A NOVEL SYNTHESIS OF VARIOUS BUTENOLIDES

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
THE MIDDLE EAST TECHNICAL UNIVERSITY

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
IN
THE DEPARTMENT OF CHEMISTRY

JULY 1996

Approval of the Graduate School of Natural and Applied Sciences

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I certify that this thesis certify all the requirements as a thesis for the degree of Doctor of Philosophy.

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Head of Department

This is the certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

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ABSTRACT

A NOVEL SYNTHESIS OF VARIOUS BUTENOLIDES

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Ph. D., Depertment of Chemistry

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July, 1996, 209 pages

The α,β-butenolide functionality is widely distributed in nature and has attracted a great deal of synthetic interests. A new approach has been developed and applied to synthesis of various butenolides.

The key step involves the synthesis of α'-acyloxy-α,β-unsaturated cyclic ketones from the corresponding α,β- unsaturated cyclic ketones by using Manganese (III) acetate in combination with 2-chloropropionic acid. The Arbuzov

reaction of α′-acyloxy enones with excess triethylphosphite gave the corresponding phosphonates. The intramolecular Horner-Emmons type cyclization reaction of the phosphonates in the presence of a base gave the target butenolides.

In addition to this study, (+/-)-Mintlactone was synthesized which shows important biological activity. α-Oxidation of enone was carried out with lead (IV) acetate as well as manganese (III) acetate. For this purpose 4-methyl cylohexanone was hydrolyzed with lead (IV) acetate and the resultant product of 2-acetoxy-4-methyl cyclohexanone hydrolyzed with K_2CO_3 in aqueous MeOH. The hydrolyzed product was reacted with chloropropionyl chloride to yield 2-chloroacyloxy 2-cyclohexanone. Application of the Arbuzov reaction followed by intramolecular Horner-Emmons type cyclization reaction provided a convenient synthesis of (+/-)-Mintlactone .

Keywords: Manganese (III) acetate, Lead (IV) acetate, Butenolide, α′-Acyloxy-α,β-unsaturated ketones, (+/-)-Mintlactone.

ÖZ

ÇEŞİTLİ BÜTENOLİDLERİN YENİ BİR YÖNTEMLE SENTEZLENMELERİ

Çalışkan, Zerenler Zerrin

Doktora, Kimya Bölümü

Tez Yöneticisi: Doç. Dr. Cihangir Tanyeli

Temmuz, 1996, 209 sayfa

α,β-Bütenolid'lerin doğada yaygın olarak bulunması, bunların sentetik olarak eldesine büyük ilgi uyandırmaktadır. Çeşitli bütenolidlerin sentezlenmesi için yeni bir yaklaşım gerçekleştirilmiştir.

α'-Asiloksi-α,β-doymamış siklik ketonların sentezinde anahtar basamak olarak uygun α,β-doymamış siklik ketonlar ile 2-chloropropionik asit varlığında mangan (III) asetat kullanılmıştır. Arbuzov reaksiyonu ile asiloksi enonlar fazla miktarda trietilfosfit ile tepkimeye sokulmuş ve uygun fosfonatlar elde edilmiştir.

Elde edilen fosfonatlar molekül içi Horner-Emmons halkalaşma reaksiyonu ile baz varlığında hedef bütenolidleri vermişlerdir.

Aynı zamanda bu çalışmada önemli biyoaktiviteye sahip (+/-)-Mintlakton yeni bir yöntemle sentezlenmiştir.

Kurşun (IV) asetat da mangan (III) asetat gibi enonlarda α-oksidasyona neden olmaktadır. Bu amaçla 4-metil siklohekzanon kurşun (IV) asetat ile tepkimeye sokulmuş ve 2-asetoksi-4-metil siklohekzanon elde edilmiştir. 2-Asetoksi-4-metil-siklohekzanon K_2CO_3 ve sulu metanol varlığında hidroliz edilmiştir. Oluşan hidroliz ürünü ile kloropropionil klorid tepkimesi sonucu 2-kloroasiloksi siklohekzanon elde edilmiştir. Çalışmanın bundan sonraki aşamasında Arbuzov reaksiyonu ve molekül içi Horner-Emmon's halkalaşması ile (+/-)-Mintlakton elde edilmiştir.

Anahtar Kelimeler: Mangan (III) asetat, Kurşun (IV) asetat, Bütenolid, α'-Asiloksi-α,β-doymamış keton, (+/-)-Mintlakton.

To My Son, DORUK, and To My Unborn Baby

ACKNOWLEDGMENT

I wish to express my most sincere thanks and gratitude to my supervisor Assoc. Prof. Dr. Cihangir Tanyeli for his everending and skillful guidance throughout the course of this work.

I am also greatly indebted to Prof. Dr. Ayhan S. Demir for his kind helps, valuable advise and criticism during the research.

I wish to extend my most profound thanks and love to my mother and to my husband Mesut Çalışkan for their support, patience and understanding. To my son, Doruk, I thank him for understanding my frequent absences.

Finally I wish to thank all in Chemistry Department who have helped in building up of this thesis.

TABLE OF CONTENTS

LIST OF TABLES

TABLE

LIST OF FIGURES

FIGURES

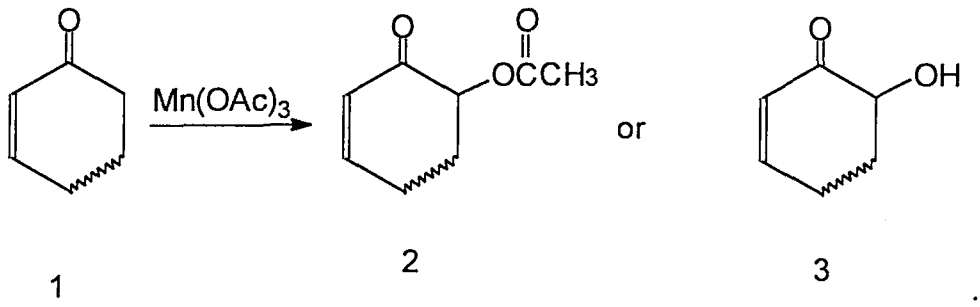
CHAPTER 1

INTRODUCTION

1. Selective Oxidation of α,β-Unsaturated Ketones at the α'-Position

1.1. Introduction

Some procedures were developed for the selective oxidation which occupy a central position of common functional groups in the synthesis of complex natural products. Literature methods gave unsatisfactory results for the oxidation of an enone 1 to an α'-acetoxyenone 2 [1]. To overcome this problem, Demir and coworker studied on the oxidation of α,β-unsaturated enones using manganese(III) acetate (eq 1) [2,3,4]. They got satisfactory result for the preparation of α'-acetoxy ketones 2 ($R=CH_3$) and subsequently investigated a general synthetic way of various α'-acyloxyenones 2. Other solutions to these problems were also reported in the literature by using procedure for the combinations of Mn(III) acetate with either different Mn(II) carboxylates or carboxylic acids [5].



1 2 3

(eq 1)

1.2. α′-Oxidation of Enones

1.2.1. Using Lead (IV) Acetate

A search for oxidants which are capable of affecting the direct α-hydroxylation of ketones is interested in the synthesis of corticosteroids [6]. Although the focus of these studies was directed on the oxidation of C-21 atom, a number of readily available steroids which have enone functionality in the A ring, and the application of lead (IV) acetate to these substrates led to C-2 oxidations. There are numerous examples which cover the C-2 oxidation of steroidal structures, (entries 12, 14, 16, 17) shown in Table 1 [7,8,10,11,12]. The regioselective oxidation of enones in both steroidal [6-12] and non steroidal [13-25] groups (Table 1) provided the α′-acetoxy enones when lead (IV) acetate in acetic acid, or toluene was used. The yields of α′-acetoxy enones were lower than the acceptable amounts.

Table 1. Oxidations of Enones Using Lead (IV) Acetate.

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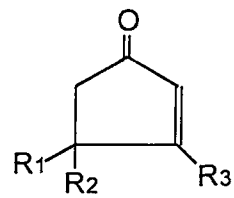
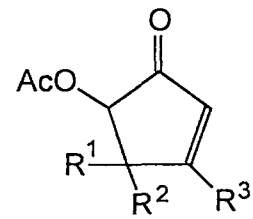
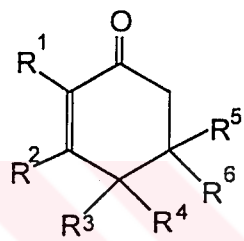
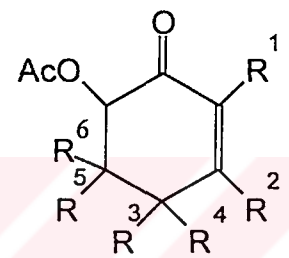
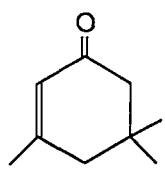
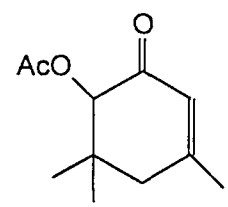
1	 R_1, R_2, R_3=H, Me	benzene, 80°C		–	9
2	 R^1, R^2, R^5=H, Me; R^3, R^4=H, Me, Ph	benzene, 80°C		–	9
3		HOAc/Ac_2O, 75-80°C, 8h BF3.Et_2O/benzene $CaCO_3$/benzene benzene,80°C,90h benzene,80°C,12h			

Table 1. (continued)

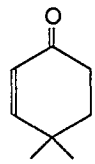
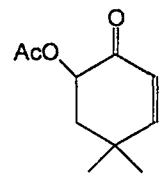
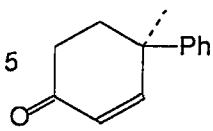
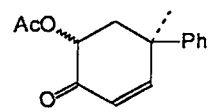
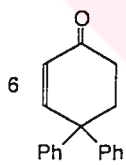
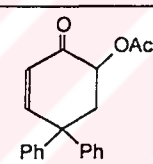
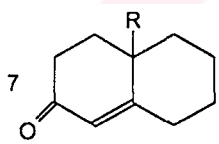
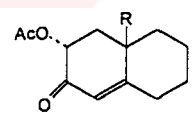
Entry	Substrate	Conditions	Products	Yield	Ref.
4		benzene,80°C,20h		36	13 19
5		toluene		64	21
6		toluene,110°C,14h		56	18
7		R=H; benzene, 80°C		15	9
		R=Me; benzene, 80°C		34	9
		R=Me; benzene, 110°C, 7h		40	18

Table 1. (continued)

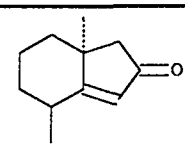
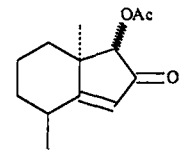
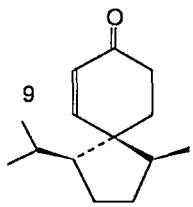
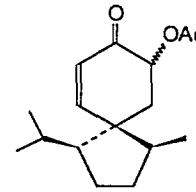
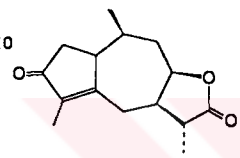
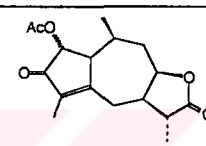
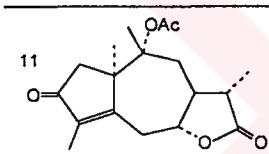
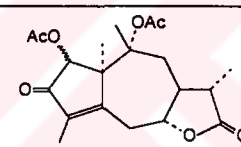
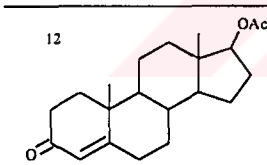
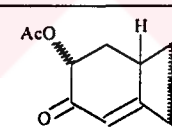
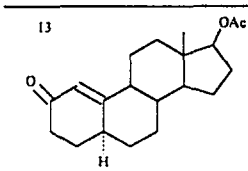
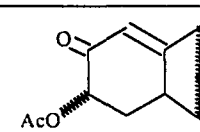
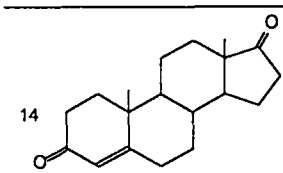
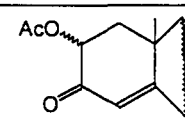
Entry Substrate	Conditions	Products	Yield	Ref.
8 	Benzene, 80°C		-	23
9 	toluene		75	7
10 	$BF_3.Et_2O$/HOAc/ Ac_2O, 25°C, 18h		69	25
11 	benzene, 80°C		11	26
12 	HOAc,70°C,42 h		44	6
13 	HOAc,100°C,24h		57	141
14 	benzene,80°C,48h		74	24

Table 1. (continued)

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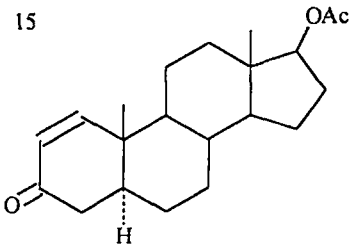
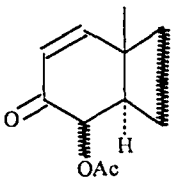
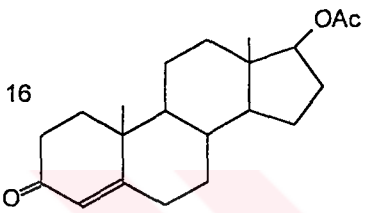
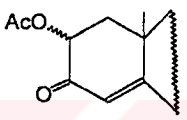
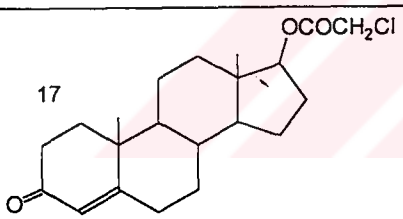
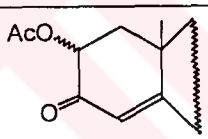
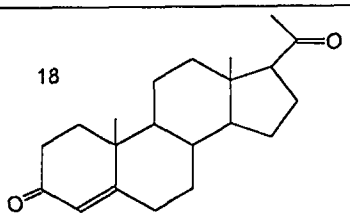
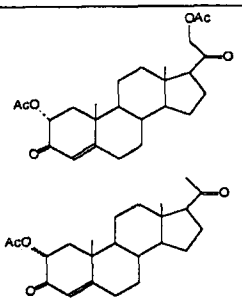
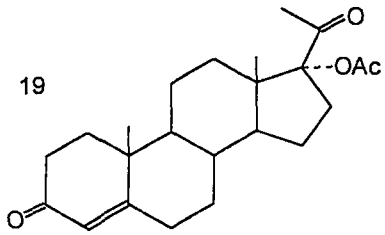
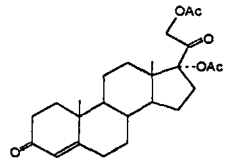
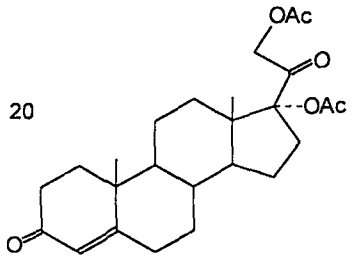
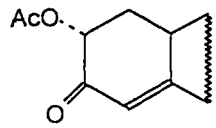
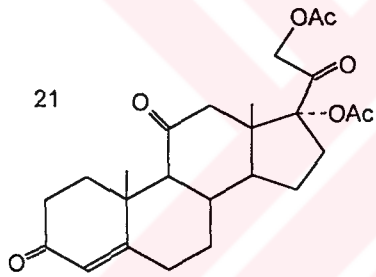
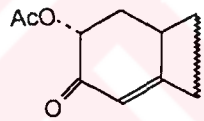
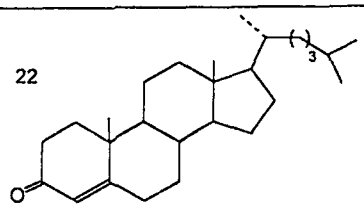
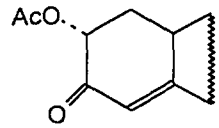
15 	HOAc,100°C		12	8
16 	HOAc,85-90°C, 3h		47	32
	HOAc,100°C,2.5h			
	benzene,80°C,48h		42	141
	benzene		71	24
			–	9
17 	benzene, 80°C		52	10
18 	HOAc,85-90°C,6h		16	32
	benzene, 80°C,48h		74	24

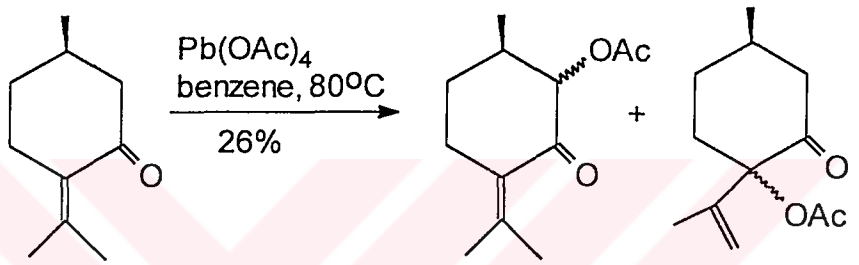
Table 1. (continued)

Entry	Substrate	Conditions	Products	Yield	Ref.
19				–	141
20		$HOAc/Ac_2O$, 100°C, 4h		25	12
21		HOAc/H2O, 100°C, 5h		22	12
22		95% HOAc/HOAc/ Ac_2O, 70°C, 24h		7 10 20	11 34 34

Henbest and coworkers [15] reported that various Lewis acids, particularly diethyl ether-boron trifluoride complex gave improved yields (Table 1, entry

3b), but other reports suggest that this way was not always effective (Table 1, entry 11) [26].

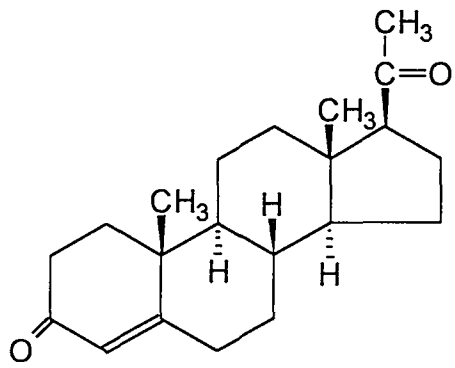
Regioselective oxidation generally occurred in the α′-site (Table 1, entry 3,4,5,6) with the exception of (+)-pulegone (4) which gave both the α- and α′-oxidation products (eq 2) 5 and 6 [20].



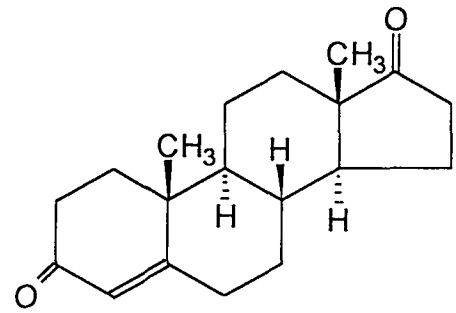
4 5 6

(eq 2)

If a compound such as progesterone (7) or 4-androstene-3,17-dione (8), has saturated ketone in its structure, the competitive oxidation causes some problems.

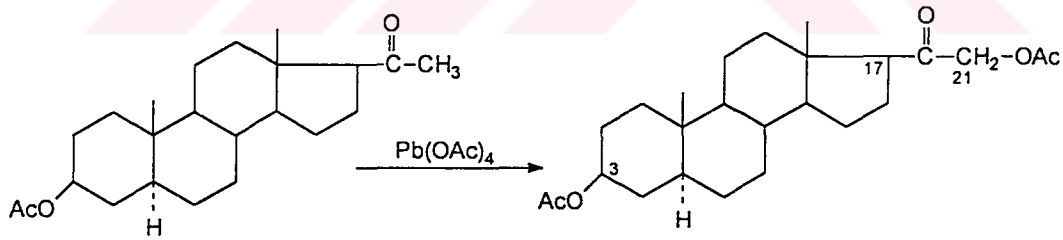


7



8

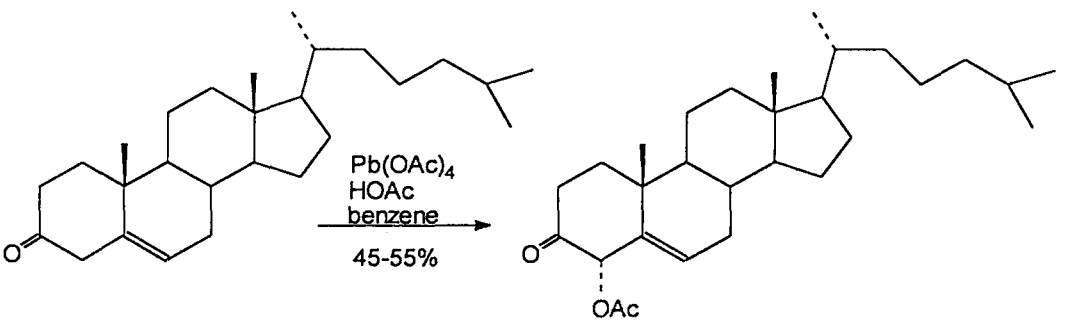
In these cases, the effect of using lead (IV) acetate showed variability in the results of previous work. According to Rushig and coworkers [27,28] lead (IV) acetate led to selective C-21 oxidation in the absence or in the presence [29] of a Lewis acid. Giral and Montigel proposed that lead (IV) acetate failed to oxidize at C-21 to a significant degree (eq 3) [30,31].



(eq 3)

Oppolzer [7] suggested that lead (IV) acetate led to selective C-2 oxidation (Table 1, entry 9) or mixtures of both products. (Table 1, entry 18) [32].

The oxidation of β,γ-unsaturated ketone, 5-cholesten-3-one (9) gave 4α-acetoxy-5-cholesten-3-one (10) [33] whereas the oxidation of 4-cholesten-3-one gave the expected 2α-acetoxy-4-cholesten-3-one in equation 4 [34].

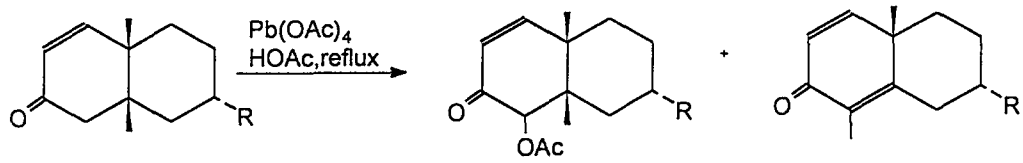


9 10

(eq 4)

Henbest and coworkers [15], and Marshall and Bundy [35] proposed the mechanism for the α′-acetoxylation of enones by using lead (IV) acetate. This mechanism involves the formation of an enol-lead triacetate derivative directly from the enone followed by intramolecular acetate transfer.

In the course of studies in the synthesis of valeranone and related compounds were planned. Marshall and Bundy [35] applied the lead (IV) acetate method to the α,β-unsaturated ketones 11 (eq 5).



11 12 13 a 30%; b 5%

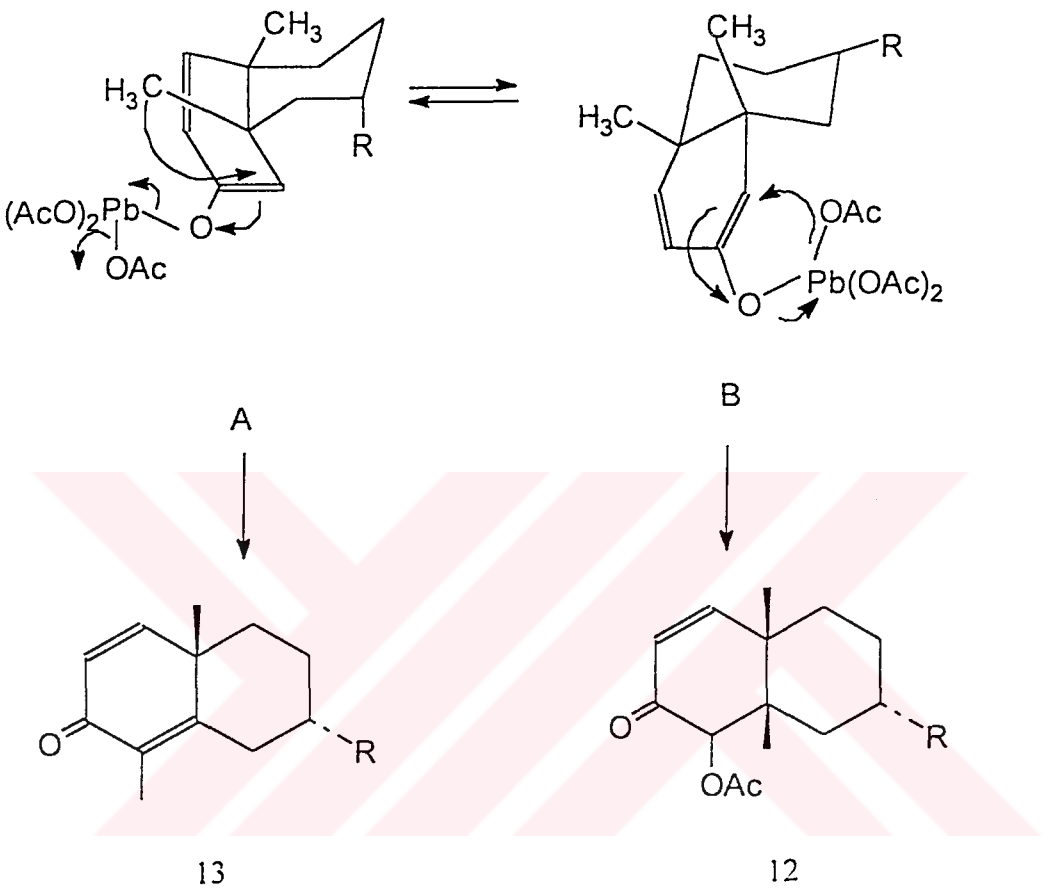
11-13	a	b
R	H	i-Pr

(eq 5)

Surprisingly this reaction afforded not only the expected acetoxy ketones 12, but also the dienones 13 (30% and 5% yield).

Accordingly, in the present case steric effects retard the usually favored attack by acetate on the enol double bond (Scheme 1, B→12) enabling methyl migration to occur (A→13). The observed disparity in the yields of dienones (R=H and R=i-Pr) can be understood in terms of the stereoelectronic requirements expected for such a methyl migration. Thus for enone (R=i-Pr), the favorable transition-state arrangement A leading to methyl migration

suffers from a serious 1,3-diaxial interaction. This causes less rotation to conformer B having an unfavorable geometry for methyl migration.



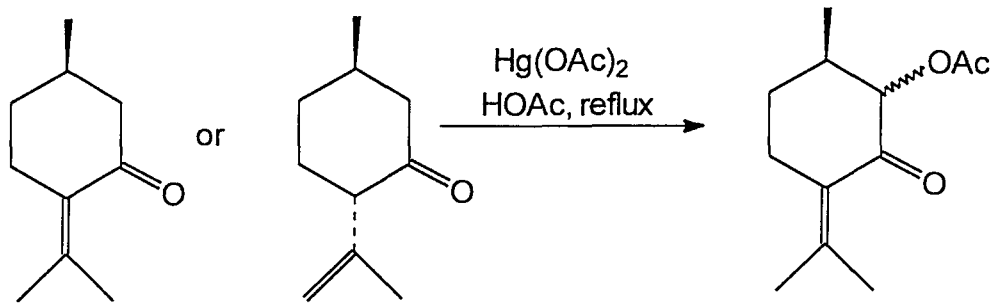
13 12

(Scheme 1)

1.2.2. Using Mercury (II) Acetate

The oxidation of (+)-pulegone (4)[36-38] or the nonconjugated isomer (14) [37,39] with mercury (II) acetate in refluxing acetic acid provided the same α'-acetoxyenone (5) in modest yield (eq 6). However, since lead (IV) acetate

produced comparable yields of (5) and since the scope of this oxidation was unexplored, there is little to recommend mercury (II) acetate for this type of oxidation.



4 14 5

(eq 6)

1.2.3. Direct Oxidation of Enolates

There are a number of methods for the direct oxidation of enolates which are derived from saturated, enolizable ketones to α-hydroxy ketones. However the extension of these procedures to the direct oxidation of unsaturated ketones is relatively rare. A few examples [40,41] involving the use of Mimoun's reagent [42](MoOPh) appear in Table 2. The yields in Table 2 are at least comparable with the yields available in the corresponding lead (IV) acetate oxidations (Table 1). It is also suggested that this approach may in

certain instances, prove to be more popular in the future than metal acetate oxidation.

Table 2. Oxidation of Enones to α′-Hydroxyenones

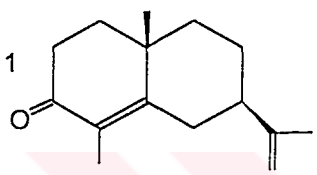
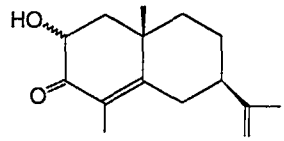
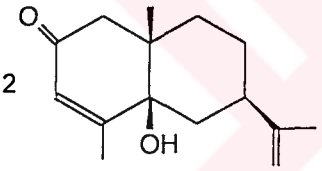
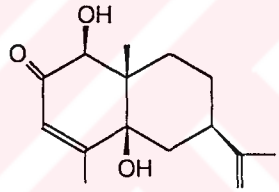
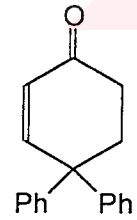
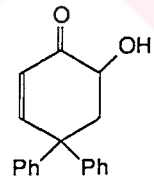
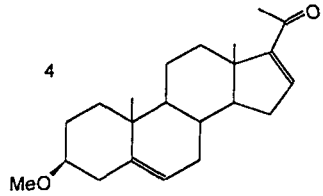
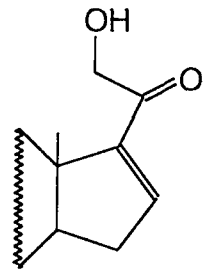
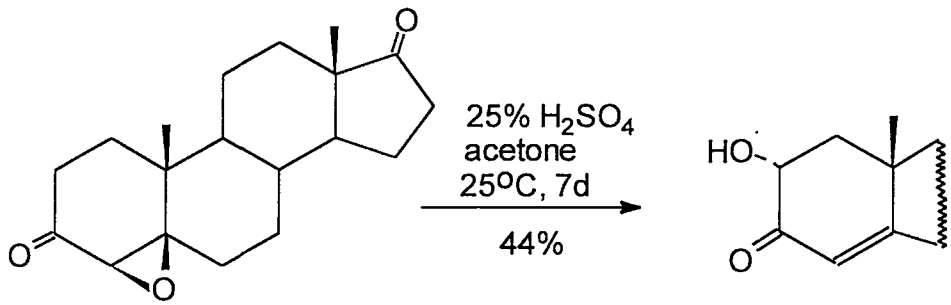
Entry	Substrate	Conditions	Product	Yield	Ref.
		LDA/MoOPh			
1		THF, 23°C		62	40
2		THF, -23°C		57	40
3		THF, -22°C		17	41

Table 2. (continued)

Entry Substrate	Conditions	Products	Yield	Ref.
	THF, -22°C		52	41

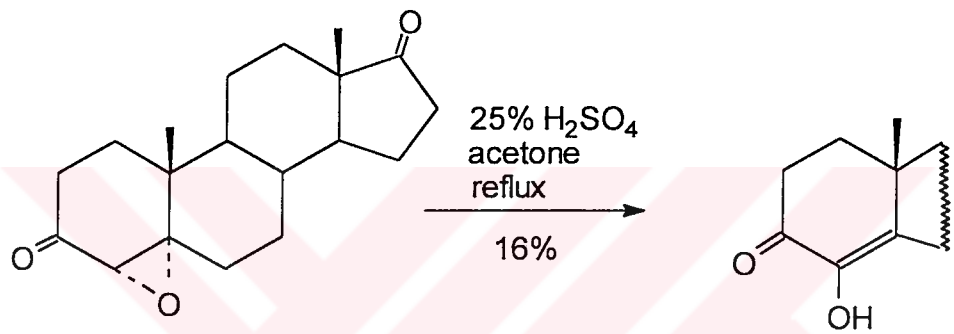
1.2.4. Via Cine-Substitution

The solvolysis of certain α,β-epoxy ketones and γ-bromo-α,β-unsaturated ketones in steroid substrates involve a cine-substitution process. This process is leading to α′-hydroxy and α′-acetoxy enones. These rearrangements involved an S_N2' substitution at the C-2 position of the enol tautomer of the starting material.[19] This starting material was illustrated by the conversion[43] of 4β-5β-epoxyandrostane-3,17-dione (15) to the α′-hydroxyenone (16) (eq 7). Under similar conditions, the diastereomeric 4α,5α-epoxy ketone (17) led to the diosphenol (18) (eq 8). This process was restricted to steroid systems, the acetolysis of γ-(bromo)-enones, such as 6β-bromo-4-androstene 3,17-dione [44] (Table 3, entry 1).



15 16

(eq 7)



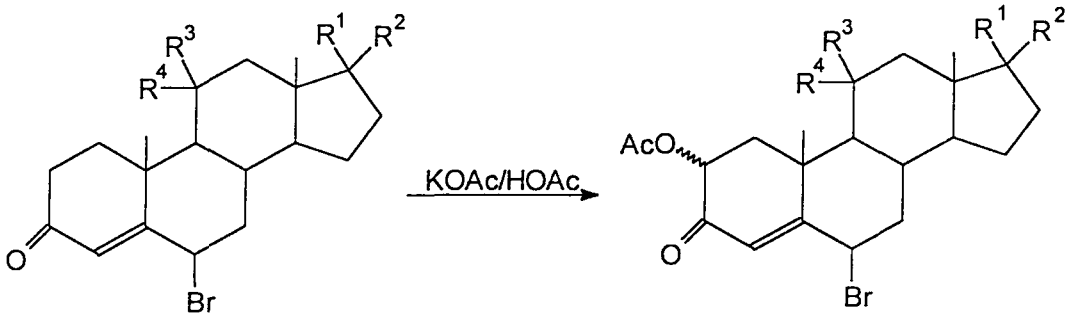
17 18

(eq 8)

Fieser[11] suggested that this process involved the rearrangement of the 6β-bromo substituent to the 2-bromo position and the subsequent solvolysis of the 2-bromo isomer to give the 2α-acetoxy enone. In agreement with this suggestion, rearrangement in the opposite sense (C-2 to C-6) was known[45]. Both the 2-bromo enone and the 6β-bromo enone gave comparable yields of the same product[12]. The rearrangement of 6β-bromoenone excludes the 6α-acetoxyenone as an intermediate. Therefore the rearrangement of this

compound is not achieved under these conditions. Whearas 6β-bromoenone can be easily rearranged to 2-acetoxyenone.[17,18]

Table 3. Cine-Substitutions as a Route to α'-Acetoxyenones



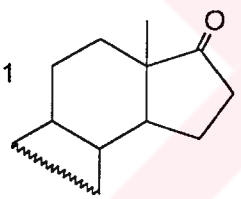
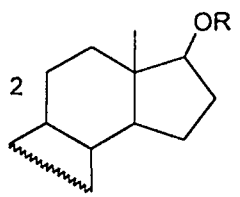
Entry	Substrate	Conditions	Product Yield	Ref.	α/β (ratio)
1		reflux,12 min	40	44	2α/2β (3:5)
		66°C, 27 h	25	6	2α/2β/6β(10:8:7)
2		R=Ac:reflux,	40-45	32	2β
		12 min	21,22	141	2β
		R=Ac: 4 h	15	141	2α
		R=$COCH_2Cl$:	21	141	-
		reflux,12 min			

Table 3. (continued)

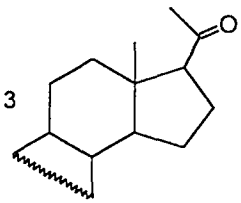
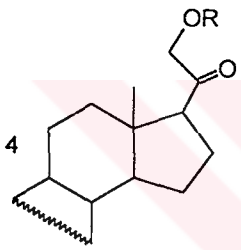
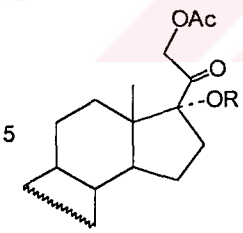
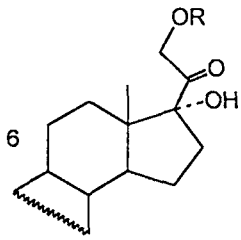
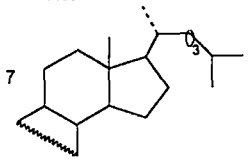
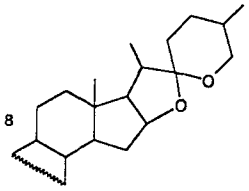
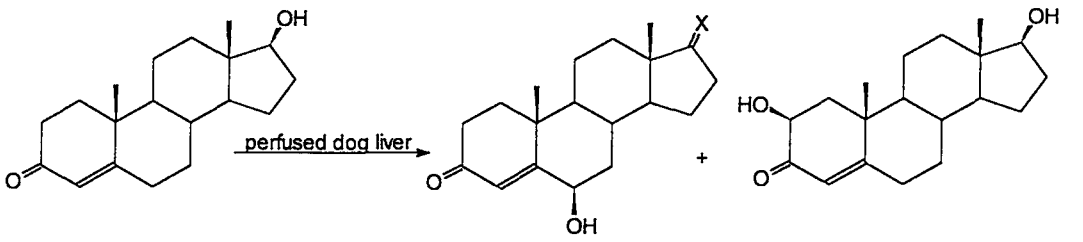
Entry	Substrate	Conditions	Product Yield	Ref.	α/β (ratio)
3		reflux, 4 h	15	141	2α
		reflux,12 min	44	44	2α/2β (1:1)
4		R=Ac: reflux, 4 h	6	141	2α
					2α
		R=Pv: reflux, 4 h	16	141	
5		R=H: reflux, 4 h	21	12	2α
					2α
		R=Ac: reflux, 4 h	17	12	
6		R=Ac: reflux, 4 h	13	12	2α
		R=Pv: reflux, 4 h	13	141	2α

Table 3. (continued)

Entry	Substrate	Conditions	Product Yield	Ref.	α/β (ratio)
7		reflux,80 min	7 17	11	2α -
8		reflux, 24 h	25	141	2α

1.2.5. Biological Hydroxylation

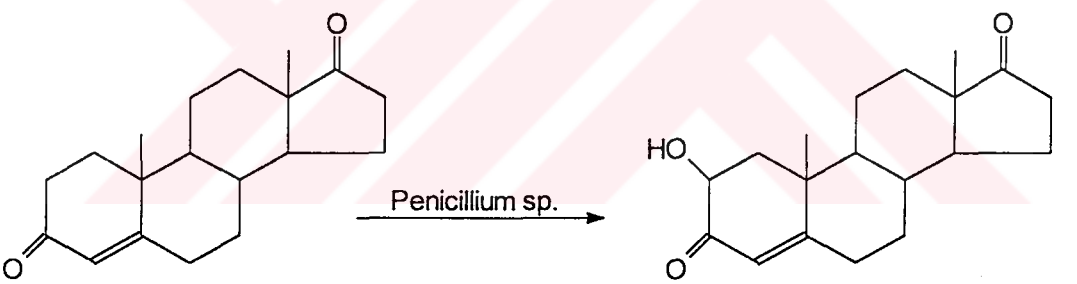
Several studies on the biological oxidation of androgens and progestagens uncovered the examples of the α'-oxidation of enone functionality in the A ring. Although the absolute or relative amounts of these metabolites were not determined (eq 9), the hydroxylation of testosterone (17) for example, in a perfused dog liver [46] led to 3-oxo-4-androstene-6β-17-β-diol (18), 6β-hydroxy-4-androstene-3,17-dione (19) and 3-oxo-4-androstene 2β,17β-diol (20).



19 20 X=H, OH 21 X=O 22

(eq 9)

Subsequently investigations [47,48] indicated the enzymatic oxidation of 4-androstene-3,17-dione (23) by a Penicillium species and also identified a 2β-hydroxylated product (24).(eq 10)

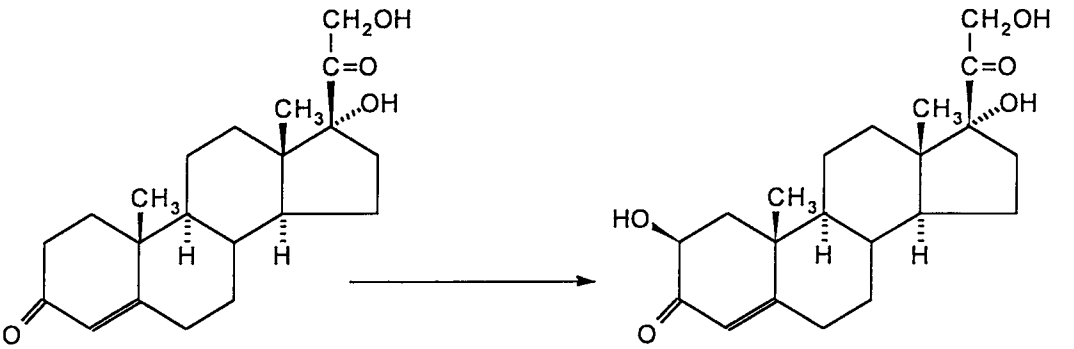


23 24

(eq 10)

In the pregnane family, studies of the microbiological oxidation of 17α,21-dihydroxy-4-pregnene-3,20-dione (25), Reichstein's compound S, by a Streptomyces species[49], Sclerotinia libertiana[50], or Rhizoctonia ferrugena[51]

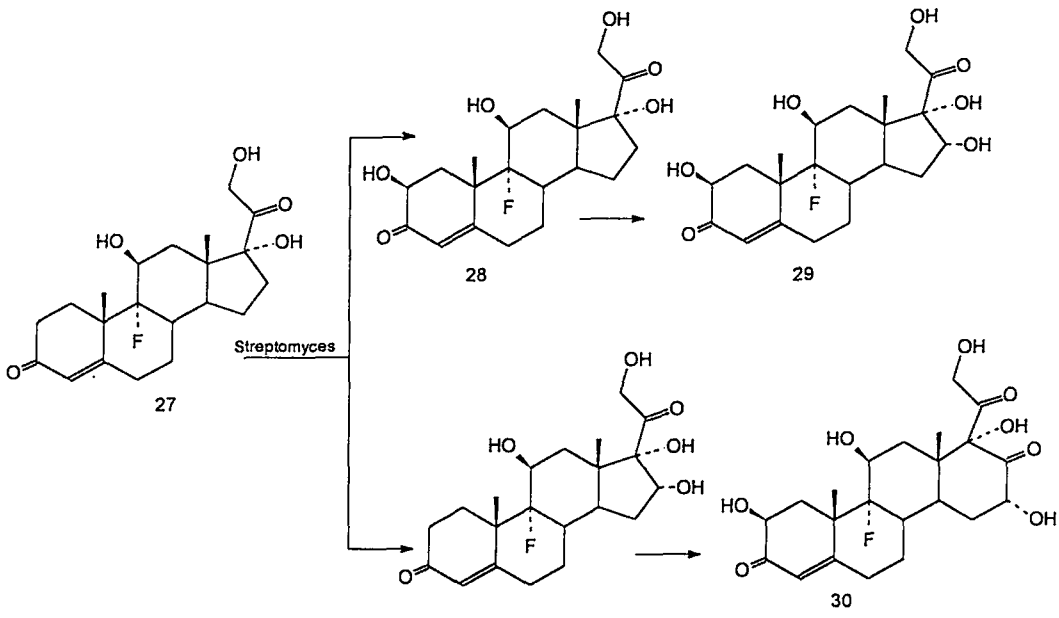
disclosed a pattern of C-1, C-2 and C-11 oxidations among which 2β,17α,21-trihydroxy-4-pregnene-3,20-dione (26) was a common metabolite.(eq 11)



25 26

(eq 11)

Application of the same Sclerotinia species [52,53] or an Actinomycetes species [54] to various pregnanes including progesterone, 17α-hydroxyprogesterone, corticosterone, and deoxycorticosterone led to C-2, C-11, C-15 and C-16 oxidations with 2β-hydroxylation again as the common denominator. Finally the oxidation of 9α-fluorohydrocortison (27) by Streptomyces roseochromogenus [55] showed a pattern of C-1, C-2 and C-16 hydroxylation having a connection with D-ring oxidation. This oxidation led to the 2β-hydroxylated derivative 28, 29, and 30 (scheme 2). These microbiological oxidations were interesting in corticosteroids which were limited preparative value for the selective production of C-2 hydroxylated steroid since the yield was 5%.[56]



(Scheme 2)

1.2.6. α′-Oxidation of Enones via Dienol Ethers

In several studies α′-oxidation occurred by using O-trimethyl silyl dienol ethers which were derived from the kinetic deprotonation of enones with chloro trimethyl silane. As summarized in Table 4, oxidants included lead tetra benzoate,[57] 3-chloro peroxybenzoic acid (MCPBA)[58,59], triphenyl phosphite ozonide (TPPO) [60,61] and cupper (II) chloride/tert-butyl hydroperoxide[62]. The overall yields for the three-step process involving silylation, oxidation with TPPO or MCPBA, and desilylation with

triethylammonium fluoride were comparable for either the TPPO or MCPBA oxidants (56-79%). Scientists proposed that TPPO oxidation showed greater stereoselectivity in the α′-hydroxyenone relative to the results from the MCPBA oxidations[61]. For example the oxidation of 1,5-dimethyl-3-trimethylsiloxy-1,3-cyclohexadiene (Table 4, entry 2) using TPPO or MCPBA gave the epimeric cis/trans α′-hydroxyenones in 1:2 or 3:2 ratios, respectively. However, it was not clear whether these ratios represented true kinetic ratios. The TPPO oxidation was successfully employed in a total synthesis of oxylubimin in which a stereoselective oxidation was required.

