SYNTHESIS OF 1,2-DIOXOLANES RELATED TO MARINE SPONGE METABOLITES

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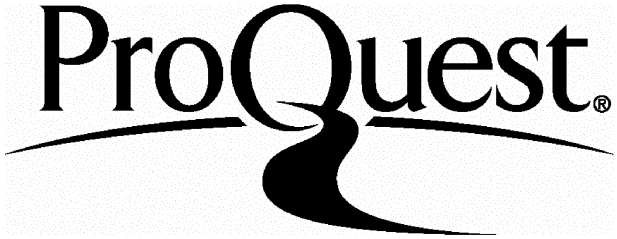

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ABSTRACT

The plakinic and epiplakinic acids A, C and D, and a related series of natural products were isolated from marine sponges. They are reported to exhibit general anti-microbial activity and bear several common structural features. They each contain a 1,2-dioxolane ring with 3,5-dimethyl substitution, a 3-carboxymethyl substituent and a large hydrophobic moiety attached to C^5 which we refer to as R^1.

This work describes the synthesis of a series of naturally occurring and other structural analogues of the plakinic acids which contain the quaternary substituted 1,2-dioxolane.

Our approach to the synthesis of the functionalised target 1,2-dioxolane was to use peroxymercuriation/ demercuriation of an appropriately substituted diene carboxylate. In the first instance, as a model system, we describe the synthesis and characterisation of ethyl 3,5-dimethylhexa-2,4-dienoate and its isomeric esters. These dienes were then treated with two mole equivalents of mercury acetate and 30% H_2O_2 followed by sodium borohydride demercuriation to produce the first unnatural analogue of the natural products.

We then describe the development of a general method of synthesis of further analogues, by variation of R^1, which in its most refined form comprises only 3 steps. LDA-induced condensation of alkan-2-ones with ethyl 3-methylbut-2-eneoate generated (2Z)-3,5-dimethyl-2,4-dienoic acids which after structural modification served as the diene substrate. Peroxymercuriation/ demercuriation of the ethyl ester analogue of the 2Z-diene acid gave the 3,5-dimethyl-1,2-dioxolane esters, which upon saponification furnished the 1,2-dioxolane acids. The first example of a naturally occurring analogue was synthesised using this route. Alternatively conversion of the 2Z-diene to the 2E-isomer followed by peroxymercuriation/ demercuriation gave the functionalised 1,2-dioxolane acid directly.

In all cases the 1,2-dioxolanes were produced as a pair of diastereoisomers. The relative stereochemistry of each isomer was determined by comparison of the ^1H NMR of the analogue where $R^1=C_7H_{15}$ with the data reported for the natural products, and from nOe experiments.

To probe structure activity relationships a series of spiro 1,2-dioxolanes were synthesised, and modifications to the carboxylate were made with the peroxide ring in place.

Finally as a model for the total synthesis of the plakinic and epiplakinic acids we describe the synthesis of an analogue where R^1 contains unsaturation which was achieved by employing Wittig methodology in the presence of the 1,2-dioxolane.

ABBREVIATIONS

AIBN	2,2-Azoisobutyrionitrile
COSy	Correlation spectroscopy
DCA	9,10-Dicyanoanthracene
DCC	Dicyclohexylcardodiimide
DCM	Dichloromethane
DMAP	Dimethylaminopyridine
DMF	Dimethyl Formamaide
EI	Electron Impact
ESP	Electrospray
EtOAc	Ethyl Acetate
FAB	Fast Atom Bombardment
Hex	Hexane
HPLC	High Performance Liquid Chromatography
IR	Infrared
LDA	Lithium diisopropylamine
MeOH	Methanol
MS	Mass Spectrometry
NBS	N-bromosuccinamide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
NOESY	nOe spectroscopy
PDC	pyridinium dichromate
PPTS	Pyridinium p-toluenesulfonate
THF	Tetrahydrofuran
TPP	Tetraphenylporphine

CHAPTER ONE

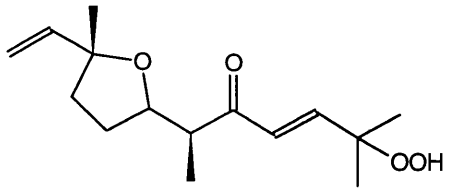
PEROXY NATURAL PRODUCTS

INTRODUCTION

Peroxidic natural products occur both terrestrially and in marine organisms. A review of the literature to 1990 by Casteel[1] provides a detailed account of the range of peroxy compounds isolated, illustrating their diversity of structure and origin.

Terrestrial Natural Peroxides

A large number and variety of terrestrial sources, from the t-RNA of a mammalian liver to the flowers of tobacco plants, yield peroxy natural products. The peroxide may be present as a hydroperoxy functionality (**1.1**) or incorporated into a ring system. The most frequently encountered ring system is a six-membered one which can be found within, amongst others, terpenoid (**1.2**) and steroidal derivatives (**1.3**). The hemiperketal endoperoxide (**1.2**) was isolated from the leaves and flowers of *Tanacetum Vulgare* along with the hydroperoxide (**1.1**) which is probably the biogenetic precursor of (**1.2**). Although six-membered endoperoxides are the most commonplace, a few examples of other ring systems are known. One of the most prominent peroxy natural products, qinghaosu (**1.4**), contains a 1,2,4-trioxane ring. This compound is of particular interest because it is an extremely potent antimalarial, the trioxane ring being an essential component regarding its activity.



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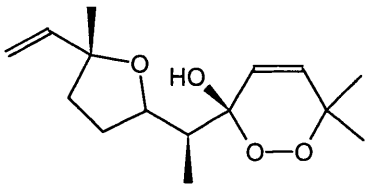

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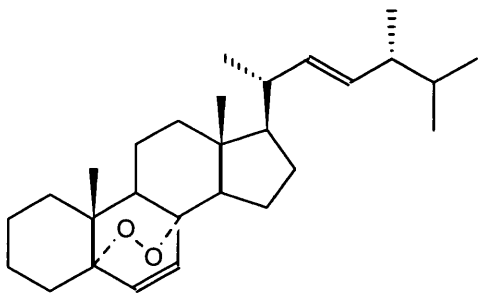

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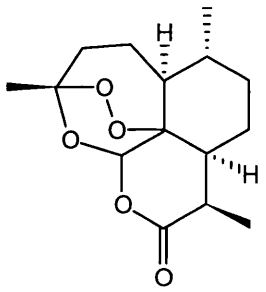
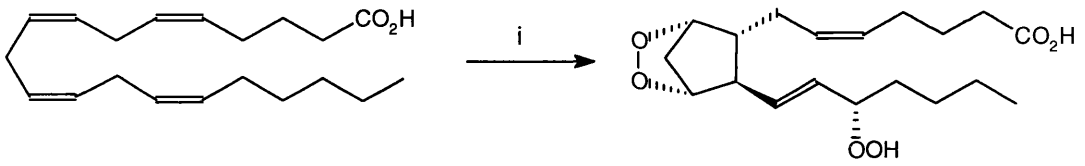


1.4

Another notable natural product, PGG_2 (**1.6**), is one of the metabolites of arachidonic acid (**1.5**) and an intermediate in the synthesis of thromboxanes, prostaglandins and prostacyclins (**Scheme 1.1**).

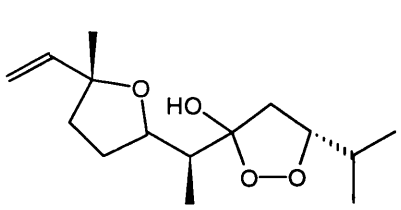
PGG_2 is unusual because it contains a bicyclic peroxide moiety that is both a 1,2-dioxane and a 1,2 dioxolane. The five-membered peroxide ring rarely occurs in nature although a few examples have been isolated where the ring is present as a hemiperketal (**1.7**) or found within a fused ring system (**1.8**). The peroxy hemiketal (**1.7**) is analogous to the 1,2-dioxane (**1.2**) and like its six-membered counterpart is isolated along with the hydroperoxy compound (**1.1**)

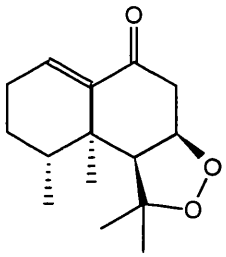


1.5 **1.6**

Scheme 1.1

i) prostaglandin endoperoxide synthase (cyclooxygenase)

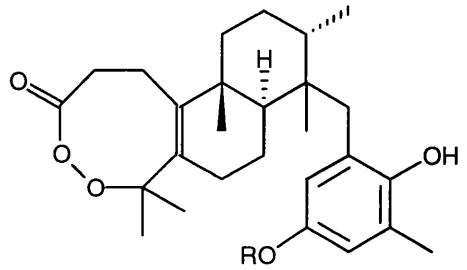




1.7 **1.8**

Marine Natural Peroxides

Large numbers of metabolites of unusual structure and exhibiting high orders of biological activity have been isolated from marine organisms,[2,3,4] a number of which contain a peroxide group. Marine sponges are the most prolific producers of peroxy metabolites, although other organisms yield some interesting compounds including the peroxylactones[5] (**1.9**) isolated from the brown seaweed *Taonia atomaria* and the alkeneyne rhodophytin[6] (**1.10**) from the red alga *Laurencia yamada*.



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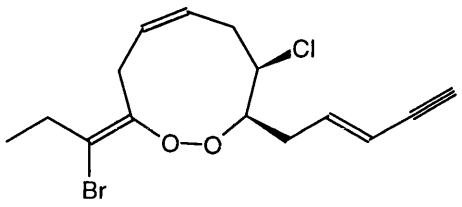
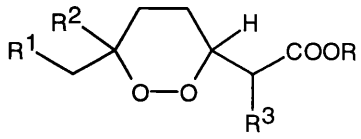


1.10

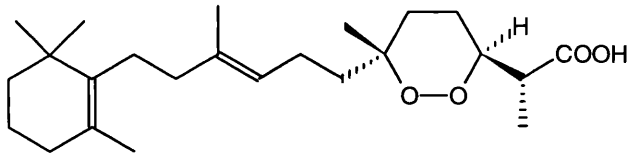
Marine sponge metabolites containing the six-membered peroxide ring

The peroxide in marine sponge metabolites is generally present as a 1,2-dioxane which may contain unsaturation. Steroidal derivatives have been isolated although carboxylic acid derivatives of terpenoids or non-terpenoids are more frequently observed. Within the latter two types of cyclic, peroxy, marine natural products there exists a remarkable structural similarity, illustrated in (**1.11**). The most noticeable features are the incorporation of the peroxy functionality as a six-membered ring which has; a secondary centre on one side and a tertiary the other; the former β to a carboxyl moiety.



1.11

In terpenoid derivatives R_3 may be H or CH_3. R^1 contains the terpenoid component of the natural product and R^2 = methyl or ethyl (**1.12** and **1.13**). The non-terpenoid derivatives are generally peroxy ketals with R^2 = OMe and R^1 is composed of a branched or straight chain (**1.14**) which may contain unsaturation. Most non-terpenoid peroxyketals are found with an unsaturated dioxane ring but recently two examples of a saturated dioxane, fatty acid derivative, were isolated from a sponge of the genus *Plakortis*[7] (**1.15**).



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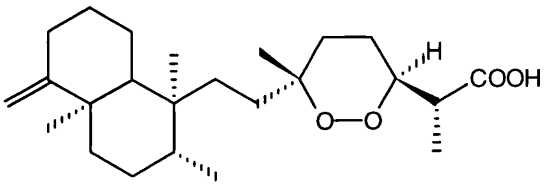

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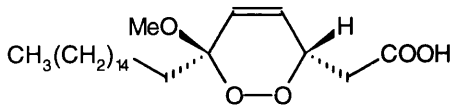

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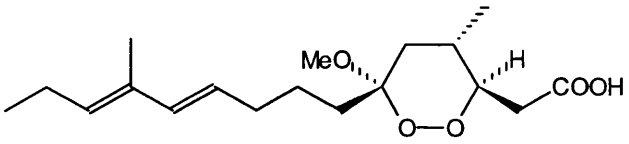


1.15

Marine sponge metabolites containing the 1,2-dioxolane

It is recognised that cyclic peroxides from marine sponges predominantly occur with a six-membered ring. However a small number of metabolites containing the five-membered 1,2-dioxolane ring have been identified.

Philipson[8] reported the first observation of a 1,2-dioxolane ring originating in a marine natural product. Plakinic acid A (**1.16**) was isolated from an unidentified species of Caribbean sponge of the family *Plakindae.* The structure was elucidated without indicating the stereochemistry about the 1,2-dioxolane, and a note added in proof recorded the isolation of another unnamed 1,2-dioxolane (**1.17**). 1,2-Dioxolane-containing natural products were next mentioned in 1989[9] when a series of five related compounds (**1.22a-e**) were identified from a sponge of the family *Halichondriidae.* They contained the same functionalised peroxide ring as (**1.16** and **1.17**), but were distinct from plakinic acid A by their long saturated hydrocarbon chain

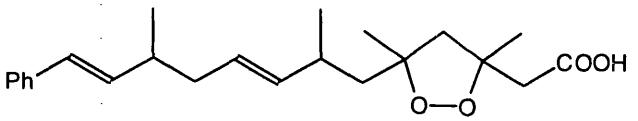
The last account, to date, of naturally occurring 1,2-dioxolanes in marine organisms, was in 1991[10]. Davidson isolated two new five-membered ring peroxides plakinic acids C and D (**1.18** and **1.20**), and their epimers, epiplakinic acid C and D (**1.19** and **1.21**), from a sponge of the family *Plakortis* collected in the Fiji Islands.

The structural analysis and identification of the plakinic acids and their natural analogues have revealed certain unifying features (see page 7). The most prominent similarity being the 1,2-dioxolane ring which has

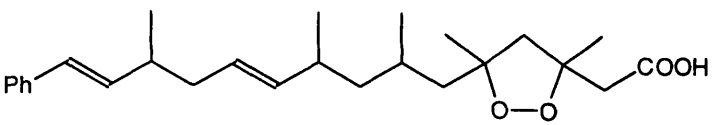
i) 3,5-dimethyl substitution,

ii) a carboxy methyl group in the 3 position, and

iii) a long hydrocarbon chain in the 5 position.



Plakinic Acid A **1.16**



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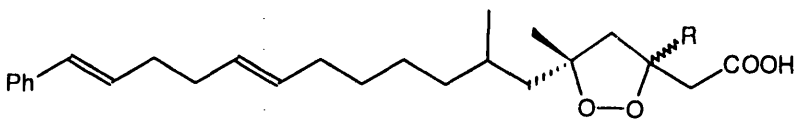
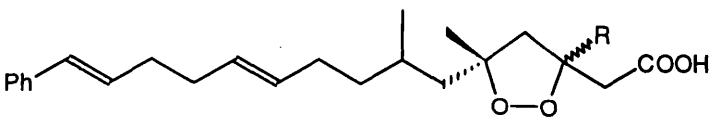


Plakinic Acid C R = β CH_3 **1.18**

Epiplakinic Acid C R = α CH_3 **1.19**



Plakinic Acid D R = β CH_3 **1.20**

Epiplakinic Acid D R = α CH_3 **1.21**

R

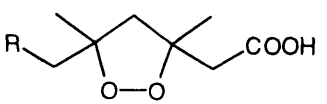
a $C_{12}H_{25}$

b $C_{13}H_{27}$

c $C_{14}H_{29}$

d $C_{15}H_{31}$

e $C_{16}H_{33}$

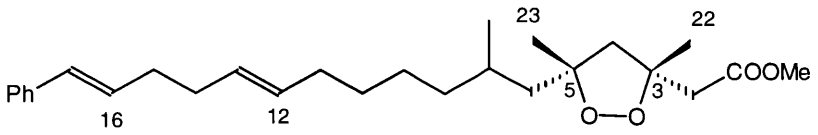


1.22

Characterisatlon of the plakinic and epiplakinic acids (1.18-1.21)

The plakinic and epiplakinic acids (**1.18-1.21**) were isolated from the marine sponge by sequential extraction with organic solvents. The first, methanolic, extraction of the freeze dried sponge yielded 2.9 g of material. Extraction by solvent partition with hexane gave 0.56 g of a hexane soluble bioactive material. After column chromatography an impure fraction of the 1,2-dioxolane acids was treated with diazomethane to give the methyl esters of (**1.18-1.21**). Isolation of the methyl esters of plakinic acids C and D and epiplakinic acids C and D was achieved by normal and reverse phase HPLC in 11.8, 9.2, 13.0, and 10.6 mg amounts respectively.

Characterisation of the plakinic acids was achieved using a number of techniques. In each case high resolution fast atom bombardment mass spectrometry established the molecular formula. The compounds were identified as acids by conversion to the corresponding methyl esters and this resulted in a typical shift in the carbonyl IR absorption from 1718cm^{-1} to 1738cm^{-1}. The presence of the styrene unit was discerned from the characteristic absorption in the UV; further identification of skeletal structure was achieved by ^{1}H and ^{13}C NMR experiments.



1.23

In the case of the methyl ester (**1.23**) of plakinic acid C (**1.18**), ^{13}C NMR showed 25 separate signals two of which were assigned to the carbons in degenerate positions of the phenyl group. The remaining carbon signals were assigned using long range heteronuclear correlation data and of the four quaternary carbons observed, the signals at δ 83.39 and 87.04 were assigned to the oxygenated ring carbons. Other homo and heteronuclear correlation experiments showed connectivity's between carbons and protons permitting further determination of skeletal structure. A COSY experiment along with long-range heteronuclear correlations enabled identification of the AB coupling pattern found in the proton NMR at δ 2.51 and 2.15 ppm as the ring protons. The methyls at C^{3} δ1.43 and C^{5} δ1.32 were also assigned using this technique. The conjugated olefin was assigned as *trans* from the proton-proton coupling constant ($J_{16,17}$ =15.5Hz). A similar coupling constant was observed for the medial olefin after irradiation of the adjacent methylenes reduced the observed multiplet to a doublet.

The isomeric relationship of (**1.18**) to (**1.19**) was indicated by mass spectral data and the observed differences in the ^{1}H NMR that occurred only in those resonances incorporated in the ring or connected to it.

NOESY experiments allowed the relative stereochemistry about the ring to be determined. The *cis* arrangement of (**1.23**) was established by the strong dipolar coupling exhibited from $C^{4}H_{A}$ to both methyls $C^{22}H_{3}$ and $C^{23}H_{3}$, while $C^{4}H_{B}$ only showed a strong correlation to the $C^{6}H_{2}$. An analogous NOESY experiment on the methyl ester of (**1.19**) displayed strong dipolar coupling between protons $C^{4}H_{A}$ and the $C^{23}H_{3}$ and from $C^{4}H_{B}$ to both $C^{22}H_{3}$ and $C^{6}H_{2}$ confirming a relative *trans* stereochemistry.

Biological activity of the plakinic acids and related 1,2-dioxolanes

All the natural products are reputed to possess biological activity (see page 172 Appendix One). Plakinic acid A (**1.16**) and compounds (**1.22a-e**) display general antimicrobial activity, while their ester derivatives are essentially inactive. However, in contrast, compounds (**1.18-1.21**) exhibited cytotoxic activity against human colorectal adenocarcinoma cells, human epidermoid carcinoma, and murine leukaemia cells both as the methyl esters and free acids.

To date there are no reports of the synthesis of this particular class of compounds. This together with the structural simplicity of the natural products and their apparent biological activity renders them attractive as synthetic targets. We therefore set out to develop a flexible synthesis of the functionalized 1,2-dioxolane, that would enable us to investigate structure-activity relationships and would provide a basis for the approach to the total synthesis of the natural products.

REFERENCES

1. Casteel D.A.; *Nat. Prod. Rep.*, **1992**, 289-312
2. Bhakuni,D.S., Sudha, J.; *Journal of Scientific and Industrial research*, **1990**, 49, 330-349.
3. Faulkner, D.J.; *Nat. Prod. Rep.*, **1990**, *7*, 269
4. Faulkner, D.J.; *Nat. Prod. Rep.*, **1993**, *10*, 497 .
5. Gonzalez, A., Martin, J., Perez, C., Rovirosa, J., Tagle, B., Clardy, J.;*Chem Lett.* **1984**,1649
6. Fenical, W., *J. Am. Chem. Soc.,* **1974**, *96*, 5580-5581
7. Ichiba, T., Scheur, P.J., Kelly-Borges, M.; *Tetrahedron,* **1995**, 51, *No. 45*, 12195-12202
8. Philipson, D.W., Rinehart, K.L.; *J. Am. Chem. Soc.,* **1983**, *105*, 7735-7736
9. Patil, A.D. *US Patent* 4,879,307 (1989); C.A., 1988, **109**, 17027f
10. Davidson, B.S.*; J. Org. Chem* , **1991**, *56*, 6722-6724

CHAPTER TWO

SYNTHESIS OF THE 3-CARBOXY METHYL-3,5,5-TRIMETHYL 1,2-DIOXOLANE

INTRODUCTION

Synthesis of 1,2-Dioxolanes

Synthesis of peroxide-containing molecules involves the formation of a C-O-O bond from a reagent already containing the O-O bond. This can be achieved in a number of ways:

i) Free radical mediated addition of oxygen
ii) Photo-oxygenation
iii) Ozonolysis
iv) Nucleophilic addition of hydrogen peroxide

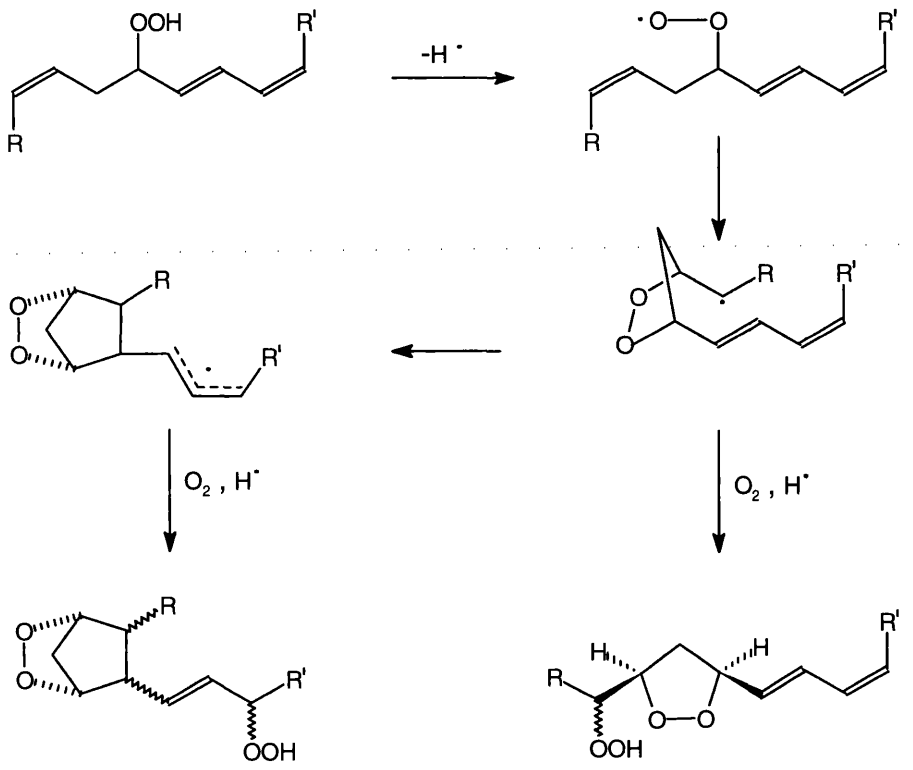
Our approach to the synthesis of the target natural products began with a consideration of the development of synthetic methods to 1,2-dioxolanes. These methods are either a one or two step procedure. A two step method involves cyclisation of preformed hydroperoxide, while other methods generate the hydroperoxide and effect cyclisation in one step.

Free Radical Mediated Addition of Oxygen

Lipid peroxidation is a complex process in which molecular oxygen and lipids react by a free radical chain sequence. Studies of the mechanisms of autoxidation by Porter[1], and Mihelich[2], have demonstrated that a homoallylic hydroperoxy radical within a polyunsaturated hydrocarbon will, via cyclisation, afford 1,2-dioxolanes (**2.2**). In both cases a recognised feature of the free radical cyclisations is the preference to give dioxolanes rather than dioxanes and to place the 3 and 5 substituents on the ring in a *cis* relationship.

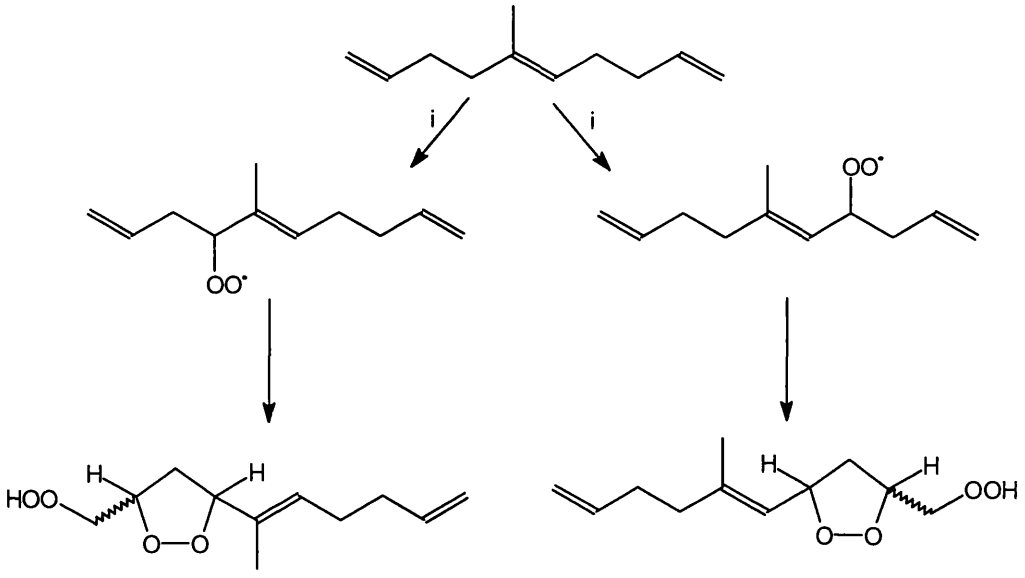
The natural product PGG_2 (**1.16**) as mentioned in Chapter One, is derived enzymatically from a 20-carbon polyunsaturated fatty acid (**1.15**) (**Scheme 1.1**). Mihelich synthesised an analogue (**2.1**) of PGG_2 by enzymatic insertion of the hydroperoxide group followed by autoxidation (**Scheme 2.1**).

Courtneidge[3] used a modified autoxidation procedure to achieve both hydroperoxidation and cyclisation, again observing the preference for dioxolane (**2.3 and 2.4**) formation but made no comment on the ring stereochemistry (**Scheme 2.2**).



2.1 **2.2**

Scheme 2.1



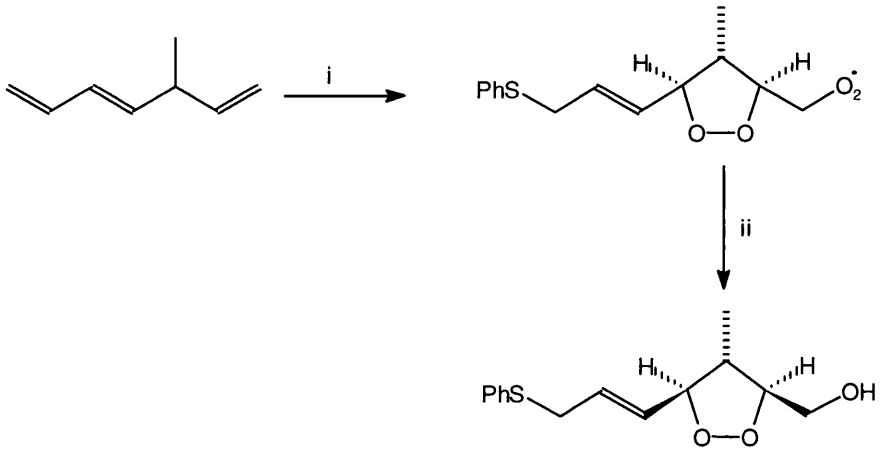
2.3 **2.4**

i) t-butyl hydrogenperoxide, AIBN, 2,2,4-trimethylpentane, O_2, 60 ^{0} C

Scheme 2.2

Other free radical methods use thiol-oxygen cooxidation (TOCO) reactions of olefins[4] and vinylcyclopropanes[5].

Beckwith demonstrated that a phenylthioradical would combine with suitable trienes in an atmosphere of oxygen to provide a functionalised 1,2-dioxolane (**2.5**) (**Scheme 2.3**).

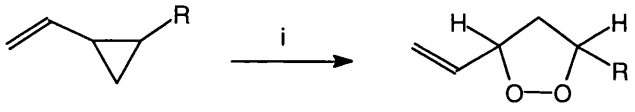


2.5

i) PhSH, O_2 ii) PhSH, PPh_3

Scheme 2.3

Feldman required a 1,2-dioxolane to use as an intermediate in the synthesis of 1,3-diol-containing natural products. Certain features of the Beckwith synthesis i.e. incorporation of the initiator and the alcohol formed on radical termination were undesirable. To this end, still using the basis of the TOCO reaction, he devised and developed a general synthesis using vinylcyclopropanes that eliminated both unwanted functionalities (**Scheme 2.4**).

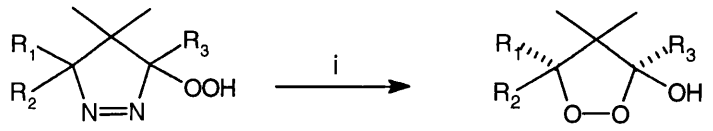


2.6

i) O_2, Ph_2Se_2, AIBN, hν

Scheme 2.4

A few examples of 3-hydroxy-1,2-dioxolanes occur in natural products[6] see Chapter One (**1.17**). Baumstark[7] synthesised a series of the hemiperketals (**2.7**) via O_2 trapping of β-keto radical intermediates, generated during the thermolysis of cyclic α-azo hydroperoxides (**Scheme 2.5**).

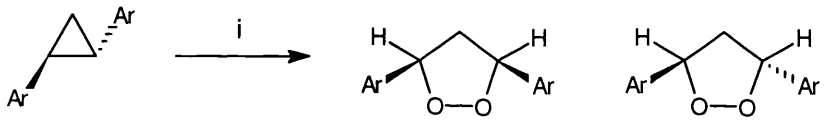


2.7

i) O_2, benzene

Scheme 2.5

Another free radical mode of addition is that of triplet oxygen with radical cations[8]. This will usually produce endoperoxides, via a chain mechanism. Mizuno and co-workers generated radical cations of diarylcyclopropanes by single electron transfer to photosensitised DCA to make the 1,2-dioxolanes (**2.8** and **2.9**) (**Scheme 2.6**).



2.8 **2.9**

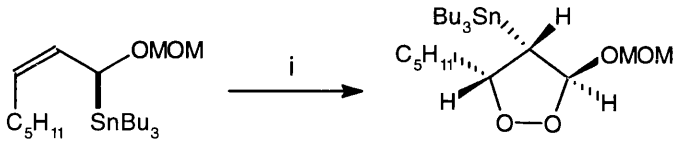
i) DCA, O_2, hν, CH_3CN

Scheme 2.6

Photo-oxygenation

Singlet oxygen undergoes several types of reactions with unsaturated hydrocarbons. One of which, the ene reaction, produces allylic hydroperoxides through an intermediate perepoxide, formed by the oxygen and olefin.

During a study of the singlet oxygenation of chiral allylstannanes, to synthesise enantiomerically enriched allylic hydroperoxides, Dussault observed small amounts of 1,2-dioxolane formation[9]. Further work[10] showed how, by modification of the allylstannane substrate, the more typical ene reaction product could be suppressed in favour of 1,2-dioxolane formation (**Scheme 2.7**).

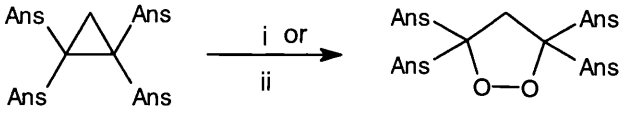


2.10 **2.11**

i) RB, O_2, $CDCl_3$, 0 ^{0}C

Scheme 2.7

Also using photooxygenation Ando[11] found the reaction of 1,1,2,2-tetranisylcyclopropane (**2.12**) with both photochemically and thermally produced singlet oxygen afforded the corresponding quaternary substituted 1,2-dioxolane (**2.13**) (**Scheme 2.8**).



2.12 **2.13**

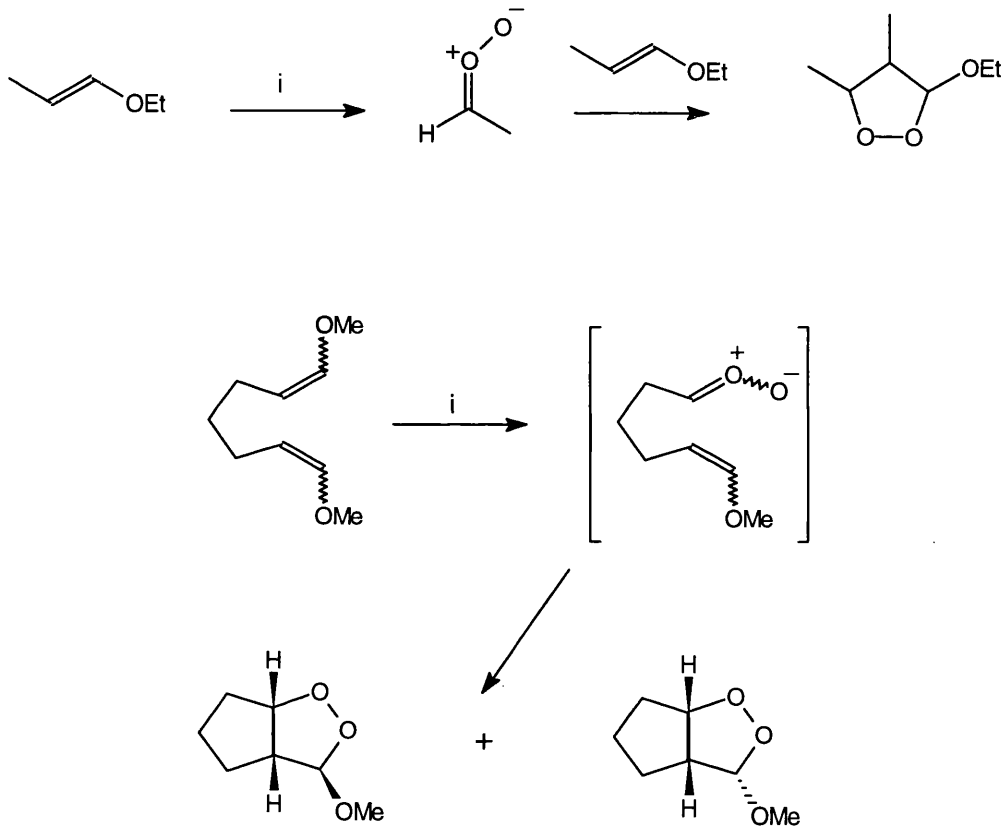
i) 1,4-dimethylnaphthalene endoperoxide, DCM, 40 ^{0}C or

ii) TPP, O_2, hv, DCM

Scheme 2.8

Ozonolysis

The reaction of ozone with organic compounds results in the formation of organic peroxides as either intermediate or stable products. Ozonolysis of alkenes leads to the formation of ozonides, the mechanism of which was formulated by Criegee[12]. One of the key intermediates in the Criegee ozonolysis mechanism is the carbonyl oxide which, although posses a high degree of 1,3 dipolar character, were found to undergo cycloadditions with only carbonyl compounds. Recent work however has shown the carbonyl oxide will participate in cycloadditions with vinyl ethers[13], to produce 1,2-dioxolanes and this methodology was employed to synthesise the fused ring 1,2-dioxolanes[14] (**2.14 2.15**) (**Scheme 2.9**).



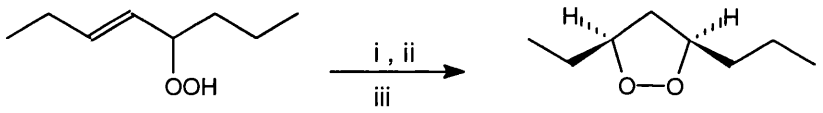
2.14 **2.15**

i) O_3, 0 ^{0}C, DCM

Scheme 2.9

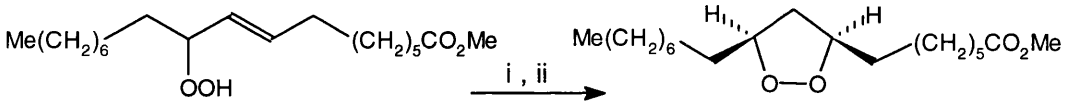
Nucleophilic Addition of Hydrogen Peroxide

The nucleophilic character of hydrogen peroxide has been exploited extensively in the synthesis of peroxide-containing molecules. Included in this is the nucleophilic addition of hydrogen peroxide and alkylhydroperoxides to alkenes, via mercurinium ions, peroxymercuriation[15] . This has provided a facile route to many endoperoxides including 1,2-dioxolanes. Similar to other methods of dioxolane synthesis, this can occur by intramolecular cyclisation of a preformed[16, 17]hydroperoxide of which the trans-allylic hydroperoxides (**2.16** and **2.18**) are an example. These hydroperoxides were generated by photo-oxygenation and on treatment with electrophilic mercury(II) salts underwent stereospecific 5-endo ring closure to the 1,2-dioxolanes (**2.17** and **2.19**) (**Scheme 2.10**).



2.16 **2.17**

i) $Hg(OAc)_2$ ii) NaBr(aq) iii) $NaOH/NaBH_4$

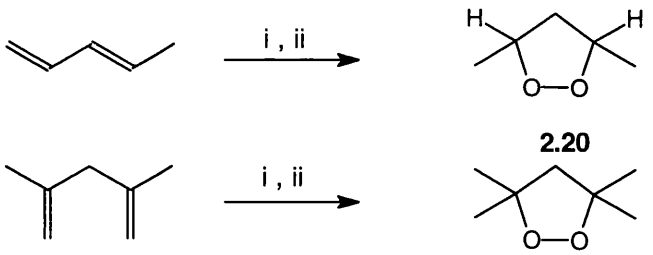


2.18 **2.19**

i) $Hg(NO_3)_2$ ii) $NaBH_4/NaOH(aq)$

Scheme 2.10

Furthermore a series of variously substituted monocyclic 1,2-dioxolanes were made from an assortment of dienes via peroxymercuriation/ demercuriation[18,19] employing two mole equivalents of mercury(II) salts and 80% hydrogen peroxide (**Scheme 2.11**). This can be considered a one step reaction as initial addition of mercury and hydrogen peroxide across one double bond generates an intermediate mercurioalkylhydroperoxy which via a second mercurinium ion undergoes an intramolecular cyclisation to form the 1,2-dioxolane.



2.20

2.21

i) 80% H_2O_2 $Hg(NO_3)_2$ ii)$NaBH_4$/NaOH(aq)

Scheme 2.11

Synthesis of the Target 1,2-Dioxolane

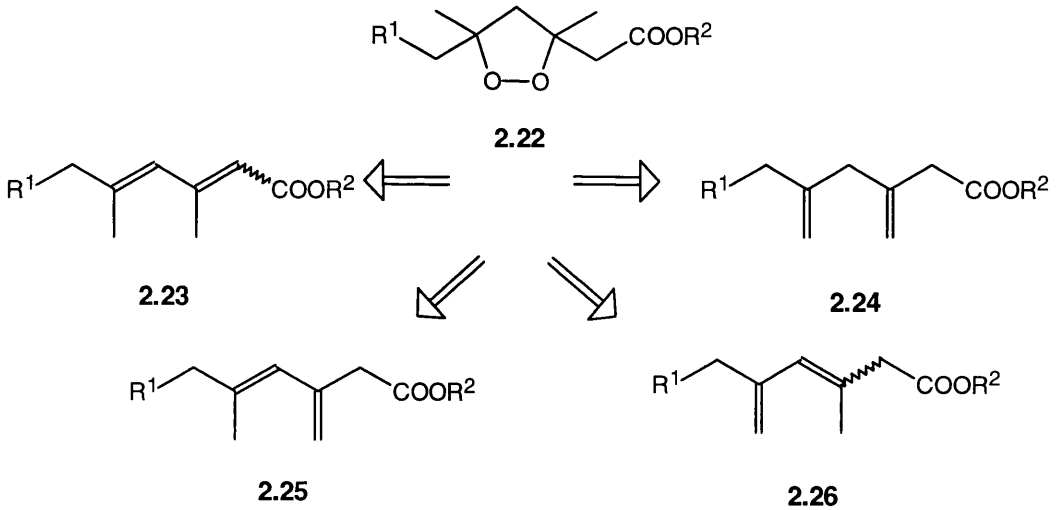
We set out to develop a synthetic strategy to compounds (**2.22**) which would

i) provide the 1,2 dioxolane with 3,5-dimethyl and 3 carboxymethyl substituents,

ii) support a variety of R^1 groups and

ii) provide a basis for approaching the total synthesis of the plakinic acids

Peroxymercuriation was an attractive approach to the target 1,2-dioxolanes as it is a proven method for the synthesis of quaternary substituted 1,2-dioxolanes[19] and tolerant of the ester moiety within a substrate. Retrosynthetic analysis on this basis suggested four possible diene carboxylate substrates (**2.23-2.6**).



2.22

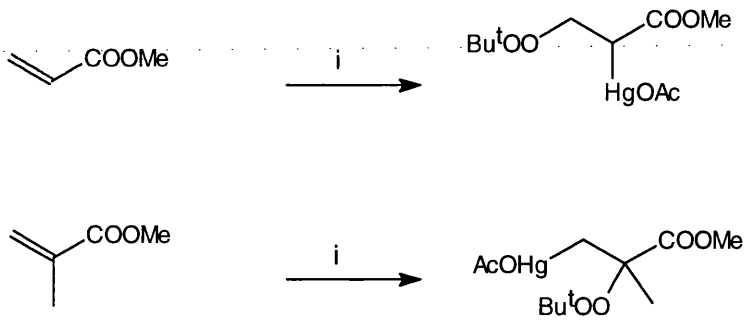
2.23

2.24

2.25

2.26

The αβγδ-unsaturated diene (**2.23**) was the preferred isomer as it was thought likely to be the most amenable to a general synthesis and, although more resistant to electrophilic attack, αβ-unsaturated carbonyls[20] will undergo peroxymercuriation (**Scheme 2.12**).



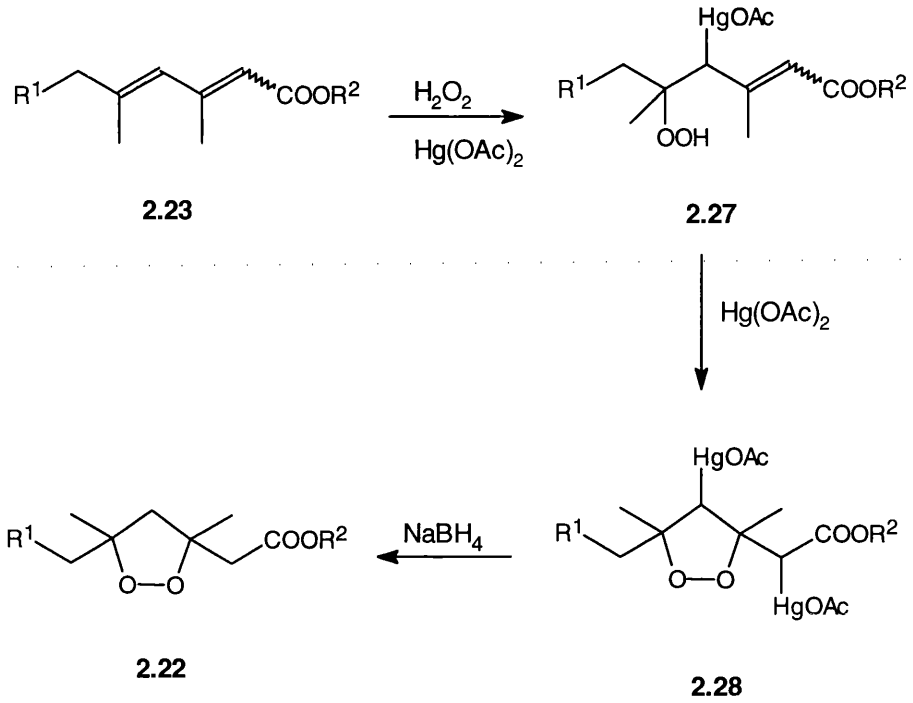
i) $Hg(OAc)_2$/ Bu^{t}OOH/ perchloric acid catalyst

Scheme 2.12

Preparation of dioxolanes[18,19] have, in the past, used 80% hydrogen peroxide. More recently Bloodworth and co-workers[21] generated alkylhydroperoxymercurials using an equimolar amount of mercury(II) acetate and alkene with a 9-fold excess of aqueous 30% hydrogen peroxide. Due to the less hazardous nature of the 30% hydrogen peroxide we decided to adopt these reaction conditions but using a two-fold excess of mercury(II) acetate.

We predicted the γδ–double bond would be the most electron rich, and this assumption was supported by molecular modelling studies of the HOMO of 3,5-dimethylocta-2,4-dienoic acid. (See Appendix One page 165) which indicated the uncoupling of the double bonds from a reactivity point of view.

This being the case we would expect the γδ–double bond to be the initial site of attack for the mercury electrophile. Assuming 1,2-addition[22] we would then expect the intermediate hydroperoxide (**2.27**) to undergo intramolecular peroxymercuriation to give the bismercuriated-1,2-dioxolane (**2.28**) more easily than the corresponding intermolecular hydroperoxymercuriation. Hydridodemercuriation following the procedure developed by Coutneidge[16] would then supply our target dioxolane (**2.22**) (**Scheme 2.13**).



2.23 **2.27** **2.22** **2.28**

Scheme 2.13

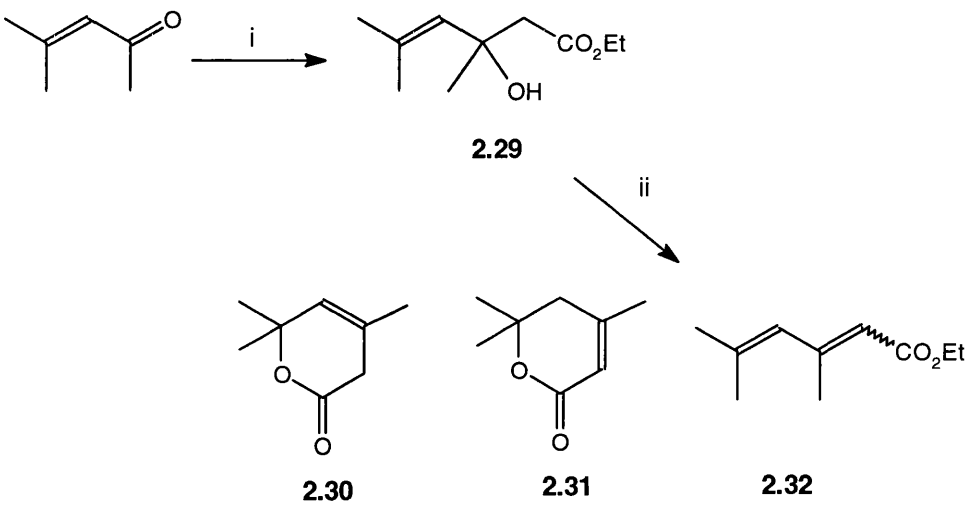
As a result of peroxymercuriation four chiral centres are generated, two of which are lost after demercuriation, to leave the dioxolane as a pair of diastereoisomers. We decided to conduct our initial investigations into the viability of the peroxymercuriation route on a diene carboxylate where R^1=H. This could be simply prepared from mesityl oxide by the Reformatsky reaction[23] and would introduce only one chiral centre, thereby reducing the complexity of the final product.

RESULTS AND DISCUSSION

Synthesis and Characterisation of Ethyl 3,5-Dimethylhexa-2,4-Dienoate and Isomeric Diene Esters.

Synthesis of the Diene Esters

The Reformatsky reaction of mesityl oxide and ethyl bromoacetate afforded the hydroxy ester (**2.29**) in a 70% yield. Subsequent dehydration with $POCl_3$ gave a 3:1 mixture of E:Z isomers of the requisite diene ester (**2.32**), accounting for 20% of the products. The stereoisomers were distinguishable by their ^1H NMR spectra; The E isomer shows a downfield shift for the C^3CH_3 methyl at δ2.25 ppm compared to δ1.89 for the Z isomer which exhibits a downfield shift of the olefinic proton at C^4 of δ6.4 ppm compared to δ5.70 for the E isomer These resonance shifts occur as the protons in each case lie in the deshielding cone of the ester carbonyl. The remainder of the product mixture was made up of δ-lactones (**2.30**) 56% and (**2.31**) 17% in agreement with previous observations[24] (**Scheme 2.14**).



i) $BrCH_2CO_2Et$, Zn ii) $POCl_3$

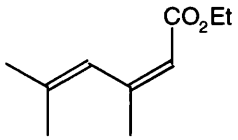
Scheme 2.14

In an attempt to increase the yield of the diene ester and avoid lactone formation we used the method of dehydration proposed by Cologne[23] et al. The hydroxyester was heated over anhydrous copper(II) sulfate under reduced pressure and, after purification by column chromatography, the diene ester was isolated in a 65% yield. Cologne suggests that this method of dehydration produces only the E isomer, which inhibits lactone synthesis, in 95% yield,. In our hands, although it eliminated lactone formation, the method led to a mixture of several isomers. The ^1H NMR exhibited signals consistent with the E and Z isomers formed in the previous dehydration. Further signals at δ 5.00-4.80 indicated the presence of terminal

double bonds and we postulated that 1,4-and 1,2-elimination had occurred. Analysis by gas liquid chromatography indicated that the mixture contained five components with similar retention times.

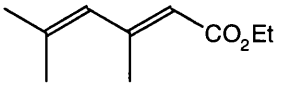
Characterisation of the diene esters

Separation by preparative glc and analysis by ^{1}H NMR of the fractions collected, established the existence of five isomers. Fractions 4 (20%) and 5 (13%) exhibited spectra compatible with those of the E (**2.33**) and Z isomers (**2.34**)



2.34

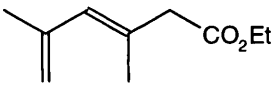
Fraction 4



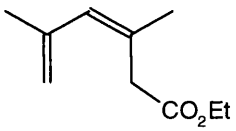
2.33

Fraction 5

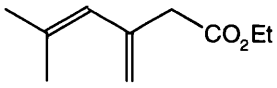
Fractions 1-3 showed signals in the ^{1}H NMR consistent with terminal olefinic protons and this along with other resonances suggested they represented the isomeric diene esters (**2.35-2.37**).



2.35



2.36

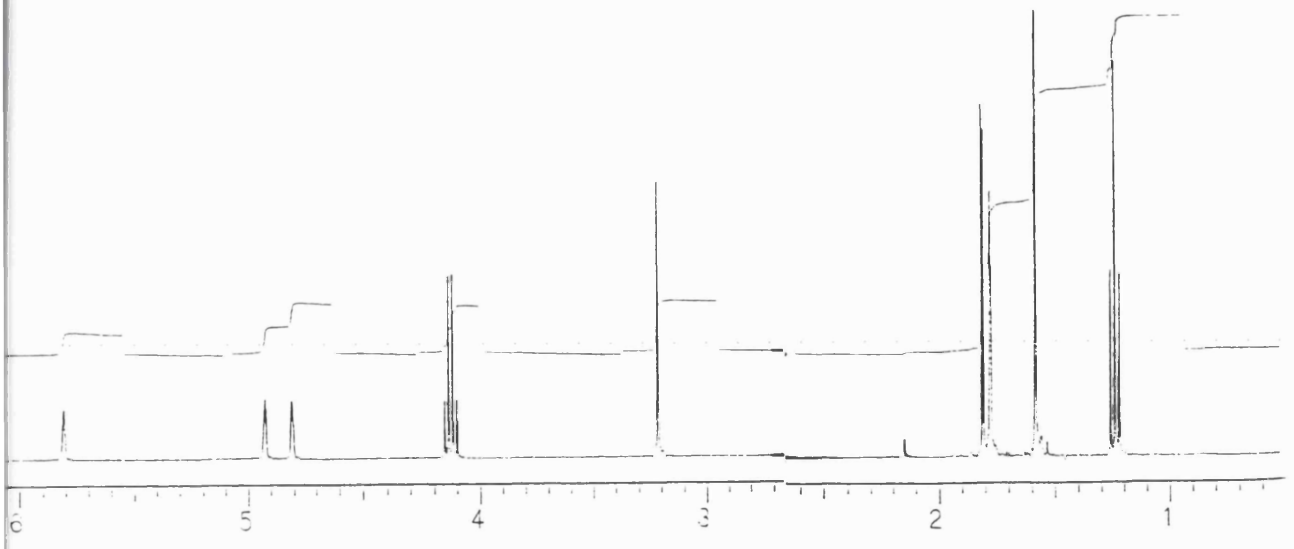


2.37

In order to ascertain the exact structure of the isomers in fractions 1-3, Nuclear Overhauser experiments were performed on each fraction. In NMR spectroscopy, changes brought about in the energy populations of one nucleus by the decoupling of a neighbouring nucleus is named the Nuclear Overhauser effect. Two conditions which always apply to the nOe are as follows

i) It arises during the double irradiation of one nucleus and affects another nucleus which must be spatially close, but which is not necessarily coupled with the irradiated nucleus.

ii) It is associated with dipolar relaxation mechanisms. NOe in ^{1}H NMR is measured by increases in signal intensities. Measurement of this increase can be detected by comparisons of the integrals of the proton before and during irradiation or by subtraction of the spectra before and during irradiation. Analysis of fractions 1-3 by irradiation of the two methyl and three olefinic protons in turn permitted assignment of the diene structures.



Fraction 1 nOe data lowfield terminal olefin (C^6H) to highfield terminal olefin (C^6H) (11%)

highfield terminal olefin (C^6H) to lowfield terminal olefin (C^6H) (7%)

highfield terminal olefin (C^6H) to CH_2 (C^2H_2) (2%)

lowfield methyl (C^3CH_3) to internal olefin (C^4H) (17%)

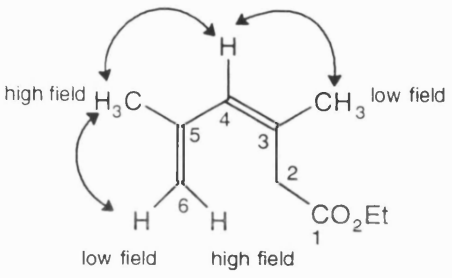
highfield methyl (C^5CH_3) to internal olefin (C^4H) (5%)

highfield methyl (C^5CH_3) to lowfield terminal olefin (C^4H) (5%)

highfield methyl (C^5CH_3) to CH_2 (C^2H_2) (2%)

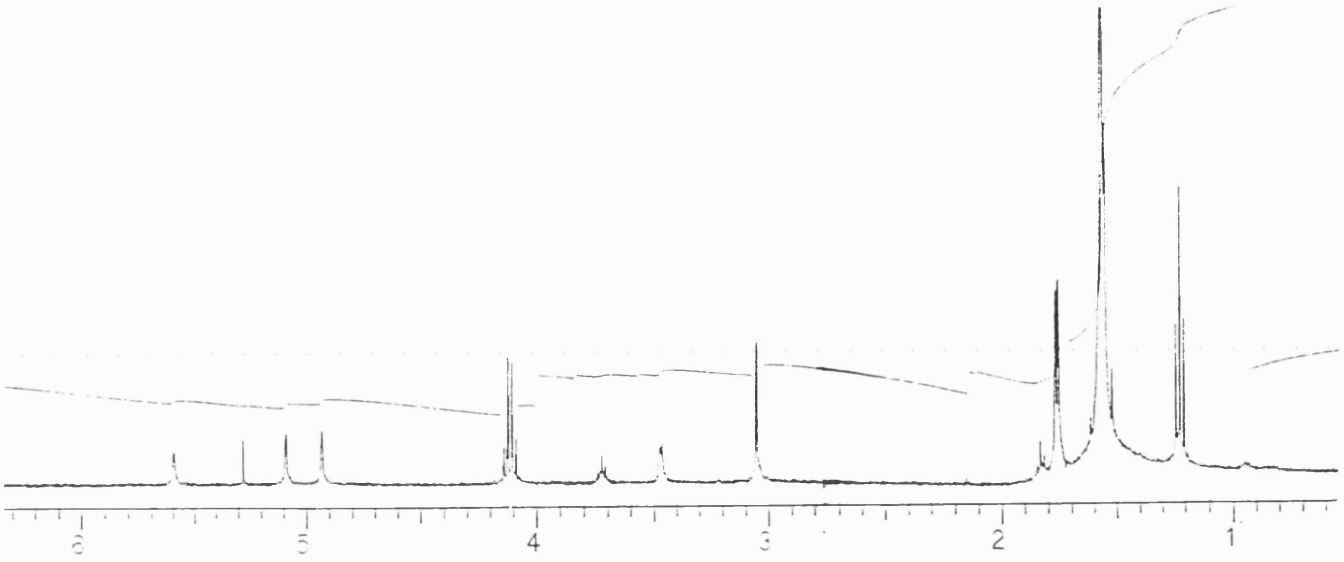
Fraction 1 (9%) showed nOe between the high field methyl protons and the internal olefinic proton and with the low field terminal olefinic proton. The low field methyl protons, however, enhanced only the internal olefinic proton.

Irradiation of the olefinic protons showed no converse effect on the methyls. This is not unexpected as the main mechanism of relaxation of the methyl protons is not by the dipolar route. The high field terminal proton exhibited nOe with the methylene moiety adjacent to the ester group and, as with the other two fractions, the terminal protons show enhancement of each other. Assuming a cisoid conformation leads us to assign the structure of diene (**2.36**) to fraction 1. The nOe results also allow for the unambiguous assignment of the signals for the methyls and the terminal protons.



2.36

The assignment of Fraction 1 to this structure is further supported by noting that no positive nOe was detected between the internal olefinic proton and the methylene as expected for structure (**2.36**). an effect which is observed in fraction 3.



Fraction 2 nOe data internal olefin (C^4H) to highfield methyl (C^6H_3) (2.5%)

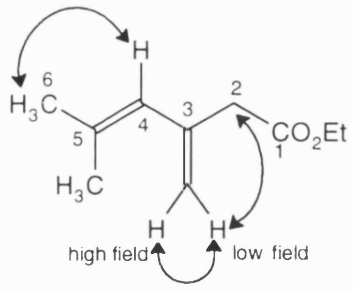
lowfield terminal olefin (C^3CH_2) to highfield terminal olefin (C^3CH_2) (10%)

lowfield terminal olefin (C^3CH_2) to CH_2 (C^2H_2) (2%)

highfield terminal olefin (C^3CH_2) to lowfield terminal olefin (C^3CH_2) (10%)

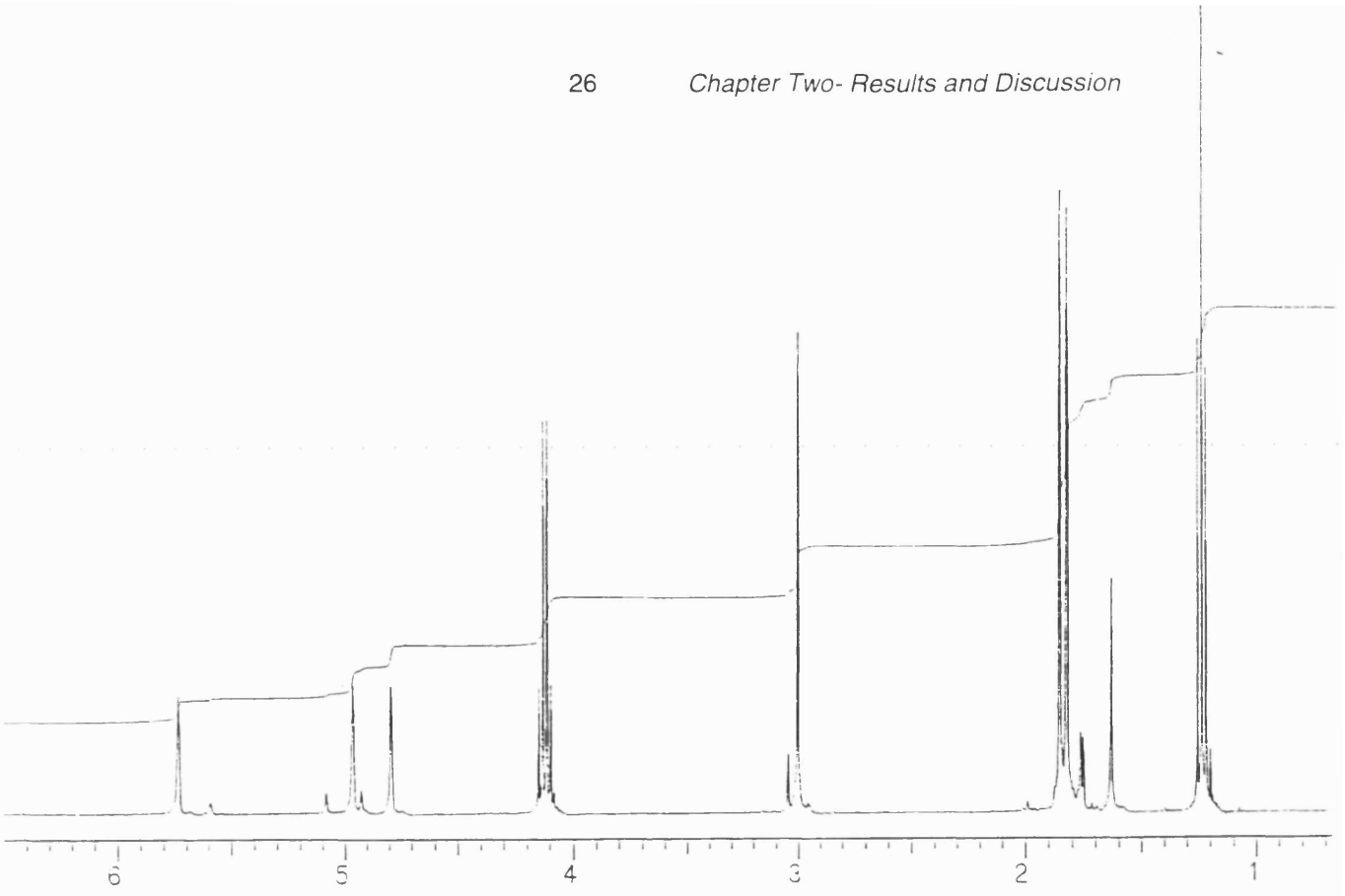
lowfield methyl and highfield methyl ($C^6H_3C^3CH_3$) to internal olefin (C^4H) (5%)

In fraction 2 (4%) all the methyl protons were irradiated simultaneously because of their similar chemical shifts and showed nOe with the internal olefinic proton only. The spatial proximity of these protons was confirmed on irradiation of the internal olefinic proton: The terminal protons showed nOe to each other and the lowfield proton showed an enhancement of the methylene signal.



2.37

From the evidence above we assigned fraction 2 as structure (**2.37**). We did not assign this diene to fraction 3 as those results show enhancement of an internal and terminal olefinic on irradiation of one methyl. An nOe of that nature would be unlikely in this structure.



Fraction 3 nOe data internal olefin (C^4H) to $CH_2(C^2H_2)$ (2.5%)

internal olefin (C^4H) to highfield methyl (C^5CH_3) (2.5%)

lowfield terminal olefin (C^6H) to highfield terminal olefin (C^6H) (14%)

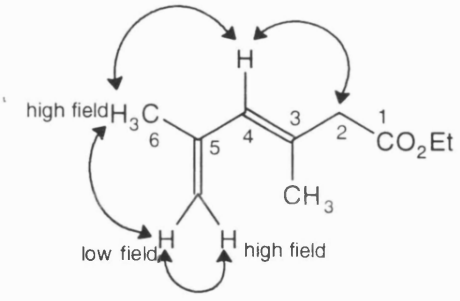
highfield terminal olefin (C^6H) to lowfield terminal olefin (C^6H) (5%)

lowfield methyl (C^3CH_3) to highfield terminal olefin (C^6H) (2%)

highfield methyl (C^5CH_3) to internal olefin (C^4H) (3%)

highfield methyl (C^5CH_3) to lowfield terminal olefin (C^4H) (3%)

In fraction 3 (55%) the major fraction of the mixture that contains terminal olefinic protons, showed nOe between the internal olefinic proton and the methylene group. There was also an indication that the high field methyl was close to the internal olefinic proton and the low field terminal proton in the molecule.



