UNIVERSITY OF SOUTHAMPTON

Approaches to the Synthesis of the Macrolide Pheromones of the Saw-Toothed Grain Beetle, *Oryzaephilus surinamensis*

by Christopher David John Boden

CONTENTS

Acknowledgements		i
Notes		ii
Abstract		iii
Chapter 1	Outline of Objectives and Overview of Synthetic Routes to Macrolides	
	1.1 Objectives.	1
	1.2 Overview of Synthetic Routes to Macrolides.	1
	1.2.1 Direct Macrolactonisation.	2
	1.2.2 Ring Expansion Routes.	6
Chapter 2	Possible Synthetic Pathways to the Target Compounds	
	2.1 General Considerations	11
	2.2 Tactical Considerations	11
	2.3 Possible Improvements to the Syntheses of the Hydroxy Acids	14
	2.4 Other Direct Macrolactonisation Approaches	17
	2.5 Possible Ring Expansion Approaches	
	2.6 Formation of the Targets via Protected 1,4-diene Containing Precursors.	18 20
Chapter 3	Formation of Protected 1,4-dienes by Cyclopropanation	
	3.1 Theory	23
	3.2 Attempted Cyclopropanation of Model Adducts	25

3.3 Generation of Disubstituted Hydrazines 27
3.4 Conclusions 30

Chapter 4 Routes Based on the Adduct [26]
4.1 Theory 32
4.2 Ozonolytic Cleavage to Diol [27] 33
4.3 Ozonolytic Cleavage to Terminally Differentiated Products 34
4.4 Other Methods of Functionalisation 36
4.5 Protecting Group Exchange 36
4.6 Conclusions 37

Chapter 5 Improved Route to the Hydroxy Acid Precursor to II
5.1 Introduction 38
5.2 Synthesis of Intermediate [47] 39
5.3 Carboxyolefination of [48] 39
5.4 Conclusions 44

Chapter 6 Experimental Section
6.1 General 45
6.2 Procedures 46

References 56

ACKNOWLEDGEMENTS

I would particularly like to thank my supervisor, Dr Ian Stevens, for his continuing support and encouragement; thanks also to Professor Philip Kocienski, both for useful advice and also his generous provision of desktop publishing facillities, without which the general appearance of this thesis would have been considerably rougher. Additional thanks to Dr Richard Whitby for several helpful suggestions.

I gratefully acknowledge the receipt of a maintainance grant from the University covering the academic year 1988-89.

It only remains for me to thank the majority of my colleagues in the department, in particular the past and present inhabitants of lab 504, for, well, for being there really. If you know what I mean.

NOTES

1) ABBREVIATIONS

The following abbreviations are used in this thesis;

HMPA = hexamethylphosphoric triamide

DMSO = dimethyl sulphoxide

THF = tetrahydrofuran

GLC = gas-liquid chromatography

TBDMS = *tert* -butyldimethylsilyl

MEM = methoxyethoxymethyl

DEAD = diethyl azodicarboxylate

TEAD = 2,2,2-trichloroethyl azodicarboxylate

PTAD = 4-phenyl-1,2,4-triazoline-3,5-dione

mp = melting point

bp = boiling point

MCPBA = m-chloroperbenzoic acid

MMPP = monoperoxyphthalic acid, dimagnesium salt

DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone

DCC = 1,3-dicyclohexylcarbodiimide

DMAP = 4-dimethylaminopyridine

2) MOLECULAR MODELLING

For the three dimensional minimised structures depicted on pages 13 and 22 the following colour coding system is adopted; BLACK = Carbon atom, GREEN = Hydrogen atom, BLUE = Nitrogen atom, RED = Oxygen atom. Minimisation was carried out on an IBM PS/2 Model 50 microcomputer with an 80287 math coprocessor, using the ALCHEMY™ molecular modelling program, © Tripos Associates 1987.

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Master of Philosophy

Approaches to the Synthesis of the Macrolide Pheromones of the Saw-Toothed Grain Beetle, *Oryzaephilus surinamensis*

by Christopher David John Boden

Attempts were made to develop commercially viable syntheses of two target compounds of the type indicated in the title. The principle routes studied involved protection of the highly sensitive skipped diene functionalities in these molecules as their homo Diels-Alder adducts with suitable azodienophiles. Two approaches to these diene-protected intermediates were studied, the first of which involved cyclopropanation of analogous adducts from 1,3-dienes and the second functionalisation of the Diels-Alder adduct formed between cycloheptatriene and 4-phenyl-1,2,4-triazoline-3,5-dione.

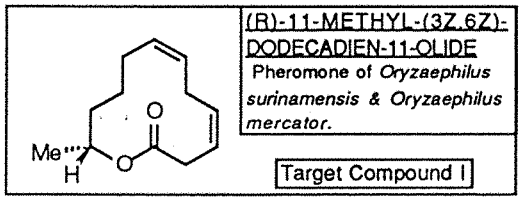
Investigations were also carried out into the synthesis of the targets via acyclic, skipped diene-containing hydroxy acid precursors. The construction of these was attempted utilising the ylid (3-3-diisopropyloxy) propylidene phosphorane as a three carbon homologating agent.

CHAPTER 1

OUTLINE OF OBJECTIVES + OVERVIEW OF MACROLIDE SYNTHESIS

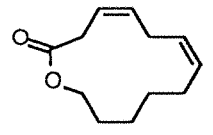
1.1 : OBJECTIVES

The saw-toothed grain beetle *Oryzaephilus surinamensis* is the major pest of stored grain in the UK, and there is a great deal of interest in the development of a suitable chemical control method. The central aim of this project was to develop efficient syntheses of the macrolide aggregation pheromones I and II, which have shown considerable promise as lures for these commercially important pests[1].



(R)-11-METHYL-(3Z,6Z)-DODECADIEN-11-OLIDE
Pheromone of *Oryzaephilus surinamensis* & *Oryzaephilus mercator.*

Target Compound I



(3Z,6Z)-TRIDECADIEN-12-OLIDE
Aggregation pheromone of *Oryzaephilus surinamensis*

Target Compound II

SCHEME 1 - THE TARGET COMPOUNDS

1.2 : APPROACHES TO THE SYNTHESIS OF MACROLIDES - AN OVERVIEW

In common with synthetic chemistry as a whole, the area of macrolide synthesis has undergone radical change in the last twenty years[2], with some dramatic improvements being made to long established procedures and the development of an array of promising new techniques. The strategies which have been used in the construction of these molecules can be broadly divided into two camps, these being

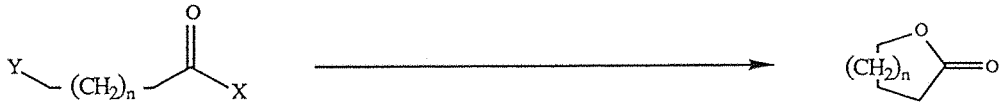
1) Approaches which rely on direct formation of the macro- ring system, either by condensation of an acyclic ω-hydroxy acid or by a similar intramolecular reaction involving functionalities other than the lactone itself. For convenience these different transformations will all be dealt with

under the general heading "direct macrolactonisation", although the range of reactions which have been applied to such ring closures is quite large.

2) Approaches which form the macro - ring indirectly, e.g. by fragmentation of suitable bicyclic (or even tricyclic) precursors. These routes will be referred to under the general heading "ring expansion").

1.2.1 : DIRECT MACROLACTONISATION

This has been by far the most widely used strategy, as for the majority (i.e. those which have ring sizes of fourteen or more) of interesting macrolides its advantages over ring expansion routes far outweigh its disadvantages. The main advantages are



X = OH, S-pyr, etc ; Y = HO, $OPPh_3$, etc

SCHEME 2

Macrolactonisation of activated hydroxy acids

i) Complex skeletal features may be constructed without the restrictions which arise when a potentially sensitive group such as an ester is present. This allows the use of a number of reactions which form an essential part of the armoury of the modern synthetic chemist (such as carbene / carbenoid processes and most reactions involving the use of "hard" organometallic reagents such as Grignard reagents or organolithiums).

ii) The fact that the skeleton can be functionalised when in an acyclic rather than a cyclic form allows greater freedom in the generation of stereochemical features, as the conformational restrictions imposed on a cyclic structure will themselves tend to create an (albeit limited) degree of

stereocontrol (by directing the mode of attack of a reagent towards a particular face of the molecule, for example) which may well be in conflict with the stereocontrol which is actually required. This is of course a mixed blessing, as stereocontrol (particularly enantiocontrol) will of course be harder to induce in an acyclic system than in a cyclic one.

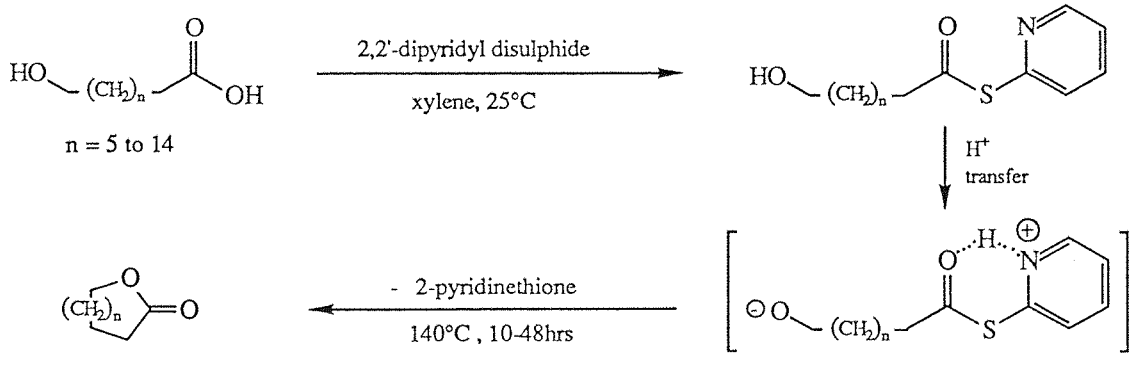
iii) There are a now several mild and efficient lactonisation techniques which can be used in the presence of a wide range of functionalities. The three most prominent ones are

a) The Corey "double activation" procedure[3]

b) Mukaiyama carboxylate activation[4], and

c) Mitsunobu hydroxyl activation[5] ("reverse activation")

Of the three processes the Mukaiyama procedure has been the most widely used[6], although the Mitsunobu lactonisation has also proven useful in some cases[7].

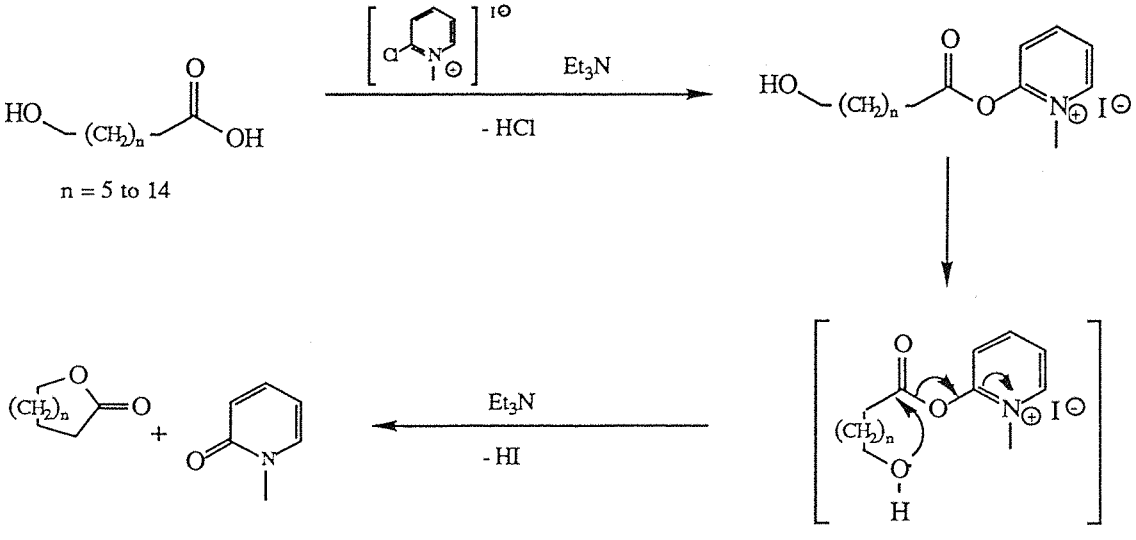


SCHEME 3

The Corey "double activation" approach to macrolactonisation

The oldest of the three is the well-established Corey "double activation" cyclisation (SCHEME 3), which activates the carboxyl group by forming the 2-pyridinethiol ester; this further drives the lactonisation by promoting proton transfer from hydroxyl to carboxyl[8]. Using this method

the Corey group (and several others) have achieved syntheses of some quite complex polyfunctional macrolides[10]. Nevertheless despite its proven worth this approach has one fundamental weakness : temperature. In order to carry out the more entropically demanding cyclisations (i.e. those of 8-13 and 18+ member rings) it typically requires slow addition of the appropriate ω–hydroxy thioester to refluxing xylene (140°C) over long periods of time (>24 hours)[11]. Clearly this poses considerable problems with temperature sensitive molecules ; if either the hydroxy acid or the lactone are prone to isomerisation the technique is likely to prove of little use.



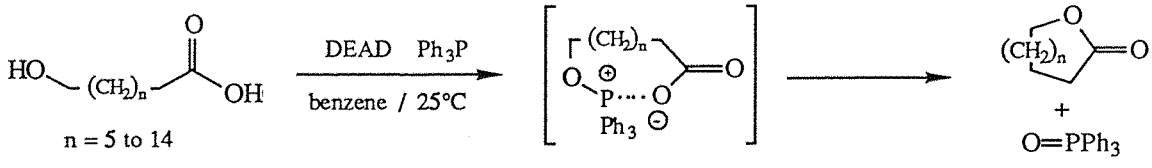
SCHEME 4

The Mukaiyama route to macrolides, illustrated for 2-chloro-1-methylpyridinium iodide.

The Mukaiyama procedure, on the other hand, proceeds under much milder conditions (refluxing acetonitrile usually suffices, and indeed refluxing dichloromethane has also been used[12]), Reaction times are generally lower too (2-8 hours is typical) and yields are often higher. Its one disadvantage with respect to the Corey procedure is that it does not proceed under completely neutral conditions; the presence of a mild base (such as triethylamine) is necessary to neutralise the acid which is formed. Nevertheless it is steadily replacing the Corey method as a means of

forming complex macrolactones via carboxyl group activation.

The last of this trio of ring closure techniques takes a different approach, as the hydroxyl (rather than the carboxyl) group is activated to facilitate ring closure. It is also allows hydroxyl groups to be condensed onto other active hydrogen bearing centres[5]; however the



SCHEME 5

The Mitsunobu lactonisation reaction

lactonisation reaction has received the most attention. Whilst yields are not usually as good as those obtained using the other two methods (formation of the lactide is harder to suppress, making the method less suitable for very difficult cyclisations) the reaction is very mild (typically a few hours at room temperature) and like the Corey method proceeds under essentially neutral conditions.

Whilst these three approaches have been the most widely used there are several other less important techniques which have been developed; these include lactonisations mediated by tin oxides[13], cyanuric chloride[14], DCC-DMAP[15], and crown ether containing thioesters[16]. Also, a method for closing macrolide rings via enzyme-catalysed transesterification of methyl esters of hydroxy acids has recently been reported[17]. In addition to these there are a large number of reactions other than ester formation which have been used to close macrocycles; Dieckmann cyclisation[18], free radical mediated methods[19] and intramolecular Wittig / Wadsworth - Emmons

olefinations are good examples[20]. Of these the last has seen the most use, as there are a number of interesting macrolides which contain α,β–unsaturated ester functionalities which can be made via intramolecular Wadsworth-Emmons reaction of the esters of ß-phosphonato acetates[21]. It also has the advantage (when performing entropically demanding ring closures) that it creates a conformationally constraining feature (i.e. the olefin) in the actual ring closure step, which is usually (though not always) preferable to having it present prior to ring closure. Its major limitation is that only E-alkenes may be produced using the relatively mild phosphonate ester-stabilised ylids; much more brutal conditions are needed to generate the unstabilised ylids needed to form Z-alkenes, and as the reaction must be carried out under high dilution with *in situ* formation of the ylid competitive enolisation of the carbonyl terminus becomes a serious problem.

In summary then direct macrolactonisation techniques are the approach of choice for systems where the ring closure itself is not especially disfavoured, and as such are the most commonly used and well studied approaches to macrolides as a class.

