SOME STUDIES TOWARDS THE SYNTHESIS OF p-ALKYLATED PHENOLS

A Thesis presented by

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ABSTRACT

The most recent developments in the synthesis of phenols from aliphatic precursors are reviewed.

Potential and novel approaches to *p*-alkylated phenols are described. These cover a wide range of routes, including electrophilic processes, Claisen rearrangements, and enamine chemistry. Cyclic acetals have been formylated using *N*-chloromethylene-*N*,*N*-dimethylammonium chloride. The products are potential precursors to phenols including ethyl 5-ethyl-2-hydroxybenzoate.

IN LOVING MEMORY OF

MY FATHER.

ACKNOWLEDGEMENTS

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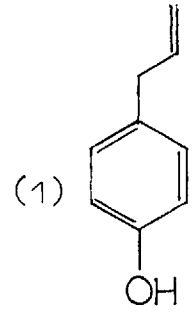
Finally, I offer my warmest gratitude and thanks to my mother for her continual support and encouragement, and to my wife Mabel for all her help and understanding.

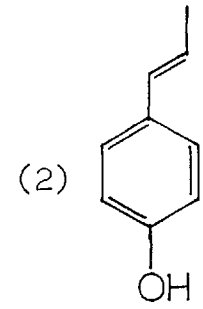
CONTENTS

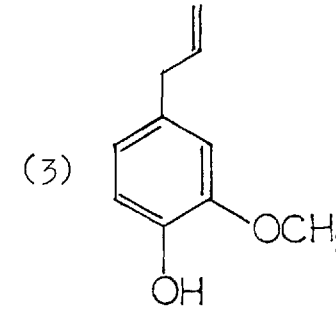
INTRODUCTION

Friedel-Crafts type alkylation of phenols usually gives ortho and para mixtures. However, in the presence of a catalytic amount of the corresponding aluminium phenoxide, high yields of the ortho isomer can be obtained[1]. Gas phase alkylation[2] of phenols over solid catalysts of the mixed oxide type also gave good selectivity for ortho alkylation. The preparation of pure p-alkyl phenols still remains a challenge to the synthetic chemist.

Our interest in p-alkylated phenols particularly included those which occur widely in the higher plants[3] and are commonly found in the higher boiling (aromatic) fractions of essential oils[4]. These include compounds like chavicol (1), p-anol (2), and eugenol (3).







As natural material is in limited supply and such phenols are of importance in the perfume and flavouring industry, novel syntheses are worthy of exploration.

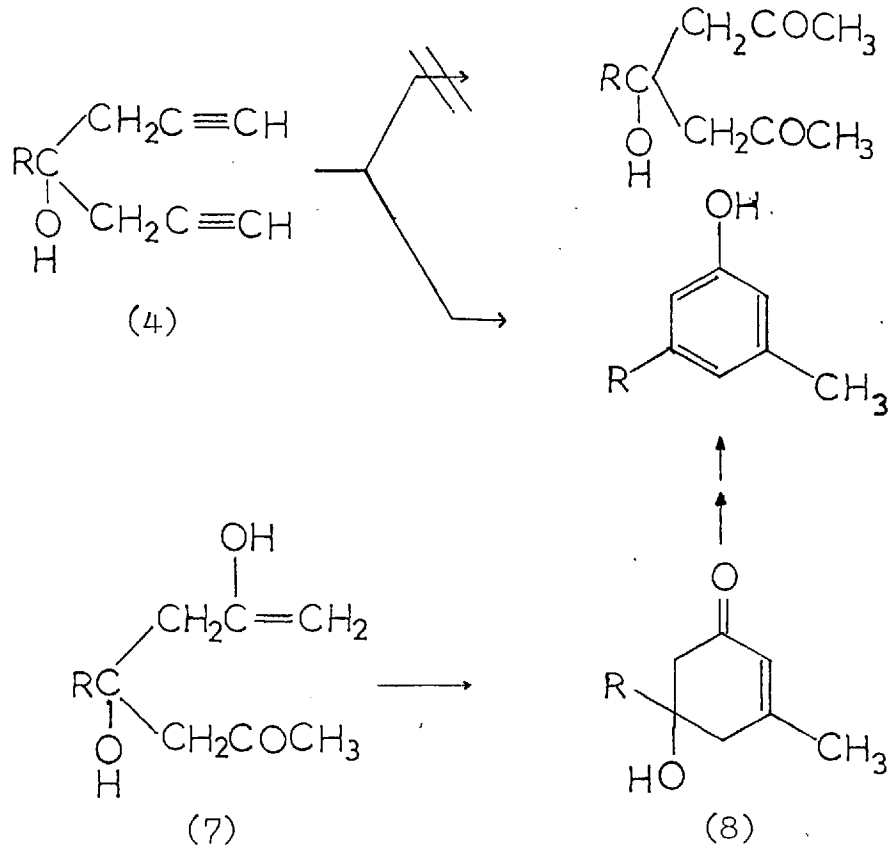
THE SYNTHESIS OF PHENOLS FROM ALIPHATIC PRECURSORS

A review on the various routes leading to phenols has been described[5]. This work summarised the literature until 1975.

The following review covers material published on the subject since 1975. A few of these syntheses represent a continuation with marked improvements on established approaches. Most are novel procedures. Phenol syntheses may be classified into five types.

1. Intramolecular Condensation Reactions

Linking together the ends of a difunctional molecule can provide an easy access to p-alkylated phenols. Plouin and Glenat[6] studied the effect of hydration on di-3-propenyl-carbinols, using mercuric salts in acidic media. It was found that hydration of the alcohols (4) using mercuric oxide did not give the expected hydroxydiketones (5) but gave directly the phenols (6). Intermediacy of enol (7) and cyclodehydration giving enone (8) was assumed. The latter in acidic media underwent dehydration to give the phenols (6) (Scheme 1).

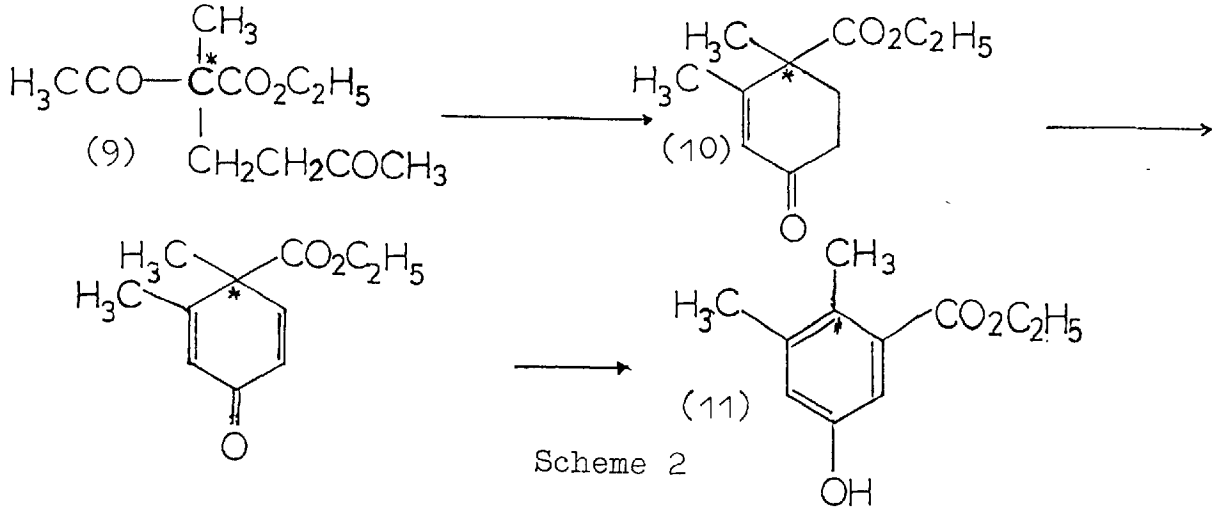


(4) (5) (6) (7) (8)

R=CH_3, C_2H_5, i-C_3H_7, t-C_4H_9, C_6H_5

Scheme 1

An old synthesis was repeated in order to prepare ^{14}C labelled phenols[7]. By an intramolecular cyclisation step, the β-keto ester (9) was converted to the enone (10). It was subsequently oxidised using selenium dioxide and aromatised using aqueous hydrogen sulphide giving ethyl 3-hydroxy-5,6-dimethylbenzoate (11) in 48% yield (Scheme 2).

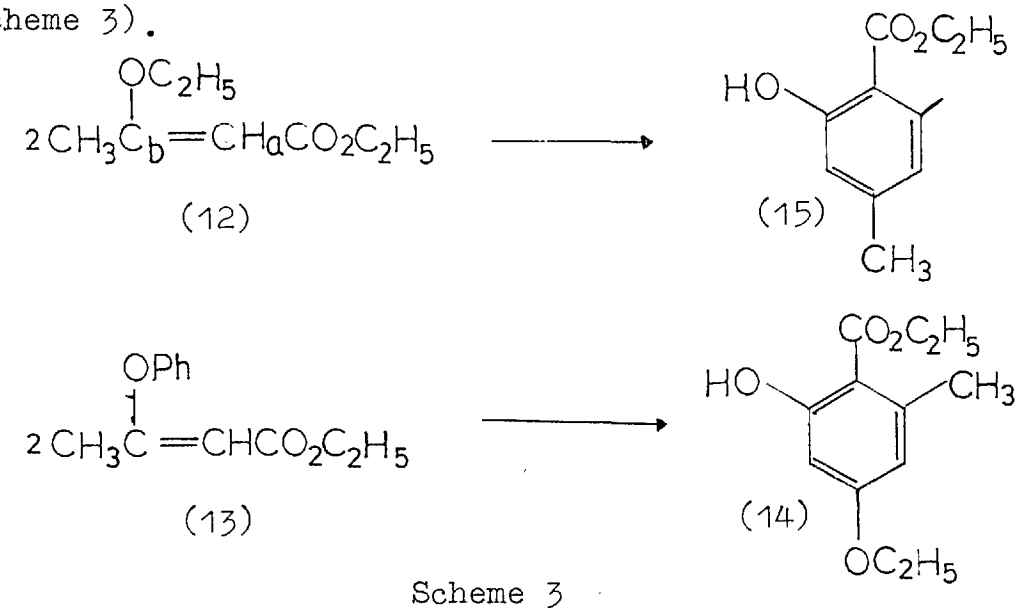


(9) (10) (11)

Scheme 2

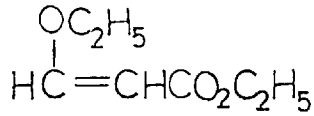
2. Intermolecular Condensation Reactions.

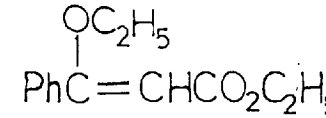
The self-condensation of functionalised aliphatic chains have provided direct entry to substituted phenols. French workers[8] tried to demonstrate that ortho (14) and para (15) orsellinic acid derivatives are formed in nature from acetoacetic acid. They obtained the phenol derivatives from enol ethers of ethyl acetoacetate, using titanium tetrachloride. Thus, ethyl β-ethoxycrotonate (12) gave the para derivative (15) while the alkyl β-aryloxycrotonate (13) gave the ortho derivative (14) (Scheme 3).



Scheme 3

The reaction mechanism is still being investigated, although in the crotonate (12) the vinylic proton H_a was necessary for the reaction as its substitution with a methyl group prevented condensation. The methyl group on the vinylic carbon C_b was also necessary as the following two esters did not cyclise.

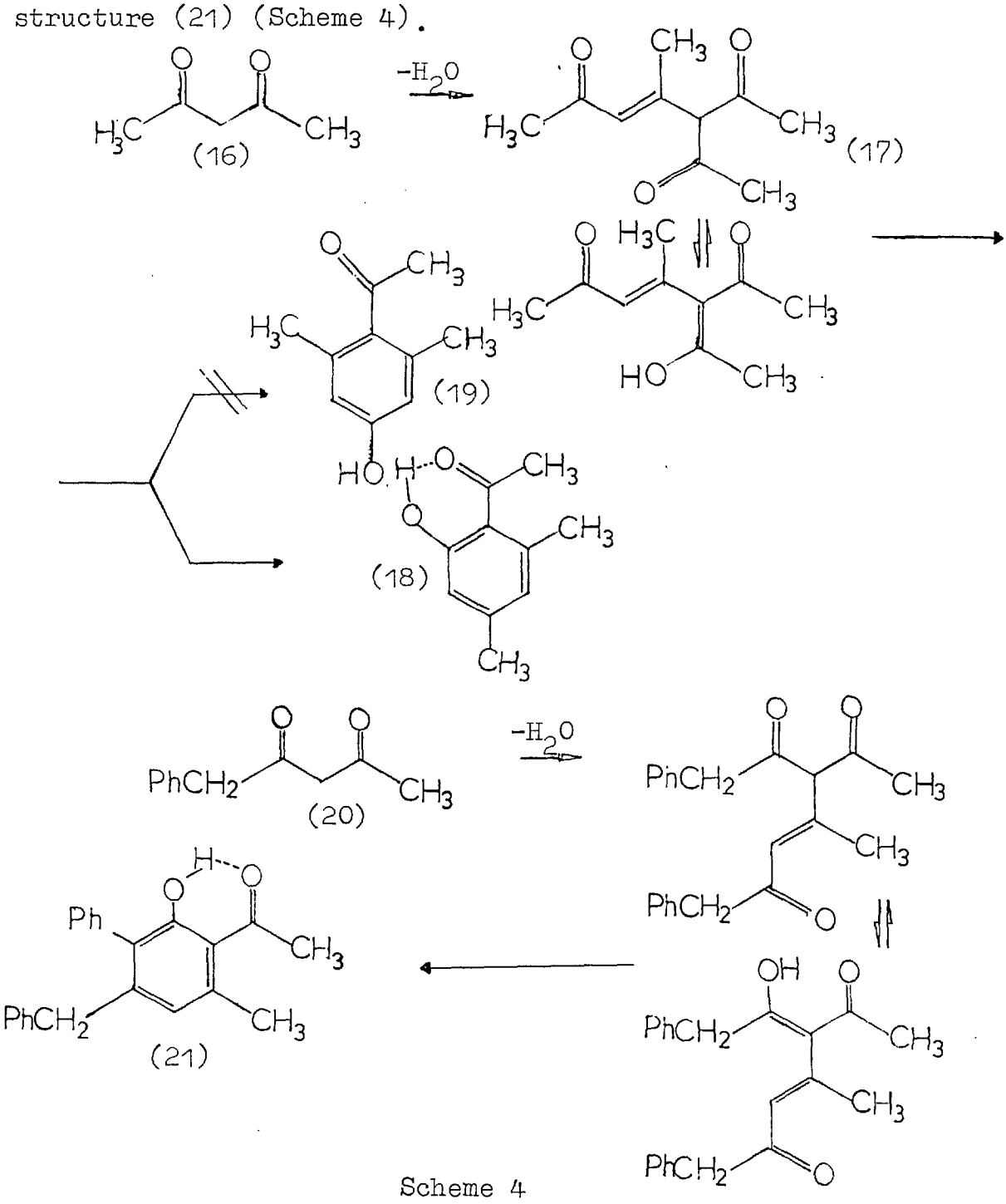




Few examples of self-condensation of β-diketones are known. Clark and Miller studied the effect of hydrogen bonding in organic synthesis, and have shown that the use of fluorides can provide fast and efficient routes to a number of organic condensation products[9]. In particular pentane-2,4-dione (16) was converted from 80% enol (in the pure liquid) to 100% enol on shaking with potassium fluoride-dimethylformamide at room temperature. A strong hydrogen-bonding was established between the fluoride anion and the enol hydrogen. Reflux of the potassium fluoride, DMF, pentane-2,4-dione mixture gave 2-hydroxy-4,6-dimethylacetophenone (18) exclusively. Although the cyclisation could have given the phenol (19) the formation of (18) only was explained by three reasons. Firstly, of the three possible positions on (17) to form a carbanion α to the carbonyl, two will result in the compound (18). Secondly, the enol tautomer of (17) is capable of stabilising the corresponding carbanion by delocalisation onto 2 carbonyl groups. Finally, the formation of (18) should be encouraged by the production of a six-membered chelate ring by intra-molecular hydrogen-bonding.

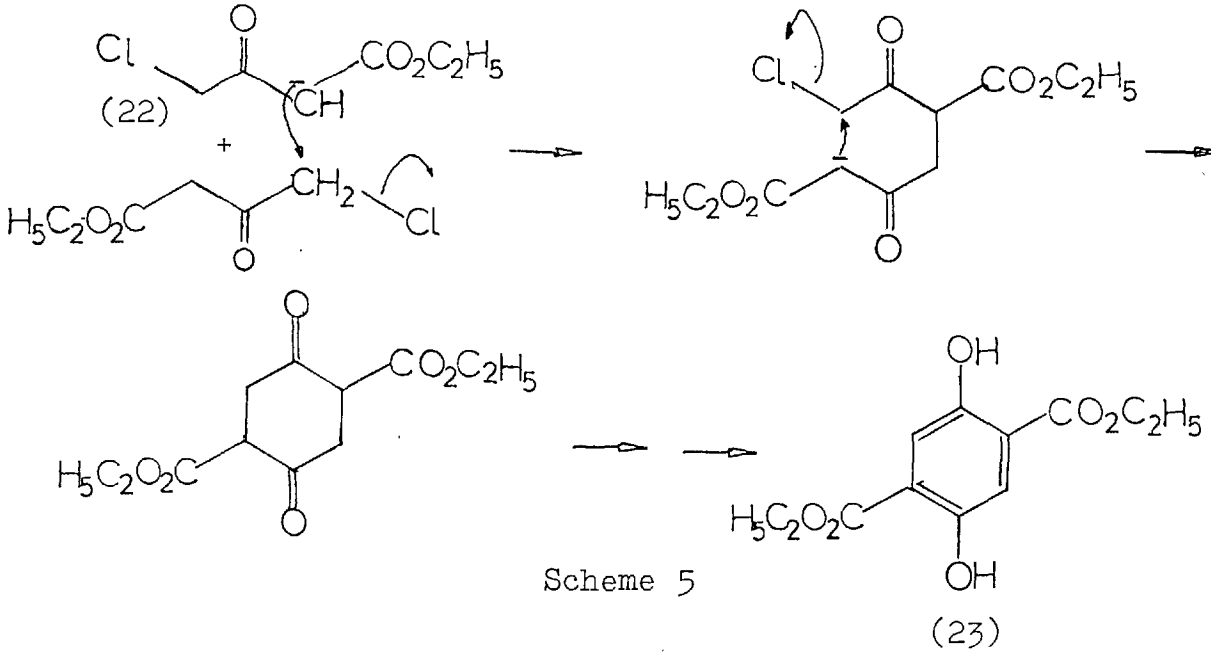
Under the same conditions, 1-phenylpentane-2,4-dione (20) was converted to 4-benzyl-2-hydroxy-6-methyl-3-phenylacetophenone (21). The acetophenones probably arise from initial aldol condensation and dehydration followed by ring closure with elimination of a second molecule of water. However, the picture here was more complex as the initial condensation

might have occured in two different ways (condensation at CH_3CO or at $PhCH_2CO$) and each of the two possible intermediates may have cyclised in four different ways. A ^1H n.m.r. study with shift reagents was consistent with formulation as structure (21) (Scheme 4).



Scheme 4

Another self-condensation[10] which gave a phenol derivative was unexpectedly obtained during the reaction of γ-chloroacetate (22) with p-toluidine. As a nitrogen free product was obtained, the reaction was repeated using only γ-chloroacetate and anhydrous potassium carbonate in dry acetonitrile. Reflux for 6h and work up gave ethyl 2,5-hydroxy-1,4-benzenedicarboxylate (23) in 80% yield (Scheme 5).



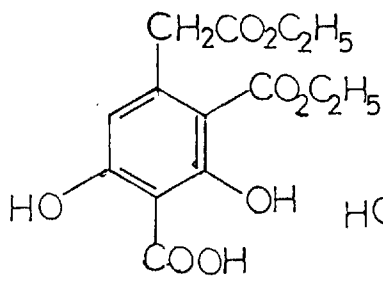
Scheme 5

(23)

Although extensive studies on the bimolecular condensation of diethyl acetonedicarboxylate have been reported in the past[11] little information about the effect of catalyst or the reaction mechanism was available. Self condensation of diethyl acetonedicarboxylate was therefore examined[12] using various catalysts. The products of the self-condensation of diethyl acetonedicarboxylate can be divided in two groups: orsellinic acid derivatives (24) and (25) and coumarin derivatives (28) and (29). During this work two more products have been found: ethyl 3-carboxy-2,4-dihydroxy-6-methylbenzoate (26) and ethyl (2-ethoxycarbonyl-3,5-

dihydroxybenzene)acetate (27). The best yields of ester (24) were obtained by using magnesium powder (30%) or zinc powder with ethyl chloroacetate (19%) while sodium ethoxide (10%) or a small amount of magnesium powder with ethyl chloroacetate (33%) were effective for good yields of (25).

Subsequently a mechanism[13] for the formation of each of the phenolic compounds was suggested. The postulated intermediate (30) from n.m.r. studies was probably due to the dissolution of magnesium with ethyl chloroacetate. When an excess of diethyl acetonedicarboxylate was present, the next intermediate (31) was smoothly formed. It could then react as a nucleophile because its structure was of metal chelated complexes of an acetyl acetonate type where the methine carbon is known[14] to be electron rich (Scheme 6).



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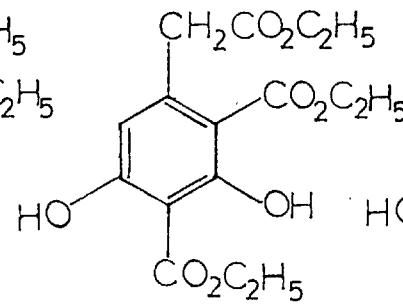

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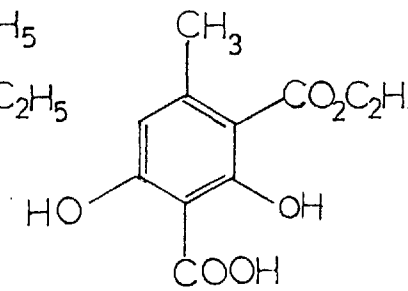

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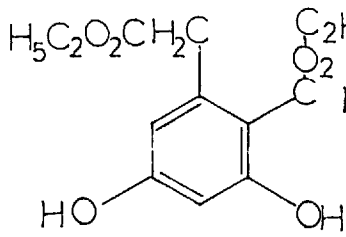

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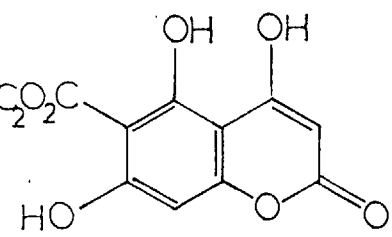

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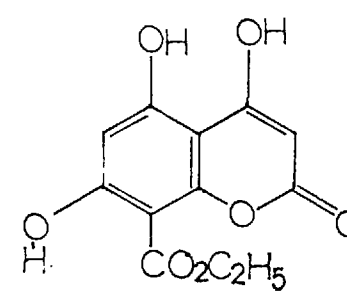

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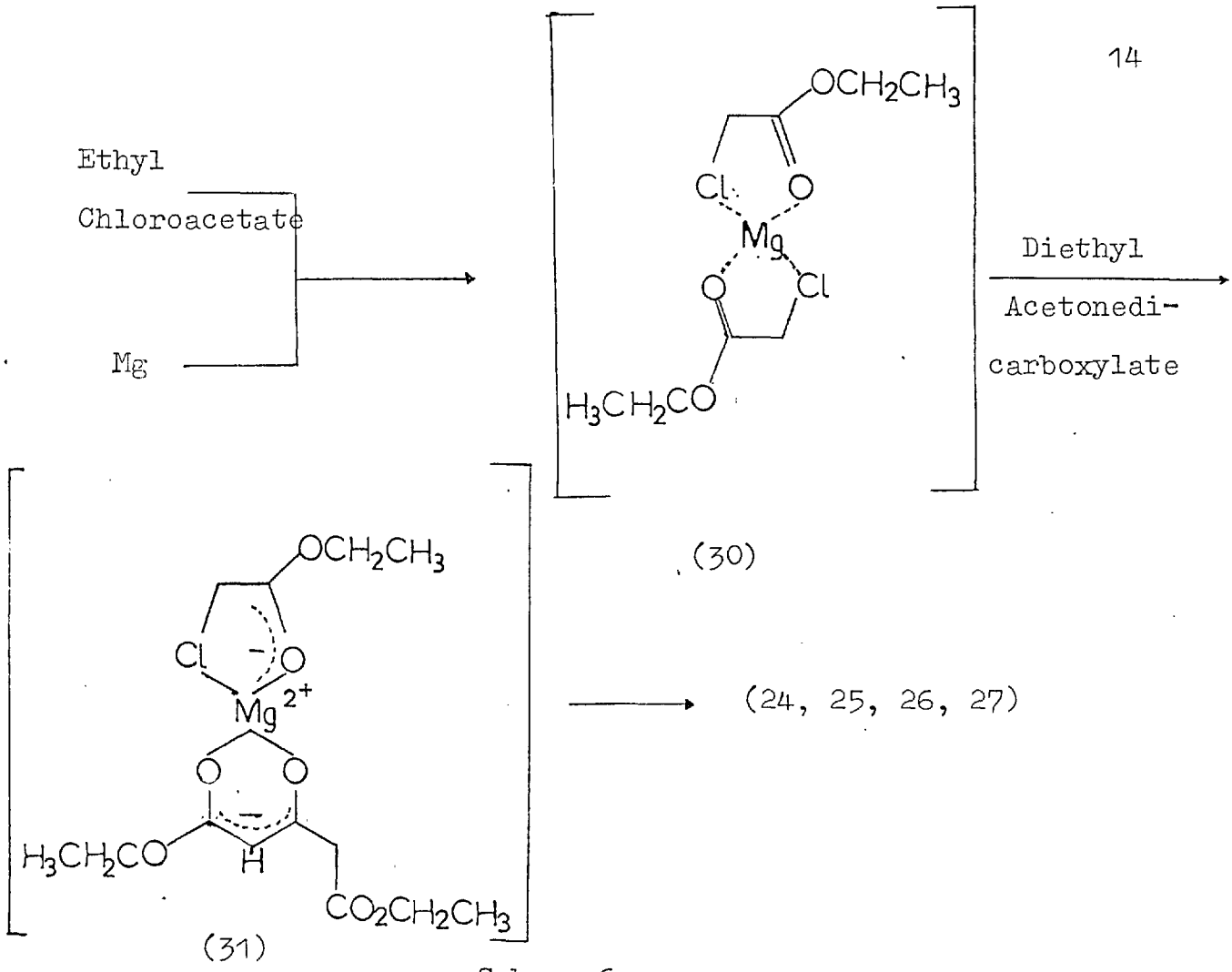
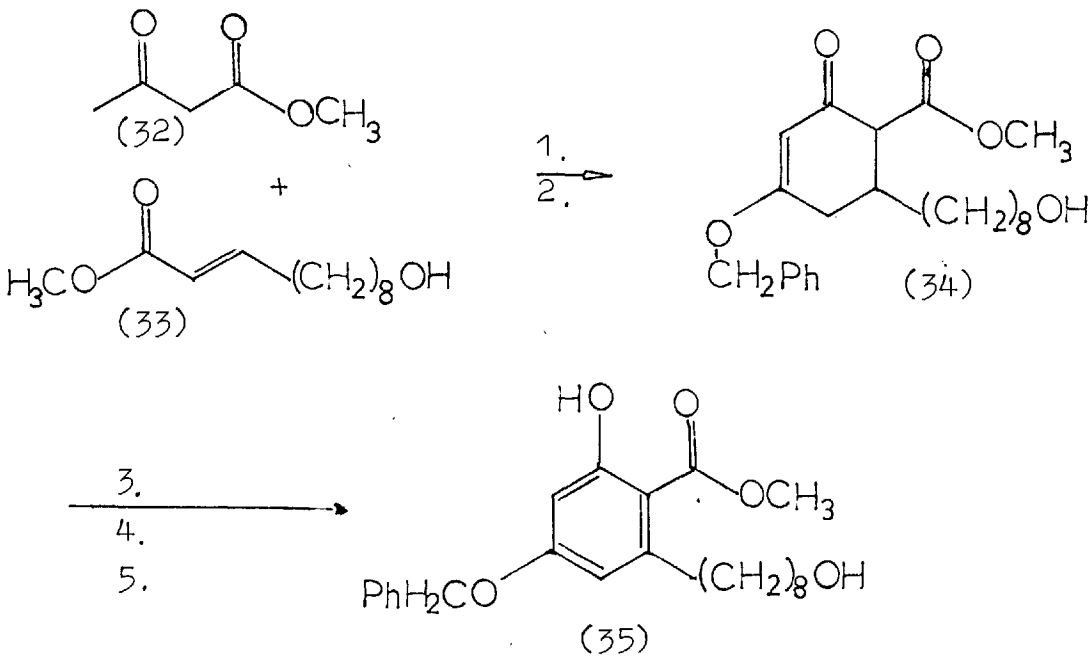


Scheme 6

3. Michael Reaction Type

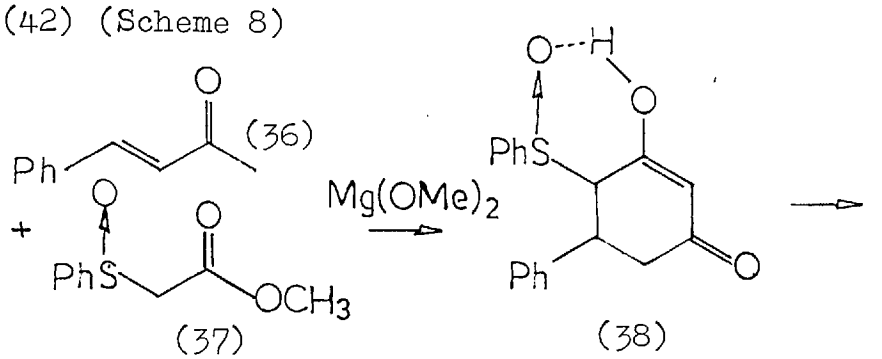
Conjugate addition of nucleophilic reagents to α,β-unsaturated carbonyl compounds have provided useful intermediates capable of leading to phenols. Thus condensation[15] between methyl acetoacetate (32) and the α,β-unsaturated ester (33) gave the dihydroresorcylic ester derivative. This was benzylated with benzyl alcohol to give the ether (34). Aromatisation was carried via oxidation with benzeneselenenyl bromide and hydrogen peroxide (Scheme 7).



