SYNTHESIS WITH TRICARBONYLIRON LACTONE COMPLEXES

A Thesis Presented by

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Contents

List of Tables and Figures	2
Abstract	3
Acknowledgements	4
Abbreviations	5
Chapter 1: β-Lactone Natural Products	6
References	27
Chapter 2: NMR studies on iron complexes	30
Chapter 3: New Starting Materials for Iron Complexes	38
Chapter 4: Towards the Synthesis of Valilactone	59
Chapter 5: Studies on 1233A	
The Structure of 1233B	82
A Relay Synthesis of 1233A	89
Towards the Total Synthesis of 1233A	98
Experimental	111
Appendices	154
References	156

List of Tables and Figures

Fig. 1.	^{1}H NMR spectrum of complex (**1**)	31
Fig. 2.	COSY spectrum of complex (**1**)	32
Fig. 3.	nOe experiments on complex (**1**)	34
Fig. 4.	^{1}H-^{13}C COSY spectrum of complex (**1**)	36
Table 1.	^{13}C Chemical shifts in iron complexes	37
Fig.5.	X-Ray structure of complex (**4**)	41
Fig.6.	^{1}H NMR spectra of pivalaldehyde acetals (**22**) and (**23**)	51
Fig.7.	^{13}C NMR spectrum pivalaldehyde acetal (**23**)	52
Fig.8.	nOe experiments on complex (**24**)	54
Fig.9.	nOe experiments on complex (**25**)	56
Fig.10.	nOe experiments on *E,E*-1-iodo-1-trimethylsilylocta-1,3-diene	77
Fig.11.	nOe experiments on the dimethyl ester of 1233B	83

Abstract

This thesis is divided into five chapters. The first is a review of β-lactone natural products, discussing their isolation, structural determination, biological properties and synthesis. A brief survey of the more modern methods of forming β-lactones is included.

The second chapter describes some proton and carbon-13 NMR studies on ferrilactone and ferrilactam complexes.

The third chapter describes the use of a variety of compounds related to *Z*-2-butene-1,4-diol as precursors to these complexes. The synthesis and reactions of the parent "isoferrilactone" are described. The stereochemical consequences of the diol reaction are also described.

The fourth chapter outlines a number of approaches to the β-lactone natural product, valilactone. These aim towards a key dienol intermediate. A brief overview of the Castro-Stephans reaction is included. The chapter concludes by assessing the prospects for this strategy in valilactone synthesis.

The fifth chapter is divided into three sections. Firstly, a small number of chemical and structural studies on 1233B are described. The other two sections describe, respectively, attempts to complete a relay and a total synthesis of 1233A. The synthesis of diphenylmethyl *E*-4-diethylphosphono-3-methylbutenoate, a useful Wadswoth-Emmons partner, is described.

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I am also grateful to ICI Pharmaceuticals for samples of 1233B, Merck, Sharp and Dohme Research Laboratories of Rahway, N.J., for samples of 1233A and Dr. Kazuo Umezawa of the Institute of Microbial Chemistry, Tokyo, for a sample of valilactone.

I would like to thank my friends and colleagues in and out of the Department for many kinds of assistance and support. I would particularly like to thank Alison, Andy, Anna, Julian, Katie, Luiza, Mark Trudel, Morag and Peter Grice.

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Finally, I would like to thank my family for their support during this work.

Abbreviations

AIBN	Azobisisobutyronitrile
9-BBN	9-borabicyclo[3,3,1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
COD	1,5-cyclooctadiene
CSA	Camphorsulphonic acid
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
d.e.	diastereoisomeric excess
DIBAL	di*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
e.e.	enantiomeric excess
GC	gas chromatography
GLC	gas-liquid chromatography
HMPA	hexamethylphosphoric triamide
HPLC	high pressure liquid chromatography
m-cpba	*meta*-chloroperbenzoic acid
MEM	2-methoxyethoxymethyl
NBS	N-bromosuccinimide
NMO	N-methylmorpholine-N-oxide
PDC	pyridinium dichromate
py	pyridine
TBDPS	*t*-butyldiphenylsilyl
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium Per-ruthenate
TBAF	tetra-*n*-butylammonium fluoride

Chapter 1. β-Lactone Natural products

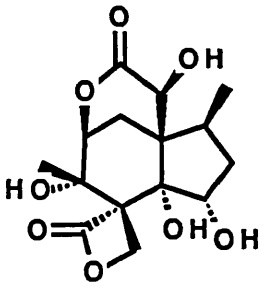
Introduction

β-lactones have been much neglected compared to their nitrogen analogues, the β-lactams. It is only recently that the pharmaceutical community has awoken to the potential of this class of compounds. The broad range of biological properties shown by the eight β-lactone natural products discovered so far holds out promise of many useful molecules of this type throughout the spectrum of pharmaceutical activity.

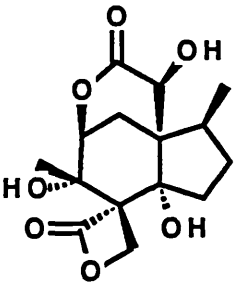
This review discusses the discovery, characterisation and activity of the β-lactone natural products and concludes with descriptions of synthetic efforts to date, (excluding the work in this thesis) including a short consideration of the methods for forming β-lactones in general.

Anisatin and Neoanisatin

The toxic and convulsant properties of the Japanese star anise have been known for centuries. The local names reflect its potency: *ashikimi* (mad fruit) in Japanese and *mang tsao* (mad herb) in Chinese.



(1)

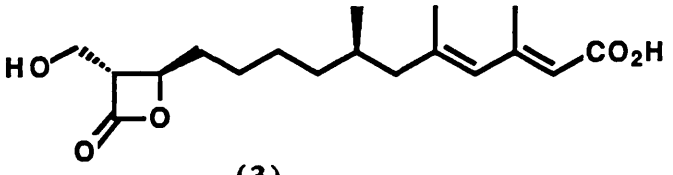


(2)

The first published attempt[1] to extract the active component was over a century ago; the first successful isolation of anisatin was achieved by Lane and co-workers fifty years later[2]. They showed that anisatin reacted with two equivalents of sodium hydroxide to give a dicarboxylate; on acidification, a monoacid, named anisatinic acid, was obtained, implying that lactonisation had occurred. From this information, coupled with the infra red spectrum, in particular absorbances at 5.51 μ (1815 cm^{-1}) and 5.87 μ (1704 cm^{-1}), they concluded that the two carbonyls were present as a cyclic anhydride. This misassignment lead their work up a blind alley. A more reasonable assignment of this infra red data is a β-lactone and a separate ester or lactone. The most interesting point to arise from Lane's work is that anisatinic acid is biologically inactive: the β-lactone is clearly vital in this respect. The structure of anisatin was finally determined to be (**1**) by Japanese workers in the 1960s who also isolated the related compound, neoanisatin (**2**).[3] No further reports have appeared on these molecules, presumably due to paucity of supply and intricacy of synthesis.

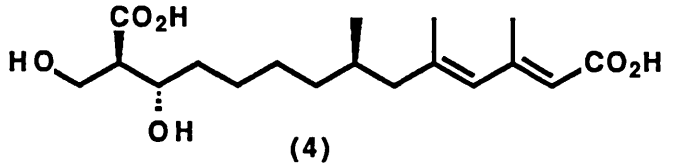
1233A (F-244, L-659,699)

A group at ICI Pharmaceuticals first isolated 1233A (**3**) from a *Cephalsporium* species in the early 1970s. They deduced the basic structure by a combination of spectroscopic and degradative studies.[4] Although they were able to establish that the β-lactone had *trans* geometry, they were unable to establish the absolute configuration of any of the stereogenic centres; their conclusions about the geometry of the diene system were tentative.



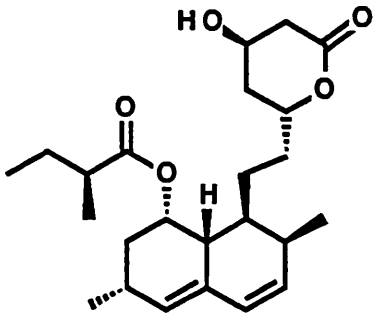
(3)

The workers at ICI were able to show that 1233A was a weak antibiotic. At this point, though, the producing strain changed in some way and began to produce a related compound, called 1233B. This proved to be identical to the product from the reaction of 1233A with water under neutral conditions. As this reaction would be expected to proceed with O-alkyl fission, 1233B was assigned the structure (4). The consequence of this was the abandonment of this project by the ICI workers.



(4)

Studies on this compound rested there until its rediscovery during fermentation of *Scopulariopsis* and *Fusarium* species by Japanese and American workers.[5] Most importantly, they showed that 1233A (now renamed F-244 and L-659,699) was a potent inhibitor of cholesterol biosynthesis. It was further shown that 1233A effects acetate, but not mevalonate uptake which indicated that the inhibited enzyme was 3-HMG synthase. This was clearly a pleasing result for the Merck, Sharp and Dohme workers as they already possessed two other sterol biosynthesis inhibitors: Mevinolin[6] (5) which inhibits HMG-CoA reductase, the next enzyme in the sequence, and L-660,631, (6)[7] containing an unusual triyne moiety, also a pre-squalene inhibitor.



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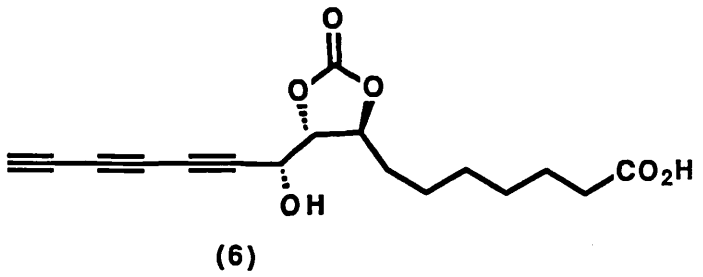
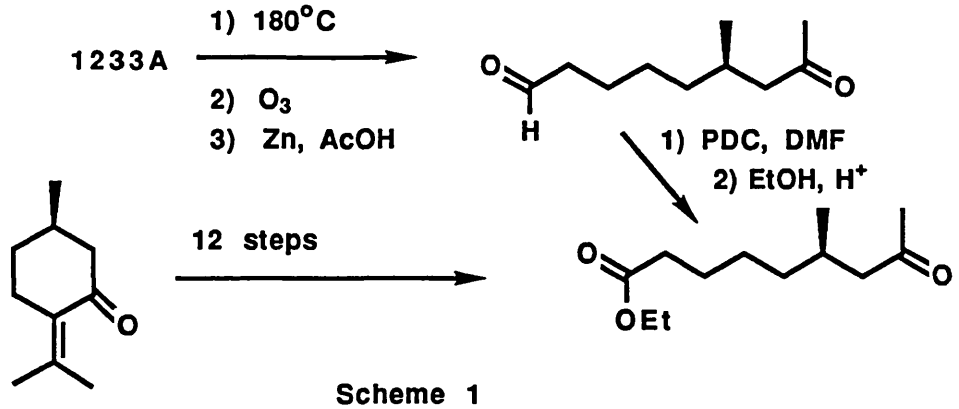


(6)

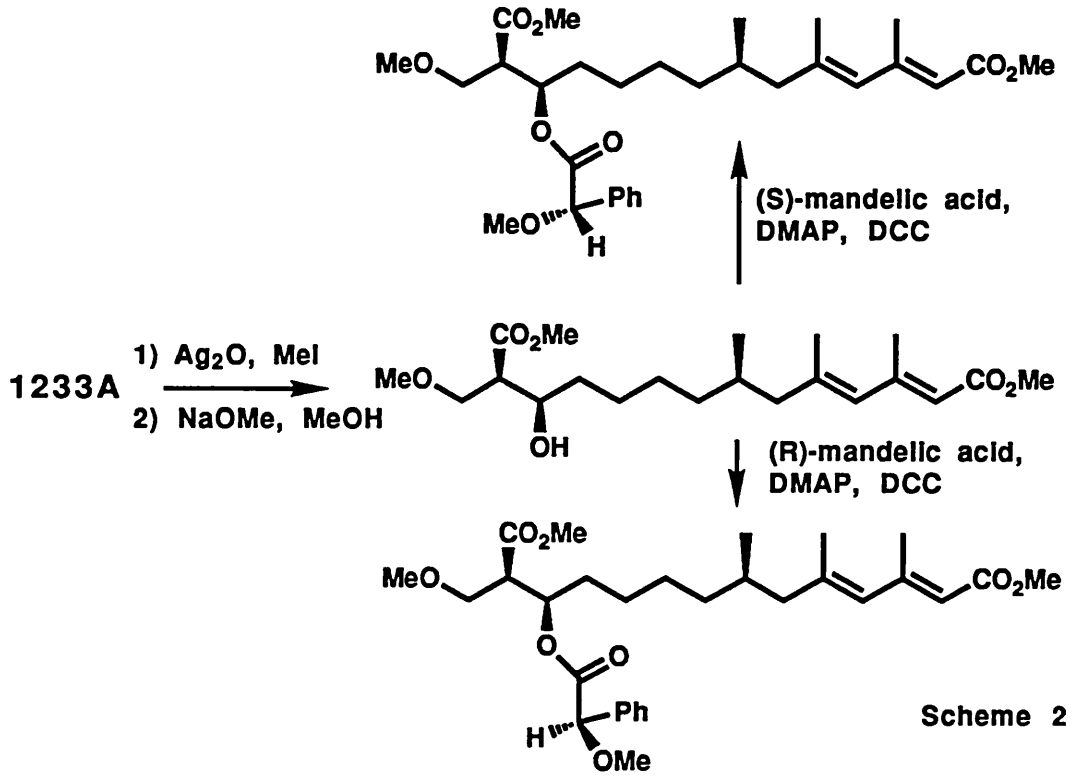
1233A is also described as an antifungal agent, but this aspect of its activity appears to have been totally overshadowed by its antihypercholesterolemic properties.

The absolute configuration was finally determined by the Merck, Sharp and Dohme workers.[8] The C(7) configuration was determined by degradation. Thermal decarboxylation, followed by exhaustive ozonolysis gave a ketoaldehyde which was oxidised and esterified to afford a ketoester. This proved to be identical to the corresponding ketoester prepared from natural (R)-(+)-pulegone, leading to the conclusion of (R) stereochemistry at C(7), (Scheme 1).

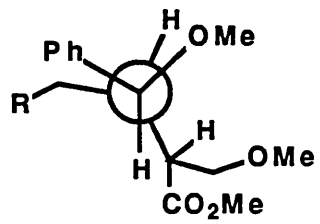


Scheme 1

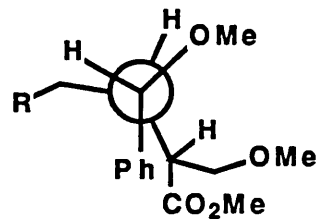
The configuration of the ring carbons was determined by the method of Dale and Mosher.[9] 1233A was first converted to a suitable monoalcohol which was then converted into its (R) and (S)-mandelates (Scheme 2).



Scheme 2



(8)

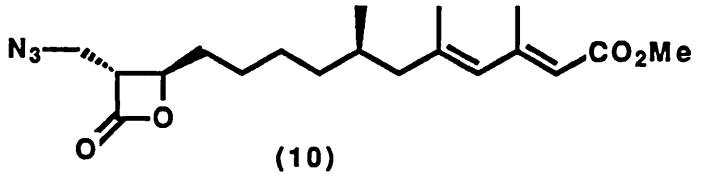


(9)

From the assumed low energy configurations of these two esters, (8) and (9), it was possible to deduce the chirality of C(12), on the basis that the resonances due to the proton eclipsed by the phenyl group will be shifted upfield relative to the corresponding proton on the other diastereoisomer. In this way it was found that both ring carbons possessed (R) stereochemistry. This has since been confirmed by two independent syntheses (*vide infra*).

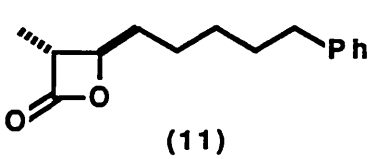
The geometry of the diene system has only recently been confirmed as *E,E*. The ICI workers had found that the 2,4-dinitrophenylhydrazone of the methyl 3-formylcrotonate isolated from ozonolysis of 1233A methyl ester was different (melting point) from the known *Z* isomer. This implied that the 2,3 double bond in 1233A had *E* geometry. *E* geometry was then assumed for the other double bond too. Recent nOe experiments at Imperial College on the dimethyl ester of 1233B have been totally consistent with this *E,E* geometry[10]; hence the entire structure is now known.

With supplies of 1233A in hand, workers at Merck, Sharp and Dohme have prepared a large number of analogues.[11] 1233A has been converted to a number of esters and salts, as well as derivatives made by substitution for the C(14') hydroxy group. Of those for which data has been published, the most active turns out to be the azido methyl ester (**10**).

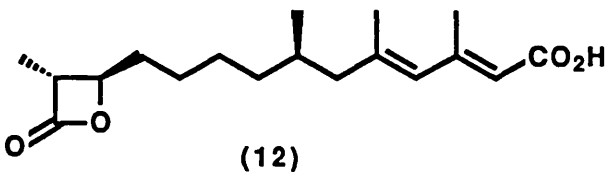


(**10**)

Varying the main chain has little effect on activity. Indeed, the racemic compound (**11**) has an IC_{50} value of 1.4×10^{-6}, compared to 10^{-7} for the compound (**12**) derived from the natural product.

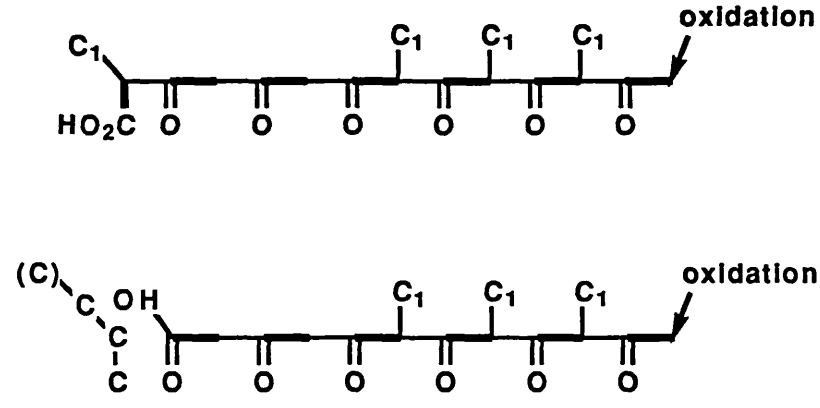


(**11**)



(**12**)

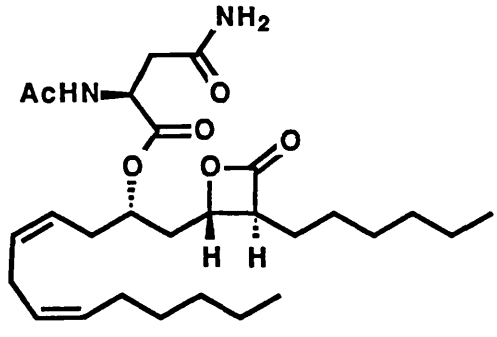
Two possible biosynthetic origins have been postulated, although no experimental studies have been undertaken.[12] Aldridge has suggested that it might be derived from a series of acetates, plus C_1 units with the hydroxymethyl substituent being derived from another C_1 unit , a C_3unit or a C_4 unit (Scheme 3).



Scheme 3

Esterastin

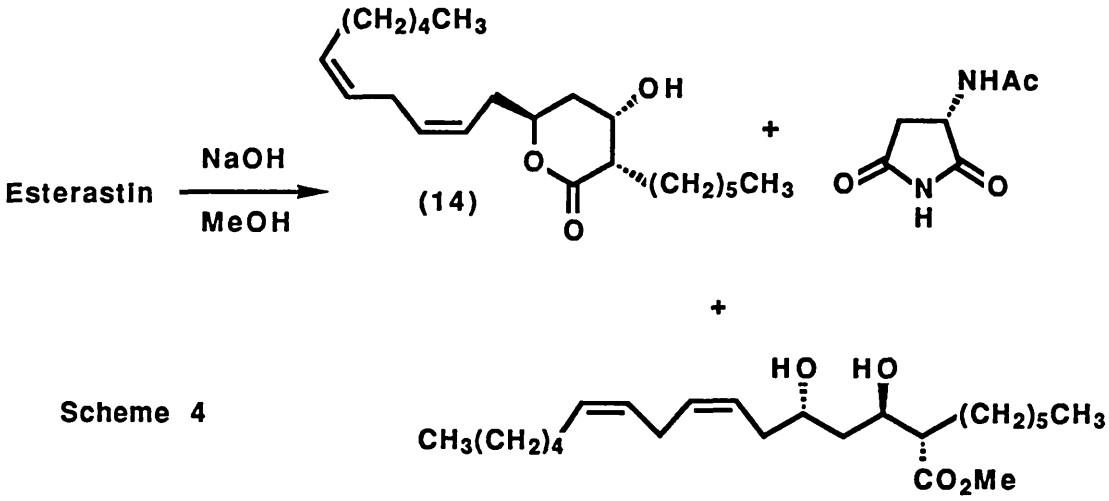
Umezawa's group isolated esterastin (**13**) from a *streptomyces* culture in 1978.[13]



(13)

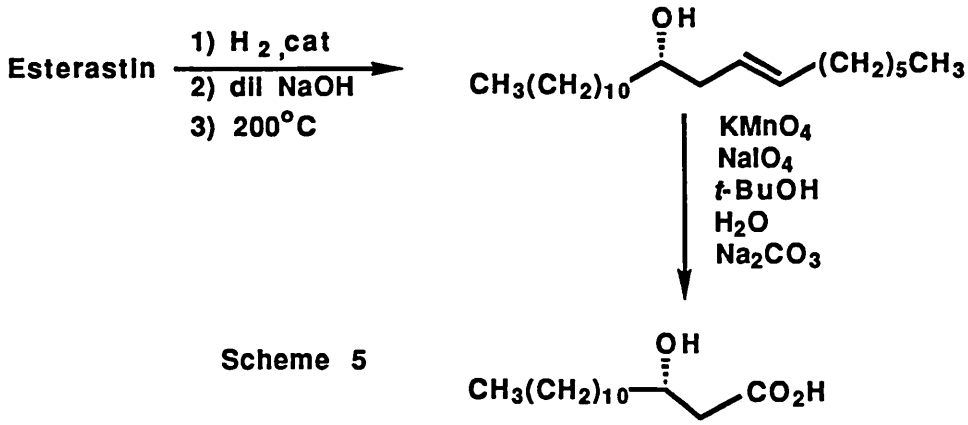
It was shown to be a powerful inhibitor of pancreatic esterase.This was a significant finding as esterase and aminopeptidase enzymes located on cellular membranes are important in the immune system. Indeed, esterastin was found to suppress immune responses.

The structure was determined by a combination of spectroscopic and degradative techniques.[14] In particular, treatment with methanolic sodium hydoxide yielded three products: the δ-lactone (**14**), its open methyl ester form and L-N-acetyl aspartimide (Scheme 4). The relative stereochemistry of the three stereogenic centres was then deduced from the coupling constants of the δ-lactone.



Scheme 4

The absolute configuration was then determined by degradation of the tetrahydroderivative. Removal of the amino acid by mild hydrolysis and decarboxylation at 200°C, followed by oxidative cleavage of the resulting double bond ($KMnO_4$, $NaIO_4$, *t*-BuOH, H_2O, Na_2CO_3) gave the known L-3-hydroxymyristic acid (Scheme 5).

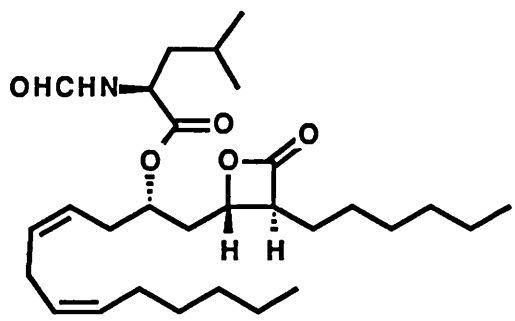


Scheme 5

Later studies showed that esterestin was more active than either of the ebelactones against rabbit liver Acid Lipase, but less active against pancreatric lipase and carboxylesterase.[15] These workers pointed out the utility of esterastin as a tool to study lipid storage diseases, such as atherosclerosis.

Lipstatin

Hoffman-La Roche workers isolated lipstatin (**15**) from soil sample fungi fermentations in 1987.[16]



(15)

It was quickly shown that lipstatin was identical to esterastin except for the amino acid residue: N-formyl leucine instead of N-acetylaspargine.[17] Not surprisingly, lipstatin was also found to be active against lipase enzymes. In particular, mice treated

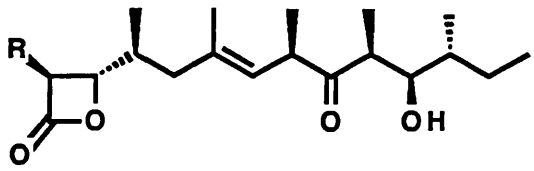
with lipstatin showed a greatly decreased uptake of glycerol trioleate. As this material has only to be converted into oleic acid in order to be absorbed, lipstatin clearly works by inhibiting the responsible lipase enzyme.

A number of lipstatin analogues were also screened: the tetrahydroderivative retained almost all the activity of the natural product but all the derivatives where the β-lactone had been opened showed loss of activity.

The use of this compound as an antiobesity agent should soon be a commercial reality. The effect of lipstatin on the immune system is not known. This information would cast some light on the structural features in esterastin required for this particular activity.

The Ebelactones

The ebelactones were discovered in 1980 during the screening of soil samples following the isolation of esterastin.[18] The extracts were found to contain two active compounds which differed by one methylene group. They were named ebelactone A and ebelactone B. Spectroscopic studies indicated the basic structures:[19] the absolute stereochemistry and double bond geometry were determined by an X-ray crystallographic study of the *p*-nitrobenzoate of ebelactone A, though this has yet to be published. The structures are of ebelactone A and ebelactone B are (**16**) and (**17**) respectively.

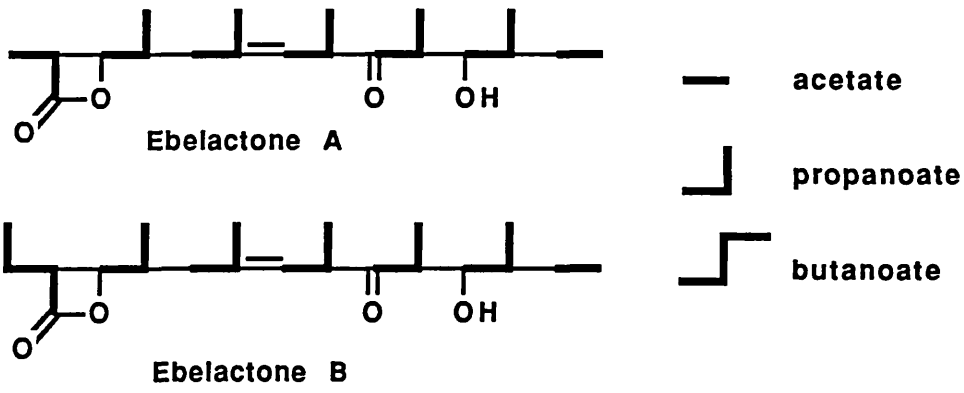


(16) R=Me
(17) R=Et

Dihydro and acetyl derivatives were also prepared; the latter were employed in mass spectroscopic studies.

The ebelactones are both more active than esterastin against Hog liver esterase but slightly less active against Hog pancreas lipase. The ebelactones also showed activity against N-formylmethionine aminopeptidase - esterastin is inactive against this enzyme. This may well be connected to the facts that the ebelactones enhanced immune responses in mice, while esterastin suppressed them.

The ebelactones are the only β-lactones for which biosynthetic studies have been carried out.[20] By the usual method of ^{13}C labelled carboxylate incorporation, as monitored by ^{13}C NMR, ebelactone A was shown to be made up of six propanoates and one acetate, while ebelactone B was made up of five propanoates, one acetate and one butanoate in a predictable fashion (Scheme 6).

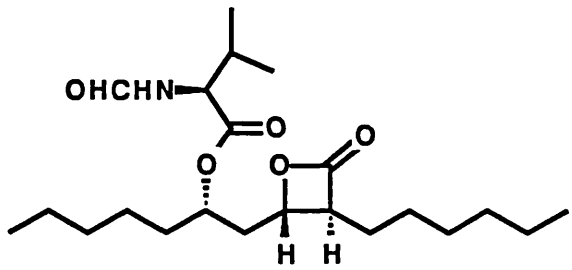


Scheme 6

Valilactone

Continued screening of Japanese soil samples furnished the Umezawa group with a further β-lactone.[21] The producing strain, related to *Streptomyces albolongus*, produced a crystalline compound whch was characterised by the usual spectroscopic techniques, though the structure (**18**) was fully determined by X-ray crystallography with the assumption of an L-valine residue.

The structural similarity to lipstatin and esterastin is clear: a hydrocarbon backbone bearing a *trans* β-lactone and a nearby amino acid.



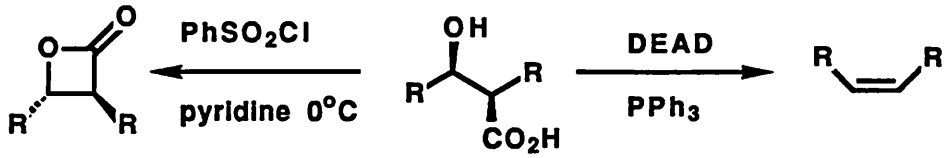
(18)

Valilactone is also an esterase inhibitor, being the most active β-lactone inhibitor of Hog pancreas lipase. Significantly it is inactive against N-formylmethionine aminopeptidase and has no immunological activity.

The Synthesis of β-Lactone Natural Products

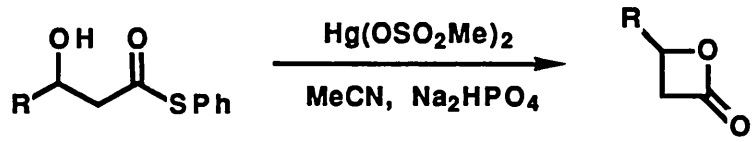
There are three modern general methods for forming β-lactones.[22] The simplest is the lactonisation of 2-hydroxycarboxylic acids. Although many reagents have been used for this reaction, the conditions of choice are benzenesulphonyl chloride in pyridine at 0°C.[23] At higher temperatures (35°C), elimination of carbon dioxide and water is observed, leading to alkenes. With other reagent systems, e.g.

diethylazodicarboxylate/ triphenylphosphine, alkene formation can be dominant or exclusive (Scheme 7).[24]



Scheme 7

A recent interesting variation on this theme is the adaption of Masamune's thioester chemistry:[25] treatment of S-phenyl-2-hydroxythioesters with mercuric mesylate provides β-lactones in moderate to good yields (Scheme 8).[26]



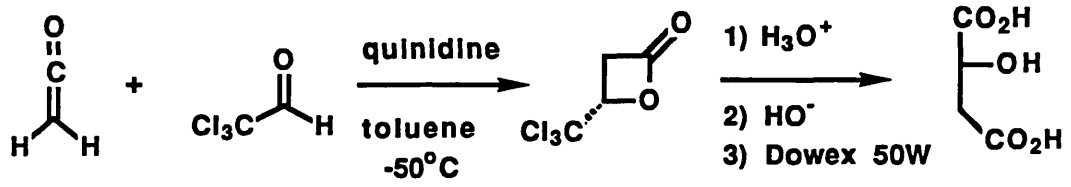
Scheme 8

The [2+2] cycloaddition of a ketene and an aldehyde gives β-lactones (Scheme 9). This reaction has been known for some time.

Scheme 9

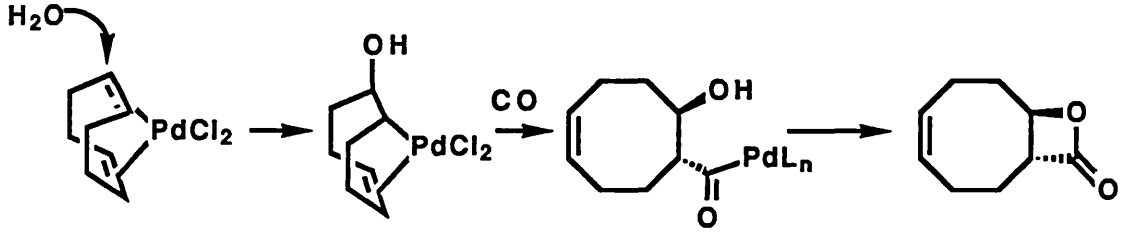
It is most efficient when stabilised ketenes such as trimethylsilyl ketene, are used.[27] Ketene itself only reacts with α-haloaldehydes. This reaction, though, has been used in a remarkable asymmetric synthesis of both enantiomers of malic acid.[28] Wynberg and Staring, as part of their pioneering studies on the use of cinchona alkaloids in synthesis, found that ketene adds to chloral in toluene at low temperatures in the presence of quinidine as a catalyst. The product was the (S)-β-lactone in 98% ee. This was converted to malic acid (Scheme 10) by acidic hydrolysis of the β-lactone, basic

hydrolysis of the trichloromethyl group and protonation of the two carboxlates by an acidic resin. Use of quinine as the catalyst gave the (R) enantiomer.



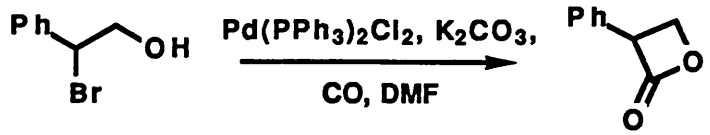
Scheme 10

Two groups have used carbon monoxide insertions, mediated by transition metals, to prepare β-lactones. The first system developed by Stille involved the formal addition of carbon dioxide to one double bond of 1,5-cyclooctadiene.[29] Nucleophilic attack by water on the palladium COD complex is followed by carbon monoxide insertion and cyclisation (Scheme 11). Although this reaction can be run catalytically, using copper(II) salts to reoxidise palladium, as in the Wacker process, the turnover is only 6.9.



Scheme 11

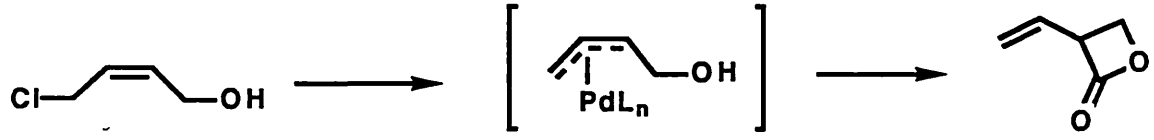
His later system, as part of a larger programme of lactone synthesis, utilised 2-haloalcohols.[30] Thus, 2-bromo-2-phenylethanol, in the presence of a palladium catalyst in DMF under a carbon monoxide atmosphere gave the β-lactone (**19**) in 63% yield (Scheme 12).



(19)

Scheme 12

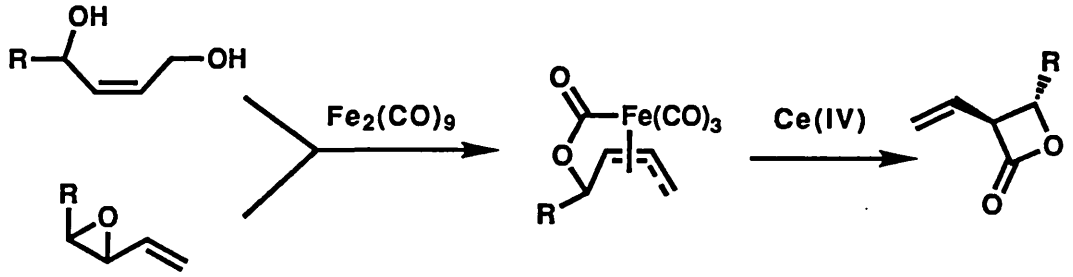
Interestingly, Z-4-chloro-2-butenol also gave a β-lactone (Scheme 13), rather than the expected δ-lactone. Presumably formation of the η^3-complex (**20**) causes this.



(20)

Scheme 13

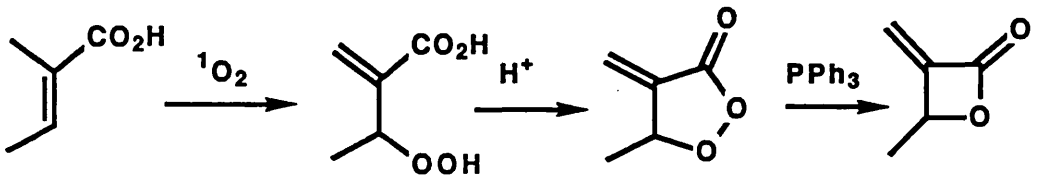
While working on iron lactone complexes, Ley and co-workers found that oxidation of these yielded β-lactones in good yields (Scheme 14).[31] The selectivity for four membered rings over six membered (which are the products under different decomplexation conditions) is similar to Stille's results (Scheme 13).



Scheme 14

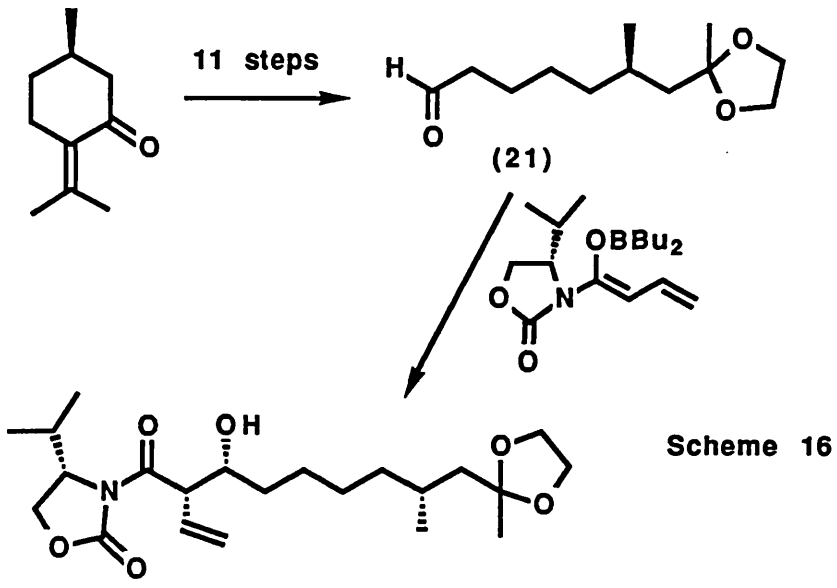
Importantly, the products retained the stereochemical characteristics of the complexes: thus, the *exo* alkyl group, R, in the complex is "*trans*" to the allyl system and becomes *trans* to the vinyl group in the product. Most efforts, however, were directed towards the analogous nitrogen complexes, leading to β-lactams.

A fourth and very recent route to the novel α-methylene-β-lactones has been published by Adam.[32] An acrylic acid was converted to a peroxylactone by singlet oxygen oxidation and cyclisation, then reduced by triphenylphosphine to a β-lactone (Scheme 15). These products are interesting as they would be expected to be Michael acceptors like their nitrogen analogues.[33]



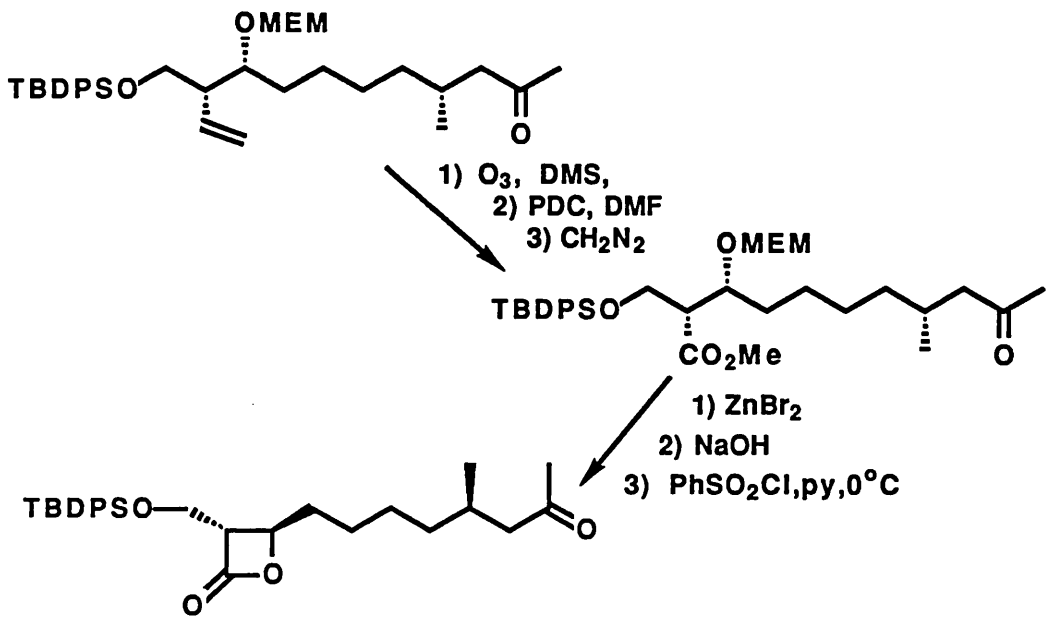
Scheme 15

Only one β-lactone natural product has been synthesised to date. Workers at Merck, Sharp and Dohme completed the total synthesis of 1233A in 1989.[34] They obtained the potentially troublesome C(7) methyl group by routine manipulation of (R)-(+)-pulegone. Eleven steps gave the chiral aldehyde (**21**) which was reacted with a chiral boron enolate of the type developed by Evans to set up the two stereogenic centres of the β-lactone moiety (Scheme 16).



Scheme 16

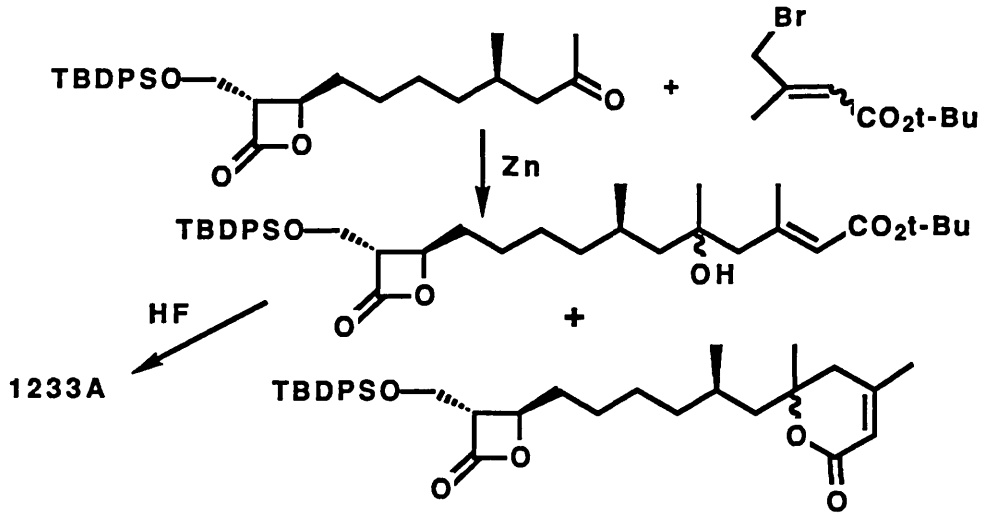
After a series of routine auxiliary removal and protection steps, the vinyl group came into its own as a masked carboxyl function. Ozonolysis, followed by oxidation and esterification gave the required functional groups, all differentially protected (Scheme 17).



Scheme 17

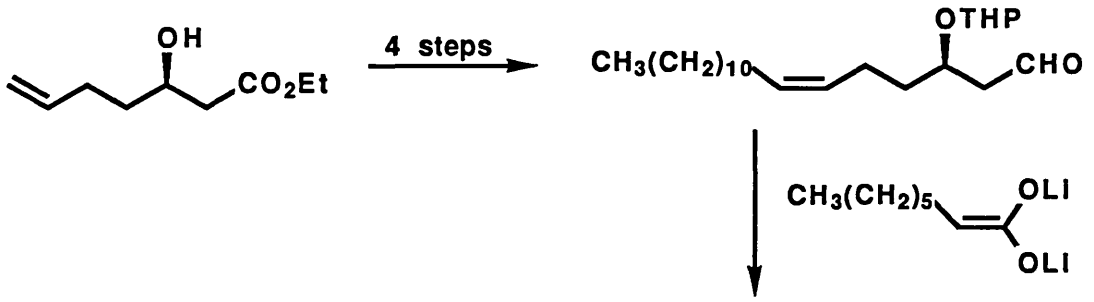
Cyclisation of the corresponding hydroxy acid under Adam's conditions gave the required β-lactone. The final steps in their synthesis proved disappointing. The Reformatsky reaction used to attach the remainder of the carbon framework gave a mixture of 2,3 double bond isomers, of which the *Z*-isomer lactonised. The hydroxy acid was then dehydrated in poor yield (Scheme 18).

1233A was finally obtained by simultaneous deprotection of the two ends of the molecule with hydrofluoric acid.

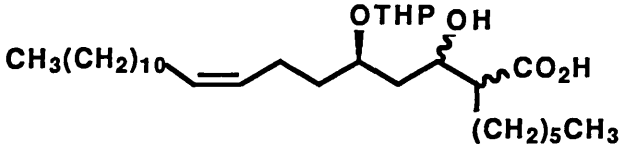


Scheme 18

The tetrahydroderivatives of lipstatin and esterastin have attracted synthetic interest, partly in order to establish the stereochemistry. Hoffmann-La Roche workers reported the first synthesis of tetrahydrolipstatin in 1987.[35] Starting from the known ethyl (R)-3-hydroxy-6-heptenoate, they set up the hydroxy acid by a non-diastereoselective carboxylic acid dianion aldol reaction(Scheme 19).



Scheme 19

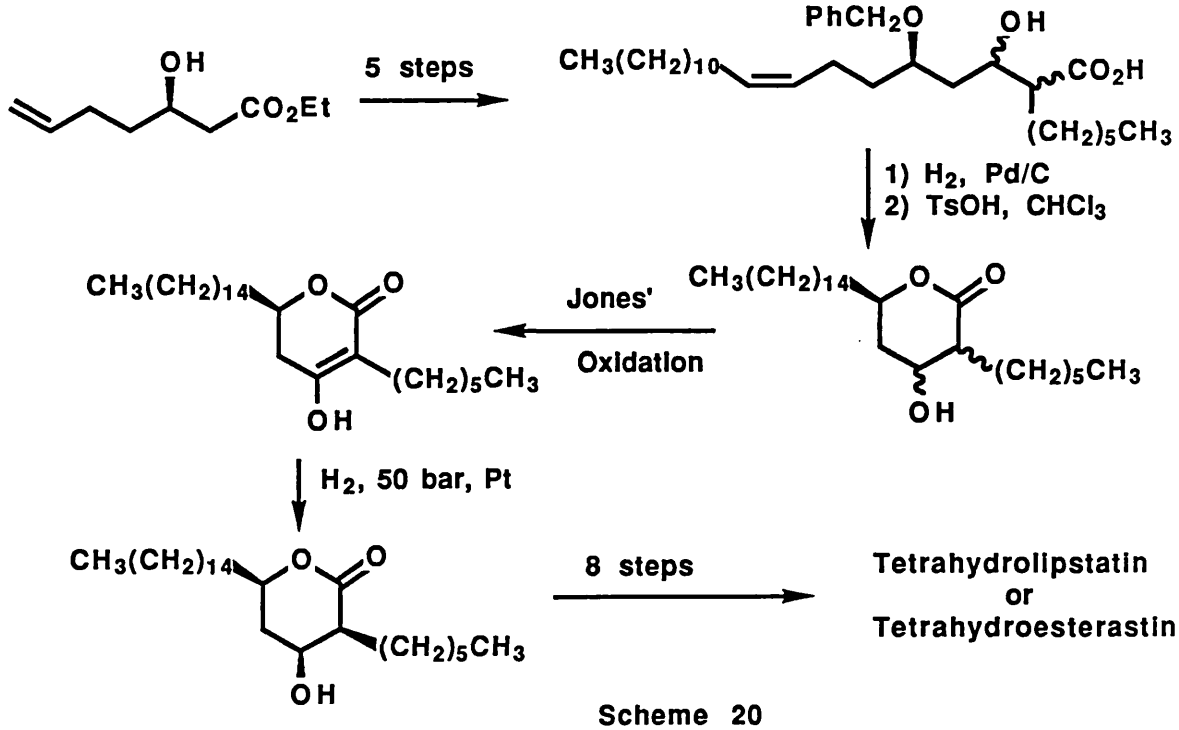


Remarkably, in a reaction pathway involving a proliferation, seperation and identification of diastereoisomers, they chose to use a tetrahydropyranyl protecting

group, thus doubling the potential number of isomers. In their later work, significantly, they switched to a benzyl group.

Isolation of the required β-lactones from the mixture of all possible isomers after Adam cyclisation and deprotection gave a compound that was easily converted into tetrahydrolipstatin by Mitsunobu esterification and hydrogenation of the carbon-carbon double bond

This synthesis, though effective, is beset by the problem of the non-selectivity of the aldol reaction. A subsequent publication outlined a solution to this problem.[36] By analogous chemistry, the benzyl (*sic*) protected aldol compound was prepared. Debenzylation and acid catalysed lactonisation gave a mixture of δ-lactones, but all having the same stereochemistry at the 6 position, carried through from the starting material.



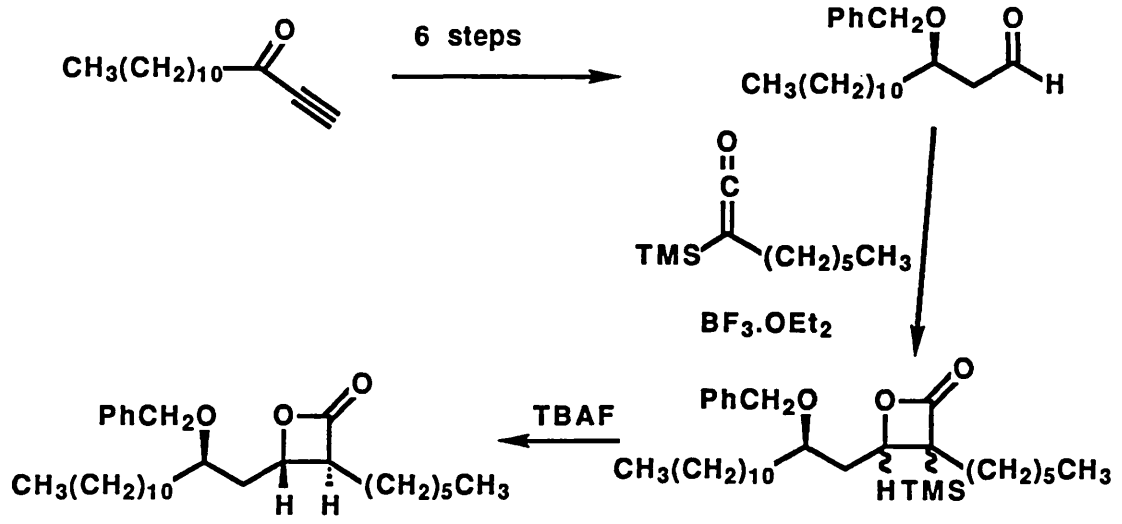
Scheme 20

Jones oxidation gave the ketolactone which existed entirely in its enol form in $CDCl_3$ solution. This was hydrogen ated exclusively from the lower face to give a single

δ-lactone with all chiral centres correct. Conversion of this to the hydroxy acid was achieved by a series of protection, deprotection and ring opening steps (Scheme 20).

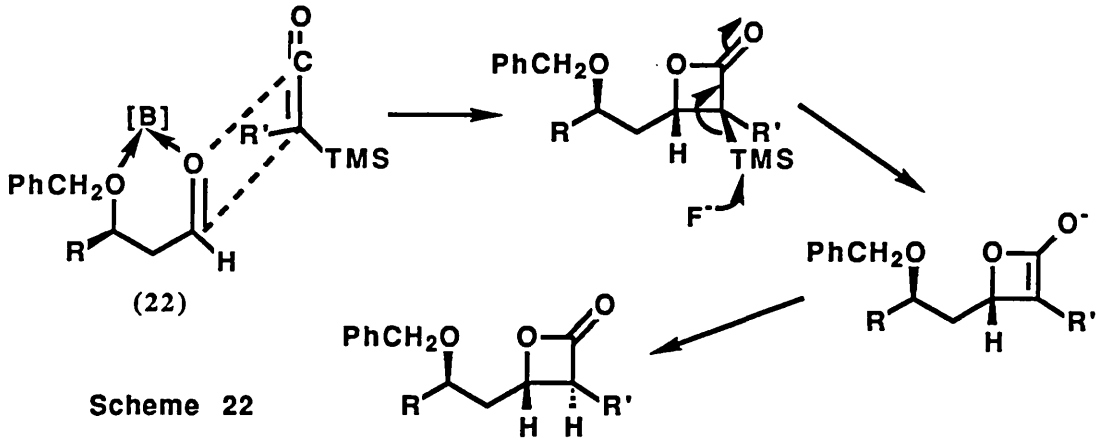
Although the concept of the enol hydrogenation is elegant, its execution requires a great number of tedious protection and deprotection reactions which detract from it. The simple adaptation of their β-lactone route to form δ-lactones is also inelegant, though expedient.

