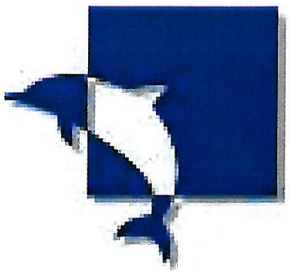

University of Southampton

Studies involving Potassium Permanganate mediated Oxidative Cyclisations of 1,5-dienes and 1,5,9-trienes.

One volume.

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Thesis submitted for the qualification of MPhil.

Supervisor: Dr. R.C.D. Brown
Advisor: Dr. M. Grossel

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Master of Philosophy

STUDIES INVOLVING POTASSIUM PERMANGANATE MEDIATED OXIDATIVE CYCLISATIONS OF 1,5-DIENES AND 1,5,9-TRIENES.

by Robert M. Hughes

The use of potassium permanganate to oxidatively cyclise 1,5-dienes has been well documented, albeit with disappointing yields. The aim of this study has been to optimise the reaction conditions for the oxidative cyclisation of a commercially available 1,5-diene using potassium permanganate.

The optimised methodology has then been applied to a selection of readily accessible isomeric 1,5,9-trienes in order to give tetrahydrofuran lactol products with differing stereochemistry. The subsequent cleavage of the lactol products to lactones has been achieved producing four diastereoisomeric *cis*-2,5-disubstituted tetrahydrofurans in order to access potential precursors to natural and unnatural biologically active molecules.

Contents

1. Introduction

1.1 Background.

1.1.1 Polyether antibiotics.

The polyether antibiotics or polyether ionophores, are a large group of natural products. There are over 120 different ionophores known to occur naturally in a host of different microbial organisms, the most prolific being the genus *streptomyces*. Many of these compounds have been identified from fermentation broths.[1]

Polyether compounds are used mainly for their antimicrobial and antibacterial action, however they do possess other actions such as controlling coccidosis in poultry and have been shown to produce a response from cardiovascular systems.[2] Novel and intriguing biological activity, coupled with interesting structural features, mean such molecules are an attractive proposition as targets for total synthesis.[3-5]

As shown in figure 1, the structures of polyether compounds are many and varied, however the most well known and documented to date is that of monensin (**1**). Monensin possesses many of the features representative of the ionophore class of compounds and also has historical and commercial importance.

As can be seen from the compounds in figure 1, the synthesis of cyclic ethers needs to be addressed in order to facilitate their total synthesis. These include substituted tetrahydropyrans, spiroketal fragments and the subject of this study, 2,5-disubstituted tetrahydrofuran (THF) systems. It should be noted that similar THF systems are present in other classes of important natural and synthetic compounds, some of which are outlined later.

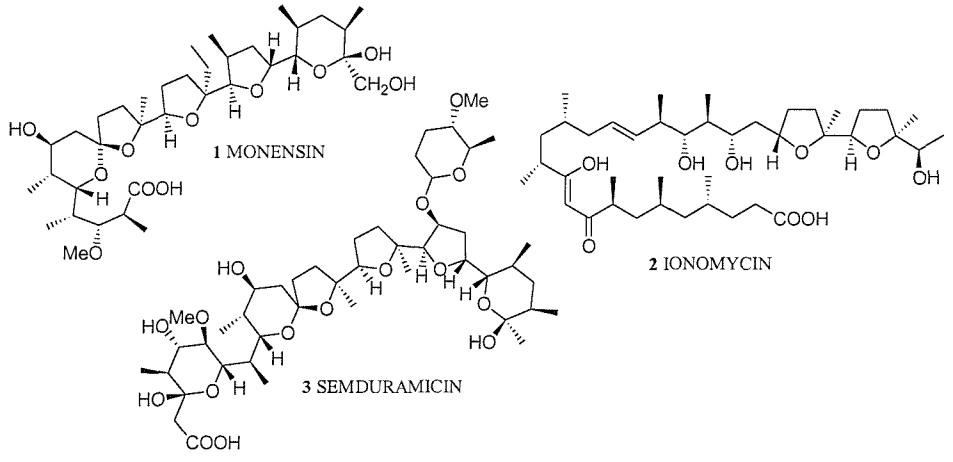


Figure 1. Examples of Polyether antibiotics.

1.1.2 Action of ionophores in biological systems.

The main biological action of the polyether antibiotics is caused by their interaction with intracellular ions. The ionophores change the permeability of the cell membrane to the ions and hence interrupt the normal function of the cell.

The polyether antibiotics appear one dimensionally to be extended molecules. However, *in vivo* they are able to fold in on themselves making a hydrophilic "pocket" which chelates to the respective metal cation (figure 2). This is made possible by the oxygen substituents that are orientated on the inside of the "pocket" and maintain its shape by hydrogen bonding.

The resulting complex **4** has a hydrophilic interior containing the metal and the nonpolar exterior allows transport of the ion across the hydrophobic lipid bilayer membrane. The change in ion transport has a potentially significant affect on the cells well being. The difference in size of the ionophore molecules means that they produce different size pockets that favour the chelation of different metal cations. Monensin (**1**) for example interacts with Na^+ ions and ionomycin (**2**) chelates Ca^{2+} ions.

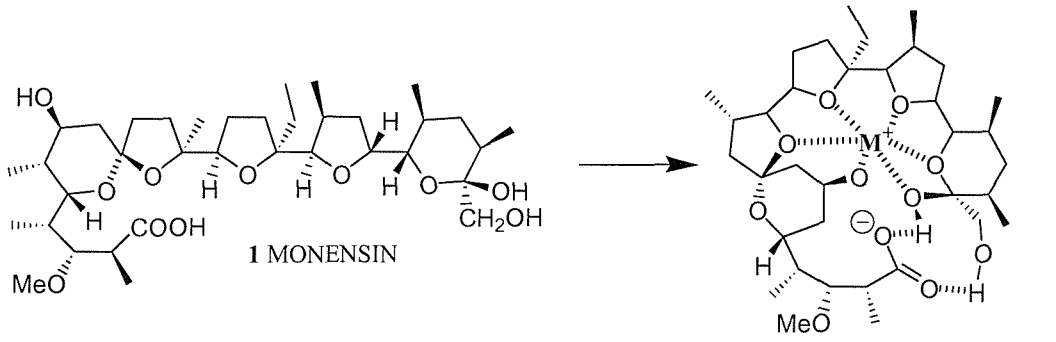


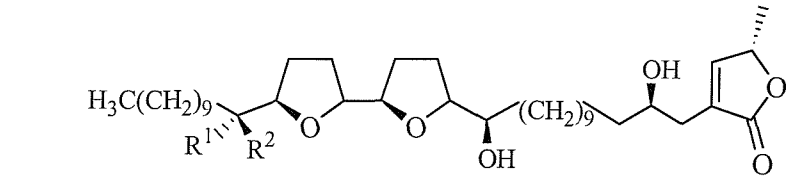
Figure 2. Monensin-sodium ion complex.

The change in ion activity brought about by monensin (**1**) interrupts the posttranslational modification of proteins and mucopolysaccharide synthesis. In turn, the result is the slowing of the intracellular transport of newly produced secretory proteins and plasma glycoproteins.[6]

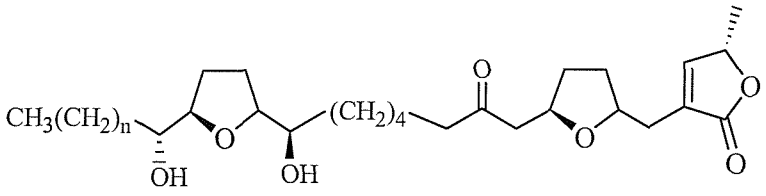
1.1.3 Other tetrahydrofuran containing compounds.

Another group of compounds of great interest as targets for total synthesis is the *Annonaceous* acetogenins. These compounds have only been found in the plant family *Annonaceae*. Extraction of acetogenins is relatively easy from the plant biomass using ethanol or chlorinated

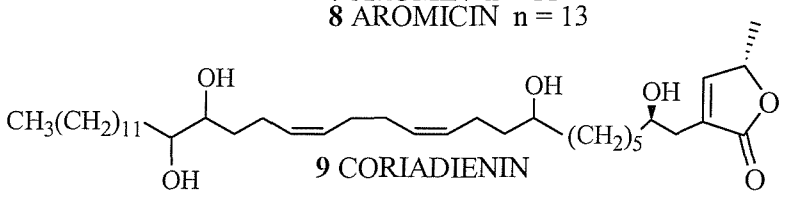
solvents such as dichloromethane and chloroform.[7] As shown in figure 3, there are a wide variety of structures that fall under the acetogenin label, many containing at least one substituted THF ring system.



5 ASIMICIN R^1= OH; R^2= H
6 BULLATACIN R^1= H; R^2= OH



7 AROMIN n = 11
8 AROMICIN n = 13



9 CORIADIENIN

Figure 3. Examples of a variety of Acetogenins.

As with the ionophores, the acetogenin compounds have the ability to affect biological systems in a number of ways. Biological properties of the acetogenins include antitumour, immunosuppressive, pesticidal, antiprotozoal, antifeedant and antimicrobial action. Recently discovered compounds have been shown to exhibit antimalarial and pesticidal properties.[7] By far the most interesting characteristic exhibited by the acetogenin compounds is their selective inhibition of the growth of cancerous cells and also their inhibition of adriamycin resistant tumour cells. Some acetogenins display a substantial selectivity against the growth of certain cell lines such prostate cancer cells.

1.1.4 Biological action of acetogenins.

The acetogenins are potent inhibitors of NADH:ubiquinone oxidoreductase, an important enzyme in the electron transport system present in the mitochondria of cells and hence is an important factor leading to oxidative phosphorylation.[8] In addition, acetogenins have an action on a similar enzyme that is exclusive to the membranes of cancerous cells: ubiquinone-linked NADH oxidase. The function of this enzyme is to allow cytosolic phosphorylation by restoring levels of

NAD^+. Since the NADH oxidase enzyme is inhibited by acetogenins, the end result is the depletion of ATP.

1.1.5 Rationally designed antitumour agent, COBRA-1.

Recently a rationally designed anticancer compound that inhibits α-tubulin was reported.[9] The combination of α-tubulin and β-tubulin as αβ-tubulin heterodimers is a major part of the formation of microtubules. Microtubules are cytoskeletal polymers that are an essential ingredient in mitotic spindle assembly and cell division. Therefore the interference of α-tubulin would disrupt the proliferation of cancer cells.

Previous drugs that have been employed to interfere with β-tubulin include taxol and vinca alkaloids however the problem with these agents is that cancer strains that have an altered β-tubulin expression profile may well be resistant to such compounds.

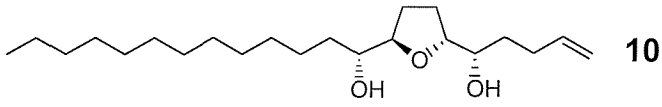


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Figure 4. The rationally designed COBRA-1 anticancer compound.

A feature of α-tubulin is the leucine and isoleucine rich hydrophobic channel and is the major difference from the binding site of taxol on β-tubulin. The binding cavity therefore forms very strong interactions with the aliphatic side chain of COBRA-1 (so named because of its "snake-like" aliphatic chain and THF "head"). The THF ring of the molecule, flanked by two hydroxyl groups ensures good hydrogen bond interaction with residue Asn226 (Asparagine).

Studies on COBRA-1 with human breast cancer and brain (glioblastoma) cells have shown that the compound does indeed cause the destruction of microtubule organization and apoptosis (cellular destruction).

1.2 Routes to 2,5-disubstituted THF fragments.

The classes of compounds described above i.e. ionophores and acetogenins, contain a common 2,5-disubstituted THF fragment. It is such fragments that are of interest during the course of this investigation. A number of different methods have been used in the past in order to access 2,5-disubstituted THFs, some of which are outlined below.

1.2.1 Cyclisation of 1,5-dienes *via* epoxidation.

The method of epoxidation followed by cyclisation is well known. Renewed interest in this area was assured by the development of the Sharpless procedure for asymmetric epoxidation. Hoye was interested in the total synthesis of the natural product Teurilene (**11**) (figure 5) and recognised the advantages the Sharpless procedure could offer in the synthesis of achiral molecules such as teurilene (**11**).[10]

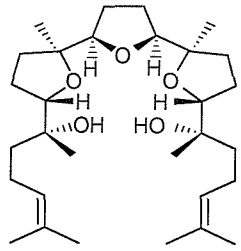

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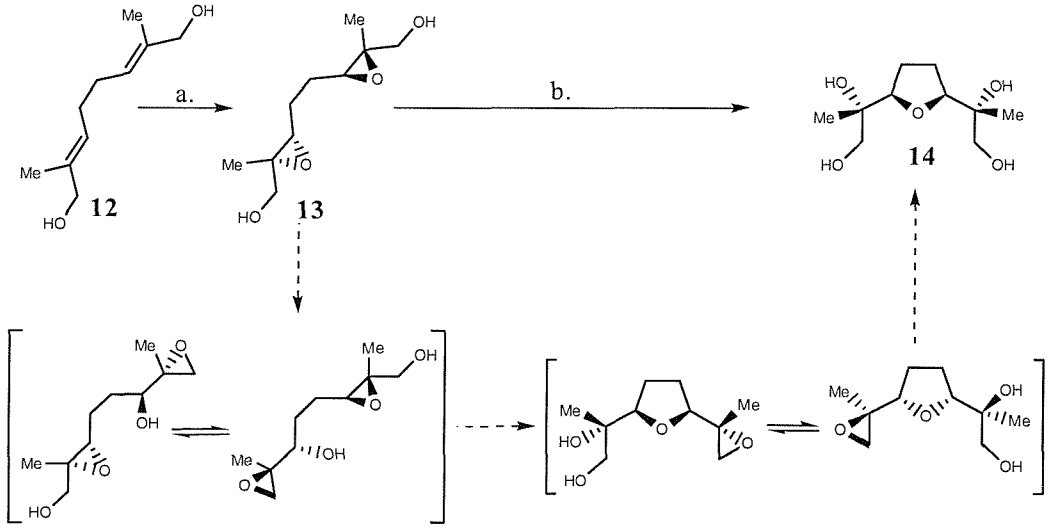
Figure 5. Structure of Teurilene, a natural product.

Hoye showed that using the Sharpless catalytic asymmetric epoxidation of the relevant dimethyloctadienediol **12** yielded the enantiomerically pure *bis* epoxide **13**. Treatment of **13** with dioxane and sodium hydroxide at 100 °C led to the production of the desired *cis*-THF **14** (figure 6). It was the resulting THF compound that was employed as a precursor in the synthesis of teurilene **11**.



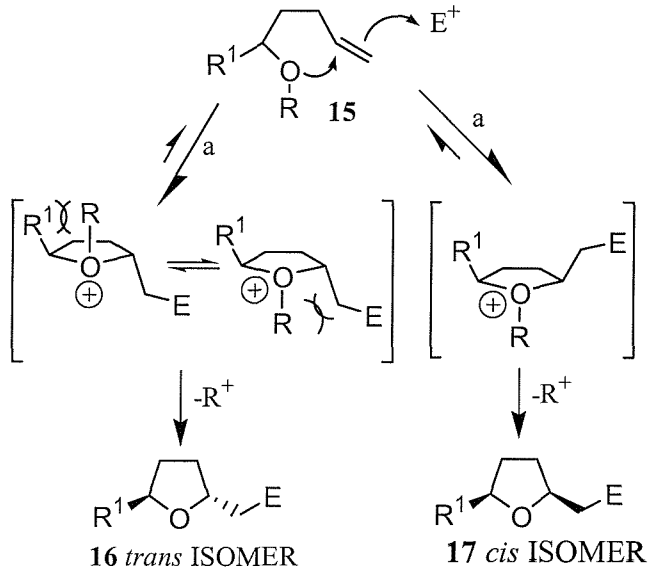
a. 5 mol % Ti(*i*-PrO)$_4$, *t*-BuOOH, diethyl Tartrate (Sharpless)
b. dioxane / NaOH / 100 °C

Figure 6. Epoxidation – Cyclisation as reported by Hoye *et al.*

1.2.2 Halocyclisation of λ,δ - unsaturated alcohols.

In the early 1980s, it was shown that γ,δ - unsaturated alcohols can be used as precursors to 2,5-disubstituted THF ring systems.[11] The stereoselectivity of the final products **16** and **17** can be controlled by the substituent groups (figure 7), in particular the nature of substituent R. The larger the substituent R, the greater the steric hindrance present in the intermediate cation leading to the *trans* isomer. When R = H it is the *trans* product **16** that is favoured, however, as the size of the R group is increased, the *cis* product **17** is preferred due to a reduction of steric interactions in the intermediate cation (see table 1).

The loss of the alkyl group R from the oxonium ion must be slow in comparison to the reversal of the formation in order for the *cis* "route" to be favoured thermodynamically as well as kinetically. There is a fine balance to be struck: if the loss of the R group is too slow, a number of side reactions can occur, such as the cleavage of other carbon-oxygen bonds within the molecule. Bearing this in mind, the poor yield for the methylether (R = CH_3, table 1) is explained. As a consequence the substituent groups chosen have to be of an adequate size so as to cause a steric effect, but cannot be too big because they may prevent cyclisation.



a. CH_3CN, 0 °C, with some exceptions where $NaHCO_3$ is added for alcohol substrates.

Figure 6. Steric interactions of cation intermediates.

Table 1.

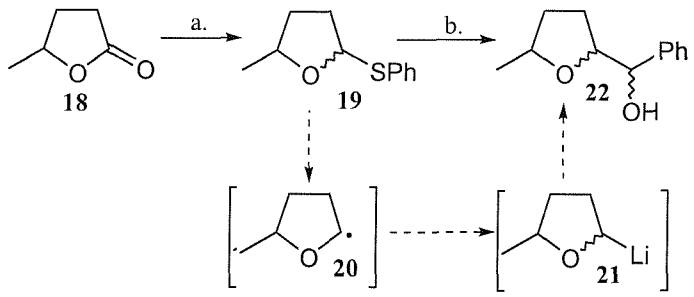
R	R^1	E	*cis / trans* ratio	yield %
H	CH_3	iodine	0.5	66
CH_3	CH_3	iodine	0.5	15
CH_2Ph	CH_3	iodine	2	60
$SiMe_2$-*t*-Bu	CH_3	iodine	3	43
Si-*t*-$BuPh_2$	CH_3	iodine	8	30
BB	CH_3	iodine	3.7	74
DCB	CH_3	iodine	21	63
H	$(CH_3)_2CH$	iodine	0.25	88
DCB	$(CH_3)_2CH$	iodine	20	95

N.B. BB = 4-bromobenzyl.
DCB = 2,6-dichlorobenzyl.

It was subsequently shown that unsaturated alcohols could be treated with a 1:1 mixture of mercuric acetate and water to afford THFs. The resulting organomercuric compound was reduced to give the desired THF system with a reasonable selectivity (90% isomeric purity in favour of the *trans* THF).[12]

1.2.3 Preparation of 2,5 disubstituted THF systems by a radical reaction.

Starting with thiophenylglycofuranoside (**19**) reductive lithiation leads to the corresponding lithio-derivative **21**. After addition to benzaldehyde a stereoselectively poor racemic mixture of the resulting 2-(hydroxybenzyl)-5-methyl THF (**22**) (figure 8) was observed. In the work of Keck *et al*, a related radical reaction was used to prepare C-allylglycofuranosides.[13] The required radical **20** was generated by using either thermal decomposition or by photo-initiation.



