SYNTHESIS OF PHENOLIC NATURAL PRODUCTS

by

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To Lucy

ABSTRACT

PhD Thomas Chaly Chemistry

SYNTHESIS OF PHENOLIC NATURAL PRODUCTS

A new method for the acetalization of carbonyl compounds using chlorotrimethylsilane under mild conditions is described. Carbonyl compounds are acetalized by ethylene glycol with chlorotrimethylsilane.

Two isomeric methyl olivetolates were synthesised by the condensation of 1,3-bis(trimethylsiloxy)-1-methoxybutadiene with the corresponding electrophilic components. This reaction has clearly indicated the discriminative behaviour of 1,3-bis(trimethylsiloxy)-1-methoxybutadiene towards different electrophilic sites thus leading to regio-selectivity.

A new method for the synthesis of olivetol is described. This method provides a shorter route to olivetol from acyclic precursors.

A new synthesis of Δ^1-tetrahydrocannabinol is described. The synthesis is patterned after biogenetic considerations.

A new method for the synthesis of poly β-carbonyl compounds using diketene and enol silyl ethers is described.

The possibility of synthesising gossypol by the cyclo-aromatization procedure was investigated.

RESUME

PhD Thomas Chaly Chimie

SYNTHESE DE PRODUITS NATURELS PHENOLIQUES

Nous décrivons ici une nouvelle méthode d'acétallisation de composés carbonyles, sous conditions douces, qui utilise le triméthylchlorosilane. Les composés carbonyles sont acétallisés par l'éthylène glycol avec du trimethylchlorosilane.

Deux olivetolates de méthyle isomères ont été synthétisés par condensation du bis(trimethylsiloxy)-1,3 methoxy-1 butadiène avec les composés électrophiles correspondant. Cette réaction a clairement mis en évidence le comportement discriminatif du bis(trimethylsiloxy)-1,3 methoxy-1 butadiène envers les différents sites électrophiles, conduisant ainsi à la régiosélectivité.

Nous décrivons par la suite une nouvelle méthode de synthèse de l'olivetol. Cette méthode fournit une route plus courte pour l'olivetol à partir de précurseurs acycliques.

Une nouvelle synthèse du Δ^1-tétrahydrocannabinol est décrite.

Nous décrivons aussi une nouvelle méthode pour la synthèse de composés poly β carbonylés utilisant le dicétène et des éthers-énoliques sililés.

Enfin la possibilité de synthétiser le gossipol par une procédure de cycloaromatisation a été examinée.

ACKNOWLEDGEMENTS

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I would like to express my thanks to Dr. J. Finkenbine and Dr. O. Mamer for the mass spectral analyses and also to Dr. F. Sauriol for the XL-200 ^{1}H nmr spectral analyses.

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LIST OF ABBREVIATIONS

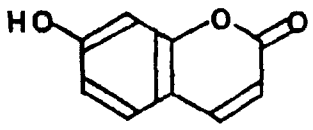
LDA	lithium diisopropylamide
THF	tetrahydrofuran
PTSA	para-toluenesulfonic acid
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl (tetramethylsilane as an internal standard in nmr)
TMSCl	chlorotrimethylsilane
Me	methyl
Et	ethyl
mCPBA	m-chloroperbenzoic acid
LAH	lithium aluminium hydride
Bz	benzyl
Bu	butyl
THC	tetrahydrocannabinol
GLC	gas liquid chromatography

I. INTRODUCTION

A. KINDS OF PHENOLIC COMPOUNDS

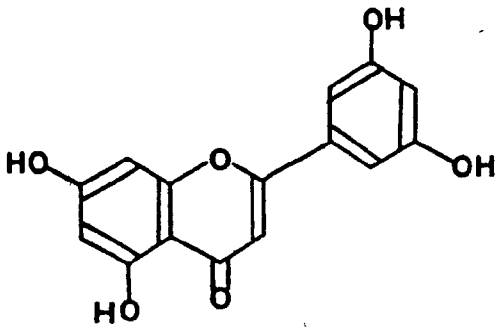
Naturally occurring phenolic compounds were studied extensively in the early stages of natural product chemistry because of their significant uses in industry and also because of their medicinal importance. These complex phenolic comopounds are widely distributed in nature from micro-organisms to higher plants and animals. Flavonoids, terpenes, coumarins, tannis, etc., are some of the common classes of plant phenolics[1].

The division into groups of plant phenolics is based on structural ground and upon information gained subsequently from the study of biosynthetic pathways. A classification of these plant phenolics based on their carbon skeleton was put forward by Harborne and Simmonds[2] in 1964. All the phenolic compounds were found to have a basic aromatic nucleus with side chain of 3, 4 or 5 carbon units or another ring. Thus the key structure in this classification of the first group is the $C_6 \cdot C_3$ skeleton. A typical example of this class of compound is the coumarin (1).



1

The flavonoids comprise the largest single family of oxygen ring phenolic natural compounds. They are known as plant pigments. All these flavonoids contain a basic skeleton of $C_6 \cdot C_3 \cdot C_6$ unit. The flavones apigenin (2) and luteolin (3)



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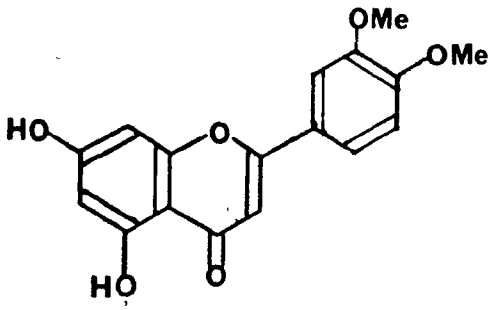
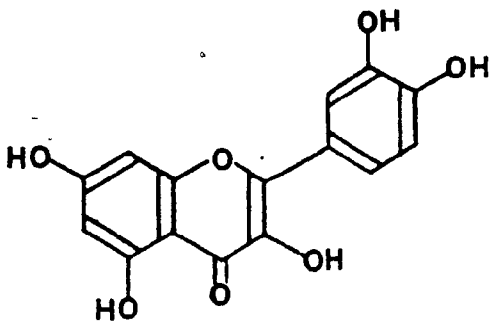


3

are widely distributed in angiosperms. The phloroglucinol rings of the flavonols, quercetin (4) (produced from buckwheat[3]) and cyanidin (5) (from red-cabbage[4]) arise from the acetate units in their biosynthesis. The 3,4-dihydroxycinnamic acid moieties are believed to be originating from the



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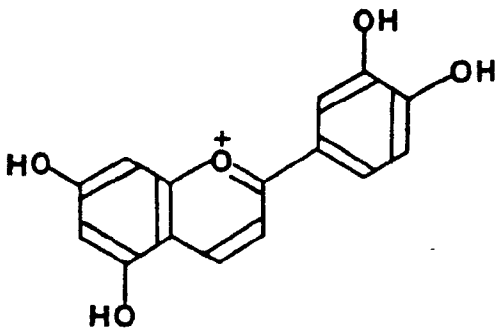
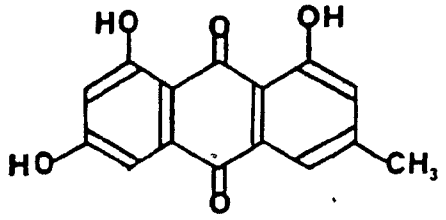


5

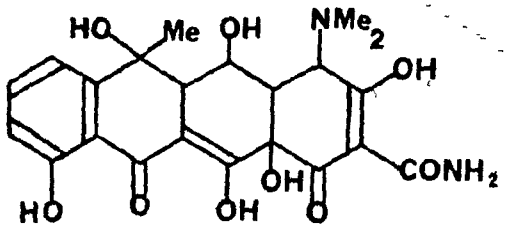
shikimic acid pathway leading to the phenylpropane-type compounds. Phenolic compounds of the benzoquinone, naphthaquinone and anthraquinone types are also found in nature. Among these, the anthraquinones are the most numerous and most widely distributed in higher plants and fungi. Emodin 6 is a well-known example of this class of compound.



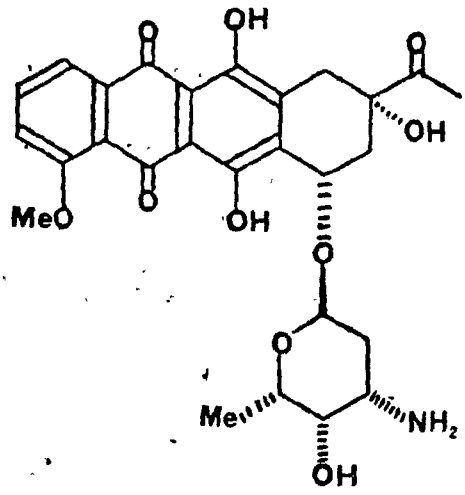
6

These naturally occurring phenolic compounds are believed to be of polyketide origin[5] and are often structurally distinguishable by the presence of substituents in the two benzenoid rings of the anthraquinone nuclei.

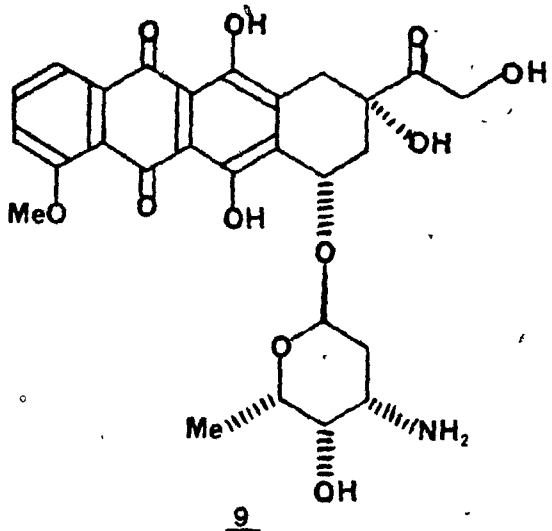
Tetracyclines and anthracyclines are among a group of closely related naturally occurring phenolic compounds with a considerable amount of therapeutic value as antibacterial and anticancer agents. Many naturally occurring tetracyclines have been isolated. Oxytetracycline (7) is an example of this class[6]. The anthracycline antibiotics daunomycin (8) and andriamycin (9) are important antitumor drugs[7,8]. Chalcones


HO
Me
OH
NMe2
OH
CONH2
HO
OH
OH
O

7

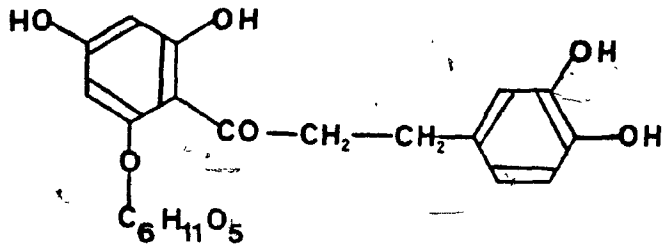

OH
O
OH
MeO
OH
O
O
Me
NH2
OH

8


OH
O
OH
OH
MeO
OH
O
O
Me
NH2
OH

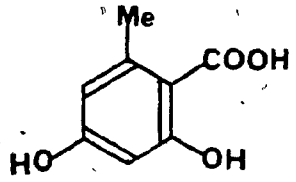
9

are also naturally occurring phenolic compounds having the general structure $C_6 \cdot C_3 \cdot C_6$. Phloridizin (10) is an example of dihydrochalcones.



10

Even though 1-3-dihydroxybenzenes are less common in nature, the 2,4-dihydroxybenzoic acids are well known. Orsellinic acid (11) is the most important of them all. The acid (12) corresponding to 5-n-pentylresorcinol (olivetol) (13), is prenylated in Cannabis Sativa and with modification yields the cannabinoid group of natural phenolic compounds.



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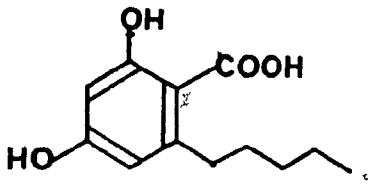

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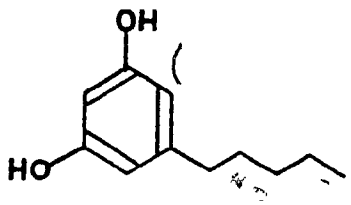
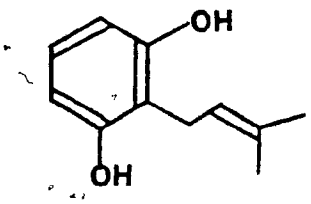


13

The m-hydroxybenzene system arises from polyketide cyclization and is quite common in nature. Phenolic compounds of this kind are frequently found incorporated into terpenoid residues and such compounds have been termed meroterpenoids[9], and occur with great structural variety. In the simplest form, such units comprise acyclic prenyl substituents as in 14 and 15.



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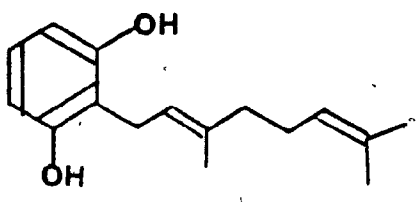
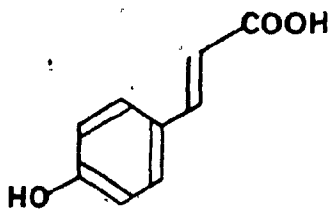


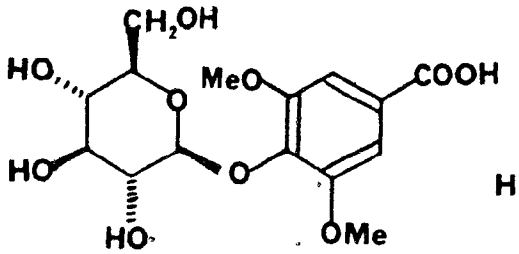
15

The characteristic feature of plant phenols derived from shikimic acid pathway[10] is the pattern of hydroxyl group present in the aromatic rings. Almost invariably a single phenolic hydroxyl group, if present, is located ortho or para to the carbon substituent. Thus, p-coumaric acid (16) is a common plant phenol. Several naturally occurring phenolic glycosides have been isolated. There are two types of

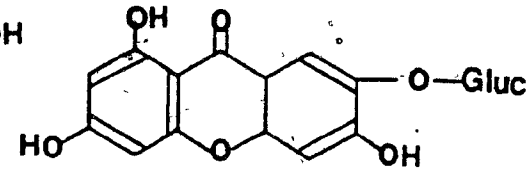


16

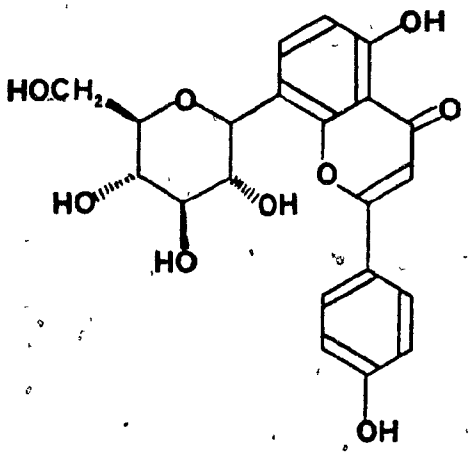
glycosides, namely, O-glycosides and C-glycosides, found in nature. Even though the principal form of combination of phenols and sugars is that of O-glycosides (e.g. 17 and 18), several C-glycosides have been identified. Of these, vitexin (19) is probably the best known[11] example. Plant stillbenes are a relatively small group of natural plant phenols found throughout the plant kingdom from algae to conifers[12]. The pentahydroxystillbene (20) was isolated from "vouacoupa macropetala".


CH2OH
HO
MeO
COOH
HO
O
O
HO
OMe

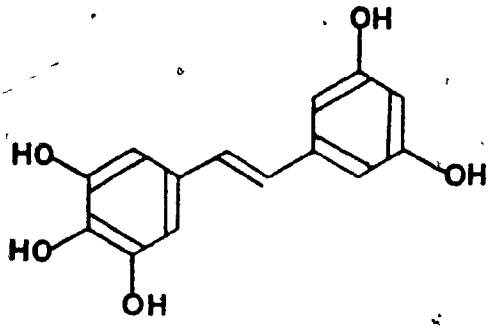
17


OH
O
O—Gluc
HO
O
OH

18


OH
HOCH2
O
O
HO
OH
HO
O
OH

19

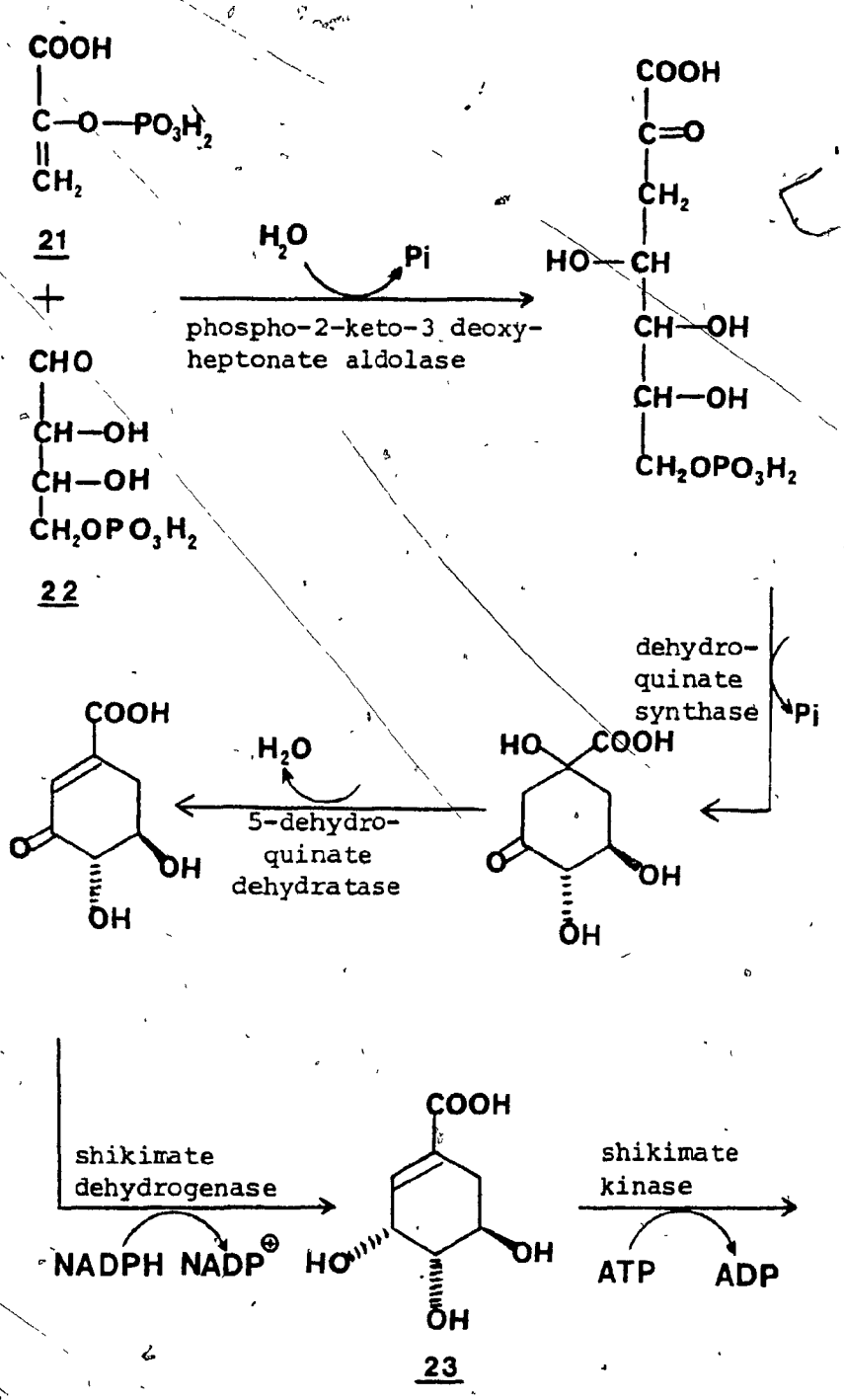

OH
HO
OH
HO
OH

20

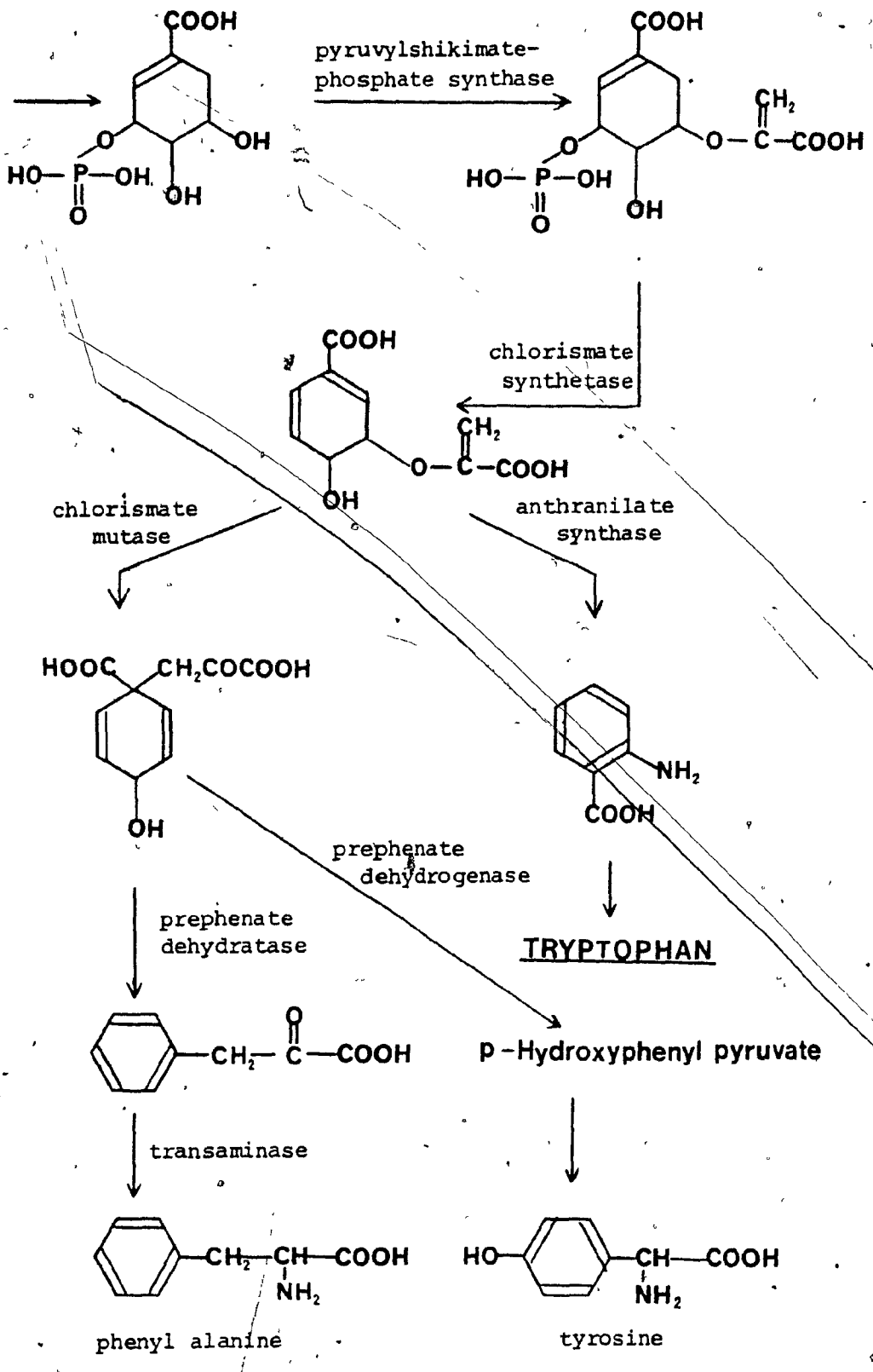
B. BIOSYNTHESIS OF PHENOLIC COMPOUNDS

Naturally occurring phenolic compounds are believed to be formed by two important biosynthetic pathways, namely the shikimic acid and the polyketide[13-15]. The formation of aromatic compounds from carbohydrates via the shikimic acid pathway was demonstrated by Davis[16] by studying the biosynthesis of aromatic amino acids in certain microorganisms. The occurrence of the shikimate pathway in higher plants was first confirmed by Brown and Neish[17]. In the shikimate pathway[18], the initial step is the condensation of phosphoenol pyruvate (21) and erythrose 4-phosphoric acid (22). Even though the intimate mechanism of the various steps are not wholly understood, the enzymes participating in the reactions have been studied well[19]. The formation of the shikimic acid (23) by this pathway is given in Scheme I.1

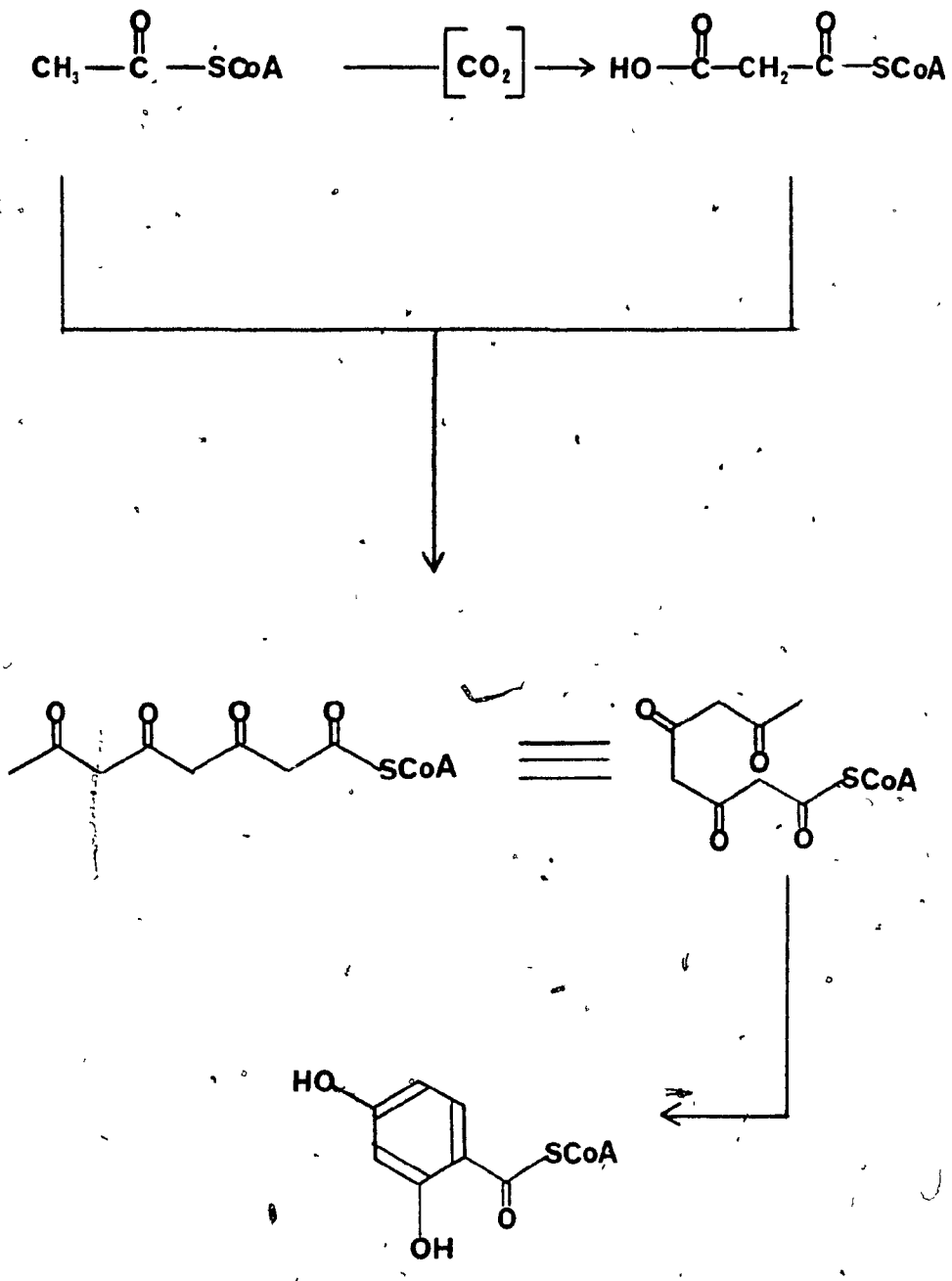
The second most important pathway by which poly functional aromatic compounds are synthesized in nature is the acetate-polyketide pathway exemplified by Scheme I.2. The formation of aromatic nucleus in nature from acetate unit was first proposed by Collie[20] on the basis of his observation that diacetyl acetone (24) would cyclize under strongly basic conditions to orcinol (25) and under milder conditions to the naphthol 26 as in Scheme I.3. Since then, a number of people have investigated this topic with a great deal of interest[21-25]. 3-Hydroxy phthalic acid (27) is an example of


COOH
C—O—PO3H2
CH2
21
+
CHO
CH—OH
CH—OH
CH2OPO3H2
22
H2O
Pi
phospho-2-keto-3 deoxy-heptonate aldolase
COOH
C=O
CH2
HO—CH
CH—OH
CH—OH
CH2OPO3H2
dehydro-quinate synthase
Pi
HO
COOH
OH
OH
H2O
5-dehydro-quinate dehydratase
COOH
O
OH
OH
shikimate dehydrogenase
NADPH NADP⊕
COOH
HO
OH
OH
23
shikimate kinase
ATP
ADP

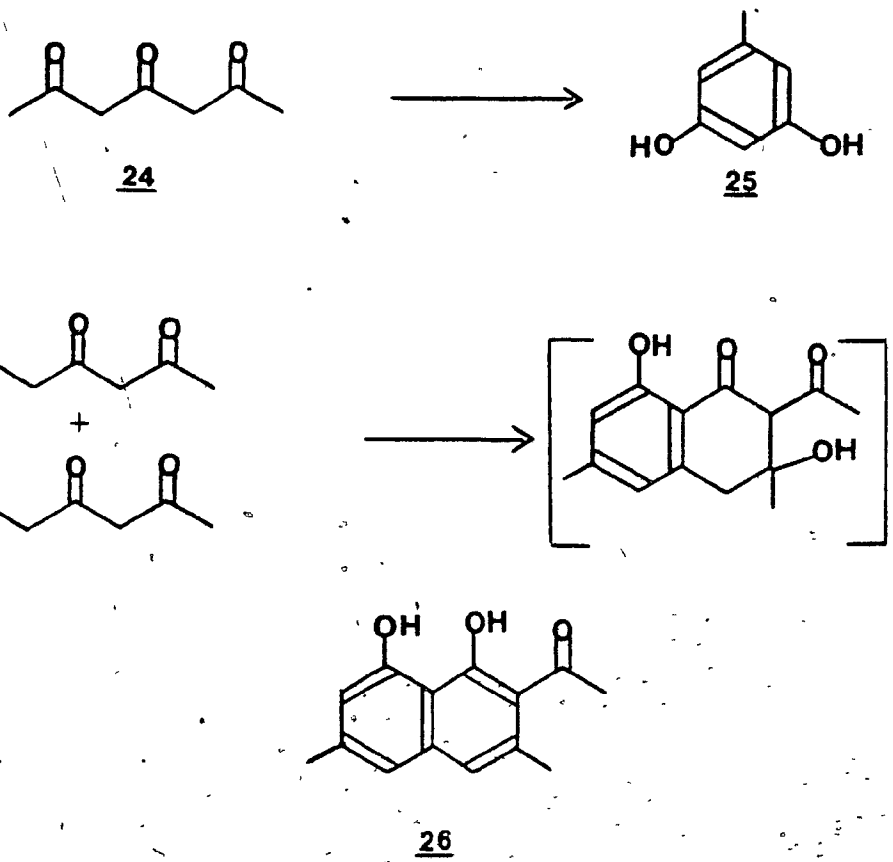
Scheme I.1



Scheme I.1 (cont'd)



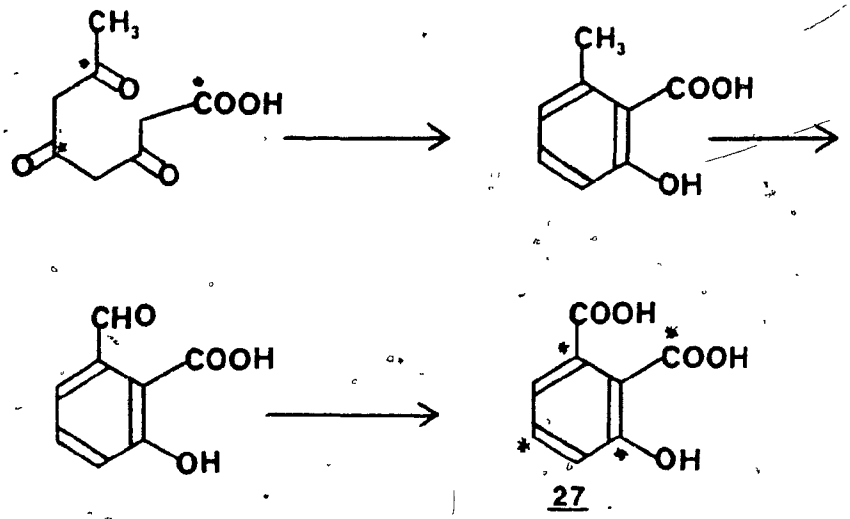
Scheme 1·2



24 25 26

Scheme I.3

a simple phenolic compound derived from a polyketide. The biosynthesis of compound 27 was studied by Gatenbeck[26] using ^{14}C-labelling, based on the ^{14}C-distribution in 3-hydroxyphthalic acid, isolated from penicillium islandicum, grown on $CH_3{}^{14}COONa$. The 3-hydroxyphthalic acid was isolated and its ^{14}C-distribution according to the radioactive pattern showed a strict conformity to the acetate theory. Gatenbeck and



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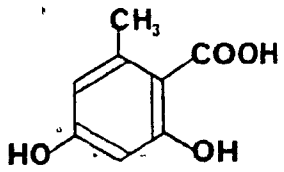
Scheme I.4

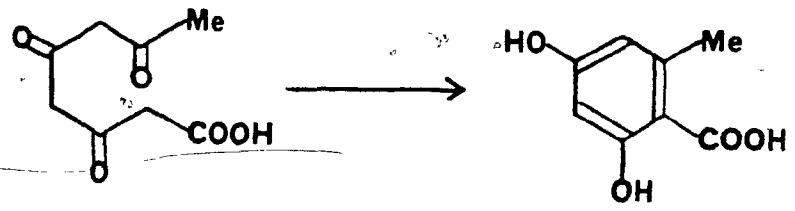
Mosbach later studied the biosynthesis of orsellinic acid[27] (28) using ^{18}O-labelling. ^{18}O-Labelled sodium acetate was



28

administered to the culture medium of the orsellinic acid producing fungus chaetomium cochliodes pall. The ^{18}O-content in the carboxyl group and in the hydroxy groups of orsellinic acid was determined. A high degree of incorporation was found, with the ^{18}O-content of the carboxyl group half that of

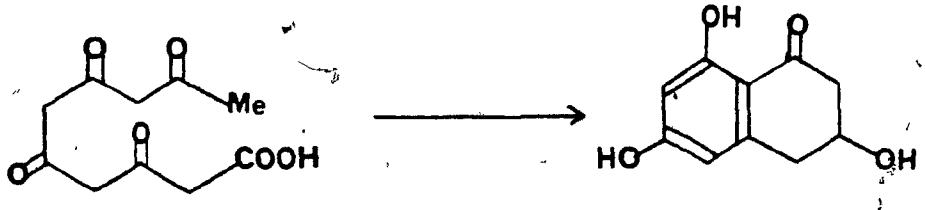
each hydroxy group. These results confirm the postulated direct condensation of the activated tetraketide 29 as an intermediate in the biosynthesis of orsellinic acid.



29

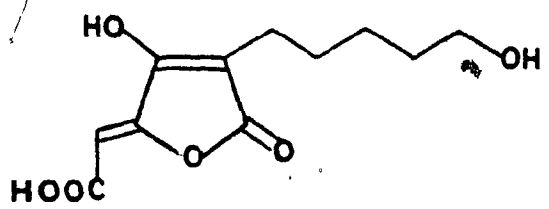
Scheme I.5

The oxygenation pattern in scytalone (31) shows a pentaketide origin as in 30. This was confirmed by the labelling technique[28,29] using ^{13}C as the labelling isotope. In the ^{13}C nmr spectrum of scytalone produced in the presence of sodium [1-^{13}C]-acetate the signals due to C_1, C_3, C_4, C_6 and C_8 are enhanced to about twice the natural intensity thus confirming the pentaketide origin.



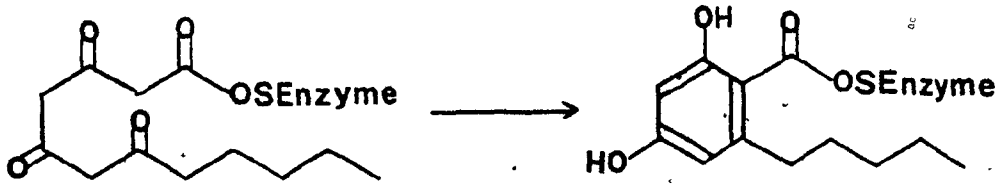
30 31

Incorporation studies using [1-^{13}C]-, [2-^{13}C]-, and [1,2-^{13}C]-acetate have shown that the biosynthesis of multicolic acid (32) in pencillium multicolor involves the intermediate formation of 6-n-pentylresorcylic acid (34) which



32

in turn is formed from a tetraketide intermediate[30] (33).

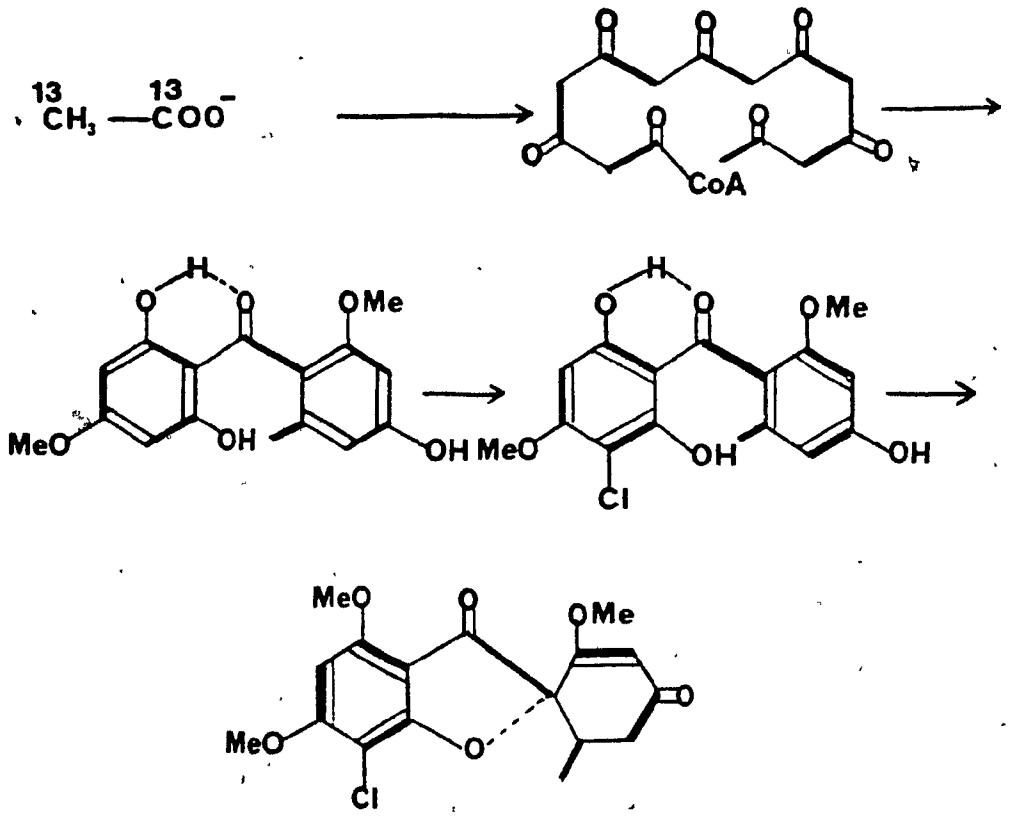


33 34

Scheme I.6

Biosynthesis of griseofulvin (35) was investigated by several groups[15,31,32] and from all these studies, the

formation of griseofulvin from acetate unit was finally supported. In 1976 Sato[33] was able to demonstrate the formation of griseofulvin from acetate units with the help of ^{13}C nmr using [1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]-acetate as tracers. The biosynthetic pathway is depicted in Scheme I.7.



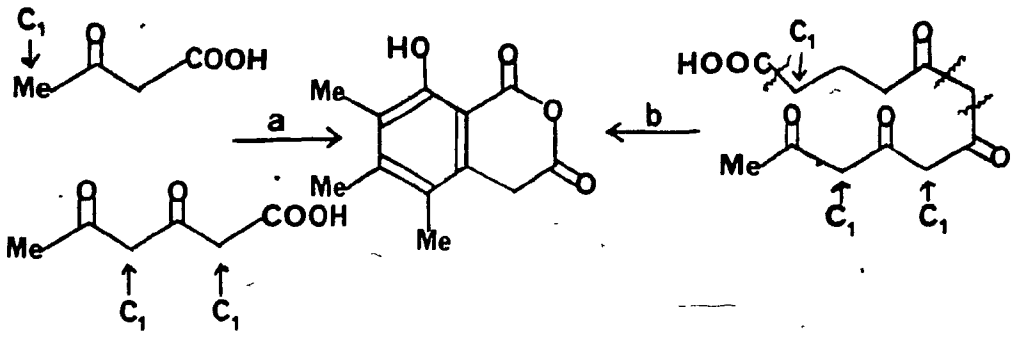
35

Scheme I.7

Incorporation studies were done with singly and doubly labelled [^{13}C]-acetate using a high producing strain of

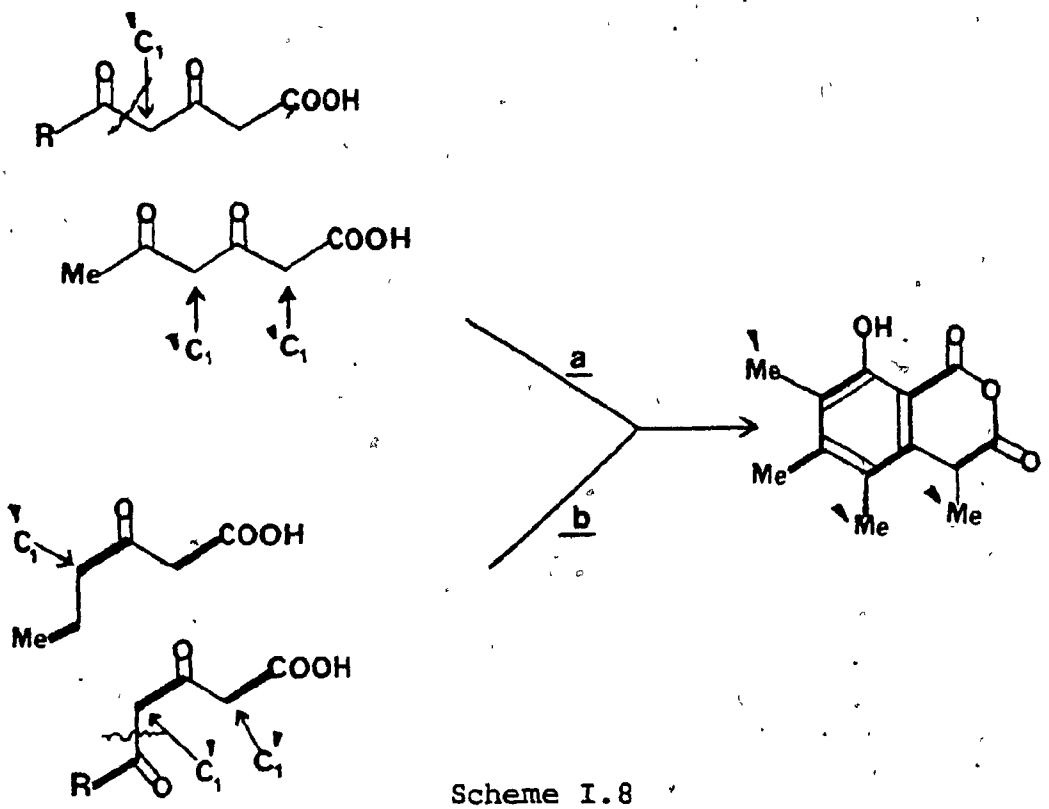
penicillium patulum. A clear preferential incorporation of label into the acetate starter unit confirmed that griseofulvin is formed from a single heptaketide chain[34].

