Studies towards the synthesis of the guaianolide skeleton: an intramolecular hetero Diels Alder approach and a carbonyl ene approach

by

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In loving memory of my father Nunzio
and my uncle Ciccio.

Abstract

Keywords: guaiane-6,12-olide skeleton, the intramolecular hetero Diels Alder reaction, the intramolecular carbonyl ene reaction, palladium catalysis.

This thesis describes the efforts towards the synthesis of the guaiane-6,12-olide skeleton, which characterises the guaianolide family of bioactive natural compounds. Two approaches have been investigated: the intramolecular hetero Diels Alder (IMHDA) reaction and the intramolecular carbonyl ene reaction.

This thesis has been divided in three sections: the first part gives a general background about the guaianolides, the second section describes the synthetic approaches we investigated and, finally, the third section reports the experimental details.

The first section gives a brief overview about the biosynthesis, the biological activities of the guaianolides, and the most interesting synthetic approaches to obtain them.

The second section describes the two different approaches we investigated and gives a theoretical background about the main chemical transformations used.
At first, the IMHDA reaction approach is described: a brief overview of palladium catalysis and Diels Alder reaction is given, and it is followed by the results and discussion of our study.
Similarly, a theoretical background of the Alder ene reaction is given, before the results and discussion of the intramolecular carbonyl ene reaction approach are described: particular importance is given to the reasoning that led to the assignment of the relative configuration of the cycloadducts obtained, and to the rationalisation of this stereochemical outcome.

Finally, the third section gives a complete description of the experimental procedures followed, and of the experimental data for the synthetic studies performed in the previous chapter.

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Abbreviations

Ac	Acetyl
AIDS	Aquired immuno deficiency syndrome
ATP	Adenosin triphosphate
°C	Degrees Celsius
cm^{-1}	Wave number
Cys	Cysteine
δ	Chemical shift
DAG	Diacylglycerol
Dba	Dibenzylideneacetone
DIBAL	Diisobutylaluminium hydride
DMPU	1,3-dimethyl-3,4,5-tetrahydro-2(1H)-pyrimidinone
DMF	Dimethyl formamide
DMS	Dimethyl sulfide
Et	Ethyl
FAB	Fast Atom Bombardment
FPTase	Farnesil protein transferase
FMO	Frontier Molecular Orbital
g	gram
GTP	Guanosin Triphosphate
h	hour
HIV	Human Immunodeficiency Virus
HDA	Hetero Diels Alder
HOMO	Highest Occupied Molecular Orbital
IMDA	Intramolecular Diels Alder
IMHDA	Intramolecular hetero Diels Alder
LUMO	Lowest unoccupaied molecular orbital
mL	Millilitre
mmol	Millimole
NCS	*N*-Chloro succinimide
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
PCC	Pyridinium Chloro Chromate
SAR	Structure activity relationship
SARS	Severe acute respiratory syndrome
STLs	Sesquiterpene lactones
TADA	Trans-annular Diels Alder
TBDMS	*Tert*-butyldimethylsilyl
TLC	Thin layer chromatography
Tf	Triflate

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPSOTf	Triisopropylsilyl triflate

Synthesis of the guaian-6,12-olide skeleton

Part I: A general background

1.1 Introduction

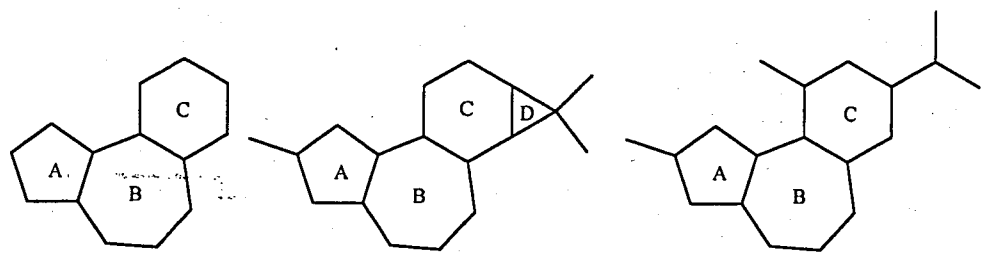
Plants have always represented an important, if not the most important, source of remedies against many types of illness. The real effectiveness of traditional remedies has often been confirmed by modern biological essays. A decoction of *Acacia caven* bark, a tree present in North and Central Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay, is traditionally used in these areas against bruises, snake bites, and skin diseases;[1] *Acacia nilotica*, and *Vitex doniana* are only two of the several plants used by traditional Nigerian healers to treat diarrhoea[2] (which annually still causes 4-5 million deaths all around the world);[3] *Gunnera perpensa* and *Hypoxis latifolia* are well known among South African healers to be effective against venereal diseases;[4] extracts from *Isatis indigotica* roots have been used in 2003 to prevent severe acute respiratory syndrome (SARS) from spreading around the countries of South East Asia.[5]

These are only a few examples from an endless list that show the fundamental role played by vegetal resources in the preservation of human health; if in economically developed countries the direct use of traditional remedies is of secondary importance, economically developing countries, especially in rural areas, still make a large use of them.[6] But if we take a deeper look at the most industrialised countries, where we often think we have reached an advanced level of scientific knowledge, and sometimes we even pretend to be able to control nature, pharmaceutical researchers need constantly to investigate on the vegetal word in order to find new biologically active compounds. This is fundamental to increase our comprehension of the mechanisms behind biological processes, which in turn have a direct relapse in terms of response to the increasing demand for more specific and effective medical treatments.

Accordingly, every year a number of studies of biologically active natural compounds (concerning the discovery, biological activity, synthesis and semi-synthesis), are published in prestigious international journals.

1.2 Aim of this project

As we have seen, the synthesis of bioactive natural compounds, is very important to provide large quantities of material needed for experimentation and biological testing. In the last few years our research group has been successfully engaged in synthesising the tigliane and daphnane families of natural compound skeletons, both characterised by the [9.3.0.$0^{2,7}$] tetradecane core [Fig. 1].

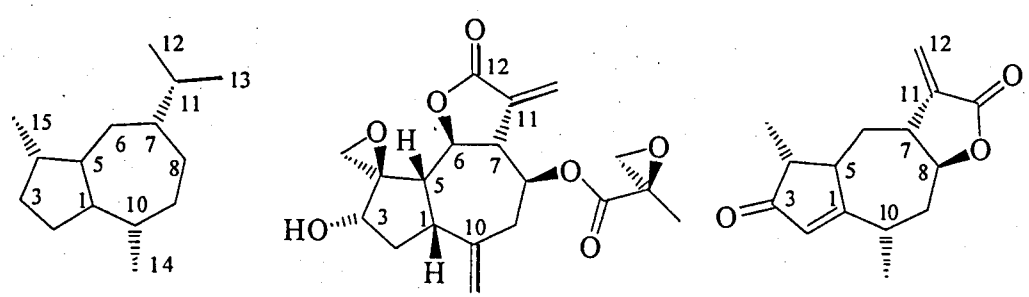


[9.3.0.$0^{2,7}$]tetradecane Tigliane Daphnane

Figure 1: Skeletons of the tigliane and daphnane families of natural compounds.

In particular tiglianes have been demonstrated to be very useful in the pharmaceutical research: the esters of the tigliane phorbol are in fact among the most potent co-carcinogens known so far and they are playing a key role in the comprehension of the mechanisms behind many types of cancer diseases.

In order to start a new challenging project, we decided to extend our synthetic interest to another important family of natural compounds: the guaianolides. This family of sesquiterpene lactones (STLs) is composed of more than 500 members (many with interesting biological activities), and it is characterised by the guaiane skeleton, based on the biciyclo [5,3,0] decane framework [Fig. 2].



Guaiane skeleton Repin Thieleanin

Figure 2: Bicyclic core of the guaianolides, and two of these naturally occurring sesquiterpene lactones.

The wide spectrum of biological activities exhibited by guaianolides is the main reason why they have become, over the last forty years, a target for many synthetic organic chemists.

The aim of this project is to access the skeleton of the guaianolide family of natural compounds through a new efficient pathway, related to that successfully developed by our research group for the synthesis of daphnanes and tiglianes. We would then be able to access three groups of bioactive natural compounds by using similar precursors and strategies, in a unified approach.

Part I of this thesis contains a short account of the proposed biosynthesis, the biological activities and the different strategies towards the synthesis of guaianolides developed so far. In Part II the two different approaches we developed to access the guaianolide skeleton are discussed.

Part III, consisting of the description of the experiments performed, concludes this thesis.

1.3 Guaianolides: a family of bioactive natural compounds

The discovery of guaianolides as a family of natural compounds dates from about 50 years ago, and was related to research on chamazulene (a very interesting counter-irritant substance, identified for the first time in chamomile oil and also extracted from the bluish-green wormwood oil).[7] After the discovery that chamazulene was formed during steam-distillation (performed to isolate the active molecules from the above mentioned materials), research was performed to find the unstable precursors, and thanks to new separation methodologies and to less drastic separation methods, this led to the discovery of medium-sized sesquiterpene lactones: the guaianolides, so called because they are characterised by the guaiane skeleton, a bicyclo [5,3,0] decane framework. A γ-lactone moiety is present as the third ring of the molecule, usually built between C-6 and C-12 (guaian-6,12-olides), and less often between C-8 and C-12 (guaian-8,12-olides). Different functionalities at C-8, C-10, and in the five membered ring, are responsible for the wide variety of structure of this family of natural compounds [Fig. 3].

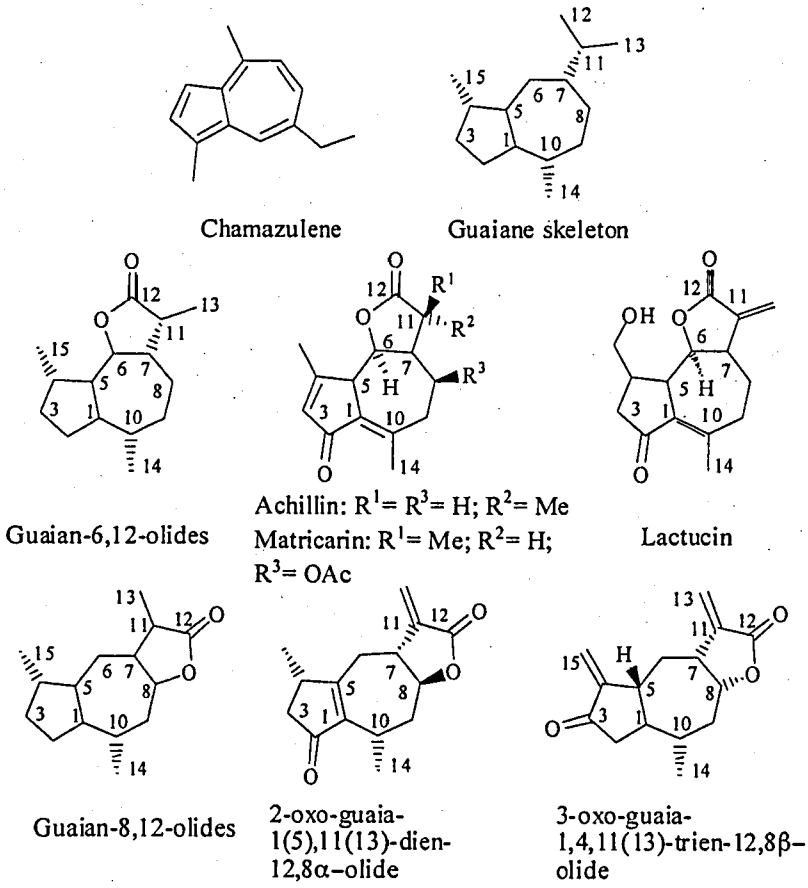


Figure 3: In addition to the guaiane framework, guaianolides contain a γ-lactone ring, built between C-6 and C-12 (guaian-6,12-olides) or between C-8 and C12 (guaian-8,12-olides).

To date, more than 500 different guaianolides have been identified, extracted from a wide number of different plants of genera Compositae,[1] such as *Achillea*, *Arnica*, *Artemisia*, *Cichorium*, *Helenium*, *Lactuca*, *Matricaria*, *Tanacetum*, and many show interesting biological activities. Their consequent potential applications in the development of new drugs make the guaianolide family of natural compounds a very interesting target for synthetic organic chemists because natural resources cannot be enough to satisfy the demand for these molecules.

1.4 Biosynthesis of the guaianolide skeleton[8]

The biogenetic hypothesis proposes that the guaianolide skeleton is formed through the acetate-mevalonate pathway to give farnesyl pyrophosphate. Cyclisation of farnesyl pyrophosphate (*farnesyl-OPP*) provides the germacradiene skeleton **A**. Enzymic oxidation at C-6 and C-12 of **A** is probably followed by lactonisation to give the germacranolides costunolide, and upon bio-epoxidation, parthenolide. Transannular cyclisation of the intermediate parthenolide would provide the guaianolide skeleton **C** *via* cation **B**. Further oxidative bio-modifications of **C** would lead to lactones **1** and **2**. [Fig. 4].

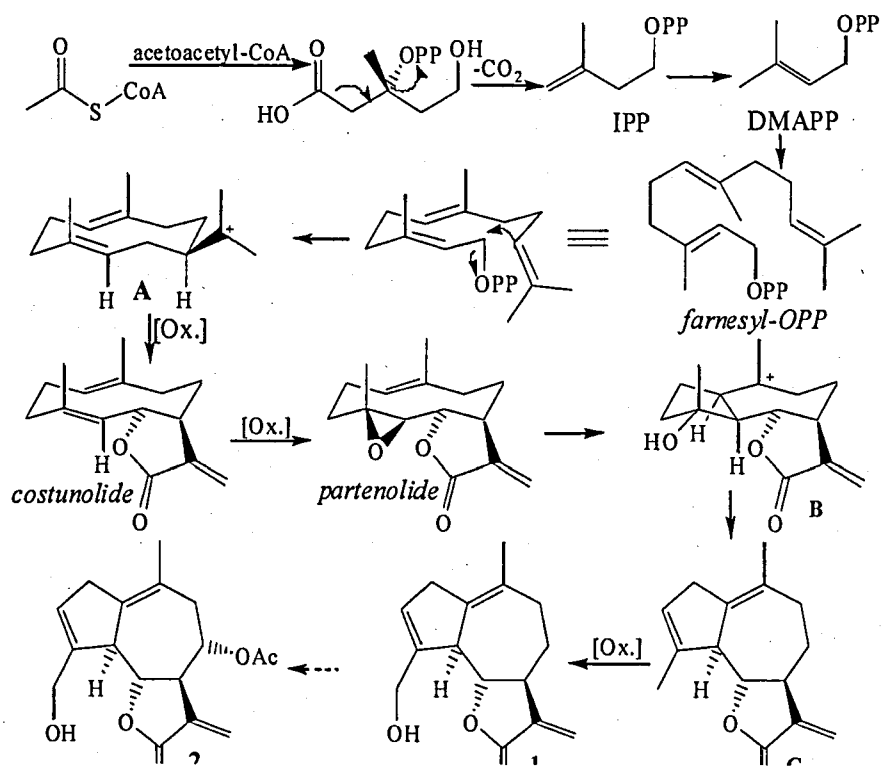


Figure 4: A suggested biosynthetic route to the guaianolide skeleton.

1.5 Biological activities

Sesquiterpene lactones (STLs) are probably synthesised by plants to protect themselves from parasites and pathogens; this accounts for their cytotoxicity against bacteria and fungus.

Many classes of STLs have been identified so far: guaianolides, pseudoguaianolides, germacranolides, furanoheliangolides, hypocretenolides and eudesmanolides being the most important [Fig 5].

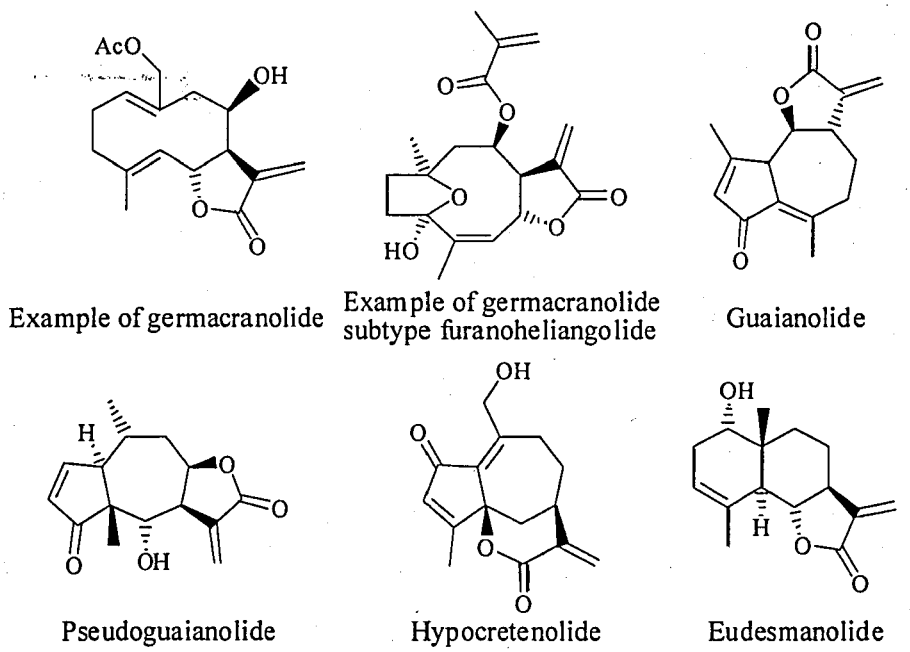


Figure 5: Examples of different families of sesquiterpene lactones (STLs).

The biological activity of STLs has been related by many structure activity relationship (SAR) studies to the presence of α-methylene-γ-lactone and/or to α,β unsaturated ketone moieties, which are acting as Michael acceptors towards a protein's nucleophilic amino-acidic residues, especially cysteine.[9] The covalent bonding with the STLs inhibits the targeted protein's activities, determining the biological effect of the molecule.

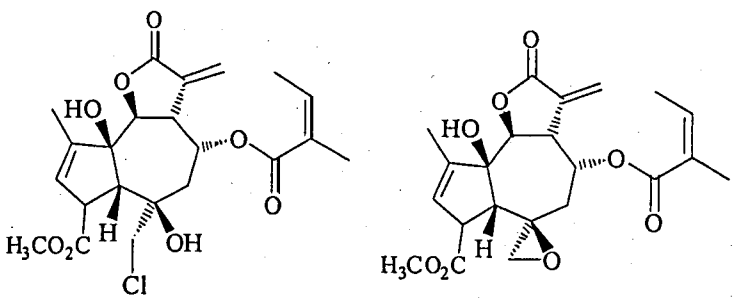
Guaianolides exert many biological activities such as cytotoxic antitumour,[10] contraceptive,[11], anthelmintic, antihistosomal and immunomodulatory,[12] antiulcer,[13] antifungal,[14] antinflammatory,[15] growth plant regulator,[16] antidiabetic[17] and antibacterial[18] behaviour. Among these, the anti-tumour and the anti-inflammatory

activities have been thoroughly investigated, as described in the following two sections of this chapter.

1.5.1 Anti-tumour activity

Since late 1960's the cytotoxic activity of STLs has been well documented.[19] In 1971 Kupchan[10d] and co-workers, in one of the first SAR studies on the anti-tumour activity of several compounds belonging to different groups of STLs, suggested the key role played by the α-methylene-γ-lactone moiety. Most of the compounds containing the α-methylene-γ-lactone moiety were significantly active and upon the reduction of the methylene moiety to a methyl group, they showed considerable loss of activity. Further, molecules containing only endocyclic α,β-unsaturated ketone or lactone moieties did not show any significant activity, and the presence of these features was demonstrated to be important only as an enhancer for the cytotoxicity of the α-methylene-γ-lactones.

It is interesting to note that, among the molecules showing *in vivo* activity, two were guaianolides: eupachlorin acetate and euparotin acetate [Fig. 6].



Eupachlorin acetate Euparotin acetate

Figure 6: Cytotoxic guaianolides used in Kupchan's SAR study on STLs anti-tumour activity.

Arteminolides B, C and D,[20] isolated from *Artemisia sylvatica Maxim* and *Artemisia argy*, [Fig. 7] are inhibitors of farnesyl protein transferase (FPTase) and may be antitumour agents against *ras*-mutated human cancers.

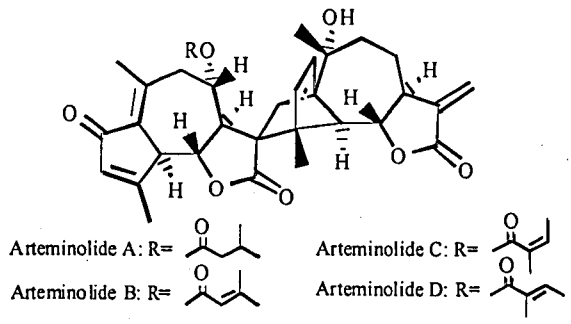
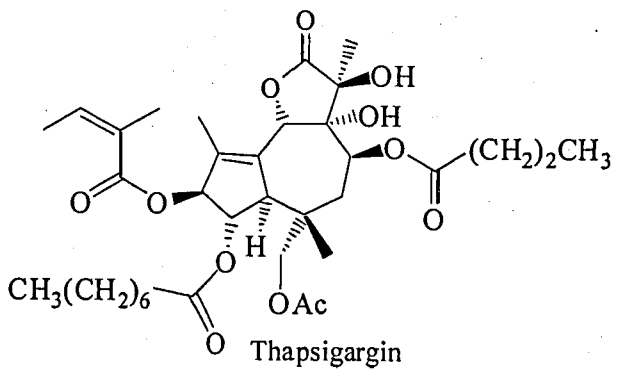


Figure 7: Dimeric guaianolides arteminolide A, B, C, D inhibit the FPTase and are potential antitumour agents against r*as*-mutated human cancers.

FPTase inhibitors work in synergy with some established anticancer treatments such as radiotherapy and chemotherapeutics agents. *Ras* proteins (the GTP-binding proteins responsible for the transduction of extra-cellular growth signals into the cell nucleus),[21] have been found in mutated forms in 30% of human cancers, principally in colon and pancreatic carcinomas. *Ras* proteins achieve the biological activity after posttranslational modifications, which includes farnesylation onto Cys 186 at the C-terminal by FPTase. Inhibition of FPTase activity leads to lack of well-processed *Ras,* and consequently to the inhibition of the *Ras* protein-induced cancer genesis.

The α-methylene-γ-lactone moiety is not always fundamental for the anti-tumour activity: thapsigargin [Fig. 8] is a potent[22] and selective[23] modulator of sarcoplasmatic-endoplasmatic reticulum Ca^{2+}ATPases (SERCA). This class of proteins, by controlling the cytosolic calcium homeostasis, exerts a strong influence on the cellular functions.[24]



Thapsigargin

Figure 8: Thapsigargin, a guaianolide very useful in research into Ca^{++} cellular homeostasis and potential anticancer compound. It is a powerful and selective inhibitor of sarcoplasmatic-endoplasmatic reticulum Ca^{++} ATPases (SERCA).

Thapsigargin is in fact often used in the study of intracellular calcium homeostasis,[25] and has been proposed as a potential anticancer drug. Despite the absence of the α-methylene group it is still able to form with the enzyme a catalytically inactive dead-end complex.[26]

1.5.2 Anti-inflammatory effects[27]

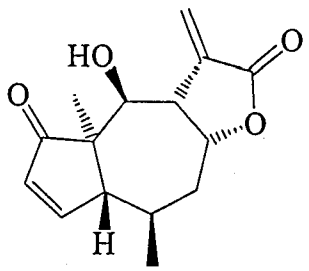
STLs have been reported to inhibit the synthesis of leukotrienes[28] and to modulate the release of histamine, serotonin and elastase, all of which are molecules involved in the inflammation process.[29]

It has been proposed that the anti-inflammatory properties of STLs are the consequence of the interaction with the transcription factor NF-*k*B and the nuclear factor of activated T-cells (NFAT),[30] which are responsible for the expression of genes codifying for proteins involved in inflammatory and immune processes such as toxic shock, asthma, rheumatoid arthritis and cancer[31].

Transcription factors are proteins that stimulate the expression of specific genes by binding the DNA in the correspondence of specific enhancer sequences.

The binding of STLs with NF-*k*B and NFAT inhibits their interaction with DNA and therefore the expression of those genes whose expression depends upon these transcription factors. In particular, NF-*k*B is usually formed of a p50 and a p65 subunit and stored in the cytoplasm bound with the inhibitory sub-unit I*k*B. The activation of this transcription factor is a consequence of the action of specific inducers (inflammatory stimulators) such as bacterial lipopolysaccharides, which by activating the phosphorylation of I*k*B induce the separation of the inhibitory sub-unit from NF-*k*B. This is now able to migrate to the nucleus and promote the expression of a pool of more than 150 genes involved in the inflammatory response.

The interaction between helenalin (a bifunctional pseudoguaianolide with two α,β-unsaturated moieties, potentially acting as Michael acceptors) [Fig. 9] and NF-*k*B has been extensively studied.

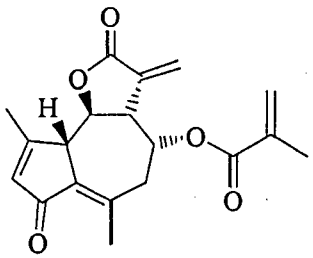


Helenalin

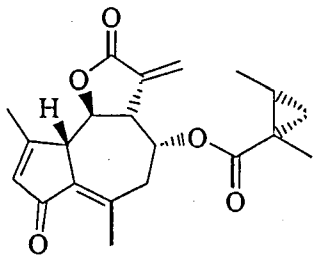
Figure 9: Helenalin, a cytotoxic bifunctional pseudoguianolide.

In accordance with the mechanism of action proposed by Merfort and Schmidt in 1999,[32] active STLs with two alkylating groups (and helenalin in particular) strongly bind the p65 subunit of NF-*k*B by alkylating two cysteine residues (Cys^{38} and Cys^{120}).[33] Between the two sulphydrilic amino-acids there is a gap containing the phenol ring of Tyr^{36}, fundamental for the interaction with the DNA backbone.[28d] It follows that the bifunctional STLs, by cross-linking Cys^{38} and Cys^{120}, prevent the interaction of Tyr^{36} with DNA and therefore the binding of the transcription factor. The strong activity of a few monofunctional compounds and the low activity of some bifunctional compounds are explained by additional non bonding interactions with the protein.

In 2004 Merfort and co-workers published the results of a very interesting quantitative structure relationships (QSAR) investigation on the NF-*k*B inhibitory activity of 103 STLs belonging to the six main structural groups (germacranolides, furanoheliangolides, guaianolides, pseudoguaianolides, hypocretenolides, and eudesmanolides, figure 5).[34] It was impossible to find a good correlation between such a wide range of skeleton structures, but when the analysis was restricted to subgroups of STLs, topological and structure-coding parameters were very important for molecules with a rigid skeleton (guaianolides and furanoheliangolides), whereas in the case of flexible skeletons (germacranolides), the activity was mostly related to reactivity coding parameters (number and type of α,β-unsaturated carbonyl functions). Finally, the authors proposed guaianolide-like structures (such as those shown in figure 10) as convenient leads to develop STLs derived anti-inflammatory drugs inhibiting the NF-*k*B. The core of the guaianolides is in fact easier to synthesise than that of germacranolides and furanoheliangolides.



2-oxo-8α-mehacryloyloxy-guaia-1(10),3,11(13)-trien-12,6β-olide



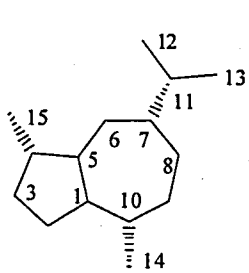
2-oxo-8α-epoxyangelicoyloxy-guaia-1(10),3,11,(13)-trien-12,6β-olide

Figure 10: Guaianolides with anti-inflammatory properties: among STLs they have been proposed as convenient structure leads for developing NF-*k*B inhibiting anti-inflammatory drugs.

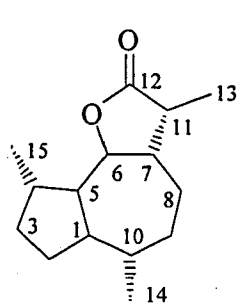
Guaianolides possess many useful biological properties, and they can be used as both research tools for the comprehension of biological mechanisms and to develop new drugs. Because of their importance in biological essays, guaianolides have become an important target for many organic chemists, and in the last three decades several approaches to the synthesis of guaianolides have been proposed. In the next chapter a brief overview of the most interesting is given.

1.6 Synthetic Approaches Towards the Guaianolide Skeleton

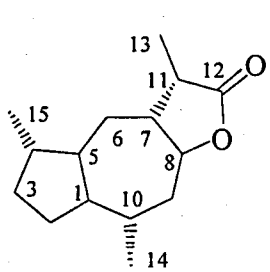
The structural core of the guaianolides is the guaiane, based on the bicyclo [5,3,0] decane framework (also known as the perhydroazulene ring system), usually existing in *cis* configuration. In addition to this bicyclic feature, a γ-lactonic ring is built between C-6 and C-12 (guaian-6,12-olides) or C-8 and C-12 (guaian-6,12-olides), and many types of substitution pattern can be present at C-8, C10 and in the cyclopentane moiety [Fig. 11].



Guaiane



Guaian-6,12-olides



Guaian-8,12-olides

Figure 11: The core and the two subfamilies of the guaianolides.

Their wide spectrum of biological properties, together with the chiral centres present on molecules, make the synthesis of the guaianolides an important and challenging target for synthetic organic chemists. In fact, in over the last four decades, many approaches towards their synthesis have been developed.

The shortest way to access guaianolides is through semi-synthesis,[35] that is chemical modification of naturally occurring guaianolides to convert them into the desired target. This allows access to both natural and unnatural compounds. The drawback of this approach is the limited availability of the precursors, which are of course obtained from natural resources. Despite this limitation, generally speaking, semi-synthesis is (from a pharmaceutical point of view) a very important method for the study of structure-activity relationships (SAR) of these molecules.

In order to be able to perform biological essays, scientists need large quantities of the product they want to test. In the case of natural compounds, the total synthesis of the desired compound (starting from readily available precursors) can be very helpful, allowing researchers access to the amount of product they need.
As regarding the total synthesis of the guaianolide skeleton, four main strategies have been developed:

- Stereocontrolled rearrangement of suitably substituted decalins into a perhydroazulene-type ring system.
- Transannular cyclisation of cyclodecanes.
- Conversion of cycloheptanes.
- Conversion of cyclopentanes.

Each of these methods is described in the following sections.

1.6.1 Rearrangement of decalins

Solvolytic rearrangement of decalins has been successfully employed to synthesise the hydroazulene framework of many natural compounds, such as pseudoguaianolides, guaianolides, phorbol, and ingenol [Fig. 12].[36]

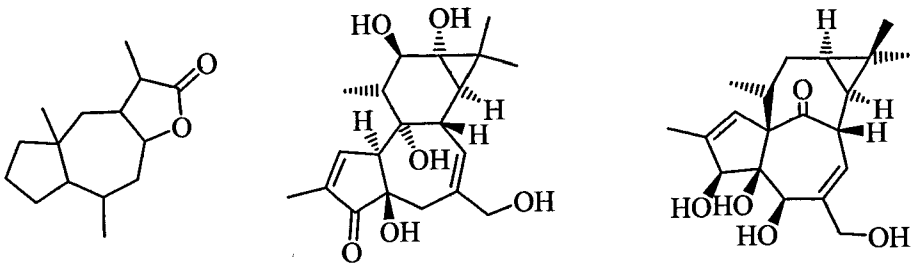
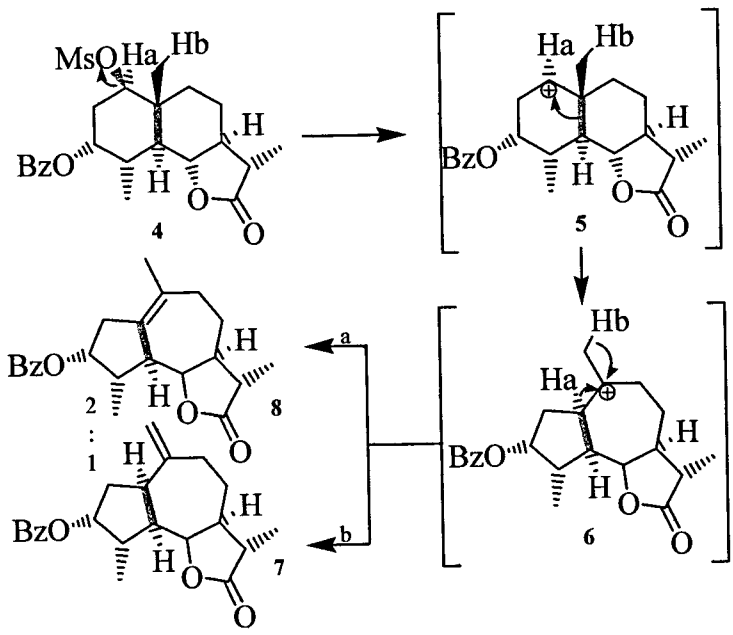


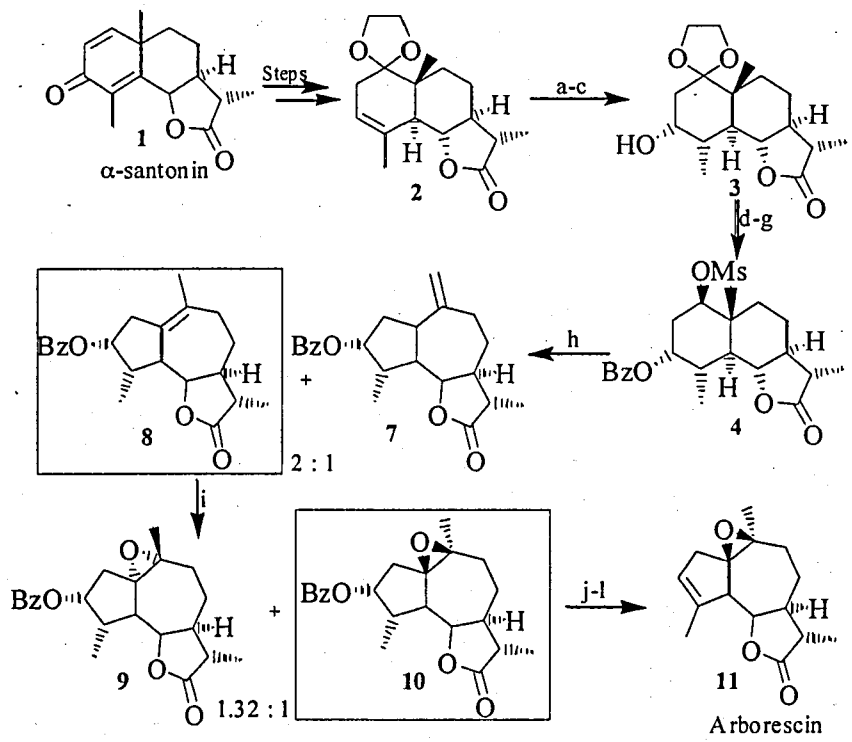
Figure 12: Natural compounds synthesised also through solvolytic rearrangement of decalins.

Under the reaction conditions the displacement of the leaving group generates the secondary carbocation **5** which undergoes rearrangement to form the more stable tertiary carbocation **6** with migration of the σ bond across the molecule; stabilisation of carbocation **6** through the loss of Ha or Hb gives respectively olefin **8** or **7** [Scheme 1].



Scheme 1: Solvolytic rearrangement of decalins: the equatorial leaving group is antiperiplanar to the bond across the molecule

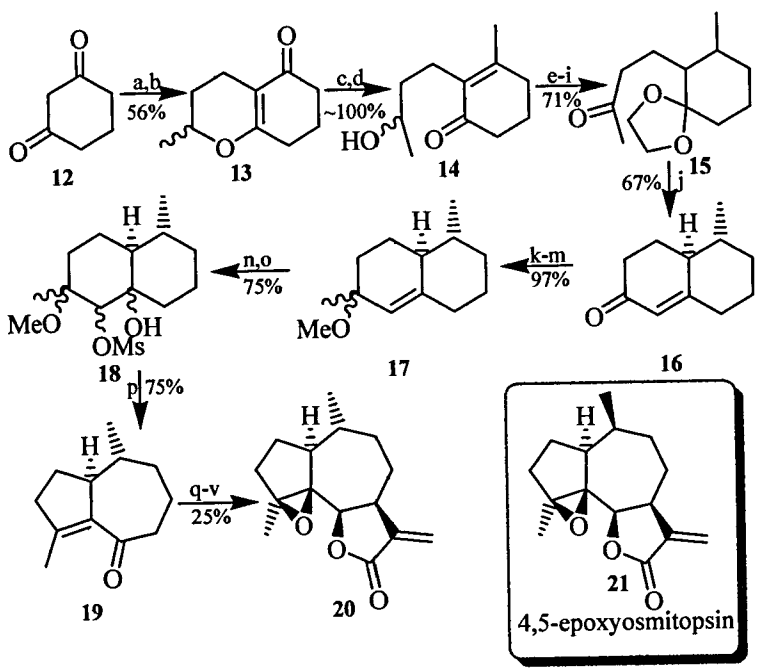
In 1982 Ando and co-workers reported the synthesis of arborescin:[37] starting from α-santonin (**1**), they synthesised the eudesmanolide **4**, a decalin derivative carrying the proper functionalities to undergo solvolytic rearrangement. Decalin **4** conversion into the guaianolide skeleton was carried out in a refluxing 0.5 M acetic acid solution of potassium acetate. This procedure afforded a mixture of the exo- and endocyclic olefins **7** and **8**. Reaction of **8** with *m*-chloroperbenzoic acid (*m*-CPBA) gave a mixture of the epoxides **9** and **10**. Epoxide **10** was debenzylated with 1M K_2CO_3 in refluxing methanol, and the following alcohol treated with methanesulfonyl chloride in pyridine. Reaction of the mesylate with Li_2CO_3 and LiBr in DMF afforded arborescin (**11**) [Scheme 2].



Scheme 2: Ando's synthesis of arborescin: the guaianolide framework was synthesised through rearrangement of a functionalised decaline obtained from α-santonin. a, *m*-CPBA, (100%); b, Al(*i*PrO)$_3$, toluene, (99%); c, H_2, Pt/C, (99%); d, BzCl, Py, (100%); e, 50% AcOH, reflux, (75%); f, $Zn(BH_3)_2$, DME, (66%); g, MsCl, Py, (91%); h, 0.5 M AcOK/AcOH, reflux, (72%); i, 0.5 M aq *m*-CPBA, (22%); j, 1 M K_2CO_3 aq, MeOH, (76%); k, MsCl, Py, (84%), l, Li_2CO_3, LiBr, DMF, Δ, (49%).

Decalins suitable to undergo the ring expansion/contraction rearrangement can also be synthesised from simple compounds: Posner and co-workers synthesised decalin **18** in order to access to hydroazulenone **19**, an intermediate for the synthesis of **20**, an epoxyguaianolide epimer at C-10 of 4,5-epoxyosmitopsin (**21**), a naturally occurring compound with significant antischistosomal activity [Scheme 3].[38]

Michael addition of 1,3-cyclohexanedione (**12**) to methyl vinyl ketone followed by reduction with sodium borohydride gave **13**, which was in turn converted into **14** by treatment with methyllithium followed by acidic aqueous workup. Acetylation of the alcoholic group, hydrogenation of the olefinic double bond followed by protection of the ketone functionality with ethylene glycol and deprotection/oxidation of the secondary alcoholic moiety gave the ketone **15**. This was converted into the octalone **16** by refluxing in acidic aqueous methanol. The 1,2 addition of methyl lithium to the ketone group and the reaction of the resulting alcohol (as the corresponding sodium alkoxide) with methyl iodide gave the allylic ether **17**. Dihydroxylation with OsO_4 followed by mesylaton gave the mixture of diastereoisomeric mesylates **18**, which, when exposed to sodium *tert*-amyloxide in benzene underwent pinacol rearrangement to afford the hydroazulenone **19** as a single product. This was converted into **20** in 6 steps [Scheme 3].

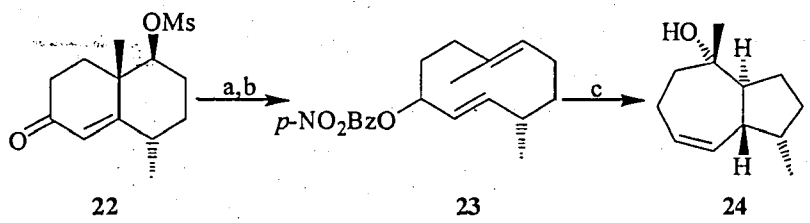


Scheme 3: Total synthesis of the C-10 epimer of 4,5-epoxyosmitopsin. a) CH_2=CHCOMe; b) $NaBH_4$; c) MeLi; d) H_3O^+; e) AcCl/Py; f) H_2/Pd-C; g) $(HOCH_2)_2$, *p*-TsOH; h) KOH(aq); i), PCC; j) MeOH/HCl; k) MeLi; l) H_3O^+; m) NaH, MeI; n) OsO_4; o) MsCl, Py; p) *t*-AmONa, benzene; q) H_2O_2, NaOH, (67%); r) *i*-Pr_2NLi, $BrCH_2CO_2Et$, (~100%); s) $NaBH_4$, DMF, (97%); t) *i*-Pr_2NLi, CH_2=$N^+Me_2I^-$, HMPA; u) MeI; v) $NaHCO_3$.

1.6.2 Transannular cyclisation of cyclodecadienes

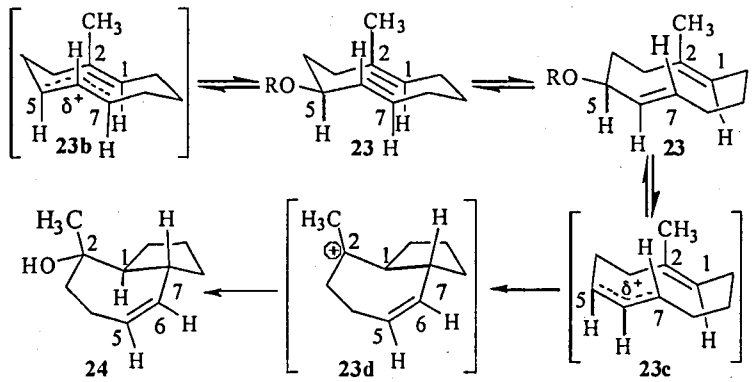
Following the suggestion that cyclodecenyl cations are implicated in the biosynthesis of the hydroazulene framework, cyclodecadienes appear to be an useful starting point for the synthesis of the guaianolide skeleton.

Marshall and co-workers reported the regio- and stereoselective solvolytic transannular cyclisation of cyclodecadiene **23** (obtained from decaline **22**) into hydroazulene **24** [Scheme 4].[39]



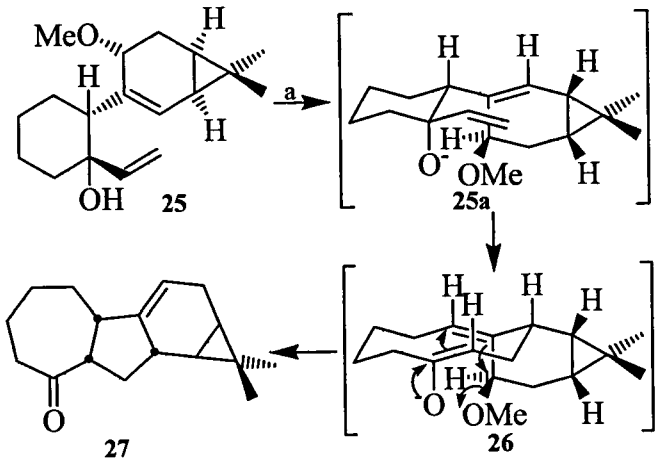
Scheme 4: Synthesis of the hydroazulene ring system **24** through transannular cyclisation of cyclodecaniene **23**. a) BH_3, then $NaOCH_3$, (22%); b) *p*-NO_2BzCl, (97%); c) $NaHCO_3$, H_2O/dioxane (55%).

The regioselective bond formation between C-1 and C-7 is thought to occur as a consequence of the strain requirements of the transition states potentially involved in the process, **23b** and **23c**. Assuming the retention of configuration of the double bond between C-6 and C-7, 1,5- and 1,7-cyclisations through **23b** would lead to strained *trans* seven membered rings. The 1,5 cyclisation through **23c** also leads to a strained *trans* seven membered ring, but not the 1,7 cyclisation, which gives the *cis* cycloheptene moiety of **24** through the favoured *cis* carbocation **23d** [Scheme 5].



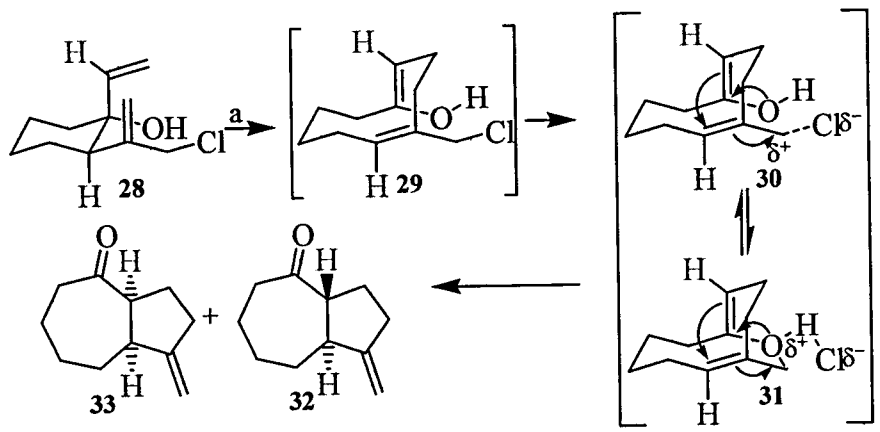
Scheme 5: Regioselective transannular cyclisation of **23** to **24**: only the 1,7 cyclisation of **23c** into **23d** provides the favoured *cis* cycloheptene moiety of **24**.

Paquette and co-workers developed a sequential oxy [3,3] sigmatropic cyclisation and transannular cyclisation procedure to access **27**, an intermediate towards the synthesis of ingenol [Fig. 12]:[40] the oxyanionic [3,3]-sigmatropic rearrangement of **25** gives the transient cyclodecadiene **26** which undergoes transannular cyclisation to afford **27** [Scheme 6].



Scheme 6: Paquette approach towards the synthesis of ingenol. The synthetic intermediate **27** is obtained through the tandem oxy [3,3] sigmatropic cyclisation and transannular rearrangement of **25**. a) KH, 18-cr-6, THF, Δ.

Similarly, Sworin accessed the bicyclic hydroazulenoid ring system through the oxy [3,3] sigmatropic rearrangement of **28** into **29**, followed by conversion of the short-lived intermediates **30** and **31** into a mixture of the perhydroazulenones **32** and **33** [Scheme 7].[41]

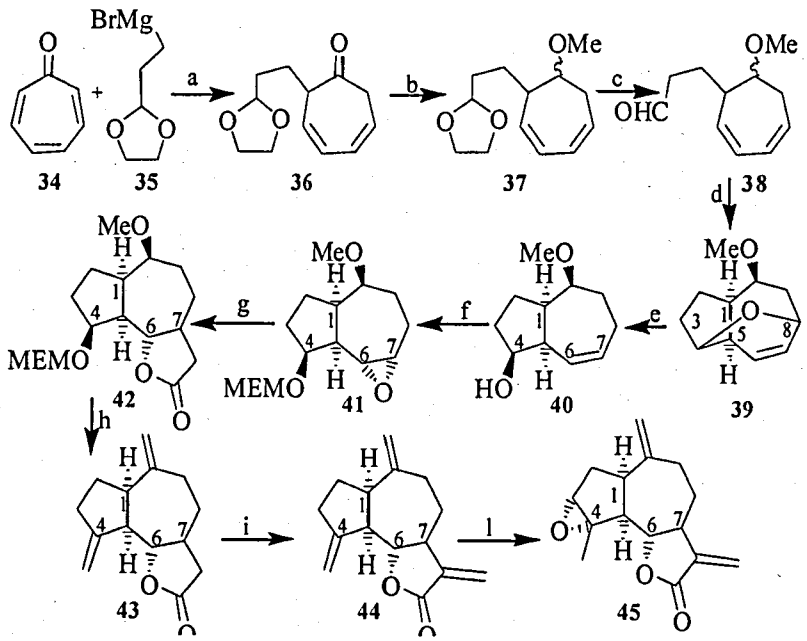


Scheme 7: Gas phase pyrolysis of **28** performed at 355 °C gives a 10:1 mixture of the perhydroazulenones **32** and **33**. According to the author, loss of HCl through the ion pair species **30** and **31** provides the driving force of the reaction.

1.6.3 Conversion of cycloheptanes

Rigby and co-workers developed a very interesting pathway for the synthesis of guaianolides such as dehydrocostus lactone, (±)-estafiatin, and (±)-grosshemin, from tropone **34** as the main precursor.[42]

Tropone was treated with 2-(2-bromoethyl)-1,3 dioxolane (**35**), to give **36**. To avoid any isomerisation of the diene system, the ketone was reduced and methylated to afford **37** as a mixture of ether epimers. Acidic hydrolysis and treatment of the resulting aldehyde **38** with $BF_3 \cdot Et_2O$ gave the intramolecular hetero Diels-Alder cycloadduct **39**. Selective cleavage of the C-O bond at C-8 with lithium metal in refluxing methylamine gave **40**, which, after protection of the alcoholic group at C-4 and stereoselective epoxidation, was converted into **41**. Regioselective oxirane ring opening with dilithioacetate afforded the lactone **42**. The alcohols at C-4 and C-10 were then deprotected with TMSCl/NaI, oxidised and then olefinated to obtain the dehydrocostus lactone **44** in 12 steps from tropone **34**. Isomerisation of the double bond at C-4 followed by regio- and stereoselctive epoxidation finally afforded estafiatin **45** [Scheme 8].

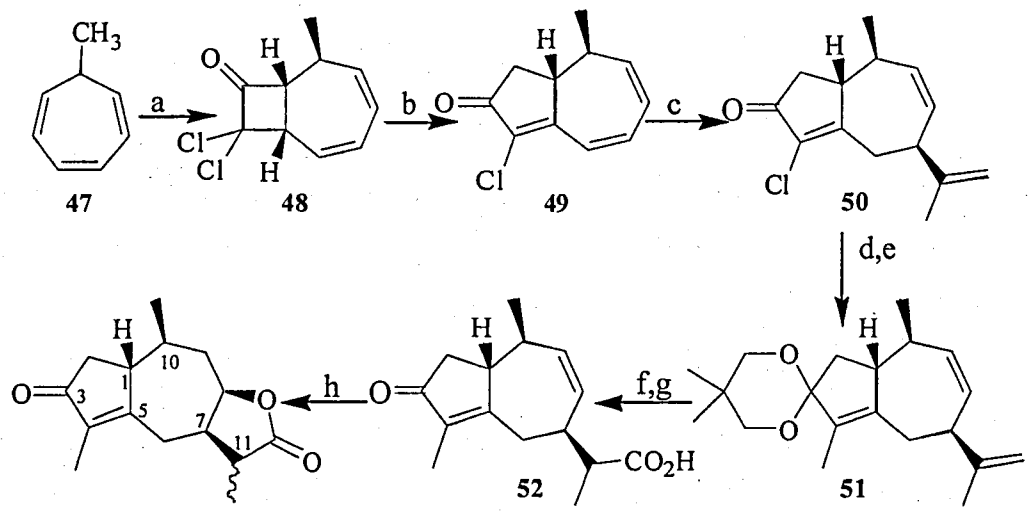


Scheme 8: Rigby synthesis of (±)-estafiatin **45** from tropone **34**: a) THF, 0 °C, 96%; b) $NaBH_4$, EtOH, 0 °C, 89% then NaH, CH_3I, 0 °C, THF, 96%; c) 5% aq TFA, acetone, 85%; d) $BF_3 \cdot Et_2O$, 0 °C, DCM, 92%, e) Li/CH_3NH_2 reflux, 82%; f) *i*-Pr_2NH, MEMCl, 97%, then *m*-CPBA, DCM, 0 °C, 1h, 54%; g) Dilithioacetate, DME, 60 °C, 4 days, 78%; h) NaI, Me_3SiCl, CH_3CN, -20 °C, 3h; $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C, 42% for two steps; N,N,P-trimethyl-P-phenylphosphinothioic amide,[43] *n*-BuLi, THF, -78 °C, 30 min. then Py, MeI, $(CH_3)_2CO$, 18 h, r.t., 15%; i) *i*-Pr_2NH, *n*-BuLi, Eschenmoser's salt,[44] THF -78 °C, 1.5 h; MeI, MeOH, r.t., 18 h, 71%; l) $BF_3 \cdot Et_2O$, benzene, r.t., 3h, 68%; *m*-CPBA, DCM 0 °C, 2.5 h, 51%.

A more recent approach dated 2003 and developed by Deprès and co-workers,[45] begins with the regio- and stereoselective [2+2] cycloaddition of dichloroketene to the readily available 7-methylcycloheptatriene **47** to give **48**. This, treated with diazomethane, undergoes regioselective ring expansion, which after dehydrochlorination gives the hydroazulenone **49**, which is in turn is converted into the guaianolide (±)-6-deoxygeigerin **54**.

Compound **49** undergoes β-1,6 conjugate addition of isopropenylmagnesium bromide under CuBr•DMS catalysed conditions to give **50**. Protection of the ketone group, followed by halogen-metal exchange and methylation gives **51**. Hydroboration-oxidation of the olefinic moiety to the corresponding primary acid with concomitant deprotection of the ketone gives **52**. Iodolactonisation/deiodination of **52** afforded a 1:1 mixture of 11-epi-6-deoxy-geigerin **53** and 6-deoxygeigerin **54** in 88% yield, with the former convertible into the latter by isomerisation with KOH.

This is the first total synthesis of a guaian-8,12-olide derivative [Scheme 9].

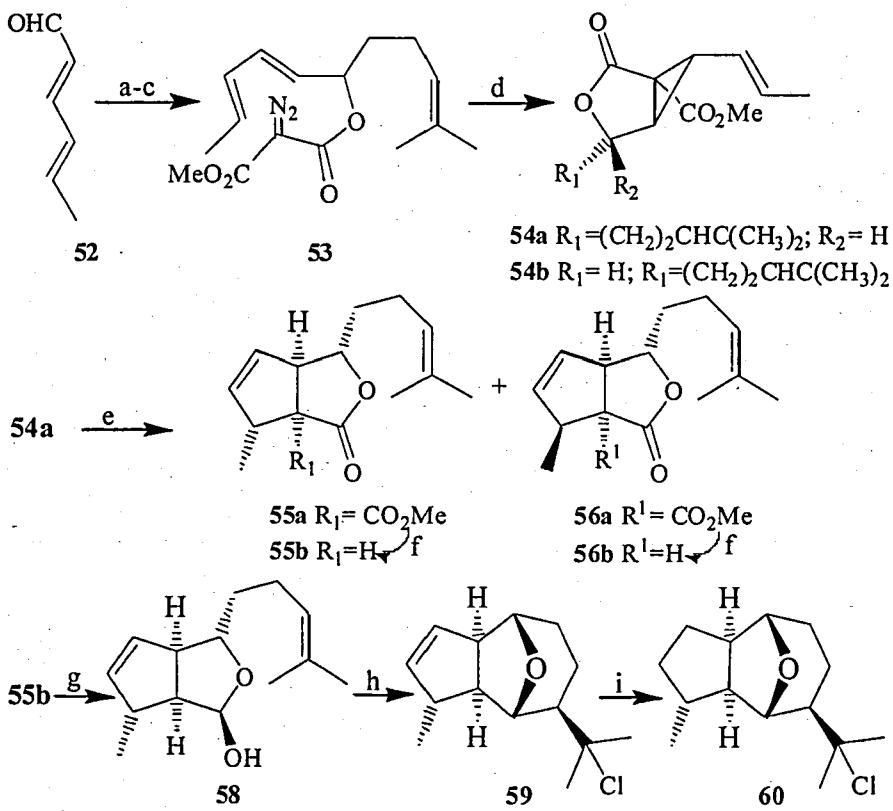


Scheme 9: Synthesis of 6-deoxygeingerin through modification of 7-methylheptatriene (**47**). a) Cl_3CCOCl, Zn-Cu, Et_2O, 76%; b) CH_2N_2, Et_2O/MeOH, DMF, 76%; c) CH_2=$(CH_3)CMgBr$, CuBr•DMS, TMSCl, THF, -80 °C, 45%; d) $(HOCH_2)_2C(CH_3)_2$, $(CH_3O)_3CH$, TsOH, DCM, 76%; e) N,N-dimethyl-1-naphtylamine, Li, THF, -80 °C, then CH_3I, -80 to 20 °C, 93%; f) 9-BBN, THF, then NaOH, H_2O_2, 83%; g), DM periodinane, DCM; $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 2-methyl-2-butene, $(CH_3)_3COH$/THF/H_2O, 75% (two steps); h) $NaHCO_3$, I_2, CH_3CN; $(C_4H_9)_3SnH$, $(C_2H_5)_3B$, O_2, toluene/THF, O °C 88% (two steps; **53**:**54**=1:1); i) (conversion of **53** into **54**) KOH, EtOH, 50%.

1.6.4 Conversion of five-membered rings

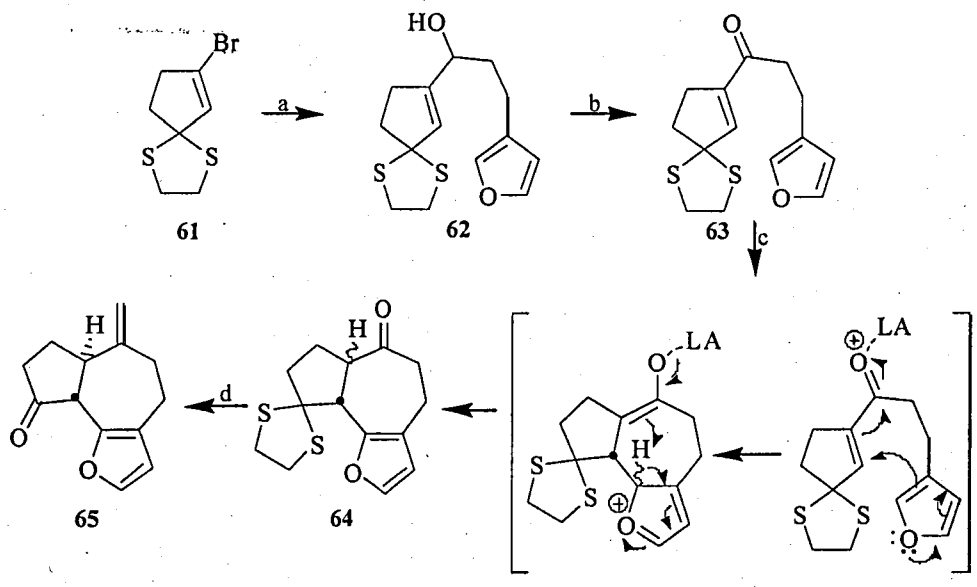
Five membered rings have extensively been used as precursors in many different approaches towards guaianolide total synthesis.

Hudlicky achieved the synthesis of the peryhydroazulene derivative **60** (which could be used as a building block in the total synthesis of guaianolides) through the Et_2AlCl catalysed cyclisation of **56**.[46] The synthesis begins with the conversion of the aldehyde **52** into **53**, which, when exposed to $CuSO_4$ in refluxing benzene, undergoes [4+1] annelation to give a mixture of the stereoisomers **54a** and **54b** (**54a**:**54b**=1.7:1). Thermolysis of **54a** affords the bicyclic lactones **55a** and **56a** as a mixture of stereoisomers (1.7:1). Decarbomethoxylation of **55a** into **55b** followed by DIBAL reduction gives **58**, which, when exposed to Et_2AlCl, cyclises into **59**. Reduction of the double bond with H_2 /PtO_2 affords the perhydroazulene ring system **60** [Scheme 10].



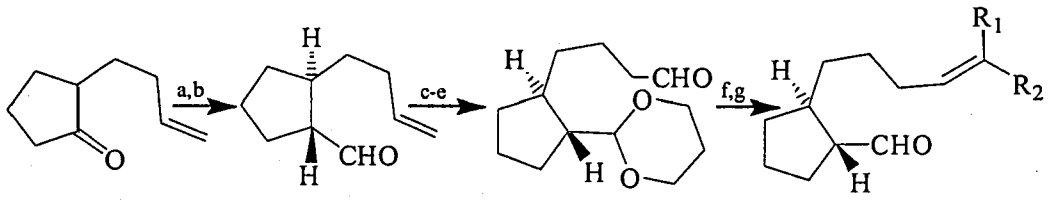
Scheme 10: Synthesis of the perhydroazulene ring system through intramolecular Lewis acid catalysed cyclisation. a) $LiCH_2CH_2CHC(CH_3)_2$/ Et_2O, 73%; b) $ClCOCH_2CO_2Me/Et_3N/DCM$, O °C, 61%; c) TsN_3/CH_3CN; d), $CuSO_4$, benzene, reflux; e) 610 °C, Vycor/$PbCO_3$, 30%; f), LiI, DMF, reflux, 90%; g) DIBAL, toluene, -78 °C, 82%; h) Et_2AlCl, dry DCM, 37%; i) EtOH, H_2 (16 psi)/PtO_2, 100%.

Furan terminated cyclisation of **63** is the key step in Tanis' approach to guaianolides and pseudoguaianolides skeletons:[47] dithioketal **61** was metallated with *n*-BuLi and then treated with 3-(3-furyl)-propanal to give alcohol **62**; this was oxidised to ketone **63**, which, when treated with $BF_3 \cdot Et_2O$, underwent furan terminated cationic cyclisation to afford the hydroazulenone derivative **64**. Treatment with $TMSCH_2Li$ followed by NCS gave the olefin **65**, a potential intermediate in the total synthesis of guiaianolides such as estafiatin **45** [Scheme 11].



Scheme 11: Synthesis of the perhydroazulene framework by furan terminated cationic cyclisation. a) *n*-BuLi, 3-(3-furyl)-propanal, 90%; b) PCC, 79%; c) $BF_3 \cdot Et_2O$ (10 eq), 64% (6:1 *trans* to *cis*); d) $TMSCH_2Li$; NCS, 80% (two steps).

Kuroda achieved the synthesis of the guaianolide skeleton by the the intramolecular cyclisation of the ω-formylallylsilanes **69a** and **69b**.[48] It is very interesting to note that this methodology allows one to obtain the seven membered ring fused to the γ-methylene lactone moiety in one step. Wittig reaction of **66** with Ph_2POCH_2OMe followed by hydrolysis gave the aldehye **67**, which, after acetalisation followed by hydroboration of the double bond and oxidation of the newly formed primary alcohol by PCC, was converted into the aldehyde **68**. This aldehyde was submitted to Hoffman's Wittig reaction and then to acidic hydrolysis conditions to afford a mixture of the aldehydes **69a** and **69b** [Scheme 12].

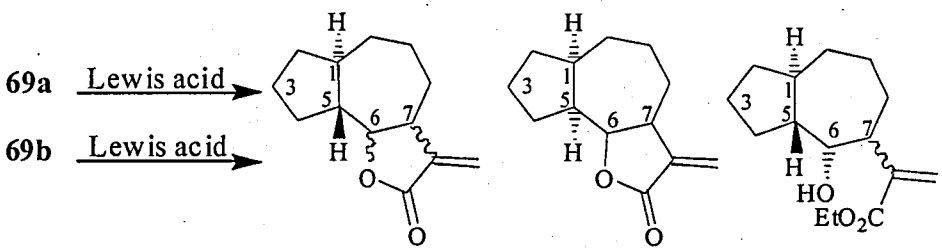


66 67 68

69a R_1= CH_2SiMe_3, R_2= CO_2Et
69b R_1= CO_2Et, R_2= CH_2SiMe_3

Scheme 12: a) Ph_2POCH_2OMe, LDA, 79%; b) 5% HCl (aq), 92%; c) $HO(CH_2)_3OH$, PPTS, 88%; d) disiamylborane, then H_2O_2, NaOH (aq), 82%; e) PDC, 70 %; f) $(EtO)_2POCH(CO_2Et)CH_2SiMe_3$, NaH; g) 5% HCl (aq).

The outcome of the cyclisation of **69a** and **69b** seems to be dependent on the stereochemistry of the olefinic moiety and on the Lewis acid employed: treatment of **69a** with BF_3•Et_2O afforded **70** as a single product in 14% yield. Exposure of **69b** to $TiCl_4$ gave **74** as the single product of the reaction in 45% yield [Scheme 13; table 1].



