THE SYNTHESIS OF TWO RELATED SESQUITERPENES

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE UNIVERSITY OF ADELAIDE

by

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1973

CONTENTS

SUMMARY

The essential oil of the wood of *Eremophila freelingii*, an Australian native shrub, contains an acetylenic furano-sesquiterpene, freelingyne ($C_{15}H_{12}O_3$). A reinvestigation of the oil has led to the isolation of a related furano-sesquiterpene, dihydrofreelingyne ($C_{15}H_{14}O_3$). The syntheses of these sesquiterpenes are described in this thesis.

In Chapter 1, the synthesis of freelingyne by two routes is discussed. The flash vacuum pyrolysis of a tertiary acetate gave a mixture of isomeric products, one of which is freelingyne. The acetate was prepared *via* the alcohol from the Reformatsky reaction of 1-bromo-3-(3'-furyl)prop-2-yne with 4-hydroxy-2-methyl-6-oxahepta-2(*Z*),4(*E*)-dienoic acid (1→4)lactone. The second synthesis of freelingyne involved the formation of a double bond by the Wittig reaction of a C_8 phosphorane with 3-(3'-furyl)propyn-1-al.

An unambiguous synthesis of a phenyl analogue of freelingyne by the Wittig reaction of a C_5 butenolide phosphorane with the C_{12} aldehyde 2-methyl-5-phenylpent-2(*E*)-en-4-yn-1-al, discussed in Chapter 2, has confirmed that freelingyne is 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(*Z*),4(*Z*),6(*E*)-trien-8-ynoic acid (1→4)lactone 86. A similar stereoselective synthesis of dihydrofreelingyne, presented in Chapter 2, has established that dihydrofreelingyne is 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(*Z*),4(*Z*),6(*E*),8(*E*)-tetraenoic acid (1→4)lactone 158.

STATEMENT

This thesis contains no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

C.F. INGHAM

ACKNOWLEDGEMENTS

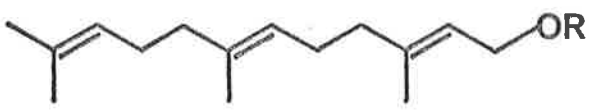
I am sincerely appreciative of the advice and encouragement given me by Dr R.A. Massy-Westropp during his supervision of this work. I would also like to thank those members of the Department who assisted me during this work. I am indebted to my wife, Helen, not only for her patience and understanding, but also for her typing of the manuscript.

This research was carried out during the tenure of a Commonwealth Post-Graduate Award, which I gratefully acknowledge.

INTRODUCTION

The terpenoids are among the most widespread and chemically interesting groups of natural products and have been the subject of chemical study since the earliest days of modern chemistry. The great variation in structure of these compounds, and their frequent occurrence has made terpene research the centre of considerable attention.[1,2,3] As a consequence, many significant advances in the theories of stereochemistry and mechanism have been made.[4]

It was not until the Biogenetic Isoprene Rule[5,6] and its later extensions[7,8] were proposed, that the wide range of cyclic and acyclic structures was rationalised. Considerable experimental evidence[9,10] has now shown that the sesquiterpenes are derived from farnesyl pyrophosphate 1 which is in turn produced by the sequential condensation of three molecules of isopentenyl pyrophosphate 2. The carbon skeletons of virtually all the sesquiterpenes can be derived by suitable cyclisations of farnesyl pyrophosphate 1.



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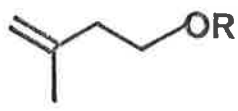

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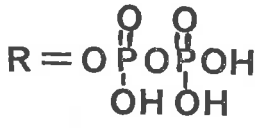
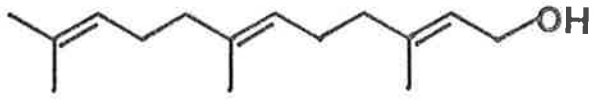


There are greater than six hundred known sesquiterpenoids which can be classified into more than forty skeletal types.[1] One

of these types, the acyclic sesquiterpenes, has about thirty members. A number of these are related to farnesol 3[11] but the majority are 3-substituted furan derivatives.



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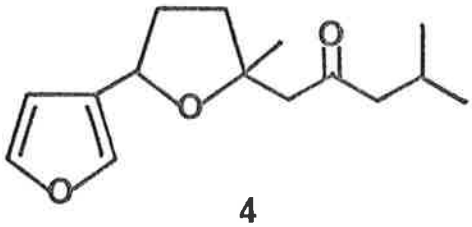
The 3-substituted furans can be arbitrarily divided into two groups, distinguished by the absence or presence of an oxygen atom at the terminal carbon atom.

Included in the first group is ngaione 4 which was isolated from the leaves of *Myoporum lactum* in 1925[12] and whose structure was elucidated in 1954.[13] Other members of this group are dendrolasin 5, which was isolated from the ant *Dendrolasius fuliginosus*,[14] dehydrodendrolasin 6[15] and myoporone 7.[16] Five other related sesquiterpenes have been isolated from *Athanasia arten*.[17]

The second group is characterised by the presence of a terminal oxygen atom. Torreyal 8, neotorreyol 9[18] and dehydrongaional 10[17] are members of this group.

A number of sesquiterpenes containing a terminal 2-substituted furan ring have been isolated, including lasiosperman 11, dehydrolasiosperman 12[19] and 13.[17]

A number of obviously related sesquiterpenes incorporate



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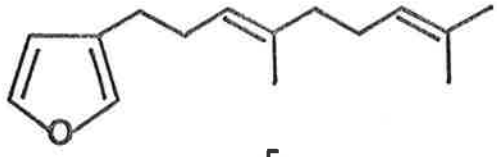

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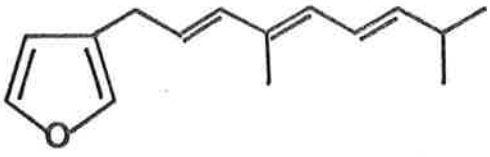

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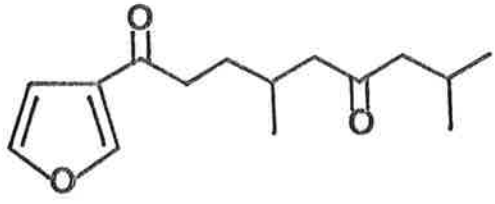

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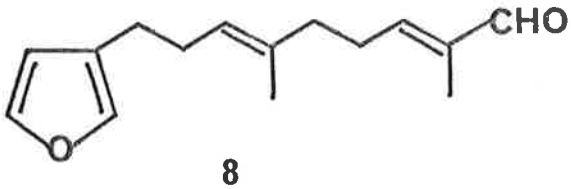

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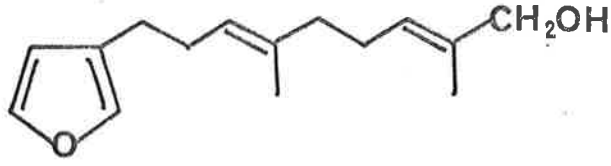

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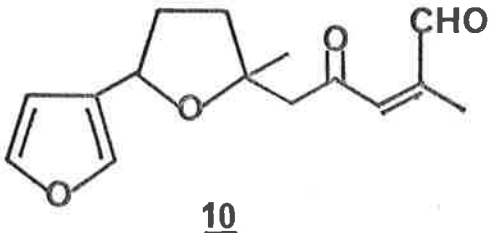

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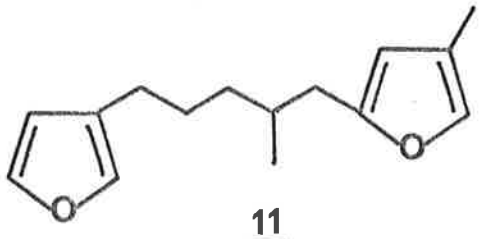

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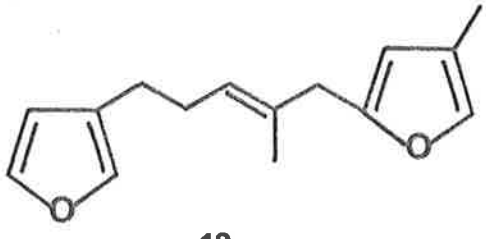

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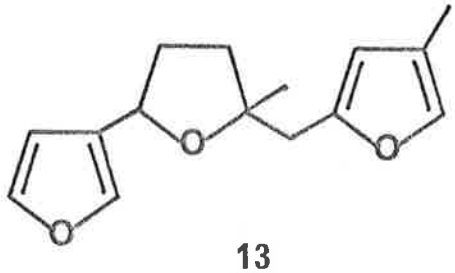

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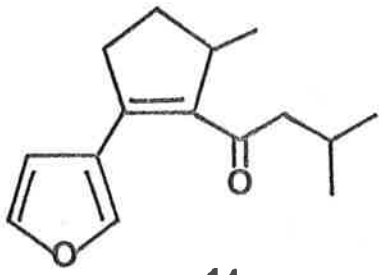
a carbocyclic ring. An intramolecular aldol cyclisation[20] of a precursor similar to myoporone 7 could lead to structures of the type found in myodesmone 14[21] and dehydroisomyodesmone 15.[22]



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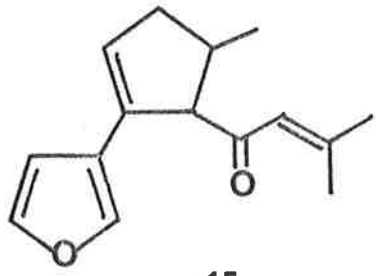

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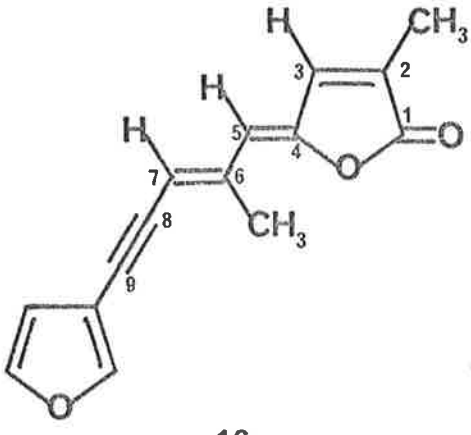
Freelingyne 16, is a 3-substituted furano-sesquiterpene isolated from the wood-oil of an Australian native shrub, *Eremophila freelingii*.[23] It is one of the few acetylenic terpenoids known[24] and is the most unsaturated of the 3-furano-sesquiterpenes that have been isolated.



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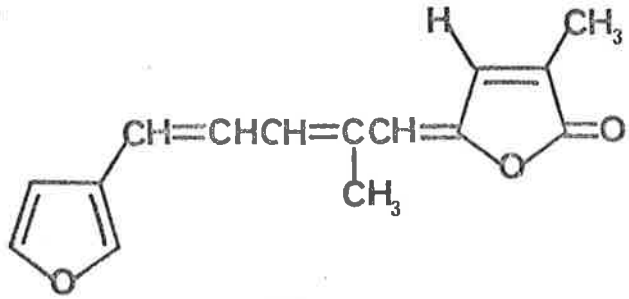

17

Freelingyne 16 is oxygenated in the terminal (C1)* position, and is similar in this respect to those sesquiterpenes of the torreyal 8 type. It is likely that freelingyne 16 is derived by the oxidation of a precursor similar to dehydrolasiosperman 12, followed by cyclisation and dehydrogenation *via* the dihydroisomer 17.[26] The spectral data of freelingyne 16 suggested the Δ^4Z,Δ^6E-stereochemistry[27] shown although the assignments were doubtful.[28]

Reynolds developed a synthetic approach to freelingyne 16 but it suffered from a number of deficiencies.[29] Firstly, the sequence was of low overall yield while the final step gave freelingyne 16 only in a 3% yield and in an insufficient quantity for positive identification. Secondly, the final reaction was not stereoselective[30] and a number of isomers were formed concomitantly. Finally, as the reaction was not stereoselective, the structural assignment of the product was dependent upon the interpretation of the NMR spectrum. This required the same doubtful assumption for the interpretation of interproton allylic coupling constants (*viz.* $J_{cisoid} > J_{transoid}$)[28] that was made with the natural product. It has been shown that in many isomeric systems the reverse relationship may hold.[28]

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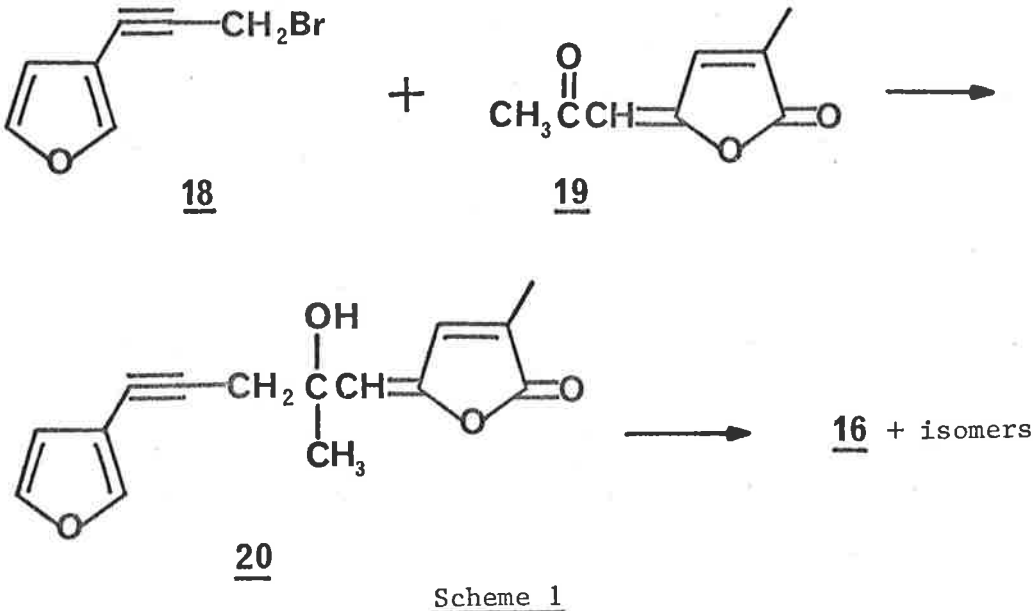
* The numbering system of freelingyne 16 is based upon the longest carbon chain in accordance with the I.U.P.A.C. rules for simple terpenes.[25]

The sequence used by Reynolds[29] for the synthesis of freelingyne 16 made use of the Reformatsky reaction[31] of the furyl propargyl bromide 18 with the enol-lactone 19 to produce the alcohol 20 in poor yield. This alcohol was treated with phosphorus oxychloride[32] to produce a mixture of isomers, one of which was freelingyne 16 (Scheme 1).



Scheme 1

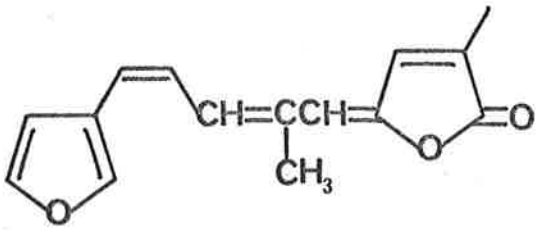
The detection of three isomers suggested that the expected double bond isomerisation was taking place during a dehydration process involving a possible carbonium ion intermediate.

A re-investigation of the wood-oil of *E. freelingii* has led to the isolation of a possible biogenetic precursor, dihydrofreelingyne 17. The stereochemistry of dihydrofreelingyne 17 was difficult to assign from the NMR spectrum, since the eight olefinic protons form a complex overlapping pattern.

Since the spectral data did not unambiguously define the stereochemistry of freelingyne 16 and dihydrofreelingyne 17, and there was little evidence regarding their photo-stability, it was necessary to develop stereoselective syntheses[30] of the possible isomers. This would give detailed spectroscopic and physical information and provide an unambiguous structural assignment of the natural products 16 and 17.

The approach of Reynolds was re-investigated in an attempt to prepare the alcohol 20 in better yield in order to study more selective dehydration procedures. A thermal elimination of an acetate or xanthate[33] may prevent the undesirable isomerisation during the preparation of the olefin 16.

The Δ^8Z-dihydrofreelingyne isomer 21 would be obtained from the *cis*-hydrogenation[34] of freelingyne 16. It was thought unlikely that the Δ^8E-dihydrofreelingyne isomer 22 could be prepared readily from the reduction of freelingyne 16 since possible reducing agents such as lithium aluminium hydride[35,36] and metal-ammonia solutions[37,38] would not be specific for the triple bond. However, a Reformatsky reaction of the enol-lactone 19 with the bromide 23 and subsequent dehydration could produce the required Δ^8E-isomer 22.



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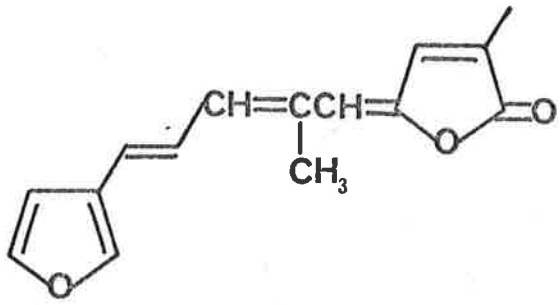

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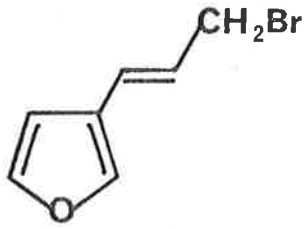

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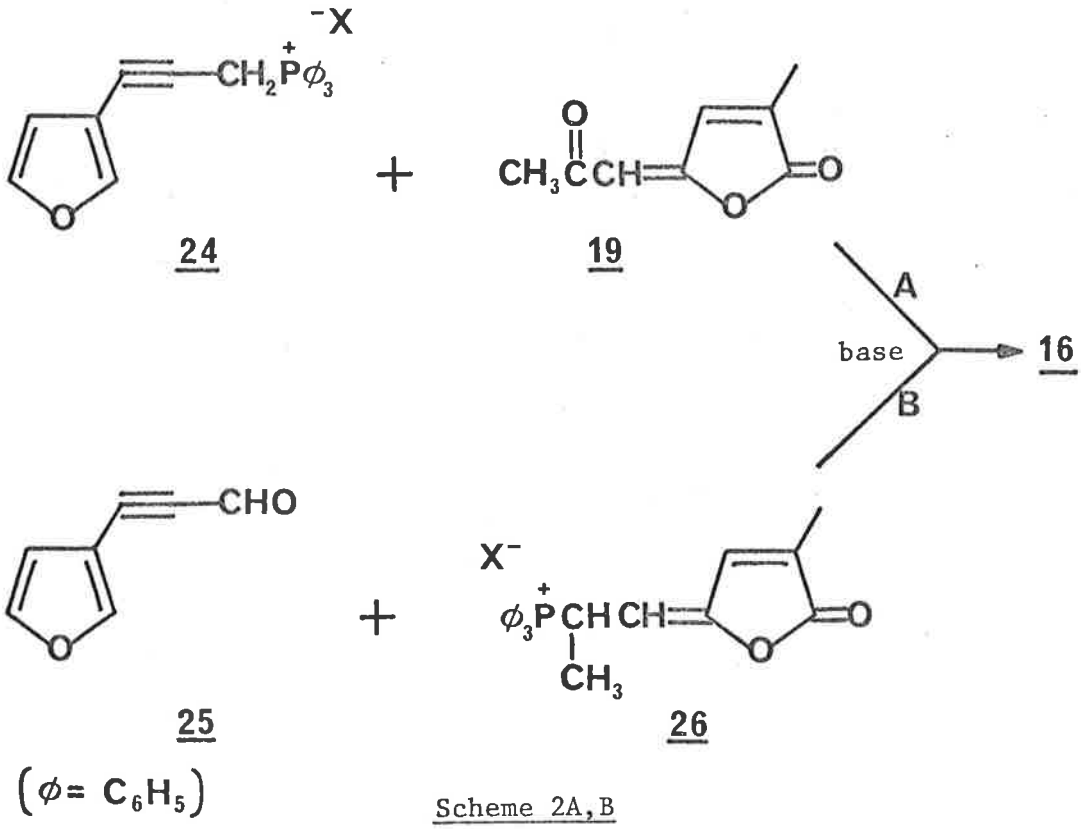
The two most widely used methods for the preparation of compounds containing double bonds in natural product syntheses are the Reformatsky reaction[31,39] and the Wittig reaction.[40] These approaches have been extensively used in carotenoid[31] and Vitamin A syntheses.[41]

The problems found with Reynolds' approach[29] are associated with the dehydration of the alcohol 20. This could be circumvented by a Wittig reaction between the two synthons[42] 18 and 19. This can be achieved in two senses (Scheme 2).



Scheme 2A,B

Previous workers in this department have shown that the Wittig reaction with stabilised phosphoranes * and the enol-lactone 19 does not produce the expected olefinic product.[29] A similar result was obtained with the reactive phosphonate carbanion 27.[44]

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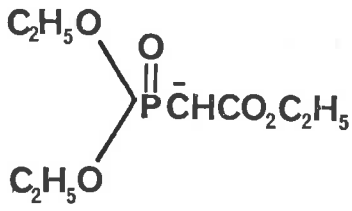
* The term stabilised phosphorane is used for those phosphoranes which have powerful electron-withdrawing groups attached to the carbanion, and are therefore resonance-stabilised.[43] Such phosphoranes can usually be isolated, purified and stored in the atmosphere.



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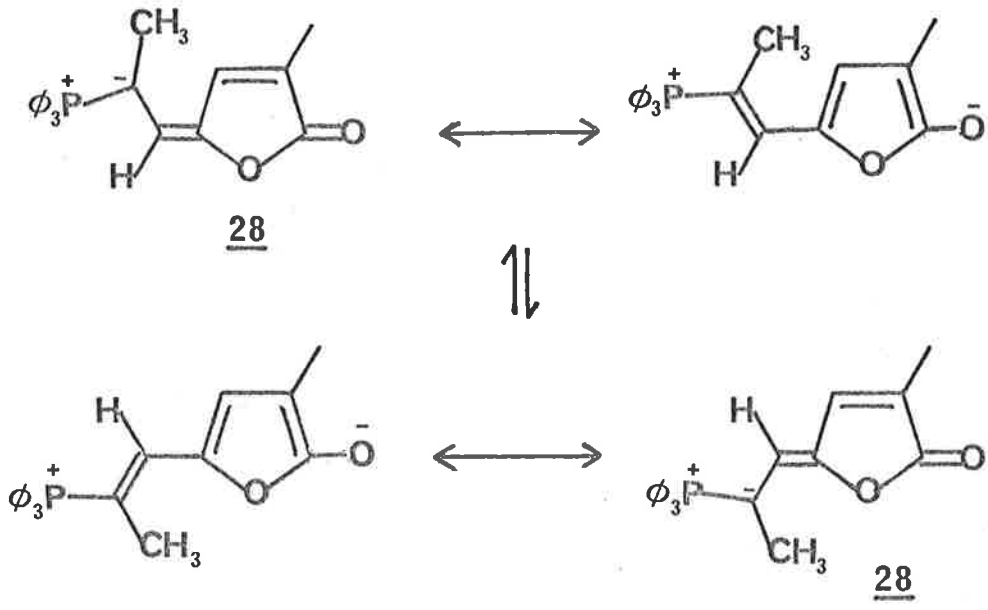
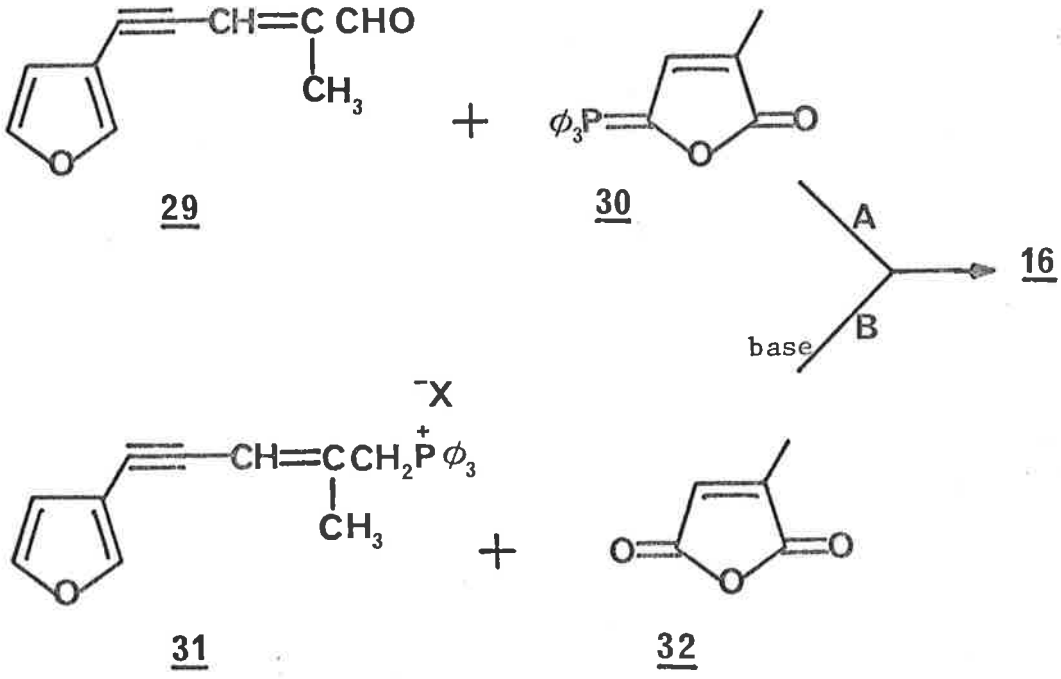
The Wittig reaction represented in Scheme 2B may be expected to proceed with greater facility, as aldehydes are more reactive than ketones towards stabilised phosphoranes.[45,46] However, the stereochemical integrity of the Δ^4-double bond of the phosphonium salt 26 could well be lost by resonance delocalisation of the negative charge when the phosphorane 28 is formed (Scheme 3). The isomerisation of the phosphorane 28 could be minimized at low temperatures[47] but the Wittig reaction may not proceed under these conditions.



28 28

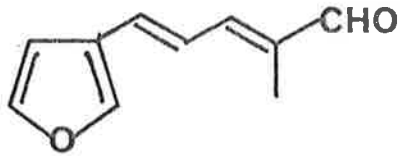
Scheme 3

A different approach by a Wittig reaction to form the Δ^4-double bond could avoid this problem of isomerisation (Scheme 4).



Scheme 4A,B

The unstable phosphorane 30 has recently been prepared but it reacts with aldehydes to give olefins only in fair yields.[48] This approach would also provide a route to the dihydrofreelingyne isomers 17 when suitable aldehydes of the type 33 were used. However, the low reactivity of the phosphorane 30 and the expected lability of the dienals 33 make this route less attractive for some of the less stable dihydrofreelingyne isomers 17.



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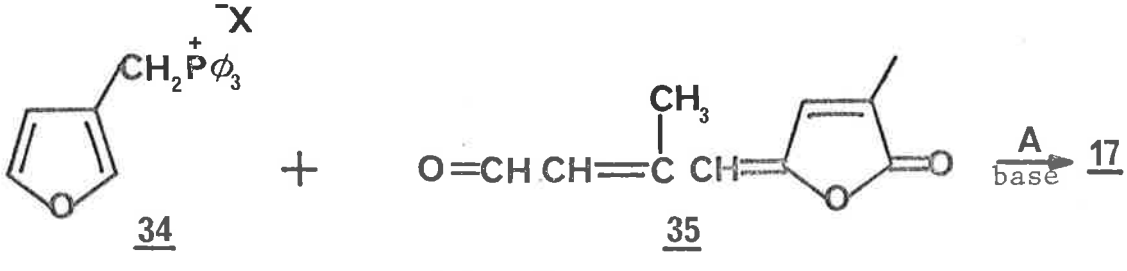
The Wittig reaction, Scheme 4B, suffers from some complications. The stereochemistry of the phosphonium salts 31 may be difficult to maintain when the corresponding phosphorane is generated. Also, although the Wittig reaction between certain stable phosphoranes and cyclic five-membered anhydrides is successful,[29,49,50] preliminary studies in this department[44,51] have suggested that reactive phosphoranes do not yield the expected enol-lactones. The phosphoranes generated from the salt 31 may well be included in this group and therefore some further preliminary studies of the reaction were carried out.

As a final approach to the dihydrofreelingyne isomers 17 the Wittig reaction to form the Δ^8-double bond was considered (Scheme 5).



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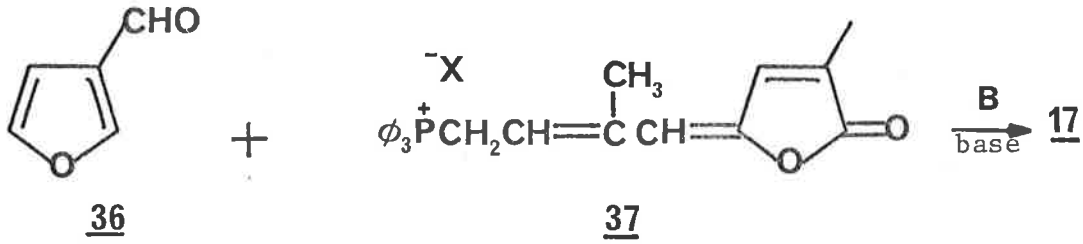
Scheme 5A

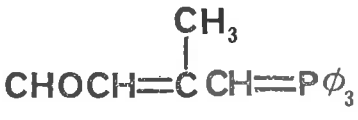


36 37

Scheme 5B

The preparation of the isomeric aldehydes 35 appeared to present some difficulties. An attractive synthesis of 35 would be a two-carbon homologation of the enol-lactone 19 by a Wittig reaction. However, the enol-lactone 19 has been shown not to produce the expected olefinic products with phosphoranes.[29] A Wittig reaction of the phosphorane 38 with citraconic anhydride 32 could provide the desired aldehyde 35.

The phosphonium salt 37 required for Scheme 4B could be obtained from the aldehyde 35 by standard procedures. Alternatively, a Grignard reaction[52] of vinyl magnesium bromide with the enol-lactone 19 would provide the allylic alcohol 39 which may be expected to undergo an allylic rearrangement with triphenylphosphonium bromide[53] to form the required salt 37.



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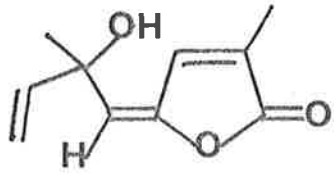

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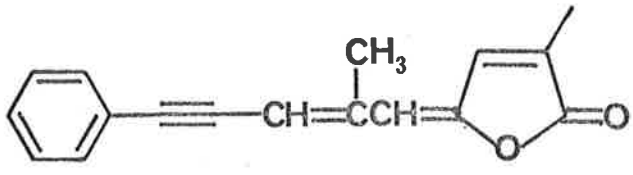
3-substituted furans are relatively inaccessible[54] and it was more practicable to direct the initial synthetic approaches to the phenyl analogues of the freelingyne isomers 40.



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The application of the approaches outlined in Schemes 1, 2, 4 and 5 to the stereoselective syntheses of freelingyne 16 and dihydrofreelingyne 17 is the subject of this thesis. Those methods which involve the final formation of the Δ^6-double bond (Schemes 1 and 2) are described in Chapter 1. The methods which require final formation of the Δ^4-double bond (Scheme 4) and the Δ^8-double bond (Scheme 5) are outlined in Chapter 2.

RESULTS AND DISCUSSION

CHAPTER 1

SYNTHESES INVOLVING THE FINAL FORMATION OF THE Δ^6-DOUBLE BOND

Section 1 Approaches using a Reformatsky reaction

Section 2 Approaches using a Wittig reaction

In the preceding introduction two routes for the syntheses of freelingyne 16 and dihydrofreelingyne 17 involving the formation of the Δ^6-double bond were outlined. The approach by a Reformatsky reaction (shown in Scheme 1) is discussed in Section 1 of this Chapter. In the latter part of this Section the approach towards dihydrofreelingyne 17 is discussed. The methods employing a Wittig reaction (shown in Scheme 2) are discussed in Section 2 of this Chapter.

Section 1 Approaches using a Reformatsky reaction

a. Preparation of enol-lactones

The Reformatsky route to freelingyne 16 (Scheme 1 p. 6) required the preparation of the intermediates 18 and 19. It was desirable that both *Z* and *E*-isomers of the enol-lactone 19 be obtained for if the dehydration of the alcohol 20 produced both isomers of the Δ^6-double bond, then all four stereoisomers of freelingyne 16 would be available.

Cyclic five-membered anhydrides have been shown to undergo a Wittig reaction with stabilised phosphoranes to give enol-lactones.[49] Extensive investigations conducted in this department[29,50,55-57] have shown that the *E*-enol-lactone is usually the predominant product.*

Reynolds has demonstrated that the treatment of citraconic anhydride 32 with methylcarbonylmethylenetriphenylphosphorane 41† gave a mixture of the enol-lactones 42, 43 and 44 (Scheme 6).[29] The enol-lactone 42 could be readily purified by chromatography, but the enol-lactone 43 was contaminated by a minor amount of 44, the product of reaction at the more sterically hindered carbonyl group.

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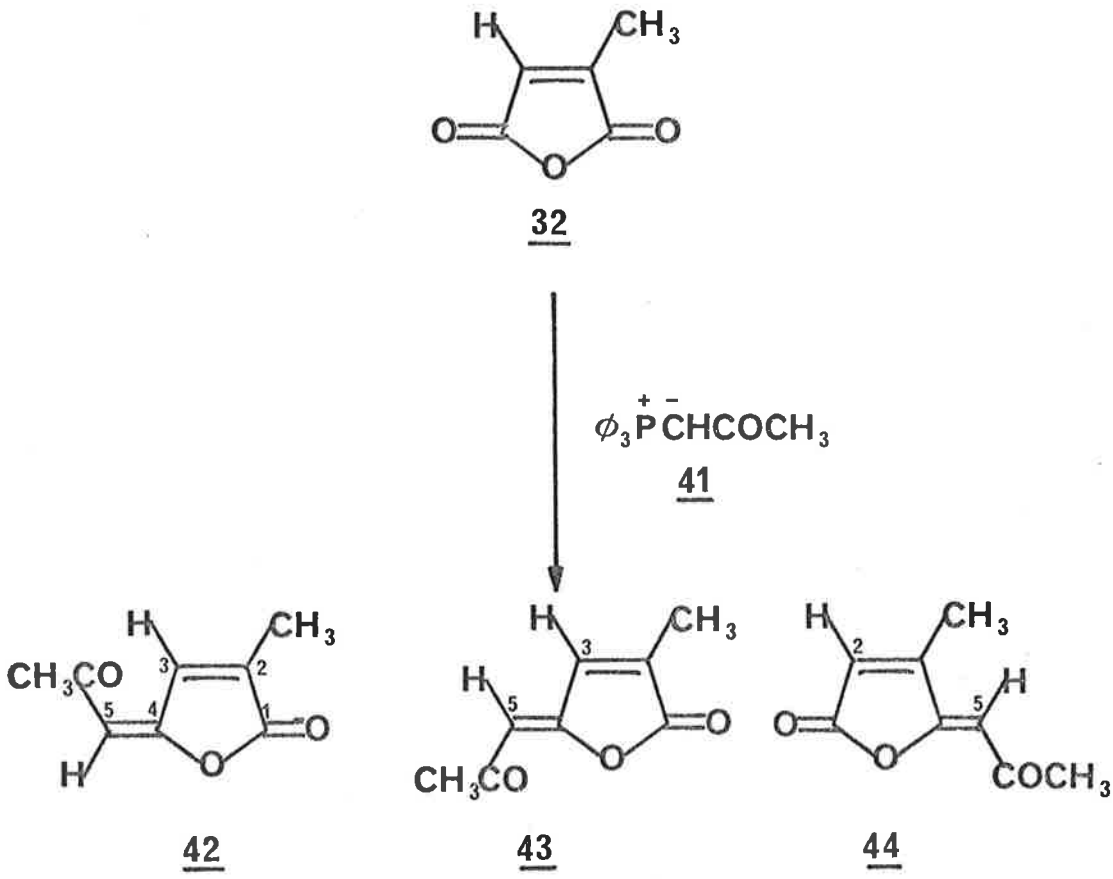
* Further aspects of this reaction are fully discussed in Chapter 2.

† The nomenclature of phosphoranes used in this thesis is that used by Pattenden and Weedon.[58]



C3 H δ8.0	7.1	C2 H 6.2
C5 H δ6.1	5.4	5.6

Scheme 6

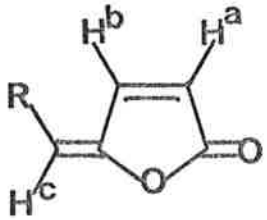
In a stereoselective synthesis of a compound it is essential that when pairs of isomers are obtained from a reaction they are correctly identified. The assignment of the stereochemistry of the enol-lactones 42 and 43, the desired intermediates in the

synthesis of freelingyne 16, has been made by interpretation of the NMR spectra.[29] The characteristic differences detailed below for the enol-lactones 42 and 43, become less distinct in the isomers of freelingyne 16. Thus a careful interpretation of these spectral differences is necessary, especially when an approach by Scheme 4 (p. 11) is considered.

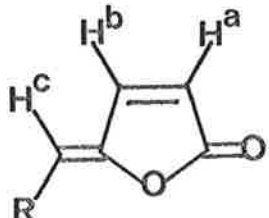
The chemical shift data (Scheme 6) show that the C3 proton of the Δ^4*E*-enol-lactone 42 resonates at lower field than the C3 proton of the Δ^4*Z*-enol-lactone 43. Protons which are in the plane of a carbonyl group and are close to it will be deshielded to a greater extent than protons which are further away.[59] Therefore it is apparent that the carbonyl group adjacent to the C3 proton of the Δ^4*E*-enol-lactone 42 will deshield it to a greater extent than the C3 proton of 43. A similar deshielding effect caused by the lactone oxygen atom[60] upon the C5 proton is observed. This proton of the Δ^4*E*-enol-lactone 42 resonates *ca.* 0.6 ppm downfield from the C5 proton of the Δ^4*Z*-isomers 43 and 44.