Sclerin (36) is a physiologically active metabolite of Sclerotinia Sclerotiorium. Its biosynthesis was investigated by several groups[35,36]. These studies support the formation of sclerin by the condensation of two separate polyacetate chains without prior cyclization as shown in Scheme I.8. This



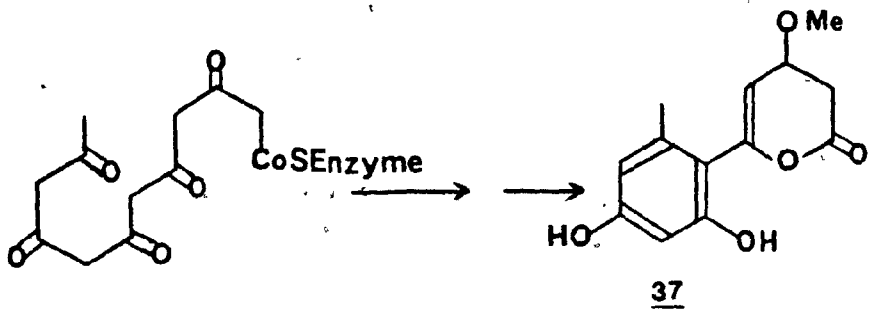
36

was reinvestigated in 1977[37] using $H^{13}COONa$ and [1-^{13}C]-sodium acetate, [2-^{13}C]-malonate and [1,2-^{13}C]-sodium acetate. Based on the ^{13}C-^{13}C coupling in the ^{13}C nmr, it was suggested that an alternative pathway in which two separate polyacetyl chains condense to form a ring once (either by a or b) and the head part of one of the two chains may be lost perhaps by oxidation during the biosynthetic process (Scheme I.8) is more likely.



Scheme I.8

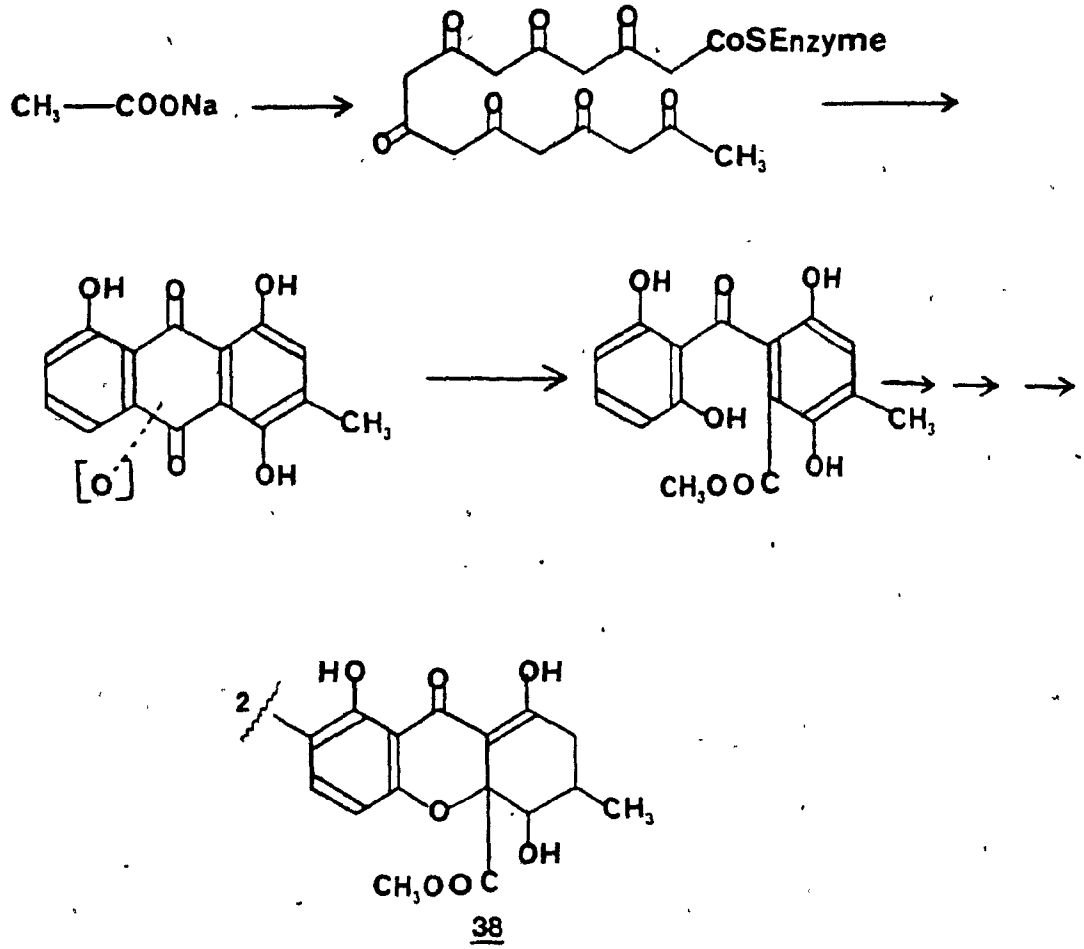
The pattern of radioactivity in aloenin (37) after administration of [1-^{13}C]-acetate, [2-^{14}C]-malonate or [methyl-^{14}C]-methionine to aloe arborescens has been determined and the results are consistent with the expected biosynthetic route[38,39].



37

Scheme 1.9

Analysis of the ^{13}C-^{13}C coupling pattern of secalonic acid (38) produced by cultures of pyrenochaeta terrestris supplemented with [^{13}C]-acetate, is consistent with the formation of the tetrahydroxanthone moiety, via ring cleavage of an anthraquinonoid precursor to give a benzophenone intermediate (Scheme I.10)[40]. Incorporation of [^{13}C]-acetate

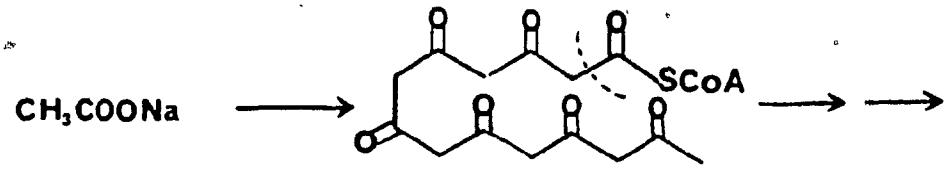


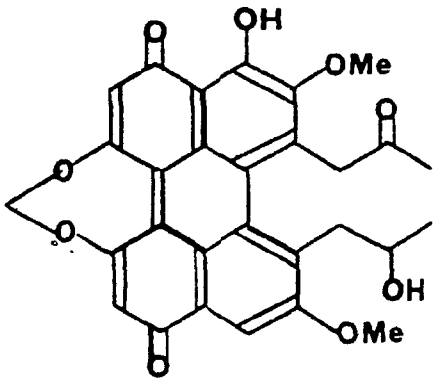
38

Scheme I.10

into cercosporin (39) by cultures cercospora kikuchii indicates its biosynthesis via oxidative coupling of two

heptaketide units, the methoxyl and methylenedioxy carbons being derived from the C_1-pool (Scheme I.11)[41]. These are a





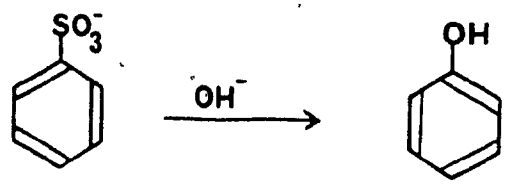
39

Scheme I.11

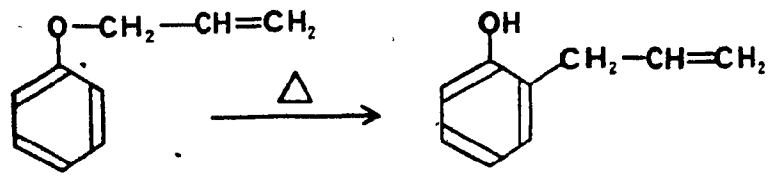
few examples of the many biosynthetic schemes reported in the literature. The idea that some of the phenolic compounds are biologically constituted by the acetate and polyketide is well supported by the experimental evidences.

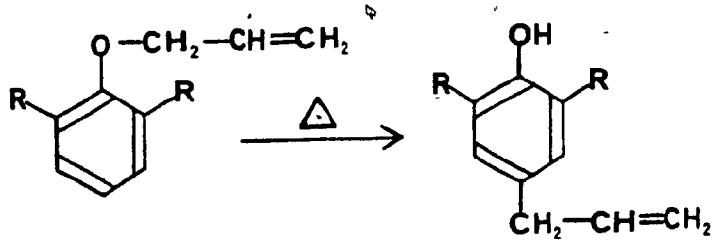
C. SYNTHESIS OF PHENOLIC COMPOUNDS

There are several methods available for the synthesis of phenolic compounds. The purpose of this section is to present a few examples from the literature. Examples will also be given to demonstrate the synthesis of polyfunctional phenolic compounds, which may be useful for the construction of some natural phenolic compounds. In general the synthesis of phenolic compounds depends on some aromatic precursors as the starting unit. An example is the synthesis of phenol itself from benzenesulfonic acid (Scheme I.12). Alkyl phenyl ethers when heated undergo Claisen rearrangement to form substituted phenols[42-44] (Scheme I.13). Aryl lithium when subjected



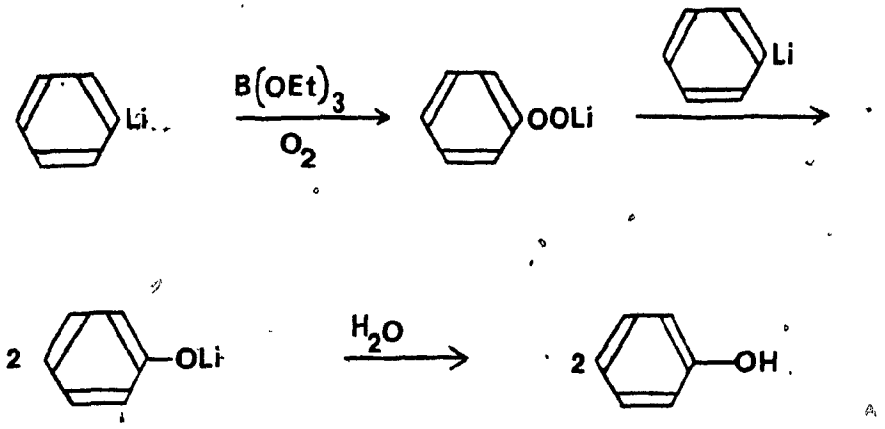
Scheme I.12





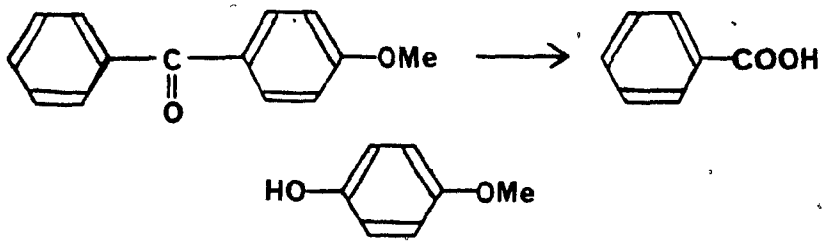
Scheme I.13

to oxidation, gives a mixture of products which include phenol[45] (Scheme I.14). The Bayer-Villiger reaction of

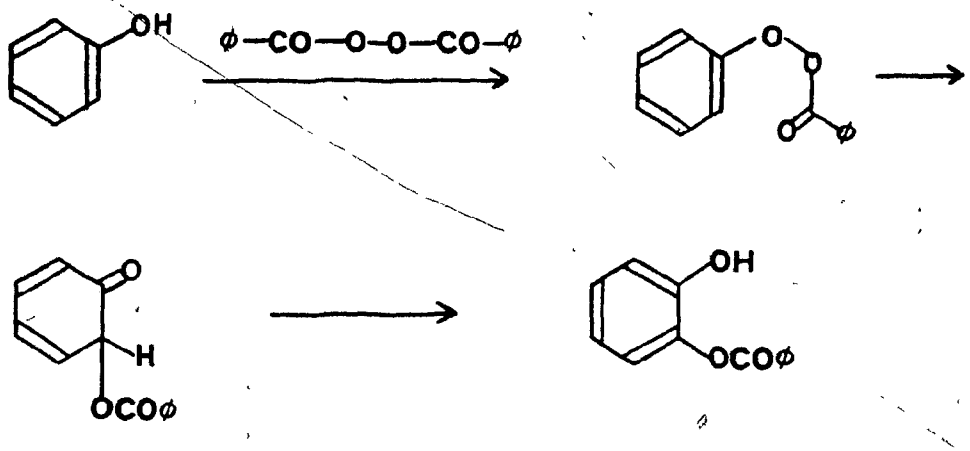


Scheme I.14

aromatic carbonyl compounds is a good method for preparing phenols[46]. Thus treatment of p-methoxybenzophenone with peracetic acid gives benzoic acid and p-methoxyphenol (Scheme I.15). Substituted phenols are also prepared by the benzoyl oxidation with benzoyl peroxide (Scheme I.16)[47]. Oxidation of aromatic aldehydes by Dakin reaction[48] using

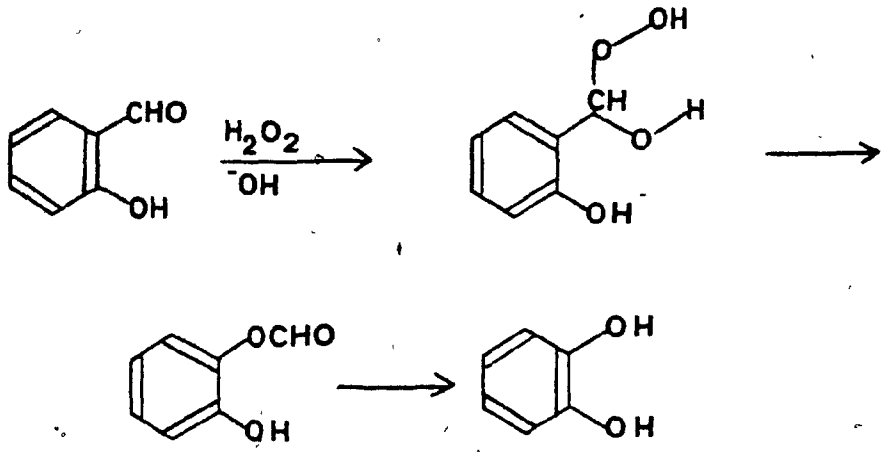


Scheme I.15



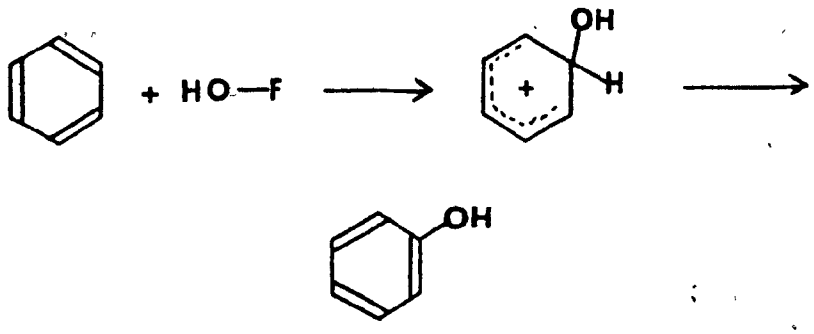
Scheme I.16

alkaline hydrogen peroxide leads via rearrangement to the formyl esters of phenols. Thus salicylaldehyde was converted to the corresponding phenol as shown in Scheme I.17.



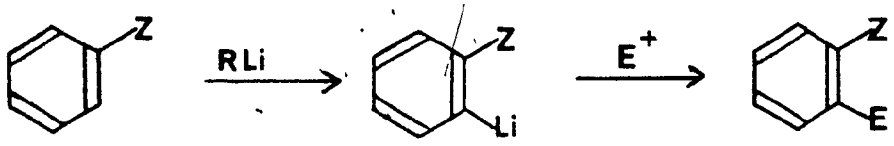
Scheme I.17

Hydroxylation of aromatic compounds with hypofluorous acid was reported by Evan et al.[49] in 1977. Thus benzene was hydroxylated as given in Scheme I.18.



Scheme I.18.

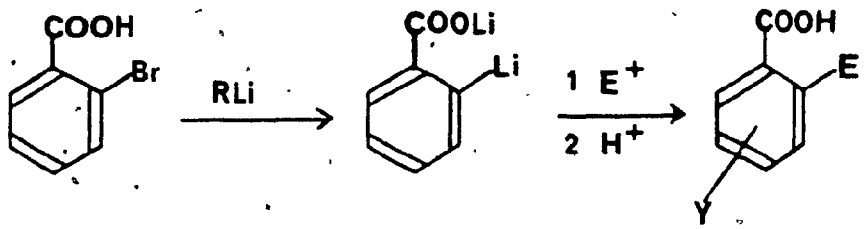
Directed metalation of aromatic tertiary amides is a recently developed synthetic approach for the preparation of polysubstituted aromatic compounds[50]. Ortho lithiation followed by electrophilic substitution is generally used. A general synthetic sequence is depicted in Scheme I.19[51].



Z = $CONR_2$, CONHR , NHCOR Etc.

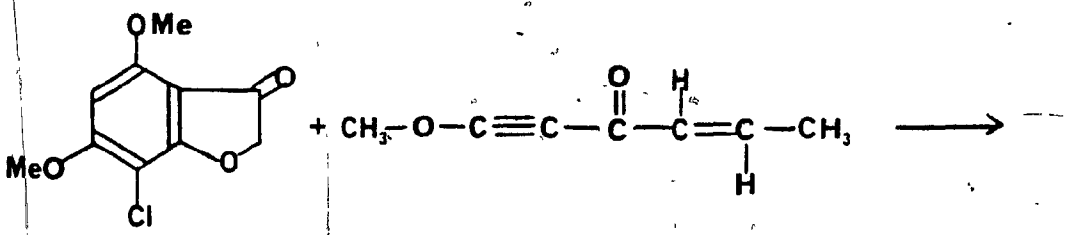
Scheme I.19

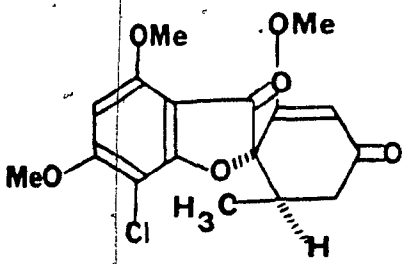
A metal-halogen exchange sequence developed by Parham, Bradsher and co-workers (Scheme I.20)[52] provides a synthetic equivalent of ortholithiated benzamide and was found to be useful for the preparation of polysubstituted aromatic compounds bearing reactive functional groups.



Scheme I.20

With this general introduction, we can discuss some examples of the total synthesis of phenolic natural products. An elegant synthesis of dl-griseofulvin (40) was achieved by Stork and Tomasz[53] in 1962 by reacting 7-chloro-4,6-dimethoxy coumaranone with methoxyethynylpropenyl ketone in the presence of potassium tertiary butoxide (Scheme I.21) by a double Michael reaction. Of the reactions discussed so far the synthesis of phenolic compounds depends completely on an aromatic precursor. It is clear that phenols with certain



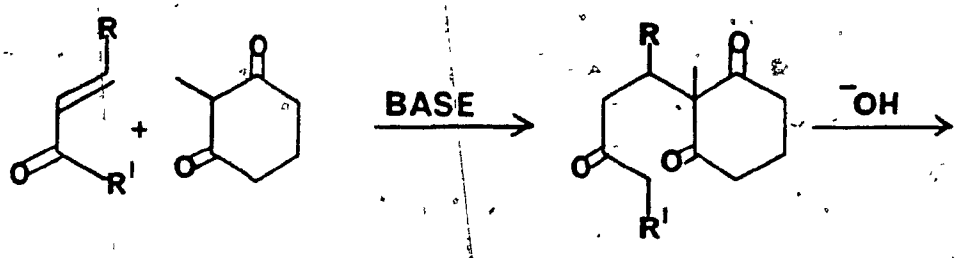


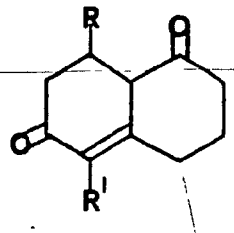
40

Scheme I.21

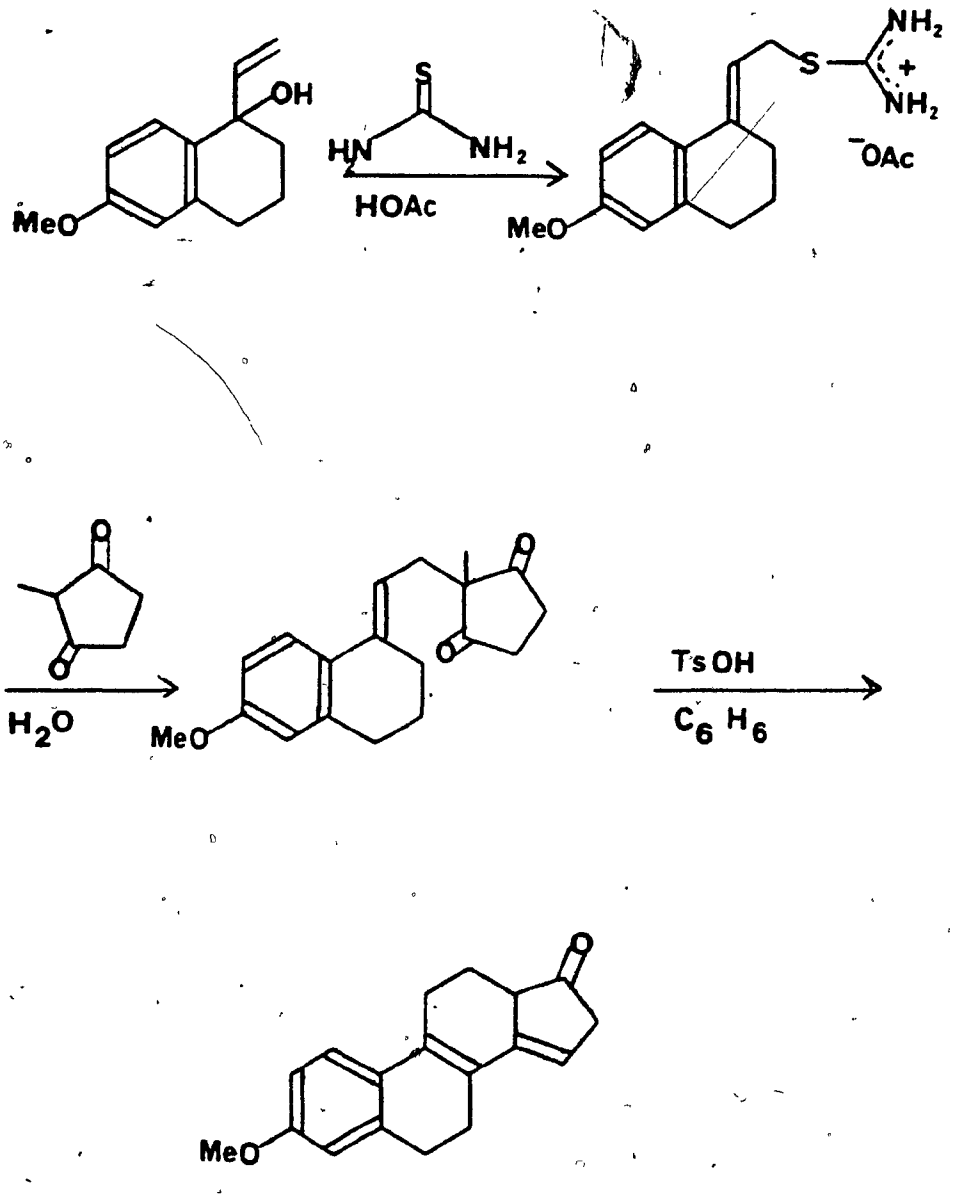
substitution patterns are not amenable to the methods described so far. Several alternative strategies have been devised for constructing aromatic rings with appropriate hydroxyl groups from non-benzenoid precursors. The two common methods available for the construction of six-membered rings are the Robinson-annelation and the Diels-Alder reaction. In the Robinson-annelation[54], the regiochemistry is essentially controlled by the direction of polarization within each fragment, represented schematically in Scheme I.22.

Robinson-annelation had been used for the synthesis of natural products like steroids and several new annelation methods are designed for this purpose. An example is depicted in Scheme I.23. The Diels-Alder reaction has been extensively



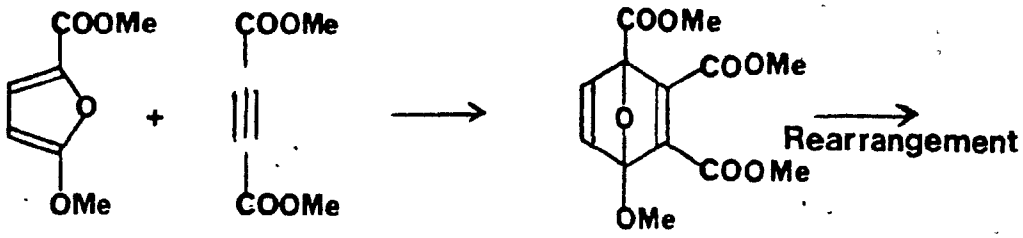


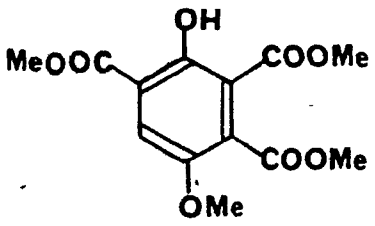
Scheme I.22.



Scheme I.23

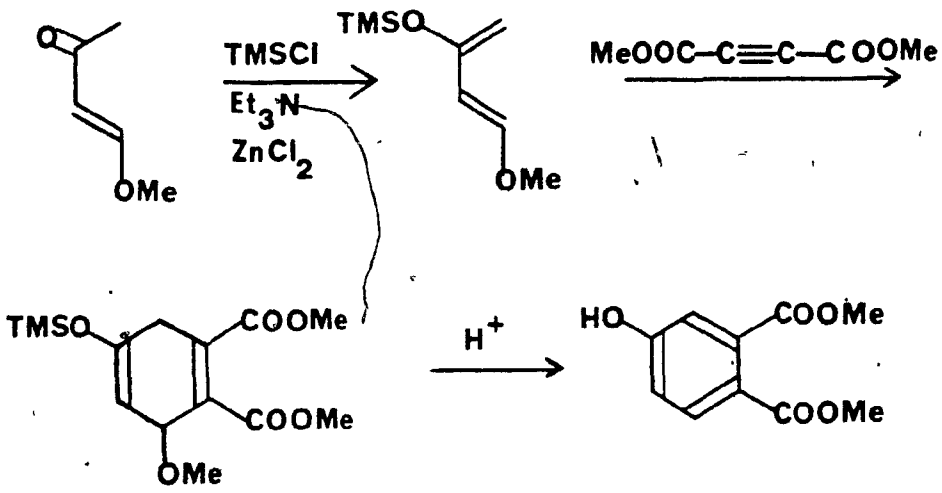
used by organic chemists for the construction of poly-substituted six-membered ring compounds. A typical example of the Diels-Alder reaction leading to a phenolic compound is given in Scheme I.24[55].





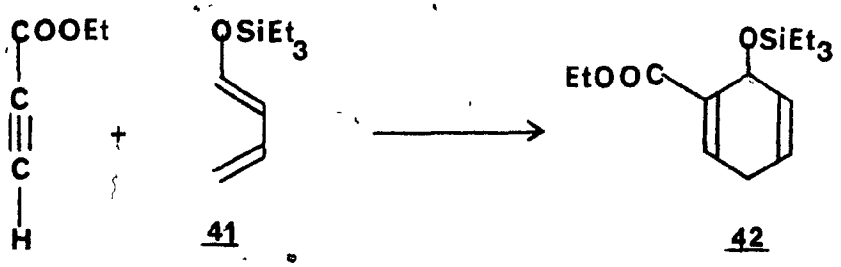
Scheme I.24

Diels-Alder reactions using siloxy-substituted 1,3-dienes has been of interest recently because of the fact that siloxy butadienes can easily be made and they provide high regio-selectivity. These dienes are extensively used for the preparation of polyfunctionalized ring systems by the Diels-Alder reaction. Danishefsky[56] has synthesized a number of compounds using O-silylated dienes. A typical example which demonstrates this methodology is exemplified in Scheme I.25.



Scheme I.25

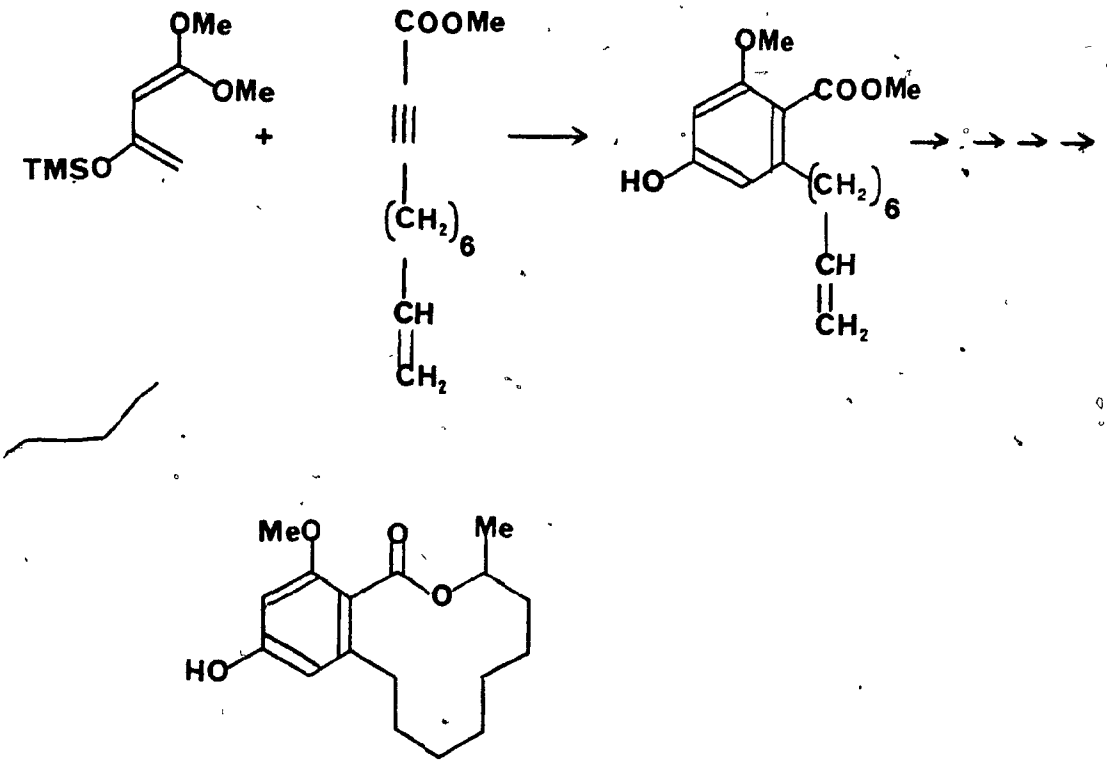
1-(Trimethylsiloxy)-butadiene (41) and ethyl propynoate give only the orthoadduct 42[57] (Scheme I.26). Application of this



Scheme I.26

methodology to the synthesis of natural products like lasiodiplodin (43)[58] has been reported by Danishefsky. A brief synthetic scheme is given in Scheme I.27. A similar methodology was adopted by Brassard and Savard[59] for the synthesis of naturally occurring quinones. The process is exemplified in Scheme I.28 for the synthesis of chrysophanol (46) by the regiospecific reaction between the vinylketene acetal (44) and 3-chlorojuglone (45). The same approach was applied to the synthesis of Steffimycin 50 by Gesson and Jacquesy[60] in 1983 (Scheme I.29) from 47 and 48 through the intermediate 49.

In this laboratory, we have been interested in the use of bis-enol silyl ethers for the preparation of highly substituted phenolic compounds by a cycloaromatization process[61]. This will be discussed later in a separate section in this thesis.



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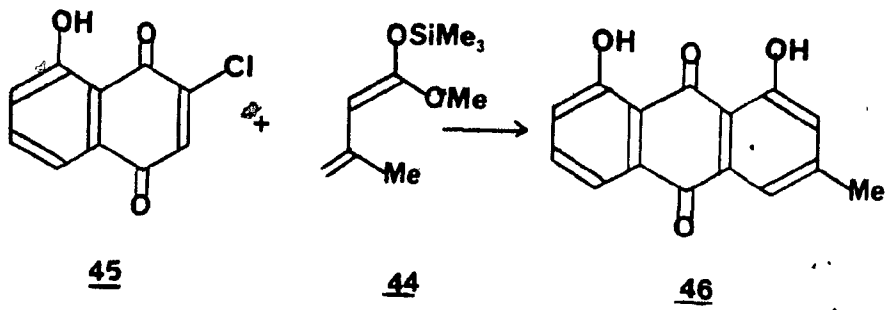
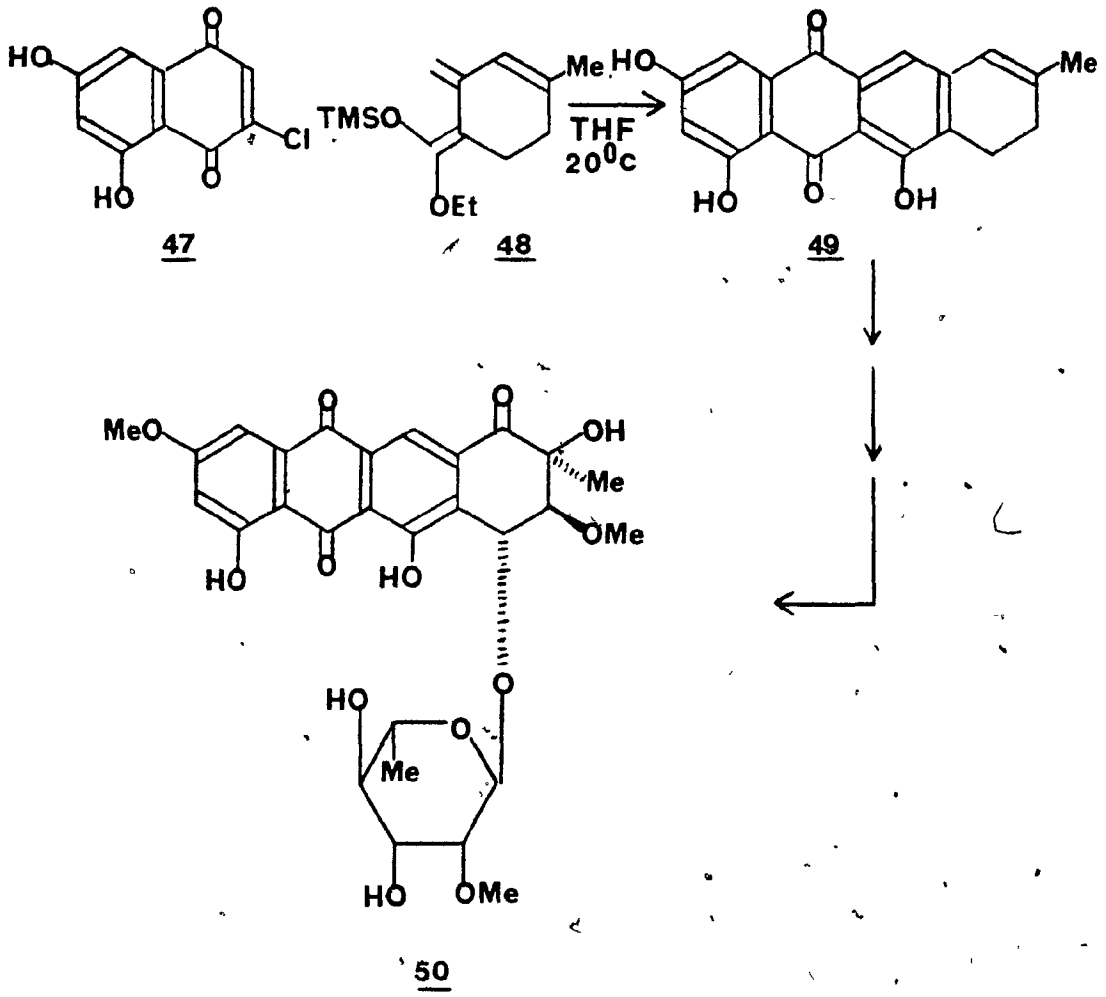
Scheme I.27



45 44 46

Scheme I.28



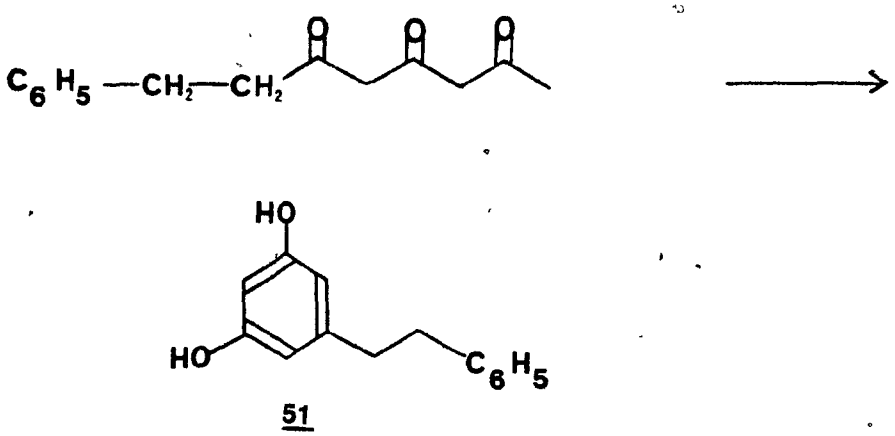
Scheme I.29

D. BIOMIMETIC TYPE SYNTHESIS

The term "biomimetic synthesis" has been chosen to describe an organic synthesis designed in such a way that it follows, at least in its major aspects, the biosynthetic pathways. The success of these types of syntheses depends upon how one can utilize reactions and conditions that

parallel the biosynthesis, but at the same time utilizing reagents and conditions that are different from the living systems, so that the chemist can capitalize on the advantages offered by organic synthesis.

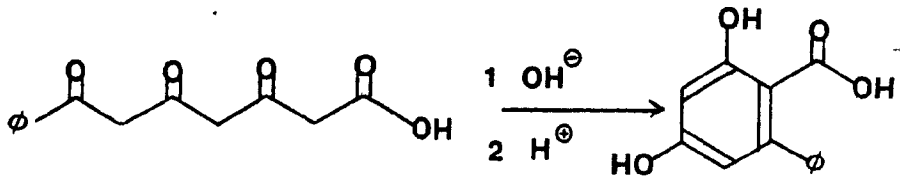
It has been established that many of the natural phenolic compounds arise in nature from acetate through the polyketide pathway[62-64]. Considerable research has been done to mimic such synthesis of phenolic compounds in the laboratory[65]. During the past decade a number of reports have appeared in the literature on the conversion of protected and unprotected poly-β-ketones and poly-β-keto acids to phenolic compounds. These results have indicated that cyclization and aromatization of the poly-β-carbonyl compounds can be duplicated in the laboratory to some extent. Collie's[62] research has laid the foundation in this respect (Scheme I.3). This work was later extended by Birch[66] through the synthesis of dihydropinosylvin (51) according to Scheme I.30. There was



51

Scheme I:30

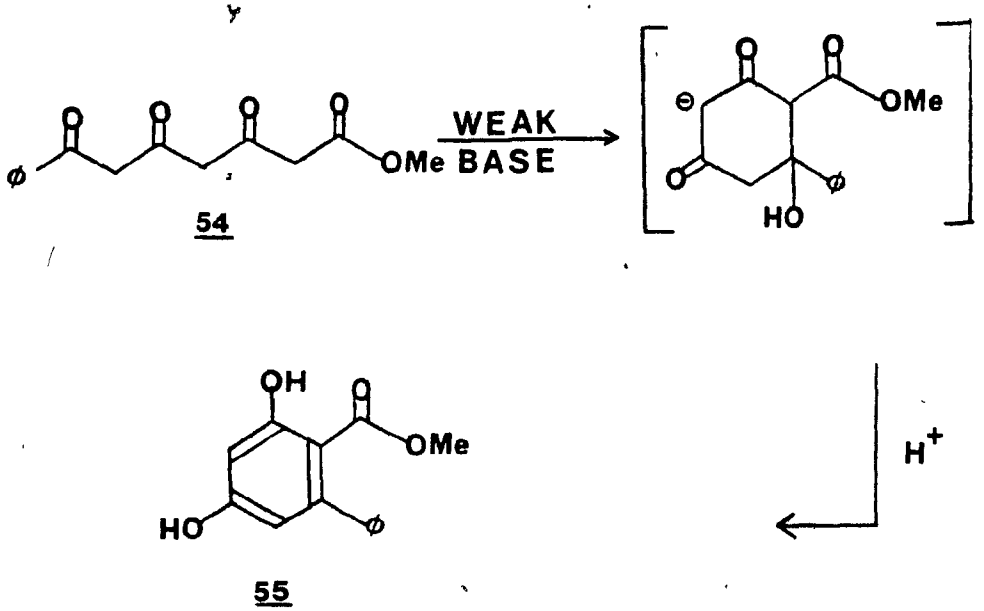
a renewed interest in this field of cyclization due to the availability of poly-β-carbonyl compounds. Aldol condensation and cyclization of the poly-β-keto acid 52 occurs in aqueous or alcoholic solution over a pH range from weakly basic to strongly basic conditions. On acidification, the cyclized intermediate undergoes dehydration to form the resorcyclic acid 53[67] (Scheme I.31). Another interesting reaction is the cyclization of the methyl ester of 3,5,7-trioxoheptanoic acid 54 in weakly basic conditions[67]. The reaction proceeds through aldol cyclization and dehydration to the phenolic compound 55 (Scheme I.32). When strong basic conditions were used for



52 53

Scheme I.31

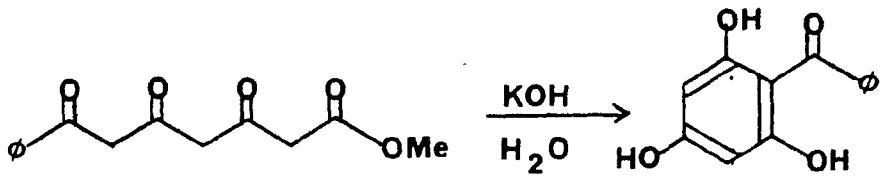
the cyclization, benzoyl phloroglucinol 56 was the main product resulting from the Claisen condensation (Scheme I.33). The



54

55

Scheme I.32

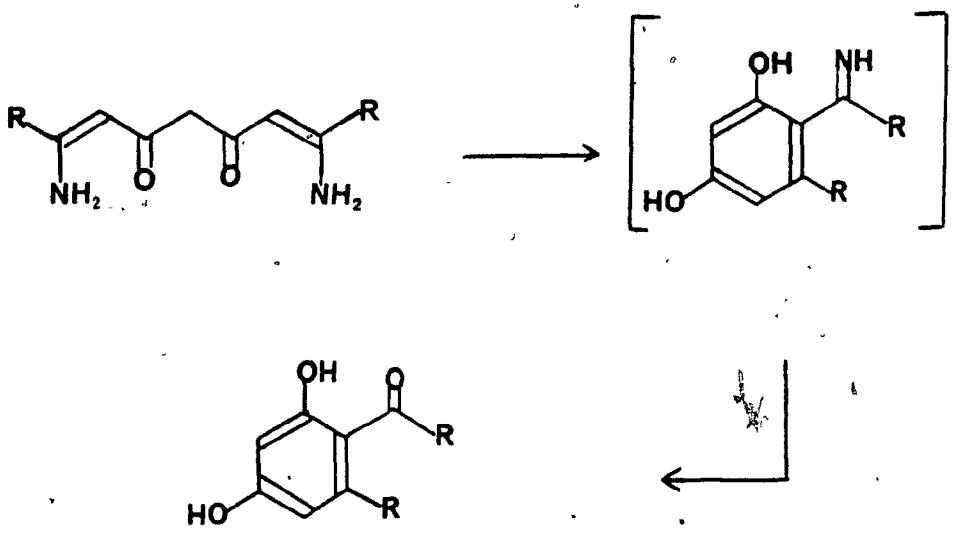


54

56

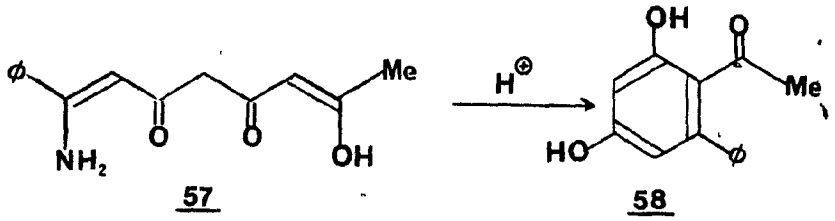
Scheme I.33

competition between the aldol and the Claisen cyclization is a drawback in this kind of cyclization-aromatization reaction. Metal ions were used for the control of regiochemistry, but the result was not promising[68]. Moreover, with increasing chain lengths, the number of possible cyclization products are also increasing rapidly. In order to avoid these problems, different strategies have been adopted. A derivative of tetra-β-polyketone in the form of enamine was used for the synthesis of resorcinols[69] as exemplified in Scheme I.34.