Table 4. Oxidations of Trimethylsilyl Dienol Ethers Using Triphenyl Phosphite Ozonide (TPPO), 3-Chloroperoxybenzoic Acid (MCPBA), or Lead Tetrabenzoate

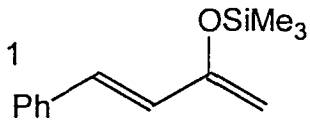
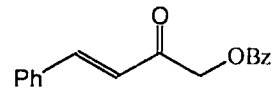
Entry	Substrate	Reagent Conditions	Product	Yield	Ref.
1		$Pb(OBz)_4/CH_2Cl_2$ -18°C		78	57

Table 4. (continued)

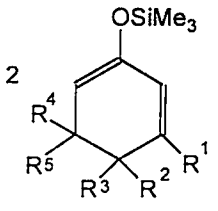
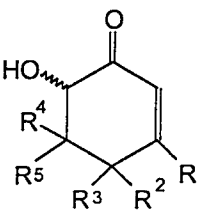
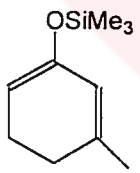
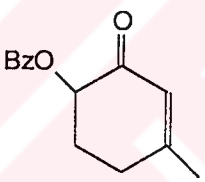
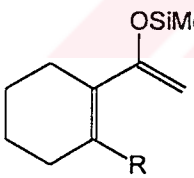
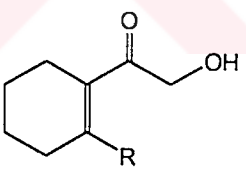
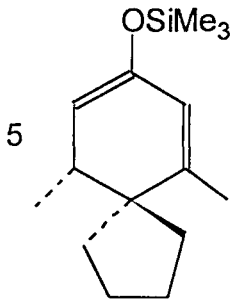
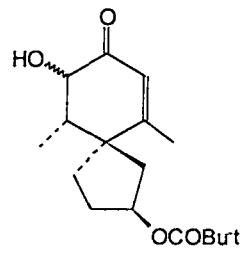
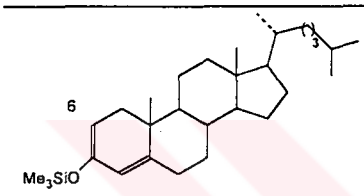
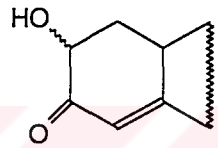
Entry Substrate	Conditions	Products	Yield	Ref.
2 	TPPO (1.1 equiv) -78°C		58-79	60
	MCPBA(1.1equiv) hexane, -15°C or		56-79	58
	CH_2Cl_2,-50°C 10% CuCl, t-BuOOH (2 equiv)/benzene		70-87 44	 62
3 	$Pb(Obz)_4/CH_2Cl_2$ -18°C		≈5	57
4 	R=H, Me:MCPBA/ hexane, -15°C		56-71	58
	R=H: $PB(OBz)_4$/ CH_2Cl_2, -18°C		68-83 54	 57

Table 4. (continued)

Entry	Substrate	Conditions	Products	Yield	Ref.
5		TPPO (1.5 equiv)/ CH_2Cl_2, -50°C		71	61
		TPPO (1.5 equiv), -50°C		59	60
		MCPBA(1.1equiv)/ hexane, -15°C		80	58

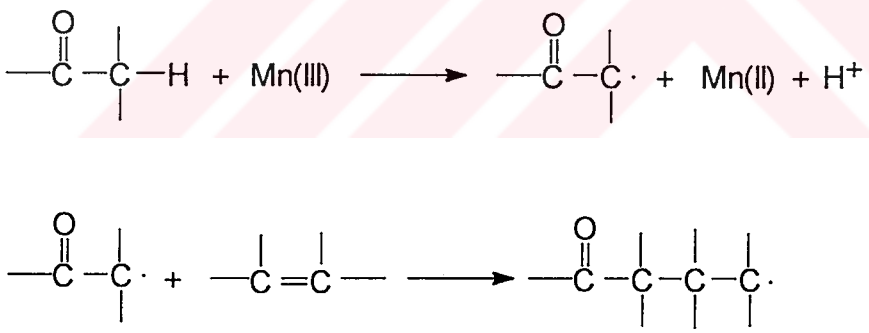
1.2.7 Oxidations Using Manganese (III) Acetate

Oxidations of manganese (III) acetate can be divided into two clases:

1) Direct Oxidation: Direct inner or outer-sphere one electron oxidation of the substrate; often determines the product is followed by the formation of manganese (III) complex where the subsequent oxidation of the

intermediate radical. Numerous examples can be found such as oxidations of alcohols, amino and thio compounds, carboxylic acids and certain aromatics.

2) Indirect Oxidation: Indirect oxidation of the substrate; takes place after formation of an intermediate adduct free radical which is formed by the interaction of Mn (III) acetate. The result is an enolizable compound or subsequent oxidation/substitution of this radical to the substrate. Most examples refer to aromatic substitution and oxidative addition of enolizable compounds to unsaturated systems. Mn (III) acetate deals with addition reaction of compounds which have α-hydrogen atom to a carbonyl group with olefinic and aromatic unsaturated systems are shown in scheme (Scheme 3).



(Scheme 3)

The fate of the primary radical adduct strongly depends on reaction conditions and the nature of the substrate. Manganese (III) acetate can be used

as a free radical generator if substrates are less reactive to common oxidants. The one-electron oxidants like Co (III), Ce (IV), and some two electron oxidants like Tl (III) and Pb (IV) also show (scheme 3) similar properties as Manganese (III) acetate. However, lower reactivity and higher selectivities is obtained with manganese (III) acetate compared with the other oxidizing agents. Many of these reactions proceed according to the simplified scheme which is shown below;

$$Mn\ (III) + substrate \rightarrow\ intermediate\ radical + Mn\ (II)$$

$$Mn\ (III) + intermediate\ R\bullet \rightarrow\ product + Mn\ (II)$$

(Scheme 4)

Complications may arise in the presence of water. Water causes disproportionation of trivalent manganese into Mn (IV) and Mn (II) and alternative two-electron oxidants may take place by Mn (IV).

1.2.8. Oxidative Addition Reaction of Acids to Olefinic Unsaturated System

According to Bush and Finkbeiner [63] and Heiba and Dessau [64] in the presence of manganese (III) acetate, the oxidative addition of carboxylic acids to olefins led to γ-butyrolactones. These reactions have been proven to be generally applicable, although the lactones are not always major products. The formation of other major products depends largely on the nature of substrate olefin, reacting acid, and the reaction conditions. The major reactions involved in the Mn (III) acetate initiated addition of acetic acid to an α-olefin in acetic anhydride-acetic acid mixtures are given in scheme (Scheme 5).

From this mechanistic scheme the following basic requirements for oxidative addition can be drawn.

1. Direct generation: If the free acids are considered, the generation of carboxyalkyl radicals is largely limited to acetic acid, propionic acid and readily enolizable acids like cyanoacetic acid,[65] the major competing reaction being formation of carboxyl radicals RCOO•.

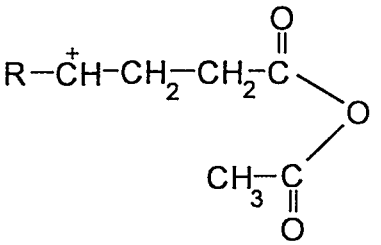
In the presence of excess anhydride, carboxyalkyl radical formation is favored and a larger variety of acids can be used [66,67]

2. No oxidation of the primary formed carboxyalkyl radical: In this respect, groups increasing the electron density on carbon α to the carbonyl group increase the tendency of carboxyalkyl oxidation by Mn(III).

3. Rapid addition of carboxyalkyl radical to the olefin: The reactivity of olefins towards the carboxymethyl radical was studied by Heiba.[65] He found that the stability of the intermediate radical adduct to be governed by steric considerations. Recently, Mc Quillin and Wood [68] have found the evidence that some carboxyalkyl radicals may add reversibly to olefins. Slow addition may lead to competing reactions such as allylic hydrogen abstraction.

4. Rapid oxidation of the intermediate radical adduct to carbenium ion: This is favored by a high Mn(III) acetate concentration, high acid concentration and high acetate concentration. The structure of carbenium ion will determine either lactonization or elimination of a proton to form a new unsaturated carboxylic acid.

In the presence of excess anhydride, formation of γ-acetoxyacid will complete strongly the ring-closure of the anhydride to a γ-lactone.



This step is sensitive if small amounts of Cu [69,70] is present which leads to the production of mixtures of γ and δ-unsaturated carboxylic acids. Low manganese (III) acetate concentrations may lead to chain transfer reaction of the intermediate adduct radical with solvent resulting in the synthesis of saturated carboxylic acids. Under these conditions when high olefin concentrations are added to the system tolomer or polymer products are produced [66].

In the literature reports, a large variety of reaction conditions and many parameters control the effective lactone production. Three main media may be used which depends on the structural constrains of the substrates olefin as a result of lactone formation. These are:

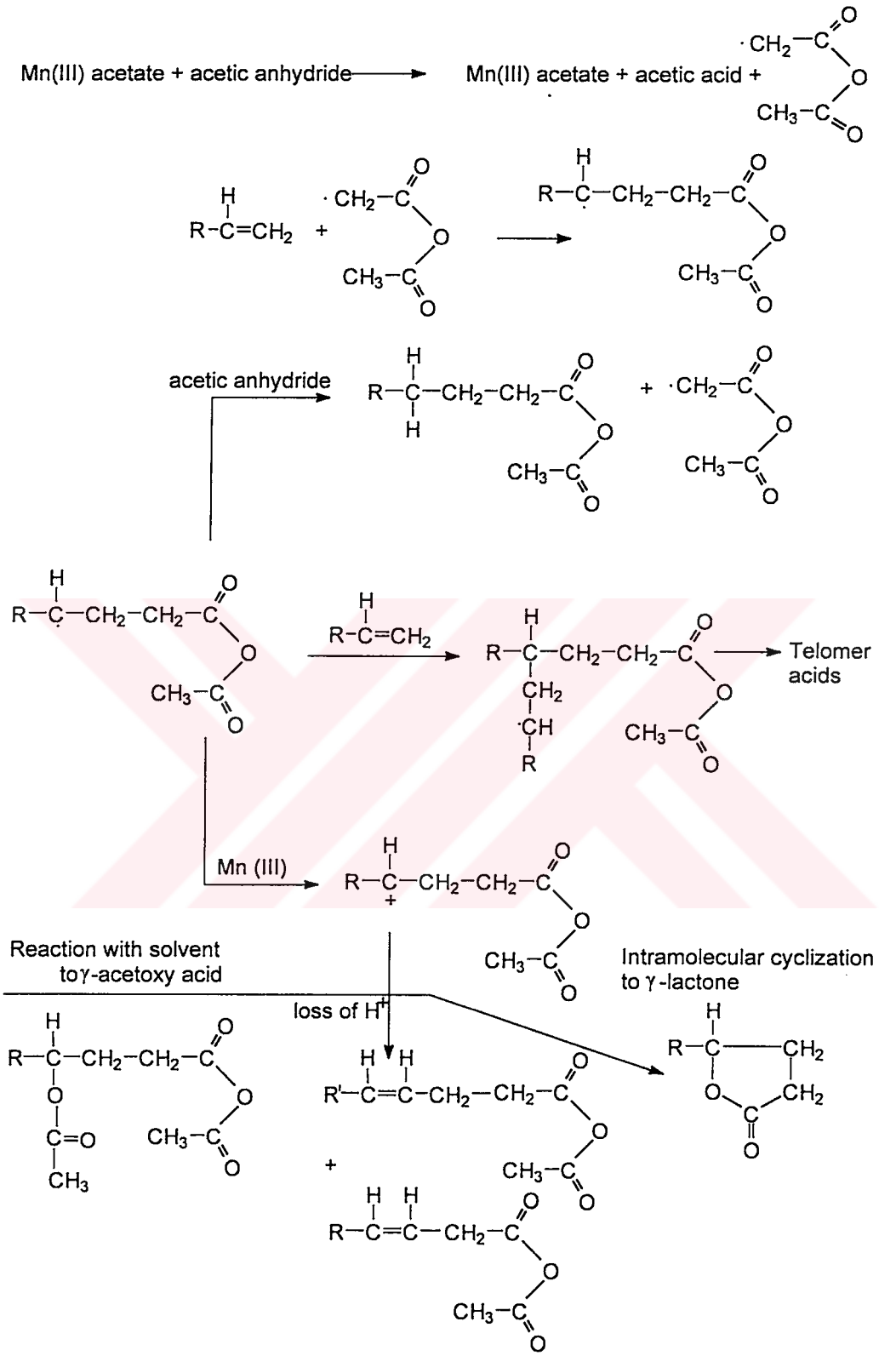
1) Acetic acid-potassium acetate or sodium acetate mixtures [64].

2) Acetic anhydride-acetic acid mixtures [63].

3) Acetic anhydride-acetic acid-potassium acetate or sodium acetate mixtures[71].

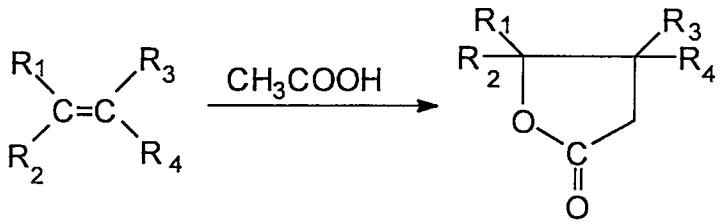
Table 5 shows the oxidative addition of acetic acid to more simple olefin. In Table 6 the results of oxidative addition of other acids such as propionic and cyanoacetic acid are summarized. Table 7 directs the oxidative addition to cycloaliphatic systems. From cyclohexene and cyclopropene poor yields of lactone are obtained. However, the acetoxy or propionoxy acids obtained may be converted to the γ-lactones by heating or alkaline hydrolysis followed by acid catalyzed ring closure. In this way 50% yields can be obtained. The side products in 1-methyl-cyclohexene are interesting in which exo-cyclic cyclohexanone derivatives are formed in rather high yields. Table 8 shows lactone formation in the indene derived benzofuran system.

Typical results of reactions of terpenes and related compounds are shown in Table 9.


Mn(III) acetate + acetic anhydride
Mn(III) acetate + acetic acid +
acetic anhydride
Telomer acids
Mn (III)
Reaction with solvent to γ-acetoxy acid
loss of H+
Intramolecular cyclization to γ-lactone

(Scheme 5)

Table 5. Oxidative Addition of Acetic Acid to Simple Olefins



Main Products

R_1	R_2	R_3	R_4	% γ-lactone	Others	Rf.
C_6H_5	CH_3	H	H	80, 30		63
C_6H_5	H	H	H	75,39		
C_6H_5	H	CH_3	H	21		
$C_6H_5CH_2$	H	H	H	16		
C_6H_5	H	H	C_6H_5	20		
$(CH_3)_3C$	H	H	H	12		
C_6H_5	C_6H_5	H	H	+		
C_4H_9	H	H	H	+		
C_2H_5	CH_3	H	H	+		
$(CH_3)_3C$	H	Cl	H	-		
H	H	H	H	73		
C_6H_5	H	H	CH_3	79		64
C_6H_5	CH_3	H	H	74		

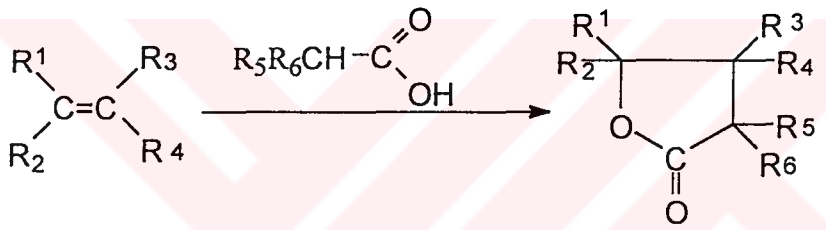
Table 5. (continued)

R_1	R_2	R_3	R_4	% γ-lactone	Others	Ref.
C_6H_{12}	H	H	H	74		
C_3H_7	H	H	C_3H_7	44		
C_6H_5	H	H	H	60		
C_6H_5	H	H	C_6H_5	16		
C_5H_{11}	H	H	H	18		
H	H	H	H	38		
CH_3	CH_3	H	H	30		65
$(CH_3)_3C$	H	H	H	48		
C_6H_5	H	H	CH_3(trans)	79		
C_6H_5	H	H	$COOCH_3$	45		
CH_2=CH(CH_2)	H	H	H	24		
CH_2=CH(CH_2)	H	H	H	26		
CH_2=CH_2	H	H	H	30		
$CH_2C(CH_3)$	H	H	H	13-37		
CH_2=CH_2	CH_3	H	H	37		
$CH_3C{\equiv}C(CH_2)_4CH_3$	H	H	H	50		
CH_3 C_6H_5	CH_3	CH_3	CH_3	Minor		71
CH_3 C_6H_5	$(CH_3)_2C$	H	H	Major		

Table 5. (continued)

R_1	R_2	R_3	R_4	% γ-lactone	Others
C_4H_9	H	H	H	19	$CH_3(CH_2)_5CH(CH_2)_2COOH$ OAc 61%
C_2H_5	H	CH_3	CH_3	55	$CH_3-CH_2-C(CH_3)(CH_2COOH)-C=CH_2$ 22%

Table 6. Oxidative Addition of Some Carboxylic Acids to Simple Olefin



Main products						% γ		
R_1	R_2	R_3	R_4	R_5	R_6	lactone	Others	Ref.
C_6H_5	CH_3	H	H	CH_3	H	25		99
C_6H_5	CH_3	H	H	CN	H	57		99
C_6H_5	H	H	H	CH_3	H	50		64
$(CH_3)_3C$	H	H	H	CN	H	+		178
$(CH_3)_3C$	H	H	H	CH_3	COOEt	44		178

Table 6 (continued)

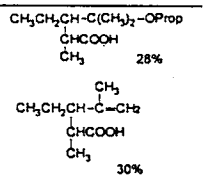
Main products						% γ	
R_1	R_2	R_3	R_4	R_5	R_6	lactone	Others Ref.
$(CH_3)_2CH$	CH_3	H	H	CH_3	COOEt	48	178
$(CH_3)_3C$	H	H	H	H	COOMe	15	178
C_6H_5	H	H	H	CN	H	41	65
C_6H_{13}	H	H	H	CN	H	60	65
C_6H_5	CH_3	H	H	CN	H	43	65
C_3H_7	H	H	C_3H_7	CN	H	49	99
C_6H_5	H	H	CH_3	CN	H	51	65
$H_2C=C(CH_3)$	H	H	H	CN	H	5	65
$CH_2=CH$	CH_3	H	H	CN	H	39	65
C_6H_{13}	H	H	H	CH_3COOH	H	25	65
C_4H_9	H	H	H	CH_3	H	15	171
CH_3	CH_3	C_2H_5	H	CH_3	H	28	

Table 7. Oxidative Addition of Carboxylic Acids to Cycloaliphatic Systems

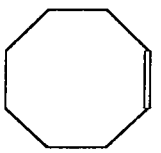
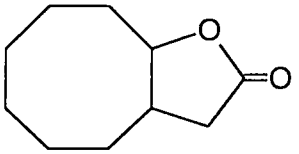
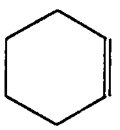
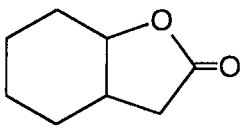
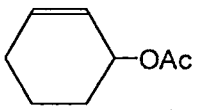
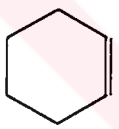
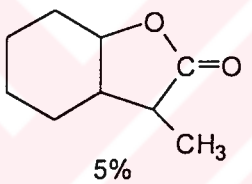
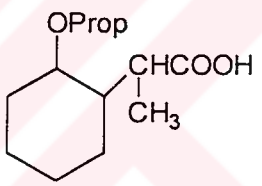
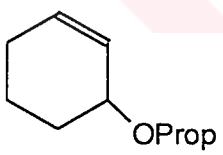
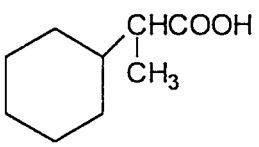
Olefin	γ-lactone (% yield)	Other main products	Ref.
	 62%		
	 10%	 22%	63
	 5%	 27%	170
		 35%	
		 33%	

Table 7. (continued)

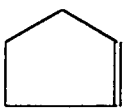
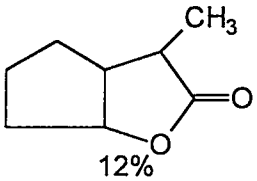
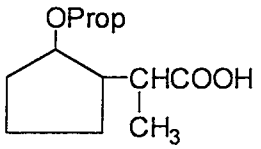
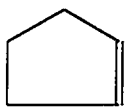
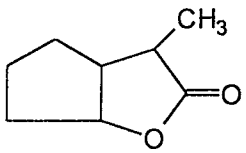
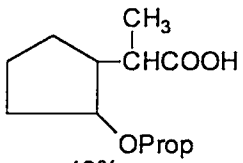
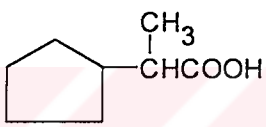
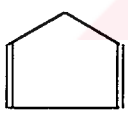
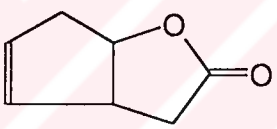
Olefin	γ-lactone (%yield)	Other main product	Ref.
	 12%		170
	 13%	 40%  35%	171
			172

Table 7. (continued)

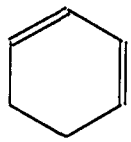
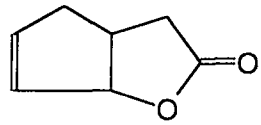
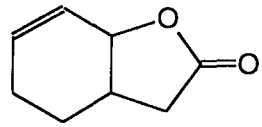
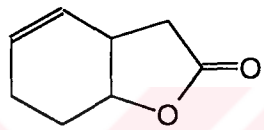
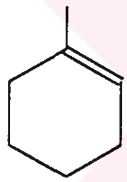
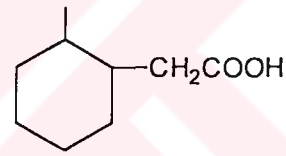
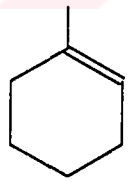
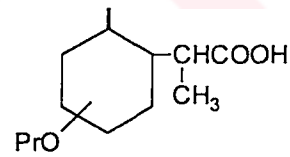
Olefin	γ-lactone (% yield)	Other main product	Ref.
	  		172
		 41%	170
		 36%	170

Table 7. (continued)

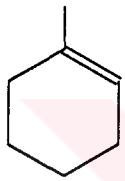
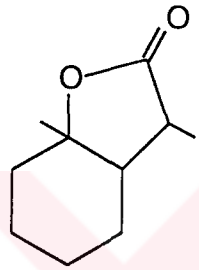
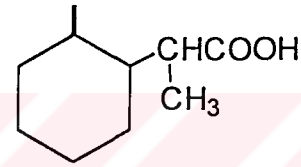
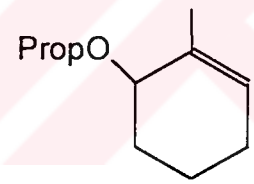
Olefin	γ-lactone (%yield)	Other main product	Ref.
	 28%	 22%	171
		 20%	

Table 7. (continued)

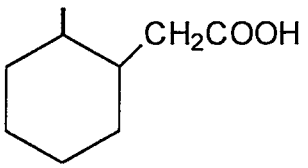
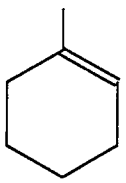
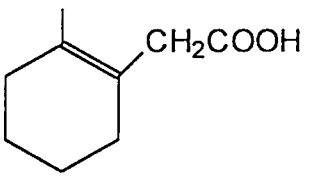
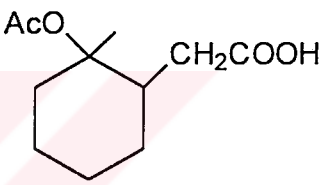
Olefin	γ-lactone (%yield)	Other main product
		
	No Lactone	
		

Table 8. Oxidative Addition of Acetic Acid to Complex Olefins

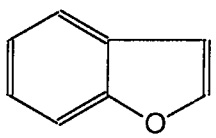
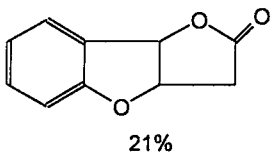
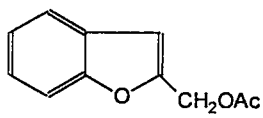
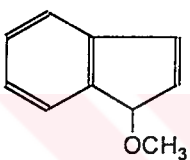
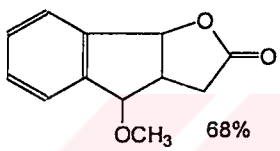
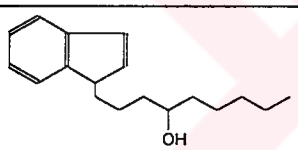
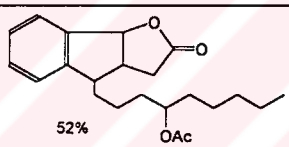
Substrate	Lactone (%yield)	Other main products	Ref.
 Benzofuran	 21%		73
 1-Methoxy-methyl-indene	 68%		174
 1-(3-Hydroxyoctyl)indene	 52%		174

Table 9. Oxidative Addition of Acetic Acid to Terpenes

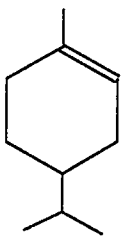
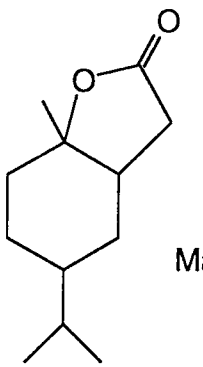
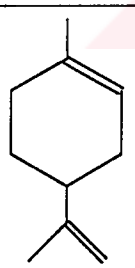
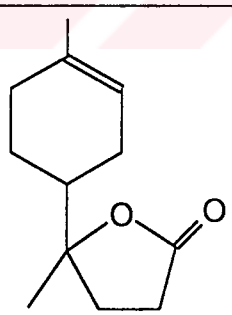
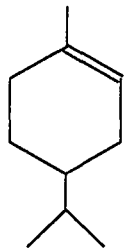
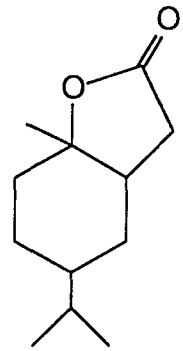
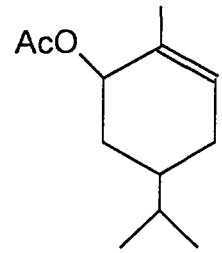
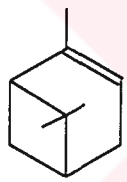
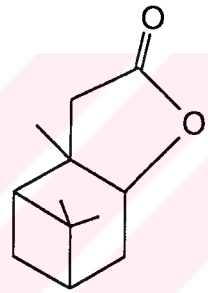
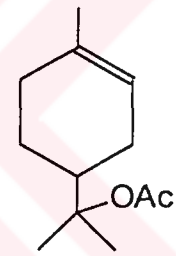
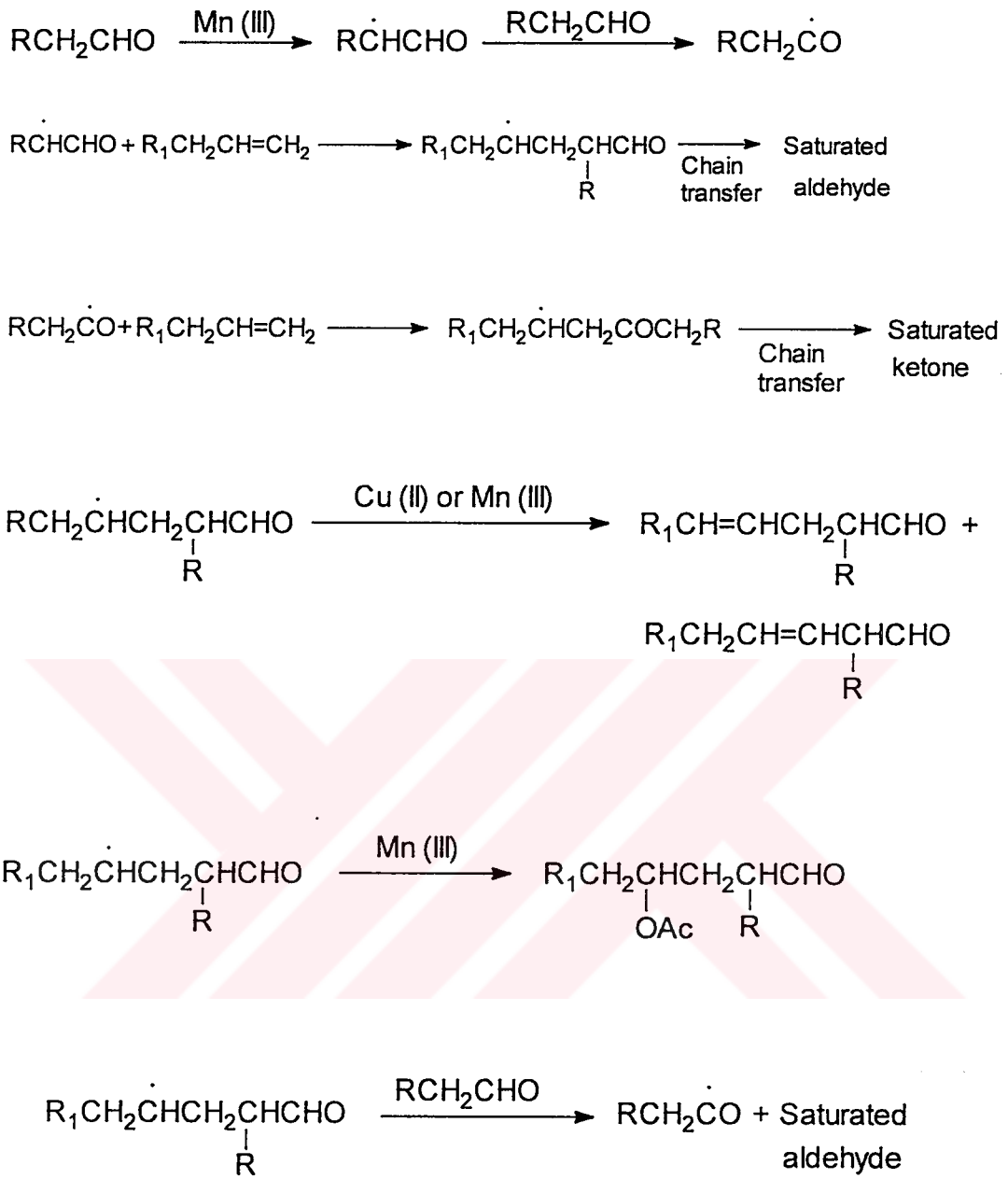
Substrate	Product	Ref.
 d-Carvomenthene	 Main product l-p-Menthanol-2-yl-acetic acid lactone	175
 d-Limonene	 1-p-Menthene-3-ol-9-yl-acetic acid lactone	101

Table 9. (continued)

Substrate	Product	Ref.
	  Mixture allyl acetates (major product with lactone)	101
	 Lactone=minor product  Major acetate -terpinel acetate	176

1.2.9. Manganese (III) Acetate-Initiated Addition of Aldehydes to Olefinic Unsaturated Systems

Most free radical addition of aldehydes to olefin yields ketones as main products. Thus, the peroxide, γ-radiation and oxygen [72] which initiated the addition of aldehydes to 1-alkenes provide a convenient way for the synthesis of ketones. The acyl radical, R-C=O, is proposed to be formed as an intermediate in these systems. In the presence of Mn (III) acetate, a free radical addition of aldehydes to olefins is also observed. However depending on reaction conditions, both the expected ketones and rather unexpected aldehydes could be formed. Working with manganese (III) acetate and by adding small amounts of Cu (II) acetate produced the formation of acyl radicals RC=O by chain transfer. In this case unsaturated aldehydes are synthesized.[73] In the absence of polar solvents like acetic acid and low concentration of manganese (III) acetate, ketones are produced in high yield. The most important reaction sequence are given in scheme 6. Since the formation of ketones is suppressed by the addition of small amount of Cu and Manganese (III) acetate, acyl radicals are most probably formed via chain transfer of intermediate radical (compound A in scheme 6) with aldehyde.


RCH2CHO
Mn (III)
RCHCHO
RCH2CHO
RCH2CO
RCHCHO + R1CH2CH=CH2
R1CH2CHCH2CHCHO
R
Chain transfer
Saturated aldehyde
RCH2CO+R1CH2CH=CH2
R1CH2CHCH2COCH2R
Chain transfer
Saturated ketone
RCH2CHCH2CHCHO
R
Cu (II) or Mn (III)
R1CH=CHCH2CHCHO +
R
R1CH2CH=CHCHCHO
R
R1CH2CHCH2CHCHO
R
Mn (III)
R1CH2CHCH2CHCHO
OAc
R
R1CH2CHCH2CHCHO
R
RCH2CHO
RCH2CO + Saturated aldehyde

(Scheme 6)

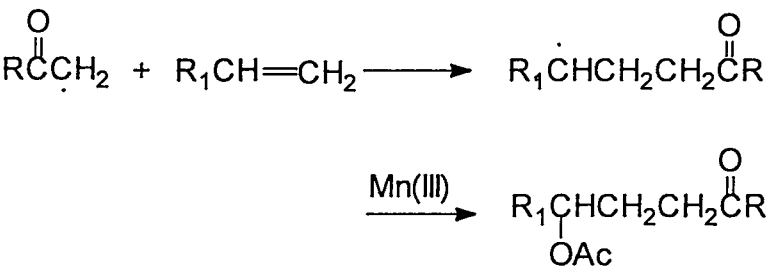
1.2.10. Manganese (III) Acetate-Initiated Addition of Ketones to Olefinic Unsaturated Systems

The one-electron oxidation of enolizable ketones by manganese (III) acetate has offered a new and convenient method for the generation of α-oxo alkyl radicals which are used for the synthesis of saturated and unsaturated ketones, substituted dihydrofurans, tetralones and diketones. The reactions are accelerated by addition of acetic acid, although product patterns may change. In the presence of Cu (II) acetate unsaturated adducts are formed.

a) Formation of Higher, Unsaturated and Acetoxy-Ketones.

In the presence of Mn (III) acetate, synthesis of higher saturated, unsaturated and acetoxy ketones can be provided by addition of simple ketones like acetone, methyl ethyl ketone, cyclic ketones, or by addition of pyruvic ester and acetyl acetone to a variety of olefins like α-olefins, styrene, isobutylene, hydroxy functional olefins and 1-alkynes [74,66]. In the absence of added acetic acid, the reaction is relatively slow and yields mainly saturated adducts. When acetic acid is added in low amounts at higher temperatures in the presence of manganese (III) acetate, the primary ketone radical adduct is

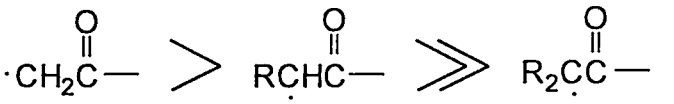
oxidized. Thus under such conditions large amounts of acetoxy ketones will be formed together with unsaturated ketones:



(eq 12)

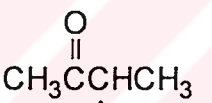
When saturated adducts are the products of choice and a fast reaction is wanted, such reactions can be performed by slowly adding both manganese (III) acetate to remove products, and olefin to prevent tolemerization to the ketone [75]. Therefore oxidation products can be removed and olefin prevented tolemerization to the ketone.

The effect of the structure of α-oxo-alkyl-radical on the rate of addition to unsaturated system was clearly demonstrated by Vinagradov.[76] According to Vinagradov primary radicals are added more readily on alkenes and alkynes than secondary and tertiary radicals:

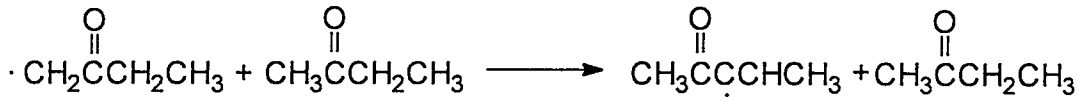


The rate of recombination of α-oxo-alkyl radicals with formation of 1,4-diketones approaches that of the addition to unsaturated systems and the tertiary α-oxo alkyl radicals are further oxidized by excess manganese (III) acetate.

There is no uniformity in the major site of attack by manganese (III) acetate on simple asymmetric ketones like methyl-ethyl ketone. Vinogradov [76] claims preferential formation of the secondary radical.



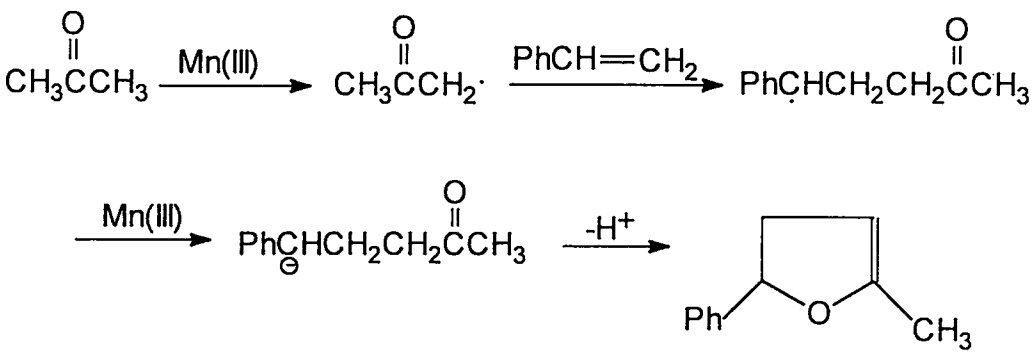
On the other hand Okano [76] finds more of 1-acetoxy-2-butanone than of 3-acetoxy-2-butanone upon oxidation of methyl-ethyl-ketone by manganese (III) acetate. Also Heiba [77] preferential formation of the least substituted α-ketoradical. This divergence of conclusions may partly come from the widely different reaction conditions used. Chain transfer from primary radicals to methylene groups such as



can occur to different degrees.

b) Formation of Dihydrofuranes:

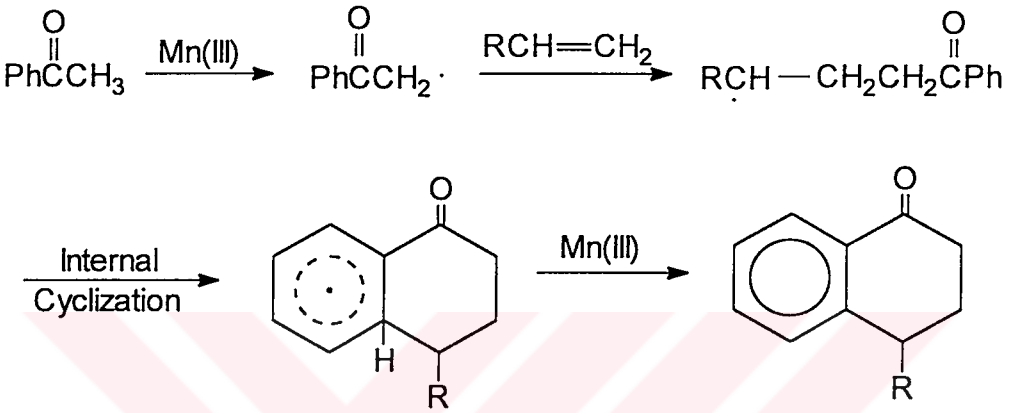
In the presence of Manganese (III) acetate, dihydrofuranes were synthesized by the reactions of readily enolizable ketones and olefins in good yield. (Table 10). This type of reaction proceeds via addition of α-oxo alkyl radicals to the olefins followed by oxidation of the intermediate adduct radical to carbenium ion; Therefore subsequent cyclization of this carbenium ion to the dihydrofuran [65,78] (eq 13)



(eq 13)

c) Formation of Tetralones

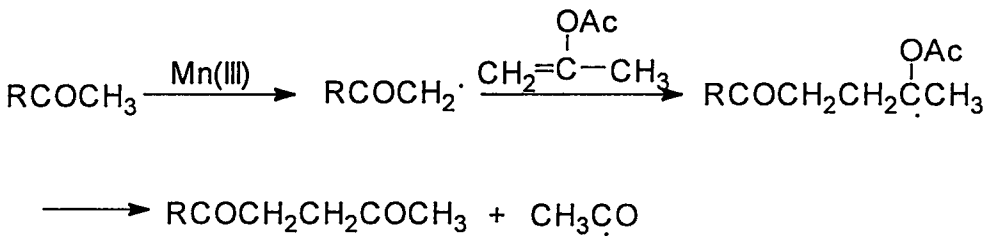
α-Tetralones can be formed by the reaction of any aromatic ketone such as acetophenone with an olefin according to the following equation[79].



(eq 14)

d) Formation of 1,4-Diketones:

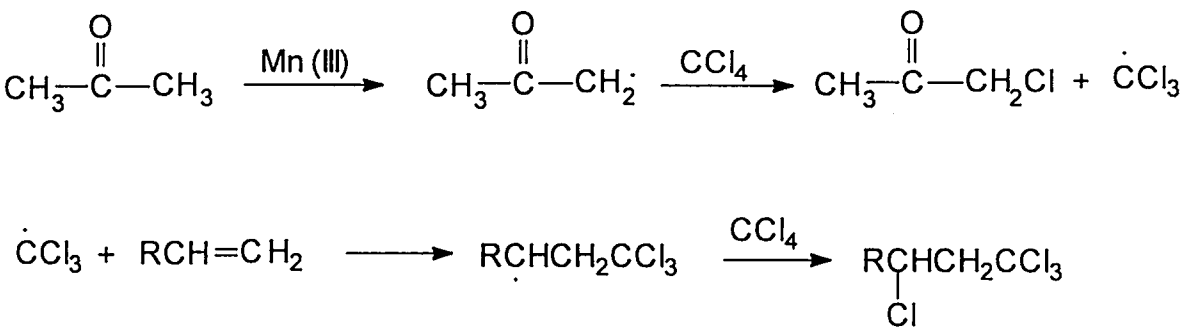
The reaction of any ketone with an isopropenyl acetate is achieved where the predominant nonpolymeric reaction products are 1,4-diketones according to the following pattern[74].



(eq 15)

1.2.11. Manganese (III) Acetate-Acetone-Initiated Addition of Haloalkanes to Unsaturated System

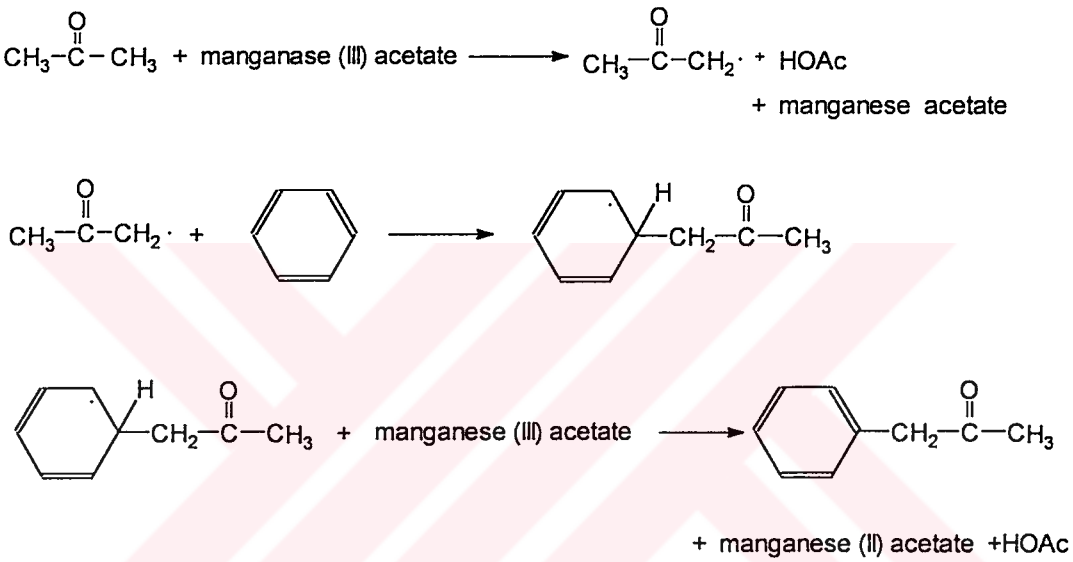
The mixture of manganese (III) acetate and acetone is used as an initiating system for the addition of haloalkanes to unsaturated systems[80]. Acetonyl radicals are readily formed from such system followed by chain transfer reactions whereas haloalkanes are synthesized from haloalkyl radicals.