1. $CH_3\bar{O}Na^+$; 2. $PhCH_2OH$; 3. $LiN(\underline{i}\text{-}C_3H_7)_2$; 4. PhSeBr ; 5. H_2O_2

Scheme 7

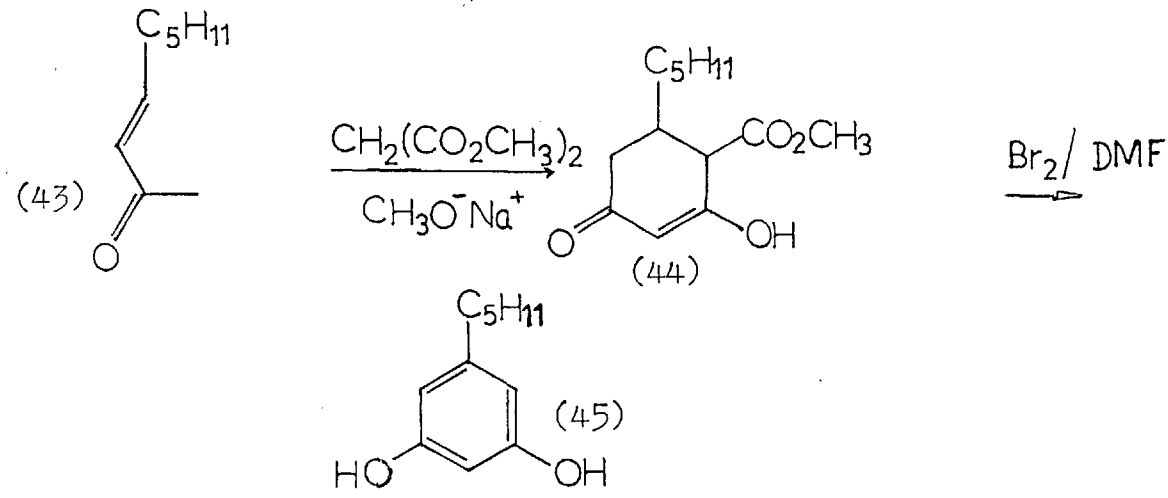
In another synthesis[16], benzylidene acetone (36) was added to a solution of methyl (phenylsulphinyl)acetate (37) and magnesium methoxide (8eq.). Stirring for 16h at room temperature and work up gave the enone (38). This on reflux in benzene gave 5-phenylresorcinol (39). Similarly were prepared 5-(4-methoxy)-phenylresorcinol (40), olivetol (41), and 5-isopropylresorcinol (42) (Scheme 8)



(39, R = Ph)
(40, R = $\underline{p}\text{-}CH_3OC_6H_4$)
(41, R = $CH_3(CH_2)_4$
(42, R = $\underline{i}\text{-}C_3H_7$)

Scheme 8

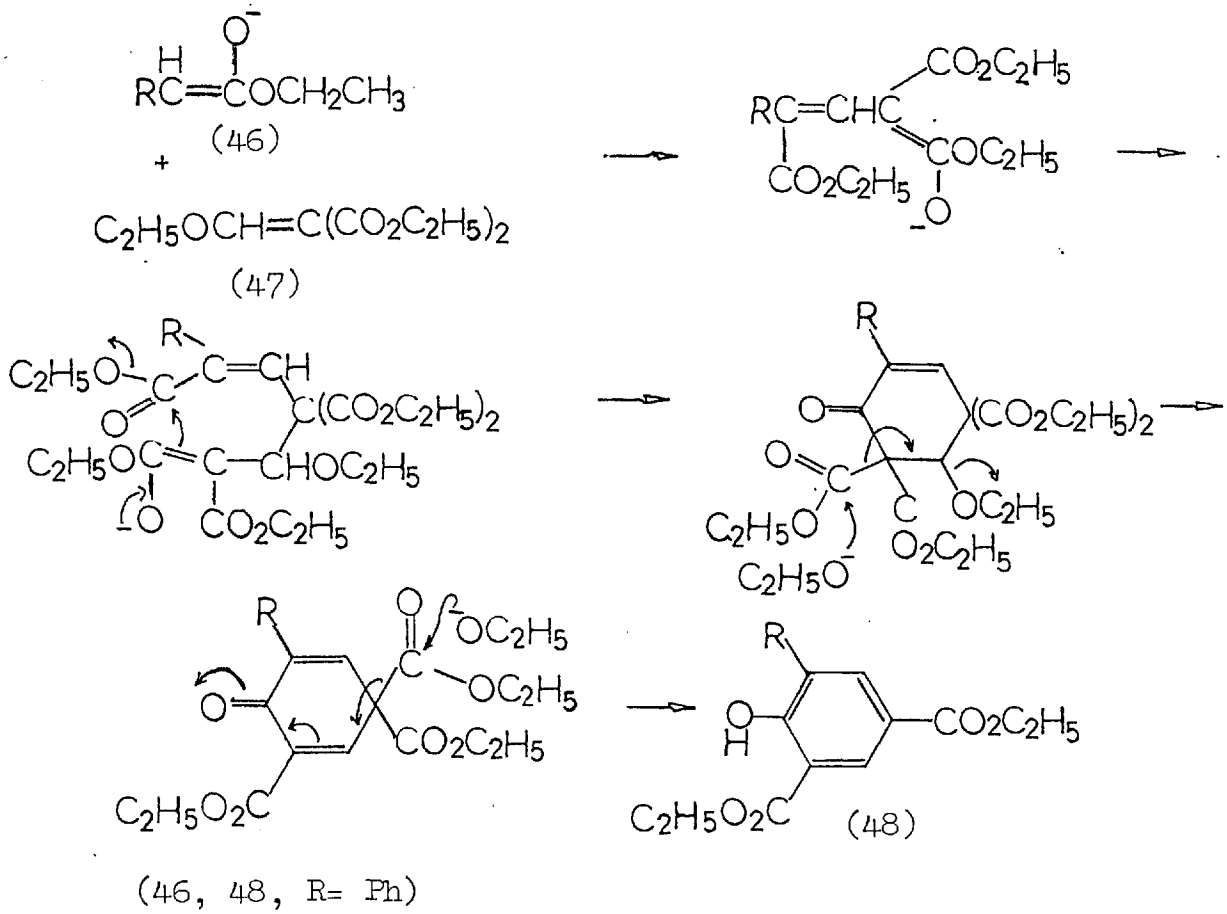
Olivetol (45), the key intermediate in the synthesis of cannabinoids and its derivatives, has been synthesized[17] in a practical and efficient way. The α,β-unsaturated ketone (43) was reacted with the sodium enolate of dimethyl malonate to give the cyclic adduct (44). Aromatisation and decarbomethoxylation using bromine in DMF, first at 0° and then at refluxing temperature gave olivetol (45) in 62% overall yield (Scheme 9).



Scheme 9

Olivetol was also prepared for labelled studies[18] through a Michael type condensation between ethyl acetoacetate and methyl oct-2-enoate and was aromatised in the usual way.

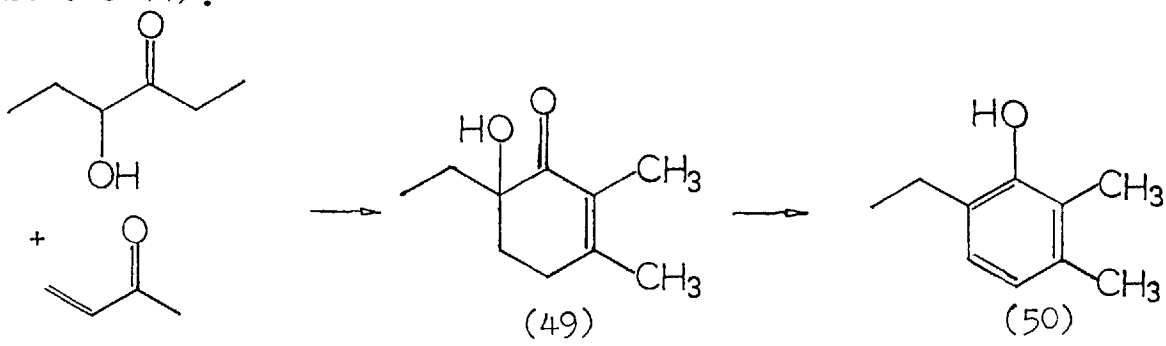
In a study of ring annelation, Bird and Wong[19] again examined the reaction between ethyl phenylacetate (46) and diethyl ethoxymethylenemalonate (47). The phenol (48) obtained was fully characterised and a plausible mechanistic sequence described in Scheme 10.



(46, 48, R= Ph)

Scheme 10

Michael Condensation[20] between 4-hydroxy-3-hexanone and methyl vinyl ketone, followed by aldol condensation and dehydration gave the enone (49). It was aromatised using phosphoric acid to give 6-ethyl-2,3-dimethylphenol (50) (Scheme 11).

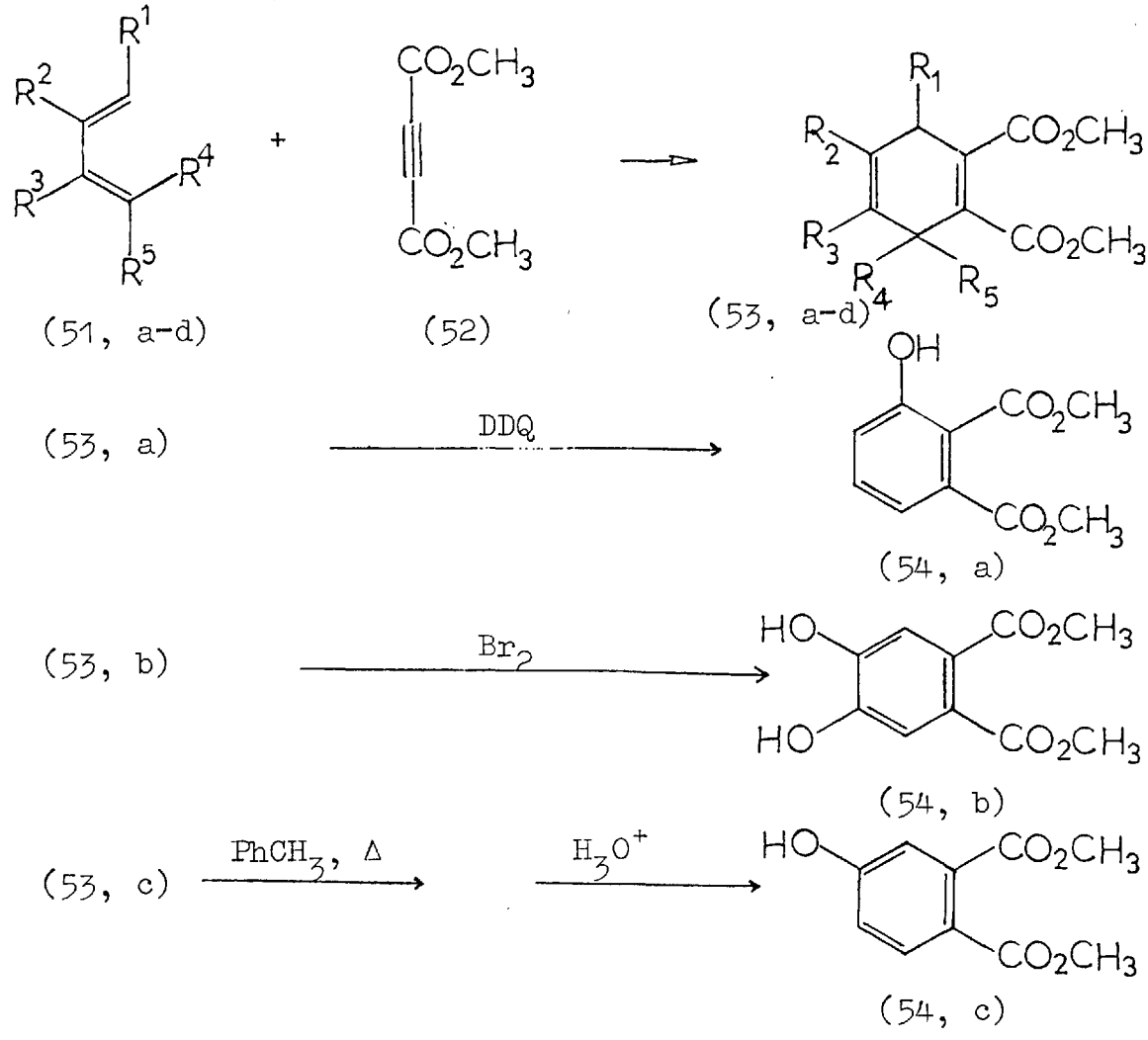


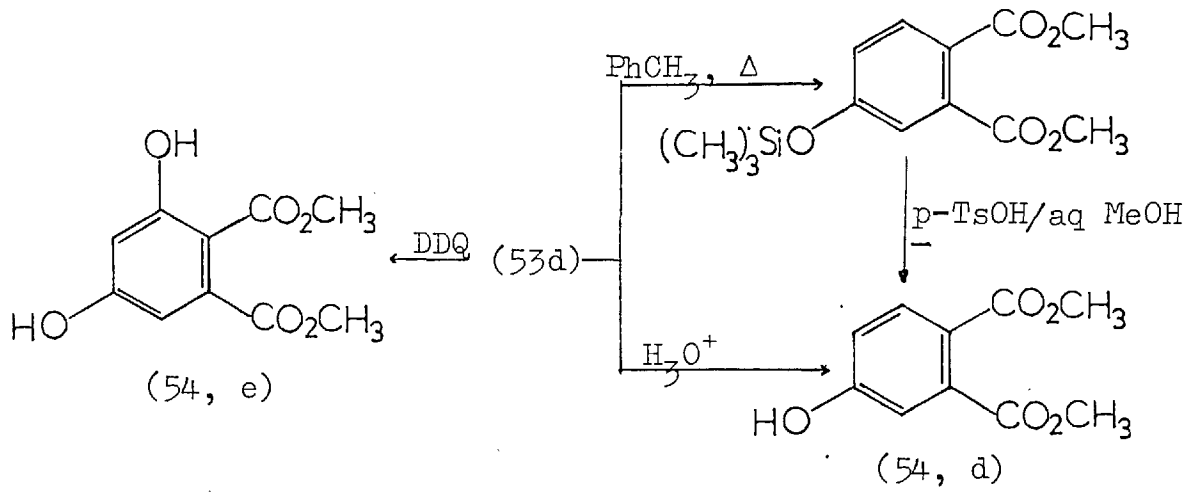
Scheme 11

4. Diels-Alder Reaction Type

The Diels-Alder reaction has become today one of the most widely employed and most successful reactions for the stereo-controlled synthesis of cyclohexene derivatives. Specifically substituted phenol derivatives are also readily available using such methodology.

The trimethylsilyloxy-substituted butadienes (51, a-d)[21], reacted readily with dimethyl acetonedicarboxylate (52). The adducts (53, a-d) were transformed into dimethyl hydroxy-substituted phthalates (54, a-e), by either facile elimination of trimethylsilanol or by oxidative aromatisation (Scheme 12).



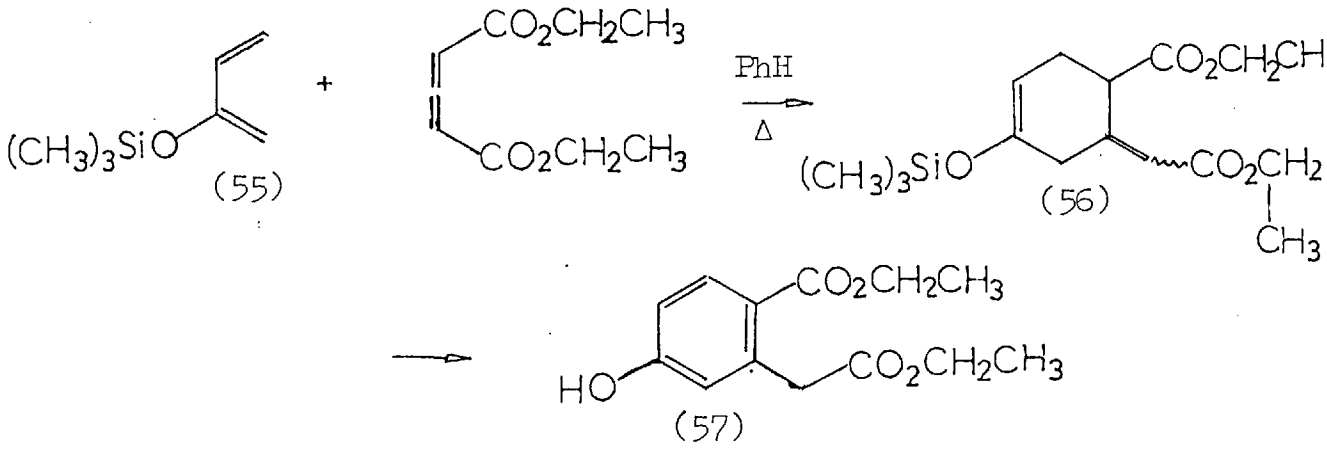


(51a, 53a, R^1= $OSi(CH_3)_3$, R^2= R^3= R^4= R^5= H)
(51b, 53b, R^1= H, R^2= R^3= $OSi(CH_3)_3$, R^4= R^5= H)
(51c, 53c, R^1= R^3= H, R^2= R^5= $OSi(CH_3)_3$, R^4= OCH_3)
(51d, 53d, R^1= R^3= $OSi(CH_3)_3$, R^2= R^4= R^5= H)

Scheme 12

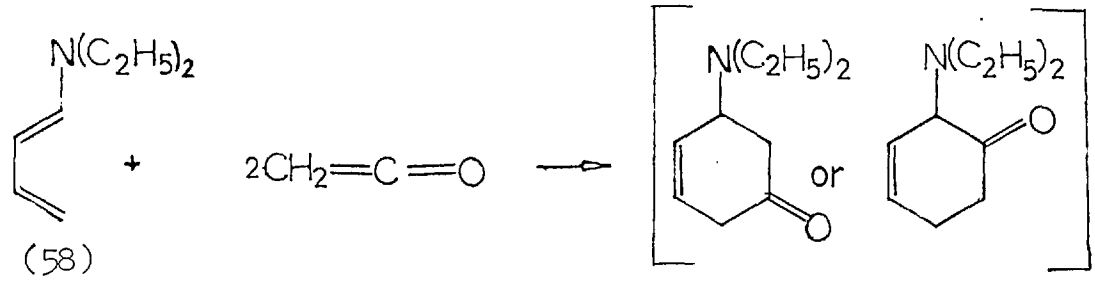
The same diene (51b) has also been used with dimethyl acetylenedicarboxylate in a synthesis of 4,5-dimethoxyphthalimides.

Another diene which has been used[23] is 2-trimethylsilyloxy-1,3-butadiene (55). This was condensed with 1,3-diethoxycarbonylallene to give the cycloadduct (56). Dehydrogenation using sublimed sulphur in boiling decalin gave diethyl 5-hydroxyhomophthalate (57) (Scheme 13).



Scheme 13

N,N-Diethylamino-1,3-butadiene (58) on condensation[24] with ketene, a reactive dienophile gave the phenol derivative (59) (Scheme 14).



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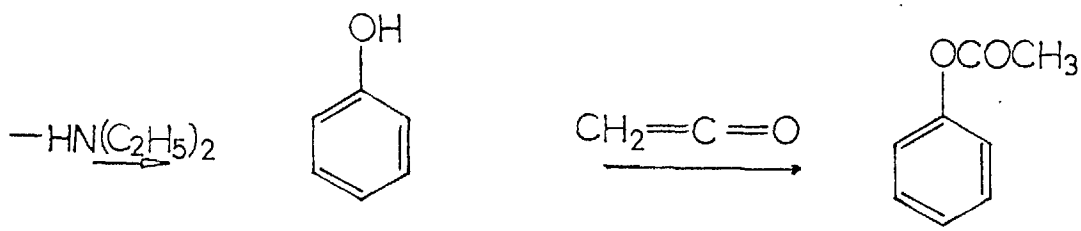
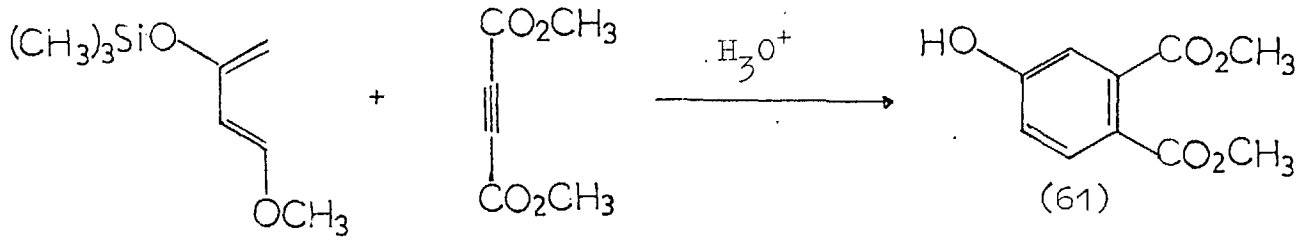


Scheme 14

(59)

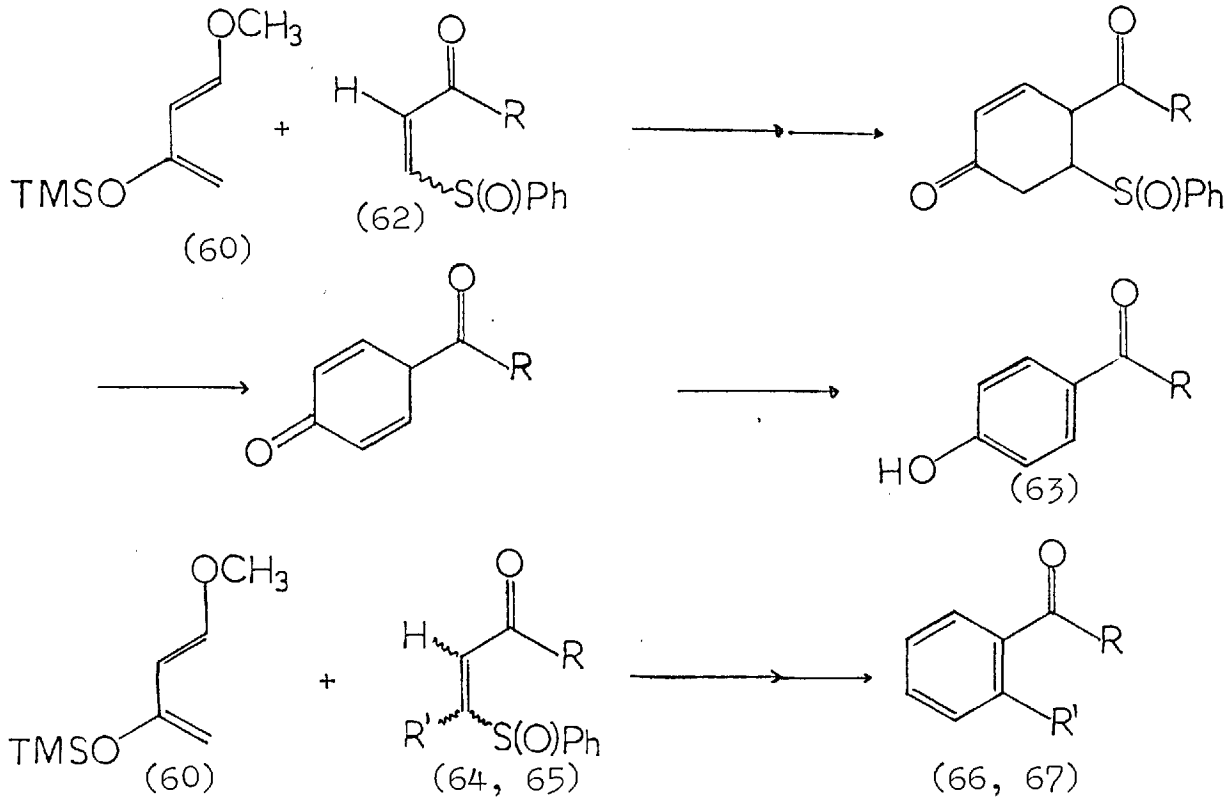
Danishefsky[25] has made a major contribution towards enlarging and extending the scope and utility of the Diels-Alder reaction. Trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (60) was prepared from the readily available trans-4-methoxybutene-2-one. Reaction of diene (60) with dimethyl acetylenedicarboxylate gave on acidic hydrolysis the known 4-hydroxy-o-phthalate (61).