Scheme I.34

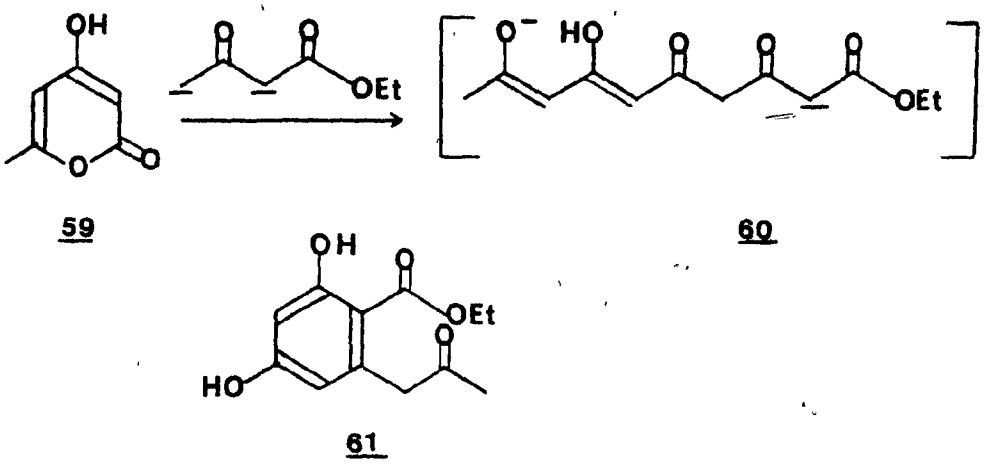
The same group has synthesized in good yield the resorcinol 58 using the enamine 57 (Scheme I.35). These two reactions show



57 58

Scheme I.35

some directional influence due to the enamine group. This has not been explored completely for the synthesis of polycyclic systems. Use of the lactone 59 as a tricarbonyl unit is noteworthy. Reaction of the lactone 59 with the dianions of ethyl acetoacetate gave the intermediate 60 which cyclized specifically to 61 as in Scheme I.36. It was observed that Claisen cleavage occurred under conditions required to open the lactone ring system. This places a limit on the

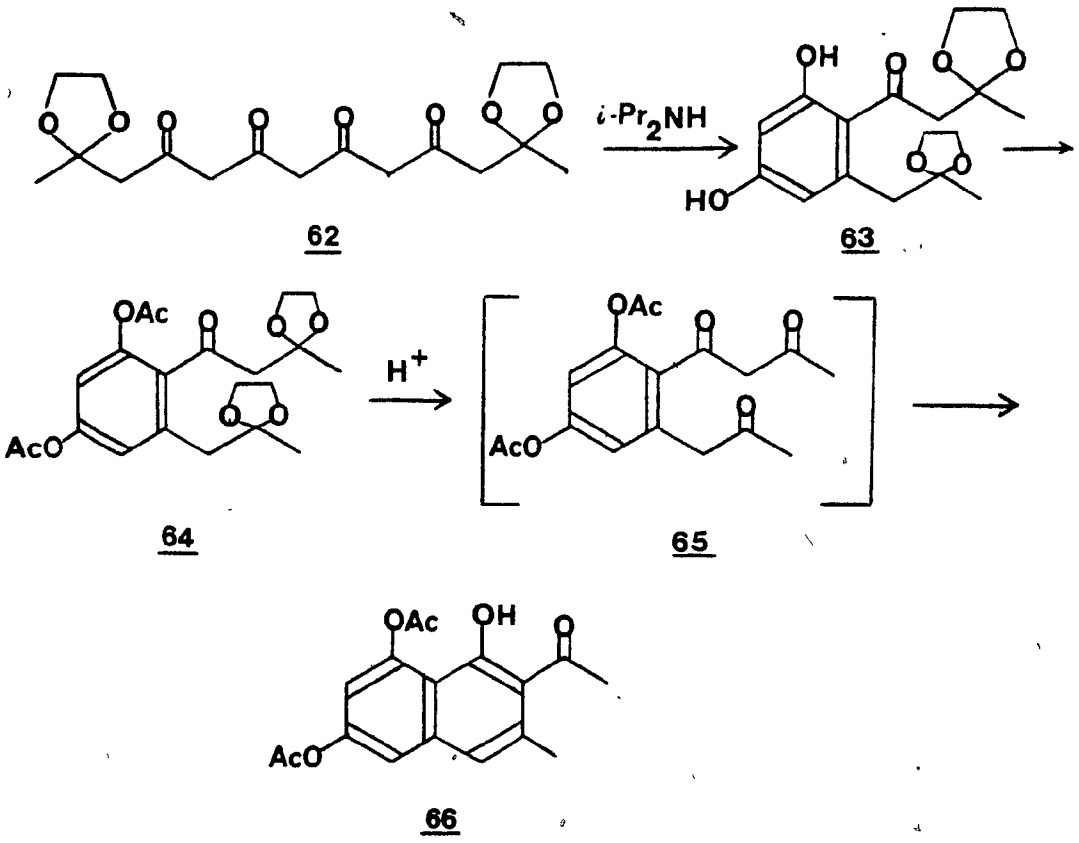


59 60 61

Scheme I.36

applicability of the pyrone approach to the synthesis of polycyclic phenols.

Many of the polyketide naphthalene and anthracene compounds arise by a reaction sequence in which the initial aldol attack must occur at the internal carbonyl group. A biomimetic type synthesis of the naphthalene 66 was reported by Harris[70]. The doubly protected hexaketone 62 with diisopropylamine gave the expected resorcinol 63. The resulting phenolic group was protected as its acetyl derivative 64. Treatment of 64 with acid gave the triketone intermediate 65 which underwent aldol cyclization immediately to give the naphthalene 66 as depicted in Scheme I.37. In the



62 63 64 65 66

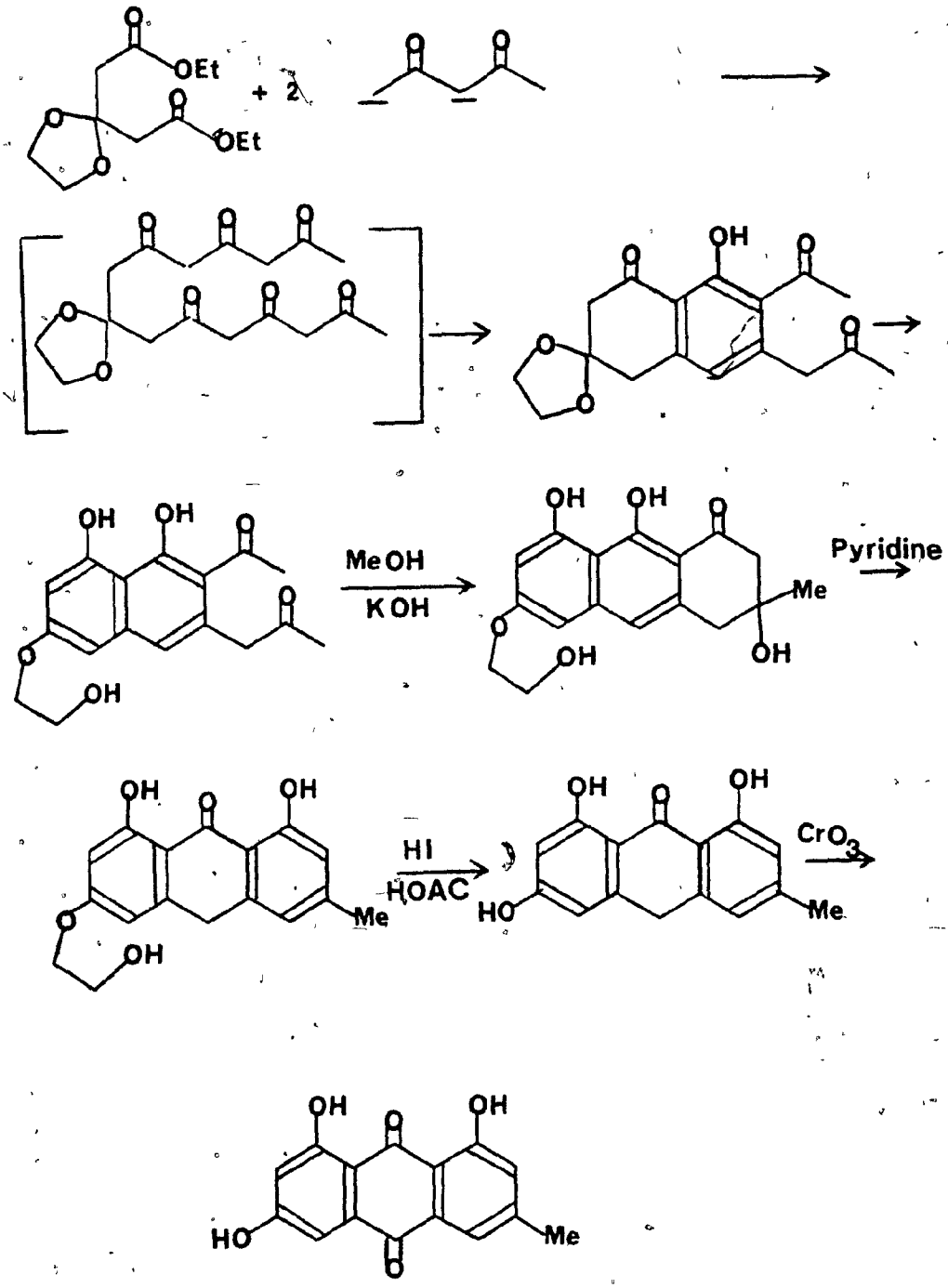
Scheme I.37

case of terminally protected heptaketone, the preferred site of cyclization is the 4-keto group and therefore terminal protection has only very limited value for the synthesis of anthracene derivatives.

A different strategy was adopted by Harris and his co-workers[71] by way of protecting the middle keto group as shown in Scheme I.38 for the synthesis of emodin (67). The chemistry of triketo acids and esters and also higher homologs has attracted considerable attention as well[72]. The cyclization and aromatization of such triketo esters and its higher homologs to resorcinols and naphthols mimic their formation in nature. A typical example of preparing such triketo esters and its cyclization to phenolic commpounds by Hill and Harris[73] is depicted in Scheme I.39.

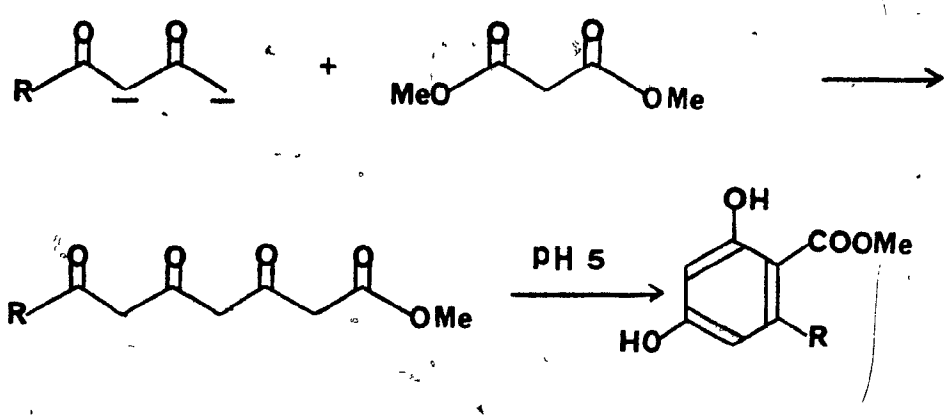
Even though there are still limitations to the synthesis of naturally ocurring phenolic compounds through this polyanion chemistry, it has taken a step closer to the natural biogenetic path. The future task is to try to attain more control over the direction of cyclization and in the preparation of poly-β-carbonyl compounds.

Recently, Brownbridge[74] in this laboratory developed the use of enol silyl ethers as the equivalent of enolate anions. With the bis-enol silyl ether (68), it can be considered as the dianion equivalent of acetoacetate. The compound 68 undergoes cyclo-aromatization with a number of 1,3-dicarbonyl equivalents to give phenolic compounds.



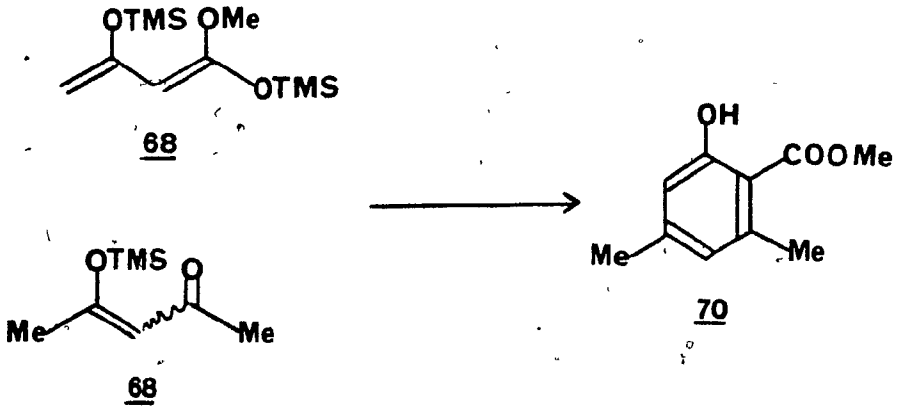
67

Scheme I.38



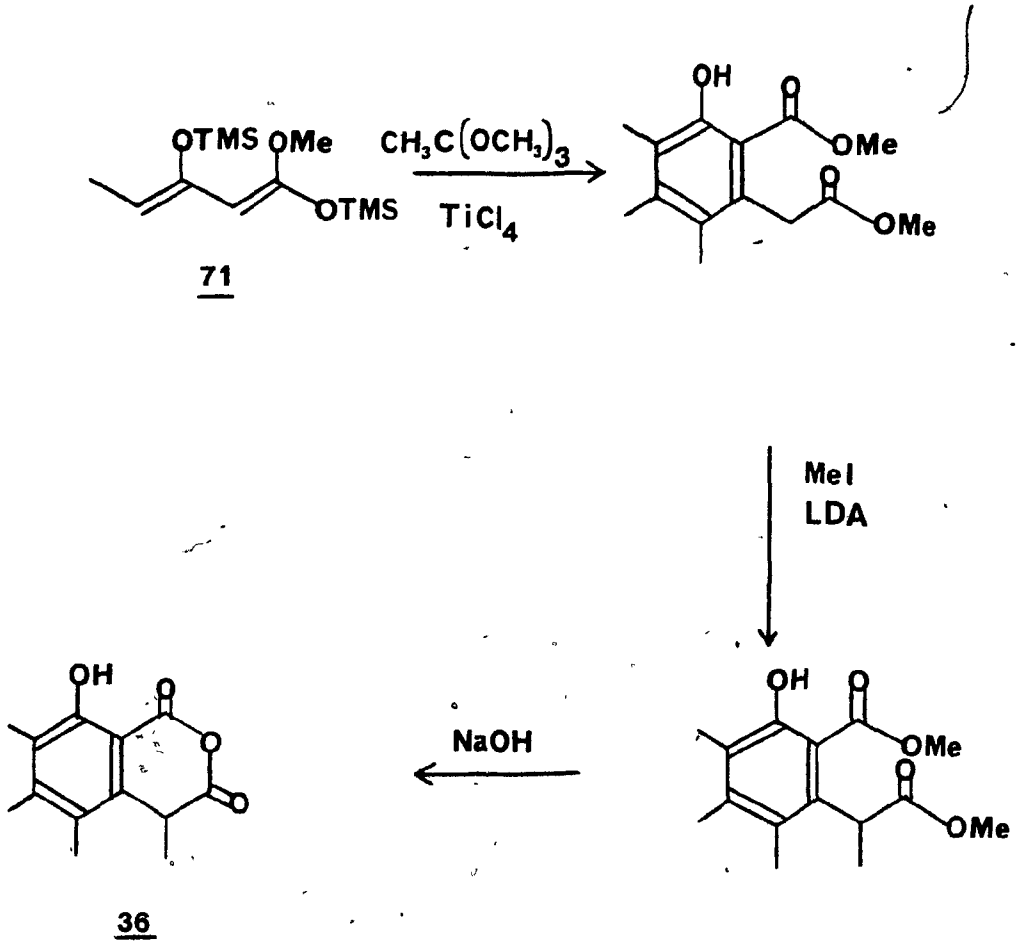
Scheme I.39

In a typical procedure, methyl 4,6-dimethyl salicylate (70) was synthesized by condensing 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (68) with 69 in the presence of titanium tetrachloride as depicted in Scheme I.40. The



Scheme I.40

control of regiochemistry of this condensation reaction is described elsewhere in this thesis. The use of this methodology for the synthesis of natural phenolic compounds is demonstrated by the synthesis of sclerin (36)[75] in Scheme I.41.



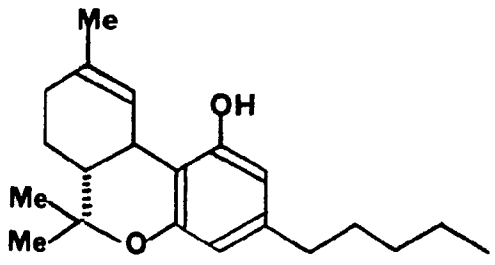
Scheme I.41

II. A BIOMIMETIC SYNTHESIS OF Δ^1-TETRAHYDROCANNABINOL

A. INTRODUCTION

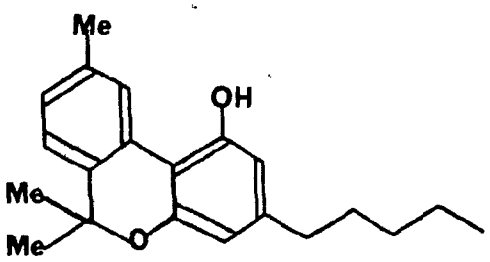
Cannabinoids are a group of phenolic compounds isolated from a plant called cannabis sativa. The flowering top of the female plant is covered with glandular hairs which secrete a resin. The cannabis resin is known as "hashish" in the Middle East and Europe, 'charas' in India and marihuana in North America. Herbal cannabis is prepared simply by collecting the flowering tops and allowing them to dry. Cannabis resin is made by separating the superficial hairs which contain the active resin from the rest of the plant. This is done by cooling dried plant material and coarsely powdering and sifting. The finest powders are rich in resin hairs and can be compressed readily into a hard, pale brownish-green mass.

Even though cannabis resin constitutes a number of closely related compounds, Δ^1-tetrahydrocannabinol(Δ^1-THC) (72) is now recognized as being responsible for the majority

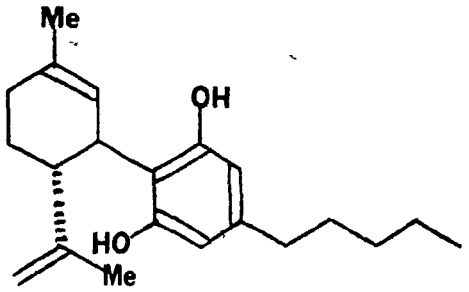


72

of the psychotomimetic activity of 'marihuana'[76]. The active principle occurs, in both fresh plant and dried or prepared material with a group of related meroterpenes. The three main cannabinoids present in cannabis preparations are Δ^1-THC, cannabinol CBN (73) and cannabidiol CBD (74). Altogether, approximately 35 different cannabinoids have been identified in cannabis.



73

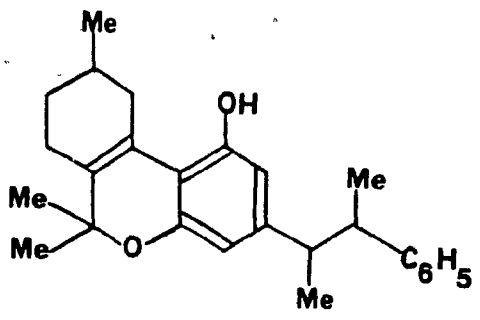


74

As illicit drugs, hashish and the other cannabis are used in different parts of the world. Apart from the bad publicity that these drugs have acquired for the past century, there is a positive side that has been discovered in the past years. The resin has been used in medicine and also as psychotomimetic drug since the ancient times[77]. A Chinese treatise, about 200 years old, has recorded the use of cannabis as an anaesthetic in surgery[78].

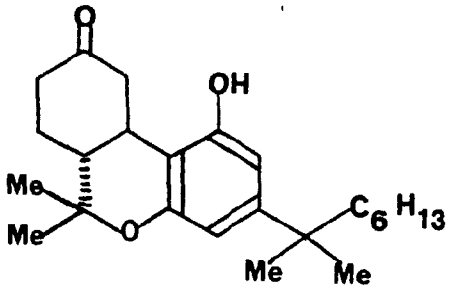
The biomedical aspect of cannabis was investigated by different groups and several reviews have been published[79-81]. In various animals, Δ^1-THC and other synthetic THCs show predominantly central nervous system (CNS) depression and ataxia, which lasts from several hours to days, depending on the dose administered. Hashish and its active components have been used for glaucoma and as an antinauseant in patients undergoing cancer chemotherapy[82]. In the case of glaucoma where patients tend to become refractory to the drug in use, the addition of a new class of drug which presumably acts by a novel mechanism is of great interest. Preliminary studies in man have already given some indication of analgesic potential for Δ^1-THC[83].

Various analogs of Δ^1-THC have been prepared and investigated for their medicinal uses. A carbocyclic analog (75) originally synthesised by Roger Adams[84] in the 1940s,



75

shows hypotensive effects[85] at doses where no CNS effects occur. This will open up a fruitful area for cardiovascular drugs. Preliminary studies have indicated the use of nabilone 76, another analog of Δ^1-THC as a tranquilizing agent[86].



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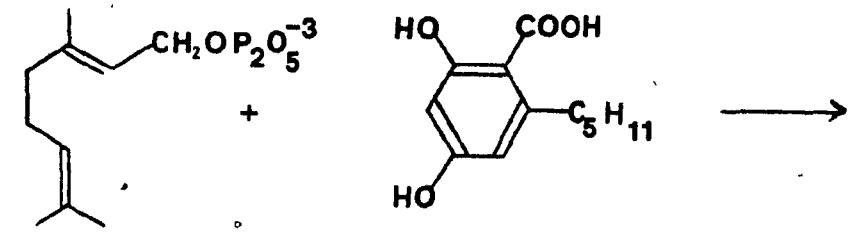
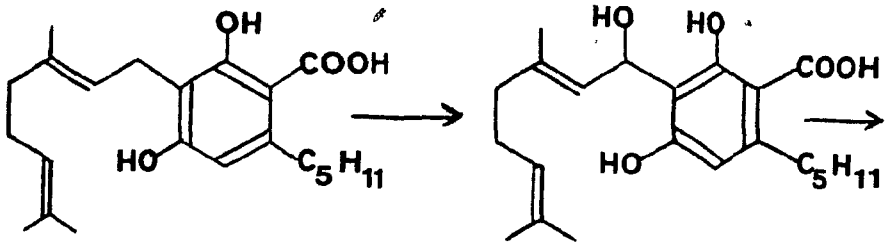
B. BIOGENESIS OF CANNABINOIDS

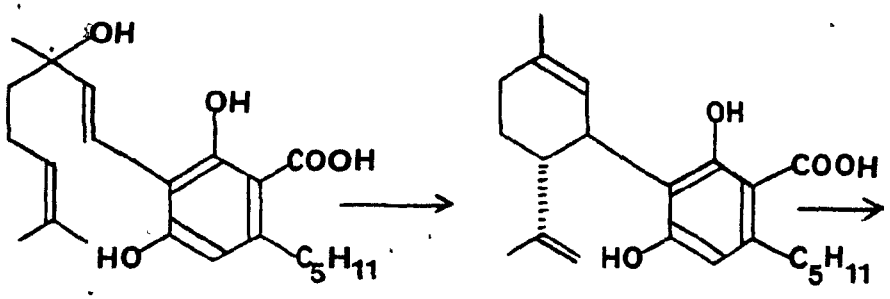
Since Todd suggested the idea[87] that the cannabinoids are originating in the plants from a condensation of a terpene derivative with olivetol, many people have investigated the biogenesis of cannabinoids. Cannabinoids occur in plants in both the free and carboxylic acid forms. Fetterman and co-workers[88] have shown that the acid form decarboxylates quantitatively when gas chromatographed. Even though the cannabinoic acid is inactive, it has been found to be converted to the active component by decarboxylation either in the plant by enzymes or outside due to heat. Therefore we have a reason to believe that the Δ^1-tetrahydrocannabinoic acid is an intermediate during the biogenesis of Δ^1-THC. The



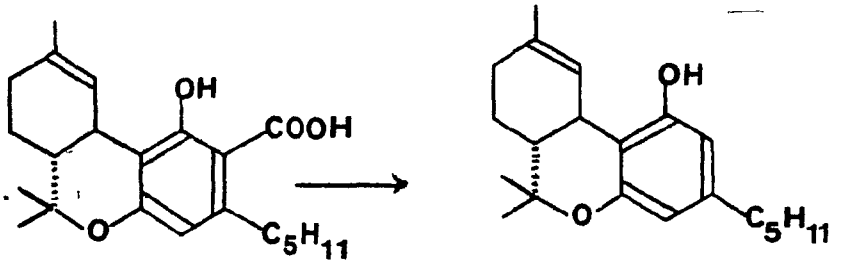
Geranyl pyrophosphate Olivetolic acid



Cannabigerol 8-Hydroxy-cannabegerol



Cannabidiol



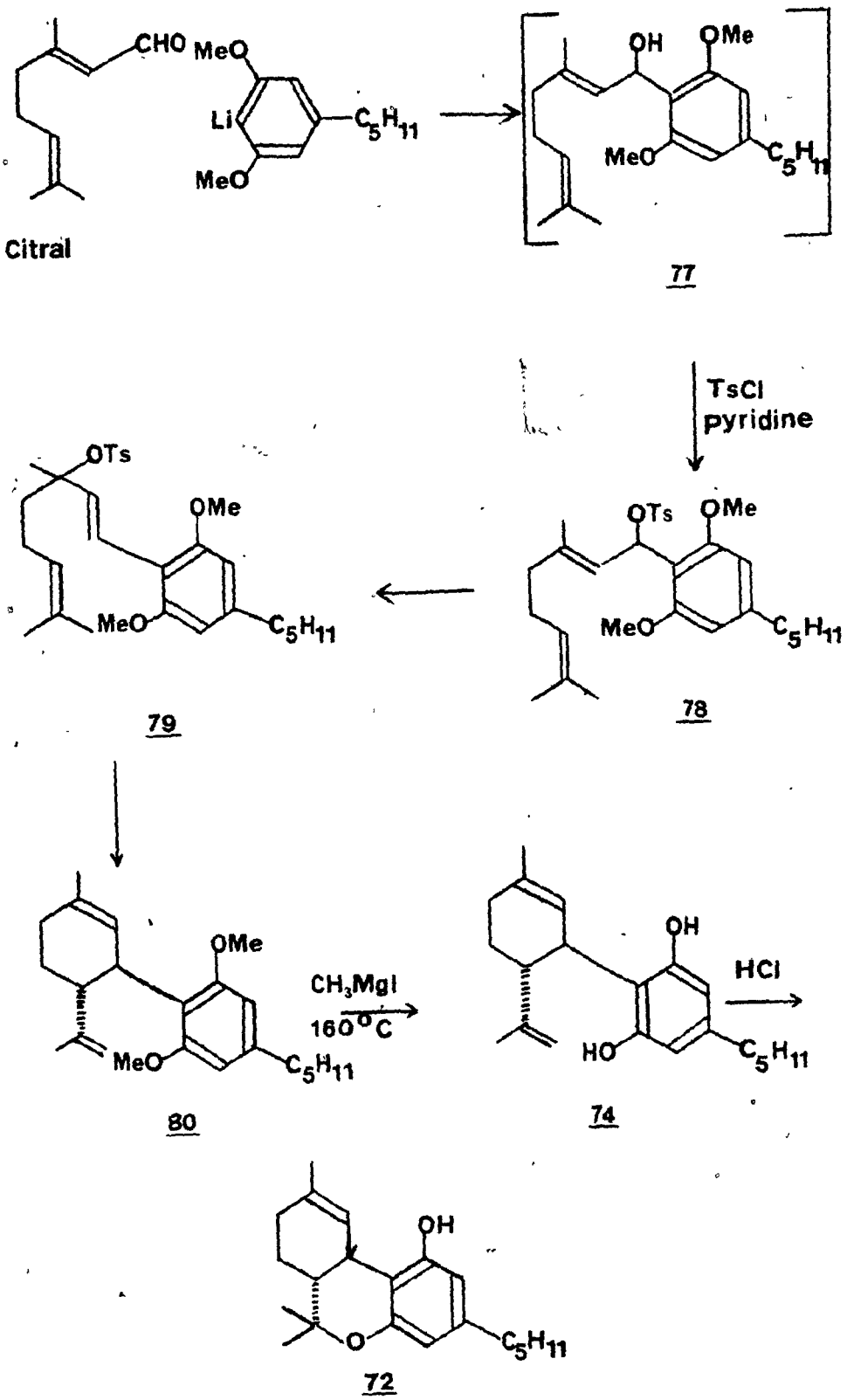
Δ^1-THC acid Δ^1-THC

Scheme II.1

assumed biogenesis of Δ^1-THC is depicted in Scheme II.1[89]. This biogenetic pathway is actually a summary of the various investigations done so far. Recent advances in the elucidation of the biogenesis of terpenes and steroids and the isolation of numerous new cannabinoids have made possible the presentation of Todd's scheme in modern terms. The presence of cannabinol and cannabinoic acid in hashish, one derived from olivetol and the other from olivetol carboxylic acid poses a problem in biogenesis. With the information available so far, it is hard to decide whether cannabigerol and cannabigerolic acid are formed independently or whether the olivetolic acid chain is the only one and the other compounds are formed by decarboxylation in the plant. The latter idea is supported by the fact that olivetolic acid was isolated during the biosynthetic studies of terpenoids. No conclusive experimental evidence has been obtained so far in this field.

C. SOME OF THE PREVIOUS SYNTHESES OF Δ^1-THC

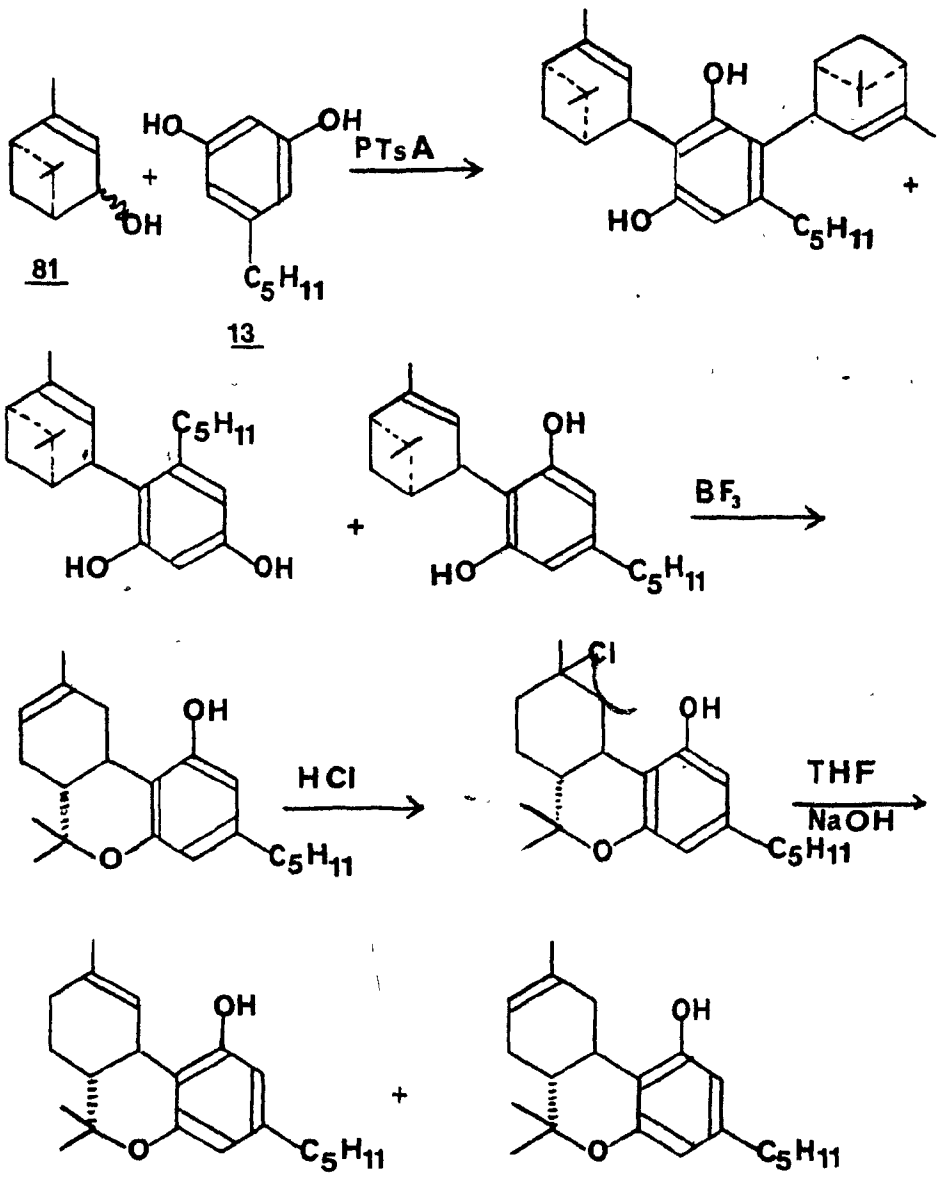
The first total synthesis of Δ^1-THC (72) was reported by Meehoulam and Gaoni[90] in 1965 as depicted in Scheme II.2. In this synthesis, the cyclization step involves a trans-cis isomerization of double bond, which formally does not participate in the reaction. It is possible that the geranyl derivative 78 isomerizes through internal return to the derivative 79 which undergoes cyclization. The olivetol part


CHO
MeO
Li
C_5H_{11}
MeO
Citral
OH
OMe
MeO
C_5H_{11}
77
TsCl
pyridine
OTs
OMe
MeO
C_5H_{11}
79
OTs
OMe
MeO
C_5H_{11}
78
OMe
CH_3MgI
160°C
MeO
C_5H_{11}
80
OH
HCl
HO
C_5H_{11}
74
OH
O
C_5H_{11}
72

Scheme II.2

was synthesized from 3,5-dihydroxy benzoic acid by many steps. The overall yield obtained in this synthesis was 2%.

Another synthesis of Δ^1-THC was reported by Mochoulam et al.[91] in 1967. In this synthesis they used verbenol (81) as the terpene part. This synthesis was planned on the basis that the attack by the resorcinol will be favoured from the



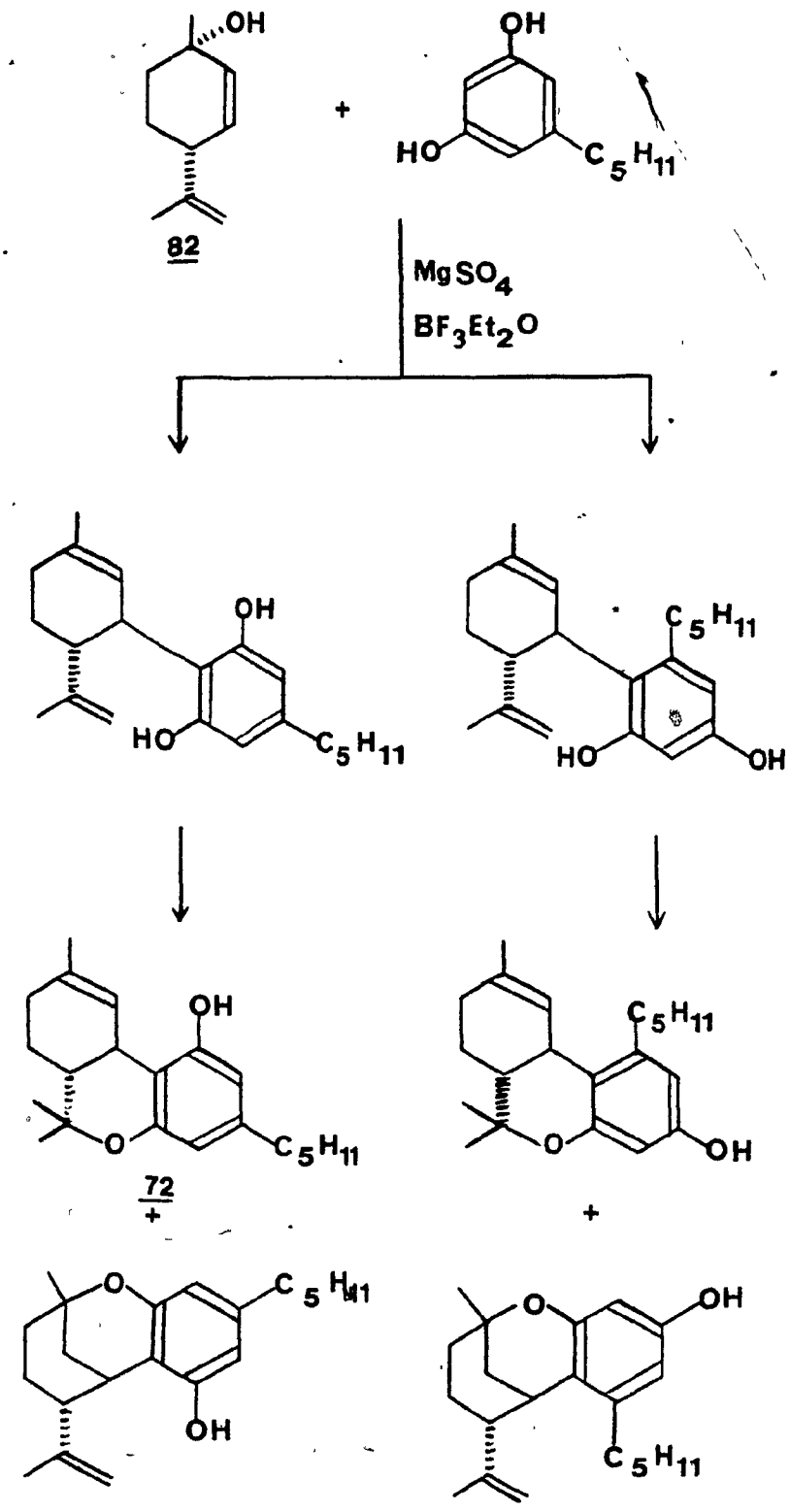
Scheme II.3

side opposite to the bulky dimethylmethylene bridge in verbenol and will thus provide stereochemical control of the reaction to give mainly trans products. The synthetic scheme is depicted in Scheme II.3.

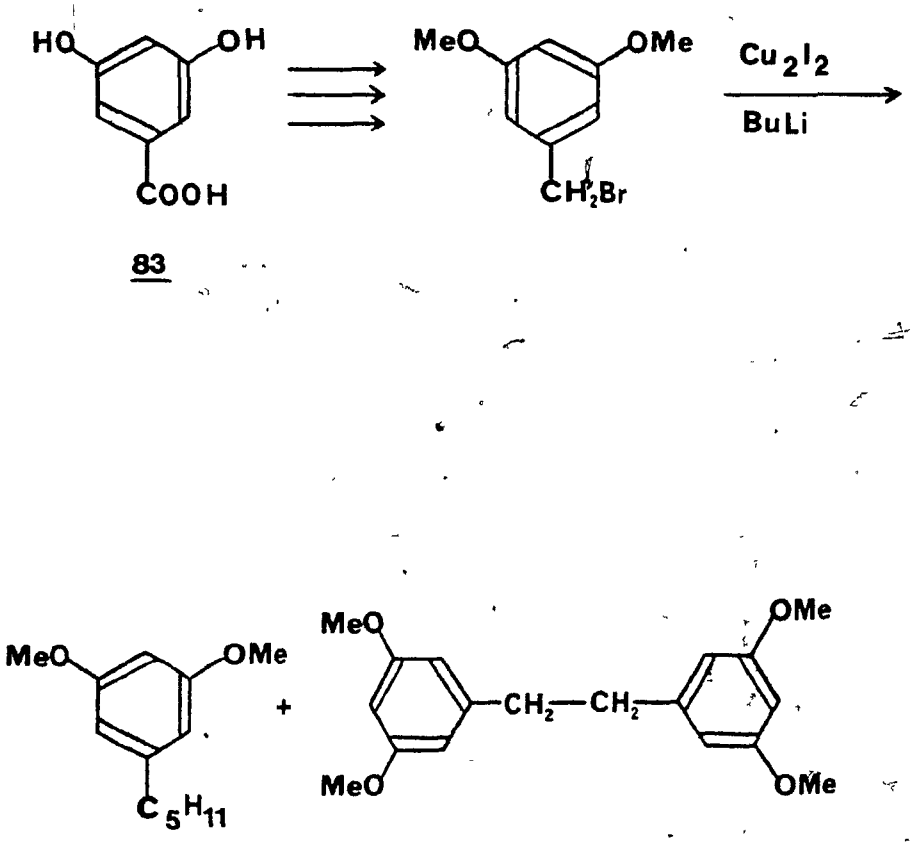
The second method, even though better in yield, still has some difficulties in isolating the intermediates and the final product. Even though this method is designed to give stereocontrol, it lacks the regioselectivity in the first step thereby giving several products.