Kocienski has recently published an approach to tetrahydrolipstatin.[37] His strategy called for a diastereoselective [2+2] cycloaddition between an aldehyde and a stable trimethylsilylketene. The aldehyde was identical to that used by the Hoffmann-La Roche workers, but prepared by a different route using an enantioselective reduction with (R)-Alpineborane®, This underwent a smooth reaction with the ketene in the presence of boron trifluoride etherate according to Brady's procedure.[27] Desilylation followed by chromatography gave the desired β-lactone in about 60% yield (Scheme 21). The remaining material consisted of the three other possible isomers.



Scheme 21

The transition state for the cycloaddition is presumably (22), so that the alkyl group of the ketene causes the ketene to approach from the opposite side. As the steric bulk of the silyl group is greater than an ordinary alkyl, it is likely that the initial product has both alkyl groups in the undesired *cis* configuration. This could convert to the *trans* compound on desilylation (Scheme 22).



Scheme 22

The correct hydroxy β-lactone, after debenzylation, was then converted into tetrahydrolipstatin by Mitsunobu esterification, as in the Hoffman-La Roche procedure.

These syntheses highlight the problem in using the Adam cyclisation for preparing β-lactones with control of the stereochemistry: the need to use long procedures to set up hydroxy acids as single diastereoisomers or enantiomers. The Evans chemistry used by the Merck, Sharp and Dohme workers is a general method but the proliferation of protecting groups required weighs against this method. The two organometallic routes both have promise. Stille's first method, with its alkene precursors, is unlikely to be applicable to chiral synthesis, although this is not inconceivable. His later procedure, on the other hand, has some potential. Ley's iron chemistry is already proven in terms of chiral synthesis of δ-lactones and should be very useful for preparing β-lactones in future. Nevertheless, the need for new methods for β-lactone synthesis remains.

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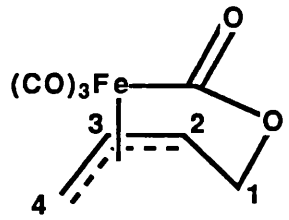
Chapter 2. NMR studies on iron complexes

From the beginning, ferrilactones were studied by NMR.[1,2] Many workers have experienced difficulties in obtaining good quality spectra due to instability of the complexes in $CDCl_3$, giving rise to significant amounts of solid and/or paramagnetic impurities especially at the relatively high sample concentrations required for the instruments available to the early workers. Acceleration of organometallic reactions involving single electron transfers by chlorinated solvents has been noted.[3] These problems were overcome by using d_6-benzene as solvent, flushing NMR tubes briefly with nitrogen or argon and using a good quality high field instrument (JEOL GSX-270) to obtain both resolution and sensitivity.

A large number of ferrilactone NMR spectra (recorded in $CDCl_3$ at 100 MHz) have been assigned by Aumann, yet he gives no indication for the basis of this assignment.[4] An unequivocal assignment was, therefore, required.

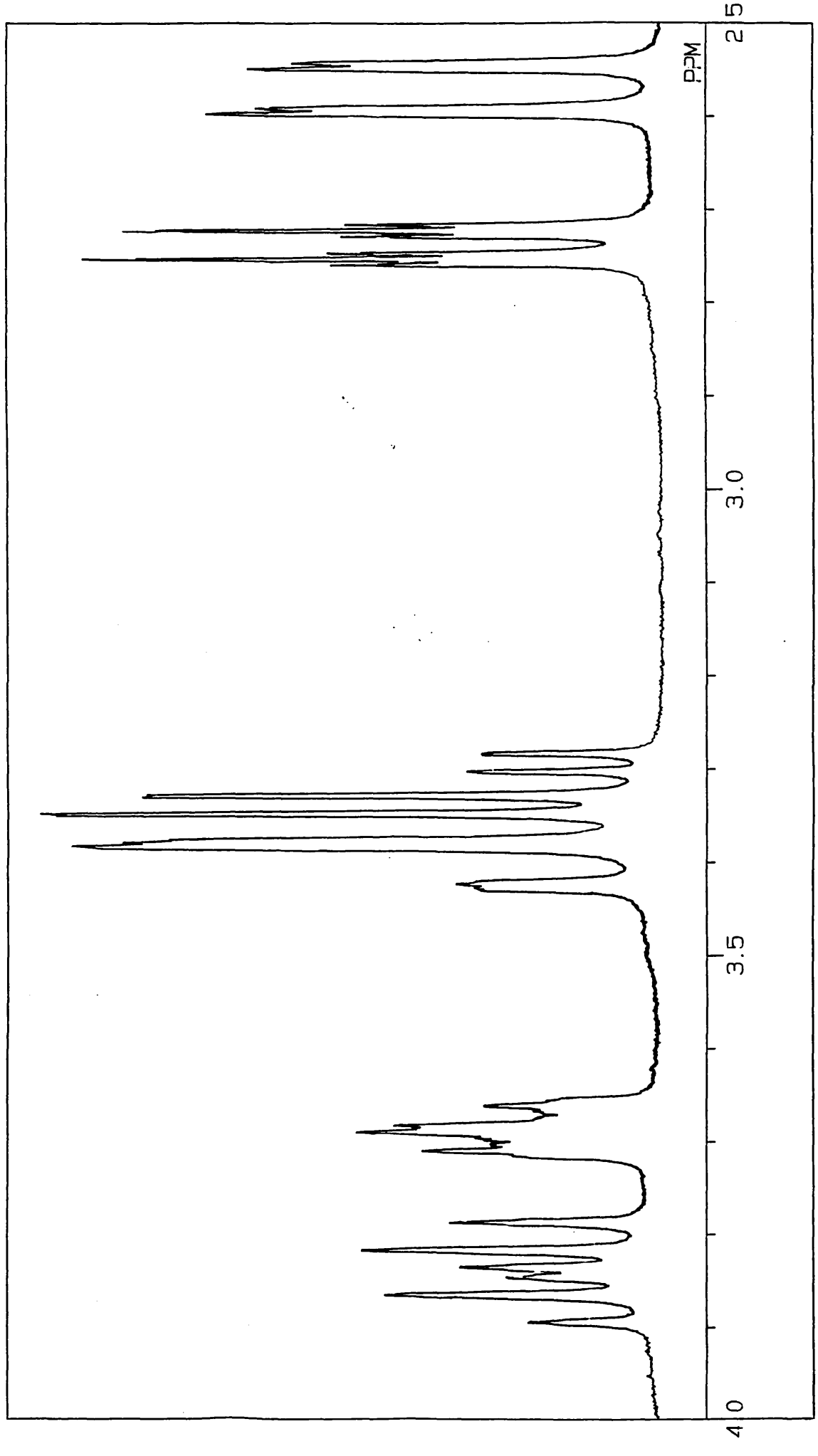
The basic ferrilactone, (**1**), shows six signals, all resolved at 270 MHz (Fig. 1).



(1)

Assignment of these by simple inspection, even with the aid of decoupling, was not possible. Application of the COSY-45 technique (Fig. 2) allowed most of the protons to be assigned. Two geminal pairs were apparent: they could be easily assigned by comparison of the geminal coupling constants. The signals at 2.54 and 2.69 ppm had J_{gem} = 1.5 Hz, characteristic of an sp^2 centre, implying that these are due to the 4-protons. The signals at 3.28 and 3.38 ppm had J_{gem} = 12 Hz, characteristic of an sp^3 centre, hence due to the 1-protons.

Fig. 1



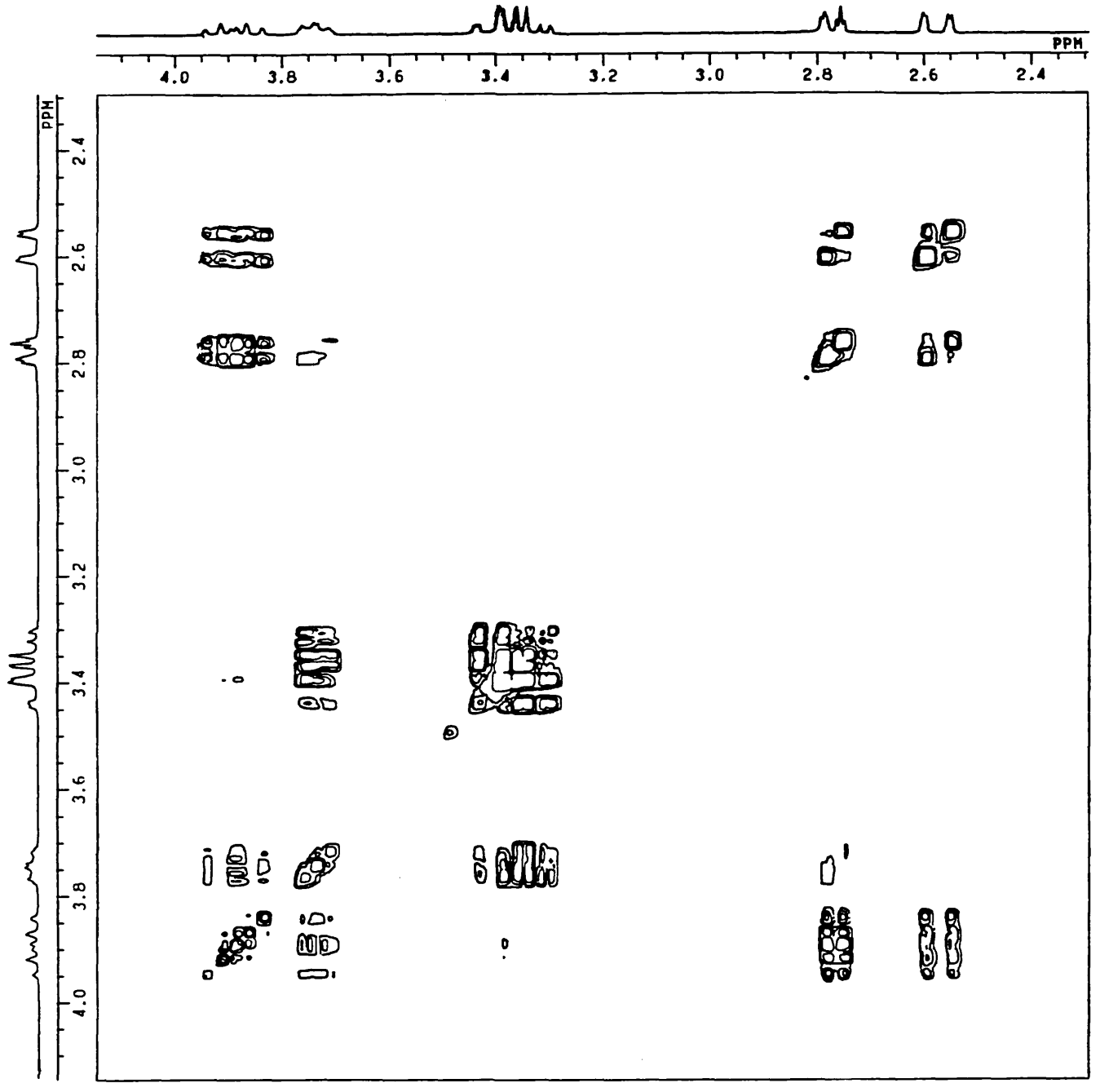


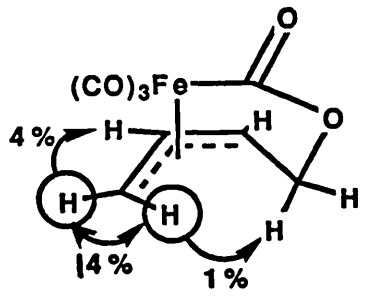
Fig. 2

The 4-protons clearly coupled to the signal at 3.78 ppm. This was assigned as due to the 3-proton. It appeared as a double double doublet with coupling constants of 12 and 8 Hz with the 4- protons and 8 Hz with the 2-proton, which clearly gave rise to the signal 3.63 ppm.

A remaining problem was the *exo/endo* identity of the 1-and 4-protons. Although conclusions have been drawn about this from simple chemical shift considerations; this cannot be reliable, especially in more complicated systems and varied solvents. Analysis of the coupling constants was considered to be more reliable. The protons on the sp^2 centre (4-C), had vicinal constants of 13 and 8 Hz. It appeared to be likely that the *trans* constant would be larger than the *cis*, as in alkenes, although early studies had shown that this was not necessarily so in allyl complexes.[6] For the 1-protons, however, the two constants were 5 and 1.5 Hz. Aumann[4] assigns these to the *endo* and *exo* protons respectively, yet does not indicate why; Moriarty[5], on the other hand, prefers the opposite assignment. Consequently, an nOe experiment was carried out in order to assign the *exo* and *endo* protons with certainty. Unfortunately, the signals due to the 1-protons were too close to be selectively irradiated. The 4-protons' signals, though, were well separated. Irradiation of the signal at 2.54 ppm led to a 14% enhancement of its geminal partner and a small (1%) but significant enhancement of the signal at 3.38 ppm. Effects were also seen at 3.78 and 3.28 ppm, but, as these integrated to zero, were clearly artefacts due to coupling. This experiment (Fig. 3) demonstrated that the signals at 3.38 and 2.54 ppm were both due to *endo* protons. This was confirmed by irradiation of the 2.69 ppm signal: this resulted in enhancement only of the signal of its geminal partner (14%) and of the signal at 3.78 ppm (4%), already assigned to the 3-proton. The coupling constants between the 1-protons and the 2-proton can then be assigned as 1.5 Hz (*endo*) and 5 Hz (*exo*): this is in agreement with Moriarty[5] and contrary to Aumann[4].

Having completed the assignment of the proton spectrum, the ^{13}C spectrum was recorded. This showed eight peaks as expected: four between 200 and 210 ppm

Fig. 3



corresponding to the carbonyls and four between 50 and 100 ppm. These were assigned with the aid of a proton-carbon heteronuclear correlation experiment (Fig.4).

Following this successful piece of work, the ^{13}C NMR spectra of a number of different ferrilactones and ferrilactams were obtained. The results and assignments are shown in table **1**. The iron complexes all gave the expected spectra which could be assigned by comparison with that of (**1**). The carbonyl carbons could not be assigned, except that the carbonyl at highest field was distinctly less intense than the other three in all cases. This, combined with a distinct chemical shift difference between ferrilactones and ferrilactams (roughly 200 ppm and 195 ppm respectively) indicates that this is the unique lactone carbonyl. Interestingly, the "isoferrilactone" (*vide infra*) showed only three carbonyl peaks: the smallest peak (at highest field) is likely to be the lactone carbonyl. The others, with an intensity ratio of about two to one are clearly due to two equivalent equatorial carbonyls (207.5 ppm) and one axial carbonyl (204.3 ppm). The structure of the complex around the iron atom must be trigonal bipyramidal.

Fig. 4

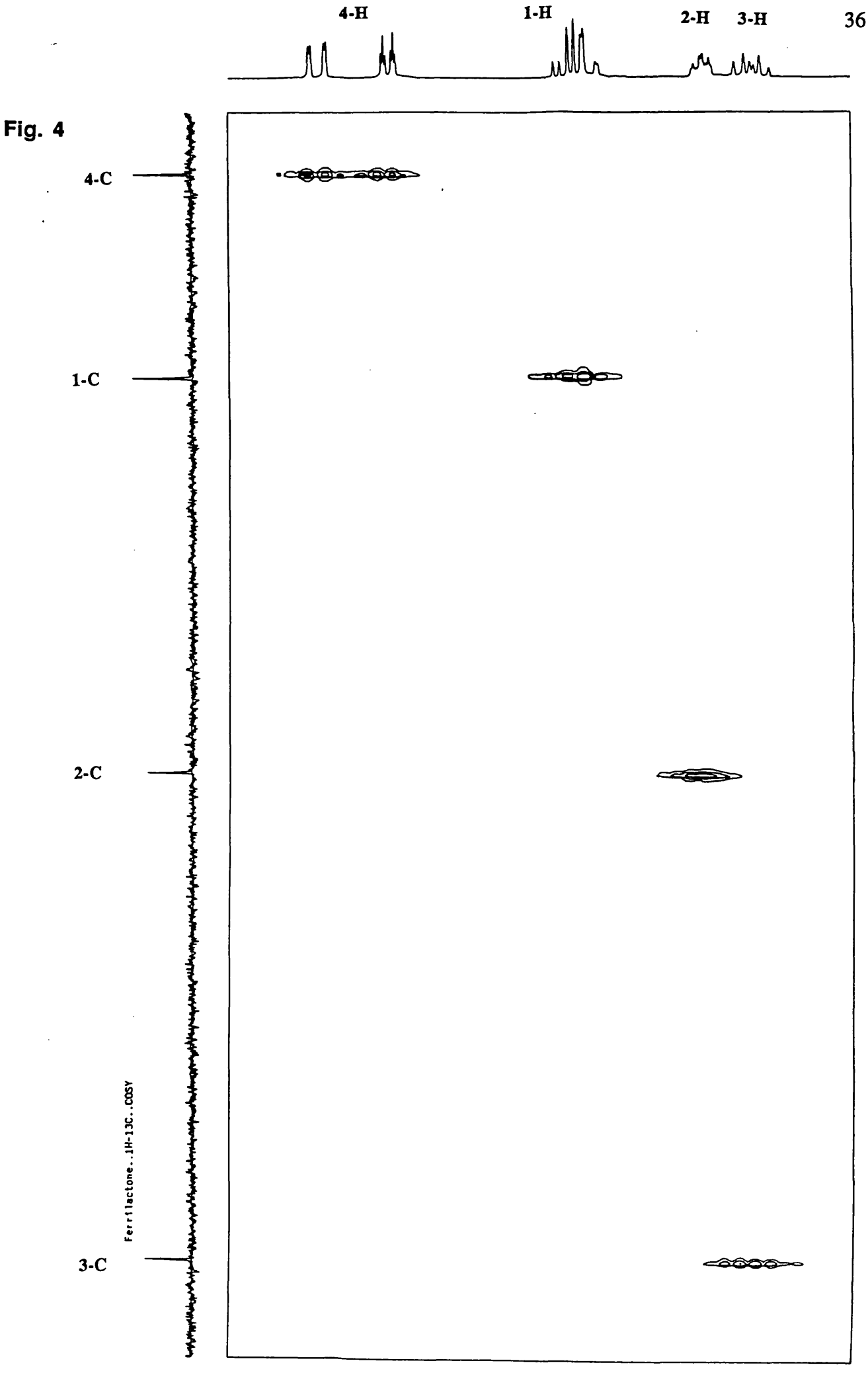
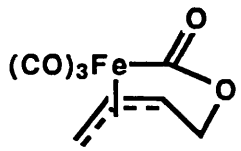
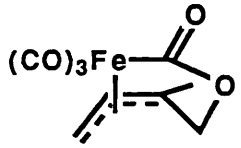
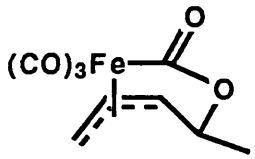
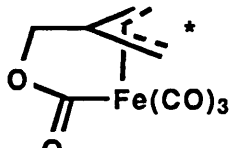
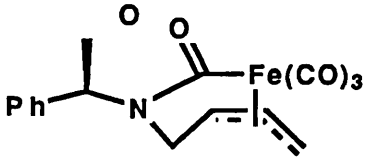
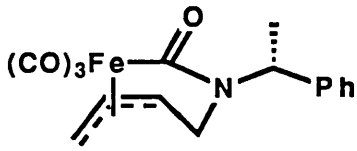
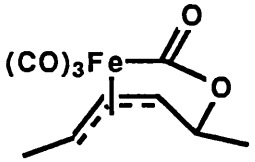
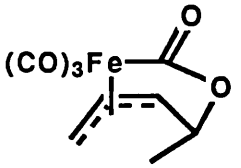
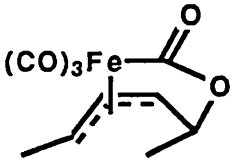
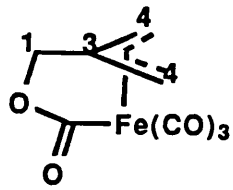


Table 1

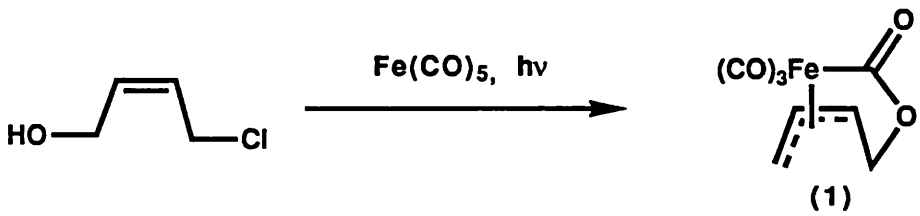
13C Chemical Shifts in Iron Complexes

Complex	1	2	3	4	Carbonyls	Other
	63.9	76.7	92.4	57.3	209.4,207.1 203.9,201.6	
	68.3	94.0	93.4	53.0	209.6,207.3 204.7,202.2	25.0(Me)
	70.3	82.5	91.9	57.4	210.4,207.2 203.9,200.3	24.0(Me)
	66.6	n/a	124.5	52.2	207.5,204.3 195.4	
	42.0	68.0	92.7	58.9	212.0,208.4 204.3,197.9	15.5(Me), 128(m,Ph), 48.9(PhC)
	39.9	66.0	90.6	57.1	210.2,206.4, 202.3,195.6	12.9(Me), 126(m,Ph) 47.1(PhC)
	71.1	79.0	93.8	77.4	211.1,207.8 205.4,201.1	20.8(1-Me) 24.5(4-Me)
	73.2	83.5	90.9	59.0	210.5,207.9, 204.3,200.5	22.2(Me)
	73.4	79.9	92.6	77.8	210.7,207.8, 205.1,201.3	21.3(1-Me) 22.2(4-Me)

*Carbons numbered according to structurally most similar in (1): 

Chapter 3. New Starting Materials For Iron Complex Formation

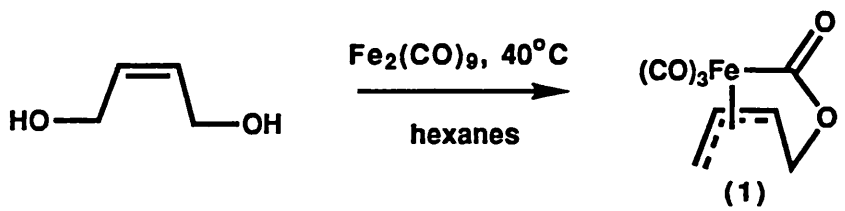
The early studies on ferrilactone chemistry utilised *Z*-4-substituted butenols as starting materials, rather than the vinyl epoxides that dominated later work. The first publication, by Heck and Boss, used the chloro substituted compound under photolytic conditions in the presence of iron pentacarbonyl (eqn. 1) in a clear continuation of their work on preparing η^3-allyl complexes.[1]



eqn.1

They succeeded in isolating a ferrilactone complex (**1**), albeit in low yield (5%). This low yield can be attributed to a number of factors, particularly the generally low conversions achieved in these reactions (20-30%) and recystallisation from a chlorinated solvent, in which ferrilactones have been found to decompose readily (*vide supra*).

Within a few months Murdoch published his studies in this area. By heating the same chloroalcohol with diiron nonacarbonyl in petroleum ether at 40°C he obtained the same ferrilactone in 25% yield.[2] Under the same conditions, however, the butenediol gave a remarkable 80% yield of the complex (**1**) (eqn. 2).

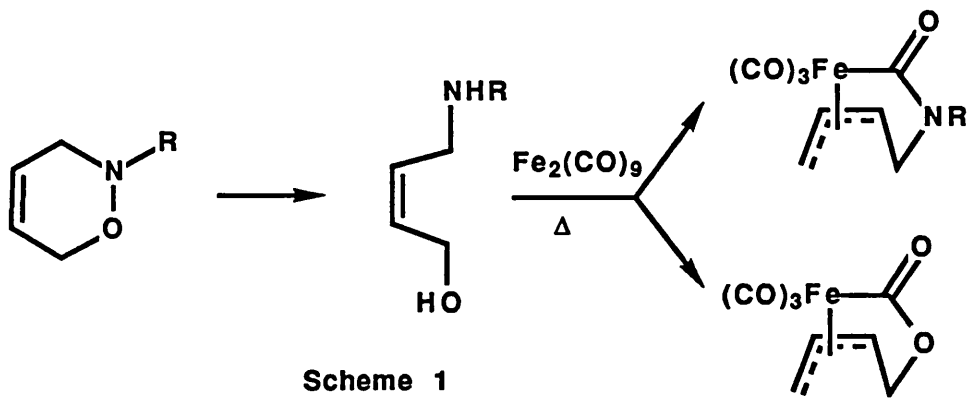


eqn. 2

It was clearly important to apply the mild conditions developed in these laboratories[7] to these substrates. It was pleasing to find that *cis*-2-butene-1,4-diol reacted with diiron

nonacarbonyl in THF and on ultrasonication in benzene at room temperature to give the complex (**1**) in 73% and 55% yields respectively. The chloroalcohol, prepared in 41% yield by the method of Colange and Poilane,[8] reacted with diiron nonacarbonyl to give a 25% yield, identical to Murdoch's result. This low yield was not due to the hydrogen chloride produced as inclusion of potassium carbonate in the reaction mixture had no effect.

Shvo has shown that *cis*-4-amino-2-butenols, either used directly or generated *in situ* by an iron(0)/water mediated reduction of 3,6-dihydro-1,2-oxazines, give ferrilactones and ferrilactams (Scheme 1).[9]

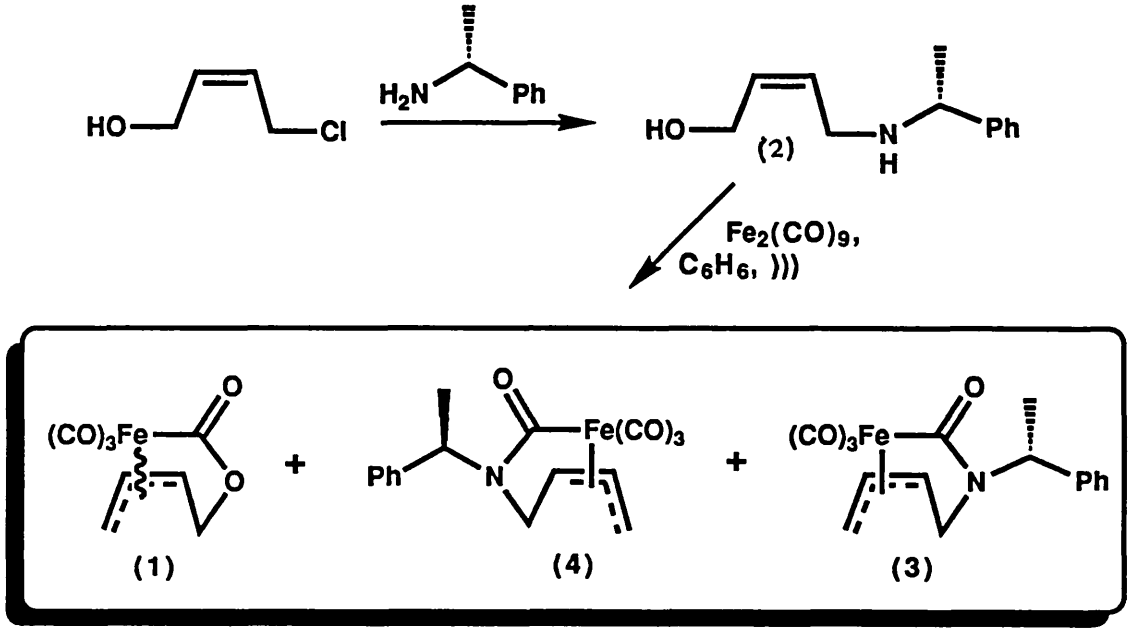


Scheme 1

In general he found that anilino substituents led to ferrilactones and a methylamino substituent gave a ferrilactam. A possibility that Shvo did not explore is the use of the alkyl substituent on nitrogen as a chiral auxiliary. Reaction of *Z*-4-chloro-2-butenol with (R)-(+)-α-methylbenzylamine (chosen because of its cheapness, availability in both enantiomeric forms and previous use in ferrilactam chemistry[10]) gave the amino alcohol (**2**) in 65% yield.

We found that this compound reacted with diiron nonacarbonyl in benzene under ultrasonic conditions to give a seperable mixture of two diastereoisomeric ferrilactams (**3** and **4**) and the ferrilactone (**1**) in a ratio of about 1:2:1 and 86% overall yield

(Scheme 2). The structure of the major diastereomer (4) was found by X-ray crystallographic analysis[11] of a sample grown from petroleum ether (bp 60-80°C) (Fig. 5). The ferrilactone produced in the reaction was shown to be racemic as treatment with (R)-(+)-α-methylbenzylamine in THF in the presence of zinc chloride TMEDA[10] gave a 1:1 mixture of the two ferrilactams.



Scheme 2

A number of attempts to convert the ferrilactams into more useful intermediates by removing the chiral auxiliary were unsuccessful. Debenzylation using catalytic hydrogenation over palladium on carbon in methanol containing formic acid,[12] sodium in liquid ammonia[13] and trimethylsilyl iodide[14] all had no effect. Substitution by water in the presence of zinc chloride TMEDA was also ineffective. Use of an azophilic Lewis acid (copper(II)) was similarly ineffective; use of protic acid led to decomposition.

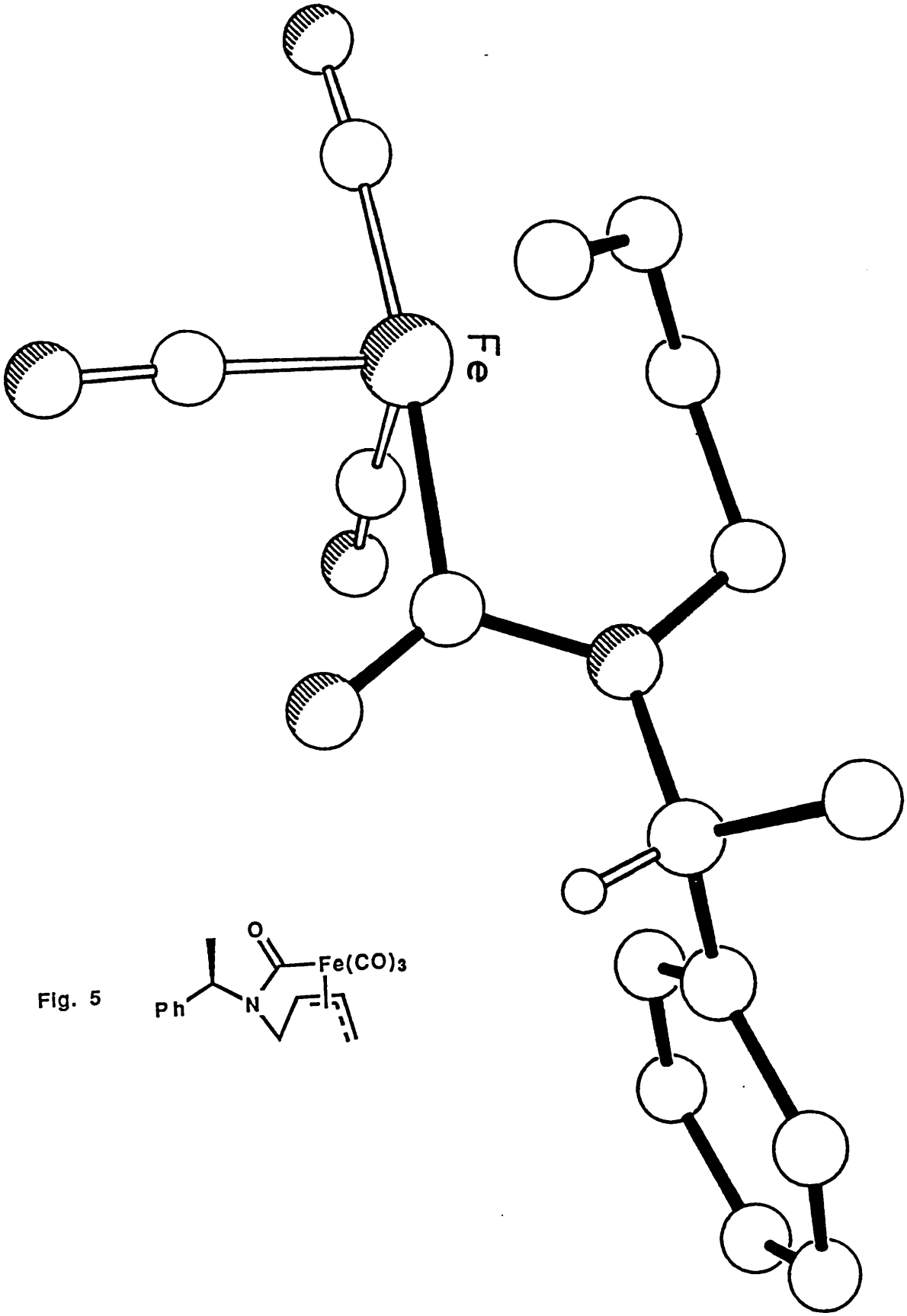
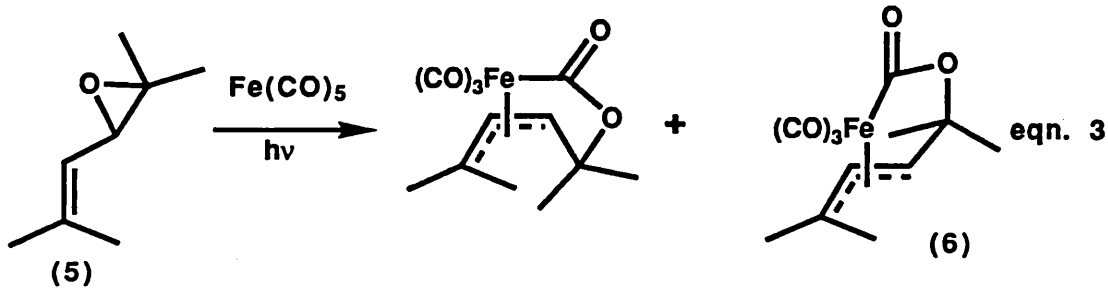


Fig. 5

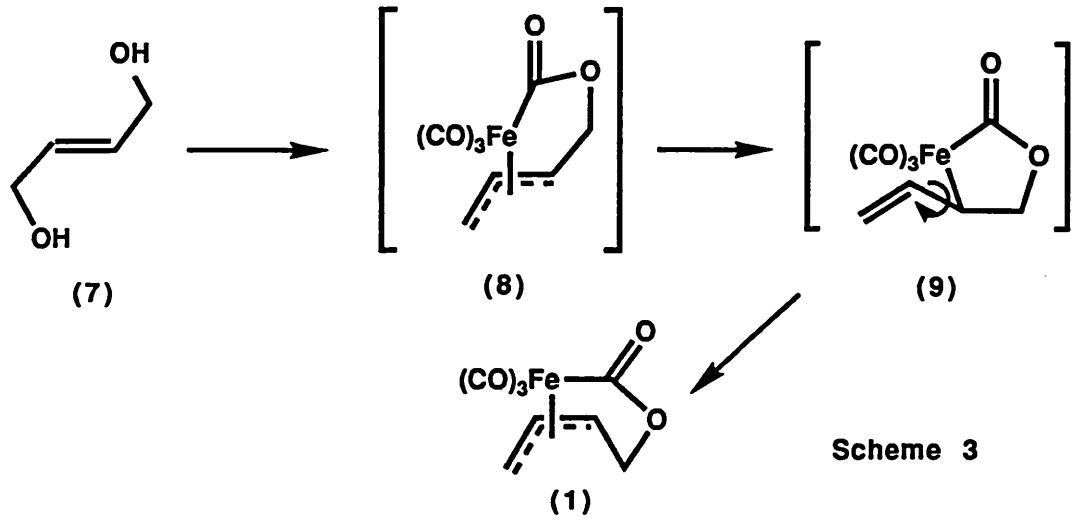
Aumann has shown that the highly substituted vinyl epoxide (**5**) gives some *trans* ferrilactone (**6**) on photolysis with iron pentacarbonyl (eqn. 3).[4]



He postulated them as intermediates in the formation of the normal *cis* ferrilactones but could not prove this. It is possible, however, that *cis* ferrilactones are produced directly from the *cisoid* conformation of the vinyl epoxide. Aumann's work does not exclude this possibility. *trans*-Butenediols are constrained to form *trans* ferrilactones as the geometry of the C2-C3 bond is fixed. Therefore, if treatment of a *trans* butenediol with diiron nonacarbonyl led to the formation of a *cis* ferrilactone, Aumann's postulated rearrangement reaction would have been clearly demonstrated.

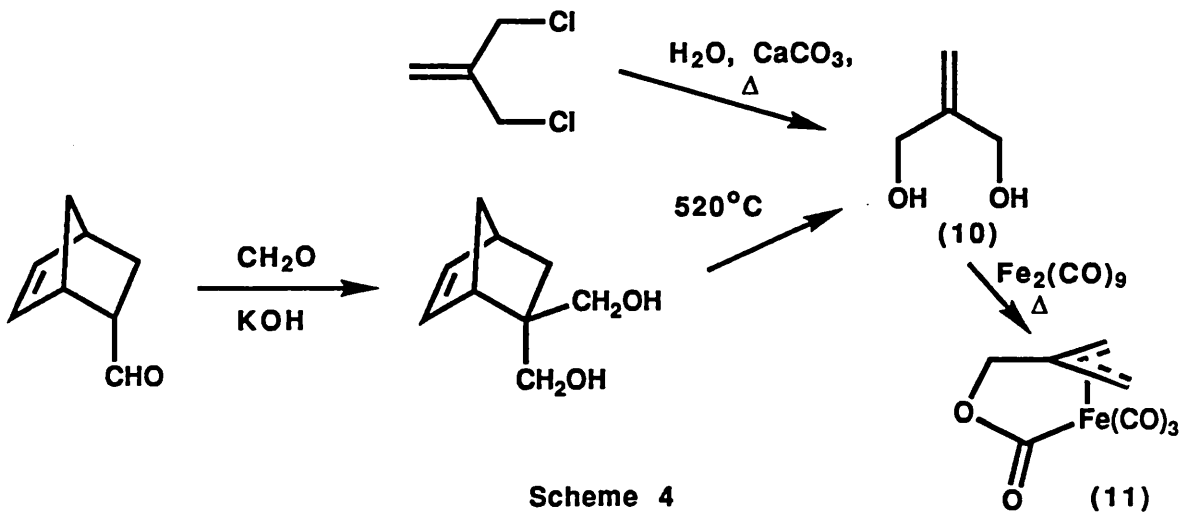
trans-2-Buten-1,4-diol (**7**) was prepared by Red-Al® reduction of 2-butyn-1,4-diol. Treatment with diiron nonacarbonyl in THF or on ultrasonication in benzene gave, by tlc, a mixture of two compounds. The less polar (R_f = 0.55 (ether/silica gel)) of these corresponded to the known *cis* ferrilactone (**1**) which was isolated in the usual way in 33% yield (THF reaction) or 11% yield (ultrasonic reaction). The other (R_f = 0.37 (ether/silica gel)) disappeared on work-up and is tentatively attributed to the *trans* ferrilactone (**8**).

This experiment indicates that *trans* to *cis* isomerisation does occur; the most likely mechanism (Scheme 3) is that postulated by Aumann involving rotation around the C2-C3 single bond in a η^1-intermediate (**9**). [4]



Scheme 3

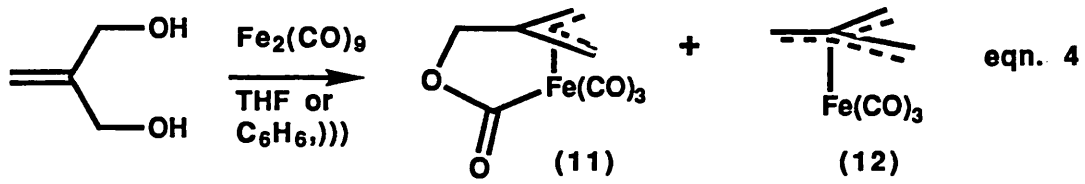
A variation that has been investigated by both Murdoch[2] and Shvo[15] concerns the "isobutene" analogue: 2-hydroxymethyl-1-propene-3-ol (**10**). This compound is easily prepared by refluxing methallyl dichloride in water in the presence of calcium carbonate[16] or through a longer route due to Corey[17] (Scheme 4). This diol has been shown by Murdoch to react with diiron nonacarbonyl on warming in an inert solvent to give the "isoferrilactone" (**11**) in good yield.[2]



Scheme 4

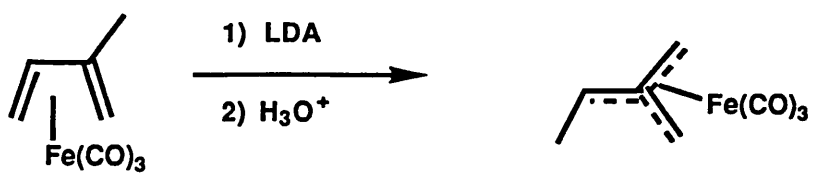
Under our mild THF conditions it was surprising to find that only a 12% yield of ferrilactone was obtained. Upon closer examination of the reaction mixture a less

polar by-product was detected (R_f = 0.03 (petrol/silica gel), 0.21 (10% ether-petrol/silica gel), 0.89 (ether/silica gel)). It was identified as trimethylenemethane-irontricarbonyl (**12**) (eqn. 4).



eqn. 4

Its formation, in a respectable 63% yield, was not surprising as treatment of methallyl dichloride with diiron nonacarbonyl under various conditions gives this product.[18] In contrast, under ultrasonic conditions, the isoferrilactone was the major product (58%) accompanied by only a trace of trimethylenemethaneirontricarbonyl (5%). This dependence of product ratio on reaction conditions is unprecedented in iron carbonyl chemistry. Whereas it has been shown that both vinyl epoxides and butene diols give different yields and ratios of isomers under the different conditions, this is the first example where the chemoselectivity changes dramatically. Significantly, η^4-diene complexes have not been isolated from the normal ferrilactone forming reactions. This can be attributed to the greater stability of trimethylenemethaneirontricarbonyl compared to the ordinary η^4-diene complexes, hence there is a greater thermodynamic driving force for its formation. This is demonstrated by the inertness of the former to many reagents except under harsh conditions which bring about decomposition.[19] Also 2-substituted diene complexes capable of forming an allylic carbanion often quench with rearrangement to give trimethylenemethane complexes (eqn. 5).[20]



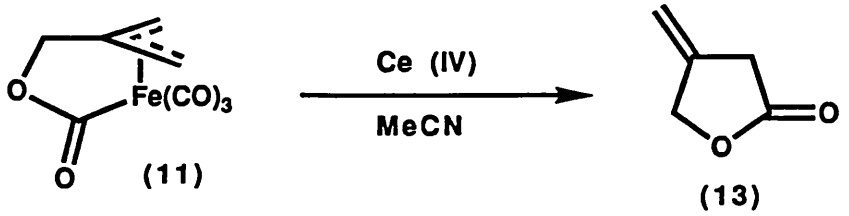
eqn. 5

The mechanistic basis for the chemoselectivity was expected to be connected to the Lewis acidity of the metallic species in solution; a more Lewis acidic mixture was expected to give more ferrilactone by coordinating to the hydroxyl group and, hence, making it into a better leaving group. The Lewis acid present in solution could only be the coordinatively unsaturated iron species $Fe(CO)_4$. This is known to coordinate to hard electron donors: complexes of the type $Fe(CO)_4(NR_3)$ are well known.[21,22] Iron tetracarbonyl would be expected to be a stronger Lewis acid in benzene than in THF as, in the latter, it would exist mainly as $Fe(CO)_4.THF$[22]. In benzene only a weak π-complex, η^2-$C_6H_6.Fe(CO)_4$ is possible.

The Lewis acid effect was confirmed by adding one equivalent of zinc chloride TMEDA to the THF reaction; pleasingly, the yield of isoferrilactone (**11**) was enhanced (40%) and only a trace of the trimethylenemethane complex was apparent.

Only a small amount of chemistry has previously been done on the isoferrilactone (**11**). Shvo showed that it underwent reactions with amines in the presence of Lewis acids.[15] Decomplexation reactions, which have been intensively studied for the normal ferrilactones and ferrilactams in these laboratories, have not been examined. We undertook a brief study.

Treatment of the complex (**11**) with ammonium ceric nitrate in acetonitrile at room temperature smoothly converted it into the β-methylene lactone (**13**) in 37% yield with no trace of the conjugated product (eqn. 6).



(11) (13) eqn. 6

This low yield was attributed to problems with the isolation of the volatile and slightly water soluble lactone.

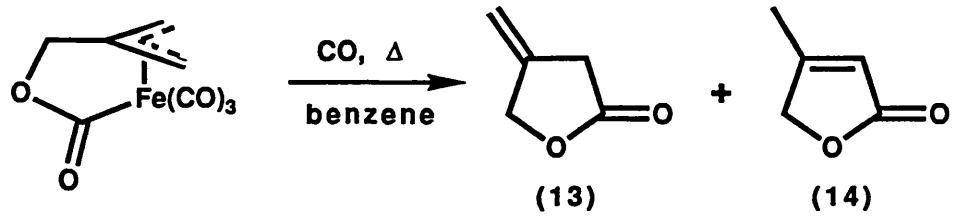
High pressure carbonylation also effected decomplexation. As has been shown in the case of δ-lactones the position of the double bond can be controlled by the reaction conditions used.[7] The double bond migration is mediated by unsaturated iron species extruded from the ferrilactone. Reduction of the pressure favours the migration reaction as it shifts the equilibrium between the coordinatively saturated pentacarbonyliron and the coordinatively unsaturated tetracarbonyliron (eqn. 7).

$$Fe(CO)_4 + CO \rightleftharpoons Fe(CO)_5 \qquad \text{eqn. 7}$$

Addition of electron defficient alkenes also suppresses the migration,[23] as they act as competitive ligands for tetracarbonyliron (eqn. 8).

eqn. 8

Indeed, heating the complex in benzene at 100°C under 150 atmospheres of carbon monoxide gave a 46% yield of the two lactones in a ratio of about 4:1 in favour of the conjugated compound (**14**). In contrast, at 90°C under 200 atmospheres of carbon monoxide and in the presence of acrolein, the unconjugated compound (**13**) was the sole product (30% yield), albeit accompanied by recovered starting material (50%) (eqn. 9).

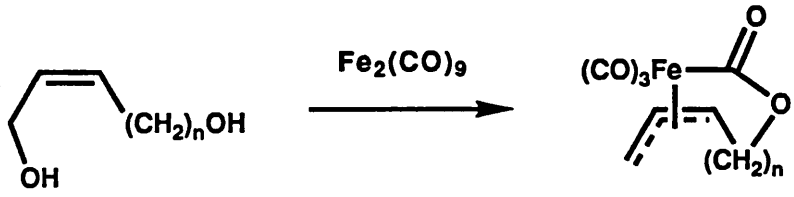


	(13)	(14)
100°C, 150 atm	9%	37%
90°C, 200 atm, acrolein	30%	-

eqn. 9

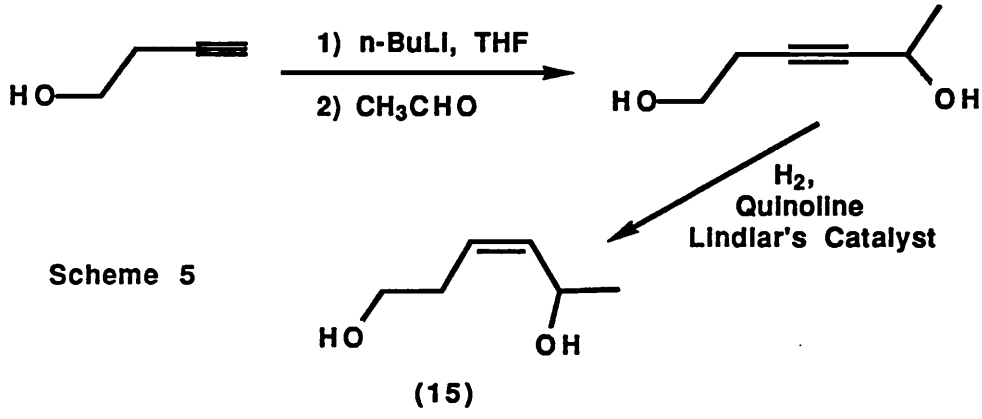
These preliminary results demonstrate that this is a potentially useful route to γ-lactones and, presumably, γ-lactams; they also demonstrate the fine chemical control that is possible in this chemistry.

Given the diol reaction, an attractive proposition was to insert methylene groups in order to open up a route to larger ferrilactones (eqn. 10).



eqn. 10

In order to investigate this *Z*-3-hexen-1,5-diol (**15**) was prepared by addition of acetaldehyde to the dilithiodianion of 3-butyn1-ol and hydrogenation of the resulting alkynediol in the presence of Lindlar's catalyst and quinoline (Scheme 5).[24]



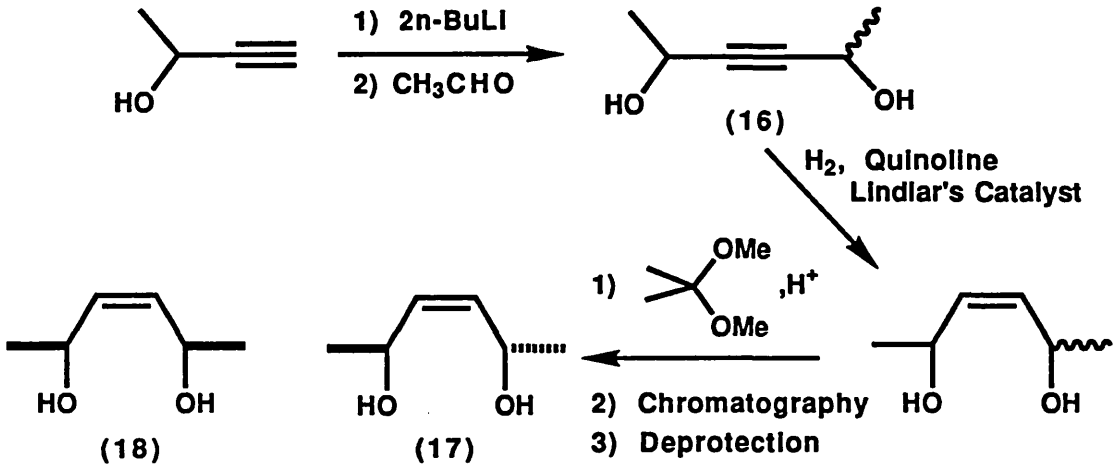
Scheme 5

(15)

This compound reacted with diiron nonacarbonyl to give a complex mixture (presumably arising from double bond migrations) which contained no ferrilactone species.