(60)

(61)

This diene was later used in a study[26] of the role of prephenic acid[27] in the shikimic acid pathway. β-Phenylsulphinylenone (62) and diene (60) on cycloaddition-elimination and subsequent aromatisation gave the phenol (63). Similarly, the sulphoxides (64 and 65) gave phenols (66 and 67) respectively (Scheme 15).



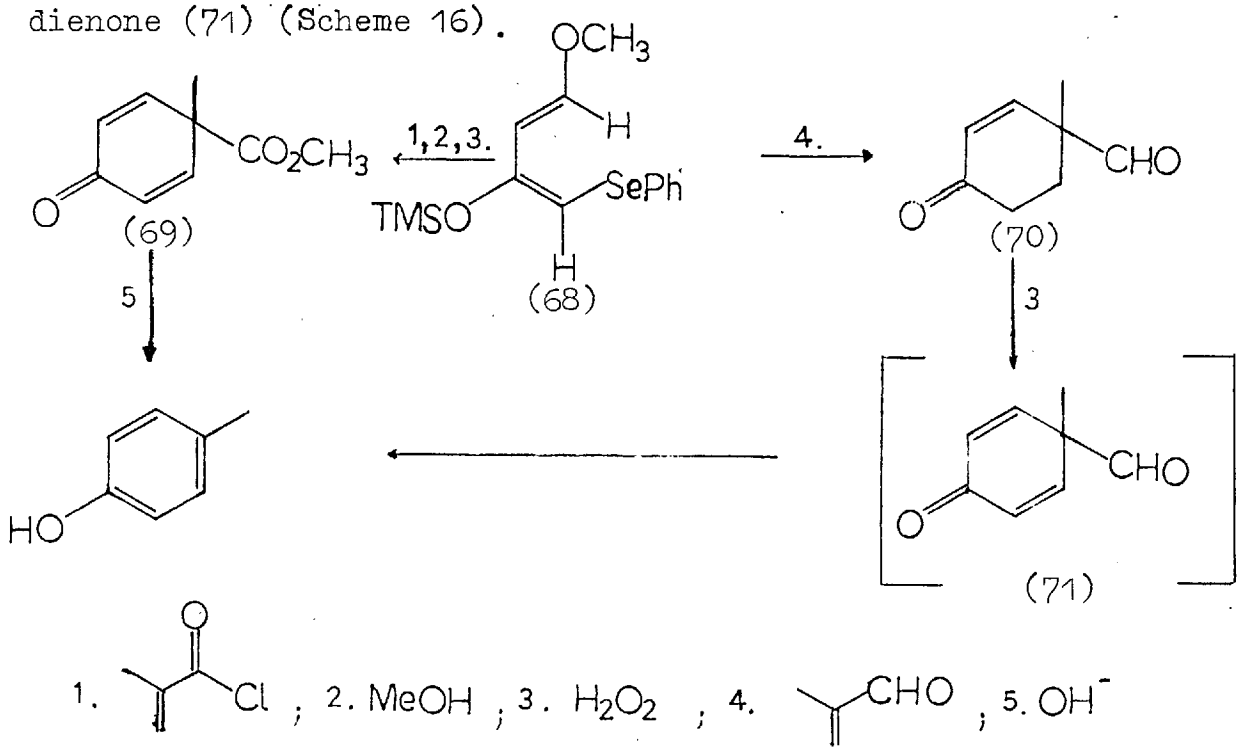
(64, R=OCH_3, R'=$CH_2CO_2CH_3$) (66, R=OCH_3, R'=$CH_2CO_2CH_3$)

(65, R=R'=OCH_3) (67, R=R'=CH_3)

Scheme 15

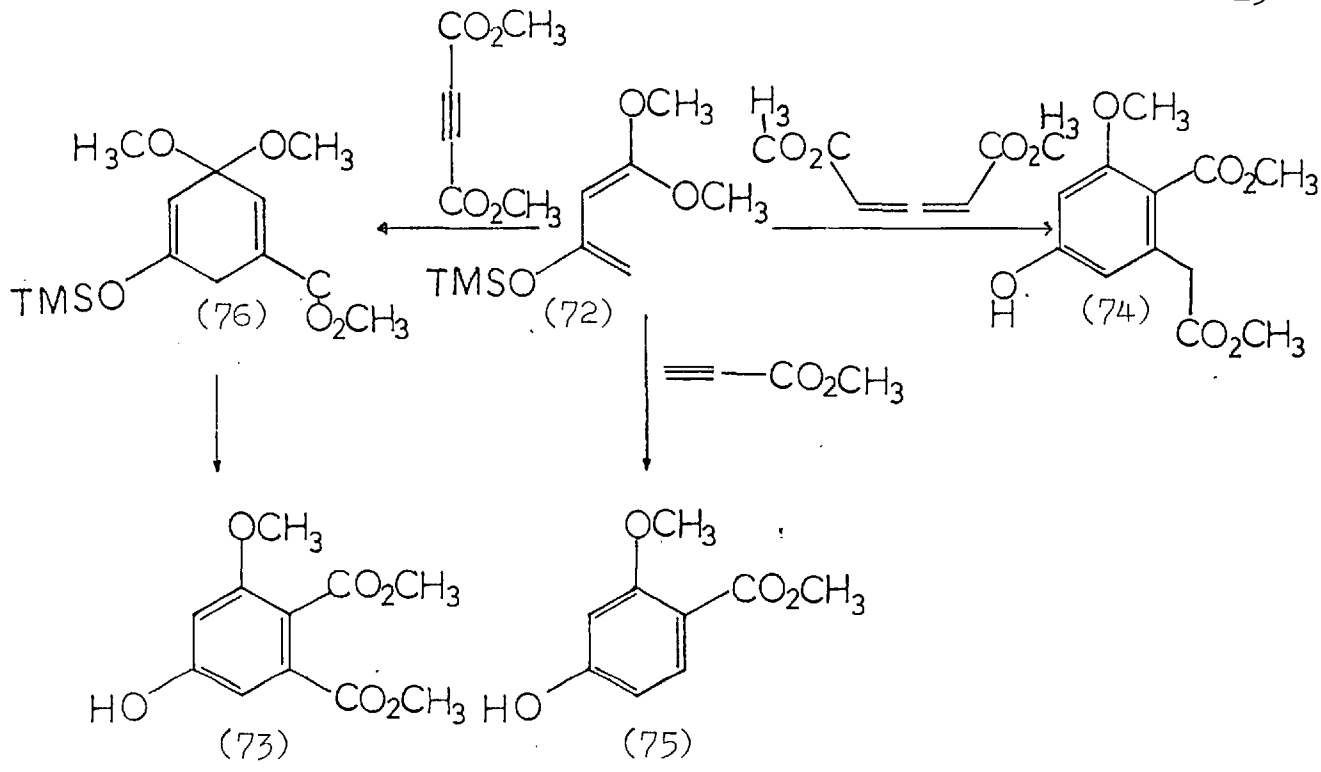
Diene (68) by incorporating[28] a phenylseleno group reacted with methacryloyl chloride to give after methanolysis, oxidation, and elimination 4-methyl-4methoxycarbonylcyclohexa-2,5-dienone

(69) in 29% yield. Treatment of dienone (69) with potassium hydroxide gave p-cresol virtually instantaneously. Also, reaction of diene (68) with methacrolein gave the enone (70). Subsequent oxidation gave almost quantitavely p-cresol, presumably formed via the labile 4-methyl-4-formylcyclohexa-2,5-dienone (71) (Scheme 16).



Scheme 16

In general diene (68) was less reactive than diene (60). Danishefsky[29] introduced 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (72) as an excellent diene for Diels-Alder reactions. Diene (72) gave the aromatic compounds (73,74,75) on reaction with dimethyl acetylenedicarboxylate, 1,3-dimethoxycarbonylallene and methyl propiolate respectively. Plausible intermediates were ketals such as (76) (Scheme 17).

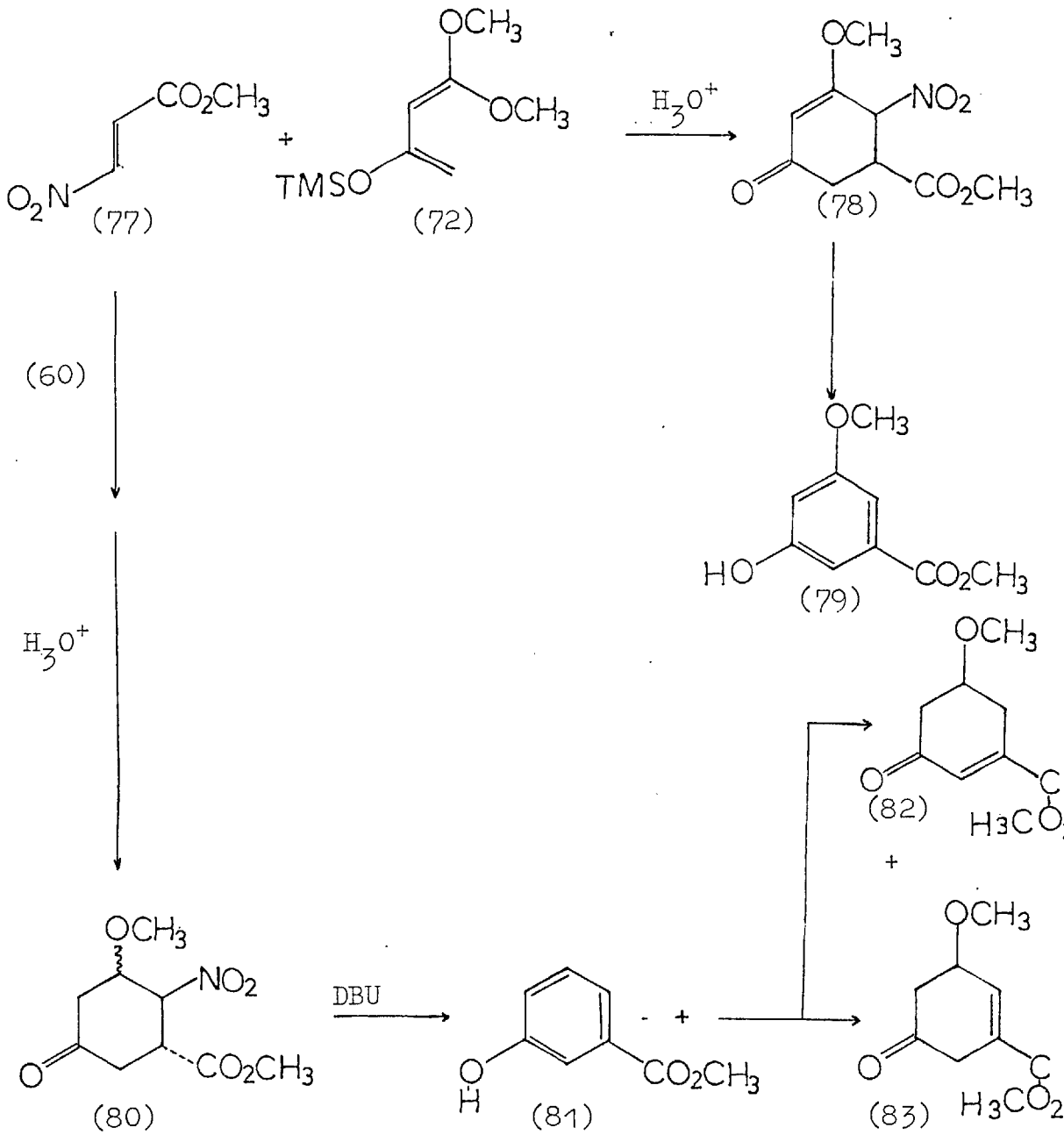


Scheme 17

The rate of cycloaddition of diene (72) was faster than diene (60). The enhanced nucleophilic character of the diene can thus overide the steric difficulties associated with an additional methoxyl function.

The dienophile was modified[30] in order to control the regioselectivity[31] of the Diels-Alder reaction. For example trans-methyl β-nitroacrylate (77) reacted with diene (72) to give enone (78) exclusively. This upon treatment with 1,5-diazabicyclo-(5,4,0,)-undec-5-ene (DBU) in tetrahydrofuran gave the resorcinol derivative (79) in 99% yield. In contrast cycloaddition of the same diene (72) with methyl propiolate gave the isomeric product (75). Reaction of trans-methyl β-nitroacrylate (77) with the diene (60) gave the nitro ester (80) as a mixture of isomers. This on treatment with DBU gave

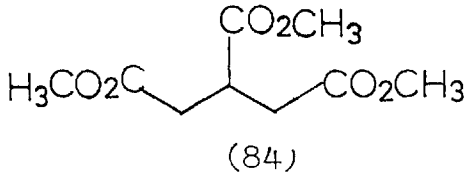
some methyl 3-hydroxybenzoate (81) and the cyclohexanone derivatives (82 and 83). The nitro group exercised a regiochemical control and provided an access to substitution patterns hitherto less readily available (Scheme 18).



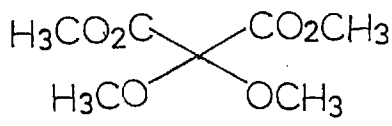
Scheme 18

5. Miscellaneous Condensation Reactions

The first synthesis of gallic acid (87) and pyrogallol (90) from aliphatic materials have now been reported[32]. The base catalysed reaction of dimethyl (3-methoxycarbonyl)-1,5-pentanedicarboxylate (84) and dimethyl (2-dimethoxy)-1,3-propanedicarboxylate (85) gave trimethyl 3,5-dihydroxy-4,4-dimethoxycyclohex-2,5-diene-1,2,6-carboxylate (86). The latter on hydrolysis and decarboxylation by heating to reflux with 48% hydrobromic acid gave gallic acid (87). Similarly condensation between the malonate (85) and dimethyl glutarate gave the diene (88). Hydrolysis gave 4,5,6-dihydroxyisophthalic acid (89) and subsequent decarboxylation pyrogallol (90) (Scheme 19).

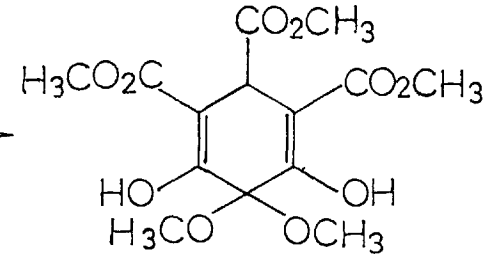


(84)



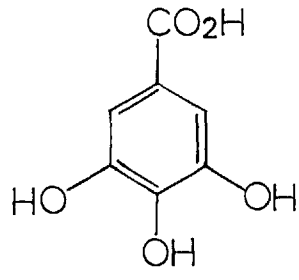
(85)

NaH

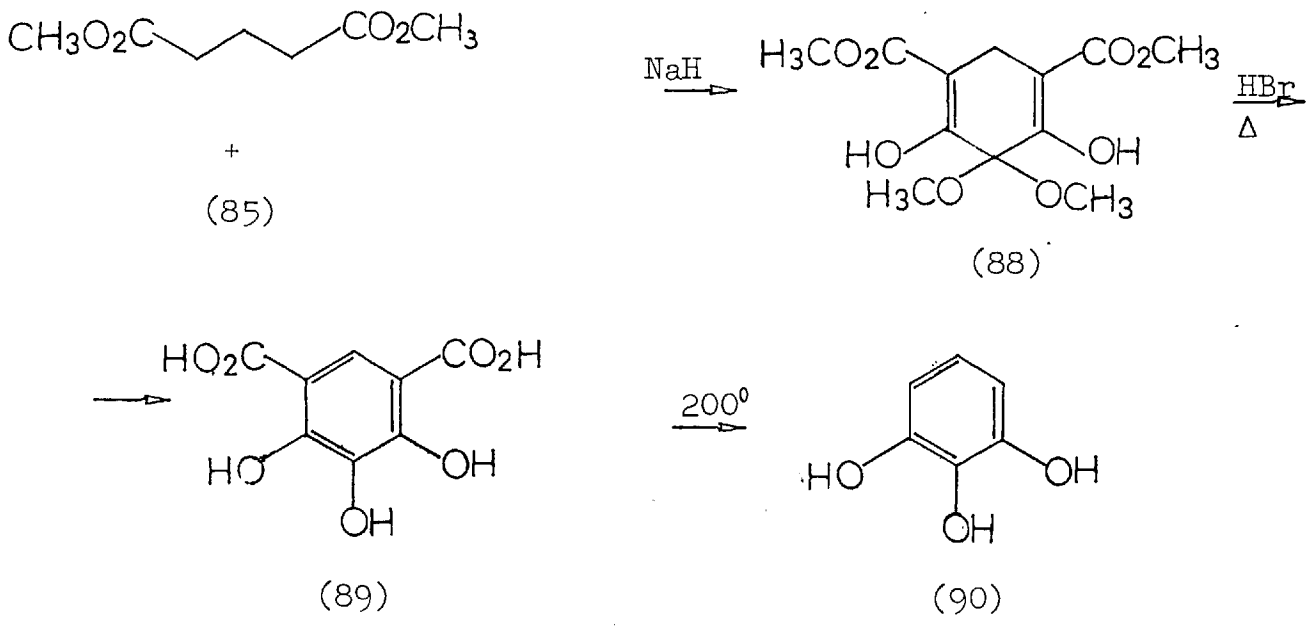


(86)

HBr
Δ

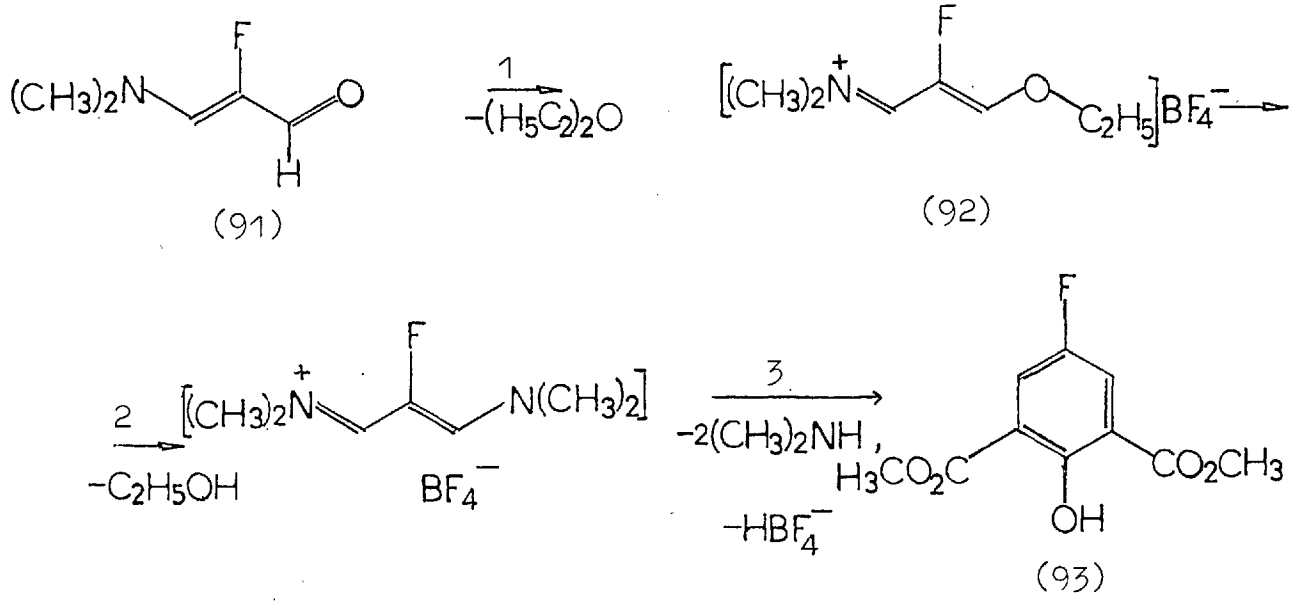


(87)



Scheme 19

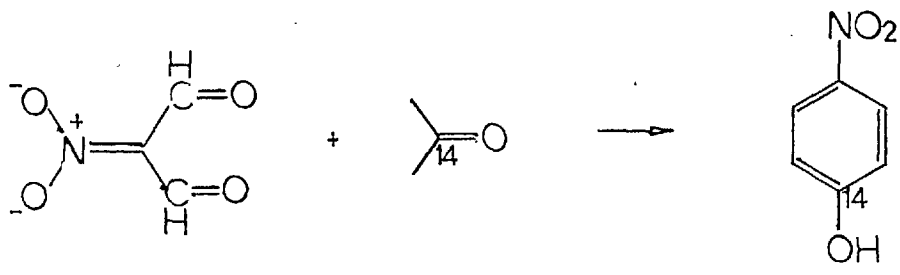
Dimethyl 5-fluoro-2-hydroxy isophthalate (93) was prepared[33] by first ethylating the propenal derivative (91). The resulting salt (92) was treated *in situ* with dimethylamine, followed by the sodium enolate of dimethyl acetonedicarboxylate to give the phenol derivative (93) (Scheme 20).



1. $(H_5C_2)_3O^+BF_4^-$; 2. $(CH_3)_2NH$; 3. $H_3CO_2C\bar{C}HCOCH_2CO_2CH_3$

Scheme 20

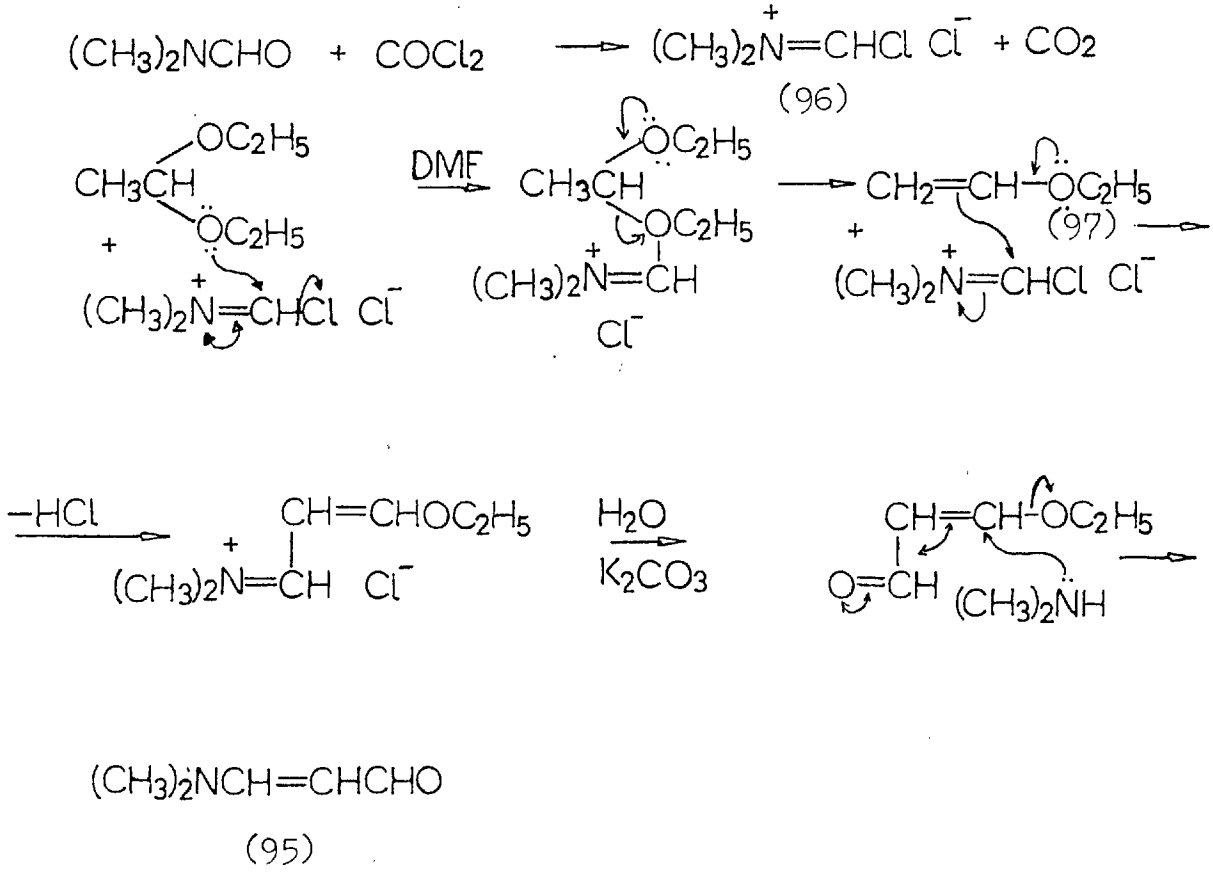
Finally, the condensation of sodium nitromalonaldehyde and 2-(^{14}C)acetone gave[34] 4-nitro-1-(^{14}C)phenol (94). This had precedent with unlabelled substrates[35].



(94)

RESULTS AND DISCUSSION

The synthesis of 3-(dimethylamino)propenal (95) was first described by Arnold and Sorm[36]. It involved the reaction of N-chloromethylene-N,N-dimethylammonium chloride (96) with 1,1-diethoxyethane. It has been established that the reaction proceeds[37] via formylation of the intermediate unsaturated ether (97). Michael attack of dimethylamine during basic work up gave (95) as the major product. Dimethylamine stemmed presumably via decarbonylation of DMF in acidic media (Scheme 21).