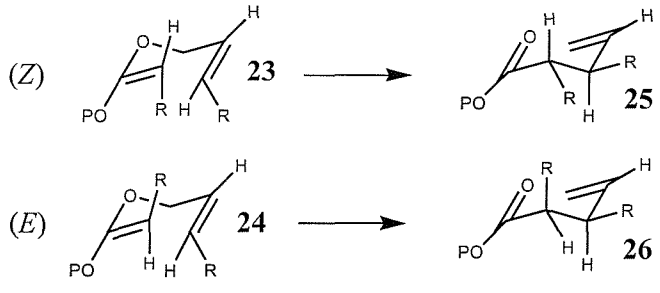
a) i) DIBAL-H / Toluene / -78 °C / 1hr. ii) PhSH / BF_3•OEt_2 / -78 °C / 5 mins / 97%
b) i) DMAN-Li / THF / -78 °C / 45min. ii) PhCHO / -78 °C / 51%.

Figure 8. Alkylation of THF ring *via* a radical intermediate.

1.2.4 Ester enolate Claisen rearrangement.

During the late 1970s, Ireland *et al* showed that it was possible to form 2,5-disubstituted THF species using a stereoselective Claisen rearrangement.[14] The methodology was first used on a number of allylic esters, preferably as their silylketene acetals, but also as their enolate ion. [3,3] Sigmatropic rearrangement provided the corresponding γ,δ-unsaturated acids (figure 9).

Enolisation was carried out using lithium diisopropylamide (LDA), where the geometry of the products could be controlled by choice of solvent. If THF was used the *Z*-enolate was favoured, whereas using THF with 23% of hexamethylphosphoramide (HMPA) produced mostly the *E*-enolate.

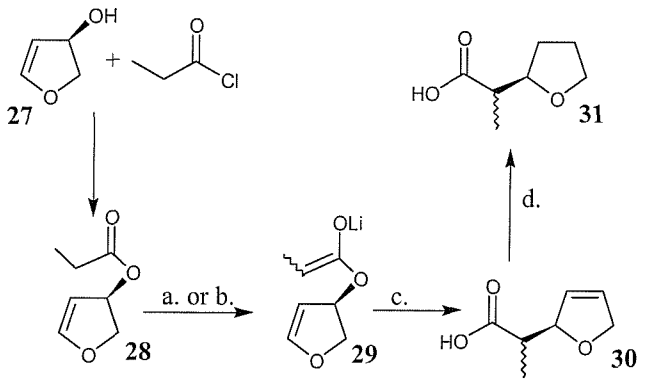


P= *t*-$BuMe_2Si$

Figure 9. The predictable stereochemical consequence of enolate rearrangement.

In later work Ireland applied this methodology to the preparation of pyranoid and furanoid systems (figure 10). It involved the use of a glycal **27** that was esterified with an appropriate acid chloride, yielding the enolate **29** after treatment with LDA.[15] Warming the intermediate enolate

29 resulted in rearrangement to give substituted dihydrofuran **30**. Hydrogenation finally yielded the corresponding substituted THF species **31**.

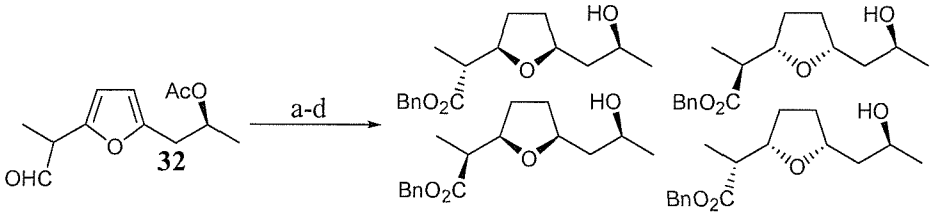


Reagents and conditions: a) LDA / THF.
b) LDA / THF / HMPA.
c) Heat.
d) H_2.

Figure 10. Enolate rearrangement as shown by Ireland *et al.*

1.2.5 Hydrogenation of substituted furans.

THF systems, put in simple terms are the saturated "relation" to the furan ring systems. Therefore hydrogenation of furans should provide access to THFs. Hence, a 2,5-disubstituted furan can be hydrogenated to form a 2,5-disubstituted THF. A major drawback of this method is the fact that it is difficult to control the stereoselectivity of the reaction and so a mixture of diastereoisomers is usually produced. Poor selectivity has been used as an advantage in the past, where the different diastereoisomers of nonactic acid (**33**) have been prepared. Taking the appropriate furan starting material **32** as a means of synthesising the different diastereoisomers of nonactin (figure 11).[16]



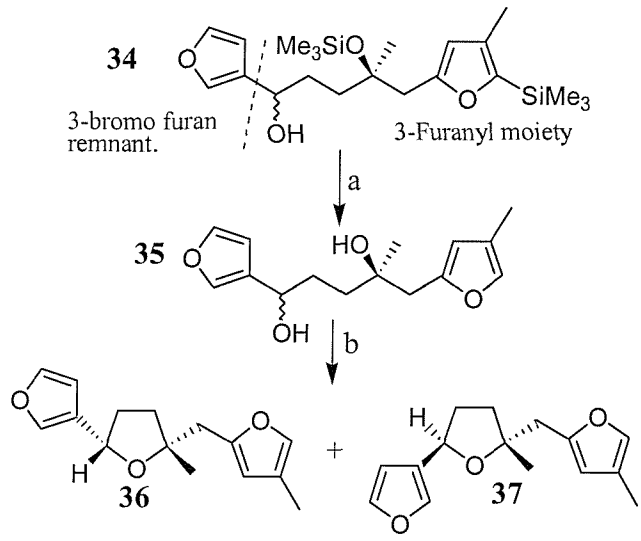
Reagents and conditions: a) Ag_2O, b) H_2 / Rh-Al_2O_3, c) KOH, d) BnCl.

33 i-iv

Figure 11. Hydrogenation of nonactic acid.

1.2.6 Cyclisation of 1,4-diols.

During an investigation in 1991 into the structure of athanasin (**36**) and its synthetic propagation, Bojack and Bornowski demonstrated a simple approach to the synthesis of THFs (figure 11).[17] In their approach 3-bromofuran was lithiated then treated with an aldehyde moiety. Having coupled the two substrates to form the trimethylsilyl protected diastereomeric pair of difuran alcohols **34**, deprotection gave the diol **35**, which was cyclised to the final product (**36, 37**). After the two products had been separated, optical rotational analysis and spectroscopic data was collected allowing the determination of the structure of athanasin (**36**) to be determined.



Reagents and conditions: a) citric acid (MeOH / H_2O), r.t., 25 hrs (53%).
b) TsCl (Pyridine), r.t., 20 hrs (89%)

Figure 12. Cyclisation of a 1,4-diol using a sulphonate.

1.3 Oxidative Cyclisation of 1,5-dienes using Potassium permanganate.

The use of potassium permanganate to achieve the oxidative cyclisation of 1,5-dienes has been well documented in the past. Despite this, the yields quoted for such reactions in the past have been disappointing, normally around 30%.[18]

Even though these results have been poor, the reaction offers great potential in that 2,5-disubstituted THF systems can be synthesised in one step from readily accessible starting materials. In addition, up to four oxygen-bearing stereocentres are created in the product.

1.3.1 The potassium permanganate oxidative cyclisation.

Usually, Potassium permanganate may be used as a dihydroxylating agent for alkenes. Its use under mild alkaline conditions converts alkenes to the corresponding diols. Under neutral or acidic conditions the major product observed is usually an α-hydroxy ketone. An alternative pathway reaction under acidic conditions is C=C bond cleavage, dominates under more strongly acidic conditions.

During any reaction involving manganese there can be a number of oxidation states present. Which state is dependent upon the pH of the reaction and the substrate being used. The longer the reaction proceeds the more alkaline it becomes due the production of OH^- ions (MnO_4^- + $2H_2O$ + $3e^-$ → MnO_2 + $4OH^-$). Bearing this in mind it is possible to manipulate which products are obtained by maintaining a constant pH using a buffer or CO_2 ebbulition.

In the case of 1,5-dienes the use of potassium permanganate causes cyclisation to 2,5-disubstituted THFs (figure 13). Permanganate oxidative cyclisation of 1,5-dienes was discovered by accident at the beginning of the century by Kotz and Steche. Particular interest has been shown to this area in the last few decades after work carried out by Klein and Rojahn in 1967. [18-26]

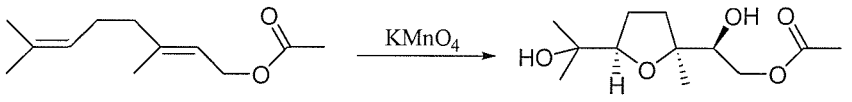


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Figure 13. Oxidative cyclisation of Geranyl acetate.

1.3.2 Stereoselectivity in the oxidation of 1,5-dienes by potassium permanganate.

Much research has been carried out on the stereoselectivity of the permanganate oxidation of 1,5-dienes. One group led by Walba used the permanganate oxidation on three isomeric dienes **40, 41** and **43** (figure 14) to produce the corresponding *cis*-2,5-disubstituted THFs **43**, **44** and **45**.[19]

They showed by gas chromatographic (GC) analysis of the reaction mixture that the reaction was >97% stereospecific, producing 4 new stereocentres in a 1 step process. Use of GC analysis with the purified THFs determined that there was very little in the way of cross contamination. The structures of the products were determined by the single crystal X-ray analysis of the bicyclic ketal derivative **46** of the THFs. The crystal structure allowed the configuration of THF **45** to be

determined and hence the relative stereochemistries of the other two THFs with the help of symmetry properties obtained from their ^{1}H and ^{13}C NMR spectra.

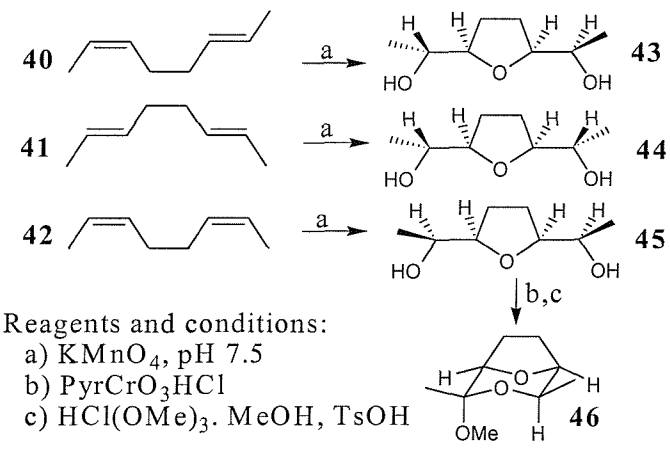


Figure 14. Oxidative cyclisation carried out by Walba *et al.*

Similar work carried out by a group in Oxford led by Baldwin at around the same time used deuterated dienes in order to investigate the stereochemistry of the oxidative cyclisation.[23] They reached a similar conclusion as to the specificity of the cyclisation, highlighting the potential advantages provided by this reaction.

1.3.3 Mechanism of the oxidative cyclisation.

Both groups have proposed mechanisms by which the oxidative cyclisation reaction progresses. The mechanism proposed by the Walba group is based upon a Sharpless type mechanism (figure 15).[19]

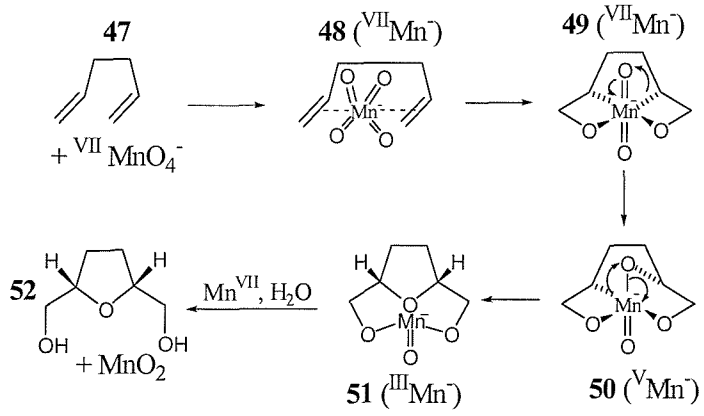


Figure 15. Walba's proposed mechanism of oxidative cyclisation.

They proposed an initial formation of a *bis*-π-complex (**48**) between the diene **47** and MnO_4^- ion, followed by the formation of an octahedral Mn(VII) intermediate **49** via two Sharpless-type [2+2]

additions. Alkyl migration then a key reductive elimination, both with retention of configuration, afforded Mn(III) diester **51**. The diester finally underwent oxidation and then hydrolysis to yield MnO_2 and the THF **52** with the correct stereochemistry.

Walba stipulated that the proposed mechanism is not absolute as there are several reasonable variations involving differences in timing of the [2+2] additions, alkyl migrations and the oxidation of the intermediate manganese species. The crucial step in the mechanism was felt to be that of the migration of the carbon from the manganese to the oxygen, in order to form the THF ring, with retention of configuration.

In distinct contrast, the Baldwin group suggested a different mechanism (figure 16).[23] They proposed an initial [3+2] cycloaddition of MnO_4^- to one of the double bonds of the deuterated diene **53**. The Mn(V) ester **54** that results is thought to undergo rapid oxidation by another permanganate molecule yielding a Mn(VI) diester **55**.

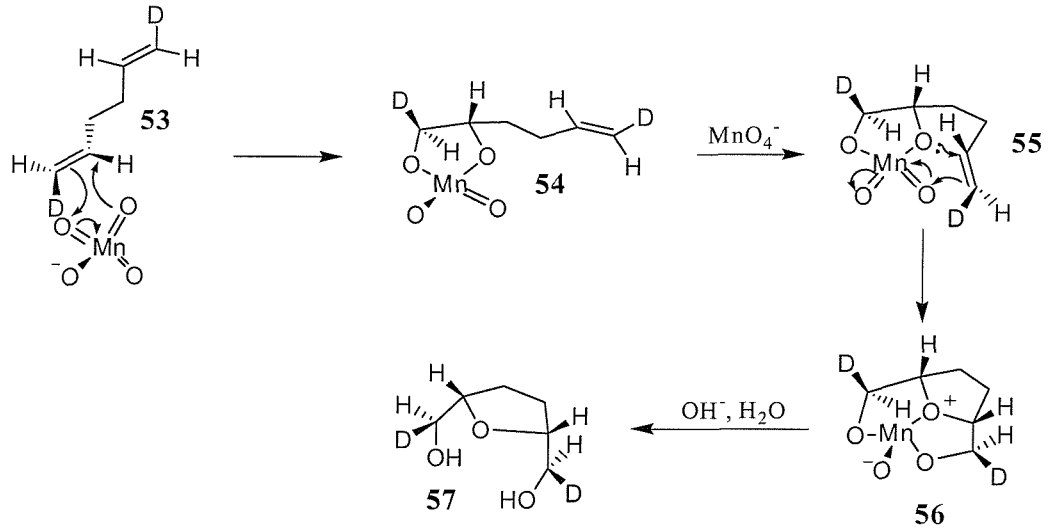


Figure 15. Baldwin's mechanism for oxidative cyclisation.

A process of intramolecular cycloaddition then ensues involving the remaining double bond of the diene to give intermediate **56**. Hydrolysis of this intermediate yields the *cis*-2,5-disubstituted THF product **57**. The mechanism put forward by the Baldwin group has the benefit of being supported by other sources of evidence. Compelling support comes from investigations carried out by Wolfe and Ingold on similar permanganate oxidations giving tetrahydrofurandiol and ketol compounds.[24] They showed using ^{18}O labelling, indirect evidence for the existence of the transient hexa- and pentacoordinated species during the course of their experiments. The findings in the work by Wolfe and Ingold are not compatible with the theory put forward by Walba. Their

results favoured a sequential oxidation of the two double bonds by means of the manganese (VI) ester similar to that of Baldwin's mechanism.

Despite added support from other groups, there is also the matter of the incorporation of solvent that has been observed in the formation of the THF diols. This cannot be as a result of a direct attack upon the terminal alkenic carbon atom of the manganese (VI) ester, because this would lead to one double bond being *cis*-oxygenated and the other undergoing a *trans*-oxygenation. It was therefore theorised that the incorporation of the solvent to carbon occurs *via* the manganese atom. This means that the penta- and hexacoordinated species transfer a labelled oxygen atom to one double bond and another oxygen atom to the other double bond.

Despite all the work in this and related areas, there is still uncertainty as to the exact mechanism of the reaction and so the debate continues as to which is correct.

1.3.4 Drawbacks of the permanganate oxidative cyclisation.

Although the attractions of this method can be easily envisaged, there are a number of crucial drawbacks that have prevented the reaction becoming widely used. Perhaps the most significant problem is the consistently low yields that have been observed by researchers carrying out this reaction. In most instances the yields achieved have been <55%, one of the best being 54% quoted by Brown and Kocienski in 1994.[4]

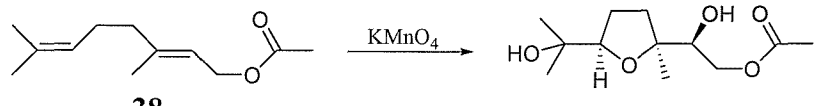
Another worrying factor is that the reaction yields THF systems that are solely of the *cis*- configuration. The structures of many natural products such as the acetogenins and polyether ionophores have a combination of *cis*- and *trans*- ring systems. As a result, in order to allow the variation of stereochemistry, the procedure has to be used in conjunction with other methodologies.[12] As a consequence, permanganate cyclisation of 1,5-dienes has not yet lived up to its predicted potential and become a mainstream procedure.

1.4 Aims and objectives.

1.4.1 Oxidative cyclisation optimisation

The methodology for the oxidative cyclisation of 1,5-dienes has shown promise in the past however disappointing yields have prevented its use as a mainstream methodology. An objective for this study is to investigate the oxidative cyclisation of geranyl acetate (**38**) by potassium permanganate and develop a procedure that produces the THF diol product **39** efficiently. The nature of the action of permanganate means

that the reaction mixture for such procedures has a constantly changing pH. One of the main factors to investigate is the effect of pH on the reaction. This is to be achieved by running reactions at a constant pH by using buffers.



38 39

Figure 16. Oxidative cyclisation of geranyl acetate.

1.4.2 Retrosynthesis of the target precursors.

Having optimised the conditions for the oxidative cyclisation of geranyl acetate **38**, the methodology is to be used on a selection of 1,5,9-trienes in order to produce lactones such as **47**, which should prove useful in the synthesis of polyether targets. The trienes were to be synthesised starting from neryl chloride (**41**) and geranyl chloride (**48**), which would define the geometry of the central double bond. A chain lengthening step will then be used employing ethylacetoacetate (**42**) in order to give a β-ketoester product such as **43** and the subsequent selective enolisation and trapping with diethyl chlorophosphate to give an enol phosphate **44** would determine the geometry of the final double bond. A selective alkylation step would finally give the desired 1,5,9-triene **45**.

