SOME REACTIONS OF 2-VINYL HETEROCYCLES WITH ALLENYL 1,3-DIESTERS. AN APPROACH TO THE NAGILACTONE SKELETON.

A thesis presented by

COLIN PETER DELL

in partial fulfilment of the

requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

OF THE UNIVERSITY OF LONDON

Harwood Laboratory,
Department of Chemistry,
Imperial College,
London SW7.

October 1984

To my parents

ACKNOWLEDGEMENT

I would like to deeply thank my supervisor Dr. Ed Smith for his constant encouragement, support and enthusiasm throughout the last three years. Grateful thanks are also extended to the technical staff at Imperial College for mass spectral, nmr and microanalytical services and to my colleagues in the Harwood Laboratory, particularly Dr. Andy Hopkins and James Milligan, for their helpful suggestions. Special thanks go to Ian, John, Andy, Melanie, Helen, Linda, Dave, Mike and Nigel for making the bumpy ride a bit smoother. Thanks also to Dr. Dennis Warburton and the people in Pharmaceutical chemistry A and Corporate Chemistry at May and Baker who made my short time there most enjoyable. Finally, thanks go to Mrs. G. Onslow-Major of Acorn Answering for the excellent typing of this thesis.

ABSTRACT

The thermal reaction of 4-(2'-furyl)but-3-en-2-yl acetate with dimethyl penta-2,3-dienedioate leads to products derived either from [4+2] cycloaddition across the endocyclic furan diene (at lower temperatures) or from electrophilic substitution into the free 5 position of the furan ring (at higher temperatures). Thermolysis of the [4+2] cycloaddition product at higher temperature results in decomposition rather than re-arrangement to the electrophilic substitution product. Similarly, 4-(5'-methyl 2'-furyl)but-3-en-2-yl acetate undergoes [4+2] cycloaddition with the allene across the endocyclic diene. At higher temperatures only decomposition of the starting material is observed. In no instance is cycloaddition of the allene across the exocyclic diene system observed.

With the analogous pair of 2-vinyl thiophenes, no [4+2] cycloadducts nor electrophilic substitution products are observed.

Substrates for an intramolecular version of the desired cycloaddition are synthesised by a three step sequence of ring opening 3-chloroglutaconic anhydride with methanol, esterification of the half acid with the requisite 2-vinyl heterocyclic alcohol and elimination of hydrogen chloride to furnish the allenes. Thermolysis of these allenes results in [4+2] cycloaddition across the exocyclic diene system. The initial adducts rearrange and dehydrogenate under the reaction conditions to yield linearly fused tricyclic benzofurans and benzothiophenes which contain two rings of the nagilactone skeleton.

ABBREVIATIONS

The following abbreviations have been used in the text:

THF	tetrahydrofuran
DMAD	dimethyl acetylene dicarboxylate
MA	maleic anhydride
MP	methyl propiolate
DMM	dimethyl maleate
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
DMSO	dimethyl sulphoxide
DCC	N,N'-dicyclohexylcarbodiimide
DMF	dimethyl formamide
^{1}H nmr	proton nuclear magnetic resonance
^{13}C nmr	carbon 13 nuclear magnetic resonance
ir	infra red
uv	ultra violet
tlc	thin layer chromatography
MN	maleonitrile
AN	acrylonitrile
TCNE	tetracyanoethylene

TABLE OF CONTENTS

		PAGE
1.0.	THE CYCLOADDITION REACTIONS OF VINYL HETEROCYCLES	
	1.1. Cycloadditions involving vinyl furans	1
	1.2. Cycloadditions involving vinyl benzofurans	15
	1.3. Cycloadditions involving vinyl thiophenes	21
	1.4. Cycloadditions involving vinyl benzothiophenes	31
	1.5. Cycloadditions involving vinyl pyrroles	33
	1.6. Cycloadditions involving vinyl indoles	44
2.0.	BIOLOGICALLY ACTIVE DILACTONES FROM PODOCARPUS	
	2.1. Structural variety and activity	54
	2.2. Synthetic efforts towards the dilactones	62
3.0.	THE INTERMOLECULAR APPROACH	
	3.1. Introduction	78
	3.2. Specific strategy	82
	3.2.1. Diene synthesis	83
	3.2.2. Allene synthesis	89
	3.3. Intermolecular Diels-Alder reactions	97
	3.3.1. Reactions involving vinyl furans	97
	3.3.2. Reactions involving vinyl thiophenes	107
	3.3.3. Reactions involving vinyl pyrroles	108
	3.3.4. Reactions involving oxygenated dienes	110
4.0.	THE INTRAMOLECULAR APPROACH	
	4.1. Reactions involving simple glutaconate esters	120
	4.2. Reactions involving allenyl diesters	128
	4.3. The use of Lewis acid catalysis	142
	4.4. The acetylene question	146
	4.5. Approaches towards trisubstituted allenyl diesters	153

PAGE

5.0. EXPERIMENTAL 162

5.1. Experimental to 3.0. 163

5.2. Experimental to 4.0. 181

6.0. REFERENCES 209

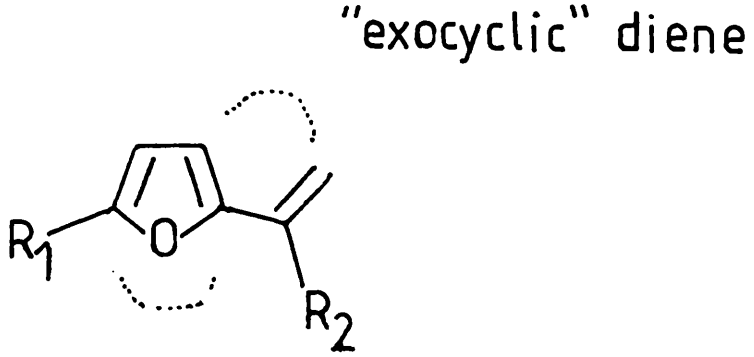
7.0. APPENDIX - X RAY CRYSTAL STRUCTURE 218

1.0 THE CYCLOADDITION REACTIONS OF VINYL HETEROCYCLES

1.0. THE CYCLOADDITION REACTIONS OF VINYL HETEROCYCLES

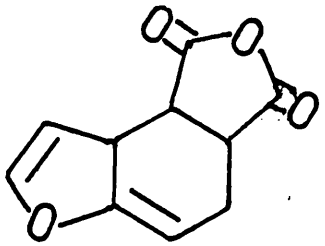
1.1. Cycloadditions involving vinyl furans

Furan is well-known for its ready participation in the Diels-Alder reaction yielding substituted 7-oxabicyclo[2.2.1]hept-2-enes.[1] Of considerable interest therefore is the reactivity towards dienophiles of 2-vinyl furans (1) which contain two alternative diene systems, the "endocyclic" syn-fixed diene of the furan ring and the "exocyclic" diene containing the non-furanoid double bond.

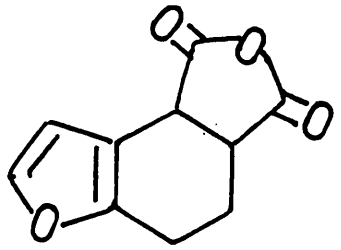


(1)

In an early study,[2] reaction of 2-vinyl furan (1, R_1=R_2=H) with maleic anhydride led to the formation of a compound which was assigned the structure of the exocyclic diene cycloadduct, 3a,4,5,6-tetrahydrobenzofuran-4,5-dicarboxylic acid anhydride (2). The question of the likely isomerisation of (2) to the furan (3) was not considered in detail.

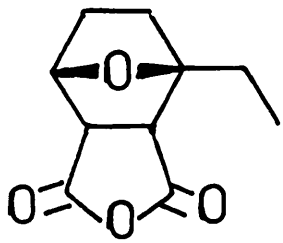


(2)

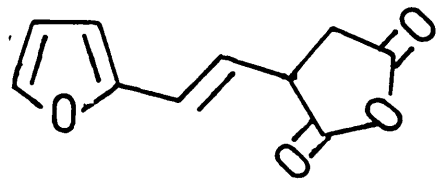


(3)

Adduct (2) crystallised out of the reaction medium in high yield (79%). Its structure was assigned on the basis of analytical and degradative evidence. Analysis showed that the product was a 1:1 adduct of 2-vinyl furan and maleic anhydride and ozonolysis produced no formaldehyde, indicating the absence of a terminal methylene group. Additional evidence was provided by hydrogenation of the isolated adduct. This produced a compound that was shown to be different from the compound (4), synthesised by hydrogenation of the Diels-Alder adduct of maleic anhydride and 2-ethyl furan.



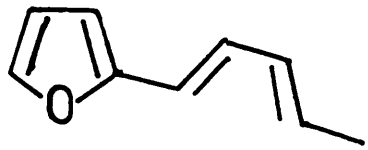
(4)



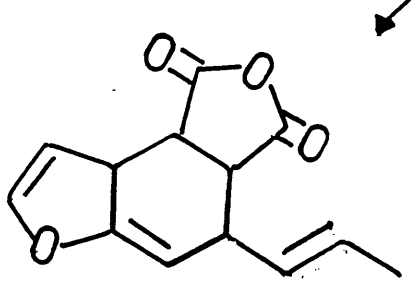
(5)

Hydrogenation studies also allowed Paul to discount the alternative structure (5) which he assumed would readily take up three equivalents of hydrogen. The observed uptake of hydrogen by the adduct was only two equivalents.

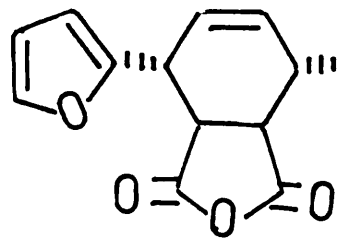
Later in a similar vein, reaction of 1-(2'-furyl)penta-1,3-diene (6) with maleic anhydride was reported to furnish a mixture of the adducts (7) and (8) resulting from addition across the two alternative exocyclic diene systems.[3]



(6)



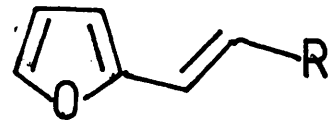
(7)



(8)

Schmidt assigned the structures (7) and (8) on the basis of analytical data and by analogy with the work of Paul.[2] No direct chemical evidence was tendered for the depicted structures, however.

The presence of strongly electron-withdrawing substituents in the side chain of the vinyl furan resulted in loss of the reactivity towards dienophiles. Hence 3-(2'-furyl) acrolein (9), 3-(2'-furyl) acrylic acid (10) and 2-(2'-nitro-vinyl) furan (11) were reported not to react with maleic anhydride.[4]



(9) R=CHO (11) R=NO_2

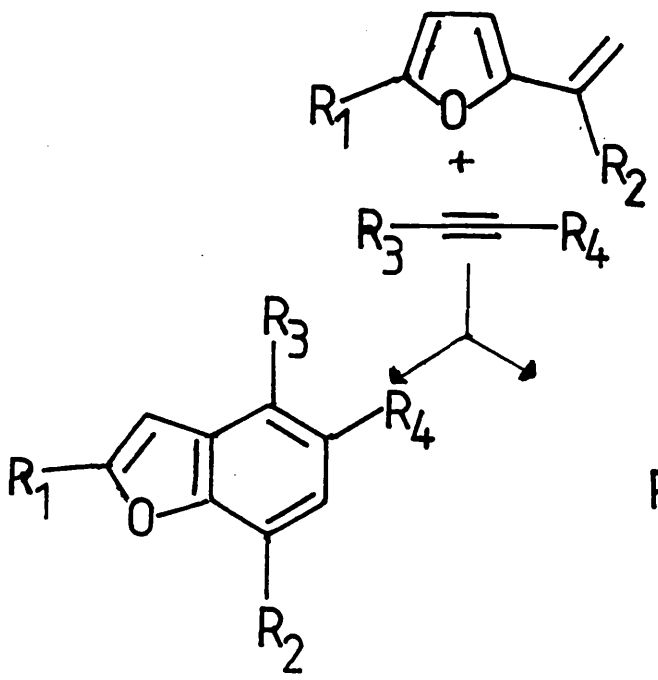
(10) R=CO_2H (12) R=$CH(OEt)_2$

This lack of reactivity is not unexpected from consideration of frontier orbital theory. If, as is thought with maleic anhydride, the important interactions to consider are those between the HOMO of the diene and the LUMO of the dienophile,[5] then in the cases (9) to (11) the energy of the HOMO of the diene is lowered by the electron-withdrawing substituent. Thus the energy gap between this orbital and the LUMO of the dienophile is increased and the reaction does not proceed.

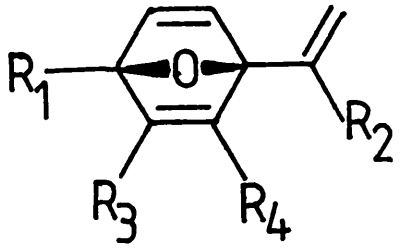
Noland[6] recently prepared the acetal (12) which would be anticipated to have a higher energy HOMO than the aldehyde (9) and thence should participate in the Diels-Alder reaction. However, acetal (12) surprisingly failed to yield any cycloadduct with maleic anhydride or dimethyl acetylene dicarboxylate, even after heating under reflux in xylene for two days.

The use of acetylenic dienophiles as partners to various 2-vinyl furans in the Diels-Alder reaction (scheme 1) has been thoroughly investigated by Davidson and Elix.[7] Their results are summarised in table 1.

Diene	R_1	R_2
(1)	H	H
(13)	H	Me
(14)	H	OAc
(15)	p-$NO_2C_6H_4$	H

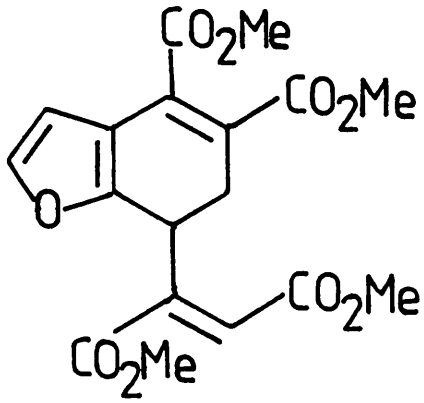


(16)–(22)



(23)–(24)

Product	R_1	R_2	R_3	R_4
(16)	H	H	CO_2Me	CO_2Me
(17)	H	H	CO_2Me	H
(18)	H	Me	CO_2Me	CO_2Me
(19)	H	Me	CO_2Me	H
(20)	H	OAc	CO_2Me	CO_2Me
(21)	p-$NO_2C_6H_4$	H	CO_2Me	CO_2Me
(22)	p-$NO_2C_6H_4$	H	CO_2Me	H
(23)	H	H	CO_2Me	CO_2Me
(24)	H	OAc	CO_2Me	CO_2Me

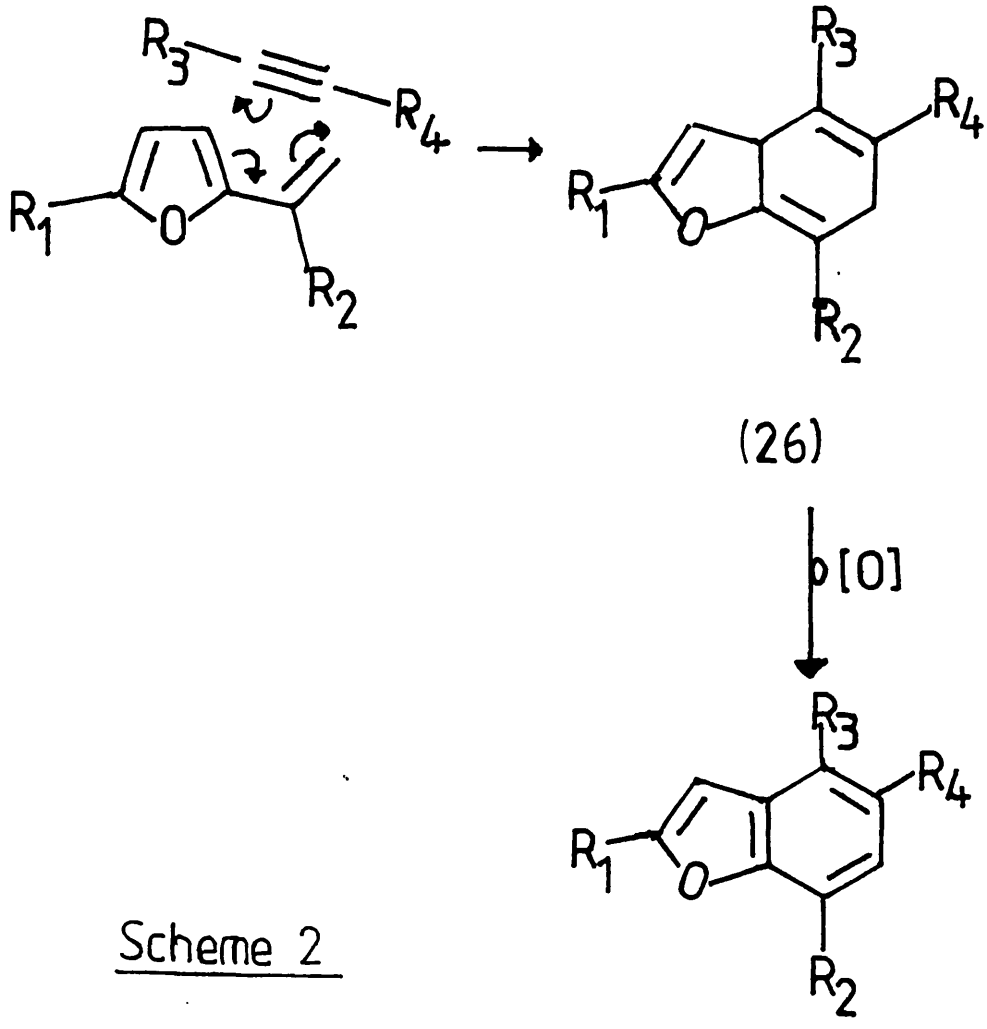


(25)

Scheme 1

Entry	Diene	Dienophile	Solvent	Temp.	Time (hours)	Products (yields,%)
1	(1)	DMAD	Et_2O	RT	96	16(5)+23(5)
2	(1)	DMAD	PhH	1 l	24	16(5)+25(3)
3	(1)	MP	PhH	1 l	24	17(5)
4	(13)	DMAD	PhH	1 l	24	18(6)
5	(13)	MP	PhH	1 l	48	19(5)
6	(14)	DMAD	Et_2O	RT	168	20(4·5)+24(4·5)
7	(15)	DMAD	xylene	1 l	24	21(40)
8	(15)	MP	xylene	1 l	48	22(6)

From these results it can be seen that in the majority of cases the acetylenic dienophile added across the exocyclic diene. The presumed intermediate 3a,6-dihydrobenzofuran (26) appeared to undergo auto-oxidation during the reaction or isolation, yielding the fully aromatic products (scheme 2). The regiochemistry of addition with methyl propiolate was as would be expected from frontier orbital theory.[5]



Scheme 2

Unexpectedly with 2-vinyl furan (1) and dimethyl acetylene dicarboxylate at room temperature (entry 1, table 1), Davidson and Elix noted competition between addition across the endocyclic and exocyclic diene systems, resulting in a 1:1 mixture of the adducts (16) and (23). The latter product was not observed when the same reaction was conducted in benzene under reflux (entry 2), the products then being the benzofuran (16) and the tetraester (25). The latter was believed to be the product of an Ene-reaction of the dienophile with the intermediate (26), the driving force being the rearomatisation of the furan ring. Analogous additions of this kind have been noted in benzenoid compounds.[8,9]

The observed competition between the two alternative dienes in the acetoxy compound (14) (entry 6) was not unexpected because of the deactivation of the exocyclic diene by the inductively electron-withdrawing acetoxy group.

The yields in these cycloadditions were generally very poor. Considerable polymerisation of the 2-vinyl furans was invoked to account for this. Only when the 2-vinyl furan was made more stable towards polymerisation and oxidation by substituting a p-nitrophenyl group into the furan (entry 7) was the yield of product enhanced. However, the strongly electron-withdrawing nature of the p-nitrophenyl group deactivated the exocylic diene to an extent that xylene rather than benzene under reflux was necessary to obtain the cycloadduct (21).

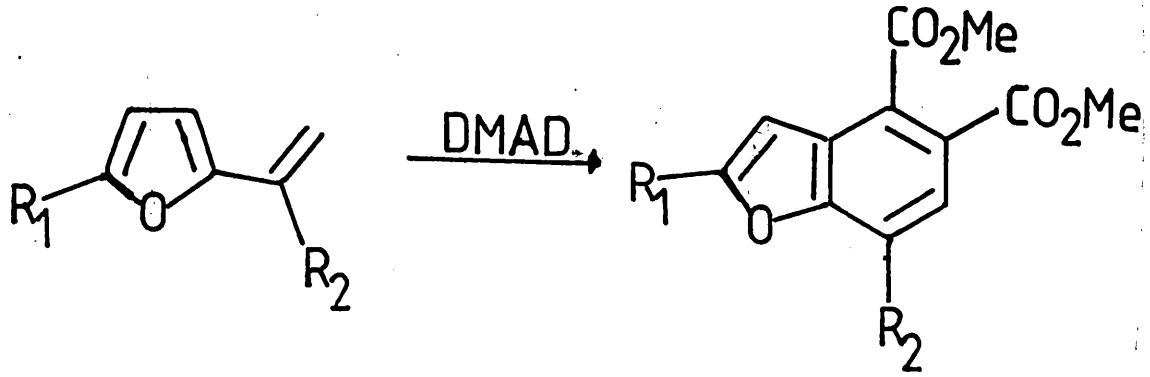
Recently, the use of high pressure has been shown to be of great use in reactions possessing a large negative activation volume, such as the intermolecular Diels-Alder reaction.[10,11]

The high pressure dramatically increases the rate of reaction and also allows it to proceed under thermally mild conditions (usually at room temperature). Kotsuki and his co-workers[12] have used this technique in an attempt to improve the yields of cycloadducts obtained from 2-vinyl furans and various dienophiles (scheme 3). This approach has met with a reasonable degree of success (table 2). For example, the yield of exocyclic diene cycloadduct (16) from dimethyl acetylene dicarboxylate and 2-vinyl furan (1) was increased from 5% (thermal) to 33% (high pressure).

Entry	Diene	Dienophile	Time (hours)	Products (yield,%)
1	(1)	DMAD	6	16(33)
2	(14)	DMAD	6	20(20) +29(25)
3	(27)	DMAD	6	28(28)
4	(1)	DMM	24	33(5) + 30(3)
5	(14)	DMM	16	34+35(≈2:1, 50)
6	(27)	DMM	8	32(48)

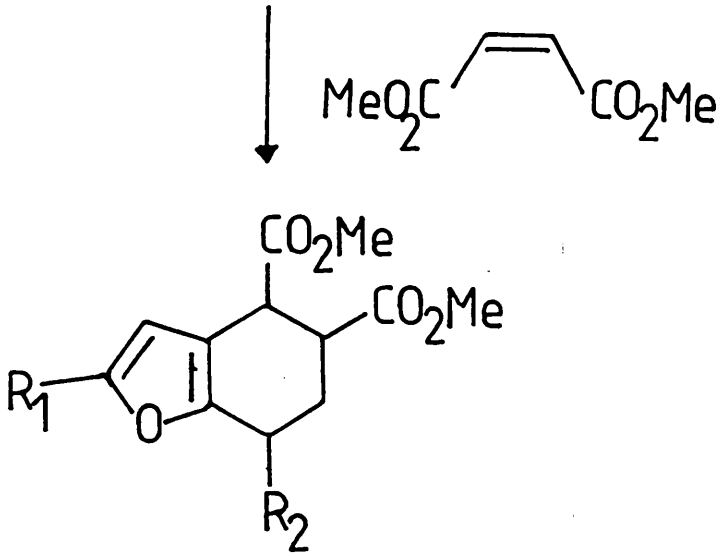
Table 2

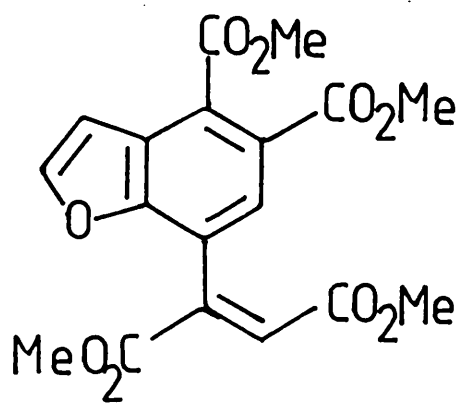
*All reactions were conducted in dichloromethane at 15 Kbar and 30°C.



Diene	R_1	R_2
(1)	H	H
(14)	H	OAc
(27)	Me	H

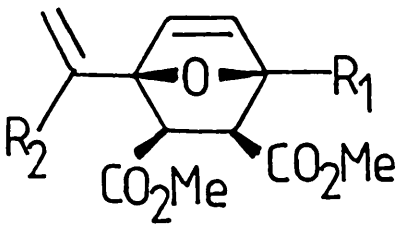
Product	R_1	R_2
(16)	H	H
(20)	H	OAc
(28)	Me	H





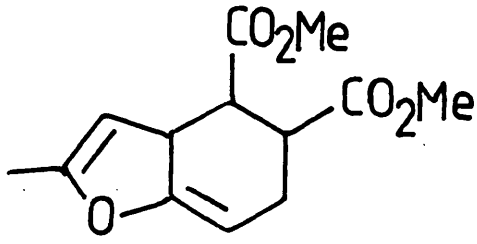
(29)

Product	R_1	R_2
(30)	H	OOH
(31)	Me	H

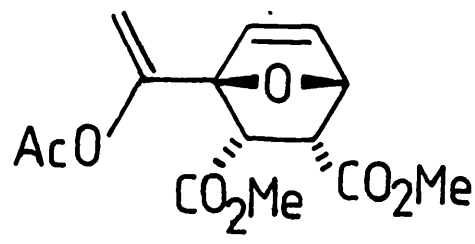


Product	R_1	R_2
(33)	H	H
(34)	H	OAc

Scheme 3



(32)



(35)

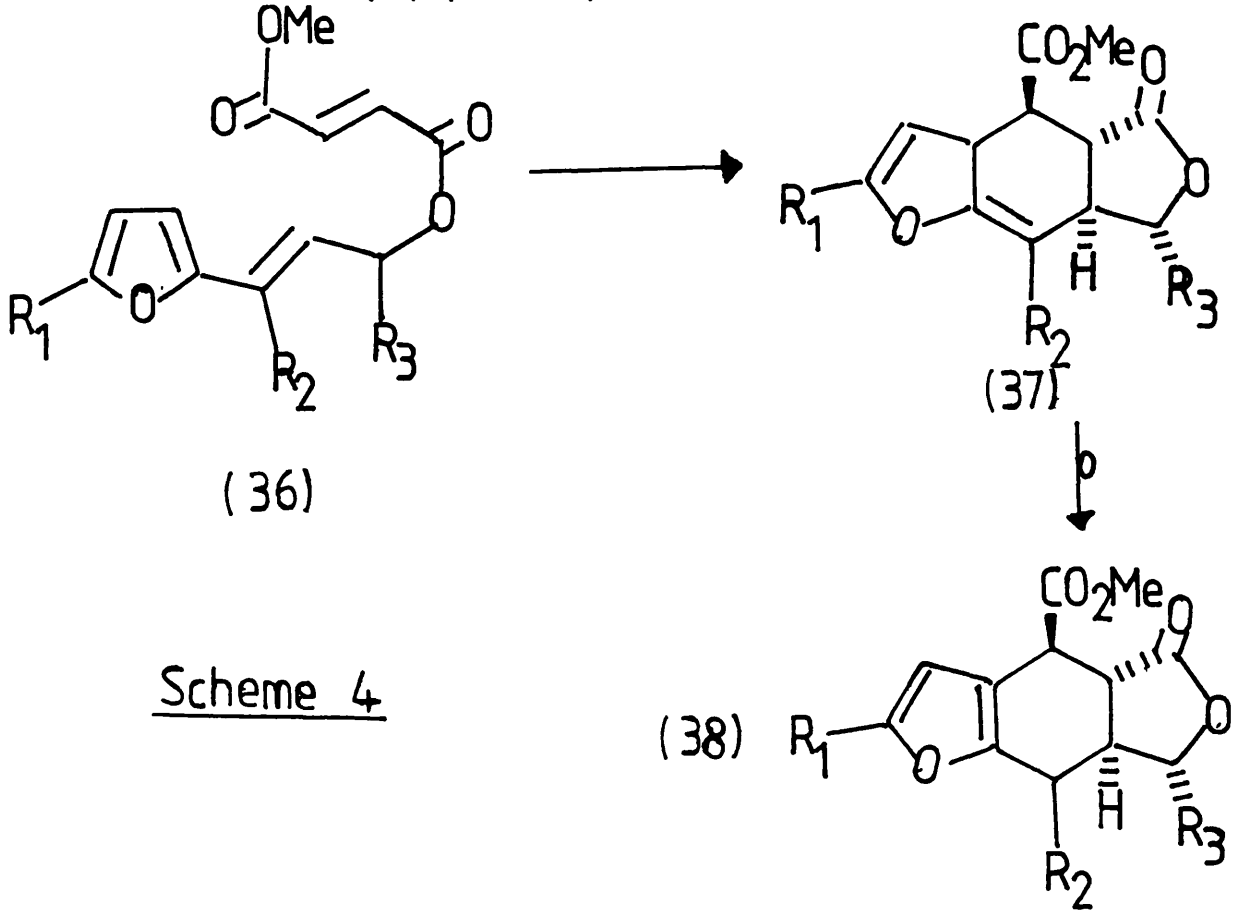
Interestingly, Kotsuki noted that under these high pressure conditions, the 2-vinyl furans reacted cleanly with dimethyl acetylene dicarboxylate to yield products resulting from exclusive addition across the exocyclic diene system. The tetraester (29) also isolated (entry 2) would appear to be a result of Ene-addition of a second equivalent of the dienophile to the initially formed adduct, followed by elimination of acetic acid.

However, with dimethyl maleate the Japanese workers noted very different tendencies for the three vinyl furans studied. 2-Vinyl furan (1) was indiscriminate in its behaviour and was reported to furnish a mixture of adducts resulting from competitive addition across both diene systems. The odd exocyclic diene adduct (30) was purported to arise from Ene-addition of molecular oxygen to the initially formed adduct.

From 5-methyl 2-vinyl furan (27) and dimethyl maleate, Kotsuki claimed to have isolated the presumed intermediate (32) in 48% yield. His spectral data were indeed consistent with the depicted bis-enol ether structure. Not surprisingly, (32) was described as "unstable" and reported to isomerise spontaneously to the furan (31) on standing at room temperature.

Finally, with the acetoxy diene (14) exclusive addition of the dimethyl maleate across the endocyclic diene, providing the adducts (34) and (35), was reported. Kotsuki interpreted the difference in behaviour of these three 2-vinyl furans with dimethyl maleate on electronic grounds. Certainly the acetoxy group being electron-withdrawing would be expected to deactivate the exocyclic diene of the 2-vinyl furan (14). However, the 5-methyl group of (27) is only mildly electron-donating and this above would appear to be an insufficient reason for the difference in reactivity observed between (1) and (27). We prefer the possibility of the involvement of a steric factor in this instance, as 2,5-disubstituted furans are noticeably more sluggish towards endocyclic cycloaddition than their monosubstituted analogues.[13]

Recently the possibility of the utilisation of 2-vinyl furans in an intramolecular Diels-Alder sense has been investigated.[14] Kotsuki reported that thermolysis of the esters (36) yielded the tricyclic γ-lactones (38) presumably via a [1,3]H sigmatropic shift from the intermediate (37) (scheme 4).



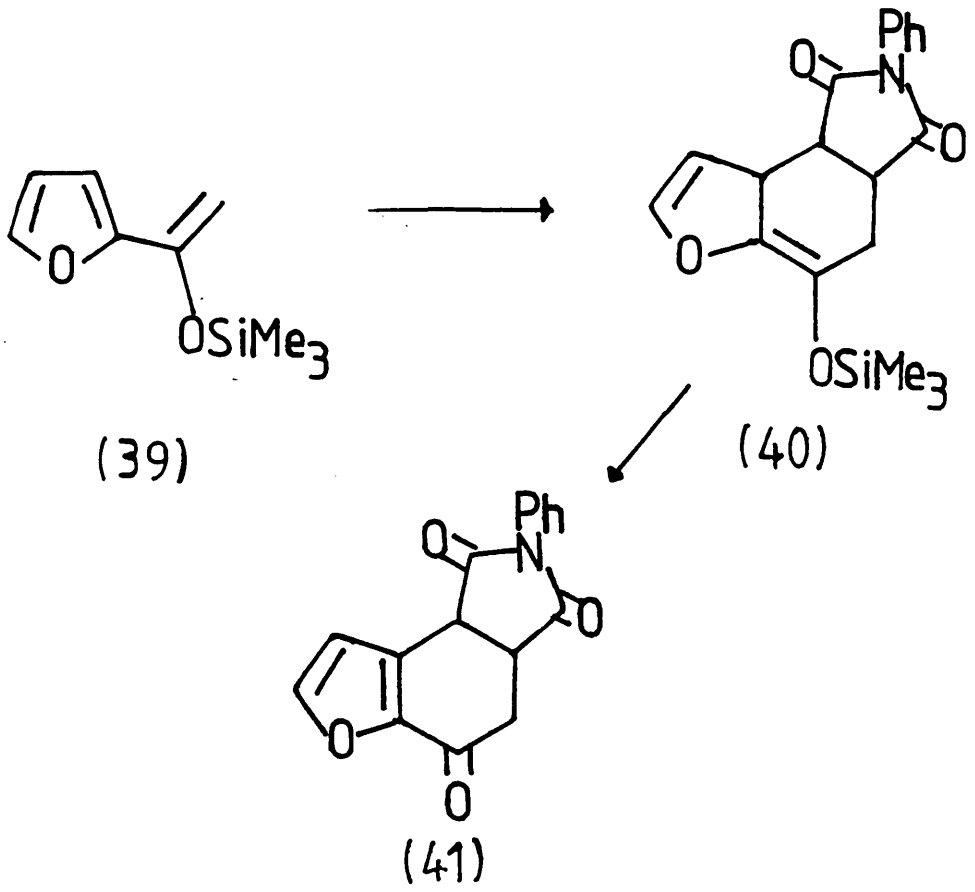
Scheme 4

The adducts were apparently obtained in good yield (table 3), although the conditions for the thermolysis (200°C, toluene, sealed tube, 20 hours) seem rather excessive for such potentially unstable esters as (36), containing a fragile allylic carbon-oxygen bond. Indeed, Kotsuki reported that the esterifications required to form (36) from monomethyl fumaryl chloride and the requisite furan allylic alcohols were difficult owing to the instability of the latter.

Substituent pattern in (36)			Yield of (38) (%)
R_1	R_2	R_3	
H	H	H	73
Me	H	H	57
H	Me	H	56
H	H	Me	46

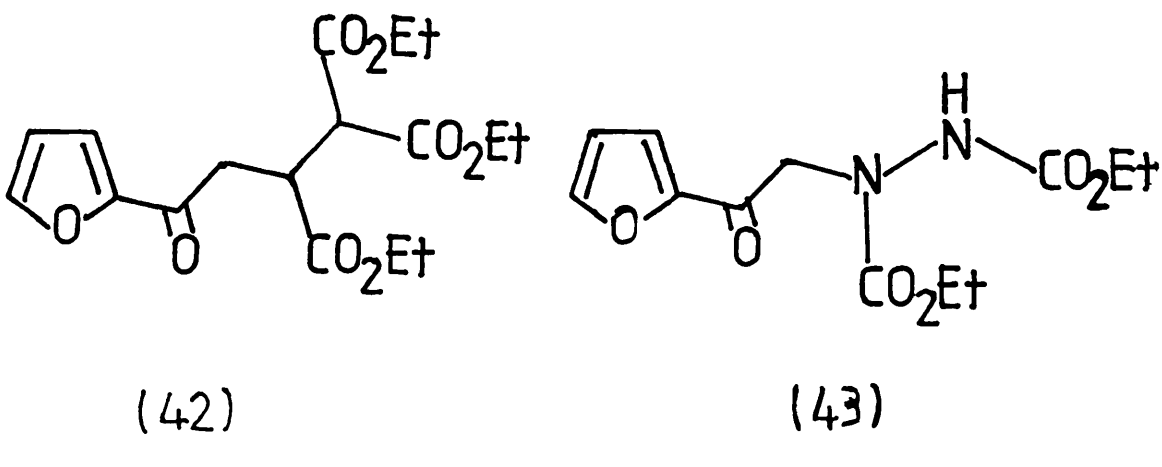
Table 3

Finally among the interesting work on 2-vinyl furans, the use of 2-(1'-trimethylsilyloxy) vinyl furan (39) as a diene has been investigated.[15] Diene (39) bears a strongly electron-donating group which would be anticipated to activate the exocyclic diene to such an extent that no competition between the two alternative dienes would be expected. This is indeed the case as with N-phenyl maleimide in benzene under reflux the adduct (41) was formed in 43% yield.

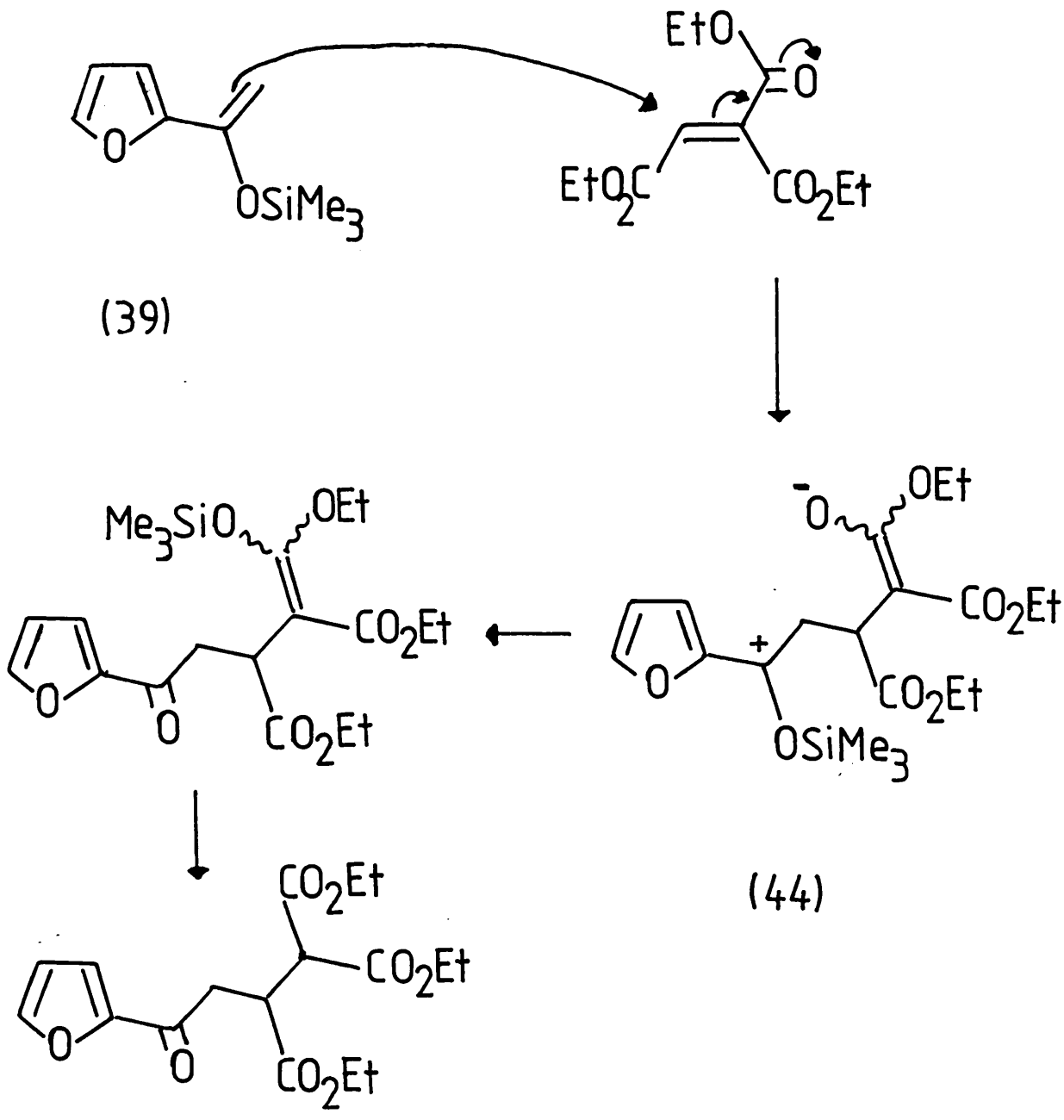


How this ketonic structure (41) arises from the presumed intermediate (40) is not explained by the Japanese workers other than being assumed to occur <u>via</u> an oxidative rearomatisation during work-up or reaction.

Interestingly, diene (39) appears to act towards other dienophiles as an enolate-equivalent rather than as an exocyclic diene. Thus reaction of (39) with triethyl ethylene carboxylate and diethyl azodicarboxylate was reported to furnish the open-chain Michael adducts (42) and (43) respectively after desilylation.



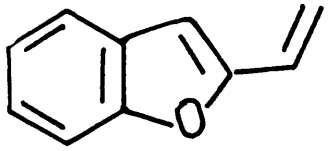
An explanation for this Michael type addition was tendered on the grounds that as the use of polarised dienophiles in Diels-Alder reactions tends to result in loss of concertedness, perhaps in this instance the zwitterionic intermediate (44) generated by a stepwise mechanism would become energetically favoured and the open-chain Michael adduct would result (scheme 5).



Scheme 5

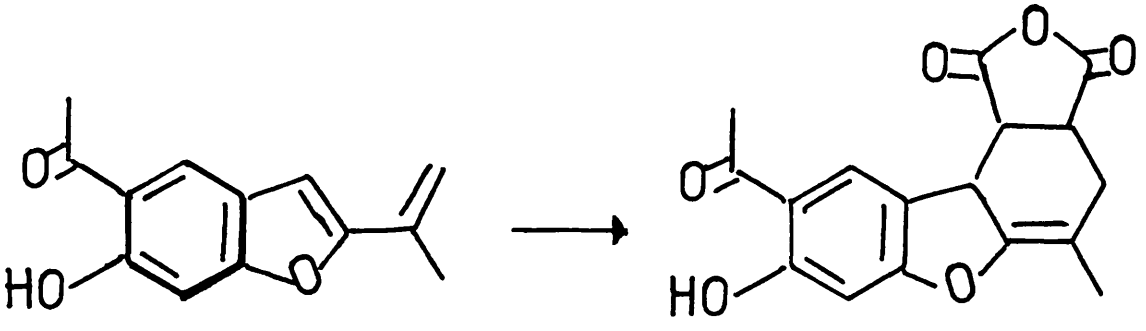
1.2. Cycloadditions involving vinyl benzofurans

In a similar manner to 2-vinyl furans, 2-vinyl benzofurans (45) also participate in the Diels-Alder reaction. However, addition of the dienophile to the latter substrates is observed to occur regiospecifically across the exocyclic diene.

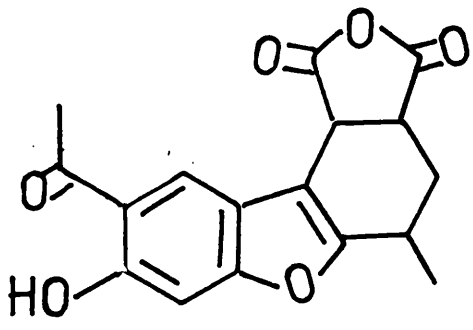


(45)

Thus in some early work,[16] the naturally occurring compound euparin (46) was shown to form a [4+2] adduct with maleic anhydride. That the structure of this adduct was (47) and not the rearomatised (48) was demonstrated by spectroscopic criteria in later work by Davidson and Elix.[17]

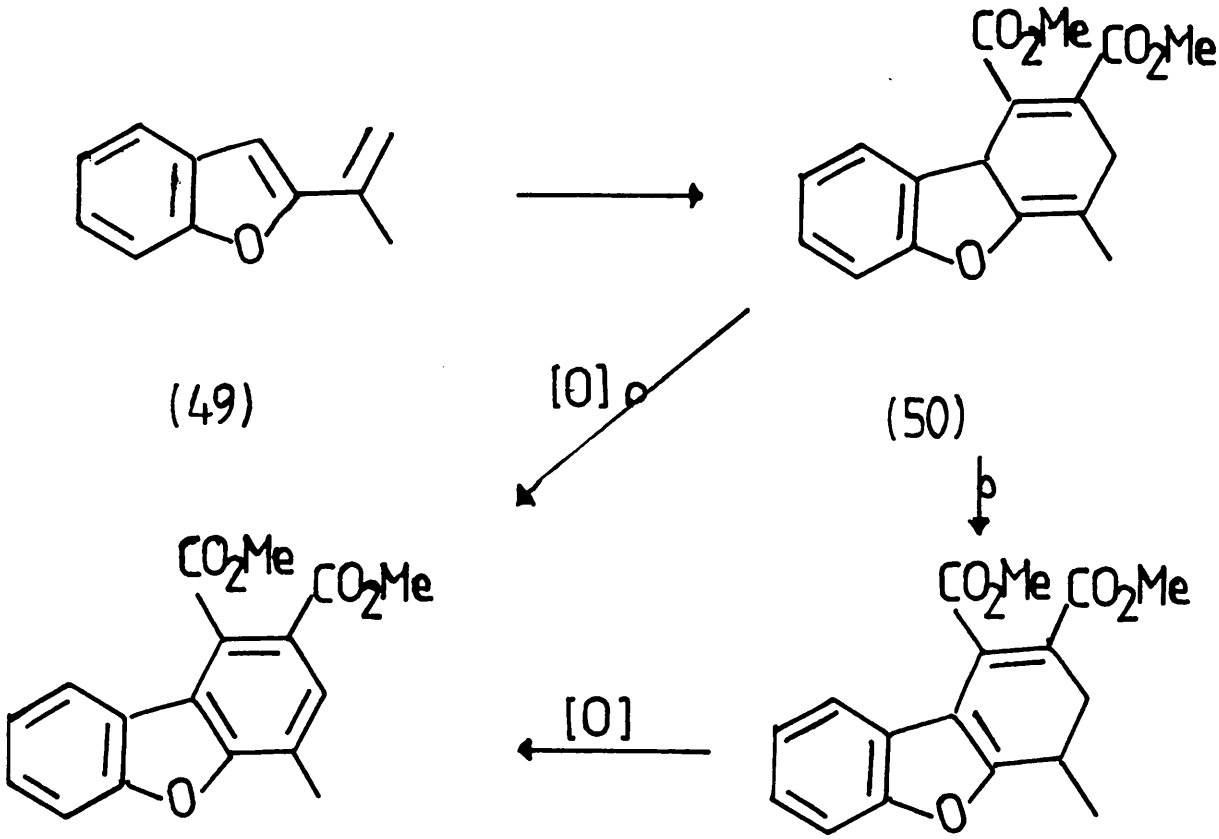


(46) (47)



(48)

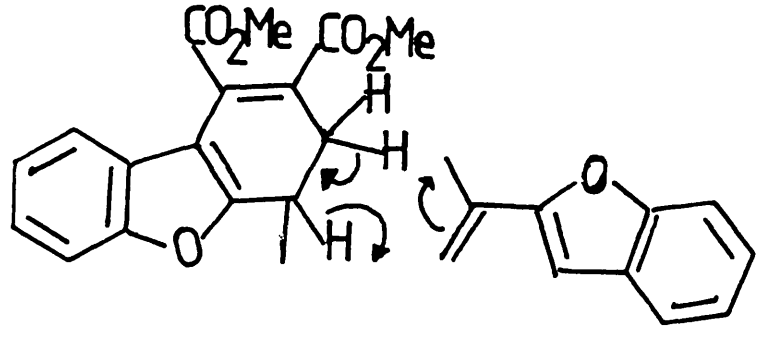
With acetylenic dienophiles, the products obtained from 2-vinyl benzofurans were the fully aromatic dibenzofurans. Thus reaction of 2-isopropenyl benzofuran (49) with dimethyl acetylene dicarboxylate in benzene at reflux afforded dimethyl 4-methyl dibenzofuran-1,2-dicarboxylate (52) in 25% yield (scheme 6).



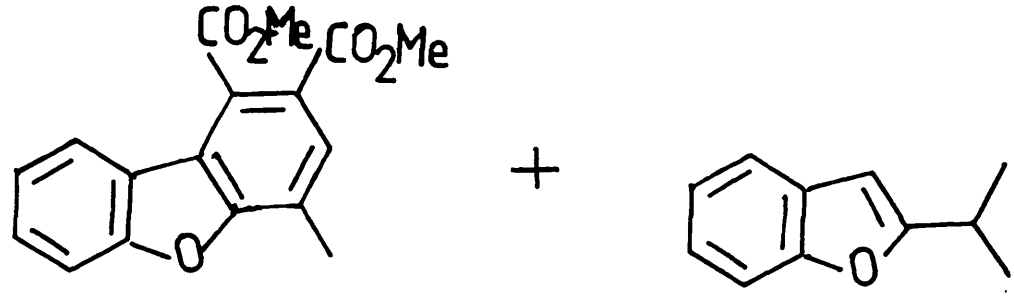
(49) (50) (51) (52)

Scheme 6

The dehydrogenation step necessary to explain the formation of the dibenzofurans was postulated to occur either <u>via</u> auto-oxidation of the intermediate (50) or <u>via</u> hydrogen transfer from the rearranged 3,4-dihydrodibenzofuran (51).[18] The latter transfer from (51) to the starting material (49) was, it was argued, a symmetry allowed process, analogous to other examples in the literature.[19,20]



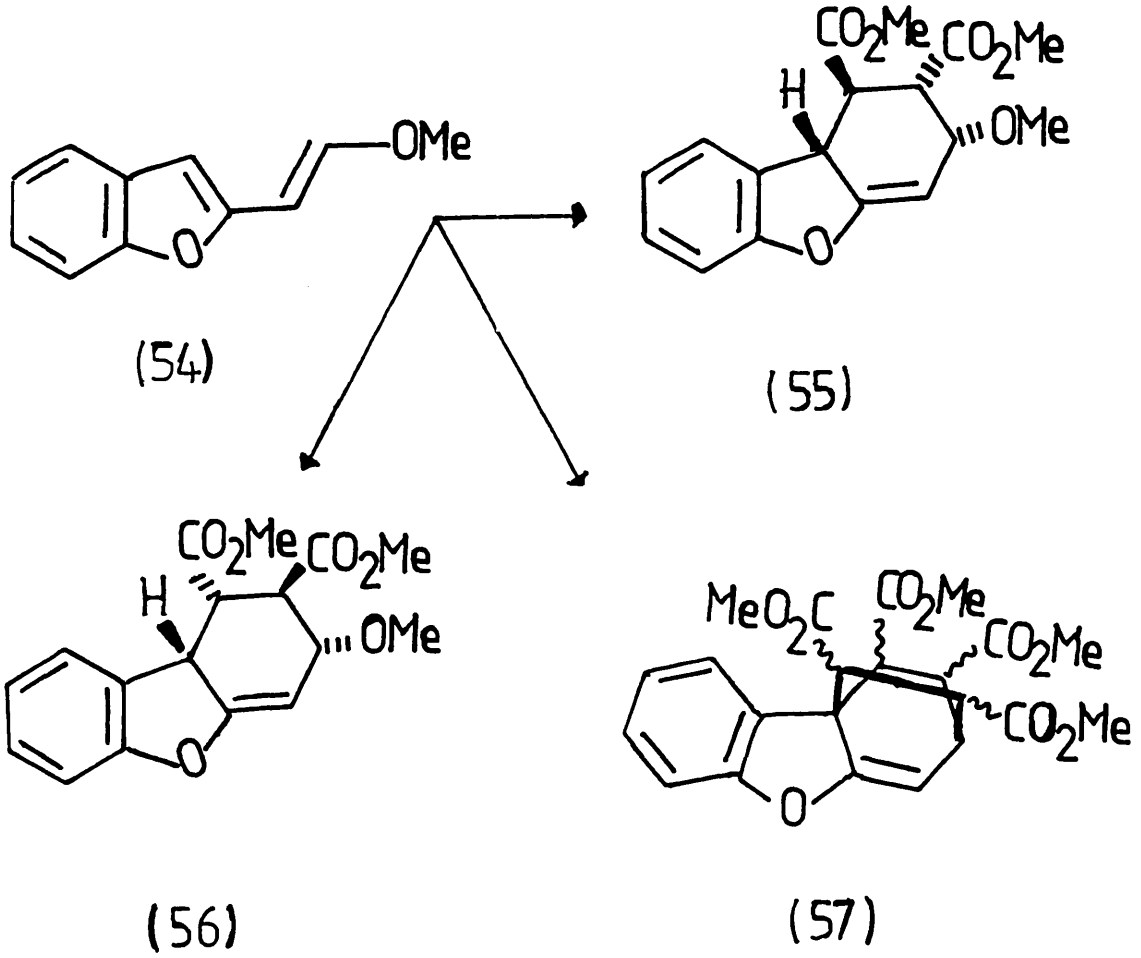
(51) (49)



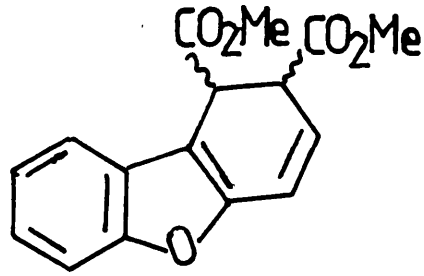
(52) (53)

Interestingly, the reduction product 2-isopropyl benzofuran (53) <u>was</u> isolated in 12% yield in this instance, adding credence to this hypothesis.

In an attempt to extend this methodology, the oxygenated diene (54) was synthesised.[17] This, it was hoped, would provide an entry into poly-functionalised 3-methoxy dibenzofurans, compounds of interest because of their structural similarity to the lichen metabolites strepsilin[21] and didymic acid.[22] Diene (54) was found to react with dimethyl fumarate to yield a mixture of the three non-aromatised adducts (55), (56) and (57).

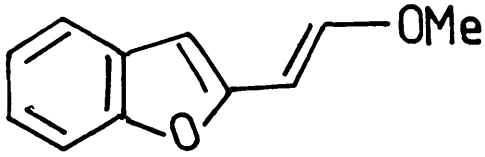


The unusual tetraester (57) was thought to arise from the addition of another equivalent of dimethyl fumarate to the 1,2-dihydro-dibenzofuran (58), the latter presumed to result from 1,4-elimination of methanol from (55) or (56).

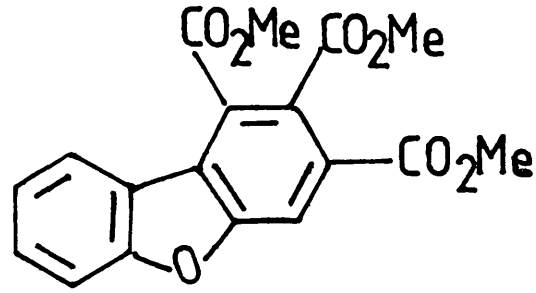


(58)

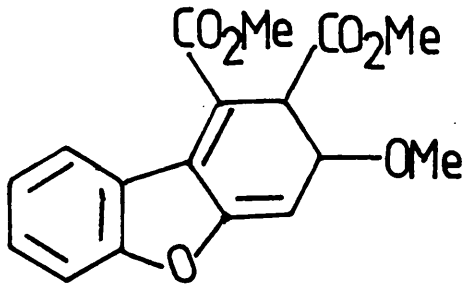
The reaction of diene (54) with dimethyl acetylene dicarboxylate similarly provided a mixture of three products.



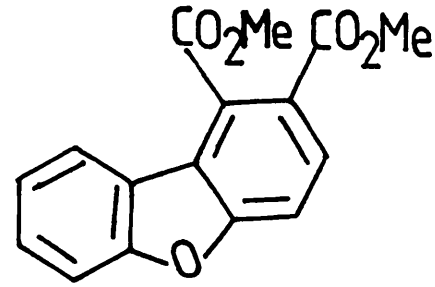
(54)



(61) (8%)

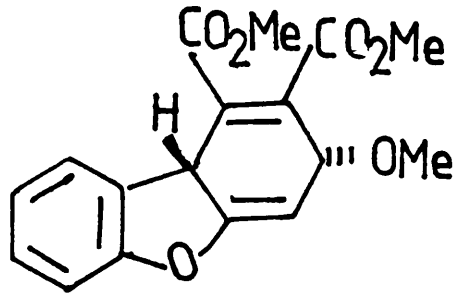


(59) (36%)

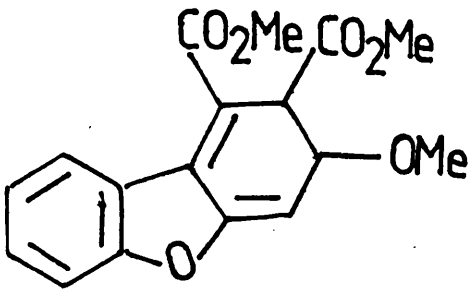


(60) (20%)

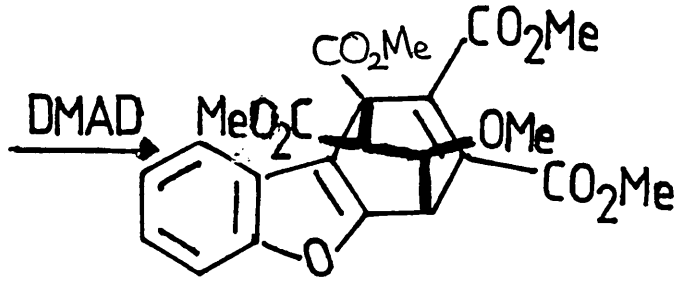
The major product was assigned the 2,3-dihydrodibenzofuran structure (59) on the basis of spectral evidence. Product (60) was presumed to arise from 1,4-elimination of methanol from (62), whereas the triester (61) was proposed to arise from addition of a second equivalent of dimethyl acetylene dicarboxylate to the diene (59), giving the adduct (63) which could undergo a retro-Diels-Alder reaction to yield (61) (scheme 7).



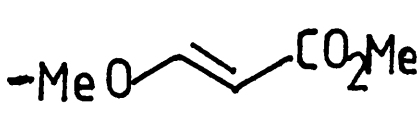
(62)

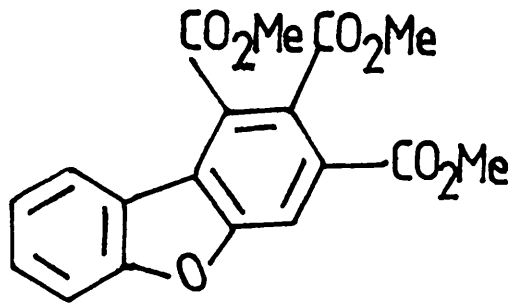


(59)



(63)





(61)

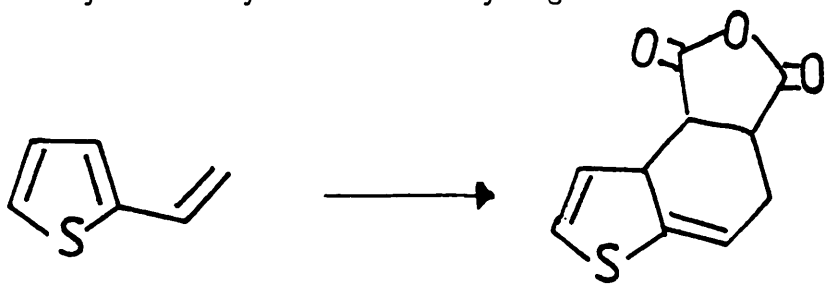
Scheme 7

Evidence for this pathway for the formation of (61) was provided by the observation that thermolysis of the dihydro compound (59) with dimethyl acetylene dicarboxylate in xylene afforded the triester (61) in 62% yield, together with the product of 1,4-elimination of methanol (60) in 26% yield.

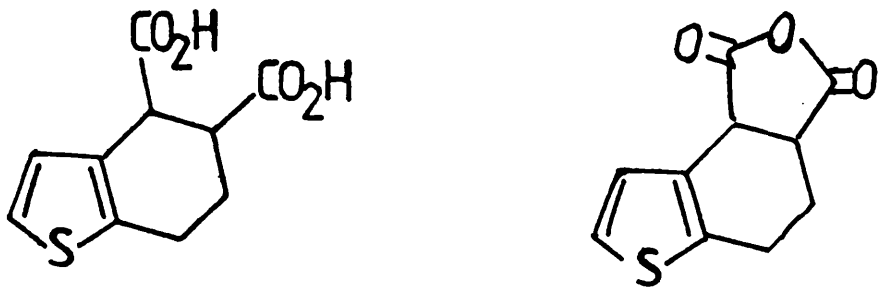
1.3. Cycloadditions involving vinyl thiophenes

In contrast to furan, cycloadditions across the thiophene ring are rare.[23] Consequently, cycloadditions in which vinyl thiophenes serve as the diene would be anticipated to exhibit greater chemoselectivity than their furan analogues.

In an early piece of work, 2-vinyl thiophene (64) was found to react with maleic anhydride in warm benzene, yielding a compound assigned the structure (65).[24,25] Analysis indicated that the compound was a 1:1 adduct. Alkaline hydrolysis of the adduct afforded the rearranged dicarboxylic acid (66) which could be transformed to benzothiophene by decarboxylation and dehydrogenation.



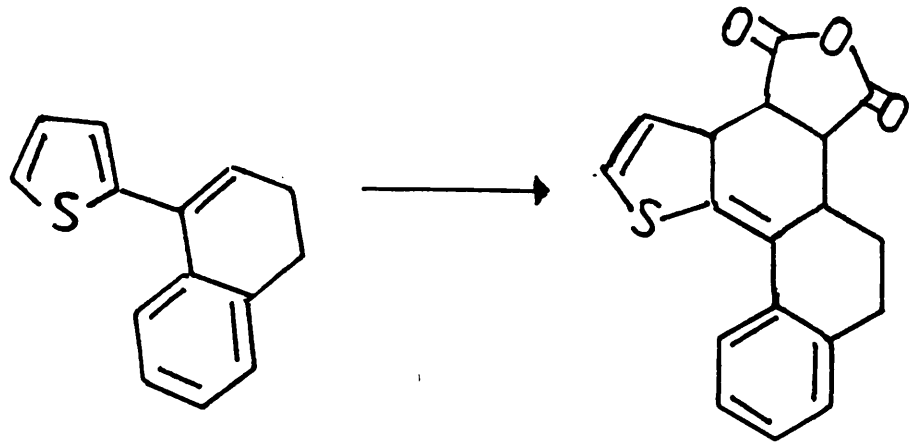
(64) (65)



(66) (67)

Later work[25] added evidence for the bis-vinylic sulphide structure (65) in that the adduct was irreversibly changed by treatment with polar solvents. For example, attempted recrystallisation of (65) from acetic acid afforded fumaric acid. However, the dicarboxylic acid (66) was unchanged on heating in acetic acid, inferring that the initial adduct did not possess the isomeric structure (67).

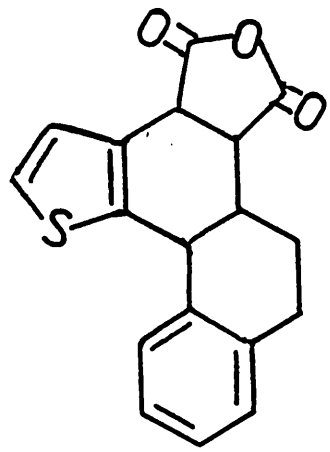
Similarly, thermolysis of the diene (68) with maleic anhydride was reported to produce the 1:1 adduct (69),[26] λ_{max}(EtOH): 237 (log ε 3.97) and317 (log ε3.97) nm.



(68)

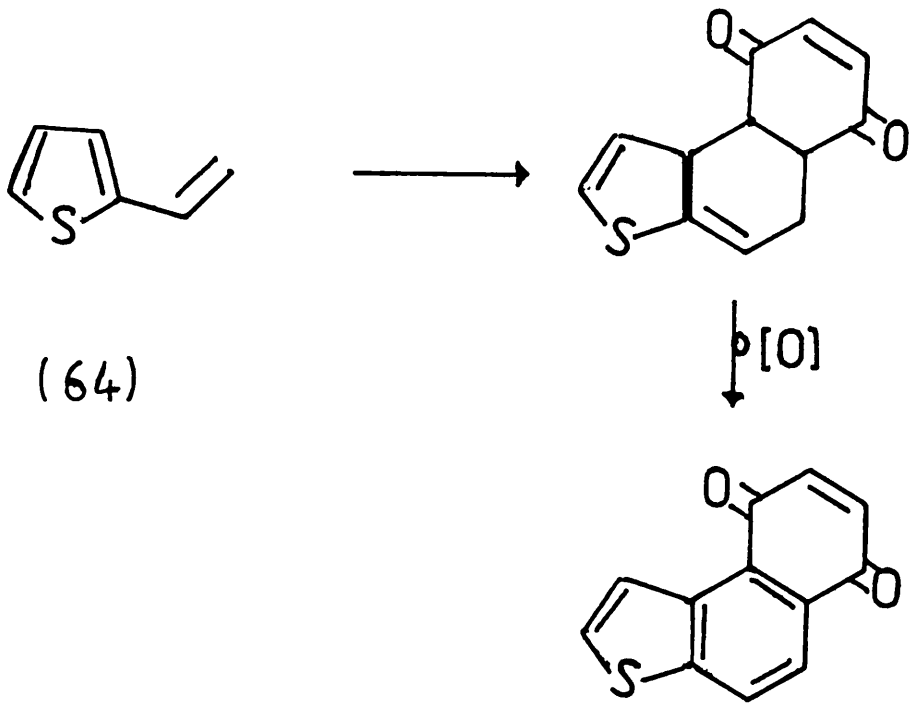
(69)

The ultraviolet spectrum of (69) was however observed to change radically over a period of days, finally displaying only a band at 250 (log ε 4.15) nm. This latter spectrum was identical to that of the starting diene so a retro-Diels-Alder reaction was assumed to have occurred. These pieces of data eliminate the possibility of structure (70) for the adduct as this would not be expected to have an absorbance at 317 nm, nor would it be expected to undergo a retro-Diels-Alder reaction.