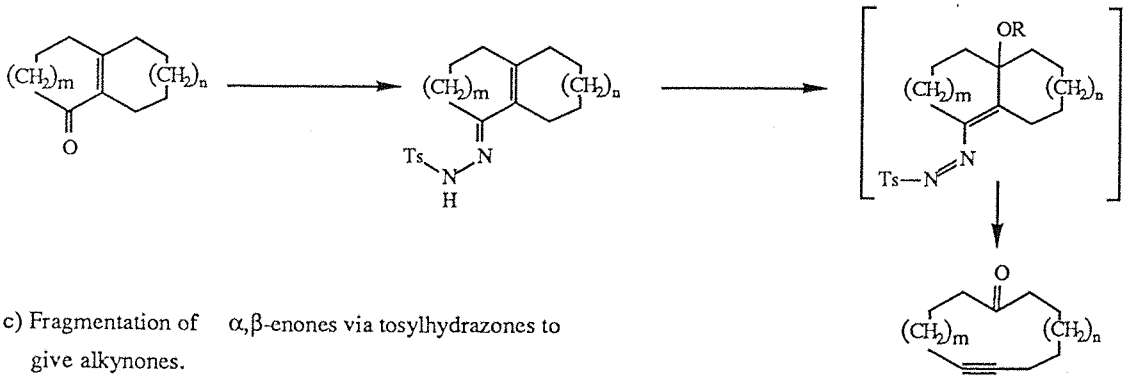
1.2.2 : RING EXPANSION ROUTES

The formation of macrocyclic lactones by either a bridge-bond severing fragmentation of a bicyclic precursor or an insertion of atoms into a cyclic precursor of less than the required ring size is an extremely versatile and valuable synthetic approach, as the problems inherent with direct formation of strained systems can be avoided. Needless to say this approach is of particular value in forming ring systems (such as 8-13 which also contain conformationally restricting features) where the difficulty of macro-ring closure precludes a synthesis by a direct macrolactonisation

strategy. The general approach (a selection of the most widely used variations of which are outlined in Scheme 6) has been extensively reviewed[22] quite recently (1988), and given the large number of possible approaches this overview will concentrate mainly on the general strategies which have been employed rather than on specific reactions. Information will however be included on important techniques which it is felt did not recieve adequate coverage in that review.

a) Oxidative cleavage of internal alkenes

b) Ring opening in cyclobutane containing molecules.



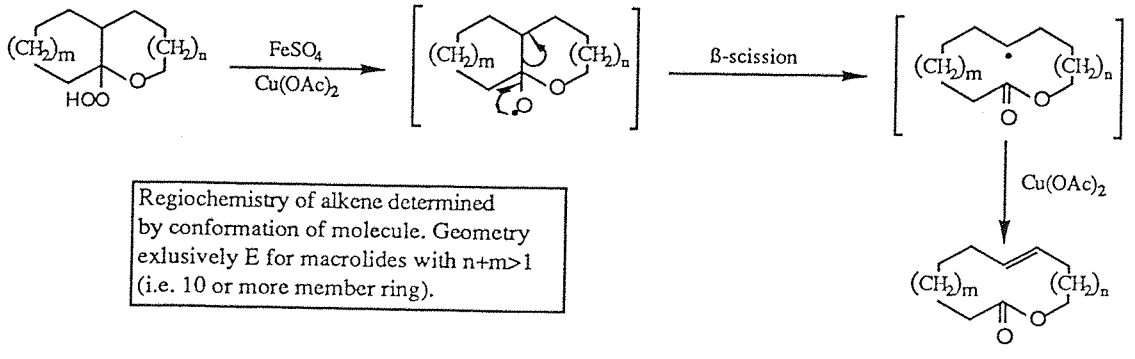
c) Fragmentation of α,β-enones via tosylhydrazones to give alkynones.

SCHEME 6

A selection of the more widely used ring expansion reactions

The simplest of these methods is the Baeyer-Villager oxidation of macrocyclic ketones to give the n+1 macrolide via an oxygen insertion. This has been used extensively[23], but has two major limitations, these being i) the need for the substitution patterns on either side of the ketone to be significantly different if any regiocontrol is to be obtained ii) the similarity of the conditions for Baeyer-Villager oxidation to those for alkene epoxidation,

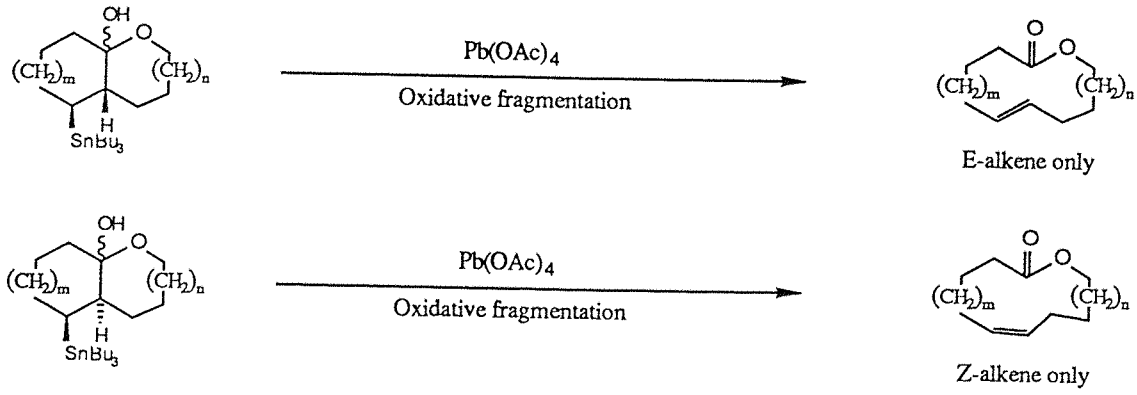
which makes selective oxidation of the ketone difficult in molecules which also contain simple alkenes. Other relatively simple methods include translactonisations from smaller macrolides bearing hydroxyl-containing side chains[24] (the driving force being provided by the release of strain on increasing the ring size), the use of Claisen type 3,3-sigmatropic rearrangements[25], and the ring opening of cyclobutenes[26]. These simple methods have not however proven as useful as the more powerful fragmentation-based techniques (such as the one shown in Scheme 6c), which are increasingly coming to dominate the field. During the last ten years a great deal of new fragmentation - based methodology has been developed, arising mainly from the application of well known fragmentations to the solution of synthetic problems.



SCHEME 7

Fragmentation of α-alkoxy hydroperoxides

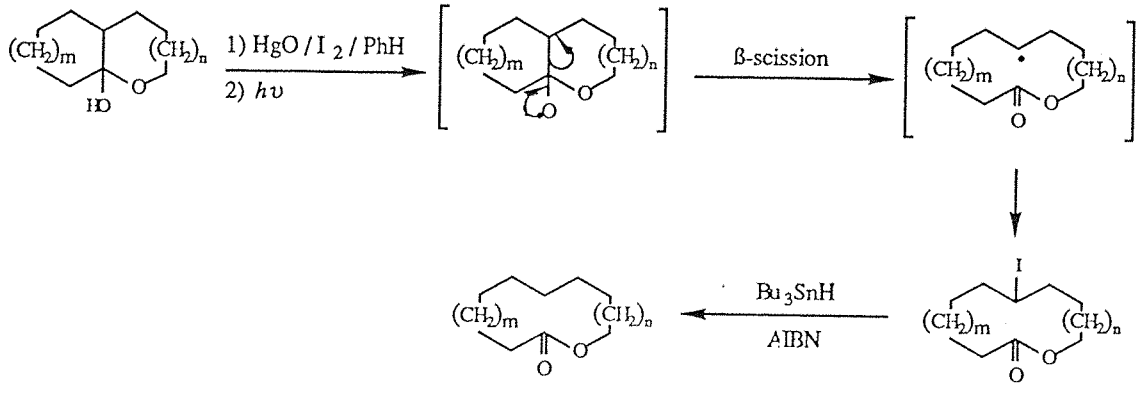
Chief among these have been the work of Schreiber on metal catalysed fragmentation of α-alkoxy hydroperoxides[27] (Criegee rearrangement, Scheme 7 - see also the related work of Suginome[28] illustrated in Scheme 9) and that of Posner*et al.* utilising the oxidative fragmentation of γ-hydroxy stannanes[29] (Scheme 8).



SCHEME 8

Formation of macrolides by fragmentation of γ-hydroxy stannanes.

The latter method is perhaps the more interesting as it allows both E and Z alkenes to be formed[30,31], the geometry being determined by the stereochemical relationship between the tributylstannyl group and the adjacent bridgehead hydrogen. Its usefulness is limited by the fact that as yet the only fully developed method for emplacing the tributylstannyl group in a non-allylic position has been via 1,4-addition of tributylstannyllithium to a suitable α,β–unsaturated ester or enone[32], although it is possible that the functionality could be generated from the equivalent alkyl halide via formation of either the Grignard reagent or the organolithium species and then transmetallation.



SCHEME 9

Preparation of macrolides by photolysis of lactol-derived hypoiodites

Other fragmentation routes which have been used in the synthesis of macrocycles include one of similarly wide utility, this being the fragmentation of bicyclic α,β–unsaturated ketones to give ω-alkynones[33] (Scheme 6, reaction c)). This has seen quite wide use in the formation of larger ring macrolides (15 member or more) but the formation of a linear acetylene unit leads to a severe penalty in thermodynamic terms due to the steric restrictions incurred. This means that the method is of very limited use for smaller ring sizes.

CHAPTER 2

POSSIBLE SYNTHETIC PATHWAYS TO THE TARGET COMPOUNDS

2.1 : GENERAL CONSIDERATIONS

When designing a synthesis of the target compounds there are several points which must be borne in mind;

1) They each contain 1,4-diene and β,γ-unsaturated ester functionalities, both of which are unstable to acid, base, heat, light and atmospheric oxidation (whilst the former is reasonably stable if stored carefully[34] the latter is extremely sensitive and in general compounds containing such a functionality are synthesised via routes which generate it as close to the end as possible[35]). The targets themselves have been reported to be unstable even at freezer temperatures[36] (-20°C).

2) The geometries of the alkenes are all Z, which for compounds of these ring sizes is the less stable isomer (the majority of naturally occurring unsaturated 11-14 member ring macrolides have E alkene geometries[37a]; the Z configuration is relatively uncommon[37b]).

3) The large number of flat sp^2 centres, taken together with the ring sizes and the unnatural alkene geometries combine to make the molecules very difficult to cyclise directly (although this has been achieved, albeit in very low yields[36]).

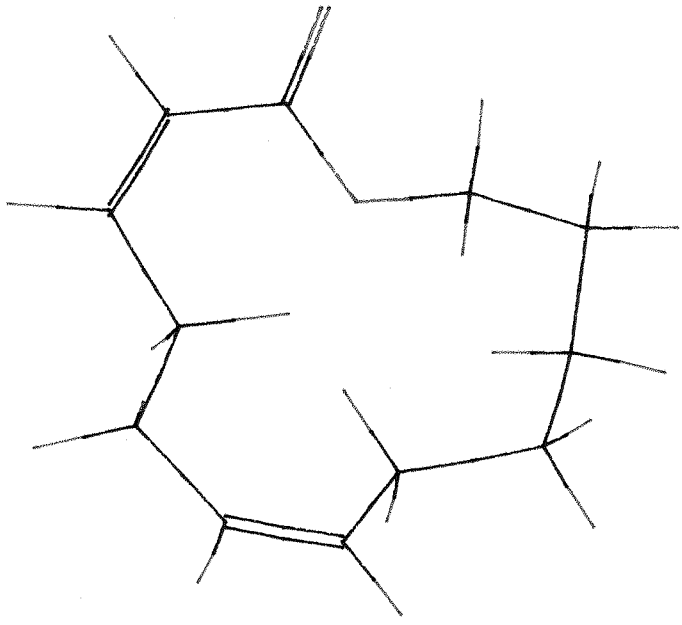
2.2 : TACTICAL CONSIDERATIONS

The problems outlined above give rise to a series of tactical limitations which must be appreciated when designing a synthesis

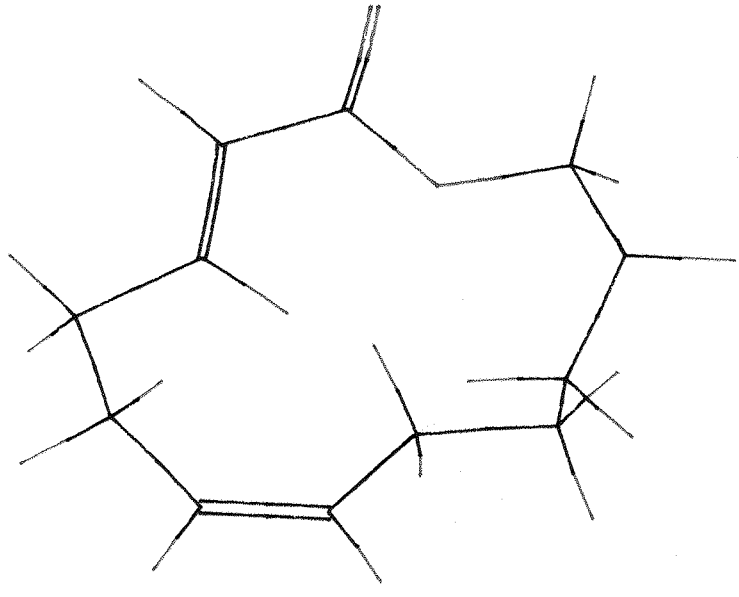
i) It is unlikely that the β,γ–unsaturated ester functionality can be created by simple deconjugation of the equivalent α,β–unsaturated ester *whilst the ε -alkene is present.* Even if the necessary pattern of unsaturation could be created, examination of the 3D structures of the two possible geometrical isomers of the hypothetical α,β–unsaturated lactone precursor suggests that the E-alkene would be far more likely to result from deconjugation than the Z (Scheme 10). This looks particularly certain for the E - isomer, which should be by far the easier of the two to make (either via Wadsworth - Emmons olefination or by selenoxide / sulphoxide elimination[38] - again modelling suggests that such elimination would give an E-geometry, which would in any case be expected for a ring of this size).

ii) Whilst the presence of the methyl group in compound I does suggest the use of the Baeyer-Villager oxidation to form the ester group (from the n-1 macroketone), the presence of non-conjugated alkenes makes selective oxidation of the ketone difficult. Although a reagent, *bis-* (trimethylsilyl) peroxide, has been introduced which displays such selectivity on acyclic and common ring size compounds, the yields which it gives are by no means encouraging[39]. Furthermore the conditions required would quite probably cause destruction of either or both of the sensitive functionalities in the targets (which, assuming that they cannot be emplaced by deconjugation, would need to be present before ring expansion could be carried out)].

These difficulties have combined to ensure that despite the great commercial potential of these compounds only one set of syntheses has been reported to date[36]. These are the syntheses of Oehlschlager & his coworkers, and the general approach taken is direct macrolactonisation, via the appropriate hydroxy acid. Although these syntheses have been repeatedly used by the Oehlschlager group they are the product of what is in many ways a poor approach, as the lactonisation steps go in very poor yield



(2Z,6Z)-TRIDECADIEN-12-OLIDE



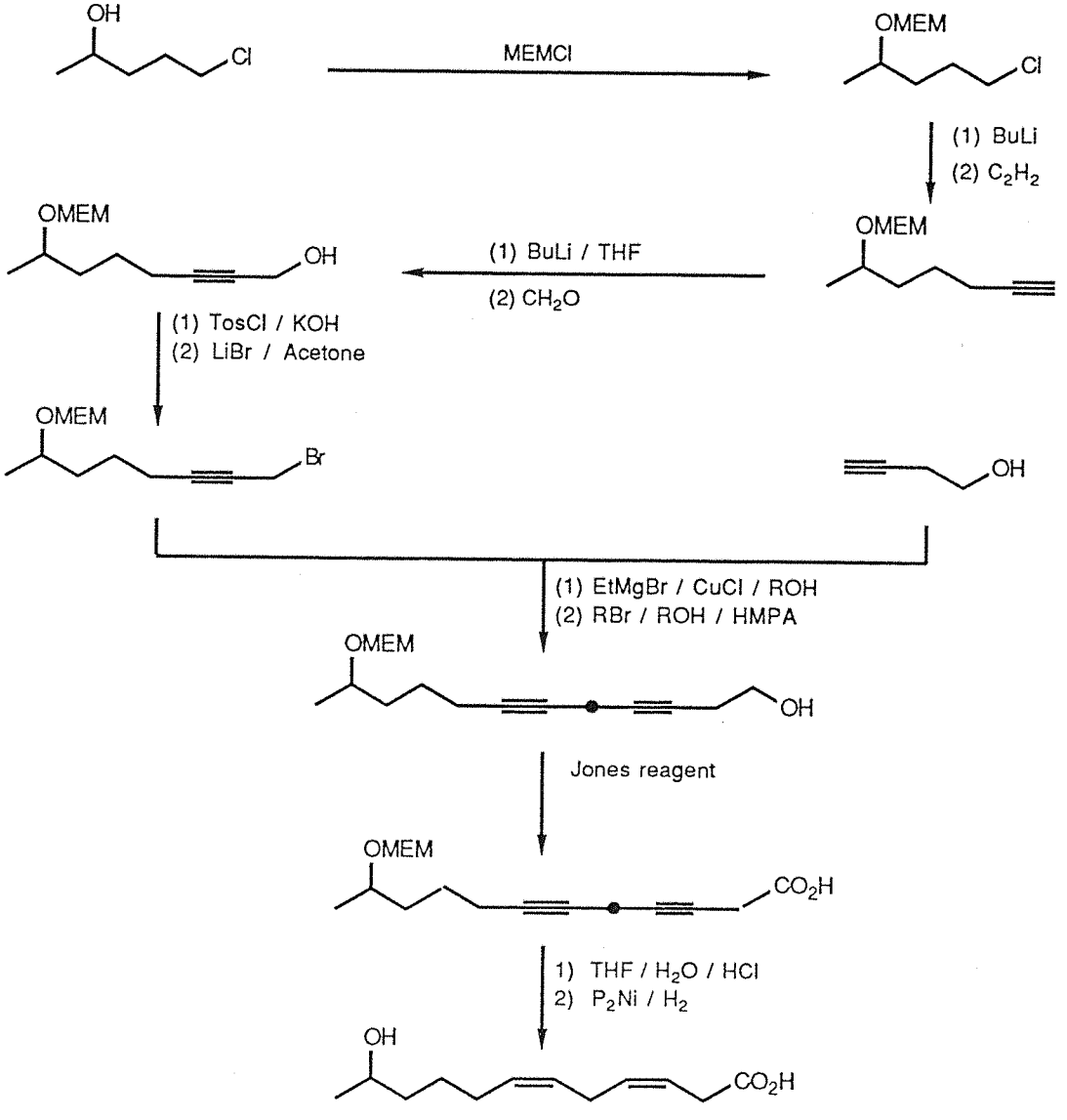
(2E,6Z)-TRIDECADIEN-12-OLIDE

SCHEME 10

Minimum energy conformations for the hypothetical "deconjugation" precursors to II

for both compounds (7% for I and 27% for II). Furthermore the routes taken (Schemes 11a,11b) give only mediocre overall yields of the *hydroxy acids*, and the potential exists for considerable improvement in these preparations. It would seem that any synthesis which is to be used on a multi-gram scale must either avoid direct macrolactonisation completely or prepare the hydroxy acid precursors in very high yields.