2.35

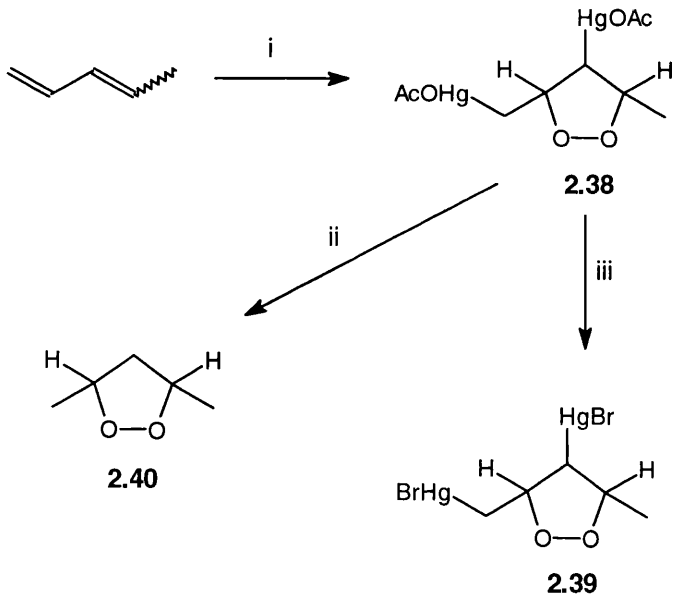
These results were consistent with the structure of isomer (**2.35**).

Again absolute assignment of the chemical shift values for the methyls and terminal protons was possible and are in agreement with those previously assigned in the *Z* isomer (**2.36**) of this configuration.

Synthesis of 3-Carboxymethyl-3,5,5-trimethyl-1,2-dioxolane

Peroxymercuriation of a Simple Diene

Initial investigations into the viability of 30% hydrogen peroxide as a potent reagent for the synthesis of 1,2-dioxolanes from dienes, were carried out on hexa-1,4-diene (**Scheme 2.15**). The diene was added to a pale orange suspension of two mole equivalents of mercury(II) acetate in nine mole equivalents of 30% H_2O_2. Following addition of the diene the reaction mixture went from pale orange to clear and after stirring for one hour a white solid appeared. This solid was isolated by filtration in a 65% yield and, after anion exchange with KBr (aq) and recrystalization from MeOH, we obtained an analytical sample of the bisbromomercuriated 1,2-dioxolane (**2.39**) in a 40% yield. Following hydridodemercuriation of the bisacetoxymercuriated dioxolane (**2.38**) the expected 1,2-dioxolane (**2.40**) was isolated by column chromatography in a 4% yield. The reduction in yield upon hydridodemercuriation is consistent with earlier work[19] where products of deoxymercuriation were found after treatment of cycloperoxymercurials with sodium borohydride.

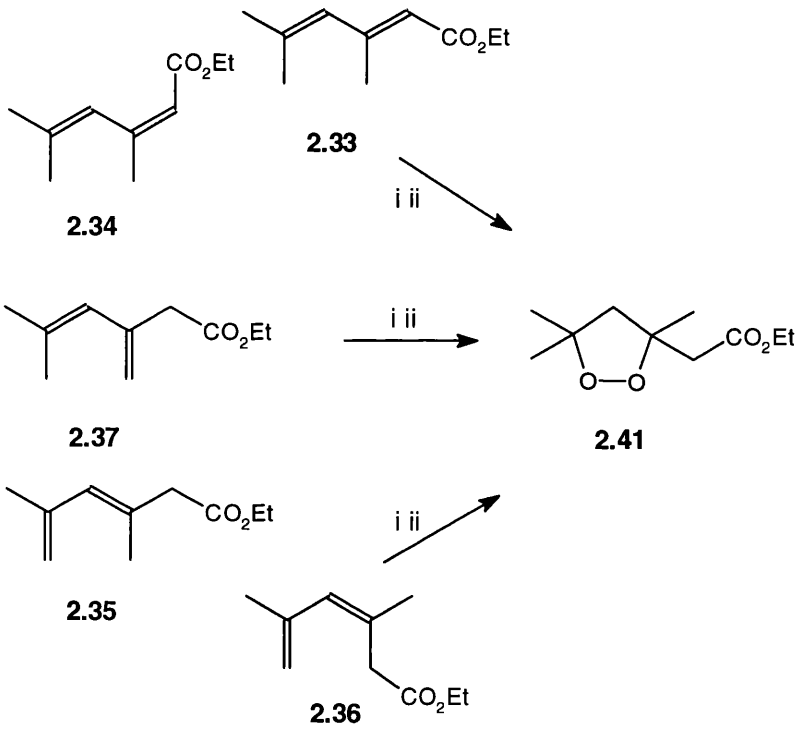


i) $Hg(OAc)_2$ 30% H_2O_2 ii) $NaBH_4$/NaOH iii) KBr(aq)

Scheme 2.15

Peroxymercuriation of the Diene Esters

Despite the low yields obtained from the preliminary investigation (**Scheme 2.15**) we went on to attempt synthesis of the target dioxolane using the diene esters (**2.33-2.37**). A typical experiment involved addition of the diene ester neat, as an oil, or as a solution in DCM, to a stirred suspension of mercury(II) acetate in 30% hydrogen peroxide. In line with peroxymercuriation of the simple diene the reaction mixture turned from pale orange to colourless after addition of the diene substrate. The time taken for the colour change to occur varied in relation to the isomeric composition of the diene ester substrate and we adopted this observation as a measure of the reactivity of the substrate to mercuriation. The intermediate bismercuriated 1,2-dioxolane was extracted from the reaction mixture with DCM and underwent hydridodemercuriation to afford the 1,2-dioxolane (**2.41**) (**Scheme 2.16**).



i) $Hg(OAc)_2$ 30% H_2O_2 ii) $NaBH_4$/NaOH

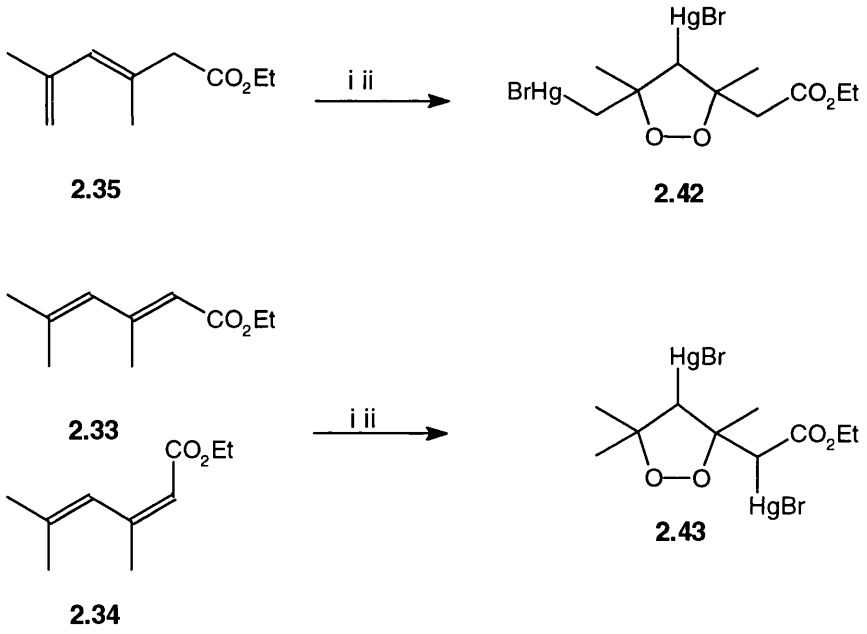
Scheme 2.16

We performed the peroxymercuriation/ demercuriation reaction on three groups of diene esters, each of which displayed subtle differences in the results. Peroxymercuriation/ demercuriation of the E/Z αβγδ diene (**2.33 2.34**) afforded the desired 1,2-dioxolane in a 13% yield from an of E:Z ratio of 3:1, and in a 30% yield from an E:Z ratio of 8:1. We also observed the diene mixture enriched with the E isomer to be less reactive. Synthesis of the 1,2 dioxolane from the mixture of five dienes (**2.33-2.37**) gave the most substantial yield,

40%, and exhibited the shortest reaction time. In each case the reaction time increased when the diene is added as a solution in DCM.

We can account for the observed differences in reaction times by considering the relative reactivities of double bonds to oxymercuriation. Brown's[25] studies showed terminal disubstituted olefins to be the most reactive; increasing substitution of internal olefins leads to a decrease in reactivity, and Z olefins are more reactive towards oxymercuriation than the corresponding E isomers. All the above findings help to rationalize the relative rates of reactivity we noted. We also found evidence to explain the disparity in yields obtained from the two-and five-diene mixtures.

Fraction 3 (**2.35**) makes up 55% of the five-diene mixture. Peroxymercuriation of this diene alone gave the bromomercuri-1,2-dioxolane (**2.42**) in an 80% yield with minor side products. Peroxymercuriation, followed by anion exchange, of the separated E (**2.33**) and Z (**2.34**) αβγδ diene afforded a 22% and 15% yield of the mercuriated dioxolanes(**2.43**) respectively after purification by column chromatography. All three mercuriated dioxolanes were isolated as mixtures of unassigned isomers (**Scheme 2.17**)

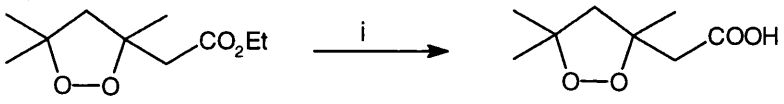


i) $Hg(OAc)_2$ 30% H_2O_2 ii)KBr

Scheme 2.17

Saponification of the dioxolane ester

Following the synthesis of the 1,2-dioxolane ester, liberation of the free acid was the final step in the synthesis of our first unnatural analogue (**2.44**) of the plakinic acids. We achieved this, albeit in low yields, by heating (**2.41**) to 40 ^{0}C in methanolic NaOH (**Scheme2.18**).

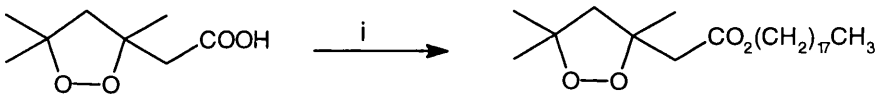


2.41 **2.44**

i) NaOH/ MeOH/ 40 ^{0}C

Scheme 2.18

Finally, for the purpose of probing the structural requirements necessary for biological activity, we synthesised a long chain ester analogue (**2.45**) by a DCC coupling[26] of octadecanol with the dioxolane acid (**2.44**) (**Scheme 2.19**).



2.44 **2.45**

i) DCC, DMAP, octadecanol, DCM

Scheme 2.19

Assignment of the ^{1}H and ^{13}C NMR spectra of (**2.41**, **2.44** and **2.45**) was achieved by comparison with the data reported by Davidson. Our trimethyl substituted 1,2-dioxolanes have only one chiral centre and the spectra are therefore less complex than those obtained from the plakinic acids. In each case the $C^{2}H_{2}$ and the ring protons $C^{4}H_{2}$ were identified as an AB (2x doublet) coupling pattern. In the ^{1}H NMR spectra of (**2.44**) the $C^{2}H_{2}$ protons resonate at δ2.73 and 2.59 ppm while the ring protons appear at a lower chemical shift of δ2.53 and 2.17 ppm. A similar pattern is observed in the spectra of both (**2.41** and **2.45**) with the protons adjacent to the carboxyl group appearing at a higher chemical shift than the ring protons. This pattern is reversed in the ^{13}C NMR where the C^{4} ring carbon appears at δ56.5 ppm and the C^{2} carbon at δ44.25 ppm: The oxygenated ring carbons were assigned to the peaks at δ84.20 and 84.10 ppm (see spectra page 40 and 41).

EXPERIMENTAL

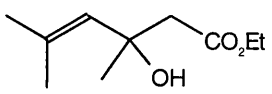
All reagents and solvents were used as supplied commercially, except as noted:
Unless otherwise stated ^{1}H and ^{13}C nmr spectra were recorded at 400MHz and 100MHz respectively on a Varian VXR-400 instrument. All spectra were recorded in $CDCl_3$ with chemical shifts quoted in parts per million (δ) relative to an internal standard of residual $CHCl_3$ ^{1}H δ 7.24 ^{13}C δ 77.0; individual peaks are reported as (number of hydrogens, multiplicity, coupling constant). J values are given in Hertz. Mass spectra were recorded by EI and FAB on a VG micromass 305 and ZAB SE respectively.Infrared spectra were recorded on a Perkin Elmer 943G spectrometer and melting points were obtained on a Reichart Melting Point apparatus. Elemental analyses were obtained from the UCL chemistry department. Thin layer chromatography was performed on pre-coated aluminium backed plates, Merck Kieselgel 60 F_{254}, and visualised using p-anisaldehyde, and acidified iron(II) isothiocyanate for the detection of peroxidic material.

Preparation of ethyl 3,5-dimethyl-3-hydroxyhexa-4-enoate. (2.29)

1 ml of a solution of mesityl oxide (10.29 ml, 0.1 mol) and ethylbromoacetate (11.2 ml, 0.105 mol) in dry ether (20 ml) and dry benzene (20 ml) was added to some activated zinc (6.85 g, 1 mol). The reaction mixture after a little warming began to bubble indicating the reaction had started. The remaining solution was added dropwise, with stirring, over an hour, ensuring that the reaction did not become too vigorous. When refluxing had ceased the reaction mixture was heated to reflux for a further hour. The reaction mixture was cooled to 0 ^{0}C and poured over ice. Concentrated H_2SO_4 was then added dropwise until the solution became acidic. The solution was diluted with ether (70 ml) and the white precipitate formed was filtered off. The aqueous layer was removed and the organic layer washed successively with sat. $NaHCO_3$(aq) (2x50 ml), H_2O (2x50 ml) and sat. NaCl(aq) (50 ml). The organic layer was dried ($MgSO_4$) and concentrated to give a bright yellow liquid, 13.16 g.

The crude product was purified by reduced pressure distillation b.p. 102 ^{0}C 15mmHg. Yield 10.20g (54%).

^{1}H NMR δ:5.20(1H, bs, **H**C=C), 4.15(2H, q, J=8, OC**H**$_2$CH$_3$)
3.70(1H, s, O**H**)
2.45 and 2.65(2H, AB, J=13,C**H**$_2$CO$_2$Et)
1.65 and 1.85(6H, s, (C**H**$_3$)$_2$C=)
1.35(3H, s, C**H**$_3$COH), 1.24(3H, t, J=8, O-CH$_2$C**H**$_3$).



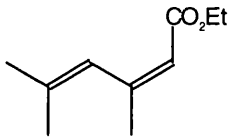
^{13}C NMR δ:172.70(**C**=O), 134.70 and 129.40(**C**=**C**), 71.00(**C**-OH), 60.45(**C**H_2O) 46.65(**C**H_2C=O), 27.10 and 28.40((**C**H_3)$_2$C=), 18.30 and 14.00 (2x**C**H_3).

Preparation of (2*E,Z*)-ethyl 3,5-dimethylhexa-2,4-dienoate. (2.30 2.31 2.34 2.33)

$POCl_3$ (1 ml, 10 mmol) was added to a solution of the hydroxyester (**2.29**) (4 g, 14 mmol) in toluene (50 ml). The reaction mixture was heated to reflux for one hour, cooled to room temperature and diluted with toluene (25 ml). The solution was then washed succesively with sat. $NaHCO_3$(aq) (2x50 ml), H_2O (2x50 ml) and sat. NaCl(aq) (50 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 3.1 g of a brown oil. Purification by column chromatography (SiO_2) gave 2 major products.

Fraction 1 Hex:EtOAc 20:1. Clear oil, 0.6 g (18%) ratio of 3:1, E:Z.

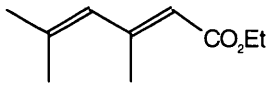
Z Isomer (**2.34**)



^{1}H NMR δ:6.45(1H, s, (H$_3$C)$_2$C=C**H**)
5.65(1H, s, C=C**H**CO$_2$Et), 4.15(2H, m, OC**H**$_2$)
1.75 and 1.89(6H, s, (C**H**$_3$)$_2$C=)
1.60(3H, s, C**H**$_3$C=), 1.26(3H, m, OCH$_2$C**H**$_3$).

^{13}C NMR δ:166.20(**C**=O), 153.45(**C**=CCO$_2$Et), 138.65((CH$_3$)$_2$**C**=C), 123.95((CH$_3$)$_2$C=**C**)
117.15(C=**C**CO$_2$Et), 59.50(O-**C**H$_2$), 27.15, 25.05 and 19.55(3x**C**H$_3$),
14.35(O-CH$_2$**C**H$_3$).

E isomer (**2.33**)

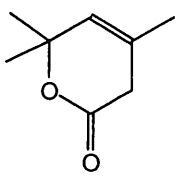


^{1}H NMR δ:5.70(1H, s, (H$_3$C)$_2$C=C**H**)
5.65(1H, s, C=C**H**CO$_2$Et), 4.15(2H, m, OC**H**$_2$),
2.25(3H, s, C**H**$_3$C=), 1.82 and 1.85(6H, s, (C**H**$_3$)$_2$C=),1.26(3H, m OCH$_2$C**H**$_3$)

^{13}C NMR δ:167.20(**C**=O), 154.20(**C**=CCO$_2$Et), 138.53((CH$_3$)$_2$**C**=C), 128.35((CH$_3$)$_2$C=**C**)
117.35(C=**C**CO$_2$Et), 59.50(O-**C**H$_2$), 27.15, 20.05 and 19.53(3x**C**H$_3$),
14.35(O-CH$_2$**C**H$_3$).

MS(EI): (M)$^+$168, (M-CH$_3$)$^+$153. (on a mixture of isomers)

Fraction 2 EtOAc. Clear oil, 1.7 g, (56%) (**2.30**)



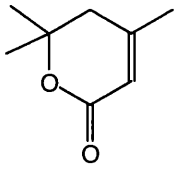
^{1}H NMR δ:5.50(1H, bs, **H**C=C), 2.90(2H, s, C**H**$_2$)
1.70(3H, s, C**H**$_3$C=), 1.42(6H, s, (C**H**$_3$)$_2$).

^{13}C NMR δ:169.20(**C**=O), 127.30(H$_3$C**C**=), 125.50(C=**C**H)
82.45(**C**-O), 33.55(**C**H$_2$), 29.25(2C, (**C**H$_3$)$_2$), 21.60(H$_3$**C**C=)

MS(EI): (M)$^+$140.

IR neat: 3000-2850 (vs), 1700(vs) 1680(s)

Fraction 3 EtOAc. Clear oil, 0.5 g (17%) (**2.31**)



^{1}H NMR δ:5.84(1H, bs, **H**C=C), 2.33(2H, s, C**H**$_2$)
1.96(3H, s, C**H**$_3$C=), 1.42(6H, s, (C**H**$_3$)$_2$).

^{13}C NMR δ:164.65(**C**=O), 155.40(H$_3$C**C**=), 115.60(C=**C**H)
79.10(**C**-O), 40.65(**C**H$_2$), 27.50(2C, (**C**H$_3$)$_2$), 23.05(H$_3$**C**C=).

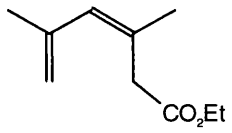
MS(FAB): $(M+H)^+$141.

IR neat : 3000-2900(vs), 1730(vs), 1650(s)

Preparation of (2*E,Z*)-ethyl 3,5-dimethylhexa-2,4-dienoate and isomeric diene esters (2.33-2.37)

The hydroxyester (**2.29**) (4 g, 21.6 mmol) was heated under reduced pressure over anhydrous $CuSO_4$ (1% by weight, 0.04 g) for one hour. Purification by column chromatography (SiO_2, Hex:EtOAc 20:1) gave 2.2 g (65%) of a clear oil. Five isomers were separated and collected by glc and three of which were identified by nOe see page 24-26

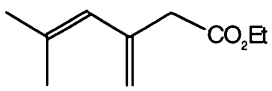
Fraction 1 (3*Z*)-Ethyl 3,5-dimethylhexa-3,5-dieneoate (**2.36**)



^{1}H NMR δ:5.82(1H, bs, **H**C=CCH$_2$), 4.95(1H, bs, **H**$_2$C=)
4.80(1H, bs, **H**$_2$C=), 4.12(2H, q, J=7, OC**H**$_2$CH$_3$)
3.2(2H, s, C**H**$_2$CO$_2$Et), 1.82(3H, bs, C**H**$_3$C=CH) 1.78(3H, bs,C**H**$_3$C=CH$_2$),
1.24(3H, t, J=7, O-CH$_2$C**H**$_3$).

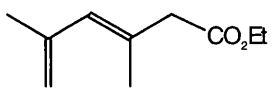
^{13}C NMR δ:171.9(**C**=O), 141.50(=**C**CH$_2$CO$_2$Et), 130.95 and 129.80(H**C**=C,**C**=CH$_2$)
114.25(H$_2$**C**=C), 60.50(O-**C**H$_2$), 38.70(**C**H$_2$CO$_2$Et), 24.40 and 23.45(2x**C**H$_3$),
14.25(O-CH$_2$**C**H$_3$)

Fraction 2 Ethyl 3-methylene-6-methylhexa-4-eneoate (**2.37**)



^{1}H NMR δ:5.60(1H, bs, (CH$_3$)$_2$C=C**H**), 5.20(1H, bs, **H**$_2$C=)
4.92 (1H, bs, **H**$_2$C=), 4.12(2H, q, J=7, OC**H**$_2$CH$_3$)
3.05(2H, s, C**H**$_2$CO$_2$Et)
1.85 and 1.75(6H, s, (C**H**$_3$)$_2$C=CH), 1.24(3H, t, J=7, O-CH$_2$C**H**$_3$)

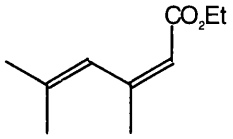
Fraction 3 (3*E*)-Ethyl 3,5-dimethylhexa-3,5-dieneoate (**2.35**)



^{1}H NMR δ:5.75(1H, bs, **H**C=CCH$_3$), 4.98(1H, bs, **H**$_2$C=)
4.8(1H, bs, **H**$_2$C=), 4.12(2H, q, J=7, OC**H**$_2$CH$_3$)
3.0(2H, s, C**H**$_2$CO$_2$Et), 1.88(3H, bs, C**H**$_3$C=CH)
1.82(3H, bs, C**H**$_3$C=CH$_2$), 1.24(3H, t, J=7, O-CH$_2$C**H**$_3$).

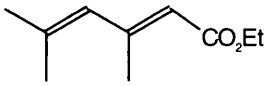
^{13}C NMR δ:171.90(**C**=O), 141.80(=**C**CH$_2$CO$_2$Et), 131.20 and 130.6(H**C**=C,**C**=CH$_2$)
115.40(H$_2$**C**=C), 61.8(O-**C**H$_2$), 46.30(**C**H$_2$CO$_2$Et), 23.70 and 18.30(2x**C**H$_3$),
14.40(O-CH$_2$**C**H$_3$).

Fraction 4 (2*Z*)-Ethyl 3,5-dimethylhexa-2,4-dieneoate (**2.34**)



^{1}H NMR δ:6.45(1H, s, (H$_3$C)$_2$=C**H**)
5.65(1H, s, C=C**H**CO$_2$Et) 4.12(2H, q, J=7, OC**H**$_2$)
1.75 and 1.89(6H, s, (C**H**$_3$)$_2$C=)
1.6(3H, s, C**H**$_3$C=),1.24(3H, t, J=7, O-CH$_2$C**H**$_3$).

Fraction 5 (2*E*)-Ethyl 3,5-dimethylhexa-2,4-dieneoate (**2.33**)



^{1}H NMR δ:5.70(1H, s, (H$_3$C)$_2$=C**H**)
5.65(1H, s, C=C**H**CO$_2$Et), 4.12(2H, q, J=7, OC**H**$_2$),
2.25(3H, s, C**H**$_3$C=),1.82 and 1.85(6H, s, (C**H**$_3$)$_2$C=),
1.24(3H, t, J=7, O-CH$_2$C**H**$_3$)

MS(EI): $(M)^+$168, $(M-CH_3)^+$153 (on a mixture of isomers).

Preparation of the bis-mercuriated 1,2-dioxolane

General Method A

The neat diene (10 mmol), was added to a stirred suspension of Hg(OAc)$_2$ (20 mmol) in 30% H$_2$O$_2$ (90 mmol, 10 ml). The reaction mixture was stirred at room temperature and went from orange to colourless in 15 minutes after which a white solid appeared. When tlc indicated no more starting material was present the white solid was filtered off and washed successively with cold water and cold ether.

Hydridodemercuriation

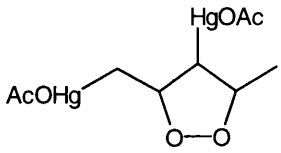
General method B

The crude mercuriated dioxolane (10 mmol) in DCM (30 ml) was cooled in an ice bath. 2M NaOH(aq) (10 ml) was added and immediately after the solution was added to a well stirred solution of NaBH$_4$ (40 mmol) in 2M NaOH(aq) (30 ml) cooled to 5^{0}C. Stirring, at 5^{0}C, was

continued for 15 minutes and then for a further 15 minutes at room temperature. The organic layer was separated and the basic aqueous layer was extracted further with DCM (3x30 ml). The organic portions were combined, dried ($MgSO_4$), and evaporated *in vacuo*.

Preparation of 3-methyl-4-acetoxymercurio- 5-acetoxymercuriomethyl -1,2-dioxolane.(2.39)

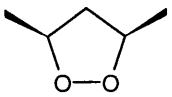
General Method A with penta-1,3-diene (0.68 g, 0.99 ml,10 mmol), $Hg(OAc)_2$ (6.38 g, 20 mmol), 30% H_2O_2 (10 ml, 90 mmol). The white solid was left to dry *in vacuo* crude weight 3.89 g. Purification by recrystalisation from warm methanol gave a white solid with 40% recovery. Found: C,17.25; H, 2.04. $C_9H_{14}Hg_2O_4$ requires: C,17.42; H,2.27%



Preparation of 3,5-dimethyl-1,2-dioxolane. (2.40)

As for General Method B with crude organomercuryacetate (**2.38**) (1.9 g, 3.07 mmol) in DCM (10 ml) and 2M NaOH(aq) (5 ml) $NaBH_4$ (0.46 g, 12.3 mmol) in 2M NaOH(aq) (15 ml). The organic extracts were evaporated off *in vacuo* over an ice bath to leave a clear oil, 0.06 g. Purification by column chromatography (SiO_2 DCM) gave 0.016 g, (5%) of (**2.40**) as a clear oil, in a 2:1 ratio of cis:trans.

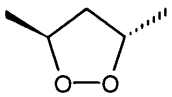
^{1}H NMR δ:4.33-4.44(2H, ddq, **H**COOC**H**)



2.83(1H, dt, J_{GEM}=12, J_{VIC}=7.2, C**H**)

1.76(1H, dt, J_{GEM}=12, J_{VIC}=7.2, C**H**)

1.28 and 1.24(6H, d, 2xC$\mathbf{H}_3$).



^{1}H NMR δ:4.2(2H, tq, J=5.9, **H**COOC**H**)

2.25(2H, t, J=5.9, C$\mathbf{H}_2$), 1.22(6H, d, 2xC$\mathbf{H}_3$).

Preparation of the mercuriated 1,2-dioxolane with the diene ester substrates

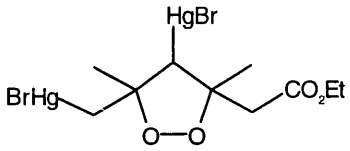
General Method C

The diene ester (10mmol) in DCM (10 ml) was added to a stirred suspension of $Hg(OAc)_2$ (20 mmol) in 30% H_2O_2 (90 mmol, 10 ml). The reaction mixture was stirred at room temperature and went from orange to colourless. When tlc indicated that no more starting material was present the reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, dried ($MgSO_4$), and evaporated *in vacuo* to give a white solid. Anion exchange was carried out by stirring KBr(aq) with a solution of the crude organomercurial. After hour the organic layer was separated and the aqueous layer extracted with DCM. The organic layers were combined, dried ($MgSO_4$), and evaporated *in vacuo*.

Preparation of 3-ethoxycarbonylmethyl-4-bromomercurio-5-bromomercuriomethyl-3,5-dimethyl-1,2-dioxolane.(2.42)

General Method C with the diene ester (**2.35**) (0.08 g, 0.47 mmol) in DCM (3 ml), $Hg(OAc)_2$ (0.381g, 1.2 mmol) and 30% H_2O_2 (0.56 ml, 5.4 mmol). The reaction mixture became colourless after 20 minutes and was left to stir for 24 hours. Yield of the crude organomercuryacetate as a glassy white solid, 0.26 g, 76%. After anion exchange 0.22 g, 63% yield, of a white solid was recovered. Purification by column chromatography (SiO_2 DCM) gave 0.18g, 52% of (**2.42**) as a glassy white/yellow solid as a mixture of isomers with a ratio of 3:1.

Both isomers



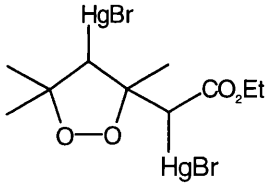
^{1}H NMR δ:4.2-4.13(2H, m, O-C**H**$_2$CH$_3$)
3.29 and 3.2(1H, s, **H**CHgBr)
2.81and.2.72(2H, AB, J=16, C**H**$_2$CO$_2$Et)
2.55, 2.48, 2.35 and 2.23(2H, AB, J=11.7, C**H**$_2$HgBr)
1.61, 1.60 and 1.54(6H, s, 2xC**H**$_3$), 1.29-1.24(3H, m, O-CH$_2$C**H**$_3$)

^{13}C NMR δ:171.50 and 171.40(**C**=O), 90.60, 90.20, 87.80 and 87.50(**C**-O-O-**C**), 87.80 and 87.50(**C**H ring), 61.20(O-**C**H$_2$CH$_3$), 46.55 and 44.35(**C**H$_2$CO$_2$Et), 45.25(**C**H$_2$HgBr), 28.80, 28.60 and 28.40(2C, 2x**C**H$_3$), 14.25(O-CH$_2$**C**H$_3$)

Preparation of 3-(1-bromomercurio-1-ethoxycarbonyl)methyl-4-bromomercurio-3,5,5-trimethyl-1,2-dioxolane.(2.43)

General Method C with the diene ester (**2.34**) (0.03 g, 0.18 mmol) in DCM (1 ml), $Hg(OAc)_2$ (0.115g, 0.36 mmol) in 30% H_2O_2 (0.25 ml, 2.5 mmol).The reaction mixture became colourless after 10 hours and was left stirring for 3 days. Yield of the crude mercuryacetate as glassy white solid, 0.08 g, 60%. After anion exchange 0.067 g, 46% yield, of a white solid was recovered. Purification by column chromatography (SiO_2 DCM), gave 0.02g, 15% yield of (**2.34**) as a powdery white solid isolated as a mixture of two isomers with 1:1ratio,

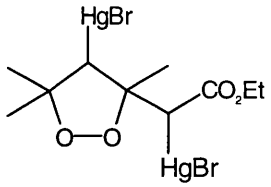
Both isomers



^{1}H NMR δ:4.3-4.05(2H, m, O-C**H**$_2$CH$_3$)
3.48, 3.39, 3.2 and 3.15(2H, s, **H**CHgBr)
1.59, 1.58, 1.52, 1.50, 1.48 and 1.43(9H, s, 3xC**H**$_3$),
1.3-1.2(3H, m, O-CH$_2$C**H**$_3$)

Preparation of 3-(1-bromomercurio-1-ethoxycarbonyl)methyl-4-bromomercurio-3,5,5-trimethyl-1,2-dioxolane.(2.43)

General Method C with the diene ester (**2.33**) (0.02 g, 0.12 mmol) in DCM (1 ml), $Hg(OAc)_2$ (0.076 g, 0.24 mmol) in 30% H_2O_2 (0.2 ml, 2 mmol). The reaction mixture became colourless after 2 days and was left stirring for a further 3 days. Crude organomercurio acetate was isolated as a glassy white solid, 0.086 g, 64% yield. Anion exchange gave 0.06 g, 66% yield, of a white solid. Purification by column chromatography (SiO_2 DCM), gave 0.02 g, 22% yield of (**2.43**) as a powdery white solid isolated as a mixture of isomers in a 3:1 ratio.



Both isomers

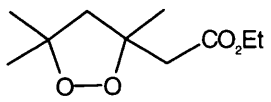
^{1}H NMR δ:4.30-4.05(2H, m, O-C**H**$_2$CH$_3$)
3.48, 3.39, 3.2 and 3.15(2H, s, **H**CHgBr)

1.59, 1.58, 1.55, 1.50, 1.47 and 1.43(3x3H, 6xs, 3xC**H**$_3$),
135-1.20(3H, m, O-CH$_2$C**H**$_3$)

^{13}C NMR δ:175.25(**C**=O), 92.30 and 90.45(**C**-O-O-**C**), 82.30(**C**H ring), 66.25 and 64.30(**C**HHgBr), 61.25(O-**C**H$_2$CH$_3$), 46.65 and 44.25(**C**H$_2$CO$_2$Et)
32.00, 30.05, 29.85, 27.30, 26.65 and 25.05(3C, 3x**C**H$_3$), 14.20(O-CH$_2$**C**H$_3$)

Preparation of 3-ethoxycarbonylmethyl-3,5,5-trimethyl-1,2-dioxolane.(2.41)

General Method C with the diene esters (**2.33 2.34**) 3:1 (0.34 g, 2 mmol), $Hg(OAc)_2$ (1.287 g, 4 mmol) in 30% H_2O_2 (2 ml, 18 mmol). The reaction mixture became colourless after 1.5 hours and was left stirring for a further 36 hours. The intermediate organomercurial 48% yield was used without purification. Hydridodemercuriation was carried out as for General Method B. Crude organomercurioacetate (0.70 g, 1 mmol) in DCM (10 ml) and 2MNaOH(aq) (5 ml) $NaBH_4$ (0.15 g, 4 mmol) in 2MNaOH(aq) (10 ml). The organic extracts were evaporated *in vacuo* to give 0.100 g (25%) of a clear oil. Purification by column chromatography (SiO_2 3:1 DCM:Hexane) gave 0.045 g (12.5%) of (**2.41**) as a clear oil.



^{1}H NMR δ:4.15(2H, q, J=7, O-C**H**$_2$CH$_3$)
2.73 and 2.59(2H, AB, J=14.5, C**H**$_2$CO$_2$Et)
2.53 and 2.17(2H, AB, J=12, C**H**$_2$ring), 1.42, 1.34 and 1.34(9H, s, 3xC**H**$_3$),
1.24(3H, t, J=7, O-CH$_2$C**H**$_3$)

^{13}C NMR δ:170.65(**C**=O), 84.20 and 84.10(**C**-O-O-**C**), 60.55(O-**C**H$_2$CH$_3$),
56.40(**C**H$_2$ring), 44.25(**C**H$_2$CO$_2$Et), 26.95, 25.70 and 24.10(3x**C**H$_3$),

14.20(O-CH_2**C**H_3)

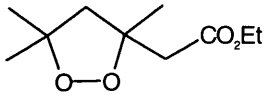
MS(EI): Acc. Mass Found:202.11855. $C_{10}H_{18}O_4$ requires: 202.12051

I.R. 2981(vs),1738(vs),1369,1205,1032.

Preparation of 3-ethoxycarbonylmethyl-3,5,5-trimethyl-1,2-dioxolane.(2.41)

General Method D with the diene ester (**2.33 2.34**) 8:1 (0.19 g, 1.13 mmol), $Hg(OAc)_2$ (0.721 g, 2.26 mmol) in 30% H_2O_2 (1.1 ml, 10 mmol). The reaction mixture became colourless after 2.5 hours and was left stirring for a further 24 hours.The intermediate organomercurial 53% yield was used without purification. Hydridodemercuriation was carried out as for General Method B. Crude organomercurioacetate (0.430 g,) in DCM (6 ml) and 2MNaOH(aq) (3 ml) $NaBH_4$ (0.17 g, 4.5 mmol) in 2MNaOH(aq) (5 ml). The organic extracts were evaporated *in vacuo* to give 0.100 g, of a clear oil. Purification by column chromatography (SiO_2 3:1 DCM:Hexane gave 0.070 g (31%) of (**2.41**) as a clear oil.

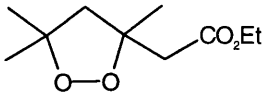
^{1}H NMR As above



Preparation of 3-ethoxycarbonylmethyl-3,5,5-trimethyl-1,2-dioxolane.(2.41)

General Method D with the diene esters (**2.33-2.37**) (0.84 g, 5 mmol), $Hg(OAc)_2$ (3.19 g, 10 mmol) in 30% H_2O_2(5 ml, 45 mmol). The reaction mixture became colourless after 0.5 hours and was left stirring overnight. The intermediate organomercurial 88% yield was used without purification. Hydridodemercuriation was carried out as for General Method B. Crude organomercurioacetate (3.16 g, 4.4 mmol) in DCM (25 ml) and 2MNaOH(aq) (15 ml) $NaBH_4$ (0.756 g, 20 mmol) in 2MNaOH(aq) (10 ml). The organic extracts were evaporated off *in vacuo* to give 0.75 g, 75% yield of a yellow oil. Purification by column chromatography (SiO_2 3:1DCM:Hexane) gave 0.404 g (40%) of (**2.41**) as a clear oil,.

^{1}H NMR As above



^{13}C NMR As above

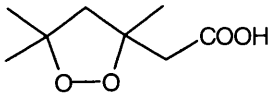
MS(EI): $(M)^+$202

Analysis Found: C,59.40; H, 8.91. $C_{10}H_{18}O_4$ requires: C,59.60; H,8.61%

Preparation of 3-carboxy methyl-3,5,5-trimethyl-1,2-dioxolane.(2.44)

The dioxolane ester (**2.41**) (0.485 g, 2.5 mmol) was dissolved in the mininum amount of methanol (5 ml) and 2M NaOH(aq) (1.25 ml, 2.5 mmol) was added and the mixture heated to 40 ^{0}C for 1 hour. The methanol and water were evaporated *in vacuo* to give a white solid. This was triturated with DCM filtered under suction and washed with DCM (30 ml), yield 0.413 g, 90%. The crude dioxolane was then dissolved in a minimum amount of water, acidified with

acetic acid and extracted with DCM (4x10 ml). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give 0.09 g (20%) of a white solid (**2.44**).



^{1}H NMR δ: 2.79 and 2.68(2H, AB, J=15, C**H**$_2$CO$_2$H)
2.50 and 2.20(2H, AB, J=12, C**H**$_2$ring),
1.46, 1.36, and 1.32(9H, s, 3xC**H**$_3$)

^{13}C NMR δ:176.20(**C**=O), 84.25 and 84.00(**C**-O-O-**C**), 56.60(**C**H$_2$ring), 44.05(**C**H$_2$CO$_2$H) 27.05, 25.60 and 23.80(3x**C**H$_3$).

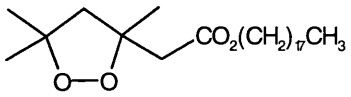
MS(EI) $(M)^+$174 $(M-O_2H)^+$ 141

I.R. 3300-3100(br), 2981(vs),1718(vs),1369,1205,1032

Analysis Found: C,54.95; H, 7.91. $C_8H_{14}O_4$ requires: C,55.15; H,8.04%.

Preparation of 3-octadecoxycarbonylmethyl-3,5,5-trimethyl-1,2-dioxolane.(2.45)

A solution of the dioxolane acid (**2.44**) (0.08 g, 0.46 mmol), dimethylaminopyridine (0.045 g, 0.365 mmol) and octadecanol (0.372 g, 1.37 mmol) in dry DCM (10 ml) was stirred in an ice bath. A solution of DCC (0.098 g, 5.06 mmol) in dry DCM (10 ml) was addded dropwise. The mixture was warmed to room temperature and stirred for 6 hours. The solution was filtered washed succesively with sat.citric acid (aq) (2x15 ml), $NaHCO_3$(aq) (2x15 ml) and H_2O (15 ml). The organic layer was dried ($MgSO_4$), and evaporated *in vacuo* to give 0.35g of a white solid. Purification by column chromatography (SiO_2 DCM), gave 0.11 g (56%) of (**2.45**) as a white waxy solid.

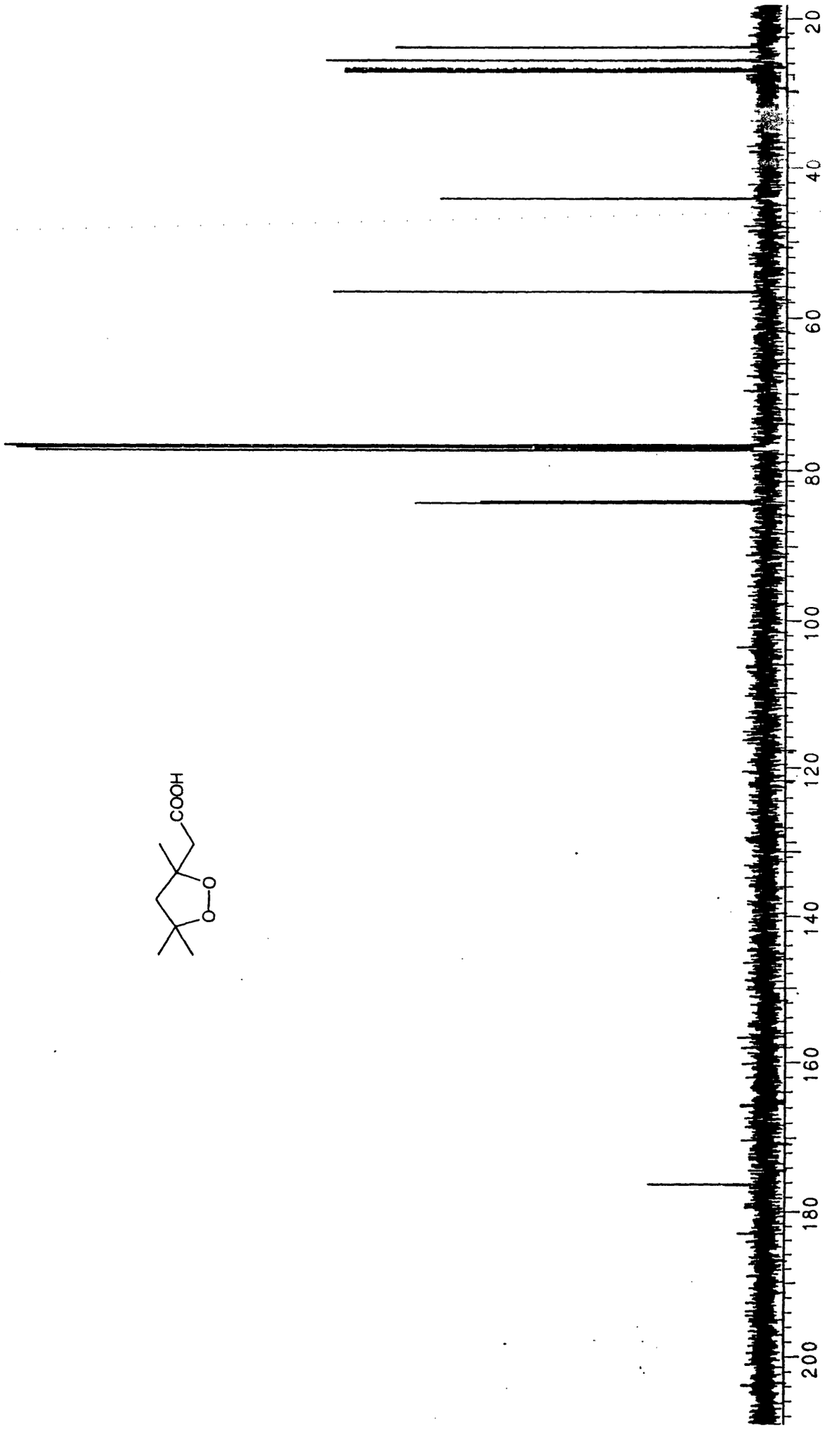


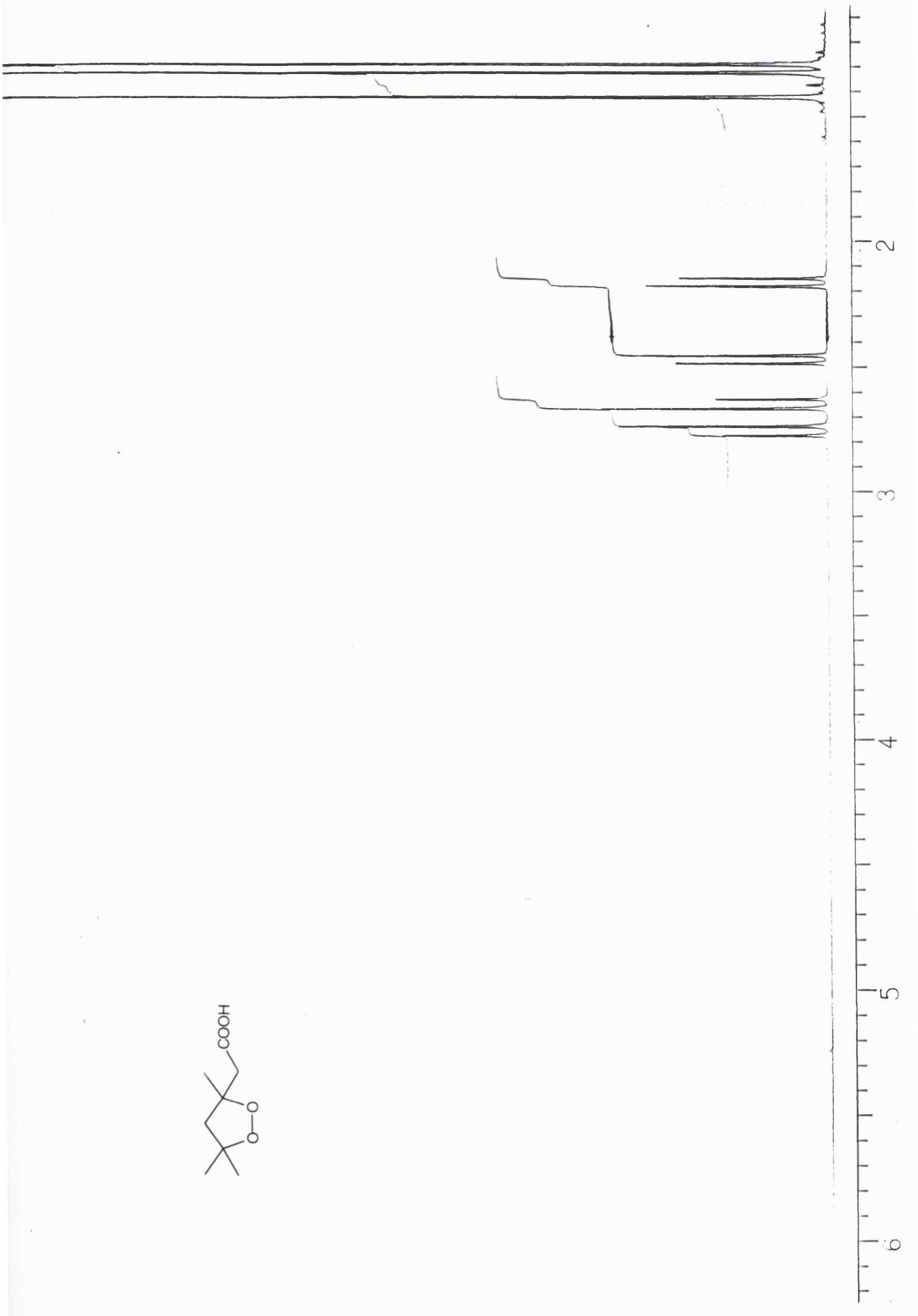
^{1}H NMR δ:4.06(2H, q, J=7, O-C**H**$_2$),
2.76 and 2.60(2H, AB, J=14.5, C**H**$_2$CO$_2$R)
2.55 and 2.18(2H, AB, J=12, C**H**$_2$ring),
1.62(2H, quin, O-CH$_2$C**H**$_2$), 1.43, 1.36 and 1.32(9H, s, 3xC**H**$_3$)
1.31-1.24(30H, bs, $(CH_2)_{15}$), 0.86(3H, t, J=7, O-$(CH_2)_{17}$C**H**$_3$).

^{13}C NMR δ:171.65(**C**=O), 84.15 and 84.05(**C**-O-O-**C**), 64.70(O-**C**H$_2$CH$_2$), 56.35(**C**H$_2$ring), 44.25(**C**H$_2$CO$_2$R), 31.05, 29.70, 29.60, 29.50, 29.45, 29.30, 28.50, 25.65 and 22.60(15C, $(\mathbf{C}H_2)_{15}$), 27.20, 26.30 and 24.05(3x**C**H$_3$), 14.10(O-$(CH_2)_{15}$**C**H$_3$).

MS(EI) Acc Mass:Found 426.37050. $C_{26}H_{50}O_4$ requires 426.37090

Analysis Found: C,72.79; H,11.93. $C_{26}H_{50}O_4$ requires: C,73.19; H,11.81%


COOH
O
O
20
40
60
80
100
120
140
160
180
200


COOH
O
O
1
2
3
4
5
6

REFERENCES

1. Porter, N.A. *Acc.Chem.Res.* 1986, *19*, 262-268.
2. O'Connor,D.E.;Mihelich,E.D.;Coleman,M.C., *J. Am. Chem. Soc.*, **1984**, *106*, 3577-3584
3. Courtneidge, J.L., *J. Chem. Soc., Chem. Commun.* **1992**, 1270-1272
4. a)Beckwith, A.L.J.; Wagner, R.D., *J. Chem. Soc., Chem. Commun.* **1980**, 485 b) Beckwith, A.L.J.; Wagner, R.D., *J. Org. Chem,* **1981**, *46*, 3638-3645.
5. a) Feldman, K.S, Kraebel, C.M., J. Org. Chem., 1992, 57, 4574-4576 b) Feldman, K.S., Simpson; R.E., Feldman, *Tet. Lett.*, **1989**, *30*, No50, 6985-6988 c) K.S., Simpson, *Synlett*, **1994**, 217-225.
6. Casteel, D.A., *Natural Product Reports*, **1992**, 289-312
7. Baumstark, A.L.; Vasquez ,P.C., *J. .Org. .Chem.*, **1992**, *57*, 393-395
8 Hashida, I.; Mizuno, K.; Otsuji, Y.; Tamai, T., *J. Org. Chem* ., **1992**, 57, 5338- 5342
9 Dassault, P.H., Lee R.J., J. *Am. Chem. Soc.*, **1994**, *116*, 4485, 4486.
10. Dussault, P.H.; Zope, U.R., *Tetrahedron Lett.*, **1995**, *36*, No13, 2187-2190
11. Akasaka,T.;Fukuoka, K.; Ando, W., *Tetrahedron Lett.*, **1991**, *32*, No.52, 7695-7698
12 Criegee, R., *Angew. Chem., Int. Ed. Engl.*, **1975**, 14, 745.
13. a)Keul, H.; Kuczkowski, R.L., *J. Am. Chem. Soc.* **1984**, *106*, 5370 b)Kuczkowski,R.L.; Pearson,W.H;Wojciechowski, *J. Org. Chem.*, **1989**, *54*, 115-121
14. Casey, M.; Culshaw, A.J., *Synlett*, 1991,214-216
15. a)Bloodworh,A.J.; Ballard, D.H., *J. Chem. Soc.,* C, **1971**, 945-949 b)Bloodworh,A.J.; Griffin, I.M., *J. Chem. Soc.,* C, **1975**, 195-200 c) Bloodworh,A.J.; Loveitt, M.E., *J. Chem. Soc.,* C, **1977**, 1031-1037
16. Courtneidge,J.L.; Bush, M.; Loh, L.S., *Tetrahedron*, **1992**, *48*, No.18, 3835-3856
17. Bascetta,E. ;Gunstone, F.D., *J. Chem. Soc. Perkin Trans.I* , **1984**,2207-
18. a)Bloodworth, A.J.; Loveitt, M.E. *J. Chem. Soc. Chem. Comm.,* **1976**, 94. b)Bloodworth, A.J.; Loveitt, M.E. *J. Chem. Soc. Perkin Trans.I* , **1978**, 522-530
19. Bloodworth, A.J.; Khan, J.A., *J. Chem. Soc. Perkin Trans.I* , **1980**, 2450-2457
20. a) Bloodworth, A.J.; Bunce,R.J., *J. Chem. Soc. Chem. Comm.,* **1970**, 753-754. b)Bloodworth, A.J.; Bunce,R.J., *J. Chem. Soc. C* , **1971**, 1453-1458
21. Bloodworth, A.J.; Spencer, M.D., *J. Organometallic Chem.*,**1990**, 299-304
22 Bloodworth, A.J.; Hutchings, M.G.; Sotowicz, A.J., *J. Chem. Soc. Chem. Comm* **1976,** 578-579

23. Cologne, J.; Varagnet, S., *Bull. Soc. Chem. Fr.*, **1961**, 237..

24. Maronc-Barnaud, Y., *Academie Des Sciences*, **1959**, *248*, 2605

25. Brown, H.C.; Geoghegan, P.J., *J. Org. Chem* ,**1972**, *37*, 1937-1941

26. Neises, B Steglich, W., *Organic Synthesis*, **1984**, *63*, 183

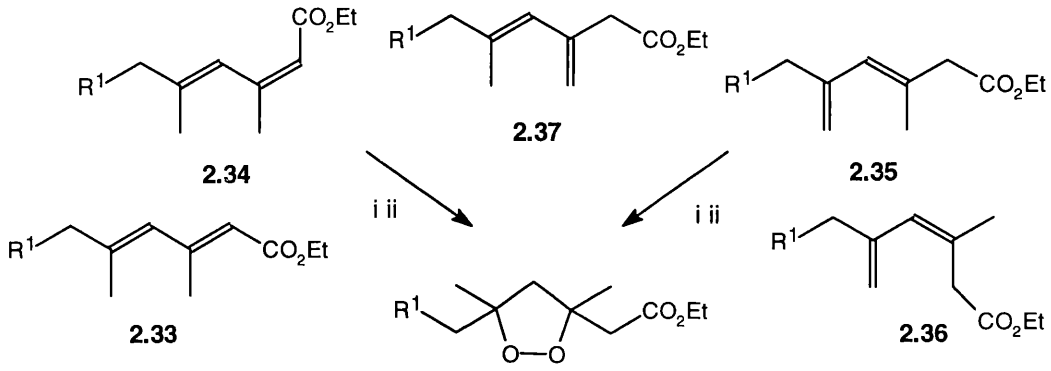
CHAPTER THREE

SYNTHESIS OF NATURALLY OCCURRING AND OTHER ANALOGUES OF THE PLAKINIC ACIDS

INTRODUCTION

Development of a General Route to the Diene Substrate

The results obtained from work on the model system, where R^1=H, validated our peroxymercuriation conditions as a suitable method for the synthesis of the target 1,2-dioxolane from diene esters (**Scheme 3.1**).



R^1=H

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

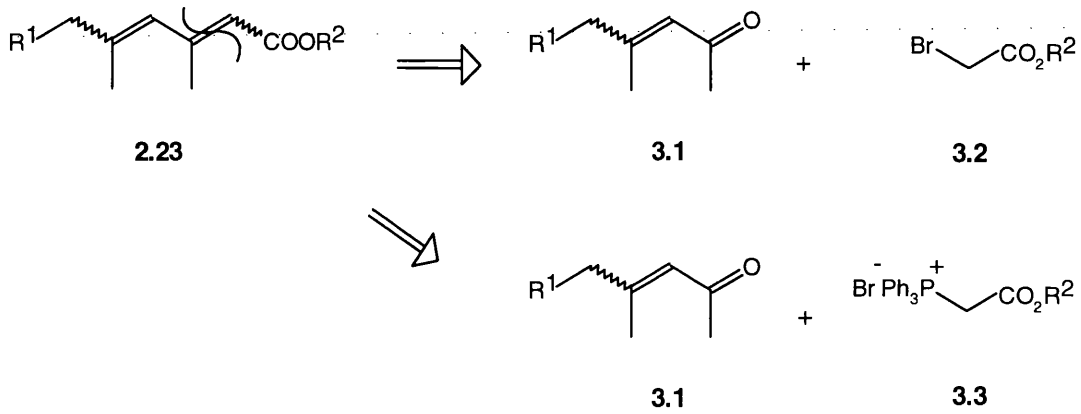
Scheme 3.1

Consequently our attention turned to producing a series of further natural product analogues, using peroxymercuriation, through modification of the 1,2-dioxolane substituents, principally by variation of R^1. To achieve this we had first to establish a strategy for the synthesis of the diene substrate. Even though the diene ester (**2.35**) gave the highest yield of a bis-mercuriated 1,2-dioxolane our priority was to construct a short flexible route, so our considerations remained centred on the fully conjugated dienes (**2.33** and **2.34**).

Although no general syntheses for these particular diene esters were found in the literature, retrosynthetic analysis of the substrate (**2.23**) resulted in a number of possibilities (**Schemes 3.2-3.5**).

Retrosynthetic Analysis of the Diene Esters

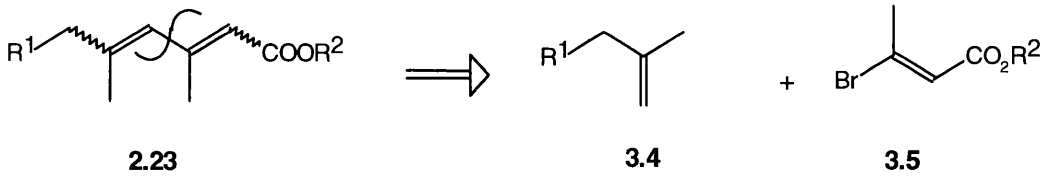
Disconnection at the αβ-double bond



Scheme 3.2

Disconnection across the αβ-double bond (**Scheme 3.2**) generates two fragments. These can be coupled by several methods including Wittig type reactions (**3.1** and **3.3**), or by the Reformatsky route (**3.1** and **3.2**), as used in the model system. These approaches were unattractive because the αβ-unsaturated ketones (**3.1**) are not commercially available and their synthesis is potentially problematic. Another drawback in employing the Wittig methodology was the possibility of 1,4 addition to the enone (**3.1**), by the ylid (**3.3**), which has been observed in similar systems[1].

Disconnection across the medial saturated bond

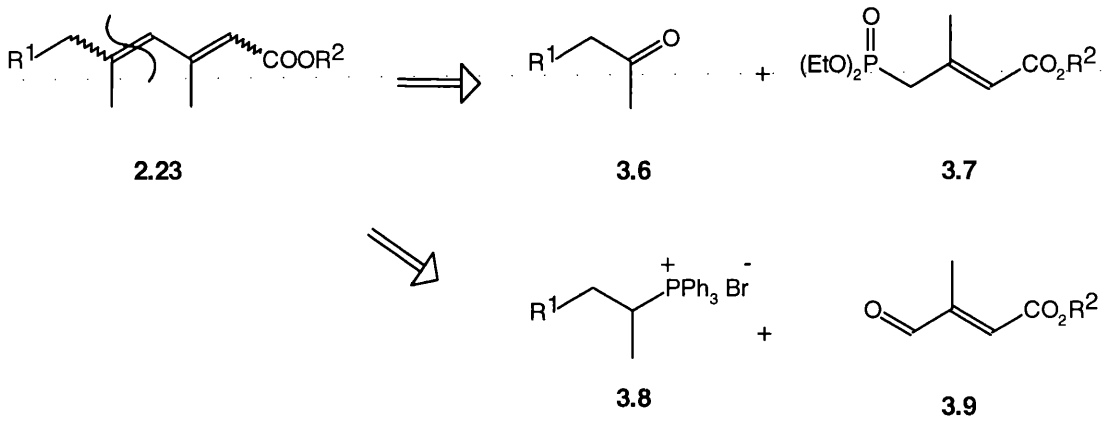


Scheme 3.3

Heck-type reactions involving palladium catalysed vinylation of organic halides[2], have proved highly successful in organic synthesis. Although disconnection across the medial saturated bond of our substrate lends itself to this type of coupling. we disregarded this method because, again, the synthons (**3.4** and **3.5**) are not commercially available and involve synthesis by several steps.

Disconnection across the γδ-double bond

1) Wittig-type disconnection



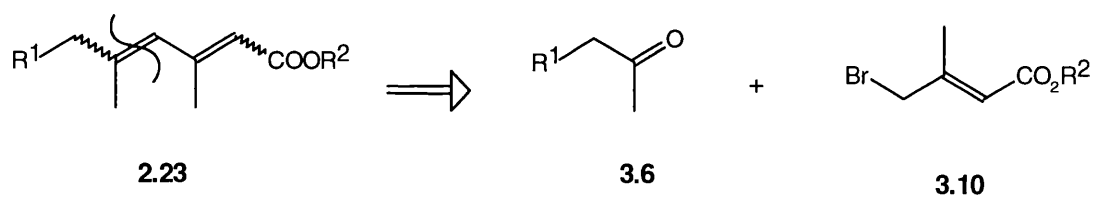
2.23 **3.6** **3.7**

3.8 **3.9**

Scheme 3.4

Two methods of forming the γδ-double bond, using a Wittig reaction, are available (**Scheme 3.4**). One possibility incorporates the coupling of methyl ketones (**3.6**), which are commercially available, and the phosphonoacetate (**3.7**), which is made by a simple two step procedure. However in this case the reaction between the ylid and the carbonyl occurs in low yields[3] making the route unfavourable. Alternatively, interchanging of the carbonyl and phosphonium moieties between fragments gives the phosphonium salt (**3.8**), and the αβ-unsaturated ester (**3.9**), which can accommodate the carbonyl as the more reactive aldehyde functionality[4].

2)Reformatsky-type disconnection



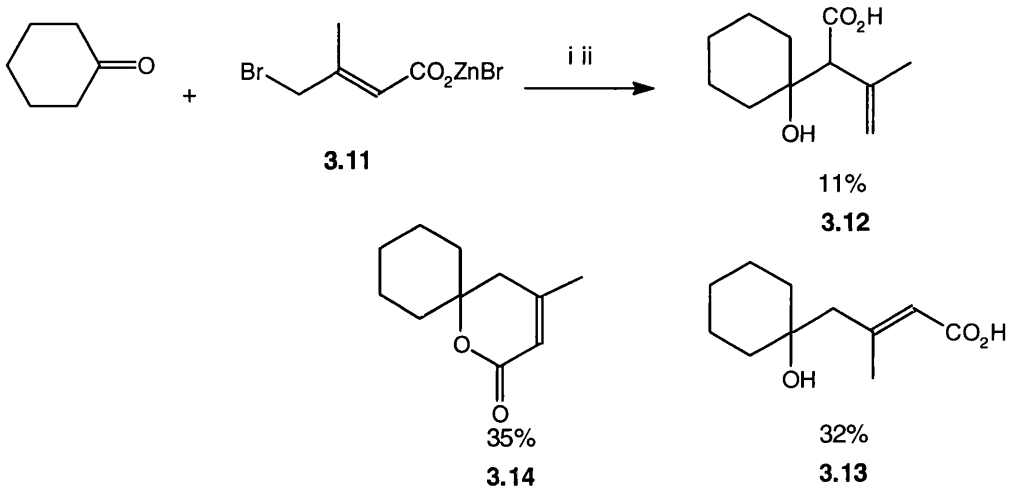
2.23 **3.6** **3.10**

Scheme 3.5

Reformatsky reactions of this nature have been reported. Bellassoued et al.[5] used 3,3-dimethylacrylic acid to generate the allylic bromide synthon (**3.10**). Reaction of (**3.11**) with

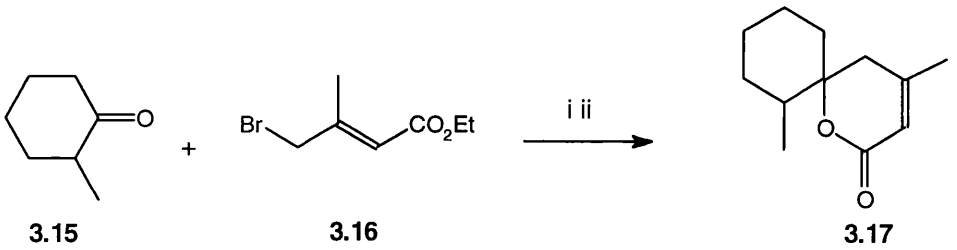
cyclohexanone gave a mixture of three products (**3.12-14**) the relative proportions of which could be altered by adjusting the reaction conditions (**Scheme 3.6**).