(eq 16)

1.2.12. Aromatic Substitution Reactions

A number of methods have been reported for aromatic substitution reactions by radicals generated by Manganese (III) acetate. Carboxymethyl, acetonyl and nitromethyl radicals are substituted on the aromatic ring as shown in equation 17 [81].



(eq 17)

a) Oxidative Carboxymethylation:

Oxidative carboxymethylation is characterized by the primarily formed aryl acetic acids. When excess manganese (III) acetate is used, aryl acetic acids are easily oxidized to benzyl acetates, benzylidine, diacetates, and benzaldehydes [82].

b) Oxidative Aromatic Substitution by Ketones:

The reaction of acetone with benzene and acetic acid results in the formation of methyl-benzyl ketone. Although the rate of aromatic substitution is high [76], in alkyl substituted benzene such as toluene is occurred with some side reactions like benzyl acetate.

c) Oxidative Nitromethylation

In acetic acid solution, manganese (III) acetate promotes the substitution of nitromethyl radicals on the aromatic rings [83,84].

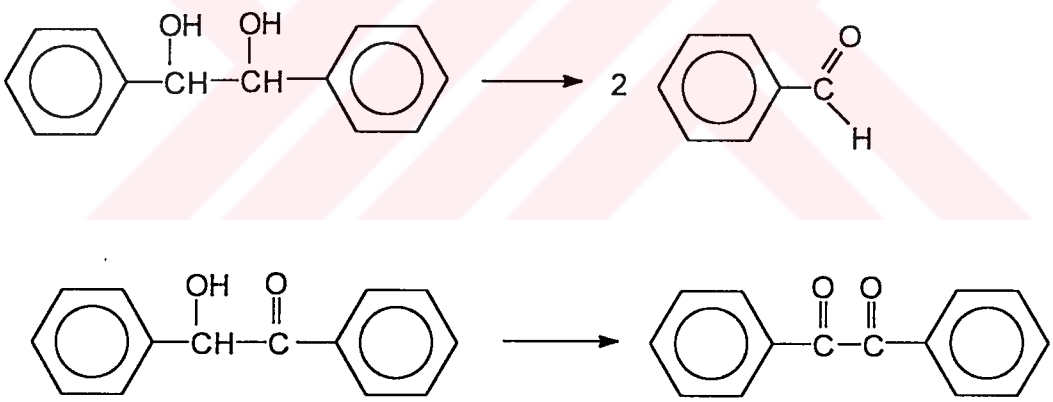
1.2.13. Direct Oxidation Reactions with Manganese (III) Acetate

In many cases direct inner or outer sphere one electron oxidations with manganese (III) acetate proceed via the primary formation of an intermediate radical. The fate of this primary radical depends on the nature of the substrate and reaction conditions. Thus, in many cases the molecule with excess manganese (III) acetate is rapidly oxidized within ligand transfer reaction resulting with acetate addition. In this method, primary radical dimerizes, disproportionates, loses and enters in a sequence of transfer or provides

addition reactions with other compounds. All these methods require one step procedure from substrates up to products.

a) Alcohols:

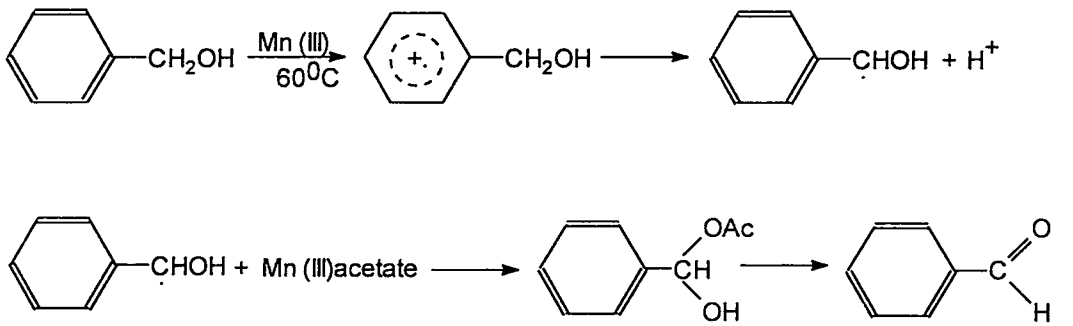
Simple alcohols like ethanol do not readily react with manganese (III) acetate in glacial acetic acid However the reactions of some more complex alcohols like α-glycols and α-keto alcohols with manganese (III) acetate gives positive results and these reactions have been extensively studied [85,86] (eq 18)



(eq 18)

The oxidation of benzyl alcohol yields benzaldehyde[87]. The first and the rate determining step in this reaction is the formation of the aromatic cation radical followed by the loss of a proton with concomitant formation of the

benzyl radical. This radical is oxidized in the subsequent step to benzaldehyde possibly by ligand transfer oxidation from benzalhemiacetate (eq 19).

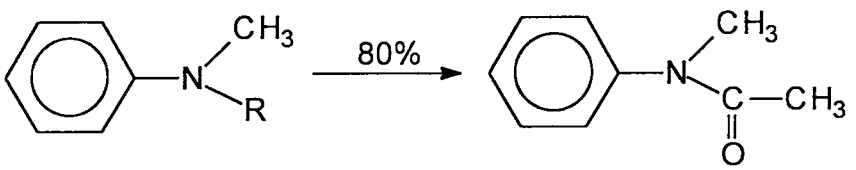


(eq 19)

b) Amino Compounds

The oxidation of N-substituted amines are studied by Rindone [88]. At room temperature, in acetic acid or chloroform-acetic anhydride mixtures, the main product from N,N-dimethyl aniline is N-methyl acetamide. In a comparative study with Pb (IV) acetate, Cu (III) acetate, Tl (III) acetate, and Mn (III) acetate, it was shown that the latter oxidant gives cleaner reactions and the highest yields of amides. With mixed N-methyl-N-alkyl amines the higher alkyl is preferentially eliminated:

The reaction most probably involves primary formation of the dialkyl-aniline cation radical followed by the loss of a proton to Ph-N$(CH)_3CH_2$•. This radical is subsequently oxidized to Ph-N$(CH_3)CH_2OAc$ which rearranges to formaldehyde and N-methyl acetanilide (eq 20).



(eq 20)

c) Thio Compounds:

Thioanisole reacts with manganese (III) acetate to form acetoxy methylenephenyl sulfite. Intermediate formation of thioanisole cation radical by electron transfer, followed by the lose of a proton gives Ph-SCH_2•. Then by ligand transfer oxidation of this radical Ph-SCH_2OAc is formed. J.M.Bronsdijk [89] was found that Mn (III) acetate is much more selective oxidant to this substrate than $Pb(OAc)_4$ and peroxides.

d) Phenols:

Simple phenols are oxidized to diphenoquinones or polymerized to produce polyphenylene ethers, depending on the reaction conditions [90,91].

e) Carboxylic Acids:

Oxidation of carboxylic acids by manganese (III) acetate depending on the structure of utilized carboxylic acids can follow two distincts pathways. Acetic acid and other α-hydrogen containing alkyl carboxylic acids are oxidized by the loss of α-hydrogen to form carboxymethyl radical. However, some carboxylic acids with manganese (III) acetate give decarboxylative oxidation, the primary step being the inner-transfer oxidation of the carboxylate moity to the carbonyl radical (eq 21).

$$RCO_2H + Mn(III) \longrightarrow RCO_2^{\cdot} + H^+ + Mn(II)$$

$$RCO_2^{\cdot} \longrightarrow R\cdot + CO_2$$

(eq 21)

Depending on the structure of R• and the reaction conditions a number of common free radical reactions could occur such as dimerization, further

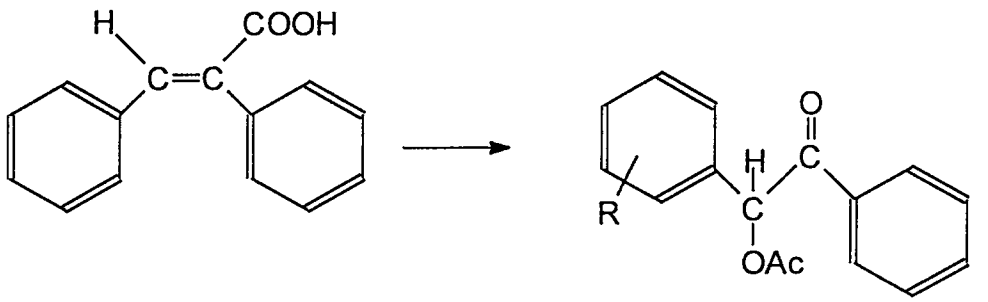
oxidation to alkanes, esters or formation of olefins in the presence of Cu (II) salts [92]. Decarboxylation with manganese (III) acetate in contrast to Pb (IV) acetate is typically a nonchain process. Thus phenyl acetic acid yields mainly benzylacetate according to the latter reaction which is probably a ligand transfer oxidation (eq 22).

$$PhCH_2COOH + Mn(III)\ acetate \longrightarrow PhCH_2^{\cdot} + CO_2 + H^+ + Mn(II)\ acetate$$

$$PhCH_2^{\cdot} + Mn(III)\ acetate \longrightarrow PhCH_2OAc + Mn(II)\ acetate$$

(eq 22)

Similar mechanism are proposed for the oxidation of α-hydroxy acids, α-keto acids, α-amino acids, pivalic acid, isobutyric acid, and n-butyric acid [93]. With simple α,β-unsaturated acids in aqueous acetic acid like cinnamic and crotonic acid α,β-bond breaking occurs after decarboxylation yielding benzaldehyde and formaldehyde from cinnamic acid [94] in a complex mechanism. On the other hand, manganese (III) acetate in glacial acetic acid can be used in a regiospecific synthesis of 2-acetoxy-1,2-diphenyl ethanone (benzoin acetate) [95] in 10%-64% yields from α-phenyl-cinnamic acids (eq 23).



(eq 23)

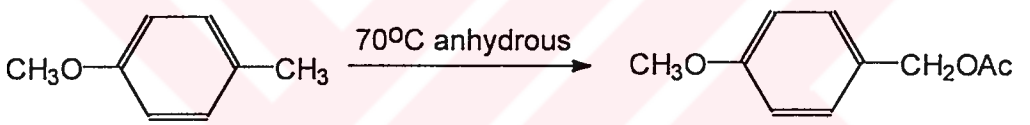
f) Aromatic Ethers:

The manganese (III) acetate oxidation of aromatic ethers proceeds via two competing mechanisms [96].

1) Aromatic ethers having ionization potentials below 8eV are oxidized by an electron transfer mechanism. In a primary step, a cation radical is formed, which loses a proton to give benzyl radical. The latter is oxidized by a second manganese (III) acetate to a methoxy substituted benzyl acetate.

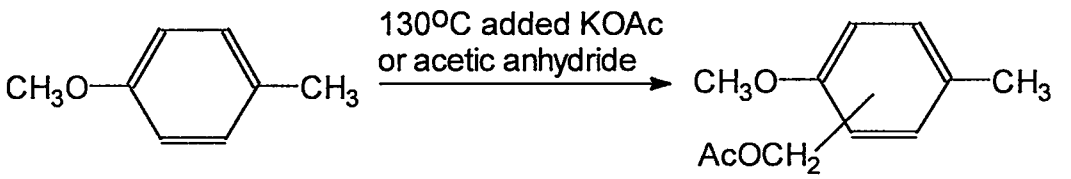
2) Compounds having ionization potentials above 8eV are substituted by carboxymethyl radicals and products are derived from the intermediate adducts substitution reaction.

The most extensively studied example of aromatic ethers being oxidized by the first mechanism is p-methoxy toluene [97, 98, 99, 100, 96, 101]. This compound is oxidized to p-methoxy benzyl acetate at 70°C, a temperature where carboxymethyl radical formation is negligible. Under anhydrous conditions yields of up to 90% can be obtained [98]. Traces of water lower the selectivity [97, 98] mainly in favor p-methoxy benzaldehyde. The reason for this is unknown, but it could reflect the sensitivity of the p-methoxy benzyl radical towards manganese (IV) species that are formed by water-induced disproportionation of manganese (III) acetate (eq 24).



(eq 24)

At higher temperatures, and in the presence of KOAc or acetic anhydride, the main reaction product from p-methoxy-toluene is a mixture of isomeric benzylacetates, being formed via substitution by carboxy methyl radicals [96] (eq 25).



(eq 25)

g) Aromatic Hydrocarbons:

The course of oxidation of aromatic hydrocarbons by manganese (III) species is highly depending on reaction conditions and structure of the substrate. Basically four types of reactions can be distinguished.

1) At temperatures lower than 100°C; aromatic compounds with an oxidation potential lower than 8eV generally undergo electron transfer to a cation radical.

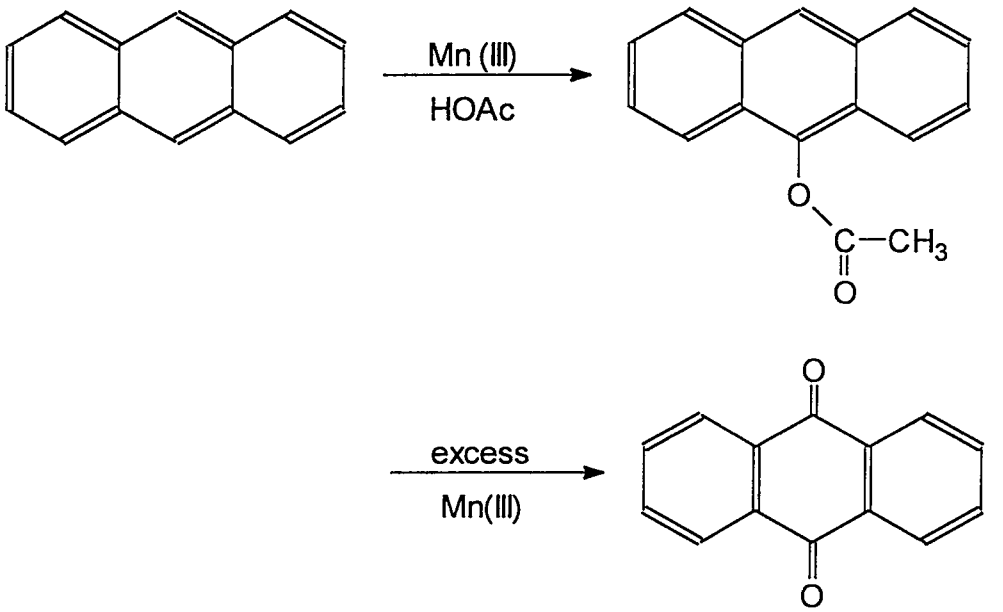
2) At temperatures higher than 100°C; carboxymethylene radicals are formed from acetic acid at an appreciable rate. Mainly displacement products will be found when the substrate has an oxidation potential higher than 8eV.

3) When bromide is added; bromine radicals are formed. At low temperature nuclear substitution can be completely prevented and main

products resulted from aliphatic side-chain halogenation and sequential reactions like acetoxylation are formed.

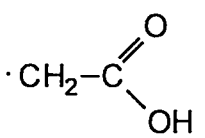
4) In the presence of strong acids; the reactivity of manganese (III) acetate is increased to such extent that even aromatic compounds with high oxidation potentials can be oxidized at low temperature to the cation radical. Depending on temperature, substrate, and further reaction conditions, a number of a consecutive reactions will determine product composition. Thus at higher temperatures and excess substrate often substituted biaryls are formed from alkyl aromatic compounds [84].

Simple polynuclear aromatics with relatively low oxidation potentials can be oxidized to acetates, quinones, or dimeric products, via electron transfer leading to the cation radical as a first step. Thus with excess manganese (III) acetate anthracene is oxidized to anthraquinone [102] or 9-acetoxyanthracene when equimolar amounts are used [102, 91] (eq 26).



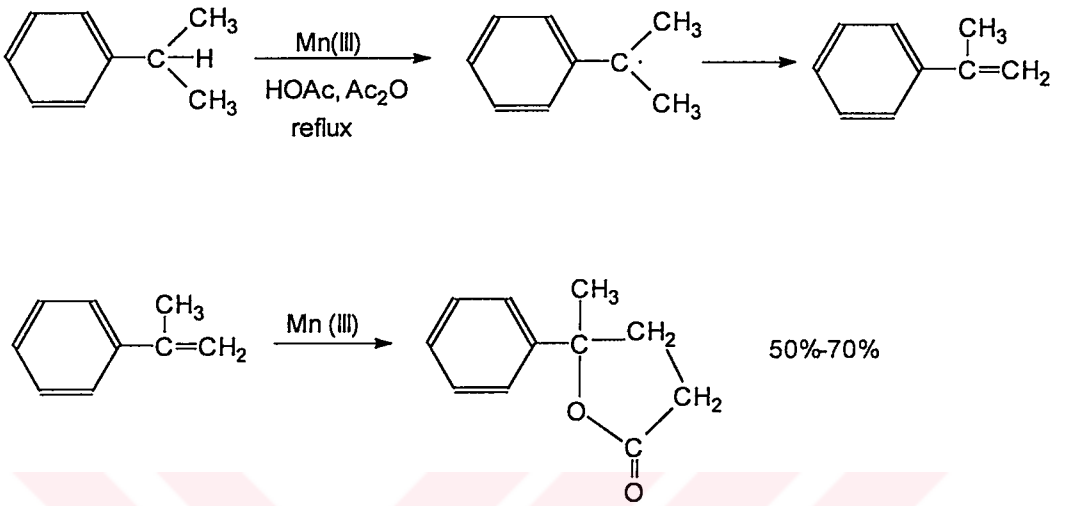
(eq 26)

At temperatures under 100°C compounds with an oxidation potential lower than 8 eV will undergo mainly electron transfer and consecutive reactions with manganese (III). At higher temperatures and higher oxidation potentials aromatic substitution by radicals and consecutive reactions become more predominant, [96] yielding more



complex reaction mixtures. Thus benzene, toluene, and chlorobenzene yield mixtures of substitution products [82]. Isopropyl substituted benzenes behave differently in that γ-butyrolactones are formed [103, 99]. This is via intermediate α-

methyl-styrene formation on which carboxy methyl radicals are readily added (eq 27).



(eq 27)

Some isopropylbenzylacetate is also formed. Manganese (III) acetate oxidations can be performed at lower temperatures and made much more selective by addition of bromine or strong acids. Thus, by addition of KBr, oxidation of toluene can be performed at 40-90°C and yields predominantly benzylacetate and benzyl bromide without nuclear substitution products [93, 82]. The intermediate benzyl radical is formed directly via molecular bromine and not via the cation radical sequence.

When strong acids like sulfuric acid or perchloric acid added [104, 105] toluene and related aromatic substituted compounds are oxidized at low temperatures to benzylacetates in high yields. The reaction proceeds exclusively through electron transfer (Table 10).

Table 10. Effect of Strong Acid on the Oxidation of Alkylaromatic Compounds by Mn (III) Acetate in Acetic Acid.[177]

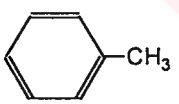
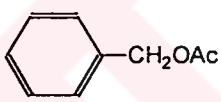
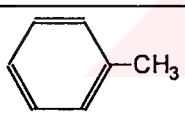
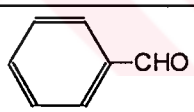
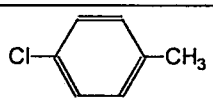
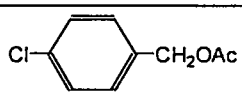
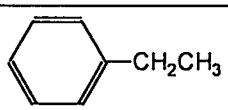
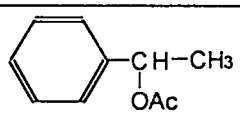
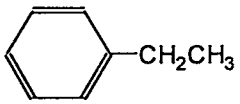
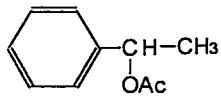
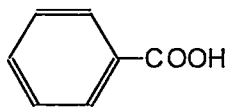
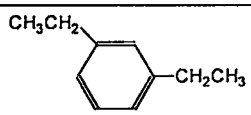
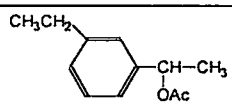
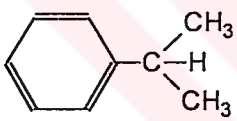
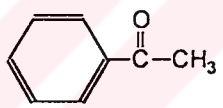
Substrate	Acid added	Atmosphere	Product	Yield (%)
	H_2SO_4	N_2		74
	H_2SO_4	N_2		71
	H_2SO_4	N_2		74
	H_2SO_4	N_2		93

Table 10. (continued)

Substrate	Acid added	Atmosphere	Product	Yield(%)
	CCl_3COOH	N_2		54
				46
	$HClO_4$	N_2		95
	H_2SO_4	N_2		75

1.2.14. Terpenes, Cycloaliphatic Compounds, Saturated and Unsaturated Hydrocarbons

It is known that manganese (III) acetate is an mild oxidizing agent. It is exemplified by its reaction with unsaturated hydrocarbons. The addition reaction of carboxy methylene radicals in acetic acid or mixtures with anhydride depends on substrates and the reaction conditions. Subsequently lactonization reaction would occur.

a) The addition reaction of manganese (III) acetate with carboxymethyl radicals gave subsequent lactonization or formation of unsaturated carboxylic acids [94].

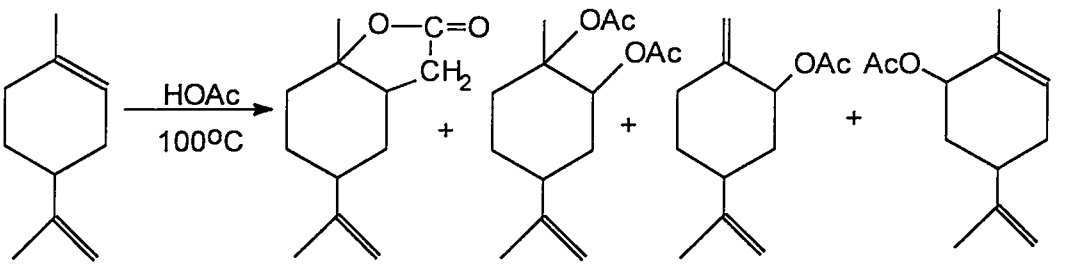
b) Sterically hindered olefins with low oxidations potentials are preferentially oxidized at the double bond to cation radical at temperatures about 100°C or lower. [95]

c) In the presence of KBr, bromine radicals are formed. At temperatures below 100°C main products would be alkyl acetates. Allyl acetate is a common minor product at high temperatures and with high manganese (III) acetate amount [96-99].

d) In substituted cyclohexenones, the double bond remains unaffected and oxidation is at the position alpha to the ketone group.[100]

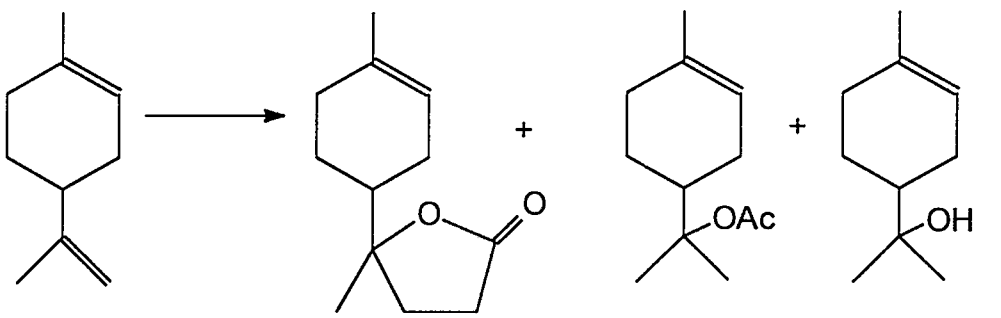
In a number of papers the oxidation of cycloaliphatic compounds and terpenes is described [101]. According to these papers, the reaction conditions are very different, and comparison of the results is therefore difficult.

When *d*-carvomenthene is oxidized with acetic acid[102] the lactone is formed as the major product next to 1,2-menthyl-diacetate and a number of allyl-acetates (eq 28):



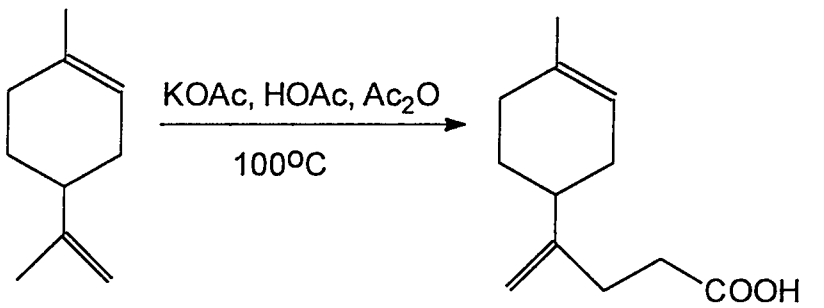
(eq 28)

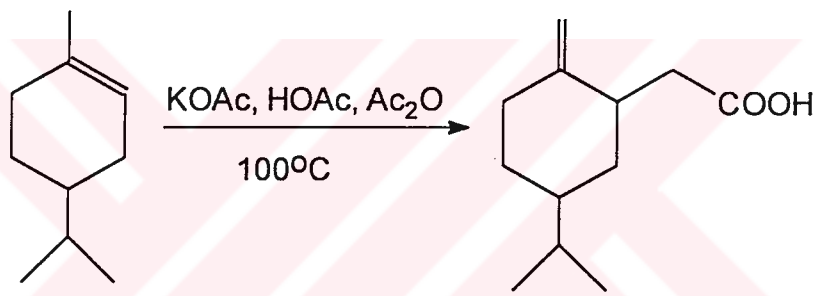
Under the same oxidation reaction condition, *d*-limonene affords the main products as γ-lactone, α-terpinyl-acetate, and α-terpineol (eq 29). [102,103]



(eq 29)

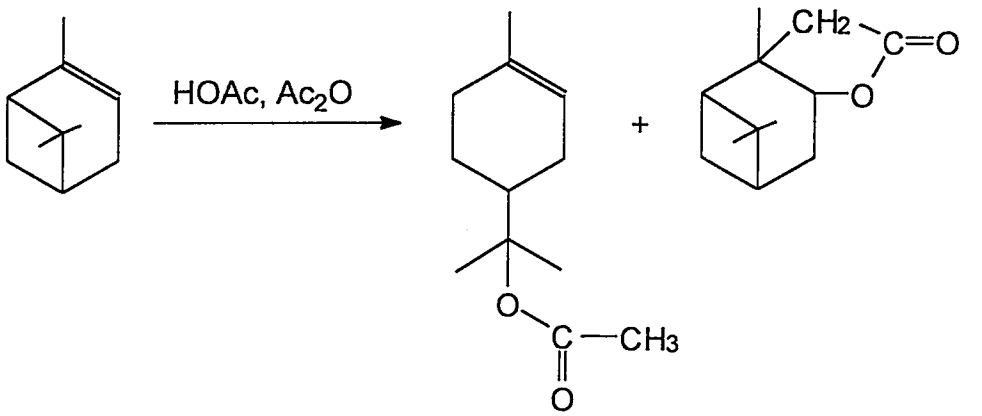
However, in the presence of KOAc and acetic anhydride the main products isolated from *d*-limonene and *d*-carvomenthene are unsaturated acids.[104]





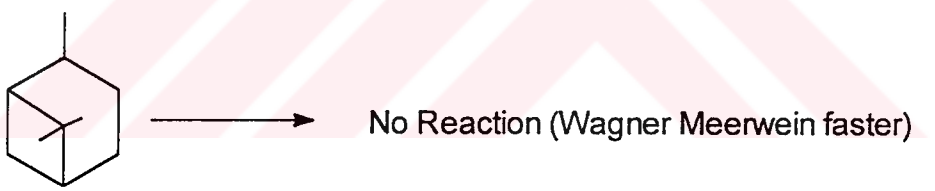
(eq 30)

When α-pinene is oxidized in acetic acid/anhydride mixture the major product is α-terpineol-acetate, and the lactone being formed as only small amounts.



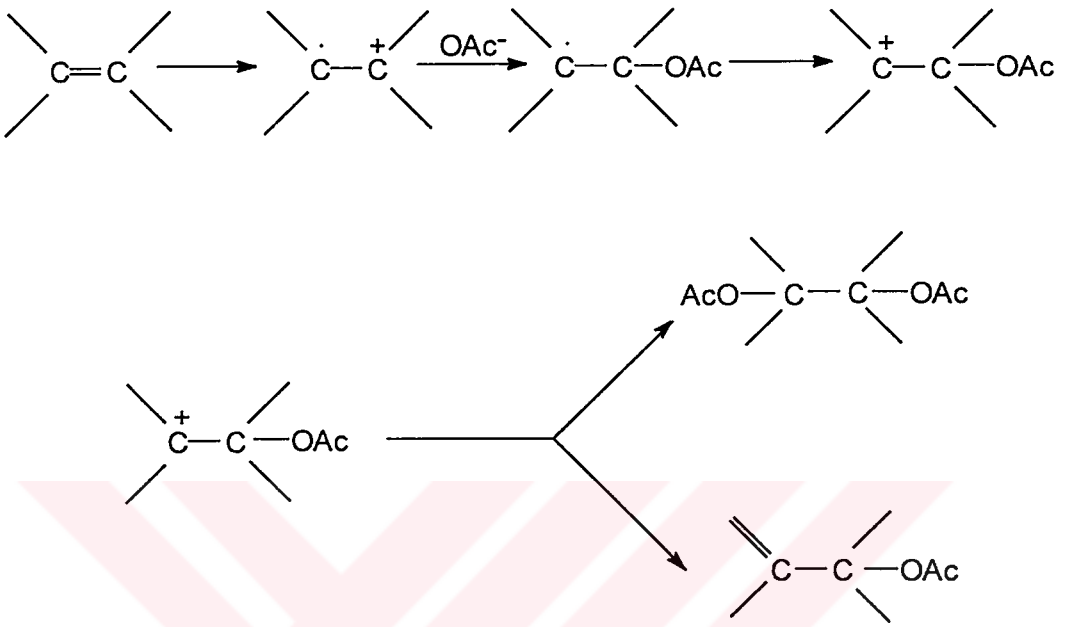
(eq 31)

In contrast, β-pinene does not react with manganese (III) acetate in $KOAc/HOAc/Ac_2O$ mixture, since by refluxing it readily undergoes Wagner-Meerwein rearrangement to the saturated acetate.[105]



These observations show that terpene structures are preferentially oxidized at the double bond to yield a cation radical when sterically hindered carboxymethylene radical is occurred or terpene structures have relatively low oxidations potentials. The resulted carboxymethylene radical is substituted with an acetoxy ion by the formation of a neutral radical which will be further

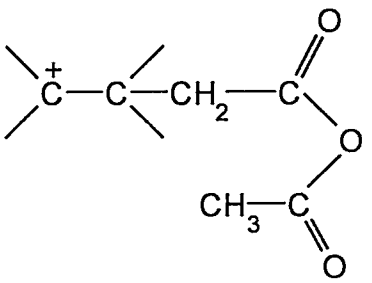
oxidized to a carbenium ion. Therefore unsaturated acetate could be formed via the removal of one acetate unit or the removal of a proton.(Scheme 7)



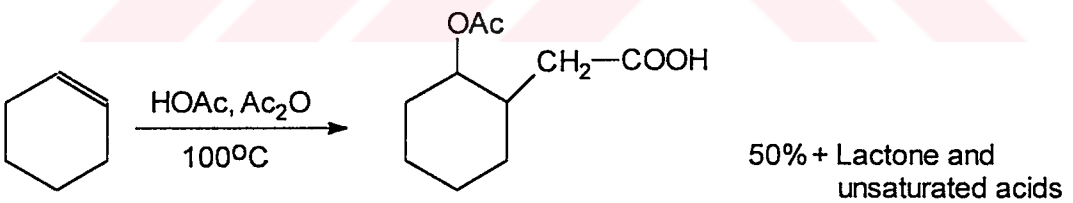
(Scheme7)

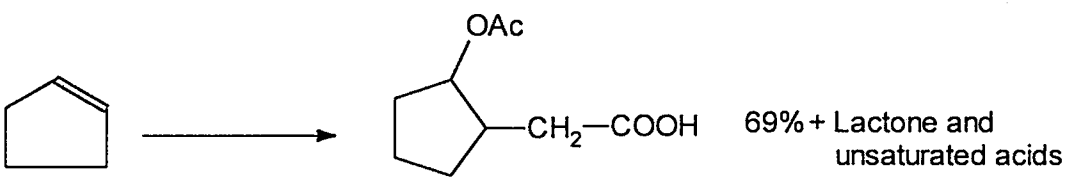
Of course some of the unsaturated acetates may also be formed from disproportionation of the intermediate acetoxy radical or by allylic abstraction of the parent substrate.

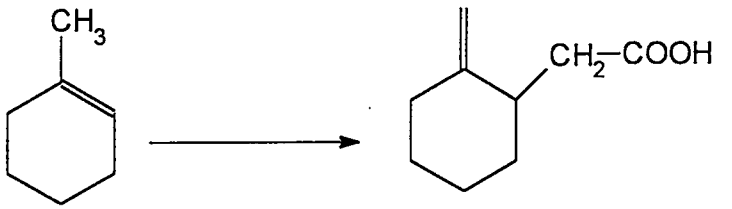
Formation of the lactone versus the unsaturated acid would depend on the presence of acetic anhydride and steric requirements for lactonization. The adduct carboxymethylene carbenium ion has lower tendency to lactonization than the free acid, assuming that in the presence of acetic anhydride carboxymethylene anhydride radicals are the major primary radicals formed with manganese (III) acetate.



Okano [104,106] demonstrated that steric and electronic factors could affect the ease addition of carboxymethylene on to cyclic olefins. Thus cyclohexene, 1-methyl cyclohexene and cyclopentene, all form adducts with carboxymethyl radicals resulted from manganese (III) acetate. Although earlier work [103] indicated that cyclohexene does not react with manganese (III) acetate. The major products from each substrate depend on the stability of the intermediate ion (eq 32).

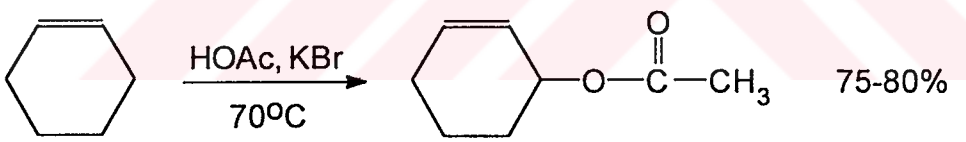






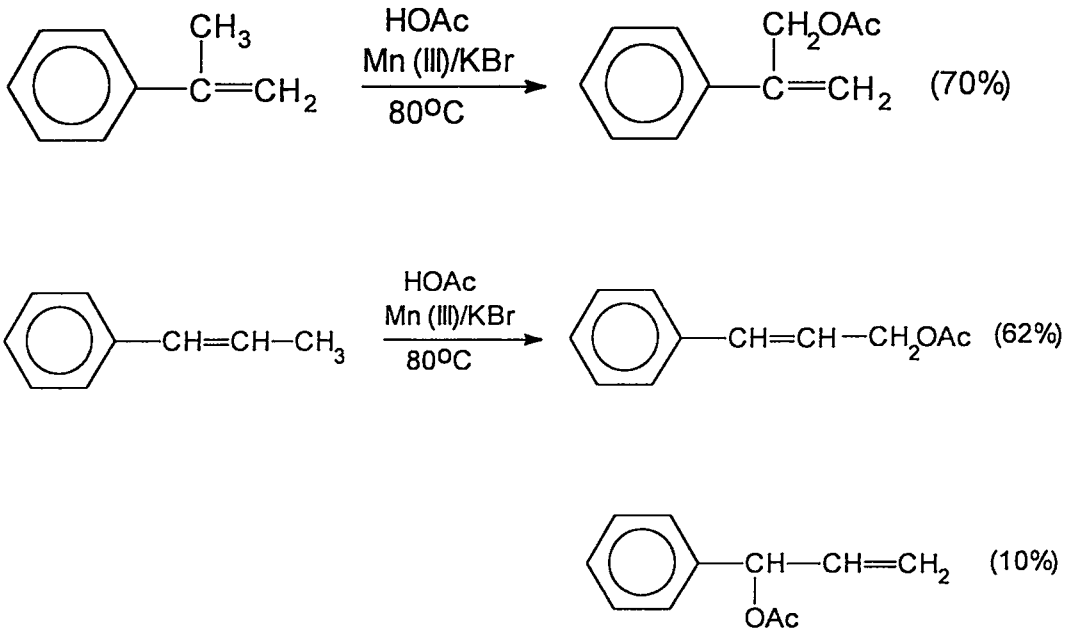
(eq 32)

No diolacetates are mentioned and only small amounts of allylic acetates. In the presence of KBr the major products of respective allylacetates [107] are occurred from cyclohexene and cyclopentene. These reactions indicated the initial hydrogen atom abstraction and further oxidation of the intermediate radical (eq 33):



(eq 33)

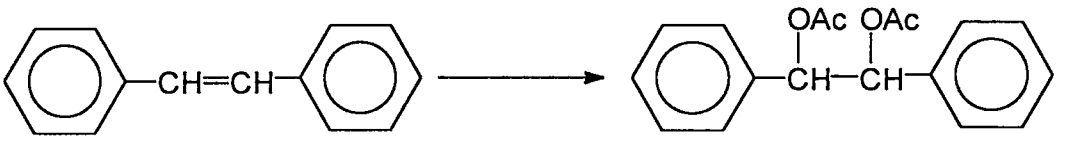
Further examples of this reaction are given by Kasahara (130)) in the allylic oxidation of α-and β-methyl styrene by manganese (III)/KBr at 80°C (eq 34):



(eq 34)

No lactones were found indeed, at 80°C very few amounts of carboxymethyl radicals are formed in acetic acid.

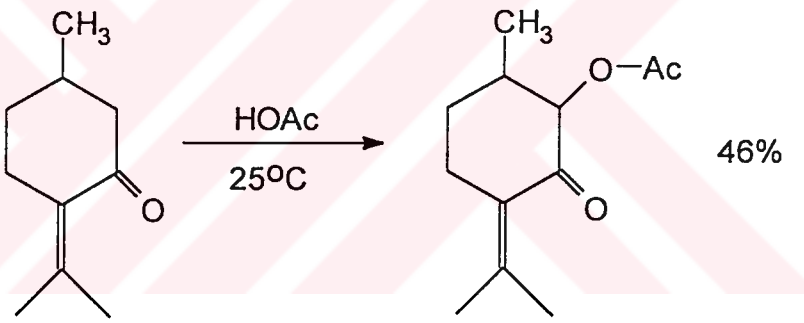
Olefins with low oxidation potentials are completely converted to the diol acetate by manganese (III) acetate in acetic acid. The oxidation of cis- or trans-stilbene [108,109] can be given as an example for this reaction.(eq 35)



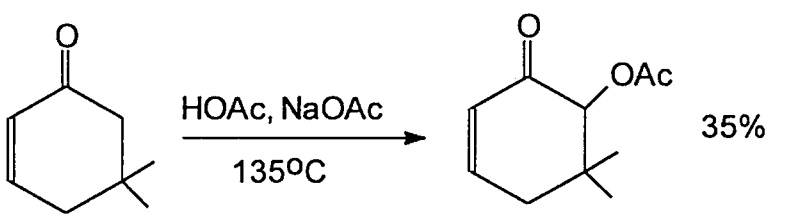
cis or trans Meso, *dl* mixture

(eq 35)

Additional examples of relatively unaffected double bonds are found in the oxidation of pulegone [110] and some other substituted cyclohexanones.[111] It is well known that the ketone function activates these molecules, giving rise to ready oxidation to the respective α-ketone acetates.(eq 36)



Pulegone Cis + trans acetoxypulegone

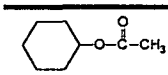
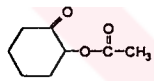
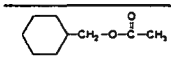
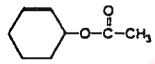


(eq 36)

Saturated hydrocarbons could easily be oxidized by manganese (III) acetate to the mixtures of hydrocarbon acetates or other esters, depending on the carboxylic acid used as a solvent.[112]

In an interesting study, Onopchenko [113] and Schulz compared the oxidation of cyclohexane with manganese (III) acetate and Co (III) acetate in the presence or absence of nucleophiles or Cu (II) acetate. (Table 11). Observations show that manganese (III) acetate is a much more selective oxidant and cyclohexylacetate is formed as a main product. When KOAc is added as a nucleophile cyclohexlymethyl acetate is formed in increasing amounts at higher KOAc levels. By adding Cu (II) acetate and NaOAc, cyclohexenyl acetate is found as a major product. There is no simple explanation how this is formed.

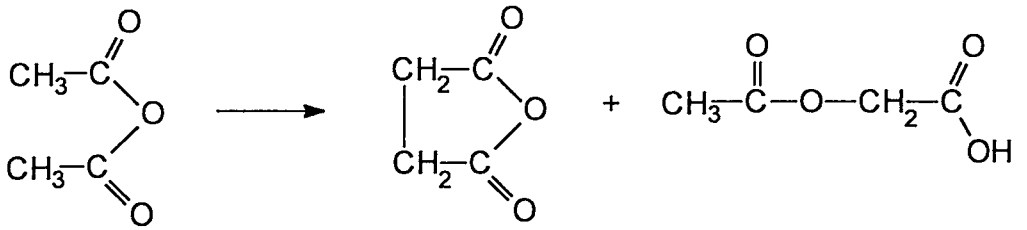
Table 11. Oxidation Products of Cyclohexane with Mn(III) Acetate in Dependence of Added Nucleophiles and Cu(II) Acetate (80°C Acetic Acid Solvent)[113]

Product	Mn(III)	Mn(III)/ KOAc	Mn(III)/ Cu(II)	Mn(III)/ Cu(II)/ NaOAc	Co(III)
	86	52	63	30	32
	9	7	–	–	10
	3	41	–	3	50
	–	–	–	67	–

1.2.15. Carbonyl-Containing Compounds

Compounds that contain enolizable carbonyl groups are ready to be oxidized to α-keto radicals. In the absence of olefins or aromatics, the product that is formed depends on reactions condition. In this case, radicals can be further oxidized or couple to dimers. Thus, high manganese (III)

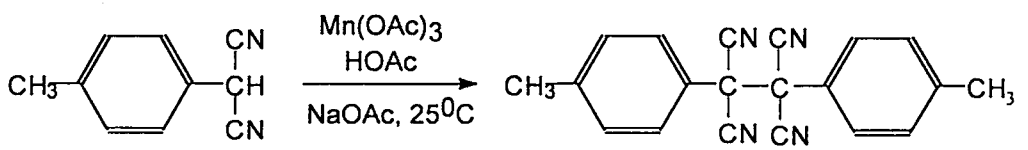
acetate/substrate ratios in the presence of acetic acid, the formation of acetates are favored.[114] However, low manganese (III) acetate/substrate ratios in the absence of acetic acid and high temperature, the formation of dimers is favorable.(eq 37)



(eq 37)

1.2.16 Oxidative Coupling of Active Group Substrates

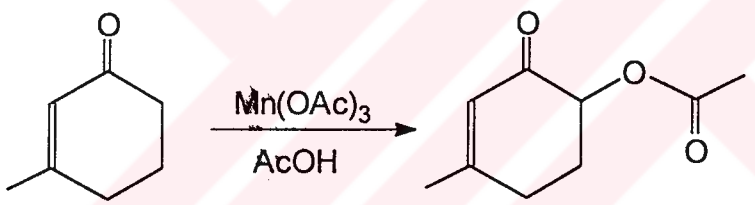
Aryl malodinitriles and aryl cyanoacetic esters are readily coupled by manganese (III) acetate [115] in acetic acid and NaOAc. (eq 38)



(eq 38)

1.2.17. Oxidation of Enones with Manganese (III) Acetate

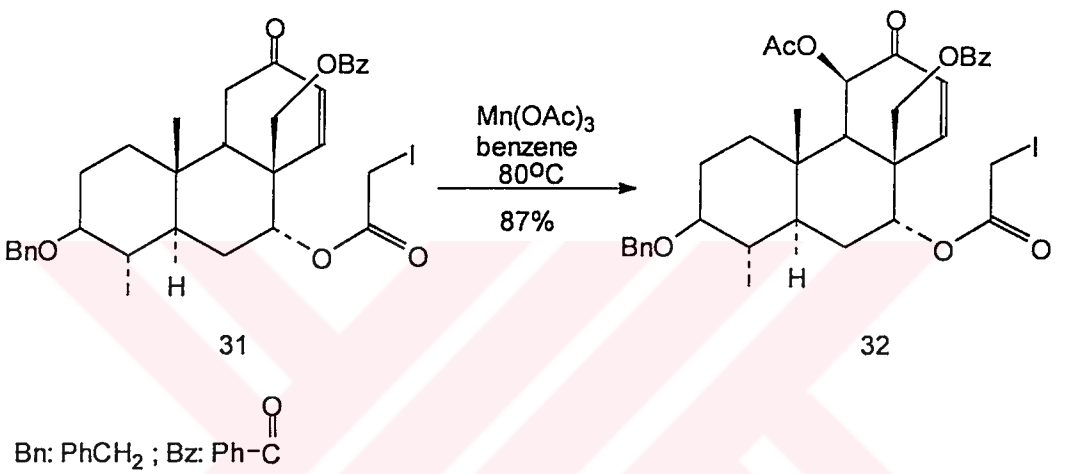
In 1976 Williams and Hunter [111] reported that manganese (III) acetate oxidation of enones led to modest yields of α′-acetoxyenones. In this type of oxidation, manganese (III) acetate instead of reacting with the double bond of enone, reacts at α′-position to give α′-acetoxylation product. They studied on the reaction of 3-methyl-cyclohex-2-en-1-one with 4 mole equivalent of manganese (III) acetate in glacial acetic acid, containing sodium acetate by refluxing at high temperature. The only product that is isolated was 6-acetoxy-3-methyl-cyclohex-2-en-1-one.(eq 39)



(eq 39)

They proposed that additional example for this purpose by using 5,5-dimethyl-cyclohex-2-ene-1-one with the same procedure gave the only product of 6-acetoxy-3-methyl-cyclohex-2-en-1-one.