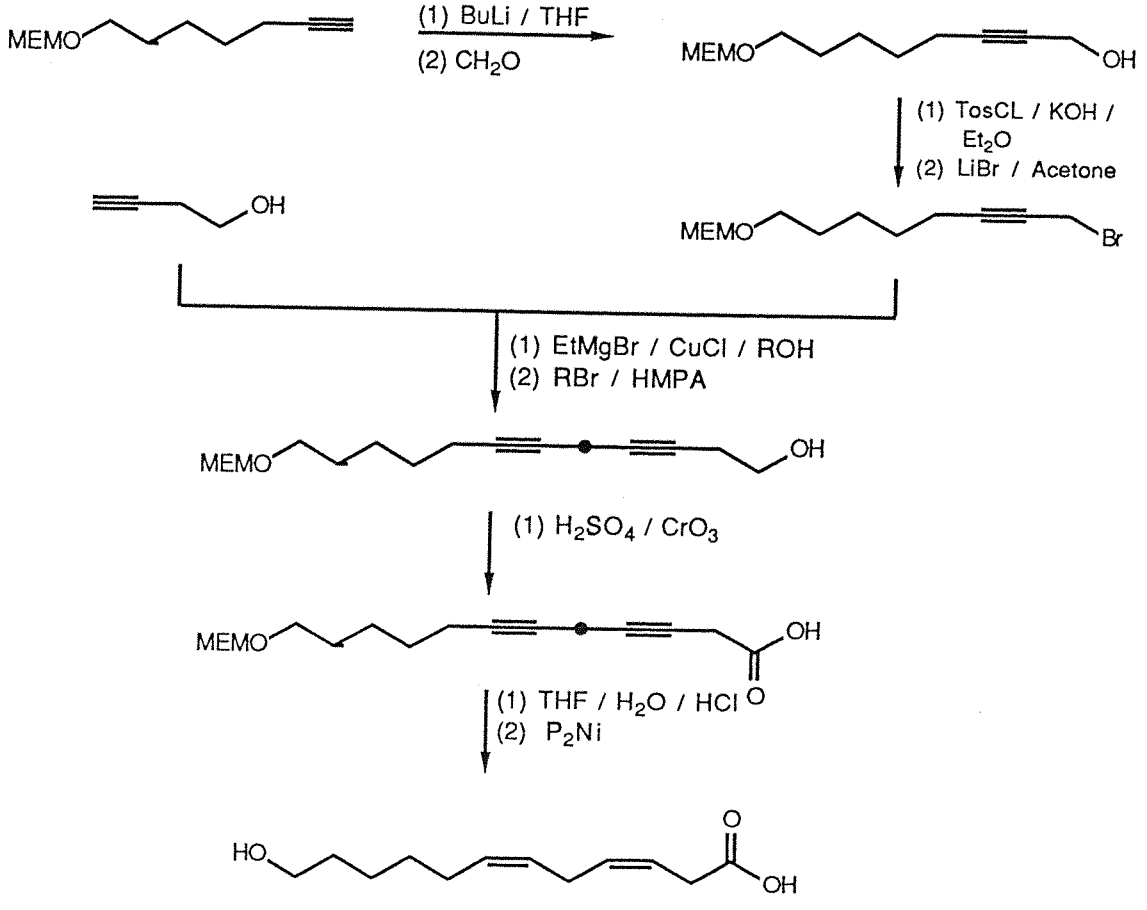
2.3 : POSSIBLE IMPROVEMENTS TO THE SYNTHESES OF THE HYDROXY ACIDS



SCHEME 11a

Oehlschlagers 1986 synthesis of precursor to I. Yield of precursor = 7% overall.

As can be seen from Scheme 11b the routes to the hydroxy acids taken by Oehlschlager involve protecting the 1,4-diene as a 1,4-diyne, thereby enabling the use of reagents which would destroy the dienes themselves.



SCHEME 11b

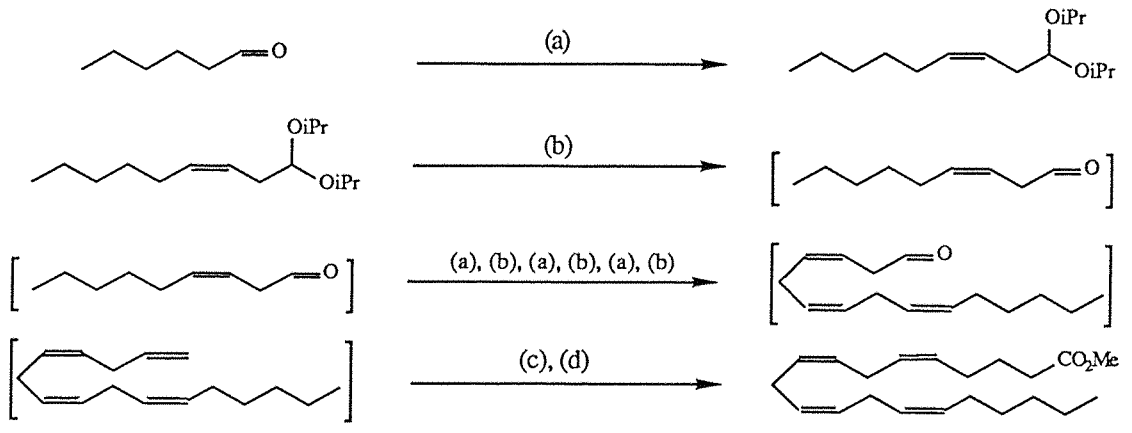
Oehlschlager's 1986 synthesis of the precursor to II. Yield = 14% overall

This approach also protects the deconjugated enoic acid group, which is generated immediately prior to cyclisation, which is performed using the Mukaiyama procedure (details in Chapter 1). No additional information about the cyclisation is given, other than a note stating that several attempts were made after which it was concluded that the cyclisation of the molecules is inherently difficult; no comment is made concerning alternative cyclisation conditions which might have been tried. However

given the molecules' and the also the hydroxy acids' sensitivity to heat it would not be unreasonable to assume that this is the only method which can be used successfully and that others were tried with no success (the Corey method would almost certainly destroy either - or more likely both - the hydroxy acids and the lactones, whilst the Mitsunobu approach could not be expected to prefer intramolecular esterification with such a strained system). Clearly, then, in the case of compound I any improvement to the preparation of the hydroxy acid would be futile as the lactonisation goes in such poor yield. However, the 27% lactonisation yield obtained with compound II could just about form part of a commercially viable route to that compound, provided that the hydroxy acid could be made cheaply enough. Recent developments in the synthesis of 1,4-diunsaturated compounds have considerably simplified the search for a suitable route, as

a) Recent work by Jeffery[40] has shown that 1,4-enynes can be made via copper halide catalysed direct coupling of terminal acetylenes and allyl chlorides, under conditions mild enough to tolerate carboxylic acids and esters. Also no deprotonation of the acetylene is required as is the case with the coupling used in the Oehlschlager syntheses. This should allow the relatively low yielding Jones oxidation steps in the Oehlschlager syntheses to be dispensed with, by enabling the coupling of the propargyl (or allyl) halide fragments with 3-butynoic acid rather than 3-butyn-1-ol.

b) Work by Santelli has indicated that skipped polyenes can be formed by Wittig reactions using the phosphonium salt (3,3-disopropyloxy)propyl triphenyl phosphonium bromide in an iterative process. This has been applied to the synthesis of methyl arachidonate[41] (Scheme 12). Given that the hydroxy aldehyde starting material which would be required in the synthesis of target compound II is readily available from cheap starting materials[42] this would appear to be an almost ideal approach.



(a) Ph_3P=C(H)C(H)(OiPr)OiPr / THF / PhMe , ylid formed using NaN(TMS)$_2$
(b) 0.1M pTsOH / THF
(c) Ph_3P=C(H)CH$_2$CH$_2$CO$_2$Na / THF / HMPA, ylid formed using NaN(TMS)$_2$
(d) CH_2N_2 / Et_2O

SCHEME 12

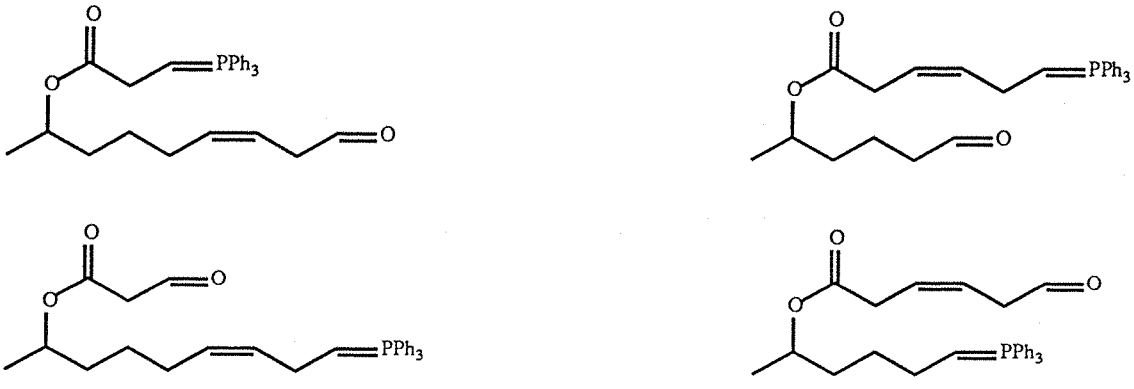
Santelli methodology for the construction of skipped polyenes

An investigation into the synthesis of compound II using this methodology forms part of this project (see Chapter 5).

2.4 : OTHER DIRECT MACROLACTONISATION APPROACHES

In addition to the alternative approaches to hydroxy acid type precursors that have become available there remains the possibility of using a reaction other than ester formation to close the ring system. However in view of the seemingly inherent difficulties in closing the ring it seems clear that this would need either to provide a powerful driving force towards intramolecular rather than intermolecular reaction, or make ring closure less demanding entropically, for instance by forming a conformationally restricting feature (via a less restricting transition state) as a direct product of the reaction used to achieve the closure. An example of this would be the use of a Wittig-type olefination reaction to close the ring by making one of the Z-alkene functionalities; unfortunately however this is not a viable route due to the need to form unstabilised ylids in order to achieve

Z-selectivity. This has always been a problem with such closures, and has meant that yields for the closure of even simple cyclic systems have been modest[43]. In the case of the target compounds the inevitable presence of base-sensitive functionalities in all of the possible precursors which might be used (see Scheme 13), taken together with the likelihood of the rate of ring closure being very slow makes isomerisation or enolisation of the starting material by far the most likely outcome.



SCHEME 13

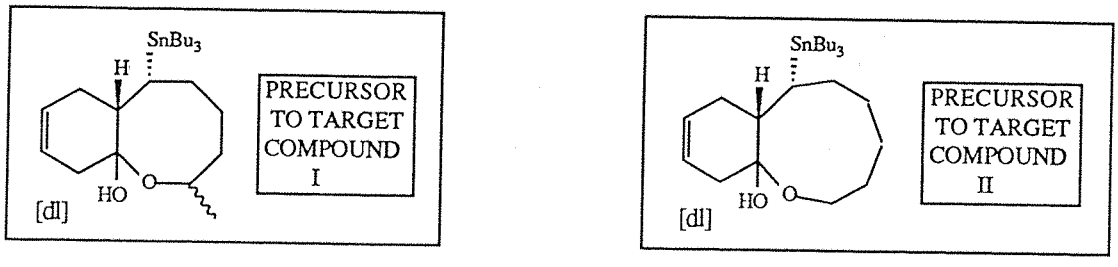
The necessary precursors for formation of II by Wittig ring closure

Many other reactions which have been applied to macro-ring closure are constrained by similar problems; in the case of radical based methodology there is the additional problem of avoiding the much more favourable formation of the more familiar ring sizes resulting from radical attack on the alkenes (which is made all the more likely by the ensuing removal of the conformationally restricting alkene functionality).

2.5 : POSSIBLE RING EXPANSION ROUTES

Formation of the target compounds by a route which avoids direct macrolactonisation is an attractive option, as it should allow the low yielding cyclisation step to be avoided. However there are fundamental difficulties in making the target systems via such a route, these being

i) The position and sensitivity to isomerisation of the double bonds. As with the direct macrolactonisation approach this is a very serious problem, as it is necessary to set up the sensitive functionalities as late as possible in the synthesis. This strongly suggests that one of the double bonds should be emplaced by a final step fragmentation which converts a bicyclic precursor to the target monocyclic product. If this is to be achieved then the method of Posner would seem to be an ideal approach, as it generates both an ester and a double bond ε- to it. However whilst the final step fragmentation itself seems viable, the synthesis of the immediate precursors which would be needed presents severe difficulties (Scheme 14).



SCHEME 14

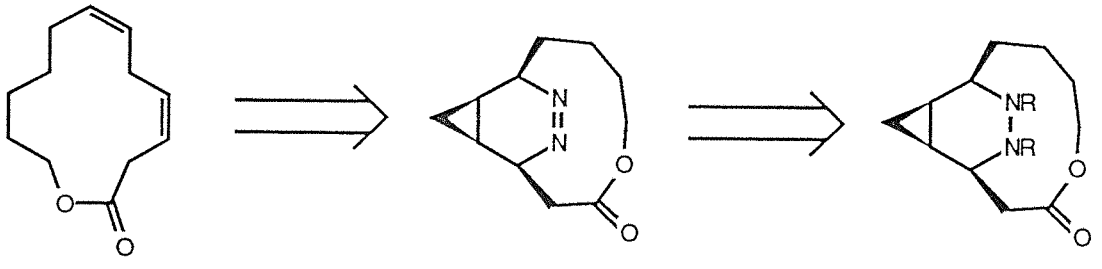
Precursors required to form target compounds, assuming oxidative fragmentation as last step

Chief among these is the formation of the 8 or 9-member lactol, which unlike the 6-member lactols which have commonly been used in this type of work cannot be formed by simple acid catalysed condensation of the equivalent hydroxy ketone. There is also the more serious problem of creating the correct (*anti*) relationship between the tributylstannyl leaving group and the bridgehead hydrogen, a process which would not be possible using the usual method of non-allylic alkyl tributyl stannane formation (Michael addition of $LiSnBu_3$ to an α,β-unsaturated ester or ketone). Of the other fragmentation routes mentioned in Chapter 1, the Schreiber method can be ruled out as the the alkene formed would almost certainly have the incorrect E-geometry[44], the method of Suginome et al would be rendered

useless both due to the difficulties in forming the lactol precursor and the problem of competing radical processes occurring under conditions of photolysis, and the α,β–enone to ω-alkynone fragmentation would be inappropriate as i) the product alkynone required would be highly strained, making its formation unlikely and ii) the problem of oxidation of the macroketone product to the macrolactone in the presence of alkenes/alkynes would remain.

2.6 FORMATION OF THE TARGETS VIA PROTECTED 1,4-DIENE CONTAINING PRECURSORS

There remains the possibility, however, of devising a route to the targets which proceeds via intermediates which contain the sensitive functionalities in a protected form, ready to be generated when the rest of the molecule has been constructed. Ideally the means of protection should



[1] [2] [3] R=H
[4] R=CO_2R'

Removal of the R' groups from [4] followed by spontaneous decarboxylation gives the disubstituted hydrazine [3]. Treatment of this with copper(II) chloride gives a thermally stable complex, which on treatment with aqueous ammonia yields [1] via the unstable intermediate [2].

Scheme 15

Formation of target compound II via 1,4-diene protected precursors-proposed final steps.