These deshielding effects are common to all the pairs of isomeric enol-lactones that have been produced by the Wittig reaction.[29,44] The structures of an extensive series of naturally occurring acetylenes containing an enol-lactone ring or a related enol-ether ring have been determined by Bohlmann.[24] He has shown that the proton H^c of the *E*-enol-lactones resonates at lower field than the *Z*-enol-lactones (Table 1). This assignment is confirmed

by the measurement of the long-range coupling constant J_{ac}. Bohlmann has noted that the *trans*-coupling constant J_{ac} of the *E*-enol-lactones is consistently larger than the *cis*-coupling constant of the Z-enol-lactones,[61,62] in agreement with other related systems.[63,64] A number of examples are presented in Table 1. The stereochemistry of the enol-lactones 47 and 48 has been assigned on a similar basis.[65,66] The enol-lactone 49, prepared in this department[29] and proposed as Δ^4E by the position of resonance of H^c, was shown to have J_{ac} 1.9Hz, in agreement with the Δ^4E-stereochemistry.[57]



E



Z

45 R = $-C\equiv C-CH=C(CH_3)SO_2CH_3$
H^c δ5.89 J_{ac} 2Hz

47 R = $COCH_3$
H^c δ6.28 J_{ac} 1.8Hz

49 R = $CO_2C_2H_5$
H^c δ5.9 J_{ac} 1.9Hz

46
H^c δ5.48 J_{ac} 0.8Hz

48
H^c δ5.58 J_{ac} 0.8Hz

Table 1

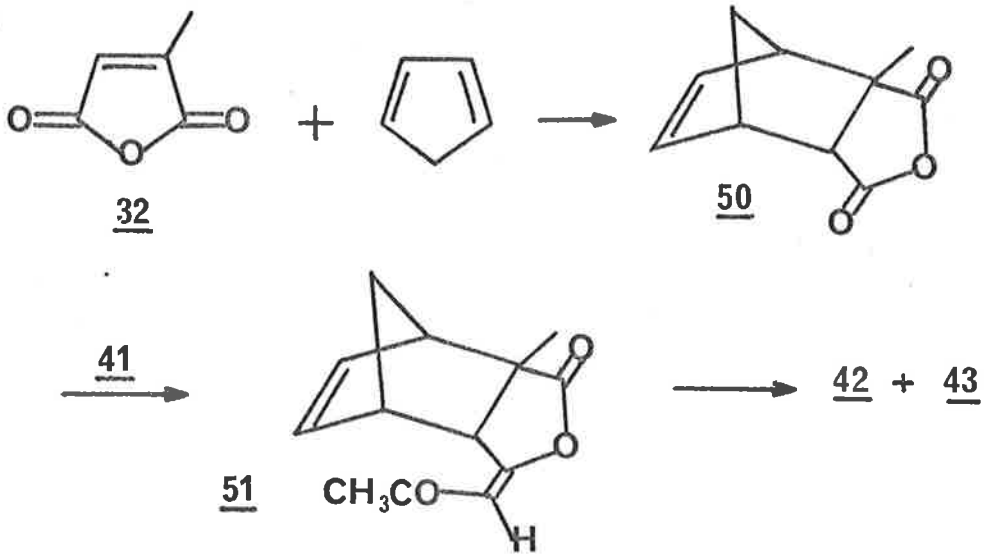
Since there was no measurable long-range coupling between the C2 and C5 protons of the enol-lactone 44, the assignment of

stereochemistry as Δ^4Z was confirmed.

The reaction between citraconic anhydride 32 and the phosphorane 41 (Scheme 6) was re-investigated using a number of solvents. It was determined that the best yields of enol-lactones 42, 43 and 44 were obtained when the reaction was performed in benzene under conditions of high dilution.

The formation of the enol-lactone 44 accompanying the isomers 42 and 43 was undesirable, as it could be separated from 43 only by careful fractional crystallization. An increased preference for a Wittig reaction at one carbonyl group of the anhydride would eventuate if the other carbonyl group was made more sterically crowded. A Diels-Alder reaction[67,68] of citraconic anhydride 32 and cyclopentadiene produced the *endo*-adduct 50. There is considerable steric interference to the approach of a phosphorane at the carbonyl group adjacent to the methyl group of 50, as the anhydride ring carbon atoms are now sp^3 hybridized. Treatment of the adduct 50 with the phosphorane 41 gave only the Δ^4E-enol-lactone 51 from reaction at the least hindered carbonyl group. The stereochemistry of 51 followed from the lowfield C5 proton resonance at δ5.9.[29] The retro-Diels-Alder reaction was achieved by distillation of the enol-lactone 51 to produce a low yield of a mixture of the Δ^4E and Δ^4Z-enol-lactones 42 and 43 (Scheme 7). This approach was not practicable on a larger scale, as there was considerable tar formation during the distillation, and

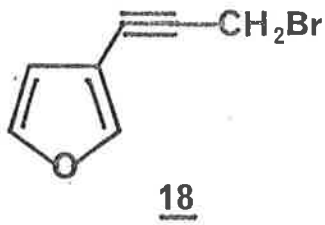
consequently this modified sequence was not pursued.



Scheme 7

b. Preparation of 1-bromo-3-(3'-furyl)prop-2-yne 18

The preparation of the propargyl bromide 18, required for the Reformatsky reaction with enol-lactones 42 and 43, requires the generation of a triple bond.

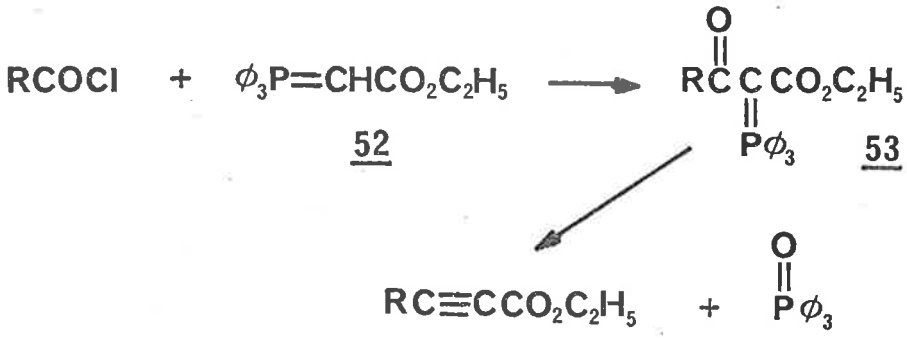


18

There are many methods available for the preparation of acetylenes.[69] The most common procedures involve the elimination

of a suitable group, such as the dehydrohalogenation of *gem*-dihalides[70,71] or the basic elimination of vinyl phosphates.[72] Another procedure involves the expulsion of a stable molecule (e.g. N_2, CO) from a cyclic precursor such as a pyrazolone[73] or an oxazolidone.[74]

A related method is the elimination of triphenylphosphine oxide by an intramolecular Wittig reaction. Acetylenic esters are produced in this manner by the pyrolysis of β-ketoalkylidenetriphenylphosphoranes 53 (Scheme 8).[75,76] The requisite phosphoranes 53 are readily produced by the C-acylation of ethoxycarbonylmethylenetriphenylphosphorane 52 with acid chlorides.[77]

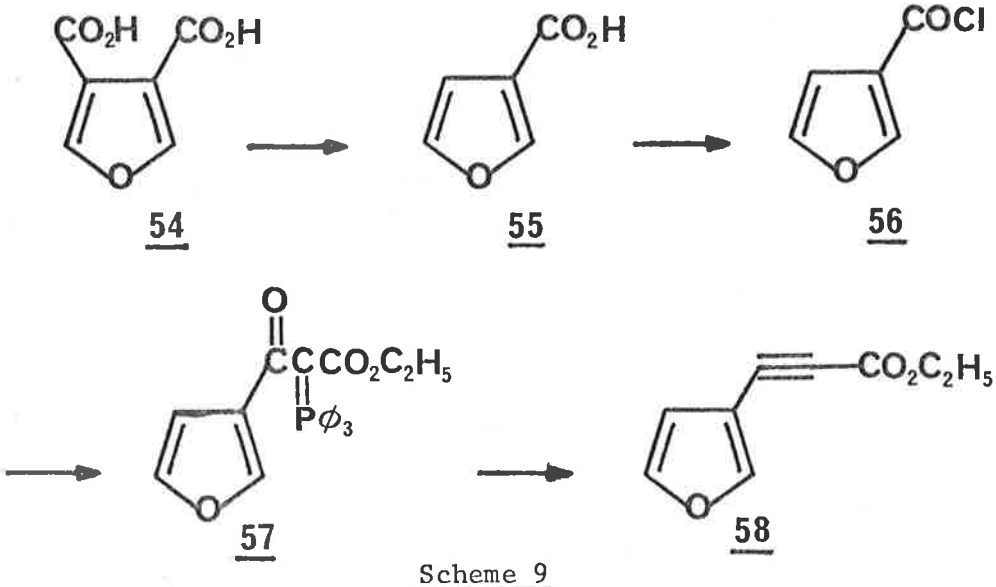


Scheme 8

Reynolds has prepared the required ethyl 3-(3'-furyl)prop-2-ynoate 58 by the pyrolysis of the phosphorane 57.[29] The phosphorane 57 was prepared in 33% overall yield from furan-3,4-dicarboxylic acid 54 (Scheme 9). 3-furoic acid 55, prepared by the copper-catalysed decarboxylation[78,79] of the diacid

54, was readily converted to the acid chloride 56 with thionyl chloride.[80] Acylation of the phosphorane 52 with the acid chloride 56 gave the β-ketophosphorane 57.

This approach was repeated a number of times and it was possible, with a number of modifications,* to form the phosphorane 57 in 75% overall yield from the diacid 54.



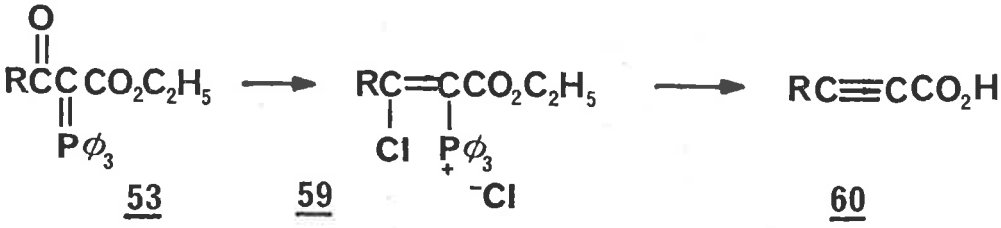
Scheme 9

The acetylenic ester 58 could be obtained in good yield by the vacuum pyrolysis of the phosphorane 57. However, there were considerable practical difficulties when the pyrolysis was performed on a large scale. Lower yields of the acetylenic ester 58 were

* The acid 55 was obtained in greatly improved yield if copper powder was used as the catalyst for the decarboxylation of 54 instead of copper chromite.[29] An improved yield of the phosphorane 57 was obtained when the acylation reaction was carried out at room temperature, rather than under reflux as previously performed.[29]

obtained as a result of considerable tar formation in the larger apparatus.

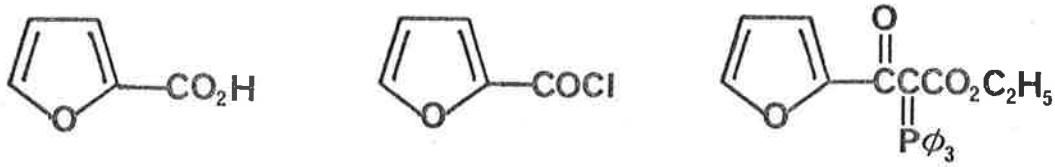
An alternative method for the conversion of the phosphoranes to acetylenic compounds has been published[81] (Scheme 10). The phosphorane 53 is chlorinated with phosphorus pentachloride and the intermediate chloro-phosphonium salt 59 treated with methanolic alkali, to give the acetylenic acid 60.



53 59 60

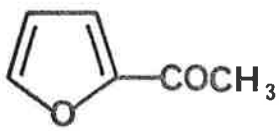
Scheme 10

Because of the problems encountered when preparing the acetylenic ester 58 on a large scale by the pyrolysis method, attempts were made to develop the procedure outlined in Scheme 10. The initial studies of the reaction were made with the phosphorane 63, which was readily prepared from 2-furoic acid 61 *via* the acid chloride 62.



61 62 63

It has been reported that the intermediate chlorophosphonium salt 59 (R=2-furyl) (Scheme 10) underwent a base catalysed elimination to the acetylenic acid 65 at pH 9, but when excess methanolic potassium hydroxide was used, the phosphorane 63 was converted to 2-acetylfuran 64.[82] This was presumably formed by the conjugate addition of the hydroxide ion to the acetylenic acid 65 to form a β-keto-acid which would readily decarboxylate to give the methyl ketone 64. In our hands, the elimination conditions at pH 9 were not severe enough to effect complete reaction, but the reaction at pH 11 produced 2-furylpropiolic acid 65 in excellent yield, with no trace of the methyl ketone 64.

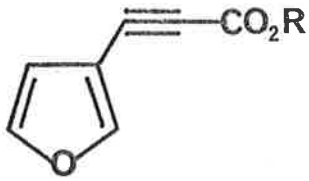


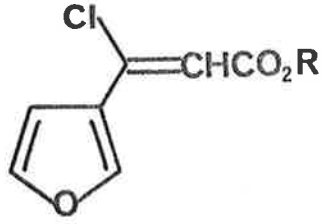
64

65

The chlorination and elimination of the 3-furylphosphorane 57 with ethanolic potassium hydroxide using the reported elimination conditions[81] of pH 9 produced a mixture of the desired acetylenic acid 66, the ethyl ester 58 and the olefinic chloro-ester 67.

When the reaction was repeated with the elimination conditions of pH 11, which were previously found to be satisfactory, a moderate yield of an inseparable mixture of the acids 66 and 68, (in the ratio of 4:1 respectively) was obtained. The olefinic



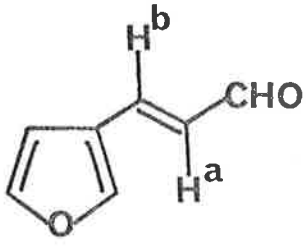


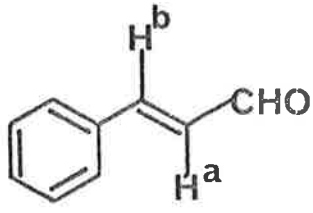
R = C_2H_5 58 R = C_2H_5 67

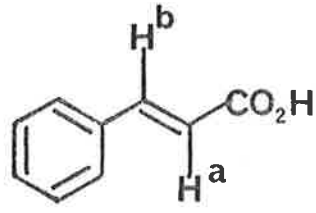
R = H 66 R = H 68

chloro-acid 68 could be converted to the acetylenic acid 66 by an extended hydrolysis procedure but the recovery of the acetylenic acid 66 was only fair and a minor amount of the chloro-acid 68 was still present.

The structures of the olefinic chloro-ester, 67 and the acid 68 follow from an examination of the NMR spectra. The olefinic protons of 67 and 68 resonate as sharp singlets at δ6.2 and δ6.3 respectively. This is in agreement with the chemical shift of the proton at the α-position of the carbonyl group in the model compounds shown below (Table 2).







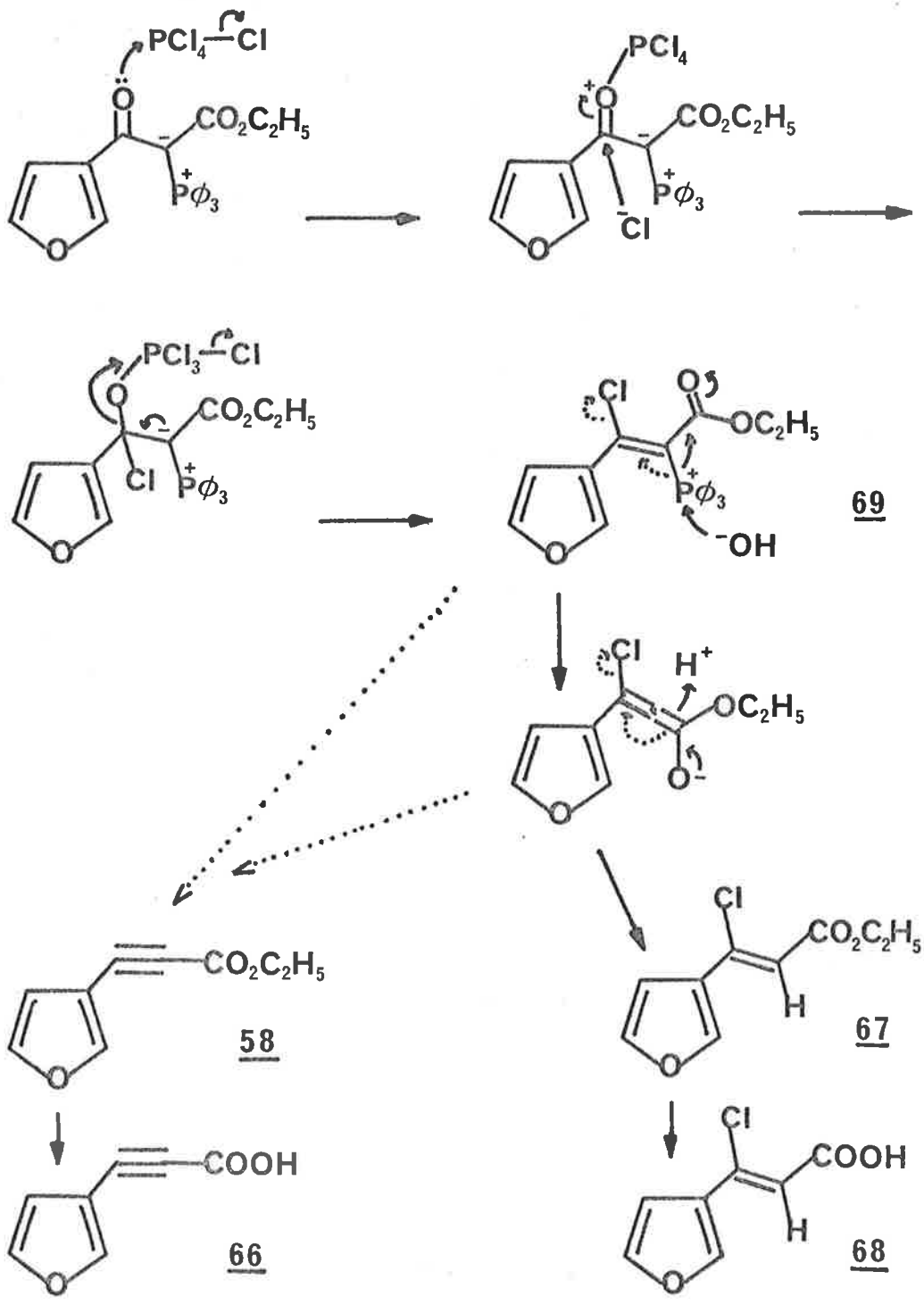
H^a	δ6.5	6.6	6.5
H^b	δ7.42	7.4	7.8

Table 2

The position of the chlorine atom in the compounds 67 and 68 is confirmed by a consideration of the probable mechanism of the reaction (Scheme 11).

The chloro-phosphonium salt 69[81] may undergo elimination to form either of the acids 66 or 68. It is apparent that the chloro-olefins 67 and 68 are not intermediates in the pathway to the acetylenic acid 66, as they undergo a base-catalysed elimination far too slowly. They are clearly more stable to base than saturated β-halo-acids, which are known to undergo rearrangements and dehydrohalogenation readily.[83]

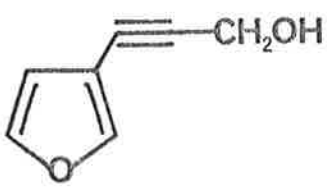
The failure of the reaction of the 3-furylphosphorane 57 to give the acetylenic acid 66 cleanly is surprising when it is considered that the 2-furylphosphorane 63 smoothly produced the acetylenic acid 65. It has been noted that only aromatic acetylenic acids can be prepared by this method.[81] The delocalised π-electron system present in the aromatic phosphoranes (e.g. 63) presumably stabilises the developing triple bond by conjugation, thus lowering the energy of the transition state. It is apparent that the 3-furyl group does not conjugate with the developing triple bond as well as the 2-furyl group. A comparison of the ultraviolet spectra of the acids 65 (λ_{max} 293nm) and 66 (λ_{max} 258nm) shows that the 2-furyl acetylenic acid 65 absorbs at a longer wavelength. This is consistent with the greater delocalisation of the π-electrons to a substituent in the 2-position than in the


PCl4—Cl
CO2C2H5
Pϕ3
PCl4
Cl
PCl3—Cl
OC2H5
OH
69
H+
67
58
66
COOH
68

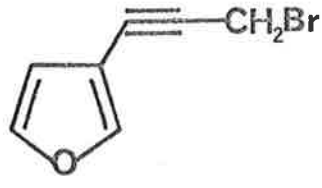
Scheme 11

3-position. The energy of the transition state leading to the 3-furyl acetylenic acid 66 is presumably higher than for the 2-furyl acetylenic acid 65 and it is possible that protonation of the anion to form the chloro-ester 67 (Scheme 11) is now able to compete effectively with the elimination of the chloride ion to form the acetylene. It may well be possible, with the judicious choice of a suitably substituted aromatic phosphorane, to favour the protonation process so that the olefinic chloro-acid becomes the major product.

As the chlorination and basic elimination procedure for the preparation of the 3-furyl acetylenic acid 66 was impracticable, the pyrolysis method was used to prepare the acetylenic ester 58. The ester 58 was cleanly reduced, without competing reduction of the triple bond, with lithium aluminium hydride at -78°.[84] The product propargyl alcohol 70 was smoothly converted to the required bromide 18 with phosphorus tribromide in ether.[85]

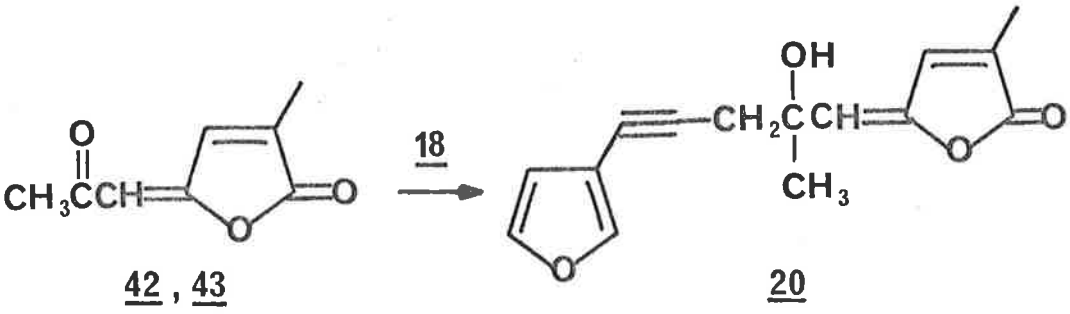


70



18

c. The Reformatsky reaction and pyrolyses

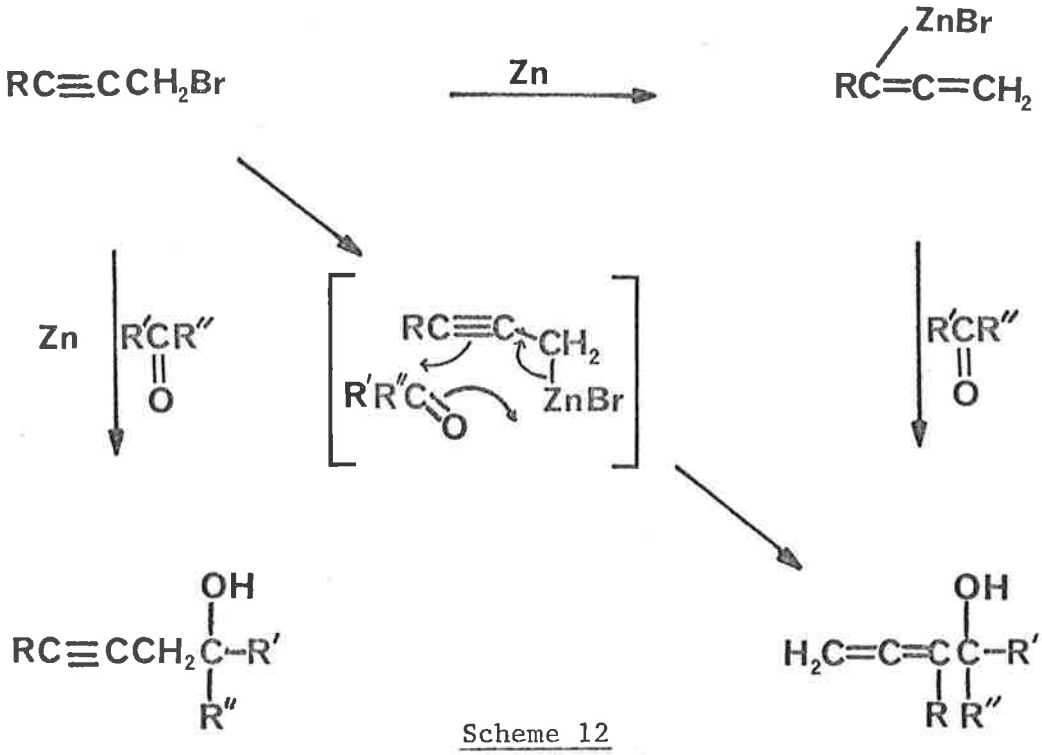


42 , 43 20

Scheme 1

The reactants required for the Reformatsky reaction (Scheme 1) were now available (Part a. and b.). It was important to find the optimum conditions for the reaction, in order to prepare the alcohol 20 in better yield than had been previously obtained.[29]

The Reformatsky reaction between propargyl zinc alkyls and aldehydes or ketones often produces a mixture of acetylenic and allenic alcohols[86,87] (Scheme 12). The relative proportions of the products are variable and depend upon the nature of the metal[88] and the solvent, and on the steric bulk of the carbonyl compound.[89] The allenic alcohol may be formed *via* a cyclic transition state, similar to that postulated with allylic Grignard reagents,[90] or by a direct reaction with an allenic zinc alkyl[89] (Scheme 12). The yield of the alcoholic products is often affected greatly by the purity and physical characteristics of the zinc used, the type of solvent and the order of addition of the reagents.[41,86,87]



Scheme 12

As the furylpropargyl bromide 18 was available in limited quantities, initial approaches to this reaction were directed towards the phenyl analogues of freelingyne 40. The Reformatsky reaction between phenylpropargyl bromide 71* and acetone was studied in order to obtain the most favourable reaction conditions. These were realised when the bromide 71 was added to a mixture of zinc and acetone in tetrahydrofuran at room temperature. A good yield of a mixture of the acetylenic alcohol 72 and the allenic alcohol 73 was obtained in the ratio of 6:1 respectively (Scheme 13).

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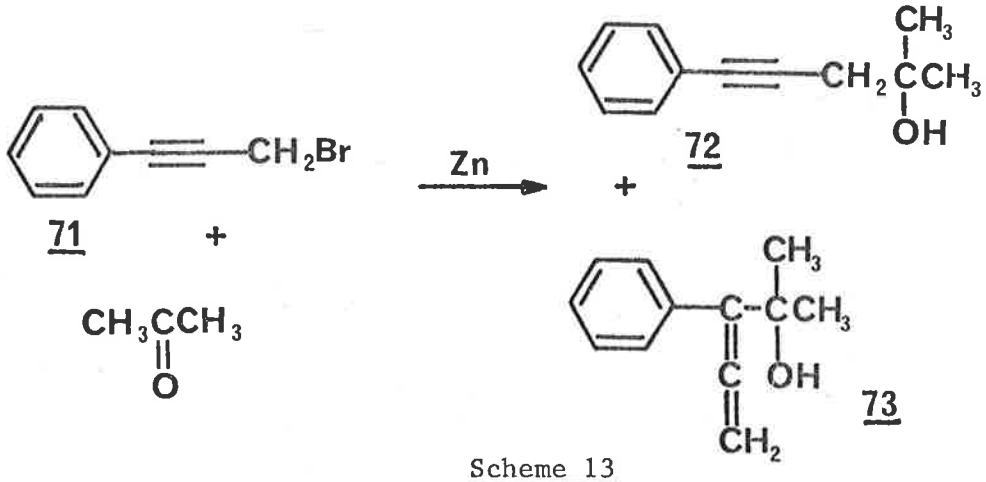
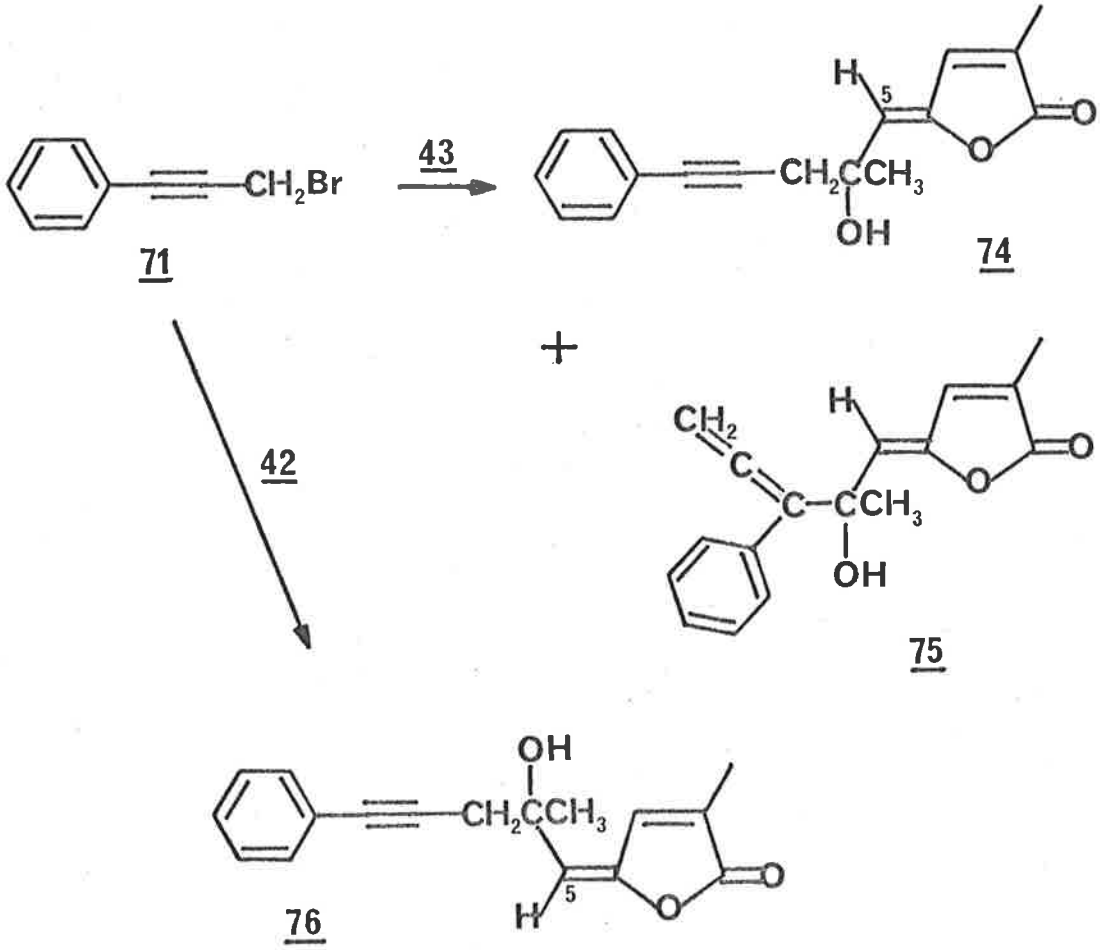
* Phenylpropargyl bromide 71 was obtained by the bromination[85] of phenylpropargyl alcohol 115 which was readily prepared from phenyl acetylene and formaldehyde.[91]



Scheme 13

However, when the Δ^4Z-enol-lactone 43 was treated under the same conditions, only a low yield of the expected alcohols 74 and 75 was obtained. This showed that the optimum conditions for these reagents were not the same as for the reaction with acetone. Further investigations revealed that the best yields for the reaction with 43 were obtained when the zinc alkyl was generated before the enol-lactone 43 was added. Under these conditions the acetylenic carbinol 74 and the allenic carbinol 75 were obtained in a ratio of 2:1 in high yield (Scheme 14). Interestingly, the reaction with the Δ^4E-enol-lactone 42 gave only the acetylenic carbinol 76. The steric requirement of the allenic zinc alkyl, or of the cyclic transition state leading to allenic products (Scheme 12), is greater than that for the formation of acetylenic products. The more hindered carbonyl group of 42 presumably would not allow the approach of the allenic zinc alkyl, and therefore no allenic carbinol was formed. The acetylenic carbinols 74 and

76 were consistently produced in yields considerably better than those obtained by Reynolds[29] and also in higher purity.

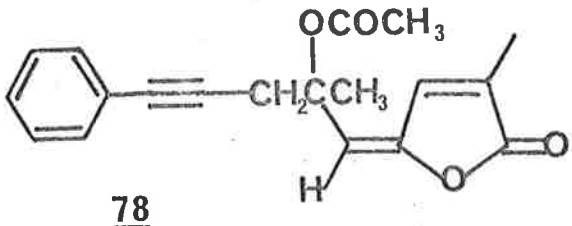


Scheme 14

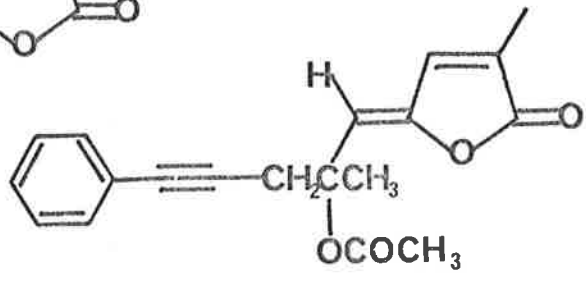
The allenic carbinol 75 was identified by an absorption at 1945 cm^{-1} in the infrared spectrum, and a sharp two proton singlet at δ5.15 in the NMR spectrum. The acetylenic carbinols 74 and 76 had retained the Δ^4-stereochemistry of the starting enol-lactones 43 and 42. The C5 proton of 76 resonated at δ5.8, 0.4 ppm lower field than the C5 proton of 74, confirming that the alcohol 76

had retained the $\Delta^4 E$-stereochemistry while the alcohol 74 had the opposite $\Delta^4 Z$-stereochemistry.

It was desirable to effect the dehydration of the carbinols 74 and 76 by a non-ionic method, since Reynolds had shown that a phosphorus oxychloride dehydration gave rise to a mixture of stereoisomers in a very low yield.[29] This was consistent with the dehydration process having some carbonium ion character which has been reported to occur when some resonance stabilisation of the transient carbonium ion is possible.[92] Similarly, an attempt to form the trifluoroacetate[93] of 74 produced only a small amount of a mixture of olefinic products. This indicated that the trifluoroacetate was labile and decomposed under the reaction conditions, presumably *via* an ionic mechanism. However, the more stable crystalline acetates 77 and 78 could be prepared by treating the corresponding carbinols 74 and 76 with acetyl chloride in N,N-dimethylaniline.[94]



78



77

The thermal decomposition of acetates or xanthates is considered to proceed through a cyclic transition state to produce olefins by a *cis*-elimination.[33] There are two conformations (A and B, Figure 1) of the acetates 77 or 78 in which a *cis*-elimination of acetic acid can occur.

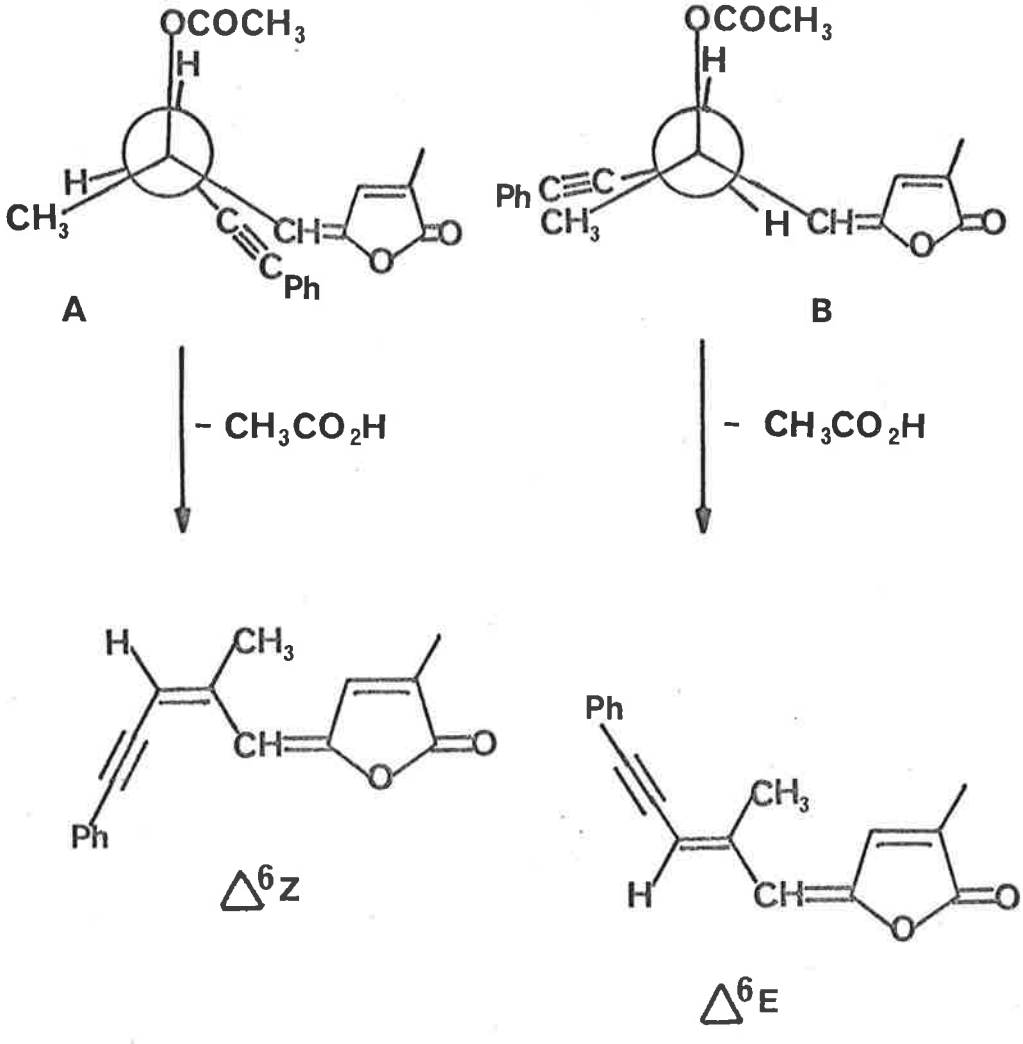
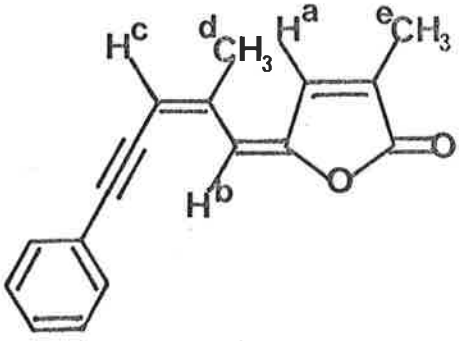


Figure 1

It is apparent that there will be very little difference in energy between the conformers A and B, since the sp-hybridised carbon atom of the acetylene group has a small steric bulk.[95] Therefore, it was expected that thermal elimination of acetic acid would occur through both conformers, producing a mixture of Δ^6Z and Δ^6E-isomers.