Using a similar method Brouillette et al.[6] treated the brominated 3,3-dimethylacrylate (**3.16**) with the cyclic ketone (**3.15**), to produce, exclusively, the corresponding δ-lactone in a 50% yield (**Scheme 3.7**).



i)Zn, THF reflux 4 hours ii) H_3O^+

Scheme 3.6

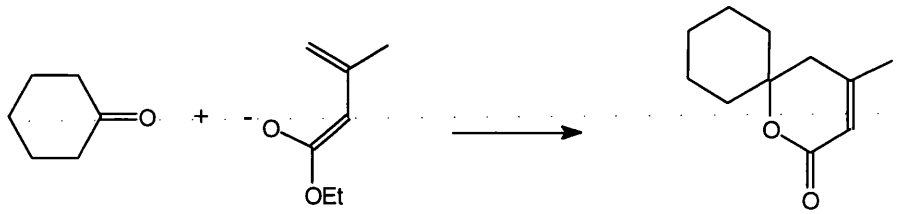


i)Zn, THF reflux 2-24 hours ii) H_3O^+

Scheme 3.7

In each case lactone synthesis can be accounted for by 1,2-addition of the s-*cis* zinc dienolate to the ketone followed by intramolecular cyclisation. Similarly, using the same mechanism of 1,2 addition of a dienolate anion, but in a more direct route, Heathcock[7] successfully isolated δ-lactones synthesised from both aldehydes and ketones. In a representative reaction ethyl 3,3-dimethylacrylate is converted to its dienolate anion (**3.18**) using 1.1 mole equivalent of base, lithium diisopropylamide, at -70 ^{0}C. Addition of the carbonyl component at -70 ^{0}C, in this case cyclohexanone, followed by warming to, and

quenching of the reaction mixture at 10 ^{0}C, produced the lactone (**3.14**) in a yield of 42% (**Scheme 3.8**).

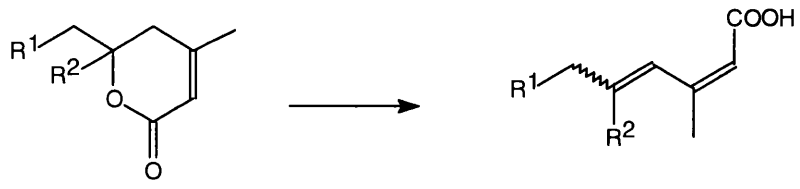


3.18 **3.14**

Scheme 3.8

Synthesis of 2Z-Diene Acids via δ-Lactones

Although the reactions mentioned above (**Schemes 3.6-3.8**) do not provide a direct route to a diene ester, conversion of δ–lactones (**3.14** and **3.17**) to the corresponding 2Z-diene acids can be effected simply by treatment with base. Base-induced ring-opening of αβ-unsaturated δ-lactones (**3.19**) is considered to be one of the most reliable methods for the synthesis of 2Z, 4Z/E-dienoic acids (**3.20**). (**Scheme 3.9**). Bases such as t-BuOK,[8] NaOMe/ NaOEt,[9]sodium in ether[10] and MeSNa[11] have been used. More recently in the search for milder conditions that can be applied to lactones containing other functional groups, n-Bu_4NF[12] was found to be an effective reagent, producing the diene acid in almost quantitative yield.



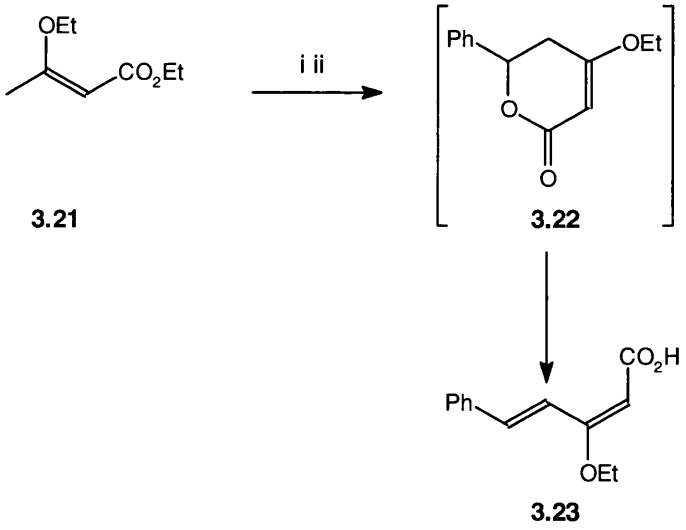
3.19 **3.20**

R^1=alkyl aryl R^2=H or Me

Scheme 3.9

One-pot procedures to 2Z-diene acids

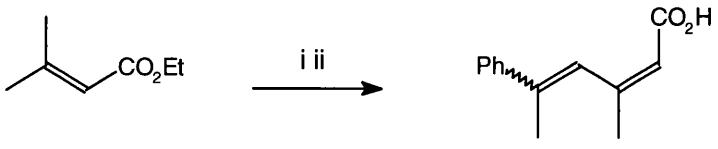
The syntheses of (2Z-4E/Z)-dienoic acids have been reported as one pot procedures[13,14] from the reaction of 3-substituted crotonoate esters with aldehydes and ketones. Smissman[13] made the diene acid (**3.23**) in a 75% yield from the condensation of benzaldehyde with the dienolate of (**3.21**) using two mole equivalents of base (**Scheme 3.10**). Attempts to prevent base-induced ring-opening of the intermediate δ-lactone (**3.22**) by reducing reaction times, or by using equivalent quantities of base served only to decrease the yield of the diene acid. Investigations by Angelhova of an analogous reaction between methyl ketones and the dienolate anion of ethyl 3,3-dimethylacrylate (**3.24**),[15] showed poor overall yields of the unsaturated acids. In particular the reaction of acetophenone with the acrylate (**3.24**), employing two mole equivalents of base, furnished the diene acid (**3.25**) in a yield of 12% (**Scheme 3.11**).



3.21 **3.22** **3.23**

i) 2 mol $LiNH_2$ ii) PhCHO

Scheme 3.10

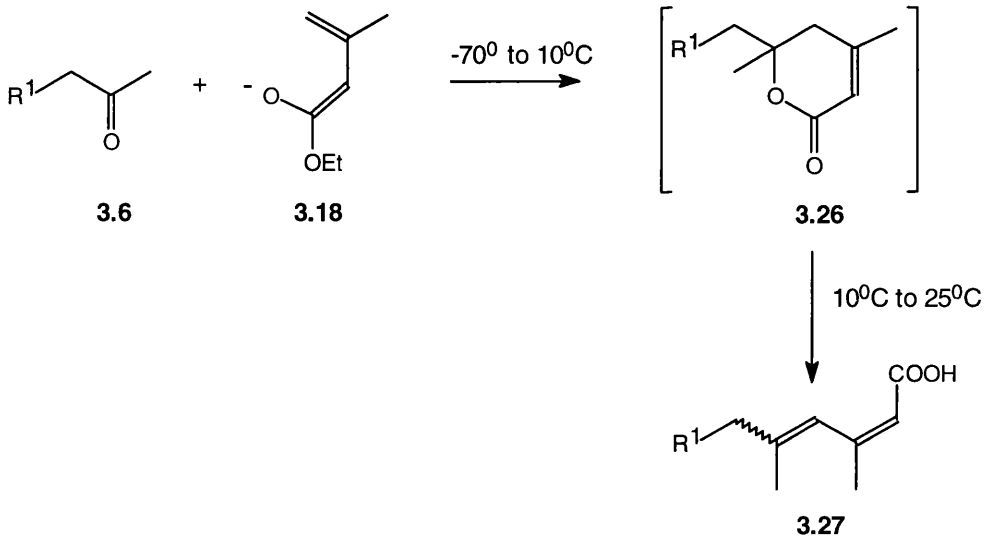


3.24 **3.25**

i) Et_2O, 2 mol $NaNH_2$ ii) $PhCOCH_3$

Scheme 3.11

Based on the work by Smissman we reasoned that with a slight alteration to Heathcock's method for lactone synthesis we could develop a one pot procedure for the synthesis of the diene acids. This was founded on the assumption that warming of the reaction mixture above 10 ^{0}C would induce ring-opening and enable isolation of the 2Z 4Z/E-diene acids directly (**3.27**) (**Scheme 3.12**).



3.6 **3.18** **3.26** **3.27**

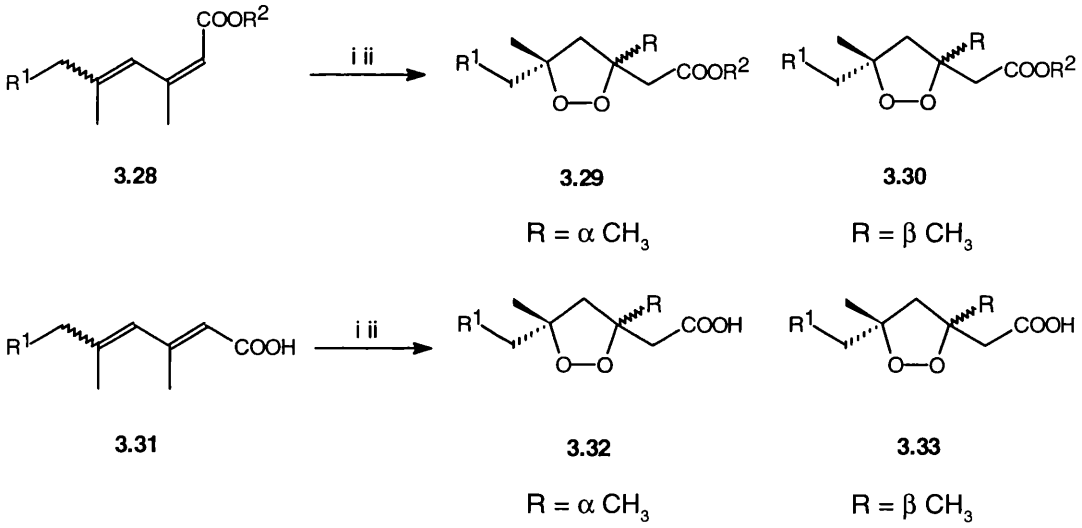
Scheme 3.12

Synthesis of the Target 1,2-Dioxolanes

Peroxymercuriation of the 2Z-Diene Acids

Peroxymercuriation as a method for the synthesis of the target 1,2-dioxolanes, cannot be implemented on the 2Z-diene acids directly. This is because appropriate alkenoic acids[16] form lactones on treatment with mercury salts by intramolecular acyloxymercuriation. It is therefore essential to modify the 2Z-diene acid to prevent this undesirable cyclisation.

From the peroxymercuriation of our model system we know that masking of the acid as an ester allows time for competing dioxolane formation, and hence esterification of the 2Z-diene acid (**3.27**) was our initial approach. Alternatively, isomerisation of the αβ-double bond to the E-isomer (**3.31**) would prevent lactone formation and possibly eliminate the need for esterification and subsequent de-esterification (**Scheme 3.13**).



$R^1 \neq H$

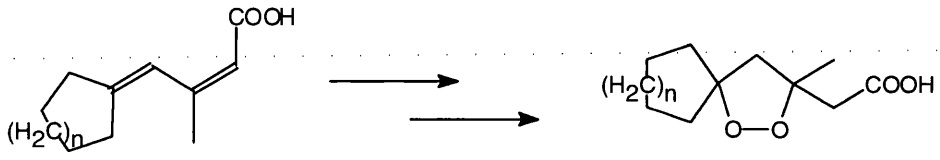
i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.13

In each case, after peroxymercuriation/ demercuriation of the dienes (**3.28** and **3.31**) we would expect to observe the product 1,2-dioxolanes as a pair of diastereoisomers (**3.29-3.30**, and **3.32-3.33**).

Through variation of R^1 we believed we could obtain a structure-activity relationship for the target 1,2-dioxolanes. Initially this would be effected by alteration of R^1 to resemble the hydrocarbon chain found in the plakinic acids (**1.16-1.21**), or be an exact example of the one of the dioxolane acids (**1.22a-e**). We also set out to ascertain the importance of the 3,5-

dimethyl substitution through the synthesis of a set of spiro 1,2-dioxolanes (**3.34**) (**Scheme 3.14**), and to investigate the possibility of modifying the carboxylic acid functionality with the peroxide in place.



3.34

Scheme 3.14

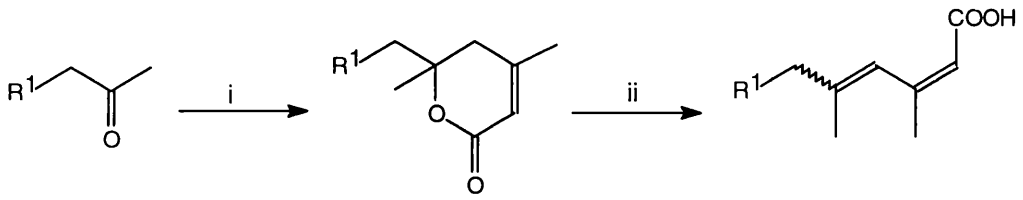
RESULTS AND DISCUSSION

Synthesis of the 2Z-Dienoic Acids

A series of 2Z, 4E/Z-dienoic acids (**3.35-3.40** and **3.47-3.51**) with differing substituents at C^5 were synthesised from a variety of procedures (**I**, **II**, **III** and **IV**) based around Heathcock's synthesis of δ-lactones.

Preparation of the 2Z-Dienoic Acids by Procedure I

Procedure **I** is a two-step route to the diene acids and includes synthesis of the intermediate lactones using Heathcock's procedure, with one exception (**3.35**), followed by base-induced ring-opening as a separate step (**Scheme 3.15**).



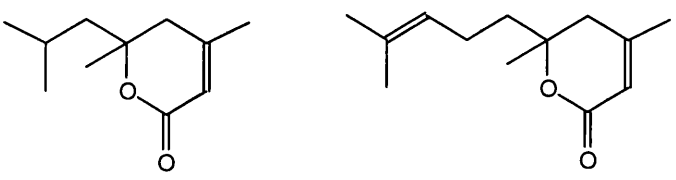
3.6 **3.26** **3.27**

i)LDA/ $(CH_3)_2C{:}CHCO_2Et$/THF/-70 ^{0}C to 10 ^{0}C ii) ROH/Na

Scheme 3.15

Lactone formation

The lactones (**3.41** and **3.42**) precursors to the dienes (**3.36** and **3.37 Table 3.1**) were made using Heathcock's procedure for lactone synthesis, and isolated in yields of 30% and 32% respectively, following purification by column chromatography. Both lactones exhibited a broad singlet at δ 5.8 ppm which is consistent with the olefinic resonance found in the ^{1}H NMR of lactone (**2.31**). Additional structural evidence was obtained from the ^{1}H NMR where the diastereotopic ring CH_2 signals, were present as two doublets (AB) δ2.38 ppm δ2.17 ppm (**3.41**), δ2.42 ppm δ2.18 ppm (**3.42**) (see spectra page 118). The intermediate lactones to the diene acids (**3.38-3.40**) were treated with base without isolation or identification.



3.41 **3.42**

Ring-opening

The diene acids (**3.37-3.40**) were synthesised quantitatively from their lactone precursors by refluxing in ethanol with excess ethoxide ion. Milder conditions, stirring with LDA at room temperature, were employed for the ring opening of (**3.41**) which produced the diene acid (**3.36**) in a 90% yield. In all cases the diene acids were isolated as the 2Z 4E,Z-isomers

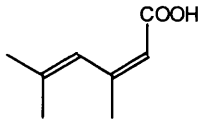
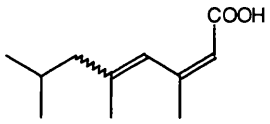
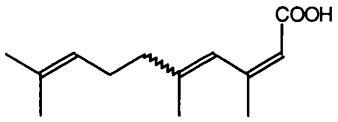
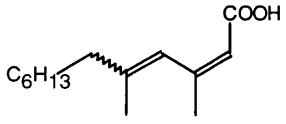
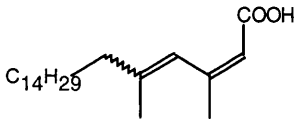
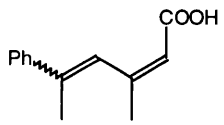
2Z-Diene Acid	Overall Yield	Isomer Ratio*
 **3.35**	65%†	
 **3.36**	35%	4E:4Z 1:1
 **3.37**	30%	4E:4Z 2:1
 **3.38**	40%‡	4E:4Z 2:1
 **3.39**	40%‡	4E:4Z 2:1
 **3.40**	40%‡	2Z 4E:Z 2:1

Table 3.1

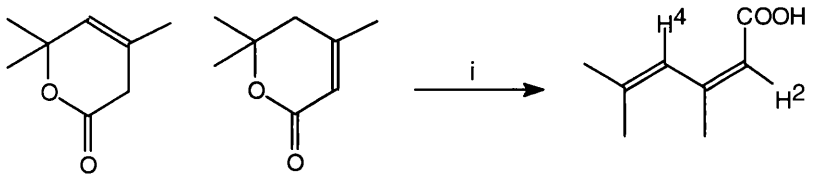
* Isomer ratio determined by nOe experiments reported herein see page 62

† Lactones (**2.30-31**) synthesised from the Reformatsky reaction of mesityl oxide Chap. 2

‡ Supplied as crude mixtures by Zeneca Specialties

Mechanism of ring-opening

The diene acid (**3.35**) was synthesised in a quantitative yield from a mixture of the conjugated and unconjugated trimethyl lactone (**2.30** and **2.31**) by refluxing in methanol with 3 mole equivalents of sodium methoxide. The diene was identified as the 2Z-isomer from the characteristic resonance of H^4 at δ6.4 ppm, which is shifted downfield from H^2 by the deshielding cone of the carbonyl moiety (**Scheme 3.16**).



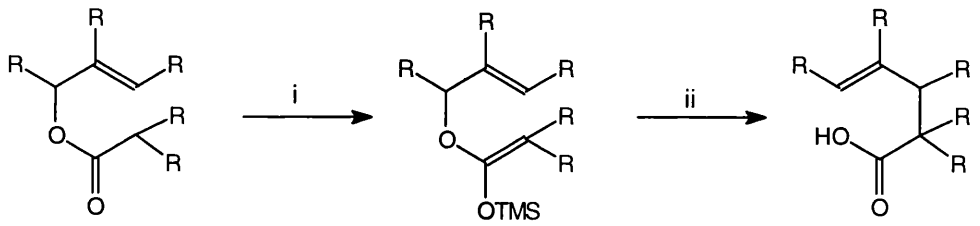
2.30 **2.31** **3.35**

i) MeOH/ Na

Scheme 3.16

We supposed that the mechanism of ring-opening for both lactones was the same and occurred via an intermediate common to both.

Dienolate anions have been reported to produce γδ-unsaturated acids via a 3,3 sigmatropic mechanism. Ireland[17] demonstrated how the rearrangement of allylic esters (**3.43**), as their enolate anions or the corresponding silyl ketene acetals (**3.44**), produced γδ-unsaturated acids (**3.45**) (**Scheme 3.17**).

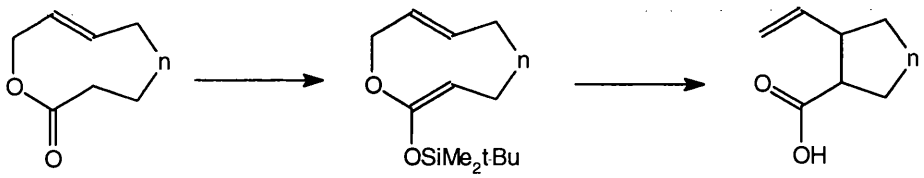


3.43 **3.44** **3.45**

i) LDA/ Me_3SiCl/ -70 ^{0}C ii) warming to 20 ^{0}C/ MeOH

Scheme 3.17

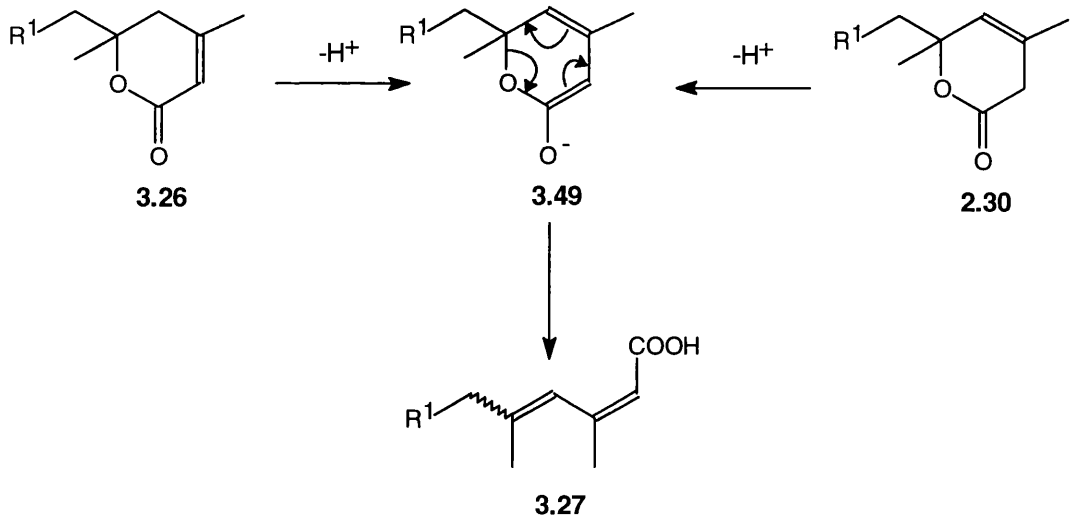
The rearrangement of substrates similar to Ireland's have also proved successful in the synthesis of unsaturated acids[18]. The medium- or large-ring lactones (**3.46**) are obvious precursors of the cyclic ketene acetals (**3.47**) and underwent carbocyclic ring contraction to form the acids (**3.48**) (**Scheme 3.18**).



3.46 **3.47** **3.48**

Scheme 3.18

We imagined that the conjugated and unconjugated δ-lactones (**2.30** and **2.31**) would on treatment with base, by abstraction of the γ-H (**3.26**) or the α-H (**2.30**), form the dienolate anion (**3.49**) which has a structure analogous to the intermediates (**3.44**) proposed by Ireland. The ring opening mechanism of the lactones herein may then proceed via this intermediate (**3.49**) by an electrocyclic or similar 3,3-sigmatropic mechanism (**Scheme 3.19**).



3.26 **3.49** **2.30**

3.27

R^1= H, alkyl or aryl

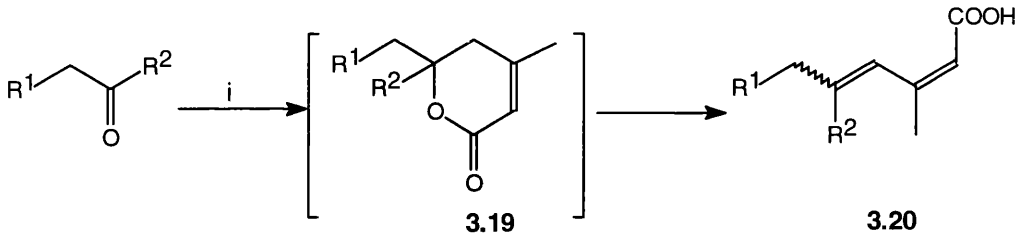
Scheme 3.19

Preparation of the 2Z-Dienoic Acids by Procedures II, III and IV

The diene acids shown in (**Table 3.2**) were made by a one-step procedure derived from Heathcock's method using Procedures **II**, **III** and **IV** which are described below.

Procedure II

Procedure **II** included a slight, but significant modification of Heathcock's method. A typical procedure involved formation of the dienolate anion using 1.1 mole equivalents of LDA. Addition of the ketone at -70 ^{0}C, followed by warming of the reaction mixture to room temperature furnished the diene acids (**3.47-3.51**) in yields comparable to those we would predict for the δ-lactones when the reaction is quenched at 10 ^{0}C (**Scheme 3.20**).



R^1= alkyl R_2= Me or R^1=R^2=$(CH_2)_n$

i)LDA/ 1 mol equiv $(CH_3)_2C$:$CHCO_2Et$/ THF / -70 ^{0}C to 25 ^{0}C

Scheme 3.20

In all cases only the desired diene acid and starting materials were recovered and no other reaction products were identified. To establish the effect of further temperature increases on the yield of the dienes, cyclohexanone was treated as above, but warmed from room temperature to 50 ^{0}C for three hours. No improvement in the yield of the acid (**3.50**) was observed from the yield obtained when the reaction temperature was maintained at room temperature, and again the only other compounds recovered were starting materials and the diene acid.

We know from the results of Procedure **I** that αβ-unsaturated δ-lactones are intermediates in the synthesis of these particular diene acids, so the base responsible for ring-opening must be present in the reaction mixture and could be the ethoxide ion which is generated in situ, or ring opening could be induced as a result of proton exchange with the dienolate anion (**3.18**). If (**3.18**) is responsible for ring-opening we reasoned that greater yields of the diene acids could be obtained by employing an excess of (**3.18**). This was the basis for Procedures **III** and **IV**

Procedures III and IV

Procedures **III** and **IV** were executed using the same methodology used for Procedure **II** but with 1.5 and 2 mole equivalents respectively of the dienolate anion (**3.18**). As a representative example we treated dodecanone under the conditions of procedures **II III** and **IV** and witnessed a corresponding increase in yield from 42% to 70% to 85% of the diene acid (**3.47**) (**Table 3.2**).

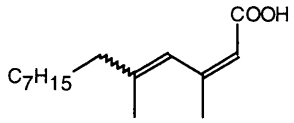
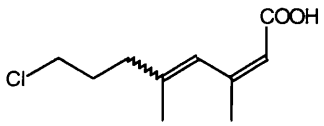
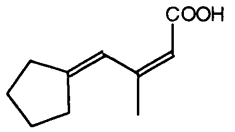
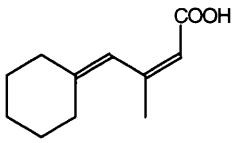
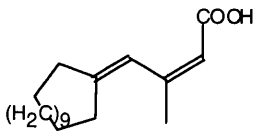
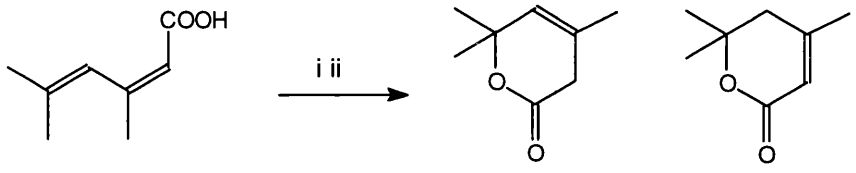
2ZDiene Acid	Overall Yield	Isomer Ratio	Procedure
 **3.47**	**42%** **70%** **85%**	**4E:4Z 2:1**	**II** **III** **IV**
 **3.48**	**60%**	**4E:4Z 2:1**	**III**
 **3.49**	**35%**		**II**
 **3.50**	**36%**		**II**
 **3.51**	**38%**		**II**

Table 3.2

Synthesis of the Target 1,2-Dioxolanes

Preparation of the 1,2-Dioxolanes from 2Z-Diene Acids

As mentioned in the introduction, it is known that appropriate alkenoic acids form lactones on treatment with mercury salts via intramolecular acyloxymercuriation[16] . To ascertain if an intermolecular reaction with H_2O_2 would compete with the intramolecular process we attempted peroxymercuriation using the standard conditions developed in Chapter 2, on the diene acid (**3.35**). We observed no peroxide-positive components at the mercuriated stage and subsequent demercuriation led to isolation of the δ-lactone in its two isomeric forms (**2.30** and **2.31**) (**Scheme 3.21**).



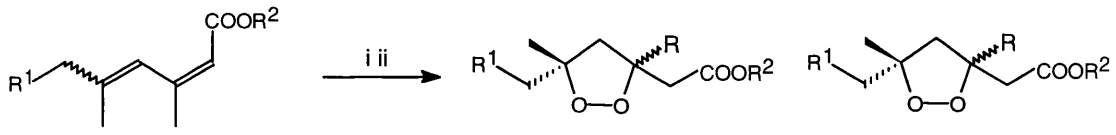
3.35 **2.30** **2.31**

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.21

Preparation of the 1,2-Dioxolanes from 2Z-Diene Esters

Initial attempts to prevent intramolecular acyloxymercuriation focused on the esterification route outlined in the introduction (**Scheme 3.13**).



3.28 **3.29** **3.30**

R = α CH_3 R = β CH_3

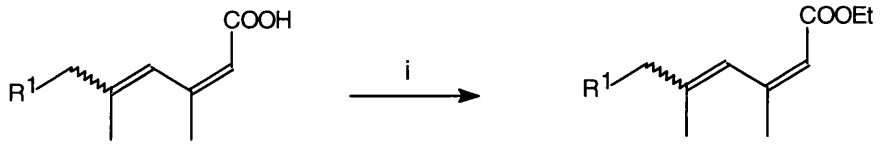
i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.13

Methods of esterification

The seemingly facile step of esterification of the diene acids proved more problematic than first imagined. Conventional acid catalysed esterification of the diene (**3.39**) $R^1=C_{14}H_{29}$ led to decomposition of the diene. We therefore began to investigate the available methods of esterification for acid sensitive substrates.

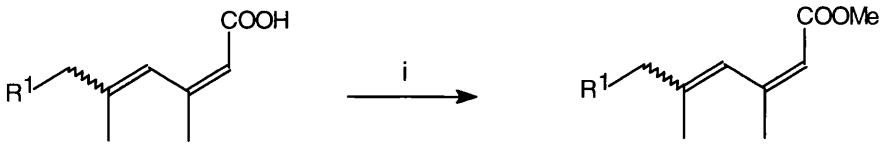
The first method[19] we attempted involved stirring the diene acids (**3.37-3.40**) at room temperature with ethanol, dicyclohexylcarbodiimide, and a catalytic amount of DMAP. This furnished us with the requisite ethyl esters (**3.52-55**) in yields varying from 50-60% (**Scheme 3.22**).



i) DCC/ DMAP/ EtOH/ DCM

Scheme 3.22

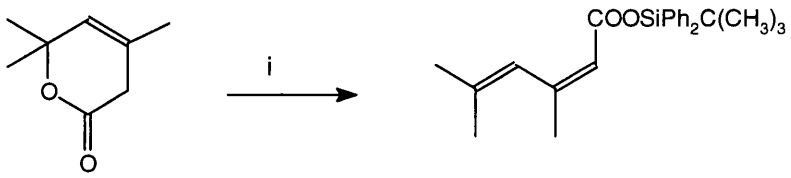
The moderate yields obtained, coupled with the difficulty in separating the DCU produced in the reaction from the diene esters, led us to try further methods. The third mode of esterification proved more successful. Carboxylic acids with a wide variety of functionalities present in their structure have been esterified[20] using the alkylating agent trimethyloxonium tetrafluoroborate in conjunction with N,N-diisopropylethylamine. When applied to our system, the diene esters were formed in approximately 90% yields, after stiring at room temperature for two hours (**Scheme 3.23**).



i) Me_3OBF_4/ N,N-diisopropylethylamine/ DCM

Scheme 3.23

The final method of esterification generated a silyl ester and was achieved by incorporating ring opening of the lactone and esterification into one step. Using the same conditions employed by Ireland[17], t-butyldiphenylsilyl chloride (TBDPS) and lactone (**2.30**) were stirred at room temperature after pre-treatment with LDA at -70 ^{0}C. After work up, the silylester of the dienoic acid was easily isolated by column chromatography in an 80% yield (**Scheme 3.24**).



2.30 **3.57**

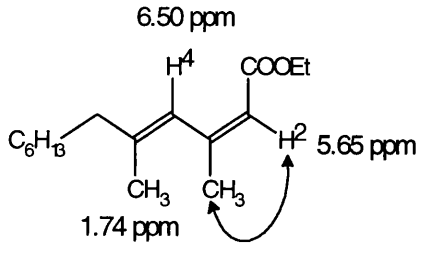
i) LDA/ $Ph_2C(CH_3)_3$/ - 70 °C warming to 20 °C

Scheme 3.24

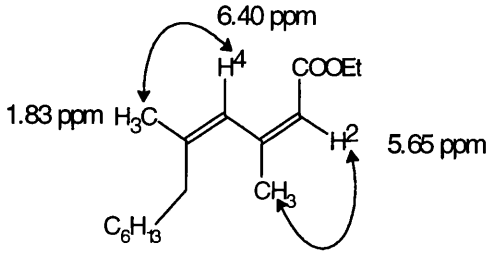
Characterisation of the isomers of the 2Z-diene esters

The diene acids synthesised using procedures **I II III** and **IV** are stereoselectively formed as the 2Z-isomers as a consequence of ring opening and the ^{1}H NMR of the diene acids (**3.36-3.40** and **3.47-3.51**) indicate they are a mixture of Z and E isomers around the C_4-C_5 double bond. Analysis of the ^{1}H NMR of the ethyl ester of the diene acid where R^1=C_6H_{13} (**3.52**) by nOe difference experiments provided information permitting assignment of the signals to the individual isomers.

In turn, all the methyl signals were irradiated. On irradiation of the methyl resonance at δ2.02 and 2.01 ppm nOe enhancement was observed on the resonance at δ5.65 ppm showing the methyl resonances to be from C^3CH_3 and cis to H^2 in the minor component. On irradiating the methyl resonance at δ1.83 ppm, nOe enhancement was observed on the resonance at δ6.40 ppm showing C^5CH_3 to be cis to H^4 in the minor component. On irradiation of the methyl peak at δ1.74 ppm no enhancement was observed on the H^4 resonance at δ6.50ppm suggesting the major component to be the E isomer. The ratio of major to minor component is 70:30, E:Z (see nOe spectra pg 119)



E Isomer



Z Isomer

Synthesis of the 1,2-dioxolane esters

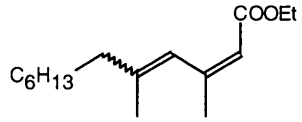
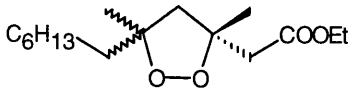
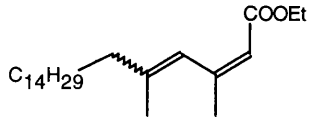
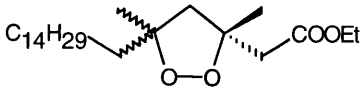
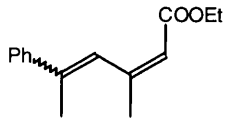
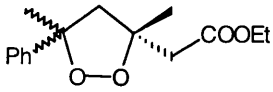
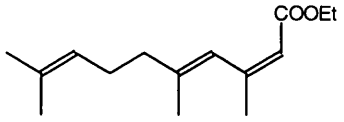
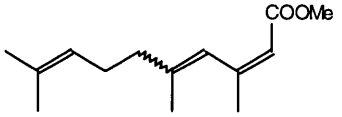
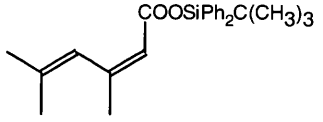
2Z-Diene Ester	Yield of ester and Isomer Ratio	1,2-Dioxolane	Yield of dioxolane and Isomer Ratio
 **3.52**	**60%** **4E:4Z 2:1**	 **3.58**	**23%** **2:1**
 **3.53**	**45%** **4E:4Z 2:1**	 **3.59**	**21%** **2:1**
 **3.54**	**55%** **4E:4Z 2:1**	 **3.60**	**5%** **1:1**[§]
 **3.55**	**60%** **4E**	**unsuccessful reaction**	**0%**
 **3.56**	**85%** **4E:4Z 1:1**	**unsuccessful reaction**	**0%**
 **3.57**	**85%**	**unsuccessful reaction**	**0%**

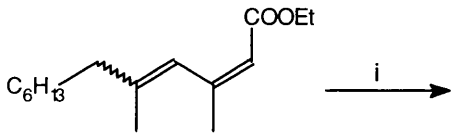
Table 3.3

[§] Isomer ratio after purification by HPLC

Peroxymercuriation/ demercuriation of the 2Z-diene alkyl esters

Peroxymercuriation/ demercuriation of the diene ester (**3.53**) $R^1=C_{14}H_{29}$ was carried out, using standard conditions, as a one-pot procedure, and the 1,2-dioxolane ester (**3.59**) was isolated in a 21% yield after purification by column chromatography.

To probe the nature of any competing reactions that may occur during peroxymercuriation purification of the reaction mixture obtained from the diene ester (**3.52**) $R^1=C_6H_{13}$ at the mercuriated stage, was attempted. The two non-mercuriated components present were isolated by column chromatography and one of which was identified as unreacted 2Z 4E/Z-diene ester (**3.52**), 13% of the original starting material. The second non-mercuriated component (**3.61**) accounted for approximately 7% by weight of the starting diene ester. The ^1H NMR of the second fraction suggested it consisted of one major component, that exhibited signals at δ 5.8 ppm and δ 3.25 ppm in a 1:1 ratio which was contaminated with minor impurities including a methyl ketone (**Scheme 3.25**).



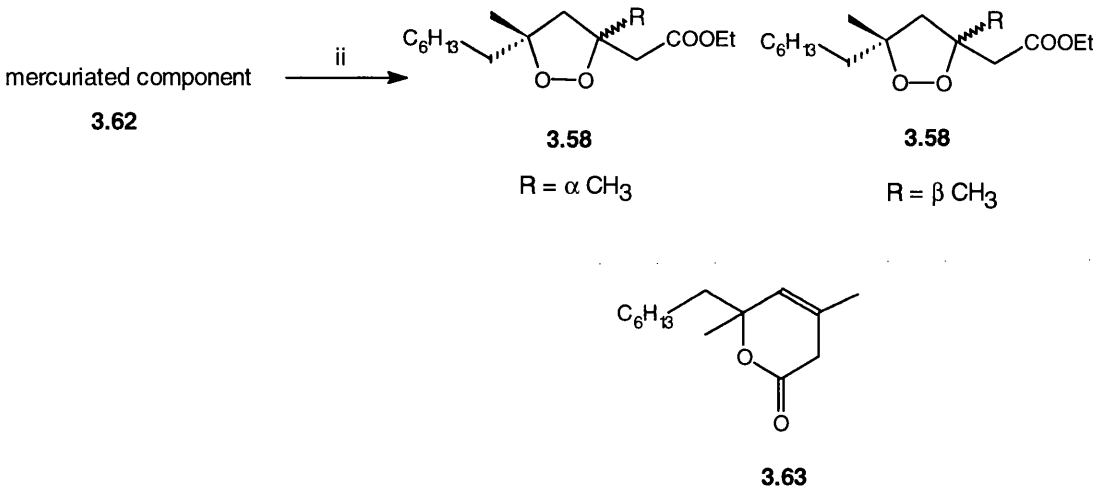
mercuriated component — major product — **3.62**

unidentified non-mercuriated component — minor product — **3.61**

i) 30% H_2O_2/ $Hg(OAc)_2$

Scheme 3.25

We encountered difficulties in separating the mercuriated components of the reaction mixture by column chromatography so sodium borohydride demercuriation was carried out on the mixture of mercuriated products. Purification by column chromatography of the products of this reaction led to the isolation of the 1,2-dioxloane ester (**3.58**) in a 23% yield, and one other major component. The second product was identified by its ^1H NMR as the corresponding δ-lactone (35%), present mainly as the unconjugated isomer (**3.63**), which must have been formed by competing intramolecular acyloxymercuriation (**Scheme 3.26**).



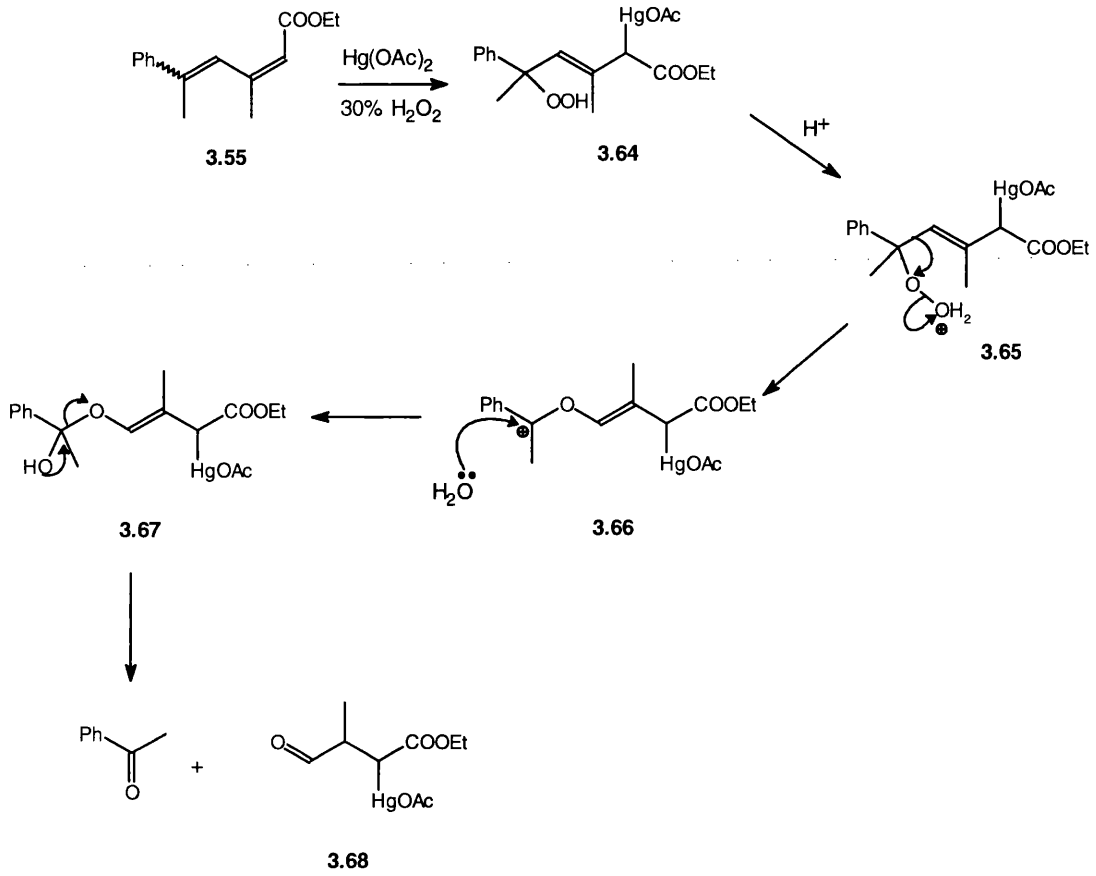
ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.26

In both cases peroxymercuriation/ demercuriation of the diene esters (**3.52** and **3.53**) furnished the 1,2-dioxolanes as a pair of diastereo isomers in a ratio of 2:1 and separation of these isomers was effected by HPLC (see spectra page 120).

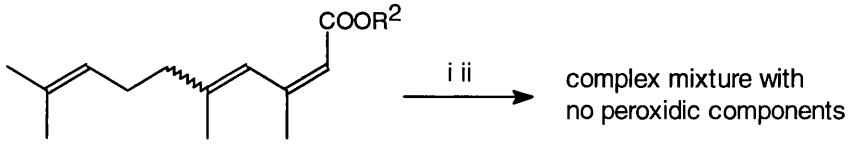
Peroxymercuriation of the diene ester (**3.54**) supplied the 1,2-dioxolane ester (**3.60**) in low yields, approximately 5%. The major product of the reaction was identified by ^1H NMR and tlc as acetophenone. This was present before demercuriation and was formed therefore from a pathway competing with 1,2-dioxolane formation or as a decomposition product of the mercuriated 1,2-dioxolane, possibly induced by a free radical rearrangement.

The production of acetophenone through a competing pathway can be rationalised by considering the initial reaction of the mercury salt and the peroxide nucleophile to involve 1,4-addition (**Scheme 3.27**). This has been observed previously in the oxymercuriation of conjugated dienes[21]. The monomercuriated intermediate (**3.64**) may then undergo rearrangement via (**3.65**) to form the enol ether (**3.66**). In acidic conditions it is known that hydroperoxides adjacent to possible migrating groups will rearrange by a mechanism known as Hock cleavage[22],protonation of the terminal oxygen of the peroxide in (**3.64**) generates (**3.65**) this initiates the loss of H_2O and migration of the vinyl group[23] to give (**3.66**). Attack of water at the cationic carbon (**3.66**) leads to the formation of the hemiacetal (**3.67**) followed by collapse of the system to acetophenone and the mercuriated aldehyde (**3.68**). The aldehyde component (**3.68**) of this rearrangement was not evident by NMR analysis at the mercuriated stage or after demercuriation.



Scheme 3.27

When the alkyl side chain of the diene ester contained a double bond (**3.55** and **3.56**) synthesis of the 1,2-dioxolane via peroxymercuriation of the diene ester was not successful. After demercuriation a complex mixture of products was detected by tlc, none of which tested positive for peroxide (**Scheme 3.28**) and attempts to separate the mixture by column chromatography were unsuccessful.



R^2=Et **3.52**

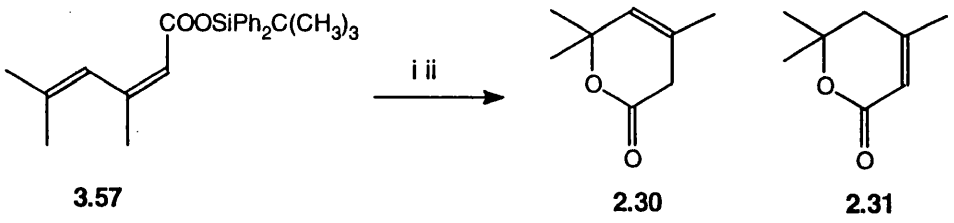
R^2=Me **3.56**

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.28

Peroxymercuriation/ demercuriation of the 2Z-diene silyl ester

Lactones (**2.30** and **2.31**) were the only products found following peroxymercuriation/ demercuriation of the silyl diene ester (**3.57**) with the unconjugated lactone (**2.30**) predominating (**Scheme 3.29**).



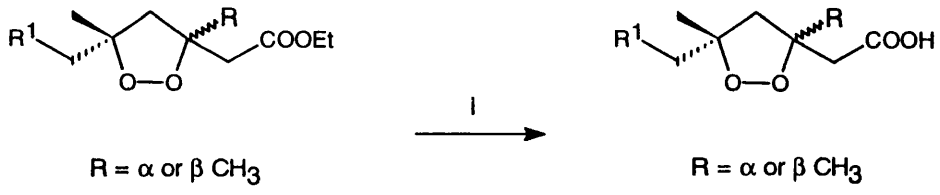
3.57 **2.30** **2.31**

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.29

Saponification of the dioxolane esters

Saponification by heating in methanolic NaOH resulted in extensive decomposition of the 1,2-dioxolane where R^1=H and milder conditions were sought and found[24]. The 1,2-dioxolane ester (**3.59**) was stirred for three days with five mole equivalents of LiOH in a mixture of THF and water to furnish the 1,2-dioxolane acid (**3.70**) which is a naturally occurring analogue of the plakinic acids[25] (**1.22e**). Ester (**3.58**) similarly gave the shorter chain analogue (**3.69**). The proton NMR of the crude reaction mixture of (**3.70**) indicated a favourable yield, however purification by flash column chromatography led to the elution of only one isomer and to a reduction in yield because of difficulties in recovering material from the column. The 1,2-dioxolane (**3.58**) gave the acid analogue (**3.69**) after isolation by base extraction in an 80% yield as a mixture of *cis* and *trans* isomers (**Scheme 3.30**).



R = α or β CH_3 R = α or β CH_3

$R^1=C_6H_{13}$ **3.58** $R^1=C_6H_{13}$ **3.69**

$R^1=C_{14}H_{31}$ **3.59** $R^1=C_{14}H_{31}$ **3.70**

i) LiOH/ THF/ H_2O

Scheme 3.30

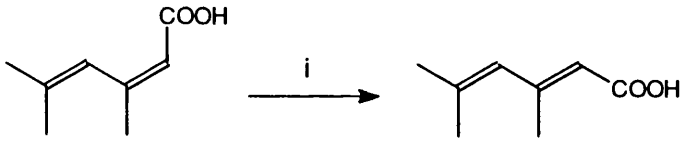
The results of the peroxymercuriation/ demercuriation of the 2Z-diene esters (**3.52-3.54**) demonstrate how, through alkyl esterification of the 2Z-diene acids, intramolecular cyclisation is inhibited sufficiently to allow competing intermolecular addition of the peroxide nucleophile. However δ-lactone formation still accounted for a significant proportion of the reaction products so our attention turned to the second method of modification of the 2Z-diene acids.

Preparation of the 1,2-Dioxolanes from the 2E-Diene Acids

Methods of isomerisation

We reasoned that isomerisation of the αβ-double bond from the Z to the E isomer would prevent lactone formation. Although this would decrease the reactivity of the double bond to mercuriation we would eliminate the need for esterification of the diene acid and hence for saponification of the dioxolane ester.

Two methods of isomerisation were tried. The 2Z-diene acid (**3.35**) was converted to 90% 2E (**3.71**) by stirring in ether with a trace of iodine after one week. The second method[14d] was far more efficient and virtually complete isomerisation was effected by refluxing (**3.35**) with a catalytic amount of thiophenol in CCl_4 for two hours (**Scheme 3.31**).



3.35 **3.71**

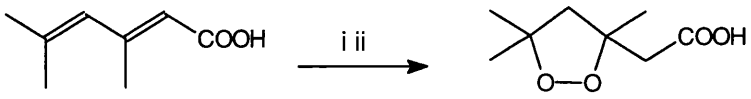
i) PhSH/ CCl_4

Scheme 3.31

Synthesis of the 1,2-dioxolane acids

Treatment of the 2E-diene acid (**3.71**) using standard peroxymercuriation/ demercuriation conditions gave the dioxolane acid (**2.44**) (**Scheme 3.32**). As demercuriation is conducted under basic conditions the reaction products were found as the conjugate base in the aqueous phase of the reaction mixture. Acidification of this phase, using 1M HCl at 5 ^{o}C, to approx pH 4, followed by extraction with DCM and ethyl acetate, supplied the impure 1,2-dioxolane acid (**2.44**) in a yield of 30%. Isolation of the 1,2-dioxolane was effected by fractional base extraction and pure (**2.44**) was obtained in a yield of 25%. No peroxidic

components were found in the DCM phase of the demercuriation reaction mixture and the ^1H NMR spectra indicated a mixture of products.

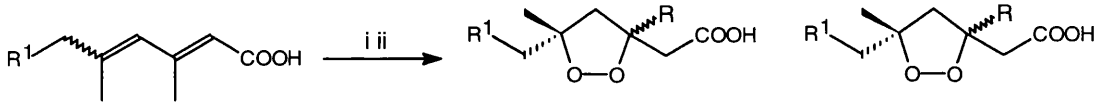


3.71 **2.44**

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.32

Following on from the success of the reaction (**Scheme 3.32**) we adopted this route for the synthesis of more plakinic acid analogues.



3.31 **3.32** **3.33**

R= α CH_3 R= β CH_3

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.13

Refluxing the 2Z-diene acids (**3.36**, **3.40** and **3.47-3.51**) with thiophenol in CCl_4 effected isomerisation with little or no decomposition of the substrate (**Table 3.4**). The diene acids were not fully converted to the 2E-isomers and similarly the concurrent isomerisation of the 4Z-double bond to the 4E-isomer was not complete. However sufficient structural modification occurred to allow formation of the 1,2-dioxolane using peroxymercuriation.

Peroxymercuriation/ demercuriation of the 2E-diene acids (3.72-3.78)

Peroxymercuriation/ demercuriation was carried out under standard conditions (**Table 3.4**). In all cases we found that separation of the 1,2-dioxolane acid from the major side products was facilitated by the work up procedure used in the synthesis of (**2.44**). The 1,2-dioxolane acids (**3.79-3.85**) were isolated by base extraction of the demercuriation product with subsequent acidification, in approximately 95 % purity, with the major impurities remaining in the DCM portion of the reaction mixture.

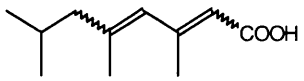
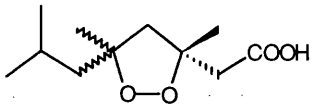
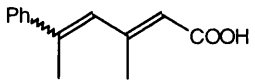
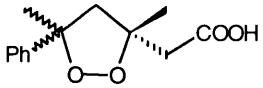
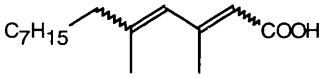
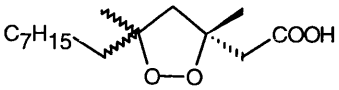
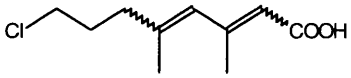
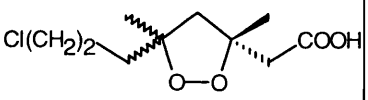
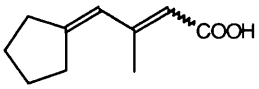
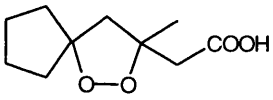
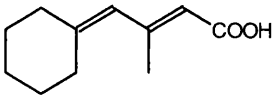
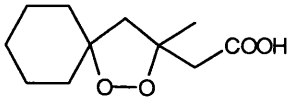
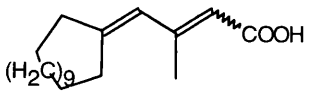
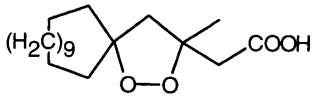
Diene Acid	Yield Isomer Ratio	1,2-Dioxolane Acid	Yield Isomer Ratio
 **3.72**	**95% 2E:2Z 3.5:1 2E,4E:2E,4Z 4:1**	 **3.79**	**23% 3.5:1**
 **3.73**	**95% 2E** 2E,4E:2E,4Z 4:1**	 **3.80**	**5% 4:1**
 **3.74**	**95% 2E:2Z 8:1 2E,4E:2E,4Z 3:1**	 **3.81**	**29% 3:1**
 **3.75**	**95% 2E:2Z 4:1 2E,4E:2E,4Z 3:1**	 **3.82**	**30% 3:1**
 **3.76**	**95% 2E:2Z 10:1****	 **3.83**	**15%**
 **3.77**	**95% 2E****	 **3.84**	**50%**
 **3.78**	**95% 2E:2Z 10:1****	 **3.85**	**10%**

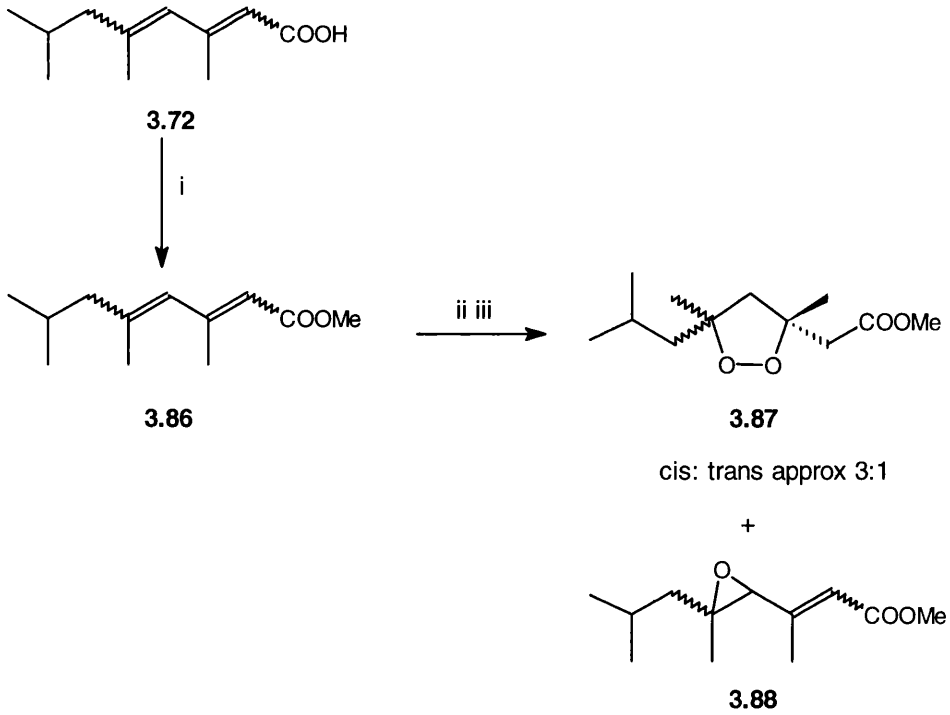
Table 3.4

** Isomer ratio after recrystalisation

Comparison of the results of the isomerisation route with those obtained from the esterification pathway are favourable. We have reduced the number of steps and, provided R^1 is not too hydrophobic, purification at each stage can be effected by base extraction. However, the yields of the 1,2-dioxolanes are still relatively low (average yield of 25%). In each case the 2Z-diene acid present will form the corresponding lactone upon mercuriation which accounts for the consumption of a percentage of the starting material. However, no evidence for unreacted 2E-diene acid was found suggesting the diene substrate had reacted to produce unidentified side products. Following the work up procedure outlined earlier the 1,2-dioxolanes were isolated along with one other minor component which exhibited resonances in the ^{1}H NMR at δ:3.20 and 5.80 ppm (see spectra pg 121). Analysis, by ^{1}H NMR, of the products found in the DCM portion of the demercuriation reaction mixtures indicated a complex mixture, not easily separable by column chromatography, which contained the parent methyl ketone of the diene acid as the major component.

Peroxymercuriation/ demercuriation of a 2E-diene ester

To assist our investigations into the nature of any competing reactions that occur, peroxymercuriation/ demercuriation of the ester analogue (**3.86**) of the diene acid (**3.72**) was attempted (**Scheme 3.33**).

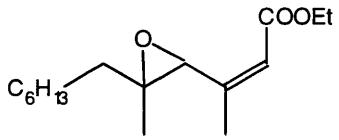


i) Me_3OBF_4/ N,N-diisopropylethylamine/ DCM
ii) 30% H_2O_2/ $Hg(OAc)_2$ iii)$NaBH_4$/ ^-OH/ DCM

Scheme 3.33

As with other peroxymercuriation/ demercuriation experiments performed on diene esters, the products were found only in the organic portion of the demercuriation reaction mixture. Evaporation of the organic solvent revealed the crude product mixture in a yield of 51%. Purification by column chromatography led to the isolation of the 1,2-dioxolane ester (**3.87**) in a yield of 25%, comparable to that of the acid analogue (**3.79**).

The other major product isolated from the column was identified as the αβ-unsaturated δγ-epoxide (**3.88**). The ^{1}H NMR exhibited resonances, characteristic of olefinic and epoxide protons respectively, at δ5.8 ppm and δ3.2 ppm, integral ratio 1:1. Characteristic carbon resonances for epoxides were also observed in the ^{13}C NMR with peaks at δ66 ppm and 64 ppm. These were identified by an attached proton test as tertiary and quaternary substituted respectively. The ^{1}H and ^{13}C NMR of (**3.88**) closely resembled the spectra of (**3.61**), the nonmercuriated product isolated after peroxymercuriation of the diene ester (**3.52**). We therefore identified (**3.61**) as the αβ-unsaturated δγ epoxide.

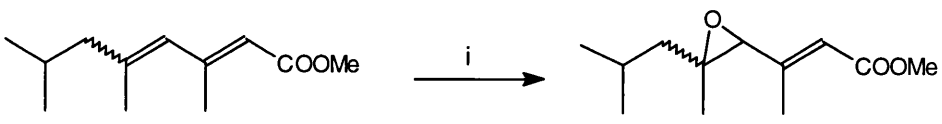


3.61

Synthesis of the αβ-Unsaturated δγ Epoxide (3.88)

Metal hydride reductions of organomercury(II) salts are mediated by the production of free radicals and β-peroxy radicals are known to be suseptible to γ-scission in which epoxides are generated[26]. As (**3.61**) was isolated before demercuriation, we eliminated this possibility in the formation of the epoxides (**3.61** and **3.88**).

We assumed the epoxidation reaction had transpired through the known reaction of olefins with peracids[27]. To confirm this the diene ester (**3.86**) 4E:4Z 4:1 was treated with peracetic acid. After work up of the reaction mixture and purification by column chromatography a product was isolated which gave identical ^{1}H and ^{13}C NMR spectra to the epoxide (**3.88**) (**Scheme 3.34**) (see spectra pg. 122).



3.86

2E 4E:Z 4:1

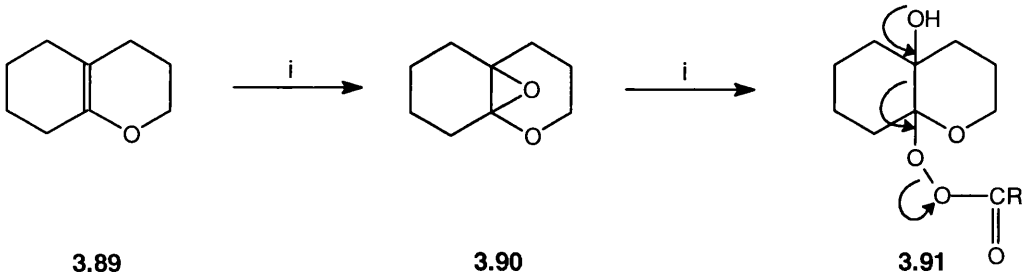
3.88

cis: trans approx 4:1

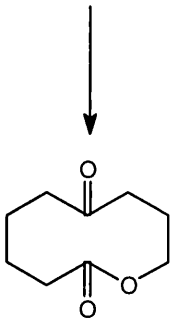
i) 35% peracetic acid in H_2O

Scheme 3.34

The formation of the αβ-unsaturated δγ-epoxides in the peroxymercuriation reaction is probably caused by the generation of an excess of peracetic acid in situ. Under these reaction conditions the epoxide is suseptible to ring opening by nucleophilic attack. Epoxidation of allyl ethers[28] (**3.89**) with an excess of peracid has been known to cause fragmentation of the substrate. This occurs via nucleophilic attack of the initially formed epoxy ether (**3.90**) by the excess peracid. The intermediate hydroxy perester (**3.91**) then cleaves to give the lactone (**3.92**). Similarly when epoxide (**3.93**) was treated with 98% H_2O_2 the substrate cleaved, generating two moles of benzaldehyde[29] (**Scheme 3.35**).

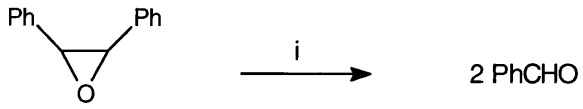


3.89 **3.90** **3.91**



3.92

i) RCO_3H

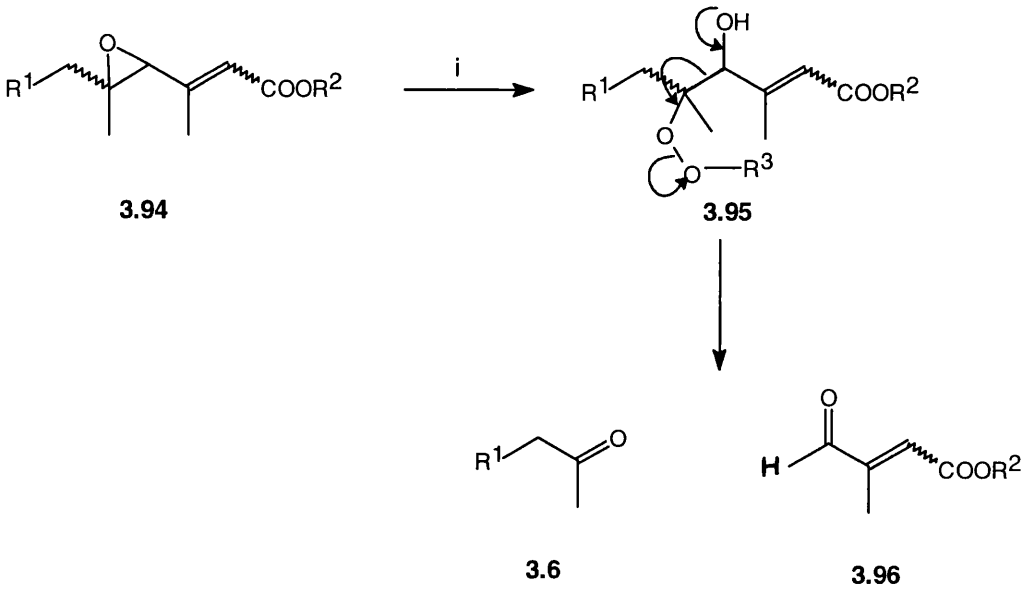


3.93

i) 98% H_2O_2/ Et_2O/ cat $HClO_4$/ 0-5^0 C

Scheme 3.35

The αβ-unsaturated δγ-epoxide (**3.94**), formed under standard peroxymercuriation conditions, is suseptible to nucleophilic attack by either peracid or H_2O_2 which could lead to collapse of the epoxide to generate the methyl ketone (**3.6**) and the aldehyde (**3.94**) (**Scheme 3.36**). This mechanism and that proposed earlier (**Scheme 3.27**) may account for the observed formation of the methyl ketone (**3.6**) however no evidence of the aldehyde fragment (**3.96**) has been found in any of the experiments we have conducted.