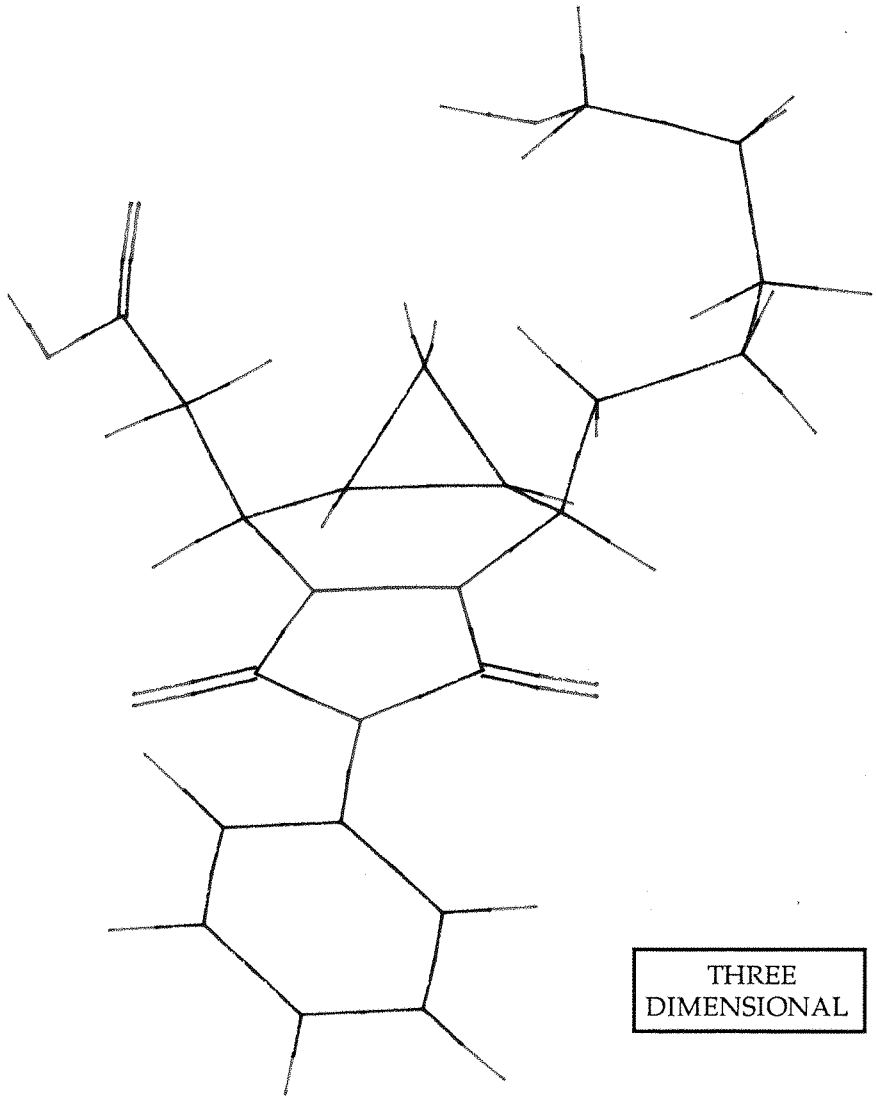
also enhance the lactonisation, for instance by reducing the ΔS value for bringing the two termini together. One possible approach would to utilise the final transformations shown in Scheme 15. The protection of the

1,4-diene as what is effectively its homo Diels-Alder adduct with a suitable azodienophile, leaving the final deprotection sequence [4] - [1], performs two functions;

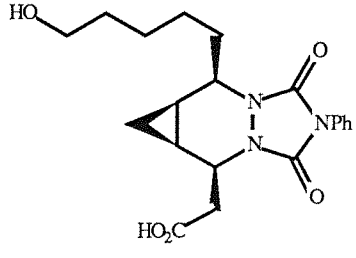
i) Protection of *both* the sensitive functionalities, allowing a much wider choice of lactonisation reagents and conditions.

ii) Reduction of the conformational freedom of the hydroxyl and carboxyl bearing chains in the hydroxy acid precursor to [4], decreasing the entropy of cyclisation relative to that seen with the direct macrolactonisation strategy by increasing the probability of the desired interaction between the termini.

In fact the siting of the chains 1,4- and *syn* on what should be an almost flat 6-member ring can be expected to give a reduction in ΔS of some considerable magnitude (see Scheme 16). When this is taken together with point (i) it is not unreasonable to predict that cyclisation should be made considerably easier. In addition to the synthetic advantages promised by this route there is the additional bonus of the potential "slow release" mechanism which arises from the cleavage of the protecting group - the cuprous azo complex formed on deprotection should be stable at room temperature[45], in marked contrast to the target compounds themselves. Simple and quantitative cleavage of such complexes gives azo-compounds, which when possesing structures analogous to those in the projected precursors have been shown to undergo the desired retro homo Diels-Alder fragmentation instantaneously and quantitatively at room temperature[45]. Control of the rate of hydrolysis, therefore, should allow control of the rate of pheromone release ; moreover the non-toxic nature of the reagents and by products involved should allow the deprotection to be carried out *in vivo* (i.e. actually inside the traps used to collect the insects). Given the great potential of this approach a study of this methodology was under taken, and forms the major part of this project (Chapters 3 & 4).



THREE DIMENSIONAL



TWO DIMENSIONAL

SCHEME 16

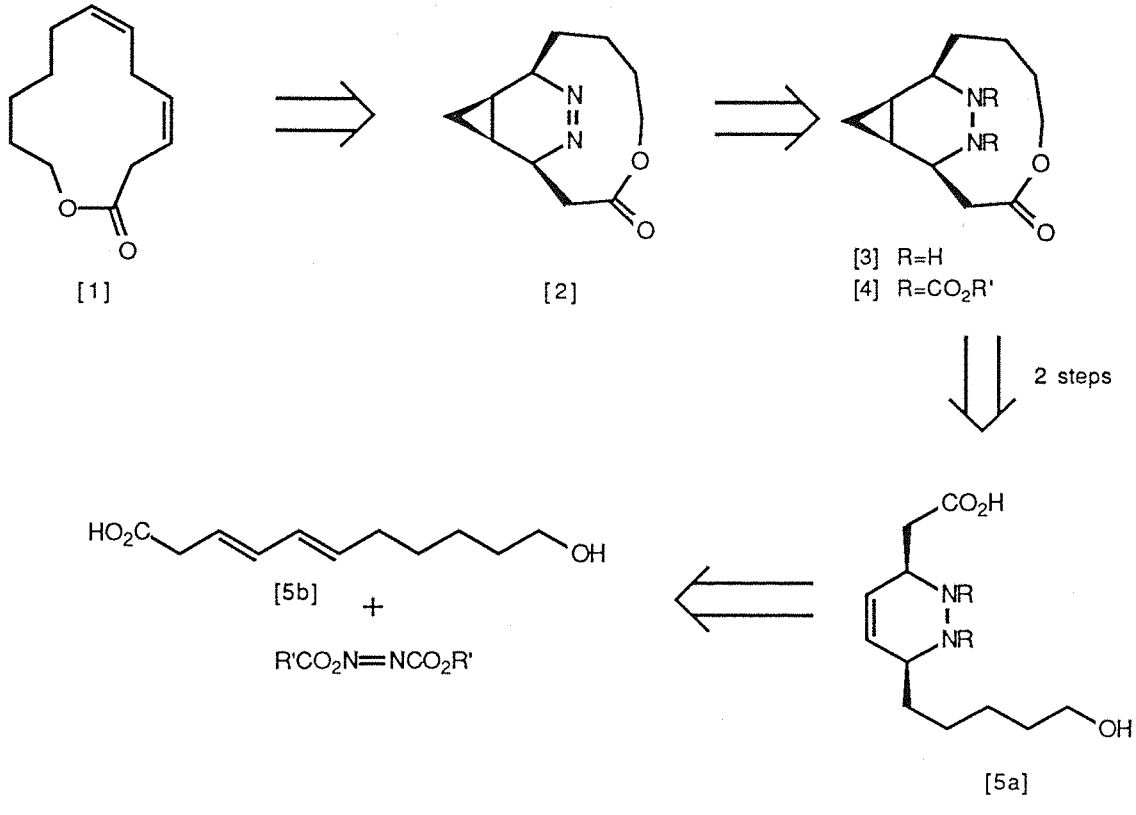
Two dimensional and minimised three dimensional structures of hydroxy acid precursor to intermediate [4] in a projected synthesis of II using the approach outlined in Scheme 15. The dienophile used is PTAD. 3D view is taken from above the aromatic ring, looking towards the cyclopropane. Note the almost flat main 6-member ring, and the proximity of the alcohol hydroxyl group and the carbonyl of the carboxylic acid (calculated distance = 4.64Å)

CHAPTER 3

FORMATION OF PROTECTED 1,4-DIENES BY CYCLOPROPANATION

3.1 : THEORY

Direct formation of homo Diels-Alder adducts cannot be achieved when (as in this case) the potential exists for the more favoured ene reaction to occur. The most conceptually simple alternative route to the desired protected 1,4-dienes is that shown in Scheme 17, i.e cycloaddition between the dienophile and the appropriate 1,3 - diene, followed by cyclopropanation of the alkene so generated, formation of the lactone and finally deprotection of the masked diene.

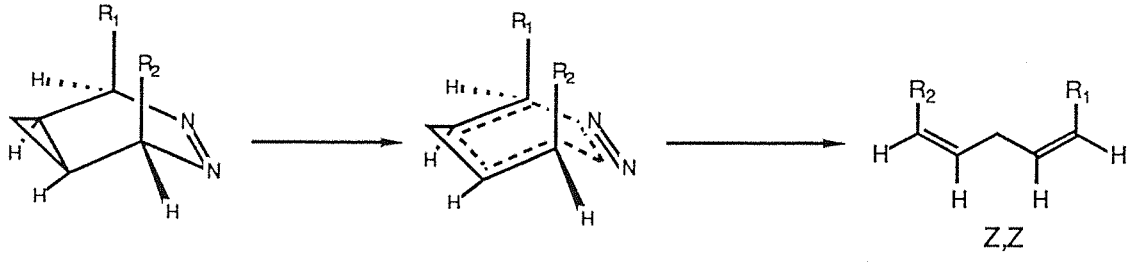


SCHEME 17

Retrosynthetic analysis for routes utilising alkene cyclopropanation.

When designing such a route the following points must be considered;

i) The stereochemistry of the cyclopropane ring (relative to both the hydroxyl and carboxyl bearing side chains and also the azo group formed on deprotection + oxidation) will be vital in determining the alkene geometries in the 1,4-diene which is formed in the final fragmentation[46]. If the necessary Z,Z geometry is to be obtained then it is clear that the cyclopropane and the side chains must have a *syn* relationship, as the fragmentation has been shown to strongly prefer an *anti* relationship between the cyclopropane methylene and the departing nitrogen molecule in the transition state [47](Scheme 18). This preference seems to be due primarily to electronic effects and is largely unaffected by steric factors; if these were the dominant factor then the opposite transition state would be expected.



SCHEME 18

The transition state for the projected final fragmentation.

ii) Adducts from most of the common azodienophiles (dialkyl azodicarboxylates, triazolinediones etc) require cleavage conditions which would almost certainly cleave the desired lactone[48]. However dienophiles have been introduced whose adducts can be converted to the required disubstituted hydrazines under mild conditions.

iii) In order to achieve the required stereorelationship between the two side chains the 1,3-diene must have exclusively the E,E-geometry (Z,Z- would also give a *syn* relationship but it is most unlikely that the Z,Z-1,3-diene would react).

iv) The β,γ,δ,ε-unsaturated acid [5b] suggested as the 1,3-diene may be prone to isomerisation, and the formation of the acid functionality may therefore be better carried out after the cycloaddition.

The following questions were posed as the subject for initial investigations;

v) Could cyclopropanation of such Diels-Alder adducts be carried out without disturbing a lactone functionality?

vi) What cyclopropane stereochemistry would be obtained? Would this be different for lactone containing (i.e. bicyclic) and hydroxy acid containing (i.e. monocyclic) adduct substrates?

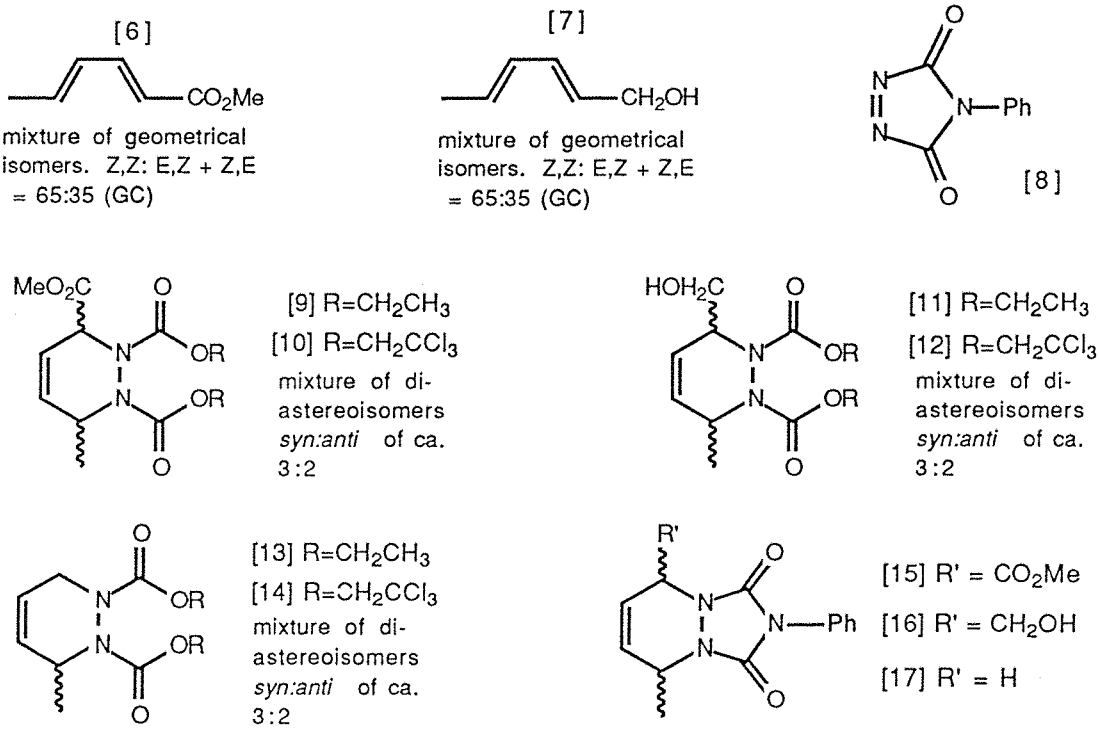
vii) Could cleavage of the urethane functionality in the protected 1,4-diene by achieved without disturbing the desired lactone?

3.2 ATTEMPTED CYCLOPROPANATION OF MODEL ADDUCTS

Investigations began with the preparation of the adducts between various model dienes and suitable azodienophiles. The dienes were chosen to produce adducts containing the functionalities to which tolerance by the cyclopropanation procedure might be required; thus the adducts between the dienes sorbyl alcohol [6], methyl sorbate [7] and piperylene, and the azodienophiles diethyl azodicarboxylate (DEAD), 2,2,2-trichloroethyl azodicarboxylate (TEAD)[49] and 4-phenyl-1,2,4-triazoline-3,5-dione [8] (PTAD) were prepared in high yields by direct cycloaddition. These adducts (Scheme 19) were then subjected to a variety of cyclopropanation techniques; the results were as follows.

a) Simmons-Smith cyclopropanation[50]. Several variations on the basic

procedure were employed[51], including the use of copper metal alone rather than a Zn-Cu couple[52]. However in every case the result was destruction of the adduct, giving only complex mixtures of low yield products. GLC monitoring of the reactions of [9] and [10] under the basic Simmons-Smith conditions revealed that the retro-cycloaddition was apparently occurring rapidly, followed by destruction of the diene and dienophile. As zinc halides (which are Lewis acids) are often used as catalysts for such retro Diels-Alder processes this seems a reasonable interpretation, and a satisfactory explanation for the results obtained with all the adducts.



SCHEME 19

The adducts used in the initial trials

b) Cyclopropanation using diazomethane and a variety of catalysts known to promote the formation of the necessary metal carbenoid species. These included $Rh(OAc)_2$ dimer[53], cuprous chloride[54], palladium (II) acetate[55] and cuprous iodide-trimethyl phosphite complex[56]. The use of this approach was restricted to the liquid adducts [8] - [14], owing to the insolubility of the

adducts [15] - [17] in the ethereal media used. Despite a claim made by Berson[47] in 1969 that the adducts between dimethyl azodicarboxylate and 2,4-hexadiene have been cyclopropanated in this way no reaction was observed for any adduct using ethereal diazomethane solutions obtained by co-distillation (concentrations of ≤ 0.5 M). This lack of reactivity can be rationalised in structural terms for the adducts [9] - [12], as the presence of the ester group can be expected to cause both increased hindrance and also a further decrease in the electron density in the alkene. As will be seen in Chapter 4, alkenes in this type of environment are already electron-poor (and are therefore resistant to attack by electrophilic species), and this probably explains the lack of reactivity shown by [9] - [14] towards the Lewis acid catalysts used for this type of cyclopropanation. The failure of [13] and [14] to react is however suprising in the light of Berson's results; the most likely explanation for this apparent discrepancy is that Berson used much higher concentration solutions of diazomethane. This hypothesis is supported by the fact that the catalyst used by Berson (cuprous chloride), whilst the most effective available at the time, is much less active than some of the catalysts which have been reported since[57]. Owing to the hazardous nature of higher concentration solutions of diazomethane this hypothesis was not tested; the question is in any case largely academic, as the hazards involved are so great as to preclude use of this method on a large scale.