70 6α-H, 7α-H
71 6α-H, 7β-H
72 6β-H, 7α-H
73 6β-H, 7β-H

74

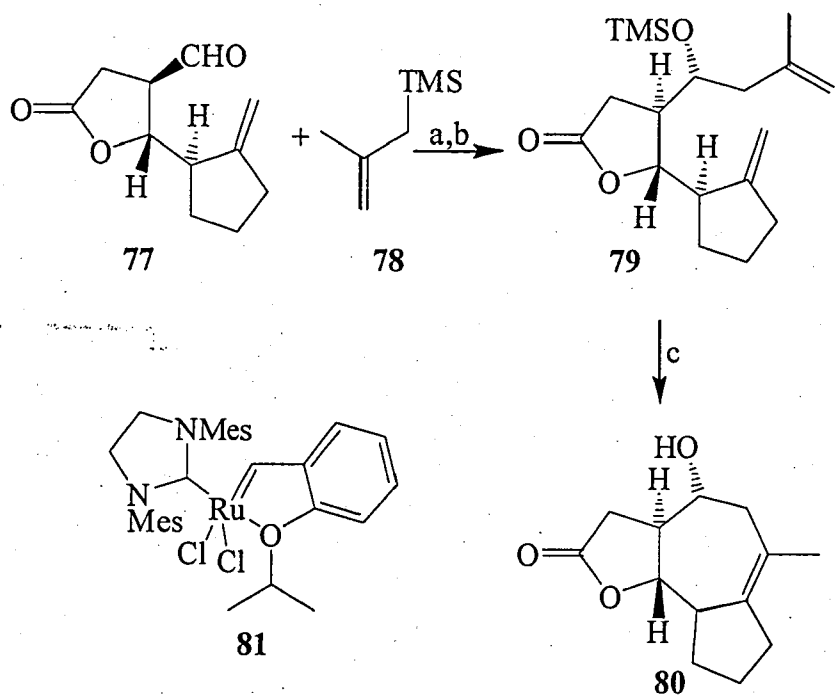
75 7α-H
76 7β-H

Scheme 13: Synthesis of the guaianolide skeleton: intramolecular cyclisation of allylsilanes **69a** and **69b**.

Substrate	Reagent	Product (ratio)	Yield %
69a	BF_3•Et_2O	70	14
69a	$TiCl_4$	75 + 76 (53 : 47)[a]	13
69a	TBAF	---	
69b	BF_3•Et_2O	70 + 71 (44 : 56)[b]	18
69b	$TiCl_4$	74	45
69b	TBAF	71 + 72 (41 : 59)[a]	32

Table 1: Intramolecular cyclisation of **69a** and **69b**.[a] Not separated, ratio determined from the ^1H NMR spectrum.[b] Separated by column chromatography.

Reiser and co-workers approached the synthesis of the guaianolide skeleton **80** through the ring closing metathesis of **79** catalysed by **81**.[49] Aldehyde-ene reaction between **77** and **78** followed by silylation of the newly formed alcoholic group provided the substrate for the cyclisation which occurred in 48% yield [Scheme 14].



Scheme 14: Synthesis of the guaianolide skeleton through ring closing metathesis. a) $BF_3{\cdot}Et_2O$, 61%; b) TMSCl, Et_3N, 93%; c) **81**, then HCl, 48%.

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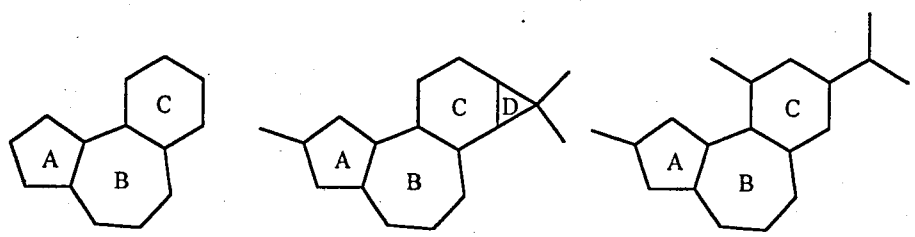
Part II: Synthesis of the Guaian-6,12-olide Skeleton: the Intramolecular Hetero Diels-Alder (IMHDA) Reaction Approach

2.1 Background

Synthesis of new useful organic compounds, and the development of original synthetic methodologies and strategies are among the most exciting and challenging tasks for an organic chemist. It is always very interesting to study the applicability of a methodology to new substrates or to find an original and more efficient pathway (shorter and with better yield than those already present in the literature) to synthesise molecules we are interested in.

Prompted by these convictions a few years ago our research group successfully developed a new synthetic approach towards the synthesis of the carbon skeleton of the daphnane[1] and tigliane families of diterpenoid natural compounds. These compounds are characterised by the same tricyclo [9.3.0.$0^{2,7}$] tetradecane core [Fig. 1].



[9.3.0.$0^{2,7}$]tetradecane Tigliane Daphnane

Figure 1: Structure of the tigliane and daphnane families of natural compounds.

Because of their biological activity many of them are important tools in the study of several biological processes such as tumour-promotion, cardiovascular disease, AIDS, irritation, analgesia, tumour reduction and cystic fibrosis.[2] Two interesting examples [Fig. 2] are the daphnane RTX,[3] which displays analgesic and irritant properties, and phorbol, a compound belonging to the tigliane group, which has become, perhaps, one of the most important tools in the research about carcinogenesis.

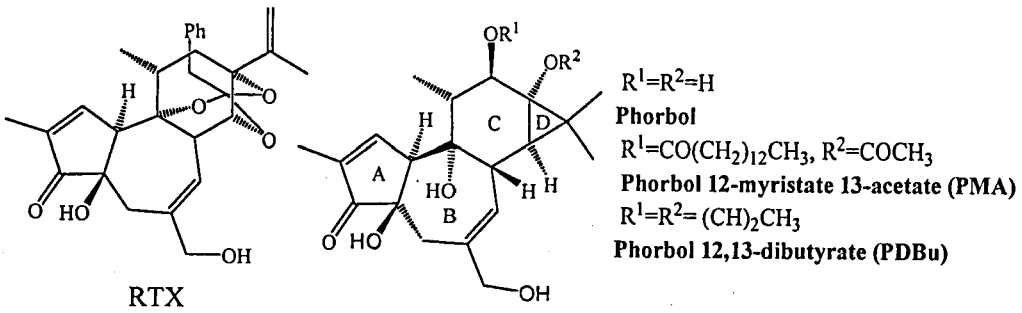


Figure 2: Structure of the daphnane RTX and of the tigliane phorbol with few of its more important derivatives.

The tigliane core is a tetracyclic structure formed of a *trans* hydroazulene ring (A, B rings) *trans*-fused, and a *gem*- dimethyl-cyclopropyl ring (D ring) *cis*-fused, to a cyclohexane ring (C ring). In 1934 phorbol was obtained by Bohm through hydrolysis of *Croton tiglium* oil.[4] Its structure was discovered in 1967 by X-ray crystallography,[5] which showed a molecule containing eight contiguous chiral centres, six of which are positioned on the six-membered C ring.

Plants make phorbol as 12,13-diesters and 12,13,20-triesters, which are very powerful cancer promoters (tetradodecanoyl phorbol acetate, PMA, is the most powerful co-carcinogen known, being active at about 0.02 μmol).[6] Phorbol esters have been used in a number of experiments, of which the target was the comprehension of tumour genesis mechanisms.[7] Much of what is known today about this area is thus due to phorbol. Phorbol and its derivatives are not, however, just tools; they also show very useful pharmaceutical activities: for example, Prostatin (12-deoxyphorbol acetate) shows protective properties in human lymphocytic cells infected with HIV-1.[8]

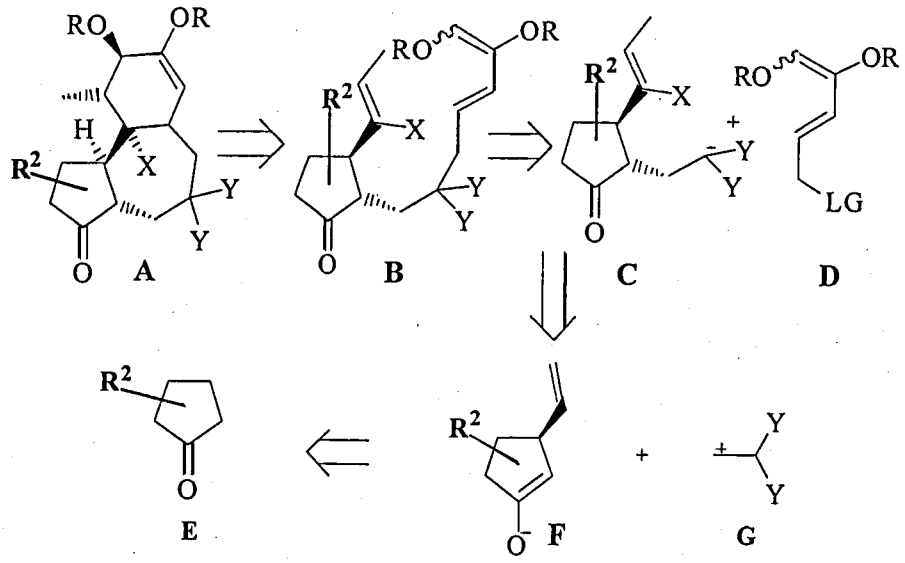
Because of its wide range of utilization it would be very advantageous if phorbol was available in large quantities so to perform more and cheaper experiments. Its availability from natural resources is today insufficient and this makes phorbol a very important synthetic target for organic chemists.

The first total synthesis of phorbol was reported by Wender in 1997,[9] a few years later he described even an enantiopure synthesis.[10] Several other researchers, Dauben,[11] Harwood,[12] Little,[13] McMills,[14] Rigby,[15] Shibasaki,[16] and of course Page,[17], are challenging this goal using different strategies, trying also to obtain related compounds, to understand much more about phorbol structure-activity

relationships, with the aim of the synthesis of a compound more simply available than phorbol but retaining all its useful properties.[18]

The synthetic path chosen by our research group has as its key step an intramolecular Diels-Alder (IMDA) reaction of a 1,8,10-triene, leading to the tigliane/daphnane *trans*- fused six/seven membered ring system **A**, that allows control of the stereochemistry of the stereocentres on the C ring.[55] This approach is made more interesting by the fact that the construction of bicyclo [5,4,0] undecane ring systems by IMDA reaction is rare, and so there is the possibility to investigate the stereocontrol of this methodology when applied to the synthesis of fused six-seven membered ring systems.

In order to maximise the overall yield and minimise the problems of cross-reaction connected with the synthesis of a medium sized molecule, the 1,8,10-triene **B** is obtained through convergent synthesis: diene **D** and dienophile **C** are realised separately and then joined together to obtain the Diels-Alder reaction substrate **B** [Scheme 1].



Scheme 1: Page approach to daphnane and tigliane families of natural compounds skeletons. Y= electron-withdrawing group.

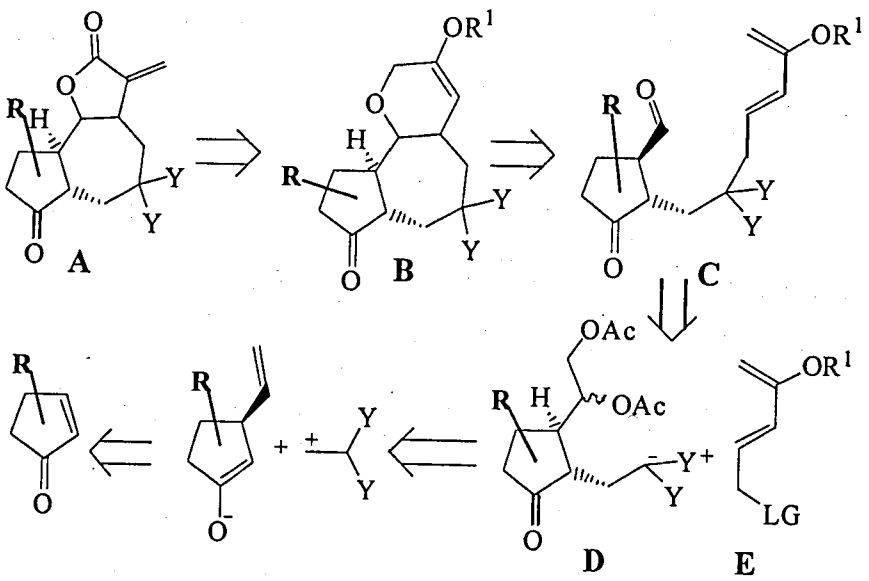
This approach is a good example of how the combination of a well known methodology (the IMDA reaction) and of a commonly used strategy (convergent synthesis), provides the opportunity to investigate a branch of the organic chemistry surprisingly poorly explored, in this case the IMDA reaction of 1,8,10 trienes.

In the same spirit, of not thinking about a new synthetic strategy merely as a cold sequence of chemical steps, but more as an opportunity to expand our knowledge of chemical reactions, the challenging task of opening the new research line regarding the synthesis of the guaianolide family of natural compounds skeleton, was begun.

2.2 Retrosynthetic studies towards the guaian-2,6-olide skeleton

Based on the background from the successful approach to the daphnane and tigliane families of natural compound skeletons, a retrosynthetic study of the guaianolide skeleton identified the possibility to investigate the poorly studied intramolecular hetero Diels-Alder (IMHDA) reaction of 1,8,10-heterotrienes.

As shown by our retrosynthetic solution in scheme 2, the γ-lactone ring of **A** might be obtained by conversion of the dihydropyrane ring of **B**, coming from the IMHDA reaction of the heterotrienes **C**, synthesised in turn by convergent synthesis through the coupling of the pro-heterodienophiles **D** with the dienes **E**.



Scheme 2: Retrosynthetic approach towards the guaianolide family of natural compounds skeleton. Y= electron-withdrawing group.

Analysing the retrosynthesis, at the first glance the similarity with that originally realised for daphnane and tigliane skeletons is very evident [scheme 1]. This highlights the versatility of the approach that would allow to access to the basic structure of three different families of natural compounds starting from similar and readily available chemical products.

The cornerstone of the synthesis of the guaianolide skeleton is the IMHDA reaction of 1,8,10-hetetrotrienes with an aldehyde as the dienophile, leading to a fused six-seven membered ring system characterised by the presence of a dihydropyran moiety. As far as we know, to date only a few examples of IMHDA reactions of this type of heterotrienes have been reported into the literature. This makes for us this area of research very fascinating and worthy of being explored while attempting to access the guaianolide skeleton.

The above mentioned heterotrienes **C** would in turn be synthesised by convergent synthesis through the Pd(0) catalysed allylation of the pro-heterodienophiles **D** with the pro-dienes **E** [scheme 2].

A convergent approach is very important because it makes the synthesis very flexible: if one step of the synthetic plan is unsuccessful, it is easier to find an alternative route to avoid the problem if it affects just a fraction and not the whole of the molecule.
In front of the several different functionalities present on our heterotriene, this procedure lowers the troubles connected with the regioselectivity of certain reactions and reduces the necessity of protecting specific functionalities because of their instability or reactivity during the synthetic process. Moreover, by this way it is easier to access to a wide range of members of the guaianolide family through the proper functionalisation of the two moieties.
Now it is time to introduce a bit of theory about the main methodologies that will be used to convert the retrosynthetic studies into a real synthetic process: the Pd(0) catalysed allylation of soft nucleophiles and the Intramolecular Hetero Diels-Alder (IMHDA) reaction.

2.3 Chemical background

2.3.1 Pd catalysed reactions[19]

2.3.1.1 Introduction

Palladium is one of the most important transition metals in organic synthesis, largely used as promoter or catalyst both in small laboratory scale and large industrial scale. Palladium provides many possibilities of interatomic bond formation (therefore it can be used with a wide range of substrates), tolerates the presence of functional groups such as hydroxy and carbonyl groups, and, finally, the efficiency of the palladium reagents is not affected very much by the presence in the reaction mixture of oxygen, moisture or acids. When dispersed on charcoal, palladium is used as heterogeneous catalyst in the hydrogenation of olefins, but it is mainly utilised in the homogeneous catalysis of bond formation reactions, employed as Pd(II) salts (stoichiometric reagents or catalysts) and Pd(0) complexes (catalysts). Palladium belongs to the VIIIB group with 10 valence electrons, and, as with all the elements, tends to be stabilised by reaching the 18 electron external shell of the closest noble gas (Xe). By sharing its empty 3d orbitals with lone pairs of electrons from any of several types of ligands (phosphines, carbonyl), it forms not only 18 but also 16 electron stable complexes that can be used as sources of Pd(0) and Pd(II) to be employed in organic reactions. The reactivity of the catalyst can be modulated by varying the ligands (mainly phosphines, figure 3), where electron and steric properties influence the behaviour of the catalyst not always in a predictable way.

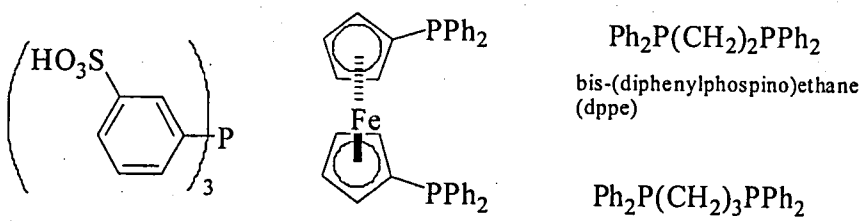


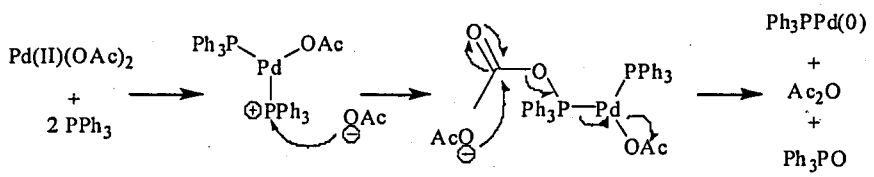
Figure 3: Different phosphines to be used as ligands of palladium.

Therefore, when optimising the conditions of a palladium-catalysed reaction, it is a good practice to test their suitability for the specific process. Tetrakis(triphenylphosphine)palladium(0), ($Pd(PPh_3)_4$) and tris(dibenzilidene-

acetone)dipalladium(0), (Pd_2dba_3) or the chloroform complex Pd_2dba_3•$CHCl_3$ (air stable), respectively 18 and 16 electron complexes, are the most common sources of Pd(0). Pd_2dba_3 is much less active, but more stable than phospine Pd(0) complexes such as $Pd(PPh_3)_4$. When mixed with Pd_2dba_3, phosphines displace the molecules of dba, producing *in situ* very reactive complexes. $PdCl_2$, even if relatively insoluble in most organic solvents, is a very useful source of Pd(II), because it is very stable and is easily converted into soluble 16 electron complexes such as $(MeCN)_2PdCl_2$, or the very air-stable bis(phosphine)palladium(II) chloride. Pd(II) species are mostly utilised as oxidants or to generate *in situ* Pd(0) complexes.

The application of Pd(II) as an oxidant is economically convenient only when it is possible to cheaply reoxidise the Pd(0) formed during the reaction, back to Pd(II). In the Wacker process for the production of acetaldehyde in industrial scale, the Pd(0) obtained during the process is oxidised by Cu(II), and the resulting Cu(I) is oxidised by oxygen. Therefore the synthesis of acetaldehyde is accomplished by using catalytic quantities of Pd(II) and Cu(II) with consumption of oxygen.

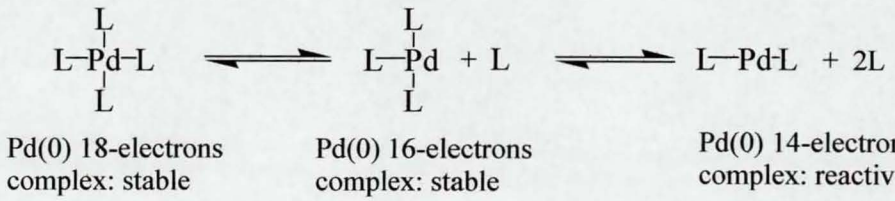
The oxidation process Pd(0)/Pd(II) is not always easy and it is very difficult to find the appropriate conditions to be used. This is why Pd(II) species are often employed in the *in situ* formation of Pd(0) complexes, reduced by phosphines, amines, alkenes and organometallics (DIBAL, *n*-buthyllithium or trialkyl aluminium species for example) [Scheme 3].



Scheme 3: Phosphines can reduce *in situ* Pd(II) to Pd(0) with formation of Pd(0) phosphine complexes and phosphine oxide.

Catalytic quantities of Pd(0) complexes make possible several important coupling reactions, such as the Heck[20], Stille, Sonogashira[21], and Suzuki[22] reactions and the allylation of nucleophiles. Probably the stable coordinatively saturated 18 electron complex, $Pd(0)L_4$ once in solution loses up to two units of ligand, forming the less stable and more reactive coordinatively unsaturated 14 electron $Pd(0)L_2$, which starts the catalytic cycle [Scheme 4]. Pd(0) catalysed allylation of nucleophiles is very

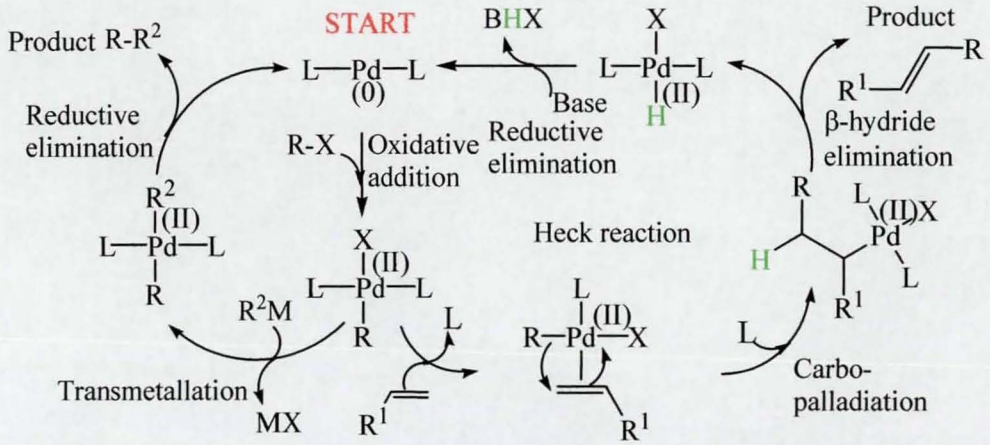
important for us because it is by this methodology that the two moieties of the IMHDA reaction substrate will be joined together, as shown in the next section.



Scheme 4: Equilibrium leading to the formation of the reactive species of Pd(0) catalysts.

2.3.1.2 The palladium(0) catalysed allylation of nucleophiles

Oxidative addition is a process that leads a general molecule X-Y to cleave its σ bond and to add to a transition metal whose formal oxidation number increases by two units because of the formation of two new σ bonds. Several σ bonds undergo oxidative addition to 14 electron Pd(0) complexes: halides of sp^2 carbons, acyl halides (RCO-X), aldehydes (RCO-H), allylic compounds (CH_2=CHCH-X, X= halogen, esters, carbonates, etc.), H-SnR_3, H-SiR_3, Ar-H, etc. Oxidative addition is the first step in many reactions catalysed by Pd(0). The newly formed organometallic product can react with several compounds, for example a double bond (carbometallation) as seen in the Heck reaction, or with a second organometallic species (transmetallation) as seen in Sonogashira or Suzuki reactions. Then, reductive elimination gives the final product of the coupling and regenerates the Pd(0) to start a new catalytic cycle [Scheme 5].

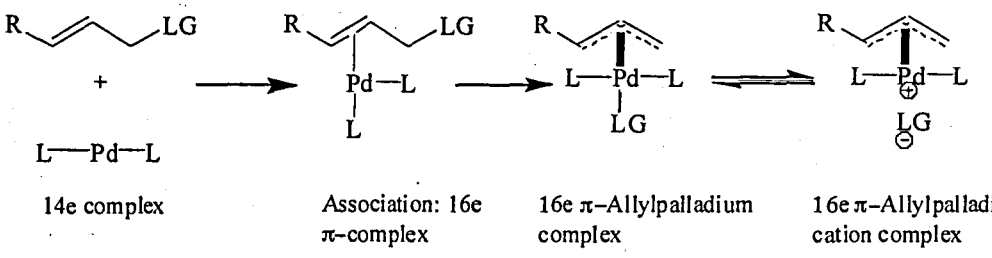


Scheme 5: Examples of Pd(0) catalytic cycles. The Heck reaction (right) and the cross coupling of organometallic and halides (left). X= halide or triflate, R^2M= organometallic species.

Carbopalladiation is the process by which organopalladium species add to double bonds: the olefin acts as a nucleophile, displacing the metal from the organic moiety, which in turn becomes attached to the less substituted end of the double bond [Scheme 5]. The newly formed organometallic species in the presence of β-hydrogens undergoes a very fast intramolecular β elimination (β-hydride elimination, a *syn* process) forming a new alkene, and a Pd(II) complex, which undergoes reductive elimination in the presence of a base to give a 14 electron Pd(0) complex [Scheme 5, right side].

In the transmetallation reaction [Scheme 5, left side], the organopalladium species exchange the counter ion X^- with the nucleophile (R^2) of a second organometallic reagent (R^2M) to form a new Pd(II) complex, $R^1R^2PdL_2$. This compex decomposes with a concerted *cis* mechanism to form $Pd(0)L_2$ and a new σ bond between R^1 and R^2 (reductive elimination).

Compounds with suitable leaving groups in the allylic position (LG= OAc, OCO_2R, $OPO(OR)_2$, OPh, Cl, Br) undergo oxidative addition to Pd(0) complexes to form stable 16 electron π-allylpalladium complexes. These π-allyl complexes exist as an equilibrium between the cationic form with the leaving group as the counter ion and the neutral form in which the previous leaving group is present as a ligand to the palladium [Scheme 6].



Scheme 6: Oxidative addition of allylic group to 14e Pd(0) complexes and formation of an electrophilic organopalladium species.

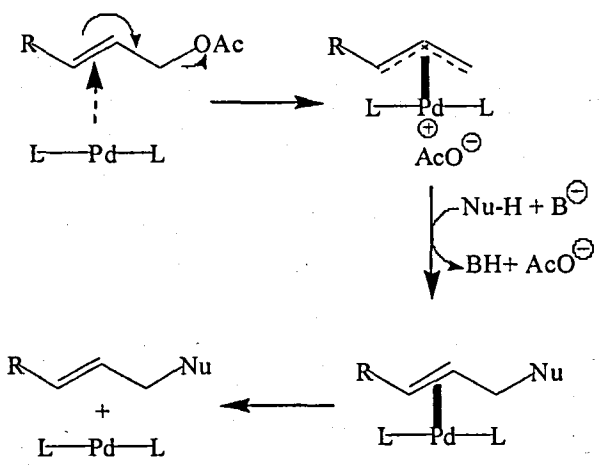
Although the organometallic compounds are considered nucleophilic, π-allylpalladium complexes are electrophilic and react with nucleophiles.

Very reactive (hard) nucleophiles, such as organometallics, add directly to the transition metal (transmetallation) forming a Pd(II) species with two organic groups, which undergoes reductive elimination.

In contrast, soft nucleophiles such as malonates, β-ketoesters and alkoxides attack directly on the allylic system displacing Pd(0) from the π-allylpalladium complex. The insertion of nucleophiles usually proceeds with high regioselectivity on the less substituted end of the allylic system to obtain the thermodynamically more stable regioisomer. [23]

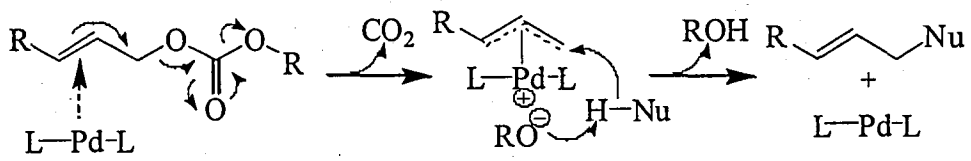
Depending on the nature of the leaving group, Pd(0) catalysed allylation of soft nucleophiles can be performed in basic or neutral conditions.

Oxidative addition of Pd to allylic acetates and phosphates is reversible and must be performed in basic conditions to activate the nucleophile by deprotonation [Scheme 7].



Scheme 7: Pd(0) catalysed allylation of soft nucleophile (Nu-H) under basic conditions.

Base sensitive compounds can react with the corresponding carbonate under neutral conditions [Scheme 8].



Scheme 8: The displacement of the carbonate generates the base that deprotonates the nucleophile. The allylation proceeds under neutral conditions.

The displacement of the leaving group generates CO_2 (the formation of this gas is the driving force of the reaction and makes the carbonate much more reactive than the

acetate derivatives) and an alkoxide ion, which is a base strong enough to activate the nucleophile but not nucleophilic enough to compete for the allylation.

2.3.2 The Intramolecular Hetero Diels-Alder (IMHDA) reaction

The key step of our approach towards the synthesis of the guaiane-6,12-olide skeleton is a intramolecular hetero-Diels-Alder reaction of 1,8,10-heterotrienes. In the next chapters an overview of the most important features of this process will be given.

2.3.2.1 Pericyclic reactions

A chemical reaction is defined as pericyclic when it occurs *via* a cyclic transition state where the electrons involved might be envisaged to move round a circle in a concerted manner.

There are three types of pericyclic reaction: cycloadditions, sigmatropic rearrangements and electrocyclic reactions [Fig. 4].

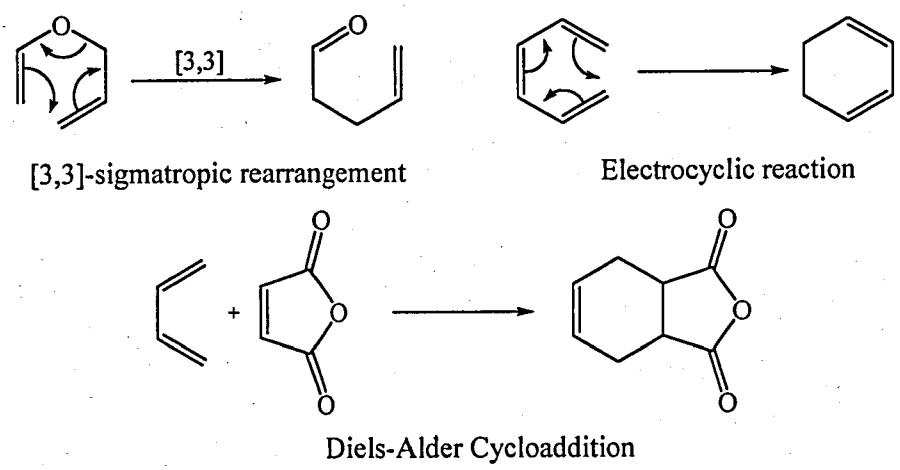


Figure 4: Some pericyclic reactions.

Among these, the Diels-Alder[24] reaction is the most frequently employed cycloaddition. Because of its stereospecifity and high stereo- and regioselectivity, it is

very useful to obtain a wide range of chiral six-membered ring systems. We can divide this cycloaddition into inter- and intramolecular reactions.

In an intermolecular reaction, the diene and dienophile functions are found in separate molecules, and their interaction is governed by steric and electronic factors, but in an intramolecular process, the two moieties are part of the same molecule and the cycloaddition process is mainly controlled by steric requirements.

2.3.2.2 The Diels-Alder reaction

In 1928 Diels and Alder reported the reaction of conjugated dienes with alkenes under thermal conditions, characterising the products obtained as well.[25] One century later, the Diels-Alder reaction has become one of the most important and well-used reactions in organic synthesis to build six-membered ring systems. In this reaction, a two π electron system bonds to a conjugated diene through positions one and four (1,4-cycloaddition). The Diels-Alder reaction is a $4\pi+2\pi$ reaction because four π electrons of the diene and two of the dienophile are involved in the bond formation.

Several types of compounds can react together as diene and dienophile to form a cycloadduct, as is generalised in figure 5 (each letter indicates the potential presence of a hetero-atom). Through the Diels-Alder reaction it is thus possible to obtain several types of six membered ring systems.[26]

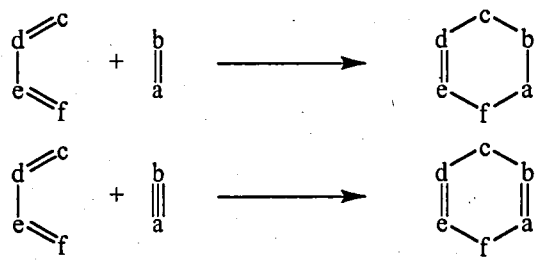
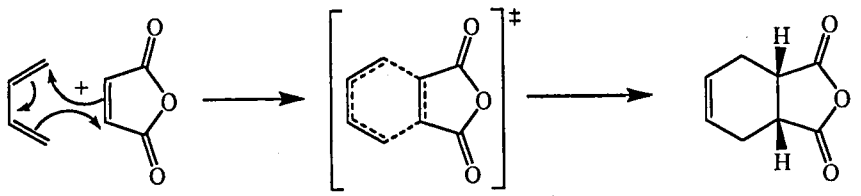


Figure 5: Different possible diene and dienophile systems.

A classic example of this is the reaction between 1,3-butadiene and maleic anhydride to give a fused two-ring system, where the stereochemistry at the ring junction is *cis*.[Scheme 9].



Diene Dienophile | Delocalised six π electrons transition state | Cycloadduct

Scheme 9: Example of Diels -Alder cycloaddition.

In this cycloaddition, a conjugated diene adds to an olefinic or acetylenic multiple bond (dienophile) through a delocalised six π electron transition state, to produce, in a single step, a six-membered ring system. Two σ and one π bonds are created and take the place of the three π bonds previously present in the reactants.

To explain the reactivity, stereospecifity, stereo- and regioselectivity of this reaction, we may consider the formation of bonds using frontier molecular orbital theory (F.M.O.).[27] From frontier molecular orbital theory we know that new bond formation occurs because of the interaction between the HOMO (Highest Occupied Molecular Orbital) of one reactant and the LUMO (Lowest Unoccupied Molecular Orbital) of the other reactant. In the case of the Diels-Alder reaction, the new σ bonds are formed between the atoms of the diene and dienophile that have the larger or smaller orbital coefficients, accounting for the regiochemistry and the regioselectivity of the reaction.

2.3.2.2.1 Reactivity

The success of the cycloaddition requires the diene to adopt a s-*cis* conformation (it can be open chain or cyclic, and have a wide range of substituents) because of the impossibility for the s-*trans* conformer to react with any double bond (and because the product would have an impossible *trans* double bond). Acyclic conjugated dienes are usually more stable as *transoid* conformers and to react they must revert into the *cisoid* conformer. Hence, cyclic conjugated dienes that are permanently in the s-*cis* conformation are often more reactive than the corresponding acyclic compounds [Fig. 6].

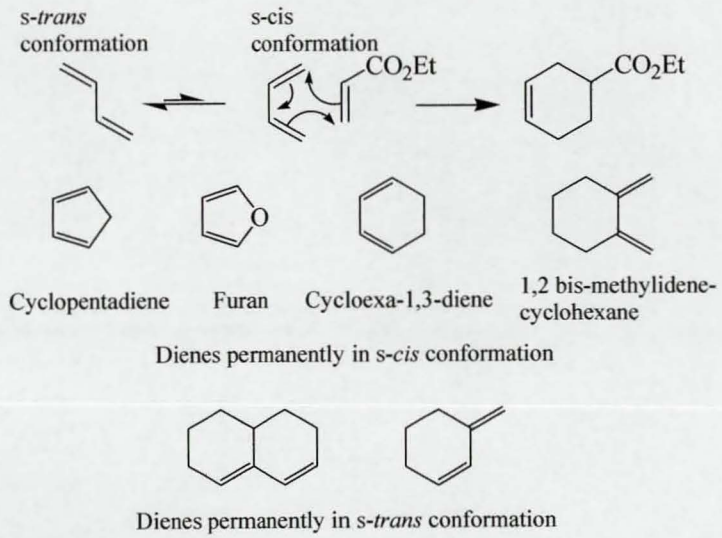


Figure 6: Different diene conformations.

Two different frontier orbitals can join together to form two new bonding molecular orbitals if they have the right symmetry and similar energy. The smaller the energy gap between them, the easier the formation of the new bond is, because the orbital overlap will be better. Between the two possible interactions, HOMO diene-LUMO dienophile and LUMO diene-HOMO dienophile, the first is favoured because of the typically smaller energy gap [Fig. 7].

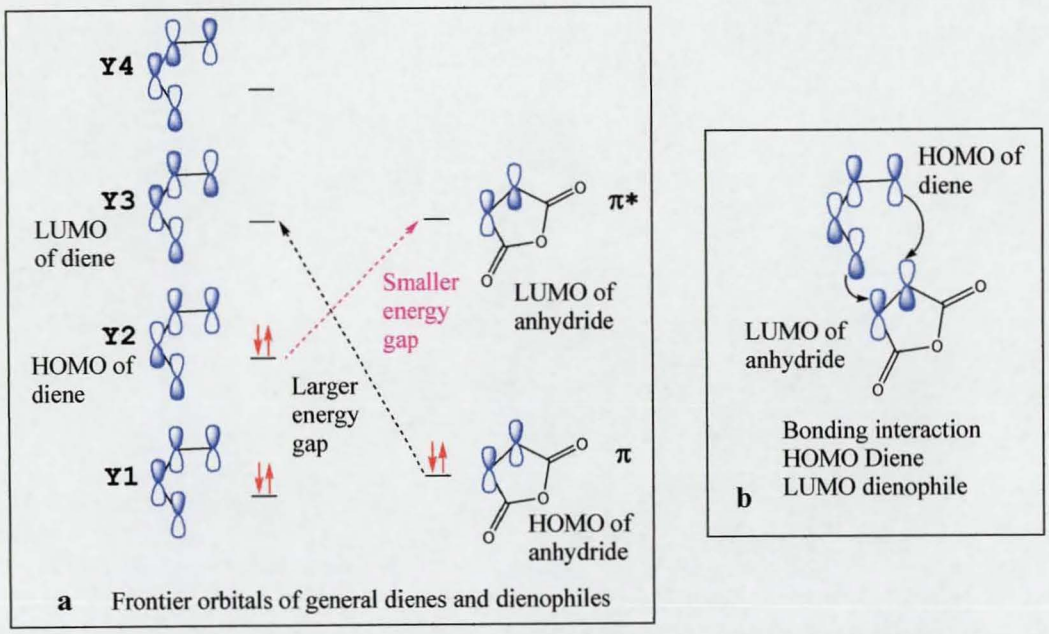


Figure 7:a) HOMO and LUMO orbitals of diene and dienophile; b) F. M. O. interaction.

The simplest Diels-Alder cycloaddition, between 1,3-butadiene and ethylene, does not occur (or occurs with a very low yield) because the dienophile is much less

reactive than when it is conjugated with an electron-withdrawing group, or even a double bond or a phenyl group. Such conjugation decreases the energy of the LUMO and therefore helps to decrease the HOMO-LUMO energy gap. In unsaturated carbonyl compounds, it is possible to obtain a further reduction of the LUMO energy level, and a larger differentiation between the atomic coefficients, using Lewis acid catalysis. The Lewis acid, coordinating to the carbonyl oxygen, acts as an electron withdrawing agent, so lowering the LUMO energy, reducing the electron density upon the β carbon and therefore increasing differentiation between the atomic coefficients of the α and the β carbon atoms of the unsaturated carbonyl system. This allows a higher regioselectivity in the cycloaddition reaction.

For the same reason, electron-donating groups increase the energy of the diene HOMO, thus facilitating the cycloaddition [Fig. 8].[28]

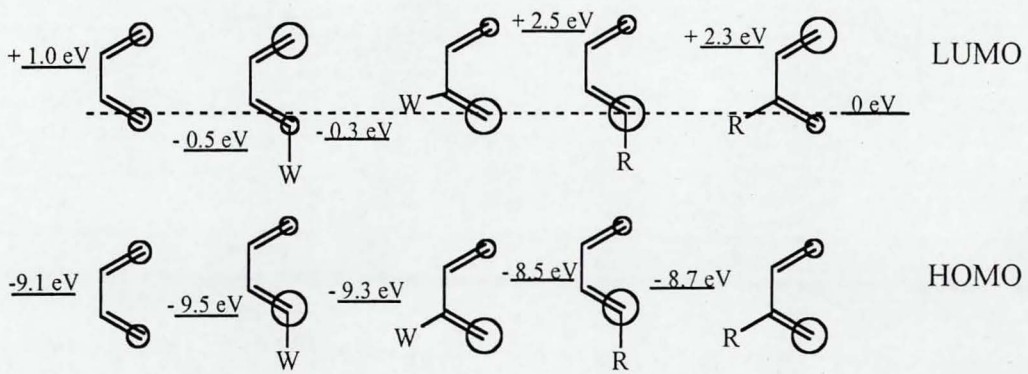
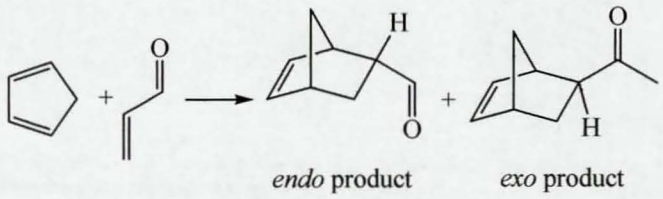


Figure 8: Dienes and F. M. O. energy level variation on the basis of different substitutions, W: electron withdrawing groups, R: electron donating groups; the dimension of the circles represents the relative orbital coefficient values.

2.3.2.2.2 Solvent

Solvent is not necessary for the reaction and often the reactants are just mixed together. Solvents are used when there is a need to dissolve the reactants, but solvent effects usually do not facilitate the reaction. It is interesting to note that adding water to an organic solvent can accelerate the reaction; furthermore, the Diels-Alder reaction of reactants that are not soluble in water is faster and more diastereoselective in water than in an organic solvent [Scheme 10] because the transition state is compressed.[29] Water can be also used as the solvent with water-soluble compounds.



Solvent	Relative rate	*endo/exo* ratio
isooctane	1	80/20
water	700	96/4

Scheme 10: Rate and diastereoselectivity in DA reaction of water-insoluble reactants in water.

2.3.2.2.3 Stereospecificity

The Diels-Alder cycloaddition is a concerted but non-synchronous process, where bond breaking and formation happens at the same time in a six π electron transition state, in which no configuration change is allowed. Hence, the stereochemistry of the diene and dienophile moieties determines the stereochemistry in the product [Fig. 9a, 9b]. The Diels-Alder reaction is thus a stereospecific process.

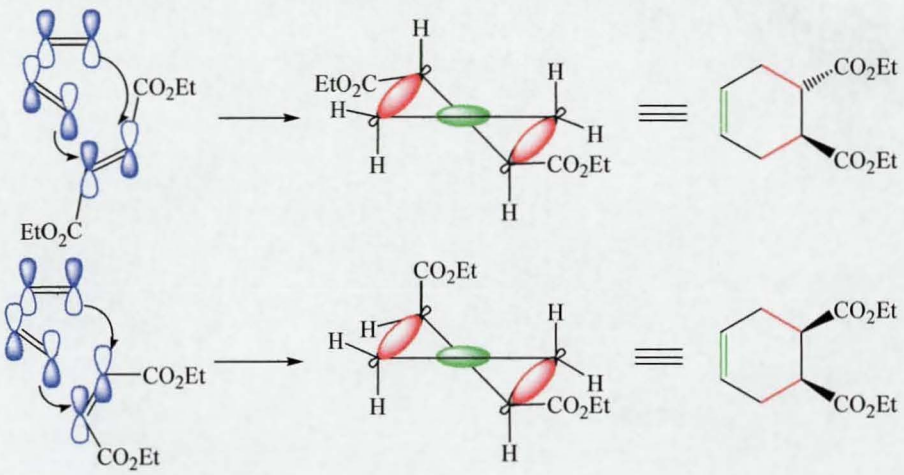


Figure 9a: Stereospecificity in dienophile moiety: dieophile substituents maintain their stereochemistry.

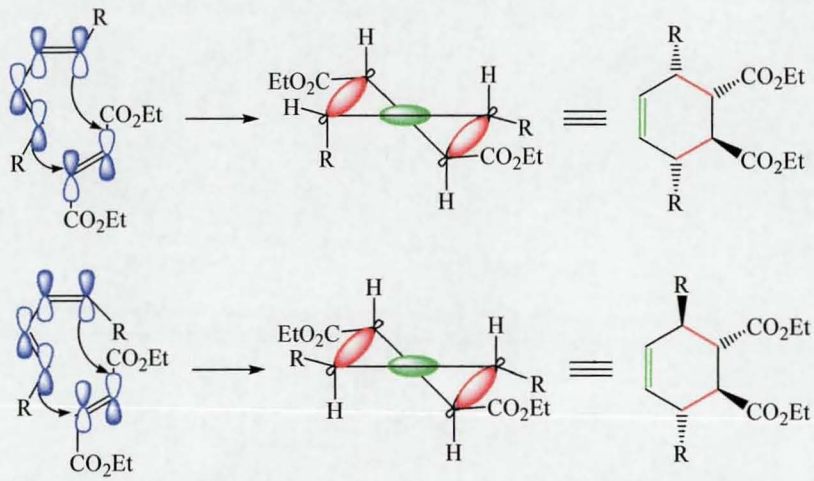


Figure 9b: Stereospecificity in diene moiety: diene substituents maintain their stereochemistry.

2.3.2.2.4 Stereoselectivity

The diene and dienophile approach each other from two different parallel planes allowing an optimal overlap between the π orbitals of the diene and dienophile, finally leading to the cycloadduct. Any other non-parallel approach would lead to very poor orbital overlap, through which the transition state would not be well stabilised [Fig. 10a]. Thus, in the transition state, the two reactants tend to be parallel, and the dienophile substituents may be oriented toward or outward from the diene single bond, giving the *endo* or *exo* diastereoisomeric adduct respectively [Fig. 10b].

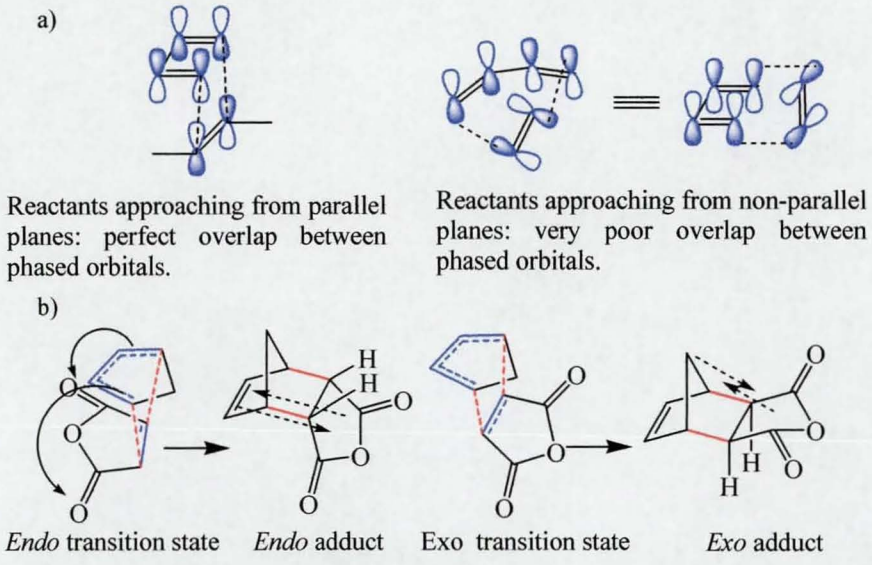


Figure 10: a) Orbital overlap in reactant's parallel and non-parallel approaches; b) Electronic and steric interactions in *endo* and *exo* transition states.

The *endo* adduct is usually favoured under kinetic conditions. This is due to π interaction between the π conjugated electron system of the diene and the π electrons of the dienophile activator groups (which are usually present). The two internal diene HOMO orbitals have the correct phase to interact with the two LUMO dienophile substituent orbitals. This interaction does not form any bonds, but it is very important in stabilising the *endo* transition state as opposed to the one formed from the *exo* approach. These kind of HOMO-LUMO interactions are also very important to compensate for the large negative entropies of activation, as they lead to an initial association between the two reacting molecules. The *exo* product is thermodynamically more stable, as it has less steric crowiding. As can be seen from figure 10b, in the *exo* product the single carbon bridge faces the dienophile moiety, whereas in the *endo* product it is the two carbon bridge facing the same moiety that generates more steric interaction. In some reversible Diels-Alder reactions, the kinetic product can be entirely converted into the thermodynamic one.

2.3.2.2.5 Regioselectivity

The Diels-Alder cycloaddition of asymmetric reactants is a concerted but not synchronous process, because the new bonds may not be formed to the same extent at the same time. Experimental evidence, and computer assisted calculations, demonstrated that, during the Diels-Alder reaction of non-symmetrical reactants, one new σ bond begins to be formed before the other, determining the regiochemistry of the reaction. Non-symmetrical substitutions generate a distortion in diene and dienophile frontier orbitals, with a differentiation between the orbital coefficients on each atom [Fig. 11].

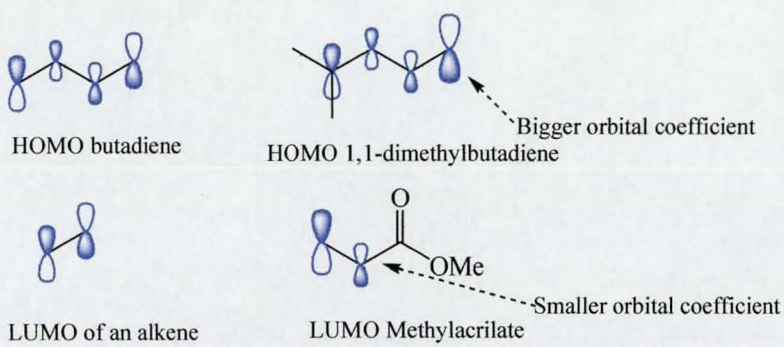
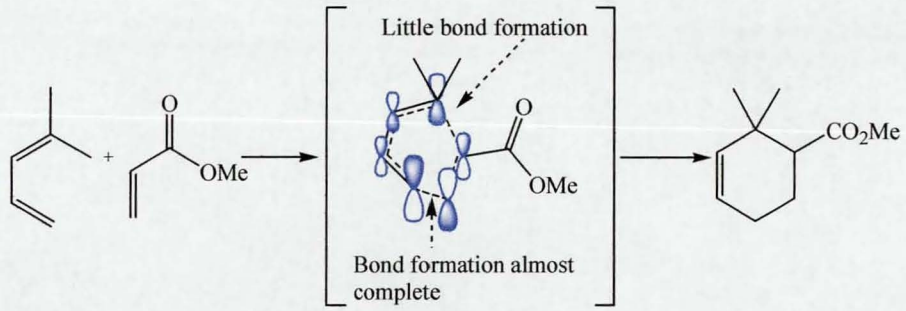


Figure 11: F.O. distortion in substituted dienes and dienophiles.

The two atoms that react first are those which have the larger orbital coefficients. The bigger the difference between the coefficients in the same orbital, the greater the regioselectivity; so it is (usually) possible to obtain, from unsymmetrically substituted reactants, one of the two possible regioisomers as the major product [Scheme 11].



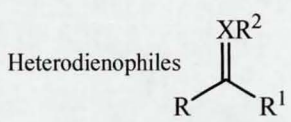
Scheme 11: Earlier interaction between bigger orbital coefficients brings regioselectivity in inter-molecular Diels-Alder cycloadditions.

2.3.2.3 The Hetero Diels-Alder (HDA) reaction[30]

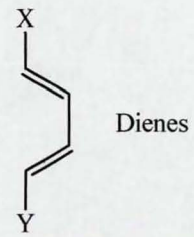
2.3.2.3.1 Introduction

The hetero Diels-Alder (HDA) reaction is a Diels-Alder reaction in which at least one of the atoms directly involved in the cycloaddition is a heteroatom (usually nitrogen, oxygen or sulphur). Aldehydes, ketones, imines (aza Diels-Alder reaction) and thioaldehydes have been found to be good dienophiles, and α,β-unsaturated carbonyl compounds have been found to be suitable dienes (inverse electron demand HDA) [Fig. 12a and 12b].

Substrates for normal electron demand HDA reaction:



Aldehydes: R=Generic organic substituent; R^1= H, X= O.
Ketones: R, R^1= Generic organic substituent; X= O.
Imines: R, R^1, R^2= Generic organic substituent; X= N.



X, Y: Electron donating groups.

Figure 12a: Reactants for normal electron demand HDA reactions.

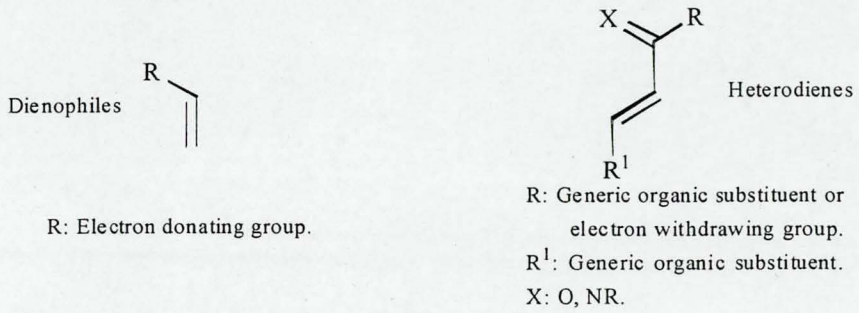


Figure 12b: Reactants for inverse electron demand HDA reactions.

The first HDA reaction of aldehydes was reported in 1949 by Gresham and Steadman: they used formaldehyde as a dienophile (heterodienophile) in a Diels-Alder reaction.[31]

The HDA reaction is today a powerful methodology to obtain in a single step six membered heterocyclic ring systems containing up to four new chiral centres, which are widely used as building blocks or as intermediates in the synthetic pathway to several biologically active compounds.[32]

In this chapter a brief overview of this interesting and useful reaction is described, focusing attention on the HDA reaction of non-activated aldehydes, which is an integral part of my project.

2.3.2.3.2 Mechanism

As in the all-carbon Diels-Alder reaction, the HDA reaction is governed by the interaction between the molecular orbitals of the reactants.[20(b-d)] According to MO theory, the closer the energy levels of the two interacting orbitals, the more efficient will be their overlap, and the lower will be the energy level of the corresponding transition state, leading to the formation of a new bond. Therefore, in the case of the HDA reaction, the success of the cycloaddition between two given reactants depends on the energy gap between their MOs.

If no heteroatom is present in the diene, the energy gap $HOMO_{diene}$/ $LUMO_{heterodienophile}$ is smaller than the $HOMO_{heterodienophile}/LUMO_{diene}$ one (as in the all-carbon DA reaction) and the cycloaddition results from the interaction $HOMO_{diene}$ $/LUMO_{heterodienophile}$ (normal electron demand HDA). If an α,β-unsaturated carbonyl compound is the heterodiene, the smallest energy gap will be between $HOMO_{dienophile}/LUMO_{heterodiene}$ (inverse electron demand HDA). It is therefore possible to enhance the feasibility of a HDA reaction by reducing the energy gap between the involved MOs; in other words, increasing the reactivity of the reactants.

In a normal electron demand HDA reaction, the diene is activated by electron donating-groups, which increase the energy level of the HOMO, and the heterodienophile is activated by the presence of an electron-withdrawing group, which decrease the energy of the LUMO.

Conversely, in an inverse electron demand HDA reaction, the heterodiene and the dienophile are activated by electron-withdrawing and electron-releasing groups respectively.

Activation of the reagents can also be achieved using Lewis acid catalysis. Lewis acids are able to bind to the heterodiene's or the heterodienophile's heteroatom, lowering the LUMO energy: the energy gap between the HOMO and the LUMO is thus bigger under non-catalysed conditions than under catalysed conditions [Fig. 13].[20(b-d)]

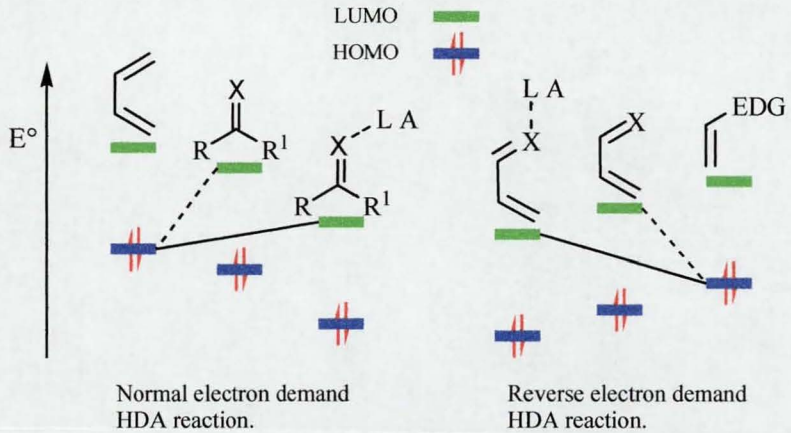
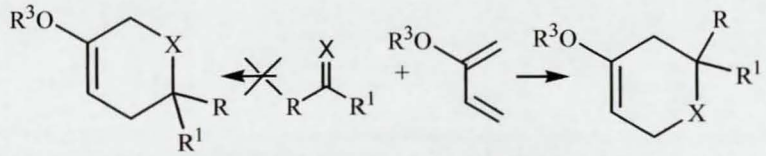


Figure 13: HOMO/LUMO energetic levels variation in Lewis acids catalysed HDA reactions. X= O, N, S; R, R^1= generic organic substituent; EDG= electron-withdrawing group.

Similarly to the DA reaction, the HDA reaction is regio- and diastereoselective. According to the FMO theory, of the two new bonds, one is formed between the two

atoms which have the biggest atomic orbital coefficients and one between the two which have the smallest atomic orbital coefficients, giving complete regioselectivity [Scheme 12].[33]



Aldehydes: R: Generic organic substituent; R^1= H,; X= O.
Ketones: R, R^1: Generic organic substituent; X= O.
Imines: R, R^1, R^2, R^3: Generic organic substituent; X= NR^2.

Scheme 12: Regioselectivity in HDA reactions.

The thermal HDA reaction is restricted to activated aldehydes. The thermal and high-pressure process usually gives the *endo* cycloadduct as the major product [Fig. 14].[34]

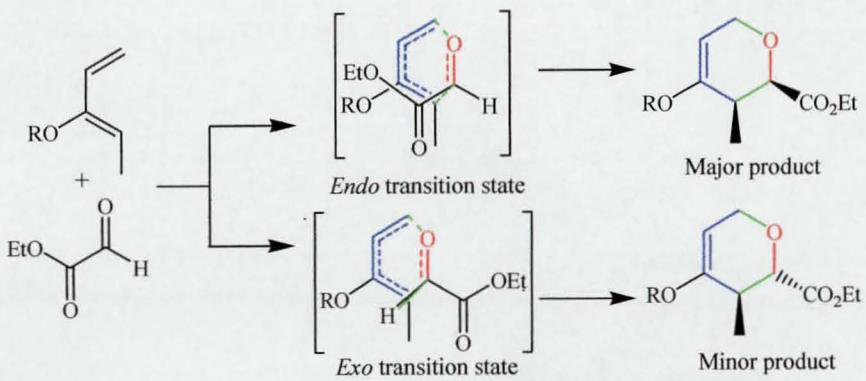
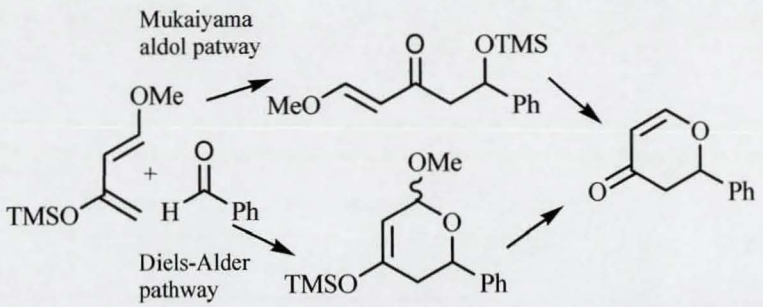
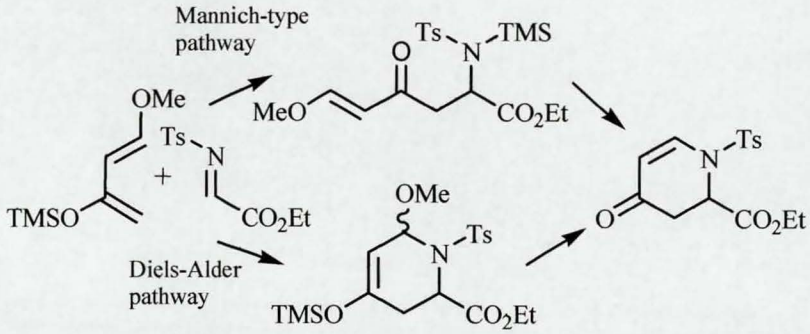


Figure 14: Diastereoselectivity in thermal and high-pressure HDA reactions.

On the basis of experimental and theoretical evidences, two different mechanisms have to be taken into account to justify the outcome of the catalysed HDA reaction: a classical concerted DA cycloaddition, and a stepwise pathway which goes through the cyclocondensation of a Mukaiyama-aldol reaction intermediate in the case of a carbonyl compound [Scheme 13], or a Mannich-type reaction intermediate in the case of imines [Scheme 14].[14b]



Scheme 13: Different possible pathways in HDA reactions of aldehydes.



Scheme 14: Different possible pathways in HDA reactions of imines.

In the case of catalysed reactions, the stereochemical outcome depends on the balance between the steric demand of the catalyst (which is expected to be *trans* to the substituent on the aldehyde) and the steric demand of the substituent α to the carbonyl. The biggest group will preferentially be *exo* with respect to the diene [Fig. 15].[35]

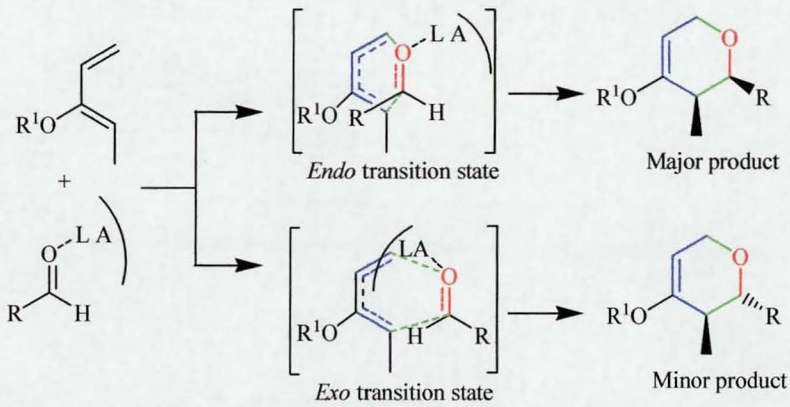


Figure 15: Diastereoselectivity in Lewis acid catalysed HDA reaction: when the steric demand of the Lewis acid is bigger than that of the substituent α to the aldehyde, the *endo* approach is preferred over the *exo*.

The final outcome of HDA reactions depends on many factors such as the chemical properties of the reactants, the catalyst employed, and the reaction conditions.

The substitution pattern of the diene is fundamental because different silyloxy groups can induce different diastereoselectivities, which may indicate the different pathways followed by the reaction. Solvent plays a key role as well, modulating the coordinating power of the Lewis acids and stabilising one of the two possible transition states.

The mechanism of the reaction of non-activated aldehydes with activated dienes is discussed below, distinguishing between non-Lewis acid catalysed reactions, and Lewis acid catalysed reactions.

2.3.2.3.3 Non-Lewis acid catalysed HDA reactions

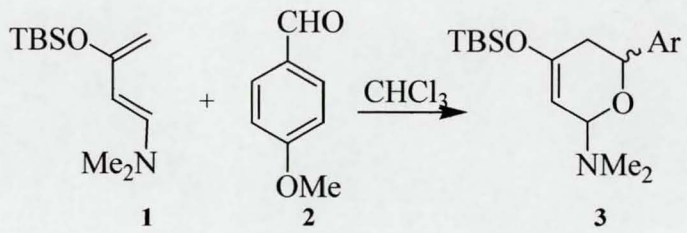
Under thermal and high-pressure conditions the reaction appears to occur by a concerted pathway.[17,36]

Non-activated aldehydes do not react as heterodienophiles in thermal HDA reactions, even using highly activated dienes. The energy gap between the $HOMO_{diene}$/ $LUMO_{heterodienophile}$ is too large, and only highly reactive aldehydes (such as glyoxaldehyde), activated by strong electron-withdrawing groups (which lower the $LUMO_{heterodienophile}$ energy level toward the $HOMO_{diene}$), can take part in the reaction under these conditions.

The reaction of highly activated (by electron-donating groups) dienes (such as 1,1-dimethoxy-3-silyloxy-1,3-butadiene, Danishefsky's diene), with unactivated aldehydes is usually unsuccessful in the absence of catalyst, and activated aldehydes are still required in order to obtain the cycloadduct (though at lower temperatures).[37]

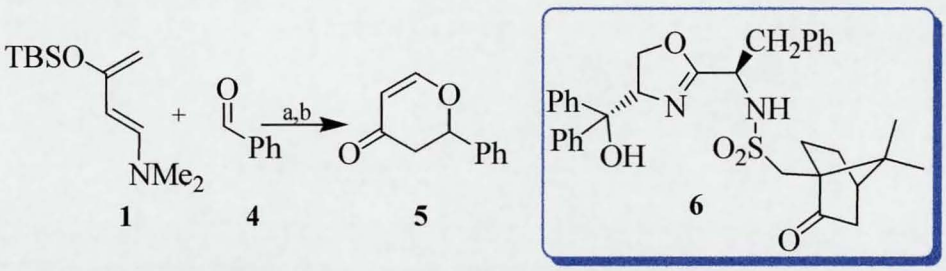
The use of activated aldehydes under thermal conditions can be avoided by performing the cycloaddition under high-pressure (15-25 Kbar) conditions: *endo* cycloadducts are usually the main compounds obtained, and a wide range of aliphatic and aromatic aldehydes has been used.[19(c,d)]

A hydrogen-bond (HB) promoted hetero-Diels-Alder reaction of unactivated aldehydes and ketones was reported in 2002 by Huang and Rawal:[38] the reaction between 1-amino-3-silyloxy-1,3-butadiene (**1**) and *p*-anisaldehyde (**2**) in chloroform gave the dihydropyrane derivative **3**. It was suggested that the hydrogen bond between the proton of the solvent and the carbonyl group would be able to make the aldehyde electrophilic enough to undergo the Diels-Alder cyclisation without the support of any acidic catalysis [Scheme 15].