(70)

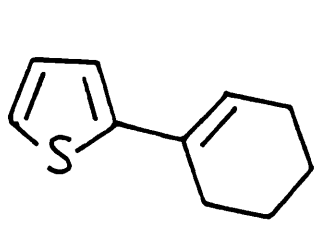
The reaction of 2-vinyl thiophene (64) with p-benzoquinone is also known.[25] In this instance, the isolated product (43%) was assigned the structure (71). The dehydrogenation observed here was attributed to the use of excess p-benzoquinone in the reaction.



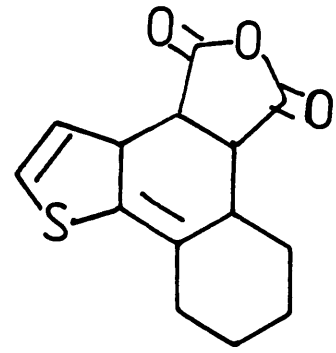
(64)

(71)

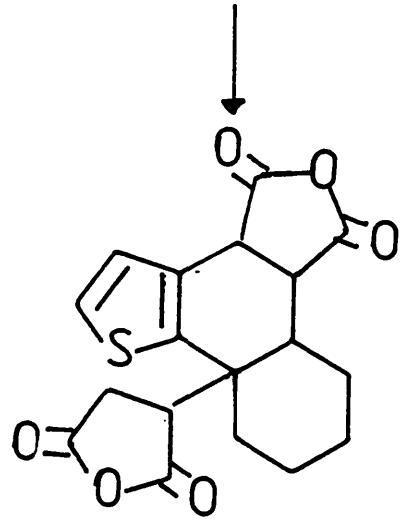
The formation of 1:2 adducts from 2-vinyl thiophenes and dienophiles has also been reported.[26] Thus analysis of the adduct obtained from 1-(2'-thienyl)-cyclohex-1-ene (72) and maleic anhydride revealed that it contained two equivalents of dienophile. No structure was assigned to the bis-adduct, although one would anticipate that a structure such as (74) resulting from Ene-addition of maleic anhydride to the presumed initial adduct (73) would be likely. Such additions of dienophiles to pre-aromatic systems are well documented.[8,9]



(72)

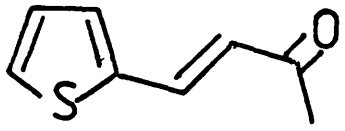


(73)

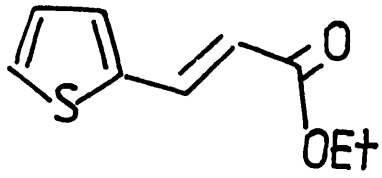


(74)

By direct analogy with the vinyl furans, conjugation of the exocyclic diene with an electron-withdrawing group would be expected to result in a loss of the Diels-Alder activity. Recently Noland[6] did indeed observe that 4-(2'-thienyl)but-3-en-2-one (75) did not react at all with dimethyl acetylene dicarboxylate in xylene under reflux over a five day period.

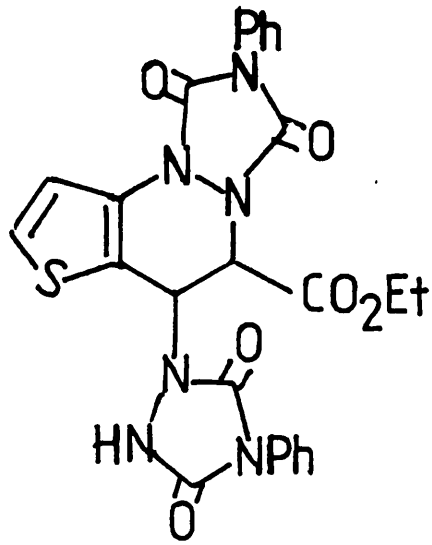


(75)

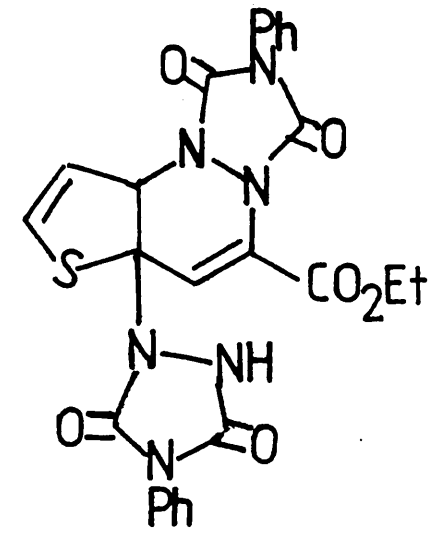


(76)

However, Rees and co-workers[27] recently found that the similarly conjugated, deactivated acrylate (76) reacted with 4-phenyl-1,2,4-triazole-3,5-dione at room temperature to yield a mixture of two 1:2 adducts (77) (46%) and (78) (8%)

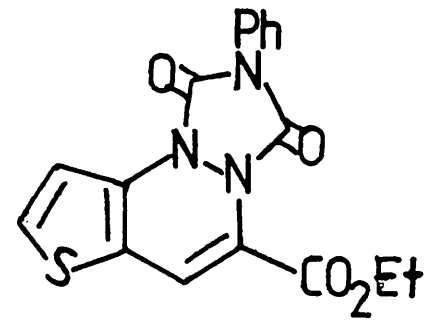


(77)



(78)

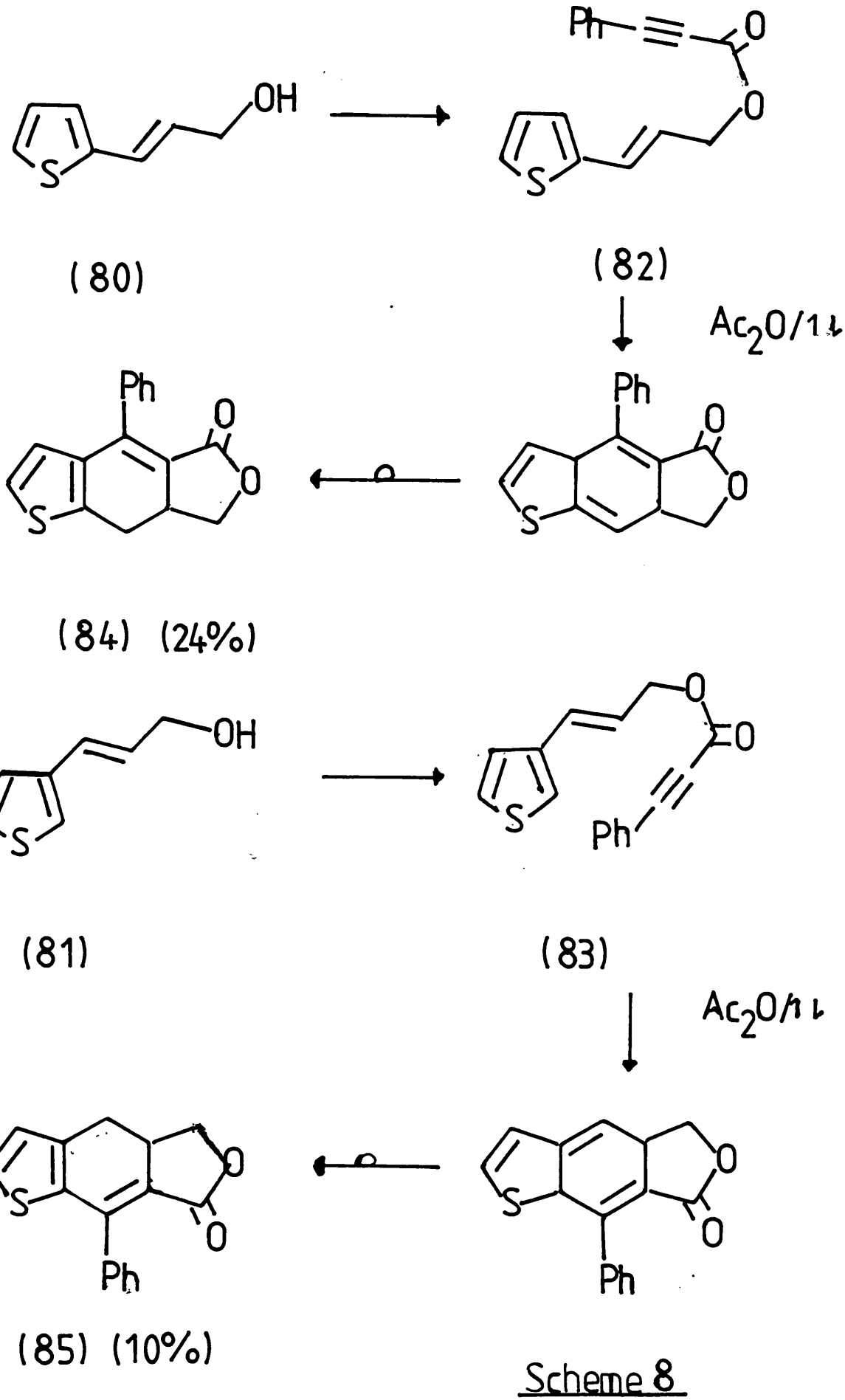
These bis-adducts appear to be the products of Ene-reactions of the initial adduct with another equivalent of the dienophile. On heating either of these bis-adducts in dimethylsulphoxide, elimination of the reduced form of the dienophile occurred, yielding the heterocycle (79).



(79)

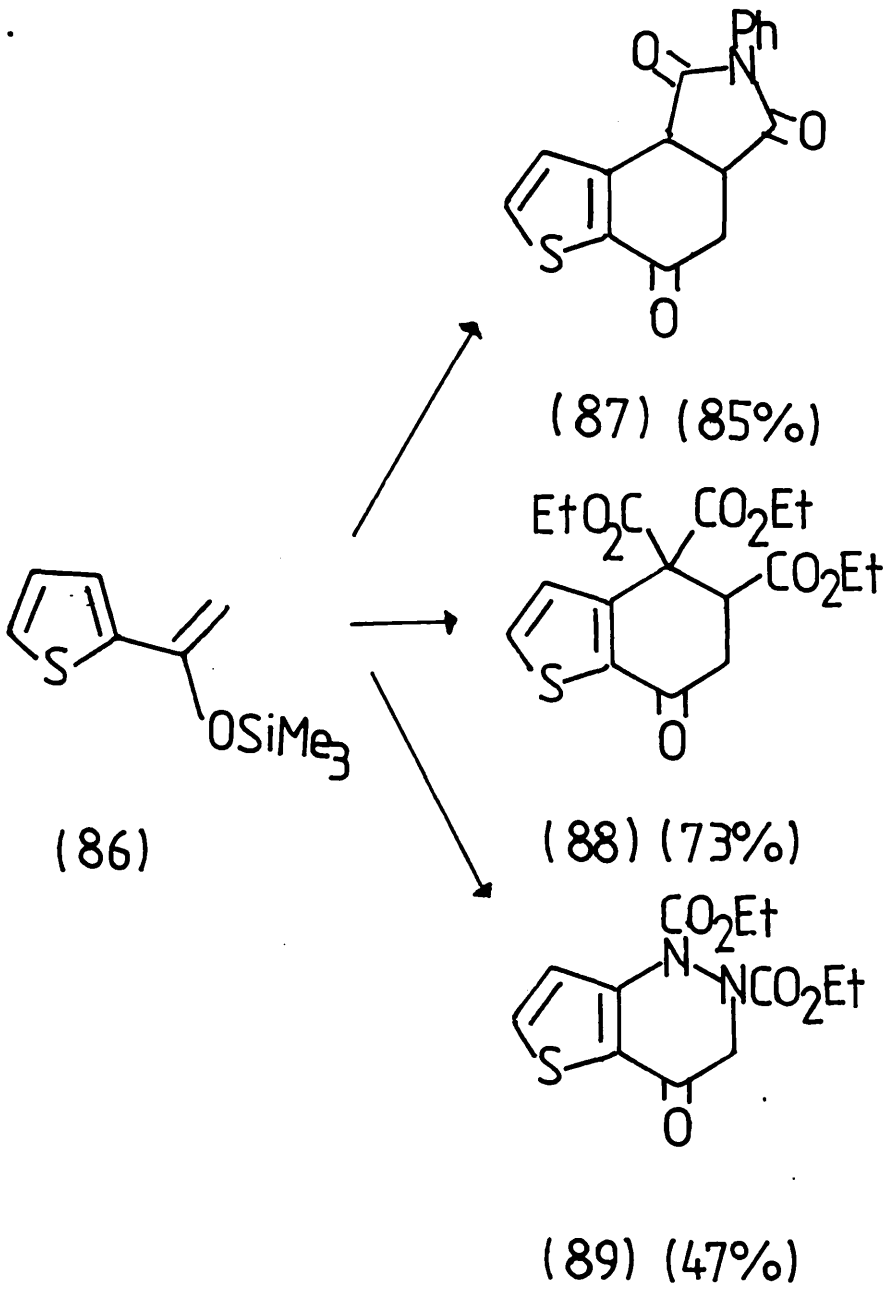
The formation of these adducts from the acrylate (76) reflects the extraordinary dienophilic properties of the triazoline dione. However, the less active azodienophile, diethyl azodicarboxylate, did not react with the acrylate (76) even on heating at 156°C.

Both 2-vinyl thiophenes and 3-vinyl thiophenes have been employed in an intramolecular Diels-Alder reaction.[28] Thus the thiophene allylic alcohols (80) and (81) were coupled with an alkynoic acid to yield the alkynyl esters (82) and (83). When heated to reflux in acetic anhydride these esters cyclised, albeit in low yield, furnishing the rearranged dihydrobenzothiophene γ-lactones (84) and (85) (scheme 8).

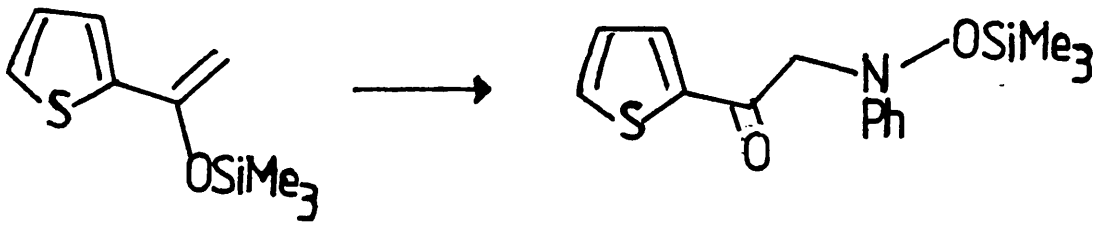

OH
Ph
O
O
S
(80)
(82)
Ac2O/1ι
Ph
O
O
S
(84) (24%)
OH
O
O
Ph
S
(81)
(83)
Ac2O/hν
O
O
Ph
S
(85) (10%)

Scheme 8

Recently, the reactions of 2-(1'-trimethylsilyloxy)vinyl thiophene (86) with dienophiles have been the subject of a study.[15] A very interesting comparison could be made between the behaviour of (86) and the furan analogue (39). It was reported that reaction of (86) with N-phenyl maleimide, triethyl ethylene carboxylate and diethyl azodicarboxylate yielded the ketonic [4+2] adducts (87), (88) and (89), in contrast to the furan (39) which yielded a [4+2] adduct with N-phenyl maleimide but Michael adducts with the other dienophiles.



Michael addition of (86) to a dienophile was apparently observed only with the very polar heterodienophile nitrosobenzene, yielding the O-trimethylsilyl hydroxylamine (90).

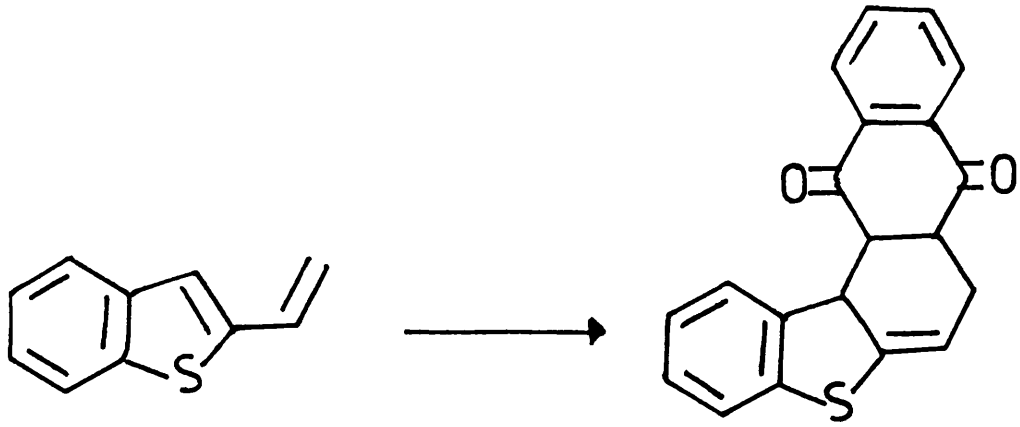


(86) (90)

The great difference observed between the silyloxyvinyl thiophene (86) and the furan (39) was explained in terms of frontier orbital theory.[5] Calculations[15] revealed that the HOMO of the vinyl thiophene (86) was higher in energy than that of the furan (39) and that the HOMO coefficient on the end of the trimethylsilyloxyvinyl group of the thiophene (86) was larger than that of the furan (39). These calculations would infer that the thiophene (86) should act as a better exocyclic diene than the furan (39), a hypothesis born out by the experimental observations.

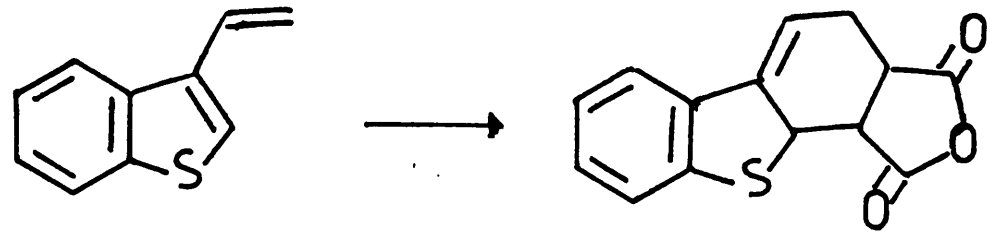
1.4. Cycloadditions involving vinyl benzothiophenes

The benzofused analogues of vinyl thiophenes are also able to participate in the Diels-Alder reaction. Most of the available literature documents the use of 3-vinyl benzothiophenes in the construction of polycyclic systems, although 2-vinyl benzothiophene (91) has been reported[29] to yield the adduct (92) on treatment with β-naphthoquinone.

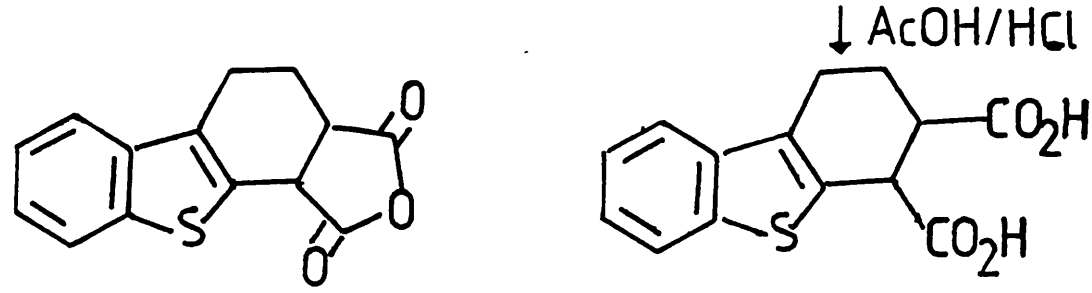


(91) (92)

Thus, reaction of 3-vinyl benzothiophene (93) with maleic anhydride in benzene at reflux yielded a 1:1 adduct believed to have the structure (94).[30] The double bond was thought not to have rearranged to yield the isomeric benzothiophene (95) on the basis of chemical evidence. Thus it was found that bromine water was decolourised by the adduct, whereas it was not decolourised by compound (96), obtained by heating the adduct (94) to reflux in acetic acid saturated with hydrogen chloride.

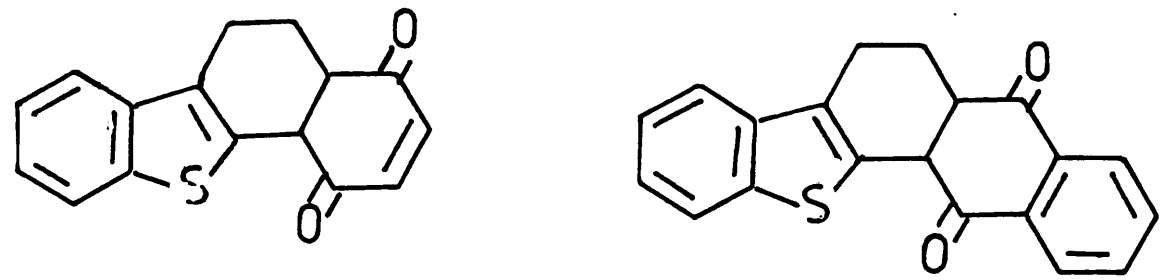


(93) (94)

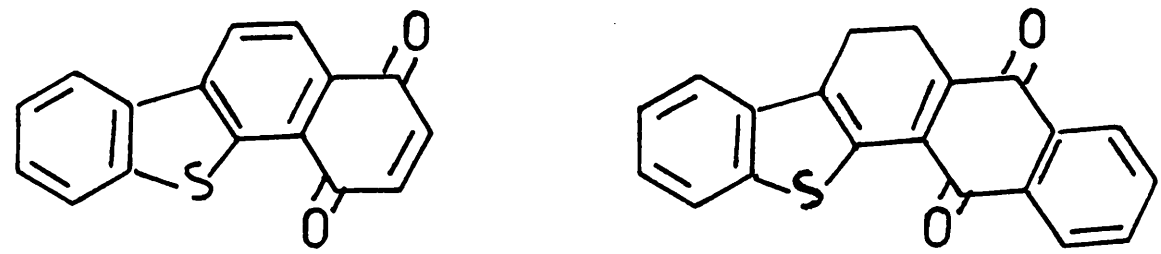


(95) (96)

Similarly, 3-vinyl benzothiophene (93) was reported to react with p-benzoquinone and p-naphthoquinone to yield the adducts (97) and (98) when excess diene was employed. However, when excess quinone was used the adducts isolated were not surprisingly the dehydrogenated compounds (99) and (100).

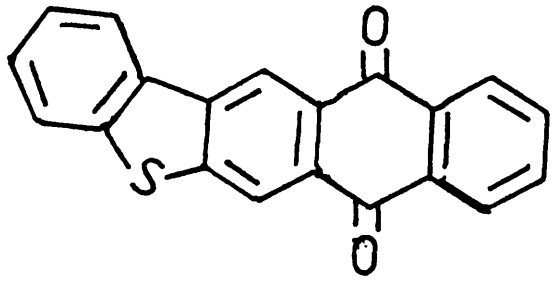


(97) (98)



(99) (100)

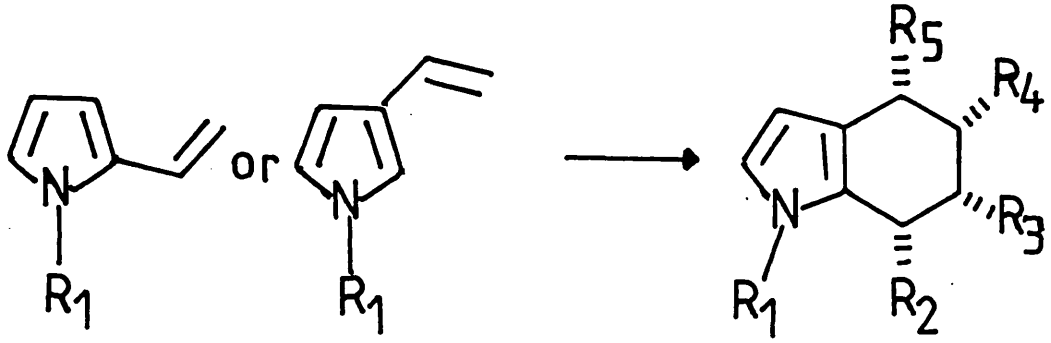
Apparently on treatment with sodium hydroxide, (98) rearranges to the linearly fused pentacyclic quinone (101).[31]



(101)

1.5. Cycloadditions involving vinyl pyrroles

Although 2-vinyl pyrrole (102) has been reported[32] to produce only polymeric mixtures resulting from Michael addition to typical dienophiles,[32,33] N-alkylated 2- and 3-vinyl pyrroles have recently been demonstrated to undergo [4+2] cycloadditions across the exocyclic diene, yielding a variety of tetrahydro- and dihydroindoles.[32] For example, 1-methyl 2-vinyl pyrrole (103) with maleic anhydride was reported to yield 1-methyl -4,5,6,7-tetrahydroindole cis-4,5-dicarboxylic acid anhydride (105) in 54% yield under exceptionally mild conditions. Similarly, 1-tert-butyl 3-vinyl pyrrole (104) with maleic anhydride produced the tetrahydroindole (109) in 75% yield. Some of Jones' results are presented in table 4.



(103) (104) (105)–(109)

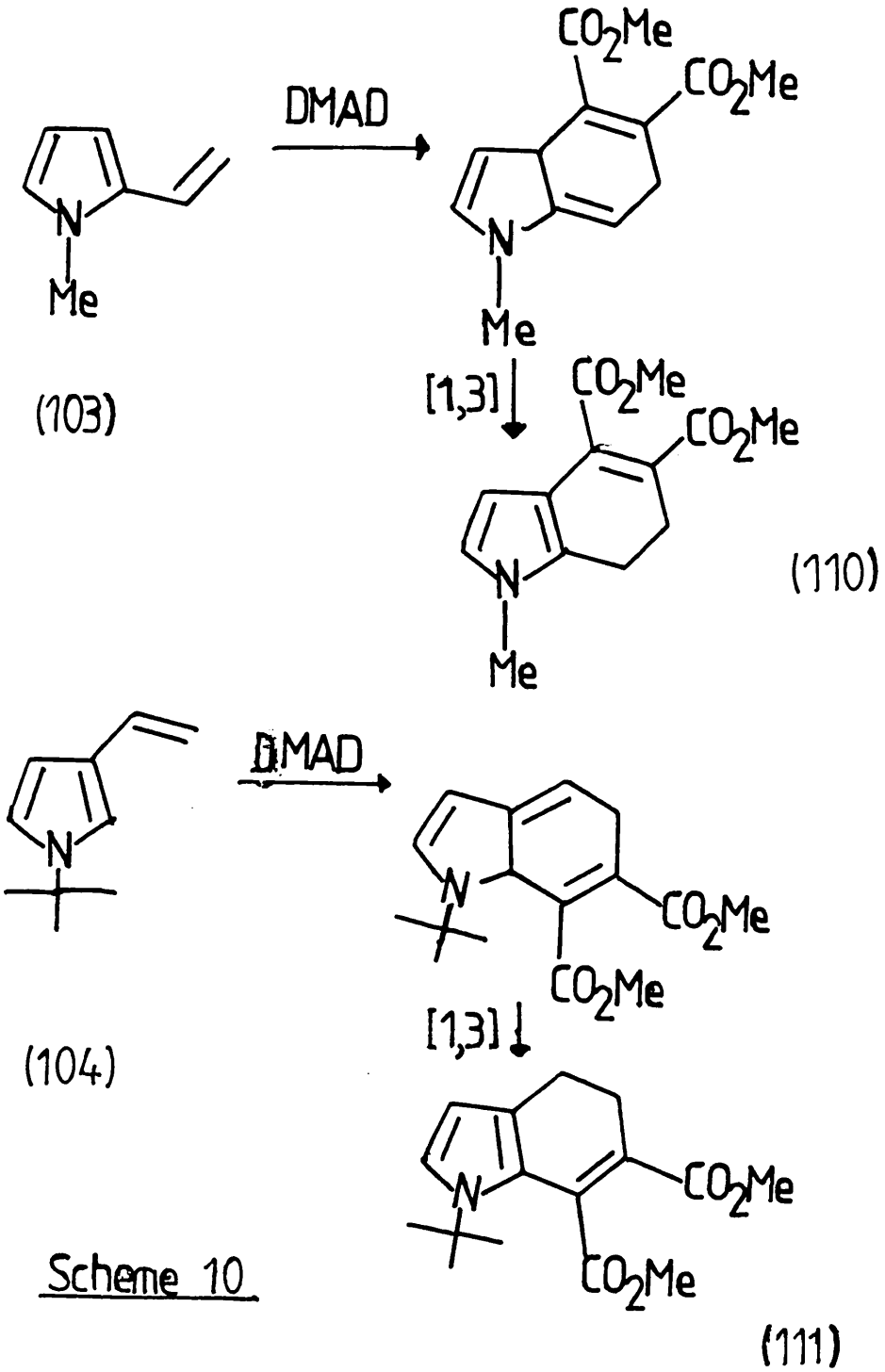
Scheme 9

Diene	Dienophile	Solvent	Temp.(°C)	Time(hrs.)	Prod(yield,%)
(103)	MA	$CHCl_3$	5	0.15	105(54)
(103)	DMM	None	140	96	106(71)
(103)	MN	$CHCl_3$	20	48	107(91)
(103)	AN	None	1	8	108(61)
(104)	MA	$CHCl_3$	20	0.1	109(75)

Table 4

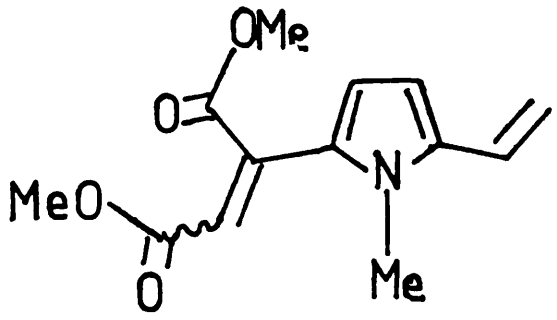
Tetrahydroindole	R_1	R_2	R_3	R_4	R_5
(105)	Me	H	H	COOOC	
(106)	Me	H	H	CO_2Me	CO_2Me
(107)	Me	H	H	CN	CN
(108)	Me	H	H	H	CN
(109)	^{t}Bu	COOOC		H	H

With dimethyl acetylene dicarboxylate at reflux in chloroform, the vinyl pyrroles (103) and (104) were reported to yield the dihydroindoles (110) and (111), following the usual formal [1,3]H sigmatropic shift of hydrogen (scheme 10). These dihydroindoles apparently did not undergo dehydrogenation under the reaction conditions, so if the fully aromatic indoles were required a separate dehydrogenation step with DDQ was found to be necessary.



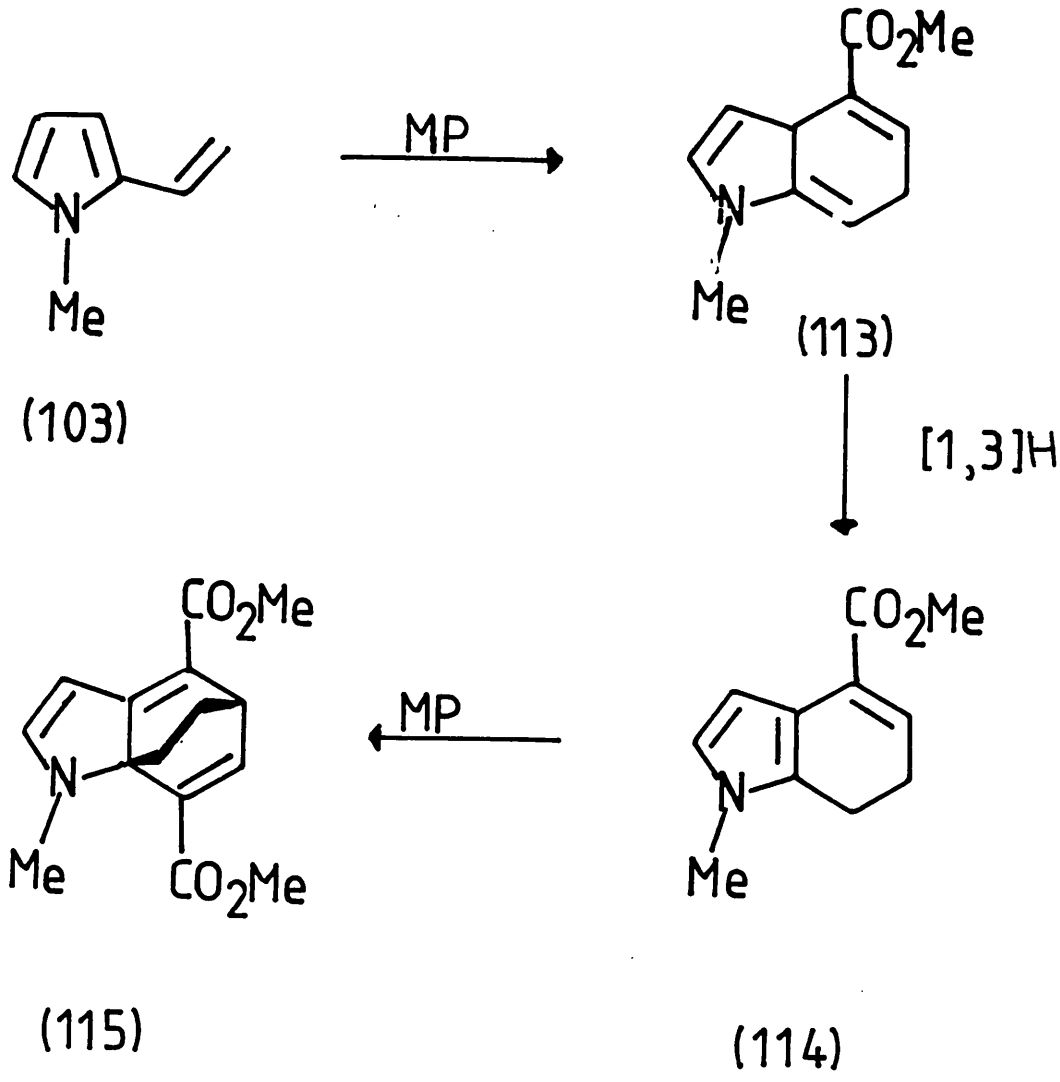
Scheme 10

Interestingly, Jones[34] noted that if the reaction between the vinyl pyrrole (103) and dimethyl acetylene dicarboxylate was conducted at room temperature, the formation of the substitution product (112) was observed to be competitive with the formation of the Diels-Alder product (110).

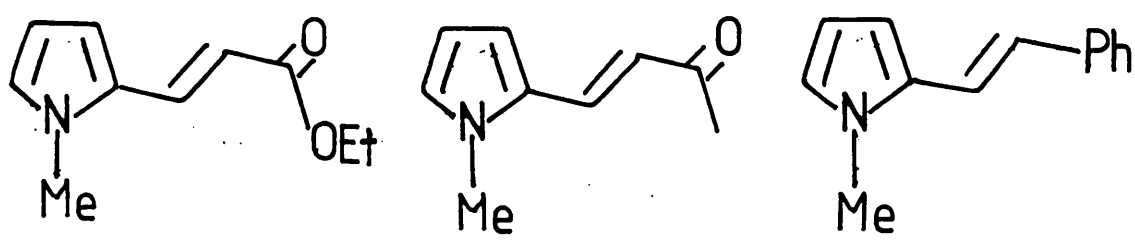


(112)

Methyl propiolate has also been observed to add in a [4+2] sense to 1-methyl 2-vinyl pyrrole (103).[32] However, in this instance the indole (116) was isolated. The rationale for the formation of this product is shown in scheme 11. In monitoring the reaction by ^{1}H nmr spectroscopy, the signals attributable to (114) were of low intensity, indicating that the subsequent steps depicted in scheme 11 were likely to be at least as fast as the first [4+2] cycloaddition. Consistent with these observations was the failure to isolate any of the dihydroindole (114).

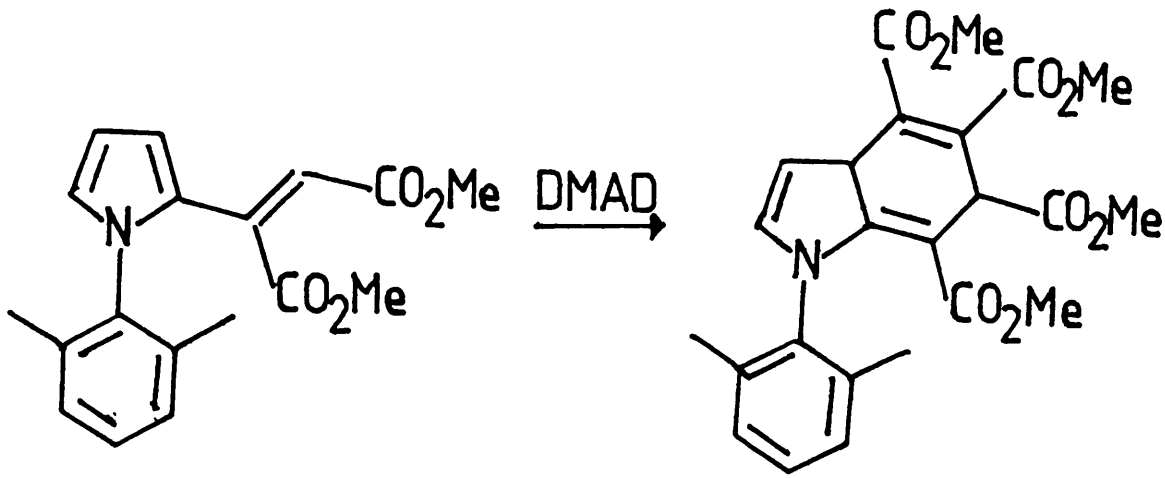

MP
CO2Me
N
Me
(103)
(113)
[1,3]H
MP
(115)
(114)
-CH2=CH2
(116)

Scheme 11


O
OEt
Ph
N
Me
(117)
(118)
(119)

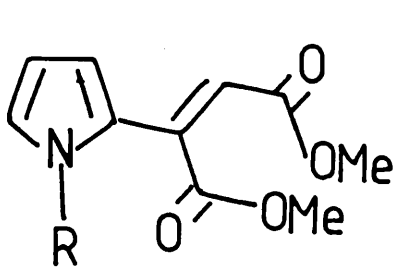
Initial indications in the literature suggested[32] that the three conjugated vinyl pyrroles (117), (118) and (119) failed to yield cycloadducts with maleic anhydride, instead furnishing "readily oxidised and thermally unstable products". The reactions of these three deactivated pyrroles with other dienophiles were stated to be very slow and incomplete. These results were consonant with their predicted low HOMO energy levels.[35]

However, recently Noland[36] has been able to obtain a compound to which he assigned the structure (121) from dimethyl (Z)-[1-(2',6'-dimethyl) phenyl-pyrrol-2-yl] maleate (120) and dimethyl acetylene dicarboxylate. Maleate (120) was the only one of a range of N-alkyl and N-aryl pyrrolyl maleates and fumarates that generated a cycloadduct.

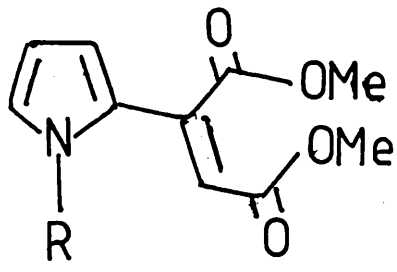


(120) (121)

Noland interpreted these results on steric grounds. He indicated that only the s-cis conformer of an N-substituted pyrrolyl maleate would be expected to be able to undergo a cycloaddition with a suitable dienophile. However, the steric interference generated between the substituent on nitrogen and the α-ester group of a typical maleate would make the s-trans conformation favourable, thus prohibiting cycloaddition.



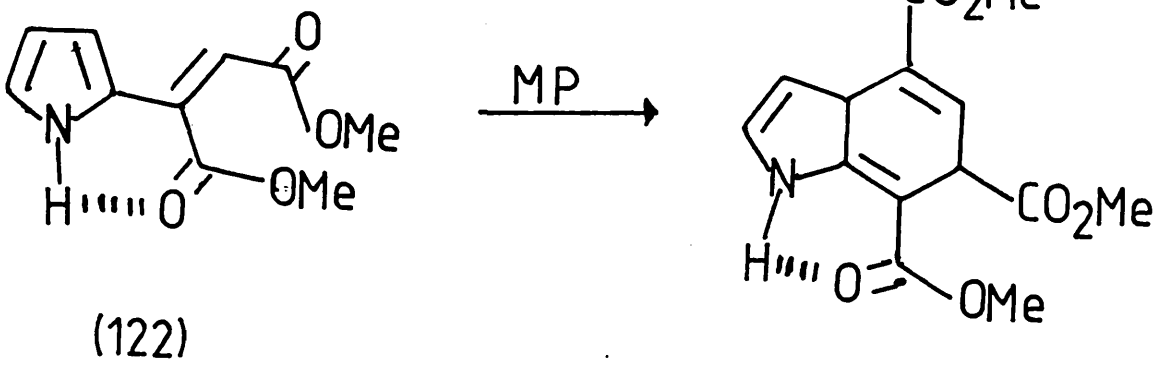
s-cis



s-trans

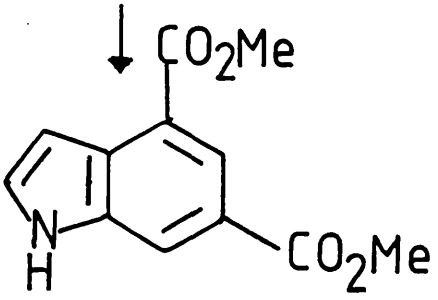
Thus the vast majority of compounds Noland studied would exist in the unsuitable s-trans conformation. However, (120) would be expected to exist in the s-cis conformation because the two ortho methyl groups on the N-phenyl substituent would be anticipated by steric buttressing to force the phenyl group out of coplanarity with respect to the pyrrole ring. This non-coplanar arrangement would, it was argued, reduce the steric interference between the phenyl group and the α-ester group, allowing attainment of the s-cis confirmation.

Similarly, it was observed[6] that the N-unsubstitued pyrrolyl maleate (122) yielded the indole (124) (24%) after reaction with methyl propiolate. Noland inferred in this instance that the s-cis conformation in the diene was preferred, owing to hydrogen bonding between the pyrrole NH and the α-ester carbonyl group. The observed loss of the 7-carbomethoxy group from the presumed intermediate (123) has literature precedent.[37]



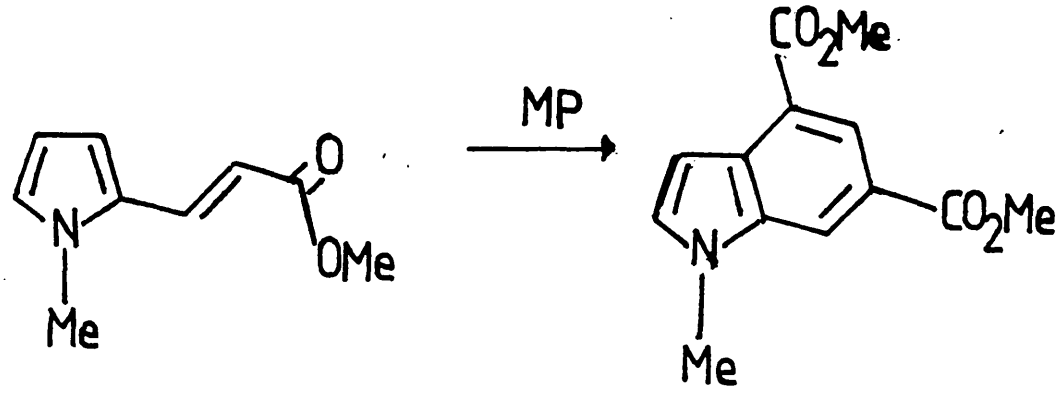
(122)

(123)

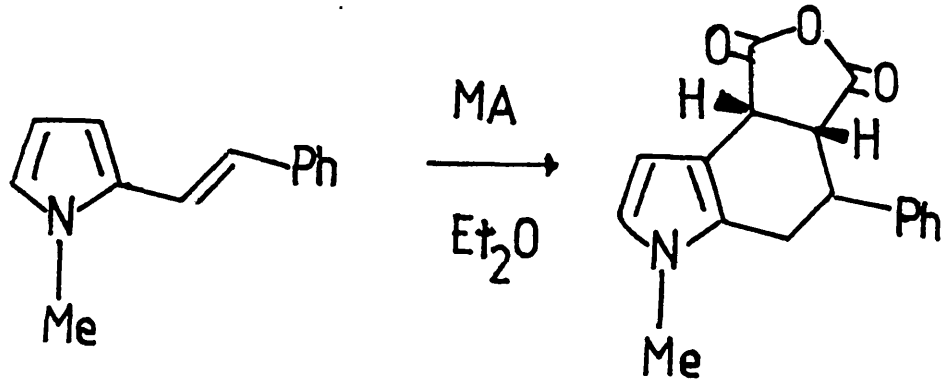


(124)

Noland also showed[6] that the acrylate (125) and the styryl pyrrole (119) would add methyl propiolate and maleic anhydride respectively to furnish the adducts (126) (32%) and (127) (34%).

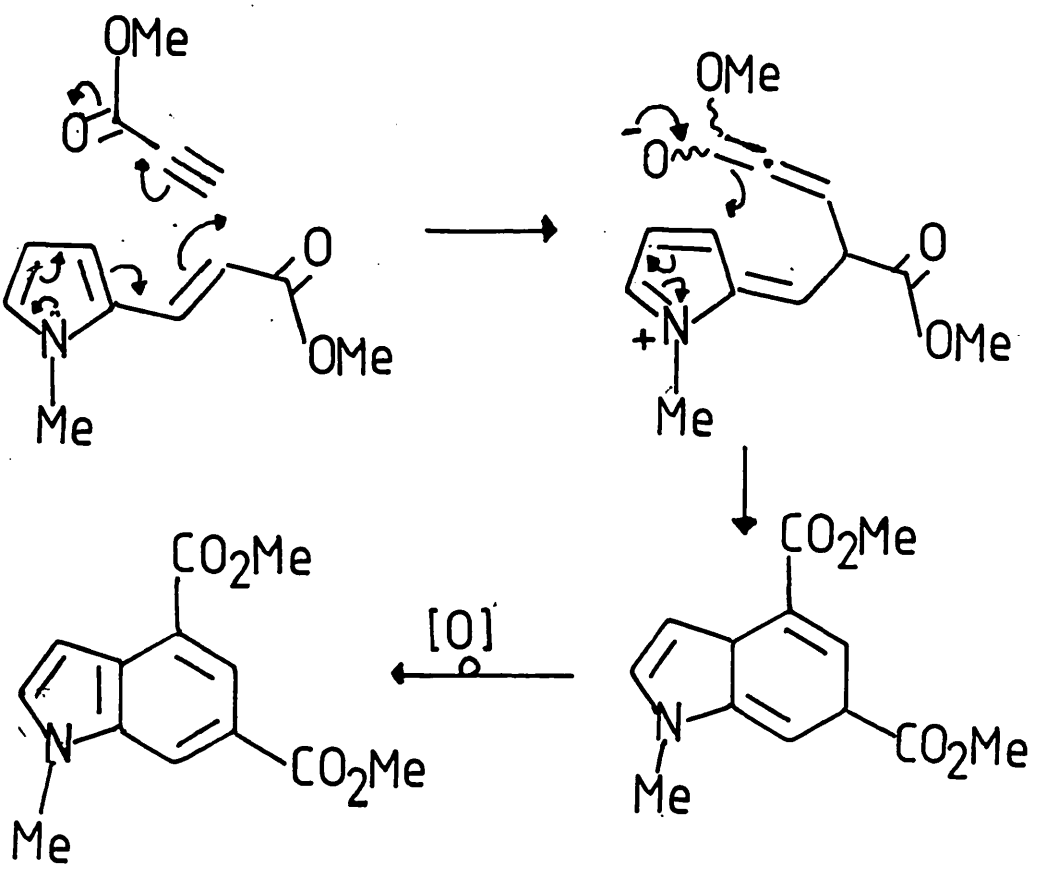


(125) (126)



(119) (127)

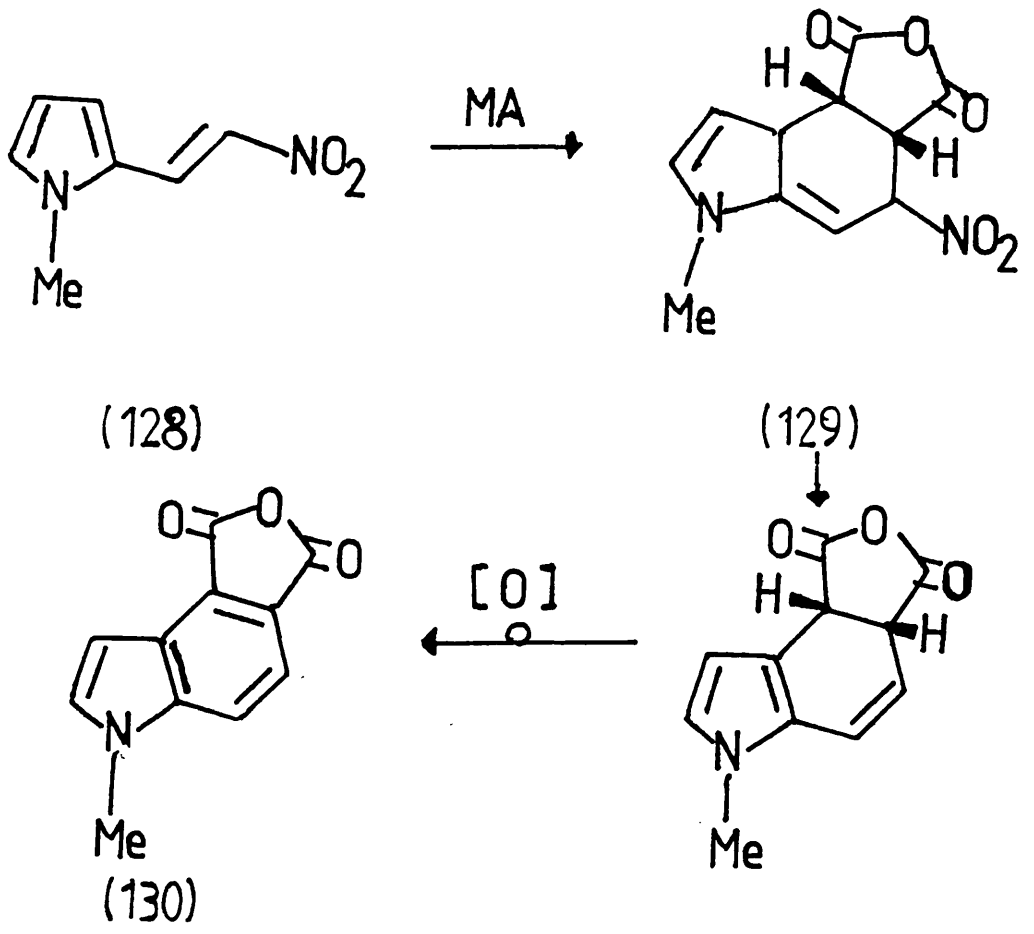
Noland argued that the only rational explanation for the ability of such deactivated vinyl pyrroles to act as dienes, whereas their furan and thiophene analogues do not, is that the cycloaddition actually proceeds via a stepwise nucleophilic addition of the pyrrole to the electron-deficient dienophile (scheme 12). Nitrogen has a greater electron-releasing ability than oxygen or sulphur and so the former is able to easily release electron density into the exocyclic diene system, promoting the reactivity of the latter.



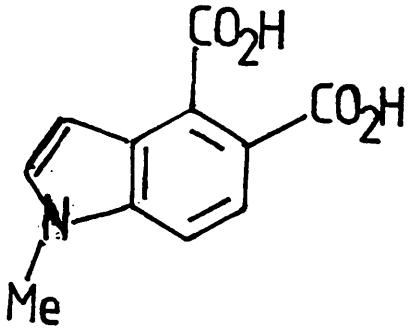
(126)

Scheme 12

The nitro-vinyl pyrrole (128) has also been utilised as an exocyclic diene.[38] Thus reaction of (128) with maleic acid or maleic anhydride was reported to produce the adduct (130) via elimination of nitrous acid from (129), followed by a simple dehydrogenation.



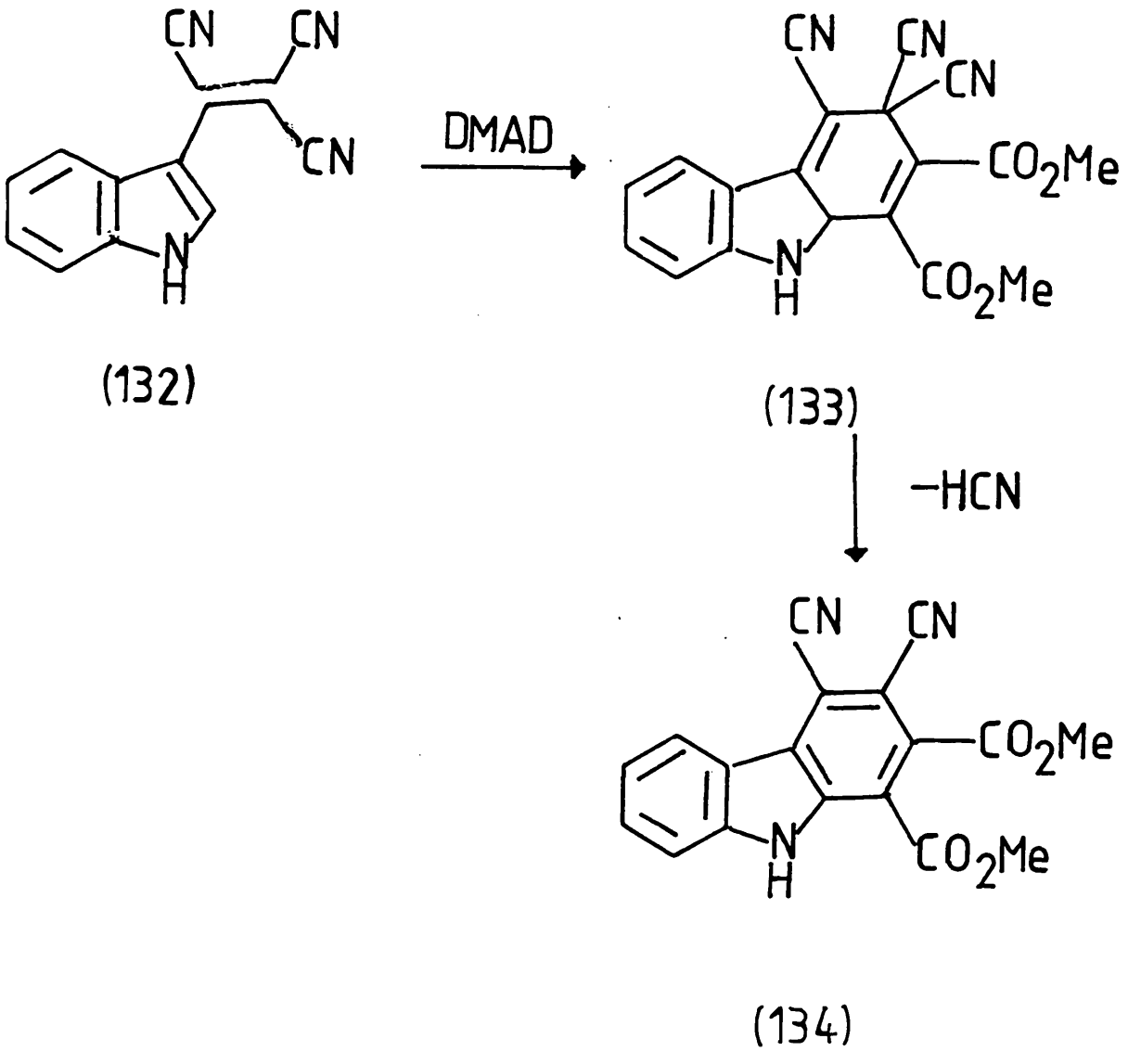
The presumed adduct (131) from (128) and maleic acid would be anticipated to cyclise to (130) under the acidic conditions generated by the liberation of nitrous acid.



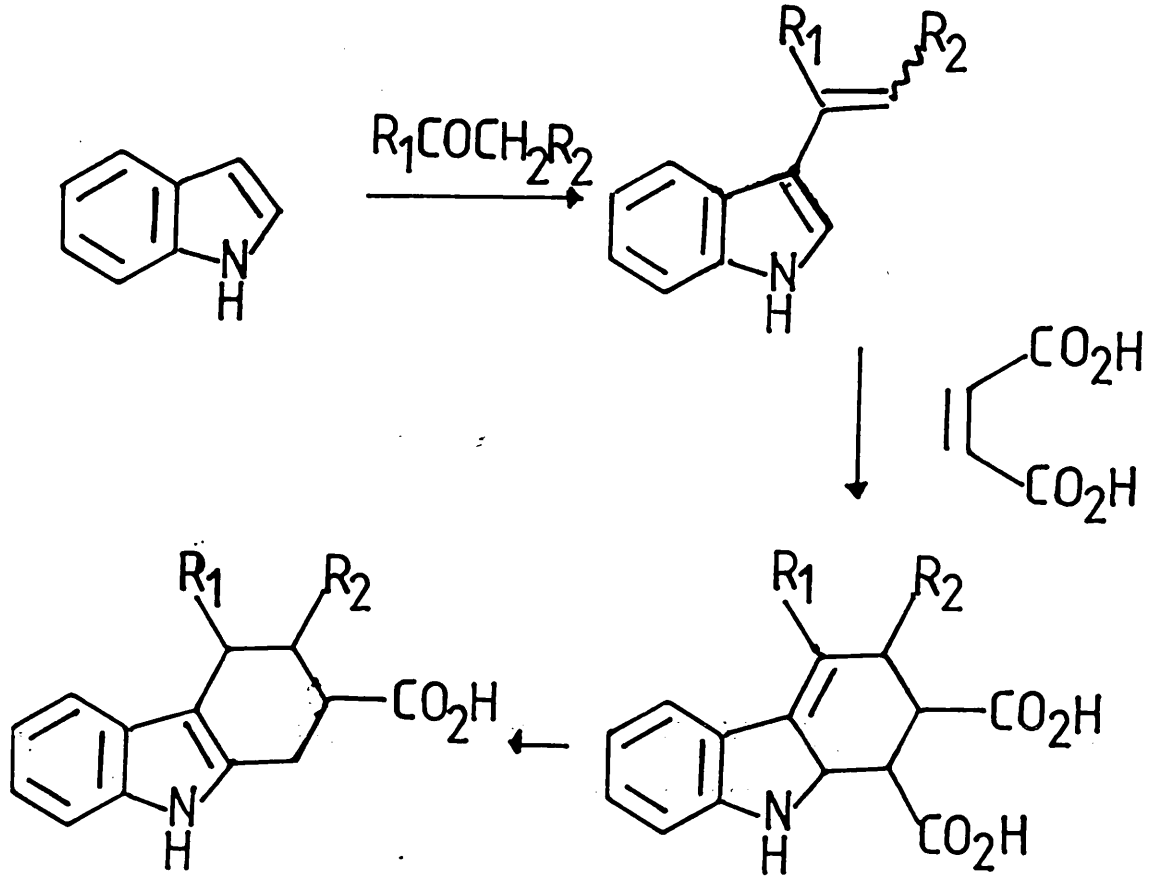
(131)

1.6. Cycloadditions involving vinyl indoles

In a search for a new route to compounds containing the carbazole ring system, the reactions of various 3-vinyl indoles with dienophiles have been investigated. The pioneering work in the field has been carried out by Noland and co-workers[39] who in 1959 discovered that 3-(tricyano)vinyl indole (132) reacted with dimethyl acetylene dicarboxylate at 230-250°C to yield the carbazole (134) presumably via loss of hydrogen cyanide from the intermediate (133).



More recently, a one-pot method for tetrahydrocarbazole synthesis direct from indole itself has been reported.[40] This method involved the in situ formation of a vinyl indole by the acid-catalysed condensation of a ketone with indole. The use of maleic acid both as a catalyst for the condensation reaction and as the dienophilic partner to the thus generated 3-vinyl indole proved very useful (scheme 13).



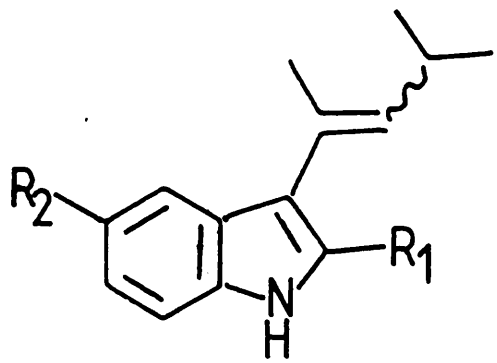
(136) (135)

Scheme 13

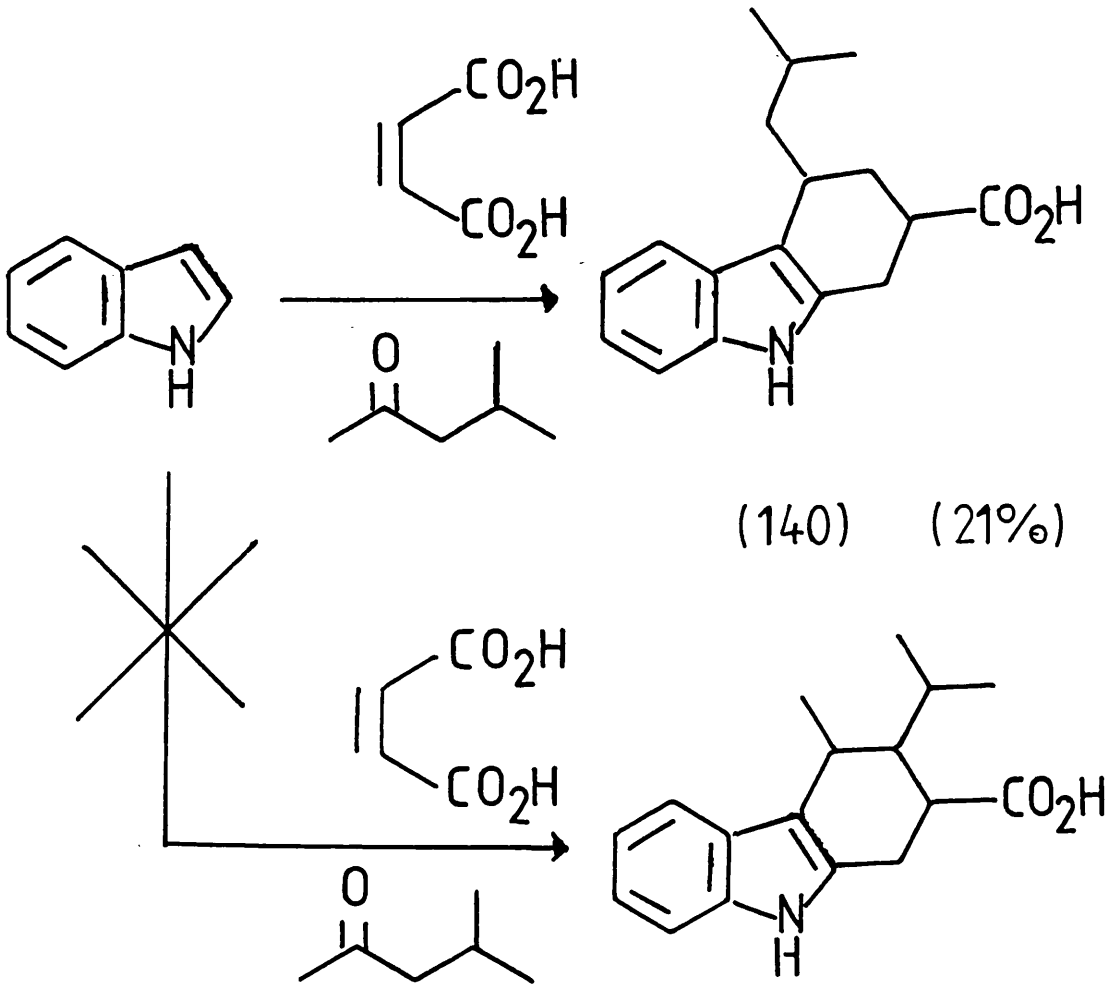
That the products contained an indole nucleus rather than the pre-aromatic unit of (135) was shown by UV spectroscopy. The loss of the carbazole 1-carboxyl group was not unexpected as it is well documented that indole 2-acetic acids undergo facile decarboxylation.[41]

This method for the preparation of tetrahydrocarbazoles appears to be very useful as it involves no isolation of the vinyl indole. 3-Vinyl indoles are typically very unstable and susceptible to rapid polymerisation at room temperature.[42]

Not surprisingly, bulky substituents on the exocyclic double bond of the 3-vinyl indole influence the course of the Diels-Alder reaction to a considerable degree. Thus although reaction of 4-methyl pentan-2-one with 2-methyl indole, 2-ethyl indole and 2-methyl 5-nitroindole apparently yields the thermodynamically more stable 3-vinyl indoles (137) - (139),[43] when a reaction is carried out by the <u>in situ</u> method with maleic acid, indole and the same ketone, the tetrahydrocarbazole (140) and not the expected isomer (141) is isolated.