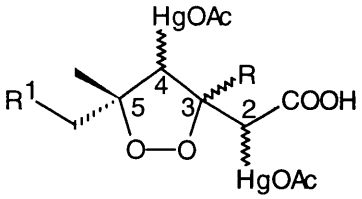
R^3 = H or $CH_3C{=}O$

i) R^3OOH

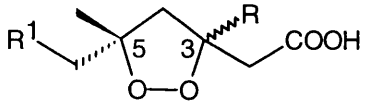
Scheme 3.36

Stereoselectivity of 1,2-Dioxolane Formation

In dioxolane formation four stereocentres are created at the peroxymercuriation step. These are at C^2 C^3 C^4 and C^5, only two of which (C^3 and C^5) remain in the mercury free compound, which is found as the *cis* and *trans* 1,2-dioxolane.

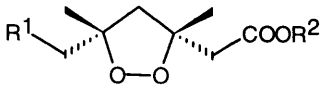


R = α CH_3



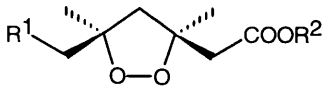
R = β CH_3

The stereochemistry at C^5 is determined by a combination of the geometry at the C^4-C^5 double bond and the face which is attacked; (4E + bottom face attack by mercury) or (4Z + top face attack) gives 5S stereochemistry whereas (4E + top face attack) or (4Z + bottom face attack) gives 5R stereochemistry. The stereochemistry at C_3 is determined solely by which face of the C^2-C^3 bond is attacked since the geometry of C^2-C^3 would only affect the stereochemistry at C^2 which is lost on demercuriation; bottom face attack by mercury of C^2-C^3 gives 3S stereochemistry and top face gives 3R.



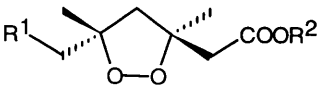
3R, 5R

3.97



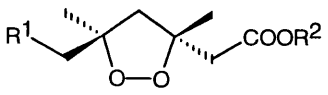
3S, 5S

3.98



3S, 5R

3.99



3R, 5S

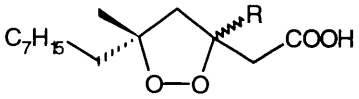
3.100

The C_7 and C_{15} 2Z-diene esters (**3.52** and **3.53**) each with ratios of 4E:4Z of 7:3 gave the dioxolane ester in a 2:1 ratio of diastereoisomers. The 2E-diene acids also gave the two dioxolane isomers in ratios similar to the 4E:4Z isomer ratio. In each case, the 2Z-diene ester and the 2E-diene acid and esters, formed the same 1,2-dioxolane isomer in the greater amounts. This close correspondence, between the isomer ratio about C^4-C^5 face of the

dienes and the isomer ratio of the 1,2-dioxolane strongly suggests that the 4E and 4Z-diene each affords predominantly one dioxolane isomer. If this is correct, these results also imply that whichever C^4-C^5 face is attacked predetermines the C^3-C^2 face that is subsequently attacked. Depending on which face is predetermined the *cis* or *trans* dioxolane is formed. To establish the mode of addition we must confirm the relative stereochemistry of the five membered peroxide rings formed in the reaction.

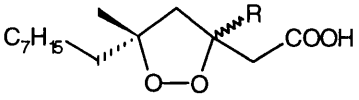
Identification of the relative stereochemistry of the plakinic acid analogues

Separation of the two isomers of the 1,2-dioxolane (**3.81**) was effected by column chromatography to give (**3.101** and **3.102**). These were taken as representative of all the plakinic acid analogues synthesised.



3.101

R= β CH_3 *cis*



3.102

R= α CH_3 *trans*

We began the identification process by comparing the ^{1}H NMR spectra of (**3.101** and **3.102**) with data reported in Davidson's paper[30] for the plakinic acids (**1.18-1.21**) which identified the relative 1,2-dioxolane isomers from NOESY experiments.

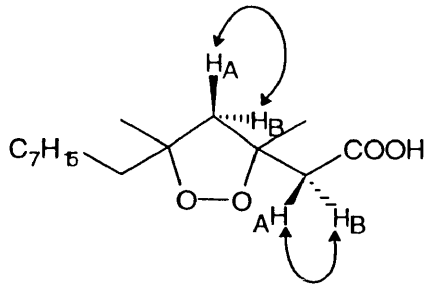
Each proton on C^2 and C^4 is represented by a doublet in the ^{1}H NMR. In the natural products the difference in chemical shift between the two doublets assigned to the protons C^2H_A and C^2H_B and that between the resonances representing the ring protons C^4H_A and C^4H_B are each greater in the *cis* isomer than in the *trans.*

The ring protons C^4H_2 of the major, less polar product (**3.101**) resonate at δ2.50 ppm and δ2.12 ppm, a difference of 0.38 ppm, while the minor, more polar isomer (**3.102**) shows analogous signals at δ2.43 and δ2.23 ppm, a difference of 0.20 ppm.

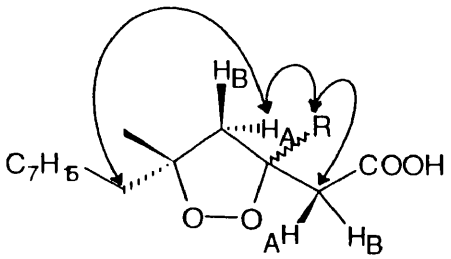
A similar pattern exists between the signals assigned to the C^2 protons, and (**3.101**) shows a greater difference in δ ppm between the doublets of C^2H_A and C^2H_B than is present for the same protons in (**3.102**). We therefore tentatively assigned (**3.101**) as the *cis* 1,2-dioxolane and (**3.102**) as the *trans* .

Difference nuclear overhauser experiments on the 1,2 dioxolanes.

We analysed each of the isomers (**3.101** and **3.102**) by difference nOe. The results obtained allowed for the absolute assignment of signals, in agreement with Davidson, and provided further evidence for assigning the relative stereochemistry of (**3.101** and **3.102**) as *cis* and *trans* respectively. As expected irradiation of the C^2 and C^4 protons, in both isomers, showed strong dipolar coupling between the protons C^2H_A and C^2H_B, and between C^4H_A and C^4H_B.



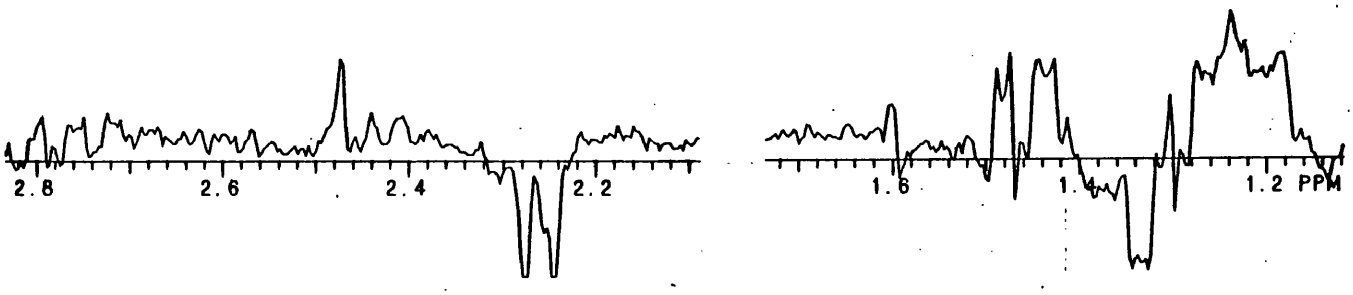
Irradiation of C^4H_A at δ2.23 ppm in (**3.102**) showed a correlation with signals in the region of δ1.40-1.50 ppm which may be assigned to the signals for C^6CH_2 and the methyl singlet at δ1.44 ppm. On irradiation at δ1.44 ppm we observed a positive nOe with the C^4H_A at δ2.23 ppm. Davidson assigned the lowfield methyl signal to the methyl at the C^3 position. Our results are in line with this as shown by the positive nOe exhibited by the C^2H_2 on irradiation at δ1.44 ppm. The results of the nOe experiments on (**3.102**) are in line with *trans* stereochemistry

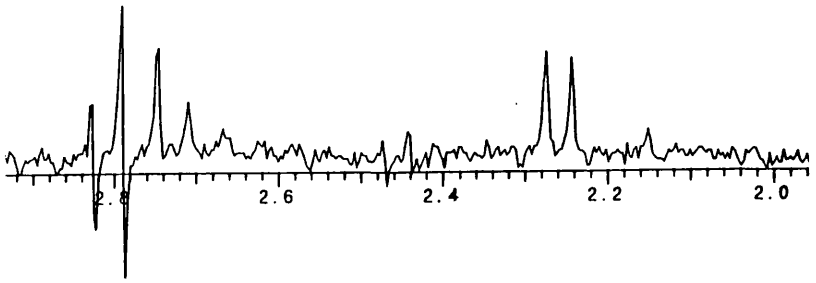


3.102

R= α CH_3

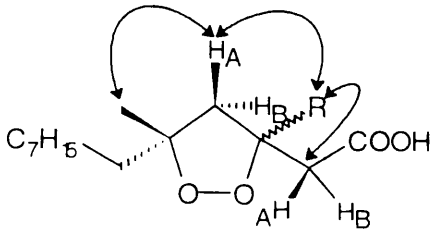
Irradiation at 2.23 ppm



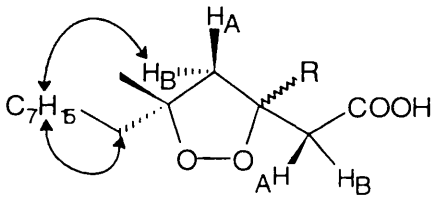


Irradiation at 1.44 ppm

The isomer (**3.101**) was unambiguously assigned as the *cis* 1,2-dioxolane through the results obtained on irradiation of the methyl singlets; irradiation at δ1.46 ppm enhanced the highfield doublet of the ring protons at δ2.12 ppm and the C^2H_2 protons while irradiation at δ1.30ppm enhanced only the doublet at δ2.12 ppm. Irradiation of the alkyl multiplet δ1.1-1.2 ppm exhibited dipolar coupling only with the ring proton doublet C^4H at δ2.50 ppm and the multiplet at δ1.6 ppm.



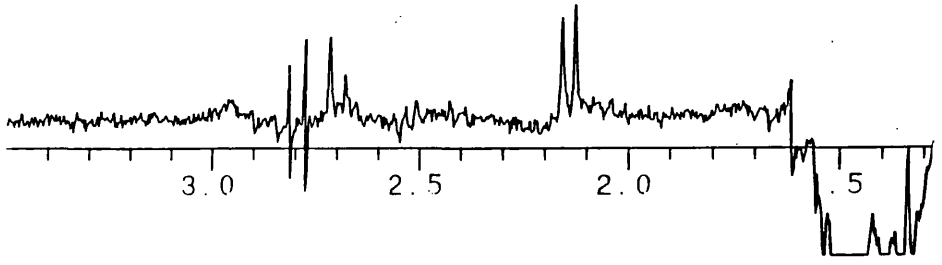
3.101

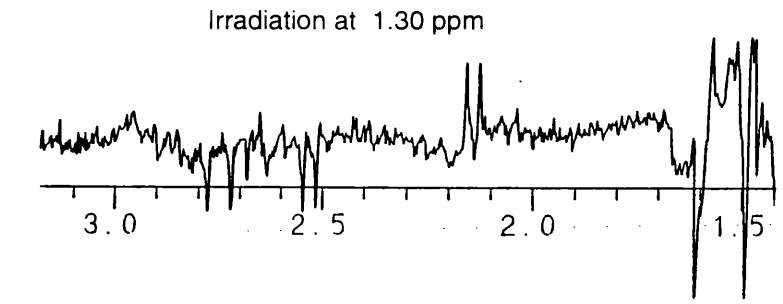


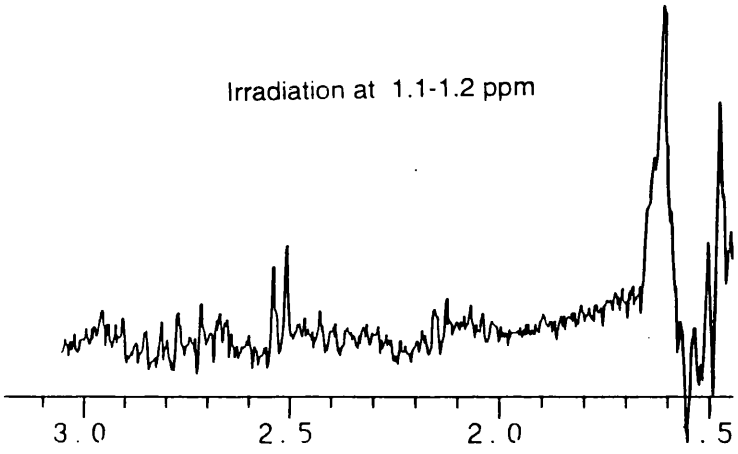
3.101

R= β CH_3

Irradiation at 1.46 ppm





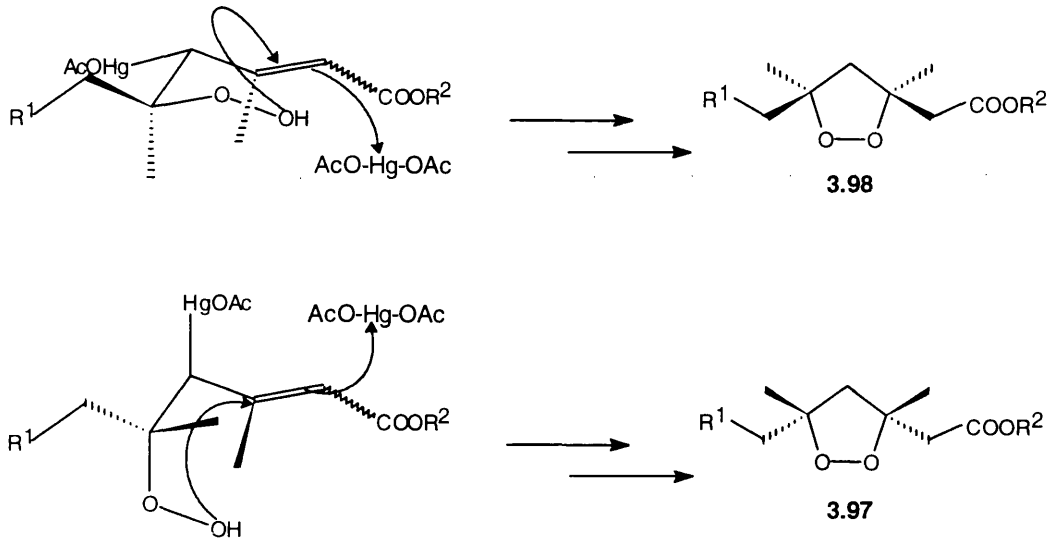


Mode of addition of peroxymercuriation

Having determined the relative stereochemistry of the major diastereoisomer of the 1,2-dioxolane as *cis* we can now draw a correlation between the 4E-isomer of the diene carboxylate and the *cis*-1,2-dioxolane, and establish the dominant mode of addition.

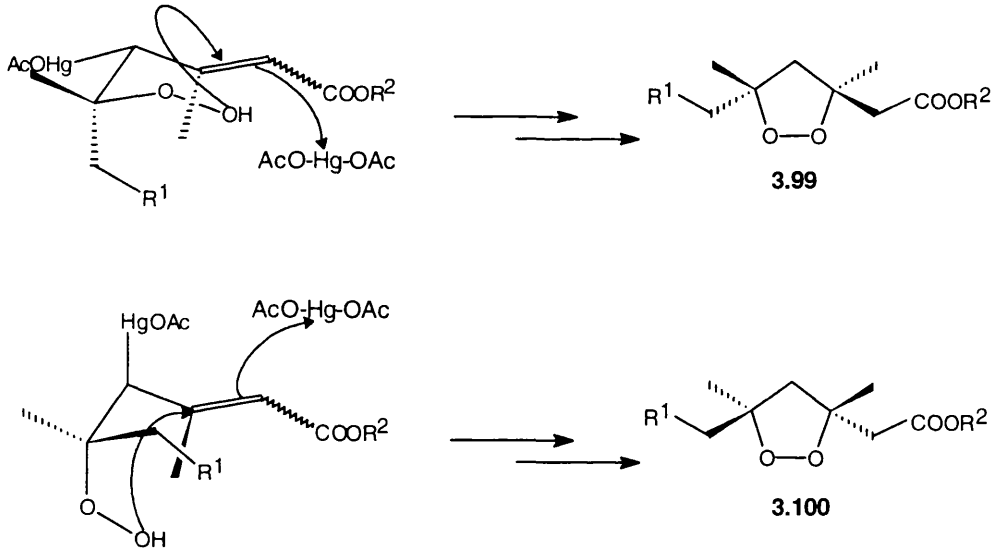
Production of the *cis* 1,2-dioxolane from the 4E-isomer of the diene carboxylate requires attack of the mercury(II) at the same face of the C^4-C^5 and C^2-C^3 double bonds and can be either bottom-bottom (**3.98**) or top-top face attack (**3.97**) (**Scheme 3.37**). Conversely this same side mode of attack produces the minor isomer *trans* 1,2-dioxolane when applied to the 4Z-diene (**3.99** and **3.100**). This is in keeping with the experimental results where the 4Z-diene is the minor component of the diene substrate used in the synthesis of the plakinic acid analogues (**Scheme 3.38**).

Bottom-bottom or top-top face attack by mercury (II) of the 4E-diene carboxylate



Scheme 3.37

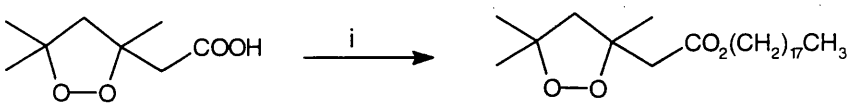
Bottom-bottom or top-top face attack by mercury (II) of the 4Z-diene carboxylate



Scheme 3.38

Modification of the Carboxyl Group

So far the 1,2-dioxolanes have been synthesised with ethyl and methyl esters and carboxylic acids substituents, all of which were present in the diene precursor. In chapter 2 we showed how the carboxylic acid could be derivatised in the presence of the peroxide ring.

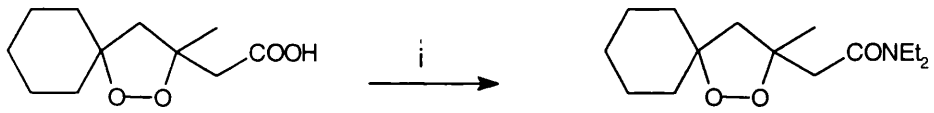


2.44 **2.45**

i) DCC/ DMAP/ octadecanol/ DCM

Scheme 2.18

DCC, as a coupling agent, is used extensively in the synthesis of amides[31],particularly peptides. As a preliminary investigation into the possibility of amide synthesis with the 1,2-dioxolane in position, we successfully converted the carboxylic acid (**3.84**) into the tertiary amide (**3.103**) in 53% yield using the DCC coupling method (**Scheme 3.39**). The ethyl groups of the amide were identified in the ^{1}H NMR spectra from the multiplet at δ 3.43-3.35 ppm and the two triplets at δ1.16 and 1.11 ppm. However in comparison to (**3.84**) the C^2CH_2 appeared as a broad singlet instead of the characteristic AB coupling pattern normally seen in the proton spectra of the quaternary substituted 1,2-dioxolanes (see spectra page 123 and 124).



3.84 **3.103**

i) DCC/ $HNEt_2$/ DCM

Scheme 3.39

EXPERIMENTAL

Preparation of the 2Z-Dienoic Acids

Procedure I

General Method A. Lactone Synthesis[7]

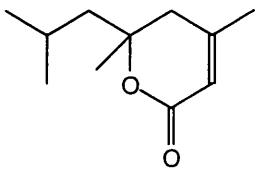
n-Butyl lithium (44 mmol) was added dropwise to a solution of diisopropylamine (44 mmol) in dry THF (60 ml) under nitrogen at -78 ^{0}C. The yellow solution was stirred for 10 minutes then 3,3-dimethylacrylate (40 mmol) was added dropwise. Stirring was continued for a further 20 minutes. The methyl ketone (40 mmol) dissolved in dry THF (20 ml) and added all at once. Stirring was continued at -78 ^{0}C for a further 5 minutes and then warmed to 10 ^{0}C (30 min). The reaction was quenched with sat NH_4Cl (aq) (40 ml) diluted with H_2O (150 ml) and extracted with ether (3x125 ml). The organic extracts were combined, washed with H_2O (2x100 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated *in vacuo*.

General Method B. Ring-opening of lactone[9]

A freshly prepared solution of sodium methoxide (45 mmol of Na, in 60 ml of MeOH) was added to a solution of the lactone (15 mmol) in methanol (25 ml) and the solution was left to reflux for 2 hours. The methanol was evaporated *in vacuo* and the residue dissolved in water. The aqueous layer was washed with DCM, acidified with dropwise addition of conc HCl and extracted with DCM. The organic extracts were combined dried and evaporated *in vacuo.*

Preparation of 5,6-dihydro-4,6-dimethyl-6-(2-methylpropyl)-2H-pyran-2-one. (3.41)

General Method A with diisopropylamine (8.65 ml, 66 mmol), n-butyl lithium (1.6M in hexane, 41.25 ml, 66 mmol), 3,3-dimethylacrylate (8.34 ml, 60 mmol), 4-methylpentan-2-one (7.5 ml, 60 mmol). Yield of crude product 11.5 g. Purification by column chromatography (SiO_2 4:1Hex:EtOAc) gave 3.3 g (30%) of (**3.41**) as a colourless oil.



^{1}H NMR δ:5.76(1H, bs C=C**H**)
2.38 and 2.17(2H, AB, J=18, C**H**$_2$ ring),
1.88(3H, s, C=CC**H**$_3$), 1.70-1.80(1H, m, (CH$_3$)$_2$C**H**),
1.62 and 1.49(2H, **AMX**, C**H**$_2$ chain J_{MX}=14.5,J_{AM}=6.3, J_{AX}=5.6)
1.32(3H, s, C**H**$_3$C-O), 0.93 and 0.90(6H, J=6.5, (C**H**$_3$)$_2$).

^{13}C NMR δ:164.60(**C**=O), 155.40(CH$_3$**C**=), 115.60(C=**C**H), 81.80(**C**-O), 48.80(**C**H$_2$), 39.80(**C**H$_2$), 25.56, 24.50, 24.30, 24.00 and 23.20(**C**H$_3$C=C, (**C**H$_3$)$_2$**C**H,**C**H$_3$)

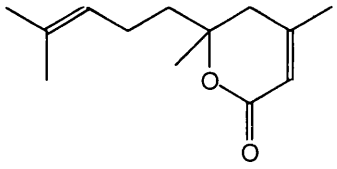
IR neat: 2943(s), 1723(s), 1651(m), 1441(s), 1374(s),1169(s).

MS(EI).: $(M)^+183$(M-(CH_3))$^+167$ (M-$(CH_3)_2CHCH_2)^+125$

MS(FAB): Acc.Mass. Found: 183.1380 $C_{11}H_{19}O_2$ (M+H)requires: 183.1385

Preparation of 5,6-dihydro-4,6-dimethyl-6-(2-methylpent-2-en-5-yl)-2H-pyran-2-one (3.42)

General Method A with diisopropylamine (6.13 ml, 44 mmol), n-butyl lithium (1.6M in hexane, 44 mmol, 27.5 ml), 3,3-dimethylacrylate (5.56 ml, 40 mmol), 6-methyl hept-5-ene-2-one (5.9 ml, 5.048 g, 40 mmol). Yield of crude 10 g. Purification by column chromatography (SiO_2 4:1 Hex:EtOAc) gave 1.09 g, (32%) (**3.42**) as a colourless oil.



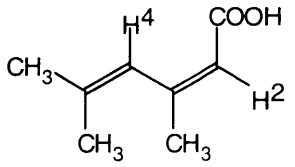
^{1}H NMR δ:5.80(1H, bs, C=C**H** ring)
5.50(1H, m, C**H**=C$(CH_3)_2$)
2.42 and 2.18(2H, AB, J=22,C$\mathbf{H}_2$ ring)
2.0-2.10(2H, m, C$\mathbf{H}_2$),
1.93(3H, s, $\mathbf{H}_3$CC= ring) 1.06-1.78(2H, m, C$\mathbf{H}_2$), 1.65(3H, s, C$\mathbf{H}_3$C=),
1.58(3H, s, $\mathbf{H}_3$C-C=), 1.38(3H, s, C$\mathbf{H}_3$),

^{13}C NMR δ:164.05(**C**=O), 155.30(CH_3-**C**=), 131.40(($CH_3)_2$**C**=), 123.60(**C**H=C$(CH_3)_2$)
115.10(H**C**=C ring), 81.20(**C**-O), 40.40(**C**H_3-C-O), 38.20(**C**H_2 -C-O),
25.40(**C**H_2 ring), 24.10(**C**H_2 chain), 22.90 and 22.10(**C**H_3x2 chain)
17.30(**C**H_3-C=)

MS(EI) : Acc.Mass. Found: 208.1468 $C_{13}H_{20}O_2$ requires: 208.1463.

Preparation of (2*Z*)-3,5-dimethylhexa-2,4-dienoic acid (3.35)

General Method B with sodium methoxide (0.281 g of Na 12.2 mmol, 30 ml MeOH), lactone (**2.30 and 2.31**) (0.656 g, 4.7mmol). On addition of the acid a solid formed, weight of crude 1.3 g. Extraction of aqueous layer gave a further 0.7 g (96%). Purification by recrystalisation from hexane gave white crystals, 49% recovery.



^{1}H NMR δ:6.42(1H, s, **H**^{4}), 5.65(1H, s, **H**^{2})
2.04, 1.85 and 1.74(3x3H, s, (C$\mathbf{H}_3$)$_3$)

^{13}C NMR δ:171.10(**C**=O), 156.05(**C**=CCO_2H),
140.20(($CH_3)_2$**C**=C), 122.50(($CH_3)_2$C=**C**), 117.50(C=**C**CO_2H),
27.20, 25.05 and 20.40(3x**C**H_3).

IR (soln CCl_4): 3200-2800(br), 1680(vs), 1631(s), 1597(s).

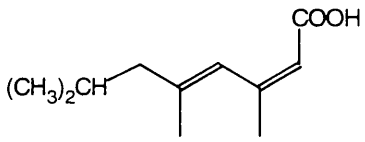
Analysis Found: C,68.60; H, 8.75. $C_8H_{12}O_2$ requires: C,68.54; H,8.63 %

MP ^{0}C 67-69

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-3,5,7-trimethyl-octa-2,4-dienoic acid (3.36)

n-Butyl lithium (2.5M in hexane, 6 ml, 15 mmol) was added dropwise to a solution of diisopropylamine (2.1 ml, 15 mmol) in dry THF (20ml) under nitrogen at -78 ^{0}C. The yellow solution was stirred for 10 minutes. The lactone (**3.41**) (2.5 g, 13.7 mmol) in dry THF (10 ml) was added dropwise and stirring continued at -78 ^{0}C or 30 minutes. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with sat NH_4Cl(aq) (40ml) acidified with conc HCl and extracted with ether (4x50 ml). The organic layers were combined dried ($MgSO_4$) and evaporated *in vacuo* to give 2.5 g of a yellow oil. Purification by column chromatography (SiO_2 4:1Hex:EtOAc), gave 2.2 g, (90%) of (**3.36**) as a colourless oil in a 1:1 ratio of 4*E*:4*Z*

2*Z*,4*E* Isomer



^{1}H NMR δ 6.27(1H, bs, **H**^{4}), 5.65(1H, bs, **H**^{2})

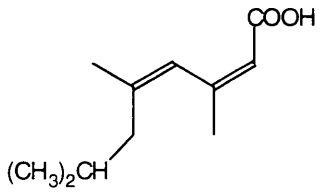
250MHz 2.04(3H, d, C^{3}C**H**$_3$, J=1.2)

1.96(2H, bs, C**H**$_2$),

1.70(3H, d, , J=1.2, C^{5}C**H**$_3$)

0.90(6H, d, (C**H**$_3$)$_2$, J=6), 1.5-2.0(1H,obs,C**H**).

2*Z*,4*Z* isomer



^{1}H NMR δ:6.37(1H, bs,**H**^{4}), 5.65(1H, bs, **H**^{2})

250MHz 2.01(3H, d, J=1.2, C^{3}C**H**$_3$)

1.98(2H, bs, C**H**$_2$),

1.80(3H, d, J=1.2Hz, C^{5}C**H**$_3$)

0.84(6H, d, J=6Hz, (C**H**$_3$)$_2$), 1.50-2.0(1H,obs, C**H**)

Both Isomers

^{13}C NMR δ:171.30 and 171.09(**C**=O), 156.30 and 156.20(**C**=CCO$_2$H),

142.05 and 141.20((CH$_3$)$_2$CHCH$_2$**C**=CH),

124.90 and 124.70((CH$_3$)$_2$CHCH$_2$C=**C**H),

117.20 and 116.80(=**C**HCO$_2$H), 42.0, 31.0, 26.40, 26.30, 26.0, 25.0, 24.0,

22.60, 22.40, 18.50, 14.20 and 14.10((**C**H$_3$)$_2$**C**H**C**H$_2$, C^5**C**H$_3$ C^3**C**H$_3$)

IR neat: 3300-2900 (br), 1697 (s), 1619 (m), 1442 (m), 950 (m).

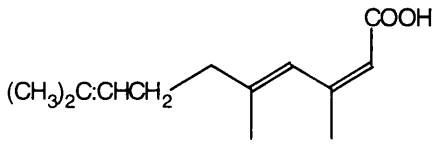
MS(NH_3Cl): $(M+H)^+$ 183, $(M+NH_4)^+$ 200.

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-3,5,9-trimethyldeca-2,4,8-trienoic acid (3.37)

General Method B with lactone (**3.42**) (1.6 g, 7.8 mmol), Na (0.53 g, 24 mmol), MeOH (30 ml). Yield of crude product 1.2 g, (88%) as a 2:1 ratio of 4*E*:4*Z*. Purification by column chromatography (SiO_2 8:1 Hex:EtOAc) gave partial separation of the two isomers. Fraction 1 contained 0.310 g of the 2*Z*,4*E* isomer as a colourless oil (**3.37a**) Fraction 2 contained 0.480 g of a mixture of both isomers (**3.37b**) as a colourless oil. Total weight 0.71g (52%) in a ratio of 2:1

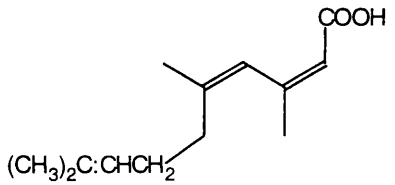
2*Z*,4*E* Isomer.

^{1}H NMR δ 6.50(1H, bs, **H**^{4}), 5.68(1H, bs, **H**^{2})
5.10(1H, m, C=**H** chain)
2.12(4H, bs, 2x$C\mathbf{H}_2$)
2.01(3H, s, $C^3C\mathbf{H}_3$)
1.75(3H, s, $C^5C\mathbf{H}_3$), 1.65 and 1.59(6H, s, $(C\mathbf{H}_3)_2$).



2*Z*,4*Z* Isomer

^{1}H NMR δ:6.35(1H, bs,**H**^{4}), 5.68(1H, bs, **H**^{2}),
5.09(1H, m, C=**H** chain)
2.10(4H, bs, 2x$C\mathbf{H}_2$), 2.01(3H, s, $C^3C\mathbf{H}_3$)
1.70(3H, s, $C^5\mathbf{H}_3$)
1.65 and 1.59(6H, s, $(C\mathbf{H}_3)_2$).



^{13}C NMR δ:169.05(**C**=O), 157.05(**C**=CCO_2H),
143.10($(CH_3)_2C$:$CH(CH_2)_2\mathbf{C}$=CH),132.20($(CH_3)_2\mathbf{C}$=C),
124.40($(CH_3)_2C$:$CH(CH_2)_2\mathbf{C}$ C=**C**H), 123.80($(CH_3)_2C$=**C**H)
117.05(=**C**HCO_2H), 41.0(2x$C\mathbf{H}_2$), 26.50 and 25.50($C^5\mathbf{C}H_3$ $C^3\mathbf{C}H_3$),
19.30 and 18.20($(\mathbf{C}H_3)_2C$=C).

MS(EI): $(M)^+$ 208, $(M\text{-}CH_3)^+$ 193. $(M\text{-}(CH_3)_2C{=}C(CH_2)_2)^+$ 125.

MS(FAB): Acc.Mass. Found: 209.1550 $C_{13}H_{21}O_2$ (M+H)requires: 209.1542

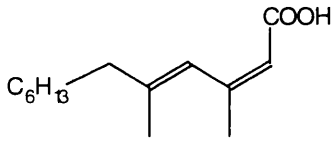
IR neat: 2928(vs), 1693(vs), 1619(vs), 1600(vs),1442(vs), 929(vs).

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-3,5-dimethyl-dodeca-2,4-dienoic acid (3.38)

General Method A with diisopropylamine (6.13 ml, 44 mmol), n-butyl lithium (1.6M in hexane, 44 mmol, 27.5 ml), 3,3-dimethylacrylate (5.56 ml, 40 mmol), non-2-one (5.9 ml, 5.048 g, 40 mmol). General method B with crude lactone. Purification by column chromatography (SiO_2 Hex:EtOAc 5:1).Yield of acid 3.38 g (35%) as a 2:1 ratio 4*E*:4*Z*.

2*Z*,4*E* Isomer

^{1}H NMR δ:6.45(1H, s, **H**^{4}), 5.65(1H, s, **H**^{2})



250MHz 2.15-2.05(2H, m, C**H**$_2$C=C),

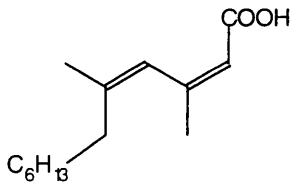
2.05 (3H, s, C^{3}C**H**$_3$)

1.70(3H, s, C^{5}C**H**$_3$),

1.60-1.10(12H, m, (C**H**$_2$)$_6$), 1.90(3H, m, (CH$_2$)$_6$C**H**$_3$).

2*Z*,4*Z* Isomer

^{1}H NMR δ:6.38(1H,s, **H**^{4}), 5.65(1H, s, **H**^{2})



250MHz 2.15-2.05(2H, m, C**H**$_2$C=C),. 2.05 (3H, s, C^{3}C**H**$_3$)

1.80(3H, s, C^{5}C**H**$_3$) 1.60-1.10(12H, m, (C**H**$_2$)$_6$)

1.90(3H, m, (CH$_2$)$_6$C**H**$_3$)

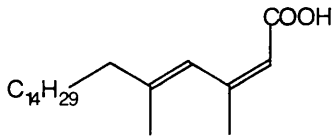
MS(EI): $(M)^+$224

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-3,5-dimethyleicosa-2,4-dienoic acid (3.39)

General Method A with diisopropylamine (6.13 ml, 44 mmol), n-butyl lithium (1.6M in hexane, 44 mmol, 27.5 ml), 3,3-dimethylacrylate (5.56 ml, 40 mmol), nonadecan-2-one (5.9 ml, 5.048 g, 40 mmol). General method B with crude lactone. Purification by column chromatography (SiO_2 Hex:EtOAc 5:1).Yield of (**3.39**) 4.4 g (33%) as amixture of isomers in a 2:1 ratio of 4*E*:4*Z*.

2*Z*,4*E* Isomer

^{1}H NMR δ:6.38 (1H, bs, **H**^{4}), 5.65(1H, bs, **H**^{2})



2.10-2.05(2H, m, C**H**$_2$C=C),

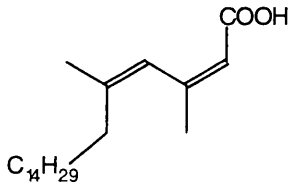
2.01(3H, s, C^{3}C**H**$_3$)

1.71(6H, s, C^{5}C**H**$_3$) 1.60-1.10(26H, m, (C**H**$_2$)$_{13}$)

1.90(3H, t, (CH$_2$)$_6$C**H**$_3$)

2*Z*,4*Z* Isomer

^{1}H NMR δ:6.30(1H, bs, **H**^{4}), 5.65(1H, bs, **H**^{2})



2.10-2.05(2H, m, C**H**$_2$C=C),.1.94(3H, s, C^{3}C**H**$_3$)

1.80(6H, s, C^{5}C**H**$_3$), 1.60-1.10(26H, m, (C**H**$_2$)$_{13}$)

1.90(3H, t, (CH$_2$)$_6$C**H**$_3$)

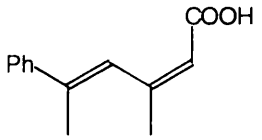
Both Isomers

^{13}C NMR δ:171.10 and 169.20(**C**=O), 156.05 and 155.05(**C**=CCO_2H), 142.20($CH_3(CH_2)_{14}$**C**=C), 124.05 and 123.30($CH_3(CH_2)_{14}C$=**C**H), 117.05 and 116.20 (C=**C**CO_2H), 41.60 and 39.70(H_2**C**C=C), 33.00, 32.30, 29.90, 29.70, 29.60, 29.50, 29.50, 29.40, 29.20, 28.0, 27.80, 25.70, 25.10, 23.70, 22.75 and18.60(13x**C**H_2,2x**C**H_3), 14.05($(CH_2)_{14}$**C**H_3)

MS(EI) $(M)^+$337

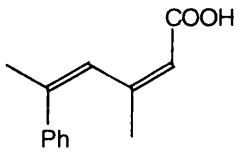
Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-3-methyl-5-phenyl-hexa-2,4-dienoic acid (3.40)

General Method A with diisopropylamine (6.13 ml, 44 mmol), n-butyl lithium (1.6M in hexane, 27.5 ml, 44 mmol), 3,3-dimethylacrylate (5.56 ml, 40 mmol), acetophenone (4.8 g, 40 mmol). General Method B with crude lactone. Purification by recrystalisation from Hexane with 1% EtOAc to give white needle like crystals.Yield 2.40 g (30%) as a mixture of isomers in a ratio of 2:1 of 4*E*:4*Z*



Both Isomers.

^{1}H NMR δ:7.2-7.5(5H, m, C_6**H**$_5$), 7.08 and 6.9(1H, bs, **H**^{4}) 5.8 and 5.6(1H, bs,**H**^{2}) 2.20, 2.15, 2.13 and 1.52 (6H, s, C^5C**H**$_3$, C^3C**H**$_3$)



Both Isomers

^{13}C NMR δ:171.10 and 172.20(**C**=O), 156.20 and 157.50(**C**=CCO_2H) 143.0 and 144.0(Ph**C**=C), 142.0 and 139.0(**C**$_6$H$_5$,qu) 128.20, 128.10, 127.70, 127.60, 126.40, 126.10 and 126.05(**C**$_6$H$_5$, t, PhC=**C**H),118.40 and 117.50(C=**C**CO_2H), 27.20, 25.30 and 24.20(3x**C**H_3), 18.05(**C**H_3).

General Method C. (Procedure II)

n-Butyl lithium (44 mmol) was added dropwise to a solution of diisopropylamine (44 mmol) in dry THF (60 ml) and under nitrogen at-78 ^{0}C. The yellow solution was stirred for 10 minutes then 3,3-dimethylacrylate (40 mmol) was added dropwise. Stirring was continued for a further 20 minutes. The methyl ketone (40 mmol) in dry THF (20 ml) was then added all at once. Stirring was continued at -78 ^{0}C for a further 5 minutes and then warmed to room temperature and stirred overnight. The reaction was quenched with sat NH_4Cl(aq) (50 ml) and washed with ether (2x40 ml). The basic aqueous layer was acidified by dropwise addition of conc HCl

and extracted with ether (4x50 ml). The organic extracts were combined, dried ($MgSO_4$), and evaporated *in vacuo.*

General Method D. (Procedure III)

Procedure as for General Method C using 1.5 mole equivalents of the dienolate anion. n-Butyl lithium (60 mmol), diisopropylamine (60 mmol), 3,3-dimethylacrylate (60 mmol).

General Method E. (Procedure IV)

Procedure as for General Method C using 2 mole equivalents of the dienolate anion. n-Butyl lithium (80 mmol), diisopropylamine (80 mmol), 3,3-dimethylacrylate (80 mmol).

Preparation of (2*Z*,4*E*) and (2*Z*,4*Z*)-3,5-dimethyl-trideca-2,4-dienoic acid (3.47)

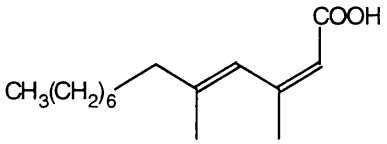
General Method C with n-butyl lithium (2M in pentane, 5.5 ml, 11 mmol), diisopropylamine (1.44 ml, 11 mmol), 3,3-dimethylacrylate (1.39 ml, 10 mmol), decan-2-one (95%) (1.64 g, 2 ml, 10 mmol). After addition sat NH_4Cl the reaction mixture was extracted with EtOAc. The organic layers were combined and washed with 1M HCl, water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give 2.45 g of a colourless oil. Purification by column chromatography (SiO_2 5:1Hex:EtOAc) gave 1.03 g (42%) of (**3.47**), of a colourless oil in a 2:1 ratio of 4*E*:4*Z*.

General Method D with n-butyl lithium (2M in pentane, 7.5 ml, 15 mmol), diisopropylamine (1.96 ml, 15 mmol), 3,3-dimethylacrylate (2.08 ml, 15 mmol), decan-2-one (95%) (1.64 g, 2 ml, 10 mmol). After addition sat NH_4Cl the reaction mixture was extracted with EtOAc. The organic layers were combined and washed with 1M HCl, water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give 3.23 g of a clear oil. Purification by column chromatography (SiO_2 5:1 Hex:EtOAc) gave 1.65 g (69%) of (**3.47**), of a colourless oil in a 2:1 ratio of 4*E*:4*Z*.

General Method E with n-butyl lithium (2M in pentane, 10 ml, 15 mmol), diisopropylamine (2.6 ml, 15 mmol), 3,3-dimethylacrylate (2.8 ml, 15 mmol), decan-2-one (95%) (1.64 g, 2 ml, 10 mmol). After addition sat NH_4Cl the reaction mixture was extracted with EtOAc. The organic layers were combined and washed with 1M HCl, water and brine, dried ($MgSO_4$) and evaporated *in vacuo* to give 3.73 g of a clear oil. Purification by column chromatography (SiO_2 5:1 Hex:EtOAc) gave 2.1 g (85%) of (**3.47**) as a colourless oil in a 2:1 ratio of 4*E*:4*Z*.

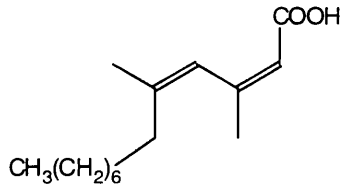
2*Z*,4*E*

^{1}H NMR δ:6.40(1H, s, **H**^{4}), 5.64(1H, s, **H**^{2})
2.07-2.03(2H, m, C**H**$_2$C=C),
2.01(3H, s, C^{3}C**H**$_3$) 1.70(3H, s, C^{5}C**H**$_3$),
1.50-1.10(12H, m, (C**H**$_2$)$_7$),
0.80(3H, m, (CH$_2$)$_7$C**H**$_3$).



2*Z*,4*Z*

^{1}H NMR δ:6.33(1H, s, **H**^{4}), 5.63(1H, s, **H**^{2})
2.07-2.03(2H, m, C**H**$_2$C=C),
2.03(3H, s, C^{3}C**H**$_3$),1.80(3H, s, C^{5}C**H**$_3$),
1.50-1.10(12H, m, (C**H**$_2$)$_7$),
0.80(3H, m, (CH$_2$)$_7$C**H**$_3$)



Both Isomers

^{13}C NMR δ:171.10(**C**=O), 156.20(**C**=CCO$_2$H), 143.0 and 142.80(CH$_3$(CH$_2$)$_7$**C**=C)
123.80 and 123.30(CH$_3$(CH$_2$)$_7$C=**C**H), 116.90 and 116.60(C=**C**CO$_2$H)
40.80, 33.70, 31.80, 29.70, 29.60, 29.50, 29.40, 29.30, 29.20, 28.0, 27.80,
25.70, 24.20, 22.6 and 14.0((**C**H$_2$)$_7$ (**C**H$_3$)$_2$ **C**H$_3$).

MS(EI): (M)$^+$238 (M-CH$_3$)$^+$223 (M-CH$_3$ (CH$_2$)$_7$)$^+$125

MS(EI): Acc.Mass. Found: 238.3680 $C_{15}H_{26}O_2$ requires: 238.3684

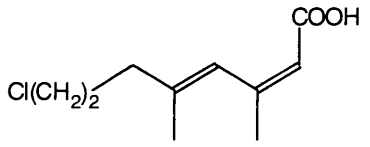
IR neat: 3400-2900(br). 1699(vs), 1620(s)

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)- 8-chloro-3,5-dimethylocta-2,4-dienoic acid (3.48)

General Method D with n-butyl lithium (2M in pentane, 30 ml, 60 mmol), diisopropylamine (7.85, 60 mmol), 3,3-dimethylacrylate (8.34 ml, 60 mmol), 5-chloro-pentan-2-one (95%) (5 g, 40 mmol). Yield 4.2 g (52%) of (**3.48**) as a yellow oil as a mixture of isomers in a ratio of 4*E*:4*Z*. 2:1

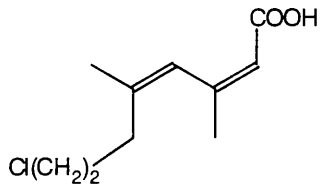
2*Z*,4*E* Isomer

^{1}H NMR δ:6.32(1H, s, **H**^{4}), 5.69(1H, s, **H**^{2}),
3.56(2H, t, J=6.7, ClC**H**$_2$),
2.25-2.15(2H, m, C**H**$_2$C=C),
2.0(3H, s, C^{3}C**H**$_3$), 1.88-1.84(2H, m, C**H**$_2$),
1.70(3H, s, C^{5}C**H**$_3$)



2*Z*,4*Z* Isomer

^{1}H NMR δ:6.30(1H,s, **H**^{4}), 5.69(1H, s, **H**^{2}),



3.47(2H, t, J=6.7, ClC**H**$_2$)

2.25-2.15(2H, m, C**H**$_2$C=C),

2.02(3H, s, C^{3}C**H**$_3$)1.88-1.84(2H, m, C**H**$_2$),

1.80(3H, s, C^{5}C**H**$_3$).

Both Isomers

^{13}C NMR δ:171.10(**C**=O), 156.05 and 155.80(**C**=CCO$_2$H),

139.90 and 139.60(Cl(CH$_2$)$_3$**C**=C) 125.20 and 124.70(Cl(CH$_2$)$_3$C=**C**H),

117.30 and 117.10(C=**C**CO$_2$H), 44.60, 44.20, 37.20, 30.70, 30.60, 30.40,

25.80, 25.60, 23.80 and 18.30((**C**H$_2$)$_3$(**C**H$_3$)$_2$).

MS(EI): (1:3 M+2:M)$^+$205 and 203 (M-Cl (CH$_2$)$_3$)$^+$125

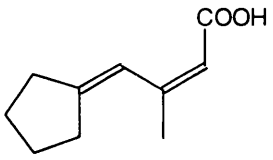
Analysis Found: C,59.62; H, 7.71. $C_{10}H_{15}$ Cl O_2 requires: C,59.25; H,7.46 %

IR neat: 3400-2900(br). 1685(vs), 1620(s), 700(m)

Preparation of (2Z)-cyclopentane-2,4-dienoic acid derivative (3.49)

General method C with n-butyl lithium (2M in pentane, 22 ml, 44 mmol), diisopropylamine (5.76 ml, 44mmol), 3,3-dimethylacrylate (5.56 ml, 40mmol), cyclopentanone (3.54 ml, 3.36 g, 40 mmol). Purification by recrystalisation from Hex gave 1.09 g (14%) of (**3.49**) as white crystals.

^{1}H NMR δ:7.35(1H, s, **H**^{4}), 5.54(1H, s, **H**^{2})



2.60-2.45(4H, m, 2xC**H**$_2$), 2.10(3H, s, C**H**$_3$)

1.70-1.81(2H, m, C**H**$_2$), 1.60-1.50(2H, m, C**H**$_2$)

^{13}C NMR δ:172.05(**C**=O), 156.20(**C**=CCO$_2$H), 146.40((CH$_2$)$_4$**C**=C),

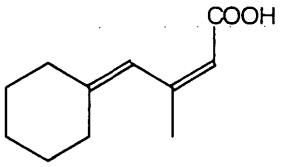
119.20((CH$_2$)$_4$C=**C**H), 114.30(C=**C**CO$_2$H), 37.70, 32.20, 27.40 and

25.40((**C**H$_2$)$_4$), 25.05(**C**H$_3$).

MS(EI): (M)$^+$166 (M-CH$_3$)$^+$151 (M-COOH)$^+$121

Preparation of (2Z)-cyclohexane-2,4-dienoic acid derivative (3.50)

General method C with n-butyl lithium (2M in pentane, 22 ml, 44 mmol), diisopropylamine (5.76 ml, 44mmol), 3,3-dimethylacrylate (5.56 ml, 40mmol), cyclohexanone (4.4 ml, 4.14 g, 40 mmol). Purification by column chromatography (SiO_2 Hex:EtOAc 4:1) then recrystalisation from Hex gave 2.52 g (35%) of (**3.50**) as white crystals.



^{1}H NMR δ:6.19(1H, s, **H**^{4}), 5.66(1H, s, **H**^{2})
2.18-2.16(4H, m, 2x**CH**$_2$), 1.99(3H, s, **CH**$_3$)
1.59-1.512(6H, m, 3x**CH**$_2$)

^{13}C NMR δ:171.10(**C**=O), 156.25(**C**=CCO_2H),
146.40($(CH_2)_5$**C**=C), 120.65($(CH_2)_5$C=**C**H), 117.05(C=**C**CO_2H), 37.70, 30.80, 28.40, 27.50 and 26.30((**C**$H_2)_5$), 26.25(**C**H_3).

MS(EI): $(M)^+$180 $(M-CH_3)^+$165 $(M-COOH)^+$135

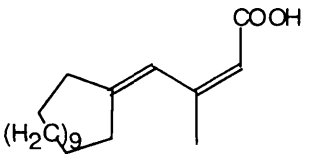
Analysis Found: C,73.20; H, 8.82. $C_{11}H_{16}O_2$ requires: C,73.30; H,8.90 %

M.P ^{0}C: 69.5-71.

IR (soln CCl_4): 3200-2855(br), 1688(vs), 1625(vs)

Preparation of (2Z)-cyclododecane-2,4-dienoic acid derivative (3.51)

General method C with n-butyl lithium (2M in pentane, 11 ml, 22 mmol), diisopropylamine (2.88 ml, 22mmol), 3,3-dimethylacrylate (2.78 ml, 20mmol), cyclododecanone (3.64 g, 20 mmol). After addition sat NH_4Cl the reaction mixture was acidified with dropwise with conc HCl and extracted with EtOAc. The organic layers were combined dried ($MgSO_4$) and evaporated *in vacuo* to give 4.4 g of a clear oil. Purification by recrystalisation from Hex:EtOAc 3:1 gave 2.1 g (38%) of (**3.51**) as white crystals.



^{1}H NMR δ:6.33(1H, s, **H**^{4}), 5.66(1H, s, **H**^{2}),
2.13-2.07(4H, m, 2x**CH**$_2$), 2.09(3H, s, **CH**$_3$),
1.58-1.23(18H, m, 9x**CH**$_2$)

^{13}C NMR δ:171.10(**C**=O), 157.05(**C**=CCO_2H),
144.20($(CH_2)_{11}$**C**=C), 124.50($(CH_2)_{11}$C=**C**H), 117.20(C=**C**CO_2H), 26.20(**C**H_3), 32.20, 30.0, 24.60, 24.30, 24.20, 24.10, 23.90, 23.70, 23.10, 22.50((**C**$H_2)_{11}$)

MS(EI): $(M)^+$264 $(M-CH_3)^+$249 $(M-COOH)^+$219

Analysis Found: C,77.21; H, 10.70 $C_{17}H_{28}O_2$ requires: C,77.22; H,10.67 %

M.P ^{0}C: 123-125

IR soln CCl_4: 3200-2855(br), 1690(vs), 1612(vs)

Esterification of (2Z) diene acids

General Method F[19]

The diene acid (15mmol), a catalytic amount of dimethylaminopyridine (200mg) and ethanol (45mmol) were dissolved in dry DCM and stirred at 0 ^{0}C under nitrogen for 10 minutes. Dicyclohexylcarbodiimide (16.5mmol) in dry DCM was added dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The white ppt of dicyclohexylurea was filtered off and the organic layer washed with 1M HCl(aq) sat.$NaHCO_3$(aq) and H_2O. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*.

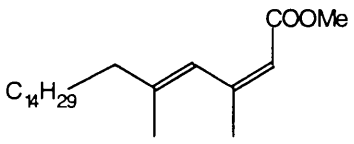
General Method G[20].

Trimethyl oxonium tetrafloroborate (11 mmol) was added portionwise to a stirred solution of the diene acid (10 mmol) and N-ethyldiisopropylamine (11mmol) in dry DCM (60 ml). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with sat $NaHCO_3$ (3x 30 ml), 1M HCl (3x30 ml) and brine (30 ml) The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*.

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-methyl-3,5-dimethyl-eicosa-2,4-dienoate

The diene acid (**3.39**) (0.924 g, 2.8 mmol) was dissolved in methanol (100 ml) with catalytic conc H_2SO_4 .The reaction mixture was set to reflux and stopped after 3 hours as tlc indicated decomposition of the starting material and reformation of the lactone. Purification by column chromatography (SiO_2 20:1Hex:EtOAc) gave 0.065 g, (7%) as a colourless oil.

2*Z*,4*E* Isomer



^{1}H NMR δ:6.42 (1H, bs, **H**^{4}), 5.62(1H, bs, **H**^{2})
3.60(3H, s, O-C**H**$_3$),
2.10-2.05(2H, m, C**H**$_2$C=C),
2.0(3H, s, C^{3}C**H**$_3$), 1.70(6H, s, C^{5}C**H**$_3$),
1.50-1.10(26H, m, (C**H**$_2$)$_{13}$), 0.85(3H, t, (CH$_2$)$_{14}$C**H**$_3$)

^{13}C NMR δ:167.20(**C**=O), 154.40(**C**=CCO$_2$H), 142.30(CH$_3$(CH$_2$)$_{14}$**C**=C), 123.05(CH$_2$)$_{14}$C=**C**H), 116.20(CH$_3$(C=**C**CO$_2$H), 51.50(O-**C**H$_3$), 41.30 and 39.20(H$_2$**C**C=C), 33.50, 32.30, 29.90, 29.70, 29.60, 29.50, 29.50, 29.40, 29.20, 28.60, 27.80, 25.70, 25.10, 23.70, 22.70, 18.60((**C**H$_2$)$_{13,}$ 2x**C**H$_3$), 14.20((CH$_2$)$_{14}$**C**H$_3$)

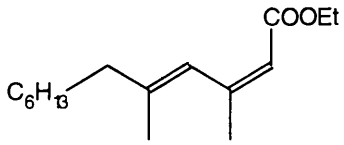
MS(EI): (M)$^+$350

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-ethyl-3,5-dimethyldodeca-2,4-dienoate (3.52)

General Method F with diene acid (**3.38**) (3.3 g, 15 mmol), dicyclohexylcarbodiimide(3.40 g, 16.5 mmol), dimethylaminopyridine (200mg), Ethanol (2.7 ml, 45 mmol). Initial purification by column chromatography (SiO_2 50:1 Hex:EtOAc) gave of (**3.52**) as a clear oil still contaminated with DCC. Final purification by Kugerhur distilation gave of (**3.52**) as a colourless oil b.p. 130 ^{0}C at 0.1atms (60%).

2*Z*,4*E* Isomer

^{1}H NMR δ:6.50(1H, s, **H**^{4}), 5.65(1H, s, **H**^{2})



4.15(2H, q, O-C**H**$_2$)

2.15-2.05(2H, m, C**H**$_2$C=C),

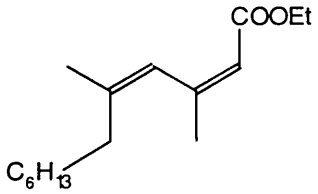
2.03(3H, s, C^{3}C**H**$_3$),

1.73(3H, s, C^{5}C**H**$_3$) 1.60-1.10(12H, m, (C**H**$_2$)$_6$)

1.90(3H, m, (CH$_2$)$_6$C**H**$_3$), 1.00-0.90(3H, m, O-CH$_2$C**H**$_3$).

2*Z*,4*Z* Isomer

^{1}H NMR δ:6.39(1H,s, **H**^{4}), 5.65(1H, s, **H**^{2})



4.05-4.15(2H, m, O-C**H**$_2$)

2.15-2.05(2H, m, C**H**$_2$C=C),

2.01(3H, s, C^{3}C**H**$_3$),

1.83(3H, s, C^{5}C**H**$_3$) 1.60-1.10(12H, m, (C**H**$_2$)$_6$)

1.90(3H, m, (CH$_2$)$_6$C**H**$_3$), 1.00-0.90(3H, m, O-CH$_2$C**H**$_3$).

Both isomers

^{13}C NMR δ:166.00(**C**=O), 153.70 and153.50(**C**=CCO$_2$Et), 142.50 and 141.70(C$_7$H$_{15}$**C**=C)124.0 and 123.0(C$_7$H$_{15}$C=**C**H), 117.30 and 117.10(C=**C**CO$_2$Et), 59.50(O-**C**H$_2$), 41.0(H$_2$**C**C=C), 33.0, 32.0, 29.60, 29.30, 29.10, 28.0, 27.90, 25.50, 25.40, 24.10, 22.60 and 18.60((**C**H$_2$)$_{5,}$2x**C**H$_3$), 14.50(O-CH$_2$**C**H$_3$), 14.05((CH$_2$)$_7$**C**H$_3$)

MS(EI).: Acc.Mass. Found: 252.2084 $C_{16}H_{28}O_2$ requires:252.2089.

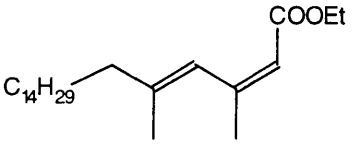
IR neat: 2920 (vs), 1728 (vs),1640 (s),1600 (s) 1445 (s),1375 (s)

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-ethyl3,5-dimethyl-eicosa-2,4-dieneoate (3.53)

General Method F with diene acid **3.39** (0.85 g, 2.5 mmol), dicyclohexylcarbodiimide (0.475 g, 2.7 mmol), dimethylaminopyridine (200mg), Ethanol (2.7 ml, 45 mmol). Crude yield 0.65 g. Purification by column chromatography (SiO_2 20:1 Hex:EtOAc) gave 0.4 g (44%) of (**3.53**) as a colourless oil as a mixture of isomers in a ratio of 3:1 of 4*E*:4*Z*.

2*Z*,4*E* Isomer

^{1}H NMR δ:6.42(1H, bs, $\mathbf{H}^4$), 5.62(1H, bs, $\mathbf{H}^2$)



4.05-4.15(2H, m, O-C$\mathbf{H}_2$)

2.10-2.05(2H, m, C$\mathbf{H}_2$C=C),

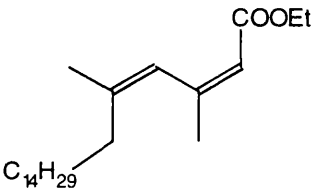
2.0(3H, s, $C^3C\mathbf{H}_3$)

1.70(6H, s, $C^5C\mathbf{H}_3$), 1.60-1.10(29H, m, $(C\mathbf{H}_2)_{13}$, O-$CH_2C\mathbf{H}_3$),

0.90(3H, t, $(CH_2)_{14}C\mathbf{H}_3$)

2*Z*, 4*Z* Isomer

^{1}H NMR δ:6.35(1H, bs, $\mathbf{H}^4$), 5.62(1H, bs, $\mathbf{H}^2$)



4.05-4.15(2H, m, O-C$\mathbf{H}_2$),

2.10-2.05(2H, m, C$\mathbf{H}_2$C=C),.

1.94(3H, s, $C^3C\mathbf{H}_3$), 1.80(6H, s, $C^5C\mathbf{H}_3$),

1.60-1.10(29H, m, $(C\mathbf{H}_2)_{13}$, O-$CH_2C\mathbf{H}_3$),

0.90(3H, t, $(CH_2)_{14}C\mathbf{H}_3$)

Both Isomers

^{13}C NMR δ:166.20(**C**=O), 153.40(**C**=CCO_2H), 142.50 and 141.20($C_{15}H_{31}$**C**=C), 124.30 and 123.40($C_{15}H_{31}C$=**C**H), 117.20 and 116.50(C=**C**CO_2H), 60.40(O-**C**H_2), 41.30(H_2**C**C=C), 33.70, 32.50, 29.90, 29.70, 29.60, 29.50, 29.50, 29.40, 29.20, 28.0, 27.80, 25.70, 25.10, 23.70, 22.70 and 18.60(($\mathbf{C}H_2)_{13}$,2x**C**H_3), 14.30 and 14.50(($CH_2)_{14}$**C**H_3 O-CH_2**C**H_3))

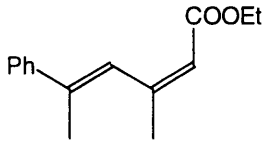
MS(EI): $(M)^+$364

Preparation of (2*Z*,4*Z*) and (2*Z*,4*E*)-ethyl 3-methyl-5-phenylhexa-2,4-dienoate (3.54)

General Method F with diene acid (**3.40**) (0.84 g, 4.2 mmol), dicyclohexylcarbodiimide(0.95 g, 4.6 mmol), dimethylaminopyridine (400mg), Ethanol (1 ml, 14 mmol). yield of crude product 1.1 g. Purification by column chromatography (SiO_2 4:1 Hex:EtOAc) gave 0.51 g (52%) of (**3.54**) as a colourless oil as a mixture of isomers in a ratio of 2:1 of 4*E*:4*Z*.

Both Isomers.

^{1}H NMR δ:7.20-7.50(5H, m, $C_6\mathbf{H}_5$),



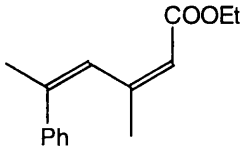
7.01 and 6.9(1H, bs, $\mathbf{H}^4$), 5.80 and 5.60(1H, bs,$\mathbf{H}^2$)

4.12-4.19(2H, m, $OC\mathbf{H}_2$),

2.20, 2.15, 2.15 and 1.55 (6H, s, $C^5C\mathbf{H}_3$ $C^3C\mathbf{H}_{3,}$),

1.24-1.31(3H, m, $OCH_2C\mathbf{H}_3$)

Both Isomers



^{13}C NMR δ:167.20 and 166.80(**C**=O),

154.10 and 154.00(**C**=CCO_2Et)

143.30 and 144.50(Ph**C**=C),

142.40 and 139.0($\mathbf{C}_6H_5$, qu), 128.20, 128.10, 127.80, 127.60, 126.40,

126.10 and 125.90($\mathbf{C}_6H_{5,}$ tr, PhC=**C**H),118.70 and 116.90(C=**C**CO_2Et),

59.60,and 59.50(O-$\mathbf{C}H_2$), 27.20, 25.40 and 24.05(3x$\mathbf{C}H_3$), 18.60($\mathbf{C}H_3$),

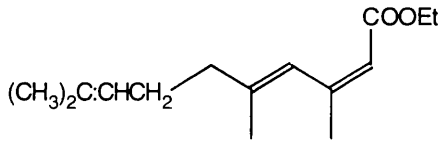
14.05(O-$CH_2\mathbf{C}H_3$)

MS(EI): $(M)^+$230(M-(CH_3))$^+$215

Preparation of (2*Z*,4*E*)-ethyl 3,5,10-trimethyldeca-2,4,8-trienoate (3.55)

General Method C with diene acid (**3.37a**) (0.31 g, 1.5mmol), DCC (0.34 g, 1.65 mmol), DMAP (0. 045 g), ethanol (I ml, 17 mmol). Purification by column chromatography (SiO_2 20:1 Hex:EtOAc).gave 0.21g (60 %) of (**3.55**) as a colourless oil.

^{1}H NMR δ 6.50(1H, bs, $\mathbf{H}^4$), 5.68(1H, bs, $\mathbf{H}^2$)



5.1(1H, m, C=**H** chain)

4.10(2H, q, J=7, O-$C\mathbf{H}_2$)

2.12(4H, bs,2x$C\mathbf{H}_2$),

2.01(3H, s, $C^3C\mathbf{H}_3$), 1.75(3H, s, $C^5C\mathbf{H}_3$), 1.65 and 1.59(6H, s, $(C\mathbf{H}_3)_2$),

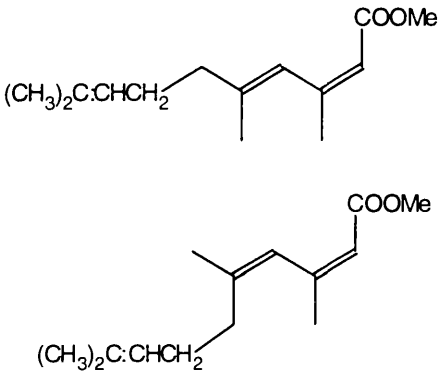
1.23(3H, t, J=3, O-$CH_2C\mathbf{H}_3$).