However, flash vacuum pyrolysis of either of the acetates 77 or 78 gave the same mixture of olefins in good yield. Extensive preparative thin layer chromatography enabled the isolation of the two major isomers while a minor amount of a third isomer was obtained mixed with the others. These isomers have been assigned the stereochemistry Δ^4E,Δ^6Z-79; Δ^4Z,Δ^6E-80; and Δ^4E,Δ^6E-81 respectively, by a consideration of their NMR spectra (Table 3).

The lactones 79, 80 and 81 are the same as those formed by the phosphorus oxychloride dehydration of the carbinols 74 and 76.[29] The stereochemistry of the Δ^4-double bond of the isomers was determined by the relative position of resonance of the C5 proton (H^b, Table 3). It has been pointed out previously that proton H^b of the Δ^4E-enol-lactone 42 (p. 18) is deshielded by the lactone oxygen atom and therefore resonates at lower field than the corresponding proton H^b of the Δ^4Z-enol-lactone 43. Similarly, the lactones 79 and 81 have Δ^4E-stereochemistry as the protons H^b

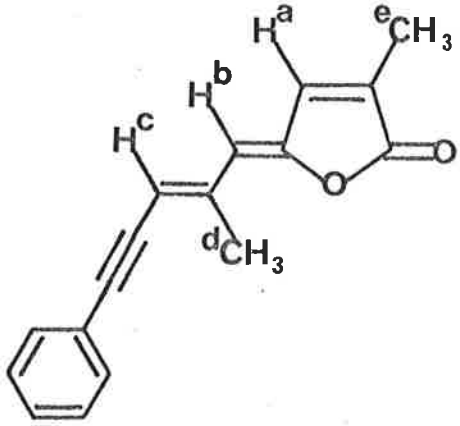


79

H^a δ7.1 J_{ae} 1.4Hz

H^b δ6.4

H^c δ5.75 J_{cd} 1.5Hz

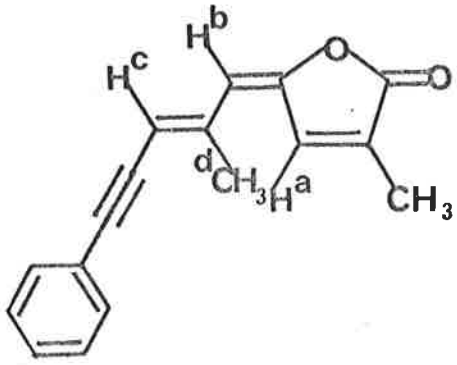


80

H^a δ7.02 J_{ae} 1.4Hz

H^b δ5.65

H^c δ6.0 J_{cd} 1.1Hz



81

H^a δ7.4

H^b δ6.34

H^c δ5.98 J_{cd} 1.0Hz

Table 3

resonate at *ca.* δ6.4, while in the Δ^4Z-isomer 80 the position of resonance is at δ5.65 (Table 3).

The assignment of stereochemistry of the Δ^6-double bond is more difficult. The stereochemistry of isomeric acyclic compounds has often been assigned on the assumption that the *cis*-allylic coupling constant (J allylic, cisoid) is larger than J allylic, transoid.[96,97] However, this relationship is unreliable and many reversals have been noted.[28,98] Nevertheless, studies in a similar system have shown that J allylic, cisoid is indeed the larger.[99,100] The Δ^4E-lactones 79 and 81 must differ in configuration about the Δ^6-double bond. The allylic coupling constant J_{cd} of 79 (1.5 Hz) is larger than that of 81 (1.0 Hz). The larger coupling constant was assigned to the *cis*-(or Z)-double bond and on this basis the olefin 79 was assigned as Δ^6Z, and the olefin 81 as Δ^6E. The isomer 80 was also assigned the Δ^6E-configuration, as the allylic coupling constant J_{cd}1.1Hz, was of the same order of magnitude as in the Δ^6E-isomer 81 (J_{cd}1.0Hz).

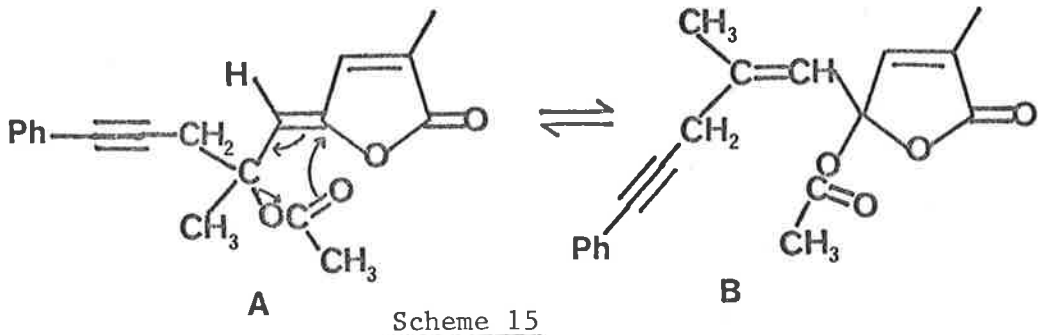
A comparison of the NMR spectra of the lactones 79, 80 and 81 with that of freelingyne 16 indicated that the lactone 80 was very similar, and that the Δ^4Z,Δ^6E-stereochemistry was probably present in freelingyne 16.

As expected the product lactones 79, 80 and 81 showed both Δ^6Z and Δ^6E-stereochemistry (Figure 1). However, the presence of a mixture of Δ^4Z and Δ^4E-configurations of the olefins

from either of the acetates 77 or 78, indicated that isomerisation was taking place. This could be occurring by a number of processes.

The thermal elimination of acetic acid is considered to be a concerted cyclic process and studies have shown that, in contrast to the dehydrohalogenation of alkyl halides in the vapour phase[101], only a small extent of charge separation exists in the transition state.[33,102] It is therefore unlikely that isomerisation of the Δ^4-double bond occurs as a result of carbonium ion charge delocalization in the transition state.

Some allylic acetates are known to undergo a reversible isomerisation process before acetic acid is eliminated.[33,103] Although the elimination could only proceed through the acetate A (Scheme 15), the reversible path to B would allow isomerisation of the Δ^4-olefinic bond to occur.

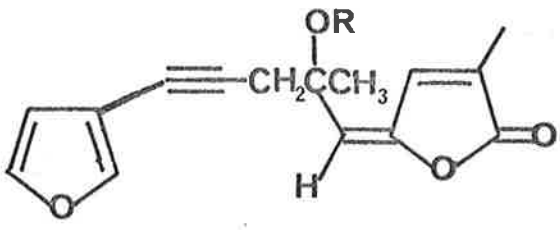


Scheme 15

It is most likely that the isomerisation process is thermal and occurs after a normal cyclic elimination of acetic acid. Although the contact time of the product olefin on the hot

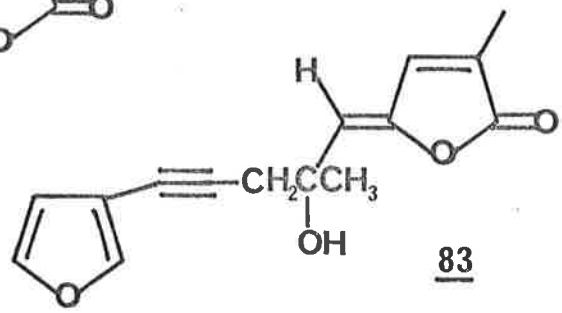
tube is short,[104] it is possible that the major isomers obtained, 79 and 80, are the most stable thermodynamically and are formed by a complete thermal isomerisation of the olefins initially produced. It was not possible to minimize this isomerisation by conducting the pyrolyses at lower temperatures, as the acetates 77 and 78 were recovered unchanged. The pyrolysis of xanthate esters usually requires lower temperatures than acetates.[33] However, an attempted preparation of a xanthate ester of the carbinol 76 was unsuccessful[29] and only a small amount of the same mixture of isomers was obtained, suggesting that the xanthate ester had decomposed under the reaction conditions.

The experiments with the phenyl analogues of freelingyne had shown that the Reformatsky reaction could be carried out in high yield. Unfortunately, it was not possible to convert the carbinols 77 and 78 stereoselectively to the 4 stereoisomers of the phenyl analogues of freelingyne 40. Nevertheless, the acetate pyrolyses did provide a method whereby two of the isomers, 79 and 80, could be obtained pure and in good yield. However, as double bond isomerisation had taken place during the pyrolyses, the stereochemistry of the carbinols 77 and 78 did not determine the configuration of the products 79, 80 and 81. It was therefore unnecessary to prepare both of the Δ^4E and Δ^4Z-carbinols 82 and 83 for the synthesis of freelingyne 16.



82 R= H

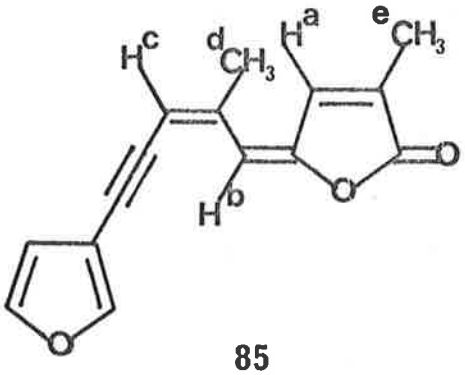
84 R= $COCH_3$



83

The initial studies had shown that the better yield in the Reformatsky reaction was obtained with the Δ^4E-enol-lactone 42 (p. 32). Therefore the Reformatsky reaction was performed with 1-bromo-3-(3'-furyl)prop-2-yne 18 and the Δ^4E-enol-lactone 42 under the conditions developed previously. A good yield (70%) was obtained of the Δ^4E-acetylenic carbinol 82 containing no trace of allene by-product. The carbinol 82 was readily converted to the acetate 84 which was subjected to flash vacuum pyrolysis to give a mixture of the lactones 85, 86 and 87 (Table 4). The lactones 85 and 86 were isolated by careful chromatography but the lactone 87 could not be obtained free from 85 and 86.

The NMR spectra of the lactones 85, 86 and 87 (Table 4) were very similar to those of the phenyl analogues 79, 80 and 81 (Table 3, p. 37) respectively. The lower field resonance of the C5 proton H^b of the lactones 85 and 87 indicated that the Δ^4-double bond had the *E*-stereochemistry, while the higher field resonance of H^b in the olefin 86 suggested the Δ^4Z configuration. The

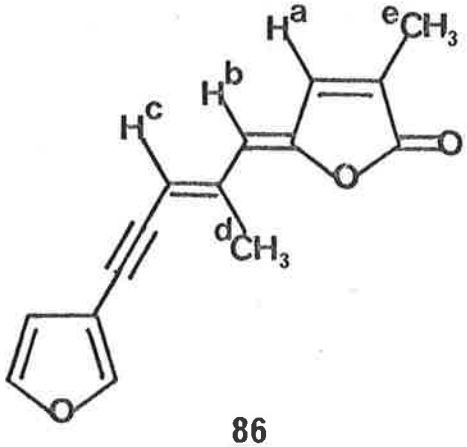


85

H^a δ7.12 J_{ae} 1.5Hz

H^b δ6.3

H^c δ5.7 J_{cd} 1.5Hz

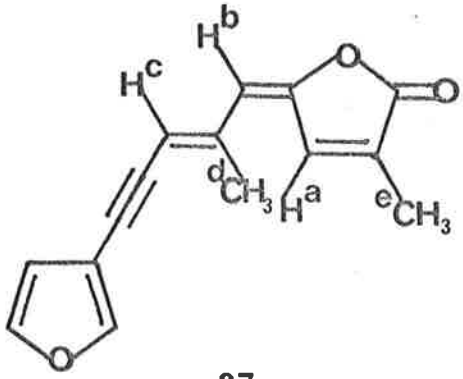


86

H^a δ7.02 J_{ae} 1.5Hz

H^b δ5.6

H^c δ5.9 J_{cd} 1.0Hz



87

H^a δ7.5 J_{ae} 1.5Hz

H^b δ6.34

H^c δ5.92 J_{cd} 1Hz

Table 4

basis for these assignments has been presented previously (p. 18). The assignment of the stereochemistry of the Δ^6-double bond was again dependent upon the relative magnitudes of the allylic coupling constant J_{cd}. The Δ^6E-configuration was assigned to the lactones 86 (J_{cd}1.0Hz) and 87 (J_{cd}1Hz) which display the smaller coupling constant.[96] The lactone 85 has a larger allylic coupling constant (J_{cd}1.5Hz) which is more consistent with a Δ^6Z-stereochemistry.[99]

It is apparent from the formation of the three compounds 85, 86 and 87 that isomerisation was also occurring during the pyrolysis of the furyl acetate 84. Some information on the stability of the compounds 85 and 86 was gained by an isomerisation study of the Δ^4E,Δ^6Z-lactone 85. A solution of 85, in deutero-benzene, was treated, in an NMR sample tube, with a crystal of iodine and irradiated by an incandescent lamp. In this manner the NMR spectra of the component olefins could be determined at suitable intervals. During this isomerisation process, only one isomer was observed to be formed, as shown by the appearance of the C6 methyl resonance (CH_3^d) at δ2.7. After an extended period of isomerisation the mixture attained equilibrium. The product was separated from the starting material 85 and shown to be the Δ^4Z,Δ^6E-lactone 86. The lactone 86 accounted for 75% of the equilibrium mixture. Consequently, the Free-energy difference between the lactone 85 and 86 is only about 650 cal/mol.[105] However, as no trace of the other two possible isomers was detected

at any stage, it is apparent that the Δ^4Z,Δ^6E and Δ^4E,Δ^6Z-isomers 86 and 85 are the most stable of the 4 possible isomers by at least 2 kcal/mol.[105] This substantiates the suggestion (p. 40) that during the acetate pyrolyses the olefins initially formed undergo thermal isomerisation to give the two most stable isomers with only a trace of a third less stable isomer.

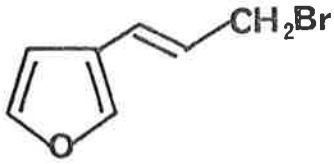
A comparison of the lactones 85, 86 and 87 with naturally occurring freelingyne 16 showed that the Δ^4Z,Δ^6E-lactone 86 was identical to the natural product by all physical and spectral criteria.

A synthesis of freelingyne 16 had therefore been achieved but unfortunately it was not stereoselective. The inherent unreliability in assigning the configuration of the Δ^6-double bond by a consideration of the allylic coupling constants[28] required that the assignment of the Δ^4Z,Δ^6E-stereochemistry of freelingyne 16 be regarded with caution. For this reason, the synthesis of freelingyne 16 was approached by other routes. These are discussed in later sections of this thesis.

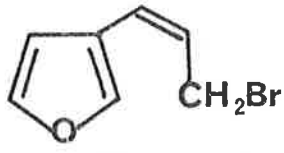
d. Approaches to dihydrofreelingyne 17

It was shown in part c. that the Reformatsky reaction of the Δ^4E-enol-lactone 42 with the 3-furylpropargyl bromide 18 produced the required carbinol 82 in good yield. It was considered that the Reformatsky reaction with the Δ^2E-bromide 23 could proceed

in an analagous manner.

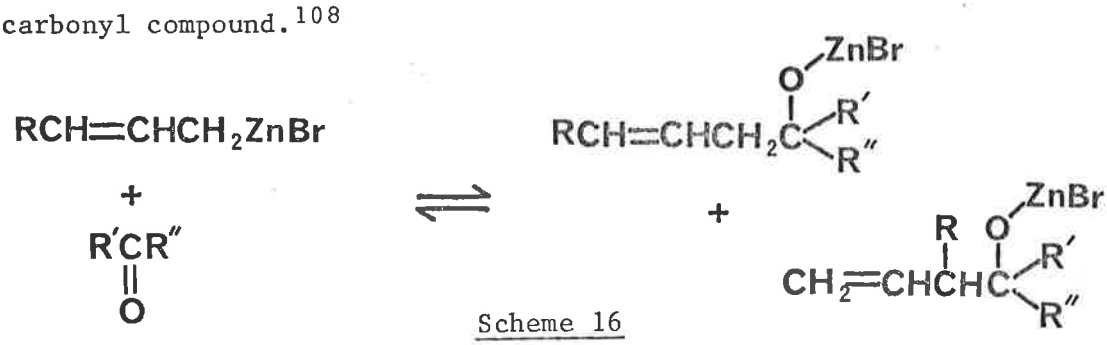


23



88

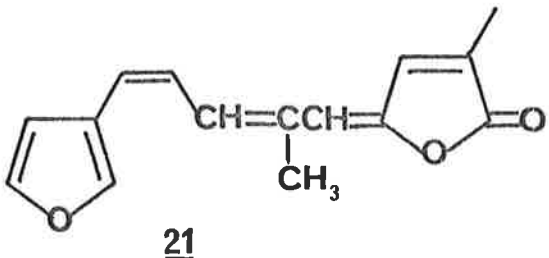
The formation of allylic metal alkyls is often complicated by rearrangements. The isomerisations of allylic Grignard reagents[90,106] and Reformatsky reagents are well known.[41] Studies have shown that the amount of rearrangement is affected by the steric bulk of the reacting carbonyl compound,[106,107] as was noted with propargylic zinc alkyls[89] (Scheme 16). The linear product is thermodynamically more stable and the reaction has a degree of reversibility which may allow an equilibration of the product carbinols to occur, depending on the steric bulk of the carbonyl compound.[108]



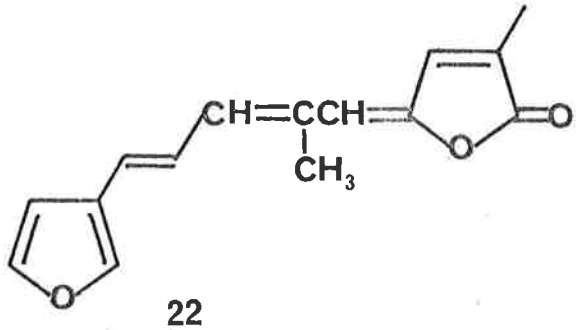
Scheme 16

It is therefore apparent that a Reformatsky reaction with the $\Delta^2 Z$-bromide 88 to form the $\Delta^8 Z$-isomer 21 is not feasible, as any reversible isomerisation of the zinc alkyl during the reaction would produce the more stable *E*-olefin. However, the $\Delta^2 E$-bromide 23

could lead to the Δ^8E-dihydrofreelingyne isomers 22.



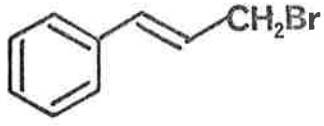
21



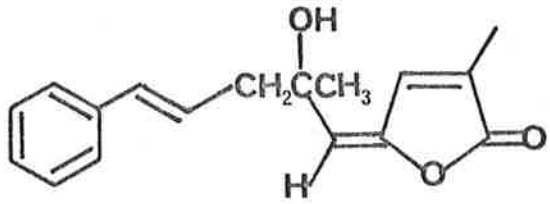
22

E-cinnamyl bromide 89 was used as a model for the furyl bromide 23 in the Reformatsky reaction with the Δ^4E-enol-lactone 42. Only a very low yield of a 1:1 mixture of the carbinols 90 and 91 was obtained under a variety of reaction conditions. The major product was formed by coupling of the zinc alkyl to give compounds of the type 92. The amount of coupling product 92 was not appreciably minimized under conditions of high dilution or by using the magnesium alkyl.[90]

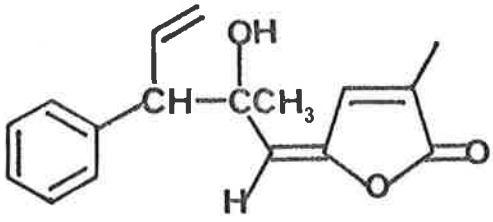
This approach to the Δ^8E-dihydrofreelingyne isomer 22 was unsatisfactory, and it was not pursued further. The preparation of the Δ^8E-isomer 22 by reduction of the freelingyne isomers 85 and 86 was not possible since the reagents which would reduce the triple bond in a *trans*-manner (e.g. lithium aluminium hydride[35,36] or metal-ammonia solutions[37,38]) would also reduce the lactone ring.



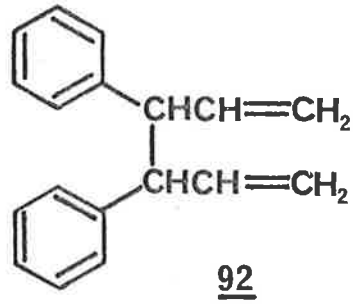
89



90

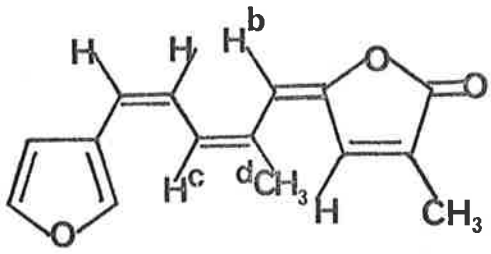


91



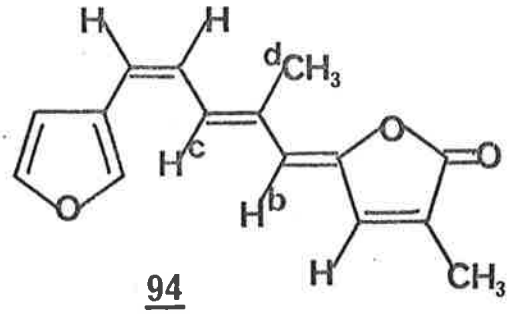
92

However, the Δ^8Z-isomers 21 were readily prepared by catalytic hydrogenation of the freelingyne isomers 85 and 86 over a poisoned catalyst.[34] Hydrogenation of the Δ^4E,Δ^6Z-isomer 85 gave the $\Delta^4E,\Delta^6Z,\Delta^8Z$-dihydrofreelingyne isomer 93. A similar hydrogenation of freelingyne 86 produced the $\Delta^4Z,\Delta^6E,\Delta^8Z$-dihydrofreelingyne isomer 94.



93

H^b δ6.34 J_{cd}1.5Hz



94

H^b δ5.65 J_{cd}1.0Hz

The Δ^4E,Δ^6E-freelingyne isomer 87 was not available in the pure state and the corresponding Δ^8Z-dihydrofreelingyne isomer was not prepared. The positions of resonance of the protons H^b and the relative magnitudes of the allylic coupling constants J_{cd} of the lactones 93 and 94 showed that the Δ^4 and Δ^6-double bonds had retained their configuration from the parent compounds 85 and 86. The analysis of the protons of the Δ^8-double bond in the NMR spectra of 93 and 94 was not possible, as this system gave rise to an ABC or an ABX spectrum which cannot be interpreted by first-order analysis.[109,110] Furthermore, some of the resonances were concealed beneath the furyl C4' proton resonance. However, as Lindlar hydrogenations are known to produce Z-isomers[34,111] the configuration of the Δ^8-double bonds of 93 and 94 was assigned

as Z.*

A comparison of the synthetic dihydrofreelingyne isomers 93 and 94 with the natural product 17 showed them to be different, thus the stereochemistry of 17 remained unknown. A successful approach to the synthesis of 17 is outlined in Chapter 2.

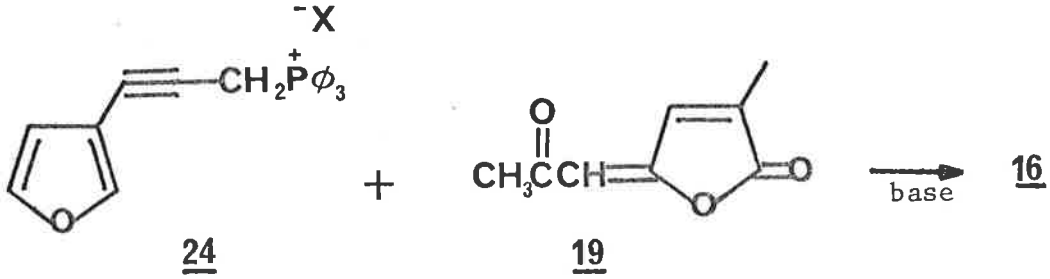
---

* The $\Delta^4Z,\Delta^6E,\Delta^8E$-dihydrofreelingyne isomer 158, prepared by an unambiguous method in Chapter 2, was shown to be different from the dihydro-isomer 94 which had been assigned the $\Delta^4Z,\Delta^6E,\Delta^8Z$-configuration. This confirmed that the hydrogenation of freelingyne 86 to 94 had proceeded in a *cis*-manner.

Section 2 Approaches using a Wittig reaction

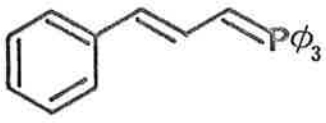
a. The reaction of phosphoranes with enol-lactones.

Perhaps the most immediately attractive route to freelingyne 16 is the Wittig reaction represented by Scheme 2A. Both isomers of the enol-lactone 19 are available (42 and 43) and the phosphonium salt 24 is readily prepared from the bromide 18.[29] The expected Wittig reaction could conceivably give a mixture of $\Delta^6 Z$ and *E*-isomers of freelingyne 16, thus providing a synthesis of the four stereoisomers of freelingyne 16.

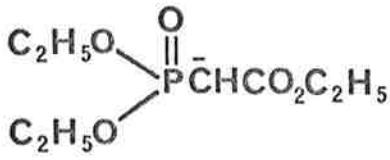


Scheme 2A

Reynolds has explored this approach but was unable to isolate any identifiable products.[29] Further investigations made in this department of the reaction of the enol-lactone 42 with *E*-cinnamyl phosphorane 95 and the phosphonate carbanion 27, have failed to provide any evidence for the expected olefins.[44]



95



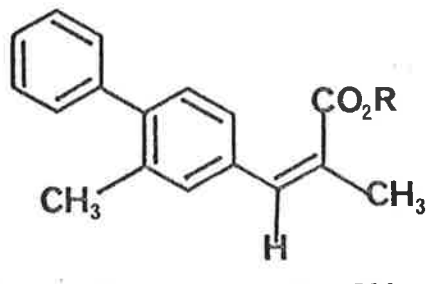
27

Since no products had been identified from these reactions, it was not possible to determine the nature of any side reactions occurring. It was considered that a careful re-investigation of the reaction may provide some useful information.

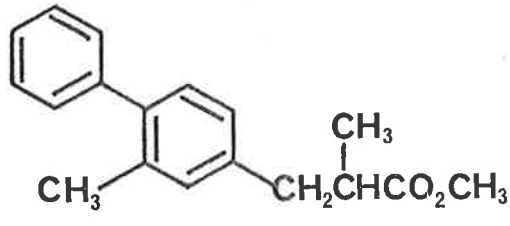
The reaction of the Δ^4*E*-enol-lactone 42 and the *E*-cinnamyl phosphorane 95 was studied at room temperature using sodium hydride as the base to generate 95. The reaction mixture was carefully purified by preparative thin layer chromatography to give a product which was consistently obtained in 25-30% yield. The mass spectrum of this compound indicated that it had the gross structure expected for a product of a 1:1 combination of reactants with the loss of triphenylphosphine oxide.

The NMR spectrum of this compound showed resonances at δ8.0 (1H, br.s), 7.4 (5H, s, aromatic), 7.2 (3H, br.s, olefinic), 6.7 (1H, br.s, olefinic), 2.36 (3H, s, =C-CH_3) and 2.0 (3H, d, J1.5Hz, =C-CH_3). Spin decoupling studies showed that the olefinic proton at δ6.7 was coupled to the methyl group at δ2.0. The broad resonance at δ8.0 was removed by D_2O exchange, indicating the

presence of an acidic proton. This was confirmed by the mass spectrum which showed a molecular ion at *m/e* 252 ($C_{17}H_{16}O_2$) together with a strong daughter ion at *m/e* 207 which was produced by the loss of $^{\bullet}COOH$ from the molecular ion (substantiated by a metastable peak at *m/e* 170). The compound was shown to be an α,β-unsaturated acid by the infrared spectrum (ν_{max} 1680cm^{-1}). The ultraviolet spectrum showed absorptions at 240 and 260nm, suggesting that two chromophoric groups were present. The structure 96 was tentatively assigned to this compound.



R=H 96 R=CH$_3$ 97

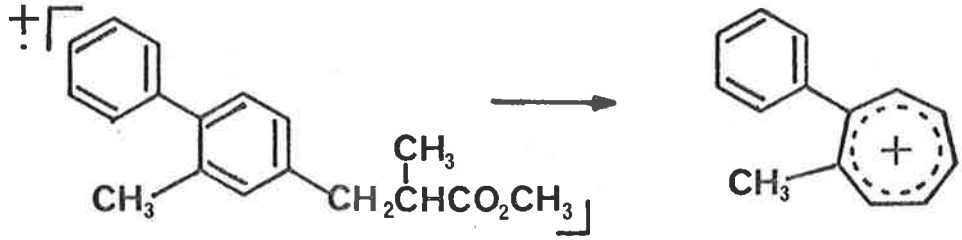


98

Several further experiments provided corroborating evidence for the structure 96. The methyl ester 97 was readily obtained by the treatment of the acid 96 with diazomethane.[112] The NMR spectrum of 97 showed a resonance at δ3.6 (3H, s, OCH_3) while the mass spectrum indicated a molecular ion at *m/e* 266 ($C_{18}H_{18}O_2$) together with a daughter ion at *m/e* 207 which was caused by the loss of $^{\bullet}CO_2CH_3$.

The unsaturated ester 97 was hydrogenated over platinum oxide catalyst[113] to produce the saturated ester 98. The infrared

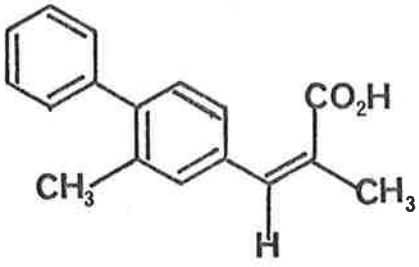
spectrum showed a carbonyl absorption at ν 1730cm^{-1} confirming that the double bond had been reduced. The ultraviolet spectrum showed only an absorption at 237nm, which was attributed to the biphenyl system,[114] with no longer wavelength absorption. The most significant evidence was provided by the mass spectrum which showed a molecular ion at *m/e* 268 ($C_{18}H_{20}O_2$) and a strong daughter ion at *m/e* 181. This was due to the loss of $^{\bullet}CH(CH_3)CO_2CH_3$ from the molecular ion (substantiated by a metastable peak at *m/e* 122) to give the stable tropylium ion 99 (Scheme 17). Further decomposition of this ion was in accord with the proposed structure 98.



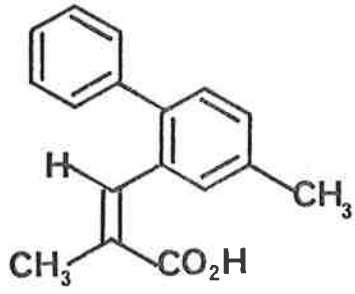
98 *m/e* 268 **99** *m/e* 181

Scheme 17

A consideration of possible reaction mechanisms suggests that two biphenyl products 96 or 100 are likely to be produced. With the limited amount of material available it has not been possible to distinguish between the two possibilities.

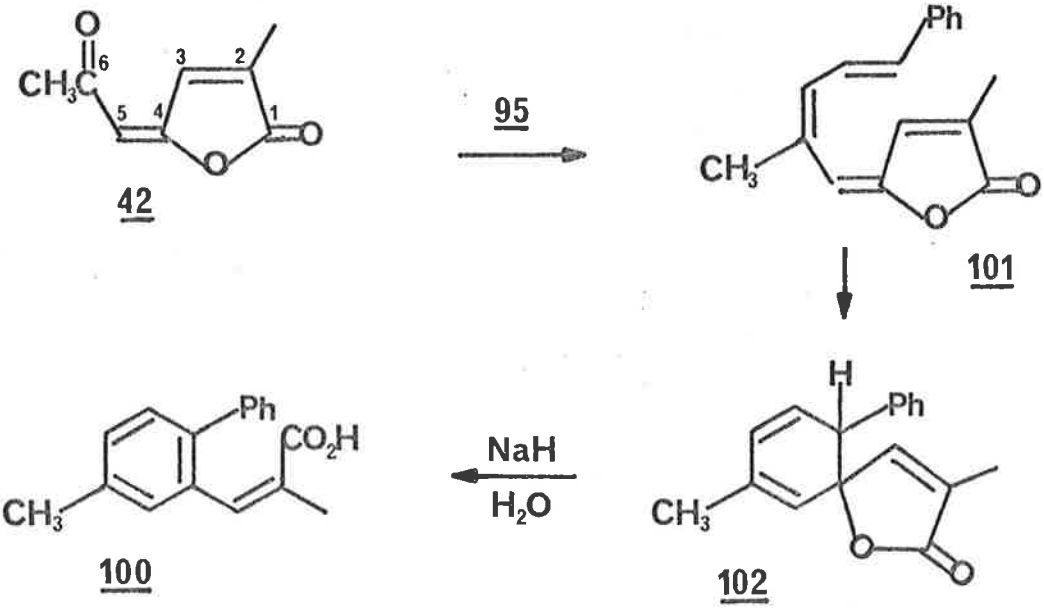


96



100

The biphenyl 96 could be formed by the initial attack of the phosphorane 95 at the C4 position of the enol-lactone 42. This may be by a direct Michael attack of the phosphorane 95 or by an initial base catalysed hydrolysis of the lactone followed by a Wittig reaction. A number of schemes can be formulated for the base catalysed cyclisation of the intermediate to form the biphenyl 96.



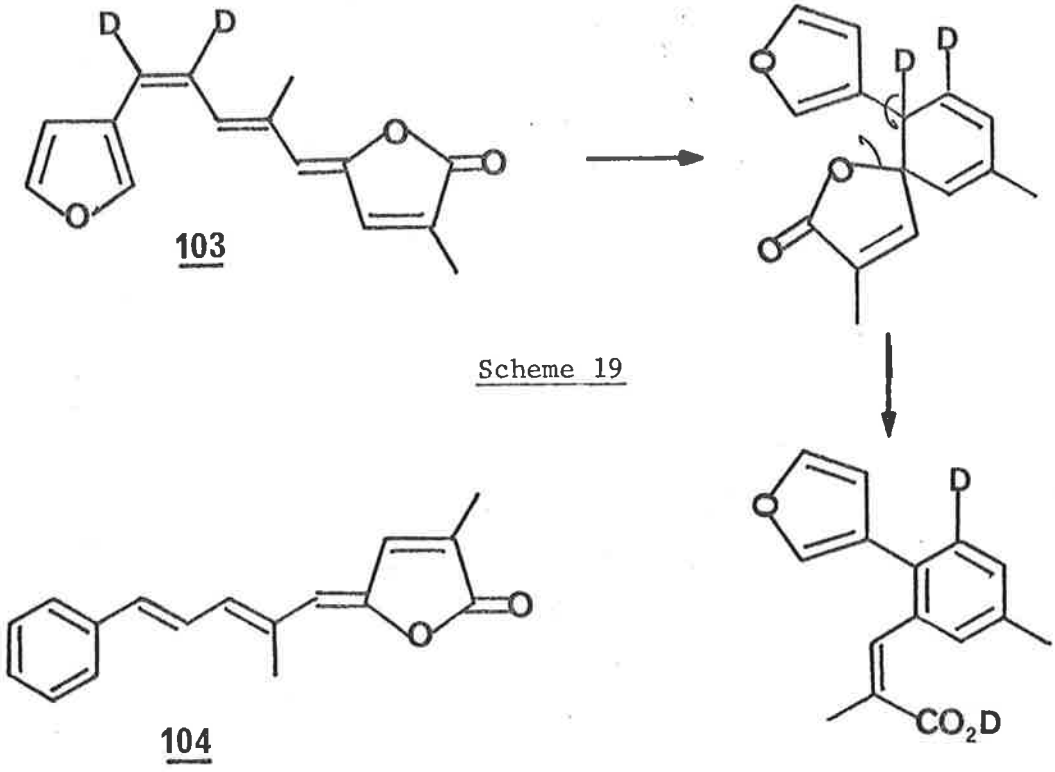
Scheme 18

A mechanism leading to the alternative product 100 is shown in Scheme 18. This involves the expected Wittig reaction of the phosphorane 95 at the C6 position of the enol-lactone 42 followed by an intramolecular Diels-Alder cyclisation[67] of the linear triene 101. In the presence of base the cyclohexadiene 102 would aromatise to give the biphenyl 100. This mechanism does not seem as plausible, since the dihydroisomer 101 can be prepared under the same reaction conditions (see Chapter 2) without the formation of any biphenyl products.

However, an analagous mechanism must be postulated for a rearrangement that has been noted in the mass spectra. It was observed that the main fragmentation in the mass spectra of the freelingyne isomers 85, 86 and 87 prepared earlier, was the loss of CO_2.

In the dihydrofreelingyne isomers 93 and 94 however, the major fragmentation of the molecular ion was the loss of $^{\bullet}CO_2H$. To determine whether the hydrogen atom came from the C8 or C9 positions, freelingyne 86 was treated with deuterium gas in the presence of Lindlar catalyst[34] to produce the di-deutero olefin 103.

The mass spectrum of 103 showed only the loss of $^{\bullet}CO_2D$ which confirmed that the hydrogen atom was coming specifically from the C8 or C9 position in the isomers 93 and 94. A Diels-Alder mechanism similar to that of Scheme 18 can account for this specificity (Scheme 19).



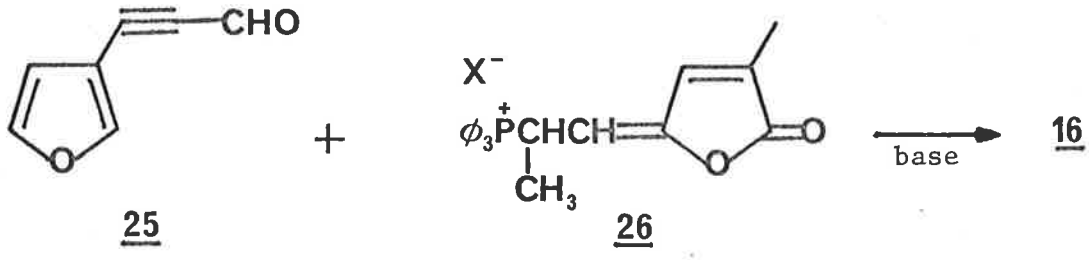
Scheme 19

It is noteworthy that the phenyl analogue of dihydrofreelingyne 104 (prepared in Chapter 2), which would be expected to rearrange by the mechanism shown in Scheme 19 to the biphenyl 100, has an identical mass spectrum to the isolated biphenyl 96 or 100. This suggests that the actual structure of the isolated biphenyl product is 100, although it is possible that the structure 96 could give rise to an identical mass spectrum.