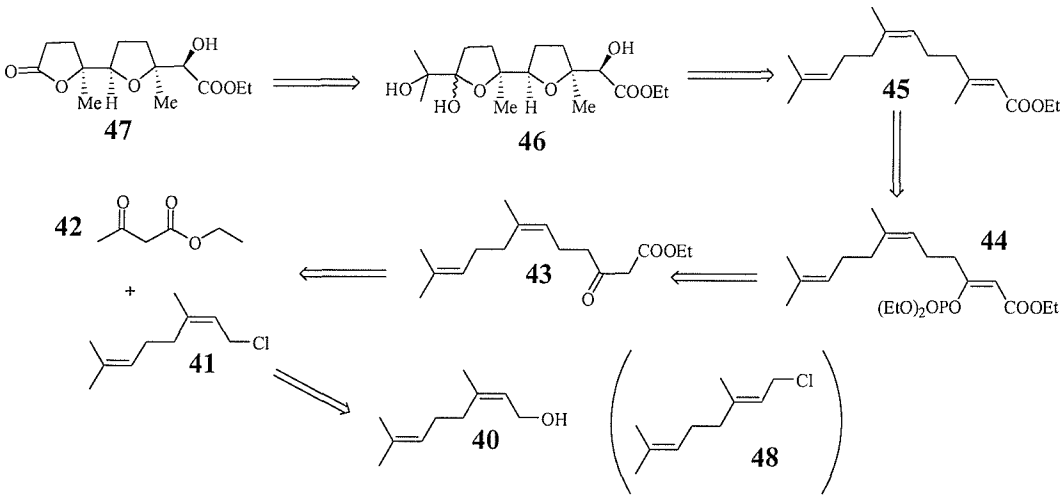


Figure 17. Retrosynthetic analysis for one target fragment.

Figure 17 shows the retrosynthesis for the (2*E*, 6*Z*)-1,5,9-triene **45** starting from nerol (**40**). Three other 1,5,9-trienes with different double bond geometries can be synthesised using the same route by varying the starting material (neryl chloride (**41**) or geranyl chloride (**48**)) and

altering the enolisation conditions to change the enol phosphate isomer produced. The different triene isomers can then be exposed to the permanganate oxidative cyclisation in order to give different lactol products such as **46** and this in turn could be undergo a diol cleavage to give lactone **47**.

2. Results and discussion

2.1 Optimisation of the potassium permanganate promoted oxidative cyclisation of geranyl acetate.

At first inspection, the low yield observed in the early work of Klein and Rojahn might simply be improved by increasing the amount of starting material that is cyclised in order to boost the yield (figure 18.).

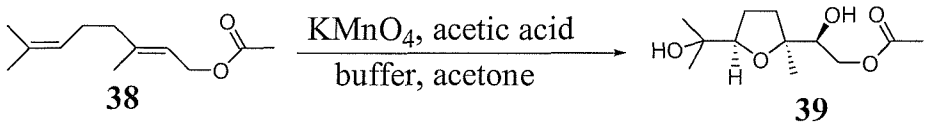


Figure 18. Permanganate oxidation of geranyl acetate.

The reaction was shown not to be as simple after preliminary reactions were carried out. There are a number of by-products associated with the reaction that need to be minimised. There are essentially three major products that are produced from the reaction, these being readily separated by TLC (see figure 19.)

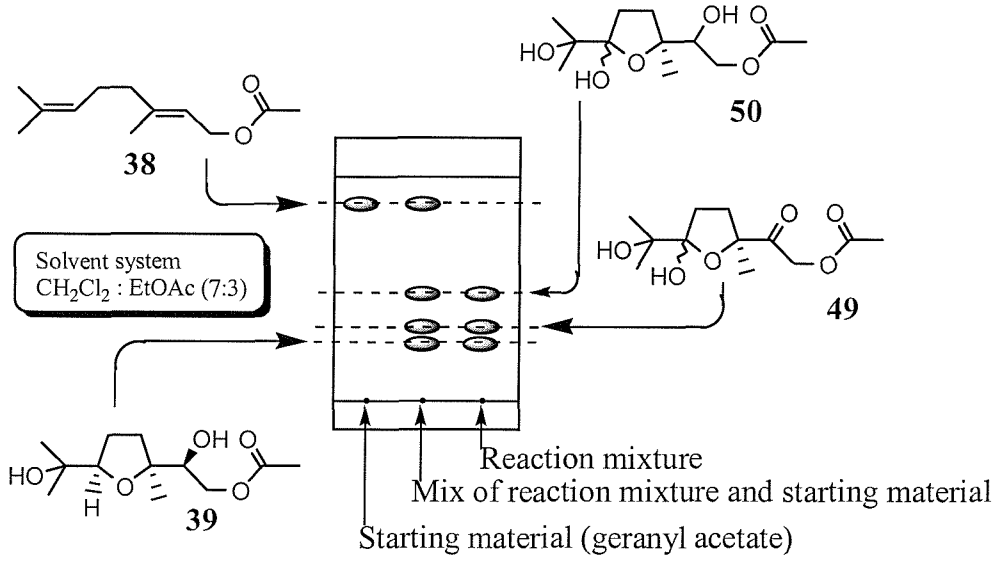


Figure 19. Typical TLC plate from cyclisation reactions of geranyl acetate.

The main by-product from the reaction is the lactol **49** which is present in all oxidative cyclisations carried out on geranyl acetate (**38**) whereas lactol **50** was only observed in small amounts in some reactions. It is our proposal that lactol **49** is produced from a different pathway to

that of the desired product **39**. This point will be discussed further later in this report.

It should be noted that in all the reactions carried out, a portion of acetic acid was added to balance the hydroxide ions produced as a result of the reduction of permanganate. The amount of acid added was however kept constant for each reaction. The amount of starting material was also kept constant along with the temperature and the amount of permanganate used (two equivalents). The pH was altered for each reaction by the addition of a specific buffer in order to observe any difference.[27] The nature of the reaction is such that during the addition of permanganate to the reaction mixture there is an initial steep decrease in pH and this is followed by a prolonged amount of fluctuation during the addition. The variation in the pH is quite pronounced and stabilisation occurs after the addition of the oxidant and stirring of the resulting mixture for a period of time (around 10-15 minutes). The addition of the buffer solution had a small effect on the pH fluctuation, however it was never held at a constant point. The buffer only served to lower the severity with which the pH varied.

The effect of the buffer on the yield of the major product **39** was found to be minimal, at values of pH 7.17 and 6.47 (table 2). The substitution of water for the buffer solution was found to improve the yield for the desired product **39** but numerous other by-products were also produced. When the reaction was conducted in the presence of a pH 6.24 buffer, a distinct improvement was observed in the yield of the major product without the complication of numerous by-products.

The result prompted the use of this buffer for subsequent reactions with the 1,5,9-trienes (**2.2**).

Table 2.

Literature [27]	Buffer substituent ratios††		added water /mL	observed pH values†		product (**39**)
pH value of the buffer solution	KH_2PO_4 (0.067 M soln.)	Na_2HPO_4 (0.067 M soln.)		pH (initial)	pH (final)	yield / %
-	-	-	2	6.6	6.4	56
7.17	3	7	-	8.1	6.9	46
6.47	7	3	-	7.1	7.1	48
6.24	8	2	-	7.1	7.4	59

† It should be noted that the observed pH readings are reported to 1 decimal place. The figures should be seen as a rough guide rather than an exact measurement. All other reaction conditions except the buffer were kept constant.

†† Figures stated are the ratios of the given solutions are mixed. The volume of the resulting buffer used is kept as a constant.

A key observation was the exothermic nature of the reaction, which made temperature control quite difficult at – 5 °C. At this temperature the permanganate solution needed to be added slowly. A short investigation into the effect of temperature on the reaction was undertaken. A reaction was carried out at -5°C (± 2°C). The same reaction was repeated at between -20°C and -25°C facilitating temperature control, with the added advantage that the addition of potassium permanganate could be achieved over a much shorter period (10-15 minutes), the temperature remaining fairly stable throughout. The temperature had little effect on the yield of the desired product **39**. The reaction run at -5°C yielded 59 % of the desired product **39**, while at around -25°C the yield was 58 %, a negligible difference.

A sequence of events leading to the formation of the major by-product **49** was proposed (figure 20). Evidence for the proposal came from the isolation of the α-ketol **51** from reactions conducted using only one equivalent of permanganate.

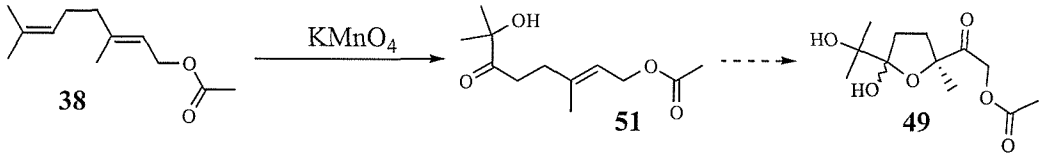


Figure 20. Underoxidation of geranyl acetate.

It is our proposal that the desired product **39** is formed by the mechanism outlined by Baldwin *et al*, shown in figure 15 (section 1.3.3). The lactol **49** is produced when the permanganate molecule attacks the first double bond and leaves before it can effect an intramolecular oxidation of the second double bond, producing the α-ketol **51** as an intermediate. The remaining double bond of α-ketol **51** is then attacked by a second permanganate molecule to give the lactol **49** (figure 20).

In order to prove that the lactol **49** is indeed formed by the oxidation of **51**, the hydroxy ketone **51** had to be isolated and re-exposed to permanganate. Unfortunately not enough of the compound could be isolated from reactions with permanganate in order to carry out an effective test. As a result, the hydroxy ketone **51** was synthesised *via* a different route (figure 21). Geranyl acetate was exposed to *m*-CPBA (*m*-chloroperbenzoic acid) in order to effect the selective epoxidation [28] to give epoxide **52** in 76 % yield. Hydrolysis of epoxide **52** gave the diol **53** in 81 % yield [29] and the final step only required the oxidation of the secondary alcohol to a ketone. The last oxidation step proved to be quite problematic.

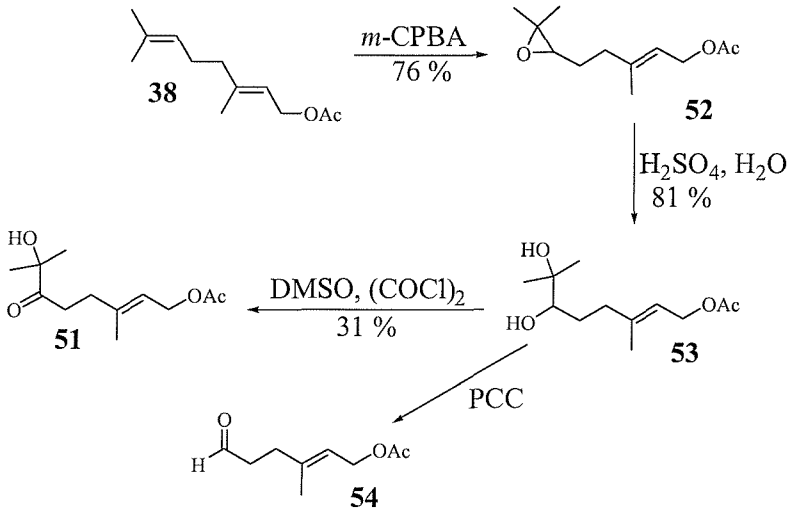


Figure 21. Synthesis of the hydroxy ketone **51**.

A number of different methods have been used in the past to oxidise secondary alcohols to ketones, and no problems were anticipated. Pyridinium chlorochromate (PCC) was first investigated, however it cleaved the vicinal diol **53** to the corresponding aldehyde **54**. The cleavage of analogous diol systems to aldehydes by PCC has been observed in the past.[30] Pyridinium dichromate was then investigated giving the same result. Dess-Martin reagent gave no reaction and sulphur trioxide pyridine complex ($SO_3 \cdot$ pyr)[31] also gave no reaction. The Swern oxidation using dimethyl sulphoxide (DMSO) and oxalyl chloride finally produced the desired hydroxy ketone **51**, albeit disappointing yield.[32-35] However, enough material was produced in order to expose the hydroxy ketone **51** to the permanganate conditions. ^{1}H NMR analysis of the crude reaction mixture from the permanganate oxidation of hydroxy ketone **51** showed the lactol **49** was indeed the major product confirming our prediction.

2.2 1,5,9-triene synthesis

we wanted next to investigate the oxidative cyclisation of 1,5,9-trienes. It was therefore necessary to be able to synthesise a number of trienes quickly and efficiently.

For the purpose of the investigation into the synthesis of the 1,5,9-trienes, nerol **40** and geranyl chloride **48** were used as starting materials, allowing the geometry of the central double bond of the 1,5,9-triene to be determined at the start of the synthesis.

An alcohol group is an exceptionally poor leaving group unless protonated or altered in some way.[36] The substitution of the –OH functionality of nerol (**40**) proved to be fairly straightforward (geranyl chloride is commercially available). The mesylation of the alcohol group was first employed, creating a much better leaving group, which was displaced by chloride ions under the reaction conditions. Collington and Meyers had previously demonstrated the conversion of allylic alcohols to allylic chlorides without rearrangement using a similar method.[37] It was shown that in the absence of lithium chloride a distinct increase in the rearranged chloride was noted. The addition of 1.0 equivalent of lithium chloride provided the chloride ion nucleophile in sufficient concentration to give a clean bimolecular displacement of the mesylate group.

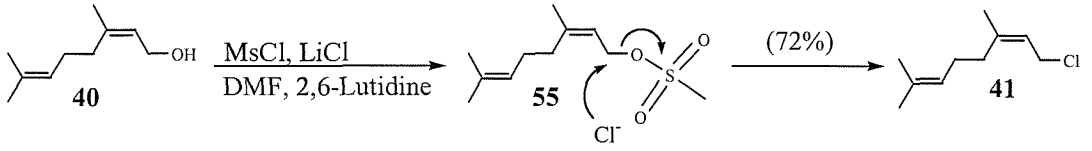


Figure 22. Mesylation of nerol to activate the alcohol functionality.

The reaction was carried out and gave a very respectable yield of neryl chloride (**41**). Despite the good result, it is our reasoning that it is possible to get much better yields from such a reaction if extra care and time is taken in the drying and purifying of the reagents. The reaction is particularly water sensitive so any water present hinders the course of the reaction. A number of the reagents used in the reaction are hygroscopic, particularly lithium chloride. It is likely that lithium chloride or other reagents may well be a source of water in the reaction mixture.

Neryl chloride (**41**) and geranyl chloride (**48**) were to be used as alkylating agents for the dianion of ethylacetoacetate (**42**) (figure 23). When treated with one equivalent of base, sodium hydride, the most acidic hydrogen is removed from ethyl acetoacetate (**42**) forming **56**. If the resulting anion was subsequently treated with a stronger base, *n*-butyl lithium, the next most acidic hydrogen can be removed, creating dianion **57**. Work in this area has been previously outlined by Huckin and Weiler[38] and when applied to our system allows a very efficient coupling of ethyl acetoacetate (**42**) to neryl chloride (**41**) and geranyl chloride (**48**).

Use of the alkylating agents neryl chloride (**41**) and geranyl chloride (**48**) has to be regulated carefully. If more than one equivalent is used a degree of dialkylation is observed, creating additional purification problems.

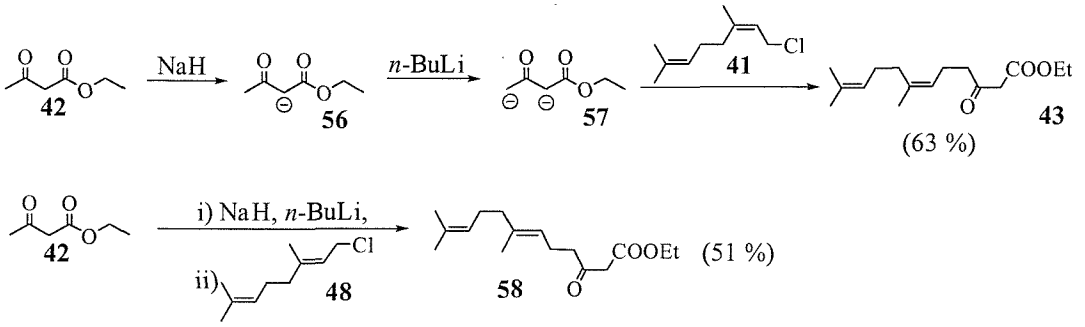


Figure 23. Dianion formation and coupling to neryl chloride and geranyl chloride.

However dialkylation was not observed in our reactions as just under one equivalent of alkylating agent was used to avoid this complication. The yield for these reaction was reasonable, around 63% for β-keto ester **43** and 51 % for β-keto ester **58**. Huckin and Weiler reported higher yields for related systems, however the alkylating agents used were normally bromides or iodides.

The next step in the synthesis of the 1,5,9-trienes was the generation of enol phosphates from the two β-keto esters produced from the dianion step. Enol phosphate intermediates have been used in the past to make tri-substituted alkenes. Sum and Weiler used β-keto esters similar to **43** and **58** to create enol phosphates quantitatively.[39] Although their methodology lent itself very well to our systems, the claim that when sodium hydride was used, the only isomer produced was the *Z* isomer was not something we could reproduce.

We treated **43** with sodium hydride in order to obtain the *Z*-enolate **59** (figure 24). After treatment with diethyl chlorophosphate the (2*Z*, 6*Z*) enol phosphate **44** was obtained. The coordination of the metal ion (sodium) with the ester group is believed to be responsible for the predominance of the *Z*-isomer.

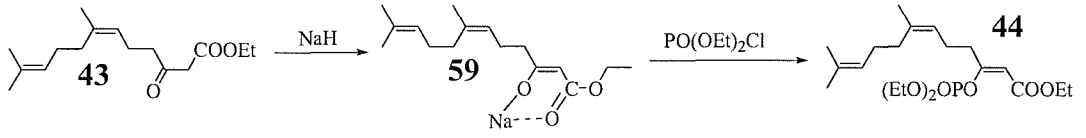
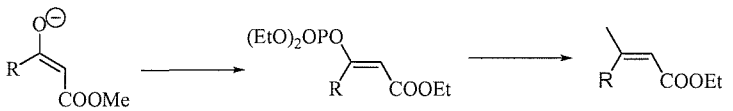


Figure 24. Enol phosphate formation from (6*E*)-β ketoester **43** *via* an enolate.

Although a very efficient reaction, the formation of some *E*-isomer detracts from the overall yield of the *Z*-isomer and also creates a significant purification problem, in that the *E*- and *Z*-isomers of the enol

phosphate are difficult to separate. Eventually a 50% yield of the (2*Z*, 6*Z*)-enol phosphate **44** was obtained, with a significant amount still remaining in a mixture with the (2*E*,6*Z*) isomer. In order to increase the selectively of this reaction it was postulated that if a base was used that possessed a counter ion that could interact more strongly with the ester functionality, the *Z*-enolate could be stabilised further and hence increase the selectivity of the reaction. Lithium was chosen as the metal and lithium hexamethyldisilazide (Li-HMDS) was used in place of sodium hydride. The substitution of the base proved to give an improvement to the selectivity of the reaction, which made purification of the (2*Z*, 6*Z*)-enol phosphate **44** much easier giving a final yield for the pure *Z* isomer of 80 %. The methodology was also applied to the (6*E*)-β keto ester **58** and (2*Z*, 6*E*)-enol phosphate **64** was obtained in 79 % yield (figure 26).

An amendment to the conditions employed to generate the enol phosphate was used in order to give the corresponding (2*E*)-enol phosphate **61**. Previously, the route to the (2*Z*)-enol phosphate had involved the formation of an enolate using Li-HMDS in diethyl ether and hence the enolate could chelate to a metal counterion. The ion pair was especially tight in a non-polar solvent like diethylether and existed as a coordinated complex **59** (figure 24).



60 **61** **62**

Figure 25. Enolate formation and eventual (2*Z*)-triene target.

The use of more polar solvents and the absence of a metal counterion means the free enolate is allowed to exist in a W-conformation, where the negatively charged oxygen and the oxygens of the ester group are allowed to distance themselves (dipolar organisation) from each other (figure 25). The enolate can then be trapped as the enol phosphate **61**.