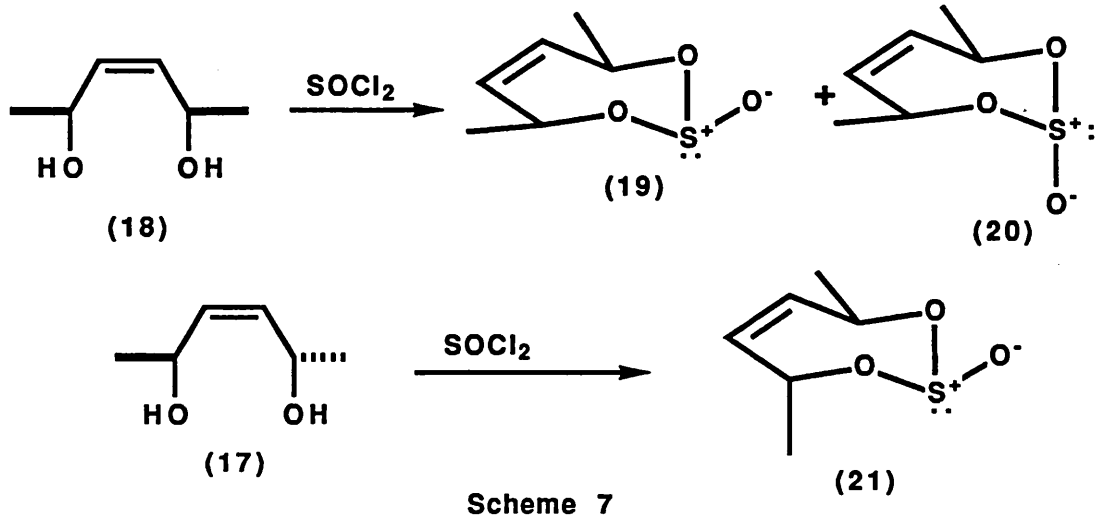
A pertinent question that remained concerned the relative geometry of the two hydroxy groups in the transition state: are they *syn* or *anti*? This was tested by using the *dl* and *meso* isomers of *cis*-3-hexene-2,5-diol (**17** and **18**). These were easily prepared

by treatment of the dilithio dianion of butyne-2-ol with an excess of acetaldehyde. The inseparable and virtually indistinguishable (by 250 MHz NMR) alkyne diols (**16**) were obtained as a 1:1 mixture in good yield (71%). Hydrogenation with Lindlar's catalyst and quinoline as before gave the two diols, now distinguishable by tlc and NMR. A simple method for separating the two was discovered serendipitously. Treatment of the mixture with less than one equivalent of 2,2-dimethoxypropane and an acid catalyst selectively formed the acetonide of only one of the diols. After separation and deprotection the *meso*- (**18**) and *dl*- (**17**) diols were each obtained in 37% yield from the alkyne (**16**) (Scheme 6).



Scheme 6

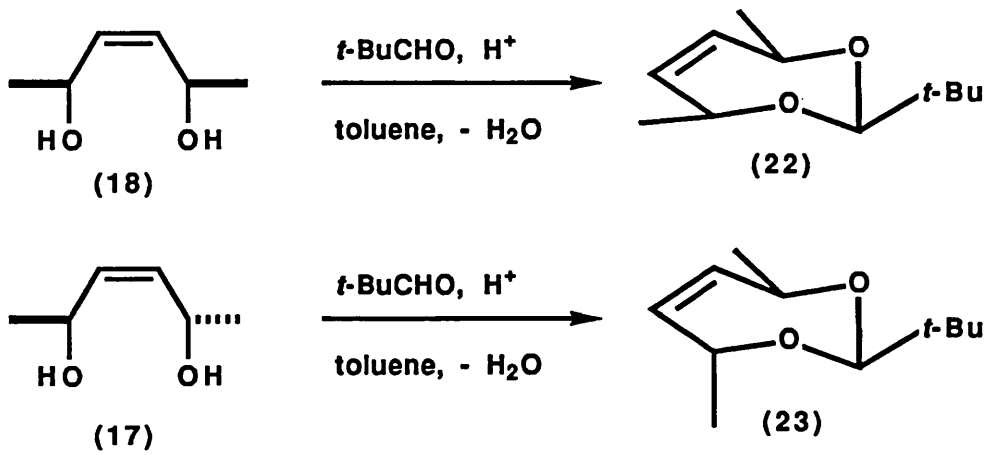
The structures of the two diols were assigned by forming cyclic derivatives. This approach was based on work by Cazoux and co-workers on cyclic sulphites.[25] They found that 3-hexene-2,5-diol forms three cyclic sulphites (separable by HPLC) on treatment with thionyl chloride (Scheme 7). In two of these, (**19**) and (**20**), only one methyl resonance was apparent, implying *cis* geometry between the methyls; hence both derived from the *meso*-diol. The difference between the two being the stereochemistry at sulphur. The third, (**21**), had two methyl resonances, implying *trans* geometry between the methyl groups and derivation from the *dl*-diol.



Scheme 7

Unfortunately these workers did not hydrolyse the sulphites back to the diols.

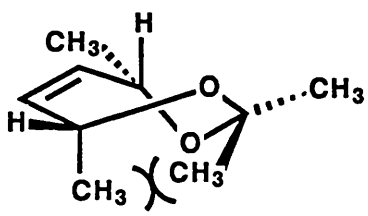
In order to use this strategy to ascertain the diol geometries, (**17**) and (**18**) were seperately converted into their pivalaldehyde acetals (Scheme 8). Cyclic sulphites were not chosen due to the additional complexity brought about by the configuration of sulphur. The bulky *t*-butyl group was expected to be exclusively equatorial, leading to single diastereoisomers. The pivalaldehyde acetals have been used as precursors for fragrances.[26]



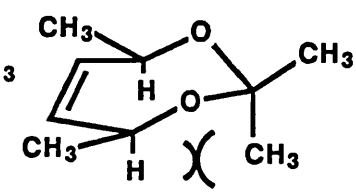
Scheme 8

The ^{1}H NMR spectra (Fig. 6) of the products clearly showed that one of the acetals was symmetrical, having only a single resonance for the methyl groups derived from the diol and one for the allylic protons. The other had two resonances for the methyl groups and two for the allylic protons. The ^{13}C NMR spectrum (Fig. 7) of the latter compound showed doubling of the signals of the corresponding carbon atoms as well as two signals for the vinylic carbons. The ^{13}C NMR spectrum of the symmetrical isomer was not obtained as the instability of this compound prevented isolation of a suitable sample.

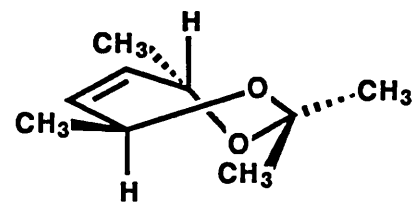
The symmetrical isomer was derived from the diol that could not form an acetonide and corresponded to the *meso*-diol (**18**), as in Cazoux's work. The unsymmetrical isomer corresponded to the *dl*-diol (**17**). Their contrasting behaviour on attempted acetonide formation can be rationalised by conformational analysis. The acetonide of the *dl*-diol can exist in a twisted conformation (**23a**) with both secondary methyl groups in pseudo-equatorial positions. The acetonide of the *meso*-diol, on the other hand, would, if in this conformation (**22a**), have a severe steric interaction between a secondary methyl group, necessarily axial, and an acetonide methyl group. The alternative chair-like conformation (**22b**) would also be disadvantaged by a 1,3-interaction between the allylic protons and an axial acetonide methyl group.



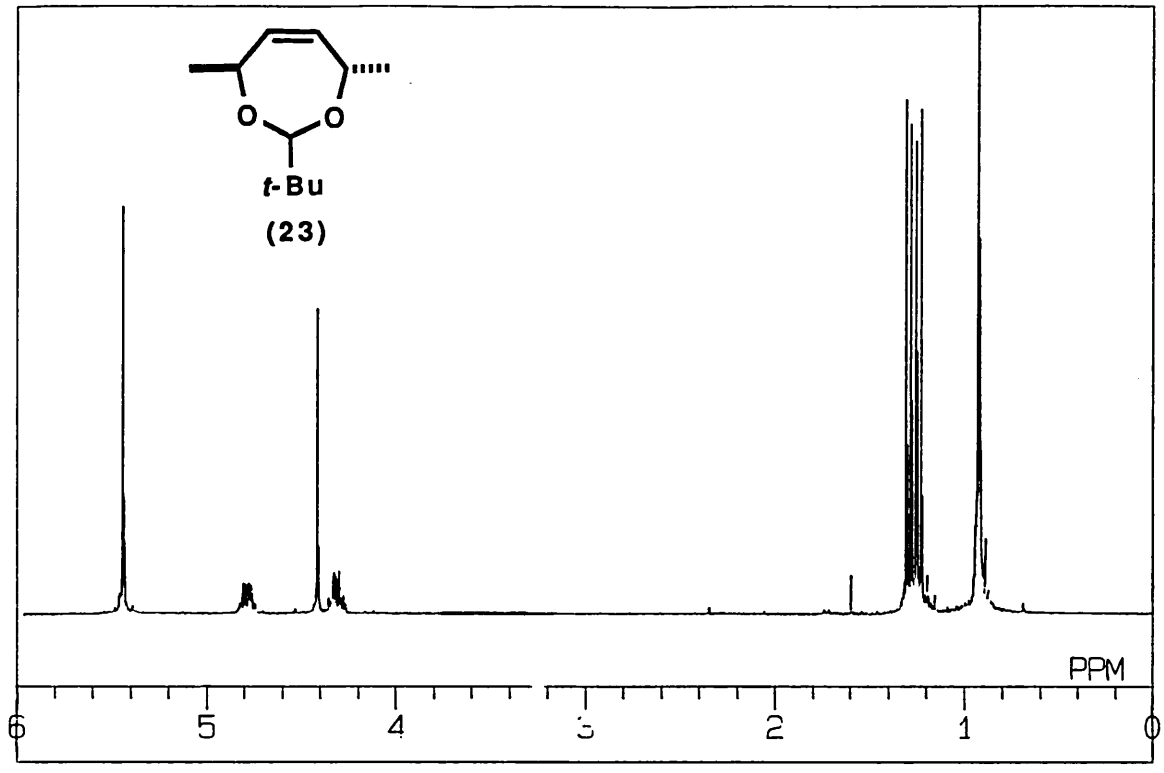
22a



22b



23a



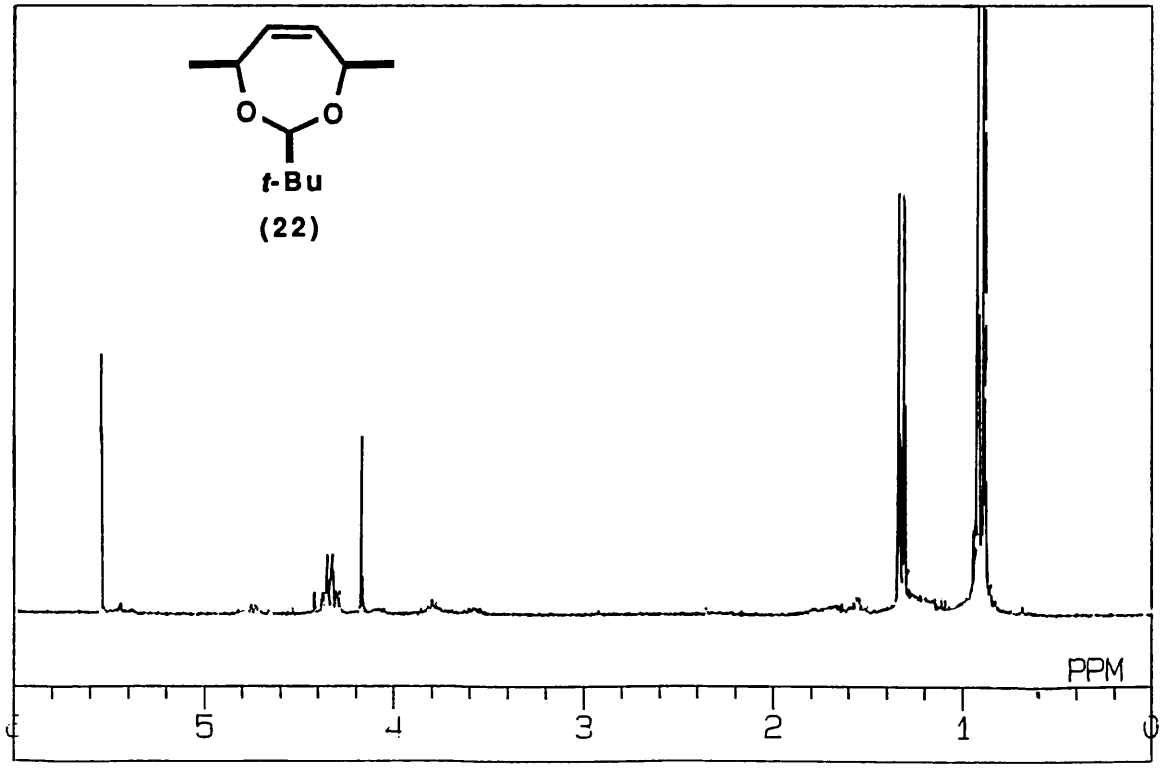


Fig. 6

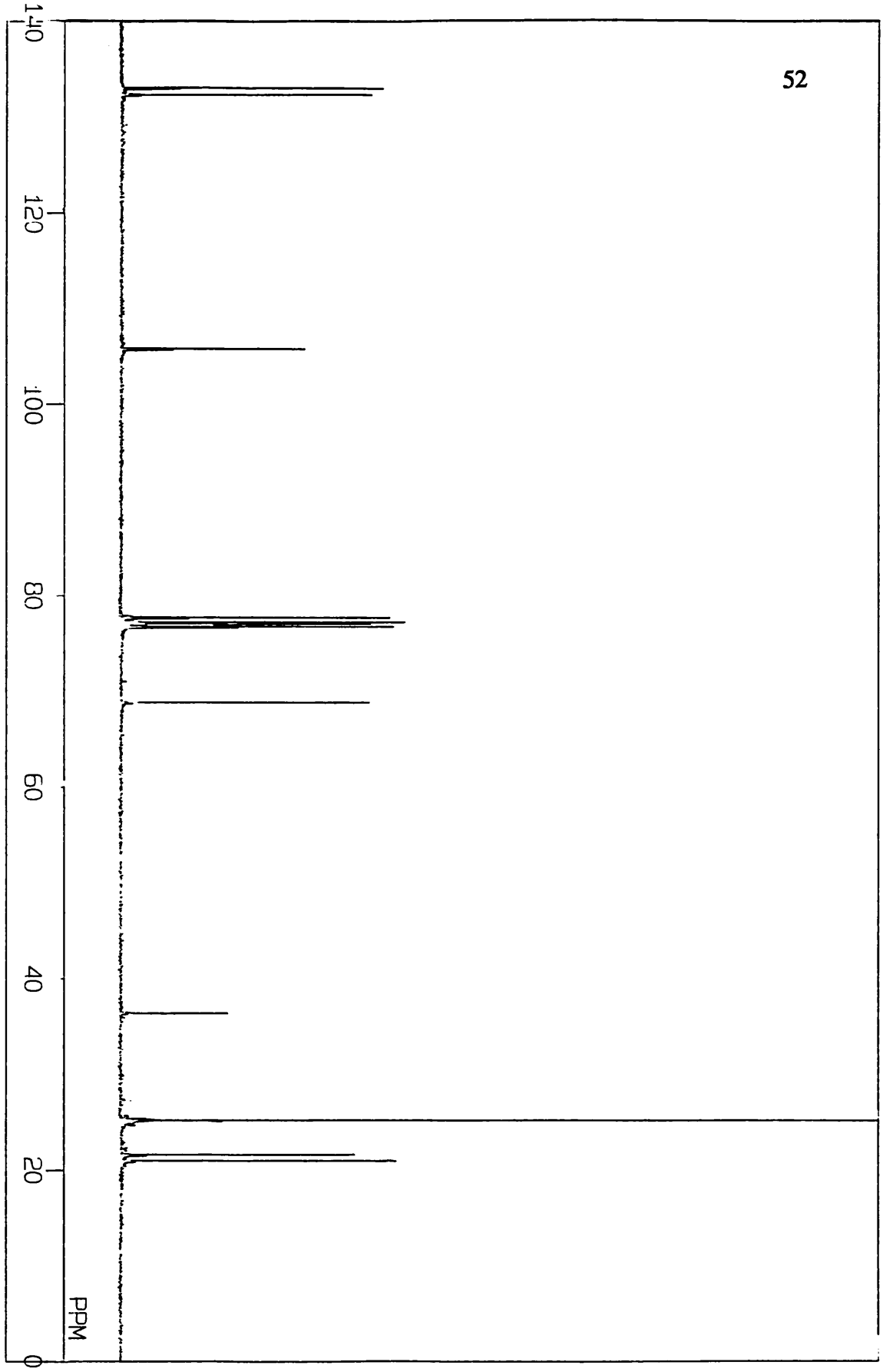
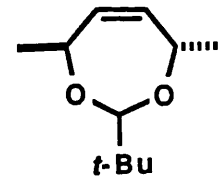


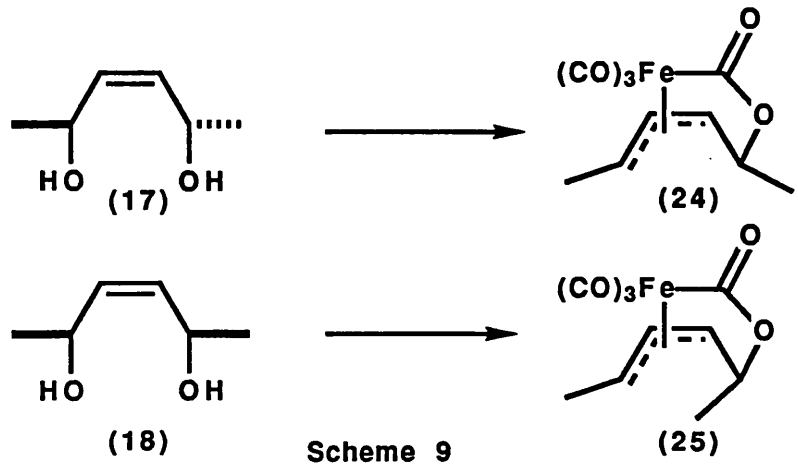
Fig. 7



(23)

On treatment with diiron nonacarbonyl in THF, each diol gave a different ferrilactone accompanied by some unidentifed products arising, probably, from double bond migration. With the aid of homonuclear decoupling of the methyl groups the NMR spectra of the two ferrilactones were assigned. By comparison with the coupling constant data obtained for the basic ferrilactone (**1**), the complete structures were deduced. The ferrilactone derived from the *dl*-diol had $J_{1,2}$ = 1.5 Hz, implying a *trans* relationship between the two protons and, hence, the methyl group in the *exo* position. The other ferrilactone, derived from the *meso*-diol, had $J_{1,2}$ = 5 Hz, implying a *cis* relationship between the protons; hence the methyl group *endo*. In both cases $J_{3,4}$ was about 12 Hz, consistent with a *trans* relationship between the 3- and 4-protons and, hence, *exo* methyl groups. These coupling constants were also in accordance with those observed by Moriarty.[5]

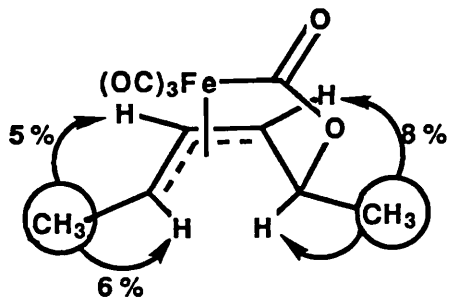
It was therefore clear that the *dl*-diol (**17**) yielded the ferrilactone with both methyl groups in the *exo* positions (**24**), while the *meso*-diol (**18**) gave the 1-methyl *endo* and the 4-methyl *exo* (**25**) (Scheme 9).



Scheme 9

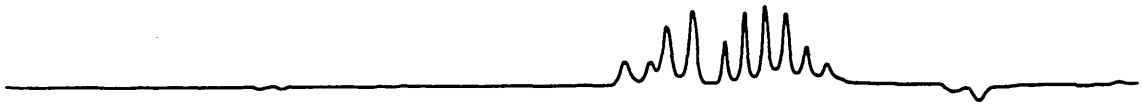
In order to gain further confirmation of these structures nOe experiments were carried out. The di-*exo* complex (**24**) gave three signals that could be selectively irradiated (Fig. 8): those due to the two methyl groups and the 3-proton.

Fig. 8

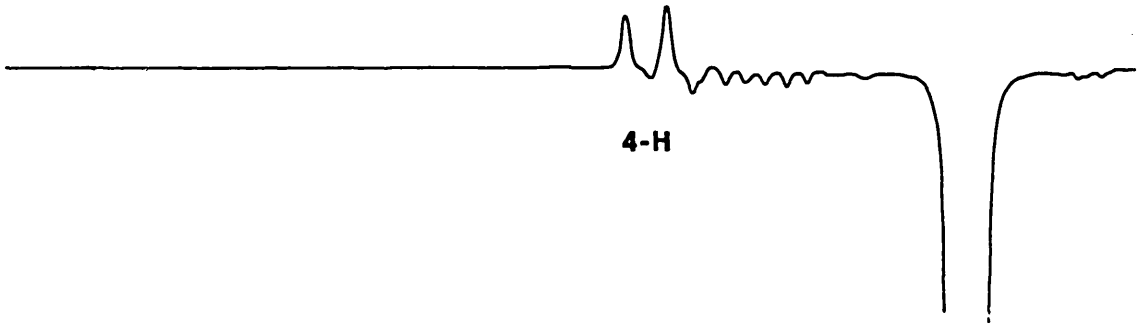


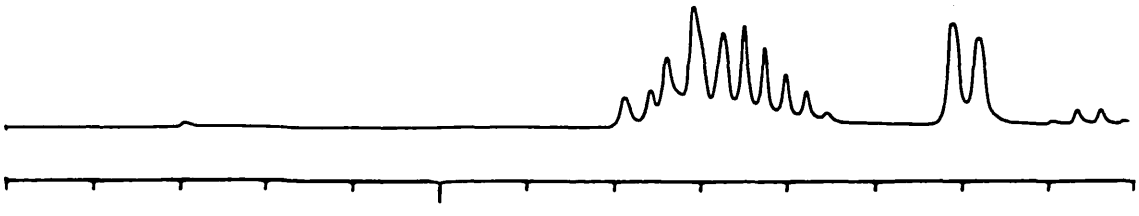
Irradiation of the 1-protons

Irradiation of the 6-protons



Irradiation of the 3-proton





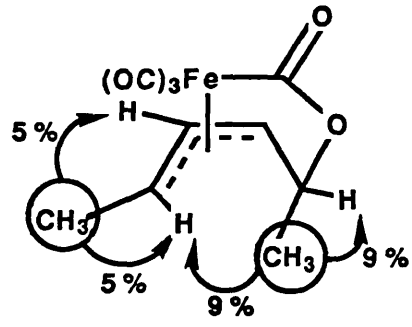
Irradiation of the methyl α to oxygen (1-protons) led to an 8% enhancement of the signal of the 3-proton, a large but unquantifiable (due to the overlap of signals in the normal spectrum) enhancement of the signal of the 2-proton, but no significant effects on the signal of the 5-proton. Irradiation of the other methyl group (6-protons) led to an enhancement of the signal of the 4-proton (5%) and the 5-proton (~6%). Finally, irradiation of the 3-proton enhanced the signals of the 4-proton (5%) and the 1-protons (1%).

The *exo-endo* complex (**25**) also had the complication of overlapping signals. Here, only the methyls could be selectively irradiated (Fig. 9) as the signals of the 3- and 4- protons and the 2- and 5-protons overlapped. Irradiation of the 6-protons clearly gave a 5% enhancement of the signal of the 5-proton. A signal that had been a complex multiplet in the proton spectrum (in the absence of decoupling) was smoothly transformed into a double-quartet in the difference spectrum on irradiation of the 6-protons. The signal of the 4-proton was also "lifted out" of its overlap with the siganl of the 3-proton in the difference spectrum by a 5% enhancement. Irradiation of the other methyl (the 1-protons) on the other hand, led to a 9% enhancement of the signals of both the 2- and 5-protons; in the diffence spectrum, the multiplet at ~4.8 ppm was almost exactly reproduced. A small enhancement (2%) of the signal of the 2-protons was also apparent.

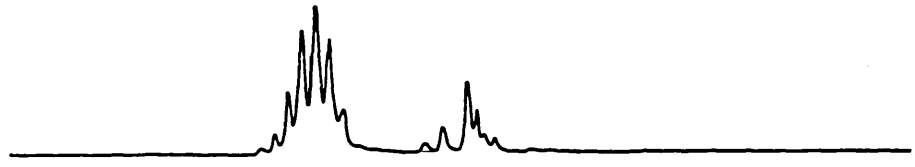
These results, especially the contrasting behaviour of the 1-protons, are entirely consistent with the structural assignments already made on the basis of the coupling constants.

These results are consistent with Aumann's proposed mechanism for the conversion of ferrilactones to ferrilactams.[4] Here, *anti*-attack by an amine on a Lewis acid coordinated ferrilactone leads to a breaking of the cyclic structure and

Fig. 9



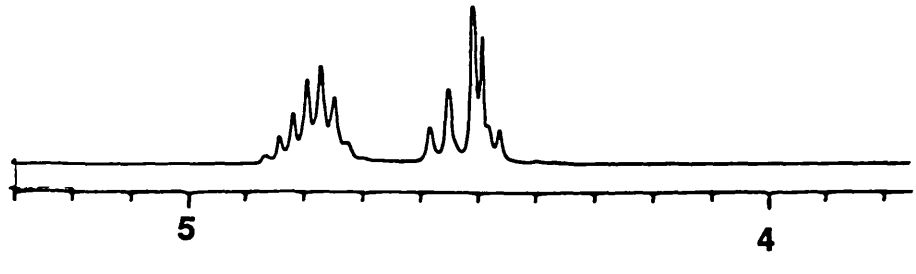
Irradiation of the 1-protons



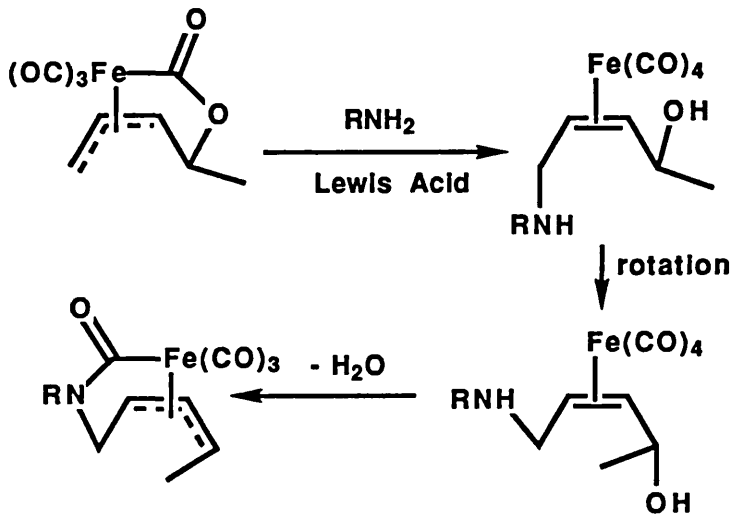
2-&5-H

Irradiation of the 6-protons

5-H 4-H

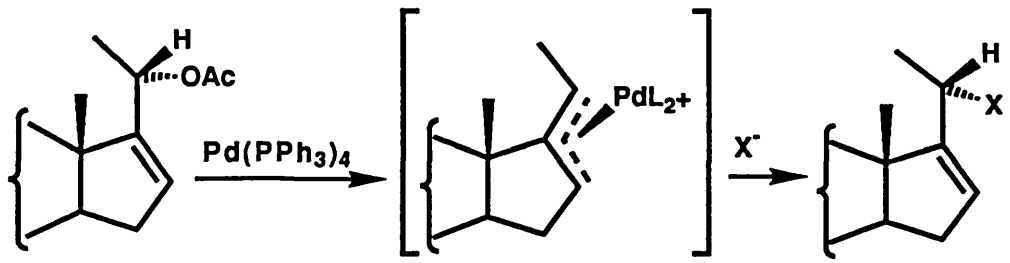


formation of a η^2-aminoalcohol intermediate. Rotation around the carbon-carbon single bonds then brings the amino group *syn* to the metal and the hydroxyl group *anti* to the metal. Subsequent cyclisation with dehydration leads to the ferrilactam. An *exo* substituent at the 1-position of the ferrilactone thus becomes an *endo*-substituent at the 4-position of the ferrilactam (Scheme 10).



Scheme 10

This reaction is also consistent with the observation that the formation of π-allyl complexes of palladium from allylic acetates proceeds with inversion, i.e. the leaving group is *anti* to the metal.[27] Subsequent nucleophilic attack is also *anti* to the metal, leading to overall retention (Scheme 11).

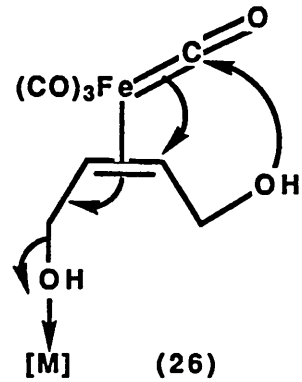


X = $CH(SO_2Ph)(CO_2Me)$

Scheme 11

The geometrical properties of the reaction are in accord with normal organometallic chemistry. In his studies on this class of compounds, Shvo has drawn an analogy with the S_N' reaction.[9] Although the reaction of a ferrilactone with an amine to form a ferrilactam is similar in regiochemistry; geometrically, this is not so. S_N' reactions usually possess a *syn* relationship between the nucleophile (here represented by an internal hydroxy or amino group) and the leaving group.[28]

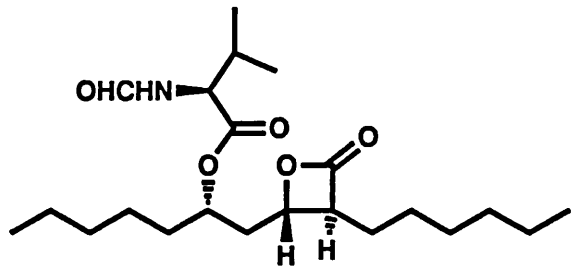
The transition state (**26**) is consistent with the required *anti* geometry of the leaving group relative to the tetracarbonyliron moiety and the participation of a Lewis acid, [M].



(26)

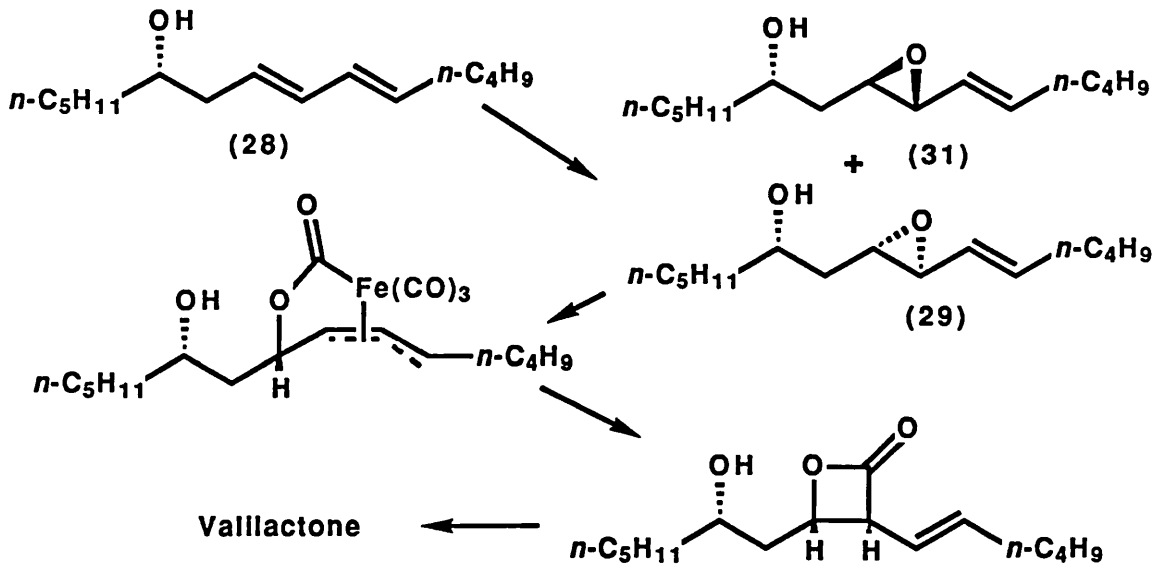
Chapter 4. Towards the Total Synthesis of Valilactone

Structurally, valilactone (**27**) is the simplest of the β-lactone natural products.[29]



(27)

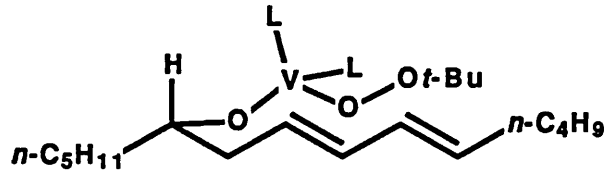
The only functionality other than the β-lactone is the easily prepared N-formyl amino acid.[30] As this represents a masked alcohol, it is a potential stereo- and regiochemical anchor for mono-epoxidation of a nearby diene. This would be expected to give the vinyl epoxide required to form a ferrilactone precursor for valilactone (Scheme 12).



Scheme 12

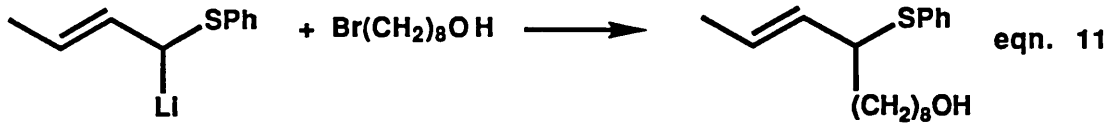
Thus, S-pentadeca-5-7-dien-10-ol (**28**) is an attractive intermediate in valilactone synthesis as homoallylic epoxidation under Sharpless' conditions[31] using vanadium or molybdenum catalysis would be expected to give the required vinyl epoxide (**29**) via

the transition state (**30**) in a ratio of about 3:2 over the isomer (**31**).[32] This epoxide would then be only four steps from the natural product.



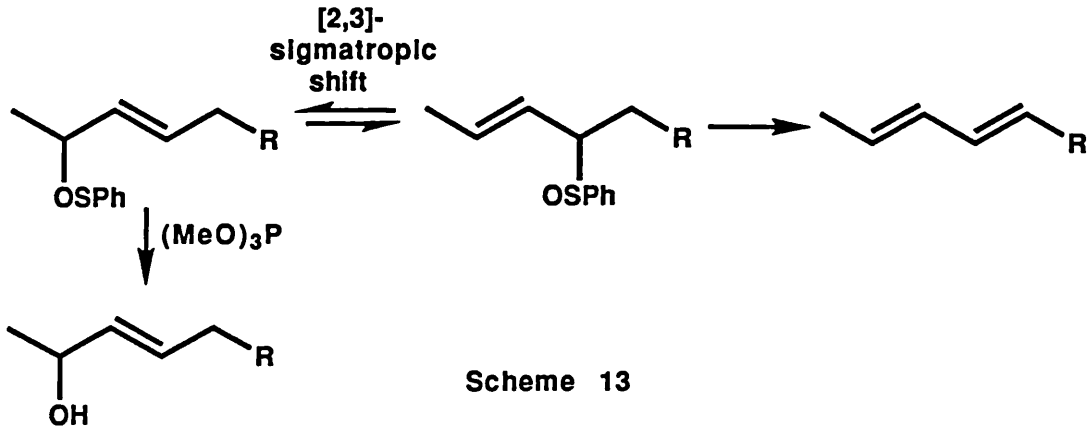
(30)

The method of Babler and Haack for preparing the coddling moth pheromone appeared to be applicable to valilactone synthesis.[33] In this piece of work the anion of an allylic sulphide was reacted with a bromoalcohol (eqn. 11) to give a hydroxysulphide.



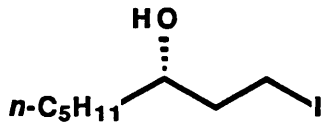
eqn. 11

Heating of the corresponding sulphoxide in the presence of an amine base led to a *syn* elimination, rather than the usual [2,3]-sigmatropic shift. This was due to the absence of a suitable thiophilic agent, such as trimethylphosphite, to breakdown the initial product of the sigmatropic shift, a sulphenate. The shift therefore reverses and the sulphoxide undergoes a slower, but irreversible *syn* elimination (Scheme 13); the amine serves to neutralise the sulphenic acid produced.

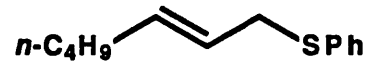


Scheme 13

For valilactone synthesis, the two fragments required for this method are (32) and (33).

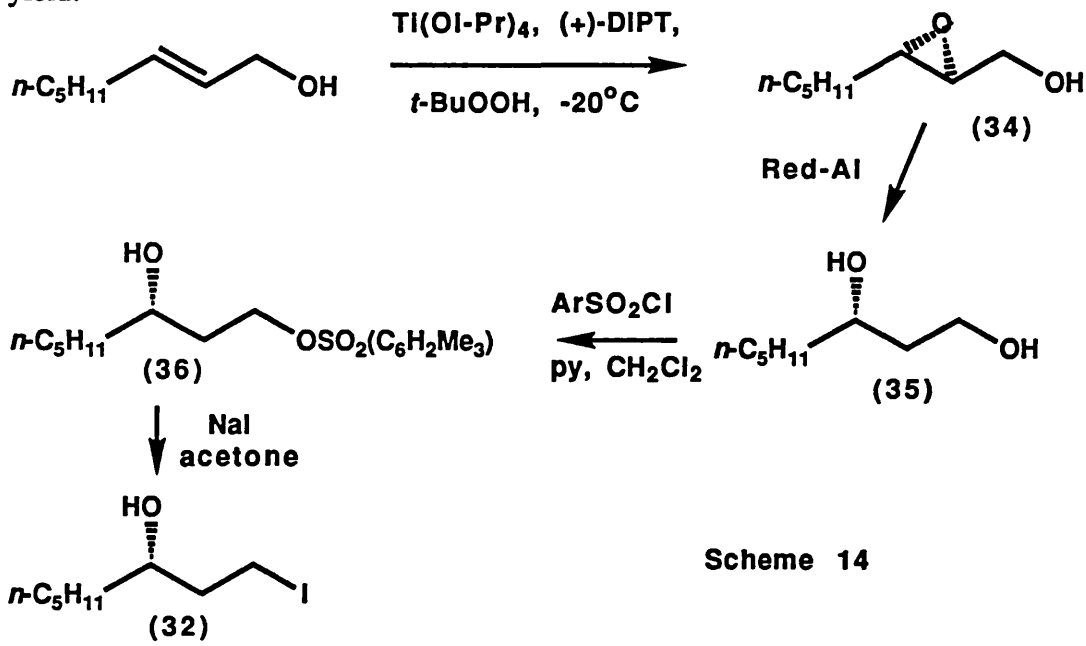


(32)



(33)

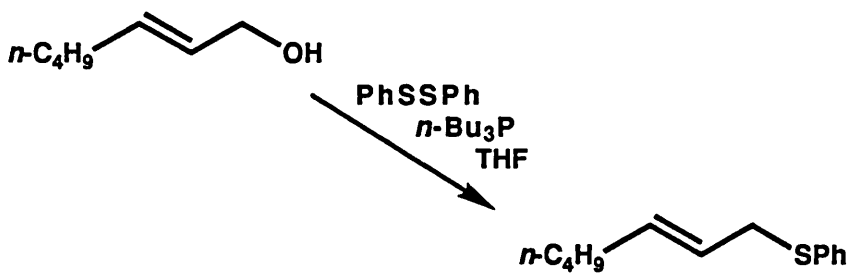
The iodide was prepared routinely (Scheme 14). Enantioselective epoxidation of *trans*-2-octenol using Sharpless' catalytic method gave the expected epoxyalcohol (34).[34] The catalytic method was used despite the fact that it usually gives a slightly lower enantiomeric excess than the stoichiometric procedure. It is though, operationally simpler, especially on work up as there is much less titanium to remove. It is also a quicker reaction, typically complete in a few hours. The epoxyalcohol was obtained after chromatography and recrystallisation from petrol at -20°C in 92% yield.



Scheme 14

Red-Al® reduction of the epoxyalcohol proceeded in excellent yield (99%) to give the 1,3-diol (**35**) only. Sulphonylation with the hindered mesitylene sulphonyl chloride in the presence of pyridine at low temperature gave a reasonable yield (48%) of the 1-functionalised material (**36**), accompanied by some of the disulphonylated compound. Finkelstein reaction (sodium iodide in acetone) gave the required iodoalcohol (**32**) in 77% yield.

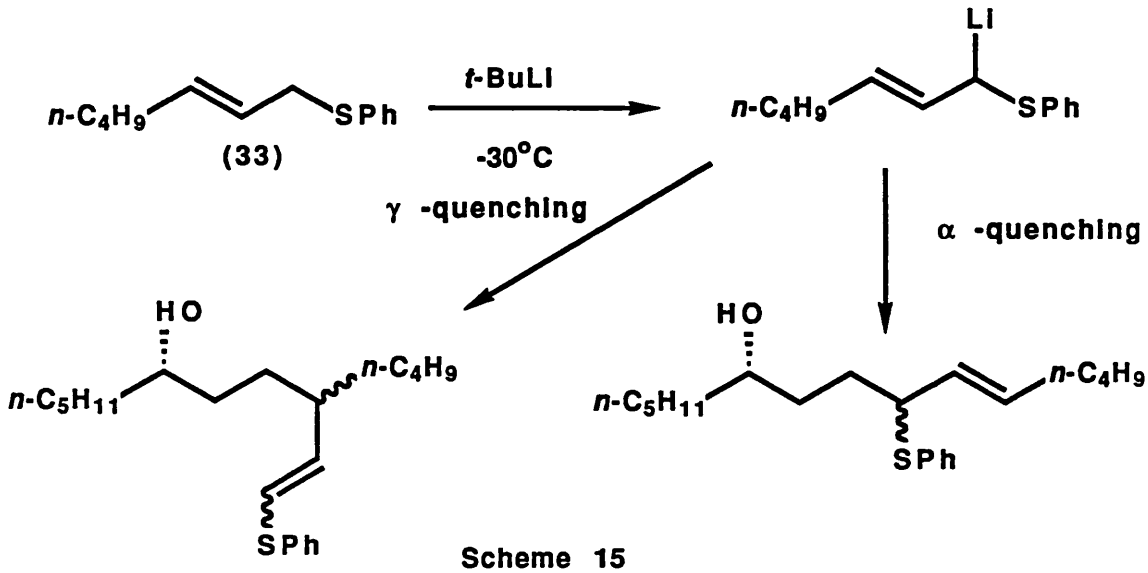
The right hand fragment was prepared by a simple transformation of a hydroxy to thio functionality using diphenyl disulphide and tri-*n*-butylphosphine (eqn. 12).[35]



eqn. 12

However, the product proved to be difficult to separate either by chromatography or distillation from diphenyldisulphide and thiophenol. Eventually, enough pure material (10% yield) for further studies was prepared by careful distillation.

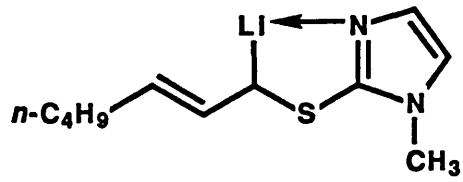
With some of the sulphide in hand, the key coupling reaction was attempted (Scheme 15). The sulphide was deprotonated with *t*-butyllithium in THF at -30°C to give an orange anion. The iodoalcohol (**32**) was slowly added to two equivalents of this anion. On consumption of the iodide, the mixture was worked up to give two fractions after chromatography. NMR analysis showed that they were predominantly the two diastereoisomers of the *trans*-thioenol ether produced by γ-quenching of the anion, accompanied by some of the *cis*-isomers.



Scheme 15

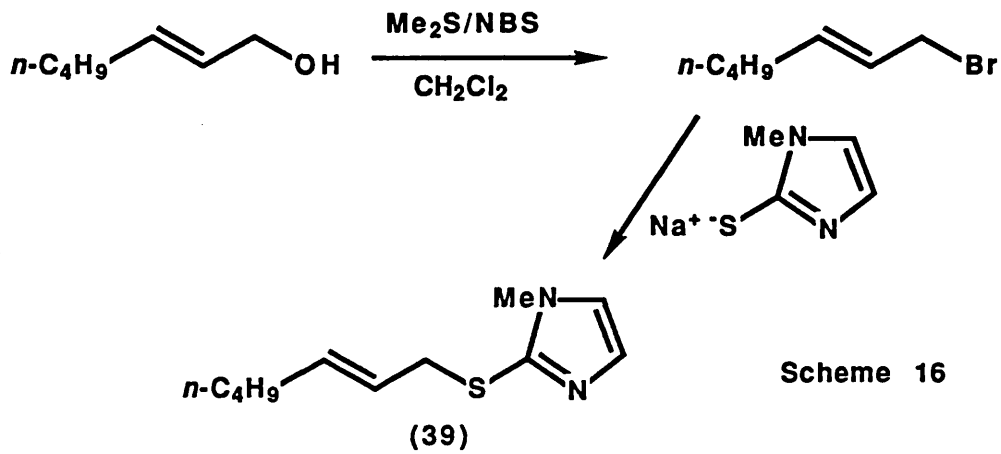
The *trans*-isomers showed characteristic fine structure: the proton α to sulphur appeared as a double doublet, having a coupling constant of 15 Hz to its vicinal partner and an allylic coupling of 1 Hz. The proton β to sulphur was also a double doublet: 15 Hz to the α-proton and 7 Hz to the γ-proton. The α-proton of one of the *cis*-diastereoisomers was well resolved and showed a 9 Hz coupling constant. γ-Quenching has generally been observed in such reactions, but α- usually predominates by about 3:1. We attributed our (undesirable) selectivity to repulsion of the carbanionic centre by the alkoxide oxygen.

A method of encouraging α-alkylation is the use of a nitrogen heterocycle, such as N-methylimidazole, in the place of the phenyl group.[36] For these compounds the ratio of α- to γ-quenching is reported to be 99:1 under normal circumstances. Chelation of the lithium by nitrogen (**38**) may be partly responsible for this effect but, as α-quenching is also enhanced in the case of 4-pyridyl compounds (though the effect is not as marked), other factors, such as electronegativity, are important.



(38)

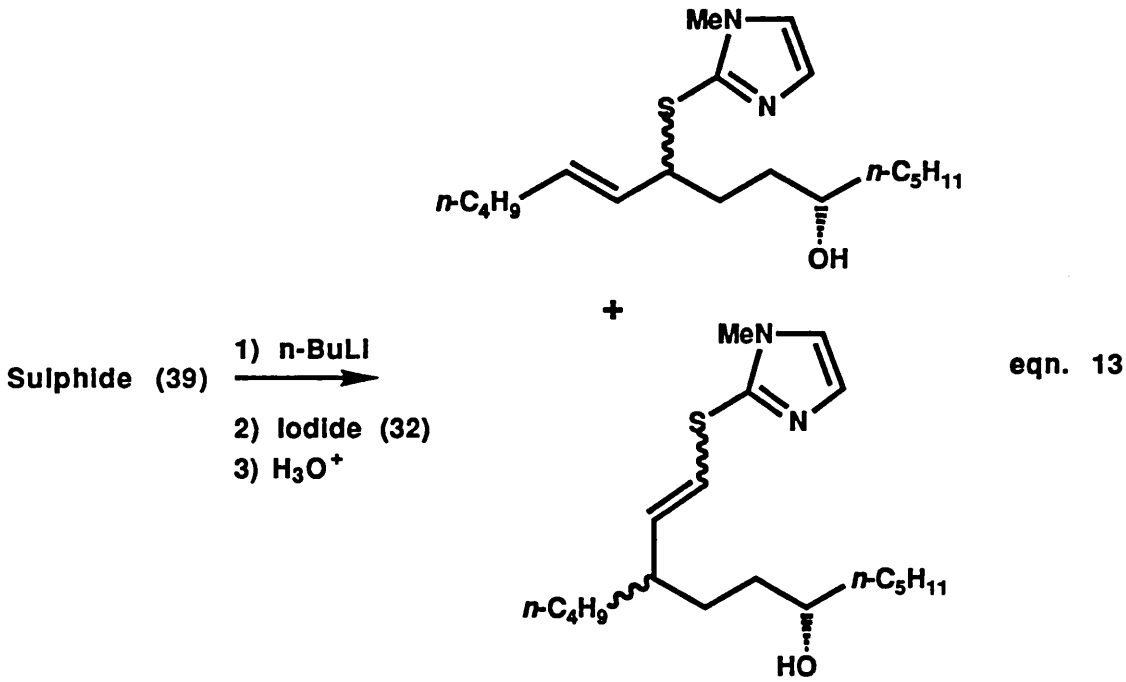
Preparation of the required sulphide was straightforward (Scheme 16). Application of the Corey-Kim-Takeda reaction to *trans*-2-heptenol gave the volatile bromide.[37] Addition of this to the sodium salt of 2-mercapto-1-methylimidazole (generated using sodium hydride as the base) in THF gave the sulphide (**39**) in good yield (76%). No S_N' product was observed.



(39)

Scheme 16

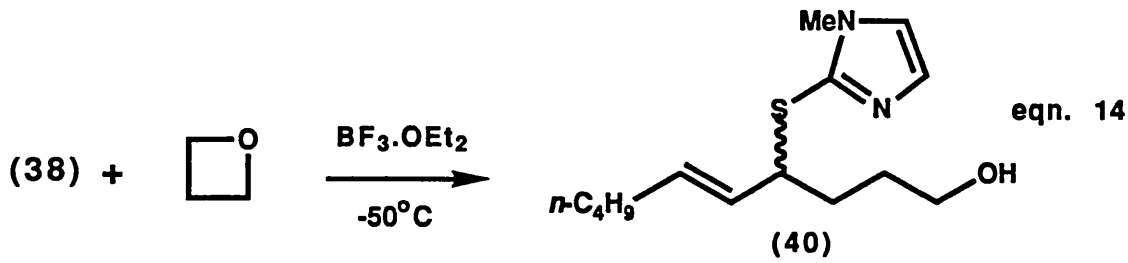
An incidental advantage of using the imidazole group proved to be the increased ease of deprotonation of the sulphide due to nitrogen-lithium coordination prior to deprotonation. Hence, treatment with *n*-butyllithium (rather than *t*-butyllithium) smoothly gave the anion. Quenching as before gave a complex and inseparable mixture of isomers in 82% yield (eqn. 13). NMR analysis indicated that α-quenching predominated over γ-quenching.



eqn. 13

The protons assigned to the α-quenched products appeared as a multiplet between 5.2 and 5.8 ppm. Between 5.9 and 6.5 ppm, peaks due to the vinylic protons of the γ-quenched products were observed: 9 Hz doublets at 6.41 and 6.25 ppm (*cis*-isomers) and 15 Hz doublets at 6.11 and 6.03 ppm (*trans* isomers). Integration of the spectrum indicated an encouraging ratio of about 3:1, α-quenching to γ-quenching. Attempts to oxidise the mixture to give sulphoxides were unsuccessful. Sodium periodate was ineffective, giving little or no reaction; *m*-cpba and OXONE® gave complex mixtures. Heating of these mixtures in toluene in the presence of triethylamine gave nothing identifiable as the desired dienol. This sulphide approach was therefore abandoned.

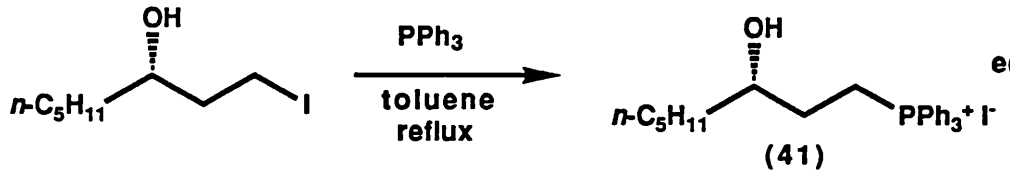
A second idea that was pursued in order to improve the α/γ-quenching ratio was to obviate the oxygen deprotonation, thereby making the atom less negative. Rather than incorporate a protection/ deprotection sequence, the use of oxetanes was briefly investigated. Treatment of trimethyleneoxide with the anion (**38**) at -50°C in the presence of boron trifluoride etherate gave the α-alkylated product (**40**) only, albeit in low yield (36%, 43% after recovered starting material) (eqn. 14).



eqn. 14

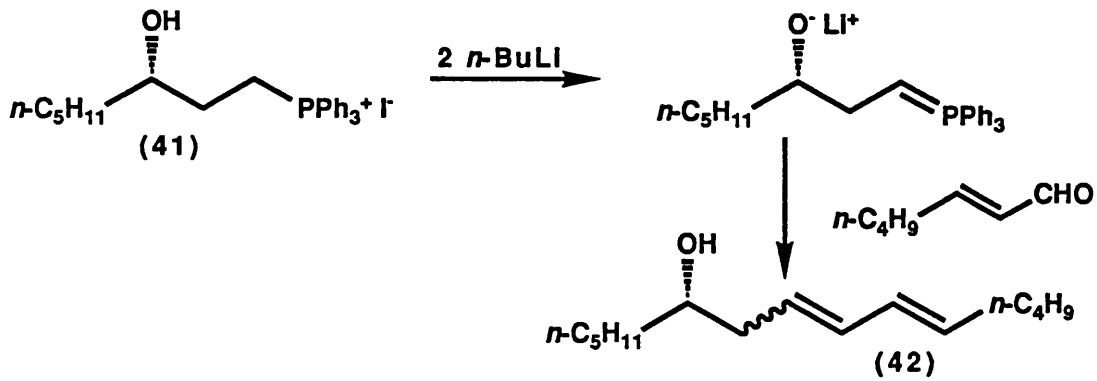
In the light of the oxidation reactions, however, this was not pursued further.The reaction serves to support the theory that the α/γ selectivity was due to the presence of an alkoxide group in proximity to the electrophilic centre.