MS(EI): $(M)^+$ 236, $(M\text{-}CH_3)^+$ 221. (M -$(CH_3)_2C{=}CCH_2)^+$153.

IR neat: 2930 (vs), 1714 (vs),1634 (s),1600 (s) 1447 (s),1375 (s)

Preparation of (2*Z*,4*E*) and (2*Z*,4*Z*)-methyl-3,5,9-trimethyl-deca-2,4,8-trienoate (3.56)

General Method D with trimethyloxonium tetrafloroborate (0.319 g, 2.156 mmol), diene acid (**3.37b**) (0.410 g, 1.96 mmol), N-ethyldiisopropylamine (0.274 g, 2.156 mmol) in DCM (20 ml). Purification by column chromatography (SiO_2, 10:1 Hex:EtOAc) gave 0.35 g (85%) of (**3.56**) as a colourless oil. Ratio of (2*Z*,4*E*)-(2*Z*,4*Z*) 1:1



Both Isomers

^{1}H NMR δ 6.50 and 6.4(1H, bs, **H**^{4}),
5.68(1H, bs, **H**^{2}),
5.20-5.10(1H, m, C=**H** chain),
3.68(3H,s, O-C**H**$_3$),
2.2-2.05(4H, m, 2xC**H**$_2$),
2.01(3H, s, C^{3}C**H**$_3$),
1.85 and 1.75(3H, s, C^{5}C**H**$_3$)
1.70, 1.66, 1.62 and 1.59(6H, s, (C**H**$_3$)$_2$).

Both Isomers

^{13}C NMR δ:169.50(**C**=O), 154.30(**C**=CCO$_2$Me),
142.20 and 141.70((CH$_3$)$_2$C:CH(CH$_2$)$_2$**C**=CH),132.05((CH$_3$)$_2$**C**=C),
124.60((CH$_3$)$_2$C:CH(CH$_2$)$_2$C=**C**H),),124.20, 123.90 and
123.70((CH$_3$)$_2$C=**C**H), 16.70(=**C**HCO$_2$Me), 50.80(O-**C**H$_3$),
41.30 and 34.80(2x**C**H$_2$),
26.70, 25.70, 25.50 and 24.10(C^5**C**H$_3$ C^3**C**H$_3$), 18.20 and 17.30((**C**H$_3$)$_2$C=C)

MS(EI): (M)$^+$222

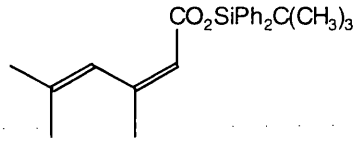
MS(FAB): Acc.Mass. Found: 223.1690 $C_{14}H_{23}O_2$ requires:223.1690..

IR neat: 2926(vs), 1717(vs),1633(s),1600(m) 1439(vs),1379(s),1050(vs)

Preparation of t-butyldiphenylsilyl 3,5-dimethylhexa-2,4-dienoate (3.57)

Under an atmosphere of nitrogen n-butyl lithium (2.5M in hexane, 1.32 ml, 3.3 mmol) was added dropwise to a stirred solution of diisopropylamine (0.463 ml, 3.3 mmol) in dry THF (8 ml) at -78 ^{0}C. The reaction mixture was stirred for 15 minutes turning bright yellow. The lactone (**2.31**) (0.421 g, 3 mmol) in dry THF (3 ml) was then added dropwise. Next the silyl chloride (0.858 ml, 3.3 mmol) in dry THF (3 ml) was added dropwise. Stirring was continued for a further 10 minutes at -78 ^{0}C then warmed to room temperature. The solution went from green to yellow. After 3 hours the reaction was quenched with sat NH_4Cl(aq) (20 ml) and extracted with hexane (3x15 ml). The organic portions were combined, dried ($MgSO_4$), and

evaporated *in vacuo* to give 1.3 g of an orange oil. Purification by column chromatography (SiO_2 Hex:EtOAc 4:1) gave 0.98 g (86%) of (**3.57**) as a colourless oil.



^{1}H NMR δ:7.80-7.30(10H, m, $C_6\mathbf{H}_5$), 6.49(1H, s, $\mathbf{H}^4$), 5.70(1H, s, $\mathbf{H}^2$), 2.07, 1.78 and 1.72(9H, s, 3x$C\mathbf{H}_3$), 1.10(9H, s, $(C\mathbf{H}_3)_3$)

^{13}CNMR δ:165.40(**C**=O), 154.30(**C**=CCO_2R), 139.60($(CH_3)_2$**C**=C), 135.30, 135.20, 132.80, 128.40 and 127.30($\mathbf{C}_6H_5$), 124.20($(CH_3)_2$C=**C**H), 118.60(C=**C**CO_2R), 27.20, 25.40 and 21.05(3x$\mathbf{C}H_3$), 19.20(**C**$(CH_3)_3$).

MS(EI) $(M)^+$378

IR neat: 3074 (s), 2933 (vs),1705 (vs),1633 (s),1591(s),1430 (s),1039 (s)

Isomerisation of the 2Z-Diene Acids

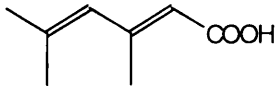
General Method H. Isomerisation catalysed by thiopenol[14d]

The diene acid (10 mmol) was dissolved in CCl_4 (20 ml) with thiophenol (1% by weight). The reaction mixture was heated at reflux for 2 hours. The solvent and thiophenol were evaporated *in vacuo* to give the crude product.

Preparation of (2*E*)-3,5-dimethylhexa-2,4-dienoic acid (3.71)

a) The diene acid (**3.35**) (0.18 g, 1.2 mmol) was dissolved in ether (10 ml) with a trace of Iodine, and stirred for 7 days. The reaction mixture was diluted with ether (20 ml), washed with $Na_2S_2O_3$ (aq) (2x20 ml), H_2O (20 ml), and brine (20 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 0.17 g (95%) of (**3.35:3.71**) 8:1 as a pale yellow solid,.

b) General Method H with diene acid (**3.35**) (0.18 g, 1.2 mmol), CCl_4 (5 ml), thiophenol (1drop). Pale yellow solid, was obtained with 100% conversion to (**3.71**) that required no purification, 0.175 g (95%)



^{1}H NMR δ:5.75 and 5.68(1H, s, $\mathbf{H}^4$, $\mathbf{H}^2$), 2.25(3H, s, $C^3C\mathbf{H}_3$), 1.82 and 1.86(6H, s, $(C\mathbf{H}_3)_2$)

^{13}C NMR δ:171.90(**C**=O), 155.35(**C**=CCO_2H), 137.80($(CH_3)_2$**C**=C), 125.15($(CH_3)_2$C=**C**H), 115.05(C=**C**CO_2H),24.20, 17.05 and 16.90(3x$\mathbf{C}H_3$).

Analysis Found: C,68.46; H, 8.74 $C_8H_{13}O_2$ requires: C,68.54; H,8.63 %

M.P ^{0}C: 72-74

IR soln CCl_4 3200-2855(br), 1687(vs), 1621(vs)

Preparation of (2*Z*,4*Z*),(2*Z*,4*E*),(2*E*,4*Z*) and (2*E*,4*E*)-3,5,7-trimethylocta-2,4-dienoic acid (3.72)

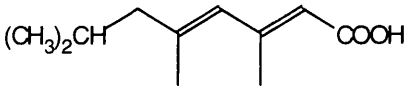
General Method H with diene acid (**3.36**) (1.8 g, 10 mmol), CCl_4 (50 ml), thiophenol (2 drops).Yield 1.7 g (100%) of (**3.72**) as a yellow oil. Ratio of isomers (2*E*:2Z) 4:1 (2*E*,4*Z*):(2*E*,4*E*) 4:1

2*Z*,4*E* and 2*Z*,4*Z* Isomers

^{1}H NMR δ:As before

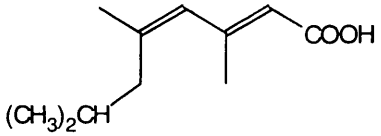
^{13}CNMR δ:As before

2*E*,4*E* Isomer



^{1}H NMR δ:5.75 and 5.7(2H, bs, **H**^{4}, **H**^{2}),
2.25(3H, d, C^{3}C**H**$_3$, J=1.2),
1.84(3H, d, C^{5}C**H**$_3$, J=1.2), 1.5-2.0(3H,obs, C**H**$_2$ C**H**),
0.90-0.80(6H, m, (C**H**$_3$)$_2$).

2*E*,4*Z* Isomer



^{1}H NMR δ:5.80 and 5.70(2H, bs, **H**^{4}, **H**^{2}),
2.20,(3H, d, C^{3}C**H**$_3$, J=1.2),
1.78(3H, d, C^{5}C**H**$_3$,J=1.2),
1.50-2.0(3H,obs, C**H**$_2$ C**H**).0.90-0.80(6H, m, (C**H**$_3$)$_2$).

All Isomers

^{13}C NMR δ:172.60 and 171.30(**C**=O), 157.30, 157.10 and 156.20(**C**=CCO$_2$H),
142.30, 141.80, 141.40 and 141.0((CH$_3$)$_2$CHCH$_2$**C**=CH),
129.60, 129.70, 124.90 and 124.70((CH$_3$)$_2$CHCH$_2$C=**C**H), 117.20 and
116.80(=**C**HCO$_2$H), 42.05, 29.20, 26.40, 26.30, 26.05, 25.60, 24.50,
22.30, 21.40, 20.90, 19.90, 18.50 and 14.1((**C**H$_3$)$_2$**C**H**C**H$_2$, C^5**C**H$_3$ C^3**C**H$_3$)

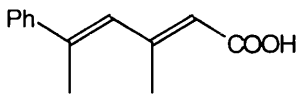
IR neat: 2955(vs), 1682(vs), 1619(vs), 1440(vs), 1257(vs).

MS(EI): $(M)^+$ 182, $(M\text{-}CH_3)^+$ 167 $(M\text{-}(CH_3)_2CHCH_2)^+$ 125.
Acc.Mass. Found: 182.1300 $C_{11}H_{18}O_2$ requires:182.1307

Preparation of (2*E*,4*Z*) and (2*E*,4*E*)-3-methyl-5-phenylhexa-2,4-dienoic acid (3.73)

General Method H with diene acid (**3.40**) (2.5 g, 12.4 mmol) CCl_4 (50 ml) thiophenol (2 drops). Crude yield of 2.5 g (100%) as 4:1 ratio of 4*E*:4*Z*. Purification by recrystalisation from hexane with 1% EtOAc to give 1.6 g of (**3.73**) as white needle like crystals.

Both Isomers.

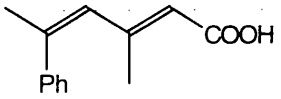


^{1}H NMR δ:7.20-7.46(5H, m, $C_6\mathbf{H}_5$),

6.30 and 6.15(1H, bs, $\mathbf{H}^4$)

5.87 and 5.60(1H, bs,$\mathbf{H}^2$), 2.37, 2.28, 2.17 and 2.15 (6H, s, $C^5\mathbf{H}_3$, $C^3\mathbf{H}_3$)

Both Isomers



^{13}C NMR δ:172.0(**C**=O), 156.20 and 157.35(**C**=CCO_2H)

143.0, 140.02(Ph**C**=C), 130.35($\mathbf{C}_6H_5$, qu)

128.30, 128.25, 127.78, 126.05($\mathbf{C}_6H_5$, tr, PhC=**C**H),

117.25(C=**C**CO_2H), 20.05, 18.30 and 17.50(2x$\mathbf{C}H_3$).

Analysis Found: C,77.40; H, 6.84. $C_{13}H_{14}O_2$ requires: C,77.20; H,6.97 %

IR soln CCl_4: 3100-2800(br), 1688(vs), 1620(s), 1607(s)

M.P ^{0}C: 81-83

Preparation of (2*Z*,4*E*),(2*Z*,4*Z*),(2*E*,4*Z*) and (2*E*,4*E*)-3,5-dimethyltrideca-2,4-dienoic acid (3.74)

General Method H with diene acid (**3.47**) 5 g, 20 mmol) CCl_4 (70 ml), thiophenol (5 drops).

Yield 5.0 g (100%) of (**3.74**) as a yellow oil. Ratio of (2E:2Z) 8:1 (2*E*,4*E*):(2*E*,4*Z*) 3:1

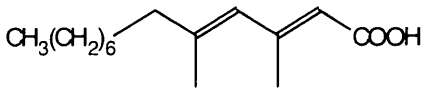
2*Z*,4*E* 2*Z*,4*Z*

^{1}H NMR δ:As before

^{13}CNMR δ:As before

2*E*,4*E*

^{1}H NMR δ:5.70 and 5.65(2H, s, $\mathbf{H}^4$, $\mathbf{H}^2$)



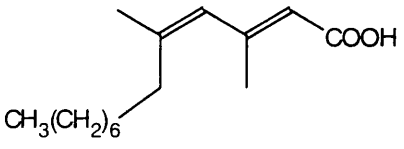
2.05-2.01(2H, m, $C\mathbf{H}_2$C=C),

2.21(3H, s, $C^3\mathbf{H}_3$),

1.80(3H, s, $C^5\mathbf{H}_3$), 1.50-1.10(12H, m, $(C\mathbf{H}_2)_7$), 0.85(3H, m, $(CH_2)_7\mathbf{C}H_3$).

2*E*,4*Z*

^{1}H NMR δ:5.70 and 5.63(1H, s, $\mathbf{H}^4$, $\mathbf{H}^2$)



2.05-2.01(2H, m, $C\mathbf{H}_2$C=C),

2.19(3H, s, $C^3\mathbf{H}_3$), 1.77(3H, s, $C^5\mathbf{H}_3$)

1.50-1.10(12H, m, $(C\mathbf{H}_2)_7$),

0.85(3H, m, $(CH_2)_7\mathbf{C}H_3$)

All Isomers

^{13}C NMR δ:172.20(**C**=O), 157.30(**C**=CCO_2H), 144.40 and 144.05($CH_2)_7$**C**=C) 129.30, 128.35 and 123.25(($CH_2)_7$C=**C**) 116.60 and 116.20(C=**C**CO_2H), 44.0, 41.15, 40.80, 33.55, 32.25., 31.80, 29.80, 29.60, 29.45, 29.30, 29.25, 29.15, 28.20, 27.85, 25.70, 24.55, 23.85, 22.60, 19.95, 19.80, 18.50 and14.05(**C**H_3 (**C**$H_2)_7$(**C**$H_3)_2$).

MS(EI): $(M)^+$238 $(M-CH_3)^+$223 $(M-CH_3(CH_2)_7)^+$125

Preparation of (2*Z*,4*E*),(2*Z*,4*Z*),(2*E*,4*Z*) and (2*E*,4*E*)-8-chloro-3,5-dimethylocta-2,4-dienoic acid (3.75)

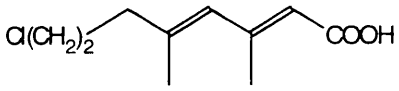
General Method H with diene acid (**3.48**) (3.6 g, 18 mmol) CCl_4 (70 ml), thiophenol (5 drops). Yield 3.6 g (100%) of (**3.75**) as a yellow oil. Ratio of isomers (2*E*):(2*Z*) 4:1 (2*E*,4*E*):(2*E*,4*Z*) 3:1

2*Z*,4*E* 2*Z*,4*Z*

^{1}H NMR δ:As before

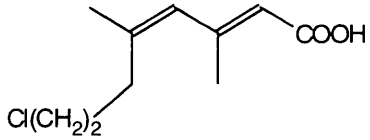
^{13}CNMR δ:As before

2*E*,4*E*



^{1}H NMR δ5.79 and 5.63(2H, s, **H**^{4} **H**^{2})
3.53-3.48(2H, m, ClC**H**$_2$),
2.25-2.15(2H, obs m, C**H**$_2$C=C),), 2.22(3H, s, C^{3}C**H**$_3$),
1.92-1.86(2H, m, C**H**$_2$), 1.83(3H, s, C^{5}C**H**$_3$)

2*E*,4*Z*



^{1}H NMR δ:5.79 and 5.62(1H, s, **H**^{4} **H**^{2}),
3.53-3.48(2H, m, ClC**H**$_2$)
2.38-2.32(2H, m, C**H**$_2$C=C),)
2.21(3H, s, C^{3}C**H**$_3$). 1.88-1.84(2H, m, C**H**$_2$), 1.79(3H, s, C^{5}C**H**$_3$)

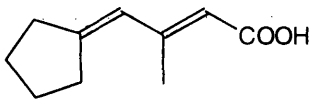
All Isomers

^{13}C NMR δ:172.10(**C**=O), 157.20(**C**=CCO_2H), 141.20 and 140.50(Cl($CH_2)_3$**C**=C) 130.15, 129.0 and 124.70(Cl($CH_2)_3$C=**C**H), 117.25, 117.18 and 116.80(C=**C**CO_2H), 44.50, 44.35, 37.87, 37.30, 31.18, 30.60, 30.51, 27.70, 25.65, 24.14, 19.90 and 18.54((**C**$H_2)_3$ (**C**$H_3)_2$).

MS(EI): (1:3 M+2:M)$^+$ 205 and 203 (M-Cl $(CH_2)_3)^+$125

Preparation of (2*E*)-cyclopentane-2,4-dienoic acid derivative (3.76)

General Method H with diene acid (**3.49**) (0.6 g, 8.5 mmol) CCl_4 (10 ml), thiophenol (1 drop). Yield 0.6 g (100%) . Ratio of isomers (2*E*):(2*Z*)10:1. Recrystalisation from Hexane gave pure E isomer 0.31 g 52% recovery of (**3.76**) as white needle like crystals.



^{1}H NMR δ:5.97(1H, s, $\mathbf{H}^4$), 5.70(1H, s, $\mathbf{H}^2$)
2.55-1.59(8H, m, 4x$C\mathbf{H}_2$), 2.34(3H, s, $C\mathbf{H}_3$)

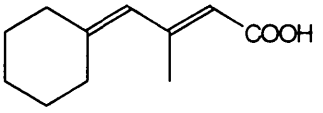
^{13}C NMR δ:172.0(**C**=O), 157.0(**C**=CCO_2H),
154.50((CH_2)$_4$**C**=C), 124((CH_2)$_4$C=**C**),118.05(C=**C**CO_2H),),
37.40, 32.20, 27.80 and 25.40(4C,(**C**H_2)$_4$), 20(**C**H_3).

MS(EI): $(M)^+$166 $(M\text{-}COOH)^+$121

Acc.Mass. Found: 166.0994 $C_{10}H_{14}O_2$ requires:166.0985

Preparation of (2*E*)-cyclohexane-2,4-dienoic acid derivative (3.77)

General Method H with diene acid (**3.50**) (1.5 g, 8.5 mmol) CCl_4 (70 ml), thiophenol (2 drops). Yield of crude product 1.5 g (100%). Ratio of isomers (2*E*):(2*Z*) 20:1. Recrystalisation from Hexane gave pure E isomer of (**3.77**) as white crystals.



^{1}H NMR δ:5.67 and 5.64(2H, s, $\mathbf{H}^4$ $\mathbf{H}^2$),
2.34-2.31(2H, m, $C\mathbf{H}_2$), 2.20(3H, s, $C\mathbf{H}_3$),
2.15-2.12(2H, m, $C\mathbf{H}_2$),
1.57-1.54(6H, m, 3x$C\mathbf{H}_2$)

^{13}C NMR δ:172.60(**C**=O), 157.50(**C**=CCO_2H), 147.30((CH_2)$_5$**C**=C), 125.0((CH_2)$_5$C=**C**H)
117.55(C=**C**CO_2H),), 38.05, 30.20, 28.65, 28.25 and 26.20((**C**H_2)$_5$),
20.0(**C**H_3)

MS(EI): $(M)^+$180 $(M\text{-}COOH)^+$135

Analysis Found: C,73.16; H, 8.76. $C_{11}H_{16}O_2$ requires: C,73.30; H,8.90 %

IR soln CCl_4: 3200-2865(br), 1687(vs), 1620(s)

Preparation of (2*E*),(2*Z*)-cyclododecane-2,4-dienoic acid derivative (3.78)

General Method H with diene acid (**3.51**) (1.0 g, 3.8 mmol) CCl_4 (30 ml), thiophenol (2 drops). Yield 1.0 g (100%). Ratio of isomers (2*E*):(2*Z*) 2:1. Recrystalisation from Hexane and 2% EtOAc gave (**3.78**) as a white solid in a ratio of isomers (2*E*):(2*Z*) 10:1.

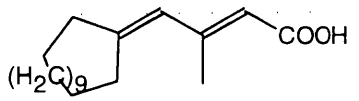
2*Z*

^{1}H NMR δ:As before

^{13}C NMR δ:As before

2*E*

^{1}H NMR δ:5.80, 5.70(2H, s, **H**^{4} **H**^{2}),



2.24-2.10(2H, m, C**H**$_2$), 2.22(3H, s, C**H**$_3$),

2.11-2.03(2H, m, C**H**$_2$),

1.56-1.32(18H, m, 9xC**H**$_2$)

^{13}C NMR δ:172.10(**C**=O), 158.15(**C**=CCO$_2$H), 146.05((CH$_2$)$_{11}$**C**=C),

129.25((CH$_2$)$_{11}$C=**C**H), 116.05(C=**C**CO$_2$H), 32.60, 28.80, 25.15, 24.64, 24.40,

24.35, 24.25, 24.15, 23.05 and 22.30((**C**H$_2$)$_{11}$), 20(**C**H$_3$).

MS(EI): $(M)^{+}$264 $(M\text{-}COOH)^{+}$219

Analysis Found: C,76.80; H, 10.57 $C_{17}H_{28}O_2$ requires: C,77.22; H,10.67 %

M.P ^{0}C: 123-125

IR soln CCl_4: 3200-2865(br), 1688(vs), 1620(s)

Synthesis of the Target 1,2-Dioxolane Esters and Acids

Peroxymercuriation of the 2Z-Diene acids and esters

General Method I. Preparation of the 1,2-dioxolane from the 2Z-diene acid substrate

The diene acid (10mmol) in DCM or THF was added to a stirred suspension of $Hg(OAc)_2$ (20 mmol) in 30% H_2O_2 (90 mmol). The reaction mixture was stirred at room temperature and went from orange to colourless. The DCM layer was separated and the reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, dried ($MgSO_4$), and evaporated *in vacuo* to give a white solid.

The mercuriated dioxolane (10 mmol) in DCM (30 ml) was cooled in an ice bath and 2M NaOH(aq) (10 ml) added. Immediately this mixture was added to a well stirred solution of $NaBH_4$ (40 mmol) in 2M NaOH(aq) (30 ml) cooled to 5 ^{0}C. Stirring, at 5 ^{0}C, was continued for 15 minutes and then for a further 15 minutes at room temperature. The aqueous phase was separated and acidified with 1M HCl (aq) dropwise at 5 ^{0}C, then extracted with DCM. The organic extracts were combined dried, ($MgSO_4$) and evaporated *in vacuo*

Attempted preparation of 3-carboxymethyl-3,5,5-trimethyl-1,2-dioxolane (2.44)

General method I with diene acid (**3.35**) (0.15 g, 1.08 mmol), in DCM (2 ml), $Hg(OAc)_2$ (0.683 g, 2.14 mmol), 30% H_2O_2 (1 ml, 10 mmol) stirred for 24 hours. Crude mercuriated dioxolane (0.38 g) in DCM (10 ml) and 2M NaOH(aq) (3ml). $NaBH_4$ (0.08 g, 5.1 mmol) in 2M NaOH(aq) (5 ml). Yield of crude product 0.08 g from the organic phase. The aqueous phase was acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM No peroxide positive components were detected by tlc. ^{1}H NMR of the crude product indicated a mixture of the lactones (**2.30**) and (**2.31**) as a colourless oil.

^{1}H NMR δ: As before

^{13}C NMR δ: As before

General Method J. Preparation of the 1,2-dioxolane with the diene ester substrate

The diene ester (10mmol) in DCM (5 ml) was added to a stirred suspension of $Hg(OAc)_2$ (20 mmol) in 30% H_2O_2 (90 mmol). The reaction mixture was stirred at room temperature and went from orange to colourless. The DCM layer was separated and the reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, dried ($MgSO_4$), and evaporated *in vacuo* to give a white solid.

The mercuriated dioxolane (10 mmol) in DCM (30 ml) was cooled in an ice bath. 2M NaOH(aq) (10 ml) was added then immediately added to a well stirred solution of $NaBH_4$ (40 mmol) in 2M NaOH(aq) (30 ml) cooled to 5 ^{0}C. Stirring, at 5 ^{0}C, was continued for 15 minutes and then for a further 15 minutes at room temperature.The organic phase was separated and the basic aqueous layer was extracted further with DCM (3x30 ml). The organic portions were combined, dried ($MgSO_4$), and evaporated *in vacuo*.

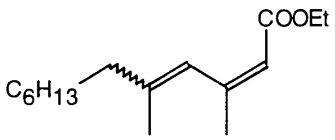
Preparation of 3-ethoxycarbonylmethyl-3,5-dimethyl-5-heptyl-1,2-dioxolane (3.58)

General Method J with diene ester (**3.52**) (0.25 g, 1 mmol), $Hg(OAc)_2$ (0.638 g, 2 mmol) 30% H_2O_2 (0.5 ml, 5 mmol). Reaction stopped after 6 hours. Yield of crude product of mercuriated dioxolane 0.55 g (75%). Purification by column chromatography (SiO_2) gave two non-mercuriated components.

Fraction 1 eluant DCM gave 0.034 g of a colourless oil.(**3.52**)

2Z,4E/Z

^{1}H NMR δ:6.50 and 6.39 (1H, s, **H**^{4}), 5.65(1H, s, **H**^{2})



4.12(2H, m, O-C**H**$_2$),

2.15-2.05(2H, m, C**H**$_2$C=C),

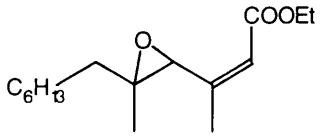
2.03 (3H, s, C^{3}C**H**$_3$)

1.73 and 1.83 (3H, s, C^{5}C**H**$_3$),

1.60-1.10(13H, m, O-CH$_2$C**H**$_3$(C**H**$_2$)$_5$), 0.90(3H, m, (CH$_2$)$_6$C**H**$_3$).

Fraction 2 eluant DCM gave 0.02g of a colourless oil with the main component (**3.61**) shown below

^{1}H NMR δ:5.80(1H, bs C=C**H**), 3.25 (1H, bs,**H**CO)



2.16 and 2.14(3H, s, C**H**$_3$) 1.37(3H, s, C**H**$_3$),

1.35-1.20(13H, m, O-CH$_2$C**H**$_3$, (C**H**$_2$)$_5$),

0.90(3H, m, (CH$_2$)$_6$C**H**$_3$).

^{13}C NMR δ:166.00(**C**=O), 152.50 and 153.60(**C**=CH), 116.65 and 115.05(C=**C**H),

66.75 and 67.60(CO**C,** tr), 64.80 and 64.50(**C**OC, qu), 60.35(O-**C**H$_2$),

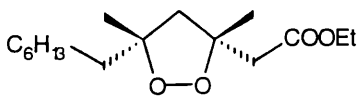
39.05, 32.65, 31.58, 30.55, 29.50, 29.55, 24.85, 21.80, 16.50, 15.40, 14.50

and 14.05((**C**H$_3$)$_2$, (**C**H$_2$)$_7$, O-CH$_2$**C**H$_3$)

Fraction 3 eluant MeOH gave 0.50 g of a white solid which gave a positive test for mercury. Hydridodemercuriation General Method G. Crude mercuriated dioxolane (0.5 g, 0.62 mmol) in DCM (10 ml) and 2M NaOH(aq) (4 ml). $NaBH_4$ (0.124 g, 2.7 mmol) in 2M NaOH(aq) (7 ml). 0.24 g, 85 % yield, of a colourless oil contaminated with mercury. Purification by column chromatography (SiO_2 Hex:EtOAc 20:1) gave two major fractions.

Fraction 1 gave 0.065 g (23%) of the 1,2-dioxolane (**3.58**) as a colourless oil. Ratio of isomers *cis*:*trans* 2:1.

^{1}H NMR δ:4.11(2H, q,J=7 O-C**H**$_2$)



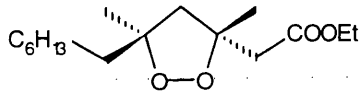
2.73 and 2.58 (2H, AB, J=14.4, C**H**$_2$CO$_2$Et)

2.54 and 2.09(2H, AB, J=12.4, C**H**$_2$ring)

1.62-1.50(2H, m, C**H**$_2$), 1.55 and 1.43(6H, s, 2xC**H**$_3$)

1.3-1.2(13H, m, (C**H**$_2$)$_5$ O-CH$_2$C**H**$_3$), 0.86(3H, m, C**H**$_3$)

^{13}C NMR δ:171.05(**C**=O), 86.70 and 83.85(**C**-O-O-**C**), 60.50(O-**C**H_2), 55.15(**C**H_2ring)
44.30(**C**H_2CO_2Et), 38.83(**C**H_2C-O-O), 31.80, 30.50, 29.10, 24.85, 24.60,
24.50, 22.85, 14.20 and 14.10(2x**C**H_3 ,(C**H**$_2)_5$C**H**$_3$,O-CH_2**C**H_3)



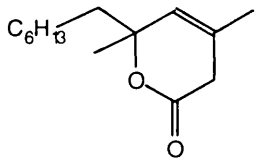
^{1}H NMR δ:4.13(2H, q, J=7 O-C**H**$_2$)
2.74 and 2.60(2H, AB, J=14.4, C**H**$_2CO_2$Et)
2.45 and 2.20(2H, AB, J=12.4, C**H**$_2$ring)
1.72-1.6(2H, m, C**H**$_2$), 1.54 and 1.41(6H, s, 2xC**H**$_3$)
1.3-1.2(13H, m, (C**H**$_2)_5$ O-CH_2C**H**$_3$), 0.86(3H, m, C**H**$_3$)

^{13}C NMR δ:171.0(**C**=O), 86.55 and 84.0(**C**-O-O-**C**), 60.60(O-**C**H_2), 55.35(**C**H_2ring)
44.20(**C**H_2CO_2Et), 39.70(**C**H_2C-O-O), 31.80, 30.50, 29.20, 24.65, 24.25,
23.40, 22.0, 14.25 and 14.10(2x**C**H_3 ,(C**H**$_2)_5$C**H**$_3$ O-CH_2**C**H_3)

MS(FAB) Acc. Mass Found:287.2230. $C_{16}H_{31}O_4Na$ requires: 287.2222

IR neat: 2981(vs),2800(m),1741(vs)1450(m),1400(s),1200(s),1000(m).

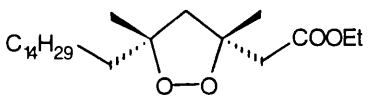
Fraction 2 gave 0.08 g (35%) of a colourless oil identified as the lactone (**3.63**).



^{1}H NMR d:5.41(1H, bs, C=C**H**), 2.9(2H, s, C**H**$_2$),
1.73(3H, s, C=CC**H**$_3$), 1.7-1.5(2H, m, C**H**$_2$),
1.37(3H, s, C**H**$_3$), 1.3-1.15(12H, m, (C**H**$_2)_6$)

Preparation of 3-ethoxycarbonylmethyl-3,5-dimethyl-5-pentadecanyl-1,2-dioxolane (3.59)

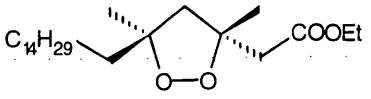
General Method J with diene ester (**3.53**) (0.4 g, 1.2 mmol) $Hg(OAc)_2$ (0.90 g, 2.4 mmol) 30% H_2O_2 (2 ml, 20 mmol) stirred for 3 hours. Crude mercuriated dioxolane (0.80 g) in DCM (10 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.147 g, 4.08 mmol) in 2M NaOH(aq) (10 ml). Crude yield of 0.35 g. (73%). Purification by column chromatography (SiO_2, DCM) gave 0.85 g (21%) of (**3.59**) as a colourless oil. Ratio of cis:trans 2:1



^{1}H NMR δ:4.13(2H, q,J=7 O-C**H**$_2$)
2.74 and 2.59(2H, AB, J=14.4, C**H**$_2CO_2$Et)
2.53 and 2.09(2H, AB, J=12.4, C**H**$_2$ring)
1.6-1.5(2H, m, C**H**$_2$), 1.55 and 1.43(6H, s, 2xC**H**$_3$)
1.3-1.2(29H, m, (C**H**$_2)_{13}$O-CH_2C**H**$_3$), 0.86(3H, m, C**H**$_3$)

^{13}C NMR δ:171.05(**C**=O), 86.70 and 83.85(**C**-O-O-**C**), 60.50(O-**C**H_2), 55.15(**C**H_2ring) 44.30(**C**H_2CO_2Et), 38.85(**C**H_2C-O-O), 31.90, 30.25, 29.70, 29.65, 29.60, 29.55, 29.35, 24.80, 24.60, 24.15, 22.35, 14.20 and 14.10(2x**C**H_3 ,(**C**H_2)$_{12}$**C**H_3,O-CH_2**C**H_3)

^{1}H NMR δ:4.12 (2H, q, J=7 O-C**H**$_2$)



2.75 and 2.60(2H, AB, J=14.4, C**H**$_2CO_2Et$)

2.45 and 2.20(2H, AB, J=12.4, C**H**$_2$ring)

1.72-1.50(2H, m, C**H**$_2$), 1.55 and 1.41(6H, 2xs, 2xC**H**$_3$)

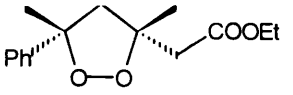
1.3-1.2(13H, m, (C**H**$_2$)$_{13}$ O-CH_2C**H**$_3$), 0.86(3H, m, C**H**$_3$)

MS(FAB): Acc. Mass Found:399.3480. $C_{24}H_{47}O_4$ (M+H) requires: 399.3474

Preparation of 3- ethoxy carbonylmethyl-3,5-dimethyl-5-phenyl-1,2-dioxolane (3.60)

As for General Method J with diene ester (**3.54**) (0.30 g, 1.3 mmol), $Hg(OAc)_2$ (0.832 g, 2.6 mmol), 30% H_2O_2 (1.5ml, 12 mmol) stirred for 5 hours. Crude mercuriated dioxolane (0.65 g) in DCM (5 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.10 g, 3 mmol) in 2M NaOH(aq) (7 ml). Purification by column chromatography (SiO_2, DCM) gave 0.06 g (8%) of a colourless oil contaminated with acetophenone. Purification by HPLC gave the (**3.60**) as a colourless oil ratio of cis:trans 1.1.

^{1}H NMR δ:4.20(2H, q, J=9, O-C**H**$_2$)

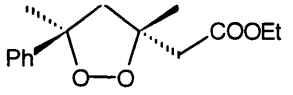


3.10 and 2.58(2H, AB, J=11, C**H**$_2$ring),

2.52(2H, bs, C**H**$_2CO_2Et$), 1.63 and 1.52(6H, 2xs, 2xC**H**$_3$)

1.25(3H, t, J=7, O-CH_2C**H**$_3$)

^{1}H NMR δ: 4.02(2H, q, J=9, O-C**H**$_2$)



2.92 and 2.82(2H, AB, J=11.7, C**H**$_2$ring)

2.88 and 2.78(2H, AB, J=14,C**H**$_2CO_2Et$)

1.60 and 1.24(6H, 2xs, 2xC**H**$_3$), 1.18(3H, t, J=7, O-CH_2C**H**$_3$)

Attempted preparation of 3-ethoxycarbonylmethyl-3,5-dimethyl-5-(4-methylpent-3-en-1-yl)-1,2-dioxolane

General Method J with diene ester (**3.55**) (0.12 g, 0.6 mmol), $Hg(OAc)_2$ (0.225 g, 2.4 mmol), 30% H_2O_2 (1 ml, 10 mmol) stirred for 3 hours. Crude mercuriated dioxolane (0.40 g) in DCM (10 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.50 g, 1.3 mmol) in 2M NaOH(aq) (6 ml). Yield of

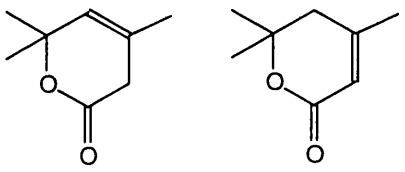
crude product of 0.90 g. 100%. Purification by column chromatography (SiO_2, DCM:MeOH 10:0.5) proved unsuccessful and no identifiable products found.

Attempted preparation of 3-methoxycarbonylmethyl-3,5-dimethyl-5-(5-methylpent-3-en-1-yl)-1,2-dioxolane

General Method J with diene ester (**3.56**) (0.10 g, 0.45 mmol) $Hg(OAc)_2$ (0.288 g, 0.9 mmol) 30% H_2O_2 (1 ml, 10 mmol) stirred for 2 days. Crude mercuriated dioxolane (0.35 g) in DCM (10 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.57 g, 1.3 mmol) in 2M NaOH(aq) (6 ml). Crude yield of 0.70 g. (65%). Purification by column chromatography (SiO_2, Hex:EtOAc 5:1) proved unsuccesful, no identifiable products found.

Attempted preparation of 3-t-butyldiphenylsilyloxycarbonylmethyl-3,5,5-trimethyl-1,2-dioxolane

General Method J with diene ester (**3.57**) (0.5 g, 1.32 mmol), $Hg(OAc)_2$ (0.842 g, 2.64 mmol), 30% H_2O_2 (2 ml, 20 mmol) stirred for 3 hours. Crude mercuriated dioxolane (0.88 g) in DCM (10 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.2 g, 5.3 mmol) in 2M NaOH(aq) (10 ml). Yield of crude product 0.45 g. No peroxide positive components were detected by tlc. ^{1}H NMR of the crude product indicated amixture of the lactones (**2.30**) and (**2.31**) and the silyating group.



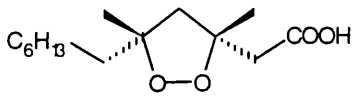
^{1}H NMR δ:As before

^{1}H NMR δ:As before

MS(NH_3Cl): $(M+H)^+$141, $(M+NH_4)^+$158.

Preparation of 3-carboxymethyl-3,5-dimethyl-5-heptyl-1,2-dioxolane (3.69)

The dioxolane ester (**3.58**) (0.055 g, 0.19 mmol) was stirred in MeOH:H_2O 3:1 (5 ml) with LiOH (40 mg, 0.96 mmol) for 24 hours. The solvent was evaporated in vaccuo and the residue dissolved in water (5 ml). The aqueous solution was washed with DCM (2x 5 ml), acidified with 1M HCl at 5^{0}C and extracted with DCM (3x 5 ml). The organic portions were combined evaporated *in vacuo* to give 0.04 g (80%) of (**3.69**) as a colourless oil. Ratio of Isomers *cis*:*trans* 2:1.



^{1}H NMR δ:2.77 and 2.69(2H, AB, J=15, C**H**$_2$CO$_2$H)

2.50 and 2.12(2H, AB, J=12.4, C**H**$_2$ring)

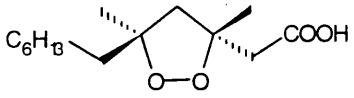
1.60-1.5(2H, m, C**H**$_2$),

1.47 and 1.32(6H, s, 2xC**H**$_3$), 1.3-1.2(10H, m, (C**H**$_2$)$_5$),

0.86(3H, m, $(CH_2)_5CH_3$)

^{13}C NMR δ:175.20(**C**=O), 86.85 and 83.65(**C**-O-O-**C**), 55.40(**C**H_2ring)
44.25(**C**H_2CO_2H), 38.75(**C**H_2C-O-O), 31.70, 29.95, 29.10, 24.85, 24.75,
23.65, 22.60 and 14.08(2x**C**H_3 ,$(CH_2)_5$**C**H_3,)

^{1}H NMR δ:2.80 and 2.72(2H, AB, J=15, C**H**$_2CO_2H$)



2.41 and 2.22(2H, ABq, J=12.4, C**H**$_2$ring)
1.72-1.65(2H, m, C**H**$_2$)
1.44 and 1.32(6H, s, 2xC**H**$_3$),1.3-1.2(10H, m, $(CH_2)_5$),
0.86(3H, m, $(CH_2)_5CH_3$)

^{13}C NMR δ:175.25(**C**=O), 86.75 and 83.70(**C**-O-O-**C**), 55.60(**C**H_2ring)
44.85(**C**H_2CO_2H), 39.70(**C**H_2C-O-O), 31.70, 29.90, 29.25, 24.80, 24.70,
23.85, 23.15 and 14.10(2x**C**H_3 ,$(CH_2)_5$**C**H_3)

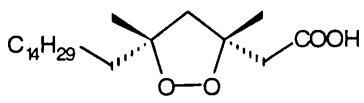
MS(FAB): Acc. Mass Found:281.1724. $C_{14}H_{26}O_4Na$ requires: 281.1729

IR neat: 3600-2980(b,vs),2800(m),1723(vs)1450(m),1400-1000(b,m).

Preparation of 3-carboxymethyl-3,5-dimethyl-5-pentadecanyl-1,2-dioxolane (3.70)

The dioxolane ester **3.59** (0.90 g, 0.23 mmol) was stirred in MeOH:H_2O 3:1 (5 ml) with LiOH (45 mg, 11 mmol) for 3 days. The reaction mixture was diluted with water and cooled in an ice bath. The aqueous solution was acidified with 1M HCl at 5 ^{0}C and extracted with DCM (3x 5 ml). The organic portions were combined evaporated *in vacuo* to give 0.065 g, 71% crude yield, of a colourless oil. Ratio of Isomers 2:1. Purification by column chromatography (SiO_2 DCM:MeOH 5:1)gave 0.02 g (55%) of (**3.70**) as a white solid.

^{1}H NMR δ:2.78 and 2.71(2H, AB, J=16, C**H**$_2CO_2H$)



2.51 and 2.07(2H, AB, J=12.4, C**H**$_2$ring)
1.6-1.5(2H, m, C**H**$_2$),
1.50 and 1.42(6H, 2xs, 2xC**H**$_3$) ,1.3-1.2(26H, m, $(CH_2)_{13}$), 0.86(3H, m, C**H**$_3$)

^{13}C NMR δ:171.0(**C**=O), 87.05 and 83.50(**C**-O-O-**C**), 55.60(**C**H_2ring)
43.70(**C**H_2CO_2H), 38.75(**C**H_2C-O-O), 31.90, 30.70, 29.70, 29.55, 29.55,
29.40, 24.90, 24.80, 23.60, 22.70
and 14.10(16C, 2x**C**H_3 ,$(CH_2)_{12}$**C**H_3,O-CH_2**C**H_3)

MS(EI): Acc. Mass Found:159.0657. $C_7H_{11}O_4$ requires: 159.0658 no molecular ion seen

MS(ESP): (M^+-H) 369

IR 3600-2980(b,vs),2800(m),1719(vs)1450(s),1400-1000(b,m).

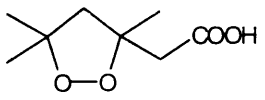
Peroxymercuriation of the 2E Diene Acids

Preparation of 3-carboxymethyl-3,5,5-trimethyl-1,2-dioxolane (2.44)

General Method I with diene acid (**3.71**) (0.3 g, 2.15 mmol), DCM (2.5 ml), $Hg(OAc)_2$ (1.36 g, 4.3 mmol), 30% H_2O_2 (2.5 ml, 22.5 mmol) stirred for 24 hours. Crude mercuriated dioxolane in DCM (15 ml) and 2M NaOH(aq) (3ml). $NaBH_4$ (0.325 g, 8.6 mmol) in 2M NaOH(aq) (10 ml). The aqueous phase was separated and acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.130 g (30 %) of (**2.44**) as a white solid. Purification by sequential base extraction gave 0.095 g (25%) of (**2.44**) as a white solid.

^{1}H NMR δ:As before

^{13}C NMR δ:As before

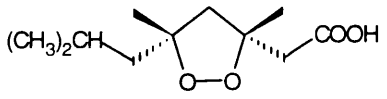


Preparation of 3-carboxymethyl-3,5-dimethyl-5-(2-methylpropyl)-1,2-dioxolane (3.79)

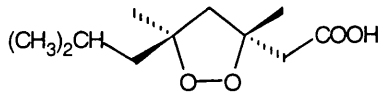
General Method I with diene acid (**3.72**) (0.5 g, 2.75 mmol), THF (3 ml), $Hg(OAc)_2$ (1.75 g, 5.5 mmol), 30% H_2O_2 (3 ml, 28 mmol) stirred for 2 days. Crude mercuriated dioxolane (2.0 g) in DCM (20 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.41 g, 11 mmol) in 2M NaOH(aq) (20 ml). The aqueous layer was separated and washed with DCM (3x 10 ml), acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.14 g (23%) of (**3.79**) as a colourless oil. The product was a mixture of *cis*:*trans* isomers in the ratio of 3.5:1.

^{1}H NMR δ:2.77 and 2.64(2H, AB, J=14, C**H**$_2$CO$_2$H)
2.51 and 2.14(2H, AB, J=12.6, C**H**$_2$ring)
1.84-1.60(2H, m, C**H**$_2$),
1.57-1.40(1H, m, C**H**), 1.44 and 1.32(6H, s, 2xC**H**$_3$), 0.89(6H, m, 2xC**H**$_3$)

^{13}C NMR δ:177.10(**C**=O), 87.0 and 83.40(**C**-O-O-**C**), 56.85(**C**H$_2$ring)
47.20(**C**H$_2$CO$_2$H), 44.30(**C**H$_2$C-O-O), 24.75, 24.55, 23.75
and 23.60(2x**C**H$_3$,(**C**H$_3$)$_2$**C**H)



^{1}H NMR δ:2.76 and 2.67(2H, AB, J=14, C**H**$_2$CO$_2$H)



2.46 and 2.20(2H, AB, J=12.6, C**H**$_2$ring)

1.72-1.65(2H, m, C**H**$_2$)

1.44 and 1.32(6H, s, 2xC**H**$_3$), 1.3-1.2(10H, m, (C**H**$_2$)$_5$),

0.86(3H, m, (CH$_2$)$_5$C**H**$_3$)

^{13}C NMR δ:177.05(**C**=O), 86.75 and 83.40(**C**-O-O-**C**), 56.95(**C**H$_2$ring)

47.90(**C**H$_2$CO$_2$H), 43.80(**C**H$_2$C-O-O) 24.70, 24.25, 24.05, 23.70 and

23.40(2x**C**H$_3$,(**C**H$_3$)$_2$**C**H)

MS(FAB): Acc. Mass Found:216.1366. $C_{11}H_{20}O_4Na$ requires: 216.1362

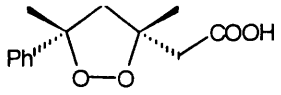
IR 3220-2882(b,vs),1712(vs)1460(m),1379, 1307,1235(m).

Analysis Found: C,61.09; H, 9.32. $C_{11}H_{20}O_4$ requires: C,61.45; H,9.59 %.

Preparation of 3-carboxymethyl-3,5-dimethyl-5-phenyl-1,2-dioxolane (3.80)

General Method G with diene acid (**3.73**) (0.832 g, 4.12 mmol), THF(3 ml), Hg(OAc)$_2$ (2.6 g, 8.2 mmol), 30% H_2O_2 (5ml, 45 mmol) stirred for 2 days. Crude mercuriated dioxolane in DCM (15 ml) and 2M NaOH(aq) (10ml). $NaBH_4$ (0.62 g, 16 mmol) in 2M NaOH(aq) (40 ml). The aqueous layer was separated and washed with DCM (3x 10 ml), acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.05 g (5%) of (**3.80**) as a white solid in a ratio of 4:1 cis:trans

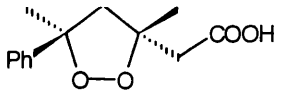
^{1}H NMR δ:3.06 and 2.60(2H, AB, J=12.4, C**H**$_2$ring),



2.60(2H, bs, C**H**$_2$CO$_2$H)

1.63 and 1.55(6H, s, 2xC**H**$_3$)

^{1}H NMR δ:2.9 and 2.75(2H, AB, J=11.7, C**H**$_2$ring)



2.88 and 2.82(2H, AB, J=14.1,C**H**$_2$CO$_2$H)

1.58 and 1.25(6H, s, 2xC**H**$_3$)

Both Isomers

^{13}C NMR δ:178.20(**C**=O), 145.55 and 139.35(**C**$_6$H$_5$, qu), 128.90, 128.70, 128.40,

126.85, 126.20, 125.05, and 124.65(**C**$_6$H$_5$, tr), 87.15 and 84.95(**C**-O-O-**C**),

58.30(**C**H$_2$ring), 47.60 and 45.70(**C**H$_2$CO$_2$H),

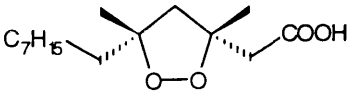
36.60(**C**H$_2$C-O-O), 28.75, 28.05 and 24.70(2x**C**H$_3$),

MS(FAB): Acc. Mass Found:259.0940. $C_{13}H_{16}O_4Na$ requires: 259.0946.

Preparation of 3-carboxymethyl-3,5-dimethyl-5-octyl-1,2-dioxolane (3.81)

General Method I with diene acid (**3.74**) (0.5 g, 2.1 mmol), THF(2.5 ml), $Hg(OAc)_2$ (1.34 g, 4.2 mmol), 30% H_2O_2 (2.5 ml, 22.5 mmol) stired for 24 hours.. Crude mercuriated dioxolane in DCM (30 ml) and 2M NaOH(aq) (6ml). $NaBH_4$ (0.24 g, 6.3 mmol) in 2M NaOH(aq) (20 ml). The aqueous layer was separated and the DCM layer washed with sat $NaHCO_3$ (aq) (3x 10 ml) The basic aqueous phases were combined, acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.16 g (29%) of (**3.81**) as a colourless oil. Purification by column chromatography (SiO_2 Hex:EtOAc 3:1) separated the two isomers.

Fraction 1 gave 0.07 g of a colourless oil (**3.101**)

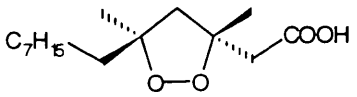


^{1}H NMR δ:2.77 and 2.66 (2H, AB, J=15, C**H**$_2$CO$_2$H)
2.50 and 2.12(2H, AB, J=12.4, C**H**$_2$ring)
1.60-1.5(2H, m, C**H**$_2$)
1.46 and 1.30(6H, s, 2xC**H**$_3$),
1.3-1.2(12H, m, (C**H**$_2$)$_6$), 0.85(3H, m, (CH$_2$)$_5$C**H**$_3$)

^{13}C NMR δ:175.0(**C**=O), 86.85 and 84.0(**C**-O-O-**C**), 55.40(**C**H$_2$ring)
44.05(**C**H$_2$CO$_2$H), 38.75(**C**H$_2$C-O-O), 24.70, 23.60
and 14.10(2x**C**H$_3$ **C**H$_3$), 31.80, 30.60, 29.50, 29.15, 24.80, 22.35((**C**H$_2$)$_6$)

Fraction 2 contained 0.2 a mixture of isomers (**3.101 and 3.102**)

Fraction 3 gave 0.015 g of a colourless oil (**3.102**)



^{1}H NMR δ:2.78 and 2.69(2H, AB, J=15, C**H**$_2$CO$_2$H)
2.43 and 2.23(2H, ABq, J=12.4, C**H**$_2$ring)
1.7-1.5(2H, m, C**H**$_2$) 1.44 and 1.30(6H, s, 2xC**H**$_3$), 1.3-1.2(12H, m, (C**H**$_2$)$_6$),
0.85(3H, m, (CH$_2$)$_5$C**H**$_3$)

^{13}C NMR δ:175.0(**C**=O), 86.75 and 83.70(**C**-O-O-**C**), 55.54(**C**H$_2$ring)
44.10(**C**H$_2$CO$_2$H), 43.88(**C**H$_2$CO$_2$H), 39.73(**C**H$_2$C-O-O), 24.5, 23.85 and
14.10,(2x**C**H$_3$ **C**H$_3$), 31.80, 30.55, 29.45, 29.25, 24.8, 24.75 and
23.15((**C**H$_2$)$_6$)

MS(FAB): Acc. Mass Found:295.1880. $C_{15}H_{28}O_4Na$ requires: 295.1885

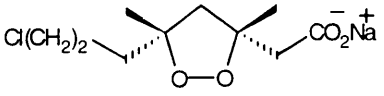
IR 3600-2980(b,vs),2800(m),1723(vs)1450(m),1400-1000(b,m).

Analysis Found: C,66.61; H, 10.52. $C_{15}H_{28}O_4$ requires: C,66.14; H,10.36 %.

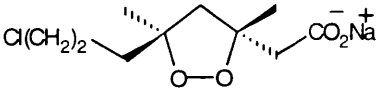
Preparation of 3-carboxymethyl-3,5-dimethyl-5-(3-chloropropyl)-1,2-dioxolane (3.82)

General Method G with diene acid (**3.75**) (0.45 g, 2.2 mmol), THF(3 ml), $Hg(OAc)_2$ (1.42 g, 4.5 mmol), 30% H_2O_2 (2.5 ml, 23 mmol) stirred for 2 days. Crude mercuriated dioxolane in DCM (20 ml) and 2M NaOH(aq) (7ml). $NaBH_4$ (0.26 g, 7 mmol) in 2M NaOH(aq) (20 ml). The aqueous layer was separated and washed with DCM (3x 10 ml), acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.14 g (30%) of (**3.82**) as a colourless oil along with approx. 5% impurities.The sodium salt of the acid was prepared by adding (**3.82**) to a solution of $NaHCO_3$ (0.05 g, 0.6 mmol) in H_2O. The water was evaporated *in vacuo* to leave a white solid. Purifcation by washing with hexane gave 0.07 g of (**3.82**) as the sodium salt.

^{1}H NMR δ: 3.55-3.52(2H, m, ClC**H**$_2$),
2.77 and 2.68(2H,AB, J=15, C**H**$_2$CO$_2$Na)
2.56 and 2.19(2H, AB, J=12.6, C**H**$_2$ring)
1.9-1.7(2H, m, C**H**$_2$), 1.49 and 1.35(6H, s, 2xC**H**$_3$)



^{1}H NMR δ:3.55-3.52(2H, m, ClC**H**$_2$),
2.82 and 2.7(2H, AB, J=15, C**H**$_2$CO$_2$Na)
2.53 and 2.25(2H, AB, J=12.4, C**H**$_2$ring)
1.9-1.7(2H, m, C**H**$_2$), 1.47 and 1.31(6H, 2xs, 2xC**H**$_3$)



Both Isomers

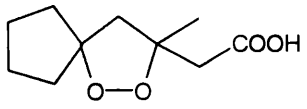
^{13}C NMR δ:178.05(**C**=O), 85.45 and 85.35 and 85.20(**C**-O-O-**C**), 57.05 (**C**H$_2$ring)
45.35, 45.25(**C**H$_2$CO$_2$Na), 36.60(**C**H$_2$C-O-O), 24.05, 23.95 and
14.15(2x**C**H$_3$), 33.60, 31.60, 28.25 and 22.35((**C**H$_2$)$_2$)

MS(FAB): Acc. Mass Found:259.0717. $C_{10}H_{17}O_4ClNa$ requires: 259.0713

Preparation of 3-carboxymethyl-3-methyl-5spirocyclopentane-1,2-dioxolane (3.83)

General Method G with diene acid (**3.76**) (0.46 g, 2.7 mmol), THF(3 ml), $Hg(OAc)_2$ (1.76 g, 5.4 mmol), 30% H_2O_2 (3 ml, 28 mmol) stirred for 2 days. Crude mercuriated dioxolane (2.0 g) in DCM (20 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.317 g, 8.4 mmol) in 2M NaOH(aq) (20 ml). The aqueous layer was separated and washed with DCM (3x 10 ml), acidified dropwise with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.05 g (15%) of (**3.83**) as a colourless oil. Purification by recrystalisation from DCM/Hex gave (**3.83**) with 80% recovery to give a white solid.

^{1}H NMR δ:2.78 and 2.72(2H, AB, J=14.9 C**H**$_2$CO$_2$H)



2.69 and 2.38(2H, AB, J=12.5, C**H**$_2$ring)

1.80-1.5(6H, m, (C**H**$_2$)$_3$),

2.15-2.09 and 1.9-1.85(2H,C**H**$_2$) 1.8-1.5(6H, m, 3xC**H**$_2$), 1.47(3H, s, C**H**$_3$),

^{13}C NMR δ:174.0(**C**=O), 94.65 and 83.40(**C**-O-O-**C**), 54.60(**C**H$_2$ring),

43.90 (**C**H$_2$CO$_2$H), 38.55 and 35.60(2x(**C**H$_2$C-O-O)), 23.70(**C**H$_3$),

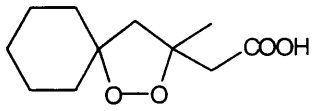
24.30 and 24.25((**C**H$_2$)$_2$)

MS(FAB): Found:201.1120; $C_{10}H_{17}O_4$ requires:201.1127

Preparation of 3-carboxymethyl-3-methyl-5spirocyclohexyl-1,2-dioxolane (3.84)

General Method G with diene acid (**3.77**) (0.5 g, 2.8 mmol) THF(3 ml) Hg(OAc)$_2$ (1.78 g, 5.6 mmol) 30% H_2O_2 (3 ml, 28 mmol) stirred for 2 days. Crude mercuriated dioxolane (2.0 g) in DCM (20 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.317 g, 8.4 mmol) in 2M NaOH(aq) (20 ml). The aqueous layer was separated and washed with DCM (3x 10 ml), acidified dropwise with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.300 g (50%) of (**3.84**) as a colourless oil. Purification by recrystalisation from DCM/Hex gave (**3.84**) with 80% recovery as a white solid.

^{1}H NMR δ:2.78 and 2.70 (2H, AB, J=14.8, C**H**$_2$CO$_2$H)



2.40 and 2.16(2H, AB, J=12.4, C**H**$_2$ring)

1.80-1.5(6H, m, (C**H**$_2$)$_3$)

1.45(3H, s, C**H**$_3$), 1.4-1.3(2H, m, C**H**$_2$).

^{13}C NMR δ:176.0(**C**=O), 86.00 and 83.50(**C**-O-O-**C**), 55.15(**C**H$_2$ring)

43.95(**C**H$_2$CO$_2$H), 35.90 and 35.25(2x(**C**H$_2$C-O-O)), 23.80(**C**H$_3$)

25.15, 23.80 and 23.25((**C**H$_2$)$_3$)

MS(EI): (M$^+$)214

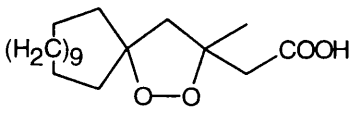
Analysis Found: C,61.55; H, 8.53. $C_{11}H_{18}O_4$ requires: C,61.66; H,8.47 %.

IR 3600-2980(b,vs),2800(m),1723(vs)1450(m),1400-1000(b,m).

Preparation of 3-carboxymethyl-3-methyl-5spirocyclododecyl-1,2-dioxolane (3.85)

General Method G with diene acid (**3.78**) (0.5 g, 1.9 mmol), THF(3 ml), $Hg(OAc)_2$ (1.2 g, 3.8 mmol), 30% H_2O_2 (2.5ml, 22.5 mmol) stirred for 2 days. Crude mercuriated dioxolane(1.2 g) in DCM (15 ml) and 2M NaOH(aq) (5ml). $NaBH_4$ (0.216 g, 5.7 mmol) in 2M NaOH(aq) (15 ml). The aqueous layer was separated and washed with DCM (3x 10 ml), acidified with 1M HCl (aq) dropwise at 5 ^{0}C, and extracted with DCM to give 0.05 g (9%) of (**3.85**) as a colourless oil with 5% impurities. Purification by column chromatography (SiO_2 Hex:EtOAc 6:1).

^{1}H NMR δ:2.78 and 2.68 (2H, AB, J=14.8,C**H**$_2$CO$_2$H)
2.45 and 2.13(2H, AB, J=12.4, C**H**$_2$ring)
1.80-1.5(4H, m, (C**H**$_2$)$_3$)
1.45(3H, s, C**H**$_3$), 1.4-1.2(18H, m, 9xC**H**$_2$).



^{13}C NMR δ:175.20(**C**=O), 89.50 and 83.60(**C**-O-O-**C**), 54.80(**C**H$_2$ring)
44.25(**C**H$_2$CO$_2$H), 32.15 and 31.60(2x(**C**H$_2$C-O-O)), 26.40, 26.25, 25.90, 23.80, 22.60, 22.55, 22.20, 22.50, 21.65, 20.25, 19.65 and 14.55((**C**H$_2$)$_{11}$ **C**H$_3$).

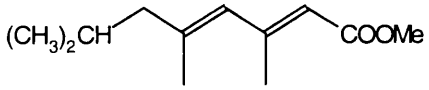
MS(FAB): Acc. Mass Found:321.2050. $C_{17}H_{30}O_4Na$ requires: 321.2040

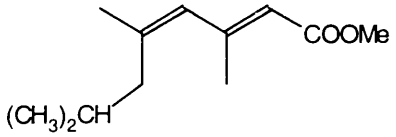
Peroxymercurlation of a 2*E* Diene Ester

Peparation of (2*Z*,4*Z*),(2*Z*,4*E*),(2*E*,4*Z*) and (2*E*,4*E*)methyl 3,5,7-trimethylocta-2,4-dienoate (3.86)

General Method D with trimethyl oxonium tetrafluroborate (0.625 g, 4.23 mmol), diene acid (**3.72**) (0.70 g, 1.96 mmol), N-ethyl diisopropylamine (0.735 ml, 4.23 mmol) in DCM (30 ml). Purification by column chromatography (SiO_2, 10:1 Hex:EtOAc) gave 0.35 g (85%) of (**3.86**) as a colourless oil. Ratio of (2*E*,4*E*):(2*E*,4*Z*) 3.5:1

2*E*,4*Z*/E Isomers





^{1}H NMR δ:5.75, 5.62, and 5.07(2H, bs, $\mathbf{H}^4$, $\mathbf{H}^2$),
3.67(3H, s, O-C$\mathbf{H}_3$),
2.21 and 2.20(3H, s, $C^3\mathbf{H}_3$),
2.10 and 1.90(2H,d, J=4 C$\mathbf{H}_2$)
1.78 and 1.75(3H, d, $C^5\mathbf{H}_3$,J=1.2),
1.50-2.0(1H,obs, C**H**),
0.90-0.80(6H, m, $(C\mathbf{H}_3)_2$).

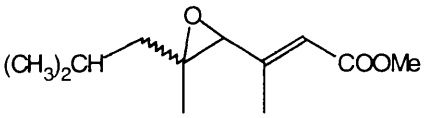
^{13}C NMR δ:168.05(**C**=O), 155.10 and 155.30(**C**=CCO_2Me),
141.50 and 140.40 ($(CH_3)_2CHCH_2$**C**=CH),
129.60, and 129.23($(CH_3)_2CHCH_2C$=**C**H),
117.2 and 116.90(=**C**HCO_2Me), 50.85 and 50.65(O-**C**H_3),
41.55, 26.40, 24.20, 22.40, 22.35, 19.70, 18.37 and
14.10($(\mathbf{C}H_3)_2\mathbf{C}H\mathbf{C}H_2$, $C^5\mathbf{C}H_3$ $C^3\mathbf{C}H_3$)

MS(EI): $(M)^+$196, $(M\text{-}CH_3)^+$ 181 $(M\text{-}(CH_3)_2CHCH_2)^+$ 139

Preparation of 3-methoxy carboxymethyl-3,5-dimethyl-5-(2-methyl-propyl)-1,2-dioxolane (3.87)

General Method J with diene ester (**3.86**) (0.6 g, 3.05 mmol), THF(4 ml), $Hg(OAc)_2$ (1.95 g, 6.1 mmol,) 30% H_2O_2 (3.5 ml, 30 mmol) stirred for 2 days. Crude mercuriated dioxolane (1.4 g) in DCM (30 ml) and 2M NaOH(aq) (10ml). $NaBH_4$ (0.46 g, 12 mmol) in 2M NaOH(aq) (20 ml). Yield of crude product 0.35 g, 51% of a colourless oil in a ratio of isomers of 3.5:1 *cis*: *trans* before purification. Purification by column chromatography (SiO_2 Hex:EtOAc 30:1) gave two major fractions.