3.3 GENERATION OF DISUBSTITUTED HYDRAZINES

Given the problems involved in cyclopropanation of the adducts, attention was redirected towards cyclopropanation of the disubstituted hydrazine intermediates obtained on urethane cleavage. It was expected that these species would prove to be more suitable as substrates, because

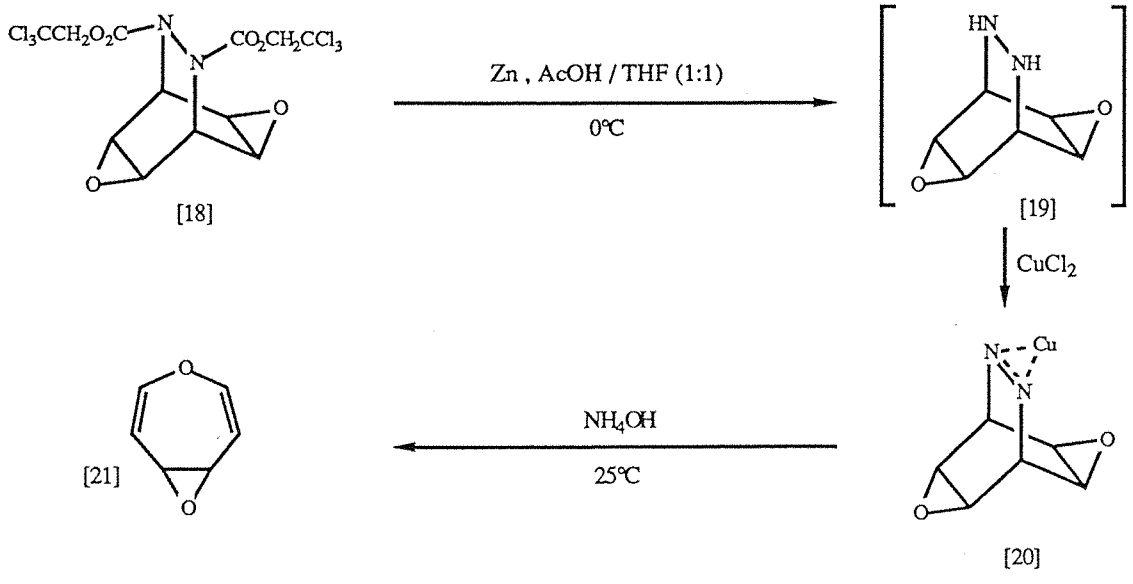
i) The extrusion of di-imide via a retrocycloaddition is much less likely than the simple reversal of the initial Diels-Alder reaction seen with [9]-[17] under Simmons-Smith type conditions. Taken together with the fact that the Simmons-Smith reaction is known to proceed particularly well on allyl alcohols and amines[58], this makes the hydrazines promising targets for cyclopropanation.

ii) The removal of the electron-withdrawing carboxylate functionalities from the urethane nitrogens should marginally increase the reactivity of the alkene, thereby increasing the chances of successful cyclopropanation using the metal-catalysed diazomethane approach.

However in order for such methodology to be useful in the synthesis of the target compounds it is desirable that the cleavage reaction used be capable of cleaving the urethane in the presence of a lactone (i.e. the conversion [4] to [3] depicted in Scheme 17). Of the azodienophiles which have been developed to produce urethanes which may be cleaved by such reactions, the most promising appeared to be TEAD [*bis*- 2,2,2-trichloroethyl azodicarboxylate). The 2,2,2-trichloroethyl group is known to be susceptible to reductive cleavage using activated metallic zinc[59], and at least three examples[45,60a,b] have been published of this being applied to the cleavage of TEAD - derived urethanes. Whilst only one of these gives experimental details, the system studied (by Rastetter - Scheme 20) is analogous to the one under development. In none of the three cases, however, were the hydrazine intermediates isolated - something which would clearly be desirable (if not essential) if they are to be cyclopropanated.

An investigation was undertaken to ascertain whether or not the hydrazine intermediates could in fact be isolated. To this end the adducts [10], [12] and [14] were treated both with Zn /AcOH[45] and with zinc-copper

couple in refluxing methanol[60a,b], the two methods reported in the literature. Whilst the former method (Rastetter published full experimental details) surprisingly gave only unreacted starting materials, the latter gave smooth cleavage of the adducts to give solutions of zinc salts. However separation of the hydrazines from these could not be accomplished, despite the use of continuous extraction, both from aqueous solutions and from the solid residues obtained on evaporation. No significant amounts of the hydrazines were obtained, even when the solids were extracted with acetic acid.

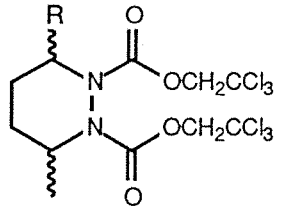


SCHEME 20

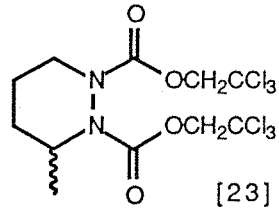
Rastetter's results with *sym*- Oxepin Oxide

In order to determine whether or not hydrazine formation had occurred the products obtained from cleavage of [10] and [12] were oxidised by the addition of 1N aqueous cupric chloride. This gave a mixture of products in low yields in the case of [10]; however in the case of [12] a trace of sorbyl alcohol was generated, although the yield was very low (5-10%). The isolation of the original diene rather than a cuprous complex reflects the powerful driving force towards retro Diels-Alder fragmentation; any

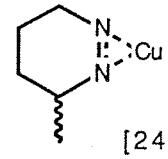
cuprous azo complex formed would be too unstable to survive. The contrast with the homo Diels Alder fragmentation seen by Rastetter (and desired here) is clear, i.e. the energy barrier to retro homo Diels-Alder fragmentation is considerably higher than with simple retro Diels-Alder, and the reduction in the driving force towards retrocycloaddition allows the copper azo complex to be isolated. As a more general test of the effectiveness of the methods used the alkene functionalities in [10], [12] and [14] were removed by catalytic hydrogenation, to give the compounds [21]. [22] and [23] respectively.



[21] R =CO_2Me
[22] R = CH_2OH
mixtures of di-astereoisomers *syn:anti* of ca. 3:2



[23]



[24]

These were then subjected to the same cleavage conditions, and upon oxidation of the intermediates with $CuCl_2$ the following was observed; [21] gave only a complex mixture of products in low individual yields, [22] gave a similar mixture (however slight traces of azo-complex were detected, but not isolated) and [23] gave the azo-complex [24] in an isolated yield of 68%.

3.4 CONCLUSIONS

The conclusions which can be drawn are; the deprotection method works adequately for simple compounds, but fails in the presence of functonalities such as esters, where the ester is situated β- to the urethane. The poor yields (relative to [24]) seen with the adducts [12] and [22] are most surprising , as the alcohol functionalities in those molecules can would not normally be expected to dramatically influence the course of a reaction carried out in methanol.

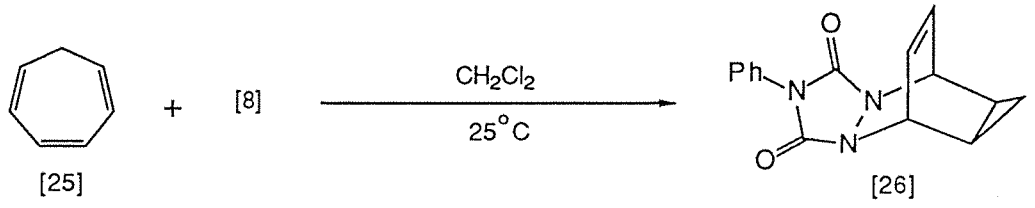
Despite these discouraging results there remain possibilities worthy of investigation. In particular there are azodienophiles other than TEAD which could conceivably be used - for example the 2,2,2-trichloroethyl group could be replaced by 2-trimethylsilylethyl (which can be removed using tetrabutylammonium fluoride[61a]) or even p-methoxy benzyl, removable using DDQ[61b]. A number of other such 2-substituted ethyl protecting groups have been developed for the carboxyl functionality[61c] and may also be of use.

CHAPTER 4

ROUTES BASED ON THE ADDUCT [26]

4.1 THEORY

The routes to the target compounds discussed in this chapter rest solely on the fortuitous creation of the required stereorelationship between the cyclopropane and the two potential alkyl functionalities in the adduct [26] which is formed by reaction of [8] with cycloheptatriene [25].



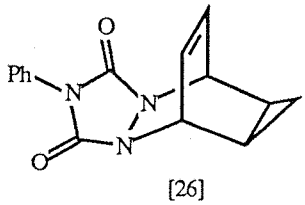
[25] [26]

Although this reaction was first reported[62] in the late 1960s, and has been verified by other workers since, to date only one claim has been made for use of this adduct in synthesis. This was made by Berson[47] in 1969, who reported that the adduct could be ozonised and the resulting ozonide reduced using sodium borohydride to give the diol [27]. No yield is given for the diol, although it is stated to be crystalline. It was decided to investigate the functionalisation of the adduct, with a view towards using it as a source of the required masked disubstituted Z,Z-1,4-diene. The following questions were posed;

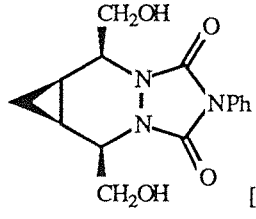
i) How efficient could the conversion to the diol be made? What other possibilities exist for ozonolytic cleavage? What other means of alkene cleavage / functionalisation can be used?

ii) Could the relatively unreactive urazole functionality be cleaved in the presence of the desired lactone? If not, could it be exchanged for a more

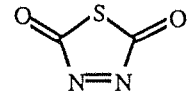
easily cleaved group before formation of the lactone? Unfortunately the periselectivity displayed by [8] towards [25] is not seen with acyclic azodienophiles, which undergo the ene reaction preferentially[63]. This rules out the use of dienophiles such as TEAD which can be cleaved under mild conditions, and unfortunately there is a dearth of cyclic dienophiles which have similar properties. Whilst it is possible to suggest such dienophiles ([28] would be a good example, as the adducts it forms should be susceptible to cleavage by treatment with triphenyl phosphine) the amount of time required to develop an efficient synthesis caused this to be excluded from consideration in the initial investigations.



[26]



[27]



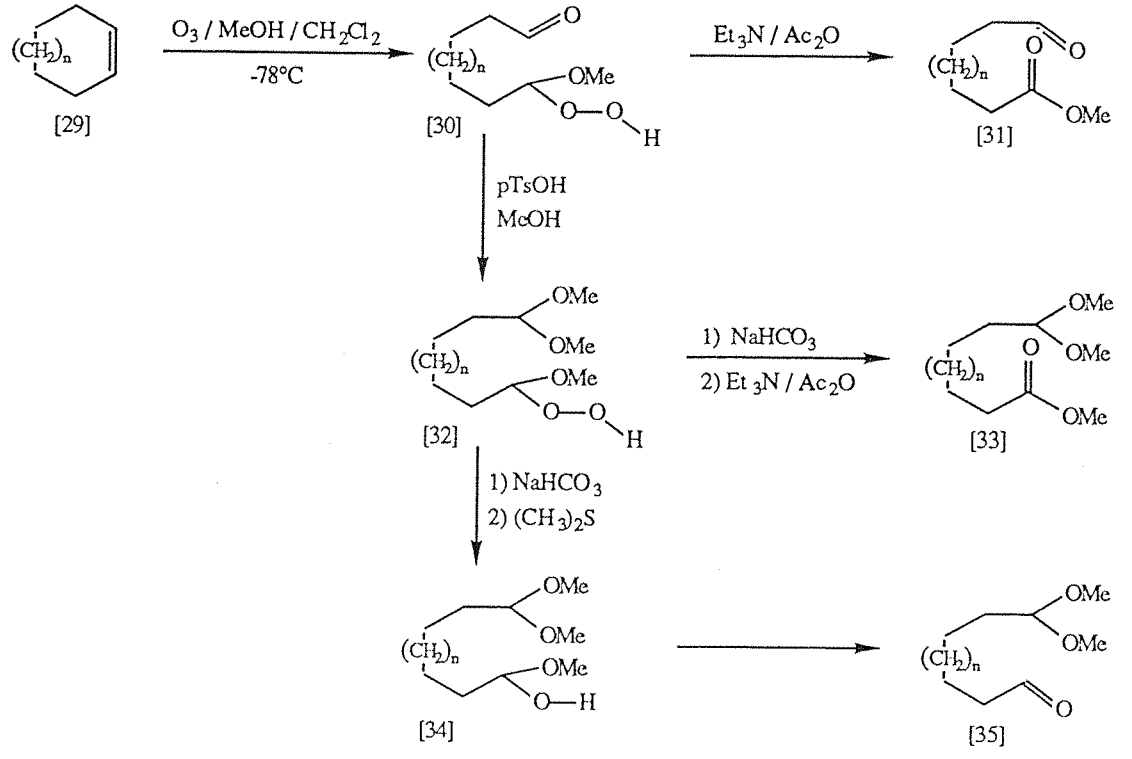
[28]

4.2 OZONOLYTIC CLEAVAGE TO THE DIOL[27]

The first investigation undertaken was to determine the efficiency of the ozonolysis as described by Berson. To this end the adduct [26] (synthesised in excellent yield (>98%) from [8] and [25]), was treated with ozone over a range of temperatures from -90°C to -20°C, utilising a range of solvents including methanol, dichloromethane, ethers and chloroform. The resulting ozonides were reduced with $NaBH_4$ at ambient temperature. After much experimentation it was established that the optimum conditions gave a yield of just over 40%. Given the probable difficulty involved in differentiating between the two primary alcohol functionalities it was judged that this did not constitute a synthetically viable approach.

4.3 OZONOLYTIC CLEAVAGE TO TERMINALLY DIFFERENTIATED PRODUCTS

The problem of differentiation between the two sides of the alkene indicated that a more useful approach would be that described by Schreiber[42], which allows the cleavage of symmetrical cycloalkenes to terminally differentiated products. The methods which are described include the conversion of the alkene to aldehyde - ester, aldehyde - acetal or ester - acetal; they work well for cycloalkenes with ring sizes of 6 or more, but yields drop dramatically for cyclopentenes. The reasons for this are not made completely clear, but it seems likely that the main factor is the ease with which scrambling can occur between the termini. The ozonolysis procedures and Schreiber's proposed mechanisms are shown in Scheme 21.

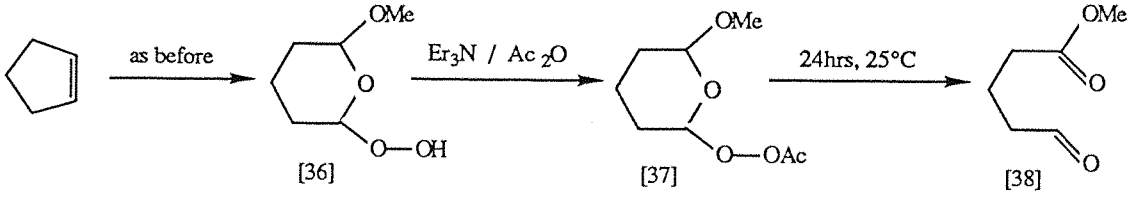


Scheme 21

The Ozonolysis / workup procedures reported by Schreiber

The fact that low yields are common to [31], [33] and [35] with n=0

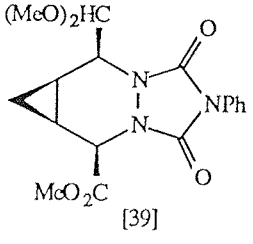
suggests that the problem lies in the formation of the species [30,n=0] rather than with any particular workup procedure. It is interesting to note that in the generation of [31] where n=0 the fragmentation is reported to take place partially from the cyclic form [36] of [30], via an initial acetylation of the hydroxyl group (Scheme 22).



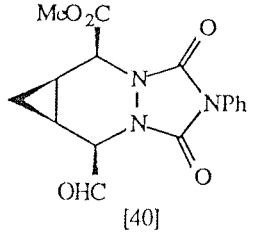
Scheme 22

The mechanism reported for the formation of [38] from cyclopentene

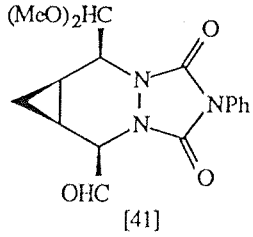
The fact that this does not occur for n≥1 almost certainly reflects greater difficulty in forming [31], due to the increase in ring size from 6 to ≥7. This phenomenon may provide a means of determining the extent of the assistance given to macrocyclisation by the *syn* relationship of the termini formed by ozonolysis of [26] (see Chapter 2, Scheme 16 and related discussion), as the 6-member ring in [26] which is cleaved on ozonolysis would not (in a monocyclic system) be expected to give a cyclic intermediate of the type [36] . However if the steric relationship between the two termini is such that cyclisation is enhanced then a significant amount of the fragmentation to the ester-aldehyde [39] may well take place via this (much slower) pathway. This may provide some indication as to whether or not the fundamental assumption underlying this synthetic approach is correct.



[39]



[40]



[41]

Accordingly attempts were made to generate the compounds [39],

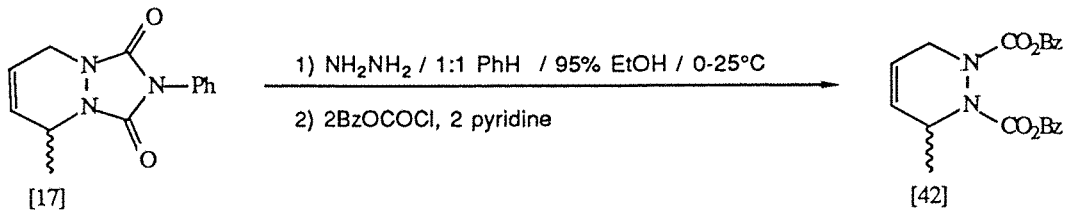
[40] and [41] from [26] using these methods. However the pattern of low yields and unexpected intermediates and side products seen with cyclopentene is unfortunately repeated with the system under investigation; the attempts to generate [39] and [40] both gave identical inseparable mixtures of mainly unidentifiable products, with a yield of [39] of perhaps 5-10% (not isolated). Attempts to form [41] gave a similar mixture, although in that case no trace of the desired product was detected.

4.4 OTHER METHODS OF FUNCTIONALISATION

Alternative methods of alkene functionalisation were investigated, consisting mainly of a variety of electrophilic additions to [26], including epoxidation (using MCPBA at elevated temperatures[64], MMPP[65], and trifluoroperacetic acid[66]) and bromohydrin formation[67]. In each case, however, only complex mixtures of products were obtained, with no trace of the desired epoxide. This reflects the pronounced deactivation of the alkene towards electrophilic attack, a phenomenon already observed for the adducts [9]-[17] during attempts at cyclopropanation (see Chapter 3).