Discouraged by these results, we chose to invert the electronics of the system and prepare a left hand side anion to quench with a right hand side electrophile. Treatment of the iodide (**32**) with triphenylphosphine in boiling toluene gave the hygroscopic phosphonium salt (**41**) (eqn. 15).



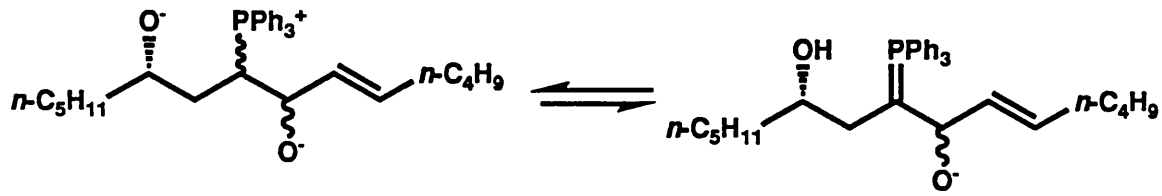
eqn. 15

Formation of the deep red ylid with *n*-butyllithium in THF in the presence of lithium bromide and Wittig reaction of this with *trans*-2-heptenal gave the required dienol (**42**) but in poor yield (14%) (Scheme 17). The isomeric ratio was, however, favourable: *E,E* predominated over *E,Z* by 6:1. The two isomers were easily identifiable by NMR, but inseparable by chromatography.



Scheme 17

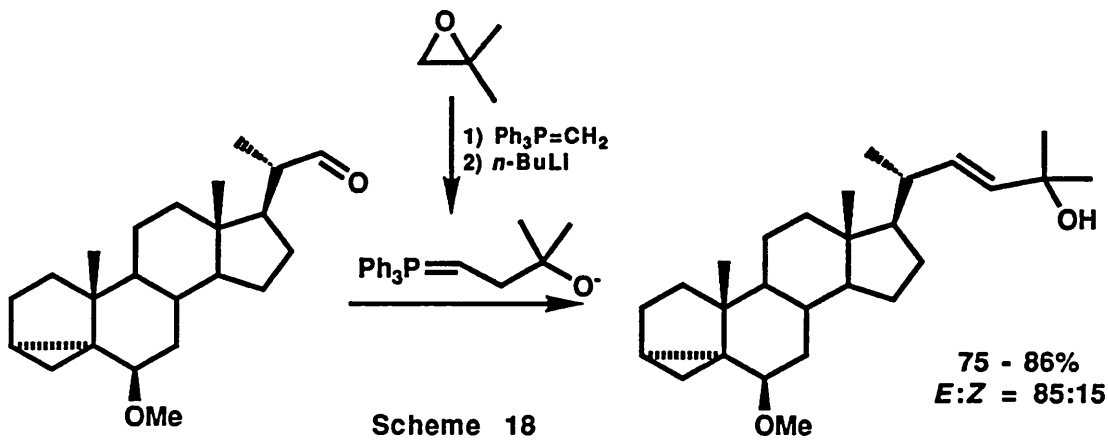
The high *EE/EZ* ratio in reactions of γ-hydroxyphosphonium salts has been noted before:[38,39] it is attributed to the presence of the alkoxide as addition of one equivalent of trimethylsilylchloride (forming *in situ* a silyl ether) before addition of the aldehyde gives a 1:1 ratio of isomers. It is probable that an intramolecular Schlosser-Wittig[40] reaction is occuring, allowing equilibration of the betaines (eqn. 16).



eqn. 16

It has also been attributed merely to the presence of a polar end group.[41] As this observation is limited to aromatic aldehydes under a particular set of solvent and base conditions, this cannot be a general explanation.

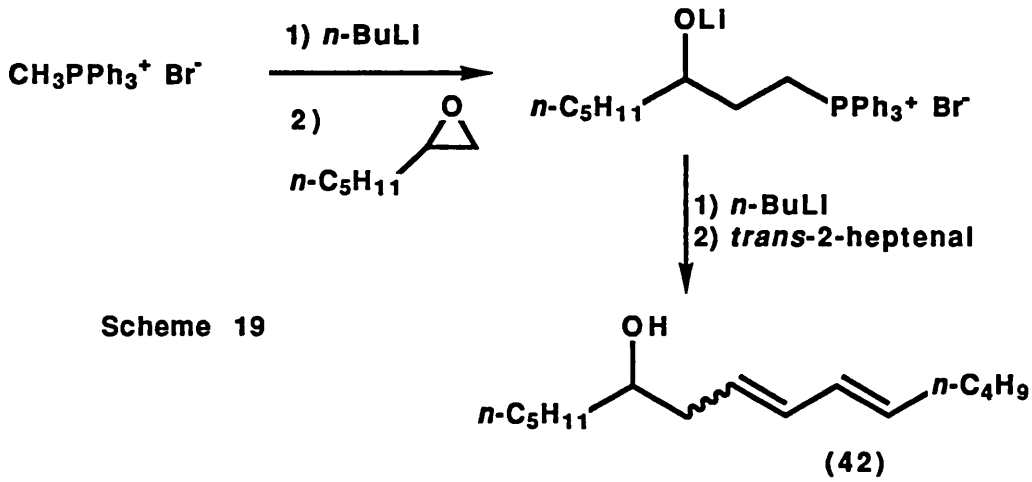
γ-Hydroxy-ylids are also available by an alternative route: opening of an epoxide by a simpler ylid followed by deprotonation with a further equivalent of *n*-butyl lithium.[38] This technique has been used in, for instance, side chain elaboration of steroids (Scheme 18).



Scheme 18

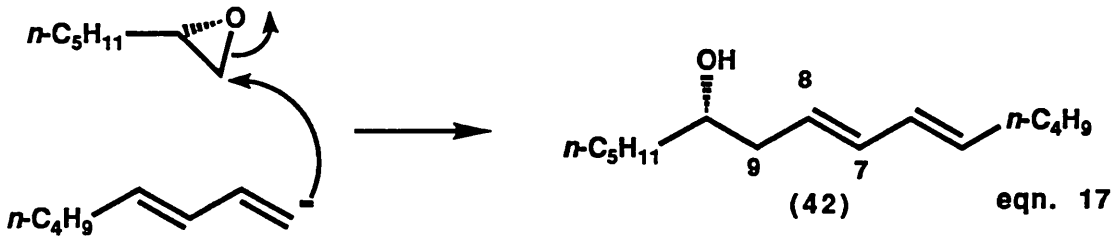
This route was explored here in case the low yield was due to a problem with the phosphonium salt (**41**). Methyltriphenylphosphonium bromide was deprotonated in the

usual way and treated with (racemic) hexene oxide (prepared by *m*-cpba oxidation of 1-hexene in buffered dichloromethane). When tlc showed that the epoxide had been consumed, a further equivalent of *n*-butyllithium was added, generating the deep red colour observed in the previous experiment, and the reaction was continued as before (Scheme 19). Unfortunately, no improvement was found.



Scheme 19

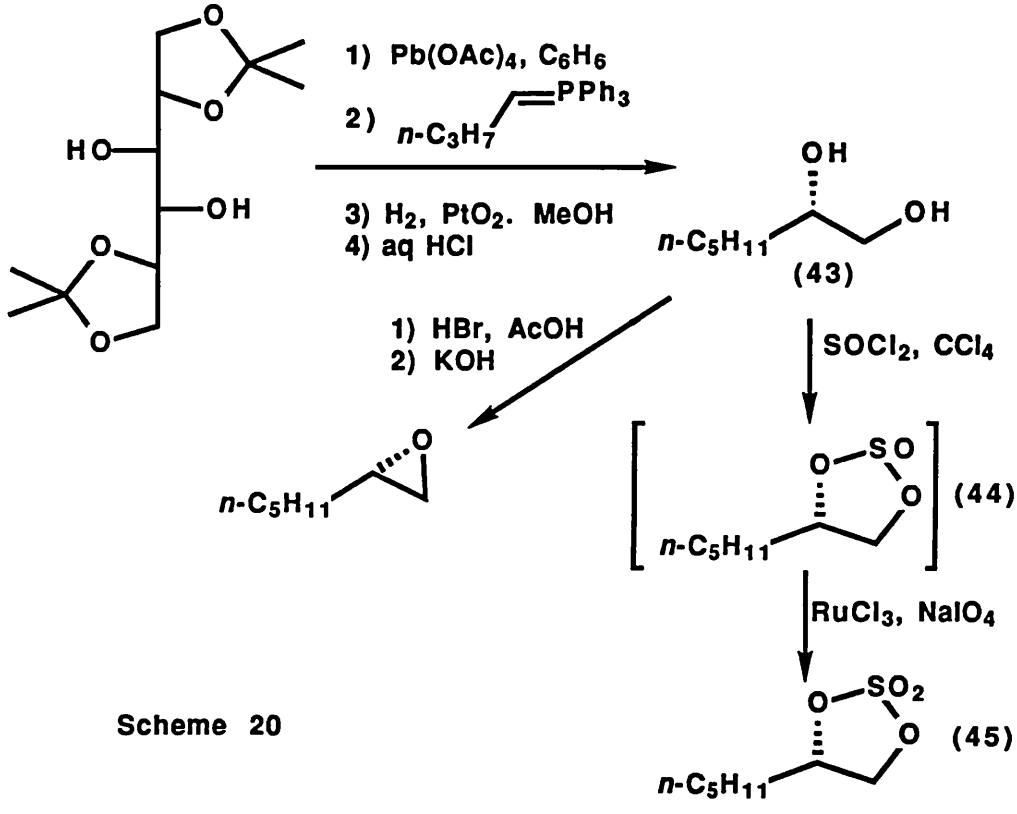
Despite the favourable *EE/EZ* ratio, an alternative strategy was sought, as the yields could not be increased to a satisfactory level. Thus far the approach was based on forming the 7-8 bond. An attractive alternative was to form the 8-9 bond by addition of a stereoselectively generated vinyl anion into an epoxide or epoxide equivalent (eqn. 17).



eqn. 17

The first requirement for such an approach is a route to (S)-1,2-epoxyheptane. Fortunately, this is a known compound. It was prepared by Mori in six steps from 1,2,5,6-di-*O*-isopropylidene-D-mannitol in his synthesis of the unnatural isomer of massoialactone.[42] His route (Scheme 20) proved easy to reproduce, albeit with minor

variations. Addition of lead tetraacetate to a suspension of the mannitol derivative (either commercial or prepared by Baer's method from mannitol and acetone[43]) in dry benzene gave, after distillation, the unstable acetonide of (R)-glyceraldehyde. This was reacted directly with butylidenetriphenylphosphorane in THF to give the alkene. The double bond of the resultant alkene was hydrogenated over a platinum catalyst in methanol. After removal of the catalyst by filtration, aqueous acid was added to the solution to yield the diol (43) in 21% yield over four steps.



Scheme 20

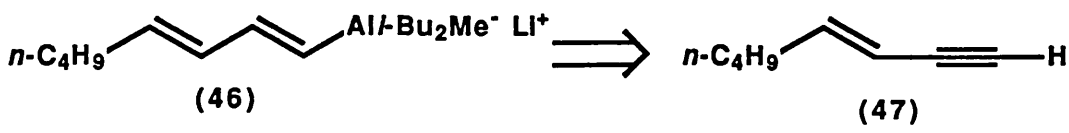
It has been shown that the diol (43) can be converted into the epoxide by treatment with hydrogen bromide in acetic acid (to give a mixture of bromo acetates) and potassium hydroxide to achieve cyclisation.[42] A more reactive version of an epoxide is a cyclic sulphate. This was easily prepared from the diol by the literature procedure.[44] The diol was first converted into its cyclic sulphite (44) by treatment with thionyl chloride in hot carbon tetrachloride. Dilution of the reaction mixture with

acetonitrile, cooling to 0°C and sequential addition of ruthenium trichloride trihydrate and sodium periodate cleanly gave the cyclic sulphate (**45**) in reasonable yield (69%). This excellent reaction, which should make cyclic sulphates a standard functional group for synthetic chemists, also has the virtue of being self-indicating. Addition of the ruthenium salt to the cyclic sulphite mixture gives a deep blue colour. This turns orange when the periodate is added. On completion the mixture is yellow.

Vinyl carbanions are potentially available by the standard method of metal-halogen exchange using vinyl halides. These compounds can be made by Wittig reactions, but this usually favours the *Z*-product. In the case of iodomethyltriphenylphosphorane the ratio of products is about *Z*:*E* = 10:1 under optimum conditions;[45] a potentially useful result for other purposes, but not useful here. A more direct and more stereoselective method for forming vinyl carbanions is hydrometallation. Hydroalumination of alkynes is a well known procedure and has been used in a number of syntheses.[46] The vinyl alanes react only with the more reactive electrophiles. Under most circumstances, they are treated with one equivalent of either butyllithium or methyllithium to form the more reactive tetracoordinate aluminium anions, known as "ate" complexes (eqn. 18).

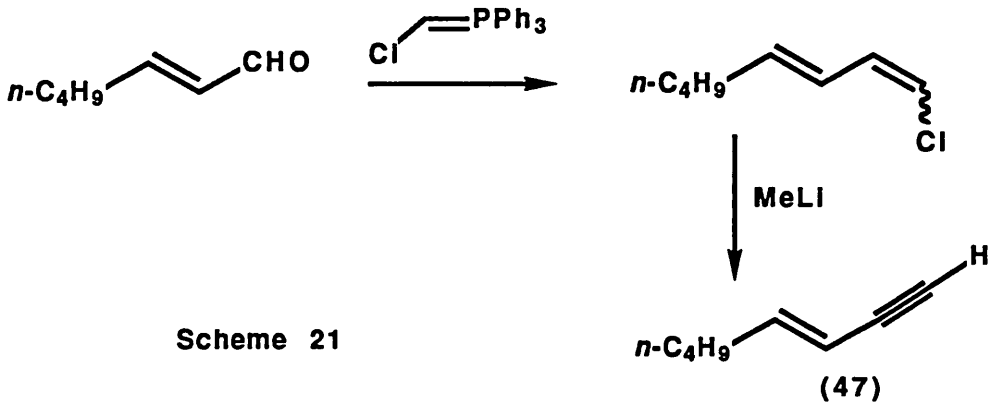
eqn. 18

These are known to react with epoxides.[46] The synthesis of valilactone would require the dienylaluminate complex (**46**) which would need to be prepared from the vinyl acetylene (**47**).



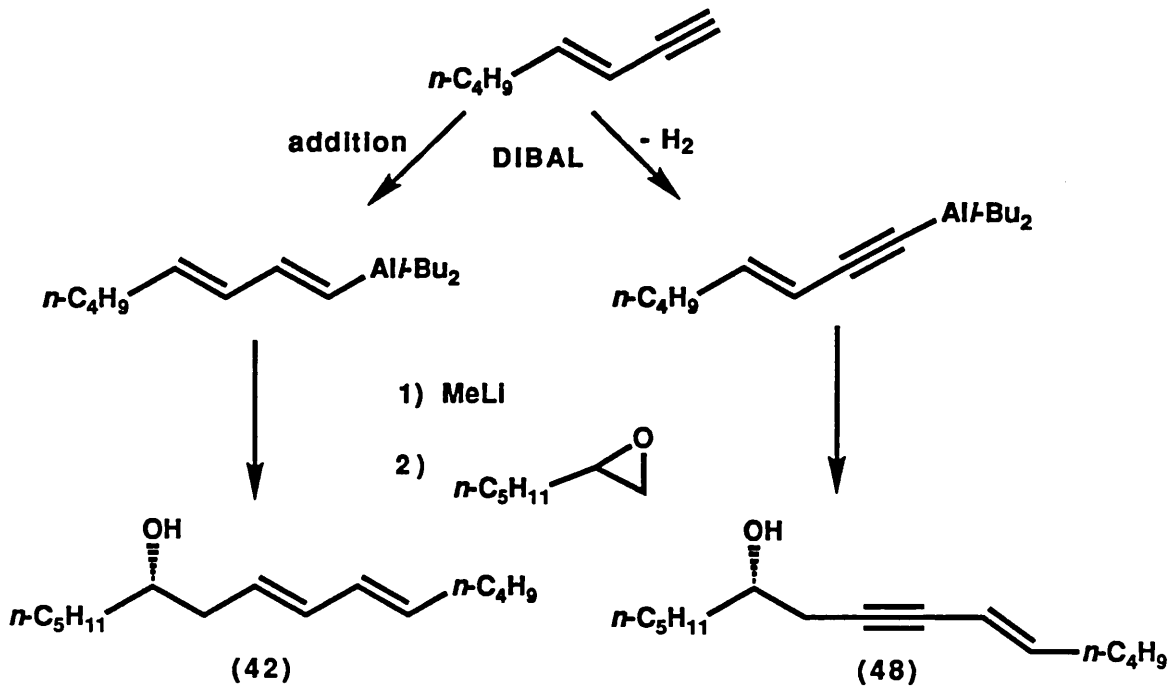
(**46**) (**47**)

Following Corey's method[47] for preparing *trans*-ene-ynes, *trans*-2-heptenal was treated with chloromethylenetriphenylphosphorane, generated by addition of *n*-butyllithium to the phosphonium salt at -78°C, to give the unstable chlorodiene as a mixture of *E,Z* and *E,E* isomers in a ratio of 6:5. Dehydrohalogenation with methyllithium in diethyl ether gave, after quenching with ammonium chloride, the volatile and evil smelling alkyne (**47**) in 58% yield from the aldehyde (Scheme 21).



Scheme 21

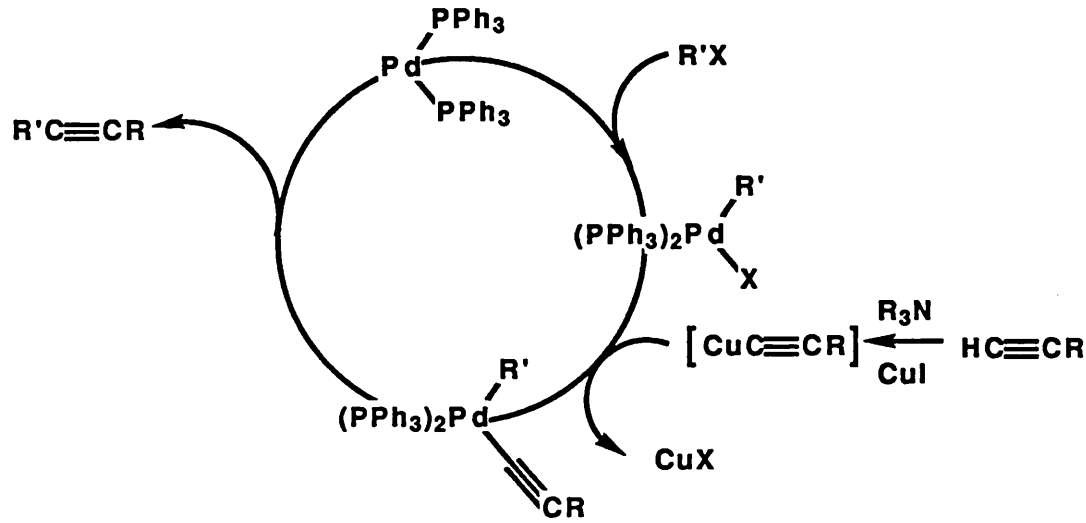
This material proved, however, to be unsuitable (Scheme 22). Hydroalumination with DIBAL in hexane followed by conversion to the "ate" complex with methyllithium and reaction with (racemic) 1,2-epoxyheptane oxide or with the cyclic sulphate (followed by acidic hydrolysis of the hemisulphate generated) gave only low yields of the required alcohol (**42**), albeit as a single geometrical isomer. It was contaminated with the alkyne (**48**). This arises by deprotonation of the ene-yne by DIBAL to give an akynyl alane. These are known to react well with epoxides.[48]



Scheme 22

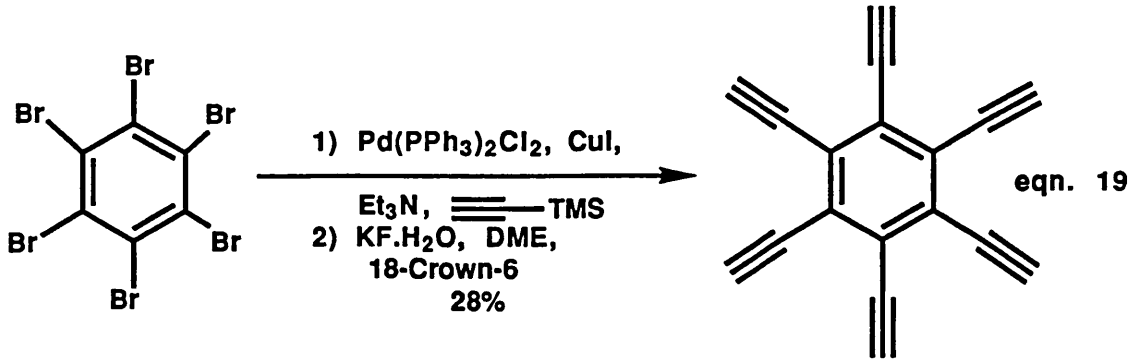
The apparent cause of this lack of selectivity is the double bond: it lowers the reactivity of the triple bond and raises the acidity of the alkynyl proton, allowing deprotonation to compete with addition.

Silylation of the alkyne prevents this side reaction.[49,50,51] It has the added advantage of improving both the stereo- and regioselectivity. Further, rather than silylate the ene-yne, an alternative preparation became practicable: the Castro-Stephans reaction. This reaction has become popular in the last few years as interest in ene-ynes has grown. It proceeds (Scheme 23) via a reductive elimination from a dialkyl palladium (II) species.[52] This is itself generated by oxidative addition of a vinyl or aryl derivative which may be bromide, chloride, iodide or triflate, to an unsaturated palladium species followed by reaction with an *in situ* generated alkynyl cuprate.



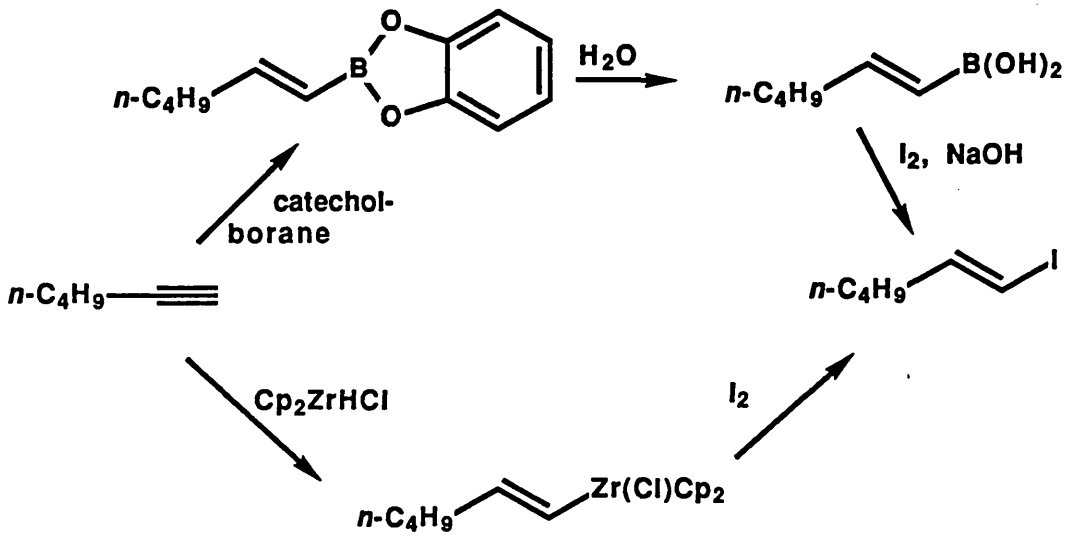
Scheme 23

The reaction is very general and tolerates a wide range of functionalities; it proceeds with retention of the geometry of the double bond of the halide. Acetylene itself can be used, but gives disubstituted alkynes.[52] Protection of one terminus with silicon and subsequent deprotection, however, is an efficient route to monosubstituted products. The Castro-Stephans reaction has recently been used by Corey[53] in his synthesis of Ginkgolide B, three times by Schreiber[54] and twice by Magnus[55] in approachs to esperamicin, by Nicolaou in syntheses of leukotriene B_4 [56] and arachidonic acid metabolites,[57] by Cacchi[58] in the preparation of 2-alkynylanilines as indole precursors and most spectacularly by Vollhardt[59] in his preparation of hexaethynylbenzene (eqn.19).



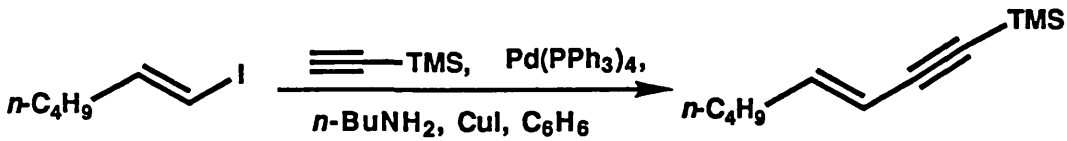
eqn. 19

trans-1-Iodohexene is available from 1-hexyne by either hydroboration with catecholborane, hydrolysis of the borate ester and iodination of the boronic acid in the presence of sodium hydroxide[60] or by hydrozirconation with zirconocene hydrochloride and iodination of the resulting vinylzirconium species[61] (Scheme 24).



Scheme 24

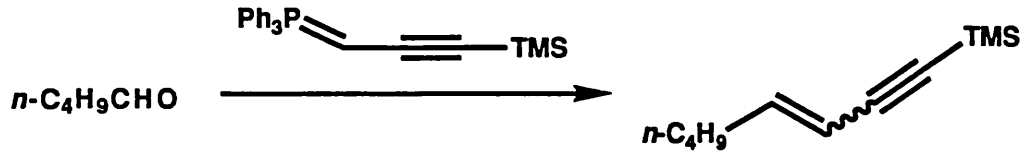
Hydroalumination-iodination is also possible but *iso*-butyl iodide, produced by competitive cleavage of aluminium-sp^3 carbon bonds is difficult to separate from the desired product. Coupling of the vinyl iodide with trimethylsilylacetylene in the presence of copper (I) iodide, tetrakis(triphenylphosphine)palladium (0) and *n*-butylamine gave the silylacetylene (**49**), 94% pure by GC[62] after distillation, in good yield (72%) (eqn. 20).



(49) **eqn. 20**

This procedure proved to be superior to the method of forming ene-ynes developed by Corey[47] in his (abortive) synthesis of (±)-histrionicotoxin. Treatment of pentanal with the ylid derived from (3-trimethylsilyl-2-propynyl)triphenylphosphonium

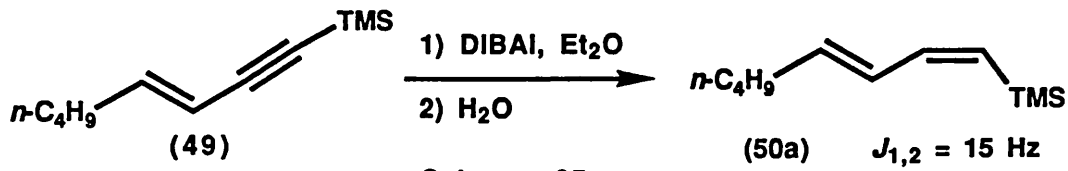
bromide did give the desired silyl acetylene (**49**) (eqn. 21), but in only 56% yield and with an isomeric ratio of 17:3 by NMR.



eqn. 21

(49)

Hydroalumination of these compounds with DIBAl has been carefully studied.[49,50,51] The silicon has been found to confer configurational lability on the 1-2 double bond of the vinyl alane. This can be suppressed by the addition of a coordinating ligand to fill the vacant site of the aluminium. Eisch employed N-methylpyrrolidine (one equivalent relative to aluminium).[49] In our hands, however, the reaction proved to be capricious and highly dependent on the amount of amine added: too much caused inhibition of the reaction, too little allowed isomerisation to occur. Zweifel studied these reactions with diethyl ether as the coordinating ligand.[51] As this is a much weaker donor than the amine, he was able to use it as solvent without slowing the reaction. Reaction of the silyl acetylene (**49**) under his conditions (Scheme 25), followed by quenching with water, gave the *Z,E*-silyldiene (**50a**) accompanied by a small amount of starting material (11%) and a smaller amount (<3%) of the *E,E* compound (**50b**) as determined by gas chromatography[62]. The structures were confirmed by NMR: in the *Z,E* compound the 1-proton appeared as a 15 Hz doublet at 5.48 ppm.



(49) (50a) $J_{1,2}$ = 15 Hz

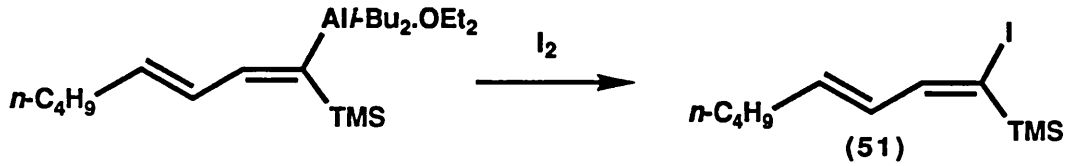
Scheme 25

Initially, the coupling constant was thought to indicate that the *E,E* isomer (**50b**) had been formed. Coupling constants in alkenes, though, are strongly dependent on the

electronegativity of the substituents. Electropositive substituents cause increases, for instance J_{cis} = 19 Hz in lithioalkenes. Electronegative substituents cause reductions: J_{cis} = 5 Hz in fluoroalkenes. 15 Hz, therefore, for a *cis*-silylalkene seemed reasonable. This was checked by measuring the coupling constant in the corresponding *E,E* isomer (**50b**) prepared by hydroalumination in hexanes: J_{trans} = 18 Hz.

(50) $J_{1,2}$ = 18 Hz

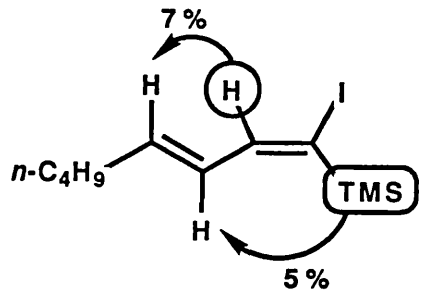
A disadvantage due to the inclusion of the trimethylsilyl group became apparent at this stage. This was the reduced reactivity of the "ate" complex caused by both steric hindrance and stabilisation of the anion. It has been reported that the "ate" complexes of 1-trialkylsilyl-1-diisobutylalanylalkenes only react with electrophiles such as methyl iodide and allyl bromide.[49,50] Indeed treatment of the "ate" complex of the alane with either the epoxide or the cyclic sulphate was ineffective. The alane did, however, react with iodine to give the *E*-iodosilane (**51**) (eqn. 21).

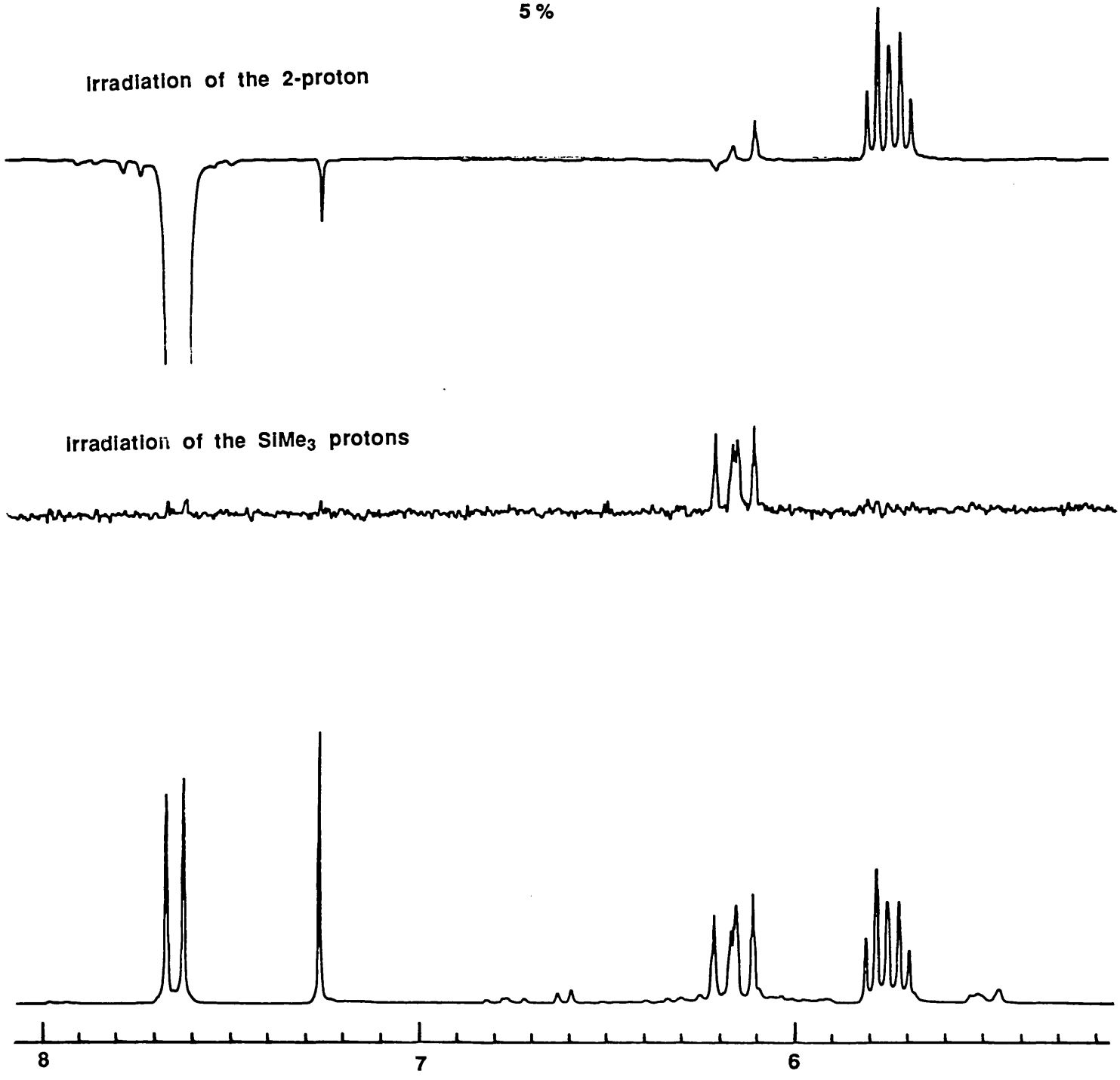


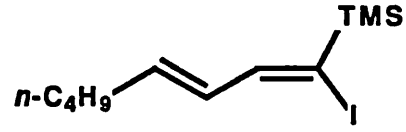
eqn. 21

The structure of this compound was confirmed by an nOe study (Fig. 10). Irradiation of the 2-proton, a highly characteristic low field doublet, led to a 7% enhancement of the signal of the 4-proton only; irradiation of the silylmethyl groups enhanced (5%) the signal of the 3-proton. This compound appeared to be promising as a precursor to a lithiosilane, cuprate or Grignard reagent. However the carbon-iodine bond proved to be very labile. On storage (-20°C) for even a short time, sufficient iodine was liberated to give complete conversion to the *Z*-iodosilane (**52**).

Fig. 10

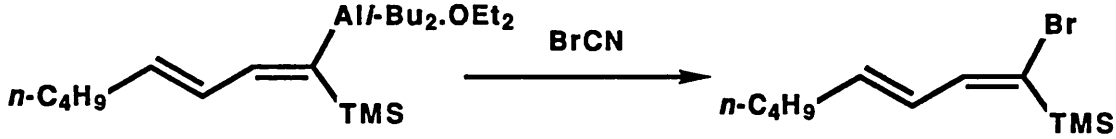

7 %
H
H
I
n-C4H9
TMS
H
5 %


Irradiation of the 2-proton
Irradiation of the SiMe3 protons
8
7
6



(52)

Facile rearrangment of 1-bromo-1-trimethylsilylalkenes has been noted.[51] Then, however, it was caused by excess bromine in the reaction mixture. Quenching of the alane with cyanogen bromide involves no free bromine and gave, in accordance with the literature,[51] the stable *E*-bromosilane (**53**), accompanied by small amounts (about 10%) of the *Z,E*-diene (eqn. 22).

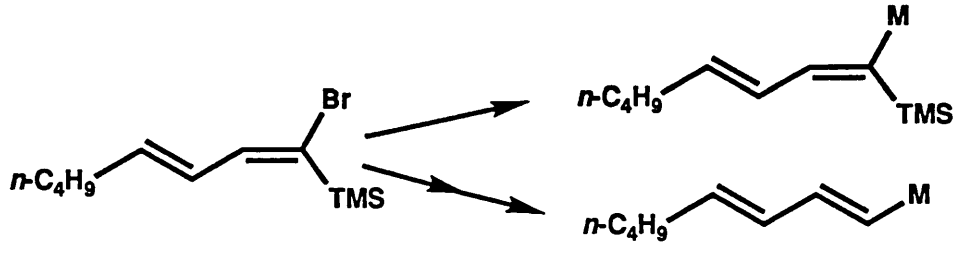


(53)

eqn. 22

The bromosilane was assigned the *E,E* geometry by comparison of the chemical shift of the 2-proton with that of the iodide. Protons *cis* to bromine are expected to be 0.36 ppm upfield compared to those *cis* to iodine.[63] This was exactly observed here.

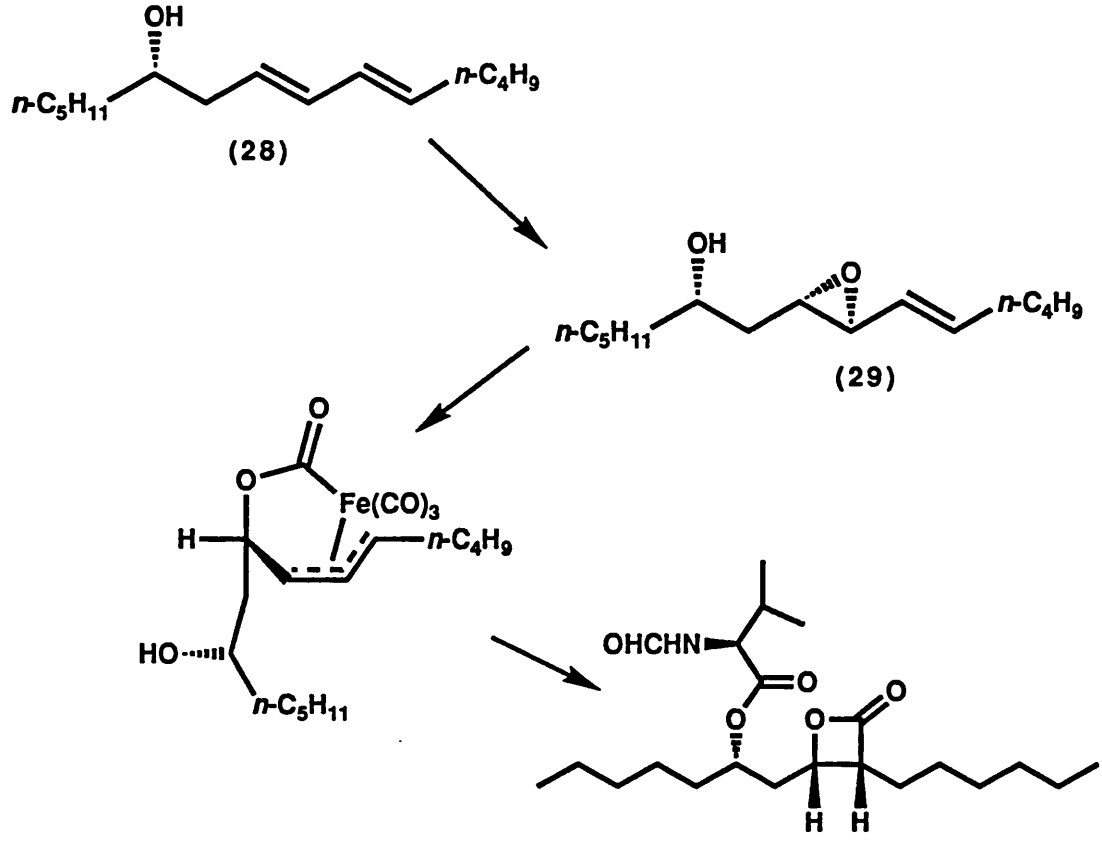
The bromo compound (**53**) is a potentially useful fragment for this strategy (Scheme 26), either by direct conversion to a lithium, copper or magnesium species or by initial protiodesilylation.[64] In the former case protiodesilylation of the homoallylic alcohol produced by reaction of the vinyl anion with an epoxide could be carried out under either normal acidic conditions or by treament with strong base leading to an internal carbon to oxygen migration by silicon.[65]



Scheme 26

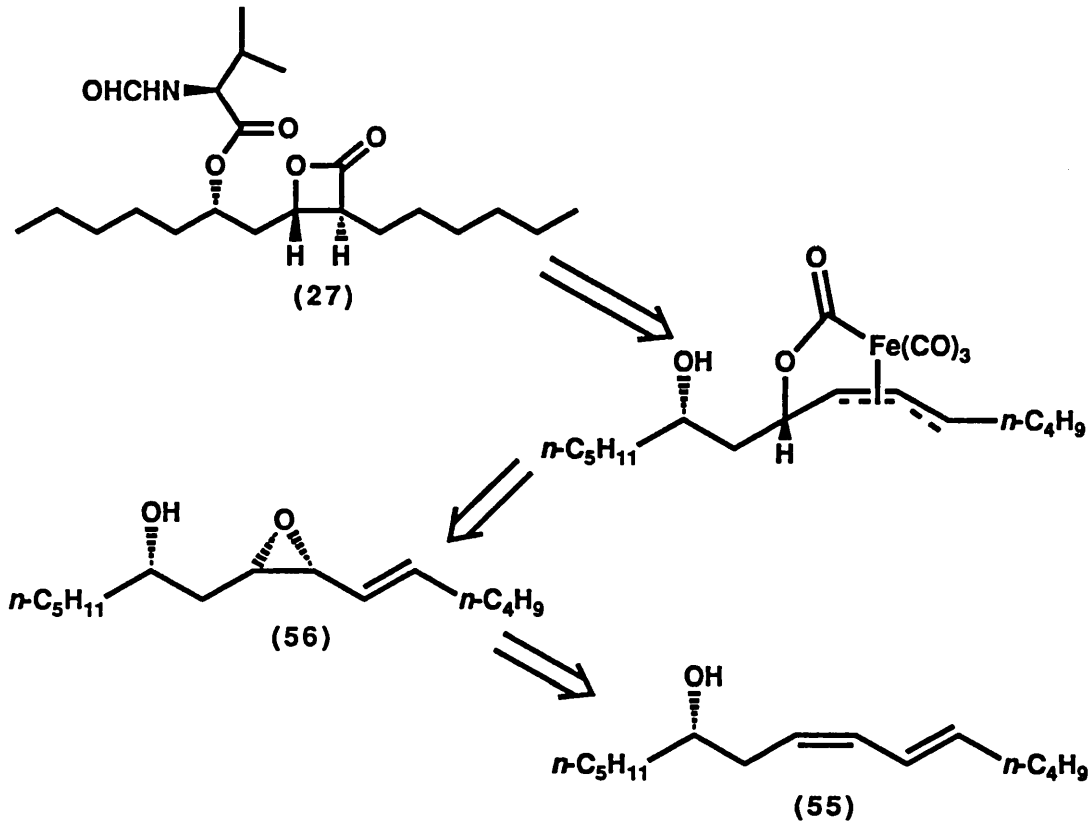
4.2. Reassessment

The observation, during the relay synthesis of 1233A (*vide infra*), that vinyl epoxides with a *trans* epoxide geometry yield predominantly *endo* ferrilactones immediately prompted a reassessment of the strategy for preparing valilactone. The initially intended epoxide would now, in the light of this knowledge, be expected to be a precursor to 4-*epi*-valilactone (**54**) (Scheme 27).



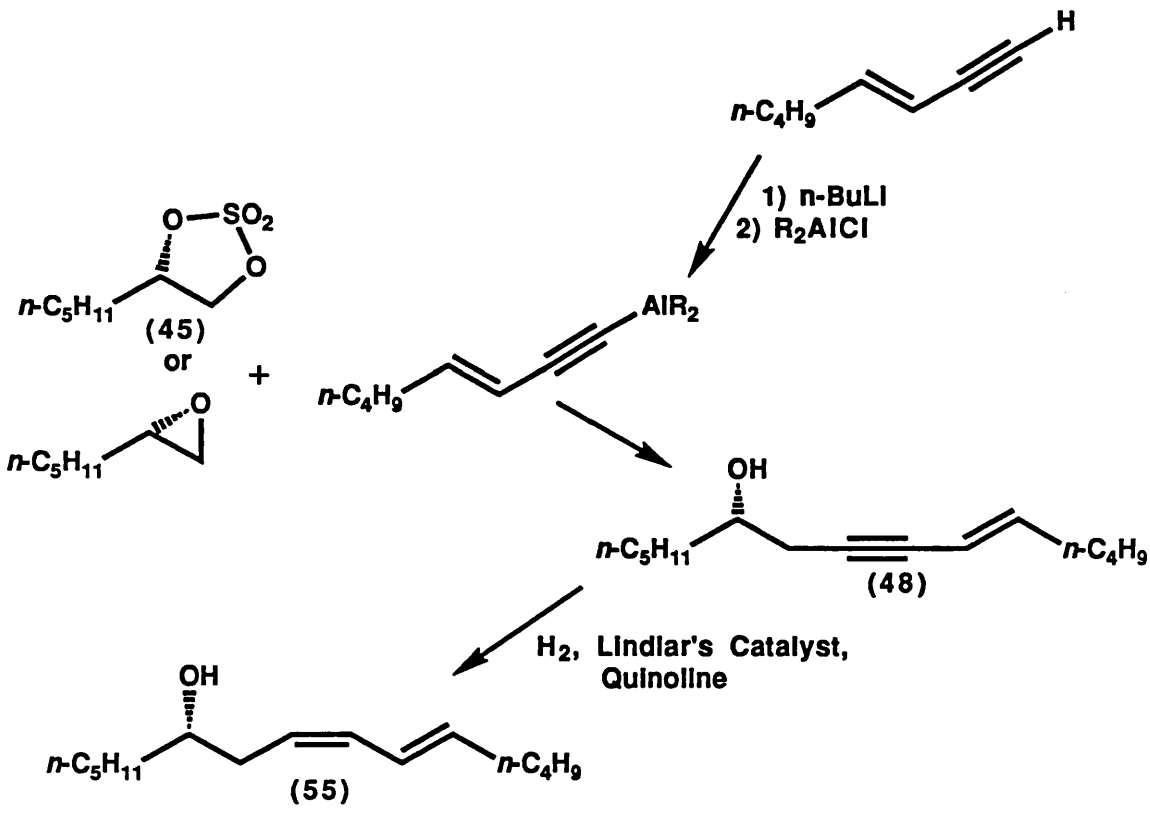
Scheme 27

The required epoxide is, therefore, that with *cis* geometry on the epoxide, leading to predominantly the *exo* ferrilactone and, hence, the *trans* β-lactone (**27**) (Scheme 28). The precursor for this epoxide would be the *E,Z* -dienol (**55**), obtained as a by-product in the Wittig reactions (Schemes 17 and 19).



Scheme 28

Synthesis of this epoxide should be practicable on the lines already laid down. For instance, reaction of (S)-1,2-epoxyheptane or the corresponding cyclic sulphate (**45**) with a dialkylaluminium acetylide derived from the ene-yne (**47**) would give the alkyne (**48**).[48] This reaction was indeed observed in the attempted formation and reaction of the vinyl aluminium "ate" complex derived from (**47**) with the epoxide or corresponding cyclic sulphate (**45**) (Scheme 22). Lindlar hydrogenation would then give the formerly undesired *E,Z*-diene (**55**) (Scheme 29). Epoxidation under Sharpless' conditions[31] with vanadium or molybdenum catalysis should then give the required vinyl epoxide (**56**). The diastereoisomeric ratio in this reaction is likely to be about 12:1 - somewhat better than in the case of the *E,E* diene.[32]

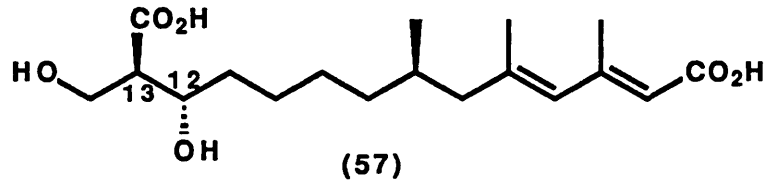

H
n-C4H9
1) n-BuLi
2) R2AlCl
O
SO2
O
n-C5H11
(45)
or
+
O
n-C5H11
AlR2
n-C4H9
OH
n-C5H11
n-C4H9
(48)
H2, Lindlar's Catalyst,
Quinoline
OH
n-C5H11
n-C4H9
(55)

Scheme 29

Chapter 5. Studies on 1233A

1. The structure of 1233B

Superficially, 1233B (**57**), the ring opened, C-12 epimer of 1233A, produced by an unidentified ICI fungus,[66] appeared to have been relatively stable on storage for nearly twenty years.