Fraction 1 gave (**3.88**) as a clear oil (27%)



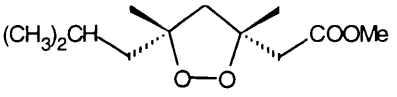
^{1}H NMR δ:5.81 and 5.79(1H, bs C=C**H**),
3.67 and 3.66(3H, s, OC**H**$_3$)
3.18 and 3.15(1H, bs,**H**CO) 2.15(3H, s, C**H**$_3$)
1.37 and 1.82-1.75(1H, m, C**H**), 1.72-1.68 and 1.21-1.29(2H, m, C**H**$_2$),
1.39 and 1.1(3H, 2xs, C**H**$_3$), 0.95-0.8(6H, m, (C**H**$_3$)$_2$CH).

^{13}C NMR δ:167.05(**C**=O), 152.60 and 152.10(**C**=CH), 116.25 and 115.35(C=**C**H),
65.7,66.2(**C**OC, t), 64 and 63.5(**C**OC, q), 51.05(O-**C**H$_3$),
47.30 and 39.35(**C**H$_2$), 25.05, 23.25 and 22.30(2x**C**H$_3$),
23.50 and 22.40(**C**H), 16.30 and 15.0((**C**H$_3$)$_2$CH).

MS(EI): (M$^+$-OCH$_3$) 181,(M$^+$-CH$_3$C:CCO$_2$CH$_3$)112

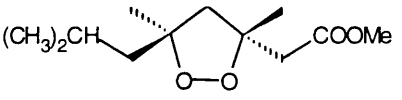
Fraction 2 contained a mixture of (**3.87** and **3.88**)

Fraction 3 gave (**3.87**) as a colourless oil (20%) as a ratio of 3:1cis:trans



^{1}H NMR δ:3.50(3H, s, O-C**H**$_3$),
2.77 and 2.64(2H, AB, J=14, C**H**$_2$CO$_2$Me)
2.51 and 2.14(2H, AB, J=12.6, C**H**$_2$ ring)
1.8-1.6(2H, m, C**H**$_2$),
1.57-1.40(1H, m, C**H**), 1.44 and 1.32(6H, s, 2xC**H**$_3$), 0.89(6H, m, 2xC**H**$_3$)

^{13}C NMR δ:177.10(**C**=O), 87.05 and 83.40(**C**-O-O-**C**), 56.80(**C**H$_2$ring)
47.20(**C**H$_2$CO$_2$Me), 44.30(**C**H$_2$C-O-O), 24.75, 24.55, 23.75 and
23.60(2x**C**H$_3$,(**C**H$_3$)$_2$**C**H)



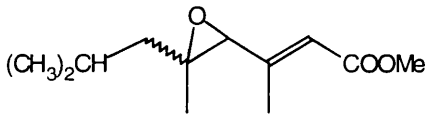
^{1}H NMR δ: 3.5(3H, s, O-C**H**$_3$),
2.76 and 2.67(2H, AB, J=14, C**H**$_2$CO$_2$Me)
2.46 and 2.20(2H, AB, J=12.6, C**H**$_2$ring) 1.72-1.65(2H, m, C**H**$_2$),
1.44 and 1.32(6H, s, 2xC**H**$_3$), 1.3-1.2(10H, m, (C**H**$_2$)$_5$),
0.86(3H, m, (CH$_2$)$_5$C**H**$_3$).

^{13}C NMR δ:177.10(**C**=O), 86.75 and 83.40(**C**-O-O-**C**), 56.95(**C**H$_2$ring)
47.90(**C**H$_2$CO$_2$Me), 43.80(**C**H$_2$C-O-O) 24.70, 24.25, 24.05, 23.70 and
23.40(2x**C**H$_3$,(**C**H$_3$)$_2$**C**H)

MS(EI): (M$^+$)230, (M$^+$-OCH$_3$)197

Preparation of methyl 3,5,7-trimethyl-4,5-epoxy-oct-2-enoate (3.88)

The diene ester (**3.86**) (0.13 g, 0.7 mmol) was dissolved in THF(2 ml) and added to a stirred solution of 35% peracetic acid (1 ml, 4.5 mmol) and 30% H_2O_2(1 ml). The rection mixture was left stiring overnight at room temperature. The reaction mixture was extracted with DCM (3x7 ml). The organic portions were combined and washed with sat. $NaHCO_3$ (aq) (15 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 0.1 g of a colourless oil. Purification by column chromatography(SiO_2 Hex:EtOAc 30:1) gave 0.05 g (45%) of (**3.88**) as a colourless oil.



^{1}H NMR δ:As before

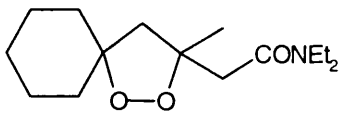
^{13}C NMR δ:As before

MS(EI): $(M\text{-}OCH_3)^+$181, $(M\text{-}CH_3C{:}CHCO_2CH_3)^+$112

Analysis Found: C,67.89; H, 9.49. $C_{12}H_{20}O_3$ requires: C,67.87; H,9.62 %.

Preparation of 3-diethylaminocarbonylmethyl-3-methyl-5-spirocyclohexyl-1,2-dioxolane (3.103)

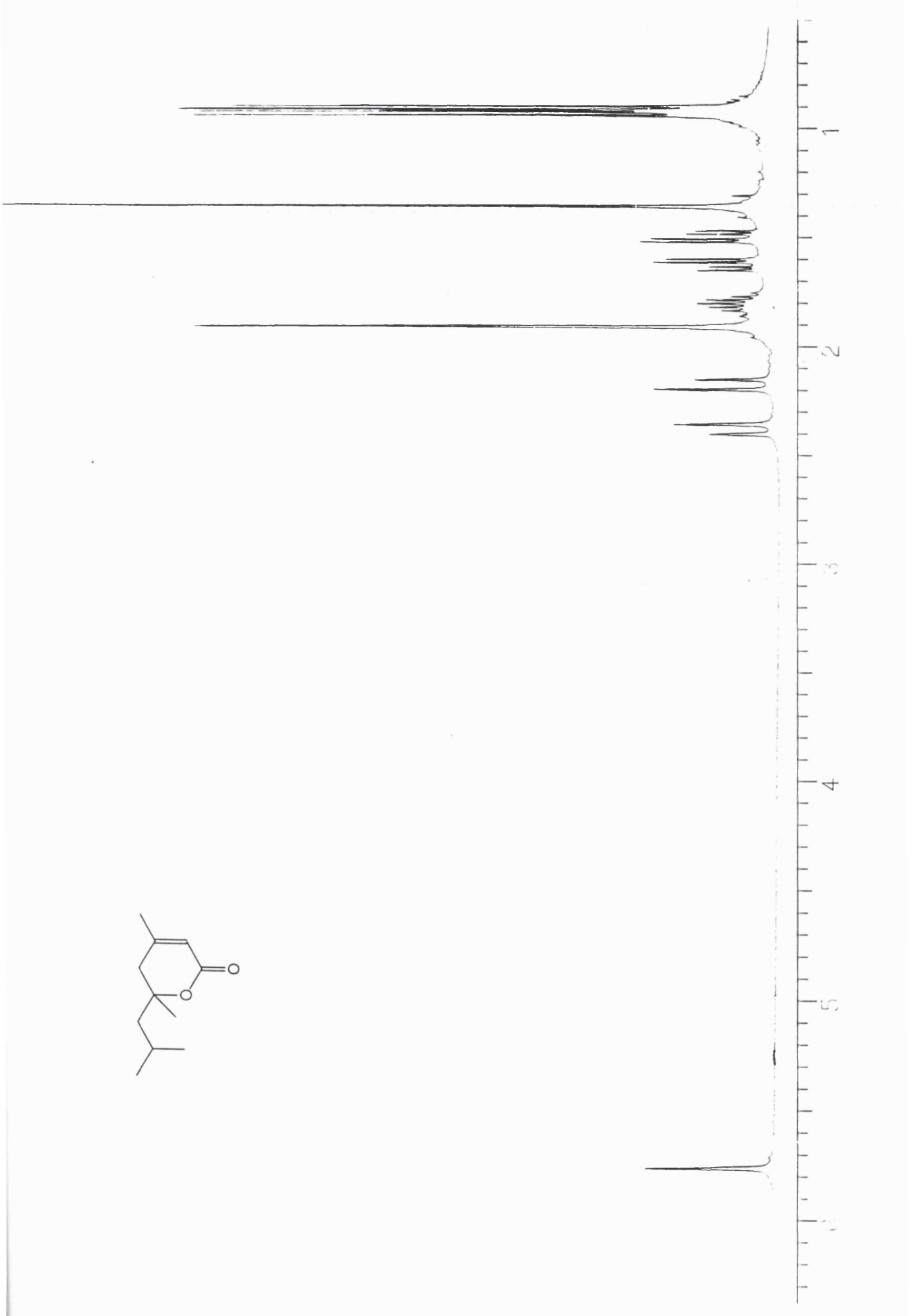
The 1,2-dioxolane (**3.84**) (0.04 g, 0.17 mmol), dicyclohexylcarbodiimide (0.034 g, 0.17 mmol), and diethylamine (0.017 ml, 0.17 mmol) were dissolved in DCM (5 ml) and cooled to 5 ^{0}C. The reaction mixture was stirred at 5 ^{0}C for 30 minutes and then at room temperature for 3 hours. The reaction mixture was diluted with DCM (10 ml) and washed with 1M HCl(10 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo* to give 0.06 g of a colourless oil. Purification by column chromatography (SiO_2 Hex:EtOAc 1:1) gave 0.02 g (45%) of (**3.103**) as a colourless oil.



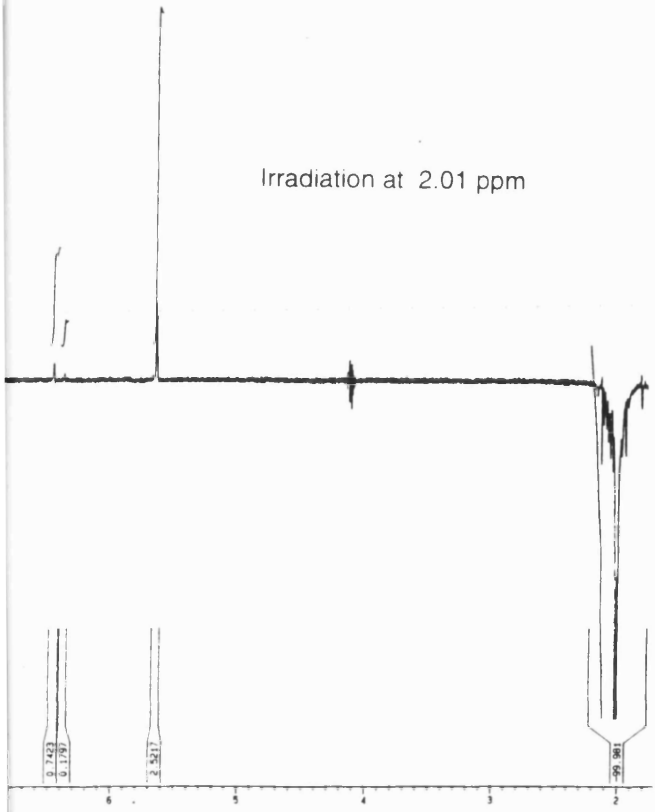
^{1}H NMR δ:3.43-3.35(4H, m, $N(C\mathbf{H}_2)_2$),
2.69(2H, s, $C\mathbf{H}_2CO_2NEt_2$)
2.55 and 2.23(2H, AB, J=12.5, $C\mathbf{H}_2$ring)
1.80-1.6(6H, m, $(C\mathbf{H}_2)_3$),1.45(3H, s, $C\mathbf{H}_3$), 1.40-1.30(2H, m, $C\mathbf{H}_2$),
1.16 and 1.11(6H, 2x t, J=7, $N(CH_2C\mathbf{H}_3)_2$),

^{13}C NMR δ:169.20(**C**=O), 86.00 and 85.15(**C**-O-O-**C**), 55.15($C\mathbf{H}_2$ring),
42.40 and 42.25($N(C\mathbf{H}_2CH_3)_2$), 39.90($C\mathbf{H}_2CO_2NEt_2$),
35.80 and 35.45(2x($C\mathbf{H}_2$C-O-O)), 23.80($C\mathbf{H}_3$), 25.20, 23.85 and
23.45(($C\mathbf{H}_2)_3$), 14.20 and 13.15($N(CH_2C\mathbf{H}_3)_2$),

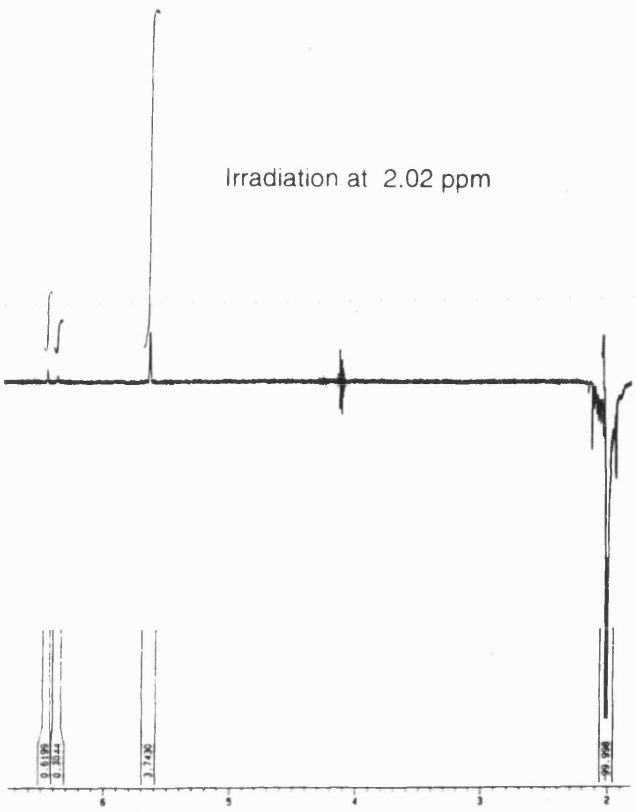
MS(FAB): Found:270.2060; $C_{15}H_{28}NO_4$ (M+H) requires:270.2069


1
2
3
4
5

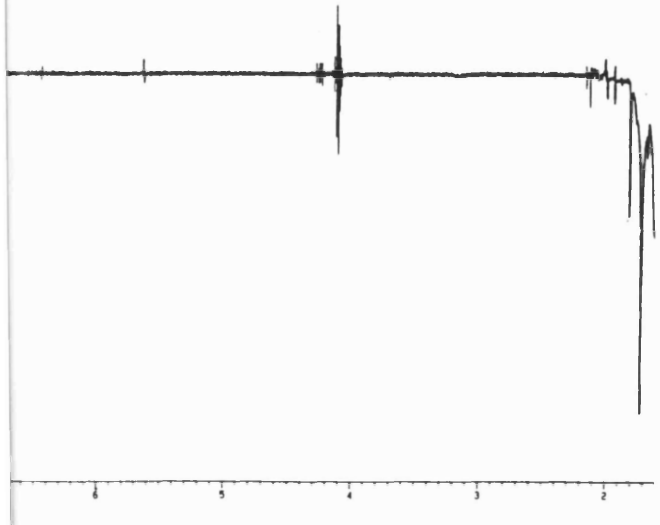
Irradiation at 2.01 ppm



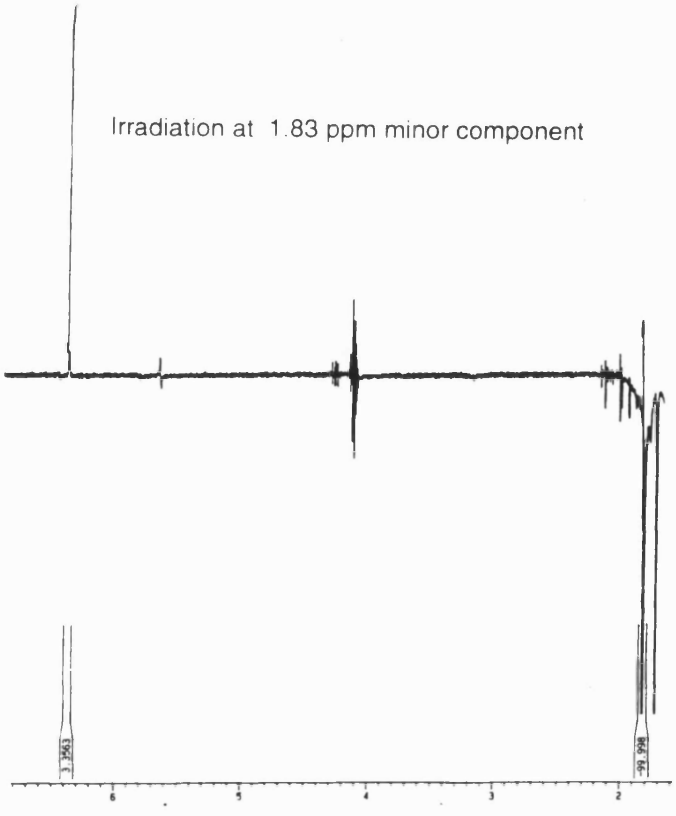
Irradiation at 2.02 ppm

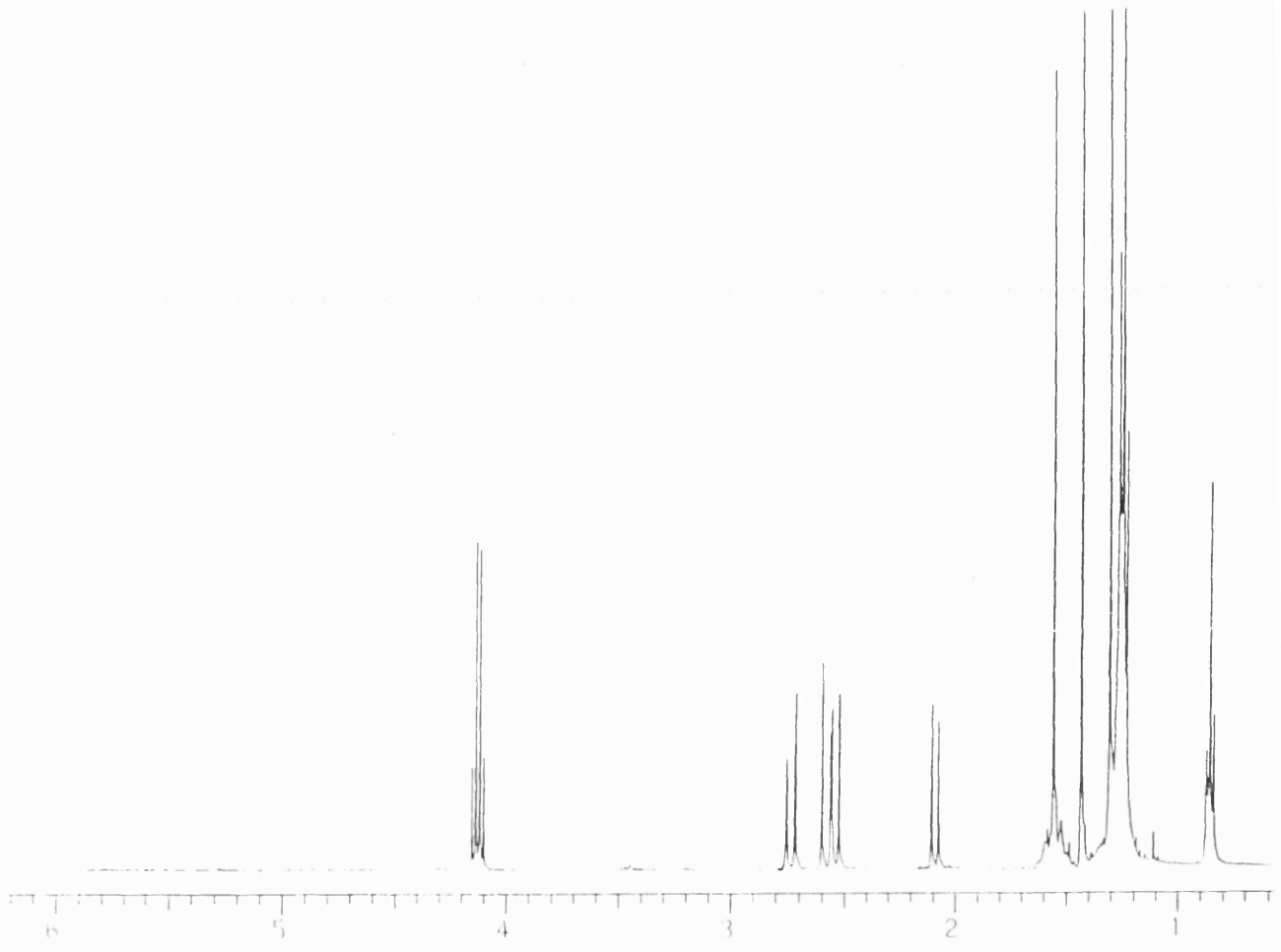


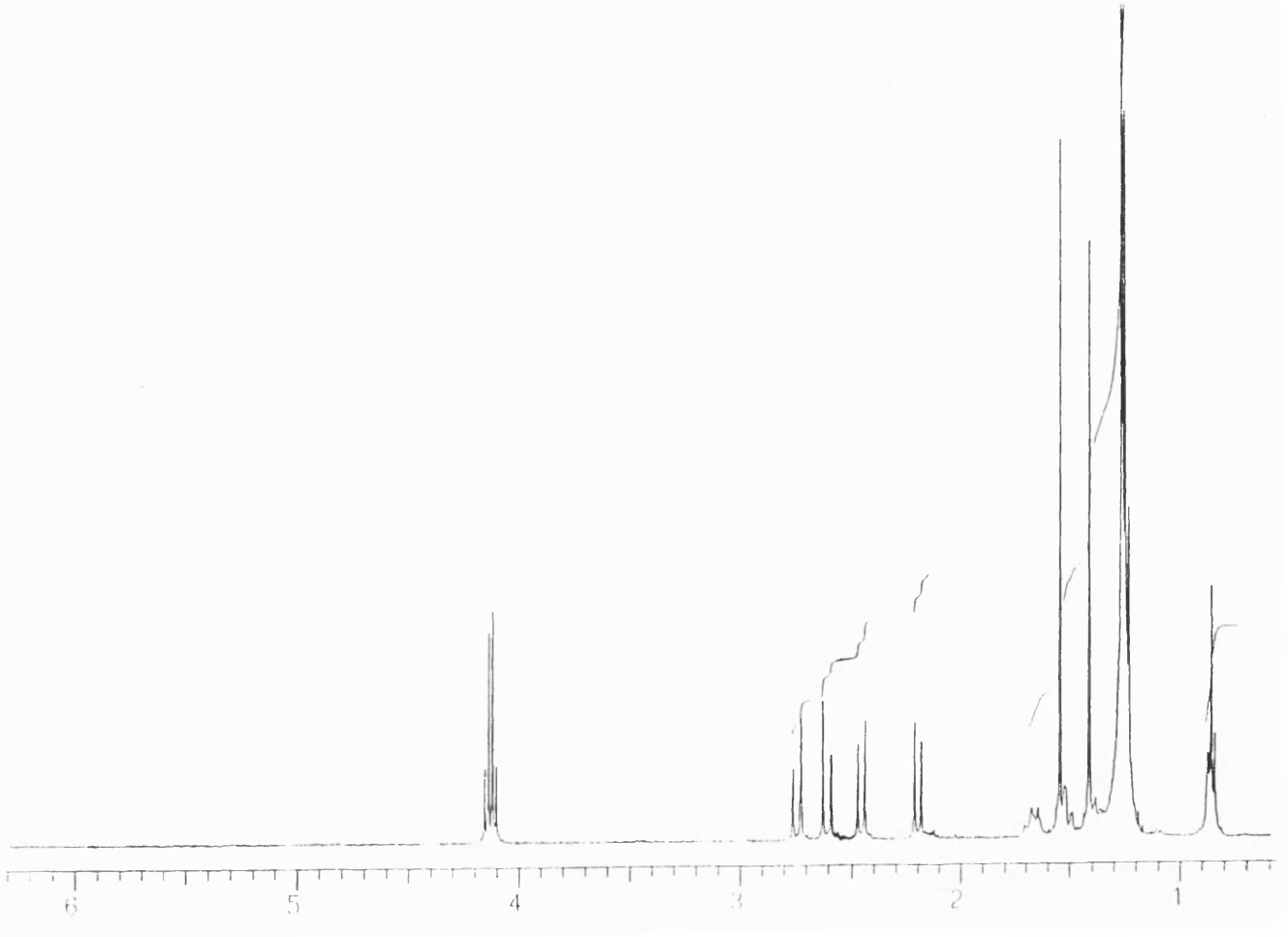
Irradiation at 1.73 ppm major component

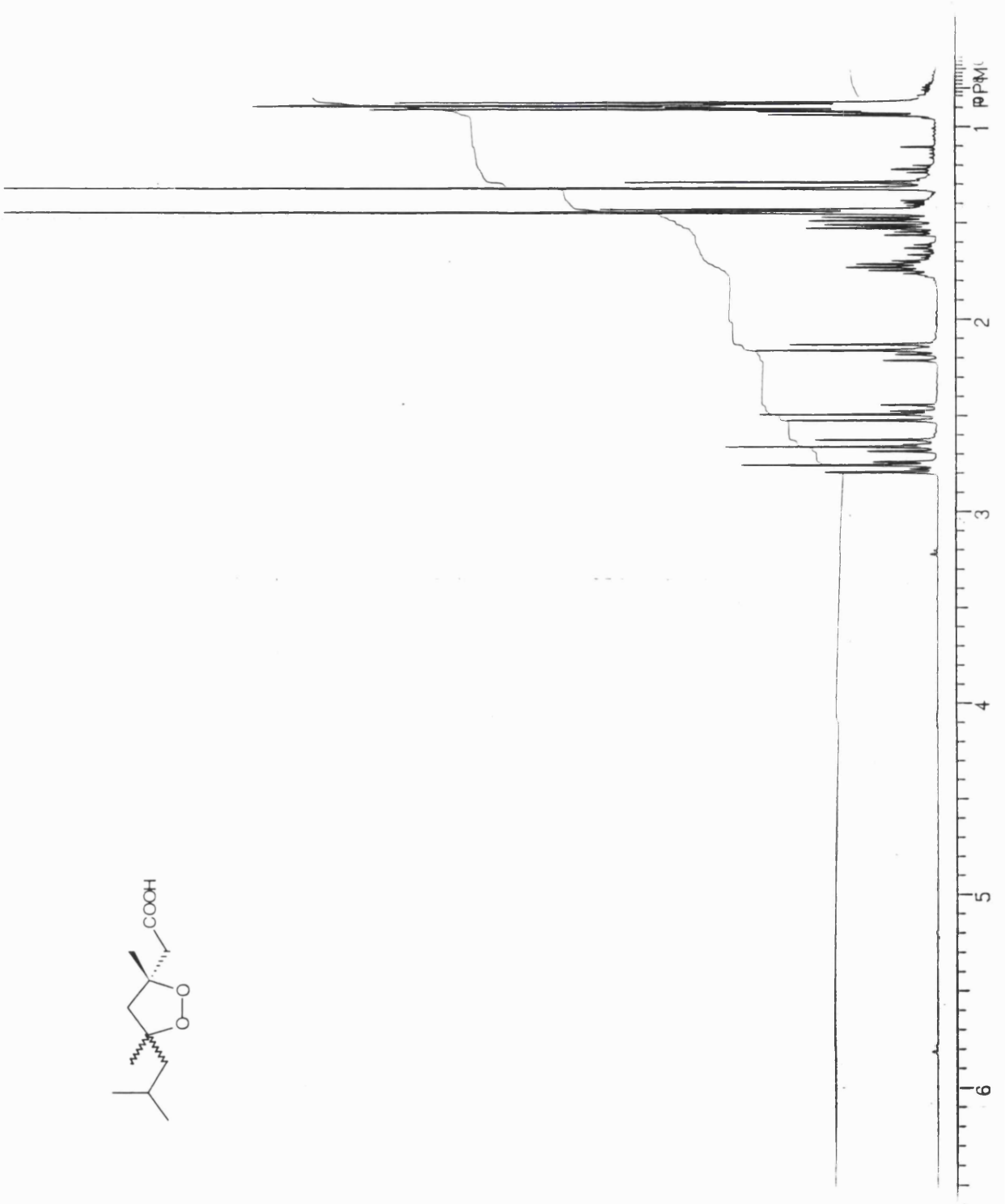


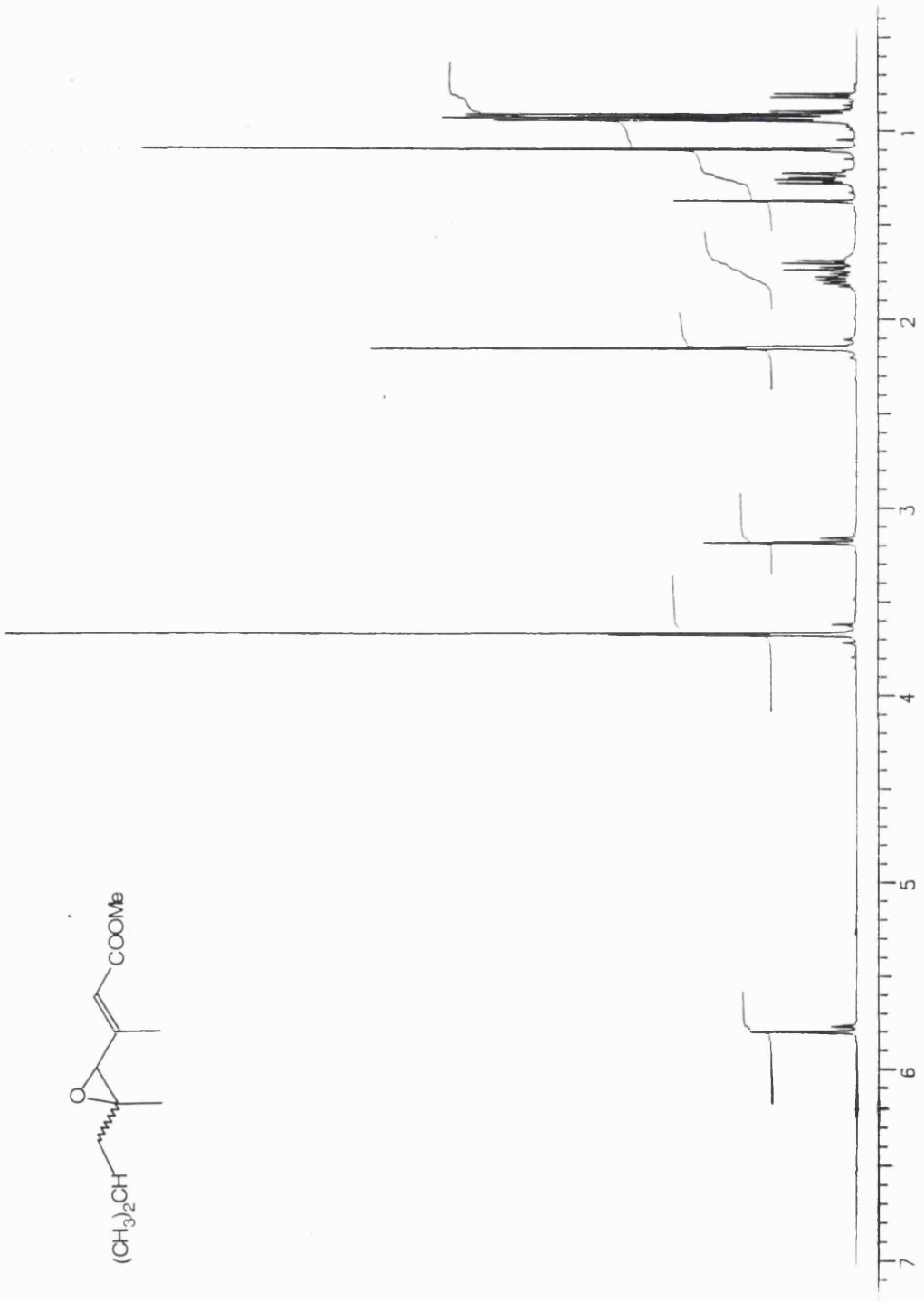
Irradiation at 1.83 ppm minor component




6
5
4
3
2
1


6
5
4
3
2
1


COOH
O
O
1
2
3
4
5
6
PPM


COOMe
(CH3)2CH
1
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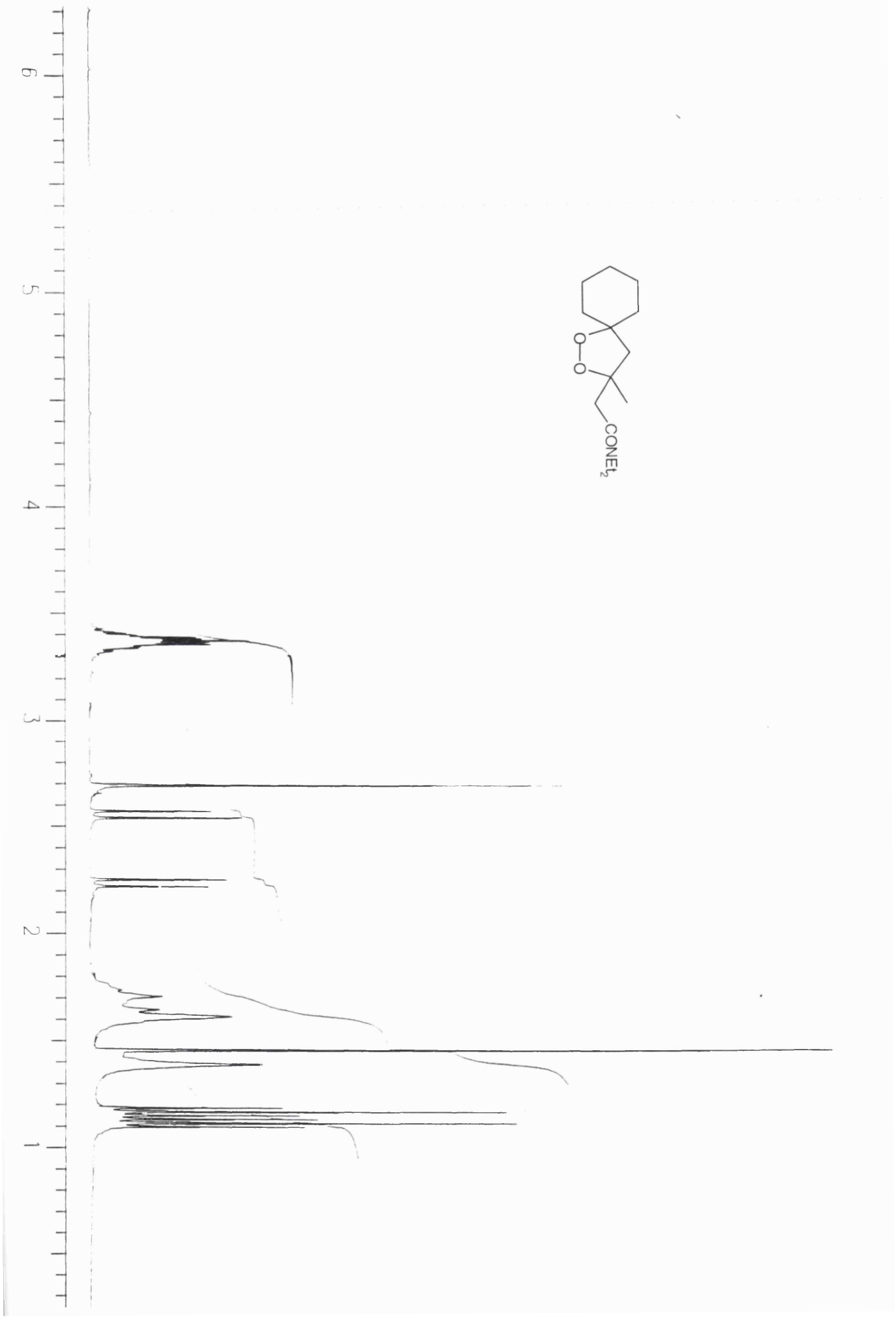
6
7


6
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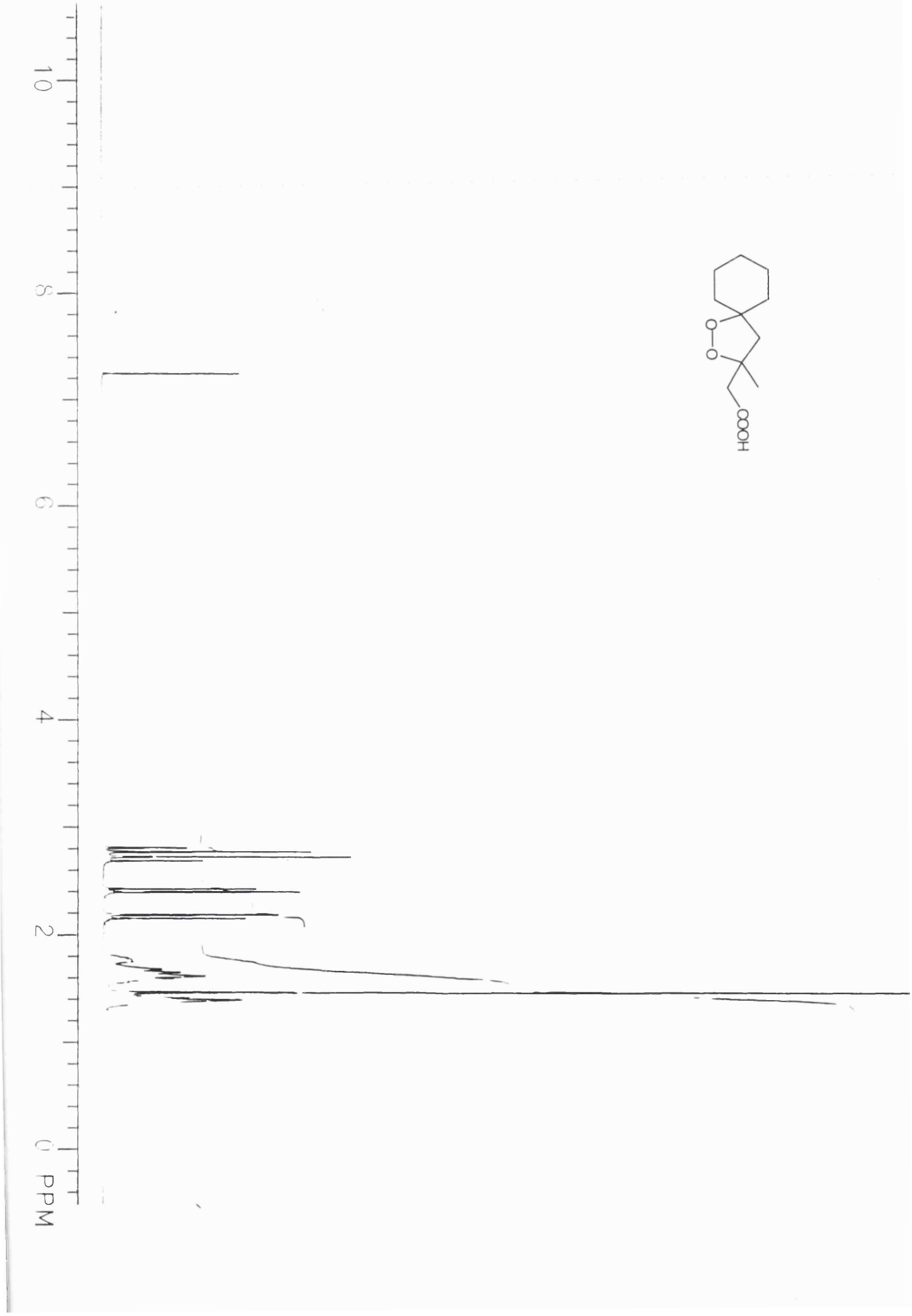
O
O
CONEt2


10
8
6
4
2
0 PPM
O
O
HOOC

REFERENCES

1. a)Bergmann, E.D.; Solomomovici, A., *Tetrahedron*, **1971**, 27, 2675-2678. b)Cossentini.M.; Deschamps, B.; Anh, N.T.; Seyden-Penne. J., *Tetrahedron*, **1977**, 33, 409-412.
2. a)Heck, R.F., *Org. React.*, **1982**, *27*, 345-390. b) Heck, R.F., *Palladium Reagents in Organic Synthesis*, Academic Press, London **1985**.
3. Brouillette, W.J.; Muccio, D.D.; Robinson, C.Y., *J. Org. Chem.*, **1989**, *54*, 1992.
4. a)Pattenden, G.; Weedon, B.L., *J.Chem.Soc.(C)*, **1968**, 1984. b)Pattenden, G.; Weedon, B.L., *J.Chem.Soc.(C)*, **1968**, 1997.
5. Bellassoued, M.; Habbachi, F.; Guademar, M., *Tetrahedron*, **1987**, *43*. No. 8, 1785.
6. Brouillette, W.J.; Muccio, D.D.; Robinson, C.Y, *J. Org. Chem.*, **1989**, *54*, 1992.
7. Dugger, R.W.; Heathcock, C.H., *J. Org. Chem.* , **1980**, *45*, 1181-1185.
8. a)Roush, W.R.; Spada, A.P., *Tetrahedron Lett.*, **1982**, *23*, 37, 3773. b)Corey, E.J.; Schmidt, G., *Tetrahedron*, **1979**, *25*, 2317. c)Cardillo, G.; Orena, M.; Sandri, S., *Tetrahedron*, **1976**, *32*, 107.
9. a)Frosch, J.W., *J. Chem. Soc. Perkin Trans.II*, **1974**, 2005. b)Wolinsky,J.; Eustace, E.J., *J. Org. Chem.* , **1972**, *37*, 3376. c)Korte, F.; Machleidt, H., *Ber. Deutsch Chem. Ges.*, **1955**, *136*, 1372. d)Eisner, U.; Elvidge, Y.A.; Linstead, R.D., *J. Chem. Soc.*, **953**, 1372.
10. Korte, F, *Ber. Deutsch Chem. Ges.*, **1962**, *95*, 1372.
11. Masamune, S.; Imperiali. B.; Garvey, D.S., *J. Am. Chem. Soc.*, **1982**, *104*, 5528.
12. Nakata, T.; Hata, N.; Oishi, T., *Heterocycles*, **1990**, *30*, 333.
13. Smissman, E.E.; Voldeng, A.N., *J. Org. Chem.*, **1964**, *29*, 3161.
14. a)Isler, O.; von Planta, C.; Ruegg, R.; Scweiter, U., *Helv. Chim. Acta.*, **1962**, *45*, 528 b)Ahmar, M.; Paris, J.; Rocher, J.Ph., *J. Heterocyclic Chem.* **1988**, 25, 599 c) Ahmar, M.; Motsios, G.; Nadi, A.I.;Paris, *Synth. Commun.*, **1991**, *21*, 6, 819-26 d) Henrich, C.A.;.Willy, W.E.;.Baum J.W.; Baer, T.A.;.Garcia, B.A.;.Master, T.A.;.Chang, S.M., *J.Org.Chem.*, **1974**, *40*, 1.
15. Anghelova, Y.; Ivanov, C., *Izvestia Po Khimia*, **1975**, 8, (1), 70.
16. Larock, R.C., *Solvomercuriation/ Demercuriation Reactions in Organic Synthesis.*, Chap 5, (B), ref therein.
17. Ireland, R.E.; Mueller, R.H.; Willard, A.K., *J. Am. Chem. Soc.*, **1976**, 98, 2868
18. Abelman, M.M.; Funk, R.L.; Munger, J.D., *J. Am. Chem. Soc.*, **1982**, *104*, 4030-4032.

19. Neises,B.; Stegliech W.,Organic Synthesis, **1984**, *63*, 183.

20. Raber, D.J.;.Gariano, P.; Gariano, A J.;.Brod, A.O., J.*Org.Chem.*, **1979**, *44*, 7, 1149.

21. Bloodworth A.J.; Hutchings M.G.; Sotowiicz A.J., *J.C.S. Chem Comm.*, **1976**, 578

22. H.Hock, *Angew Chem.*, **1936**, *49*, 595.

23. Gardner, H.W; Planter, R.D., *Lipids*, **1984**, *19*, 294.

24. Dussault, P.; Lee, I.Q., *J. Org. Chem*, **1995**, *60*, 218-226

25. Patil, A.D., *US Patent* 4,879,307 (1989); C.A., 1988, **109**, 17027f

26. Bloodworth, A.J.; Khan, J.A., *J. Chem. Soc. Perkin Trans.II*, **1980**, 2450.

27. a)Bartlett, P., *Rec. Chem. Prog.*, **1957**, *18*, 111. b)Kwart; Hoffmann, *J. Org. Chem.* , **1966**, *31*, 419. c)Hanzlick; Shearer, *J. Am. Chem. Soc.*, **1975**, *97*, 5231.

28. a)Borowitz I. J.; Gonis G.; Kelsey R.; Rapp R.; Williams G.J., *J. Org. Chem* **1966**, 31, 3032-3036. b)Belleau B.; Gallagher T.F., *J. Am. Chem. Soc.*, **1952**, *74*, 2816

29. Subramanyam V.; Brizuela C.L.; Soloway A.H., *J.C.S. Chem Comm.*, **1976**, 508-509.

30. Davidson, B.S., *J. Org. Chem* ., **1991**, 56, 6722-6724.

31. Klausner; Bodansky, *Synthesis*, **1972**, 453-463.

CHAPTER FOUR

APPROACH TO THE TOTAL SYNTHESIS OF THE PLAKINIC ACIDS

INTRODUCTION

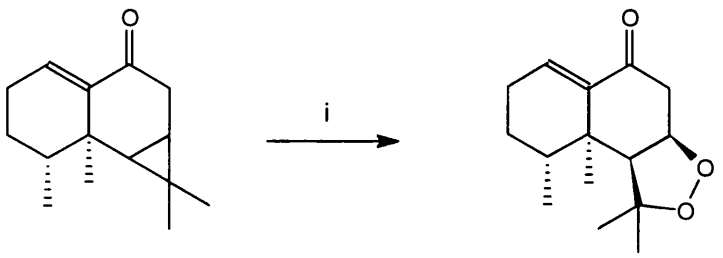
Synthesis of Peroxy Natural Products

Approaches to the Synthesis of Peroxy Natural Products

Methods of synthesising peroxy natural products have been channelled towards introducing the peroxide group in the final step, and have frequently used natural products as substrates. This approach inevitably restricts the syntheses to those of molecules with a relatively simple structure or with readily available precursors. Recently, however, other approaches have lead to the production of more complex peroxy natural products. These methods involve functional group interconversions in the presence of the peroxide moiety and, what is more important, employ strategies that incorporate C-C and C=C bond formation in the presence of a protected hydroperoxide.

Insertion of the peroxide group in the final step

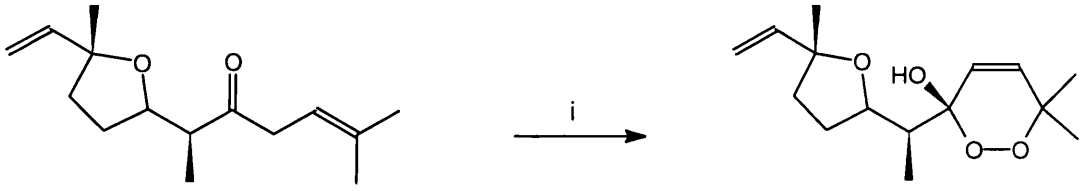
Synthesis of peroxy natural productsby inserting the peroxide group in the final step has been achieved by autoxidation (**Scheme 4.1**)[1] and, more commonly, through photo-oxygenation[2] (**Scheme 4.2**).



4.1 **1.8**

i) $^3O_2$/ ArOH/ Heat

Scheme 4.1



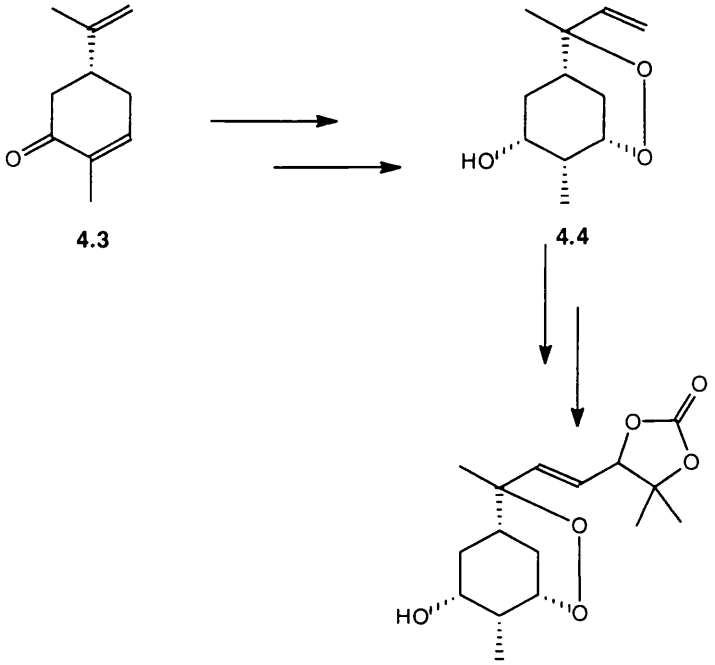
4.2 **1.2**

i) hv O_2/ MeOH/ Methylene blue

Scheme 4.2

Substrate modification in the presence of the peroxide moiety

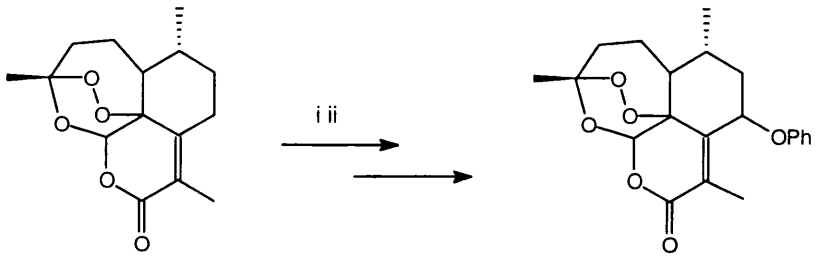
Strategies for the total synthesis of peroxy natural products in many cases are based around one central principle, namely the assumed instability of the peroxide linkage. However, recent work has shown the peroxide group to be more robust than hitherto supposed. Work on the synthesis of Yingzhaosu[3] illustrates this point. The 1,2-dioxane ring is introduced halfway through a multi-step procedure and remains intact after treatment under various reaction conditions including ozonolysis, hydrogenation of an internal double bond and C=C bond formation (**Scheme 4.3**).



4.3 **4.4** **4.5**

Scheme 4.3

Another example of the robustness of some peroxide groups is shown in through the functionalisation of iso-artemisitene (**4.6**)[4] where the trioxane ring persists after exposure to a number of reagents (**Scheme 4.4**).



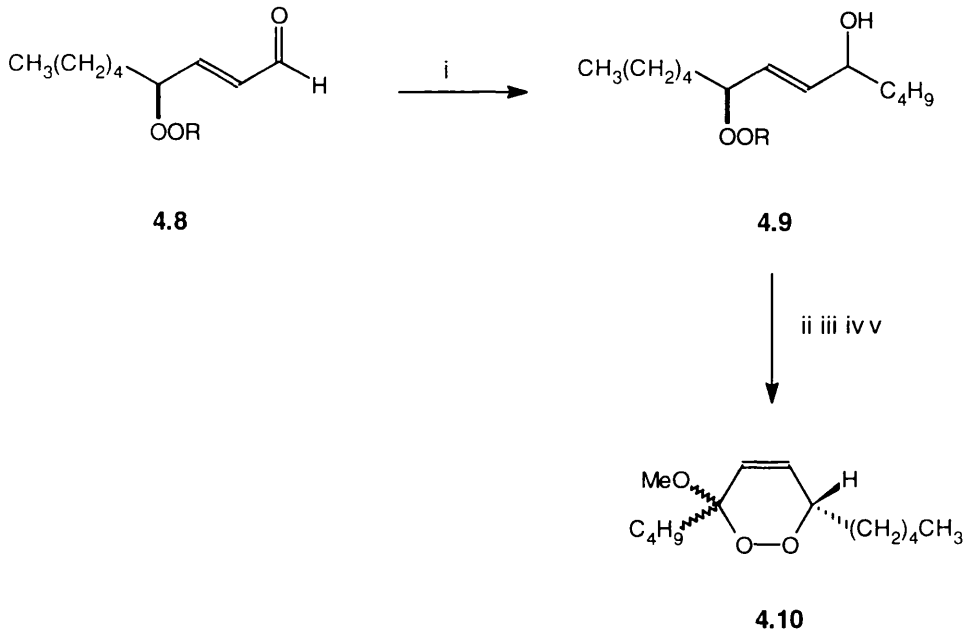
4.6 **4.7**

i) NBS/dibenzyl peroxide ii) PhOH/ NaH/ DMF

Scheme 4.4

Much of the work in this field has been undertaken by Dussault and co-workers[5]. In particular their investigations have demonstrated the tolerance of the peroxide bond to reagents and conditions required for the formation of C-C and C=C bonds.

Dussault's initial success centred on the addition of organometallic nucleophiles to aldehydes in the presence of a masked hydroperoxide[6]. This approach was used (**Scheme 4.5**) to synthesise an alkoxydioxine (**4.10**), an analogue of chondrollin (**1.14**) which, as mentioned in Chapter 1, is an example of a pervasive class of peroxy natural products isolated from marine sponges (**Scheme 4.5**).



4.8 **4.9** **4.10**

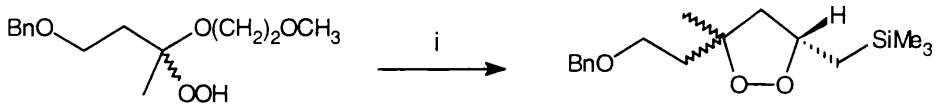
R=$C(CH_3)_2OCH_3$

i)n-BuMgBr/ THF 0 ^{0}C ii)PDC iii) AcOH iv) hv v) MeOH PPTS

Scheme 4.5

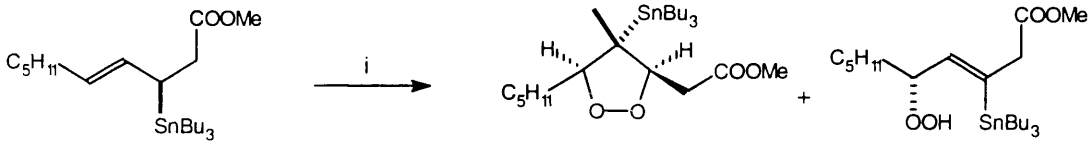
Further attempts to construct saturated carbon-carbon bonds used a Lewis acid-promoted reaction of a monoperoxyketal with an electron-rich alkene through a peroxycarbenium ion. Cyclic[7] and dialkyl[8] peroxides were synthesised in this manner and hydroperoxy ketals were found to undergo homologation to form 1,2-dioxolanes[9]. In work published after the present project was well advanced, as a model for synthetic approaches to the plakinic acids, Dussault synthesised a functionalised hydroperoxy ketal that furnished the trisubstituted 1,2-dioxolane (**4.12**) in a yield of 12%. Other attempts to produce the substituted 1,2-dioxolanes found in the plakinic acids used the reaction of singlet oxygenation with alkoxyalkyl stannanes as discussed in Chapter 2. Photooxygenation of the alkene containing an ester functionality

functionality led to the synthesis of the 1,2-dioxolane with a carboxy methyl group in the 3 position along with the corresponding ene product[10] (**Scheme 4.6**).



4.11 **4.12**

i) $SnCl_4$/ CH_2=$CHCH_2SiMe_3$

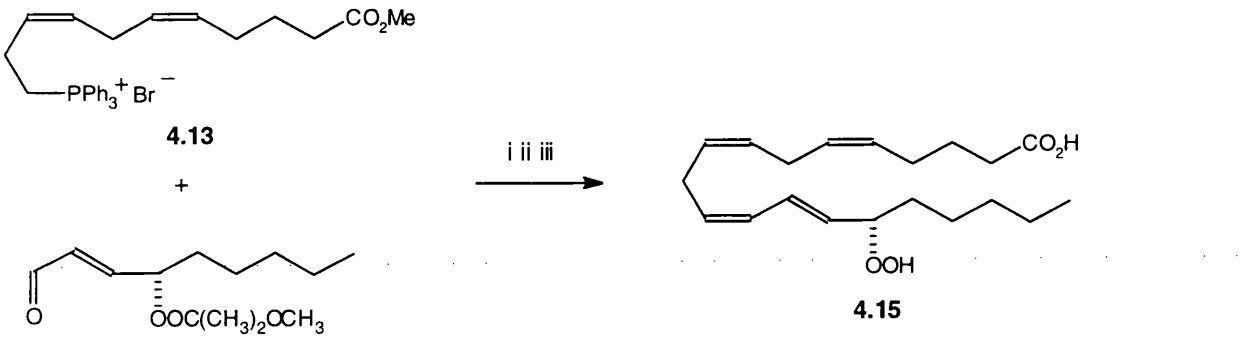


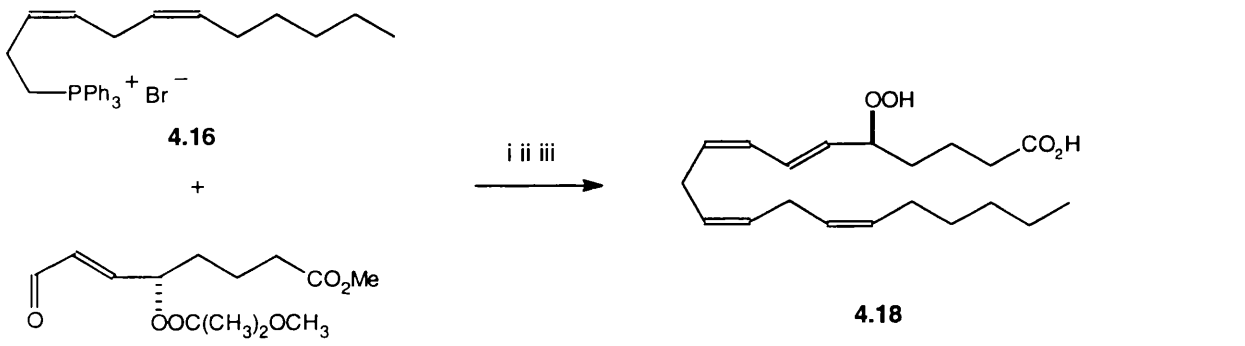
11 % 56 %

i) TPP/ DCM O_2

Scheme 4.6

Other work by Dussault adopted an olefination-based route[11] leading to the total synthesis of enantiomerically pure 15 (S)-(**4.15**)[12] and 5(S)-(**4.18**)[13]. In both cases the final step incorporated coupling of two intermediates (**4.13** to **4.14** and **4.16** to **4.17**) by a Wittig reaction (**Scheme 4.7**).

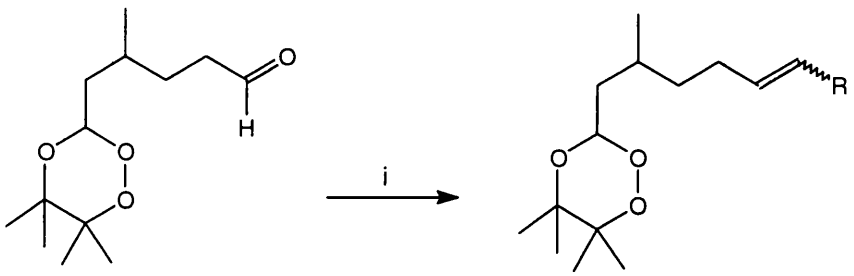




i) $LiN(SiMe_3)_2$ THF/ HMPA ii) AcOH/ H_2O iii) LiOH/ H_2O/ THF

Scheme 4.7

Using a similar approach Bloodworth and co-workers successfully carried out chain homologation, via Wittig methodology, in the presence of a trioxane ring[14] (**Scheme 4.8**).

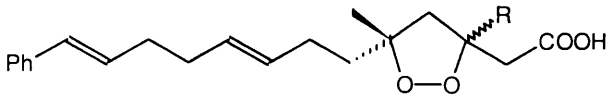


i) $RCH_2PPh_3^+ Br^-$ BuLi R= Bu, 4-Me C_6H_4

Scheme 4.8

Approach to the Synthesis of the Plakinic Acids

The plakinic and epiplakinic acids (**1.16-21**), have several common structural features which include a similarly constructed side chain as well as the functionalised 1,2-dioxolane ring. The hydrophobic chains R^1 differ in length, from C-8 to C-12, and in the positioning and number of methyl substituents found in the chain. However they all terminate with a phenyl ring and contain two double bonds α and ε to the phenyl. As a model for our synthetic approach to the various plakinic acids we attempted the synthesis of an analogue (**4.19**) that incorporated only the features common to all the plakinic acids (**1.16-21**).

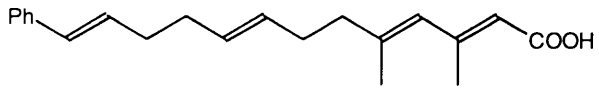


4.19

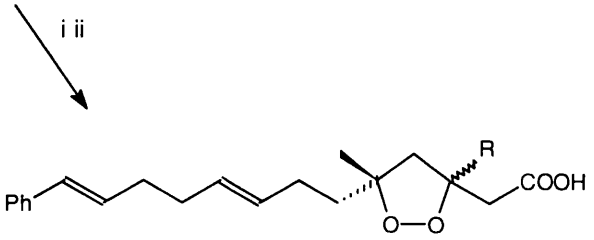
R= α or β CH_3

Disconnection strategy

Two disconnection strategies were considered, each maintaining the peroxymercuriation route to the 1,2-dioxolane and the one-step synthesis of the αβ γδ-unsaturated acid that we have developed. The first approach, which was always considered a high risk, incorporated dioxolane synthesis as the final step. This would therefore involve synthesis of the tetraene (**4.20**) followed by peroxymercuriation (**Scheme 4.9**). However from our work on the diene esters (**3.52** and **3.56**) we know that synthesis of our target 1,2-dioxolanes, through peroxymercuriation, is not possible when the hydrocarbon side chain contains unsaturation (see page 66).



4.20



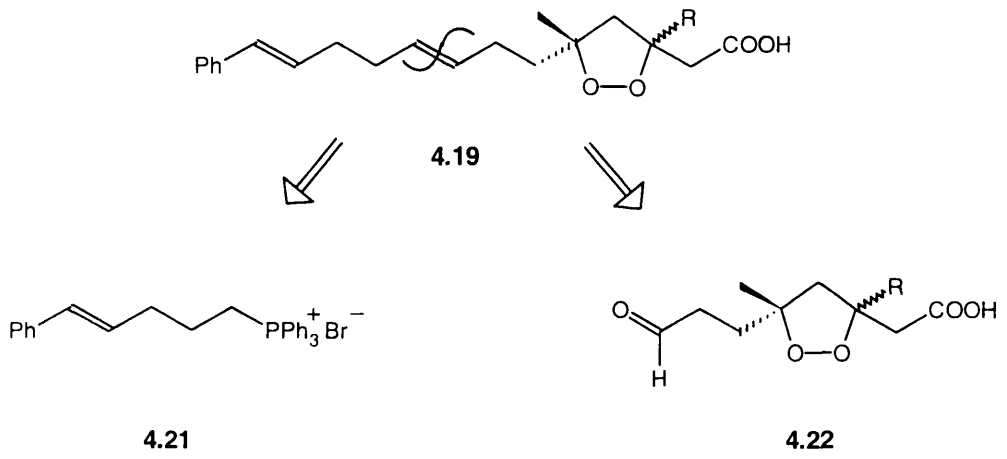
4.19

R= α or β CH_3

i) $Hg(OAc)_2$ 30% H_2O_2 ii) $NaBH_4$/NaOH/ DCM

Scheme 4.9

Using Dussault's and Blooodworths work as a precedent, our second thoughts centred on a final step involving the joining of two intermediates, one containing the target 1,2-dioxolane moiety. Disconnection of (**4.19**) across the C^8-C^9 double bond generates two synthons that can be coupled by a Wittig reaction. In theory either half could be the phosphonium salt but the favoured approach was to synthesise the phosphonium salt as the left hand portion (**4.21**) leaving the 1,2-dioxolane synthon (**4.22**) to bear the aldehyde functionality (**Scheme 4.10**).