In connection with their synthetic work in the quassinoid area Watt et al.[2,3] required a reliable procedure for the α′-oxidation of sterically hindered enone (eq 40) without affecting a benzyl ether protecting group, (31). After many studies, they determined that manganese (III) acetate provided an efficient general solution to this problem.



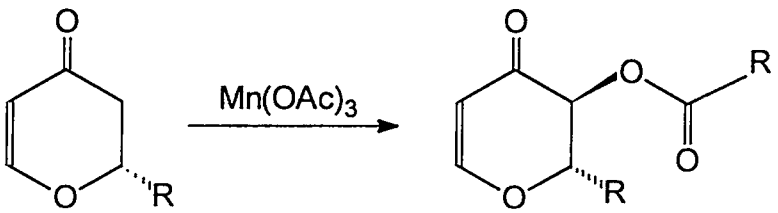
(eq 40)

Williams and Hunter [111] reported that manganese (III) acetate might be less reactive than lead (IV) acetate. They reported also that the presence of a Lewis acid [111, 117] or the absence of water might improve the yields. Watt et al. reinvestigated this reaction [2, 116, 117] and obtained acceptable yields of the desired α′-acetoxyenone 32 (eq 40).

Danishefsky used Watt's procedure in the α′-acetoxylation of 2-substituted 2,3-dihydro-4H-pyran-4-one (33). He reported that for all

substrates except (R=H) the oxidation is a stereoselective process yielding almost exclusively the trans products (34) [118]

.

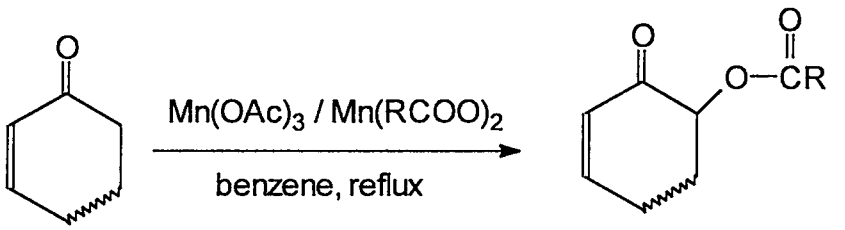


33 34

(eq 41)

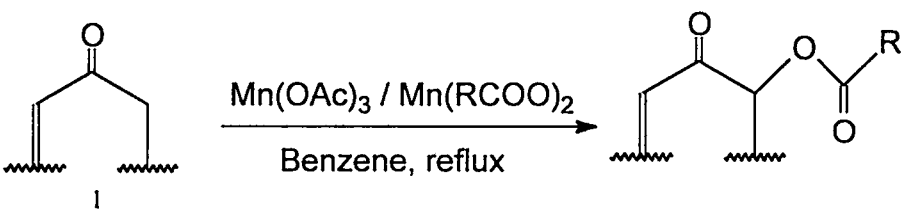
The condition was mild enough to allow the survival of potentially sensitive functionality. Lead (IV) acetate was not useful for this transformation.

Demir et al. proposed that the oxidation of enones provided a convenient synthesis of α′-acyloxyenones. For this purpose manganese (III) acetate was used in the presence of various carboxylic acids or manganese (II) salts of these carboxylic acids. [5, 121] Demir et al. required the enantioselective route to the quassinoids. Therefore an effective procedure for the α′-oxidation of enones was developed as shown in equation 42.



(eq 42)

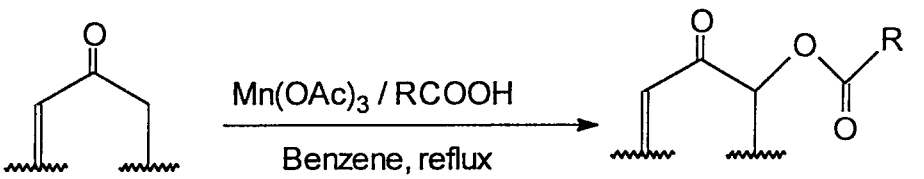
Although the application of manganese (III) acetate for the oxidation of model enones was succesful, under conditions where manganese (III) propionate, pivalete and benzoate was unsuccesful [122]. However, the application of manganese (III) chloroacetate, propionate, pivalate and benzoate were prepared according to the procedure of Vaerman and Bertrand [123]. In each case, the oxidation of an enone 1 with these manganese (III) acetate compounds led to efficient oxidants to the desired α′-acyloxyenones (eq 43) [88] as summarized in Table12.



1

(eq 43)

Additionally, oxidations conducted with six equivalent of manganese (III) acetate in combination with twelve equivalent of a carboxylic acid (eq 44) also proved to be particularly convenient procedure, as summarized in Table 13 [5].



(eq 44)

Table 12. Oxidation of Enones Using Manganese (III) Acetate in the Presence of Manganese (II) Carboxylates in Benzene at 80°C.[5]

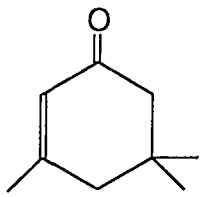
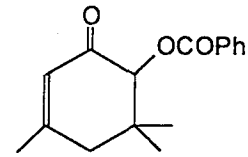
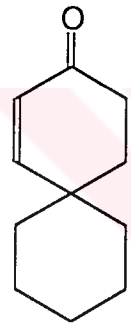
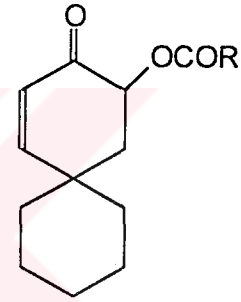
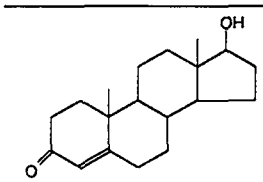
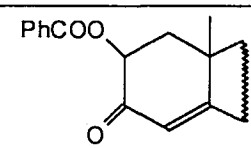
Enones	$Mn(OCOR)_2$	Time(h)	Product
 a	$Mn(OCOPh)_2$	24	
			
b	$Mn(OCOCH_2Cl)_2$	30	$R=CH_2Cl$
c	$Mn(OCOEt)_2$	30	R=Et
d	$Mn(OCOt\text{-}Bu)_2$	28	R=t-Bu
e	$Mn(OCOPh)_2$	24	R=Ph
	$Mn(OCOPh)_2$	30	

Table 13. Oxidation of Enones Using Manganese (III) Acetate in the Presence of Carboxylic Acids in Benzene at 80°C.[5]

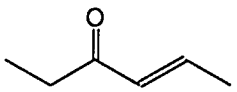
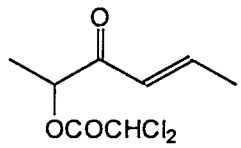
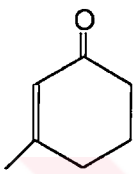
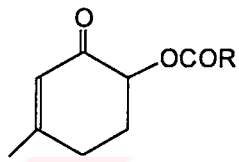
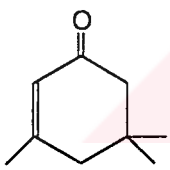
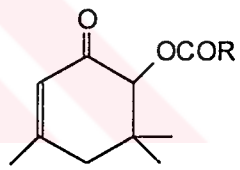
Enones	RCO_2H	Time (h)	Product
	Cl_2CHCO_2H	18	
	$PhCH_2CO_2H$	20	
	$PhCO_2H$	6	
			R=CH_2Ph
			R=Ph
	$ClCH_2CO_2$	18	
	$CH_3O_2C(CH_2)_2$-	18	
	CO_2H		
			R=CH_2Cl
			R=$(CH_2)_2CO_2CH_3$

Table 13. (continued)

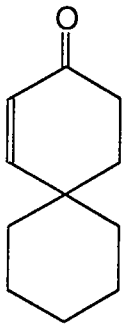
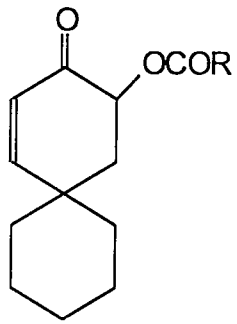
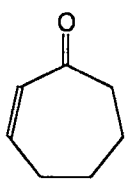
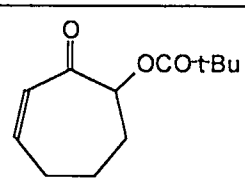
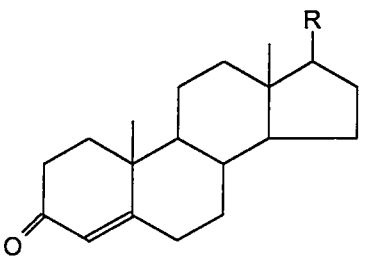
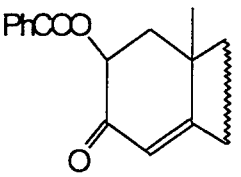
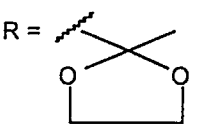
Enones	RCO_2H	Time (h)	Product
			
	$ClCH_2CO_2H$	6	$R=CH_2Cl$
	Cl_2CHCO_2H	16	$R=CHCl_3$
	$EtCO_2H$	18	R=Et
	$i\text{-}PrCO_2H$	9	R=i-Pr
	$t\text{-}BuCO_2H$	12	R=t-Bu
	(S)-(+)-C_2H_5-	48	R=(S)-(+)-
	$CH(CH_3)CO_2H$		$C_2H_5CHCH_3$
	$PhCO_2H$	15	R=Ph
	$p\text{-}CH_3OC_6H_4CO_2H$	18	$R=C_6H4\text{-}p\text{-}OCH_3$
	$t\text{-}BuCO_2H$	6	

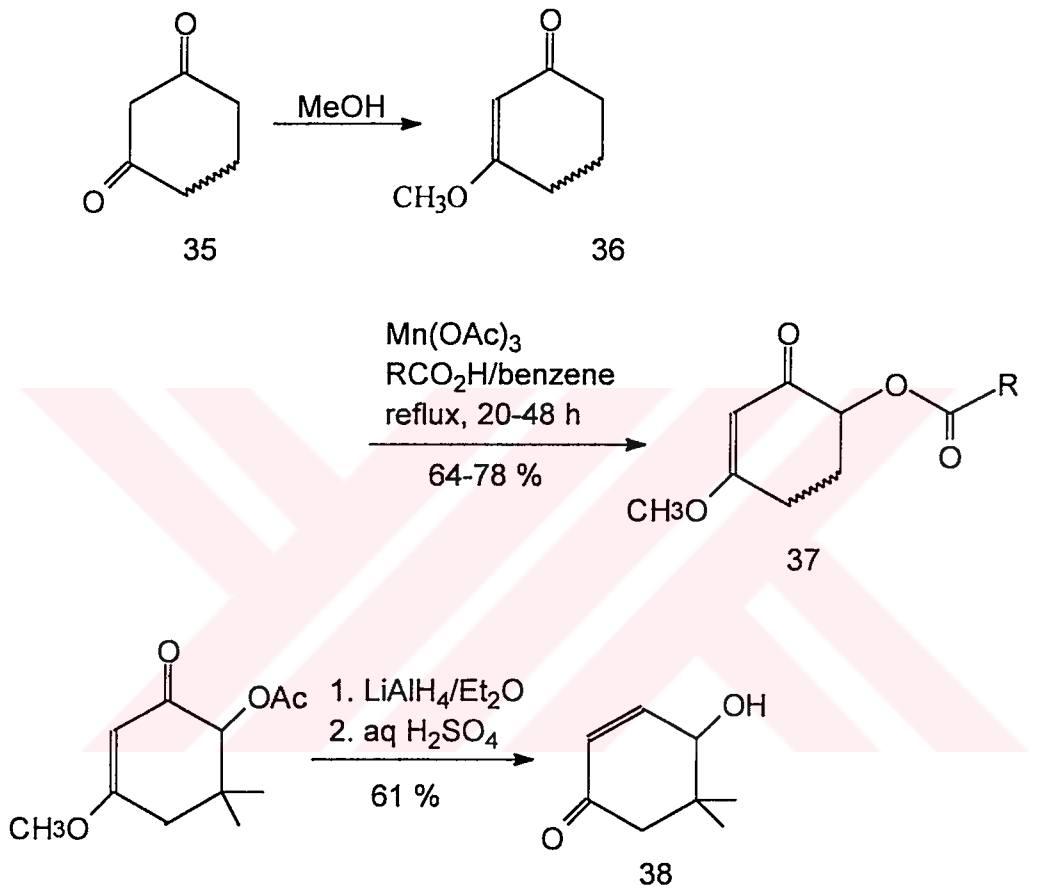
Table 13. (continued)

Enones	RCO_2H	Time (h)	Product
			
	$PhCO_2H$	18	$R=COCH_3$
	$PhCO_2H$	6	$R=COCH_2OAc$
	$PhCO_2H$	16	

1.2.18. Oxidation of β-Alkoxyenones with Manganese (III) Acetate

The oxidation of β-alkoxy-α,β-unsaturated ketones using manganese (III) acetate in the presence of an excess manganese (II) carboxylate or a carboxylic acid provided a general synthesis of α′-acyloxy-β-alkoxy-α,β-unsaturated ketones. These α′-acyloxy-β-alkoxy-α,β-unsaturated ketones (37) are useful intermediates in the synthesis of natural products [124-129]. Demir et al. reported that cyclic β-alkoxy-α,β-unsaturated ketones (36), which exhibits the

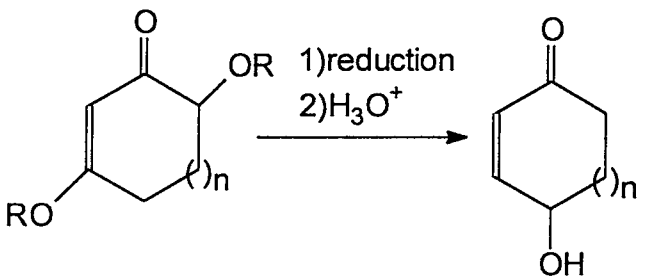
same regiochemical preference for oxidation at α′ position to afford the α′-acyloxy-β-alkoxy-α,β-unsaturated ketones (37) in good yield (eq 45). General procedures for the synthesis of (37) are not involve multiple steps [119].



(eq 45)

Quesada proposed the conversion of cyclic β-diketones (35) to the β-alkoxy α,β-unsaturated ketones (36) [130]. The oxidation of (36) using six equivalents of manganese (III) acetate [119] in combination with twelve equivalents of a carboxylic acid led to the α′-acyloxy-α,β-unsaturated ketones

(37) in good yield (Table 14). These synthesized products were used for the synthesis of γ-hydroxy enones via reduction and elimination reactions.



(eq 46)

Demir et al. [118] reported that the use of manganese (III) carboxylates other than manganese (III) acetates as the sole oxidant was not successful. He also suggested that an initial reaction between the manganese (III) acetate and the carboxylic acid led to active ''mixed'' manganese (III) complex. This complex have both acetate and other carboxylate ligands. Therefore the interaction of the enol or enolate of (36) with this mixed manganese (III) complex provided the desired product (37). Since the reduction and hydrolysis of α-acyloxy-β-alkoxy-α,β-unsaturated ketones (37) provided access to γ-hydroxy-α,β-unsaturated ketones as exemplified in the case of 5,5-dimethyl-4-hydroxy-2-cyclohexanone (38) (eq 45). This process extended the utility of the manganese (III) oxidant procedure to the oxidation of α,β-unsaturated ketones at either α′- or γ-positions [119].

Table 14. Oxidation of β-alkoxy-α,β-unsaturated Ketones Using Manganese (III) Acetate in the Presence of Various Carboxylic Acids to α′-acyloxy-β-alkoxy-α-β-unsaturated Ketones.

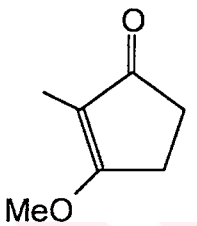
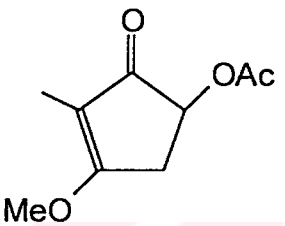
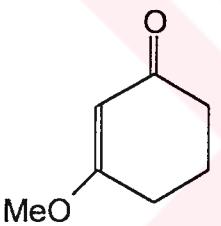
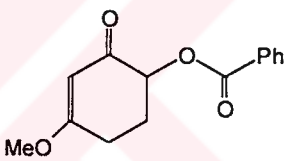
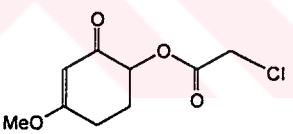
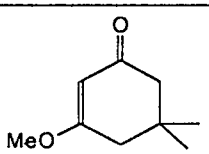
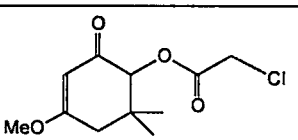
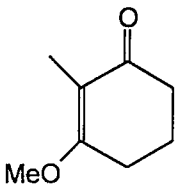
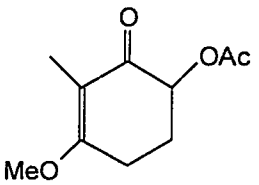
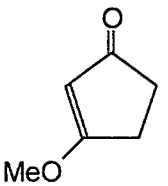
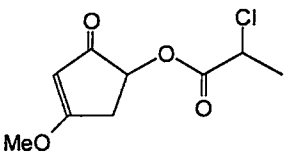
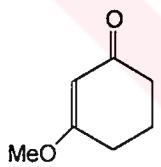
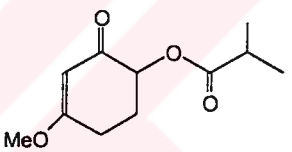
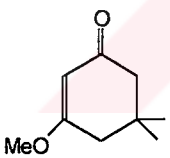
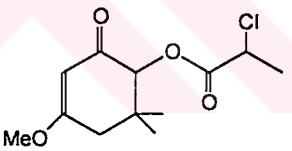
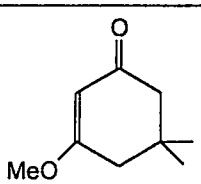
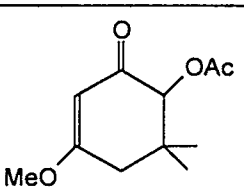
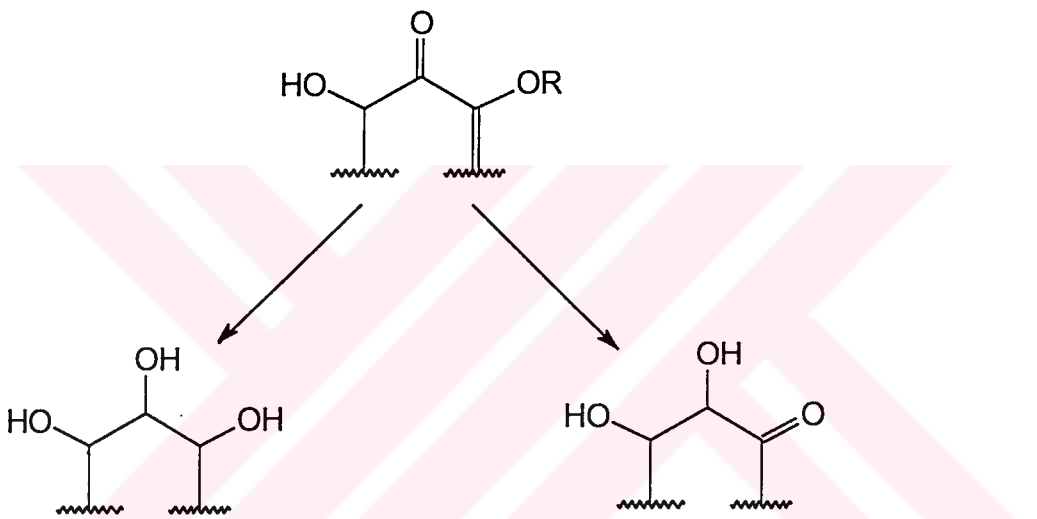
Reactants	Carboxylic Acid	Reaction Time (h)	Products	Yield (%)
	none	48		65
	$PhCO_2H$	46		72
	$ClCH_2CO_2H$	20		70
	$ClCH_2CO_2H$	28		78

Table 14. (continued)

Reactants	Carboxylic Acid	Reaction Time	Products	Yield (%)
	none	26		75
	$MeCHClCO_2H$	30		66
	Me_2CHCO_2H	32		68
	$MeCHClCO_2H$	24		71
	none	48		74

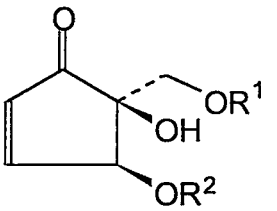
1.2.19. α′-Acyloxy-α-Alkoxy Enones in the Natural Product Chemistry

It is known that α-alkoxy and α-hydroxy enones are used as coffee aromates [131]. The reduction reactions of α′-acyloxy-α-methoxy and α-acetoxy-α′-acyloxy enones, dihydroxy and polyhydroxy, derivatives can be synthesized (eq 47).

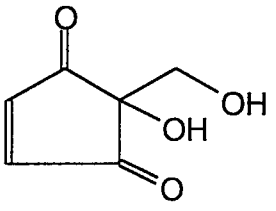


(eq 47)

For the synthesis of various petnanomycin antibiotics, these dihydroxy and polyhydroxy derivatives can be used as starting materials [132-135]. These antibiotics such as Pentanomycin I (39a), Pentanomycin II (39b), Pentanomycin III (39c) and dehydropentenomycin I (40) and other poly hydroxy compounds show anticancer activity (eq 48).



39



40

a. $R^1=R^2=H$

b. $R^1=H : R^2=Me$

c. $R^1=Ac : R^2=H$

(eq 48)

α′-Acyloxy-α-methoxy enones [119] is that γ-lactone derivatives of the corresponding molecules can be synthesized by the lactonization reactions. These type of reactions are important in the synthesis of anti-cancer drugs.

CHAPTER 2

RESULTS AND DISCUSSIONS

2.1. Aim of the Work

The aim of this study is to synthesize various butenolides, which have important biological activity.

Although there are some methods for the isolation of butenolides, the synthetic methods of butenolides are relatively rare.

We have involved in the development of a new and applicable way to synthesize butenolides. The key step involves the synthesis of α′-acyloxy-α,β-unsaturated cyclic ketones from the corresponding α,β-unsaturated cyclic ketones using manganese (III) acetate in combination with 2-chloro propionic acid. In chapter 1 it was reported that the oxidation of α,β-unsaturated ketones with manganese (III) acetate provided an efficient synthesis of α′-acetoxy-α,β-unsaturated ketones and the oxidation by using manganese (III) acetate in the presence of carboxylic acids afforded a general synthetic way for the formation

of α′-acyloxy-α,β-unsaturated ketones. In general, manganese (III) acetate oxidations are characterized by α′-regioselectivity, the higher chemical yield and milder reaction conditions that can tolerate many sensitive groups.

In the second step of this study, we applied the Arbuzov reaction. In this reaction, the treatment of 2-chloro propionyloxy enones with excess triethyl phosphite gives corresponding phosphonates. The aim of Arbuzov reaction is to create a carbanionic centre located between carbonyl and phosphonate groups. The ylides are more reactive and when we use an electron withdrawing group, cyclization is occurred. The only convenient way is to make cyclization reaction at one step. It is known that Horner-Emmons type reaction is widely used and has several advantages. Therefore the end product is obtained via Horner-Emmons type intramolecular cyclization reaction.

The general strategy of our work covers the synthesis of butenolides, which are described at only three steps. It is short and efficient way to synthesize butenolides.

In the later study, lead (IV) acetate is used in the synthesis of the Mintlactone. α-Oxidation of enones are carried out with lead (IV) acetate as well as manganese (III) acetate. For this purpose 4-methyl cyclohexanone is

reacted with lead (IV) acetate as an alternative mild α-oxidation method to produce 4-methyl-α-acetoxy cyclohexanone.

In the second step 4-methyl-α-hydroxy cyclohexanone is attained 4-methyl cyclohexanone with K_2CO_3 in aqueous MeOH. And then 4-methyl-α-hydroxy cyclohexanone is reacted with chloropropionyl chloride to yield 4-methyl-α-(2-chloro) propionyloxy cyclohexanone. Arbuzov reaction of this compound with triethyl phosphite is performed and phosphonated product is obtained. Intramolecular cyclization of phosphonated product was carried out to yield target compound.

The importance of the final products of butenolides are to be basic substances for the synthesis of natural products and have many functional groups for a wide range of chemical manipulations.

2.2. Manganese (III) Acetate is an Oxidizing Agent.

A great amount of work has been done using manganese (III) acetate, but relatively little is known about the compound itself. Basically two forms are distinguished:

i) The hydrated form, conforms molecular formula $Mn(III).(OAc)_3.2H_2O$ with cinnamon brown color and is easy to prepare reproducibility [136].

ii) The anhydrous form conforms variable molecular formula with dark brown color and is difficult to prepare. Since many oxidants with manganese (III) acetate species are known to be influenced by small amount of water, the latter form is preferred by many workers, especially; for kinetic works. Even small amounts of water causes disproportionation of manganese (III) acetate in glacial acetic acid. Both the hydrated and anhydrous forms have been made in various ways. Many workers introduced special modifications, which certainly have affected the chemical composition and reactivity of anhydrous form. In Table 15 the most important routes to manganese (III) acetate are given.

Table 15. Routes to Manganese (III) Acetate

Reactants	Oxidizing Agent	Product
$Mn(OAc)_2.4aq\ HOAc$	$KMnO_4$	Dihydrate
$Mn(NO_3)_2.6H_2O.Ac_2O$	$KMnO_3$	Anhydrous
$Mn(OAc)_2.HOAc.AcO_2$	$KMnO_4$	Anhydrous
$Mn(OAc)_2$	O_3	Anhydrous
$Mn(NO_3)_2.4H_2O$	Treating with acetic anhydride	Anhydrous

Table 15. (continued)

$Mn(OAc)_2.4aq$	Anodic oxidation	Dihydrate
$Mn(OAc)_2.4aq$	Cl_2	Dihydrate
$Mn(OAc)_2.(Et)_3N.HOAc$	O_2	Dihydrate
$Mn(OAc)_2.ketone$	O_2	Anhydrous

2.3. Anhydrous Manganese (III) Acetate

Hessel [137] studied the synthesis and chemical constitution of manganese (III) acetate in detail. He found that the chemical constitution of anhydrous manganese (III) acetate conform to the formula $Mn_3(CH_3COO)_8OH$ or $[Mn_3O(CH_3COO)_6.CH_3COOH]^+ (CH_3COO)^-$. When the compound is properly washed and recrystallized, this empirical formula is independent of chemical route followed, like oxidation with $KMnO_4$, Pb(IV) acetate or O_3 of Mn(II) acetate or treating $Mn(NO_3).6H_2O$ with acetic anhydride.

The crystal structure of manganese (III) acetate has been determined by X-ray analysis and they concluded its formula as $Mn_3O(OAc)_7$ [139].

Infrared spectra of anhydrous manganese (III) acetate were studied by Klein and Hessel [137, 138]. They assumed that the presence of acetic acid in the solid compound, although the absorption maxima assigned to acetic acid, are at 1730 and 1710 cm^{-1}, respectively.

Manganese (III) acetate dehydrate [139] was prepared according to the procedure of Heiba et al. [96] and carefully dried prior to use. There are other literature procedures [139, 140] reported to furnish anhydrous manganese (III) acetate, but only the material prepared using one of these procedures [140] affected the desired oxidations in comparable yield.

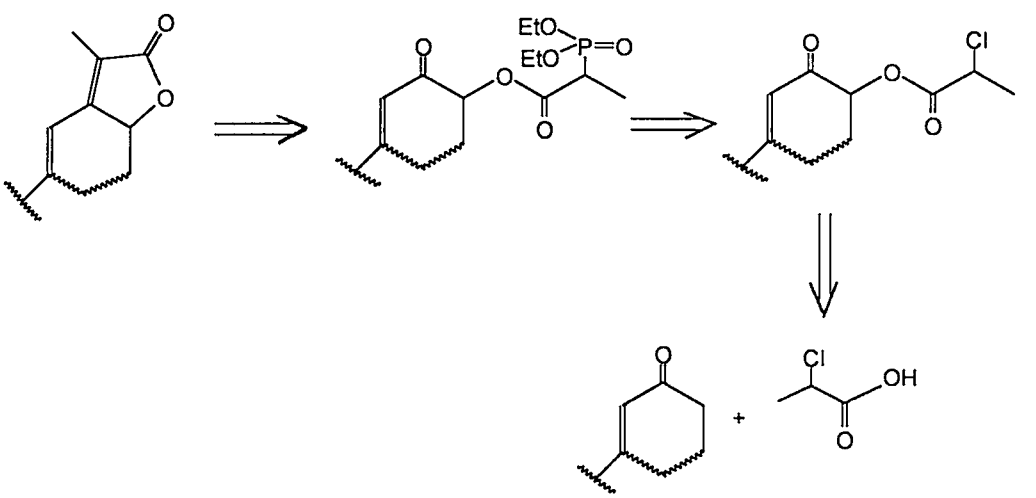
Anhydrous manganese (III) acetate dissolves slowly in most solvents at room temperature. Moreover, it can be dissolved in many solvents without appreciable reduction by gentle warming. Examples are ethanol, pyridine and to some extent benzene and chloroform. It reacts relatively at low temperature (80°C) with enolizable solvents such as acetone or methyl ethyl ketone but is less reactive with ethyl acetate. It is hardly soluble in acetonitrile and petroleum ether and decompose in water.

In this study manganese (III) acetate was prepared from manganese nitrate $Mn(NO_3)_2 6H_2 0$ and acetic anhydride.

2.4. A Novel Synthesis of Monoterpenes

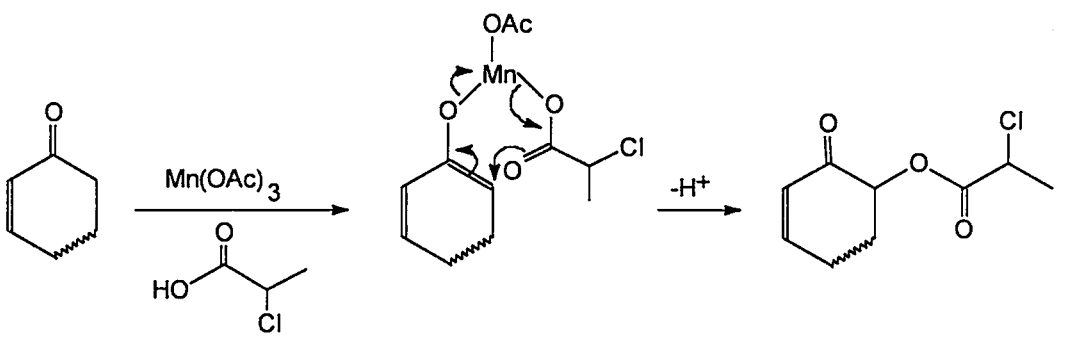
In order to develop the new synthetic way, we achieved the synthesis of various cyclic products, which have some biological activities. The following retroanalytical approach was applied for the synthesis of the monoterpenes. The key step involves the synthesis of α′-acyloxy-α,β-unsaturated cyclic ketones from the corresponding α,β-unsaturated systems using manganese triacetate in combination with 2-chloropropionic acid. Second step is an Arbuzov reaction. In this reaction the treatment of α′-(2-chloro) propionyloxy enone with excess triethyl phosphite gives the corresponding phosphonates. And then the end product is obtained via Horner-Emmons type intramolecular cyclization reaction.

Retro Analysis of Target Butenolides



2.4.1. Mechanism of the Enones versus Manganese (III) Acetate

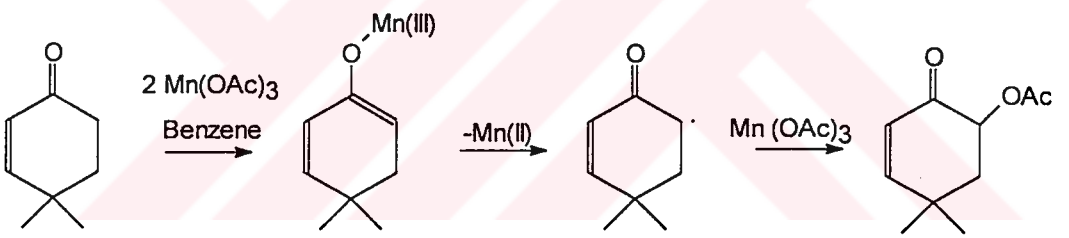
The mechanism for oxidation of enones to α′-acetoxy enones was not fully described. Several mechanisms were suggested for this oxidation. One might expected the initial reaction takes place between manganese triacetate and carboxylic acid, that results in a mixed manganese complex having both acetate and carboxylate ligands. The interaction of the α′-acetoxy and α′-alkoxy-α,β-unsaturated ketones with this complex should result in carboxylate transfer via metal enolate formation, analogous to the enol-lead (IV) acetate oxidation reaction of ketones. We suggested that also the formation of a metal enolate followed by acetate transfer, analogous to lead (IV) acetate oxidation (scheme 8). However, the oxidation of carbonyl compounds with manganese (III) acetate [141] has been reported to involve an α-oxo radical from the oxidation of both enolate anion and carboxylate anion by manganese (III) acetate.



(Scheme 8)

Watt and coworkers developed a reliable procedure for the oxidation of α,β-unsaturated ketones to α′-acetoxy-α,β-unsaturated ketones using excess dried manganese (III) acetate in benzene at reflux. The reaction proceeds by formation of the manganese (III) enolate, which loses Mn (II) give unsaturated α′-keto radical. Oxidation of this radical by a second equivalent of manganese (III) acetate provides acetate in high yield.

In 1996 Snider and coworkers proposed that oxidative free-radical cyclizations of unsaturated 2-cyclohexenones with manganese (III) acetate afford unsaturated α′-keto radicals (this reaction is being shown below).



They have recently shown that manganese (III) acetate based oxidative free radical cyclization of unsaturated ketones in AcOH at 80°C is a versatile synthetic procedure with broad applicability. They have suggested that intramolecular trapping of unsaturated α′-keto radicals by suitably situated double bonds should be much faster than intermolecular addition and might be able to compete with acetoxylation. However, they concluded that unsaturated

α′-keto radicals formed by oxidation of 4-alkenyl-2-cyclohexenones can be trapped efficiently in 6-exo cyclizations [142].

2.4.2. The Synthesis of α′-Acyloxy Enones

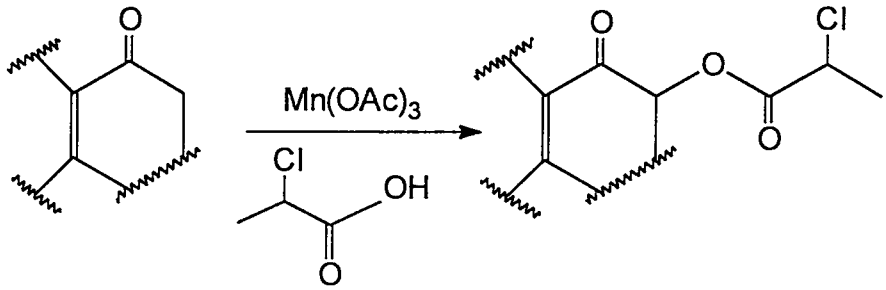
According to the retro analysis of the target monoterpenes, the first step is the synthesis of α′-acyloxy cyclic enones. These type of reactions are important to functionilize the α′-positions of enones with high regioselectivity and chemical yields. Manganese (III) acetate was used as a selective and mild oxidizing agent for this purpose. It was prepared according to the procedure of Heiba et. al.[74] The yields of the desired α′-acyloxy enones in these oxidations were particularly sensitive to the moisture content of oxidizing agent. Drying the manganese (III) acetate over phosphorous pentoxide improved the yield to acceptable levels.

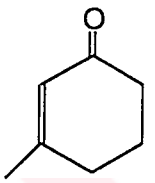
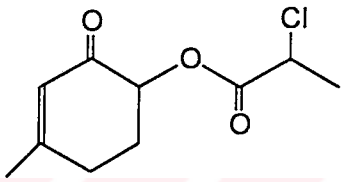
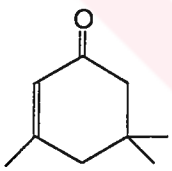
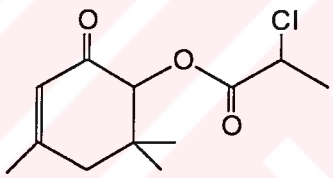
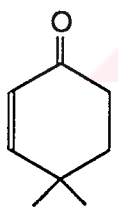
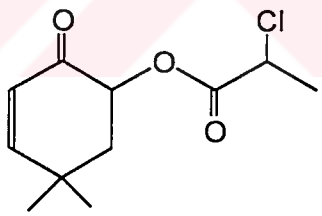
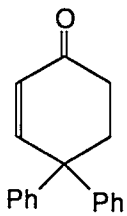
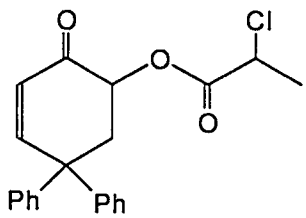
Selective α′-oxidation of α,β-unsaturated enones by the use of manganese (III) acetate in the presence of 2-chloro propionic acid provides a convenient synthesis of α′-acyloxy and α′-acetoxy derivatives. Since we interested in the synthesis of α′-acyloxy enones, we used flash column chromatography for the separation of predominant α′-acyloxy enones from the minor α′-acetoxy enone content of the reaction mixture.

We improved an effective procedure for α′-oxidation of enones by the use of 4 equivalents of manganese (III) acetate in combination with 12 equivalents of 2-chloro propionic acid under reflux in the presence of dry benzene, which gave the α′-(2-chloro)-propionyloxy α-β-unsaturated ketones from the corresponding cyclic enones in good yields (Table 16). The best yield was obtained by choosing benzene as solvent and Dean-Stark trap was used in the reflux system.

In this study, various α′-acyloxy cyclic enones have been synthesized with high yields according to the procedure mentioned above. All these reactions were monitored by TLC and products were purified by column chromatography with EtOAc:Hexane 1:4 as eluent system. These products are important as structural units of natural products and can be used for the synthesis of some biologically active compounds.

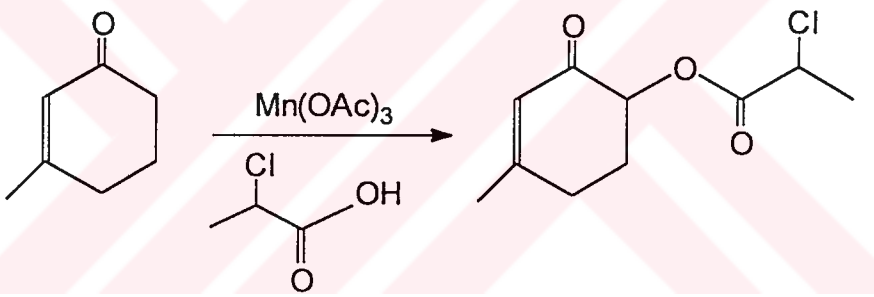
Table 16. Manganese (III) Acetate Oxidation of Enones to α′-Acyloxy Enones



Substrate	Reflux Time (h)	Product	Yield (%)
	40		55
	10		75
	6		80
	8		72

2.4.2.1. The Synthesis of 3-Methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one

The oxidation of 3-methyl cyclohex-2-en-1-one (41) using manganese (III) acetate in the presence of 2-chloropropionic acid, produced 3-methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (42) (eq 49).



(41) (42)

(eq 49)

The ^{1}H-NMR spectrum of 3-methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (42) shows the typical doublet at 1.7 ppm for the $CHCl\underline{CH_3}$ and singlet at 1.9 ppm for the CH_3 group attached to double bond. For the CH_2 protons of the ring at the 4th and 5th position have been observed as

multiplet at 2.10-2.50 ppm. Whereas the CHCl proton appeared as quarted at 4.30-4.61 ppm. The signals of the α'-CH was observed as doublet of doublet at 5.20-5.45 ppm. Finally olefinic proton showed singlet at 5.85 ppm.

In IR spectrum of compound (42) shows two characteristic peak at 1752, 1665 cm^{-1} for the carbonyl absorption.

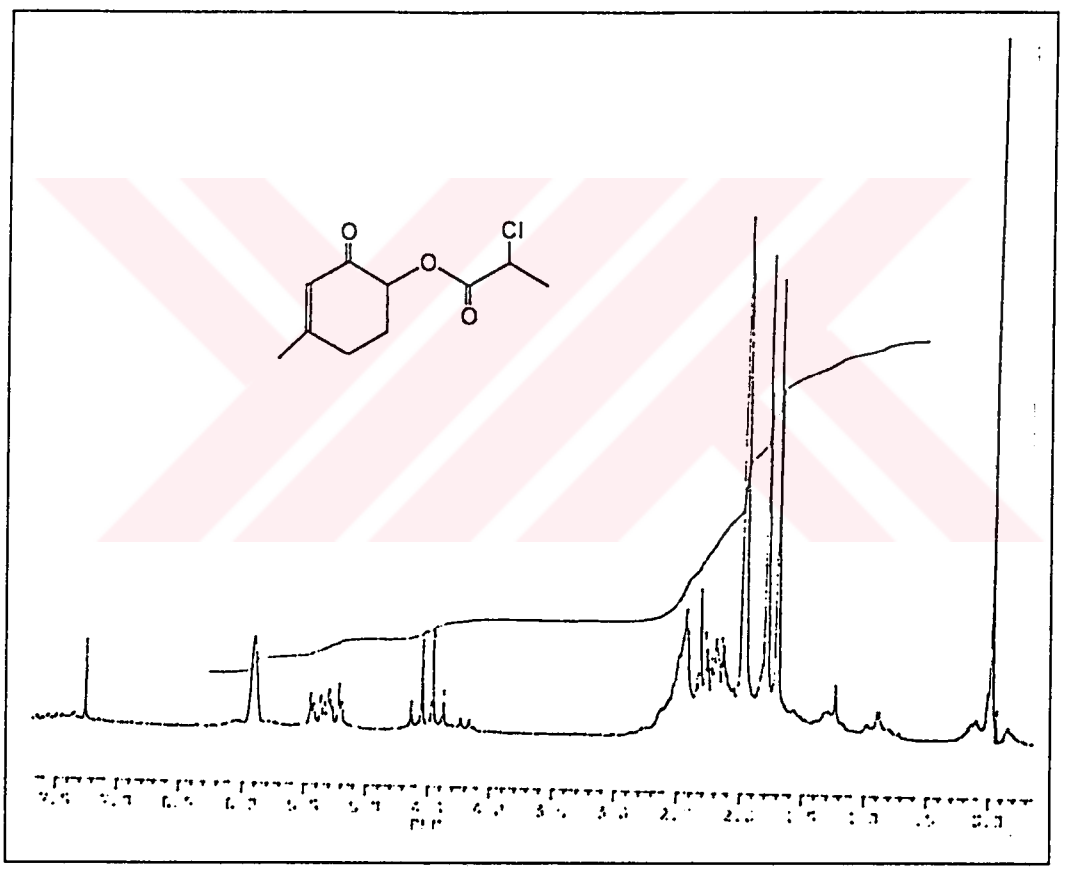
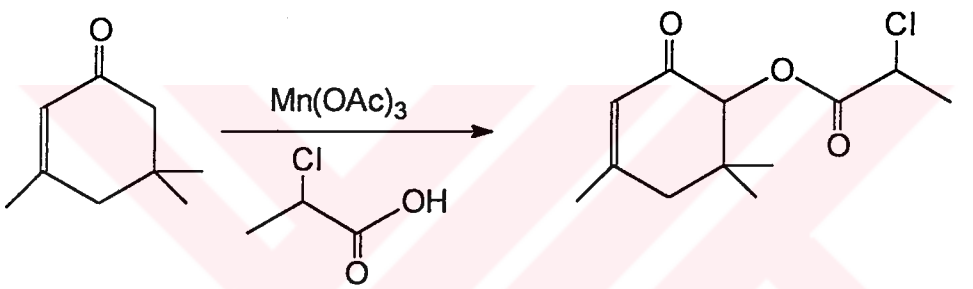


Figure 1. The ^{1}H-NMR Spectrum of 3-Methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (42)

2.4.2.2. The Synthesis of 6-(2-Chloro propionyloxy)-3,5,5-trimethyl-cyclohex-2-en-1-one

The similar reaction was carried out with (isophorone) 3,5,5-trimethyl-cyclohex-2-en-1-one (43) and manganese (III) acetate in the presence of 2-chloropropionic acid to synthesize 6-(2-chloro propionyloxy)-3,5,5-trimethyl-cyclohex-2-en-1-one (44) (eq 50).