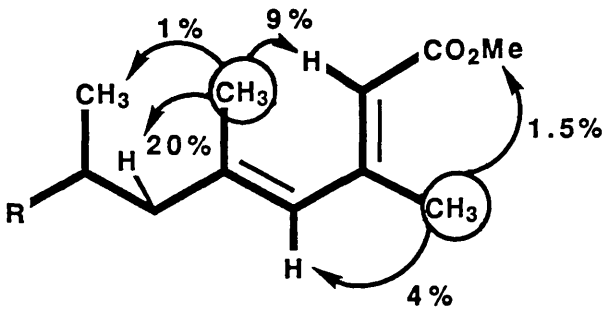
(57)

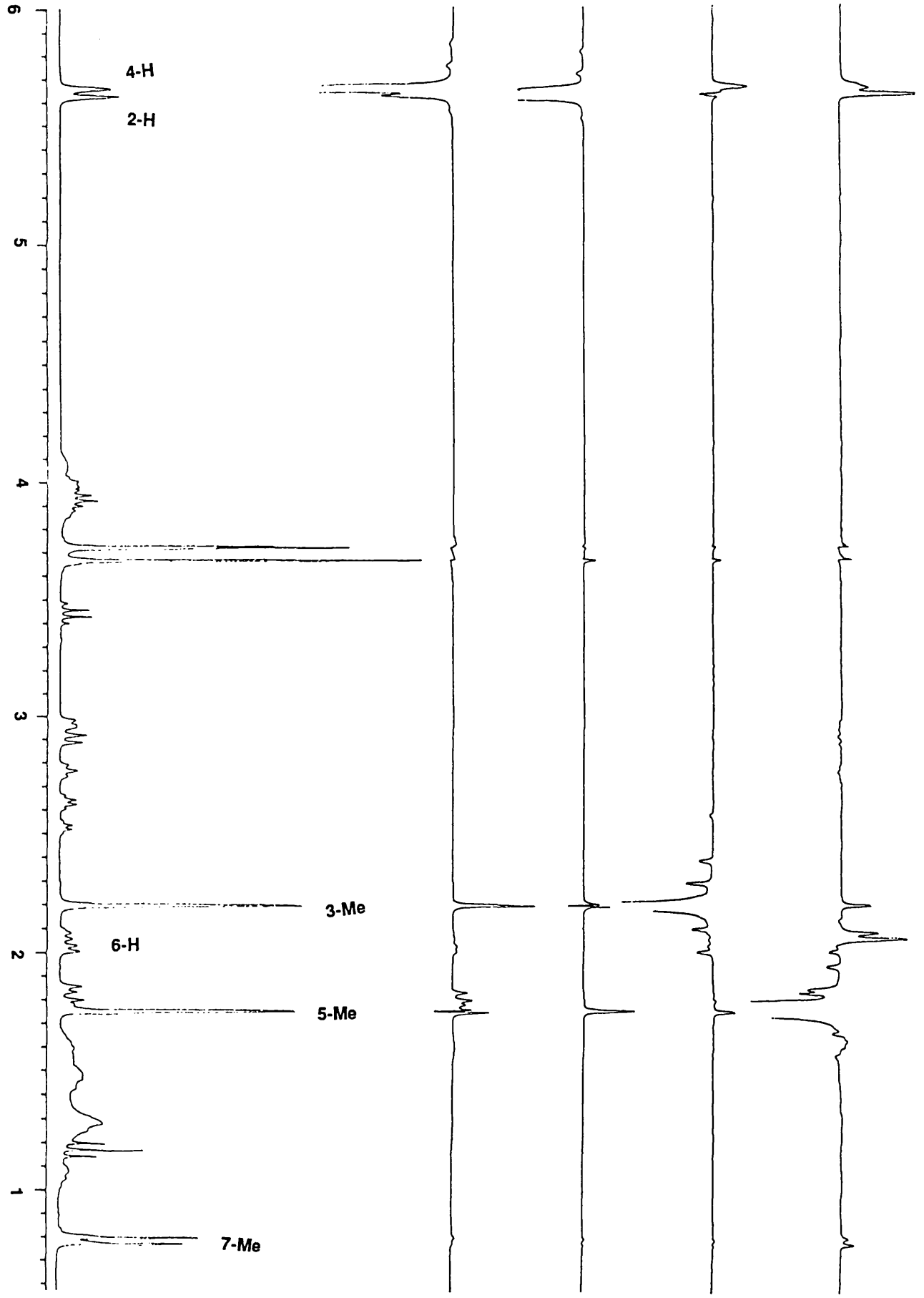
One chiral centre had, however, racemised to a large extent, presumably C-13, α to a carboxylic acid. This became clear when 1233B was converted to its dimethyl esters (**60** and **61**) by treatment with ethereal diazomethane. The NMR spectrum of the product showed doubling of a number of peaks. The doubled peaks were only those associated with the C-12 to C-14 portion of the molecule. The signals of the dienoic system were sharp. This enabled an nOe experiment (Fig. 11) to be undertaken in order to define the previously assumed *E,E* geometry of this system.

Firstly the dienoic system was fully assigned. The signals at 1.75 and 2.2 ppm were assigned (by chemical shift considerations) to the 5- and 3-methyls respectively. Sequential decoupling of these showed that the signals at 5.65 and 5.68 ppm were due to the 4- and 2-protons respectively.

Irradiation of the 5-methyl group led to a small (1%) enhancement of the signal of the 7-methyl and a large (20%) enhancement of the signal of one of the allylic protons. This served to confirm its assignment. More importantly there was a 9% enhancement of the signal of the 2-proton and a small (1%) enhancement of the signal of the other diene methyl group. Irradiation of the 3-methyl group led to a small (1.5%)

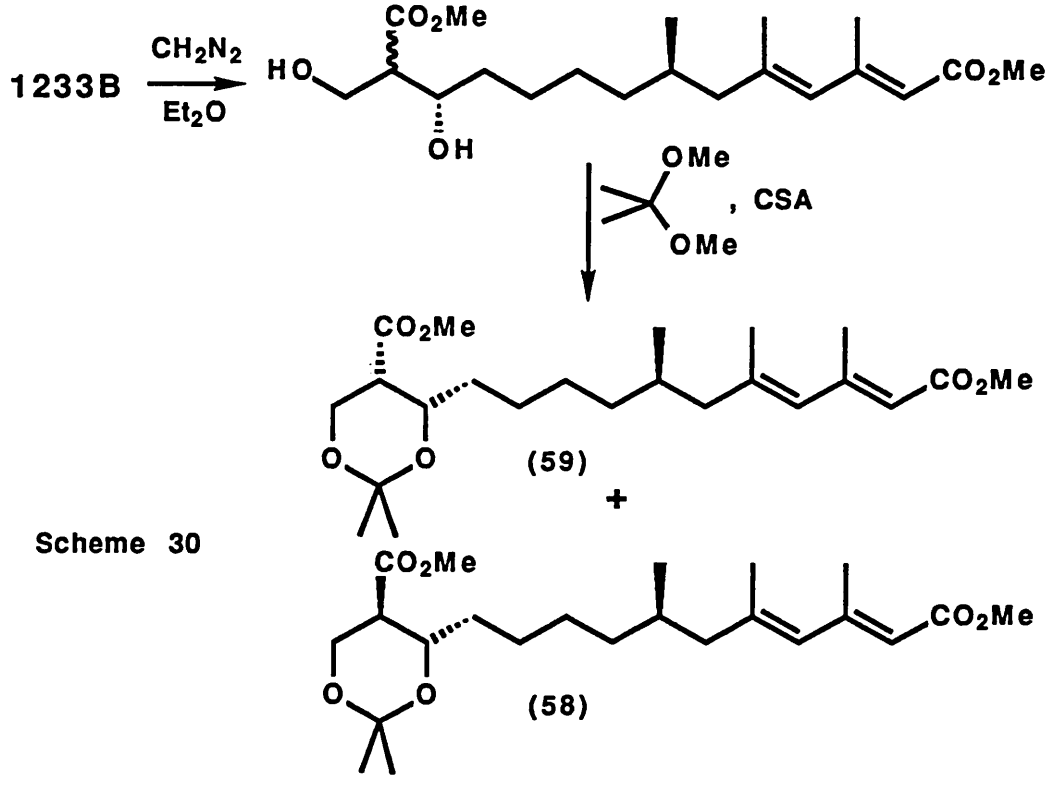
Fig. 11





enhancement of the signal of the ester methyl (also serving to confirm its assignment) and a 4% enhancement of the signal of the 4-proton. These results, where each methyl has an nOe interaction with the dienyl proton to which it is not coupled, are consistent with an *E,E*-diene in a distorted *cisoid* conformation. Irradiation of the diene protons gave results which were consistent with this structure, although the closeness of the two signals made the interpretation less clear-cut.

The problem of separating and identifying the two diastereoisomers in the elderly sample of 1233B was solved by converting the mixture of dimethyl esters into their acetonides by a ketal exchange reaction (Scheme 30). These were easily separated by flash chromatography (R_f = 0.72 and 0.65 (ether/silica gel); 0.54 and 0.36 (1:1ether/petrol/silica gel)). This process was rendered more efficient by performing the esterification and ketalisation reactions in one pot. From this the two dimethyl ester acetonides were isolated in 33% and 41% yields.

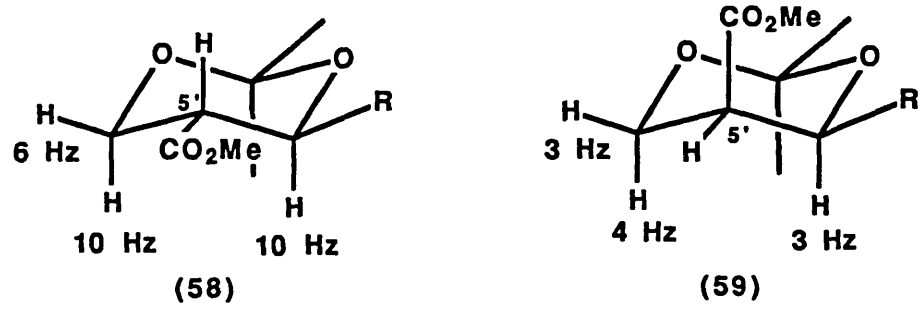


Scheme 30

Careful NMR analysis of the signals of the protons around the six membered rings indicated the relative geometries of the two, a technique also used in Umezawa's determination of the structure of esterastin.[67]

In the less polar compound the signals of the 4'- and 6'-protons were not resolved at 270 MHz. The required coupling constants were found from the signal of the 5'-proton, α to the ester group. This signal appeared as a double double doublet at 2.58 ppm. The values of the coupling constants were observed to be 10, 10 and 6 Hz. Constants as large as 10 Hz in a cyclohexane system can only be due to interactions between axial protons, hence the 5'-proton and two protons vicinal to it must all be axial. For this to be so, the two substituents must both be in equatorial positions. This compound was therefore assigned the structure (**58**).

In the more polar isomer the signals of all the ring protons were resolved. In addition to a large geminal coupling constant (12 Hz) between the 4'-protons and normal coupling constants (8 and 5 Hz) between the 6'- and 11-protons, the coupling constants between the 5'-proton and its neighbours were measured. These were either 3 or 4 Hz, consistent with the 5'-proton being equatorial. This compound was assigned the structure (**59**).

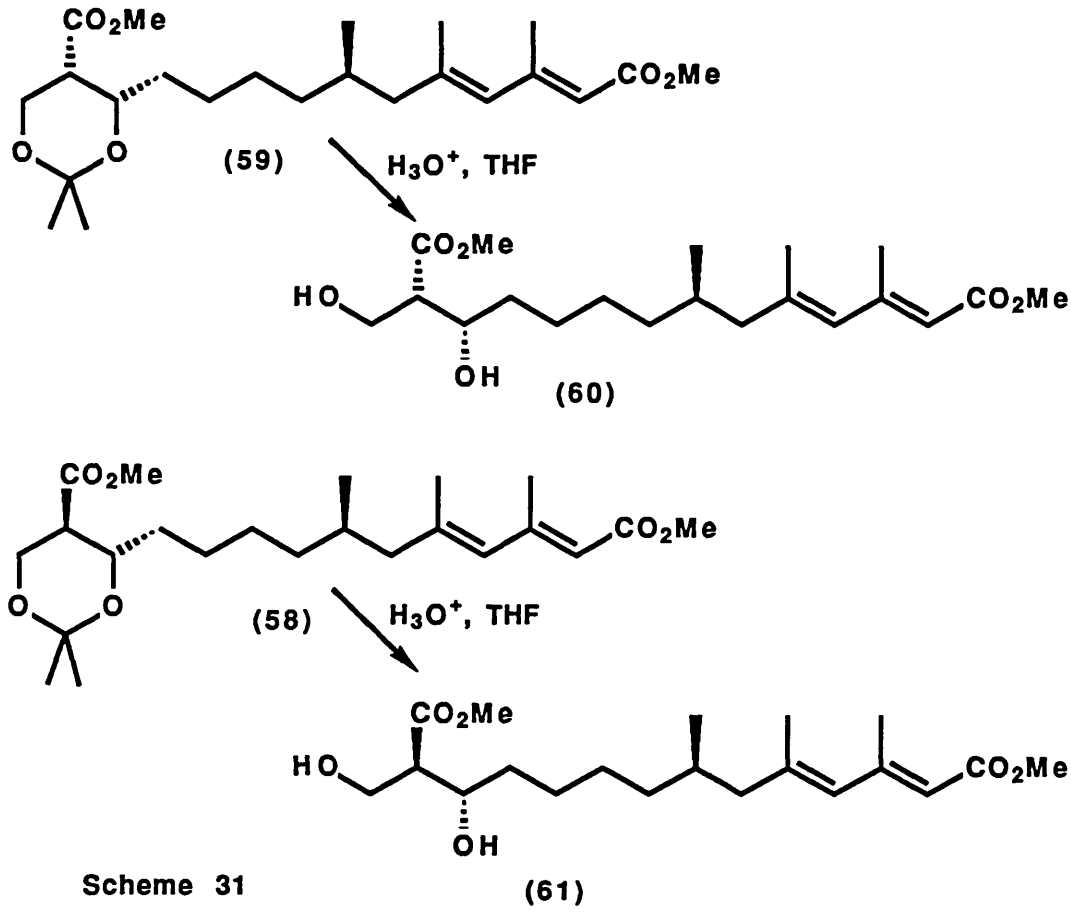


(58) (59)

The Coupling Constants of 5'-H

Hydrolysis of the acetonides with hydrochloric acid in aqueous THF yielded the free diols, (**60**) and (**61**), in 88 and 90% yields respectively (Scheme 31). Pleasingly,

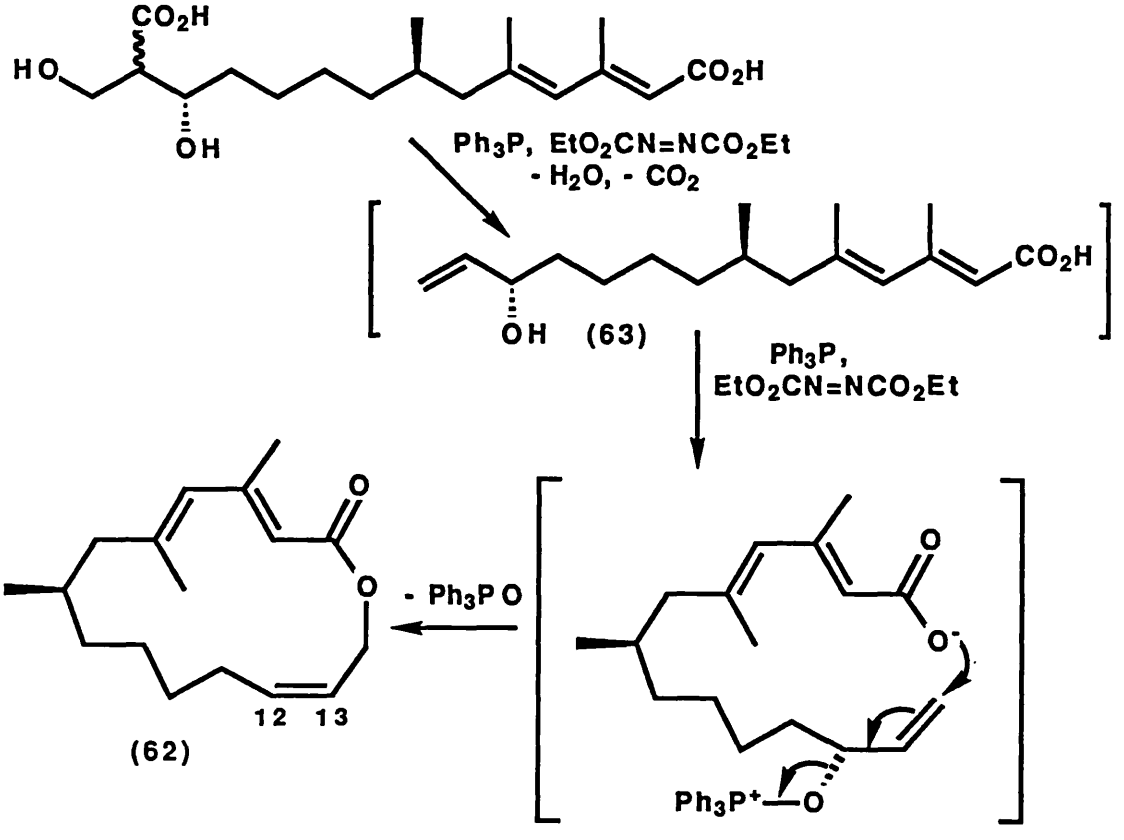
the rates of hydrolysis reflected the structures of the acetonides. The more stable, di-equatorial acetonide (**58**) took substantially longer (7 hours) than the axial-equatorial acetonide (**59**) (1.5 hours).



Scheme 31

1233B did not prove to be a useful starting material for the preparation of 1233A *via* ferrilactone chemistry. One interesting reaction, however, was discovered. Treatment of β-hydroxy carboxylic acids with diethylazodicarboxylate and triphenylphosphine is known to cause dehydroxy-decarboxylation.[68] When this reaction was applied to 1233B the only product isolated was the macrolide (**62**) in

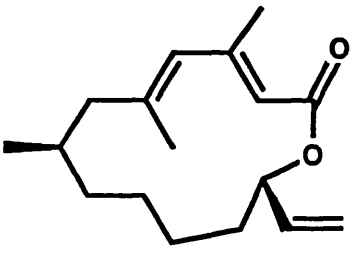
28% yield, produced by elimination of carbon dioxide and water, followed by cyclisation. Use of diethylazodicarboxylate and triphenylphosphine for macrolactonisation of ϖ-hydroxy carboxylic acids is well known.[69] The monomeric nature of the compound was shown by mass spectrometry which indicated a distinctive molecular ion of 262. The *Z* geometry of the newly formed carbon-carbon double bond was shown by the 5 Hz coupling constant between the 12- and 13- protons.



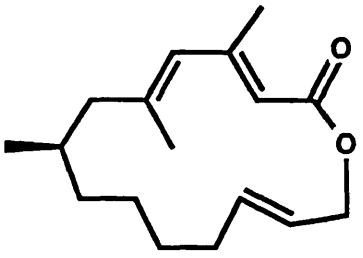
Scheme 32

The dehydroxydecarboxylation reactions are rapid (typically minutes).It is highly likely that, in this case, dehydroxydecarboxylation precedes cyclisation. Given the bulk of the triphenylphosphine-diethylazodicarboxylate adduct, it is also likely that it is the primary hydroxyl group that is activated to leave, leading to the terminal alkene (**63**). Cyclisation *via* an S_N' displacement of the remaining hydroxy group, activated by a second triphenylphosphine-diethylazodicarboxylate adduct, would then give the

observed product (Scheme 32). Two alternative pathways would both lead to more strained products with an unacceptable number of *E*-double bonds for their ring sizes: direct cyclisation of the terminal alkene intermediate without an S_N' rearrangement to give the ethenyl compound (**64**) or formation of a third E double bond on cyclisation to give the *E,E,E*-triene (**65**).



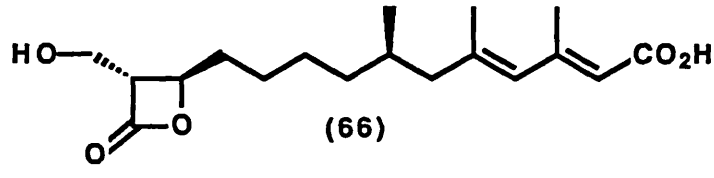
(64)



(65)

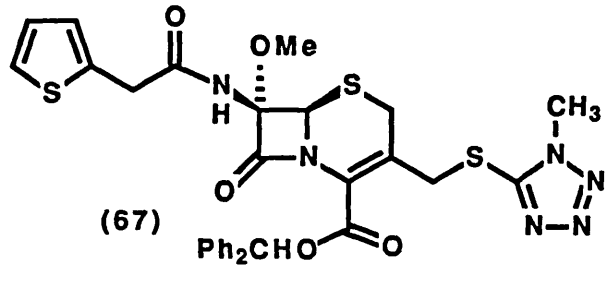
5.2. Relay Synthesis of 1233A

The biological activity and structural uncertainties of 1233A (**66**) necessitated further study. With a small supply of the natural product available, a relay synthesis *via* a ferrilactone intermediate was appropriate.



(66)

Given the difficulty of handling carboxylic acids (especially during silica gel chromatography) and the intrinsic incompatability of an acidic functionality with a vinyl epoxide, the first requirement was to find a suitable protecting group. The workers at Merck, Sharp and Dohme had used the *t*-butyl group which was removed under mild acidic conditions.[70] Another useful protecting group for carboxylic acids is the benzhydryl (diphenylmethyl) group. It was originally promoted by Zervas to protect peptides.[71] It was removed by catalytic hydrogenation, by mineral acid or by trifluoroacetic acid in the presence of phenol as a cation scavenger. Hydrogenation is not applicable in any synthesis of 1233A as there is the problem of competitive double bond hydrogenation. Similarly, Glaxo chemists found that catalytic hydrogenation was inappropriate during studies on Cephalosporins such as (**67**).[72]

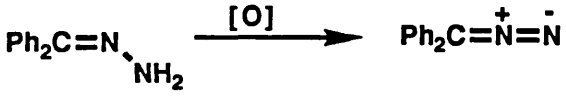


(67)

In this case the presence of sulphur as well as unsaturation in the substrate forbade the use of palladium catalysis. In contrast, the trifluoroacetic acid method, with anisole as

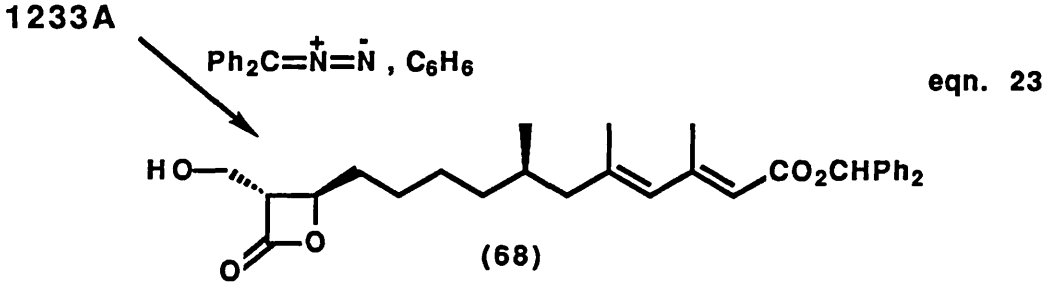
the cation scavenger instead of phenol, worked extremely well. We therefore chose to use this methodology in the β-lactone chemistry.

Benzhydryl esters can be prepared by treatment of the silver salt of the carboxylic acid with diphenylmethylchloride, but the yields tend to be low. A more convenient and efficient method was discovered by Hardegger: treatment of the carboxylic acid with diphenyldiazomethane.[73] This diazo compound, stabilised by two phenyl groups, can be easily prepared by oxidation of the commercially available benzophenone hydrazone (eqn. 22). The oxidant of choice is lead tetraacetate,[74] rather than the original mercuric oxide.[75] The crude reaction product, a deep purple oil or solid, was suitable for use in our experiments and could even be stored for some days.



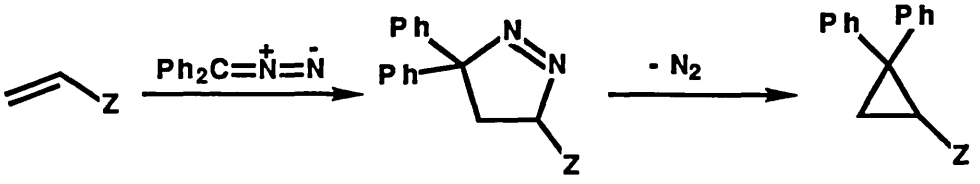
eqn. 22

Treatment of 1233A in hot benzene with a slight excess of diphenyldiazomethane cleanly gave the ester (68) in 86% yield (eqn. 23).



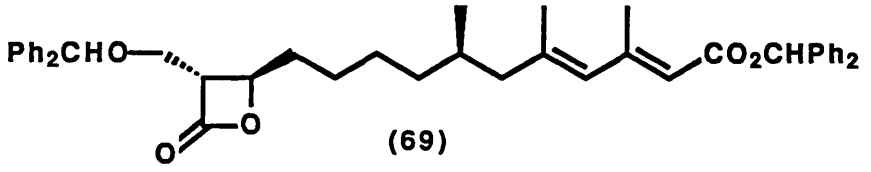
eqn. 23

Diazo compounds are known[76] to undergo [3+2] cycloaddition reactions with double bonds, especially electron poor double bonds, to give pyrazolines (Scheme 33).



Scheme 33

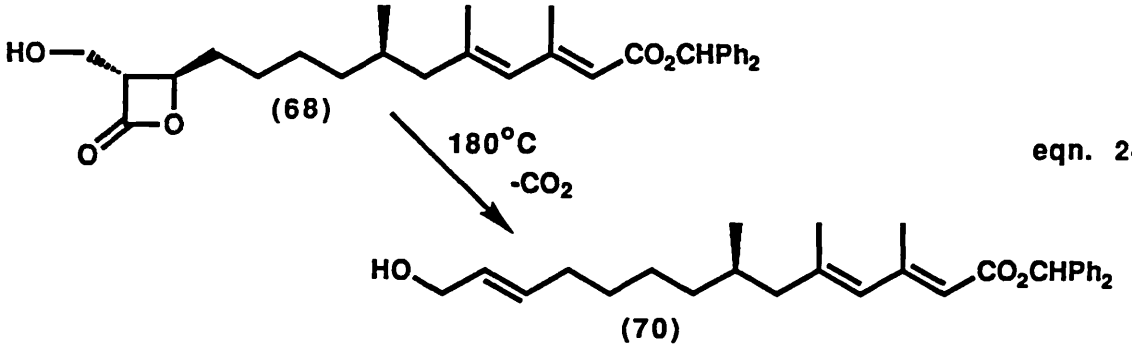
These subsequently extrude dinitrogen to yield cyclopropanes *via* a diradical. No such product was, however, observed in our work. Indeed, the only by-product obtained was a small amount of the bis(diphenylmethyl) compound (**69**) produced by alkylation of both the acid and alcohol functions. It was only produced when a larger than normal excess (1.4 equivalents) of the diazo compound was employed in the protection reaction.



(69)

The suitability of this protecting group was shown by deprotecting the ester (**68**). Treatment with trifluoroacetic acid and anisole in dichloromethane at -10 to -20°C regenerated 1233A in good yield (77%).

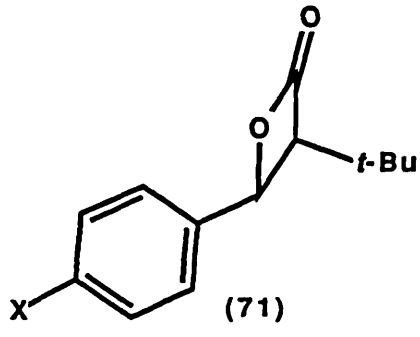
Heating the ester (**68**) at 180°C in the absence of solvent cleanly brought about a decarboxylation reaction to give the allylic alcohol (**70**) in 82% yield (eqn. 24).



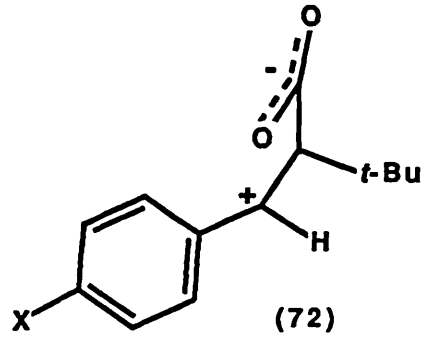
(68) (70) eqn. 24

This reaction has been shown to be stereoselective, retaining the β-lactone geometry in the alkene.[77] It has been studied for the β-lactones (**71**) in a number of solvents.[78] The rate of the reaction increased by a factor of 438 on changing the solvent from decalin to formanilide and by over five orders of magnitude on changing the aryl substituent X

from an electron withdrawing group (nitro) to an electron releasing group (methoxy). This indicated the intermediacy of a zwitterionic species (**72**) - the reaction is, therefore, stepwise and not concerted.



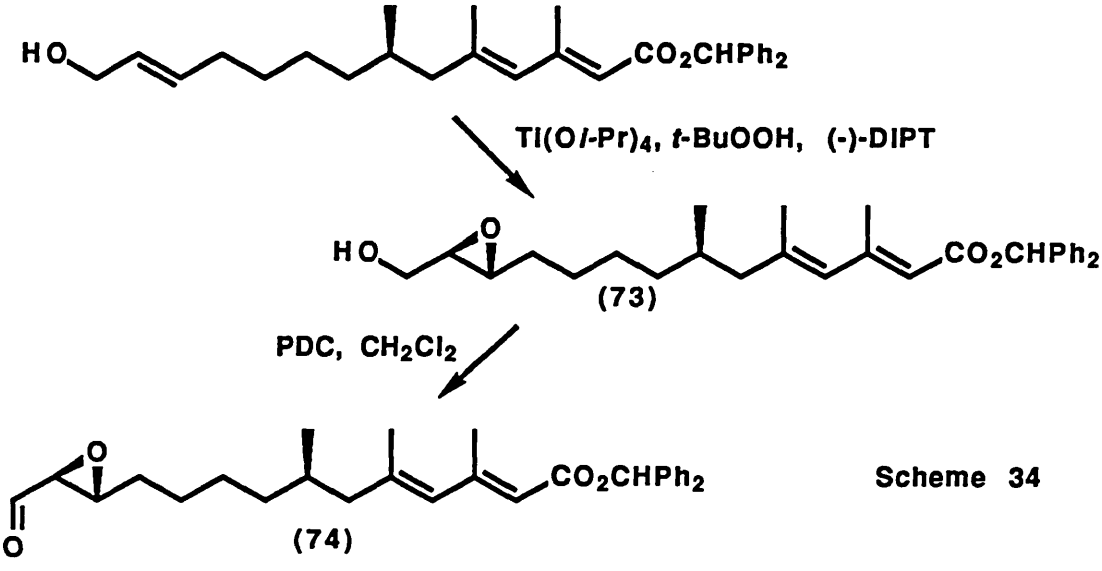
(71)



(72)

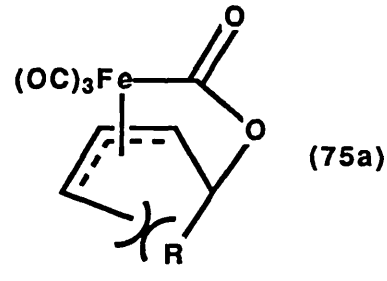
Benzhydryl esters are often thermally unstable. Decomposition does not, however, occur under decarboxylation conditions as higher temperatures are required. Mass spectroscopic samples of the ester (**68**), though, gave no molecular ion - the highest peak being that due to loss of carbon dioxide and the diphenylmethyl radical.

Epoxidation of the allylic alcohol (**70**) using Sharpless' catalytic conditions[34] afforded the epoxy alcohol (**73**) in good yield (84%) and diastereoisomeric excess (94%) (Scheme 34). This d.e. was assessed by integration of the NMR signal of the unique proton of the diphenylmethyl group. Oxidation of the epoxy alcohol (**73**) with PDC in the presence of powdered 4Å molecular sieves smoothly gave the acid sensitive aldehyde (**74**) in 84% yield. Previous studies[79] had shown that PDC was superior to the Swern conditions for this class of oxidations. TPAP oxidations have been used in some examples,[80] but in this case it gave a disappointing 33% yield of (**74**).



Scheme 34

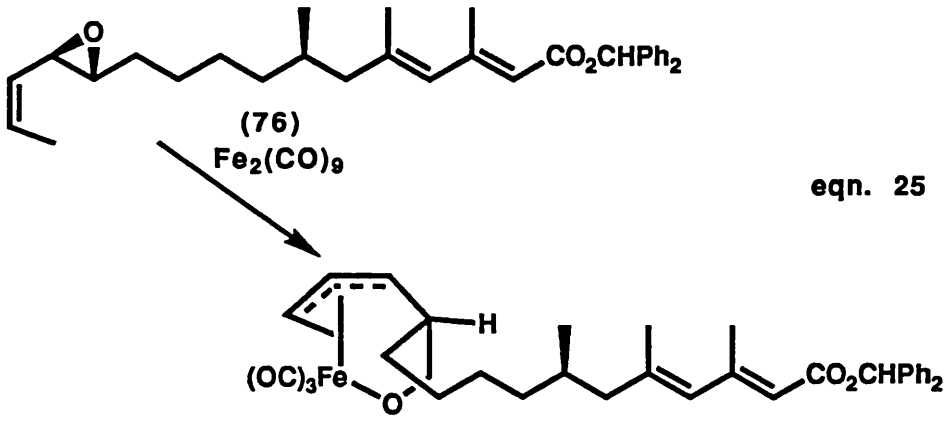
The ferrilactone required for later conversion to the β-lactone was that with the main alkyl chain in the *exo* position. This should yield a *trans* β-lactone directly on oxidation. In order to encourage this, the aldehyde was olefinated with ethylidene-triphenylphosphorane. It was anticipated that the addition of the methyl group would ensure that the *endo* complex (**75a**) would be strongly disfavoured by the steric interaction between two *endo* groups.



(75a)

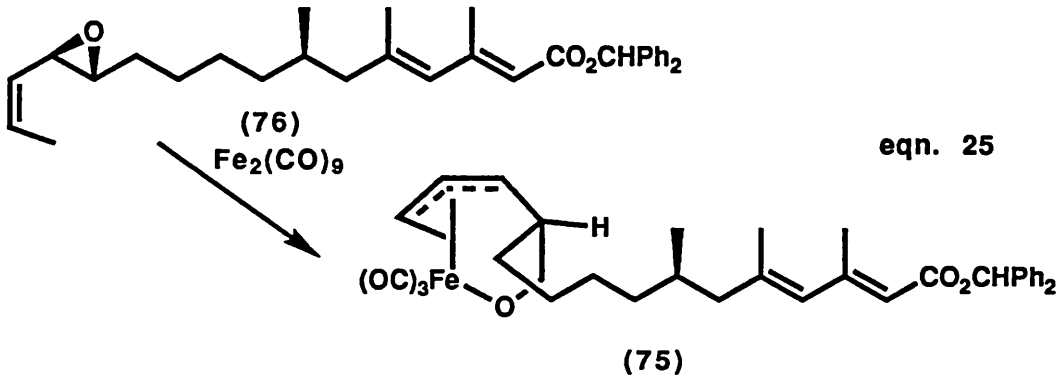
The Wittig reaction (Scheme 35) was carried out under lithium-free conditions by using potassium hexamethyldisilazide as the base. The highly Lewis acidic lithium cation generally causes total destruction of the sensitive vinyl epoxides. The product was the *Z*-isomer (**76**), as expected for a "salt-free" Wittig reaction, in 78% yield.

Reaction of the aldehyde with methylenetriphenylphosphorane under the same conditions gave the corresponding vinyl epoxide (**77**) in 83% yield.



eqn. 25

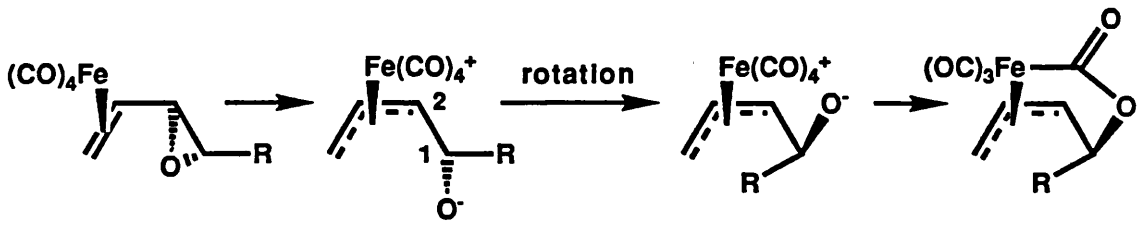
(75) . Treatment of the ethylidene compound (76) with diiron nonacarbonyl under either the THF or ultrasonic conditions gave exclusively the *endo* complex (75) in 54% yield (eqn. 25).



eqn. 25

(75)

The structure of the ferrilactone was clearly shown by a 5 Hz coupling constant between the NMR signals due to the 12- and 13-protons. This initially unexpected result was easily rationalised by consideration of the mechanism of the reaction (Scheme 36).

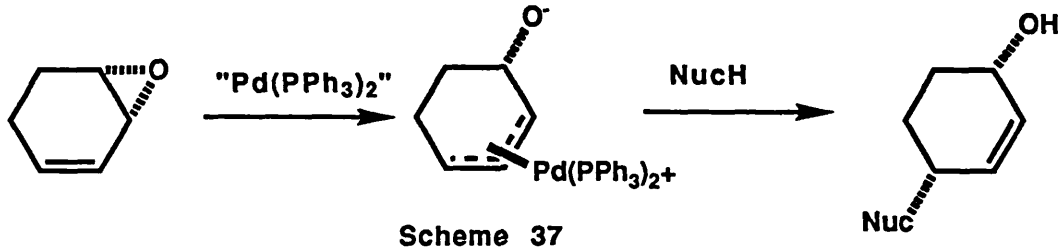


Scheme 36

The first step is likely to be coordination of tetracarbonyliron to the double bond. Ring

opening of the epoxide in an *anti* sense relative to the iron would give a zwitterionic η^3-intermediate. Rotation around the 1,2 bond is required for cyclisation, bringing an *exo* group, R, into the *endo* position. Thus the geometry of the epoxide is inverted in the product.

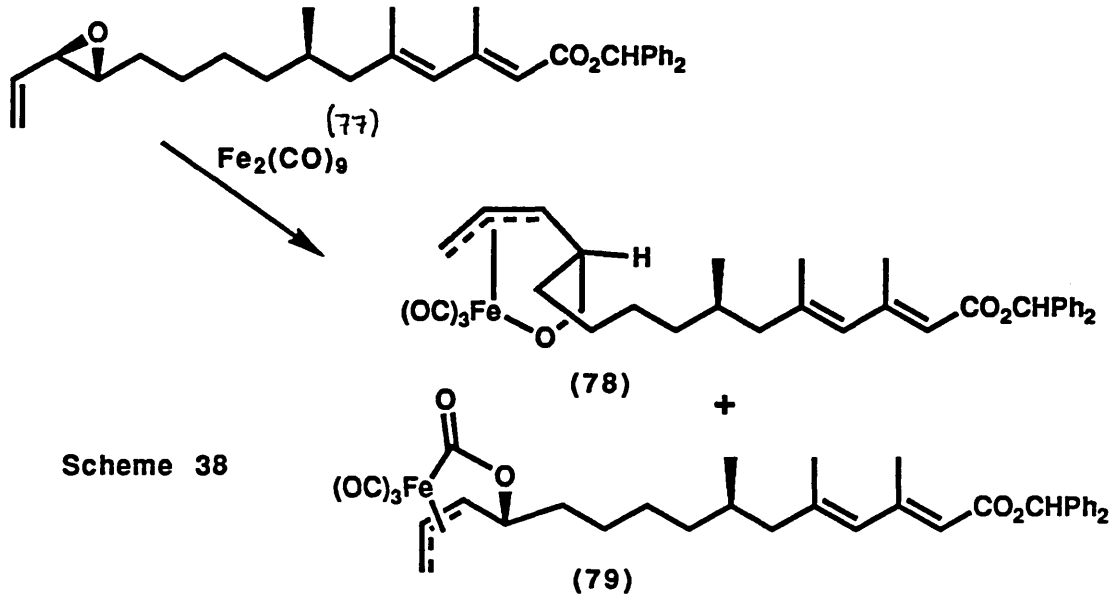
This is analagous to Trost's palladium chemistry (Scheme 37).[81]



Scheme 37

In this instance, as isolation of the intermediate palladium complexes was not possible, the stereochemical consequence was shown in the product. Monoepoxycyclohexadiene gave the *cis* compound *via* a double inversion. *Anti* opening of the epoxide would also be expected by analogy with the chemistry of the butenediols.

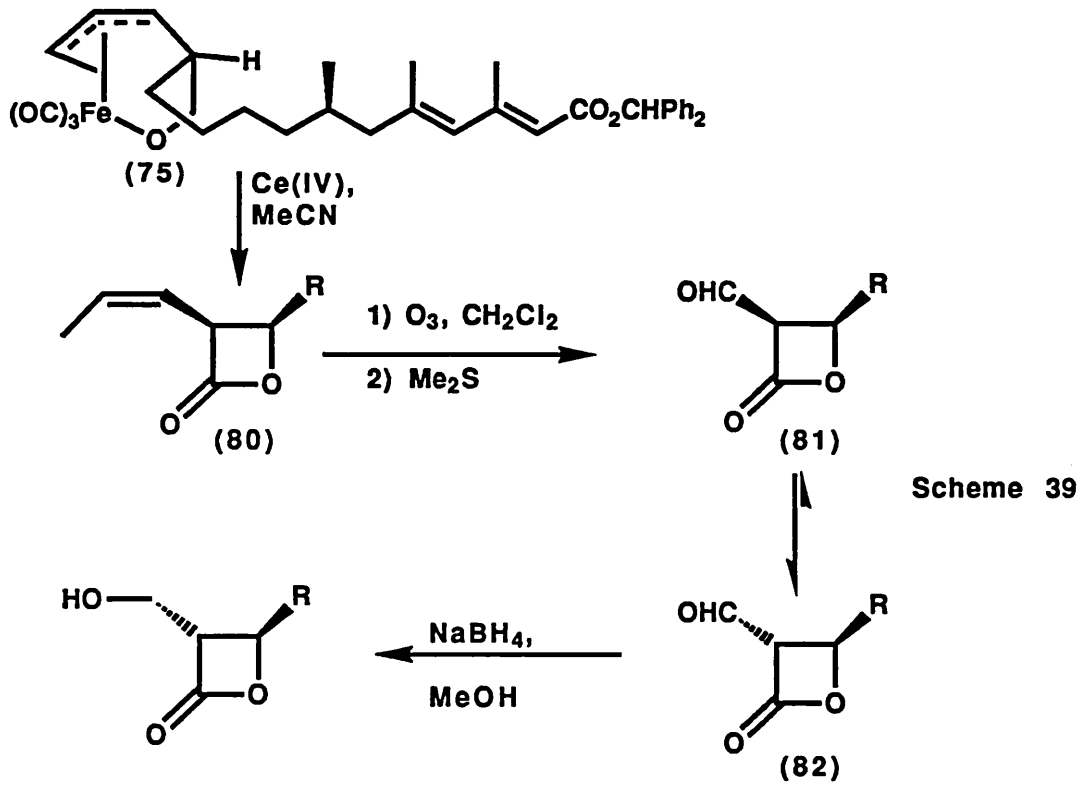
Some *syn* ring opening was shown to be possible. Treatment of the methylene compound (**77**) under similar conditions gave a separable 9:2 ratio of the *endo* (**78**) and *exo* (**79**) complexes in 47% yield (Scheme 38). The NMR spectrum of the *endo* complex showed only multiplets for the ferrilactone protons. In the *exo* complex, on the other hand, the signals were well resolved. A characteristically small coupling constant (<1 Hz) between the 12- and 13-protons was apparent. Even so, the optimum required material for the formation of the *exo* complex would, therefore, be the *cis* epoxide.



Scheme 38

Nevertheless, in order to form the hydroxymethyl side chain it would be necessary to cleave the double bond of the vinyl β–lactone (**80**) that should be produced on oxidation of the ferrilactones (Scheme 39). Ozonolysis with a mild reductive work up would give a *cis* aldehyde (**81**). By analogy with the formal synthesis of theinamycin,[82] it was expected that this *cis* aldehyde (**81**) would isomerise to the more stable *trans* compound (**82**) in the presence of a catalytic amount of base or acid .

Reaction of a small amount of ferrilactone with ammonium ceric nitrate in acetonitrile in a preliminary experiment transformed it into a new compound which was identified as a β-lactone on the basis of its crude infra red spectrum which showed a distinctive band at 1822 cm^{-1}. Ozonolysis of the crude product in dichloromethane at -78°C and work-up sequentially with dimethyl sulphide and methanolic sodium borohydride gave, after careful chromatography, a small amount of material identical by 500 MHz NMR to the diphenylmethyl ester of 1233A (**68**).

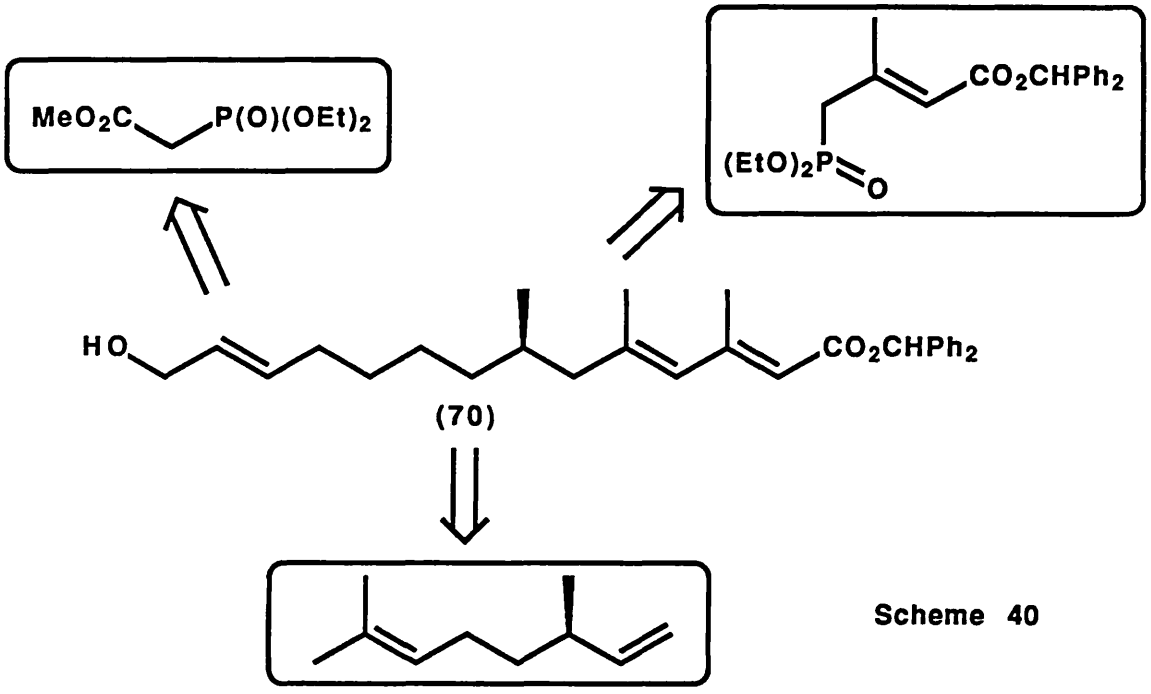


Scheme 39

This relay synthesis serves to establish the Merck, Sharp and Dohme structure as correct, as the chiral centres of the β-lactone in our work were independently established *via* a Sharpless epoxidation. This process has no known exceptions to its selectivity rule. For a total synthesis to be claimed, however, more studies are required on the conversion of the ferrilactone (**75**) to the ester (**68**).

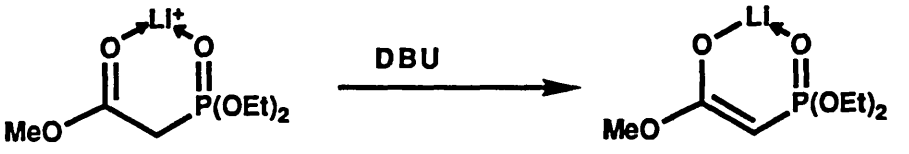
5.3. Attempted Total Synthesis of 1233A

With a relay synthesis of 1233A in hand, it was attractive to use the same methodology in a total synthesis using the allylic alcohol (**70**) as an intermediate. This molecule possesses three important features: a *trans* allylic alcohol, an optically pure methyl substituent and a dienoic ester (Scheme 40).



Scheme 40

It was envisaged that the C12-C13 and C4-C5 double bonds could be formed using Wadsworth-Emmons reactions of phosphonoesters. Methyl diethyl phosphonoacetate was selected for construction of the C12-C13 double bond as the methyl ester should be easily reduced to an alcohol by DIBAl, in the presence of the much more sterically hindered benzhydryl ester. The excellent Masamune-Roush[83] variation of the Wadsworth-Emmons reaction represents the best way of achieving this transformation. In this reaction, coordination of the phosphonate to lithium increases its acidity and allows milder bases, such as DBU, to be used (eqn. 26).

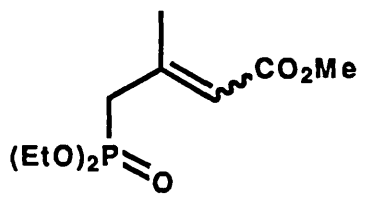


eqn. 26

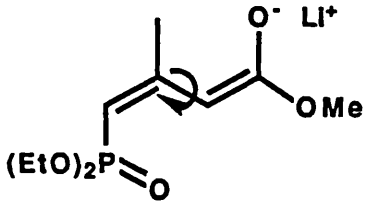
The stereoselectivity of the reaction is also enhanced. The *E*-isomer is produced virtually exclusively in contrast with traditional systems (e.g. sodium hydride, THF, 0°C) which give ratios of about 10:1. As the C12-C13 double bond would be required for a later Sharpless enantioselective epoxidation, geometrical purity was essential.

The dienoic portion is synthetically more challenging. It contains two trisubstituted double bonds. Forming it *via* a Wadsworth-Emmons reaction to give the C3-C4 double bond appeared to be promising as phosphonates of the type (**82**) are well known.[84] The compound (**82**) in this series has been used in a variety of dienoic ester syntheses.[85,86,87]

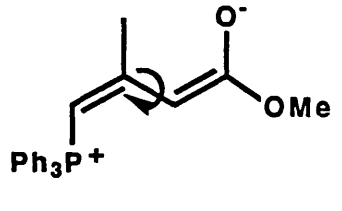
The reactions of this class of phosphonates have been studied in detail by Corey and Erikson.[88] They prepared both the phosphonate and the corresponding phosphonium salts. Interestingly, they found that both the lithium salt of the phosphonate (**83**) and the ylid (**84**) were configurationally unstable (even in THF at -78°C).



(**82**)



(**83**)

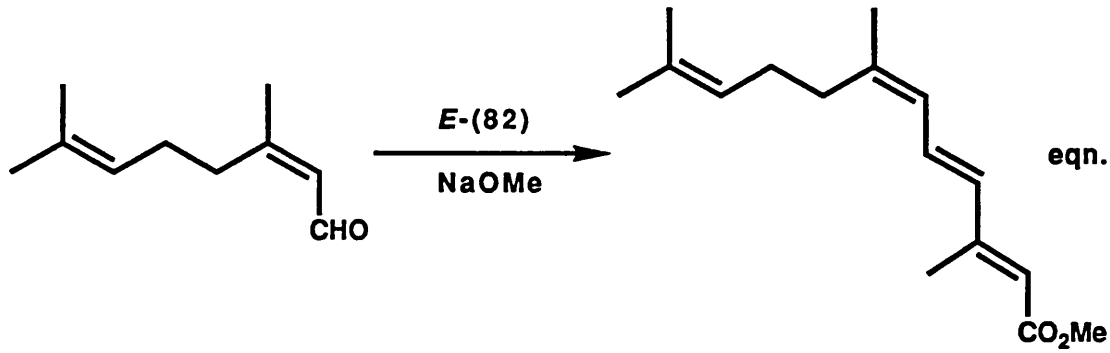


(**84**)

Presumably, the bulk of the negative charge resides on the oxygen atom leading to the predomination of the enolate form and allowing fairly free rotation about the C2-C3 bond. The encouraging fact that was apparent from Corey's work was that the newly

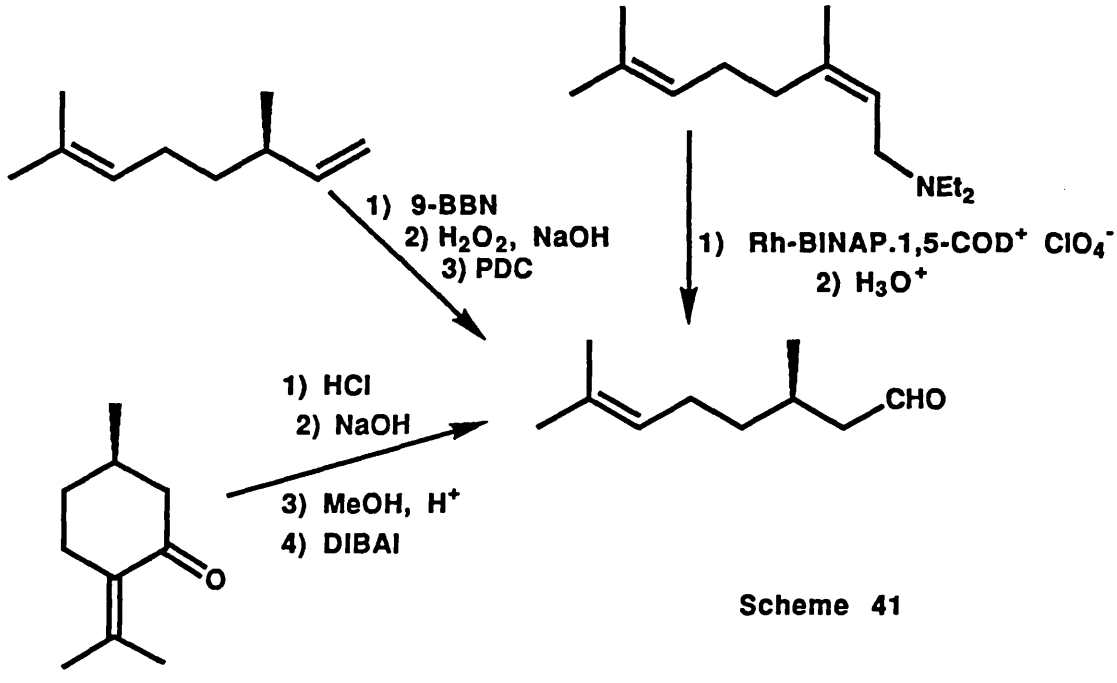
formed C3-C4 double bonds after reaction of the phosphonate anion with aldehydes, largely had the necessary *E* geometry.