Petrzilka et al.[92] reported the synthesis of Δ^1-THC using (+)-cis- or trans-p-mentha-2,8-diene-1-ol (82) which was later modified by Razdan[93] and co-workers. They were able to isolate the Δ^1-THC in 31% yield. The main difficulties were associated with the separation of the various isomers. Since the aromatic ring of olivetol has 3 sites for electrophilic substitution it was difficult to control the reaction in its regioselectivity. The reaction is depicted in Scheme II.4.

In all the syntheses described so far, they have in common as the critical step the condensation of a monoterpene with olivetol (13) which is generally synthesized from an aromatic precursor such as 3,5-dihydroxybenzoic acid (83). Olivetol has been synthesized by several groups[94-96] and a synthesis by Corey in 1967 is an example of such an approach (Scheme II.5). In a similar approach, Krishnamurty and Prasad[97] have described two new methods for the synthesis of olivetol in 1975. The reaction scheme is depicted in Scheme II.6.

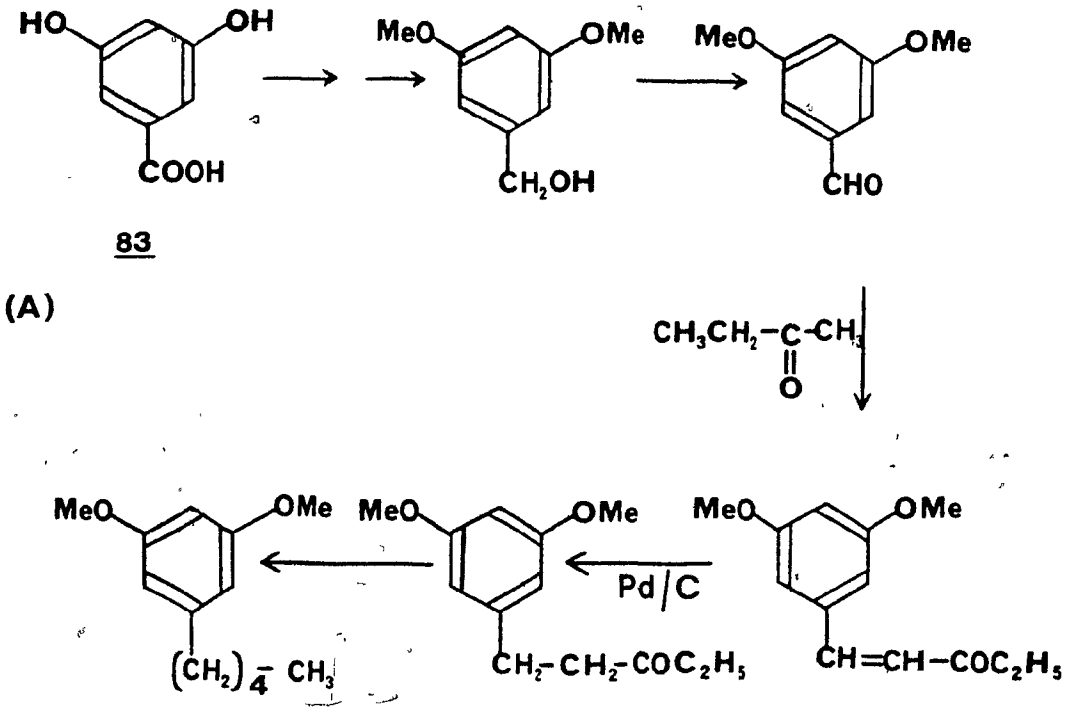


Scheme II.4



83

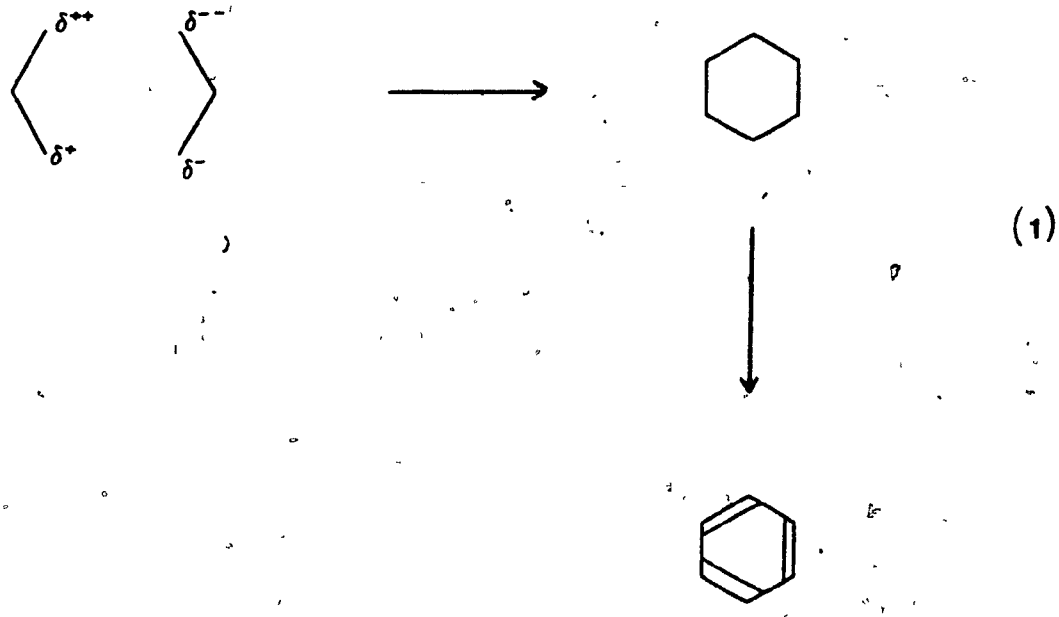
Scheme II.5


HO
OH
COOH
MeO
OMe
CH2OH
CHO
83
(A)
CH3CH2-C-CH3
O
Pd/C
(CH2)4 CH3
CH2-CH2-COC2H5
CH=CH-COC2H5
CH2-OH
CH2-Cl
CH2MgCl
n-C4H9 OTs
(B)
(CH2)4-CH3
13

Scheme II.6

D. CYCLOAROMATIZATION REACTION

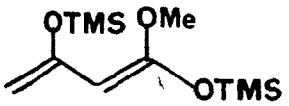
The problem of making benzenoid compounds from acyclic precursors remains a challenge due to the lack of a well established method. Recently a novel cycloaromatization reaction involving the condensation of two three-carbon units, one with two nucleophilic sites and the other containing two electrophilic sites was reported from our laboratory as in equation 1[74]. The regiochemistry in the reaction depends on



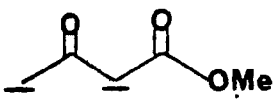
(1)

the differential reactivities of the electrophile and the nucleophile. The nucleophilic unit used in this case was 1,3-bis-(trimethylsiloxy)-1-methoxy-buta-1,3-diene (68), a dianion equivalent (84) of methyl acetoacetate. This reaction is of

particular importance, since the acetoacetate unit is the fundamental building block in the biogenesis of many natural



68

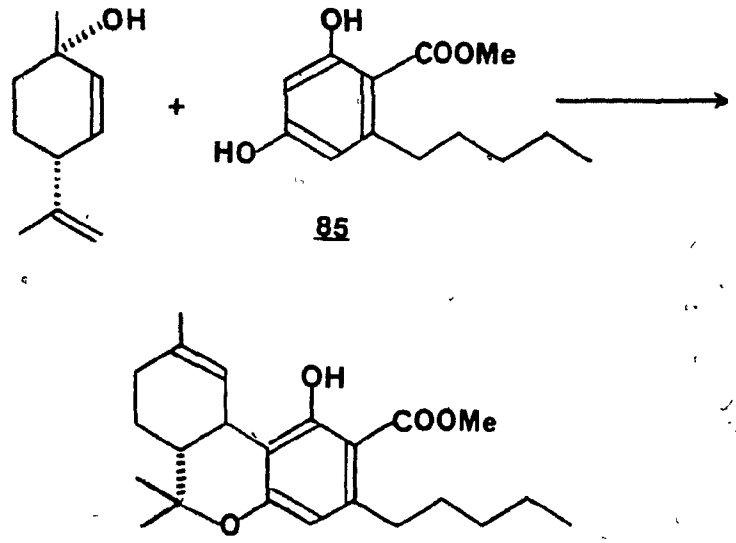


84

products. Condensation of 68 with various equivalents of β-dicarbonyl compounds in the presence of titanium tetrachloride gave substituted methyl salicylates. The regiochemistry is controlled by the order of reactivity of the electrophilic sites, which is conjugate position of enone > ketone > mono-thioacetal, acetal, etc. Essentially the construction of six-membered rings by this method is different from the classical methods such as Diels-Alder reaction or Robinson annelation which consists of the union of two fragments, one with two carbon atoms and the other with four carbons. Moreover the regiochemistry in these reactions is essentially controlled by the direction of polarization within each fragment. This new methodology provides a novel way of making phenolic compounds and will have some advantage for the synthesis of naturally occurring phenolic compounds.

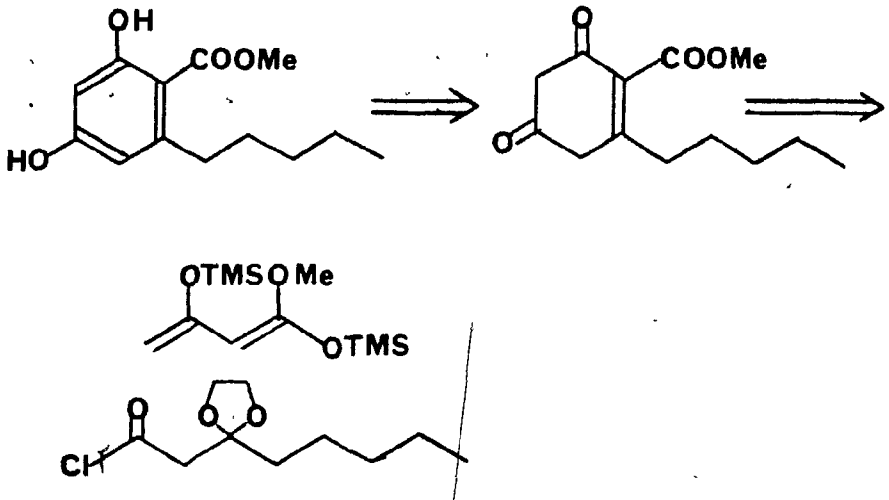
E. THE PROPOSED SYNTHESIS OF Δ^1-TETRAHYDROCANNABINOL

In this thesis, we wish to propose an alternative synthesis of Δ^1-THC based on the cycloaromatization reaction. The basic strategy adopted for the synthesis of Δ^1-THC includes the condensation of methyl olivetolate (85) with an optically active monoterpene, para-mentha-2,8-diene-1-ol (82), as shown in SchemeII.7. The methyl olivetolate part can be



Scheme II.7

synthesised by the cycloaromatization process described earlier. A retro synthesis of methyl olivetolate is described in Scheme II.8. There is an advantage in using methyl olivetolate instead of olivetol as shown in Scheme II.7. In the final condensation process, the three reaction sites in olivetol are reduced to two sites in the case of methyl olivetolate. This may enhance the regioselectivity of the condensation reaction.



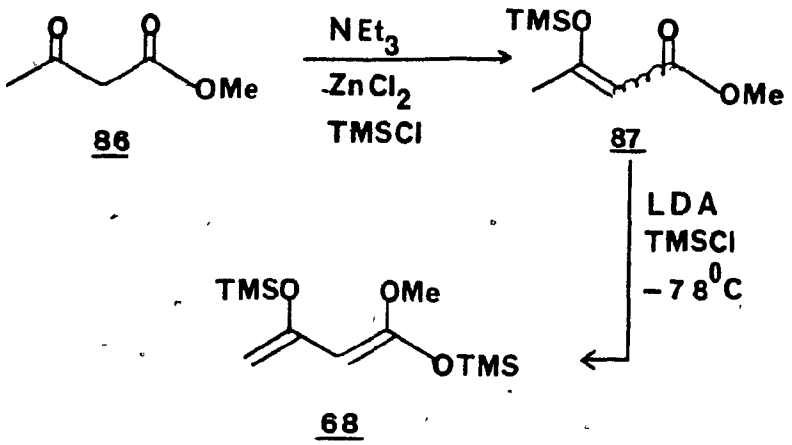
Scheme II.8

III. RESULTS AND DISCUSSION

A. NUCLEOPHILIC COMPONENT

Preparation of 1,3-bis-(trimethylsiloxy)-1-methoxybutadiene

1,3-bis(Trimethylsiloxy)-1-methoxybutadiene (68), the dinucleophilic component required for the cycloaromatization reaction was synthesised by a two-step procedure as shown in Scheme III.1[74]. Direct silylation of the dianion of methyl acetoacetate was not carried out because of competitive C-silylation[98]. The monosilylated compound (87) was prepared



86 87 68

Scheme III.1

by a procedure developed by Danishefsky[99], in which the silyl group was introduced in basic media using zinc chloride as a

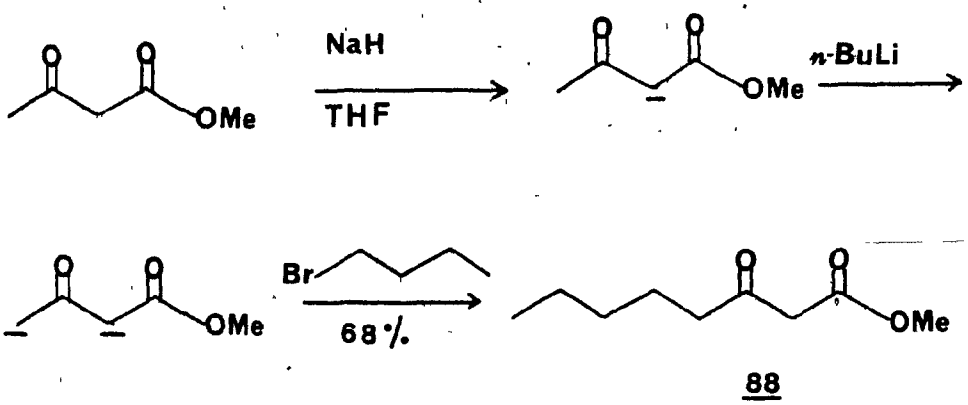
catalyst. Compound 87 was distilled at reduced pressure and was reasonably stable at 4°C under anhydrous conditions. Compound 87 was then converted to the bis-enol-silyl ether 68 by a procedure developed in our laboratory[74]. Compound 68 was found to rearrange with heat and was therefore usually not purified by distillation. Compound 68 was of reasonable purity and can be used as such for the next step.

B. PREPARATION OF THE ELECTROPHILIC COMPONENTS

The electrophilic component consists of carbonyl equivalents with different reactivity at the 3 carbon unit sites. In order to make the regioisomers of methyl olivetolate, two different electrophilic components were required.

Preparation of methyl 3-oxo-octonoate (88)

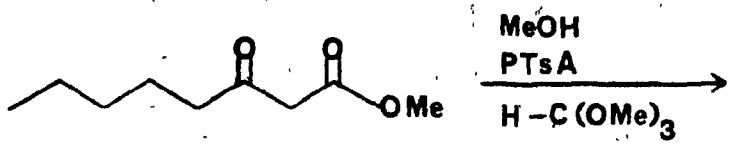
The dianion of methyl acetoacetate was prepared by a procedure developed by Weiler[100]. The dianion was then condensed with n-bromobutane in THF. The required methyl 3-oxo-octanoate (88) was obtained in 68% isolated yield. This reaction is depicted in Scheme III.2. The compound was identical in all respects to that reported in the literature[100,101]. Conversion of the keto ester 88 to the corresponding methyl 3,3-dimethoxyoctanoate (89) by the usual

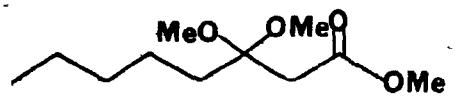


88

Scheme III.2

literature procedure of refluxing with dry methanol, trimethylorthoformate and para-toluenesulfonic acid (PTSA) as shown in Scheme III.3 The acetal was isolated in 78% yield.

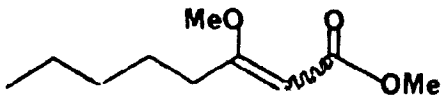




89

Scheme III.3

The crude reaction mixture contained some of the elimination product 90 which we were able to separate by column chromatography. In its ^1H nmr, compound 90 shows the vinylic



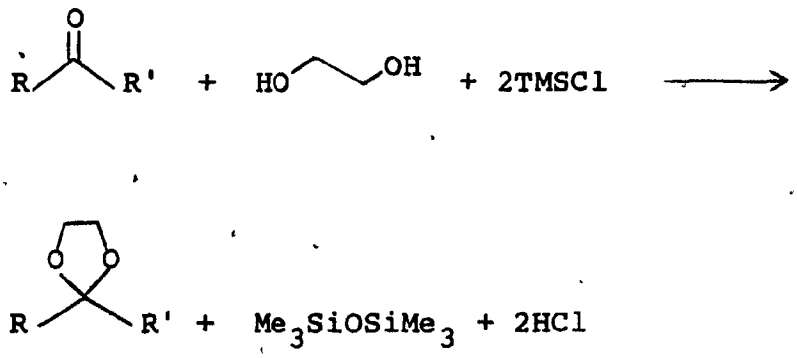
90

proton at δ 4.96 and the vinylic-OMe proton at δ 3.66 compared to the acetal proton in compound 89 at δ 3.20. In the ^1H nmr of compound 89, the expected upfield shift of the methylene protons at the C-2 position was observed (δ 2.67) compared to that of the keto ester 88 (δ 3.40). The singlet at δ 3.67 is assigned to the methyl protons of the ester and the singlet at δ 3.20 was assigned to the ketal protons. The multiplet between δ 0.96-1.83 is assigned to the n-pentyl protons. In the ir spectrum, 89 showed a carbonyl absorption at 1750 cm^{-1}.

C. KETALIZATION

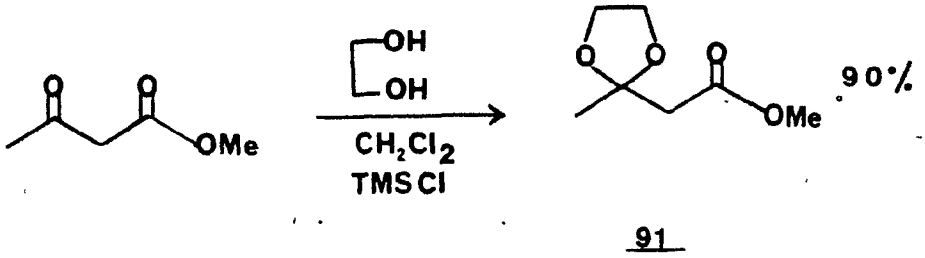
Acetalization of aldehydes and ketones is very commonly used in organic synthesis. Many methods are available in the literature for this purpose[102,103]. For the synthesis of

olivetol, we required an ethylene ketal as one of the starting materials. The acetal was prepared by a new procedure developed by us. The new procedure can be carried out under milder conditions utilizing readily available chemicals. Ketones are converted to the corresponding 1,3-dioxolanes by reaction with a small excess of ethylene glycol in the presence of trimethylchlorosilane. In essence, trimethylchlorosilane was used as the condensing agent for the acetalization reaction. A general scheme is depicted here (Scheme III.4).



Scheme III.4

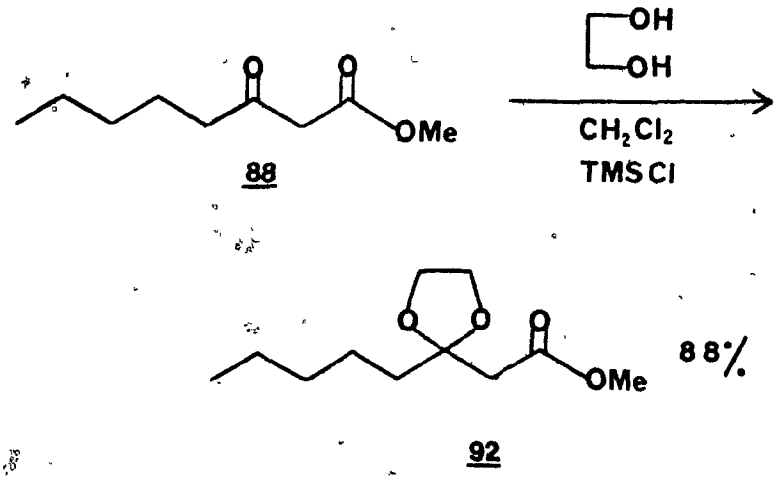
Using this methodology methyl acetoacetate was converted to the corresponding 1,3-dioxolane 91 in 90% yield. The reaction is represented in Scheme III.5.



91

Scheme III.5

In a similar way, methyl 3-oxo-octanoate (88) was converted to the corresponding dioxolane derivative 92 in 88% yield (Scheme III.6). In the ^1H nmr of compound 92 the singlet

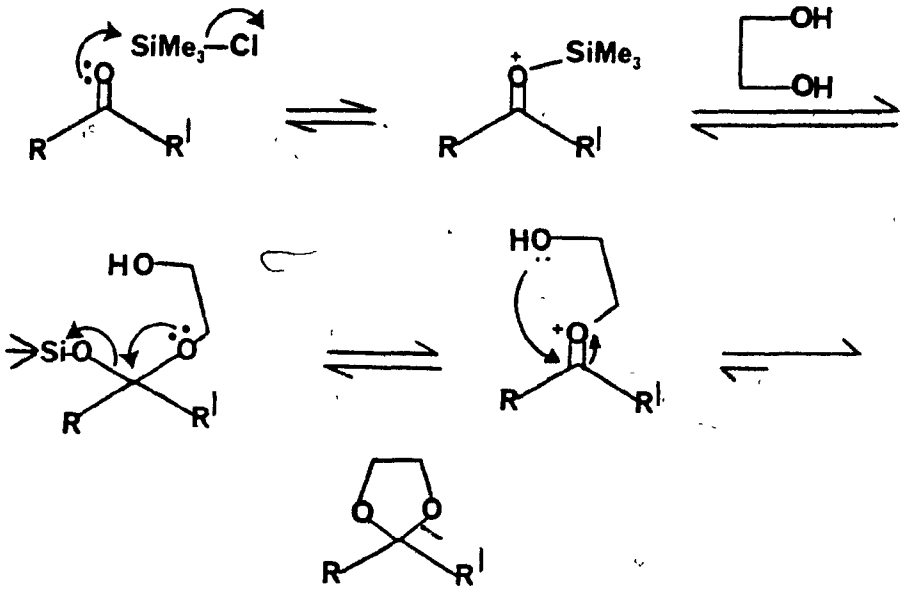


88

92

Scheme III.6

at δ 3.63 is assigned to the ester methyl protons and the singlet at δ 3.93 is assigned to the ethylene ketal protons. The methylene protons at the 3 position appear at δ 2.60. The mechanism of the formation of the ketal is believed to involve some kind of complexation or bonding between the carbonyl oxygen and chlorotrimethylsilane. A plausible mechanism is depicted in Scheme III.7. This reaction has been



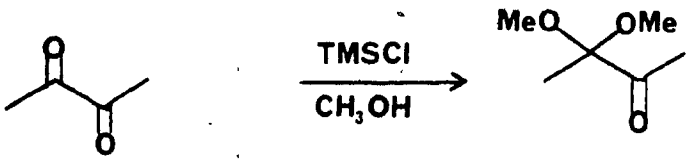
Scheme III.7

extensively investigated later by Brook[104,105] of our laboratory. The salient features of the reaction are summarized below.

(1) For normal non-activated aldehydes and ketones, acetal formation can only occur with ethylene glycol but not with methanol or ethanol.

(2) The acetalization with ethylene glycol can be carried out in methanol as solvent. This is useful in cases where solubility may pose a problem in the conventional procedure.

(3) For activated carbonyl compounds such as 1,2-dicarbonyl compounds or α,α-dichloroketones, acetalization with methanol can also be achieved. Thus diacetyl is selectively converted to the mono acetal under these conditions (Scheme III.8).

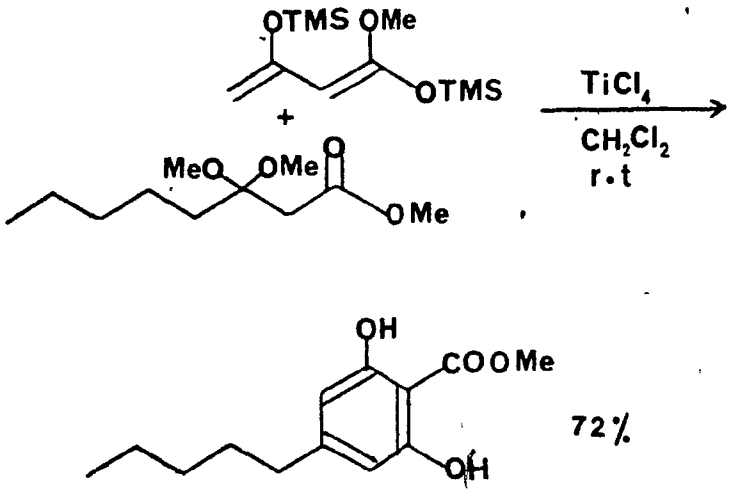


Scheme III.8

D. REGIOCONTROLLED SYNTHESIS OF METHYL OLIVETOLATES

(1) Synthesis of methyl 2,6-dihydroxy-4-pentylbenzoate

The condensation of methyl 3,3-dimethoxyoctanoate (89) with the bis enol silyl ether 68 to give the aromatic product was carried out in the following manner. The acetal 89 was mixed with the bis enol silyl ether 68 in dry methylene chloride. On addition of titanium tetrachloride and overnight stirring at room temperature, formation of the methyl olivetolate (93) was realised in 72% yield. The reaction was monitered by GLC. The synthetic route is represented in Scheme III.9. The methyl olivetolate thus obtained was



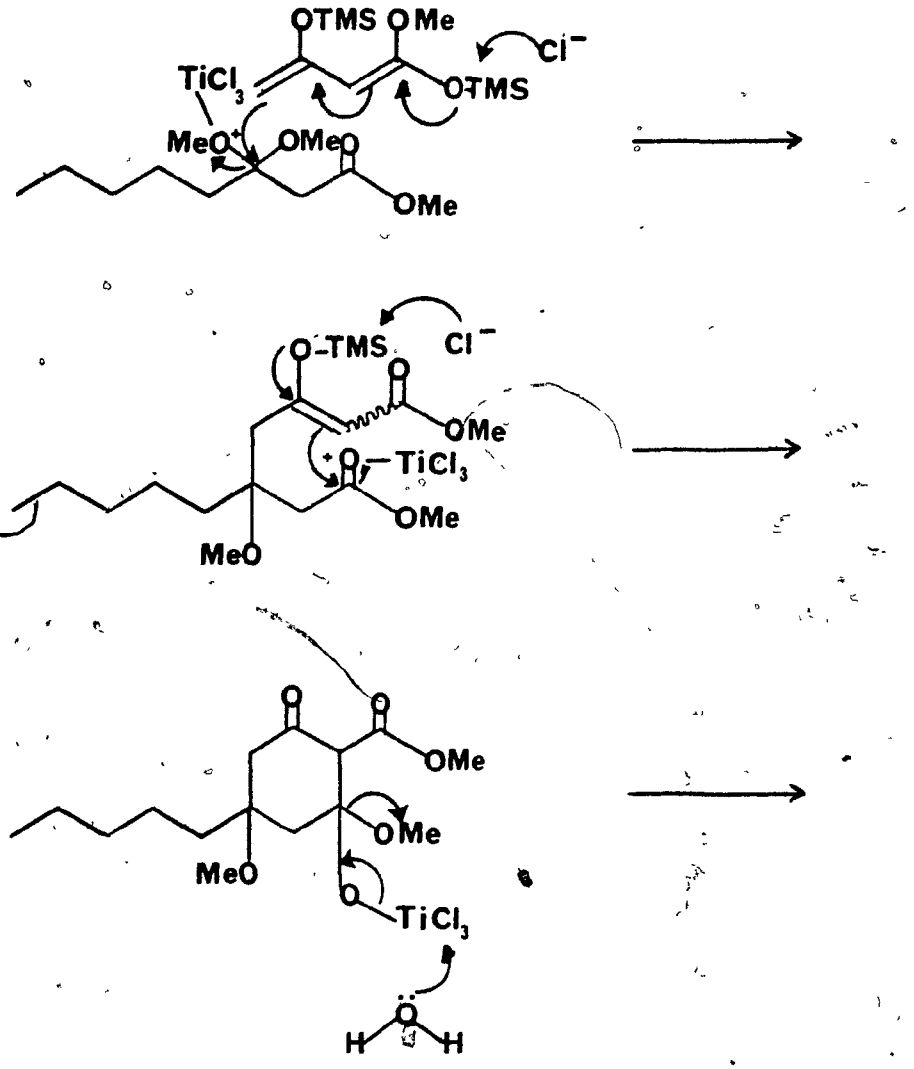
93

Scheme III.9

purified by column chromatography. The resulting product was a white crystalline solid with a mp 29-30°C.

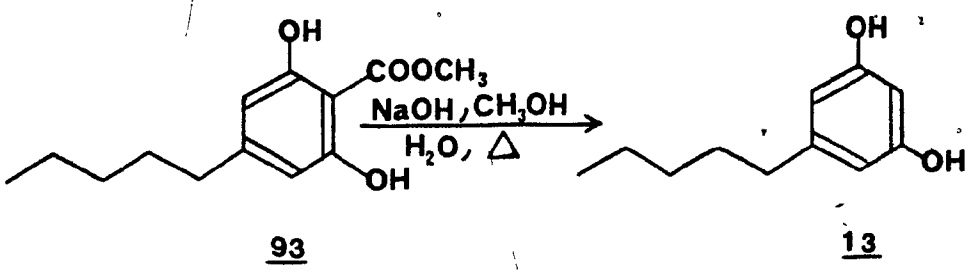
In the ^1H nmr, the singlet at δ 4.03 is assigned to the methyl ester protons (-O-$\underline{CH_3}$). The multiplet at the high field is assigned to the n-pentyl protons. Since the aromatic protons are equivalent, they appear as a singlet at δ 6.27. Similarly the phenolic protons are also equivalent. Since the phenolic protons are hydrogen bonded to the adjacent carbonyl group, the position of the peak is shifted downfield at δ 9.30. Its infrared spectrum contained a carbonyl band at 1675 cm^{-1} and a characteristic hydrogen bonded phenolic band at 3460 cm^{-1}. These data, coupled with the mass spectrum m/z 238 (M^+), indicated that the aromatic compound 93 had been formed. Further proof for this structure was obtained by conversion of 93 to olivetol (13).

A plausible mechanism of the formation of methyl olivetolate is schematically represented in Scheme III.10. The methyl olivetolate was hydrolysed and decarboxylated in one step with sodium hydroxide in methanol and water to give olivetol as shown in Scheme III.11. The compound obtained was a light brown solid with a mp of 41-42°C (literature mp 42-44°C)[94,97]. The compound was identical in all respects with the spectral data of olivetol reported in the literature. This constitutes a new and convenient synthesis of olivetol. However, for the synthesis of Δ'-tetrahydrocannabinoate in the proposed scheme, compound 93 is of the wrong regiochemistry.



93

Scheme III.10

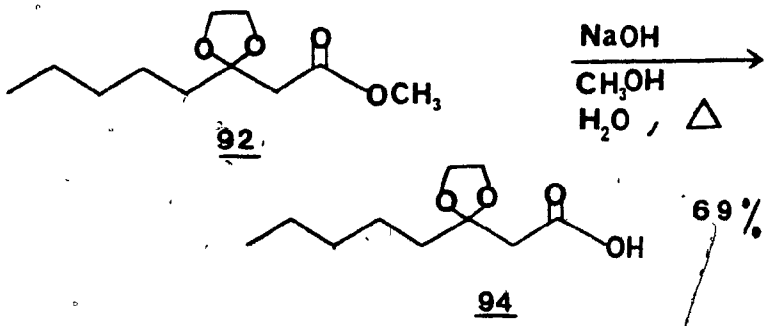


93 13

Scheme III.11

The regiochemistry of the cycloaromatization reaction must be reversed to get the correct isomer of methyl olivetolate 96. This was realised in the following manner.

First of all the ethylene ketal (92) was hydrolysed using sodium hydroxide in methanol and water. The product isolated was the expected acid 94 in 69% yield. The yield depended upon the acidification of the crude reaction mixture. The reaction mixture had to be sufficiently acidic to get the maximum yield without hydrolyzing the ketal. The optimum pH was 3. The reaction is represented in Scheme III.12. The

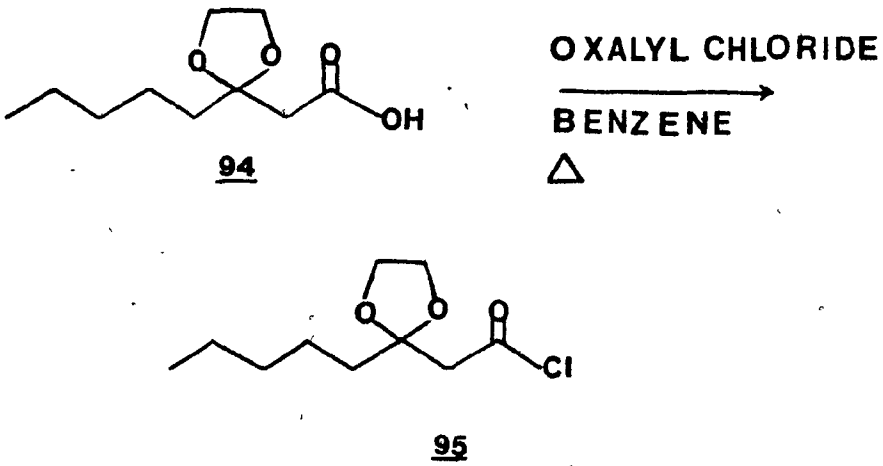


92 94

Scheme III.12

acid obtained was identified on the basis of spectral data. The disappearance of the methyl protons and the appearance of the acid proton was easily noticeable. The acid 94 was found to decompose gradually at room temperature.

The acid 94 thus obtained was converted to the acid chloride 95 by heating the acid in dry benzene and oxalyl chloride. The product obtained was almost pure and the yield was nearly quantitative. The reaction is depicted in Scheme III.13. In the proton nmr, the product was easily recognisable due to the disappearance of the acid proton and the downfield shift of the methylene proton (δ 3.17). The



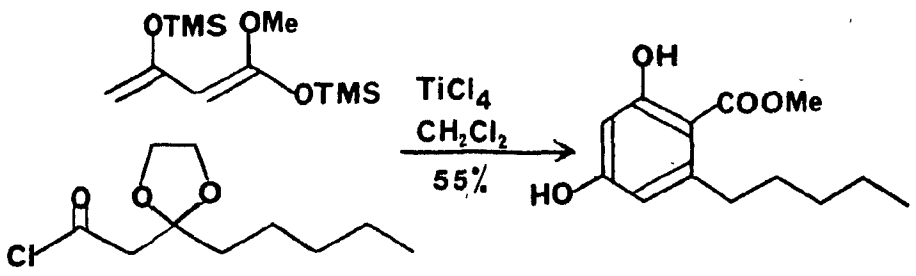
94 95

Scheme III.13

acid chloride was found to be very unstable. Hence it had to be prepared and used immediately for the next condensation reaction with the bis enol silyl ether. By converting the ethylene ketal 92 to the acid chloride 95, we have changed the relative electrophilicity of the two carbonyl functions (the acid chloride being more electrophilic than the ketal). Removal of any trace of oxalyl chloride completely from the acid chloride was essential for the success of the condensation reaction with the bis enol silyl ether. This was achieved by high vacuum evaporation of the crude acid chloride (1-2 h).

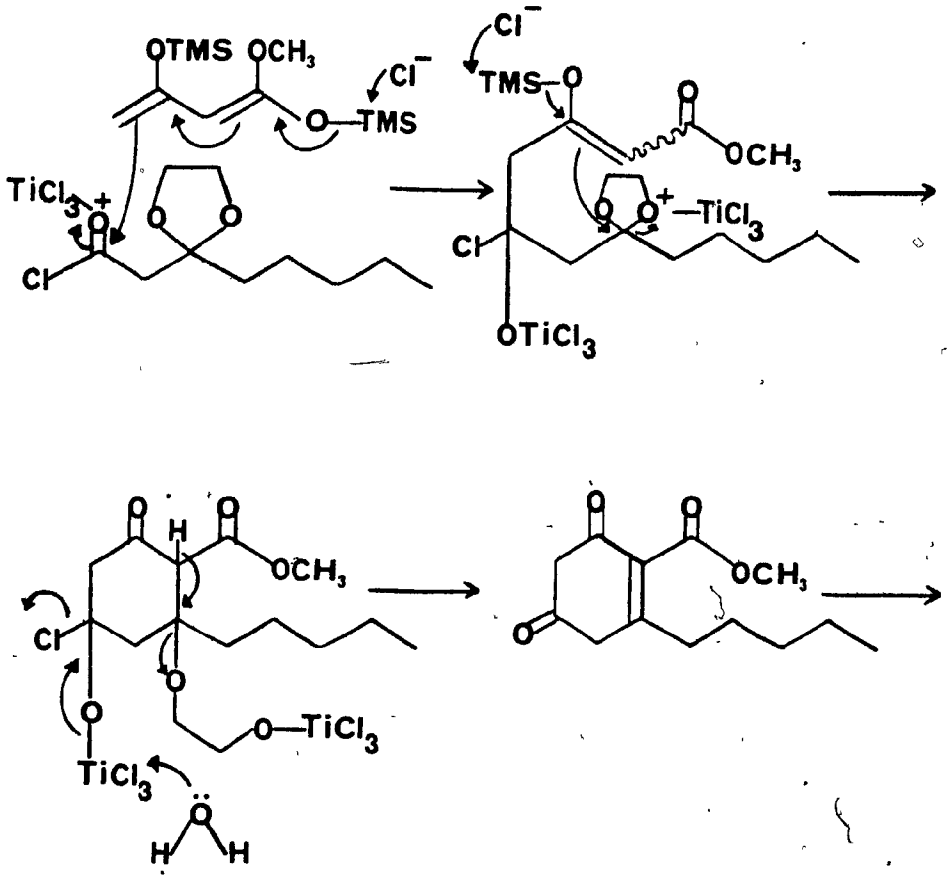
(2) Synthesis of methyl 2,4-dihydroxy-6-pentyl-benzoate (96)

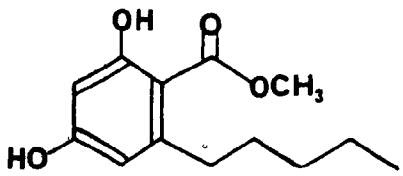
The condensation of 95 with 68 to give the aromatic product was carried out in the following manner. The acid chloride was dissolved in dry methylene chloride under nitrogen followed by the addition of the bis enol silyl ether. On addition of titanium tetrachloride and stirring for 48 h at room temperature, formation of the olivetolate 96 was realised in 55% yield. The progress of the reaction was monitered by GLC. The methyl olivetolate (96) was isolated from the crude reaction mixture by column chromatography. The product obtained was a white solid with m.p. 65-68°C. The reaction is represented in Scheme III.14. In the proton nmr the singlet at δ 11.58 is assigned to the phenolic proton



Scheme III.14

adjacent to the carbomethoxy group. The downfield shift of this phenolic proton is quite as expected due to hydrogen bonding. The non-hydrogen-bonded phenolic proton at the 4 position is assigned to the peak at δ 5.78-6.05. The multiplet at 6.13-6.33 is assigned to the two non-equivalent aromatic protons. The infrared spectrum was quite characteristic. It contained a carbonyl band at 1660 cm^{-1} and the phenolic bands at 3600 and 3400 cm^{-1} (broad). The mass spectrum of compound 96 gave the molecular ion at m/z = 238 ($M^{+\cdot}$) and the fragmentation pattern was at m/z = 207 ($M^{+\cdot}$-OMe), 206 (207-H) and 182 (206-CO). A plausible mechanism is given in Scheme III.15. The methyl olivetolate 96 was hydrolyzed and decarboxylated in one step with sodium hydroxide in methanol and water to give olivetol 13 (Scheme III.16). The compound was identical in all respects with the spectral data of olivetol reported in the



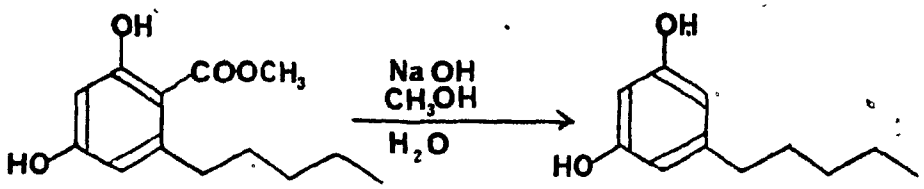


96

Scheme III.15

literature[94,97]. It is appropriate at this stage to mention that none of the methyl olivetolates were contaminated by the other isomer during their synthesis. In short, the regioselectivity was achieved with complete control.

The methyl olivetolate (96) thus prepared has the desired characteristics to undergo condensation with the terpene component with one advantage by reducing the reaction sites from three to two by the incorporation of the ester group. Since hydrolysis and decarboxylation of the ester group can be achieved easily after the reaction with the terpene, the presence of the ester group is really advantageous for this synthesis.



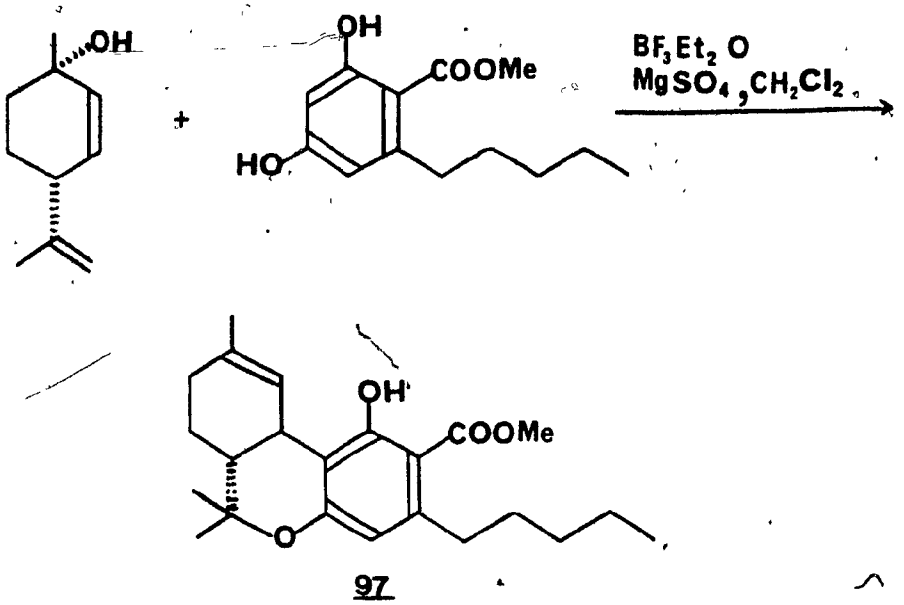
96 13

Scheme III.16

E. SYNTHESIS OF METHYL TETRAHYDROCANNABINOLATE

Condensation of 96 with an equivalent of (+)-trans-p-mentha-2,8-diene-1-ol[106] was carried out under strictly controlled conditions[107,108] as described below.