(43) (44)

(eq 50)

The ^{1}H-NMR spectrum of 6-(2-chloro propionyloxy)-3,5,5-trimethyl-cyclohex-2-en-1-one (44) show typical singlet at 1.00 ppm for C-5 attached CH_3 protons and doublet at 1.0-1.1 ppm for CHCl-$\underline{CH_3}$. The C-3 attached CH_3 protons exhibit singlet at 2.0 ppm and also singlet at 2.2 ppm belongs to CH_2 protons of the ring. The signal of the C$\underline{H}$Cl appears as quarted at 4.50-4.65 ppm. The α′-CH proton and olefinic proton show singlets at 5.2 ppm and 5.9 ppm, respectively.

The IR spectrum of compound (44) shows the carbonyl group absorption peaks at 1743 and 1687, respectively.

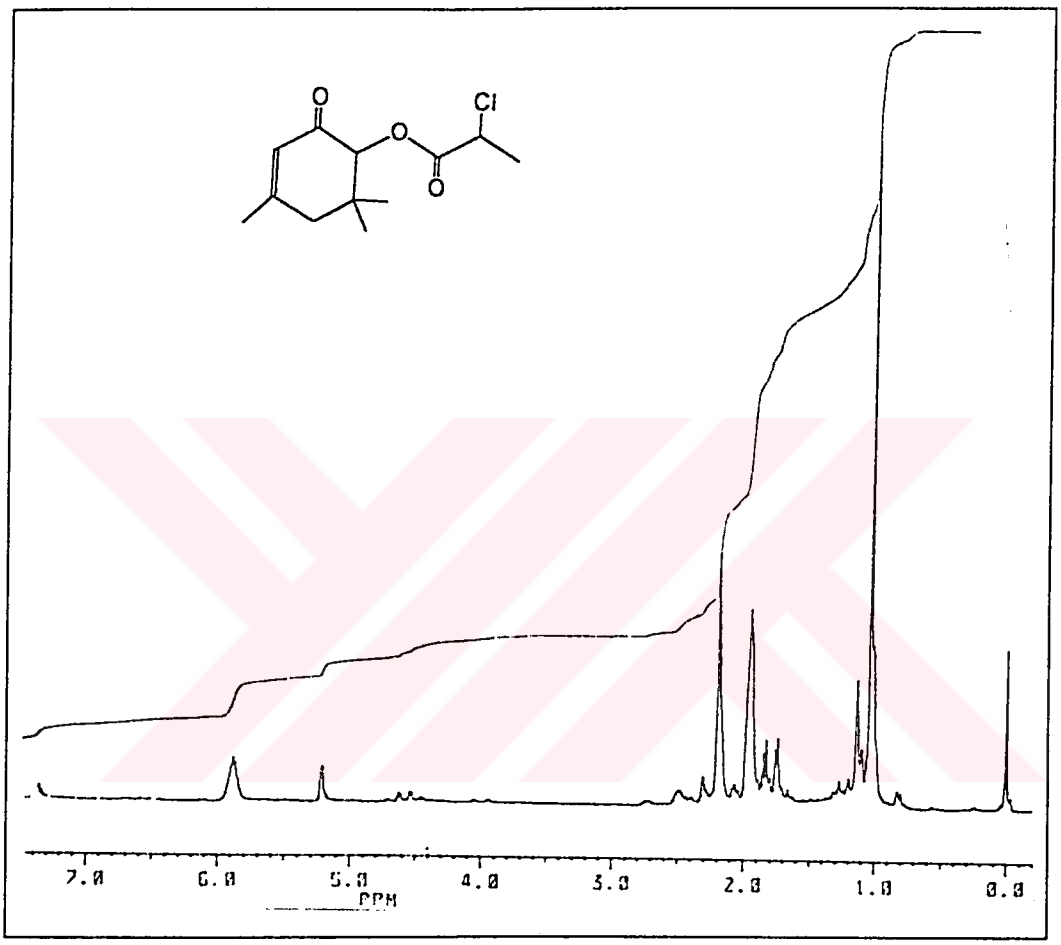
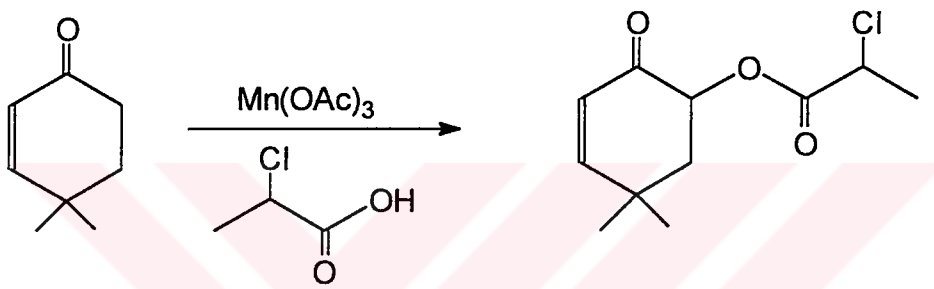


Figure 2. The 1H-NMR Spectrum of 6-(2-Chloro propionyloxy)-3,5,5-trimethyl- cyclohex-2-en-1-one

2.4.2.3. The Synthesis of 4,4-Dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one

The oxidation of 4,4-dimethyl cyclohexenone (45) using manganese (III) acetate in the presence of 2-chloropropionic acid, produced 4,4-dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (46) (eq 51).



(45) (46)

(eq 51)

The ^{1}H-NMR spectrum of 4,4-dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (46) shows singlet at 1.15 ppm for the C-4 attached CH_3 protons and doublet at 1.2-1.3 ppm for the CHCl$\underline{CH_3}$ protons. The CH_2 protons of α′-acyloxy 4,4-dimethyl cyclohexenone show doublet to doublet at 1.7 ppm, because of their diastereotopic properties. The C$\underline{H}$Cl proton shows quarted at 4.35-4.65 ppm. The α′-CH exhibits doublet to doublet at 5.80 ppm. The olefinic protons show doublets at 6.60 ppm and 6.75 ppm for α- and β-positions, respectively.

The IR spectrum shows two peaks at 1757, 1706 cm^{-1} for the carbonyl absorption.

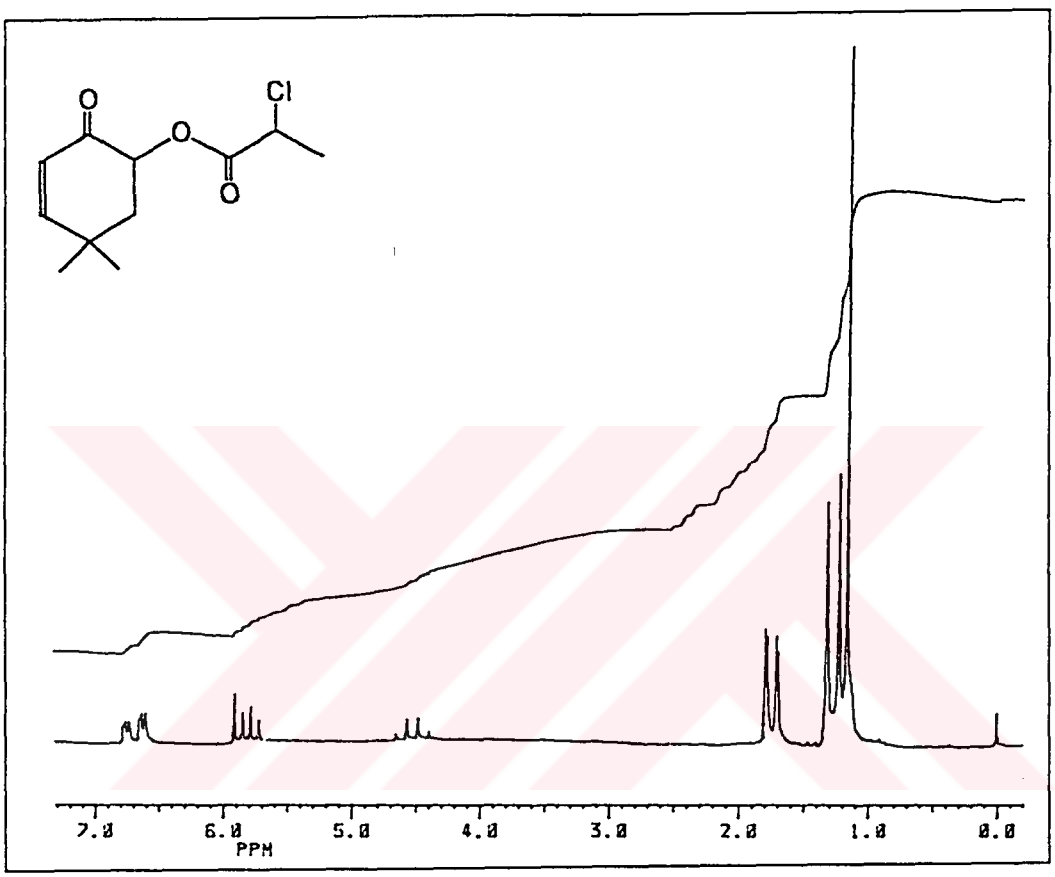
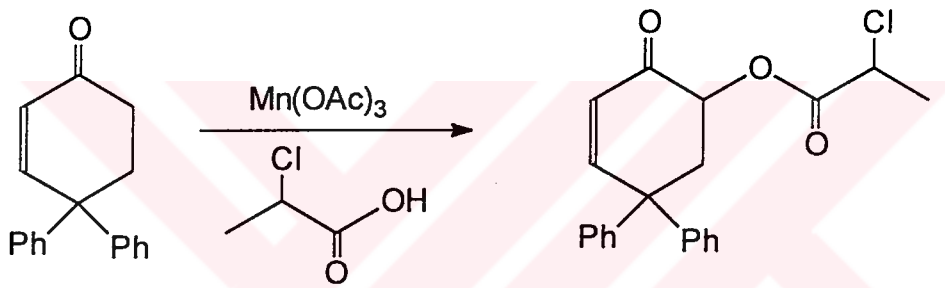


Figure 3. The ^{1}H-NMR Spectrum of 4,4-Dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (46)

2.4.2.4. The Synthesis of 4,4-Diphenyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one

The compound 4,4-diphenyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (48) was synthesized by the oxidation of 4,4-diphenyl cyclohexenone (47) with manganese (III) acetate in the presence of 2-chloropropionic acid (eq 52).



(47) (48)

(eq 52)

The ^{1}H-NMR spectrum of 4,4-diphenyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (48) shows doublet at 1.6-1.7 ppm for the CHCl-$\underline{CH_3}$ protons. The C-5 CH_2 methylene protons show multiplet at 2.3-3.0 ppm. The C$\underline{H}$Cl proton exhibits quarted at 4.3-4.6 ppm. The α'-CH shows doublet to doublet at 5.25-5.55 ppm. Olefinic protons exhibits doublets for α- and β-positions at 6.1 ppm and 6.21 ppm, respectively. Finally the phenyl protons show multiplet at 7.00-7.25 ppm.

The IR spectrum of compound (48) shows two characteristic carbonyl absoption peaks at 1752 and 1706 cm^{-1}.

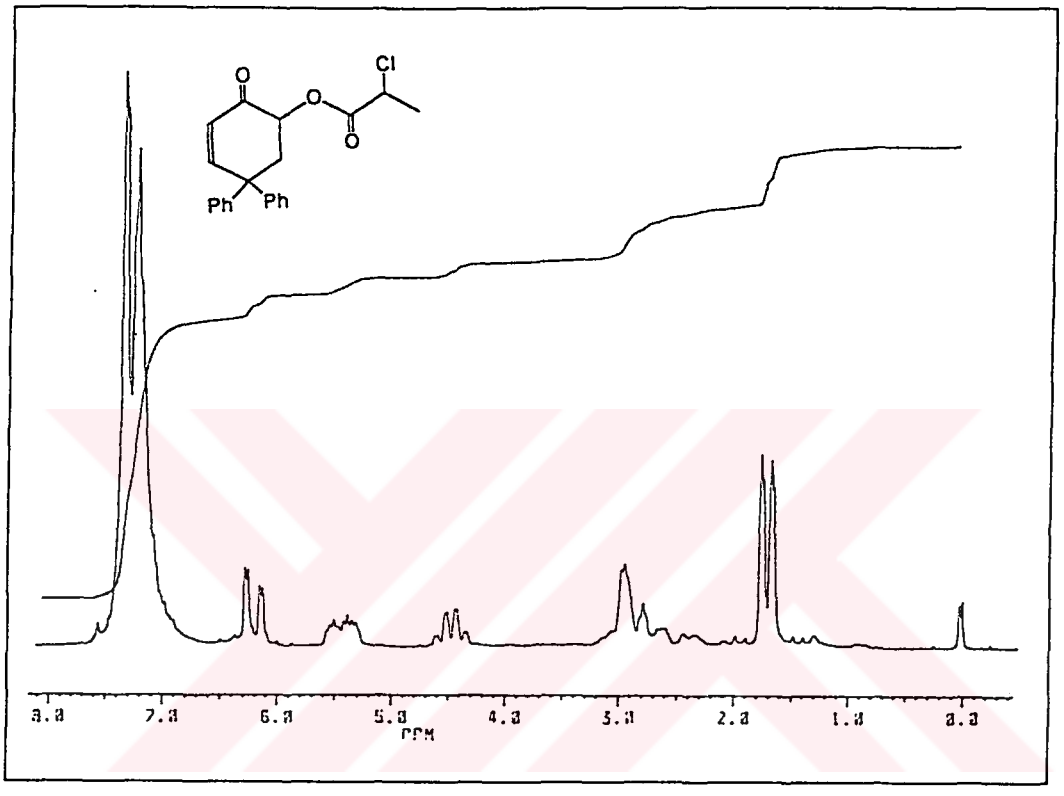
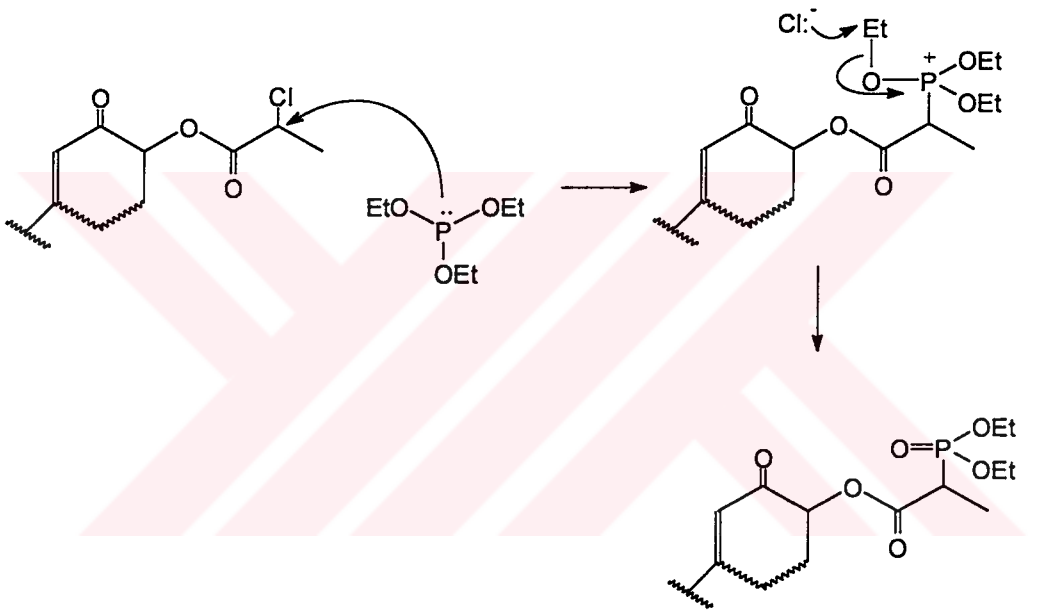


Figure 4. The ^{1}H-NMR Spectrum of 4,4-Diphenyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (48)

2.5. Mechanism of the Arbuzov Reaction and Horner Emmons Cyclization Reaction

Arbuzov reaction has several advantages over the use of phosphoranes. Phosphonated products can easily be prepared by the Arbuzov reaction. The mechanism of the key step of the Arbuzov reaction is as follow in scheme 10.

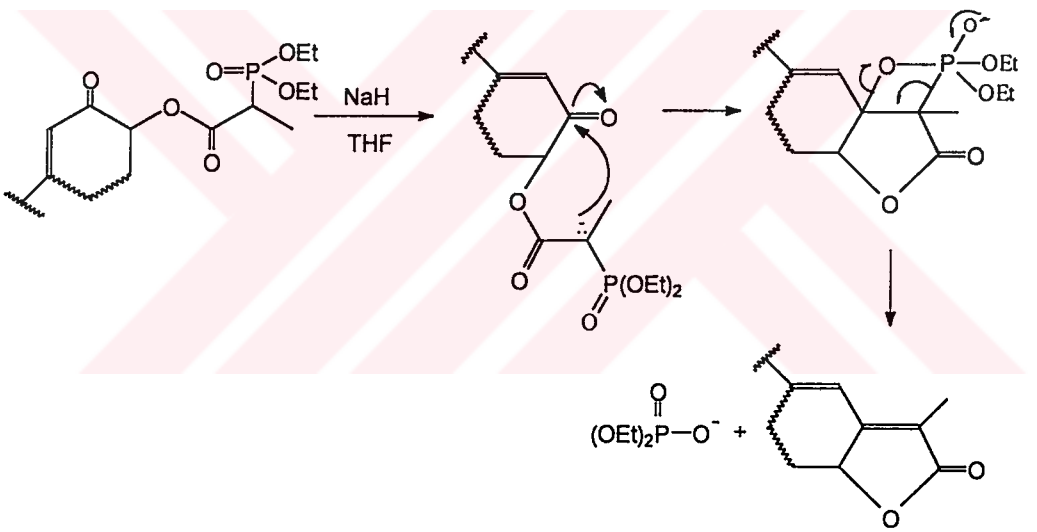


(Scheme 10)

In the retroanalysis, before the ring construction step of the monoterpenes, we suggested that the system required a carbanion located between carbonyl and phosphanate groups. For this purpose Arbuzov reaction

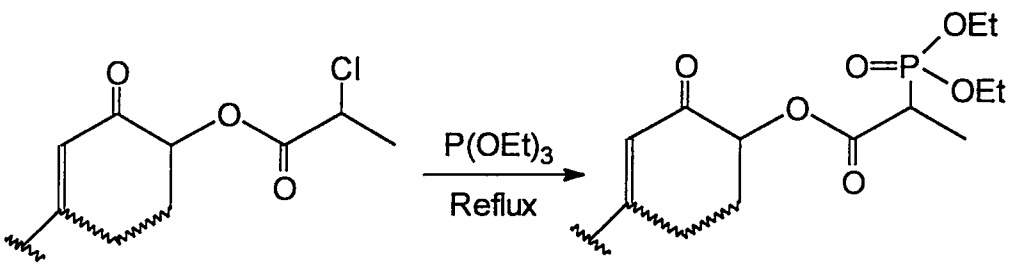
was the feasible way to create a potent carbanionic center. The products of the Arbuzov reaction are shown in Table 18.

The final step of the retroanalysis was the intramolecular cyclization of the Horner-Emmons intermediate structure in the presence of the base. Potent carbanionic centre was created with NaH in THF which is stabilized by the carbonyl and the phosphonate groups. The possible mechanism is shown in scheme 11. Intramolecular cyclization products are shown in Table 19.



(Scheme 11)

Table 17. Arbuzov Reactions of α′-Acyloxy Enones



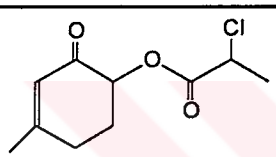
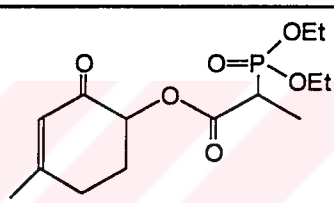
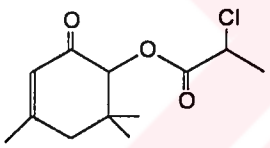
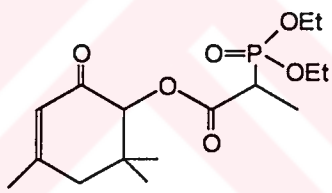
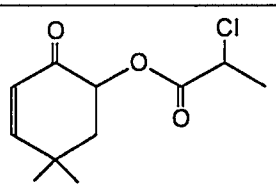
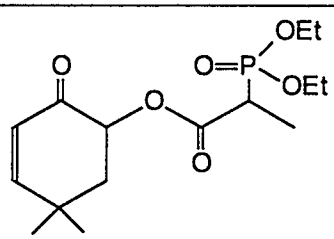
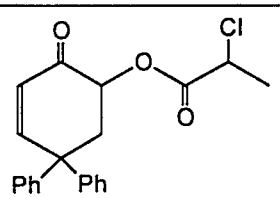
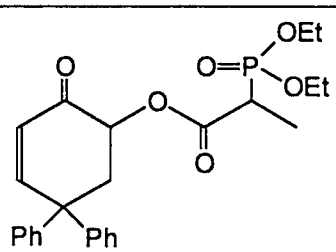
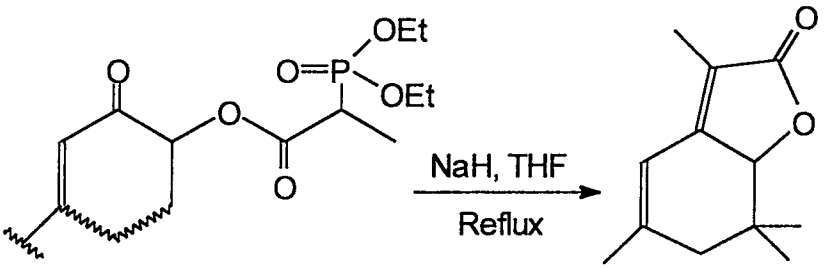
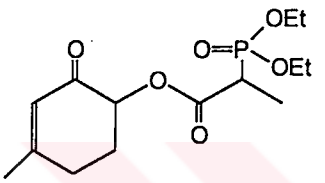
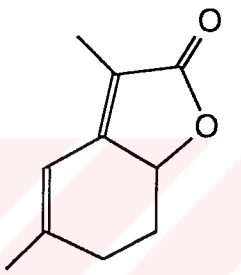
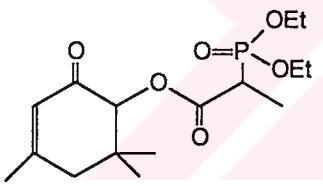
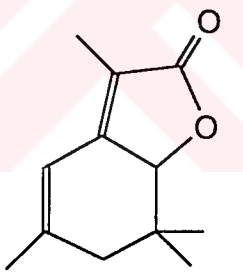
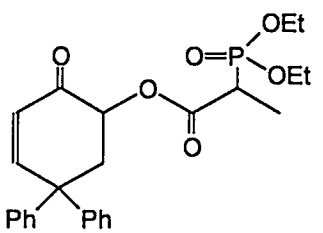
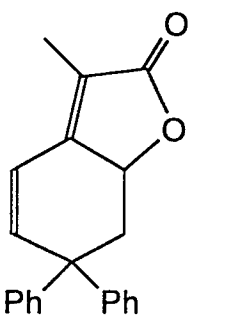
Substrate	Reflux Time (h)	Product	Yield (%)
	3		80
	3		79
	3		84
	3		75

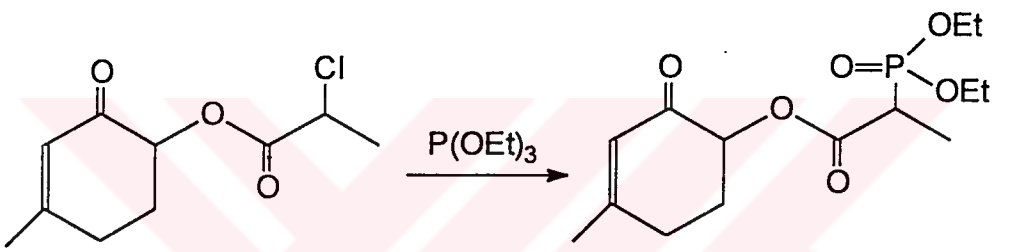
Table 18. Horner-Emmons Reactions of α′-Acyloxy Enones



Substrate	Reflux Time (h)	Product	Yield (%)
	4		70
	4		72
	4		76

2.5.1. The Synthesis of 3,5-Dimethyl-6,7a-dihydro-2-(2H) benzofuranone

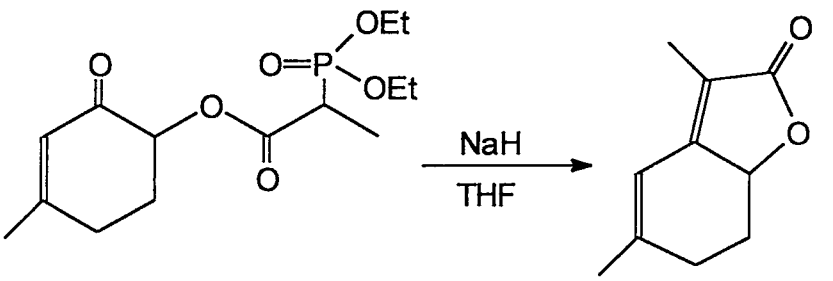
The 3-Methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one undergoes the Arbuzov type reaction with triethyl phosphite to afford 3-methyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (49) (eq 53).



(42) (49)

(eq 53)

The 3-methyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (49) gives Horner-Emmons cyclization product (50) in the presence of NaH in THF (eq 54).



(49) (50)

(eq 54)

The ^{1}H-NMR spectrum of 3,5-Dimethyl-6,7a-dihydro-2-(2H) benzofuranone (50) shows singlet at 1.95 ppm for the 2xCH_3 protons. The CH_2 protons of the ring are observed as multiplet at 2.20-2.52 ppm. The signal of C<u>H</u>O proton shows doublet to doublet at 5.35 ppm. The olefinic proton exhibits singlet at 5.90 ppm.

The IR spectrum of compound (50) shows carbonyl absorption band at 1740 cm^{-1}.

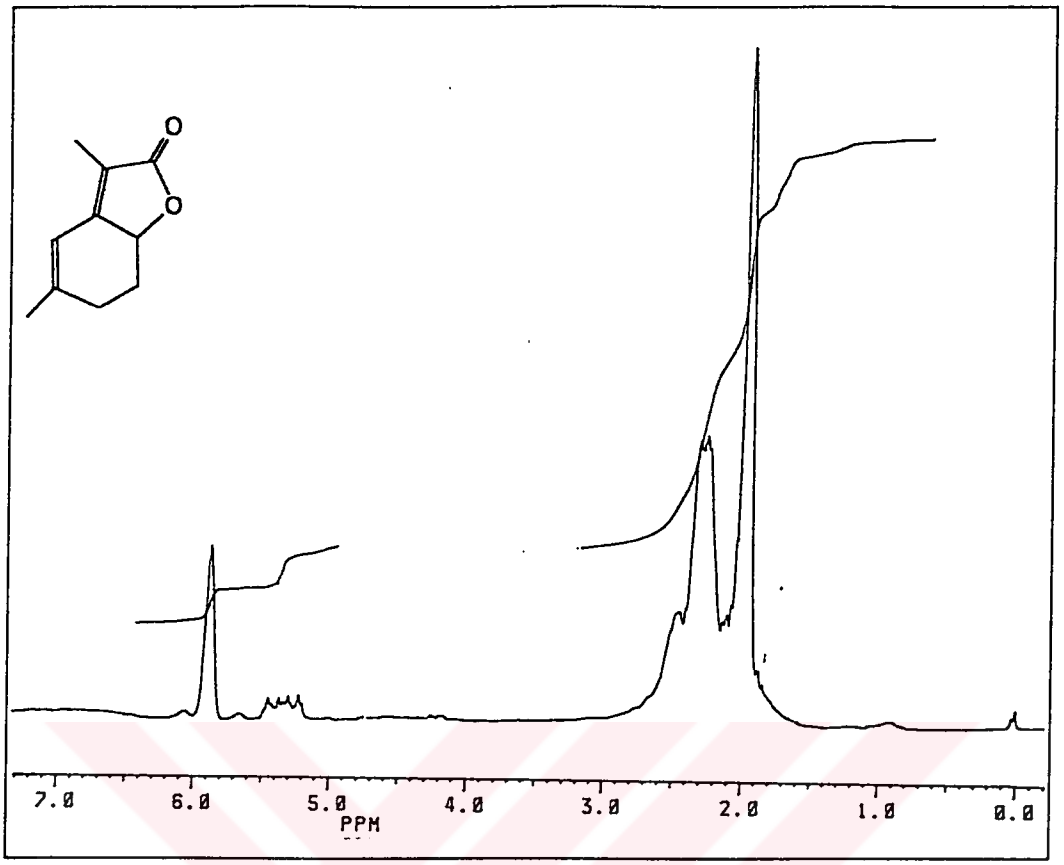
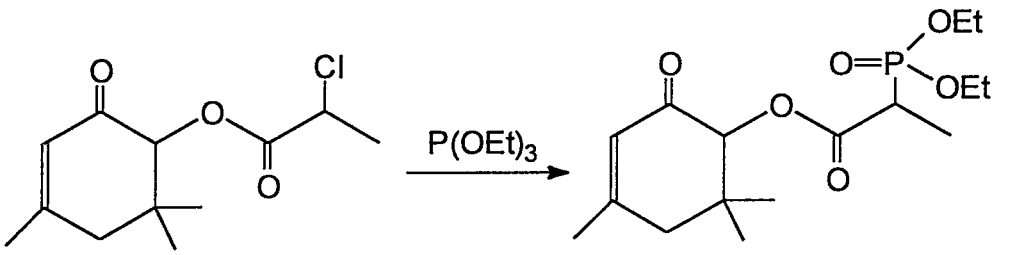


Figure 5. The ^{1}H-NMR Spectrum of 3,5-Dimethyl-6,7a-dihydro-2-(2H) benzofuranone

2.5.2. The Synthesis of 3,5,7,7a-Tetrahydro-6,7a-dihydro-2-(2H) benzofuranone

In the Arbuzov reaction 6-(2-chloro propionyloxy)-3,5,5-trimethyl-cyclohex-2-en-1-one (44) with excess triethyl phosphite gives the 6-(2-

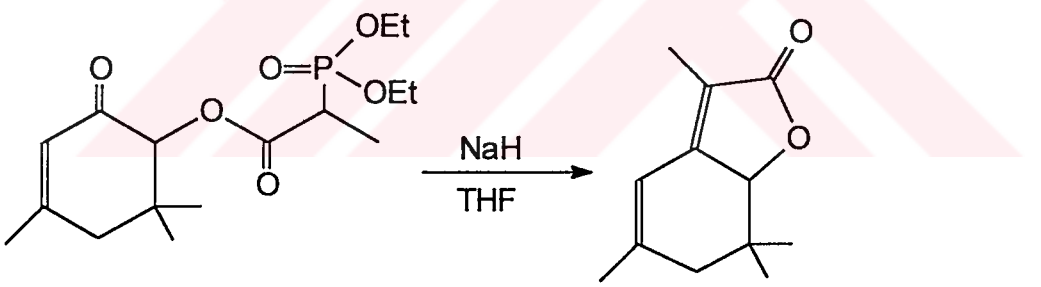
diethoxy phosphoryl)- propionyloxy-3,5,5-trimethyl-cyclohex-2-en-1-one (51) (eq 55).



(44) (51)

(eq 55)

The end product (52) was obtained by Horner-Emmons cyclization reaction which is shown below (eq 56).



(51) (52)

(eq 56)

The ^{1}H-NMR Spectrum of 3,5,7,7a-tetrahydro-6,7a-dihydro-2-(2H) benzofuranone (52) shows singlet at 1.10 ppm for C-7 attached CH_3 protons, singlet at 1.95 ppm for C-3 CH_3. The CH_2 which belongs to the ring shows

singlet at 2.17 ppm however, C-5 CH_3 protons show singlet at the same ppm value. CHO proton exhibits singlet at 5.00 ppm whereas the olefinic proton appears as singlet at 6.55 ppm.

The IR spectrum of compound (52) shows an absorption band at 1750 cm^{-1} for carbonyl group.

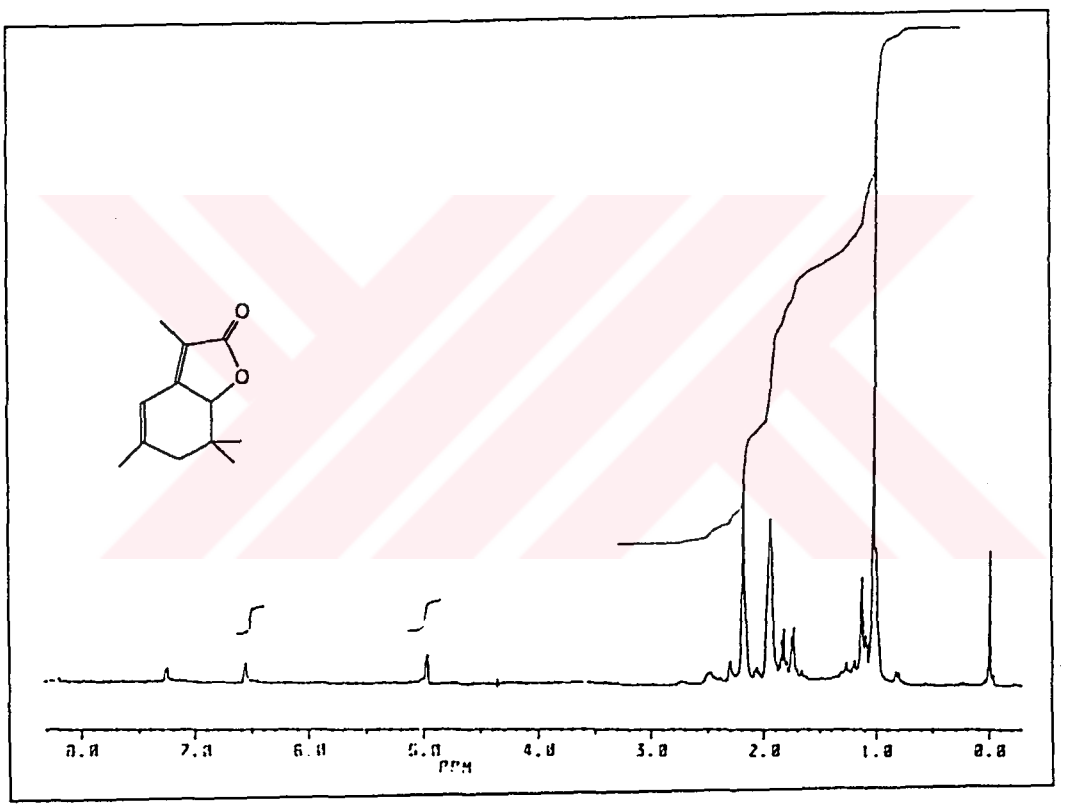
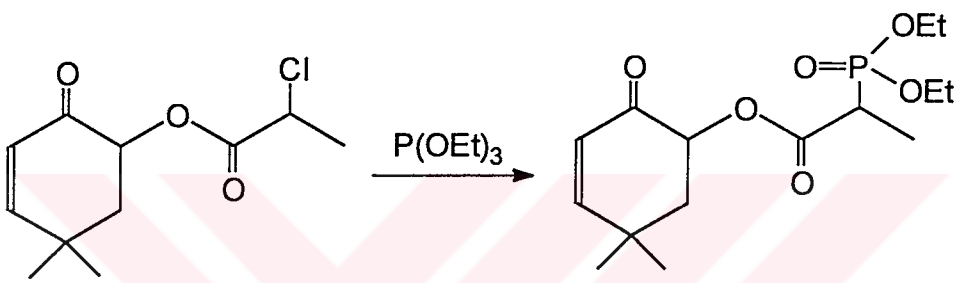


Figure 6. The ^{1}H-NMR Spectrum of ^{1}H-NMR Spectrum of 3,5,7,7a-Tetrahydro-6,7a-dihydro-2-(2H) benzofuranone

2.5.3. The Synthesis of 4,4-Dimethyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one

4,4-Dimethyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (53) was obtained as a result of Arbuzov reaction of 4,4-dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (46) with triethyl phosphite (eq 57).



(46) (53)

(eq57)

In the ^{1}H-NMR spectrum of 4,4-Dimethyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (53), the CH_3 protons at the fourth position of the ring appear as singlet at 1.1ppm. The CHP$\underline{CH_3}$ protons appear at 1.20-1.85 ppm as a doublet however, in these ppm range $\underline{CH_3}CH_2$ protons exhibit signals and block the CHP$\underline{CH_3}$ protons. The CH_2 protons of the ring exhibit multiplet at 2.10-2.26 ppm. The $CH_3\underline{CH_2}$ protons appear multiplet at 4.00-4.25 ppm, however, it is reported that the proton for the C$\underline{H}$P may as well appear at the same ppm range. The α′-CH proton shows doublet to doublet at 5.6-5.92

ppm, and the olefinic proton of α-position exhibit doublet at the same ppm range. Finally the olefinic proton for β-position appears as doublet at 6.70 ppm

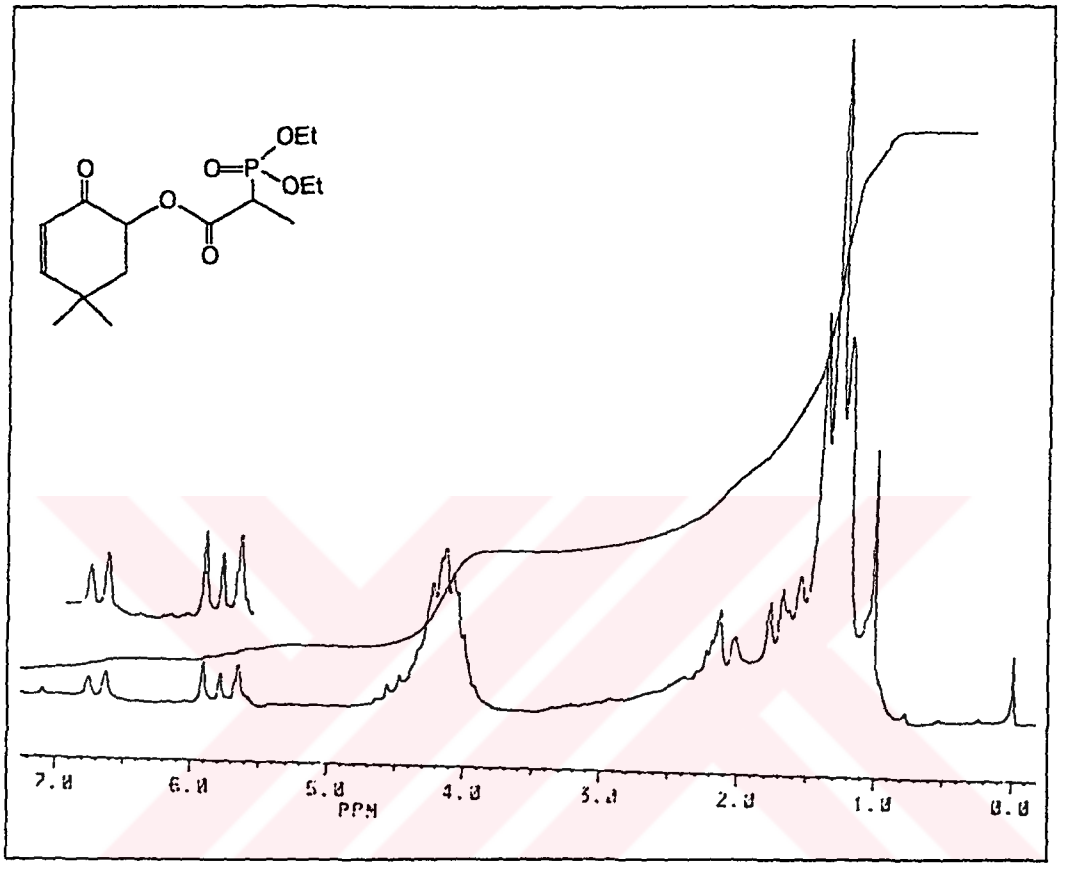
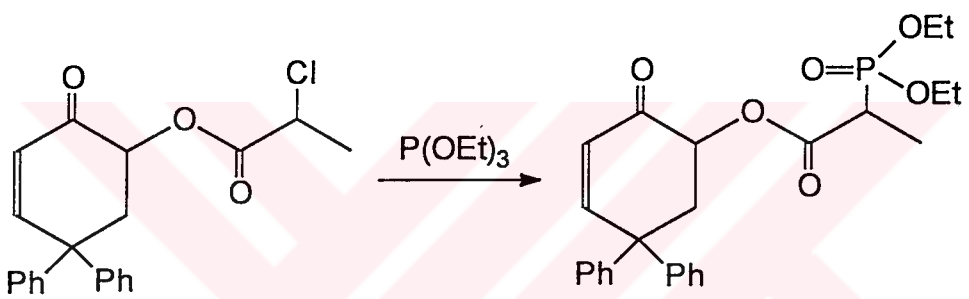


Figure 7. The ^{1}H-NMR Spectrum of 4,4-Dimethyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one

2.5.4. The Synthesis of 3-Methyl-6,6-diphenyl-7,7a-dihydro-2-(2H) benzofuranone

Arbuzov reaction was performed by 4,4-diphenyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (48) and triethyl phosphite as a result 4,4-diphenyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (54) was obtained with high chemical yield (eq58).



(48) (54)

(eq58)

The ^{1}H-NMR spectrum of the 4,4-diphenyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (54) shows multiplet at 1.10-1.50 ppm for $\underline{CH_3}CH_2$ protons, whereas for the CHP$\underline{CH_3}$ protons and CH_2 protons which belongs the ring exhibit at the same ppm range. The $CH_3\underline{CH_2}$ protons appear multiplet at 2.90-3.05 ppm. The C$\underline{H}$P proton shows quarted at 4.15 ppm. And then C$\underline{H}$O proton appear doublet to doublet at 5.65 ppm. The olefinic protons

exhibit two doublets at 6.05 ppm and 6.35 ppm for α- and β- positions respectively. Finally the phenyl protons show multiplet at 6.95-7.60 ppm.

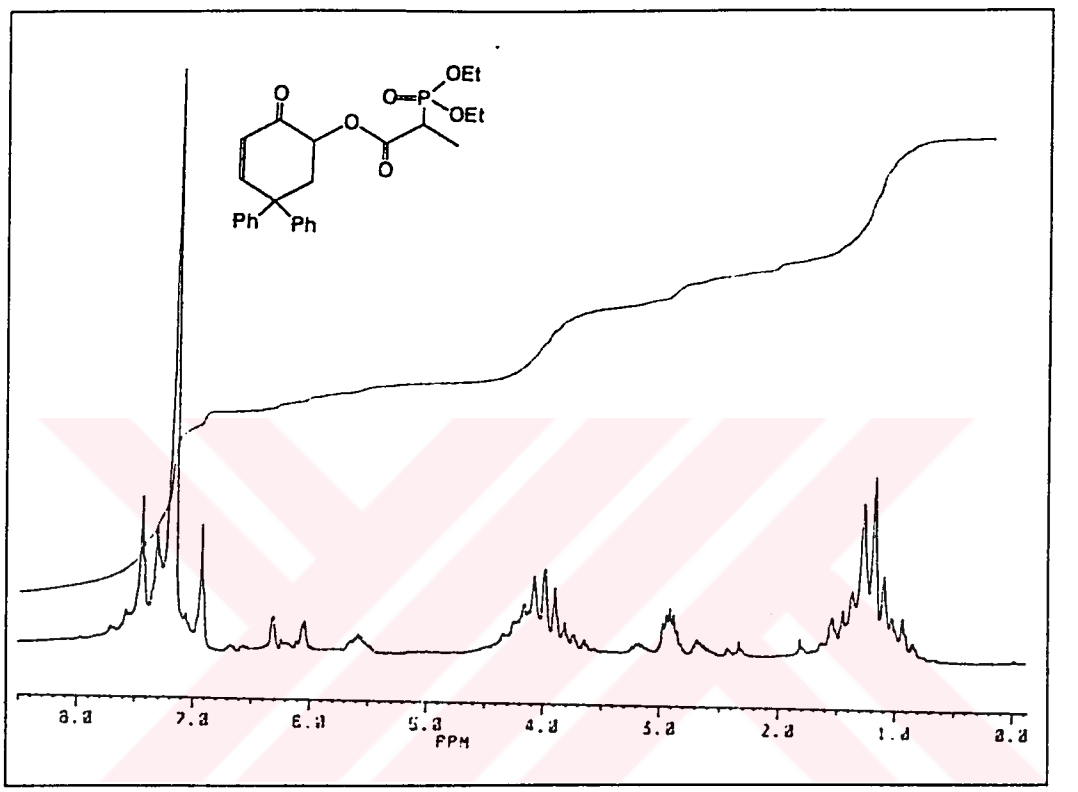
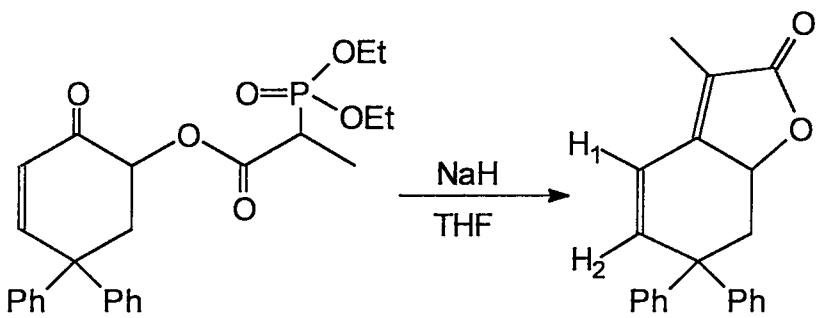


Figure 8. The ^{1}H-NMR Spectrum of 4,4-Diphenyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (54)

Subsequent Horner-Emmons cyclization reaction was carried out on this product to attain target compound (55) (eq59).