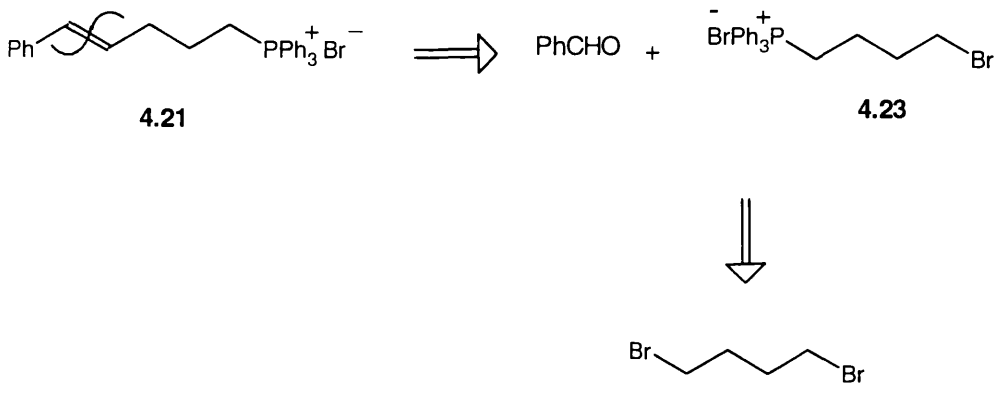


R= α or β CH_3

Scheme 4.10

Synthesis of the left hand fragment

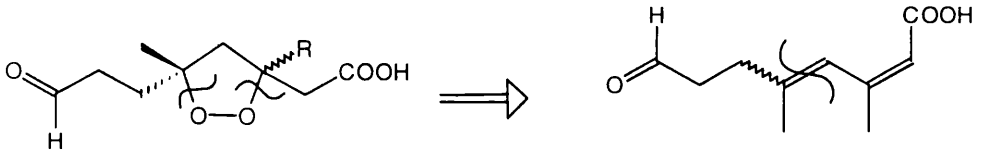
This is the least structurally complex of the two portions and further disconnection of the molecule indicates a facile synthesis from 1,4-dibromobutane (**Scheme 4.11**).



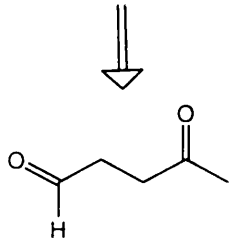
Scheme 4.11

Synthesis of the right hand fragment

Synthesis of the second half of the molecule is less straightforward. Using peroxymercuriation as the method of assembly of the 1,2-dioxolane, disconnection of (**4.22**) generates the diene acid (**4.24**) which in turn, disconnects to the dicarbonyl methyl ketone (**4.25**) required when using our established method of 2Z-diene acid synthesis (**Scheme 4.12**).



4.22 **4.24**

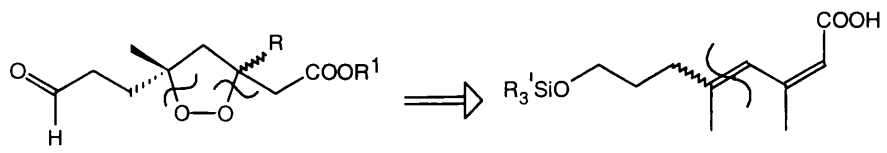


4.25

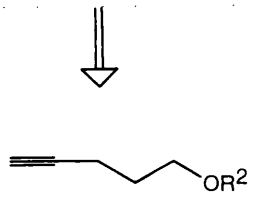
R = α or β CH_3

Scheme 4.12

Introduction of the aldehyde at the very beginning of the synthesis of (**4.22**) is undesirable and would complicate all subsequent reactions. Masking of the aldehyde moiety prior to the final Wittig coupling would help to avoid unwanted side reactions. This could be achieved through the use of a conventional aldehyde protecting group or by performing a functional group interconversion once the 1,2-dioxolane is in place. The latter was the preferred route and one way to accomplish this would be to camouflage the aldehyde as a silyl ether (**Route 1**). We imagined the methyl ketone, required for the synthesis of the diene acid substrate (**4.26**), could be made from pent-4-yn-1ol, with protection of the alcohol taking place either before or after conversion of the alkyne to the ketone (**Scheme 4.13**). The methyl ketone would then undergo condensation with dimethyl acrylate to give the 2Z-diene acid. Esterification at this stage would be advantageous to facilitate the final Wittig coupling. Following peroxymercuriation of the diene acid the hydroxyl group would be revealed with TBAF and oxidised to the desired aldehyde (**4.22**).



4.22 **4.26**

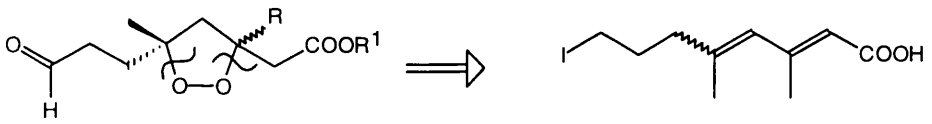


4.27

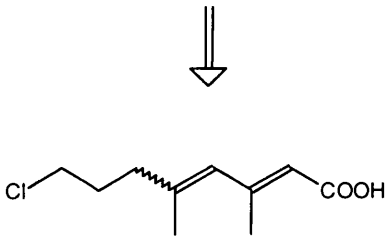
R = α or β CH_3 R^1 = alkyl R^2=H or SiR'_3

Route One Scheme 4.13

Alternatively we could perform peroxymercuriation/ demercuriation on an iodo substituted diene acid (**4.25**). This would generate a 1,2-dioxolane with an iodo moiety in the alkyl side chain which could undergo functional group interconversion to an aldehyde (**Route 2**). The iodo diene acid is easily made from the chloro diene acid (**3.75**) which we prepared previously (**Scheme 4.14**).



4.22 **4.28**



3.75

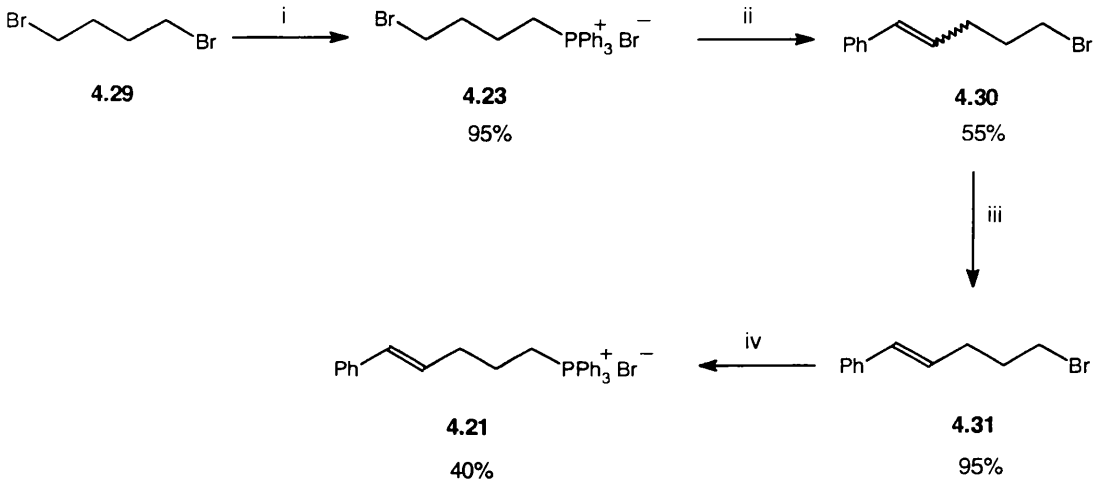
R^1 = alkyl R = α or β CH_3

Route Two Scheme 4.14

RESULTS AND DISCUSSION

Synthesis of the Left Hand Fragment

Synthesis of (**4.21**) was effected in a four step procedure. The ω-unsaturated bromide (**4.30**) was synthesised by a Wittig reaction[15] of the ω-bromoalkyltriphenylphosphonium salt (**4.23**)[16] with benzaldehyde in an overall yield of 53% and with a ratio of 1:1 E:Z. Complete isomerisation of (**4.30**) to the E isomer (**4.31**) by refluxing with a catalytic amount of thiophenol* brought the intermediate in line with the analogous double bond found in the plakinic acids. Conversion of (**4.31**) to the phosphonium salt (**4.21**) completed the synthesis of the left hand fragment (**Scheme 4.15**).



i) Butanone/ PPh_3 ii) NaOH/ DCM/ H_2O PhCHO iii) PhSH/ CCl_4 iv) Toluene/ PPh_3

Scheme 4.15

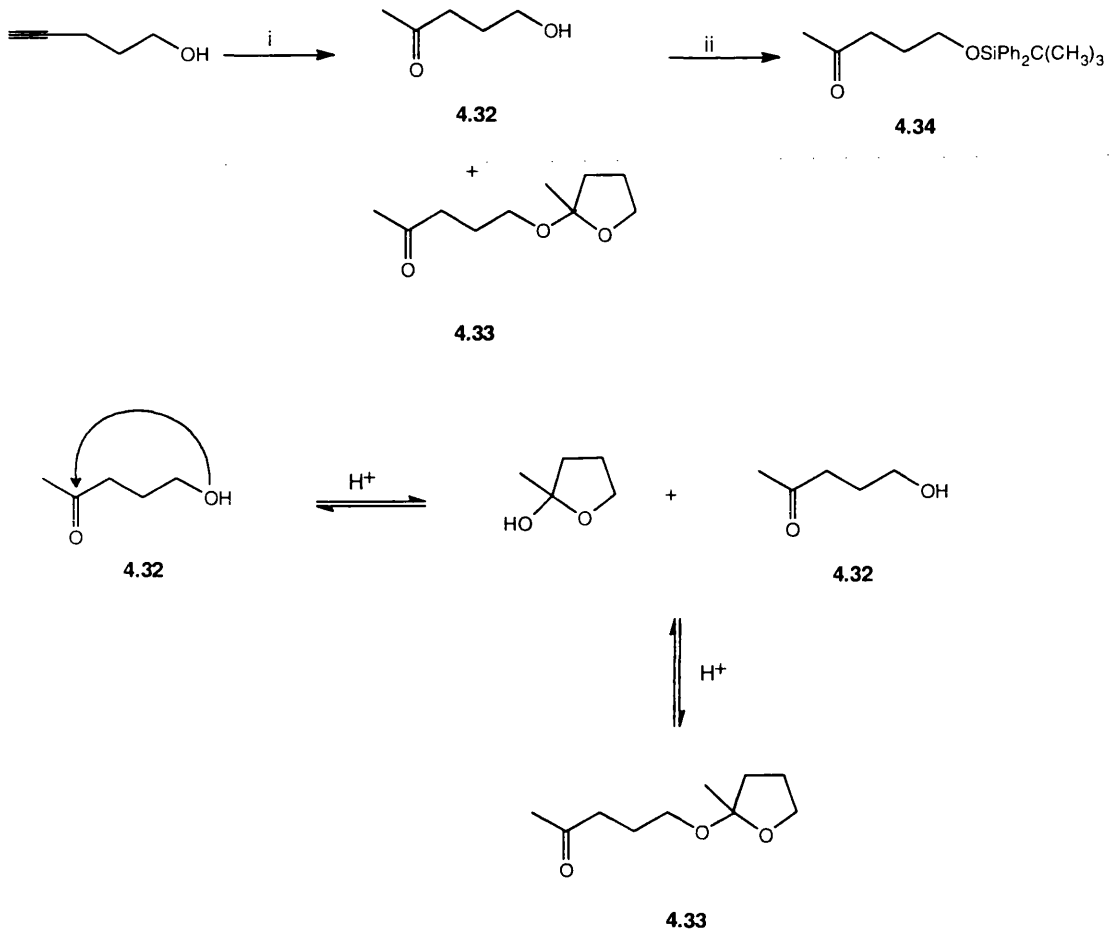
Synthesis of the Right Hand Fragment by Route One

Synthesis of the Methyl Ketone (4.34)

The hydration of terminal triple bonds using mercury(II) salts as the catalyst generally gives methyl ketones and has been reported to be successful when the molecule contains a hydroxyl group[17]. Treatment of pent-4-yne-1-ol with mercury(II) sulfate and 4% sulfuric acid in water gave a mixture of two products which could not be separated by column chromatography. The ^1H NMR indicated the presence of the desired methyl ketone (**4.32**) and another, major product which was identified as (**4.33**). We believe the acetal (**4.33**) was formed by an acid catalysed intramolecular addition of the alcohol to the ketone followed by an intermolecular addition of (**4.32**) to the hemiacetal. Separation of the mixture was achieved

* See ref 14d Chapter 3

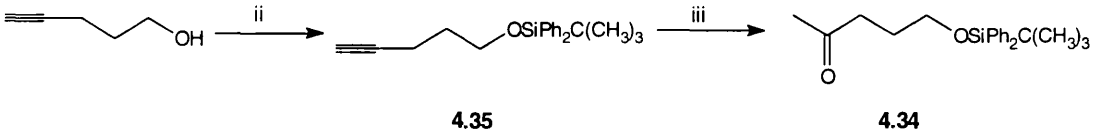
after silylation with TBDPSCl[18] to give the methyl ketone (**4.34**) in an overall yield of 33%. (**Scheme 4.16**).



i) $HgSO_4$/ H_2SO_4/H_2O ii) DMF/ Imidazole/ TBDPSCl

Scheme 4.16

In an attempt to improve the overall yield we reversed the order of silylation and hydration. Silylation of pent-4-yn-1ol using the same procedure as above gave (**4.35**) in a quantitative yield. Hydration of this intermediate under aqueous conditions was unsuccessful due to the insolubility of (**4.35**). However, modification of the reaction conditions to a two phase system of ether and water combined with vigorous stirring furnished a quantitative yield of the methyl ketone (**4.34**) after 2 days (**Scheme 4.17**).

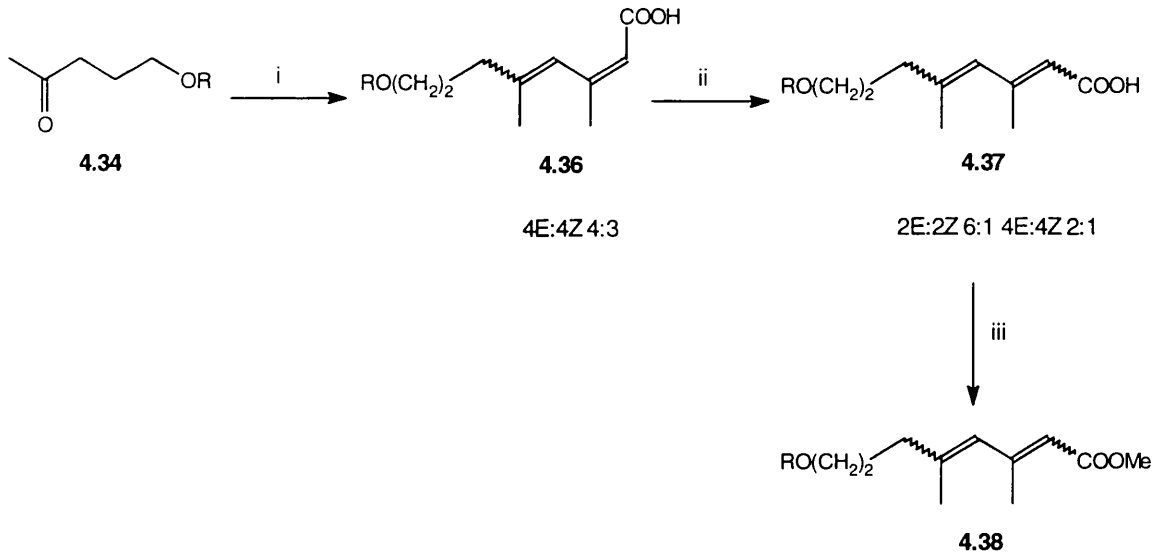


ii) DMF/ Imidazole/ TBDPSCl iii) $HgSO_4$/ H_2SO_4/H_2O/ Et_2O

Scheme 4.17

Synthesis of the Diene Acid (4.37) and Ester (4.38)

The diene acid was prepared from the methyl ketone (**4.34**) following procedure III[†] in a yield of 55%. Attempts to increase the yield of the diene acid by employing procedure IV resulted in the isolation of the diene acid in a slightly improved yield of 65%. Thiophenol-catalysed isomerisation of the diene acid under the usual conditions of refluxing for 2 hours resulted in partial decomposition of the diene acid. After reducing the reaction time to 45 minutes the diene acid (**4.37**)was isolated with little evidence of decomposition with a 2*E*:2*Z* ratio of, 6:1 and a 4*E*:4*Z* ratio of 2:1. Finally, conversion of the diene acid to the corresponding methyl ester (**4.38**) was accomplished by reaction with trimethyloxonium tetrafluroborate[‡] (**Scheme 4.18**). Synthesis of the methyl ester was necessary because the carboxylic acid proton, in the final Wittig coupling, would quench the preformed ylid converting it back to the phosphonium salt (**4.21**).



4.34 **4.36** **4.37**

4E:4Z 4:3

2E:2Z 6:1 4E:4Z 2:1

4.38

i) 2 mol equiv LDA/ $(CH_3)_2C{:}CHCO_2Et$/ THF / -70^0 C to 25^0 C ii) PhSH/ CCl_4

iii) Me_3OBF_4/ N,N-diisopropylethylamine/ DCM

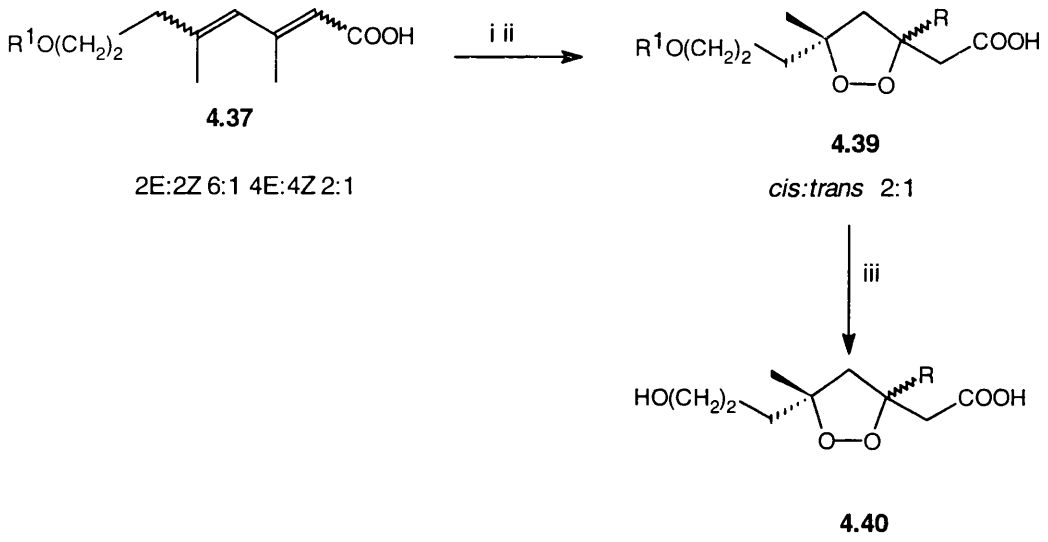
Scheme 4.18

[†] See Chapter 3 page 59

[‡] See Chapter 3 ref 20

Peroxymercuriation/ Demercuriation of the Diene Acid (4.37) and Ester (4.38)

Peroxymercuriation of the diene acid (**4.37**) was carried out under standard conditions. However, following demercuriation an emulsion of the aqueous and organic phases formed. The emulsion was cooled in an ice bath and acidified by dropwise addition of 1M HCl which enabled separation of the two phases. The desired 1,2-dioxolane was found in the organic phase of the reaction mixture, along with the methyl ketone (**4.34**) and other unidentified side products. Purification by column chromatography resulted in a 9% overall yield of the silyloxyalkyl 1,2-dioxolane (**4.39**). Exposure of the hydroxyl by TBAF-desilylation led to the recovery of the hydroxy alkyl 1,2-dioxolane (**4.40**) in a 50% yield. The reduced yield was thought to be due to the water solubility of (**4.40**) (**Scheme 4.19**).



4.37

2E:2Z 6:1 4E:4Z 2:1

4.39

cis:trans 2:1

4.40

R = α or β CH_3 R^1=$SiPh_2C(CH_3)_3$

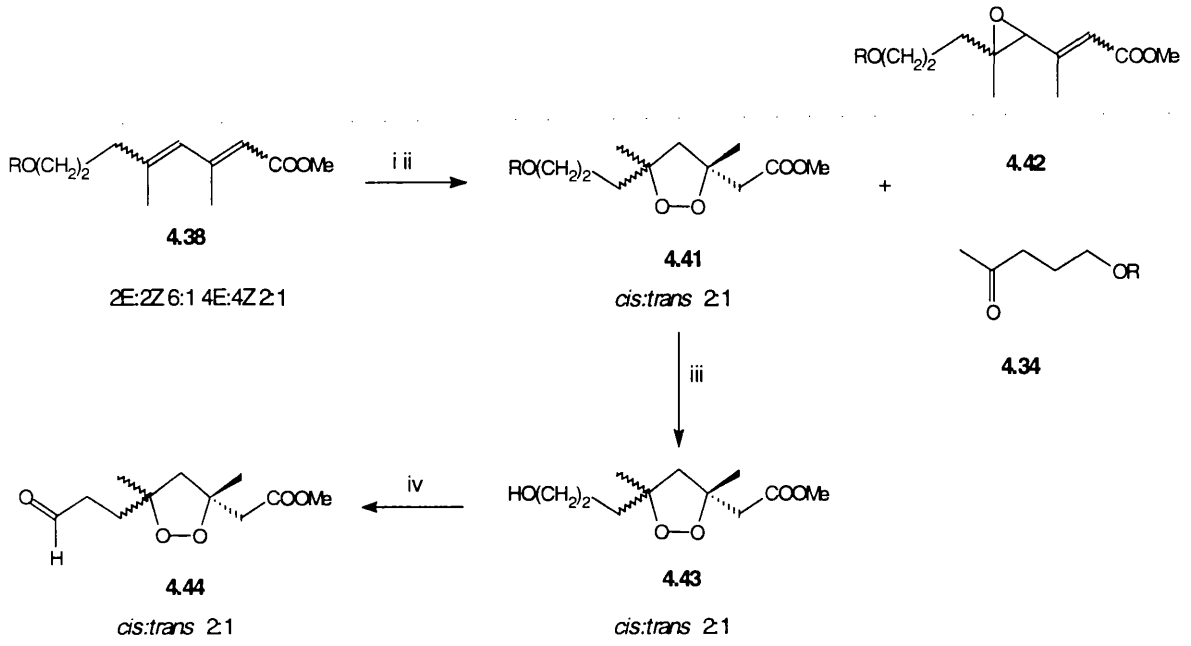
i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM iii) TBAF/ THF

Scheme 4.19

Peroxymercuriation/ demercuriation of the diene ester (**4.38**) followed by TBAF desilylation gave the hydroxy 1,2-dioxolane (**4.42**) in an overall yield of 12 %, as a 2:1 ratio of *cis* and *trans* (see spectra page 159)

Following demercuriation of the crude peroxymercuriated reaction of (**4.38**), evaporation of the DCM revealed a mixture of three products, detected by tlc, in a yield amounting to 75% of the mass of the starting diene ester. Analysis by ^{1}H NMR of this mixture of reactant products suggested the two side products, to be the methyl ketone (**4.34**) and the δγ-epoxy αβ-unsaturated carboxylate (**4.42**) in line with the experimental results noted in chapter 3). Finally

in this sequence pyridinium dichromate oxidation[19] of the alcohol (**4.43**) to the aldehyde supplied the 1,2-dioxolane (**4.44**) in a 55% yield (**Scheme 4.20**).



R=$SiPh_2C(CH_3)_3$

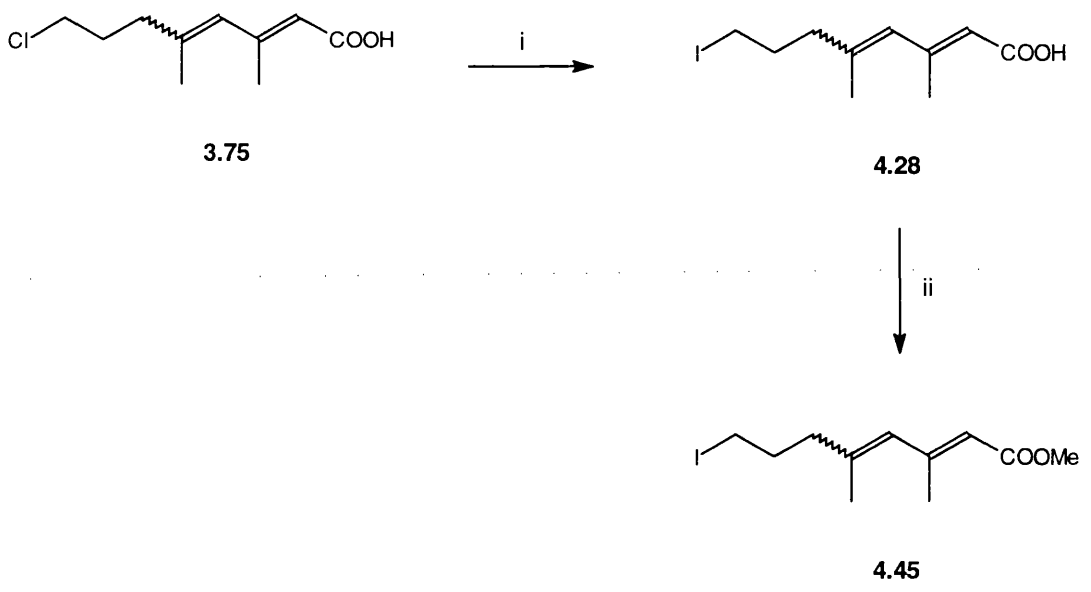
i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM iii) TBAF/ THF iv) PDC/ DCM

Scheme 4.20

Synthesis of the Right Hand Fragment by Route Two

Synthesis of the Iodo Diene Ester (4.45)

Although we made the desired 1,2-dioxolane (**4.44**) using Route One the peroxymercuriation/ demercuriation step led to a significant reduction in yield, so our attention turned towards Route Two. We know from previous work (see pg 70) that the chloro-substituted diene acid (**3.75**) gives the corresponding 1,2-dioxolane (**3.82**) in a yield of 30% and we imagined the iodo-substituted diene acid would react similarly. Synthesis of the the iodo diene methyl ester (**4.45**) was achieved in a two step procedure. Reaction of the chloro substituted diene ester (**3.75**) in refluxing acetone with NaI followed by esterification using the trimethyloxonium method furnished (**4.45**) in an overall yield of 80% (**Scheme 4.21**).



3.75 **4.28** **4.45**

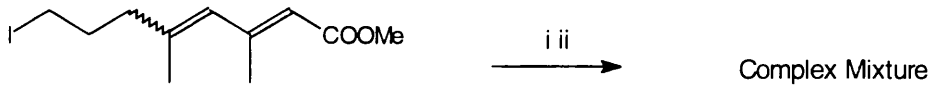
i) Acetone/ NaI/ reflux ii) Me_3OBF_4/ N,N-diisopropylethylamine/ DCM

Scheme 4.21

Peroxymercuriation/ Demercuriation of the Iodo-Diene Ester

The diene ester (**4.45**) was treated using standard peroxymercuriation conditions and stirred overnight. Peroxymercuriation reactions of the diene carboxylates generally gives a colourless reaction mixture after stirring overnight but in this case an orange yellow precipitate was observed. Demercuriation of the crude reaction mixture was carried out as usual and tlc indicated a complex reaction mixture. Attempts to separate the only peroxide positive component by column chromatography resulted in a partial separation and analysis by ^{1}H NMR of this fraction did not show signals consistent with the desired 1,2-dioxolane (**Scheme 4.22**). One explanation for the observed results is suggested by considering the possibility of nucleophilic substitution reactions on the alkyl iodide. Alkyl hydroperoxides have been synthesised by nucleophilic displacement of halide from alkyl bromides and chlorides assisted by silver salts using high strength H_2O_2[20]. In our case a similar substitution reaction could possibly have occurred, assisted by mercury(II) acetate behaving as a Lewis acid. To assess this theory we repeated the experiment but using 0.5 mole equivalents of mercury(II) acetate. The same insoluble orange precipitate appeared and after work up of the reaction mixture we noticed a considerable weight loss which is consistent with the loss of iodine from the molecule. Analysis of the ^{1}H NMR spectra of the crude reaction product indicated a mixture. The spectra did not exhibit signals corresponding to the protons of CH_2-I found at δ3.1-3.2 ppm, which are present in the spectra of the starting diene ester, but showed a

complex multiplet further downfield at δ3.7-4.0 ppm suggesting the incorporation of (per) oxygen substituents. In light of these results Route Two was abandoned.



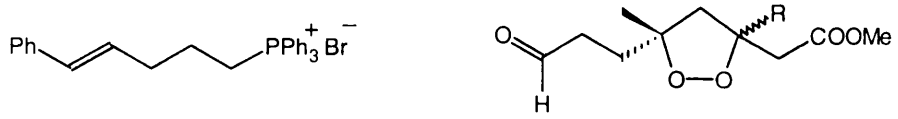
4.45

i) 30% H_2O_2/ $Hg(OAc)_2$ ii)$NaBH_4$/ ^-OH/ DCM

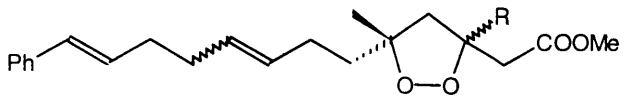
Scheme 4.22

Wittig Coupling of the Right and Left Hand Fragments

The final Wittig coupling of the two fragments (**4.21** and **4.44**) was attempted. Treatment of (**4.21**) with n-butyllithium in dry THF at -70 ^{0}C under an atmosphere of nitrogen followed by warming to 10 ^{0}C with stirring for one hour produced a clear deep orange/ red reaction mixture indicating formation of the ylid. On recooling to -70 ^{0}C the 1,2-dioxolane was introduced as a solution in dry THF. No reaction was observed whilst the temperature of the reaction mixture was maintained at -70 ^{0}C but on warming a cream precipitate appeared. After stirring at room temperature for a further 30 minutes the THF was evaporated *in vacuo* and the crude oil extracted with hexane. Analysis of the crude material by ^{1}H NMR indicated that it contained predominantly the desired material and purification by column chromatography led to the isolation of (**4.46**) in a yield of 26 % (**Scheme 4.23**).



4.21 **4.44**

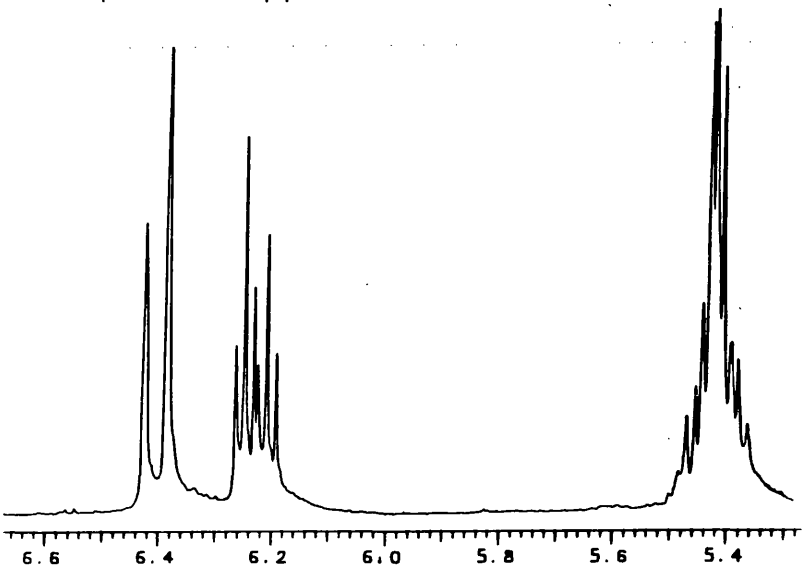


4.46

i) BuLi/ diisopropylamine/ THF

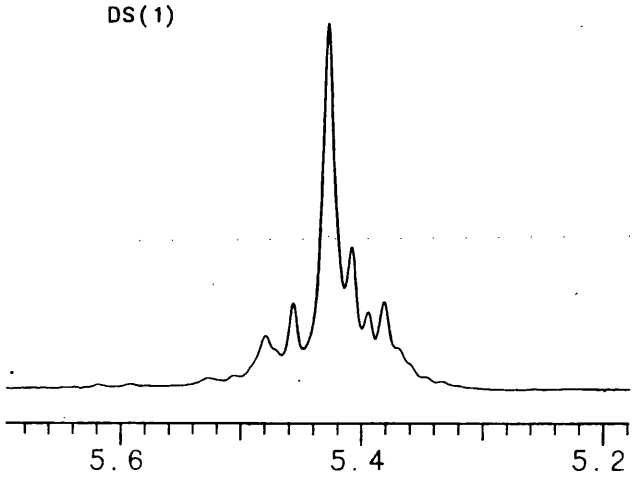
Scheme 4.23

The ^{1}H NMR spectra of (**4.46** see page 160) exhibited the characteristic AB doublets of the $C^{4}H_2$ and $C^{2}H_2$ protons although the signals assigned to the allylic CH_2 overlap in the region δ2.0-2.2 ppm. The olefinic protons are found further downfield with the 2 protons of the newly formed medial olefin resonating at around δ5.45 ppm, which is in line with the data reported by Davidson for the plakinic and epiplanikic acids.



He noted how the two signals for $C^{12}H$ and $C^{13}H$ in (**1.23**) overlapped in a 200 MHz spectra and were only partially resolved in a 500 MHz spectra and decoupling experiments were carried out to determine the stereochemistry of the double bond. He found that after irradiation of the adjacent methylene groups the signal for each proton collapsed to a broad doublet (J = 15.5 Hz) indicating a *trans* orientation.

The ^{13}C NMR of (**4.46** see spectra page 161) suggests the stereochemistry of the C^{8}-C^{9} double bond to be a mixture of cis and trans. Ten signals are present in the region of δ140-125 ppm; four signals can be assigned to the phenyl ring and two correspond to the C^{12}-C^{13} double bond which leaves four signals to be assigned to the C^{8}-C^{9} double bond. In an attempt to determine the cis:trans ratio of the C^{8}-C^{9} double bond we we carried out a decoupling experiment. The multiplet at δ5.45 ppm in our spectra is shown overleaf along with the results of the decoupling experiment. Irradiation of the methylene $C^{7}H_2$ adjacent to $C^{8}H$ led to the collapse of the multiplet to the signal shown in DS1. Although the multiplet was simplified the result of this 1H NMR experiment is inconclusive and provides no evidence of the cis:trans ratio of the C^{8}-C^{9} double bond.



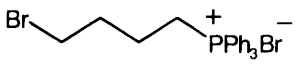
To conclude, although (**4.46**) was not made in exclusively trans stereochemistry around the medial double bond, we have shown how the methodology adopted here provides a route to the total synthesis of the plakinic and epiplakinic acids (**1.16-1.21**) acids. The functionalised 1,2-dioxolane common to all the natural products (**1.66-1.22a-e**), can be synthesised frm the peroxymercuriation/ demercuriation reaction, we developed, of an appropriately substituted 2,4-diene carboxylate. This cyclic peroxide is robust enough to withstand several functional group interconversions and homologation of the C^5 side chain, providing a method of synthesis of the marine sponge secondary metabolites.

EXPERIMENTAL

Synthesis of the Left Hand Fragment (4.21)

Preparation of 4-bromobutyltriphenylphosphonium bromide (4.23)[15]

Triphenylphosphine (10 g, 38 mmol) and 1,4-dibromobutane (5.47 g, 3.02 ml, 25 mmol) were dissolved in butanone (70 ml) and heated under reflux for 18 hours. The reaction mixture was cooled to room temperature and then in an ice bath. The solid obtained was filtered off and washed with butanone to give 9.5 g (95%) of (**4.23**) as a white solid, Purification was by recrystalisation from water (80% recovery).



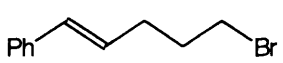
^{1}H NMR δ:8.02-7.63(15H, m, $(C_6\mathbf{H}_5)_3$)
4.05-3.80(2H, m, $C\mathbf{H}_2P$),
3.60(2H, t, J=8.3, $C\mathbf{H}_2Br$)
2.40-2.25(2H, m, $C\mathbf{H}_2CH_2P$)
1.93-1.75(2H, m, $C\mathbf{H}_2CH_2Br$).

MP ^{0}C 208-210

Preparation of (*E,Z*)-1-phenyl-5-bromopenta-1-ene (4.30)[16]

The phosphonium salt (**4.23**) (21.03 g, 44 mmol), benzaldehyde (4.24 g, 4.06 ml, 40 mmol) and powdered NaOH (2.0 g, 50 mmol) were added to DCM (100 ml plus a couple of drops of water) and the resulting suspension was stirred at reflux for 18 hours. The reaction mixture was cooled to room temperature, diluted with DCM (50 ml) and washed with water (3x 100 ml). The organic portion was dried ($MgSO_4$) and evaporated *in vacuo* to give 5.5 g of a yellow oil. Purification by column chromatography (SiO_2, Hexane) gave 5.0 g (55%) of (**4.30**) a clear oil. The ratio of *E* and *Z* isomers was 1:1.

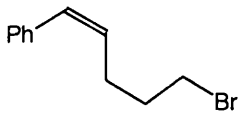
E Isomer



^{1}H NMR δ:7.37-7.21(5H, m, $C_6\mathbf{H}_5$)
6.46(1H, d, J=16, Ph**H**C=)
6.19(1H, dt, J=16, J=6, C=C**H**)
3.47(2H, t, J=7, $C\mathbf{H}_2Br$), 2.40(2H, br q, J=6, $C\mathbf{H}_2C$=), 2.08-2.02(2H, m, $C\mathbf{H}_2$).

^{13}C NMR δ:137.05, 128.50, 127.25 and 126.05($\mathbf{C}_6H_5$), 131.30 and 128.40(**C**=**C**),
32.90, 32.25 and 31.30(3x$C\mathbf{H}_2$)

Z Isomer



^{1}H NMR δ:7.37-7.21(5H, m, $C_6\mathbf{H}_5$)
6.50(1H, d, J=12, Ph**H**C=)
5.61(1H, dt, J=12, J=6, C=C**H**)
3.44(2H, t, J=8 $C\mathbf{H}_2$Br), 2.51(2H, br q, J=6, $C\mathbf{H}_2$C=), 2.1-1.97(2H, m, $C\mathbf{H}_2$)

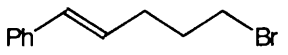
^{13}C NMR δ:137.05, 128.50, 127.15, 126.05($\mathbf{C}_6H_5$), 130.50 and 130.25(**C**=**C**),
33.20, 30.30 and 27.20(3x$\mathbf{C}H_2$)

MS(EI): $(M+2)^+$226 $(M)^+$224 (M^+-Br)145

Preparation of (*E*)-1-phenyl-5-bromopenta-1-ene (4.31)

(*E*,*Z*)-1-phenyl-5-bromopenta-1-ene (**4.30**) (2 g, 8.9 mmol) and thiophenol (1 drop) were dissolved in CCl_4 (60 ml) and heated under reflux for 3 hours. The solvent was evaporated *in vacuo*. Purification by vacuum distillation gave 1.9 g of the E isomer (**4.31**) (95%) as a colourless oil, b.p. 116 ^{0}C 0.5 mmHg.

^{1}H NMR δ:As above



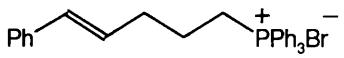
^{13}C NMR δ:As above

Analysis Found: C,58.59; H,5.75; Br,36.07. Calc for $C_{11}H_{13}Br$: C,58.68; H,5.82; Br,35.49 %.

Preparation of (*E*)-5-phenyl-pent-4-en-1yltriphenylphosphoniumbromide (4.21)

Under an atmosphere of nitrogen (**4.31**) (1.5 g, 6.6 mmol) and triphenylphosphine (1.9 g, 7.3 mmol) were dissolved in dry toluene (20 ml) and refluxed for 5 hours. The toluene was evaporated *in vacuo* to leave a glassy white solid. Purification by recrystalization from acetonitrile gave 1.2 g (40%) of (**4.21**) as pale yellow needles.

^{1}H NMR δ:7.87-7.65(15H, m, $(C_6\mathbf{H}_5)_3$),



7.30-7.16(5H, m, $C_6\mathbf{H}_5$),
6.44(1H, d, J=16, Ph**H**C=),
6.09(1H, dt, J=16, J=7, C=C**H**), 3.91(2H, m, $C\mathbf{H}_2$P),
2.62(2H, q, J=7, $C\mathbf{H}_2$C=), 2.85-1.75(2H, m, $C\mathbf{H}_2$)

^{13}C NMR δ:137.0, 128.50, 127.10 and 126.05($\mathbf{C}_6H_5$), 131.30, 128.40(**C**=**C**),
32.90, 32.20 and 31.35(3x$\mathbf{C}H_2$)

MS(EI).: $(M-HBr)^+$407

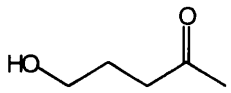
Analysis Found: C,68.95; H,5.84; Br,16.91.$C_{29}H_{28}BrP$ requires: C,71.49; H,5.79; Br,16.91 %.

Synthesis of the Right Hand Fragment (4.44)

Route One

Preparation of 5-hydroxypentan-2-one (4.32)[17a]

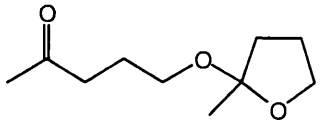
Pent-4-yn-1-ol (2.52 g, 2.776 ml, 30 mmol) was dissolved in water (20 ml) with a catalytic amount of $HgSO_4$ (0.134 g, 0.45 mmol). A 4% sulfuric acid solution (7.5 ml, 3 mmol) was added dropwise not allowing the temperature to exceed 25 ^{0}C and the mixture was stirred for 3 days. The reaction mixture was taken to pH 6.5 by the addition of $CaCO_3$ filtered and extracted with EtOAc (4x 20 ml). The organic portions were combined, dried ($MgSO_4$), and evaporated *in vacuo* to give 2.57 g, of a clear oil. Purification by column chromatography (SiO_2, Hex:EtOAc 1:1) gave, 2.4 g, of a colourless oil which contained the desired ketone (**4.32**) mixed with acetal (**4.33**).



^{1}H NMR δ:3.59(2H, t, J=6, C**H**$_2$OH)
2.54(2H, t, J=10, C**H**$_2$C=O)
2.13(3H, s, C**H**$_3$CO) 1.60-2.0(2H, m, C**H**$_2$).

^{13}C NMR δ:208.35(**C**=O), 62.45(**C**H$_2$OH), 41.60(**C**H$_2$CO), 30.40(**C**H$_3$CO), 27.05(**C**H$_2$).

MS(EI): $(M-H)^+$101 $(M-OH)^+$85



^{1}H NMR δ:3.88-3.72(2H, m, C**H**$_2$O ring)
3.42-3.31(2H, m, C**H**$_2$OC chain)
2.44(2H, t, J=10, C**H**$_2$C=O)
2.09(3H, s, C**H**$_3$CO)
1.6-2.0(6H, m, C**H**$_2$ (C**H**$_2$)$_2$), 1.4(3H, s, C**H**$_3$C-O) .

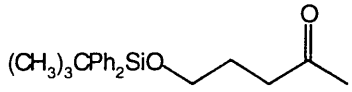
^{13}C NMR δ:208.35(**C**=O) 108.25(O-**C**-O), 64.00(**C**H$_2$O ring), 60.05(**C**H$_2$O chain), 41.35(**C**H$_2$C=O), 30.50(**C**H$_3$C=O), 27.65(**C**H$_2$), 24.10 and 24.40(**C**H$_2$ ring), 22.05(**C**H$_3$)

MS(EI): $(M-CH_3O)^+$155 $(M-CH_3C=O(CH)_2)^+$115

MS(FAB): (M+1)187

Preparation of 5-t-butyldiphenylsilyloxypentan-2-one (4.34)[18]

A mixture of the hydroxy ketone (**4.32**)and the acetal (**4.33**) (0.5 g, 5 mmol), t-butyldiphenyl silyl chloride (1.45 g, 1.38 ml, 5 mmol) and imidazole (0.272 g, 10 mmol) were dissolved in dimethyl formamide (2 ml) and stirred for 18 hours. The reaction mixture was then diluted with 1M HCl (15 ml) and extracted with ether (4x 15 ml). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give, 1.5 g of a clear oil. Purification by vacuum distillation gave 0.51 g, 33% yield, of (**4.34**) as a colourless oil b.p. 165 ^{0}C 0.15 mm Hg.



^{1}H NMR δ:7.65-7.34(10H, m, **C**$_6$H$_5$)
3.66(2H, t, J=6, C**H**$_2$O)
2.53(2H, t, J=7, C**H**$_2$C=O)
2.12(3H, s, C**H**$_3$CO), 1.85-1.79(2H, m, C**H**$_2$), 1.09(9H, s, (C**H**$_3$)$_3$).

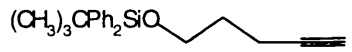
^{13}C NMR δ:209.05(**C**=O), 135.05, 130.20,128.35 and 134.30(**C**$_6$H$_5$), 63.00(**C**H$_2$OH), 40.25(**C**H$_2$CO), 30.35(**C**H$_3$CO), 26.90(3x**C**H$_3$), 26.60(**C**H$_2$), 19.20(**C**(CH$_3$)$_3$)

MS(EI): (M-t-Bu)$^+$283

IR(neat): 2943(vs),2871(vs),1717(vs),1471(vs),1092(vs).

Preparation of 5-t-butyldiphenylsilyloxypent-1-yne (4.35)[18]

Pent-4-yn-1-ol (7.45 g, 84 mmol), t-butyl diphenylsilylchloride (23.15 g, 84 mmol) and imidazole (11.4 g, 168 mmol) were dissolved in DMF (25 ml) and stirred for 18 hours. The reaction mixture was diluted with ether (100 ml) and washed with 1M HCl (3x60 ml) and brine (60 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 26 g (96%) of (**4.35**) as a colourless oil that required no further purification.



^{1}H NMR δ:7.65-7.34(10H, m, C$_6$**H**$_5$)
3.76(2H, t, J=6, C**H**$_2$O),
2.37(2H, dt, J$_1$=8, J$_2$=2, C**H**$_2$CCH), 1.94(1H, t, J=2, CC**H**)
1.82-1.75(2H, m, C**H**$_2$), 1.09(9H, s, (C**H**$_3$)$_3$).

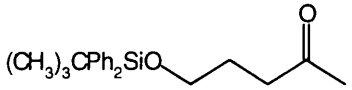
^{13}C NMR δ:135.05, 130.20, 128.35 and 134.25(**C**$_6$H$_5$),
84.30 and 68.05(2C, **CC**H), 62.60(**C**H$_2$OH), 32.25(**C**H$_2$), 26.90((**C**H$_3$)$_3$),
19.05(**C**(CH$_3$)$_3$), 15.30(**C**H$_2$CCH).

MS(EI): (M-t-Bu)$^+$266

IR neat: 2943(vs),2871(vs),1717(vs),1471(vs),1092(vs).

Preparation of 5-t-butyldiphenylsilyloxypentan-2-one (4.34)[17a]

The silyloxy alkyne (**4.34**) (21.0 g, 65 mmol) was added to a mixture of water (100 ml) and ether (100 ml). $HgSO_4$ (148 mg, 0.5 mmol) and 10% H_2S0_4(aq) (75 ml) were added and the reaction mixture was stirred vigorously for 18 hours. The ether layer was separated and washed with water (75 ml) and brine (75 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 21.1 g (95%) of (**4.34**) as a colourless oil requiring no further purification.



^{1}H NMR δ:As above

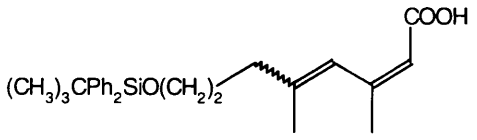
^{13}C NMR δ:As above

MS(EI): As above

Preparation of (2*Z*,4*E*) and (2*Z*,4*Z*)-8-t-butyldiphenylsilyloxy-3,5-dimethylocta-2,4-dienoic acid (4.36)

n-Butyl lithium (2M in hexane, 40 ml, 80 mmol) was added dropwise to a solution diisopropylamine (10.45 ml, 80 mmol) in dry THF (100 ml) under nitrogen at -78 ^{0}C. The yellow solution was stirred for 10 minutes then ethyl 3,3-dimethylacrylate (9.2 ml, 80mmol) was added dropwise. Stirring was continued for a further 20 minutes. The methyl ketone (**4.34**)(44mmol) in dry THF (20ml) was then added all at once. Stirring was continued at -78 ^{0}C for a further 5 minutes and then the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with sat NH_4Cl(aq) (80 ml) diluted with H_2O (150 ml) and extracted with ether (3x150 ml). The organic layers were combined and washed with H_2O (2x100ml) and brine (100ml), dried ($MgSO_4$) and evaporated *in vacuo* to give 20 g of a yellow oil. Purification by column chromatography (SiO_2, Hex:EtOAc 10:1) to collect starting materials; 5:1 to collect product gave 10.9 g (65%) of the diene acid (**4.37**) as a colourless oil The isomer ratio was (2*Z*,4*E*):(2*Z*,4*Z*) 4:3.

Both isomers



^{1}H NMR δ:7.7-7.60(4H, m, $C_6\mathbf{H}_5$)

7.43-7.31(6H, m, $C_6\mathbf{H}_5$)

6.40 and 6.32(1H, br s, $\mathbf{H}^4$)

5.69 and 5.63(1H, br s, $\mathbf{H}^2$)

3.69-3.60(2H, m, $ROC\mathbf{H}_2$), 2.22-2.15(2H, m, $C\mathbf{H}_2C{=}C$)

2.00 and 2.01(3H, $C^3C\mathbf{H}_3$), 1.72-1.6(2H, m, $C\mathbf{H}_2$)

1.80 and 1.70(3H, $C^5C\mathbf{H}_3$), 1.03(9H, s, $(C\mathbf{H}_3)_3$).

^{13}C NMR δ:172.05 and 171.50(**C**=O), 159.70 and 156.05(**C**=CCO_2H),
142.05($RO(CH_2)_3$**C**=C), 135.05, 134.20, 129.40 and 128.35($\mathbf{C}_6H_5$)
124.35 and 123.50($RO(CH_2)_3C$=**C**), 116.80 and 115.65(C=**C**CO_2H),
63.70 and 63.35($RO\mathbf{C}H_2$), 37.30, 31.80, 30.75, 30.20, 27.75, 25.80, 24.40
and 20.4 ($\mathbf{C}H_2\mathbf{C}H_2C$=C, $C^5\mathbf{C}H_3$,$C^3\mathbf{C}H_3$), 26.80(($\mathbf{C}H_3)_3$)
19.05 and 18.60($\mathbf{C}(CH_3)_3$)

MS(EI).: $(M\text{-t-Bu})^+$365

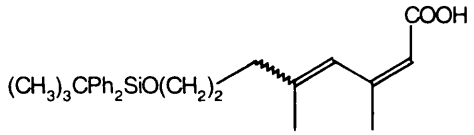
Preparation of (2*Z*,4*E*),(2*Z*,4*Z*),(2*E*,4*E*) and (2*E*,4*E*)-8-t-butyldiphenylsilyloxy-3,5-dimethylocta-2,4-dienoic acid (4.37)

The diene acid (**4.36**) (5.6 g, 13.3 mmol) was dissolved in CCl_4 (100 ml) and thiophenol (0.056 g, 4drops, 1% by weight) was added. The reaction mixture was heated under reflux for 45 minutes. The solvent and thiophenol were evaporated *in vacuo* to give 5.6 g,(100%) of (**4.37**) as a yellow oil and as a mixture of isomers with overall ratios of 2*E*:2*Z*, 6:1 and 4*E*:4*Z*, 2:1.

(2*Z*,4*E*),(2*Z*,4*Z*) Isomers

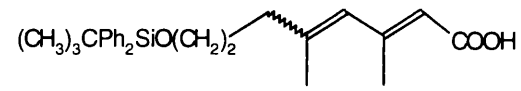
^{1}H NMR δ:As above

^{13}C NMR δ:As above



(2*E*,4*E*),(2*E*,4*Z*) Isomers

^{1}H NMR δ:7.66-7.64(4H, m, $C_6\mathbf{H}_5$)
7.40-7.34(6H, m, $C_6\mathbf{H}_5$)



5.72, 5.68 and 5.64(1H, $\mathbf{H}^4$, $\mathbf{H}^2$)), 3.67-3.63(2H, m, $RO\mathbf{C}H_2$)
2.31-2.26 and 2.19-2.15(2H, $C\mathbf{H}_2C$=C), 2.21(3H, s, $C^3C\mathbf{H}_3$)
1.79 and 1.77(3H, $C^5C\mathbf{H}_3$), 1.72 and 1.70(2H, m, $C\mathbf{H}_2$)
1.03(9H, s, $(C\mathbf{H}_3)_3$).

All Isomers

^{13}C NMR δ:172.05(**C**=O), 156.90 and 157.15(**C**=CCO_2H), 142.70($RO(CH_2)_3$**C**=C)
135.05, 134.20, 129.40 and 127.35($\mathbf{C}_6H_5$) 128.23 ($RO(CH_2)_3C$=**C**),
116.70 and 116.30(C=**C**CO_2H),
63.70 and 63.15($RO\mathbf{C}H_2$), 37.20, 31.40, 30.05, 29.70, 27.35, 24.25, 19.90,
19.25 and 18.50($\mathbf{C}(CH_3)_3$, $\mathbf{C}H_2\mathbf{C}H_2C$=C, $C^5\mathbf{C}H_3$, $C^3\mathbf{C}H_3$), 26.80(($\mathbf{C}H_3)_3$)

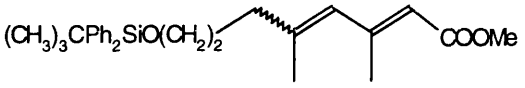
MS(EI): $(M\text{-t-Bu})^+$365

Preparation of (2*Z*,4*E*),(2*Z*,4*Z*),(2*Z*,4*E*) and (2*E*,4*E*)-methyl-8-t-butyldiphenylsilyloxy-3,5-dimethylocta-2,4-dienoate (4.38)

Trimethyloxonium tetrafluroborate (1.92 g, 13 mmol) was added in portions to a stirred solution of the diene acid (**4.37**) (5.0 g, 11.8 mmol) and N-ethyl diisopropylamine (2.27 ml, 13 mmol) in dry DCM (60 ml). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with sat $NaHCO_3$ (aq) (2x45 ml), 1M HCl (2x45 ml) and brine (45 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 5.0 g of a colourless oil. Purification by column chromatography (SiO_2, Hex:EtOAc 25:1) gave 4.4 g (86%) of (**4.38**) as a colourless oil. The overall isomer ratios were 2*E*:2*Z*, 6:1 and 4*E*:4*Z*, 2:1.

(2*E*,4*E*)-(2*E*,4*Z*)

Both isomers



^{1}H NMR δ:7.66-7.64(4H, m, $C_6\mathbf{H}_5$)

7.40-7.34(6H, m, $C_6\mathbf{H}_5$)

5.69, 5.63 and 5.6(2H, $\mathbf{H}^4$, $\mathbf{H}^2$)), 3.69(3H, s, O-$C\mathbf{H}_3$)

3.66-3.62(2H, m, RO$C\mathbf{H}_2$), 2.31-2.26,2.17-2.13(2H, $C\mathbf{H}_2$C=C)

2.19(3H, s, $C^3C\mathbf{H}_3$), 1.77 and 1.76(3H, s, $C^5C\mathbf{H}_3$),

1.70 and 1.61(4H, m, $C\mathbf{H}_2$), 1.04 and 1.02(18H, $(C\mathbf{H}_3)_3$).

Both Isomers

^{13}C NMR δ:167.05(**C**=O), 154.60(**C**=CCO_2CH_3), 141.80($RO(CH_2)_3$**C**=C)

135.05, 134.25, 129.40 and 127.35($\mathbf{C}_6H_5$)

128.15 and 128.30($CH_3RO(CH_2)_3C$=**C**), 116.90(C=**C**CO_2Me),

63.70 and 63.45(RO**C**H_2), 51.25(O-**C**H_3)

37.20, 31.40, 30.05, 29.70, 27.35, 24.25, 19.50, 19.20, 18.35

(**C**$(CH_3)_3$, $\mathbf{CH}_2\mathbf{CH}_2$C=C, $C^3\mathbf{CH}_3$, $C^5\mathbf{CH}_3$), 26.80(($\mathbf{CH}_3)_3$).

MS(EI): $(M\text{-t-Bu})^+$ 379

IR(neat): 2943 (vs), 1717 (vs), 1658 (s), 1431 (s).

Analysis Found: C,73.74; H,8.16; $C_{27}H_{36}O_3Si$ requires: C,74.26; H,8.30 %.

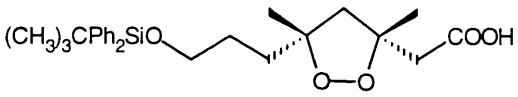
General Method A. Preparation of 1,2-dioxolane

The diene acid (10 mmol) in THF (5 ml) was added to a stirred suspension of $Hg(OAc)_2$ (20 mmol) in 30% H_2O_2 (90 mmol). The reaction mixture was stirred at room temperature and went from orange to colourless. Stirring was continued until tlc indicated no more starting material present .The reaction mixture was diluted with H_2O (5 ml) and extracted with DCM

(6x 6 ml). The organic extracts were combined, dried ($MgSO_4$) and the organic layer evaporated *in vacuo* . The crude mercuriated dioxolane (10 mmol) in DCM (30 ml) was cooled in an ice bath and 2M NaOH(aq) (10 ml) was added. Immediately after this mixture was added to a well stirred solution of $NaBH_4$ (40 mmol) in 2M NaOH(aq) (30 ml) cooled to 5 ^{0}C. Stirring at 5^{0}C was continued for 15 minutes and then for a further 15 minutes at room temperature. The reaction mixture was transferred to a separating funnel and the organic layer was separated. The basic aqueous layer was extracted further with DCM (3x10 ml). The organic extracts were combined and washed with 1M HCl, dried ($MgSO_4$), and evaporated *in vacuo*.

Preparation of 3-carboxymethyl-3,5-dimethyl-5-(3-t-butyldiphenylsilyloxypropyl)-1,2-dioxolane (4.39)

General Method A with diene acid (**4.37**) (0.33 g, 0.78 mmol) in THF (1 ml), $Hg(OAc)_2$ (0.5 g, 1.56 mmol) and 30% H_2O_2 (1 ml, 7 mmol). Reaction mixture was stirred for 18 hours and extracted with DCM (6x 6 ml). The crude mercuriated dioxolane (0.52 g) in DCM (10 ml) and 2M NaOH(aq) (5 ml) added to a solution of $NaBH_4$ (0.09 g, 3 mmol) in 2M NaOH(aq) (5 ml). The reaction mixture formed an emulsion which was cooled in an ice bath and acidified with dropwise addition of 1M HCl to effect separation of the two phases. The organic layer was separated and the aqueous layers extracted with DCM. All the organic extracts were combined, dried ($MgSO_4$), and evaporated *in vacuo* to give 0.24 g of a colourless oil. Purification by column chromatography (SiO_2, Hex:EtOAc 4:1) gave, 0.015 g (9%) of the *cis* 1,2-dioxolane (**4.39**).



^{1}H NMR δ:7.67-7.36(10H, m, 2xC_6**H**$_5$),
3.71-3.52(2H, m, ROC**H**$_2$)
2.73 and 2.67(2H, AB, J=15, C**H**$_2$CO_2H)
2.57 and 2.19(2H, AB, J=12.5, C**H**$_2$ring)
1.7-1.53(4H, m, 2xC**H**$_2$), 1.49 and 1.33(6H, s, 2xC**H**$_3$), 1.05(9H, s, C(C**H**$_3$)$_3$)

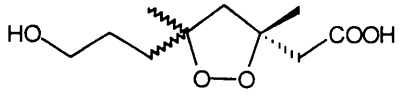
^{13}C NMR δ:171.05(**C**=O), 135.55, 134.05, 129.60 and 127.65(**C**$_6$H$_5$),
86.60 and 83.90(**C**-O-O-**C**), 63.80(HO**C**H$_2$), 55.55 (**C**H$_2$ring)
43.80(**C**H$_2$CO_2H), 35.09(**C**H$_2$C-O-O),
27.95, 24.75 and 23.70(**C**H$_2$ 2x**C**H$_3$), 26.85(C(**C**H$_3$)$_3$), 19.25(**C**(CH$_3$)$_3$).

Preparation of 3-carboxymethyl 3,5-dimethyl-5-(3-hydroxylpropyl)-1,2-dioxolane (4.40)

The silylated dioxolane (**4.39**) (0.35 g, 7.7 mmol) was dissolved in THF (5 ml), t-butyl ammonium tetrafluroborate (0.242 g, 8.5 mmol) was added and the mixture stirred for 18 hours. The THF was evaporated off. The crude reaction mixture was dissolved in EtOAc (20 ml) and washed with 1M HCl (10 ml). The dioxolane was isolated by base extraction with sat $NaHCO_3$ (aq) (3x 5 ml). The aqueous layers were combined cooled to 5 ^{0}C, acidified with cold 1M HCl and extracted with DCM to give 0.08 g (50%) of (**4.40**) as a colourless oil in a ratio of cis:trans of 1:1.

Cis Isomer

^{1}H NMR δ:3.61-3.56(2H, m, HOC**H**$_2$)



2.79 and 2.69(2H, AB, J=14.8, C**H**$_2$CO$_2$H)

2.52 and 2.19(2H, AB, J=12.6, C**H**$_2$ring), 1.8-1.53(4H, m, 2xC**H**$_2$),

1.50 and 1.37(6H, 2xC**H**$_3$)

Trans Isomer

^{1}H NMR δ:3.61-3.56(2H, m, HOC**H**$_2$), 2.81 and 2.74(2H, AB, J=14.8, C**H**$_2$CO$_2$H)

2.52 and 2.27(2H, AB, J=12.6, C**H**$_2$ring),1.8-1.53(4H, m, 2xC**H**$_2$),

1.48 and 1.33(6H, 2xC**H**$_3$)

Both Isomers

^{13}C NMR δ:174.80(**C**=O), 86.45, 86.30, 83.95(**C**-O-O-**C**), 62.75 and 62.60(HO**C**H$_2$),

55.85 and 55.10(**C**H$_2$ring), 44.0 and 43.90(**C**H$_2$CO$_2$H),

35.75 and 34.85(**C**H$_2$C-O-O),

27.55, 27.40, 26.50, 24.40, 23.70 and 24.35(2x**C**H$_3$ 2x**C**H$_2$).

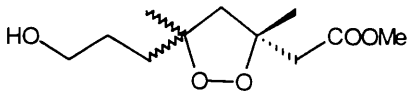
Preparation of 3-methoxy carbonylmethyl-3,5-dimethyl-5-(3-hydroxylpropyl)-1,2-dioxolane (4.43)

General Method A with diene ester (**4.38**) (3.53 g, 8.08 mmol) in THF (9 ml), $Hg(OAc)_2$ (5.15 g, 16.16 mmol) and 30% H_2O_2 (9 ml, 80 mmol). The reaction mixture was stirred for 2 days and extracted with DCM (6x 20 ml). The crude mercuriated dioxolane in DCM (40 ml) and 2M NaOH(aq) (10 ml) added to a solution of $NaBH_4$ (0.912 g, 24 mmol) in 2M NaOH(aq) (30 ml). After separation and extraction the combined organic layers were separated, dried ($MgSO_4$), and evaporated *in vacuo* to give 2.4 g of the crude silylated dioxolane as a colourless oil.

This was dissolved in THF (10 ml) along with t-butylammonium tetrafluroborate (1.63 g, 5.2 mmol) and stirred at room temperature. After 18 hours the THF was evaporated off and the residue dissolved in EtOAc (30 ml) and washed with 1M HCl (15 ml) and water (15 ml). The

organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo* to give 1.85 g, of a colourless oil. Re-extraction of the aqueous washings gave a further 0.4 g of crude dioxolane. Purification by column chromatography (SiO_2 Hex:EtOAc 1:1) gave 0.21 g (12%) of (**4.43**) as a colourless oil. The isomer ratio was *cis*: *trans* 3:2.

Cis Isomer



^{1}H NMR δ:3.62,(3H, s, O-C**H**$_3$),
3.61-3.56(2H, m, HOC**H**$_2$)
2.69 and 2.58(2H, AB, J=14.4, C**H**$_2$CO$_2$Me)
2.44 and 2.17(2H, AB, J=12.4, C**H**$_2$ring), 1.8-1.53(4H, m, 2xC**H**$_2$),
1.36 and 1.23(6H, 2xC**H**$_3$)

Trans Isomer

^{1}H NMR δ:3.61,(3H, s, O-C**H**$_3$), 3.61-3.56(2H, m, HOC**H**$_2$)
2.67 and 2.56(2H, AB, J=14.4, C**H**$_2$CO$_2$Me)
2.50 and 2.09(2H, AB, J=12.4, C**H**$_2$ring) 1.8-1.53(4H, m, 2xC**H**$_2$),
1.38 and 1.27(6H, 2xC**H**$_3$)

Both Isomers

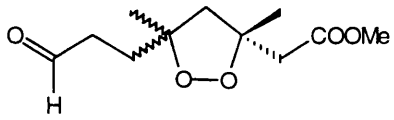
^{13}C NMR δ:171.05(**C**=O), 86.20, 86.15, 83.90 and 83.75(**C**-O-O-**C**)
62.55 and 62.50(HO**C**H$_2$), 55.50 and 55.20(**C**H$_2$ring)
51.65 and 51.60(O-**C**H$_3$), 43.85 and 43.80(**C**H$_2$CO$_2$Me)
35.60 and 34.80(**C**H$_2$C-O-O) 27.70, 27.45, 24.20 and 24.0(**C**H$_3$)
23.80 and 22.85(**C**H$_2$).