This approach to freelingyne 16 was not pursued further as it appeared that, under the reaction conditions employed, the cyclisation process leading to the product of the type 100 was more favourable than the formation of the desired linear olefin 104.

b. Reaction of the phosphorane 28 with aldehydes

Although the Wittig reaction of the enol-lactone 42 with the phosphorane 95 discussed in part a. was unsuccessful in producing the freelingyne type isomers, the reaction shown in Scheme 2B appeared promising, as aldehydes are more reactive than ketones towards stabilised phosphoranes.[45,46]

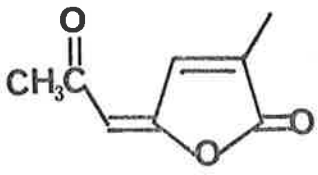


25 + 26 → 16

Scheme 2B

Previous workers had tried unsuccessfully to prepare the phosphonium salt 26.[29,57] The enol-lactone 42 was reduced to the alcohol 105 and a variety of mild methods were used in attempts to effect the conversion to the halide 106. As the halide 106 was very unstable, the conversion to the phosphonium salt 26 could not be carried out.

It is likely that any reaction carried out on the alcohol 105 which involves the formation of an intermediate carbonium ion at C6 would lead to isomerisation of the Δ^4-double bond. Similarly, generation of the phosphorane 28 from the phosphonium salt 26 could also lead to equilibration of the



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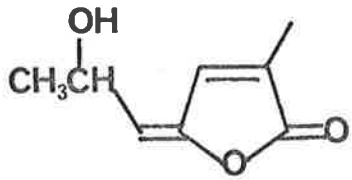

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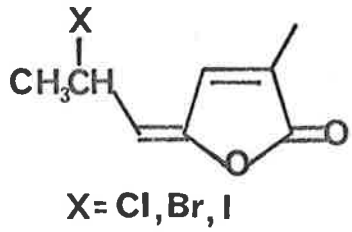
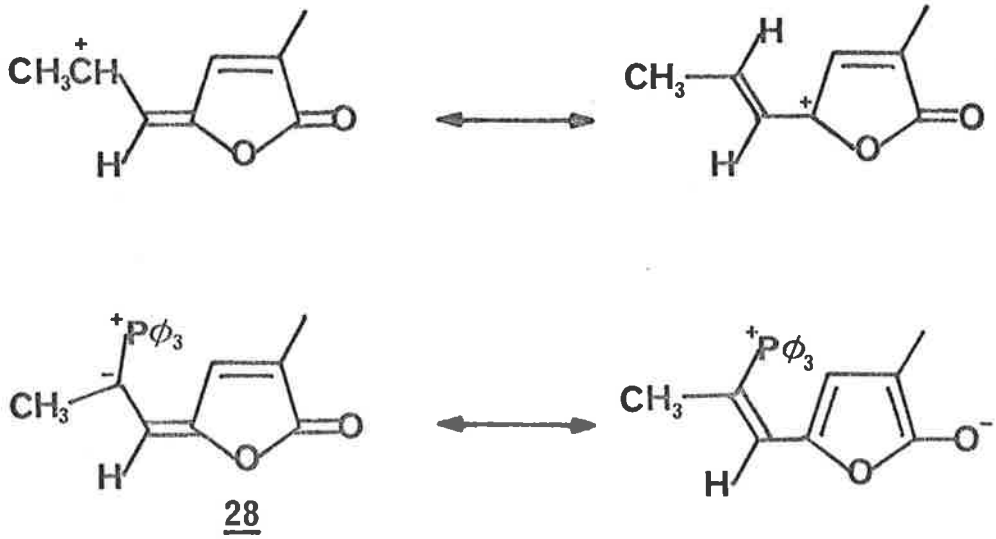


106

Δ^4-double bond by charge delocalisation (Figure 2). The rate of this isomerisation would be considerably slower at lower temperatures,[47] and some selectivity could therefore be achieved providing that the Wittig reaction proceeds at these temperatures.

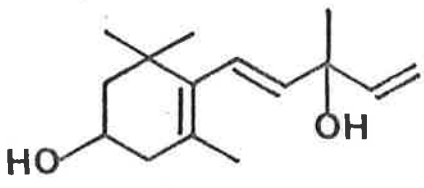


28

Figure 2

A mild method for the formation of phosphonium salts directly from allylic alcohols by the treatment with triphenylphosphonium bromide[53] has been used successfully.[58] The

E-phosphonium salt 108 has been formed by the rearrangement of the allylic alcohol 107 when it was treated with triphenylphosphonium bromide.[115] This suggests that the salt formation involves a carbonium ion intermediate and that the product phosphonium salt 108 is the thermodynamically most stable isomer. Therefore, it is probable that such a reaction with the alcohol 105, although avoiding the isolation of the unstable halide 106, would allow isomerisation of the Δ^4-double bond.



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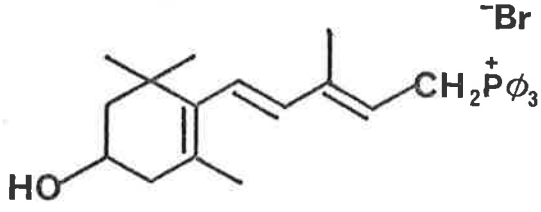
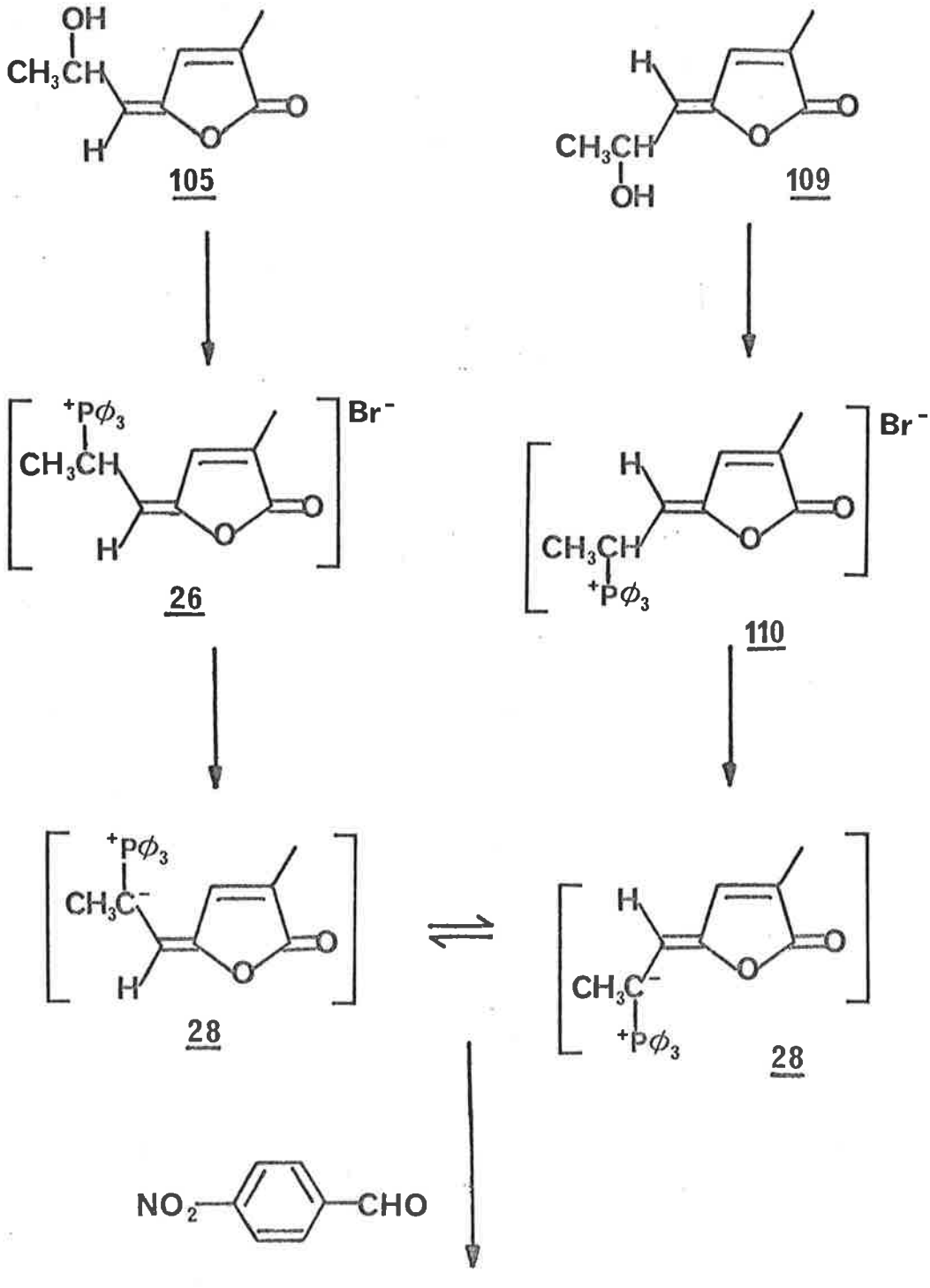


108

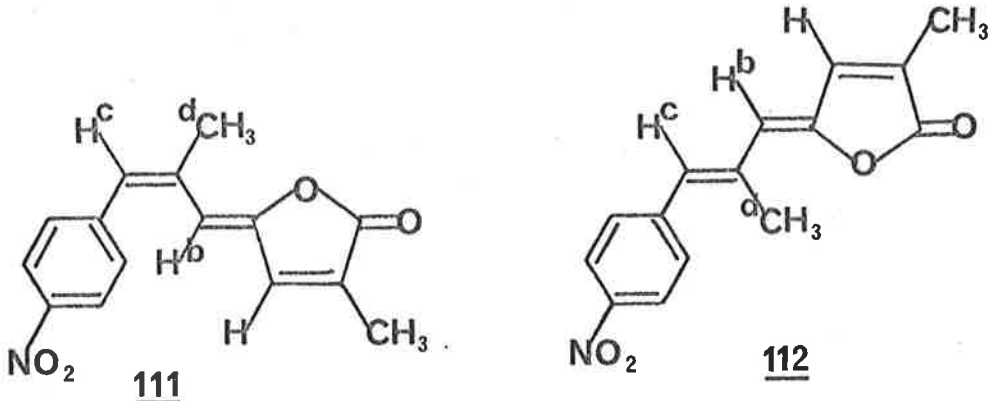
The alcohols 105 and 109 were formed cleanly by the reduction of the enol-lactones 42 and 43 respectively under neutral conditions with zinc borohydride[116] (Scheme 20). The NMR spectra showed that the stereochemistry of the Δ^4-double bond had been retained in both alcohols 105 and 109. The C5 proton of the Δ^4*E*-alcohol 105 resonated 0.37 ppm downfield from the C5 proton of the Δ^4*Z*-alcohol 109. This is due to the deshielding influence of the adjacent oxygen atom of the lactone ring in 105, as previously discussed (p. 18).

The phosphonium salt 26 was obtained by the treatment of the Δ^4*E*-alcohol 105 with triphenylphosphonium bromide. Since the



111 + 112

Scheme 20 continued



Scheme 20

NMR spectrum of 26 was complex it was not possible to determine whether the Δ^4-double bond had retained the *E*-configuration. The Δ^4Z-alcohol 109 was similarly converted to the phosphonium salt 110 of unknown stereochemistry. The phosphonium salts 26 and 110 were purified by preparative TLC but were not obtained crystalline.

The phosphonium salt 26 was converted into the phosphorane 28 with base in the presence of *p*-nitrobenzaldehyde,* and two olefinic products 111 and 112 were isolated, (Scheme 20). The same two products 111 and 112 were obtained when the phosphonium salt 110 was treated with base under the same conditions.

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* *p*-nitrobenzaldehyde was used for the initial studies of the reaction because it was expected that the NMR spectra of the product olefins would be more readily interpreted. A more appropriate model would be cinnamaldehyde but the products would have a complex olefinic region and identification of the resonances would be more difficult.

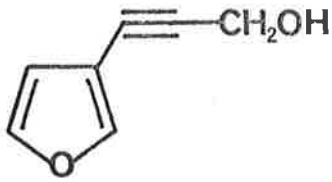
The isomerisation of the Δ^4-double bond could well have occurred when the phosphonium salts 26 and 110 were prepared, since it was not possible to determine whether the salts were isomerically pure. However, it is also likely that the phosphoranes 28 were in equilibrium, leading to complete isomerisation of the Δ^4-double bond.

The stereochemistry of the lactones 111 and 112 was assigned from a consideration of the NMR spectra, (Scheme 20). The configuration of the Δ^6-double bond followed from the relative magnitude of J_{cd}. As previously discussed, it is considered that the larger coupling constant occurs in the olefin with the *Z*-configuration.[99] On this basis, the lactone 111 was assigned the $\Delta^6 Z$-stereochemistry (J_{cd}1.4Hz) and the lactone 112 the $\Delta^6 E$-stereochemistry (J_{cd}0.9Hz). The position of resonance of the proton H^b for both lactones 111 and 112 was in the region (<δ6.0) noted for similar lactones (80,86) with $\Delta^4 Z$-stereochemistry. The lower field resonance of proton H^b in the lactone 111 can be attributed to the deshielding influence of the adjacent (*cis*-) phenyl group.*

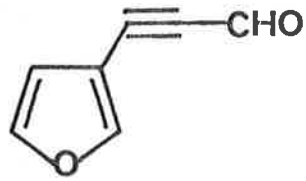
---

* A similar effect is observed in the NMR spectra of the isomeric acids 165 and 166. The C3 proton (H^b) of the $\Delta^4 Z$ acid 166 is deshielded by the phenyl group and resonates 0.3 ppm at lower field relative to the proton H^b of the $\Delta^4 E$ acid 165 (p. 92).

The preparation of freelingyne 16 by a Wittig reaction with the phosphorane 28 required the furyl propargyl aldehyde 25 which was prepared in fair yield[117] by the oxidation of the furyl propargyl alcohol 70 (p. 29) with manganese dioxide.[118]*



70



25

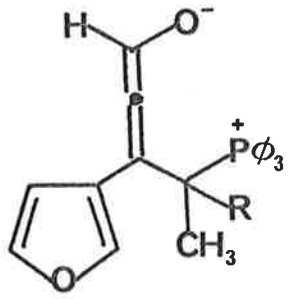
The reaction of the phosphorane 28 with the aldehyde 25 at room temperature gave a mixture of two isomers in low yield. These were identified as the Δ^4E,Δ^6Z-lactone 85 and the Δ^4Z,Δ^6E-lactone 86 (freelingyne) by comparison of their spectral properties with the lactones 85 and 86 prepared in Section c. The formation of only 85 and 86 of the four possible isomers confirmed the earlier suggestion (p. 43 and 44) that these are the most stable thermodynamically.

The low yield of the lactones 85 and 86 may have been due to a competing Michael-type attack[122] of the phosphorane 28 on

---

* An attempt to oxidise the alcohol 70 with acetic anhydride and dimethylsulphoxide[119] produced only the acetate. This was surprising, for phenyl propargyl alcohol 132 could be oxidised to the aldehyde 134 in good yield. Apparently the alcohol 70 is converted to the acetate at a faster rate than it is oxidised, a fact that has been observed with some other alcohols.[120,121]

the acetylenic aldehyde 25. Similar additions of phosphoranes to activated double bonds have been observed.[123] This would form an allenic betaine 113 that would be incapable of further reaction to give the desired olefins.

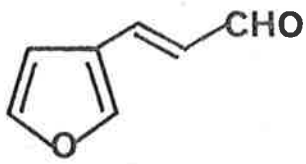


113

Although this approach provided a second route to freelingyne 86, it was not stereoselective. Some increase in stereoselectivity may have been achieved at lower temperatures, when the rate of isomerisation would be considerably slower. However, as the reaction was of low yield this modification was not explored. The stereochemical assignment of freelingyne 86 prepared by this route was still dependent upon the assumption that the allylic coupling constant J_{cisoid} is larger than $J_{transoid}$.[96]

Initially this approach appeared very attractive since it could be used for the preparation of the dihydrofreelingyne isomers 17 from the aldehyde 114. However, since isomerisation of the Δ^4-double bond was taking place, either during the phosphonium salt formation or when the phosphorane 28 was generated, this approach could lead to a complex mixture of the stereoisomers of

17. This mixture would not be readily separated nor the component isomers identified. A more successful approach outlined in Chapter 2 rendered this synthetic route to the dihydrofreelingyne isomers 17 unnecessary and it was not pursued.



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CHAPTER 2

SYNTHESES INVOLVING THE FINAL FORMATION OF THE Δ^4 AND Δ^8-DOUBLE BONDS

Section 1 Syntheses involving the final formation of the Δ^4-double bond

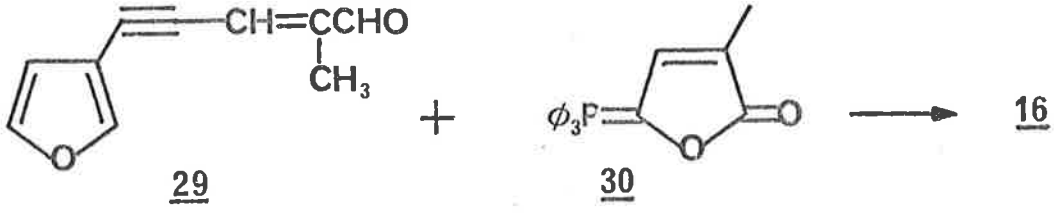
Section 2 Syntheses involving the final formation of the Δ^8-double bond

In the introduction, two routes for the syntheses of freelingyne 16 and dihydrofreelingyne 17 involving the formation of the Δ^4-double bond were outlined. The approaches (Schemes 4A,B) employing a Wittig reaction are discussed in Section 1 of this Chapter. The approach to dihydrofreelingyne 17 which involves the formation of the Δ^8-double bond (Scheme 5) is outlined in Section 2 of this Chapter.

Section 1 Syntheses involving the final formation of the Δ^4-double bond

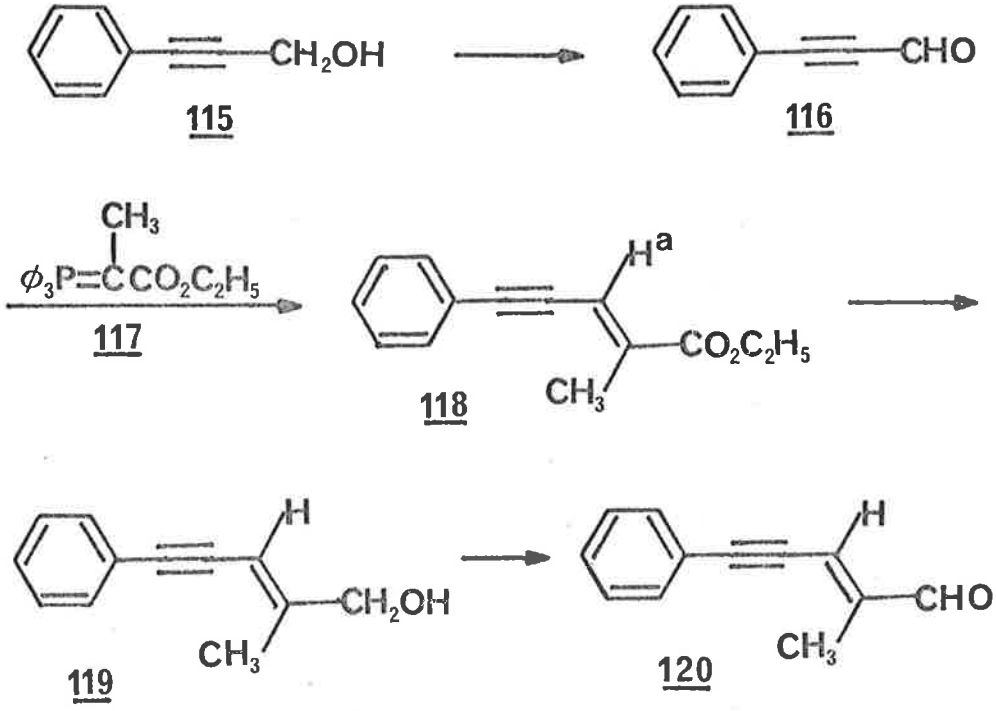
a. Reaction of the butenolide phosphorane 30 with yn-ene aldehydes

Two non-stereoselective syntheses of freelingyne 16 were described in Chapter 1. The structures of the freelingyne isomers 85, 86 and 87 were assigned from an interpretation of the NMR spectra. The stereochemistry of the Δ^6-double bond of the isomers 85, 86 and 87 was in some doubt since it has been shown that the relationship between the magnitude of allylic coupling constants and the stereochemistry of the double bonds is variable.[28,99] The stereochemistry of the Δ^4-double bond was more certain, as it could be related to the known enol-lactones of the type 42. It was therefore desirable to prepare freelingyne 16 by an approach in which the assignment of the stereochemistry of the Δ^6-double bond was unambiguous. Such a method is outlined in Scheme 4A. This required the preparation of an aldehyde such as 29 in which the double bond had a known stereochemistry. The aldehyde 29 could then undergo a Wittig reaction with the phosphorane 30 to produce freelingyne 16 with the concurrent formation of the Δ^4-double bond.



Scheme 4A

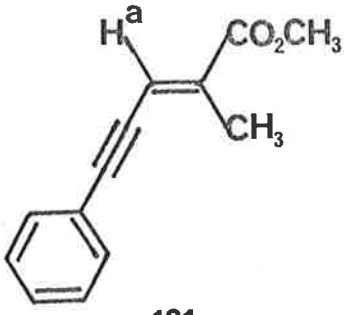
As the 3-substituted furan compounds were relatively inaccessible, the syntheses were carried out using the phenyl analogues. The NMR spectra of the phenyl analogues of the freelingyne isomers 79, 80 and 81 were very similar to those of the furyl isomers 85, 86 and 87 respectively (compare Tables 3 and 4, Chapter 1). Therefore, an unambiguous synthesis of the phenyl analogue of freelingyne could be accurately related to the correct structure of freelingyne. The aldehyde required for the reaction with the phosphorane 30 was therefore 120. A number of methods for the preparation of some related pentadiene aldehydes are discussed in part b. (p. 82). As a consequence of this study, the aldehyde 120 was prepared by the route outlined in Scheme 21.



Scheme 21

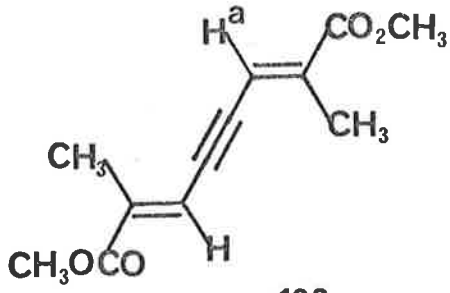
The readily available[91] alcohol 115 was converted to the aldehyde 116 with dimethylsulphoxide and acetic anhydride.[119] Other oxidation procedures attempted gave poorer yields. Reactions with manganese dioxide[118] and dipyridine-chromium(VI) oxide[124] gave unsatisfactory recoveries of the aldehyde 116, possibly because of co-ordination of the triple bond with the metal salts.[125] Similarly, a procedure with nickel peroxide,[126] which has been used with other acetylenic alcohols,[127] gave the aldehyde 116 in only fair yield.

The Wittig reaction between the phosphorane 117[128] and the aldehyde 116 gave an excellent yield of the olefinic ester 118. This reaction would be expected to yield the ester 118 with the stereochemistry shown, *via* the intermediate *threo*-betaine.[129,130] The *E*-configuration of the ester 118 followed conclusively from the NMR spectrum which showed, amongst other resonances, δ6.8 (1H, q, J1.5Hz, C3H(H^a)) and 2.14 (3H, d, J1.5Hz, =C-CH_3). No resonance attributable to the *Z*-olefin was observed in the NMR spectrum and gas chromatographic analysis confirmed that the ester 118 was homogeneous. The chemical shift of the olefinic proton H^a of 118 agreed well with those reported for the *E*-methyl ester 121[131] and the *E*,*E*-ester 122.[132]



121

H^a δ6.83

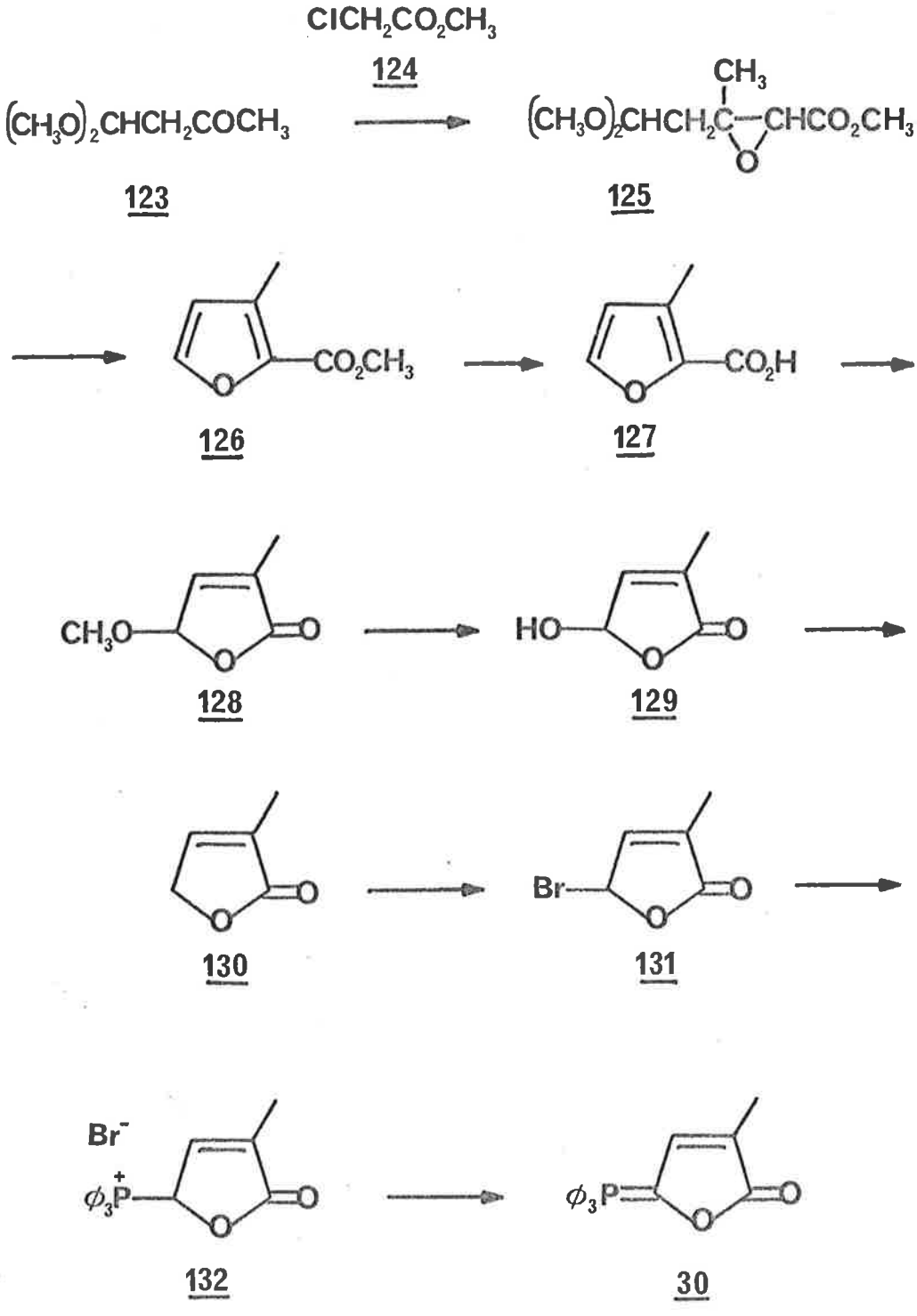


122

H^a δ6.81

The *E*-olefinic ester 118 was reduced to the *E*-alcohol 119 with aluminium hydride, prepared *in situ* from lithium aluminium hydride and aluminium chloride.[133,134] The aldehyde 120 was obtained in good yield by the oxidation of 119 with silver carbonate on celite.[135] The NMR spectrum showed that only one olefinic proton was present (δ6.5, q, J1.4Hz) whilst the chemical shift and the magnitude of the coupling constant indicated that the aldehyde 120 had retained the *E*-stereochemistry. This was confirmed when the aldehyde 120 was converted to the known[131] *E*-methyl ester 121 with manganese dioxide and sodium cyanide.[136] This mild conversion is known to proceed without causing double bond isomerisations.[136]

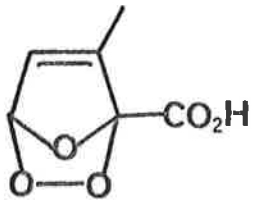
The known phosphorane 30, required for the Wittig reaction with the aldehyde 120 was prepared by the method outlined in Scheme 22. A Darzens glycidic ester condensation[137] between methyl chloroacetate 124 and the dimethoxybutanone 123 gave the glycidic ester 125 which underwent a thermal cyclisation to give methyl 3-methyl-2-furoate 126. The acid 127, prepared by


ClCH2CO2CH3
124
(CH3O)2CHCH2COCH3
123
CH3
(CH3O)2CHCH2C—CHCO2CH3
O
125
CO2CH3
126
CO2H
127
CH3O
128
HO
129
130
Br
131
Br⁻
ϕ3P⁺
132
ϕ3P
30

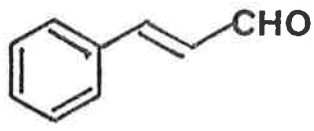
Scheme 22

hydrolysis of the ester 126, was obtained in 52% overall yield from the ketone 123.

Dye-sensitised photo-oxygenation[138] of the acid 127 gave the intermediate cyclic peroxide adduct 133 by the addition of singlet oxygen to the diene system.[139] The adduct 133 reacted with the methanol used as the solvent to form the pseudoester 128, which was hydrolysed by acid during the isolation procedure to form the hydroxylactone 129.



133

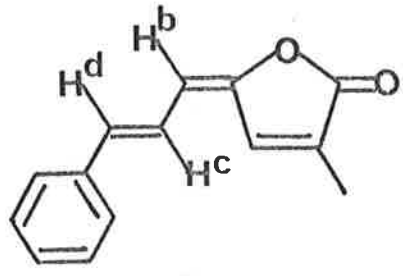


134

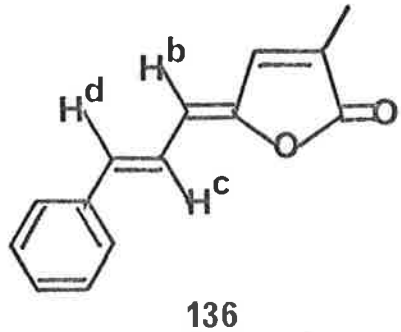
Some practical difficulties were encountered with the oxygenation procedure. Occasionally the oxygenation ceased as the sensitiser apparently became oxidised. When this occurred it became necessary to hydrolyse the mixture and separate the hydroxylactone 129 from the acid 127, a tedious and inefficient process. The reason for this anomalous behaviour is unclear, but it was found to be less prevalent when the reaction was performed in a water-cooled vessel and rose bengal was used as the sensitiser in place of methylene blue. Under these conditions, the hydroxylactone 129 could be obtained in greater than 90% yield. The reduction of 129 with alkaline sodium borohydride[138] gave the

lactone 130[140] which was converted to the bromolactone 131 on treatment with N-bromosuccinimide.[141] The reaction of the bromolactone 131 and triphenylphosphine gave the phosphonium salt 132 as a sticky solid. The phosphorane 30, obtained as a yellow solid from the salt 132 by treatment with alkali, was unstable and decomposed slowly on storage at -5^{o} and rapidly at room temperature.

The Wittig reaction of the phosphorane 30 with *E*-cinnamaldehyde 134 was studied to determine suitable reaction conditions for the aldehyde 120. It was found that the best yields were obtained when the phosphorane 30 was generated from the salt 132 with sodium hydride *in situ* with cinnamaldehyde 134. Under these conditions the product olefin was obtained in 39% yield. The NMR spectrum (Table 5) indicated that the product was a 1:1 mixture of the $\Delta^{4}E,\Delta^{6}E$-isomer 135 and the $\Delta^{4}Z,\Delta^{6}E$-isomer 136.



135



136

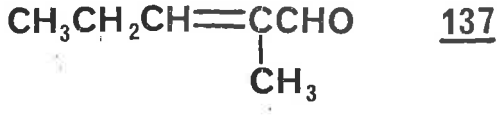
H^{b}	δ6.35, d, J_{bc} 10Hz	H^{b}	δ5.9, d, J_{bc} 11Hz
H^{c}	~δ7.3	H^{c}	~δ7.3
H^{d}	δ6.8, d, J_{cd} 16Hz	H^{d}	δ6.8, d, J_{cd} 16Hz

Table 5

The proton H^b resonated at lower field in the Δ^4E-isomer 135 due to the deshielding effect of the oxygen atom of the lactone ring (p. 18). The coupling constant (J_{cd}16Hz) confirmed that the Δ^6-double bond had retained the *E*-stereochemistry of the aldehyde 134.[142]

When the phosphorane 30 was generated in the presence of the aldehyde 120, no products were obtained. The reaction was attempted under a wide variety of conditions but in all cases only the aldehyde 120 was isolated and there was no evidence of any olefin formation.

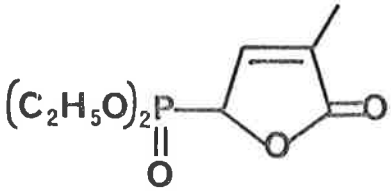
It was apparent that the phosphorane 30 would not react with an aldehyde with an α-methyl group, as the reaction with 2-methyl-2-pentenal 137[143] also failed. Apparently, the increased steric hindrance of the methyl group prevents the attack of the phosphorane 30 on the carbonyl group. The phosphorane 30 is stabilised by conjugation of the carbanion with the unsaturated lactone and de-stabilised by the oxygen atom of the lactone ring. Therefore the degree of negative charge character at the C4 position may be sufficiently lowered to make the phosphorane 30 a poor nucleophile, and hence less reactive toward aldehydes such as 120 and 137.



137

Phosphonate carbanions are known to be more reactive in olefin-forming reactions than phosphoranes.[40,144] However, a number of different attempts to prepare the required phosphonate ester 138 from the bromolactone 131 failed, as the bromolactone did not appear to be stable under the reaction conditions.[145,146] Trialkyl phosphoranes are known to be more nucleophilic than the corresponding triarylphosphoranes.[147] The electron donating alkyl groups attached to the phosphorus atom apparently increase the electron density on the adjacent carbanion, whilst the aryl groups exert an electron withdrawing effect.[148] It was expected that a trialkyl phosphorane prepared from the bromolactone 131 would be sufficiently nucleophilic to react with α-methyl substituted aldehydes.

The bromolactone 131 was converted into the oily phosphonium bromide 139 with tri-*n*-butylphosphine. This was in turn converted into the readily purified crystalline salt 140 by the addition of an equivalent amount of sodium tetraphenylborate.[149]



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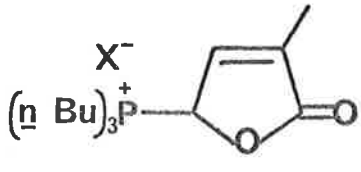
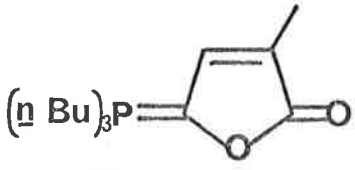


139 X=Br

140 X=B(C$_6$H$_5$)$_4$

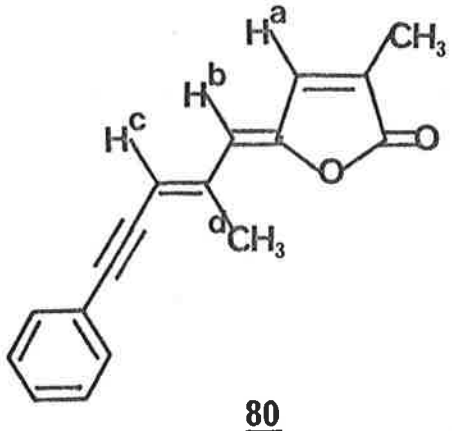


141

When the phosphorane 141 was generated with sodium hydride in the presence of cinnamaldehyde 134, the olefins 135 and 136 (in the ratio of 1:5) were isolated in a yield of 46%, a slight increase over that obtained with the triphenylphosphorane 30.

The reaction of the α-methyl aldehyde 120 and the tributylphosphorane 141 proceeded in the desired manner to give a mixture of two compounds in a yield of 50%. Only the Δ^4E and Δ^4Z isomers were expected from this Wittig reaction, since the stereochemistry of the Δ^6-double bond was determined as *E* by the configuration of the aldehyde 120. Therefore the two products isolated in the ratio of 2:1 were the Δ^4Z,Δ^6E and Δ^4E,Δ^6E-isomers. The assignment of the Δ^4-stereochemistry was dependent upon the chemical shift of the proton H^b (Table 6). It has previously been established (p. 18) that the deshielding effect of the lactone ring oxygen atom causes the C3 proton (H^b) of the Δ^4E-isomer to resonate at lower field than the proton H^b of the Δ^4Z-isomer. Therefore the product with the proton H^b at δ6.32 was assigned the Δ^4E,Δ^6E-stereochemistry and the product with the proton H^b at δ5.64 the Δ^4Z,Δ^6E-stereochemistry.