(54) (55)

(eq 59)

The ^{1}H-NMR spectrum of of 3-methyl-6,6-diphenyl-7,7a-dihydro-2-(2H) benzofuranone exhibits singlet at 1.28 ppm for the C-3 attached CH_3 protons and a broad unresolved signal at 2.50 for the C-7 CH_2 protons. The CH-O proton shows broad multiplet at 5.6 ppm. The olefinic proton H_1 appears doublet at 6.01ppm. The olefinic proton H_2 shows doublet at 6.43 ppm. Finally aromatic protons are observed as multiplet at 7.20-7.40 ppm.

The IR spectrum of compound (55) exhibits an absorption band at 1748 cm^{-1} for carbonyl group.

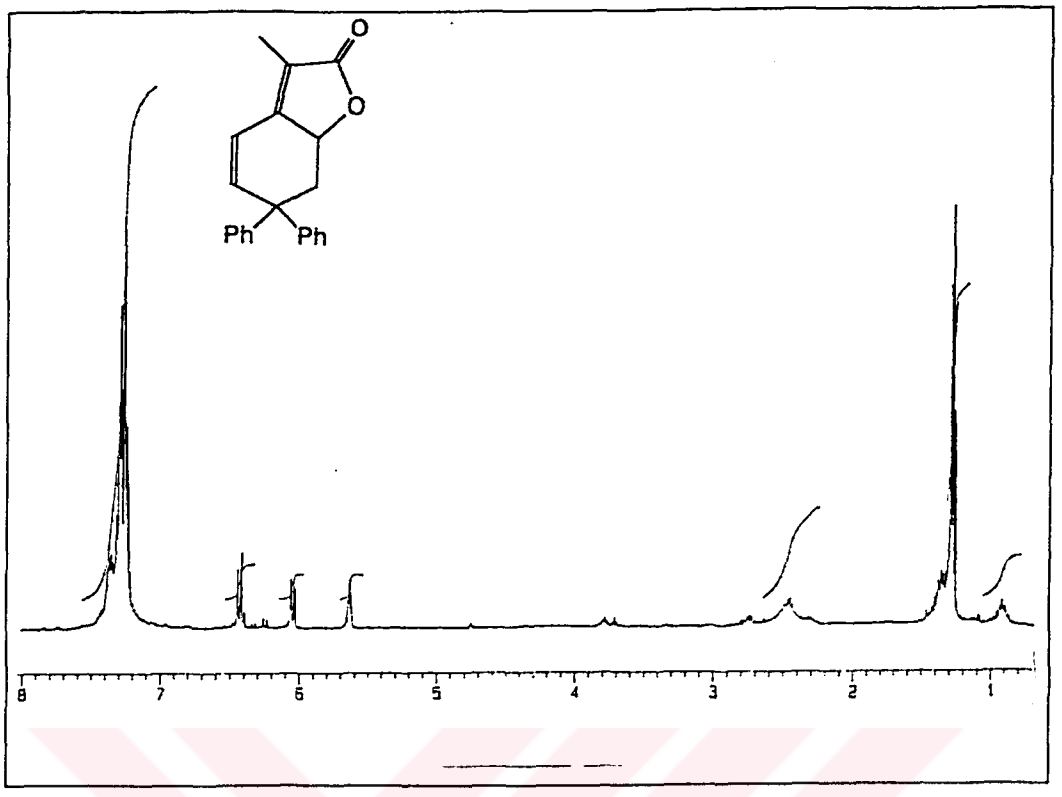


Figure 9. The ^{1}H-NMR Spectrum of 3-Methyl-6,6-diphenyl-7,7a-dihydro-2-(2H) benzofuranone

2.6. The Synthesis of Mintlactone

We have designed a new and short way for the synthesis of (+/-)-Mintlactone. In the retro-analysis of (+/-)-Mintlactone, 4-methyl cyclohexanone was chosen as the starting compound. In order to oxidize, 4-methyl cyclohexanone, another oxidation method was applied by using lead (IV) acetate as the mild oxidizing agent. By comparing the efficiency of the lead (IV) acetate oxidation with manganese (III) acetate oxidation in the synthetic strategy, it could be seen that lead (IV) acetate oxidation could not directly introduce 2-chloropropionyl moity to 4-methyl cyclohexanone. This procedure requires one more step to introduce 2-chloropropionyl group. The reaction of 4-methyl cyclohexanone with lead (IV) acetate afforded the 2-acetoxy-4-methyl cyclohexanone. And then 2-acetoxy-4-methyl cyclohexanone was hydrolyzed with K_2CO_3 in aqueous MeOH. 2-Hydroxy-4-methyl cyclohexanone was reacted with chloropropionyl chloride to yield 4-methyl-2-(2-chloro propionyloxy) cyclohexanone. Subsequent application of the Arbuzov reaction followed by Horner-Emmons type intramolecular cyclization reaction yielded (+/-)-Mintlactone.

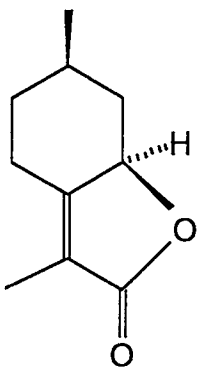
In a number of papers the synthesis of (+/-)-mintlactone are described. This monoterpene possesses a butenolide moity as the essential component which shows some biological activities.

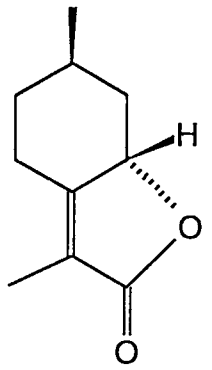
The essential oil of Mentha piperita L. (peppermint of Mitcham) is one of the most important commercial flavoring materials. It is produced in many countries, and especially on a large scale in the U.S.A.[143]

(-)-Menthol (40%), (-)-menthone (25%), cineol (6.5%), (-)-menthylacetate (3.5%), (+)-isomenthone (3.5%), (+)-pulegone (1%), (-)-piperitone (0.5%) and (+)-3-octanol (0.3%) were found to be major constituents of this oil.[143]

In addition to these main constituents, approximately 300 other components have been reported as minor and trace volatile components [143, 144]. In spite of a number of works, the flavor profile of this oil has not been completely made clear.

Takahashi [143] and et al. identified that eighty-one constituents from the oil of Mentha piperita L which include (-)- mintlactone (57) and (+)-isomintlactone (58). Minor components of (-)-mintlactone (0.03%) and (+)-isomintlactone (0.003%) in Peppermint oil had a strong sweet aroma.

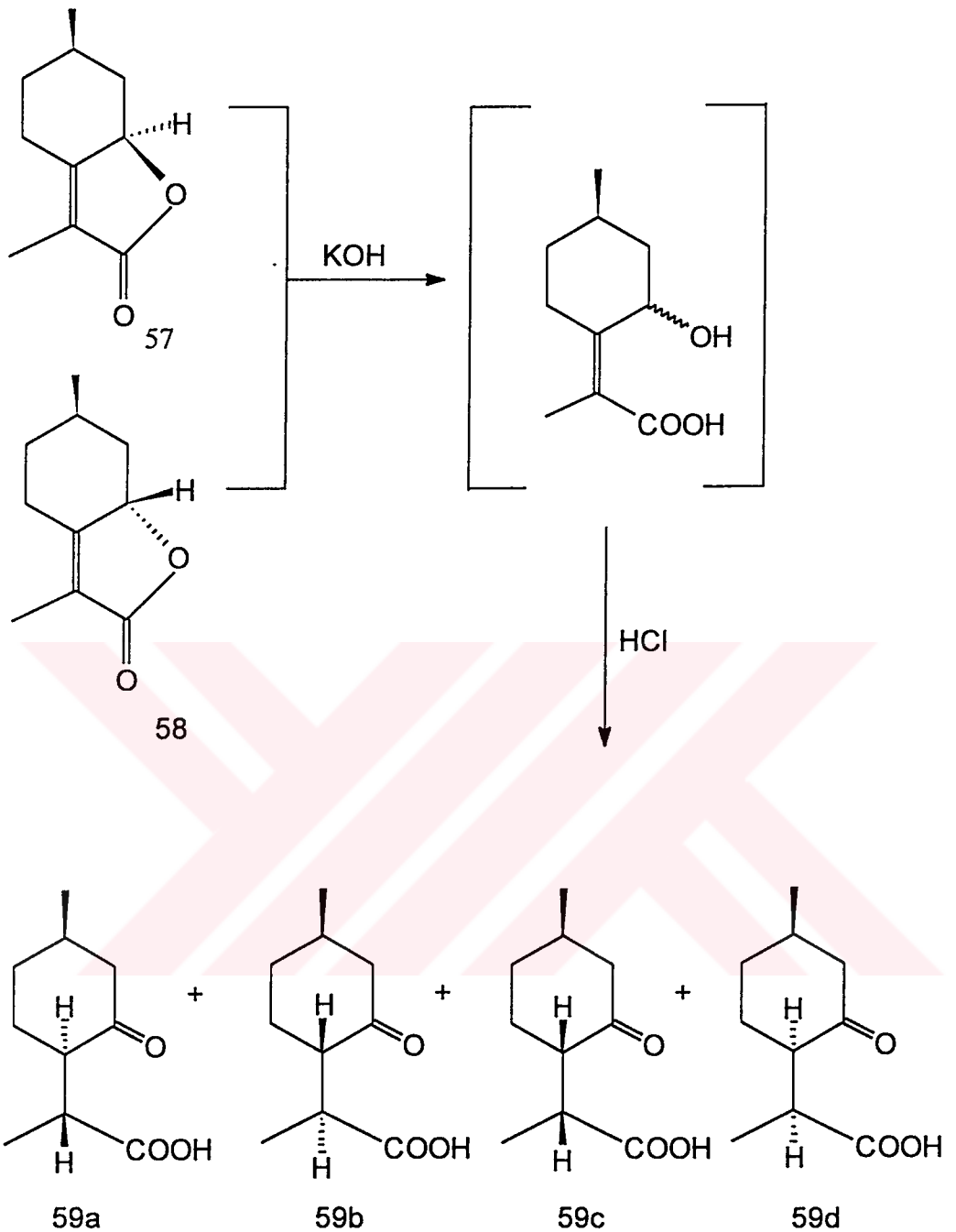




(57) (58)

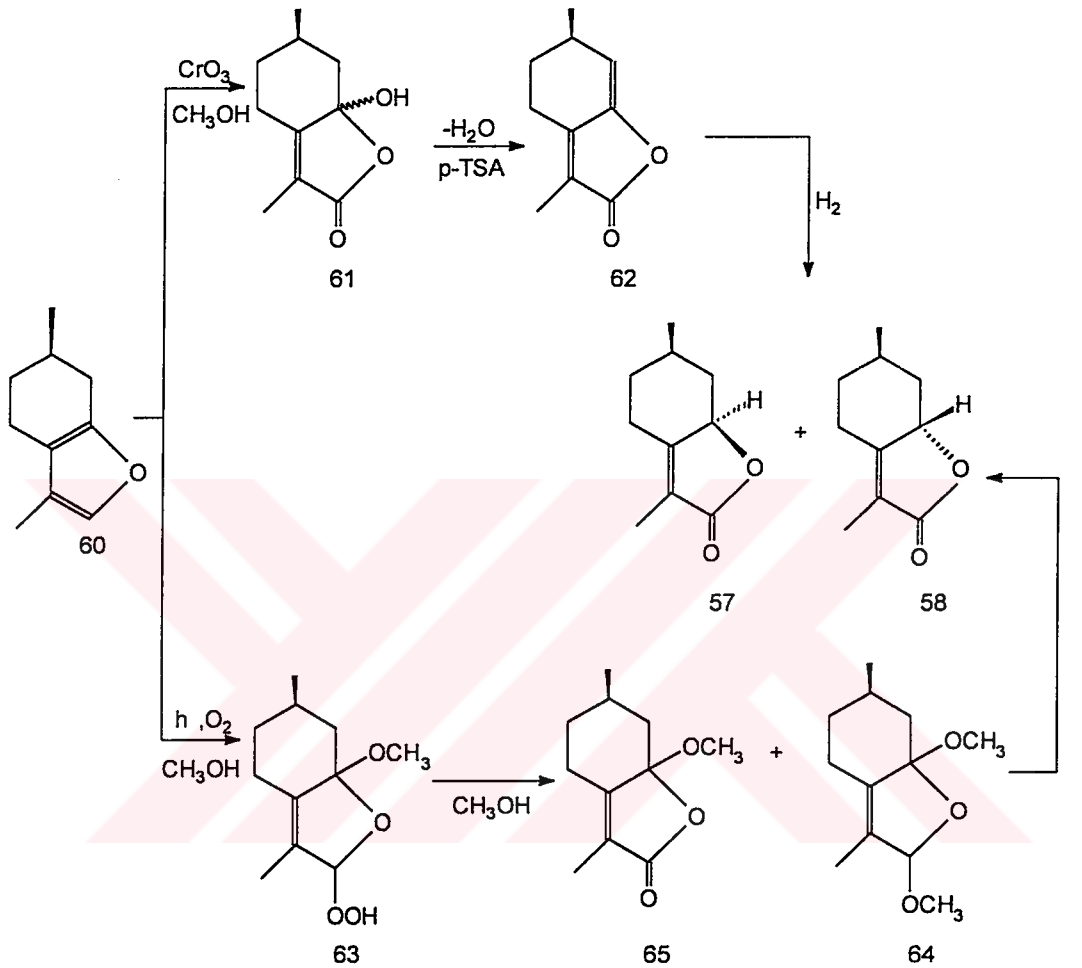
In 1968 Muraki found an unknown (-)-mintlactone (57), having a considerably powerful sweet and characteristic aroma in spearmint oil (0.01-0.05%) in the oils of Mentha aryensis (0.01%) and Mentha piperita (0.01-0.05%) for the first time in nature [145].

Takahaski et al. demonstrated that absolute configuration of (-)-mintlactone (57) (6 R, 7a R)-3,6-dimethyl-5,6,7,7a-tetrahydro-2-(4H) benzofuranone. The spectral properties of (58) (+)-isomintlactone were almost identical with those of (57) (-)-mintlactone. Saponification of (58) gave the same four diastereo-isomers of keto acids (59a-d) as the saponification of (57). These facts suggested that (58) was an epimer of (57) as shown in scheme 8.



(Scheme 8)

In order to confirm the absolute configuration, (58) was synthesized from (-)-menthofuran (60) by two methods as shown in equation 60.



(eq 60)

One method was through oxidation by chromium trioxide of (60) and dehydration of 3,6-dimethyl-7a-hydroxy-5,6,7,7a-tetrahydro-2(4H) benzofuranone (61) followed by hydrogenation of the dehydrated product (62).

The other was through the improved sensitized photooxidation of Foote et

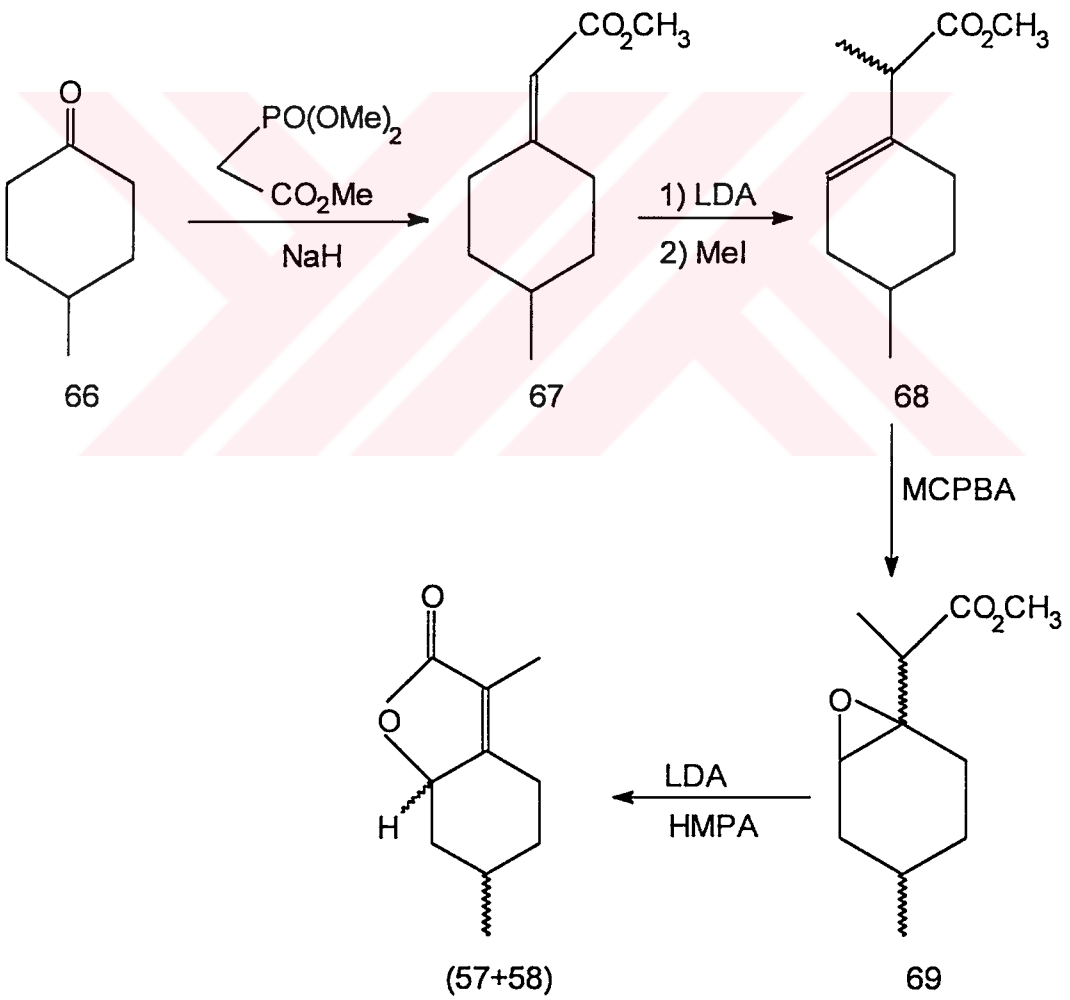
al. [146, 147] Photooxidation of (60) in methanol in the presence of Rose Bengal as a photosensitizer gave 9-hydroperoxy-3-methoxy-3,9-dihydromenthofuran [146]. This compound (63) was further converted to 3,9-dimethoxy-3,9-dihydromenthofuran (64) [147] 3,6-dimethyl-7a-methoxy-5,6,7,7a-tetrahydro 2(4H) benzofuranone (65). On treatment of the mixture with concentrated HCl, (64) gave (57) and (58) in the ratio of 10:1. The physical properties and spectral data of the synthetic (57) and (58) were completely identical with those of the isolated samples from peppermint oil respectively. Therefore the absolute configuration of (+)-menthofuran (60), the absolute configuration of (-)-isomintlactone (58) was confirmed to be (6R, 7aS)-3,6-dimethyl -5,6,7,7a-tetrahydro 2(4H)-benzofuranone by Takahashi and et al.[143]

In 1972 [148] Fujita and et al. were reported mintlactone to be contained in Mentha pulegium.

In 1973 Sakata and Hashizume were also reported, mintlactone to be contained a variety of Mentha aryensis "Shibi" in Japanese.[149] 3,6-Dimethyl-7a-hydroxy-5,6,7,7a-tetrahydro 2(4H)-benzofuranone (61), which was an

intermediate in the course of (-)-mintlactone synthesis and had already been reported in various Mentha species was also identified in this oil.[147,148,150,151]

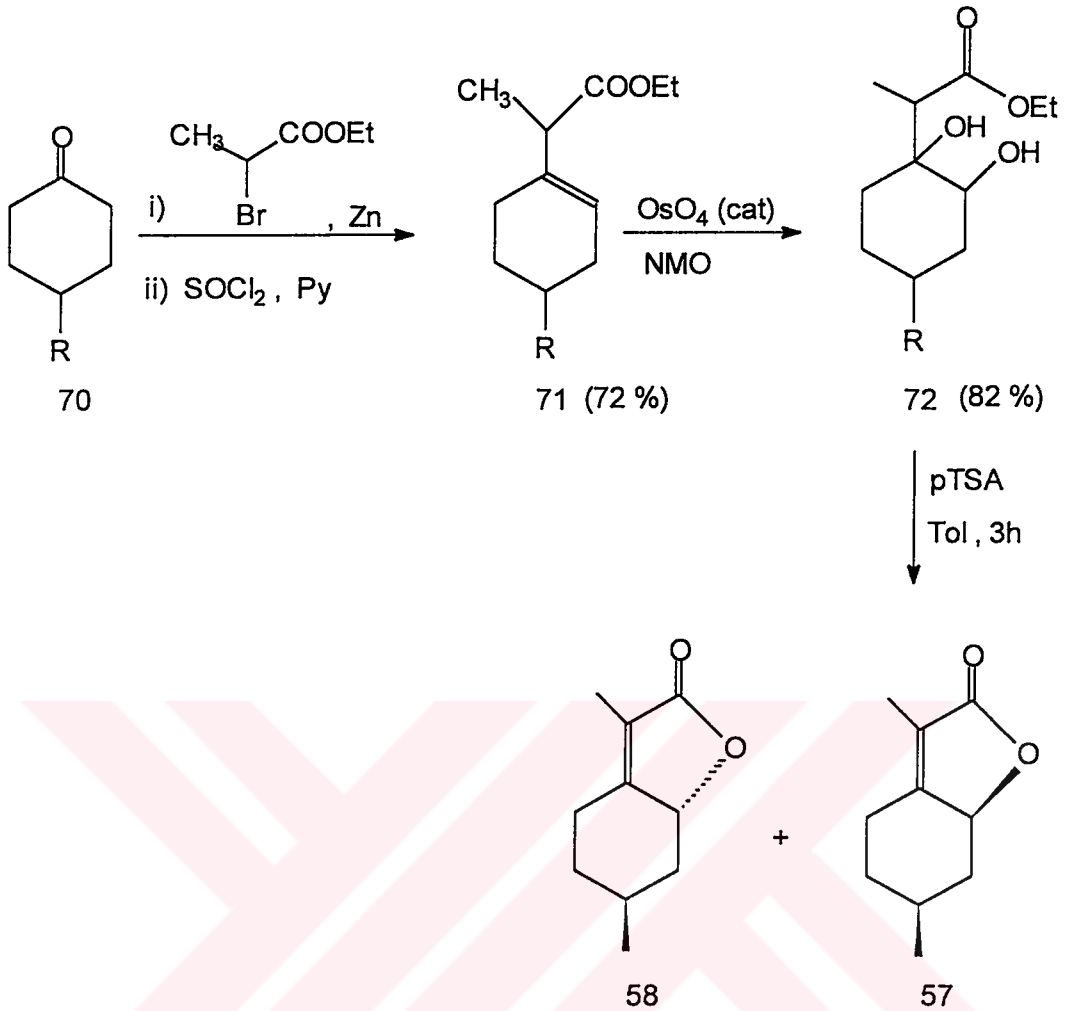
According to Cory and et al.[152] the synthesis of mintlactone and isomintlactone started with Emmons-Wadsworth olefination of 4-methyl-cyclohexanone ([MeO]$_2$ $POCH_2CO_2Me$, NaH, benzene, 60-65°C), which afforded α,β-unsaturated ester (67) in 65% yield.



(eq 61)

Alkylative deconjugation to (68) (mixture of diastereomers) and epoxidation to (69) (also a mixture) proceeded without difficulty, and the key rearrangement step, performed under basic conditions, gave a 9:1 mixture of (+/-)-mintlactone (57) and (+/-)-isomintlactone (58) from which (+/-)-mintlactone could be isolated pure in 68% yield. Rearrangement of epoxy ester (69) under acidic conditions gave a complex mixture of products.[152]

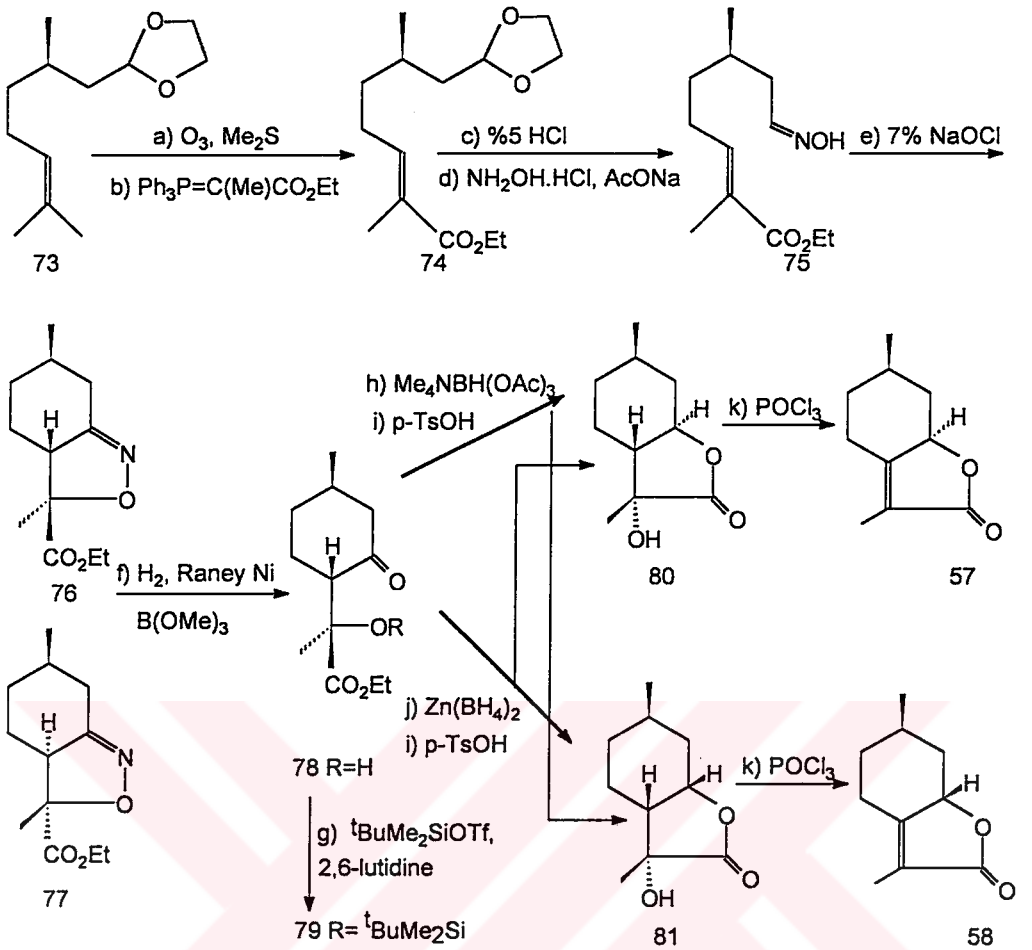
Chavan and et al. reported that another method for the formation of (+/-)-mintlactone and (+/-)-isomintlactone in 1992. According to Chavan's method Reformatsky reaction was occurred when 4-methyl-cyclohexanone (70) reacted with corresponding alcohol, which on dehydration using thionyl chloride and pyridine provided (71) afforded (72) as a mixture of diastereomers. The conversion of the diol (72) to butenolide was accomplished by refluxing it with *p*-TSA in toluene (3 hr) to afford (+/-)-mintlactone (57) and (+/-)-isomintlactone (58) in 80% yield as a mixture of diastereomers.[153] (It is shown in eq 62).



(eq 62)

The efficient and diastereoselective total synthesis of (-)-mintlactone and (+)-isomintlactone described by Shishido and et al. They were developed a method for the construction of fused butenolides based on an intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide[154].

The olefinic acetal (73) derived from (+)-citronellal was ozonized (as shown as eq 63). The resulting aldehyde was condensed with ethyl 2-(triphenyl phosphoranylidene) propionate to provide an unsaturated ester (74). Acidic hydrolysis of the acetal (74) and subsequent oxime formation provided (75) in 57% yield from (71). Treatment of (75) with 7 % aqueous sodium hypochloride in dichloromethane at room temperature afforded a chromotographically separable diastereoisomeric mixture of isoxalines (76), and (77), in a ratio of 20:1 in 84% yield. The structure of the cyclo adducts was tentatively assigned as shown from the mechanistic viewpoint.[155] Reductive hydrolysis of the major adduct (76) with trimethyl borate in aqueous methanol in the presence of a catalytic amount of Raney nickel under a hydrogen atmosphere provided (78) in 81% yield .

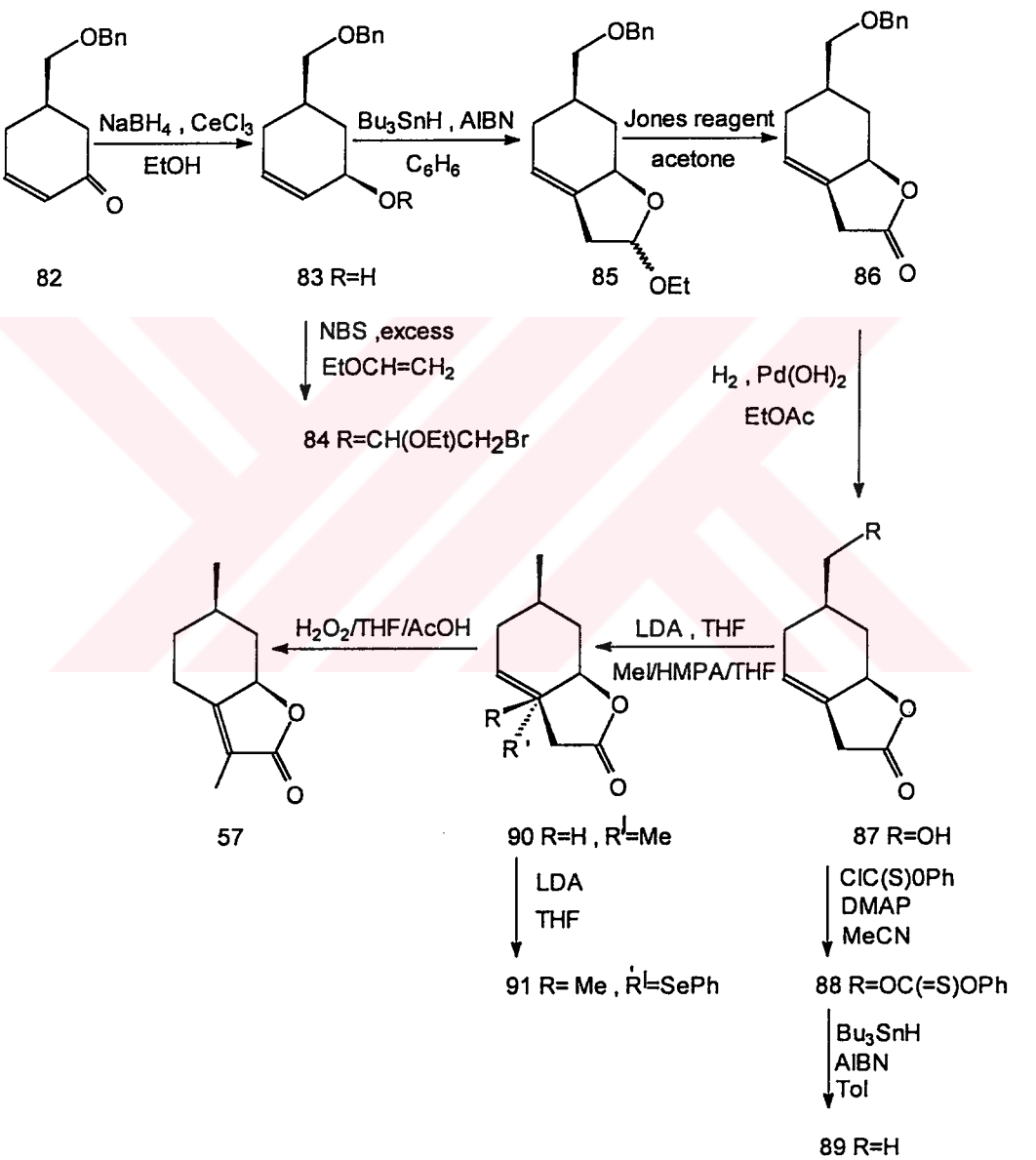


(eq 63)

Initial experiments for the conversion into (57) focused on the Evans[156] intramolecular hydride delivery of β-hydroxy ketone. Treatment of (78) with tetramethylammonium triacetoxyborahydride in acetonitrile-acetic acid at 40°C-room temperature for 6.5 hour afforded the corresponding diol. This diol was immediately treated with a catalytic amount of *p*-toluene sulfonic acid in methylene chloride to provide the lactones, (80) and (81) in 88% yield. A

mixture of these diastereomers (80 & 81) was easily separated in 30:1.[155] (eq 63)

Carda and et al. was described the total stereodirected synthesis of (-)-mintlactone in 1991.[157] (As shown in eq 64).

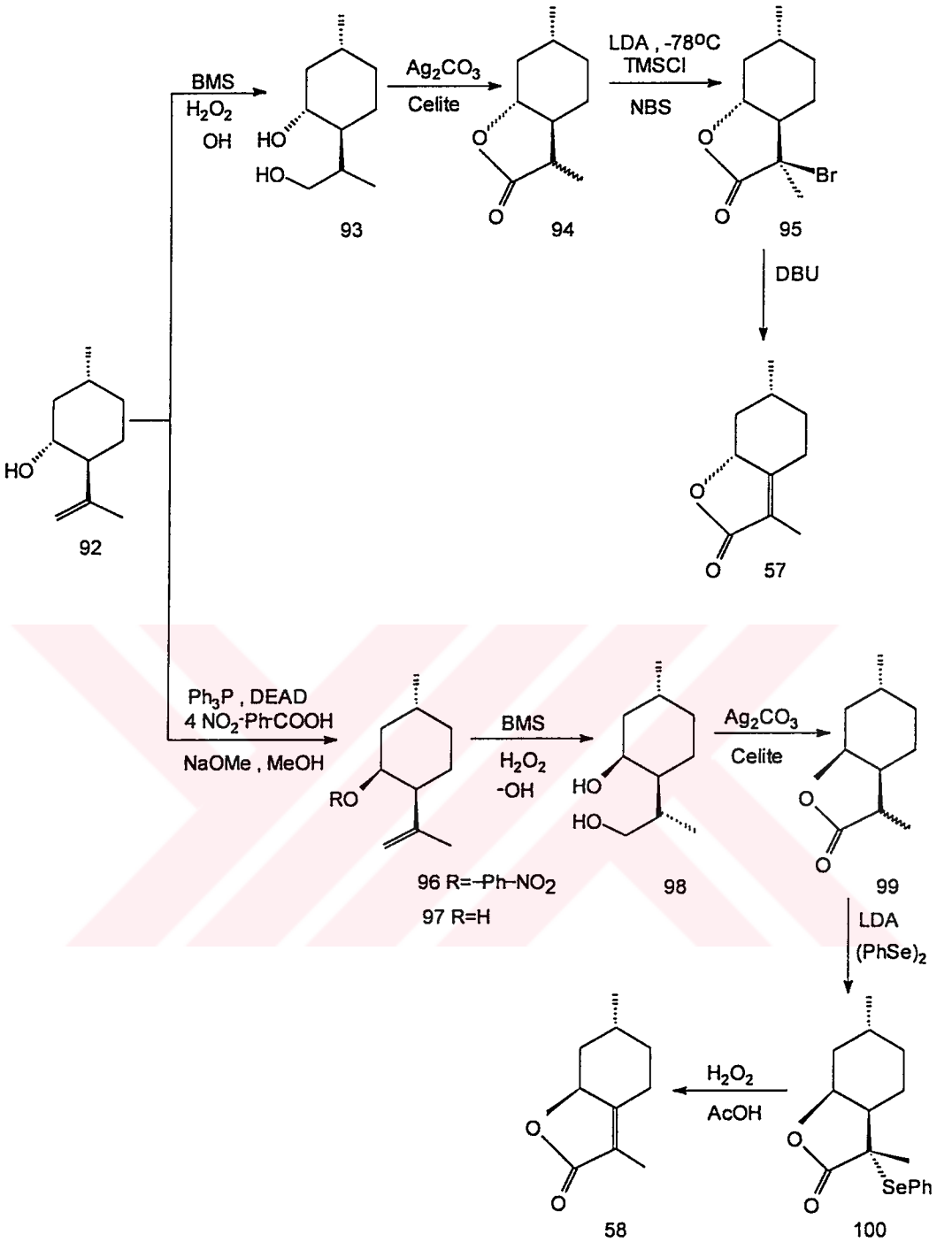


(eq 64)

Hydride reduction of (-)-(82) (>95% ee) [158] gave the allylic alcohol (83), which was then transformed into the bromoacetal by reaction with NBS at -40°C in vinyl ether as solvent [159]. Tri-n-butyltin hydride promoted the reductive ring closure under homolytic conditions [159,160] to the acetal (85) (diastereoisomeric mixture), which was then oxidized by Jones reagent to the stereocemically homogenous lactone (86) [161]. Debenzylation to (87) was best performed by hydrogenolysis with $Pd(OH)_2$ as catalyst, [162] which proved superior to Pd/C in terms of both yield and reactivity. Acylation of (87) with O-phenyl chlorothionoformate [163] gave (88), which was then treated with tri-n-butyltin hydride and AIBN in refluxing toluene. Lactone (89) was obtained in 62% overall yield from (87). Methylation of (89) via the enolate generated with LDA took place stereoselectivity from the less hindered α face, yielding (90), a dihydro derivative of (-)-mintlactone.

In 1993 Chavan and et al. [164] proposed that (-)-iso-pulegol (92) as a starting material for both (-)-mintlactone (57) as well as (+)-isomintlactone (58). Convertion of (-)-iso-pulegol (92) to (-)-mintlactone (57) was achieved by the following set of reactions. Hydroboration of (92) furnished the desired diol (93) in excellent yields (98%). The 1,4-diol (93) thus obtained was smoothly transformed to the butyrolactone (94) using Ag_2O_3/celite [165] in high yields (85%) as a mixture of diastereomers. Having constructed

dihydromintlactone (94), the next task was accomplished as follows. Treatment of the lactone (94) with LDA at -78°C and subsequent treatment of the resultant enolate, with chlorotrimethyl silane and NBS [166] furnished the bromolactone (95) in 95% yield. The final dehydrohalogenation of (95) was smoothly achieved by refluxing it in benzene (1 hour) in the presence of DBU [167] to furnish (-)-mintlactone (57) in 89% yield (eq 65).

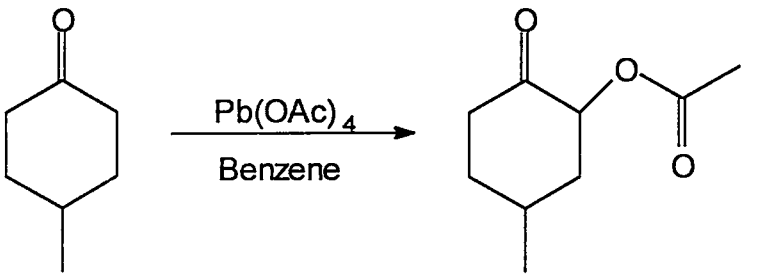

BMS
H_2O_2
OH
HO
HO
93
Ag_2CO_3
Celite
O
O
94
LDA , -78°C
TMSCl
NBS
O
O
Br
95
DBU
O
O
57
HO
92
Ph_3P , DEAD
4 NO_2-PhCOOH
NaOMe , MeOH
RO
96 R=-Ph-NO_2
97 R=H
BMS
H_2O_2
-OH
HO
HO
98
Ag_2CO_3
Celite
O
O
99
LDA
$(PhSe)_2$
H_2O_2
AcOH
O
O
58
O
O
SePh
100

(eq 65)

Iso-mintlactone (58) was also conveniently obtained from (92) by the following set of reactions. The stereochemistry at the C-OH centre was inverted by employing a modified version of Mitsonobu conditions [168]. Thus neo-iso-pulegol (97) was obtained from (92) through its 4-nitrobenzoate (96) followed by hydrolysis in 83% overall yields. Compound (97) was subjected to hydroboration to furnish diol (98) in excellent yields. Selective oxidation of the primary alcohol to the secondary alcohol with Ag_2CO_3/celite [165] in refluxing toluene at elevated temperature the lactone (99) was obtained in 69% yield. Treatment of (99) with LDA followed by quenching the anion with diphenyl diselenide furnished the selenolactone (100) in 82% yield. Oxidation of (100), with H_2O_2 furnished (+)-isomintlactone (58) [164].

2.6.1. The Synthesis of 2-Acetoxy-4-methyl cyclohexanone

In order to synthesize 2-acetoxy-4-methyl cyclohexanone (102), lead (IV) acetate was chosen as an alternative mild oxidizing agent and was treated with 4-methyl cyclohexanone (101) (eq 66).



(101) (102)

(eq 66)

We characterized the structure of 2-acetoxy-4-methyl cyclohexanone (102) by ^{1}H-NMR spectroscopy which shows two doublets arising from diastereomeric nature of the structure at 1.1 ppm for the CH_3 group attached to ring at 4th position and singlet at 2.1 ppm for methyl protons of acetyl group. The CH_2 protons of that ring at the 2nd, 3th, 5th positions have observed as multiplet at 1.60-2.45ppm. The chacteristic C<u>H</u>O proton exhibits doublet to doublet at 5.15 ppm.

The IR spectrum of compound (102) gives strong absorption band at 1734 cm^{-1} which belongs to carbonyl group.

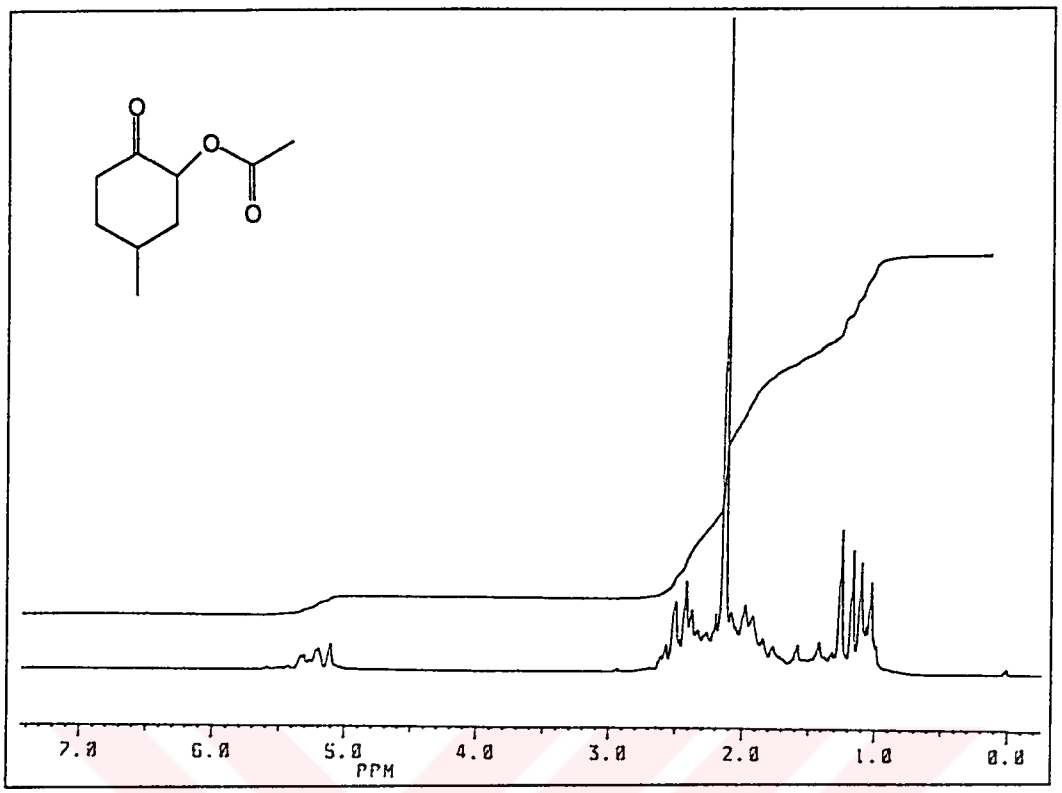
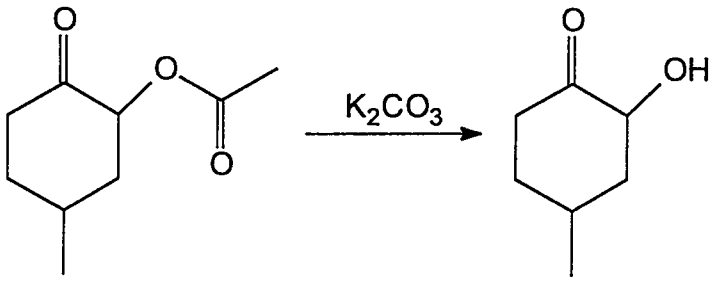


Figure 10. The ^{1}H-NMR Spectrum of 2-Acetoxy-4-methyl cyclohexanone

2.6.2. The Synthesis of 2-Hydroxy-4-methyl cyclohexanone.

In order to get 2-hydroxy-4-methyl cyclohexanone (103), K_2CO_3 was used in aqueous MeOH. The hydrolysis of 2-acetoxy-4-methyl cyclohexanone (102) with K_2CO_3 afforded the 2-hydroxy-4-methyl cyclohexanone (103) with high conversion (eq 67).