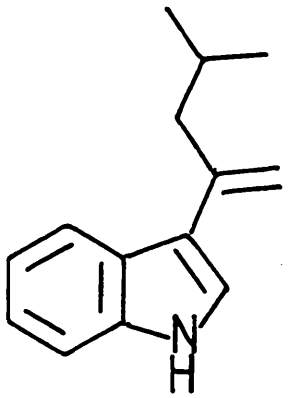
	R_1	R_2
(137)	Me	H
(138)	Et	H
(139)	Me	NO_2



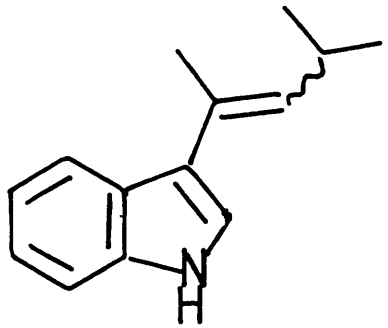
(140) (21%)

(141)

Tetrahydrocarbazole (140) would necessarily therefore originate from the expectedly less stable 3-vinyl indole isomer (142).

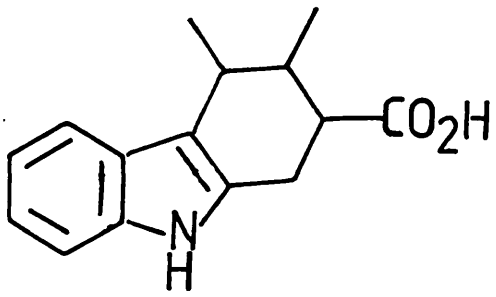


(142)

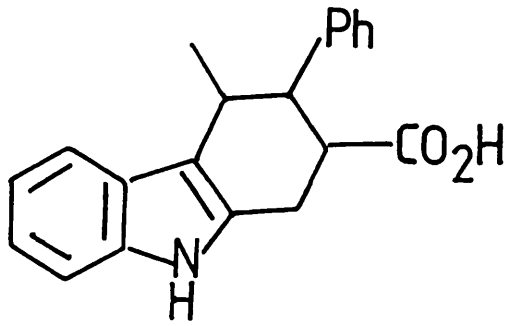


(143)

One possibility here is that the thermodynamically more stable isomer (143) is too sterically hindered to undergo a Diels-Alder reaction and simply undergoes (some) isomerisation to (142) under the acidic conditions of the reaction. The new diene (142) is less hindered than (143) and would thus be more easily able to react with maleic acid to yield tetrahydrocarbazole (140). However, use of butan-2-one and 1-phenylpropan-2-one as the ketone partners to indole and maleic acid resulted <u>only</u> in the formation of the adducts (144) and (145) respectively, formed from the thermodynamically more stable vinyl indole in each instance.

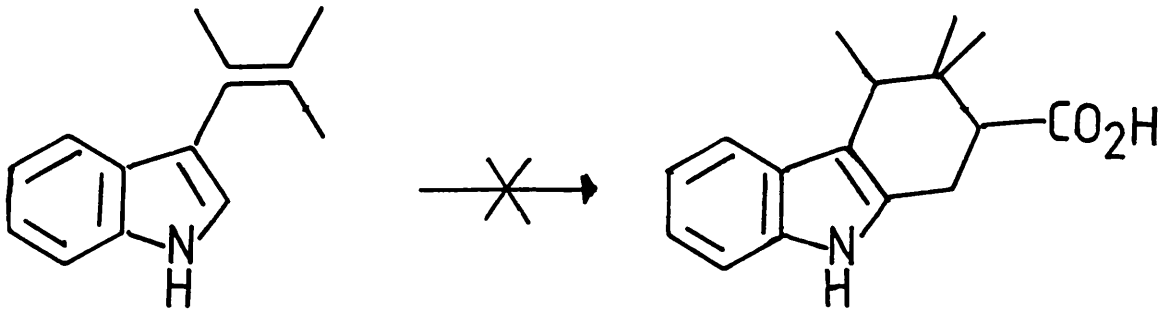


(144)



(145)

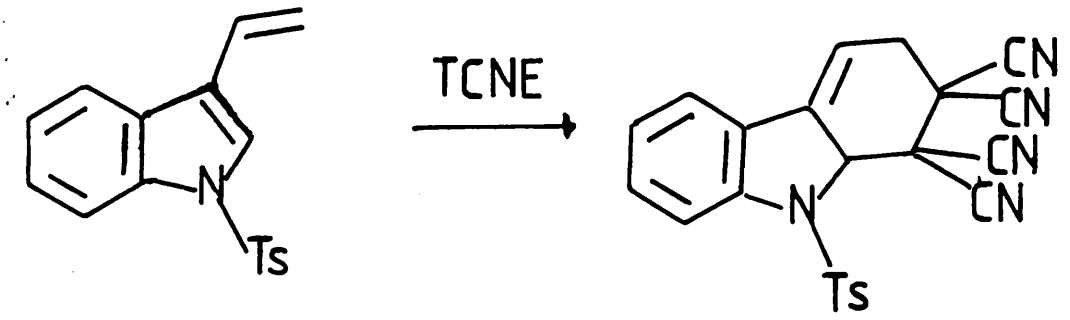
Furthermore, when 3-methyl butan-2-one was reacted with indole and maleic acid, no tetrahydrocarbazole (147) was formed. Experimental evidence suggested that the 3-vinyl indole (146) was produced but for steric reasons it did not undergo the [4+2] cycloaddition.



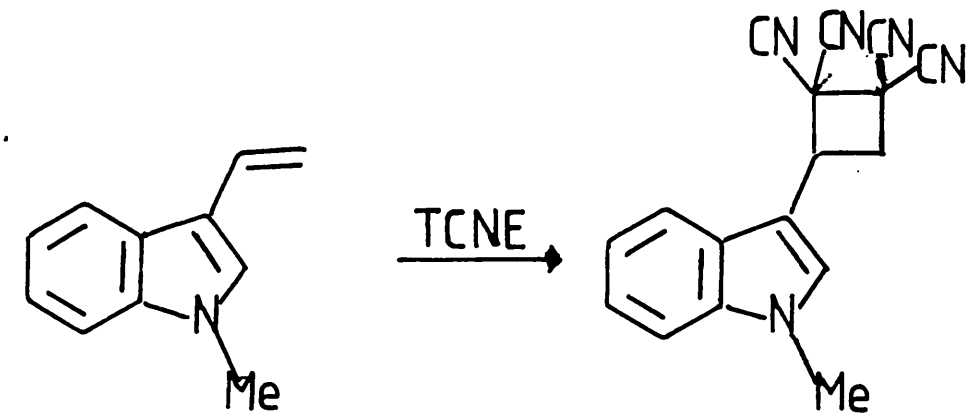
(146) (147)

Taken together, Noland believed this experimental evidence indicated that "the Diels-Alder reaction proceeds with the 3-vinyl indoles which are formed by kinetic control until its steric limits are exceeded".

Some very interesting observations have been made in the reactions of a variety of 3-vinyl indoles with tetracyanoethylene.[42] Thus although diene (148) was reported to yield the tetrahydrocarbazole structured compound (149), diene (150) apparently produced a compound assigned a cyclobutane structure (151) on reaction with the same dienophile.

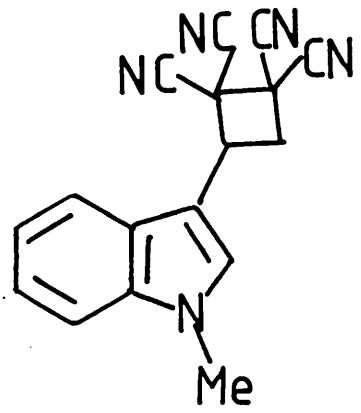


(148) (149)

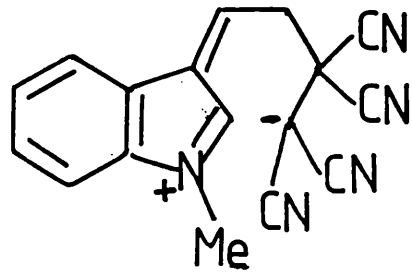


(150) (151)

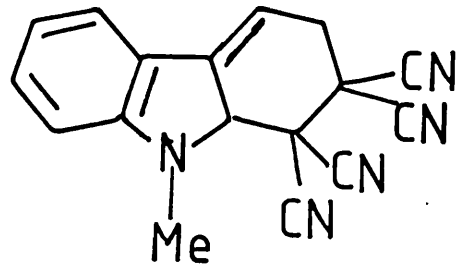
In the latter case, it was thought that an equilibrium existed between the cyclobutylindole (151) and the tetrahydrocarbazole structure (153). Thus production of the former was favoured in liquid sulphur dioxide at -35°C, whereas the latter was favoured in benzene at room temperature. The authors invoked the intermediacy of the resonance stabilised zwitterion (152) to account for the solvent dependent product distribution.



(151)

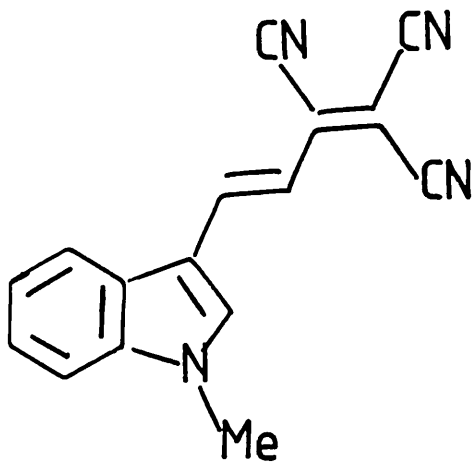


(152)



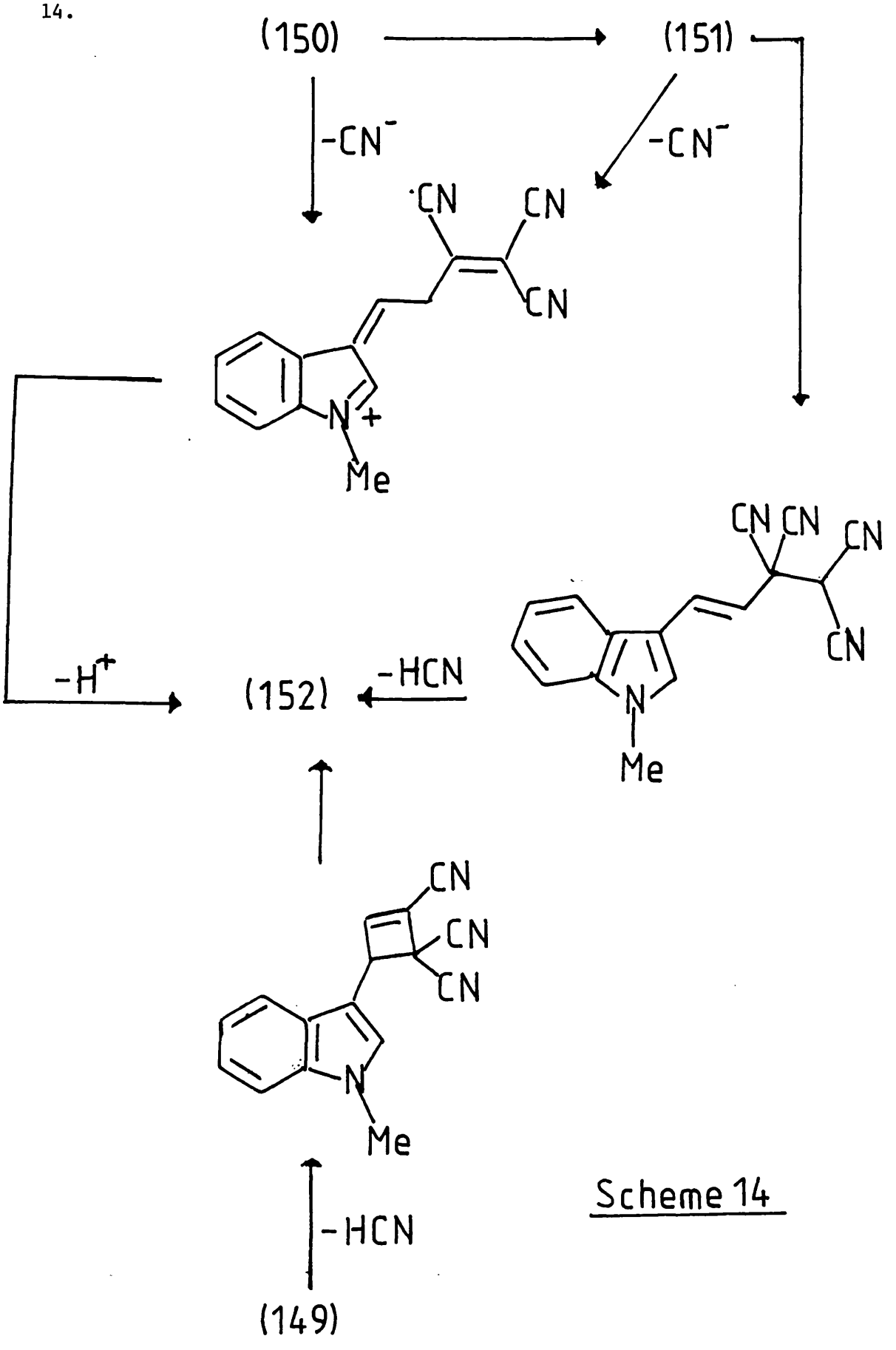
(153)

Both compounds (151) and (153) were reported to be very unstable decomposing in polar media or in air to the indolyl butadiene (154).



(154)

Several pathways were suggested to explain the formation of the butadiene (154). The most likely ones are shown in scheme 14.



Scheme 14

More interesting material in similar vein to that already discussed concerning vinyl indoles may be found in the work of Noland's group.[44-51]

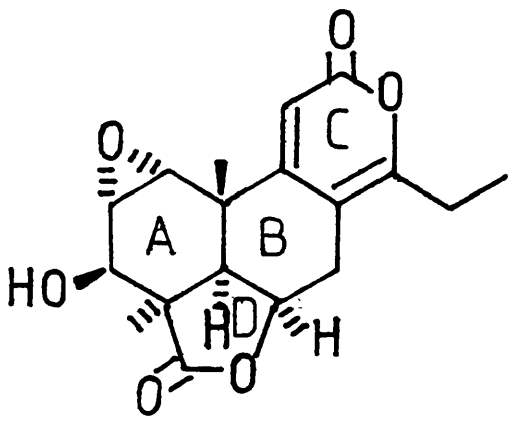
2.0 BIOLOGICALLY ACTIVE DILACTONES FROM PODOCARPUS

2.0. BIOLOGICALLY ACTIVE DILACTONES FROM PODOCARPUS

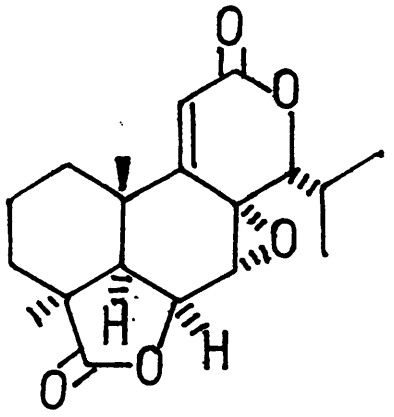
2.1. Structural variety and activity

Recent phytochemical studies of various species of the genus Podocarpus, a plant distributed throughout the southern hemisphere and eastern Asia,[52] have led to the discovery of a new family of terpenoids, including the very important nor- and bisnorditerpenoid dilactones, these latter two classes being the subject of this review.

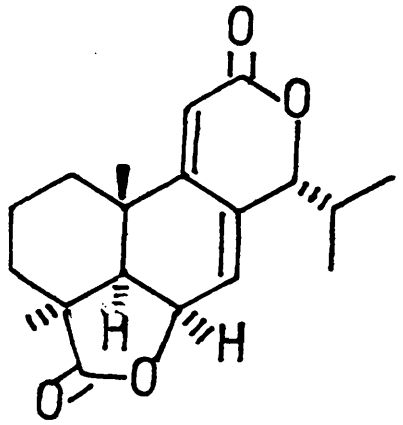
Since 1968 more than forty of these structurally novel, biologically active dilactones have been isolated.[53-62] These compounds may be conveniently divided into three major types, dependent upon the structure of the B/C ring portion.[63] Representative structures of each type are depicted below.



(155)



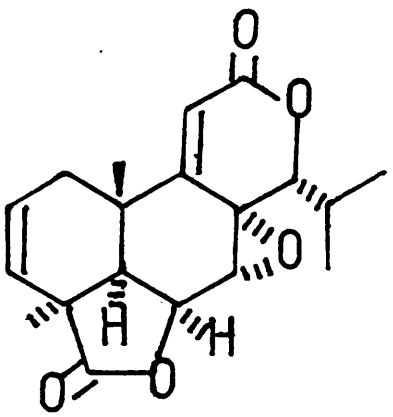
(156)



(157)

Thus the B/C ring portion may contain an α-pyrone moiety (155), an epoxy enolide system (156) or dienolide functionality (157).

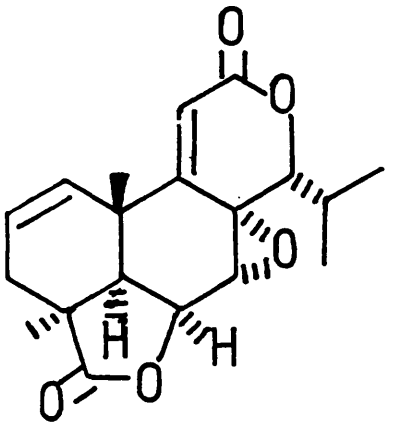
Not surprisingly, it is the structure of the B/C ring that influences the nature and potency of the biological activity of the dilactones. The most interesting property is the anti-tumour activity of some of these dilactones.[59,64-5] Thus nagilactone F (157)[66] and its oxygenated congener nagilactone G (156),[67] recently isolated from the bark constituents of Podocarpus milanjianus and Podocarpus sellowii, were both shown to possess significant cytotoxic activity in vitro against the 9kB nasopharyngeal cell culture system (10^{-2} µg cm^{-3}).[67] Similarly podolide (158), isolated from Podocarpus gracilior,[59] was observed to exhibit activity in vitro against cells derived from human nasopharyngeal carcinoma and against P388 murine leukaemia. Podolide (158) also exhibited in vivo activity against P388 leukaemia in mice.



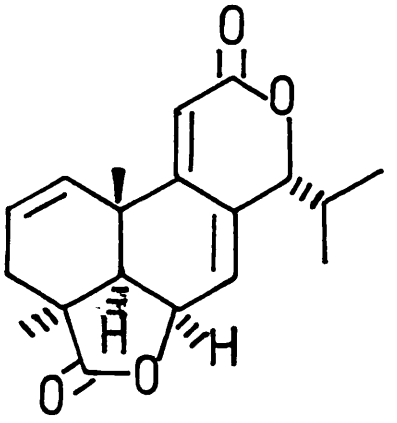
(158)

A comparison of the *in vitro* cytotoxicity of fifteen of these naturally occurring dilactones and their derivatives against cultured Yoshida sarcoma cells indicated that nagilactone G (156) was the most potent agent.[64] Correlation of the structural features of the tested dilactones with their activity suggested that the epoxy enolide or dienolide functionality was essential for the activity, whereas the γ-lactone functionality on the A/B ring was not.

Further work on extracts from *Podocarpus milanjianus* and *Podocarpus sellowii* resulted in the isolation of two more dilactones containing the dienolide moiety, milanjilactones A (159) and B (160).[60] These were found to possess similar activity to the structurally very similar nagilactones F (157) and G (156) in that they were cytotoxic towards kB nasopharynx carcinoma cells.

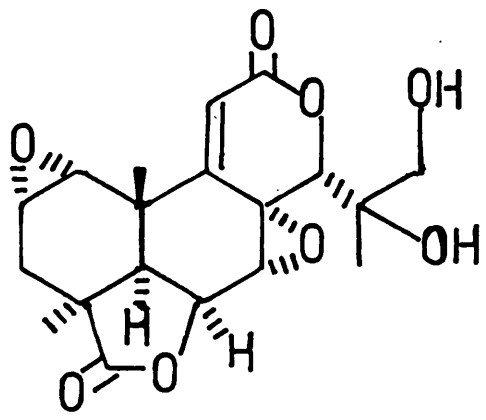


(159)

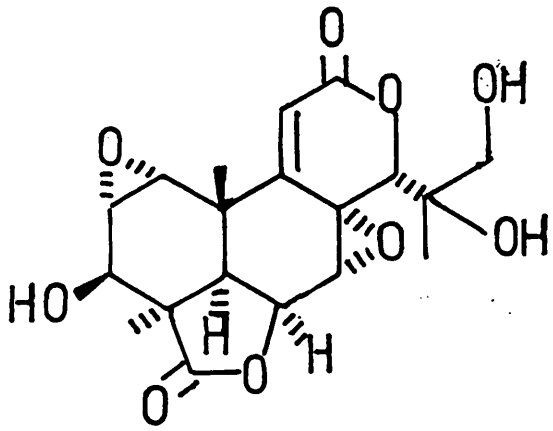


(160)

As well as the important anti-tumour properties, the family of dilactones can exhibit plant growth inhibitory activity.[63,66,68] For example, two epoxy enolide compounds podolactones A (161) and B (162), isolated from an Australian Podocarpus, were reported to strongly inhibit the growth of hook and apical segments of pea stems.[68] Podolactone A (161) was also noted to inhibit cell division in the Jerusalem artichoke system.[68]

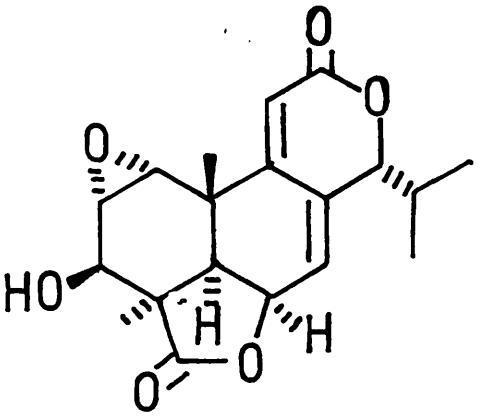


(161)



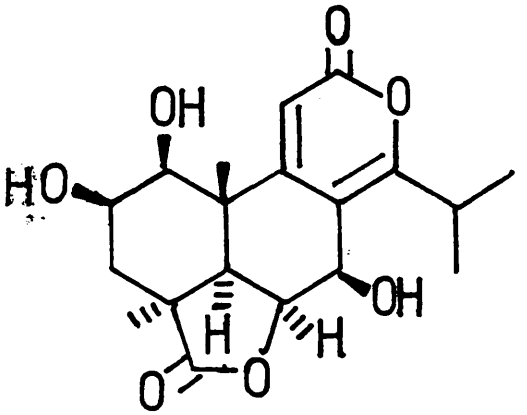
(162)

The dienolide functionality is also compatible with this activity. Thus ponalactone A (163) has been reported to inhibit the expansion and mitosis of plant cells.[69]



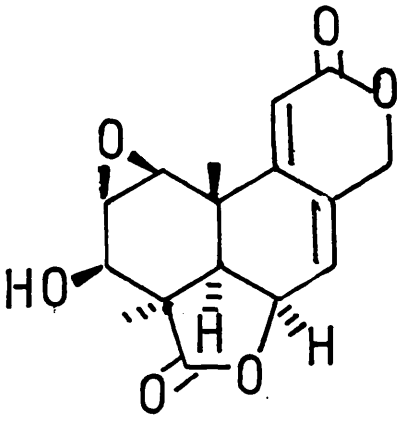
(163)

It is most interesting to note, however, that whereas the epoxy enolide and dienolide compounds show a simple proportional relationship between the dilactone concentration and the inhibitory effect, dilactones containing the α-pyrone unit, for example nagilactone B (164), demonstrate inhibition of growth at high concentrations but growth promotive activity at lower concentrations.[63] The workers here suggest that this is in accord with the α-pyrone type dilactones acting as plant growth regulators.

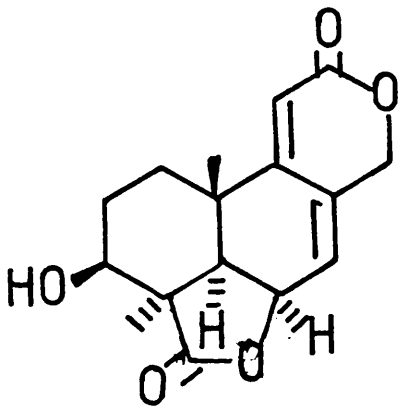


(164)

The recently isolated fungal metabolites wentilactones A (165) and B (166) have also been assayed for plant growth regulatory behaviour.[70] Wentilactone B (166) was found to be inactive in this respect at low concentrations, but at high concentrations in the wheat coleoptile bioassay it was found to be more inhibitory than the rather potent wentilactone A (165).



(165)

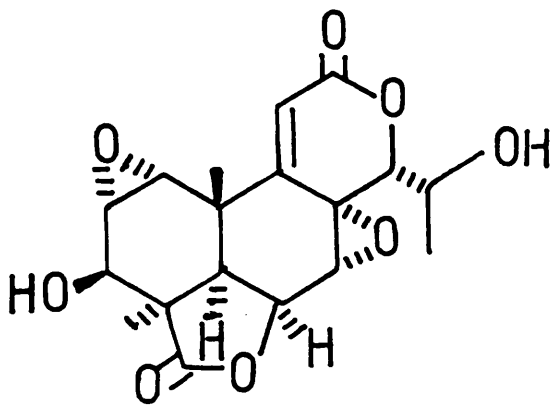


(166)

Unfortunately, wentilactone A (165), although a useful plant growth inhibition agent, has been reported to be toxic having an LD_{50} of 7mg kg^{-1} in one day old chicks on oral administration.[70] Wentilactone B (166) showed no such toxicity up to 250 mg kg^{-1}.

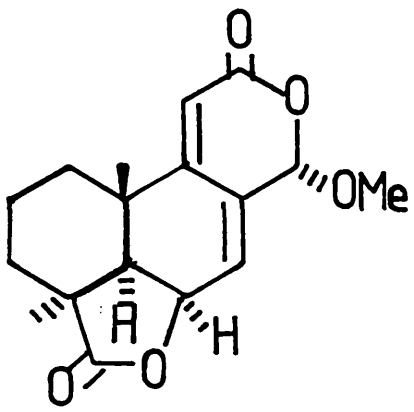
The Podocarpus dilactones have also been reported to possess some insect toxicity.[71] In a comparison of the effect of twelve nor- and bisnorditerpenoid dilactones on the adult housefly, nagilactone D (155) was found to have the most profound effect, being 10 to 100 times more active than the other lactones tested. Nagilactone D (155) was also discovered to be the most active of six of these dilactones when tested for their effect on the larval development, pupation and adult emergence of the housefly.

Finally, in terms of biological activity, two of the dilactones have been found to possess termiticidal properties.[72] These active compunds were nagilactone D (155) and inumakilactone A (167).[54]



(167)

It has been suggested[73] that the dilactones play a dual role in nature. Their first function may be to act as toxins to protect Podocarpus from insect damage and their second may be to control the pattern of plant colonisation around the Podocarpus plants. It was further suggested[73] that the dilactones may be biosynthesised for the Podocarpus plants by mycorrhizal fungi. Possible evidence for this was tendered on the grounds that the structurally very similar antifungal mold metabolite (168) has been isolated[74.75] from a fungus commonly found infecting plant roots or inhabiting the rhizosphere.



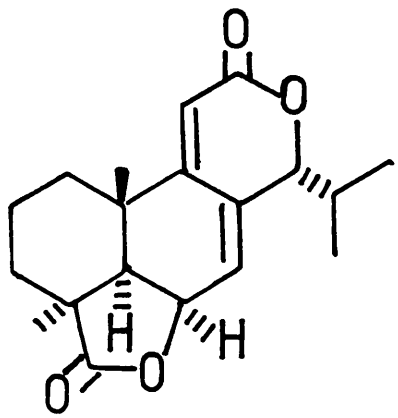
(168)

Similarly, the wentilactones A (165) and B (166) are fungal metabolites.[70] It should be noted that in common with (168) these also lack a carbon side chain at C-14.

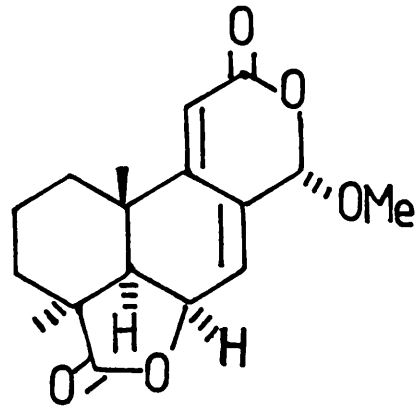
Hence it was postulated that the family of dilactones bearing a C-14 side chain may simply be plant altered fungal metabolites.

2.2. Synthetic efforts towards the dilactones

Only three total syntheses of members of the biologically active dilactone group have been reported. Two of these were concerned with the tetranorditerpenoid antifungal mold metabolite LL-Z1271α (168) and the other with nagilactone F (157).[78]



(157)



(168)

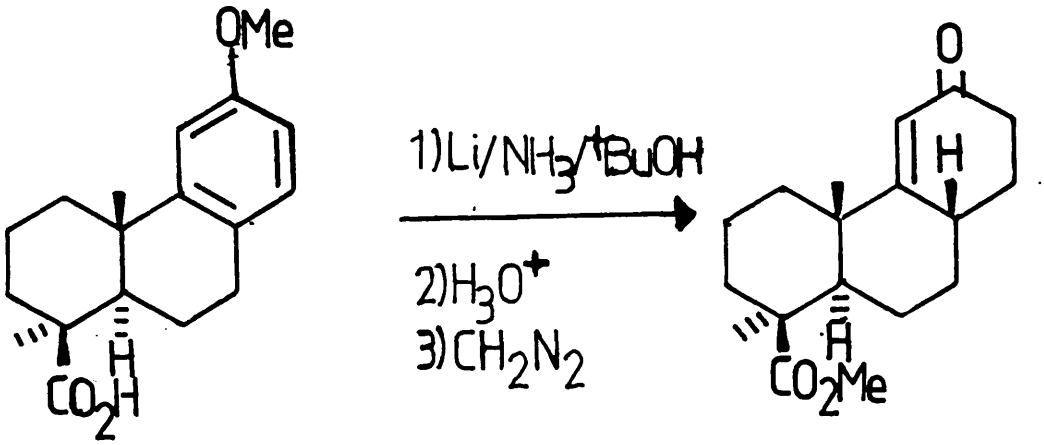
Nagilactone F (157) was chosen by Japanese workers[78] as a synthetic target as it represents the most biologically active and structurally the simplest of the family of dilactones.

The starting material chosen was the tricyclic S-(+)-podocarpic acid O-methyl ether (169), a reasonably cheap and readily available chiral building block, containing three of the stereocentres necessary for nagilactone F (157).

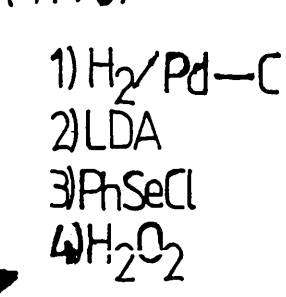
The synthesis is very long, owing to the many steps necessary to convert the aromatic ring of (169) to a lactone moiety and to introduce the necessary C-14 isopropyl group in a stereocontrolled manner. The early steps are shown in scheme 15.

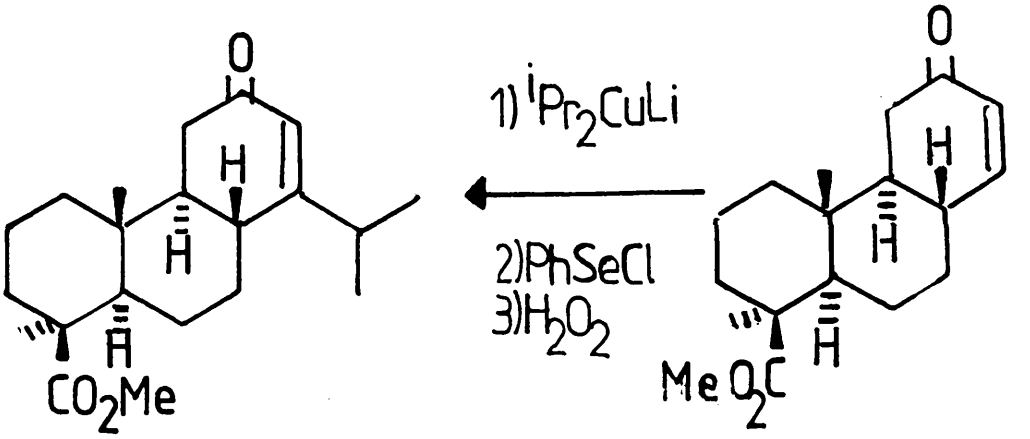
Birch reduction of the O-methyl ether (169) followed by sequential work-up with methanolic HCl/diazomethane afforded the $\Delta^{9,11}$ enone (170) in 41% yield. Catalytic hydrogenation of the enone (170), followed by introduction of a double bond in the 13,14 position *via* oxidative elimination of the 13-phenylselenenyl ketone gave (171) in high yield. The isopropyl group was then introduced by means of lithium di-isopropyl copper dimethyl sulphide complex. The intermediate enolate formed was directly trapped with phenylselenenyl chloride to yield a 13-phenylselenenyl ketone which was again transformed to an enone by oxidative elimination, furnishing (172) in good yield. Ozonolysis of this enone, followed by Jones oxidation, produced the important ketoacid (173).

With the ketoacid (173) in hand, the Japanese workers now hoped to assemble the lactone moiety present in the natural product without much problem. However, diborane reduction of (173) followed by treatment with diazomethane afforded a mixture of the undesired 14β-isopropyl lactone (174) (46%) and the hydroxyester (175) (40%). The latter could be lactonised under vigorous conditions (tosic acid/benzene/reflux) to yield the epimeric lactone (176) (95%).

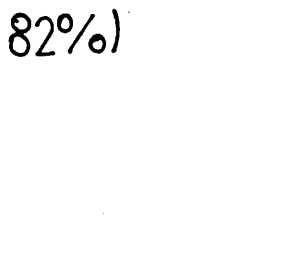


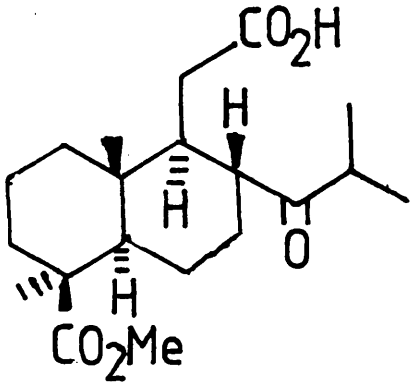
(169) (170) (41%)





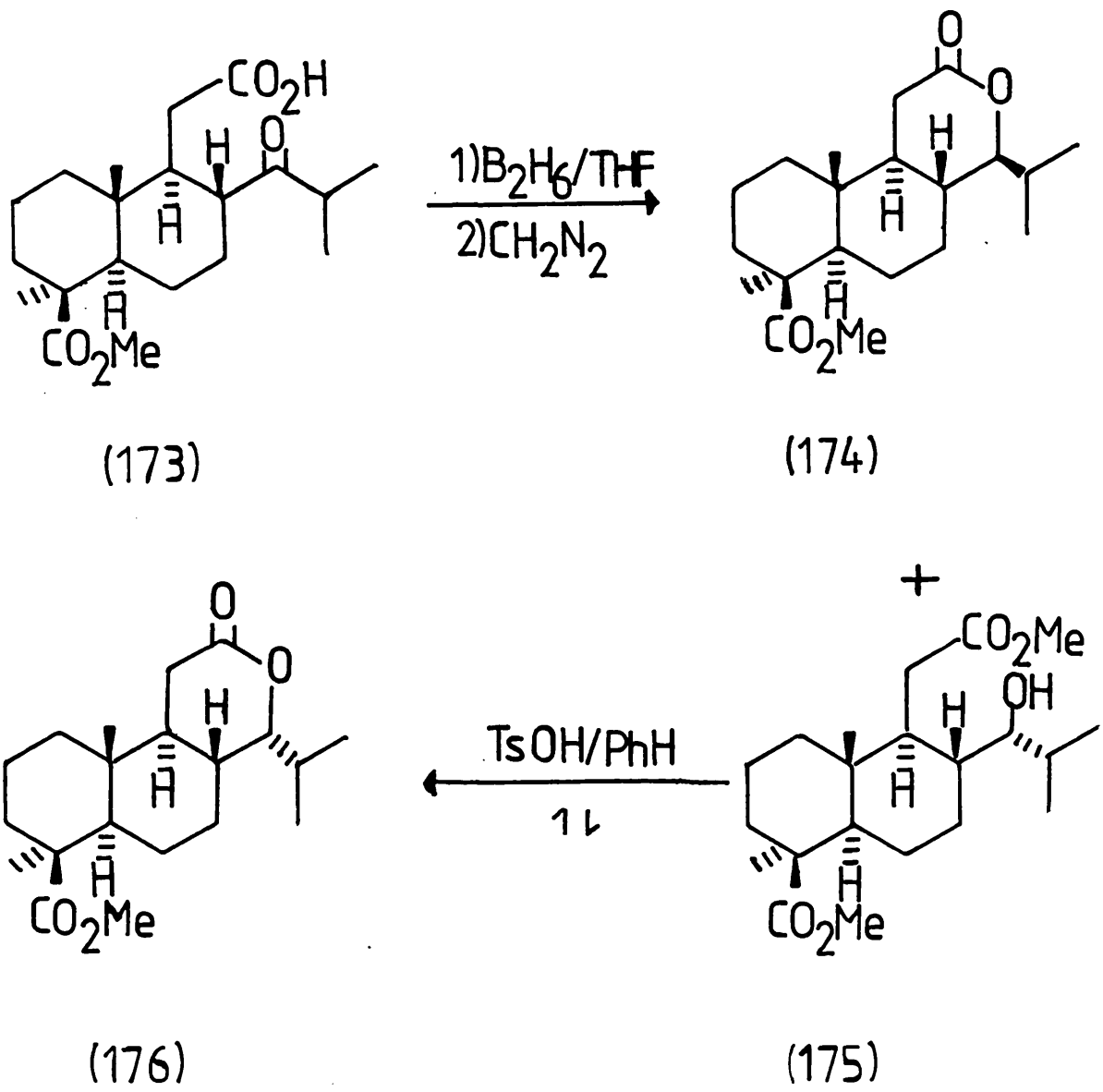
(172) (75%) (171) (82%)



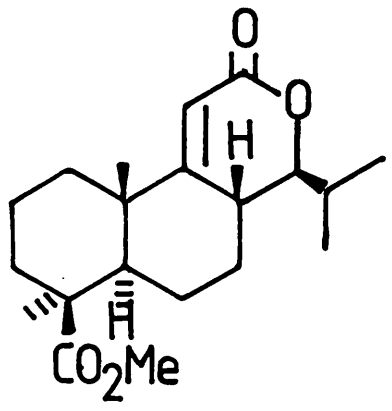


(173) (72%)

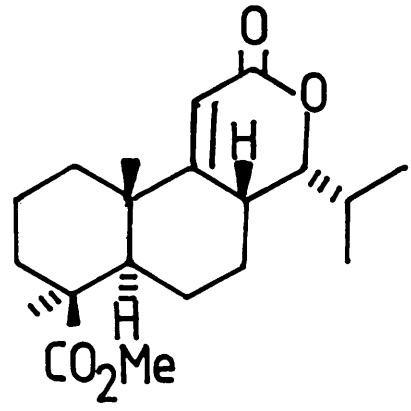
Scheme 15



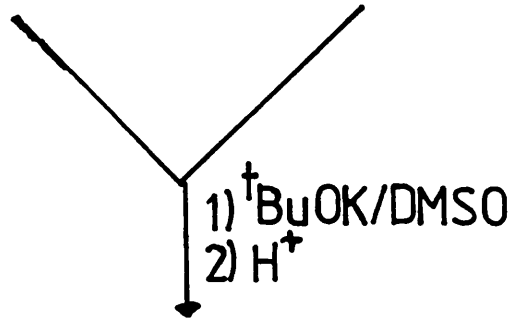
Obviously rather than wasting half of their precious lactone as the undesired 14β-isomer, the Japanese workers decided to carry both (174) and (176) through to a common precursor to nagilactone F (157). Thus (174) and (176) underwent the usual α-selenenylation - oxidative elimination procedure to produce the enolides (177) and (178) respectively. The reaction of each of these enolides with potassium tert-butoxide (three equivalents) in dimethylsulphoxide at room temperature resulted in the quantitative formation of the same carboxylic acid (179).

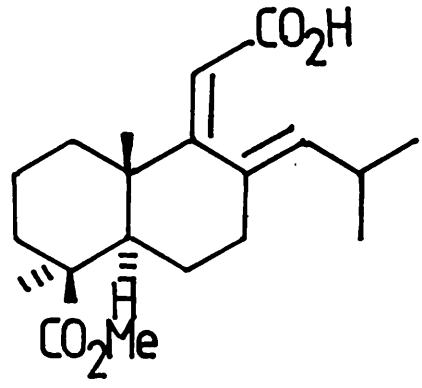


(177)



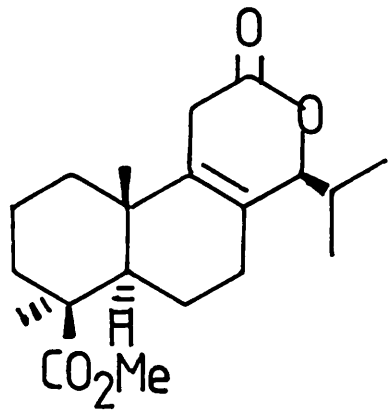
(178)



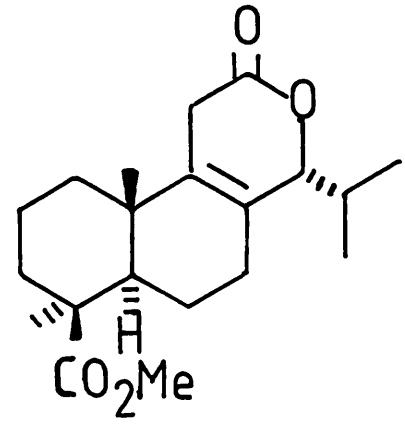


(179)

It was discovered that on heating (179) at 210°C for one minute, two isomeric lactones (180) and (181) were formed quantitatively in a ratio of 5:3. Fortuitously, on irradiation in ethanol at 0°C, (179) was transformed in 90% yield to a single enolide assigned structure (181) by comparison with an authentic sample produced by degradation of nagilactone F (157).

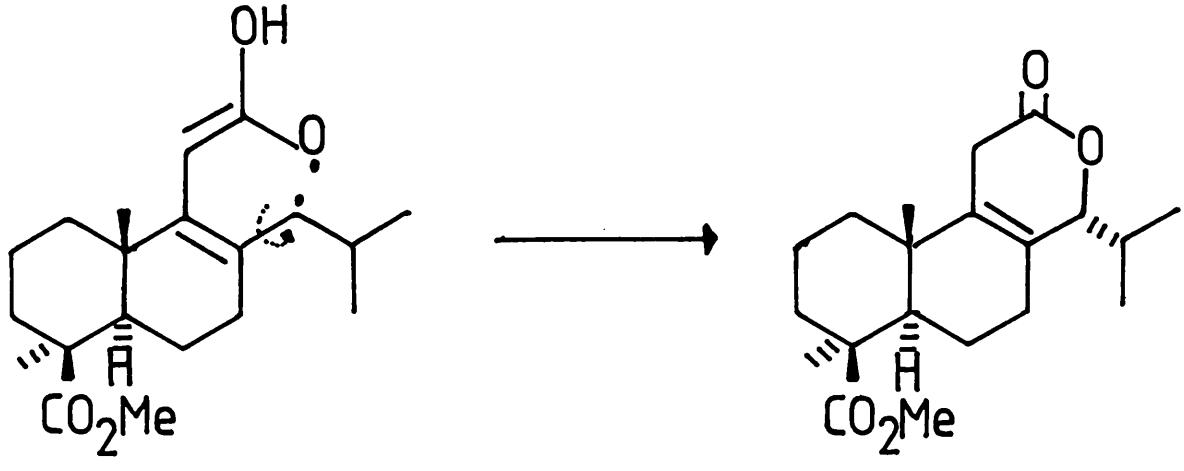


(180)



(181)

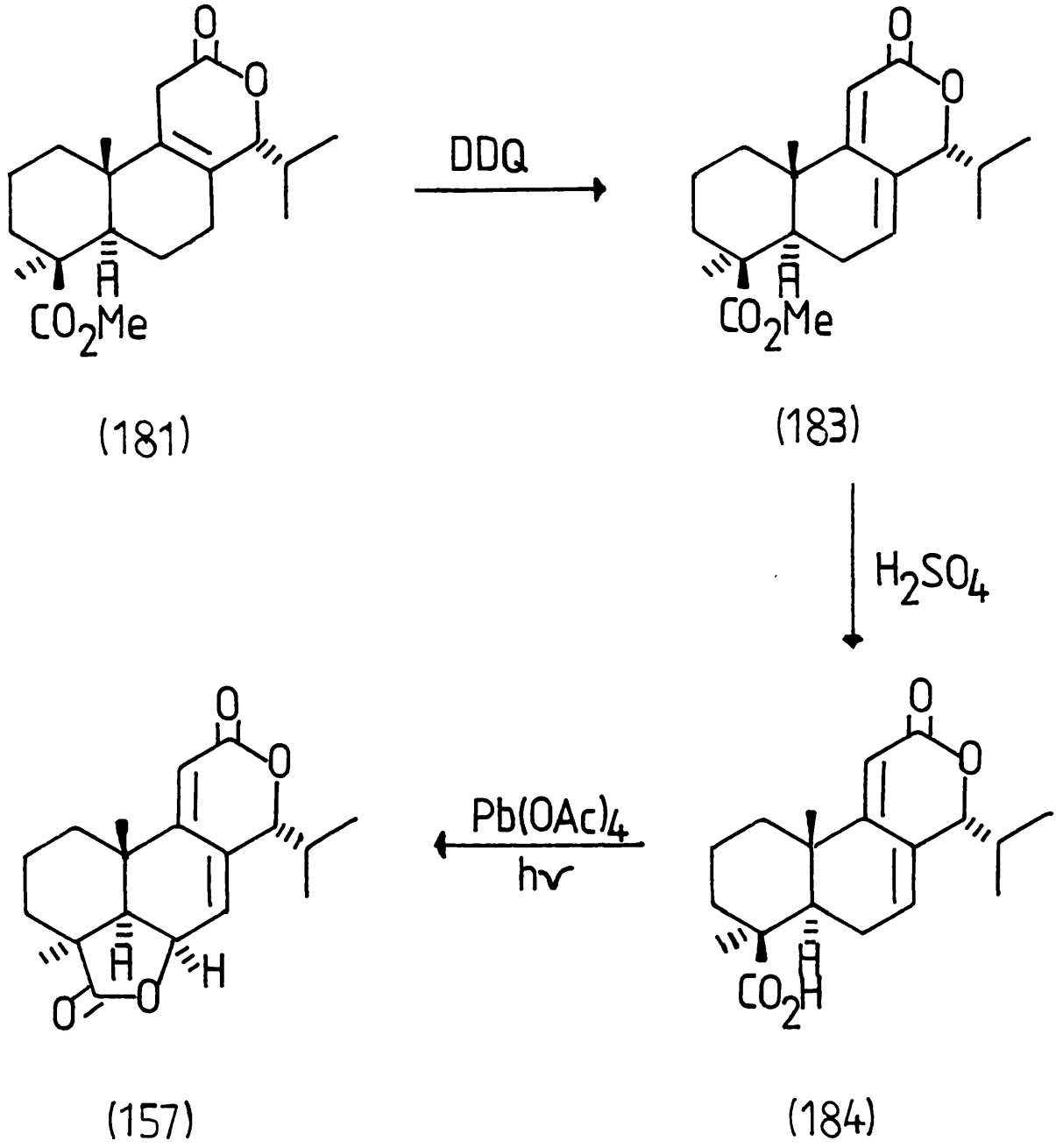
A possible explanation tendered for the unexpected production of a single enolide on photolysis involved a cyclisation proceeding via diradical (182), in which the bulky isopropyl group would attempt to avoid non-bonded interference with the C-10 angular methyl group. Bond rotation to accomplish this would be thus anticipated to furnish only the 14α-isopropyl lactone (181).



(182)

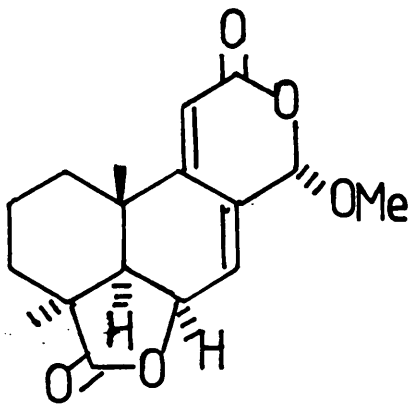
(181)

Elaboration of the β,γ-unsaturated lactone (181) to nagilactone F (157) was achieved straightforwardly by dehydrogenation to the dienolide (183), using dichlorodicyano-p-benzoquinone in the presence of boron trifluoride etherate, hydrolysis of the methyl ester to the acid (184) with concentrated sulphuric acid and finally lead tetraacetate-induced photochemical γ-lactone generation.

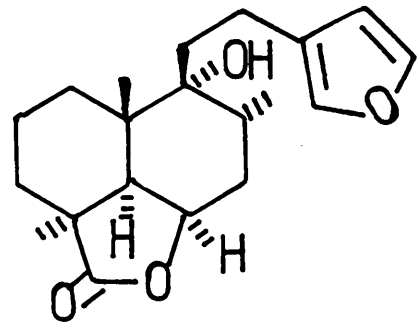


(181) (183) (157) (184)

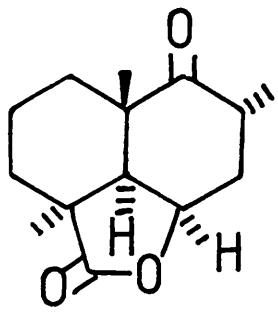
In contrast to the above, the first literature synthesis of LL-Z1271α (168) was of interest because of its brevity.[76] Once more, the chosen starting material was a chiral substance, in this case the ketolactone (186) readily available from degradation of marrubiin (185).[79] Thus bromination of this ketone with bromine in acetic acid followed by dehydrobromination using 1,5-diazabicyclo-[4.3.0]-non-5-ene (DBN) produced the enone (187) in 86% yield.



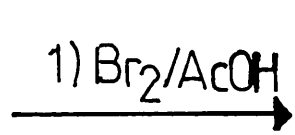
(168)

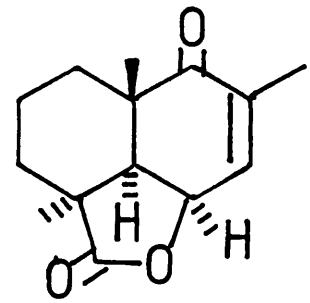


(185)



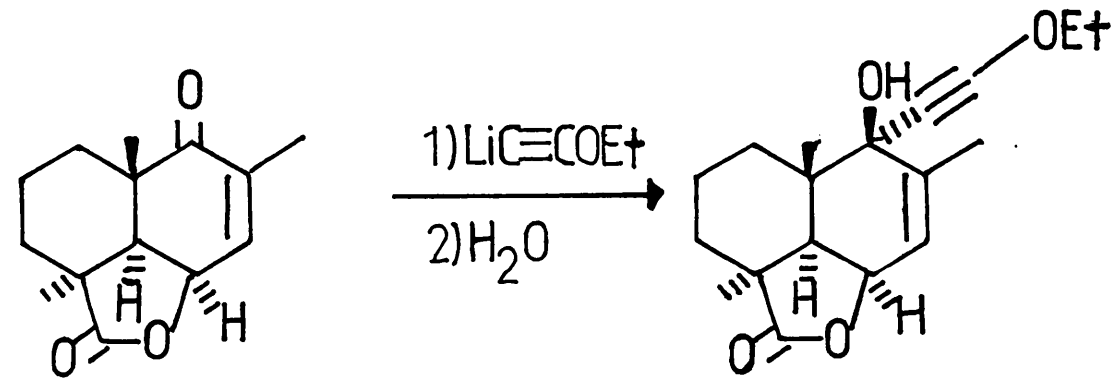
(186)



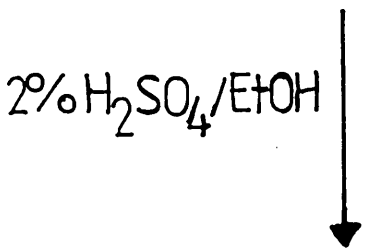


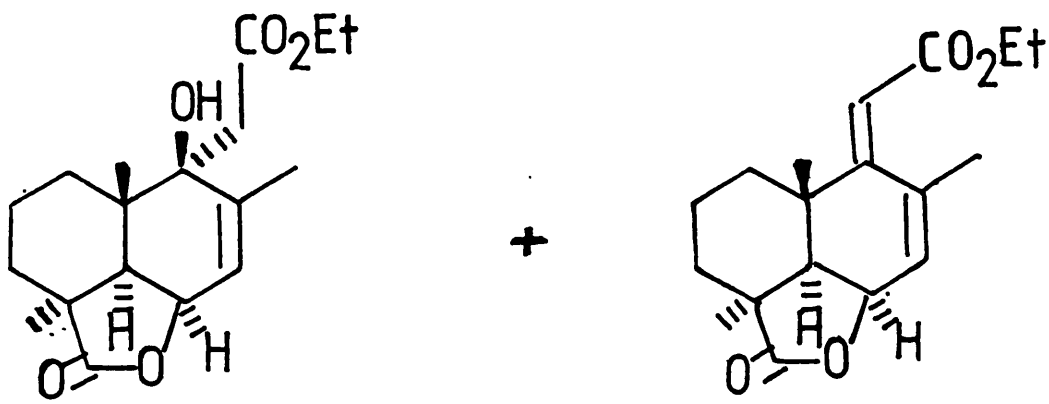
(187)

Treatment of the enone (187) with lithium ethoxyacetylide produced the tertiary alkynyl alcohol (188) (90%) which was assigned the depicted 9β-hydroxy configuration on the basis of attack of the carbanion from the least hindered α-face. Brief exposure of the alkynyl alcohol to 2% sulphuric acid in ethanol then resulted in generation of the unsaturated ester (189) (65%) together with the β-hydroxyester (190)(28%).



(187) (188)

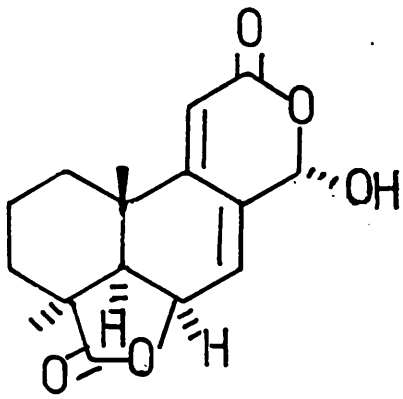




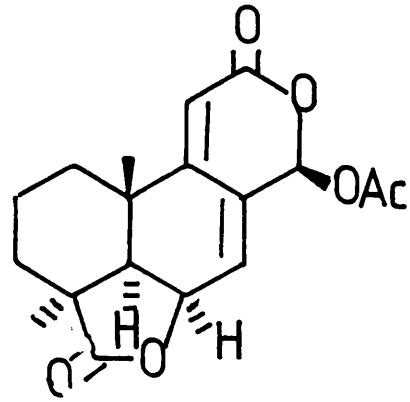
(190) (189)

The configuration of the diene ester (189) was assigned as shown on the basis of the observed five bond coupling constant of 1.5Hz between the two vinylic protons.

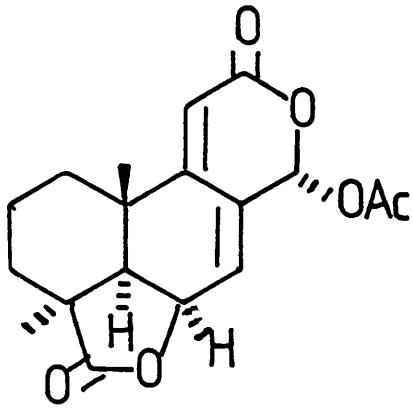
Allylic oxidation of the diene ester (189) with two equivalents of selenium dioxide in acetic acid resulted in the formation of four products, the lactol (191) (55%), the two epimeric lactol acetates (192) (30%) and (193) (10%) and the lactone (194) (5%).



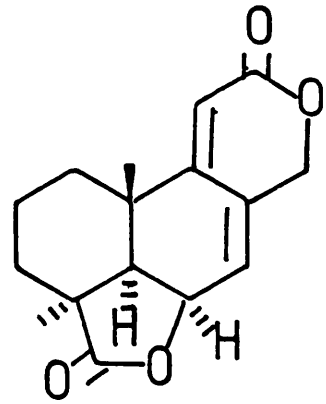
(191)



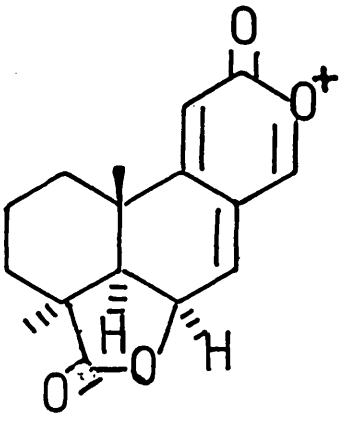
(192)



(193)

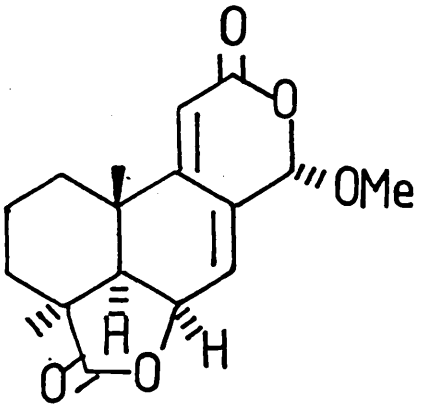


(194)

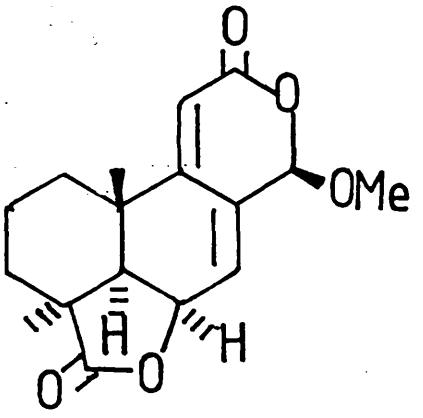


(195)

It was postulated that the two epimeric acetates (192) and (193) existed in an equilibrium <u>via</u> the cation (195) as the acetate (193), when treated under the same conditions as used for the selenium dioxide oxidation, yielded a 3:1 mixture of (192) and (193). Simple treatment of either (192), (193) or the mixture of (192) and (193) isolated from the reaction (or from the acetylation of lactol (191), ratio of (192): (193),1:2) with methanolic HCl resulted in the formation of the desired natural product (168) and its epimer (196) in an unfavourable 1:2·5 ratio in very high yield.

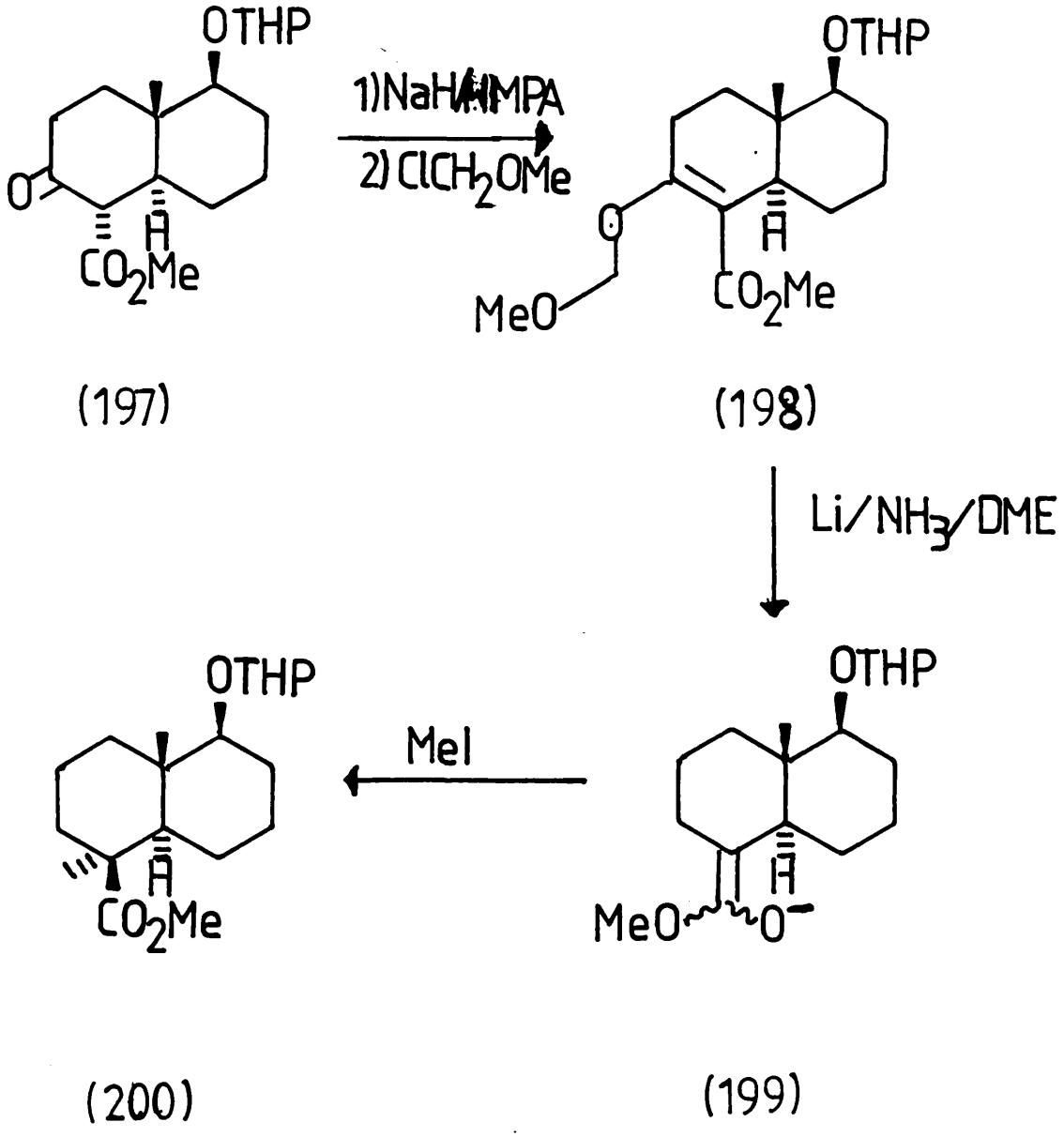


(168)

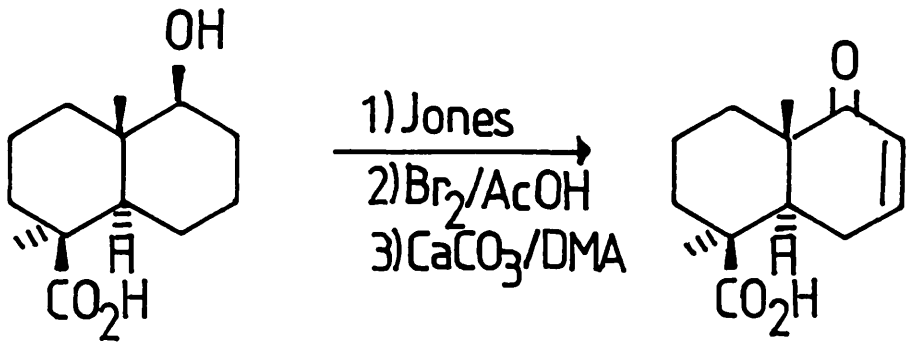


(196)

Unlike the Italian work,[76] the American synthesis of LL-Z1271α (168)[77] was a racemic one and of much greater length. Welch employed ketoester (197) as the starting material because of its ready synthesis from the Wieland-Miescher diketone. On treatment with sodium hydride in HMPA and quenching with chloromethyl methyl ether, (197) afforded (198) in high yield. Generation of the exocyclic enolate (199) via a reductive elimination technique and quenching with methyl iodide formed the desired ester (200) with an equatorial methyl group.