Previous work by Weiler *et al.* showed that using HMPA (hexamethylphosphoramide) as a solvent with triethylamine as base *E*-enol phosphates were prepared in good yield and excellent selectivity.[40] Our approach employed DMPU (dimethylpropyleneurea) rather than HMPA. The reaction proceeded with in good yield for (2*E*, 6*Z*)-enol phosphate **63** (figure 26). (2*E*, 6*E*)-enol phosphate **65** was obtained in slightly higher yield.

The completion of these reactions meant that all four enol phosphate isomers could then be taken forward to the alkylation step.

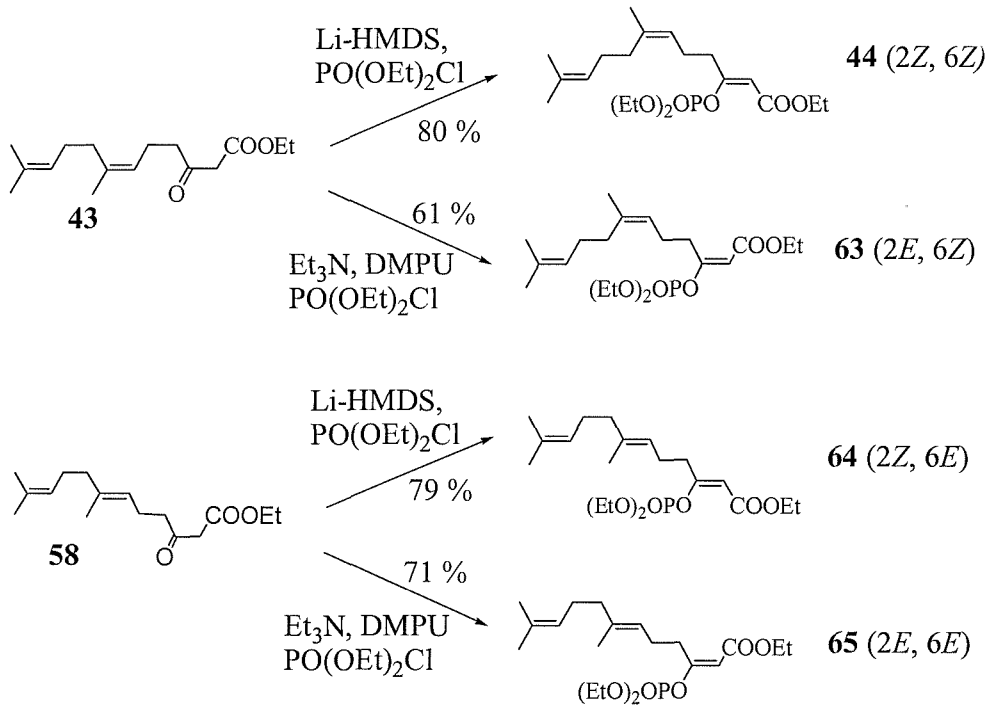


Figure 26. Synthesis of four isomeric enol phosphates.

The use of cuprates as alkylating agents has been well documented. They have been shown to possess tolerance for many functional groups even free –OH groups.[41] The tolerance of copper reagents for funtionalities like alcohols and other carbonyls, within the substrate makes them very versatile and useful in synthesis.

The use of lithium dimethyl cuprate ($LiMe_2Cu$) for the alkylaton of an enol phosphate has been used a number of times in the past.[39, 42] The formation of the reagent is fairly straightforward. It can be achieved *in situ* by mixing two equivalents of methyl lithium with one equivalent of copper(I)iodide at 0°C (figure 27). The subsequent addition of (2*Z*, 6*Z*)-enol phosphate **44** at low temperature yielded the desired (2*E*, 6*Z*)-1,5,9-triene **45** stereospecifically.

After seeing the work of Sum and Weiler on the dialkyl cuprate alkylation, Eis and Schmalz reported that reactions were carried out at –78 °C for 3 hours and then at –50 °C for 1 hour, giving a 94% yield.[42] Initially, we ran the reaction at -78 °C and followed its progress by TLC. It appeared that the reaction did not proceed at all at this temperature. Gratifyingly, the reaction proceeded much more rapidly when the reaction mixture was warmed to around -50 °C. It is our belief that the

addition of the enol phosphate should be done at the lower temperature (-78 °C) and the reaction mixture can then be immediately warmed to -50 °C for around 2 hours. Using the revised temperatures and times, the reaction gave a yield of 85% for the (2*E*, 6*Z*)-1,5,9-triene **45** (figure 27).

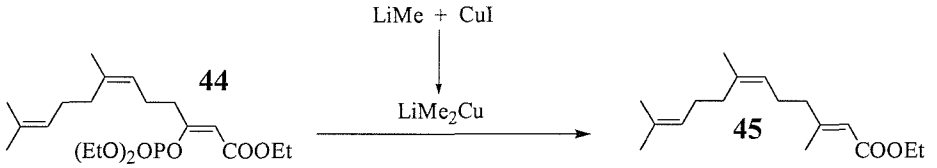


Figure 27. Dialkyl cuprate alkylation of (2*Z*, 6*Z*)-enol phosphate **44**.

The methyl lithium used in the reaction was a 1.6 M solution in diethylether. Using this, the reaction yielded superb results. However, due purely to serendipity, one dialkyl cuprate reaction was run using methyl lithium in THF/cumene (10/90). No complications were anticipated however, preliminary investigations revealed that there were in fact two products produced in this reaction. It must be noted that the predominant product was that of the desired (2*E*, 6*Z*)-1,5,9-triene **45**. The other component proved to be inseparable by flash chromatography, although two peaks could be resolved by GC. Analysis by GC-MS has since shown that the second product is 14 AMU smaller suggesting the possibility that instead of adding a methyl group the reaction has added hydrogen, giving **65** (figure 28). The ^{1}H NMR of the mixture confirms the formation of the reduced product.

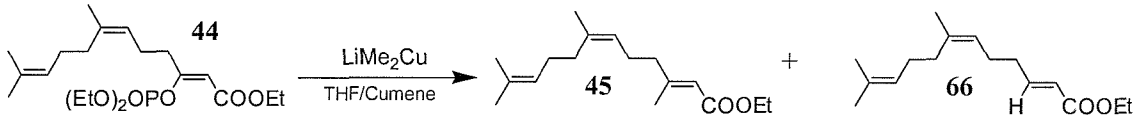
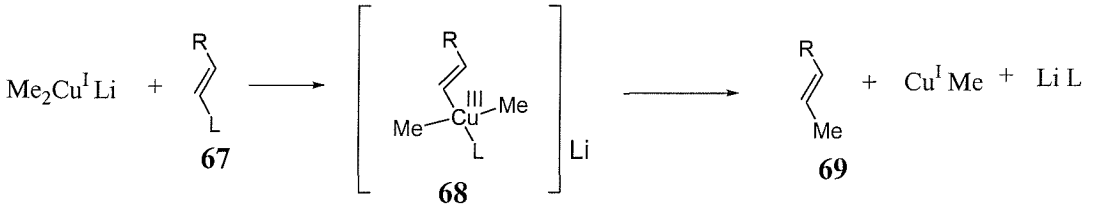


Figure 28. Unexpected reduced by-product.

To date very little is known about the mechanism for the cuprate alkylation. Effectively it is a nucleophilic substitution of sp^2 carbon atom, which is very difficult to achieve using other nucleophiles. One mechanistic proposal is the addition of the d^{10} cuprate and the olefinic species **67** giving a planar copper(III) d^8 intermediate **68**.[41] A reductive elimination then follows giving the coupled product **69**.



L= Suitable leaving group, usually a halide atom.

Figure 29. Possible mechanism for the dialkyl cuprate reaction.

It is also a possibility that the reaction could proceed by a radical mechanism of sorts. Such a proposal becomes a realistic proposition if the results for the cuprate reaction that gave the reduced product **66** are kept in mind. The structure of cumene (**70**) is such that if it was to act as a hydride donor, trapping a radical intermediate **71**, the resulting tertiary radical **72** would be relatively stable, thereby explaining how the reduced product **66** came about, although we might have expected double bond isomerisation if this mechanism were in operation.

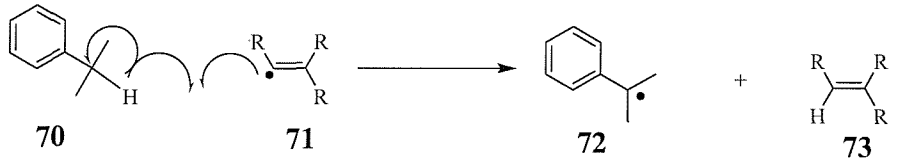


Figure 30. Possible radical trap mechanism involving cumene.

A radical mechanism such as described would be fairly difficult to prove, the only possibility being to trap out the radical intermediate with a purposely-added radical trap. It is likely that the lifespan of intermediate **71** is very short, as the copper centred radical alkylating agent would be in very close proximity. The fact that cumene would have been able to trap out radical intermediate **71** would be thanks to the fact that it was present in the reaction in such a large excess.

Reagent problems aside, the methodology seemed to be an ideal way in which to access the 1,5,9-trienes from their corresponding enol phosphates. However, when the (2*E*, 6*Z*) enol phosphate **63** was exposed to the cuprate alkylation in order to access the (2*Z*, 6*Z*)-1,5,9-triene we uncovered a problem. The reaction gave a near 1:1 mixture of *E*- and *Z*-isomers determined by GC analysis (figure 31). The existing cuprate method therefore could not be used as a means of accessing all the isomeric trienes and an alternate method was sought.

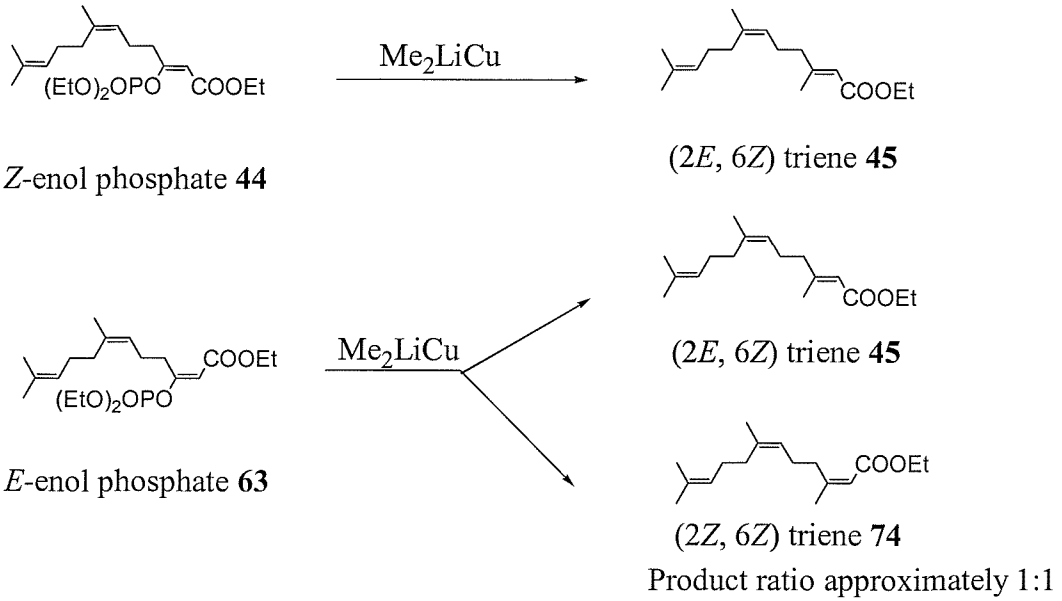


Figure 31. Failed use of the dimethyl lithium cuprate reagent

The failure of the cuprate alkylation meant that an alternative had to be found. Work by Weiler *et al.* demonstrated the use of a copper catalysed methyl Grignard reagents in the alkylation of analogous enol phosphate systems with excellent selectivity and good yield.[40, 43]

Initially the copper-catalysed Grignard reaction was used to alkylate the (2*Z*, 6*Z*)-enol phosphate **44** that had undergone clean alkylation with the cuprate reagent. The new reagent proved to be very impressive, providing a yield for the (2*E*, 6*Z*)-1,5,9-triene **45** of 82 % and excellent selectivity (virtually no *Z*-isomer was detected by GC analysis). An interesting point to note is that ^{1}H NMR of the crude product after work up was very clean and that very little in the way of purification was needed.

In a similar fashion the other three enol phosphates where alkylated using the copper catalysed methyl Grignard reagent with the same efficiency and excellent selectivity (figure 32). The copper-catalysed Grignard reaction allowed the completion of the synthesis of the 1,5,9-trienes with good overall yields and these compounds could then be exposed to the permanganate oxidative cyclisations.

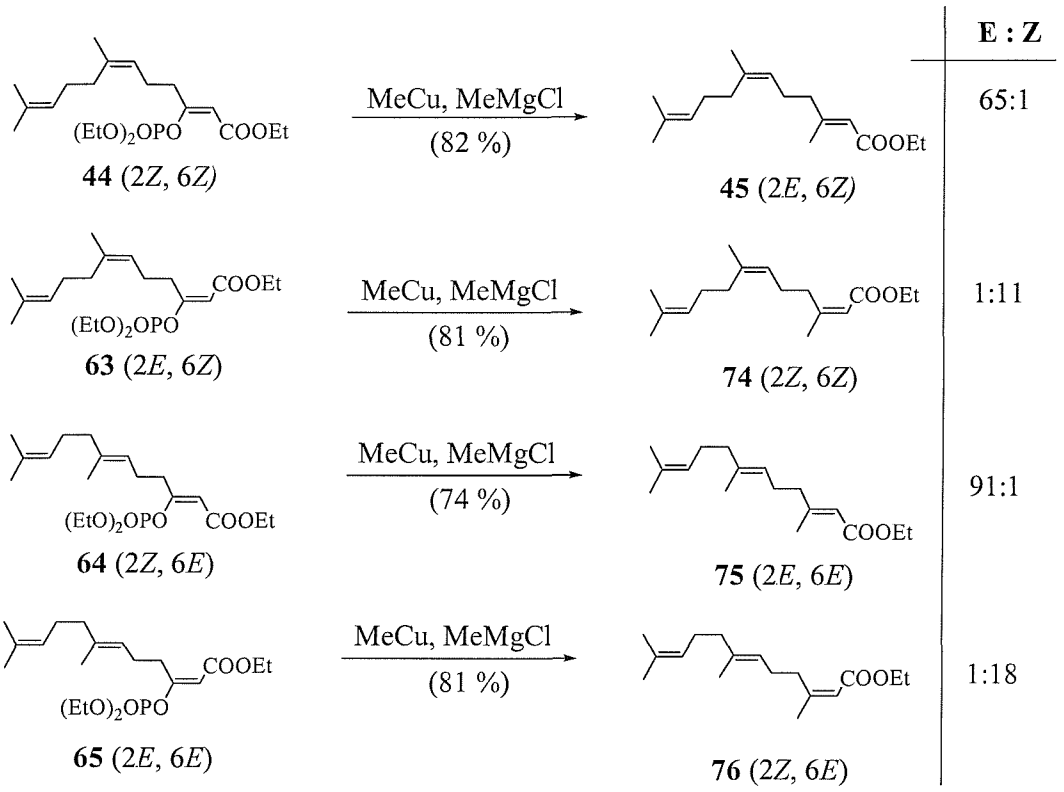


Figure 32. Synthesis of the isomeric 1,5,9-trienes from the corresponding enol phosphates and the product ratios determined by GC analysis.

2.3 Permanganate oxidation of 1,5,9-trienes

The optimised methodology for the oxidative cyclisation of geranyl acetate (**38**) was employed in order to convert the triene isomers into the corresponding THF systems (figure 33). Three equivalents of potassium permanganate were used (one equivalent per double bond), as around two equivalents were used for the reaction with geranyl acetate.

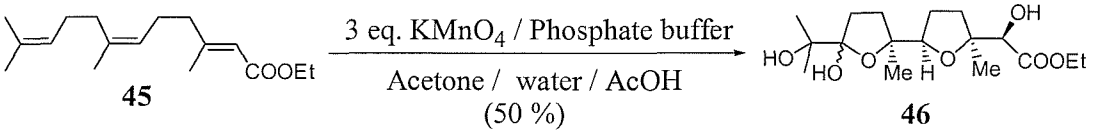
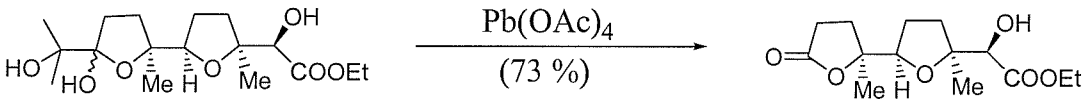


Figure 33. Permanganate oxidation of the 1,5,9-triene **45**.

A number of repetitions for the permanganate oxidative cyclisation of triene **45** were carried out in order to try and improve the poor yield obtained in the initial reactions. The problem of low yield was tracked down to the high solubility of **46** in the aqueous layer during work up. Eventually, saturation of the aqueous layer with NaCl improved the yield of THF triol **46** to 50 %. The lactol products indeed proved to be very polar by TLC and as a result were reasonably tricky to purify by flash chromatography, especially as the contaminating by-products were of a similar polarity and the products exist as a mixture of epimers. The lactol ring opens and closes *via* a hydroxy ketone intermediate and was isolated as a mixture of epimers.

A number of different reagents have been used previously for the cleavage of vicinal diols in good yield including pyridinium chlorochromate (PCC)[44], silver oxide[45] and sodium periodate.[46,47] The periodate method seems to have the best results, however, previous work had shown that the use of this method to generate the lactone **47** from lactol **46** led to the decomposition of the substrate.[48] For this reason the initial study of the cleavage step involved to use of lead tetraacetate in the presence of sodium carbonate (figure 34).[49]



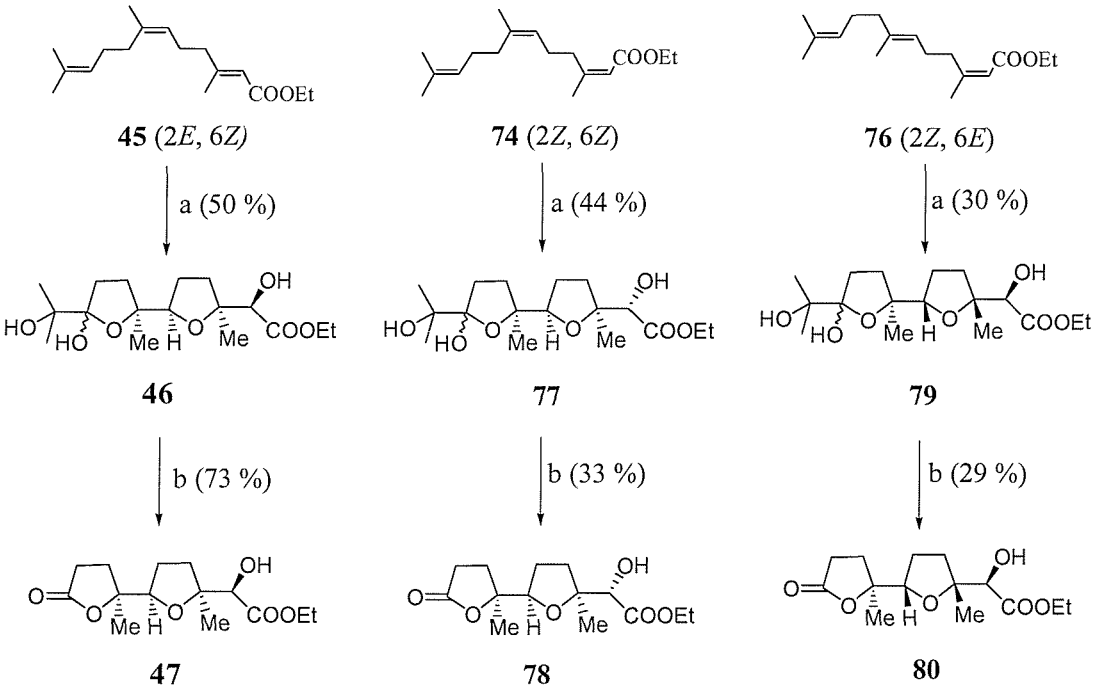
46 **47**

Figure 34. Lactol cleavage by lead tetraacetate.