4.5 PROTECTING GROUP EXCHANGE

A parallel line of investigation concerned the cleavage of the urazole functionality and the reprotection of the resulting disubstituted hydrazine with a group more amenable to cleavage in the presence of a lactone. The standard cleavage conditions for urazoles were introduced by De Lucchi[68], and involve treatment of the urazole with hydrazine hydrate. A modified version of this procedure was employed, followed by di-acylation of the hydrazine with benzyl chloroformate - pyridine.



[17] [42]

Scheme 23

Deprotection / reprotection of [17]

Accordingly this method was applied both to adduct [26] and also to an acyclic model system, this being the adduct [17]. Benzyl chloroformate was chosen as benzyl esters are known to be susceptible to cleavage under mild, neutral conditions by catalytic hydrogenation[61c]. Despite the use of brutal conditions (120°C reflux) [26] did not react: this is in line with results obtained by De Lucchi. However [17] underwent smooth cleavage and reprotection in excellent yield. This is a promising development and appears to contradict some of De Lucchi's results, as the alkene functionality survives intact rather than undergoing di-imide reduction as claimed[68].

4.6 CONCLUSIONS

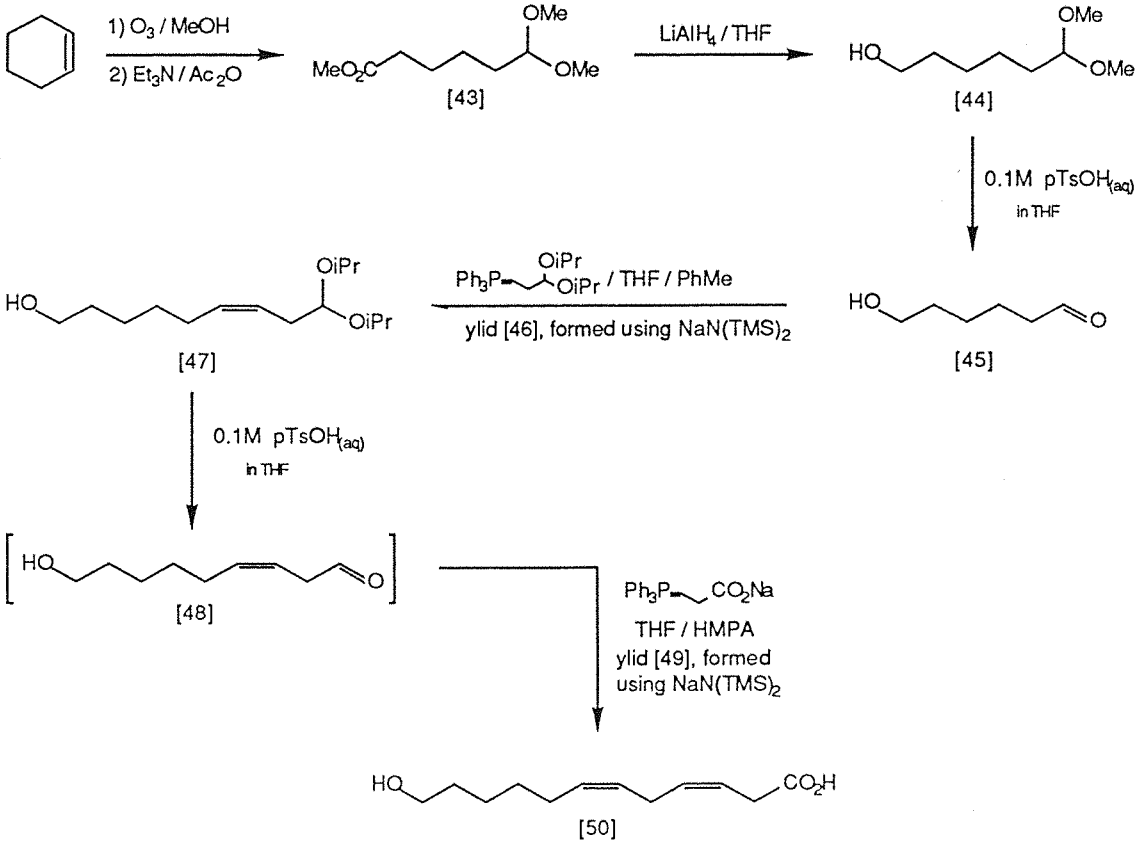
The severe difficulties encountered in functionalisation of the alkene in [26] strongly suggest that this type of route is not likely to be viable, although the successful exchange of protecting groups does offer some hope if the first problem can be surmounted. The considerable potential of this methodology as a source of protected, geometrically pure Z,Z-skipped dienes may justify further investigations.

CHAPTER 5

IMPROVED ROUTE TO THE HYDROXY ACID PRECURSOR TO II

5.1 INTRODUCTION

A number of methods (outlined in Chapter 2) are now available by which the Oehlschlager synthesis of the hydroxy acid precursor [50] to II might be improved. The most promising of these stems from the methodology recently developed by Santelli, which it is hoped will allow the construction of the hydroxy acid [50] efficiently from extremely cheap starting materials (cyclohexene, acrolein and acrylic acid). The route envisaged is shown in Scheme 24.



Scheme 24

The proposed route to [50] using Santelli's methodology

Note that the conversion of cyclohexene to methyl 6,6-dimethoxy hexanoate [43] by ozonolysis / dehydration has been well documented[42], as has the reaction of unstabilised phosphoranes with hydroxy aldehydes. The potential advantages of this route are;

i) The extremely low cost of the starting materials.

ii) The fact that all the various processes involved have been widely used on a multigram scale, thus lessening the risk of problems in scaling up.

A further potential advantage lies in the possible extension of the route to include the synthesis of chiral target I, as the required chiral lactol[69] starting material should be readily obtainable[70]. It was decided to investigate both these routes, beginning with the route to II shown in Scheme 24.

4.2 SYNTHESIS OF INTERMEDIATE [47]

Crude [43] was prepared from cyclohexene using the method described by Schreiber[42], and then reduced using lithium aluminium hydride in ether. This furnished the hydroxy acetal [44] in 71% yield from cyclohexene. Hydrolysis of the acetal group followed by reaction of the crude hydroxy aldehyde [45] with the preformed ylid [46] in THF / toluene gave the hydroxy diisopropyl acetal [47] in 70% yield from [44], with a ratio of Z:E of ≥98:2 (isomers separable by flash chromatography). Thus the precursor [47] to the desired hydroxy acid [50] has been produced from cyclohexene in 52% overall yield. This leaves only the final steps [47] to [48] (not isolated) and [48] to [50].

4.3 CARBOXYOLEFINATION OF [48]

The ylid [49] has been widely used in the preparation of β,γ–unsaturated carboxylic acids, and indeed has long been (along with

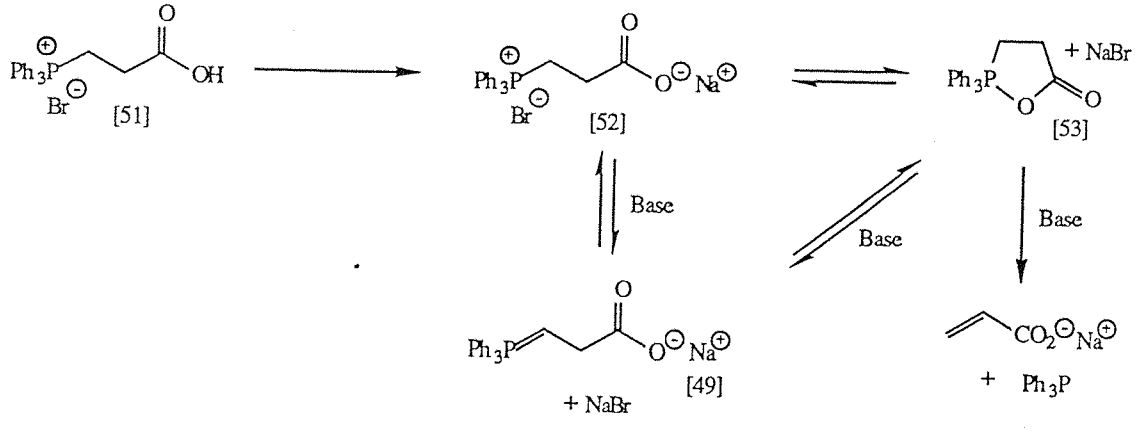
deconjugation) one of the methods of choice for making them, as

i) The protection of the acid group as its sodium salt during the reaction greatly decreases the acidity at the activated α-position in the product, thus preventing the isomerisation which often occurs with other approaches.

ii) The aldehydes needed are generally readily available.

iii) Both the phosphonium chloride and particularly the phosphonium bromide[71] can be made easily and efficiently from acrylic acid.

However there are drawbacks to this method as well, of which the most serious is that the ylid [49] is unstable, decomposing to give triphenyl phosphine and various minor products. A mechanistic rationale for this is proposed in Scheme 25.



SCHEME 25

Decomposition of ylid [49] from [51] - suggested pathways.

The problem has generally[72] been overcome by *in situ* trapping of the newly formed ylid with the carbonyl substrate; i.e base is added to a mixture of substrate and phosphonium salt. This tends to suggest that deprotonation of the acid leads initially to mainly the double salt [52], with

the equilibrium between it and the oxa-phosphorane [53] lying well to the left (most of the work done on the system has used highly polar dimethyl sulphoxide as solvent, which can be expected to solvate the sodium carboxylate and phosphonium bromide functionalitites particularly well). Further deprotonation should lead to almost entirely the desired ylid [49] (this conclusion being based on the known pK_a values for protons α- to phosphonium salt and sodium carboxylate functionalities, and on the assumption made above concerning the equilibrium between [52] and [53]). The likelihood of direct decomposition of the ylid [49] to triphenyl phosphine and sodium acrylate would seem slight, suggesting that some form of equilibration must be occurring between the ylid [49] and the oxa-phosphorane [53].

Whilst the mechanism of the decomposition may at first seem an irrelevant detail, it becomes significant when it is realised that the extreme sensitivity to enolisation of the β,γ-unsaturated aldehyde substrate [48] rules out *in situ* trapping of the ylid [49] as a means of preventing its decomposition (the simple fact of non-enolisation of the aldehyde in the presence of unstabilised ylids is surprising enough, and the likelihood of preferential deprotonation of the phosphonium salt in the presence of the aldehyde seems remote). The question thus remains of how decomposition of [49] can be prevented in a way compatible with the carboxyolefination of [48]. The following general observations can be made;

i) In order to prevent the decomposition of the ylid it is necessary (assuming that the mechanism suggested is correct) to prevent the formation of the oxa-phosphorane [53]. One way of doing this might be to use a solvent with an even higher polarity than DMSO, on the grounds that even more effective solvation of the phosphonium salt and sodium carboxylate functionalities in [52] should shift the equilibrium between it and [53]

towards the former.

ii) The use of sodium bases to form the ylid, although widely practised, may not be particularly helpful in terms of preventing formation of [53]. The sodium cation does not co-ordinate strongly to oxygen anions, and this failure to co-ordinate may well increase the tendency for internal oxygen to phosphorus co-ordination. If, on the other hand, a lithium base (such as lithium di-isopropylamide) were used instead, the more oxophilic lithium cation could be expected to become more tightly bound to the carboxylate anion (formed on removal of the first proton). This may well increase the lifetime of the ylid [49] formed on further deprotonation by shifting the equilibrium between [52] and [53] to the left.

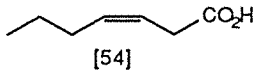
iii) The use of a phosphonium salt which contains the acid functionality in a protected form (such as an ester or even orthoester), followed by hydrolysis to the acid is a possible alternative which merits investigation. It should be noted that this creates the subsequent problem of hydrolysing the protected form of the acid in the presence of the newly-created 1,4-diene and β,γ-unsaturated ester functionalities (assuming the carboxyl group is protected as an ester). One possible solution might be the use of the *tert* - butyldimethylsilyl ester, which can be cleaved under mild, almost neutral conditions[69]. The stability of silyl esters to Wittig reactions using stabilised ylids has been documented[73]; however, no examples have been published regarding their stability towards attack by unstabilised ylids.

Hence the following experiments were conducted;

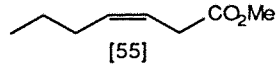
a) Isolation of the oxa-phosphorane [53]. This was accomplished by the simple expedient of dissolving the phosphonium bromide [51] in water, neutralising the resulting solution by the addition of sodium bicarbonate,

and then continuously extracting with chloroform.

b) Formation of the ylid from a suspension of the phosphonium bromide in in HMPA / THF, with varying amounts of time being allowed between addition of base and subsequent addition of aldehyde (the aldehyde used for these trials was butyraldehyde).



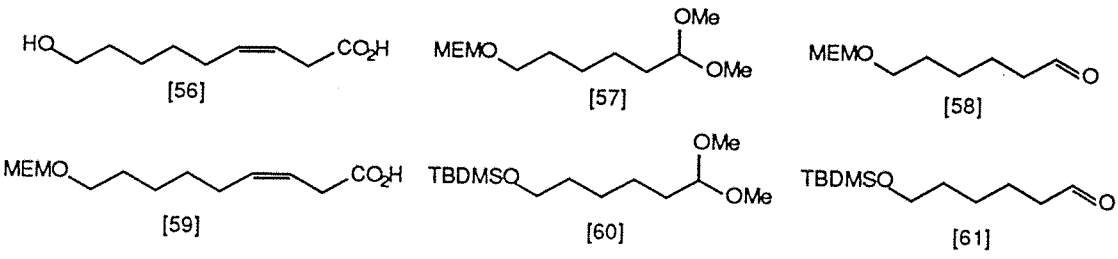
[54]



[55]

The acid [54] so obtained was esterified with diazomethane prior to isolation. The yields of [55] recorded were low (<20%) with delays of <30 minutes, gradually increased with longer delays to a maximum of 84% with a delay of 90 minutes, and began to drop dramatically once the delay reached 3 hours or more, reaching zero with a six hour delay. The most plausible explanation for this pattern of results is that formation of the ylid is slow (due to the heterogeneous nature of the system employed), and that gradual decomposition of the ylid occurs as soon as it is formed; this accounts for the low yields obtained with both short and long delays.

It was concluded that the ylid could be used to generate the β,γ–unsaturated acid required, and as a trial the hydroxy aldehyde [45] was reacted with the ylid using the optimum conditions for ylid formation determined using butyraldehyde. However, no trace of the desired product [56] was obtained, only a highly polar gummy residue showing no discrete peaks by nmr or ir analysis. The MEM-protected aldehyde [58] (generated from the compound [57], which in turn was obtained from [44] using the standard procedure[74]) similarly gave no trace of the desired product [59]. The TBDMS-protected compound [60] was formed[69] (again from [44]), but it proved impossible to selectively hydrolyse the acetal group in this compound to form [61].



5.4 CONCLUSIONS

The failure of the ylid [49] to form the desired products with [45] and [58] is surprising; there seems to be no obvious explanation given the apparent success with butyraldehyde. This lack of success casts considerable doubt as to the viability of the synthetic pathway, although several experiments remain to be conducted, including the use of lithium rather than sodium bases and in particular the use of carboxyl-protected ylids.

CHAPTER 6

EXPERIMENTAL SECTION

6.1 : GENERAL

Where solvents and / or reagents are stated to be dry the following dehydration procedures were employed; for tetrahydrofuran, benzene, toluene and diethyl ether distillation from sodium wire; for dichloromethane, HMPA and triethylamine, distillation from granular calcium hydride ; for methanol, distillation from iodine-activated magnesium turnings; for dimethylformamide, distillation at reduced pressure from activated 3Å molecular sieves (Laporte), and for acetic anhydride distillation from phosphorus pentoxide. The silica used for flash chromatography was Sorbsil C60, 40-60 mesh.

Nuclear magnetic resonance spectra were recorded using either a JEOL FX90q (operating at 90 MHz for ^{1}H and 22.5 MHz for ^{13}C) or a JEOL GX270 (operating at 270 MHz for ^{1}H and 67.5 MHz for ^{13}C). All samples were run in chloroform-d, and unless otherwise stated the residual chloroform peak is used as the internal standard (values are given using the δ–scale, with values of δ7.27 and δ77.15 respectively being attributed to the standard for ^{1}H and ^{13}C spectra). ^{13}C multiplicities were assigned using the well-known DEPT technique, with pulses of 90° and 135° being employed in each case; the multiplicities observed are recorded using the notation: s = singlet (quarternary carbon), d = doublet (methyne) t = triplet (methylene) and q = quartet (methyl). ^{1}H multiplicities are recorded using the notation : s = singlet , d = doublet ..... (etc), m = multiplet, br = broad.

Infrared spectra were recorded using a Perkin-Elmer 1600 series FT-IR, and calibrated using an external polystyrene film. The notation used is : s = strong, m = medium, w = weak, br = broad, with v (= very) being used as intensifier where appropriate.

6.2 PROCEDURES

CYCLOADDITION OF DIETHYL AZODICARBOXYLATE (DEAD) ONTO DIENES [6], [7] AND PIPERYLENE - GENERAL PROCEDURE

Diene (1.0mmol) and DEAD (freshly distilled, 0.95mmol) were dissolved in dry benzene (5ml, for [7] and piperylene) or dry toluene (5ml, for [6]) and the resulting mixture refluxed until the deep orange colour of the dienophile had disappeared (24-48hrs). The resulting thick oils were then purified by fractional distillation to give the adducts as thick oils.