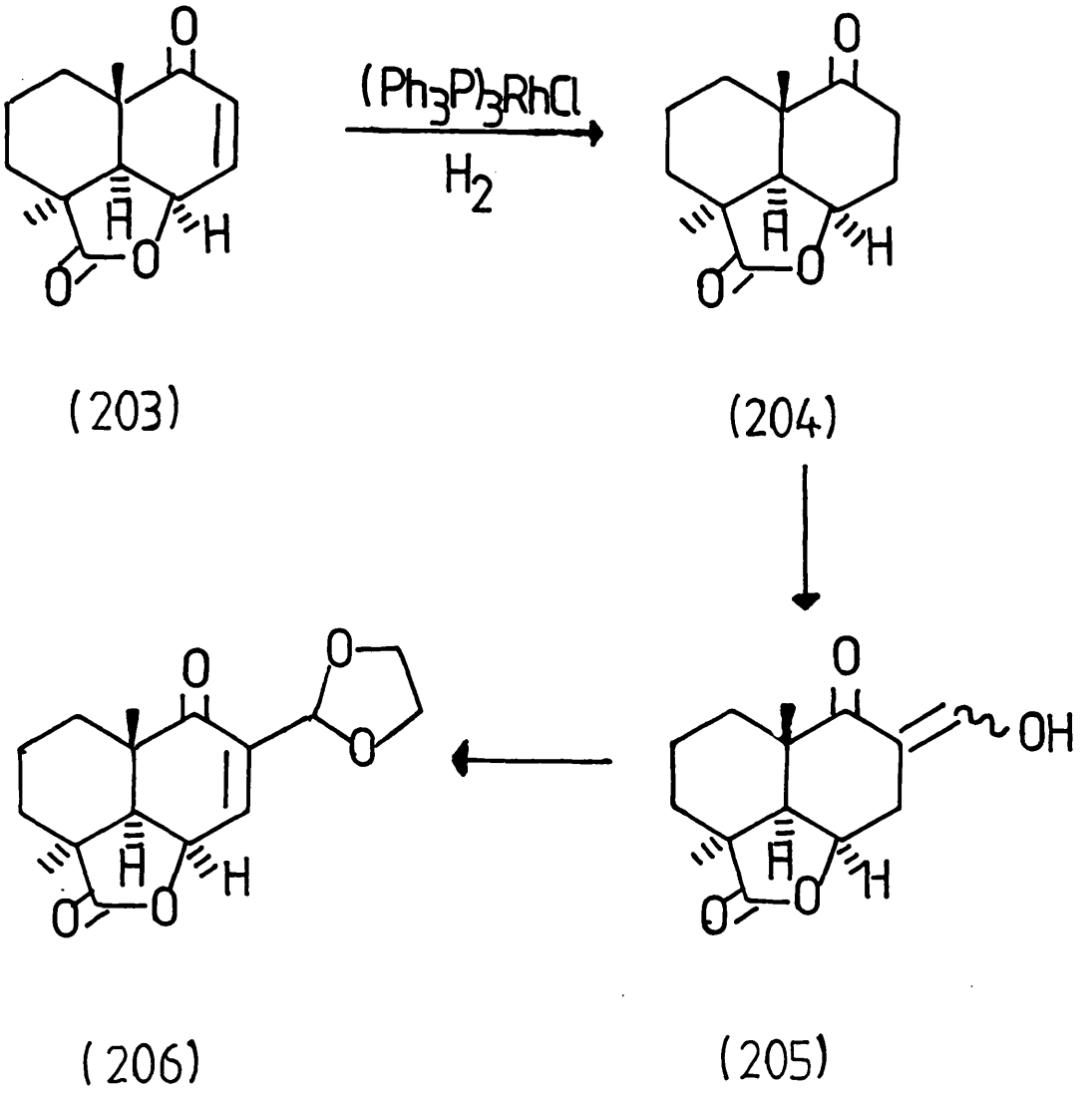


Ester (200) was then demethylated by lithium n-propyl mercaptide in HMPA, followed by acidification to remove the tetrahydropyranyl group, furnishing alcohol (201). This was converted to the enone acid (202) by Jones oxidation to the ketone followed by a bromination/dehydrobromination procedure.



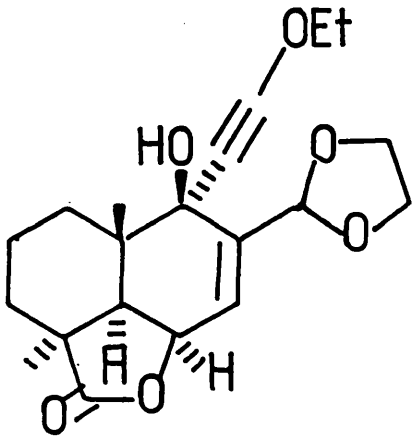
(201) (202)

Ketoacid (202) was transformed to δ-lactone (203) by simple treatment with bromine in carbon tetrachloride, following by potassium carbonate in DMF. After catalytic hydrogenation using tris (triphenylphosphine) rhodium (I) chloride to ketone (204), a hydroxymethylene functional group was introduced via condensation of the sodium enolate of (204) with ethyl formate. This hydroxymethylene ketone (205) was converted to the unsaturated ketoacetal (206) by sequential reaction with triethylamine, phenylselenenyl chloride, m-chloroperbenzoic acid and ethylene glycol.



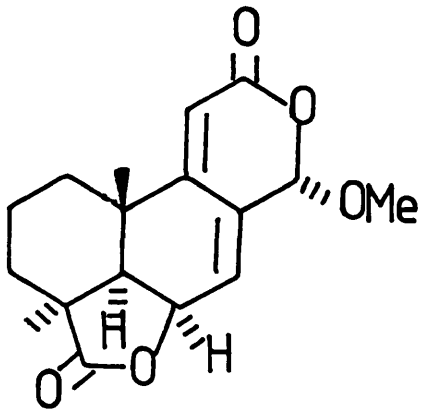
(203) (204) (205) (206)

Welch finally employed lithium ethoxyacetylide as a reagent to transform (206) to alkynyl alcohol (207) which on treatment with 5% sulphuric acid in methanol produced the desired natural product (168) and its epimer (196) in 42% combined yield in a favourable ratio of 7:3.



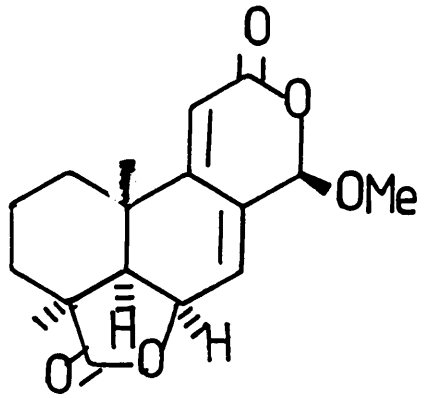
(207)

$5\%\ H_2SO_4$ / MeOH



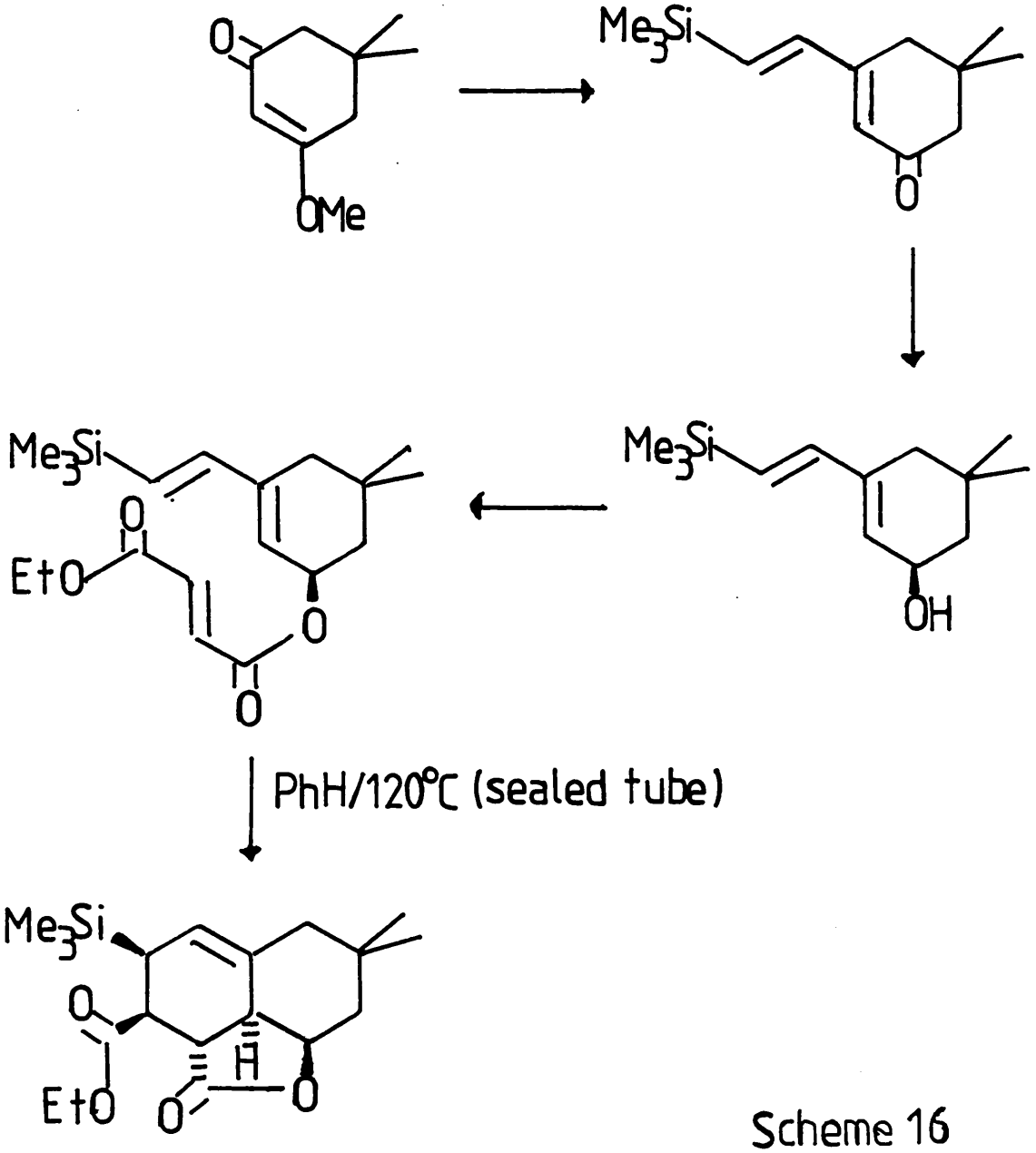
(168)

+



(196)

The three described syntheses lack a flexibility of approach that would allow access to other members of the dilactone family. However, Burke[80,81] has recently contributed some work on the rapid and efficient synthesis of tricyclic nagilactone model systems via an intramolecular Diels-Alder reaction (scheme 16). Hopefully further work in this interesting area will provide a general entry to the nagilactones.


Me3Si
OMe
O
Me3Si
OH
Me3Si
EtO
O
O
O
PhH/120°C (sealed tube)
Me3Si
O
EtO
O
H
O

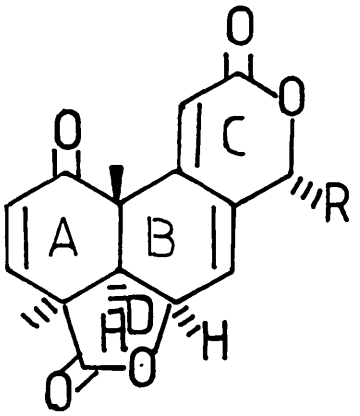
Scheme 16

3.0 THE INTERMOLECULAR APPROACH

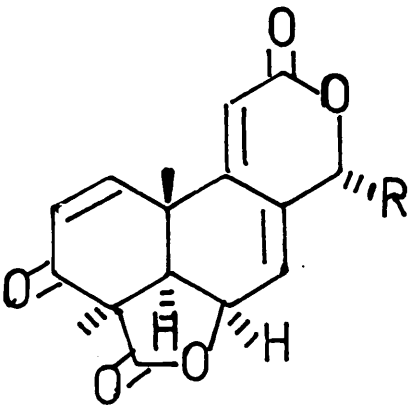
3.0. THE INTERMOLECULAR APPROACH

3.1. Introduction

Any synthetic efforts towards the nagilactones must be able to demonstrate a generality in approach to allow for the construction of the often highly functionalised ring A portion. It was reasoned that the assembly of ring A as either of the enones (208) or (209) via an aldol condensation would allow access to any of the oxygenation patterns found in the natural products.

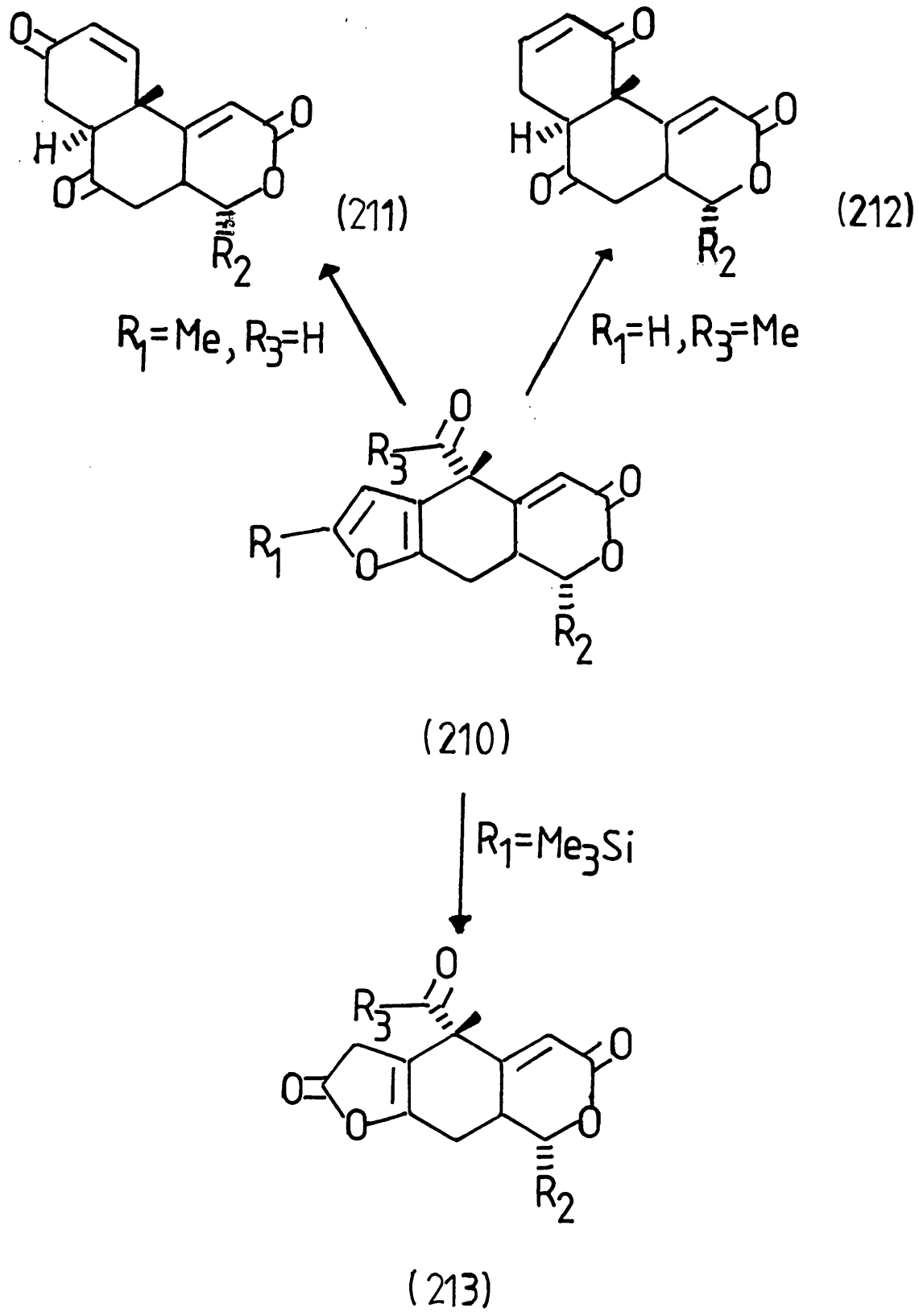


(208)



(209)

The synthetic plan envisaged ring A generation as being a late step in the synthesis, thus simplifying the initial target to the linearly fused tricycle (210) in which the heterocycle could function either as a latent form of the γ-lactone or of the ring A enone (scheme 17).

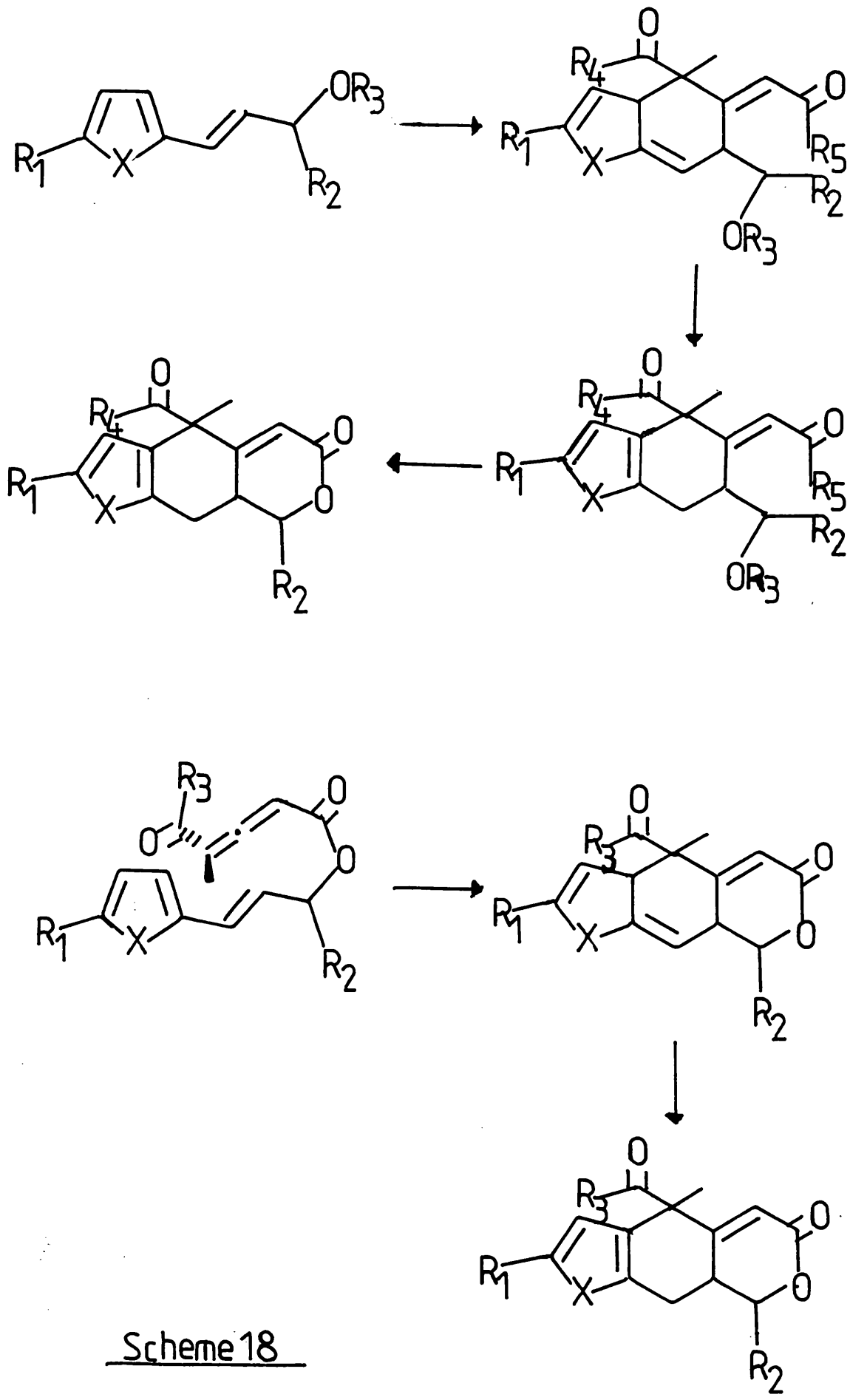


Scheme 17

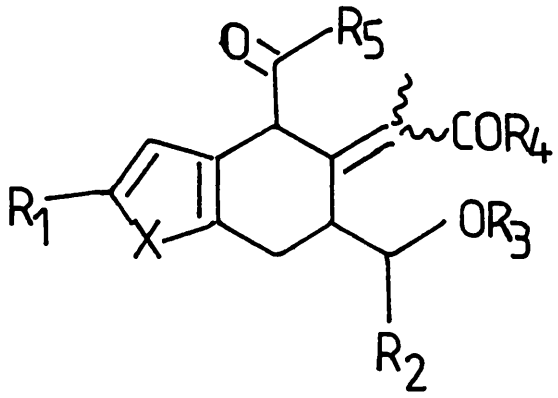
Thus ring-opening of the furan to the 1,4-dicarbonyl compound[82-88] followed by aldol condensation would be anticipated to yield enones (211) or (212), depending upon the substituents present in tricycle (210). Alternatively, silicon-directed epoxidation followed by rearrangement could lead to the unsaturated γ -lactone (213).[89]

A particularly interesting route to the tricyclic lactone (210) skeleton would involve the known reactivity of vinyl heterocycles as exocyclic dienes and the powerfully dienophilic nature of allenyl 1,3-dicarbonyl compounds in a Diels-Alder reaction,[90-95] carried out either in an inter- or intramolecular fashion (scheme 18).

Regiochemical problems were anticipated in the intermolecular variant, owing to the known deactivating effect of a methyl substituent on the allene, which could possibly lead to the undesired regioisomer (214). Thus initial studies were to be carried out using a symmetrical allene.



Scheme 18

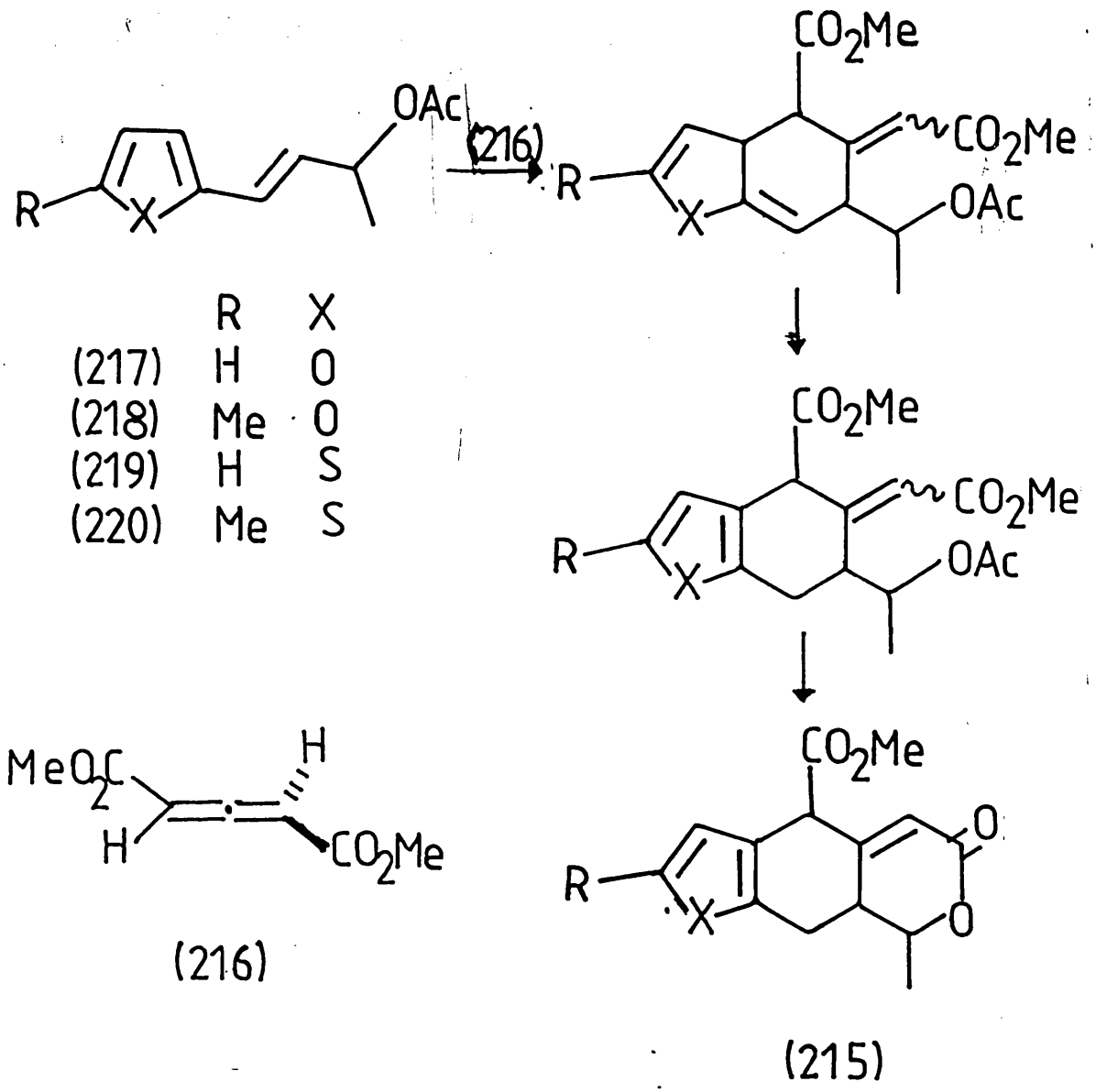


(214)

It was envisaged that not only vinyl furans (X=O) but vinyl thiophenes (X=S) could be utilised in this projected synthesis. Although thiophenes are not as readily ring opened to the 1,4-dicarbonyl compound as furans, methods do exist for such a transformation.[96-99]

3.2. Specific strategy

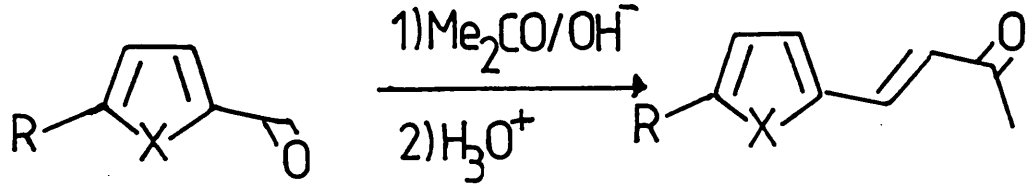
As outlined in the introduction, preliminary efforts directed towards the synthesis of a model tricyclic lactone (215) would encompass an investigation of the Diels-Alder reaction between a range of vinyl heterocycles and the allenyl diester, dimethyl penta-2,3-diene dioate (216).[100] For convenience, the dienes chosen were the allylic acetates (217)-(220).



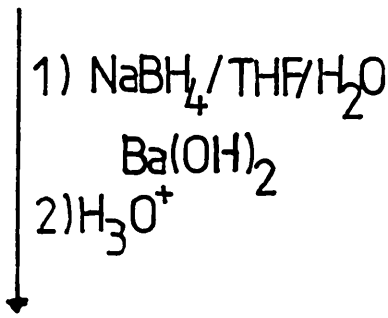
3.2.1. Diene synthesis

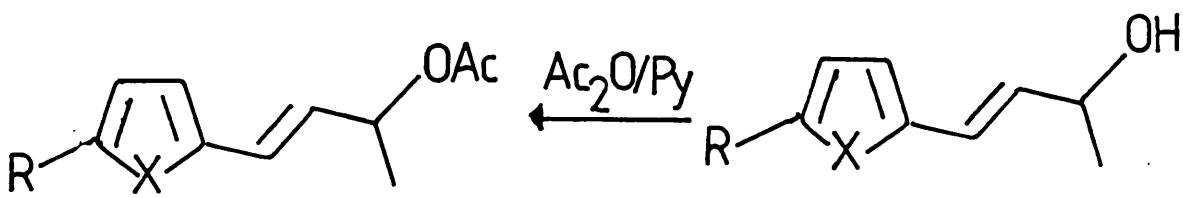
The dienes (217)-(220) were synthesised by a simple three step procedure (scheme 19). Thus Claisen-Schmidt condensation of the requisite heteroaromatic aldehyde with acetone provided the α,β-enones (221)-(223) and (75) in fair to good yield. The enones[87,101-3] were smoothly reduced to the allylic alcohols (224)-(227) by a modification of the procedure of Francke and Reith,[104] involving the use of a four-fold excess of sodium borohydride over a longer period than originally suggested would be necessary.

No problem with over-reduction to the fully saturated side-chain alcohols was formed as evidenced by the ^1H nmr spectra of the allylic alcohols. It was unnecessary to distil or chromatograph the furan allylic alcohols (224) and (225) as they were of sufficient purity when isolated to be used directly in any required esterification reaction. However, the thiophene allylic alcohols (226) and (227) had to be chromatographed over neutral alumina to remove some heavily coloured, more polar contaminant. Distillation of all four allylic alcohols resulted in substantial decomposition and so is not recommended as a purification procedure. To retard polymerisation and decomposition, the sensitive allylic alcohols were routinely stored at $-10^{\circ}C$.



Enone	R	X	Yield(%)
(221)	H	O	41
(222)	Me	O	73
(75)	H	S	75
(223)	Me	S	64





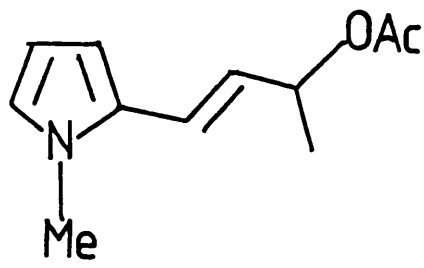
Acetate	R	X	Yield(%)
(217)	H	O	80
(218)	Me	O	80
(219)	H	S	75
(220)	Me	S	60

Alcohol	R	X	Yield(%)
(224)	H	O	92
(225)	Me	O	99
(226)	H	S	86
(227)	Me	S	85

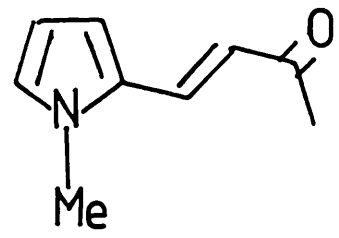
Scheme 19

The allylic alcohols were transformed to the acetates (217)-(220) by treatment with acetic anhydride and pyridine in either toluene or THF. These acetates were thermally more stable than the corresponding alcohols, although they were still sensitive enough to decompose to some extent on distillation or on standing at room temperature, presumably *via* elimination of acetic acid.

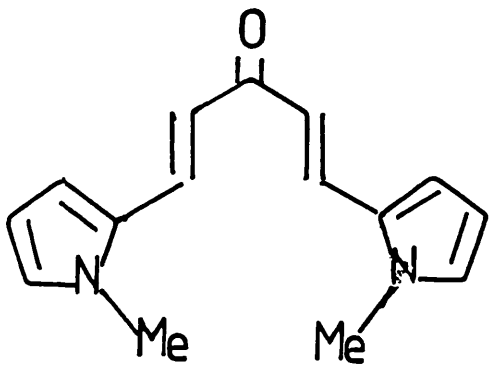
It was also of interest to synthesise the corresponding 1-methyl pyrrole allylic acetate (228), owing to the reported high activity of 2-vinyl pyrroles as exocyclic dienes. A literature report[105] suggested that typical Claisen-Schmidt condensation of 1-methyl 1*H*-pyrrole 2-carboxaldehyde with acetone in the presence of 0.2 equivalents of potassium hydroxide yielded not the desired enone (118) but the product (229) resulting from condensation of two equivalents ofthe pyrrole with acetone.



(228)



(118)



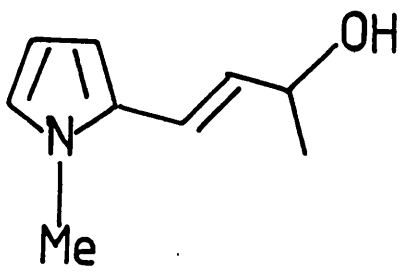
(229)

However, we found that the desired enone (118) was formed under our typical condensation conditions, although the reaction required 17 hours rather than the usual 6 hours. The ^{1}H nmr spectrum of the crude product indicated the presence of the bis-enone (229) in approximately 9% yield by comparison of the integrals of the vinylic and aromatic protons with that of the methyl ketone singlet. However, on distillation the enone (118) was the only isolated product (77%) as a yellow oil which is solid below 0°C. Thus the ir spectrum showed typical carbonyl and pyrrole bonds at 1680,1660,1640,1615 and 1590 cm^{-1} and the ^{1}H nmr spectrum showed the exocyclic vinyl protons as a well-separated AB-quartet at 6.38 and 7.35 ppm, the pyrrole protons as two multiplets at 6.08 and 6.63ppm, the N -methyl group as a singlet at 3.70 ppm and the methyl ketone as a singlet at 2.30 ppm.

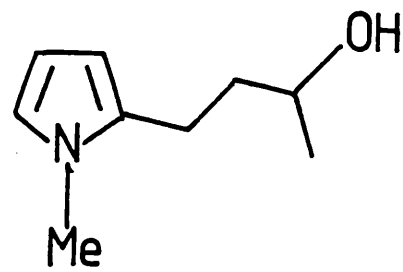
These data are only consistent with the enone (118) since the bis-enone (229) contains no methyl ketone singlet at 2.30 ppm in the ^{1}H nmr, shows lower frequency carbonyl bands in the ir at 1635, 1605 and 1565 cm^{-1} and is a yellow crystalline solid, mp 141°C.

This represents a most convenient synthesis of the enone (118), as the existing literature method[106] involves Wittig reaction between 1-methyl 1H-pyrrole 2-carboxaldehyde and acetylmethylenetriphenylphosphorane over a three day period in benzene at reflux (62% yield).

Unfortunately, however, attempts to reduce the enone (118) to the allylic alcohol precursor of the desired acetate (228) under the standard conditions (four equivalents of sodium borohydride) resulted in the isolation of a complex mixture of products (Hc) as a brown gum. The ^{1}H nmr spectrum of the crude product suggested the presence of some of the required alcohol (230) as shown by a doublet at 1.38 ppm (methyl group), a broad signal at 1.60 ppm (OH) and the collapse of the well-defined AB-quartet to a multiplet. However, the ^{1}H nmr spectrum also suggested that in this instance some over-reduction to the alcohol (231) had occurred, indicated by the presence of a triplet (J=7Hz) at 2.60 ppm, consistent with the methylene group adjoining the pyrrole ring.



(230)

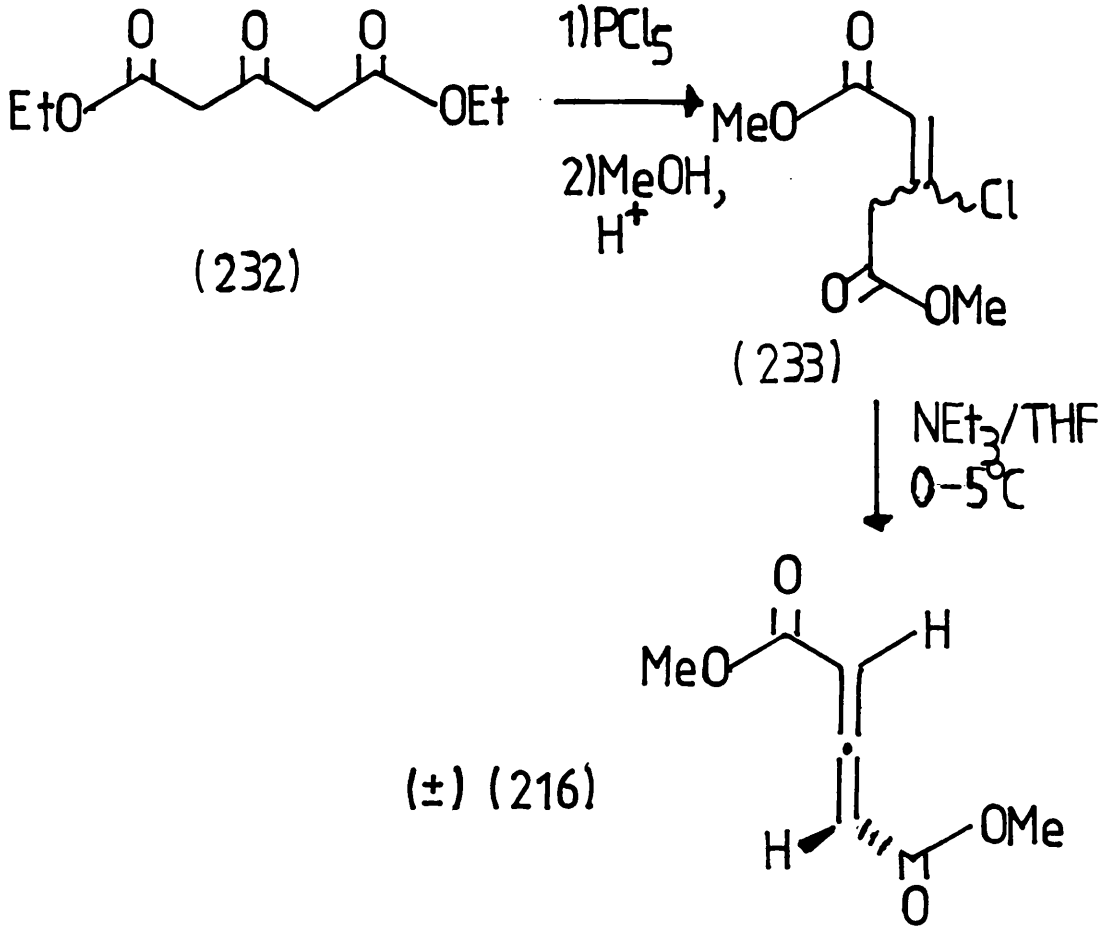


(231)

Surprisingly, reduction of the enone (118) with one equivalent of sodium borohydride was also not a clean reaction, yielding an oil which rapidly resinified. Owing to the unpromising results from these reductions, it was resolved to investigate the use of the enone (118) as a partner to dimethyl penta-2,3-diene dioate (216) in the Diels-Alder reaction. Noland has recently shown that even such deactivated vinyl pyrroles can still function as exocyclic dienes.

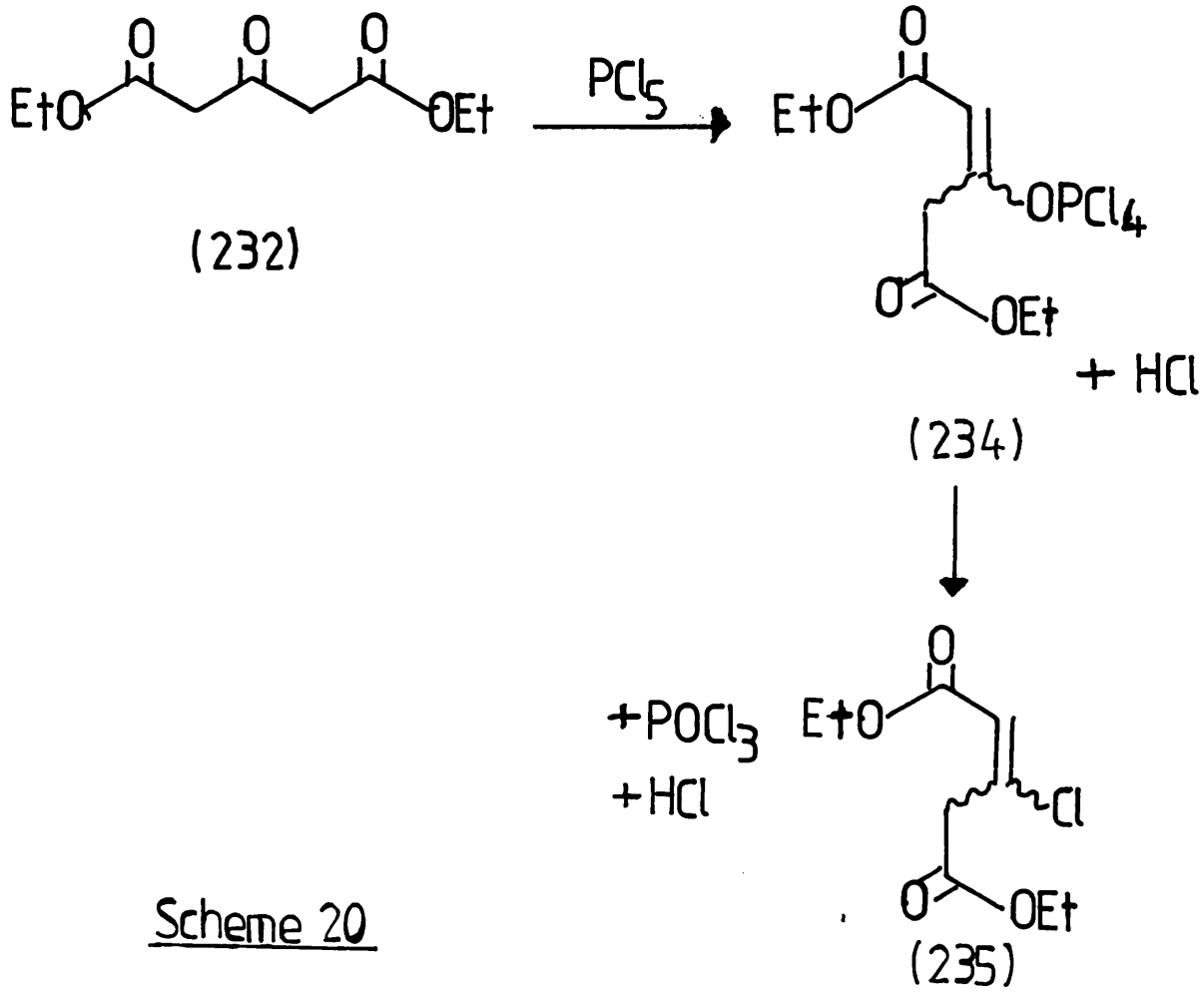
3.2.2. Allene synthesis

Dimethyl penta-2,3-diene dioate (216) is a reportedly potent dienophile, available *via* a three step synthetic sequence from diethyl 3-oxoglutarate (232).[100]



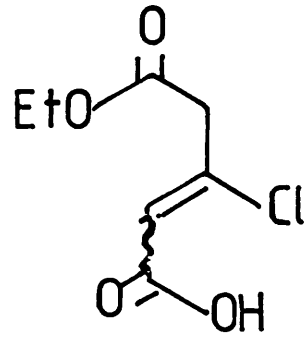
It was found that in order to obtain the best yields of the β-chloro-α, β-unsaturated ester (233) it was necessary to heat the mixture of diethyl 3-oxoglutarate and phosphorus pentachloride to *ca* 65°C, rather than the 40-45°C reported in the literature.

Failure to do so resulted in quite substantial loss of material, presumably via the anticipated intermediate phosphorus compound (234) which had not undergone conjugate addition of chloride ion followed by loss of phosphorus oxychloride (scheme 20).

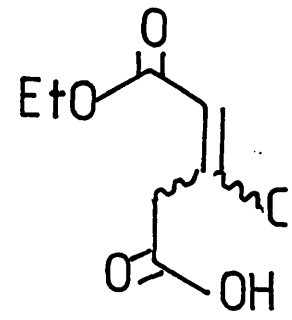


Scheme 20

The transesterification step with methanol was necessary as the use of phosphorus pentachloride has recently been reported[107] to generate not only the required diester (235) but also quantities of the positionally isomeric monoesters (236) and (237). This de-ethylation may be a result of the soft nucleophilic character of chloride ion.



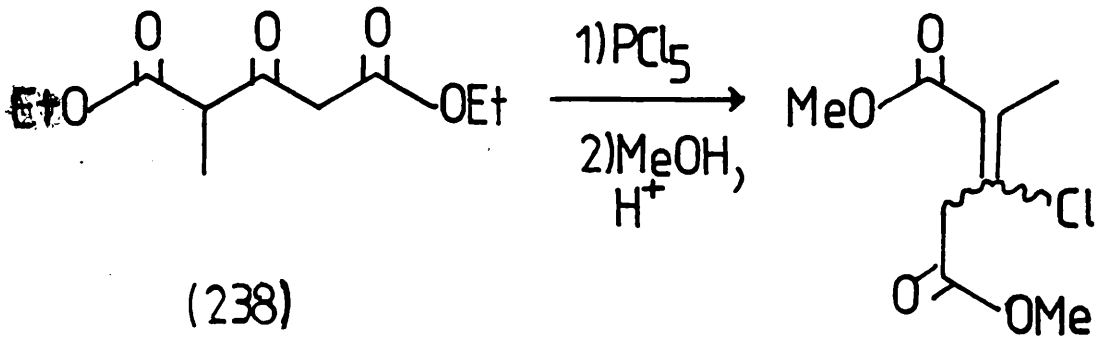
(236)



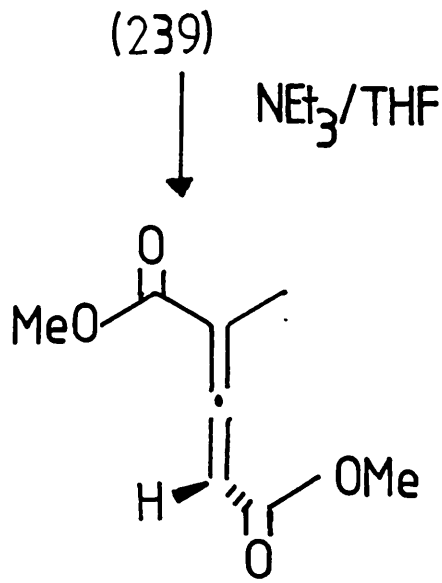
(237)

Even after considerable experimentation, the yield of pure diester (233) isolated was usually in the range 40-45% as opposed to the quoted 59-60%. The diester (233) was then simply transformed to the allenyl diester (216) by elimination of hydrogen chloride using triethylamine in dry THF at 0-5°C. The isolated allenyl diester was stored as a dilute solution in ether or THF at -10°C to retard its reported susceptibility towards polymerisation.

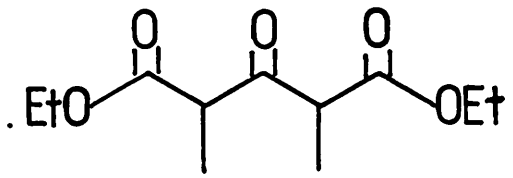
It was also of interest to apply this synthetic procedure to the two alkylated β-ketoesters (238)[108] and (241)[109] in the hope of synthesising the tri- and tetrasubstituted allenes (240) and (243) (scheme 21).



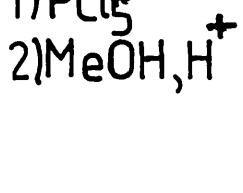
(238) (239)

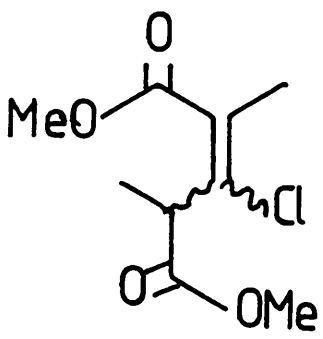


(±) (240)

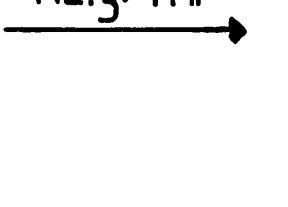


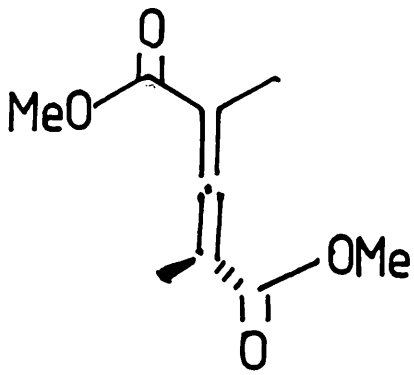
(241)





(242)



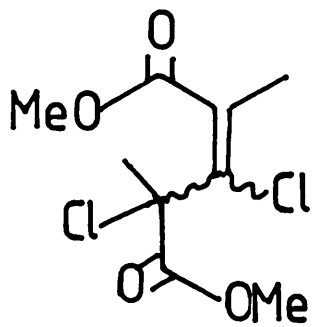


(±) (243)

Scheme 21

Treatment of (238) with phosphorus pentachloride followed by the transesterification step indeed seemed to produce the expected chlorinated compound (239) with the tetra-substituted double bond, showing the vinylic methyl group as a singlet at 2.07 ppm in the ^{1}H nmr spectrum, a typically sharp C=C-Cl absorption at 1640 cm^{-1} in the ir spectrum and a parent ion at m/z 206 in the mass spectrum. Other work has shown that this diester can be converted into the tri-substituted allene (240) on treatment with triethylamine, although the overall yield for the two steps is low.[110]

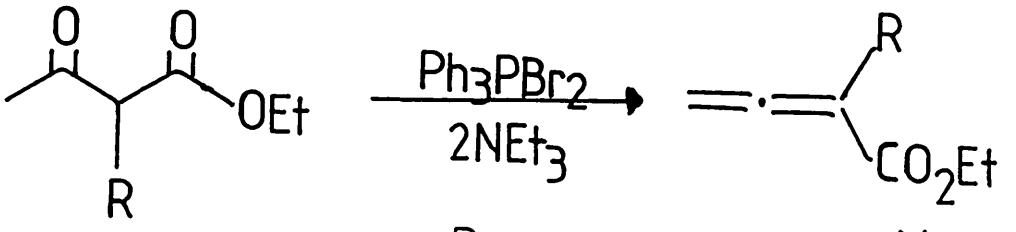
However, reaction of the 2,4-dimethylated 3-oxoglutarate (241)[109] with phosphorus pentachloride in the usual manner followed by treatment with acidic methanol failed to furnish the expected diester (242). Although a vinylic methyl group was present in the ^{1}H nmr spectrum (2.07 ppm), the expected higher field methyl doublet and the lower field methine quartet were not visible. Instead, a singlet (1.40 ppm, 3H) had appeared. The mass spectrum also failed to indicate the presence of a monochlorinated product. It appeared that the expected product (242) had undergone an allylic chlorination to produce the dichlorinated compound (244), which would be expected to show a methyl singlet at about 1.4 ppm in the ^{1}H nmr.



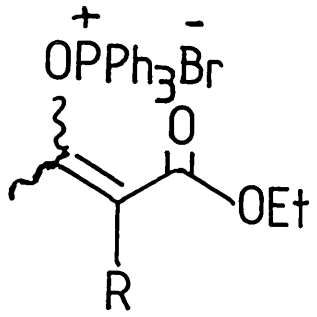
(244)

The low yields and long reaction times (generally 2½ days) for the three step allene synthesis and the inability to synthesise the tetra-substituted allene (243) led to a search for an alternative synthesis which would hopefully employ the same starting 3-oxoglutarate esters.

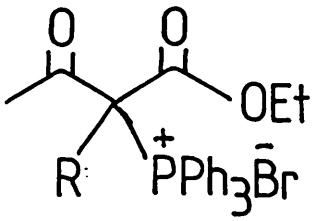
In 1972, Buono had treated the substituted acetoacetates (245) - (248) with triphenylphosphine dibromide and two equivalents of triethylamine and had obtained the allenes (249)-(252) in fair yield.[111]



	R		Yield (%)
(245)	Me	(249)	50
(246)	Et	(250)	53
(247)	nPr	(251)	46
(248)	iPr	(252)	36



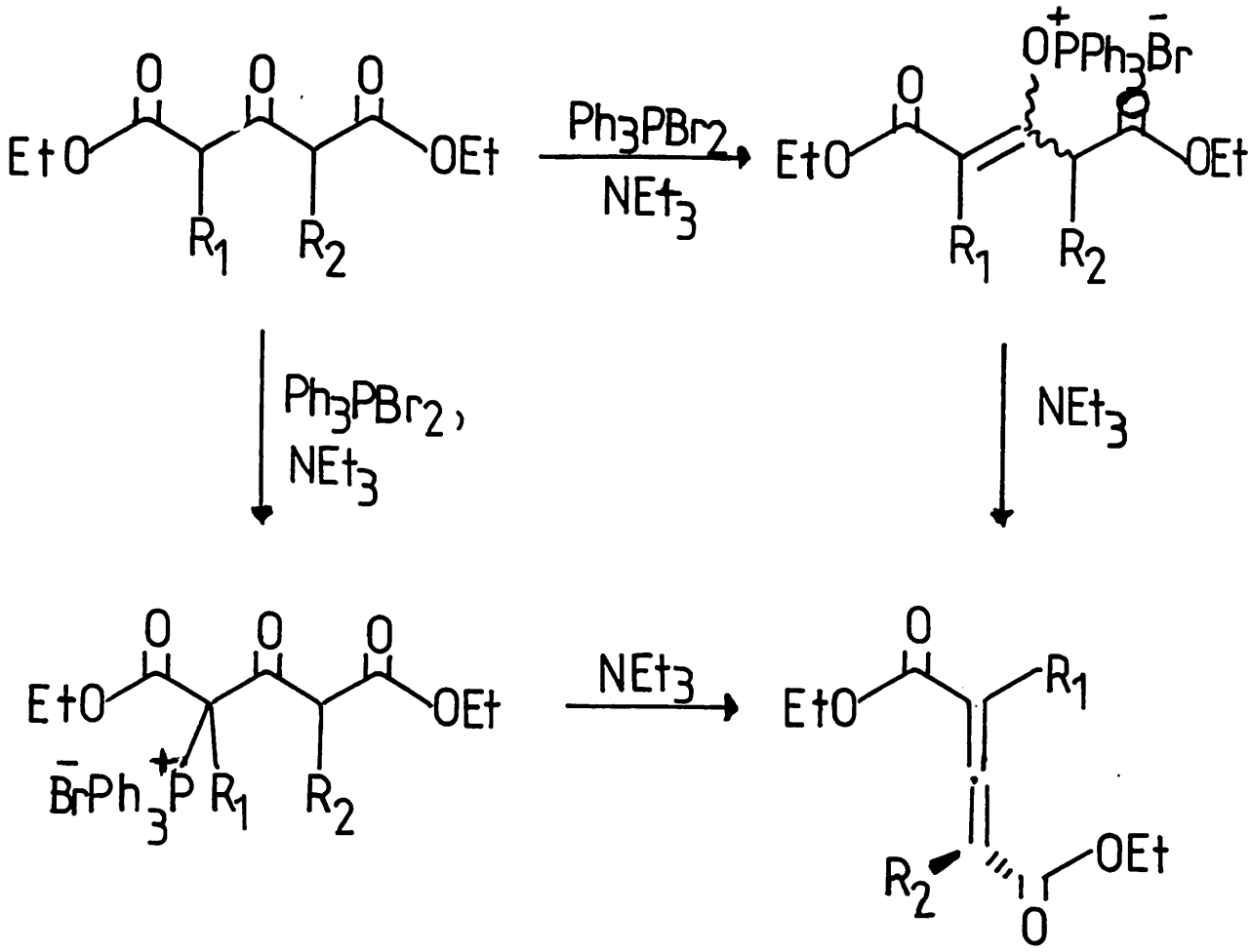
(253)



(254)

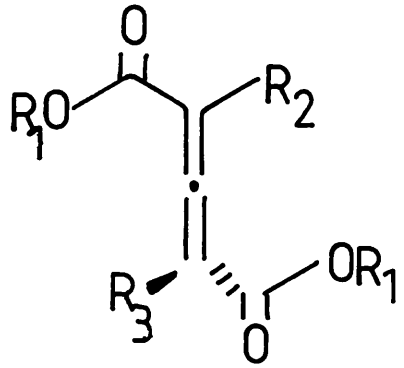
The reaction was thought to proceed via either the C- or O- phosphonium salts (253) or (254) respectively.

It was reasoned that this strategy could possibly be adapted to the 3-oxoglutarate esters as they bear the same β-ketoester grouping as the acetoacetates (245)-(248). Indeed proton removal from the intermediate phosphonium salt by the second equivalent of triethylamine should be facilitated in this case by the adjacent activating ethoxycarbonyl group.

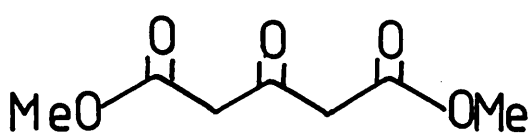


No experimental details were given in Buono's paper. However, it was found that addition of the 3-oxoglutarate ester, followed by two equivalents of triethylamine, to a suspension of triphenylphosphine dibromide in benzene resulted in an exothermic reaction. Monitoring of the reaction by ir spectroscopy showed that the allenyl diester was rapidly produced (νmax 1960-1970 cm^{-1}).

In the cases of the 3-oxoglutarates (232), (238) and (255), the respective allenes (256), (257) and (216) were isolated after work-up and distillation after a 75 minute reaction time at room temperature. However, the tetra-substituted allene (258) was only isolated after the reaction mixture had been warmed to 60°C for 3 hours. The yields were generally only low to fair but in terms of convenience (time) and the previous inaccessibility of the unknown allene (258), the method is superior to the three step chlorination/transesterification/elimination sequence.



Allene	R_1	R_2	R_3	Yield (%)
(256)	Et	H	H	50
(257)	Et	H	Me	27
(258)	Et	Me	Me	15
(216)	Me	H	H	12



(255)

3.3. Intermolecular Diels-Alder reactions

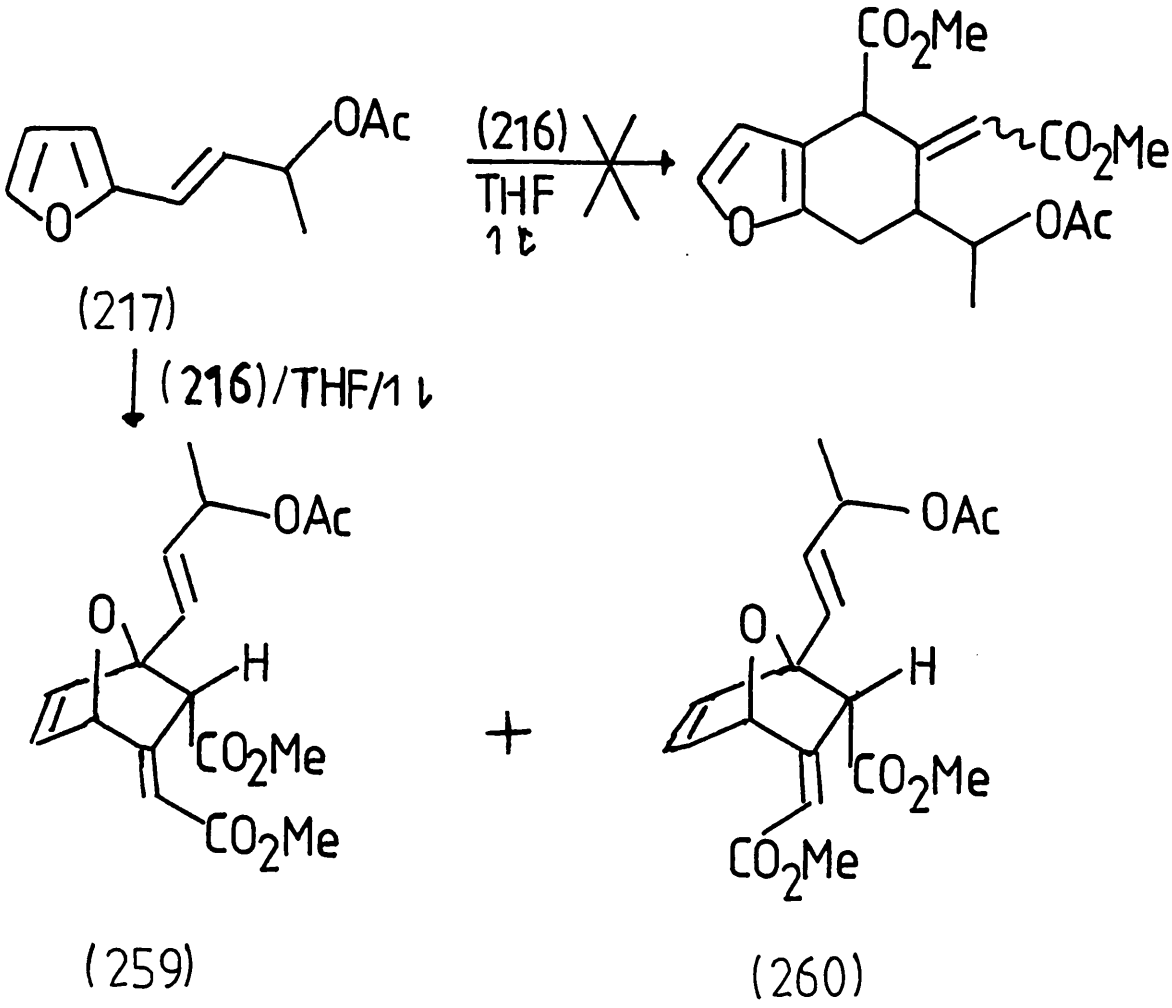
3.3.1. Reactions involving vinyl furans

With the range of allylic acetates (217)-(220) in hand it was now possible to investigate their reactions with dimethyl penta-2, 3-dienedioate (216).

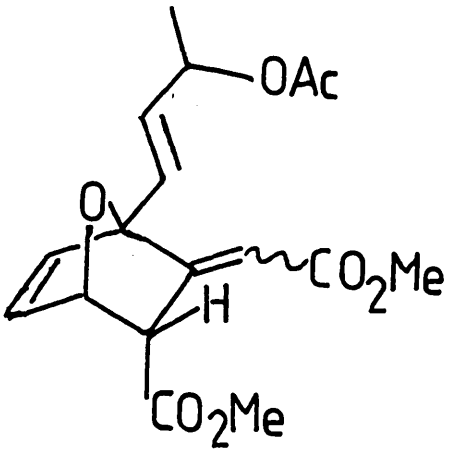
Preliminary experiments concerned the reaction of the mono-substituted furan allylic acetate (217) with the dienophile (216). On heating a solution of these two compounds under reflux in dry THF, a lower -R_f spot appeared slowly on tlc. After one week at reflux, evaporation of the solvent followed by flash chromatography over silica resulted in the recovery of the acetate (217) (16%) followed by isolation of an inseparable mixture of 1:1 adducts (54%). It was immediately apparent from ^{1}H nmr spectral data that the allenyl diester (216) had not undergone cycloaddition across the furan exocyclic diene system. This was particularly evident from the absence of the expected low field α-furan proton (δ 7.22 ppm in (217)) and the appearance of a broadened singlet at 5.25 ppm and a doublet ($J \leq 2$Hz) at 5.18 ppm in the 250MHz ^{1}H nmr spectrum. The latter two signals are fully consistent with the bridgehead protons (H6) in isomeric structures of the 7-oxabicyclo-[2.2.1]-hept-2-ene type. The presence of the bridgehead carbon atoms was unambiguously indicated by a series of singlets and doublets in the 85-90 ppm range in the off-resonance decoupled ^{13}C nmr spectrum.

A full study of the 250MHz ^{1}H nmr and 62.9 MHz ^{13}C nmr spectra of the mixture of adducts led to the assumption that there were three isomers present in an approximate ratio of 2:2:1.

By analogy with the work of Kametani on the cycloadditions of ditrimethylsilyl penta-2,3-dienedioate to furfuryl benzyl ether and furan,[112] the major two isomers (259) and (260) were assigned the regio- and stereochemistry shown.

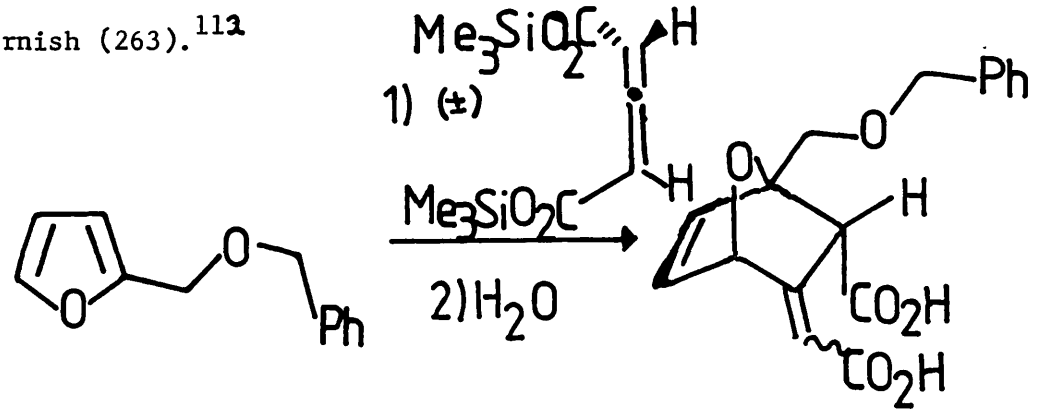


Thus the proton alpha to the methoxycarbonyl group (3.51 and 3.68 ppm) and the bridgehead proton (5.18 and 5.25 ppm) showed only minor coupling ($J \leq 2Hz$) consistent with the depicted regiochemistry, possibly controlled by steric factors. The other regioisomers (261) would have been anticipated to show a coupling of approximately 5Hz between the bridgehead and α-methoxycarbonyl protons.[113]



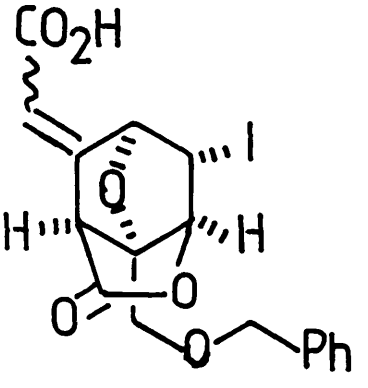
(261)

Kametani demonstrated the endo stereochemistry of the adducts by showing that his proposed adduct (262) underwent halolactonisation to furnish (263).[111a]



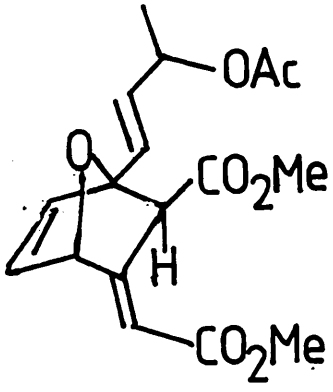
(262)

$I_2/KI/NaHCO_3$

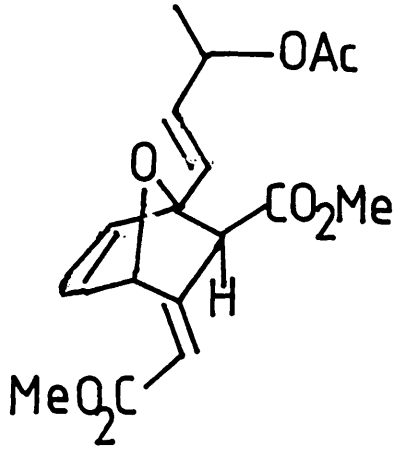


(263)

The exo isomers of (259) and (260) cannot entirely be eliminated as the bridgehead protons in (264) and (265) could either appear as singlets or as broadened singlets with very small coupling to the α-methoxycarbonyl proton. However, owing to the similarity between the present system and that of Kametani, the endo assignment of stereochemistry is preferred.