The two products were compared with the isomers 79, 80 and 81 prepared by the pyrolysis of the acetates 77 or 78 (Chapter 1). The product assigned the Δ^4Z,Δ^6E-stereochemistry had identical physical and spectral properties to the isomer 80 which had previously been assigned the Δ^4Z,Δ^6E-stereochemistry solely by

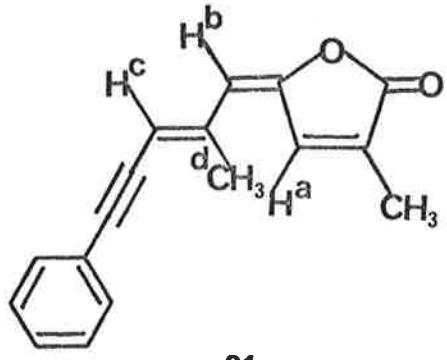


80

H^a δ7.02

H^b δ5.64

H^c δ5.99, J_{cd} 1.2Hz



81

H^a δ7.4

H^b δ6.32

H^c δ5.96, J_{cd} 1.0Hz

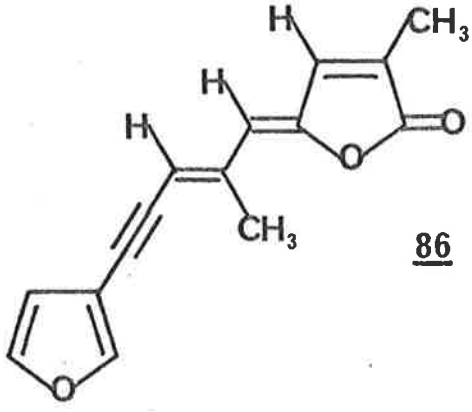
Table 6

a consideration of the NMR spectrum. Similarly, the other product (assigned Δ^4E,Δ^6E) had identical spectral properties to the isomer 81, previously assigned as Δ^4E,Δ^6E. This isomer had not been obtained pure by the acetate pyrolysis route, but was readily purified when prepared by this method, and therefore complete physical and spectral properties were available.

The complete agreement of these stereochemical assignments

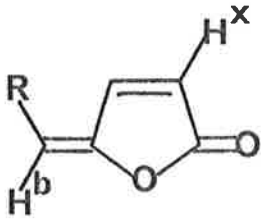
confirmed that the previous interpretations of the NMR spectra that had been made were correct. Thus in these isomers, J allylic, cisoid (79 J_{cd}1.5Hz) is indeed larger than J allylic, transoid (80, J_{cd}1.2Hz; 81 J_{cd}1.0Hz).

Therefore, the configuration of the isomer 80 is firmly established as Δ^4Z,Δ^6E. It follows, from the complete agreement of the NMR spectra of 80 and freelingyne 86 (Tables 3 and 4, Chapter 1) and from the correct interpretation of these spectra, that freelingyne 86 also has the Δ^4Z,Δ^6E-stereochemistry.

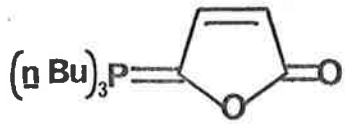


86 Freelingyne

In Chapter 1 it was shown that the stereochemistry of the Δ^4-double bond of the freelingyne isomers was readily assigned by the chemical shift of the C5 proton (H^b, Table 6). This assignment has been confirmed in systems (e.g. 142) where the long-range coupling constant J_{bx} can be measured[61-66] (p. 19).

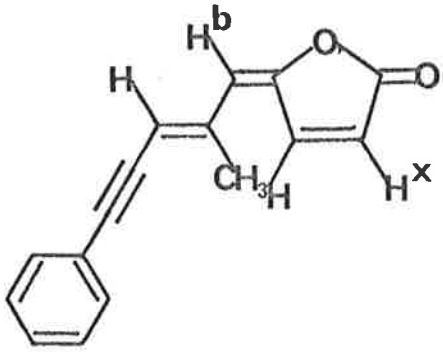


142



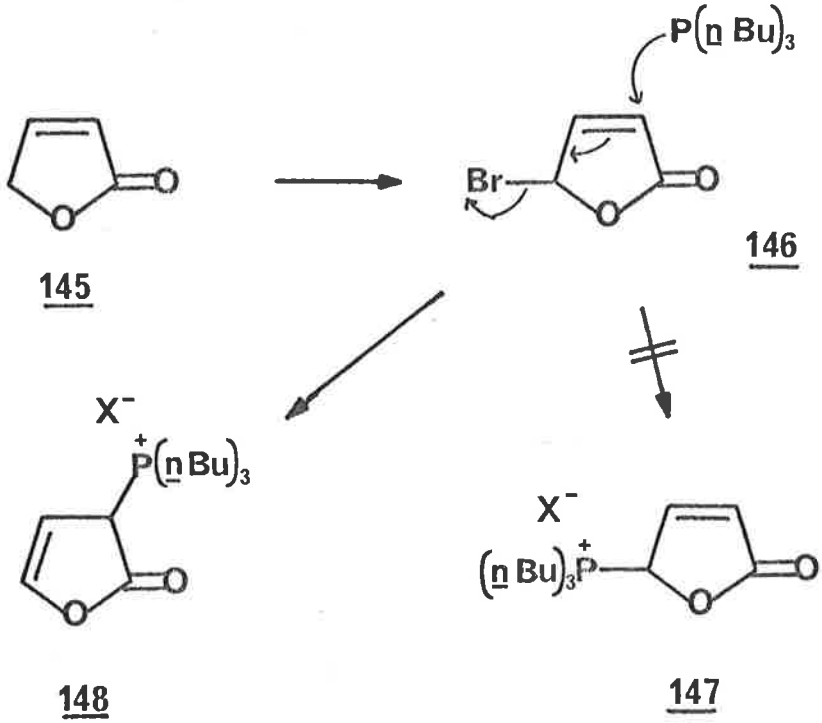
143

Therefore, if the phosphorane 143 could be prepared, a reaction with the aldehyde 120 would give rise to products of the type 144, in which the assignment of the Δ^4-stereochemistry could be confirmed by the measurement of the long-range coupling constant J_{bx}.



144

Crotonolactone 145[150] was converted to the bromolactone 146 by treatment with N-bromosuccinimide.[141] The bromolactone 146 was treated with tri-*n*-butylphosphine and the intermediate oily bromide was converted into the crystalline tetraphenylborate salt (Scheme 23).



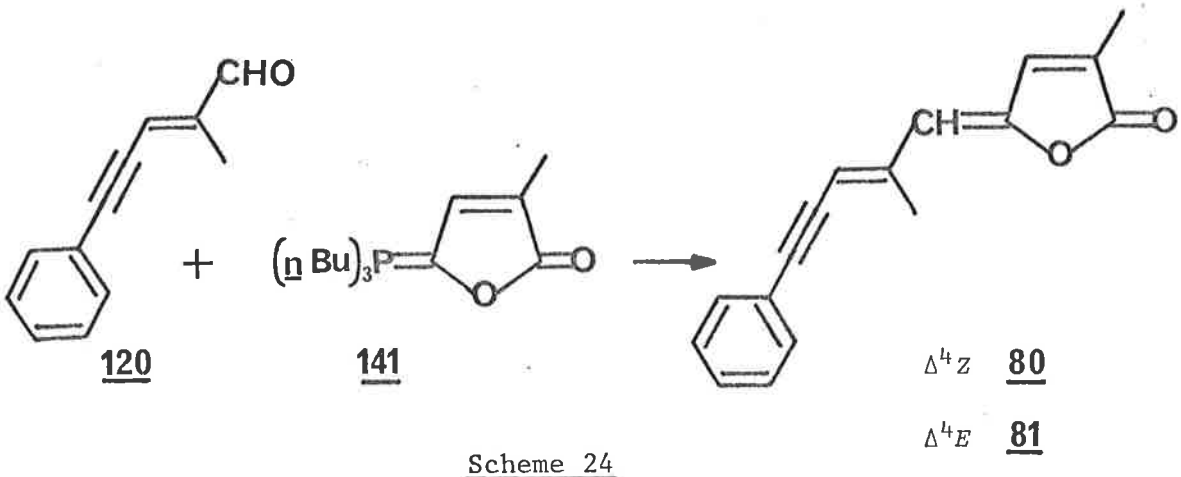
Scheme 23

However, the infrared spectrum (ν 1820cm^{-1}) of the salt was characteristic of a β,γ-unsaturated-γ-lactone.[151] Since infrared spectroscopy confirmed that the bromolactone 146 contained the α,β-unsaturated-γ-lactone chromophore (ν 1780cm^{-1}),[151] the salt 148 was presumably formed by an allylic displacement of the bromide ion by the attack of tri-*n*-butylphosphine at the α-position of the carbonyl group (Scheme 23). The allylic displacement of bromide ion by a phosphine has been shown to occur when steric hindrance

prevents the S_N2 displacement route.[152] Apparently the α-methyl group of the bromolactone 131 prevented a similar allylic displacement from taking place when the phosphonium salt 139 was prepared. The phosphorane generated from the salt 148 was unreactive towards a number of aldehydes, presumably because it is less nucleophilic than the phosphorane 141. In view of this rearrangement, the route to the isomers of the type 144 was not pursued further.

b. Reaction of the butenolide phosphorane 30 with diene aldehydes

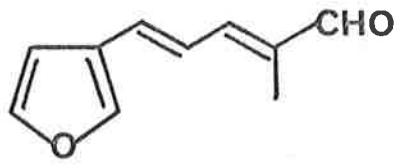
In the previous Section it was shown that the Wittig reaction between the yn-ene aldehyde 120 and the tributylphosphorane 141 gave the two olefins 80 and 81 (Scheme 24).



Scheme 24

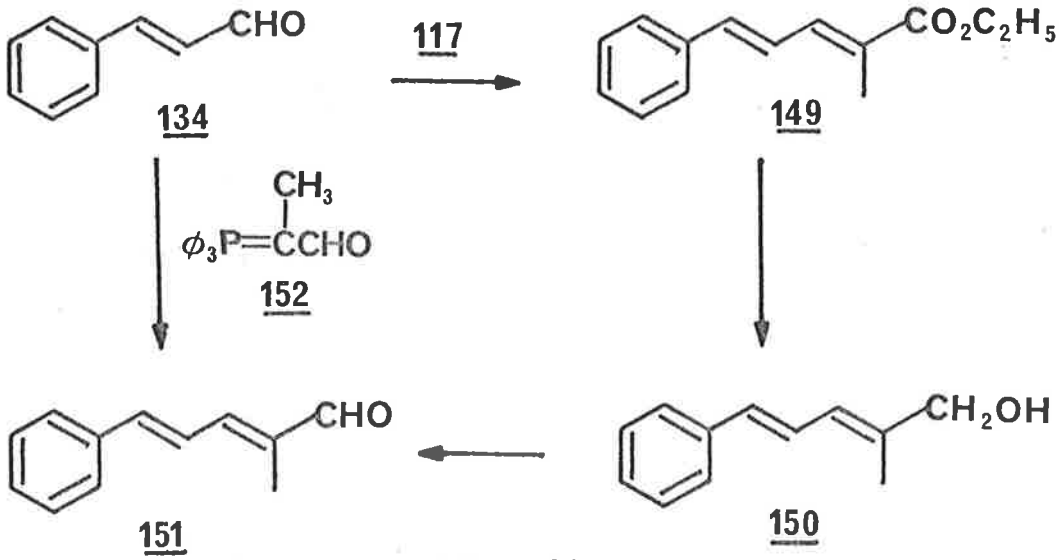
It was apparent that the dihydrofreelingyne isomers 17 could be prepared by this approach if a diene aldehyde such as 33 was used. If the four stereoisomers of 33 could be prepared it

could well be possible to obtain all of the dihydrofreelingyne isomers 17 by this route.



33

The initial endeavours, which were directed towards the synthesis of the *E*-phenyl analogues, required the preparation of the *E*,*E*-olefinic aldehyde 151. This was achieved by the method shown in Scheme 25.

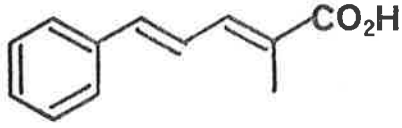


Scheme 25

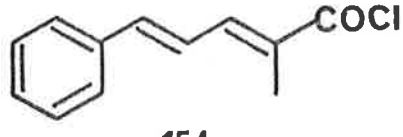
The most straightforward approach, by the Wittig reaction of the phosphorane 152 (prepared in poor yield by the formylation of methylenetriphenylphosphorane[153]) with *E*-cinnamaldehyde 134, gave

a good yield of the aldehyde 151, although the reaction was very slow. An alternative method using the more readily available phosphorane 117 was developed. The ester 149, obtained in excellent yield, was expected to be the *E*,*E*-isomer as reactions between stabilised phosphoranes and aldehydes are known to give the *E*-olefins almost exclusively.[129,130] The olefinic resonances in the NMR spectrum were obscured by the phenyl resonance and it was therefore not possible to verify the stereochemistry of 149. However, the known *E*,*E*-acid 153[131] was formed by the basic hydrolysis of 149, thereby confirming the 2*E*,4*E*-stereochemistry of 149.

The acid 153 was converted to the acid chloride 154 with oxalyl chloride, but studies of the selective reduction of 154 with lithium aluminium tri-*t*-butoxyhydride[154] failed to produce the aldehyde 151 cleanly.



153

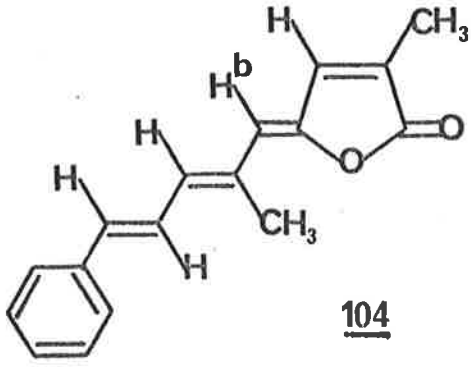


154

The reduction of the ester 149 with lithium aluminium hydride was complicated by the reduction of the conjugated double bonds. This undesired, but not unexpected, reaction could be suppressed by the addition of one equivalent of ethanol to the reaction mixture to produce the more selective reducing agent

lithium aluminium monoethoxyhydride.[155] This modification enabled the alcohol 150 to be obtained in good yield, although it was subsequently found that better yields of the alcohol 150 could be achieved when aluminium hydride[133,134] was used as the reducing agent. The oxidation of the alcohol 150 could be achieved satisfactorily with either Collins reagent[125] or silver carbonate on celite.[135] The aldehyde 151 was identical to the known *E,E*-aldehyde which had been prepared by a different route.[156]

The Wittig reaction between the aldehyde 151 and the tributylphosphorane 141 gave only one product, which was shown by the NMR spectrum to be the Δ^4Z-isomer 104. The chemical shift of the proton H^b(δ5.65) was in the region expected for an olefin of Δ^4Z-configuration (see p. 18-19).



104

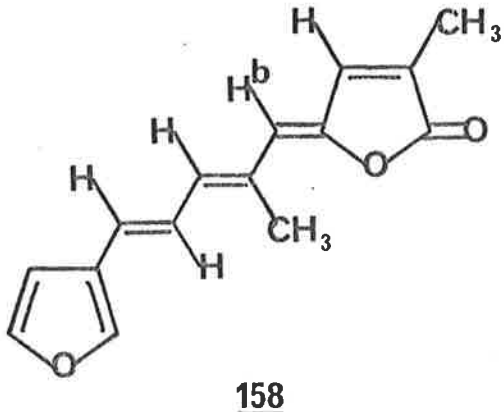
It was not possible to analyse the resonances of the protons of the Δ^6 and Δ^8-double bonds as they gave rise to an ABC or ABX spectrum which cannot be interpreted by first order analysis.[45,46] However, since the olefins 80 and 81, prepared by

the Wittig reaction with the aldehyde 120 (p. 76) had retained the stereochemistry of the aldehyde 120 it is reasonable to assume that the *E*,*E*-stereochemistry of the aldehyde 151 had also been retained. Thus the olefin 104 had $\Delta^4Z,\Delta^6E,\Delta^8E$-configuration.

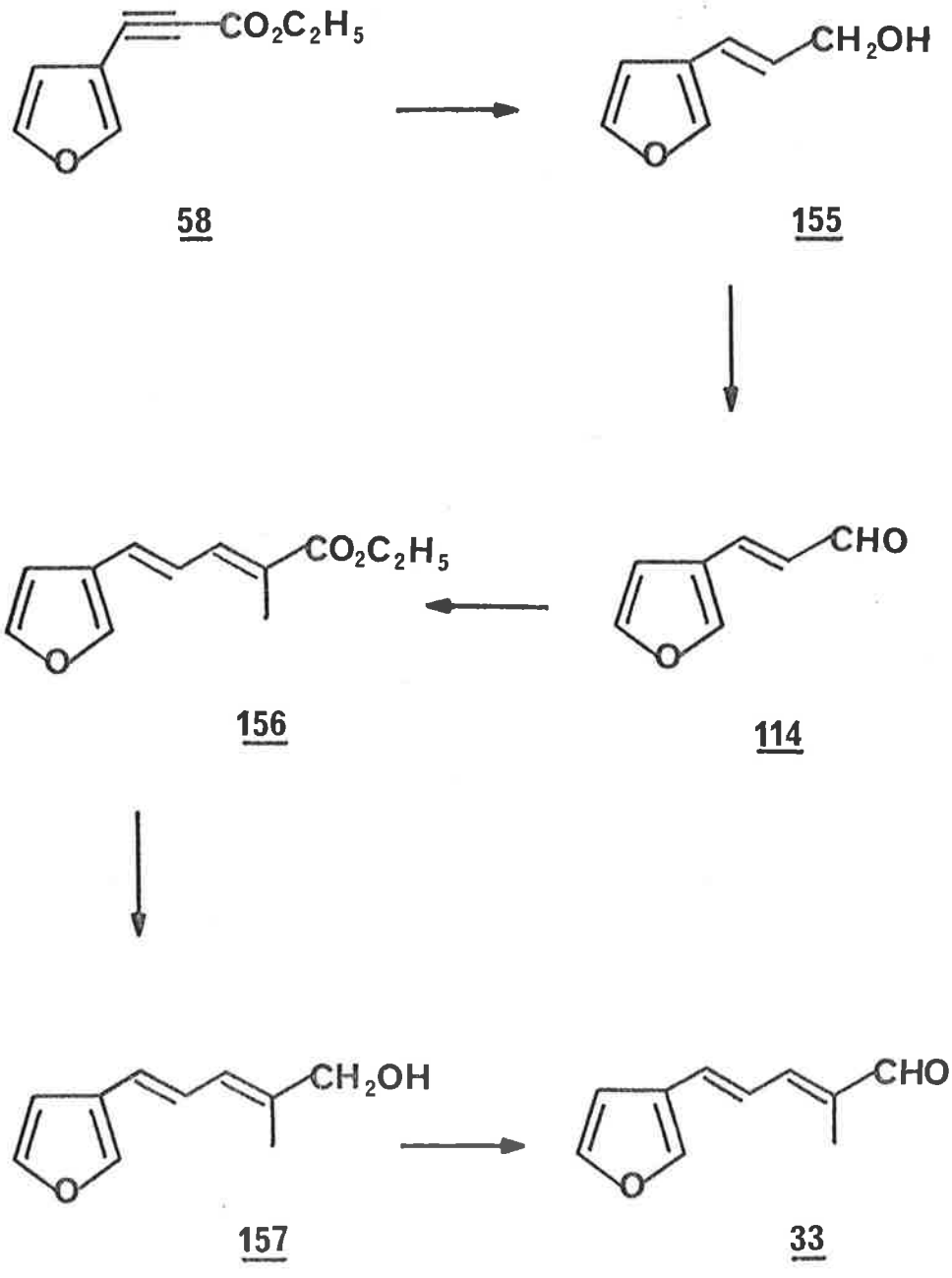
The furan analogue, the *E*,*E*-aldehyde 33, which was required for the synthesis of the dihydrofreelingyne isomers 17 was prepared in an analagous manner to the aldehyde 168 (Scheme 26).

The acetylenic ester 58 was reduced with lithium aluminium hydride in refluxing tetrahydrofuran, to form the *E*-alcohol 155 which was then oxidised to the aldehyde 114. The Wittig reaction of 114 with the phosphorane 117 followed by reduction and oxidation gave the *E*,*E*-aldehyde 33 in good yield.

The Wittig reaction of 33 with the tributylphosphorane 141 gave only the $\Delta^4Z,\Delta^6E,\Delta^8E$-dihydrofreelingyne isomer 158, as evidenced by the NMR spectrum, in which the proton H^b (δ5.64) resonated in the region expected for an olefin of Δ^4Z-configuration (see p. 18-19).



158



Scheme 26

The NMR resonances of the Δ^6 and Δ^8-olefinic protons could not be interpreted by first order analysis, but the stereochemistry was defined by the starting material, the *E*,*E*-aldehyde 33. The $\Delta^4 Z$,$\Delta^6 E$,$\Delta^8 E$-isomer 158 was identical in all physical and spectral properties with the naturally occurring dihydrofreelingyne 17. It is therefore formally related to freelingyne 16 by the replacement of the triple bond by a *trans* double bond.

Both of the olefins 104 and 158 formed by the Wittig reaction had the $\Delta^4 Z$-stereochemistry. This was also the stereochemistry of the major product 80 when the acetylenic aldehyde 120 was used in the Wittig reaction with the phosphorane 141 (p. 76). A consideration of the two intermediate betaines, A and B (Figure 3), provides a ready explanation for the preference for the $\Delta^4 Z$-product.

The decomposition of the intermediate betaine in the Wittig reaction is favoured by a substituent, such as an α,β-unsaturated carbonyl group, which can stabilise the developing double bond by orbital overlap.[130] This is only possible when the substituent is coplanar with the developing double bond. It is apparent that in betaine B, the steric interference between the C3 hydrogen atom and the C6 methyl group would tend to twist the lactone ring out of the plane of the developing $\Delta^{4,5}$-double bond. Therefore, the reaction would be expected to proceed *via* the betaine A where steric interference is absent and stabilisation of the

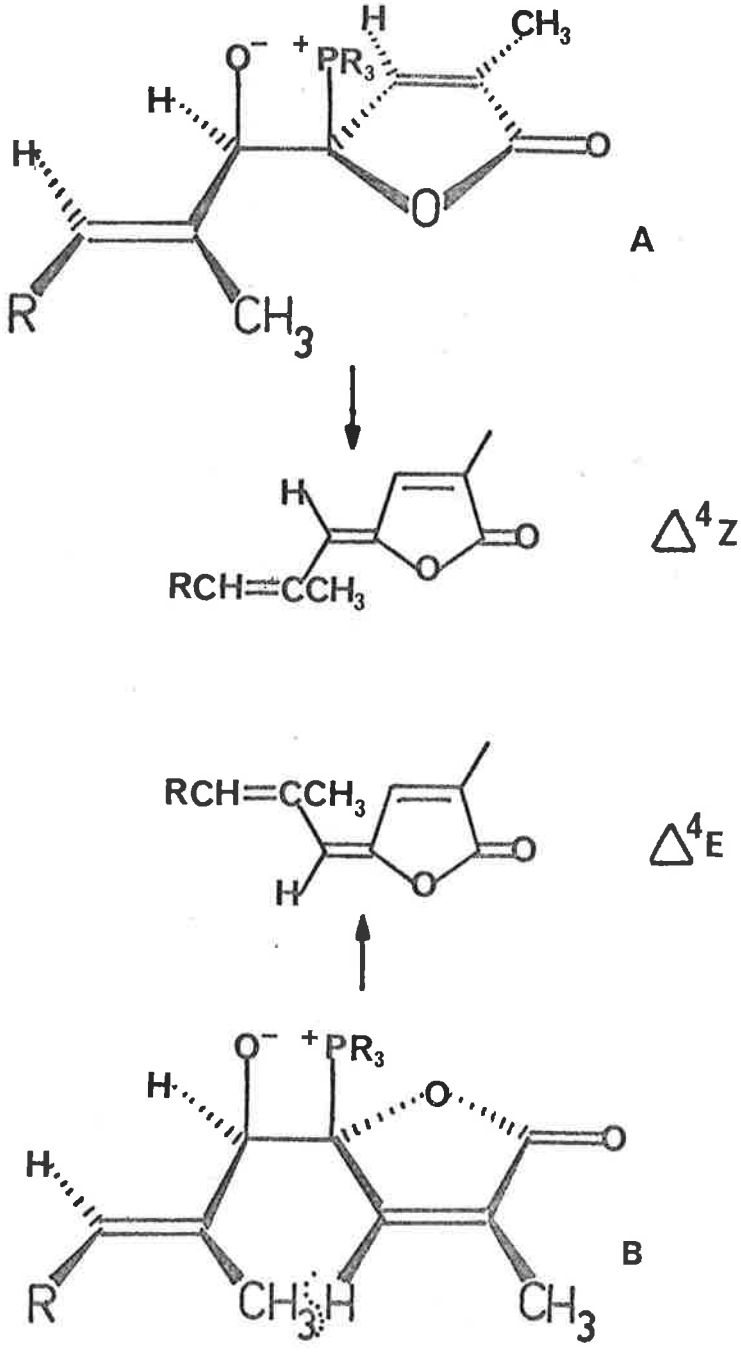
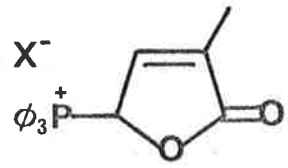

H
CH3
O⁻
+PR3
H
H
O
O
R
CH3
A
H
O
RCH=CCH3
Δ4Z
RCH=CCH3
O
H
Δ4E
O⁻
+PR3
H
O
O
H
R
CH3
H
CH3
B

Figure 3

developing double bond is possible. Also, the rate of decomposition of a betaine is decreased when a trialkylphosphorane is used, as the phosphorus atom has a higher electron density.[157] Since the formation of the betaines A and B is reversible,[158] a decrease in the rate of decomposition of the betaines would allow a more complete equilibration to occur, and the reaction would thus proceed *via* the lower energy betaine, A, to give the olefin with the *trans*-carbon chain, in this case the Δ^4Z-olefin.

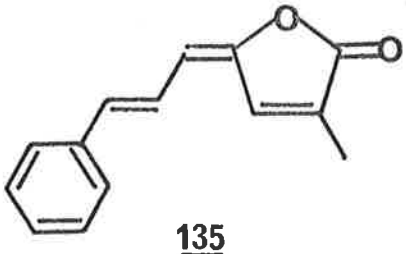
Since the phosphorane 141 was generated *in situ*, the product distribution may well have been influenced by the salt present. In the Wittig reaction with reactive phosphoranes, the amount of *trans*-product formed is significantly increased in the presence of dissolved salts, especially lithium tetraphenylborate.[159] The phosphorane 141 appears to be of intermediate stability between the stabilised and reactive phosphoranes and therefore the presence of the tetraphenylborate anion may have had some effect upon the product ratio. To test this hypothesis, the triphenyl phosphonium salts 132 and 159 were treated with base in the presence of cinnamaldehyde 134, and the ratio of the product isomers 135 (Δ^4*E*) and 136 (Δ^4Z) determined by the NMR spectra, as before (p. 73) (Table 7).

It was found that the proportion of the Δ^4Z-isomer 136, with the all-*trans*-carbon chain, was significantly increased when

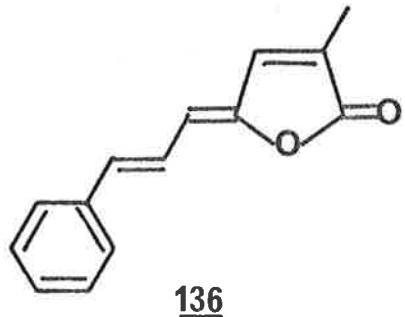


132 X = Br

159 X = $B(C_6H_5)_4$



135



136

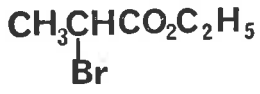
	Δ^4E		Δ^4Z
132	1	:	1
159	1	:	2.5

Table 7

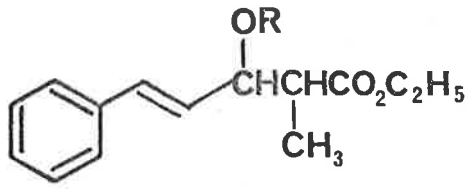
the anion present was tetraphenylborate. This confirms that 30 and 141 are reactive phosphoranes, although their reactivity is decreased somewhat by conjugation with the unsaturated lactone group, and also provides further evidence for the predominance of the Δ^4Z products from the Wittig reaction.

Since the Wittig approach had been successful in producing the $\Delta^4Z,\Delta^6E,\Delta^8E$-dihydrofreelingyne 158 and the phenyl analogue 104 it was considered that the reaction with aldehydes of different stereochemistry might produce isomers of dihydrofreelingyne with different configurations about the Δ^6 and Δ^8-double bonds.

A Reformatsky reaction between *E*-cinnamaldehyde 134 and ethyl 1-bromopropionate 160 gave the alcohol 161 which was converted into the acetate 162.



160



161 R = H

162 R = $COCH_3$

It was expected that the pyrolysis of the acetate 162 would produce a mixture of the $\Delta^2 Z$ and $\Delta^2 E$-olefinic esters 149, since the acetate 162 exists as a mixture of diastereoisomers, A and B (Figure 4).

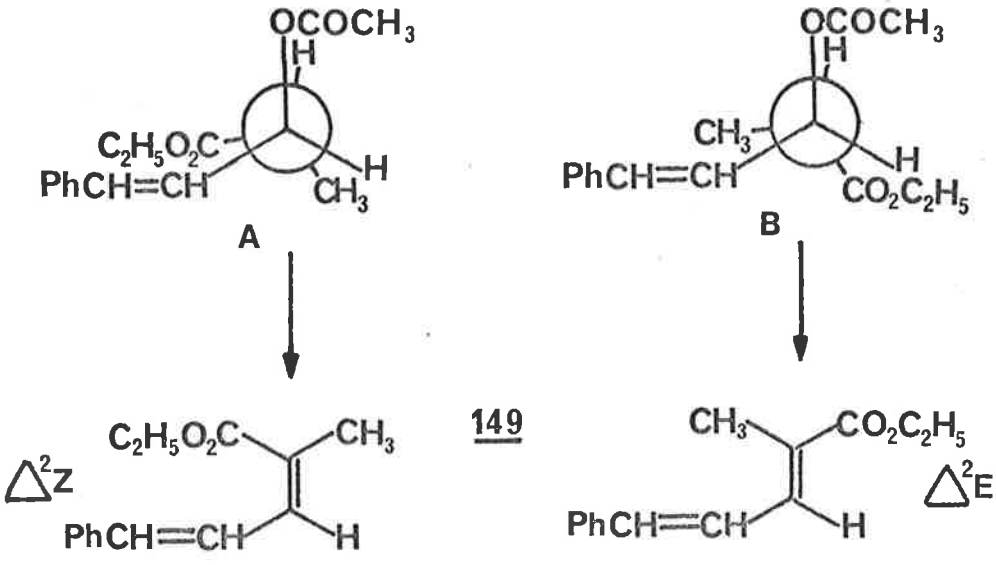
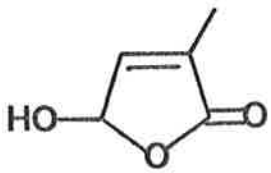


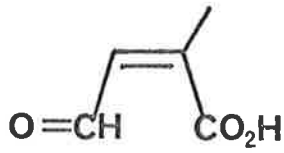
Figure 4

However, upon pyrolysis of the acetate 162, the $\Delta^2 E$-ester 149 was formed almost exclusively (>95% by gas chromatographic analysis). Apparently the initially produced $\Delta^2 Z$-ester underwent a thermal isomerisation to the more stable $\Delta^2 E$-ester 149.

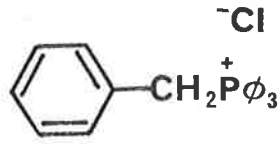
A different approach to isomers of the aldehyde 151 involved the Wittig reaction of the phosphorane generated from benzyltriphenylphosphonium chloride 163[160] with the hydroxylactone 129 (which was converted to the *cis*-aldehydic acid 164 under the basic reaction conditions).



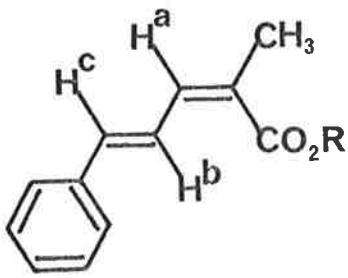
129



164



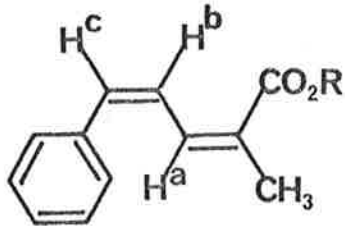
163



165 R = H

167 R = CH_3

H^a δ6.5
H^b δ7.92
J_{bc} 16Hz



166 R = H

168 R = CH_3

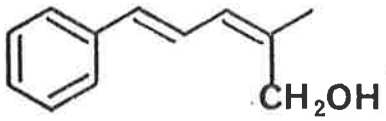
H^a δ6.8
H^b δ7.2
J_{bc} 11Hz

Table 8

The product olefins from this reaction were separated by fractional crystallisation to give the pure Δ^2Z,Δ^4E-acid 165 in 48% yield and the Δ^2Z,Δ^4Z-acid 166 in 22% yield. The NMR spectral characteristics were in accord with the published data for these isomers.[131] The stereochemistry of the Δ^4-double bond followed from the magnitude of J_{bc}[144] (Table 8). The proton H^a of the

isomer 166 was deshielded by the phenyl group and therefore resonated downfield from the proton H^a of 165. The proton H^b of the isomer 166 was deshielded by the adjacent carbonyl group but the proton H^b of 165 was deshielded by both the carbonyl group and the phenyl group, and therefore resonated at lower field.

The acids 165 and 166 were readily converted with ethereal diazomethane[112] to the methyl esters 167 and 168 which were reduced with aluminium hydride[133] to the Δ^2Z,Δ^4E-alcohol 169 and the Δ^2Z, Δ^4Z-alcohol 170 respectively. However, oxidation of the alcohols 169 and 170 by a variety of mild methods[118,125,135,161] consistently produced inseparable mixtures of the isomeric aldehydes 151, 171 and 172. The analysis of the product mixtures was simplified by the distinct chemical shifts of the aldehydic protons.



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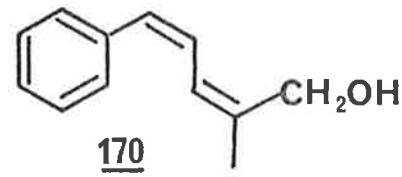

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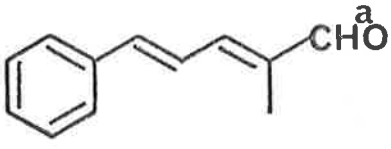
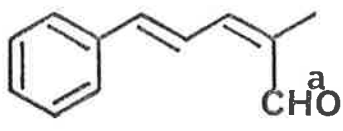


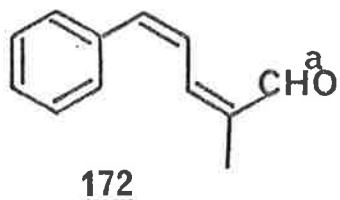
151

H^a δ9.5



171

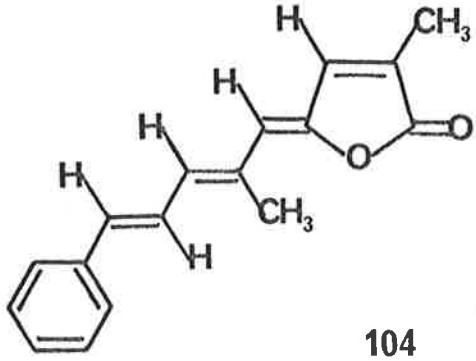
H^a δ10.4



172

H^a δ9.6

It was apparent that the Δ^2Z,Δ^4E-aldehyde 171 and the Δ^2Z,Δ^4Z-aldehyde 172 were labile and even under very mild conditions readily isomerised to the stable Δ^2E,Δ^4E-isomer 151. The conditions for the Wittig reaction of the aldehydes with the tributylphosphorane 141 would readily cause isomerisation even if a pure sample of 171 or 172 could be obtained. This would lead to a complex mixture of isomers of the dihydro product 104. In view of this facile isomerisation, the preparation of the isomers 171 and 172 was not continued.

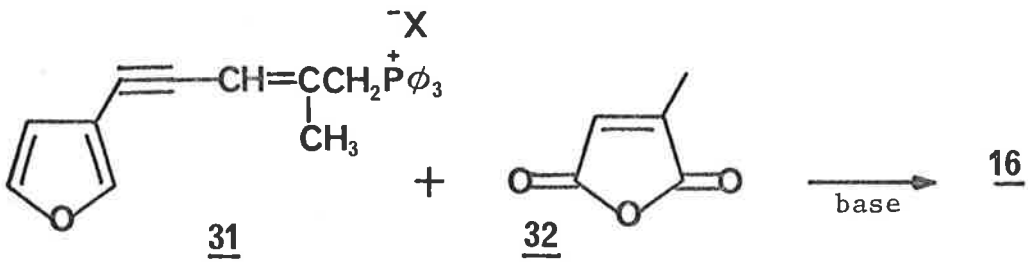


104

The approach to the isomers 80, 81, 104 and 158 by the Wittig reaction of aldehydes with the phosphorane 141 represents a chain extension by one isoprene unit. This method therefore complements other Wittig reactions and related reactions for the introduction of a five carbon unit,[31] and may well find application in the carotenoid field.

c. Reaction of phosphoranes with cyclic anhydrides

It was shown earlier (Chapter 1, Section 1) that citraconic anhydride 32 and the phosphorane 41 underwent a Wittig reaction to give a mixture of the enol-lactones 42, 43 and 44. The enol-lactones 42 and 43 were key intermediates in the synthesis of freelingyne 16 and the dihydrofreelingyne isomers 93 and 94. A different approach to freelingyne 16 (Scheme 4B) involves the reaction of the phosphorane from the phosphonium salt 31 with citraconic anhydride 32.

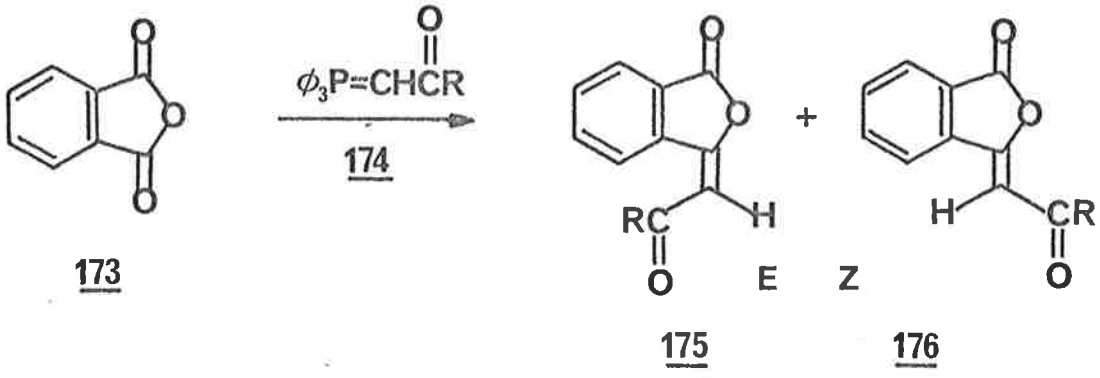


Scheme 4B

However, there was no information regarding the reaction of reactive phosphoranes with cyclic anhydrides. Also, it was clear that isomerisation of the phosphorane generated from the salt 31 could lead to isomeric products unless the reaction conditions involved low temperatures. The phosphorane generated from the salt 31 would be a reactive phosphorane, but of reduced reactivity because the anion would be delocalised over the conjugated system. Therefore it was desirable to explore the scope of the reaction of anhydrides with reactive phosphoranes and those of intermediate

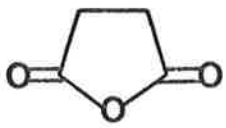
reactivity, to determine whether the approach suggested in Scheme 4B was feasible.