MS(FAB): Acc. Mass Found:233.1380 $C_{11}H_{21}O_5$ $(M+H)^+$requires: 233.1389

Preparation of 3-methoxycarbonylmethyl-3,5-dimethyl-5-(propan-3-al-1-yl)-1,2-dioxolane (4.44)

The hydroxy dioxolane (**4.43**) (0.14 g, 0.6 mmol) was dissolved in DCM (4 ml) and stirred with pyridinium dichromate (0.328 g, 0.95 mmol) for 24 hours. The DCM was evaporated *in vacuo* and the residue taken up in ether and filtered. Toluene was added to the solution to form an azetropic mixture with the pyridine. The organic solvents were evaporated *in vacuo* to give 0.10 g, of a yellow oil. Purification by column chromatography (SiO_2 Hex:Et_2O 2:1) gave 0.075 g (55%) of (**4.44**) as a colourless oil. The isomer ratio was *cis:trans* 3:2.

Both Isomers



^{1}H NMR δ:9.78 and 9.74(1H, **HC**=O),
3.65(3H, s, O-C**H**$_3$),
2.79 - 2.15(6H, m, C**H**$_2$CO$_2$Me, C**H**$_2$ring, C**H**$_2$CHO)
2.4-1.70(2H, m, C**H**$_2$), 1.41, 1.40, 1.29 and 1.24(6H, C**H**$_3$)

^{13}C NMR δ:201.20(H**C**=O), 170.90 and 170.70(**C**=O),
85.30, 85.20, 84.20 and 84.05(**C**-O-O-**C**)
55.85 and 55.35(**C**H$_2$ring), 51.70, 51.65(O-**C**H$_3$)
44.05 and 43.55(**C**H$_2$C-O-O), 39.10 and 39.05 (**C**H$_2$CO$_2$Me),
31.40, 30.75(OHC**C**H$_2$), 24.40, 24.05, 23.55 and 22.50(4x**C**H$_3$).

MS(FAB): Acc. Mass Found:231.1240 $C_{11}H_{19}O_5$ $(M+H)^+$requires: 231.1232

Route Two

Preparation of (2*Z*,4*E*),(2*Z*,4*Z*),(2*E*,4*E*) and (2*E*,4*Z*)-8-iodo-3,5-dimethylocta-2,4-dienoic acid (4.28)

The chloro diene acid (**3.75**) (2.0 g, 10 mmol) and sodium iodide (4.47 g, 30 mmol) were dissolved in acetone (20 ml) and heated to reflux for 2 days. The organic solvent was evaporated off and the residue taken up in ethyl acetate (40 ml) and washed with H_2O (2x 30 ml). The organic layer was separated dried ($MgSO_4$) and evaporated *in vacuo* to give 2.7 g (80%) of (**4.28**) as a yellow oil. Isomer ratios were (2*E*):(2*Z*) 4:1 (2*E*,4*E*):(2*E*,4*Z*) 3:1

2*E*,4*E*, 2*E*,4*Z*

^{1}H NMR δ5.78, 5.66 and 5.60(2H, s, **H**^{4} **H**^{2})
3.10-3.23(2H, m, IC**H**$_2$),
2.40-2.15(2H, m, C**H**$_2$C=C))
2.22(3H, s, C^{3}C**H**$_3$), 2.0-1.9(2H, m, C**H**$_2$), 1.8 and 1.75 (3H, s, C^{5}C**H**$_3$)

All Isomers

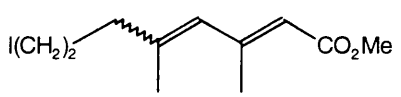
^{13}C NMR δ:172.05(**C**=O),157.50(**C**=CCO$_2$H), 140.50 and 140.20(I(CH$_2$)$_3$**C**=C),
130.05, 129.0 and 124.50(I(CH$_2$)$_3$C=**C**),117.20, 117.10 and
116.80(C=**C**CO$_2$H), 41.25, 34.80, 31.90, 31.20, 20.50 and
18.05(2x(**C**H$_2$),2x(**C**H$_3$)), 6.05(I**C**H$_2$).

MS(EI): $(M)^+$294 $(M\text{-}OH)^+$277 $(M\text{-}I(CH_2)_3)^+$125

Preparation of (2*Z*,4*E*),(2*Z*,4*Z*),(2*E*,4*E*) and (2*E*,4*E*) methyl 8-iodo-3,5-dimethylocta-2,4-dienoate (4.45)

The diene acid (**4.28**) (0.410 g, 1.96 mmol) and N-ethyl diisopropylamine (0.274 g, 2.156 mmol)were dissolved in DCM (20 ml) and trimethyl oxonium tetrafloroborate (0.319 g, 2.156 mmol) was added dropwise. Purification by column chromatography (SiO_2 Hex:EtOAc 30:1) gave 0.35 g (80%) of (**4.45**) as a clear oil. Isomer ratios of (2*E*):(2*Z*) 4:1 and (2*E*,4*E*):(2*E*,4*Z*) 3:1.

2E,4E, 2E,4Z



^{1}H NMR δ5.75, 5.66 and 5.60(2H, s, **H**^{2} **H**^{4})
3.67 and 3.63(3H, s, O-C**H**$_3$),
3.10-3.23(2H, m, IC**H**$_2$),
2.30-2.10(2H, m, C**H**$_2$C=C),)
2.22(3H, s, C^{3}C**H**$_3$), 2.0-1.90(2H, m, C**H**$_2$), 1.80 and 1.75 (3H, s, C^{5}C**H**$_3$)

All Isomers

^{13}C NMR δ:167.0(**C**=O), 154.25(**C**=CCO$_2$Me), 140.50 and 139.55(I(CH$_2$)$_3$**C**=C), 130.40, 129.60 and 124.50(I(CH$_2$)$_3$C=**C**), 117.50, 117.20 and 117.15(C=**C**CO$_2$Me), 51.80, 50.50(O-**C**H$_3$), 41.60, 34.20, 32.30, 31.20, 20.80 and 18.0((**C**H$_2$)$_2$ 2x(**C**H$_3$)), 6.2(I**C**H$_2$).

MS(EI): $(M)^+$306 $(M\text{-}OMe)^+$277 $(M\text{-}I(CH_2)_3)^+$139

IR neat: 2940(vs), 1715(vs), 1627(s)

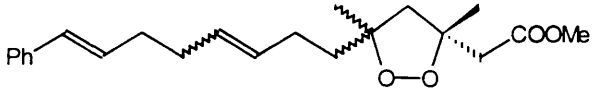
Analysis Found: C,42.43; H, 5.47 $C_{11}H_{17}IO_2$Requires: C,42.87; H,5.56

Attempted preparation of 3-methoxy carbonylmethyl-3,5-dimethyl-5-(3-iodopropyl)-1,2-dioxolane

General Method A with diene ester (**4.45**) (1.54 g, 5 mmol) in THF (5 ml), $Hg(OAc)_2$ (3.19 g, 10 mmol) and 30% H_2O_2 (5 ml, 45 mmol). The reaction mixture was stirred overnight and an orange yellow precipitate appeared. The reaction mixture was extracted with DCM (6x 20 ml). The crude mercuriated dioxolane in DCM (15 ml) and 2M NaOH(aq) (15 ml) was added to a solution of $NaBH_4$ (0.50 g, 13.2 mmol) in 2M NaOH(aq) (30 ml). After separation and extraction the combined organic layers were separated, dried ($MgSO_4$), and evaporated *in vacuo* to give 0.50 g of a colourless oil. Analysis by ^{1}H NMR indicated a complex mixture.

Preparation of 3-methoxycarbonylmethyl-5-(8-phenylocta-3E,7E-dieneyl)-3,5-dimethyl-1,2-dioxolane

Under an atmosphere of nitrogen the phosphonium salt (**4.21**) (0.13 g, 0.26 mmol) was dissolved in dry THF (8 ml) and cooled to -78 ^{0}C. n-Butyllithium (2.5M in pentane, 0.1 ml, 0.25 mmol) was added. The mixture was stirred at -78 ^{0}C for 20 minutes and then warmed to room temperature to ensure complete ylid formation. The reaction mixture went from yellow to a clear deep orange. The solution was re-cooled to -78 ^{0}C and the aldehyde dioxolane (**4.44**) (0.05 g, 0.217 mmol) in dry THF (8 ml) was added dropwise. Stirring was continued at -78 ^{0}C for 30 minutes and the mixture was then warmed to 5 ^{0}C. A cream precipitate formed and stirring was continued for 1 hour. The THF was evaporated *in vacuo* and the crude residue treated with hexane (10 ml). The hexane extract was separated from the yellow solid and evaporated *in vacuo* to give 0.05 g, of a colourless oil. ^{1}H NMR indicated that this was approx. 90% of desired product. purification by column chromatography (SiO_2 Hex:Et_2O 5:1), gave 0.02 g, 26% yield, of (**4.46**) as a colourless oil. The isomer ratio around the 1,2-dioxolane ring was *cis:trans* 1.2:1



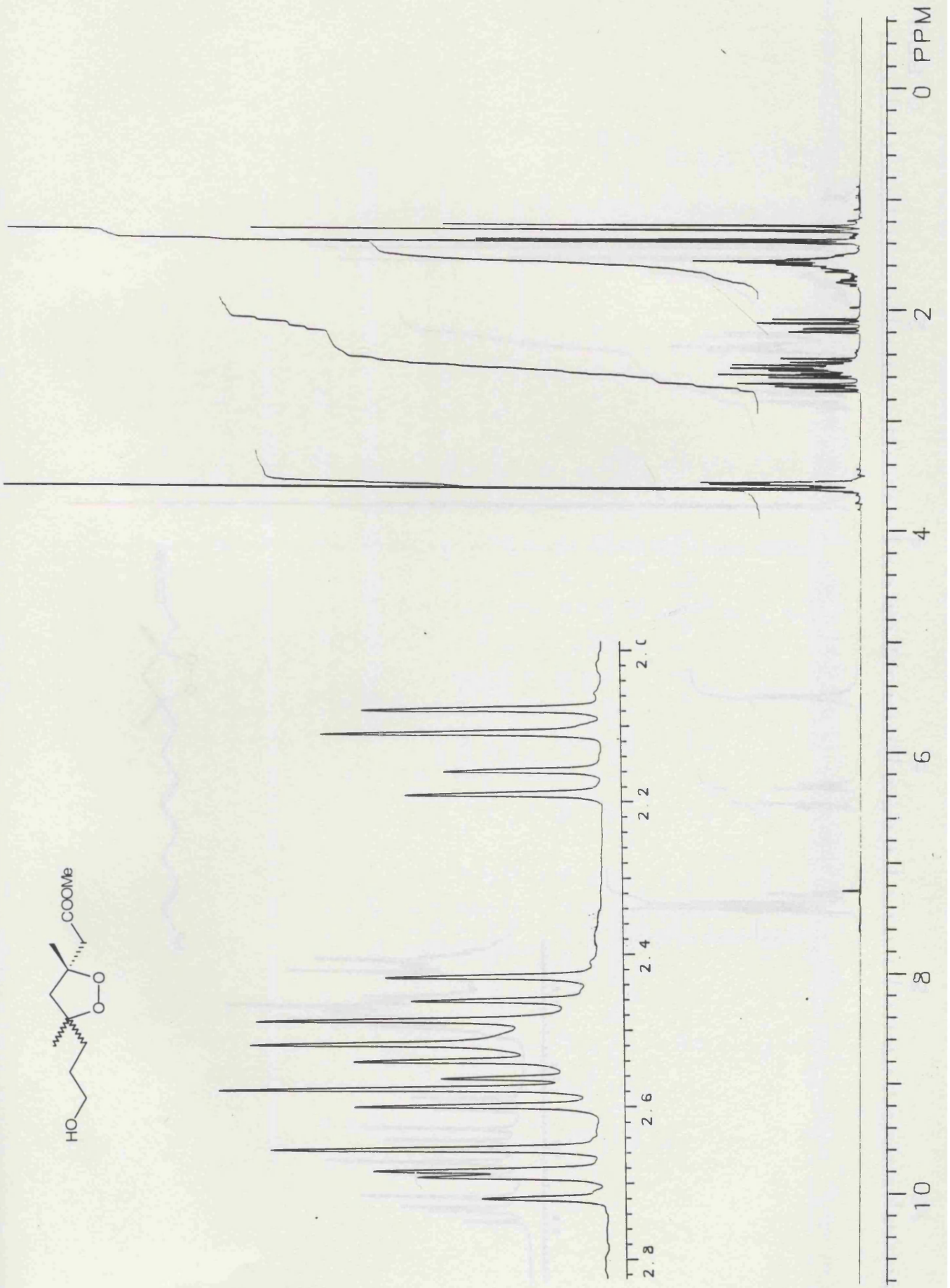
Both Isomers

^{1}H NMR δ:7.35-7.19(5H, m, $C_6\mathbf{H}_5$), 6.40(1H, d, J=16, Ph**H**C=C),
6.23(1H, dt, J=16, J=6.6, PhHC=C**H**),
5.47-5.36(2H, m, **H**C=C**H**), 3.70 and 3.68(3H, s, O-C$\mathbf{H}_3$)
2.78 and 2.66, 2.75 and 2.62 (2H, AB, J=14.4, C$\mathbf{H}_2$CO$_2$Me)
2.49 and obs, 2.57 and obs (2H, AB, J=12.4, C$\mathbf{H}_2$ring)
2.3-2.09(6H, m, 3xC=CC$\mathbf{H}_2$), 1.82-1.52(2H, m, C$\mathbf{H}_2$C-O-O),
1.43, 1.46, 1.34and 1.30(6H, s, 2xC$\mathbf{H}_3$)

Both Isomers

^{13}C NMR δ:171.05(**C**=O), 138.20, 123.05, 127.20 and 126.40(**C**$_6$H$_5$),
130.20, 130.25, 129.75, 129.60, 129.50, 129.30(**C**=**C**),
86.20, 86.15, 84.15 and 83.90(**C**-O-O-**C**), 55.80 and 55.65(**C**H$_2$ring),
51.80(O-**C**H$_3$), 44.05(**C**H$_2$CO$_2$Me), 39.50 and 38.50(**C**H$_2$C-O-O),
35.60 and 28.20(C=CC**H**$_2$), 24.30, 24.25, 24.10 and 23.20(4x**C**H$_3$),
22.80 and 22.20(2x**C**H$_2$).

MS(FAB): Acc. Mass Found:381.2050 $C_{22}H_{30}O_4Na$ requires: 381.2042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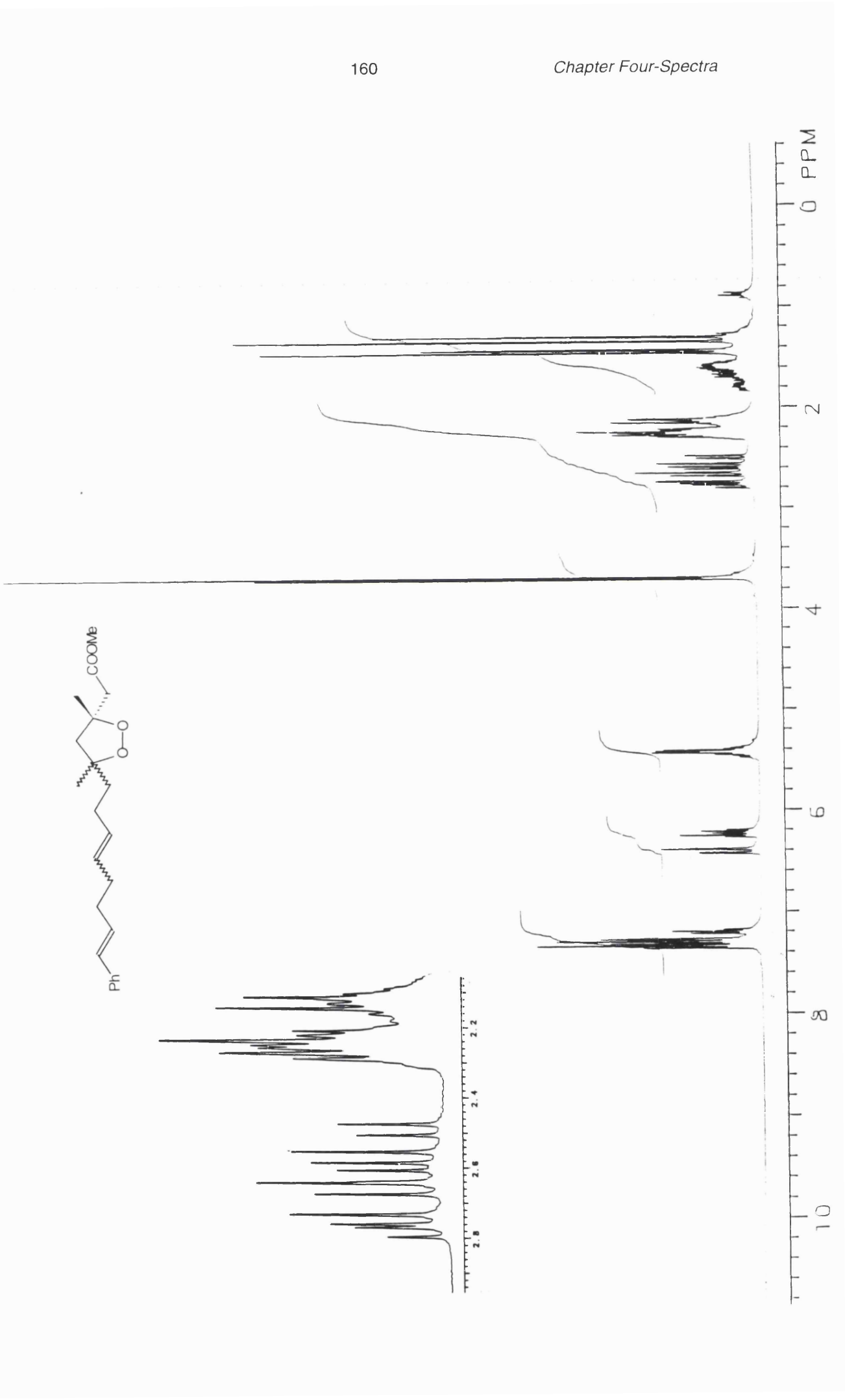
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180

1 Rucker G.; Olbrich A., *Tetrahedron Lett.*, **1988** 29, 4703

2 a)Carte B.; Kernan M.R.; Barrabee, E.B.; Faulkner D.J., *J. Org. Chem.*, **1986**, *51*, 3528 b) Appendino G.; Gariboldi P.; Nano G.M.; Tetenyi P., *Phytochemistry*, **1984**, *23*, 2545.c) Marco J.A.; Sanz J.F.; Falco E.; Jacupovic. A.; Lex J., *Tetrahedron*, **1990**, *46*, 7941 d) Wahlberg I.; Nordfors K.; Vogt C.; Nishida T.; Enzell C.R., *Acta. Chem. Scand. Ser. B.***1983**, *37*, 653. e) Lee K.H.; Nozaki H.; McPhail A.T., *Tetrahedron Lett.*, **1984**, *25*, 707.f) Guyot M.; Morel E.; Belaud C., J.Chem. Res. **1983**, 188

3 Huang D.Z.; Xu X.X.; Zhou W.S.; Zhu J., *Tetrahedron Lett.*, **1991** 32, 5785

4 Venugopalan B.; Bapat C.P., *Tetrahedron Lett.*, **1993**, *34*, 36, 5787-5790

5 Dussault P., *Synlett* **1995**, 997-1003

6 Dussault P.; Sahli A.; Westermeyer T., *J. Org. Chem.*, **1993**, 58, 5469-5474

7 Dussault P.; Lee H.J.; Niu Q.J., *J. Org. Chem.*, **1995**, 60, 784-785.

8 Dussault P.; Lee Q., *J. Am. Chem. Soc.*, **1993**, 115, 6458-6459

9 Dussault P.; Zope U., *Tetrahedron Lett.*, **1995**, *36*, 21, 3655-3658

10 Dussault, P.; Zope, U.R., *Tetrahedron Lett.*, **1995**, *36*, 13, 2187-2190.

11 a)Dussault P.; Sahli A., *Tetrahedron Lett.*, **1990**, *31*, 36, 5117-5120 b) Dussault P.; Lee Q. Kriefels S., *J. Org. Chem* **1991**, *56*, 13, 40874091

12 Dussault P.; Lee Q.J., *J. Org. Chem* **1992**, 57, 1952-1954

13 Dussault P.; Lee I.Q., *J. Org. Chem.*, **1995**, 60, 218-226

14 Bloodworth, A.J.; Hagen, T.; Lenoir, I.; Moussey, C., *Tetrahedron Lett* in preparation.

15 Dicker; Whiting, *J. Chem. Soc.*, **1958**, 1994-2000

16 Ding M-W.; Huang W-F.; Shi D.Q.; Xiao W-J., *Synthetic Communications*, **1994**, 24(22), 3235-3239

17 a) Schanach W., *Arch Pharm*, **1974**, 307, 7, 517-523 b) Nagata W.; Narisda M.; Onoue, H., *Heterocycles*, **1977**, 7, 839.

18 Badertscher, V.; Dilli, R.; Hagen, J.P.; Heathcock., C.; Young, S.D., *J. Org. Chem.*, **1985**, 50, 2095

19 Corey E.J.; Schmidt G., *Tetrahedron Lett.*, **1979**, 5, 399-402

20 a) Huttel R.; Ross H., *Chem. Ber.* **1956**, 89, 2641. b) Huttel R.; Ross H., *Chem. Ber.* **1956**, 89, 2641

Appendix One

Molecular Modelling Studies

Molecular modelling studies on the (2*E*,4*Z*)-3,5-dimethylocta-2,4-dienoic acid

The molecular modelling studies were carried out using the following packages and methodologies by Dr Mike Charlton of Zeneca Specialties Blackley Manchester.

Modelling Package: Sybil Version 6.1

Tripos Associates Ltd

Centennial House

Bracknell

RG12 1NN

Molecular orbital and geometry optimisations (Fig. 1)

Mopac: A General Molecular Orbital Package

QCPE Program 455

Creative Arts Building

181, Indiana Uni

Bloomington

IN 47405

Electrostatic Field Mapping (Fig. 2 and 3)

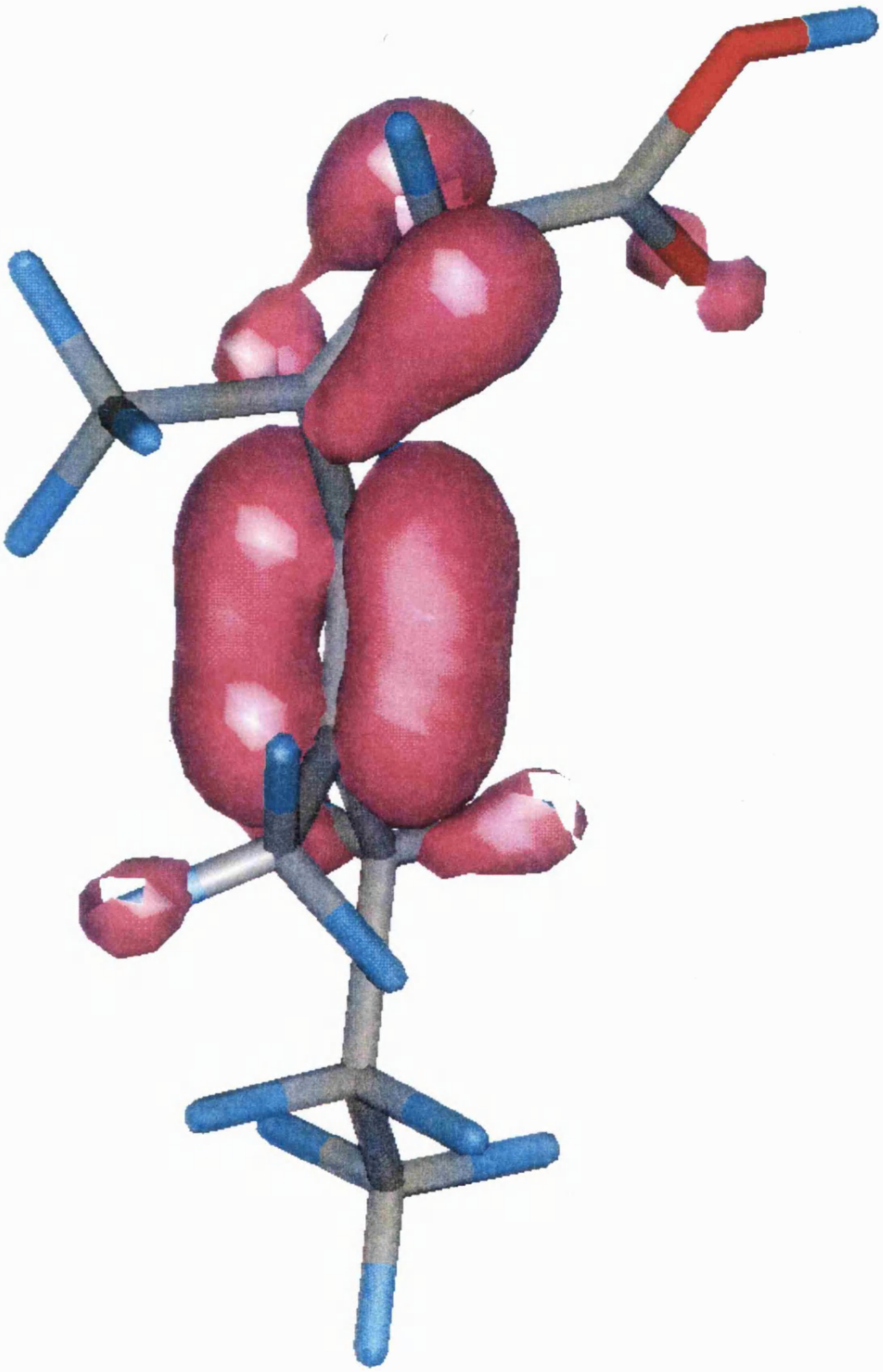
AM1: Dewer, M.J.S.; Healy, E.F.; Stewart, J.J.; Zoebisch, E.G., *J. Am. Chem. Soc.,* **1985**, 107, 3902.

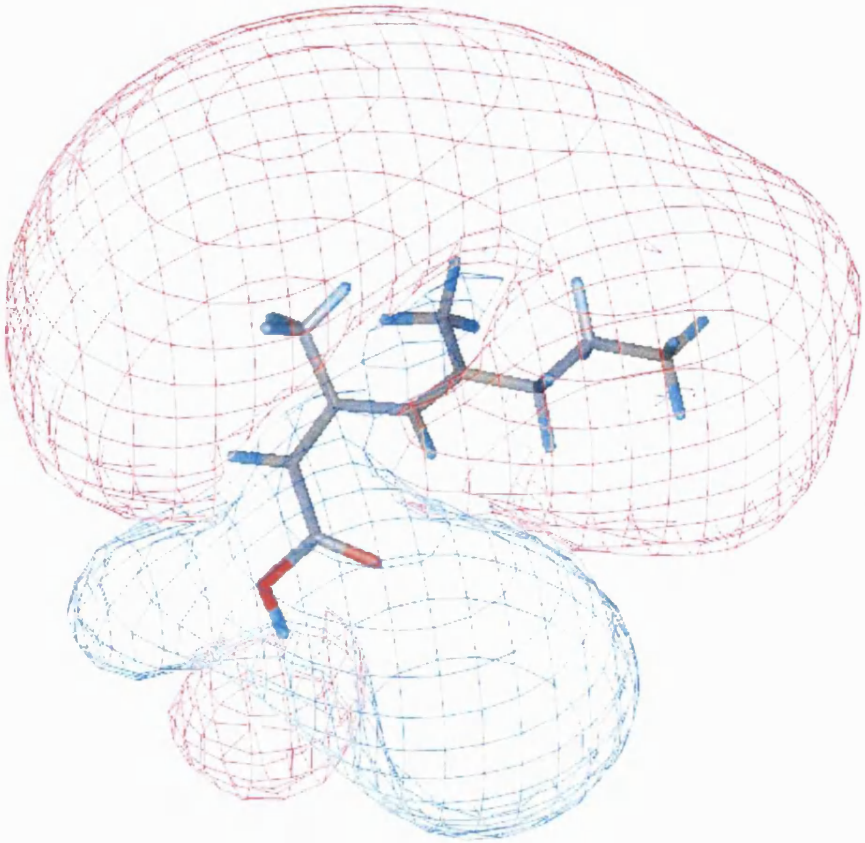
Figure page 165

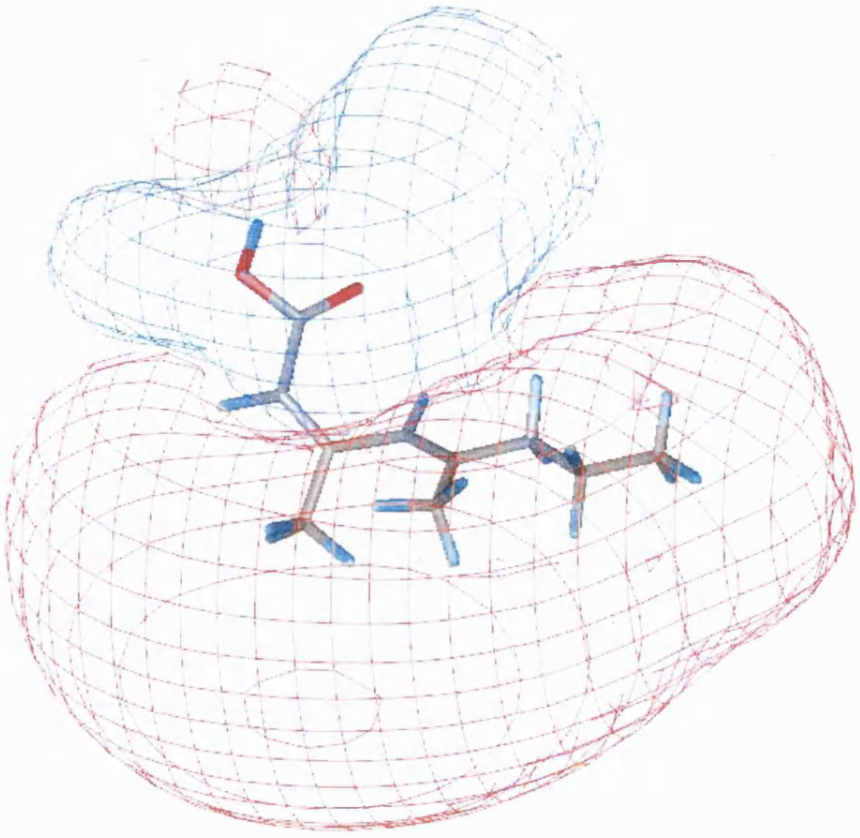
This figure represents the relative electron density of the HOMO (shown in pink) of the double bonds in the diene acid (2*E*,4*Z*)-3,5-dimethyl-octa-2,4-dienoic acid. The model shows how the individual double bonds are uncoupled and the αβ-double bond has a reduced and polarised electron density in comparison to the γδ-double bond. We can therefore presume the γδ-bond to be more reactive to electrophilic attack.

Figure page 166

These models show the net electrostatic charge experienced by a point positive charge around the top and bottom face of the diene acid (2*E*,4*Z*)-3,5-dimethylocta-2,4-dienoic acid. The red zone represents an area where the a positive charge will experience a net repulsive force while the blue zone indicates an area where the point charge will feel an attractive force. The left hand figure shows that the γδ-double bond, on one face, is covered with an net positive electrostatic field on one face while electrostatic mapping of the opposite side (right hand figure) indicates there is a small pocket of a net negative charge on one face of the diene acid.







APPENDIX TWO

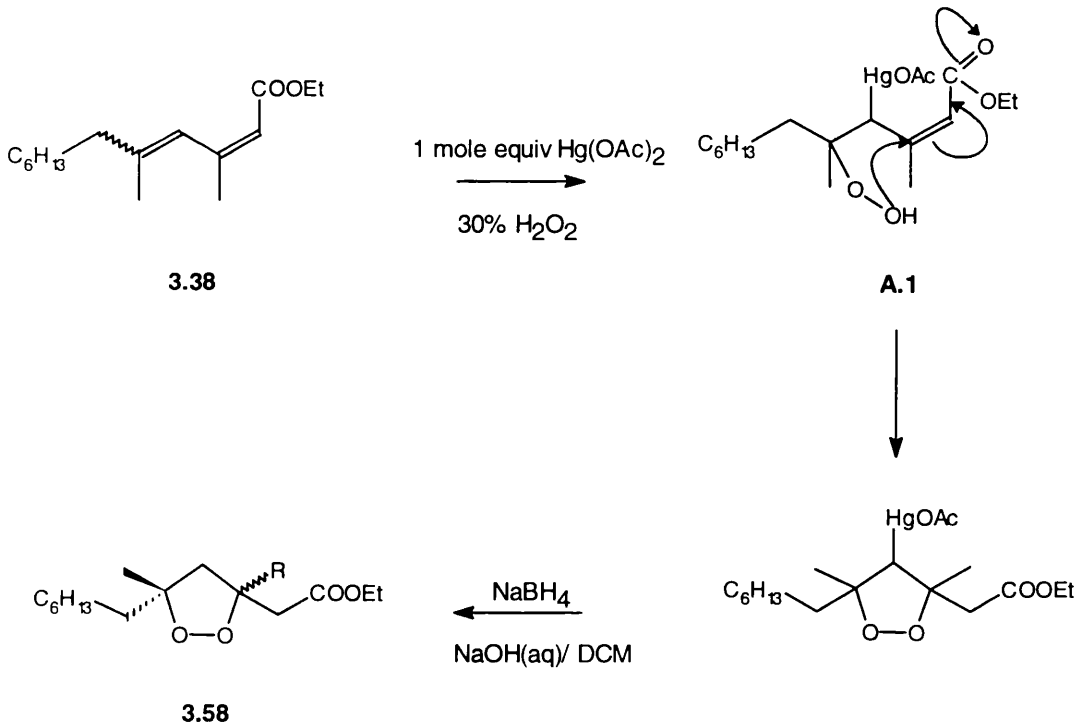
ALTERNATIVE ATTEMPTS TO SYNTHESISE THE TARGET 1,2-DIOXOLANE

Alternative Attempts to Synthesise the Target 1,2-Dioxolane

Modification of the Peroxymercuriation Route to the 1,2-Dioxolane

Our first attempt to find an alternative synthesis of the target 1,2-dioxolanes involved modification of the standard peroxymercuriation conditions used herein. We imagined the intermediate alkyl hydroperoxide (**A.1**), generated by insertion of hydrogen peroxide using peroxymercuriation across the γδ-double bond, could cyclise through an intramolecular Michael type addition. (**Scheme A.1**). To investigate this hypothesis we treated the diene ester (**3.38**) with one mole equivalent of mercury acetate and 30 % H_2O_2.

After stirring the reaction at room temperature for three days the reaction mixture was worked up and the crude mercuriated product was analysed by ^1H NMR. If cyclisation was effected without the assistance of mercury we would expect to see the characteristic AB coupling pattern of the $C^2\mathbf{H}_2CO_2Et$ protons, however we saw no evidence of this. After demercuriation of the crude mercuriated reaction mixture we isolated the 1,2-dioxolane ester (**3.58**), in a yield lower than the yield obtained when using standard peroxymercuriation/ demercuriation conditions.



3.38 **A.1**

3.58

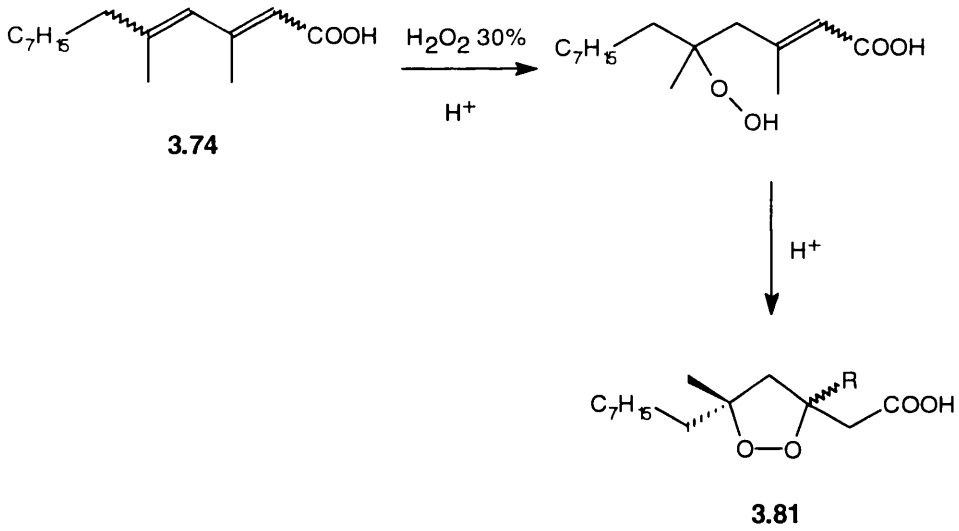
R = α or β CH_3

Scheme A.1

Acid Catalysed Insertion of Hydrogen Peroxide

The toxicity of organomercury compounds is well known and the use of mercuric reagents in commercial syntheses is not viable. On this basis we sought to find a replacement for the mercury electrophile in our synthetic route to the target 1,2-dioxolanes. Our thoughts centred on the known H_2SO_4 acid catalysed addition of 90% H_2O_2 to alkenes[*]. Other acid catalysts that have been employed in this manner include Dowex 50-X8[†] used in conjunction with 50% H_2O_2.

We set out to develop a synthesis using acid catalysed addition of 30% H_2O_2. We believed the γδ-double bond would be more reactive double bond and therefore the prefered site for initial insertion of the hydroperoxy group. Addition across the less reactive αβ-double bond would then occur via an intramolecular cyclisation (**Scheme A.2**).



3.74 **3.81**

R = α or β CH_3

Scheme A.2

A typical reaction involved stirring the diene acid (**3.74**) as a solution with the acid catalyst and 30% H_2O_2. Initially the diene acid (**3.74**) was treated with the commercially available acid activated K10 montmorillonite and then with a K10 montmorillonite iron(III) exchanged catalyst. Acid activated and cation-exchanged clays[‡] can act as catalysts for a range of

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[*] a)Davies, A.G.; White, *Nature*, **1952**, *170*, 668.b)Davies , A.G.; Foster; White, *J. Org. Chem.*, **1953**, 1541.

[†] Patent CA, *67*, 2778, **1967**

[‡] a)Cornelis, A.; Laszlo P., *Synlett*, **1994**, 155. b)Solid Supports and Catalysts in Organic Synthesis, Chap4 ref therein, (Ed. K.Smith), Ellis Horwood, Chichester (1992).

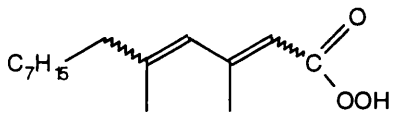
addition reactions to alkenes. The first step involves protonation of the alkene to give a carbocation intermediate, followed by reaction with a wide variety of available nucleophiles. Further experiments using different acid catalysts employed the acid resins Dowex 50-X8 and Amberlyst-15.

In each case the reaction temperature was increased to 40 ^{0}C after stirring at room temperature for 24 hours. (**Table A.1**).

Catalyst	Solvent	Time	Temperature
K10 montmorillonite	THF	48 Hours	25 - 40 ^{0}C
K10 montmorillonite	DCM	48 Hours	25 - 40 ^{0}C
K10 montmorillonite/ Fe^{3+}	THF	48 Hours	25 - 40 ^{0}C
K10 montmorillonite/ Fe^{3+}	DCM	48 Hours	25 - 40 ^{0}C
Dowex 50-X8	THF	48 Hours	25 - 40 ^{0}C
Amberlyst-15	THF	48 Hours	25 - 40 ^{0}C

Table A.1

Analysis by tlc of the crude reaction mixture, from the clay catalysed reactions, indicated they consisted of one component which gave a positive test for peroxide and co-eluted with the starting diene acid. The ^{1}H NMR of the crude reaction mixtures exhibited signals consistent with the starting diene acid plus a broadening of the base line from δ8.8-9.8 ppm. We believed formation of the peracid (**A.2**) had occurred. An EI mass spectrum gave a molecular ion M^{+}at 254 consistent with the formation of (**A.2**).



A.2

Only starting material was recovered from the reactions using ion exchange resins.

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APPENDIX THREE

ANTI-MICROBIAL ACTIVITY OF THE NATURAL PRODUCTS AND THE TARGET 1,2-DIOXOLANES

Anti-Microbial Activity of the Natural Products and the Target 1,2-Dioxolanes

Activity of the Natural Products

Plakinic acid A 1.16 and the naturally occurring analogues 1.22a-e

Plakinic acid A was tested for their antifungal activity. Zones of inhibition of 24 and 25 mm were recorded respectively against the fungi *Saccharomyces cerevisiae* and *Penicillium atrovenetum* at 100 μg/ disk. The methyl ester of **1.16** was reported to be essentially inactive. The natural products **1.22a-e** were screened against the bacteria *Bacillus subtilis* and the fungus *Saccharomyces cerevisiae.* Again these were measured in zones of inhibition. The acids **1.22a-e** showed a 20 mm zone of inhibition at a concentration of 25μg/ disc against the bacteria and a 32mm zone at 10μg/ disc against the fungi. They declare the activities reported in the patent show that the acids **1.22a-e** are effective for inhibiting the growth of bacteria and fungi.

Plakinic and epiplakinic acids C 1.18 and 1.19 and D 1.20 and 1.21and their methyl esters

These compound were tested for their cytotoxicity against tumour cells (L1210) murine leukemia cells, (KB) human epidermoid carcinoma cells and (LoVo) human colorectal adenocarcinoma cells.

Structure	L1210[a]	KB[b]	LoVo[b]
plakinic acid C 1.18	**0.017**	**0.01**	**0.1**
plakinic acid C methyl ester	**0.013**	**1.00**	**1.0**
epiplakinic acid C 1.19	**0.026**	**0.001**	**0.001**
epiplakinic acid C methyl ester	**0.0043**	**1.0**	**0.1**
plakinic acid D 1.20	**0.052**	**0.01**	**1.0**
plakinic acid D methyl ester	**0.29**	**0.1**	**0.1**
epiplakinic acid D 1.21	**0.017**	**0.1**	**1.0**
epiplakinic acid D methyl ester	**0.003**	**0.1**	**0.1**

[a] IC_{50} in μg/ ml [b] MIC in μg/ ml

Activity of the Target 1,2-Dioxolanes

The 1,2-dioxolanes were tested in a primary screen against fungi and gram positive and negative bacteria.

Bacteria		Fungi	
Bacillus subtilis	Bs	*Aspergillus niger*	An
Escherichia coli	Ec	*Aureobasidium pullulans*	Ap
Pseudomonas aeruginosa	Pa	*Candida albicans*	Ca
Staphylococcus aureus	Sa	*Gliocladium roseum*	Gr
		Penicillium funiculosum	Pf

The activities are measured as a Minimum Inhibitory Concentration (MIC) which is defined as the minimum concentration of the active material required for the inhibition of growth. The concentrations are expressed in parts per million. Twelve concentrations are measured, successively decreasing by a factor of two, in the range of 500-0.25 ppm equivalent to 50µg/ ml- 0.0024µg/ ml. Those compounds with an MIC of below 1.0 ppm are significant enough to warrant further investigation.

Activities of Some 2Z Diene Acids Table A.2

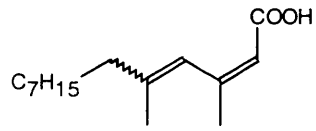
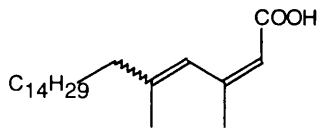
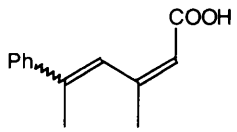
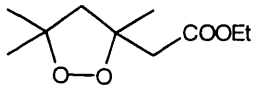
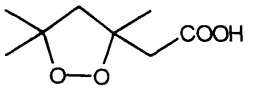
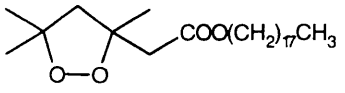
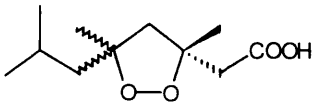
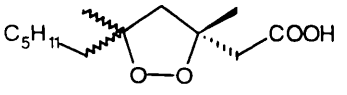
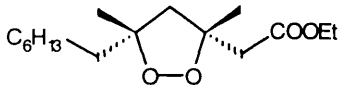
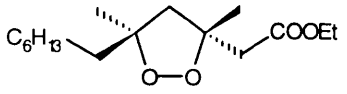
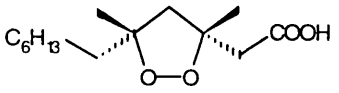
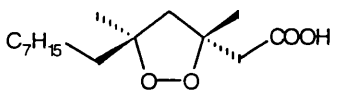
Structure	An	Ap	Ca	Gr	Pf	Bs	Ec	Pa	Sa	Notes
 **3.38**	125	125	250	32	125	8	250	250	125	
 **3.39**	500	250	250	250	250	500	250	250	500	
 **3.40**	999	100	999	100	999	999	999	999	999	

Table A.2

Activities of Some Target 3,5-Dimethyl Substituted 1,2-Dioxolane Acids and Esters Table A.3

Structure	An	Ap	Ca	Gr	Pf	Bs	Ec	Pa	Sa	Notes
 **2.41**	999	999	999	999	999	999	999	999	999	
 **2.44**	999	999	999	999	999	999	999	999	999	
 **2.45**	999	999	999	999	999	999	999	999	999	
 **3.79**	125	0.5	32	0.25	125	125	125	250	125	3:1 *cis: trans*
 **A.3**	62.5	62.5	32	16	62.5	8	125	250	0.25	supplied by Zeneca
 **3.58**	250	250	250	250	250	500	250	250	250	*cis*
 **3.58**	250	250	250	250	250	500	250	250	250	*trans*
 **3.69**	16	0.25	4	0.25	16	125	250	250	125	*cis*
 **3.102**	62.5	0.25	4	0.25	32	62.5	250	250	125	*trans*

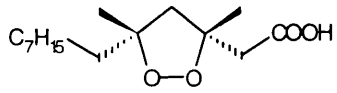
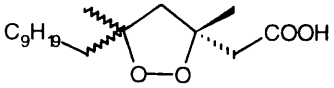
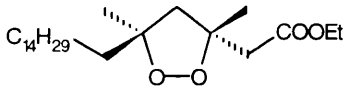
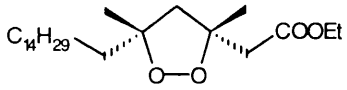
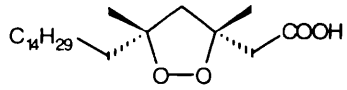
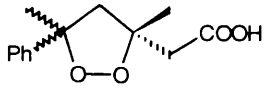
Structure	An	Ap	Ca	Gr	Pf	Bs	Ec	Pa	Sa	Notes
 **3.101**	32	0.25	32	1	32	62.5	125	250	62.5	*cis*
 **A.4**	62.5	32	16	16	32	1	62.5	125	8	supplied by Zeneca
 **3.59**	250	250	250	250	250	500	250	250	250	*trans*
 **3.59**	250	250	250	250	250	500	250	250	250	*cis*
 **3.70**	250	250	250	250	250	250	250	250	250	*cis*
 **3.80**	250	0.5	250	0.25	250	250	250	250	250	4:1 *cis*: *trans*

Table A.3

Activity of some Spiro 1,2-Dioxolanes Table A.4

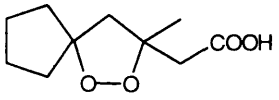
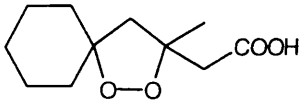
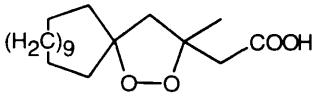
Structure	An	Ap	Ca	Gr	Pf	Bs	Ec	Pa	Sa	Notes
 **3.83**	125	0.25	62.5	0.25	125	125	125	250	125	
 **3.84**	125	0.25	32	0.25	125	62.5	125	250	125	
 **3.85**	62.5	0.25	16	0.25	62.5	62.5	250	250	32	

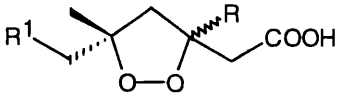
Table A.4

Evaluation of the Biological Results

The activities of the compounds tested in the primary assay are presented in **Tables A.2-4** above.

Table A.2. This table contains the test results of a small range of 2Z-diene acids. All three acids exhibit negligible activity.

Table A.3. This table contains the test results of the plakinic acid analogues which have the 3,5-dimethyl substituted 1,2-dioxolane ring shown below.



R = α or β CH_3

The trimethyl 1,2-dioxolane acid R^1 = H (**2.44**) and ester analogues (**2.41** and **2.45**) were essentially inactive, however an increase in activity is shown with homologation of R^1. When R^1 = saturated alkyl chain C_3-C_9 the dioxolane acids (**3.69, 3.79, 3.102, 3.101, A.3** and **A.4**) show significant activity against the fungi Ap and Gr with MIC's of 0.25 ppm. This trend is also reflected in the activity of the dioxolane acid (**3.80**) where the alkyl chain is replaced by a phenyl group directly attached to the 1,2-dioxolane ring. These dioxolane acids also show a degree of anti-microbial activity towards the other fungi and to a lesser extent with the bacteria although (**A.3**) shows an exceptional potency towards the bacteria Sa. However

when $R^1 = C_{14}$ the dioxolane acid exhibits negligible activity against all the organisms, which is in contrast to the results published in the original patent published by Patil.

Comparison of the activities of the dioxolane acid (**3.69**) and the ester analogue (**3.58**) indicates the importance of the acid functionality to activity.

To ascertain the nature of any difference in activity between the *cis* and *trans* isomers of the dioxolane acids, (**3.101** and **3.102**) were tested separately. Each isomer exhibited similar activity against all organisms. However the *cis* isomer (**3.101**) had an MIC of 1 ppm against the fungi Gr in comparison to an MIC of 0.25 ppm shown by the *trans* isomer (**3.102**).

Table A.4. This table contains the results of the activities of the spiro 1,2-dioxolane acids. These compounds, in line with their 3,5-dimethyl substituted analogues, show MIC's of 0.25 ppm against the funghi Ap and Gr. They also show a degree of potency towards the bacteria and other fungi. This activity is enhanced by a parallel increase in ring size from $(CH_2)_4$ to $(CH_2)_{10}$.

In summary we can make a number of positive statements concerning the factors which contribute to the activity of our target 1,2-dioxolanes,

i) By comparison of the results from **Table A.2** and **A.3** we know the peroxide ring is important to activity.

ii) The hydrophobicity of the saturated alkyl chain R^1 is essential although surprisingly between C_{10} and C_{15} a reduction in activity is observed.

iii) By comparison of the results of the 1,2-dioxolane esters and acids in **Table A.3** we find that the acid moiety is important to activity.

iv) Altering the 3,5-dimethyl substitution around the 1,2-dioxolane ring by making a spiro compound at C^5 has no adverse effect on activity.

Pergamon

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A Short Synthesis of Naturally Occurring and Other Analogues of Plakinic Acids that Contain the 1,2-Dioxolane Group

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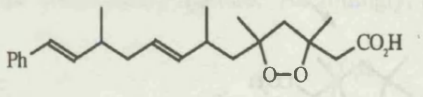
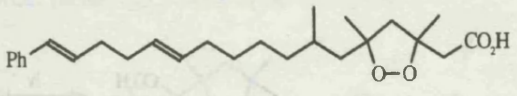
Abstract: Natural and unnatural analogues **4** of plakinic acids A, C and D have been prepared in three steps from alkan-2-ones by (i) LDA-induced condensation with ethyl 3-methylbut-2-enoate to give (2*Z*)-3,5-dimethylalka-2,4-dienoic acids **10**, then (ii) isomerisation to the 2*E*-isomers **5** and finally (iii) peroxymercuriation with 30% hydrogen peroxide and reduction *in situ* with sodium borohydride.

Marine sponges are a rich source of cyclic peroxides many of which exhibit biocidal and cytotoxic properties[1]. Most of these natural products contain 6-membered peroxide rings, but plakinic acid A (**1**)[2], plakinic (and diastereoisomeric epiplakinic) acids C (**2**)[3] and D (**3**)[3] and saturated analogues **4a-e**[4] are exceptional in that they are 1,2-dioxolanes. Other common features of these naturally occurring 1,2-dioxolanes are methyl substituents at the 3- and 5-positions and a CH_2CO_2H group at the 3-position of the five-membered ring. The compounds are claimed to have antitumour, antibacterial and antifungal activity[2-4].



(1)



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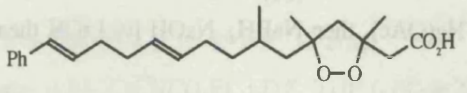
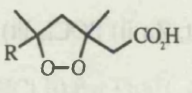


(3)



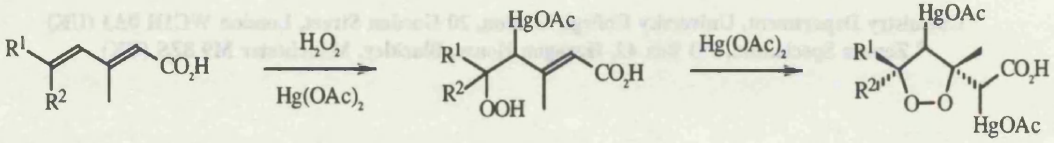
(4)

	R
a	$C_{13}H_{27}$
b	$C_{14}H_{29}$
c	$C_{15}H_{31}$
d	$C_{16}H_{33}$
e	$C_{17}H_{35}$

We set out to develop a general synthesis of compounds of structure **4** that would support a variety of R-groups, including the C_{13}-C_{17} saturated alkyls of the natural products, and would provide a basis for approaching the total synthesis of the plakinic acids. We now report such a method which in its most refined form comprises just three steps.

Our synthetic strategy was based on the belief that the required 1,2-dioxolanes could be created by peroxymercuriation of suitable dienes with hydrogen peroxide[5]. Retrosynthetic analysis on this basis suggested

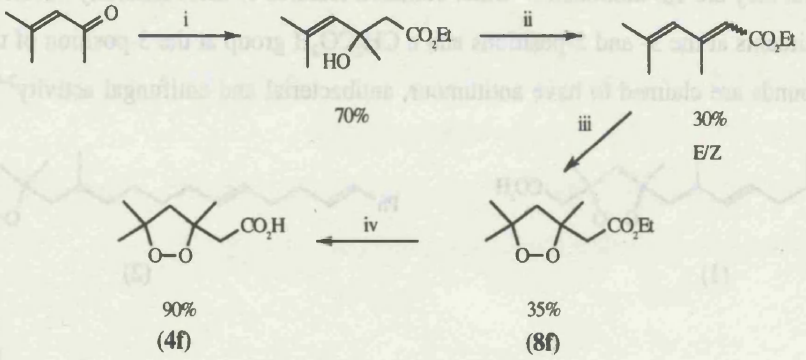
four candidate dienes (ignoring *E/Z* isomerism), of which the αβγδ-unsaturated acid **5** was thought likely to be the most amenable to a general synthesis. With mercury(II) acetate as the electrophile, diene **5** was expected to show 1,2-addition only[6], with the more electron-rich γδ-double bond being the site of initial attack. Thus, hydroperoxymercuriation[7] was expected to give intermediate hydroperoxide **6** which would then undergo intramolecular peroxymercuriation at the αβ-double bond, more easily than the corresponding intermolecular process[8] but with the same orientation, to give the required product in the bis-mercuriated form **7**. Demercuriation of **7** with sodium borohydride[5] would then afford the target 1,2-dioxolane **4**.



(5) **(6)** **(7)**

R^1 = Me, R^2 = R or R^1 = R, R^2 = Me

Initial studies centred on 3,5-dimethylhexa-2,4-dienoic acid (**5**, R = Me). An *E/Z* mixture of the ethyl ester of this acid was prepared from 4-methylpent-3-en-2-one (mesityl oxide) by the Reformatsky route[9]. Peroxymercuriation-demercuriation[11] afforded the ethyl ester **8f**[12] of the desired 1,2-dioxolane in 13-35% yield, the *E* ester giving a better yield than the *Z* isomer. Saponification then gave the target acid **4f**[12], the first unnatural analogue of the plakinic acids.

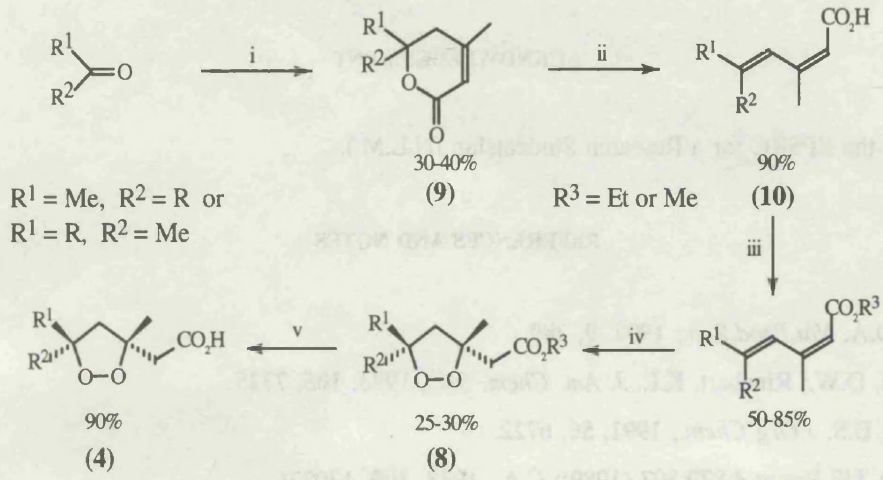


(4f) **(8f)**

Reagents: i) $BrCH_2CO_2Et$, Zn ii) $POCl_3$ iii) 30% H_2O_2, $Hg(OAc)_2$ then $NaBH_4$, NaOH iv) LiOH then HCl

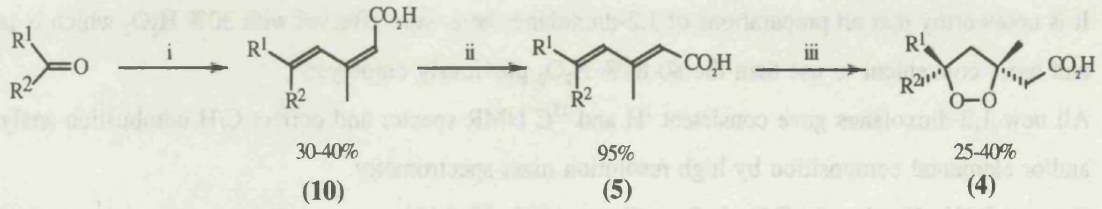
This work established the viability of the peroxymercuriation-based route to plakinic acid analogues, but a different route to the precursor diene was required if the method was to be generally applicable. The route chosen was the condensation of alkan-2-ones with ethyl 3-methylbut-2-enoate to give lactones **9**[13], followed by base-induced ring-opening[14] to provide the 2*Z* diene acids **10** as a 1:2 mixture of the 4*Z* and 4*E* isomers. The diene acids **10** could not be used directly in the peroxymercuriation step because intramolecular acyloxymercuriation, to re-form lactone, was preferred under these conditions. However, by first esterifying the

acids, lactone formation was sufficiently suppressed to allow 1,2-dioxolanes **8** and thence **4** to be prepared in 25-30% yields.



Reagents: i) $Me_2C{:}CHCO_2Et$, LDA, THF (-78°→10°) then aq NH_4Cl ii) NaOEt, EtOH then aq HCl iii) DCC, DMAP, EtOH or $Me_3O^+ BF_4^-$, $^iPr_2NEt$ iv) 30% H_2O_2, $Hg(OAc)_2$ then $NaBH_4$, NaOH v) LiOH then aq HCl

We reasoned that if we could isomerise the 2*Z* diene acids **10** to the 2*E* isomers **5**, which cannot ring-close to the lactone, the esterification and saponification steps of the above synthesis could be eliminated. Several methods of isomerisation were tried, but treatment of **10** with a catalytic amount of thiophenol in carbon tetrachloride at reflux[15] was found to be best, giving a *ca* 4:1 mixture of **5** and **10** which was used in the final step. The synthetic route was further simplified by omitting the isolation of lactone **9** by modifying the work up of the condensation mixture. Accordingly, the current method of choice is shown below.



R1 = Me, R2 = R or R1 = R, R2 = Me

Reagents: i) $Me_2C{:}CHCO_2Et$, LDA, THF (-78°→20°) then aq HCl ii) cat PhSH, CCl_4, reflux iii) 30% H_2O_2, $Hg(OAc)_2$ then $NaBH_4$, NaOH then aq HCl

Using the three methods described, we have prepared four unnatural plakinic acid analogues, where R = Me (**4f**), Me_2CHCH_2 (**4g**), Ph (**4h**) and C_7H_{15} (**4i**), as well as the naturally occurring analogue **4c**. Each product (apart from **4f**) was obtained as a mixture of *cis* and *trans* isomers, the ratio of which closely matched the ratio of geometric isomers about the γδ double bond of the precursor diene acid or ester. Since the PhSH-

catalysed isomerisation enriched not only the amount of 2*E* isomers but also of 4*E* isomers, the acid route provided 1,2-dioxolanes with greater stereoselectivity.

Work is in progress to try to extend the method to the preparation of the plakinic acids.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. Casteel, D.A. *Nat.Prod.Rep.*, 1992, **9**, 289.
2. Phillipson, D.W.; Rinehart, K.L. *J. Am. Chem. Soc.*, 1983, **105**, 7735.
3. Davidson, B.S. *J.Org Chem.*, 1991, **56**, 6722.
4. Patil, A.D. US Patent 4,879,307 (1989); C.A., 1988, **109**, 17027f
5. Bloodworth, A.J.; Loveitt, M.E. *J. Chem. Soc., Chem. Commun.*, 1976, 94; *J. Chem. Soc., Perkin Trans. 1*, 1978, 522; Bloodworth, A.J.; Khan, J.A. *J. Chem. Soc., Perkin Trans 1.*, 1980, 2450.
6. Bloodworth, A.J.; Hutchings, M.G.; Sotowicz, A.J. *J. Chem. Soc., Chem. Commun.*, 1976, 578-579.
7. Bloodworth, A.J.; Spencer, M.D. *J. Organometallic Chem.*, 1990, **386**, 299.
8. Bloodworth, A.J.; Bunce, R.J. *J. Chem. Soc., Chem. Commun.*, 1970, 753-754; *J. Chem. Soc. (C)*, 1971, 1453-1458.
9. Dehydration of the Reformatsky alcohol with anhydrous copper(II) sulfate[10] additionally gave $Me_2C{:}CHC(:CH_2)CH_2CO_2Et$ and (*E/Z*) $CH_2{:}C(Me)CH{:}C(Me)CH_2CO_2Et$, which as expected from the retrosynthetic analysis also afforded **8f** upon peroxymercuriation-demercuriation.
10. Cologne, J.; Varagnet, S. *Bull. Soc. Chim. Fr.*, 1961, 237.
11. It is noteworthy that all preparations of 1,2-dioxolanes here were effected with 30% H_2O_2 which is safer and more convenient to use than the 80-85% H_2O_2 previously employed[5].
12. All new 1,2-dioxolanes gave consistent ^1H and ^{13}C NMR spectra and correct C/H combustion analyses and/or elemental composition by high resolution mass spectrometry.
13. Dugger, R.W.; Heathcock, C.H. *J. Org. Chem.*, 1980, **45**, 1181.
14. Eishner, U.; Elvidge, Y.A.; Linstead, R.P. *J. Chem. Soc.*,1953,1372; Korte, F.; Machelot, H. *Chem. Ber.*, 1955, **88**, 136; Korte, F.; Scharf, D. *Chem Ber.*, 1962, **95**, 443; Wolinsky, J.; Eustace, E.J. *J. Org. Chem.*, 1972, **37**, 3376; Frosch, J.W.; Harrison, I.T.; Lythgoe, B.; Saksena, A.K. *J. Chem. Soc., Perkin Trans 1.*, 1974, 2005; Corey, E.J.; Schmidt, G. *Tetrahedron Lett.*, 1979, 2317; Nakata, T.; Hata,N.; Oishi,T. *Heterocycles*, 1990, **30**, 333.
15. Henrich, C.A.; Willy, W.E.; Baum, J.W.; Baer, T.A.; Garcia, B.A.; Master, T.A.; Chang; S.M. *J. Org. Chem.*, 1974, **40**, 1.

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