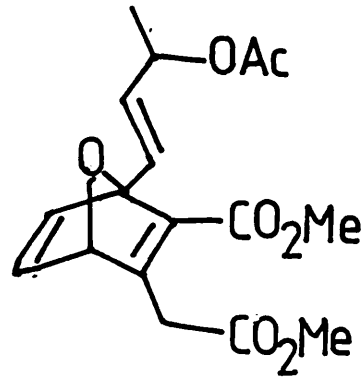


(264)



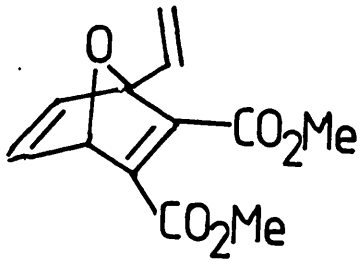
(265)

The minor isomer detected was assigned the structure (266) on the basis of the presence of a CH_2CO group, indicated by the presence of a triplet at 60 ppm in the off-resonance decoupled ^{13}C nmr spectrum and by an AB-quartet at 4.05 ppm in the 250MHz ^1H nmr spectrum. The bridgehead proton in this isomer would be expected to appear as a singlet. The remainder of the spectral details showed the same gross structure as those of the adducts (259) and (260).

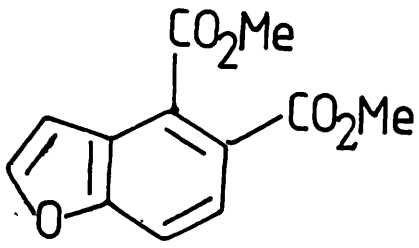


(266)

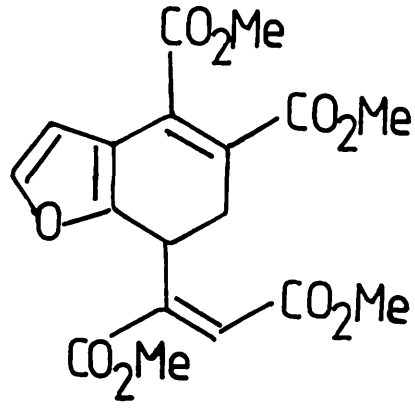
In earlier work, Davidson and Elix[7] had isolated the endocyclic diene cycloadduct (23) and the exocyclic diene cycloadduct (16) from the reaction of dimethyl acetylene dicarboxylate with 2-vinyl furan (1) at room temperature, but only the exocyclic diene adduct (16) and the derived Ene product (25) on reaction at reflux in benzene. They argued that there was a possibility that the endocyclic diene adduct (23) was a kinetic product which isomerised via retro-Diels-Alder reaction and by exocyclic diene cycloaddition led to the thermodynamic adduct (16) at the higher temperature.



(23)

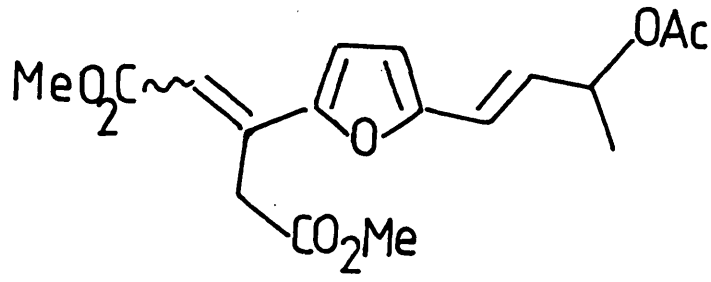


(16)



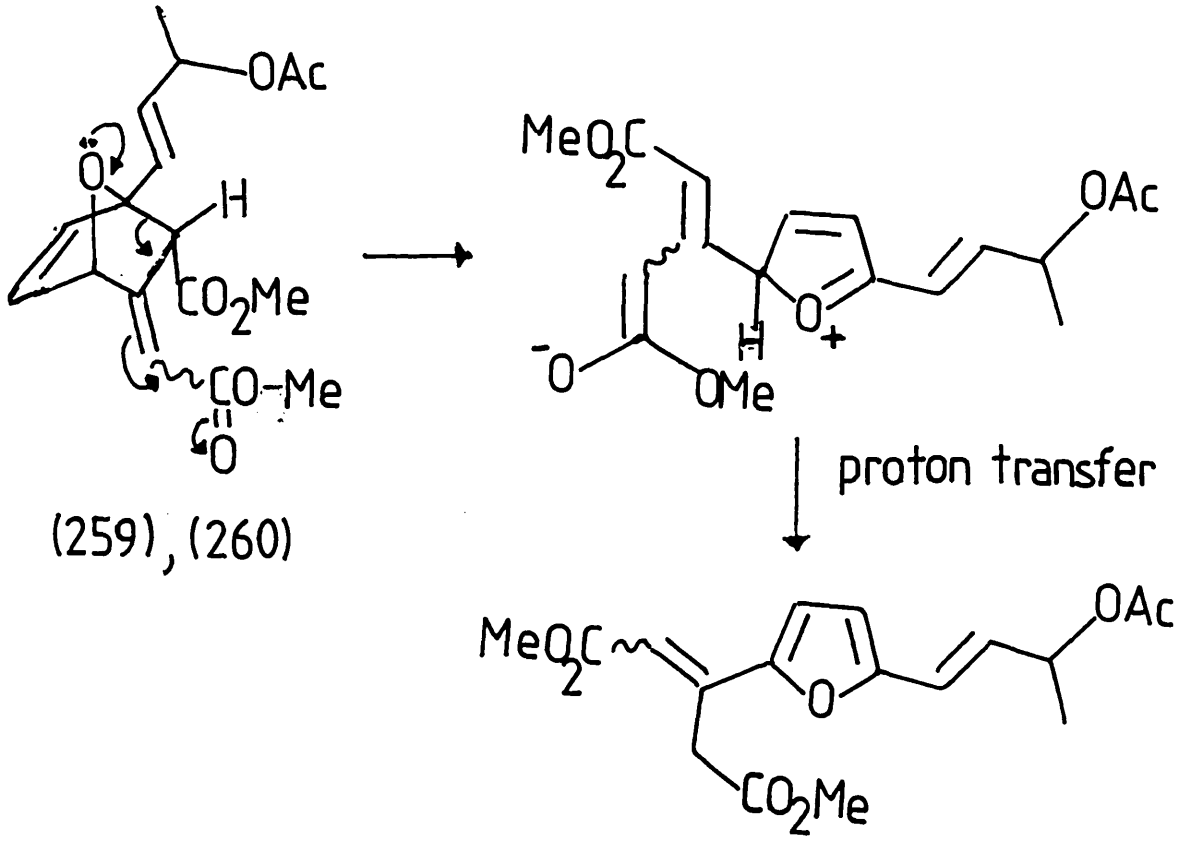
(25)

It was decided to explore the possibility of the kinetic/thermodynamic isomerisation in the present case. However, on heating a solution of the allylic acetate (217) and the allene (216) in dry xylene at reflux for 43 hours, again no exocyclic diene cycloadduct was detected. After chromatography on alumina, a new product was isolated in moderate yield (42%). The absence of the α-furan proton (7.22 ppm) and the allene singlet (5.95 ppm) in the ^{1}H nmr spectrum and the noticeable presence of two chemically distinct methoxycarbonyl singlets (3.67 and 3.73 ppm) and a new two proton singlet (4.00 ppm) led to the assignment of the structure (267) to this new product. The presence of this glutaconate side chain was confirmed by comparison of the ^{1}H nmr spectrum of (267) with those of other glutaconate esters prepared in this work.



(267)

One possible pathway to explain the formation of this compound (267) is <u>via</u> the adducts (259) and (260) by a push-pull mechanism (scheme 22).

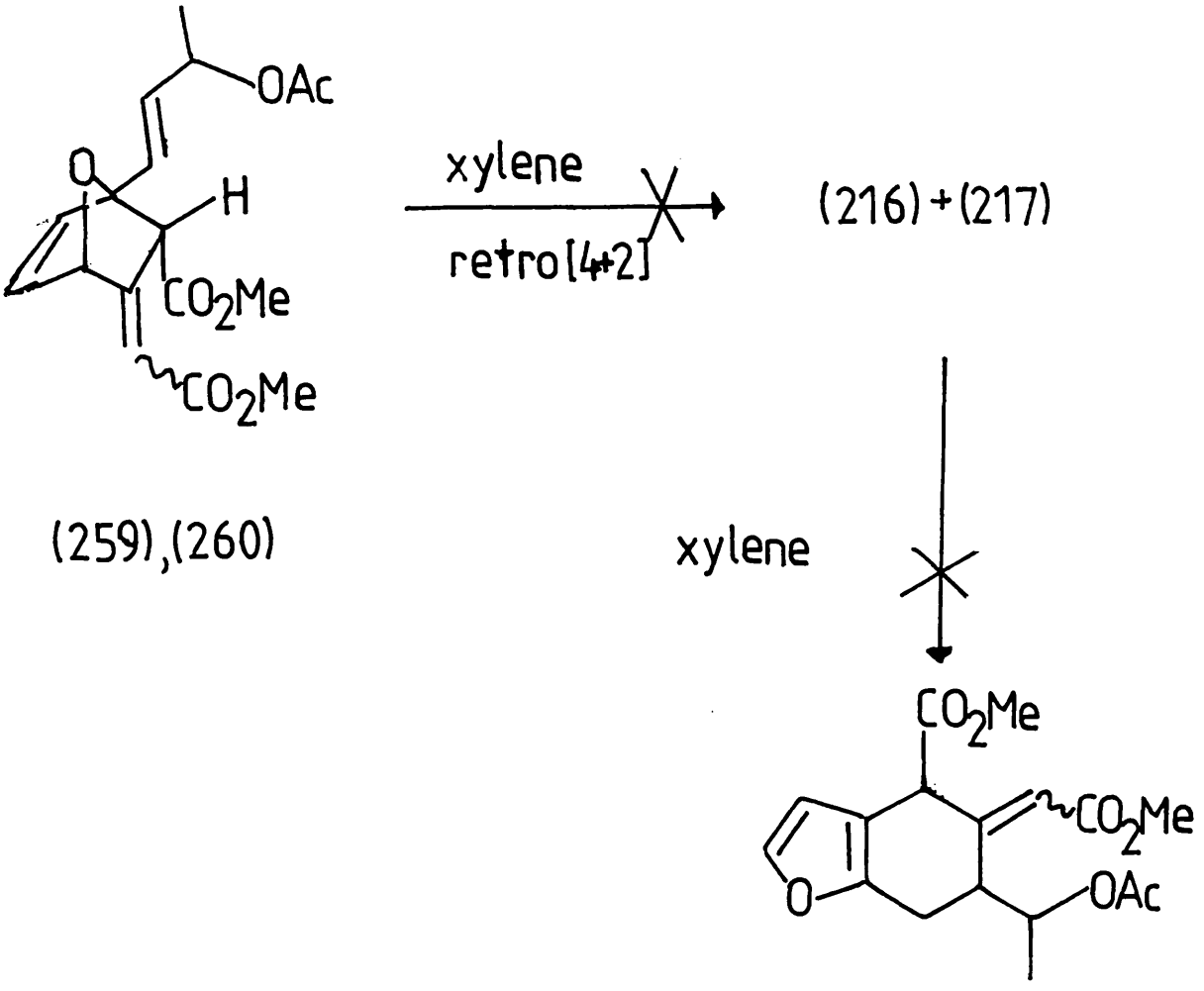


(259), (260)

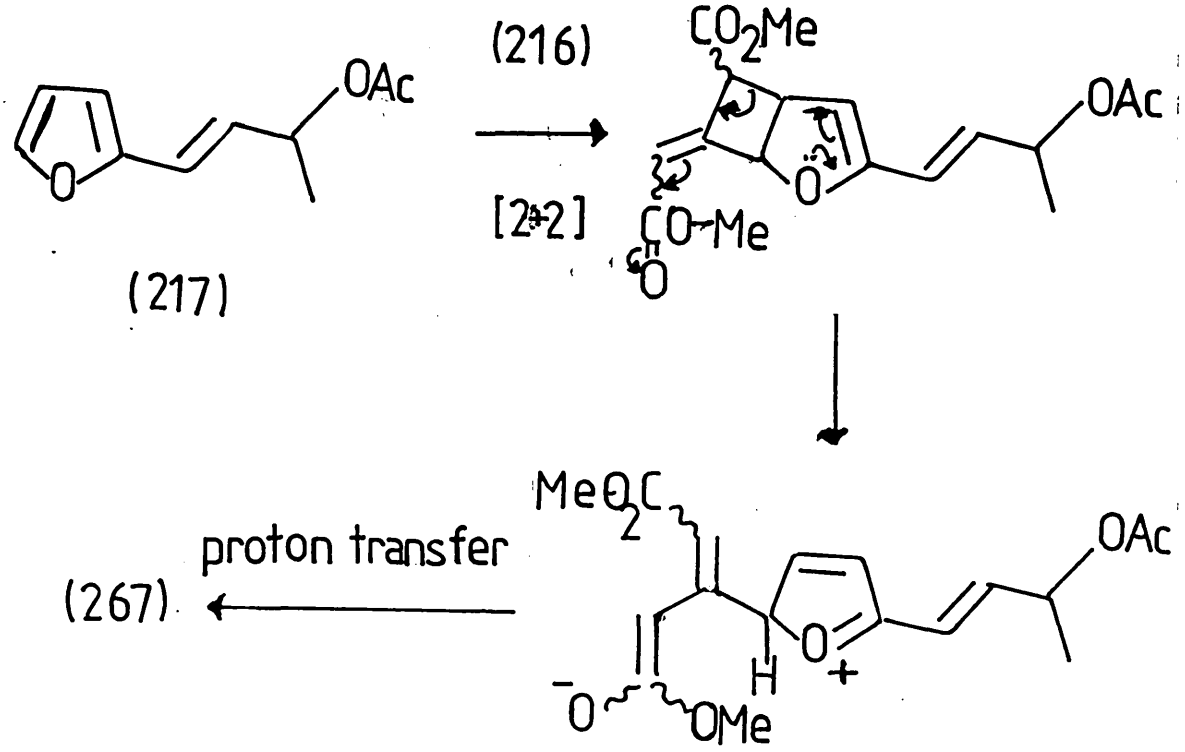
Scheme 22

(267)

This mechanism was ruled out immediately by the production of only low polarity unidentified material on thermolysis of the mixture of (259) and (260) under identical conditions to those used for the formation of (267). This discovery clearly rules out too the reversal of the initial Diels-Alder reaction between (216) and (217) at these higher temperatures.



Other alternative mechanisms possible for the formation of (267) are simple electrophilic substitution of the allenyl diester (216) into the free α-furan position or [2+2]cycloaddition followed by furan oxygen-assisted cyclobutane ring opening (scheme 23). At this time there is no evidence to distinguish between these, or any other, mechanisms.

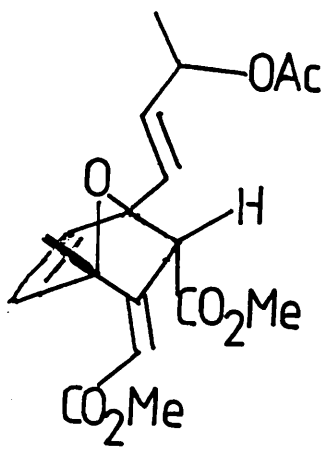


Scheme 23

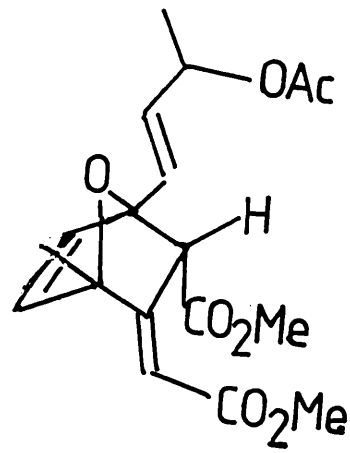
After the set-back with the chemoselectivity of the Diels-Alder reaction involving 4-(2'-furyl)but-3-en-2-yl acetate (217), the 2,5-disubstituted furan allylic acetate (218) was selected for study. It was reasoned that the use of this compound would have two advantages over the use of (217) in that, firstly, any substitution reactions would be blocked by the presence of the 5-methyl group and, secondly, the additional steric buttressing provided by the 5-methyl group would perhaps result in preferential addition of the dienophile across the exocyclic diene system.

The additional hindrance to cycloaddition was indeed noticeable as no reaction was observed between the acetate (218) and the allenyl diester (216) at reflux in THF over a 6 day period.

However, on boiling a solution of the diene (218) and the dienophile (216) in dry benzene for 160 hours, a mixture of two major isomers was isolated in 36% yield after chromatography, together with recovered acetate (56%). From a consideration of the simularity between the high field ^{1}H nmr and ^{13}C nmr spectra of the mixture and the spectra of the mixture of adducts (259) and (260) it was apparent that once again the endocyclic rather than exocyclic diene had participated in the cycloaddition. Particularly noticeable were the signals due to the bridgehead methyl groups at 1.70 and 1.77 ppm in the 250MHz ^{1}H nmr spectrum, well differentiated from the observed chemical shift of the 5-methyl group in (218) (2.30 ppm), and the bridgehead carbon atoms at 88-90 ppm in the ^{13}C nmr spectrum, shifted downfield compared to the unsubstituted cases (259) and (260) by the methyl groups.[114] By analogy with the adducts (259) and (260), the two major isomers isolated here were assigned the geometrically isomeric structures (268) and (269).



(268)



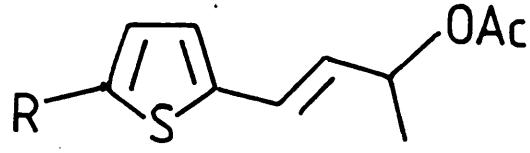
(269)

It was hoped that raising the reaction temperature from that of boiling benzene to that of boiling xylene would alter the course of the cycloaddition. However, under the latter conditions only decomposition of the allylic acetate (218) and polymerisation of the allenyl diester occurred. The latter course was indicated by the isolation after chromatography of material showing a small vinylic signal and a complex multiplet at 3.7 ppm consisting of CO_2Me signals. The ir spectrum of this material showed no allene absorption at 1970 cm^{-1}. The decomposition of the acetate resulted in the production of a solid polymer, mp > 260°C, insoluble in xylene at room temperature.

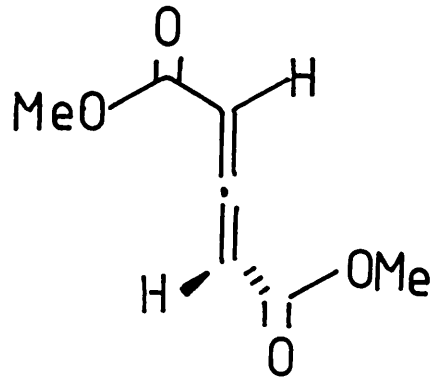
Thus although the exocyclic diene system in 2-vinyl furans has been reported to be more reactive towards cycloaddition than the endocyclic diene, the present results show that the exocyclic diene systems in the allylic acetates (217) and (218) show no tendency to undergo cycloaddition in the desired sense. The strong possibility exists that the approach of the allenyl diester to the exocyclic diene is greatly hindered by the bulky acetoxyethyl side chain to the vinyl group, resulting in reaction of the dienophile at the less hindered furan ring. The possible involvement of this steric factor was not investigated though.

3.3.2 Reactions involving vinyl thiophenes

As the vinyl furans showed no promise as exocyclic dienes, attention was turned to the thiophene allylic acetates (219) and (220) as partners to the allenyl diester (216). As cycloadditions across the thiophene ring are very rare,[23] it was anticipated that cycloaddition across the exocyclic diene would occur.



(219) R=H
(220) R=Me

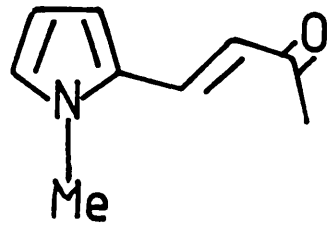


(216)

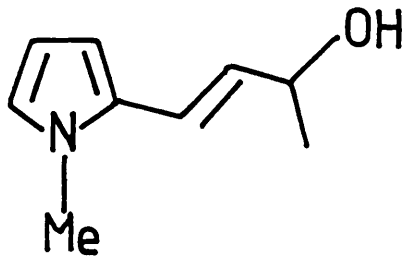
However, on heating the acetate (219) with (216) in toluene under reflux, no reaction occurred over a 128 hour period apart from allene polymerisation (^{1}H nmr analysis). In xylene at reflux, total polymerisation occurred. The acetate (220) similarly showed no tendency to undergo any reaction in boiling THF, benzene or toluene. The only isolated materials here were recovered (220) and allene polymer. At higher temperatures in xylene or decalin, the acetate (220) decomposed as evidenced by the loss of the OAc signal at 2.03 ppm in the ^{1}H nmr spectrum of the crude product. The total failure of the vinyl thiophenes to undergo cycloaddition was a great disappointment.

3.3.3. Reactions involving vinyl pyrroles

Owing to the inability to reduce 4-(1-methyl 1H-pyrrol-2-yl) but-3-en-2-one (118)[106] cleanly to the alcohol (230), it was decided to use the enone (118) itself as a partner to dimethyl penta-2,3-dienedioate in a Diels-Alder reaction. Noland has recently shown that even such deactivated vinyl pyrroles can still function as dienes.[6]

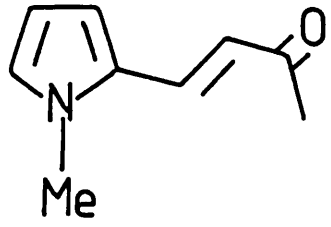


(118)



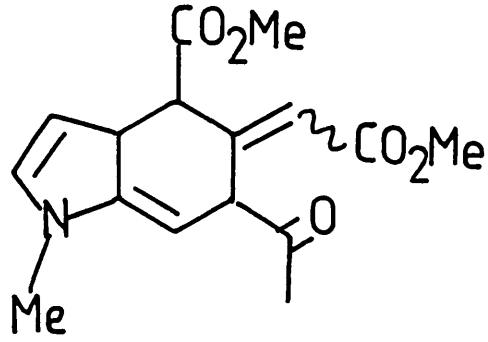
(230)

It was anticipated that [4+2] cycloaddition here, even via a stepwise polar mechanism, would lead after a dehydrogenation step to the indole (270).

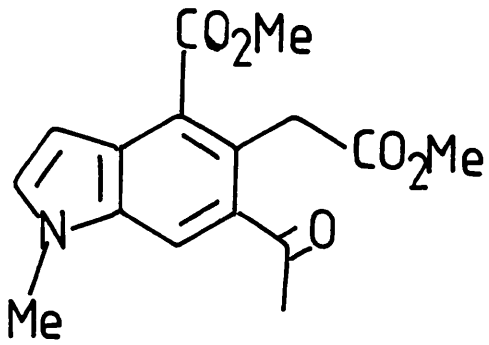


(118)

(216)



[O]

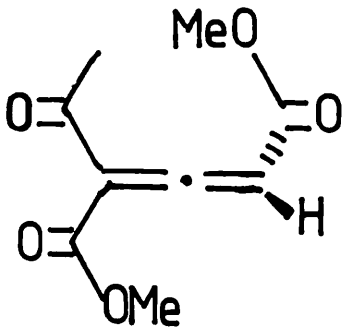


(270)

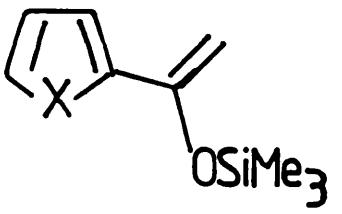
However, reaction of the enone (118) with the allene (216) at reflux in toluene for 48 hours, or with no solvent at 135°C for 17 hours, did not proceed to give the indole (270). The reaction in toluene produced allene polymer and recovered pyrrole enone (118). The reaction with no solvent yielded an unidentified gum which showed neither indole nor methyl ketone protons in its ^{1}H nmr spectrum.

3.3.4 Reactions involving oxygenated dienes

The failure of the vinyl furans (217) and (218), the vinyl thiophenes (219) and (220) and the vinyl pyrrole (118) to undergo exocyclic cycloaddition with dimethyl penta-2,3-diene-dioate (216) prompted a reconsideration of the strategy. It was reasoned that exocyclic diene reactivity could be encouraged by following one of two paths. Firstly, the dienophilic nature of the allenyl component could be increased by the use of a more electron deficient allene, for example (271). This enhancement in reactivity could perhaps lead to some exocyclic cycloaddition. Secondly, the exocyclic diene of the vinyl heterocycle could be made more electron rich by the use of a suitable substituent, for example the trimethysilyloxy group. This second alternative was preferred and it was decided to investigate the reactions of 2-(1'-trimethylsilyloxy)vinyl furan (39)[114] and 2-(1'-trimethylsilyloxy)vinyl thiophene (86)[115] with diethyl penta-2,3-dienedioate (256).



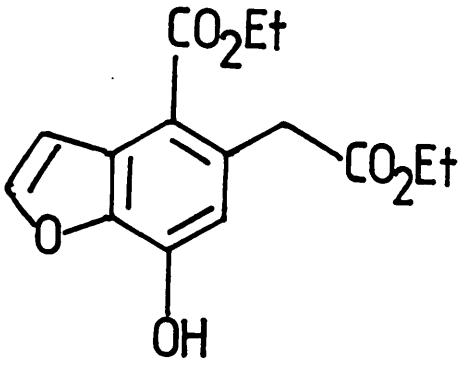
(271)



(39) X=O
(86) X=S

The trimethylsilyloxydienes (39) and (86) were easily prepared from 2-acetyl furan and 2-acetyl thiophene respectively by treatment with triethylamine (2.5 equivalents) and chlorotrimethylsilane (2.5 equivalents) in dry DMF at reflux.

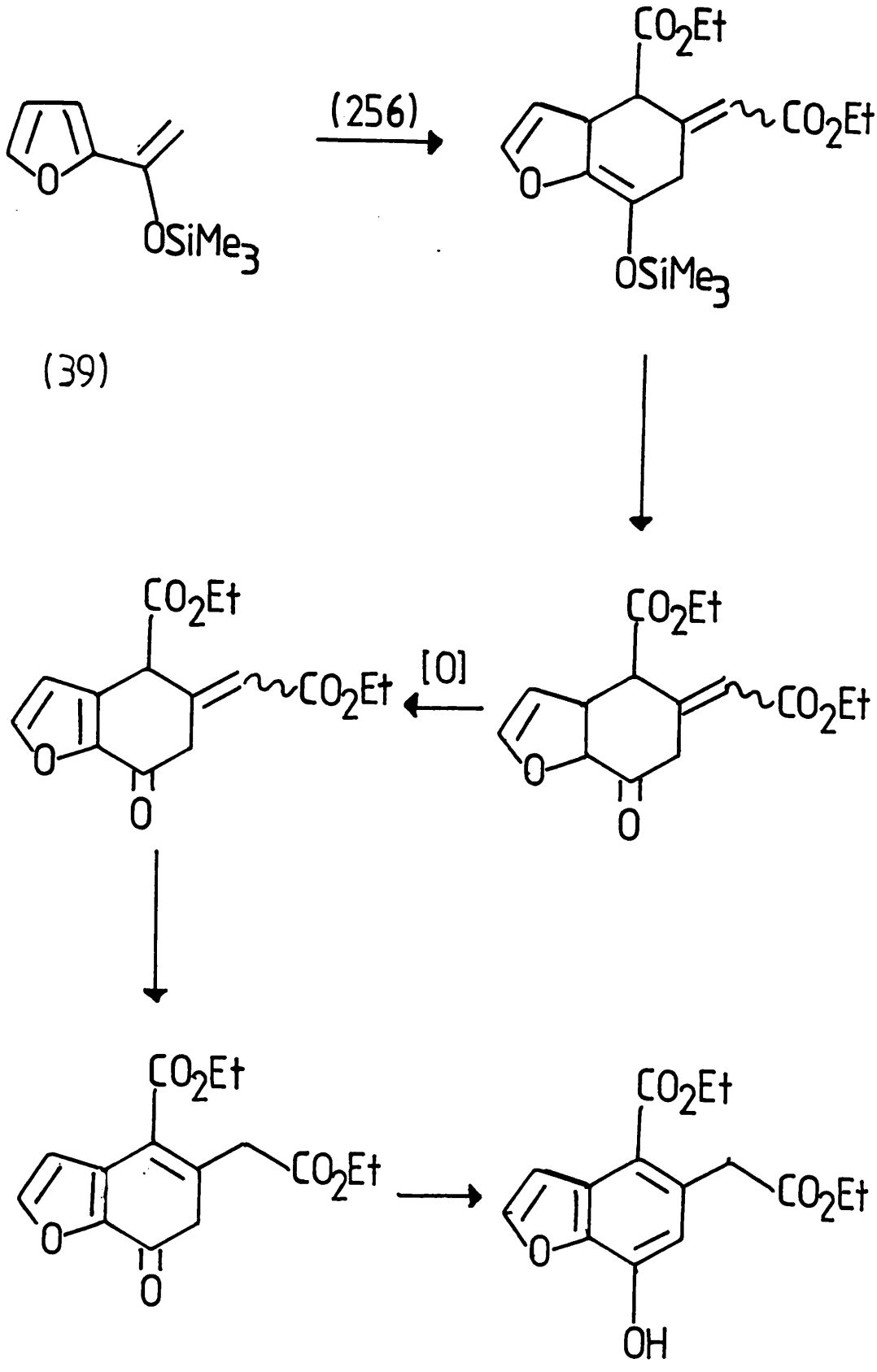
When a solution of the oxydiene (39) and diethyl penta-2,3-dienedioate (256) in benzene was heated at reflux overnight, products of two very different gross structures were isolated. The minor product (10%) was a white crystalline solid to which the phenolic structure (272) has been assigned.



(272)

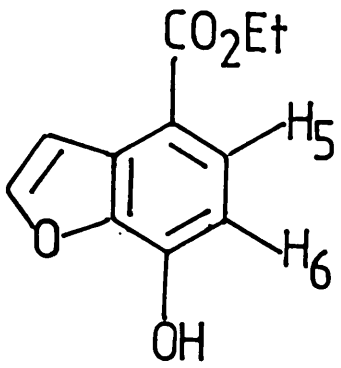
This structure was fully apparent from the spectral details. Thus the ir spectrum showed a broad OH band (3250cm^{-1}) and two ester carbonyls (1710 and 1700cm^{-1}). The uv spectrum showed maxima at 228, 283 and 320 nm, typical of a benzofuran structure. Moreover, on the addition of one drop of aqueous sodium hydroxide to the solution used for the uv determination, the maxima appeared at 221, 242 and 321 nm with greatly increased intensities, typical behaviour for a phenol. The structure was confirmed by an examination of the 250MHz ^{1}H nmr spectrum which showed two doublets at 7.91 and 7.31 ppm and a singlet at 6.82 ppm (the three aromatic protons), a singlet at 4.03 ppm (two methylene protons), and two quartets (4.09 and 4.34 ppm) and two triplets (1.21 and 1.39 ppm) corresponding to the two ethyl groups.

This product is likely to arise from cycloaddition across the exocyclic diene followed by desilylation on work-up, a dehydrogenation step (common in systems close to being aromatic) and ketone-phenol tautomerism (scheme 24).

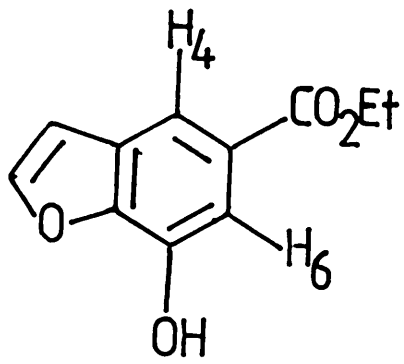

(256)
OSiMe3
CO2Et
CO2Et
OSiMe3
(39)
[O]
CO2Et
CO2Et
O
CO2Et
CO2Et
O
CO2Et
CO2Et
O
CO2Et
CO2Et
O
OH
(272)

Scheme 24

The regiochemistry of cycloaddition of the allenyl diester (256) to (39) was predicted to be as shown by a consideration of frontier orbital theory and by analogy with some Japanese work. An indication that this regiochemistry prevailed was obtained by the production of the benzofuran (273) from ethyl propiolate and the oxydiene (39). This benzofuran (273) showed the expected coupling between H5 and H6 of 8Hz, consistent only with ortho-coupling. The alternative regio-isomer (274) would have shown two signals with meta-coupling ($J \approx 2Hz$[115]) corresponding to H4 and H6 in the ^1H nmr spectrum. More rigorous evidence for the regiochemistry of cycloaddition is presented later in the case of the addition to the oxydiene (86).

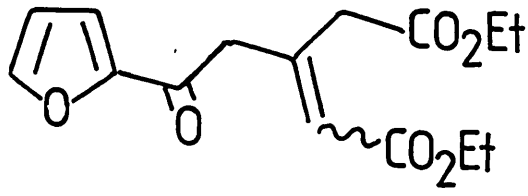


(273)



(274)

The major products from the reaction between (39) and (256) (40-45%) appeared to be the isomeric compounds (275), resulting from Michael addition of the trimethylsilyl enol ether (39) to the allene. The isomers (275) were inseparable by distillation or chromatography and were contaminated by the presence of a third minor component.

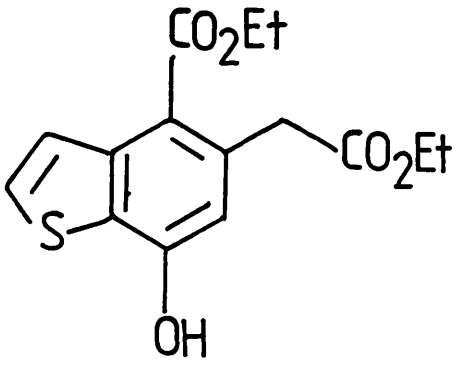


(275)

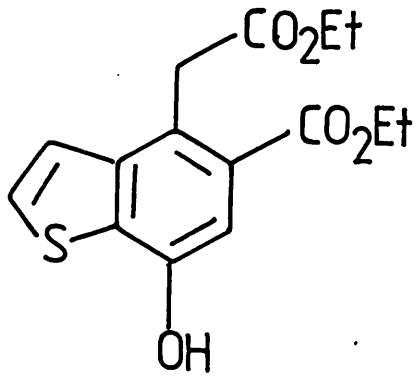
The evidence for the structure of these Michael adducts (275) was provided by spectroscopic data. Thus the ^{1}H nmr spectrum of the mixture showed a typical 2-acetyl furan pattern with three signals at 7.60, 7.48 and 6.52 ppm corresponding to the heterocyclic ring protons, a broadened vinylic signal at 6.04 ppm and a number of singlets in the region 3.6-4.0 ppm corresponding to the CH_2 groups of (275). The ir spectrum showed the presence of an ester carbonyl (1740 cm^{-1}), an α,β-unsaturated ester carbonyl (1725 cm^{-1}) and a 2-acetyl furan carbonyl (1680 cm^{-1}). The minor component was not readily identified from the additional peaks present in the ^{1}H nmr spectrum.

The Japanese workers suggested that the diene (86) containing a vinyl thiophene moiety was a better exocyclic diene than the vinyl furan (39), the latter typically behaving more as a silyl enol ether than as a diene. However, on heating a solution of (86) and the allene (256) in benzene under reflux overnight, again two distinct types of products were formed. The minor product (10%) was the phenol (276), identified by the close similarity of its spectral data to those of the furan analogue (272). In this instance, the regiochemistry of addition was proven by a nuclear Overhauser effect experiment.

It was anticipated that irradiation of the singlet due to the exocyclic methylene group would cause an enhancement in the signal of the adjacent aromatic proton (H6) if the product were isomer (276). Irradiation of the CH_2 in the regioisomeric phenol (227) would not result in any enhancement of the aromatic proton (H6) intensity as the protons are separated by too great a distance.



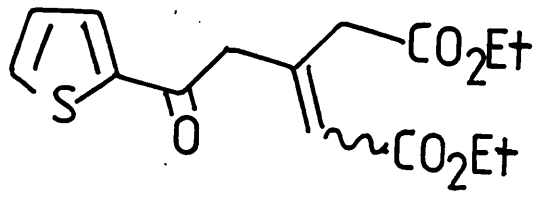
(276)



(277)

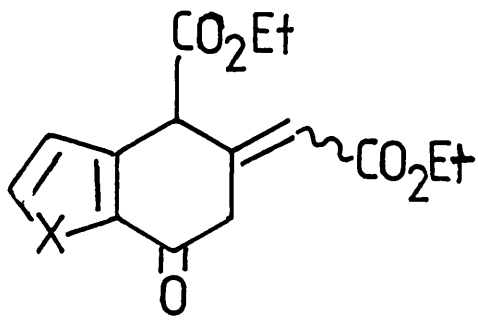
In agreement with this expectation, a nuclear Overhauser effect difference spectrum showed that irradiation of the CH_2 signal caused a 12% enhancement in the intensity of H6 and that irradiation of H6 caused a 3% enhancement in the intensity of the CH_2 signal, thus confirming the regiochemistry of addition as shown for (276).

The major products from the reaction between (86) and (256) appeared again to be the products of Michael addition to the allene (40-45%). This assignment was once more based on spectral data and again the mixture of isomers (278) was contaminated with a minor unidentified component.



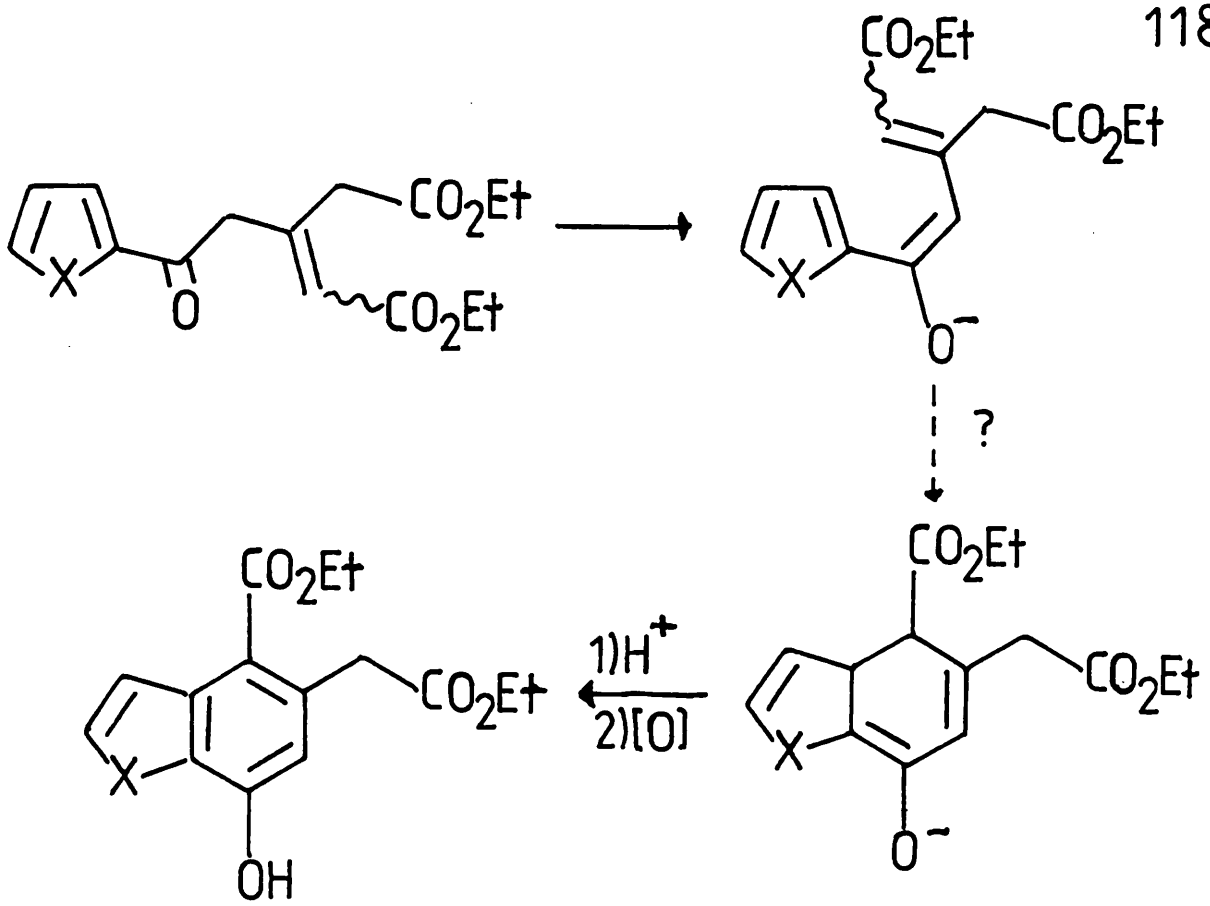
(278)

This preference of the vinyl thiophene (86) to behave predominantly as a silyl enol ether was not expected. However, it was encouraging to note that exocyclic cycloaddition had at last been observed, even though the yields were low and the resultant 7-hydroxy benzo-fused heterocycles would appear to be of less use in an approach to the nagilactone natural products than a non-aromatised adduct, for example (279).



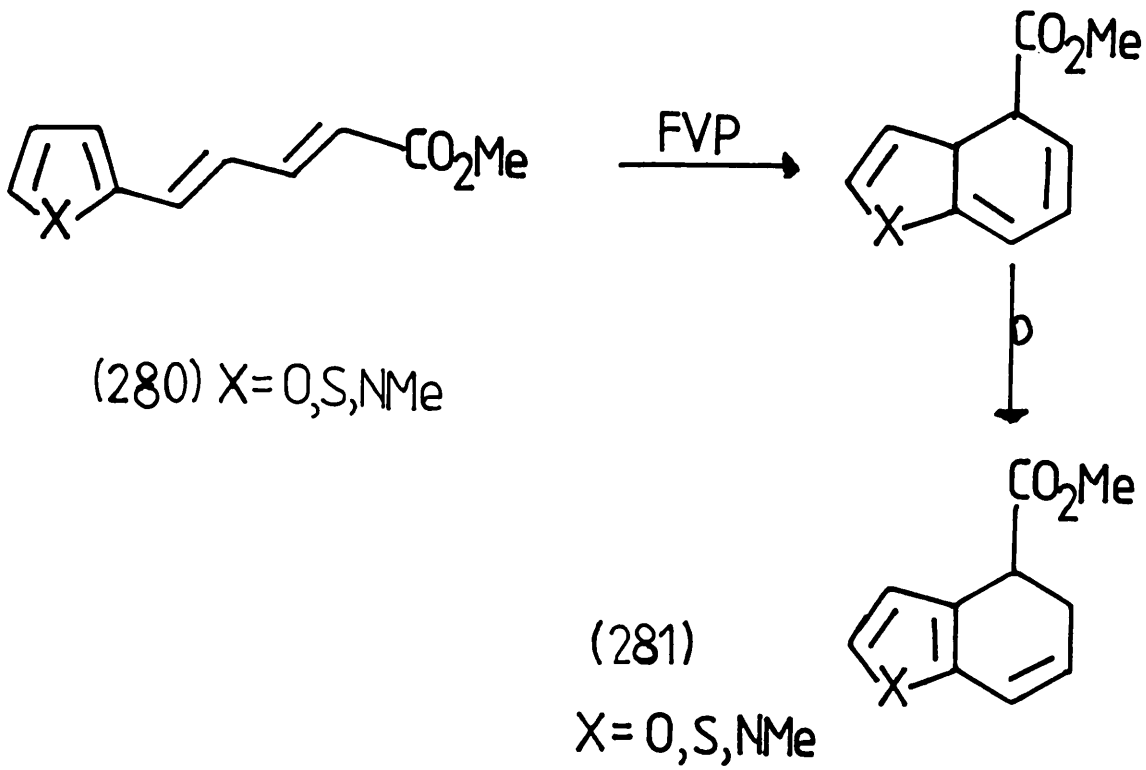
(279)

It is possible to conceive of the Michael adducts (275) and (278) providing access to greater quantities of the phenol products by attempting to induce a derived enolate to undergo an electrocyclic reaction (scheme 25).



Scheme 25

The basis of this hope was the knowledge that under flash vaccuum pyrolysis conditions the trienes (280) rearrange in good yields via an electrocyclic process and further rearrangement to the fused structures (281).[116]

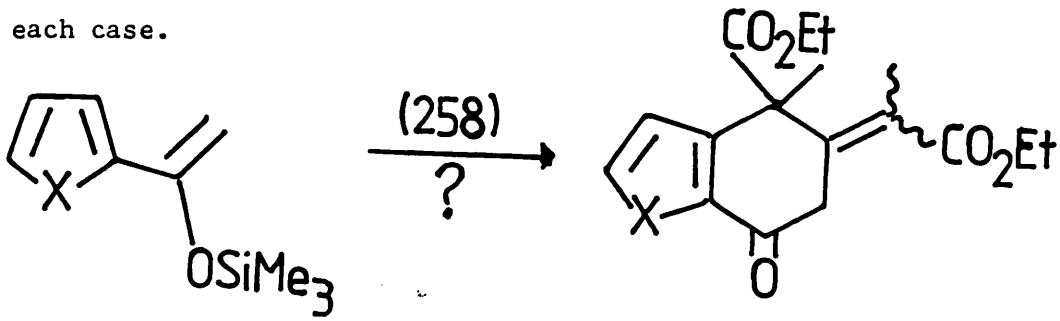


(280) X= O,S,NMe

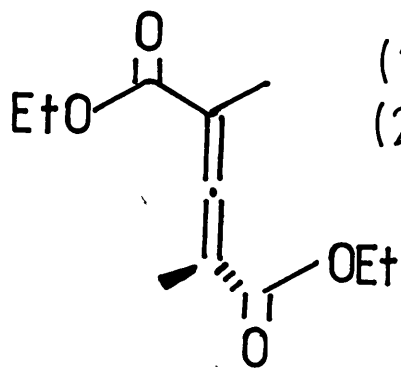
(281)
X= O,S,NMe

It was hoped that generation of the (potassium) enolate of (275) or (278) with potassium tert-butoxide in THF followed by thermolysis would possibly result in a rearrangement reaction. However, the generated potassium enolate of (278) did not rearrange at -78°C over 1½ hours nor at 25°C over 1½ hours. However, at reflux in THF over a 4 hour period, a lower-R_f spot did appear on tlc. Chromatography of the mixture after work-up with trifluoroacetic acid led to the isolation of starting material (278) (51%) and the lower-R_f component (13%). This lower-R_f product was not further investigated as the ^1H nmr spectrum showed that it certainly was not the phenol (276) nor a precursor to it.

In order to prevent the formation of a benzo-fused heterocycle in the Diels-Alder reaction, the reactions of the tetra-substituted allene (258) with the oxydienes (39) and (86) were investigated. However, reaction of the allene (258) with an excess of either (39) or (86) in toluene at reflux over a 48 hour period produced none of the desired cycloadducts (282) or (283), the allene and the 2-acetyl heterocycle (from desilylation of the enol ether) being isolated in each case.



(39) X = O
(86) X = S



(258)

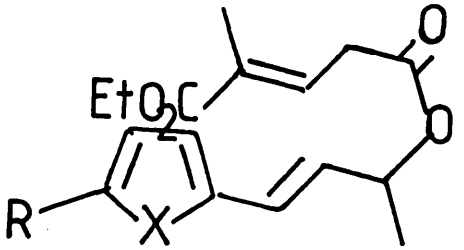
(282) X = O
(283) X = S

4.0 THE INTRAMOLECULAR APPROACH

4.0. THE INTRAMOLECULAR APPROACH

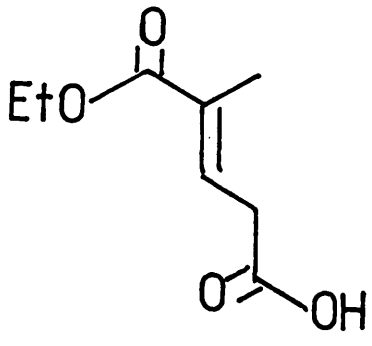
4.1. Reactions involving simple glutaconate esters

The failure of the initial intermolecular cycloadditions to provide access to the desired exocyclicdiene cycloadducts prompted an examination of an intramolecular Diels-Alder strategy. The first approach to be considered involved the mixed glutaconate esters (284) and (285) incorporating the vinyl heterocycle component.



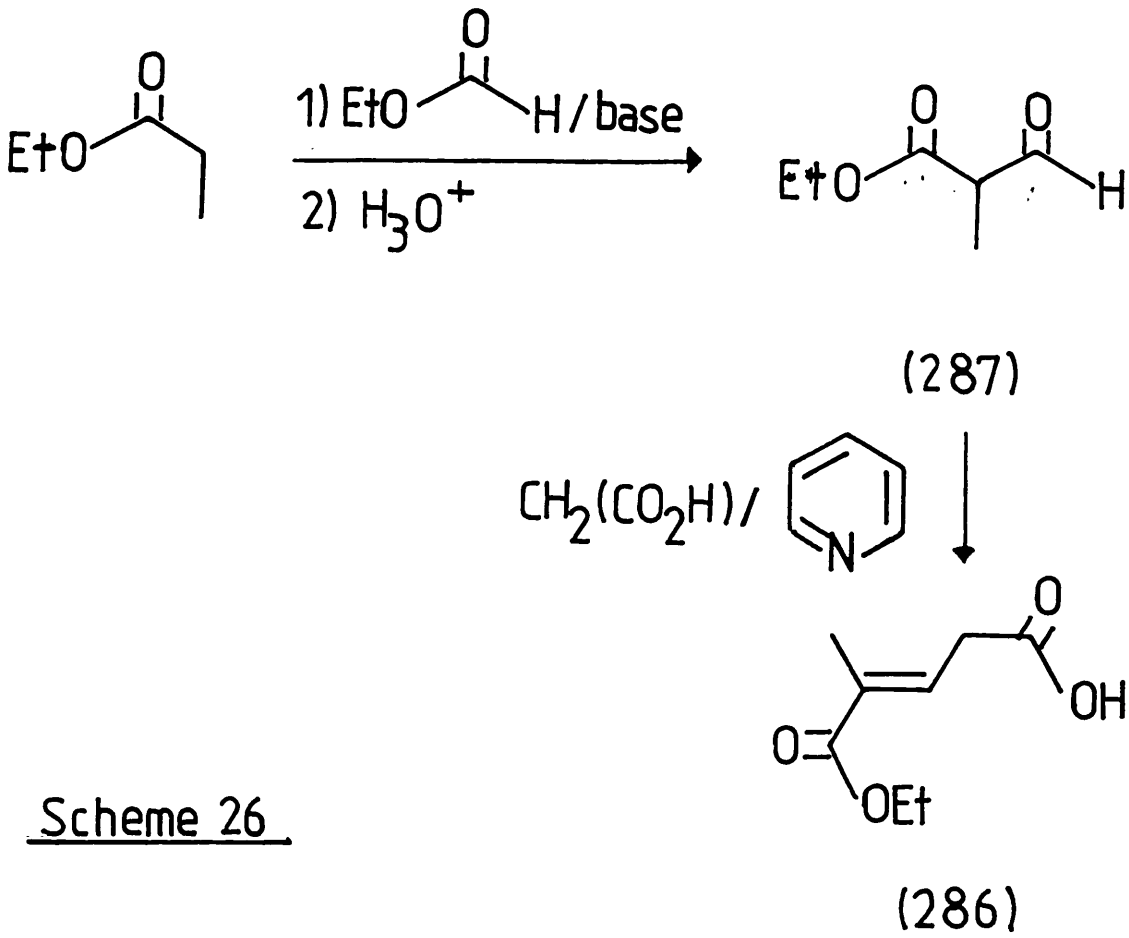
	R	X
(284)	H	O
(285)	H	S

The esters (284) and (285) could in principle be readily available from coupling of the furan and thiophene allylic alcohols (224) and (226) with the known glutaconic half-ester (286).[117]



(286)

However, considerable problems were encountered with the two steps in the synthesis of (286) (scheme 26) in which yields were much lower than those reported in the literature.

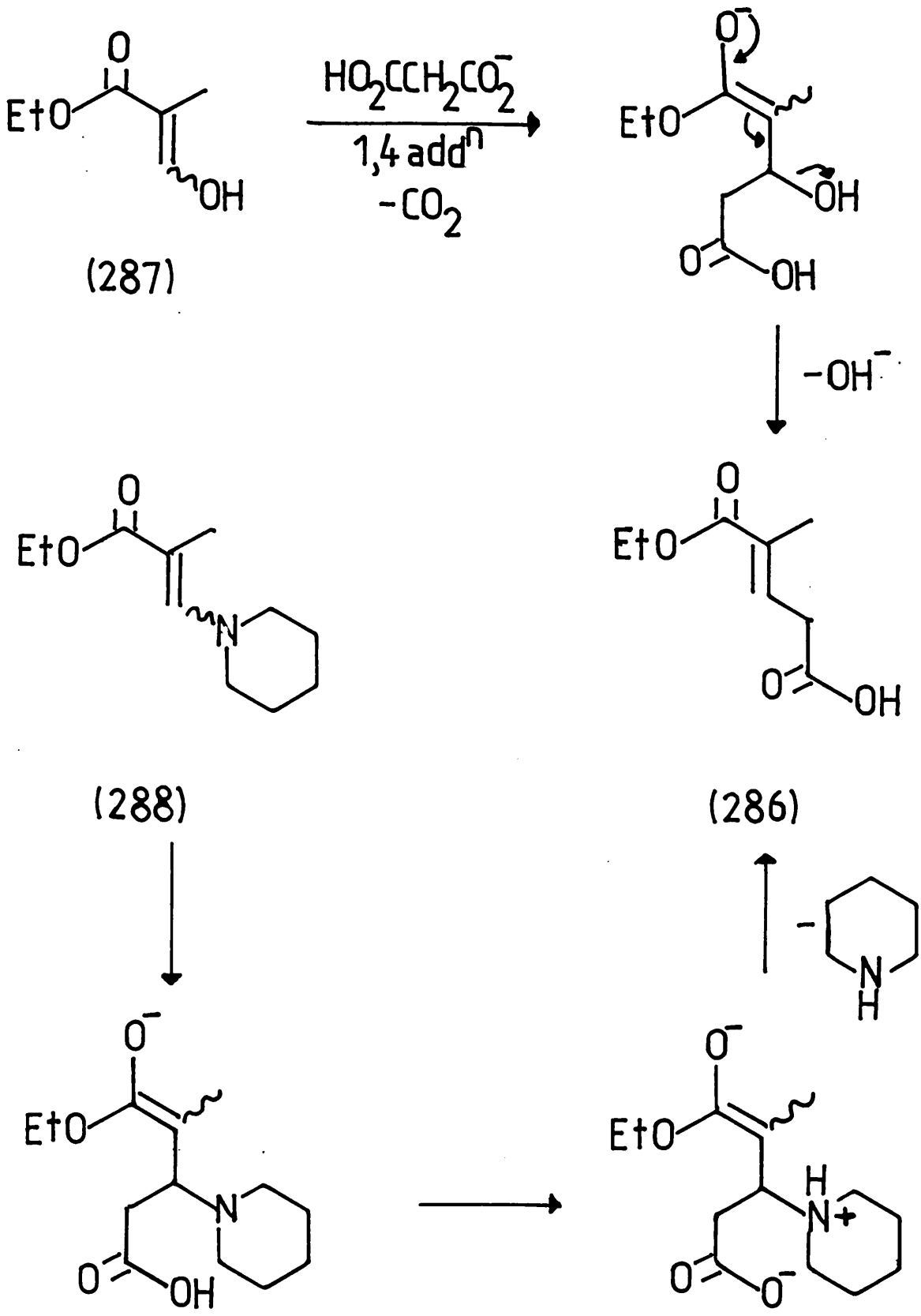


Scheme 26

Thus condensation of ethyl propionate with ethyl formate provided ethyl 2-formyl propionate (287),[118] albeit in low and variable yield under a wide range of experimental conditions. The best method employed LDA as base to generate the ester enolate of ethyl propionate at -70°C followed by quenching with ethyl formate (1 equivalent) to afford a 21% yield of aldehydoester (287) after acidic work-up.

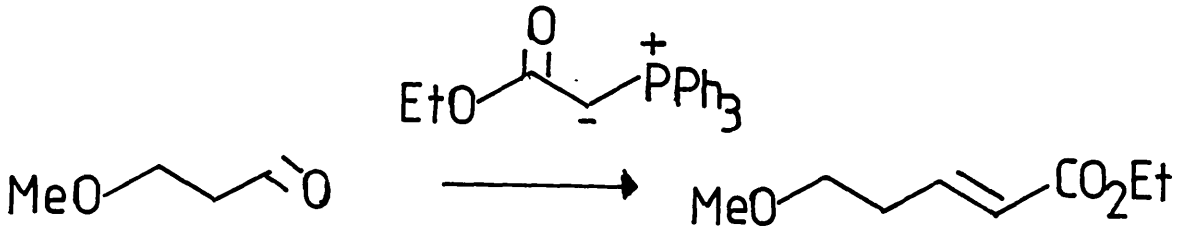
The subsequent Doebner condensation of malonic acid with (287) is reported to provide acid (286) in 47% yield.[117] However, it was found in a number of repetitions of this literature procedure that it uniformly resulted in isolation of a very low yield (< 10%) of compound (286).

It was therefore necessary to modify the procedure for the Doebner condensation. This was done by forming the carboethoxy enamine (288) by treatment of (287) with piperidine and potassium carbonate. The enamine thus prepared was then heated with malonic acid and pyridine to afford the glutaconate half-ester (286) in an optimised yield of a meagre 16%. The rationale for the use of the enamine (288) had involved a consideration of the likely mechanism of the Doebner condensation (scheme 27) in which the better leaving group ability of a protonated amine compared with hydroxide should favour the reaction.


EtO
O
OH
(287)
$HO_2CCH_2CO_2^-$
1,4 addⁿ
$-CO_2$
O^-
EtO
OH
O
OH
$-OH^-$
EtO
O
N
(288)
EtO
O
OH
(286)
N
H
O^-
EtO
N
O
OH
O^-
EtO
H
N^+
O
O^-

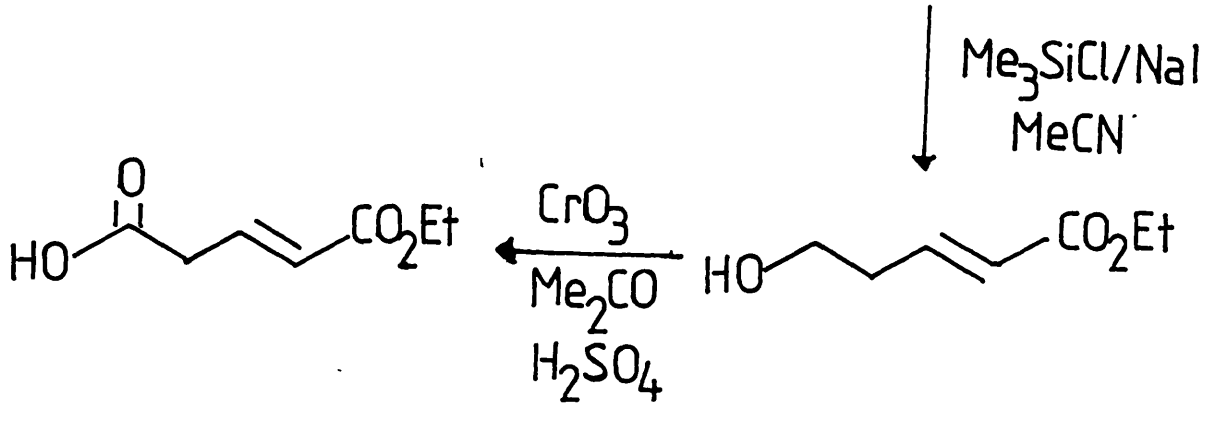
Scheme 27

This low-yielding sequence led to a consideration of alternative approaches to the synthesis of glutaconate monoesters. A moderately successful strategy was found, involving three steps from 3-methoxypropanal (289) (scheme 28).[119]



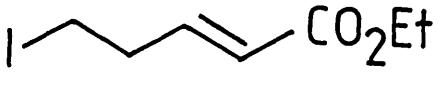
(289) (290)

Solvent	Yield(%)	E:Z ratio
MeCN	50	9:1
THF	54	17:1
PhH	85	24:1



(292) (291)

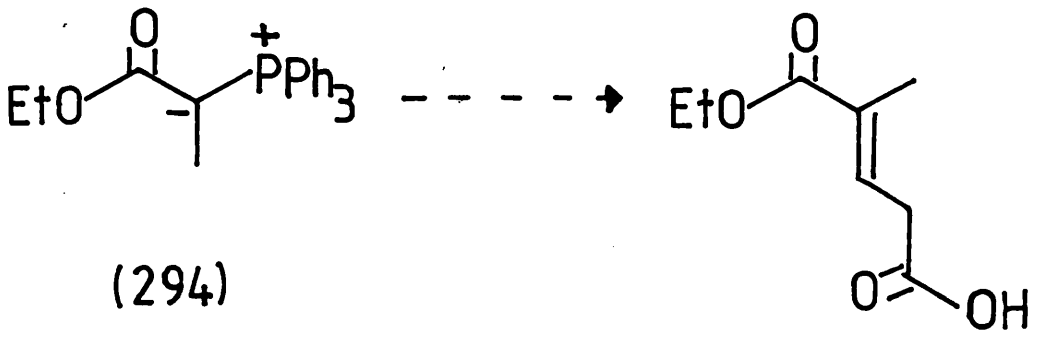
Scheme 28



(293)

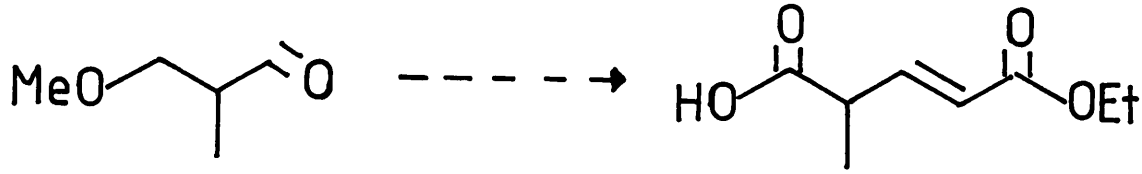
Thus Wittig reaction between carboethoxymethylenetriphenylphosphorane and 3-methoxypropanal[119] (289) afforded the unsaturated esters (290) easily separable by chromatography. The isomer ratio appeared to be solvent dependent, benzene offering the best yield and ratio of E:Z isomers. The methyl ether group of (290) was readily cleaved by treatment with iodotrimethylsilane generated *in situ* in acetonitrile,[120] providing the alcohol (291) in high yield. In some cases, when an excess of chlorotrimethylsilane and sodium iodide was used, the alcohol (291) was contaminated with the iodide (293), particularly if a long reaction time was employed. The use of excess cleavage reagent was necessary though as the use of only one equivalent resulted in a sluggish reaction and so careful control of conditions was necessary for the success of this reaction. The oxidation step was conveniently carried out using Jones' reagent,[121] providing the acid (292) in high crude yield. Purification of the acid was not facile as basification, extraction to remove the neutral material and reacidification surprisingly provided a low recovery of the pure acid (292).

In principle, this three step route could provide access to a variety of alkylated glutaconate half-esters by employing the ylid (294) and the methacrolein derivative (295), although neither of these were attempted.



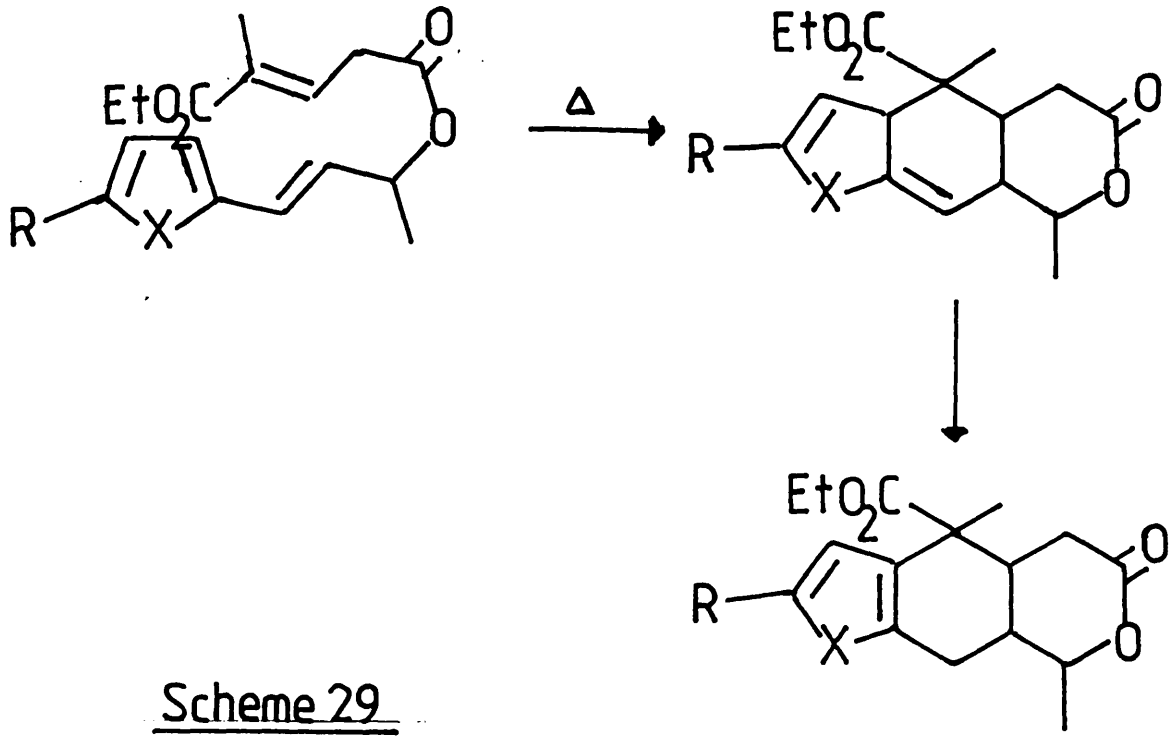
(294)

(286)



(295)

The esters (284) and (285) were prepared by N, N'-dicyclohexyl-carbodiimide[122] promoted coupling of the alcohols (224) and (226) with (286) in 40% and 63% yields respectively. These esters were chosen for the trial cycloaddition reactions since if Diels-Alder reaction were observed the necessary quaternary centre in ring B would be generated (scheme 29).