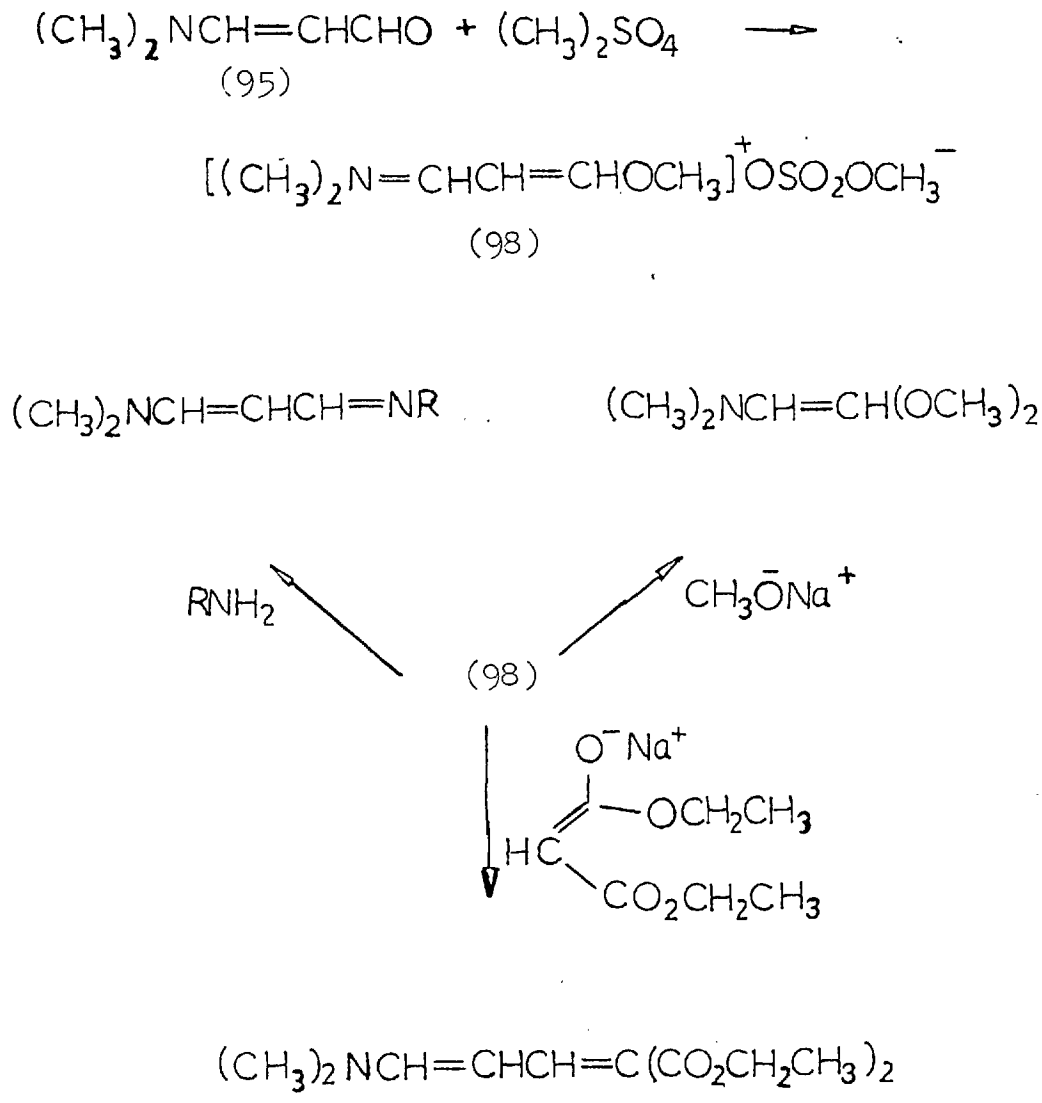


$(CH_3)_2NCH{=}CHCHO$

(95)

Scheme 21

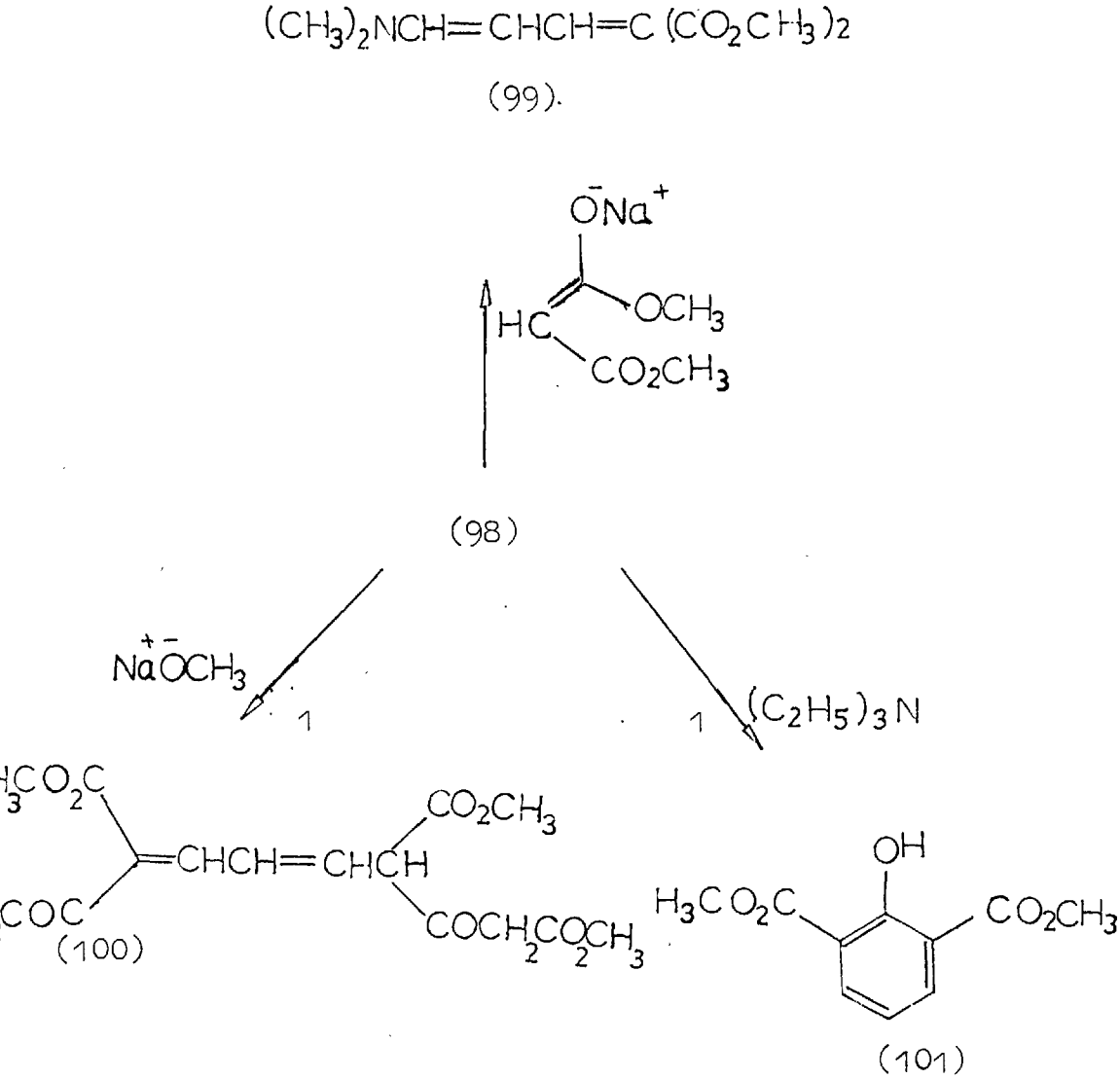
The dimethylaminopropenal (95) was reacted[38] with dimethyl sulphate and the adduct (98) treated with a variety of nucleophilic reagents[39] (Scheme 22).



Scheme 22

As this dimethyl sulphate adduct provided considerable versatility, its use as a starting material for phenol substituted syntheses was examined. The salt (98) was first fully characterised as the tetraphenyl boron salt. Condensation

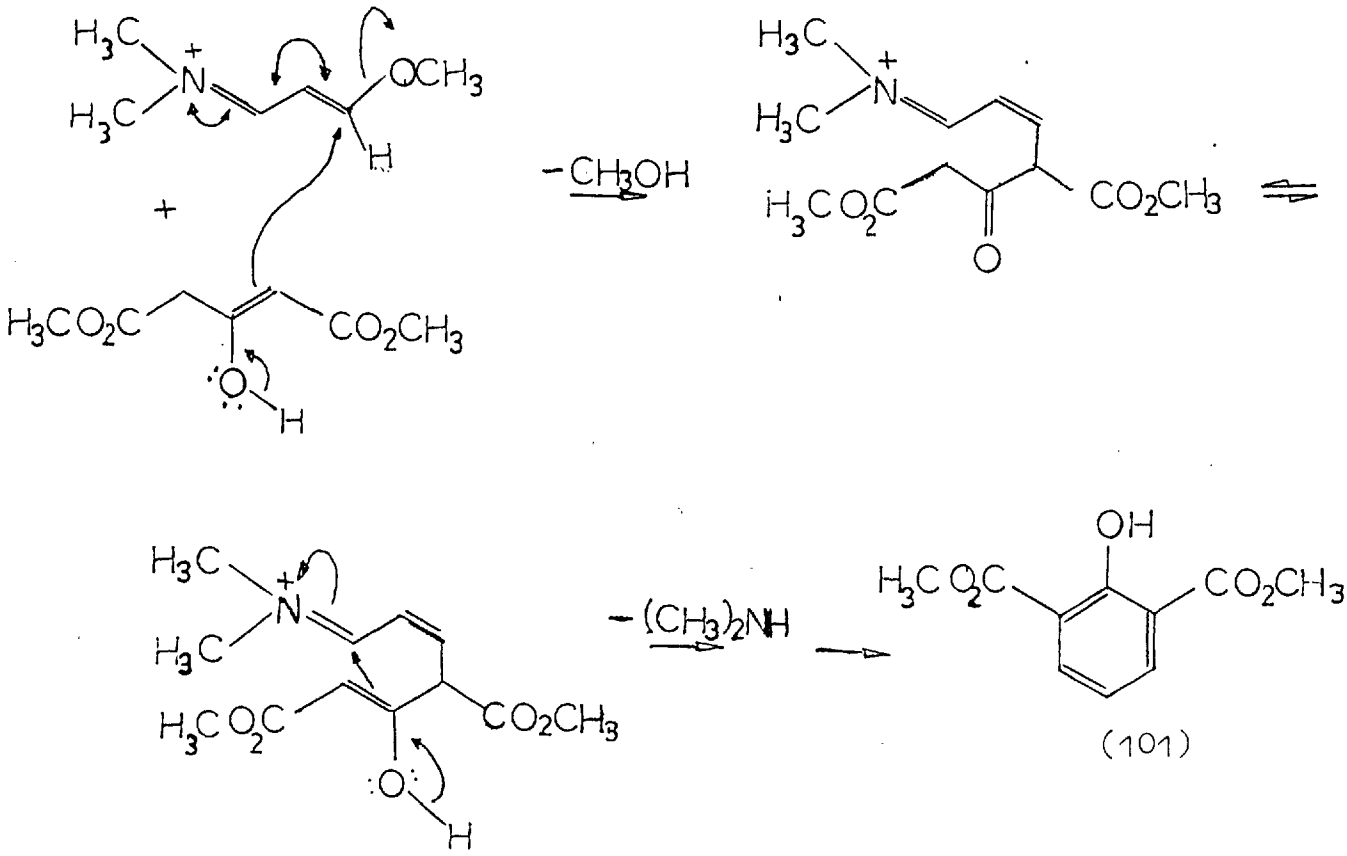
with the sodium enolate of dimethyl malonate gave the dienoate (99) in 30% yield. Dimethyl acetonedicarboxylate was examined since it has two inherent sites for electrophilic attack. Using sodium methoxide as base, condensation occured at both ends of the imino sulphate (98) to give the tetracarboxylate (100). However, using triethylamine, dimethyl 2-hydroxy-1,3-benzene-dicarboxylate (101) was obtained but in only 14% yield (Scheme 23).



1. $H_3COOCCH_2COCH_2COOCH_3$

Scheme 23

The phenol was probably formed via Scheme 24.



Scheme 24

Due to the poor yield of the diester (101), another approach was examined. The synthesis by Hill[35] of p-nitrophenol from acetone and the sodium salt of nitromalonaldehyde was reexamined. We reasoned that under the same conditions the sodium salt of malonaldehyde and acetone would undergo similar condensation. However , no phenol was obtained. It became clear, that the nitro group on the malonaldehyde provided through delocalisation an electrophilic aldehyde capable of entering into nucleophilic condensation.

In order to increase the electrophilicity of the malonaldehyde, it was condensed with toluene-4-sulphonyl chloride. This reaction was best carried out in dimethylformamide or ether but the unstable product (102) was detected only by n.m.r. spectroscopy.

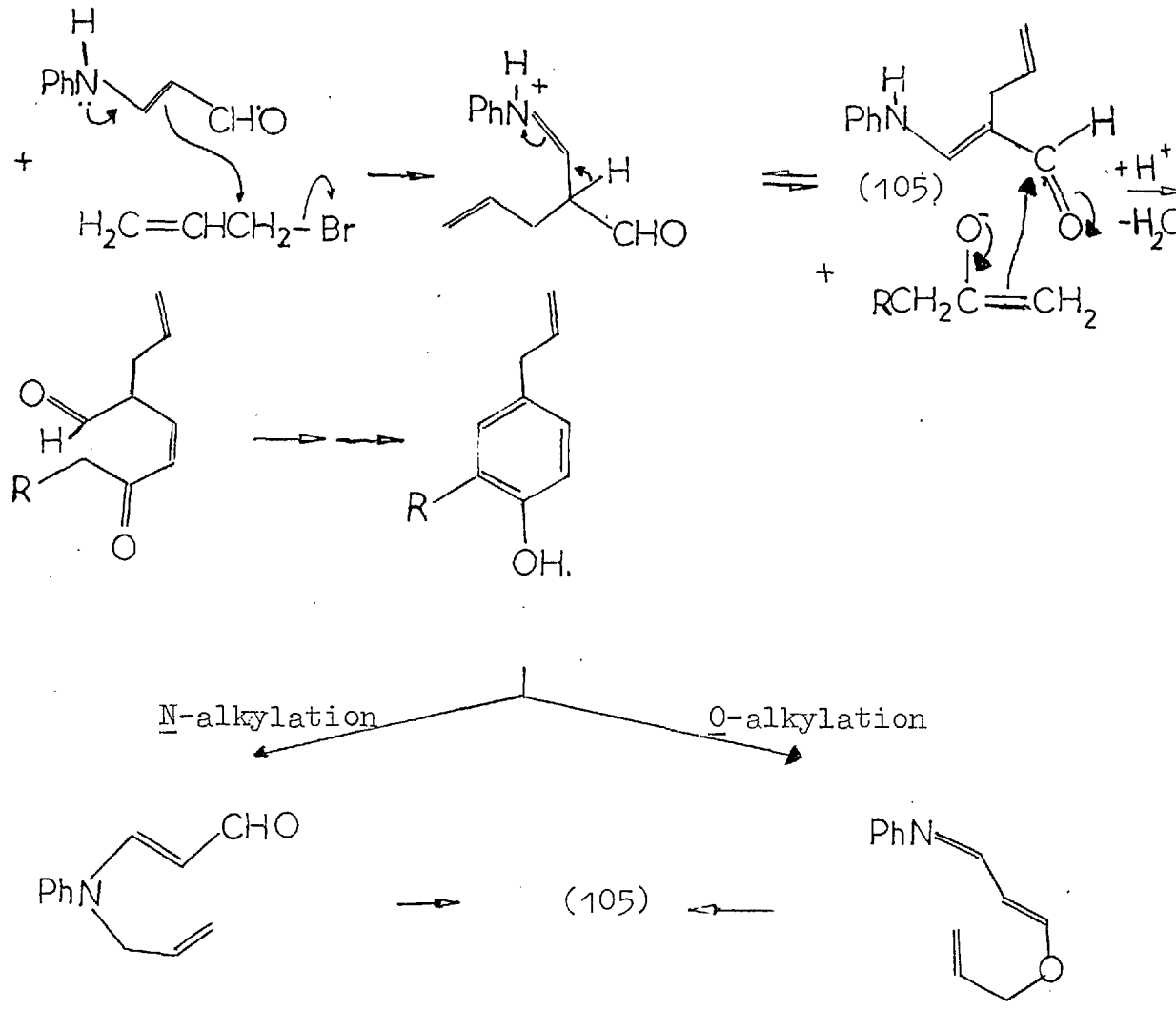
$$OHCCH{=}CHO^{-}K^{+} + \underline{p}\text{-}TsCl \xrightarrow{-KCl} \underset{(102)}{OHCCH{=}CHOTs}$$

The tosylate derivative (102) was therefore condensed *in situ* with aniline. This should provide a protected malonaldehyde (103) capable of acting as a nucleophile. Two products were obtained, the major one (104) due to condensation on the aldehyde group while the desired Michael product (103) was obtained in only 23% yield.

$$\underset{(102)}{OHCCH{=}CHOTs} + PhNH_2 \longrightarrow \underset{(103)}{PhNHCH{=}CHCHO} + \underset{(104)}{(PhNH)_2CHCH{=}CHOTs}$$

The anilinopropenal (103) provided a simple molecule capable of being further homologated. Condensation with allyl bromide, followed by nucleophilic condensation with an acetonyl derivative should provide an enamine product (105). Hydrolysis, followed by intramolecular condensation and aromatisation should give the required phenol derivative. Otherwise,

condensation via N or O-alkylation would necessitate first a Claisen rearrangement (Scheme 25).



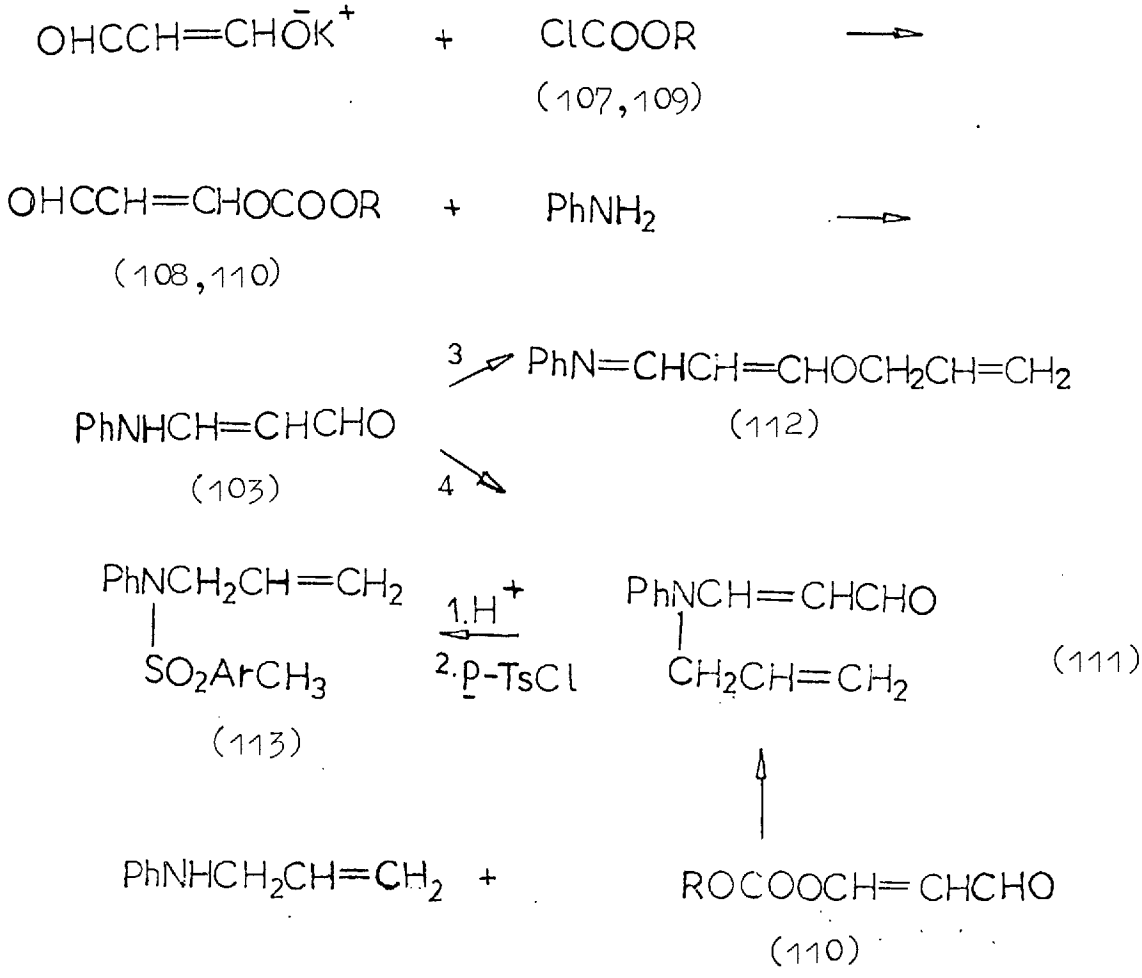
Scheme 25

For this scheme to become viable, the yield of the anilinopropenal had to be improved. An established method[40] was therefore employed. The potassium salt of malonaldehyde (106) reacted with ethyl chloroformate (107) giving the carbonate (108). This on subsequent treatment with aniline gave the anilino-

propenal (103) in moderate yield (34%). In order to raise the yield, steric hindrance around the carbonyl group was increased. 3-(Isopropyloxycarbonyloxy)propenal (109) was prepared by condensing the potassium salt of malonaldehyde and isopropyl chloroformate (109). Subsequent condensation with aniline gave the anilinopropenal in 85% yield. It was reacted with allyl bromide to give two different products, depending on the conditions of the reaction. At room temperature, N-alkylation (111) predominated, whilst in tetrahydrofuran at reflux O-alkylation (112) was the major pathway. Since spectral data was ambiguous the position of alkylation was determined chemically. Hydrolysis and toluene-4- sulphonylation of the product (111) at room temperature gave the known[41] N-allyl-p-toluenesulphonanilide (113). In addition 3-(isopropyloxycarbonyloxy)propenal (110) was condensed with N-allylaniline to give the N-alkylated product (111) identical to that previously obtained (Scheme 26).

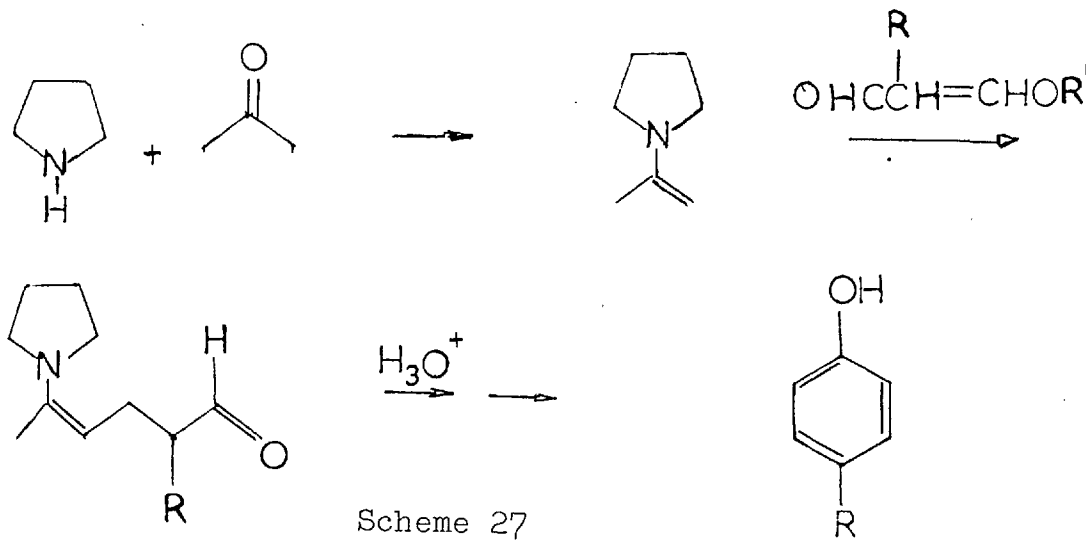
An attempted Claisen rearrangement (Scheme 25) of the N-alkylated product (111) gave but polymeric material.

Efforts in this direction were therefore discontinued. However, an approach along similar lines was devised, founded on enamine methodology (Scheme 27).



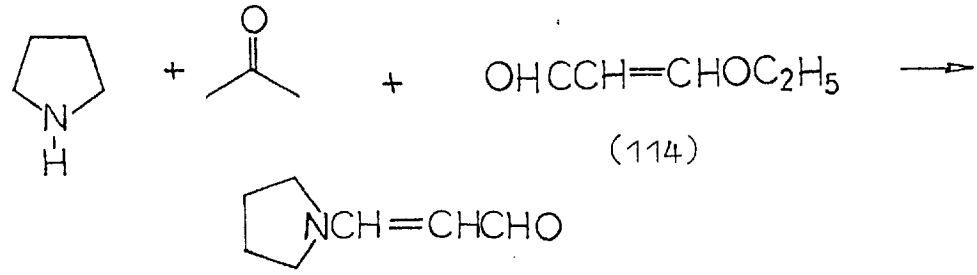
3. $CH_2=CHCH_2Br/THF/\Delta$; 4. $CH_2=CHCH_2Br$/room temperature.
(107, 108 R=C_2H_5). (109,110 R=<u>iso</u>-C_3H_7).

Scheme 26



Scheme 27

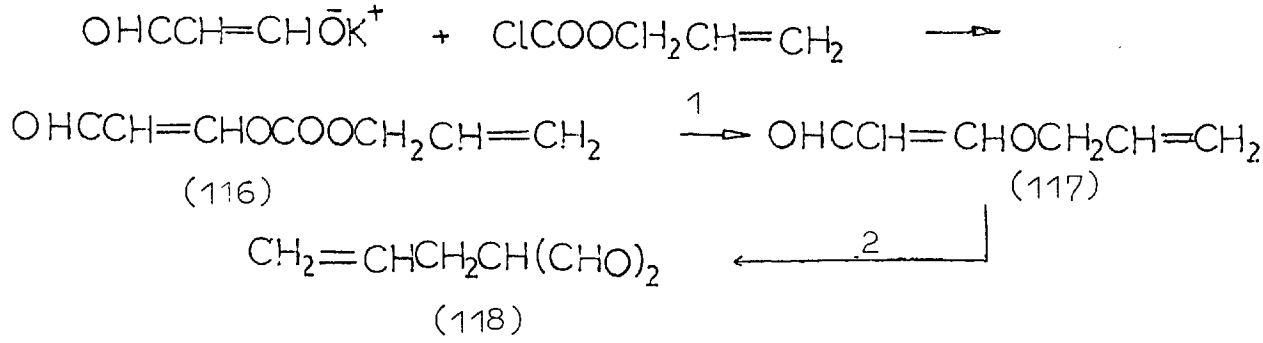
Since N-(2-propenyl)pyrrolidine is unstable[42], attempts were made to prepare it *in situ*, in the presence of the propenal derivative (114). The rate of addition, however, of the pyrrolidine to the propenal derivative (114) was much faster than with acetone. The Michael product (115) was isolated as the only product.



(114)

(115)

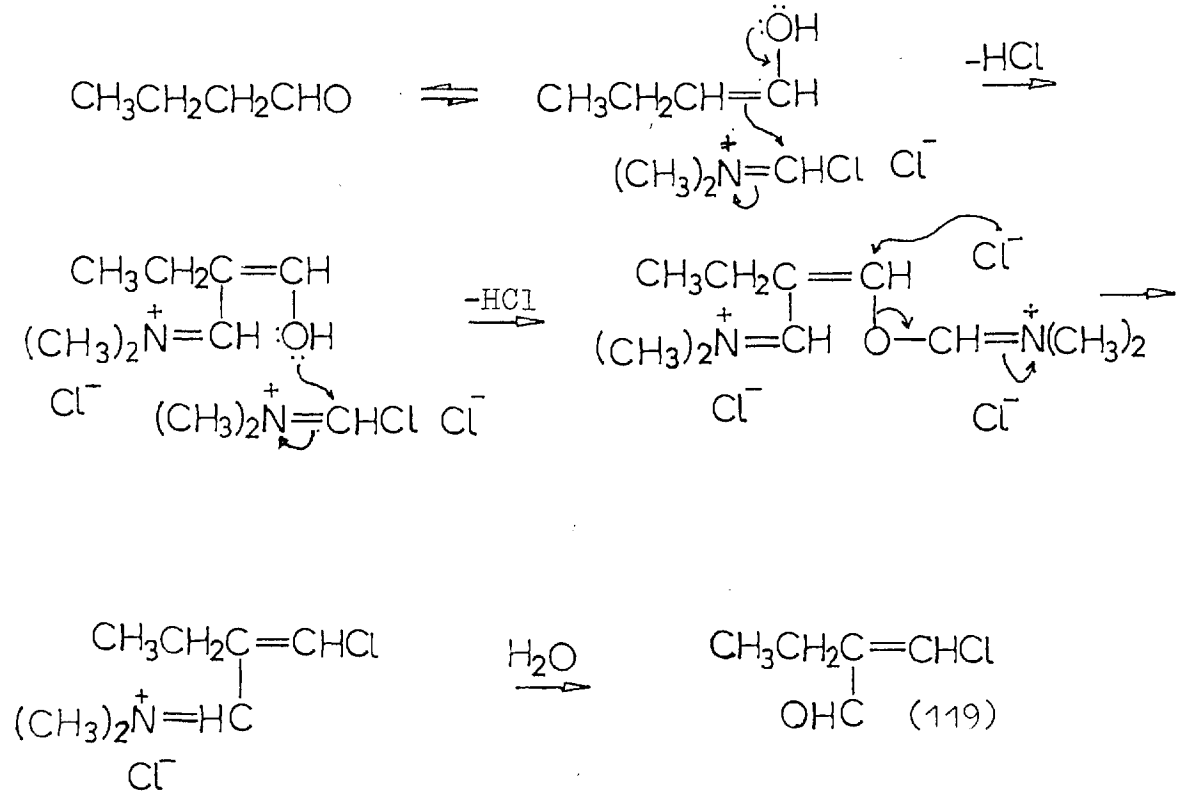
The preparation of 2-(formyl)-4-pentenal (118) by Claisen rearrangement of 3-(allyloxy)-2-propenal (117) was examined. The allyl ether (117) was prepared by condensation of the potassium salt of malonaldehyde with allyl chloroformate and the product (116) decarboxylated using toluene-4-sulphonic acid. Following the rearrangement by u.v., the spectral value changed from λ_{max} 239 (ε=19200) to λ_{max} 265 (ε=11000), before it started to decrease. Although the λ value was encouraging, the extinction value was about half the expected value[43]. It seemed that the product was too unstable as a free β-dialdehyde. This direction was therefore discontinued.