Scheme 15: Hetero Diels-Alder reaction of unactivated aldehyde promoted by hydrogen bonding with the solvent.

Inspired by this discovery, Sigman and co-workers developed a new class of oxazoline-based hydrogen bond catalysts (such as **6**) designed for enantioselective HDA reactions [Scheme 16].[39] They reported the HDA reaction using electron poor aromatic aldehydes in good yield and high degree of enantioselectivity. Electron rich aromatic aldehydes needed higher temperatures to achieve moderate yields.



Scheme 16: a) 20 mol % catalyst **6**, toluene, –55 °C, 2 days; b) CH_3COCl, DCM, -78 °C, 62% (2 steps), 90% ee.

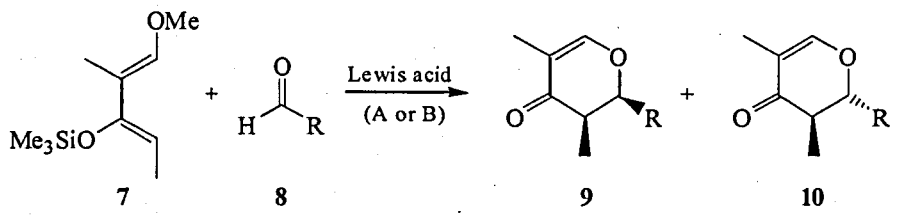
2.3.2.3.4 Lewis Acid catalysed HDA reaction

The use of Lewis acids as catalysts has provided a fundamental improvement in the evolution of the HDA reaction because it has opened the way to the use of a wide range of unactivated aldehydes as heterodienophiles, and has therefore enabled access to a large number of new organic compounds.

2.3.2.3.4.1 Zinc chloride and boron trifluoride etherate

In 1982 Danishefsky reported the first detailed study of the HDA reaction between oxygenated dienes (such as **7**) and unactivated aldehydes (**8**) under $ZnCl_2$ catalysis,[40] and in the same year published a further study in which $BF_3 \cdot Et_2O$ was used as

catalyst.[41] Both Lewis acids were able to catalyse the cycloaddition but with different diastereoselectivities [Scheme 17].



7 8 9 10

R	Method	9 yield (%)	10 yield (%)
C_5H_{11}	A (BF_3•Et_2O -CH_2Cl_2,, -78 °C; TFA)	21	69
	B ($ZnCl_2$-THF, 25 °C; $NaHCO_3$; TFA)	91	2
Ph	A	23	68
	B	78	2
$Ph(CH_2)_3$	A	17	64
	B	83	2
$BnOCH_2$	A	17	68
	B	66	24

Scheme 17: HDA reactions of aldehydes using BF_3•Et_2O and $ZnCl_2$ catalysis.

As shown in scheme 17, the use of $ZnCl_2$ catalysis in tetrahydrofuran provides mainly the *cis* dihydropyrones **9**; however, when BF_3•Et_2O is used in dichloromethane as solvent, the *trans* dihydropyrones **10** are the main products.

According to the authors, the *cis* stereochemistry is consistent with a concerted DA reaction pathway: the catalyst/solvent complex is expected to be *anti* to the substituent of the aldehyde, and, if its steric demand is bigger than that of the side chain of the aldehyde, it will be orientated *exo* to the diene, leading to an *endo/cis* cycloadduct. The authors also suggest that when the HDA reaction is performed with BF_3•Et_2O as the catalyst in dichloromethane, the reaction goes through the stepwise aldol path which allows a high *trans* stereoselectivity in the synthesis of the dihydropyrone.

Under these conditions, alongside the major *trans* dihydropyrone product, it is possible to isolate the products of the aldol reaction between the diene and the aldehyde, the β-hydroxy or the β-silyloxy-methoxy enones, which cyclise into the *trans* dihydropyrone when treated with TFA.

The reaction conditions and the structure of the diene influence the outcome of the reaction as well. The concerted pathway is favoured when the diene is in a stable *s-cis* conformation. The number and dimension of the substituents can obviously drive the *s-cis/s-trans* equilibrium toward one of the two conformations, favouring one of the two possible pathways (concerted or stepwise). For example, the *s-cis* conformation is favoured in the TBDMS-butadiene compared to the TMS-butadiene because of a bigger trialkilsilyloxy group which interacts with the terminal double bond, driving it towards the s-*cis* conformation [Fig. 16].[42]

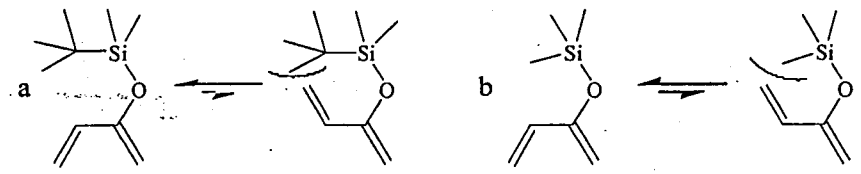
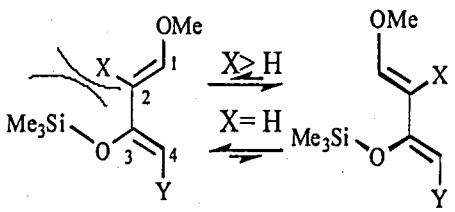


Figure 16: Bulky diene substituents drive the dienes towards the s-*cis* conformation.

BF_3•Et_2O catalysed HDA reactions of multi-substituted dienes are especially sensitive: the choice of silyloxy ligand can drive the diene toward a *s-cis* or a *s-trans* conformation, making possible or impossible the pericyclic pathway [Fig. 17].[23]



X, Y: Generic organic substituents.

Figure 17: The conformation of the diene depends on the size of its substituents.

As shown in figure 17, when the substituent in position 2 is bigger than a proton, the equilibrium is in favour of the *s-trans* conformation (because of the steric repulsion between the bulky silyloxy group and the substituent in position 2), which does not alllow a pericyclic transition state, and drives the reaction towards a Mukaiyama-aldol pathway giving *trans* cyclocondensation compounds; if in position 2 there is just a proton, the reaction seems to prefer a concerted pathway. Furthermore, pericyclic products are obtained in BF_3•Et_2O catalysed reactions using Et_2O (BF_3•Et_2O in Et_2O is a milder Lewis acid than in dichloromethane) or toluene as solvent.[43]

2.3.2.3.4.2 Magnesium bromide and titanium tetrachloride

If a heteroatom bearing a lone pair is present as a substituent at the α or β carbon of the heterodienophiles, Lewis acid catalysts such as $MgBr_2$ and $TiCl_4$ will form a complex in which the catalyst and the substituent are *syn*: the *endo* approach is then disfavoured due to steric interactions [Figure 18].

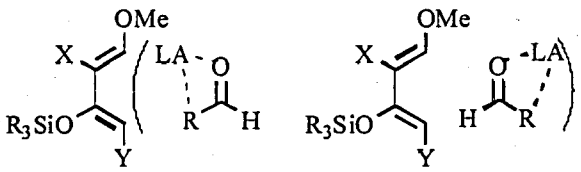
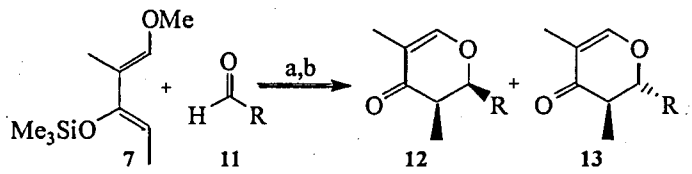


Figure 18: Chelation control in Lewis acid-catalysed HDA reactions.

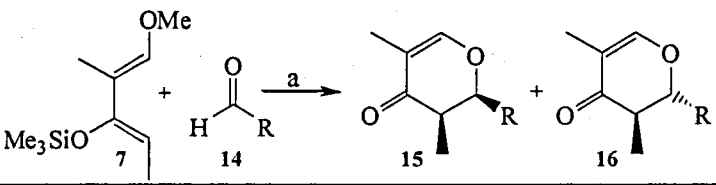
Therefore, the diastereoselectivity obtained is opposite to that obtained with non-chelating heterodienophiles. For example, using $MgBr_2$ as a catalyst, the HDA reaction of chelating aldehydes (R= $BnOCH_2$-) gives preferentially *exo* products **13** through a pericyclic cycloaddition; when non-chelating aldehydes (R= Ph-) are used, opposite diastereoselectivity is obtained and the *endo* products are preferentially formed [Scheme 18].[44]



R	*Endo (cis) %*	*Exo (trans) %*
Ph	38	1
$BnOCH_2$	<1	>99
BnOCHMe	<1	>99

Scheme 18: HDA reactions under $MgBr_2$ catalysed conditions: a) $MgBr_2$, THF; b) H^+.

Danishefsky reported the formation of *cis* compounds **15** using $TiCl_4$ as catalyst [Scheme 19];[45] according to studies by Mukaiyama and Reetz, the mechanism is thought to be stepwise.[46]



R	*Cis %*	*Trans %*
Ph	1	8
CH(Me)OBn	>99	<1

Scheme 19: HDA reactions under $TiCl_4$ catalysed conditions: a) $TiCl_4$, THF, then H^+.

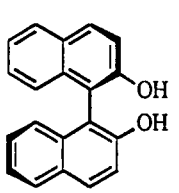
2.3.2.3.4.3 Lanthanide catalysts

Lanthanide(III) complexes (such as $Eu(fod)_3$, $Yb(OTf)_3$,) are very good catalysts for HDA reactions, affording good yields and stereoselectivity. Introduced by Danishefsky in 1983,[47] they are mild Lewis acids, strong enough to activate the heterodienophiles without any desilylation of the cycloadduct, which can be isolated in good yields. They promote a concerted pathway and an *endo* approach toward the diene (they coordinate to the lone pair of the aldehyde *anti* to the substituent of the aldehyde, forcing it to be *endo* to the diene in the transition state, in order to minimise the steric repulsions),[48] but because of their large steric hindrance, the diastereoselectivity observed is greater than that observed with the smaller $ZnCl_2$ or $MgBr_2$. A substituent in the position 2 of the diene will increase the *endo*-selectivity, leading to a stronger steric interaction with the catalyst in the *exo* approach.

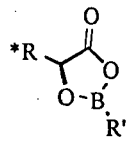
Because of their mildness, lanthanide complexes have been reported to catalyse HDA reactions of acid-sensitive highly oxygenated dienes such as 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene.[49] Lanthanide complexes have also been reported to improve the reactivity of 1-methoxy-1,3-butadiene with aldehydes under high pressure conditions, whereas the use of classical catalysts such as $ZnCl_2$ or $BF_3 \cdot Et_2O$ failed.[50]

2.3.2.3.4.4 Chiral Lewis acids

Chiral Lewis acid catalysts can allow one to perform highly enantioselective HDA reactions and so allow the preparation of non-racemic chiral molecules. These catalysts can be complexes between chiral bulky ligands (such as BINOL and its derivatives or H_2salen (bis(salicyliden)ethylenediamine) and Lewis acids (such as Al(III), B(III) and lanthanide(III) derivatives), or chiral organic molecules including a metal atom, as in the case with the chiral acycloxyborane catalysts (CAB) [Figure 18].

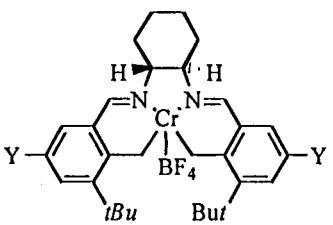


[1,1']Binaphthalenyl-2,2'-diol (BINOL)



R*=chiral substituent

Acyloxyborane (CAB)

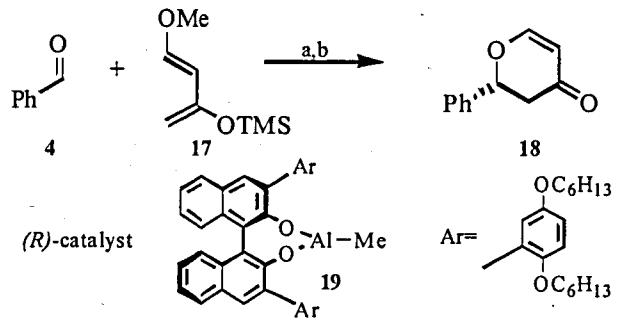


bis(salicyliden)ethylenediamine (H_2salen)

Figure 18: Chiral ligands and molecules for HDA chiral catalysed reactions.

If we consider a normal electron demand HDA reaction, the chiral organic molecule creates an asymmetric environment around the metal and therefore around any heterodienophile that is associated with it. For any subsequent reaction there will then be two diastereomeric transition states, one of which will be of lower energy and so preferred over the other. It is therefore possible to realise highly enantioselective cycloadditions no matter which reaction pathway is followed.

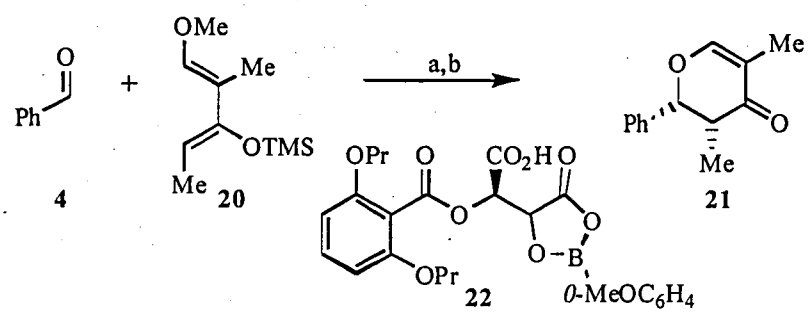
BINOL-AlMe complexes[51] have been reported to catalyse the stepwise cycloaddition between Danishefsky-type dienes (such as **17**) and benzaldehyde (**4**), affording cycloadducts such as **18** with up to 97% yield and 99% *ee* [Scheme 20].[52]



Scheme 20: Diastereoselectivity in HDA reactions catalysed by BINOL-AlMe complex **19**: a) **19** 10 mol %; 2) TFA, 97% yield, 99% *ee*.

Theoretical investigation of the reaction shown in scheme 20, have suggested that the non-catalytic process probably occurs through a concerted pathway, while for the aluminium catalysed reaction a two steps mechanism have been proposed.[51]

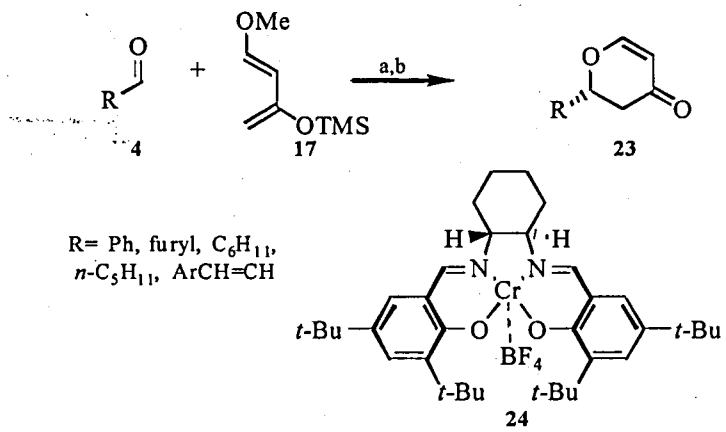
Chiral acyloxyborane catalysts (such as **22**)[53] (which are air and moisture stable) have been shown to catalyse HDA reaction of aldehydes and Danishefsky-type dienes **20** with up to 95% yield and 97% *ee* [Scheme 21].[34(a,b)]



Scheme 21: Chiral acyloxyboranes as catalyst in asymmetric HDA reactions: a) catalyst 20%; b) TFA, 95% yield, 97% ee.

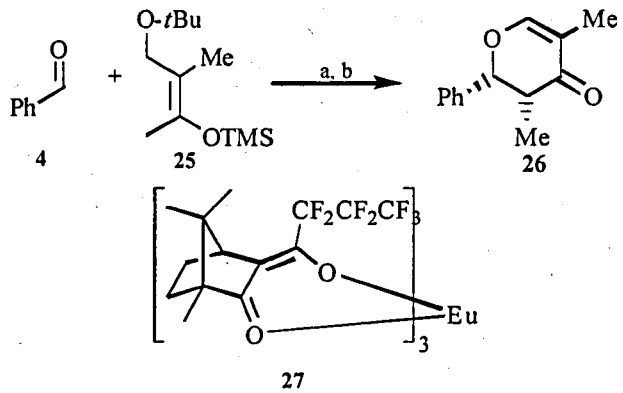
BINOL-Ti(IV) complexes catalyse only the aldol addition of dienes to aldehydes, but it is then possible to obtain the desired cycloadducts in good yield and enantioselectivity by treating the product mixture with TFA.[54]

Chiral H_2 salen-chromium(III) complexes **24** have been reported to catalyse efficiently the pericyclic HDA reaction of Danishefsky's diene **17** with aliphatic, aromatic and conjugated aldehydes **17** [Scheme 22].[55]



Scheme 22: Chiral H_2 salen **24** as catalyst in asymmetric HDA reactions: a) **24**, 2 mol %; b) TFA, 65-92% yields, 70-96% *ee*.

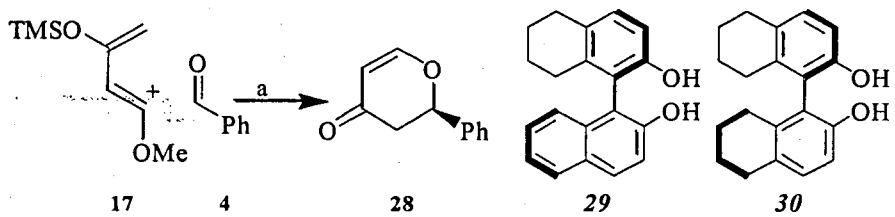
Lanthanide(III) complexes have been used successfully as catalysts in HDA reactions: $Eu(hfc)_3$ (hfc= 3-(heptafluoro-propylhydroxymethylene)camphorate) **27** is able to catalyse the cycloaddition of benzaldehyde with activated dienes **25**, giving up to 58% *ee* in $CHCl_3$ as solvent [Scheme 23].[56]



Scheme 23: Chiral Eu complex as catalyst in asymmetric HDA reactions: a) **27** 10 mol %;b) TFA, 58% *ee*.

Ding studied the properties of a combinatorial library of titanium(IV) complexes as catalysts in the HDA reaction of Danishefsky's diene with aldehydes.[57]

By combining thirteen BINOL derivatives as **L**igands (**L*m*** and **L*n***) with $Ti(O^iPr)_4$, a library of 103 complexes **L*m*/Ti/L*n*** was generated. Among the ligands tested, compounds ***29*** and ***30*** conferred to the catalytic complexes **L*29*/Ti/L*29*** and **L*29*/Ti/L*30*** the best properties as regard the reaction time, amount of catalyst loaded, yield and enantioselectivity. The catalysts were also very efficient when the reactions were carried out on a gram scale and under solvent-free conditions [Scheme 24].



17 4 28 *29* *30*

Scheme 24: Enantioselective HDA reaction catalysed by Ti(IV) chiral complexes. a) solvent-free conditions, catalyst **L*29*/Ti/L*29*** 0.05%, room temperature, 24 hours, then quench with CF_3COOH, >99%, 99.3% ee.

2.3.2.4 Intramolecular Hetero Diels-Alder (IMHDA) reaction

Because the IMHDA reaction of heterotrienes carrying an aldehyde as the dienophile has not been deeply explored, the IMDA reaction will be taken as an example to explain the main features of the cyclisation process. For an IMDA reaction to take place, a conjugated diene and a double or triple bond must be in the same molecule, separated at least by a three atom chain, (long enough to form a relatively unstrained bridged or fused ring system). There are six possible arrangements for trienes to cyclise, on the basis of diene structure and of linking chain length [Fig. 19][58]:

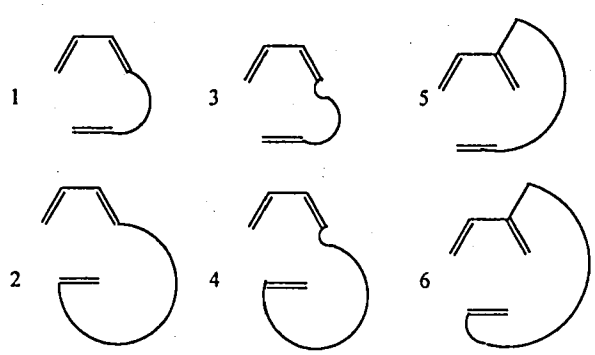


Figure 19: Different trienes in intramolecular Diels-Alder cycloaddition.

E-trienes (referred to the *E* configuration of the internal double bond of the diene) can cyclise through mode 1 and 2, but through mode 2 only if they have a link chain longer than four atoms; *Z*-trienes (referred to the *Z* configuration of the internal double bond of the diene) can react by modes 3 and 4, and the ratio depends on many factors; trienes where the bridging chain begins from position 2 or 3 of the diene give bridged compounds, through modes 5 and 6.
From this we can easily understand how important steric considerations are; and how non-bonding interactions are important in the various diastereoisomeric transition states. Diene and dienophile are present in the same molecule, and therefore through-space electronic interactions, very important in intermolecular processes to hold the reacting moieties together, are now less significant.

With respect to the bimolecular reaction, the reactivity is enhanced because of the favourable entropic effect of medium-size ring closure, while the *endo* adduct is not always preferred to the *exo* under kinetic conditions because the transition state stability is no longer determined largely by electronic effects, but also by steric factors. Substituents on the tether chain that can bring together the two reactant moieties, (such as a geminal substitution) can increase the rate of the reaction. Regioselectivity is no longer ruled only by atomic coefficients, and so it is possible to obtain compounds with regiochemistry that would be impossible to obtain in intermolecular reactions.

If the bonding between the atoms that have the bigger atomic coefficients results in an adduct that is too strained, the two σ new bonds occur between atoms where atomic coefficients are not the largest. In the transition state, the first bond-making that takes place is often the one that better stabilises the whole structure. This bond is more advanced than the other, and so determines the final regio-and stereoselectivity through an unsymmetrical transition state.[59] But, as the transition state is still pseudoaromatic and concerted (but not synchronous), the stereospecifity is maintained [Fig. 20].

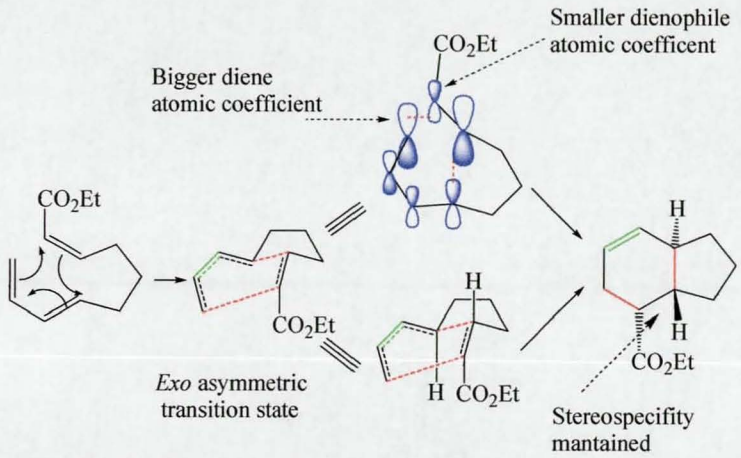
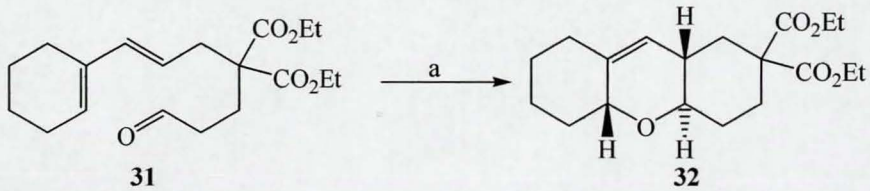


Figure 20: Regioselectivity in IMDA reactions: an asymmetric transition state allows the reaction of two carbon atoms with wrong orbital coefficients.

While the bimolecular hetero Diels-Alder reaction of carbonyl dienophiles has been widely developed and today is a frequently employed in organic synthesis, this has not happened with the corresponding intramolecular process. Surprisingly, the literature reports few examples of intramolecular carbonyl Diels-Alder reactions.

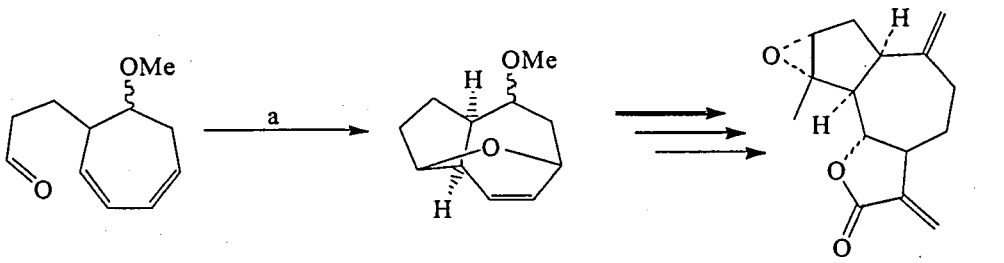
Trost in 1984 reported the convergent synthesis of a 1,7,9-heterotriene **31** that cyclised at room temperature under Lewis acid catalysed conditions to give **32**. In this example it is very interesting to note that conformational constraints, deriving from the folding of the molecule, favour the *exo* approach of the aldehyde towards the diene, leading to a *trans* junction between the two newly formed six-membered rings [Scheme 25].[60]



31 **32**

Scheme 25: One of the first examples of IMHDA reactions of aldehydes: a) $MeAlCl_2$, 75%.

In the same year Rigby and co-workers reported the total synthesis of the guaianolide (±)-estafiatin (**35**): they used the intramolecular HDA reaction of the aldehyde **33** to obtain **34**, a synthetic precursor of the guaianolide sesquiterpene [Scheme 26].[61,62]



33 34 (±)-estafiatin (35)

Scheme 26: IMHDA reaction as an useful tool in the total synthesis of natural compounds. a) $BF_3 \cdot Et_2O$, 0 °C, DCM, 92%.

2.4 References

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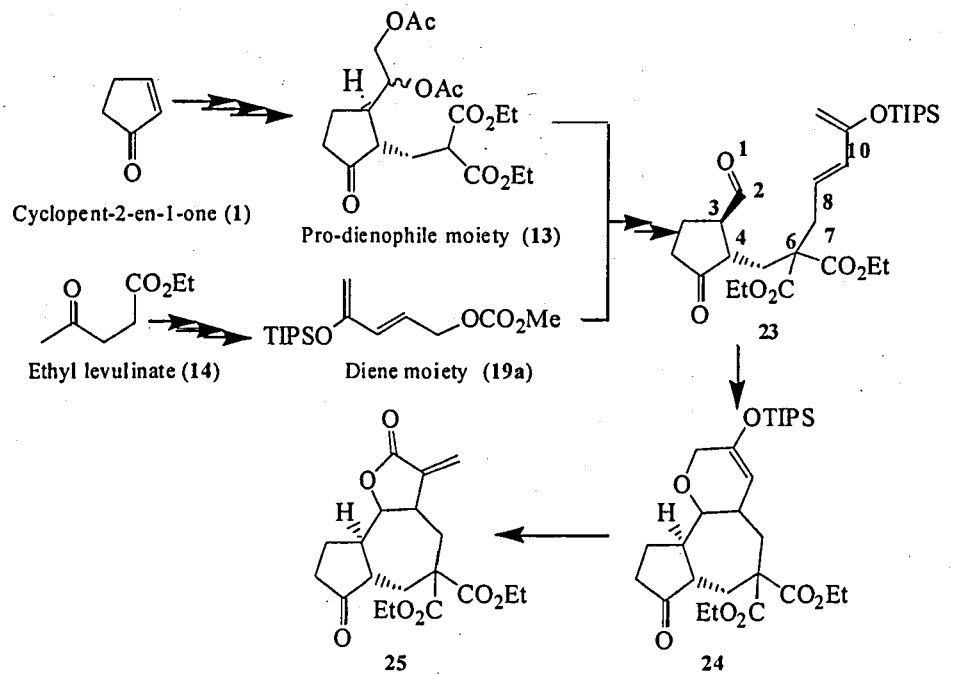
3 The IMHDA Reaction Approach: Results and Discussion

3.1 Introduction

In our studies towards the synthesis of the guaianolide skeleton, we identified the IMHDA reaction of 1,8,10 heterotrienes (with an aldehyde as the dienophile) as the key step to access a fused six-seven-five membered ring system, which would be in turn converted into the guaianolide skeleton. We also envisaged the possibility of studying the stereochemical outcome of the cyclisation, which has not been deeply explored in any detail so far.

In accordance with our retrosynthetic studies (scheme 2, page 33), the synthetic plan sees the pro-heterodienophile and the diene moieties being obtained in a few steps from readily available compounds, cyclopent-2-en-1-one (**1**) and ethyl laevulinate (**14**) respectively. The two fragments are joined together by mean of a Pd(0) catalysed coupling reaction to obtain a pro-heterotriene that in turn is converted into the heterotriene (**23**). The aldehyde on one side and the silyl enol ether activating the diene moiety on the other, should guarantee enough reactivity for the cycloaddition to occur. The dihydropyrane ring of the obtained cycloadduct **24**, after methylaton of the silylenolether will be converted in the γ-lactone proper of the guaianolides **25** [Scheme 27].



Scheme 27: Synthetic approach toward the synthesis of the guaian-6,12-olide skeleton.

The reasons behind the design of heterotriene **23** are outlined below:

- The heterodienophile: the aldehyde is a reactive dienophile, but it is not the best and requires activation by an electron-withdrawing group to react under thermal conditions with any diene.

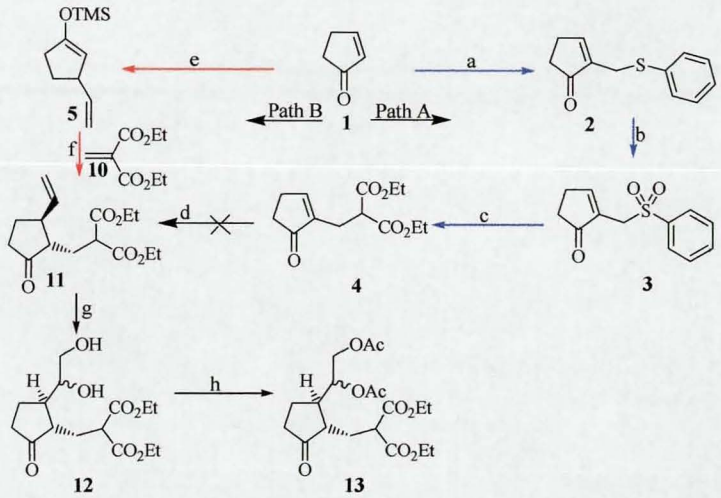
  This is one of the reason why nowadays, most of the experiments reported on the Diels-Alder reaction of unactivated aldehydes use Lewis acid catalysed conditions. On the other hand, the necessity of using Lewis acids opens a wide range of opportunities regarding the possibility of controlling the stereochemical outcome of the reaction by using the proper chiral catalyst.
- The chain connecting diene and heterodienophile: ring chain and *gem*-disubstitution in the linking chain limit remarkably the number of conformations the molecule can adopt. Compared with a simple linear alkylic linking chain, these features reduce the loss of entropy connected with the ring closure and consequently contribute to make more positive the ΔG of the reaction and therefore the cyclisation more lakely to occur. In particular, two *gem*- substituents push the heterodienophile and the diene towards each other, making the interaction between them easier.
- The diene moiety: the bulkiness of the triisopropylsilyloxy group forces the diene to adopt a stable s-*cis* conformation, essential for the success of the reaction (a diene in s-*trans* conformation will never react in a concerted Diels-Alder reaction). Moreover, the electron-donating property of the triisopropyloxy group increases the energy level of the HOMO and therefore produces a strong positive effect on the reactivity of the diene pushing the HOMO diene towards the LUMO dienophile, and it is also certain that the closer these orbitals are the more probable the cycloaddition is to occur.

  For these reasons, and also because they are easy to make from available starting materials, molecules with trialkylsilylenolether functionalities (such as Danishefsky diene) are of great use in hetero Diels-Alder reactions.

3.2 Pro-heterodienophile synthesis

Malonate **11** was a fundamental synthetic intermediate in the synthesis of the pro-heterodienophile moiety **13**. Two alternative synthetic routes were investigated.

In the first, path A, the target was to be reached through a Michael addition of vinylmagnesium copper bromide to 2-(5-oxo-cyclopent-1-enylmethyl)-malonic acid diethyl ester (**4**). In the second, path B, the Mukaiyama coupling of a silyl enol ether (**5**) with methylidene malonate diethylester (**10**) was the key step [Scheme 28].

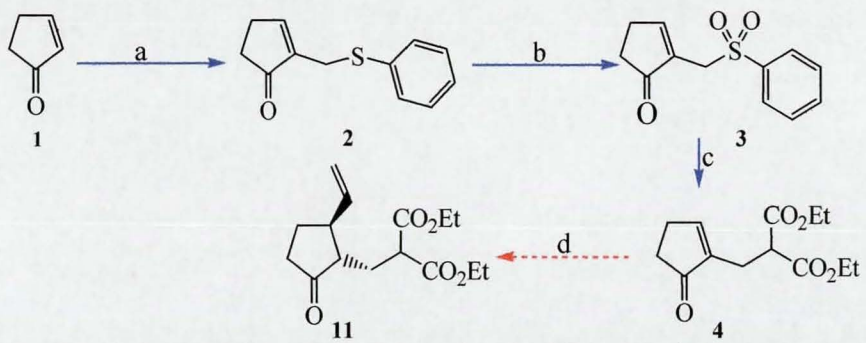


Scheme 28: Two different synthetic path towards the pro-heterodienophile moiety **13** starting from cyclopentenone **1**. a) CH_2O, PhSH, Et_3N, EtOH, reflux, 4 days, 49%; b) Oxone, EtOH, 15 hours, 85%; c) $CH_2(CO_2Et)_2$, NaH, DMF, r.t., 2 hours, 69%; d) CH_2=CHMgBr, CuBr•DMS, THF, -78 °C, 18 hours, rx failed; e) CH_2=CHMgBr, DMPU, TMSCl, CuBr•MS, THF, from –78 °C to –50 °C, 2 hours, 65%; f) **10**, $SnCl_4$, DCM, -78 °C, 2 hours, 55%.

3.3 Attemped synthesis of malonate 11: pathway A

Path A was the first to be investigated: although longer, it was expected to provide a good overall yield due to the chemistry being simple and easily scalable. These factors are very important in the early steps of a natural product synthesis.

Unfortunately, the last step, the Michael addition of vinylmagnesium copper bromide to malonate **4** failed [Scheme 29].



Scheme 29: Path A and the failure of the Michael addition of vinyl magnesium bromide to malonate **4**: a) CH_2O, PhSH, Et_3N, EtOH, reflux, 4 days, 49%; b) Oxone, EtOH, 15 hours, 85%; c) $CH_2(CO_2Et)_2$, NaH, DMF, r.t., 2 hours, 69%; d) CH_2=CHMgBr, CuBr•DMS, THF, -78 °C, 18 hours, rx failed.

The synthesis started with phenylthiomethylation of cyclopentenone **1**: formaldehyde, benzothiazole and triethylamine in ethanol were refluxed for 5 days to give, after Kugelrohr distillation; the phenylthio derivative **2** as a pale yellow oil (49%). This is an interesting reaction employed for the first time on α-β unsaturated ketones by Kirk and Petrow,[1] that presumably goes through a mechanism similar to the Baylis-Hillman reaction.[2]

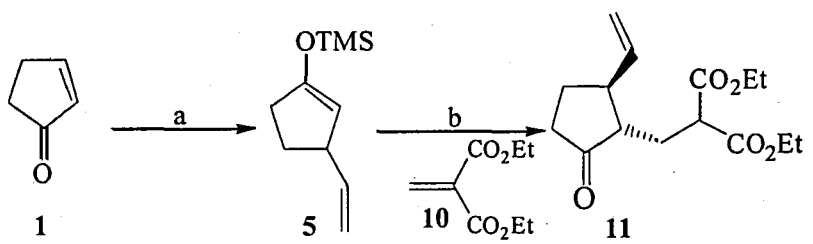
The phenylthioether **2** was oxidised by treatment with Oxone®[3] in a 3/2 mixture of water and ethanol as the solvent, at room temperature over twenty hours to afford the sulfone **3** as a waxy white solid in 85% yield.[4] The sulfone moiety of **3** acted as a good leaving group in the third step, where it is displaced by diethylmalonate anion to give **4**. In this step, a solution of the phenylsulphonic compound **3** in dry dimethylformamide was added by cannula at 0 °C to a stirred solution of diethylmalonate anion (obtained by the addition at 0 °C of a solution of diethylmalonate in dry dimethylformamide to a stirred suspension of sodium hydride in dry dimethylformamide). The reaction was almost immediate: the diethylmalonate anion displaced the phenylsulphone functionality, a very good leaving group, by an S_N2 reaction to give the malonate **4** as a colourless oil in 69% yield after Kügelrohr distillation. A solution of malonate **4** was then treated with five equivalents of vinylmagnesium bromide in the presence of a catalytic amount of CuBr•DMS in order to obtain by transmetallation the corresponding vinylcopper bromide, which is more selective towards 1,4 conjugate addition, rather than the 1,2 addition to the carbonyl group. After stirring the solution at –78 °C for five hours only unreacted starting material was detected by ^{1}H NMR spectroscopy. Alternatively, when the reaction, after being stirred at –78 °C, was allowed to reach room temperature and then stirred for a further eighteen hours, ^{1}H NMR analysis showed a complex mixture, with only traces of starting material and perhaps product being detected. The area around 4.2 ppm and 1.5 ppm (corresponding to the ethoxy groups of the malonic esters) was very complex, suggesting that polymerisation had occurred: the first equivalent of the organo-copper species reacts with the malonic proton, and then further reagent was expected to undergo a 1,4 conjugate addition to the substrate. It is possible that the organo-copper reagent, despite the large excess, is not reactive enough under the reaction conditions, and the malonate anion reacts as a nucleophile

adding to a second molecule of malonate (acting as a Michael acceptor) and so on, leading to extensive polymerisation.

After a general examination, this approach did not maintain the premise of the beginning: the first step was very unsatisfactory as regards the yield (49%), the reaction time (five days) and the toxicity of reagents formalin and thiophenol.
For these reasons a stand-by position was given to the path A, and we decided to try to obtain compound **7** by a different method, path B, shorter than the previous route but at the same time with some drawbacks, including the poorer stability of intermediate compounds that have to be prepared, and the complexity of some aspects of the synthesis.

3.4 Attempted synthesis of malonate 11: pathway B

The unsatisfactory results of the attempt at the synthesis of malonate **11** by the phenylthiomethylation route (pathway A), drove us towards a different strategy that we envisaged would provide our target **11** in only two steps [Scheme 30].



Scheme 30: Path B with a successful Mukaiyama coupling led to the synthesis of the synthetic intermediate **11**: a) CH_2=CHMgBr, DMPU, TMSCl, CuBr•MS, THF, from –78 °C to –50 °C, 2 hours, 65%; b) **10**, $SnCl_4$, DCM, -78 °C, 2 hours, 55%.

The trimethyl silyl enol ether **5** was synthesised in 65% yield by trapping the enol intermediate of the Michael addition reaction between cyclopent-2-en-1-one (**1**) and vinylcopper bromide (obtained, as described above, by mixing vinylmagnesium bromide and a catalytic amount of CuBr•DMS in dry tetrahydrofuran) with TMSCl. To a suspension of the organo-copper reagent, in dry tetrahydrofuran, at –78 °C, was added a mixture of cyclopent-2-ene-1-one (**1**), trimethylsilylchloride and DMPU (which had been pre-dried over molecular sieves for thirty minutes), by syringe over five minutes, and the resulting mixture stirred for two hours.

The presence of the co-solvent DMPU enhanced the reactivity of the Grignard reagent by reducing the oligomerisation in solution, so increasing the reactivity. The Grignard reagents are in fact hard nucleophiles and in the presence of α,β-unsaturated ketones they prefer to react with the carbonyl moiety, giving rise to a mixture of products of 1,2- and 1,4-addition. On the contrary the less reactive organo-copper compounds, prefer to react through 1,4-addition.

Once obtained, the silyl enol ether **5** is unstable, easily undergoing desilylation with consequent formation of 3-vinylcyclopentan-1-one. For this reason, to prevent any loss of compound, it must be purified by Kügelrohr distillation immediately after synthesis and stored under a nitrogen atmosphere in a freezer and utilised in the following step as soon as possible.

The second step of the synthesis is the Mukaiyama coupling of the silyl enol ether **5** with the Michael acceptor methylidene malonate diethylester (**10**).[5] A solution of the catalyst $SnCl_4$ in dry dichloromethane was added dropwise to a stirred solution of compounds **5** and **10** in dry dichloromethane at –78 °C and under a nitrogen atmosphere. The mixture was stirred for two hours to afford malonate **11** in 55% yield. Polymerisation is believed to be responsible for the poor yield of this step. In fact, by flash column chromatography, in addition to the desired product, two main fractions were isolated in 10 and 30% yield. The first fraction was the product of the desilylation of **5**. As regard the second fraction, ^{1}H NMR analysis suggested polymerisation, from the presence of very complex signals around 4.3 and 1.5 ppm (areas corresponding to the ethoxy groups of the malonic esters). Areas corresponding to the signals of the ring system were also very complex and not as intense as expected if compared to the signals of ethoxy groups; ^{13}C NMR analysis showed the presence of several different carboxylic and carbonyl signals, and finally LC-MS analysis showed the presence of several compounds different by a mass of 177 (the molecular weight of **10**) with *m/z* values going up to over 1000.

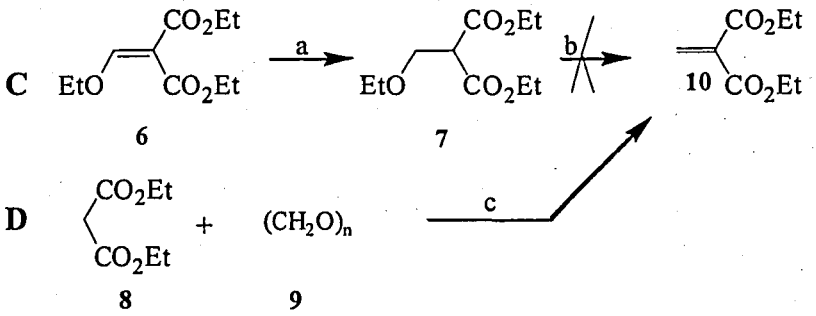
It is possible that an appreciable percentage of the first formed 1,4-addition intermediate (as a consequence of the reaction of **5** with **10**), instead of stopping the reaction at this stage, was able to carry on two or more rounds of Michael addition on new units of methylidene malonate, forming chains of variable length. To increase the

yield of this key reaction, increased dilutions, and shorter and longer catalyst addition times were investigated unsuccessfully. The same destiny was reserved for the use of a different catalyst: Mukaiyama demonstrated that $TiCl_4$ was more efficient than $SnCl_4$ in catalysing the aldol reaction of silyl enol ethers with aldehydes and ketones.[6] Unfortunately, when using $TiCl_4$, the amount of polymer formed was higher than that observed in presence of $SnCl_4$. A final attempt of reducing the polymerisation was made by adding dropwise simultaneously the catalyst and the methylidene malonate diethylester (**10**) to a stirred solution of the silyl enol ether (**5**) under standard reaction conditions, but also in this case the outcome was also very disappointing.

As mentioned above, this path is short but problematic: beside the Mukaiyama coupling step, the synthesis of the methylidene malonate diethylester (**10**) was also fraught with difficulties, as described below.

3.5 Synthesis of the methylidene malonate diethylester (10)

The methylidene malonate diethyl ester (**10**) is very reactive and unstable (it polymerises very readily), therefore it is best to use it immediately after synthesis. Two methods (**C** and **D**) were investigated to find the best method to obtain **10**, and are shown in scheme 31.



Scheme 31: Two approaches to the synthesis of the methylidene malonate diethyl ester. Path C: a) H_2/Pd-C, AcOEt, r.t., 18 hours, 70%; b) Distillation from 60 to 180-220 °C, 1 mbar. Path D: c) AcOK, $Cu(OAc)_2$, CH_3COOH, 90 °C, 1 hour, then distillation at 140 °C, 1 mbar, 44%.

The first route chosen to prepare the electrophile was pathway **C**: compound **10** was supposed to be obtained by the distillation of ethoxymethylene malonate diethyl ester (**7**), which in turn was obtained by catalytic hydrogenation of ethoxy methylidene malonate diethylester (**6**) in 70% yield. Under the initial distillation conditions (80 °C, 1 mbar), **7** was expected to eliminate ethanol to give the target **10**, which was then to be collected as the second fraction of the distillation by slowly increasing the

temperature of the distillation head up to 180-220 °C.[7] This procedure was attempted many times but always led to polymerisation, with only a small amount of desired product isolated.

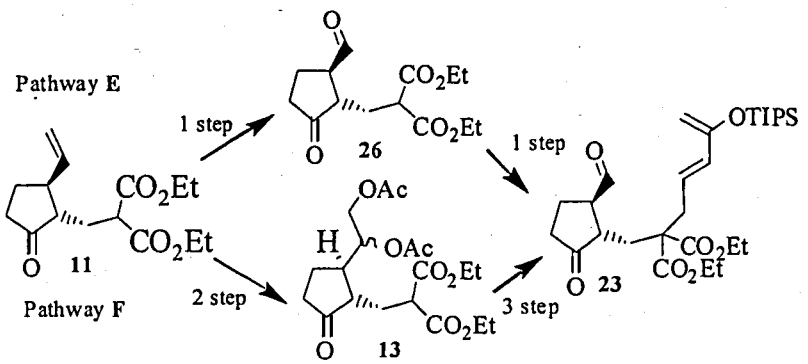
The alternative pathway, **D**, was successful: reaction of **8** with **9** under Knoevenagel condensation[8] conditions gave reasonable yield of the product **10** after distillation.

3.6 Synthesis of the pro-heterodienophile moiety 13

As shown in the synthetic plan, the heterodienophile was intended to be the aldehyde **23**. Therefore, if at one point the vinyl group of **11** has to be converted into the carbonylic functionality, it would be better to do so before the coupling with the diene moiety, in order to avoid any unwanted reaction of the diene system. This task was tackled in two different ways [Scheme 32].

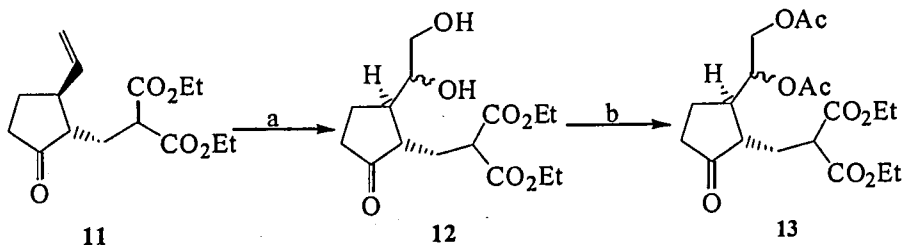
The first, pathway **E** goes through the direct conversion of the double bond into the aldehyde **26** followed by the coupling with the diene moiety. This is the shortest route but has drawbacks in the relatively poor stability of aldehydes and their tendency to racemise when a chiral centre is present in the α position.

The second option, pathway **F**, induces the partial oxidation of the double bond into a *vic*- diacetate **13**, which, after coupling with the diene, it is possible to convert into an aldehyde without affecting the conjugated π system. This path is three steps longer than the first (1 more oxidation and 2 steps for the protection and deprotection of the diol) but avoids any hypothetical interference from the aldehyde before and during the coupling [Scheme 32].



Scheme 32: Two different approaches towards the heterotriene **23**.

The first approach to be tested was the longest but safest pathway **F** [Scheme 33].



11 12 13

Scheme 33: Synthesis of the pro-heterodienophile moiety through osmium catalysed *vic*-dihydroxylation (path F): a) $OsCl_3$, NMO, THF/H_2O, r.t., 8 hours, 70%; b) DMAP, Ac_2O, Py , r.t., 2 hours, 95%.

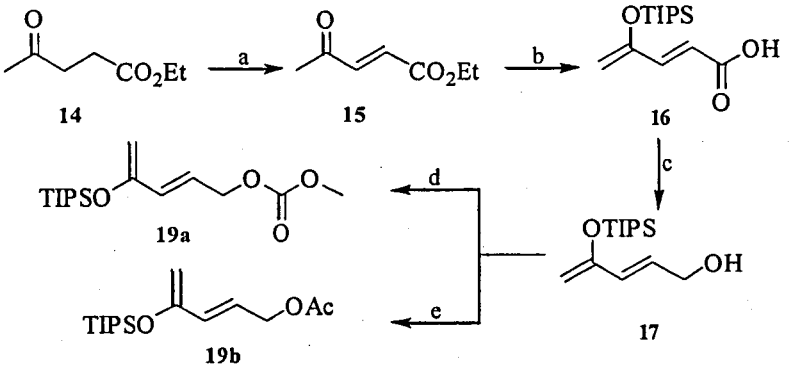
The vinyl group of **11** was oxidised by treatment with OsO_4 (produced *in situ* from $OsCl_3$ and NMO) to give the diol **12** and was obtained as a colourless oil in 70% yield.[9] Using this methodology, a catalytic amount of osmium is introduced into the reaction system as $OsCl_3$, and then oxidised by the secondary oxidant NMO into OsO_4, the oxidant species. After every oxidation cycle, Os(IV) is regenerated by the excess of NMO, avoiding a large use of osmium, which is very toxic and expensive.

To avoid any interference during the coupling with the diene moiety, the two new hydroxy groups were then protected by acetylation (Ac_2O:Py= 1:1 in presence of DMAP as the catalyst) to give the pro-heterodienophile moiety **13** as a pale yellow oil in 95% yield.

Now the "pro-heterodienophile" moiety was ready to be coupled with the diene moiety by a palladium catalysed reaction to obtain the "pro-heterotriene" **20**.

3.7 Synthesis of the diene moieties 19a and 19b

Previous research in our group[10] had shown that the best way to perform the malonic synthesis of the pro-heterotriene **20** was through a Pd(0) catalysed allylation reaction, which had been proven to be very efficient.[11] Based on the structure of the target heterotriene, we thought that ethyl laevulinate (**14**) would provide the correct backbone and functionalities to obtain the heterotriene moiety precursors **19a, b** and would also fit the requirements to be employed in the planned coupling reaction [Scheme 34].



Scheme 34: Synthesis of the diene portion precursors: a) Br_2, DCM, 0 °C, 2 hours, then Et_3N, reflux, 2 hours, 57%; b) TIPSOTf, Et_3N, DCM, 0 °C, from 0 °C to r.t., 2 hours, 85%; c) DIBAL, THF, -78 °C, 2 hours, 84%; d), *n*-BuLi, THF, –78 °C, 10 min. then MeOCOCl (**18**), 45 min.; 84%; e) DMAP, Ac_2O/Py, 4 hours, 72%.

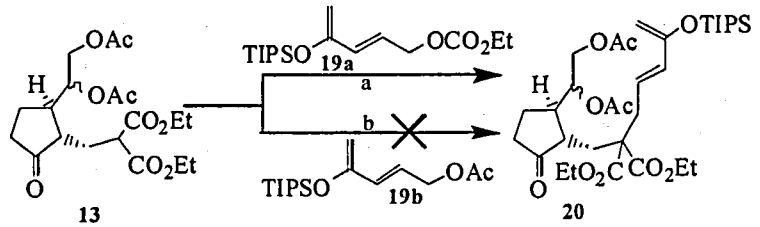
The reaction between ethyl laevulinate (**14**) and bromine produced the corresponding β bromo ester, which after refluxing for two hours in the presence of triethylamine, eliminated HBr to afford the *E* α,β-unsaturated keto-ester **15**. This was in turn converted by reaction with trisopropylsilylmethanesulphonate (TIPSOTf), in the presence of triethylamine in dichloromethane as the solvent, into ethyl-4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dienoate (**16**).[12] Reduction of **16** with 2.5 equivalents of DIBAL in dry tetrahydrofuran gave the alcohol **17,** which was then reacted with *n*-buthyllithium and methyl chloroformate (**18**) in a one-pot reaction performed in dry tetrahydrofuran, at –78 °C to give the carbonate **19a**. This is unstable and it must be used immediately to minimise its decomposition. In fact, the only problem associated with these compounds is that all the silyloxy derivatives, **16, 17, 19a**, are unstable and lose the triisopropyl silyl group very easily (especially under acidic conditions) to give the corresponding ketone. They were therefore purified on silica gel deactivated with water (5% w/w) and stored in a freezer and under an atmosphere of nitrogen.

Because of the instability of the carbonate **19a**, the corresponding acetate was also synthesised: dissolution of **17** in a mixture of pyridine and acetic anhydride with DMAP as the catalyst afforded **19b**.

The two precursors of the diene moiety (**19a, b**), corresponding to the requirements necessary to be employed in a Pd(0) catalysed allylation of the malonate **13**, were therefore obtained in four steps, starting from ethyl laevulinate (**14**).

3.8 Synthesis of the pro-heterotriene 20

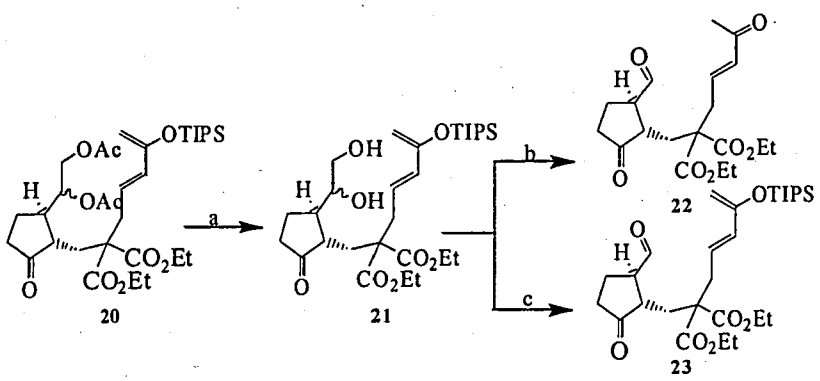
At this stage, the convergent approach of the strategy was to be realised: after being synthesised separately, the two portions, diene **19(a, b)**, and malonate **13**, would be joined together by a Pd(0) catalysed reaction to give **20** [Scheme 35].



Scheme 35: Synthesis of the pro-heterotriene **20**: a) $Pd_2(dba)_3$, PPh_3, **19a**, DCM, 18 hours 70%; b) $Pd_2(dba)_3$, PPh_3, **19b**, NaH, THF, 18 hours rx failed.

The first attempt at the synthesis of **20** was performed under basic conditions. After reaction with sodium hydride, a solution of **13** in dry degassed tetrahydrofuran was transferred into a solution of the acetate **19b**, $Pd_2(dba)_3$ and PPh_3 in dry degassed tetrahydrofuran. After the solution was heated under reflux for eighteen hours only a mixture of the unreacted starting materials was detected. The coupling under neutral conditions was, however, successful: $Pd_2(dba)_3$ and PPh_3 were added to a degassed solution of the malonate **13** and the carbonate **19a**, and the mixture heated under reflux for eighteen hours to afford the pro-heterotriene **20** as a pale yellow oil. The reaction showed different yields when performed in dry dichloromethane (70%) and dry tetrahydrofuran (55 %). It is important to note that even though Pd(0) complexes are not extremely sensitive to oxygen and moisture, the use of dry degassed solvents was fundamental for the positive result of the reaction.

3.9 Synthesis of heterotriene 23



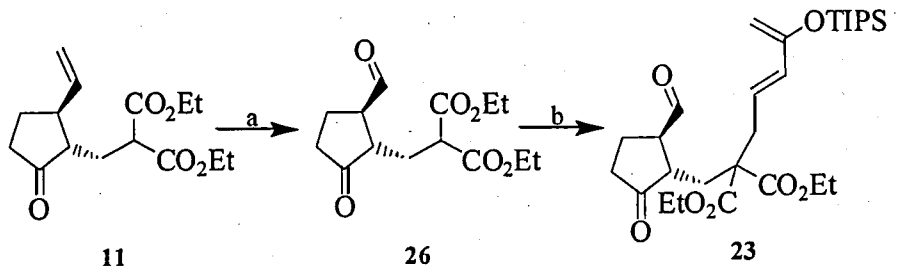
Scheme 36: Synthesis of the heterodienophile **23** through a sequence of hydrolysis and oxidative cleavage: a) Amberlite® 400 Cl, MeOH, r.t, 16 hours, 95%; b) $NaIO_4/SiO_2$, THF, quantitative; c) $NaIO_4$, THF/H_2O, 5 hours, 90%.

The conversion of **20** to **23** proceeds through a sequence of hydrolysis and oxidative cleavage of the diacetyl moiety [Scheme 36].

Compound **20** was deacetylated with Amberlite® 400 Cl (a basic resin previously activated with KOH) in MeOH. The mixture was stirred for 16 hours to afford the diol **21**. The attempt to converting the diol moiety of **21** into the required aldehyde by oxidative cleavage with $NaIO_4$ supported on silica gel in tetrahydrofuran afforded the desilylated aldehyde **22**. The silyl enol ether may have been too sensitive to the acidity of the silica gel used as support. This problem was solved by avoiding the use of silica and performing the reaction in tetrahydrofuran:/water= 1:1 as the solvent.[13] This methodology afforded the heterotriene **23** as a colourless oil in 90% yield (85% overall yield for the conversion of **20** to **23**). The one-pot conversion was not as efficient: addition of $NaIO_4$ to the hydrolysis mixture, after the conversion of **20** to **21** was complete, afforded the aldehyde **23** only in 56% yield. Compounds **20**, **21**, and **23** are unstable and therefore had to be stored in freezer under nitrogen atmosphere and used immediately after synthesis.

3.10 An interesting short cut

As noted above, the oxidation of a double bond into an aldehyde in a two step procedure is not the shortest route but prevents interference from the aldehyde in the coupling step. It was at this stage worth trying the direct coupling of the aldehyde with the diene: as we already had an authentic sample of **23**, it made it easier to follow the reaction outcome. As shown in scheme 37, this short cut would enable us to avoid three steps and the use of the very toxic and expensive $OsCl_3$.



11 **26** **23**

Scheme 37: Synthesis of the heterotriene **23**. A short cut to avoid use of $OsCl_3$ and save three steps: a) O_3, DCM, 30 min., PPh_3, 1 hour, 50%; b) $Pd_2(dba)_3$, PPh_3, **19a**, DCM, reflux, 18 hours, 33%.

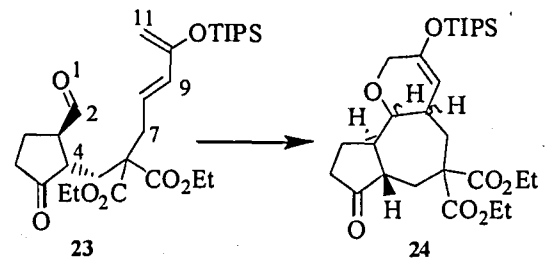
A stream of ozone[14] was bubbled into a stirred solution of the malonate **11** at –50 °C. After 30 minutes the reaction colour turned deep blue indicating an excess of ozone and therefore complete consumption of the starting material. The reaction was quenched with PPh_3 to afford after purification the aldehyde **26**.

The attempt at the coupling between the aldehyde **26** and the carbonate **19b** was performed using the same conditions previously employed for the successful coupling of **13** and **19b**: $Pd_2(dba)_3$ and PPh_3 were added to a degassed mixture of the aldehyde **26** and the carbonate **19b** in dry dichloromethane and the solution refluxed for 18 hours. ^1H NMR analysis performed on the crude product mixture showed the presence of large quantities of both the starting materials. The target heterotriene **23** was isolated after purification of the crude by flash column chromatography only in 33% yield.

By comparing the overall yield of the two paths tested, we decided to proceed through the synthesis of diacetyl malonate **13**: even if the synthetic route was longer, the overall yield was almost twice that observed with the direct coupling of the aldehyde **24**. Moreover, the malonate **13** can be stored for longer than the aldehyde **26**, and this is very important when challenging the synthesis of natural compounds.

3.11 The IMHDA reaction of 1,8,10-heterotriene 23

The intramolecular hetero Diels-Alder (IMHDA) reaction of carbonyls is not very common, and only few examples are present in the literature. The lack of data drove us to refer to the intermolecular hetero Diels-Alder (HDA) reaction of aldehydes that has been extensively studied in the last two decades. HDA reactions are mainly performed under thermal or Lewis acid catalysed conditions. In this work, the conversion of the heterotriene **23** into the IMHDA reaction adduct **24** [Scheme 38] has been attempted following both procedures and they are treated separately.



Scheme 38: IMHDA reaction of heterotriene **23** would lead to the tricyclic compound **24** characterised by a fused 6,7 membered ring system.

3.11.1 The IMHDA reaction of 1,8,10 heterotriene 23 under thermal conditions

It is well known that unactivated (by an electron withdrawing group) aldehydes cannot react as dienophiles in a bimolecular HDA reaction. As far as we know, there are not many examples of the intramolecular version of the reaction, especially with heterotrienes leading to the formation of fused six-seven membered ring systems. Therefore it was interesting to attempt the cyclisation of heterotriene **23** just under thermal conditions to see if the enthalpic gain deriving from the intramolecular cyclisation would help to reach the amount of energy required for the reaction.

A solution of the heterotriene **23** in dry, degassed toluene was heated at 70 and 100 °C in a sealed tube for 24 hours: no reaction occurred and only starting material was detected by ^{1}H NMR analysis. When the reaction was performed at 160 °C for 24 hours in a sealed tube, many spots were present on TLC, and NMR analysis did not show any aldehydic or vinylic signals. The other signals were very confused probably because of decomposition or polymerisation of the heterotriene. In order to try to understand something more about the nature of the molecules present in the crude material, a LC-MS experiment was performed. One of the most important signals corresponded to the addition of a molecule of oxygen to the starting material. Also the use of microwaves was unsuccessful: compound **23** did not react when adsorbed onto silica or dissolved in toluene and irradiated with microwaves at 80 or 120 °C for 5, 10 and 20 minutes.

These results are summarised in table 10.

Starting material	Conditions	Time	Outcome
23	Toluene/70 °C	24 h	Starting material
23	Toluene/160 °C	24 h	Decomposition
23	Toluene/Microwaves 80/120 °C	5, 10, 20 minutes	Starting material

Table 10: Attempts at IMHDA reaction of **23** under thermal conditions.

3.11.2 The IMHDA reaction of the 1,8,10-heterotriene 23 under Lewis acid catalysed conditions

Lewis acids promote the HDA reaction of unactivated carbonyls by coordinating to the lone pair of the oxygen atom. This lowers the LUMO energy level and makes easier the interaction with the HOMO of the diene. Usually the diene needs to be activated by electron-donating functionalities such as silyloxy goups. Because of the sensitivity of silyl enol ethers to acids, it is very important to find the correct conditions to avoid the formation of desilylated products. The feasibility of the IMHDA reaction of **23** was investigated using a range of catalysts and conditions, as summarised in table 11.

Starting material	Catalyst/Conditions	Time	Outcome
23	$ZnCl_2$/THF, r.t.	6 days	Partial desilylation
23	$ZnCl_2$/THF, reflux in sealed tube	20 h	Decomposition
23	BF_3•Et_2O (1 eq), Et_2O or THF, –78 °C	1 to 20 min.	Starting material
23	BF_3•Et_2O (2.5 eq)/ THF –78 °C to r. t.	24 h	Desilylation
23	$Yb(OTf)_3$ or $Sc(OTf)_3$ (1 eq)/ THF, 0 °C to r. t.	1 to 3 days	Starting material
23	$Yb(OTf)_3$ or $Sc(OTf)_3$ (2.5 eq)/ THF, –78 °C to r. t.	4 h	Desilylation
23	$Yb(OTf)_3$ (1eq), toluene Microwaves, 80 °C	20 min.	Decomposition
23	DCM, 19 Kbar	48 h	Partial desilylation

Table 11: Attempts at IMHDA reaction of **23**: Lewis acid catalysed and ultra high-pressure conditions.

At first, the cyclisation of **23** was attempted using the conditions described by Danishefsky in one of his early publications describing the Lewis acid catalysed diene aldehyde cyclocondensation.[15]. The heterotriene and a stoichiometric amount of freshly dried $ZnCl_2$ were dissolved in tetrahydrofuran and stirred at room temperature: no reaction occurred after 36 hours, and after 6 days partial desilylation of the molecule was observed. Refluxing the same mixture in a sealed tube for 20 hours led to decomposition of the starting material. NMR data of the major product of the reaction was consistent with the cyclopentanone methyl diethylmalonate portion of the heterotriene and the TIPS group without any trace of aldehydic proton or carbon.

The next Lewis acid to be tested was $BF_3 \cdot Et_2O$, which, according to Palenzuela[16] and coworkers, is able to catalyse the concerted HDA reactions of monoactivated dienes with unactivated aldehydes in good yields. A stoichiometric amount of $BF_3 \cdot Et_2O$ was added to a stirred solution of the heterotriene at –78°C and the reaction quenched with Et_3N after 5 or 20 minutes. In both cases only unreacted substrate was recovered. When 2.5 equivalent of $BF_3 \cdot Et_2O$ was added at –78 °C and the mixture left to warm up to room temperature over 18 hours, complete desilylation was observed. No difference was observed between the use of diethyl ether or tetrahydrofuran.