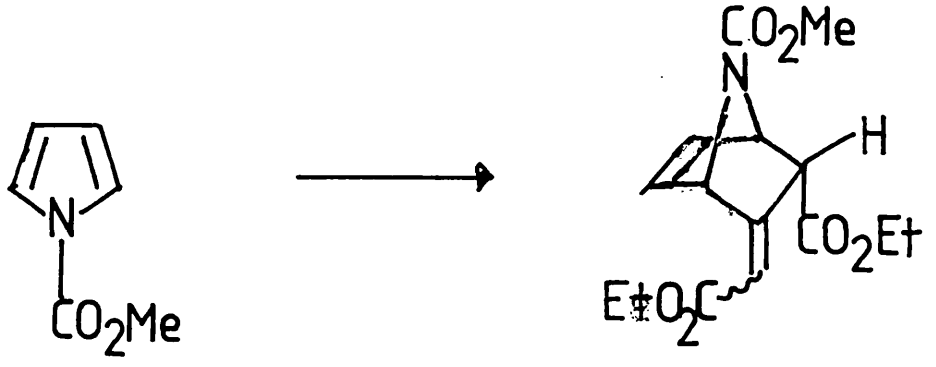


Scheme 29

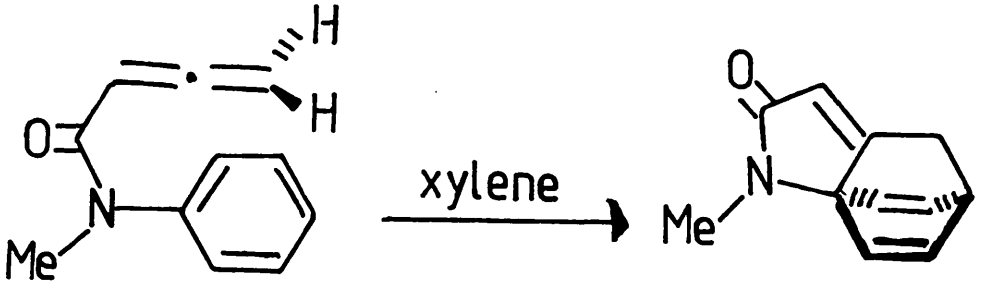
Thermolysis of the vinyl furan glutaconate (284) in toluene (2½ hours) produced no change (^{1}H nmr spectroscopy) other than the deposition from the cooled solution of a red polymeric solid (< 10%). However, on thermolysis in xylene (19 hours), the material polymerised extensively to yield an insoluble solid (mp > 260°C). The small amount of residue after filtration of this solid and evaporation showed no evidence (^{1}H nmr spectroscopy) of cycloaddition. On the other hand, thermolysis of the more stable ester (285) in toluene (48 hours) or in acetic anhydride[28] (24 hours) resulted in recovery of starting material. Although forcing conditions were not attempted using the vinyl thiophene (285), it was apparent that the glutaconate moiety was simply not an active enough dienophile to undergo intramolecular cycloaddition with the vinyl heterocycles.

4.2. Reactions involving allenyl diesters

After the failure of the mixed glutaconate esters (284) and (285) to undergo the desired cycloaddition, the incorporation of an allenyl 1,3-diester dienophilic component was considered. Allenes bearing electron-withdrawing groups are known to possess excellent dienophilic properties, for example, diethyl penta-2, 3-dienedioate (256) is known[13] to add across the pyrrole ring of (296) providing (297) in 60% yield. In an intramolecular sense, the allenyl amide (298) has been observed to undergo an extraordinary Diels-Alder reaction, with a benzene ring acting as the diene component.[95]

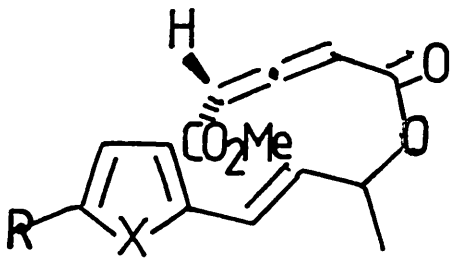


(296) (297)



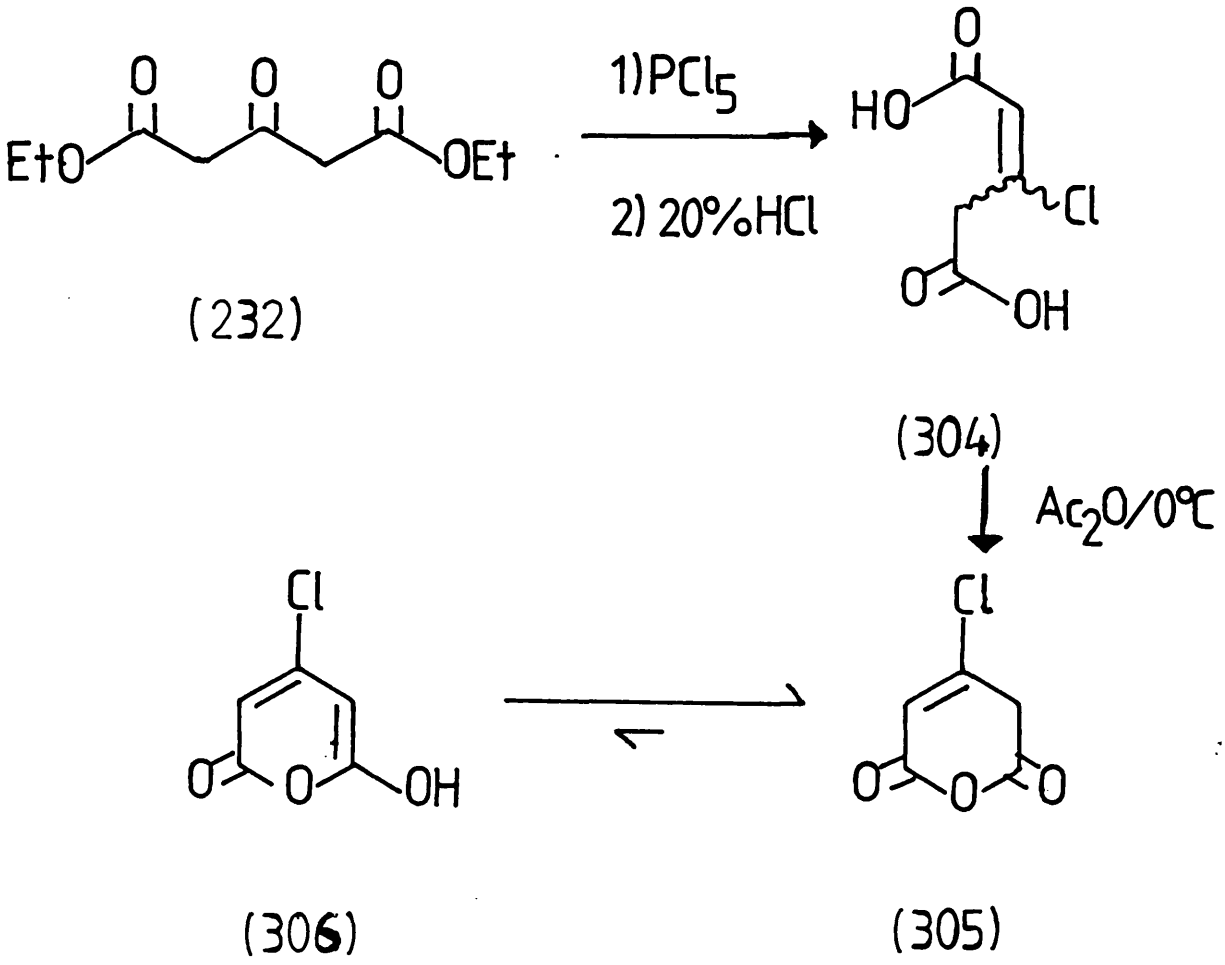
(298) (299)

Thus the synthesis of the mixed allenyl diesters (300) - (303) was considered. This was envisaged to involve the coupling of the furan and thiophene allylic alcohols (224) - (227) with a suitable 3-chloroglutaconic half ester. On elimination of hydrogen chloride with triethylamine, as in the literature synthesis of dimethyl penta-2,3-dienedioate, these should provide the mixed allenyl diesters.



	R	X
(300)	H	O
(301)	Me	O
(302)	H	S
(303)	Me	S

The substrate chosen for initial synthetic studies was the known 3-chloroglutaconic anhydride (305),[123] available in three steps from diethyl 3-oxoglutarate (232) (scheme 30).

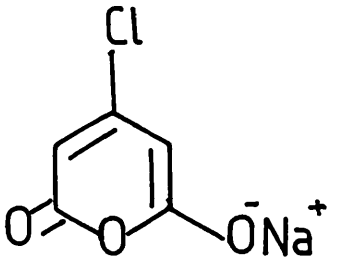


Scheme 30

Thus addition of phosphorus pentachloride to diethyl 3-oxoglutarate (232), warming to 60-65°C for 30 minutes and aqueous work-up, followed by heating the crude product to reflux with 20% hydrochloric acid (2½ hours) yielded the crude diacid (304). This was digested with cold acetic anhydride to provide the crystalline anhydride (305) in 31% overall yield.

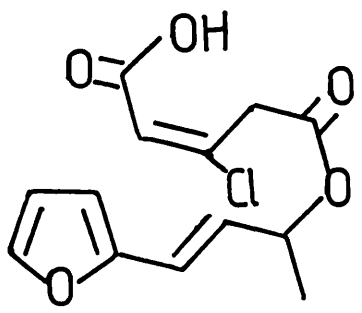
The predominant existence of the anhydride (305) as the depicted tautomer was indicated by the ir spectrum showing typical anhydride absorptions at 1805 and 1750 cm^{-1}, the ^1H nmr spectrum showing a doublet (J=2Hz) at 3.77 ppm ($\underline{CH_2}CO$) and a triplet (J=2Hz) at 6.38ppm ($\underline{CH}$=C) and by a typical $\underline{\beta}$-chloro-$\underline{\alpha}$, $\underline{\beta}$-unsaturated carbonyl chromophore at 228 nm in the uv spectrum.

The presence of a shoulder at 346 nm (ε 2300) in the last indicated the presence of a minor amount of the hydroxy pyrone tautomer (306). The addition of one equivalent of aqueous sodium hydroxide to an acetonitrile solution of the anhydride resulted in an eight-fold increase in the absorbance at 346 nm in the uv spectrum, presumably due to generation of the extended enolate (307).



(307)

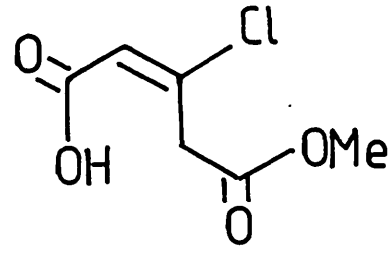
An attempt to ring open the anhydride (305) with 4-(2'-furyl) but-3-en-2-ol (224) produced not the desired half-ester (308) but an intractable tar. Part of the problem here may be due to steric hindrance in the alcohol (224) which is secondary allylic. Evidence for this steric problem arises from the empirical observations that ring opening of the anhydride (305) with propan-2-ol, butan-2-ol, and benzyl alcohol proceeded very sluggishly.



(308)

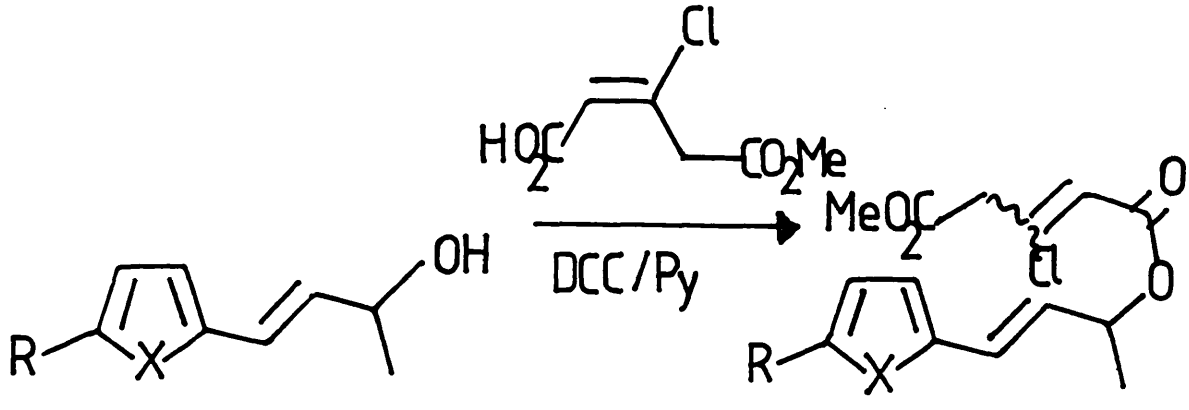
Ring opening of (305) with the lithium salt of the alcohol (224) not surprisingly failed too, presumably due to deprotonation of the anhydride (305) by the basic alkoxide. Aqueous work up resulted in recovery of the alcohol (224) (81%).

However, treatment of the anhydride (305) with neutral methanol produced a single crystalline half-ester in excellent yield (91%). That this was just one of the four possible regio- and steroisomeric monomethyl esters was shown by the presence of only six signals in the ^{13}C nmr spectrum of the product. The expected regiochemistry of ring opening, that produced by attack of methanol at the non-conjugated carbonyl as observed with glutaconic anhydride[117], and the retention of the (E)-configuration of the double bond was demonstrated by a single crystal X-ray structure determination revealing the structure to be (309).[124]



(309)

Coupling of this half-acid (309) with the furan and thiophene allylic alcohols (224) - (227) using N,N'-dicyclohexylcarbodiimide and pyridine in ether/dichloromethane provided the desired mixed 3-chloroglutaconate esters (310)-(313) in good yield.

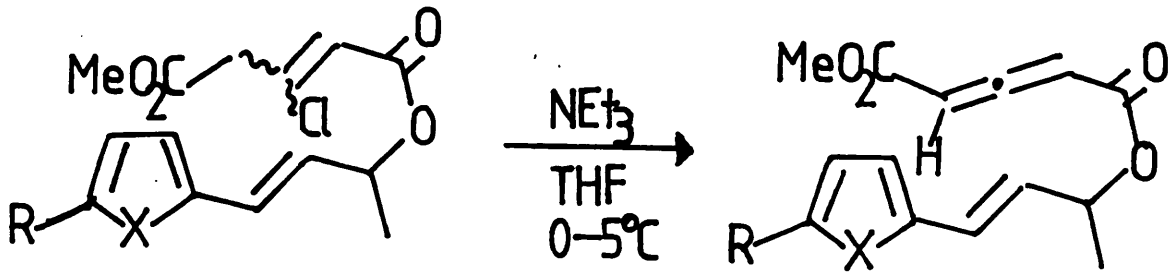


(224)–(227)

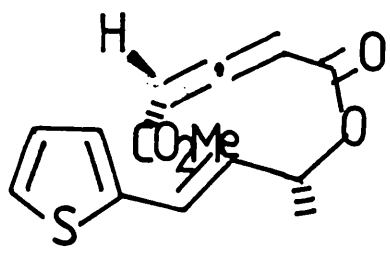
	R	X	Yield (%)
(310)	H	O	94
(311)	Me	O	71
(312)	H	S	83
(313)	Me	S	57

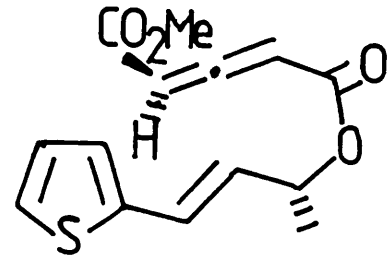
The mixed esters (310) - (313) were thought to be formed as one isomer, since the ^{13}C nmr spectrum of (311) showed 15 signals prior to chromatography. However, even routine purification over grade 5 neutral alumina caused conversion of the chlorodiesters (310) - (313) to a mixture of (E) and (Z) isomers. This was shown by the presence of 28 signals in the ^{13}C nmr spectrum of (310) and (312) and 30 signals in the spectra of (311) and (313). Purification of the esters (310) - (313) on higher activity alumina was precluded by the observation that partial elimination of hydrogen chloride occurred to provide the allenyl diesters after such treatment. The esters (310) - (313) decomposed totally on silica gel.

Elimination of hydrogen chloride from the labile chloro compounds (310) - (313) was found to proceed readily on treatment with a slight excess of dry triethylamine in THF at 0-5°C. The formation of the allenes could conveniently be monitored by the appearance of a typical cumulene absorption in the ir spectrum at 1970 cm^{-1} and by the loss of the methylene singlets in the ^1H nmr spectrum. Not surprisingly, the allenes were formed as diastereomeric mixtures. This was particularly noticeable in the 250MHz ^1H nmr spectrum of (302) which showed doublets at 6.82 and 6.89 ppm corresponding to the vinyl proton H4 and two C-methyl doublets at 1.41 ppm.



	R	X	Yield(%)
(300)	H	O	78
(301)	Me	O	75
(302)	H	S	88
(303)	Me	S	74

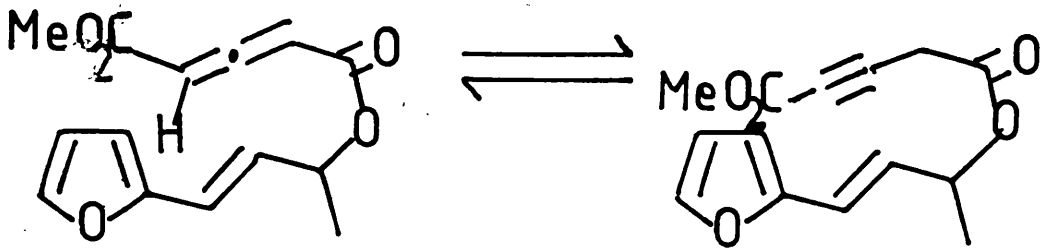




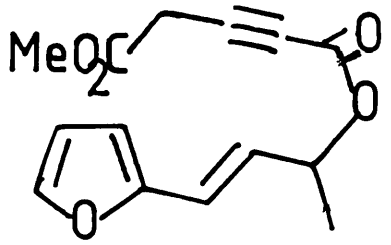
(302)

Not surprisingly, the allenes polymersed if left neat. To circumvent this, they were stored as dilute (@.04M) solutions in toluene at $-10^{o}C$.

It was of interest to note that in carbon tetrachloride at $55^{o}C$, the typical spectral features of the allene (300) (ir ν_{max} $1970cm^{-1}$, ^{1}H nmr δ 6.0ppm) disappeared. However, the close similarity of the ^{1}H nmr spectrum to the starting material and the appearance of singlets at ca 4ppm seemed to indicate that isomerisation of the allene (300) to the acetylenes (314) and (315) was occurring (scheme 31). Although the latter process is well documented in the literature for other allenes, the parent allene acid (316) is thermodynamically much more stable than the acetylene isomer (317), so much so that the latter has never been detected.[125]

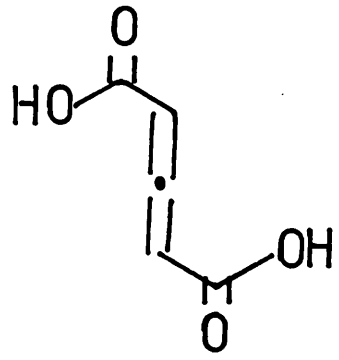


(300) (314)

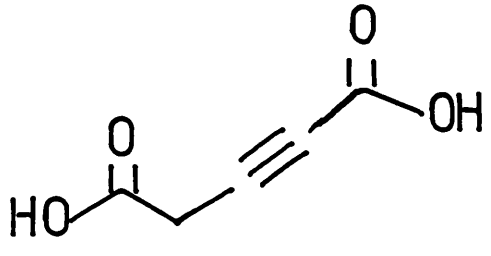


(315)

Scheme 31

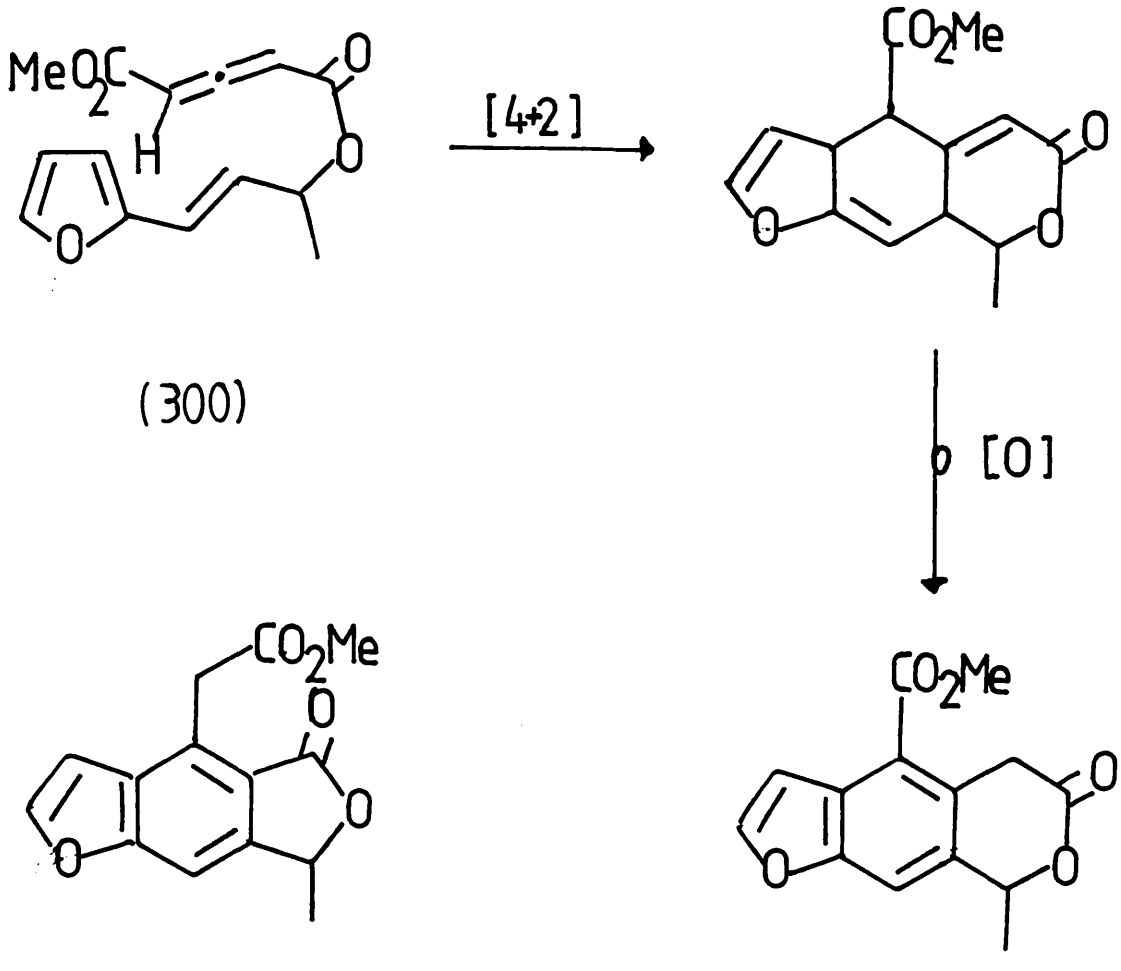


(316)



(317)

With the allenes (300) - (303) now in hand, some trial intramolecular cycloadditions were attempted. On reflux in toluene (44 hours) under argon, a dilute (0.1M) solution of allenyl diester (300) containing 2 mol% hydroquinone produced a large amount of insoluble polymer. However, chromatography of the non-polymeric residue resulted in the isolation of a waxy solid in poor yield (4%). That this still contained some polymeric material was evident by ^{1}H nmr spectroscopy. However, this data also indicated that the solid was likely to be the benzofuran (318), resulting from intramolecular cycloaddition, rearrangement and dehydrogenation (scheme 32).



(300)

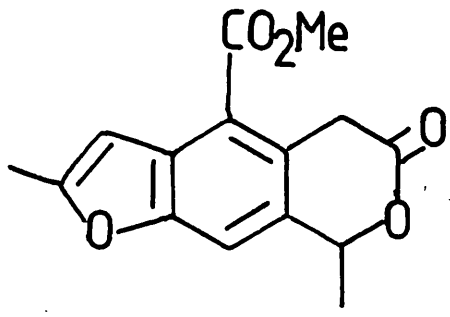
(319)

(318)

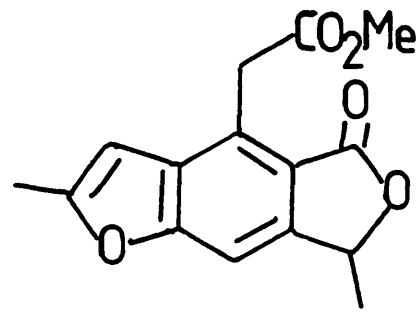
Scheme 32

The low yield and impurities prevented the unambiguous assignment of the structure of the adduct as the $\underline{\delta}$-lactone (318) rather than the isomeric $\underline{\gamma}$-lactone (319), resulting from [4+2]cyclo-addition to the alternative allene double bond, at this stage. However, by comparison with the spectra of the adducts from the allenes (301) - (303), the former was shown to be the case.

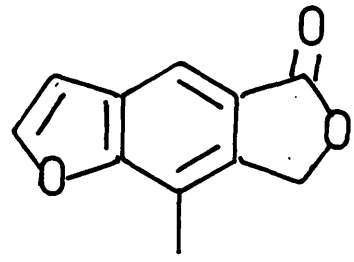
Intramolecular cycloaddition of the 5-methyl furan analogue (301) occurred more sluggishly (128 hours) in toluene at reflux but resulted in a higher yield (12%) of pure crystalline cyclo-adduct after chromatography on alumina and silica. The benzo-furan skeleton was immediately apparent from the uv spectrum, showing absorbances at 226, 268 and 310 nm. The ^{1}H nmr spectrum of the adduct showed a C-methyl doublet at 1.8ppm, shifted down-field by 0.4ppm from that observed in the starting allene (301), a new aromatic singlet at 7.45ppm, and most significantly an AB-quartet (J=18.5Hz) centred at 4.15ppm, corresponding to the lactone CH_2 group. The presence of the latter signal demonstrated that the allene had undergone cycloaddition to form the $\underline{\delta}$-lactone structure (320) rather than the isomeric $\underline{\gamma}$-lactone (321). In the $\underline{\gamma}$-lactone the methylene group is in a non-rigid position remote from the centre of chirality and would thus be expected to resonate as a singlet in the ^{1}H nmr spectrum. The assignment of ring size was confirmed by the ir absorption at 1740cm^{-1} (the known[14] $\underline{\gamma}$-lactone (322) exhibits ν_{max} 1760 cm^{-1}) and by the mass spectrum which showed an exceptionally facile loss of carbon dioxide, only consistent with a $\underline{\delta}$-lactone structure in which retro-[4+2]cleavage can occur.



(320)



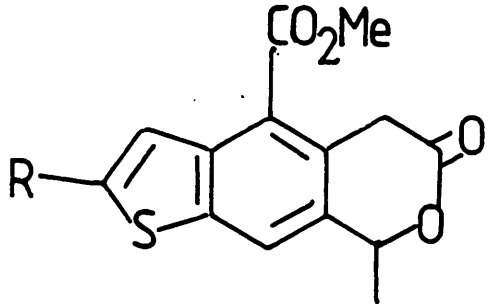
(321)



(322)

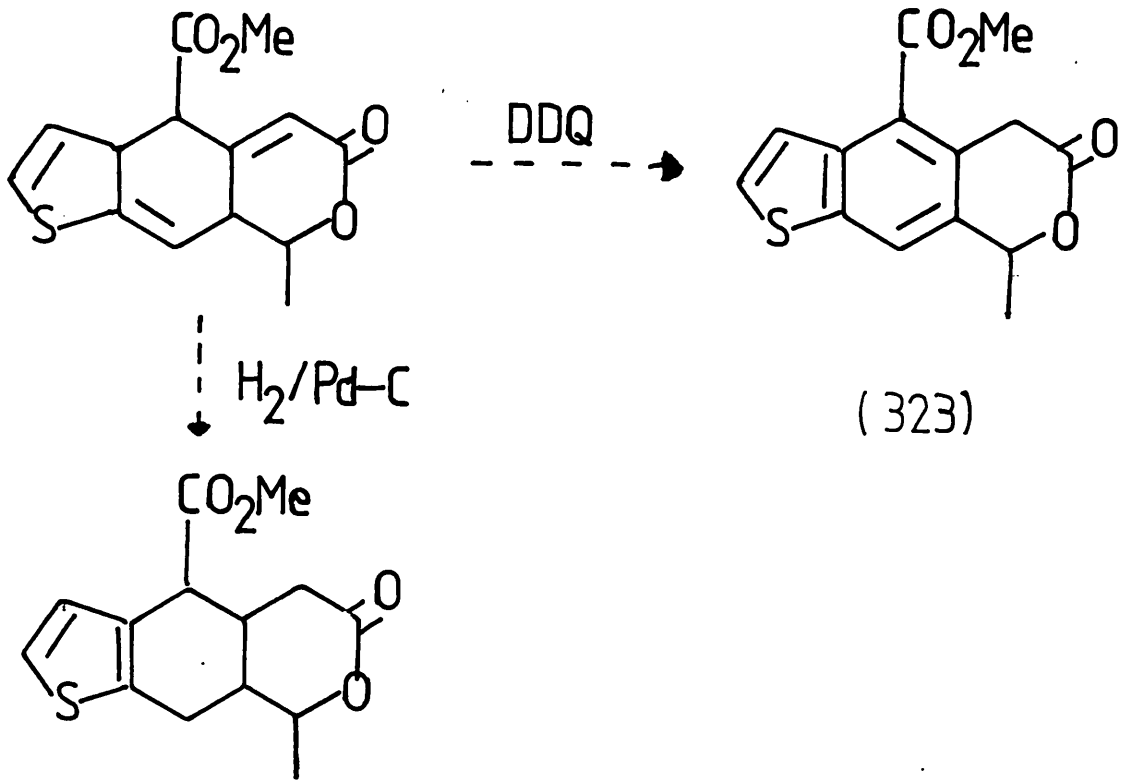
The ^{1}H nmr spectra of other fractions from the column indicated that probably as much again of the benzofuran δ-lactone (320) was present, mixed with co-eluting contaminants of indeterminate structure. Owing to the known instability of furans, particularly α-unsubstituted ones, towards acid and the prolonged reaction times necessary for cycloaddition, the glassware was routinely silylated as a precaution.

In a similar manner to the vinyl furan allenes (300) and (301), the thiophene analogues (302) and (303) cyclised in toluene under reflux to form the benzothiophenes (323) and (324). The yields of cycloadduct were again low (6% and 10% respectively) but the cycloaddition occurred at a strikingly faster rate than in the furan series (4 hours as compared to >40 hours).



(323) R=H
(324) R=Me

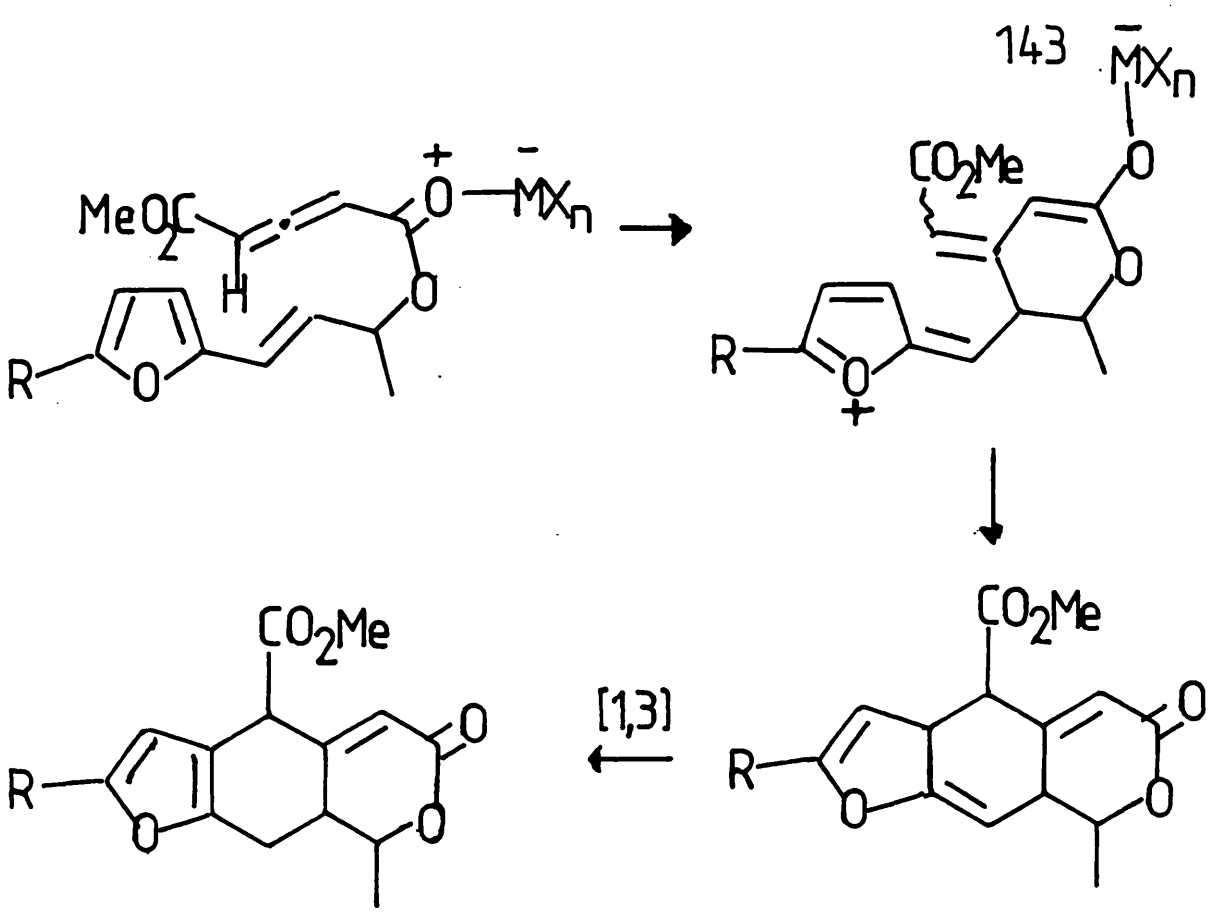
The thiophene series was of interest in that the benzothiophenes did not appear to form a major proportion of the non-polymeric material until after chromatography. This appeared to indicate that some of the benzothiophene was being formed directly from a precursor on the column. An attempt was made to convert the crude cyclo-adducts fully to the aromatic lactones by treatment with dichloro-dicyano-p-benzo-quinone. However, only complex mixtures were obtained. Alternatively, attempted hydrogenation of the crude adducts in an attempt to remove any non-thiophene unsaturation resulted in the uptake of one equivalent of hydrogen producing a product that was unstable to silica gel chromatography, suggesting that it still contained an unsaturated moiety. Perhaps in this instance the catalyst was poisoned by the thiophene. These trapping experiments were not investigated further.



(323)

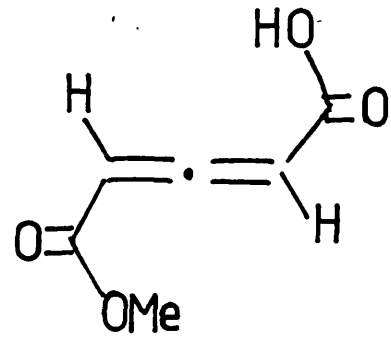
4.3. The use of Lewis acid catalysis

In an attempt to accelerate formation of the cycloadduct in the furan series, and hopefully to improve the yield, the Lewis acid catalysed Diels-Alder reaction was studied. It is well known[5] that Lewis acids can promote Diels-Alder reactivity by decreasing the energy gap between the HOMO of the diene and the LUMO of the dienophile. This is achieved by complexation of the Lewis acid with a carbonyl group of the dienophile. Two alternative mechanisms are possible, the normal concerted [4+2] cycloaddition with the complexed Lewis acid simply altering the electronic characteristics of the dienophile, or the stepwise ionic mechanism (scheme 33).



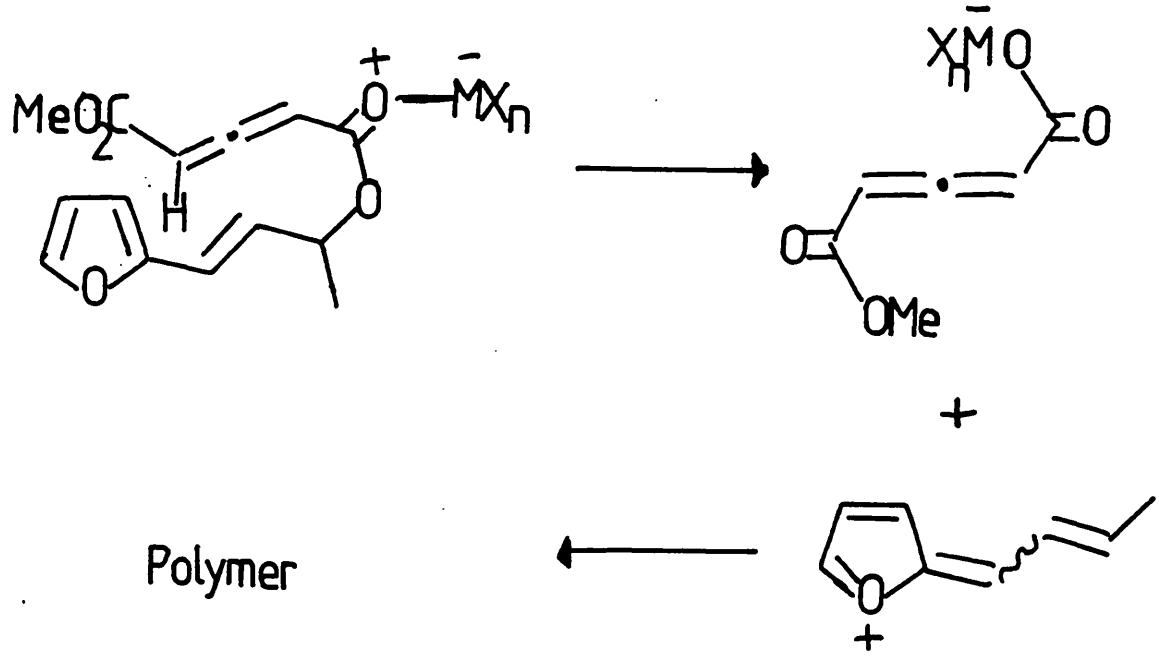
Scheme 33 M = a metal, X = a ligand

Treatment of the allene (300) with the mild Lewis acid aluminium tri-isopropoxide gave no reaction (^{1}H nmr spectroscopy) whereas treatment with magnesium bromide, zinc iodide or diethyl aluminium chloride at room temperature all rapidly resulted in the development of a deep blue colour. This was accompanied by the formation of a highly insoluble solid. Work up in the case of the zinc iodide reaction led to the isolation in small quantity of material assigned the structure (325) on the basis of a broad CO_2H band at 3100cm^{-1}, an allene signal at 1970cm^{-1} and a carbonyl at 1720cm^{-1} in the ir spectrum, and by a two proton singlet at 6.02ppm and a three proton singlet at 3.75ppm in the ^{1}H nmr spectrum. In the other cases no product other than polymer was isolated.



(325)

It was thought, therefore, that the exclusive pathway here was Lewis acid accelerated cleavage of the labile allylic C-O bond leading to the allenyl fragment (325) (scheme 34).



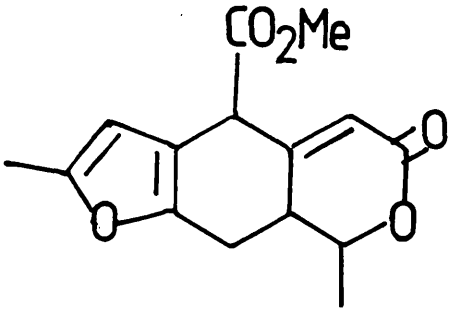
Scheme 34

(326)

The blue colour generated could be attributed to the ion (326) A similarly conjugated pyrrole related cation is blue. The colour was certainly due to the vinyl furan system and not the allene as treatment of the furan allylic acetate (217) with magnesium bromide produced a similar deep blue colour.

As a possible solution to this problem, one equivalent of the transition metal complex dicyclopentadienyl titanium dichloride [$(Cp)_2TiCl_2$] was added to a solution of the allene (300). It was hoped that this would increase the electrophilic nature of the central allenyl carbon by coordination of the transition metal with a carbon-carbon double bond of the allene. By altering the site of coordination of the metal from the carbonyl group, as in the case of the earlier mentioned Lewis acids, to the carbon-carbon double bond, it was hoped to alter the reaction pathway from fragmentation (scheme 34) to Michael addition (scheme 33). No reaction was noted however. A similar attempt using tetrakis triphenylphosphine palladium (0) was equally unsuccessful.

However, when the allene (301) was treated with diethyl aluminium chloride (1.1 equivalents) in toluene/dichloromethane at -78°C, a product was isolated (42% crude) which possessed spectral data possibly consistent with the δ-lactone structure (327). Thus the ir spectrum showed a carbonyl at 1730cm^{-1} and absorptions at 1715 and 1665cm^{-1} consistent with an α, β-unsaturated δ-lactone and the ^1H nmr spectrum showed a two proton multiplet centred at 3.06ppm, possibly consistent with the CH_2 group adjoining the furan.



(327)

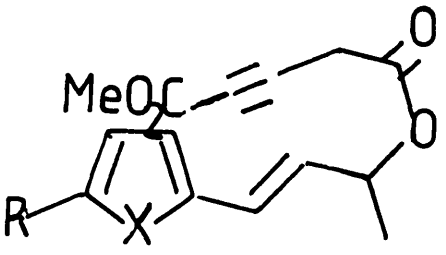
Unfortunately, all attempts to repeat this reaction on a larger scale failed and only polymeric material was isolated.

Thus although the thermal Diels-Alder reactions of the vinyl heterocycle allene systems only generated low yields of cyclo-adduct, and the adduct was fully aromatised, these reactions were more successful than the attempted Lewis acid catalysed cyclo-additions. It was believed that two possible explanations for the poor yields are possible. The first was allylic C-O cleavage, particularly noticeable in the Lewis acid catalysed reactions, but also thought to account for the polymer in the thermal reactions. The second was simple isomerisation to the isomeric acetylenes which did not undergo cycloaddition and were simply decomposed during the repeated chromatography necessary to isolate the benzo heterocycle.

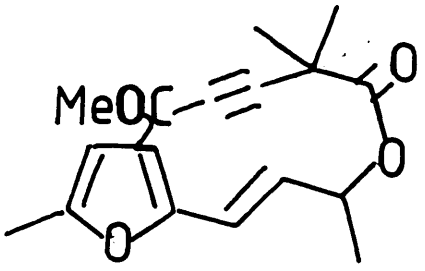
4.4. The acetylene question

It was felt that it would be of interest to determine whether the cycloadditions were occurring via the allenes (300) - (303) or via the isomeric acetylenes (328), or whether isomerisation to the acetylenes was simply providing an exit from the cycloaddition pathway.

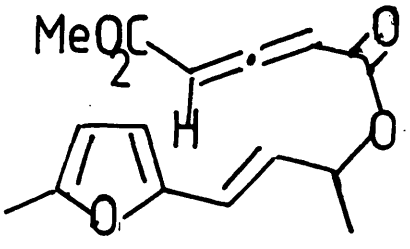
The lower activity of propiolic esters compared with the potency of allenyl 1,3-diesters in cycloaddition would seem to argue against the participation of the former in the Diels-Alder step. However, to investigate this point it would be necessary to synthesise a "blocked" acetylene, incapable of undergoing isomerisation to an allene, or a "blocked" allene, incapable of undergoing isomerisation to an acetylene. The former was chosen as it presented the easier synthetic challenge. An alkynyl diester such as (329) would be suitable even though it contains a bulky gem-dimethyl substituent and so possesses a different steric environment from (301).



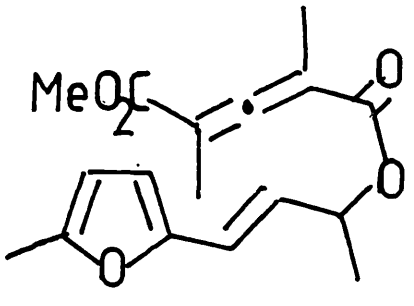
(328)



(329)

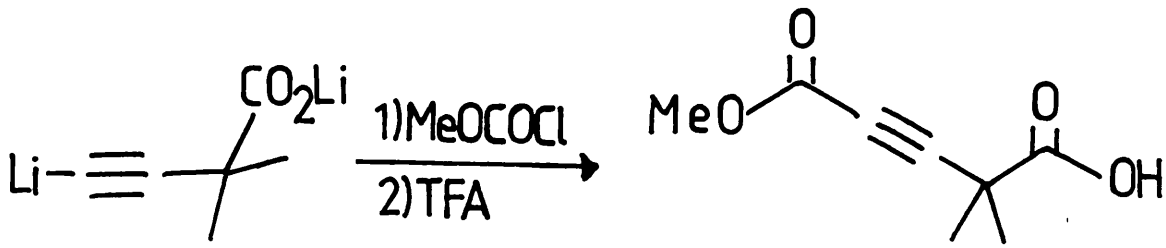


(301)



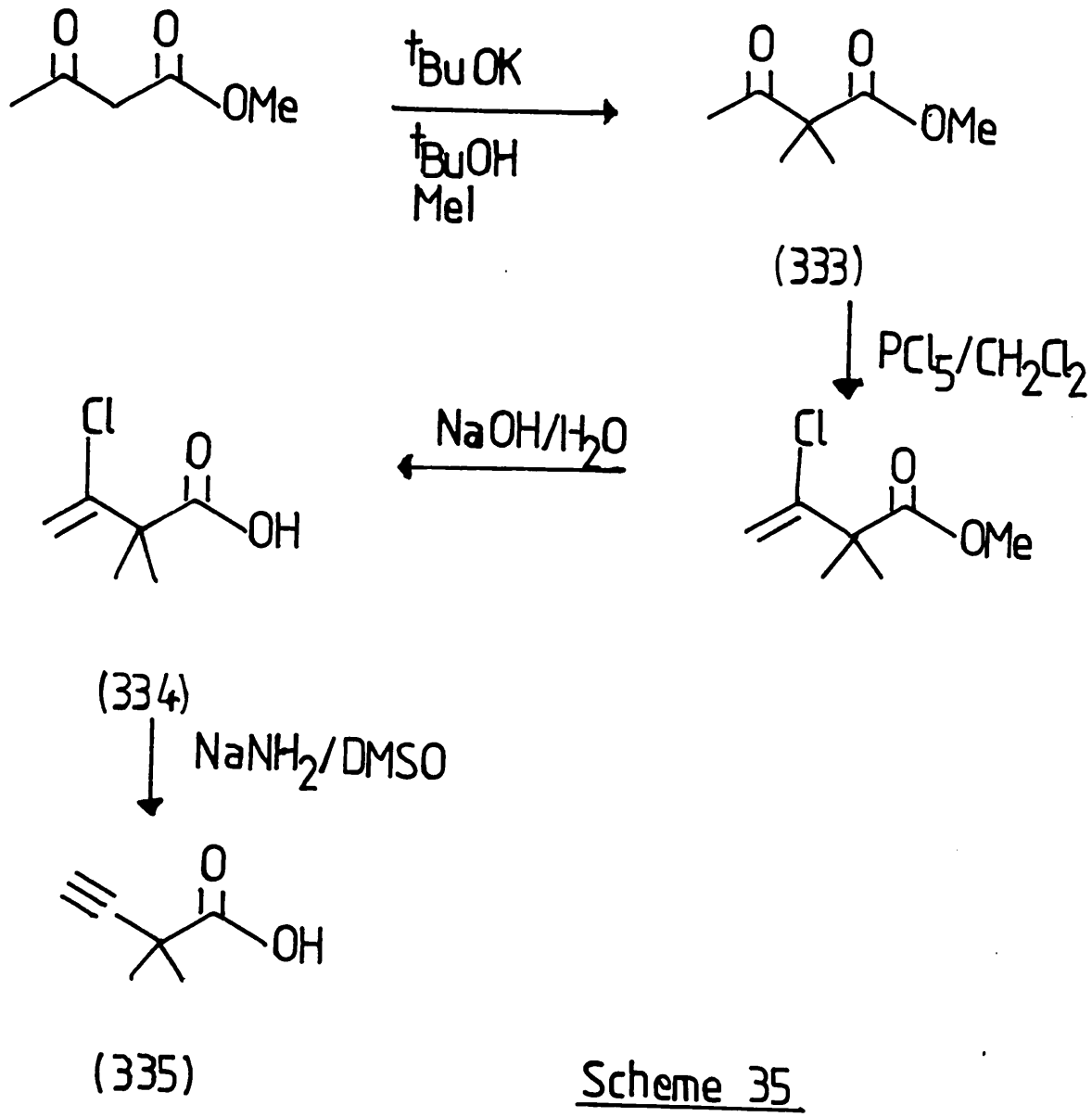
(330)

In order to be able to synthesise the alkyne (329), the carboxylic acid (332) would need to be available. It was reasoned that the latter could be made by quenching the dianion (331) with methyl chloroformate.



(331) (332)

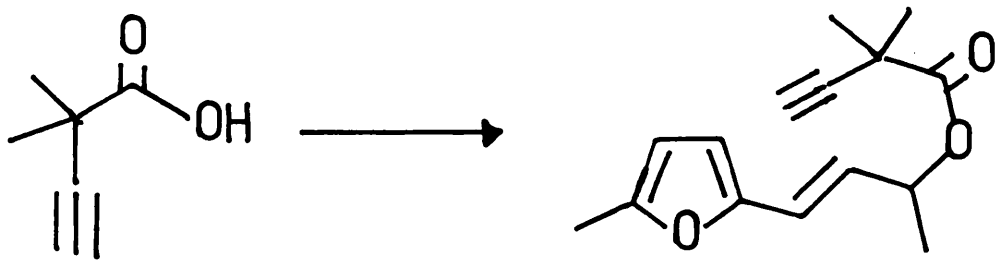
The known parent acid (335) was made by the lengthy four step literature procedure (scheme 35).[126]


OMe
tBuOK
tBuOH
MeI
(333)
PCl5/CH2Cl2
Cl
OMe
NaOH/H2O
Cl
OH
(334)
NaNH2/DMSO
OH
(335)

Scheme 35

Thus gem-dimethylation of methyl acetoacetate was achieved with two equivalents of methyl iodide using potassium tert-butoxide as base. Sequential treatment of the resultant ester (333) with phosphorus pentachloride and hot aqueous sodium hydroxide provided the crystalline carboxylic acid (334). This was smoothly converted to the desired alkynyl acid (335) on treatment with sodamide (3 equivalents) in dry dimethylsulphoxide. As anticipated, quenching of the dianion (331), formed by reaction of (335) with 2.1 equivalents of n-butyllithium at -78°C in THF, with methyl chloroformate provided the desired C-acylated product (332) in 50% yield.

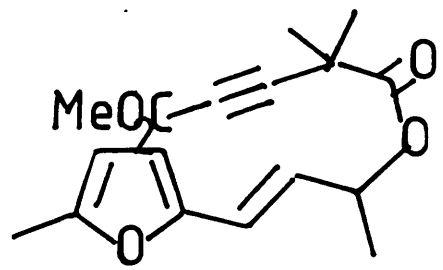
However, coupling of the now available acid (332) with either a furan or thiophene allylic alcohol proved to be very difficult, presumably owing to the very hindered neo-pentyl type environment of the CO_2H group in (332). Thus DCC promoted coupling between (332) and (225) proceeded very slowly indeed even in the presence of 0.2 equivalents of the hyper nucleophilic acylation catalyst 4-dimethylaminopyridine.[127] In view of this, the strategy was altered slightly. It was found that the ester (336) could be synthesised (56% yield) from the coupling of alcohol (225) and acid (335) using 1.8 equivalents of DCC and 1 equivalent of 4-dimethylaminopyridine. Ester (336) showed the expected sharp alkynyl CH signal in the ir spectrum (3300cm^{-1}) and the expected methine multiplet in the ^1H nmr spectrum (5.37 ppm). Transformation of (336) to the desired alkynyl diester (329) was carried out by metallation of (336) with one equivalent of n-butyllithium in THF at -78° followed by quenching with methyl chloroformate. Spectroscopic data revealed the conjugated alkynyl ester nature of the product (ν_{max} 2240 and 1725 cm^{-1}). The incorporation of the CO_2Me group was particularly noticeable by the appearance of a singlet at 3.73 ppm in the ^1H nmr spectrum.



(335)

(336)

1) ^{n}BuLi 2)MeOCOCl

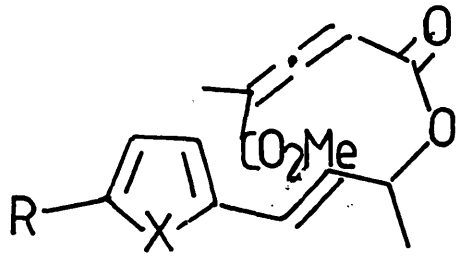


(329)

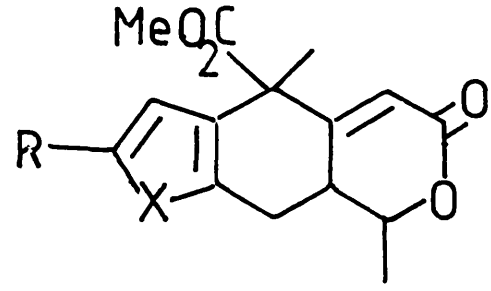
However, on heating a solution of ester (329) in toluene at reflux for 75 hours, ^{1}H nmr spectroscopy of the crude product mixture revealed no signals consist with a cycloadduct, although extensive purification of the mixture was not attempted.

4.5. Approaches towards trisubstituted allenyl diesters

The failure of the intramolecular cycloadditions to provide a non-aromatic central ring in the tricyclic lactone prompted an investigation of possible routes to a trisubstituted allene of general structure (337). On cyclisation this should generate a quaternary centre in ring B.

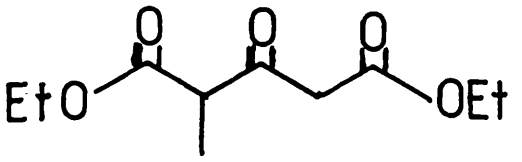


(337)

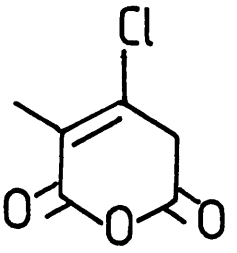


(338)

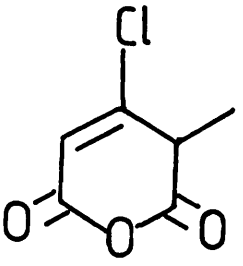
A number of routes were investigated. Firstly, sequential treatment of the monomethylated 3-oxoglutarate ester (238) with phosphorus pentachloride, 20% hydrochloric acid and acetic anhydride provided the anhydride (339). The chemical shift of the methyl group in the ^{1}H nmr spectrum (2.00ppm) fully established the structure as being (339) and not the isomeric (340).



(238)

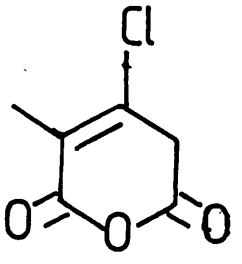


(339)

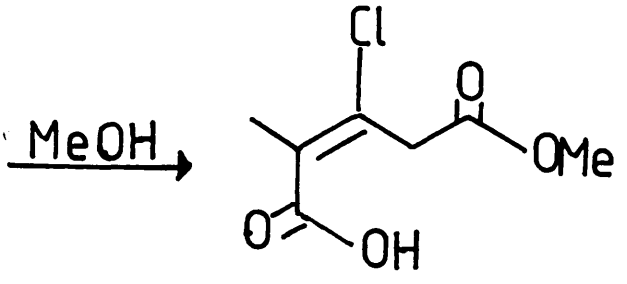


(340)

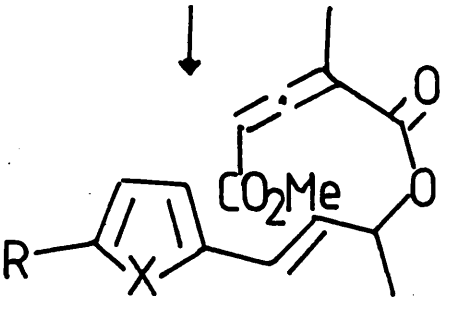
The anhydride (339) would be unsuitable as a precursor to (337) as ring opening with methanol would be anticipated to furnish isomer (341) by analogy with the parent 3-chloroglutaconic anhydride (305).[124] This could only ultimately lead to the useless regioisomeric trisubstituted allene (342).



(339)

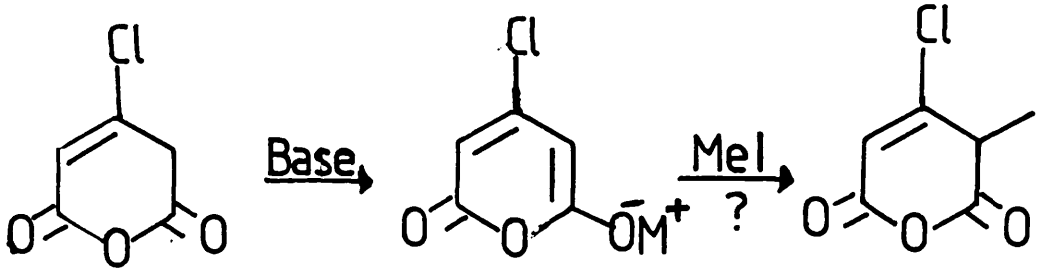


(341)



(342)

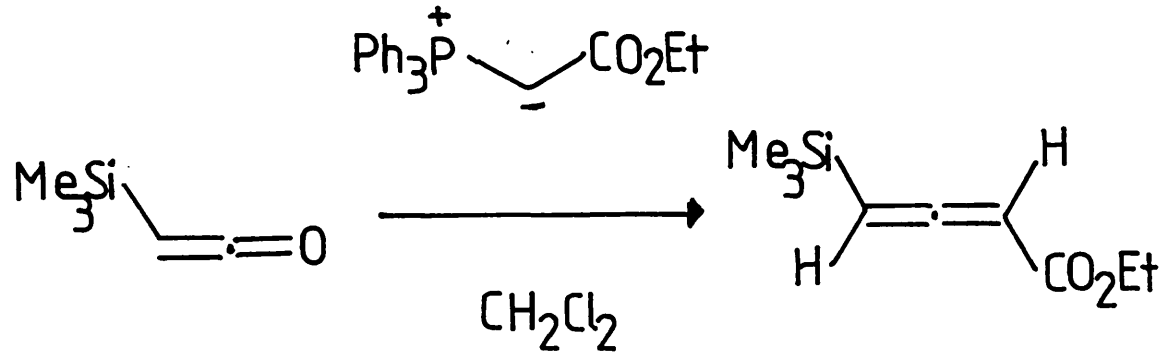
The second approach necessitated C-alkylation of the parent 3-chloroglutaconic anhydride (305). That the pyrone enolate (343) could be formed by treatment of (305) with base was shown conclusively earlier by uv spectroscopic data.



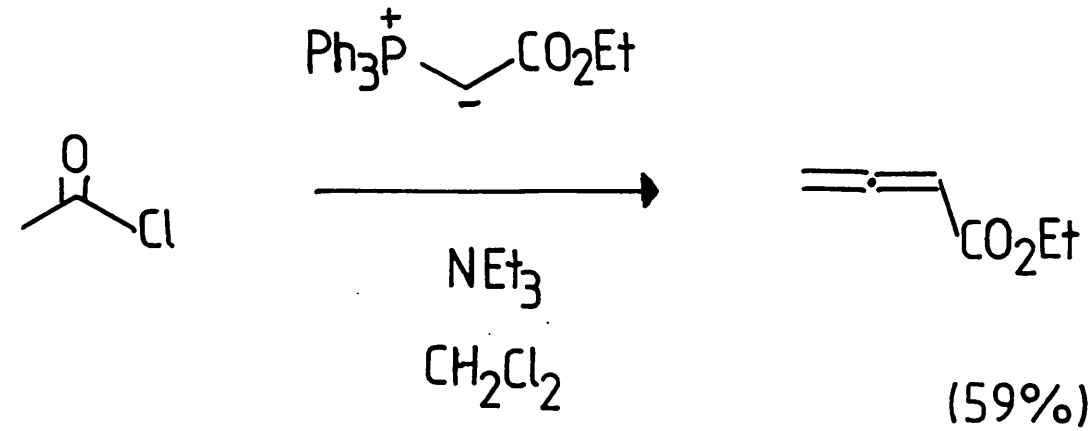
(305) (343) (340)

However, although the enolate was generated, no C or O-methylation was noticed under a wide variety of conditions. In all instances, the anhydride was either recovered on non-aqueous work up in low yield, or the reaction proceeded to provide unidentifiable orange gums. Methyl iodide was chosen as the alkylating agent and the bases employed included sodium methoxide in THF or methanol, potassium tert-butoxide in THF/tert-butanol, lithium methoxide in methanol and triethylamine in THF. Even an attempt to trap the pyrone enolate generated by n-butyl lithium at -70°C with chlorotrimethylsilane failed to yield an isolable O-silyl derivative. The results were perplexing as ^{1}H nmr spectroscopy gave no guide as to the course of the reaction. These discouraging results prompted the investigation of an alternative strategy.

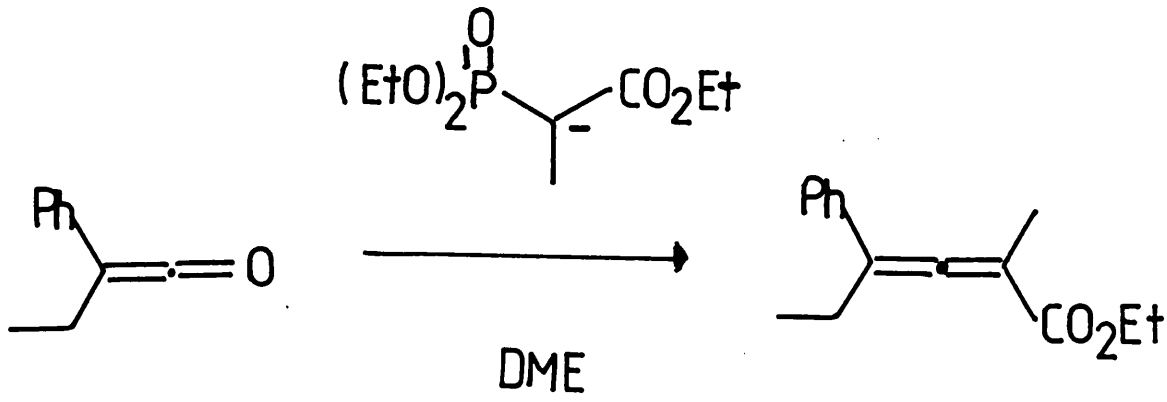
It is well known that the reaction of either phosphonate salts or phosphorus ylids with ketenes or with acid chlorides in the presence of a base produce allenes.[128-31] A number of representative examples from the literature are shown (scheme 36).



(85%)



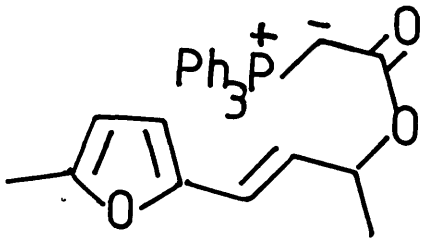
(59%)



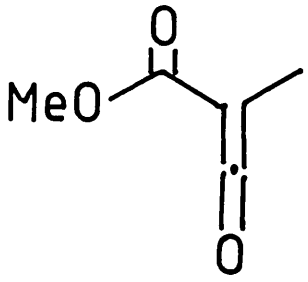
(75%)

Scheme 36

It was reasoned that synthesis of the stabilised ylid (344) and its subsequent reaction with a ketene (345) bearing an ester and a methyl group could lead to the allene (337).