(116) (117) (118)

1. p-TsOH ; 2. Claisen Rearrangement.

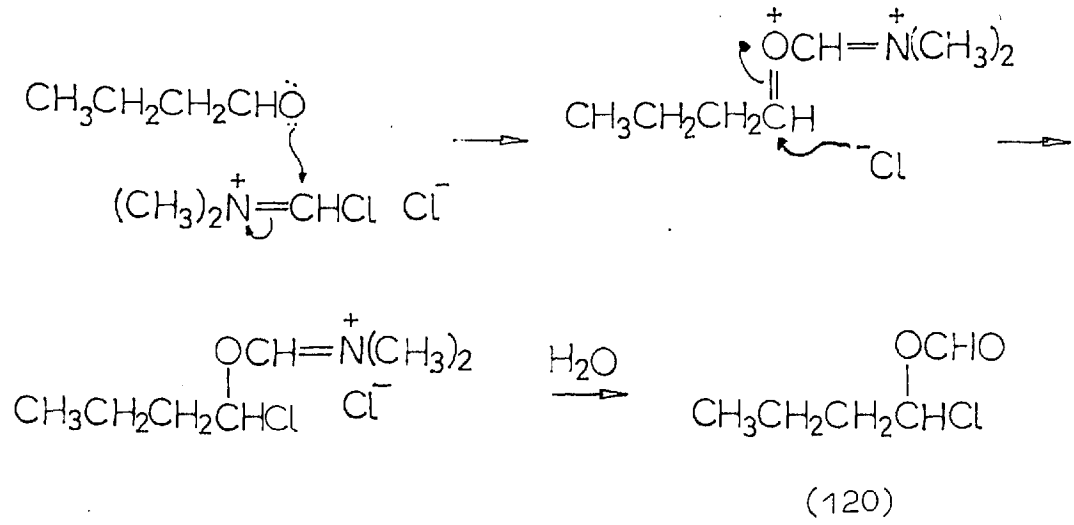
N-Chloromethylene-N,N-dimethylammonium chloride (96) was examined in detail as a C-formylating reagent in the synthesis of malonaldehyde derivatives. The formylation of simple aldehydes using the Vilsmeier reagent (96) has attracted little attention. However, Arnold and Zemlicka[44] formylated butyraldehyde to obtain 2-(chloromethylene)butanal (119) in 28% yield. The reagent was prepared using phosgene in an excess of dimethylformamide. The following mechanism describes the transformation (Scheme 28).



Scheme 28

This reaction was repeated under slightly different conditions. Firstly, the Vilsmeier salt (96) (2.5eq.) was

purified by evaporation to remove most of the excess $COCl_2$ and HCl. The salt was suspended in dichloromethane and reacted. Under these conditions, the unstable 1-chloro-1-formyloxybutane (120) was obtained (Scheme 29).



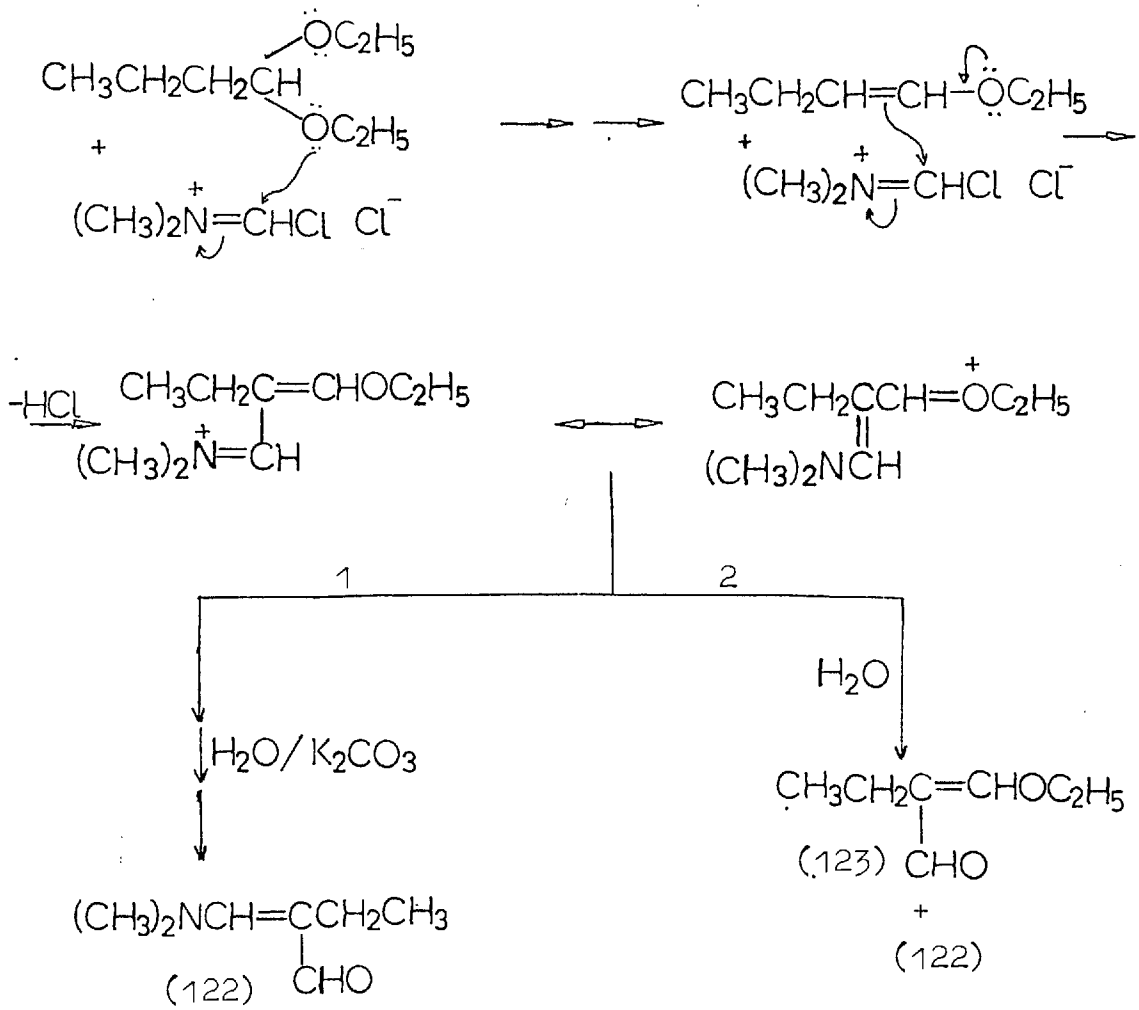
(120)

Scheme 29

Although all the spectral data were consistent with this structure, satisfactory microanalysis could not be obtained. Thus, depending on the medium, whether dichloromethane or dimethylformamide different products were obtained.

Arnold and Sorm[36] condensed 1,1-diethoxybutane (121) with the Vilsmeier salt (96) under two different conditions. Using an excess of dimethylformamide 2-(N,N-dimethylaminomethylene)-butanal (122) was obtained. However, using an excess of phosgene (2eq) and just one equivalent of DMF 2-(ethoxymethylene)butanal

(123) was also obtained. Those results demonstrated the importance of the solvent medium during formylation. Repetition of the above reaction using an excess of Vilsmeier salt (2.5eq) previously isolated and resuspended before use gave a mixture of the ethoxy derivative (123) and the dimethylamino derivative (122) (2:3) (Scheme 30)



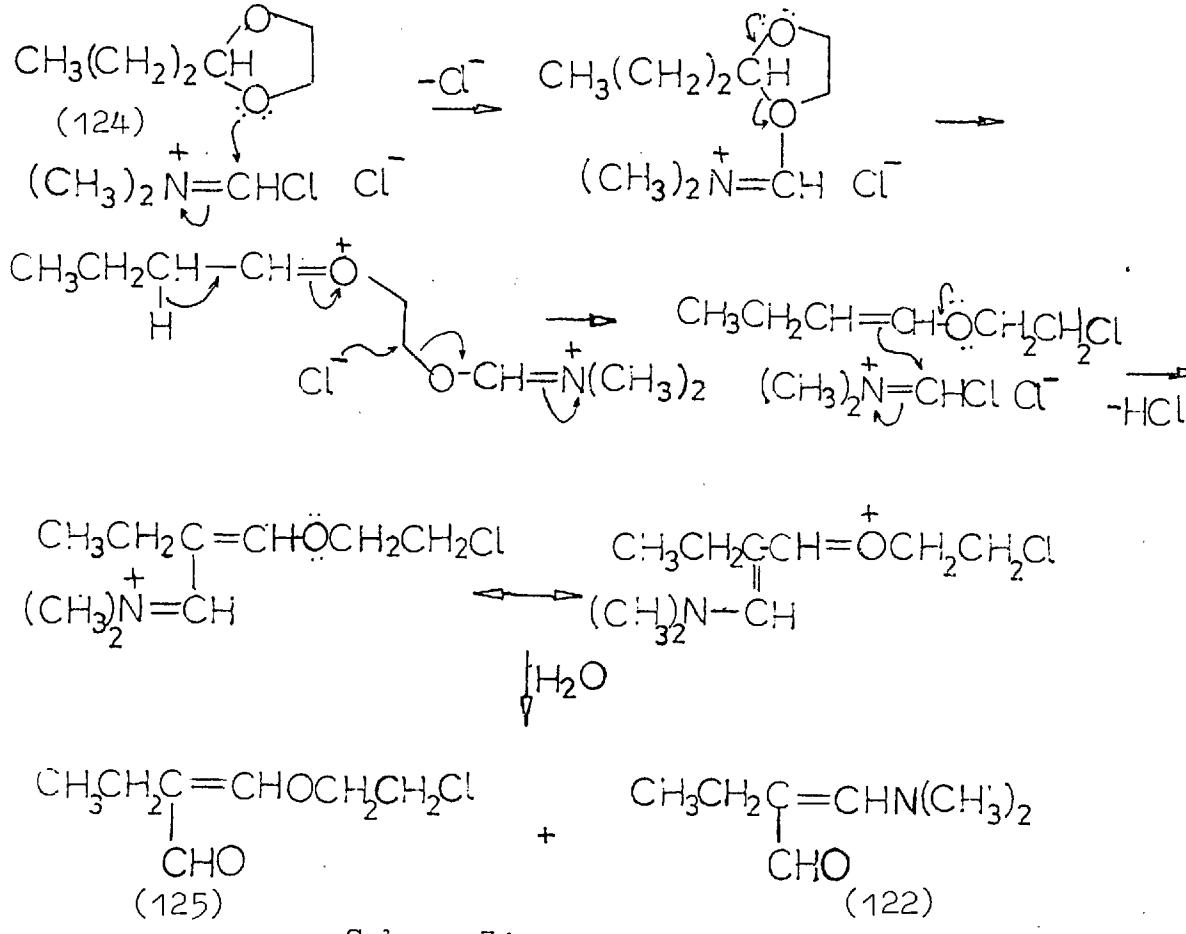
1. Excess DMF ; 2. CH_2Cl_2

Scheme 30

Following those results, the formylation of cyclic acetals was carried out in order to obtain protected malonaldehyde derivatives.

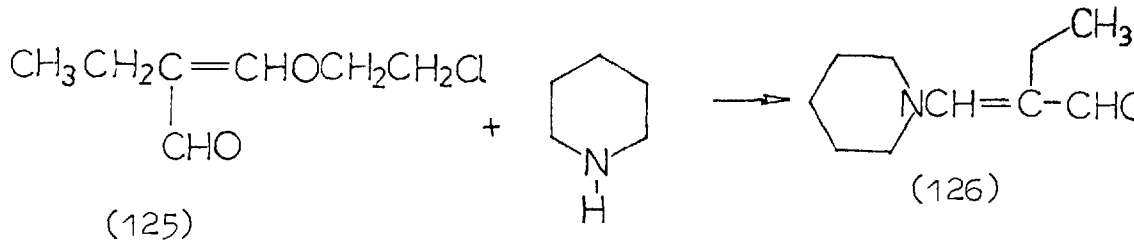
The dioxolane derivative (124) was prepared from the condensation of butyraldehyde and ethane-1,2-diol, catalysed by anhydrous toluene-4-sulphonic acid.

Formylation of the acetal (124) using the Vilsmeier salt (96) gave after hydrolysis at pH 9 two products. The major product (64%) was identified as 2-(2-chloroethoxymethylene)-butanal (125). The minor component was 2-(dimethylaminomethylene)butanal (122) (9%). Scheme 31 describes the transformations.



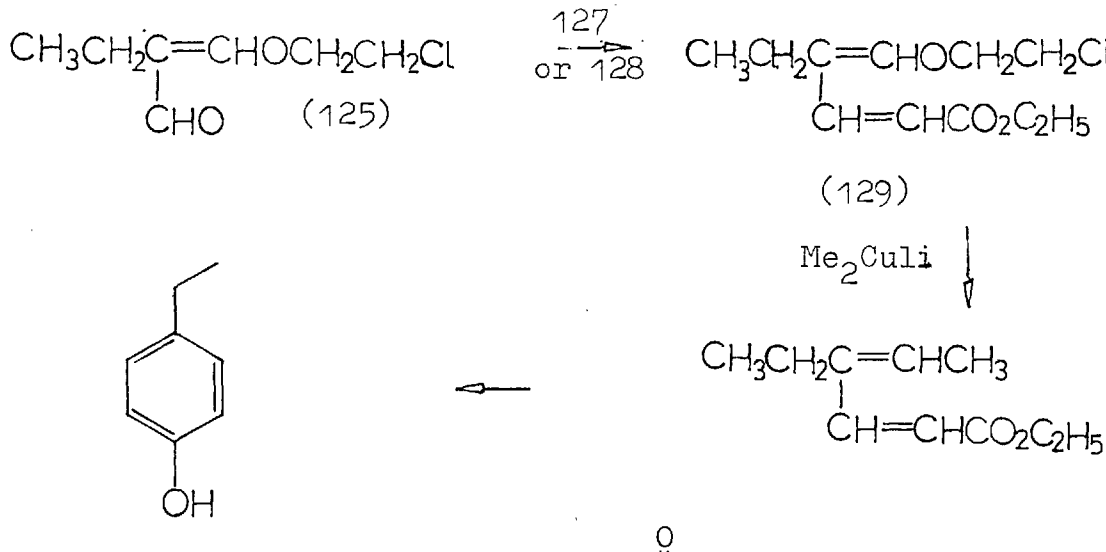
Scheme 31

Attention was directed towards homologation of the chloroethoxy derivative (125). The Knoevenagel reaction using dimethyl malonate gave a complex mixture of products. The additional use of piperidine gave a product derived from its Michael addition. The reaction was repeated without dimethyl malonate to yield the 2-(piperidinomethylene)butanal (126) in 84% yield.



(125) (126)

The Wittig reaction was examined. Subsequent conjugate addition of lithium dimethylcuprate should give a phenol derivative precursor (Scheme 32).

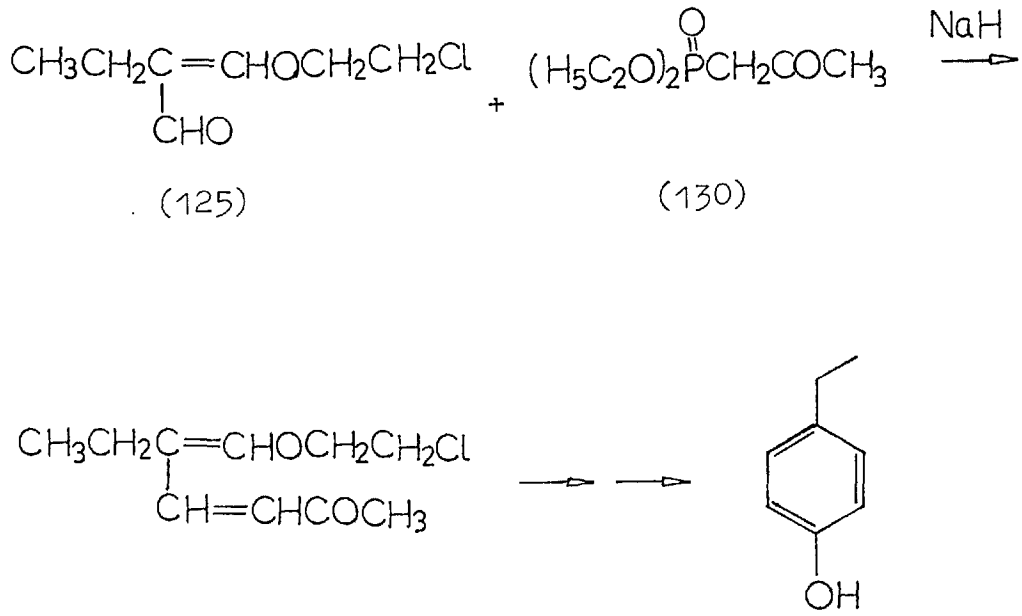


127. $Ph_3\overset{+}{P}CH_2CO_2C_2H_5\ Br^-$; 128. $(H_5C_2O)_2\overset{O}{\overset{\|}{P}}CH_2CO_2C_2H_5$.

Scheme 32

The first step of this scheme was carried out successfully; the phosphonium salt (127) and propylene oxide as proton scavenger, or the phosphonate (128) and sodium hydride as base gave the dienoate (129). However, addition of lithium dimethylcuprate failed as shown by n.m.r. and t.l.c. The use of THF as co-solvent may have been the cause for the inhibited addition as shown recently by House and Wilkins[45].

Another Wittig sequence was examined. Condensation between the chloroethoxy derivative (125) and diethyl 2-oxopropenylphosphonate (130) should conceivably give a precursor suitable for cyclisation (Scheme 33).

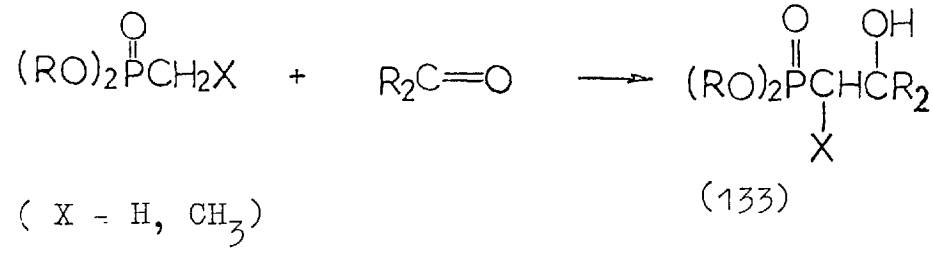


Scheme 33

Numerous attempts to effect the condensation between the

enolate anion and the aldehyde failed. Starting aldehyde was recovered, while hydrogen evolution showed clearly that the anion of the phosphonate had been formed. The failure of this reaction was due to insufficient reactivity of the butanal derivative on account of the vinylic oxygen substituent.

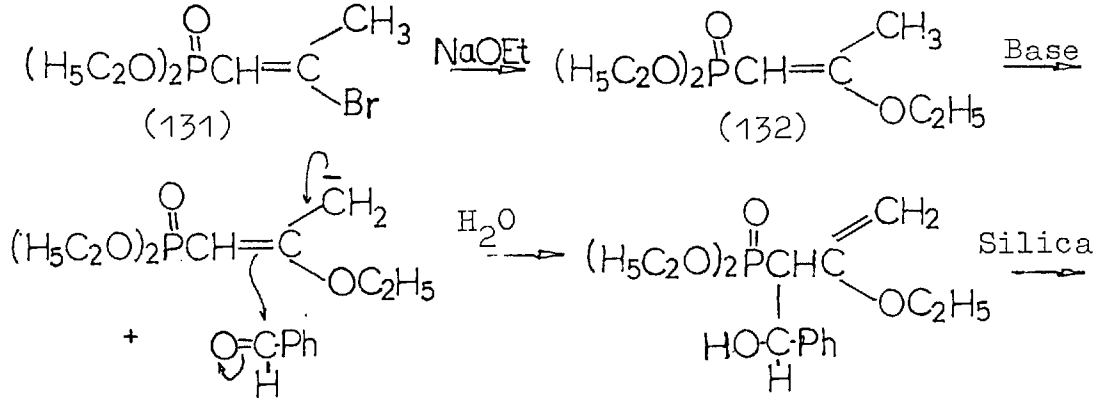
In order to circumvent this problem, the reactivity of diethyl 2-ethoxy-1-propenylphosphonate (132) was explored. It was prepared from the corresponding bromo derivative[46] (131), diethyl 2-bromo-1-propenylphosphonate. The derived anion of the phosphonate (132) formed with n-butyllithium, sodium hydride or the sodium salt of hexamethyldisilazane was reacted with benzaldehyde. The n.m.r. spectrum of the product showed that the benzaldehyde PhCHO peak disappeared rapidly. However, the subsequent elimination giving the olefin and the phosphonate ester proceeded in poor yield. Literature precedents state that non-stabilized phosphonates[47] do form the condensed intermediates (133). However, those intermediates were not applicable to olefin synthesis since neither adduct (133) nor the conjugate bases underwent efficient or facile cycloelimination to form an ethylenic bond under a wide range of conditions.



(X = H, CH_3)

(133)

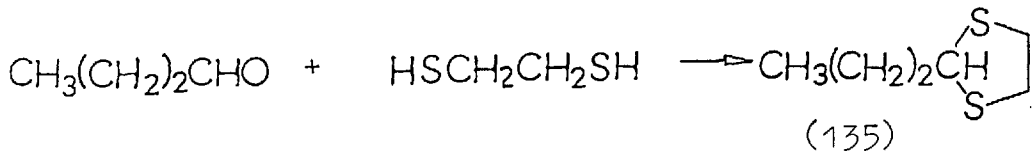
In this case, a silmilar intermediate was presumably formed. Cycloelimination on silica chromatography gave the (E)-benzylidene acetone (134) in varying yieds. Thus n-butyllithium gave 17%, sodium hydride 33%, and the sodium salt of hexamethyldisilazane 15%. The yields were considered too low to be of industrial value, and the Scheme 34 was therefore abandoned.



(131) (132) (134)

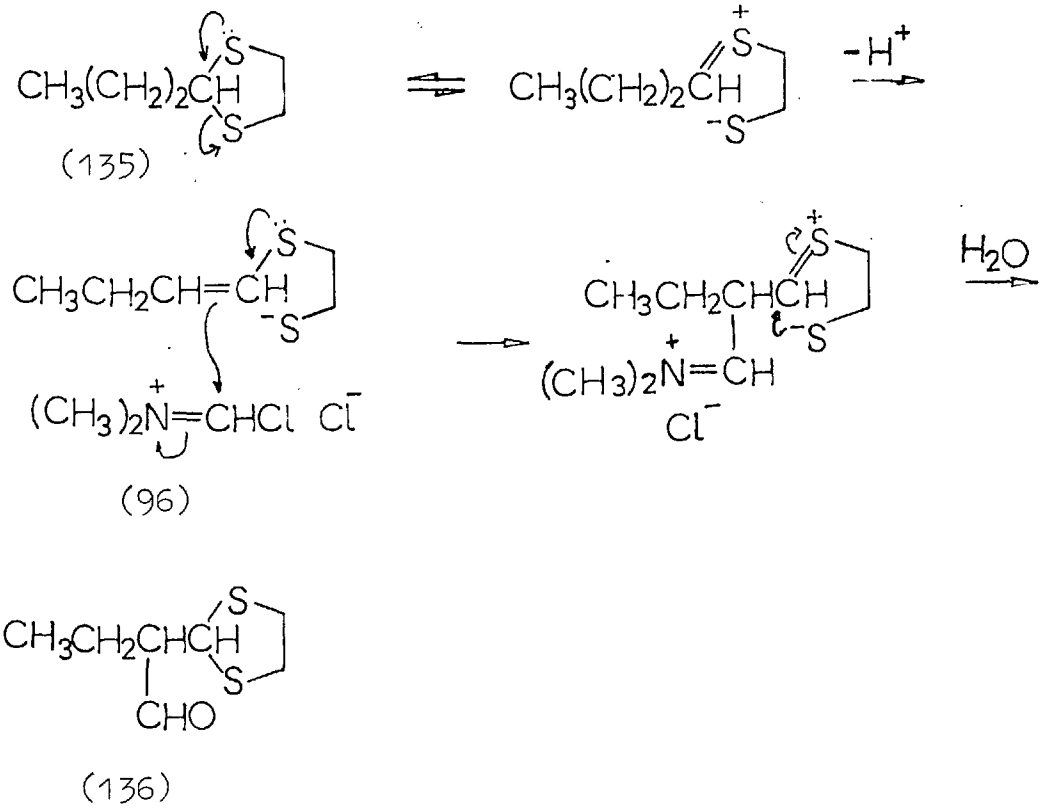
Scheme 34

Next the formylation of 2-propyl-1,3-dithiolane (135) was examined, in order to obtain a more reactive masked malonaldehyde. The dithiolane derivative (135) was prepared by condensing butyraldehyde with ethane-1,2-dithiol catalysed by boron trifluoride etherate.



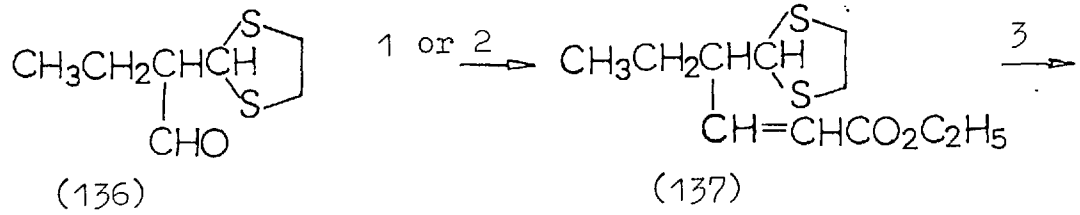
(135)

Subsequent formylation with the Vilsmeier salt (96) gave the formyl derivative (136). The cyclic thioacetal remained intact as the soft sulphur was not expected to condense with the hard carbon of the Vilsmeier salt (Scheme 35).