(102) (103)

(eq 67)

The ^{1}H-NMR spectrum of 2-hydroxy-4-methyl cyclohexanone exhibits two doublets at 0.78-1.1 ppm for C-4 attached CH_3 and multiplet at 1.6-2.25 ppm for the CH_2 protons of the ring at the 2nd, 3th, 5th positions. The OH proton gives broad peak at 3.6 ppm. And finally C<u>H</u>O proton appears as doublet to doublet at 4.9 ppm.

The IR spectrum of compound (103) shows characteristic OH absorption at 3469 cm^{-1} and characteristic carbonyl absorption at 1715 cm^{-1}.

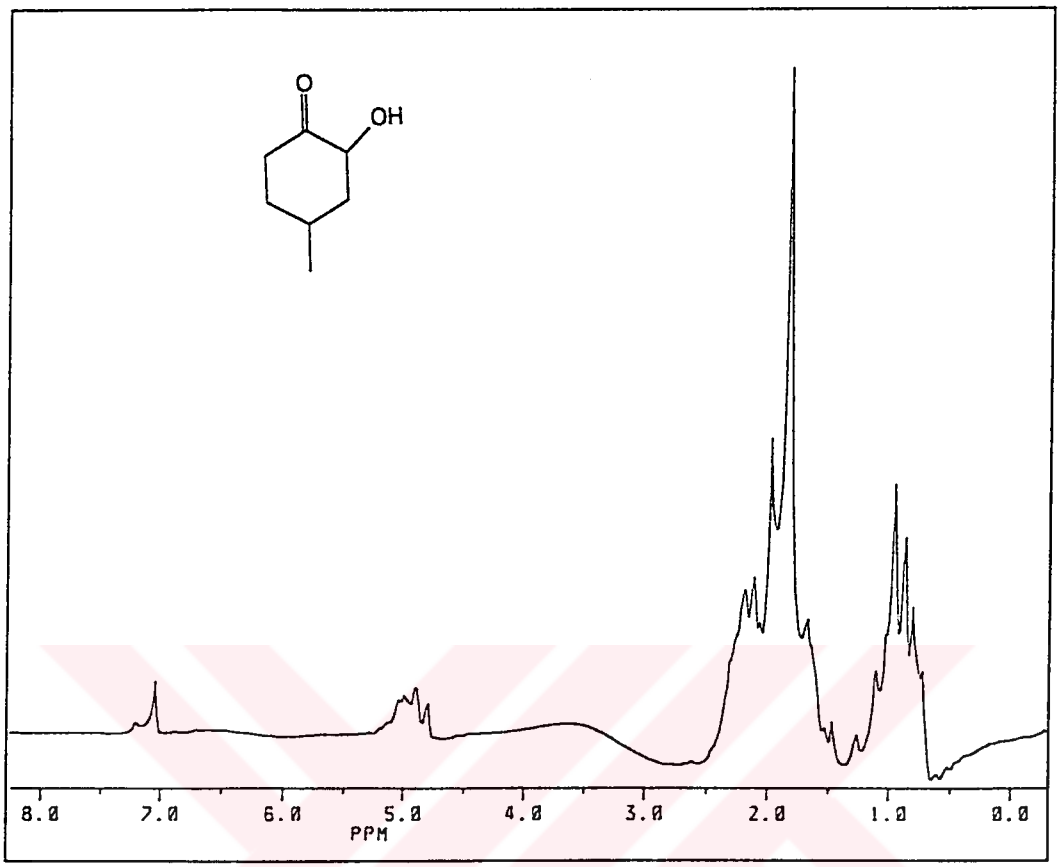
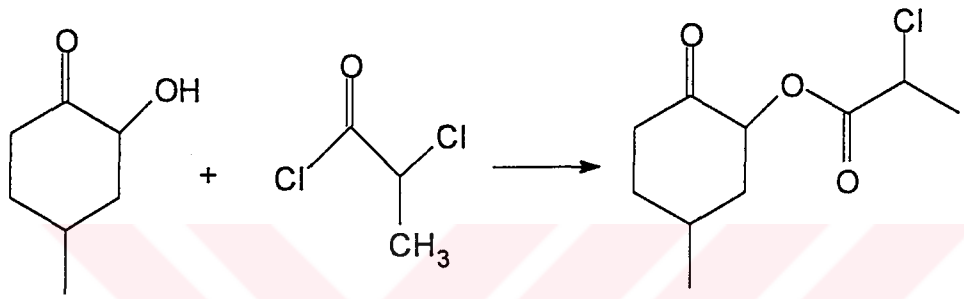


Figure 11. The ^{1}H-NMR Spectrum of 2-Hydroxy-4-methyl cyclohexanone

2.6.3. The Synthesis of 2-(2-Chloro propionyloxy)-4-methyl cyclohexanone

2-Hydroxy-4-methyl cyclohexanone (103) was reacted with chloropropionyl chloride in the presence of pyridine to yield 2-(2-chloro propionyloxy)-4-methyl cyclohexanone (104) (eq 68).



(103) (104)

(eq 68)

The ^{1}H-NMR spectrum of 2-(2-chloro propionyloxy)-4-methyl cyclohexanone (104) exhibits quarted at 4.45 ppm for C<u>H</u>Cl proton and, doublet to doublet at 5.1 ppm for the C<u>H</u>O proton.

The IR spectrum of compound (104) shows CH streching band between 3175-2927 cm^{-1}. The carbonyl groups give intense band at about 1734 cm^{-1}.

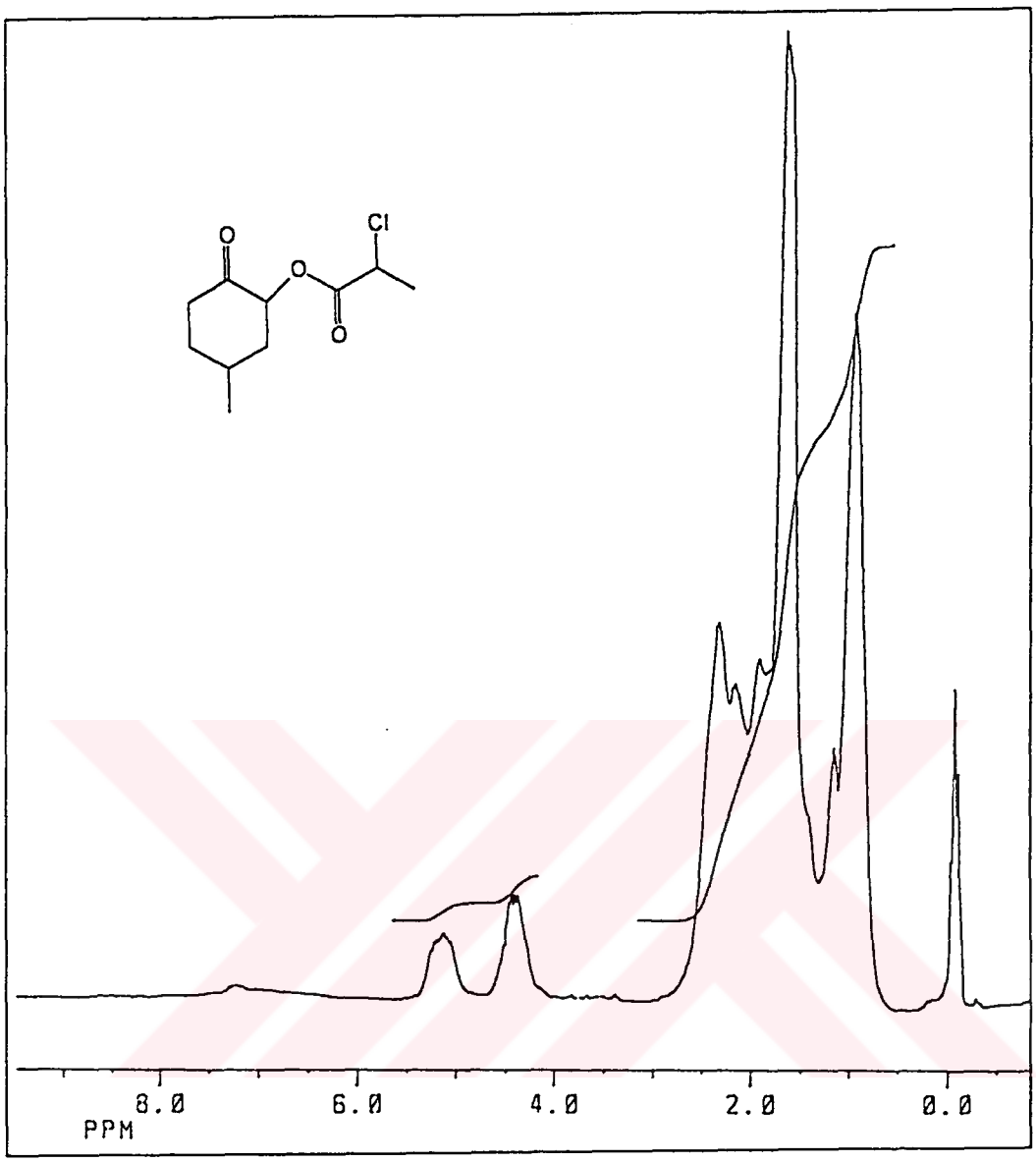
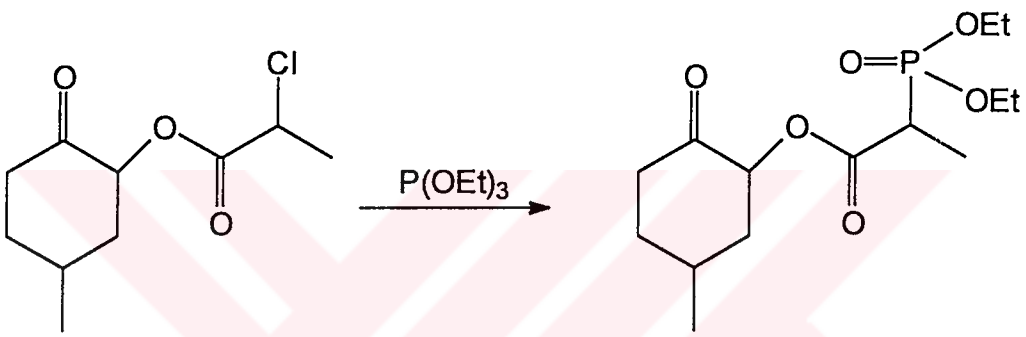


Figure 12. The 1H-NMR Spectrum of 2-(2-Chloro propionyloxy)-4-methyl cyclohexanone

2.6.4. The Synthesis of 3,6-Dimethyl-5,6,7,7a tetrahydro 2-(4H) benzofuranone (Mintlactone)

Arbuzov reaction of the compound (104) with triethyl phosphite was performed to obtain 2-(2-diethoxy phosphoryl) propionyloxy-4-methyl cyclohexanone (105) (eq 69).



(104) (105)

(eq 69)

The ^{1}H-NMR spectrum of 2-(2-diethoxy phosphoryl) propionyloxy-4-methyl cyclohexanone (105) exhibits multiplet at 0.7-0.95 ppm for $\underline{CH_3}$-CH_2 protons. The CH_3 protons which belongs to the ring appear two doublets at 1.18-1.40 ppm. The CH_2 protons of the ring show multiplet at 1.40-2.30 ppm. The CH_3-$\underline{CH_2}$ protons exhibit multiplet at 3.55-4.05 ppm. The C<u>H</u>P shows multiplet at 4.30-4.45 ppm. And then finally C<u>H</u>O proton appears doublet to doblet at 4.86-5.15 ppm.

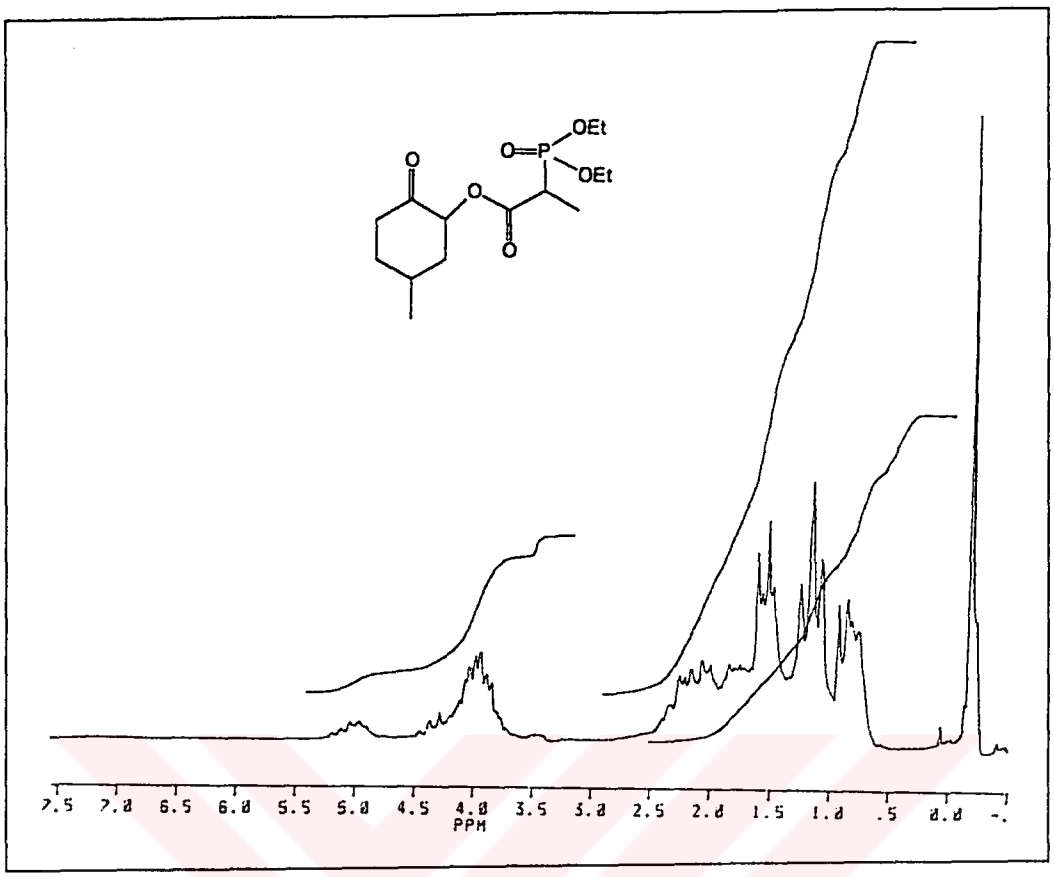
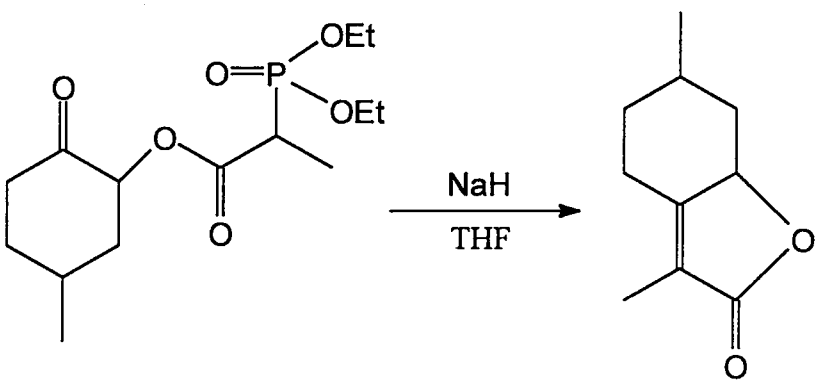


Figure 13. The ^{1}H-NMR Spectrum of 2-(2-Diethoxy phosphoryl) propionyloxy-4-methyl cyclohexanone

Intramolecular cyclization of 2-(2-diethoxy phosphoryl) propionyloxy-4-methyl cyclohexanone (105) in the presence of NaH was carried out to attain the mintlactone (106) (eq 70).



(105) (106)

(eq 70)

The ^{1}H-NMR spectrum of 3,6-dimethyl-5,6,7,7a-tetrahydro-2-(4H) benzofuranone (106) exhibits doublet at 0.98 ppm for the C-6 attached CH_3 and singlet at 1.25 ppm for the C-3 attached CH_3. The CH_2 protons of that ring the 4th, 5th, 6th positions have observed as multiplet at 1.40-2.60 ppm. Finally the CHO proton shows doublet of doublet at 4.18 ppm. All these data are in accordance with the literature values.

The IR spectrum of compound shows carbonyl absorption band at 1750 cm^{-1}.

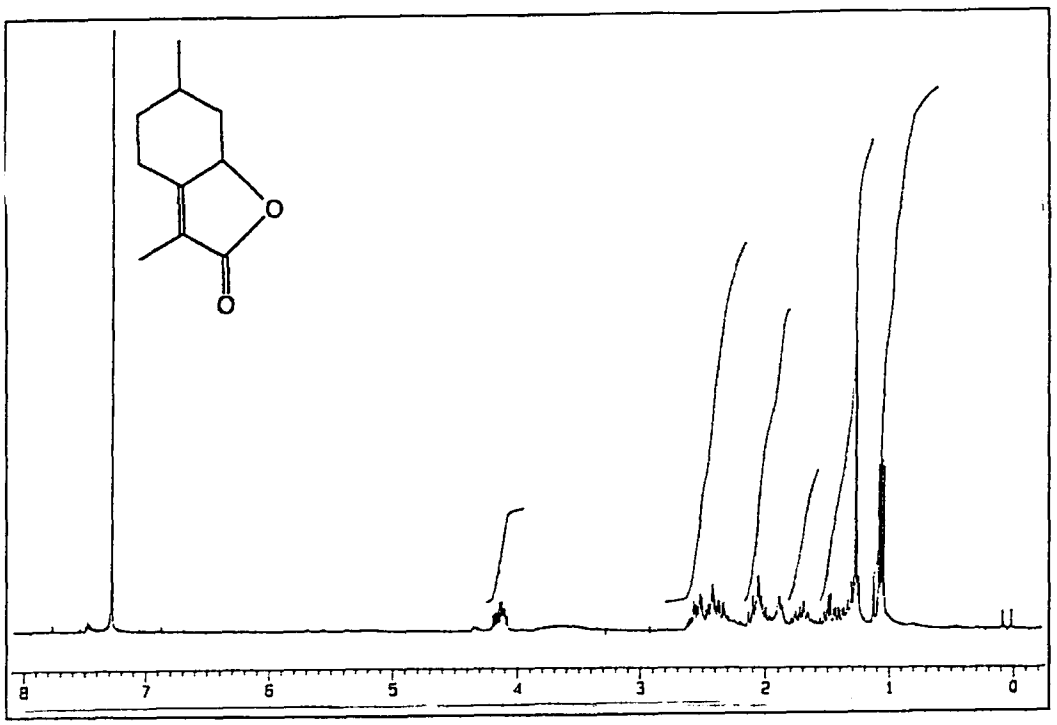
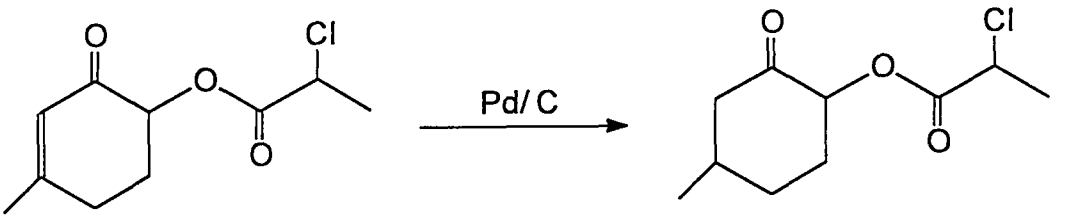


Figure 14. The ^{1}H-NMR Spectrum of The Mintlactone

2.7. The Synthesis of 2-(2-Chloro propionyloxy)-5-methyl cyclohexanone

The aim of this part of the work is to show the applicability of the manganese (III) acetate oxidation to the synthesis of some target butenolides, containing saturated cyclic six-membered moity. For this purpose 3-methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (42) was hydrogenated with in the presence of Pd/C to afford 2-(2-chloro propionyloxy)-5-methyl cyclohexanone.

This route proves us the manganese (III) acetate oxidation is able to be applicable to the synthesis of some butenolide containing saturated six-membered cyclic moity.



(42) (104)

(eq 71)

The ^{1}H-NMR spectrum of the 2-(2-chloro propionyloxy)-5-methyl cyclohexanone in high field region gives complex signals which belong the methyl protons of the ring. Some characteristic signals can be resolved such as CHCl signals gives quarted at 4.4-4.65 ppm, and CHO gives doublet of doublet at 5.08-5.30 ppm.

The IR spectrum of the compound (104) for the carbonyl groups have been observed at 1715 and 1637 cm^{-1}.

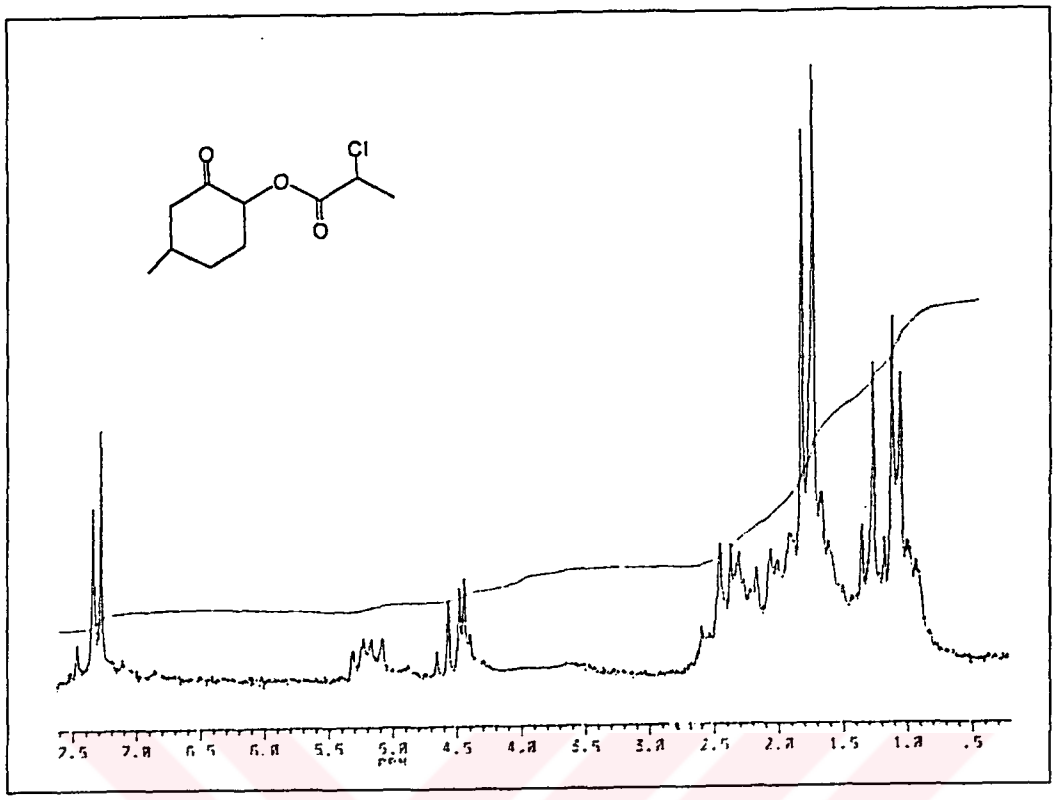


Figure 15. The ^{1}H-NMR Spectrum of The 2-(2-Chloro propionyloxy)-5-methyl cyclohexanone

CHAPTER 3

EXPERIMENTAL

The compounds in this study were identified by the instruments mentioned below.

Nuclear magnetic resonance (^1H) spectra were carried out with a Brucker GmbH DPX-400, 400 MHz High Performance Digital FT-NMR Spectrometer (TUBITAK) and Brucker AC 80 MHz FT-NMR spectrometer by using $CDCl_3$ as a solvent and TMS as an internal reference.

Infrared spectra were recorded with Perkin Elmer 16 PC FT-IR spectrometer by using $CHCl_3$ as a solvent or a neat.

Flash column chromatography was performed using thick-walled glass columns and flash grade silica (Machery-Nagel Kieselgel 60-400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25-mm silica gel plates purchased from Machery-Nagel. The relative

proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio.

3.1. Synthesis of Anhydrous Manganese (III) Acetate

150 ml of acetic anhydride was taken in a round bottomed flask and heated to 50°C. At this temperature 40 g (0.16 mol) of Manganese (II) nitrate tetrahydrate was slowly added. The mixture was warmed for 4 hour at 70°C. Then the mixture was allowed to cool to room temperature and after 24 hour the dark brown solids washed with 100 ml of dry ether and dried over P_2O_5 for 2 hours (30 g, 75% yield).

3.2. Synthesis of α′-Acyloxy Enones

3.2.1. Synthesis of 3-Methyl-cyclohex -2-en-1-one

130g (1.0 mol) of ethylacetoacetate, 15g (0.5 mol) of powdered paraformaldehyde and 5g (0.059 mol) of piperidine was mixed at room temperature. After 20 minutes the mixture was heated up and the solid paraformaldehyde began to dissolve. The reaction was moderated by cooling in ice-water. After the vigorous reaction was over the mixture was refluxed for 1 hour. Then 300 ml of glacial acetic acid, 30 ml of H_2SO_4 and 200 ml of H_2O

was added and solution was refluxed for 6 hours. 254 g of NaOH in 700 ml of water was added to the cooling mixture. Then the mixture was extracted with ether and dried over Na_2SO_4. The product was purified by distillation under reduced pressure (70 g, 53 %). $C_7H_{10}O$: 109.9 g/mol B.P.: 55° C at 17 mm-Hg.

1H-NMR ($CDC1_3$) :

δ (ppm): 1.8 (s, 3H, CH_3)

1.90-2.30 (m, 6H, CH_2)

5.60 (s,1H,H)

IR (neat):

ν (max): 3010-2890, 1690 cm^{-1}

Rf : 0.55 (Silica gel - EtOAc-Hex:1:2)

3.2.2. Synthesis of 3-Methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (42)

A mixture of 2.12g (10 mmol) of manganese (III) acetate and 3.25 g (30 mmol) of 2-chloro propionic acid in 100 ml of benzene was refluxed for 2.5 hour under a Dean-Stark trap. 0.455g (2.5 mmol) of 3-Methyl-cyclohexanone

was added and the mixture was refluxed for 40 h and it was cooled to 25°C. The mixture was diluted with ethyl acetate; washed successively with 1M aqueous HCl solution (3x75 ml), saturated aqueous $NaHC0_3$ solution; and brine and dried over anhydrous $MgS0_4$. The product was isolated by column chromatography (flash silica gel-1:4 EtOAc - Hexane solvent system) as an oil. Yield 55 %

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.70 (d, 3H,CH_3)

1.90 (s, 3H,CH_3)

2.10-2.50 (m, 4H, CH_2)

4.30-4.61 (q, 1H, CHCl)

5.20-5.45 (d.d, 1H, α'-CH)

5.85 (s,1H, α-CH_{olef})

IR ($CDCl_3$):

ν (max): 1752,1665 cm^{-1}

Rf: 0.43 (Silica gel-EtOAC:Hexane:1:4)

3.2.3. The Synthesis of 6-(2-Chloro propionyloxy) 3,5,5-trimethyl cyclohex-2-en-1-one (44)

A mixture of 3.47g (0.015 mol) manganese (III) acetate and 4.89g (0.045 mol) 2-chloropropionic acid in 100ml benzene was refluxed for 2 h under Dean- Stark trap. The mixture was cooled to 25°C, and 1.38g (0.01 mol) of isophorone was added. The mixture refluxed for 10 h and it was cooled to 25°C, diluted with ethyl acetate, washed with 1M hydrochloric acid solution, aqueous saturated sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulfate. The crude product was isolated by column chromatography (flash silica gel-1:4: EtOAc:Hexane solvent system) as an oil. Yield 75%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.00 (s, 6H, CH_3)

1.00-1.10 (d, 3H, $CHClCH_3$)

2.00 (s,3H,CH_3)

2.20 (s, 2H, CH_2)

4.50-4.65 (q, 1H, CHCl)

5.20 (s, 1H, α'-CH)

5.90 (s, 1H, α-CH_{olef})

IR ($CDCl_3$):

ν (max): 1743,1687 cm^{-1}

Rf: 0.51 (Silica gel- EtOAc:Hexane:1:4)

3.2.4. The Synthesis of 4,4-Dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one (46)

A mixture of 3.47g (0.015 mol) manganese (III) acetate and 4.89g (0.045 mol) 2-chloropropionic acid in 100ml benzene was refluxed for 2 h under Dean- Stark trap. The mixture was cooled to 25°C, and 1.24 g (0.01 mol) of 4,4-dimethyl cyclohexenone was added. The mixture refluxed for 6 h and it was cooled to 25°C, diluted with ethyl acetate, washed with 1M hydrochloric acid solution, aqueous saturated sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulfate. The crude product was isolated by column chromatography (flash silica gel-1:4: EtOAc:Hexane solvent system) as an oil. Yield 80%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.15 (s, 6H, CH_3)

1.20-1.30 (d, 3H, $CHClCH_3$)

1.70-2.50 (m, 2H, CH_2)

4.35-4.65 (q, 1H, CHCl)

5.80 (d.d, 1H, α'-CH)

6.60 (d, 1H, H_{olef})

6.75 (d,1H, α-CH_{olef})

IR ($CDCl_3$):

ν (max): 1752,1706 cm^{-1}

Rf: 0.65 (Silica gel-EtOAC:Hexane:1:4)

3.2.5. The Synthesis of 4,4-Diphenyl-6-(2-chloro propionyloxy) cyclohex-2en-1-one (48)

A mixture of 2 g ($8.6x10^{-3}$ mol) manganese (III) acetate and 2.80 g (0.0258 mol) 2-chloropropionic acid in 100ml benzene was refluxed for 2 h under Dean- Stark trap. The mixture was cooled to 25°C, and 1.00 g ($4.3x10^{-3}$ mol) of isophorone was added. The mixture refluxed for 8 h and it was cooled to 25°C, diluted with ethyl acetate, washed with 1M hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulfate. The crude product was isolated by column chromatography (flash silica gel-1:4: EtOAc:Hexane solvent system) as an oil. Yield 72 %

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.60-1.70 (d,3H, $CHClCH_3$)

2.30-3.00 (m, 2H, CH_2)

4.30-4.60 (q,1H CHCl)

5.25-5.55 (d.d, 1H, α′-CH)

6.10 (s,1H, H_{olef})

6.25 (s, 1H, α-CH_{olef})

7.00-7.25 (m,10H, C_6H_5)

IR ($CDCl_3$):

ν (max): 1752,1706 cm^{-1}

Rf: 0.60 (Silica gel-EtOAc:Hexane:1:4)

3.2.6. The Synthesis of 2-(2-Chloro propionyloxy)-5-methyl cyclohexanone (104)

A mixture of 3-methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one 0.57 g ($2.6x10^{-3}$ mol) and Pd/C 0.05 g ($5.2x10^{-4}$ mol) in 50 ml ethanol was stirred under hydrogen atmosphere at room temperature for 10 h. Filtration through a filter funnel and evaporation of the filtrate under vacuum yielded 3-methyl-α-(2-chloro) propionyloxy cyclohexanone. Yield 75%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.02-1.10 (d, 3H, $CHClCH_3$)

1.65-1.70 (d, 3H, CH_3)

1.90-2.50 (m, 6H, CH_2)

4.40-4.65 (q, 1H, CHCl)

5.08-5.30 (d.d, 1H, CHO)

IR ($CDCl_3$):

ν (max): 1715,1637 cm^{-1}

Rf: 0.22 (Silica gel-EtOAc:Hexane:1:4)

3.3. Products of Arbuzov Reaction

3.3.1. The Synthesis of 3-Methyl-6-(2-diethoxy phosphoryl)-propionyloxy cyclohex-2-en-1-one (49)

A mixture of 3-methyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one 0.57 g ($2.60x10^{-3}$ mol) and triethyl phosphite 1.73 g (0.0104 mol) was refluxed under Argon atmosphere for 3 h. The excess of triethyl phosphite was distilled off under vacuum. Yield 80%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.4-1.75 (m, 6H, $\underline{CH_3}$-CH_2)

1.70 (d, 3H, CHCl$\underline{CH_3}$)

1.90 (s, 3H, CH_3)

2.25-2.55 (m, 4H, CH_2)

3.90-4.10 (m, 4H, CH_3-$\underline{CH_2}$)

3.90-4.10 (m, 1H, C$\underline{H}$P)

5.30 (d.d, 1H, α′-CH)

5.85 (s, 1H, α-CH)

R_f = 0.30 (Silica gel-EtOAc:Hexane:1:4)

3.3.2. The Synthesis of 6-(2-Diethoxy phosphoryl)-propionyloxy 3,5,5 trimethyl cyclohex-2-en-1-one (51)

A mixture of 6-(2-chloro propionyloxy) 3,5,5-trimethyl cyclohex-2-en-1-one 1.00 g ($4.08x10^{-3}$ mol) and triethyl phosphite 2.03 g (0.012 mol) was refluxed under Argon atmosphere for 3 h. The excess of triethyl phosphite was distilled off under vacuum. Yield 79%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.00 (s, 6H, CH_3)

1.20-1.40 (m, 6H, $\underline{CH_3}$-CH_2)

2.00 (s, 3H, CH_3)

2.20 (s, 2H, CH_2)

2.60 (m, 1H, C$\underline{H}$P)

4.00-4.50 (m, 4H, CH_3-$\underline{CH_2}$)

5.20 (s, 1H, α'-CH)

5.85 (s, 1H, α-CH)

R_f = 0.33 (Silica gel-EtOAc:Hexane:1:4)

3.3.3. The Synthesis of 4,4-Dimethyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one (53)

A mixture of 4,4-dimethyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one 0.5 g (2.17×10^{-3} mol) and triethyl phosphite 1.21 g (7.3×10^{-3} mol) was refluxed under Argon atmosphere for 3 h. The excess of triethyl phosphite was distilled off under vacuum. Yield 84%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.1 (s, 6H, CH_3)

1.20-1.85 (d, 3H, CHP$\underline{CH_3}$)

1.20-1.85 (m, 6H, $\underline{CH_3}$-CH_2)

2.10-2.26 (m, 2H, CH_2)

4.00-4.25 (m, 4H, CH_3-$\underline{CH_2}$)

4.00-4.25 (m, 1H, C$\underline{H}$P)

5.6-5.92 (d.d, 1H, α'-CH)

5.6-5.92 (d, 1H, α-CH)

6.70 (d, 1H, β-CH)

R_f = 0.60 (Silica gel-EtOAc:Hexane:1:4)

3.3.4. The Synthesis of 4,4,-Diphenyl-6-(2-diethoxy phosphoryl)-propionyloxy cyclohex-2-en-1-one (54)

A mixture of 4,4-diphenyl-6-(2-chloro propionyloxy) cyclohex-2-en-1-one 0.6 g (2.70 x10^{-3} mol) and triethyl phosphite 0.9 g (5.75x10^{-3} mol) was refluxed under Argon atmosphere for 3 h. The excess of triethyl phosphite is distilled under vacuum. Yield 75%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.05-1.50 (m, 6H, $\underline{CH_3}$-CH_2)

1.20-1.30 (d, 3H, CHP$\underline{CH_3}$)

2.85-2.98 (m, 2H, CH_2)

3.80-4.20 (m, 4H, CH_3-$\underline{CH_2}$)

3.80-4.20 (m, 1H, C$\underline{H}$P)

5.10 (d.d, 1H, α′-CH)

6.01 (d, 1H, α-CH)

6.24 (d, 1H, β-CH)

6.90-7.50 (m, 10H, C6H5)

R_f = 0.50 (Silica gel-EtOAc:Hexane:1:4)

3.4. Products of Horner Emmons Cyclization Reaction

3.4.1. The Synthesis of 3,5-Dimethyl-6,7a-dihydro-2-(2H) benzofuranone (50)

3-Methyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one 0.86 g ($2.70x10^{-2}$) was dissolved in anhydrous THF (30 ml) and added dropwise NaH 0.13 g ($5.4x10^{-3}$ mol) in the same solvent under Argon atmosphere. The mixture was refluxed for 4 h. The cooled mixture was

quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Yield 70%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.85 (s, 3H, CH_3)

1.95 (s, 3H, CH_3)

2.20-2.52 (m, 4H, CH_2)

5.35 (d.d, 1H, CHO)

5.90 (s,1H, H_{olef})

IR ($CDCl_3$):

ν (max): 1740, 1600 cm^{-1}

R_f = 0.30 (Silica gel-EtOAc:Hexane:1:4)

3.4.2. The Synthesis of 3,5,7,7a-Tetramethyl-6,7a-dihydro-2-(2H) benzofuranone (52)

6-(2-Diethoxy phosphoryl) propionyloxy 3,5,5-trimethyl cyclohex-2-en-1-one 0.50 g ($1.44x10^{-2}$) was dissolved in anhydrous THF (30 ml) and added dropwise NaH 0.062 g ($2.59 x10^{-3}$ mol) in the same solvent under Argon atmosphere. The mixture was refluxed for 4 h. The cooled mixture was

quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Yield 72%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.10-1.22 (s,3H, CH_3)

1.40 (s,3H,CH_3)

1.50 (s,3H, CH_3)

2.20 (s, 2H, CH_2)

4.97 (s, 1H, CHO)

6.55 (s, 1H, H_{olef})

IR ($CDCl_3$):

ν (max): 1750, 1600 cm^{-1}

R_f = 0.52 (Silica gel-EtOAc:Hexane:1:4)

3.4.3. The Synthesis of 3-Methyl-6,6-diphenyl-7,7a-dihydro-2-(2H) benzofuranone (55)

4,4-Diphenyl-6-(2-diethoxy phosphoryl) propionyloxy cyclohex-2-en-1-one 0.80 g ($1.75x10^{-3}$) was dissolved in anhydrous THF (30 ml) and added dropwise NaH 0.075 g ($3.15x10^{-3}$ mol) in the same solvent under Argon

atmosphere. The mixture was refluxed for 4 h. The cooled mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Yield 76%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.28 (s, 3H, CH_3)

1.25-1.35 (d, 2H, CH_2)

4.10 (d.d, 1H, CHO)

6.01 (d, 1H, H_{olef})

6.43 (d, 1H, α-H)

IR ($CDCl_3$):

ν (max): 1748, 1670 cm^{-1}

R_f = 0.58 (Silica gel-EtOAc:Hexane:1:4)

3.5. The Synthesis of Mintlactone

3.5.1. The Synthesis of 2-Acetoxy-4-methyl cyclohexanone (102)

4-Methyl cyclohexanone 1.12 g ($4x10^{-2}$ mol) and lead (IV) acetate 3.95 g ($4x\ 10^{-2}$) in 15 ml benzene were heated at 80°C until no test for the oxidant is

obtained. The mixture was washed with H_2O (4x20), and dried with $MgSO_4$. Yield 80%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 0.75-0.98 (m, 3H, CH_3)

2.10 (s, 3H, CH_3)

1.60-2.45 (m, 6H, CH_2)

5.15 (d.d, 1H, CHO)

IR ($CDCl_3$):

ν (max): 1734 cm^{-1}

R_f = 0.54 (Silica gel-EtOAc:Hexane:1:4)

3.5.2. The Synthesis of 2-Hydroxy-4-methyl cyclohexanone (103)

1.6 g (0.0117 mol) K_2CO_3 was dissolved in MeOH until small portions of K_2CO_3 was remained, by using small as possible amount of water remaining K_2CO_3 was dissolved. It was added to mixture slowly and solution is stirred at

RT for 15 minutes. After acidification by 1N HCl, the solution was extracted with ethyl acetate. Yield 95%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 0.78-1.10 (m, 3H, CH_3)

1.60-2.25 (m, 6H, CH_2)

3.60 (broad, 1H, OH)

5.10 (d.d, 1H, CHO)

IR ($CDCl_3$):

ν (max): 3469, 1715 cm^{-1}

R_f = 0.26 (Silica gel-EtOAc:Hexane:1:4)

3.5.3. The Synthesis of 2-(2-Chloro propionyloxy)-4-methyl cyclohexanone (104)

2-Hydroxy-4-methyl cyclohexanone 1.00 g (0.0078 mol) dissolved in 15 ml benzene was mixed with dry pyridine 0.6 g (0.0083 mol). This mixture was kept and stirred in ice bath for 20 minutes. Then to this mixture chloro propionyl chloride 1.38 g (0.0111 mol) was added dropwise under Argon

atmosphere. Mixture was kept 1.5 h in ice bath and 2 h at RT. Then the mixture was extracted with water (2x10). Yield 84%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 1.65 (d, 3H,CH_3)

1.80 (d, 3H, $CHClCH_3$)

1.85-2.45 (m, 6H, CH_2)

4.45 (q, 1H, CHCl)

5.10 (d.d, 1H, CHO)

IR ($CDCl_3$):

ν (max): 1734 cm^{-1}

R_f = 0.62 (Silica gel-EtOAc:Hexane:1:4)

3.5.4. The Synthesis of 2-(2-Diethoxy phosphoryl) propionyloxy-4-methyl cyclohexanone (105)

A mixture of 2-(2-chloro propionyloxy)-4-methyl cyclohexanone 0.57 g (0.0026 mol) and triethyl phosphite 1.73 g (0.010 mol) was refluxed under Argon atmosphere for 3 h. The excess of triethyl phosphite was distilled off under vacuum. Yield 77%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 0.7-0.95 (m, 6H, $\underline{CH_3}$-CH_2)

1.18 (d, 3H, CH_3)

1.40-2.30 (m, 6H, CH_2)

3.55-4.05 (m, 4H, CH_3-$\underline{CH_2}$)

4.30-4.45 (m, 1H, C$\underline{H}$P)

4.86-5.15 (d.d, 1H, C$\underline{H}$O)

R_f = 0.45 (Silica gel-EtOAc:Hexane:1:4)

3.5.5. The Synthesis of Mintlactone (106)

2-(2-Diethoxy phosphoryl) propionyloxy-4-methyl cyclohexanone 0.70 g (0.0022 mol) was dissolved in anhydrous THF (30 ml) and added dropwise NaH 0.096 g (0.004 mol) in the same solvent under Argon atmosphere. The mixture was refluxed for 4 h. The cooled mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (flash silica gel 1:4 EtOAc:Hexane solvent system). Yield 75%

^{1}H-NMR ($CDCl_3$):

δ (ppm): 0.98 (d, 3H, CH_3)

1.25 (s, 3H, CH_3)

1.10-1.28 (m, 6H, CH_2)

4.18 (d.d, 1H, CHO)

IR ($CDCl_3$):

ν (max): 1750, 1690 cm^{-1}

R_f: 0.75 (Silica gel-EtOAc:Hexane:1:4)

CHAPTER 4

CONCLUSION

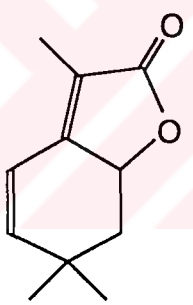
In this study, we developed a short and efficient synthetic pathway to obtain various butenolides. We focused our attention to the synthesis of butenolides because of their biological activity.

In the last part of this study, we applied short and efficient synthetic route described in the thesis to the synthesis of (+/-)-Mintlactone.

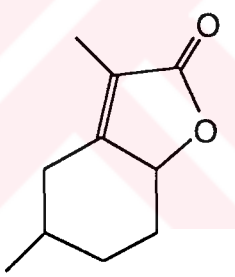
In the beginning of the butenolide synthesis, regioselective oxidation of the α′-position of various cyclic enones in the presence of manganese (III) acetate and chloropropionic acid was achieved. The resultant α′-chloro acyloxy products, which were shown in Table 16, occur frequently as the structural units of many natural products and they have functionalities suitable for a wide range of chemical manipulations.

Second reaction was an Arbuzov reaction. In this reaction α′-(2-chloro propionyloxy) cyclic enones with excess triethyl phosphite gave the corresponding α′-(2-diethoxy phosphoryl) propionyloxy enones with high chemical yield (shown in Table 17)

Finally Horner-Emmons type cyclization reactions, which gave butenolides were achived (shown in Table 18). At the end of cyclization reactions we observed that, some separation problems were arose for 3,6,6-trimethyl-7,7a-dihydro-2-(2H) benzofuranone (56) and 3,5-dimethyl-5,6,7,7a-tetrahydro-2-(4H) benzofuranone (107).