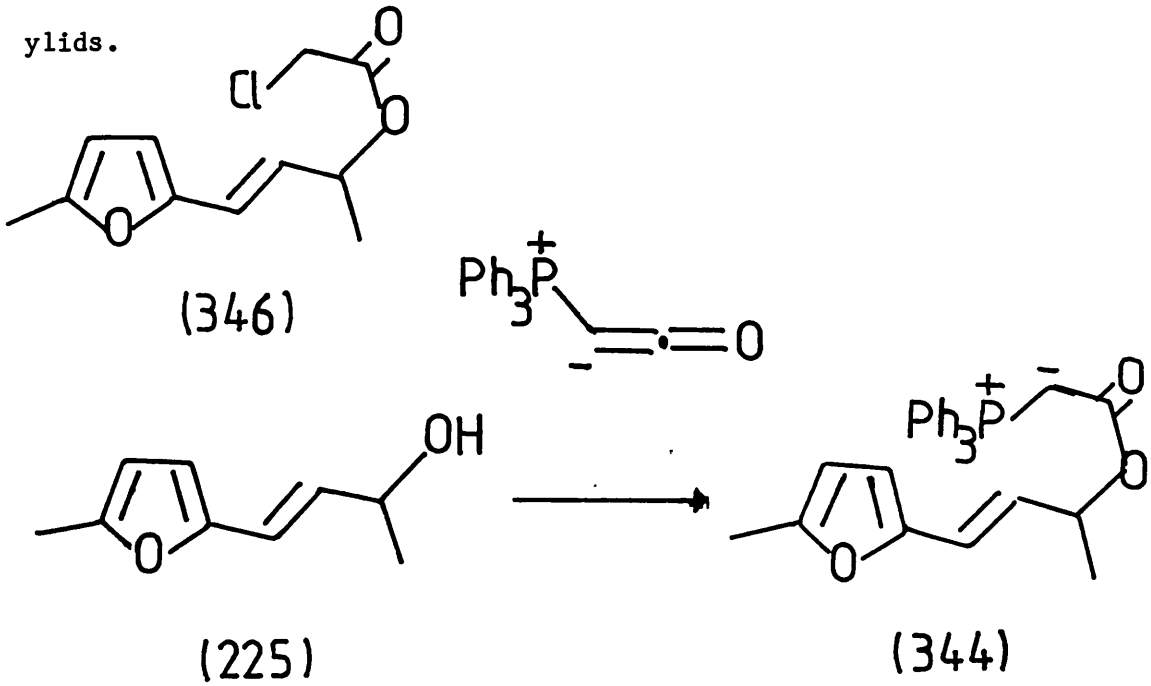
(344)



(345)

A suitable precursor to the ylid (344) would be the allylic chloroacetate (346). This was readily prepared by reaction of the furan allylic alcohol (225) with chloroacetyl chloride and pyridine in THF or ether. However, the chloroacetate was a very unstable compound. Work up of reaction led to the isolation of an oil that rapidly blackened as the last of the solvent was removed. Attempted flash distillation (ultra-high vacuum, 30°C) resulted in complete polymerisation to yield an intractable black solid. However, rapid chromatography of the reaction product on alumina allowed the chloroacetate to be isolated in solution (one spot ~~Hc~~). Solvent exchange allowed the ^{1}H nmr spectrum to be recorded. This showed the expected methine multiplet at 5.5ppm, fully consistent with the ester functionality being present. However, reaction of this compound with triphenyl phosphine in benzene produced no ylid over 36 hours at room temperature. On warming the mixture, the chloroacetate polymerised to form an orange-red gum.

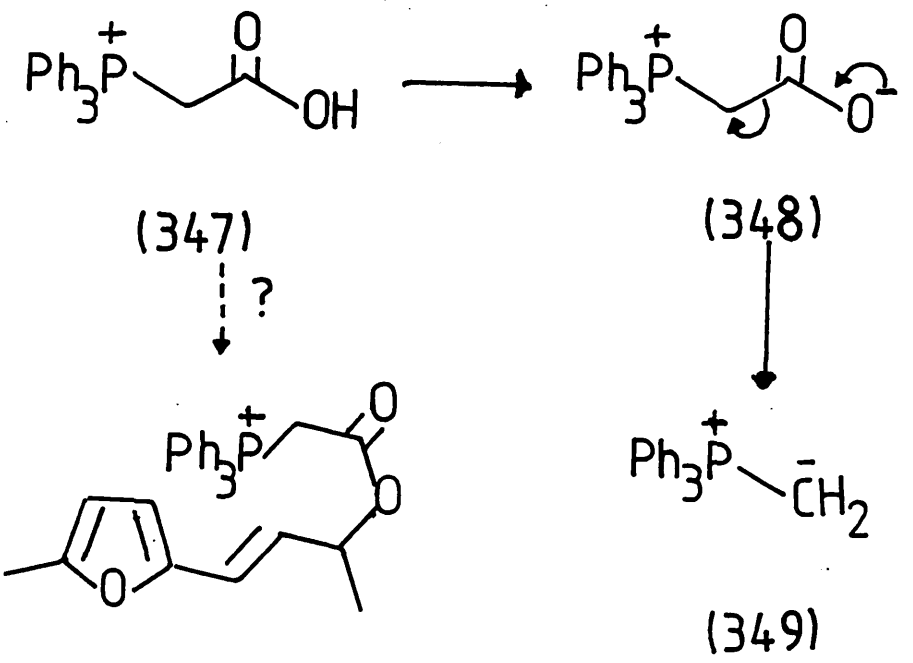
Owing to the lability of the allylic chloroacetate (346), an alternative approach to the synthesis of the ylid (344) was considered. This was envisaged to involve reaction of the allylic alcohol (225) with ketenylidene triphenylphosphorane.[132] The latter is known[132] to react rapidly with simple alcohols to form stabilised ylids.



(346) (225) (344)

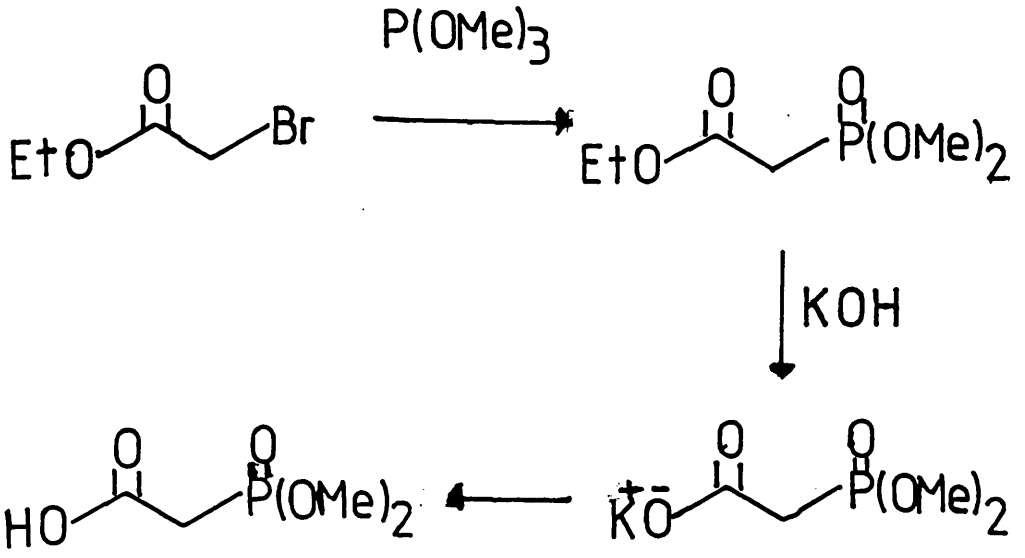
However, reaction between the alcohol (225) and ketenylidene triphenylphosphorane was non-existent if a solvent was employed. Even stirring a mixture of the viscous alcohol (225) and ketenylidene triphenylphosphorane in the absence of solvent only resulted in a very slow reaction from which only a gum bearing no spectral features consistent the desired product was isolated.

Esterification of the alcohol (225) with the acetic acid derivative (347) was considered. However, it is well known that if the $CO_2\underline{H}$ proton is removed from (347), as would be necessary in a DCC type coupling reaction, the phosphonium salt (348) simply decarboxylates to provide ylid (349). Thus this route was not investigated.



(347) (348) (349)

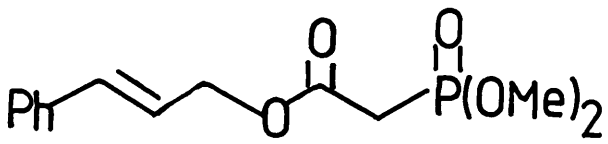
It was thought that the problems in these cases probably lay with the charged nature of the desired product. It was reasoned that the phosphonate method, involving neutral species, could provide an answer to the problem. Thus the necessary carboxylic acid (350) was synthesised by the literature method (scheme 37).[133]



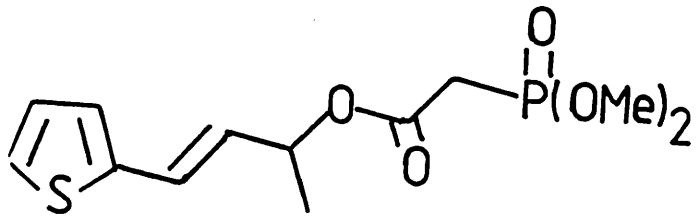
(350)

Scheme 37

A number of trial esterifications were carried out with this carboxylic acid using DCC as the coupling agent. It was also necessary to employ the highly efficient acylation catalyst 4-dimethylaminopyridine[127] in order to achieve a reasonable rate of reaction. In this way were synthesised the cinnamyl and thiophene allylic phosphonates (351) and (352) in 58% and 68% yield respectively.

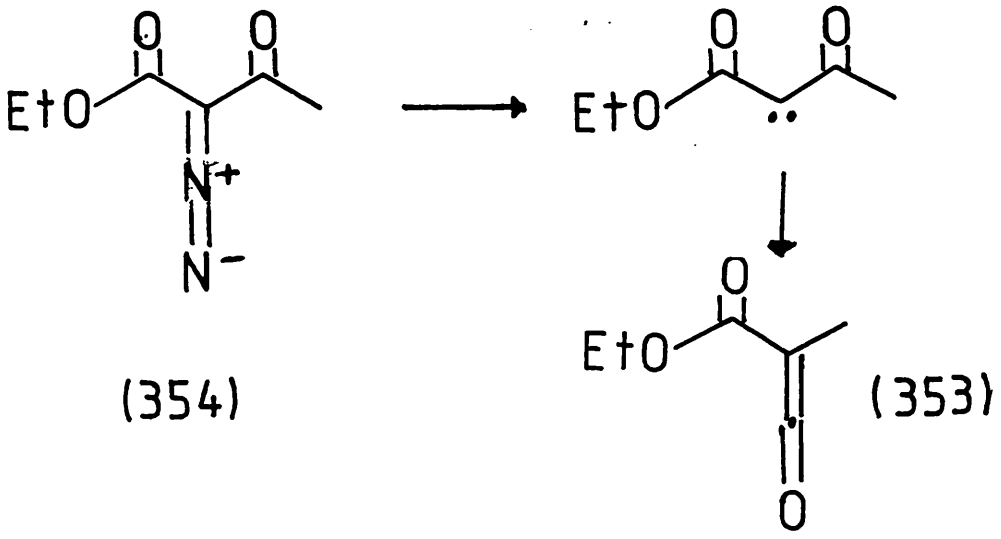


(351)



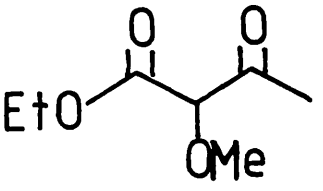
(352)

With the phosphonate (352) in hand, it was now necessary to investigate synthetic routes towards the ketene (353). This was envisaged to be available from the diazoacetoacetate (354)[134] by either metal catalysed or photolytic loss of nitrogen and re-arrangement of the carbene.



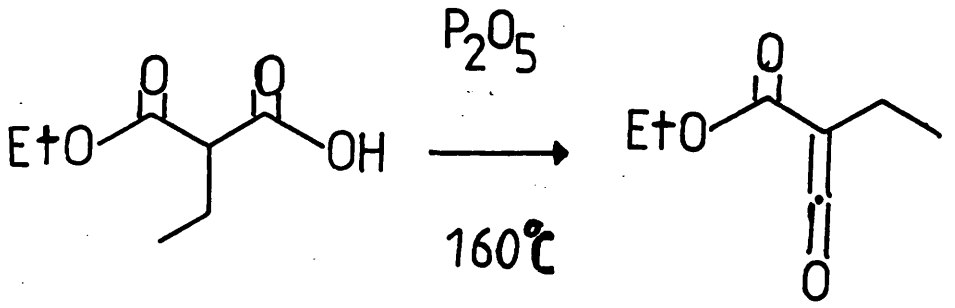
(354) (353)

However, the diazoacetoacetate (354) showed no tendency to decompose and rearrange to the desired ketene (353) on treatment with copper (II) acetoacetonate in benzene at various temperatures, with silver oxide in benzene or with palladium allyl chloride dimer in dimethoxyethane.[135] Treatment of (354) with rhodium acetate in benzene seemed to generate the rhodium based carbenoid which rather than rearrange was trapped by added methanol to form the C-methoxy compound (355).



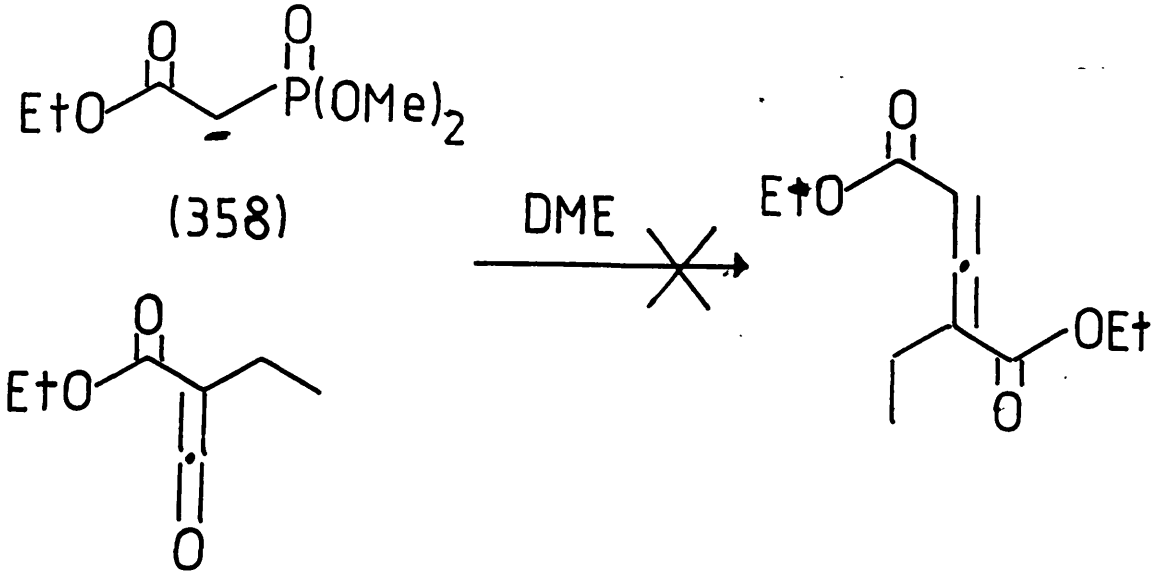
(355)

Photolysis of (354) at low temperature is known to produce the desired ketene.[136] It was found that this indeed occurred but the ketene dimerised above -30°C in the absence of trapping agents. This was not surprising, considering the known instability of ketene (356) which has to be collected in a CO_2/acetone or liquid nitrogen cooled trap to retard dimerisation. With access to the desired ketene (353)[137] an unforeseen difficulty, the slightly more stable ketene (356) was prepared by pyrolysis of the malonyl half ester (357) in the presence of phosphorus pentoxide.[137]



(357) (356)

The ketene (356) was stored as a dilute solution in THF at -10°C. A model reaction between (356) and the anion (358) was then carried out to investigate the viability of this allene synthesis. The conditions used were those carefully optimised by the German workers in this field.[131] Thus the solution of the ketene (356) was added rapidly to a suspension of the anion (358) in dimethoxyethane (prepared over one hour at 0°C) just as the solvent began to reflux. Standard work up however failed to provide any detectable quantities of allene. This ketene work was showing no encouraging results and was therefore abandoned as a route to trisubstituted allenes.



(358) (356)

5.0. EXPERIMENTAL

5.0. Experimental

Spectra

Ir spectra were recorded using a Perkin-Elmer 298 grating infra red spectrophotometer. Spectra of liquids were either taken neat between sodium chloride plates or as dilute solutions in dichloromethane, chloroform or carbon tetrachloride. Spectra of solids were taken as potassium bromide discs or as nujol mulls.

^{1}H nmr spectra were recorded at 60 MHz on a Varian EM360A spectrometer, at 90MHz on a Jeol FX90Q spectrometer or at 250MHz on a Bruker WM250 spectrometer with tetramethylsilane as an internal standard employing chloroform-d, carbon tetrachloride or acetone-d_6 as solvent. Signals are quoted as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), multiplet (m) or broad (br).

Uv spectra were recorded on a Pye Unicam SP1800 spectrometer as solutions in ethanol. Mass spectra were recorded on A.E.I. MS9 or V.G. Micromass 7070 instruments.

Solvents

Unless specified, general purpose reagents were used. Anhydrous ether and THF were obtained from inert atmosphere potassium-benzophenone ketyl stills. Anhydrous dichloromethane was obtained by reflux over and distillation from phosphorus pentoxide. Anhydrous benzene, toluene and xylene were stored over sodium wire. Dry acetonitrile and triethylamine were obtained by reflux over and distillation from calcium hydride.

Chromatography

Thin layer chromatography was carried out on silica or alumina plates with visualisation by the use of iodine or ultra violet light.

Column chromatography was carried out over Merck kiesel gel 60 (230-400 mesh) or BDH alumina (neutral or basic) using redistilled solvents. 40-60, and 60-80 petrol refers to petroleum ether, of boiling point ranges 40-60°C and 60-80°C respectively.

5.1. Experimental to 3.0.

Synthesis of the enones (221)-(223) and (75)

4-(2'-Furyl)but-3-en-2-one (221)[101]

To a stirred solution of freshly distilled furfural (32.08g, 334mmol), AR acetone (42.40g, 730mmol) and water (300cm^3) was added dropwise a solution of sodium hydroxide (1.42g,35.5mmol) in water (5cm^3) over one minute. The solution rapidly assumed a deep yellow milkiness. After being stirred at room temperature for six hours, dilute (10% w/v) sulphuric acid was added to the mixture until an aliquot from the reaction was acidic to litmus. The lower phase was then separated and dried ($MgSO_4$).

Rotary evaporation after filtration provided an orange oil that was distilled to yield the enone (221) as a yellow liquid which solidified as it distilled (18.65g, 41%), bp 49°C/0.07mm Hg, mp 39.5 - 41°C (lit.[101] 114 - 118°C/10mm Hg, 38 - 9°C): δ ($CDCl_3$) 7.43 (1H,d,J=2Hz), 7.23(1H,½ABq,J=16Hz), 6.50(3H,m) and 2.33(3H,s) ppm.

The enones (222) - (223) and (75) were prepared by the same general procedure. The amounts of materials, yields and data are presented below.

4-(5'-Methyl 2'furyl)but-3-en-2-one (222)[87]

From redistilled 5-methyl furfural (55.26g,502mmol),AR acetone ($100cm^3$, 1.36mol), water ($350cm^3$) and sodium hydroxide (4g, 0.1mol); 58.49g, 78% crude, bp 68-72°C/0.02mmHg (solidified on standing at room temperature). This was recrystallised from 40-60 petrol to yield the enone (222) as yellow needles (55.05g, 73%), mp 32-3°C (lit.[87] 35 - 6°C); ν max(melt) 1688 and 1615cm^{-1}; δ ($CDCl_3$) 7.16 (1H,½ABq,J=16Hz), 6.51 (1H,d,J=3Hz), 6.49 (1H,½ABq,J=16Hz),6.03 (1H,d,J=3Hz), 2.33 (3H,s) and 2.30 (3H,s) ppm.

4-(2'-Thienyl)but-3-en-2-one (75)[102]

From redistilled thiophene 2-carboxaldehyde (4.22g, 37.6mmol), AR acetone (5.20g, 89.5mmol), water ($15cm^3$) and sodium hydroxide (0.22g, 5.5mmol); 4.27g, 75%, bp 72-5°/0.08mmHg (lit.[102] 112-4°/3mmHg), solidified on standing at room temperature, mp 32-3°C (lit. 34-5°C); ν max(melt) 1685, 1665, 1615 and 1595cm^{-1}; δ ($CDCl_3$) 7.52 (1H,½ABq, J=16Hz), 7.10 (3H,m), 6.43 (1H,½ABq,J=16Hz) and 2.32 (3H,s)ppm.

4-(5'-methyl 2'-thienyl)but-3-en-2-one (233)[103]

From redistilled 5-methyl thiophene 2-carboxaldehyde (6.00g, 47.6mmol), AR acetone (6.09g, 105mmol), water (20cm^3) and sodium hydroxide (0.2g, 5 mmol); 5.06 g, 64%, bp 72-6°/0.02mmHg; ν_{max}(film) 1690, 1670, 1615, and 1595cm^{-1}; δ($CDCl_3$) 7.45 (1H, ½ABq, J=16Hz), 6.97 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 6.28 (1H, ½ABq, J=16Hz), 2.47 (3H, s) and 2.30 (3H, s) ppm.

4-(1-Methyl 1H-pyrrol-2-yl)but-3-en-2-one (118)[106]

To an ice-cooled, stirred mixture of 1-methyl 1H-pyrrole 2-carboxaldehyde (22.34g, 205mmol), AR acetone (17.8g, 306mmol) and distilled water (50cm^3) was added dropwise a solution of sodium hydroxide (1.00g, 25mmol) in water (3cm^3) over five minutes. The ice bath was removed and the mixture stirred vigorously at room temperature for 17 hours. The solution became deep yellow within 15 minutes and turned orange overnight. After 17 hours, dilute (10% w/v) sulphuric acid was added until an aliquot from the mixture was acidic to litmus. The two phase system was diluted with ether (200cm^3) and the ether layer separated. This was washed with saturated sodium bicarbonate solution (1x150cm^3), water (1x150cm^3) and dried ($MgSO_4$). Rotary evaporation after filtration yielded an orange red oil (27.87g) that was distilled to yield the enone (118) (23.40g, 77%), bp(Kugelrohr oven temperature) 50°C/0.01mmHg (lit.[106] 154-6°C/12mmHg); ν_{max}(film) 1680, 1660, 1640, 1615 and 1590cm^{-1}; δ($CDCl_3$) 7.35(1H, ½ABq, J=16Hz), 6.63 (2H, m), 6.38 (1H, ½ABq, J=16Hz), 6.08 (1H, m), 3.70 (3H, s) and 2.30 (3H, s) ppm.

Synthesis of the allylic alcohols (224) - (227)

4-(2'-Furyl)but-3-en-2-ol (224)[104]

To a well-stirred, ice-cooled suspension of sodium borohydride (2.57g, 67.9 mmol) in THF/water (9:1, 150cm^3) containing barium hydroxide (ca 0.5g) was added dropwise a solution of 4-(2'-furyl) but-3-en-2-one (221) (30.04g, 221 mmol) in THF/water (9:1, 100cm^3) such that the temperature remained in the range 3 - 5°C during the addition (40 minutes). The mixture was stirred at room temperature for seven hours before being transferred to the cold room for the weekend. More sodium borohydride (0.50g, 13 mmol) was added after this period, followed by stirring at room temperature for a further two hours. After quenching with dilute sulphuric acid until at pH 6.5 to destroy the borohydride, the solution was made basic (pH9) by the addition of saturated sodium carbonate solution. The two phase mixture was then rotary evaporated to remove most of the THF and the resulting aqueous suspension extracted with ether (3x150cm^3). The combined extracts were washed with saturated sodium bicarbonate solution (1x250cm^3), water (1x250cm^3), brine (3x250cm^3) and dried (Na_2SO4). Rotary evaporation after filtration yielded the alcohol (224) as a very pale yellow oil (27.87g, 92%); νmax(film) 3350, 2965, 2920, 2860, 1660 and 1600cm^{-1}; δ($CDCl_3$) 7.27 (1H,d,J=2Hz), 6.20 (4H,m), 4.33 (1H, quintet,J=6Hz), 2.33 (1H,bs,D_2Oexch.) and 1.33 (3H,d,J=6Hz) ppm.

The allylic alcohols (225) - (227) were prepared by the same general procedure. The amounts of materials, yields and data are presented below.

4-(5'-Methyl 2'-furyl)but-3-en-2-ol (225)

From sodium borohydride (2.00g,52.9mmol) and the enone (222) (22.55g, 150mmol) in THF/water (9:1,350cm^3). After 1½ hours an additional quantity of sodium borohydride (3.20g, 84.6mmol) was added and the mixture stirred at room temperature for a further 13 hours. Rotary evaporation yielded a very pale yellow oil (22.51g, 99%); νmax (film) 3345,2980,2940,2880,1660 and 1595cm^{-1}; δ($CDCl_3$) 6.03 (4H,m), 4.37 (1H,quintet,J=6Hz), 2.28 (3H,s), 1.92 (1H,bs,D_2Oexch.) and 1.32 (3H,d,J=6Hz) ppm; m/z 152 (M^+,100%), 137 (28), 135 (13), 109 (69) and 95 (82) (Found: C, 71.2; H, 7.9. $C_9H_{12}O_2$ requires C, 71.07; H, 7.95%).

4-(2'-Thienyl)but-3-en-2-ol (226)

From sodium borohydride (1.06g, 28.0mmol) and the enone (75) (4.24g, 27.9mmol) in THF/water (9:1, 35cm^3). The mixture was stirred for 21 hours in this case. The alcohol was obtained as a yellow oil that was purified by chromatography on neutral alumina (grade 4, 70g) with ethyl acetate/benzene (1:10) as eluant. Pale yellow oil (3.68g, 86%); νmax (film) 3920,3050,2920,2880,2810 and 1650cm^{-1}; δ ($CDCl_3$) 7.00 (3H,m), 6.61 (1H,½ABq,J=16Hz), 6.01 (1H, 2x½ABq,J_1=16Hz,J_2=6Hz), 4.35 (1H, quintet,J=6Hz), 1.97 (1H, bs, D_2O exch.) and 1.35 (3H,d,J=6Hz) ppm; m/z 154 (M^+,59%), 139 (26), 111 (100), 97 (100) and 55 (43).

4-(5'Methyl 2'-thienyl)but-3-en-2-ol (227)

From sodium borohydride (1.14g, 120mmol) and the enone (223) (5.00g, 30mmol) in THF/water (9:1,20cm^3). The mixture was stirred for 48 hours at room temperature. The alcohol was purified by chromatography on neutral alumina (grade 4, 50g) with ethyl acetate/benzene (1:10) as eluant.

Pale yellow oil (4.30g, 85%); ν_{max} (film) 3400,3090,2995,2945,2900 and 1646cm^{-1}; δ($CDCl_3$) 6.50 (3H,m), 5.83 (1H,2x½ABq,J_1=16Hz,J_2=6Hz), 4.33 (1H,quintet,J=6Hz), 2.40 (3H,s), 1.93 (1H,6s,D_2O exch.) and 1.30 (3H,d,J=6Hz) ppm; m/z 168 (M^+,45%), 153 (20), 151 (28), 125 (55), 111 (100) and 97 (20). This alcohol was fully characterised by analysis of the derived acetate (220).

Synethesis of the allylic acetates (217) - (220)

4-(2'-Furyl)but-3-en-2-yl acetate (217)

To an ice-cooled, stirred solution of acetic anhydride (29.6g, 287mmol) and dry pyridine (17.4g,220mmol) in dry toluene (150cm^3) was added dropwise over five minutes a solution of the alcohol (224) (20.00g,145mmol) in dry toluene (20cm^3). The solution was kept at 4°C in the refrigerator for 36 hours, the solvents removed by rotary evaporation and the residue distilled to yield the acetate (217) as a very pale yellow oil (20.75g,80%, bp 74 - 5°C/0.35mmHg; ν_{max}($CHCl_3$) 1725cm^{-1}; δ_H($CDCl_3$) 7.22 (1H,d,J=2Hz), 6.20 (4H,m), 5.37 (1H,quintet,J=6Hz), 2.03 (3H,s) and 1.33 (3H,d,J=6Hz) ppm; δ_c($CDCl_3$) 170.0 (s), 151.9 (s), 142.0 (d), 127.3 (d), 119.6 (d), 111.1 (d), 108.5 (d), 70.4 (d), 21.1 (q), and 20.1 (q) ppm. (Found: C, 66.80; H,7.10. $C_{10}H_{12}O_3$ requires C,66.65; H 6.70%).

The allylic acetates (218) - (220) were prepared by the same general procedure. The amounts of materials, yields and data are presented below.

4-(5'Methyl 2'-furyl)but-3-en-2-yl acetate (218)

From acetic anhydride (8.61g,84.3mmol), pyridine (4.75g,60.0mmol) and the alcohol (225) (6.50g,42.7mmol).

Pale yellow oil (6.64g,80%), bp 90-5°/0.4mmHg (some decomp.); ν_{max} (film) 1740 and 1662cm^{-1}; δ ($CDCl_3$) 6.04 (4H,m), 5.35 (1H,quintet, J=6Hz), 2.30 (3H,s), 2.05 (3H,s) and 1.35 (3H,d,J=6Hz)ppm; m/z 194 (M^+, 18%), 151 (20), 135 (28), 134 (24), 91 (22) and 43 (100). (Found: C, 68.3; H, 7.5. $C_{11}H_{14}O_3$ requires C,68.0; H,7.25%).

4-(2'Thienyl)but-3-en-2-yl acetate (219)

From acetic anhydride (3.50g,34.3mmol), pyridine (2.00g,25.3mmol) and the alcohol (226) (3.07g,19.9mmol). Purified by chromatography on silica gel (25g) with benzene as eluant. Very pale yellow oil (2.94g,75%); ν_{max} (film) 1735 and 1650cm^{-1}; δ ($CDCl_3$) 6.93 (3H,m), 6.60 (1H,½ABq,J=15Hz), 5.85 (1H,2x½ABq,J_1=15Hz,J_2=6Hz), 5.35 (1H, quintet,J=6Hz) 2.00 (3H,s) and 1.30 (3H,d,J=6Hz) ppm; m/z 196 (M^+,25%), 153 (22), 137 (32), 136 (32), 135 (60), 97 (25) and 43 (100). (Found: C, 61.2; H, 6.33. $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.16%).

4-(5'-Methyl 2'-thienyl)but-3-en-2-yl acetate (220)

From acetic anhydride (3.64g,35.7mmol), pyridine (1.41g,17.8mmol) and the alcohol (227) (2.00g,11.9mmol). Purified by chromatography on silica (20g) with benzene as eluant. Very pale yellow oil (1.50g,60%), ν_{max} (film) 1740 and 1648cm^{-1}; δ($CDCl_3$) 6.58 (3H,m), 5.78 (1H, 2x½ABq, J_1=16Hz,J_2=6Hz), 5.35 (1H,quintet, J=6Hz), 2.42 (3H,s), 2.03 (3H,s) and 1.33 (3H,d,J=6Hz)ppm; m/z 210 (M^+,36%), 168 (38), 151 (69), 150 (52), 149 (60), 137 (71), 135 (76) and 134 (100%). (Found: C, 62.6; H,6.85. $C_{11}H_{14}O_2S$ requires C, 62.83; H, 6.71%).

Dimethyl 3-chloropent-2-enedioate (233)[100]

Prepared in 42% yield, bp 52-74°C/0.15mmHg (lit. 50-60°C/0.02 mmHg), δ ($CDCl_3$) 6.20 (s), 6.13 (s)[together 1H], 4.05 (s), 3.42 (s) [together 2H] and 3.75 (6H,s) ppm.

Dimethyl penta-2,3-dienedioate (216)[100]

Prepared in 57% yield, νmax (film) 1970 and 1725cm^{-1}; δ ($CDCl_3$) 5.95 (2H,s) and 3.75 (6H,s) ppm

Diethyl 2-methyl 3-oxoglutarate (238)[108]

Prepared in 84% yield, bp 69°C/0.03mmHg (lit. 99-100°C/0.8mmHg), δ ($CDCl_3$) 4.12 (4H,q,J=7Hz), 3.70 (1H,m), 3.55 (2H,s), 1.33 (3H,d,J=6Hz) and 1.27 (6H,t,J=7Hz) ppm.

Diethyl 2,4-dimethyl 3-oxoglutarate (241)[109]

Prepared in 77% yield, bp 72-5°C/0.015mmHg (lit.119-22°C/4.5mmHg), δ ($CDCl_3$) 4.12 (4H,q,J=7Hz), 3.73 (2H,m) and 1.25 (12H,m) ppm.

Dimethyl 3-chloro-2-methyl pent-2-enedioate (239)

To rapidly stirred diethyl 2-methyl 3-oxoglutarate (238) (1.0747g, 4.97mmol) was added portionwise phosphorus pentachloride (1.1030g, 5.30mmol) over five minutes. A reaction began to occur after about half of the phosphorus halide had been added. The mixture was then heated at a bath temperature of 65°C for 30 minutes. The red solution was allowed to cool and poured onto ice (ca 10g). To this was added dichloromethane/water (1:1,10cm^3) and the two phase system vigorously stirred for 30 minutes whilst cooling in ice. The organic layer was separated and the aqueous phase extracted with dichloromethane (3x5cm^3). The combined organics were washed with brine (3x20cm^3) and dried (Na_2SO_4).

Rotary evaporation after filtration yielded a red oil which was dissolved in absolute methanol ($10cm^3$) containing concentrated sulphuric acid ($1cm^3$). This solution was heated to reflux overnight. After cooling, most of the methanol was removed by rotary evaporation and the remaining yellow solution poured into water ($5cm^3$) and saturated with salt. The mixture was extracted with ether ($8 \times 5cm^3$) and the combined extracts washed with saturated aqueous sodium bicarbonate solution ($1x20cm^3$), brine ($1x20cm^3$) and dried (Na_2SO_4). Distillation after rotary evaporation afforded a colourless oil (357.2mg,35%), νmax (film) 1745,1725 and 1640cm^{-1}; δ ($CDCl_3$) 6.20 (1H,s), 3.90 (2H,s), 3.73 (6H,s) and 2.07 (3H,s) ppm; m/z 206 ($M^{\cdot+}$).

Chlorination of diethyl 2,4-dimethyl 3-oxoglutarate (241)

To rapidly stirred diester (241) (0.7053g3.06mmol) was added portionwise phosphorus pentachloride (0.6742g,3.24mmol) over five minutes. The resulting mixture was then stirred at a bath temperature of 65°C, whereupon a vigorous reaction commenced and the phosphorus pentachloride dissolved. After heating for 30 minutes, the solution was allowed to cool and then poured onto ice. Work up and transesterification with methanol as for (239) yielded after distillation a colourless oil (198.9mg), bp 44°C/$5x10^{-5}$mmHg, δ ($CDCl_3$) 3.73 (6H,s), 2.06 (3H,s) and 1.40 (3H,s) ppm.

Diethyl penta-2,3-dienedioate (256)

To a stirred solution of triphenyl phosphine (5.24g, 20.0mmol) in dry benzene ($30cm^3$) was added dropwise bromine ($1.03cm^3$, 20.1mmol) over one minute.

The resulting pale yellow solid was diluted with dry benzene ($30cm^3$) and the suspension stirred at room temperature for five minutes. To this was added dropwise a solution of diethyl 3-oxoglutarate (232) (4.04g, 20.0mmol) in dry benzene ($5cm^3$) over two minutes. The mixture was then stirred vigorously whilst dry triethylamine (4.04g, 39.9mmol) was added dropwise over 15 minutes. An exothermic reaction set in with the temperature rising to 40-5°C and the colour deepening to yellow-orange. After being stirred at room temperature for one hour, the mixture had assumed a red colour. It was filtered and the solid washed with dry benzene (2 x $30cm^3$). The red filtrate was rotary evaporated and then triturated with 60-80 petrol (4 x $20cm^3$). After refiltration, the solvent was evaporated to yield a red oil that was distilled (Kugelrohr) to furnish the allene (256) as a colourless oil (1.8488g, 50%), bp (oven temp) 100-60°C/0.015mmHg, νmax (film) 1970 and $1720cm^{-1}$; δ ($CDCl_3$), 5.95 (2H,s), 4.14 (4H,q,J=7Hz) and 1.23 (6H,t,J=7Hz) ppm.

Diethyl 2-methyl penta-2,3-dienedioate (257)

By the same procedure as for (256), employing triphenyl phosphine (2.62g, 10.0mmol), bromine ($0.52cm^3$, 10.1mmol), diethyl 2-methyl 3-oxoglutarate (238) (2.16g, 10.0mmol) and dry triethylamine (2.02g, 20.0mmol) in dry benzene ($25cm^3$). Reaction time, 75 minutes. Colourless oil (0.54g, 27%), bp (oven temp) 98-125°C/0.1mmHg, νmax (film) 1960 and $1720cm^{-1}$; δ ($CDCl_3$), 5.78 (1H,q,J=3Hz), 4.16 (4H,q,J=7Hz), 1.95 (3H,d,J=3Hz) and 1.28 (6H,t,J=7Hz) ppm.

Diethyl 2,4-dimethyl penta-2,3-dienedioate (258)

By the same procedure as for (256), employing triphenyl phosphine (5.24g,20.0mmol), bromine (1.03cm^3,20.1 mmol) and dry triethylamine (4.0g,40.0mmol) in dry benzene (30cm^3). Reaction time, 3 hours at 60°C. Colourless oil (0.64g, 15 %), δ ($CDCl_3$) 4.15 (4H,q,J=7Hz), 1.93 (6H,s) and 1.27 (6H,t,J=7Hz) ppm.

Dimethyl penta-2,3-dienedioate (216)

By the same procedure as for (256), employing triphenyl phosphine (5.24g,20.0mmol), bromine (1.03cm^3,20.1 mmol), dimethyl 3-oxoglutarate (3.48g,20.0mmol) and dry triethylamine (4.04g,40.0mmol) in dry benzene (30cm^3). Reaction time, 75 minutes. Colourless oil (0.37g,12%), νmax (film) 1970 and 1725cm^{-1}, δ ($CDCl_3$) 5.97 (2H,s) and 3.75 (6H,s) ppm.

Cycloaddition of dimethyl penta-2,3-dienedioate (216) to 4-(2'-furyl) but-3-en-2-yl acetate (217).

A solution of the allene (216) (0.54g, 3.5mmol) and the acetate (217) (0.62g, 3.5mmol) in dry THF ($30cm^3$) was heated at a bath temperature of 70^oC for 160 hours. After cooling and rotary evaporation, the residue was subjected to flash chromatography on silica gel (80g) using firstly ethyl acetate/40-60 petrol (1:12) as eluant to isolate the starting acetate (0.1g, 16%) followed by ethyl acetate/dichloromethane (1:4) to elute the adducts as an orange-yellow oil (0.61g, 54%), ν_{max} (film) 1745,1720 and $1680cm^{-1}$; δ_H(250MHz, $CDCl_3$) 6.46-5.80 (complex multiplet, vinylic protons), 5.36 (sextuplet, 3x$\underline{CH}$OAc), 5.25 (bs, bridgehead proton, one isomer), 5.18 (d, J<2Hz, bridgehead proton, two isomers), 4.05 (ABq, J=12Hz, $\underline{CH_2}CO_2Me$), one isomer), 3.68 (m, J<2Hz, $\underline{CH}CO_2Me$, one isomer), 3.60 (3xs, $CO_2\underline{Me}$), 3.51 (bs, $\underline{CH}CO_2Me$, one isomer), 2.00 (3xs, $OCO\underline{CH_3}$) and 1.26 (3xd, CH$\underline{Me}$OAc) ppm; δ_c($CDCl_3$) 169.6, 169.3, 169.1, 166.0, 165.9, 155.2, 155.2, 154.7 (8 x s, carbonyls), 139.5, 139.4, 136.2, 136.2, 134.6, 134.0, 133.6, 133.1, 133.1, 132.8,132.6, 125.3, 125.2, 123.6, 113.8, 113.2, 112.9 (17 vinylic carbons), 90.5, 89.6, 82.9, 81.6 (4 bridgehead carbons), 69.5, 69.4, 69.3 (3x$\underline{CH}$OAc), 60.0 (1x$\underline{CH_2}CO_2Me$), 54.5, 54.4, 53.9, 51.6, 51.4, 51.4, 51.1 (6x$CO_2\underline{Me}$ + 2x$\underline{CH}CO_2Me$), 20.9, 19.9 and 19.8 ppm. (Several signals were missing presumably through overlap).

Substitution reaction between dimethyl penta-2,-3-dienedioate (216) and 4-(2'-furyl)but-3-en-2-yl acetate (217)

A solution of the allene (216) (0.54g, 3.5mmol) and the acetate (217) (0.62g, 3.5mmol) in dry xylene ($30cm^3$) was heated at a bath temperature of $130-140^oC$ for 42 hours.

The solution was cooled, evaporated under high vacuum and the resultant red oil chromatographed on neutral alumina (grade 3, 80g) using ethyl acetate/dichloromethane (1:20) as eluant. Rotary evaporation of the early fractions yielded a yellow-orangeoil (0.49g, 42%), νmax (film) 1740 and 1710cm^{-1}; δ ($CDCl_3$) 6.53 (2H,m), 6.23 (3H,m), 5.43 (1H, quintet, J=6Hz), 4.00 (2H,s), 3.73 (3H,s), 3.67 (3H,s), 2.07 (3H,s) and 1.38 (3H,d,J=6Hz) ppm; m/z 336 (M^+,35%), 276 (100), 245 (50) and 157 (42). (Found: C, 60.4; H,6.30.$C_{17}H_{20}O_7$ requires C, 60.71; H, 5.99%).

Cycloaddition of dimethyl penta-2,3-dienedioate (216) to 4-(5'-methyl 2'-furyl)but-3-en-2-yl acetate (218)

A solution of 4-(5'-methyl 2'-furyl)but-3-en-2-yl acetate (218) (0.29g, 1.49mmol) and dimethyl penta-2,3-dienedioate (216) (0.28g, 1.79mmol) in dry benzene (6cm^3) containing a few crystals of hydroquinone was heated to reflux for 160 hours. After cooling, the solvent was removed in vacuo and the residue flash chromatographed on silica gel (50g) using ethyl acetate/40-60 petrol (1:6) to elute the recovered acetate (218) (161mg, 56%), then ethyl acetate/40-60 petrol (1:1) to elute the mixture of adducts (268) and (269) as a yellow oil (188.6mg, 36%), νmax (film) 1745,1720 and 1680cm^{-1}, δ (250MHz, $CDCl_3$) 6.4-5.9 (m,vinylic protons, two isomers), 5.45 (sextuplet, CH (OAc), two isomers), 3.69 (2xs, CO_2Me, two isomers), 2.06 (2xs, OAc, two isomers), 1.77 (s,MeCOR, one isomer), 1.70 (s,MeCOR, one isomer) and 1.38-1.30 (2xd,MeCH (OAc), two isomers), δ_c ($CDCl_3$) 170.4, 169.8, 169.6, 166.5, 159.4, 158.6 (all s,CO), 140-132 (number of vinylic carbons, multiplicity uncertain), 125.9, 124.4, 112.2, 111.8 (all d, vinylic), 89.4 (s,C(OR)), 89.0 (s,C(OR)), 88.5 (s,C(Me)OR), 87.8 (s,C(Me)OR), 56.4 (d,$CHCO_2Me$), 56.3 (d,$CHCO_2Me$), 51.8 (q), 51.3 (q), 21.1 (q), 20.2 (q), 15.4 (q) and 15.1 (q) ppm.

Rearrangement of (259) and (260)

A solution of the isomeric adduct mixture (259) and (260) (89.7mg, 027mmol) in dry xylene (15cm^3) was heated to a bath temperature of 130-40°C for 40 hours. Removal of the solvent and volatiles under high vacuum yielded a yellow oil which possessed no CO_2Me or vinylic protons in the ^{1}H nmr spectrum. The major feature of the ^{1}H nmr spectrum was the large multiplet at 7.0-7.5ppm. Chromatography on silica gel (8g) with ethyl acetate/dichloromethane (1:30) as eluant yielded an inseparable mixture of three products (56.5mg) which retained the aromatic multiplet. This result was not investigated further as rearrangement to (267) had not occurred.

Attempted cycloadditions involving vinyl thiophenes

1) A solution of 4-(2'-thienyl)but-3-en-2-yl acetate (219) (0.30g, 1.53mmol) and dimethyl penta-2,3-dienedioate (0.34g, 2.18mmol) in dry toluene (10 cm^3) containing a few crystals of hydroquinone was treated at reflux for 128 hours. After this time, ^{1}Hnmr spectroscopy showed the presence of the starting acetate and what appeared to be allene dimer/polymer. Thus the toluene was removed in vacuo and replaced with dry xylene (10 cm^3) containing a fresh quantity of dimethyl penta-2,3-dienedioate (0.34g, 2.18mmol). The solution was heated at reflux for 40 hours whereupon it assumed a red-black colour. After cooling, the solvent was removed and the residue chromatographed on basic alumina (grade 5, 70g). A ^{1}H nmr spectroscopic investigation of the fractions revealed that no cycloaddition had occurred, the acetate (219) having decomposed, (loss of the OAc signal at 2.00ppm).

2) A solution of 4-(5'-methyl 2'-thienyl)but-3-en-2-yl acetate (220) (0.45g, 2.14mmol) and dimethyl penta-2,3-dienedioate (0.40g, 2.56mmol) in dry THF ($8cm^3$) was heated at reflux for 188 hours. After this time, ^1H nmr spectroscopy revealed that no cycloaddition had occurred, although most of the allenyl diester appeared to have polymerised (substantiated by loss of the absorption at $1970cm^{-1}$ in the ir spectrum). Thus the solvent was removed and replaced with dry benzene ($8cm^3$) containing a fresh quantity of the allenyl diester (0.65g, 4.16mmol). This solution was boiled for 144 hours. The solvent was removed and the residue chromatographed on silica gel (40g) to yield recovered allylic acetate (220) (0.35g). A ^1H nmr spectroscopic investigation of the other fractions failed to reveal the presence of any cycloadduct.

3) A solution of 4-(5'-methyl 2'-thienyl)but-3-en-2-yl acetate (220) (0.56g, 2.66mmol) and dimethyl penta-2,3-dienedioate (216) (0.50g, 3.20 mmol) in dry toluene ($12cm^3$) was heated at reflux for 168 hours. After cooling, the solvent was removed and a sample of the residue (580.8mg) subjected to flash chromatography on silica gel (50g) with ethyl acetate/40-60 petrol (1:6) then ethyl acetate/40-60 petrol (1:1) as eluant, yielding fractions containing material containing either no acetate (2.03ppm) or methyl doublet (1.33 ppm) signals (110.7mg) in the ^1H nmr spectrum. An identical experiment employing decalin as solvent also resulted in decomposition of the starting materials.

2-(1'-Trimethylsilyloxy) vinyl furan (39)[114]

Prepared according to the literature, δ (d_6Me_2CO) 7.43 (1H,m), 6.40 (2H,m), 4.80 (1H,d,J=2Hz), 4.33 (1H,d,J=2Hz) and 0.27 (9H,s) ppm.

2-(1'-Trimethylsilyloxy) vinyl thiophene (86)[114]

Prepared according to the literature, δ (d_6Me_2CO) 7.13 (3H,m), 4.77 (1H,d,J=2Hz), 4.27 (1H,d,J=2Hz) and 0.33 (9H,s) ppm.

Cycloaddition between (39) and (256)

A solution of 2-(1'-trimethylsilyloxy) vinyl furan [+] (1.16g, 6.36mmol) and diethyl penta-2,3-dienedioate (1.16g,6.30mmol) in dry benzene ($30cm^3$) containing hydroquinone (25mg) was heated at reflux under argon for 20 hours.

After cooling, the solution was evaporated to yield a red oil that was chromatographed on silica gel (100g) with ethyl acetate/60-80 petrol (1:2) as eluant yielding firstly the Michael adduct* (275) (0.80g,45%), ν_{max} (film) 3130,2980,1740,1725 and 1680cm^{-1}, δ(90MHz, $CDCl_3$) 7.60 (1H,d,J=2Hz), 7.48 (1H,m), 6.52 (1H,d,J=2Hz), 6.04 (1H,bs), 4.15 (4H,m), 3.75 (2H,s), 3.60 (2H,s) and 1.35 (6H,m) ppm, then the phenol (272) (0.17g,10%) as a pale yellow solid. This was washed repeatedly with warm 40-60 petrol and then dried in vacuo to yield a white fluffy solid, mp 149°C, ν_{max} (nujol) 3250 (br), 1710 and 1700cm^{-1}, λ_{max} (EtOH) 228 (ε 47,600 $dm^3 mol^{-1} cm^{-1}$), 283 (25050) and 320 (2500) nm, λ_{max} (EtOH plus 2 drops 1M NaOH(aq)) 221 (ε >83,000 $dm^3 mol^{-1} cm^{-1}$), 242 (45,100) and 321 (50,900) nm,

δ(250MHz, d_6Me_2CO) 7.91 (1H,d,J=2.5Hz), 7.31 (1H,d,J=2.5Hz), 6.82 (1H,s), 4.34 (2H,q,J=8Hz), 4.09 (2H,q,J=8Hz), 4.03 (2H,s), 1.39 (3H,t,J=8Hz) and 1.21 (3H,t,J=8Hz) ppm. (Found: C,61.2; H,5.37. $C_{15}H_{16}O_6$ requires C,61.63; H,5.52%).

+ The TMS enol ether contained 0.13g 2-acetyl furan.

* Repeated chromatography and distillation failed to separate this mixture of the two Michael adducts from a minor unidentified component.

Cycloaddition between (86) and (256)

A solution of 2-(1'-trimethylsilyloxy) vinyl thiophene (1.25g, 6.3 mmol) and diethyl penta-2,3-dienedioate (0.93g, 5mmol) in dry benzene ($25cm^3$) containing hydroquinone (25mg) was heated at reflux under argon for 20 hours.

After cooling, the solution was evaporated to yield an oil that was chromatographed on silica gel (80g) with ethyl acetate/60-80 petrol (1:2) as eluant yielding firstly the Michael adduct (278) (0.66g, 42%), ν_{max} (film) 1735, 1725 and 1675cm^{-1}, δ ($CDCl_3$) 7.67-7.00 (3H,m), 5.90 (1H,6s), 4.12 - 3.65 (8H,m) and 1.20 (6H,m) ppm, m/z 310 (M^+, 23%), 265 (48), 264 (44), 237 (14), 236 (30) and 111 (100), followed by the phenol (276) (0.16g, 10%) as a fluffy white solid, mp 142°C, δ (250MHz, d_6Me_2CO). 7.90(1H,d,J=2.5Hz), 7.75(1H,d,J=2.5Hz), 6.84(1H,s), 4.38(2H,q,J=8Hz), 4.10(2H,q,J=8Hz), 4.00(2H,s), 1.40(3H,t,J=8Hz) and 1.22(3H,t,J=8Hz) ppm. (Found: C, 58.0; H, 5.13. $C_{15}H_{16}O_5S$ requires C, 58.43; H, 5.23%).

Attempted rearrangement of (278)

To a stirred solution of potassium tert-butoxide (56.1mg, 0.50mmol) in dry THF ($12cm^3$) at -78°C under argon was added dropwise a solution of the Michael adduct (278) (155mg, 0.50mmol) in dry THF ($2cm^3$) over 10 minutes. A deep orange colour rapidly developed. This deepened to red over 1½ hours at -78°C.

The red solution was allowed to warm to room temperature during 1 hour and then stirred at ambient temperature for 1½ hours. Analysis by ~~H~~c after work up of an aliquot with TFA showed no phenol (276). Thus the red solution was heated at reflux under argon for 3½ hours. A lower R_f spot (with the same R_f as the phenol) appeared during this time. The solution was cooled to room temperature and TFA ($2cm^3$) added. The now orange solution was evaporated to afford a brown oil that was chromatographed on silica (10g) with ethyl acetate/60-80 petrol (2:5) as eluant. The early fractions contained recovered (278) (80mg, 51%) whilst the latter fractions contained the unidentified lower R_f component (20mg, 13%), $\delta(d_6Me_2CO)$ 7.67-7.18 (4H,m), 6.70 (1H,s), 6.08 (1H,s), 4.13 (4H,q,J=7Hz), 3.57 (2H,s) and 1.23 (6H,t,J=7Hz) ppm.

5.2. Experimental to 4.0

Ethyl 2-formyl propionate (287)[118]

To a stirred solution of dry diisopropylamine (4.00cm^3, 28.6mmol) in dry THF (30cm^3) under argon at -78°C was added n-butyllithium (1.6N in hexane, 16.0cm^3, 25.6mmol) via syringe. The solution was stirred at -78°C for 10 minutes and then allowed to warm to 3°C where it was stirred for 15 minutes. The solution of LDA was then re-cooled to -78°C and dry ethyl propionate (2.90cm^3, 25.3mmol) added dropwise over 5 minutes. The ester enolate was then allowed to form at -78°C over 30 minutes. Then dry ethyl formate (2.05cm^3, 25.4mmol) was added dropwise over 10 minutes at -78°C. The mixture was then stirred at this temperature for one hour, quenched with dilute hydrochloric acid (15cm^3) at -78°C and allowed to warm to room temperature over 30 minutes. The organic layer was separated and the aqueous phase extracted with ether (2 x 15cm^3). The combined organics were dried ($MgSO_4$). Rotary evaporation followed by distillation afforded ethyl 2-formyl propionate (287) (700mg, 21%), bp 90-4°C/40mmHg, ν_{max} (film) 3350 (enol OH), 2980, 2930, 1715 and 1665cm^{-1}; δ ($CDCl_3$) 11.27 (½H,d, J=2Hz), 9.77 (½H,d,J=3Hz), 6.93 (½H,d,J=2Hz), 4.23 (2H,q,J=7Hz), 3.37 (½H,m), 1.68 (1½H,s) and 1.30 (4½H,m) ppm. The latter spectrum indicates that the aldehydoester exists as a 1:1 mixture of the aldehyde and enol tautomers in $CDCl_3$.

(E)-4-carboethoxy-pent-3-enoic acid (286)[117]

To well stirred, ice-cooled piperidine (1.05cm^3, 10.6mol) on anhydrous potassium carbonate (ca 100mg) under argon was added dropwise ethyl 2-formyl propionate (287) (1.25g, 9.60mmol) over 20 minutes.

A yellow heavy oil formed within two minutes. After stirring the heavy oil for a further ten minutes, it was decanted from the potassium carbonate and added to malonic acid (1.28g,123mmol). This mixture was heated on an oil bath to 90°C for 1 hour until effervescence (decarboxylation) ceased. After cooling, the solution was poured onto ice (5g) and stirred until the ice melted. The solution was then acidified to pH2 with dilute hydrochloric acid whereupon a precipitate appeared. This was collected by filtration and recrystallised from hexane to yield the acid (286), (265mg, 16%) as white needles, mp 65-6°C (lit.[117] 66-7°C).

4-(2'-Furyl)but-3-en-2-yl (E)-4''-carboethoxy-pent-3''-enoate (284)

To a stirred solution of the acid (286) (32.8mg, 0.190mmol), 4-(2'-furyl)but-3-en-2-ol (224) (27.0mg,0.196mmol) and dry pyridine (2 drops) in dry dichloromethane (1.5cm^3) was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (40.0mg,0.194mmol) in dry dichloromethane (1.5cm^3). The colour of the solution deepened from yellow to orange and a precipitate appeared. The mixture was stirred overnight at room temperature and then refluxed for 1¾ hours to complete reaction. After filtration, the solution was rotary evaporated. The residue was triturated with ether, the solution re-filtered and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, water and dried (Na_2SO_4). Rotary evaporation yielded the ester (284) (24mg,40%) as a pale yellow oil, $\nu_{max}(CCl_4)$ 2960,2930,2860,1740 and 1715cm^{-1}; δ (CCl_4) 7.25 (1H,6s), 6.80 (1H,t,J=6Hz), 6.17 (4H,m), 5.40 (1H,q,J=6Hz), 4.15 (2H,q,J=7Hz), 3.12 (2H,d,J=6Hz), 1.83 (3H,s) and 1.33 (6H,m) ppm; m/z 292 (M^+,15%), 155 (22), 138 (54), 137 (42), 121 (100), 99 (51) and 91 (41).

4-(2'-Thienyl)but-3-en-2-yl 4"-carboethoxypent-3"-enoate (285)

To a stirred solution of 4-(2'-thienyl)but-3-en-2-ol (226) (0.22g,1.43mmol), (E)-4-carboethoxypent-3-enoic acid (286) (0.25g, 1.45mmol) and dry pyridine (0.13cm^3,1.61 mmol) in dry ether/dichloromethane (8:1, 15cm^3) was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (1.00g,4.85mmol) in dry dichloromethane (3cm^3) over 5 minutes. A precipitate appeared during the addition. The mixture was stirred for 24 hours at room temperature. The precipitate was then filtered off and washed with dry ether. The filtrate was treated with acetic acid/methanol (1:1) and stirred for 15 minutes before being filtered again. The filtrate was then evaporated and the residual yellow-orange oil chromatographed on neutral alumina (grade 4, 50g) with ethyl acetate/dichloromethane (1:6) as eluant. The ester (285) was present in the early fractions as a yellow oil (275.4mg, 63%), υmax (film) 1740, 1715 and 1650cm^{-1}, δ(90MHz, $CDCl_3$) 7.12 (4H,m), 6.72 (1H,½ABq,J=16Hz), 6.00 (1H,d½ABq,J_1=16Hz, J_2=7Hz), 5.50 (1H,quintet, J=7Hz), 4.25 (2H,q,J=7Hz), 3.25 (2H,d, J=7Hz), 1.84 (3H,6s) and 1.32 (6H,m) ppm, m/z 308 (M^+).

(Analytical data were not obtained for the glutaconates (284) and (285) as they did not provide tricyclic lactones on themolysis).

3-Methoxypropanal (289)[119]

To a stirred solution of sodium (200mg, 8.7mmol) in absolute methanol (105cm^3) at -10°C was added dropwise freshly distilled acrolein (41.95g, 748mmol) over one hour such that the temperature remained in the range -10 - -2°C. The green solution was then stirred at -5°C for 75 minutes before acidification to pH6 with glacial acetic acid. After removal of solvent in vacuo the residue was distilled to yield 3-methoxy propanal (289) (19.8g, 30%), bp 30-46°C/22mmHg δ(CCl_4) 9.63 (1H,t,J=2Hz), 3.62 (2H,t,J=6Hz), 3.28 (3H,s) and 2.53 (2H,dt,J_1=2Hz,J_2=6Hz) ppm.

Carboethoxy methylene triphenylphosphorane

Prepared in 76% yield, mp 121.5 - 122.5°C (lit. 125 - 127.5°C).

Ethyl 5-methoxypent-2-enoate (290)

A solution of carboethoxymethylenetriphenylphosphorane (23.74g, 68.1mmol) and 3-methoxypropanal (9.00g, 102 mmol) in dry benzene (200cm^3) was stirred under argon at room temperature for 26 hours. The solvent was removed and an ethereal solution of the residue passed through a short column of silica (40g) to remove the bulk of the triphenylphosphine oxide. The column filtrate was rotary evaporated and the residue chromatographed on silica (330g) with ether/60-70 petrol (1:1) as eluant to yield firstly the pure (E) isomer (8.77g, 81.4%) νmax(CCl_4) 1715 and 1655cm^{-1}; δ_H(250MHz, $CDCl_3$) 6.97 (1H,dt, J_1=16Hz,J_2=7Hz), 5.92 (1H,dt,J_1=16Hz,J_2=2Hz), 4.20(2H,q,J=7Hz), 3.51 (2H,t,J=7Hz), 3.36 (3H,s), 2.49 (2H,ddt,J_1=7Hz,J_2=7Hz,J_3=2Hz) and 1.28 (3H,t,J=7Hz) ppm; δ_c($CDCl_3$) 166.4 (s), 145.4 (d), 123.1 (d), 70.8 (t), 60.2 (t), 58.6 (q), 32.6 (t) and 14.3 (q) ppm: m/z 158 (M^+, 1 %), 126 (30), 113 (100) and 85 (28).

(Found: C, 61.00; H,9.13, $C_8H_{14}O_3$ requires C, 60.74; H,8.92%) and then the (Z) isomer (0.37g, 3.4%), $\delta(CCl_4)$ 6.20 (1H, dt,J_1=11Hz,J_2 =7Hz), 5.67 (1H,d,J=11Hz), 4.07 (2H,q,J=7Hz), 3.39 (2H,t,J=6Hz), 3.24 (3H,s), 2.88 (2H,m) and 1.27 (3H,t,J=7Hz) ppm.

(E) - Ethyl 5-hydroxy pent-2-enoate (291)

To a stirred solution of (E) - ethyl 5-methoxypent-2-enoate (290) (361.6mg, 2.29mmol) and sodium iodide (flame dried in vacuo immediately prior to use, 684.8mg, 4.57mmol) in dry acetonitrile ($5cm^3$) under argon was added dropwise via syringe chlorotrimethylsilane ($0.58cm^3$, 4.57mmol).[120] The flask was wrapped in aluminium foil and the solution stirred at room temperature for 4¾ hours before being placed in the refrigerator overnight. The following day, the reaction mixture was stirred at room temperature for a further 2¾ hours and then poured into water ($20cm^3$). The product was extracted with ether (3 x $15cm^3$) and the combined extracts washed with dilute aqueous sodium thiosulphate solution (1 x $15cm^3$), brine (1 x $15cm^3$) and dried (Na_2SO_4). Filtration followed by rotary evaporation afforded a pale yellow oil (322.4mg, 98%), bp 88-92°C/1mmHg, ν_{max} (film) 3450,2980,2900,1715 and 1655cm^{-1}; $\delta(CDCl_3)$ 6.93 (1H,dt,J_1=15Hz, J_2=7Hz), 5.85 (1H,dt,J_1=15Hz,J_2=2Hz), 4.16 (2H,q,J=7Hz), 3.73 (2H,t, J=7Hz), 3.32 (1H,s,D_2O exch.), 2.45 (2H,M) and 1.30 (3H,t,J=7Hz) ppm.

Jones oxidation of alcohol (291)

To a stirred solution of the alcohol (291) (143.0mg,0.992mmol) in acetone ($6cm^3$) was added dropwise a solution of chromium trioxide (137.2mg,1.37mmol) in a mixture of concentrated sulphuric acid ($3cm^3$) and water ($3cm^3$). The resulting green solution was stirred for 10 minutes at room temperature, diluted with water ($40cm^3$), extracted with ether (4 x $25cm^3$) and the combined extracts dried ($MgSO_4$).

Rotary evaporation yielded the crude acid (292) as a syrup (144.5mg, 92%), ν_{max} (film) 3500-3000, 2980, 1715, 1705 and 1655cm^{-1}; δ (CCl_4) 10.94 (1H, bs, D_2Oexch.), 6.83 (1H, dt, J_1=15Hz, J_2=6Hz), 5.80 (1H, d, J=15Hz), 4.10 (2H, q, J=7Hz), 3.20 (2H, m) and 1.28 (3H, t, J=7Hz) ppm.

3-Chloroglutaconic anhydride (305)[123]

To a well-stirred diethyl 3-oxoglutarate (232) (60.01g,297mmol) was added portionwise phosphorus pentachloride (68.55g,329mmol) over a period of 30 minutes during which time the solution warmed to 60°C and attained a red colour. The solution was heated at 60-65°C for 30 minutes and then cooled in ice. Excess phosphorus reagent was decomposed by carefully pouring the solution onto ice (ca 100g) with vigorous stirring. The flask was rinsed with dichloromethane/water (1:1,300cm^3) and this added to the ice-quenched reaction mixture. The two phase system was stirred vigorously for a further 15 minutes whilst cooling in ice. After separating the organic phase, the aqueous phase was extracted with dichloromethane (3x100cm^3). The organic layer and extracts were combined and rotary evaporated to yield a red oil (48.95g). This oil was suspended in hydrochloric acid (20%, 250cm^3) and the mixture boiled for 2½ hours. After cooling, the solution was evaporated to dryness firstly on the rotary evaporator and then under high vacuum. The resultant crude orange diacid (304) was dried over phosphorus pentoxide in vacuo overnight to yield an orange-brown solid (32.92g, 67.5%). The crude diacid (5.00g, 30.4mmol) was added to redistilled acetic anhydride (25cm^3, 244mmol) cooled in an ice bath and the mixture stirred with slight warming to effect solution. The solution was stored at -10°C for two hours prior to removal of the solvent on a CO_2-rotary evaporator. The red solid residue was extracted with portions of hot cyclohexane.

On cooling, these extracts deposited the anhydride (305) as pale yellow needles (2.05g, 46%, 31% overall), mp 108-112°C (lit.[123] 113-4°C), νmax ($CHCl_3$) 1805, 1750 and 1640cm^{-1}, λmax (MeCN) 228 (ε 12,600$dm^3mol^{-1}cm^{-1}$) and 346 (2300)nm, δ ($CDCl_3$) 6.38 (1H,d,J=2Hz) and 3.77 (2H,d,J=2Hz)ppm, m/z 146 (M^+, 3%), 102 (68) and 67 (100%). (Found: C,40.72;H,2.12; Cl,23.74. $C_5H_3ClO_3$ requires C,40.99; H,2.06; Cl,24.19%).

(E)-4-Carbomethoxy-3-chlorobut-2-enoic acid (309)

3-Chloroglutaconic anhydride (305) (2.2374g, 15.27mmol) was dissolved in absolute methanol (30cm^3) and the solution stirred at room temperature for 5½ hours. Rotary evaporation afforded a yellow solid (2.47g, 91%), mp54-6°C. This material was satisfactory for most purposes but an analytical sample could be obtained by recrystallisation from 40-60 petrol as very pale yellow crystals (2.19g, 79%), mp 58-60°C, νmax($CHCl_3$) 3480-2580, 1720, 1700 and 1635cm^{-1}, δ_H($CDCl_3$) 10.70 (1H,6s,D_2Oexch.), 6.30 (1H,s), 4.13 (2H,s) and 3.82 (3H,s) ppm, δ_c($CDCl_3$) 168.8 (s), 168.1 (s), 149.6 (s), 121.4 (d), 52.4 (q) and 41.6 (t) ppm, m/z 178 (M^+,9%), 147 (56) 146 (57), 118 (18), 99 (24) and 59 (100). (Found: C,40.11; H,3.88: Cl,19.36. $C_6H_7ClO_4$ requires C,40.36; H,3.95; Cl,19.85%).