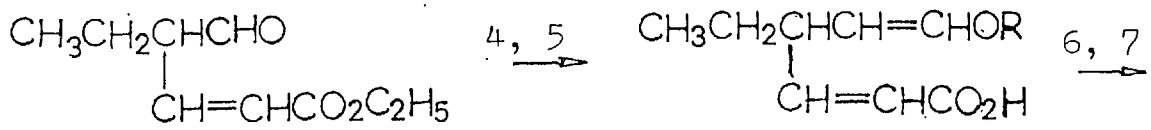


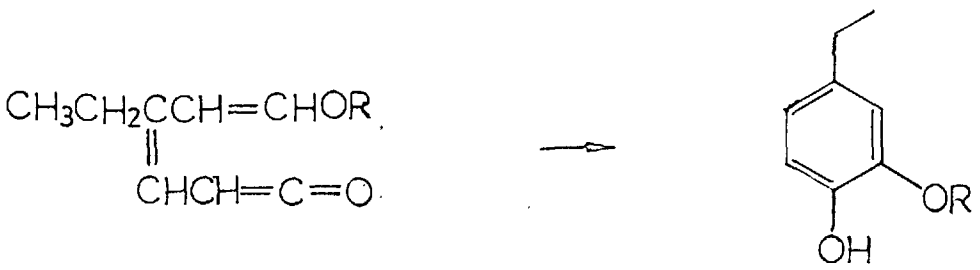
Scheme 35

An attempt to oxidise this dithiolane using benzeneseleninic anhydride[48] gave an intractable mixture of products. Homologation of the dithiolane derivative (136) by Wittig methodology was thus examined. Further treatments could lead to a phenol derivative (Scheme 36).



(136) (137)

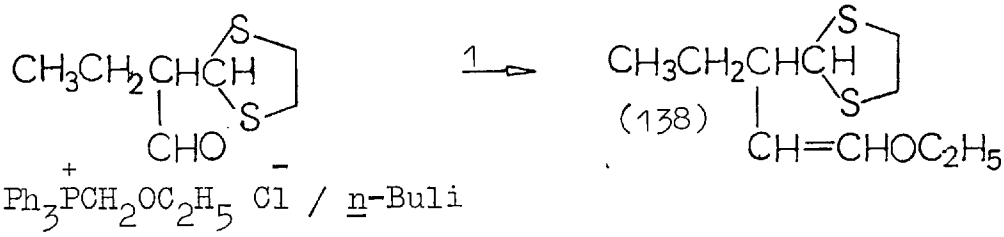




1. $Ph_3\overset{+}{P}CH_2CO_2C_2H_5\ Br^-$; 2. $(C_2H_5O)_2\overset{O}{\overset{\|}{P}}CH_2CO_2C_2H_5$; 3. Oxidation;
4. Hydrolysis; 5. Wittig; 6. $SOCl_2$; 7. $(C_2H_5)_3N$

Scheme 36

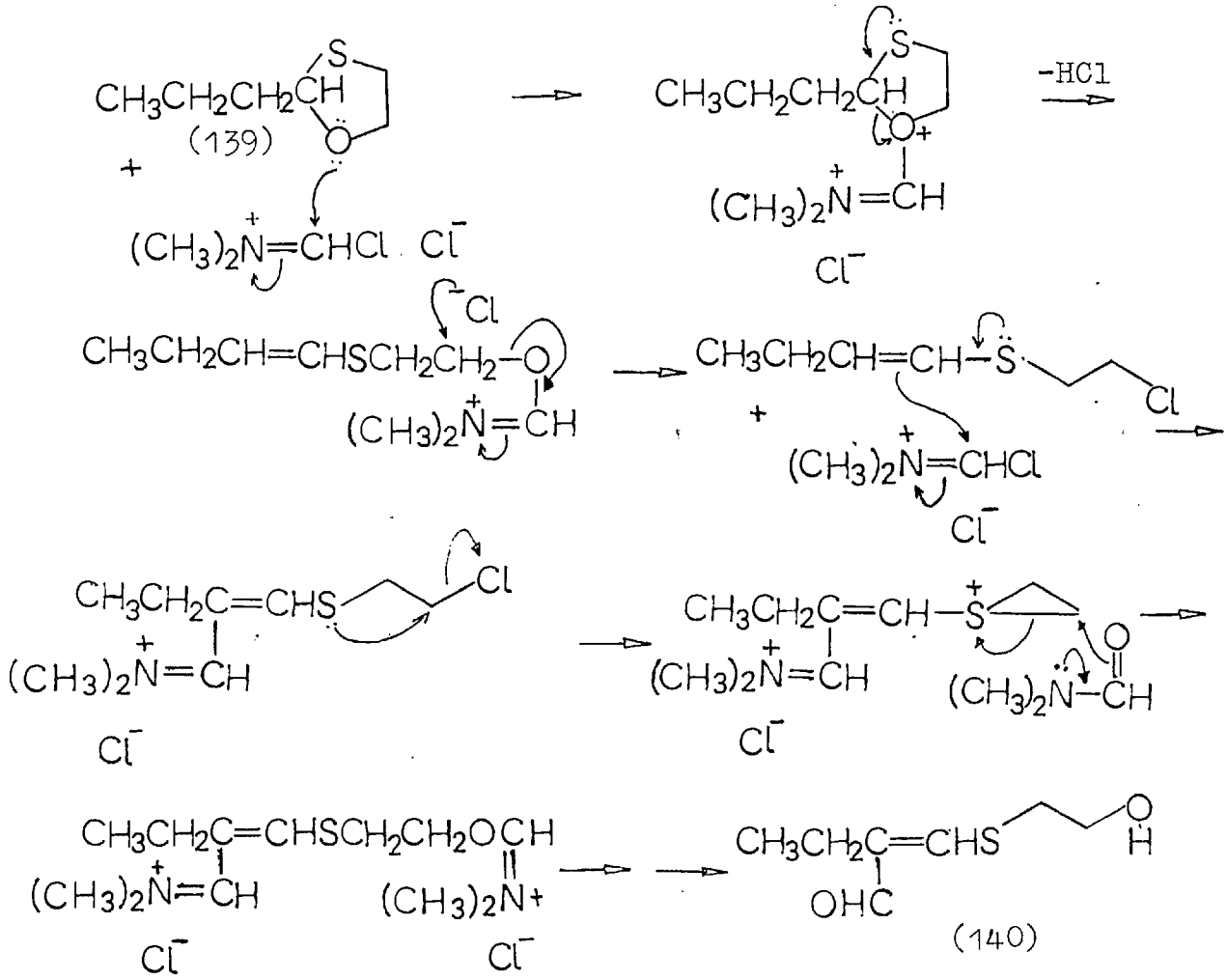
Reaction with etoxymethyltriphenylphosphonium chloride gave the expected vinyl ether (138) in 66% yield.



1. $Ph_3\overset{+}{P}CH_2OC_2H_5\ \overset{-}{Cl}$ / n-Buli

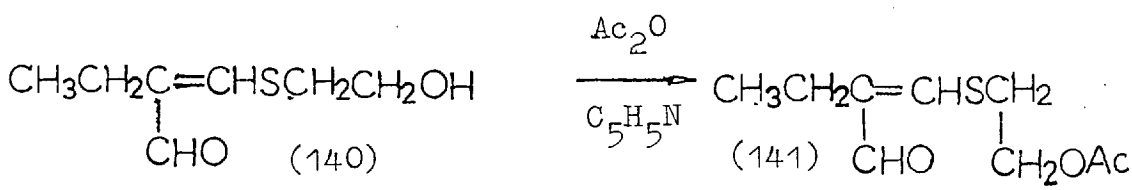
Alternatively, reaction with ethoxycarbonylmethyltriphenylphosphonium bromide or triethyl phosphonoacetate gave the α,β-unsaturated ester (137). Attempted oxidation using, (benzeneseleninic anhydride, N-chlosuccinimide, silver nitrate, methyl iodide, mercuric chloride, mercuric oxide and propylene oxide) of dithiolane (137) gave unidentifiable mixtures.

Formylation of the oxathiolane derivative (139) was examined. The hydroxy derivative (140) was obtained as the major product. Its formation presumably involved displacement of the iminium residue by chloride ion, followed by formation of an episulphide. It was opened by a molecule of DMF which on work up gave the hydroxy compound (140) through the formate derivative. The scission of the C-O bond in preference to the C-S bond during acid hydrolysis has been reported previously[49,50] (Scheme 37).

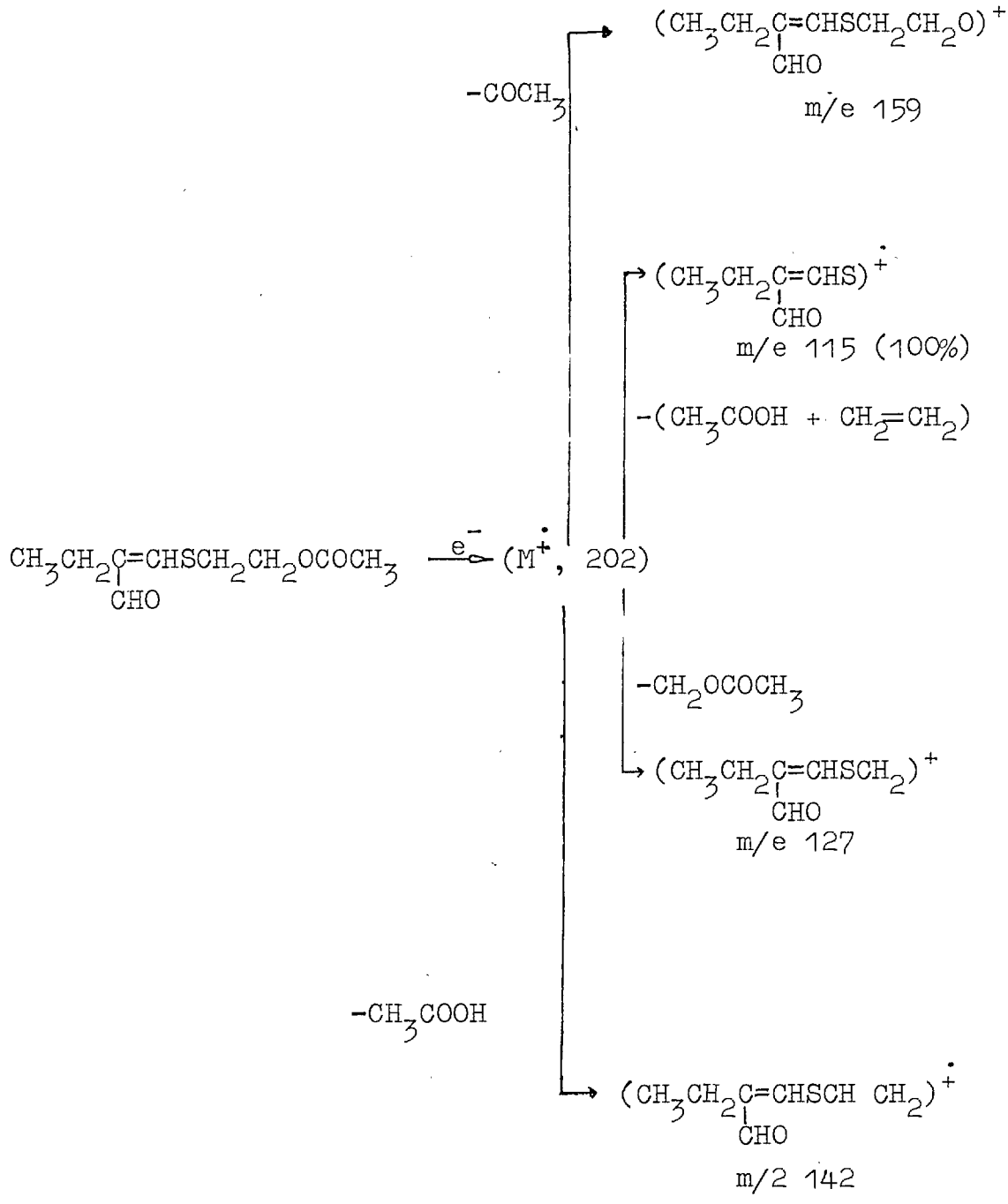


Scheme 37

In order to confirm that a sulphur and not an oxygen derivative was obtained, the butanal derivative (140) was acetylated to give the acetate (141).

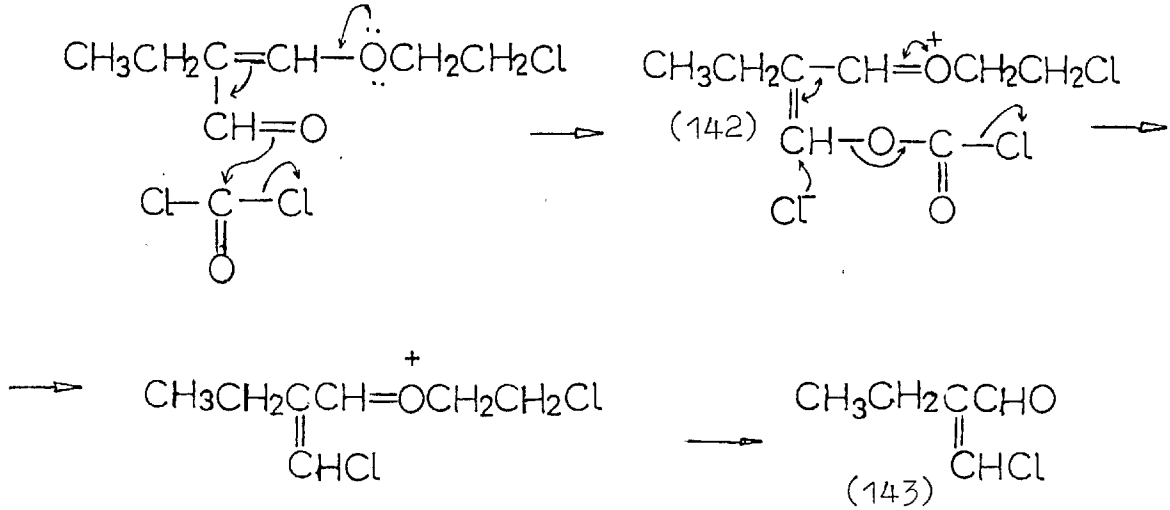


Fragmentation patterns in the mass spectrometer proved beyond doubt the structure of the compound.



In summary, various potential routes to p-alkylated phenols from aliphatic precursors have been described. Although, they did not provide the required phenol derivatives, some of the intermediates were considered still worthy of investigation.

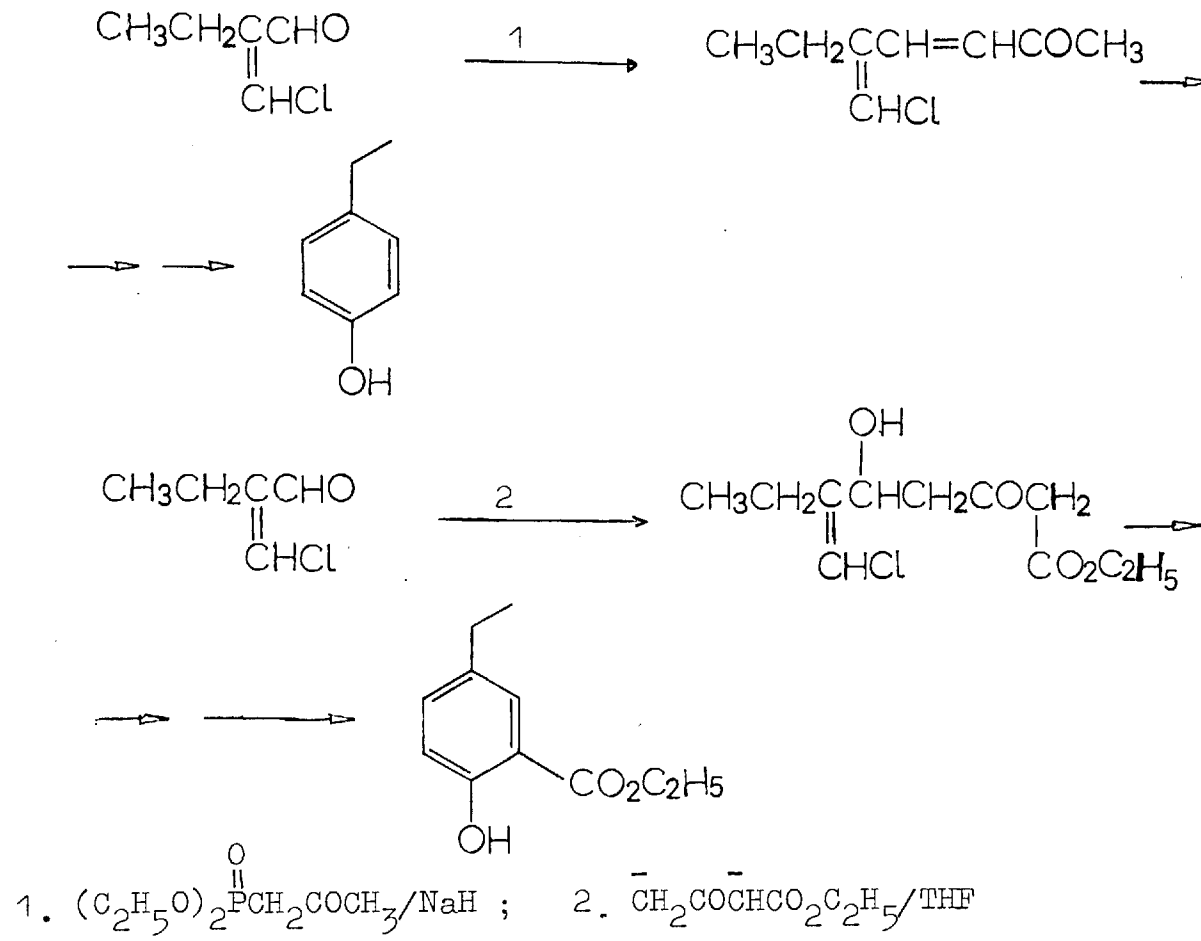
As the chloroethoxy derivative (125) was unreactive towards nucleophiles, it was decided to activate it by reaction with phosgene. Chloroacylation of the carbonyl generated a highly electrophilic species (142) which reacted readily with the chloride anion and gave after hydrolysis the 2-(chloromethylene)butanal (143) together with a 2-chloroethanol derivative (Scheme 38).



Scheme 38

This has analogy where 2-(dimethylaminomethylene)butanal (121) was converted to the same 2-(chloromethylene)butanal (143) with phosgene[51]. As the by-product from the chloroethoxy

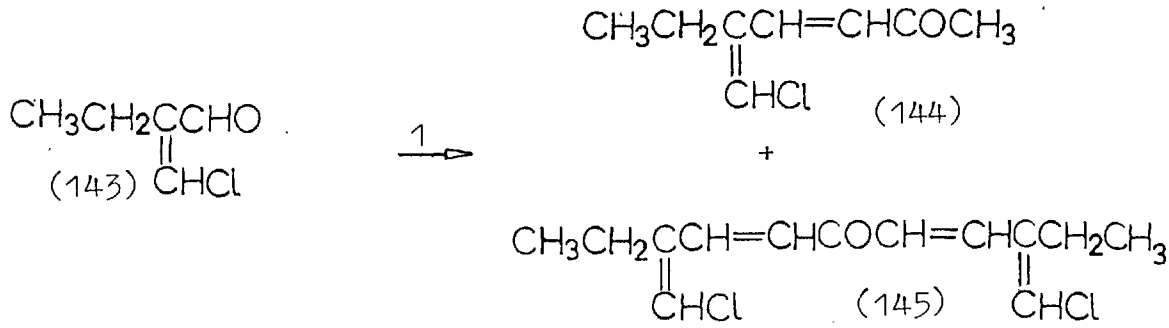
derivative (125) was difficult to separate, the dimethylamino derivative (121) was the precursor of choice. Two different paths towards the substituted phenols were devised. It involved Wittig methodology, followed by condensation and aromatisation or, aldol condensation followed by dehydration and cyclisation (Scheme 39).



Scheme 39

The Wittig reaction was carried out using two modes of

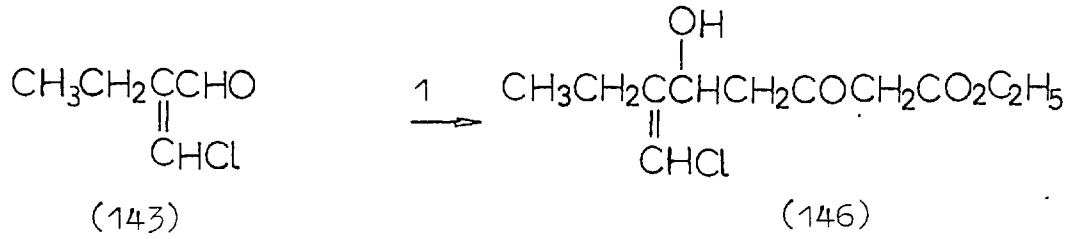
addition. Adding the phosphonate anion to the vinyaldehyde derivative (143) gave two products: the expected enone derivative (144) which partly reacted further with another molecule of (143) to give (145).



1. $(C_2H_5O)_2\overset{O}{\overset{\|}{P}}CH_2COCH_3$/ NaH

However, direct addition gave only the required (E)-dienone (144) in 62% yield. Attempts to cyclise this compound by isomerisation and cyclisation using (stannic chloride, N,N,N'N'-tetramethylguanidine, boron trifluoride etherate, trifluoroacetic acid, and a saturated solution of hydrogen chloride in dichloromethane failed to give the cyclised product.

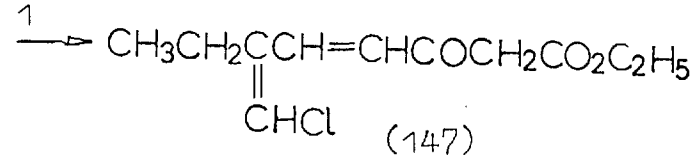
Condensation of the dianion of ethyl acetoacetate[52] with the vinylaldehyde derivative (143) gave mostly (> 90%) (146), condensation via the carbon γ to the ester carbonyl. It was separated by p.l.c. from a minor by-product derived from condensation of the carbon α to the ester carbonyl.



(143) (146)

1. $\bar{C}H_2COCHCO_2C_2H_5$/ THF

The hydroxy compound (146) was treated with thionyl chloride in benzene at room temperature. P.l.c. and distillation gave the unsaturated ester (147) in 68% yield.



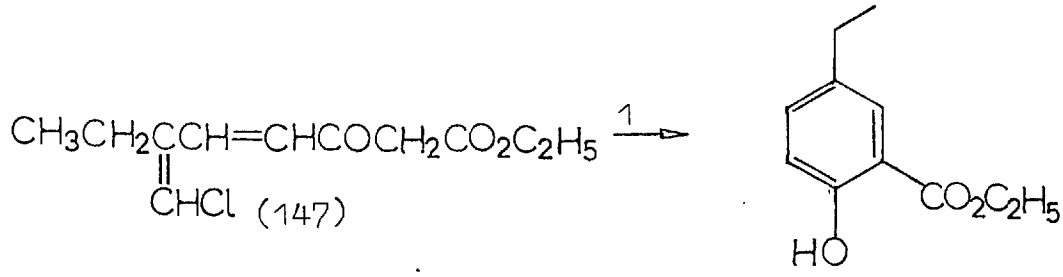
(146) (147)

1. $SOCl_2$/ C_6H_6

The n.m.r. spectrum was complex presumably due to the presence of keto-enol tautomers. Some of the signals were indistinguishable. 1.08 (3H, t, J 8Hz, CH_3CH_2-), 1.33 (3H, t, J 7Hz, CH_3CH_2O-), 2.43 (2H, q, J 8Hz, CH_3CH_2-), 3.57 (2H, s, $COCH_2CO$), 4.16 (2H, q, J 7Hz, CH_3CH_2O-); from the rest of the spectrum, one set was assumed to belong to the enol form: 6.27 (1H, d, J 16Hz, =CHC(OH)), 6.47 (1H, s, =CHCl), 7.07 (1H,

d, J 16Hz, CH=CHC(OH)), while the other was assumed to belong to the keto form: 5.83 (1H, d, J 16Hz, =CHCO), 6.3 (1H, s, =CHCl), 6.9 (1H, d, J 16Hz, CH=CHCO).

The dienoate was treated with pyrrolidine in dioxane, at reflux for 2h. Work up and distillation gave ethyl 5-ethyl-2-hydroxybenzoate (148) in 82% yield. The n.m.r. spectrum was very similar to that from ethyl 2-hydroxy-5-methylbenzoate described in the literature[53]: δ ($CDCl_3$) 1.4 (3H, t, $CO_2CH_2CH_3$) 2.28 (3H, bs, CH_3), 4 39 (2H, q, $CO_2CH_2CH_3$), average $\delta_{3,4}$ 7 06 (2H, $\Delta\nu_{3,4}$ 24.1Hz, J 8.6Hz, δ_6 7.63 (1H, $J_{4,6}$ 2.4Hz), 10.63 (1H, s, OH).



(148)

1. Pyrrolidine/ Dioxane

This short synthesis should provide alternative p-alkylated phenols less readily available by existing methodology.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer 257 grating spectrophotometer. Ultraviolet spectra were recorded on a Unicam SP 800 B spectrophotometer.

^{1}H Nuclear magnetic resonance (n.m.r.) were taken in deuterochloroform with tetramethylsilane as an internal reference on a Varian T 60 spectrometer. Signals are reported in the order of chemical shift designated on the δ scale and within parentheses intensity, multiplicity with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet) dd (doublet of doublets), m (multiplet), b (broad), bs (broad singlet), coupling constant in Hz and assignment.

Mass spectra were recorded with a Perkin Elmer 270 low resolution spectrometer

All solvents were purified according to standard procedures[54] Merck Kieselgel GF 254 was used for analytical (t.l.c.) and preparative (p.l.c.; 1mm layers) thin layer chromatography. Hopkin and Williams Silica gel M.F.C. (100-200mesh) or neutral alumina of Brockman activity III were used for column chromatography.

Organic solutions were dried over sodium sulphate.

Light petroleum refers to the redistilled fraction with b.p. 40-60°. Ether refers to diethyl ether. THF refers to tetrahydrofuran. The 'usual work up' refers to dilution with

sodium hydrogen carbonate, extraction with ether, washing with brine, drying, and evaporation (Buchi rotary evaporator).

Preparation of 3-(Dimethylamino)propenal (95)

To a cooled and stirred solution of N,N-dimetylformamide (10,3g, 150mmol) in dichloromethane (20ml) was added a solution of phosgene in dichloromethane (30% w/v, 20ml). After 10 minutes, a solution of 1,1-diethoxypropane (7.08g, 60mmol) in dichloromethane (5ml) was slowly added to the cooled reaction mixture. The reaction was heated to reflux for 30 minutes, cooled and hydrolysed with excess ice cold potassium carbonate solution (15% w/v, 30ml). The organic phase was washed several times with water, brine, dried and evaporated. Distillation gave the pure aldehyde (95) (3g,51%), b.p. 80-82°/0.02 mmHg; (lit.[36] b.p. 100°/0.25 mmHg)

Preparation of 3-(N,N'-Dimethylimino-1-methoxy)propene Methoxysulphonate (98)

3-(Dimethylamino)propenal (990mg, 10mmol) was stirred overnight with dimethyl sulphate (1.26g, 10mmol) to give a dark oil (2.2g, 94%); λ_{max} (EtOH) 289nm (ε 15500); δ 3.48 (3H, s, CH_3SO_4), 3.7 (6H, s, $(CH_3)_2N$), 4.11 (3H, s, OCH_3), 6.18 (1H, dd, J 11,12 Hz, methine), 8.26 (1H, d, J 11Hz, $(CH_3)_2C\underline{H}=$), 8.73 (1H, d, J 12 Hz, $CH_3OC\underline{H}=$).