Initial analysis of the reaction mixture appeared to imply that the reaction had worked well. The reaction was followed by IR (infrared) spectroscopy and this showed the shrinking of the broad alcohol peak at around 3500 cm^{-1} and the emergence of a C=O peak around 1780 cm^{-1}, corresponding to the formation of the lactone. Supporting evidence for the diol cleavage was gained by the presence of a significantly less polar product by TLC. The purification of the lactone **47** was much more straightforward than the lactol **46** and the reaction was determined to give a yield of 73 % for lactone **47**.

Oxidative cyclisations and diol cleavages have been carried out using two of the other trienes and employing the same methods that were used for producing lactol **46** and lactone **47** (figure 35). The reactions were one off experiments and as a result the yields are low, around 40 % for the lactols **77** and **79** and slumping to around 30 % for each of the cleavages to give lactones **78** and **80**. It is our belief that more

experiments would have allowed the optimisation of the yields on a par with the yields for lactol **46** and lactone **47**. Despite the disappointing yields for these reactions, enough of compounds **77**, **78**, **79** and **80** were isolated to allow characterisation.



Reagents and conditions:
a) 3 Eq. $KMnO_4$ (Aq.), phosphate buffer, acetone.
b) Pb $(OAc)_4$, Na_2CO_3, CH_2Cl_2.

Figure 35. Synthesis of the lactone targets.

The oxidative cyclisation of the (2*E*, 6*E*)-triene **75** using permanganate was not undertaken as it has been carried out in previous work.[48] The lactol derived from the oxidation of triene **75** produced has had its stereochemistry confirmed by X-ray crystallography. 2-D COSY NMR and NOE experiments on lactone **78** have confirmed the *cis*- arrangement of the substituents at the 2,5-positions on the THF ring (Me and H). A substantial NOE interaction was observed between H^b and Me^1 and also H^a and Me^1 (Figure 36). Sizeable interactions were also noted between Me^1 and H^e and H^e and Me^2 supporting the substituents being arranged in a *cis*-configuration.

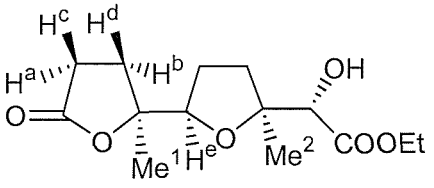


Figure 36. NOE interactions for lactone **78**.

3. Conclusions

- An efficient procedure has been determined for the oxidation of geranyl acetate (**38**) to the corresponding THF diol **39** minimising the formation of by-products.
- The identification of the hydroxy ketone **51** and its subsequent synthesis and exposure to the permanganate oxidative cyclisation conditions to give lactol **49** has verified the route by which the major by-product is formed.
- A group of four trisubstituted isomeric 1,5,9-trienes has been synthesised in high yield from the corresponding enol phosphate intermediates. The synthesis has been achieved selectively to give pure, single isomers, proven by GC analysis, from 1,5 dienes (neryl chloride (**41**) and geranyl chloride (**48**)).
- Three of the 1,5,9-trienes synthesised have been exposed to the permanganate oxidative cyclisation conditions. A good optimised yield for lactol **46** of 50 % was obtained and one-off reactions to give lactols **77** and **79** were also achieved.
- The cleavage of lactol **46** to its corresponding lactone **47** using lead tetraacetate was achieved with a 73 % yield. The cleavage of lactones **77** and **79** to give lactones **78** and **80** in one-off reactions proceeded in lower yields, however there is reason to believe that these reactions can be optimised in the future.
- The use of potassium permanganate in order to produce THF systems from readily accessible 1,5,9-trienes has been shown to proceed stereoselectively and with good yield. The introduction of a large amount of functionality and stereochemistry in one step provides a powerful synthetic method, which should find wider application in synthesis.

4. Further Work

- Optimisation of the yields for lactols **77** and **79** and lactones **78** and **80**.
- The feasibility of the combination of phase-transfer conditions in conjunction with permanganate oxidative cyclisations.
- Synthesis of optically enriched THF systems using an asymmetric potassium permanganate oxidative cyclisation.
- The application of the oxidative cyclisation reaction with disubstituted 1,5,9-trienes in order to afford fragments for the total synthesis of *Annonaceous* acetogenins.

5. Experimental

General Information

All ^{1}H-NMR and ^{13}C-NMR spectra were recorded in a $CDCl_3$ solution and NOE experiments with a C_6D_6 solution. The machines used were a Bruker AC300 (300 MHz), a Bruker AM300 (300 MHz) and a Bruker DPX400 (400 MHz). Chemical shifts are given in δ units. Abbreviations used for reporting data are s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet) and m (multiplet). Coupling constants (*J*) are given in Hz. All spectra are reported uncorrected.

IR spectra were recorded on a Bio-rad FTS 135 spectrometer or on a Nicolet impact 400 spectrometer. Abbreviations used for reporting data are s (strong), m (medium), w (weak) and b (broad).

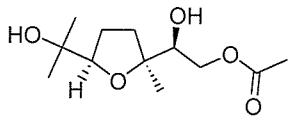
Mass spectra were recorded by a GC-MS method on a Thermoquest trace MS single Quadrupole mass spectrometer. The GC column used a RTX5 capillary column with helium carrier gas, the reagent gas being ammonia and the source temperature 200 °C for the chemical ionisation mode used (unless stated otherwise).

All solvents were dried or purified where appropriate.

General procedure for oxidative cyclisation of geranyl acetate using potassium permanganate.

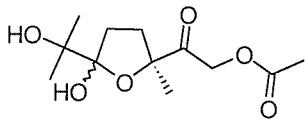
A stirred mixture of geranyl acetate (660 μL, 3.06 mmol) in acetone (30 mL) with either water or buffer of the required pH (2 mL) was cooled to around – 20 °C. $KMnO_4$ (16.25 mL of a 0.4 M solution in water, 6.5 mmol) containing acetic acid (333 μL, 5.82 mmol) was added dropwise so as not to raise the temperature of the reaction above – 18 °C. The mixture was stirred for a further 15 minutes before being quenched using a saturated aqueous solution of sodium meta bisulphite ($Na_2S_2O_5$) over ice (exothermic) until decolourised. The aqueous layer was extracted with diethyl ether (1 x 100 mL) and dichloromethane (12 x 50 mL). The fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oily solid. Purification was by recrystallisation from diethylether/hexane and after filtering, the mother liquor was further purified by flash chromatography on silica (2.5 x 12 cm) eluting with dichloromethane:ethyl acetate (8:2 then 7:3, 6:4, 1:1) to give the desired product **39** as a white solid and lactol **49** as a pale yellow oil.

(39) - (2*S*)-2-hydroxy-2-[(2*S*, 5*R*)-5-(1-hydroxy-1-methylethyl)-2-methyl tetrahydro-2-furanyl] ethyl acetate.



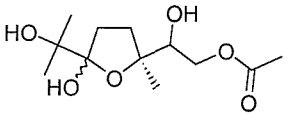
m.p = 106.5-107.5 °C.
IR (cm^{-1}) 3307 (br), 2970 (m), 2885 (m), 1730 (s), 1449 (w), 1248 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 4.32 (1H, dd, *J* = 11.0 and 2.9 Hz, C**H**$_2$-OAc), 4.12 (1H, dd, *J* = 11.7 and 8.1 Hz, C**H**$_2$-OAc), 3.88 (1H, t, *J* = 7.4 Hz, C**H**-O), 3.70 (1H, dd, *J* = 8.8 and 2.9 Hz, C**H**OH), 2.24-2.16 (1H, m, C**H**$_2$), 2.12 (3H, s, O-COC**H**$_3$), 2.03-1.90 (2H, m, C**H**$_2$), 1.65 (1H, dt, *J* = 11.8 and 5.9 Hz,), 1.28 (3H, s, C**H**$_3$), 1.23 (3H, s, C**H**$_3$), 1.14 (3H, s, C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 171.6 (**C**OO), 85.8 (**C**H-O), 84.2 (**C**H-OH), 75.4 (O-**C**-CH$_3$), 72.0 ((CH$_3$)$_2$**C**OH), 66.2 (O-**C**H$_2$), 35.7 (**C**H$_2$C-CH$_3$), 27.8 (**C**H$_2$CH-O), 26.7 ((**C**H$_3$)$_2$COH), 25.4 ((**C**H$_3$)$_2$COH), 23.1 (C-**C**H$_3$), 21.2 (OCO**C**H$_3$).
Mass spec. *m/z* **(relative intensity and ion)** 229.1 (100 [M - OH]$^+$), 247.1 (4 [M+H]$^+$).

(49) - 2-[rac-5-hydroxy-5-(1-hydroxy-1-methylethyl)-2-methyl tetrahydro-2-furanyl]-2-oxo ethyl acetate.



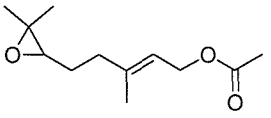
IR (cm^{-1}) 3479 (br), 2988 (s), 2933 (m), 1741 (s), 1462 (m), 1385 (s).
^{1}H-NMR (CDCl$_3$, δ ppm) 5.23 (1H, d, *J* = 17.9 Hz, C**H**$_2$-OAc), 5.03 (1H, d, *J* = 17.9 Hz, C**H**$_2$-OAc), 2.58-2.42 (1H, m, C**H**$_2$), 2.16 (3H, s, O-COC**H**$_3$), 2.14-1.82 (3H, m, C**H**$_2$), 1.36 (3H, s, C**H**$_3$), 1.32 (3H, s, C**H**$_3$), 1.27 (3H, s, C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 207.7 (**C**OO), 170.8 (O-**C**O-CH$_3$), 110.9 (**C**(OH)-O), 88.7 (O-**C**-CH$_3$), 74.4 ((CH$_3$)$_2$**C**-OH), 65.9 (O-**C**H$_2$), 34.2 (**C**H$_2$), 31.8 (**C**H$_2$), 24.5 (C-(**C**H$_3$)$_2$), 23.7 (O-CO**C**H$_3$), 20.7 (**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 243.0 (77 [M – OH]$^+$), 260.1 (11 [M]$^+$), 278.1 (4 [M+H$_2$O]$^+$).

(50) - (2S)-2-hydroxy-2[rac-5-hydroxy-5-(1-hydroxy-1-methylethyl)-2-methyltetrahydro-2-furanyl] ethyl acetate.



IR (cm^{-1}) 3496 (br), 2975 (m), 2924 (m), 2855 (w), 1745 (s), 1378 (m), 1241 (m).
^{1}H-NMR(CDCl$_3$, δ ppm) 4.0 (1H, dd, J = 5.2 and 2.2 Hz C**H**OH), 3.88 (2H, dd, J = 6.6 and 5.1 Hz C**H**$_2$-OAc), 2.18 (3H, s, O-CO-C**H**$_3$), 2.10 (3H, s, C**H**$_3$), 1.98-1.80 (2H, m, C**H**$_2$), 1.75-1.62 (2H, m, C**H**$_2$), 1.49 (3H, s, C**H**$_3$), 1.33 (3H, s, C**H**$_3$).
^{13}C-NMR(CDCl$_3$, δ ppm) 171.0 (**C**OO), 113.3 (**C**(OH)-O), 88.1 (O-**C**-CH$_3$), 80.4 (**C**HOH), 70.4 ((CH$_3$)$_2$**C**-OH), 64.1 (O-**C**H$_2$), 35.7 (**C**H$_2$), 32.4 (**C**H$_2$), 25.6 ((**C**H$_3$)$_2$COH), 24.5 (O-CO**C**H$_3$), 21.1 (**C**H$_3$).
Mass spec. *m/z* **(relative intensity and ion)** 227.1 (45 [M-H$_2$O and OH]$^+$), 245.1 (100 [M – OH]$^+$), 262.1 (3 [M]$^+$).

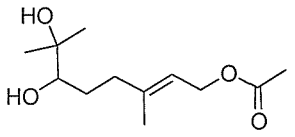
(52) - (*E*)-6,7-epoxy-3,7-dimethyl-1-acetoxy-2-octene



Geranyl acetate (5.0 g, 25.5 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled using an ice bath. To this was added $NaHCO_3$ (4.62 g, 54.9 mmol) followed by *m*-CPBA (6.3 g of a 50-60% mixture, 15.7-18.8 mmol) which was added in portions over a 20-minute period. A further portion of *m*-CPBA (2.0 g of a 50-60% mixture, 5.0-6.0 mmol) was added subsequently. After a further 30 minutes the resulting white slurry was washed with water (50 mL), sat. aqueous Na_2CO_3 (2 x 50 mL), water (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Purification by short path distillation (80-88 °C, 0.2 mmHg) afforded the title compound as a colourless oil (2.94 g, 13.87 mmol, 54 %).

IR (cm^{-1}) 2955 (w), 2925 (w), 1731 (s), 1669 (w), 1445 (m), 1373 (m), 1230 (s), 1117 (m), 1019 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 5.34 (1H, t, *J* = 6.9 Hz, C=C**H**), 4.53 (2H, d, *J* = 7.4 Hz, C**H**$_2$-OAc), 2.65 (1H, t, *J* = 6.0 Hz, (R)$_2$COC**H**CH$_2$), 2.2 (2H, m, C**H**$_2$(CH$_3$)C=), 2.0 (3H, s, C**H**$_3$CO), 1.68 (3H, s, C**H**$_3$C=), 1.65-1.54 (2H, m, (R)$_2$COCHC**H**$_2$), 1.28 (3H, s, (C**H**$_3$)$_2$COCH$_2$), 1.21 (3H, s, (C**H**$_3$)$_2$COCH$_2$).
^{13}C-NMR (CDCl$_3$, δ ppm) 171.1 (**C**O), 141.3 (CH$_3$**C**=C), 119.0 (=**C**H), 63.9 (**C**H-O), 61.3 (**C**H$_2$-O), 58.4 (**C**-O), 36.4 (**C**H$_2$(CH$_3$)C=), 27.1 ((R)$_2$COCH**C**H$_2$), 24.9 ((**C**H$_3$)$_2$CO), 21.1 ((**C**H$_3$)$_2$CO), 18.8 (**C**H$_3$CO), 16.5 ((**C**H$_3$)C=).
Mass Spec. *m/z* **(relative intensity and ion)** 170 (7), 153 (100), 137 (96).

(53) - (*E*)-6,7-dihydroxy-3,7-Dimethyl-1-acetoxy-2-octene

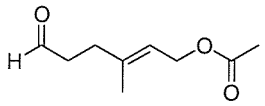


To a stirred mixture of epoxide **52** (1.0 g, 4.72 mmol) in water was added aqueous sulphuric acid (0.2 mL of 10%). The mixture was stirred at ambient temperature for 2 ½ hours, by which time the reaction mixture became homogeneous. The product was extracted with EtOAc (2 x 20 mL) and the combined extracts were washed with NaHCO$_3$ (2 x 20 mL), and brine (2 x 20 mL). The aqueous layers were combined and back-extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo* to yield a yellow oil (1.2 g). Purification was by short-path distillation (bp 110-122 °C, 0.05 mm/Hg) afforded the title compound as a colourless oil (874 mg, 3.8 mmol, 81%).

IR (cm^{-1}) 3421 (br), 2971 (w), 2930 (w), 1731 (s), 1716 (s), 1368 (m), 1234 (s), 1158 (m), 1076 (m), 1025 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 5.36 (1H, t, *J* = 6.6 Hz, R$_2$C=C**H**CH$_2$), 4.56 (2H, d, *J* = 6.5 Hz, C**H**$_2$-O), 3.30 (1H, dd, *J* = 10 and 2 Hz, C**H**-OH), 2.57 (H, broad s,), 2.50-2.25 (H,m,), 2.03 (H,s,), 1.69 (H,s,), 1.64-1.53 (H, m,), 1.47-1.37 (H,m,), 1.17 (H, s,), 1.13 (H, s,).

^{13}C-NMR ($CDCl_3$, δ ppm) 171.1 (**C**=O), 142.2 (R(CH_3)**C**=), 118.8 (C=**C**H), 78.1 (**C**H-OH), 73.2 (R_3**C**-OH), 61.5 (**C**H_2-O), 36.7 (**C**H_2(CH_3)C=), 29.6 (RCHOH**C**H_2), 26.6 (HO(**C**H_3)$_2$C), 23.3 (HO(**C**H_3)$_2$C), 21.2 (**C**H_3CO), 16.6 ((**C**H_3)C=).
Mass Spec. *m/z* **(relative intensity and ion)** 153 (37), 137 (15), 111 (69), 94 (100).

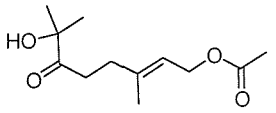
(54) - (*E*)-3-methyl-6-oxo-2-hexenylacetate



Pyridinium chlorochromate (851 mg, 3.95 mmol) and NaOMe (9 mg, 0.11 mmol) were suspended in CH_2Cl_2 (4 mL) with 4 Å Molecular sieves under nitrogen. A solution of diol **53** (600 mg, 2.63 mmol) dissolved in CH_2Cl_2 (5 mL) was added in one portion and the mixture stirred for 2 hours. The crude mixture was diluted with Et_2O (10 mL) and the supernatant decanted from the remaining black gum. The left over residue was washed with Et_2O (3 x 10 mL) and all the organic layers were combined, filtered through a bed of silica and concentrated *in vacuo* to give a promising crude recovery (370 mg). Purification was by flash chromatography on silica (3 x 8 cm) eluting with ether/hexane (200 mL of 2:8 then 200 mL of 3:7) to give the undesired title compound as an oil.

IR (cm^{-1}) 2935 (w), 2832 (w), 2720 (w), 1726 (s), 1440 (w), 1363 (m), 1230 (s), 1025 (m), 953 (m).
^{1}H-NMR ($CDCl_3$, δ ppm) 9.75 (1H, t, J = 1.5 Hz, C**H**O) 5.33 (1H, tt, J = 1.5 and 5.9 Hz, =C**H**), 4.54 (2H, d, J = 6.6 Hz, C**H**$_2$-O), 2.55 (2H, dt, J = 1.5 and 7.4 Hz, C**H**$_2$CHO), 2.35 (2H, t, J = 7.4 Hz, C**H**$_2$(CH_3)C=), 2.05 (3H, s, C**H**$_3$CO), 1.69 (3H, s, C**H**$_3$C=).
^{13}C-NMR ($CDCl_3$, δ ppm) 201.8 (**C**HO), 171.3 (**C**OO), 140.1 ((CH$_3$)**C**=), 119.4 (=**C**H), 61.2 (**C**H_2-O), 41.8 (**C**H_2CHO), 31.5 (**C**H_2(CH_3)C=), 21.1 (**C**H_3O), 16.7 (**C**H_3C=).
Mass Spec. *m/z* **(relative intensity and ion)** 126 (34), 110 (46), 95 (36), 81 (73).