It is known that cyclic five-membered anhydrides react with stabilised phosphoranes to give enol-lactones,[29,49] but the effect of substituents and electronic factors on the stereochemistry of the products is poorly understood. A number of hypotheses have been put forward to account for these effects. Chopard noted that in the reaction of phthalic anhydride 173 with a series of stabilised phosphoranes 174, the proportion of *E*-enol-lactone product 175 decreased as the substituent R (Scheme 27) of the phosphorane 174 was changed from a good to a poor electron donor ($R=OCH_3$; CH_3).[49] He proposed that a π-π^* interaction of the RCO- substituent with the benzene ring in the intermediate betaine accounted for the preference of the *E*-enol-lactone product 175. This was at a maximum when the substituent R was a good electron donor.

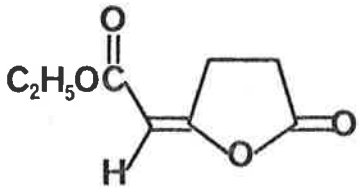


Scheme 27

Subsequent investigations have shown that the ratios of some of the product enol-lactones 175 and 176 were incorrect, although the general trend of product proportions was the same.[55,56,158] It has been found that the reaction of succinic anhydride 177 with the phosphorane 174 ($R=OC_2H_5$) gave solely the *E*-enol-lactone 178,[29] suggesting that π-bonding may not be the only factor involved in determining the product stereochemistry.



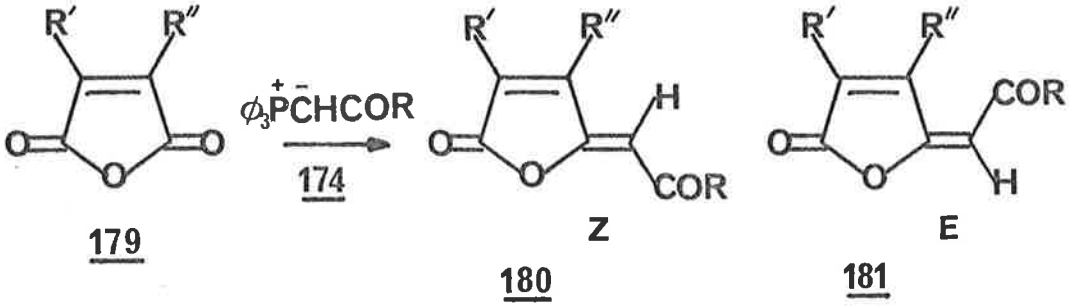
177



178

When the reactions of the phosphoranes 174 with anhydrides of the type 179 were carried out, it was noted that with the larger substituents R' and R'' the proportion of the *Z*-enol-lactone 180 was increased (Scheme 28). It was proposed[57] that the dipolar repulsion force between the lactone oxygen atom and the carbonyl group of the phosphorane favours the betaine leading to the *E*-enol-lactone 181. When the substituents R' and R'' are large, the steric repulsion between R'' and R favours the *Z*-enol-lactone 180.

There are, however, exceptions to this proposal, since the reaction of the anhydride 179 ($R',R''=CH_3$) and the phosphorane 174 ($R=CH_3$) gave only the *Z*-enol-lactone 180, while the reaction of 174 ($R=CH_3$) with phthalic anhydride 173, (which has a comparable



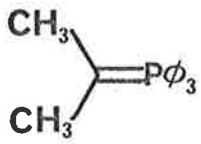
Scheme 28

steric environment about the carbonyl groups) gave the *E*-enol-lactone 175 as the major product.[29]

A final hypothesis suggests that when the *E*-enol-lactones are formed, the reaction is subject to kinetic control.[129] This occurs when the rate of triphenylphosphine oxide elimination from the betaine becomes greater than the rate of equilibration of the initially formed intermediate betaines. With less nucleophilic phosphoranes, e.g. 174 ($R=CH_3$), the rate of betaine decomposition to products is considered to be decreased thereby allowing time for the betaines to equilibrate. Consequently, the thermodynamic product,[130] the *Z*-enol-lactone, is produced. It has subsequently been shown that the *E*-enol-lactone 175 ($R=CH_3$) is completely converted to the *Z*-enol-lactone 176 ($R=CH_3$) in acid, thereby confirming that the *Z*-isomer is thermodynamically more stable.[55]

It was hoped that the study of the reaction of anhydrides with reactive phosphoranes, including those of intermediate reactivity in which there is delocalisation of the carbanion over

a π-system, could also provide information about the reaction mechanism from a consideration of the changes in the isomer ratios of the product enol-lactones. Phthalic anhydride 173 was used for the study since its symmetry would reduce the possible number of reaction products. The phosphoranes used were 182 and 183.



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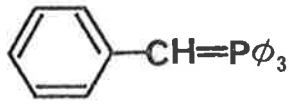
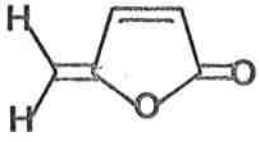


183

The phosphoranes 182 and 183 were generated from the salts[162] and added to the anhydride 173 under a variety of conditions. However, extensive chromatography of the reaction mixtures failed to give any of the expected reaction products, although a small amount of triphenylphosphine oxide was obtained. It was possible that the products may have undergone polymerisation (protoanemonin 184 is known to dimerise readily,[163] although the enol-lactone 185 is stable[164]). However, it is more likely that the expected product enol-lactones, e.g. 186 would be stable and it therefore seemed unlikely that they had been formed.



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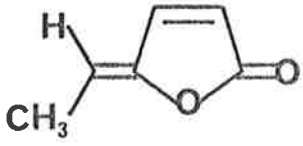

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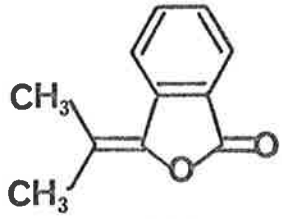
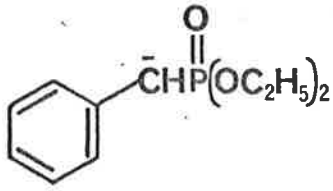


186

Phosphonate carbanions are known to be more reactive than the corresponding phosphoranes in olefin-forming reactions,[40,144] and it was considered that they may yield the desired enol-lactones with anhydrides. A number of reactions of phthalic anhydride 173 with the diethylbenzylphosphonate carbanion 187[145] were attempted but the only material identified was recovered diethylbenzylphosphonate. It is possible that the phosphonate carbanion 187 added to the anhydride 173 to give the intermediate 188 which would exist as the ring-opened acid 189. This could have condensed with a second molecule of anhydride 173, thus effectively removing the anhydride 173 from the reaction mixture, and producing only polymeric material and the phosphonate ester on termination of the reaction.



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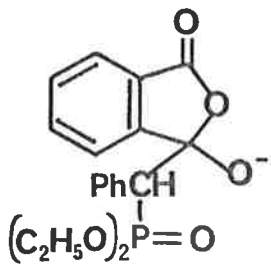

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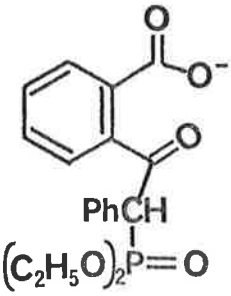
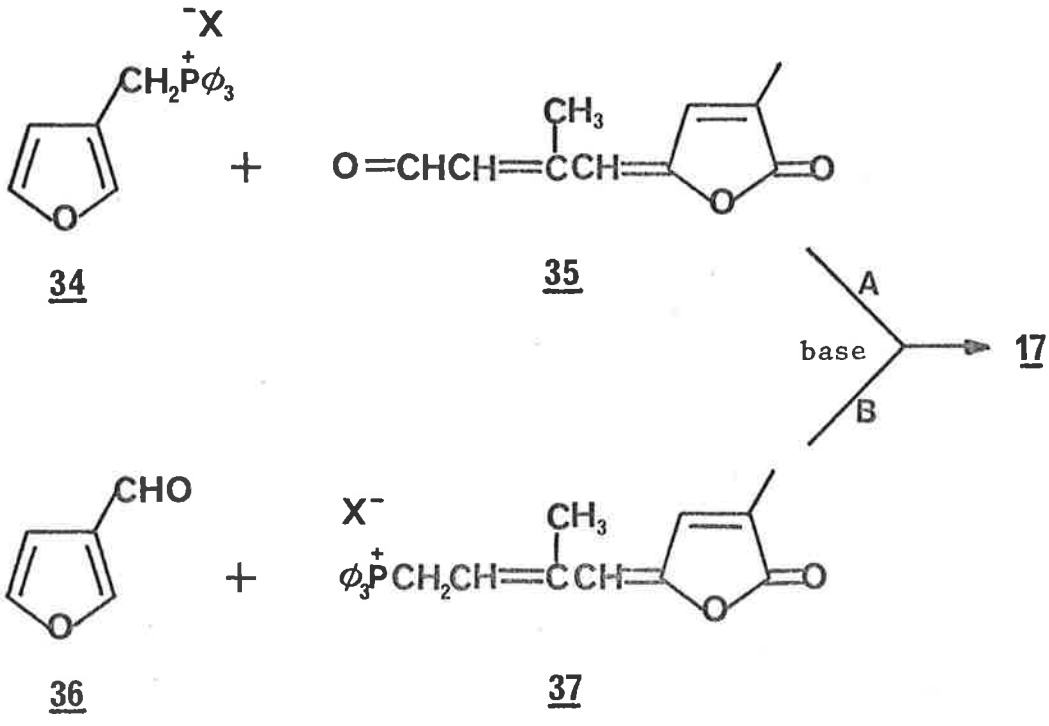


189

In view of the complete lack of formation of any of the expected enol-lactone products, this study was abandoned. It is clear that the reaction of cyclic five-membered anhydrides to give enol-lactones is only applicable to stabilised phosphoranes. The approach outlined in Scheme 4B (p. 95) was therefore unlikely to be successful and was not pursued.

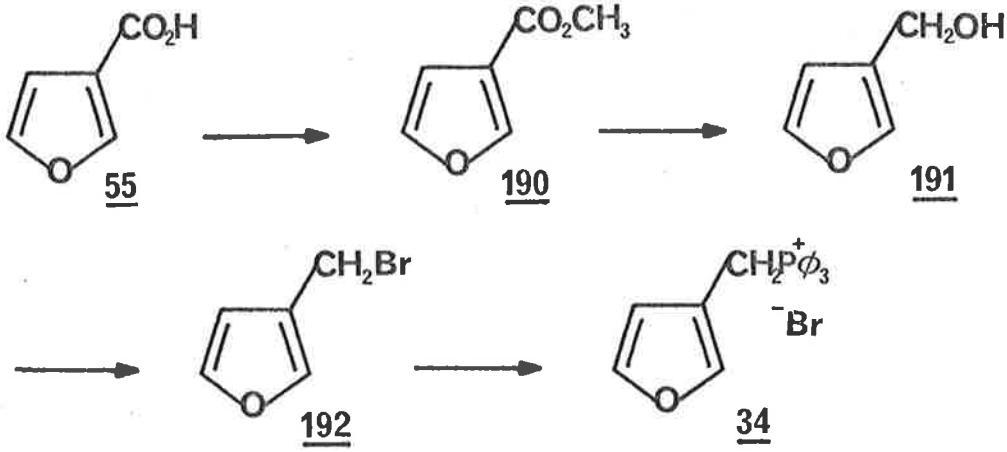
Section 2 Syntheses involving the formation of the Δ^8-double bond

Although the method outlined in Scheme 4A (p. 67) was shown in Section 1 to be successful for the preparation of the phenyl analogue of freelingyne 80, and dihydrofreelingyne 158, attempts to prepare other isomers of dihydrofreelingyne by this method were unsuccessful because of the lability of the starting aldehydes 171 and 172. A different, although unsuccessful approach to the isomers of dihydrofreelingyne is outlined in Scheme 5.



Scheme 5A,B

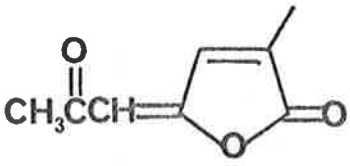
The approach by Scheme 5A required the preparation of the phosphonium salt 34. This was readily obtained from 3-furoic acid 55 by the method outlined in Scheme 29.



Scheme 29

The methyl ester 190 was readily prepared by the treatment of the acid 55 with boron trifluoride etherate in methanol.[164] Reduction of 190 with lithium aluminium hydride gave the alcohol 191 which was brominated with phosphorus tribromide.[85] The product bromide 192 was converted to the phosphonium salt 34 with triphenylphosphine.

The preparation of the aldehyde 35 presented difficulties. An attractive starting material for the synthesis of 35 would be the enol-lactone 19. However, it was shown earlier (Chapter 1, Section 2) that enol-lactones do not give the expected olefins with phosphoranes. An alternative route to 35 appeared to be *via* the Wittig reaction of the phosphorane 38 with citraconic anhydride 32. The investigations of the reaction of cyclic five-membered



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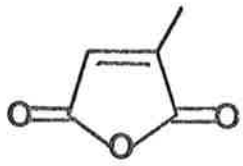

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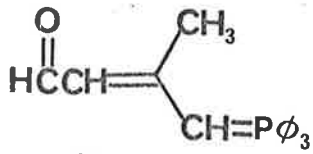
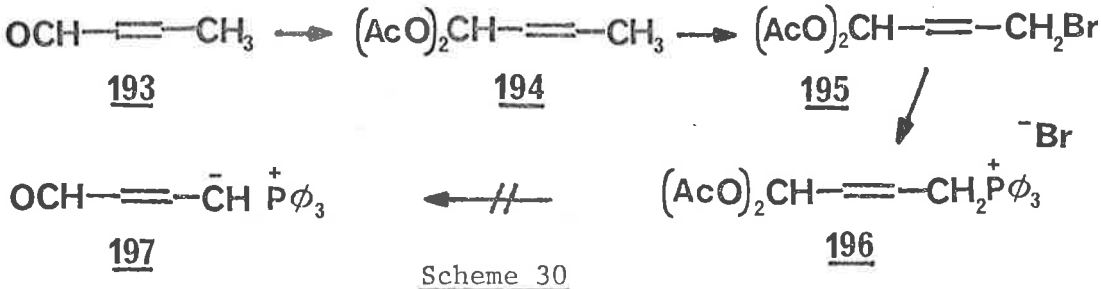


38

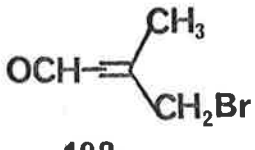
anhydrides with phosphoranes discussed earlier (Chapter 2, Section 1 c.) showed that the Wittig reaction only proceeded with some stabilised phosphoranes. However, it was considered that the phosphorane 38 could well be of the required type, since extensive resonance stabilisation of the carbanion would be possible.

Initial approaches were directed towards the phosphorane 197 since the starting materials were more readily accessible. Crotonaldehyde 193 was protected as the diacetate 194[165] and converted into the allylic bromide 195 with N-bromosuccinimide[166] (Scheme 30). An acetal could not be used as a protecting group since bromination also proceeds at the carbon atom substituted with the acetal group.[166] When the phosphonium salt 196 was generated at room temperature, a considerable amount of tar was formed. This could be minimized by carrying out the reaction at 5°.



Scheme 30

It was thought that the treatment of the salt 196 with two equivalents of base would hydrolyse the acetate groups and generate the phosphorane 197. However, the attempted generation of the phosphorane 197 in the presence of the anhydride 32 or a number of aldehydes failed to give any of the desired olefins. A subsequent report has indicated that the phosphorane 197, prepared in an unspecified yield, reacted with *p*-nitrobenzaldehyde to give the product olefin in only 12% yield.[152] Furthermore, the phosphorane 38 could not be prepared from the corresponding bromide 198 since triphenylphosphine displaced the bromide ion in an allylic manner to form the rearranged salt 199.[152]



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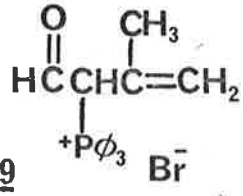

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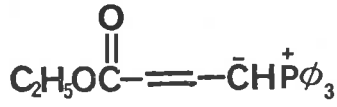

200

The related phosphorane 200 was prepared[167] and its reaction with the anhydride 32 examined. No olefinic products were formed, even after an extended reaction time, although the NMR spectrum of the mixture showed the presence of resonances which could be attributed to the intermediate betaine. This suggests that the Wittig reaction with cyclic five-membered anhydrides may be further limited to stabilised phosphoranes in which the stabilisation does not extend over an allylic system. In view of the failure of the phosphorane 200 to react with the anhydride 32,

no further attempts were made to prepare dihydrofreelingyne 17 by this route.

The approach to dihydrofreelingyne 17 by the Wittig reaction outlined in Scheme 5B could provide another route to a number of new isomers. However, since the structures of both natural products had been unambiguously determined as 86 and 158, this approach was not attempted.

EXPERIMENTAL

General

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared spectra were recorded on either a Perkin-Elmer 337 or a Unicam SP200 spectrophotometer. All data refer to mulls in Nujol unless otherwise stated. Where relevant, the characteristics of the infrared bands are expressed as follows: s, strong; m, medium; w, weak.

Ultraviolet spectra were recorded, in methanol solution, on a Unicam SP800 spectrophotometer.

Mass spectra were measured on a Hitachi-Perkin-Elmer RMU-7D double focusing mass spectrometer operating at 70eV.

Nuclear magnetic resonance (NMR) spectra were obtained with a Varian T-60 spectrometer and, unless otherwise stated, are for deuterochloroform solutions. NMR data are given in the following manner: chemical shifts (δ) are in ppm from the internal standard, tetramethylsilane; multiplicity is expressed as follows - s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; exch. implies that the signal exchanges on the addition of D_2O to the sample. Only first order analysis was attempted; the coupling constants J are measured in Hz.

Analytical gas-liquid chromatography (GLC) was carried out with a Perkin-Elmer 881 gas chromatograph equipped with a flame

ionization detector using nitrogen as the carrier gas at a flow rate of 30 ml/min.

The chromatographic adsorbent used was Sorbsil silica gel. Analytical and preparative thin layer chromatography (TLC) were carried out on glass slides coated with a layer of an equal mixture of Merck Kieselgel G and HF_{254}.

The solvents were purified by standard procedures.[170] Light petroleum refers to the fraction b.p. 50-60°. All organic extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

CHAPTER 1

Section 1

Isolation of freelingyne 16 and dihydrofreelingyne 17

The ground heart-wood of *E. freelingii* was covered with ether and allowed to stand protected from the light at room temperature for 24 hr. The solvent was removed and evaporated to give an oil (11.4g) which was chromatographed on silica gel (1000g) using chloroform as the eluent.

The first yellow fractions were combined and the solvent removed to give freelingyne 16 (1.38g, 12%), recrystallised from benzene as yellow prisms m.p. 162-163° (lit.[29] m.p. 164°).

The latter yellow fractions were combined and repurified by careful preparative TLC (chloroform). The fraction of low rf. was dihydrofreelingyne (0.2g, 1.8%) which was recrystallised from chloroform-ether as yellow needles m.p. 181-183°. (Found: C, 74.5; H, 5.9; M^+ at *m/e* 242. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%; M, 242).

ν_{max} ($CHCl_3$) 1750, 1610, 1580, 1160, 1060, 1020, 990, 960, 940, 900 and 870cm^{-1}.

λ_{max} 383 nm, ε 25000.

δ7.54 (1H, d, furyl C2 H), 7.42 (1H, t, furyl C5 H), 7.03 (1H, q, J1.5Hz, C3 H), 6.9-6.3 (4H, br.m, furyl C4 H, C7 H, C8 H, C9 H), 5.64 (1H, s, C5 H), 2.26 (3H, br.s, C6 CH_3) and 2.02 (3H, br.s, J1.5Hz, C2 CH_3).

Wittig reaction of the phosphorane 41 with citraconic anhydride 32

To a solution of methylcarbonylmethylenetriphenylphosphorane 41[169] (63.6g, 0.2 mol) in dry benzene (31) heated under reflux in an atmosphere of nitrogen was added a solution of citraconic anhydride 32 (22.4g, 0.2 mol) in dry benzene (1l) over 1 hr. The mixture was heated under reflux for a further 3 hr, cooled and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel. Elution with ether-light petroleum (2:3) afforded 4-hydroxy-2-methyl-6-oxahepta-2(Z),4(*E*)-dienoic acid (1→4)lactone 42 which was recrystallised from ether-light petroleum as pale yellow needles (4.72g, 16%) m.p. 88-89° (lit.[29] 88-89°).

M^+ at *m/e* 152, $C_8H_8O_3$ requires M, 152.

ν_{max} 1775, 1685, 1630 and 1610cm^{-1}.

λ_{max} 290 nm, ε 23000.

δ8.0 (1H, d, J2Hz, C3 H), 6.1 (1H, s, C5 H), 2.3 (3H, s, $COCH_3$) and 2.1 (3H, d, J2Hz, $=CCH_3$).

Elution with ether afforded a mixture of 4-hydroxy-2-methyl-6-oxahepta-2(Z),4(Z)-dienoic acid (1→4)lactone 43 and 4-hydroxy-3-methyl-6-oxahepta-2(Z),4(Z)-dienoic acid (1→4)lactone 44 (1.49g, 5%). Extensive fractional crystallisation of the mixture from ether-light petroleum gave a pure sample of each component.

The 2-methyl-2(Z),4(Z)-lactone 43 was obtained as pale yellow needles m.p. 124.5-125.5° (lit.[29] 123°). M^+ at *m/e* 152,

$C_8H_8O_3$ requires M, 152.

ν_{max} 1770, 1690, 1640 and 1620cm^{-1}.

λ_{max} 285 nm, ε 22000.

δ7.1 (1H, d, J2Hz, C3 H), 5.4 (1H, s, C5 H), 2.5 (3H, s, $COCH_3$) and 2.15 (3H, d, J2Hz, C2 CH_3).

The 3-methyl-2(Z),4(Z)-lactone 44 was obtained as off-white needles m.p. 92-94°. (Found: C, 63.4; H, 5.5; M^+ at *m/e* 152. $C_8H_8O_3$ requires C, 63.15; H, 5.3%; M, 152).

ν_{max} 1800, 1790, 1655, 1640 and 1610cm^{-1}.

λ_{max} 280 nm, ε 6400.

δ6.2 (1H, br.s, C2 H), 5.6 (1H, s, C5 H), 2.5 (3H, s, $COCH_3$) and 2.2 (3H, d, C3 CH_3).

1,4-*exo*-methylene-*exo*-5-methylcyclohex-2-en-*endo*-5,6-dicarboxylic anhydride 50

Cyclopentadiene (23g, 0.35 mol) in benzene (20 ml) was added dropwise to a solution of citraconic anhydride 32 (39 g, 0.35 mol) in benzene (20 ml) and the mixture maintained at 0° for 48 hr. The benzene was removed under reduced pressure to give a gummy solid which was recrystallised from light petroleum to give the adduct 50 (58g, 93%) as a colourless solid m.p. 134-136° (lit.[170] 138°).

Wittig reaction between the phosphorane 41 and the adduct 50

A solution of the adduct 50 (12.45g, 70 mmol) in chloroform (50 ml) was added in an atmosphere of nitrogen to a solution of the phosphorane 41 (22.3g, 70 mmol) in chloroform (50 ml) and the mixture heated under reflux for 24 hr. The solvent was removed under reduced pressure and the residue distilled at 120°/0.5 mm. The distillate was redistilled at 170°/90 mm to effect the retro-Diels-Alder reaction and the yellow distillate obtained was chromatographed on silica gel. Elution with ether-light petroleum (2:3) afforded the $\Delta^4 E$-enol-lactone 42 (0.8g, 7%). Elution with ether gave the $\Delta^4 Z$-enol-lactone 43 (0.7g, 6%).

3-furoic acid 55

A modification of the procedure of Reichstein was used.[78] A mixture of furan-3,4-dicarboxylic acid 54 (2g, 13.8 mmol), copper powder (0.5g) and quinoline (10 ml) was heated under reflux until 1 equivalent of carbon dioxide was evolved. The cooled reaction mixture was diluted with ether, filtered and the filtrate extracted with a dilute sodium hydroxide solution. The extracts were washed with ether, acidified with a dilute hydrochloric acid solution and extracted with ether. The ether extract was dried and concentrated to give 3-furoic acid 55 (1.2g, 85%) as an off-white powder. The crude acid 55 was purified by sublimation at 80°/0.2 mm to give colourless crystals m.p. 120-121° (lit.[78] 122-123°).

3-furoyl chloride 56

A solution of 3-furoic acid 55 (17.1g, 0.153 mol) in thionyl chloride (90g) was heated under reflux for 1.5 hr and the excess of thionyl chloride was removed by distillation. The residue was distilled to give 3-furoyl chloride 56 (17.7g, 89%) as a colourless liquid b.p. 83-84°/62 mm (lit.[54] 65°/47 mm).

1-ethoxycarbonyl-3-furacylidenetriphenylphosphorane 57

A solution of 3-furoyl chloride 56 (4.68g, 35.7 mmol) in benzene (40 ml) was added with stirring to a solution of ethoxycarbonylmethylenetriphenylphosphorane 52[171] (24.8g, 71.4 mmol) in benzene (100 ml) over a period of 1 hr. The reaction mixture was allowed to stand at room temperature for 15 hr, and the precipitate was removed by filtration. The filtrate was washed with cold water and benzene was removed to give the phosphorane 57 as a solid in quantitative yield. A sample was recrystallized from chloroform-hexane as light brown plates m.p. 135-136° (lit.[29] 134°).

Ethyl 3-(3'-furyl)prop-2-ynoate 58

The phosphorane 57 (4.43g, 10 mmol) was placed in a flask connected *via* a side arm and U-tube, cooled at -78°, to a vacuum pump. The flask was heated at 260° and the liquid which distilled

from the flask was collected. This was redistilled to give ethyl 3-(3'-furyl)prop-2-ynoate 58 (1.18g, 72%) as a colourless liquid b.p. 64-66°/0.2 mm (lit.[29] 55°/0.05 mm). M^+ at 164, $C_9H_8O_3$ requires M, 164.

ν_{max} (film) 3200, 2250, 1705, 1220, 1160 and 1030cm^{-1}.

δ7.8 (1H, d, furyl C2 H), 7.4 (1H, t, furyl C5 H), 6.5 (1H, d, furyl C4 H), 4.3 (2H, q, OCH_2-) and 1.35 (3H, t, $-CH_2-\underline{CH_3}$).

2-furoyl chloride 62

Using the procedure described for the preparation of 3-furoyl chloride 56, 2-furoic acid 61 (10g, 89.3 mmol) was converted into 2-furoyl chloride 62 (9.13g, 78%) b.p. 67°/13 mm (lit.[172] 66°/10 mm).

1-ethoxycarbonyl-2-furacylidenetriphenylphosphorane 63

Using the procedure described for the preparation of the phosphorane 57, 2-furoyl chloride 62 was converted into the phosphorane 63 m.p. 113-114° (lit.[82] 114-115°).

3-(2'-furyl)prop-2-ynoic acid 65

The synthetic details were based on the method of Märkl.[81] The phosphorane 63 (3.57g, 8.1 mmol) was dissolved in phosphorus

oxychloride (15 ml). Phosphorus pentachloride (2.12g, 10.2 mmol) was added and the reaction mixture heated at 80° for 15 min. The phosphorus oxychloride was removed *in vacuo* and the residue dissolved in chloroform, washed well with cold water and dried. The chloroform was removed *in vacuo*, the residue dissolved in methanol (20 ml) and methanolic potassium hydroxide (50%) added until pH 11 was maintained. The mixture was heated under reflux for 30 min, diluted with water (methanol-water, 4:1) and extracted with light petroleum. The extracts were dried and evaporated to dryness, and the residue was recrystallized from chloroform-light petroleum to give the acid 65 (0.99g, 90%) as colourless crystals m.p. 110-112° (lit.[82] 113-114°).

3-(3'-furyl)prop-2-ynoic acid 66

a. Using the procedure described above for the preparation of the acid 65, but using the hydrolysis procedure with ethanolic potassium hydroxide at pH 9, the phosphorane 57 (14g, 31.6 mmol) was converted to a colourless liquid (1.43g) b.p. 54°/0.6 mm. A portion of the liquid was purified by preparative TLC (ether-light petroleum, 1:3).

The material of higher rf. was ethyl 3-chloro-3-(3'-furyl)prop-2-enoate 67, a colourless liquid b.p. 70°/0.2 mm. (Found: C, 53.7; H, 4.45; O, 24.2; M^+ at *m/e* 200. $C_9H_9O_3Cl$ requires C, 53.9;

H, 4.5: O, 23.9%; M, 200).

ν_{max} (film) 3000, 1720, 1620, 1030 and 890cm^{-1}.

δ8.2 (1H, br.s, furyl C2 H), 7.35 (1H, br.s, furyl C5 H), 6.9 (1H, br.s, furyl C4 H), 6.18 (1H, s, olefinic H), 4.1 (2H, q, OCH_2CH_3) and 1.15 (3H, t, OCH_2-$\underline{CH_3}$).

The material of lower rf. was ethyl 3-(3'-furyl)prop-2-ynoate 58.

The aqueous methanolic washings were acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were dried and evaporated to give 3-(3'-furyl)prop-2-ynoic acid 66 (0.94g, 22%). A sample was recrystallized from chloroform-hexane and sublimed at 100°/1 mm to afford colourless prisms m.p. 129.5-133°. (Found: C, 61.3; H, 3.0; M^+ at *m/e* 136. $C_7H_4O_3$ requires C, 61.8; H, 3.0%; M, 136).

ν_{max} 2220, 1670, 1600, 1250, 1160 and 880cm^{-1}.

δ8.7 (1H, br.s, exch., COOH), 7.8 (1H, d, furyl C2 H), 7.4 (1H, t, furyl C5 H) and 6.5 (1H, d, furyl C4 H).

b. Using the procedure described for the preparation of 3-(2'-furyl)prop-2-ynoic acid 65 with the hydrolysis procedure at pH 11, the phosphorane 57 (3.57g, 8 mmol) was converted into a light brown solid (0.62g, 54%). The NMR spectrum showed it to be a 4:1 mixture of 3-(3'-furyl)prop-2-ynoic acid 66 and 3-chloro-3-(3'-furyl)prop-2-enoic acid 68.

δ9.5 (1H, br.s, exch., COOH); 8.18 (·2H, d, furyl C2 H, 68), 7.9 (·8H, br.s, furyl C2 H, 66), 7.4 (1H, br.s, furyl C5 H), 6.9 (·2H, br.s, furyl C4 H, 68), 6.6 (·8H, d, furyl C4 H, 66) and 6.3 (·2H, s, olefinic H, 68).

3-(3'-furyl)prop-2-ynol 70

To a stirred suspension of lithium aluminium hydride (3.48g, 90 mmol) in dry ether (225 ml) at -78° in an atmosphere of nitrogen was added a solution of ethyl 3-(3'-furyl)prop-2-ynoate 58 (6g, 36.6 mmol) in dry ether (150 ml) over a period of 15 min. After 30 min the mixture was treated with water (3.48 ml), 15% sodium hydroxide solution (3.48 ml) and water (10.5 ml).[173] The mixture was allowed to warm to room temperature, the precipitate removed by filtration and the filtrate was dried. Removal of the ether gave 3-(3'-furyl)prop-2-ynol 70 (4.35g, 98%) as a colourless oil. A sample was purified by distillation b.p. 55-56°/.05 mm. (Found: C, 68.8; H, 4.9; M^+ at *m/e* 122. $C_7H_6O_2$ requires C, 68.8; H, 4.95%; M, 122).

ν_{max} (film) 3450, 3150, 2230, 1165, 1090, 1025, 885 and 800cm^{-1}.

δ7.55 (1H, d, furyl C2 H), 7.3 (1H, t, furyl C5 H), 6.4 (1H, d, furyl C4 H), 4.4 (2H, s, OCH_2) and 3.9 (1H, br.s, exch., OH).

1-bromo-3-(3'-furyl)prop-2-yne 18

The method used was a modification of the procedure of Smith and Swenson.[85] A solution of phosphorus tribromide (2.45g, 9 mmol) in dry ether (15 ml) was added dropwise to a solution of 3-(3'-furyl)prop-2-ynol 70 (3g, 24.6 mmol) and dry pyridine (.3 ml) in dry ether (45 ml) at 0^{o}. After 5 min addition (about $^{1}/_{8}$) the remainder was added at room temperature. The mixture was heated at 55^{o} for 2 hr, cooled and poured into ice-cold water (50 ml). The mixture was extracted with ether and the ether extracts washed successively with aqueous sodium bicarbonate (saturated, 2 X 20 ml), water (2 X 20 ml) and saturated brine (1 X 20 ml). The evaporation of the solvent from the dried solution gave a residue which was distilled to give 1-bromo-3-(3'-furyl)prop-2-yne 18 (4g, 88%) as a pale yellow liquid b.p. 62^{o}/0.2 mm. (Found: C, 45.6; H, 2.8; Br, 42.8; M^{+} at *m/e* 185. C_7H_5OBr requires C, 45.4; H, 2.7; Br, 43.2%; M, 185).

ν_{max} (film) 3100, 2250, 1210, 1165, 1015, 880 and 800cm^{-1}.

δ7.6 (1H, d, furyl C2 H), 7.35, (1H, t, furyl C5 H), 6.4 (1H, d, furyl C4 H) and 4.05 (2H, s, CH_2Br).

Phenylpropargyl bromide 71

Using the procedure described above, phenylpropargyl

alcohol 132[91] (20g, .15 mol) was converted into phenylpropargyl bromide 71 (21.4g, 78%), b.p. 80°/0.5 mm (lit.[85] 110-120°/8 mm).

Reformatsky reaction of phenylpropargyl bromide 71 with acetone

Phenylpropargyl bromide 71 (0.49g, 2.5 mmol) in dry tetrahydrofuran (4 ml) was added dropwise at 10° over 2 hr under a nitrogen atmosphere to a stirred mixture of zinc wool (0.328g, 5 mmol), acetone (0.145g, 2.5 mmol) and mercuric chloride (10 mg). The reaction was initiated by warming the mixture at 40° for 30 sec. The mixture was stirred for 1 hr and then added to a mixture of ammonium hydroxide (2 ml), saturated aqueous ammonium chloride (10 ml) and water (10 ml). The mixture was extracted with ether (4 X 10 ml) and the extracts dried (K_2CO_3). The solvent was removed *in vacuo* and the residual oil was purified by preparative TLC (ether-light petroleum, 1:1).

The material of higher rf. was 2-methyl-3-phenylpenta-3,4-dien-2-ol 73 (46 mg, 10%) which was purified by distillation at 70°/1.5 mm to give colourless crystals m.p. 47-49.5°. (Found: C, 82.4; H, 7.9; M^+ at *m/e* 174. $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%; M, 174).

ν_{max} 3210, 1940, 1600, 1150, 850, 770 and 700cm^{-1}.

λ_{max} 214 nm, ε 8100; 244 nm, t 6900

δ7.3 (5H, m, phenyl H), 4.95 (2H, s, C=C=CH_2), 2.9 (1H, br.s, exch., OH) and 1.4 (6H, s, CH_3).

The material of lower rf. was 2-methyl-5-phenylpent-4-yn-2-ol 72 (0.273g, 63%) a colourless liquid b.p. 85°/0.6 mm. (Found: C, 82.4; H, 8.2; M^+ at *m/e* 174. $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%; M, 174).

ν_{max} (film) 3360, 1600, 1140, 900, 750 and 690cm^{-1}.

λ_{max} 240 nm, ε, 22500; 251 nm, t, 21000

δ7.25 (5H, m, phenyl H), 2.55 (2H, s, C≡C-CH_2), 2.3 (1H, br.s, exch., OH) and 1.35 (6H, s, CH_3).

Reformatsky reaction of phenylpropargyl bromide 71 with the Δ^4*E*-enol-lactone 42

A solution of phenylpropargyl bromide 71 (3.2g, 15.4 mmol) in dry tetrahydrofuran (20 ml) was added at room temperature to a stirred mixture of zinc wool (2g, 30 mmol) and mercuric chloride (50 mg) in dry tetrahydrofuran (10 ml). The mixture was stirred at 20° for 2 hr and added dropwise over 40 min to a stirred solution of the Δ^4*E*-enol-lactone 42 (2.5g, 15.4 mmol) in dry tetrahydrofuran (20 ml) in an atmosphere of nitrogen. The mixture was stirred at 20° for 24 hr and hydrolysed with a mixture of ammonium hydroxide (10 ml), saturated aqueous ammonium chloride (50 ml) and water (50 ml). The mixture was extracted with ether and the extracts dried (K_2CO_3). The ether was evaporated to give an oil which was chromatographed on silica gel. Elution with ether afforded

4,6-dihydroxy-2,6-dimethyl-9-phenylnona-2(Z),4(E)-dien-8-ynoic acid (1→4)lactone 76 (2.66g, 60%) as a pale yellow oil.

ν_{max} (film) 3420, 2250, 1760, 1740, 1660, 1610, 760 and 690cm^{-1}.

δ7.9 (1H, q, C3 H), 7.3 (5H, m, phenyl H), 5.8 (1H, s, C5 H), 3.1 (1H, br.s, exch., OH), 2.8 (2H, s, C≡C-CH_2), 2.0 (3H, d, C2 CH_3) and 1.6 (3H, s, C6 CH_3).

Reformatsky reaction of phenylpropargyl bromide 71 with the Δ^4Z-enol-lactone 43

Using the procedure described above, the Δ^4Z-enol-lactone 43 (0.19g, 1.2 mmol) was converted into the crude acetylenic carbinol which was purified by preparative TLC (ether-light petroleum, 3:1).

The material of lower rf. was 4,6-dihydroxy-2,6-dimethyl-9-phenylnona-2(Z),4(Z)-dien-8-ynoic acid (1→4)lactone 74 (0.143g, 46%), a pale yellow oil.

ν_{max} (film) 3450, 2250, 1760, 1660, 1620, 755 and 690cm^{-1}.

δ7.3 (5H, m, phenyl H), 7.0 (1H, q, C3 H), 5.4 (1H, s, C5 H), 3.1 (1H, br.s, exch., OH), 2.9 (2H, s, C≡C-CH_2), 1.95 (3H, d, C2 CH_3) and 1.7 (3H, s, C6 CH_3).