We then decided to operate under milder conditions with the catalysts $Yb(OTf)_3$ and $Sc(OTf)_3$. We were moderately confident about the use of the Yb catalyst because lanthanides usually avoid desilylation of the cycloadduct.

A solution of the substrate **23** was added at 0 °C to a solution of a stoichiometric amount of catalyst in the presence of grounded molecular sieves. After 24 hours no trace of any reaction was present in either case. The same result was observed after 3 days. The load of catalyst was then increased to 2.5 equivalents and the temperature of the addition was reduced to –78 °C. After 1 hour the reaction was allowed to reach room temperature. Three hours later, complete desilylation had occurred with both catalysts. Tetrahydrofuran was used as the solvent. The use of toluene as the solvent (to favour the concerted cyclisation) with $Yb(OTf)_3$ led, again, to desilylation. The heterotriene also decomposed when irradiated at 80 °C with microwaves for 20 minutes in the presence of $Yb(OTf)_3$.

Finally, we attempted to promote the cycloaddition by application of ultra high-pressure. A solution of **23** in dichloromethane was submitted to 19 Kbar for 48 hours to afford a mixture of starting material and desilylated compound.

At this stage it was necessary to try to understand the reasons for all these unsatisfactory results, and so to find a useful solution.

While the lack of reactivity of **17a** under thermal conditions may be due to the low reactivity of the aldehydic group, the non-reactivity under catalytic conditions is more difficult to understand. There are very few examples of intramolecular hetero-Diels-Alder reactions with unactivated aldehydes as dienophile, which means that they are rarely attempted or are difficult to perform. Instead, examples of the bimolecular

process are very common, and they present some common factors such as the regioselectivity, which is opposite with respect to that which we need for our cycloaddition.

The bimolecular HDA reaction leads to dihydropyran-4-one derivatives (coming from the bonding between the aldehydic carbon and the C-1, of the diene) after hydrolysis of the silyl enol ether, and not to dihydropyran-3-one derivatives, which would be the type of cycloadduct expected in the case of the IMHDA reaction of the heterotriene **23** [Fig. 19 and scheme 14].

As for all-carbon bimolecular Diels-Alder reactions, this regioselectivity can be justified on the basis of the new bond formations between the atoms of the diene and of the dienophile that have the highest or the lowest atomic coefficients.

In the case of intramolecular reactions, this rule is not always followed, and it is possible to see bonding between the atoms which do not have the lowest or the highest atomic coefficients: the enthalpic gain (coming from the fact that a general intramolecular process has more probability to take place than an intermolecular one, the two reactive entities being on the same molecule) is in this case responsible for the positive outcome of the cycloaddition.

In the $ZnCl_2$ catalysed reaction, which is supposed to go through a concerted pathway, the failure of the cyclisation of **23** is probably due to the fact that this regioselectivity is forbidden: the atomic coefficients of the aldehydic oxygen and of the C-11 (considering just the triene chain and not the cyclopentanone moiety) are not both the highest or the lowest of the dienophile and of the diene moiety respectively.

To verify this statement, we calculated the surface properties of both the diene and the dienophile moieties through extended Hükel semi-empirical calculations (Chem. 3D.8 Pro). It was calculated an energy level of -11.851039 eV and of -2.583996 eV for the HOMO diene and the LUMO dienophile respectively.
Moreover, if we look at the HOMO diene density, the highest value is on the C-11, but the highest density of the LUMO dienophile, is on the C-2 (triene numbering), the aldehydic carbon. Probably the enthalpic gain deriving from the intramolecular ring closure is not enough to cover the non-correspondence of the atomic coefficients [Fig. 20].

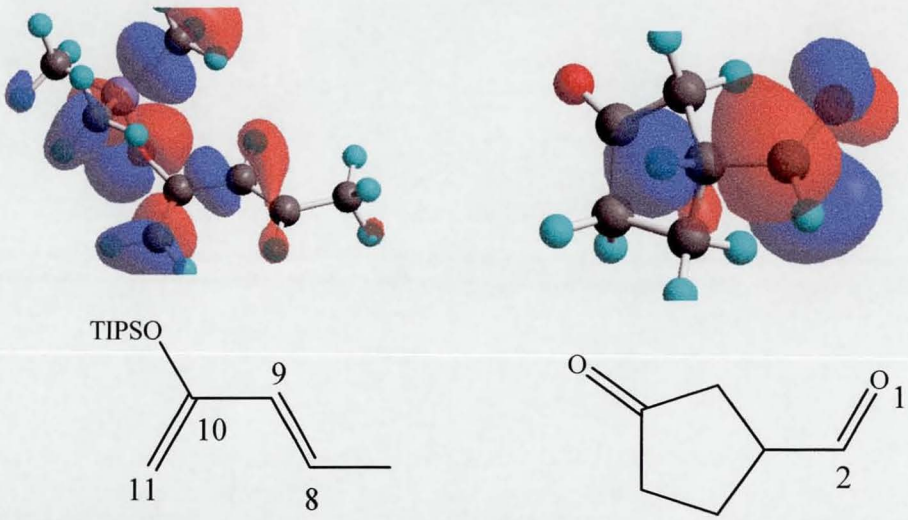


Figure 20: Distribution of the HOMO in the diene moiety of heterotriene **23** (left); distribution of the LUMO in the hetero-dienophile moiety of heterotriene **23**.

In the BF_3•Et_2O catalysed reaction, a Mukaiyama-aldol pathway seems to be usually preferred: in the case of our heterotriene **23**, through this pathway it would also be impossible to achieve the desired HDA cycloadduct because there would be bond formation between C-2 and C-11.

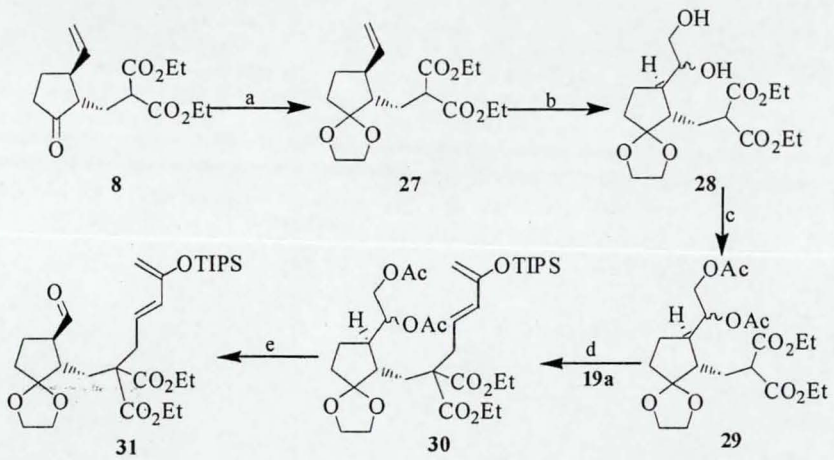
If our understanding is correct, to realise this cycloaddition it is very important to make a few changes in the heterotriene **23** structure, in order that it is properly activated towards an IMHDA reaction.

Accordingly, and in order to understand more about this almost unexplored type of HDA reaction, we thought that it would be useful to modify the structure of the diene and of the bridge linking it to the heterodienophile.

3.12 Modification of the linking chain

As already outlined, the bridge linking the diene and the dienophile is very important for an IMDA reaction: geminal substitutions can bring closer the two reacting moieties, raising the speed of the reaction, and, in the case of unsaturated substituents, stabilising the transition state by secondary π interactions. The original heterotriene **23** already has a geminal ethyloxycarbonyl disubstitution, but we thought that it would be interesting to try a further modification by converting the ketone group into a cyclic ketal. The interaction between the two ethoxycarbonyl groups and the new

five-membered ring should bring more rigidity to the system and push the diene moiety toward the heterodienophile. Moreover, making this new ring involves just one more step in the synthesis of the pro-dienophile moiety [Scheme 39].

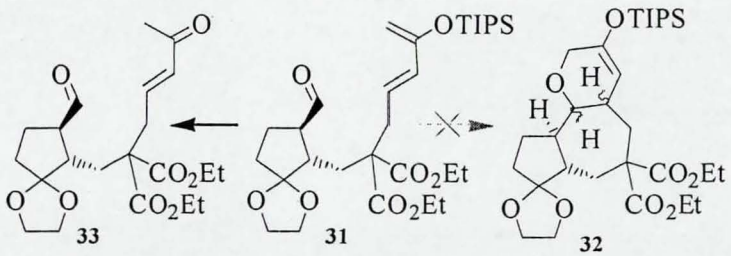


Scheme 39: More substitution on the linking chain: a) Ethylene glycol, pTSA, toluene, reflux, 5 hours, 74%; b) $OsCl_3$, NMO, THF/H_2O, 20 hours, 94%; c) DMAP, Py, Ac_2O, 6 hours, 97%; d) **19a**, $Pd_2(dba)_3$, PPh_3, DCM, reflux, 16 hours, 30%; e) Amberlite® 400 Cl, MeOH, 15 hours, then $NaIO_4$, THF/H_2O, 4 hours, 43% (2 steps).

A mixture of malonate **8**, ethylene glycol and a catalytic amount of p-toluene sulphonic acid in dry toluene was heated under reflux for 5 hours in a flask fitted with a Dean-Stark distillation head to afford, after purification, the ketal **27** as a colourless oil in 74% yield. The same procedure described for the conversion of ketone **8** into the heterotriene **23** was applied to the ketal: **27** was treated with $OsCl_3$/NMO at room temperature for 20 hours in tetrahydrofuran:water (1/1), to give the *vic*-diol **28** (94% yield colourless oil), which was in turn converted into the diacetate **29** (colourless oil, 97% yield) in acetic anhydride:pyridine (1/1) in the presence of DMAP as the catalyst. Pd(0) catalysed allylation of **29** was unsatisfactory, affording the pro-heterotriene **30** as a colourless oil in only 30% yield. Beside the target compound, the carbonate **19a** and the malonate **29** were recovered in 70% and 38% yields respectively (percentage referred to the amount of starting materials employed). Also, the conversion of **30** into **31** was unsatisfactory, especially if compared with the conversion of the ketone **20** into **23**: hydrolysis with Amberlite® 400 Cl in methanol, followed by oxidative cleavage of the obtained diol with 2.5 equivalents of $NaIO_4$ in 1:1= tetrahydrofuran: water for 15 minutes, gave the heterotriene **31** in 43% yield for two steps. It is not easy to understand the reasons for this poor yield. A new batch of $NaIO_4$ was used and surprisingly, after 15 minutes, analysis by TLC showed no starting material and only the spot of the aldehyde present. The diol was not purified

because it was very unstable, but NMR analysis of the crude mixture showed a very clean compound, obtained in 88% yield; of course it is still possible that the presence of inorganic material, unseen by NMR spectroscopy, could have caused decomposition. It is also possible that something deleterious happened in the oxidation step, in the work up, or during the flash column chromatography (performed on silica gel unactivated with H_2O, 5% w/w): TLC showed a single compound, and the NMR analysis of the crude and of the purified compound were very similar. No further compounds were collected when flushing the column with 100% ethyl acetate.

In order to obtain the IMHDA reaction of the heterotriene **31** to give the cycloadduct **32** [Scheme 40], the former was submitted to several different reaction conditions, which are summarised in table 12.



Scheme 40: Influence of the cyclic ketal on the IMHDA reaction of heterotriene **31**.

Heterotriene	Conditions	Time	Outcome
31	Microwaves, toluene	5 to 20 minutes	**31** + **33**
31	$Yb(OTf)_3$ 2.5 eq/THF –78 °C to room temp.	4 h	**33**
31	19 Kbar, DCM	48 h	**31** + **33**

Table 12: Attempts at the IMHDA reaction of **31** under several different conditions.

Use of microwaves was again unsuccessful: when irradiated at 120 °C for up to 20 minutes **31** did not react, and only a small amount of desilylated aldehyde **33** was detected.

When the heterotriene was added at –78 °C to a solution of $Yb(OTf)_3$ and the mixture stirred for 4 hours while warming up to room temperature, complete desilylation occurred.

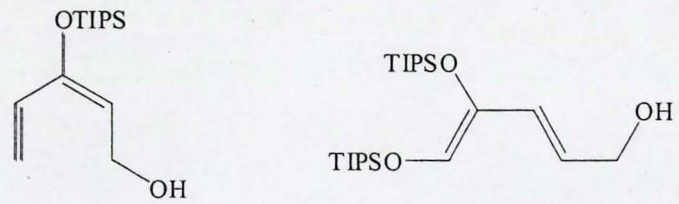
Finally, when submitted to ultra high-pressure conditions (19 Kbar) for 48 hours, **31** underwent partial desilylation.

The results obtained with the attempts at the IMHDA reaction of the heterotriene **30** are consistent with those obtained with the ketone **23**, and therefore the presence of the cyclic ketal did not have any effect, under the conditions that have been tested, on the reactivity of the heterotriene towards the IMHDA reaction.

3.13 Modifications to the diene moiety

The intermolecular Diels-Alder reaction is highly regioselective because the interactions between the two atoms of the diene and the dienophile that have the highest orbital coefficients and the two that have the lowest one are favoured. In all-carbon IMDA reactions, if conformational strengths hinder this interaction, it may still be possible for the cycloaddition to take place, but with an opposite regioselectivity to that which would be obtained in an intermolecular reaction.

As underlined at the end of the previous chapter, the substitution pattern of the diene moiety which had been used up to this point, is probably not ideal for the desired cycloaddition work and therefore attention was turned to different substitution patterns of the diene, which would be able to promote the formation of the desired cycloadduct. Two promising molecules were identified, **31** and **40** [Fig. 21].

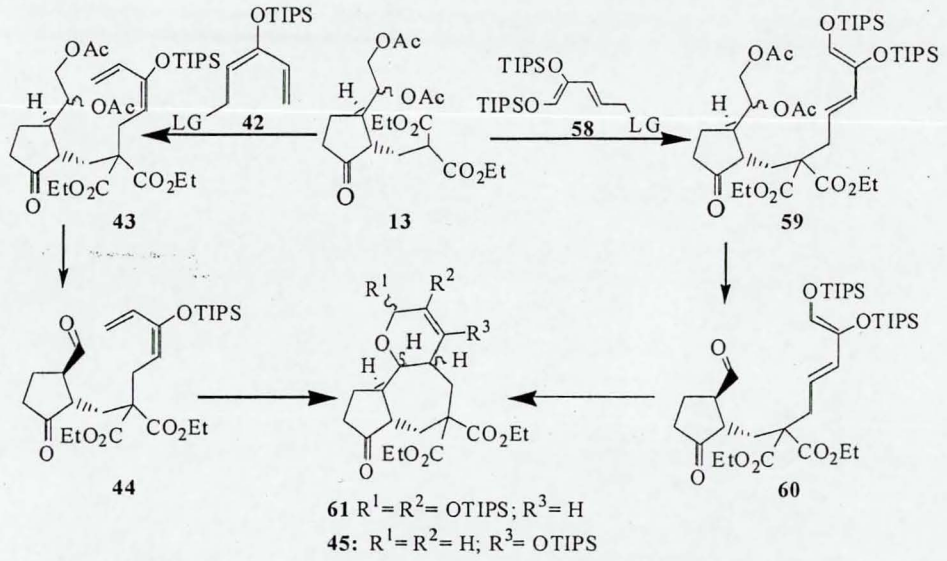


31 **40**

Figure 21: Two new dienophile moieties.

The convergent approach which has been chosen since the beginning should allow us to follow the synthetic path developed and to not waste all the experience gained up

to this point: it is in fact still possible to use compound **13** as the pro-heterodienophile moiety, and probably the Pd(0) catalysed allylation of **13** would also be feasible with the new diene framework. Once the new pro-heterotrienes are obtained there is no reason why conversion into the corresponding heterotrienes should not work with the same procedure that has already been developed [Scheme 41].



Scheme 41: Two new interesting heterotrienes (**44** and **60**) and their hypothetical cycloaddition products; LG= leaving group.

The attempts at the synthesis and the problems connected with the use of each new diene moiety are discussed in the following paragraphs.

3.14 Activation of the position 9 of the heterotriene

As mentioned above, in concerted bi-molecular Diels-Alder reactions the formation of the two new bonds preferentially occurs between atoms of the diene and the dienophile with the highest atomic coefficients and between those with the lowest atomic coefficients.

Semi-empirical extended Hükel surface calculations (Chem 3D.8 Pro) have shown a HOMO energy value for a diene moiety with an activating group in position 9 [Fig. 22] of -11.865507 eV. If we compare this value with that obtained for the diene with an activating group in position 10 [Fig. 20], we can see that the different activating

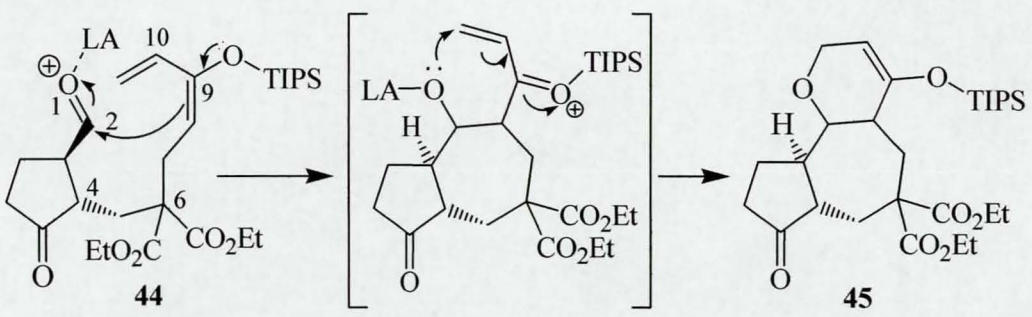
pattern does not affect the energy value of the HOMO diene (being the difference between the two orbitals of only -0.015 eV).

On the contrary the distribution of the HOMO over the two dienes is very different: the presence of an activating group at the C-9 of the diene generates a rearrangement of the orbital, which is now more concentrated over the C-8 and C-9 than over the C-10 and C-11 atoms [Fig. 22].

Figure 22: Activating group at C-9 on the diene moety of the heterotriene **44**: the highest electron density is present on C-8.

We suggest that this should allow C-8 to have the highest atomic coefficient of the diene moiety and therefore to efficiently interact with C-2 leading to the desired ring closure [Scheme 41].

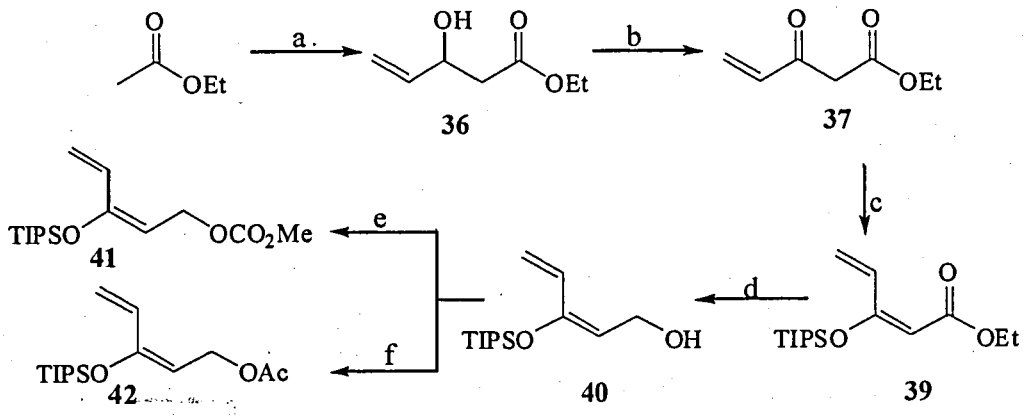
If the cycloaddition did not proceed through a concerted pathway, there would still be the possibility that the desired ring closure could occur through an aldol-like stepwise pathway [Scheme 42].



Scheme 42: Stepwise HDA reaction of **44** gives cycloadduct **45**.

We decided to prepare the heterotriene **44** to test our theory. Our strategy towards **44** is to prepare the carbonate **40** or the acetate **41**, which would be suitable substrates for the Pd(0) catalysed allylation of the pro-heterodienophile **13**.

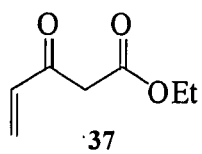
Compounds **40** and **41** can be prepared starting from the hydroxy-ester **36** in four steps [Scheme 43].



Scheme 43: Synthesis of the diene moiety **42**: a) LDA, THF, –78 °C, 45 min., then CH_2=CHCHO, 0 °C, 15 min., 93%; b) DMP, DCM, 30 min., 43%, or Jones' reagent, acetone, 4 hours, from 0 °C to r.t., 70%; c) TIPSOTf, Et_3N, DCM, 0 °C, 15 hours, 79%, d) DIBAL, THF, –78 °C, 5 hours, 56%; e) *n*-BuLi, $MeCO_2Cl$, THF, –78 °C, unidentified compounds; f) DMAP, Ac_2O, Py, 0 °C, 6 hours, 80%.

The first step of the synthesis is the 1,2-addition of the lithium enolate of ethyl acetate to acrolein: ethyl acetate was added at –78 °C to a solution of lithium diisopropylamide (LDA),[17] and the mixture quenched 45 minutes later with acrolein to afford the hydroxy ester **36** as a colourless oil in 93% yield. To convert the hydroxy group into a ketone, the Swern oxidation was attempted first:[18] dry dimethylsulphoxide was added to a solution of oxalyl chloride in dry tetrahydrofuran at –65 °C followed by the addition of a solution of the hydroxy ester **36**. The reaction was quenched with triethylamine, but after work up, ^{1}H NMR analysis of the crude material showed that the reaction had not occurred and that only unreacted starting material had been recovered.

The oxidation was successfully achieved using Dess-Martin periodinane (DMP):[19] the oxidising agent was added at room temperature to a solution of **36** in dichloromethane and the mixture stirred for thirty minutes. After work up and purification by Kügelrohr distillation, a mixture of the keto-ester **37** and the enol-ester **38** was obtained as a colourless oil in 43% yield [Fig. 23].



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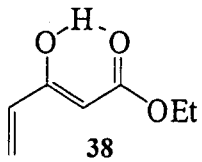

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Figure 23: Oxidation of the allylic alcohol **36** afforded a mixureof the keto-ester **37** and the enol-ester **38.**

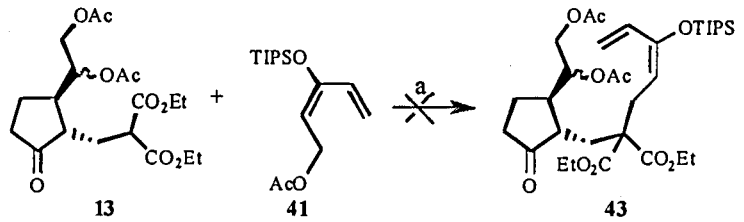
The oxidation of **36** was improved using Jones' reagent (CrO_3 dissolved in conc. H_2SO_4/water in a 1:9 ratio):[20] to a stirred solution of the hydroxy ester **36** in acetone, Jones' reagent was added in portions at 0 °C over two hours. Anhydrous magnesium sulphate was then added (to absorb the Cr(III) species formed), and the mixture was stirred for a further two hours while warming up to room temperature, to afford the keto-ester **37** as a colourless oil in 70% yield.

Compound **37** was then converted into the *E*-diene **39** by treatment with triisopropylsilyltriflate in the presence of triethylamine in dry dichloromethane over 15 hours. The configuration of the trisubstituted double bond was determined using a 2D-nOe ^1H NMR experiment, which showed enhancement of the triisopropylic proton signals when the vinylic proton on C-2 was irradiated.

A solution of the ester **39** in dry tetrahydrofuran at –78 °C was reduced using DIBAL to afford the alcohol **40**. Conversion of **40** into carbonate **41** using the same procedure employed to synthesise the carbonate **19a** was unsuccessful; deprotonation of **40** with *n*-BuLi at –78 °C in dry tetrahydrofuran gave the corresponding alcoholate, but its reaction with methylchloroformate gave a complex mixture of compounds, which we were unable either to purify or to identify. However, acetylation of **40** in acetic anhydride:pyridine= 1:1 in the presence of a catalytic amount of DMAP gave the acetate **42** in 80% yield.

As seen above, the silylenol ethers **39**, **40** and **42** are very unstable and must be stored in a freezer under a nitrogen atmosphere.

Unfortunately, the Pd(0) catalysed allylation (under basic conditions) of the malonate **13** using the acetate **42**, aiming to prepare the pro-heterotriene **43**, failed [Scheme 44].

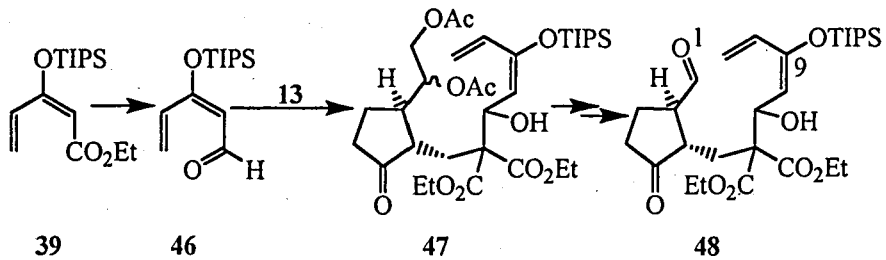


Scheme 44: a) NaH or $CsCO_3$, $Pd_2(dba)_3$, PPh_3 or dppe, dry degassed THF, reflux, 18 hours.

The malonate **13** was deprotonated with either $CsCO_3$ or NaH in dry degassed tetrahydrofuran at 0 °C. A mixture of the acetate **42**, $Pd_2(dba)_3$ and PPh_3 in dry degassed tetrahydrofuran was added and the mixture heated under reflux for 18 hours. Analysis of the ^1H NMR spectrum of the crude reaction mixture showed only unreacted starting materials.

In order to minimise the steric interactions between the bulky phosphine ligands (PPh_3) present on the catalyst and the triisopropylsilyloxy group next to the allylic system, which could prevent the formation of the π-allylpalladium complex, the coupling was attempted in the presence of dppe (bis-(diphenylphosphino)propane), which is a less bulky phosphine than PPh_3. Unfortunately, after heating under reflux for 18 hours in tetrahydrofuran, a mixture of only the unreacted starting materials was detected using ^1H NMR spectroscopic analysis.

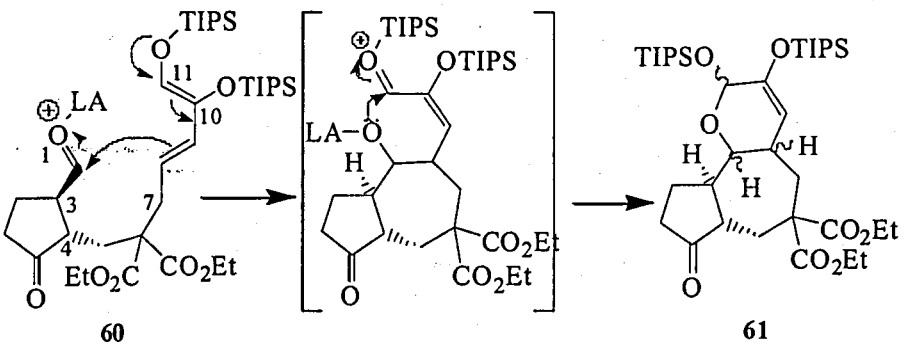
The failure to obtain the pro-heterotriene **43** compromised further work using this pathway. However, further investigation could be dedicated to the synthesis of dienes with appropriate substitution patterns. A solution to the problem encountered above might be to prepare a new pro-heterotriene (**47**, bearing a hydroxyl group next to the diene system), by 1,2-addition of the malonate **13** to the aldehyde **46** [Scheme 45].



Scheme 45: A different approach towards the synthesis of heterotrienes bearing the diene activation group in position C-9.

3.15 Activation of the positions 10 and 11 of the heterotriene

A second substitution pattern of interest was the double activation in positions 10 and 11 (triene numbering) by two silyl enol ether groups. The second substituent would increase the reactivity of the diene moiety to give the desired cycloadduct **61** [Fig. 46].



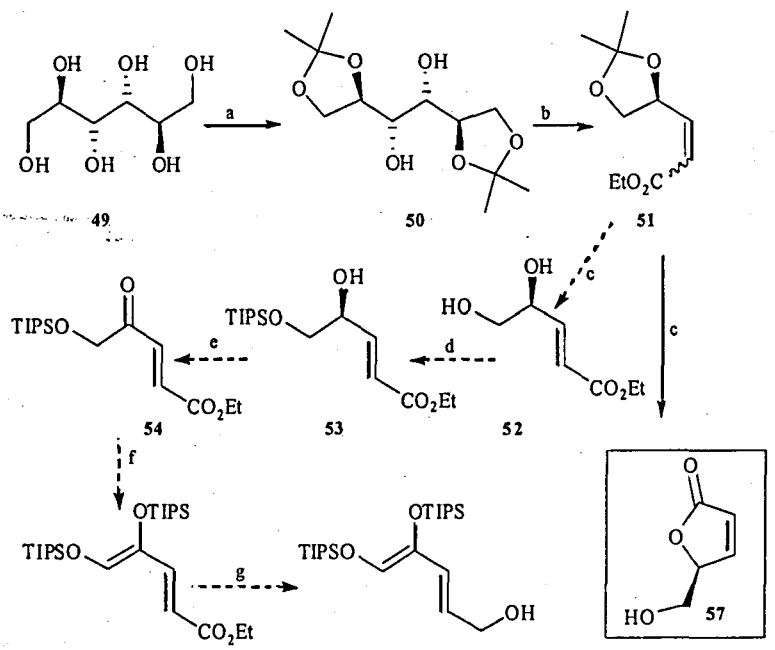
Scheme 46: Intramolecular cycloaddition of heterotriene **60** through the stepwise pathway.

A second electron-releasing substituent vastly increases the reactivity of the diene, but, because of steric hindrance, the rate of the cycloaddition may be reduced or even prevented. This has been demonstrated a few years ago by our research group during the synthetic studies towards the synthesis of the tigliane and daphnane skeletons: the intramolecular Diels-Alder (IMDA) reaction of 1,9,10 trienes with a double triisopropyl silyloxy activation of the diene system in positions 10 and 11 is much slower than the cycloaddition of trienes with a single silyloxy group in position 10. The steric repulsion between the bulky group in position 11 and the electron withdrawing group activating the dienophile is probably responsible for the slow rate of the reaction.

Despite this drawback, we decided to synthesise the dienol **56**, a molecule suitable to be converted into a carbonate or an acetate that could give us access to the heterotriene **60** using Pd(0) catalysed allylation of the malonate **13**.

We should be able to synthesise dienol **40** in 7 steps starting from D-mannitol (**49**): D-mannitol (**49**) is converted into the 1,3-5,6-D-mannitol diacetonide (**50**),[21] oxidative cleavage of **50** using $NaIO_4$ followed by a Wittig reaction using (triphenyl-

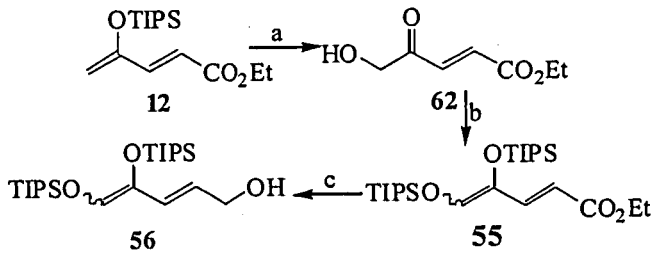
λ^5-phosphonylidene)-acetic acid ethyl ester ($Ph_3P{=}CHCO_2Et$), gives **51**. Diol **52** is obtained by hydrolysis of the ketal moiety using TFA and it is selectively monoprotected at the primary alcohol with a TIPS group to give (**53**). Oxidation of the secondary alcohol using Dess-Martin periodinane followed by enolisation with another TIPS group and reduction of the ester moiety should give us the desired dienol **56** [Scheme 47].



Scheme 47: First attempt to synthesise dienol **56**: a) 2,2-dimethoxy propane, *p*TSA, DMSO, from 0 °C to r.t., 18 hours, 30%; b) $NaIO_4$, H_2O, from 0 °C to r.t., 30 min., then $Ph_3P{=}CHCO_2Et$, from 0 °C to r.t., 15 hours, 82%, c) aq TFA, 63%; d) TIPSOTf, DCM; e) DMP, DCM; f) TIPSOTf, DCM; f) DIBAL, THF, –78 °C.

Protection of D-mannitol (**49**) with 2,2-dimethoxypropane and p-TSA as the catalyst in dry DMSO gave, after crystallisation from cyclohexane, 1,2-5,6-mannitol diacetonide **50** as a colourless solid in 30% yield. This was converted in one pot into the ester **51** through oxidative cleavage using $NaIO_4$ followed by a Wittig reaction with $(Ph)_3P{=}CHCO_2Et$ in water. The *cis* isomer was obtained as the major compound. All attempts to hydrolyse the acetonide moiety of the major isomer with aqueous TFA or HCl[22] gave the lactone **57** as a colorless solid in 63% yield.

It is still possible to pursue the synthesis of the diene moiety [Scheme 48].



Scheme 48: A second pathway towards dienol **56**: a) DMDO, acetone/THF, r.t., 30 min., 50%; b) TIPSOTf, Et_3N, DCM; c) DIBAL, THF.

The *E*-keto-ester **62** has been obtained through an easy and short pathway: compound **12**, an intermediate in the synthesis of dienol **13**, was oxidized using DMDO in acetone to give **62** as a colourless solid in 50% yield.

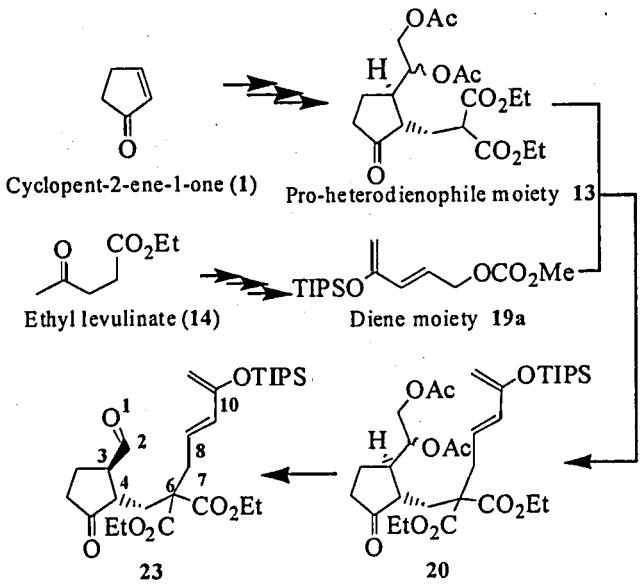
Due to time constraints, however, we decided against further work using this synthetic pathway.

3.16 Conclusions

The aim of this project was to synthesise the skeleton of the guaianolide family of natural compounds.

The synthetic aproach was centred on the very unusual intramolecular hetero-Diels-Alder (IMHDA) reaction of aldehydic 1,8,10-heterotrienes obtained through convergent synthesis.

The heterotriene **23** was successfully synthesised [Scheme 49].

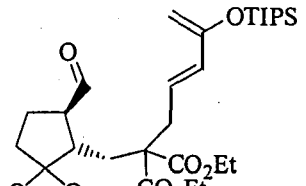


Scheme 49: Synthetic approach towards heterotriene **23**.

Starting from cyclopent-2-ene-1-one the pro-heterodienophile part **13** was obtained in four steps and the diene moiety **19a** was synthesised in four steps from ethyl laevulinate. The diene moiety was reacted together with the pro-heterodienophile using a Pd(0) catalysed allylation reaction to give the pro-heterotriene **20**, which was then converted into the heterotriene **23** in two steps

Several methodologies were applied to **23** in order to promote its IMHDA reaction and obtain the cycloadduct **24**, but, unfortunately, all attempts failed.
Use of thermal conditions, microwave irradiation, Lewis acids and ultra high-pressure were all unsuccessful, affording either unreacted, partially desilylated or decomposed starting material.

The introduction of a cyclic ketal into the chain linking the two reactant moieties was intended to push them towards each other and therefore favour the reaction. The cyclisation of the new spiro heterotriene **31** [Fig. 23] was attempted under several reaction conditions including thermal, Lewis acids, microwave irradiation and ultra high-pressure: no cyclisation occurred, and the results obtained were consistent with those reported using **23**.

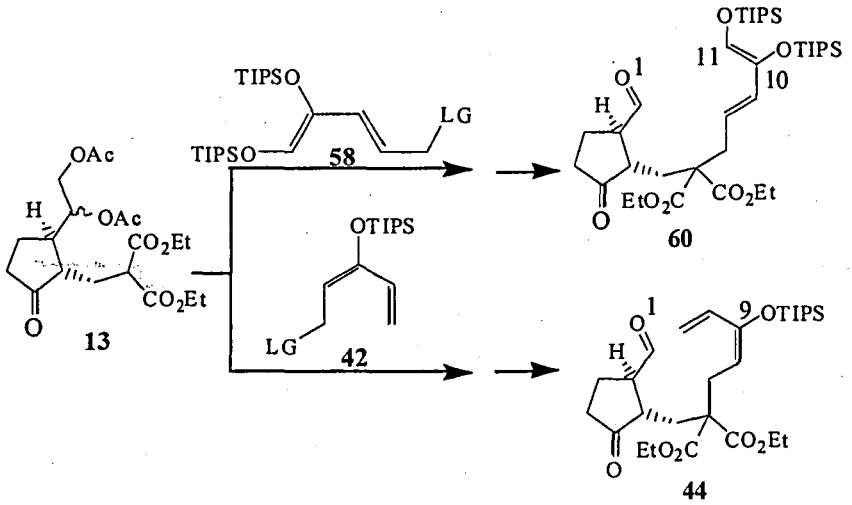


31

Figure 24: Modification at the linking chain: the spiro heterotriene **31**.

Meanwhile, our interest had been driven towards the modification of the diene activation pattern in order to obtain dienes more suitable for the regiochemistry required in our target **24**; by modifying the position of the triisopropylsilyloxy substituent along the diene framework, it is possible to redistribute the electron density of the π conjugated system in a way that would meet the demands for a successful IMHDA reaction.

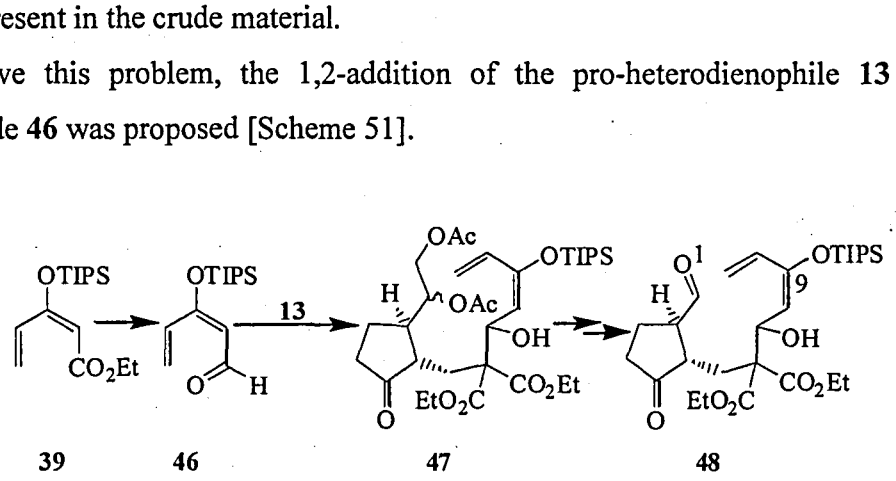
We proposed that the heterotriene **44** with a single activation in position C-9 and **60** with a double activation in positions C-10 and C-11 would be the desired precursors. The synthesis of these two heterotrienes takes place through the synthesis of the diene moieties **42** and **58**, which would then be employed in the Pd(0) catalysed allylation of **13** [Scheme 50].



Scheme 50: Different activation patterns of the heterotriene structure; LG= leaving group.

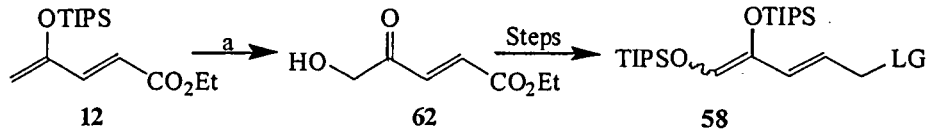
The diene **42** was synthesised in 5 steps starting from acrolein but the allylation performed under basic conditions, was unsuccessful and only the starting materials were present in the crude material.

To solve this problem, the 1,2-addition of the pro-heterodienophile **13** on the aldehyde **46** was proposed [Scheme 51].



Scheme 51: Proposal for an alternative pathway towards heterotrienes activated at C-9.

The synthesis of **58** has not been accomplished as the first approach we attempted, *via* the glyceraldehyde acetonide, was abandoned because it was too long when compared to the one going through the DMDO oxidation of the diene **12** [Scheme 52].



Scheme 52: a) DMDO, acetone/THF, r.t., 30 min., 50%; LG= leaving group.

Therefore, despite the fact that the IMHDA reaction of 1,8,10 trienals we were aiming for has not been accomplished yet, this investigation still represents an important starting point to successfully realise, in the near future, this intriguing class of intramolecular hetero Diels-Alder reaction.

3.17 References

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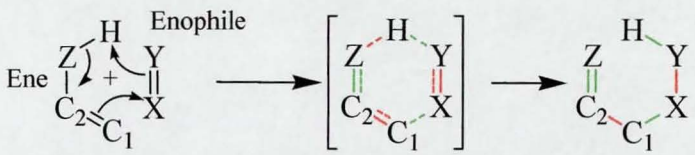
4 Synthesis of the Guaiane-6,12-olide Skeleton: The Carbonyl Ene Reaction Approach

4.1 Chemical background: The Alder ene reaction

4.1.1 Introduction

The reaction between an electron-poor multiple bond (enophile) and a compound carrying an allylic proton (ene) with consequent transposition of the double bond and formation of two new σ-bonds was first identified and characterised by Alder in 1943.[1] This process is well known as the Alder ene reaction, and nowadays is an efficient methodology for C-C and C-X (X= heteroatom) bond formation with migration of the allylic proton to the Y atom of the enophile reagent, migration of the allylic double bond from C-1 to C-2, and formation of the second σ-bond between C-1 and X, where X, Y, Z can be either carbon atoms or hetero-atoms.

In fact, enols, allylic metal derivatives, and vinyl- and allylsilane derivatives have all been used as the ene component. The same is true for the enophile component, which is not limited only to electron-deficient alkenes or alkynes but also extends to carbonyl derivatives, imines and iminium compounds, singlet oxygen, azo and nitroso compounds, S=O, S=N, Se=O species [Fig. 1].[2]



X=Y: C=C,C≡C, C=O, C=N, N=N, C=S,S=N, S=O, O=O, Se=O; Z: C, O, Si

Figure 1: The thermal Alder ene reaction goes through a concerted transition state.

The reaction can be promoted by high temperatures or Lewis acids; if the ene and the enophile are tethered it is possible to realise interesting fused bicyclic systems by the intramolecular Alder ene reaction.[3]

In the next few paragraphs a brief overview of the mechanism and principal features of this reaction are described, with particular attention given to the carbonyl-ene reaction

(with aldehydes as the enophile component), which is the basis of our approach towards the synthesis of the guaianolides skeleton described in this part of the thesis.

4.1.2 Mechanism

Inter- and intramolecular Alder ene reactions can be successfully performed under either thermal or acid catalysed conditions with the latter usually occurring under milder conditions than the former.

The transition state is characterised by a suprafacial interaction of the reagents, with the allylic proton pointing towards the enophile. To minimise the steric interaction originating during the reaction, the substituents on the enophile can be oriented under the allylic system (*endo* approach) or be pointing outwards from it (*exo* approach) [Fig. 2].

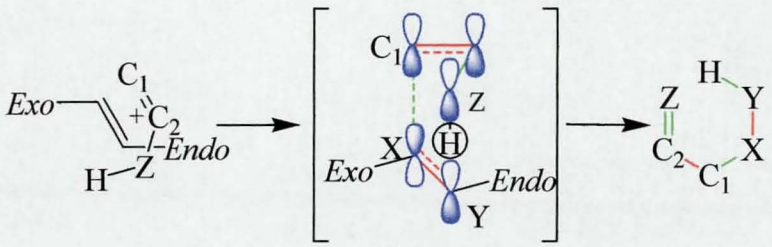


Figure 2: Suprafacial interaction and *endo* approach of the two reagents in the transition state of an Alder-ene reaction.

The thermal Alder ene reaction probably goes through a six-electron concerted transition state as suggested by the highly negative entropies of activation[4] and the *cis* addition to the enophile[5] in the intermolecular processes.

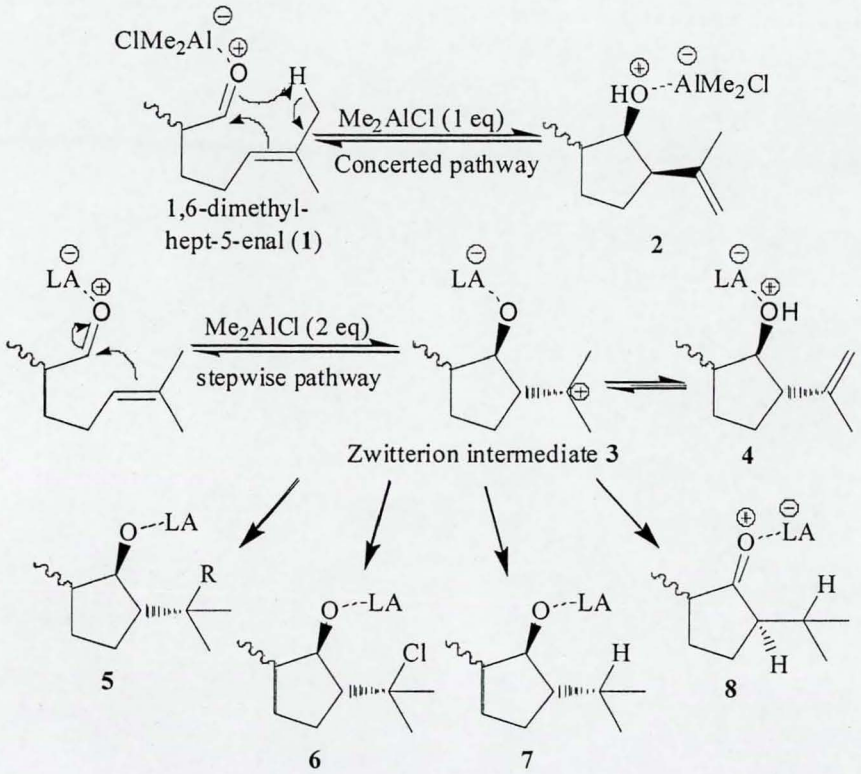
A stepwise biradical mechanism has been reported for the thermal reaction of cyclopentene and cyclohexene with azodicarboxylate promoted by free-radical initiators. The rigidity of the cyclic ene component probably prevents the formation of the optimum transition state for a concerted process, while the stability of the cyclic radicals favours a stepwise pathway.[6]

The similarity to the Diels-Alder (DA) reaction mechanism is evident, with a six-electron pericyclic transition state being involved in both cases:[2; b; 3 (b c); 3d] in the Alder ene reaction the allylic C-H bond replaces the second double bond of the DA reaction.

This increases the transition state energy level because the energy required to move the two σ-electrons is higher than that necessary to shift the corresponding two π-electrons in the DA reaction.

As regards the acid catalysed reactions, a continuum from concerted[7] to cationic[8] mechanism has been considered. Experimental evidence supports both mechanisms, and probably, when for steric reasons it is impossible to obtain the optimum geometry of the transition state, the concerted pathway gives way to the stepwise process.

The intramolecular ene cyclisation of 2,6-dimethyl-hept-5-enal (**1**) depends on the amount of Me_2AlCl used as catalyst, as shown in scheme 1: if one equivalent of Lewis acid is used, formation of a *syn* cyclopentanol **2** (which suggests a concerted pathway) is observed, but the presence of two equivalents of catalyst stabilises a zwitterion species **3**, which, on the basis of the reaction temperature, rearranges to different compounds (**4-8**).[9]



Scheme 1; The amount of Lewis acid used, determines the mechanism of the cyclisation.

The molecular orbitals involved are the HOMO of the ene and the LUMO of the enophile, and therefore, as explained for the Diels-Alder reaction, the reactivity of the enophile component is enhanced by the presence of electron-withdrawing groups

which reduce the energy level of the LUMO towards the HOMO energy level helping to accomplish the reaction. Multiple bonds are more reactive when conjugated with esters, acyl chlorides or carbonyl groups than when isolated; furthermore the presence of the carboxyl or carbonyl group allows the use of Lewis acid catalysis, which has been demonstrated to increase the rate of the reaction. Aldehydes are more reactive when activated by electron-withdrawing groups, as in the case of chloral or glyoxylate derivatives. The latter enable the use of chiral auxiliaries, very useful when performing asymmetric synthesis.

The reactivity of the ene component is strongly related to the nature of the enophile, the reaction conditions and, if employed, the Lewis acid. Usually the reactivity observed for alkenes is 1,1-di- > tri- >, tetra- >>, mono- >1,2-disubstitued [Fig. 3].

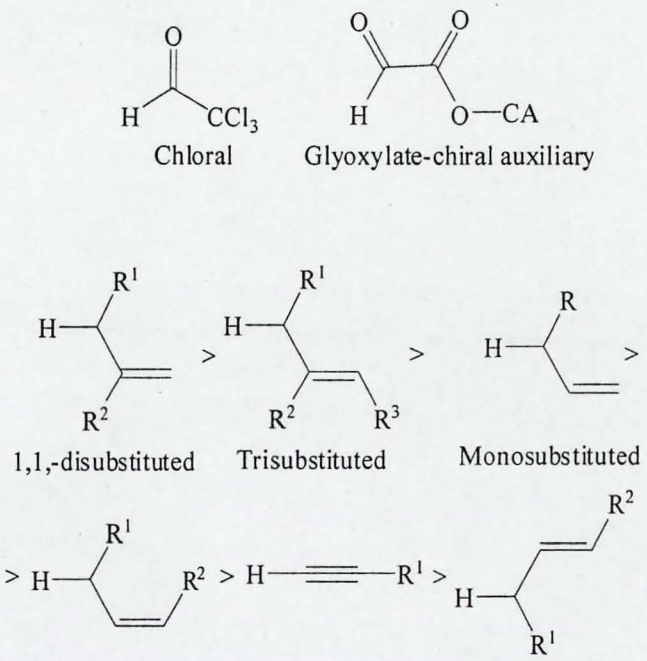
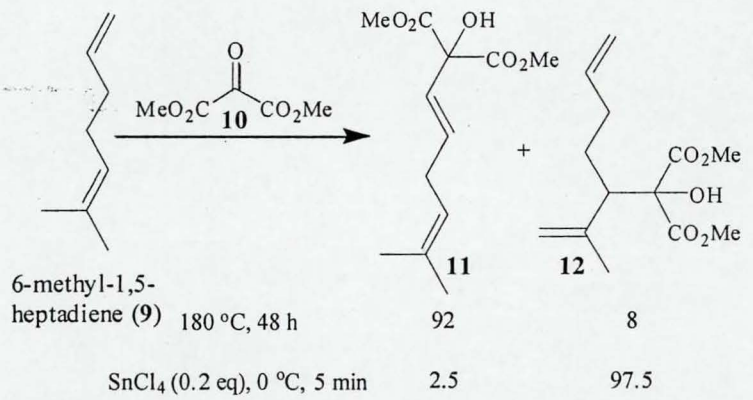


Figure 3: Examples of activated aldehydes as enophile components (top), and order of reactivity of different multiple bonds as ene component (bottom).

Strain in the ene component (which favours the migration of the allylic proton) and the correct alignment of the reactants are other factors facilitating the process.

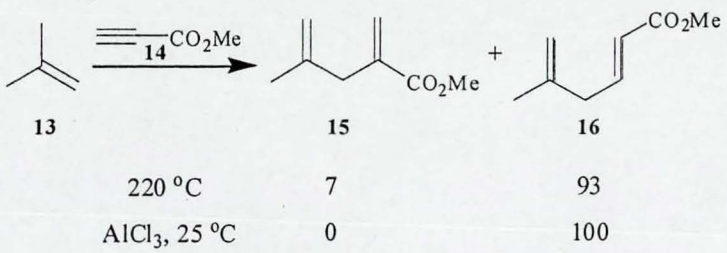
The electronic effects are very important in acidic catalysed reactions; regardless of the mechanism, a positive charge is developed during the reaction and consequently 1,1-disubstituted alkenes are more reactive than mono- or 1,2-disubstituted alkenes, because they are better able to stabilise the developing positive charge.[10] On the

contrary, the accessibility to reagents is the leading factor in thermally activated Alder ene reactions. This is demonstrated in scheme 2, where the results of the reaction between diethyloxomalonate (**10**) and 6-methyl-1,5-heptadiene (**9**) under Lewis acid and thermal conditions are compared: under thermal conditions the less hindered terminal double bond reacts as the enophile to give **11** as the major compound, while under Lewis acid catalysed conditions the more electron rich but more hindered trisubstituted double bond is the reactive moiety and **12** becomes the major product of the reaction.[11]



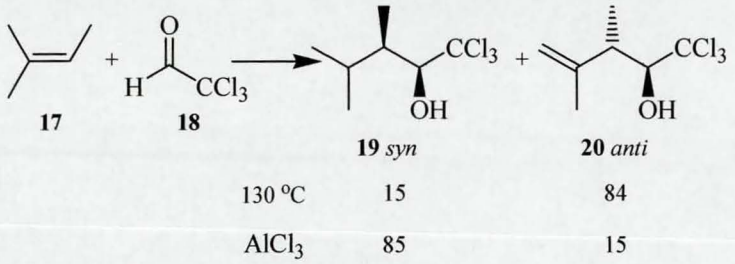
Scheme 2: Different regioselectivity in thermal and Lewis acid promoted carbonyl-ene reaction.

The use of Lewis acids can also increase the regioselectivity of the thermal process by differentiation of the potentially reactive sites; in the case of α,β-unsaturated esters, complexation to the carboxylic group polarises the multiple bond, and the β-carbon becomes more electrophilic increasing the regioselectivity of the reaction [Scheme 3].[11] The reaction of **13** with **14** under Lewis acid catalysed conditions gives exclusively **16** the product of the 1,4-addition to the ester **14**. On the contrary, under thermal conditions a small amount of **15** is formed.



Scheme 3: Use of Lewis acids can increase the regioselectivity of the Alder-ene reaction.

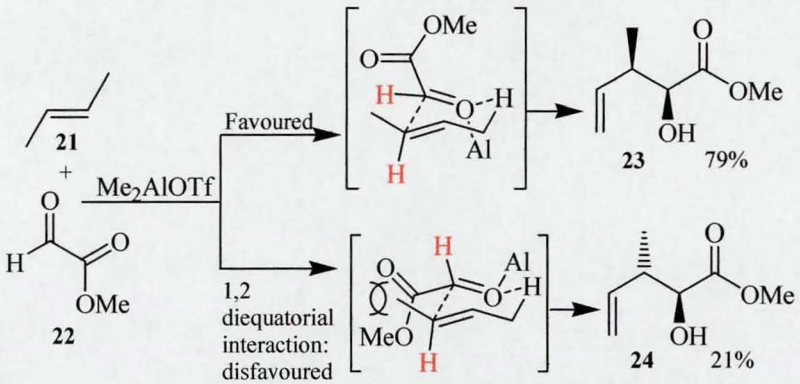
Different diastereoselectivities have been observed in thermal and Lewis acid catalysed Alder ene reactions, with formation of *anti* (**20**) and *syn* (**19**) isomers respectively as the major products [Scheme 4].[12]



Scheme 4: Thermal carbonyl ene reaction of chloral (**18**) leads to the *anti* isomer (**20**) as the major diastereoisomer; under Lewis catalysed conditions, the stereoselectivity is reversed.

These are only examples, and the reaction conditions, substrates and Lewis acids can determine a different stereochemical outcome.

To predict the stereochemical outcome of these reactions it is always useful to refer to the models of the transition states potentially involved in the process and to try to find the less energetic, that is usually the one less sterically encumbered. To justify the *syn* diastereoselectivity for Lewis acid catalysed carbonyl-ene reactions, Mikami and Nakai proposed a 6-membered chair-like transition state [Scheme 5].[13]



Scheme 5: 6-membered chair-like transition states explain the selectivity of the aluminium catalysed ene reaction of glyoxylate (**22**) with *trans*-2-butene (**21**) towards the *syn* isomer (**23**): the reaction goes through the less hindered transition state (top). The transition state leading to the *anti* isomer (**24**) is disfavoured because of the 1,2 diequatorial interaction between the ester group of the glyoxylate and the methyl group of the *trans*-2-butene.

4.1.3 Intramolecular reaction

As with all the intramolecular processes, the intramolecular Alder-ene reaction is more favourable than the intermolecular version because the entropy of activation is less negative: the two reactants are part of the same molecule and therefore the probability of useful interactions between them is much higher than in a bimolecular process.

According to Mikami, in the intramolecular Alder ene reaction, six different modes of cyclisation can be defined [Figure 4].[14]

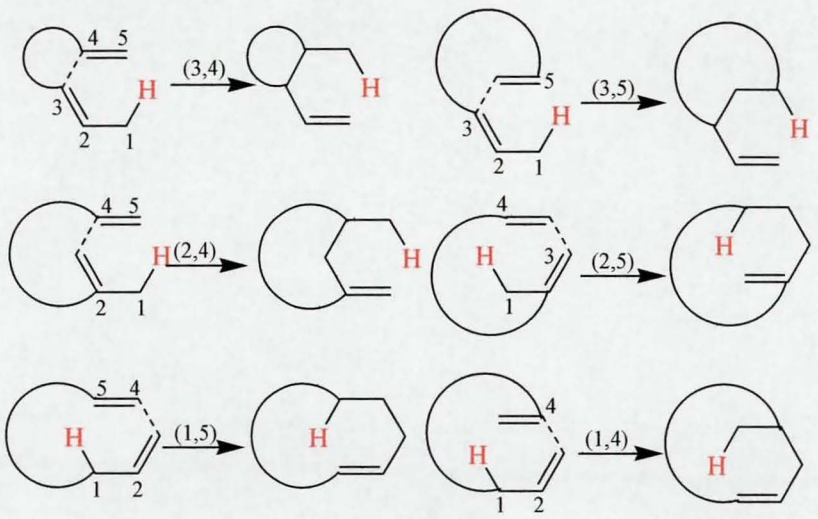


Figure 4: Modes of cyclisation in Alder-ene reaction.

On the basis of the atom numbering shown in figure 4, the carbons of the [1,5] hydrogen shift system which are connected by the tether are reported in the (*m, n*) notation and the size of the ring formed by the cyclisation by the prefix *l*-.

The modes (3,4), (2,4), (1,5) are coincident with those defined by Oppolzer as types I, II and III.[15]

Depending on the tether length, (3,4) cyclisations lead mostly to 5-, 6- and rarely to ≥ 7-membered ring systems with the formation of 5-membered favoured over the 6-membered rings. Opposite behaviour has been reported for carbonyl enophiles. Usually, *syn* 5-membered rings and *anti* 6-membered rings are formed as the major compounds in (3,4) ene cyclisations.

Formation of 6- or 7-membered rings has been reported for (2,4) ene cyclisations[16] while (1,5) cyclisations afford medium sized rings.[17]

Internal activation of the enophile favours the 6-(3,5)[18] ene cyclisation rather than the 5-(3,4) ring closure. Finally the (1,4) cyclisation has been used to obtain cyclohexenol and cycloheptenol from trifluoromethyl ketones[19].

The Alder ene reaction represents such a wide topic that it would be beyond the purpose of this thesis to analyse deeper the features of this process. This is why the attention of the next few paragraphs is centred on the intramolecular Alder ene reaction with carbonyls (mostly aldehydes) as the enophile components, which is the approach we have used towards the synthesis of the guaianolide skeleton, the subject matter of the next chapter.

4.1.4 The Carbonyl-ene reaction

The difference in electronegativity between the atom of carbon and oxygen polarises the C=O bond of carbonyl compounds: a partial negative charge δ^- is present over the atom of oxygen and a partial positive charge δ^+ is present around the atom of carbon. This carbon atom, being electron deficient, becomes a site suitable for the attack not only of nucleophiles but also for alkenes active as ene components in the Alder ene reaction.

When carbonyl compounds (the aldehydes are more reactive than the ketones because of the higher polarisation of the C=O double bond) act as enophiles, the corresponding Alder ene reaction is also known as the carbonyl-ene reaction.

Over the past decades many research groups have investigated the inter- and intramolecular process under thermal and acid catalysed conditions and have attempted to rationalise the outcome of the carbonyl–ene reaction, especially with regard to regio,- diastereo- and enantioselectivity.

4.1.4.1 Intramolecular carbonyl-ene reaction

Depending on the length of the tether linking the two reactant moieties, the intramolecular carbonyl-ene reaction leads to differently sized cycloalkanols. Formation of five, six and seven membered rings is commonly encountered but cyclisation to higher systems has been reported as well. The presence of the reactants on the same molecule favours the process, and unactivated aldehydes can now react under thermal conditions (we have seen that this is not possible for the intermolecular reaction). The polarisation of the carbonylic group makes it a better enophile than an all-carbon double bond, and consequently the former reacts faster than the latter.

4.1.4.2 Types of cyclisation

Three modes of cyclisation have been reported so far for the carbonyl-ene reaction: 5- or 6-(3,4), 6- or 7-(2,4) and >7-(1,5) cyclisations according to Mikami or respectively types I, II and III using Oppolzer's definition of these modes of cyclisation [Fig. 5].

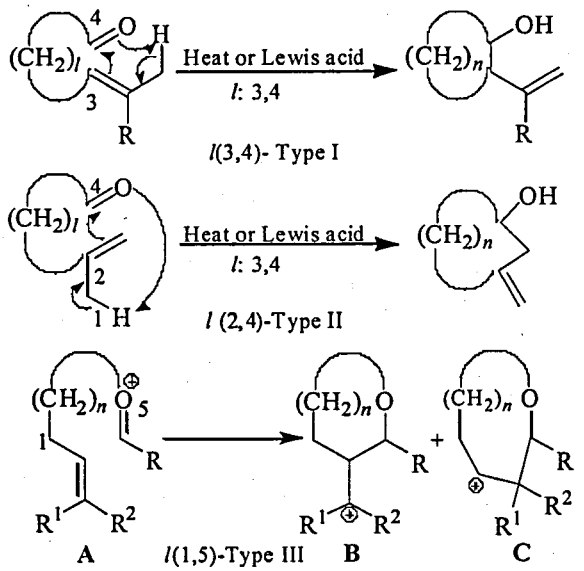


Figure 5: Types of cyclisation in intramolecular carbonyl-ene reaction.

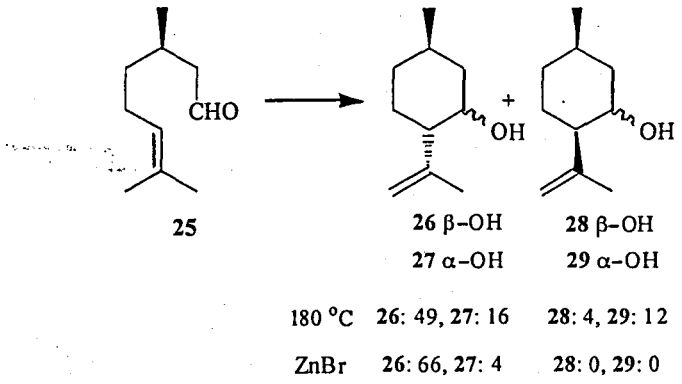
For ease of description, Oppolzer's definition will be followed.

4.1.4.3 Type I reactions

In type I reactions, 5- or 6-membered rings are obtained: formation of cyclohexanols is faster than the formation of cyclopentanols, due to the higher ring strain of the latter.

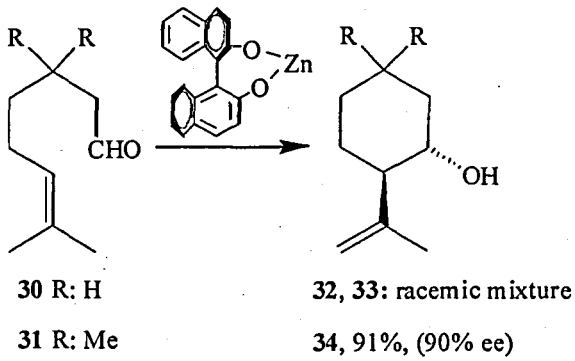
4.1.4.3.1 Formation of cyclohexanols

Formation of *anti*-compounds as the major products is usually observed under both thermal and Lewis acid catalysed conditions, with a very interesting internal diastereoselectivity shown by the Lewis acid catalysed reaction [Scheme 6].[20] Under Lewis acid catalysed conditions, the process is more diastereoselective than under thermal conditions.



Scheme 6: Type I cyclisation of an unsaturated aldehyde leading to a mixture of cyclohexanols.

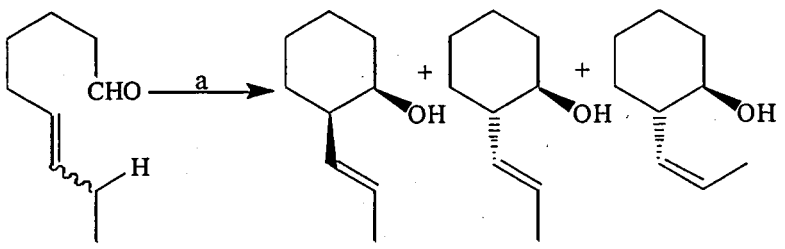
Yamamoto has demonstrated the importance of a substituent on the linking chain for the stereoselectivity of the process: the absence of any substitution leads to racemic mixtures even in the presence of chiral Lewis acids, but with *gem*-disubstitution, high levels of enantioselectivity are reached [Scheme 7].[21]



Scheme 7: *gem*-disubstitution allows high enantioselectivity of the ring closure.