This result was supported by the work of Pattenden and Weedon.[87] During their preparation of carotenoid compounds they found that condensation of the *E*-phosphonoester with aldehydes in the presence of sodium methoxide gave exclusively the *E,E* products (eqn. 27). It is likely that the less oxyphilic sodium cation caused greater carbanion character, sufficiently disfavouring enolisation to allow maintenance of the C2-C3 bond geometry.



eqn. 27

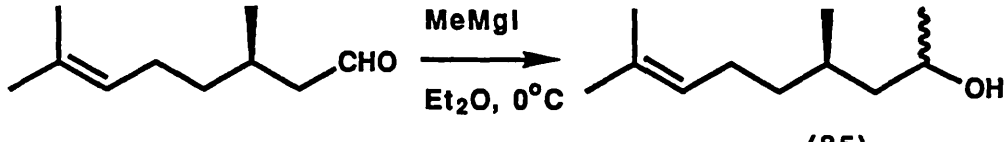
Finally, it was anticipated that the single chiral centre of (**70**) could come from citronellal. However, this natural product is usually available in only 70% e.e. or less. It can be prepared in good e.e. by an asymmetric hydride migration reaction,[89] by transformation of natural (R)-pulegone[91] or by hydroboration-oxidation of citronellene (Scheme 41).



Scheme 41

The last of these options was chosen as the most suitable for the synthesis of 1233A.

Hydroboration of citronellene with 9-BBN followed by oxidation with alkaline hydrogen peroxide gave citronellol. Further oxidation with pyridinium dichromate in the presence of powdered 4Å molecular sieves gave citronellal contaminated with a less polar by-product. Treatment of the mixture with methylmagnesium iodide in ether according to the Merck, Sharp and Dohme procedure[91] gave the alcohol (**85**) as a mixture of diastereoisomers (eqn. 28).

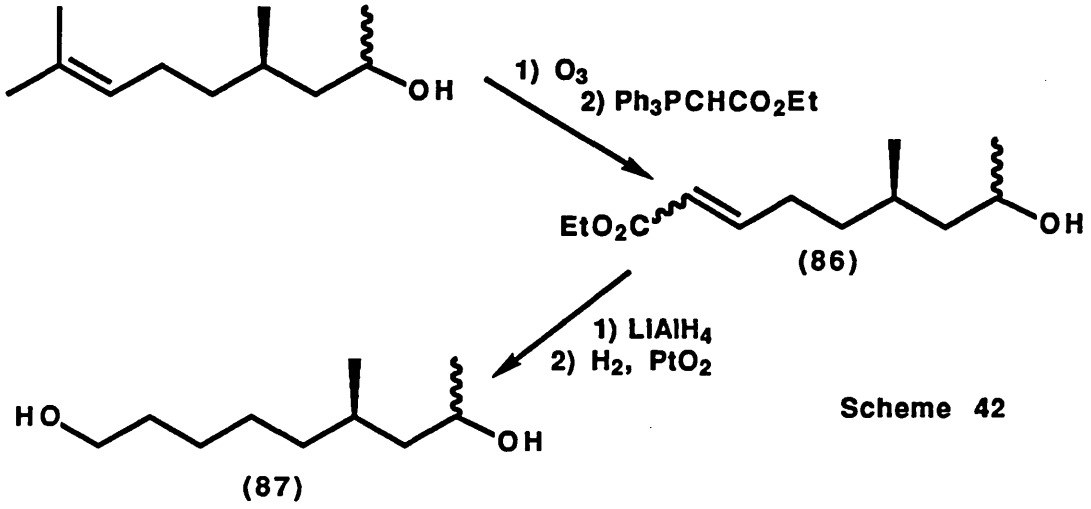


eqn. 28

(**85**)

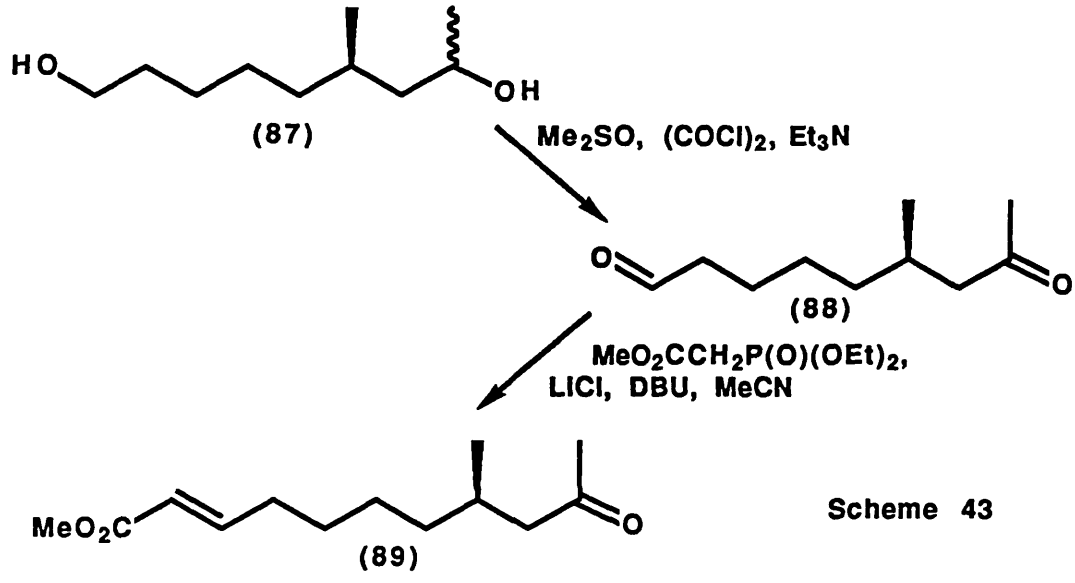
Ozonolysis of the double bond of (**85**) in dichloromethane at -78°C followed by a dimethyl sulphide work-up and Wittig reaction in the same pot with a stabilised ylid

afforded the α,β-unsaturated ester (**86**). Reduction of the double bond of (**86**) with hydrogen over platinum and the ester with lithium aluminium hydride in ether gave the key diol (**87**) (Scheme 42).



Scheme 42

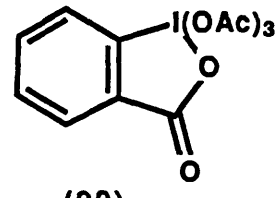
Oxidation of this diol (**87**), however, did not give good yields of the ketoaldehyde (**88**) using either Swern conditions (71%) or PDC (67%). Ruthenium based oxidation systems (TPAP/NMO and Ruthenium dioxide/ *t*-butyl-hydroperoxide) gave complex mixtures including starting material and traces of the desired product. The ketoaldehyde (**88**) was found to be extremely unstable and subsequent reaction by the usually reliable Masamune-Roush[83] method gave only a 34% yield of the ketoester (**89**). It was, though, pleasing to find that there was no detectable reaction at the ketone and only *E*-geometry at the newly formed carbon-carbon double bond.



Scheme 43

A number of combined oxidation-olefinations of (87) were then attempted in order to minimise the losses caused by having to isolate the ketoaldehyde (88). Filtration of the crude Swern mixture through florisil directly into a Masamune-Roush mixture to which 4Å molecular sieves had been added, gave a slow reaction, but a yield of the desired ketoester (89) that was improved over the two step process. The sieves which were added to the reaction mixture served to remove traces of water which otherwise would be strongly competitive ligands for the lithium cations and prevent coordination of the phosphonate. The slowness of the olefination reaction could be due to the use of a dichloromethane/acetonitrile solvent mixture. The lower polarity of the reaction medium would lower the solubility of the lithium phosphonate complex. To counteract this, the incorporation of some acetonitrile in the Swern mixture was investigated. After preparation of the sulphonium species as usual, the diol was added in acetonitrile followed by the normal addition of triethylamine. Although a respectable 42% yield was obtained (equivalent to 75% for each step), the reaction now produced a number of non-polar by-products. It is likely that the use of a more polar solvent - which enhances the Wadsworth-Emmons reaction - is detrimental to the Swern oxidation as it encouraged side-reactions such as nucleophilic displacements.

An oxidising agent which may be used in acetonitrile is the Dess-Martin periodinane (**90**).[92]

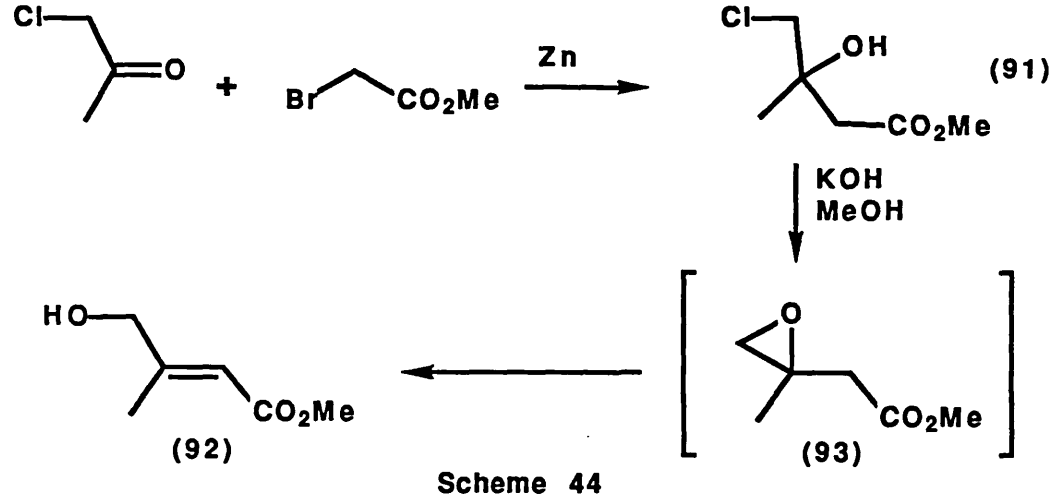


(**90**)

Although this reagent is no longer commercially available due to hazards associated with its manufacture, it may be easily prepared according to the literature procedure. Oxidation of the diol proceeded slowly. Filtration of the reaction mixture into the Masamune-Roush mixture as before lead to the ketoester, but in only 39% yield.

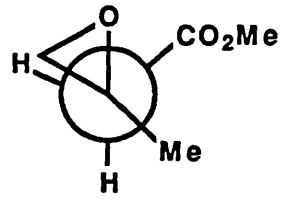
With limited quantities of the ketoester in hand, the crotonic phosphonate (**99**) was prepared in order to test the viability of the Wadsworth-Emmons reaction. There are two literature methods for forming isomerically pure phosphonates of this class. The original method involved allylic bromination of 2,2-dimethylacrylate derivatives followed by heating the product with triethylphosphite to effect an Arbusov reaction. Clearly the allylic bromination is not stereoselective and a separation of isomers is required at some stage. Pattenden and Weedon required both isomers for their studies on carotenoids and opted for separation of the phosphonate isomers by fractional distillation and preparative GLC.[87] Most workers, however, have required only the *E*-isomers and have used Johnson's method for obtaining single isomers.[85] In this procedure allylic bromination of 2,2-dimethylacrylic acid itself is followed by base-induced lactonisation of the unwanted isomer. Methylation[94] and Arbusov reaction then gave the commonly used methyl ester. Corey considered that this method had a number of disadvantages and consequently sought an alternative.[88] Epstein and Sonntag had found that the Reformatsky reaction between chloroacetone and methyl bromoacetate gave the expected hydroxyester (**91**) product.[95] They converted it by treatment with

base to the hydroxyester (**92**) *via* an epoxide intermediate (**93**) and a highly stereo-selective ring opening (Scheme 44).



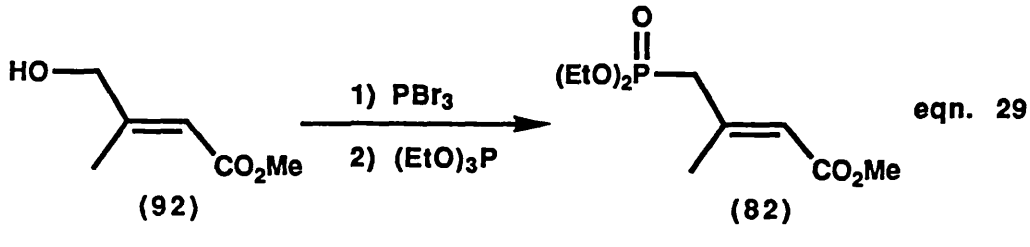
Scheme 44

They observed only traces (2 to 3%) of products derived from the other isomer of the hydroxyester. This was attributed to the favouring of the conformation (**93a**) of the intermediate epoxide.



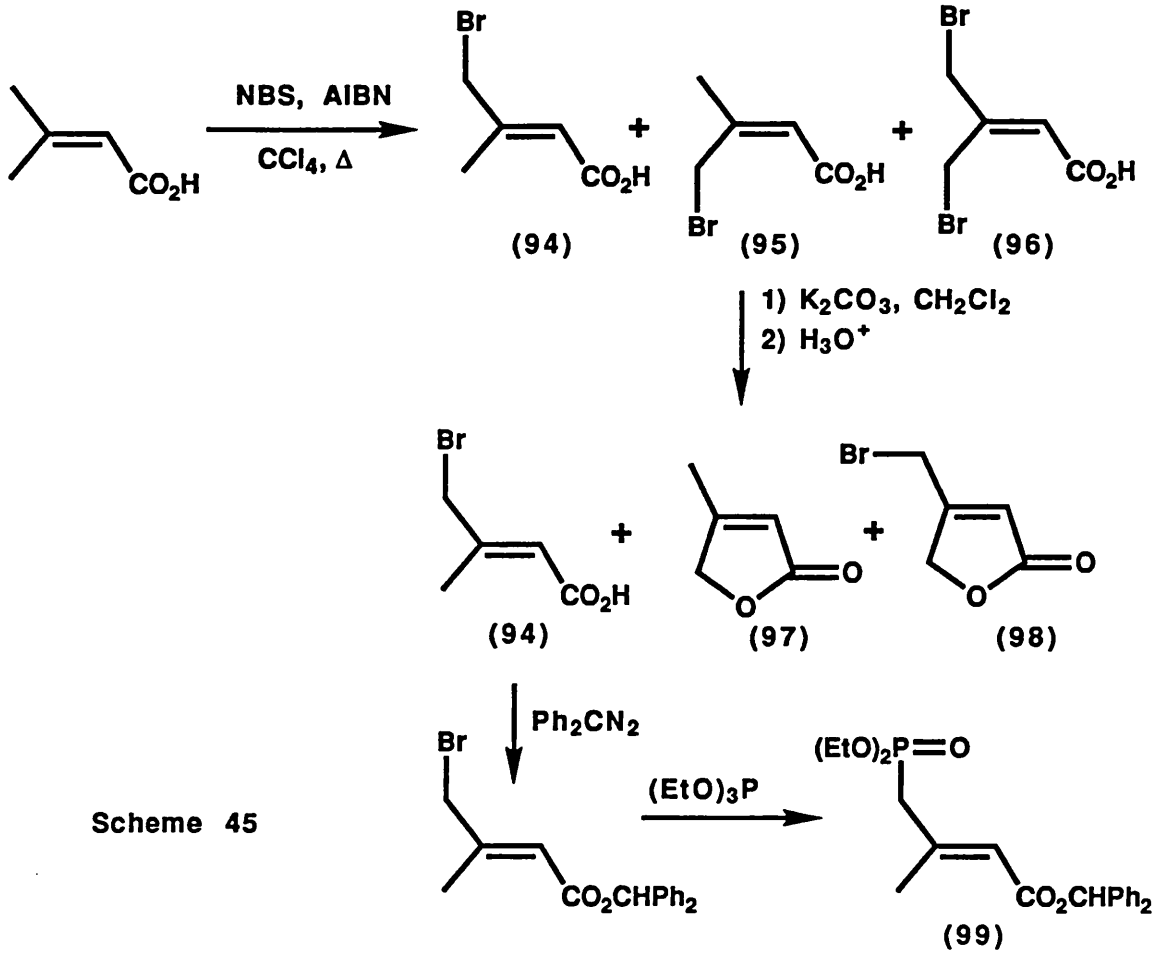
(**93a**)

Corey converted the hydroxyester (**92**) into the phosphonate (**82**) in two routine steps (eqn. 29).[88]



eqn. 29

However, in our view, the Johnson method appeared to be more amenable to inclusion of a benzhydryl ester which was required in our synthesis.

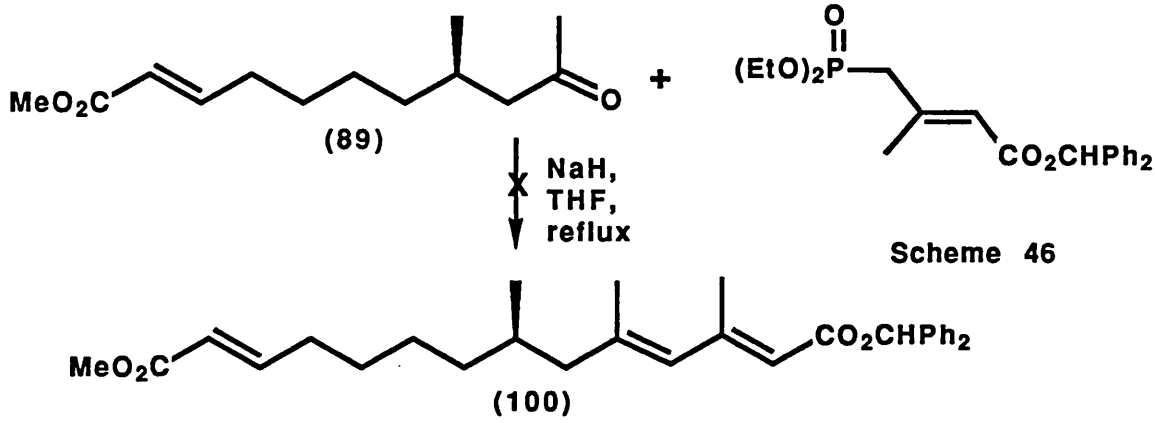


Scheme 45

In our hands, allylic bromination of 2,2-dimethylacrylic acid gave a mixture of *E* and *Z*-bromoacids, (**94**) and (**95**), contaminated with a small amount of starting material and 2,2-(dibromomethyl)acrylic acid (**96**). Upon a standard acid/base work-up, the *Z*-isomer failed to lactonise, contrary to Johnson's report. Indeed, stirring the mixture for 24 hours in dichloromethane in the presence of anhydrous potassium carbonate was required. Subsequent acid/base separation then gave *E*-2-bromomethyl-2-methylacrylic acid (**94**), contaminated with about 20% of other acids, but less than 2% of *Z*-bromomethyl compounds. Both 4-methyl-2(5*H*)-furanone (**97**) and 4-

bromomethyl-2(5*H*)-furanone (**98**) were isolated from the neutral phase. Esterification in the usual way with diphenyldiazomethane gave the corresponding mixture of esters. Arbusov reaction with triethylphosphite at 180°C yielded the phosphonate (**99**) in 20% yield from 2,2-dimethylacrylic acid (Scheme 45). The newly formed phosphorus-carbon bond in (**99**) was clearly demonstrated by the coupling constants between the phosphorus and the 4-atom in the proton and carbon-13 NMR spectra: $J_{P\text{-}H}$ = 24 Hz; $J_{P\text{-}C}$ = 135 Hz.

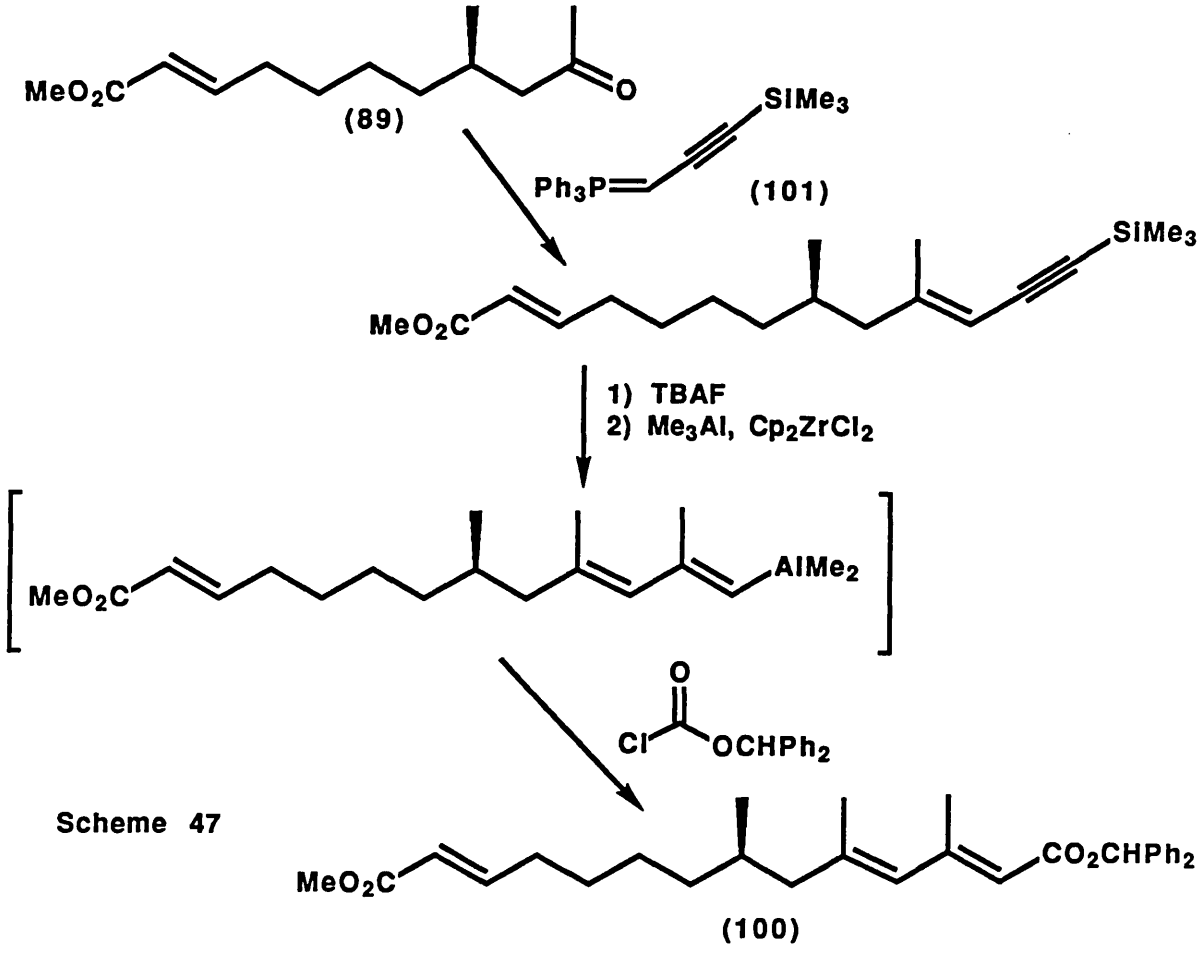
Reaction of the phosphonate with the ketoester (**89**) under standard Wadsworth-Emmons conditions (sodium hydride, THF, reflux) (Scheme 46) gave no detectable products. Even addition of HMPA to the reaction mixture did not improve the situation.[84] The β-branched methylketone proved to be too sterically hindered to react successfully with the phosphonate anion.



Scheme 46

An alternative route from the ketone to the trienoic ester (**100**) was therefore sought. One possible route to (**100**) would be to use a Negishi carbometallation[96] of a triple bond to set up the C2-C3 double bond system and quench the intermediate vinyl aluminium with a chloroformate to afford the desired product. The required acetylene is potentially available by a Wittig reaction of the ketoester (**89**) (Scheme 47). However, the Wittig reaction of propargylic phosphonium salts has been shown to give cummulenes unless the acetylene is protected by a trimethylsilyl group.[47] When this is

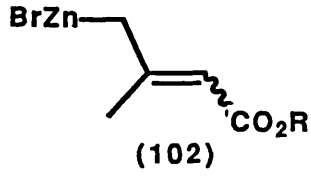
so, the product is predominantly the *trans* isomer. Such silyl acetylenes may be easily deprotected under a variety of conditions.



Scheme 47

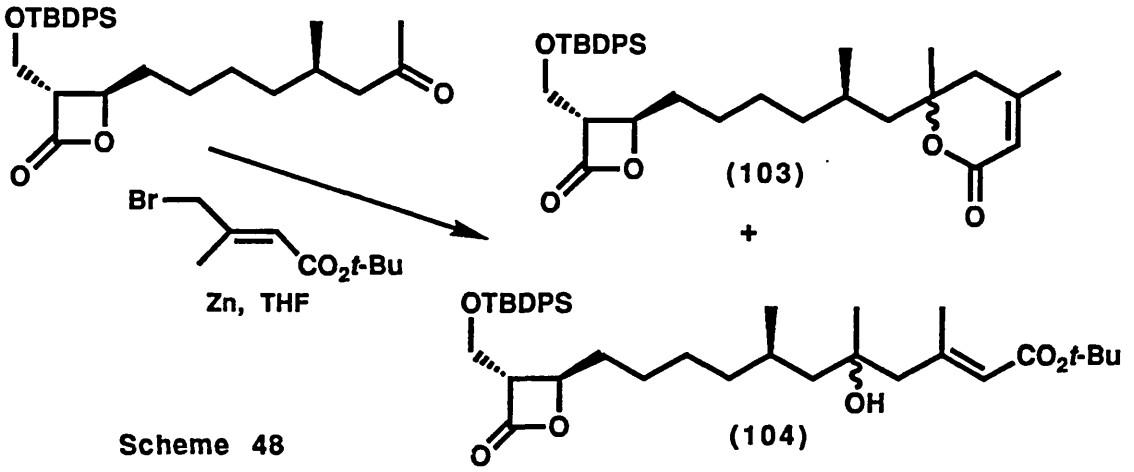
Unfortunately, the ketoester (**89**) proved to be resistant to the ylid (**101**), even in boiling THF, although aldehydes are known to react at 0°C. This approach was, therefore, impracticable.

Merck, Sharp and Dohme workers showed in their total synthesis of 1233A that the Reformatsky reagent (**102**) is sufficiently reactive.[91]



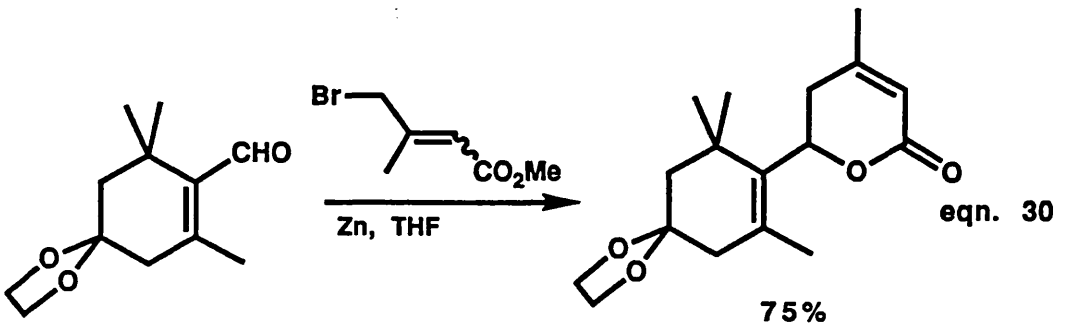
(102)

These zinc enolates, however, like the ylids and phosphonates studied by Corey,[88] are not configurationally stable. The Merck, Sharp and Dohme workers obtained a δ-lactone (**103**) as the major product of this reaction during their total synthesis (Scheme 48), although it was accompanied by some of the required tertiary alcohol (**104**).[91] The δ-lactone (**103**) arises by isomerisation of the Reformatsky reagent (**102**) from its *E* - to its *Z*- form. Lactonisation of the tertiary alcohol derived from the *Z*-form leads to the δ-lactone. This process has recently been studied in some depth by Brouilette and Muccio.[84]



Scheme 48

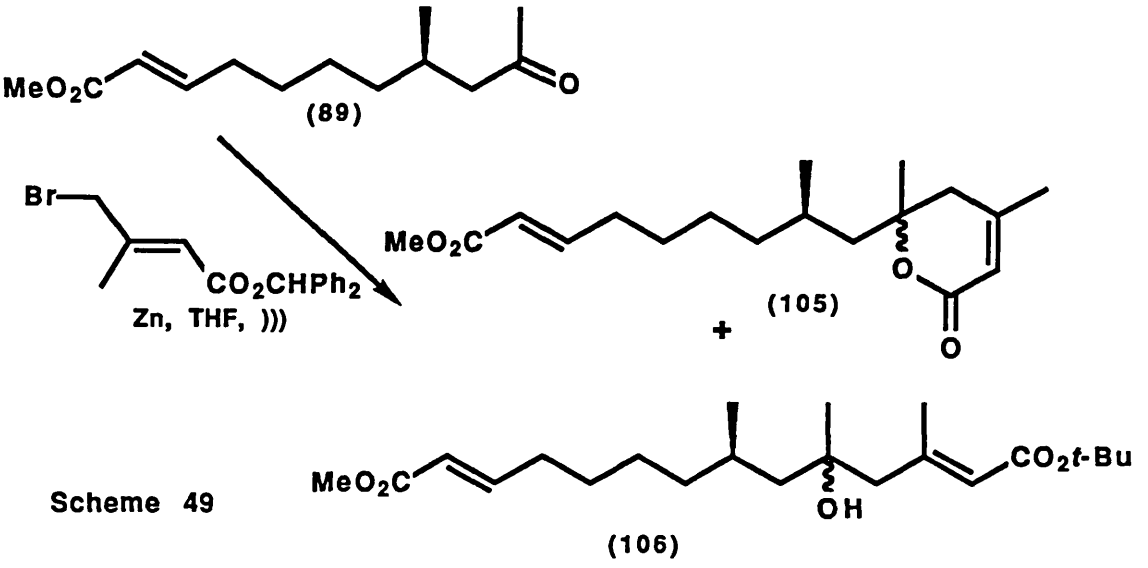
Indeed, Constantino used this isomerisation-lactonisation process to form a δ-lactone in his synthesis of (±)-abscisic acid (eqn.30).[97]



eqn. 30

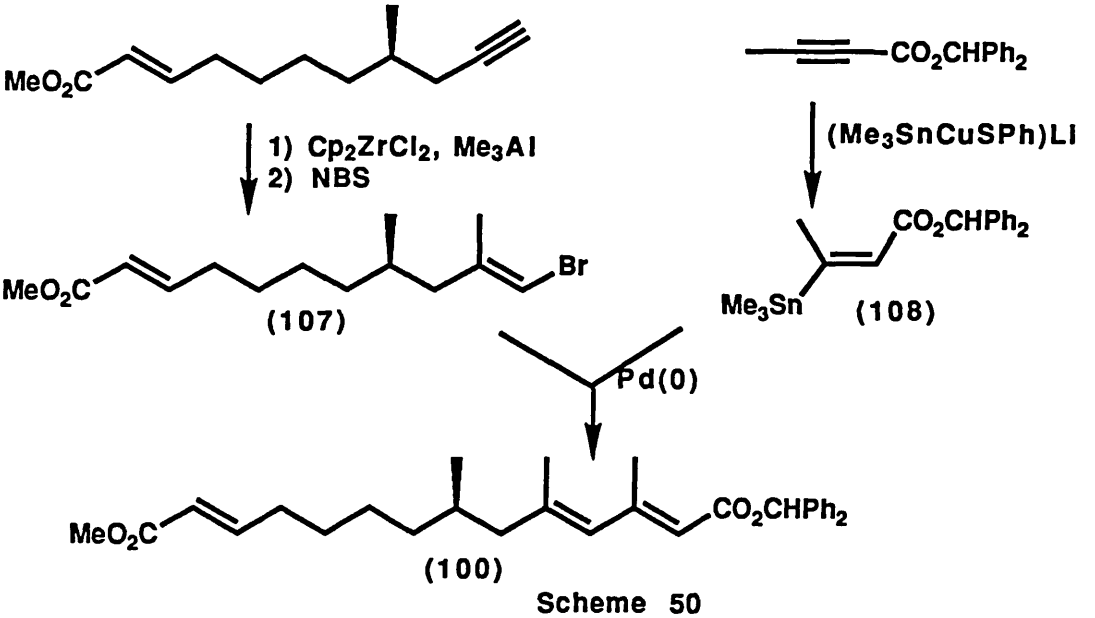
The process was confirmed by a preliminary experiment (Scheme 49) carried out under Boudjouk's ultrasonic conditions.[98] The δ-lactone (**105**), arising from the

isomerisation-lactonisation, predominated and only a small amount of tertiary alcohol (**106**) was isolated.



Scheme 49

An alternative approach to the diene system is clearly necessary. A palladium (0) mediated cross coupling[99] between a vinyl bromide (**107**), generated by Negishi chemistry,[100] and a vinyl stannane (**108**) generated by stannyl cuprate addition to an acetylenic ester, is an attractive proposition for the synthesis of the ester (**100**) (Scheme 50). Owing to insufficient time, this route was not investigated.



Scheme 50

Experimental

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Boiling points refer to Kugelrohr oven temperatures. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer using thin films between NaCl discs or in CH_2Cl_2 solution. NMR spectra were obtained for solutions in *d*-chloroform or d_6-benzene with residual protic solvent as internal standard, and were recorded on Bruker WM-250 (250 MHz), JEOL GSX-270 (270 MHz), Bruker WM-400 (400 MHz) or Bruker AM-500 (500 MHz) instruments. Mass spectra were obtained with a VG micromass 7070B instrument. Microanalyses were performed by the Imperial College Chemistry Department microanalytical laboratory. Optical rotations were measured on an Optical Activity AA-1000 polarimeter.

Thin layer chromatography (tlc) was used analytically and was performed on Merck precoated F_{254} plates. Flash chromatography was carried out on columns of Merck Kieselgel 60 (230-400 Mesh) or BDH Chemicals Florisil (200-300 Mesh). Analytical gas chromatography was performed on a Perkin-Elmer Sigma 3 gas chromatograph using an RSL-150 column and a Perkin-Elmer LCI-100 Laboratory Computing Integrator.

Ultrasonication was carried out in a Semat ultrasound cleaning bath (80 W, 55 kHz) or using a Heat Systems W-380 ultrasonic processor equipped with a microtip probe.

High pressure carbonylation was carried out in a glass "sleeve" contained inside a steel autoclave ("bomb"). The sleeve was cleaned before use by washing with dilute hydrochloric acid, water, pH7 buffer solution and distilled water, followed by oven drying.

Petrol refers to light petroleum with a boiling range of 40-60°C unless otherwise stated and was distilled before use. Ether refers to diethyl ether and was distilled from sodium-benzophenone ketyl under argon before use, as was THF. Toluene, benzene and hexane were distilled from sodium; dichloromethane and acetonitrile from phosphorus pentoxide. Ammonium ceric nitrate and phosphonium salts were dried before use by being placed under vacuum overnight. Diiron nonacarbonyl was obtained from the Aldrich Chemical Company and used without purification.

Solutions were dried over anhydrous magnesium or sodium sulphate, evaporated with a rotary evaporator and, where appropriate, by static evaporation with an oil pump or (non-volatile iron complexes) under a strong stream of inert gas.

General Method for the Preparation of Ferrilactones: Procedure A

A solution of the substrate in dry THF under argon or nitrogen was added to solid diiron nonacarbonyl (1.3 to 3 equivalents) via *cannula* or by syringe, under argon or nitrogen. The mixture was stirred until tlc showed that the substrate was consumed or until all the diiron nonacarbonyl had dissolved (1-4 hours). The solution was concentrated to about half its volume, diluted with ether and toluene (about 1 ml per 100 mg of substrate) and stirred for a few minutes. The solids were removed by filtration through talc and the ether and THF were evaporated. The resulting toluene solution was applied directly to the top of a column of silica gel. Purification by flash chromatography, eluting initially with 5% ether-petrol gave the products.

General Method For the Preparation of Ferrilactones: Procedure B

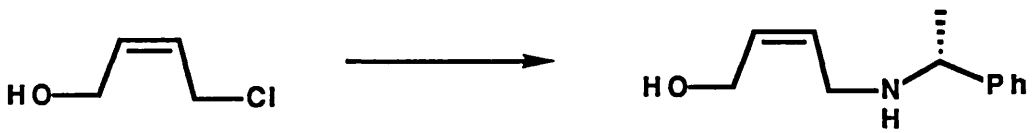
Diiron nonacarbonyl (two equivalents) was added from a solid addition tube to a suspension or solution of the substrate in benzene under argon or nitrogen. The mixture

was sonicated until either the substrate or the diiron nonacarbonyl was consumed. The mixture was worked up as above.

Preparation of 2-4-η^3-(1-formyloxybut-3-en-2-ylato)tricarbonyl iron (1)

Treatment of *cis*-2-buten-1,4-diol (49 mg, 0.56 mmole) with diiron nonacarbonyl (246 mg, 0.73 mmole) according to procedure A and flash chromatography on silica gel (5 g) eluting with 5% ether petrol and ether gave the ferrilactone (1) (97 mg, 73%) as a white solid, $\delta(C_6D_6)$: 3.78 (1 H, ddd, 8, 8 and 13 Hz, 3-H); 3.63 (1H, ddd, 8, 5 and 2 Hz, 2-H); 3.38 (1 H, dd, 12 and 2 Hz, 1-H_{endo}); 3.28 (1 H, dd, 12 and 5 Hz, 1-H_{exo}); 2.69 (1H, dd, 8 and 1.5 Hz, 4-H_{exo}); 2.55 (1H, dd, 13 and 1.5 Hz, C(4)-H_{endo}); identical to the reported material.[1,2]

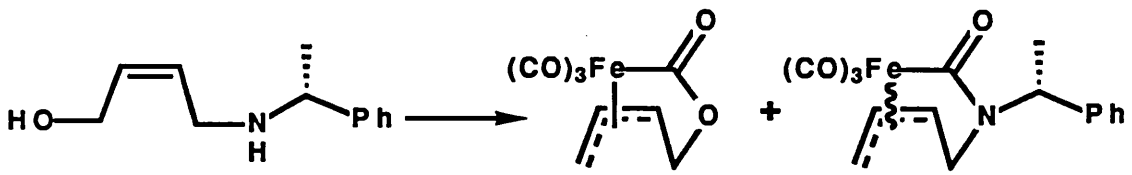
Preparation of *Z*-(1'R)-4-(1'-methylbenzylamino)-2-butenol (2)



A solution of *Z*-4-chloro-2-butenol (143 mg,1.3 mmole) and (R)-(+)-α-methylbenzylamine (520 µl, 4 mmole) in dry dichloromethane (2 ml) was stirred at room temperature overnight. The mixture was poured into water and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated to give a dark oil which was purified by flash chromatography on silica gel (6 g) eluting with 20 - 60% acetone/petrol to give the aminoalcohol (2) as a pale brown solid, mp 50-52°C; Found C 75.05, H 9.05, N 7.22%, $C_{12}H_{17}NO$ requires C 75.35, H 8.96 N 7.32%; $\delta(CDCl_3)$: 7.2-7.4 (5H, m, Ph); 5.82 (1H, m, C<u>H</u>CH_2OH); 5.75 (1H, m,

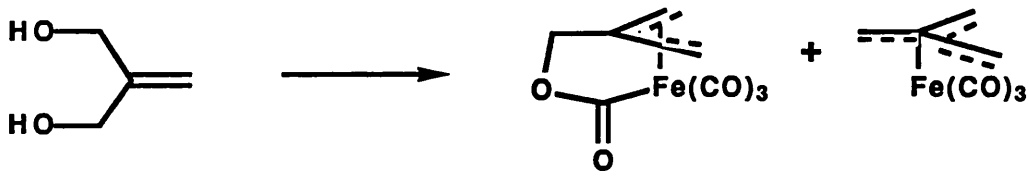
C<u>H</u>CH_2N); 4.11 (2H, d, 5.9 Hz, CH_2OH); 3.79 (1H, q, 6.3 Hz, PhC<u>H</u>N); 3.12 (2H, d, 5.9 Hz, CH_2N); 2.93 (2H, brs, OH and NH); 1.39 (3H, d, 6.3 Hz, Me); ν_{max}(CH_2Cl_2): 3603 (N-H); 3200 (OH); 2850-3030 (CH); and 1603 cm^{-1} (C=C); m/z: 191 (M^+), 176 (M^+-CH_3), 173 (M^+-H_2O), 105 ($PhCHCH_3^+$); $[\alpha]_D^{29}$ = +33.5° (c = 0.46, CH_2Cl_2).

<u>Preparation of 2-4-η^3-(1-[formyl-1'(R)-methylbenzyl amino]but-3-en-2-ylato) tri-carbonyliron (3) and (4)</u>



Treatment of the aminoalcohol (**2**) (49 mg, 0.26 mmole) with diiron nonacarbonyl (186 mg, 0.5 mmole) in benzene (3 ml) according to procedure B and purification by flash chromatography on silica gel (5 g) eluting with 10-100% ether/petrol gave the minor diastereomeric <u>ferrilactam</u> (**3**) as an oil, $\delta(C_6D_6)$ 7.1 (5H, m, Ph); 5.63 (1H, q, 7Hz, NC<u>H</u>Me); 3.94 (1H, ddd, 13, 8 and 7 Hz, 3-H); 3.56 (1H, ddd, 7.7 and 1 Hz, 2-H); 3.01 (1H, d, 8 Hz, 4-H_{exo}); 2.85 (1H, dd, 12 and 7 Hz, 1-H_{exo}); 2.54 (1H, d, 13 Hz, 4-H_{endo}); 2.46 (1H, dd, 12 and 1 Hz, 1-H_{endo}) 1.1 (3H, d, 7 Hz, Me); ν_{max}: 2950-3050 (C-H), 1993, 2067 (FeC=O), 1579 (N(C=O)Fe), 1491 cm^{-1} (=C-H); m/z: 341 (M^+), 313 (M^+-CO), 285 (M^+-2CO), 257 (M^+-3CO), 201 (M^+-$Fe(CO)_3$), 173 (M^+-$Fe(CO)_4$), 105 ($PhCHCH_3^+$); the major <u>ferrilactam</u> (**4**) as needles, mp 92-93°C, $\delta(C_6D_6)$: 7.2 (5H, m, Ph); 5.7 (1H, q, 6 Hz, NC<u>H</u>Me); 3.99 (1H, ddd, 13, 8 and 8 Hz, 3-H); 3.48 (1H, m, 2-H); 3.0 (1H, dd, 8 and 2.5 Hz, 4-H_{exo}); 2.55 (3H, m, 4-H_{endo}, 1-H_{exo} and $_{endo}$); 0.95 (3H, d, 6 Hz, Me); ν_{max}: 2850-3000 (C-H), 1988, 1072 (Fe(C=O), 1579 cm^{-1} (N(C=O)Fe); m/z: 341 (M^+), 313 (M^+-CO), 285 (M^+-2CO), 257 (M^+-3CO), 201 (M^+-$Fe(CO)_3$), 173 (M^+-$Fe(CO)_4$), 105 ($PhCHCH_3^+$); and the <u>ferrilactone</u> (**1**).

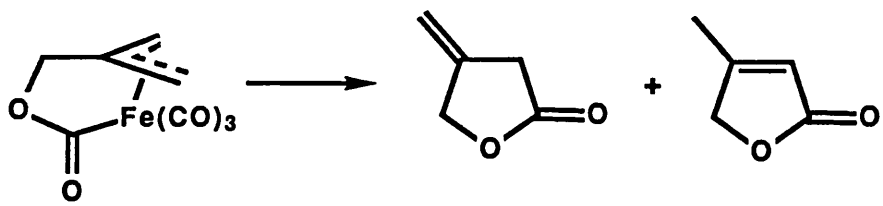
Preparation of 1-3-η^3-(2-formyloxymethylprop-2-en-1-ylato) tricarbonyliron (**11**)



i) 2-Hydroxymethylprop-2-en-1-ol (**10**) (59 mg, 0.67mmole) was treated with diiron nonacarbonyl (559 mg, 1.54 mmole) in THF (4 ml) according to procedure A and purified by flash chromatography on silica gel (7 g) eluting with petrol, 10% ether/petrol and ether to give trimethylenemethaneirontricarbonyl (**12**) (82 mg, 63%) followed by the ferrilactone (**11**) (19 mg, 12%).as a solid. $\delta(C_6D_6)$: 3.36 (2H, s, CH_2O); 2.97 (2H, d, 0.7 Hz, H_{exo}); 1.63 (2H, d, 0.7 Hz, H_{endo}); ν_{max}(DCM): 2900-3050 (CH), 2086, 2019 (FeC=O), 1663 cm^{-1} (O(C=O)Fe); m/z: 238(M^+), 210 (M^+-CO), 194 (M^+-CO_2), 182 (M^+-2CO), 166 (M^+-CO-CO_2), 154 (M^+-3CO), 138 (M^+-2CO-CO_2), 126 (M^+-4CO), 110 (M^+-3CO-CO_2); both compounds identical to the reported materials.[2,18]

ii) The diol (**10**) (100 mg, 1.1 mmole) in benzene (8 ml) was treated with diiron nonacarbonyl (618 mg, 1.7 mmole) according to procedure B. Purification as above gave trimethylenemethaneirontricarbonyl (**12**) (11 mg, 5%) and the ferrilactone (**11**) (151 mg, 58%).

Preparation of 4-methyl-2(*5H*)-furanone (**14**) and 3-methylenebutenolide (**13**)



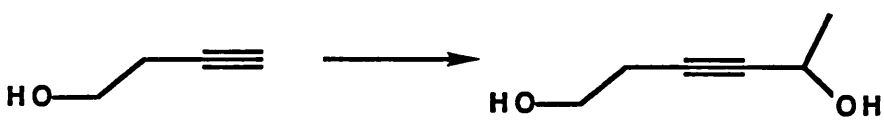
i) A solution of the ferrilactone (**11**) (166 mg, 0.7 mmole) in benzene (6 ml) was heated at 100°C under 150 atm of carbon monoxide for twelve hours. The mixture was

allowed to cool under pressure, then filtered through talc, concentrated and purified by flash chromatography on silica gel (7 g) eluting with 5-50% ether/petrol (bp 30-40°C) to give the butenolide (**13**) (6 mg, 9%) as a colourless oil, $\delta(CDCl_3)$: 5.42 (1H, d, 1 Hz, C=CH); 5.356 (1H, d, 1 Hz, C=CH); 5.0 (2H, s, CH_2O); 4.25 (2H, s, $CH_2C=O$); ν_{max}: 2850-3000 (C-H); 1771 (C=O); 1658 (C=C); m/z 98 (M^+), followed by the furanone (**14**) (25 mg, 37%), identical to reported material[95] and a sample prepared independently[101].

ii) A solution of the ferrilactone (197 mg, 0.83 mmole) and acrolein (1 ml) in benzene (8 ml) was heated at 80°C under 260 atm of carbon monoxide for twelve hours. The mixture was purified as above to give the furanone (**13**) (16 mg, 20%) and the recovered ferrilactone (**11**) (135 mg, 69%).

iii) Ammonium ceric nitrate (2.9 g, 5.3 mmole) was added to a solution of the ferrilactone (251 mg, 1.05 mmole) in acetonitrile (5 ml) at room temperature and filtered, washing with ether. The ether-acetonitrile solution was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (5 g) as above to give the furanone (**13**) as a colourless oil.

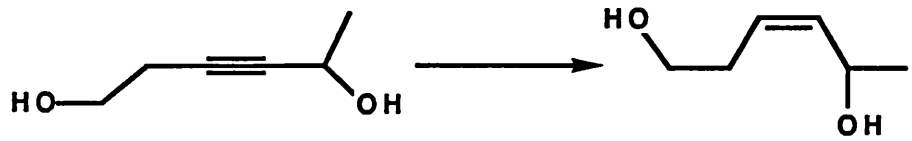
Preparation of 3-hexyn-1,5-diol



A solution of 3-butyn-1-ol (391mg, 5.59 mmole) in THF (40 ml) under argon was cooled to -78°C and treated dropwise with *n*-BuLi (4.9 ml of a 2.5 M solution in hexanes, 12.3 mmole). The mixture was stirred at -30°C for twenty five minutes, then cooled to -70°C. Acetaldehyde (500 µl, 8.4 mmole) was added and the mixture was allowed to warm slowly to -10°C. Saturated ammonium chloride and brine were added

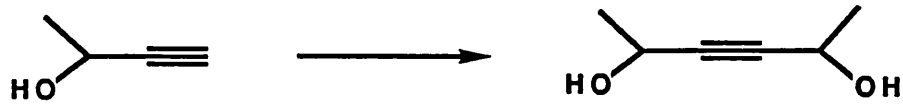
and it was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography on silica gel (15 g) eluting with 1:1 ether/petrol and ether gave the diol (271 mg, 43%) as an oil, δ($CDCl_3$): 4.51 (1H, brq, C<u>H</u>OH); 3.72 (2H, t, Hz, C<u>H</u>$_2$OH); 3.1 and 2.9 (2H, two brs, OH); 2.46 (2H, dt, 5 and 2 Hz, C<u>H</u>$_2$C<u>H</u>$_2$OH); 1.43 (3H, d, 7 Hz, Me); ν_{max}; 3335 (OH), 2920-3000 (CH), 2248 (w, C=C), 1073, 1046 cm^{-1} (C-O); m/z: 114 (M^+), 113 (M^+-H), 99 (M^+-Me), 43 (CH_3CO^+).

Preparation of Z-3-hexen-1,5-diol (**15**)



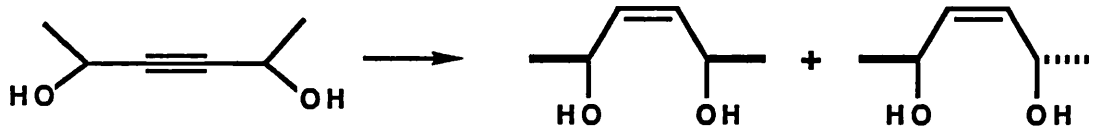
A slurry of Lindlar's catalyst (16 mg) in dry THF (6 ml) containing the alkyne (159 mg, 1.39 mmole) and quinoline (3 drops) was vigorously stirred under an atmosphere of hydrogen gas for three hours. The flask was flushed with argon and the catalyst was removed by filtration through talc. Evaporation of the solvent and flash chromatography of the residue on silica gel (6 g) eluting with 1:1 ether/petrol, 3:1 ether/petrol and ether gave the alkene (**13**) (113 mg, 70%) as an oil. δ($CDCl_3$): 5.63 (1H, ddt, 11, 8, 1 Hz, CH(OH)<u>C</u>H=); 5.48 (1H, dddd, 11, 9, 7 and 1 Hz, CH$_2$<u>C</u>H=); 4.6 (1H, ddq, 8 1 and 8Hz, CH$_3$C<u>H</u>(OH)); 3.73 (1H, ddd, 14, 7 and 7 Hz, C<u>H</u>(H)OH); 3.58 (1H, ddd, 14 Hz, 12 and 6 Hz, CH(<u>H</u>)OH); 2.6 (2H, brs, OH); 2.5 (1H, m, =CCH); 2.2 (1H, m, =CHC<u>H</u>); 1.25 (3H, d, 8 Hz, Me); m/z: 116 (M^+), 101 (M^+-Me), 98 (M^+-H_2O); ν_{max}: 3330 (OH), 2920-3010 (CH), 1653 cm^{-1} (C=C); found C 61.94%, H 10.54%, $C_6H_{12}O_2$ requires C 62.04%, H 10.41%.

Preparation of 3-hexyn-2,5-diol (**16**)



A solution of 1-butyn-3-ol (601 mg, 8.6 mmole) in THF (50 ml) under argon was cooled to -78°C and treated dropwise with *n*-butyl lithium (9.6 ml of a 2.5 M solution in hexanes 24 mmole) The mixture was stirred at -78°C for fifteen minutres and at -20 to -30°C for one hour. After recooling to -78°C, it was treated with acetaldehyde (0.7 ml, 12.9 mmole) and allowed to warm to room temperature. Saturated ammonium chloride and brine were added and it was extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography on silica gel (18 g) eluting with 1:1 ether/petrol and ether gave the diol (**16**) (691 mg, 71%) as a pale yellow oil. $\delta(CDCl_3)$: 4.55 (2H, q, 8 Hz, C<u>H</u>OH); 3.26 (2H, brs, OH); 1.43 (6H, two d, 8Hz, CH(OH)C<u>H</u>$_3$); ν_{max}: 3326 (br, OH), 2930-3000 cm^{-1} (CH); m/z: 114 (M^+), 99 (M^+-Me), 96 (M^+-H_2O), 43 (CH_3CO^+).