(98) was analysed as the teraphenyl boron salt and recrystallised from ethyl acetate and light petroleum, m.p. 150-151°. (Found: C, 83.04; H, 7.43; N, 2.98. $C_{30}H_{32}BNO$ requires C, 83.12; H, 7.44; N, 3.23%).

Preparation of Methyl 2-(Methoxycarbonyl)-5-dimethylamino-2,4-pentadienoate (99)

To a solution of the sulphonate (98) (579mg, 2.58mmol) in methanol (3ml) under nitrogen was added a solution of sodium methoxide [from sodium (59mg, 2.58mmol)] in methanol (1.5ml). After 10 minutes dimethyl malonate (340mg, 2.58mmol) in methanol (2ml) was slowly added. The resulting solution was stirred for 24h at room temperature, and refluxed for 2 days. The mixture was cooled, the solvent evaporated, and the residue partitioned between water and ethyl acetate. The organic phase was washed with 10% hydrochloric acid, brine and dried. Removal of the solvent and p.l.c. (50% ether / light petroleum) gave the dienoate (99) (120mg, 30%). Recrystallisation from ethyl acetate and light petroleum gave yellow needles, m.p. 108-109°; ν_{max} 1690, 1619, 1560, 1380 cm^{-1}; λ_{max}(EtOH) 370 and 259 nm (ε 40900 and 9800); δ 3.06 (6H, s, CO_2CH_3), 3.80 (6H, s, $(CH_3)_2N$), 6.22 (1H, t, J 11 Hz, $=CHCO_2CH_3$), 7.05 (1H, dd, J 12,11 Hz, =CH), 7.76 (1H, d, J 12 Hz, $(CH_3)_2NCH=$); m/e 213 (M^+), 182 (100%), 152, 113, 94, 82. (Found: C, 56.09; H, 6.87; N, 6.47. $C_{10}H_{15}NO_4$ requires C, 56.32; H, 7.09; N, 6.56%).

Reaction between the Sulphonate and Dimethyl Acetonedicarboxylate

To a solution of the sulphonate (98) (237mg, 1.05mmol) in methanol (2ml) under nitrogen, was added a solution of sodium methoxide (from sodium (24mg, 1mmol)) in methanol (1ml). After 20 minutes dimethyl acetonedicarboxylate (182mg, 1mmol) in methanol (1ml) was slowly added. The resulting solution was stirred for 24h at room temperature, and refluxed for 3 days. The reaction was cooled, solvent evaporated, and the residue partitioned between water and ethyl acetate. The organic phase was washed with 10% hydrochloric acid, brine and dried . Removal of the solvent and p.l c. (50% benzene-ether) gave a crystalline product (100) (104mg, 56%). An analytical sample prepared by recystallisation from benzene and light petroleum gave <u>dimethyl 4,8-methoxycarbonyl-5,7-undecadiene-dioate (100)</u>, as yellow crystals, m.p. 171-173°; ν_{max} 1745, 1660, 1612, 1438, 1355cm^{-1}; δ 2.13 (4H, s, 2 $COCH_2CO$), 3.21 (1H, d, J 6Hz, $\underline{H}CCO_2CH_3$), 3.96 (12H, s, 4 CO_2CH_3), 5.01 (1H, m, =C$\underline{H}$CH-), 6.87 (1H, d, J 7Hz, =CHCH=), 8.29 (1H, t, J 7Hz, =HCC$\underline{H}$=CH), m/e 383 (M^+), 352, 320 (100%), 288, 261, 179. (Found: C, 53.33; H, 4.75; $C_{17}H_{20}O_{10}$ requires C,53.16; H, 4.72%).

<u>Preparation of Dimethyl 2-Hydroxy-1,3-benzenedicarboxylate (101)</u>

To a solution of the sulphonate (98) (112mg, 0.5mmol) in THF (1ml), under nitrogen, was added a solution of triethylamine (50mg, 0.5mmol) in THF (1ml). To the stirred solution, dimethyl acetonedicarboxylate (87mg, 0.5mmol) in THF (1ml), was slowly

added. The mixture was refluxed for 3 days, cooled, poured into water, and extracted with ether. The organic phase was washed with 10% hydrochloric acid, brine, and dried. Evaporation of the solvent under reduced pressure, and p.l.c. (30% ether/light petroleum) gave a crystalline solid which was recrysallised from benzene and light petroleum to yield the phenolic ester (101) (15mg, 14%), m.p 70-71° (lit.[55] m.p. 72°) 3.96 (6H, s, CO_2CH_3), 6.86 (1H, t, $J_{5,6}$ 7Hz, C5-H), 8.00 (2H, d, $J_{4,5}$ 7Hz, C4-H + C6-H).

Attempted Preparation of Phenol

The sodium salt of malonaldehyde[40] (423mg, 3.7mmol) was dissolved in aqueous sodium hydroxide (25%, 4ml) and acetone (58mg, 1mmol) added. After 2 days, as no phenol was formed (t.l.c.), the solution was irradiated with a Tungsten lamp 100W, and left for 2 more days. No phenol was formed while t.l.c. showed polymeric material, none of which was identified.

Attempted Preparation of 3-(Toluene-4-sulphonyloxy)propenal (102)

a. In Dioxane

To a mixture of potassium malonadehyde (110mg, 1mmol) and toluene-4-sulphonyl chloride (190mg, 1mmol) were added dioxane and various amounts of pyridine (0.1eq to 1eq). The reaction instantly became black and the n.m r. spectrum showed no aldehydic peak.

b. In Dimethylformamide

To a mixture of potassium malonaldehyde (55mg, 0.5mmol)

and toluene-4-sulphonyl chloride (95mg, 0.5mmol) was added dimethyl formamide (1.5ml). The reaction was complete after 1h: δ 2.32 (3H, s, $ArCH_3$), 6.46 (1H, dd, J 13.8Hz, =CHCHO), 7.56 (2H, d, J 8Hz, Ar-H), 7.66 (2H, d, J 8Hz, Ar-H), 8.0 (1H, d, J 13Hz, =CHO-), 9.5 (1H, d, J 8Hz, -CHO). Attempts to isolate the product were unsuccessful due to decomposition.

Preparation of 3,3-Bis-N-Anilino-1-(toluene-4-sulphonyloxy)-propene (104) and 3-(N-Anilino)propenal (103)

To a stirred suspension of the potassium salt of malonaldehyde (165mg, 1.5mmol) in dry ether (1 5ml) was added a solution of toluene-4-sulphonyl chloride (285mg, 1.5mmol) in ether (1.5ml). After 1h a solution of aniline (141mg, 1.5mmol) in ether (1ml) was added. A yellow solid precipitated immediately. The reaction was stirred for 1h, and filtered. The solid was recrystallised from ether and light petroleum to yield the tosyloxypropene derivative (104) as orange needles (315mg, 53%), m.p. 195-196°; ν_{max} 1640, 1590, 1498, 1218cm^{-1}; λ_{max} (EtOH) 372 and 242nm (ε 13000 and 3100); δ 2.13 (3H, s, CH_3Ar), 6.33-6.66 (1H, m, CH=), 7.18-7.98 (15H, bs, Ph+=CH), 8.73 (1H, unresolved d, -CHO); m/e 222 (M^+-72, 100%), 221, 145, 130, 109, 77. (Found: C, 67.18; H, 5.76; N, 7.37. $C_{22}H_{22}N_2O_3S$ requires C, 66.98; H, 5.62; N, 7.10%).

The filtrate was evaporated and p.l.c. (80% ether/light petroleum) of the residue gave the propenal derivative (103) (48mg, 23%), which was recrystallised from benzene and light petroleum to give yellow plates, m.p. 122-123°; ν_{max} 3400, 2820, 1640, 1570, 998cm^{-1}; λ_{max} (EtOH) 225 and 322nm

(ε 9300 and 40300); δ 1.01 (1H, bs, ArNH), 5.02 (1H, dd, J 7.1Hz, =CHCHO), 5.61 (1H, dd, J 12, 7Hz, =CHNH), 7.0 (5H, m, ArH), 9.33 (1H, m, -CHO); m/e 147 (M^+, 100%), 119, 93, 78,69. (Found: C,73.11; H, 6.04; N, 9.64. C_9H_9NO requires C, 73.44; H, 6.16; N, 9.51%).

Preparation of (E)-3-(Ethoxycarbonyl)propenal (108)

To a suspension of the potassium salt of malonaldehyde (550mg, 5mmol) in ether (3ml) was added a solution of ethyl chloroformate (400mg,3.38mmol) in ether (2ml). Filtration and distillation gave (380mg, 52%), b.p. 84-86°/ 20mmHg (lit.[40] b.p. 61-63.5°/ 1.5mmHg).

Preparation of 3-(N-Anilino)-propenal (103) using the Propenal Derivative (108)

To a solution of E-3-(ethoxycarbonyloxy)propenal (108) (144mg, 1mmol) in ethanol (1ml) was added a solution of aniline (93mg, 1mmol) in ethanol (1ml), at 10°, under nitrogen. The mixture was stirred for 4h, at room temperature. The ethanol was removed in vacuo, and the residue purified by p.l.c. (80% ether/ light petroleum) to give the propenal derivative (103) (31mg,34%) identical to the compound described above

Preparation of 3-(Isopropoxycarbonyloxy)propenal (109)

To a stirred suspension of the potassium salt of malonaldehyde (110mg, 1mmol) in dry ether (1ml) was added

a solution of isopropyl chloroformate[56] (61mg, 0.5ml) in dry ether (1ml). The mixture was stirred for 1h, the inorganic salts were removed by filtration, and the ether was evaporated *in vacuo*. The residue was distilled to yield the carbonate (116mg, 74%), b.p. 72-74°/ 1.5 mmHg; ν_{max} 1780, 1688, 1650, 1320cm^{-1}; λ_{max} (EtOH) 229nm (ε 30600); δ 1.36 (6H, d, *J* 6Hz, $(CH_3)_2CH$), 5.03 (1H, septet, $(CH_3)_2CH$), 6.0 (1H, dd, *J* 12, 8Hz, =C*H*CHO), 7 93 (1H, d, *J* 8Hz, -OCH=), 9 06 (1H, d, *J* 12Hz, -CHO); m/e 158 (M^+), 157, 137, 113, 97, 71 (100%). (Found: C, 52.98; H, 6.22. $C_7H_{10}O_4$ requires C, 53.16; H, 6.37%).

Preparation of 3-(N-Anilino)propenal (103) using the Propenal Derivative (109)

To a solution of 3-(isopropyloxycarbonyloxy)propenal (447mg, 2.82mmol) in ethanol (2ml) was gradually added a solution of aniline (282mg, 3.0mmol) in ethanol (2ml) at 10°. The mixture was stirred overnight, ethanol removed *in vacuo*, and the residue purified by p.l.c. (80% ether / light petroleum) to give the pure propenal (103) (375mg, 85%), identical with the compound reported above.

Preparation of 3-(N-Allylanilino)propenal (111)

To a stirred suspension of sodium hydride (99mg of a 80% dispersion in oil, 3mmol) in THF (2ml) was added a solution of 3-(N-anilino)propenal (103) (61mg, 0.4mmol) in THF. The mixture was stirred overnight, under nitrogen, and allyl

bromide (245mg, 2mmol) in THF (1ml) was added. The mixture was stirred for 5h, and worked up as usual. A fine solid was obtained (60mg, 78%). Crystallisation from ether and light petroleum (1:9) gave the enamine (111) as yellow needles (42mg, 53%), m.p. 57-58°; ν_{max} 2920, 1648, 1610, 1588cm^{-1}; λ_{max} (EtOH) 302 and 226nm (ε 28400 and 9900); δ 4.20 (2H, unresoved d, $CH_2CH=$), 4.93-6.23 (4H, m, $NCH_2C\underline{H}=C\underline{H}_2$ + $+C\underline{H}CHO$), 6.66-7.66 (6H, br, ArH + NCH=), 8.63 (1H, d, J 8Hz, -CHO); m/e 187 (M^+), 159, 158, 144, 133, 93, 73(100%). (Found: C, 77.10; H, 7.06; N, 7.22. $C_{12}H_{13}NO$ requires C, 76.96; H, 7.00; N, 7.48%).

Preparation of 7-(N-Phenylimino)-4-oxa-1,5-heptadiene (112)

To a stirred suspension of sodium hydride (80mg of an 80% dispersion in oil, 2.6mmol) in THF (2ml) under nitrogen was added a solution of 3-(N-anilino)propenal (80mg, 0.42 mmol) in THF (1ml). The solution was stirred for 2h, and allyl bromide (65mg, 0.5mmol) in THF (1ml) was added. The mixture was heated to reflux for 3h, cooled and worked up as usual. P.l c. (20% ether/ light petroleum) gave a product plausibly, the aniline derivative as white needles (10mg, 10%), m.p. 55-57°; ν_{max} 3380,2900, 2825, 1640, 1610cm^{-1}; λ_{max} (EtOH) 270 and 302nm (ε 10600 and 10650); δ 3.75 (2H, m, $OC\underline{H}_2CH=$), 4.61 (2H, m, $C\underline{H}_2=CH-$), 4.88-6.01 (3H, m, $\underline{H}C=C\underline{H}O-$ + $C\underline{H}=CH_2$), 6.58 (1H, m, -CH=N), 7.23 (5H, br, ArH); m/e 187 (M^+), 159, 146, 119, 83 (100%).

Confirmation of the Structure of the Propenal Derivative (111)

a) To a stirred solution of 3-(isopropyloxycarbonyloxy)propenal (109) (158mg, 1mmol) in ethanol (2ml) was added N-allylaniline[57] (133mg, 1.1mmol) in a dilute solution of sodium hydrogen carbonate. The mixture was stirred overnight, ethanol evaporated, and the residue purified by p.l.c. (10% ethanol / light petroleum) to give (111) (19mg, 11%) identical with the material described above

b) To a solution of 3-(N-allylanilino)propenal (111) (40mg, 0.2mmol) in THF (1ml) was added a solution of sulphuric acid (10%) in THF (2ml,1:1). The solution was heated to reflux for 2 days. Evaporation of the solvent gave an oil, which was treated with toluene-4-sulphonyl chloride (100mg, 0.52 mmol) and a solution of potassium hydroxide 2N (1ml). Acidification and work up gave the N-allyl-p-toluenesulphonanilide (113), m.p. 67-68° (lit.[41] m.p. 69°).

Attempted Rearrangement of 3-(N-Allylanilino)propenal (111)

3-(N-Allylanilino)propenal (111) (100mg) was heated in a kinetic flask for 1h at 80° using ethylene dichloride. Polymeric material was obtained, none of which could be identified.

Preparation of (E)-3-Ethoxypropenal (114)

3-(Ethoxycarbonyloxy)propenal (108) (282mg, 2mmol) in

dry ether (2ml) was treated with a few crystals of toluene-4-sulphonic acid anhdrous to give after complete evolution of carbon dioxide and work up the aldehyde (114) (144mg, 72%) b.p. 80-82° / 16 mmHg; (lit.[58], b.p. 54-55° / 5mmHg).

Reaction of (E)-3-Ethoxypropenal with Acetone in the presence of Pyrrolidine

To a solution of 3-ethoxypropenal (114) (72mg, 0.72 mmol) in dry benzene (1ml) was added acetone (42mg, 072mmol) and pyrrolidine (51mg, 0.72mmol) in benzene (1ml). The mixture was heated to reflux for 3 days, cooled, the solvent evaporated, and the residue purified by p.l.c. (50% ether/ light petroleum). The product was obtained as an oil (56mg, 62%) b.p. 110-112°/ 0.1 mmHg and identified as 3-(N-pyrrolidino)propenal (115), ν_{max} 2840, 1598, 1400, 1114cm^{-1}; λ_{max} (EtOH) 289nm (ε 22500) δ 2.0 (4H, bs, 2xCH_2-), 3.32 (4H, bs, 2xNCH_2-, 5.06 (1H, dd, J 13, 8Hz, -CH=), 7 23(1H, d, J 13Hz, NCH=), 9.1 (1H, d, J 8Hz, -CHO); m/e 125 (M^+, 100%), 108, 96, 85, 83, 69. (Found: C, 67.01; H, 8.76; N, 10.93. $C_7H_{11}NO$ requires C, 67.16; H, 8.85; N, 11.19%).

Preparation of 3-(Allyloxycarbonyloxy)propenal (116)

To a stirred suspension of the potassium salt of malonaldehyde (550mg, 5mmol) in anhydrous ether (2ml) was added allyl chloroformate[59] (600mg, 5mmol). The mixture was stirred for 1h, the inorganic salts were removed by filtration, and

the ether evaporated in vacuum. The residue was fractionally distilled to yield the pure carbonate (116) (752mg, 58%), b.p. 48-50° / 2mmHg; ν_{max} 1778, 1690, 1648, 1368, 940cm^{-1}; λ_{max} (EtOH) 225 nm (ε 12000); δ 4.73 (2H, d, J 5Hz, OCH_2-), 5.01-6.02 (4H, m, $=CH_2$ + $-CH=CH_2$ + $OHCCH=$), 7.93 (1H, d, J 12Hz, $OCH=$), 9.63 (1H, d, J 8Hz, -CHO); m/e 156 (M^+), 111,97, 83, 71, 58, 41 (100%). Found: C, 53.72; H, 4.96. $C_7H_8O_4$ requires C, 53.84; H, 5.16%).

Preparation of 3-(Allyloxy)propenal (117)

To a solution of 3-(allyloxycarbonyloxy)propenal (116) (541mg, 3.5mmol) in dichloromethane (4ml) at 25-30°, was added toluene-4-sulphonic acid anhydrous (10mg). Vigorous evolution of carbon dioxide ensued. When the decomposition was complete, the solution was worked up as usual. The residue was purified by p.l.c. (30% ether / light petroleum) to give the pure propenal derivative (117) (258mg, 68%), b.p. 40°/ 0.3 mmHg; ν_{max} 2815, 1670, 1635, 1615, 1140cm^{-1}; λ_{max} (EtOH) 239 nm (ε 19200); δ 4.5 (2H, d, J 5Hz, $-CH_2O$), 5.0-6.36 (4H, m, $=CH_2$ + $HC=CH_2$ + $OHCCH=$), 7.38 (1H, d, J 12Hz, $OCH=$), 9.41 (1H, d, J 8Hz, -CHO); m/e 112 (M^+), 83, 71 (100%), 57, 41. (Found: C, 64.12; H, 7.22. $C_6H_8O_2$ requires C, 64.27; H, 7.19%).

Attempted Rearrangement of 3-(Allyloxy)propenal

3-(Allyloxy)propenal (117) (500mg) was heated to 110°, in the presence of hydroquinone (10mg) in a kinetic flask.

Aloquots were removed at regular intervals of 1h and checked by u.v., after treatment with a dilute solution of potassium hydroxide (10%, 1ml). The wavelenght changed from the initial value of 239 to 265nm with an extinction calue of 11000. However the extinction value declined with further heating, and t.l.c. showed polymeric material.

Reaction between Butyraldehyde and N-Chloromethylene-N,N-dimethylammonium Chloride (96)

N,N-Dimethylformamide (5.84g, 80mmol) was added to a solution of phosgene in dichloromethane (50% w/v, 40ml) with stirring. After 30 minutes at room temperature, the solvent was evaporated in vacuo and the residue suspended in dichloromethane (40ml). A solution of n-butyraldehyde (3.6g, 50mmol) in dichloromethane (5ml) was added slowly. N-Chloromethylene-N,N-dimethylammonium chloride dissolved after a few minutes, and the solution was heated to reflux for 2h. After cooling the reaction was quenched by the addition of a saturated solution of potassium carbonate (20%, 30ml) and ice. The organic phase was separated, and the aqueous phase saturated with solid potassium carbonate (15g), and extracted with ether. The solvent was removed in vacuo and distillation gave plausibly the 1-chloro-1-formyloxy-butane (120) (4.1g, 61%), b.p. 60°/ 10 mmHg; ν_{max} 3415, 2824, 1735, 1682, 1355cm^{-1}; δ 1.0 (3H, t, J 6Hz, $CH_2\underline{CH_3}$), 1.16-2.33 (4H, m, $CH_3\underline{CH2}$ + $\underline{CH_2}CHCl$), 6.53 (1H, t, J 6Hz, CHCl), 8.06 (1H, s,-CHO); m/e 101 (M^+-35), 9o, 73, 65, 55 (100%).

Preparation of 2-(N,N-Dimethylaminomethylene)butanal (122) and 2-(Ethoxymethylene)butanal (123)

The Vilsmeier salt was prepared as above using N,N-dimethylformamide (3.65g, 50mmol) and phosgene (5.1g, 55mmol). A solution of butyraldehyde diethyl acetal (121) (2.9g, 20 mmol) was slowly added to the suspended salt in dichloromethane (20ml). The suspension was heated to reflux for 4h and worked up as above. Distillation, b.p. 85-87° / 1mmHg gave an oil (1.587g) which by n.m.r. was a mixture of two components in the ratio of 2:3 (ethoxymethylene derivative (123): dimethylamino derivative (122)). Each was separated and purified by p.l.c., 2-ethoxymethylene)butanal by silica p.l.c. (20% ether/ light petroleum) while 2-(N,N-dimethylaminomethylene)butanal by alumina p.l.c. 15% ether/ light petroleum. 2-(ethoxymethylene)butanal δ 1.06 (3H, t, J 7Hz, CH_3CH_2-), 1.43 (3H, t, J 6Hz, CH_3CH_2O-), 2.5 (2H, q, J 7Hz, CH_3CH_2-), 4.46 (2H, q, J 6Hz, CH_3CH_2O-), 7.06 (1H, s, =CH-), 9.16 (1H, s, -CHO). b.p. 90-92° / 1mmHg, (lit.[36] 102-105° / 13mmHg; 2-(N,N-dimethylaminomethylene)butanal: δ 1.13 (3H, t, J 7Hz, CH_3CH_2-), 2.3 (2H, q, J 7Hz, CH_3CH_2-), 3.26 (6H, s, $(CH_3)_2N$-), 6.83 (1H, s, =CH-), 8.73 (1H, s, -CHO); b.p. 90-92° / 0.3mmHg (lit.[36] 80° / 0.1mmHg).

Preparation of 2-Propyl-(1,3-dioxolane) (124)

To a solution of butyraldehyde (10g, 0.13mol) in benzene (80ml) was added a solution of ethylene glycol (9.9g, 0.14mol) and anhydrous toluene-4-sulphonic acid (1.2g, 6.9mmol). The

solution was heated to reflux for 6h using a soxhlet apparatus filled with activated Linde type 4a molecular sieves (20g). After cooling the reaction was worked up as usual. Fractional distillation of the residue gave the pure dioxolane (124) (9.3g, 57%), b.p. 40°/ 15mmHg; ν_{max} 3455, 2843, 2770, 1450, 1100cm^{-1} ; δ 0.96 (3H, t, J 6Hz, $C\underline{H}_3CH_2$-), 1.2-1.63 (4H, m, $CH_3C\underline{H}_2$- + $C\underline{H}_2CH$-), 3.73 (4H, d, J 3Hz, OCH_2CH_2O-), 4.63 (1H, t, J 4Hz, $CHCH_2$); m/e 116 (M^+), 115, 86, 73(100%). (Found: C, 61.76; H, 10,47. $C_6H_{12}O_2$ requires C, 62.04; H, 10.41%).

Preparation of 2-(2-Chloroethoxymethylene)butanal (125)

N,N-Dimethylformamide (5.84g, 80mmol) was added to a solution of phosgene in dichloromethane (25% w/v, 40ml) with stirring. After 30 minutes at room temperature, the solvent was evaporated in vacuo, and the residue was stirred in dichloromethane (40ml). A solution of the acetal (124) (3.92g, 34mmol) was slowly added and the mixture heated to reflux. After 1h, the Vilsmeier salt dissolved and the solution was heated to reflux overnight. The mixture was cooled and hydrolysed by slowly pouring into a buffer solution (pH 9). The organic phase was separated, and the aqueous phase was saturated with solid potassium carbonate and extracted with ether. The organic phases were combined, washed with brine, dried, and the solvent evaporated in vacuo. Distillation gave (a mixture of 2 products) (3.97g), in the ratio 1:9 (n.m.r. and u.v.). Fractional distillation gave as the smaller fraction 2-(N,N-dimethylaminomethy-

lene)butanal (122) identical with the compound described previously, while the major product was identified as the 2-(2-chloroethoxymethylene)butanal (125) (3.5g, 64%), b.p. 110° / 1.5mmHg; ν_{max} (EtOH) 248nm (ε 18400); δ 1.0 (3H, t, J 7Hz, $C\underline{H}_3CH_2$-), 2.25 (2H, q, J 7Hz, $CH_3C\underline{H}_2$-), 3.76 (2H, t, J 6Hz, $OC\underline{H}_2CH_2$), 4 40 (2H, t, J 6Hz, CH_2CH_2Cl), 6.96 (1H, s, =CH), 9.16 (1H, s, -CHO); m/e 164, 162 (M^+), 149,147,127,100, 99 (100%). (Found: C, 51.55; H, 6.88. $C_7H_{11}ClO_2$ requires C, 51.70; H, 6.82%).

Attempted Reaction of the Chloroethoxyaldehyde (125) with Dimethyl Malonate

To a solution of 2-(2-chloroethoxymethylene)butanal (125) (100mg, 0.61mmol) in pyridine (2ml) was added a solution of dimethyl malonate (161mg, 1.2mmol). The reaction was stirred overnight at room temperature, and heated to reflux for 2h. T.l.c. and n.m.r. showed a complex mixture of products and hence no attempt was made at separation.

Preparation of 2-(piperidinomethylene)butanal (126)

To a solution of 2-(2-chloroethoxymethylene)butanal (410mg, 2.5mmol) in pyridine (2ml) was added a solution of piperidine (225mg, 2.67mmol) in pyridine (1ml). The reaction was refluxed for 2h, cooled and the solvent evaporated in vacuo. P.l.c. (90% ether / light petroleum) gave the piperidine derivative (126)(344mg, 84%), as an oil b.p. 82-84° / 0.1 mmHg; ν_{max} 2952, 2948, 2750, 1594cm^{-1}; λ_{max} (EtOH) 292nm (ε 31400); δ

1.0 (3H, t, J 7Hz, $CH_3\underline{CH_2}$-), 1.66 (6H, bs, 3xCH_2-), 2.38 (2H, q, J 7Hz, $CH_3\underline{CH_2}$-), 3 43 (4H, bs, 2xCH_2N), 6.4 (1H, s, CH=), 8 83 (1H, s, -CHO); m/e 167 (M^+), 152 (100%), 150, 138, 124. (Found: C, 71.67; H, 10.36; N, 8.20. $C_{10}H_{17}NO$ requires C, 71.87; H, 10.25; N, 8.37%).