Cyclisation in the presence of the less reactive 1,2-disubsituted ene moiety is dependent on the stereochemistry of the double bond: ring closure of (*E*) alkenes gives mixtures

of *syn* and *anti* diastereoisomers **37**, **39**, **38**, with the latter as the major products, while cyclisation of (*Z*) alkenes exclusively gives the *syn* stereoisomer **37** [Scheme 8].[22]



	37	38	39
35 (*Z*)	75%	0%	0%
36 (*E*)	12%	54%	10%

Scheme 8: Different stereochemical outcome in the carbonyl-ene cyclisation of unsaturated aldehydes with 1,2 disubstituted double bond: a) Me_2AlCl, 1eq.

4.1.4.3.2 Formation of cyclopentanols

As shown above in scheme 1, the carbonyl ene reaction seems to be controlled by the strength or concentration of the Lewis acid employed to perform the reaction. This determines the reaction pathway and, therefore, the chemical and stereochemical outcome of the reaction.

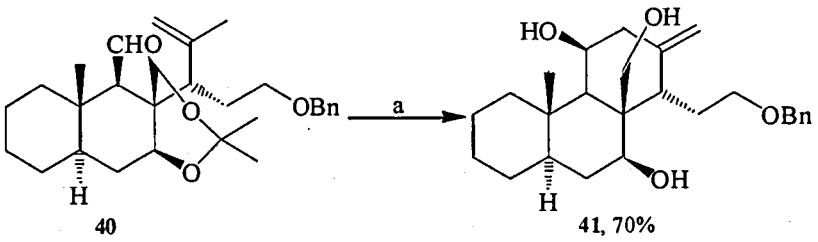
4.1.4.4 Type II reactions

Thermal or Lewis acid catalysed type II carbonyl-ene cyclisation is restricted to formation of 3-methylenecyclohexanols and 3-methylenecycloheptanols. Cyclisation of γ,δ-unsaturated aldehydes and ketones is stepwise and a zwitterionic species is formed which rearranges into cyclopentanones or 3-methylenecyclopentanols.

4.1.4.4.1 Formation of cyclohexanols

This type of cyclisation, regardless of the concerted or stepwise mechanism, is often characterised by the formation of an exocyclic double bond and of an axial hydroxy group. It is worth noting that the axial orientation is maintained also in the less

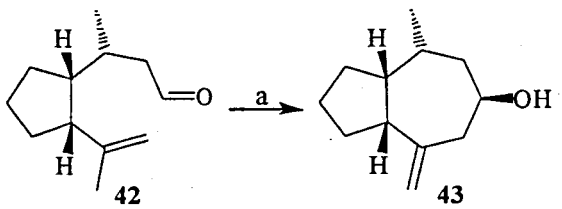
favourable conditions, when axial substituents are present next to the newly formed alcohol [Scheme 9].[23]



Scheme 9: Type II formation of cyclohexanols often occurs with formation of exocyclic double bond and axial hydroxy group: a) $SnCl_4$, DCM, 0 °C, 3 min, 70%.

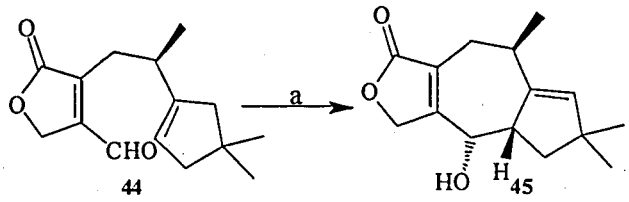
4.1.4.4.2 Formation of cycloheptanols

The first application of type II carbonyl-ene cyclisation for the synthesis of cycloheptanols was carried out by Marshall while synthesising the hydroazulene ring system: the presence of a β-methyl group on the aldehyde **42** makes the cyclisation highly diastereoselective, and only the corresponding cycloheptanol **43** was formed [Scheme 10].[24]



Scheme 10: Diastereoselective formation of cycloheptanols through intramolecular carbonyl-ene reaction: a) Silica gel.

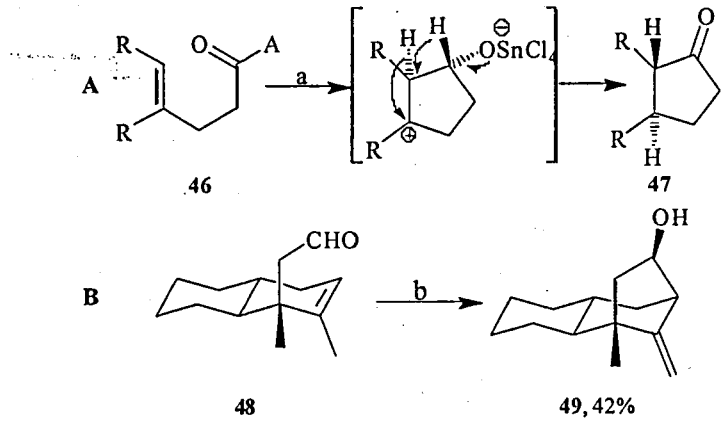
The reaction takes place through the less hindered transition state: in the reaction shown in scheme 11, the aldehyde attacks from the less hindered face opposite to the methyl group present on the tether to give **45**.[25]



Scheme 11: The methyl group on the tether drives the aldehyde to attack from the α-face: a single diastereoisomer is formed: a) Me_2AlCl, 35%.

4.1.4.4.3 Formation of cyclopentanols and cyclopentanones

A proper concerted carbonyl-ene cyclisation of γ,δ-unsaturated aldehydes and ketones is not possible because the 2-carbon tether is too short to allow proper alignment of the reacting components. Under Lewis acid catalysed conditions, the reaction occurs through the formation of a zwitterion species, which can rearrange with a double [1,2] hydride shift to give cyclopentanones eg **47** [Scheme 12 **A**][26] or alternatively can lose a proton to give methylene alcohols eg **49** [Scheme 12 **B**].[27]



Scheme 12: Cyclisation of γ,δ-unsaturated aldehydes gives ketones (**47**) or cyclopentanol derivatives (**49**): a) $SnCl_4$, yield from 37 to 57% depending on the R groups; b) $SnCl_4$, 42%.

4.1.4.5 Type III reactions

Acetals, hemiacetals and enol ethers **A** under acidic conditions form electrophilic cationic species which cyclise to give cyclic ethers **B** or **C** depending on the substitution pattern of the double bond: formation of the most stable (most substituted) carbocation is favoured, and therefore **B** is formed when the external end of the double bond is more substituted [Fig. 6].

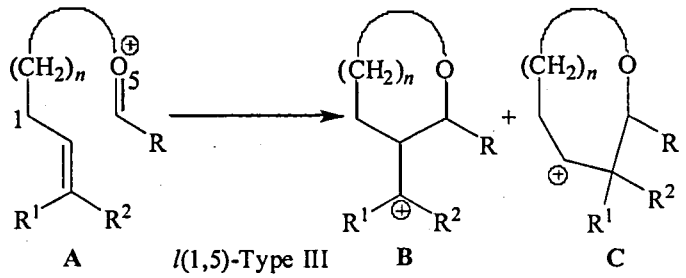
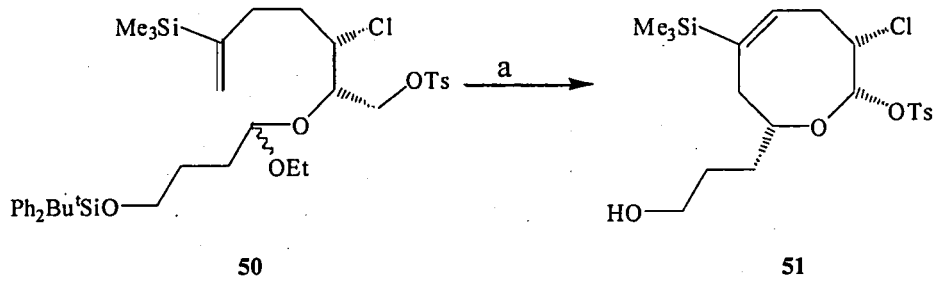


Figure 6: Type III intramolecular carbonyl-ene cyclisation.

An interesting application of this cyclisation is the formation of eight- and nine-membered ring systems [Scheme 13].[28]



50 51

Scheme13: Formation of eight membered cyclic ethers:a) $SnCl_4$, 37%.

4.2 References

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5 The Carbonyl Ene Reaction Approach: Results and Discussion

5.1 Introduction

The problems associated with the intramolecular hetero Diels-Alder (IMHDA) reaction approach drove us to look for alternative pathways to synthesise the skeleton of guaianolide-type natural compounds. A synthetic approach similar to that used in the synthesis of the tigliane and daphnane skeletons was researched, so that we were able to access three different families of natural compounds through similar pathways and building blocks.

The potential answer to our needs lays in the convergent synthesis of a functionalised perhydroazulene ring system, which could be converted into the desired guaianolide skeleton.

According to our retrosynthetic study, the guaiane-6,12-olide skeleton **1** and in particular the α-methylene-γ-lactone ring, should be accessible by allylic oxidation of the perhydroazulenones **3**, the product of the intramolecular carbonyl-ene reaction of the aldehydes **4**, which are obtained by coupling the malonates **6** and the prenyl derivative **7**. Malonates **6**, as reported above, are obtained from substituted cyclopentenones and vinylmagnesium bromide [Fig. 7].

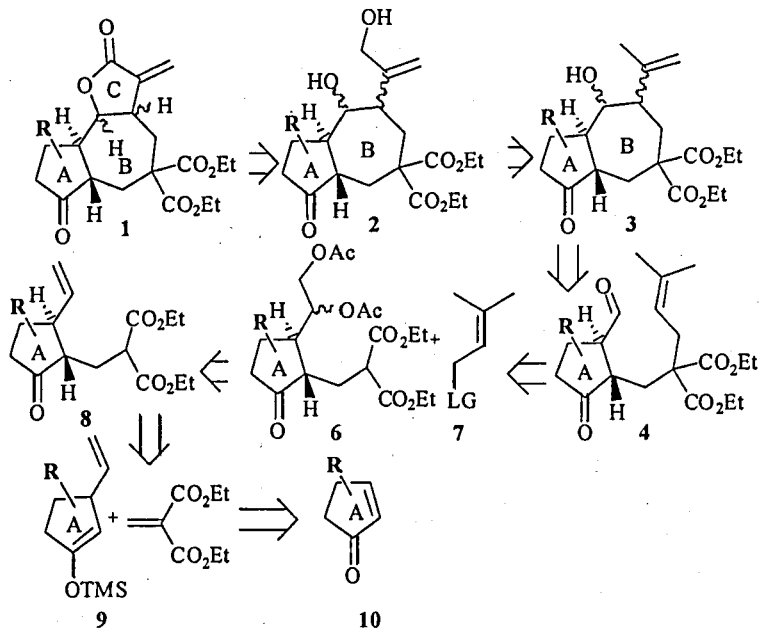
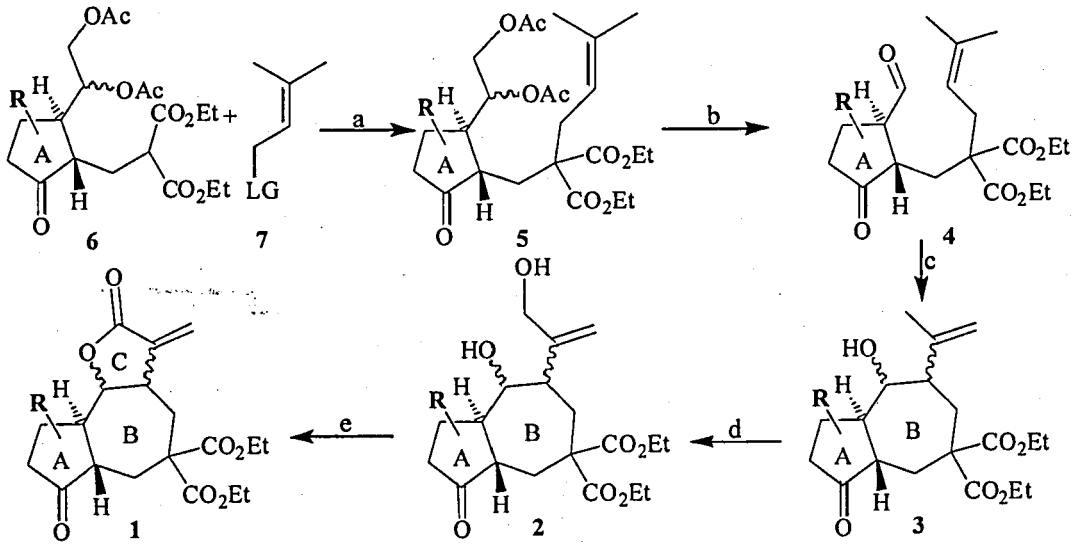


Figure 7: Retrosynthetic approach towards the guaianolide skeleton *via* an intramolecular carbonyl-ene reaction.

This synthetic strategy incorporates the displacement of the leaving group (LG) of **7** by the malonates **6** to obtain the aldehydes **4**, which undergo a type I carbonyl-ene cyclisation to give **3**. Allylic oxidation of the propene moiety followed by treatment with TPAP should provide the α-methylene-γ-lactone ring and therefore the desired guaianolide skeleton **1** [Scheme 14].



Scheme 14: Convergent synthetic approach towards the guaianolide skeleton: a) Base; b) Amberlite® 400 CI, $NaIO_4$; c) Lewis acid; d) SeO_2; e) TPAP.

This synthetic route responds to the needs outlined above: the convergent approach has been maintained and the malonates **6** has been used as a substrate. Moreover this pathway is, in theory, shorter than previous, as the precursors of **7** are commercially available.

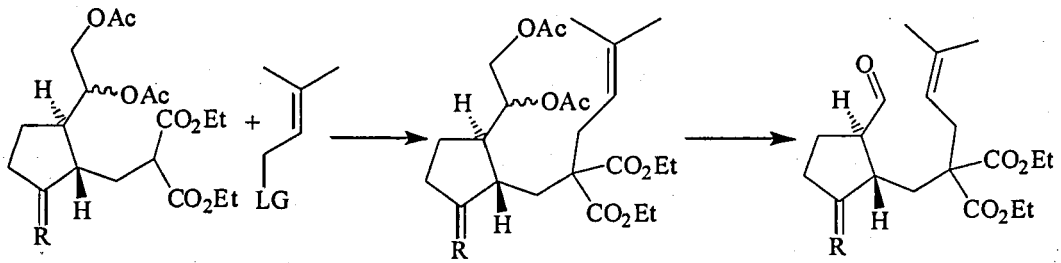
The synthesis of the perhydroazulene ring system has been achieved through metallo-ene,[1] type II carbonyl-ene[2] and Prins[3] reactions among others, but, as far as we know, formation of cycloheptanol rings by a type I carbonyl-ene cyclisation has not been reported. Therefore, this approach also gives us the opportunity to investigate the type I ene-cyclisation of unsaturated aldehydes leading to seven membered rings.

In this chapter the synthesis of aldehydes such as **4** and the cyclisation attempts using carbonyl-ene reactions are described.

5.2 Synthesis of the unsaturated aldehydes 67 and 70

As mentioned above, our aim was to find an efficient synthetic pathway towards the guaianolide skeleton, an alternative to the similar IMHDA reaction approach.

With this concept in our mind, we decided to synthesise the unsaturated aldehydes **67** and **70** by a convergent route similar to the one used in the synthesis of the heterotrienes **23** and **31**: malonates **13** and **29** (already used as pro-heterodienophile moiety precursors), were coupled with an prenyl unit **64**, the ene component, to obtain the pro-aldehydes **65** and **68**, which were converted into the aldehydes **67** and **70** by a sequence of hydrolysis and oxidative cleavage reactions [Scheme 15].



29: R= $O(CH_2)_2O$ **64** **65**: R= $O(CH_2)_2O$ **67**: R= $O(CH_2)_2O$
13: R= O **68**: R= O **70**: R= O

Scheme 15: Synthetic approach towards the unsaturated aldehydes **67** and **70**.

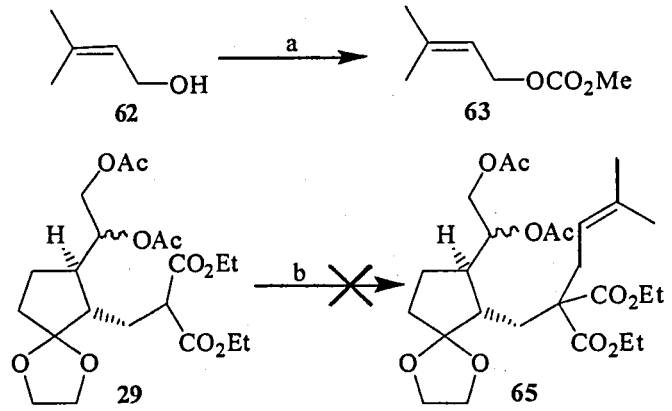
The ketal **29** was initially used because protection of the ketone group should prevent from any interference during the coupling with the ene component.

5.2.1 Synthesis of the pro-aldehydes 65 and 68

A palladium(0) catalysed allylation of the malonate **29** with the carbonate **63** was initially attempted. Compound **63** was obtained by treatment of alcohol **62** with *n*-BuLi followed by methyl-chloroformate in dry tetrahydrofuran.

$Pd_2(dba)_3$ and PPh_3 were added to malonate **29** and carbonate **63** in dry dichloromethane. ^1H NMR analysis of the crude reaction mixture indicated that no reaction had occurred and that only malonate starting material had been recovered from the reaction.

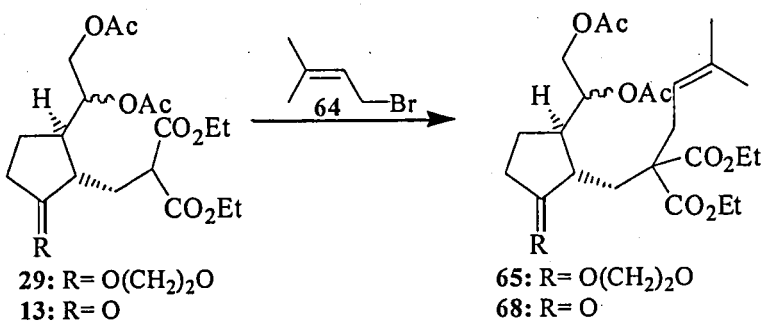
The same result was obtained when tetrahydrofuran was used as the solvent [Scheme 16].



Scheme 16: Synthesis of the carbonate **63** (top), substrate for the Pd(0) catalysed allylation of malonate **29**, which unfortunately was unsuccessful (bottom). a) *n*-BuLi, THF, -78 °C, 15 min., then $ClCO_2Me$, 45 min., 60%; b) **63**, PPh_3, $Pd_2(dba)_3$, DCM or THF, reflux, 18 hours, the reaction failed.

We attempted a different strategy with the displacement of the halogen in **64** by the malonate anion of **29**: a solution of malonate **29** in tetrahydrofuran was added to a solution of lithium diisopropylamide (LDA) at –78 °C. Prenyl bromide **64** was added and the solution stirred for 18 hours. The crude material was purified by flash column chromatography to give the pro-aldehyde **65** as a mixture of two diastereoisomers in 79% yield.

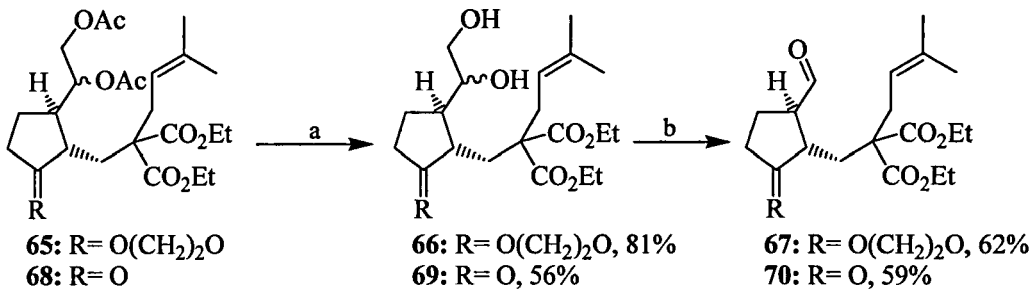
Malonate **13** was deprotonated by *n*-buthyllithium, and treated with prenyl bromide **64** to obtain the pro-ketoaldehyde **68** as a diastereoisomeric mixture in 57% yield [Scheme 17].



Scheme 17: Synthesis of the pro-aldehydes **65** and **68**: a) **29**, LDA, THF, from –78 °C to r.t.; 79%; b) *n*-BuLi, THF, from –78 °C to r.t.; 57%.

5.2.2 Synthesis of the aldehydes 67 and 70

The two pro-aldehydes **65** and **68** were deacetylated with activated Amberlite® 400 Cl in methanol for eighteen hours: the hydrolysis of the ketal **65** was more efficient than hydrolysis of the ketone **68** with the diol **66** being obtained in 81% yield as a colourless oil, and the ketone **69** in 56% yield (colourless oil). The oxidative cleavage also favoured the reaction of the ketal **66**: compound **67** was obtained as a colourless oil in 62% yield, while **70** was obtained in 59% yield [Scheme 18].



65: R= $O(CH_2)_2O$
68: R= O

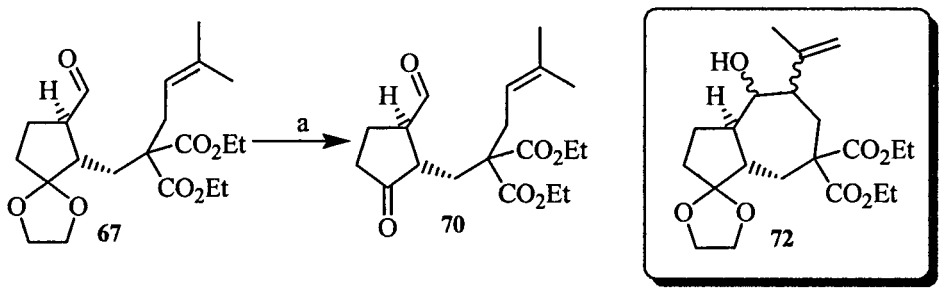
66: R= $O(CH_2)_2O$, 81%
69: R= O, 56%

67: R= $O(CH_2)_2O$, 62%
70: R= O, 59%

Scheme 18: A hydrolysis/oxidative cleavage sequence to synthetise the unsaturated aldehydes **67** and **70**: a) Amberlite® 400 Cl, MeOH, r.t., 18 hours; b) $NaIO_4$, $MeOH/H_2O$, 30 min.

5.2.3 Attempts at the intramolecular carbonyl-ene reaction of 67

Cyclisation was first attempted on the aldehyde **67** [Scheme 19].



Scheme 19: Attempt at the cyclisation of **67**, led to the ketoaldehyde **70**. No trace of the expected cycloheptanol **72** was isolated: a) Lewis acid.

ZnI_2 was initially used as catalyst. A solution of the aldehyde **67** in dry dichloromethane or tetrahydrofuran was treated with Lewis acid until complete consumption of the starting material was observed. TLC and ^1H NMR analysis of the crude reaction mixture indicated that a complex mixture of compounds had formed.

Purification of the crude material allowed us to identify the ketoaldehyde **70** as the major product of the reaction. Cyclised product **72** was not observed by ^{1}H NMR analysis of the crude reaction mixture. The same result was obtained when 1 or 2.5 equivalents of $Yb(OTf)_3$ in dry tetrahydrofuran were used [Table 1]. The use of 10 equivalents of $BF_3 \cdot Et_2O$ at –78 °C was also unsuccessful, giving only the ketone **70** [Table 1].

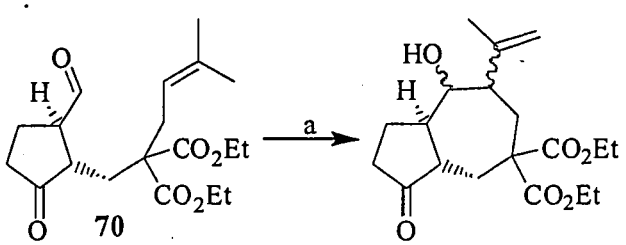
Substrate	Catalyst	Conditions	Outcome/yield
67	ZnI_2; 1, 2.5 eq	0 °C to r.t., 16 h	70/(33%)
67	$Yb(OTf)_3$; 1, 2.5 eq	0 °C to r.t., 16 h	70/(50%)
67	$BF_3 \cdot Et_2O$	THF, -78 °C to r.t., 24 h	70/(78%)

Table 2: Attempts at the intramolecular carbonyl-ene cyclisation of the ketal **67**.

5.2.4 Attempts at the intramolecular carbonyl-ene reaction of 70

The results of the attempts at the cyclisation of **67** indicate that the ketal is the first moiety of our substrate to react with the catalyst, releasing keto-aldehyde **70** and ethylene glycol. The latter could cause consumption of Lewis acid making the activation of the aldehyde towards the ene process more difficult. Moreover, the presence in our substrate of many nucleophilic oxygen atoms, which are able to coordinate with the Lewis acids used, represents a second potential reason of depletion of available catalyst.

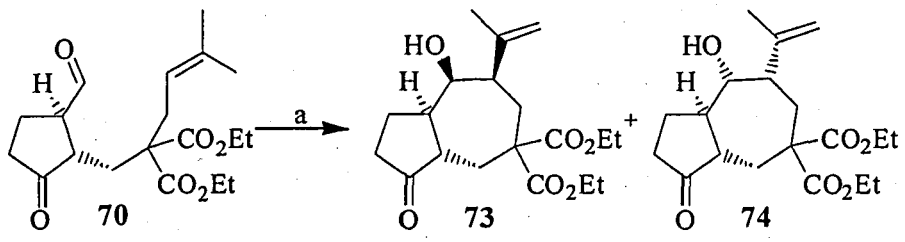
For these reasons we switched our attention towards the ketoaldehyde **70** as a new cyclisation substrate [Scheme 20].



Scheme 20: Carbonyl-ene cyclisation of the unsaturated aldehyde **70**: a) Lewis acid.

We used a large excess of catalyst, to compensate for the amount potentially inactivated by the interaction with the ester groups and the ketone group: five equivalents of BF_3•Et_2O were added at –78 °C to a solution of **70** in tetrahydrofuran, and the reaction stirred for four hours at –78 °C before being allowed to reach room temperature.

At this stage the result was very interesting; TLC analysis showed the formation of two new spots just beneath the starting material. After 24 hours, the conversion of the starting material was complete, and ^1H NMR analysis of the crude showed no presence of any aldehydic or vinylic signals but two singlets at around 5 ppm indicated with high probability the presence of two methylene protons. Moreover, the presence of a triplet at 3.35 ppm and a singlet at 3.82 ppm was consistent with the presence of two protons on carbon atoms bearing an alcoholic group and belonging to two different stereoisomers. This result was very encouraging and by purification of the crude material it was possible to isolate two isomers in a 4/1 ratio as colorless oil, in 50% overall yield [Scheme 21].



Scheme 21: Carbonyl-ene cyclisation of the unsaturated aldehyde **70**: a) BF_3•Et_2O (5 eq), THF, from –78 °C to r.t., 24 hours, **73** (40%), **74** (10%).

As confirmed by full spectroscopic characterization, the two new compounds isolated were **73** and **74**, the result of the Lewis acid catalysed carbonyl-ene cyclisation of **70**. Encouraged by this positive result, we investigated the use of different catalysts.

When aldehyde **70** was stirred at 0 °C or at room temperature in either dichloromethane or tetrahydrofuran for 1 to 10 days in the presence of up to 10 equivalents of ZnI_2, no reaction occurred.

The same conditions and reaction time were used when $Sc(OTf)_3$ was employed as promoter of the reaction, but again no reaction occurred.

The reaction of **70** with 5 equivalents of $Yb(OTf)_3$ in dry tetrahydrofuran at room temperature for five days afforded compound **73** (colourless oil, in 46% yield), as the only product isolated after purification.

Aldehyde **70** was also submitted to microwave irradiation, (toluene,120 °C in sealed tube, 10 minutes), but only starting material was detected by ^1H NMR analysis after the reaction.

All these results are summarized in Table 3.

Substrate	Catalyst	Conditions	Outcome (yield%)
70	$BF_3 \cdot Et_2O$ 5 eq.	THF,-78 °C to r. t., 24 h	**73** (40%), **74** (10%)
70	ZnI_2 1, 2, 5, 10 eq	THF or DCM, 0 °C to r. t., 5 days	Starting material
70	$Sc(OTf)_3$ 1, 2, 5, 10 eq	THF or DCM, 0 °C to r. t., 5 days	Starting material
70	$Yb(OTf)_3$ 5 eq	THF, 0 °C to r. t., 5 days	**73** (46%)
70	//	Microwaves toluene/120 °C/ 10'	Starting material

Table 3: Attempts at the intramolecular carbonyl-ene cyclisation of ketoaldehyde **70**.

5.3 Determination of structure and stereochemistry of 73 and 74

Full spectroscopic characterization gave us the opportunity to demonstrate that the structure of the compounds obtained as a 4:1 mixture after submitting **70** to $BF_3 \cdot Et_2O$ catalysed conditions were **73** and **74**, the product of the carbonyl-ene cyclisation of **70**.

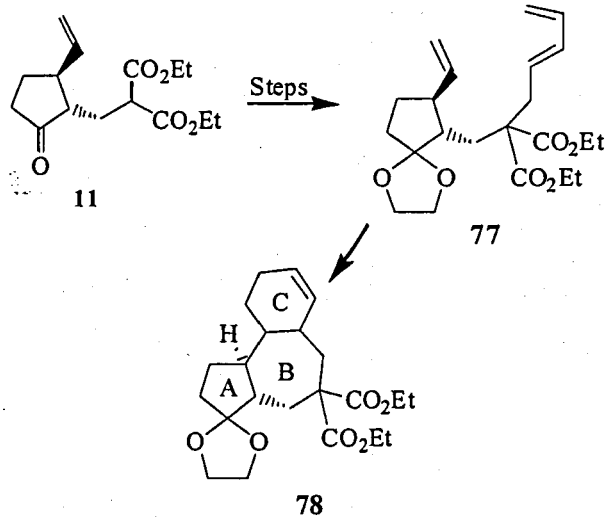
High resolution mass spectrometry analysis gave the *m/z*: 352.1823 (M^+), ($C_{19}H_{28}O_6$ requires 352.1886) for both **73** and **74**.

1H NMR spectroscopy analysis was very exhaustive and fundamental to assigning the correct structure to **73** and **74**: the total number of carbon atoms, the number of quaternary, secondary, tertiary or primary carbon atoms, ^1H NMR correlation spectroscopy (COSY) experiments and ^1H ^{13}C NMR correlations (HMQC) experiment were all consistent with the structures we finally assigned to **73** and **74**. Rather than attempt to describe fully the reasoning and correlations which led us to assign the structures to the cyclisation products, a few key points are: the presence of two singlets (or, better, two multiplets with very small coupling constants) in the area between 4.95 and 4.76 ppm, integrating for one proton each and correlated with the same secondary carbon atom (according to HMQC analysis), together with the singlet at around 1.8 ppm integrating for three protons, suggest the presence of an isoprenyl group.
Ring closure, and therefore the presence of proton H-6, was suggested by the signal at 3.82 ppm for **73** and at 3.35 ppm for **74**, correlated in both cases with a tertiary carbon atom (according to HMQC analysis) consistent with secondary alcoholic carbon atom.

The next step was the determination of the stereochemistry of the two compounds obtained, which was fundamental to rationalise the cyclisation process.

Because of the shortage of substrate, we were not able to synthesise any crystalline derivatives of **73** and **74** to be submitted for X ray analysis, which would have been ideal to obtain the relative stereochemistry of our molecules. Consequently we decided to perform 1D and 2D nOe NMR experiments, with the aim of obtaining enough data to assign at least the configuration at C-6, C-7 relative to that at C-5 and C-1.

Before we analyse the gradient NOESY (nuclear Overhauser effect spectroscopy) experiments performed on cycloadducts **73** and **74**, it is fundamental to note that the ring fusion between rings A and B is *trans*. As mentioned above, our research group realised the synthesis of the daphnane and tigliane families of natural compound skeletons by the IMDA reaction of **77**, which was synthesized using compound **11** as a synthetic intermediate. The junction between rings A and B of compound **78** was demonstrated through the X ray analysis to be *trans* [Scheme 22].[4]



Scheme 22: X ray experiment demonstrated the *trans* ring fusion between rings A and B of cycloadduct **78**.

Therefore, the substituents at C-1 and C-5 (guaianolide numbering) of malonate **11** are *trans* to each other. The chemical transformations undergone by this intermediate during our synthetic approach towards the guaianolide skeleton conserve this stereochemistry, and the configuration cannot change until the formation of the aldehydes **67** and **70**.

According to the ^{1}H NMR analysis of cycloadduct **73**, the coupling constant between H-1 and H-10 (double doublet at 1.89 ppm) is of 10.8 Hz, consistent with an *anti* arrangement of the two atoms (the coupling constant between H-1 and the second H-10 proton at 2.61 ppm is of 2.9 Hz, consistent with an *syn* arrangement of the two atoms). It follows that, as we consider H-1 to be oriented upward, the proton H-10 at 1.89 ppm will be oriented downward and will be named H-10β.

Analysis of the 2D NOESY ^{1}H NMR spectrum (enclosures 1 and 2), identifies enhancement of the signal between H-7 and H-5, and between H-6 and H-10β, (H-10β is *anti* to H-1 and therefore s*yn* with H-5), demonstrating that they all were on the same side of the molecule [Fig. 8].

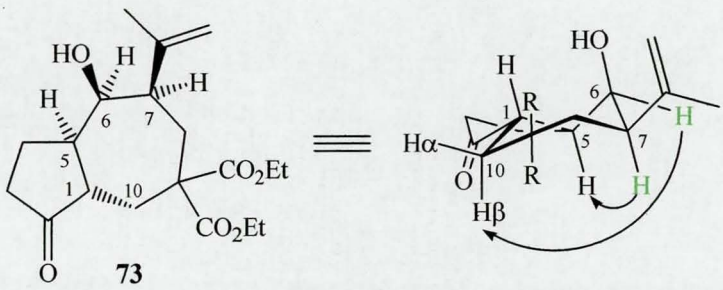


Figure 8: Assignement of the configuration at C-6 and C-7 relatively to H-5 in cycloadduct **73** by nOe experiments.

It follows that the correct stereochemistry of **73** is the one represented in scheme 21 and in figure 8.

As regards the determination of the stereochemistry at C-6 and C-7 of compound **74**, the 2D nOe experiment (enclosures 3 and 4), shows enhancement of signal between H-1, H-6 and H-8α (double doublet at 1.86 ppm), demonstrating that they all are on the same side of the molecule and pseudo-axially oriented (equatorial orientation would position them too far away from each other to allow any enhancement of signal). It follows that, with H-1 and H-5 *anti* to each other, H-5 and H-6 are also *anti*. Moreover, the ^{1}H NMR signal of H-6 is a double doublet, looking like a triplet because H-6 couples with H-5 and H-7 with the same coupling constant (9.5 Hz). Such a coupling constant is consistent with either a *syn* or an *anti* arrangement between H-6 and H-7. At this stage, the 2D nOe experiment is again helpful: there is in fact enhancement of signal between H-7, H-8 α and H-8β. With H-7 antiplanar to H-6 (J^3= 9.5 Hz), there would not be any nOe interaction with H-8α (the dihedral angle H-7/H-8α being in this case close to 180°) [Fig. 9].

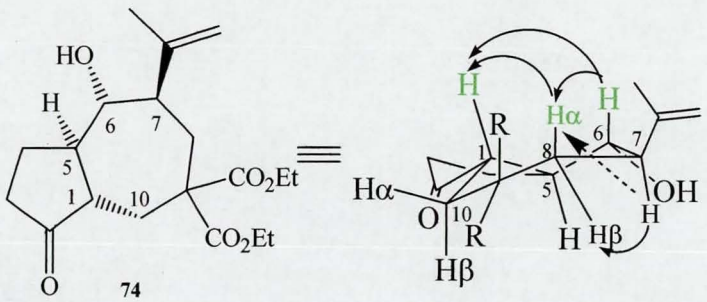


Figure 9: Cycloaduct **74**: *anti* configuration between H-6 and H-7 leads to a diehedral angle H-7/H-8α close to 180 ° that denies nOe interaction between these two protons.

With H-7 synplanar to H-6 and H-8α axially oriented, the molecule has a configuration that is simultaneously consistent with the coupling constant between H-6 and H-7 (9.5 hertz) and the nOe between H-7 H-8α and H-8β. Therefore the configuration of cycloadduct **74** is that shown in scheme 21 and in figure 10.

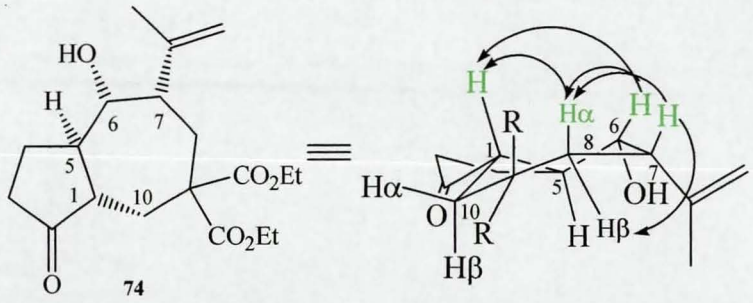


Figure 10: Cycloadduct **74**: *syn* arrangement of H-6 and H-7 allows nOe interaction between H-7, H8α and H-8β. It is also consistent with a coupling constant value of 9.5 Hertz.

Even if the lack of nOe effect between two atoms gives us no information about their real arrangement it is unlikely that, if the protons H-1 and H-5 were in *cis* configuration, there would not be any enhancement between H-5 and H-6 in the presence of nOe interaction between H-6 and H-1. It follows that rings A and B are *trans* fused, confirming the statement above.

5.4 Rationalisation of the stereochemical outcome

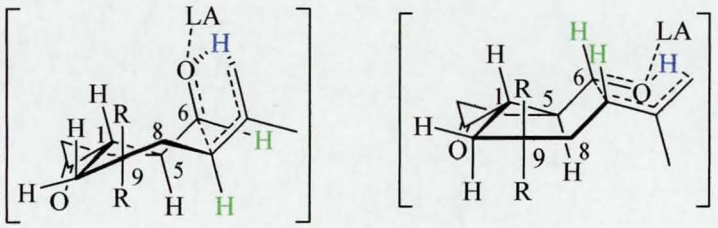
As shown above, the intramolecular carbonyl-ene reaction of the unsaturated aldehyde **70** catalysed by $BF_3 \cdot Et_2O$, gave a 4:1 mixture of compounds **73** and **74**. Otherwise, when $Yb(OTf)_3$ was used as the catalyst, **73** was the only cycloadduct detected.

As far as we know, not many examples of Alder-ene reaction leading to seven-membered cycloheptanols have been reported, and therefore it was not possible to rationalise the stereochemical outcome of the cyclisation with the support of previous experience.

Based on the fact that a concerted pericyclic process prefers to proceed through the most stable transition state, and that the stereochemistry of the products is determined within the formation of the correspondent transition state, we performed a qualitative analysis of the models of the transition states potentially involved in the process. The

aim was of identify the most probable transition states the reaction could have gone through, by discarding those with evident intolerable steric tensions and those conformationally not adaptable to afford any concerted cyclisation.

In the case of the carbonyl-ene cyclisation, a temporary (virtual) fused bicyclic transition state (formed by the new cycloalkanol and the boat or chair shaped six membered ring formed by aldehyde, the ene moiety and the shifting proton), has to be taken into account [Fig. 11].



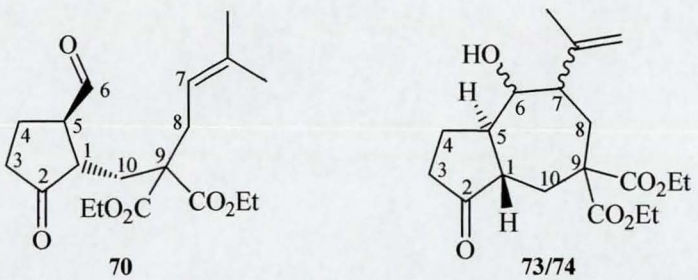
Bicyclic transition state with a chair-shaped six-membered part

Bicyclic transition state with a boat-shaped six-membered part

Figure 11: Bicyclic transition states.

In particular, the folding of the chain linking the two reactanting moieties is very important for the stability of the transition state because it must hold the reactant groups in the optimal position to interact, at the same time minimising the steric tensions originating during the process.

Before starting to describe our deductions it is worth pointing out that IUPAC perhydroazulene ring numbering is used, and that as the aldehyde **70** was obtained as a mixture of (±) *trans* enantiomers at H-1 and H-5 (guaianolide ring system numbering), the analysis is done only for a single enantiomer, the one with H-1 in the α position [Fig. 12].



70 **73/74**

Figure 12: Guaianolides ring system numbering applied to the unsaturated aldehyde 70 and to the cycloadducts 73 and 74: to be noted the α orientation of H-1.

If we consider the position of the Lewis acid coordinating the aldehydic oxygen, this is expected to be *trans* oriented to the cyclopentanone ring with the respect to the carbonylic double bond. This configuration allows minimisation of the steric interactions between the catalyst and the bulky α substituent of the aldehyde [Fig. 13].

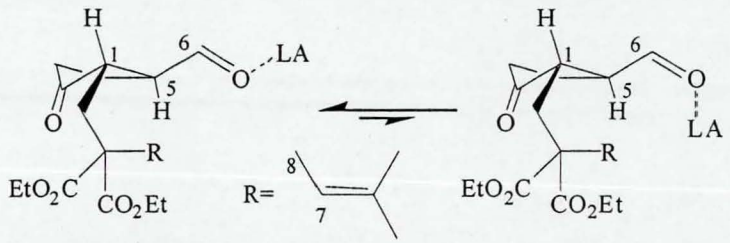


Figure 13: The positon of the Lewis acid is supposed to be *trans* to the cyclopentanone ring with the respect to the carbonylic double bond.

The aldehydic proton can point downward (β orientation) or upward (α orientation) following the rotation of the aldehyde around the σ-bond linking C-6 and C-5 [Fig. 14].

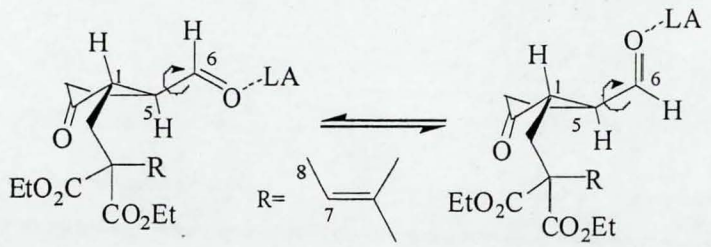


Figure 14: Following the rotation around the C-6/C-5 σ bond, during the transition state the aldehydic proton can point downward (right) or upward (left) (assuming β the orientation of H-5).

The five carbon linker of **70** incorporates two atoms (C-1 and C-5) that being part of a five membered ring have a reduced ability to move. Assuming that H-5 is in the β position, it follows that C-10 is β too, and therefore the relative position of four carbon atoms (C-6, C-5, C-1, C-10) of the final seven membered ring can be considered (with a good degree of approximation) to be fixed during the evolution of the transition states [Fig. 15].

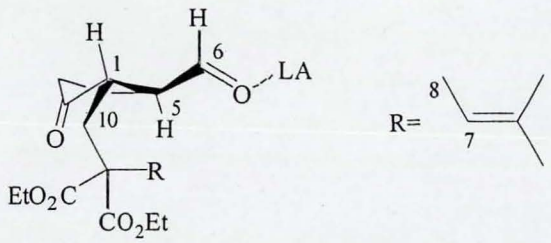
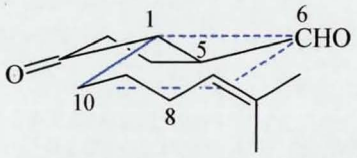


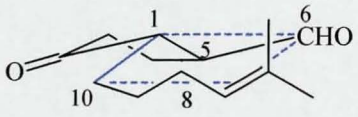
Figure 15: The position of the four carbon atoms C-6, C-5, C-1, and C-10 can be considered as fixed.

It follows that the position of the carbon atoms C-8, and C-9 plays a fundamental role in determining the transition states involved in the cyclisation.

At first it is better to focus our attention at the position of C-8 and C-5 relative to each other, as they are the two closest atoms to those directly involved in the cyclisation (C-7 and C-6) and therefore they have considerable influence on the arrangement of the reacting moieties. When C-8 is synplanar with C-5, with respect to the plane passing through carbons C-6, C-1 and C-10, it is possible to define the corresponding family of transition states **TS-S** (Synplanar) [Fig. 16, left]. Similarly, the family of transition states with C-6 antiplanar (on the opposite side of the plane) to C-5 with respect to the same plane, will be as shown in **TS-A** (Antiplanar) [Fig. 16, right].



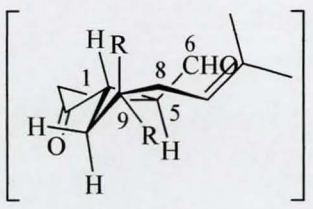
Synplanar arrangment between C-8 and C-5: **TS-S** family of transition states.



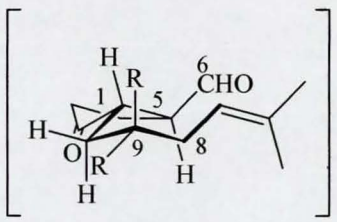
Antiplanar arrangment between C-8 and C-5: **TS-A** family of transition states.

Figure 16: Syn- and antiplanar arrangement between carbon atoms C-8 and C-5 (the substituents on C-9 have been omitted for the easiness of the description).

The antiplanar arrangement is likely to develop less steric interactions between C-8 and C-5 than the synplanar and therefore it is probably preferred over the latter. For either transition states **TS-A** and **TS-S**, three subfamilies can be identified on the basis of the position of C-9 (the carbon atom bearing the ethoxycarbonyl disubstitution): **TS-A(A, S, C)** and **TS-S(A, S, C)**. In both **TS-AA** and **TS-SA** transition states, C-9 is antiplanar to C-5 with respect to the plane passing through the carbon atoms C-6, C-1, and C-10 [Fig. 17].



TS-AA



TS-SA

Figure 17: C-9 antiplanar to C-5 with the respect of the plane passing through C-6, C-1, and C-10: transition states **TS-AA** and **TS-SA** can be defined.

Similarly, in **TS-AS** and **TS-SS**, C-5 and C-9 are synplanar with respect to the plane passing through C-6, C-1, and C-10 [Fig. 18].

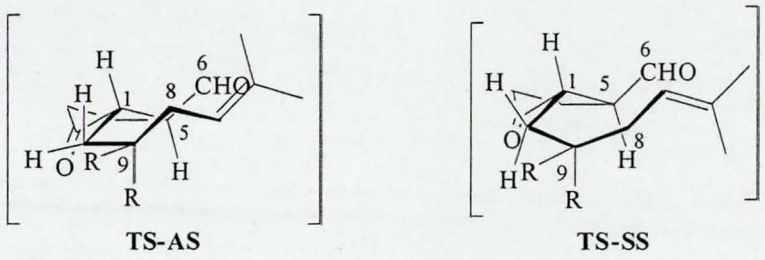


Figure 18: C-9 synplanar to C-5: transition states **TS-AS** and **TS-SS**.

Finally, when the carbon atoms C-10, C-9, and C-8 are in the same plane (**C**oplanar), **TS-AC** and **TS-SC** have to be taken into account [Fig. 19].

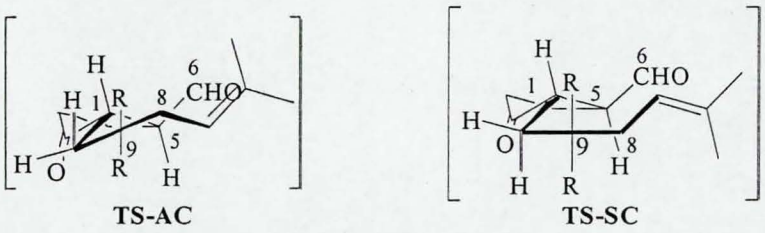


Figure 19: C-10, C-9, and C-8 on the same plane: transition states **TS-AC** and **TS-SC**.

In either families of transition states **TS-A(A, S, C)** and **TS-S(A, S, C)** the position of C-9 seems not to affect the position of C-8 (compare figure 7, 8, and 9); from now on, for the simplicity, we will carry on the reasoning only for a single component of each family assuming that it will be valid for the others as well, and that the final outcome would then still be the same.

Taking into consideration the two subfamilies **TS-AC** and **TS-SC**, when the three carbon atoms C-10, C-9, and C-8 are in the same plane, the seven-membered portion of the transition state assumes a twist chair conformation (**TS-AC**) or a twist boat conformation (**TS-SC**) with the bulky substituents on C-9 being in an isonclinal position, which allows release of most of the steric tension deriving from the disubstitution.

It is well known that *gem*-disubstituted seven-membered rings prefer to assume a twist chair conformation with the substituents in isoclinal position (this means that the two fold molecular symmetry axis passes through the substituted carbon atom).[5]

In these rings the two isoclinal positions are equivalent and energetically very close to the equatorial positions which are the most stable. Therefore, positioning two *gem*-substituents into the isoclinal positions is energetically similar to having them at the same time in an equatorial position, which is much more stable than having them one in axial and the other in equatorial orientations as in the not isoclinal positions [Fig. 20].[6]

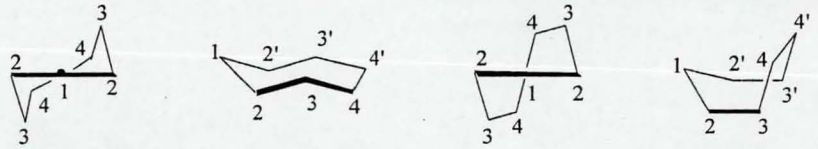


Figure 20: The four families of cycloheptanes conformations: the two substitution positions on carbon atom C1 of the twist chair and twist boat conformations are named isoclinals and they are isoenergetic.

The carbon atom C-9 is fundamental to determine the orientation of the allylic proton at C-7. To avoid developing steric repulsion forces between the ester groups on C-9 and the methyl groups of the ene component, this proton prefers to assume an equatorial position rather than axial. We can therefore discard from our reasoning the transition states with the ene moiety axially oriented (which we will call **TS-ACa** and **TS-SCa**) and focus our attention on those in which the ene component is equatorial, that is **TS-ACe** and **TS-SCe** [Fig. 21].

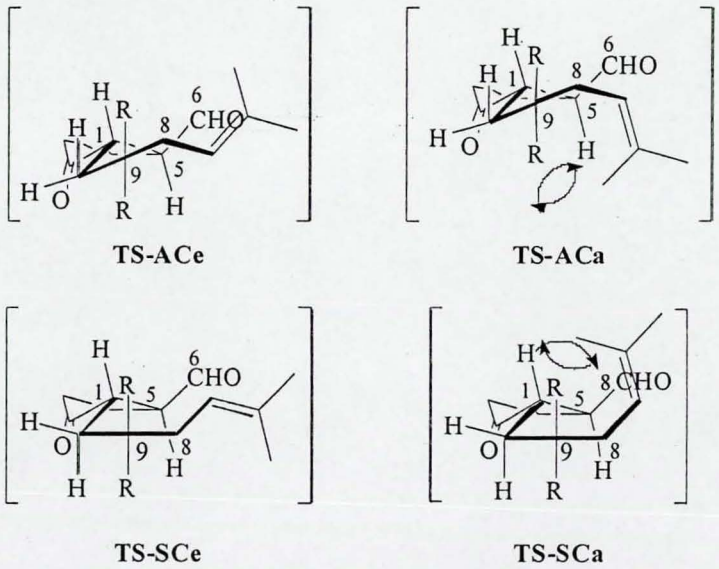


Figure 21: Equatorial orientation of the ene moiety favoured over the axial: less steric interactions with the *gem* disubstitution on C-9. **TS-ACe** favoured over **TS-ACa** and **TS-SCe** favoured over **TS-SCa**.

In either **TS-AC** and **TS-SC** structures, the aldehydic C=O group can point in the same direction of H-5 (β arrangement) or in the opposite direction (α arrangement) due to the rotation around the σ bond between C-6 and C-5; our qualitative prediction of the final stereochemical outcome of the cyclisation of **70** follows from the analysis of the four transition state structures **TS-AC(α, β)** and **TS-SC(α, β)** [Fig. 22].

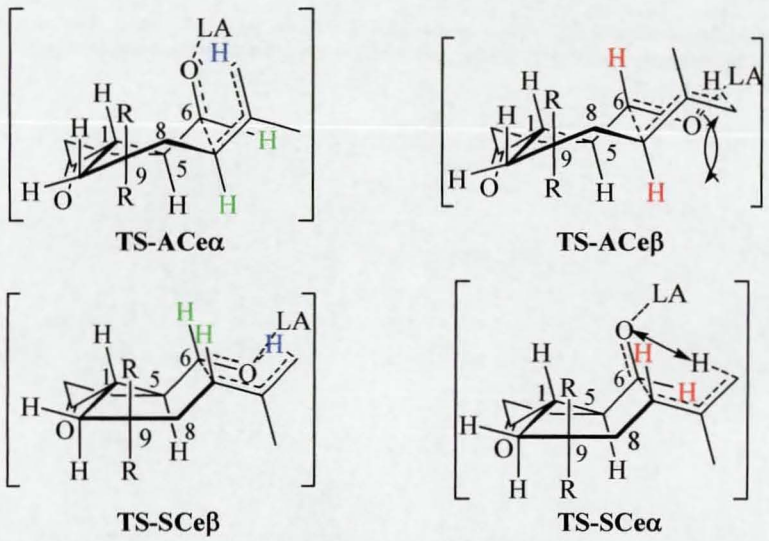
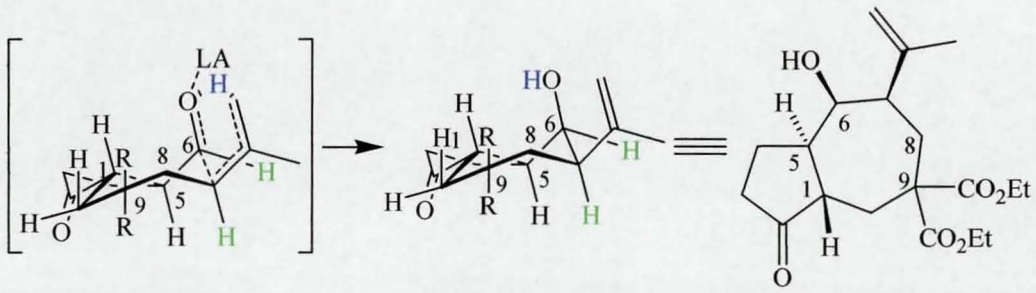


Figure 22: The final four candidate structures to be the transition states of the Lewis acid catalysed cyclisation of **70**: **TS-ACeβ** to be discarded because of the *endo* approach towards the allylic system; **TS-SCeα** to be discarded because the aldehyde is too far from any allylic proton suitable for the cyclisation. Probably the cyclisation goes through : **TS-ACeα** and **TS-SCeβ**.

In the **TS-ACeα** transition state, the Lewis acid is halfway between a pure *exo* (favoured) and an *endo* (disfavoured) orientation with respect to the allyl group. In the **TS-ACeβ** transition state, the Lewis acid is pointing straight towards the allylic group in a full highly disfavoured *endo* approach to the ene component. It follows that **TS-ACeα** is favoured over **TS-ACeβ**, and therefore we expect the correspondent cycloadduct **ACeα** to be one of the compounds obtained by carbonyl-ene cyclisation of **70**.

In fact cycloadduct **ACeα** is compound **73**, the material obtained as the major diasteroisomer in the BF_3•Et_2O catalysed cyclisation of **70** and the only cycloadduct isolated when $Yb(OTf)_3$ was used as the catalyst [Scheme 23].



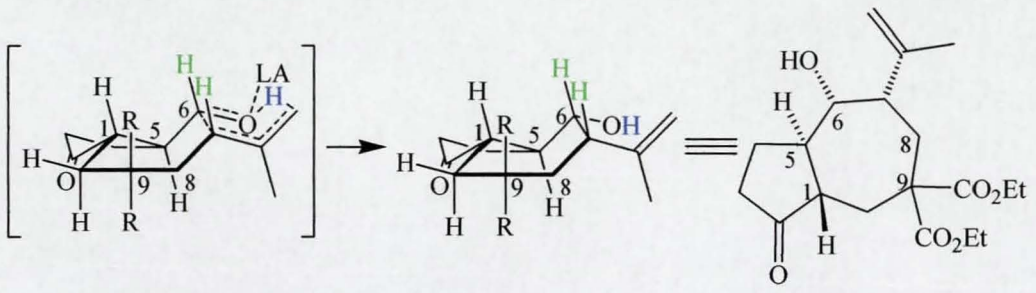
TS-ACeα Cycloadduct **ACeα** **73**

Scheme 23: Cyclisation of the unsaturated aldehyde **70** through transition state **TS-ACeα** leads to compound **73**.

Turning to transition states **TS-SCeα** and **TS-SCeβ**, the concerted cyclisation through **TS-SCeα** is very difficult because the carbonyl group is too far from any allylic proton. **TS-SCeβ** is then more likely to be the transition state the reaction goes through in the case of a productive synplanar arrangement of C-8 and C-5, affording the cycloadduct **SCeβ**.

In transition state **TS-SCeβ** the Lewis acid seems to be aligned with one of the two allylic methyl groups; the steric interactions between the catalyst and the methyl group could in theory also make this transition state too unstable to allow the cyclisation.

Cycloadduct **SCeβ** and compound **74** (obtained as the minor diastereoisomer when the cyclisation was performed under $BF_3 \cdot Et_2O$ catalysed conditions) are, however, the same molecule [Scheme 24].



TS-SCeβ Cycloadduct **SCeβ** **74**

Scheme 24: Cyclisation of the unsaturated aldehyde **70** through transition state **TS-SCeβ** leads to compound **74**.

It could be argued that the reaction could proceed through a stepwise pathway *via* transition state **TS-SCeα**: it has been proposed that the stepwise pathway through carbocationic species occurs only when any other arrangement leading to the proper alignment of the reagent parts to perform a concerted cyclisation cannot occur. It

follows that the stepwise cyclisation probably does not occur because of the presence of the alternative transition states **TS-SCeβ** and **TS-ACeα**, which guarantee the possibility of a concerted pathway.

It is important at this point to highlight that our prediction, about the **TS-A** transition states being more stable than **TS-S** transition states, has been experimentally confirmed: under $BF_3 \cdot Et_2O$ catalysed conditions, the cyclisation of **70** afforded a 4:1 mixture of compound **73** and **74**, deriving from transition states **TS-ACeα** and **TS-SCeβ** respectively. The more stable transition state gives the major component of the mixture.
It is noteworthy that in the **TS-ACeα** transition state, the shift of the six electrons and of the allylic proton involved in the cyclisation describe a transient six-membered chair- like ring. During the cyclisation through **TS-SCeβ**, the electron and proton shift occurs with a less stable boat-like ring [Fig. 22]. This is one more important reason why **TS-ACeα** is more stable than **TS-SCeβ**.

To explain why with $Yb(OTf)_3$ no trace of compound **74** was recovered, we propose an answer resulting from the particular arrangement of **TS-SCeβ**. As shown in figure 11, the Lewis acid is oriented along one of the allylic methyl groups; when small catalysts such as $BF_3 \cdot Et_2O$ are employed, the steric interaction with the methyl group is not strong enough to destabilise totally the transition state and it is still possible for the cyclisation to occur.
When a bulky Lewis acid such as $Yb(OTf)_3$ is used, the interaction with the methyl group is too strong, and this prevents the formation of the transition state **TS-SCeβ**.

5.5 Conclusions

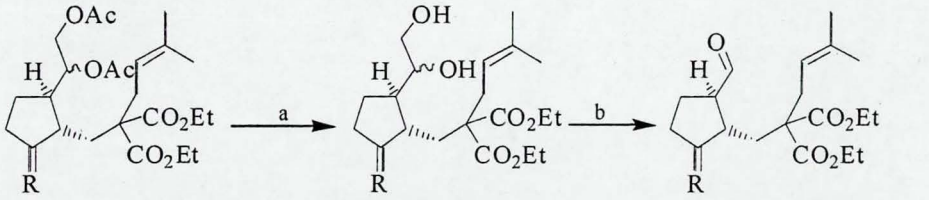
Many compounds belonging to the guaianolide family of naturally occurring sesquit erpene lactones have demonstrated to be bioactive, and therefore they have become a very important target for organic chemists.

As a first potential pathway to access to the guaianolide framework, we attempted the intramolecular hetero Diels-Alder (IMHDA) reaction of 1,8,10 trienals, which were obtained through convergent synthesis. As fully described above (chapter 2), this

approach has not given the expected results, and this drove us to look for a different strategy, where some of the intermediates already synthesised for the IMHDA approach could be used.

The intramolecular carbonyl-ene reaction of unsaturated aldehydes responds to these needs and it has demonstrated to be an interesting alternative to access to the perhydroazulene framework, characteristic of the guaianolide skeleton.

The reaction between the pro-heterodienophile **13** (which in this approach becomes the pro-enophile moiety) and prenyl bromide **64** under basic conditions, gave the pro-aldehyde **68**, which after deacetylation and oxidative cleavage, afforded the unsaturated aldehyde **70** [Scheme 25].



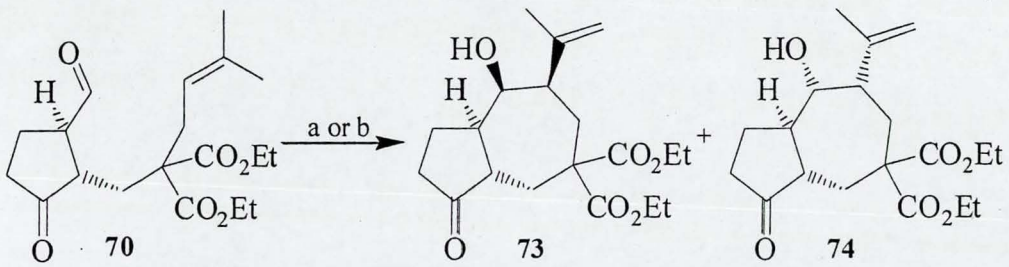
65: R= $O(CH_2)_2O$
68: R= O

66: R= $O(CH_2)_2O$, 81%
69: R= O, 56%

67: R= $O(CH_2)_2O$, 62%
70: R= O, 59%

Scheme 25: Synthesis of the unsaturated aldehyde **70**: a) Amberlite® 400 CI, MeOH, r.t., 18 hours; b) $NaIO_4$, $MeOH/H_2O$, 30 min.

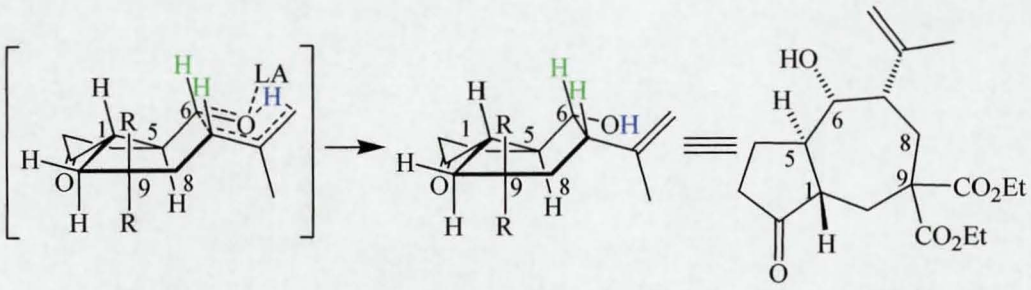
Aldehyde **70** was then treated with many different Lewis acids such as ZnI_2, $BF{\bullet}Et_2O$, $Yb(OTf)_3$ $Sc(OTf)_3$; cyclisation occurred only in the presence of $BF{\bullet}Et_2O$, $Yb(OTf)_3$. Cabonyl-ene cyclisation of **70** under $BF{\bullet}Et_2O$ gave a 4:1 mixture of cycloheptanols **73** and **74**, and when **70** was reacted with $Yb(OTf)_3$, compound **74** was isolated as the only cycloaddition product [Scheme 26].



Scheme 26: Carbonyl-ene cyclisation of the unsaturated aldehyde 70: a) $BF_3{\bullet}Et_2O$, 4/1= **73/74** (^1H NMR analysis of the crude material), 50%; b) $Yb(OTf)_3$, **73**, 46%.

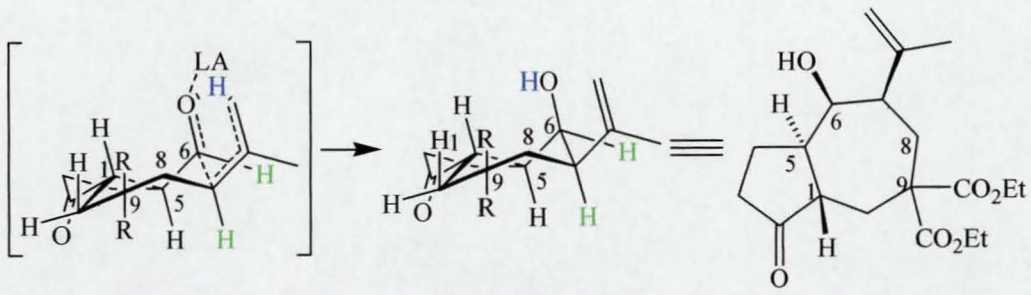
The relative stereochemistry of **73** and **74** at C-6 and C-7 was determined on the basis of nOe experiments, J^3HH coupling constants and conformational analysis.