[9]

Yield = 81% ; mixture of diastereoisomers (syn : anti of ca.3:2); bp = 100-120°C at 0.05mm Hg

IR (film,mixture of diastereoisomers) 2985m 1720sbr 1465m 1415s 1375s 1300sbr 1175s 1115m 1075m 1060m 1025m 950w 895w 845w 775w 760w

^{1}H NMR (360 MHz; $CDCl_3$, *syn* isomer) 1.20 (6H,t,7.1 Hz) 1.415 (3H,d,6.9 Hz) 3.75 (3H,s) 4.17 (4H,m) 4.73 (2H,brs) 5.56 (1H,dd,10,1.5 Hz) 6.16 (1H,ddd,10,5,1.5 Hz)

^{13}C NMR (90 MHz; $CDCl_3$, *syn* isomer) 169.1(s) 156.6(s) 135.7(d) 120.6(d) 63.0(t) 62.5(t) 57.75(d) 52.8(q) 51.3(d) 18.0(q) 14.55(q)

^{1}H NMR (360 MHz; $CDCl_3$, *anti* isomer) 1.20 (6H,t,7.1 Hz) 1.23 (3H,d,6.9 Hz) 3.75 (3H,s) 4.17 (4H,m) 4.73 (2H,brs) 5.56 (1H,dd,10,1.5 Hz) 6.16 (1H,ddd,10,5,1.5 Hz)

^{13}C NMR (90 MHz; $CDCl_3$, *anti* isomer) 169.1(s) 156.6(s) 135.7(d) 120.6(d) 62.7(t) 62.2(t) 57.75(d) 52.4(q) 51.3(d) 18.0(q) 15.3(q)

[11]

Yield = 85% ; mixture of diastereoisomers (syn : anti of ca.3:2); bp = 110-120°C at 0.1torr

IR (film): 3465mbr 2980m 2935m 2875w 1715sbr 1465m 1410s 1380s 1310s 1175s 1135s 1115s 1095s 1060s 1040s 965w 895w 865w 835w 760m 735w 705w

^{1}H NMR (360 MHz; $CDCl_3$, *syn* isomer) 1.26 (3H,d,7 Hz) 1.27 (6H,t,7 Hz) 3.55 (1H,m) 3.79 (1H,m) 4.11 (4H,m) 4.58 (2H,m) 5.44 (1H,d,10 Hz) 5.82

(1H,ddd,10,4.5,2 Hz)

^{1}H NMR (360 MHz; $CDCl_3$, *anti* isomer) 1.27 (6H,t,7 Hz) 1.56 (3H,d,6 Hz) 3.55 (1H,m) 3.79 (1H,m) 4.11 (4H,m) 4.58 (2H,m) 5.45 (1H,d,10 Hz) 5.68 (1H,dd,10,4 Hz)

^{13}C NMR (90 MHz, $CDCl_3$, *syn* isomer) 156.7(s) 154.9(s) 64.2(t) 62.2(t) 61.9(t) 61.0 (d) 49.9(d) 18.0(q) 14.5(q) 14.4(q)

^{13}C NMR (90 MHz, $CDCl_3$, *anti* isomer) 156.7(s) 154.9(s) 62.8(t) 62.2(t) 61.9(t) 61.0 (d) 49.9(d) 20.5(q) 14.5(q) 14.4(q)

[13]

bp = 100-150°C at 0.3mm Hg

IR (film) 3000m 2970m 2940w 1720sbr

^{1}H NMR (90 MHz, $CDCl_3$) 1.25 (6H,t,7 Hz) 1.25 (3H,d,7 Hz) 3.725 (1H,m) 4.17 (4H,t,7Hz) 4.62 (2H,m) 5.73 (2H,brs)

^{13}C NMR (22.5 MHz, $CDCl_3$) 155(s) 129.2(d) 122.2(d) 61.9(t) 61.7(t) 50.5(d) 42.7(t) 18.15(q) 14.3(q)

CYCLOADDITION OF (2,2,2)-TRICHLOROETHYL AZODICARBOXYLATE ONTO DIENES [6], [7], AND PIPERYLENE

Diene (1.0mmol) was dissolved in benzene (dry, 10ml) and TEAD (0.95mmol) added slowly with stirring at ambient temperature. The resulting mixture was stirred at room temperature ([7] and piperylene) or refluxed ([6]) until the bright yellow colour of the dienophile had disappeared (2-3hrs). Removal of the solvent at reduced pressure and then fractional distillation gave the desired products as clear glassy materials.

[10]

Yield = 95% (mixture of diastereoisomers, syn : anti of 3:2); bp = 240-250°C at 0.5torr

IR (film, mixture of syn and anti) 2955m 2905w 2845w 1730sbr 1650w 1430s 1345s 1285s 1200s 1170s 1090s 1050s 910w 885m 810s 750s 720s 660w 570s

^{1}H NMR (270 MHz, $CDCl_3$, both diastereoisomers) 1.50(3H,d,7 Hz) 3.67 (3H,s) 4.56 (1H,d,12 Hz) 4.65 (5H,m) 5.62 (1H,d,11.5 Hz) 6.15 (1h,dd,11.5,2 Hz)

^{13}C NMR (66.5 MHz, $CDCl_3$, syn diastereoisomer) 168.1(s) 154.4(s) 153.4(s) 133.8 (d) 120.2(d) 94.7(s) 75.9(t) 58.3(d) 52.9(q) 51.6(d) 17.7(q)

^{13}C NMR (66.5 MHz, $CDCl_3$, anti diastereoisomer) 168.1(s) 154.6(s) 153.4(s) 133.1 (d) 120.7(d) 94.9(s) 75.7(d) 58.3(d) 52.9(q) 51.6(d) 17.7(q)

[12]

Yield = 98%; bp = 230-250°C at 0.15torr

IR (film): 3500sbr 3-45m 2955s 2875m 1730sbr 1390s 1295s 1135s 950m 920m 865s 720s

^{1}H NMR (270 MHz, $CDCl_3$, both diastereoisomers) 1.33 (3H,d,7 Hz) 3.65 (1H,brs) 3.90 (2H,m) 4.75 (6H,brm,) 5.58 (1H,dd,22,10 Hz)

^{13}C NMR (66.5 MHz, $CDCl_3$, *syn* isomer) 154.2(s) 152.8(s) 131.3(d) 124.5(d) 94.8 (s) 75.2(t) 63.7(t) 61.6(d) 50.6(d) 18.4(q)

^{13}C NMR (66.5 MHz, $CDCl_3$, *anti* isomer) 154.2(s) 152.8(s) 130.75(d) 125.1(d) 94.8 (s) 75.5(t) 63.7(t) 60.55(d) 51.6(d) 18.8(q)

[14]

Yield = 96% (presumed racemic); bp = 200-210°C at 0.5mm Hg

IR (film) 3045w 2990m 2790m 2860w 1725sbr 1420sbr 1380m 1355m 1340m 1340s 1290s 1215s 1115s 1090m 1050s 1020w 985w 935w 875w 810sbr 785m 745m 720s 520s

^{1}H NMR (90 MHz, $CDCl_3$) 1.375(3H,d,7) 4.0 (2H,m) 4.75 (5H,m) 5.80(2H,s)

^{13}C NMR (22.5 MHz, $CDCl_3$) 153.1(s) 129.0(d) 121.85(d) 95.0(s) 75.5(t) 51.35(d) 43.1(t) 18.4(q)

ADDUCTS BETWEEN [8] AND [6], CYCLOHEPTATRIENE AND PIPERYLENE - GENERAL PROCEDURE

4-phenyl-1,2,4-triazoline-3,5-dione ([8], PTAD, 1.0mmol) was dissolved in dichloromethane (5ml) at 0°C and diene (1.0mmol) added slowly until the strong red

colour of the dienophile had completely discharged. The solvent was removed to give the product as a white amorphous solid.

[15]

Yield = 97% (EtOAc / hexanes) ; mp = 124-127°C

IR (film): 1770m 1735m 1715s 1600w 1505m 1460s 1420m 1375m 1325w 1295m 1220m 1145m 1125w 1060w 985w 960w 905w 870w 800m 765m 725w 690m 645m

^{1}H NMR (270 MHz, $CDCl_3$) 1.58 (3H,d,7 Hz) 3.65 (3H,s) 4.33 (1H,d) 5.00 (1H,d,2 Hz) 5.76 (1H,d,10 Hz) 5.90 (1H,dd,10,2 Hz) 7.3-7.5 (5H,m)]

^{13}C NMR (67.5 MHz, $CDCl_3$) 167.2(s) 152.6(s) 152.0(s) 131.05(s) 130.6(d) 128.95 (d) 128.1(d) 125.6(d) 117.65(d) 54.9(d) 53.0(q) 51.7(d) 19.25(q)

[17]

Yield = 95% (EtOAc / hexanes) ; mp = 134-136°C

IR (film): 2925s 2855s 1770m 1710brs 1505w 1455m 1425m 1365w 1320w 1285m 1245w 1145m 1125m 1075m 995w 930w 885w 865w 765m

^{1}H NMR (270 MHz, $CDCl_3$) 1.40 (3H,t,6.5 Hz) 4.01 (1H,dd,16,3 Hz) 4.27 (1H,d,16) 4.57 (1H,m) 5.88 (2H,s) 7.3-7.5 (5H,m)

^{13}C NMR (67.5 MHz, $CDCl_3$) 153.1(s) 151.8(s) 131.2(s) 129.1(d) 128.1 (d) 127.4(d) 125.4(d) 119.6(d) 50.3(d) 43.5(t) 17.5(q)

[26]

Yield = 96% (EtOAc / hexanes) ; mp = 170-175°C (dec)

IR (film): 1765m 1710sbr 1600w 1500m 1455m 1400s 1375m 1310w 1240m 1225w 1135m 1075w 1050m 1025m 960m 920w 890vw 890vw 870m 820w 785w 770m 730m 720m 690m 645m 630m

^{1}H NMR (270 MHz, $CDCl_3$) 0.29 (1H,dt,6.5,4 Hz) 0.63 (1H,dt,6.5,7.5 Hz) 1.59 (2H,m,) 5.19 (2H,m) 6.08 (2H,dd,4,4 Hz) 7.35 (1H,m) 7.43 (4H,m)

^{13}C NMR (67.5 MHz, $CDCl_3$) 156.7(s) 131.5(s) 129.1(d) 128.2(d) 125.5(d) 125.2(d) 56.7(d) 8.3(t) 6.2(d)

HYDROGENATION OF ADDUCTS [10], [12] AND [14]- TYPICAL PROCEDURE

Adduct (3.329mmol) was dissolved in ethyl acetate (30ml) and 5mol% Pd on charcoal (100mg) added; the resulting suspension was flushed with hydrogen and then stirred vigorously under a slight excess pressure of hydrogen until uptake ceased (30-90 minutes). The suspension was filtered and the filtrate concentrated to give the crude product, which was purified by fractional distillation at reduced pressure.

[21]

Yield = 93%; bp = 220-230°C at 0.2torr

IR (film): 2950s 2110w 1730 svbr 1200mvvbr 920m 710s 655s

^1H NMR (270 MHz, $CDCl_3$) 1.35 (3H,d,6.5 Hz) 1.50 (2H,m) 1.82 (2H,m) 3.73 (3H,s) 4.6 (4H,m) 4.85 (2H,m)

[23]

Yield = 92%; bp = 200-220°C at 0.5torr

IR (film): 2960m 2860ww 1760sbr 1455m 1420sbr 1360m 1325m 1300s 1260s 1205s 1190m 1160m 1120s 1060m 960w 840m 810m 790m

^1H NMR (90 MHz, $CDCl_3$) 1.30 (3H,d,7 Hz) 1.60 (2H,m) 3.15 (2H,brm) 4.25 (1H,brm) 4.75 (4H,m)

CHAPTER 4

PROTECTING GROUP EXCHANGE: [26] to [42]

Adduct [17] (524mg, 2.154mmol) was dissolved in ethanol-benzene (20ml, 1:1) and the resulting solution thoroughly flushed with nitrogen. Hydrazine hydrate (100%, 0.15ml, 155mg, 3.08mmol) was added at 0°C and the reaction mixture gently warmed to reflux, at which it was maintained for 90 minutes. Cooling to 25°C followed by addition of benzyl chloroformate (1.50ml, 1.71g, 10.0mmol) and then pydridine (1ml, 12.3mmol) gave a white ppt. Removal of the solvent and replacement with

dichloromethane (30ml) gave a fine suspension; the insoluble material was removed by filtration and the filtrate concentrated to give a thin yellow oil. The crude product was purified by flash chromatography (silica, ether-light petroleum 1:1) to give the product [42] (mp = 68-70°C (ethanol), 729mg, 1.990mmol, 92%).

IR (nujol) 3450m 3380m 3310m 3240m 3035m 1770s 1705sbr 1585mbr 1535m 1500s 1455s 1420s 1380s 1280sbr 1245s

^{1}H NMR (270 MHz, $CDCl_3$) 1.33 (3H,d,6.5 Hz) 3.93 (1H,d,6.8 Hz) 4.20 (1H,d,6.8 Hz) 4.48(1H,m) 5.07 (4H,s) 5.81 (2H,s) 7.25 (6H,m) 7.41(4H,m)

^{13}C NMR (67.5 MHz, $CDCl_3$) 153.1(s) 151.8(s) 135.6(s) 131.2(s) 129.2(d) 128.65(d) 128.5(d) 128.3(d) 128.2(d) 127.5(d) 125.5(d) 119.6(d) 67.9(t) 50.4(d) 43.5(t) 17.6(q)

CHAPTER 5

HYDROXY DI-ISOPROPYL ACETAL [47]

Phosphonium salt[75] (6.371g, 12.70mmol, 3.06eqv, dried twice in flask by azeotropic distillation with dry benzene at reduced pressure) was suspended in THF-toluene (120ml, 1:3) under a nitrogen atmosphere. A solution of sodium *bis* -trimethylsilylamide in THF (1.0M, 11.70ml, 11.70mmol) was added slowly with stirring at 0°C over a period of ca.5 minutes, and the resulting solution allowed to stir for 2 hrs at 25°C. After cooling to -100°C a solution of crude hydroxy acetal [45] (freshly prepared from 4.14mmol of [44] using the procedure given below) in THF (10ml) was added and the resulting mixture allowed to warm to 25°C over 4 hrs. Sat. aqueous ammonium chloride (15ml) was added to destroy excess ylid, followed by diethyl ether (100ml). The organic phase was separated and the aqueous extracted with more ether (2x50ml). The combined extracts were washed with sat. aqueous sodium chloride, dried ($MgSO_4$) and concentrated to give a thick oil. The crude product was purified by flash chromatography (silica, ether-light petroleum 1:1) to give the pure product (740mg,

2.864mmol, 70% from [44]).

IR (Film) 3410mbr 2970s 2930s 2860s 1465w 1380m 1330m 1230w 1180m 1125s 1030vs 880w 810w

^{1}H NMR (270MHz) 1.13 (6H,d,6 HZ) 1.18 (6H,d, 6Hz) 1.35 (4H,m) 1.55 (2H,tt,7,7 Hz) 1.80 (1H,brs) 2.04 (2H,m) 2.32 (2H,dd,6,6 Hz) 3.61 (2H,t,6.5 Hz) 3.85 (2H,sept,6 Hz) 4.52 (1H,t,5.8 Hz) 5.41 (2H,m)

homodecoupling gives Jcc(alkene) as 10.8 Hz.

^{13}C NMR (67.5 MHz, CDCl) 131.9 (d) 124.5(d) 100.1(d) 67.9(d) 62.7(t) 33.8(t) 32.7(t) 29.4(t) 27.5(t) 25.5(t) 23.4(q) 22.6(q)

MEM-PROTECTION OF [44]

Hydroxy - acetal [44] (764mg, 4.709mmol) was dissolved in THF (dry, 20ml) and a solution of n-butyllithium in hexanes (2.5M, 1.90ml, 4.75mmol) added dropwise at 0°C under an inert atmosphere. MEM-chloride (0.650ml, 709mg, 5.693mmol, 1.2eq) was added and the resulting solution stirred at 0°C for 1 hour and then 25°C for 3 hrs. Dilution with ether (50ml) and sat. aqueous sodium bicarbonate (20ml), followed by separation of the organic phase, re-extraction of the aqueous with further ether (2x40ml) and then combination, washing (10ml sat. aqueous sodium chloride), drying ($MgSO_4$) and concentration of the organic layers gave the crude product as a thin oil. The crude product was purified by flash chromatography (silica, ether-light petroleum 1:1) giving a thin colourless oil (100-120°C at 0.1torr, 1.067g, 4.262mmol, 90.5%).

IR (film) 2940m 2880m 1460w 1385w 1130sbr 1050sbr 850w

^{1}H NMR (270 MHz, $CDCl_3$) 1.33 (4H,m) 1.55 (4H,m) 3.26 (6H,s) 3.35(3H,s) 3.52 (4H,m) 3.63 (2H,m) 4.31 (1H,t,6 Hz) 4.66 (2H,s)

^{13}C NMR (67.5 MHz, $CDCl_3$) 104.3(d) 95.2(d) 71.7(t) 67.5(t) 66.5(t) 58.5(q) 52.2(q) 32.3(t) 29.4(t) 25.8(t) 24.1(t)

REDUCTION OF [43] TO HYDROXY ACETAL [44]

Crude ester-aldehyde [43] (ca.90% pure, 7.610g, 40.10mmol) was dissolved in anhydrous THF (30ml) and added dropwise to a stirred suspension of $LiAlH_4$ (2.277g, 60.1mmol) in THF (120ml) at -20°C over a period of 10 minutes. The reaction mixture was allowed to warm to 25°C over 1 hr and then quenched by the sequential addition of water (2.5ml), 2M aqueous sodium hydroxide solution (7.5ml) and then more water (7.5ml). The resulting suspension was stirred until all the excess $LiAlH_4$ has been consumed and then filtered, the solid being washed with further THF (2x50ml). The solvent was removed from the combined filtrates to give the crude product as a thin yellow oil. The crude product was purified by flash chromatography (silica, diethyl ether-light petroleum 4:1) to give the product [44] (120-140°C at 0.1torr, bulb to bulb, 5.221g, 32.2mmol, 89%).