Preparation of *dl*- and *meso*- *Z*-3-hexen-2,5-diol (**17**) and (**18**)

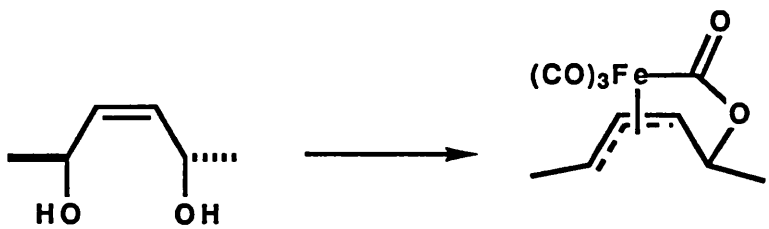


A slurry of Lindlar's catalyst (60 mg) in dry THF (20 ml) containing the alkyne (**16**) (516 mg, 4.53 mmole) and quinoline (0.8 ml) was vigorously stirred under an atmosphere of hydrogen gas for three hours. The flask was flushed with argon, the catalyst was removed by filtration through celite and the solvent was evaporated. Flash chromatography of the residue on silica gel (15 g) eluting with 1:1 ether/petrol and ether gave the diols (420 mg, 80%) as a viscous oil, ν_{max}: 3345 (O-H), 2920-3000 (C-H), 1095 (C-O); m/z: 101 (M^+-Me), 98 (M^+-H_2O), 83 (M^+-Me-H_2O), 43 (CH_3CO^+); found C 61.74%, H 10.50%, $C_6H_{12}O_2$ requires C 62.04%, H 10.41%.

The diols were taken up in dry dichloromethane (20 ml), cooled to 0°C and treated with camphor sulphonic acid (a few crystals) and 2,2-dimethoxypropane (350 µl, 2.9 mmole). After four hours, the mixture was warmed to room temperature and treated with anhydrous potassium carbonate. The solids were removed by filtration, the solution was concentrated and purified by flash chromatography on silica gel (10 g) eluting with 10% ether/petrol (bp 30-40°C) to give the volatile acetonide; and ether to give the *meso*-diol (**18**) (194 mg, 37%). δ($CDCl_3$): 5.5 (2H, dd, 5 and 2 Hz, C=CH); 4.68 (2H, m, CHOH); 2.5 (2H, brs, OH); 1.28 (6H, d, 4 Hz, Me).

The acetonide containing fractions were carefully concentrated, taken up in THF and treated with five drops of 1 M hydrochloric acid. After one hour, anhydrous potassium carbonate was added. The solids were removed by filtration and the solvent was evaporated to give the *dl*-diol (**17**) (192 mg, 37%) as a white solid. mp 92-94°C, δ($CDCl_3$): 5.47 (2H, dd, 5 and 2 Hz, C=CH); 4.68 (2H, m, CHOH); 2.05 (2H, brs, OH); 1.29 (6H, d, 4 Hz, Me).

Preparation 2-*exo*-5-*exo*-3-5-η^3-(2-formyloxyhex-4-en-3-ylato) tricarbonyliron (**24**)

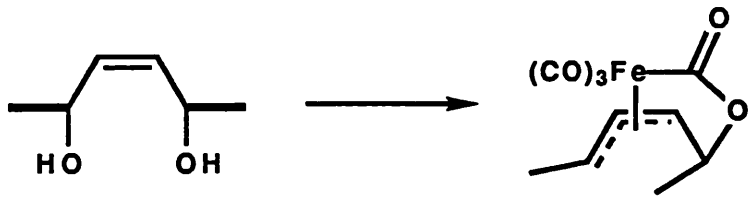


i) Treatment of the *dl*-diol (**17**) (57 mg, 0.49 mmole) with diiron nonacarbonyl (358 mg, 0.98 mmole) in THF (4 ml) according to procedure A and flash chromatography on silica gel (1.5 g) eluting with 5% and 30% ether/petrol gave the ferrilactone (**24**) (41 mg, 31%) as a white solid. δ(C_6D_6): 3.78 (1H, dd, 7 and 11 Hz, 3-H); 3.74 (1H, dq, 1.5 and 7 Hz, 1-H); 3.66 (1H, dq, 11 and 5 Hz, 4-H); 3.43 (1H,

dd, 7 and 1.5 Hz, 2-H); 1.14 (3H, d, 5 Hz, 4-Me); 0.98 (3H, d, 7 Hz, 1-Me), identical to the reported material.[5]

ii) Treatment of the *dl*-diol (**17**) (43 mg 0.37 mmole) with diiron nonacarbonyl (404 mg, 1.11 mmole) in benzene (3 ml) according to procedure B and purification as above gave the ferrilactone (**24**) (54 mg, 55%).

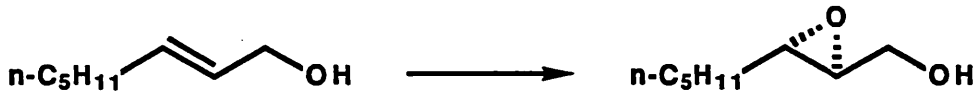
Preparation of 2-*endo*-5-*exo*-3-5-η^3-(2-formyloxyhex-4-en-3-ylato)tricarbonyliron (25)



i) Treatment of the *meso*-diol (**18**) (30mg, 0.25 mmole) with diiron nonacarbonyl (188 mg, 0.52 mmole) in THF (2 ml) according to procedure A and flash chromatography on silica gel (1 g) eluting with 5% and 25% ether/petrol gave the ferrilactone (**25**) (17 mg, 25%) as a white solid. $\delta(C_6D_6)$: 3.86 (1H, dq, 11 and 6 Hz, 4-H); 3.81 (1H, dq, 5 and 7 Hz, 1-H); 3.57 (1H, dd, 8 and 11 Hz, 3-H); 3.52 (1H, dd, 8 and 5 Hz, 2-H); 1.16 (3H, d, 6 Hz, 4-Me); 0.95 (3H, d, 7 Hz, 1-Me); identical to the reported material.[5]

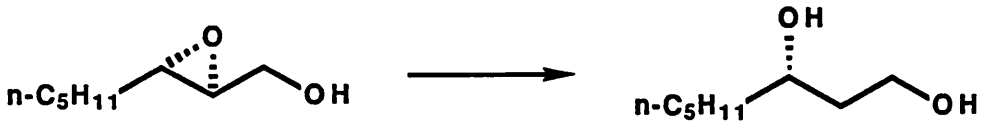
ii) Treatment of the *meso*-diol (**18**) (41 mg, 0.35 mmole) with diiron nonacarbonyl (386 mg, 1.06 mmole) in benzene (3 ml) according to procedure B and purification as above gave the ferrilactone (**25**) (4 mg, 4%).

Preparation of (S),(S)-2,3-epoxy-1-octanol (34)



Titanium tetraisopropoxide (115 µl, 0.39 mmole) was added slowly to a solution of (+)-diisopropyltartrate (90 µl, 0.43 mmole) in dichloromethane (5 ml) containing freshly activated crushed 4Å molecular sieves at -20°C under argon. The mixture was stirred at this temperature for thirty minutes. *t*-Butyl hydroperoxide (1.9 ml of a 3 M solution in isooctane, predried over molecular sieves, 5.81 mmole) was added dropwise. After stirring for ten minutes at -20°C, a solution of the alkenol (496 mg, 3.88 mmole) in dichloromethane (2 ml) was added. After stirring for three hours at -20°C, the mixture was allowed to warm to 0°C and poured into an ice-cold solution of ferrous sulphate and tartaric acid. The two phase mixture was stirred for ten minutes, filtered through celite and extracted with ether. The combined organic extracts were treated with 30% (w/v) sodium hydroxide solution and brine at 0°C for one hour and reextracted with ether. The organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (15 g), eluting with 30 and 50 % ether/petrol to give the epoxide (**34**) as a solid (514 mg, 92%). $\delta(CDCl_3)$: 3.9 (1H, m, 2-H); 3.85 (1H, m, 3-H); 2.91 (2H, m, 1-H_2); 2 (1H, brs, OH); 1.2-1.6 (10H, m, alkyl methylenes); 0.88 (3H, t, 6 Hz, Me); ν_{max}: 3125 (O-H), 2850-3000 cm^{-1} (C-H); m/z: 127 (M^+-OH), 113 (M^+-CH_2OH); identical to the reported material.[34]

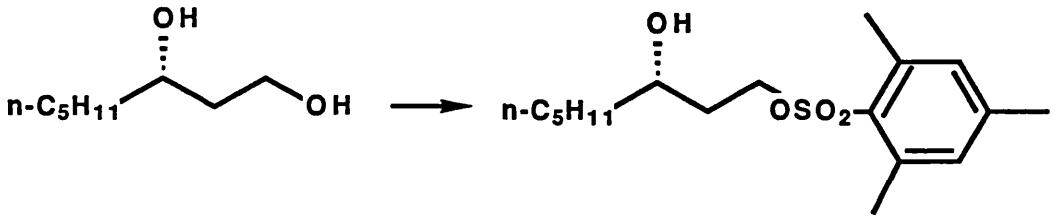
Preparation of (S)-Octene-1,3-diol (35)



Red-Al® (2.5 ml of a 3.4 M solution in toluene, 8.64 mmole) was added dropwise to a solution of the epoxy alcohol (**34**) (1.04 g, 7.2 mmole) in anhydrous

THF (25 ml) under argon at 0°C. After thirty minutes it was warmed to room temperature and stirred for fifteen hours. Water was added cautiously. When a thick jelly had formed, excess sodium bicarbonate was added and the mixture was stirred until a precipitate formed. This was removed by filtration and the solvents were evaporated to give the diol (**35**) (1.05 g, 99%). $\delta(CDCl_3)$: 3.8 (3H, m, 1-H_2, 3-H); 3.2, 3.05 (2H, two brs, OH); 1.2-1.8 (10H, m, CH,CH_2); 0.85 (3H, t, 6 Hz, Me); ν_{max}: 3300 (br, O-H), 2850-2950 cm^{-1} (C-H); m/z: 146 (M^+), 128 (M^+-H_2O); found C 65.63%, H 12.64%, $C_8H_{18}O_2$ requires C 65.71%, H 12.41%.

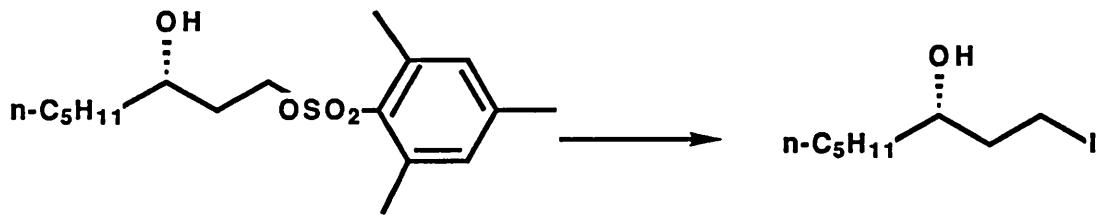
Preparation of (S)-3-hydroxy-1-mesitylenesulphonyloxyoctane (**36**)



Mesitylenesulphonyl chloride (360 mg, 1.64 mmole) was added to a solution of the diol (**35**) (200 mg, 1.37 mmole) in purified chloroform (2 ml) containing pyridine (220 µl, 1.37 mmole) at -20°C. The mixture was stirred for twenty hours, then poured into ether and washed with aqueous ammonium chloride and sodium bicarbonate solutions. The aqueous layers were reextracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (10 g) eluting with 20% ether/petrol gave (S)-1,3-dimesitylenesulphonyloxyoctane (85 mg, 12%), $\delta(CDCl_3)$: 7.98, 7.92 (4H, two s, aromatic H); 4.58 (1H, quin, 7 Hz, 3-H); 4.03 (1H, ddd, 7, 7 and 11 Hz, 1-H); 3.92 (1H, ddd, 7, 7 and 11 Hz, 1-H); 2.57, 2.59 (12H, two s *ortho*-Me); 2.32, 2.29 (6H, two s, *para*-Me); 1.98 (2H, ddd, 7,7 and 7 Hz, 2-H_2); 1.5 (2H, m, 4-H) 1.05-1.3 (6H, m, alkyl methylenes); 0.82 (3H, t, 7 Hz, CH_2Me); m/z: 510 (M^+), 200 ($ArSO_3H^+$), 183 ($ArSO_2^+$), 119 (Ar^+); and 1:1 ether/petrol to give the hydroxysulphonate (**36**) (217 mg, 48%) as an oil. $\delta(CDCl_3)$:

6.96 (2H, s, aromatic H); 4.16 (1H, ddd, 5, 9 and 10 Hz, 1-H); 4.03 (1H, ddd, 5, 6 and 10 Hz, 1-H); 3.7 (1H, m, 3-H); 2.6 (6H, s, *ortho*-Me); 2.3 (3H, s, *para*-Me); 2.05 (1H, brs, OH); 1.83 (1H, m, 1-H); 1.6 (1H, m, 1-H); 1.1-1.5 (8H, m, alkyl methylenes); 0.85 (3H, t, 7 Hz, CH_2Me); m/z: 328, (M^+), 310 (M^+-H_2O); 200 ($ArSO_3H^+$); 183 ($ArSO_2^+$); 119 (Ar^+).

Preparation of (S)-3-Iodo-1-octanol (37)



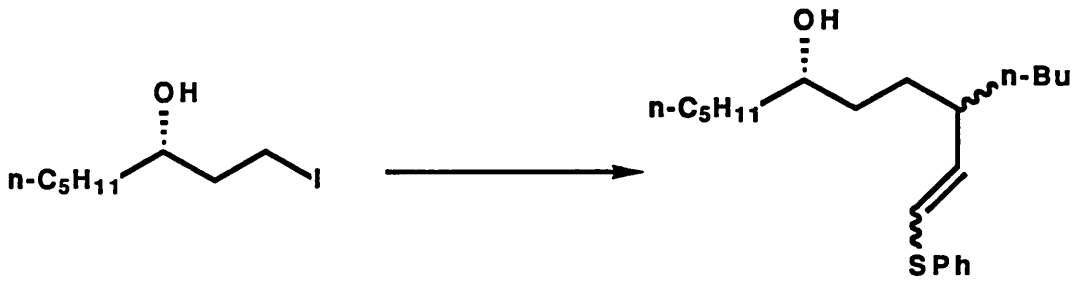
Sodium iodide (2 g, 13.3 mmole) was added to a solution of the hydroxysulphonate (**36**) (722 mg, 2.41 mmole) in dry acetone (5 ml) protected from light. After fifteen hours, the mixture was poured into water and extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated to give the iodide (**37**) (474 mg, 77%) as an unstable yellow oil. $\delta(CDCl_3)$: 3.73 (1H, m, 3-H); 3.3 (2H, m, CH_2I); 1.95 (2H, m, 2-H_2); 1.2-1.6 (9H, m, CH_2 and OH); 0.9 (3H, t, 7 Hz, Me); ν_{max}: 3340 (O-H); 2850-2930 cm^{-1} (C-H); m/z: 256 (M^+).

Preparation of *E*-2-heptenylphenylsulphide

tri-n-Butylphosphine (7.95 ml, 32 mmole) was added to a solution of *E*-hept-2-en-1-ol (3.64 g, 32 mmole) and diphenyldisulphide (6.79 g, 32 mmole) in THF (40 ml) under argon at 0°C. The mixture was stirred at this temperature for thirty minutes, warmed to room temperature and stirred overnight. The now dark mixture was poured into water and extracted with ether. The combined organic extracts were dried ($MgSO_4$)

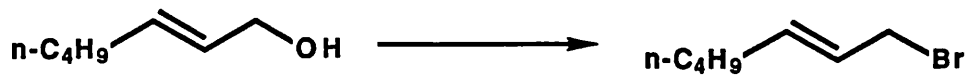
and evaporated to give an oil which was taken up in petrol and filtered through a pad of silica. Evaporation of the solvent and careful distillation of the residue gave the sulphide (1 g, 15%) as a yellow oil, bp 100°C, 1 mmHg; δ($CDCl_3$): 7.2-7.4 (5H, m, Ph); 5.45-5.55 (2H, m, vinylic H); 3.52 (2H, dd, 6 and 1 Hz, $C\underline{H}_2SPh$); 2.0 (2H, m, allylic CH_2); 1.2-1.4 (4H, m, alkyl methylene); 0.84 (3H, t, 7 Hz, Me) m/z: 206 (M^+), 110 ($PhSH^+$), 96 (M^+-PhSH), and some mixed fractions.

Preparation of 8-(S)-hydroxy-5-(2'-phenylthioethenyl)-tridecane



t-Butyllithium (860 µl of a 1.7 M solution in hexanes, 1.46 mmole) was added slowly to a solution of the sulphide (360 mg, 1.75 mmole) in anhydrous THF at -78°C under argon. The mixture was stirred at -30°C for thirty minutes; the iodide (149 mg, 0.58 mmole) in THF (1 ml) was added gradually over one hour. The mixture was allowed to warm to room temperature over three hours, poured into water and extracted with ether. The commbined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (10 g) eluting with 0-10% ether/petrol gave the hydroxy sulphide as an intractable mixture of isomers.

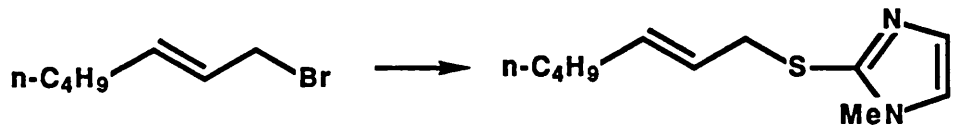
Preparation of *E*-1-bromo-2-heptene



Dimethylsulphide (4.41 ml, 60.1 mmole) was added slowly to a solution of N-bromosuccinimide (9.59 g, 55.1 mmole) in dichloromethane (250 ml) at 0°C under

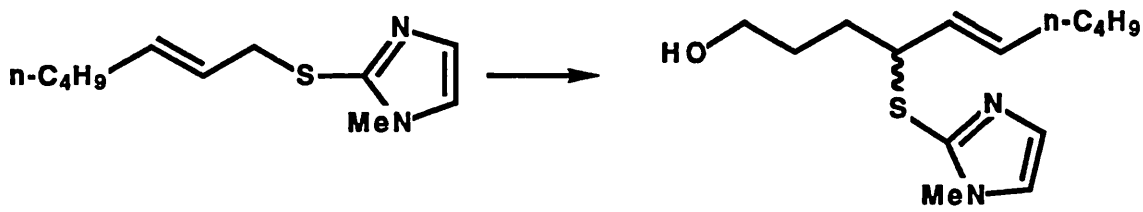
argon. The yellow mixture was cooled to -25°C and the alcohol (5.71 g, 50.09 mmole) was added. The mixture was allowed to warm to room temperature and stirred overnight, poured into ice-cold brine and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. The semi-solid residue was taken up in 1:1 ether/petrol (bp 30-40°C) and filtered through a pad of silica gel. Evaporation of the solvent gave the bromide (6.47 g, 73%) as a volatile oil. $\delta(CDCl_3)$: 5.6-5.85 (2H, m, vinylic H); 3.95 (2H, d, 7 Hz, CH_2Br); 2.1 (2H, m, 4-H); 0.8-1.4 (7H, m, alkyl H); ν_{max}: 2850-3000 (C-H), 1659 (C=C str), 965 cm^{-1} (C=C oop).

Preparation of 1-Methyl-2-thio-(*E*-2'-heptenyl)imidazole (39)



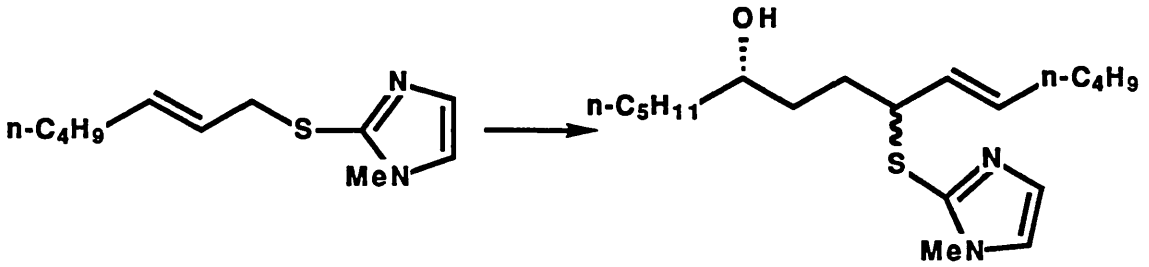
2-Mercapto-1-methylimidazole (169 mg, 1.48 mmole) was added from a solid addition tube to a stirred slurry of sodium hydride (65 mg of a 60% w/w suspension in mineral oil, 1.63 mmole, prewashed with dry petrol) in THF (1 ml) under argon. After fifteen minutes, a solution of the bromide (261 mg, 1.48 mmole) was added. The mixture was stirred for five minutes, then poured into water and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 g) eluting with 1:1 ether/petrol gave the sulphide (**39**) (235 mg, 76%) as an oil. bp 130°C, 0.3 mmHg, $\delta(CDCl_3)$: 7.05 (1H, m, HCNMe); 6.90 (1H, d, 1.2 Hz, HCN=CS); 5.5 (2H, m, vinylic H); 3.6 (5H, m, NMe and SCH_2); 1.9 (2H, m, 4-H); 1.2 (4H, m, alkyl methylenes): 0.85 (3H, t, 7 Hz, CH_2Me). ν_{max}: 2850-3000 (C-H), 1660 cm^{-1} (C=C); m/z: 210 (M^+), 114 ($ArSH^+$); found C 62.93%, H 8.60%, N 13.40%, $C_{11}H_{18}N_2S$ requires C 62.81%, H 8.63%, N 13.32%.

Preparation of 4-(2'-thio-1-methylimidazole)-5-decenol (40)



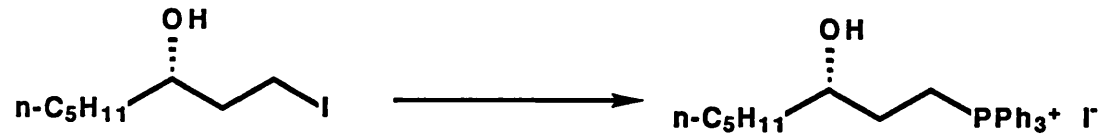
n-Butyllithium (321 µl of a 1.5 M solution in hexanes, 0.48 mmole) was added to a solution of the sulphide (101 mg, 0.48 mmole) in THF (1 ml) at -30°C under argon. The resulting orange-yellow solution was stirred at this temperature for twenty minutes, then cooled to -65°C. After ten minutes, trimethylene oxide (31 µl, 0.48 mmole) and boron trifluoride etherate (59 µl, 0.48 mmole) were added. The mixture was stirred for seven hours at -55°C, quenched with aqueous ammonium chloride solution, neutralised with sodium bicarbonate and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography on silica gel (5 g) eluting with 20% acetone/petrol gave the recovered sulphide (17 mg, 17%) and 50% acetone/petrol gave the hydroxysulphide (**40**) (46 mg, 36%) as an oil. $\delta(CDCl_3)$; 7.02 (1H, m, HCNMe); 6.95 (1H, d, 1 Hz, HCN=CS); 5.2-5.4 (2H, m, vinylic H); 3.5-4.0 (3H, m, CH_2O, CH_2S); 3.29 (3H, s, NMe); 1.8-2 (4H, m, 2-H_2, 7-H_2); 1.5-1.8 (2H, 3-H_2); 1.1-1.3 (4H, m, alkyl methylenes); 0.84 (3H, t, 6 Hz, CH_2Me); ν_{max}: 3270 (O-H), 1670 cm^{-1} (C=C); m/z: 268 (M^+), 251 (M^+-OH); 154 (M^+-ArSH); 114 (M^+-ArSH).

Preparation of 10-(S)-7-(N-methylthioimidazoyl)-5*E*-pentadecen-10-ol



n-Butyllithium (1.56 ml of a 1.5 M solution in hexanes, 2.3 mmole) was added to a solution of the sulphide (**40**) (531 mg, 2.53 mmole) in THF (6 ml) at -30°C under argon. The resulting orange-yellow solution was stirred at this temperature for twenty minutes, then cooled to -65°C. After ten minutes, the iodide (240 mg, 0.94 mmole) in THF (1 ml) was added. The mixture was stirred at -50°C for five hours, poured into saturated ammonium chloride solution, neutralised with sodium bicarbonate and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography on silica gel (15 g) eluting with 10% acetone/petrol gave the recovered sulphide (163 mg) and 15-50% acetone/petrol gave the hydroxysulphides (259 mg, 82%) as an oil. δ($CDCl_3$): 6.8-7.2 (2H, m, imidazole-H); 5.2-5.8 (2H, m, vinylic-H); 3-4 (5H, m, CHOH, NMe, CHS); 1.1-2.1 (18H, m, alkyl methylene); 0.85 (6H, m, CH_2Me).

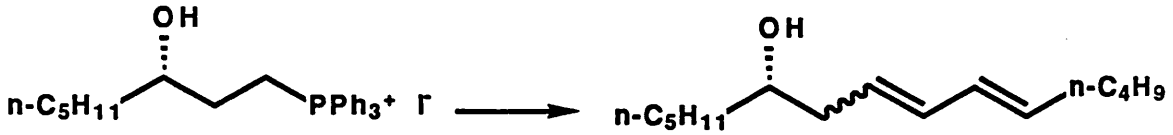
Preparation of (S)-3-hydroxyoctyltriphenylphosphonium iodide (**41**)



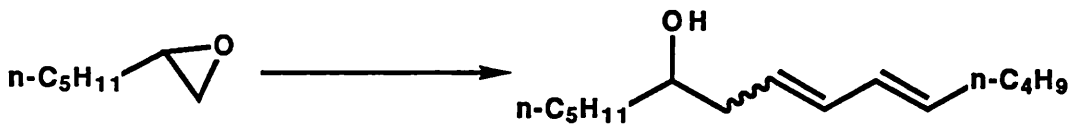
A solution of the iodide (**32**) (43 mg, 0.168 mmole) and triphenylphosphine (44 mg, 0.168 mmole) in toluene (1 ml) was heated at 100°C with the exclusion of moisture for seventy two hours. The mixture was allowed to cool to room temperature and the supernatant toluene was removed by pippette. The residual thick oil was washed with petrol and dried *in vacuo* to give the crude phosphonium salt (**41**) as a

hygroscopic foam. $\delta(CDCl_3)$: 7.6-8.1 (15H, Ph); 3.5-4.1 (3H, m, 3-H, 1-H); 1.1-1.8 (10H, m, 2-H_2); 0.8 (3H, t, 7 Hz).

Preparation of *E,E* and *E,Z* -(S)-pentadeca-5,7-dien-10-ol (42)



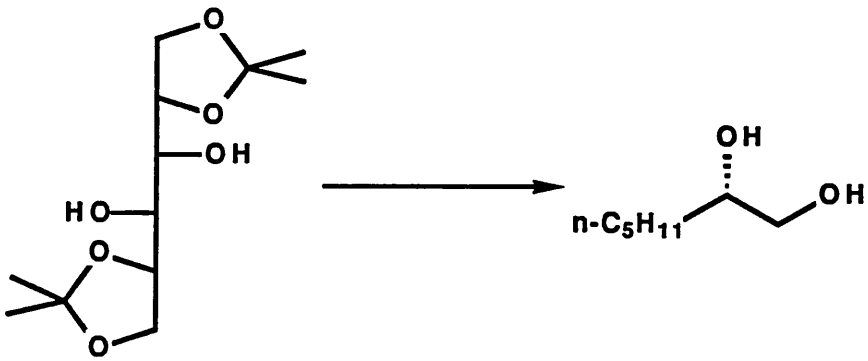
i) n-Butyllithium (446 µl of a 2.5 M solution in hexanes, 1.12 mmole) was added to a solution of the phosphonium salt (**41**) (286 mg, 0.56 mmole) and lithium bromide (145 mg, 1.67 mmole) in THF (5 ml) at 0°C under argon to give a deep red solution. The mixture was stirred for thirty minutes, then cooled to -50°C. The aldehyde (73 µl, 0.56 mmole) was added and the mixture was allowed to warm to room temperature over five hours, poured into aqueous ammonium chloride solution and extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography on silica gel (15 g) eluting with 5% ether/petrol gave the dienol (**42**) (20 mg, 14%) as an oil.



ii) *n*-Butyllithium (446 µl of a 2.5 M solution in hexanes, 1.12 mmole) was added to a solution of methyltriphenylphosphonium bromide (109 mg, 0.31 mmole) and lithium bromide (133 mg, 1.5 mmole) in THF (2 ml) at 0°C under argon. After one hour, 1,2-epoxyheptane (42 µl, 0.31 mmole) was added and the mixture was stirred until tlc showed that the epoxide was consumed (R_f = 0.77 (1:1 ether/petrol/silica gel) - about two hours) A further equivalent of *n*-butyl lithium was added to give a deep red solution. After stirring for three hours, the mixture was cooled to -60°C and the aldehyde (40 µl, 0.31 mmole) was added. The reaction was continued and worked up as before to give the dienol (**42**) (10 mg, 14%) as an oil. $\delta(CDCl_3)$: *E,E* isomer: 6.2-

5.95 (2H, m, 6- and 7-H), 5.63 (1H, ddd, 14, 8 and 8 Hz, 5-H); 5.55 (1H, ddd, 14, 8, 8 Hz, 8-H); *E,Z* isomer: 6.31 (1H, dd, 15 and 11 Hz, 6-H); 6.13 (1H, dd, 10 and 11 Hz, 7-H); 5.72 (1H, ddd, 15, 7 and 7 Hz, 5-H); 5.34 (1H, ddd, 10, 8 and 8 Hz, 8-H); both isomers: 3.63 (1H, m, 10-H); 2-2.4 (4H, m, allylic H); 1.2-1.6 (13H, m, methylene and OH); 0.9 (6H, m, two Me); m/z 224 (M^+), 223 (M^+-H), 154 (M^+-pentene).

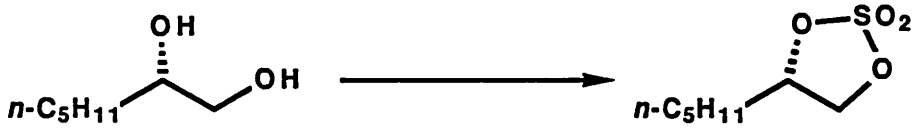
Preparation of (S)-heptane-1,2-diol (43)



Lead tetraacetate (2.77 g, 6.26 mmole) was added portionwise from a solid addition tube to a suspension of 1,2,5,6-di-*O*-isopropylidene-D-mannitol (1.64 g, 6.26 mmole) in sodium dried benzene (50 ml). After stirring for twenty minutes, the white precipitate was removed by filtration through celite, washing with ether. The filtrate was carefully concentrated, filtered again through celite and again carefully concentrated. The residue was distilled (Kugelrohr, 80°C, water pump) to give the crude aldehyde. This was taken up in dry THF (3 ml) and added to a solution of butylidenetriphenylphosphorane (generated by adding *n*-butyllithium (5 ml of a 2.5 M solution in hexanes, 12.5 mmole) to a suspension of butyltriphenylphosphonium bromide (5 g, 12.5 mmole) in THF (40 ml) at 0°C under argon). The mixture was stirred at room temperature for six hours, then treated with a few drops of aqueous ammonium chloride and diluted with petrol (bp 30-40°C). The heterogenous mixture

was filtered through celite; the filtrate was evaporated and taken up in petrol (bp 30-40°C), filtered through celite again, concentrated and distilled (Kugelrohr, 100°C, water pump) to give a clear oil. This was taken up in methanol (5 ml) and added to a suspension of platinum oxide (20 mg, 0.09 mmole) in methanol (5 ml) under hydrogen (1 atm). The mixture was stirred overnight, flushed with argon and filtered through celite. Aqueous hydrochloric acid (2 ml of a 3 M solution) was added to the filtrate. The mixture was stirred for three hours, poured into sodium bicarbonate solution, treated with brine and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated to give the diol (**43**) (342 mg, 21%) as an oil. $\delta(CDCl_3)$: 3.7 (1H, m, 2-H); 3.65 (1H, dd, 11 and 3 Hz, 1-H); 3.42 (1H, dd, 11 and 7.5 Hz, 1-H), 2.25 (2H, brs, OH); 1.2-1.5 (8H, m, $-CH_2-$); 0.9 (3H, t, 7 Hz, CH_3); ν_{max}: 3371 (O-H), 2870-2950 (C-H), 1070 cm^{-1} (C-O); m/z: 132 (M^+), 131 (M^+-H), 114 (M^+-H_2O), 101 (M^+-CH_2OH); identical to the reported material.[42]

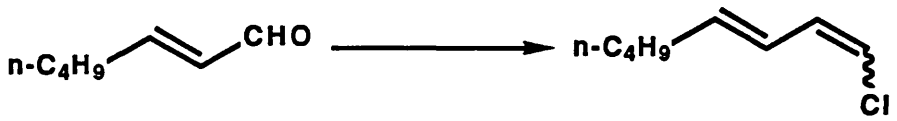
Preparation of (S)-1,2-heptanediol cyclic sulphate (**45**)



Thionyl chloride (5.6 ml, 77 mmole) was added to a solution of the diol (6.74 g, 51.06 mmole) in dry carbon tetrachloride (50 ml). The solution was heated at reflux for thirty minutes. By tlc, the diol (R_f = 0.31 ether/silica gel) was converted into a new compound, the cyclic sulphite, (R_f = 0.82 (ether/silica gel); 0.67 (1:1 ether/petrol/silica gel)). The mixture was cooled to 0°C and treated cautiously and sequentially with aqueous acetonitrile (50 ml in 75 ml of water), ruthenium trichloride trihydrate (62 mg, 0.3 mmole) and sodium periodate (22 g, 102 mmole). The black mixture was stirred and gradually turned green, then yellow, when tlc showed conversion of the sulphite to a new compound (R_f = 0.35 (1:1 ether/petrol/silica gel)). The mixture was poured into

water and extracted twice with ether. The combined organic layers were washed with saturated sodium bicarb onate solution and dried ($MgSO_4$) in the presence of talc. Evaporation of the solvent and distillation of the residue gave the cyclic sulphate (**45**) (6.81 g, 69%) as an oil, bp 130°C, 10 mmHg; δ($CDCl_3$): 4.97 (1H, ddt, 6 , 4.5 and 8.5 Hz, 2-H); 4.71 (1H, dd, 8.5 and 6 Hz, 1-H); 4.34 (1H, dd, 8.5 and 8.5 Hz, 1-H); 1.95 (1H, m, 3-H); 1.75 (1H, m, 3-H); 1.3-1.6 (6H, m, 4-, 5-, 6-H); 0.9 (3H, t, 7 Hz, Me); ν_{max}: 2933, 2866 (C-H), 1465 (C-O), 1390, 1210 (S=O str), 849 cm^{-1} (S-O); m/z: 165 (M^+-Et), 137 (M^+-n-Bu), 123 (M^+-C_5H_{11}), 96 (SO_4^+); found C 43.60%, H 7.37%, C $_7H_{14}SO_4$ requires C 43.28 %, H 7.26%; $[a]_D^{29}$ = -18.6° (neat).

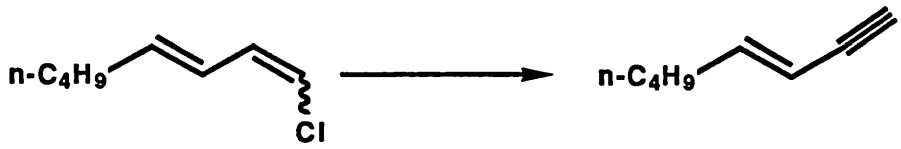
Preparation of *E,E* and *Z,E*-1-chlorooctadiene



n-Butyllithium (4.73 µl of a 2.5 M solution in hexanes, 11.8 mmole) was added dropwise to a suspension of chloromethyltriphenylphosphonium chloride (4.11 g, 11.8 mmole) in THF (40 ml) at -78°C under argon. The deep red solution was stirred for thirty minutes at -78°C. The aldehyde (515 µl, 3.94 mmole) was added and the mixture was allowed to warm to 0°C, stirred for one hour, warmed to room temperature and stirred for a further thirty minutes. The excess ylid was quenched with water, the mixture was diluted with petrol and filtered through silica, washing with 10% ether/petrol (bp 30-40°C). The solvents were evaporated and the semi-solid residue was slurried with petrol (bp 30-40°C) and filtered through celite. The petrol was evaporated and the residue was purified by flash chromatography on silica gel (12 g) eluting with petrol (bp 30-40°C) to give the chlorodienes (370 mg, 65%) as an oil. δ($CDCl_3$): *Z,E* isomer: 6.45 (1H, dd, 13 and 11 Hz, 3-H); 6.25 (1H, dd, 10 and 7 Hz, 2-H); 5.88 (1H, d, 7 Hz, 1-H); 5.88 (1H, dt, 16 and 7Hz, 4-H); 2.0-2.22 (2H,

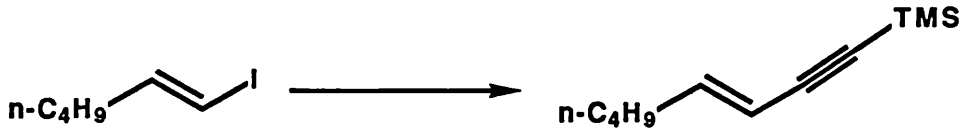
m, allylic CH_2); 1.2-1.5 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$); 0.9 (3H, t, 7 Hz, CH_3); *E,E* isomer: 6.42 (1H, dd, 13 and 11 Hz, 2-H); 6.08 (1H, d, 13 Hz, 1-H); 5.98 (1H, dd, 15 and 11 Hz, 3-H); 5.70 (1H, dt, 15 and 7 Hz, 4-H); 2.0-2 2 (2H, m, allylic CH_2); 1.2-1.5 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$); 0.9 (3H, t, 7 Hz, CH_3). ν_{max}: 2850-2950 (C-H), 1696, 1646 cm^{-1} (C=C).

Preparation of *E*-oct-3-ene-1-yne (47)



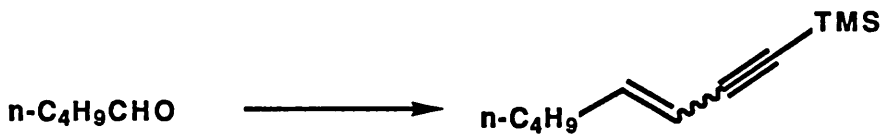
Methyllithium (10 ml of a 1.4 M solution in ether, 14 mmole) was added to a solution of the chlorodiene (370 mg, 2.55 mmole) in ether. After 36 hours, water was cautiously added, followed by ammonium chloride solution. The mixture was extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was taken up in petrol (bp 30-40°C) and filtered through a pad of silica gel. Evaporation of the solvent gave the volatile acetylene (**47**) (245 mg, 89%) as a yellow oil. $\delta(CDCl_3)$: 6.25 (1H, dt, 16 and 7 Hz, 4-H); 5.45 (1H, dm, 16 Hz, 3-H); 2.77 (1H, d, 2 Hz, 1-H); 2.2 (2H, m, allylic CH_2); 1.2-1.5 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$); 0.9 (3H, t, 7 Hz, CH_3); ν_{max}: 3311 (alkynyl C-H), 2850-2960 (CH), 2105 (C≡C), 1628 cm^{-1} (C=C); m/z: 108 (M^+), 93 (M^+-Me), 79 (M^+-Et), 65 (M^+-*n*-Pr).

Preparation of *E*-1-Trimethylsilyl-3-octene-1-yne (49)



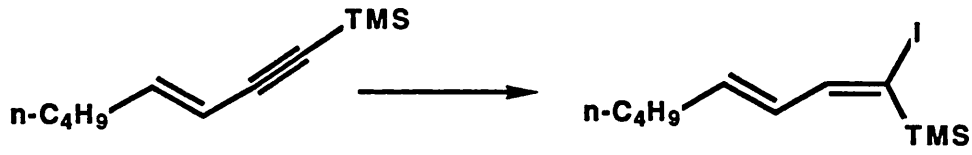
i) Anhydrous copper (I) iodide (2.06 g, 10.8 mmole) and tetrakis(triphenyl-phosphine)palladium (0) (3.13 g, 2.7 mmole) were added from a solid addition tube to

a solution of *E*-1-iodo-1-hexene (11.37 g, 54 mmole), trimethylsilylacetyene (7.6 ml, 54 mmole) and *n*-butylamine (8 ml, 81.2 mmole) in dry benzene (300 ml) under argon with the exclusion of light. After stirring for four hours, the mixture was poured into water and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. The solvent was evaporated and the reidue was distilled in a Kugelrohr apparatus (100°C, 0.15 mmHg) to give the silylacetylene (**49**) (763 mg, 76%) as a yellow oil. δ($CDCl_3$): 6.23 (1H, dt, 16 and 7 Hz, 4-H); 5.50 (1H, dt, 16 and 1.6 Hz, 3-H); 2.1 (2H, m, allylic CH_2); 1.2-1.4 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$); 0.9 (3H, t, 7 Hz, $CH_2C\underline{H}_3$); 0.18 (9H, s, $SiMe_3$); ν_{max}: 2900-3000 (CH), 2137 (C≡C), 1710 cm^{-1} (C=C); m/z: 180 (M^+), 165 (M^+-Me), 73 (Me_3Si^+), found C 73.16%, H 11.03%, $C_{11}H_{20}Si$ requires C 72.84%, H 11.67%.



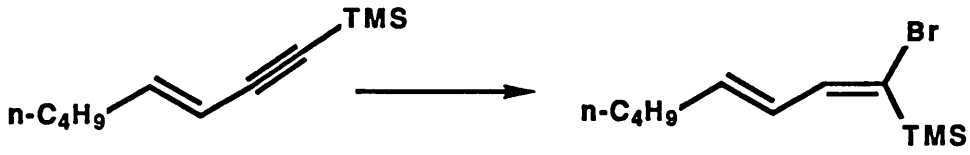
ii) *n*-Butyllithium (407 μl of a 1.6 M solution in hexanes, 0.65 mmole) was added to a suspension of (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide (295 mg, 0.65 mmole) in THF (4 ml) at -78°C. The mixture was stirred at -40°C for thirty minutes and recooled to -78°C. Pentanal (46 μl, 0.43 mmole) was added. The mixture was stirred at -78°C for five minutes, warmed to 0°C, stirred for one hour and quenched with one drop of aqueous ammonium chloride solution. The mixture was diluted with petrol and filtered through a pad of florisil. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (2 g) eluting with petrol (bp 30-40°C) to give the mixture of isomeric silyl acetylenes (**49**) (43 mg, 56%) as a yellow oil. δ($CDCl_3$): (*Z*-isomer): 5.93 (1H, dt, 11 and 8 Hz, 4-H); 5.46 (1H, dt, 11 and 1.5 Hz, 3-H); 2.1 (2H, m, allylic CH_2); 1.2-1.4 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$); 0.9 (3H, t, 7 Hz, CH_2CH_3); 0.18 (9H, s, $SiMe_3$).

Preparation of Z-1-iodo-1-trimethylsilylocta-1,3-diene (51)



DIBAL (825 µl of a 1 M solution in hexanes, 0.825 mmole) was added to a solution of the silyl acetylene (99 mg, 0.55 mmole) in anhydrous ether (2 ml). The mixture was refluxed under argon for one hour and cooled to -78°C. A solution of iodine (237 mg, 0.94 mmole) in ether (1.5 ml) was added slowly. The mixture was stirred for one hour at -78°C with the exclusion of light, then quenched with 5% w/v aqueous sodium thiosulphate solution and allowed to warm to room temperature. When a thick jelly formed, solid sodium bicarbonate was added. When a precipitate had formed, the solids were removed by filtration. The solvents were evaporated, the residue was taken up in petrol (bp 30-40°C) and filtered through silica. Evaporation of the petrol gave the Z-iodosilane (**51**) as a light sensitive yellow oil which isomerised on standing. $\delta(CDCl_3)$: 7.64 (1H, d, 11 Hz, 2-H); 6.16 (1H, ddt, 15, 11 and 1.5 Hz, 3-H); 5.75 (1H, dt, 15 and 7 Hz, 4-H); 2.0 -2.1 (2H, m, 5-H); 1.2-1.4 (4H, m, 6,7-H); 0.9 (3H, t, 7 Hz, CMe); 0.3 (9H, s, $SiMe_3$); ν_{max}: 2850-2950 (C-H), 1629 (C=C), 841, 758 cm^{-1}; (Si-Me γ); m/z: 308 (M^+), 293 (M^+-Me), 252 (M^+-C_4H_8), 73 ($SiMe_3^+$).

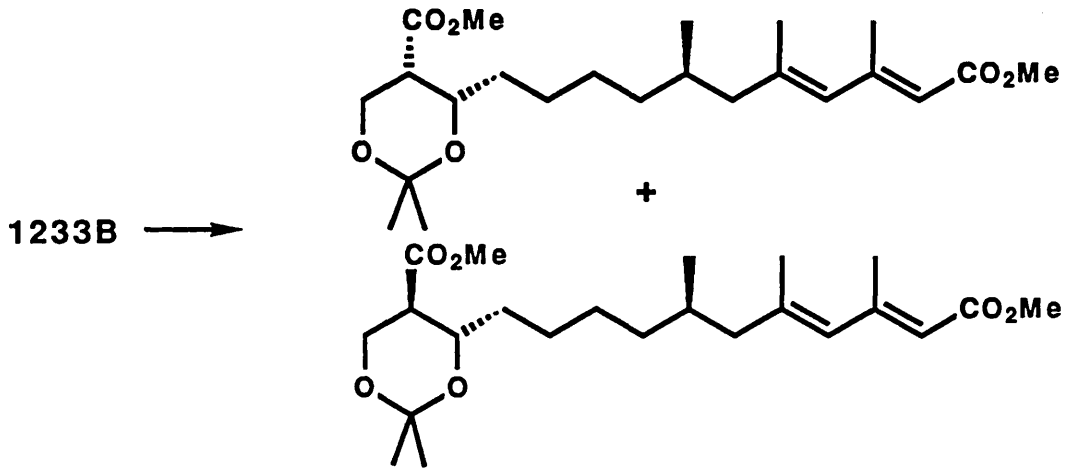
Preparation of Z-1-bromo-1-trimethylsilylocta-1,3-diene (53)



DIBAL (2.32 ml of a 1 M solution in hexanes, 2.32 mmole) was added to a solution of the silyl acetylene (261 mg, 1.45 mmole) in anhydrous ether (2 ml). The mixture was refluxed under argon for one hour and cooled to -5°C and treated with a

solution of cyanogen bromide (277 mg, 2.61 mmole) in ether (4 ml). The mixture was stirred at -5°C for thirty minutes, at room temperature for three hours, then quenched with water and allowed to warm to room temperature. When a thick jelly formed, solid sodium bicarbonate was added. When a precipitate had formed, the solids were removed by filtration. The solvents were evaporated, the residue was taken up in petrol (bp 30-40°C) and filtered through silica. Evaporation of the petrol gave the Z-bromosilane (**53**) (305 mg, 68%) as a yellow oil, $\delta(CDCl_3)$: 7.25 (1H, d, 11 Hz, 2-H); 6.16 (1H, dd, 14 and 11 Hz, 3-H); 5.75 (1H, dt, 14 and 7 Hz, 4-H); 2.0 -2.1 (2H, m, 5-H); 1.2-1.4 (4H, m, 6-, 7-H); 0.9 (3H, t, 6 Hz, $CH_2\underline{Me}$); 0.29 (9H, s, $SiMe_3$); ν_{max}: 2870-2960 (C-H), 1699, 1633 (C=C), 843, 759 cm^{-1} (Si-Me γ); m/z: 262/ 260 (M^+), 206/ 204 (M^+-C_4H_8), 191/ 189 (M^+-$SiMe_3$), 139/ 137 (Me_2SiBr^+), 73 ($SiMe_3^+$) ; containing some *E,Z*-diene (**50a**) (about 16%).

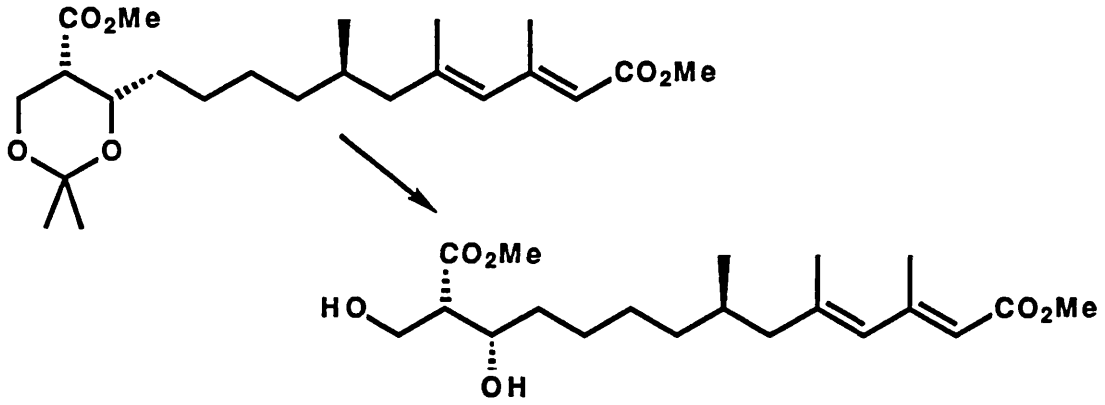
Preparation of Methyl (7R,12S,13R)-*E,E*-11-(5',6'-*trans*-5'-methoxycarbonyl-2,2-dimethyl-1,3-dioxa-6'-cyclohexanyl)-3,5,7-trimethylundeca-2,4-dienoate (58) and Methyl (7R,12S,13S)-*E,E*-11-(5',6'-*cis*-5'-methoxycarbonyl-2,2-dimethyl-1,3-dioxa-6'-cyclohexanyl)-3,5,7-trimethyl-undeca-2,4-dienoate (59)



Diazomethane (generated from diazald® (1.4 g) and potassium hydroxide (2.1 ml of a 180 mg/ml aqueous solution) in ethanol (20 ml)) was carried on a stream of argon into a well stirred suspension of 1233B (152 mg, 0.44 mmole) in ether (10 ml). When all the diazomethane had reacted or decomposed, the bulk of the ether was removed by a stream of argon. The residue was diluted with dichloromethane and treated with 2,2-dimethoxypropane (3 ml) and a trace of camphorsulphonic acid. After four hours, the mixture was poured into aqueous sodium bicarbonate and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (8 g) eluting with 10-30% ether/petrol to give the *trans* acetonide (58) (62 mg, 33%) as an oil, $\delta(CDCl_3)$: 5.68 (1H, m, 4-H); 5.65 (1H, m, 2-H); 3.71-4.00 (3H, m, 4'- and 6'-H); 3.69 (3H, s, OMe); 3.67 (3H, s, OMe); 2.58 (1H, ddd, 10, 10 and 6 Hz, 5'-H); 2.22 (3H, d, 1,2 Hz, 3-Me); 2.0-2.1 (2H, m, 6-H); 1.78 (3H, d, 1.5 Hz, 5-Me); 0.8-1.5 (12H, m); ν_{max}: 2850-2950 (C-H); 1733 (C=O of saturated ester), 1716 (C=O of saturated ester), 1623, 1600 (C=C),

1153 cm^{-1} (C-O str), m/z: 410 (M^+), 395 (M^+-Me), 363 (M^+-Me_2CHO), 139 ($CH_3CH=CHC(CH_3)CHCO_2CH_3^+$). Found C 67.27%, H 9.41%; $C_{23}H_{38}O_6$ requires C 67.3%, H 9.33%; and the *cis* acetonide (**59**) (75 mg, 41%) as an oil, δ($CDCl_3$): 5.68 (1H, m, 4-H); 5.65 (1H, m, 2-H); 4.13 (1H, dd, 12 and 3 Hz, 4'-H); 4.08 (1H, dd, 12 and 4 Hz, 4'-H); 3.98 (1H, ddd, 8, 5 and 3 Hz, 6'-H); 3.72 (3H, s, OMe); 3.69 (3H, s, OMe); 2.45 (1H, ddd, 4, 3 and 3 Hz, 5'-H); 2.22 (3H, d, 1 Hz, 3-Me); 2.07 (2H, m, 11-H); 1.80 (2H, m, 6-H); 1.78 (3H, d, 1 Hz, 5-Me); 1-1.7 (7H, m, alkyl H), 0.8 (3H, d, 7 Hz, 7-Me); ν_{max}: 2850-2950 (C-H); 1740 (C=O of saturated ester), 1714 (C=O of saturated ester), 1623, 1600 (C=C), 1153 cm^{-1} (C-O str), m/z: 410 (M^+), 395 (M^+-Me), 363 (M^+-Me_2CHO), 139 ($CH_3CH=CHC(CH_3)CHCO_2$-CH_3^+); Found C 67.70%, H 9.47%; $C_{23}H_{38}O_6$ requires C 67.3%, H 9.33%.