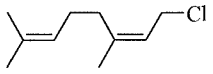
(51) - (*E*)-7-hydroxy-3,7-Dimethyl-6-oxo-2-octenylacetate



A solution of oxalyl chloride (0.11 mL, 1.19 mmol) in CH_2Cl_2 (8 mL) was cooled to between –50 °C and –60 °C. Me_2SO (0.19 mL, 2.38 mmol) was subsequently added dropwise (care – exothermic, gas evolved) so as not to raise the internal temperature above –50 °C. The resulting mixture was stirred for a further 2 minutes. A solution of diol **53** (250 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) was added over 5 minutes and the resulting white mixture stirred for a further 15 minutes. Et_3N (0.76 mL, 5.4 mmol) was added and allowed to stir for 5 minutes before finally being allowed to warm to room temperature. The mixture was diluted with water (20 mL) and the mixture extracted with CH_2Cl_2 (2 x 15 mL). The organic layers were combined, washed with brine (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil (260 mg). Purification by flash chromatography on silica (2.5 x 10 cm) eluting with ether:hexane (1:9 then 1:4) afforded the title compound as a pale yellow oil (83 mg, 0.36 mmol, 31 %).

IR (cm^{-1}) 3473 (br), 2976 (w), 2930 (w), 1737 (s), 1711 (s), 1670 (w), 1440 (m), 1368 (m), 1230 (s), 1194 (w), 1158 (w).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.35 (1H, t, J = 6.6 Hz, =C**H**), 4.57 (2H, d, J = 6.6 Hz, C**H**$_2$-O), 2.69 (2H, t, J = 8.2 Hz, RCOC**H**$_2$), 2.35 (2H, t, J = 7.6 Hz, C**H**$_2$(CH$_3$)C=), 2.05 (3H, s, C**H**$_3$CO), 1.72 (3H, s, R(C**H**$_3$)C=), 1.38 (6H, s, HO(C**H**$_3$)$_2$C).
^{13}C-NMR ($CDCl_3$, δ ppm) 213.8 (R**C**OR), 171.2 (**C**=O), 140.6 (CH$_3$-**C**=), 119.2 (=**C**H), 76.4 (HO(CH$_3$)$_2$**C**), 61.3 (**C**H$_2$O), 33.9 (**C**H$_2$(CH$_2$)C=), 33.1 (RCO**C**H$_2$CH$_2$), 26.6 (HO(**C**H$_3$)$_2$C), 21.2 (OCO**C**H$_3$), 16.8 (R(**C**H$_3$)C=).
Mass Spec. *m/z* **(relative intensity and ion)** 151 (7), 125 (64), 107 (9).

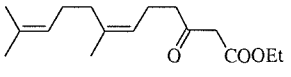
(41) - (2*Z*)-1-Chloro-3,7-dimethyl-2,6-octadiene (neryl chloride).



To a solution of nerol (17.61 mL, 0.1 mol) in 2,6-lutidine (13.4 mL, 115 mmol) was added lithium chloride (4.24g, 0.1 mol) in dry DMF (60 mL). The mixture was cooled to between 2 and 4 °C and mesyl chloride (8.54 mL, 0.11 mol) was added dropwise to the solution. The resulting pale yellow mixture was stirred for a further 1 hour at room temperature. Further 2,6-lutidine (2.5 mL, 21.5 mmol) and mesyl chloride (1.5 mL, 19.4 mmol) was added to the mixture. After stirring for 1 hour the mixture was dissolved in ether (200 mL), washed with distilled water (5 x 50 mL), HCl (3 x 20 mL, 1 M aq.), brine (2 x 30 mL) and $NaHCO_3$ (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a black oil. Purification by short path distillation (43 °C, 0.1 mmHg) gave the title product as a colourless oil (12.4 g, 72 mmol, 72 %). Spectrascopic data were in agreement with that reported in the literature.[50]

IR (cm^{-1}) 3050 (s), 2859 (s), 2856 (s), 1659 (m).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.45 (1H, t, J = 8.0 Hz, =C**H**CH_2-Cl), 5.10 (1H, br s, =C**H**), 4.09 (2H, d, J = 8.0 Hz, -C**H**$_2$Cl), 2.05-2.20 (4H, m, -C**H**$_2$-C**H**$_2$-), 1.77 (3H, s, C**H**$_3$), 1.70 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 142.8 ($(CH_3)_2$**C**=), 132.5 ((CH_3)**C**=), 123.6 ($(CH_3)_2$C=**C**H), 121.3 (=**C**H), 41.1 (-**C**H_2Cl), 32.0 (R-**C**H_2-R), 26.6 (R-**C**H_2-R), 25.8 (**C**H_3), 23.6 (**C**H_3), 17.8 (**C**H_3).

(43) - Ethyl (6*Z*)-7,11-dimethyl-3-oxo-6,10-dodecadienoate.

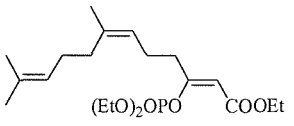


Sodium hydride (2.79 g of a 60 % dispersion in mineral oil, 69.65 mmol) was suspended in dry THF (25 mL) under nitrogen and cooled in an ice bath. Ethyl acetoacetate (8.81 mL, 69.55 mmol) was added dropwise and stirred for 10 minutes. n-Butyl lithium (27.86 mL of a 2.5 M solution in hexanes, 69.65 mmol) was added and stirred for a further 10 minutes. A

solution of neryl chloride **41** (12 g, 69.50 mmol) dissolved in dry THF (20 mL) was added to the reaction and the mixture allowed to warm to room temperature. After stirring for 30 minutes a solution of conc. HCl (70 mL of a 3.4 M solution) and diethyl ether (50 mL) was added to quench the reaction. Extraction was carried out using diethyl ether (3 x 20 mL) and all extracts combined, washed with water until neutral, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash chromatography on silica eluting with diethyl ether:hexane (3:97) gave the title compound as a pale yellow oil (11.66 g, 43.8 mmol, 63 %). Spectrascopic data were in agreement with that reported in the literature.[51]

IR (cm^{-1}) 2970 (m), 2918 (m), 2855 (m), 1756 (s), 1710 (s), 1630 (m), 1447 (m), 1241 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.05 (2H, m, =C**H**), 4.14 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 3.39 (2H, s, O=CC**H**$_2$C=O), 2.52 (2H, t, J = 7.4 Hz, CH_2CH_2C=O), 2.24 (2H, q, J = 7.4 Hz =CHC**H**$_2$), 2.1 (4H, broad s, =CHC**H**$_2$C**H**$_2$), 1.63 (6H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.23 (3H, t, J = 7.0 Hz, O-CH_2C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 202.6 (**C**=O), 167.3 (**C**OO), 136.8 ((CH$_3$)**C**=), 131.7 ((CH$_3$)$_2$**C**=), 124.2 ((CH$_3$)$_2$C=**C**), 123.1 ((CH$_3$)C=**C**H), 61.4 (O-**C**H$_2$), 49.4 (OC-**C**H$_2$-CO), 43.3 (CH$_2$-**C**H$_2$-C=O), 32.0 (**C**H$_2$-(CH$_3$)C=), 26.6 ((CH$_3$)$_2$C=CH**C**H$_2$), 25.8 ((**C**H$_3$)$_2$C=), 23.4 (**C**H$_3$), 22.0 (CH$_3$), 17.7 (**C**H$_3$), 14.2 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 267 (90 $[M+H]^+$).

(44) - Ethyl (2*Z*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (using Sodium hydride).

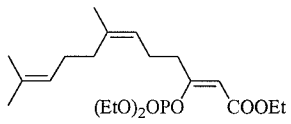


A suspension of sodium hydride (303 mg of a 60 % dispersion in mineral oil, 7.6 mmol) in dry diethyl ether (20 mL) under nitrogen was cooled in an ice bath. A solution of the β-keto ester **43** (2 g, 7.51 mmol) in dry diethyl ether (15 mL) was added and stirred for 20 minutes, after which diethyl chlorophosphate (1.1 mL, 7.6 mmol) was added and the resulting

mixture stirred at room temperature for 2 hours. The reaction was quenched with excess aqueous ammonium chloride, washed with saturated aqueous $NaHCO_3$ solution (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (for reactions less than 5 mmol scale the reaction was quenched with excess solid ammonium chloride, filtered through celite and concentrated *in vacuo*). Purification was by flash chromatography on silica eluting with diethyl ether:hexane (2:98 then, 3:97, 10:90) to afforded the title compound as a yellow oil (1.51 g, 3.76 mmol, 50 %).

IR (cm^{-1}) 2985 (m), 2935 (m), 2855 (m), 1729 (s), 1661 (s), 1452 (m), 1285 (s), 1212 (s), 990 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.32 (1H, s, (PO)C=C**H**), 5.05 (2H, t, J = 6.3 Hz, =C**H**), 4.23 (4H, qu, J = 7.2 Hz, P-OC**H**$_2$), 4.14 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 2.40 (2H, t, J = 7.4 Hz, C**H**$_2$C(OP)), 2.24 (2H, q, J = 7.4 Hz, C**H**$_2$CH$_2$C(OP)), 2.03-1.96 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.65 (6H, s, (C**H**$_3$)$_2$C=), 1.57 (3H, s, (C**H**$_3$)C=), 1.33 (6H, t, J = 7.0 Hz, P-OCH$_2$C**H**$_3$) 1.23 (3H, t, J = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 163.9 (**C**OO), 161.5 ((PO)**C**=), 137.1 ((CH$_3$)**C**=), 131.8 ((CH$_3$)$_2$**C**=), 124.2 ((CH$_3$)$_2$C=**C**H), 122.7 ((CH$_3$)C=**C**H), 105.4 ((PO)C=**C**H), 64.9 (P-O**C**H$_2$), 64.7 (P-O**C**H$_2$), 60.0 (O-**C**H$_2$), 35.5 (**C**H$_2$C(OP)=), 32.0 (**C**H$_2$C(CH$_3$)=), 26.6 ((CH$_3$)$_2$C=CH**C**H$_2$), 25.8 (**C**H$_3$), 24.8 ((CH$_3$)C=CH**C**H$_2$), 23.4 (**C**H$_3$), 17.7 (**C**H$_3$), 16.2 (P-OCH$_2$**C**H$_3$), 16.1 (P-OCH$_2$**C**H$_3$), 14.3 (O-CH$_2$**C**H$_3$).
^{31}P-NMR ($CDCl_3$, δ ppm) –8.07 (P$^{(V)}$).
Mass Spec. *m/z* **(relative intensity and ion)** 403 (81 [M+H]$^+$).

(44) - Ethyl (2*Z*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate (using Li-HMDS).

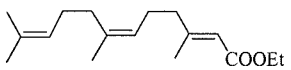


Li-HMDS (7.56 mL of a 1.0 M solution in THF, 7.56 mmol) in dry diethyl ether (20 mL) was cooled to 0 °C under nitrogen. A solution of the β-keto ester **43** (2 g, 7.51 mmol) in dry diethyl ether (40 mL) was added and after stirring the mixture for 15 minutes diethyl chlorophosphate (1.09 mL, 7.56 mmol) was added and stirred at room

temperature for 3.5 hours. The reaction was quenched with excess aqueous ammonium chloride and the organic layer washed with saturated ammonium chloride solution (20 mL), $NaHCO_3$ (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark orange/brown crude oil. Purification by flash chromatography on silica (3 x 12 cm) eluting with diethyl ether:hexane (3:97 then 5:95, 1:9) afforded the title compound as a yellow oil (2.39 g, 5.93 mmol, 79 %).

IR (cm^{-1}) 2985 (m), 2935 (m), 2855 (m), 1729 (s), 1661 (s), 1452 (m), 1285 (s), 1212 (s), 990 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.32 (1H, s, (PO)C=C**H**), 5.05 (2H, t, J = 6.3 Hz, =C**H**), 4.23 (4H, qu, J = 7.2 Hz, P-OC**H**$_2$), 4.14 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 2.40 (2H, t, J = 7.4 Hz, C**H**$_2$C(OP)), 2.24 (2H, q, J = 7.4 Hz, C**H**$_2$CH$_2$C(OP)), 2.03-1.96 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.65 (6H, s, (C**H**$_3$)$_2$C=), 1.57 (3H, s, (C**H**$_3$)C=), 1.33 (6H, t, J = 7.0 Hz, P-OCH$_2$C**H**$_3$) 1.23 (3H, t, J = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 163.9 (**C**OO), 161.5 ((PO)**C**=), 137.1 ((CH$_3$)**C**=), 131.8 ((CH$_3$)$_2$**C**=), 124.2 ((CH$_3$)$_2$C=**C**H), 122.7 ((CH$_3$)C=**C**H), 105.4 ((PO)C=**C**H), 64.9 (P-O**C**H$_2$), 64.7 (P-O**C**H$_2$), 60.0 (O-**C**H$_2$), 35.5 (**C**H$_2$C(OP)=), 32.0 (**C**H$_2$C(CH$_3$)=), 26.6 ((CH$_3$)$_2$C=CH**C**H$_2$), 25.8 (**C**H$_3$), 24.8 ((CH$_3$)C=CH**C**H$_2$), 23.4 (**C**H$_3$), 17.7 (**C**H$_3$), 16.2 (P-OCH$_2$**C**H$_3$), 16.1 (P-OCH$_2$**C**H$_3$), 14.3 (O-CH$_2$**C**H$_3$).
^{31}P-NMR ($CDCl_3$, δ ppm) –8.07 (P$^{(V)}$).
Mass Spec. *m/z* **(relative intensity and ion)** 403 (81 [M+H]$^+$).

(45) - Ethyl (2*E*, 6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (using Me_2CuLi reagent)

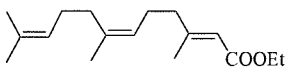


Methyl lithium (3.1 mL, 1.6 M in Et_2O, 4.96 mmol) was added to a suspension of copper iodide (472 mg, 2.48 mmol) in diethyl ether under nitrogen at –10 °C for 30 minutes. After initially turning yellow the resulting colourless mixture was cooled to –78 °C and enol phosphate **44** (500 mg, 1.24 mmol) added. The mixture was allowed to warm up to –50 °C and stirred for 3 hours after which the reaction was quenched with saturated ammonium chloride solution and the aqueous layer extracted with diethyl ether (2 x 20 mL). The combined organic extracts were

washed twice with a dilute ammonia and brine mixture (20 mL), brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow oil. Purification was by flash chromatography on silica eluting with diethyl ether:hexane (1:99 then 2:98) to give the title compound as a pale yellow oil (278 mg, 1.05 mmol, 85 %). Spectrascopic data were in agreement with that reported in the literature.[51]

IR (cm^{-1}) 2971 (m), 2930 (m), 2854 (m), 1718 (s), 1653 (s), 1377 (m), 1219 (s), 1143 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.60 (1H, s, =C**H**COO), 5.40-5.25 (2H, m, =C**H**CH_2), 4.08 (2H, q, J = 7.3 Hz, O-C**H**$_2$$CH_3$), 2.09 (4H, br s, =CHC**H**$_2$C**H**$_2$), 1.97 (4H, br s, =CHC**H**$_2$C**H**$_2$), 1.63 (6H, s, (C**H**$_3$)$_2$C=), 1.55 (3H, s, (C**H**$_3$)C=), 1.21 (3H, t, J = 7.0 Hz, O-CH_2C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 167.0 (**C**OO), 159.9 (**C**=CHCOO), 136.4 ((CH$_3$)**C**=), 131.8 ((CH$_3$)$_2$**C**=), 124.3 ((CH$_3$)$_2$C=**C**), 123.8 ((CH$_3$)C=**C**H), 115.7 (C=**C**HCOO), 59.6 (O-**C**H$_2$), 41.4 (**C**H$_2$C(CH$_3$)=CHCOO), 30.4 (**C**H$_2$C(CH$_3$)=), 26.7 ((CH$_3$)$_2$C=**C**CH$_2$), 26.0 ((**C**H$_3$)$_2$C=), 25.9 ((CH$_3$)C=CH**C**H$_2$), 23.5 ((**C**H$_3$)C=), 19.0 ((**C**H$_3$)C=CHCOO) 17.8 ((**C**H$_3$)$_2$C=), 14.5 (O-CH_2**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 265 (48 $[M+H]^+$).

(45) - Ethyl (2*E*, 6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate (using MeCu/MeMgCl reagent).

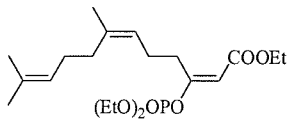


CuI (211 g, 1.11 mmol) was suspended in THF (10 mL) under nitrogen and cooled to 0 °C. MeLi (0.70 mL of a 1.6 M solution in diethyl ether, 1.11 mmol) was added dropwise. The orange mixture was stirred at 0 °C for 10 minutes, before cooling to –30 °C. MeMgCl (0.61 mL of a 3 M solution in THF, 1.85 mmol,) was added dropwise maintaining the temperature below –25 °C, producing a light tan brown coloured suspension. After a further 20 minutes a solution of enol phosphate **44** (150 mg, 0.37 mmol) in THF (10 mL) was added and the mixture stirred for 3 hours. The reaction was quenched by pouring quickly onto ice-cold

ammonium chloride containing a small amount of aqueous NH_3. The organic layer was diluted with diethylether (20 mL) and washed with an aqueous mixture of NH_4Cl and ammonia until no longer blue. The organic layer was washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow/orange oil. Purification was by flash chromatography on silica (2.5 x 8 cm) eluting with diethylether:hexane (2:98 then 3:97) afforded the title compound as a yellow oil (80 mg, 0.30 mmol, 82 %).

IR (cm^{-1}) 2971 (m), 2930 (m), 2854 (m), 1718 (s), 1653 (s), 1377 (m), 1219 (s), 1143 (s).
^{1}H-NMR (CDCl$_3$, δ ppm) 5.60 (1H, s, =C**H**COO), 5.40-5.25 (2H, m, =C**H**CH$_2$), 4.08 (2H, q, J = 7.3 Hz, O-C**H**$_2$CH$_3$), 2.09 (4H, br s, =CHC**H**$_2$C**H**$_2$), 1.97 (4H, br s, =CHC**H**$_2$C**H**$_2$), 1.63 (6H, s, (C**H**$_3$)$_2$C=), 1.55 (3H, s, (C**H**$_3$)C=), 1.21 (3H, t, J = 7.0 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 167.0 (**C**OO), 159.9 (**C**=CHCOO), 136.4 ((CH$_3$)**C**=), 131.8 ((CH$_3$)$_2$**C**=), 124.3 ((CH$_3$)$_2$C=**C**), 123.8 ((CH$_3$)C=**C**H), 115.7 (C=**C**HCOO), 59.6 (O-**C**H$_2$), 41.4 (**C**H$_2$C(CH$_3$)=CHCOO), 30.4 (**C**H$_2$C(CH$_3$)=), 26.7 ((CH$_3$)$_2$C=C**C**H$_2$), 26.0 ((**C**H$_3$)$_2$C=), 25.9 ((CH$_3$)C=CH**C**H$_2$), 23.5 ((**C**H$_3$)C=), 19.0 ((**C**H$_3$)C=CHCOO) 17.8 ((**C**H$_3$)$_2$C=), 14.5 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 265 (48 [M+H]$^+$).

(63) - Ethyl (2*E*, 6*Z*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate.