IR (film) 3415brs 2940s 2860s 1460m 1385m 1370m 1190m 1130s 1055brs 915m

^1H NMR (90 MHz, $CDCl_3$) 1.26 (8H,m) 3.15 (6H,s) 3.40 (2H,t,6.5 Hz) 4.20 (1H,t,5.8 Hz)

^{13}C NMR (22.5 MHz, $CDCl_3$) 104.6(d) 62.1(t) 52.4(q) 32.5(t) 25.5(t) 24.2(t)

SILYLATION OF HYDROXY-ACETAL [44] TO GIVE [60]

Hydroxy acetal [44] (2.379g, 14.294mmol) was added slowly to a solution of TBDMS-chloride (2.876g, 19.08mmol) and imidazole (1.491g, 21.901mmol, 1.53eq) in dry DMF (40ml) at 25°C. The resulting reaction mixture was stirred for 30 min at 25°C and then poured into water (100ml) and the solution extracted with ether (3x150ml); the ethereal extracts were washed with water (150ml) and saturated brine (100ml), dried ($MgSO_4$) and concentrated to give a thin oil. The crude product was purified by flash chromatography (silica, ether-light petroleum 19:1) to give the silyl acetal [61] (100-120°C / 0.2torr, bulb to bulb, 2.806g, 10.15mmol, 71%)

IR (film) 2930(s) 2860(m) 1465(w) 1385(w) 1360(w) 1255(m) 1100(s) 1075 (m) 835(s) 775(m)

^{1}H NMR (90 MHz, $CDCl_3$) 0.05 (6H,s) 0.88 (9H,s) 1.4 (8H,mbr) 3.30 (6H,s) 3.60 (2H,t,6.7 Hz) 4.35 (1H,t,7 Hz)

^{13}C NMR (22.5 MHz, $CDCl_3$) 104.9(d) 63.3 (t) 52.8 (q) 33.0(t) 26.1(q) 25.9(t) 24.6(t) -5.1(q)

HYDROLYSIS OF HYDROXY-ACETAL [44] TO [45]

Hydroxy acetal (310mg, 1.910mmol) was dissolved in THF (20ml) and pTsOH (0.1M aqueous, 3ml, 0.3mmol) added. The resulting solution was refluxed gently for 3 hrs, cooled and diluted with light petroleum (50ml). The organic phase was separated and the aqueous extracted with diethyl ether (2x30ml). The combined extracts were washed with water (10ml) and sat. aqueous sodium chloride (2x10ml), dried ($MgSO_4$) and concentrated to give a colourless oil.This was further dried by azeotropic distillation with anhydrous benzene at reduced pressure before being used for further steps.

An analytical sample of the crude product was purified by flash chromatography (silica, diethyl ether) to give the pure [45] in an extrapolated 96% yield.

REACTION OF YLID [49] WITH BUTYRALDEHYDE IN THF / HMPA

Phosphonium salt [51] (852mg, 2.05mmol) was suspended in THF / HMPA (4ml, 2:1) under nitrogen and a solution of sodium bis- trimethylsilyl amide in THF (1.0M, 4.0ml, 4.0mmol) added over 5 minutes at 25°C. The resulting slurry was stirred at 25° for 1 hr and then cooled to -100°C; butyraldehyde (810µl, 66.2mg, 915µmol) was added and the reaction mixture allowed to warm to 0°C over 3-4 hrs. Sat. aqueous ammonium chloride (5ml) was added to destroy excess ylid; the resulting solution was acidified to pH2 using 2M HCl and then extracted with diethyl ether (3x30ml). The combined extracts were washed with water (5ml) and brine (2x5ml), dried ($MgSO_4$) and concentrated to give an oil. This was redissolved in ether (30ml) and esterifed at 0°C using freshly distilled ethereal diazomethane; excess diazomethane was destroyed with

acetic acid and the resulting ethereal solution washed with sat. aqueous sodium bicarbonate (5ml), dried ($MgSO_4$) and concentrated to give an oil. The crude product was purified by flash chromatography (silica, ether-light petroleum 1:39) to give the product [55] (108mg, 759μmol, 84%).

IR (film) 3025w 2960s 2930s 2870w 1745s 1460m 1435s 1330m 1255m 1195m 1165s

^1H NMR (90 MHz, $CDCl_3$) 0.82 (3H,t,6 Hz) 1.17 (2H,m) 1.95 (2H,m) 3.0 (2H,d,6 Hz) 3.6 (3H,s) 5.45 (2H,m)

^{13}C NMR (22.5 MHz, $CDCl_3$) 133.3(d) 121.1(d) 51.7(q) 32.9(t) 29.5(t) 22.6(t) 13.7(q)

ISOLATION OF [53]

Phosphonium salt [51] (930mg, 2.0mmol) was dissolved in water (20ml) and sodium bicarbonate (,2.0mmol) added carefully with stirring. The resulting soltuion was extracted continuously with 200ml chloroform for 3hrs, and the extract dried (sodium sulphate) and concentrated, to give the hydrated oxa-phosphorane [53].

IR (nujol); 3385mvbr 2925s 1590s 1460s 1440s 1375s 1305m 1190w 1130w 1110m 1020w

^1H NMR (90 MHz, $CDCl_3$) 2.52 (2H,m) 3.53 (2H,m) 7.62 (12H,pseudo-t) 7.72 (3H,m)

^{13}C NMR (67.5 MHz, $CDCl_3$) 172.6(d,J_{cccP}=14 Hz) 135.0(dd,J_{ccccP}=3 Hz) 133.3(dd, J_{CCCP}=10 Hz) 130.4(dd, J_{CCP}=12 Hz) 118.9(d, J_{CP}=86 Hz) 29.7(t) 20.35(dt, J_{CP}=51 Hz)

REFERENCE SECTION

1) A.M.Pierce, H.D.Pierce Jr, A.C.Oehlschlager, E.Czyzewska, J.H.Borden, *J. Chem. Ecol.*, **13**, 1525, 1543 (1987) and references contained therin.

2) Recent general reviews include; T.G.Back, *Tetrahedron* , 33, 3041-3059 (1977); I.Paterson, M.M.Mansuri, *Tetrahedron* , **41**(18), 3569-3624 (1985). The field is becoming increasingly divided into specialised sub-areas - some of the more recent reviews in these include; M.Kinoshita, *Org Synth, Mod Trends PROC, IUPAC Sym 6* , 1986, 85; S.Masume, P.A.McCarthy, *Macrolide Antibiot.* , 1984, 127-198; H.Suginome, *Proc IUPAC Macromol Sym 26th* , 1982, 216.

3) E.J.Corey, K.C.Nicolaou, *J. Am. Chem. Soc.* , **96**(17), 5614 (1974).

4) T.Mukaiyama, M.Usui, K.Saigo, *Chem .Lett.* , 1976, 49-50.

5) O.Mitsunobu, Y.Nakajima, T.Kurihara, *Tetrahedron Lett.*, **28**, 2455-2458 (1976)

6) A recent example is in the total synthesis of the immunosupressant FK-506; T.K.Jones, S.G.Mills, R.A.Reamer, D.Askim, R.Desmond, R.P.Volante, I.Shinkai, *J. Am. Chem. Soc.* , **111**(3), 1157, (1989).

7) Y.Fukuyama, C.L.Kirkemo, J.D.White, *J. Am. Chem. Soc.* , **99**, 646 (1977)

8) E.J.Corey, D.J.Brunelle, P.J.Stork, *Tetrahedron Lett.*, **17**, 3405 (1976);

9) R.H.Wollenberg, J.S.Nimitz, D.Y.Gokcek, *Tetrahedron Lett.*, **21**, 2791 (1980)

10) For example E.J.Corey, P.Ulrich, J.M.Fitzpatrick, *J. Am. Chem. Soc.* , **98**, 22 (1976)

11) A recent example illustrates the point well; K.Smith, I.K.Morris, P.G.Owen, R.J.Bass, *J. Chem. Soc. Perkin Trans. 1*, 77 (1988)

12) The use of dichloromethane is, however, restricted to the less demanding cyclisations.

13) J.Otera, T.Yano, Y.Himemo, H.Nozaki, *Tetrahedron Lett.*, **27**, 4501 (1986); K.Steilou, M.A.Poupart, *J. Am. Chem. Soc.*, **105**, 7130 (1983); K.Steilou, A.Szczygielska-Nowosielska, A.Favre, M.A.Poupart, S.Hanessian, *J. Am. Chem. Soc.*, 102, 7579 (1980).

14) K.Venkataraman, D.R.Wagle, *Tetrahedron Lett.*, **21**, 1893 (1980)

15) E.P.Boden, G.E.Keck, *J.Org. Chem.*, **50**, 2394 (1985).

16) W.H.Rastetter, D.P.Phillion, *J. Org. Chem.*, **46**, 3209-3214 (1981)

17) Y.Yamada, T.Nihira, A.Makita, *Tetrahedron Lett.*, **28**(7), 805-8 (1987).

18) R.N.Hurd, D.H.Shah, *J. Org. Chem.*, **38**, 390 (1973).

19) N.H.Porter, V.T.H.Chang, *J. Am. Chem. Soc.*, **108**, 4976 (1987)

20) For example O.Yonemitsu, Y.Oikawa, T.Tanaka, *Tetrahedron Lett.*, **27**(31), 3647 (1986)

21) K.C.Nicolaou, S.R.Seitz, M.R.Pavia, *J. Am. Chem. Soc.*, **103**, 1222 (1981)

22) H.Stach, M.Hesse, *Tetrahedron* , **44**, 1573-90 (1988)

23) B.D.Mookherjee, R.W.Trenkle, R.R.Patel, *J. Org. Chem.*, **37**, 3846 (1972) and references therin.

24) B.Milenkov, M.Hesse, *Helv. Chim. Acta.*, **70**, 308 (1987) for example.

25) P.A.Wender, S.M.Sieberth, *Tetrahedron Lett.*, **22**, 2471 (1981)

26) W.M.Horspool, *Synthetic Organic Photochemistry* , Plenum Press, New York (1984), p272. (and references therin)

27) S.L.Schreiber, B.Hulin, Wai-Fong Liew, *Tetrahedron* , **42**, 2945 (1986); S.L.Schreiber, Wai-Fong Liew, *J. Am. Chem. Soc.*, **107**, 2980 (1985).

28) H.Suginome, S.Yamada, *Chem Lett.*, 245-248 (1988) and references contained therin.

29) G.H.Posner, E.Asirvatham, K.S.Webb, S.S.Jew, *Tetrahedron Lett.*, **28**, 5071 (1987)

30) J.E.Baldwin, R.M.Adlington, J.Robertson, *Tetrahedron* , **45**, 909-922 (1989)

31) K.Nakatini, S.Isoe, *Tetrahedron Lett.*, **26**, 2209 (1985)

32) W.C.Still, *J. Am. Chem. Soc.*, **99**, 4836 (1977).

33) C.Fehr, G.Ohloff, G.Buchi, *Helv. Chim. Acta.*, **62**, 2655 (1979)

34) For example the commercially available arachidonic acid has a shelf life of several weeks if stored in the dark at 0°C under an inert atmosphere.

35) See for example S.Hanessian et al, *J. Am. Chem. Soc.*, **108**, 2776 (1986)

36) J.C.Millar, A.C.Oehlschlager, *J. Org. Chem.*, **49**, 2232 (1984); A.C.Oehlschlager, E.Czyzewska, R.Aksela, H.D.Pierce, *Can. J. Chem.*, **64**, 1407 (1986).

37a) For example O.Yonemitsu, Y.Oikawa, T.Tanaka, *Tetrahedron Lett.*, **27**(31), 3647 (1986).b) A notable recent exception is the phtyotoxin Seiricuprolide; A.Ballio, E.Antonio, A.Graniti, G.Randazzo, L.Sparapano, *Phytochemistry*, **27**, 3117 (1988)

38) H.J.Reich, J.M.Renga, I.L.Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).

39) M.Suzuki, H.Takada, R.Noyori, *J. Org. Chem.*, **47**, 902 (1982).

40) T.Jeffery, *Tetrahedron Lett.*, **30**(17), 2225 (1989)

41) M.Santelli, J.Viala, *J. Org. Chem.*, **53**, 6121 (1988)

42) S.L.Screiber, R.E.Claus, J.Reagan, *Tetrahedron Lett.*, **23**, 3867 (1982)

43) K.B.Becker, *Helv. Chim. Acta.*, **60**, 68 (1977), for example.

44) W.F.Liew, *Diss. Abst. Int.B.*, **47**, 3773 (1987).

45) W.H.Rastetter, *J. Am. Chem. Soc.*, **98**, 6350 (1976).

46) J.C.Hinshaw, E.L.Allred, A.L.Johnson, *J. Am. Chem. Soc.*, **91**, 3382 (1969); J.C.Hinshaw, E.L.Allred, *Chem Comm*, 1021 (1969); see also ref 47.

47) J.A.Berson, SS.Olin, *J. Am. Chem. Soc.*, **91**, 778 (1969).

48) Typically alcoholic potassium hydroxide or potassium t-butoxide in DMSO - for urazoles see also ref 68.

49) TEAD was prepared in house using the method of R.D.Little, M.G.Venegas, *Organic Syntheses*, **61**, 17 (1983)

50) A.Vogel, "*Elementary Practical Organic Chemistry;Volume 1* ", Longman, London, 3rd Edition (1980), p195.

51) O.Repic, S.Vogt, *Tetrahedron Lett.*, **23**, 2729 (1982).

52) N.Kawabata, I.Kamemura, M.Naka, *J. Am. Chem. Soc.*, **101**, 2139 (1979).

53) A.J.Hubert, *Tetrahedron Lett.*, 600 (1976); A.J.Hubert, A.F.Noels, A.J.Anciaux, P.Teyssie, *Synthesis*, 601 (1976).

54) P.Blickle, H.Hopf, M.Bloch, T.B.Jones, *Chem. Ber.*, **112**, 3691 (1979). See also ref 47.

55) I.V.Kazimirchik et al, *Zhurnal Org. Khim.*, **20**, 1691 (1984).

56) B.W.Peace, F.Carman, D.S.Wulfmann, *Synthesis*, 658 (1971).

57) For a general review of such catalysts see M.P.Doyle, *Chem. Rev.*, **86**, 919-939 (1986).

58) R.Perraud, P.Arnaud, *Bull. Chim. Soc. Fr.*, 1540 (1968). The Simmons-Smith reaction performed on allylic alcohols is a widely used procedure; for a recent example see G.A.Molander, L.S.Harring, *J.Org. Chem.*, **54**, 3525 (1989)

59) For example see T.A.Montzka, J.D.Matiskella, R.A.Partyka, *Tetrahedron Lett.*, 1325 (1974).

60 a) Y.C.Toong, W.T.Borden, A.Gold, *Tetrahedron Lett.*, 1549 (1975); b) M.F.Semelhack, J.S.Foos, S.Katz, *J. Am. Chem. Soc.*, **95**, 7325 (1973).

61 a) P.Sieber, *Helv. Chim. Acta.*, **60**, 2771 (1977); b) Y.Oikawa, T.Yoshioka, O.Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982); c) See T.W.Greene, "Protecting Groups in Organic Synthesis", John Wiley & Sons, New York, 1981, pp 165-173.

62) R.C.Cookson, S.S.H.Gilani, I.D.R.Stevens, *Tetrahedron Lett.*, 615 (1962).

63) For the reaction of DEAD with cycloheptatriene see Cinnamon, Weiss, *J.Org. Chem.*, **26**, 2644 (1962). Experiments performed in house indicate that TEAD undergoes a similar ene process.

64) Y.Kishi, M.Aratani, H.Tanino, T.Fukuyama, *J. Chem. Soc. Chem. Commun.*, 64 (1972).

65) P.Brougham, M.S.Cooper, D.A.Cummerson, H.Heaney, N.Thompson, *Synthesis*, 1015 (1987).

66) W.D.Emmons, A.S.Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

67) D.R.Dalton, V.P.Dutta, D.C.Jones, *J. Am. Chem. Soc.*, **90**, 5498 (1968).

68) D.Adam, L.A.Arias, O.De Lucchi, *Synthesis*, 545 (1981).

69) This assumes that the first step consists of reaction between ylid [46] and a suitable chiral lactol, in the manner of E.J.Corey, A.Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

70) E.Fouque, G.Rousseau, *Synthesis*, 661 (1989); the chiral ester so produced can be reduced to the lactol using DIBAL-H - for example see ref 69.

71) V.W.Armstrong, N.H.Chishti, R.Ramage,*Tetrahedron Lett.*, 373 (1975).

72) H.S.Corey, J.R.D.McCormick, W.E.Swensen, *J. Am. Chem. Soc.*, **86**, 1884 (1964).

73) I.Lombardo, R.J.K.Taylor, *Synthesis*, 131 (1978).

74) E.J.Corey, J-L.Gras, P.Ulrich, *Tetrahedron Lett.*, 809 (1976).

75) This is conveniently prepared from acrolein, triphenyl phosphine and 48% HBr; the aldehydic phosphonium salt so produced is acetalised using tri-isopropyl orthoformate; J.Viala, M.Santelli, *Synthesis*, 395 (1988).