A mixture of the olivetolate 96 and the monoterpene 82 was stirred with methylene chloride under nitrogen. After the addition of anhydrous magnesium sulfate (vacuum dried), the mixture was stirred for another 20 min. After cooling the reaction mixture in an ice bath, freshly distilled borontrifluoride etherate (distilled from calcium hydride) was added. The reaction mixture was stirred at 0°C for 1.5 h and anhydrous sodium bicarbonate was added. Stirring continued until the brown colour faded, and the reaction mixture was filtered and evaporated to give a colourless gum. The crude product was purified with flash column chromatography on silica gel. The major component isolated was identified as (-)-trans-Δ^1-methyl-tetrahydrocannabinoate (97) in 55% isolated yield. A small amount of the Δ^6-isomer (98) was also detected in the proton nmr of the crude product, but was not isolated from the column. The rest of the material was a dark tar which also could not be isolated from the column. The reaction is as depicted in Scheme III.17. In the ^{1}H nmr, the singlets at δ 1.09 and δ 1.43 are assigned to the geminal methyl protons. The singlet at δ 1.68 is assigned to the vinylic methyl protons. The ester methyl proton is assigned to the singlet at δ 3.91. The singlet at δ 6.21 is assigned

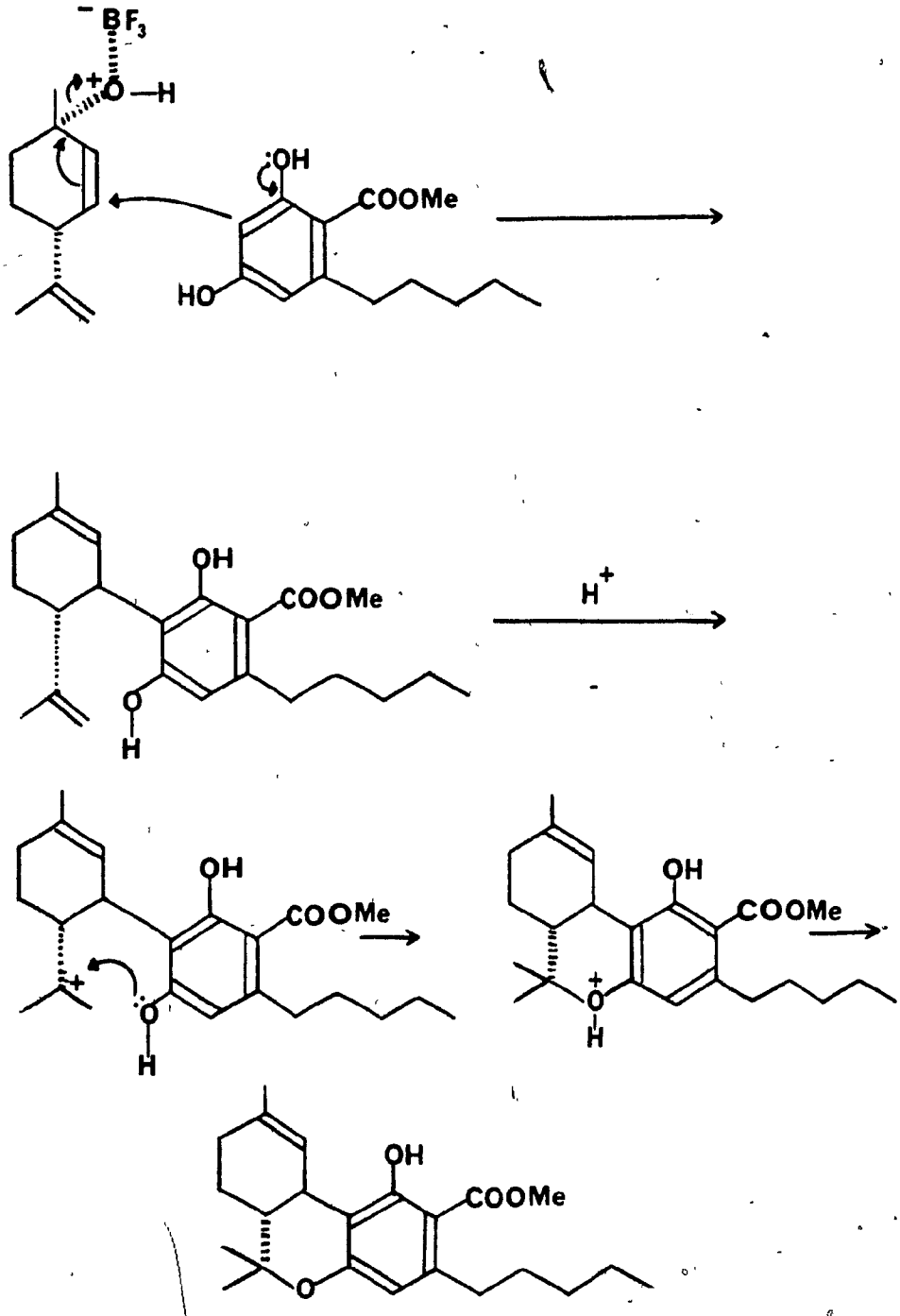


97

Scheme III.17

to the only aromatic proton in this molecule. The vinylic proton appears at δ 6.39 as a broad singlet. The singlet at δ 12.32 is assigned to the phenolic proton and the downfield shift of this proton was quite as expected due to intramolecular hydrogen bonding with the adjacent carbonyl group. Only one kind of vinylic proton was found in the ^1H nmr supporting the existence of only one form of the isomeric methyl-Δ^1-tetrahydrocannabinoate. In the mass spectrum of compound 97 there was the molecular ion at m/z = 372 ($M^{+\cdot}$) and a peak at m/z = 340 which indicate the loss of MeOH. The infrared spectrum of the product contained sharp bands at 1650 and 3400 cm^{-1}. Optical rotation measurement observed for this compound is $[\alpha]_D$ = -188.4° (0.16 $CHCl_3$). Further proof for this structure was obtained by conversion of compound 97 to

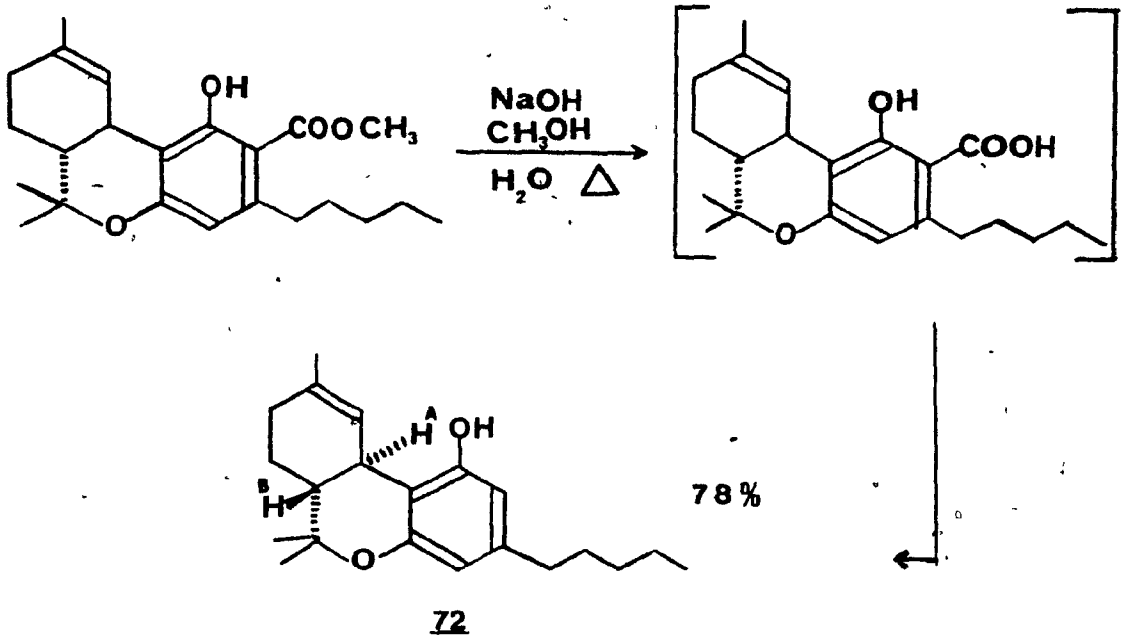
Δ^1-THC. A mechanism of the formation of Δ^1-tetrahydrocannabinoate is given in Scheme III.18.



Scheme III.18

F. PREPARATION OF Δ^1-THC FROM METHYL Δ^1-TETRAHYDROCANNABINOLATE

The hydrolysis and decarboxylation of methyl Δ^1-tetrahydrocannabinoate (97) to Δ^1-THC was achieved in a one pot reaction using sodium hydroxide in methanol and water. Compound 97 was refluxed with sodium hydroxide in methanol and water for 5 h. The reaction mixture was cooled and the product was extracted with ether. The crude product was purified by flash column chromatography[109]. The decarboxylation proceeded easily because of the presence of the orthophenolic group. The compound isolated was identified as (-)-Δ^1-tetrahydrocannabinol (72) in 78% yield. The reaction is represented in Scheme III.19. The spectral data



72

Scheme III.19

of the compound 72 were identical in all respects to that reported in the literature. In the proton nmr spectrum, the geminal methyl protons appear as two separate singlets (δ 1.09, δ 1.40). The singlet at δ 1.68 is assigned to the vinyl methyl protons. The broad doublet at δ 3.21 (J = 9.1 Hz) is assigned to the proton H_A. The large splitting in this signal is attributed to the trans-diaxial coupling to H^B. The broadening of H_A might have been caused by the unresolved splitting originate from coupling to the adjacent vinyl H and to both C_8 methylene and C_9 methyl protons[110]. The phenolic proton was shifted upfield (δ 4.71) due to the absence of any intramolecular hydrogen bonding. In the FT-IR spectrum the band at 3634 is assigned to the phenolic group. The mass spectrum of compound 72 gave the molecular ion at m/z 314 (M^+). Optical rotation measurement observed for this compound is $[\alpha]_D$ = -170° (C 0.04 $CHCl_3$) compared to the literature value of $[\alpha]_D$ = -174° reported for an authentic sample in chloroform[111].

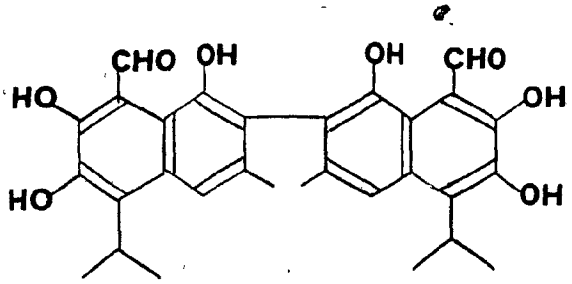
With this we have completed the biomimetic synthesis of Δ^1-tetrahydrocannabinol. Several features of the present synthesis are of interest. Condensation of 68 with 89 or 95 represents a controlled condensation of a tetra-β-carbonyl unit in a biomimetic way and can be regarded as a general way to construct natural products with resorcinol skeleton. Secondly, in the condensation of the methyl olivetolate (97) with 82, we observed chromenylation only at the carbon ortho

to the two-hydroxy groups. This is different from the reaction of olivetol where chromenylation also occurs at the carbon between the OH and the alkyl side chain. Thus we believe that the present biomimetic synthesis provides a convenient and efficient synthesis of Δ^1-THC and possibly its analogs.

IV. AN APPROACH TO THE SYNTHESIS OF GOSSYPOL

A. INTRODUCTION

Gossypol (98), a polyphenolic binaphthyl compound, is a yellow pigment that is produced by certain species of cotton plants. It was first isolated from the seed and root bark of the cotton plants by Marchlewski who derived its name from "gossyp(uim phen)ol" to indicate its origin. This compound has some renewed interest because of the reports from the People's Republic of China concerning its efficacy as a male antifertility agent[112]. Large scale clinical trials in China indicate that the drug is safe, effective, inexpensive and reversible in its effects.



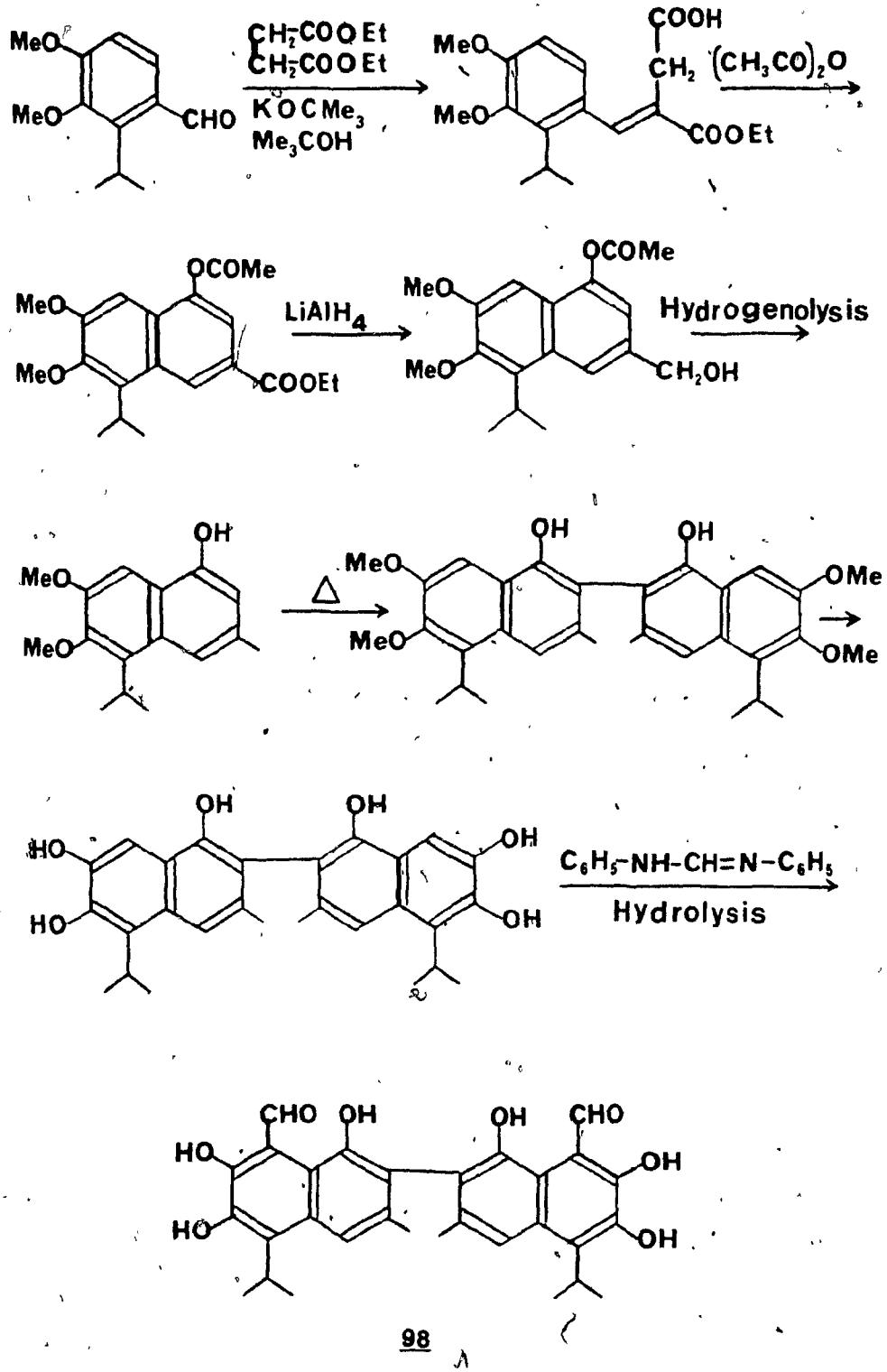
98

The compound is interesting biochemically because it is a non-steroidal drug that works by inhibiting sperm production in male animals and humans. Thus it is different in its biological activity from the steroid-based oral contraceptives. It may offer a new direction in birth control.

Gossypol is known to have toxic effects in both animals and humans, but the effective dose for an antifertility effect appears to be 100 to 700 times less than the toxic levels based on animal data[113]. At higher concentrations gossypol can cause circulatory problems, heart failure, diarrhea and hair discoloration.

There have been several studies about gossypol, but the most important synthetic and degradative studies were done by Adams and Edwards[114], especially the total synthesis by the latter as depicted in Scheme IV.1.

A recent synthesis of gossypol by Venuti[115] also used the same aromatic precursor as the starting material. Even though these synthetic methods are useful for making gossypol as such, a different approach using an acyclic precursor might be useful for making synthetic analogs of gossypol.

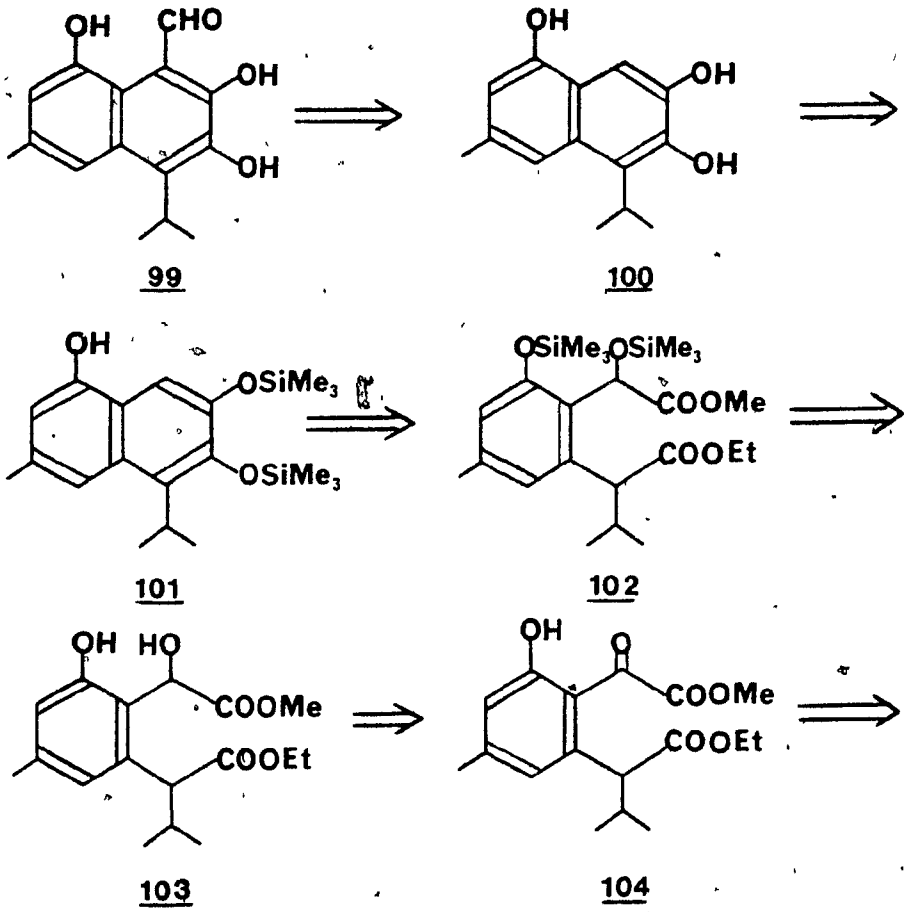


98

Scheme IV.1

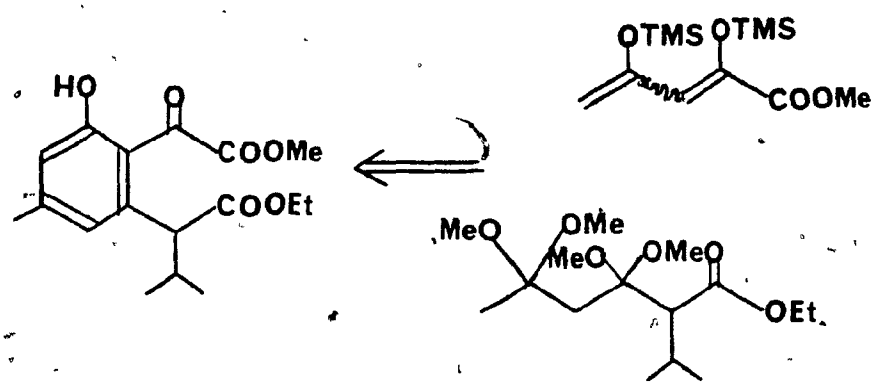
B. THE PROPOSED SYNTHESIS OF GOSSYPOL

The basic strategy involved in our approach to the synthesis of gossypol is to utilize the cycloaromatization reaction to make the aromatic skeleton from acyclic precursors. Gossypol is a dimer of two naphthol units. Hence in all total syntheses, the aim is to make the monomer. A retro synthesis is depicted in Scheme IV.2. Therefore in our approach, there are two stages for the total synthesis of



Scheme IV.2

gossypol. In our first stage we have to synthesise the molecule 104. In order to make this molecule, our approach is again through the cycloaromatization reaction. A retro synthesis of molecule 104 is given in Scheme IV.3. Again the electrophilic and the nucleophilic components have to be synthesised from appropriate starting materials.



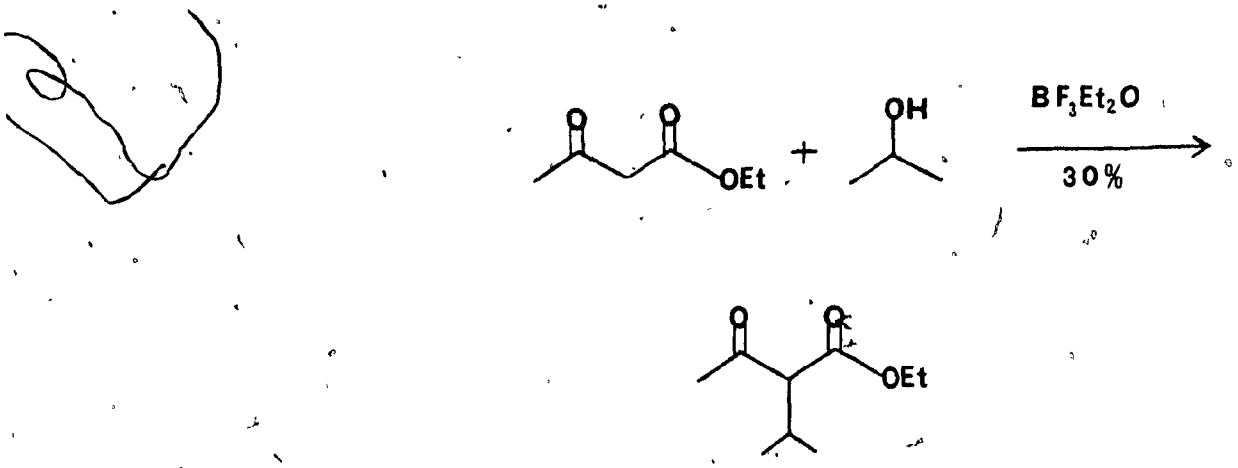
106

Scheme IV.3

V. RESULTS AND DISCUSSION

A. PREPARATION OF ETHYL 2-ISOPROPYL-3-OXO-BUTANOATE

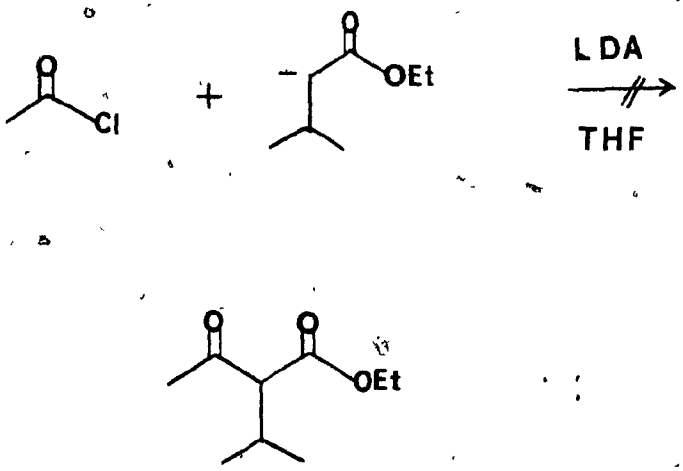
Our initial attempt to make the compound 107 by the literature-cited procedure[116] using ethyl acetoacetate and isopropanol in the presence of boron trifluoride etherate was not satisfactory. By this procedure, compound 107 was obtained in 30% yield. The reaction is reproduced in Scheme V.1. Since compound 107 is one of the starting materials required for the synthesis, we had to look for a new way of making this compound with a better yield. In search of a new method, we first tried the anion chemistry by preparing the lithium enolate of ethyl isovalerate (108) using LDA and



107

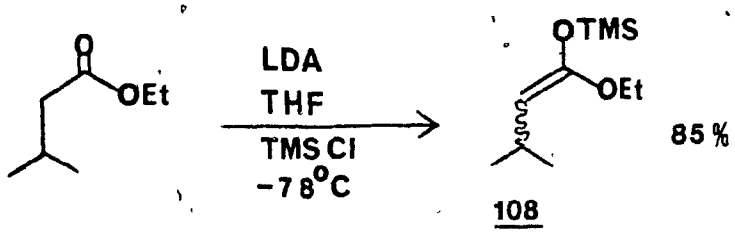
Scheme V.1

then reacting it with acetyl chloride (Scheme V.2). Compound 107 was never isolated by this method. Instead the starting material ethyl isovalerate was recovered.



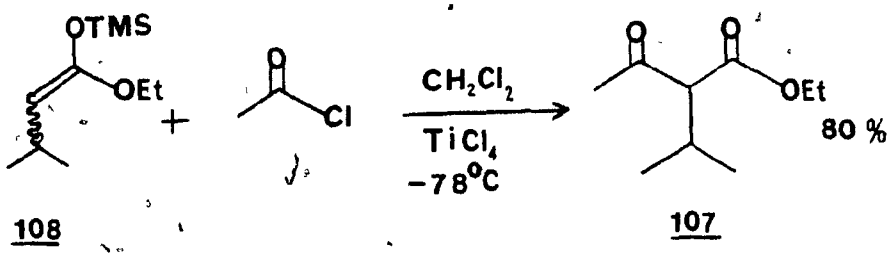
Scheme V.2

The use of silyl enol ethers in organic synthesis is becoming increasingly popular[117]. O-Silylated enolates have several practical advantages as synthetic equivalents of conventional metal enolates and enol intermediates. They react regiospecifically with a variety of electrophiles. Therefore in our approach, ethyl isovalerate was converted to the sylyl enol ether 108 using LDA and chlorotrimethylsilane in dry THF at -78°C. The crude product was distilled under reduced pressure to give the pure compound in 85% yield.



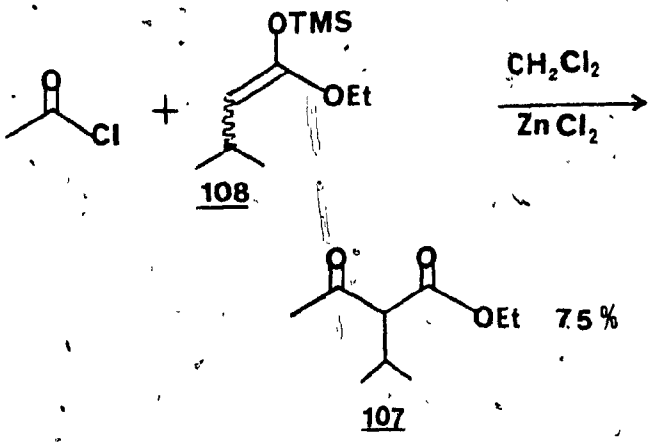
Scheme V.3

Condensation reaction of compound 108 with acetyl chloride was carried at -78°C in dry methylene chloride using titanium tetrachloride as the activating agent. The crude product was distilled under reduced pressure to give pure 107 in 80% yield. The compound was identical in all aspects to that reported in the literature[116]. Alternatively, compound 107 was prepared by condensing compound 108 with acetyl chloride in dry methylene chloride at room temperature using $ZnCl_2$ as the activating agent. $ZnCl_2$ was found to be a better



Scheme V.4

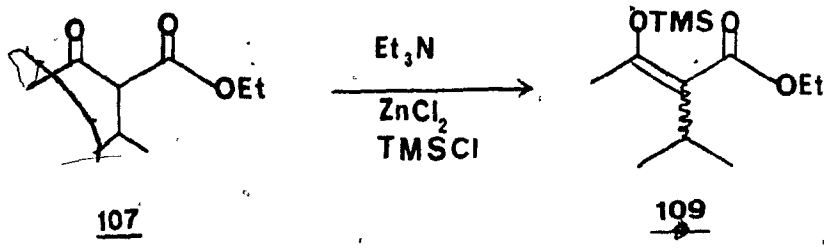
choice in this case, because of the simplicity in the workup procedure.



Scheme V.5

B. PREPARATION OF 1,3-BIS(TRIMETHYLSILOXY)-1-ETHOXY-2-ISOPROPYL-1,3-BUTADIENE (110)

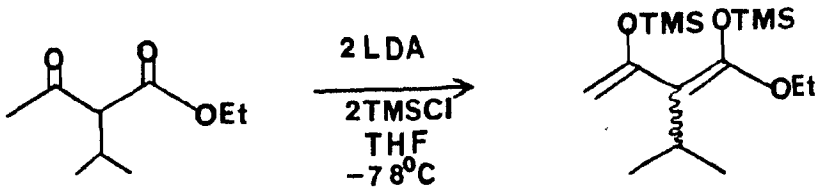
The mono silylated compound 109 was prepared by refluxing 107 with triethyl amine, $ZnCl_2$ and TMSCl in benzene[99]. The crude product was a mixture of the mono and bis enol silyl ether in 60:40 ratio. They were separated by fractional distillation under reduced pressure.



Scheme V.6

Compound 109 was converted to the bis enol silyl ether 110 by treating ethyl 2-isopropyl 3-trimethyl siloxy crotonate (109) with lithium diisopropylamide in THF at -78°C followed by quenching with TMSCl. Compound 110 was identified on the basis of spectral data. In its proton nmr spectrum the two singlets at δ 4.10 and δ 4.27 are assigned to the vinylic protons. The presence of only one doublet for the isopropyl group is a clear indication that the two methyl groups are not diastereotopic as they were in 107. Mass spectrum of compound 110 gave the molecular ion at m/z = 316 ($M^{+\cdot}$).

Compound 110 was also prepared by an alternate procedure from 107 using 2 equivalents of LDA and TMSCl. The reaction was nearly quantitative and no C-silylated product was observed. The second method was more convenient and was used for further preparation of 110.

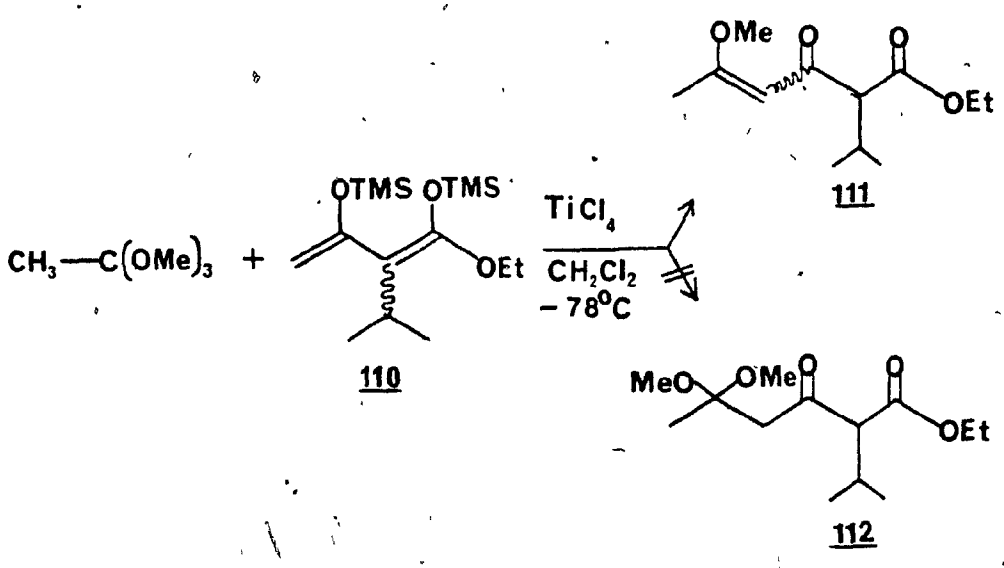


107 110

Scheme V.7

C. CONDENSATION REACTION OF 110

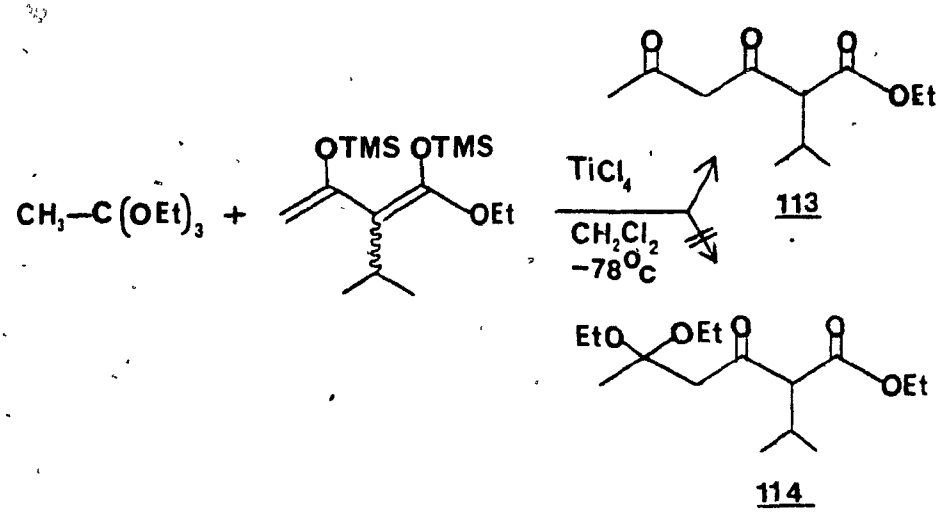
The next attempt was to prepare the acetal 112 by reacting 110 with trimethyl orthoacetate in dry methylene chloride using titanium tetrachloride as the activating agent. The crude product was distilled under reduced pressure and the pure compound obtained was the elimination product 111 in 75% yield. Even though this is not surprising, we expected to get some of the acetal 112 during the reaction. The reaction is represented in Scheme V.8. In another experiment, the bis



Scheme V.8

enol silyl ether 110 was condensed with triethyl orthoacetate in methylene chloride at -78°C using $TiCl_4$ as the activating agent. The product obtained was the ketone 113. The reaction

is depicted in Scheme V.9. Probably the acetal 114 was formed

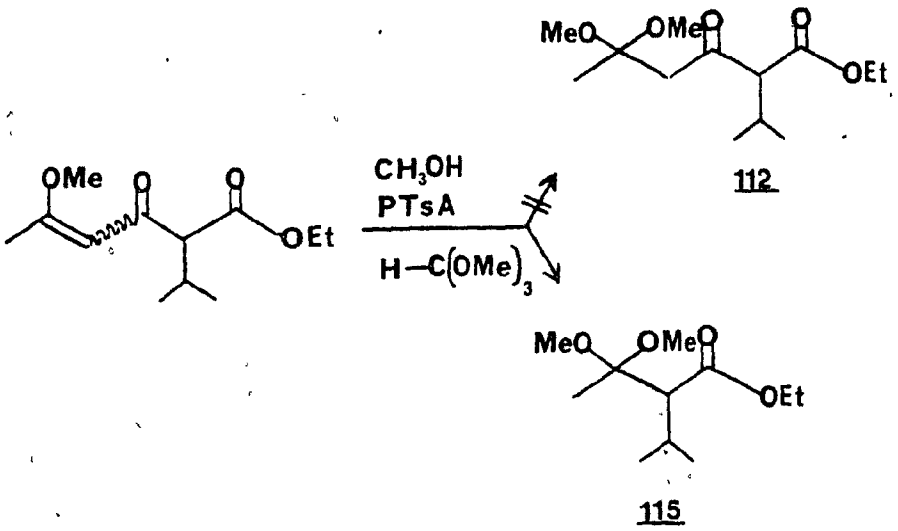


Scheme V.9

but it has undergone titanium tetrachloride-promoted deketalization which will be discussed later in this thesis. In order to avoid the deketalization, in another experiment, the workup was carried out at a low temperature. But only the keto ester was obtained.

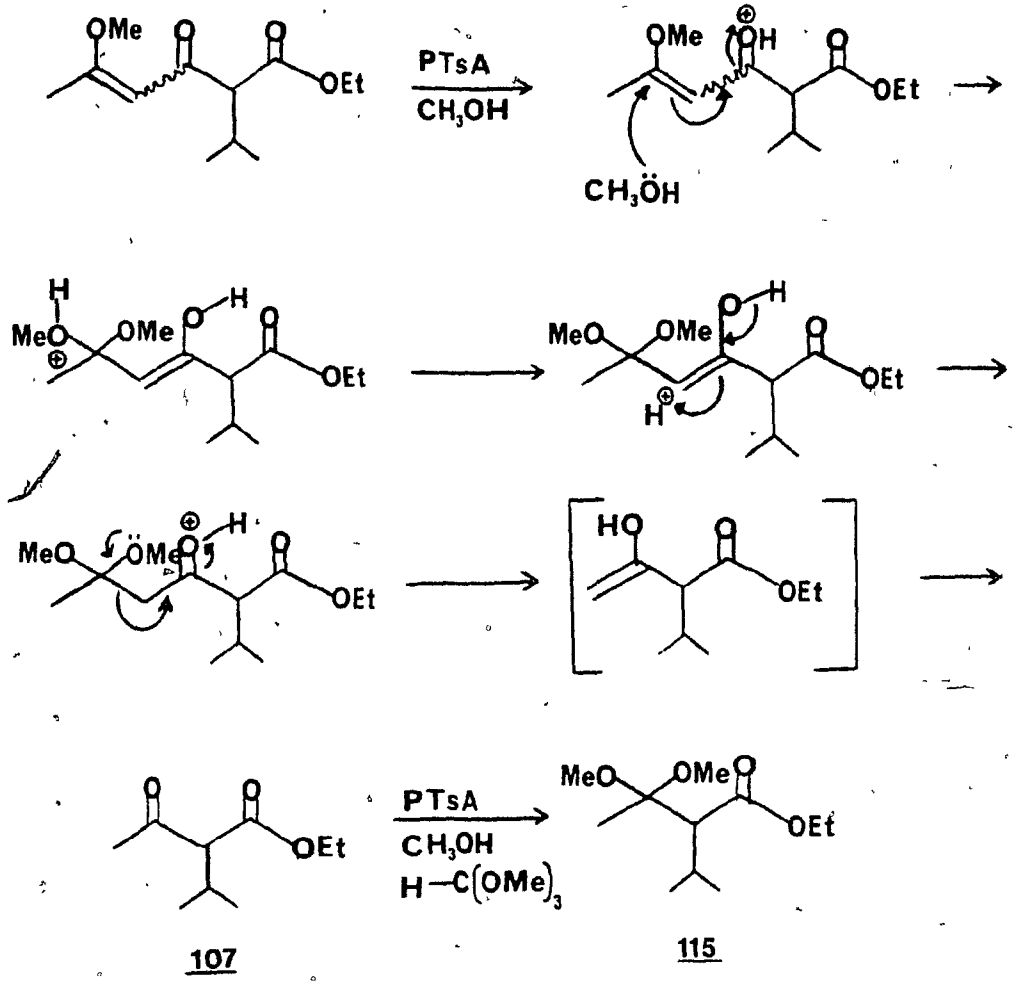
Our next attempt was to convert the elimination product 111 to the acetal. In an attempt to make the acetal 112, the elimination product 111 was refluxed with trimethyl orthoformate, methanol and paratoluenesulfonic acid (catalytic amount). Surprisingly the product obtained was not the expected acetal 112. The proton nmr of the product obtained showed methyl protons at δ 1.43 and a singlet corresponding to

the acetal protons at δ 3.13. But the methylene proton at the 4-position expected for the acetal 112 was not present in the ^1H nmr. The mass spectral measurement of this compound was not successful because of decomposition in the mass spectrometer. We suspected the formation of compound 115.



Scheme V.10

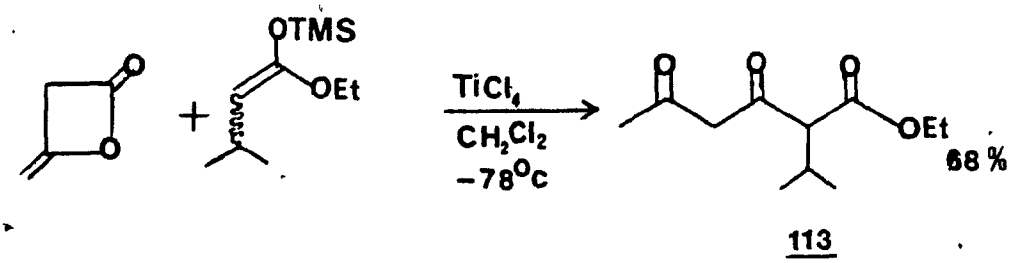
Probably the reaction might have gone through the path described in Scheme III.11 which is similar to a reverse-Claisen reaction. The structure of compound 115 was confirmed by synthesising it from 107 by refluxing with methanol, trimethyl orthoformate and paratoluenesulfonic acid. The compound obtained was identical in all respects to compound 115 obtained in the previous experiment.



107 115

Scheme V.11

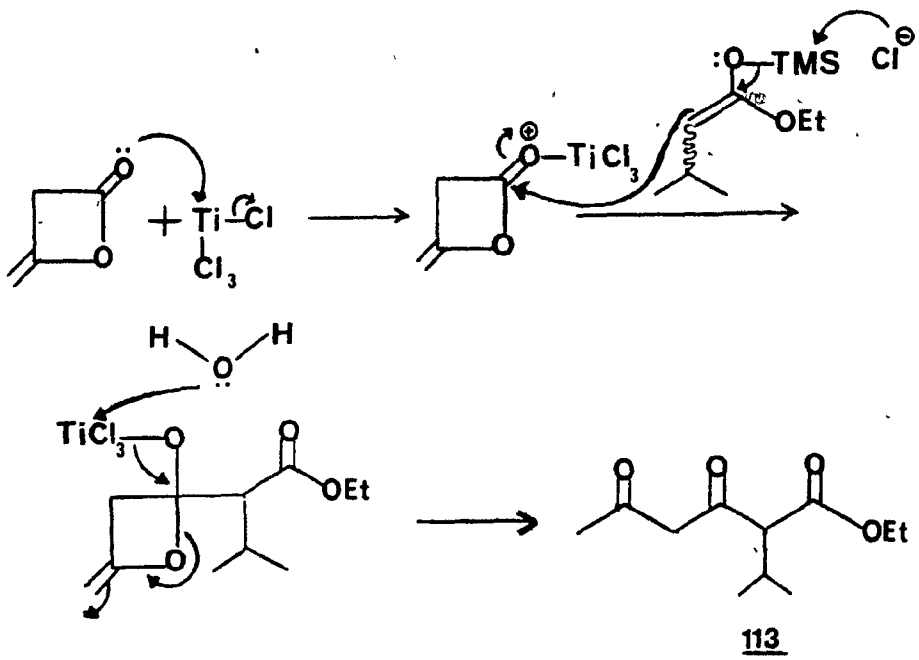
In the meantime a facile method for the synthesis of the ketone 113 was developed by us using diketene as given in Scheme V.12. Diketene was dissolved in dry methylene chloride followed by the addition of 108. The reaction mixture was



113

Scheme V.12

cooled to -78°C and titanium tetrachloride was added dropwise. After workup the crude product obtained was purified by flash column chromatography. The product obtained was 113 in 68% yield. The ^1H nmr spectrum of 113 reveals the presence of a vinylic proton at δ 5.47 and a broad singlet at δ 15.08 indicating that the product exists in the enol form. The doublet at δ 2.87 is assigned to the proton at the 2-position. The two doublets centered at δ 0.50 and 0.60 are assigned to the isopropyl methyl protons. The infrared spectrum of the product contained broad bands at 1620 and 1740 cm^{-1}. The mass spectrum of compound 113 gave the molecular ion at m/z = 214 (M^+). This reaction may have some utility for the preparation of polycarbonyl compounds. A plausible mechanism is depicted in Scheme V.13.