Rationalisation of the stereochemical outcome was also performed; on the basis of conformational analysis of the most likely transition states, it was possible to find consistency between the experimental outcome of the cyclisation and the most stable proposed transition states. It was also possible to rationalise the high diastereoselectivity of the cyclisation under $Yb(OTf)_3$ catalysed conditions: the bulkiness of the catalyst destabilises the transition state that gives rise to cycloadduct **74** [Figure 23], but does not seriously affect that leading to **73**, which becomes the only product of the cycloaddition [Figure 24].



TS-SCeβ Cycloadduct **SCeβ** **74**

Figure 23: Bulky Lewis acids destabilise **TS-SCeβ**.



TS-ACeα Cycloadduct **ACeα** **73**

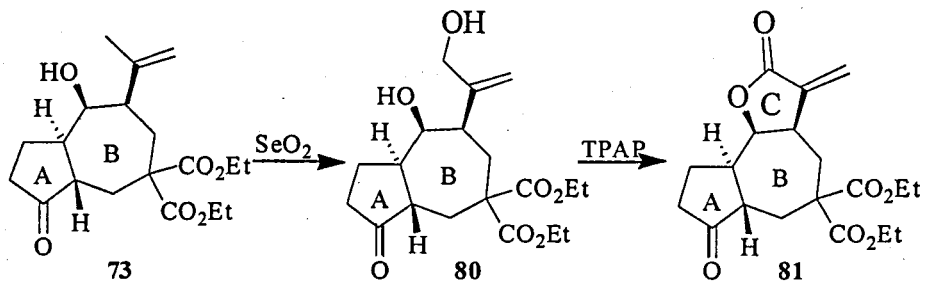
Figure 24: The stability of this TS-ACeα is not seriously affected by the bulkiness of the Lewis acid.

The carbonyl-ene reaction approach has demonstrated to be a good strategy for the synthesis of the guaianolide skeleton: compound **74** could be converted into the guaianolide skeleton in 2 steps, as shown below.

5.6 Proposals

5.6.1 Conversion of 73 into the guaiane-6,12-olide skeleton

Even if the synthesis of the perhydroazulene part represents an important piece of progress, the total synthesis of the guaianolide skeleton is far to be accomplished. In order to obtain the missing α-methylene-γ-lactone ring, we propose a two step conversion of **73** into **81**: allylic oxidation[7] should provide the alchol **80**, which in turn would be converted into **81** by oxidation, for example with TPAP (tetrapropylammonium perruthenate) [Scheme 27].[8]



73 **80** **81**

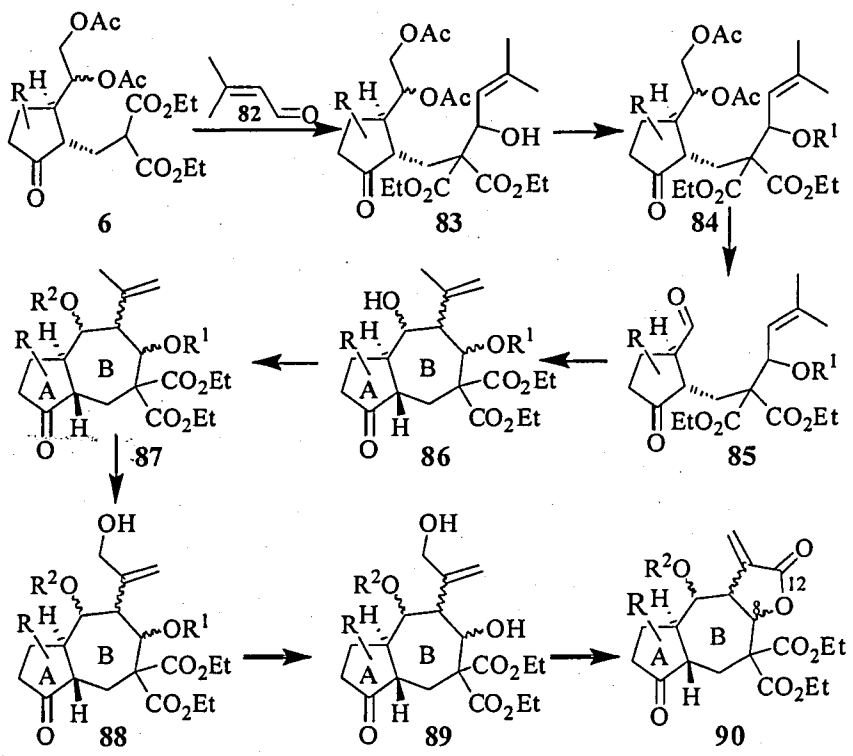
Scheme 27: Conversion of cycloheptanol **73** into the guaiane-6,12-olide skeleton **81**.

5.6.2 Synthesis of the the guaiane-8,12-olide skeleton

The convergent approach through which we access the perhydroazulene framework allows us to combine different types of pro-enophile and ene moieties: this makes the approach very flexible and therefore potentially enables us to synthesise many different guaianolides by choosing the proper pro-enophile and ene moieties to be combined.

Moreover it would be possible to access to the class of the guaiane-8,12-olides as shown in scheme 28 by the reaction between the malonates **6** and the aldehyde **82** to provide the alcohols **83**, which, after protection with an acid stable protecting group R^1 followed by oxidative cleavage would be converted to the aldehydes **85**, which would be in turn submitted to Lewis acid catalysed carbonyl-ene reaction to obtain the cycloadducts **86**. The newly obtained hydroxyl group would in turn be protected with a second agent (R^2) stable under the conditions of deprotection of R^1. Allylic oxidation

of C-11 followed by deprotection of the alcoholic group on C6, and oxidation/lactonisation with TPAP would provide the guaian-8,12-olide skeleton **90**.



Scheme 28: Towards the synthesis of the guaian-8,12-olide skeleton.

The successful realisation of this synthetic pathway would be a very important result because with a similar convergent approach and similar starting materials, we would be able to access to three different families of biologically active natural compounds: daphnanes, tiglianes and guaianolides.

5.7 References

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Part III Experimental section

All the solvents employed in this work were freshly distilled, or dried in accordance with the literature prior to use. Where light petroleum 40/60 has been used it is referred to in the term "petrol". Commercial compounds were used without further purification. Vacuum distillations were performed using a kugelrohr distillation apparatus, chromatographic purifications were done on silica gel 60. TLC were performed on Merck UV aluminium plates coated with 0.2 mm silica 60 F_{254}. Melting point measurement was performed on Stuart Scientific (SMP3) melting point apparatus. IR spectra were obtained on a Perkin Elmer Paragon FT-IR spectrometer as liquids films. All the mass spectra were measured at high resolution.

Air sensitive reactions were run under nitrogen atmosphere.

^{1}H and ^{13}C NMR spectra were obtained in commercial $CDCl_3$ solution, coupling constant (*J*) values are given in Hz.

^{1}H NMR spectra were obtained on a Bruker DPX-400 MHz spectrometer operating at 400.13 MHz for protons, employing a high-resolution broad-band HX probe. Spectra were recorded using the zg30 pulse program with P_{90} = 11.8 μs covering a sweep width of 171.16 ppm (6868 Hz) with 64k time domain data points giving an acquisition time of 4.77 seconds, Fourier transformed using 128k data points and referenced to an internal $CHCl_3$ standard at 7.26 ppm.

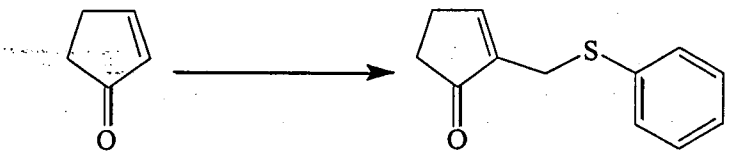
^{13}C NMR spectra were obtained on a Bruker DPX-400 MHz spectrometer operating at 100.61 MHz for carbon and 400.13 MHz for proton decoupling, employing a high-resolution broad-band HX probe. Spectra were recorded over a sweep width of 250 ppm (25252 Hz) with 64k time domain data points giving an acquisition time of 1.30 seconds, Fourier transformed using 128k data points and referenced to an internal $CHCl_3$ standard at 7.26 ppm. Acquisitions are halted when the signal to noise ratio reached 150 for the MC spectra (corresponding to ~100-120 for the phase corrected spectra).

6 Synthesis of the Guaian-6,12-olide skeleton: IMHDA Reaction Approach: Experimentals

6.1 Synthesis of the dienophile moiety (8)

6.1.1 2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (8) : path A

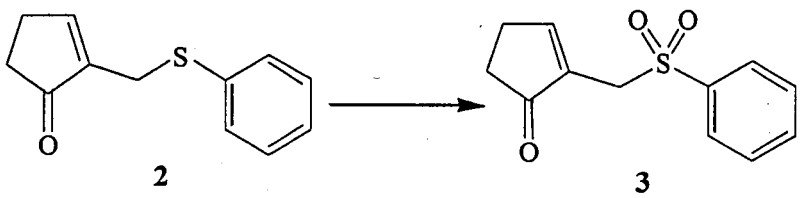
6.1.1.1 2-Phenylsulfanylmethyl-cyclopent-2-enone (2)[1]



1 2

A solution of cyclopent-2-en-1-one (**1**) (12.3 g, 12.55 mL, 0.15 mol), triethylamine (21 mL, 0.15 mol), thiophenol (15.5 mL, 0.15 mol) and 37% aqueous formaldehyde (12.5 g, 0.15 mol) in ethanol (200 mL) was heated under reflux for sixty-five hours before a solution of 37% aqueous formaldehyde (1.22 mL, 15.0 mmol) was added and the mixture heated again under reflux for a further twenty-four hours. A second amount of 37% solution of aqueous formaldehyde (1.22 mL, 15.0 mmol) was added and the mixture heated under reflux for a further twenty-four hours. After cooling to room temperature the ethanol was removed by reduced pressure distillation to give an orange oil. This was poured into water (200 mL) and dichloromethane (250 mL) and the phases were separated. The aqueous layer was further extracted with dichloromethane (3 × 70 mL) and the combined organic fractions quickly washed with a 5% solution of sodium hydroxide (3 × 50 mL), water (50 mL) and brine (50 mL), dried over magnesium sulfate, and evaporated to dryness. The resulting brown-orange oil was purified by high vacuum distillation (153-158 °C, 1 mbar), to give 2-phenylsulfanylmethyl-cyclopent-2-enone (**2**) as a pale yellow oil (15.0 g, 49%), b.p.: 153-158 °C 1 mbar (lit. b.p.= 145-150 °C, 0.8 mm);[1] δ_H (250 MHz, $CDCl_3$) 7.38 (1 H, dd, J_1= 2.5, J_2= 1.4, -C*H*=CRCO), 7.34-7.12 (5 H, m, aromatic protons), 3.67 (2 H, d, J= 1.4, -CH_2SPh), 2.56-2.52 (2 H, m, CH_2CH_2C=O).

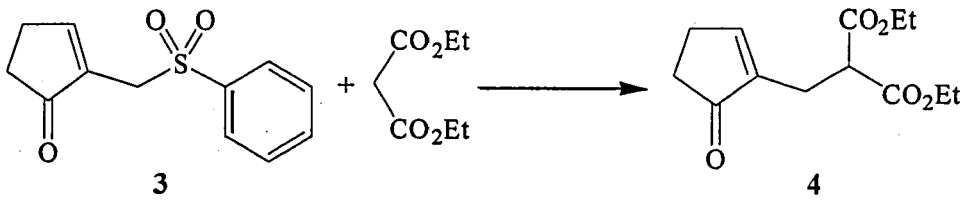
6.1.1.2 2-Benzenesulfonylmethyl-cyclopent-2-enone (3)[2]



2 3

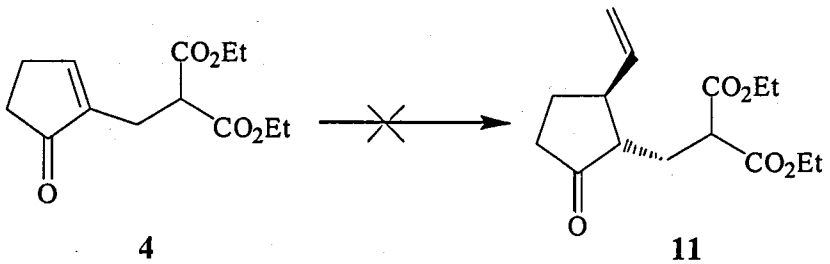
A solution of Oxone® (55.0 g, 89.41 mmol) in water (300 mL) was added to a solution of 2-phenylsulfanylmethyl-cyclopent-2-enone (**2**) (7.6 g, 37.25 mmol) in ethanol (200 mL) over ninety minutes and the mixture was stirred for twenty hours. The white solid precipitate was filtered off and added to dichloromethane (100 mL) and stirred for one hour before being filtered. The filtrate was dried over anhydrous magnesium sulfate and evaporated to dryness to give of 2-benzenesulfonylmethyl-cyclopent-2-enone (**3**) as a white waxy solid (6.0 g). The original hydro-alcoholic solution was concentrated under vacuum and the solid residue extracted with dichloromethane (3 × 30 mL). The combined organic layers were extracted with cold saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and evaporated to dryness to give 2-benzenesulfonylmethyl-cyclopent-2-enone (**3**) as a white waxy solid (1.5 g). Both solids had the same spectroscopic and physical properties (7.5 g, 85%); m.p.= 143.5-145.8 °C; ν_{max} (film)/cm^{-1} 1696.7 (C=O), 1631.6 (C=C), 1085.6 (S=O), 750.5 (C-S); δ_H (400 MHz, $CDCl_3$) 7.93-7.89 (1 H, m, C*H*=CRCO), 7.85-7.8 (2 H, m, aromatic *oC*); 7.67-7.62 (1 H, m, aromatic *pC*), 7.56-7.51 (2 H, m, aromatic *mC*), 4.02-4.01 (2 H, m, CH_2SO$_2$Ph), 2.71-2.66 (2 H, m, CH_2CH=CRCO), 2.34 (1 H, d, *J*=9.2, H_aCH$_b$CO), 2.32 (1 H, t, *J*= 2.6, H$_a$CH_bCO); δ_C (100 MHz, $CDCl_3$) 206.7 (*C*=O), 165.5 (H*C*=CRC=O), 138.9 (C=*C*-C=O), 134.4 (aromatic *p C*), 134.1 (arom. *quat. C*), 129.6 (aromatic *oC*), 128.7 (aromatic *mC*), 51.5 (*C*H$_2$SO$_2$), 33.8 (*C*H$_2$C=O), 27.7 (*C*H$_2$CH$_2$C=O); *m/z* (EI$^+$) 236.0507 (M$^+$), $C_{12}H_{12}O_3S$ requires 236.0507.

6.1.1.3 2-(5-oxo-cyclopent-1-enylmethyl)-malonic acid diethyl ester (4)



A solution of diethyl malonate (2.90 g, 18.2 mmol) in dry dimethylformamide (15 mL) was added to a stirring suspension of sodium hydride (60% mineral oil dispersion, 0.41 g, 17.3 mmol) in anhydrous dimethylformamide (145 mL) at 0 °C and under an atmosphere of nitrogen. The mixture was allowed to reach room temperature and, when the effervescence had subsided, it was added *via* cannula over five minutes to a solution of 2-benzenesulfonylmethyl-cyclopent-2-enone (**3**) (3.9 g, 16.50 mmol) in anhydrous dimethylformamide (130 mL). The solution was stirred for one hour under nitrogen atmosphere, the excess of sodium hydride was quenched upon careful addition of some drops of water, and the solvent was evaporated to dryness. The residue was partitioned between water (90 mL) and dichloromethane (90 mL) and the phases were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic layers washed with water (60 mL) and brine (60 mL), dried over anhydrous magnesium sulfate, and evaporated to dryness to give a pale yellow oil (4.93 g). This was partitioned in two aliquots: 2.27 g were purified by column flash chromatography (20-25% ethyl acetate/light petroleum) to give 2-(5-oxo-cyclopent-1-enylmethyl)-malonic acid diethyl ester (**4**) as a colourless oil (1.40 g); the remaining 2.66 g were purified by high vacuum distillation (160-180 °C, 1 mbar), to give 2-(5-oxo-cyclopent-1-enylmethyl)-malonic acid diethyl ester (**4**), as a colourless oil (1.47 g). Compound **4** was obtained as a colourless oil (2.87g, 69%); b.p.= 160 °C (1 mbar); ν_{max} (film)/cm^{-1} 2981-2924 (C-H), 1748 (CH=O), 1701 (EtOC=O), 1635 (C=C), 1228 (C-O); δ_H (400 MHz, $CDCl_3$) 7.38-7.35 (1 H, m, C*H*=CRC=O), 4.17 (4 H, q, *J*= 7.0, $CH(CO_2CH_2CH_3)_2$), 3.68 (1 H, t, *J*= 7.5, $CH_2CH(CO_2Et)_2$), 2.79 (2 H, m, $CH_2CH(CO_2Et)_2$), 2.56-2.51 (2 H, m, CH_2CH_2C=O), 2.43 (1 H, d, *J*= 9.4, H_aCH_bCO), 2.41 (1 H, t, *J*= 2.0 H_aCH_bCO); 1.20 (6 H, t, *J*= 7.0, $CH(CO_2CH_2CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 209.4 (*C*=O), 169.1 (CO_2Et), 160.1 (*C*H=CRC=O), 61.9 ($CO_2CH_2CH_3$), 50.3 ($CH_2CH(CO_2Et)_2$), 34.7 (($CH_2CH(CO_2Et)_2$), 27.0 (CH_2C=O), 24.8 (CH_2CH_2C=O), 14.0 (OCH_2CH_3); *m/z* (EI$^+$), 254.1156 (M$^+$), $C_{13}H_{18}O_5$ requires 254.1154.

6.1.1.4 (±)-*trans*-2-(1-(2,2-bis(carboxyethyl)-3-vinylcyclopentan-1-one (11)

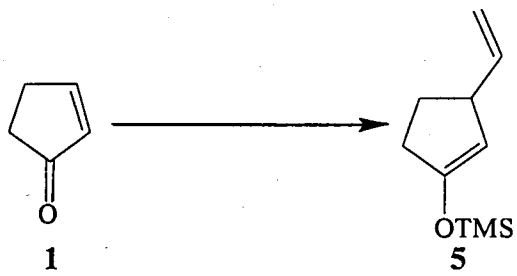


4 11

Vinylmagnesium bromide (1.0M in tetrahydrofuran, 2.82 mL, 2.82 mmol) was added to a stirring suspension of CuBr•DMS (26 mg, 0.124 mmol) in anhydrous tetrahydrofuran (5mL) at –78 °C under nitrogen atmosphere, and the mixture was stirred for thirty minutes. A solution of 2-[1-(2,2-bis-(carboxyethyl) ethyl)]-cyclopent-2-en-1-one (4) (288 mg, 1.13 mmol), DMPU (317 mg, 0.38 mL, 2.23 mmol), TMSCl (270 mg, 0.32 mL, 2.49 mmol) in dry tetrahydrofuran (15 mL) was added, and the mixture stirred for one hour at –78 °C, allowed to reach –45 °C and stirred at this temperature for a further eighteen hours. The solution was allowed to reach 0 °C and treated with a saturated aqueous ammonium chloride (30 mL). The two layers were separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and evaporated to dryness to give a pale yellow crude material (500 mg). ^{1}H NMR analysis showed a complex mixture, with only traces of starting material and perhaps product being detected. The area around 4.2 ppm and 1.5 ppm (corresponding to the ethoxy groups of the malonic esters) was very complex, suggesting that polymerisation had occurred.

6.1.2 2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (8): path B

6.1.2.1 (±)-Trimethyl-(3-vinyl-cyclopent-1-enyloxy)-silane (5)[3]

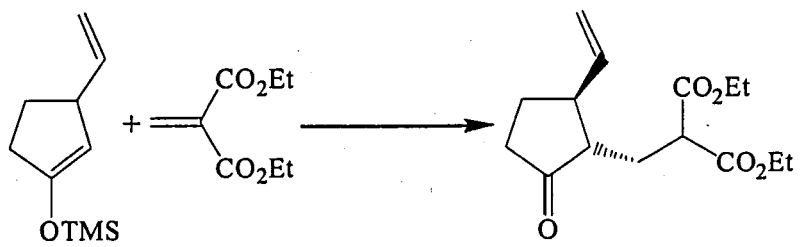


1 5

Vinyl magnesium bromide (1.0M in tetrahydrofuran, 71.6 mL, 71.6 mmol) was added over thirty minutes to a suspension of CuBr•DMS (800 mg, 3.87 mmol) in anhydrous tetrahydrofuran (150 mL) at –78 °C, under an atmosphere of nitrogen, and the resulting mixture was stirred for thirty minutes. A mixture of cyclopent-2-en-1one (**1**) (4.7 g, 57.24 mmol), TMSCl (14.6 mL, 114.8 mmol), in DMPU (13.9 mL, 114.8 mmol) (previously dried over molecular sieves for one hour), was added over twenty minutes. The mixture was stirred at –78 °C for one hour, allowed to reach –50 °C, stirred for a further 1.5 hour, treated with triethylamine (19 mL), and allowed to reach 0 °C. The mixture was diluted with petroleum ether (200 mL), washed with saturated aqueous ammonium chloride (3 × 140 mL), and brine (3 × 140 mL). The combined aqueous layers were extracted with dichloromethane (2 × 200 mL); the combined organic fractions were dried over anhydrous magnesium sulfate, and concentrated to dryness to give a brown oil (7.5 g). The crude product was found to be very unstable and was distilled shortly after the synthesis. Distillation was performed under high vacuum by Kügelrohr distillation apparatus (60-70 °C, 6 mbar), to obtain (±)-trimethyl-(3-vinyl-cyclopent-1-enyloxy)-silane (**5**) as a colourless oil (6.2 g, 60%); b.p.= 60 °C, (6 mbar); ν_{max} (film)/cm^{-1} 2960 (C-H), 1700 (*C*=*C*-OSi), 1641 (C=C), 1259 (Si-Me); 1092 (Si-O); δ_H (400 MHz, $CDCl_3$) 5.55 (1 H, ddd, J_1= 17.1, J_2= 9.9, J_3= 7.0, CH_2=C*H*), 4.75 (1 H, dd, J_1= 17.1, J_2= 2.0, *Ha*$_{\underline{trans}}$CHb=CH-), 4.64 (1 H, dd, J_1= 9.9, J_2= 2.0 *Hb*$_{\underline{cis}}$CHa=CH), 4.34 (1 H, d, *J*= 1.9, CHC*H*=C-OSi), 3.03 (1 H, m, CHCH=C-OSi), 2.05 (2 H, m, C*H*$_2$C-OSi), 1.88 (1 H, m, *Ha*CHbCH$_2$C-OSi), 1.36 (1 H, m, HaC*Hb*CH$_2$C-OSi), 0.00 (9 H, s, Si(C*H*$_3$)$_3$; δ_C (100 MHz,$CDCl_3$) 155.8 (CH=*C*(OTMS)CH$_2$), 143.8 (CH_2=*C*H-), 112.0 (*C*H$_2$=CH), 105.2 (CH*C*H=C-OSi),

46.0 (*C*HCH=C-OSi), 33.2 (*C*H_2C-OSi), 28.7 (*C*H_2CH_2C-OSi), 0.00 (Si(*C*H_3)$_3$); *m/z* (EI$^+$) 182.1128 (M^+), $C_{10}H_{18}OSi$ requires 182.1127.

6.1.2.2 (±)-*trans*-2-(2-Formyl-5-oxo-cyclopentylmethyl)-malonic acid diethyl ester (11)[4]

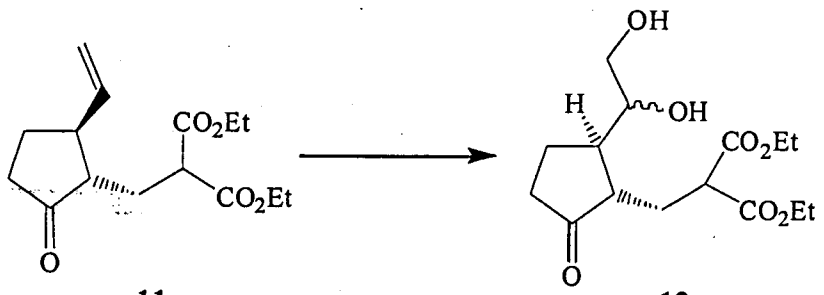


5 **10** **11**

A solution of $SnCl_4$ (3.0 mL, 25.6 mmol) in anhydrous dichloromethane (20 mL) was added over thirty minutes to a stirring solution of (±)-*trans*-trimethyl-(3-vinyl-cyclopent-1-enyloxy)-silane (**5**) (4.3 g, 23.63 mmol) and diethyl methylene malonate (**10**) (4.3 g, 25.00 mmol) in anhydrous dichloromethane (120 mL) at –78 °C under an atmosphere of nitrogen. The solution was stirred for two hours at –78 °C and then neutralised with saturated aqueous sodium hydrogen carbonate. The obtained gel was filtered through a pad of celite and washed through with dichloromethane (5 × 50 mL). The two liquid layers were separated and the aqueous phase was washed with dichloromethane (3 × 80 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and evaporated to dryness to give a crude yellow oil (6.5 g). Purification by flash column chromatography (7-30% ethyl acetate/light petroleum) gave (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-malonic acid diethyl ester (**11**), pale yellow oil, (3.1 g, 45%); b.p.= 170 °C, (3 mbar); ν_{max} (film)/cm^{-1} 3076 (C=*C*-*H*), 2980-2936 (C-H), 1731 (C=O), 1641 (C=C), 1230 (C-O); δ_H (400 MHz, $CDCl_3$) 5.75 (1 H, ddd, J_1= 17.1, J_2= 10.3, J_3= 7.9, CH_2=C*H*), 5.16 (1 H, dd, J_1= 17.1, J_2= 0.8, *trans* *Ha*CHb=CH-), 5.09 (1 H, dd, J_1= 10.3, J_2= 0.8, *cis* HaC*Hb*=CH-), 4.17 (4 H, q, *J*= 7.1, ($CO_2C\mathit{H}_2CH_3$)$_2$), 3.92 (1 H, t, *J*= 7.9, C*H*(CO_2Et)$_2$), 2.48-2.30 (2 H, m, *Ha*CHbC=O, CH_2=CHC*H*), 2.24-2.00 (4 H, m, *Ha*CHbCH_2C=O, HaC*Hb*C=O, CH_2CH(CO_2Et)$_2$), 1.99-1.91 (1H, m, CHC*H*RC=O), 1.70-1.55 (1 H, m, HaC*Hb*CH_2C=O) 1.24 (6 H, t, *J*=7.1, ($CO_2CH_2C\mathit{H}_3$)$_2$); δ_C (100 MHz,$CDCl_3$) 218.6 (*C*=O), 169.3 (*C*O_2Et), 169.2 (*C*O_2Et), 139.7 (CH_2=*C*H), 116.1 (*C*H_2=CH), 61.3 ($CO_2C\mathit{H}_2CH_3$), 51.2 (CHCHRCO), 49.2 (*C*H(CO_2Et)$_2$), 47.7 (CH_2=CHCH), 37.2 (*C*H_2C=O), 27.7 (*C*H_2CH_2C=O), 27.2

($CH_2CH(CO_2Et)_2$, 14.0 (OCH_2CH_3); *m/z* (EI^+) 282.1465 (M^+); $C_{15}H_{22}O_5$ requires 282.2147.

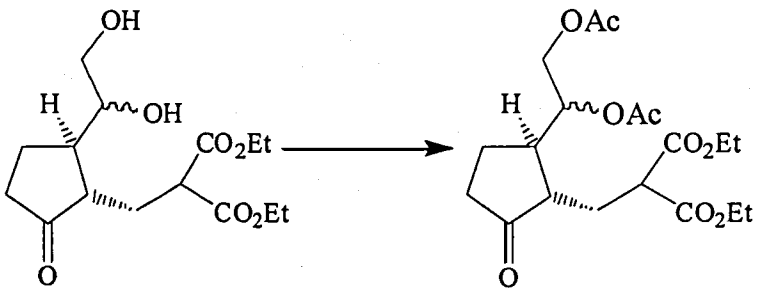
6.1.2.3 (±)-*trans*-2-[2-(1,2-Dihydroxyethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (12)



11 **12**

A solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-malonic acid diethyl ester (**11**) (2.0 g, 7.09 mmol), $OsCl_3$ (32 mg, 0.106 mmol) and *N*-methyl morpholine *N*-oxide monohydrate, (2.4 g, 17.7 mmol), in 1/1 mixture of tetrahydrofuran: water (120 mL) was stirred at room temperature for eight hours. The reaction was diluted with dichloromethane (200 mL) and washed with saturated aqueous potassium hydrogen sulfate (3 × 100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness to give a black oil (2.1 g) that was purified by flash column chromatography (80% ethyl acetate/light petroleum) to give 2-[2-(1,2-dihydroxyethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (**12**) as a colourless oil (1.5 g, 67%); ν_{max} (film)/cm^{-1} 3443 (O-H), 2980-2936 (C-H), 1736 (C=O), 1731 (EtO*C*=*O*), 1236 (C-O); δ_H (400 MHz, $CDCl_3$) 4.29-4.02 (4 H, m, $CH(CO_2CH_2CH_3)_2$), 3.97-3.87 (2 H, m, $CH(CO_2CH_2CH_3)_2$, *C*HOH), 3.74-3.51 (2 H, m, CH_2OH), 2.40-1.40 (8 H, m, *C*HCHRCO, CHC*H*RCO, $CH_2CH(CO_2Et)_2$, CH_2CH_2C=O, CH_2CH_2C=O), 1.20-1.26 (6 H, m, $CH(CO_2CH_2CH_3)_2$); δ_C (100 MHz,$CDCl_3$) 219.6 (*C*=O), 170.0 (CO_2Et), 169.5 (CO_2Et), 70.1 (*C*HOH), 65.0 (CH_2OH), 61.6 ($CO_2CH_2CH_3$), 49.4 ($CH(CO_2CH_2CH_3)_2$, 47.4 (CHCHRCO), 44.8 (*C*HCHRCO), 36.9 ($CH_2CH(CO_2Et)_2$), 26.6 (CH_2CO), 19.8 (CH_2CH_2CO), 13.9 ($CO_2CH_2CH_3$); *m/z* (FAB^+) 317.1600 (M + H^+), $C_{15}H_{24}O_7$ + H^+ requires 317.1600.

6.1.2.4 (±)-*trans*-2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (13)

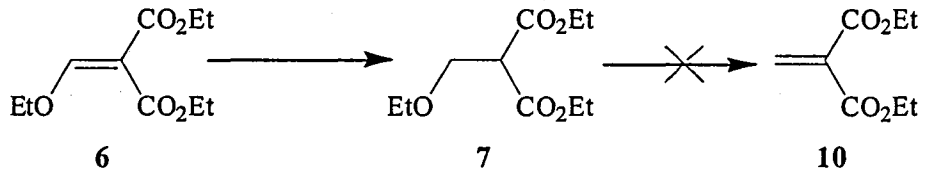


12 **13**

A solution of (±)-*trans*-2-[2-(1,2-dihydroxyethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (**12**) (1.5 g, 4.76 mmol) and dimethylamino pyridine (DMAP), (75 mg, 0.61 mmol) in 1:1= pyridine:acetic anhydride (34 mL), was stirred for 4 hours and evaporated to dryness. The residue was dissolved in ethyl acetate (150 mL), washed with 0.5M HCl (3 × 100 mL), and with saturated aqueous sodium hydrogen carbonate (3 × 100 mL). The organic layer was dried over anhydrous magnesium sulfate, and evaporated to dryness to give a red oil (3.9 g) that was purified by flash column chromatography (25-35% ethyl acetate/light petroleum) to give 2-[2-(1,2-diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (**13**) as a pale yellow oil (1.9 g, 100%); ν_{max} (film)/cm^{-1} 2981-2940 (C-H), 1741 (C=O), 1241 (C-O); δ_H (400 MHz, $CDCl_3$) 5.24 (1 H, ddd, J_1= 7.6, J_2= 4.2, J_3= 4.2, C*H*OAc), 4.32-4.05 (7 H, m, CH_2OAc, CH($CO_2CH_2CH_3$)$_2$), 2.72-2.42 (14 H, m, 2 × CH_3CO, C*H*CHRCO, CHC*H*RCO, CH_2CH(CO_2Et)$_2$, CH_2CH_2C=O, CH_2CH_2C=O), 1.23 (6 H, t, J= 7.1, CH($CO_2CH_2CH_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 218.0 (*C*=O), 170.5 (CH_3CO), 170.1 (CH_3CO), 169.1 (CO_2Et), 169.0 (CO_2Et), 70.2 (*C*HOAc), 64.0 (CH_2OAc), 61.8 ($CO_2CH_2CH_3$), 49.3 (*C*H($CO_2CH_2CH_3$)$_2$, 47.5 (CH*C*HRCO), 43.6 (*C*HCHRCO), 37.3 (*C*H_2CH(CO_2Et)$_2$), 27.6 (*C*H_2CO), 21.5 (*C*H_2CH_2O), 21.2 (*C*H_3CO), 21.1 (*C*H_3CO), 14.4 ($CO_2CH_2CH_3$), 14.3 ($CO_2CH_2CH_3$); *m/z* (EI^+) 400.1724 (M^+), $C_{19}H_{28}O_9$ requires 400.1733.

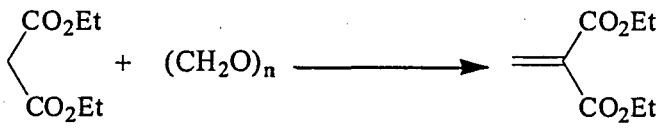
6.1.3 Methylidene malonate diethyl ester (10)

2.6.1.3.1 Methylidene malonate diethyl ester (10): path C



A mixture of ethyloxy methylidene malonate diethylester (**6**) (21.0 g, 97.13 mmol) and 10% palladium on carbon (710 mg, 3% w/w) in ethyl acetate (210 mL) was stirred at room temperature under an atmosphere of hydrogen for eighteen hours. The mixture was filtered through a pad of celite and the solution concentrated to dryness to give a 3:1 mixture of ethyloxy methyl malonate diethyl ester (**7**), and methyl malonate diethyl ester (19.1 g). The mixture (8.0 g) was placed in a distillation apparatus and initially heated to 80 °C (distillation head) by Bunsen flame to perform 1,2 elimination of ethanol (removed by distillation). When all the ethanol had come out, the temperature was gently increased until achievement of 100 °C (distillation head) before the second distillation had started. The flask was then heated to perform a slow distillation. About 1.5 g of fore run was collected before the temperature of the vapour raised 200 °C. A main fraction was collected between 200 and 230 °C (3.1 g). ^{1}H NMR analysis performed on both fractions showed the presence of the title compound but also a large amount of polymerised product. The spectrum region about 4 ppm does not show a simple quartet (methylene groups in the ester moiety), but a lot of signals characteristic of lots similar but not equivalent methylene groups. The spectrosopic data of compound **7** were consistent with those reported in literature for ethyloxy methyl malonate diethylester. Ethyloxy methyl malonate diethylester (**7**), pale yellow oil (14.3 g, 68%); δ_H (400 MHz, $CDCl_3$) 4.15 (4 H, q, *J*=6.8, $CO_2CH_2CH_3$), 3.81 (2 H, d, *J*= 7.6,-OCH_2CH-), 3.61 (1 H, t, *J*= 7.6, -OCH_2CH-), 3.45 (2 H, q, *J*= 6.8, OCH_2CH_3), 1.20 (3 H, t, *J*= 6.8, $CO_2CH_2CH_3$), 1.10 (3 H, t, *J*= 6.8, OCH_2CH_3); δ_C (100 MHz,$CDCl_3$) 168.0 (2 × CO_2Et), 68.2 (OCH_2CH-), 67.0 (OCH_2CH), 61.8 ($CO_2CH_2CH_3$), 53.0 (OCH_2CH), 15.2 (OCH_2CH_3), 14.3 ($CO_2CH_2CH_3$).

6.1.3.2 Methylidene malonate diethyl ester (10): path D[5]

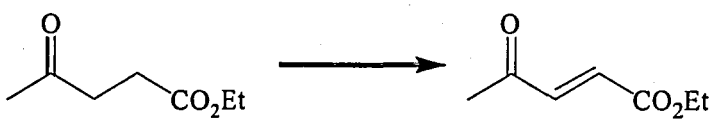


8 **9** **10**

A stirring mixture of diethyl malonate (19 mL, 20.0 g, 0.125 mol), paraformaldehyde (7.5 g, 0.25 mol), copper acetate (1.30 g), and potassium acetate (1.30 g) in glacial acetic acid (50 mL) was heated between 95 and 105 °C for 1 hour. The mixture was cooled to room temperature and evaporated to dryness under reduced pressure. The deep blue residue was distilled under vacuum (80-100 °C, 15 mbar) to give methylidene malonate diethyl ester (**10**) as a colourless oil (9.5g, 44%), which polymerises very quickly at room temperature. Spectroscopic and physical data were consistent with those reported in the literature. B.p.= 80-85 °C, 15 mbar; δ_H (400 MHz, $CDCl_3$) 6.45 (2 H, s, CH_2=C(CO_2Et)$_2$), 4.21 (4 H, q, *J*= 7.2, CH_2=C($CO_2CH_2CH_3$)$_2$), 1.26 (6 H, t, *J*= 7.2, CH_2=C($CO_2CH_2CH_3$)$_2$); δ_C (100 MHz,$CDCl_3$) 163.7 (CO_2Et), 134.9 (CH_2=C(CO_2Et)$_2$), 133.9, (CH_2=C(CO_2Et)$_2$), 61.2 (CH_2=C($CO_2CH_2CH_3$)$_2$), 13.7 (CH_2=C($CO_2CH_2CH_3$)$_2$).

6.2 Synthesis of the diene moiety (19a, 19b)

6.2.1 Ethyl-4-oxo-(E)-pent-2-enoate (15)

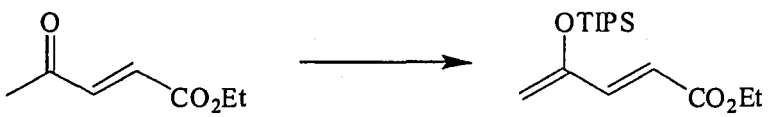


14 **15**

A portion (5 mL) of a solution of bromine (22.0 g, 7.16 mL, 138 mmol) in carbon tetrachloride (100 mL) was added at room temperature to a stirring solution of ethyl levulinate (**14**) (20.0 g, 19,7 mL, 138 mmol) in carbon tetrachloride (250 mL). The colourless solution was cooled to 0 °C and the remaining amount of bromine solution was added drop-wise over two hours. The mixture was allowed to reach room

temperature and washed with saturated aqueous sodium hydrogen carbonate (3 × 60 mL), dried over anhydrous magnesium sulfate, and evaporated to dryness to give a colourless oil (30.0 g). This was dissolved in dichloromethane (200 mL), triethylamine (21.0 g, 29 mL, 208 mmol) was added over fifteen minutes, and the resulting mixture stirred under reflux for two hours. The solution was allowed to cool to room temperature, washed with 1M HCl (3 × 50 mL), water (2 × 50 mL), brine (2 × 50 mL). The combined aqueous washings were extracted with dichloromethane (2 × 60 mL) and the combined organic layers dried over anhydrous magnesium sulfate, and concentrated to dryness to give a black oil (15.0 g) that was purified by distillation (r. t., 1 mbar) to give ethyl-4-oxo-(*E*)-pent-2-enoate (**15**) as a pale yellow oil (11.1 g, 57%); ν_{max} (film)/cm^{-1} 2985-2360 (C-H), 1727 (C=O), 1682 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 6.74 (1 H, d, *J*= 16.0, COCH=C*H*CO_2Et), 6.38 (1 H, d, *J*= 16.0, COC*H*=CHCO_2Et), 3.10 (2 H, q, *J*= 7.2, $CO_2CH_2CH_3$), 2.10 (3 H, s, CH_3CO), 1.05 (3 H, t, *J*= 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz,$CDCl_3$) 198.0 (CH_3CO), 165.8 (CO_2Et), 140.3 (COCH=CHCO_2Et), 132.0 (COCH=CHCO_2Et), 61.8 (COCH=CHCO_2Et), 28.4 (CH_3CO), 14.4 ($CO_2CH_2CH_3$); *m/z* (EI$^+$) 142.0628 (M^+), $C_7H_{10}O_3$ requires 142.0630.

6.2.2 Ethyl-4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dienoate (16)

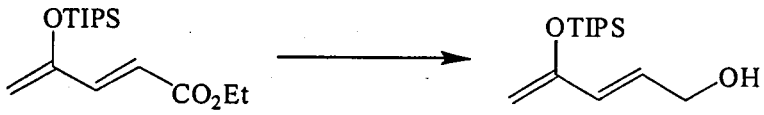


15 **16**

Triisopropylsilyloxy triflate (TIPSOTf) (3.2 mL, 3.64 g, 11.8 mmol) was added over five minutes to a stirring solution of ethyl-4-oxo-(*E*)-pent-2-enoate (**15**) (1.24 g, 8.72 mmol) and triethylamine (2.1 mL, 14.8 mmol), in anhydrous dichloromethane (40 mL), at 0 °C under an atmosphere of nitrogen. The reaction mixture was allowed to attain room temperature, stirred for a further two hours, diluted with dichloromethane (30 mL) and washed with saturated aqueous sodium hydrogen carbonate (3 × 50 mL). The organic phase was dried over magnesium sulfate and evaporated to dryness to give a yellow-orange oil (3.2 g) that was purified by flash column chromatography (5% ethyl acetate/light petroleum) on deactivated silica gel (5% w/w water) to give ethyl-4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dienoate (**16**) as a colourless oil (2.22 g, 85%);

ν_{max} (film)/cm^{-1} 2944-2867 (C-H), 1718 (C=O), 1637 (*C*=*C*-OSi), 1592 (*C*=*C*-CO_2Et), 1255, (C-Si) 1160 (C-O); δ_H (400 MHz, $CDCl_3$) 7.06 (1 H, d, *J*= 15.3, C*H*=CHCO_2Et), 6.17 (1 H, dd, J_1= 15.3, J_2= 0.5, CH=C*H*CO_2Et), 4.62 (1 H, d, *J*= 0.8, H_aCH=C(OTIPS)CH=CH), 4.60 (1 H, s, H_bCH=C(OTIPS)CH=CH), 4.20 (2 H, q, *J*= 7.4, $CO_2CH_2CH_3$), 1.29 (3 H, *J*= 7.4, $CO_2CH_2CH_3$), 1.24 (3 H, sept, *J*= 7.9, OSi(C*H*$(CH_3)_2)_3$), 1.09 (18 H, d, *J*= 7.4, OSi(CH(C*H*$_3)_2)_3$); δC(100 MHz,$CDCl_3$) 167.5 (*C*O_2Et), 154.2 (CH_2=*C*(OTIPS)), 142.8 (*C*H=CHCO_2Et), 119.4 (CH=*C*HCO_2Et), 102.0 (*C*H_2=C(OTIPS), 60.8 ($CO_2CH_2CH_3$), 18.4 (OSi(CH(*C*$H_3)_2)_3$), 14.7 ($CO_2CH_2CH_3$), 13.1 (OSi(*C*H$(CH_3)_2)_3$); *m/z* (EI^+) 298.1969 (M^+), $C_{16}H_{30}O_3Si$ requires 298.1964.

6.2.3 4-(Triisopropylsilyloxy)-(*E*)-penta-2,4-dien-1-ol (17)

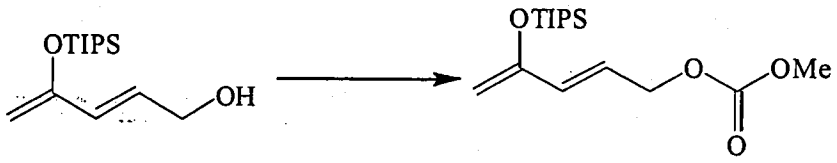


16 **17**

A solution of diisobutylaluminium hydride (DIBAL) (1M in toluene, 22.0 mL, 22.0 mmol) was added over thirty minutes to a stirring solution of ethyl-4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dienoate (**16**) (2.57 g, 8.62 mmol) in anhydrous tetrahydrofuran (40 mL) at –78 °C under nitrogen atmosphere, and the solution stirred between –78 and –65 °C for two hours. The mixture was allowed to reach room temperature, 60 mL of saturated aqueous sodium potassium tartrate (La Rochelle salt) was added, and the mixture stirred for a further one hour, until two-layer separation. The two layers were separated and the aqueous extracted with dichloromethane (3 × 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness to give a pale yellow oil (2.3 g) that was purified by flash column chromatography (12% ethyl acetate/light petroleum) on deactivated silica gel (5% w/w water) to give 4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dien-1-ol (**17**) as a pale yellow oil (2.20 g, 84%); ν_{max} (film)/cm^{-1} 3404 (O-H), 2943-2865 (C-H), 1665 (CH_2=COSi), 1591 (C=C), 1096 (Si-O), 1015 (C-O); δ_H (400 MHz, $CDCl_3$) 6.19 (1 H, dt, J_1= 15.3, J_2= 5.3 CH=C*H*CH_2OH), 6.08 (1 H, dt, J_1= 15.3, J_2= 1.3, C*H*=CHCH_2OH), 4.30 (1 H, s, H_aCH_b=C(OTIPS)-), 4.26 (1 H, s, H_aCH_b=C(OTIPS)-), 4.23 (2 H, d, *J*= 15.3, CH_2OH), 1.73 (1 H, broad, CH_2OH), 1.23 (3 H, sept, *J*= 7.1,

(Si(C*H*(CH$_3$)$_2$)$_3$), 1.10 (18 H, d, *J*= 7.1, (Si(CH(C*H$_3$*)$_2$)$_3$); δ_C (100 MHz,CDCl$_3$) 154.7 (CH$_2$=*C*(OTIPS)), 129.1 (CH=*C*HCH$_2$OH), 128.8 (*C*H=CHCH$_2$OH), 94.9 (*C*H$_2$=C(OTIPS)), 62.9 (*C*H$_2$OH), 18.4 (Si(CH(C*H$_3$*)$_2$)$_3$), 13.2 (Si(*C*H(CH$_3$)$_2$)$_3$); *m/z* (EI$^+$) 257.1942 (M + H$^+$), $C_{14}H_{28}O_2Si$ + H$^+$ requires 257.1937.

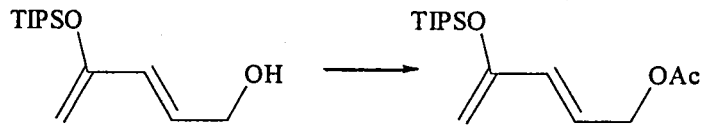
6.2.4 Carbonic acid methyl ester 3-triisopropylsilanyloxy-buta-1,3-dienyl ester (19a)



17 **19a**

n-Butyllithium (2.5M in hexanes, 1.1 mL, 2.75 mmol) was added to a stirring solution of 4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dien-1-ol (**17**) (520 mg, 2.03 mmol) in dry tetrahydrofuran (10 mL) at –78 °C under an atmosphere of nitrogen. After ten minutes methylchloroformate (0.2 mL, 2.64 mmol) was added and the mixture allowed to reach room temperature. After forty-five minutes the reaction was cooled to 0 °C, quenched with a few drops of water and evaporated to dryness. The crude was purified by flash column chromatography (5% ethyl acetate/light petroleum) on deactivated silica gel (5% w/w water) to give carbonic acid methyl ester 3-triisopropylsilanyloxy-buta-1,3-dienyl ester (**19a**) as a colourless oil (540 mg, 84%); ν_{max} (film)/cm^{-1} 2944-2886 (C-H), 1753 (C=O), 1660 (*C*=*C*-OSi), 1593 (C=C), 1262 (Si-O), 1029 (C-O); δ_H (400 MHz, CDCl$_3$) 6.20 (1 H, d, *J*= 15.3, C*H*=CHCH$_2$OCO$_2$Me), 6.10 (1 H, dt, J_1= 15.3, J_2= 5.3, CH=C*H*CH$_2$OCO$_2$Me) 4,67 (2 H, d, *J*= 4.7, C*H*$_2$OCO$_2$Me), 4.33 (1 H, s, *H$_a$*CH$_b$=C(OTIPS)), 4.28 (1 H, s, H$_a$C*H$_b$*=C(OTIPS)), 3.75 (3 H, s, OCO$_2$C*H$_3$*), 1.20 (3 H, sept, *J*= 6.8, (Si(C*H*(CH$_3$)$_2$)$_3$), 1.07 (18 H, d, *J*= 6.8, (Si(CH(C*H$_3$*)$_2$)$_3$); δ_C (100 MHz, CDCl$_3$) 155.5 (CH$_2$=*C*(OTIPS)), 154.1 (O*C*O$_2$CH$_3$), 132.0 (CH=*C*HCH$_2$OCOCH$_3$), 123.0 (*C*H=CHCH$_2$OCOCH$_3$), 96.0 (*C*H$_2$=C(OTIPS)) 67.5 (CH=CH*C*H$_2$OCO$_2$Me), 54.6 (OCO$_2$*C*H$_3$), 17.9 (Si(CH(*C*H$_3$)$_2$)$_3$), 12.6 (Si(*C*H(CH$_3$)$_2$)$_3$); *m/z* (EI$^+$) 314.19073 (M+ H$^+$), $C_{16}H_{31}O_3Si$ + H$^+$ requires 314.1934.

6.2.5 Acetic acid 4-triisopropylsilanyloxy-penta-2,4-dienyl ester (19b)

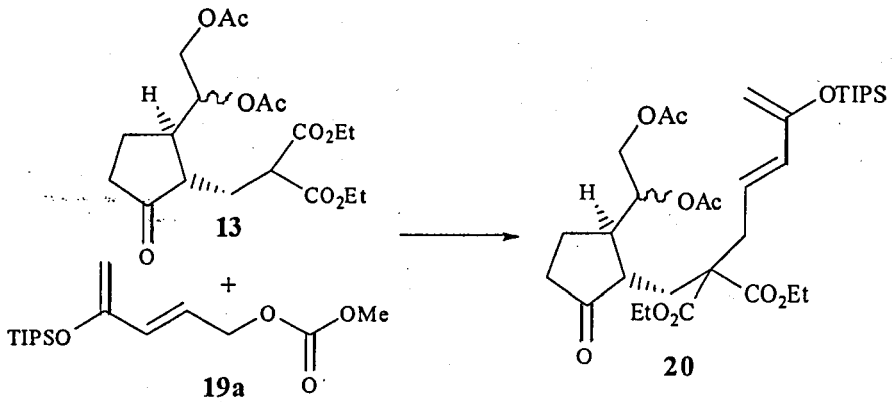


17 **19b**

A mixture of 4-(triisopropylsilyloxy)-(*E*)-penta-2,4-dien-1-ol (**17**) (1 g, 3.90 mmol), DMAP (50 mg, 0.41 mmol), in 1:1= pyridine: acetic anhydride (20 ml) was stirred at room temperature for four hours. The solution was concentrated to dryness to give a crude material that was purified by flash column chromatography (4% ethyl acetate/light petroleum) to afford acetic acid 4-(triisopropylsilanyloxy)-(*E*)-penta-2,4-dienyl ester (**19b**) as a pale yellow oil (0.840 g, 72%); ν_{max} (film)/cm^{-1} 2944 (C-H), 2891 (C-H), 2866 (C-H), 1743 (C=O), 1593 (C=C), 1239 (CSi), 1026 (C-O); δ_H (400 MHz, $CDCl_3$) 6.13-6.06 (2 H, m, C*H*=C*H*), 4.64 (2 H, d, d, *J*= 4, CH_2OAc), 4.35 (1 H, s, *Ha*CHb=CTIPS), 4.30 (1 H, s, HaC*Hb*=CTIPS), 2.10 (3 H, s, CH_3CO_2), 1.22 (3 H, sept, *J*= 4, $CH(CH_3)_2 \times 3$), 1.09 (18 H, d, *J*= 4, $CH(CH_3)_2 \times 3$); δ_C (100 MHz, $CDCl_3$) 170.6 (CH_3C=O), 154.1 (CH_2=*C*OTIPS), 95.5 (*C*H_2=COTIPS), 64.0 (*C*H_2OAc), 20.8 (*C*H_3C=O), 17.7 ($CH(CH_3)_2$), 12.6 ($CH(CH_3)_2$); *m/z* (FAB^+) 299. 2041 ($M + H^+$), $C_{16}H_{30}O_3Si + H^+$ requires 299.2041.

6.3 (±)-trans-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropyl silanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (23)

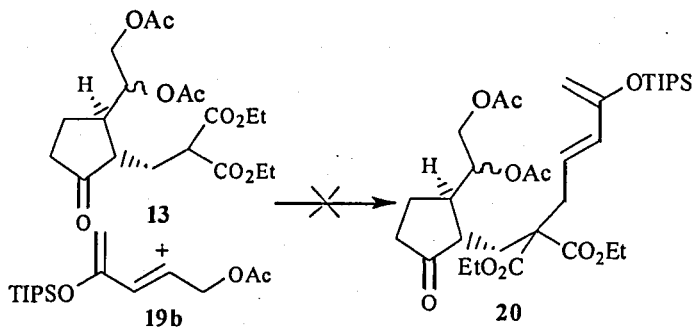
6.3.1 (±)-*trans*-2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(4-triisopropyl silanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (20): neutral conditions



A solution of (±)-*trans*-2-[2-(1,2-diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (**13**) (1.0 g, 2.5 mmol) and carbonic acid methyl ester 4-triisopropylsilanyloxy-penta-2,4-dienyl ester (**19a**) (1.04 g, 3.3 mmol) in anhydrous dichloromethane (15 mL) was degassed by a stream of nitrogen for 30 minutes. Then, triphenylphosphine (263 mg, 1 mmol) and $Pd_2(dba)_3$ (114 mg, 0.125 mmol) were added and the mixture heated under reflux and under an atmosphere of nitrogen for eighteen hours. The reaction was allowed to reach room temperature and filtered through a pad of silica gel (50% ethyl acetate/light petroleum). The solution was concentrated to dryness to give a crude material that was purified by flash column chromatography (15% ethyl acetate/light petroleum) on deactivated silica gel (water 5% w/w) to give (±)-*trans*-2-[2-(1,2-diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**20**) as a pale yellow oil as a couple of diastereoisomers (1.3 g, 80%); ν_{max} (film)/cm^{-1} 2942-2865 (C-H), 1743 (C=O), 1590 (C=C), 1220 (Si-O), 1029 (C-O); δ_H (400 MHz, $CDCl_3$) 5.95-5.88 (2 H, m, *H*C=C*H*CH_2), 5.12-5.10 (1 H, m, C*H*OAc), 4.34 (1 H, dd, J_1= 12.1, J_2= 3.2, *Ha*CHb(OAc)),4.22 (1 H, s, *Ha*CHb=C(OTIPS)), 4.17 (1 H, s, HaC*Hb*=C(OTIPS)), 4.13 (4 H, q, *J*= 7.1, $C(CO_2CH_2CH_3)_2$), 4.09-4.04 (1 H, m, dd, HaC*Hb*(OAc)), 2.76 (2 H, d, *J*= 5.8, CH=CHCH_2), 2.04 (3 H, s, CH_3CO_2), 2.03 (3 H, s, CH_3CO_2), 1.92-1.30 (7 H, m, C*H*RC=O, C*H*CHRC=O, $CH_2C(CO_2Et)_2$, CH_2C=O,

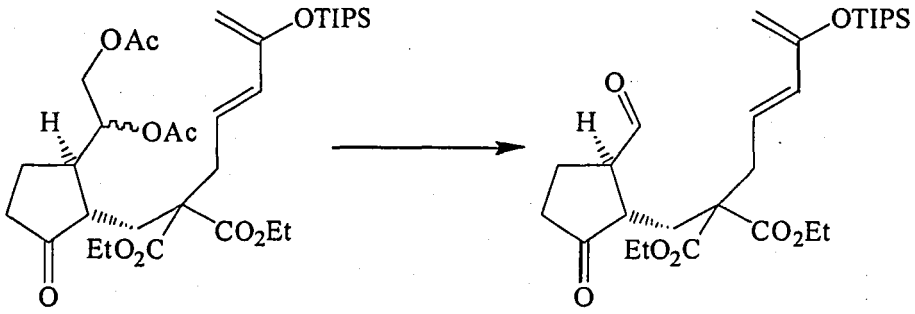
*Hc*CHdCH$_2$C=O), 1.76-1.62 (1 H, m, HcC*Hd*CH$_2$C=O), 1.15-1.21 (9 H, m, C(CO$_2$CH$_2$C*H$_3$*)$_2$, Si(C*H*(CH$_3$)$_2$)$_3$), 1.06 (18 H, d, *J*= 7.1, Si(CH(C*H$_3$*)$_2$)$_3$); δ_C (100 MHz, CDCl$_3$) 218.0 (*C*=O), 170.0 and 170.6 (C(*C*O$_2$Et)$_2$), 170., 170.4 (CH$_3$*C*O$_2$), 154.6 (CH$_2$=*C*(OTIPS)), 132.1 (CH=*C*HCH$_2$-), 124.7 (*C*H=CHCH$_2$-), 94.2 (*C*H$_2$=C(OTIPS)), 73.7 (*C*HOAc), 63.3 (*C*H$_2$OAc), 61.5 and 61.3 (C(CO$_2$*C*H$_2$CH$_3$)$_2$), 57.1 (*C*(CO$_2$CH$_2$CH$_3$)$_2$), 47.3 (*C*HCHRC=O), 43.2 (-*C*HRC=O), 36.7 (-HC=CH*C*H$_2$-), 35.7 (*C*H$_2$C(CO$_2$Et)$_2$), 33.3 (*C*H$_2$C=O), 23.2 (*C*H$_2$CH$_2$C=O), 20.9 (*C*H$_3$CO$_2$-), 20.7 (*C*H$_3$CO$_2$-), 18.0 (Si(CH(*C*H$_3$)$_2$)$_3$), 14.0 and 13.9 (C(CO$_2$CH$_2$*C*H3)$_2$), 12.7 (Si(*C*H(CH$_3$)$_2$)$_3$); *m/z* (FAB$^+$) 639.3576 (M + H$^+$); C$_{33}$H$_{55}$O$_{10}$Si + H$^+$ requires 639.3565.

6.3.2 (±)-trans-2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(4-triisopropyl silanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (20): basic conditions



A solution of (±)-*trans*-2-[2-(1,2-diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (**13**) (400 mg, 0.001 mol)in anhydrous degassed dichloromethane (5 mL) was reacted with NaH (90% dispersion in mineral oil, 24 mg, 0.0011 mol) at 0 °C and under an atmosphere of nitrogen for thirty minutes. Then, a solution of the acetate **19b** (360 mg, 0.0012 mol), Pd$_2$(dba)$_3$ (46 mg, 0.05 mmol) and triphenylphosphine (105 mg, 0.4 mol) in anhydrous degassed dichloromethane (5 mL) was added and the mixture heated under reflux for eighteen hours under an atmosphere of nitrogen. The reaction was then allowed to reach room temperature and filtered through a pad of silica gel (50% ethyl acetate/light petroleum). The organics were concentrated to dryness to give a brown crude material, which, according to ^{1}H NMR analysis, was a mixture of unreacted starting materials with no trace of any target compound (**20**).

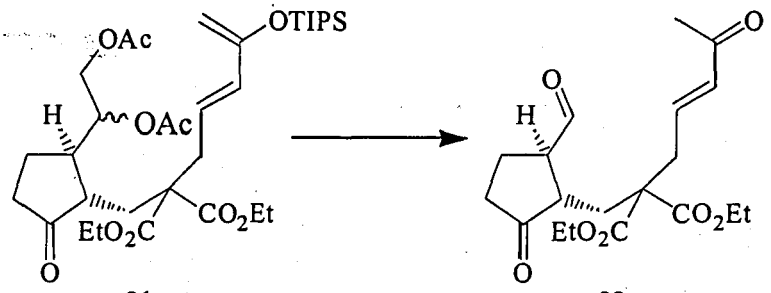
6.3.3 (±)-trans-2-[2-(1,2-Dihydroxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(4-triisopropyl silanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (23): sodium periodate dissolved in 1:1= THF/H_2O



A solution of 2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(4-triisopropyl silanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**20**) (1.07 g, 1.68 mmol) in methanol (30 mL) was stirred in presence of activated Amberlite 400® Cl (1.5 g) basic resin at room temperature for eighteen hours. The resin was then filtered off using a sintered glass funnel and washed with methanol (30 mL). The solution was then concentrated to dryness to give a crude pale yellow oil (**16a**, 0.95 g) which, without any further purification, was dissolved in 20 mL of a mixture of water: tetrahydrofuran (1/1) and reacted with sodium periodate (0.9 g, 4.2 mmol) at room temperature for five hours. The solution was then diluted with dichloromethane (60 mL), the organic layer separated from the aqueous and washed with brine (3 × 20 mL). The combined aqueous fractions were extracted with dichloromethane (3 × 20 mL), the organic fractions were dried over anhydrous magnesium sulfate, and concentrated to dryness to give a pale yellow oil (840 mg). This was purified by flash column chromatography (15% ethyl acetate/light petroleum) on deactivated silica gel (5% w/w water), to give (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**23**), as a colourless oil (750 mg, 85%). ν_{max} (film)/cm^{-1} 2943-2863 (C-H), 1745 (CH=O), 1731 (R^1R^2-C=O), 1591 (C=C), 1258 (C-Si), 1189 (Si-O), 1027 (C-O); δ_H (400 MHz, $CDCl_3$) 9.64 (1 H, s, C*H*O), 5.90-5.78 (2 H, m, C*H*=C*H*-), 4.18-4.05 (6 H, m, H_2C=C(OTIPS), (OCH_2CH$_3$) × 2), 2.80-2.70 (1 H, m, C*H*CHC=O), 2.69-2.64 (2 H, m, CH=CH-CH_2-), 2.63-2.55 (1 H, m, CHC*H*C=O), 2.40-2.30 (1 H, m, H_aCH$_b$=O), 2.30-2.00 (3 H, m, H_aCH$_b$CH$_2$=O, H$_a$CH_b=O, H_aCH$_b$C(CO$_2$Et)$_2$), 1.90-1.80 (2 H, m, H$_a$CH_bCH$_2$=O, H$_a$CH_b-C(CO$_2$Et)$_2$), 1.20-1.19 (9 H, m, (OCH$_2$CH_3) × 2, (CH(CH$_3$)$_2$) × 3), 1.03-1.01 (18 H, d, *J*= 7.1, (CH(CH_3)$_2$) × 3); δ_C (100 MHz, $CDCl_3$) 216.5 (R^1*C*OR^2), 201.5 (*C*HO), 171.2 (*C*O$_2$Et), 155.0

(H_2C=C(OTIPS), 132.7 (CH=CH-CH_2), 124.6 (CH=CH-CH_2), 94.8 (H_2C=C(OTIPS), (62.1 (O$CH_2$$CH_3$), 61.8 (O$CH_2$$CH_3$), 57.4 ($C$($CO_2Et$)$_2$), 55.3 ($C$HCHC=O), 46.5 (CH$C$HC=O), 37.7 (CH=CH-$CH_2$-), 36.2 ($CH_2$C=O), 33.0 ($CH_2CH_2$C=O), 21.6 ($CH_2$C($CO_2Et$)$_2$), 18.4 (Si(CH($CH_3$)$_2$)$_3$), 14.4 (O$CH_2$$CH_3$), 13.2 ($CH$($CH_3$)$_2$); *m/z* ($FAB^+$) 522.3013 ($M^+$), ($C_{28}H_{46}O_7Si$) requires 522.3003.