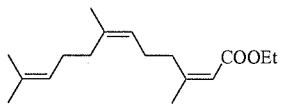


To a stirred solution of DMAP (51 mg, 0.42 mmol), Et_3N (0.59 mL, 4.2 mmol) in *N,N* –dimethylpropyleneurea (DMPU, 8 mL) at 0 °C was added a solution of β-keto ester **43** (1.0 g, 3.75 mmol) in DMPU (7 mL). The mixture was stirred for 45 minutes and cooled to – 20 °C after which diethyl chlorophosphate (0.61 mL, 4.2 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 36 hours. The reaction was quenched by diluting with diethylether (30

mL) and acidifying with excess HCl (2 N aqueous solution). The aqueous layer was extracted with diethylether (2 x 20mL) and the organic layers combined, washed with saturated $CuSO_4$ solution (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a rusty orange coloured oil. Purification by flash chromatography on silica (3.5 x 13 cm) eluting with diethylether:hexane (1:99 then 5:95, 1:9) afforded the title compound as a pale yellow oil (923 mg, 2.29 mmol, 61 %).

IR (cm^{-1}) 2976 (w), 2914 (w), 2853 (w), 1716 (m), 1644 (m), 1445 (w), 1373 (w), 1281 (m), 1122 (m), 1030 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.82 (1H, d, J = 1.5 Hz, =C**H**COO), 5.15 (1H, t, J = 7.0 Hz, =C**H**), 5.12-5.04 (1H, m, =C**H**), 4.17 (4H, qu, J = 7.4 Hz, P-OC**H**$_2$), 4.12 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 2.79 (2H, dt, J = 1.5 and 7.7 Hz, =CHC**H**$_2$), 2.25 (2H, q, J = 7.6 Hz, C**H**$_2$C(CH$_3$)=), 1.98-2.10 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.66 (6H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.35 (6H, t, J = 7.4 Hz, P-OCH$_2$C**H**$_3$), 1.24 (3H, t, J = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 166.3 (**C**OO), 166.2 (**C**(OP)=), 136.7 (**C**(CH$_3$)=), 131.7 ((CH$_3$)$_2$**C**=), 124.3 (=**C**H), 123.4 (=**C**H), 105.5 (**C**HCOO), 64.9 (P-O**C**H$_2$), 64.8 (P-O**C**H$_2$), 60.2 (O-**C**H$_2$), 32.2 (**C**H$_2$C(CH$_3$)=), 32.0 (**C**H$_2$C(OP)=), 26.7 (=CH**C**H$_2$), 25.8 ((**C**H$_3$)$_2$C=), 25.4 (**C**H$_3$C=), 23.5 (=CH**C**H$_2$), 17.7 ((**C**H$_3$)$_2$C=), 16.2 (P-OCH$_2$**C**H$_3$), 16.1 (P-OCH$_2$**C**H$_3$), 14.3 (O-CH$_2$**C**H$_3$).

(74) - Ethyl (2*Z*, 6*Z*)-3,7,11-trimethyl-2,6,10-dodecatrienoate

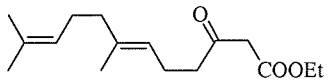


CuI (1.14 g, 5.96 mmol) was suspended in THF (25 mL) under nitrogen and cooled to 0 °C. MeLi (3.73 mL of a 1.6 M solution in diethyl ether, 5.96 mmol) was added dropwise. The orange mixture was stirred at 0 °C for 10 minutes, before cooling to – 30 °C. MeMgCl (3.31 mL of a 3 M solution in THF, 9.94 mmol,) was added dropwise maintaining the temperature below – 25 °C, producing a light tan brown coloured

suspension. After a further 20 minutes a solution of enol phosphate **63** (800 mg, 1.99 mmol) in THF (25 mL) was added and the mixture stirred for 3 hours. The reaction was quenched by pouring quickly over ice cold ammonium chloride containing a small amount of aqueous NH_3. The organic layer was diluted with diethylether (30 mL) and washed with an aqueous mixture of NH_4Cl and ammonia until no longer blue. The organic layer was washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification was by flash chromatography on silica (2.5 x 8 cm) eluting with diethylether:hexane (2:98 then 3:97) to afford the title compound as a yellow oil (434 mg, 1.54 mmol, 81 %). Spectrascopic data were in agreement with that reported in the literature.[51]

IR (cm^{-1}) 2971 (m), 2919 (m), 2853 (w), 1716 (s), 1644 (m), 1450 (m), 1378 (m), 1240 (m), 1163 (s), 1143 (s).
^{1}H-NMR (CDCl$_3$, δ ppm) 5.65 (1H, s, =C**H**COO), 5.19 (1H, t, J = 7.7 Hz, =C**H**), 5.19-5.08 (1H, m, =C**H**), 4.13 (2H, q, J = 7.0, O-C**H**$_2$), 2.64 (2H, t, J = 7.7 Hz, =C(CH$_3$)C**H**$_2$), 2.17 (2H, t, J = 7.6 Hz, =CHC**H**$_2$), 2.05-2.02 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.88 (3H, s, C**H**$_3$C=CHCO$_2$Et), 1.68 (6H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.27 (3H, t, J = 7.0 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 166.4 (**C**OO), 160.2 (**C**=CHCOO), 135.9 (**C**=CH), 131.6 ((CH$_3$)$_2$**C**=), 124.6 (=**C**H), 124.5 (=**C**H), 116.4 (=**C**HCOO), 59.5 (O-**C**H$_2$), 33.8 (**C**H$_2$C=CH), 32.0 (**C**H$_2$C=CH), 26.8 (=CH**C**H$_2$), 25.9 (**C**H$_3$), 25.5 (**C**H$_3$), 23.5 (**C**H$_3$C=CHCO$_2$Et), 17.8 (**C**H$_3$), 14.5 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* (relative intensity and ion) 265 (8 $[M+H]^+$), 264 (13 $[M]^+$), 221 (21), 191 (19).

(58) - Ethyl (6*E*)-7, 11-dimethyl-3-oxo-6, 10-dodecadienoate.

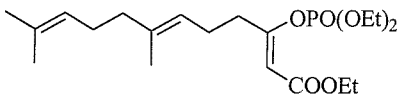


Sodium hydride (932 mg of a 60 % dispersion in mineral oil, 23.3 mmol) was suspended in dry THF (20 mL) under nitrogen and cooled in an ice bath. To this, ethyl acetoacetate (2.94 mL, 23.2 mmol) was added dropwise and stirred for 10 minutes. n-Butyl lithium (13.47 mL of a 1.73 M solution in hexanes, 23.3 mmol) was added and stirred for a further 10 minutes. Geranyl chloride **48** (4.0 g, 23.15 mmol) dissolved in dry THF

(20 mL) was then added to the reaction mixture. The resulting solution was allowed to warm to room temperature and stirred for 30 minutes before a solution of conc. HCl (10 mL) in water (25 mL) and diethyl ether (25 mL) was added to quench the reaction. The organic and aqueous layers were separated and the latter extracted with diethyl ether (3 x 20 mL) and all organic layers combined, washed with water until neutral, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash chromatography on silica (3.5 x 15 cm) eluting with diethyl ether:hexane (3:97, 5:95, 1:9) afforded the title compound as a pale yellow oil (3.12 g, 11.7 mmol, 51 %). Spectrascopic data were in agreement with that reported in the literature.[52]

IR (cm^{-1}) 2966 (m), 2914 (m), 2858 (m), 1741 (s), 1716 (s), 1649 (m), 1629 (m), 1445 (m), 1404 (m), 1368 (m), 1312 (s), 1235 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.08 (2H, t, J = 6.3 Hz, =C**H**), 4.20 (3H, q, J = 7.3 Hz, OC**H**$_2$), 3.44 (2H, s, COC**H**$_2$CO), 2.58 (2H, t, J = 7.4 Hz, CH$_2$C**H**$_2$CO), 2.30 (2H, q, J = 7.3 Hz, =CHC**H**$_2$), 2.15-2.0 (4H, m, =CHC**H**$_2$C**H**$_2$C=), 1.69 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$), 1.59 (3H, s, C**H**$_3$), 1.29 (3H, t, J = 7.0 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 202.8 (**C**O), 167.4 (**C**OO), 136.9 ((CH$_3$)**C**=), 131.6 ((CH$_3$)$_2$**C**=), 124.3 ((CH$_3$)$_2$C=**C**H), 122.2 (C(CH$_3$)=**C**H), 61.5 (O-**C**H$_2$), 49.5 (CO**C**H$_2$CO), 43.2 (**C**H$_2$CO), 39.8 (=C(CH$_3$)**C**H$_2$), 26.7 (=CH**C**H$_2$), 25.8 (**C**H$_3$), 22.3 (COCH$_2$**C**H$_2$), 17.8 (**C**H$_3$), 16.1 (**C**H$_3$), 14.2 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 194 (4), 177 (12), 136 (42).

(64) - Ethyl (2*Z*, 6*E*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate.

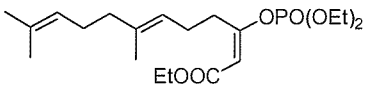


Li-HMDS (3.80 mL of a 1.0 M solution in THF, 3.80 mmol,) in dry diethyl ether (20 mL) was cooled to 0 °C under nitrogen. A solution of the β-keto ester **58** (1 g, 3.75 mmol) in dry diethyl ether (20 mL) was added and after stirring the mixture for 15 minutes diethyl

chlorophosphate (0.55 mL, 3.80 mmol) was added and stirred at room temperature for 3.5 hours. The reaction was quenched with excess aqueous ammonium chloride and the organic layer washed with saturated ammonium chloride solution (20 mL), $NaHCO_3$ (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark orange/brown crude oil. Purification by flash chromatography on silica (3.5 x 10 cm) eluting with diethyl ether:hexane (5:95 then 1:9, 15:80, 2:8) afforded the title compound as a yellow oil (1.20 g, 2.97 mmol, 79 %).

IR (cm^{-1}) 2981 (w), 2919 (w), 2858 (w), 1721 (m), 1665 (m), 1445 (w), 1373 (w), 1281 (m), 1199 (m), 1143 (m), 1025 (s), 984 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.34 (1H, s, =C**H**COO), 5.11-5.03 (2H, m, =C**H**), 4.25 (4H, qu, J = 7.4 Hz, P-OC**H**$_2$), 4.13 (2H, q, J = 7.1 Hz, O-C**H**$_2$CH$_3$), 2.44 (2H, t, J = 7.4 Hz, C**H**$_2$C(OP)=), 2.25 (2H, q, J = 7.1 Hz, =CHC**H**$_2$), 2.15-1.92 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.66 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.58 (3H, s, C**H**$_3$), 1.34 (6H, t, J = 7.4 Hz, PO-CH$_2$C**H**$_3$), 1.25 (3H, t, J = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 163.9 ((PO)**C**=), 161.5 (**C**OO), 137.1 ((CH$_3$)**C**=), 131.6 ((CH$_3$)$_2$**C**=),124.3 ((CH$_3$)$_2$C=**C**H), 121.9 (=**C**H), 105.5 ((PO)C=**C**H), 64.9 (P-O**C**H$_2$), 64.8 (P-O**C**H$_2$), 60.0 (O-**C**H$_2$), 39.7 (**C**H$_2$C=), 35.4 (**C**H$_2$C(OP)=), 26.7 (=CH**C**H$_2$), 25.8 (**C**H$_3$), 25.0 (=CH**C**H$_2$), 17.8 (**C**H$_3$), 16.2 (P-OCH$_2$**C**H$_3$), 16.1(P-OCH$_2$**C**H$_3$), 14.4 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 403 (3 $[M+H]^+$), 357 (5), 287 (8).
Elemental analysis Calculated: C = 59.70 %, H = 8.76 %, O = 23.84 %, P = 7.70 %. Found: C = 59.94 %, H = 8.87 %.

(65) - Ethyl (2*E*, 6*E*)-3-[(diethoxyphosphoryl)oxy]-7,11-dimethyl-2,6,10-dodecatrienoate.

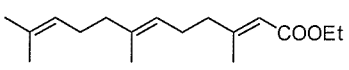


To a stirred solution of DMAP (51 mg, 0.42 mmol), Et_3N (0.59 mL, 4.2 mmol) in *N,N* –dimethylpropyleneurea (DMPU, 5 mL) at 0 °C was added a solution β-keto ester **58** (1.0 g, 3.75 mmol) in DMPU (5 mL). The mixture was stirred for 45 minutes and cooled to – 20 °C after which

diethyl chlorophosphate (0.61 mL, 4.2 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 36 hours. The reaction was quenched by diluting with diethylether (30 mL) and acidifying with excess HCl (2 N aqueous solution). The aqueous layer was extracted with diethylether (3 x 20mL) and the organic layers combined, washed with saturated $CuSO_4$ (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow/orange oil (1.76 g). Purification by flash chromatography on silica (2.5 x 15 cm) eluting with diethyl ether:hexane (5:95 then 1:9, 15:80, 2:8) afforded the title compound as a yellow oil (1.07 g, 2.66 mmol, 71 %).

IR (cm^{-1}) 2981 (w), 2914 (w), 2853 (w), 1721 (m), 1644 (w), 1440 (w), 1372 (m), 1281 (m), 1163 (m), 1122 (m), 1030 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.84 (1H, s, =C**H**COO), 5.16, (1H, t, J = 7.4 Hz, =C**H**), 5.08 (1H, t, J = 5.9 Hz, =C**H**), 4.20 (4H, qu, J = 7.4 Hz, P-OC**H**$_2$), 4.15 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 2.83 (2H, t, J = 7.7 Hz, C**H**$_2$C(PO)=), 2.28 (2H, q, J = 7.4 Hz, =CHC**H**$_2$), 2.11-1.92 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.67 (3H, s, C**H**$_3$), 1.62 (3H, s, C**H**$_3$), 1.59 (3H, s, C**H**$_3$), 1.37 (6H, t, J = 7.0 Hz, PO-CH$_2$C**H**$_3$), 1.26 (3H, t, J = 7.0 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 166. 4 (**C**OO), 166.3 ((PO)**C**=), 136.7 ((CH$_3$)**C**=), 131.5 ((CH$_3$)$_2$**C**=), 124.4 (=**C**H), 122.4 (=**C**H), 105.6 ((PO)C=**C**H), 65.0 (P-O**C**H$_2$), 64.9 (P-O**C**H$_2$), 60.2 (O-**C**H$_2$), 39.8 (**C**H$_2$C(CH$_3$)=), 32.0 (**C**H$_2$C(OP)=), 31.9 (=CH**C**H$_2$), 26.8 (**C**H$_3$), 25.8 (=CH**C**H$_2$), 25.4 (**C**H$_3$), 17.8 (**C**H$_3$), 16.3 (P-OCH$_2$**C**H$_3$), 16.2 (P-OCH$_2$**C**H$_3$), 14.4 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 403 (2 [M+H]$^+$), 357 (12), 313 (7), 155 (100).

(75) - Ethyl (2*E*, 6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienoate

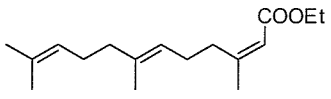


CuI (1.14 g, 5.96 mmol) was suspended in THF (25 mL) under nitrogen and cooled to 0 °C. MeLi (3.73 mL of a 1.6 M solution in diethyl ether, 5.96 mmol) was added dropwise. The orange mixture was stirred at 0 °C for 10 minutes, before cooling to – 30 °C. MeMgCl (3.31 mL of a 3 M solution in THF, 9.94 mmol,) was added dropwise maintaining the

temperature below – 25 °C, producing a light tan brown coloured suspension. After a further 20 minutes a solution of enol phosphate **64** (800 mg, 1.99 mmol) in THF (25 mL) was added and the mixture stirred for 4 hours. The reaction was quenched by pouring quickly over ice cold ammonium chloride containing a small amount of aqueous NH_3. The organic layer was diluted with diethylether (30 mL) and washed with an aqueous mixture of NH_4Cl and ammonia until no longer blue. The organic layer was washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a rusty orange colour oil. Purification was by flash chromatography on silica (2.5 x 15 cm) eluting with diethylether:hexane (1:99 then 2:98) to afford the title compound as a yellow oil (390 mg, 1.48 mmol, 74 %). Spectrascopic data were in agreement with that reported in the literature.[52]

IR (cm^{-1}) 2971 (w), 2919 (w), 2853 (w), 1716 (s), 1650 (m), 1445 (m), 1378 (m), 1224 (s), 1143 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 5.67 (1H, s, =C**H**COO), 5.12-5.03 (2H, m, =C**H**), 4.14 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 2.23-2.15 (4H, m, =CHC**H**$_2$C**H**$_2$), 2.16 (3H, s, C**H**$_3$C=CHCOO), 2.05 (2H, t, J = 5.9 Hz, C**H**$_2$C(CH$_3$)=), 2.02-1.96 (2H, m, =CHC**H**$_2$), 1.68 (3H, s, C**H**$_3$), 1.60 (6H, s, C**H**$_3$), 1.27 (3H, t, J = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 167.0 (**C**OO), 159.9 (**C**=CHCOO), 136.2 (CH$_3$**C**=), 131.5 ((CH$_3$)$_2$**C**=), 124.3 ((CH$_3$)$_2$C=**C**H), 123.0 (CH$_3$C=**C**H), 115.8 (=**C**HCOO), 59.6 (O-**C**H$_2$), 41.1 (**C**H$_2$C(CH$_3$)=), 39.8 (**C**H$_2$C(CH$_3$)=), 26.8 (=CH**C**H$_2$), 26.1(=CH**C**H$_2$), 25.8 (**C**H$_3$), 18.9 (**C**H$_3$), 17.8 (**C**H$_3$), 16.1 (**C**H$_3$C=CHCOO), 14.5 (O-CH$_2$**C**H$_3$).
Mass Spec. *m/z* (relative intensity and ion) 265 (3 [M+H]$^+$), 264 (5 [M]$^+$), 219 (11), 191 (14).

(76) - Ethyl (2*Z*, 6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienoate

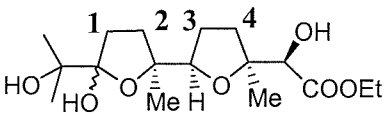


CuI (1.14 g, 5.96 mmol) was suspended in THF (25 mL) under nitrogen and cooled to 0 °C. MeLi (3.73 mL of a 1.6 M solution in diethyl ether, 5.96 mmol) was added dropwise. The orange mixture was stirred at 0 °C for 10 minutes, before cooling to – 30 °C. MeMgCl (3.31 mL of a 3 M solution in THF, 9.94 mmol,) was added dropwise maintaining the

temperature below – 25 °C, producing a light tan brown coloured suspension. After a further 20 minutes a solution of enol phosphate **65** (800 mg, 1.99 mmol) in THF (25 mL) was added and the mixture stirred for 4 hours. The reaction was quenched by pouring quickly over ice cold ammonium chloride containing a small amount of aqueous NH_3. The organic layer was diluted with diethylether (30 mL) and washed with an aqueous mixture of NH_4Cl and ammonia until no longer blue. The organic layer was washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a rusty orange colour oil. Purification was by flash chromatography on silica (2.5 x 17 cm) eluting with diethylether:hexane (1:99) to afford the title compound as a yellow oil (426 mg, 1.61 mmol, 81 %). Spectrascopic data were in agreement with that reported in the literature.[52]

IR (cm^{-1}) 2971 (m), 2914 (m), 2858 (w), 1716 (s), 1650 (m), 1445 (m), 1373 (m), 1240 (w), 1209 (w), 1153 (s).
^{1}H-NMR (CDCl$_3$, δ ppm) 5.66 (1H, s, =C**H**COO), 5.17 (1H, t, J = 7.0 Hz, =C**H**), 5.10 (1H, tt, J = 6.6 and 1.5 Hz, =C**H**), 4.14 (2H, q, J = 7.1 Hz, O-C**H**$_2$), 2.66 (2H, t, J = 7.7 Hz, C**H**$_2$C(CH$_3$)=), 2.18 (2H, q, J = 7.6 Hz, =CHC**H**$_2$), 2.12-1.95 (4H, m, =CHC**H**$_2$C**H**$_2$), 1.90 (3H, s, C**H**$_3$C=CHCO$_2$Et), 1.69 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.28 (3H, t, J = 7.4 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 166.5 (**C**OO), 160.4 (**C**=CHCOO), 135.9 (CH$_3$**C**=), 131.5 ((CH$_3$)$_2$**C**=), 124.5 (CH$_3$**C**=), 123.7((CH$_3$)$_2$**C**=), 116.4 (=**C**HCOO), 59.6 (O-**C**H$_2$), 39.8 (**C**H$_2$C(CH$_3$)=), 33.6 (**C**H$_2$C(CH$_3$)=), 26.8 (=CH**C**H$_2$), 25.8 (**C**H$_3$), 25.5 (**C**H$_3$), 17.8 (**C**H$_3$), 16.1 ((**C**H$_3$)C=CHCOO), 14.5 (OCH$_2$**C**H$_3$).
Mass Spec. *m/z* (relative intensity and ion) 265 (5 [M+H]$^+$), 264 (12 [M]$^+$), 221 (18).