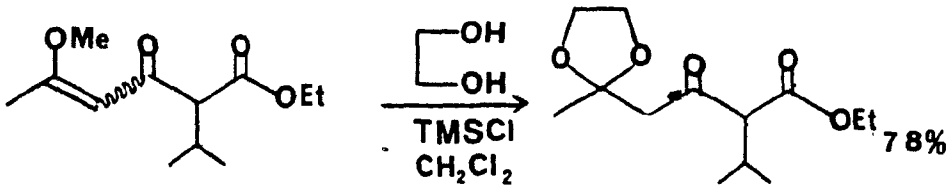
113

Scheme V.13

In an attempt to ketalize 113, the compound was refluxed with methanol, trimethyl orthoformate and paratoluene sulfonic acid (catalytic amount). The product obtained was again the reverse-Claisen product 115. In order to avoid the reverse-Claisen reaction described in Scheme V.11, the reaction time was shortened or the reaction temperature was lowered to room temperature. In the former case, the ketal 115 was still isolated and in the latter case only starting material was recovered.

Since the approach to compound 112 has turned out to be difficult, we decided to look for other alternatives. The

ethylene acetal 116 was synthesised by refluxing 111 with ethylene glycol and chlorotrimethylsilane in dry methylene chloride as given in Scheme V.14. The crude product was purified by column chromatography to give the pure compound in 78% yield. In the proton nmr the doublet at δ 0.98 is

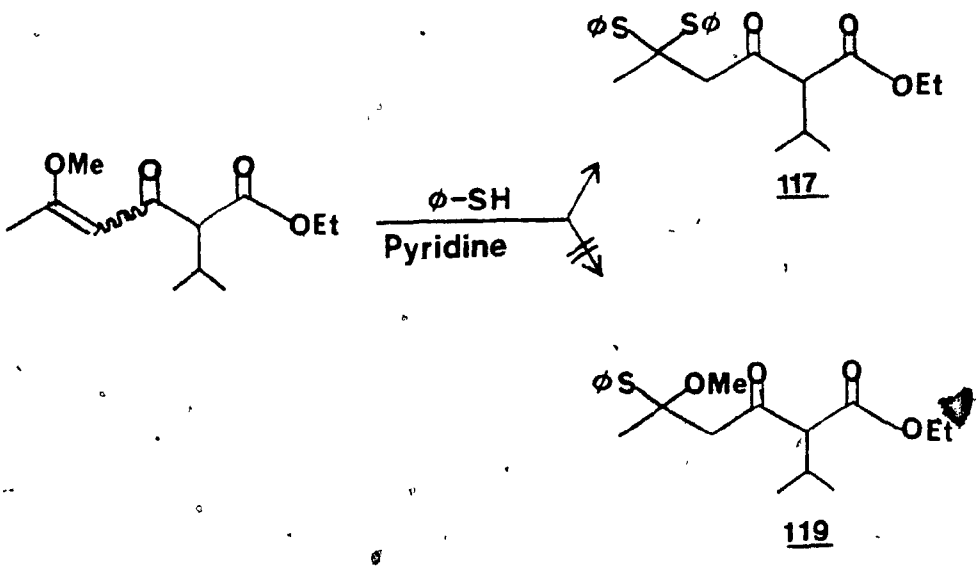


111 116

Scheme V.14

assigned to the isopropyl methyl protons. The proton at the 2-position appears as a doublet at δ 3.40 and the methylene proton at the 4-position appears at δ 3.00-3.07. The singlet at δ 1.43 is assigned to the methyl proton. The triplet centered at δ 1.33 and the quartet at δ 4.20 is assigned to the ethyl protons. The ethylene protons of the acetal shows up as a singlet at δ 4.30. The infrared spectrum of compound 116 shows two strong bands at 1710 and 1740 cm^{-1}. Another potential candidate, the dithioacetal 117, was prepared by reacting compound 111 with benzenethiol and pyridine[74] in

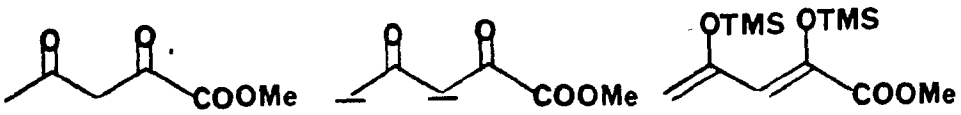
carbon tetrachloride at room temperature. The crude product obtained was purified by fractional distillation under reduced pressure to give the pure compound in 84% yield. The reaction is depicted in Scheme V.15. No hemithioacetal was isolated from this reaction. In the proton nmr, the two doublets centered at δ 0.80 and 0.92 are assigned to the isopropyl methyl protons. The triplet at δ 1.17 and the quartet at δ 4.10 are assigned to the ethyl protons. The proton at the 2-position appears as a doublet and is assigned to the peak centered at δ 3.13. The singlet at δ 3.37 is assigned to the methylene proton at the 4-position. Infrared spectrum shows two strong bands at 1700 and 1740 cm^{-1}. All these compounds (111, 116 and 119) can be considered as the 3-carbon electrophilic unit required for the condensation and cyclo-aromatization reaction to form the aromatic ring.



Scheme V.15

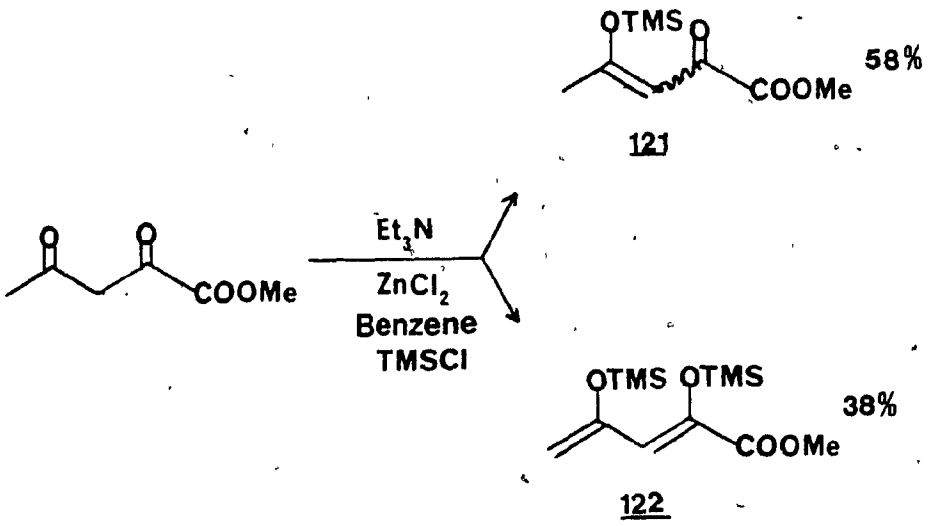
D. SYNTHESIS OF NUCLEOPHILIC COMPONENT

The nucleophile required for the cycloaromatization reaction was the dianion equivalent 118 of methyl acetopyruvate (120) which can provide the other 3-carbon unit required for the formation of the aromatic ring. Methyl 2,4-bis(trimethyl siloxy)-pentadienoate (122) was synthesised in two steps from 120.



120 118 122

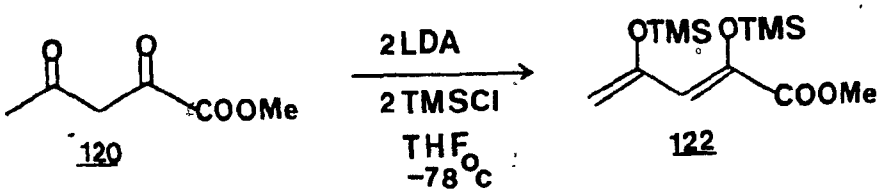
The first step involves the formation of a monosilylated compound using triethylamine, $ZnCl_2$ and TMSCl as in Scheme V.16. The product obtained was a mixture of the mono-



Scheme V.16

silylated compound 121 and the bis silylated compound 122 in a ratio of 60:40. These compounds were separated by fractional distillation under reduced pressure. Conversion of compound 121 to 122 was carried out using one equivalent of LDA and TMSCl in THF.

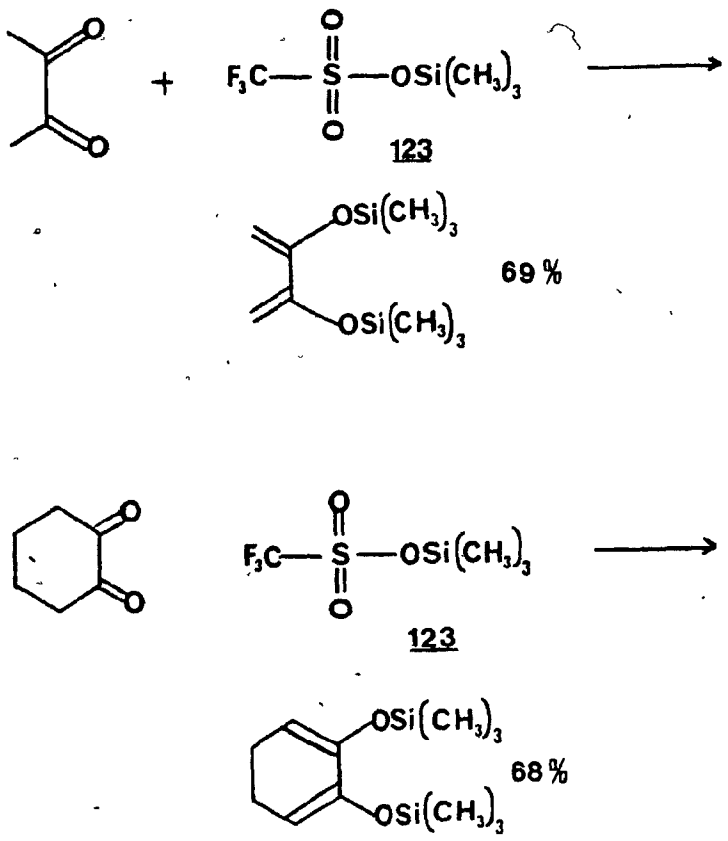
We were able to prepare compound 122 from 120 in one-step using 2 equivalents of LDA and TMSCl in THF at -78°C.



Scheme V.17

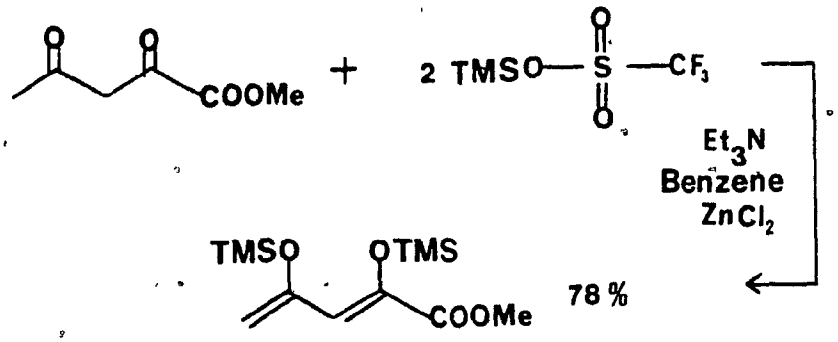
In both cases described above, the workup procedure was rather tedious. Filtration of the crude product, after treatment with hexane to remove the inorganic salt, was difficult.

Recently, the synthesis of enol silyl ethers using trimethylsilyl trifluoromethanesulfonate (123) was reported by Simchen and Kober[118]. (For examples see Scheme V.18). We have adopted this procedure to make compound 122. Therefore, when 120 was refluxed with zinc chloride and



Scheme V.18.

triethylamine in benzene after the addition of 2 equivalents of trimethylsilyl trifluoromethanesulfonate (123). The bis enol silyl ether 122 was isolated in good yield. The reaction is depicted in Scheme V.19. The method was found to be much

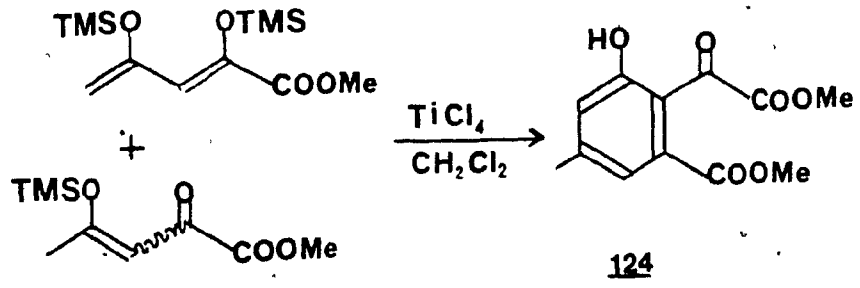


Scheme V.19

simpler in its workup. The only drawback in this case is the high cost of the reagent 123.

E. CYCLOADDITION REACTION USING COMPOUND 122

Cycloaddition reaction of compound 122 was first tested by reacting the compound with the monosilylated compound 121 in the presence of titanium tetrachloride as the activating agent as shown in Scheme V.20.

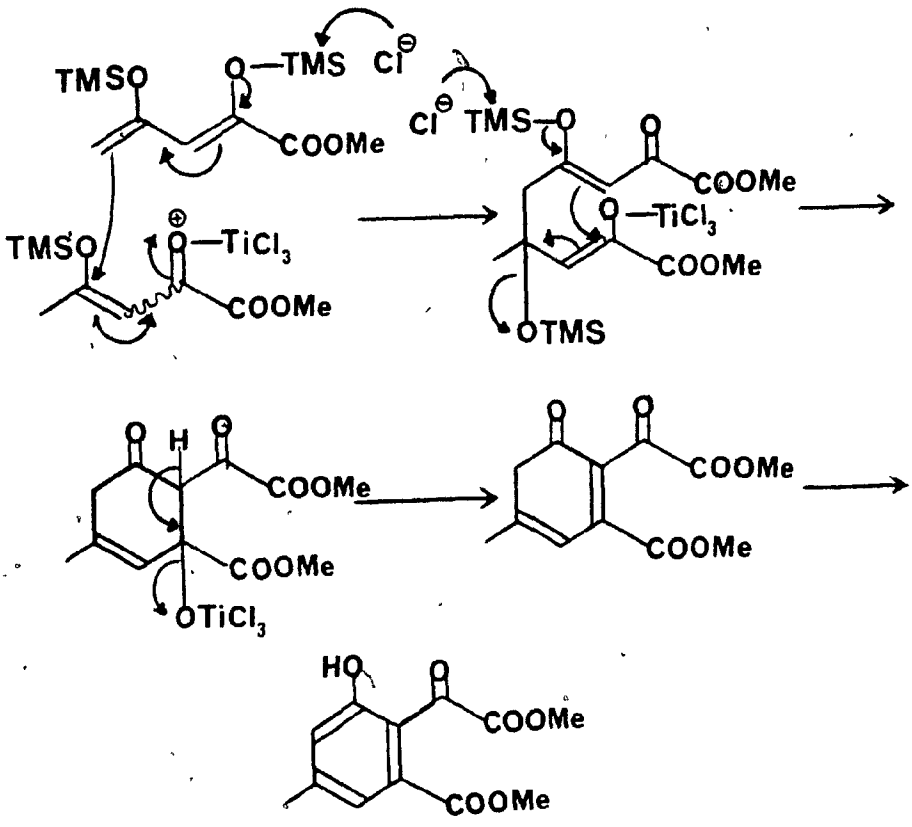


124

Scheme V.20

Compound 124 was the expected aromatic compound obtained by the cycloaromatization reaction. In the proton nmr spectrum of 124, the singlet at δ 2.20 is assigned to the methyl protons on the aromatic ring. The ester methyl protons are assigned to the singlets at δ 3.83 and 3.90. The aromatic protons appear at δ 6.90 and 8.13. The phenolic hydroxyl was confirmed by deuterium oxide exchange (peak at δ 6.5) in ^1H nmr.

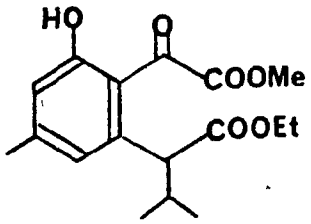
A mechanism for the formation of compound 124 is represented by the path described in Scheme V.21. Since



124

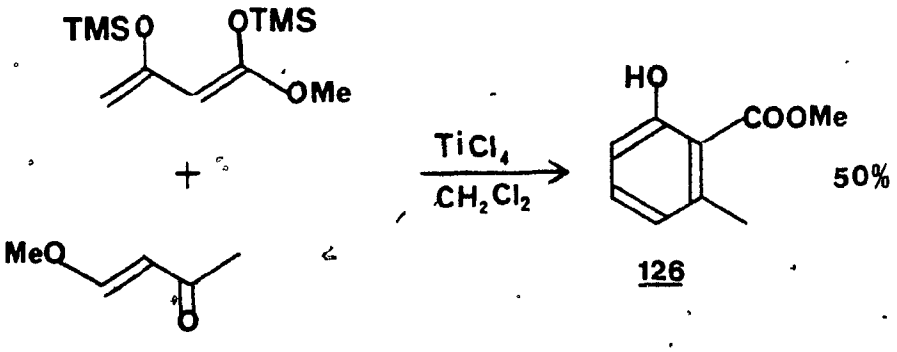
Scheme V.21

compound 122 is indeed capable of undergoing the cyclo-aromatization reaction by acting as the nucleophilic component, our next aim was to synthesise the target intermediate 104. Since it has been reported from this laboratory



104

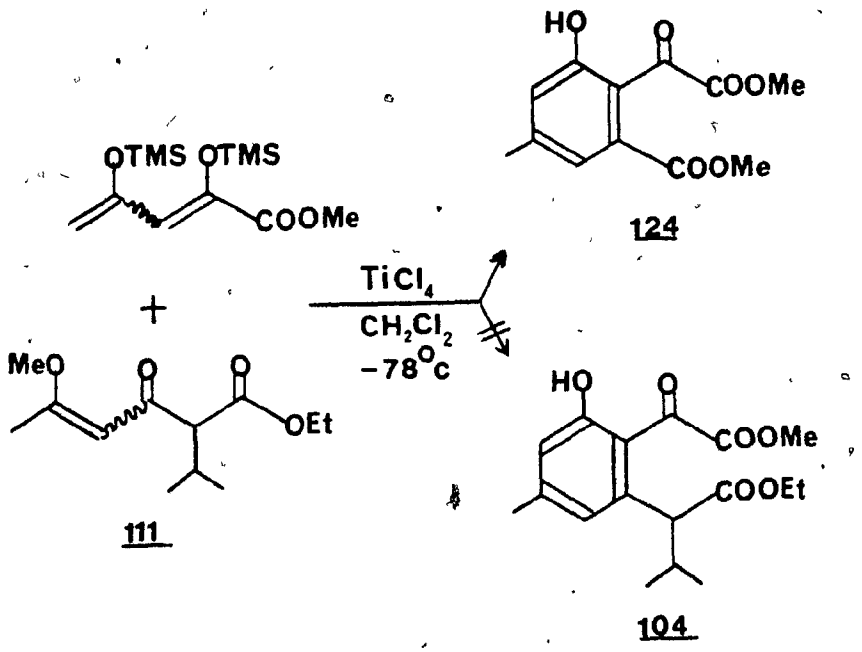
that the condensation of 4-methoxy but 3-en-2-one (125) with 1,3-bis(trimethylsiloxy)-1-methoxy buta-1,3-diene gave 6-methyl salicylic acid (126)[74], we attempted the condensation



125 126

Scheme .V. 22

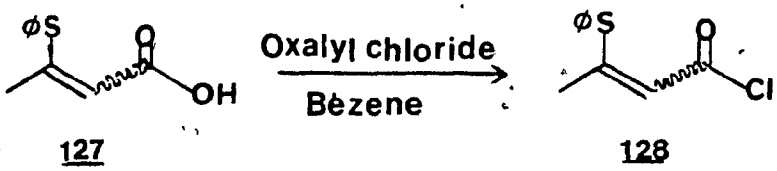
of 111 with the bis enol silyl ether 122 using $TiCl_4$ as the activating agent in dry methylene chloride. Unfortunately no expected cycloaromatization reaction was observed. The crude reaction mixture on purification by column chromatography gave the starting material 111 along with the self condensation product 124. Repeating the reaction at room temperature using



Scheme V.23

the same activating agent did not give the expected compound 104. Using $ZnCl_2$ as the activating agent, the condensation reaction was repeated, but the results were the same, except that no self condensation product resulted.

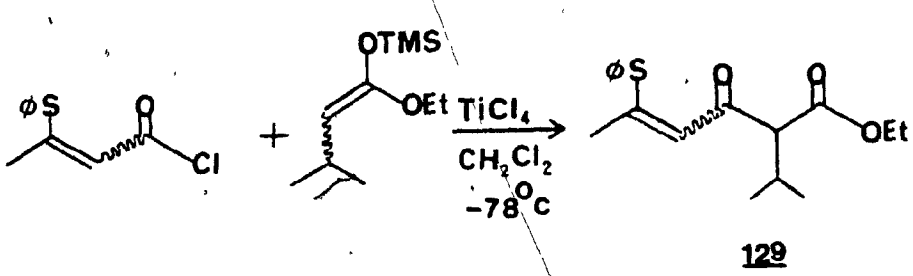
Since sulfur can stabilize the positive charge better than oxygen, we thought it reasonable to make the thio analog of 111, ethyl 5-phenylthio-2-isopropyl-3one hex-4-enoate (129). The starting material, 3-phenylthio-crotonic acid (127), required for this purpose, was synthesised in our laboratory[119] by reacting diketene with benzenethiol in the presence of concentrated H_2SO_4. Compound 127 was converted to the acid chloride 128 by reacting it with oxalyl chloride in dry benzene. The reaction was completed in 10 min and the acid chloride 128 was obtained in quantitative yield (Scheme V.24). Compound 128 was found to be very unstable



127 128

Scheme V.24

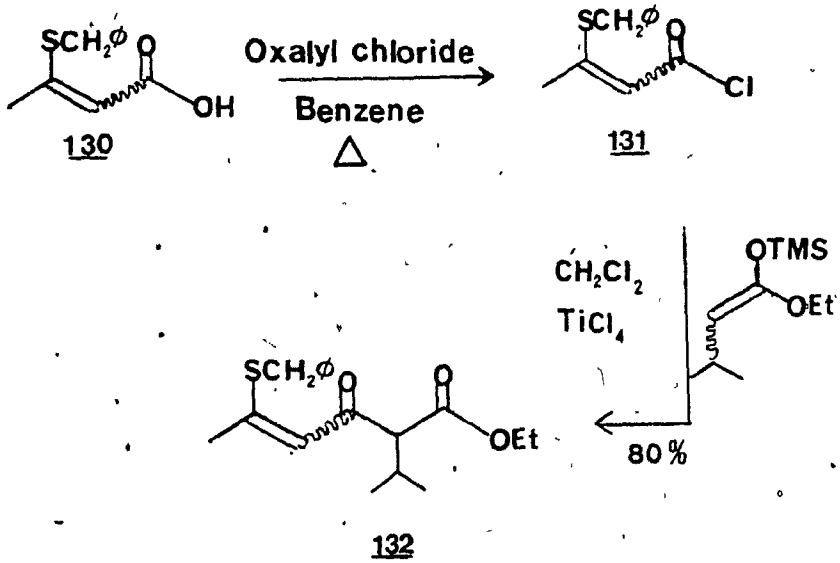
and was therefore immediately condensed with 108 in the presence of $TiCl_4$ as the activating agent. The resulting product was the expected compound 129 in 70% isolated yield. It existed as a mixture of two geometric isomers which could not be separated. The reaction is represented in Scheme V.25.



129

Scheme V.25

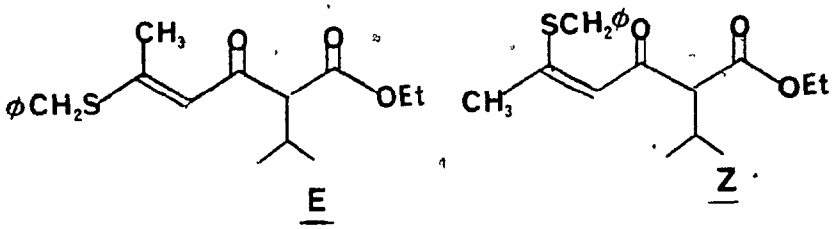
In a similar approach, the benzylthio derivative, ethyl 5-benzylthio-2-isopropyl-3one-hex-4-enoate (131) was prepared starting from 3-benzylthio-crotonic acid (130) as depicted in Scheme V.26. Compound 132 was a mixture of 2 geometric



130 131 132

Scheme V.26

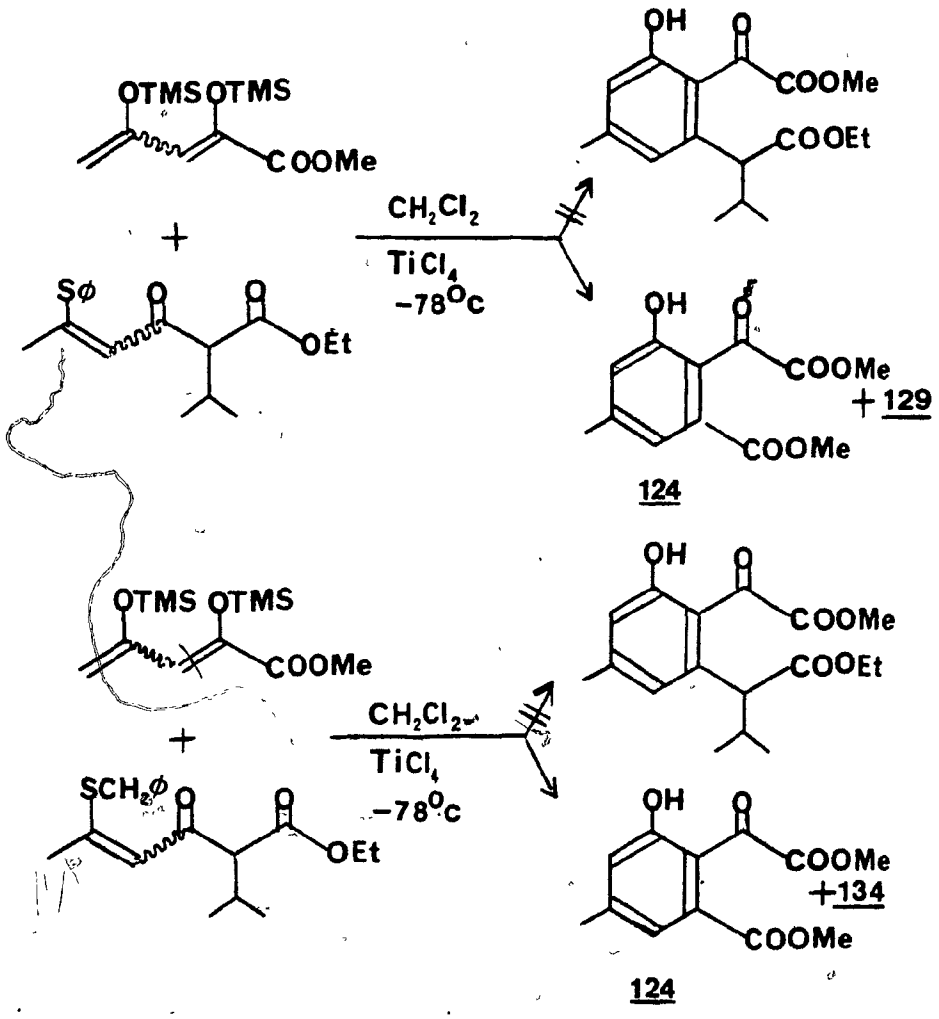
isomers in the ratio of 75:25. We were able to separate the isomers by column chromatography. The isomers were characterized on the basis of nuclear Overhauser effect (NOE)[120,121]. The major isomer was the one in which the vinyl hydrogen and the methyl group are trans to each other. This was assigned on the basis that there was no increase in the intensity of the methyl signal in the ^1H nmr spectrum upon double irradiation of the vinyl hydrogen. The major isomer was therefore the E isomer 133. In the case of the minor isomer in which the methyl and the hydrogen are cis to each other, there was a considerable increase in the intensity of the methyl peak upon double irradiation. On this basis, the minor isomer was assigned the Z stereochemistry (134).



133 134

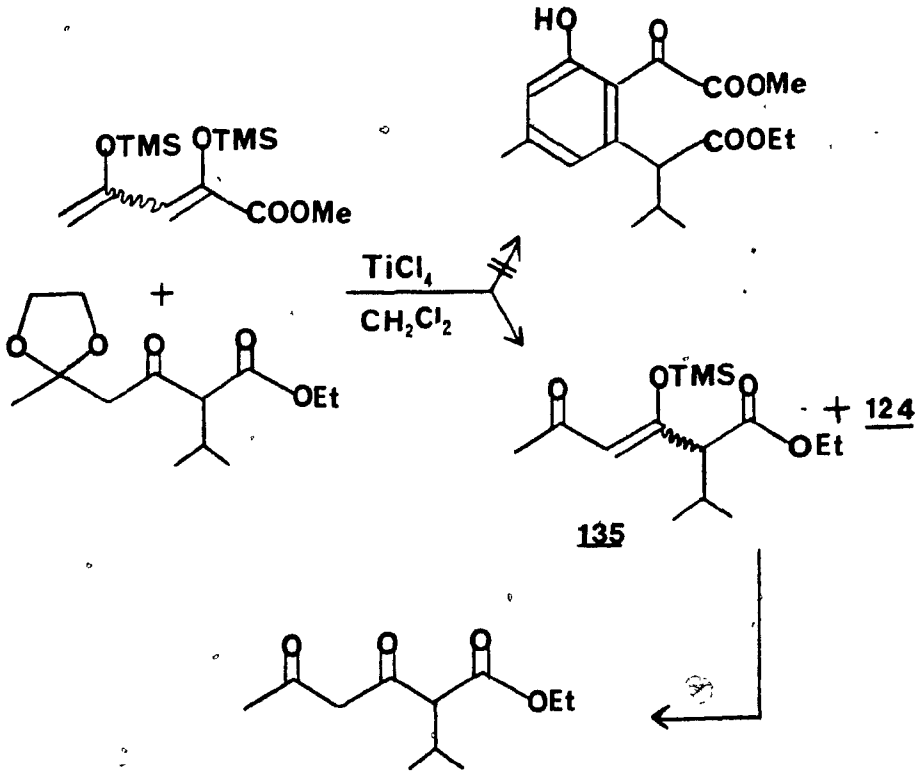
Ketalization of the compounds 129 and 132 were not successful. The condensation reaction of both these compounds

129 and 132 was carried out with the bis enol silyl ether 122 in the presence of $TiCl_4$ as the activating agent. No new aromatic compound was detected in the ^1H nmr of the crude product. Purification of the crude product by column chromatography resulted in the isolation of the starting material and a small amount of the self condensation product 124.



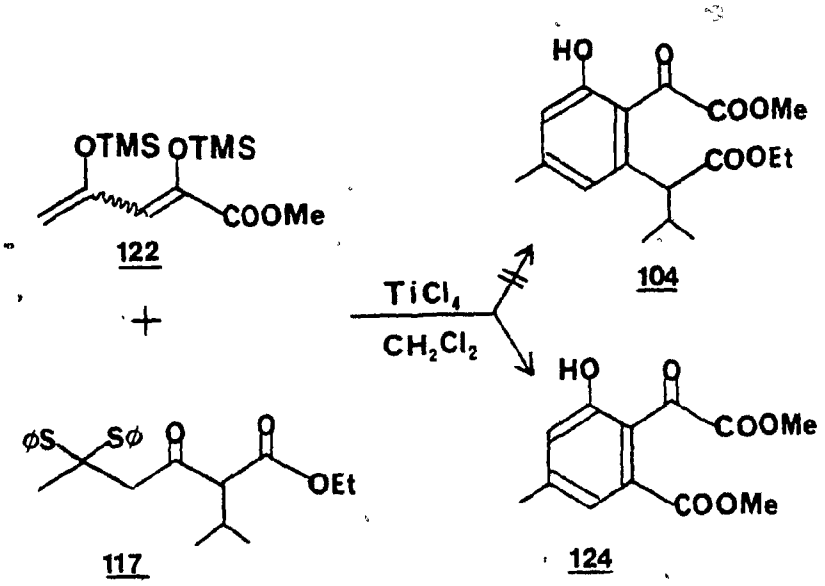
Scheme V.27

Before we came to any conclusion, we decided to do the condensation reactions of the other acetals which we had already prepared (Schemes V.14 and V.15). Thus the ethylene acetal 116 was reacted with the bis enol silyl ether 122 in the presence of $TiCl_4$ as the activating agent. ^1H nmr of the crude product indicated the absence of any new aromatic product. There was some evidence for the formation of a silylated keto ester 135 and the self condensation product 124. Purification of the crude product by column chromatography gave 113 and 124.



Scheme V.28

A similar condensation reaction was carried out with the dithioacetal 117 and 122 in the presence of $TiCl_4$ as the activating agent. But unfortunately no expected aromatic compound was isolated. There were some peaks in the crude ^1H nmr spectrum between 6 ppm and 7 ppm. These peaks disappeared from the fractions obtained after column chromatography. They cannot be assigned to any aromatic compound. The only product isolated was the self condensation product 124.



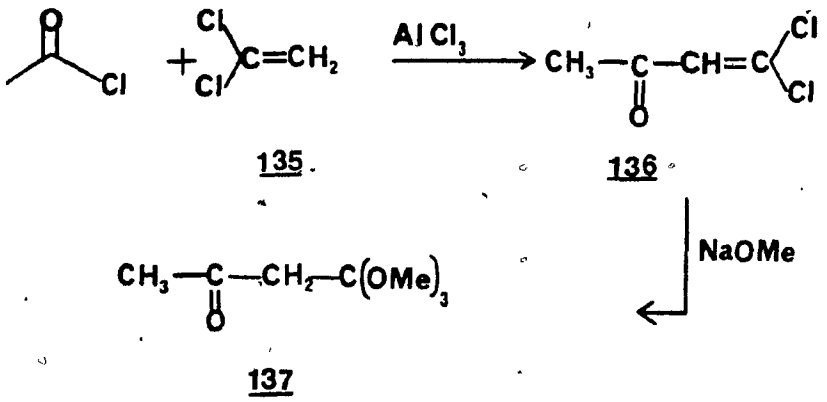
Scheme V.29

At this stage, we assume that 1,3-keto ester functionality in the compounds 111, 116, 119, 129 and 132

might have contributed negatively in rendering the cycloaromatization reaction. One possibility is that these compounds probably undergo silylation during the reaction. Another possibility is that the steric hinderance due to the isopropyl group may prevent either the complexation with $TiCl_4$ or the approach of the nucleophile, either of which will not lead to cycloaromatization.

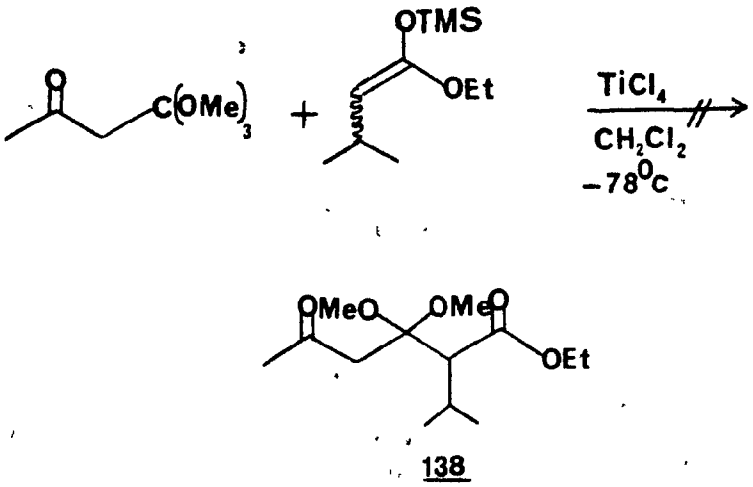
The next approach was to avoid the first problem mentioned above by protecting the keto group at the 3-position. Direct ketalization of the carbonyl at the 3-position in compounds 116, 119, 129 and 132 were unsuccessful. This may be due to the steric hinderance of the adjacent isopropyl group. Therefore, the only possibility is to incorporate an acetal or an equivalent at the 3-position while the molecule is being constructed.

With this in mind, the orthoester 137 was synthesised according to the literature procedure[122,123]. 4,4-Dichloro-but-3-en-2-one (136) was prepared by reacting acetyl chloride with vinylidene chloride (135) in the presence of $AlCl_3$. Compound 136 was then reacted with sodium methoxide to get the compound 137 as in Scheme V.30. Compound 137 (4,4,4-tri-methoxybutan-2-one) was then reacted with the enol silyl ether 108 in the presence of $TiCl_4$ at -78°C. The expected acetal 138 was not obtained, but methyl acetoacetate and ethyl isovalerate were recovered from the crude reaction mixture. The reaction is depicted in Scheme V.31.



135 136 137

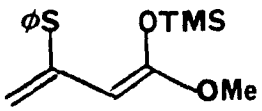
Scheme V.30



138

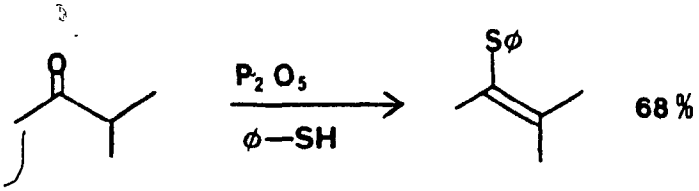
Scheme V.31

At this time, a new thio enol silyl ether, 1-trimethylsiloxy-3-phenylthio-1-methoxy-buta-1,3-diene (139)[119] was prepared in our laboratory and its nucleophilic reactivity was tested with a number of electrophiles. As in the case of



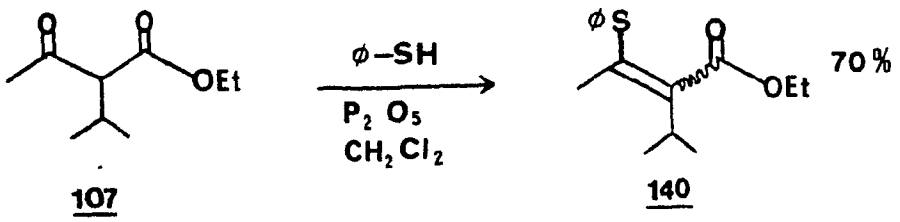
139

1,3-bis-(trimethylsiloxy)-1-methoxy-buta-1,3-diene, the site at C_4 was found to be more reactive than that at C-2[124]. We decided to use this information to create a new dianion equivalent of ethyl-2-isopropyl-3-oxo-butanoate. We also take advantage of a methodology to make vinyl sulfide using P_2O_5 as published by Trost in 1983[125] (Scheme V.32). In a similar



Scheme V.32

way, we were able to make the required vinyl sulfide, ethyl 3-phenylthio-2-isopropyl-but-2-enoate (140) by stirring ethyl 2-isopropyl-3-oxo-butanoate (107) with benzenethiol and P_2O_5 for 20 h as in Scheme V.33. Compound 140 was converted to the

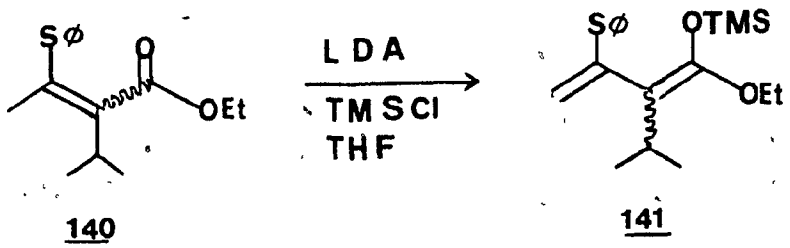


107 140

Scheme V.33

corresponding enol sily ether (1-trimethylsiloxy-1-ethoxy-2-isopropyl-3-phenylthio buta-1,3-diene (141) by the following procedure. LDA was prepared in THF at 0°C and the solution was cooled to -78°C followed by the addition of 140. The solution was stirred at -78°C for 10 min and then quenched with TMSCl and allowed to warm to room temperature. After the workup procedure, the nmr of the crude product showed the formation of the expected enol silyl ether. But the product contained some impurities. Since the compound was found to be very unstable, further purification was not possible. The formation of the enol silyl ether was confirmed

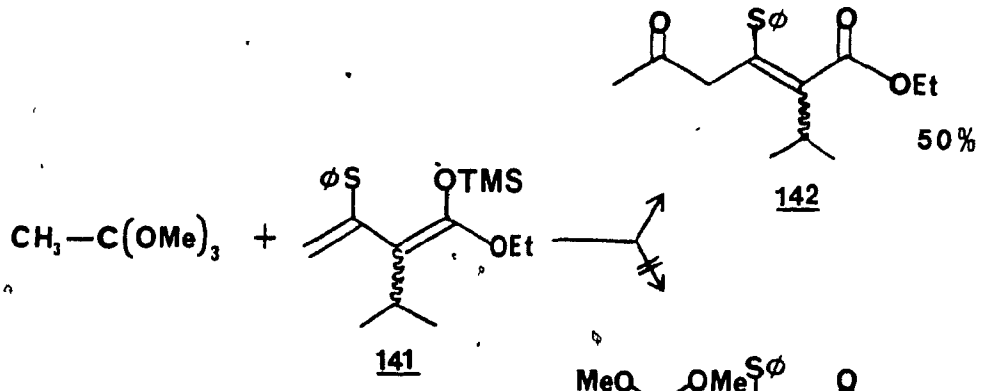
on the basis of its reaction with trimethyl orthoacetate as follows.