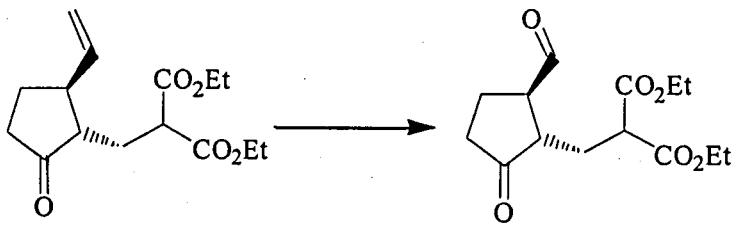
6.3.4 (±)-*trans*-2-(2-Formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropyl silanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (23): sodium periodate adsorbed on silica



Activated Amberlite® 400 Cl (250 mg) (previously activated by a wash with a 3M solution of NaOH and then methanol) was added to a solution of (±)-*trans*-2-[2-(1,2-diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**21**) (192 mg, 0.03 mmol) in methanol (5 mL), and the mixture stirred for eighteen hours at room temperature, filtered trough a sintered glass funnel, and the resin washed with methanol (3 × 10 mL). The solvent was concentrated to dryness to give a crude material (160 mg) that was dissolved in dichloromethane (6 mL) and treated with $NaIO_4/SiO_2$ (sodium periodate adsorbed on silica, 90 mg) and the mixture stirred for twenty minutes. The silica was filtered off through a sintered glass funnel and washed with dichloromethane (3 × 15 mL), the organic solvent was evaporated to dryness to give (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(4-oxo-pent-2-enyl)-malonic acid diethyl ester (**22**) as a pale yellow oil (85 mg, 77% for two steps). ν_{max} (film)/cm^{-1} 2960 (C-H), 1730 (C=O), 1675 (C=C), 1254 (C-O); δ_H (400 MHz, $CDCl_3$) 9.67 (1 H, d, *J*= 2.8, C*H*O), 6.73 (1 H, dt, J_1= 16, J_2= 7.6, CH=C*H*CH_2), 6.06 (1 H, dt, J_1= 16, J_2= 1.2, C*H*=$CHCH_2$), 4.22-4.07 (4 H, m, O$CH_2$$CH_3$ × 2), 2.90-2.78 (3 H, m, C*H*CHO, HC=CHCH_2), 2.61-2.56 (1 H, m, C*H*CHCHO), 2.42-1.96 (9 H, m, CH_3CO, CH_2CO, CH_2CH_2CO, (CO_2Et)$_2$CCH_2CHCO), 1.23 (3 H, t, *J*= 7.2, OCH_2CH_3), 1.22 (3 H, t, *J*= 7.2,

OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 215.6 (R^1C=OR^2), 200.5 (*C*HO), 198.1 (CH_3C=O), 170.0 (CO_2Et), 141.6 (CH=*C*HCH_2), 134.4 (*C*H=$CHCH_2$), 61.7 (OCH_2CH_3), 61.5 (OCH_2CH_3), 56.3 ($C(CO_2Et)_2$), 54.8 (*C*HCHO), 45.4 (*C*HCHCHO), 36.5 (CH_2C=O), 35.6 (CH_2CH_2C=O), 32.2 (CH=$CHCH_2$), 26.5 (CH_3C=O), 21.2 ($CH_2C(CO_2Et)_2$), 13.7 (OCH_2CH_3); *m/z* (CI) low resolution mass spectrum: 384 ($M + NH_4^+$), $C_{19}H_{30}NO_7$ requires 384.2022.

6.4 (±)-trans-2-(2-Formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (23): coupling of the aldehyde 26 with the pro-diene moiety (19a)



11 26

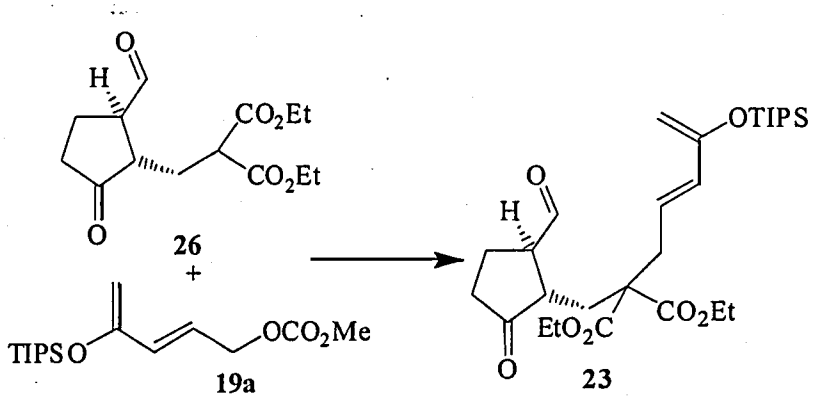
6.4.1 (±)-*trans*-2-(2-Formyl-5-oxo-cyclopentylmethyl)-malonic acid diethyl ester (26)

A stream of ozone was bubbled through a stirring solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-malonic acid (**11**) (900 mg, 3.19 mmol) in dichloromethane (50 mL), at –50 °C until the solution turned deeply blue (thirty minutes). The stream of ozone was stopped and oxygen was allowed through the solution until when it turned colourless. Triphenylphosphine (2.0 g, 7.6 mmol) was added and the solution was stirred for a further one hour and allowed to reach room temperature.

The solution was concentrated to dryness to give a yellow oil that was purified by flash column chromatography (50% ethyl acetate/light petroleum) to give (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-malonic acid diethyl ester (**26**) as a colourless oil (440 mg, 49%); ν_{max} (film)/cm^{-1} 2981 (C-H), 2938 (C-H), 2727 (H-CO), 1731 (C=O), 1233 (C-O); δ_H (400 MHz, $CDCl_3$) 9.71 (1 H, d, *J*= 2.1, C*H*O), 4.19-4.13 (4 H, m, OCH_2CH_3 × 2), 3.66 (1 H, dd, J_1= 8.4, J_2= 6.3, $CH(CO_2Et)_2$), 2.93-2,78, (1 H, m, *CH*CHC=O), 2.58-2.49 (1 H, m, CHC*H*C=O), 2.47-2.37 (1 H, m, H_aCH_bC=O), 2.31-

2.18 (3 H, m, $H_aCH_bCH(CO_2Et)_2$, $HaCHbCH_2C{=}O$, $H_aCH_bC{=}O$), 2.06-1.84 (2 H, m, $H_aCH_bCH(CO_2Et)_2$, $HaCHbCH_2C{=}O$), 1.199 (3 H, t, J= 7.2 OCH_2CH_3), 1.197 (3 H, t, J= 7.2 OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 216.0 (C=O), 200.6 (CHO), 169.0-168.0 (CO_2Et), 61.6 (OCH_2CH_3),54.4 (CHCHC=O), 49.4 ($CH(CO_2Et)_2$), 46.5 (CHCHC=O), 36.5 (CH_2C=O), 27.9 ($CH_2CH(CO_2Et)_2$), 21.4 (CH_2CH_2C=O), 13.9 (OCH_2CH_3); *m/z* (FAB^+) 284.1267 (M^+), $C_{14}H_{20}O_6$ requires 284.1260.

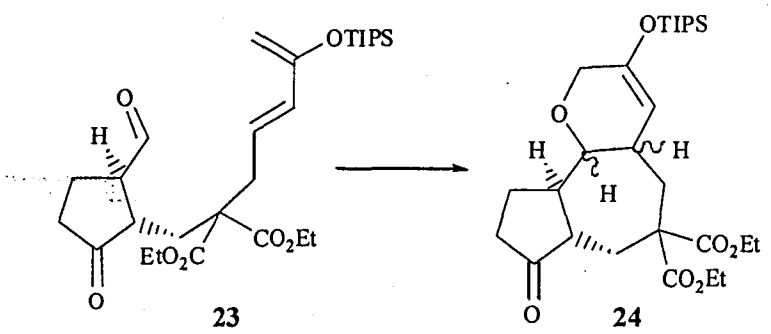
6.4.2: (±)-*trans*-2-(2-Formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (23): coupling of the aldehyde 26 with the pro-diene 19a



A solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-malonic acid diethyl ester (**26**) (440 mg, 1.55 mmol) and carbonic acid methyl ester 4-triisopropylsilanyloxy-penta-2,4-dienyl ester (**19a**) (630 mg, 2.02 mmol) in anhydrous dichloromethane (5mL) was degassed by a stream of nitrogen for thirty minutes before triphenylphosphine (160 mg, 0.61 mmol) and $Pd_2(dba)_3$ (71 mg, 0.077 mmol) were added and the mixture heated under reflux and under an atmosphere of nitrogen for eighteen hours. The reaction was allowed to attain room temperature and filtered trough a pad of silica gel (50% light petroleum/ethyl acetate). The solution was concentrated to dryness and the crude material purified by flash column chromatography (15% ethyl acetate/light petroleum) to give 130 mg (33% yield) of a colourless oil which spectral properties were consistent with those of compound **23**.

6.5 3-Oxo-8-triisopropylsilanyloxy-2,3,3a,4,6a,9,10a,10b-octahydro-1H,6H-10-oxa-benzo[e]azulene-5,5-dicarboxylic acid diethyl ester (24)

6.5.1 3-Oxo-8-triisopropylsilanyloxy-2,3,3a,4,6a,9,10a,10b-octahydro-1H,6H-10-oxa-benzo[e]azulene-5,5-dicarboxylic acid diethyl ester (24): thermal method



A solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**23**) (100 mg, 0.19 mmol) and hydroquinone (20 mg, 0.038 mmol) in anhydrous toluene (5 mL) was degassed by a stream of nitrogen and ultrasounds for thirty minutes in a sealed tube (previously washed with triethylamine and then oven-dried). The samoples heated up to 70 or 100 °C, for twenty-four hours, concentrated to dryness to give a crude material that according to ^{1}H-NMR analysis was mainly starting material **23**.

When the solution was heated at 160 °C for twenty-four hours, ^{1}H NMR analysis showed a complex mixture containing, beside some unidentified compounds, starting material **23** and a side product that LC-MS analysis suggested to be originated from the addition of a molecule of oxygen to the heterotriene **23**.

6.5.2 3-Oxo-8-triisopropylsilanyloxy-2,3,3a,4,6a,9,10a,10b-octahydro-1H,6H-10-oxa-benzo[e]azulene-5,5-dicarboxylic acid diethyl ester (24): microwave method

A solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**23**) (100 mg, 0.19 mmol) in toluene (3 mL) in a sealed tube was submitted to microwaves irradiation (full power, 120 °C, 10 minutes). The solution was concentrated to dryness to give a pale

yellow oil (100 mg) that according to ^{1}H NMR analysis was un-reacted starting material (**23**).

6.5.3 3-Oxo-8-triisopropylsilanyloxy-2,3,3a,4,6a,9,10a,10b-octahydro-1H,6H-10-oxa-benzo[e]azulene-5,5-dicarboxylic acid diethyl ester: Lewis acid method

Accordingly with the reaction conditions specified in table 1, (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**23**) (300 mg, mol) in 5 mL of anhydrous solvent (dichloromethane or tetrahydrofuran) was reacted with the amount of Lewis acid indicated in table 1. The reaction was stirred for up to six days, monitored by TLC analysis, washed with saturated aqueous sodium hydrogen carbonate (2 × 5 mL), brine (2 × 5 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give un-reacted starting material **23** or desilylated starting material **22**.

Starting material	Catalyst/Conditions	Time	Outcome
23	$ZnCl_2$/THF, r.t.	6 days	Partial desilylation
23	$ZnCl_2$/THF, reflux in sealed tube	20 h	Decomposition
23	BF_3•Et_2O (1 eq), Et_2O or THF, -78 °C	1 to 20 min.	Starting material
23	BF_3•Et_2O (2.5 eq)/ THF -78 °C to r. t.	24 h	Desilylation
23	$Yb(OTf)_3$ or $Sc(OTf)_3$ (1 eq)/ THF, 0 °C to r. t.	1 to 3 days	Starting material
23	$Yb(OTf)_3$ or $Sc(OTf)_3$ (2.5 eq)/ THF, –78 °C to r. t.	4 h	Desilylation
23	$Yb(OTf)_3$ (1eq), toluene Microwaves, 80 °C	20 min.	Decomposition
23	DCM, 19 Kbar	48 h	Partial desilylation

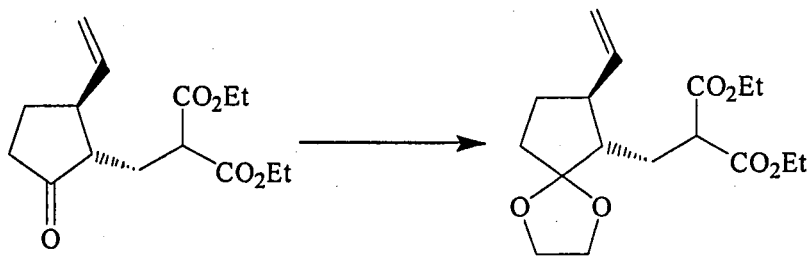
Table 4: Reaction conditions and chemical outcome of the attempts at the IMHDA reaction of **23**.

6.5.4 3-Oxo-8-triisopropylsilanyloxy-2,3,3a,4,6a,9,10a,10b-octahydro-1H,6H-10-oxa-benzo[e]azulene-5,5-dicarboxylic acid diethyl ester: ultra high-pressure method

A solution of (±)-*trans*-2-(2-Formyl-5-oxo-cyclopentylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**23**) (300 mg, 0.59 mmol), in anhydrous dichloromethane (5 mL) was submitted to ultra high-pressure (19 Kbar) for forty-eight hours. The solution was concentrated to dryness to give a pale yellow oil (300 mg), which, according to ^{1}H NMR analysis, was a mixture of unreacted starting material **23** and desilylated starting material **22**.

6.6 2-(7-Formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (31)

6.6.1 (±)-*trans*-2-(7-Vinyl-1,4-spiro[4.4]non-6-ylmethyl)-malonic acid diethyl ester (27)

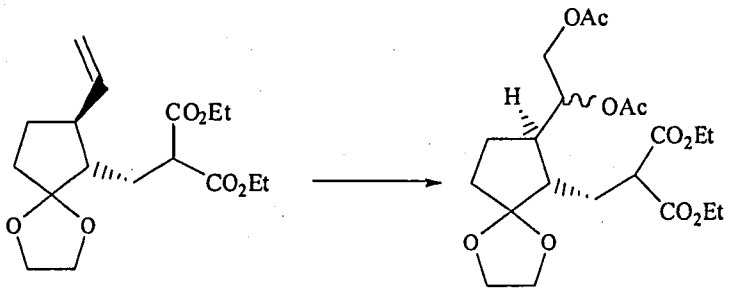


11 **27**

A solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-malonic acid (**11**), (1.0 g, 3.5 mmol), ethylene glycol (5 mL) and *para*-toluenesulphonic acid (*p*-TSA, 60 mg, 0.35 mmol), in anhydrous toluene (60 mL), was heated under reflux for four hours in a round bottom flask fitted with a Dean-Stark distillation head. The reaction was allowed to reach room temperature, washed with saturated aqueous sodium hydrogen carbonate (3 × 20 mL), the aqueous layers extracted with dichloromethane (3 × 20 mL), the combined organic fractions were dried over anhydrous magnesium sulfate, and

concentrated to dryness to give a brown oil (1.2 g) that was purified by flash column chromatography (10% light petroleum/ethyl acetate) to give (±)-*trans*-2-(7-vinyl-1,4-spiro[4,4]non-6-ylmethyl)-malonic acid diethyl ester (**27**) as a colourless oil (0.850 g, 74%) ν_{max} (film)/cm^{-1} 2960 (C-H), 1734 (C=O), 1443 (C=C), 1260 (C-O); δ_H (400 MHz, $CDCl_3$) 5.66 (1 H, ddd, J_1= 17.0, J_2= 10.1, J_3= 8.6, CH_2=C*H*-), 5.02 (1 H, ddd, J_1= 17.0, J_2= 1.7, J_3= 0.8, *Ha*CH_b=CH), 4.95 (1 H, dd, J_1= 10.1, J_2= 1.7, Ha*Hb*=CH), 4.21-4.08 (4 H, m, O*H*$_2$CH$_3$ × 2), 3.95-3.87 (4 H, m, O*H*$_2$C*H*$_2$O), 3.58 (1 H, dd, J_1= 8.8, J_2= 6.5, C*H*(CO_2Et)$_2$), 2.27-2.15 (1 H, m, C*H*CHC($C_2H_4O_2$), 1.99-1.92 (2 H, m, C*H*$_2$CH(CO_2Et)$_2$), 1.82-1.64 (4 H, m, C*H*C($C_2H_4O_2$), C*H*$_2$C($C_2H_4O_2$), *Ha*CHbCH$_2$C($C_2H_4O_2$)), 1.45-1.35 (1 H, m, HaC*Hb*CH$_2$C($C_2H_4O_2$)), 1.22 (6 H, t, *J*= 7.1, OCH$_2$C*H*$_3$ × 2); δ_C (100 MHz, $CDCl_3$) 169,7 (*C*O$_2$Et), 169.4 (*C*O$_2$Et), 141.4 CH$_2$=*C*H), 117.3 (*C*($C_2H_4O_2$), 114.8 (*C*H$_2$=CH), 64.2 (OCH$_2$CH$_2$O), 63.9 (OCH$_2$*C*H$_2$O), 61.1 (O*C*H$_2$CH$_3$), 61.0 (OCH$_2$CH$_3$), 49.7 *C*H(CO_2Et), 48.4 (*C*HCHC($C_2H_4O_2$)), 48.1 (*C*HC($C_2H_4O_2$), 35.3 (*C*H$_2$C($C_2H_4O_2$)), 28.5 (*C*H$_2$CH$_2$($C_2H_4O_2$)), 26.7 (*C*H$_2$CH(CO_2Et)$_2$), 14.0 (OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 326.1726 (M$^+$), $C_{17}H_{26}O_6$ requires 326.1729.

6.6.2 (±)-*trans*-2-[7-(1,2-Diacetoxy-ethyl)-vinyl-1,4-spiro[4.4]non-6-ylmethyl]-malonic acid diethyl ester (29)

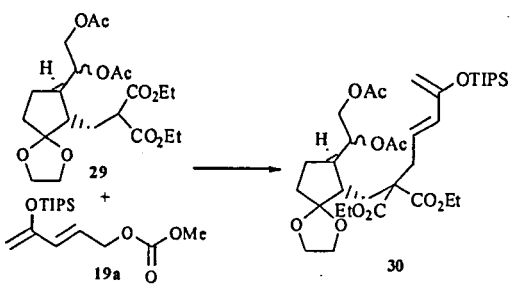


27 **29**

A mixture of $OsCl_3$ (9.0 mg, 0.30 mmol), *N*-methylmorpholine-*N*-oxyde, (NMO) (0.725 mg, 5.4 mmol), and 2-(7-vinyl-1,4-spiro[4,4]non-6-ylmethyl)-malonic acid diethyl ester (**27**) (0.700 g, 2.14 mmol) in a 1/1 mixture of tetrahydrofuran: water (20 mL) was stirred at room temperature for eight hours. The solution was diluted with dichloromethane (200 mL) and washed with saturated aqueous potassium hydrogen sulfate (3 × 100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under vacuum to give a black oil (2.1 g). The residue was dissolved in

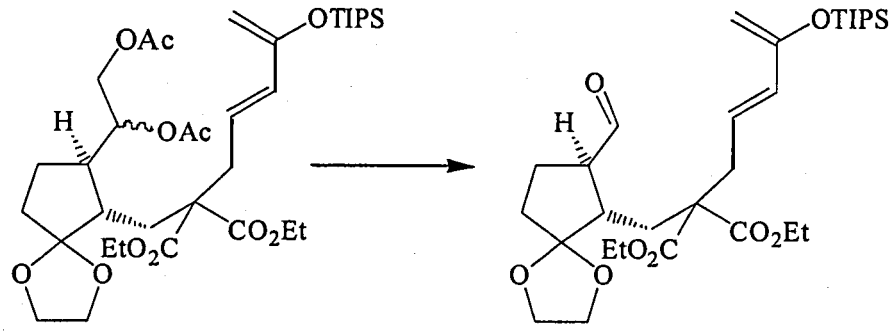
1:1= pyridine:acetic anhydride (10 mL), dimethylaminopyridine (DMAP, 10 mg, 82 μmol) was added, the solution stirred for four hours and concentrated to dryness. The residue was dissolved in ethyl acetate (150 mL), washed with 0.5M HCl (3 × 100 mL), and with saturated aqueous sodium hydrogen carbonate (3 × 100mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness to give a red oil (0.720 g) that was purified by flash column chromatography (20-30% ethyl acetate/light petroleum) to give (±)-*trans*-2-[7-(1,2-diacetoxy-ethyl)-vinyl-1,4-spiro[4,4]non-6-ylmethyl]-malonic acid diethyl ester (**29**) as a couple of diastereoisomers, as a colourless oil (0.717 g, 78%); ν_{max} (film)/cm^{-1} 2978 (C-H), 2890 (C-H), 1745 (C=O), 1036 (C-O); δ_H (400 MHz, $CDCl_3$) 5.16-4.97 (1 H, m, C*H*OAc), 4.33-4.24 (1 H, m, *Ha*CHbOAc), 4.19-4.13 (4 H, q, *J*= 7.13, OC*H*$_2$CH$_3$ × 2), 4.06-3.99 (1 H, m, HaC*Hb*OAc), 3.96-3.83 (4 H, m, OC*H*$_2$C*H*$_2$O), 3.64-3.56 (1 H, m, C*H*(CO$_2$Et)$_2$), 2.11-1.57 (14 H, m, C*H*$_3$CO$_2$ × 2, C*H*$_2$C=O, C*H*$_2$CH$_2$C=O, C*H*CHC=O, CHC*H*C=O, C*H*$_2$CH(CO$_2$Et)$_2$), 1.23 (6 H, t, *J*= 7.13, OCH$_2$CH$_3$ × 2); δ_C (100 MHz, $CDCl_3$) 170.7 (CH$_3$*C*O$_2$), 170.6, (CH$_3$*C*O$_2$), 170.4 (CH$_3$*C*O$_2$), 169.7 (*C*O2Et), 169.6 (*C*O2Et), 169.5 (*C*O2Et), 169.2 (*C*O2Et), 117.3 (*C*(C$_2$H$_4$O$_2$)), 117.2 (*C*(C$_2$H$_4$O$_2$)), 74.9 (*C*HOAc), 71.4 (*C*HOAc), 64.6 (O*C*H$_2$CH$_2$O), 64.4 (O*C*H$_2$CH$_2$O), 64.0 (OCH$_2$*C*H$_2$O), 63.9 (OCH$_2$*C*H$_2$O), 63.8 (*C*H$_2$Ac), 63.7 (*C*H$_2$Ac), 61.4 (O*C*H$_2$CH$_3$), 61.33 (O*C*H$_2$CH$_3$), 61.30 (O*C*H$_2$CH$_3$), 61.28 (O*C*H$_2$CH$_3$), 49.83 (*C*H(CO$_2$Et)$_2$), 49.79 (*C*H(CO$_2$Et)$_2$), 43.5 (*C*HCHC(C$_2$H$_4$O$_2$)), 43.0 (*C*HC(C$_2$H$_4$O$_2$)), 34.4 (*C*H$_2$C(C$_2$H$_4$O$_2$)), 34.3 (*C*H$_2$C(C$_2$H$_4$O$_2$), 30.1 (*C*H$_2$CH(CO$_2$Et)$_2$), 27.7 (*C*H$_2$CH(CO$_2$Et)$_2$), 24.3 (C*H*$_2$CH$_2$C(C$_2$H$_4$O$_2$)), 22.2 (C*H*$_2$CH$_2$C(C$_2$H$_4$O$_2$)), 21.1 (*C*H$_3$CO$_2$), 20.9 (*C*H$_3$CO$_2$), 20.8 (*C*H$_3$CO$_2$), 14.1(OCH$_2$*C*H$_3$); *m/z* (FAB$^+$) 444.1991 (M$^+$), $C_{21}H_{32}O_{10}$ requires 444.1995.

6.6.3 2-[7-(1,2-diacetoxy-ethyl)-vinyl-1,4-spiro[4.4]non-6-ylmethyl]-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (30)



A solution of 2-[7-(1,2-diacetoxy-ethyl)-vinyl-1,4-spiro[4,4]non-6-ylmethyl]-malonic acid diethyl ester (**29**) and carbonic acid methyl ester 4-triisopropylsilanyloxy-penta-2,4-dienyl ester (**19a**) (1.04 g, 3.3 mmol) in anhydrous dichloromethane (15 mL) was degassed by a stream of nitrogen for 30 minutes. Triphenylphosphine (263 mg, 1.0 mmol) and $Pd_2(dba)_3$ (114 mg, 0.125 mmol) were then added and the mixture heated under reflux under an atmosphere of nitrogen for eighteen hours. The reaction was allowed to reach room temperature and filtered through a pad of silica gel (50% ethyl acetate/light petroleum). The solution was concentrated to dryness and the residue purified by flash column chromatography (15% ethyl acetate/light petroleum) on deactivated silica gel (water 5% w/w) to give 2-[7-(1,2-diacetoxy-ethyl)-vinyl-1,4-spiro[4.4]non-6-ylmethyl]-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**30**) as a colourless oil (187 mg, 30%); ν_{max} (film)/cm^{-1} 2942-2865 (C-H), 1739-1729 (C=O), 1465 (C=C), 1368 (C=C), 1125 (Si-O), 1032 (C-O); δ_H (400 MHz, $CDCl_3$) 5.93-5.86 (2 H, m, C*H*=C*H*), 5.16-5.05 (1 H, m, C*H*OAc), 4.30-3.91 (8 H, O$CH_2$$CH_3$ × 2, CH_2OAc, CH_2=C(OTIPS)), 3.83-3.70 (4 H, m, O$CH_2$$CH_2$O), 2.81-2.63 (2 H, m, CH=CHCH_2), 2.34-2.25 (1 H, m, *Ha*CHbC(CO_2Et)$_2$), 2.08-1.99 (6 H, m, CH_3CO_2 × 2), 1.94-1.85 (1 H, m, C*H*C(OC_2H_4O), 1.84-1.56 (6 H, m, HaCH_bCCH(CO_2Et)$_2$, C$H_2$$CH_2$C($OC_2H_4O$), C$H_2$C($OC_2H_4O$), C*H*CHC($OC_2H_4O$), 1.20-1.13 (9 H, m, OCH_2CH_3 × 2, C*H*(CH_3)$_2$ × 3), 1.06-1.03 (18 H, d, *J*= 6.7, CH(CH_3)$_2$ × 3); δ_C (100 MHz, $CDCl_3$) 171.3 (RCO_2R^1), 170.94 (RCO_2R^1), 170.89 (RCO_2R^1), 170.8 (RCO_2R^1), 170.6 (RCO_2R^1), 170.55 (RCO_2R^1), 170.49 (RCO_2R^1), 170.4 (RCO_2R^1), 154.8 (CH_2=*C*(OTIPS)), 154.7 (CH_2=*C*(OTIPS)), 131.5 (*C*H=CHCH_2), 131.4 (*C*H=CHCH_2), 125.2 (CH=*C*HCH_2), 125.1 (CH=*C*HCH_2), 117.2 (*C*($C_2H_4O_2$)), 117.1 (*C*(OC_2H_4O)), 93.7 (*C*H_2=C(OTIPS)), 93.6 (*C*H_2=C(OTIPS)), 74.3 (C*H*OAc), 72.0 (C*H*OAc), 64.4 (O$CH_2$$CH_2$O), 64.1 (O*C*$H_2$$CH_2$O), 63.6 (O$CH_2$*C*$H_2$O), 63.5 (O$CH_2$*C*$H_2$O), 64.0 (*C*$H_2$OAc), 63.8 (*C*$H_2$OAc), 61.0 (O*C*$H_2$$CH_3$), 60.9 (O*C*$H_2$$CH_3$), 57.5 (*C*($OC_2H_4O$)), 57.0 (*C*($OC_2H_4O$)), 44.2 (*C*HC($OC_2H_4O$)), 43.4 (*C*HCHC($OC_2H_4O$)), 42.0 (*C*HCHC($OC_2H_4O$)), 35.9 (CH=CH*C*$H_2$), 35.0 (*C*$H_2$C($CO_2Et$)$_2$), 33.8 (*C*$H_2$C($CO_2Et$)$_2$), 22.8 (*C*$H_2$$CH_2$C($OC_2H_4O$)), 21.5 (*C*$H_2$$CH_2$C($OC_2H_4O$)), 21.0 (*C*$H_3CO_2$), 20.9 (*C*$H_3CO_2$), 20.7 (*C*$H_3CO_2$), 20.6 (*C*$H_3CO_2$), 17.9 (CH(*C*$H_3$)$_2$), 13.9 ($OCH_2$*C*$H_3$), 13.8 ($OCH_2$*C*$H_3$), 12.6 (*C*H($CH_3$)$_2$); *m/z* ($FAB^+$) 683.3821 ($M + H^+$), $C_{35}H_{59}O_{11}Si$ requires 683.3821.

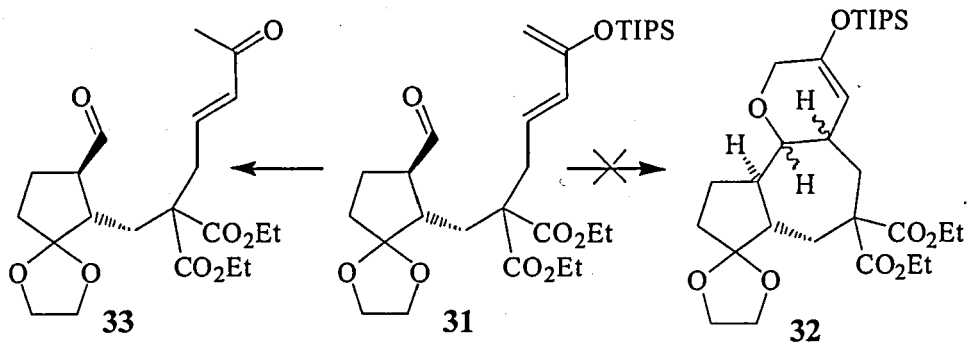
6.6.4: (±)-*trans*-2-(7-Formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (31)



Activated Amberlite® 400 Cl (1.0 g) was added to a solution of (±)-*trans*-2-[7-(1,2-diacetoxy-ethyl)-vinyl-1,4-spiro[4.4]non-6-ylmethyl]-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**30**) (187 mg, 0.28 mmol) in methanol (10 mL) and the mixture stirred at room temperature for eighteen hours. The resin was filtered off through a sintered glass funnel and the solution concentrated to dryness to give a pale yellow oil, which, without any further purification, was dissolved in 1:1= tetrahydrofuran/water (5 mL) and reacted with sodium periodate at room temperature. The solution was stirred for four hours, concentrated under vacuum and the aqueous residue extracted with dichloromethane (3 × 5 mL). The combined organic fractions were dried over anhydrous magnesium sulfate and concentrated to dryness to give a pale yellow oil that was purified by flash column chromatography (15% ethyl acetate/light petroleum) to give *trans*-2-(7-formyl-1,4-dioxa-spiro-[4.4]-non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**31**) as a colourless oil (45 mg, 28%); ν_{max} (film)/cm^{-1} 2942 (C-H), 2714 (*H*-*C*=O), 1734 (H*C*=*O*), 1729 (EtO*C*=*O*), 1590 (C=C), 1183 (Si-O), 1028 (C-O); δ_H (400 MHz, $CDCl_3$) 9.56 (1 H, d, *J*= 2.1, C*H*O), 5.95-5.82 (2 H, m, C*H*=C*H*), 4.22-4.04 (6 H, m, CH_2=C(OTIPS), OCH_2CH$_3$ × 2), 3.93-3.82 (4 H, m, OCH_2CH_2O), 2.75 (1 H, dd, J_1= 14.3, J_2= 6.7, CH=CH-*Ha*CHb), 2.67 (1 H, dd, J_1= 14.3, J_2= 7.5, CH=CH-HaC*Hb*), 2.55-2.49 (1 H, m, C*H*CHC(OC$_2$H$_4$O)), 2.44-2.40 (1 H, m, C*H*C(C$_2$H$_4$O$_2$)), 2.24 (1 H, dd, J_1= 15.0, J_2= 3.3, *Ha*CHbCH$_2$C(C$_2$H$_4$O$_2$)), 1.90-1.75 (4 H, m, HaC*Hb*CH$_2$C(OC$_2$H$_4$O), *Ha*CHbC(OC$_2$H$_4$O), CH_2C(CO$_2$Et)$_2$), 1.66-1.59 (1 H, m, HaC*Hb*C(OC$_2$H$_4$O)),1.24-1.15 (9 H, m, OCH$_2$CH_3 × 2, C*H*(CH$_3$)$_2$ × 3), 1.08-1.07 (18 H, d, *J*=6.9, CH(CH_3)$_2$ × 3); δ_C (100 MHz, $CDCl_3$) 202.5 (*C*HO), 171.3 (CO_2Et), 171.2

(CO_2Et), 154.8 (CH_2=*C*(OTIPS), 132.0 (*C*H=CHCH_2), 124.5 (CH=*C*HCH_2), 117.7 *C*(OC_2H_4O), 94.0 (*C*H_2=C(OTIPS), 61.3 (O*C*H_2CH_3), 61.2 (O*C*H_2CH_3), 64.8 (O*C*$H_2C$$H_2O$), 64.4 (O$CH_2$*C*$H_2O$), 61.3 (O*C*$H_2CH_3$), 61.2 (O*C*$H_2CH_3$), 57.0 (*C*($CO_2Et$)$_2$), 54.8 (*C*HCHC($OC_2H_4O$)), 40.9 (CHC($OC_2H_4O$)), 36.3 (CH=CH*C*$H_2$), 33.2 (*C*$H_2$C($OC_2H_4O$)), 32.1 (*C*$H_2CH_2$C($OC_2H_4O$)), 21.5 (*C*$H_2$C($CO_2Et$)$_2$), 18.0 (CH(*C*$H_3$)$_2$), 13.98 (O$CH_2$*C*$H_3$), 13.91 (O$CH_2$*C*$H_3$), 12.7 (*C*H($CH_3$)$_2$); *m/z* ($FAB^+$) 567.3348 ($M + H^+$), $C_{30}H_{51}O_8Si$ requires 567.3348.

6.7 Attempt at the IMHDA reaction of (±)-*trans*-2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (31)



6.7.1 Attempt at the IMHDA reaction of (±)-*trans*-2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (31): microwaves irradiation

A solution of (±)-*trans*-2-(7-formyl-1,4-dioxa-spiro-[4.4]-non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**31**) (300 mg, 0.53 mmol) in anhydrous toluene in a sealed tube was submitted to microwaves irradiation at 120 °C and full power,. The reaction time ranged from five to twenty minutes with increments of 5 minutes. At the end of the experiment the solution was concentrated to dryness to give a pale yellow crude material, which, according to ^{1}H NMR analysis, was a mixture of the starting material **31** and of the desilylated starting material 2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-oxo-pent-2-enyl)-malonic acid diethyl ester (**33**): ν_{max} (film)/cm^{-1} 2979 (C-H), 1731 (C=O), 1673 (C=C), 1191 (C-O);

δ_H (400 MHz, $CDCl_3$) 9.55 (1 H, d, *J*= 2.0, C*H*O), 6.64 (1 H, dt, J_1= 16.0, J_2= 7.6, CH=C*H*CH_2), 6.08 (1 H, dt, J_1= 16.0, J_2= 1.2, C*H*=$CHCH_2$), 4.21-4.07 (4 H, m, OCH_2CH_3 × 2), 3.95-3.85 (4 H, m, OCH_2CH_2O), 2.87-2.75 (2 H, m, $CH=CHCH_2$), 2.66-2.62 (1 H, m, C*H*CHO), 2.48-2.42 (1 H, m, C*H*CHCHO), 2.30-2.20 (4 H, m, CH_3CO, *Ha*CHb$CH_2C(OCH_2CH_2O)$), 1.97-1.75 (4 H, m, $CH=CHCH_2C(CO_2Et)_2CH_2$, $CH_2C(OCH_2CH_2O)$), 1.65-1.59 (1 H, m, Ha*Hb*$CH_2C(OCH_2CH_2O)$), 1.23 (3 H, t, *J*= 7.2, OCH_2CH_3) 1.22 (3 H, t, *J*= 7.2, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 204.3 (*C*H=O), 201.7 (CH_3C=O), 170.3 (CO_2Et), 142.0 (CH=*C*HCH_2), 134.2 (*C*H=$CHCH_2$), 117.2 ($C(OCH_2CH_2O)$), 64.4 (OCH_2CH_3), 61.4 (OCH_2CH_2O), 56.4 ($C(CO_2Et)_2$), 54.6 (*C*HCH=O), 40.1 (*C*HCHCH=O), 35.9 ($CH=CHCH_2$), 33.0 ($CH_2C(OCH_2CH_2O)$), 31.7 ($CH_2CH_2C(OCH_2CH_2O)$), 25.5 (CH_3C=O), 21.6 ($CH_2C(CO_2Et)$), 13.8 (OCH_2CH_3); *m/z* (CI) low resolution mass spectrum: 428 (M + NH_4^+), $C_{21}H_{34}NO_8$ requires 428.2284.

6.7.2 Attempt at the IMHDA reaction of (±)-*trans*-2-(7-Formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (31): Lewis acid method

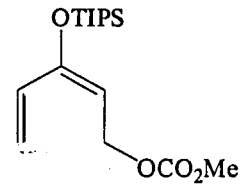
A solution of 2-(7-formyl-1,4-dioxa-spiro-[4.4]-non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**31**) (300 mg, 0.53 mmol), in anhydrous tetrahydrofuran (5 mL), was reacted with $Yb(OTf)_3$ (0.820 g, 1.32 mmol) at –78 °C for 4 hours. The mixture was washed with saturated aqueous sodium hydrogen carbonate (3 × 5 mL) and brine (3 × 5 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a pale yellow oil, which, according to ^{1}H NMR analysis, was desilylated starting material **33.**

6.7.3 Attempt at the IMHDA reaction of (±)-*trans*-2-(7-Formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (31): ultra high-pressure method

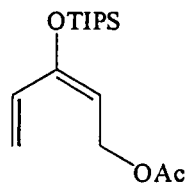
A solution of 2-(7-formyl-1,4-dioxa-spiro-[4.4]-non-6-ylmethyl)-2-(4-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (**31**) (300 mg, 0.53 mmol), in anhydrous dichloromethane (5 mL) was submitted to ultra high-pressure

conditions (19 Kbar) for 48 hours. The solution was concentrated to dryness to afford a pale yellow oil, which, accordingly to ^{1}H NMR analysis, was a mixture of un-reacted starting material **31** and desilylated starting material **33**.

6.8 Carbonic acid methyl ester 3-triisopropylsilanyloxy-penta-2,4-dienyl ester (41) and acetic acid 3-triisopropylsilanyloxy-penta-2,4-dienyl ester (42)

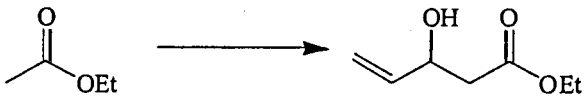


41



42

6.8.1 3-Hydroxy-pent-4-enoic acid ethyl ester (36)

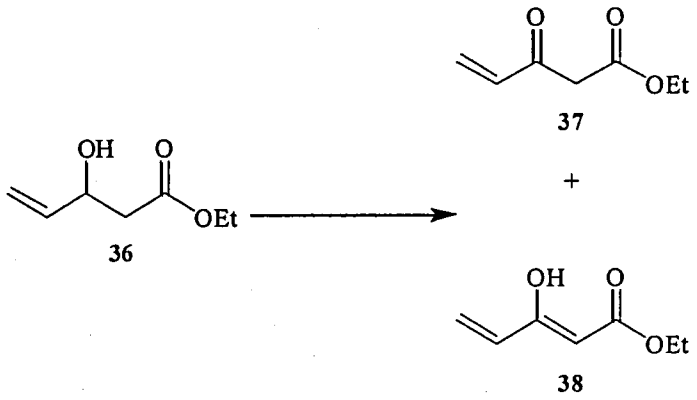


36

n-Butyllithium (2.5M in hexanes, 22 mL, 55 mmol) was added dropwise to a stirring solution of diisopropylamine (7.7 mL, 55 mmol) in anhydrous tetrahydrofuran (200 mL) at –78 °C under an atmosphere of nitrogen over twenty minutes. The mixture was stirred for twenty minutes, treated with ethyl acetate (5 mL, 50 mmol) (dropwise addition over 5 minutes) and stirred for a further forty-five minutes. A solution of acrolein (3.3 mL, 49.25 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise in twenty minutes. The solution was stirred for thirty minutes, allowed to reach room temperature, quenched with saturated aqueous ammonium chloride (20 mL), and stirred at room temperature for a further 30 minutes. The two phases were separated and the aqueous washed with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness to give a pale brown oil (8.1 g) that was purified by flash column chromatography (20-30% ethyl acetate/light petroleum) to afford 3-hydroxy-pent-4-enoic acid ethyl ester (**36**) as a pale yellow oil (6.6 g, 93%); ν_{max} (film)/cm^{-1} 3447 (O-

H), 2984-2907 (C-H), 1732 (C=O), 1647 (C=C), 1275 (C-O); δ_H (400 MHz, $CDCl_3$) 5.86 (1 H, ddd, J_1= 17.2, J_2= 10.5, J_3= 5.5, CH_2=C*H*), 5.29 (1 H, ddd, J_1= 17.2, J_2= 1.5, J_3= 1.3, *Ha*CHb=CH), 5.13 (1 H, ddd, J_1= 10.5, J_2= 1.5, J_3= 1.3, HaC*Hb*=CH), 4.52 (1 H, ddddd, J_1= 8.2, J_2= 5.5, J_3= 4.2, J_4= 1.5, J_5= 1.5, CH_2=CHC*H*OH), 4.15, (2 H, q, J= 7.1, OC*H*$_2$CH$_3$), 3.06-2.92 (1 H, broad, O-*H*), 2.56 (1 H, dd, J_1= 16.1, J_2= 4.2, *Ha*CHbCO$_2$Et), 2.49 (1 H, dd, J_1= 16.1, J_2= 8.2, *Ha*CHbCO$_2$Et), 1.25 (3 H, t, J= 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 172.2 (*C*O$_2$Et), 138.8 (CH_2=*C*H), 115.3 (*C*H$_2$=CH), 68.9 (*C*HOH), 60.7 (O*C*H$_2$CH$_3$), 41.1 (*C*H$_2$CO$_2$Et), 14.1 (OCH$_2$*C*H$_3$); *m/z* (EI^+) 144.0788 (M^+), $C_7H_{12}O_3$ requires 144.0787.

6.8.2 3-Oxo-pent-4-enoic acid ethyl ester (37): DMP method



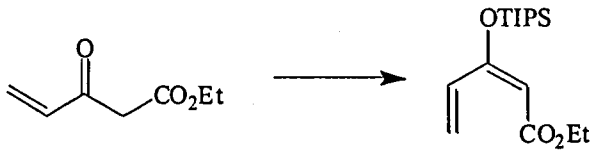
Dess-Martin periodinane (DMP, 12 g, 28.36 mmol) was added to a stirring solution of 3-hydroxy-pent-4-enoic acid ethyl ester (**36**), (2.0 g, 13.88 mmol) in dichloromethane (150 mL), and the mixture stirred at room temperature for two hours. The reaction was quenched with 150 mL of a mixture of saturated aqueous sodium hydrogen carbonate: saturated aqueous sodium thiosulfate (1/1) and stirred for two hours. The two layers were separated and the aqueous extracted with dichloromethane (3 × 60 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness to give a yellow oil that was purified by Kügelrohr distillation (45 °C, 0.1 mbar) to afford a mixture of 3-oxo-pent-4-enoic acid ethyl ester (**37**) and 3-hydroxy-penta-2,4-dienoic acid ethyl ester (**38**) as a colour less oil (0.850 g, 43%);. ν_{max} (film)/cm^{-1} 2984-2849 (C-H), 1740 (C=O), 1684 (C=C), 1033 (C-O); (**37**) δ_H (400 MHz, $CDCl_3$) 6.39 (1 H, dd, J_1= 17.6, J_2=10.5, CH_2=C*H*), 6.24 (1 H, dd, J_1= 17.6, J_2= 0.8, *Ha*CHb=CH), 5.94 (1 H, dd, J_1= 17.6, J_2= 0.8, HaC*Hb*=CH), 4.19 (2 H, q, J= 7.1,

OCH_2CH_3), 3.60 (2 H, s, $COCH_2CO_2Et$), 1.27 (3 H, t, J= 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 192.7 ($COCH_2CO_2Et$), 168.6 (CO_2Et), 135.7 (CH_2=CH), 130.2 (CH_2=CH), 61.4 (OCH_2CH_3), 46.4 ($COCH_2CO_2Et$), 14.2 (OCH_2CH_3); (**38**) δ_H (400 MHz, $CDCl_3$) 11.78 (1 H, s, O*H*), 6.07 (2 H, m, *Ha*CHb=CH, CH_2=C*H*), 5.52 (1 H, m, HaC*Hb*=CH), 5.04 (1 H, d, J= 0.4, COH=C*H*CO_2Et), 4.17 (2 H, q, J= 7.1, OCH_2CH_3), 1.27 (3 H, t, J= 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$), 172.7 (*C*OH=CHCO_2Et), 168.6 (CO_2Et), 131.2 (CH_2=*C*H), 122.5 (*C*H_2=CH), 91.8 (COH=*C*HCO_2Et), 60.2 (OCH_2CH_3), 14.0 (OCH_2CH_3); *m/z* (EI^+) 142.0628, $C_7H_{10}O_3$ requires 142.0630.

6.8.4 3-Oxo-pent-4-enoic acid ethyl ester (37): Jones' reagent method

Jones' reagent (3.36M, 22 mL) was added portion-wise over two hours to a stirring solution of 3-hydroxy-pent-4-enoic acid ethyl ester (**36**) (3.2 g, 0.022 mol) in acetone (220 mL) at 0 °C. Following the formation of a blue precipitate, anhydrous $MgSO_4$ (11 g) was added. When the addition of Jones' reagent was complete, the cold bath was removed and the reaction stirred for a further two hours. The solution was then filtered through a pad of silica gel (30% ethyl acetate/light petroleum), concentrated to dryness to give a green oil that was re-dissolved in ethyl acetate, re-filtered through a pad of silica gel (30% ethyl acetate/light petroleum) and concentrated to dryness to give 3-oxo-pent-4-enoic acid ethyl ester (**37**) as an orange oil (2.55 g, 81%).

6.8.4 3-Triisopropylsilanyloxy-penta-2,4-dienoic acid ethyl ester (39)

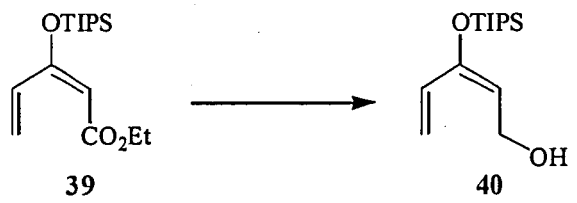


37 **39**

Triisopropylsilyl triflate (TIPSOTf, 2.3 mL, 8.4 mmol) was added dropwise to a stirring solution of 3-oxo-pent-4-enoic acid ethyl ester (**37**) (0.9 g, 6.3 mmol) in anhydrous dichloromethane (25 mL) at 0 °C under an atmosphere of nitrogen over five minutes. The reaction was stirred for two hours at 0 °C and at room temperature for eighteen hours. The solution was washed with saturated aqueous sodium hydrogen

carbonate (2 × 25 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give an orange oil that was purified by flash column chromatography (5% ethyl acetate/light petroleum) to afford 3-triisopropylsilanyloxy-penta-2,4-dienoic acid ethyl ester (**39**) as a colourless oil (1.5 g, 79%); ν_{max} (film)/cm^{-1} 2947-2893 (C-H), 1709 (C=O), 1636 (C=C), 1277 (C-Si), 1138 (Si-O), 1064 (C-O); δ_H (400 MHz, $CDCl_3$) 7.64 (1 H, dd, J_1= 17.0, J_2= 10.7, CH_2=C*H*), 5.99 (1 H, ddd, J_1= 17.0, J_2= 2.1, J_3= 0.4, *Ha*CHb=CH), 5.46 (1 H, ddd, J_1= 10.7, J_2=2.1, J_3=1.5, *Ha*CHb=CH), 5.17 (1 H, d, J= 1.5, C=C*H*CO_2Et), 4.13 (2 H, q, J= 7.1, O$CH_2$$CH_3$), 1,27 (3 H, sept, J= 7.1, C*H*$(CH_3)_2$ × 3), 1.26 (3 H, t, J= 7.1, OCH_2C*H*$_3$), 1.11 (18 H, d, J= 7.1, CH(C*H*$_3$)$_2$ × 3); δ_C (100 MHz, $CDCl_3$) 167.1 (*C*O_2Et), 163.5 (H*C*=CHCO_2Et), 130.6 (CH_2=*C*H), 121.3 (*C*H_2=CH), 100.1 (HC=*C*HCO_2Et), 59.6 (O$CH_2$$CH_3$), 17.9 (CH(*C*$H_3$)$_2$, 14.4 (O$CH_2$*C*$H_3$), 12.8 (*C*H$(CH_3)_2$); *m/z* (FAB$^+$) 298.1967 ($M^+$), $C_{16}H_{30}O_3Si$ requires 298.1964.

6.8.5 3-Triisopropylsilanyloxy-penta-2,4-dien-1-ol (40)

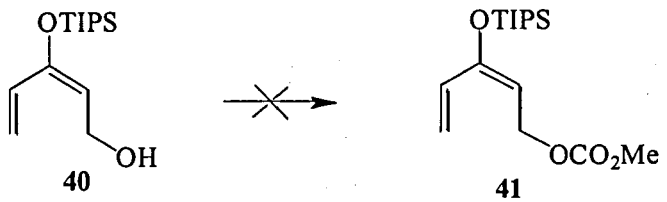


39 40

Diisobutylaluminum hydride (DIBAL, 1.5 M in toluene, 5.15 mL, 7.73 mmol) was added dropwise to a stirring solution of 3-triisopropylsilanyloxy-penta-2,4-dienoic acid ethyl ester (**39**) (0.920 g, 3.09 mmol), in anhydrous tetrahydrofuran (20 mL) at –78 °C under an atmosphere of nitrogen over twenty minutes. The solution was stirred at –78 °C for 2 hours and then for a further 3 hours while reaching room temperature. The reaction was quenched with saturated aqueous K, Na tartrate (25 mL) and stirred for 2 hours. The two layers were separated and the aqueous washed with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness to give a pale yellow oil that was purified by flash column chromatography (5-10% ethyl acetate/light petroleum) on deactivated silica gel (5% w/w in H_2O) to give 3-triisopropylsilanyloxy-penta-2,4-dien-1-ol (**40**) as a colourless oil (0.39 g, 56%); ν_{max} (film)/cm^{-1} 3327 (O-H), 3101 (C=*C*-*H*), 3030 (C=*C*-*H*), 2945

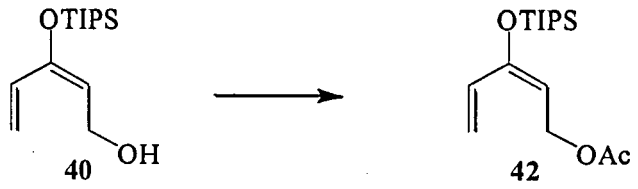
(C-H), 2891 (C-H), 2867 (C-H), 1643 (C=C), 1592 (C=C), 1260 (C-Si), 1055 (Si-O), 997 (C-O); δ_H (400 MHz, $CDCl_3$); 6.55 (1 H, ddd, J_1= 16.8, J_2= 10.6, J_3= 0.3, CH_2=C*H*), 5.68 (1 H, ddd, J_1= 16.8, J_2= 2.2, J_3= 0.6, *Ha*CHb=CH), 5.18 (1 H, ddd, J_1= 10.6, J_2= 2.2, J_3= 1.8, HaC*Hb*=CH), 5.06 (1 H, dddt, J_1= 8.0, J_2= 1.8, J_3= 0.6, J_4= 0.3, C(OTIPS)=C*H*), 4.17 (2 H, d, J= 8.0, CHCH_2OH), 1.21 (3 H, m, (C*H*(CH_3)$_2$) × 3), 1.08 (18H, d, J= 8.0 (CH(CH_3)$_2$) × 3), δ_C (100 MHz, $CDCl_3$) 151.7 (C=*C*(OTIPS)), 128.7 (CH_2=C*H*), 116.3 (CH_2=CH), 108.6 (C=*C*HCH$_2$OH), 57.8 (CH_2OH), 17.8 (CH(CH_3)$_2$), 12.9 (*C*H(CH_3)$_2$); *m/z* (FAB$^-$) 255.17845 (M–H), $C_{14}H_{27}O_2Si$ requires 255.17803.

6.8.6 Carbonic acid methyl ester 3-triisopropylsilanyloxy-penta-2,4-dienyl ester (41)



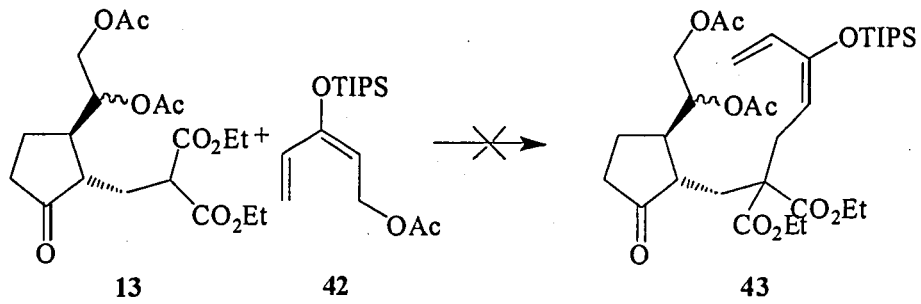
A solution of *n*-buthyllithium (2.5M in hexanes, 0.87 mL, 2.18 mmol) was added to a stirring solution of 3-triisopropylsilanyloxy-penta-2,4-dien-1-ol (**40**) (500 mg, 1.95 mmol) in dry tetrahydrofuran (20 mL) at –78 °C under an atmosphere of nitrogen, and the mixture stirred for fifteen minutes. Methyl chloroformate (0.18 mL, 2.34 mmol) was added the reaction stirred for a further forty-five minutes, and allowed to reach room temperature. The reaction was quenched at 0 °C with a few drops of water and concentrated to dryness to give a mixture of a pale yellow oil and a white solid. ^{1}H NMR of the crude material showed a complex mixture of compounds which we were not able to separate by flash column chromatography (5% ethyl acetate/light petroleum).

6.8.7 Acetic acid 3-triisopropylsilanyloxy-penta-2,4-dienyl ester (42)



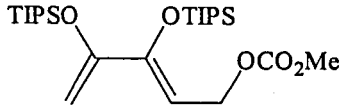
A solution of 3-triisopropylsilanyloxy-penta-2,4-dien-1-ol (**40**) (965 mg, 3.90 mmol), DMAP (50 mg, 0.41 mmol) in a 1/1 mixture of pyridine: acetic anhydride (10 mL) was stirred at room temperature for six hours. The solution was concentrated to dryness and purified by flash column chromatography (5% ethyl acetate/light petroleum) to give acetic acid 3-triisopropylsilanyloxy-penta-2,4-dienyl ester (**42**) as a colourless oil (1.1 g, 98%). ν_{max} (film)/cm^{-1} 2945 (C-H), 2892 (C-H), 2867 (C-H), 1741 (C=O), 1644 (C=C), 1592 (C=C), 1219 (C-Si), 1057 (C-O); δ_H (400 MHz, $CDCl_3$) 6.61 (1 H, dd, J_1= 16.3, J_2= 10.2, CH_2=C*H*), 5.51 (1 H, ddd, J_1= 16.7, J_2= 2.2, J_3= 0.7, *Ha*CHb=CH), 5.26 (1 H, ddd, J_1= 10.6, J_2= J_3= 2.0, HaC*Hb*=CH), 5.02 (1 H, dt, J_1= 8.5, J_2= 1.6, R^1R^2C=C*H*CH_2), 4.66 (2 H, d, J= 8.3, CH_2OAc), 2.03 (3 H, s, CH_3CO_2), 1.27-1.12 (3 H, m, (C*H*$(CH_3)_2$ × 3), 1.09 (18 H, d, J= 7.0, (CH(C*H*$_3$)$_2$ × 3); δ_C (100 MHz, $CDCl_3$) 171.0 (CH_3CO_2), 153.3 (TIPSO-*C*=CH), 135.2 (CH_2=*C*H), 117.2 (CH_2=CH), 103.8 (TIPSO-C=*C*H), 60.1 (*C*H_2OAc), 20.4 (*C*H_3CO_2), 18.3 (CH(*C*H_3)$_2$), 12.5 (*C*H(*C*H_3)$_2$; *m/z* (FAB$^+$) 298. 1964, $C_{16}H_{30}O_3Si$ (M^+) requires 298.1957.

6.8.8 (±)-2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(3-triisopropylsilanyloxy-penta-2,4-dienyl)-malonic acid diethyl ester (43)



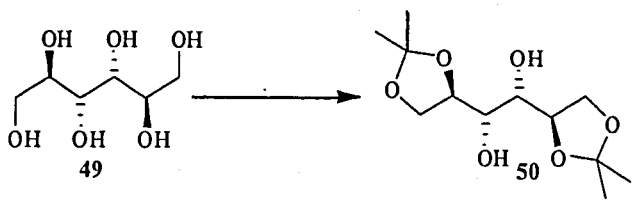
A solution of (**13**) (500 mg, 1.25 mmol) in anhydrous degassed tetrahydrofuran (5 mL) was added to NaH (60% dispersion in mineral oil, 55 mg, 1.37 mmol) contained in a round bottom flask at 0 °C under an atmosphere of nitrogen. After fifteen minutes a solution of (**42**) (410 mg, 1.37 mmol), $Pd_2(dba)_3$ (0.0001249 mol,)and PPh_3 (260 mg, 0.9992 mmol) or dppe (412 mg, 0.9992 mmol), in anhydrous degassed tetrahydrofuran (5 mL) was added and the mixture heated under reflux for eighteen hours. The reaction was allowed to reach room temperature and was filtered through a pad of silica gel (50% light petroleum/ethyl acetate). The solution was concentrated to dryness to give a pale yellow oil that according to ^1H NMR analysis was a mixture of unreacted starting materials **13** and **43**.

6.9 Carbonic acid 3,4-bis-triisopropylsilanyloxy-penta-2,4-dienyl ester methyl ester (56)[6]



56

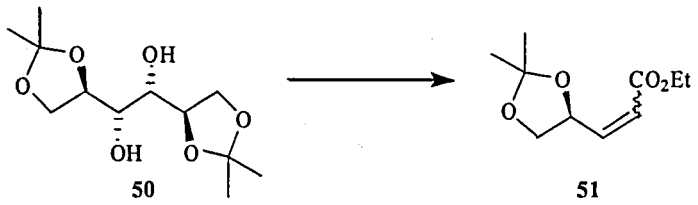
6.9.1 1,2-Bis-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethane-1,2-diol (50)[7]



A mixture of powdered D-mannitol (**49**) (5.5 g, 30 mmol), *p*-toluenesulfonic acid (45 mg, 0.26 mmol), 2,2-dimethoxypropane (7.8 g, 30 mmol) in anhydrous DMSO (10 mL) was stirred for sixteen hours at room temperature and under anhydrous conditions. The reaction was poured into 3% sodium hydrogen carbonate solution (30 mL), extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were washed with water (3 × 100 mL), dried over anhydrous magnesium sulfate,and concentrated to dryness. The residue was recrystallised from hot hexane (80 mL). The resulting crystals were filtered off, washed with a 1/3 mixture of diethyl ether: *n*-

hexane, and dried under high *vacuum* to give 1,2-bis-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethane-1,2-diol (**50**) as a white crystalline solid (2.2 g, 28%). Concentration of the mother liquors and re-crystallisation of the residue from diethyl ether/hexane (1:3) yielded an additional 0.40 g of (**50**) (9%); δ_H (400 MHz, CD_6SO) 4.72 (2 H, d, *J*= 7.8, O*H*), 4.03-3.98 (2 H, m, CH_2CH), 3.95 (2 H, dd, J_1= 8.2, J_2= 6.3, *Ha*CHbCH), 3.85 (2 H, dd, J_1= 8.2, J_2= 5.0, HaC*Hb*CH), 3.42 (2 H, t, *J*= 7.9, C*H*OH), 1.29 (6 H, s, CH_3 × 2), 1.25 (6H, s, CH_3 × 2); δ_C (100 MHz, CD_6SO) 108.1 ($(CH_3)_2C$), 74.8 (CH_2CH), 70.2 (*C*HOH), 66.6 (CH_2CH), 26.8 (CH_3), 25.4 (CH_3); *m/z* (FAB^+) 263.1499 ($M + H^+$), $C_{12}H_{22}O_6 + H^+$ requires 263.1495.

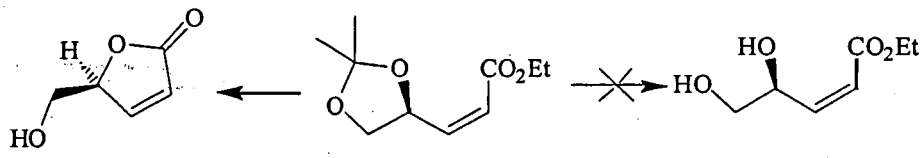
6.9.2 (*E-Z*)-3-[(*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-acrylic acid ethyl ester (51) [8]



$NaIO_4$ (2.36 g, 11.03 mmol) was added at 0 °C to a stirring solution of 1,2-bis-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethane-1,2-diol (**50**) (1.45 g, 5.53 mmol) in water (40 mL). The solution was stirred at 0 °C for 30 minutes and at room temperature for a further 1.5 hour. A solution of (triphenyl-λ^5-phosphanylidene)-acetic acid ethyl ester ($Ph_3P{=}CHCO_2Et$, 4.6 g, 13.20 mmol) in tetrahydrofuran (40 mL) was added and the mixture stirred for fifteen hours. The white precipitate formed during the addition of the yilid was filtered off and the liquid diluted with dichloromethane (100 mL). The two layers were separated and the aqueous extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated to dryness to give a white solid (5 g) That after flash column chromatography (20% light petroleum/ethyl acetate) afforded (*Z*)-3-[(*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-acrylic acid ethyl ester (**51a**) as a colourless oil (1.6 g, 72%), and (*E*)-3-[(*S*)-(2,2-dimethyl-[1,3]dioxolan-4-yl)]-acrylic acid ethyl ester (**51b**) (0.2 g, 9%). For the major isomer (**51a**): ν_{max} (film)/cm^{-1} 2985 (C-H), 2937 (C-H), 1722 (C=O), 1662 (C=C), 1062 (C-O); δ_H (400 MHz, $CDCl_3$) 6.33 (1 H, dd, J_1= 11.5, J_2= 6.7, C*H*=$CHCO_2Et$), 5.82 (1 H dd, J_1= 11.5, J_2= 1.7, CH=C*H*CO_2Et), 5.47 (1 H, dddd, J_1= 11.5, J_2= 8.4, J_3= 6.7, J_4= 1.7, C*H*CH=$CHCO_2Et$), 4.35 (1 H, dd, J_1= 8.4, J_2= 7.1,

*Ha*CHbCHCH=CHCO$_2$Et), 4.14 (2 H, q, J_1= 7.1, OC*H*$_2$CH$_3$), 3.59 (1 H, dd, J_1= 8.4, J_2= 6.7, HaC*Hb*CHCH=CHCO$_2$Et) 1.42 (3 H, s, C*H*$_3$CCH$_3$), 1.36 (3 H, s, CH$_3$CC*H*$_3$), 1.26 (3 H, t, J= 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz, CDCl$_3$) 149.2 (*C*H=CHCO$_2$Et), 120.7 (CH=*C*HCO$_2$Et), 109.6 (CH$_3$*C*CH$_3$), 73.5 (*C*HCH=CHCO$_2$Et), 69.3 (*C*H$_2$CHCH=CHCO$_2$Et), 60.4 (OCH$_2$CH$_3$), 26.5 (*C*H$_3$CCH$_3$), 25.3 (CH$_3$C*C*H$_3$), 14.1 (OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 200.1053 (M$^+$), $C_{10}H_{16}O_4$ requires 200.1049.

6.9.3 (*Z*-*S*)-4,5-dihydroxy-pent-2-enoic acid ethyl ester (52): TFA method[6]



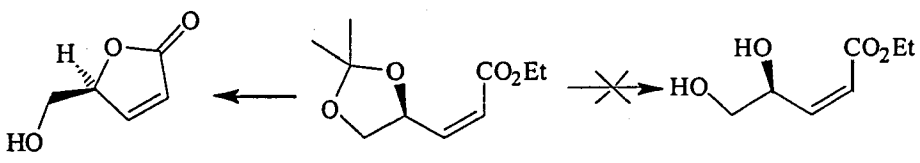
57 **51a** **52**

(*Z*)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester (**51a**) (280 mg, 1.4 mmol) was dissolved in cold aqueous trifluoro acetic acid (TFA) (0.1M 5 mL) and the mixture stirred at 0 °C for thirty minutes and at room temperature for one further hour. The solution was neutralised with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to dryness to give a colourless oil (110 mg) that according to ^{1}H NMR analysis was starting material (**51a**).

51a (280 mg, 1.4 mmol) was dissolved in aqueous trifluoroacetic acid (TFA, 10M, 5 mL) at 0 °C and the solution stirred for one hour. The solution was neutralised with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate, and concentrated to dryness to give a colourless oil that was purified by flash column chromatography (50% ethyl acetate/light petroleum) to afford (*S*)-5-hydroxymethyl-5H-furan-2-one (**57**) as a white solid (100 mg, 63%), which experimental data are consistent with those reported in the literature; ν_{max} (film)/cm^{-1} 3413 (O-H), 3107 (C=*C*-*H*), 2932 (C-H), 2878 (C-H), 1743 (C=O), 1651 (C=C), 1080 (C-O), 1054 (C-O); δ_H (400 MHz, CDCL$_3$) 7.55 (1 H, dd, J_1= 5.8, J_2= 1.5, C*H*=CHCO$_2$); 6.19 (1 H, dd, J_1= 5.8, J_2= 2.0, CH=C*H*CO$_2$), 5.18 (1 H, m, C*H*CH=CHCO$_2$), 3.99 (1 H, dd, J_1= 12.4, J_2= 3.8, *Ha*CHbOH), 3.79 (1 H, dd, J_1= 12.4, J_2= 4.9, HaC*Hb*OH); δ_C (100 MHz, CDCl$_3$)

173.6 (*C*O2), 154.2 (*C*H=CHCO$_2$), 122.6 (CH=*C*HCO$_2$), 84.3 (*C*HCH=CHCO$_2$), 61.9 (*C*H$_2$OH); *m/z* (EI$^+$) 114.0315 (M$^+$), $C_5H_6O_3$ requires 114.0317.