(46) - Ethyl-2*R*-hydroxy-2-[(5*S*-methyl tetrahydro-2-furanyl)-propanol)-5*S*-methyl tetrahydro-2*R*-furanyl] ethanoate.

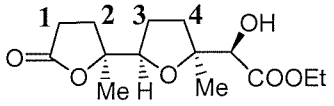


A rapidly stirred mixture of 1,5,9 triene **45** (400 mg, 1.51 mmol) and phosphate buffer (2 mL, pH 6.2) in acetone (25 mL) at –20 °C was treated dropwise with $KMnO_4$ (11.35 mL of a 0.4 M solution in water,

4.54 mmol) acidified with acetic acid (365 μL). The resulting mixture was allowed to stir for 30 minutes and quenched using ice cooled saturated $Na_2S_2O_5$ solution until the mixture decolourised. The crude aqueous layer was extracted using CH_2Cl_2 (8 x 30 mL). The aqueous layer was saturated with NaCl and extracted further with CH_2Cl_2 (4 x 30 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid and colourless oil. Purification was by flash chromatography on silica (2 x 15 cm) eluting with methanol:dichloromethane (4:96) to afford the title compound as a white solid (260 mg, 0.75 mmol, 50 %).

m.p. = 89 – 90.5 °C.
IR (cm^{-1}) 3437 (b), 2976 (m), 2930 (w), 2873 (w), 1716 (s), 1644 (w), 1450 (m), 1368 (m), 1224 (m), 1148 (s).
^{1}**H-NMR (CDCl$_3$, δ ppm)** 4.20 (2H, q, J = 7.2 Hz, COOC**H**$_2$), 4.0 (1H, dd, J = 9.0 and 6.5 Hz, C^{3}H$_2$-C**H**), 3.95 (1H, s, C**H**-OH), 2.38-2.30 (1H, m, C**H**$_2$), 2.20-2.04 (2H, m, C**H**$_2$), 1.84-1.63 (2H, m, C**H**$_2$), 1.54-1.48 (1H, m, C**H**$_2$), 1.25 (3H, t, J = 7.5 Hz, O-CH$_2$C**H**$_3$), 1.20 (3H, s, CH$_2$-C-C**H**$_3$), 1.28 (3H, s, CH$_2$-C-C**H**$_3$), 1.1 (6H, s, (C**H**$_3$)$_2$C-OH).
^{13}**C-NMR (CDCl$_3$, δ ppm)** 172.9 (**C**OO), 109.6 (O-**C**-OH), 86.9 (**C**HOH), 85.2 (C^{3}H$_2$**C**-O), 84.2 ((CH$_3$)$_2$**C**-OH), 76.7 (C^{4}H$_2$**C**), 74.0 (C^{2}H$_2$**C**-CH$_3$), 62.1 (O**C**H$_2$CH$_3$), 36.0 (**C**H$_2$), 33.1 (**C**H$_2$), 30.1 (**C**H$_2$), 28.3 (**C**H$_2$), 25.2 (C-**C**H$_3$), 25.0 (C-**C**H$_3$), 24.5 ((**C**H$_3$)$_2$C-OH), 23.8 ((**C**H$_3$)$_2$C-OH), 14.6 (OCH$_2$**C**H$_3$).
Mass Spec. (ES+ ionisation)*m/z* **(relative intensity and ion)** 369.5 (48, [M+Na]$^+$), 347.4 (5, [M+H]$^+$), 329.4 (20, [M – OH]$^+$).
Elemental analysis Calculated: C = 58.94 %, H = 8.73 %, O = 32.33 %. Found: C = 58.47 %, H = 8.96 %.

(47) – 5*S*-methyl, 5-[ethyl-2*R*-hydroxy-2-(5*S*-methyl tetrahydro-2*R*-furanyl) ethanoate] tetrahydro-2-furanone.

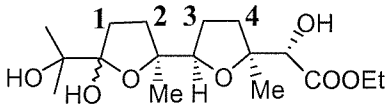


To a stirred solution of lactol **46** (30 mg, 0.086 mmol) in dry CH_2Cl_2 (5 mL) was added Na_2CO_3 (9.5 mg, 0.09 mmol) under nitrogen. $Pb(OAc)_4$

(39 mg, 0.088 mmol) was added in one portion and the mixture stirred overnight. Celite was added and the mixture stirred for a further 15 minutes and the solids filtered off. The organic layer was washed with saturated $NaHCO_3$ (2 x 15 mL). The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (2 x 15 mL). The extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Purification was by flash chromatography on silica (1 x 7 cm) eluting with diethyl ether to afford the title compound as a colourless oil (18 mg, 0.063 mmol, 73 %).

IR (cm^{-1}) 3411 (b), 2976 (w), 2940 (w), 1767 (s), 1731 (s), 1455 (m), 1373 (m), 1081 (s), 944 (s).
^{1}H-NMR (CDCl$_3$, δ ppm) 4.20 (2H, m, COOC**H**$_2$), 3.94 (1H, dd, J = 9.0 and 6.1 Hz, C^{1}H$_2$-C**H**)) 3.92 (1H, s, C**H**OH), 2.65 (1H, ddd, J = 18.1, 10.5 and 8.0 Hz, C^1**H**$_2$), 2.44 (1H, ddd, J = 18.1, 10.5 and 5.0 Hz, C^1**H**$_2$), 2.35-2.22 (2H, m, C**H**$_2$), 1.86-1.73 (2H, m, C**H**$_2$), 1.69-1.57 (2H, m, C**H**$_2$), 1.30 (3H, s, C-C**H**$_3$), 1.25 (3H, s, C-C**H**$_3$), 1.25 (3H, t, J = 3.5 Hz, O-CH$_2$C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 177.5 (C^{1}H$_2$COO) 173.1 (**C**OO), 87.7 ((CH$_3$)**C**C^{4}H$_2$), 85.6 (**C**HOH), 83.7 (C^{3}H$_2$**C**H), 76.6 (C^{2}H$_2$**C**(CH$_3$)), 62.5 (O-**C**H$_2$), 35.8 (**C**^{1}H$_2$), 29.9 (**C**H$_2$), 28.9 (**C**H$_2$), 28.5 (CH$_2$C-**C**H$_3$), 24.3 (**C**H$_2$), 24.2 (CH$_2$C-**C**H$_3$), 14.6 (OCH$_2$**C**H$_3$).
High Res. Mass Spec. (CI) Calculated: $C_{14}H_{26}NO_6$ = 304.1760, $C_{14}H_{23}O_6$ = 287.1495. Found: 304.1753 (62.18, $[M+NH_4]^+$), 287.1499 (15.90, $[M+H]^+$).

(77) - Ethyl-2*S*-hydroxy-2-[(5*S*-methyl tetrahydro-2-furanyl)-propanol)-5*S*-methyl tetrahydro-2*R*-furanyl] ethanoate.

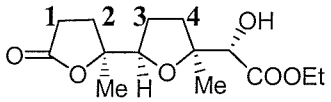


A rapidly stirred mixture of 1,5,9 triene **74** (200 mg, 0.76 mmol) and phosphate buffer (2 mL, pH 6.2) in acetone (20 mL) at –20 °C was treated dropwise with $KMnO_4$ (5.68 mL of a 0.4 M solution in water, 2.27 mmol) acidified with acetic acid (134 μL). The resulting mixture was allowed to stir for 30 minutes and quenched using ice cooled

saturated $Na_2S_2O_5$ solution until the mixture decolourised. The crude aqueous layer was extracted using CH_2Cl_2 (10 x 20 mL). The aqueous layer was saturated with NaCl and extracted further with CH_2Cl_2 (5 x 20 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification was by flash chromatography on silica (3.5 x 12 cm) eluting with methanol:dichloromethane (1:99 then 2:98, 3:97, 4:96) to afford the title compound as a pale yellow oil (115 mg, 0.33 mmol, 44 %).

IR (cm^{-1}) 3426 (b), 2976 (m), 2868 (m), 1731 (s), 1460 (m), 1373 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 4.34-4.23 (2H, m, O-C**H**$_2$), 4.11 (1H, s, C**H**-OH), 4.07 (1H, dd, J = 5.9 and 2.2 Hz, C^{3}H$_2$C**H**), 2.35-2.16 (4H, m, C^1**H**$_2$C^2**H**$_2$), 2.00-1.85 (2H, m, C**H**$_2$), 1.77-1.55 (2H, m, C**H**$_2$), 1.33 (3H, t, J = 7.0 Hz, O-CH$_2$C**H**$_3$), 1.28 (3H, s, (C**H**$_3$)$_2$C-OH), 1.25 (3H, s, (C**H**$_3$)$_2$C-OH), 1.23 (3H, s, CH$_2$C-C**H**$_3$), 1.19 (3H, s, CH$_2$C-C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 173.0 (**C**OO), 109.4 (C^1**C**(OH)O), 86.4 (C^{4}H$_2$**C**-CH$_3$), 84.7 (C^{2}H$_2$**C**-CH$_3$), 84.1 (**C**H-OH), 76.2 (C^3-**C**H), 73.5 ((CH$_3$)$_2$**C**-OH), 62.3 (O-**C**H$_2$), 34.7 (**C**H$_2$), 33.1 (**C**H$_2$), 29.4 (**C**H$_2$), 27.6 (**C**H$_2$), 25.1 (C^{2}H$_2$C-**C**H$_3$), 24.8 (C^{4}H$_2$C-**C**H$_3$), 24.0 ((**C**H$_3$)$_2$C-OH), 22.5 ((**C**H$_3$)$_2$C-OH), 14.3 (O-CH$_2$**C**H$_3$).

(78) - 5*S*-methyl, 5-[ethyl-2*S*-hydroxy-2-(5*S*-methyl tetrahydro-2*R*-furanyl) ethanoate] tetrahydro-2-furanone.

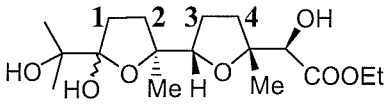


To a magnetically-stirred solution of lactol **77** (40 mg, 0.12 mmol) in dry CH_2Cl_2 (5 mL) was added Na_2CO_3 (21 mg, 0.2 mmol) under nitrogen. $Pb(OAc)_4$ (71 mg, 0.16 mmol) was added in one portion and the mixture stirred overnight. Celite was added and the mixture stirred for a further 15 minutes and the solids filtered off. The organic layer was washed with saturated $NaHCO_3$ (2 x 15 mL). The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (3 x 20 mL). The extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Purification by flash chromatography on silica (1 x 7 cm) eluting with

diethylether:hexane (5:95 then 1:9, 2:8, 4:6, 1:1) afforded the title compound as a colourless oil (11 mg, 0.4 mmol, 33 %).

IR (cm^{-1}) 3483 (b), 2971 (w), 2940 (w), 2873 (w), 1767 (s), 1737 (s), 1455 (m), 1373 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 4.27 (2H, q, J = 7.4 Hz, OC**H**$_2$), 4.07 (1H, dd, J = 9.6 and 5.9 Hz, C**H**C^{3}H$_2$), 4.03 (1H, s, C**H**-OH), 3.05-2.97 (1H, broad s, -O**H**), 2.78 (1H, ddd, J = 18.0, 10.3 and 7.4 Hz, C^1**H**H), 2.54 (1H, ddd, J = 16.5, 10.3 and 5.1 Hz, C^{1}H**H**), 2.39-2.26 (2H, m, C**H**$_2$), 1.98-1.80 (2H, m, C**H**$_2$), 1.80-1.58 (2H, m, C**H**$_2$), 1.38 (3H, s, C^{2}H$_2$C-C**H**$_3$), 1.32 (3H, t, J = 7.7 Hz, OCH$_2$C**H**$_3$) 1.24 (3H, s, C^{2}H$_2$C-C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 177.2 (C^1**C**OO), 173.2 (**C**OO), 87.4 (C^2**C**-CH$_3$), 84.8 (C^4**C**-CH$_3$), 83.3 (**C**H-OH), 76.1 (C^3**C**H), 62.1 (O-**C**H$_2$), 34.3 (**C**H$_2$), 29.7 (**C**H$_2$), 28.8 (**C**H$_2$), 27.3 (**C**H$_2$), 23.9 (**C**H$_3$), 22.8 (**C**H$_3$), 14.3 (O-CH$_2$**C**H$_3$).
High Res. Mass Spec. (CI) Calculated: $C_{14}H_{22}O_6$ = 287.1495. Found: 287.1484 (91.60, $[M+H]^+$).

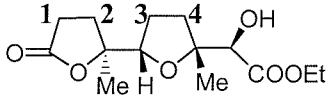
(79) - Ethyl-2*R*-hydroxy-2-[(5*S*-methyl tetrahydro-2-furanyl)-propanol)-5*R*-methyl tetrahydro-2*S*-furanyl] ethanoate.



A mechanically-stirred mixture of 1,5,9 triene **76** (200 mg, 0.76 mmol) and phosphate buffer (2 mL, pH 6.2) in acetone (20 mL) at –20 °C was treated dropwise with $KMnO_4$ (5.68 mL of a 0.4 M solution in water, 2.27 mmol) acidified with acetic acid (134 μL). The resulting mixture was allowed to stir for 30 minutes before quenching with ice-cooled saturated $Na_2S_2O_5$ solution until the mixture decolourised. The crude aqueous layer was extracted using CH_2Cl_2 (8 x 20 mL). The aqueous layer was saturated with NaCl and extracted further with CH_2Cl_2 (5 x 20 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purification was by flash chromatography on silica (2 x 15 cm) eluting with methanol:dichloromethane (1:99 then 2:98, 3:97) to afford the title compound as a colourless oil (80 mg, 0.23 mmol, 30 %).

IR (cm^{-1}) 2437 (b), 2976 (m), 2935 (w), 2968 (m), 1726 (s), 1460 (m), 1378 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 4.25 (2H, q, J = 7.4 Hz, O-C**H**$_2$), 4.19 (1H, s, C**H**-OH), 3.91 (1H, dd, J = 9.9 and 6.3 Hz, C^{3}H$_2$C**H**), 2.43 (2H, tt, J = 11.8 and 4.0 Hz, C^{3}**H**$_2$), 2.26 (2H, td, J = 12.5 and 8.8 Hz, C**H**$_2$), 1.94-1.81 (2H, m, C**H**$_2$), 1.73-1.60 (2H, m, C**H**$_2$), 1.31 (3H, t, J = 4.4 Hz, O-CH$_2$C**H**$_3$), 1.29 (6H, s, (C**H**$_3$)$_2$C-OH), 1.27 (3H, s, -C**H**$_3$), 1.14 (3H, s, -C**H**$_3$).
^{13}C-NMR (CDCl$_3$, δ ppm) 171.8 (**C**OO), 109.7 (C^{1}**C**(OH)O), 85.0 (C^{4}H$_2$**C**-CH$_3$), 84.8 (C^{2}H$_2$**C**-CH$_3$), 82.9 (**C**H-OH), 77.3 (C^{3}H$_2$**C**H), 73.3 ((CH$_3$)$_2$**C**-OH), 61.5 (O-**C**H$_2$), 33.4 (**C**H$_2$), 32.7 (**C**H$_2$), 31.9 (**C**H$_2$), 28.0 (**C**H$_2$), 24.7 (C^{2}H$_2$-**C**H$_3$), 24.5 (C^{4}H$_2$-**C**H$_3$), 24.2 ((**C**H$_3$)$_2$C-OH), 24.0 ((**C**H$_3$)$_2$C-OH), 14.3 (O-CH$_2$**C**H$_3$).

(80) - 5*S*-methyl, 5-[ethyl-2*R*-hydroxy-2-(5*R*-methyl tetrahydro-2*S*-furanyl) ethanoate] tetrahydro-2-furanone.



To a magnetically-stirred solution of lactol **79** (40 mg, 0.12 mmol) in dry CH_2Cl_2 (6 mL) was added Na_2CO_3 (21 mg, 0.2 mmol) under nitrogen. $Pb(OAc)_4$ (71 mg, 0.16 mmol) was added in one portion and the mixture stirred overnight. Celite was added and the mixture stirred for a further 15 minutes before the solids were filtered off. The organic layer was washed with saturated $NaHCO_3$ (2 x 15 mL). The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (3 x 15 mL). The extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to give a colourless oil. Purification was by flash chromatography on silica (1 x 7 cm) eluting with diethyl ether:hexane (2:8 then 3:7, 4:6) to afford the title compound as a colourless oil (10 mg, 0.035 mmol, 29 %).

IR (cm^{-1}) 3473 (b), 2976 (w), 2930 (w), 2873 (w), 1767 (s), 1731 (s), 1455 (m), 1383 (m).
^{1}H-NMR (CDCl$_3$, δ ppm) 4.28 (2H, q, J = 7.4 Hz, -OC**H**$_2$), 4.02 (1H, s, C**H**-OH), 3.95 (1H, t, J = 7.7 Hz, C^{3}H$_2$C**H**), (1H, ddd, J = 19.9, 10.3 and 11.8 Hz, C^{1}**H**H), 2.54-2.40 (2H, m, C^{2}**H**$_2$), 2.34 (1H, ddd, J = 20.6, 7.4 and 12.5 Hz, C^{1}H**H**), 2.05-1.95 (2H, m, C^{3}**H**$_2$), 1.98-1.89 (1H, m, C^{4}**H**H),

1.69 (1H, dt, J = 12.5 and 8.1 Hz, $C^4H\mathbf{H}$), 1.36 (3H, s, $C^2H_2C\text{-}C\mathbf{H}_3$), 1.32 (3H, t, J = 14.0 Hz, $O\text{-}CH_2C\mathbf{H}_3$), 1.20 (3H, s, $C^4H_2C\text{-}C\mathbf{H}_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 177.9 (C^1COO), 173.3 (**C**OO), 85.7 ($C^2C\text{-}CH_3$), 84.8 ($C^4C\text{-}CH_3$), 84.7 (**C**H-OH), 75.7 (C^3CH), 62.1 ($O\text{-}CH_2$), 34.7 (C^1H_2), 32.0 (C^2H_2), 29.7 (C^3H_2), 26.2 (C^4H_2), 24.4 (CH_3), 22.1 (CH_3), 14.3 ($O\text{-}CH_2CH_3$).

High Res. Mass Spec. (CI) Calculated: $C_{14}H_{22}O_6$ = 287.1495. Found: 287.1495 (87.34, $[M+H]^+$).

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