140 141

Scheme V.34

Compound 141 was reacted with trimethyl orthoacetate in the presence of $TiCl_4$ hoping to get the acetal 143. Unfortunately the product isolated was the ketone 142 which might have arisen from the acetal 143 by cleavage with $TiCl_4$ (Scheme V.35). It is clear from this reaction that the enol

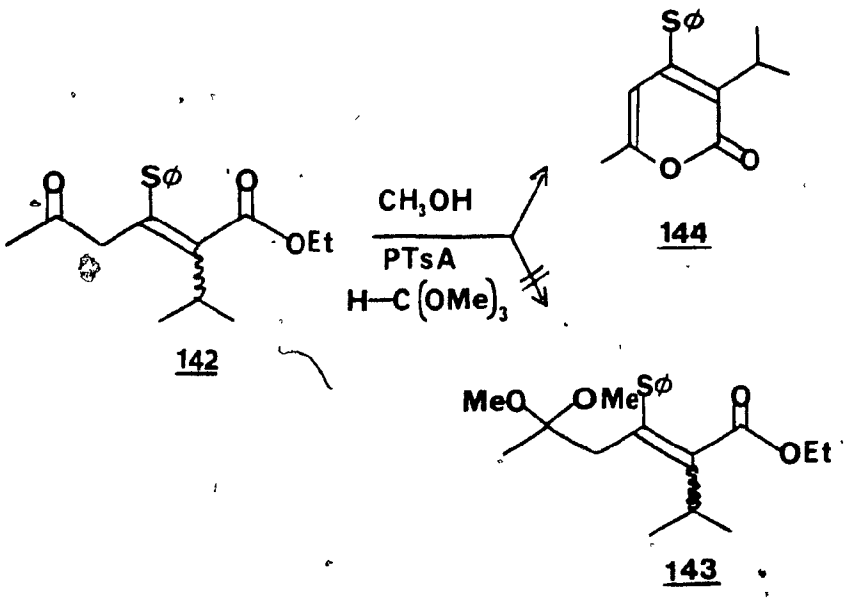


141 142 143

Scheme V.35

silyl ether 141 is capable of undergoing condensation reaction which can be used for the chain elongation reaction to create new vinyl sulfides.

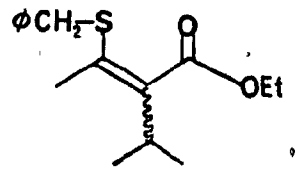
The ketone 142 is also a potential intermediate which, we thought, might be able to convert to the required acetal 143. Therefore, the ketone was refluxed with methanol, trimethyl-orthoformate and paratoluene sulfonic acid. Unfortunately, no expected acetal was isolated. Instead, a light yellow crystalline compound, 144, was obtained (Scheme V.36). In the



Scheme V.36

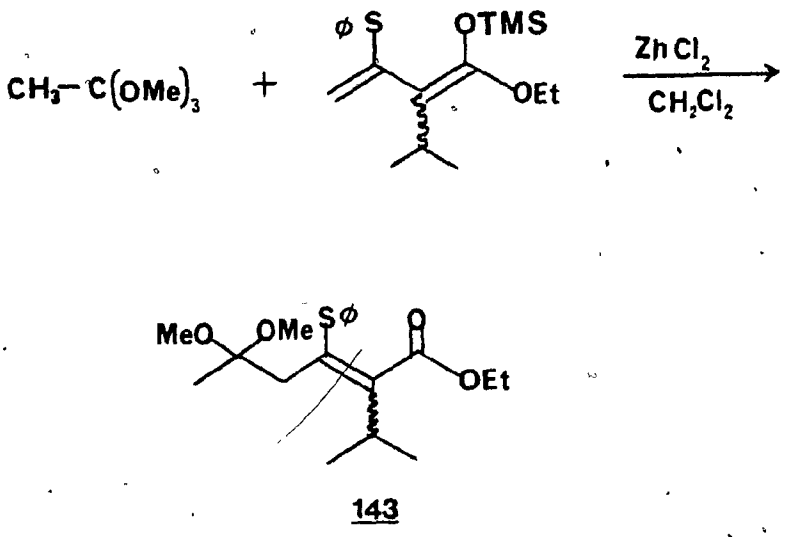
^{1}H nmr, the doublet at δ 1.41 is assigned to the isopropyl methyl protons and the multiplet at δ 3.10-3.57 is assigned to the methine proton (-CH$\begin{smallmatrix}\diagup CH_3\\ \diagdown CH_3\end{smallmatrix}$) on the isopropyl group. The

vinylic proton appears at δ 5.40. The singlet at δ 7.48 is assigned to the ring proton. The infrared spectrum of the compound showed bands at 1630 and 1710 cm^{-1}. We have also prepared the vinyl sulfide 145, but the preparation of the corresponding enol silyl ether was not successful.



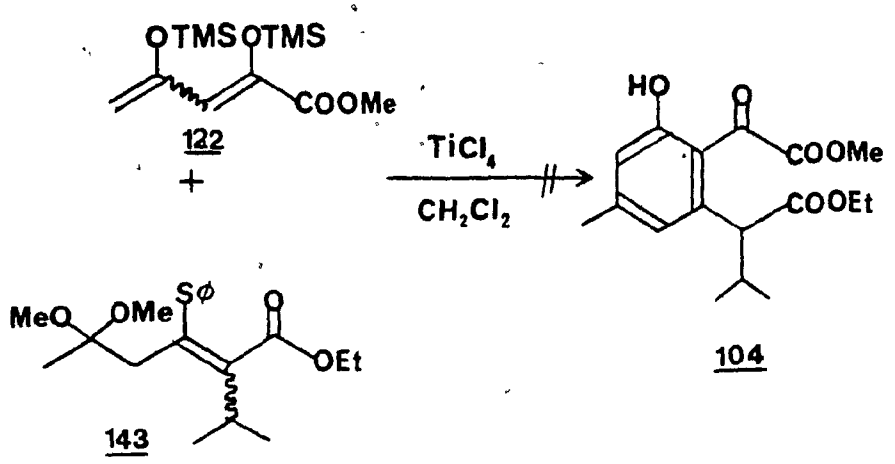
145

In an alternate method for the preparation of the acetal 143, compound 141 was reacted with trimethyl orthoacetate in the presence of $ZnCl_2$ as a catalyst. ^1H nmr of the crude product indicated the formation of the expected acetal (143). Purification of the compound by column chromatography or distillation under reduced pressure resulted in the decomposition of the compound 143. We decided to do the condensation reaction with the bis enol silyl ether 122 using the crude product before purification. Therefore compound 143 was mixed with the bis enol silyl ether 122 in methylene chloride and $TiCl_4$ was added dropwise. But no expected aromatic compound was isolated (Scheme V.38). In order to



143

Scheme V.37

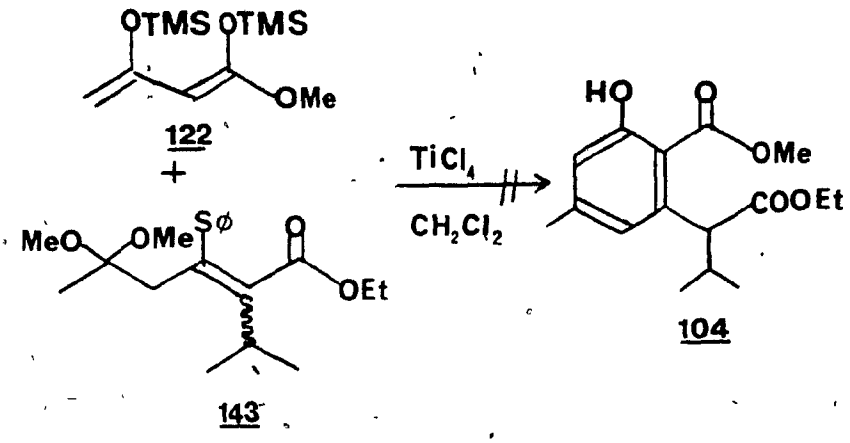


104

143

Scheme V.38

check the reactivity of 143, the condensation reaction was repeated with 1,3-bis(trimethylsiloxy)-1-methoxy-buta-1,3-diene (which was used for the synthesis of olivetol)[126] as depicted in Scheme V.39. Again only starting materials were recovered.

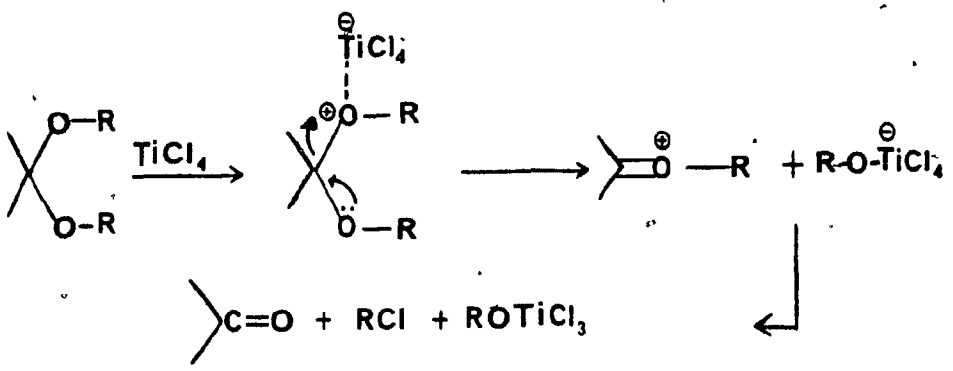


Scheme V.39

Considering all the reactions that we have done so far one can come to some conclusions, namely, in spite of the many different carbonyl equivalents used (ketal, thioketal, enol ether, enol thioether), the condensation of 122 with a 3,5-diketoester bearing a 2-isopropyl group has not been successful. We can only attribute the difficulty to the presence of the isopropyl group. The difficulty is manifested in several ways. The first is the possibility of a retro-Claisen (or Aldol) type reaction as observed in Scheme V.10. The second manifestation is that titanium tetrachloride, instead of complexing with the ketal function to promote the condensation reaction, leads to the deketalization reaction. This is the case of the reaction of 141 with trimethyl ortho-

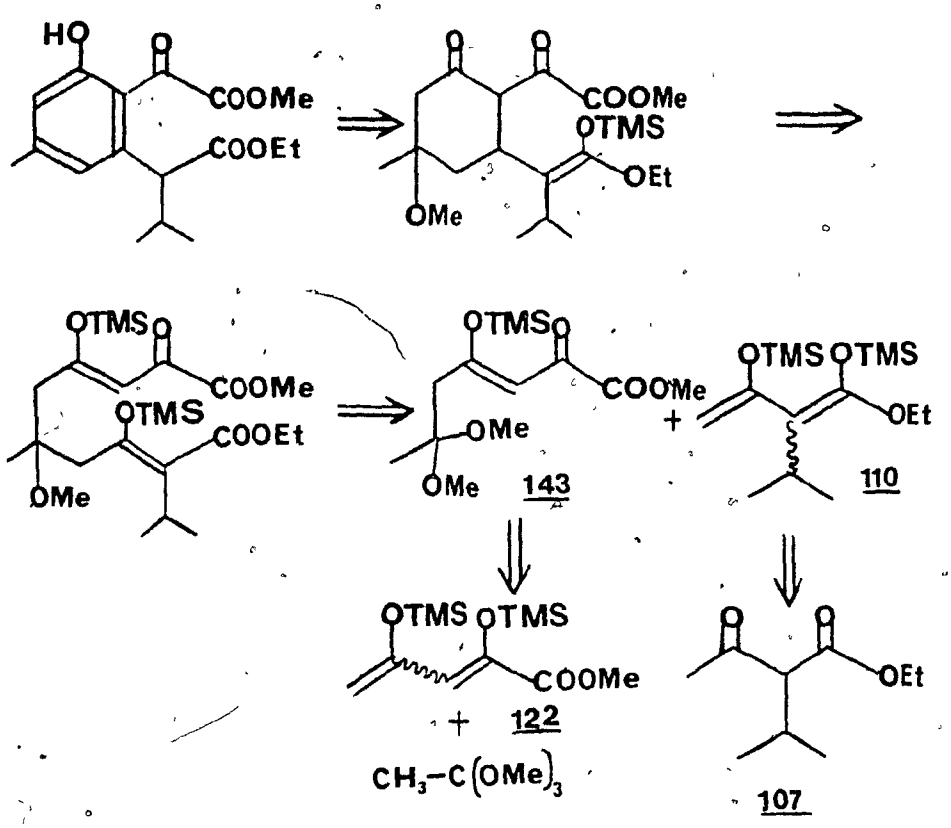
acetate (Scheme V.35). The ketal of 143 is converted to the ketone 142.

Recently it was reported in the literature[127] that acetals and ketals can be converted to carbonyl compounds by using $TiCl_4$ as a promoting agent (Scheme V.40).



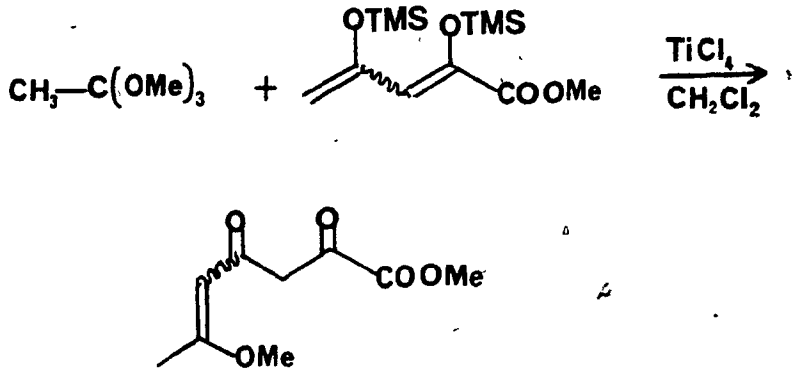
Scheme V.40

With the conclusion that it is the 2-isopropyl group which prevents the condensation of 122 with a tri-carbonyl equivalent in mind, we attempted two possibilities. The first question was: Is the cycloaromatization possible if the isopropyl group is in the nucleophilic component instead? If the target intermediate 104 is bisected in another fashion, one can see that it may be constructed by the condensation of 110 with 143 according to the retro-synthesis depicted in Scheme V.41. Our first attempt was to make the compound 143.



Scheme V.41

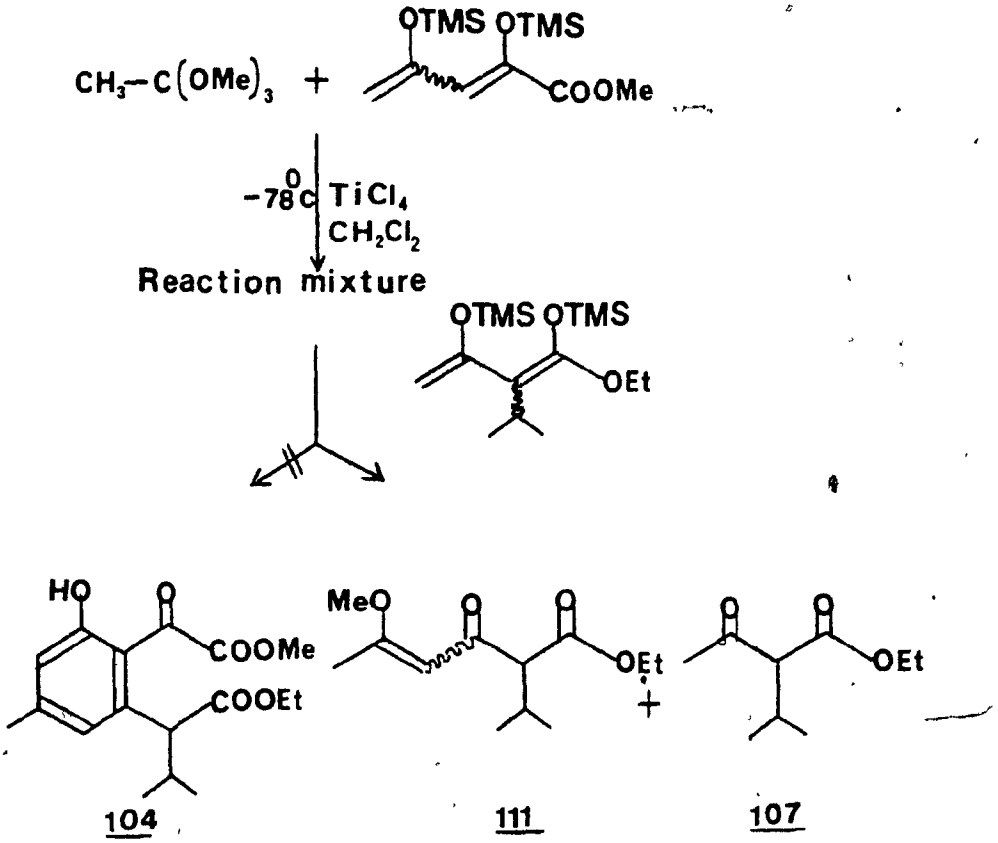
Therefore 122 was reacted with trimethyl orthoacetate in methylene chloride using $TiCl_4$ as the activating agent. Unfortunately no expected acetal 143 was formed. Instead, a small amount (10%) of the elimination product 146 was isolated. The rest was a polymerised tar (Scheme V.42).



146

Scheme V.42

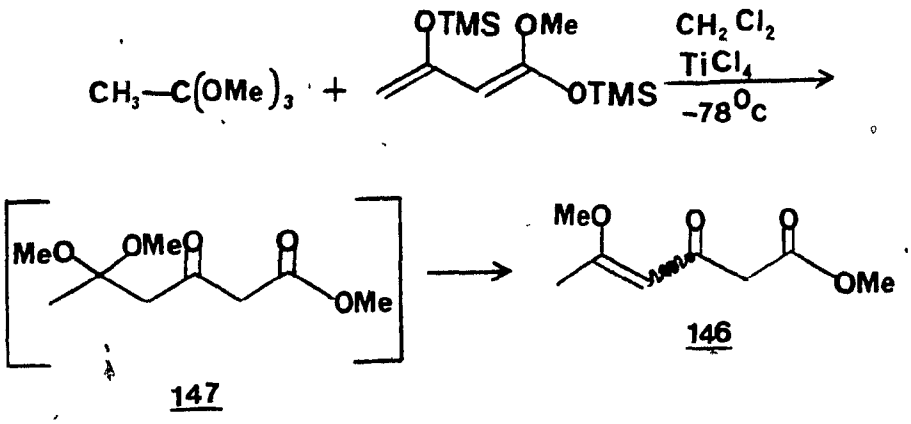
Since the reaction did not work as we expected, we tried a 'one-pot reaction' to avoid any elimination during the workup. In this case we first mixed the trimethyl orthoacetate and 122 at-78°C and then $TiCl_4$ was added to the reaction mixture. The reaction mixture was stirred for 2 h at -78°C followed by the addition of compound 110 and $TiCl_4$. No expected aromatic compound was isolated. The crude product on purification gave 111 along with the keto ester 107. Compound 111 was formed by a single condensation reaction of the bis enol silyl ether 122 with trimethyl orthoacetate similar to what was reported in Scheme III.8. Ethyl 2-isopropyl-3-oxobutanoate (107) was formed from the bis enol ether 110 during workup procedure. The reaction is depicted in Scheme V.43.



Scheme V.43

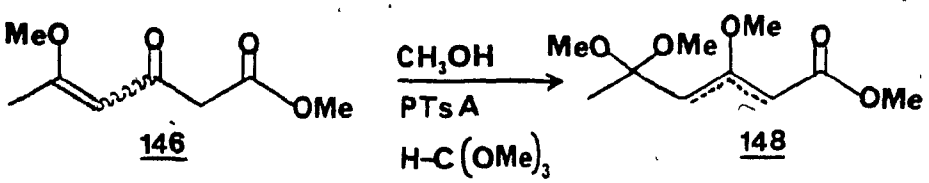
We therefore asked the second question, if the isopropyl group is absent in either the nucleophilic or the electrophilic component, can condensation of compound 122 with a tricarbonyl compound take place? We therefore decided to make the acetal 147. 1,3-Bis(trimethylsiloxy)-1-methoxy buta-1-3-diene was condensed with trimethyl orthoacetate (excess) using $TiCl_4$ as the activating agent. The compound

isolated was the elimination product 146 in 62% yield. The reaction is depicted in Scheme V.44. Compound 146 was then



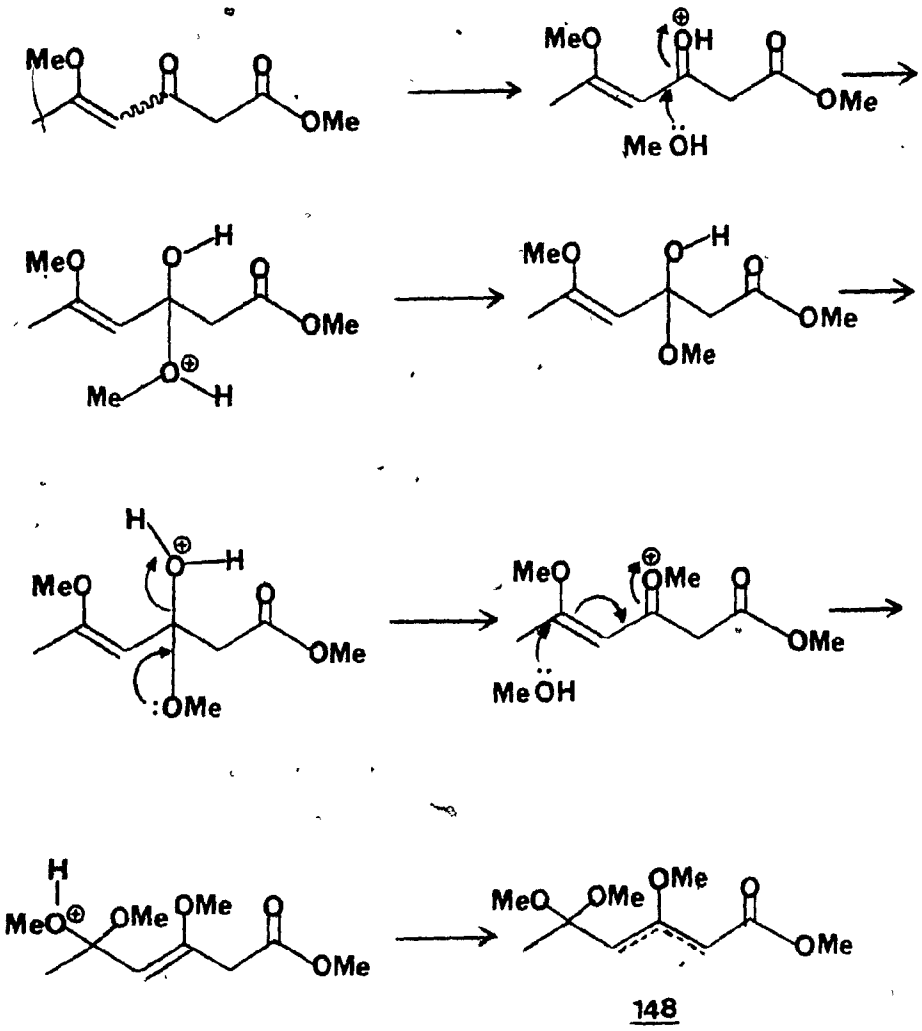
Scheme V.44

subjected to ketalization using methanol, paratoluenesulfonic acid and excess of trimethyl orthoformate. The resulting compound was the acetal 148 with a methoxy group in the 3-position (Scheme V.45). Essentially, compound 148 has all the



Scheme V.45

characteristics that can undergo cycloaromatization reaction with the nucleophile 122. A plausible mechanism for the formation of 148 is represented in Scheme V.46. When 148 was

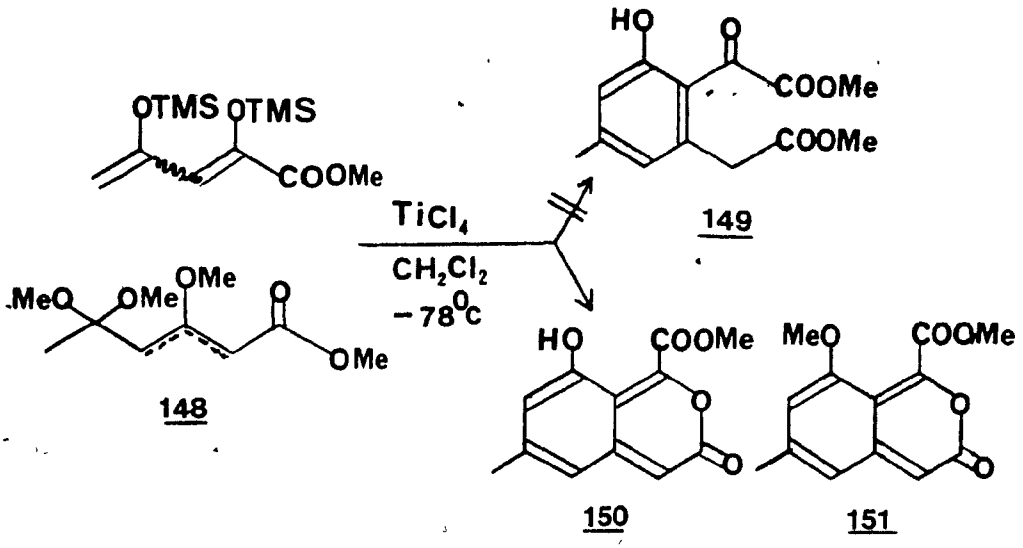


148

Scheme V.46

condensed with the bis enol silyl ether 122 in dry methylene chloride at -78°C using $TiCl_4$ as the activating agent, new

aromatic compounds were detected in the ^1H nmr of the crude product. Purification of the crude reaction mixture gave two new aromatic compounds. The spectral data of these compounds do not fit the properties expected for aromatic compound 149. The structures of these compounds were assigned on the basis of their spectral data and also from their chemical behaviour as 150 and 151. The condensation reaction was repeated with a



Scheme V.47

shorter reaction time (12 h) and only one compound, 150, was formed. From this, we believe that compound 151 might have been formed from 150.

In the proton nmr of **150**, the singlet at δ 2.31 is assigned to the methyl group on the ring and the singlet at δ 3.83 is assigned to the methyl protons of the ester. The singlets at δ 6.72, 6.85 and 7.24 are assigned to the protons on the ring. The phenolic proton appears at δ 10.65 indicating that it is intramolecularly hydrogen bonded to the adjacent carbonyl group. Infrared spectrum showed bands at 1680, 1720 and at 3400 cm^{-1}. Mass spectrum of **150** gave the molecular ion at m/z = 234 ($M^{+\cdot}$). ^{13}C nmr indicated the presence of 12 different carbons at δ 22.14, 52.89, 105.16, 113.52, 118.75, 119.08, 134.88, 142.49, 149.50, 160.29, 161.64 and 164.61.

The attached proton tests (APT) have been found very useful for the identification of quaternary, CH, CH_2 and CH_3 carbons in ^{13}C nmr spectroscopy[128-130]. Such a test was carried out for **150**. The negative peaks at δ 22.19 and 52.19 are assigned to the methyl on the aromatic ring and the ester methyl respectively. The other three negative peaks at 113.54, 118.51 and 118.92 are assigned to the vinylic CH carbons. The positive peaks at δ 105.16, 134.84, 142.44, 149.53 and 161.56 are assigned to the quaternary carbons.

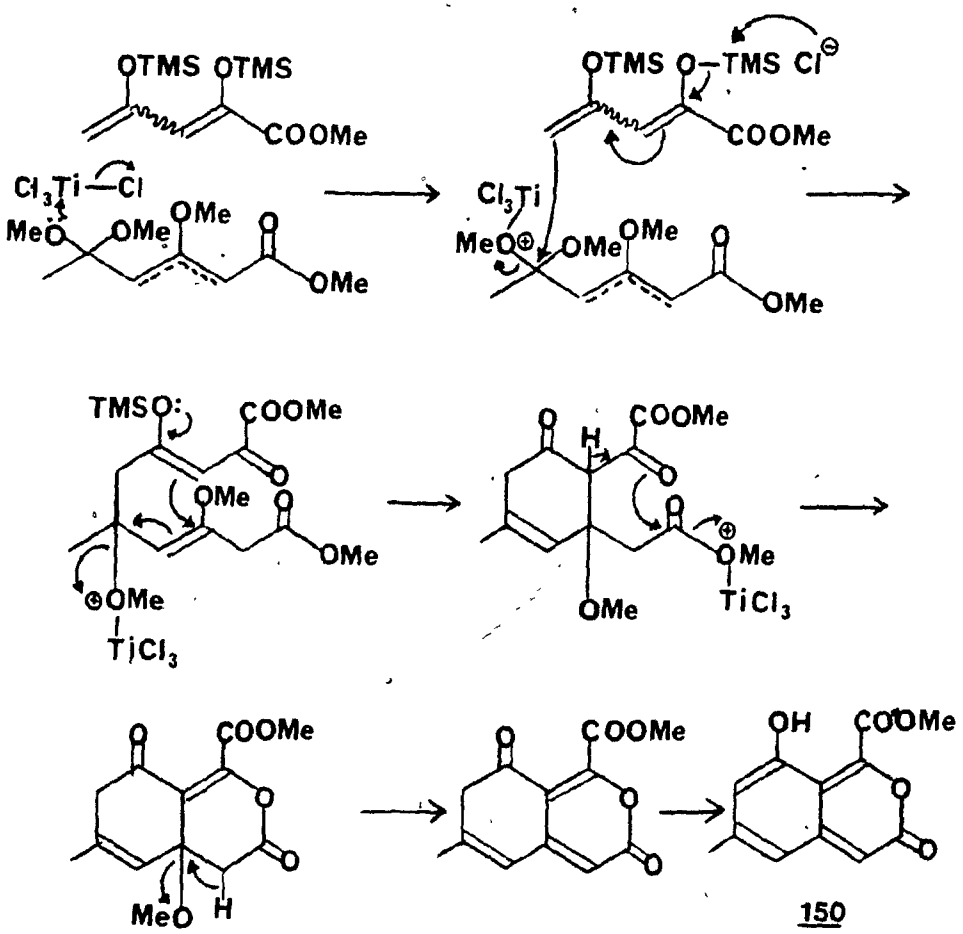
In the proton nmr of **151** the singlet at δ 2.40 is assigned to the methyl protons on the ring. There were two singlets at δ 3.82 and 3.93 corresponding to the $-OCH_3$ protons. The singlets at δ 6.81 (2H) and δ 7.23 are assigned

to the vinylic proton on the ring. In the infrared spectrum, there were two strong bands at 1720 and 1740 cm^{-1} and no band corresponding to the hydroxyl group was present. Mass spectrum gave the molecular ion at m/z = 248 ($M^{+\cdot}$) and the fragmentation pattern was at m/z = 233 ($M^{+}-CH_3$) and 189 (M^{+}-COOMe). ^{13}C nmr indicated the presence of 13 different signals at δ 22.10, 52.78, 56.34, 87.14, 112.17, 113.74, 119.99, 137.6, 138.21, 143.57, 147.67, 160.83, and 161.69.

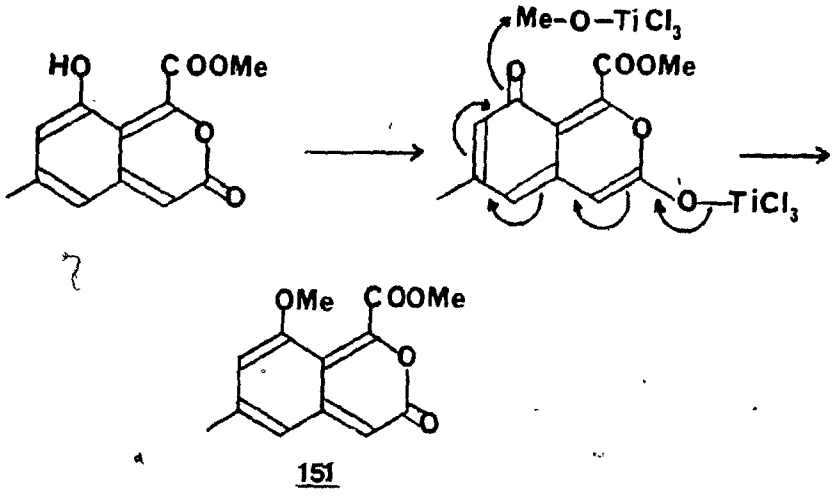
It seems that the condensation reaction proceeded in the desired manner, except that the reaction went one step further by cyclizing the ester side chains. We tried to stop the second cyclization by further reducing the reaction time. However, no condensation reaction was observed. Hence we believe that the first cyclization is slower than the second cyclization. Use of $ZnCl_2$, instead of $TiCl_4$ as the activating agent failed to give any condensation products.

A plausible mechanism accounting for the formation of **150** and **151** is depicted in Schemes V.48 and V.49 respectively. The structure of **150** was confirmed by chemical transformation. Compound **150** was reacted with sodium methoxide. The product obtained was the acid **152**. The acid **152** might have been formed by the simple hydrolysis of the ester by a trace amount of NaOH present in the reaction system (Scheme V.50).

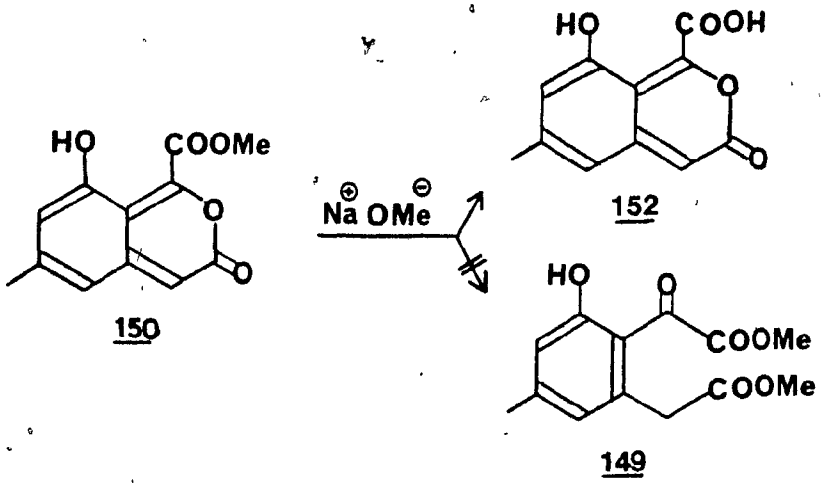
The above hydrolysis was repeated using 10% NaOH, methanol and water. The hydrolysis was completed in 10 min



Scheme V.48

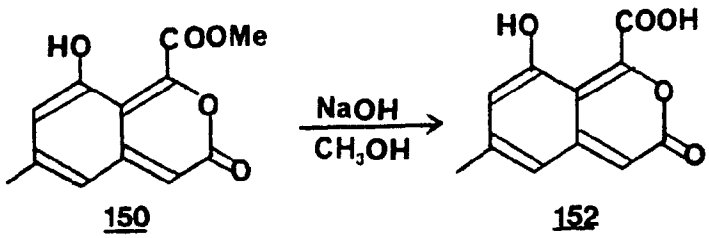


Scheme V.49



Scheme V.50

at room temperature in quantitative yield. The light yellow solid thus obtained was insoluble in most organic solvents. The compound was recrystallized from petroleum ether. In the



Scheme V.51

proton nmr the singlet at δ 2.5 is assigned to the methyl protons on the aromatic ring. The singlets at δ 6.90, 7.10 and 7.60 are assigned to the ring protons. The singlet at δ 10.70 is assigned to the intramolecularly hydrogen-bonded phenolic protons. The acid proton appears as a broad singlet at δ 3.5. Infrared spectrum of the acid showed strong bands at 1695, 1725 and two broad bands at 3200 and 3500 cm^{-1}. These broad bands are characteristic of phenolic and carboxylic acid absorptions. Mass spectrum of the acid gave the molecular ion at m/z = 220 ($M^{+\cdot}$). In the fragmentation pattern, mass spectrum shows the loss of COOH with a fragment at m/z = 175 ($M^{+\cdot}$-COOH).

We can therefore conclude that cycloaromatization between 122 and a tricarbonyl equivalent such as 148 can indeed occur. The presence of the isopropyl group, however, rendered the cycloaromatization impractical. Any future design in the synthesis of gossypol, using the cycloaromatization approach, must take this fact into consideration.

VI. EXPERIMENTAL

Melting points (mp) and boiling points reported were uncorrected. Melting points were determined on a Gallenkamp instrument.

Infrared spectra (ir) were obtained using a Perkin-Elmer model 297 spectrophotometer. Both solution and KBr pellet methods were used. FT-IR spectra were recorded on a Nicolet 7000 series instrument.

Mass spectra (ms) were obtained on a Dupont 21-492B mass spectrometer either by a direct insertion probe or by a batch inlet and on a Hewlett-Packard model 5984A coupled gas chromatograph-mass spectrometer.

Proton magnetic resonance (^{1}H nmr) spectra were recorded on a Varian T-60, T-60A, or XL-200 spectrometer, using either tetramethylsilane (TMS) or chloroform as the internal standard. The peaks were designated as singlets (s), doublets (d), triplets (t) and quartets (q) or multiplets (m). The doublets and triplets were recorded at the centre of the peaks.

^{13}C nmr spectra were recorded on a Varian XL-200 or Brucker WH-90 spectrometer.

Analytical TLC was performed on Kieselgel 60 F254 (Art. 5554-MERCK). For the visualization of the compounds, a dip solution containing ammonium molybdate (2.5 g) and ceric sulfate (1 g) in concentrated sulfuric acid/water (10 mL/90 mL) was used.

Column chromatography was performed by flash column chromatography as described by Still[109]. For flash column chromatography, silica gel (Kieselgel 60, 40-63 μ) supplied by Merck was used.

Solvents used for the reactions were completely dried. THF was dried over sodium and benzophenone (indicator). Benzene was dried over sodium and kept over sodium wire. Triethylamine was dried over phosphorous pentoxide.

Optical rotations were measured using a Perkin-Elmer 141 polarimeter and elemental analyses were determined by Guelph Chemical Laboratory, Guelph, Ontario.

Preparation of methyl 3-trimethylsiloxy-but-2-enoate (87)[99]

Anhydrous powdered zinc chloride (2 g) was added to trimethyl amine (115 g, 1.1 mol). The mixture was stirred for 1 h at room temperature until the salt was suspended in amine. To this was added a solution of methyl acetoacetate (58 g, 0.5 mL) in 150 mL of benzene followed by chlorotrimethylsilane (108.5 g, 1 mol). An exothermic reaction was noted after 30 min. The temperature was then raised to 40°C and the reaction mixture was stirred at that temperature overnight. After cooling, the reaction mixture was added to 1 L of ether (dry) and filtered. The filtrate and combined ether washings were concentrated in vacuum to give a brown oil. Distillation through a vigreux column gave 60% of the monosilylated

compound (87). The spectral data were identical to the ones reported in the literature[99].

Preparation of 1,3-bis-(trimethylsiloxy)-1-methoxy-butadiene (68)[74]

To a solution of dry diisopropylamine (34 mL, 24 mmol) in dry THF (50 mL) under nitrogen at 0°C was added n-butyl-lithium (16 mL of 1.5 M in hexane, 24 mmol). This was followed by the addition of dry TMEDA (3.2 mL). The solution was cooled to -78°C and methyl 3-trimethylsiloxy but-2-enoate (3.8 g, 20 mmol) was added. The yellow anion was quenched after 10 min with chlorotrimethylsilane (4 mL). The mixture was allowed to warm to 0°C and concentrated in vacuum. The residue was triturated with dry hexane (200 mL) and was then filtered. The filtrate was concentrated under high vacuum, to give the bis enol silyl ether as a yellow oil. The hexane treatment was repeated (in case any salt was again precipitated) using 100 mL of dry hexane. The compound was not stable enough to be distilled and therefore was used as such for the next reaction. The compound was identified by comparison with the known spectral data[74]. ^{1}H nmr ($CDCl_3$), δ: 0.14 (s, 9H,), 0.20 (s, 9H), 3.48 (s, 3H), 3.88 (d, 1H), 4.09 (d, 1H).

Preparation of 2-methylaceto-2-methyl-1,3-dioxolane (91)

To a well-stirred solution of methyl acetoacetate (1.16 g, 10 mmol) and ethylene glycol (1.24 g, 20 mmol) in 25 mL methylene chloride (dry) at room temperature was added slowly over a period of 20 min chlorotrimethylsilane (1.63 g, 15 mmol). An exothermic reaction was noticed. The reaction mixture was refluxed for 20 h, cooled and washed with 5% aqueous sodium carbonate solution. The methylene chloride solution was dried over anhydrous magnesium sulfate, filtered and evaporated. The crude product was distilled to get the pure dioxolane in 90% yield as a colourless oil:

bp 36-38°C/0.25 torr;

^{1}H nmr ($CDCl_3$), δ: 3.96 (s, 4H), 3.66 (s, 3H), 2.66 (s, 2H) and 1.46 (s, 3H);

Anal. calcd. for $C_7H_{12}O_4$: C 52.48; H 7.55; found: C 52.38; H 7.60.

Preparation of methyl 3-oxo-octonate (88)[100]

Dry tetrahydrofuran (25 mL) was distilled into a 50 mL flask containing 54 mg of sodium hydride under nitrogen. The flask was cooled in ice and methyl acetoacetate (1.16 g, 10 mmol) was added dropwise and the colourless solution was stirred at 0°C for 10 min. Then 4.8 mL (10.5 mmol) of n-butyllithium in hexane was added dropwise. The orange solution was stirred at 0°C for an additional 10 min. A solution of

n-bromobutane (1.50 g, 11 mmol) in 2 mL THF was added and the reaction mixture was stirred at room temperature for 15 min. The mixture was acidified with conc. HCl and was diluted with 5 mL of water and 15 mL of ether. The organic phase was washed with water many times until the aqueous extracts were neutral to pH. The ether solution was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The crude product was distilled under reduced pressure to give a colourless oil in 68% yield:

bp 56-58°C/0.54 torr; lit. bp 53-54°C (0.4 torr)[100];

^{1}H nmr ($CDCl_3$), δ: 0.77-1.87 (m, 9H), 2.55 (t, 2H). 3.40 (s, 2H), 3.67 (s, 3H);

ir (CCl_4): 1740, 1750 cm^{-1}.

Preparation of the 1,3-dioxolane 92

To a well-stirred solution of methyl 3-oxo-octonoate (1.72 g, 10 mmol) and ethylene glycol (1.24 g, 20 mmol) in dry methylene chloride at room temperature was added chlorotrimethylsilane (1.63 g, 15 mmol) over a period of 20 min. The reaction mixture was refluxed for 24 h, cooled and washed with a 5% aqueous sodium carbonate solution. The ethylene chloride solution was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The crude product was distilled under reduced pressure to give a colourless oil in 88% yield:

bp 84-85°C/0.5 torr; lit. bp 97-99°C (1 torr)[101];

^{1}H nmr ($CDCl_3$), δ: 0.77-1.53 (m, 9H), 1.73 (t, 2H), 2.60 (s, 2H), 3.63 (s, 3H), and 3.93 (s, 3H);

ir (CCl_4): 1780 cm^{-1};

Anal. calcd. for $C_{11}H_{20}O_4$: C 61.08; H 9.32;

found: C 61.13; H 9.35.

Preparation of methyl 3,3-dimethoxy-octanoate (89)

A mixture of methyl 3-oxo-octanoate (1.72 g, 10 mmol), dry methanol (30 mL), trimethyl orthoformate (5 mL) and a trace amount of para-toluenesulfonic acid were refluxed for 24 h. The reaction mixture was cooled and poured into a 5% sodium carbonate solution and extracted with ether. The ether extract was washed once with water and dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under vacuum. The crude product was purified by passage through flash column chromatography (eluent: ethyl acetate/hexane 1:9, v/v). A colourless oil was obtained as the pure product in 78% yield:

^{1}H nmr ($CDCl_3$), δ: 0.87-1.93 (m, 11H), 2.67 (s, 2H), 3.20 (s, 6H) and 3.67 (s, 3H);

ir (CCl_4): 1750 cm^{-1}.