The material of higher rf. was 4,6-dihydroxy-2,6-dimethyl-7-phenylnona-2(Z),4(Z),7,8-tetraenoic acid (1→4)lactone 75 (78 mg, 25%), a pale yellow oil.

ν_{max} (film) 3450, 1945, 1760, 1660, 1620, 1050, 755 and 690cm^{-1}. δ7.4 (5H, m, phenyl H), 6.9 (1H, q, C3 H), 5.45 (1H, s, C5 H), 5.15 (2H, s, C=C=CH_2), 3.0 (1H, br.s, exch., OH), 2.0 (3H, d, C2 CH_3) and 1.7 (3H, s, C6 CH_3).

Acetylation of the acetylenic carbinols 74 and 76

The general procedure of Nevitt and Hammond was used.[94]

1. A solution of the Δ^4Z-carbinol 74 (0.245g, 0.91 mmol) in purified[174] N,N-dimethylaniline (0.5 ml) and chloroform (0.5 ml) at 0° was treated dropwise with acetyl chloride (0.2 ml). The mixture was kept at room temperature for 90 hr and poured into an excess of ice-cold water. The mixture was then extracted with ether and the ether extract was washed successively with water, dilute hydrochloric acid, water, 5% sodium bicarbonate solution, water and dried. The solvent was removed and the residue purified by preparative TLC (ether-light petroleum, 2:1). Recrystallisation from ether-light petroleum gave 6-acetoxy-4-hydroxy-2,6-dimethyl-9-phenylnona-2(Z),4(Z)-dien-8-ynoic acid (1→4)lactone 77 (0.235g, 83%) as colourless crystals m.p. 68.5-71°. (Found: C, 73.5; H, 5.80; M^+-CH_3CO_2H at *m/e* 250. $C_{19}H_{18}O_4$ requires C, 73.5; H, 5.85%; M, 310).

ν_{max} 1780, 1740, 1675, 1625, 1600, 1240, 1050, 800, 760 and 695cm^{-1}. δ7.25 (5H, m, phenyl H), 6.9 (1H, q, C3 H), 5.4 (1H, s, C5 H),

3.15 (2H, s, C≡C-CH_2), 2.05 (3H, s, -OCOCH_3), 2.0 (3H, br.s, C2 CH_3) and 1.82 (3H, s, C6 CH_3).

2. Using the procedure described above, the Δ^4*E*-carbinol 76 (0.256g, 0.96 mmol) was converted into 6-acetoxy-4-hydroxy-2,6-dimethyl-9-phenylnona-2(*Z*),4(*E*)-dien-8-ynoic acid (1→4)lactone 78 (0.217g, 73%) which was crystallised from ether-light petroleum as colourless crystals m.p. 81.5-83°. (Found: C, 73.5; H, 6.0; M^+-CH_3CO_2H at *m/e* 250. $C_{19}H_{18}O_4$ requires C, 73.5; H, 5.85%; M, 310). ν_{max} 1770, 1740, 1665, 1625, 1600, 1240, 1060, 1000, 760 and 695cm^{-1}. δ7.4 (1H, q, C3 H), 7.3 (5H, m, phenyl H), 5.8 (1H, s, C5 H), 3.5 (2H, q, J_{gem} 17Hz, C≡C-CH_2), 2.1 (3H, s, -OCOCH_3), 2.0 (3H, d, C2 CH_3) and 1.8 (3H, s, C6 CH_3).

Pyrolysis of the acetates 77 and 78

The acetate was distilled under vacuum (~ .03 mm) through a Vycor tube (50 cm X 2.5 cm) packed with silica beads heated at 450°, and the pyrolysate collected on a cold-finger. The pyrolysate was purified by extensive preparative TLC to give the component olefins.

1. In this manner, the Δ^4*E*-acetate 78 (0.217g, 0.7 mmol) was converted into a mixture of olefins (0.157g, 90%) which were purified by preparative TLC (ether-light petroleum, 2:1).

The material of highest rf. was 4-hydroxy-2,6-dimethyl-9-phenylnona-2(*Z*),4(*E*),6(*Z*)-trien-8-ynoic acid (1→4)lactone 79 (43 mg, 25%) which was recrystallised from light petroleum as yellow plates m.p. 101-103° (lit.[29] 101-103°). M^+ at *m/e* 250, $C_{17}H_{14}O_2$ requires M, 250.

ν_{max} ($CHCl_3$) 3100, 2180, 1760, 1640, 1600, 1050, 990 (s), 950 (s) and 895 (s)cm^{-1}.

λ_{max} 403 nm, ε 20000.

δ7.32 (5H, m, phenyl H), 7.1 (1H, q, J1.4Hz, C3 H), 6.5 (1H, s, C5 H), 5.75 (1H, d, J1.5Hz, C7 H), 2.3 (3H, d, J1.5Hz, C6 CH_3) and 2.03 (3H, d, J1.4Hz, C2 CH_3).

The material of lowest rf. was 4-hydroxy-2,6-dimethyl-9-phenylnona-2(*Z*),4(*Z*),6(*E*)-trien-8-ynoic acid (1→4)lactone 80 (30 mg, 17%) which was recrystallised from light petroleum as yellow crystals m.p. 153-155° (lit.[29] 152-156°). M^+ at *m/e* 250, $C_{17}H_{14}O_2$ requires M, 250.

ν_{max} ($CHCl_3$) 3100, 2200, 1760, 1640, 1050, 990 (s), 940 (m) and 895 (s)cm^{-1}.

λ_{max} 398 nm, ε 19000.

δ7.33 (5H, m, phenyl H), 7.02 (1H, q, J1.4Hz), 6.0 (1H, br.s, J1.1Hz, C7 H), 5.65 (1H, s, C5 H), 2.4 (3H, d, J1.1Hz, C6 CH_3) and 2.03 (3H, d, J1.4Hz, C2 CH_3).

The fractions of intermediate rf. were shown by the NMR spectra to be mixtures of the two olefins 79 and 80 and a third

isomer, which was identified as 4-hydroxy-2,6-dimethyl-9-phenylnona-2(*Z*),4(*E*),6(*E*)-trien-8-ynoic acid (1→4)lactone 81. The olefin could not be obtained pure by this route, and the spectral characteristics are recorded in a later preparation by a different route (p. 147).

2. The 9-phenyl-4(*Z*)acetate (0.198g, 0.64 mmol) also gave the 4(*E*),6(*Z*)-olefin 79 (37 mg, 23%) and the 4(*Z*),6(*E*)-olefin 80 (27 mg, 17%), as evidenced by their m.p., m.m.p. and spectral characteristics, and the impure 4(*E*),6(*E*)-olefin 81.

Reformatsky reaction of 1-bromo-3-(3'-furyl)prop-2-yne 18 with the Δ^4E-enol-lactone 42

Using the procedure described for the Reformatsky reaction of phenylpropargyl bromide 71 and the enol-lactone 42, 1-bromo-3-(3'-furyl)prop-2-yne 18 (4g, 21.6 mmol) and the Δ^4E-enol-lactone 42 (3.26g, 21.6 mmol) were converted into the crude acetylenic carbinol which was purified by chromatography on silica gel. Elution with ether gave 9-(3'-furyl)-4,6-dihydroxy-2,6-dimethylnona-2(*Z*),4(*E*)-dien-8-ynoic acid (1→4)lactone 82 (3.9g, 70%) as a pale yellow oil.

ν_{max} (film) 3450, 1750, 1660, 1620, 1160, 1075, 1000, 880, 795 and 760cm^{-1}.

δ7.75 (1H, d, furyl C2 H), 7.5 (1H, d, furyl C5 H), 7.3 (1H, q, C3 H), 6.38 (1H, d, furyl C4 H), 5.7 (1H, s, C5 H), 3.0 (1H, br.s, exch., OH),

2.7 (2H, s, C≡C-CH_2), 2.0 (3H, br.s, C2 CH_3) and 1.55 (3H, s, C6 CH_3).

Acetylation of the carbinol 82

Using the procedure described for the acetylation of the carbinols 74 and 76, the carbinol 82 (3.9g, 15.2 mmol) was converted into 6-acetoxy-9-(3'-furyl)-2,6-dimethylnona-2(*Z*),4(*E*)-dien-8-ynoic acid (1→4)lactone 84 (3.4g, 75%) which was recrystallised from ether-light petroleum as colourless needles m.p. 83.5-85°.
(Found: C, 68.3; H, 5.55, M^+ at *m/e* 300. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.4%; M, 300).
ν_{max} 1740, 1700, 1670, 1620, 1080, 875 and 800cm^{-1}.
δ7.5 (1H, d, furyl C2 H), 7.35 (2H, br.m, furyl C5 H; C3 H), 6.35 (1H, d, furyl C4 H), 5.78 (1H, br.s, C5 H), 3.05 (2H, q, J_{gem}17Hz, C≡C-CH_2), 2.08 (3H, s, -OCOCH_3), 2.0 (3H, br.s, C2 CH_3) and 1.8 (3H, s, C6 CH_3).

Pyrolysis of the acetate 84

Using the conditions previously described for the pyrolysis of the acetates 77 and 78, the Δ^4*E*-acetate 84 (0.50g, 1.68 mmol) was converted into a mixture of olefins which were purified by preparative TLC (ether-light petroleum, 2:1).

The component of highest rf. was 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(*Z*),4(*E*),6(*Z*)-trien-8-ynoic acid (1→4)lactone 85

(87 mg, 20%) which was recrystallised from light petroleum as yellow needles m.p. 86-88°. (Found: C, 75.2; H, 5.2; M^+ at *m/e* 240. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%; M, 240).

ν_{max} ($CHCl_3$) 2200, 1760, 1630, 1050, 990 (s), 950 (s), 890 (m) and 870 (s)cm^{-1}.

λ_{max} 369 nm, ε 25000.

δ7.64 (1H, d, furyl C2 H), 7.38 (1H, t, furyl C5 H), 7.12 (1H, q, J1.5Hz, C3 H), 6.48 (1H, m, furyl C4 H), 6.3 (1H, s, C5 H), 5.7 (1H, q, J1.5Hz, C7 H), 2.25 (3H, d, J1.5Hz, C6 CH_3) and 2.06 (3H, d, J1.5Hz, C2 CH_3).

The component of lowest rf. was 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(*Z*),4(*Z*),6(*E*)-trien-8-ynoic acid (1→4)lactone 86 (98 mg, 24%) which was recrystallised from benzene as yellow prisms m.p. 162-163.5°. (Found: C, 75.1; H, 5.1; M^+ at *m/e* 240. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%; M, 240).

ν_{max} ($CHCl_3$) 3100, 2200, 1760, 1630, 1610, 1040, 980 (s), 950 (m), 890 (s) and 870 (s)cm^{-1}.

λ_{max} 368 nm, ε 35000.

δ7.65 (1H, d, furyl C2 H), 7.4 (1H, t, furyl C5 H), 7.02 (1H, q, J1.5Hz, C3 H), 6.48 (1H, m, furyl C4 H), 5.9 (1H, br.s, J1Hz, C7 H), 5.6 (1H, br.s, C5 H), 2.36 (3H, d, J1.0Hz, C6 CH_3) and 2.02 (3H, d, J1.5Hz, C2 CH_3). The spectral data of this olefin 86 were identical to the natural product freelingyne 16, m.p. 164°, m.m.p. 162-163°.

A further isomer was shown by the NMR spectra to be present in the impure fractions of intermediate rf. It was identified as 9-(3'-furyl)-4-hydroxy-2,6-dimethyl-2(*Z*),4(*E*),6(*E*)-trien-8-ynoic acid (1→4)lactone 87.

δ7.65 (1H, d, furyl C2 H), 7.5 (1H, q, J1.5Hz, C3 H), 7.4 (1H, t, furyl C5 H), 6.34 (1H, br.s, C5 H), 5.92 (1H, br.s, J1Hz, C7 H), 2.26 (3H, br.s, J1Hz, C6 CH_3) and 2.02 (3H, d, J1.5Hz, C2 CH_3).

Reformatsky reaction of *E*-cinnamyl bromide 89 with the Δ^4*E*-enol-lactone 42

In a typical experiment, a solution of *E*-cinnamyl bromide 89 (0.245g, 1.25 mmol) in dry tetrahydrofuran (5 ml) was added at -10° over 1 hr to a stirred mixture of zinc wool (0.164g, 2.5 mmol) and mercuric chloride (10 mg) in dry tetrahydrofuran (2 ml). The mixture was stirred at 0° for 3 hr and a solution of the Δ^4*E*-enol-lactone 42 (0.188g, 1.25 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. The temperature was allowed to reach room temperature over 3 hr, and the mixture was stirred for 48 hr. The mixture was hydrolysed in the usual way, extracted with ether and the ether extracts dried (K_2CO_3). The ether was removed *in vacuo* to give an oil which was purified by preparative TLC (ether-light petroleum, 3:2).

The fraction of higher rf., a colourless oil (60 mg), was

dicinnamyl 92.

δ7.2 (10H, br.m, phenyl H), 6.0 (4H, v.br.m, olefinic H), 5.0 (2H, br.m, olefinic H), and 2.5 (2H, br.m, allylic H).

The fraction of lower rf. was a 1:1 mixture of the carbinols 90 and 91 (52 mg, 15%), colourless crystals m.p. 81-98°. ν_{max} 3420, 1750, 1660, 1620, 1070, 990, 920 and 700cm^{-1}.
δ7.6 (1H, q, C3 H), 7.2 (5H, br.s, phenyl H), 6.3 (1H, v.br.m, C8, C9 H of 90), 5.6 (1H, s, C5 H), 5.0 (2H, br.m, vinyl H of 91), 3.4 (1H, d, C≡C-CH_2 of 90), 2.2 (1H, br.s, exch., OH), 1.98 (3H, br.s, C2 CH_3) and 1.32 (3H, br.s, C6 CH_3).

Other experiments performed at different temperatures and different concentrations gave the same mixture of carbinols 90 and 91.

Lindlar hydrogenation of the Δ^4E,Δ^6Z-olefin 85

The olefin 85 (100 mg, 0.42 mmol) in ethyl acetate (20 ml) was stirred in an atmosphere of hydrogen with Lindlar catalyst[34] (0.10g) and quinoline (20 mg) until one equivalent of hydrogen was consumed. The mixture was filtered through a celite pad, washed with dilute hydrochloric acid and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by preparative TLC (chloroform) to give 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(Z), 4(E),6(Z),8(Z)-tetraenoic acid (1→4)lactone 93 (90 mg, 90%) which

was recrystallised from light petroleum as yellow crystals, m.p. 108-110°. (Found: C, 74.3; H, 5.9; M^+ at *m/e* 242. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%; M, 242).

ν_{max} ($CHCl_3$) 3000, 1760, 1650, 1625, 1595, 1150, 1030, 975 (s), 930 (s) 905 (w) and 850 (s)cm^{-1}.

λ_{max} 380 nm, ε 48000.

δ7.52 (1H, br.s, furyl C2 H), 7.42 (1H, t, furyl C5 H), 7.1 (1H, q, J1.5Hz, C3 H), 6.6 (3H, br.m, furyl C4 H, C8 H and C9 H), 6.34 (1H, br.s, J1.5Hz, C5 H), 6.16 (1H, s, C7 H), 2.26 (3H, d, J1.5Hz, C6 CH_3) and 2.02 (3H, d, J1.5Hz, C2 CH_3).

Lindlar hydrogenation of freelingyne 86

Using the procedure described above for the hydrogenation of the olefin 85, the Δ^4Z,Δ^6E-olefin 86 (freelingyne) (0.160g, 0.66 mmol) was hydrogenated to give 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(*Z*), 4(*Z*),6(*E*),8(*Z*)-tetraenoic acid (1→4)lactone 94 (0.152g, 94%) which was recrystallised from light petroleum as yellow crystals, m.p. 117-119°. (Found: C, 74.2; H, 5.9; M^+ at *m/e* 242. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%; M, 242).

ν_{max} ($CHCl_3$) 3000, 1760, 1610, 1580, 1210, 1170, 1050, 1030, 990 (s), 965 (m), 930 (m), 900 (w), 875 (s) and 850 (m)cm^{-1}.

λ_{max} 383 nm, ε 65300.

δ7.58 (1H, br.s, furyl C2 H), 7.42 (1H, t, furyl C5 H), 7.0 (1H, q,

J1.5Hz, C3 H), 6.9 (1H, br.m, C7 H), 6.6 (1H, t, furyl C4 H), 6.4 (2H, br.m, C8 H, C9 H), 5.65 (1H, s, C5 H), 2.24 (3H, d, J1.0Hz, C6 CH_3) and 2.02 (3H, br.s, J1.5Hz, C2 CH_3).

Section 2

Wittig reaction of the phosphorane 95 with the Δ^4*E*-enol-lactone 42

A solution of cinnamyltriphenylphosphonium chloride[175] (0.414g, 1 mmol) and the enol-lactone 42 (0.152g, 1 mmol) in dry dichloromethane (10 ml) was added dropwise under nitrogen to a suspension of sodium hydride (48 mg, as a 50% suspension in oil, 1 mmol) in dry dichloromethane (5 ml). The mixture was stirred at room temperature for 41 hr and water (10 ml) was added. The mixture was extracted with dichloromethane and dried. The solvent was removed in vacuum and the residue purified by preparative TLC (ether-light petroleum, 3:2). The biphenyl 96 was obtained as a pale yellow solid (60 mg, 25%) m.p. 135-144°. M^+ at *m/e* 252, $C_{17}H_{16}O_2$ requires M, 252.

ν_{max} 2600, 1680, 1630, 1240, 910 (s), 820 (s), 760 (s) and 700 (s)cm^{-1}.

λ_{max} 240 nm, ε ~ 14500; 260 nm, ε ~ 11000.

δ8.0 (1H, br.s, exch., -OH), 7.4 (5H, s, phenyl H), 7.2 (3H, br.s, olefinic H), 6.7 (1H, br.s, C3 H), 2.36 (3H, s, =C-CH_3) and 2.0 (3H, d, J1.5Hz, =C-CH_3).

Esterification of the biphenyl acid 96

A solution of the acid 96 (15 mg, 0.06 mmol) in ether (30 ml) was added to a stirred, ice-cold solution of ethereal diazomethane[112] (*ca.* 0.3 mmol). The solution was stirred at 0° and allowed to warm slowly to room temperature. After 3 hr at room temperature the solution was warmed on a water bath to drive off the excess of diazomethane, and the solvent was removed under reduced pressure to give the methyl ester 97 (12 mg, 75%) as a pale yellow oil. M^+ at *m/e* 266, $C_{18}H_{18}O_2$ requires M, 266.

ν_{max} (film) 1710, 1640, 1610, 1130, 1110, 900 (w), 815 (s), 760 (s), 740 (s) and 700 (s)cm^{-1}.

λ_{max} 235, 275 nm.

δ7.3 (5H, s, phenyl H), 7.2 (2H, br.s, olefinic H), 7.0 (1H, s, olefinic H), 6.55 (1H, br.s, olefinic H), 3.6 (3H, s, OCH_3), 2.36 (3H, s, $=C-CH_3$) and 2.0 (3H, d, J1.5Hz, $=CCH_3$). Spin decoupling studies confirmed that the proton at δ6.55 was coupled to the methyl group at δ2.0.

Hydrogenation of the biphenyl ester 97

A solution of the ester 97 (10 mg, 0.037 mmol) in ethyl acetate (10 ml) was stirred in an atmosphere of hydrogen with platinum dioxide[113] (20 mg) until one equivalent of hydrogen had

been consumed. The mixture was filtered through a celite pad and the solvent evaporated to give the saturated ester 98 (7 mg, 70%) as a colourless oil. M^+ at *m/e* 268, $C_{18}H_{20}O_2$ requires M, 268. ν_{max} (film) 1730, 1610, 1160, 820 (s), 765 (s) and 700 (s)cm^{-1}. λ_{max} 237 nm.

Preparation of the di-deutero olefin 103

Using the conditions described for the hydrogenation of freelingyne 86, a solution of freelingyne 86 (40 mg, 0.16 mmol) in ethyl acetate (15 ml) was stirred in an atmosphere of deuterium gas with Lindlar catalyst[34] (40 mg). The crude product was purified by preparative TLC (chloroform) to give the 2(Z),4(Z),6(E),8(Z)-di-deutero lactone 103 (37 mg, 93%) which was recrystallised from light petroleum as yellow crystals, m.p. 115-117°. M^+ at *m/e* 244, $C_{15}H_{12}D_2O$ requires M, 244.

δ7.58 (1H, br.s, furyl C2 H), 7.42 (1H, t, furyl C5 H), 7.02 (1H, q, J1.5Hz, C3 H), 6.9 (1H, br.m, C7 H), 6.6 (1H, t, furyl C4 H), 5.65 (1H, s, C5 H), 2.24 (3H, d, J1Hz, C6 CH_3) and 2.02 (3H, br.s, J1.5Hz, C2 CH_3).

4,6-dihydroxy-2-methylhepta-2(Z),4(*E*)-dienoic acid (1→4)lactone 105

A solution of zinc borohydride in ether[116] (50 ml, 0.147M) was added to a stirred solution of the Δ^4*E*-enol-lactone 42 (0.456g, 3 mmol) in ether (20 ml) in an atmosphere of nitrogen. After 30 min, water (8 ml) was added cautiously to the cooled reaction mixture, followed by a solution of acetic acid (2.8 ml) in water (8 ml). The mixture was extracted with ether and the ether extracts were washed successively with an aqueous 5% sodium bicarbonate solution, water and brine, and dried. The solvent was removed *in vacuo* and the residue purified by preparative TLC (ether-light petroleum, 9:1) to give 4,6-dihydroxy-2-methylhepta-2(Z),4(*E*)-dienoic acid (1→4)lactone 105 (0.370g, 80%) as colourless crystals m.p. 53-55° (lit.[57] 54-57°). M^+ at 154, $C_8H_{10}O_3$ requires M, 154. δ7.45 (1H, br.s, J1.5Hz, C3 H), 5.62 (1H, d, $J_{5,6}$8Hz, C5 H), 4.65 (1H, d.d, $J_{5,6}$8Hz, $J_{6,7}$8Hz, C6 H), 3.0 (1H, br.s, exch., OH), 2.0 (3H, d, J1.5Hz, C2 CH_3) and 1.38 (3H, d, J6Hz, C6 CH_3).

4,6-dihydroxy-2-methylhepta-2(Z),4(Z)-dienoic acid (1→4)lactone 109

Using the procedure described above for the preparation of the alcohol 105, the Δ^4Z-enol-lactone 43 (0.456g, 3 mmol) was converted into 4,6-dihydroxy-2-methylhepta-2(Z),4(Z)-dienoic acid (1→4)lactone 109 (0.30g, 65%), a colourless oil. M^+ at *m/e* 154, $C_8H_{10}O_3$ requires M, 154.

ν_{max} (film) 3400, 2900, 1760, 1670, 1620, 995 (s), 950 (m), 930 (m), 890 (m) and 750 (s)cm^{-1}.

δ7.02 (1H, q, J1.5Hz, C3 H), 5.25 (1H, d, J9Hz, C5 H), 5.0 (1H, d.q, $J_{5,6}$9Hz, $J_{6,7}$8Hz, C6 H), 2.55 (1H, br.s, exch., OH), 2.0 (3H, d, J1.5Hz, C3 H) and 1.38 (3H, d, $J_{6,7}$8Hz, C6 CH_3).

Accurate analysis figures could not be obtained as the alcohol 109 underwent decomposition upon distillation.

Preparation of the phosphonium salts 26 and 110

1. A solution of the alcohol 105 (0.217g, 1.4 mmol) and triphenylphosphonium bromide[53] (0.482g, 1.4 mmol) in chloroform (9 ml) was allowed to stand at room temperature for 70 hr. The solvent was removed under reduced pressure and the residue purified by preparative TLC (methanol-ether, 1:4). The material of low rf., the phosphonium salt 26 (0.38 g, 57%), was dried by adding benzene and removing it *in vacuo* and was used immediately without further purification.

2. In a similar manner the alcohol 109 (0.270g, 1.75 mmol) was converted into the phosphonium salt 110 (0.437g, 52%) which was used immediately.

Wittig reaction of the phosphonium salts 26 and 110 with *p*-nitrobenzaldehyde

1. To a stirred suspension of sodium hydride (0.115g, as a 50% suspension in oil, 2.4 mmol) in dry dichloromethane (10 ml) was added a solution of the phosphonium salt 26 (0.38g, 0.79 mmol) in dry dichloromethane (15 ml) under nitrogen. A solution of *p*-nitrobenzaldehyde (0.119g, 0.79 mmol) in dry dichloromethane (10 ml) was added and the mixture was stirred at room temperature for 40 hr. Water (5 ml) was added to the mixture, followed by dilute hydrochloric acid (0.5 ml), and the mixture was extracted with dichloromethane and the extracts were dried. The solvent was evaporated and the residue purified by preparative TLC (ether-light petroleum, 3:2). The fraction of intermediate rf. was recovered *p*-nitrobenzaldehyde (40 mg).

The fraction of highest rf. was 4-hydroxy-2,6-dimethyl-7-(4'-nitrophenyl)hepta-2(Z),4(Z),6(Z)-trienoic acid (1→4)lactone 111 (38 mg, 17%). Recrystallisation from ether-light petroleum and sublimation at 140°/.05 mm gave yellow needles m.p. 155-157°. (Found: C, 66.4; H, 5.0; O, 23.5; M^+ at *m/e* 271. $C_{15}H_{13}O_4N$ requires C, 66.4; H, 4.8; O; 23.6%; M, 271).

ν_{max} ($CHCl_3$) 1760, 1595, 1340, 1050, 990 (s), 950 (s), 870 (m) and 850 (w)cm^{-1}.

λ_{max} 361 nm, ε 33000.

δ8.2 (2H, d, phenyl H), 7.4 (2H, d, phenyl H), 7.04 (1H, q, J1.5Hz, C3 H), 6.6 (1H, q, J1.4Hz, C7 H), 5.94 (1H, s, C5 H), 2.4 (3H, d, J1.4Hz, C6 CH_3) and 2.08 (3H, d, J1.5Hz, C2 CH_3).

The fraction of lowest rf. was 4-hydroxy-2,6-dimethyl-7-(4'-nitrophenyl)hepta-2(*Z*),4(*Z*),6(*E*)-trienoic acid (1→4)lactone 112 (35 mg, 16%), recrystallised from ether-light petroleum as yellow crystals m.p. 141-144°. (Found: C, 66.4; H, 4.8; N, 5.3; M^+ at *m/e* 271. $C_{15}H_{13}O_4N$ requires C, 66.4; H, 4.8; N, 5.2%; M, 271). ν_{max} ($CHCl_3$) 1760, 1595, 1340, 1050, 990 (s), 950(s), 900 (s), 870 (w) and 850 (w)cm^{-1}.

λ_{max} 363 nm, ε 27700.

δ8.22 (2H, d, phenyl H), 7.42 (2H, d, phenyl H), 6.8 (1H, q, J0.9Hz, C7 H), 5.74 (1H, s, C5 H), 2.16 (3H, d, J0.9Hz, C6 CH_3) and 2.08 (3H, d, J1.5Hz, C2 CH_3).

2. Using the above procedure, the phosphonium salt 110 (0.437g, 0.91 mmol) and *p*-nitrobenzaldehyde (0.110g, 0.73 mmol) gave the 4(*Z*),6(*Z*)-lactone 111 (30 mg, 14%) and the 4(*Z*),6(*E*)-lactone 112 (20 mg, 10%).

3-(3'-furyl)propyn-1-al 25

A solution of the alcohol 70 (0.48g, 3.9 mmol) in dichloromethane (30 ml) was stirred at room temperature with manganese dioxide[118] (3.2g) for 10 hr. The mixture was filtered through a

celite pad and the solvent evaporated to give an oil which was purified by preparative TLC (ether-light petroleum, 3:7). 3-(3'-furyl)propyn-1-al 25 (0.205g, 44%) was obtained as an unstable colourless liquid b.p. 70^{o}/1.5 mm. (Found: C, 69.5; H, 3.5; M^{+} at *m/e* 120. $C_7H_4O_2$ requires C, 70.0; H, 3.4%; M, 120).

ν_{max} (film) 3150, 2850, 2220, 1660, 1040, 1010, 930, 880, 810 and 740cm^{-1}.

δ9.42 (1H, s, CHO), 7.82 (1H, d, furyl C2 H), 7.42 (1H, t, furyl C5 H) and 6.56 (1H, d, furyl C4 H).

Attempted oxidation of the alcohol 70 with dimethylsulphoxide[119]

A solution of the alcohol 70 (1.41g, 11.5 mmol) in dimethylsulphoxide (35 ml) and acetic anhydride (23 ml) was allowed to stand at room temperature for 23 hr and then poured into water (150 ml). After 30 min, the mixture was extracted with ether and the extracts washed with a saturated sodium bicarbonate solution, water and dried. The solvent was removed *in vacuo* and the residue purified to give the acetate (1.28g, 68%), as a colourless oil b.p. 118-124^{o}/20 mm. M^{+} at *m/e* 164, $C_9H_8O_3$ requires M, 164.

ν_{max} (film) 3100, 2200, 1735, 1650, 970, 875 and 800cm^{-1}.

δ7.62 (1H, br.s, furyl C2 H), 7.36 (1H, t, furyl C5 H), 6.45 (1H, br.s, furyl C4 H), 4.85 (2H, s, OCH_2) and 2.1 (3H, s, $COCH_3$).

Wittig reaction of the phosphonium salt 26 with the aldehyde 25

Using the procedure described above for the reaction of the phosphonium salts with *p*-nitrobenzaldehyde, the phosphonium salt 26 (0.62g, 1.3 mmol) and the aldehyde 25 (0.157g, 1.3 mmol) in the presence of sodium hydride (0.166g, as a 50% suspension in oil, 3.9 mmol) were converted to a mixture which was purified by preparative TLC (chloroform).

The fraction of highest rf. was a 3:1 mixture of the Δ^4E Δ^6Z-lactone 85 and the Δ^4Z,Δ^6E-lactone 86 (10 mg, 3%). This was determined by the NMR spectrum of the mixture which was identical to the superimposed spectra of the pure lactones 85 and 86 previously prepared.

CHAPTER 2

Section 1

3-phenylpropyn-1-al 116

Phenylpropargyl alcohol 115 (1.35g, 10 mmol) was oxidised by the method of Albright and Goldman[119] (detailed on page 137) to give 3-phenylpropyn-1-al 116 (0.88g, 67%) as a colourless liquid b.p. 140°/24 mm (lit.[176] b.p. 114-115°/17 mm).

Ethyl 2-methyl-5-phenylpent-2(*E*)-en-4ynoate 118

A solution of 3-phenylpropyn-1-al 116 (0.875g, 6.7 mmol) and 1-ethoxycarbonylethylenetriphenylphosphorane 117[128] (2.46g, 6.8 mmol) in benzene (100 ml) was heated under reflux for 27 hr. The solvent was removed under reduced pressure and the residue extracted with hexane (3 X 50 ml). The extracts were filtered, dried and evaporated to give an oil which was distilled to give ethyl 2-methyl-5-phenylpent-2(*E*)-en-4-ynoate 118 (1.2g, 85%) as a colourless liquid b.p. 120°/0.1 mm. (Found: C, 78.3; H, 6.4; M^+ at *m/e* 214. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.6%; M, 214).

ν_{max} (film) 3080, 2200, 1720, 1620, 1120, 1040, 1000 (s), 970 (w), 915 (w), 755 (s) and 740 (s)cm^{-1}.

λ_{max} 296 nm, ε 21000.

δ7.35 (5H, m, phenyl H), 6.8 (1H, q, J1.5Hz, C3 H), 4.21 (2H, q, $O\underline{CH_2}CH_3$), 2.14 (3H, d, J1.5Hz, C2 CH_3) and 1.32 (3H, t, $OCH_2\underline{CH_3}$).

GLC analysis using a 10 ft X $^1/_8$ in 15% NPGS on Chromosorb W column at 220° showed that the ester 118 was pure.

2-methyl-5-phenylpent-2(*E*)-en-4-yn-1-ol 119

Aluminium chloride (0.4g, 3 mmol) was added to a stirred, cooled suspension of lithium aluminium hydride (0.285g, 7.5 mmol) in dry ether (20 ml) under an atmosphere of nitrogen, and the mixture stirred at room temperature for 1 hr. A solution of the ester 118 (1.07g, 5 mmol) in dry ether (20 ml) was added over a period of 10 min, and the mixture was stirred at room temperature for 30 min. The cooled mixture was treated with water (.29 ml), 15% sodium hydroxide solution (.29 ml) and water (.87 ml).[173] The mixture was allowed to warm to room temperature, the precipitate removed by filtration and the filtrate was dried. Removal of the ether gave an oil which was purified by preparative TLC (ether-light petroleum, 2:1). 2-methyl-5-phenylpent-2(*E*)-en-4-yn-1-ol 119 (0.69g, 80%) was obtained as a colourless liquid b.p. 140°/.05 mm. A sample was converted into the acetate.[177] (Found: C, 78.7; H, 6.6. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.6%).

M^+ at *m/e* 172. $C_{12}H_{12}O$ requires M, 172.

ν_{max} (film) 3330, 2210, 1605, 1070, 1020, 915 (w), 850 (w), 825 (m),

760 (s) and 700 (s)cm^{-1}.

δ7.3 (5H, m, phenyl H), 5.74 (1H, q, J1.4Hz, C3 H), 4.1 (2H, s, OCH_2), 3.4 (1H, br.s, exch., OH) and 2.0 (3H, d, J1.4Hz, C2 CH_3).

2-methyl-5-phenylpent-2(*E*)-en-4-yn-1-al 120

A solution of the alcohol 119 (0.5g, 2.9 mmol) in benzene (150 ml) was heated under reflux with silver carbonate on celite[135] (16.5g, 30 equiv.) for 11 hr. The cooled mixture was filtered through a celite pad and the filtrate evaporated. The residue was purified by preparative TLC (ether-light petroleum, 2:3). 2-methyl-5-phenylpent-2(*E*)-en-4-yn-1-al 120 (0.45 g, 92%) was obtained as a colourless oil b.p. 95°/.05 mm. (Found: C, 84.6; H, 6.0; M^+ at *m/e* 170. $C_{12}H_{10}O$ requires C, 84.7; H, 5.9%; M, 170).

ν_{max} (film) 2820, 2720, 2210, 1670, 1620, 1080, 1060, 1010 (s), 995 (m), 925 (w), 860 (m), 845 (s), 770 (s) and 700 (s)cm^{-1}.

λ_{max} 319 nm, ε 20000.

δ9.5 (1H, s, CHO), 7.4 (5H, m, phenyl H), 6.5 (1H, q, J1.4Hz, C3 H), and 2.0 (3H, d, J1.4Hz, C2 CH_3).

Methyl 2-methyl-5-phenylpent-2(*E*)-en-4-ynoate 121

The aldehyde 120 (41 mg, 0.25 mmol) was converted into the methyl ester 121 (22 mg, 50%) using the established procedure of Corey.[136] The NMR spectrum of 121 was identical to the known ester

121.[131]

δ7.3 (5H, m, phenyl H), 6.8 (1H, q, J1.5Hz, C3 H), 3.72 (3H, s, OCH_3) and 2.14 (3H, d, J1.5Hz, $=C-CH_3$).

4-hydroxy-2-methylbut-2-enolide 129

A solution of 3-methyl-2-furoic acid[137] (4g, 31.8 mmol) and rose bengal (50 mg) in methanol (200 ml) was irradiated with a 500 watt tungsten lamp in a water-cooled apparatus, while oxygen was bubbled through the solution. The irradiation was continued until there was no change in the ultraviolet spectrum of the solution (*ca.* 48 hr). The solvent was removed under reduced pressure and the residue dissolved in water (30 ml) to which concentrated hydrochloric acid (4 drops) had been added. The solution was left for 48 hr at 25°, during which time a few ml of water was removed *in vacuo* four times. The solution was evaporated to dryness and the residue purified by sublimation *in vacuo* to afford 4-hydroxy-2-methylbut-2-enolide 129 (3.44g, 96%) as colourless crystals m.p. 71-74° (lit.[48] 73-74.5°).

2-methylbut-2-enolide 130

A solution of the hydroxylactone 129 (7.4g, 65.5 mmol) in methanol (100 ml) was reduced with alkaline sodium borohydride by the method of Foote[138] to give 2-methylbut-2-enolide 130

(5.2g, 82%) as a colourless liquid b.p. 90-92°/9 mm (lit.[178] 82°/7 mm).

4-bromo-2-methylbut-2-enolide 131

A solution of 2-methylbut-2-enolide 130 (2.25g, 23 mmol) and benzoyl peroxide (10 mg) in carbon tetrachloride was brominated with N-bromosuccinimide (4.18g, 23.5 mmol) by the method of Steyn,[141] to give 4-bromo-2-methylbut-2-enolide 131 (4.1g, quant.) as an unstable yellow oil which was used immediately without purification.

ν_{max} (film) 1780, 1720, 1650 and 950cm^{-1}.

δ7.2 (1H, m, C3 H), 6.8 (1H, m, C4 H) and 2.0 (3H, m, C2 CH_3).

Preparation of the butenolide phosphorane 30

A solution of the bromolactone 131 (5.4g, 29 mmol) and triphenylphosphine (8.1g, 31 mmol) in benzene (50 ml) was heated under reflux for 4 hr. The gummy precipitate 132 was filtered off and crystallised from dichloromethane-tetrahydrofuran as a brown solid m.p. 228-230°. The phosphonium bromide 132 was dissolved in warm water (200 ml) and the solution thoroughly extracted with ether (6 X 50 ml). The solution was cooled to 5° and an ice-cold solution of sodium hydroxide (10%) added slowly to the stirred solution until pH 9 was maintained. The precipitated phosphorane 30 was filtered off, dried *in vacuo* and stored at -10° as a yellow

solid (6.25g, 60%) m.p. 180-183° (lit.[48] 186-189°).

Wittig reaction of the phosphorane 30 with cinnamaldehyde 134

Using the procedure for the Wittig reaction described on page 135, the crude phosphonium salt 132 (0.70g, 1.7 mmol) and cinnamaldehyde 134 (0.20g, 1.53 mmol) were heated under reflux in dichloromethane for 15 hr and worked up in the usual manner. The crude product was purified by preparative TLC (ether-light petroleum, 3:1).

The fraction of higher rf. (0.14g) was mainly cinnamaldehyde 134 with about 25% of the product olefins present.