Preparation of Ethyl 4-(2-Chloroethoxymethylene)-2-hexenoate (129)

a. Using Carboethoxymethyl triphenylphosphonium Bromide (127)

To a suspension of the salt[60] (127) (729mg, 1.28mmol) in dichloromethane (2ml) was added propylene oxide (269mg, 4.71 mmol). The mixture was stirred overnight, before the aldehyde (125) (208mg, 1.28mmol) was added, and the reaction stirred for 2 days. Filtration, evaporation of the solvent, and distillation gave the pure carboxylate (129) (122mg, 41%), b.p. 68-70° / 0.02mmHg; ν_{max} 2920, 2870, 1705, 1645, 1630, 1605, 980cm^{-1}, λ_{max} (EtOH) 288 nm (ε 18600); δ 1.0 (3H, t, J 7Hz, $C\underline{H_3}CH_2$-), 1.26 (3H, t, J 7Hz, $C\underline{H_3}CH_2O$-), 2.25 (2H, q, J 7Hz, $CH_3\underline{CH_2}$-), 3.75 (2H, t, J 6Hz, CH_2O-), 4.06 (2H, q, J 7Hz, $CH_3\underline{CH_2}O$-), 4.40 (2H, t, J 6Hz, CH_2Cl), 5.70 (1H, d, J 15Hz, =CH-), 6.43 (1H, s, =CHO-), 7.23 (1H, d, J 15Hz, =CH); m/e 157 (M^+-75, 100%), 127, 111, 99, 83, 57. (Found: C,56.60; H, 7.52. $C_{11}H_{17}ClO_3$ requires C, 56.78; H, 7.36%).

b. Using Triethyl Phosphonoacetate (128)

To a stirred suspension of sodium hydride (201mg of a 50% dispersion in oil, 4.18mmol) in T.H.F. (1ml) was added a solution of triethyl phosphonoacetate (896mg, 4mmol) in THF

(2ml) under nitrogen. The mixture was stirred at room temperature, until no more hydrogen was evolved. The solution was slowly added to the aldehyde (125) (650mg, 4mmol) in THF (1ml). The reaction mixture was stirred overnight, and poured into water, extracted with ether, and washed with brine and dried. Evaporation of the solvent and distillation gave the adduct (290mg, 32%) identical to the compound described previously by i.r., u.v., and n.m.r. spectroscopy.
Propylene oxide as acid scavenger gave no reaction, and the starting aldehyde was recovered quantitavely.

Attempted addition of Lithium Dimethylcuprate to the Carboxylate (129)

To a stirred solution of dry copper iodide (130mg, 0.68 mmol) in ether (1ml) at -15^0 under nitrogen, was added a solution of methyllithium (1.44M, 1ml) in ether. The solution soon became colourless, and was warmed to 0^0, and added to the dienoate in THF (2ml). After warming to room temperature, the mixture was stirred overnight, and the solution poured into ammonium chloride. Extraction with ether in the usual way gave after evaporation a crude product which by n.m.r. contained mostly starting material. T.l.c. also showed mostly a compound identical to the starting material.

Attempted condensation between the aldehyde (125) and the Phosphonate (130)

To a stirred suspension of sodium hydride (96mg of a 50% dispersion in oil, 2mmol) in dimethoxyethane (1ml) was added a solution of the phosphonate[61] (1ml). The mixture was stirred at room temperature until no more hydrogen was evolved, and added to a solution of the aldehyde (125) (200mg, 1.23mmol) in dimethoxyethane (1ml). The reaction mixture was stirred for 5h at room temperature and heated to reflux for 2 days. The solution was cooled and solvent removed *in vacuo* but n.m.r. showed only starting material, of which 92% was recovered.

Preparation of Diethyl 2-Bromo-2-propenylphosphonate (131)

Freshly distilled 2,3-dibromopropane (16.4g, 0.06mmol) (prepared by bromination of allyl bromide in carbon tetrachloride[62], and dehydrobromination using sodium hydroxide in water[63]) was slowly added to triethyl phosphite (10,4g, 0.06mmol) while heating to 130°. Ethyl bromide slowly distilled off. Distillation of the product gave the bromopropenyl phosphonate (131) (12.1g, 81%), b.p. 90-92° / 0.7mmHg (lit.[46] 98° / 1mmHg).

Preparation of Diethyl 2-Ethoxy-1-propenylphosphonate (132)

Diethyl 2-bromo-2propenylphosphonate (131) (11.8g, 0.046 mmol) was added at room temperature under nitrogen to a solution of sodium ethoxide (from sodium (1.2g, 0.05mmol)) in ethanol (35ml). A precipitate separated very quickly, and the suspension was heated to reflux overnight. After cooling,

the ethanol was removed and the mixture was worked up as usual. Distillation gave the phosphonate (132) (5.7g, 46%) b p. 104-106°/ 1mmHg (lit.[46] 98°/ 0.9mmHg).

Preparation of 4-Phenyl-3-buten-2-one(134)

a. Using n-Butyllithium

To a solution of the phosphonate (132) (224mg, 1mmol) in THF (1.5ml) was added at -40° a solution of n-butyllithium (1.5M, 0.66ml). The mixture was stirred for 1h at -40° and a solution of benzaldehyde (106mg, 1mmol) in THF (1ml) was slowly added. The reaction was slowly warmed to room temperature and left overnight. Evaporation of the solvent, and the usual work up gave a residue which was subjected to silica column chromatography (10% ether / light petroleum) to give the enone (134) (25mg, 17%); ν_{max} 1670, 1630,1612, 1580, 1450 1360, 972cm^{-1} ; δ 2.33 (3H, s, $CH_3C(=O)$), 6.68 (1H, d, J 16Hz, $=CHC(=O)$), 7.45 (6H, b , ArH + CH=) (c.f.lit.[64] 2.35 (3H, s, $CH_3C(=O)$); 6.70 (1H, d, J 16Hz, $=CHC(=O)$), 7.48 (6H, b , ArH + CH=).

b. Using Sodium Hydride

To a suspension of sodium hydride (72% of a 50% dispersion in oil, 1.5mmol) in a mixture of hexamethylphosphoric triamide/ benzene (1:1), (1ml) was added the phosphonate (132) (164mg, 0.73mmol) in the same solvent system (1ml). The mixture was heated to 50° until no more evolution was observed, after which, the solution was cooled to 0°, and a solution of benzaldehyde (78mg, 0.73mmol) in the same solvent mixture was

added (1ml). The reaction mixture was stirred for 2h at room temperature and then warmed to 60° for 5h. After cooling, usual work up and silica chromatography gave (25mg, 33%) pure product (134) identical with the compound reported above; δ 2.34 (3H, s, $CH_3C(=O)$), 6.68 (1H, d, J 16Hz, $=CHC(=O)$), 7.45 (6H, b., ArH, + -CH=); (c.f. lit.[64] 2.35 (3H, s, $CH_3C(=O)$), 6.70 (1H, d, J 16Hz, $=CHC(=O)$), 7.48 (6H, b, ArH + -CH=).

c. Using Sodium Hexamethyldisilazine

To a solution of the phosphonate (132) (224mg, 1mmol) in THF (1ml) at -20° was added a solution of the sodium salt of hexadimethyldisilazine (183mg, 1mmol) in THF (1ml). The solution was warmed to room temperature, and stirred for 5h Usual work up and chromatography yielded benzalacetone (134) (22mg, 15%) identical with the compound reported above; δ 2.33 (3H, s, $CH_3C(=O)$), 6.68 (1H, d, J 16Hz, $=CHC(=O)$), 7.45 (6H, br, ArH + -CH=); (c.f. lit.[64] 2.35 (3H, s, $CH_3C(=O)$), 6.70 (1H, d, J 16Hz, $=CHC(=O)$), 7.48 (6H, b, ArH + -CH=)

Preparation of 2-Propyl-1,3-dithiolane (135)

To a stirred refluxing solution of n-butyraldehyde (6.4g, 88mmol) and ethane-1,2-dithiol (8.6g, 91mmol) in anhydrous ether (80ml) was added dropwise, over 10 minutes, boron trifluoride etherate (12.6g, 88mmol). After an additional hour of reflux, the solution was allowed to cool, and worked up as usual. The solvent was removed in vacuo and distillation gave the pure dithiolane (135) (9.7g, 81%), b.p 95-97° / 10 mmHg; ν_{max} 2915, 2876, 1458, 1425, 1383cm^{-1}; δ 0.96 (3H, unresolved t, CH_3CH_2-)

1.16-2.13 (4H, m, $CH_3C\underline{H}_2$- + $C\underline{H}_2CH$-), 3.2 (4H, s, 2xCH_2S-), 4.43 (1H, t, J 6Hz, $CH_2C\underline{H}$-); m/e 148 (M^+), 105 (100%), 89, 71 61. (Found: C, 48.64; H, 8.28 $C_6H_{12}S_2$ requires C, 48.59; H, 8.15%).

Preparation of 2-(1-formylpropyl)1,3-dithiolane (136)

N,N-Dimethylformamide (9.17g, 125mmol) was added to a solution of phosgene in dichloromethane (20% w/v, 100ml) with stirring. After 30 minutes at room temperature, the solvent was evaporated in vacuo and the residue was stirred in dichloromethane (100ml). A solution of 2-propyl-1,3dithiolane (7.5g, 50mmol) was slowly added, and soon after, anhydrous toluene-4-sulphonic acid (860mg, 5mmol) was added to the suspension. The reaction mixture was heated to reflux for 12h cooled and worked up by addition of a saturated solution of sodium hydrogen carbonate and ice. The organic phase was separated, washed with brine and dried. Evaporation of the solvent and distillation gave the formylation product (136) (6.8g, 77%) b.p. 93-95^0/ 0.1 mmHg; ν_{max} 2904, 2828, 2720, 1713, 1390, 1140, 980cm^{-1}; δ 0.95 (3H, t, J 7Hz, $C\underline{H}_3CH_2$-), 1.76 (2H, m, $CH_3C\underline{H}_2$-), 2.33-2.83 (1H, m, -CHCH(=O)), 3.2 (4H, s, 2 CH_2S-), 4.66 (1H, d, J 7Hz, $CH_2C\underline{H}$-), 9.73 (1H, d, J 2Hz, -CHO); m/e 176 (M^+), 147, 105 (100%), 88, 85, 83. (Found: C, 47.70; H, 7.00; S, 36.61. $C_7H_{12}OS_2$ requires C, 47.69; H, 6.86; S, 36.37%).

Attempted Oxidation of the Dithiolane (136).

To a solution of 2-(1-formylpropyl)-1,3-dithiolane (136)

(176mg, 1mmol) in THF (2ml) was added a solution of benzeneseleninic anhydride (360mg, 1mmol) in THF (1.5ml). The reaction mixture was stirred overnight at room temperature. Evaporation of the solvent afforded a crude residue, the n.m.r. of which showed no signals in the aldehydic region. T.l.c. showed a great number of compounds, none of which was identifiable.

Preparation of 2-(1-Ethoxypent-1-en-3-yl)-1,3-dithiolane (138)

To a rapidly stirred suspension of ethoxymethyltriphenylphosphonium chloride (1.42g, 4mmol) in THF (3ml) was added under nitrogen a solution of n-butyllithium (1.58M, 2.65ml). The mixture was stirred for 30 minutes, and a solution of the dithiolane (136) (665mg, 3.77mmol) in THF (2ml) was slowly added. Stirring was continued overnight at room temperature; the suspended solid was removed by filtration, and the solvent removed in vacuo. P.l.c. (3%ether/ light petroleum) and distillation gave the enol ether (138) (543mg, 66%), b.p. 90-92°/ 2mmHg; ν_{max} 2905, 2860, 1668, 1648, 1501, 1380, 930, 910cm^{-1}; λ_{max} 210 nm (ε 8500); δ 0.93 (3H, t, J 7Hz, CH_3CH_2-), 1.23 (3H, t, J 7Hz, CH_3CH_2O-), 1.50-2.35 (3H, m, CH_3CH_2- + CH_2CH-), 3.15 (4H, s, 2xCH_2S-), 3.70 (2H, q, J 7Hz, CH_3CH_2O-), 4.48 (1H, d, J 7Hz, CH_2CHS-), 4.51 (1H, dd, J 12, 8 Hz, CH=), 6.26 (1H, d, J 12Hz, =CH); m/e 218 (M^+), 173, 113 (100%), 105, 99, 85, 67. (Found: C, 55.29; H, 8.62. $C_{10}H_{18}OS_2$ requires C, 55.00; H, 8.30%).

Preparation of Ethyl 4-(1,3-Dithiolane-2-yl)-2-hexenoate (137)

a. Using Carboethoxymethyltriphenylphosphonium Bromide

To a stirred suspension of the salt (1.29g, 3.0mmol) in THF (4ml) was added propylene oxide (329mg, 5.7mmol) in THF (1ml). The reaction was stirred for 3h, after which a solution of the dithiolane (136) (500mg, 2.84mmol) in THF (2ml) was added. The reaction was stirred at room temperature for 2 days, the solid filtered off, and the solvent removed in vacuo. P.l.c (20% ether / light petroleum) and distillation gave the α,β-unsaturated ester (137) (520mg, 74%) b.p. 88-90° / 0.2 mmHg; ν_{max} 2924, 1714, 1654, 1458, 970, 853cm^{-1}; λ_{max} (EtOH) 208 nm (ε 11500); δ 0.9 (3H, t, J 7Hz, CH_3CH_2-), 1.30 (3H, t, J 7Hz, CH_3CH_2O-), 1.43-2.23 (3H, m, CH_3CH_2- + CHCH=), 3.18 (4H, s, 2xCH_2S-), 4.20 (2H, q, J 7Hz, CH_3CH_2O-), 4.57 (1H, d, J 7Hz, CH_2CHS_2), 5.87 (1H, d, J 16Hz, =CH), 6.83 (1H, dd, J 16.7Hz, CH=); m/e 246 (M^+), 201, 176 (100%), 147, 107, 105. (Found: C, 53.43; H 7.21; S, 25.96. $C_{11}H_{18}O_2S_2$ requires C, 53.62; H, 7.36; S, 26.02%).

b. Using Triethyl Phosphonate

To a stirred suspension of sodium hydride (96mg of a 50% dispersion in oil, 2mmol) in THF (1ml) was added a solution of the phosphonate (349mg, 1.55mmol) in THF (2ml). The mixture was stirred until evolution hydrogen ceased. A solution of the dithiolane (136) was added. The mixture was stirred

overnight at room temperature, diluted with water, and extracted with ether. The ether extracts were washed with brine and dried. P.l.c. and distillation gave (137) (159mg, 47%) identical with the compound reported above.

Attempted Oxidation of the Dithiolane (137)

a. To a solution of the dithiolane (137) (30mg, 0.12mmol) in THF (1ml) was added a solution of benzeneseleninicanhydride (43.2mg, 0.12mmol) in THF (0.5ml). The reaction was stirred for 1h, after which t.l.c. showed a mixture of products, none of which was identified as n.m.r. showed no peaks in the aldehydic region.

b. Similarly, a mixture of N-chlorosuccinimide and silver nitrate in acetonitrile-water failed to give the correct product. Likewise methyl iodide, mercuric chloride, mercuric oxide, and propylene oxide proved unsuccessful.

Preparation of 2-Propyl(1,3-oxathiolane (139)

To a refluxing solution of n-butyraldehyde (3.6g, 0.05 mol) and 2-mercaptoethanol (3.9g, 0.05mol) in anhydrous ether (30ml) was added a solution of boron trifluoride etherate (9g, 0.06mol). Reflux for 1h and usual work up gave the oxathiolane derivative (139) (6 02g, 61%); b p 50-51°/ 10 mmHg (lit.[65] 61-62°/ 18 mmHg).

Preparation of 2-(2-Hydroxyethylthiomethylene)butanal (140)

N,N-Dimethylformamide (2.04g, 27mmol) was added to a

solution of phosgene in dichloromethane (20% w/v, 20ml) with stirring. After 30 min at room temperature, the solvent was evaporated *in vacuo*, and the residue was stirred in dichloromethane (20ml). A solution of 2-propyl(1,3-oxathiolane) (1.5g 9.9mmol) was slowly added, and the reaction mixture heated to reflux for 12h. After cooling, the solution was worked up by addition to a saturated solution of sodium hydrogen carbonate and ice. The organic phase was separated, washed with brine, and dried. Evaporation and p.l.c. (80% ethyl acetate/ light petroleum) gave a solid which on recrystallisation (benzene in light petroleum) gave the aldehyde (140) as white plates (918mg, 52%), m.p. 50-52°; ν_{max} 3400, 2940, 2880, 2820, 1648, 1580cm^{-1}; λ_{max} (EtOH) 290 nm (ε 30600); δ 1.0 (3H, t, *J* 7Hz, CH_3CH_2-), 2.28 (2H, q, *J* 7Hz, CH_3CH_2-), 3.06 (2H, t, *J* 6Hz, CH_2S-), 3.88 (2H, t, *J* 6Hz, CH_2O-), 7.31 (1H, s, =CH), 9.26 (1H, s, -CHO); m/e 160 (M^+), 148, 130, 115 (100%), 89, 87, 71. (Found: C, 52.43; H, 7.52; S, 20.02. $C_7H_{12}O_2S$ requires C, 52.47; H, 7.54; S, 20.01%).

Confirmation of the structure of the Dithiolane (140)

To a solution of the dithiolane (140) (160mg, 1mmol) in anhydrous pyridine (2ml) was added acetic anhydride (1.5ml). The reaction was stirred overnight at room temperature and poured into ice-water, and extracted with ether. Rapid chromatography on silica gave the acetate (141) (169mg, 84%), b.p. 110°/ 0.8 mmHg; ν_{max} 2980, 2948, 1742, 1670, 1588, 1082, 913cm^{-1}; λ_{max} (EtOH) 287nm (ε 18900); δ 1.0 (3H, t, *J* 7Hz,

$C\underline{H}_3CH_2$-), 2.1 (3H, s, $CH_3C(=O)$), 2.17 (2H,, q, J 7Hz, $CH_3C\underline{H}_2$-), 3.13 (2H, t, J 6Hz, CH_2S-), 4.32 (2H, t, J 6Hz, CH_2O-), 7.23 (1H, s, =CH), 9.28 (1H, s, -CHO); m/e 202 (M^+), 159, 142, 127, 115 (100%), 99, 85.(Found: C, 53.68; H, 7.17; S, 15.64. $C_9H_{14}O_3S$ requires C, 53.44; H, 6.97; S, 15.85%).

Preparation of 2-(Chlromethylene)butanal (143)

a. From 2-(2-Chloroethoxymethylene)butanal (125)

To a solution of 2-(2-chloroethoxymethylene)butanal (125) (500mg, 3.07mmol) in dichloromethane (2ml) was added a solution of phosgene in dichloromethane (20% w/v, 5ml). The solution was stirred for 1h and was added to aqueous sodium hydrogen carbonate and ice, and extracted with ether. The organic phase was washed with brine, and dried. Evaporation of the solvent and distillation (50^0/ 20 mmHg) gave a mixtur of 2 products. Attempts to separate the two by distillation failed but one was plausibly 2-(chloromethylene) butanal (143). δ 1.03 (3H, t, J 7Hz, $C\underline{H}_3CH_2$-), 2.36 (2H, q, J 7Hz, $CH_3C\underline{H}_2$-), 7.01 (1H, s, =CH(Cl)), 9.36 (1H, s, -CHO).

b. From 2-(N,N-Dimethylaminomethylene)butanal (122)

To a solution of the butanal derivative (122) (254mg, 2mmol) in dichloromethane (2ml) was added phosgene (600mg). The solution was left for 1h and worked up as described previously. Distillation gave the vinylaldehyde (143) (189mg, 80%), b.p. 50^0/ 20mmHg (lit.[66] b.p. $50-55^0$/ 22 mmHg); 1.03 (3H, t, J 7Hz, $C\underline{H}_3CH_2$-), 2.36 (2H, q, J 7Hz, $CH_3C\underline{H}_2$-), 7.01 (1H, s, =CH(Cl), 9.36 (1H, s, CH(=O)).

Preparation of 5-(Chloromethylene)-3-hepten-2-one (144) and 3,9-(Chloromethylene)-4,7-undecadiene-6-one (145)

a. By Inverse addition

To a stirred suspension of sodium hydride (305mg of a 50% dispersion in oil, 6.3mmol) in dimethoxyethane (3ml) was added a solution of diethyl 2-oxopropyl phosphonate (1.2g, 6.3mmol) in dimethoxyethane (1ml). The mixture was stirred at room temperature until no more hydrogen was evolved, and added to the aldehyde (143) (720mg, 6.3mmol) in dimethoxyethane (1ml). The reaction was stirred overnight at room temperature, after which it was poured into water, and extracted with ether. The organic phase was separated, washed with brine, and dried. Evaporation of the solvent and p.l.c. (20% ether / light petroleum) of the residue gave two major bands. The less polar band was identified as the undecadiene (145) (237mg, 24%), m.p. 80-81°; ν_{max} 2940, 2880, 1740, 1700, 1605, 1320, 980cm^{-1}; λ_{max} (EtOH) 313 nm (ε 6300); δ 1.06 (6H, t, J 7Hz, 2xCH_3CH_2-), 2.46 (4H, q, J 7Hz, 2xCH_3CH_2-), 6.4 (2H, s, 2x=CH(Cl)), 6.41 (2H, d, J 16Hz, 2x=CH), 7.66 (2H, d, J 16Hz, 2x=CH=CH(Cl)), m/e 258 (M^+), 223 (100%), 195, 187, 159, 143. (Found: C, 60.27; H, 6.38. $C_{13}H_{16}Cl_2O$ requires C, 60.24; H, 6.22%).

The more polar band was identified as the dienone (144) (200mg, 20%), b p. 50°/ 0.5 mmHg; ν_{max} 2930, 2880, 1678, 1613, 1350, 970cm^{-1}; λ_{max} (EtOH) 276nm (ε 11700); δ 1.07 (3H, t, J 7Hz, CH_3CH_2-), 2.3 (3H, s; $CH_3C(=O)$), 2.46 (2H, q, J 7Hz, CH_3CH_2O-), 6.17 (1H, d, J 16Hz, =CH-), 6.47 (1H, s, =CH(Cl)), 7.03 (1H, d, J 16Hz, =CHC=CH(Cl)); m/e 158 (M^+), 143, 123 (100%),

79. (Found: C, 60.31; H, 7.12; Cl, 22.61. $C_8H_{11}ClO$ requires C, 60.57; H, 6.99; Cl, 22.35%).

b. By Direct addition

Using the same conditions as above, the aldehyde (143) (700mg, 6.93mmol) was added to a solution of the salt (1.34g, 6.9mmol). Work up and distillation gave the dienone (144) (678mg, 62%) identical to the compound described above.

Attempted Rearrangement of 5-(Chloromethylene)-3-hepten-2-one (144)

To a solution of the dienone (40mg, 0.25mmol) in dichloromethane (0.5ml) was added stannic chloride (65mg, 0.25mmol). The solution was stirred overnight, but no cyclisation occured (by n.m.r.). Under the same conditions, boron trifluoride etherate (35.5mg, 0.25mmol), trifluoroacetic acid (27.5mg, 0.25mmol), N,N,N',N'-tetramethyl guanidine (28.7mg, 0.25mmol) and a saturated solution of hydrogen chloride in dichloromethane were used. No change was observed by n.m.r., and attempts to raise the temperature caused decomposition, from which no compound could be identified.

Preparation of Ethyl 6-(Chloromethylene)-5-hydroxy-3-oxo-octanoate (146)

To a stirred and cooled (0^0) suspension of sodium hydride (483mg of a 50% dispersion in oil, 10mmol) in THF (20ml), under nitrogen, was added dropwise ethyl acetoacetate (1.17g, 9mmol). The solution became colourless, and was stirred at 0^0 for 10 minutes. n-Butyllithium (6.6ml, 1.5M) was added

dropwise, and the orange solution stirred at 0^0 for another 10 minutes. The vinyl aldehyde (143) (1.06g, 9mmol) in THF (2ml) was added, and the reaction mixture was stirred at room temperature for 1h. The mixture was quenched with concentrated hydrochloric acid, diluted with water and extracted with ether. The organic phase was washed with brine, dried, and the solvents removed under reduced pressure. P.l.c. (30% ether/ light petroleum) and distillation of the material gave the octanoate (146) (1.51g, 68%), b.p. 110^0 / 0.1 mmHg ; ν_{max} 3500, 2860, 1740, 1714, 1635cm^{-1}; λ_{max} (EtOH) 245nm (ε 1500); δ 1.06 (3H, t, J 8Hz, $C\underline{H}_3CH_2$-), 1.24 (3H, t, J 7Hz, $C\underline{H}_3CH_2O$-), 2.07 (2H, q, J 8Hz, $CH_3C\underline{H}_2$-), 2.67 (2H, d, J 6Hz, $C\underline{H}_2CHOH$), 3.35 (2H, s, $COCH_2CO$), 4.13 (2H, q, J 7Hz, $CH_3C\underline{H}_2O$-), 4.5 (1H, t, J 6Hz, $C\underline{H}OH$), 6.08 (1H, s, CH(Cl)); m/e 230 (M^+-18), 213, 195, 167, 143, 121, 83 (100%). (Found: C, 53.01; H, 7.10. $C_{11}H_{17}ClO_4$ requires C, 53.12; H, 6.89%).

Preparation of Ethyl 6-(Chloromethylene)-3-oxo-4-octenoate (147)

To a solution of the hydroxy ester (147) (496mg, 2mmol) in benzene (2ml) was added a solution of thionyl chloride (357mg, 3mmol) in benzene (1ml). The solution was stirred for 5h at room temperature after which time it was poured into a saturated solution of sodium hydrogen carbonate, and extracted with ether. The organic phase was separated, washed, with brine, and dried. Evaporation of the solvent and p.l.c.

of the residue (5% ether / light petroleum) gave the unsaturated ester (147) (312mg, 68%), b.p. 95-97°/ 0.1 mmHg; ν_{max} 1740, 1690, 1640, 1600, 1572, 1301, 918cm^{-1}; λ_{max} (EtOH) 288nm (ε 19500); n.m.r. described in the discussion; m/e 230 (M^+), 213, 195 (100%), 167, 143, 130, 121, 102. (Found: C, 57.47; H, 6.65. $C_{11}H_{15}ClO_3$ requires C, 57.27; H, 6.55%).

Preparation of Ethyl 5-Ethyl-2-hydroxybenzoate (148)

To a solution of the ester (147) (115mg, 0.5mmol) in dioxane (1ml) was added a solution of pyrrolidine (35.5mg, 0.5mmol) in dioxane (1ml). The solution was heated to reflux for 2h cooled, poured into dilute hydrochloric acid (10%), and extracted with ether. The organic phase was separated, washed with brine, dried, and the sovent evaporated in vacuo. Distillation gave the phenolic ester (148) (79mg, 82%), b.p. 130-132°/ 0.1 mmHg; ν_{max} 3200, 2920, 1673, 1618, 1490cm^{-1}; λ_{max} (EtOH) 208, 238, 313 nm (ε 16800, 5700, 2500 respectively). δ 1.2 (3H, t, J 7Hz, $C\underline{H}_3CH_2$-), 1.4 (3H, t, J 7Hz, $C\underline{H}_3CH_2O$-), 2.58 (2H, q, J 7Hz, $CH_3C\underline{H}_2$-), 4.46 (2H, q, J 7Hz, $CH_3C\underline{H}_2O$-), 6.93 (1H, d, $J_{3,4}$ 7.2Hz, C3-H), 7.31 (1H, dd, $J_{4,3}$ 7.2Hz, $J_{4,6}$ 2Hz, C4-H), 7.65 (1H, d, $J_{6,4}$ 2Hz, C6-H); m/e 194 (M^+), 148 (100%), 133, 77. (Found: C, 67.81; H, 7.39. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27%).

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