Preparation of the 1,3-dioxolane 94

The ketal 92 (2.16 g, 10 mmol) was refluxed with a 30% sodium hydroxide solution (20 mL) for 24 h. The reaction mixture was cooled and acidified with hydrochloric acid (water/conc. HCl, 50:50, v/v) to pH 3. During neutralization, the reaction mixture was cooled in ice water. The product was quickly extracted with ether and washed once with distilled water. The ether solution was dried over anhydrous magnesium sulfate and filtered. The filtrate was evaporated to get the acid in 69% yield. The acid was a colourless thick oil, which solidified on cooling:

^{1}H nmr ($CDCl_3$), δ: 0.77-1.50 (m, 9H), 1.57-2.00 (m, 2H), 2.63 (s, 2H), 3.60 (s, 4H), and 10.40 (s, 1H).

Preparation of the 1,3-dioxolane 95

The acid 94 (2.02, 10 mmol) was dissolved in dry benzene under nitrogen. The benzene solution was stirred at room temperature for 10 min. Oxalyl chloride (1.26 g, 10 mmol) was added dropwise. The reaction mixture was slowly refluxed for 2 h, cooled and benzene was removed by evaporation in vacuum. The crude product was a light yellow oil in 90% yield. The product decomposed at room temperature:

^{1}H nmr ($CDCl_3$), δ: 0.77-1.50 (m, 9H), 1.57-1.93 (m, 2H), 3.17 (s, 2H) and 3.97 (s, 4H).

Synthesis of methyl 2,6-dihydroxy-4-pentylbenzoate (93)

The ketal 89 (0.218 g, 1 mmol) was mixed with the bis enol silyl ether 68 (0.260 g, 1 mmol) in dry methylene chloride (20 mL) under nitrogen at room temperature. Titanium tetrachloride (0.378 g, 2 mmol) was added dropwise and the reaction mixture was stirred for 48 h at room temperature. The crude mixture was poured into a sodium bicarbonate solution (10%, 10 mL) and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and concentrated by rotoevaporation. The last trace of the solvent was removed by high vacuum. The crude product was subjected to flash column chromatography (eluent: hexane/methylene chloride, 3:5, v/v). The major fraction was a white solid of the methyl olivetolate (methyl 2,6-dihydroxy-4-pentyl benzoate (93) in 72% yield. The minor fractions were the starting material methyl acetoacetate and methyl-3-oxooctanoate:

mp 29-30°C;

^{1}H nmr ($CDCl_3$), δ: 0.70-1.90 (m, 9H), 2.37-2.67 (m, 2H), 4.03 (s, 3H), 6.27 (s, 2H) and 9.70 (s, 2H);

ir (CCl_4): 1675, 3200 (br) and 3460 cm^{-1};

ms m/z (relative intensity): 238 (M^+, 20), 207 (6), 206 (10), 182 (42), 150 (100).

Preparation of olivetol (5-pentyl-resorcinol) (13)

The methyl olivetolate (0.238 g, 1 mmol) was dissolved in methanol (10 mL) and sodium hydroxide (2 mL, 30% aqueous solution) was added. The reaction mixture was refluxed for

5 h, cooled and acidified with 1N HCl and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered, concentrated and evaporated to dryness under high vacuum. Olivetol was obtained as a light brown solid in 85% yield:

mp 41-42°C, lit. mp 42-44°C[94,97];

^{1}H nmr ($CDCl_3$), δ: 0.40-1.21 (m, 9H), 2.24-2.65 (m, 2H), 6.01 (s, 2H), 6.20 (s, 2H), 6.31 (s, 1H);

ir (CCl_4): 3610 cm^{-1};

ms m/z (relative intensity): 180 (25, M^+), 137 (30), 124 (100), 124 (45), 55 (24);

Anal. calcd. for $C_{11}H_{16}O_2$: C 73.29%; H 8.94%; O 17.7541; found: C 73.38%; H 8.84%.

Synthesis of methyl 2,4-dihydroxy-6-pentylbenzoate (96)

The acid chloride 95 (1.1 g, 5 mmol) was mixed with 1,3-bis-(trimethylsiloxy)-1-methoxybutadiene (1.30 g, 5 mmol) in dry methylene chloride under nitrogen at room temperature. Titanium tetrachloride (2.64 g, 14 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into a 5% sodium bicarbonate solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and evaporated under vacuum to remove the solvent. The crude product was subjected to flash column chromatography (eluent: ethylacetate/hexane, 20:80, v/v). The major fraction isolated was the methyl olivetolate in 55% yield. Methyl olivetolate is a white solid:

mp 65-68°C;

^{1}H nmr ($CDCl_3$), δ: 0.73-1.45 (m, 9H), 2.68-3.00 (m, 2H), 3.82 (s, 3H), 5.78-6.05 (m, 1H), 6.13-6.33 (m, 2H), 11.58 (s, 1H);

ir ($CDCl_3$): 1660, 3400, 3600 cm^{-1};

ms m/z (relative intensity): 238 (48, M^+), 207 (25), 206 (94), 182 (70), 150 (100), 43 (50).

Synthesis of methyl Δ^1-tetrahydrocannabinolate (97)

A mixture of methyl 2,4-dihydroxy-6-pentylbenzoate (96) (0.238 g, 1 mmol), (+)-trans-p-mentha-2,8-diene-1-ol (0.182 g, 1.2 mmol) and anhydrous magnesium sulfate (25 mg, pre-dried under vacuum) was stirred with dry methylene chloride under nitrogen for 20 min. The reaction mixture was cooled to 0°C and boron trifluoride etherate (0.312 g, 22 mmol, pre-dried by distilling over calcium hydride) was added. Stirring continued at 0°C until the red colour was faded (to almost colourless in 2 h). The reaction mixture was filtered (more dry methylene chloride was used to wash the flask) and the filtrate was concentrated by high vacuum. The crude product was subjected to flash column chromatography (eluent: carbon tetrachloride/methylene chloride, 4:1, v/v). Fraction one was the minor fraction containing a mixture of (+)-trans-p-mentha-2,8-diene-1-ol and a small percentage (< 10%) of the methyl Δ^6-tetrahydrocannabinoate which was not isolated in pure form. Fraction two was a colourless gum identified as methyl Δ^1-tetrahydrocannabinoate in 55% yield:

^{1}H nmr ($CDCl_3$), δ: 0.89 (t, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.40-2.40 (m, 12H), 1.43 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.53-2.93 (m, 2H), 3.91 (s, 3H, OCH_3), 6.21 (s, 1H, aromatic), 6.39 (s, br, 1H, vinylic proton), 12.32 (s, 1H, phenolic proton);

ir (CCl_4): 1650 and 3400 cm^{-1};

ms m/z: (relative intensity): 372 (35, M^+), 340 (80), 325 (25), 257 (60), 256 (100);

$[\alpha]_D$: -188.4° (0.16 $CHCl_3$);

Anal. calcd. for $C_{23}H_{32}O_4$: mol. wt. 372.4908; found: 372.4912.

Preparation of (-)-trans-Δ^1-tetrahydrocannabinol (72) from methyl Δ^1-tetrahydrocannabinolate

The (-)-trans-Δ^1-methyltetrahydrocannabinolate (0.10 g, was refluxed with aqueous sodium hydroxide (25%, 5 mL) in methanol (10 mL) for 5 h. The reaction mixture was cooled, acidified with 1N HCl and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and the solvent was removed by high vacuum. The crude product was subjected to flash column chromatography (eluent: ethyl acetate/hexane, 15:85, v/v). Fraction one was the major fraction and was identified as (-)-trans-Δ^1-tetrahydrocannabinol in 78% isolated yield:

200-MHz nmr ($CDCl_3$), δ: 0.88 (t, 3H, CH_3), 1.09 (s, 3H, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.26-2.33 (m, 11H), 1.68 (s, 3H, olefinic CH_3), 2.44 (t, 2H), 3.21 (d, br, 1H), 4.71 (s, 1H, phenolic OH),

6.10 (s, 1H, aromatic), 6.21 (s, 1H, aromatic), 6.34 (s, 1H, vinylic);[131]

FT-IR (CCl_4): 3634 cm^{-1} (phenolic OH)[131];

uv (ethanol)[131]: 275 and 281 nm;

ms m/z (relative intensity): 314 (15, M^+), 299 (20, M^+-CH_3), 271 (6), 231 (40), 205 (45), 100 (100);

ms (TMS derivative of THC) m/z (relative intensity): 386 (100, M^+), 371 (68), 343 (24), 330 (17), 315 (43), 303 (37), 73 (86);

$[\alpha]_D$: -170° (C 0.04 $CHCl_3$); lit.[93] $[\alpha]_D$: -174°.

Preparation of 1-ethoxy-1-trimethylsiloxy 3-methyl butene (108)

To a solution of diisopropyl amine (3.4 mL, 24 mmol) in dry THF (50 mL) under nitrogen at 0°C was added n-butyllithium (16 mL of 1.5 M in hexane, 24 mmol) dropwise. The solution was cooled to -78°C. After 10 min a solution of ethyl isovalerate (2.6 g, 20 mmol) in THF (5 mL) was added dropwise. The solution was stirred at -78°C for 30 min and the light yellow anion was quenched with chlorotrimethylsilane (4 mL). The reaction mixture was allowed to warm to room temperature and stirred for another hour and the solvent was removed under reduced pressure. The residue was triturated with dry hexane (150 mL) and the precipitate was removed by filtration. The filtrate was concentrated under vacuum to give the enol silyl

ether as a colourless oil. The crude product was distilled under reduced pressure to give the pure compound in 85% yield:

bp 28°C/0.2 torr;

^{1}H nmr ($CDCl_3$), δ: 0.11 (s, 9H, →Si-), 0.83 (d, 6H), 0.12 (t, 3H, J = 6 Hz), 2.16-2.70 (m, 1H), 3.56 (d, 1H), 3.70 (q, 2H, J = 6 Hz);

ms m/z (relative intensity): 202 (2, M^+), 147 (20), 103 (50), 84 (100).

Preparation of ethyl 2-isopropyl-3-oxo-butanoate (107)

The enol silyl ether 108 (2.02 g, 10 mmol) was stirred with acetyl chloride (1.17 g, 15 mmol) in dry methylene chloride under nitrogen for 10 min. The reaction mixture was cooled to -78°C and titanium tetrachloride (2.27 g, 12 mmol) was added and gradually allowed to warm to room temperature and stirred for another 24 h at room temperature. The mixture was poured into a 10% sodium bicarbonate solution, extracted with ether, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was subjected to fractional distillation. The keto ester was obtained in 80% yield:

bp 30-32°C/0.05 torr; lit.[116] bp 36-38°C (0.06 torr);

^{1}H nmr ($CDCl_3$), δ: 0.87 (d, 3H), 1.00 (d, 3H), 1.10-1.50 (m, 1H), 1.27 (t, 3H, J = 6 Hz), 2.23 (s, 3H), 3.20 (d, 1H, J = 8 Hz), 4.18 (q, 2, J = 6 Hz);

ir (CCl_4): 1700, 1730 cm^{-1}.

Preparation of ethyl 2-isopropyl 3-trimethylsiloxy-butenoate (109)

Anhydrous powdered zinc chloride (0.2 g) was added to triethylamine (2.02 g, 20 mmol) and the mixture was stirred under nitrogen for 1 h at room temperature until the salt was suspended in the amine. To this was added a solution of ethyl 2-isopropyl-3-oxo-butanoate (1.72 g, 10 mmol) in 10 mL of benzene followed by chlorotrimethylsilane (1.08 g, 10 mmol). The reaction mixture was stirred at 40°C for 24 h, cooled, added to dry ether and filtered. The filtrate was concentrated and finally distilled under reduced pressure. Fraction one, the monosilylated compound was obtained in 60% yield:

bp 48-52°C/0.05 torr;

^{1}H nmr ($CDCl_3$), δ: 0.23 (s, 9H), 1.03 (d, 6H), 1.30 (t, 3H, J = 6 HZ), 2.05 (s, 3H), 2.73-3.26 (m, 1H), 4.17 (q, 2H, J = 6 Hz);

ms m/z (relative intensity): 244 (25, M^{+}), 229 (75), 183 (60), 130 (95), 43 (100).

Fraction two (bp 78-80°C/0.05 torr) identified as 1,3-bis(trimethylsiloxy)-1-ethoxy-2-isopropyl buta-1,3-diene (110) in 30% yield. Spectral characteristics of the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.23 (s, 9H), 0.25 (s, 9H) 0.93 (d, 6H), 1.17 (t, 3H), J = 6 Hz), 2.43-2.86 (m, 1H), 3.87 (q, 2H, J = 6 HZ), 4.10 s, 1H), 4.27 (s, 1H);

ms m/z (relative intensity): 316 (10, M^{+}), 301 (65), 197 (20), 73 (100).

A-one step preparation of 1,3-bis(trimethylsiloxy)-1-ethoxy-2-isopropyl but-1,3-diene (110)

To a solution of diisopropyl amine (6.8 mL) in dry THF (100 mL) under nitrogen at 0°C was added n-butyllithium (32 mL, of 1.5 M in hexane) dropwise. The solution was cooled to -78°C (after 10 min) and a solution of ethyl 2-isopropyl-3-oxo-butanoate (3.44 g, 20 mmol) in dry THF (10 mL) was added dropwise. The solution was stirred at -78°C for 30 min and the yellow anion was quenched with chlorotrimethylsilane (8 mL). The reaction mixture was allowed to warm to room temperature and stirred for another hour and the solvent was removed under reduced pressure. The residue was triturated with dry hexane (200 mL) and the precipitate was removed by filtration. The filtrate was concentrated under vacuum to give the bis enol silyl ether in almost quantitative yield. The crude product was distilled under reduced pressure (bp 80-81°C/0.05 torr). The spectral data were identical in all respects to those of 110 reported in the previous experiment.

Condensation reaction of 1,3-bis(trimethylsiloxy)-1-ethoxy-2-isopropyl-buta-1,3-diene with trimethyl orthoacetate

The bis enol silyl ether 110 (3.16 g, 10 mmol) was stirred with trimethyl orthoacetate (1.20 g, 10 mmol) under nitrogen in dry methylene chloride for 10 min. The solution was cooled to -78°C and then $TiCl_4$ (2.5 mL, 10 mmol) was added dropwise. The

reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was poured into an aqueous sodium bicarbonate solution (10%, 50 mL) and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by fractional distillation (bp 78°-80°C/0.05 torr). The compound obtained was identified as ethyl 2-isopropyl-3-oxo-5-methoxy hex-4-enoate (111) in 74% yield. The spectral data for the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.75 (d, 3H), 0.86 (d, 3H), 0.60-1.00 (m, 1H), 1.13 (t, 3H, J = 5 Hz), 2.17 (s, 3H), 2.98 (d, 1H, J = 8 Hz), 3.87 (s, 3H), 4.18 (q, 2H, J = 5 Hz), 5.53 (s, 1H), vinylic proton);

ir (CCl_4) ν: 1600, 1690 and 1740 cm^{-1};

ms m/z (relative intensity): 228 (5, M^+), 123 (40), 99 (50), 73 (65), 43 (100).

Condensation reaction of 1,3-bis(trimethyl siloxy)-1-ethoxy-2-isopropyl buta-1,3-diene with trimethylorthoformate

The procedure was exactly the same as described for the preparation of 111. The crude product obtained after workup was subjected to flash column chromatography (eluent: ethyl acetate/hexane, 10:90, v/v). Fraction one was ethyl 2-isopropyl-3,5-dioxo-hexanoate (113) in 65% yield. The

compound exists in its enol form. The spectral data for the compound are:

^{1}H nmr ($CDCl_3$), δ; 0.83 (d, 3H), 0.97 (d, 3H), 0.67-1.13 (m, 1H), 1.20 (t, 3H, J = 6 Hz), 2.00 (s, 1H), 2.87 (d, 1H, J = 8 Hz), 4.13 (q, 2H, J = 6 Hz), 5.47 (s, 1H), 15.08 (s, br, 1H);

ir (CCl_4) ν: 1620, 1740 cm^{-1};

ms m/z (relative intensity): 214 (5, $M^{+\cdot}$), 172 (30), 130 (70), 115 (75), 43 (100);

Anal. calcd. for $C_{11}H_{18}O_4$: C 61.66% ; H 8.46% ; O 29.87% ; found: C 61.69% , H 8.52% ; O 29.90% .

Preparation of ethyl 2-isopropyl-3,5-dioxo-hexanoate (113) from diketene

Diketene (1.00 g, 10 mmol) was mixed with the enol silyl ether 108 (2.02 g, 10 mmol) in dry methylene chloride under nitrogen. The solution was cooled to -78°C and $TiCl_4$ (2.83 g, 15 mol) was added dropwise into the solution. The reaction mixture was slowly allowed to warm to room temperature and stirred for 24 h. The mixture was poured into a 5% aqueous sodium bicarbonate solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was subjected to flash column chromatography (eluent: ethyl acetate/hexane, 10:90, v/v). Fraction one was the desired keto ester in 68% yield as a colourless oil. The spectral data are identical in all respects to those reported for the compound 113 in the previous experiment.

Attempted acetalizaton of 111

Compound 111 (2.28 g, 10 mmol) was mixed with dry methanol (30 mL), trimethyl orthoformate (4 mL, excess) and a catalytic amount of para-toluenesulfonic acid. The reaction mixture was refluxed for 24 h. The cooled mixture was poured into an aqueous sodium carbonate solution (20%, 30 mL) and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered, concentrated and distilled under reduced pressure. Compound 115 was obtained as a colourless liquid (bp 68-71°C/0.04 torr). The spectral data for the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.83 (d, 3H), 1.00 (d, 3H), 0.70-1.10 (m, 1H), 1.23 (t, 3H, J = 5 Hz), 1.43 (s, 3H), 2.57 (d, 1H, J = 8 Hz), 3.13 (s, 6H), 4.06 (q, 2H, J = 5 Hz);
ir (CCl_4) ν: 1590, 1680 and 1730 cm^{-1}.

Preparation of the ethylene acetal 116 from 111

Compound 111 (2.28 g, 10 mmol) was mixed with ethylene glycol (3 mL, excess) and dry methylene chloride (30 mL) under nitrogen. The solution was stirred vigorously for 15 min at room temperature and chlorotrimethylsilane (2.16 g, 20 mmol) was added. An exothermic reaction was noticed. The reaction mixture was refluxed for 20 h, cooled and poured into a 5% aqueous sodium carbonate solution (30 mL). The methylene chloride solution was separated and dried over anhydrous

magnesium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography using ethyl acetate and hexane (15:85, v/v) as eluent. The ethylene acetal 116 was obtained in 78% isolated yield. The spectral data for the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.98 (d, 6H), 1.23-1.57 (m,1H), 1.33 (t, 3H, J = 6 Hz), 1.43 (s, 3H), 3.00 (s, 1H), 3.07 (s, 1H), 3.40 (d, 1H, J = 8 Hz), 4.30 (s, 4H), 4.20 (q, 2H, J = 6 Hz);

ir (CCl_4) ν: 1710 and 1740 cm^{-1};

ms m/z (relative intensity): 243 (40, M^+-CH_3), 213 (10).

Preparation of ethyl 2-isopropyl-3-oxo 5,5-bis(phenyl-thio-)hexanoate (117)

Benzene thiol (1.32 g, 12 mmol) was mixed with 111 (2.28 g, 10 mmol) in dry CCl_4 (30 mL) under nitrogen. To this was added pyridine (2 mL) and the reaction mixture was stirred for 24 h at room temperature. The CCl_4 solution was evaporated and the crude product was distilled under reduced pressure to yield 84% of the dithio acetal (bp 64-68°C/0.05 torr). The spectral data for the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.80 and 0.92 (2d, 6H), 0.78-1.00 (m, 1H), 1.17 (t, 3H, J = 6 Hz), 2.13 (s, 3H), 3.13 (d, 1H, J = 8 Hz), 3.37 (s, 2H), 4.10 (q, 2H, J = 6 Hz), 7.13 (s, 10H);

ir (CCl_4) ν: 1700 and 1740 cm^{-1}.

Preparation of methyl 2,4-bis(trimethylsiloxy)-pentadienoate (122) by LDA method

Diisopropyl amine (3.4 mL, 24 mmol) was added to dry THF (100 mL) under nitrogen. The solution was cooled to 0°C and n-butyllithium (16 mL, 24 mmol) was added dropwise. The solution was cooled to -78°C and methyl acetopyruvate (1.44 g, 10 mmol) in 10 mL dry THF, was added dropwise. The solution was stirred at -78°C for 1 h and chlorotrimethylsilane (4 mL) was added and the reaction mixture was warmed to room temperature and stirred for another hour. Then the solvent was removed under vacuum and triturated with dry hexane (100 mL), filtered and concentrated under reduced pressure. The crude product was distilled under reduced pressure to give the pure product in 70% yield (bp 72-76°C/0.04 torr). The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.10 (s, 9H), 0.13 (s, 9H), 3.57 (s, 3H), 4.43 (d, 1H, J = 1 Hz), 4.87 (s, 1H), 5.90 (d, 1H, J = 1 Hz);

ir (neat) ν: 1630 and 1730 cm^{-1};

ms m/z (relative intensity): 288 (38, M^+), 273 (65), 245 (60), 147 (30), 73 (100);

Anal. calcd. for: $C_{12}H_{24}O_4Si_2$: mol wt. 288.4821; found: mol. wt. 288.4850.

Preparation of methyl 2,4-bis(trimethylsiloxy)-pentadienoate (122) using trimethylsilyl trifluoromethanesulfonate

Methyl acetopyruvate (2.05 g, 14 mmol) was dissolved in dry benzene (30 mL) under nitrogen. Triethylamine (2.90 g,

0.26 mmol) was added and the solution was cooled to 0°C. Trimethylsilyl trifluoromethanesulfonate (6.2 g, 28 mmol) was added dropwise and the rection mixture was refluxed for 2 h with a catalytic amount of anhydrous zinc chloride. The reaction mixture was cooled and after removing the solvent under reduced pressure, the crude product was triturated with dry hexane (50 mL). The hexane solution was separated and concentrated under reduced pressure (bp 88-90°C/0.06 torr). The product obtained was a light yellow oil in 88% isolated yield. The spectral data were identical in all respects to the bis enol silyl ether 122 obtained by the LDA method.

Preparation of methyl 2-oxo-4-trimethylsiloxy pent-3-enoate (121)

Anhydrous powdered zinc chloride (0.2 g) was added to triethylamine (2.02 g, 20 mmol) and the mixture was stirred under nitrogen for 1 h at room temperature until the salt was suspended in the amine. To this was added a solution of methyl acetopyruvate (1.44 g, 10 mmol) in dry benzene (10 mL), followed by chlorotrimethylsilane (1.08 g, 10 mmol). The reaction mixture was stirred at 40°C for 24 h, cooled, poured into dry ether (100 mL) and filtered. The filtrate was concentrated and distilled under reduced pressure. Fraction one (bp 60-62°C/0.1 torr) was the monosilylated compound 121 in 58% yield. Fraction two was identified as methyl 2,4-

bis(trimethylsiloxy)-pentadienoate (122). The spectral data of 121 are:

^{1}H nmr ($CDCl_3$), δ: 0.20 (s, 9H), 1.87 (s, 3H), 3.67 (s, 3H), 6.07 (s, 1H).

Synthesis of methyl (2-hydroxy-6-methoxy carbonyl-4-methyl phenyl-1-oxoacetate (124)

The bis enol silyl ether 122 (1.44 g, 5 mmol) was mixed with 121 (1.08 g, 5 mmol) in dry methylene chloride under nitrogen. The reaction mixture was stirred at room temperature for 20 min and $TiCl_4$ (2.27 g, 12 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and poured into a 20% solution of aqueous sodium bicarbonate (30 mL). The mixture was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was subjected to flash column chromatography (ethyl acetate alone). The product obtained was an orange solid (61% yield). The compound was recrystallized from CCl_4 (mp 138-140°C). The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), δ: 2.20 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 6.47 (s, 1H), 6.90 (d, 1H, J = 2 Hz), 8.13 (m, 1H);

ir (CCl_4) ν: 1550, 1730, 3610 cm^{-1};

ms m/z (relative intensity): 252 (20, M^+), 193 (100), 133 (5), 77 (10);

Anal. calcd. for $C_{12}H_{12}O_6$: C 57.16 %; H 4.79 %; O 38.07 %; found: C 57.22% ; H 4.89% ; O 38.15% .

Preparation of 3-phenylthio-crotonyl chloride (128)

The acid of 3-phenylthio-crotonic acid[119] (1.94 g, 10 mmol) was dissolved in dry benzene (20 mL) under nitrogen. Oxalyl chloride (1.27 g, 10 mmol) was added dropwise to the above solution. A brisk effervescence was noticed. The reaction was followed by GLC and was completed in half an hour. The solvent was removed by high vacuum and the title compound was obtained in almost quantitative yield. The compound was unstable. The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), δ: 2.40 (s, 3H, Me), 5.10 (s, 1H), 7.43 (s, 5H, aromatic).

Preparation of ethyl-2-isopropyl-3-oxo-5-phenylthio hex-4-enoate (129)

The acid chloride 128 (2.28 g, 10 mmol) was dissolved in dry methylene chloride (100 mL) and the enol silyl ether 108 (2.02 g, 10 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was poured into a 5% aqueous sodium bicarbonate solution and extracted with ether. The ether extract was dried and concentrated under reduced pressure. The crude product was distilled to give the title compound as a mixture of geometric isomers in 70% yield (bp 146-148°C/0.01 torr). The spectral characteristics of the compound are:

^{1}H nmr ($CDCl_3$), δ: 0.67 (d, 3H), 0.83 (d, 3H), 0.88-1.50 (m, 1H), 1.10 (t, 3H, J = 6 Hz), 2.33 (s, 3H), 2.87 (d, 1H, J = 8 Hz), 3.93 (q, 2H, J = 6 Hz), 5.67 (s, 1H), 7.33 (s, 5H);
ir (CCl_4) ν: 1600 br, 1670 and 1730 br cm^{-1}.

Preparation of 3-benzyl thio-crotonyl chloride (131)

The acid 130[119] (2.09 g, 10 mmol) was suspended in dry benzene (50 mL) and oxalyl chloride (1.27 g, 10 mmol) was added. The reaction mixture was refluxed for 1 h, cooled and the solvent was removed in vacuum, when the title compound was obtained as a mixture of geometric isomers in the ratio 50:50 in quantitative yield. The acid chloride thus obtained was 90% pure. Being very unstable it could not be purified further. The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), (two isomers) δ: 2.20 and 2.33 (2S, 6H, isomeric methyl), 4.00 and 4.07 (2s, 4H, isomeric methylene proton), 5.83 and 6.03 (2s, 2H, isomeric vinylic proton), 7.27 (s, 10H, aromatic proton).

Preparation of ethyl 5-benzylthio-2-isopropyl-3 one-hex-4-enoate (132)

The acid chloride 131 (2.26 g, 10 mmol) was dissolved in dry methylene chloride under nitrogen. The enol silyl ether 108 (2.02 g, 10 mmol) was added and the reaction mixture was cooled to -78°C and $TiCl_4$ (2.26 g, 12 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was poured into a 20% sodium bicarbonate solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was obtained as a mixture of geometric isomers (E:Z = 75:25) in 80% yield (combined). The crude product was subjected to flash column chromatography (eluent: ethylacetate/hexane, 15:85, v/v). Fraction two was assigned to the E stereochemistry and fraction 3 was assigned to the Z stereochemistry on the basis of NOE experiment[120,121]. The spectral data of the compounds are:

E-isomer

^1H nmr ($CDCl_3$), δ: 0.43 (d, 3H), 0.60 (d, 3H), 0.40-0.65 (m, 1H), 1.23 (t, 3H, J = 6 Hz), 2.33 (s, 3H), 3.03 (d, 1H, J = 7 Hz), 4.00 (s, 2H), 4.06 (q, 2H, J = 6 Hz), 6.11 (s, 1H), 7.33 (s, 5H);

ir (CCl_4) ν: 1560 br, 1670 br and 1730 cm^{-1}.

Z-isomer

^{1}H nmr ($CDCl_3$), δ: 0.90 (d, 3H), 1.00 (d, 3H), 0.88-1.03 (m, 1H), 1.27 (t, 3H, J = 4 Hz), 2.30 (s, 3H), 3.17 (d, 1H, J = 8 Hz), 4.07 (s, 2H), 4.17 (q, 2H, J = 4 Hz), 6.37 (s, 1H), 7.27 (s, 5H);

ir (CCl_4) ν: 1535, 1650 and 1730 cm^{-1}.

Preparation of ethyl 3-phenylthio-2-isopropyl but-2-enoate (140)

To a stirred solution of ethyl 2-isopropyl-3-oxo-butanoate (107) (1.61 g, 9.36 mmol) and thiophenol (1.03 g, 9.36 mmol, 0.96 mL) in dry methylene chloride was added solid P_2O_5 (2.65 g, 18.7 mmol). The reaction mixture was stirred for 18 h and the methylene chloride solution was separated from the residue by centrifugation. The residue was washed with methylene chloride (20 mL) and the combined methylene chloride solution was washed with a sodium hydroxide solution (10%, 15 mL) followed by a saturated sodium chloride solution (30 mL). The methylene chloride solution was dried over potassium carbonate solution, filtered and concentrated under vacuum. The crude product was distilled under reduced pressure yielding 70% of the desired product (bp 100-104°C/ 0.05 torr). The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), δ: 1.13 (d, 6H), 1.90 (t, 3H, J = 6 Hz), 3.07-3.67 (m, 1H), 4.27 (q, 2H, J = 6 Hz), 7.30 (s, 5H);
ir (CCl_4) ν: 1720 cm^{-1}.

Preparation of 1-trimethylsiloxy-3-phenylthio-1-ethoxy-2-isopropyl buta-1,3-diene (141)

Diisopropyl amine (3.4 mL, 12 mmol) was mixed with tetrahydrofuran (50 mL) under nitrogen. The solution was cooled to 0°C and n-butyllithium (8 mL, 12 mmol) was added dropwise. The solution was cooled to -78°C and the vinyl sulfide (3.16 g, 12 mmol) was added dropwise. The reaction mixture was stirred at -78°C for 10 min and TMSCl (2 mL) was added. The solution was stirred again for another 10 min and allowed to warm to room temperature. The solvents were removed under vacuum. The product was triturated with dry hexane (50 mL), filtered and concentrated under vacuum. The compound was unstable. The spectral data of the geometric isomer are:

^{1}H nmr ($CDCl_3$), δ: 0.30 and 0.33 (2s, 18H, isomeric >S-O-protons), 1.00 and 1.13 (2d, 12H, isomeric methyl protons) 1.33 and 1.37 (2t, 6H), 2.36-3.13 (m, 2H), 3.9 and 4.20 (2q, 4H), 4.7, 4.80, 4.93 and 4.98 (4s, 4H, isomeric vinylic protons), 7.13-7.67 (m, 10H, isomeric aromatic ring protons).

Condensation reaction of 141 with trimethyl orthoacetate

The enol silyl ether 141 (1.68 g, 5 mmol) was mixed with trimethyl orthoacetate (0.6 g, 5 mmol) in dry CH_2Cl_2 (20 mL). The solution was cooled to -78°C and $TiCl_4$ (0.95 g, 5 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was poured into a 5% aqueous sodium bicarbonate solution and extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was subjected to flash column chromatography (eluent: ethylacetate/hexane, 10:90, v/v) to give the ethyl 2-isopropyl-3-phenylthio-5-oxo-hex-2-enoate (142) in 50% yield. The spectral data of the compound are:

^1H nmr ($CDCl_3$), δ: 1.16 (d, 6H), 1.27 (t, 3H, J = 5 Hz), 2.00 (s, 3H), 3.27 (s, 2H), 3.10-3.36 (m, 1H), 4.17 (q, 2H, J = 5 Hz), 7.23 (s, 5H);

ir (CCl_4) ν: 1700 and 1720 cm^{-1};

ms m/z (relative intensity): 306 (25, M^+), 261 (28), 155 (75), 109 (100).

Attempted acetalization of 142

The compound 142 (1.53 g, 5 mmol) was dissolved in dry methanol (50 mL) under nitrogen and the trimethyl orthoformate (3 mL, excess) was added followed by a catalytic amount of para-toluenesulfonic acid. The reaction mixture was refluxed for 20 h, cooled and poured into a 5% aqueous sodium carbonate

solution. The product was extracted with ether, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was a solid which was recrystallized from petroleum ether to give a light yellow crystalline compound (mp 106-107°C). The spectral data of the compound 144 are:

^1H nmr ($CDCl_3$), δ: 1.40 (d, 6H), 2.05 (s, 3H), 3.10-3.57 (m, 1H), 5.40 (s, 1H), 7.48 (s, 5H);
ir (CCl_4) ν: 1630 and 1710 cm^{-1};
ms m/z (relative intensity): 260 (75, M^+), 245 (95), 232 (60), 217 (80), 183 (100);
Anal. calcd. for $C_{15}H_{16}O_2S$: C 69.20% ; H 6.20% ; O 12.29% ; S 12.32% ; found: C 69.32% ; H 6.29% ; O 12.35% ; S 12.45% .

Preparation of ethyl 3-benzylthio-2-isopropylbut-2-enoate (145)

The keto ester 107 (1.61 g, 9.4 mmol) was dissolved in dry methylene chloride (50 mL) under nitrogen. Benzyl thio (1.24 g, 10 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. Solid P_2O_5 (2.64 g, 18.7 mmol) was added to the above reaction mixture and was again stirred at room temperature for another 20 h. The methylene chloride solution was separated by centrifugation and the residue was washed once with CH_2Cl_2 (20 mL). The combined methylene chloride solution was washed with an aqueous NaOH solution (10%, 20 mL) followed by saturated sodium chloride solution (20 mL). The solution was dried over potassium carbonate, filtered and concentrated under reduced

pressure to give the title product in 68% yield (bp 118-120°C/ 0.05 torr). The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), (isomers) δ: 7.33 and 7.36 (2d, 12H, isomeric methyl protons), 0.93 and 1.00 (2t, 6H), 1.76 and 1.80 (2s, 6H, isomeric vinylic methyl proton), 2.43-3.27 (m, 2H), 3.66 and 3.73 (2s, 4H), 3.80 and 3.87 (2q, 4H), 6.93 (s, 10H);

ir (CCl_4) ν: 1720 br cm^{-1};

ms m/z (relative intensity): 278 (5, $M^{+}\cdot$), 233 (10, $M^{+}\cdot-\phi C_2H_5$), 187 (60, $M^{+}\cdot-CH_2\phi$), 91 (100).

Preparation of ethyl 2-isopropyl-3-phenylthio-5,5-dimethoxyhex-2-enoate (143)

The enol silyl ether 141 (0.524 g, 2 mmol) was mixed with trimethyl orthoacetate (1 mL, excess) in dry methylene chloride under nitrogen and a catalytic amount of zinc chloride was added. The reaction mixture was stirred at room temperature for 24 h. The crude product was filtered and concentrated under reduced pressure. The product was formed in 75% yield (from the nmr of the crude product). The compound was very unstable and attempts to purify the compound by column chromatography or distillation resulted in the decomposition of the product. The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), δ: 1.00 (d, 6H), 1.23 (t, 3H, J = 4 Hz), 1.43 (s, 3H), 2.43 (s, 2H), 1.96-2.80 (m, 1H),

3.17 (s, 6H, acetal), 4.07 (q, 2H, J = 6 Hz), 7.10 (s, 5H).

Condensation of 143 with the bis enol silyl ether 122

The bis enol silyl ether 122 (1.44 g, 5 mmol), was mixed with 143 (1.68 g, 5 mmol) in dry methylene chloride. The solution was cooled to -78°C and $TiCl_4$ (2.27 g, 12 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 24 h. The mixture was poured into a 5% aqueous sodium bicarbonate solution and extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered and concentrated. No expected aromatic compound was detected in the nmr of the crude product. 60% Of the compound 142 was recovered and the rest was a polymerized mass.

Attempted in-situ synthesis of 104

The bis enol silyl ether 122 (1.44 g, 5 mmol) was mixed with trimethyl orthoacetate (0.60 g, 5 mmol) in dry methylene chloride (100 mL) under nitrogen. The solution was cooled to -78°C and $TiCl_4$ (1.13 g, 5 mmol) was added dropwise. The reaction mixture was allowed to warm to 0°C and the bis enol silyl 110 (1.58 g, 5 mmol) was added followed by titanium tetrachloride (2.26 g, 12 mmol). The reaction mixture was allowed to warm to room temperature and stirred for another

28 h. The crude reaction mixture was poured into an aqueous sodium bicarbonate solution (20%, 50 mL) and extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was subjected to flash column chromatography (eluent: ethyl acetate/hexane, 10:90, v/v). Fraction one was identified as 2-isopropyl-3-oxo-butanoate (107) and fraction two was 111 by comparison with the spectral data reported earlier for these compounds.

Preparation of methyl 3-oxo-5-methoxy hex-4-enoate (146)

Trimethyl orthoacetate (4.80 g, 40 mmol) was dissolved in dry methylene chloride (50 mL) under nitrogen and cooled to -78°C and $TiCl_4$ (2.16 g, 10 mmol) was added dropwise followed by the bis enol silyl ether 68 (2.60 g, 10 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The mixture was poured into a 5% aqueous sodium bicarbonate solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was subjected to flash column chromatography (eluent: ethylacetate/hexane, 20:80, v/v). Fraction three was the title compound in 62% yield. The product was distilled under

reduced pressure (bp 74-76°C/0.05 torr). The spectral data of the compound are:

^{1}H nmr ($CDCl_3$), δ: 2.27 (s, 3H), 3.40 (s, 2H), 3.63 (s, 3H), 3.67 (s, 3H), 5.43 (s, 1H);

ms m/z (relative intensity): 172 (25, M^+), 140 (5), 99 (100), 59 (45);

Anal. calcd. for $C_8H_{12}O_4$: mol. wt. 172.1802; found: mol. wt. 172.1808.

Preparation of methyl 3,5,5-trimethoxy-hex-3-enoate (148)

Compound 146 (3.44 g, 20 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and trimethyl orthoformate (10 mL) was added followed by a catalytic amount of para-toluenesulfonic acid. The reaction mixture was refluxed for 24 h, cooled and poured into an aqueous sodium carbonate solution (30 mL). The product was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was distilled under reduced pressure (bp 75-76°C/0.04 torr) to give the acetal 148 in 70% yield:

^{1}H nmr ($CDCl_3$), δ: 1.23 (s, 3H), 3.17 (s, 6H), 3.2 (s, 3H), 3.57 (s, 2H), 3.60 (s, 3H), 5.03 (s, 1H);

ms m/z (relative intensity): (M^+) not detected, 187 (30) and 89 (100);

Anal. calcd. for $C_{10}H_{18}O_5$: C 55.03% ; H 8.31% ; O 36.66% ; found: C 55.15% ; H 8.42% ; O 36.71% .

Condensation reaction of methyl 3,5,5-trimethoxy-hex-3-enoate 148 with methyl 2,4-bis(trimethylsiloxy)-pentadienoate (122)

The acetal 148 (0.436 g, 2 mmol) was dissolved in dry methylene chloride (30 mL) under nitrogen. The solution was cooled to -78°C and $TiCl_4$ (0.756 g, 4 mmol) was added followed by the addition of the bis enol silyl ether 122 (0.576 g, 2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for another 48 h. The mixture was poured into an aqueous sodium bicarbonate (20%, 20 mL) solution and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was a light yellow solid. The compound thus obtained was purified by flash column chromatography (eluent: methylene chloride). After collecting the first fraction, ethyl acetate was used as eluent to collect the second fraction. Fraction one was 1-carbomethoxy- 8-hydroxy benzopyran-3-one (150) isolated as a colourless crystalline compound in 55% yield. The compound was recrystallized from cyclohexane (mp 158-159°C). The spectral data of the compound are:

^1H nmr ($CDCl_3$), δ: 2.31 (s, 3H), 3.83 (s, 3H), 6.72 (s, 1H), 6.85 (s, 1H), 7.24 (s, 1H), 10.65 (s, 1H);

ir ($CHCl_3$) ν: 1680, 1720, 3400 cm^{-1};

ms m/z (relative intensity): 234 (100, M^{+}) and 175 (40, $M^{+}-COOCH_3$), 119 (25).

^{13}C nmr ($CDCl_3$), δ: 22.14, 52.89, 105.16, 113.52, 118.75, 119.08, 134.88, 142.49, 149.50, 160.29, 161.64, 164.61;

Anal. calcd. for $C_{12}H_{10}O_5$: mol. wt. 234.0527; found: mol. wt. 234.0589.

APT Pulse sequence[128-130] for 150

APTPS δ ($CDCl_3$): 22.19 (negative, $\underline{CH_3}$), 52.95 (negative $O\underline{CH_3}$), 105.16 (positive), 113.54 (negative), 118.51 (negative), 134.84 (positive), 142.44 (positive), 149.53 (positive), 161.56 (positive).

Fraction two was 1-carbomethoxy-8-methoxybenzopyran-3-one (151) isolated as a light yellow crystalline solid. The compound was recrystallized from methanol and gave a melting point of 198-200°C (yield 25%). The spectral data of the compound are:

^1H nmr ($CDCl_3$), δ: 2.40 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 6.81 (s, 2H) and 7.23 (s, 2H);

ir ($CHCl_3$) ν: 1720 and 1740 cm^{-1};

ms m/z (relative intensity): 248 (100, $M^{+}\cdot$), 233 (20, $M^{+}\cdot-CH_3$) and 189 (45, $M^{+}\cdot-COOCH_3$);

^{13}C nmr ($CDCl_3$), δ: 22.1, 52.78, 56.34, 87.14, 112.17, 113.74, 119.99, 137.6, 138.21, 143.57, 147.67, 160.83 and 161.69;

Anal. calcd. for $C_{13}H_{12}O_5$: mol. wt. 248.0684; found: mol. wt. 248.0665.

Preparation of 8-hydroxy benzopyran-3-one-1-carboxylic acid (152)

The ester 150 (0.23 g, 1 mmol) was dissolved in methanol (10 mL) and aqueous sodium hydroxide (10%, 5 mL) was added. The solution was stirred at room temperature for 10 min and acidified with hydrochloric acid. The product was extracted with ether, the ether extract was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was a light yellow solid, recrystallized from petroleum ether giving quantitative yield of the acid 152. The compound melts at 264-265°C. The spectral data of the compounds are:

^{1}H nmr (DMSO-d_6): 2.5 (s, 3H), 6.9 (s, 1H), 7.1 (s, 1H), 7.60 (s, 1H), 10.7 (s, 1H);

ir (KBr) ν: 1695, 1725, 3200 br and 3600-3400;

ms m/z (relative intensity): 220 (100, $M^{+}\cdot$), 175 (35, $M^{+}\cdot$-COOH), 119 (98), 65 (60);

Anal. calcd. for: $C_{11}H_8O_5$: mol. wt. 220.0371; found: mol. wt. 220.0332.

CLAIMS TO ORIGINAL WORK

A new method for the preparation of acetals using chlorotrimethylsilane was developed. The new procedure can be carried out under mild conditions utilizing readily available chemicals.

Two isomeric methyl olivetolates were synthesised for the first time from acyclic precursors utilizing the cyclo-aromatization procedure.

A new method for the synthesis of olivetol was developed. This synthesis provides a shorter route to olivetol from acyclic precursors.

A new biomimetic synthesis of Δ^1-THC was developed. This synthesis demonstrates the potential of being a general approach to the synthesis of phenolic natural products with a m-cresol skeleton.

A new method for the synthesis of poly β-carbonyl compounds using diketene and enol silyl ethers was developed.

The possibility of synthesising gossypol by the cyclo-aromatization method was investigated.

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