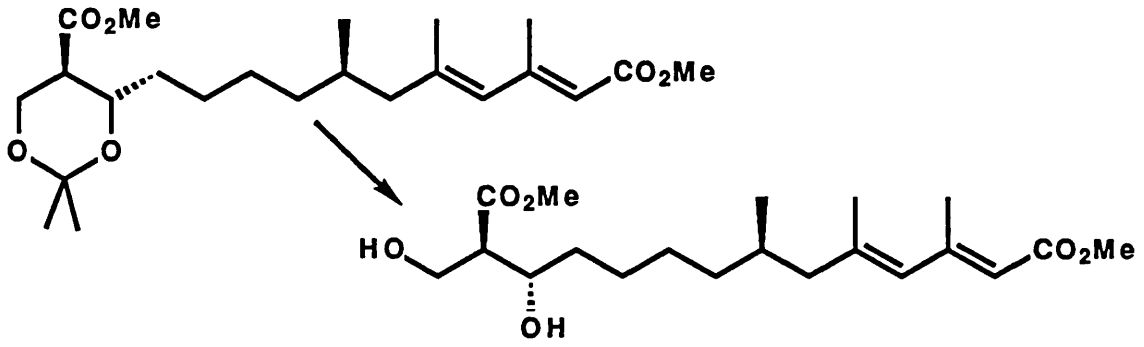
Preparation of Dimethyl (7R,12S,13S)-*E,E*-12-Hydroxy-13-hydroxymethyl-3,5,7-trimethyl-2,4-tetradecatrien-1,14-dioate (60)



The *cis* acetonide (59) (23.8 mg, 0.06 mmole) was dissolved in THF (0.5 ml) and treated with hydrochloric acid (1 ml of a 1.5 M aqueous solution). The mixture was stirred for ninety minutes, poured into sodium bicarbonate solution and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and evaporated to give the diol (60) (19 mg, 88%) as an oil. δ($CDCl_3$): 5.68 (1H, m, 4-H); 5.65 (1H, m, 2-H); 4.015 (1H, dd, 11 and 5 Hz, 14-H); 3.95 (1H, dd, 11 and 6 Hz, 14-H); 3.93 (1H, dt,

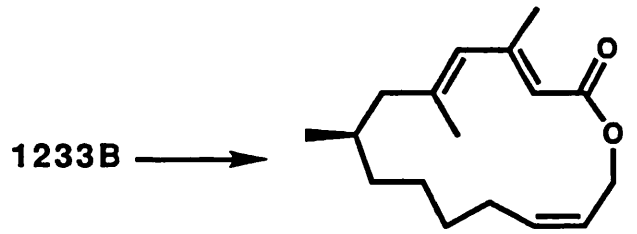
9 and 4.5 Hz, 12-H); 3.76 (3H, s, OMe); 3.71 (3H, s, OMe); 2.66 (1H, ddd, 6, 5 and 4.5 Hz, 13-H); 2.24 (3H, d, 1 Hz, 3-Me); 2.08 (1H, ddd, 13, 6 and 1 Hz, 6-H); 1.83 m(1H, dd, 13 and 7 Hz, 6-H); 1.80 (3H, d, 1 Hz, 5-Me); 1.2-1.6 (8H, m, 8-11-H); 1.1 (1H, m, 7-H); 0.81(3H, d, 6 Hz, 7-Me); ν_{max}: 3434 (O-H), 2850-2950 (C-H), 1713 (C=O), 1621 (C=C), 1155 cm^{-1} (C-O); m/z: 370 (M^+), 355 (M^+-Me), 338 (M^+-MeOH), found C 64.54%, H 9.34%, $C_{20}H_{34}O_6$ requires C 64.84%, H 9.25%.

Preparation of Dimethyl (7R,12S,13R)-*E,E*-12-Hydroxy-13-hydroxymethyl-3,5,7-trimethyl-2,4-tetradecatrien-1,14-dioate (**61**)



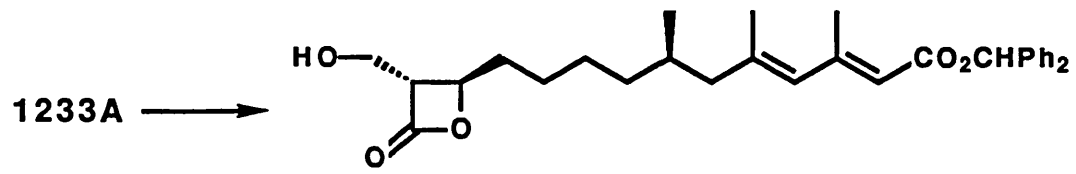
The *trans* acetonide (**58**) (9.3 mg, 0.019 mmole) was dissolved in THF (0.25 ml) and treated with hydrochloric acid (0.5 ml of a 1.5 M aqueous solution). The mixture was stirred for seven hours, poured into sodium bicarbonate solution and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and evaporated to give the diol (**61**) (8 mg, 90%) as an oil. $\delta(CDCl_3)$: 5.68 (1H, m, 4-H); 5.65 (1H, m, 2-H); 4.15 (2H, m, 14-H); 4.05 (1H, m, 12-H); 3.76 (3H, s, OMe); 3.70 (3H, s, OMe); 2.8 (1H, m, 13-H); 2.23 (3H, d, 1 Hz, 3-Me); 2.08 (1H, ddd, 13, 6 and 1 Hz, 6-H); 1.83 (1H, dd, 13 and 8 Hz, 6-H); 1.80 (3H, d, 1 Hz, 5-Me); 1.2-1.6 (8H, m, 8-11-H); 1.1 (1H, m, 7-H); 0.81 (3H, d, 6 Hz, 7-Me); otherwise identical to compound (**60**).

Preparation of (8R)-*E,E,Z*-4,6,9-Trimethyl-1-oxa-2-oxo-cyclopentadeca-3,5-13-triene (62)



Diethylazodicarboxylate (30 µl, 0.193 mmole) was added to a vigorously stirred solution of 1233B (33 mg, 0.096 mmole) and triphenylphosphine (51 mg, 0.193 mmole) in dry benzene (2.5 ml). The mixture was stirred for four days, applied directly to the top of a column of silica gel (5 g) and purified by flash chromatography eluting with 10% ether/petrol to give the macrolide (**62**) (7 mg, 28%) as an oil. $\delta(CDCl_3)$: 5.72 (1H, m, 5-H); 5.69 (1H, m, 3-H); 5.66 (1H, dt, 5 and 4 Hz, 14-H); 5.57 (1H, m, 13-H); 4.09 (2H, d, 4 Hz, 15-H); 2.22 (3H, d, 1 Hz, 4-Me); 2-2.18 (4H, m, 12-H and 7-H); 1.8 (3H, d, 1 Hz, 6-Me); 1.2-1.6 (8H, m, 6-,8-,9-,11-H); 1.1 (1H, m, 8-H); 0.82 (3H, d, 6 Hz, 8-Me); ν_{max} (CH_2Cl_2): 2850-3000 (C-H), 1702 (C=O), 1617 cm^{-1} (C=C); m/z: 262 (M^+), 183 ($C_{11}H_{19}O_2^+$).

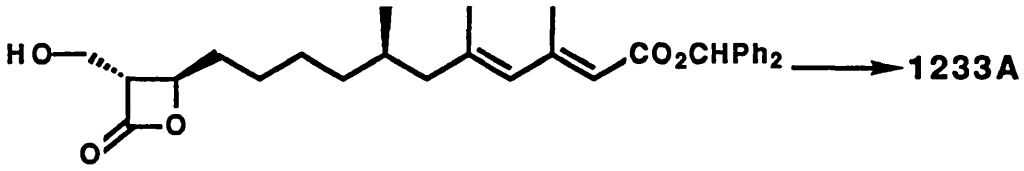
Preparation of Diphenylmethyl (2'R,3'R,7R)-*E,E*-(3'-hydroxymethyl-4'-oxo-2'-oxetanyl)-3,5,7-trimethylundeca-2,4-dienoate (68)



1233A (43.4 mg, 0.134 mmole) was added to a solution of diphenyldiazomethane in benzene (1 ml, sodium dried). The mixture was heated at 70°C until all the 1233A was consumed by tlc (about twenty minutes), cooled and applied directly to the top of a column of silica gel (4 g). Flash chromatography, eluting with 10-50%

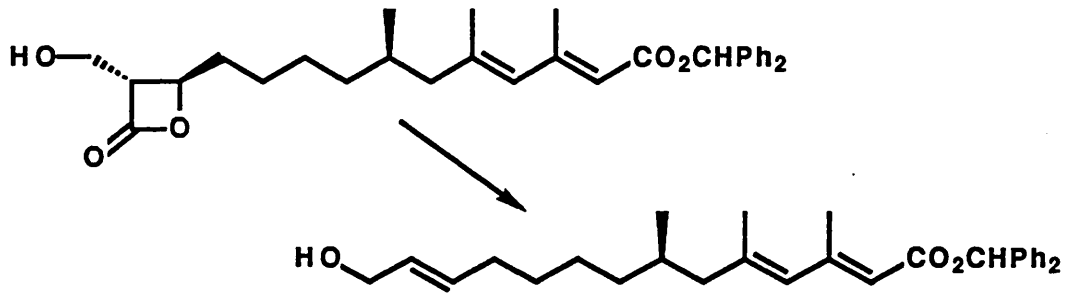
ether/petrol gave the ester (**68**) (56.2 mg, 86%) as an oil. $\delta(CDCl_3)$: 7.3 (10H, m, Ph); 6.92 (1H, s, $Ph_2C\underline{H}$); 5.8 (1H, m, 4-H); 5.7 (1H, m, 2-H); 4.58 (1H, ddd, 4, 6, and 7 Hz, 2'-H); 4.04 (1H, m, HOC<u>H</u>(H)); 3.87 (1H, m, HOCH(<u>H</u>)); 3.4 (1H, ddd, 5,5 and 5 Hz, 3'-H); 2.22 (3H, d, 1 Hz, 3-Me); 2.1 (1H, dd, 13 and 6 Hz, 6-H); 1.9 (1H, m, 6-H); 1.8 (3H, d, 1 Hz, 5-Me); 1.2-1.6 (8H, m, $-CH_2-$); 1.1 (1H, m, 7-H); 0.83 (3H, d, 7 Hz, 7-Me); $\delta(^{13}C)$: 169.86 (14'); 166.12 (1); 155.52 (3); 141.66 (5); 140.68 (*ipso*-C); 129.61 (2); 127.20, 127.79, 128.51 (*o,m,p*,-C); 117.22 (4); 76.22 ($C\underline{H}Ph_2$); 75.07(2'); 58.68 (3'); 58.13 (2'); 49.07 (6); 25.26, 26.68, 30.97, 34.08, 36.67 (7-11 inclusive); 19.92 (3-Me); 19.44 (7-Me); 18.59 (5-Me); ν_{max}: 3942 (OH), 2926 (CH), 1818 (β-lactone C=O), 1707 (ester C=O), 1601cm^{-1} (C=C); m/z: 279 ($M^+-CO_2-Ph_2CH$), 261 ($M^+-CO_2-Ph_2CH-H_2O$), 167 (Ph_2CH^+). Found C 75.69%, H 7.91%; $C_{31}H_{38}O_5$ requires C 75.89%, H 7.81%; $[\alpha]_D^{29} = +32^o$ (c = 0.081, CH_2Cl_2)

<u>Deprotection of Diphenylmethyl *E,E*-(3'-hydroxymethyl-4'-oxo-2'-oxetanyl)-3,5,7-trimethylundeca-2,4-dienoate (68)</u>



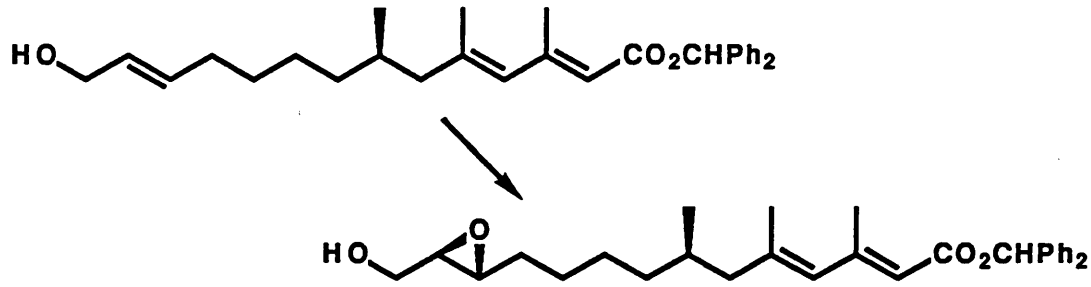
Anisole (14 µl, 0.13 mmole) and trifluoracetic acid (43 µl, 0.25 mmole) were added to a solution of the ester (**68**) (8 mg, 0.016 mmole) at -20°C under argon in anhydrous dichloromethane (0.2 ml). The mixture was stirred between -20°C and -10°C for twenty five minutes. The volatiles were removed *in vacuo* ; the residue was taken up in chloroform and purified by flash chromatography on silica gel (500 mg) eluting with 0-50% acetone/chloroform to give <u>1233A</u> (4.1 mg, 77%) as a solid, identical to the natural product.

Preparation of Diphenylmethyl *E,E,E*-14-hydroxy-3,5,7-trimethyltetradeca-2,4,12-trienoate (**70**).



The ester (**68**) (123 mg, 0.25 mmole) was heated at 180°C under a stream of dry argon for twenty minutes. It was allowed to cool to room temperature, taken up in toluene and purified by flash chromatography eluting with 10 and 20% ether/petrol to give the allylic alcohol (**70**) (92 mg, 82%) as an oil. $\delta(CDCl_3)$: 7.3 (10H, m, Ph); 6.92 (1H, s, Ph_2CH); 5.8 (1H, m, 4-H); 5.6-5.75 (3H, m, 2-,12-,13-H); 4.1 (2H, m, 14-H): 2.22 (3H, d, 1 Hz, 3-Me); 2-2.1 (3H, m, 6-H and 11-methylene); 1.85 (1H, m, 6-H); 1.8 (3H, d, 1 Hz, 5-Me); 1-1.5 (8H, m); 0.83 (3H, d, 7 Hz, 7-Me); $\nu_{max}(CH_2Cl_2)$: 3602 (OH), 3030-2850 (CH), 1705 (C=O), 1612 cm^{-1} (C=C); m/z: 279 (M^+-Ph_2CH), 261 (M^+-Ph_2CH-H_2O), 167 (Ph_2CH^+). Found C 80.77%, H 8.72%; $C_{30}H_{38}O_3$ requires C 80.68%, H 8.58%.

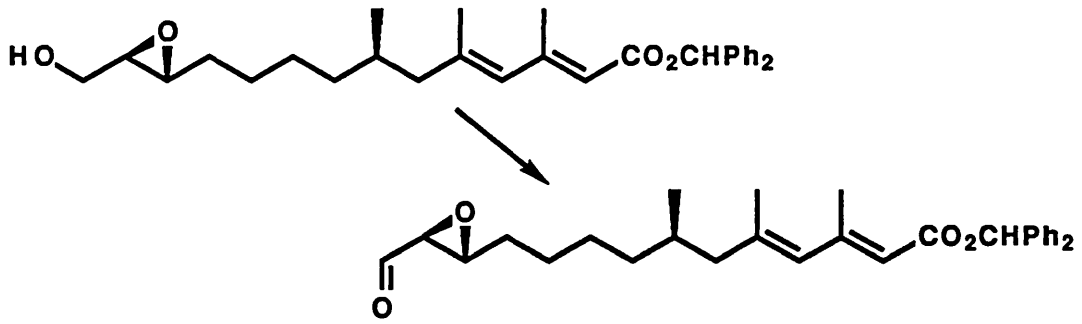
Preparation of Diphenylmethyl *E,E*-12,13-epoxy-14-hydroxy-3,5,7-trimethyl tetradeca-2,4-dienoate (73)



A solution of (-)-diisopropyltartrate (5 mg, 0.022 mmole) in dry dichloromethane (0.5 ml) was added to a slurry of activated powdered 4Å sieves (heated under vacuum with a bunsen burner prior to use) in dichloromethane (2 ml) under an atmosphere of dry argon. The mixture was cooled to -20°C; a solution of titanium tetraisopropoxide (5.5 mg, 5.8 µl, 0.020 mmole) in dichloromethane (0.5 ml) was added. After five minutes, *t*-butylhydroperoxide (98 µl of a 3M solution in isooctane; briefly predried over molecular sieves prior to use) was added dropwise. The mixture was stirred at -20°C for twenty minutes, then cooled to -35°C. The alcohol (**70**) (87 mg, 0.2 mmole) in dichloromethane (1 ml; briefly predried over molecular sieves) was added slowly. The mixture was stirred between -30 and - 35°C for two hours. A solution of citric acid in 10% acetone/ ether (0.6 ml of a 70 mg/ 10 ml solution) was added. The cooling bath was removed and stirring was continued for twenty minutes. The precipitated solids were removed by filtration through celite and the volatiles were evaporated under reduced pressure. The residue was taken up in toluene and purified by flash chromatography, eluting with 30-50% ether/petrol gave the epoxy alcohol (**73**) (78 mg, 84%) as an oil. δ($CDCl_3$): 7.3 (10H, Ph); 6.93 (1H, s, $Ph_2C\underline{H}$); 5.8 (1H, m, 2-H); 5.7 (1H, m, 4-H); 3.9 (1H, dd, 12 and 2.6 Hz, 14-H); 3.65 (1H, dd, 12 and 4.4 Hz, 14-H); 2.9-3 (2H, m, 12- and 13-H); 2.25 (3H, d, 1.5 Hz, 3-Me); 1.8-2.15 (2H, m, 6-H); 1.8 (3H, d, 1.5 Hz, 5-Me); 1-1.8 (10H, m); 0.83 (3H, d, 7 Hz, CH<u>Me</u>);

$\delta(C_6D_6)$: 7-7.5 (10H, Ph); 7.28 (1H, C<u>H</u>Ph_2); 6.07 (1H, 5-H); 5.66 (1H, 3-H); 3.59 (1H, 14-H); 3.36 (1H, 14-H); 2.77 (1H, dt, 2.2 and 5.7 Hz, 12-H); 2.63 (1H, ddd, 4.4, 2.6 and 2.2 Hz, 13-H); 2.35 (1H, 3-Me); 1.96 (1H, 6-H); 1.70 (1H, 6-H); 1.61 (3H, 5-Me); 1.1-1.5 (9H, alkyls); 0.81 (3H, 7-Me); ν_{max}: 3431 (OH), 2900-3000 (C-H), 1710 (C=O), 1615 (C=C), 1138, 1024 cm^{-1} (C-O). m/z: 462 (M^+), 444 (M^+-H2O), 295 (M^+-Ph_2CH), 279 (M^+-Ph_2CHO), 167 (Ph_2CH^+); Found C 77.68%, H 8.56%; $C_{30}H_{38}O_4$ requires C 77.89%, H 8.28%.

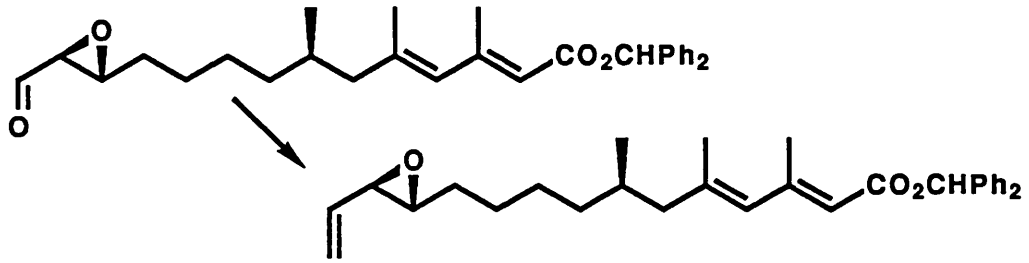
<u>Preparation of Diphenylmethyl *E,E*-12,13-epoxy-3,5,7-trimethyl-14-oxo-2,4-tetradeca-2,4-dienoate (74)</u>



Pyridinium dichromate (80 mg, 0.21 mmole) was added to a solution of the epoxyalcohol (65.2 mg, 0.14 mmole) in dichloromethane (5 ml) containing powdered 4Å molecular sieves. After four and a half hours, the mixture was diluted with ether and filtered through a thick pad of florisil, washing with dichloromethane. The volatiles were evaporated to give the <u>epoxyaldehyde</u> (74) (54.2 mg, 84%). $\delta(CDCl_3)$: 9.02 (1H, d, 6 Hz, CH=O); 7.3 (10H, m, Ph); 6.92 (1H, s, Ph_2C<u>H</u>); 5.82 (1H, m, 4-H); 5.7 (1H, m, 2-H): 3.23 (1H, ddd, 6, 5 and 2 Hz, 12-H); 3.14 (1H, dd, 6 and 2 Hz, 13-H); 2.25 (3H, d, 1.5 Hz, 3-Me); 2.08 (1H, dd, 13 and 6 Hz, 6-H); 1.85 (1H, dd, 13 and 8 Hz, 6-H); 1.82 (3H, d, 1.5 Hz, 5-Me); 1-1.8 (9H, m); 0.85 (3H, d, 7 Hz, CH<u>Me</u>); ν_{max}: 2850 -3050 (CH), 1724 (CH=O), 1708 (ester C=O), 1606 cm^{-1} (C=C); m/z: 460 (M^+), 293 (M^+-Ph_2CH), 277 (M^+-Ph_2CHO), 167 (Ph_2CH^+). Found (sample

additionally purified by flash chromatography on florisil) C 78.49%, H 8.05%; $C_{30}H_{36}O_4$ requires C 78.23%, H 7.88%.

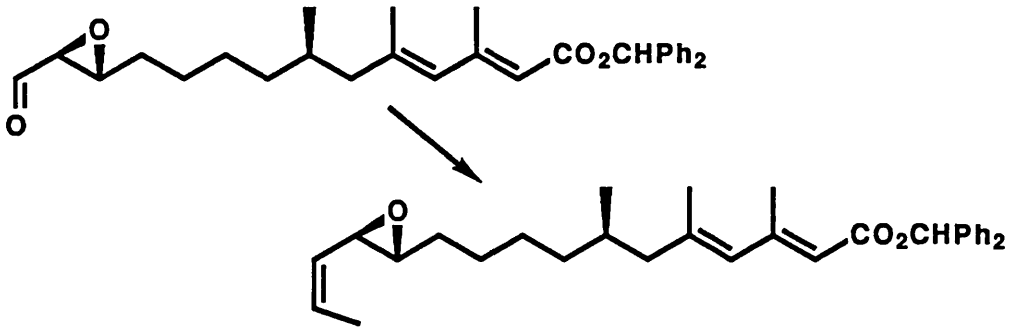
Preparation of Diphenylmethyl *E,E*-12,13-epoxy-3,5,7-trimethylpentadeca-2,4,14-trienoate (77)



Hexamethyldisilazide (368 μl, 1.75 mmole) was added to a slurry of potassium hydride (183 mg of a 35% w/w suspension in mineral oil prewashed with dry petrol, 1.59 mmole) in THF (2 ml). The mixture was heated at 40°C for one hour and then cooled to 0°C. Methyltriphenylphosphonium bromide (680 mg, 1.90 mmole) was added from a solid addition tube to give a yellow solution. After stirring for twenty minutes a solution of the aldehyde (146 mg, 0.32 mmole) in toluene (1 ml) was added. The mixture was stirred for ten minutes, diluted with petrol and filtered through a pad of talc on celite, washing with 1:1 ether/petrol. The more volatile solvents were evaporated and the residual toluene solution was purified directly by flash chromatography on florisil (5 g), eluting with 0-10% ether/petrol to give the vinyl epoxide (77) (120 mg, 83%) as an oil. δ($CDCl_3$): 7.1-7.8 (10H, m, Ph); 6.94 (1H, s, $CHPh_2$); 5.82 (1H, m, 4-H); 5.72 (1H, m, 2-H); 5.58 (1H, ddd, 17, 10 and 7 Hz, 14-H); 5.44 (dd, 17 and 2 Hz, *Z*-15-H); 5.25 (1H, dd, 10 and 2 Hz, *E*-15-H); 3.09 (1H, dd, 7 and 2 Hz, 13-H); 2.83 (1H, dt, 2 and 6 Hz, 12-H); 2.25 (3H, d, 1 Hz, 3-Me); 2.09 (1H, dd, 13 and 6 Hz, 6-H); 1.84 (1H, dd, 8 and 13 Hz), 6-H); 1.81 (3H, d, 1 Hz, 5-Me); 1.2-1.7 (8H, m, $-CH_2-$); 1.13 (1H, m, 7-H); 0.83 (3H, d, 7 Hz, 7-Me);

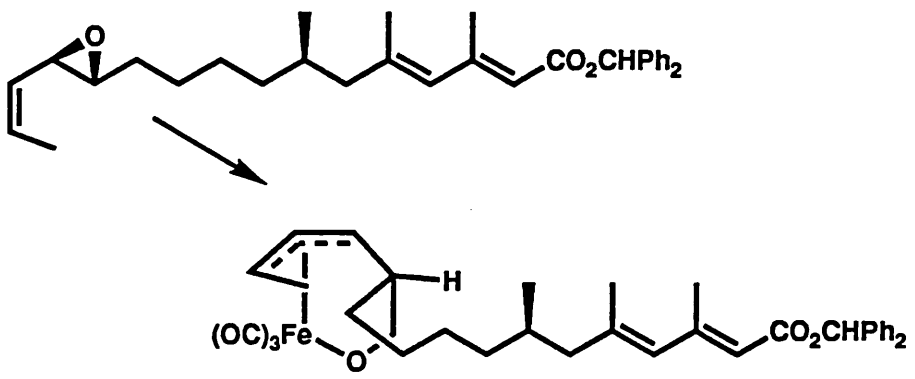
ν_{max}: 2920-3061 (C-H), 1713 (C=O), 1617, 1602 (C=C), 1138 cm^{-1} (C-O); m/z: 458 (M^+), 440 (M^+-H_2O), 292 (M^+-Ph_2CH),183 (Ph_2CHO^+), 167 (Ph_2CH^+).

Preparation of Diphenylmethyl *E,E,Z*-12,13-epoxy-3,5,7-trimethylhexadeca-2,4,14-trienoate (76)



Potassium hexamethyldisilazide solution was prepared by adding hexamethyldisilazane (172 ml) to potassium hydride (94 mg of a 35% w/w slurry in mineral oil, prewashed with dry petrol) in THF (1 ml), stirring at room temperature for thirty minutes and at 40°C for one hour. A portion (190 ml, 0.13 mmole) was added to a slurry of ethyltriphenylphosphonium bromide (48 mg, 0.13 mmole) in toluene (0.5 ml) at 0°C. The orange solution was stirred for ten minutes at this temperature. A solution of the aldehyde (12 mg, 0.026 mmole) in THF (1 ml) was added. After five minutes, the mixture was quenched with one drop of water and diluted with petrol. The mixture was filtered through a double layer of celite and florisil and evaporated to give the crude vinyl epoxide (**76**) (10 mg, 78%) as an oil. $\delta(CDCl_3)$: 7.2-7.4 (10H, m, Ph); 6.92 (1H, s, $CHPh_2$); 5.7-5.9 (3H, m, 2-H, 4-H, 15-H); 5.08 (1H, ddq, 9.5, 9.5 and 1.8 Hz, 14-H); 3.37 (1H, ddd, 9.5, 2.4, 1.8 Hz, 13-H); 2.80 (1H, ddd, 6, 6 and 2.4 Hz, 12-H); 1.9-2.15 (2H, m, 6-H); 2.25 (3H, d, 1.5 Hz, 3-Me); 1.81 (3H, d, 1.8 Hz, 5-Me); 1.8 (3H, dd, 7 and 1.8 Hz, 16-H); 1.1-1.8 (9H, m, 7-H and CH_2); 0.85 (3H, d, 7 Hz, 7-Me).

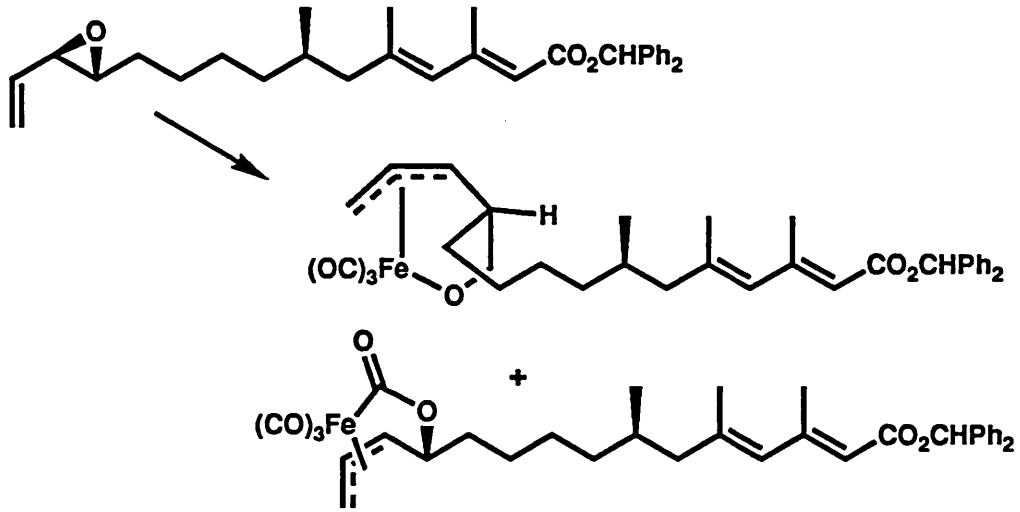
Preparation of *E,E*-1-Diphenylmethoxy-3,5,7-trimethyl-1-oxo-[12-*endo*-15-*endo*-13-15-η^3-(12-formyloxyhexadeca-2,4,14-trien-13-ylato)tricarbonyliron] (75)



i) Reaction of the vinyl epoxide (**76**) (13.4 mg, 0.028 mmole) with diiron nonacarbonyl (52 mg,0.142 mmole) according to method B and purification by flash chromatography on silica gel (1 g) eluting with 5 and 10% ether/petrol gave the ferrilactone (**75**) (9.6 mg, 54%) as a yellow oil. $\delta(C_6D_6)$: 7-7.5 (11H, m, Ph_2CH); 6.11 (1H, brs, 2-H); 5.68 (1H, brs, 4-H); 4.11 (1H, dd, 9 Hz, 4.5 Hz, 13-H); 3.95 (1H, m, 12-H); 3.82 (1H, dq, 9 and 7 Hz, 15-H); 3.3.8 (1H, dd, 9 and 9 Hz, 14-H); 2.40 (3H, s, 5-Me); 1.6-2.1)2H, m, 6-H); 1.64 (3H, s, 5-Me); 1.60 (3H, d, 7 Hz, 16-H); 0.8-1.6 (9H, m, CH_2,CH); 0.83 (3H, d, 7 Hz, 7-Me).

ii) Reaction of the vinyl epoxide (**76**) (14.5 mg, 0.031 mmole) with diiron nonacarbonyl (56 mg,0.154 mmole) according to method B and purification by flash chromatography on silica gel (1 g) eluting with 5 and 10% ether/petrol gave the ferrilactone (**75**) (4.5 mg, 23%) as a yellow oil.

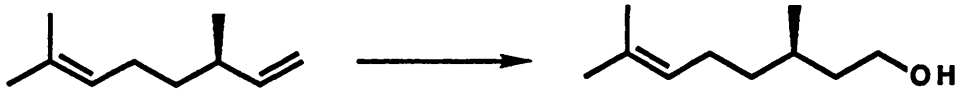
Preparation of *E,E*-1-Diphenylmethoxy-3,5,7-trimethyl-1-oxo-[12-*endo*-13-15-η^3-(12-formyloxypentadeca-2,4,14-trien-13-ylato)tricarbonyliron] (78) and *E,E*-1-Diphenylmethoxy-3,5,7-trimethyl-1-oxo-[12-*exo*-13-15-η^3-(12-formyloxypentadeca-2,4,14-trien-13-ylato)tricarbonyliron] (79)



Reaction of the vinyl epoxide (**77**) (114 mg, 0.35 mmole) with diiron nonacarbonyl (182 mg, 0.5 mmole) in benzene (1 ml) according to method B and purification by flash chromatography on silica gel (5 g) eluting with 5 - 15% ether/ petrol gave the *endo*-ferrilactone (**78**) (60 mg, 39%) as an oil; $\delta(C_6D_6)$: 7.5-7 (11H, m, Ph_2CH); 6.1 (1H, m, 4-H); 5.68 (1H, m, 2-H); 3.7-3.9 (m, 12-,13-,14-H); 2.84 (1H, ddd, 11,8 and 1.3 Hz, 15-H); 2.39 (1H, d, 1 Hz, 3-Me); 1.95 (1H, m, 6-H); 1.75 (1H, m, 6-H); 1.62 (3H, d, 1 Hz, 5-Me); 0.9-1.6 (9H, m, 7- to 11-H); 0.83 (3H, d, 6 Hz, 7-Me); ν_{max}: 2926-3030 (C-H), 2006, 2079 (FeC=O), 1708 (C(C=O)O), 1670 (O(C=O)Fe), 1623 (C=C, conjugated to ester), 1656 (C=C, not conjugated to ester), 1138 cm^{-1} (C-O); m/z: 318 (M^+-Ph_2CH-Fe$(CO)_3$-H), 167 (Ph_2CH^+), 140 ($Fe(CO)_3^+$); followed by the *exo*-ferrilactone (**79**) (13 mg, 8%) as an oil. $\delta(C_6D_6)$: 7.5-7 (11H, m, Ph_2CH); 6.1 (1H, m, 4-H); 5.68 (1H, m, 2-H); 3.92 (1H, ddd, 13, 8 and 7.5 Hz, 14-H); 3.79 (1H, dd, 8 and 1 Hz, 13-H); 3.60 (1H, dm, 6 Hz, 12-H); 2.66 (1H, dd, 8 and 1 Hz, 15 H_{exo}); 2.63 (1H, dd, 13 and 1 Hz, 15-H_{endo}); 2.39 (1H,

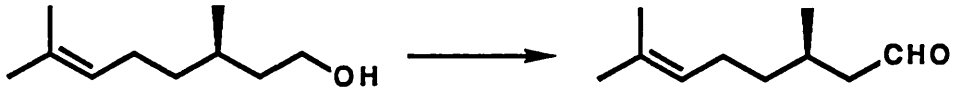
d, 1 Hz, 3-Me); 1.95 (1H, m, 6-H); 1.75 (1H, m, 6-H); 1.62 (3H, d, 1 Hz, 5-Me); 0.9-1.6 (9H, m, 7- to 11-H); 0.83 (3H, d, 6 Hz, 7-Me).

Preparation of citronellol



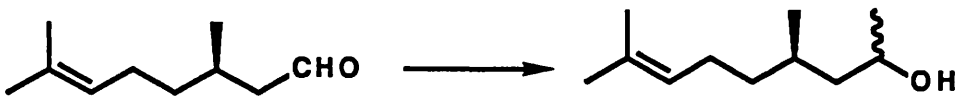
Citronellene (361 mg, 2.61 mmole) was added dropwise to a solution of 9-BBN dimer (338 mg, 1.39 mmole) in THF (5 ml) under argon at room temperature. After four hours, the mixture was cooled to 0°C and treated cautiously with a mixture of ethanol (1.7 ml), 80% hydrogen peroxide (1 ml) and aqueous sodium hydroxide (0.5 ml of a 6M solution, prepared with Analar grade sodium hydroxide). When the initial violent reaction had subsided, the mixture was heated at 50°C for one hour, cooled to room temperature and extracted with ether. The organic extracts were dried ($MgSO_4$) and evaporated to give an oily residue which was purified by flash chromatography on silica gel (10 g) to give citronellol (230 mg, 60%) identical to an authentic sample.

Preparation of citronellal



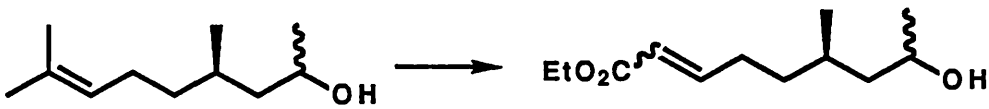
Pyridinium dichromate (24 g, 65 mmole) was added portionwise to a solution of citronellol (6.7 g, 43.3 mmole) in dichloromethane (50 ml) at 0°C containing powdered 4Å molecular sieves. The mixture was stirred at room temperature for four hours, then filtered through a pad of florisil. Evaporation of the solvent gave an oil (6.1 g) containing citronellal (by tlc and nmr comparison with an authentic sample), which was used in the next reaction without further purification.

Preparation of (4R)-4,8-dimethyl-7-nonen-2-ol (85)



Methyl magnesium iodide (292 µl of a 3 M solution in ether, 0.88 mmole) was added dropwise to a solution of crude citronellal (90 mg) in dry ether at 0°C. After twenty minutes at this temperature, the mixture was treated sequentially with ice-water and saturated ammonium chloride, then extracted with ether. The combined organic extracts were dried ($MgSO_4$), evaporated and purified by flash chromatography eluting with 5 and 50% ether/petrol to give the alcohol (85) as a 1:1 mixture of diastereoisomers (70 mg, 70%). δ($CDCl_3$): 5.1 (1H, m, C=CH); 3.9 (1H, m, CHOH); 1.95 (2H, m, $C{=}CHCH_2$); 1.6, 1.67 (6H, two s, $C{=}CMe_2$); 1-1.6 (9H, m, $CH_2CH(Me)CH_2CHOH$); 0.9 (3H, two d, 6 Hz, CHMe) ν_{max}: 3350 (OH), 2900-3000 (CH), 1451cm^{-1} (C=C); m/z 170 (M^+), 152 (M^+-OH), 69 ($Me_2C{=}CHCH_2^+$); found C 76.75%, H 13.18%, C $_{10}H_{20}O$ requires C 76.86%, H 12.90%.

Preparation of ethyl (6R)-8-hydroxy-6-methyl-2-nonenoate (86)



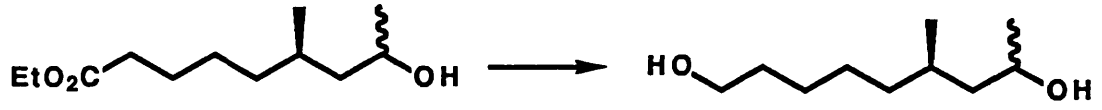
A stream of ozone in oxygen (80 lhr^{-1}, 140 V discharge) was passed through a solution of the alkene (3.14 g, 18.5 mmole) in dichloromethane (100 ml) at -78°C. After six hours, the solution became blue; it was flushed with oxygen, treated with dimethylsulphide (3 ml) and allowed to warm to room temperature. Carbethoxymethylenetriphenylphosphorane (7.7 g, 22.2 mmole) was added and the mixture was stirred at room temperature overnight. The mixture was diluted with petroleum ether and filtered through silica gel. The solvents were evaporated and the off-white solid was taken up in 5% ether/petrol and filtered through a pad of celite. The

solvent was evaporated and the residue was purified by flash chromatography on silica gel (90 g), eluting with 1:1 ether/petrol to give the ester (**86**) (2.82 g, 71%) as a mixture of diastereoisomers and geometrical isomers. $\delta(CDCl_3)$: (*trans* isomers only) 6.95 (1H, dt, 16 and 6 Hz, $O_2CCH=C\underline{H}$); 5.82 (1H, dt, 16 and 1 Hz, $O_2CC\underline{H}=CH$); 4.2 (2H, q, 7 Hz, $C\underline{H}_2CH_3$); 3.9 (1H, m, C<u>H</u>OH); 2.2 (2H, m, $=CHC\underline{H}_2$); 1.1-1.7 (11H, m); 0.9 (3H, two d, 7 Hz, $CH_2C\underline{H}_3$); ν_{max}: 3425 (OH), 2920-3000 (CH), 1718 (C=O), 1649 (C=C)cm^{-1} m/z: 214 (M^+), 213 (M^+-H), 196 (M^+-H_2O), 153 (M^+-Ac), 141 (M^+-CO_2Et); found C 67.05%, H 10.15%, $C_{12}H_{22}O_3$ requires C 67.26%, H 10.35%.

Preparation of ethyl (6R)-8-hydroxy-6-methylnonanoate

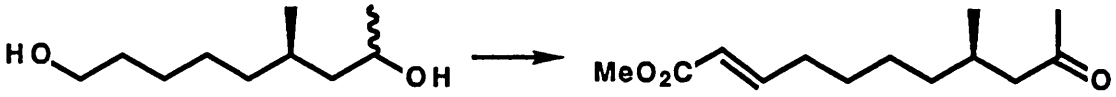
A flask containing a suspension of platinum oxide (20 mg, 0.088 mmole) in ethanol (100 ml) was flushed with nitrogen and then with hydrogen. A solution of the alkene (2.76 g, 12.9 mmole) in ethanol (50 ml) was added and the mixture was stirred under hydrogen (1 atm) overnight. The flask was flushed again with nitrogen and the mixture was filtered through celite, washing with ether. The solvents were evaporated to give the ester (2.73 g, 98%) as a colourless oil. $\delta(CDCl_3)$: 4.12 (2H, q, 7 Hz, $C\underline{H}_2CH_3$); 2.29 (2H, t, 7 Hz, $EtO_2CC\underline{H}_2$); 1.1-1.7 (12H, m) 0.9 (3H, two d, 7 Hz, CH<u>Me</u>); ν_{max}: 3420 (OH), 2870-3000 (CH) 1735 cm^{-1} (C=O); m/z: 215 (M^+-H), 201 (M^+-OH), 172 (M^+-Ac).

Preparation of (6R)-6-methylnonane-1,8-diol (87)



A solution of the ester (2.71 g, 12.55 mmole) in ether was added cautiously *via* cannula to a slurry of lithium aluminium hydride (713 mg, 18.8 mmole) in ether (30 ml) at 0°C. The mixture was stirred at room temperature for one hour, then recooled to 0°C and treated cautiously with water. The resulting white precipitate was removed by filtration and washed with ethyl acetate. The washings and filtrate were combined and evaporated to give the diol (87) (2.12g, 97%) as an oil. Found: C, 68.6%; H, 13.0%; $C_{10}H_{22}O_2$ requires C, 68.9%; H, 12.7%; δ($CDCl_3$): 3.90 (1H, m, C<u>H</u>OH); 3.63 (2H, t, 6 Hz, C<u>H</u>$_2$OH); 1.1-1.7 (11H, m); 0.9 (3H, two d, 7 Hz, Me); ν_{max}: 3334 (O-H), 2850-2950 (C-H), 1056 cm^{-1} (C-O str); m/z: 174 (M^+), 155 (M^+-OH).

Preparation of Methyl (8R)-*E*-methyl-10-oxo-2-undecenoate (89)

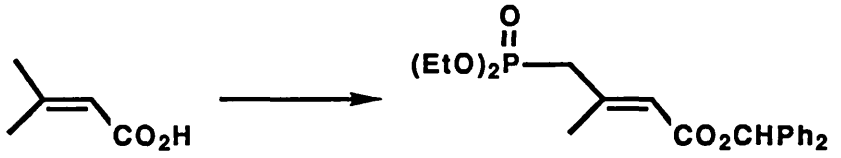


A solution of dimethylsulphide (84 µl, 1.19 mmole) in dichloromethane (0.5 ml) was added dropwise to a solution of oxalyl chloride (52 µl, 0.59 mmole) in dichloromethane (0.5 ml) under argon at -60°C. The mixture was stirred at -60°C for ten minutes. A solution of the diol (43 mg, 0.25 mmole) in acetonitrile (1 ml) was added dropwise; the mixture was stirred for fifteen minutes at -60°C, treated with triethylamine (344 µl, 2.5 mmole), stirred for a further fifteen minutes at -60°C, then allowed to warm to room temperature to give a solution of the ketoaldehyde (88) (R_f = 0.30 (1:1 ether/petrol/silica gel)).

The mixture was filterred through a pad of florisil, washing with acetonitrile (2 ml). Anhydrous lithium chloride (12 mg, 0.28 mmole), 4Å molecular sieves, DBU (37

μl, 0.25 mmole) and methyl diethylphosphonoacetate (51 μl, 0.28 mmole) were added and the mixture was stirred overnight. The mixture was filtered through celite, diluted with ether and washed sequentially with sodium bicarbonate and ammonium chloride solutions. The organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (1.5 g) eluting with 3-10% ether/petrol to give the ketoester (**89**) (24 mg, 42%) as an oil. (R_f = 0.41 (1:1 ether/ petrol/ silica gel)), δ($CDCl_3$): 6.95 (1H, dt, 16 and 7 Hz, 3-H); 5.82 (1H, dt, 16 and 1.5 Hz, 2-H); 3.73 (3H, s, OMe); 2.39 (1H, dd, 16 and 6 Hz, 9-H); 2.1-2.3 (3H, m, 4, 9-H); 2.12 (3H, s, 11-H); 2.0 (1H, m, 8-H); 1.1-1.5 (6H, m, 5,6,7-H); 0.9 (3H, d, 7 Hz, 8-Me); ν_{max}: 2850-2950 (C-H), 1716 (two C=O), 1653 cm^{-1} (C=C); m/z: 227 (MH^+), 226 (M^+), 211 (M^+-Me), 208 (M^+-H_2O), 194 (M^+-MeOH), 183 (M^+-CH_3CO).

Preparation of Diphenylmethyl *E*-4-diethylphosphono-4-methyl-2-butenoate (**99**)



N-Bromosuccinnimide (20 g, 112 mmole, recrystallised from boiling water) and AIBN (100 mg, 0.52 mmole) were added sequentially to a solution of 2,2-dimethylacrylic acid (10.2 g, 102 mmole) in dry carbon tetrachloride (100 ml). The mixture was refluxed for one hour, then allowed to cool to room temperature. The solids were removed by filtration; the filtrate was concentrated and diluted with anhydrous dichloromethane (100 ml). Anhydrous potassium carbonate (14 g, 102 mmole) was added and the mixture was stirred for twenty four hours at room temperature. The mixture was diluted with ether and water. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and evaporated to give the crude bromoacid (**94**)[101] (6 g) as a yellow solid.

The crude acid (6 g) was added to a solution of diphenyldiazomethane (7.86 g, 40.5 mmole) in dry benzene (100 ml). The effervescing mixture was heated at 70°C for one hour, concentrated and applied to the top of a column of silica gel. Flash chromatography, eluting with 5% ether/petrol gave the ester,[101] contaminated with diphenylmethyl 2,2-dimethylacrylate, as an oil.

The crude ester (10 g) and triethyl phosphite (6 ml) were heated at 160°C under argon for twenty minutes, allowed to cool to room temperature and purified by flash chromatography on silica gel (200 g) eluting with 1:1 ether/petrol, 3:1 ether/petrol and ether gave the phosphonoester (**99**) (8.2 g, 20% overall) as an oil. $\delta(CDCl_3)$: 7.2-7.4 (10H, m, Ph); 6.90 (1H, s, $C\underline{H}Ph_2$); 5.94 (1H, dm, 5 Hz, $CHCO_2$); 4.10 (4H, m, CH_2O); 2.52 (2H, dd, 24 and 1 Hz, CH_2P); 2.31 (3H, dd, 3.5 and 1.2 Hz, $=CCH_3$); 1.32 (6H, t, 7 Hz, CH_2CH_3); $\delta(^{13}C)$: 164.5 (d, 4 Hz, C=O); 150.75 (d, 11 Hz, 3-C); 140.14 (s, *ipso*-C); 128.18, 127.51, 126.79 (*o,m,p*-C); 119.35 (d, 11 Hz, 2-C); 76.03 (s, $\underline{C}HPh_2$); 61.84 (d, 7.5 Hz, OCH_2); 38.40 (d, 135 Hz, 4-C); 19.90 (d, 2Hz, 3-Me); 16.10 (d, 6 Hz, $CH_2\underline{C}H_3$). ν_{max}: 3050-2920 (CH), 1716 (C=O), 1643 (C=C), 1624 (asym POC str), 1251 (C-O), 1207 (P=O), 1136 (C-O), 700 cm^{-1} (P-C). m/z: 402 (M^+), 167 ($PhCH_2CH^+$). Found C 65.59%, H 6.98%; $C_{22}H_{27}O_5P$ requires C 65.66%, H 6.76%.

Appendix 1. Crystal Data for Compound (4)

Crystal Data: $C_{16}H_{15}FeNO_4$, M = 341.1, orthorhombic, a = 7.084(1), b = 11.868(2), c = 18.680(4) Å, V = 1570 $Å^3$, space group $P2_12_12_1$, Z = 4, D_c - 1.44 gcm^{-3}, Cu radiation, λ =1.54178 Å, μ(Cu-K_α) = 79 cm^{-1}, F(000) - 704. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ϖ-scans. A crystal of dimensions 0.04 x 0.08 x 0.57 mm was used. 1253 independent reflections ($2\theta \leq 116^o$) were measured, of which 1076 had $|Fo| > 3\sigma(|Fo|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; a numerical adsorption correction (face-indexed crystal) was applied; the maximum and minimum transmission factors were .764 and .471. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were located from a ΔF map, their positions were idealised C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and were allowed to ride on thier parent carbon atoms. The methyl group was refined as a rigid body. The absolute configuration chirality of the molecule was confirmed by refinement of a free variable η which multiplies all f''. This parameter refined to a value of 1.03(2) giving a definitive assignment. Refinement was by block-cascade full-matrix least-squares to R = 0.041, Rw = 0.039 [$w^{-1} = \sigma^2(F) + 0.00068F^2$]. The maximum and residual electron densities in the final ΔF map were 0.23 and -0.22 $eÅ^{-3}$, respectively. The mean and maximum shift/error in the final refinement were 0.018 and 0.079 respectively. Computations were carried out on an Eclipse S140 computer using the SHELTXL program system.

Appendix 2. Spectroscopic Data for 2,2-dimethylacrylate derivatives

4-Methyl-2(5*H*)-furanone (**97**): $\delta(CDCl_3)$: 5.82 (1H, s, CH); 4.73 (2H, s, CH_2); 2.12 (3H, s, CH_3); m/z: 98 (M^+), 69 (M^+-CHO), 54 (M^+-CO_2).

4-Bromomethyl-2(5*H*)-furanone (**98**): $\delta(CDCl_3)$: 6.1 (1H, s, CH); 4.9 (2H, s, CH_2O); 4.2 (2H, s, CH_2Br); ν_{max}: 3100-2900 (CH), 1743 (C=O), 1640 (C=C); m/z: 178/176 (M^+), 149/147 (M^+-CHO), 121/119 ($BrCH_2CHCH^+$).

E-4-bromo-3-methylbutenoic acid (**94**): $\delta(CDCl_3)$: 6.0 (1H, s, CH); 3.95 (2H, s, CH_2); 2.3 (3H, s, CH_3).

Z-4-bromo-3-methylbutenoic acid (**95**): $\delta(CDCl_3)$: 6.15 (1H, s, CH); 4.20 (2H, s, CH_2); 2.18 (3H, s, CH_3).

Diphenylmethyl *E*-4-bromo-3-methylbutenoate: $\delta(CDCl_3)$: 7.4-7.2 (10H, m, Ph); 6.93 (1H, s, C<u>H</u>Ph_2); 6.12 (1H, m, =CH); 3.95 (2H, d, 1 Hz, CH_2Br); 2.28 (3H, d, 1.3 Hz, CH_3); ν_{max} 2920-3070 (CH), 1715 (C=O), 1644 (C=C), 1600 (C=C in Ph); m/z: 346/344 (M^+), 266 (MH^+-Br), 167 (Ph_2CH^+).

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101. Data for intermediates and by-products in this preparation can be found in appendix 2.