The fraction of lower rf. (74 mg, 22%) was a 1:1 mixture of 4-hydroxy-2-methyl-7-phenylhepta-2(Z),4(*E*),6(*E*)-trienoic acid (1→4)lactone 135 and the 2(Z),4(Z),6(*E*)-isomer 136, recrystallised from ether-light petroleum as pale yellow prisms m.p. 138-142°. (Found: C, 79.4; H, 5.8; M^+ at *m/e* 212. $C_{14}H_{12}O_2$ requires C, 79.2; H, 5.7%; M, 212).

ν_{max} 1750, 1600, 1570, 960, 885, 865 and 750cm^{-1}.

λ_{max} 358 nm, ε 23000.

δ7.4 (12H, br.m, phenyl H + C6 H of 135,136), 7.1 (2H, m, C3 H of 135,136), 6.8 (2H, d, $J_{6,7}$16Hz, C7 H of 135,136), 6.35 (1H, d, $J_{5,6}$10Hz, C5 H of 135), 5.9 (1H, d, $J_{5,6}$11Hz, C5 H of 136) and 2.02 (6H, br.s, C2 CH_3 of 135,136).

Wittig reaction of the phosphorane 30 with the aldehydes 120 and 137

a. Using the conditions described above, the crude phosphonium salt 132 and the aldehyde 120 were heated under reflux but no reaction took place, as evidenced by the ultraviolet spectrum of the reaction mixture. The reaction was attempted under different conditions, using butyl lithium, sodium hydride and sodium hydroxide as the base, and dichloromethane, dichloroethane and tetrahydrofuran as the solvent.

b. A similar reaction of the crude phosphonium salt 132 with 2-methyl-2-pentenal 137 (prepared by an aldol condensation of propanal[143]) also failed to give any olefinic products.

Attempted preparation of the phosphonate ester 138

a. The bromolactone 131 (0.5g, 2.82 mmol) and triethylphosphite (0.5g, 2.82 mmol) were heated together under reflux at 120-140^{o} for 6 hr. The cooled mixture was distilled under vacuum, with considerable tar formation to give two fractions which were both shown to be complex mixtures by TLC and the NMR spectra. The NMR spectra, however, did not show the resonances of the expected phosphonate ester 138.

b. An attempt to prepare 138 by the method of Meisters,[145] using the bromolactone 131, diethylphosphonate and sodium in liquid ammonia,

also failed to produce the phosphonate ester 138.

Preparation of the tri-*n*-butylphosphonium salt 140

A solution of the bromolactone 131 (1.78g, 10 mmol) and tri-*n*-butylphosphine (2.02g, 10 mmol) in benzene (40 ml) was heated under reflux for 3 hr in an atmosphere of nitrogen. The solvent was removed *in vacuo* and the oily phosphonium bromide salt 139 dissolved in ethanol (10 ml). A solution of sodium tetraphenylborate (3.42g, 10 mmol) in ethanol (10 ml) was added and the mixture cooled. The precipitated salt 40 (3.09g, 50%) was isolated and recrystallised from dichloromethane-hexane as colourless needles m.p. 153-155°. (Found: C, 79.5; H, 8.4; P, 5.2 $C_{41}H_{52}O_2PB$ requires C, 79.6; H, 8.5; P, 5.0%).

ν_{max} 1780, 1580, 1050, 745 and 710cm^{-1}.

Wittig reaction of the phosphonium salt 140 with the aldehyde 120

Using the procedure for the Wittig reaction described on page 135, a mixture of the phosphonium salt 140 (0.572g, 0.92 mmol), the aldehyde 120 (0.157g, 0.92 mmol) and sodium hydride (45 mg, as a 50% suspension in oil, 0.92 mmol) was heated under reflux in dry dichloroethane (25 ml) for 40 hr under nitrogen. The mixture was worked up as usual and the residue purified by preparative

TLC (chloroform).

The material of higher rf. was the Δ^4Z,Δ^6E-lactone 80 (79 mg, 34%), with identical physical and spectral characteristics to the compound 80 m.p. 153-155° (prepared previously p. 122), m.m.p. 152-154°.

The material of lower rf. was 4-hydroxy-2,6-dimethyl-9-phenylnona-2(*Z*),4(*E*),6(*E*)-trien-8-ynoic acid (1→4)lactone 81 (32 mg, 14%), which was recrystallised from light petroleum as yellow prisms m.p. 154.5-157°. (Found: C, 81.4; H, 5.7; M^+ at *m/e* 250. $C_{17}H_{14}O_2$ requires C, 81.6; H, 5.6%; M, 250).

ν_{max} ($CHCl_3$) 3000, 2200, 1760, 1605, 1060, 1030 (m), 1000 (s), 900 (m) and 875 (s)cm^{-1}.

λ_{max} 377 nm, ε 51500; 400 nm, ε 2900.

δ7.4 (6H, m, phenyl H, C3 H), 6.32 (1H, s, C5 H), 5.96 (1H, br.s, J1.0Hz, C7 H), 2.3 (3H, d, J1.0Hz, C6 CH_3) and 2.06 (3H, d, J1.4Hz, C2 CH_3).

4-bromobut-2-enolide 146

Using the procedure outlined for the preparation of the bromolactone 131, crotonolactone 145[150] (1.68g, 20 mmol) was brominated with N-bromosuccinimide (3.72g, 21 mmol) to give 4-bromobut-2-enolide 146 (2.6g, 80%), a pale yellow oil which was used without further purification.

ν_{max} (film) 3050, 1785, 1600, 1040, 975, 870, 820, 740 and 690cm^{-1}.
δ7.62 (1H, d.d, $J_{2,3}$6Hz, $J_{2,4}$1.6Hz, C2 H), 6.92 (1H, t, J1.6Hz, C4 H) and 6.2 (1H, d.d, $J_{2,3}$6Hz, $J_{3,4}$1.6Hz, C3 H).

Preparation of the phosphonium salt 148

Using the procedure described for the preparation of the tributylphosphonium salt 140, the bromolactone 146 (2.6g, 16 mmol) and tri-*n*-butylphosphine (3.22g, 16 mmol) were converted into the tetraphenylborate phosphonium salt 148 (2.97g, 31%), recrystallised from dichloromethane-light petroleum as off-white crystals m.p. 144-145°. (Found: C, 79.8; H, 8.4; P, 4.9. $C_{40}H_{50}O_2PB$ requires C, 79.5; H, 8.3; P, 5.1%).
ν_{max} 1825, 1600, 1580, 1040, 850, 740 and 710cm^{-1}.

Wittig reaction of the phosphonium salt 148 with *p*-nitrobenzaldehyde

Using the procedure outlined for the Wittig reaction on page 135, a mixture of the phosphonium salt 148 (0.604g, 1 mmol) and *p*-nitrobenzaldehyde (0.151g, 1 mmol) and sodium hydride (48 mg, as a 50% suspension in oil, 1 mmol) was heated under reflux in dichloromethane (15 ml) for 16 hr. The mixture was worked up as usual and the product purified by preparative TLC (chloroform) but only *p*-nitrobenzaldehyde (0.118g) was recovered.

Ethyl 2-methyl-5-phenylpenta-2(*E*),4(*E*)-dienoate 149

Using the procedure described for the preparation of the ester 118, the reaction between cinnamaldehyde 134 (1.06g, 8 mmol) and the phosphorane 117[128] (2.9g, 8 mmol) gave ethyl 2-methyl-5-phenylpenta-2(*E*),4(*E*)-dienoate 149 (1.52g, 88%) as a pale yellow oil b.p. 140°/4 mm (lit.[179] 123-124°/1 mm). M^+ at *m/e* 216, $C_{14}H_{16}O_2$ requires M, 216.

ν_{max} (film) 1700, 1620, 990, 745, 740 and 690cm^{-1}.

δ7.4 (6H, m, phenyl H, olefinic H), 6.8 (2H, m, olefinic H), 4.2 (2H, q, OCH_2CH_3), 2.0 (3H, d, C2 CH_3) and 1.3 (3H, t, OCH_2CH_3).

2-methyl-5-phenylpenta-2(*E*),4(*E*)-dienoic acid 153

A solution of the ester 149 (0.71g, 3.3 mmol) and potassium hydroxide (0.27g, 4.8 mmol) in methanol (10 ml) was heated under reflux for 4 hr. The precipitated potassium salt was removed, washed with ether, and dried under vacuum. To a solution of the potassium salt (0.59g) in water (10 ml) was added dilute hydrochloric acid until the solution was acidic. The precipitated acid 153 (0.42g, 70%) was removed and recrystallised from benzene-cyclohexane as colourless crystals m.p. 156-159° (lit.[131] 161-163°.).

Reduction of the acid chloride 154 with $LiAl(O^tBu)_3H$

A solution of the acid 153 (0.202g, 1.1 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of oxalyl chloride[180] (1.02g, 8 mmol) in dichloromethane (10 ml). The mixture was heated under reflux for 1 hr, cooled and the solvent removed *in vacuo*. Two portions of benzene were added and evaporated to give the crude acid chloride 154 (0.21g, 94%) as a yellow solid which was used immediately without further purification.

ν_{max} 1725 and 1620cm^{-1}.

To a solution of the acid chloride 154 (0.21g, 1 mmol) in dry diglyme (10 ml) at -78° was added a solution of lithium tri-*t*-butoxyaluminium hydride (0.28g, 1.1 mmol) in diglyme (10 ml) over 30 min in an atmosphere of nitrogen. The stirred mixture reached room temperature after 1 hr and sulphuric acid (10 ml, 1N) was added. The mixture was extracted with ether and the extracts were washed with a saturated solution of sodium bicarbonate, water and dried. The solvent was evaporated and the residue purified by preparative TLC (ether-light petroleum, 2:3) to give an oil (60 mg) which was a mixture of the aldehyde 151 and diglyme.

2-methyl-5-phenylpenta-2(*E*),4(*E*)-dien-1-ol 150

Using the procedure described for the preparation of the alcohol 119, the ester 149 (0.756g, 3.5 mmol) was reduced with a mixture of aluminium chloride (0.28g, 2.1 mmol) and lithium aluminium hydride (0.20g, 5.25 mmol) in dry ether (30 ml) to give 2-methyl-5-phenylpenta-2(*E*),4(*E*)-dien-1-ol 150 (0.59g, 97%), recrystallised from methanol-water as colourless crystals m.p. 86-88°. A sample was converted into the acetate[177]. (Found: C, 77.6; H, 7.6. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.5%).

M^+ at *m/e* 174. $C_{12}H_{14}O$ requires M, 174.

ν_{max} 3250, 1460, 1000, 960, 750 and 695cm^{-1}.

λ_{max} 282, 292, 299, 311 nm, ε 34000, 37500, 32000, 20000.

δ7.3 (5H, m, phenyl H), 7.2 (1H, d.d, $J_{4,5}$15Hz, $J_{3,4}$10Hz, C4 H), 6.9 (1H, d, $J_{4,5}$15Hz, C5 H), 6.4 (1H, d.q, $J_{3,4}$10Hz, C3 H), 4.15 (2H, s, OCH_2), 1.9 (3H, br.s, C2 CH_3) and 1.75 (1H, br.s, exch., OH).

GLC analysis using a 5 ft X $^1/_8$ in 15% FFAP on Chromosorb W column at 180° showed that the alcohol 150 was pure.

The reduction of the ester 149 with lithium aluminium monoethoxyhydride[155] produced the crude alcohol 150 in 90% yield.

2-methyl-5-phenylpenta-2(*E*),4(*E*)-dien-1-al 151

a. A solution of *E*-cinnamaldehyde 134 (0.264g, 2 mmol) and the phosphorane 152[153] (0.626g, 2 mmol) in benzene (150 ml) was heated under reflux for 256 hr in a nitrogen atmosphere. The solvent was removed *in vacuo* and the residue purified by preparative TLC (ether-light petroleum, 2:3), to give 2-methyl-5-phenylpenta-2(*E*), 4(*E*)-dien-1-al 151 (0.290g, 84%) as colourless crystals. A sample was purified by vacuum sublimation to give needles m.p. 60-61° (lit.[156] 58-59.5°).

ν_{max} 1670, 1615, 970, 860, 760, 740 and 680cm^{-1}.

δ9.5 (1H, s, CHO), 7.3 (5H, m, phenyl H), 6.9 (3H, br.m, C3 H, C4 H, C5 H) and 1.9 (3H, br.s, C2 CH_3).

b. The alcohol 150 (0.174g, 1 mmol) was oxidised with Collins reagent[124] to give the aldehyde 151 (0.117g, 68%).

c. The alcohol 150 (0.174g, 1 mmol) was oxidised with silver carbonate on celite[135] by the procedure described for the preparation of 120, to give the aldehyde 151 (0.148g, 86%).

Wittig reaction of the phosphonium salt 140 with the aldehyde 151

Using the procedure for the Wittig reaction described on page 135, a mixture of the phosphonium salt 140 (0.927g, 1.5 mmol),

the aldehyde 151 (0.172g, 1 mmol) and sodium hydride (72 mg, as a 50% suspension in oil, 1.5 mmol) was heated under reflux in dry dichloromethane (25 ml) for 37 hr under nitrogen and the mixture worked up as usual. The crude product was dissolved in dichloromethane (4 ml) and the product lactone 104 precipitated by the addition of a few drops of ether. The orange crystals were filtered from the solution to give 4-hydroxy-2,6-dimethyl-9-phenylnona-2(Z),4(Z),6(*E*),8(*E*)-tetraenoic acid (1→4)lactone 104 (47 mg, 19%). A sample was recrystallised from chloroform as yellow needles m.p. 173-175°. (Found: C, 81.0; H, 6.5; M^+ at *m/e* 252. $C_{17}H_{16}O_2$ requires C, 80.9; H, 6.4%; M, 252).

ν_{max} 1745, 985 (w), 960 (s), 930 (s), 900 (s), 875 (m), 745 (s) and 685 (m)cm^{-1}.

λ_{max} 279 nm, ε 11000; 389 nm, ε 73500.

δ7.4 (5H, m, phenyl H), 7.3 (1H, m, C3 H), 7.05-6.4 (3H, br.m, C7 H, C8 H, C9 H), 5.65 (1H, s, C5 H), 2.3 (3H, s, C6 CH_3) and 2.02 (3H, br.s, J1.5Hz, C2 CH_3).

3-(3'-furyl)prop-2(*E*)-en-1-ol 155

A solution of the acetylenic ester 58 (2g, 12.2 mmol) in dry tetrahydrofuran (30 ml) was added to a stirred suspension of lithium aluminium hydride (1.37g, 36 mmol) in dry tetrahydrofuran (50 ml) at room temperature. The mixture was heated under reflux

for 3 hr, cooled and quenched by the successive addition of water (1.35 ml), sodium hydroxide solution (1.35 ml, 4N) and water (4.05 ml).[173] The mixture was filtered and the dried filtrate evaporated to give the crude product which was purified by preparative TLC (ether-light petroleum, 4:1). 3-(3'-furyl)prop-2(*E*)-en-1-ol 155 (1.32g, 88%), a colourless liquid was distilled at 55-56°/0.05 mm to give a colourless solid m.p. 18-20°. (Found: C, 67.35; H, 6.5; M^+ at *m/e* 124. $C_7H_8O_2$ requires C, 67.7; H, 6.5%; M, 124).

ν_{max} (film) 3400, 2900, 1660, 1160, 1080, 1030, 975, 885 and 790cm^{-1}.

δ7.25 (2H, d, furyl C2 H, C5 H), 6.4 (1H, d, furyl C4 H), 6.38 (1H, d.d, $J_{2,3}$16Hz, $J_{1,3}$1.0Hz, C3 H), 5.9 (1H, d.t, $J_{2,3}$16Hz, $J_{1,2}$5Hz, C2 H), 4.15 (1H, d, $J_{1,2}$5Hz, OCH_2) and 4.0 (1H, s, exch., OH).

3-(3'-furyl)prop-2(*E*)-en-1-al 114

The alcohol 155 (1.32g, 10.6 mmol) was oxidised with chromium trioxide (6.4g) and pyridine (10.1g) in dichloromethane (160 ml) by the method of Ratcliffe and Rodehorst.[124] The crude product was purified by preparative TLC (ether-light petroleum, 1:1) to give 3-(3'-furyl)prop-2(*E*)-en-1-al 114 (0.88g, 63%) as a colourless liquid b.p. 58°/0.1 mm. (Found: C, 69.1; H, 4.95; M^+ at *m/e* 122. $C_7H_6O_2$ requires C, 68.8; H, 4.95%; M, 122).

ν_{max} (film) 3140, 2830, 2730, 1750, 1680, 1165, 1130, 1090, 1025, 975, 880, 800 and 740cm^{-1}.

λ_{max} 286 nm.

δ9.7 (1H, d, $J_{1,2}$8Hz, CHO), 7.7 (1H, br.s, furyl C2 H), 7.46 (1H, br.s, furyl C5 H), 7.35 (1H, d, $J_{2,3}$16Hz, C3 H), 6.7 (1H, br.s, furyl C4 H) and 6.38 (1H, d.d, $J_{2,3}$16Hz, $J_{1,2}$8Hz, C2 H).

Ethyl 5-(3'-furyl)-2-methylpenta-2(*E*),4(*E*)-dienoate 156

Using the procedure described for the preparation of the ester 118, the reaction between the aldehyde 114 (1.03g, 8.5 mmol) and the phosphorane 117[128] (3.05g, 8.5 mmol) gave, after chromatography of the crude product on silica gel, the ester 156 (1.61g, 92%) as a colourless liquid b.p. 94°/0.2 mm. (Found: C, 69.5; H, 6.9; M^+ at *m/e* 206. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%; M, 206).

ν_{max} (film) 1705, 1630, 1110, 1085, 1030, 975, 885, 790 and 755cm^{-1}.

λ_{max} 305 nm, ε 21200.

δ7.45 (1H, d, furyl C2 H), 7.35 (1H, t, furyl C5 H), 7.02 (1H, d.d, C3 H), 6.75 (1H, s, furyl C4 H), 6.4 (2H, br.m, C4 H, C5 H), 4.2 (2H, q, $O\underline{CH_2}CH_3$), 2.0 (3H, br.s, J1.5Hz, C2 CH_3) and 1.3 (3H, t, $OCH_2\underline{CH_3}$).

5-(3'-furyl)-2-methylpenta-2(*E*),4(*E*)-dien-1-ol 157

Using the procedure described for the preparation of the alcohol 119, the ester 156 (0.5g, 2.43 mmol) was converted into the alcohol 157 which was purified by preparative TLC (ether-light petroleum, 3:2) to give the alcohol 157 (0.308g, 78%) as an unstable white solid m.p. 71-77°. A sample was converted into the acetate.[177] (Found: C, 69.8; H, 6.8. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%).
M^+ at *m/e* 164. $C_{10}H_{12}O_2$ requires M, 164.
ν_{max} 3300, 1640, 1160, 1080, 1025, 975, 890, 875, 790 and 750cm^{-1}.
λ_{max} 274 nm, ε 15000.
δ7.42 (2H, m, furyl C2 H, furyl C5 H), 6.6 (1H, d, furyl C4 H), 6.9-6.5 (2H, m, C4 H, C5 H), 6.2 (1H, m, C3 H), 4.1 (2H, s, OCH_2), 1.8 (3H, br.s, J1.5Hz, C2 CH_3), and 1.7 (1H, br.s, exch., OH).

5-(3'-furyl)-2-methylpenta-2(*E*),4(*E*)-dien-1-al 33

Using the procedure described for the preparation of the aldehyde 120, the alcohol 157 (0.4g, 2.47 mmol) was converted into the crude aldehyde which was purified by preparative TLC (ether-light petroleum, 2:3) to give the aldehyde 33 (0.325g, 82%), colourless crystals m.p. 51.5-53°. (Found: C, 74.1; H, 6.2;
M^+ at *m/e* 162. $C_{10}H_{10}O_2$ requires C, 74.05; H, 6.2%; M, 162).
ν_{max} (film) 1740, 1650, 1190, 1165, 1085, 1020, 965, 875, 850, 770

and 735cm^{-1}.

λ_{max} 323 nm, ε 10100.

δ9.55 (1H, s, CHO), 7.6 (1H, t, furyl C2 H), 7.4 (1H, t, furyl C5 H), 6.85 (3H, br.s, C3 H, C4 H, C5 H), 6.62 (1H, d, furyl C4 H) and 1.95 (3H, br.s, C2 CH_3).

Wittig reaction of the phosphonium salt 140 with the aldehyde 33

Using the procedure for the Wittig reaction described on page 135, the aldehyde 33 (0.324g, 2 mmol) and the phosphonium salt 140 (1.42g, 2.3 mmol) gave 9-(3'-furyl)-4-hydroxy-2,6-dimethylnona-2(*Z*),4(*Z*),6(*E*),8(*E*)-tetraenoic acid (1→4)lactone 158 (83 mg, 17%). A sample was recrystallised from chloroform-ether as yellow needles m.p. 181-183°. (Found: C, 74.6; H, 5.9; M^+ at *m/e* 242. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%; M, 242).

ν_{max} ($CHCl_3$) 1750, 1610, 1580, 1160, 1060, 1020 (m), 990 (s), 960 (s), 940 (w), 900 (w) and 870 (s)cm^{-1}.

λ_{max} 383 nm, ε 21800.

δ7.54 (1H, d, furyl C2 H), 7.42 (1H, d, furyl C5 H), 7.03 (1H, q, J1.5Hz, C3 H), 6.9-6.3 (4H, br.m, furyl C4 H, C7 H, C8 H, C9 H), 5.64 (1H, s, C5 H), 2.26 (3H, s, C6 CH_3) and 2.02 (3H, br.s, J1.5Hz, C2 CH_3).

The lactone 158 had indentical physical and spectral properties with the naturally occurring dihydrofreelingyne 17,

m.p. 181-183°, m.m.p. 181-183°.

Preparation of the phosphonium salt 159

A solution of the crude phosphonium bromide 132 (prepared from the bromolactone 131 as described on page 143) in ethanol was treated with a solution of an equivalent amount of sodium tetraphenylborate in ethanol. The precipitated tetraphenylborate salt 159 was filtered off and recrystallised from chloroform-hexane as colourless prisms m.p. 192-195°. (Found: C, 83.0; H, 6.1; P, 4.6. $C_{47}H_{40}O_2PB$ requires C, 83.2; H, 5.9; P, 4.6%).

Reaction of the phosphonium salt 159 with cinnamaldehyde 134

The procedure for the Wittig reaction described on page 135 was repeated using the phosphonium salt 159 (1.04g, 1.53 mmol) and cinnamaldehyde 134 (0.2g, 1.53 mmol). The reaction mixture was worked up and purified by preparative TLC as before to give a 1:2.5 mixture of the lactones 135 and 136 (72 mg, 22%).

Ethyl 3-acetoxy-2-methyl-5-phenylpent-4(*E*)-enoate 162

A solution of cinnamaldehyde 134 (13.2g, 0.1 mol) and ethyl 1-bromopropionate 160 (21.7g, 0.12 mol) in dry tetrahydrofuran

(70 ml) was added to a stirred mixture of zinc wool (8.05g, .134 mol) and tetrahydrofuran (20 ml). After the initial reaction had abated, the mixture was heated under reflux for 1 hr, cooled and a solution of glacial acetic acid (12 ml) in water (200 ml) added. The mixture was extracted with ether and the extracts successively washed with water, a saturated solution of sodium bicarbonate, and water, and dried. The solvent was evaporated to produce the crude hydroxy-ester 161.

ν_{max} (film) 3400, 1720, 970, 750 and 690cm^{-1}.

Using the procedure described previously for the acetylation of the carbinol 74, the crude hydroxy-ester (28.1g, 0.12 mol) was converted into the acetate 162 (12.8g, 47%), a pale yellow liquid b.p. 133°/0.1 mm. (Found: C, 69.8; H, 7.35; M^+ at *m/e* 276. $C_{16}H_{20}O_4$ requires C, 69.5; H, 7.30%; M, 276).

ν_{max} (film) 1740, 1720, 970, 750 and 690cm^{-1}.

δ7.3 (5H, m, phenyl H), 6.65 (1H, d.d, $J_{4,5}$15Hz, $J_{3,4}$3Hz, C4 H), 6.38 (1H, d, $J_{3,4}$15Hz, C5 H), 5.5 (1H, br.m, C3 H), 4.1 (2H, q, OCH_2CH_3), 2.7 (1H, m, C2 H), 2.0 (3H, s, OCH_3), 1.2 (3H, t, OCH_2CH_3) and 1.1 (3H, d, J2Hz, C2 CH_3).

Pyrolysis of the acetate 162

Using the procedure described for the flash vacuum pyrolysis of the acetate 77, the acetate 162 (12.03g, 44.5 mmol) was

converted into the ester 149 (7.0g, 70%) at 550°/0.01 mm.

The ester 149 had identical spectra to the ester prepared on page 149 by a Wittig reaction. GLC analysis using the following columns and conditions showed that the ester was 96% pure and that it was identical to the 4(*E*)-ester 149 prepared previously: 5 ft X $^1/_8$ in 15% FFAP on Chromosorb W, 222°; 5 ft X $^1/_8$ in 15% NPGS on Chromosorb W, 220°; 5 ft X $^1/_8$ in 10% SE 52 on Chromosorb W, 200°; 10 ft X $^1/_8$ in 20% Carbowax on Chromosorb W, 220°.

Wittig reaction of the phosphonium salt 163 with the hydroxylactone 129

Using the procedure described by Pattenden and Weedon,[131] the hydroxylactone 129 (3.2g, 28 mmol) was treated with the phosphorane generated from the salt 163 (21.4g, 57 mmol). The crude product was purified by fractional crystallisation from ether to give the 2(Z),4(*E*)-acid 165 (2.46g, 48%) as colourless flakes m.p. 173-176° (lit.[131] 174-176°).

ν_{max} 1660, 1610, 1595, 995, 980, 935, 775 and 755cm^{-1}.

δ7.92 (1H, d.d, $J_{4,5}$16Hz, $J_{3,4}$11Hz, C4 H), 7.3 (5H, br.m, phenyl H), 6.6 (1H, d, $J_{4,5}$16Hz, C5 H), 6.5 (1H, d.m, $J_{3,4}$11Hz, C3 H) and 2.0 (3H, s, C2 CH_3).

The mother liquors from the above crystallisations gave the 2(Z),4(Z)-acid 166 (1.15g, 22%) as colourless crystals m.p. 106-109° (lit.[131] 107-108°).

ν_{max} 1670, 1615, 1590, 1090, 920, 810, 790, 740 and 700cm^{-1}.

δ7.3 (5H, m, phenyl H), 7.2 (1H, m, C4 H), 6.8 (1H, d.m, $J_{3,4}$11Hz, C3 H), 6.64 (1H, d, $J_{4,5}$11Hz, C5 H) and 2.0 (3H, s, C2 CH_3).

Esterification of the acids 165 and 166

a. Using the procedure described for the preparation of the ester 97, the 2(Z),4(*E*)-acid 165 (2.13g, 11.3 mmol) was treated with an ethereal solution of diazomethane[112] (1.05g, 25 mmol) to give methyl 2-methyl-5-phenylpenta-2(Z),4(*E*)-dienoate 167 (2.29g, 92%) as a colourless liquid b.p. 120°/0.5 mm. (Found: C, 77.3; H, 7.0; M^+ at *m/e* 202. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%; M, 202).

ν_{max} (film) 1700, 1620, 1600, 1015, 975, 910, 860, 820, 770, 745 and 690cm^{-1}.

λ_{max} 311 nm, ε 18200.

δ7.92 (1H, d.d, $J_{4,5}$16Hz, $J_{3,4}$11Hz, C4 H), 7.3 (5H, br.m, phenyl H), 6.6 (1H, d, $J_{4,5}$16Hz, C5 H), 6.5 (1H, d.m, $J_{3,4}$11Hz, C3 H), 3.7 (3H, s, OCH_3) and 2.0 (3H, br.s, C2 CH_3).

GLC analysis using a 5 ft X $^1/_8$ in 15% NPGS on Chromosorb W column at 220° indicated that the ester 167 was 98% pure. The impurity (2%) was the 2(*E*),4(*E*)-isomer.

b. In a similar manner, the 2(Z),4(Z)-acid 166 (1.36g, 7.2 mmol) was converted into methyl 2-methyl-5-phenylpenta-2(Z),4(Z)-dienoate

168 (1.35g, 93%), a colourless liquid b.p. 100°/0.8 mm. (Found: C, 76.8; H, 6.9; M^+ at *m/e* 202. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%; M, 202).

ν_{max} (film) 1710, 1620, 1600, 1015, 975, 915, 840, 820, 790, 770, 740 and 700cm^{-1}.

λ_{max} 306 nm, ε 16400.

δ7.3 (5H, m, phenyl H), 7.2 (1H, m, C4 H), 6.8 (1H, d.m, $J_{3,4}$11Hz, C3 H), 6.64 (1H, d, $J_{4,5}$11Hz, C5 H), 3.75 (3H, s, OCH_3) and 2.0 (3H, s, C2 CH_3).

GLC analysis using the conditions as above, showed that the ester 168 was 90% pure. The contaminants were the ester 167 (9%) and the 2(*E*),4(*E*)-isomer (1%).

Reduction of the esters 167 and 168

a. Using the procedure described for the preparation of the alcohol 119, the 2(*Z*),4(*E*)-ester 167 (1.12g, 5.5 mmol) was converted into 2-methyl-5-phenylpenta-2(*Z*),4(*E*)-dien-1-ol 169 (0.93g, 97%), a white solid (m.p. 80-86°) which was rapidly converted into an oil. M^+ at *m/e* 174. $C_{12}H_{14}O$ requires M, 174.

ν_{max} 3250, 1005, 965, 750 and 695cm^{-1}.

δ7.3 (5H, m, phenyl H), 7.0 (1H, d.d, $J_{4,5}$16Hz, $J_{3,4}$11Hz, C4 H), 6.6 (1H, d, $J_{4,5}$16Hz, C5 H), 6.1 (1H, d, $J_{3,4}$11Hz, C3 H), 4.3 (2H, s, OCH_2), 2.0 (3H, br.s, C2 CH_3) and 1.8 (1H, s, exch., OH).

b. In a similar manner, the 2(Z),4(Z)-ester 168 (0.54g, 2.68 mmol) was converted into 2-methyl-5-phenylpenta-2(Z),4(Z)-dien-1-ol 170 (.46g, 99%) as an unstable white solid. M^+ at *m/e* 174. $C_{12}H_{14}O$ requires M, 174.

ν_{max} 3250, 1020, 975, 750 and 700cm^{-1}.

δ7.3 (5H, m, phenyl H), 6.4 (3H, br.m, C3 H, C4 H, C5 H), 4.3 (2H, s, OCH_2), 2.4 (1H, s, exch., OH) and 1.8 (3H, br.s, C2 CH_3).

Oxidation of the alcohols 169 and 170

The alcohols 169 and 170 were oxidised using manganese dioxide,[118] chromium trioxide,[124] silver carbonate on celite,[135] and dimethylsulphoxide-dicyclohexylcarbodiimide.[161] In all cases, mixtures of the aldehydes 151, 171 and 172 were obtained. In a typical reaction, the 2(Z),4(*E*)-alcohol 169 (94 mg) was treated with manganese dioxide (1g) for 19 hr at 5°, and the mixture was filtered. The solvent was evaporated to leave an oil (40 mg) which was shown by the NMR spectrum to be a 1:3 mixture of the 2(Z),4(*E*)-aldehyde 171 (δ10.4, CHO) and the 2(*E*),4(*E*)-aldehyde 151 (δ9.5, CHO).

Section 2

Wittig reaction of phthalic anhydride 173 with reactive phosphoranes

a. In a typical reaction, a solution of benzyltriphenylphosphonium chloride 163[160] (3.89g, 10 mmol) and phthalic anhydride 173 (1.5g, 10 mmol) in dimethylsulphoxide (300 ml) was added to a mixture of sodium hydride (0.48g, as a 50% suspension in oil, 10 mmol) and dimethylsulphoxide (20 ml)[162] and the mixture stirred at room temperature for 60 hr. The mixture was poured into water, extracted with ether and the extracts were washed and dried. The solvents were evaporated and the residue was purified by chromatography on silica gel. Only triphenylphosphine oxide (0.4g) was isolated.

b. In a similar manner, isopropylenetriphenylphosphorane 182[181] was generated and phthalic anhydride 173 added, but no products were identified from the mixture.

Reaction of phthalic anhydride 173 with the phosphonate 187

In a typical reaction, a slurry of potassium *t*-butoxide (0.56g, 5 mmol) in dry dimethoxyethane (20 ml) was added dropwise to a stirred solution of diethylbenzylphosphonate 187[145] (1.14g, 5 mmol) and phthalic anhydride 173 (0.74g, 5 mmol) in dimethoxyethane (20 ml) at -78°. The mixture reached room temperature over 9 hr

and stirring was continued for a further 30 hr. A solution of brine (100 ml) was added, the mixture was extracted with ether and the extracts were dried. The solvent was evaporated and the residue purified by chromatography on silica gel. Only the phosphonate 187 (1.07g) was recovered; no other products were identified.

Methyl 3-furoate 190

A solution of 3-furoic acid 55 (1g, 8.9 mmol) and boron trifluoride etherate (3.17g, 22 mol) in methanol (20 ml) was heated under reflux for 16 hr,[164] cooled and water (100 ml) added. The mixture was extracted with ether and the extracts washed and dried. The solvent was evaporated to give methyl 3-furoate 190 (1.0g, 89%) as a colourless liquid b.p. 145° (lit.[182] 78-80°/42 mm).
ν_{max} (film) 1725, 1580, 1080, 990, 880, 795 and 760cm^{-1}.
δ7.98 (1H, d, C2 H), 7.4 (1H, t, C5 H), 6.7 (1H, d, C4 H) and 3.8 (3H, s, OCH_3).

3-furylmethanol 191

Using the procedure described for the preparation of the alcohol 155, the ester 190 (0.97g, 7.7 mmol) was converted into the alcohol 191 (0.645g, 85%), a colourless liquid b.p. 120°/100 mm (lit.[183] 79°/17 mm).

ν_{max} (film) 3350, 1590, 1150, 1020, 980, 880, 800 and 720cm^{-1}.
δ7.3 (2H, d, C2 H, C5 H), 6.3 (1H, d, C4 H), 4.35 (2H, s, OCH_2) and 3.4 (1H, br.s, exch., OH).

Bromination of 3-furylmethanol 191

Using the procedure described for the preparation of the bromide 18, the alcohol 191 (0.31g, 3.2 mmol) was converted into the bromide (0.41g, 81%), a pale yellow liquid which was used without further purification.

ν_{max} (film) 3100, 1590, 1020, 880, 800, 730 and 680cm^{-1}.
δ7.4 (2H, m, C2 H, C5 H), 6.4 (1H, m, C4 H) and 4.35 (2H, s, CH_2Br).

Preparation of the phosphonium salt 34

A solution of 3-bromomethylfuran 191 (0.41g, 2.6 mmol) and triphenylphosphine (0.66g, 2.6 mmol) was heated under reflux in benzene for 2 hr, cooled, and the precipitated phosphonium salt 34 removed. The salt 34 (0.51g, 47%) was recrystallised from methanol-ether as white crystals m.p. 296-298^{o}. (Found: C, 65.4; H, 4.8; P, 7.1; Br, 18.6. $C_{23}H_{20}OPBr$ requires C, 65.3; H, 4.8; P, 7.3; Br, 18.9%).

ν_{max} 1580, 1010, 810, 760, 740, 730 and 690cm^{-1}.

Crotonaldehyde diacetate 194

Crotonaldehyde 193 (35g, 0.5 mol), acetic anhydride (78.1g, 0.75 mol) and concentrated sulphuric acid (5 drops) were allowed to stand at room temperature for 34 hr. Anhydrous sodium acetate (0.6g) was added and the mixture was distilled. The diacetate 194 (71.7g, 83%) was obtained as a colourless liquid b.p. 98-100°/17 mm (lit.[165] 89-90°/8.5 mm).

Bromination of the diacetate 194

A solution of the diacetate 194 (70g, 0.41 mol) in carbon tetrachloride (180 ml) was brominated with N-bromosuccinimide (72.5g, 0.41 mol) by the method of Schmid.[166] The 4-bromocrotonaldehyde diacetate 195 (49.2g, 49%) was obtained as a pale yellow liquid b.p. 86°/0.1 mm (lit.[166] 90-94°/2 mm).

Preparation of the phosphonium salt 196

A solution of the bromide 195 (14.8g, 59 mmol) and triphenylphosphine (16g, 59 mol) in benzene (50 ml) was stirred at 5° for 29 hr. At intervals of 5 hr the precipitated salt 196 was removed and dried *in vacuo*. In this manner, the salt 196 (17.4g, 57%) was obtained as a pink solid which was recrystallised

from methanol-ether as colourless crystals m.p. 125-128°. (Found: C, 60.7; H, 5.0; P, 6.0; Br, 15.4. $C_{26}H_{26}O_4PBr$ requires C, 60.9; H, 5.1; P, 6.0; Br, 15.6%).

Wittig reaction of the phosphonium salt 196 with citraconic anhydride 32

In a typical reaction, an aqueous solution of the salt 196 (1.2g, 2.3 mmol) was treated with a dilute ammonia solution (4.6 mmol) and the precipitated yellow solid collected and dried. To a solution of this phosphorane (0.19g, 0.65 mmol) in chloroform (10 ml) was added a solution of citraconic anhydride 32 (72 mg, 0.65 mmol) in chloroform (10 ml) and the mixture heated under reflux for 22 hr under an atmosphere of nitrogen. The solvent was evaporated and the residue purified by preparative TLC (ether-light petroleum, 2:1). None of the fractions isolated (four, each of about 10 mg) had retained the anhydride group or had an enol-lactone chromophore, as evidenced by the infrared spectra.

Similar reactions with anisaldehyde using an *in situ* generation of the phosphorane from the salt 196 with sodium hydride or potassium *t*-butoxide in chloroform and dimethoxyethane respectively gave only recovered anisaldehyde.

Preparation of the phosphorane 200

The phosphorane 200 was prepared from ethyl 4-bromocrotonate by the method of Howe[167] to give yellow crystals which were purified by chromatography on alumina, m.p. 165-168° (lit.[167] 186-188°).

Reaction of the phosphorane 200 with citraconic anhydride 32

A solution of the phosphorane 200 (0.4g, 1 mmol) and citraconic anhydride 32 (0.11g, 1 mmol) in deuterochloroform (0.5 ml) was allowed to stand at room temperature for 156 hr. The NMR spectrum of the solution showed that after 24 hr, no further change had taken place, and although the spectrum was different to the starting materials, there was no resonance at ~δ6.0 characteristic of the C5 proton of the Δ^4-double bond of the expected product.

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