Synthesis of the chlorodiesters (310) - (313)

4-(2'-Furyl)but-3-en-2-yl 4"-carbomethoxy-3"-chlorobut-2"-enoate (310)

To a stirred solution of 4-(2'furyl)but-3-en-2-ol (224) (0.6894g,4.99mmol), (E)-4-carbomethoxy-3-chlorobut-2-enoic acid (309) (0.8907g, 4.99mmol) and dry pyridine (0.46cm^3, 5.69mmol, 1.14 equiv.) in dry dichloromethane (20cm^3) was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (1.2497g, 6.06mmol, 1.21 equiv.) in dry dichloromethane (5cm^3) over five minutes. The colour of the solution deepened from yellow to yellow-brown during the addition and a heavy precipitate appeared. The mixture was stirred at ambient temperature for 23 hours. The precipitate was filtered off and washed with dry ether (2x10cm^3). The filtrate was rotary evaporated and the resulting deep red residue taken up in dry ether (20cm^3) and treated with glacial acetic acid/methanol (1:1, 2cm^3). After a further filtration, the solution was rotary evaporated and the residue azeotroped with toluene (to remove acetic acid) and then with methanol (to remove toluene). The resulting red oil (1.51g) was chromatographed on neutral alumina (grade 5, 70g) with dichloromethane/ethyl acetate (5:1) as eluant to yield the ester (310) as a yellow oil (1.4050g,94%), ν_{max}(film) 1740,1720,1665 and 1640cm^{-1}, δ_H(250MHz,$CDCl_3$) 7.35 (2x1H,bs), 6.31 (2x5H,m), 5.52 (2x1H,sextuplet), 4.11 (2x2H,2xs), 3.72 (2x3H,2xs) and 1.40 (2x3H, 2xd,J=6Hz) ppm (two geometrical isomers, $\approx$ 1:1), δ_c($CDCl_3$) 168, 164 (both 2xs, C1" and CO_2Me), 152,148 (both 2 x s, C2' and C3"), 143,127.5,122,120,111,109.5 (all 2xd, C3,C4,C3',C4',C5' and C2"), 71 (2xd,C2), 53 (2xq,OMe), 42 (2xt,C4") and 20 (2xq,Cl)ppm, m/z 298 ($M^{\cdot+}$,13%), 161 (100), 138 (22), 137 (43) and 121 (78). (Found: $M^{\cdot+}$, 298.0608 $C_{14}H_{15}{}^{35}ClO_5$ requires $M^{\cdot+}$, 298.0607).

4-(5'-Methyl 2'-furyl)but-3-en-2-yl 4"-carbomethoxy-3"-chlorobut-2"-enoate (311)

Prepared by the same method as for ester (310) using 4-(5'-methyl 2'-furyl)but-3-en-2-ol (225) (0.5130g, 3.37mmol), (E)-4-carbomethoxy 3-chlorobut-2-enoic acid (309) (0.6033g, 3.38mmol) dry pyridine (0.31cm^3, 3.8mmol) and DCC (0.84g, 4.1mmol) in dry ether/dichloromethane (1:1,22cm^3). Yellow oil after chromatography as before, (0.7507g, 71%), νmax (film) 1735,1720,1665 and 1640cm^{-1}, δ_H(250MHz,$CDCl_3$) 6.08 (2x5H,m), 5.43 (2x1H,quintet), 4.15 (2x2H,2xm), 3.70 (2x3H,2xs), 2.28 (2x3H,2xs) and 1.40, (2x3H,2xd,J=7Hz) ppm (two geometrical isomers, $\approx$ 3:1), δ_c($CDCl_3$) 168.2, 163.3 (C1" and CO_2Me), 152.4,150.4,146.7 (C2', C5' and (3"), 125.1,122.4,120.5, 110.2,107.5 (C3,C4,C3',C4' and C2"), 71.6 (C2), 52.3 (OMe), 41.5 (C4"), 20.3 (C1) and 13.5 (C5'-Me)ppm (values given for major isomer), m/z 312 (M^+,9%), 161 (53), 151 (57) and 135 (100).

4-(2'Thienyl)but-3-en-2-yl 4"-carbomethoxy-3"-chlorobut-2"-enoate (312)

Prepared by the same method as for ester (310) using 4-(2'-thienyl)but-3-en-2-ol (226) (0.3263g,2.12mmol), the acid (309) (0.3977g,2.23mmol), dry pyridine (0.19cm^3, 2.35mmol) and DCC (0.4574g, 2.24mmol) in dry ether/dichloromethane (9:1,10cm^3).

Pale orange oil (0.5514g,83%) after chromatography on basic alumina (grade 4) with dichloromethane/ethyl acetate (10:1) as eluant, ν_{max} (film) 1735,1720 and 1645cm^{-1}, δ_H(250MHz, $CDCl_3$) 7.18 (2x1H,2xd,J=5Hz), 6.98 (2x2H,m), 6.74 (2x1H,2xd,J=16Hz), 6.28 (2x1H, 2xs), 6.00 (2x1H, 2xdd,J_1=7Hz,J_2=16Hz), 5.51 (2x1H,sextuplet), 4.11 (2x2H,m), 3.73 (3H,s,major isomer), 3.71 (3H,s,minor isomer), 1.41 (3H,d,J=7Hz,major isomer) and 1.36 (3H,d,J=7Hz, minor isomer) ppm (two geometrical isomers, $\approx$ 3:1), δ_C($CDCl_3$) 170.1,164.5 (C1" and $\underline{C}O_2Me$), 146.9,141.2 (C2' and C3"), 127.7,127.4,126.4,125.2,124.7, 122.3 (C3,C4,C3',C4',C5' and C2"), 71.3 (C2), 52.3 (OMe), 41.5 (C4") and 20.2 (C1) ppm (values given for major isomer), m/z 314(M^+,99%), 161 (64), 153 (38), 137 (100) and 97 (58).

4-(5'-Methyl 2'-thienyl)but-3-en-2-yl 4"-carbomethoxy-3"-chlorobut-2"-enoate (313)

Prepared by the same method as for ester (310) using 4-(5'methyl 2'-thienyl)but-3-en-2-ol (0.9435g,5.61 mmol), the acid (309) (1.0533g, 5.90mmol), dry pyridine (0.50cm^3, 6.18 mmol) and DCC (1.2319g,5.97mmol) in dry ether/dichloromethane (3:1, 13cm^3). Pale orange oil (1.0510g,57%) after chromatography on basic alumina (grade 4) with dichloromethane/ethyl acetate (10:1) as eluant, ν_{max} (film) 1750,1720 and 1645cm^{-1}, δ_H(250MHz,$CDCl_3$) 6.86 (2x1H, 2xd,J=4Hz), 6.75 (2x1H,2xd,J=18Hz), 6.68 (2x1H,2xd,J=4Hz), 6.31 (2x1H, 2xs), 5.92 (2x1H,2xdd,J_1=8Hz,J_2=18Hz), 5.50 (1H,quintet), 4.14 (2x2H, m), 3.70 (2x3H,2xs), 2.43 (2x3H,2xs) and 1.39 (2x3H,2xd,J=7Hz), m/z 328 (M^+,16%), 168 (28), 167 (31), 161 (14), 151 (80) and 111 (100).

The chlorodiesters (310) - (313) were not characterised by analytical data owing to their very low stability.

Synthesis of the allenes (300) - (303)

4-(2'-Furyl)but-3-en-2-yl 4"-carbomethoxybuta-2",3"-dienoate (300)

To a stirred ice-cooled solution of ester (310) (1.4050g, 4.70mmol) in dry THF ($20cm^3$) under an argon atmosphere was added dropwise dry triethylamine (0.57g, 5.6mmol) over three minutes. The solution was then stored at 4^oC for 22 hours, during which time a precipitate had appeared. The latter was filtered off and washed with dry ether ($3x15cm^3$). The filtrate was then washed with dilute (0.2M) hydrochloric acid ($3x70cm^3$), water ($1.50cm^3$), brine ($1x50cm^3$) and dried (Na_2SO_4). After filtration, the solution was evaporated to afford the allene (300) as a yellow oil (0.9600g,78%), νmax(film) 1970,1720 and 1665cm^{-1}, δ ($CDCl_3$) 7.27 (1H,d,J=2Hz), 6.25 (4H,m), 6.00 (2H,s), 5.52 (1H,m), 3.75 (3H,s) and 1.42 (3H,d,J=6Hz), m/z 262 (M^+,18%), 203 (24), 137 (82), 125 (47), 121 (100) and 91 (94).

4-(5'-Methyl 2'-furyl)but-3-en-2-yl 4"-carbomethoxy-buta-2",3"-dienoate (301)

Prepared by the same method as for allene (300) using ester (311) (0.2846g,910 mmol) and dry triethylamine (0.11g,1.09mmol) in dry THF ($5cm^3$). Orange oil (0.188g, 75%), νmax (film) 1970, 1720 and 1665cm^{-1}, δ ($CDCl_3$) 6.15 (6H,m), 5.43 (1H,m), 3.73 (3H,s), 2.28 (3H,s) and 1.38 (3H,d,J=6Hz)ppm. (Found: C, 65.40; H,6.40. $C_{15}H_{16}O_5$ requires C,65.20;H,5.85%. These were the best analytical figures available for (301). Considering the nature of the compound, the data was considered to be satisfactory.).

4-(2'-Thienyl)but-3-en-2-yl 4"-carbomethoxybuta-2",3"-dienoate (302)

Prepared by the same method as for allene (300) using ester (312) (0.3556g,1.130mmol) and dry triethylamine (0.17g, 1.68mmol) in dry THF (5cm^3). Yellow-orange oil (0.2755g, 88%), ν_{max} (film) 1970 and 1730cm^{-1}, δ_H(250MHz, $CDCl_3$) 7.37 (2x1H,2xd,J=16Hz), 6.28 (2x2H,2xs), 6.09 (2x1H,2xdd,J=9Hz,J'=16Hz), 5.54 (2x1H,quintet), 3.75 (2x3H,2xs) and 1.41 (2x3H,2xd,J= Hz)ppm (two diasteromers, $\approx$1:1), δ_c($CDCl_3$) 219.5ppm (allenyl central carbon), m/z 278 (M^+,10%), 219 (39), 154 (33), 138 (78) and 97 (100). (Found: C,60·6; H,5.60. $C_{14}H_{14}O_4S$ requires C,60·4; H,5.05%. Once again, these figures were the best available and were considered satisfactory owing to the nature of the compound).

4-(5'-Methyl 2'-thienyl)but-3-en-2-yl 4"-carbomethoxybuta-2", 3"-dienoate (303).

Prepared by the same method as for allene (300) using ester (313) (0.9240g,2.81mmol) and dry triethylamine (0.34g,3.36mmol) in dry THF (10cm^3). Deep orange oil (0.6094g,74%), ν_{max} (film) 1970 and 1725cm^{-1}, δ ($CDCl_3$) 6.68 (3H,m), 6.10 (2H,s), 5.80 (1H,dd, J_1=7Hz,J_2=15Hz), 5.40(1H,quintet), 3.62 (3H,s), 2.38 (3H,s) and 1.35 (3H,d,J=8Hz)ppm. (Found: C,61·7; H,5.75. $C_{15}H_{16}O_4S$ requires C,61·6; H,5·5%).

Intramolecular cycloadditions

6-(1'-Hydroxyethyl)-4-carbomethoxybenzofuran-5-acetic acid lactone (318)

A solution of the allene (300) (0.700g, 2.67mmol) in dry toluene ($20cm^3$) containing a few crystals of hydroquinone was heated to reflux under nitrogen in pre-silylated glassware for 44 hours. After cooling to room temperature, the solution was filtered to remove polymeric material (0.239g, mp $>260^{\circ}C$). The filtrate was evaporated and the dark brown residue chromatographed on neutral alumina (grade 5, 45g) with ethyl acetate/benzene (1:2) as eluant. This yielded in orange oil (70mg) which clearly contained the benzofuran lactone (318) although this was contaminated greatly with other material (approximate yield of lactone (318) by integration, 28mg, 4%), δ (CCl_4) 7.70 (1H,d,J=2.5Hz), 7.60 (1H,s), 7.10 (1H,d,J=2.5Hz), 5.45 (1H,q,J=6Hz), 4.27 (2H,ABq,J=18Hz), 3.98 (3H,s) and 1.82 (3H,d,J=6Hz)ppm, plus peaks at 3.50-3.75(m), 6.0 -6.3(m) and 7.28(m) ppm, m/z 260 ($M^{+\cdot}$).

6-(1'Hydroxyethyl)-2-methyl-4-carbomethoxybenzofuran-5-acetic acid lactone (320)

A solution of the allene (301) (0.115g,0.416mmol) in dry toluene ($8.5cm^3$) containing hydroquinone (10mg) was heated to reflux under argon in pre-silylated glassware for 128 hours. After cooling, the orange-brown solution was filtered and rotary evaporated. The gummy residue was triturated repeatedly with ether/petrol (2:3) and the soluble material subjected to column chromatography on neutral alumina (grade 5,10g) with ethyl acetate/benzene (1:2) as eluant.

The desired lactone eluted with another compound as a yellow oil (44mg) in the early fractions. This mixture was rechromatographed on neutral alumina (grade 4,10g) with ethyl acetate/toluene (1:7) as eluant. This second column yielded the lactone (320) as a yellow solid which was recrystallised from ethyl acetate/cyclohexane to provide pale yellow needles of the benzofuran (320) (14mg, 12%), mp 110-11°C, ν_{max} ($CHCl_3$) 1740 and 1720cm^{-1}, λ_{max} (ETOH) 226 (ε 39,900dm^3 mol^{-1} cm^{-1}), 268 (12,100) and 310 (9100) nm, δ (250MHz, $CDCl_3$) 7.45 (1H,s), 6.67 (1H,s), 5.38 (1H,q,J=6Hz), 4.15 (2H,ABq,J=19Hz), 3.95 (3H,s), 2.43 (3H,s) and 1.80 (3H,d,J=6Hz)ppm, m/z 274 ($M^{+\cdot}$,84%), 259 (25), 243 (19), 231 (100), 203 (20), 199 (20) and 115 (18). (Found: C, 65.45; H,5.15. $C_{15}H_{14}O_5$ requires C, 65.70; H, 5.15%)

6-(1'-Hydroxyethyl)-4-carbomethoxybenzothiophene-5-acetic acid lactone (323)

A solution of the allene (302) (4 66.2mg, 1.68mmol) and hydroquinone (30mg) in dry toluene (7.5cm^3) was heated under reflux for 4 hours. After cooling, the solution was rotary evaporated and the residue triturated with ether/petrol (2:3). The soluble material was subjected to chromatography on neutral alumina (grade 5,20g) with ethyl acetate/benzene (1:20) as eluant. Early fractions were combined to yield a yellow-orange oil (165.3mg) which was rechromatographed on silica gel (15g) using ethyl acetate/benzene (1:7) as eluant.

Fractions containing the product were concentrated to a yellow oil (99.7mg) which solidified on standing. This was recrystallised from ether/cyclohexane to yield the benzothiophene (323) as cream crystals (28mg, 6%), mp 142-3°C, ν_{max} ($CHCl_3$) 1740 and 1725 cm^{-1}, δ (250MHz, $CDCl_3$) 7.92 (1H,6s), 7.69 (1H,dd,J_1=0.8Hz,J_2=6Hz), 7.61 (1H,d,J=6Hz), 5.57 (1H,q,J=7Hz), 4.18 (2H,ABq,J=19Hz), 4.06 (3H,s) and 1.87 (3H,d,J=7Hz) ppm, m/z 276 ($M^{+\cdot}$, 100%), 261 (23), 245 (20), 233 (90) and 216 (10). (Found: $M^{+\cdot}$,276.0458. $C_{14}H_{12}O_4S$ requires $M^{+\cdot}$,276.0456).

6-(1'-Hydroxyethyl)-2-methyl-4-carbomethoxy benzothiophene-5-acetic acid lactone (324)

A solution of the allene (609.4mg,2.08mmol) and hydroquinone (50mg) in dry toluene (12cm^3) was heated under reflux for 3¾ hours. After cooling, the reaction mixture was rotary evaporated and the resultant orange oil triturated with ether/petrol (2:3). The soluble material (547.1mg) was chromatographed on silica gel (60g) using ethyl acetate/benzene (1:7) as eluant. Concentration of the early fractions afforded a yellow oil (239.7mg) which was subjected to a further column (basic alumina, grade 4, 25g) with ethyl acetate/benzene (1:20) as eluant. Fractions containing the product were concentrated to a yellow solid. This was recrystallised from ethyl acetate/cyclohexane to give the benzothiophene (324) as pale yellow needles (60mg, 10%), mp 98-99.5°C, ν_{max}($CHCl_3$) 1740 and 1725cm^{-1}, δ (250MHz, $CDCl_3$) 7.77 (1H,s), 7.33 (1H,s), 5.53 (1H,q, J=7Hz), 4.09 (2H,ABq,J=19Hz), 4.03 (3H,s), 2.62 (3H,s) and 1.84 (3H,d,J=7Hz), m/z 290 ($M^{+\cdot}$,100%), 275 (27), 259 (17), 247 (99) and 231 (8). (Found: C,61.78;H,4.90. $C_{15}H_{14}O_4S$ requires C,62.05; H, 4.85%).

Lewis acid/transition metal catalysed reactions

1) To a solution of the allene (300) (25.0mg,95μmol) in $CDCl_3$ ($1cm^3$) was added aluminium isopropoxide (18.0mg, 88μmol). The suspension was left under argon. ^1H nmr spectra recorded over the next week showed no change was occurring.

2) The allene (300) (23mg,88μmol) was dissolved in dry dichloromethane ($2cm^3$) and treated with bis(cyclopentadienyl) titanium dichloride (22mg,88μmol). The red solution was left to stand under argon at room temperature. ^1H nmr spectra recorded over the next three days showed no change was occurring.

3) To a solution of the allene (300) (56.5mg,0.215mmol) in dry dichloromethane ($1.5cm^3$) under argon was added dropwise diethyl aluminium chloride (0.200mmol) via syringe. The yellow solution immediately turned deep blue, then black and had solidified totally after 20 minutes. To this was added water ($5cm^3$) and the mixture extracted with ether ($2x5cm^3$). The combined extracts were dried (Na_2SO_4). Rotary evaporation afforded a gum (9.5mg), δ ($CDCl_3$) 7.3 (br.m), 6.3 (d), 6.0 (s), 3.7 (br.m) and 1.4 (br.m) ppm.

4) To a solution of the allene (300) (18mg,69μmol) in dry dichloromethane ($2cm^3$) was added magnesium bromide-diethyl ether complex (1 drop). The solution immediately turned blue. Quenching after five minutes with water ($5cm^3$) yielded a suspension of magnesium salts which was stirred vigorously for 30 minutes. The layers were separated after filtration and the aqueous phase extracted with ethyl acetate ($1x2cm^3$). The combined organics were dried (Na_2SO_4). Rotary evaporation yielded no material at all.

5) To a solution of the allene (300) (164mg, 0.64mmol) in dichloromethane ($12.5cm^3$) under argon was added dropwise via syringe an ethereal solution of anhydrous zinc iodide (0.60mmol). A blue colour developed instantly. After 25 minutes, the suspension was rotary evaporated and the residue treated with $CDCl_3$. The mixture was filtered through glass wool, νmax ($CHCl_3$) 3100 (br), 1968 and 1721 cm^{-1}, δ ($CDCl_3$) 6.02 (2H,s) and 3.75 (3H,s) ppm.

6) The solution from lewis acid/transition metal catalysis experiment 2 (Cp_2TiCl_2) was rotary evaporated to remove the dichloromethane. This was replaced with $CDCl_3$ ($1cm^3$). To this was added magnesium bromide-diethyl ether complex (1 drop). The solution colour deepened to ruby overnight. ^1H nmr analysis over the next four days revealed the appearance of a complex multiplet (4.2 ppm), the doubling up of the O-methyl singlet and the diminishing in intensity of the allenyl singlet. No peaks attributable to cycloadduct were present, however.

7) To a solution of the allene (300) ($5cm^3$ of a 0.05M solution in dichloromethane) under argon was added sequentially bis(cyclopentadienyl) titanium dichloride (63mg, 0.25mmol) and anhydrous zinc iodide (1M in ether, 0.25mmol) via syringe. A blue colour appeared instantly and after one hour a large amount of solid material had been deposited.

8) To a stirred solution of 4-(2'-furyl)but-3-en-2-yl acetate (217) (0.18g, 1.0mmol) in dry dichloromethane ($25cm^3$) under argon was added dropwise magnesium bromide-ether complex ($0.25cm^3$). The deep blue colour developed as before.

9) To a stirred solution of (301) (54mg,195μmol) in dry toluene/dichloromethane (1:1,5cm^3) at -78^{o}C under argon was added dropwise via syringe diethyl aluminium chloride (0.20cm^3,200 mol) over one minute. The originally yellow solution immediately developed a red colour. The solution was stirred at -78^{o}C for 70 minutes. It was then poured into saturated aqueous sodium bicarbonate (10cm^3). Dichloromethane (10cm^3) was added and the layers deparated. The aqueous phase was extracted with dichloromethane (2x5cm^3) and the combined organics dried (Na_2SO_4). Rotary evaporation yielded a pale yellow oil which solidified under high vacuum (24.1mg), νmax ($CDCl_3$) 1730,1715 and 1665cm^{-1}, δ ($CDCl_3$) 6.00 (2H,m), 4.80 (1H,br), 3.72 (5H,m), 3.08 (2H,m), 2.22 (3H,s) and 1.48 (3H,d,J=7Hz), m/z 276 ($M^{\cdot+}$). Some aliphatic material was present (^{1}H nmr spectroscopy) too.

Methyl 2,2-dimethyl 3-oxobutanoate (333)

Prepared according to the literature,[126] bp 24°C/0.03mmHg, δ ($CDCl_3$) 3.68 (3H,s), 2.12 (3H,s) and 1.37 (6H,s) ppm.

Methyl 3-chloro-2, 2-dimethyl but-3-enoate

Prepared according to the literature,[126] δ ($CDCl_3$) 5.25 (2H,s), 3.70 (3H,s) and 1.43 (6H,s) ppm.

3-Chloro-2,2-diemthyl but-3-enoic acid (334)

Prepared according to the literature,[126] mp 62.5-4°C (lit. 60.5-63°C).

2,2-Dimethyl but-3-ynoic acid (335)

Prepared according to the literature.[126]

4-(5'-Methyl 2'-furyl)but-3-en-2-yl 2",2"-dimethyl but-3"-ynoate (336)

To a stirred solution of 4-(5'-methyl 2'-furyl) but-3-en-2-ol (225) (65mg, 0.43mmol), 2,2-dimethyl but-3-ynoic acid (335) (48mg, 0.43mmol), dry pyridine (0.04cm^3, 0.49mmol) and 4-dimethylaminopyridine[127] (53mg, 0.43mmol) in dry THF (6cm^3) was added dropwise a solution of N, N'-dicyclohexylcarbodiimide (160mg, 0.78mmol) in dry THF (0.5cm^3) over 2 minutes. The mixture was stirred for 22 hours at room temperature. Standard work up followed by chromatography on neutral alumina (grade 5, 10g) with dichloromethane/ethyl acetate (20:1) as eluant afforded the ester (336) as a pale yellow oil (59.3mg, 56%), ν_{max} (film) 3300, 2980, 2925 and 1740cm^{-1}, δ ($CDCl_3$) 6.00 (4H,m), 5.37 (1H, quintet, J=7Hz), 2.36 (1H,s), 2.23 (3H,s), 1.48 (6H,s) and 1.38 (3H, d,J=7Hz)ppm, m/z 246 ($M^{\ddagger}$, 21%), 151 (33), 135 (91), 91 (37) and 43 (100). (Found: $M^{\ddagger}$, 246.1250. $C_{15}H_{18}O_3$ requires $M^{\ddagger}$, 246.1256).

4-(5'-Methyl 2'-furyl)but-3-en-2-yl 4"-carbomethoxy-2",2"-dimethyl but-3"-ynoate (329)

To a stirred solution of ester (336) (45.1mg,0.18mmol) in dry THF (4cm^3) under argon at -78°C was added dropwise via syringe n-butyllithium (1.55M,0.12cm^3,0.19mmol) over 3 minutes. The yellow anion was stirred at -78°C for 15 minutes, before the addition of methyl chloroformate (0.02cm^3,0.26mmol) in one portion. The colour of the solution became paler. After warming to room temperature during 1 hour, the solution was diluted with ether (10cm^3), washed with water (2x5cm^3), brine (2x5cm^3) and dried (Na_2SO_4). After evaporation of the solvent, the orange residue was chromatographed on neutral alumina (grade 5, 10g) with dichloromethane/ethyl acetate (10:1) as eluant. The ester was obtained as a yellow oil (29.0mg,52%), ν_{max} (film) 2960,2925,1740 and 1725cm^{-1}, $\delta(CDCl_3)$ 6.03 (4H,m), 5.41 (1H,m), 3.73 (3H,s), 2.28 (3H,s), 1.48 (6H,s) and 1.37 (3H,d, J=7Hz)ppm, m/z 304 (M^+, 1%), 246 (13), 151 (27), 135 (71) and 91 (16). (Found: M^+, 304.1308. $C_{17}H_{20}O_5$ requires M^+, 304.1311).

2-Methyl 3-chloroglutaconic anhydride (339)

This was prepared from diethyl 2-methyl 3-oxoglutarate (238) by the same three step procedure as for 3-chloroglutaconic anhydride (305), mp 79-84°, $\delta(CDCl_3)$ 3.82(m) and 2.00(m). m/z 180 (M^+, 4%). This was contaminated with ca 15% of 3-chloroglutaconic anhydride, from cyclisation of non alkylated starting material. Fractional crystallisation failed to separate the two compounds and thus satisfactory analytical data could not be obtained.

Attempted alkylations of 3-chloroglutoconic anhydride (305)

1) Employing potassium tert-butoxide as base

To a solution of potassium tert-butoxide (2.61mmol) in dry tert-butanol maintained at 50°C under an argon atmosphere was added a solution of the anhydride (305) (0.3684g, 2.51mmol) in dry THF (10cm^3). The resulting suspension was stirred at 50°C for 20 minutes whereupon an orange/red colour developed. Then dry methyl iodide (1.43g, 10.0mmol, 4equiv.) was added. After 20 minutes, the mixture was cooled to -10°C and stored at this temperature overnight. The mixture was filtered and the filtrate evaporated to yield a red gum that was insoluble in $CDCl_3$. It was also insoluble in a hot mixture of carbon tetrachloride and ethyl acetate. On the addition of one equivalent of trifluoroacetic acid, the residue dissolved. Rotary evaporation (after decolourising with charcoal) yielded a solid (0.10g), mp100-105°C, δ ($CDCl_3$) 6.37 (1H,t,J=2Hz) and 3.73 (2H,d,J=2Hz)ppm. (recovered anhydride).

2) Employing sodium methoxide as base

To a solution of sodium methoxide (2.77mmol) in methanol (4cm^3) under argon was added the solid anhydride (305) (0.4090g, 2.77mmol) and the mixture stirred to effect solution. The colour rapidly assumed a pale orange hue. To this was added methyl iodide (1.43g, 10.0mmol). The orange solution was stirred for two hours. Rotary evaporation afforded a solid insoluble in $CDCl_3$ (the enolate). The solid was taken up in dry DMF (5cm^3) containing methyl iodide (4g) and the solution heated to 70°C for 30 minutes. The orange solution rapidly turned red then black. Rotary evaporation afforded a gum that possessed no recognisable signals in the ^{1}H nmr spectrum.

3) Employing lithium methoxide as base

To a stirred solution of lithium methoxide (1.55mmol) in methanol ($6cm^3$) under argon was added the anhydride (305) (0.2288g, 1.56mmol). The resulting pale orange solution was stirred for 15 minutes before being rotary evaporated to afford the solid lithium enolate. This was divided into two portions, one being treated with methyl iodide (1.43g,10.0mmol) and the other with methyl iodide/methanol (1:1,$4cm^3$). In the first case, the solid was insoluble in the methyl iodide and although a red colour developed ^1H nmr analysis revealed no alkylation had occurred. In the second case, rotary evaporation afforded a red gum that again showed no signals attributable to either starting material or alkylated product in the ^1H nmr spectrum.

4) Employing triethylamine as base

To a solution of the anhydride (305) (66.5mg, 0.45mmol) in dry THF ($2.5cm^3$) was added dropwise a solution of dry triethylamine (46.4mg, 0.46mmol) in dry THF ($0.5cm^3$). The initially yellow solution became orange but no precipitate appeared. After 15 minutes, a solution of methyl iodide (0.10g, 0.70mmol) in dry THF ($0.5cm^3$) was added and the solution stirred at room temperature for 19 hours. The solution had turned red overnight. Rotary evaporation afforded a red oil, the ^1H nmr spectrum of which showed neither starting material nor alkylated product.

4-(5'-Methyl 2'-furyl)but-3-en-2-yl chloroacetate (346)

To a stirred ice-cooled solution of 4-(5'-methyl 2'-furyl) but-3-en-2-ol (225) (1.52g,10.0mmol) and dry pyridine (0.83g,10.5mmol) in dry THF ($12cm^3$) was added dropwise chloroacetyl chloride (1.12g, 10.0mmol) over 5 minutes. A heavy white precipitate formed during the addition. The mixture was stirred in the cold room for a further 16 hours. The white precipitate was removed by filtration and washed with ether ($3x20cm^3$). The filtrate was then washed with dilute hydrochloric acid (0.2M, $3x60cm^3$), saturated sodium bicarbonate ($2x60cm^3$), brine ($3x60cm^3$) and dried (Na_2SO_4). Rotary evaporation after filtration yielded initially a yellow oil which turned black within 1 minute. This black material was rapidly chromatographed on neutral alumina (grade 5,50g) with ethyl acetate/40-60 petrol (1:24) as eluant. The chloroacetate was obtained as a highly unstable red oil (0.61g,27%), δ ($CDCl_3$) 6.08 (4H,m), 5.47 (1H,quintet,J=7Hz), 4.03(2H,s), 2.28 (3H,s) and 1.33 (3H,d, J=7Hz) ppm.

Treatment of (346) with triphenyl phosphine

A solution of chloroacetate (346) (0.61g, 2.67mmol) and triphenyl phosphine (0.70g, 2.67mmol) in dry benzene ($3.5cm^3$) was stirred at room temperature for 24 hours. No ylid was precipitated. On warming the solution, the colour deepened to dark red. Examination by ^1H nmr spectroscopy of the gum obtained on evaporation failed to indicate the presence of the desired ylid.

Ketenylidene triphenylphosphorane

Prepared according to the literature,[132] ν_{max} (KBr) $2100cm^{-1}$.

Dimethyl phosphonoacetic acid (350)

Prepared according to the literature[133] as a colourless syrup, $\delta(CDCl_3)$ 8.23 (1H,6s), 3.87 (3H,s), 3.68 (3H,s) and 2.93 (2H,d,J= 21Hz) ppm.

Cinnamyl dimethylphosphonoacetate (351)

To a stirred solution of cinnamyl alcohol (1.28g,9.54mmol), dimethylphosphonoacetic acid (2.08g, 12.4mmol), dry pyridine ($1.00cm^3$,12.4mmol) and 4-dimethylaminopyridine[127] (20mg) in dry dichloromethane ($25cm^3$) was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (6.00g, 29.1mmol) in dichloromethane ($10cm^3$) over 15 minutes. A precipitate rapidly appeared. The mixture was stirred at room temperature for 17 hours. The mixture was then filtered and the solid washed with dry dichloromethane. The filtrate was rotary evaporated, treated with dry ether ($30cm^3$) and refiltered. The excess DCC was decomposed by the addition of acetic acid/methanol (1:1) and the solution refiltered. The residue after evaporation was azeotroped with toluene followed by methanol and then chromatographed on basic alumina (grade 4,130g) with dichloromethane/ethyl acetate (10:1) as eluant to afford the ester (351) as a pale yellow oil (1.58g,58%), ν_{max} (film) 1740 and 1275cm^{-1}, $\delta(CDCl_3)$ 7.32 (5H,s), 6.67 (1H,½ABq,J=16Hz), 6.22 (1H,m), 4.75 (2H,d,J=6Hz), 3.90 (3H,s), 3.72 (3H,s) and 2.98 (2H,d,J=22Hz) ppm, m/z 284 (M^+, 9%), 176 (13), 151 (41), 134 (88), 105 (63), 92 (100) and 78 (54). (Found: C,54.65; H,6.28. $C_{13}H_{17}O_5P$ requires C,54.93: H,6.03%).

4-(2'-Thienyl)but-3-en-2-yl dimethylphosphonoacetate (352)

To a stirred solution of 4-(2'-thienyl)but-3-en-2-ol (226) (1.20g, 7.78mmol), dimethylphosphonoacetic acid (1.70g,10.1mmol), dry pyridine (0.82cm^3, 10.1mmol) and 4-dimethylaminopyridine (60mg) in dry dichloromethane (40cm^3) was added dropwise a solution of N,N'-dicyclohexylcarbodiimide (5.00g, 24.2mmol) in dry dichloromethane (10cm^3) over 5 minutes. The mixture was stirred at room temperature for 72 hours. Work up as for (351) followed by chromatography on basic alumina (grade 4, 120g) with dichloromethane/ethyl acetate (10:1) as eluant yielded the ester (352) as a yellow oil (1.60g,68%). The analytical sample was obtained by chromatography on basic alumina (grade 4) with ethyl acetate (60-80 petrol as eluant, δ (90MHz, $CDCl_3$) 7.18 (1H,m), 6.96 (2H,m), 6.78 (1H,½ABq, J=15Hz), 6.00 (1H,d½ABq,J_1=15Hz,J_2=7Hz), 5.53 (1H,quintet, J=7Hz), 3.86 (3H,s), 3.74 (3H,s), 2.98 (2H,d,J=22Hz) and 1.44 (3H,d,J=7Hz) ppm, m/z 304 (M^+). (Found: C,47.11; H,5.70. $C_{12}H_{17}O_5PS$ requires C, 47.37; H,5.63%).

Reaction of ethyl dimethylphosphonoacetate with ketene (356)

To a stirred slurry of sodium hydride (57% dispersion, 0.44g, 10.5 mmol) in dry dimethoxyethane (100cm^3) at 0°C was added dropwise ethyl dimethylphosphonoacetate (1.96g, 10.0 mmol) over 20 minutes. The mixture was stirred for 1 hour and then transferred to an oil bath pre-heated to 110°C. As the DME started to boil, the ketene (356) (1.42g, 10.0 mmol) was added in one portion and the mixture heated at reflux for 1 hour. After cooling, the solution was diluted with water (500cm^3) and extracted with 40-60 petrol (3x100cm^3). The dried ($MgSO_4$) organic layers yielded an orange oil (0.47g) after evaporation, υmax (film) 1730cm^{-1}, δ ($CDCl_3$) 4.18 (q), 3.76 (m) and 1.27 (m) ppm.

2-Carboethoxy butanoic acid (357)

Prepared according to the literature[137] as a colourless syrup, δ ($CDCl_3$) 11.15 (1H,s), 4.16 (2H,q,J=7Hz), 3.23 (1H,t,J=7Hz), 1.88 (2H,quintet, J=7Hz), 1.27 (3H,t,J=7Hz) and 0.97 (3H,t,J=7Hz) ppm.

Carboethoxy ethyl ketene (356)

Prepared according to the literature[137] as a colourless liquid, νmax (PhH/d_8PhMe) 2200,1720cm^{-1}, δ (d_8PhMe) 3.87 (2H,q,J=7Hz), 1.93 (2H,q,J=6Hz), 1.00 (6H,m) ppm.

Ethyl diazoacetoacetate (354)

Prepared according to the literature[134] in 77% yield, νmax (film) 2140,1725 and 1664cm^{-1}, δ ($CDCl_3$) 4.24 (2H,q,J=7Hz), 2.47 (3H,s) and 1.32 (3H,t,J=7Hz) ppm.

Treatment of (354) with silver oxide

A stirred solution of ethyl diazoacetoacetate (354) (0.32g,2.05mmol) in dry benzene (25cm^3) containing methanol (1cm^3) and silver oxide (15mg) was heated at 80°C under argon for 8 hours. The ^{1}H nmr spectrum of an aliquot revealed that no reaction had occurred.

Treatment of (354) with copper (11) acetoacetonate

A solution of ethyl diazoacetoacetate (354) (0.16g,1.02mmol) and copper (11) acetoacetonate (12mg) in dry benzene (6cm^3) was stirred at 50°C for 2½ hours. The ^{1}H nmr spectrum of an aliquot revealed that the starting material had not decomposed.

Treatment of (354) with allyl palladium chloride dimer

To a stirred solution of the diazoacetoacetate (354) (0.60g, 3.84mmol) in dry DME ($10cm^3$) containing methanol ($0.5cm^3$) under argon was added allyl palladium chloride dimer (10mg). Brief effervescence was noted at first. The yellow solution was stirred at room temperature. ^1H nmr spectroscopy again showed that the starting material was not decomposing.

Treatment of (354) with Rhodium acetate

To a solution of ethyl diazoacetoacetate (0.16g, 1.02mmol) in dry methanol ($2cm^3$) was added rhodium acetate (10mg). Rapid effervescence was noted on brief warming to 40°C. After 2½ hours, evaporation afforded a yellow oil completely lacking a diazo signal in the ir spectrum, $\delta(CDCl_3)$ 4.13 (2H,q,J=7Hz), 4.11 (1H,s), 3.43 (3H,s), 2.23 (3H,s) and 1.27 (3H,t,J=7Hz) ppm.

Photolysis of (354)[136]

A stirred solution of ethyl diazoacetate (354) (1.00g, 6.40mmol) in dry THF ($125cm^3$) was photolysed at -50°C under argon for 3¾ hours. Aliquots were taken at 30 minute intervals, quenched with methanol and examined by ^1H nmr spectroscopy. This revealed the total lack of the expected CO_2Me signal (from quenching of the ketene with methanol). However, the signals due to the ethyl groups at 4.18 and 1.28ppm had become very complex.

6.0. REFERENCES

6.0. References

1) F.M. Dean, Adv. Heterocycl. Chem., 1982, 31, 237 and references therein.

2) R. Paul, Bull. Soc. Chim. Fr., 1943, 163.

3) C.H. Schmidt, Naturwissenschaften, 1953, 40, 581.

4) W. Herz, J.Am. Chem. Soc., 1946, 68, 2732.

5) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", J. Wiley, London, 1976, p137.

6) W.E. Noland, C.K. Lee, S.K. Bae, B.Y. Chung, C.S. Hahn and K.J. Kim, J. Org. Chem., 1983, 48, 2488

7) W.J. Davidson and J.A. Elix, Aust. J. Chem., 1973, 26, 1059.

8) K. Alder and R. Schmitz-Josten, Justus Liebigs Ann. Chem., 1955, 1.

9) I.T. Millar and K.E. Richards, Aust. J. Chem., 1968, 21, 1551.

10) N.S. Isaacs, "Liquid Phase High Pressure Chemistry", Wiley, New York, 1981.

11) T. Asano and W.J. le Noble, Chem. Rev., 1978, 78, 407.

12) H. Kotsuki, A. Kondo, H. Nishizawa, M. Ochi and K. Matsuoka, J. Org. Chem., 1981, 46, 5455.

13) A.P. Kozikowski, W.C. Floyd and M.P. Kuniak, J. Chem. Soc., Chem. Commun., 1977, 582.

14) H. Kotsuki, A. Kawamura, M. Ochi and T. Tokoroyama, Chem. Lett., 1981, 917

15) T. Sasaki, Y. Ishibashi and M. Ohno, Heterocycles, 1983, 20, 1933.

16) B. Kamthong and A. Robertson, J. Chem. Soc., 1939, 925.

17) W.J. Davidson and J.A. Elix, Aust. J. Chem., 1970, 23, 2119.

18) J.D. Brewer and J.A. Elix, Tetrahedron Lett., 1969, 4139.

19) W. von E. Doering and J.W. Rosenthal, J. Am. Chem. Soc., 1967, 89, 4535.

20) R.B. Woodward and R. Hoffmann, Angew. Chem., Int. Ed. Eng., 1969, 8, 781.

21) S. Shibata, J. Pharm. Soc. Japan, 1944, 64, 50.

22) S. Shibata, J. Pharm. Soc. Japan, 1944, 64, 20.

23) B. Iddon, Heterocycles, 1983.

24) J.F. Scully and E.V. Brown, J. Am. Chem. Soc., 1953, 75, 6329.

25) W. Davies and Q.N. Porter, J. Chem. Soc., 1957, 4958.

26) J. Szmuszkovicz and E.J. Modest, J. Am. Chem. Soc., 1950, 72, 571.

27) C.J. Moody, C.W. Rees and S.C. Tsoi, J. Chem. Soc., Perkin Trans. 1, 1984, 915

28) L.H. Klemm and K.W. Gopinath, J. Heterocycl. Chem., 1965, 2, 225.

29) B.C. Ennis, Ph.D. Thesis, University of Melbourne, 1961;

30) W. Davies and Q.N. Porter, J. Chem. Soc., 1957, 4961.

31) W.H. Cherry, W. Davies, B.C. Ennis and Q.N. Porter, Aust. J. Chem., 1967, 20, 313.

32) R.A. Jones, M.T.P. Marriott, W.P. Rosenthal and J.S. Arques, J. Org. Chem., 1980, 45, 4515.

33) R.A. Jones and G.P. Bean, "The Chemistry of Pyrroles", Academic Press, London, 1977.

34) R.A. Jones and J.S. Arques, Tetrahedron, 1981, 37, 1597.

35) M.T.P. Marriott, Ph D. Thesis, University of East Anglia, 1979.

36) W.E. Noland, K.J. Kim, C.K. Lee, S.K. Bae and C.S. Hahn, J. Org. Chem., 1980, 45, 4852.

37) B.J.F. Hudson and R. Robinson, J. Chem. Soc., 1941, 715.

38) R.S. Hosmane, S.P. Hiremath and S.W. Schneller, J. Chem. Soc., Perkin Trans. 1, 1973, 2450.

39) W.E. Noland, W.C. Kuryla and R.F. Lange, J. Am. Chem. Soc., 1959, 81, 6010.

40) W.E. Noland and S.R. Wann, J. Org. Chem., 1979, 44, 4402.

41) M. Gorman, N. Neuss, N.J. Cone and J.A. Deyrup, J. Am. Chem. Soc., 1960, 82, 1142.

42) R. Bergamasco, Q.N. Porter and C. Yap, Aust. J. Chem., 1977, 30, 1531.

43) R.C. Simurdak, Ph. D. Thesis, University of Minnesota, 1972; Diss. Abstr. Int. B, 1974, 34, 3175.

44) A.-M.M. Makky, M.S. Thesis, University of Minnesota, 1961.

45) R.W. Campbell, Ph. D. Thesis, University of Minnesota, 1961; Diss. Abstr., 1962, 22, 3851.

46) D.C. Johnson, Ph. D. Thesis, University of Minnesota, 1961; Diss. Abstr., 1962, 23, 834.

47) J.M. Weinmann, Ph. D. Thesis, University of Minnesota, 1964; Diss. Abstr., 1964, 25, 1588.

48) S.-H. Zee, M.S. Thesis, University of Minnesota, 1964.

49) R.A. Johnson, Ph. D. Thesis, University of Minnesota, 1965; Diss. Abstr., 1966, 26, 5719.

50) S.E. Lindberg, Ph. D. Thesis, University of Minnesota, 1969; Diss. Abstr. Int. B., 1969, 30, 2610.

51) W.E. Noland, M.R. Venkiteswaran and C.G. Richards, J. Org. Chem., 1961, 26, 4241.

52) W. Dallimore and A.B. Jackson, "A Handbook of Coniferae and Ginkogoaceae", revised by S.G. Harrison, Edward Arnold, London, 1966.

53) Y. Hayashi, S. Takahashi, H. Ona and T. Sakan, Tetrahedron Lett., 1968, 2071.

54) S. Ito, M. Kodama, M. Sunagawa, T. Takahishi, H. Imamura and O. Honda, Tetrahedron Lett., 1968, 2065.

55) S. Ito and M. Kodama, Heterocycles, 1976, 4, 595.

56) Y. Hayashi, Y. Yuki, T. Matsumoto and T. Sakan, Tetrahedron Lett., 1977, 2953.

57) Y. Hayashi, Y. Yuki, T. Matsumoto and T. Sakan, Tetrahedron Lett., 1977, 3637.

58) Y. Hayashi, T. Matsumoto, Y. Yuki and T. Sakan, Tetrahedron Lett., 1977, 4215.

59) S.M. Kupchan, R.L. Baxter, M.F. Ziegler, P.M. Smith and R.F. Bryan, Experientia, 1975, 31, 137.

60) J.A. Hembree, C.-J. Chang, J.L. McLaughlin and J.M. Cassady, Experientia, 1980, 36, 28.

61) B. Dasgupta, B.A. Burke and K.L. Stuart, Phytochemistry, 1981, 20, 153.

62) Y. Hayashi, T. Matsumoto and T. Sakan, Heterocycles, 1978, 10, 123.

63) Y. Hayashi and T. Sakan, Proc. 8th Int. Conf. Plant Growth Substances, 1974, 525.

64) Y. Hayashi, T. Matsumoto and T. Tashiro, Gann, 1979, 70, 365

65) Y. Hayashi, T. Sakan, Y. Sakurai and T. Tashiro, Gann, 1975, 66, 587

66) Y. Hayashi, J. Yokoi, Y. Watanabe, T. Sakan, Y. Masuda and R. Yamamoto, Chem. Lett., 1972, 759.

67) J.A. Hembree, C.-J. Chang, J.L. McLaughlin, J.M. Cassady, D.J. Watts, E. Wenkert, S.F. Fonseca and J.P. Campello, Phytochemistry, 1979, 18, 1691.

68) M.N. Galbraith, D.H.S. Horn, J.M. Sasse and D. Adamson, J. Chem. Soc., Chem. Commun., 1970, 170.

69) S. Ito, M. Kodama, M. Sunagawa, M. Koreeda and K. Nakanishi, J. Chem. Soc., Chem. Commun., 1971, 855.

70) J.W. Dorner, R.J. Cole, J.P. Springer, R.H. Cox, H. Cutler and D.T. Wicklow, Phytochemistry, 1980, 19, 1157.

71) P. Singh, G.B. Russell, Y. Hayashi, R.T. Gallagher and S. Fredericksen, Entomol. Exp. Appl., 1979, 25, 121;

72) I. Saeki, M. Sumimoto and T. Kondo, Holzforschung, 1970, 24, 83;

73) K.S. Brown and W.E. Sanchez, Biochem. Syst. Ecol., 1974, 2, 1

74) G.A. Ellestad, R.H. Evans and M.P. Kunstmann, J. Am. Chem. Soc., 1969, 91, 2134.

75) G.A. Ellestad, R.H. Evans, M.P. Kunstmann, J.E. Lancaster and G.O. Morton, J. Am. Chem. Soc., 1970, 92, 5483.

76) M. Adinolfi, L. Mangoni, G. Barone and G. Laonigro, Tetrahedron Lett., 1972, 695; M. Adinolfi, L. Mangoni, G. Barone and G. Laonigro, Gazz. Chim. Ital., 1973, 103, 1271; L. Mangoni, M. Adinolfi, G. Laonigro and R. Caputo, Tetrahedron, 1972, 28, 611.

77) S.C. Welch, C.P.Hagan, D.H. White, W.P. Fleming and J.W. Trotter, J. Am. Chem. Soc., 1977, 99, 549

78) Y. Hayashi, T. Matsumoto, T. Hyono, N. Nishikawa, M. Vemura, M. Nishizawa, M. Togami and T. Sakan, Tetrahedron Lett., 1979 3311; Y. Hayashi, T. Matsumoto, M. Nishizawa, M. Togami, T. Hyono, N. Nishikawa, M. Vemura and T. Sakan, J. Org. Chem., 1982, 47, 3428.

79) L.Mangoni and M Adinolfi, Gazz.Chim.Ital., 1968, 98, 122.

80) S.D. Burke, S.M.S. Stickland and T.H. Powner, J. Org. Chem., 1983, 48, 454.

81) S.D. Burke, T.H. Powner and M. Kageyama, Tetrahedron Lett., 1983, 4529.

82) "Advances in Heterocyclic Chemistry, Volume 2", Interscience, New York, 1960, p67.

83) W.S. Johnson, T. Li, C.A. Harbert, W.R. Bartlett, T.R. Herrin, B. Staskun and D.H. Rich, J. Am. Chem. Soc., 1970, 92, 4461.

84) W.S. Johnson, M.B. Gravestock and B.E. McCarry, J. Am. Chem. Soc., 1971, 93, 4332.

85) N. Finch, J.J. Fitt and I.H. C. Hsu, J. Org. Chem., 1971, 36, 3191.

86) M.A. Tobias, J. Org. Chem., 1970, 35, 267.

87) K. Alder and C.-H. Schmidt, Chem. Ber., 1943, 76, 183.

88) G. Büchi and H. Wüest, J. Org. Chem., 1966, 31, 977.

89) I. Kuwajima and H. Urabe, Tetrahedron Lett., 1981, 5191.

90) P. Kurtz, H. Gold and H. Disselnkötter, Justus Liebigs Ann. Chem., 1959, 1.

91) M. Bertrand and J. LeGras, Bull. Soc. Chim. Fr., 1967, 4336.

92) G. Büchi and J. A. Carlson, J. Am. Chem. Soc., 1968, 90, 5336.

93) Z. M. Ismail and H.M.R. Hoffman, J. Org. Chem., 1981, 46, 3549.

94) J.-L. Gras, J. Chem. Res. (S), 1982, 300.

95) G. Himbert and L. Henn, Angew. Chem., Int. Ed. Engl., 1982, 21, 620; G. Himbert, K. Diehl and G. Maas, J. Chem. Soc., Chem. Commun., 1984, 900.

96) W.G. Blenderman, M.M. Joullie and G. Preti, Tetrahedron Lett., 1979, 4985.

97) W. Adam and H.J. Eggelte, Angew. Chem., Int. Ed. Engl., 1978, 17, 765.

98) C.N. Skold and R.H. Schlessinger, Tetrahedron Lett., 1970, 791.

99) H.H. Wasserman and W. Strehlow, Tetrahedron Lett., 1970, 795.

100) T.A. Bryson and T.M. Dolak, Org. Synth., 1978, 57, 62.

101) G.J. Leuck and L. Cejka, Org. Synth., 1944, 1, 283.

102) H. Keskin, R.E. Miller and F.F. Nord, J. Org. Chem., 1951, 16, 199.

103) L.A. Kutulya, L.P. Pivovarevich, Y.N. Surov, L.M. Satanovskii and S.F. Tsukerman, J. Org. Chem., USSR, 1975, 11, 2130.

104) W. Francke and W. Reith, Justus Liebigs Ann. Chem., 1979, 1.

105) W. Herz and J. Brasch, J. Org. Chem., 1958, 23, 1513.

106) R.A. Jones and J.A. Kindner, Aust. J. Chem., 1965, 18, 875.

107) M.E. Jung, M. Node, R.W. Pfluger, M.A. Lyster and J.A. Lowe, J. Org. Chem., 1982, 47, 1150.

108) R.L. Beach, T. Aogaichi and G.W.E. Plant, J. Biol. Chem., 1977, 252(8), 2702.

109) E.A. Coulson and J.B. Ditcham, J. Chem. Soc., 1957, 356.

110) K.J. Wheeler, 3rd Year Dissertation, Imperial College.

111) G. Buono, Tetrahedron Lett., 1972, 3257.

112) T. Suzuki, S. Kagaya, A. Tomino, K. Unno and T. Kametani, J. Chem. Soc., Perkin Trans. 1, 1980, 2801.

113) H. Günther, "NMR Spectroscopy", John Wiley, New York, 1980, p.371.

114) T. Asano, S. Ito, N. Saito and K. Hatakeda, Heterocycles, 1977, 6, 317.

115) D.H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", McGraw-Hill, London, 1980, p.145.

116) T.H. Kinstle, J. Lawson and P. Habash, "Abstracts of Papers", 173rd National Meeting of the American Chemical Society, New Orleans, LA, 1977; American Chemical Society: Washington, D.C. 1977: ORG 208.

117) J. Kagan, L. Tolentino and M.G. Ettlinger, J. Org. Chem., 1975, 40, 3085.

118) W. Wislicenus, Chem. Ber., 1887, 20, 2930.

119) H.J. Hagemeyer and M.A. Perry, U.S. Patent, 3267133 (Chem. Abs., 1966, 65, 13552h).

120) G.A. Olah, S.C. Narang, B.G.B. Gupta and R. Malhotra, J. Org. Chem., 1979, 44, 1247.

121) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis, Volume 1", J. Wiley, New York, 1967, p.142.

122) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis, Volume 1", J. Wiley, New York, 1967, p.231.

123) R. Malachowski and T. Kalinski, Roczniki Chem., 1926, 6, 768. See also C.K. Ingold and L.C. Nicholls, J. Chem. Soc., 1922, 1638 and J.A. Ray and T.M. Harris, Tetrahedron Lett., 1982, 1971.

124) B.L. Allwood, C.P. Dell, E.H. Smith and D.J. Williams, unpublished work.

125) E.R.H. Jones, G.H. Mansfield and M.C. Whiting, J. Chem. Soc., 1954, 3208

126) M.A. Schexnayder and P.S. Engel, J. Am. Chem. Soc., 1975, 97, 4825.

127) G. Höfle, W. Steglich and H. Vorbrüggen, Angew. Chem., Int. Ed. Eng., 1978, 17, 569.

128) R.W. Lang and H.J. Hansen, Helv. Chim. Acta, 1980, 63, 438.

129) W.S. Wadsworth and W.D. Emmons, J. Am. Chem. Soc., 1961, 83, 1733.

130) R.A. Ruden, J. Org. Chem., 1974, 39, 3607.

131) G. Kresze, W. Runge and E. Ruch, Justus Liebigs Ann. Chem., 1972, 112; G. Kresze, W. Runge and E. Ruch, Justus Liebigs Ann. Chem., 1975, 1361.

132) H.J. Bestmann, Angew. Chem. Int. Ed. Engl., 1977, 16, 349; H.J. Bestmann, Chem. Ber., 1980, 113, 274.

133) S.F. Donovan, M.A. Avery and J.E. McMurray, Tetrahedron Lett., 1979, 3287.

134) M. Regitz, Chem. Ber., 1966, 99, 3128.

135) S. Bien and Y. Segal, J. Org. Chem., 1977, 42, 1685.

136) W.A. Herrmann, I. Steffl, M.L. Ziegler and K. Weidenhammer, Chem. Ber., 1979, 112, 1731.

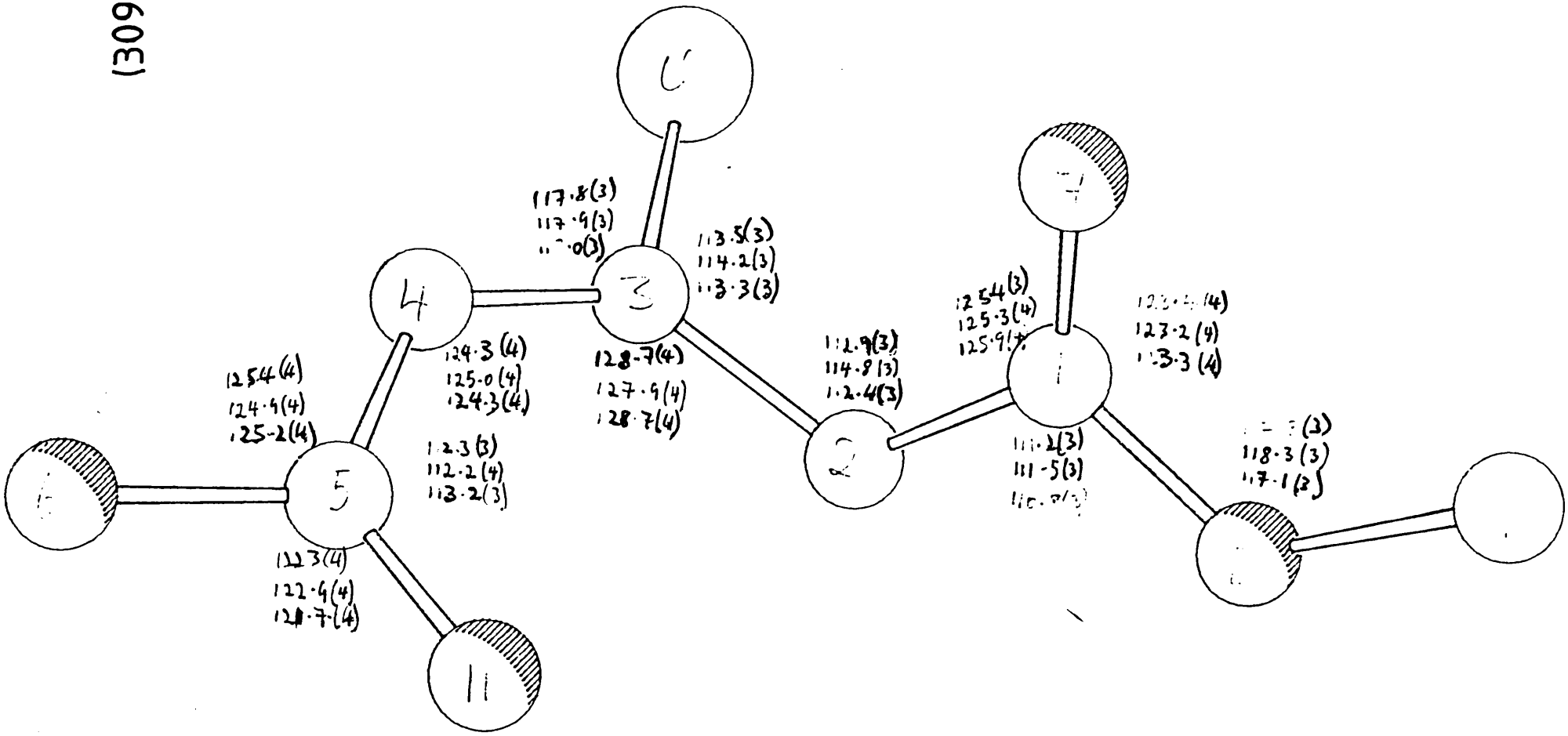
137) C.D. Hurd, R.N. Jones and F.H. Blunch, J. Am. Chem. Soc., 1935, 57, 2033.

7.0. APPENDIX

(309)

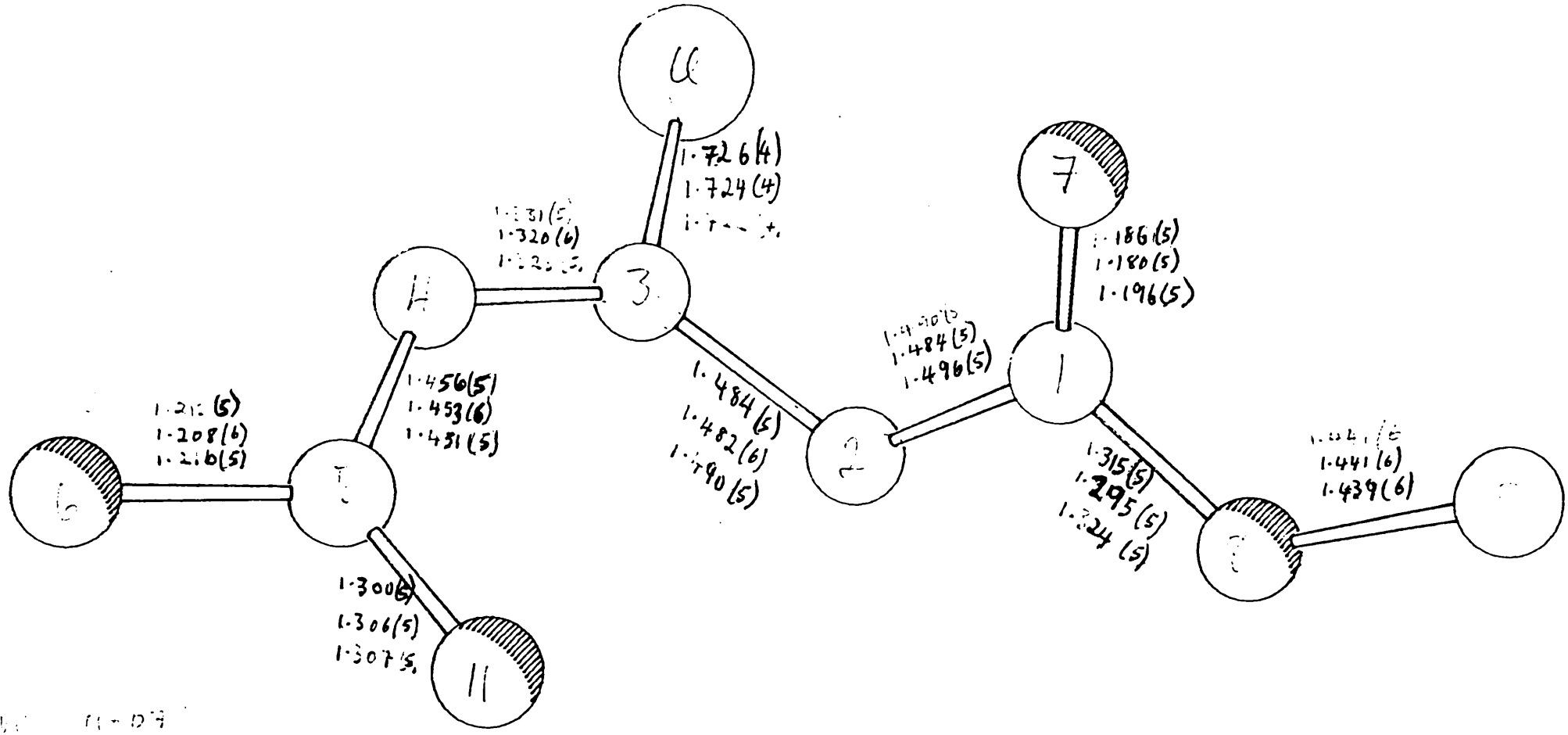
BOND ANGLES

The 3 figures represent the 3 crystallographically different molecules in the structure (in order strongest).

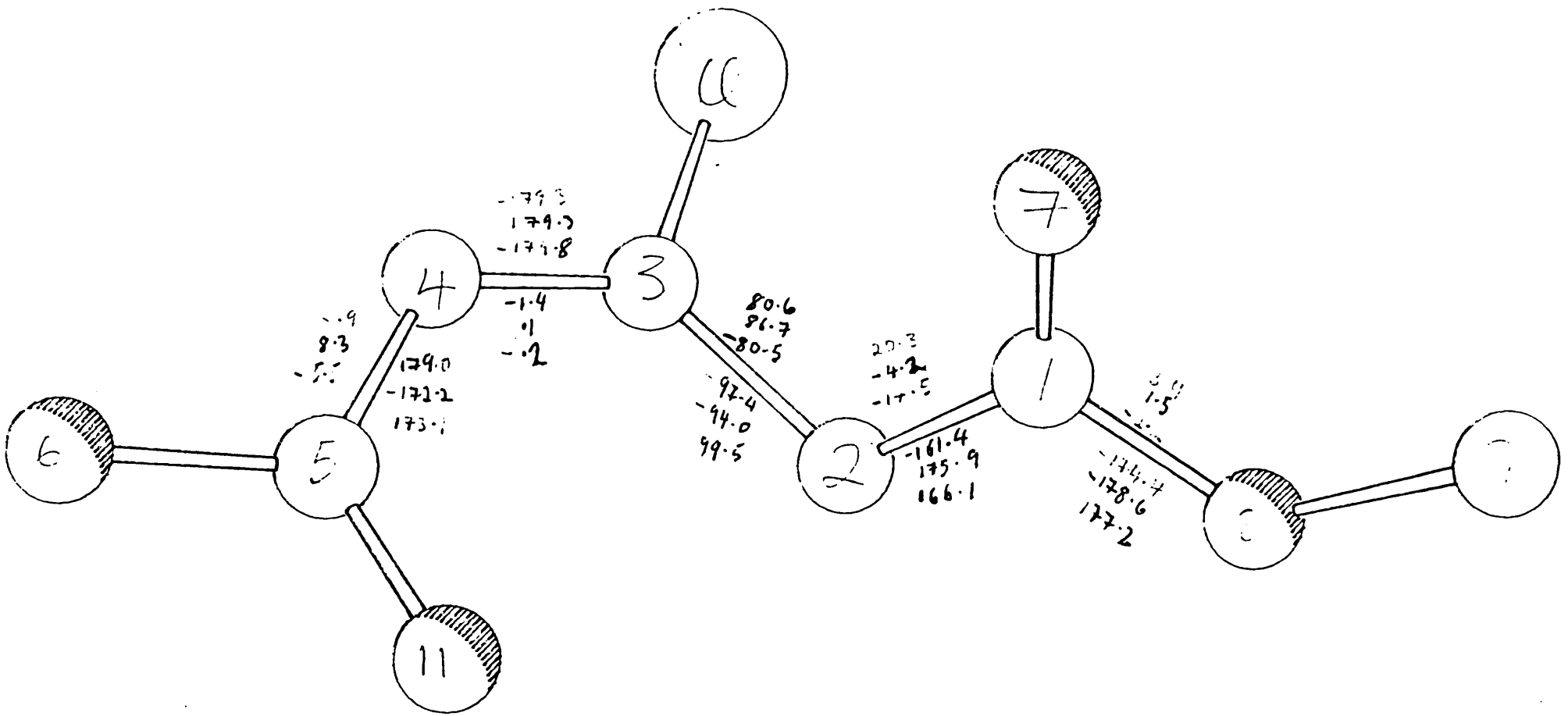


219

BOND LENGTHS



TORSION ANGLES



3-2-1
2-1-7