(56)

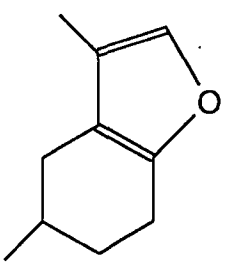


(107)

The resultant product of 3,6,6-trimethyl-7,7a-dihydro-2-(2H) benzofuranone (56) was synthesized starting from the 4,4-dimethyl cyclohex-2-ene-1-one. From the NMR spectrum of this compound, we could decide that, the cyclization reaction was achieved. However the NMR spectrum also show

the aromatic signals. Because of separation problem, we could not determine the structure of the mixture.

In order to synthesize isomenthofuran (108), which is another important butenolide system 3-methyl-cyclohex-2-en-1-one was selectively oxidized with manganese (III) acetate and chloropropionic acid, and subsequent reduction with Pd/C catalyst yielded 2-(2-chloropropionyloxy)-3-methyl cyclohexanone (104). The Arbuzov reaction of compound (104) and then intramolecular Horner-Emmons type cyclization provided a synthesis of 3,5-dimethyl-5,6,7,7a-tetrahydro-2-(4H) benzofuranone. The 3,5-dimethyl-5,6,7,7a-tetrahydro-2-(4H) benzofuranone could be obtained by this way but because of purification problem, it was not determined. If we solved this problem, we could be get isomenthofuran via reduction of this compound by using DIBAL-H.



(108)

In addition to this study, we obtained (+/-)-Mintlactone, which was minor components of important essential oils found in peppermint oil and spearmint oil (+/-)-Mintlactone possesses a butenolide moity as the essential component.

There are several literature methods on the synthesis of (+/-)-mintlactone. Carda et al reported the synthesis of (-)-mintlactone via intramolecular cyclization as the key step comprising of more than twelve steps. [157]

Recently Shishido et al reported the total synthesis of (+/-)-mintlactone involving an intramolecular [3+2] cycloaddition reaction to generate the butenolide as key step more than nine steps.[154]

(+/-)-Mintlactone could be isolated with six steps by Corey et al. [169]

Chavan et al have also reported the synthesis of (+/-)-mintlactone from (-)-isopulegol was achieved by the six steps. [164]

We have described a short and efficient synthesis of (+/-)-Mintlactone from easily available starting material. In our study (+/-)-Mintlactone could be synthesized with five step. It was realized that 4-methyl cyclohexanone ideal

starting material for (+/-)-Mintlactone. Conversion of 4-methyl cyclohexanone to (+/-)-Mintlactone was achieved by the following set of reactions; Alternative mild oxidation reaction was performed by using lead (IV) acetate. In this way 2-acetoxy-4-methyl cyclohexanone was obtained. Hydrolysis of 2-acetoxy-4-methyl cyclohexanone was done by using K_2CO_3 in aqueous MeOH. The 2-(2-chloro propionyloxy)-4-methyl cyclohexanone was obtained by using 2-hydroxy-4-methyl cyclohexanone and chloro propionyl chloride. And then Arbuzov reaction followed by intramolecular Horner-Emmons type cyclization reaction provided a convenient synthesis of (+/-)-Mintlactone.

All products were characterized by ^{1}H-NMR and IR spectroscopy.

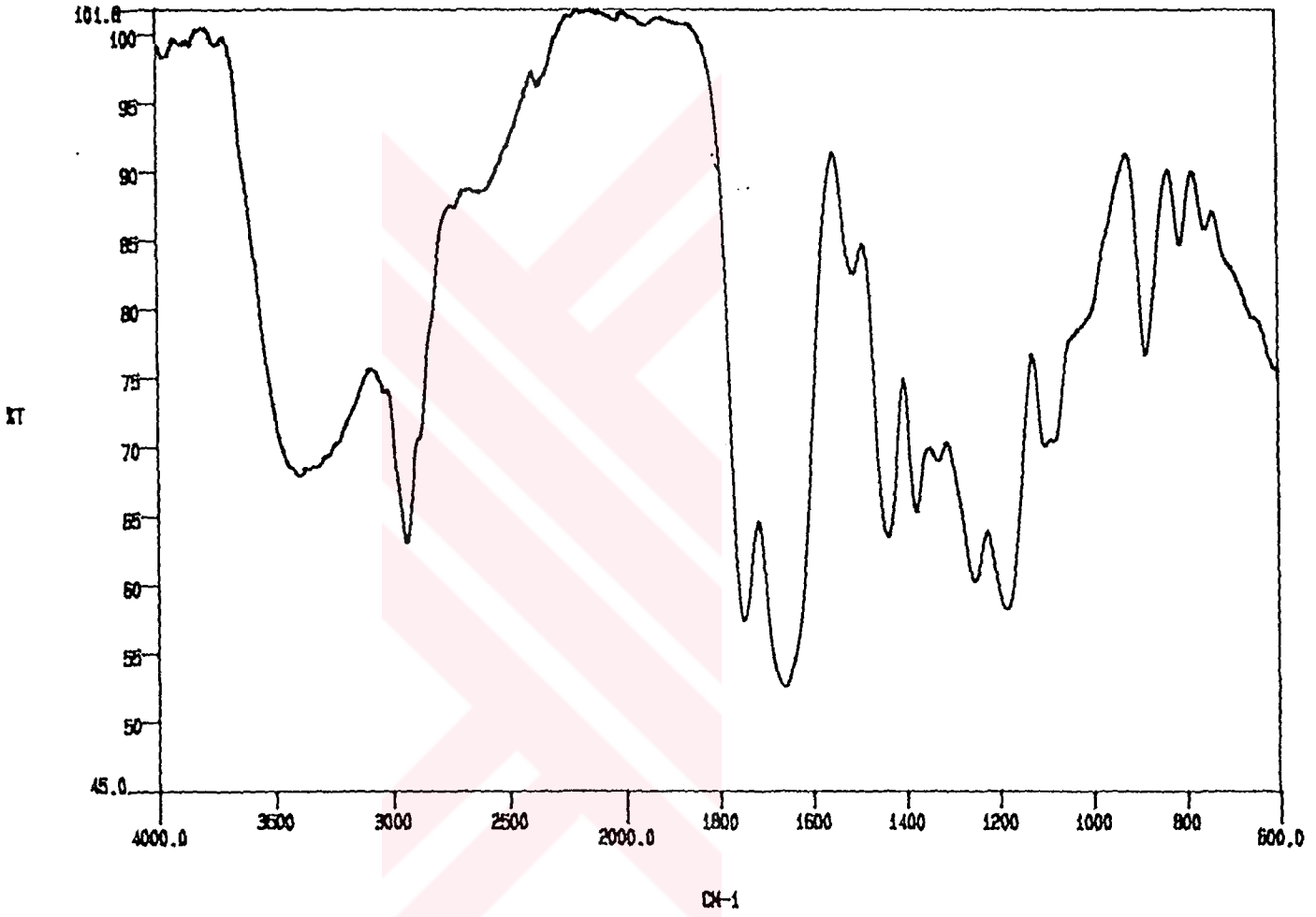


Figure 16. The IR Spectrum of 3-Methyl-6-(chloropropionyloxy) cyclohex-2-en-1-one

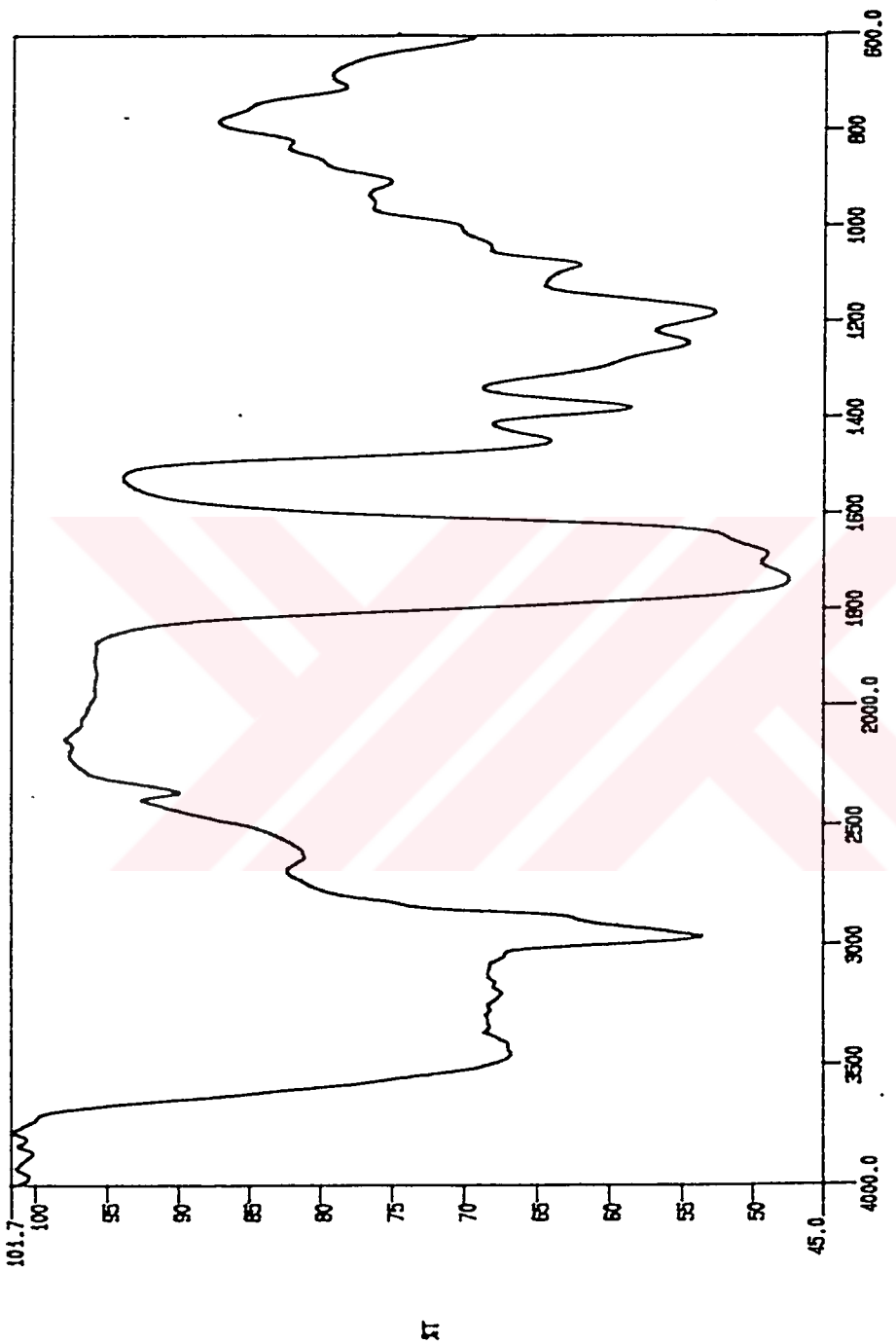


Figure 17. The IR Spectrum of 6-(2-chloropropionyloxy)-3,5,5-trimethyl-cyclohex-2-en-1-one

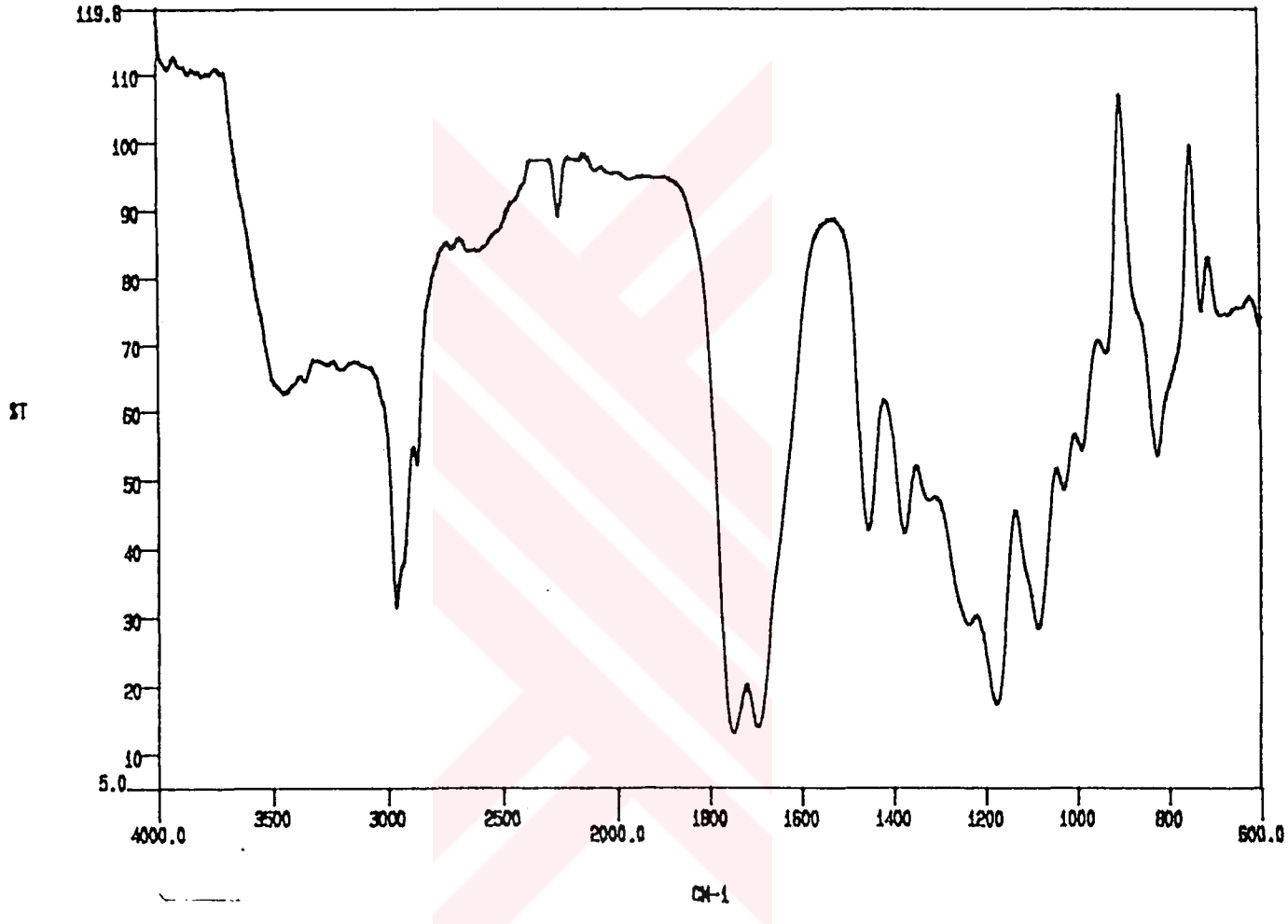


Figure 18. The IR Spectrum of 4,4-Dimethyl-6-(2-chloropropionyloxy) cyclohex-2-en-1-one

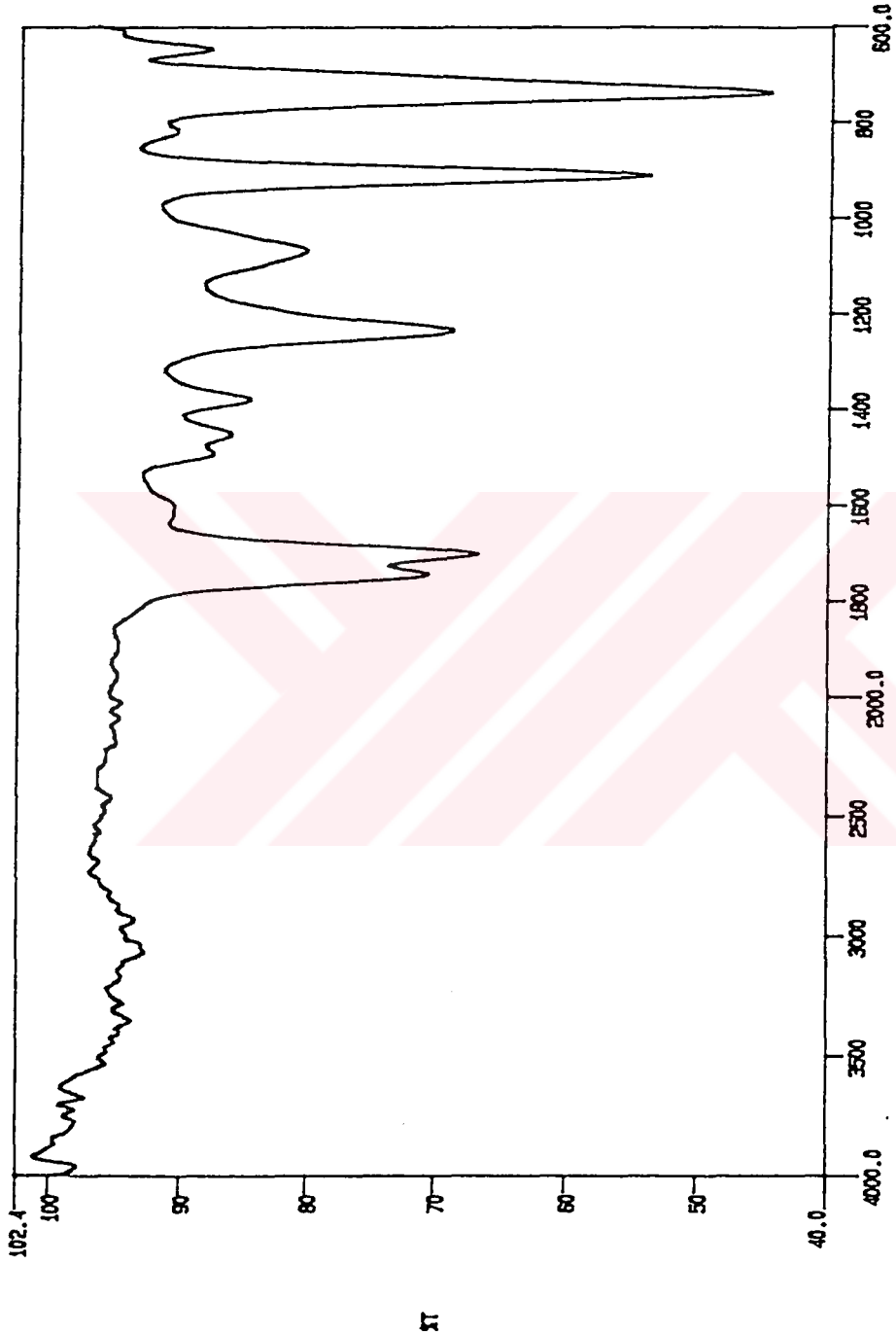


Figure 19. The IR spectrum of 4,4-Diphenyl-6-(2-chloropropionyloxy) cyclohex-2-en-1-one

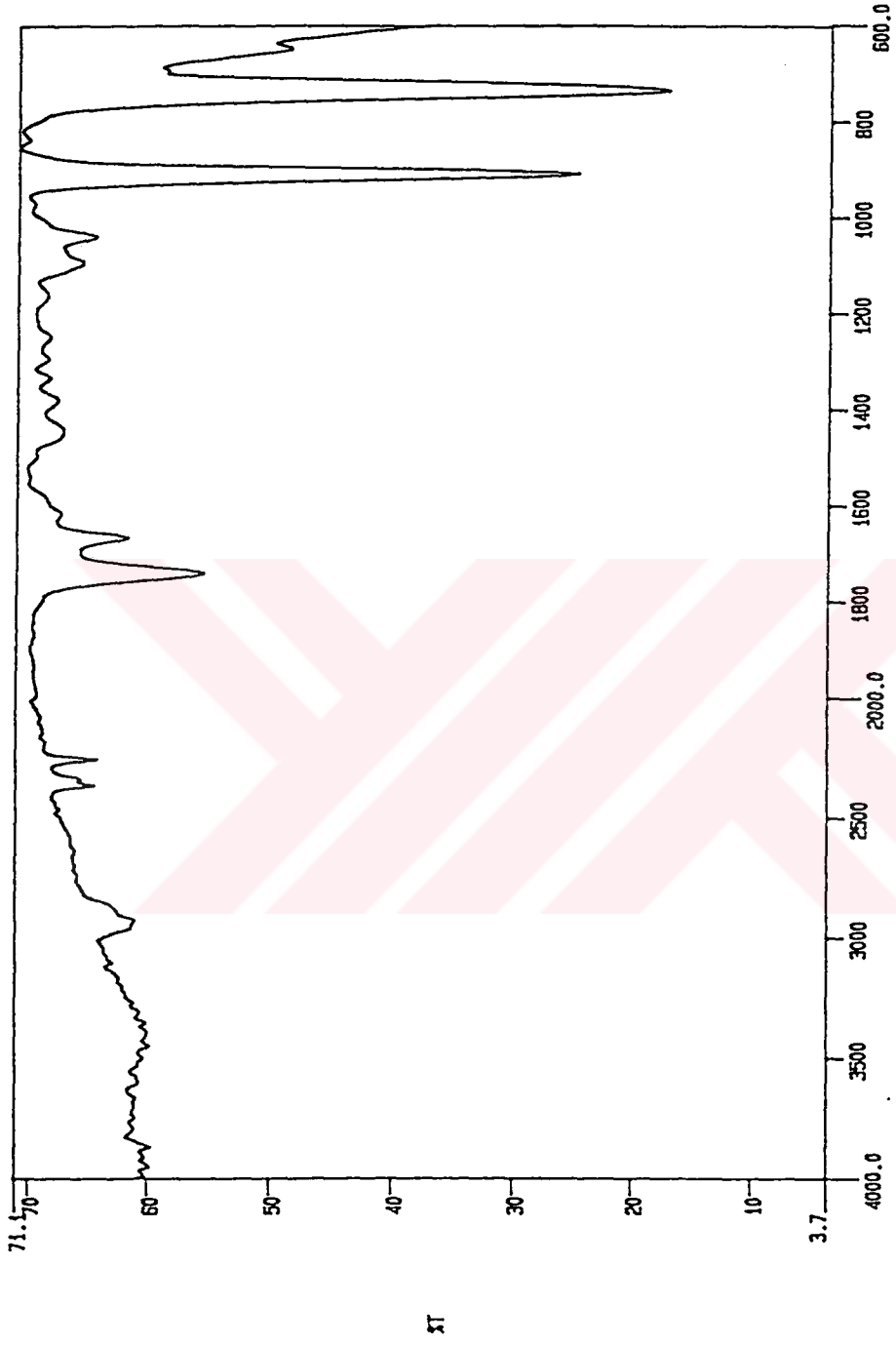


Figure 20. The IR Spectrum of 3,5-Dimethyl-6,7a-dihydro-2-(2H) benzofuranone

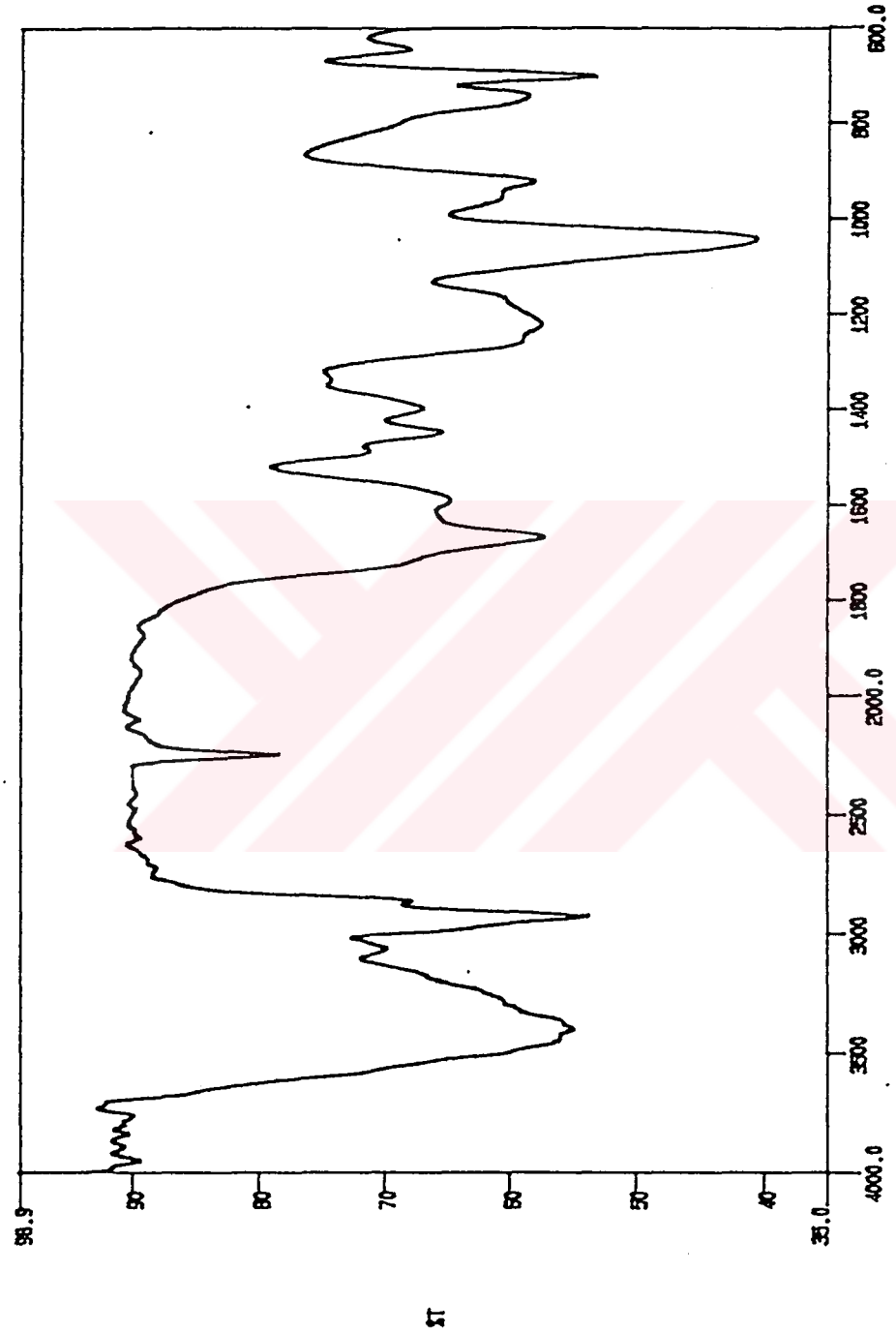


Figure 21. The IR Spectrum of 3-Methyl-6,6-diphenyl-7,7a-dihydro-2-(2H) benzofuranone

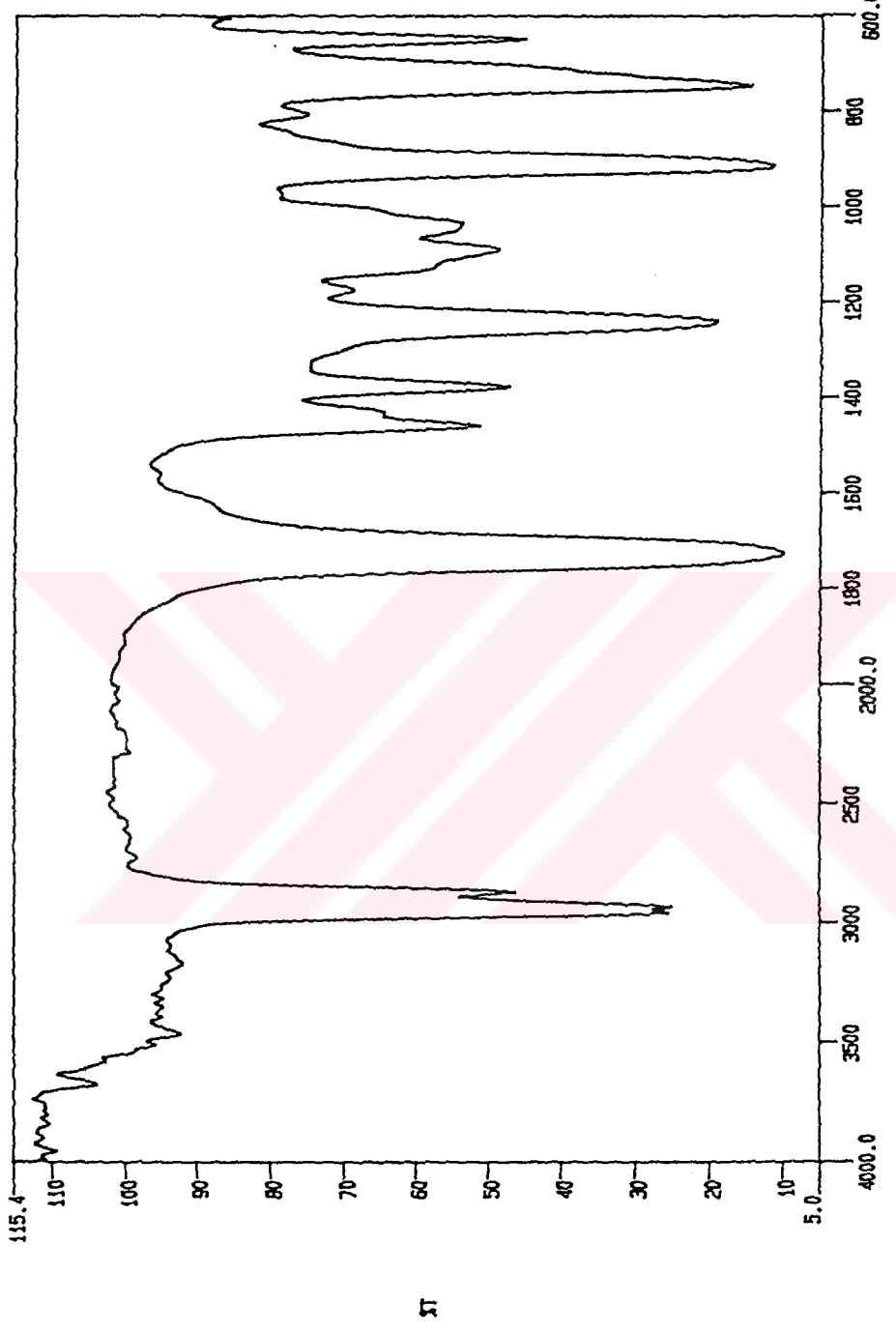


Figure 22. The IR Spectrum of 2-Acetoxy-4-methyl cyclohexanone

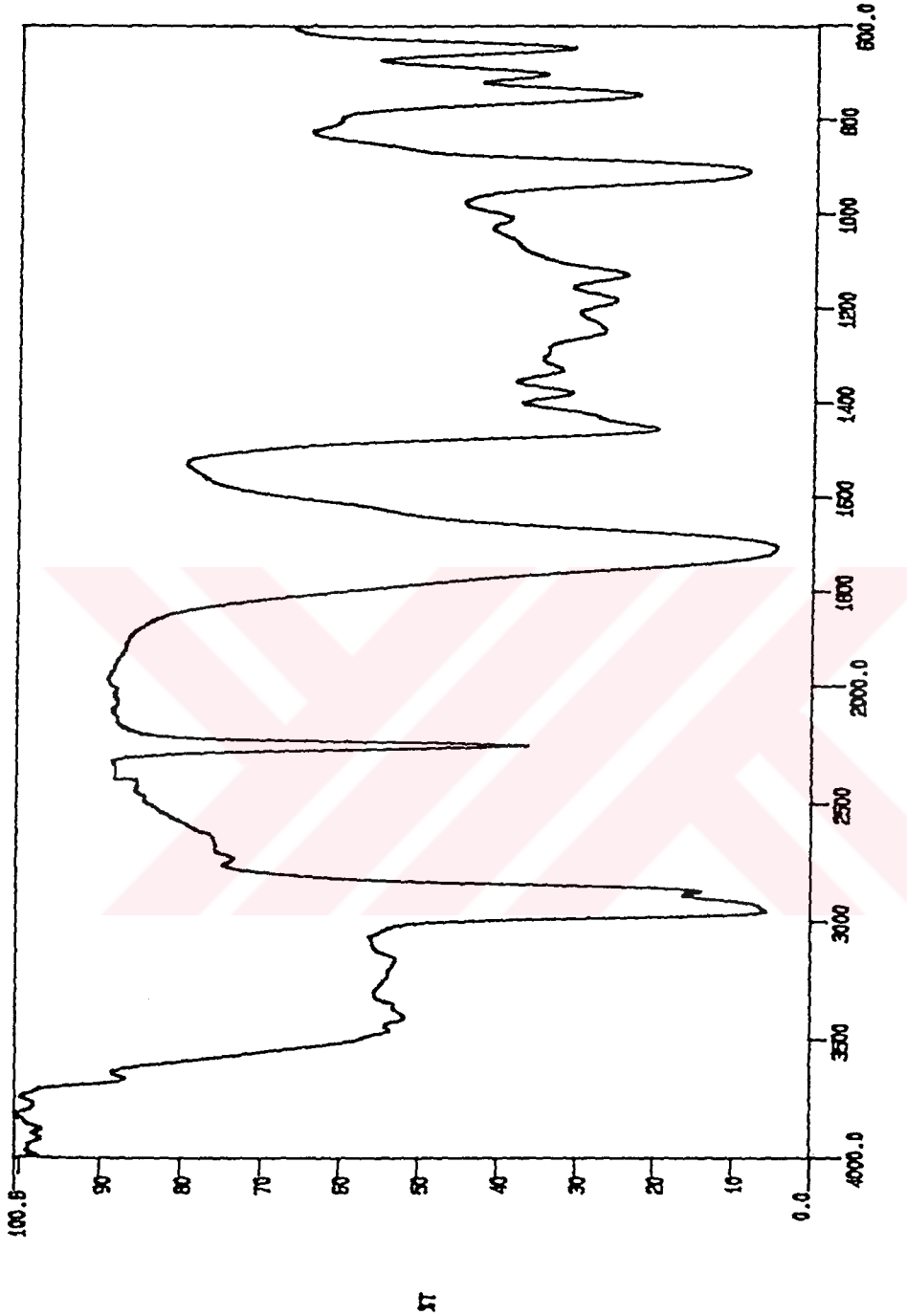


Figure 23. The IR Spectrum of 2-Hydroxy-4-methyl cyclohexanone

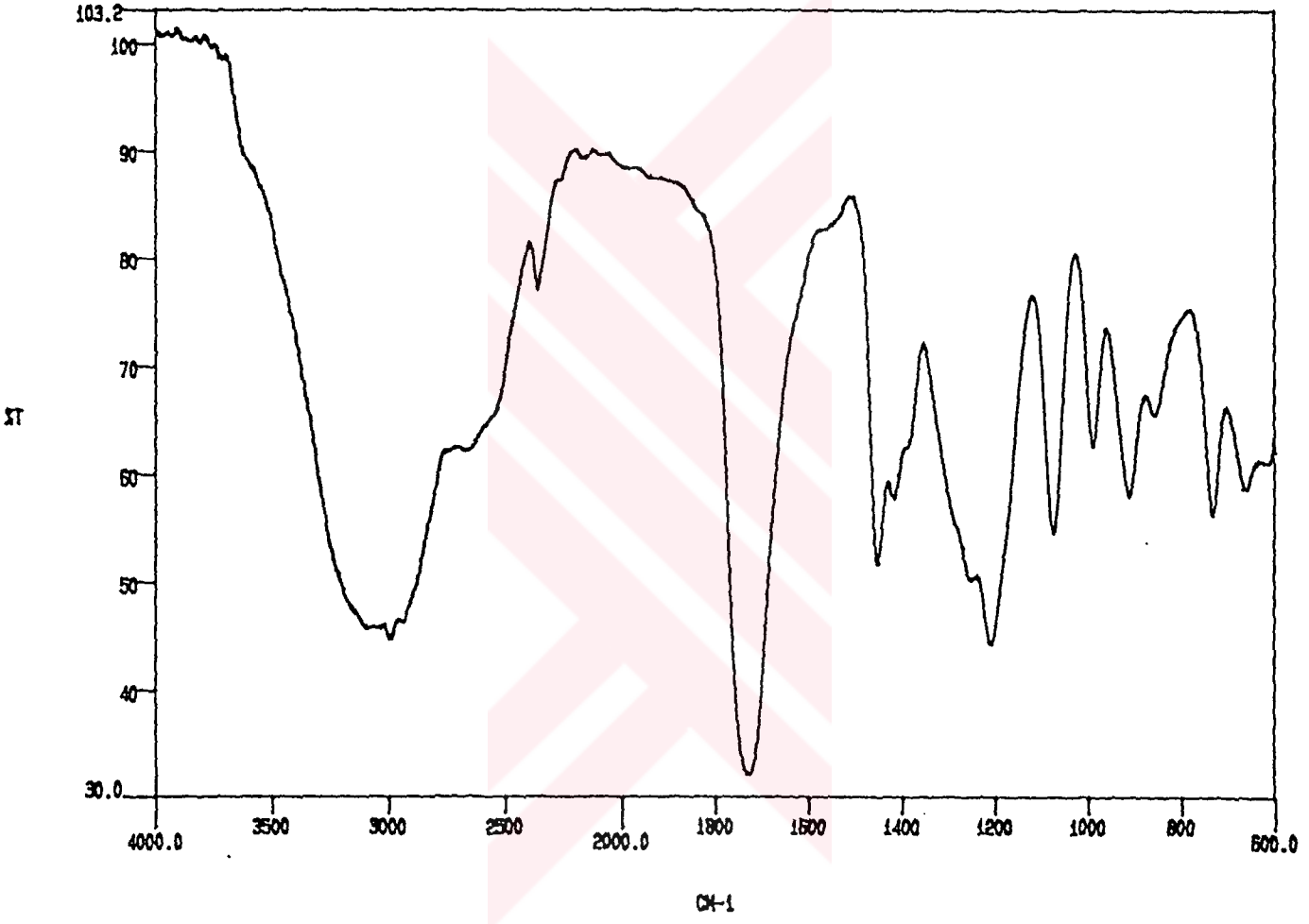


Figure 24. The IR Spectrum of 2-(2-Chloropropionyloxy)-4-methyl chlorohexanone

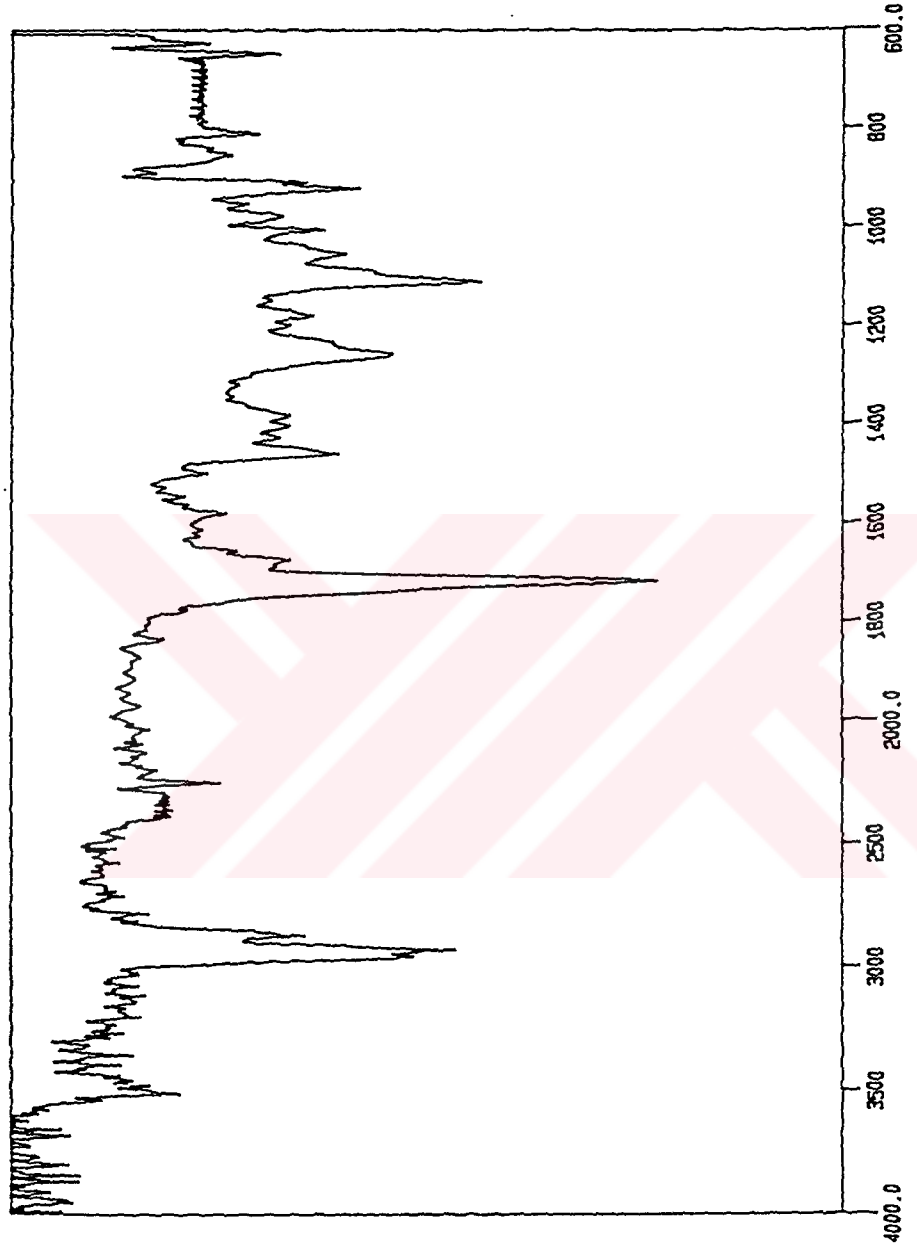


Figure 25. The IR Spectrum of The Mintlactone

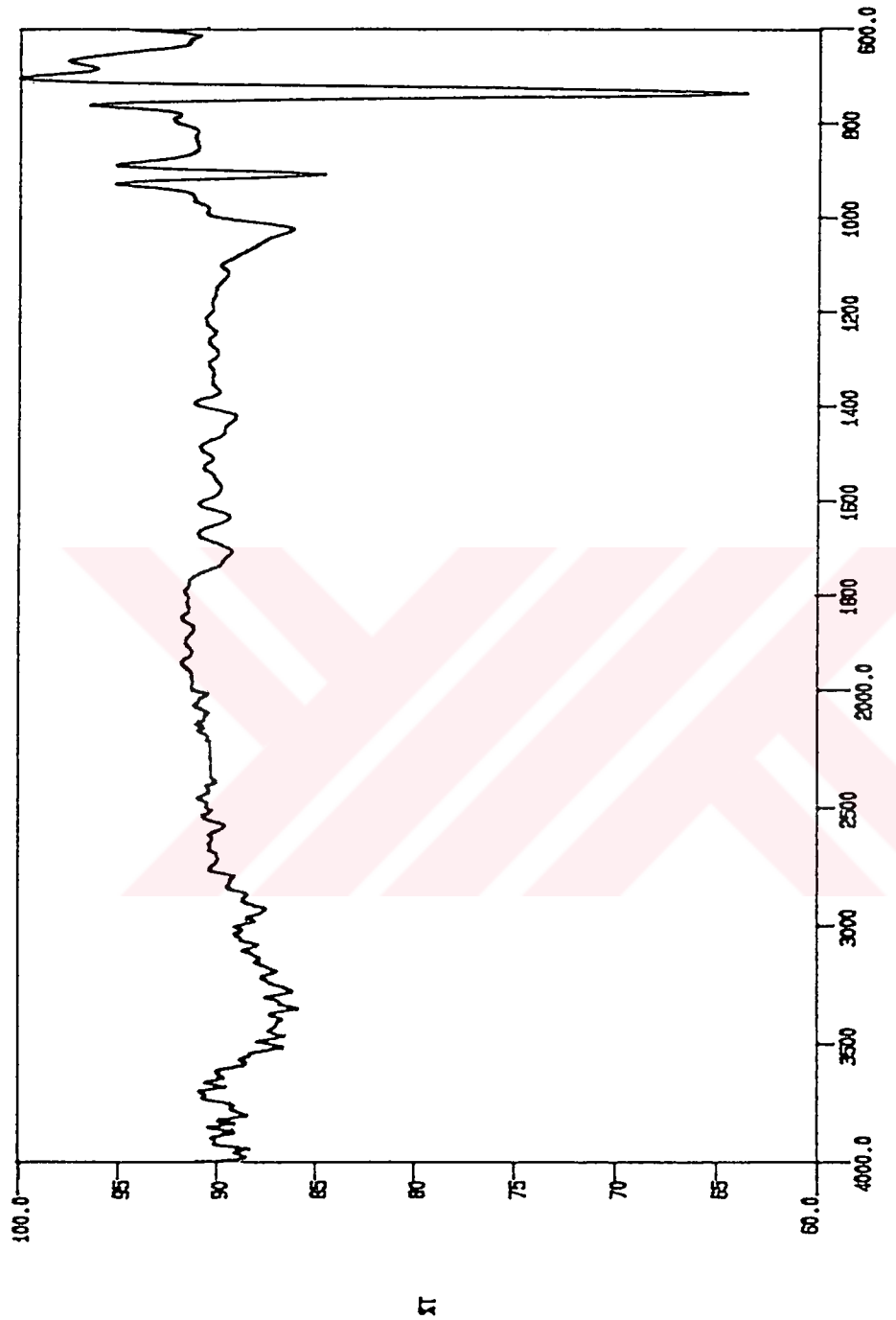


Figure 26. The IR Spectrum of 2-(2-Chloropropionyloxy)-5-methyl chlorocyclohexanone

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PRESENTATION

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