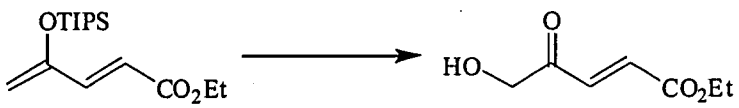
6.9.4 (*Z*)-4,5-Dihydroxy-pent-2-enoic acid ethyl ester (52): HCl method



57 **51a** **52**

A solution of HCl (2M, 1.3 mL) was added to a solution of (*Z*)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester (**35**) (360 mg, 1.8 mmol), in wet acetonitrile (12 mL containing 0.720 m of water) at 0 °C The mixture was stirred at room temperature for four hours, neutralised with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (3 × 15 mL). The combined extracts were dried over anhydrous magnesium sulfate and concentrated to dryness to give a pale yellow oil (150 mg) that was purified by flash column chromatography (50% ethyl acetate/lihght petroleum) to give (*S*)-5-hydroxymethyl-5H-furan-2-one (**57**) as a white solid (120 mg, 59%)

6.9.5 (*E*)- 5-hydroxy-4-oxo-pent-2-enoic acid ethyl ester (62)



16 **62**

A solution of 3,3-dimethyl-dioxirane in acetone (DMDO, 0.07M, 29.5 mL, 2.07 mmol) was added dropwise over twenty minutes to a stirring solution of 4-triisopropylsilanyloxy-penta-2,4-dienoic acid ethyl ester (**16**) (560 mg, 1.88 mmol) in tetrahydrofuran (20 mL) at 0 °C. The solution was stirred for two hours at room temperature and concentrated to dryness under vacuum. The residue was purified by flash column chromatography (30% ethyl acetate/light petroleum) afforded (*E*)-5-hydroxy-4-oxo-pent-2-enoic acid ethyl ester (**62**) as a pale yellow oil (149 mg, 50%), and starting material **16** (250 mg, 44%).

*(E)*5-Hydroxy-4-oxo-pent-2-enoic acid ethyl ester (**62**): ν_{max} (film)/cm^{-1} 3468 (O-H), 2939-2867 (C-H), 1708 (C=O), 1642 (C=C), 1027 (C-O); δ_H (400 MHz, $CDCl_3$) 7.11 (1 H, d, *J*= 16.1, CH=C*H*CO_2Et), 6.81 (1 H, d, *J*= 16.1, C*H*=CHCO_2Et), 4.53 (2 H, s, C*H*$_2$OH), 4.30 (2 H, q, *J*= 7.1, OC*H*$_2$CH$_3$), 1.34 (3 H, t, *J*= 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 198.1 (CH_2OHCO), 164.9 (CO_2Et), 134.7 (*C*HCO_2Et), 132.5 (*C*H=CHCO_2Et), 67.9 (*C*H$_2$OH), 61.8 (O*C*H$_2$CH$_3$), 14.1 (OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 159.0652 (M + H$^+$), $C_7H_{10}O_4$ + H$^+$ requires 159.0657.

6.9.6 References

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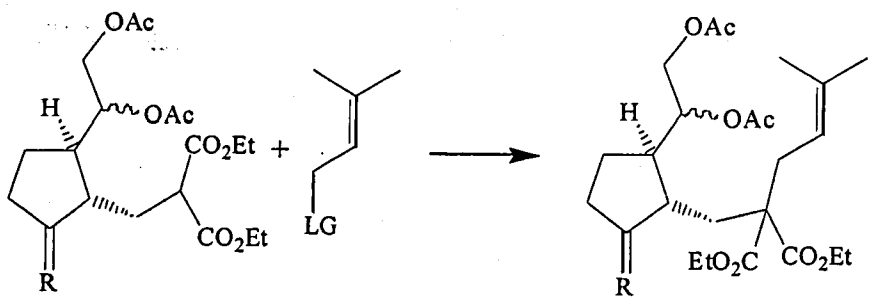
7 Synthesis of the Guaian-6,12-olide Skeleton: Carbonyl ene reaction approach: Experimentals

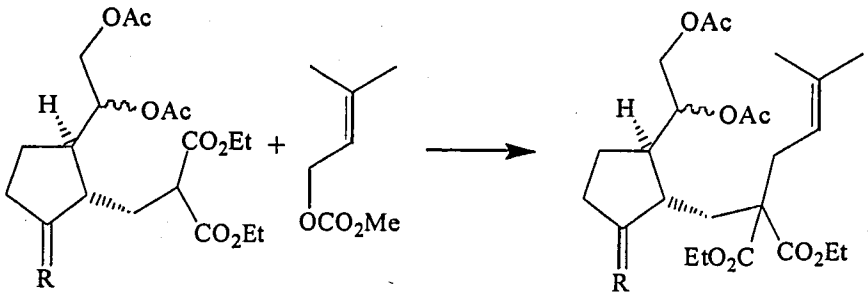
7.1 (±)-trans-2-[2-(1,2-Diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (68) and (±)-trans-2-[7-(1,2-diacetoxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (65)



R= $O(CH_2)_2O$, **29**
R= O, **13**

R= $O(CH_2)_2O$, **65**
R= O, **68**

7.1.1 Palladium catalysed allylation of malonates 29 and 13 under neutral conditions



R= $O(CH_2)_2O$, **29**
R= O, **13**

63

R= $O(CH_2)_2O$, **65**
R= O, **68**

A solution of **13** (190 mg, 0.5 mmol) and carbonate **63** (90 mg, 0.6 mmol) in dry tetrahydrofuran (5 mL) was degassed with nitrogen for 20 minutes. $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and PPh_3 (52 mg, 2.0 mmol) were added under nitrogen, and the mixture heated under reflux under an atmosphere of nitrogen for 18 hours. The reaction was

cooled to room temperature, and TLC analysis showed that no reaction had occurred. A further 30 mg of $Pd_2(dba)_3$ and 100 mg of carbonate **63** were added to the mixture and the reaction heated under reflux for a further 16 hours. TLC analysis showed again only the presence of the starting materials. After being cooled to room temperature, the mixture was filtered through a pad of silica gel (50% ethyl acetate/light petroleum) and concentrated to dryness to give a yellow crude oil, which according to the ^1H NMR analysis was mainly the malonate starting material **13**.

Similar reactions of **29** with **63** were also unsuccessful.

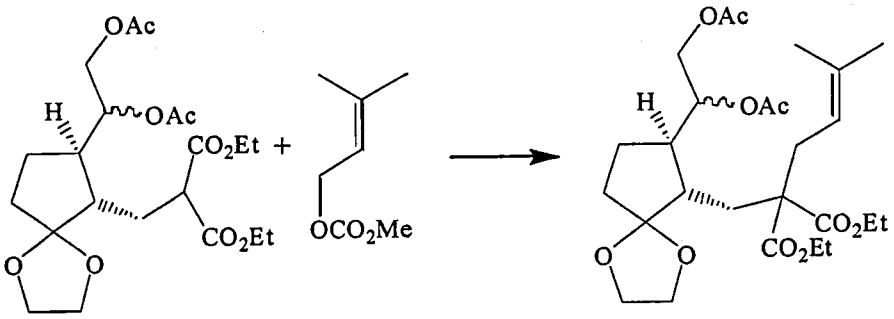
The use of different solvents (acetonitrile and dichloromethane) instead of tetrahydrofuran did not change the outcome of the palladium catalysed allylation of malonates **13** and **29**.

7.1.2 Methyl-3-methyl-but-2-enyl carbonate (63)

62 **63**

A solution of *n*-butyllithium (2.5M in hexanes, 4.8 mL, 0.014 mol) was added to a stirring solution of 3-methyl-but-2-en-1-ol (**62**) (1.0 g, 0.012 mol) in dry tetrahydrofuran (20 mL) at –78 °C under an atmosphere of nitrogen. The mixture was stirred for fifteen minutes, methylchloroformate (1.14 ml , 0.015 mol) added, and the reaction stirred for a further forty-five minutes, allowed to reach room temperature, quenched with water (0.5 mL), and concentrated to dryness, to give a crude material that was purified by flash column chromatography (5% ethyl acetate light/petroleum) to give methyl-3-methyl-but-2-enyl carbonate (**63**), as a colourless oil (1.04 g, 60%); ν_{max} (film)/cm^{-1} 2957 (C-H), 1746 (C=O), 1443 (C=C), 1264 (C-O); δ_H (400 MHz, $CDCl_3$) 5.30 (1 H, m, C=C*H*), 4.55 (2 H, d, *J*= 7.2, C=CHCH_2), 3.70 (3 H, s, OCH_3), 1.79 (3 H, s, CH_3C=CH), 1.65 (3 H, s, CH_3C=CH); δ_C (100 MHz, $CDCl_3$) 155.9 (O*C*O_2), 140.0 ((CH_3)$_2$*C*=CH), 118.0 (C=*C*H), 64.6 (*C*H_2OCO$_2$Me), 54.6 (O*C*H_3), 25.7 (*C*H_3C=CH), 18.0 (*C*H_3C=CH); *m/z* (EI$^+$) 144.0788 (M$^+$); $C_7H_{12}O_3$ requires 144.0787.

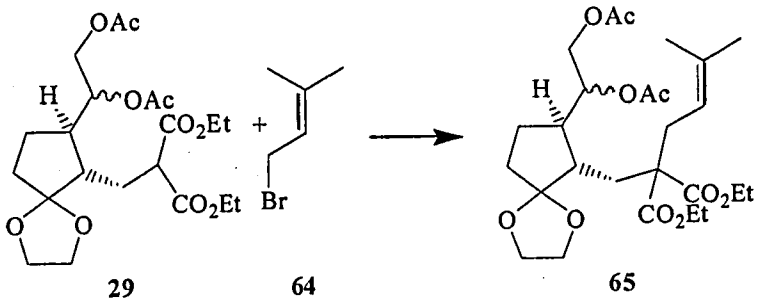
7.1.3 (±)-*trans*-2-[7-(1,2-Diacetoxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (65): palladium catalysed allylation of malonate 29 under basic conditions



29 63 65

A solution of malonate **29** (200 mg, 0.5 mmol) in dry degassed tetrahydrofuran (3 mL) was added at 0 °C to a suspension of sodium hydride(NaH, 60% dispersion in mineral oil, 30 mg, 0.75 mmol) in dry degassed tetrahydrofuran (2 mL) under an atmosphere of nitrogen. After the effervescence had subsided, the resulting solution was added to a stirring solution of $Pd_2(dba)_3$ (50 mg, 0.055 mmol) and PPh_3 (120 mg, 4.7 mmol) in dry degassed tetrahydrofuran (3 mL). The mixture was heated under reflux for twelve hours under an atmosphere of nitrogen, filtered through a pad of silica gel (washed with ethyl acetate) and concentrated to dryness to give an orange crude material, which, according to ^1H NMR analysis, was mainly composed by malonate **29**.

7.1.4 (±)-*trans*-2-[7-(1,2-Diacetoxyethyl)-1,4-dioxaspiro[4.4]non-6-ylmethyl]-2-(3-methylbut-2-enyl)-malonic acid diethyl ester (65)



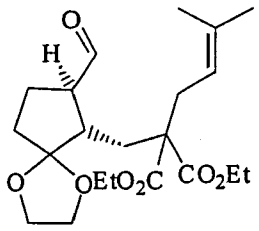
29 64 65

A solution of (±)-*trans*-2-[7-(1,2-diacetoxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-malonic acid diethyl ester (**29**) (1.1 g, 0.0025 mol) in dry tetrahydrofuran (10

mL) was added by cannula to a solution of lithium diisopropylamide (LDA) (prepared by adding a solution of *n*-butyllitium (2.5M in hexanes, 1 mL, 0.0025 mol) to a stirring solution of diisopropylamine (0.35 ml, mol), in dry tetrahydrofuran (2.5 mL), at –78 °C under an atmosphere of nitrogen and stirring the mixture for twenty minutes). The mixture was stirred for thirty minutes at –78 °C and transferred by cannula (positive pressure of nitrogen) into a solution of prenyl bromide (**64**) (0.5 ml, 4.0 mmol) in dry tetrahydrofuran (10 mL), at -78 °C. The reaction was allowed to reach room temperature, stirred for eighteen hours, quenched with water (2 mL), diluted with dichloromethane (60 mL), washed with saturated aqueous ammonium chloride (3 × 30 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a yellow material (1.4 g), which, after purification by flash column chromatography (10-20% ethyl acetate/light petroleum), afforded the title compound **65** as a mixture of diastereoisomers as a yellow oil (1.0 g, 79%); ν_{max} (film)/cm^{-1} 2977 (C-H), 1742 (C=O), 1732 (C=O), 1224 (C-O); δ_H (400 MHz, $CDCl_3$) 5.16-5.07 (2 H, m, C*H*OAc × 2), 5.03-4.93 (2 H, m, $(CH_3)_2C$=C*H*), 4.29 (1 H, dd, J_1= 12.3 Hz, J_2= 2.5 Hz, *Ha*CHbOAc), 4.21-4,02 (10 H, m, O*C*H_2CH$_3$ × 4, CH_2OAc), 3.98 (1 H, dd, J_1= 12.3, J_2= 5.9, HaC*Hb*OAc); 3.87-3.71 (8 H, m, O*C*H_2*C*H_2O × 2), 2.70 (1 H, dd, J_1= 16.1, J_2= 8.3, $(CH_3)_2$C=CH-*Ha*CHb), 2.62 (2 H, d, *J*= 7.2, C=CHCH_2), 2.57 (1 H, dd, J_1= 15.7, J_2= 8.8, $(CH_3)_2$C=CH-HaC*Hb*), 2.35-2.26 (2 H, m, *Ha*CHbC$(CO_2Et)_2$ × 2), 2.10 (3 H, s, C*H*$_3CO_2$), 2.04 (3 H, s, C*H*$_3CO_2$), 2.03 (3 H, s, C*H*$_3CO_2$), 2.02 (3 H, s, C*H*$_3CO_2$), 2.06-1.99 (1 H, m, (OCH_2CH_2O)CC*H*), 1.97-1.86 (4 H, m, (OCH_2CH_2O)CC*H*, (OCH_2CH_2O)CCHC*H*, *Ha*CHbC$(CO_2Et)_2$ × 2), 1.82-1.78 (2 H, m, *Ha*CHbCH_2C(OCH_2CH_2O), *Ha*CHbC(OCH_2CH_2O)), 1.72-1.64 (12 H, m, (OCH_2CH_2O)CCHC*H*, HaC*Hb*C(OCH_2CH_2O), (OCH_2CH_2O)CCH_2, (OCH_2CH_2O)CCH_2CH_2, (C*H*$_3$)$_2$=CH), 1.59 (3 H, s, (C*H*$_3$)(CH$_3$)=CH), 1.58 (3 H, s, (CH$_3$)(C*H*$_3$)=CH), 1.41-1.34 (1 H, m, (OCH_2CH_2O)CCH_2HaC*Hb*), 1.23-1.18 (12 H, m, OCH_2C*H*$_3$ × 4); δ_C (100 MHz, $CDCl_3$) 171.8 (*C*O_2R), 171.5 (*C*O_2R), 171.46 (*C*O_2R), 171.45 (*C*O_2R), 170.74 (*C*O_2R), 170.66 (*C*O_2R), 170.55 (*C*O_2R), 170.51 (*C*O_2R), 134.84 ($(CH_3)_2$*C*=CH), 134.81 ($(CH_3)_2$*C*=CH), 117.99 (C=*C*H), 117.96 (C=*C*H), 117.2 ((OCH_2CH_2O)*C*), 117.1 ((OCH_2CH_2O)*C*), 74.3 (*C*HOAc), 72.0 (*C*HOAc), 64.4 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 64.0 (OCH_2CH_2O), 63.8 (*C*H_2OAc), 63.7 (*C*H_2OAc), 63.6 (OCH_2CH_2O), 61.1 (OCH_2CH_3), 61.0 (OCH_2CH_3), 60.87 (OCH_2CH_3), 60.85 (OCH_2CH_3), 57.2 (*C*$(CO_2Et)_2$), 56.8 (*C*$(CO_2Et)_2$), 44.2 (OCH_2CH_2O)CCH, 43.7 ((OCH_2CH_2O)CCH), 42.10 ((OCH_2CH_2O)CCHCH), 42.06 ((OCH_2CH_2O)CCHCH),

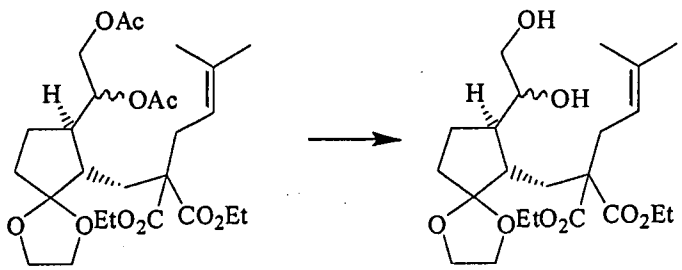
34.0 ((OCH_2CH_2O)CCH_2), 33.3 ((OCH_2CH_2O)CCH_2), 33.0 ($CH_2C(CO_2Et)_2$), 32.2 ($CH_2C(CO_2Et)_2$), 31.3 (C=$CHCH_2$), 30.8 (C=$CHCH_2$), 25.96 (CH_3)(CH_3)C=H), 25.92 (CH_3)(CH_3)C=H), 23.0 ((OCH_2CH_2O)CCH_2CH_2), 21.9 ((OCH_2CH_2O)CH_2CH_2), 21.1 (CH_3CO_2), 21.0 (CH_3CO_2), 20.78 (CH_3CO_2), 20.73 (CH_3CO_2), 17.92 (CH_3)(CH_3)C=H), 17.88 (CH_3)(CH_3)C=H), 13.98 (OCH_2CH_3), 13.96 (OCH_2CH_3), 13.95 (OCH_2CH_3), 13.91 (OCH_2CH_3); *m/z* (EI^+) 512.2628 (M^+); $C_{26}H_{40}O_{10}$ requires 512.2621.

7.2 (±)-*trans*-2-(7-Formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (67)



67

7.2.1 (±)-*trans*-2-[7-(1,2-Dihydroxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (66)

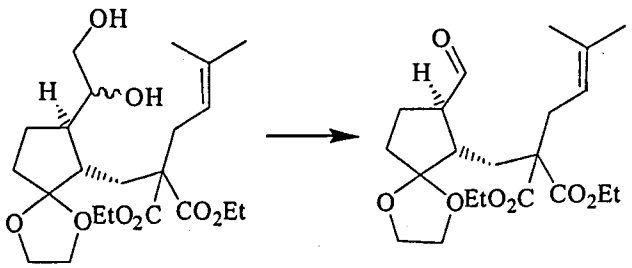


65 66

A mixture of activated Amberlite® 400 Cl (6.5 g) and (±)-2-[7-(1,2-diacetoxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**65**) (0.86 g, 1.7 mmol) in methanol (40 mL) was stirred at room temperature for nineteen hours. The resin was filtered off through a sintered glass funnel and washed with methanol (150 mL). The organic solvent was concentrated to dryness to give a pale yellow oil material (0.74 g), which was purified by flash column chromatography (50% ethyl acetate/light petroleum) to afford the title compound (±)-*trans*-2-[7-(1,2-Dihydroxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-2-(3-methyl-but-2-enyl)-

malonic acid diethyl ester (**66**) as mixture of diastereoisomers as a pale yellow oil; (0.719 g, 81%). ν_{max} (film)/cm^{-1} 3465 (O-H), 2975 (C-H), 2935 (C-H), 1732 (C=O), 1283 (C=O); δ_H (400 MHz, $CDCl_3$) 4.93-4.88 (2 H, m, C=C*H*), 4.21-3.97 (8 H, m, OCH_2CH_3 × 4), 3.92-3.86 (1 H, m, C*H*-OH), 3.84-3.73 (8 H, m, OCH_2CH_2O × 2), 3.59 (1 H, dd, J_1= 10.9, J_2= 2.9, *Ha*CHb-OH), 3.39 (1 H, dd, J_1= 11.1, J_2= 3.6, HaC*Hb*-OH), 3.34 (1 H, dd, J_1= 11.0, J_2= 6.9, HaC*Hb*-OH), 2.66-2.46 (4 H, m, C=CHCH_2 × 2), 2.11-1.93 (5 H, m, (OCH_2CH_2O)C*H* × 2, CH_2C(CO_2Et)$_2$, *Ha*CHbC(CO_2Et)$_2$), 1.77 (1 H, dd, J_1= 15.1, J_2= 3.2, HaC*Hb*C(CO_2Et)$_2$), 1.70-1.58 (14 H, m, (OCH_2CH_2O)CCHC*H* × 2, (OCH_2CH_2O)CCH_2 × 2, *Ha*CHbCH$_2$C(OCH_2CH_2O) × 2, (C*H*$_3$)(CH_3)C=CH × 2), 1.55 (6 H, s, (CH_3)(C*H*$_3$)C=CH × 2), 1.49-1.38 (1 H, m, HaC*Hb*CH$_2$C(OCH_2CH_2O)), 1.21-1.15 (13 H, m, OCH_2CH_3 × 4, HaC*Hb*CH$_2$C(OCH_2CH_2O)); δ_C (100 MHz, $CDCl_3$) 172.8 (*C*O_2R), 172.5 (*C*O_2R), 172.2 (*C*O_2R), 172.0 (*C*O_2R), 135.3 ((CH_3)$_2$*C*=CH), 135.2 ((CH_3)$_2$*C*=CH), 117.7 (C=*C*H), 117.6 (C=*C*H), 117.4 ((OCH_2CH_2O)*C*), 117.0 ((OCH_2CH_2O)*C*), 76.1 (*C*H-OH), 70.7 (*C*H-OH), 65.1 (*C*H$_2$-OH), 64.7 (*C*H$_2$-OH), 64.2 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 63.9 (OCH_2CH_2O), 63.7 (OCH_2CH_2O), 61.2 (OCH_2CH_3), 61.1 (OCH_2CH_3), 61.0 (OCH_2CH_3), 57.3 (CH$_2$*C*(CO_2Et)$_2$), 57.1 (CH$_2$*C*(CO_2Et)$_2$), 45.8 ((OCH_2CH_2O)C*C*H), 45.5 ((OCH_2CH_2O)C*C*H), 43.2 ((OCH_2CH_2O)CCH*C*H), 42.0 ((OCH_2CH_2O)CCH*C*H), 33.7 (C=CH*C*H$_2$), 33.6 (*C*H$_2$C(CO_2Et)$_2$), 33.3 ((OCH_2CH_2O)C*C*H$_2$), 33.0 ((OCH_2CH_2O)C*C*H$_2$), 30.4 (*C*H$_2$C(CO_2Et)$_2$), 25.93 (*C*H$_3$)(CH_3)C=CH), 25.89 (*C*H$_3$)(CH_3)C=CH), 23.6 ((OCH_2CH_2O)CCH$_2$*C*H$_2$), 18.9 ((OCH_2CH_2O)C*C*H$_2$), 17.89 (CH_3)(*C*H$_3$)C=CH), 17.86 (CH_3)(*C*H$_3$)C=CH), 13.8 (OCH_2CH_3); *m/z* (EI$^+$) 428.2415 (M$^+$); $C_{22}H_{36}O_8$ requires 428.2410.

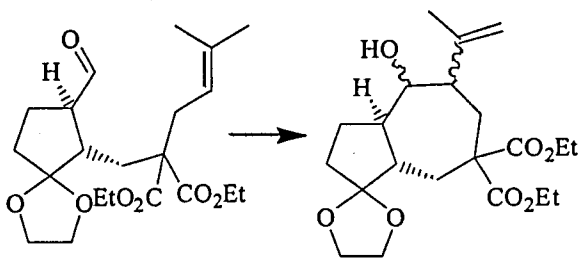
7.2.2 (±)-*trans*-2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (67)



66 **67**

$NaIO_4$ (1.50 g, 7.0 mmol) was added to a stirring solution of (±)-2-[7-(1,2-dihydroxy-ethyl)-1,4-dioxa-spiro[4.4]non-6-ylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**66**) (580 mg, 1.4 mmol) in 1:1= tetrahydrofuran:water (35 mL) at 0 °C, and the reaction mixture stirred for five hours while reachng room temperature. The mixture was diluted with dichloromethane (40 mL), the organic layer washed with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a pale yellow oil that was purified by flash column chromatography (10% ethyl acetate/light petroleum) to give the title compound (±)-*trans*-2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**67**) as a colourless oil (0.330 g, 62%); ν_{max} (film)/cm^{-1} 2978 (C-H), 2935 (C-H), 2721 (CHO), 1727 (C=O), 1297 (C-O); δ_H (400 MHz, $CDCl_3$) 9.52 (1 H, d, *J*= 2.3 Hz, C*H*O), 4.97-4.92 (1 H, m, C=C*H*), 4.19-4.02 (4 H, m, OCH_2CH_3), 3.93-3.82 (4 H, m, OCH_2CH_2O), 2.65-2.87 (3 H, m, $C=CHCH_2$, $(OCH_2CH_2O)CCHCH$), 2.38-2.34 (1 H, m, $(OCH_2CH_2O)CCH$), 2.23 (1 H, dd, J_1= 15.0, J_2= 3.4, *Ha*CHbC$(CO_2Et)_2$, 1.88-1.73 (4 H, m, HaC*Hb*C$(CO_2Et)_2$, $(OCH_2CH_2O)CCH_2CH_2$, *Ha*CHbC(OCH_2CH_2O)), 1.64 (3 H, d, *J*= 1.2, $CH_3C=CH$), 1.62-1.58 (4 H, m, $CH_3C=CH$, HaC*Hb*C(OCH_2CH_2O)), 1.20 (3 H, t, *J*= 7.14, OCH_2CH_3)), 1.19 (3 H, m, *J*= 7.13, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 202.4 (*C*HO), 171.6 (CO_2Et), 171.5 (CO_2Et), 135.3 ($(CH_3)_2C=CH$), 117.6 ($(OCH_2CH_2O)C$), 117.5 (C=*C*H), 64.7 (OCH_2CH_2O), 64.4 (OCH_2CH_2O), 61.13 (OCH_2CH_3), 61.07 (OCH_2CH_3), 56.8 ($CH_2C(CO_2Et)_2$, 54.7 ($(OCH_2CH_2O)CCHCH$), 40.9 ($(OCH_2CH_2O)CCH$), 33.2 ($(OCH_2CH_2O)CCH_2$), 31.8 ($C=CCH_2$), 31.5 ($CH_2C(CO_2Et)$, 26.0 ($CH_3C=CH$), 18.0 ($CH_3C=CH$), 14.0 (OCH_2CH_3), 13.9 (OCH_2CH_3), 21.5 ($(OCH_2CH_2O)CCH_2CH_2$); *m/z* (EI^+) 396.2142 (M^+); $C_{21}H_{32}O_7$ requires 396.2148.

7.3 Intramolecular carbonyl-ene reaction of (±)-*trans*-2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (67)



67 **72**

7.3.1 Intramolecular carbonyl-ene reaction of 67: $Yb(OTf)_3$ catalysis

$Yb(OTf)_3$ (2.35 g, 2.5 eq) was added to a solution of the 2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**67**) (360 mg, 0.91 mmol) in 20 mL of dry solvent (tetrahydrofuran or diethyl ether), at 0 °C, under an atmosphere of nitrogen, and the mixture stirred for sixteen hours. The reaction was diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate (2 × 15 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a colourless crude oil (280 mg). This was purified by flash column chromatography (10-30% ethyl acetate/light petroleum) to afford starting material **67** (20 mg, 6%) and deprotected starting material **70** (160 mg, 50 %).

7.3.2 Intramolecular carbonyl-ene cyclisation of 67: ZnI_2 catalysis

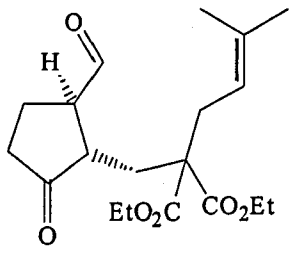
ZnI_2 (80 mg, 0.25 mmol) was added to a solution of 2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**67**) (40 mg, 0.1 mmol) in dry dichloromethane (5 mL) at 0 °C, under an atmosphere of nitrogen, the mixture stirred for sixteen hours, and allowed to reach room temperature. The reaction was then diluted with dichloromethane (15 mL), washed with saturated aqueous sodium hydrogen carbonate (2 × 8 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give of a red crude oil (50 mg). This was purified by flash column chromatography (10-30% ethyl acetate/light petroleum) to afford deprotected starting material **70** (36 mg, 33%).

7.3.3 Intramolecular carbonyl-ene cyclisation of 67: $BF_3 \cdot Et_2O$ catalysis

$BF_3 \cdot Et_2O$ (0.850 mL, 6.7 mmol) was added to a stirring solution of 2-(7-formyl-1,4-dioxa-spiro[4.4]non-6-ylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**67**) (260 mg, 0.66 mmol) in dry tetrahydrofuran (20 mL) at –78 °C under an atmosphere of nitrogen. The mixture was allowed to reach room temperature and stirred for twenty-four hours. The solution was diluted with dichloromethane (40 mL), washed with saturated aqueous sodium hydrogen carbonate (2 × 20 mL), dried over

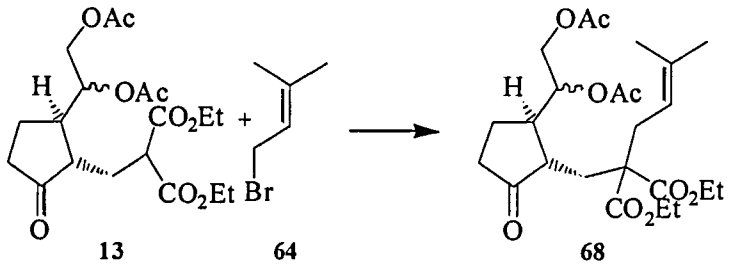
anhydrous magnesium sulfate, and concentrated to dryness to give a yellow crude oil (300 mg). This was purified by flash column chromatography (10-30% ethyl acetate/light petroleum) to afford deprotected starting material **70** (180 mg, 78%).

7.4 (±)-*trans*-2-(2-Formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (70)



70

7.4.1 (±)-*trans*-2-[2-(1,2-diacetoxyethyl)-5-oxocyclopentylmethyl]-2-(3-methylbut-2-enyl)-malonic acid diethyl ester (68)

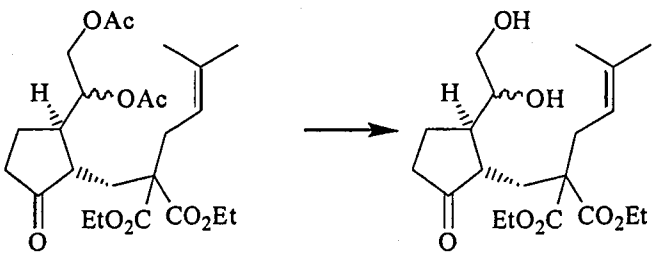


13 **64** **68**

A solution of *n*-butyllithium (2.5M in hexanes, 3.4 mL, 0.011 mol) was added to a solution of (±)-*trans*-2-[2-(1,2-diacetoxy-ethyl)-5-oxo-cyclopentylmethyl]-malonic acid diethyl ester (**13**) (3.0 g, 7.5 mmol) in dry tetrahydrofuran (50 mL), at –78 °C under an atmosphere of nitrogen, and the solution stirred for twenty minutes before being added by syringe to a solution of prenyl bromide (**64**) (1.53 mL, 0.013 mol) in dry tetrahydrofuran (10 mL), at –78 °C and under an atmosphere of nitrogen. The reaction was stirred for eighteen hours while reaching room temperature, cooled to 0 °C, quenched with water ((4 mL), diluted with dichloromethane (100 mL) and washed with a saturated solution of ammonium chloride (3 × 50 mL). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated to dryness to give a yellow material (3.5 g). This was purified by flash column chromatography (10-

20% ethyl acetate/light petroleum) to give (±)-*trans*-2-[2-(1,2-diacetoxyethyl)-5-oxocyclopentylmethyl]-2-(3-methylbut-2-enyl)-malonic acid diethyl ester (**68**), as a mixture of diastereoisomers as a colourless oil (2.0 g, 57%); ν_{max} (film)/cm^{-1} 2977 (C-H), 1740 (C=O), 1224 (C-O); δ_H (400 MHz, $CDCl_3$) 5.25-5.21 (1 H, m, C*H*OAc), 5.15-5.11 (1 H, m, C*H*OAc), 4.99-4.94 (2 H, m, C=C*H*), 4.38 (1 H, dd, J_1= 12.1, J_2= 3.1, *Ha*CHbOAc), 4.26 (1 H, dd, J_1= 11.6, J_2= 5.1, *Ha*CHbOAc), 4.21-4.04 (10 H, m, OCH_2CH$_3$ × 4, HaC*Hb*OAc × 2), 2.67 (3 H, m, *Ha*CHbCH=C(CH$_3$)$_2$, CH_2CH=C(CH$_3$)$_2$), 2.58 (1 H, dd, J_1= 15.1, J_2= 7.1, HaC*Hb*CH=C(CH$_3$)$_2$), 2.32 (1 H, ddd, J_1= 12.5, J_2= 9.02, J_3= 3.7, HaC*Hb*C(CO$_2$Et)$_2$), 2.30-1.94 (25 H, m, CH_3CO$_2$R × 4, COC*H* × 2, COCHC*H* × 2, COCH_2 × 2, CH_2C(CO$_2$Et)$_2$, *Ha*CHbCH$_2$C=O × 2, HaC*Hb*C(CO$_2$Et)$_2$), 1.93-1.83 (1 H, m, HaC*Hb*C(CO$_2$Et)$_2$), 1.71-1.65 (7 H, m, (CH_3)C=CH, HaC*Hb*CH$_2$C=O, (CH_3)C=CH), 1.60 (3 H, s, (CH_3)C=CH), 1.59 (3 H, s, (CH_3)C=CH), 1.19-1.14 (12 H, m, OCH$_2$CH_3 × 4); δ_C (100 MHz, $CDCl_3$) 218.3 (*C*=O), 218.2 (*C*=O), 171.4 (*C*O$_2$R), 171.2 (*C*O$_2$R), 171.0 (*C*O$_2$R), 170.7 (*C*O$_2$R), 170.74 (*C*O$_2$R), 170.6 (*C*O$_2$R), 170.3 (*C*O$_2$R), 135.6 ((CH$_3$)$_2$*C*=CH), 117.7 (C=*C*H), 117.5 (C=*C*H), 73.9 (*C*HOAc), 70.6 (*C*HOAc), 63.4 (*C*H$_2$OAc), 63.2 (*C*H$_2$OAc), 61.4 (O*C*H$_2$CH$_3$), 61.2 (O*C*H$_2$CH$_3$), 61.1 (O*C*H$_2$CH$_3$), 56.9 (*C*(CO$_2$Et)$_2$), 56.5 (*C*(CO$_2$Et)$_2$), 47.8 (*C*HC=O), 46.9 (*C*HC=O), 43.1 (*C*HCHC=O), 43.0 (*C*HCHC=O), 36.2 (*C*H$_2$C(CO$_2$Et)$_2$), 36.0 (*C*H$_2$C=O), 32.7 (*C*H$_2$C(CO$_2$Et)$_2$), 32.7 (C=CH*C*H$_2$), 32.3 (C=CH*C*H$_2$), 31.9 (*C*H$_2$C=O), 26.0 ((*C*H$_3$)C=CH), 23.3 (*C*H$_2$CH$_2$C=O), 21.0 (*C*H$_3$CO$_2$), 20.9 (*C*H$_3$CO$_2$), 20.8 (*C*H$_3$CO$_2$), 20.75 (*C*H$_3$CO$_2$), 18.0 ((*C*H$_3$)C=CH), 14.0 (OCH$_2$*C*H$_3$), 13.95 (OCH$_2$*C*H$_3$), 13.92 (OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 468.2362 (M$^+$); $C_{24}H_{36}O_9$ requires 468.2359.

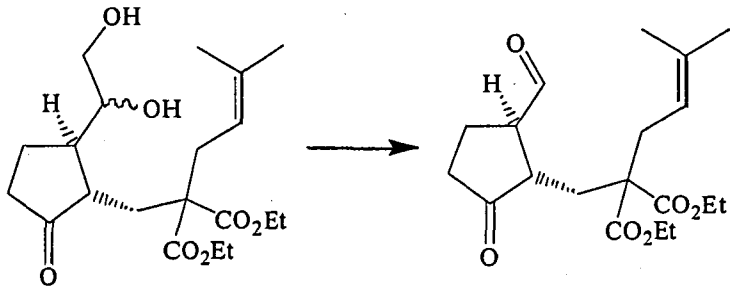
7.4.2 (±)-*trans*-2-[2-(1,2-dihydroxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (69)



68 **69**

A mixture of (±)-*trans*-2-[2-(1,2-dihydroxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**68**) (230 mg, 0.49 mmol) and activated Amberlite® 400 Cl (1.1 g) in methanol (10 mL) was stirred at room temperature for nineteen hours. The resin was filtered off through a sintered glass funnel and washed with methanol (50 mL). The organic solvent was concentrated to dryness to give a crude pale yellow oil material (200 mg). This was purified by flash column chromatography (50% ethyl acetate/light petroleum) to afford the title compound (±)-*trans*-2-[2-(1,2-dihydroxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**69**) as a mixture of diastereoisomers as a pale yellow oil (100 mg, 56%); ν_{max} (film)/cm^{-1}, 3459 (O-H), 2978 (C-H), 2931 (C-H), 1732 (C=O), 1297 (C-O); δ_H (400 MHz, $CDCl_3$), 4.88 (2 H, s, C=C*H* × 2), 4.20-3.95 (9 H, m, O*CH*$_2$CH$_3$ × 4, C*H*OH), 3.72-3.63 (3 H, m, C*H*OH, C*H*$_2$OH), 3.60-3.45 (2 H, m, C*H*$_2$OH), 2.65 (2 H, dd, J_1= 14.8, J_2=7.0, C=CHC*H*$_2$), 2.55 (2 H, m, C=CHC*H*$_2$), 2.45-2.22 (5 H, C*H*C=O × 2, *Ha*CHbC=O × 2, *Ha*CHbCH$_2$C=O), 2.08, 1.83 (6 H, m, C*H*CHC=O, *Ha*CHbC=O × 2, *Ha*CHbC(CO$_2$Et)$_2$ × 2, *Ha*CHbCH$_2$C=O), 1.75-1.67 (4 H, m, C*H*CHC=O, HaC*Hb*CH$_2$C=O × 2, HaC*Hb*C(CO$_2$Et)$_2$), 1.634 (3 H, s, (C*H*$_3$)C=CH), 1.626 (3H, s, (C*H*$_3$)C=CH), 1.55 (6 H, s, (C*H*$_3$)C=CH × 2), 1.21-1.15 (12 H, OCH$_2$C*H*$_3$ × 4); δ_C (100 MHz, $CDCl_3$) 219.5 (C=O), 218.7 (C=O), 173.5 (*C*O$_2$Et), 172.6 (*C*O$_2$Et), 171.1 (*C*O$_2$Et), 136.1 ((CH$_3$)$_2$*C*=CH), 136.0 ((CH$_3$)$_2$*C*=CH), 117.2 (C=*C*H), 117.1 (C=*C*H), 77.0 (*C*HOH), 69.3 (*C*HOH), 64.5 (*C*H$_2$OH), 64.4 (*C*H$_2$OH), 61.6 (O*C*H$_2$CH$_3$), 61.5 (O*C*H$_2$CH$_3$), 57.8 (*C*H$_2$C(CO$_2$Et)$_2$), 57.1 (*C*H$_2$C(CO$_2$Et)$_2$), 50.2 (C*H*C=O), 47.2 (C*H*C=O), 45.4 (*C*HCHC=O), 45.1 (C*H*CHC=O), 36.9 (CO*C*H$_2$), 35.5 (*C*H$_2$C=O), 34.3 (C=CH*C*H$_2$), 34.1 (C=CH*C*H$_2$), 32.7 (*C*H$_2$CH$_2$C=O), 30.1 (*C*H$_2$C(CO$_2$Et)$_2$), 25.94 ((*C*H$_3$)C=CH), 25.87 ((*C*H$_3$)C=CH), 23.4 (*C*H$_2$C(CO$_2$Et)$_2$), 18.9 (*C*H$_2$CH$_2$C=O), 17.9 ((*C*H$_3$)C=CH), 17.8 ((*C*H$_3$)C=CH), 13.8 (OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 384.2153 (M$^+$); $C_{20}H_{32}O_7$ requires 384.2148.

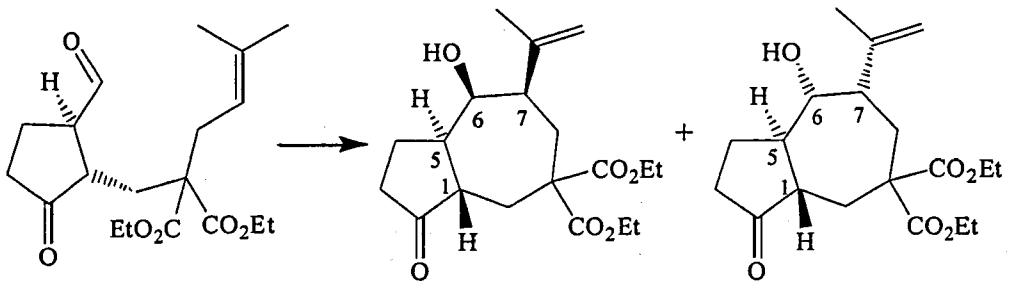
7.4.3 (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (70)



69 **70**

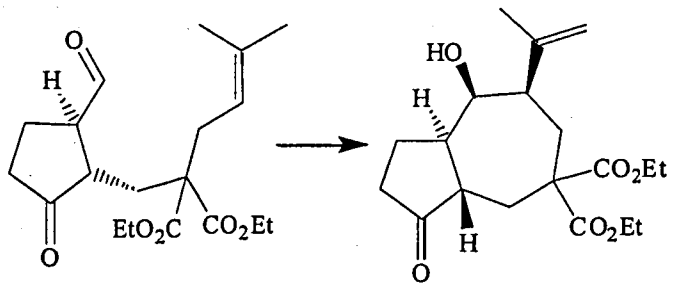
Sodium periodate ($NaIO_4$, 5.5 g, 0.025 mol) was added at 0 °C to a stirring solution of (±)-*trans*-2-[2-(1,2-dihydroxy-ethyl)-5-oxo-cyclopentylmethyl]-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**69**) (0.920 g, 0.0024 mol) in 1:1= tetrahydrofuran:water (120 mL). The mixture was stirred at room temperature for five hours, diluted with dichloromethane (40 mL), the organic layer extracted with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a pale yellow oil (0.850 g) that was purified by flash column chromatography (10% ethyl acetate/light petroleum) to give (±)-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) as a mixture of diastereoisomers as a colourless oil (0.495 g, 59%); ν_{max} (film)/cm^{-1}, 2979 (C-H), 2930 (C-H), 1727 (C=O), 1221 (C-O); δ_H (400 MHz, $CDCl_3$), 9.65 (1 H, d, *J*= 2.9, C*H*O), 4.97-4.05 (1 H, m, C=C*H*), 4.20-4.05 (4 H, m, (OC*H*$_2$CH$_3$ × 2), 2.87-2.80 (1 H, m, C*H*CHC=O), 2.66-2.53 (3 H, m, C*H*C=O, C=CHC*H*$_2$), 2.39-2.30 (1 H, m, *Ha*CHbC=O), 2.23-2.08 (3 H, m, *Ha*CHbC(CO$_2$Et)$_2$, HaC*Hb*CO, *Ha*CHbCH$_2$C=O), 2.00-1.87 (2 H, m, HaC*Hb*C(CO$_2$Et)$_2$, HaC*Hb*CH$_2$C=O), 1.65 (3 H, d, *J*= 1.65, (C*H*$_3$)C=CH), 1.57 (3 H, s, (C*H*$_3$)C=CH), 1.211 (3 H, t, *J*= 7.0, OCH$_2$C*H*$_3$), 1.207 (3 H, t, *J*= 7.3, OCH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 216.1 (CH$_2$*C*O-CH), 201.1 (*C*HO), 171.2 (*C*O$_2$Et) 171.1 (*C*O$_2$Et), 136.0 ((CH$_3$)$_2$*C*=CH), 117.3 (C=*C*H), 61.5 (O*C*H$_2$CH$_3$), 61.3 (OCH$_2$CH$_3$), 56.9 (*C*(CO$_2$Et)$_2$), 54.9 (*C*HCHC=O), 46.0 (*C*HC=O), 35.8 (*C*H$_2$C=O), 32.7 (C=CH*C*H$_2$), 32.0 (CH$_2$*C*(CO$_2$Et)$_2$), 25.9 ((*C*H$_3$)C=CH), 21.2 (*C*H$_2$CH$_2$C=O), 17.9 ((*C*H$_3$)C=CH), 13.89 (OCH$_2$*C*H$_3$), 13.86 (OCH$_2$*C*H$_3$); *m/z* (EI$^+$) 352.1891 (M$^+$); $C_{19}H_{28}O_6$ requires 352.1886.

7.4 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73) and (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (74)



70 73 74

7.4.1 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73) and (±)-8-hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (74): BF_3•Et_2O catalysis



70 73

BF_3•Et_2O (0.86 mL, 7.0 mmol) was added to a solution of (±)-trans-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) (490 mg, 0.0014 mol) in dry tetrahydrofuran (25 mL), at –78 °C under an atmosphere of nitrogen. The mixture was stirred for twenty-four hours at room temperature, diluted with dichloromethane (40 mL), washed with saturated aqueous sodium hydrogen carbonate (2 × 20 mL), dried over anhydrous magnesium sulfate and concentrated to dryness to give a crude material that was filtered through a pad of silica gel (50% ethyl acetate/light petroleum) to give a yellow oil (400 mg). This was purified by flash column chromatography (15-35% ethyl acetate /light petroleum) to afford (±)-8-hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester

(**73**) as a colourless oil (200 mg, 41%) and8-hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (**74**) as a colourless oil (50 mg, 10%); Cycloadduct **73**: ν_{max} (film)/cm^{-1} 3542 (O-H), 2978 (C-H), 1730 (C=O), 1645 (C=C), 1245 (C-O); δ_H (400 MHz, $CDCl_3$), 4.87 (1 H, m, *Ha*CHb=CCH_3), 4.76 (1 H, s, HaC*Hb*=CCH_3), 4.18-4.05 (4 H, m, OCH_2CH_3 × 2), 3.82 (1 H, s, C*H*OH), 2.61 (1 H, dd, J_1= 15.2, J_2= 2.9, *Ha*CHβCHC=O), 2.45-2.32 (3 H, m, *Ha*CHbCH($CH_3C=CH_2$), *Ha*CHbC=O, COC*H*), 2.17-2.06 (3 H, m, HaC*Hb*C=O, C*H*($CH_3C=CH_2$), HaC*Hb*CH($CH_3C=CH_2$)), 1.99-1.85 (4 H, m, *Ha*CHbCH_2C=O, HaC*Hb*CH_2C=O, COCHC*H*, HαC*Hβ*CHC=O), 1.76 (3 H, s, CH_3C=CH_2), 1.18 (3 H, t, *J*= 7.1, OCH_2CH_3), 1.17 (3 H, t, *J*= 7.1, OCH_2CH_3), δ_C (100 MHz, $CDCl_3$) 218.7 (*C*=O), 172.4 (*C*O_2Et), 172.3 (*C*O_2Et), 148.7 ($CH_3C=CH_2$), 111.7 ($CH_3C=CH_2$), 67.8 (*C*HOH), 61.4 (OCH_2CH_3), 61.3 (OCH_2CH_3), 55.2 (*C*($CO_2Et)_2$), 50.1 (*C*HCHC=O), 47.0 (*C*H($CH_3C=CH_2$)), 44.9 (*C*HC=O), 37.3 (CH_2C=O), 32.6 (CH_2CHC=O), 29.5 (CH_2CH($CH_3C=CH_2$)), 23.3 ($CH_3C=CH_2$), 22.7 (CH_2CH_2C=O), 13.9 (OCH_2CH_3), 13.8 (OCH_2CH_3); *m/z* (EI$^+$) 352.1823 (M$^+$), $C_{19}H_{28}O_6$ requires 352.1886.

Cycloadduct **74** ν_{max} (film)/cm^{-1} 3533 (O-H), 2979 (C-O), 1737 (C=O), 1731 (C=O), 1646 (C=C), 1255 (C-O); δ_H (400 MHz, $CDCl_3$), 4.95 (1 H, m, *Ha*CHb=CH), 4.84 (1 H, s, HaC*Hb*=CH), 4.12-4.20 (4 H, m, OCH_2CH_3 × 2), 3.35 (1 H, dd, J_1= J_2= 9.5, C*H*OH)), 2.71 (1 H, d, *J*= 14.2, *Ha*CHβCHC=O), 2.49-2.43 (1 H, m, *Ha*CHbCH_2C=O), 2.41 (1 H, d, *J*= 8.8, *Ha*CHbC=O), 2.25 (1 H, d, *J*= 15.1, HαC*Hβ*CH($CH_3C=CH_2$)), 2.20-2.10 (2 H, m, HaC*Hb*C=O, CH(OH)C*H*($CH_3C=CH_2$)), 2.03-1.83 (3 H, m, COC*H*, HαC*Hβ*CHC=O, *Ha*CHβCH($CH_3C=CH_2$)), 1.80-1.70 (4 H, m, CH_3C=CH_2, C*H*CHCO), 1.60-1.49 (1 H, m, HaC*Hb*CH_2C=O), 1.23 (3 H, t, *J*= 7.2, OCH_2CH_3), 1.22 (3 H, t, *J*= 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 217.3 (C=O), 172.2 (*C*O_2Et), 171.7 (*C*O_2Et), 146.4 (CH($CH_3C=CH_2$)), 113.5 ($CH_3C=CH_2$), 77.1 (*C*HOH) 61.7 (OCH_2CH_3), 61.6 (OCH_2CH_3), 54.9 (*C*($CO_2Et)_2$), 51.7 (*C*HCHC=O), 49.4 (*C*H($CH_3C=CH_2$), 47.8 (*C*HC=O), 36.7 (CH_2C=O), 34.3 (CH_2CH($CH_3C=CH_2$), 31.6 (CH_2CHC=O), 26.3 (CH_2CH_2C=O), 19.2 ($CH_3C=CH_2$), 14.0 (OCH_2CH_3), 13.9 (OCH_2CH_3); *m/z* (EI$^+$) 352.1823 (M$^+$), $C_{19}H_{28}O_6$ requires 352.1886.

7.4.2 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73): $Yb(OTf)_3$ catalysis

$Yb(OTf)_3$ (640 mg, 1.2 mmol) was added to a stirring solution of (±)-*trans*-2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) (80 mg, 0.24 mmol) in dry tetrahydrofuran (10 mL), at 0 °C under an atmosphere of nitrogen. The mixture was stirred at room temperature for five days, diluted with dichloromethane (20 mL), extracted with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a colourless crude oil (120 mg). This was purified by flash column chromatography (10-35% ethyl acetate/light petroleum) to give **73** (37 mg, 46%) and starting material **70** (14 mg, 18%).

7.4.3 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73) and (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (74): ZnI_2 catalysis

ZnI_2 (0.450 g, 0.0014 mol) was added to a solution of 2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) (100 mg, 0.28 mmol) in dry tetrahydrofuran or dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen, and the mixture stirred at room temperature. The reaction was monitored for 3 days, but only starting material was detected by TLC analysis. At this stage a further five equivalents of catalyst (450 mg) were added. After two more days (five days overall) no trace of product was detected by TLC analysis. The solution was diluted with dichloromethane (10 mL), extracted with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give an orange oil (120 mg), which, according to the ^1H NMR analysis, was starting material **70**.

7.4.4 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73) and (±)-8-hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (74): $InCl_3$ catalysis

$InCl_3$ (314 mg, 0.0014 mol) was added to a solution of 2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) (100 mg, 0.28 mmol) in dry tetrahydrofuran (5 mL) and the mixture stirred at room temperature for sixteen hours. At this stage TLC analysis showed that no reaction had occurred yet, a further amount of catalyst was added (320 mg), and the mixture stirred for a further four days. Again, only starting material was detected by TLC analysis. The solution was diluted with dichloromethane (15 mL), extracted with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a colourless oil (86 mg). Purification of this residue by flash column chromatography (10-30% ethyl acetate/light petroleum) gave starting material **70** (40 mg).

7.4.5 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73) and (±)-8-hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (74): $Sc(OTf)_3$ catalysis

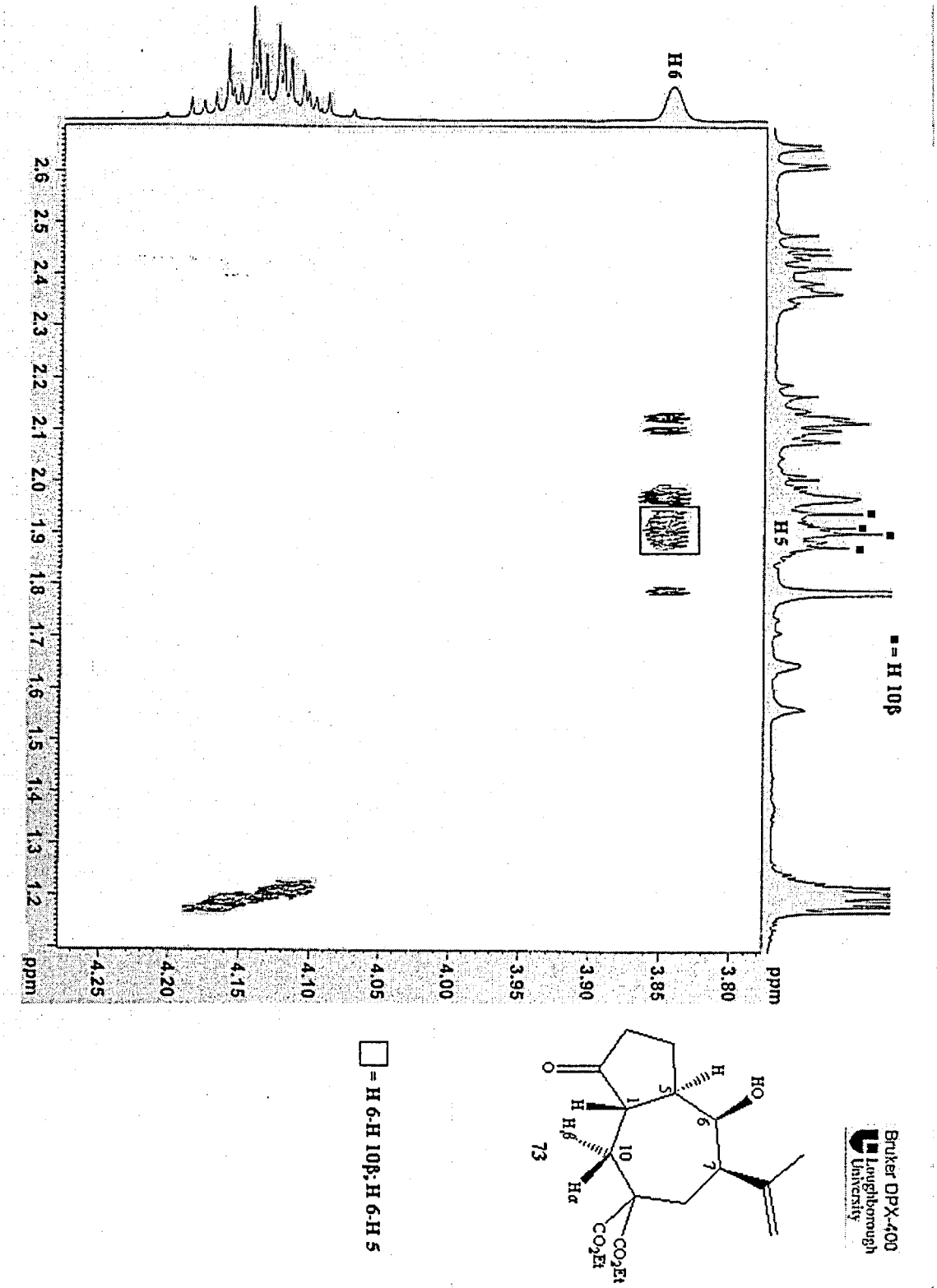
$Sc(OTf)_3$ (0.690 g, 0.0014 mol) was added to a solution of 2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) (100 mg, 0.28 mmol) in dry tetrahydrofuran or dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen and the mixture stirred at room temperature. The reaction was checked daily for 3 days, but starting material only was detected by TLC analysis. It was then decided to add five more equivalents of catalyst (0.690 g). After two more days (five days overall), no trace of product was detected by TLC analysis. The solution was diluted with dichloromethane (10 mL), extracted with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness to give a pale yellow oil (110 mg), which, according to ^1H NMR analysis, was starting material **70**.

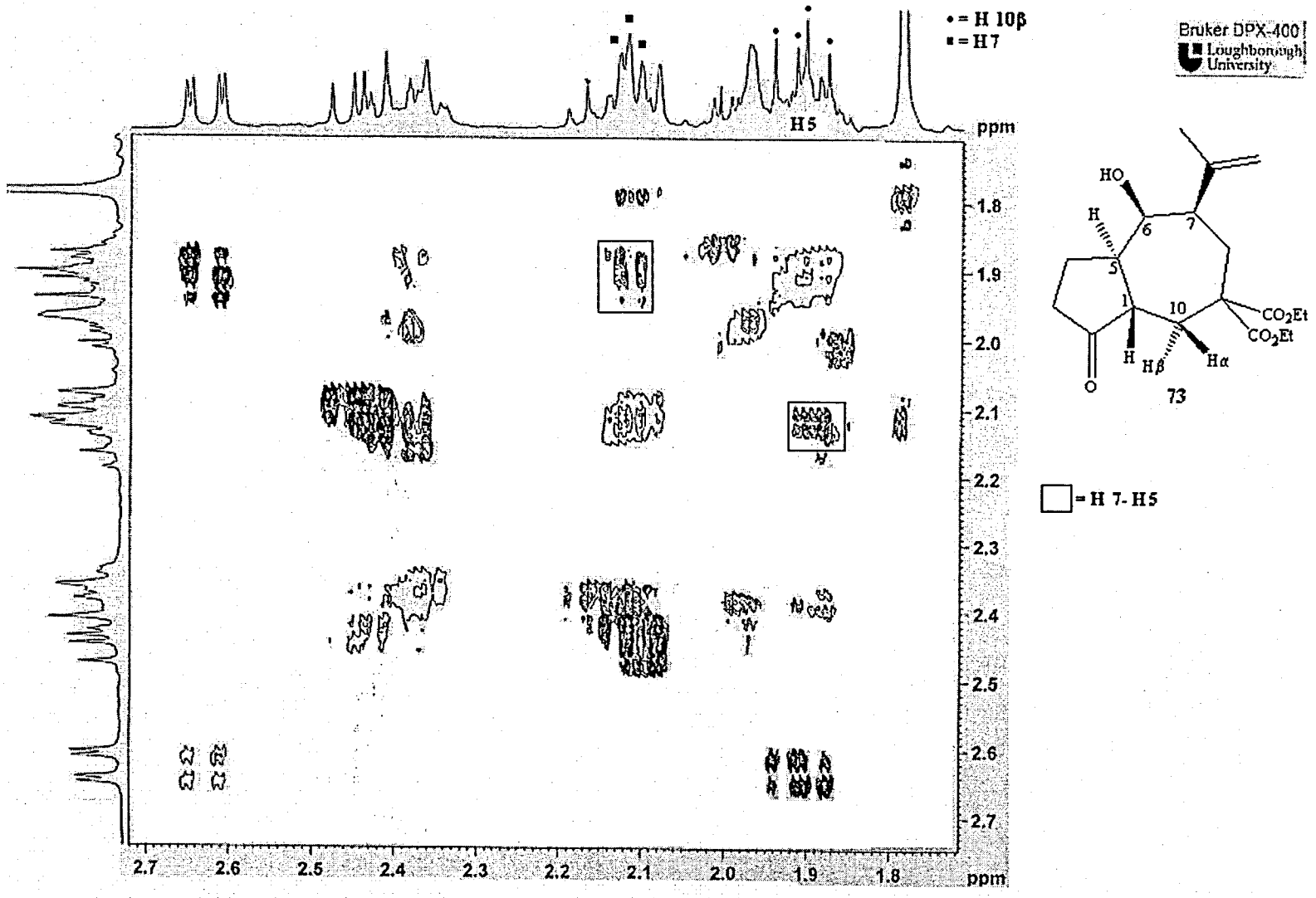
7.4.6 (±)-8-Hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (73) and (±)-8-hydroxy-7-isopropenyl-3-oxo-octahydro-azulene-5,5-dicarboxylic acid diethyl ester (74): microwaves irradiation.

A solution of 2-(2-formyl-5-oxo-cyclopentylmethyl)-2-(3-methyl-but-2-enyl)-malonic acid diethyl ester (**70**) (180 mg, 0.5 mmol) in toluene (3 mL) was submitted to microwaves irradiation (120 °C, max power) for 10 minutes. The solution was then concentrated to dryness to give a pale yellow oil (180 mg), which, according to ^{1}H NMR analysis, was starting material **70**.

8 Enclosures

8.1

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Hα
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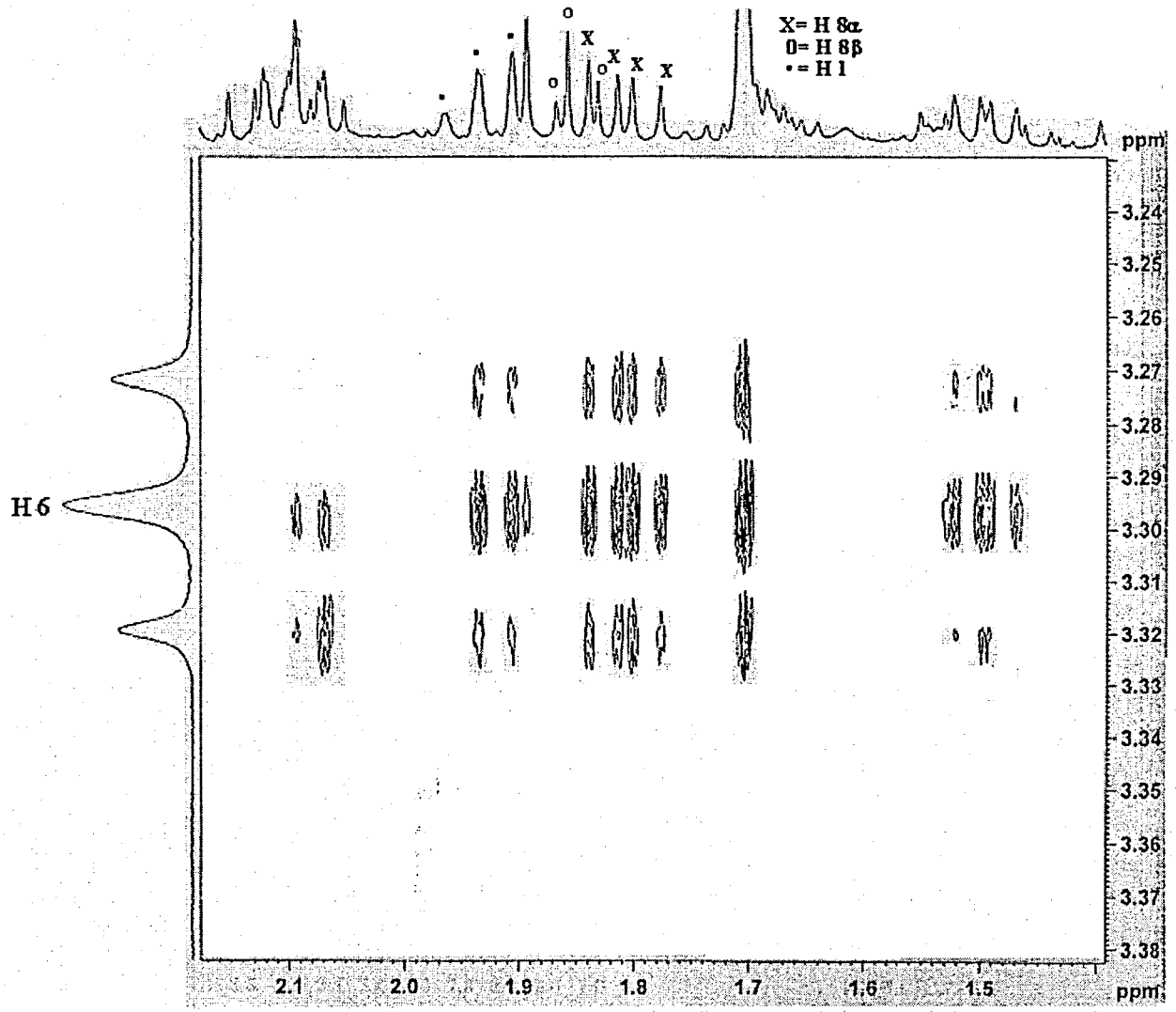
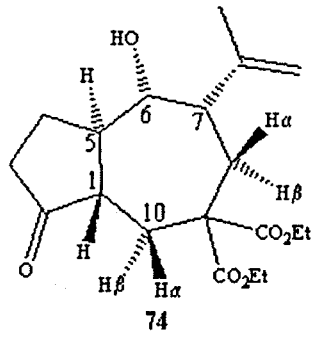
8.2





74

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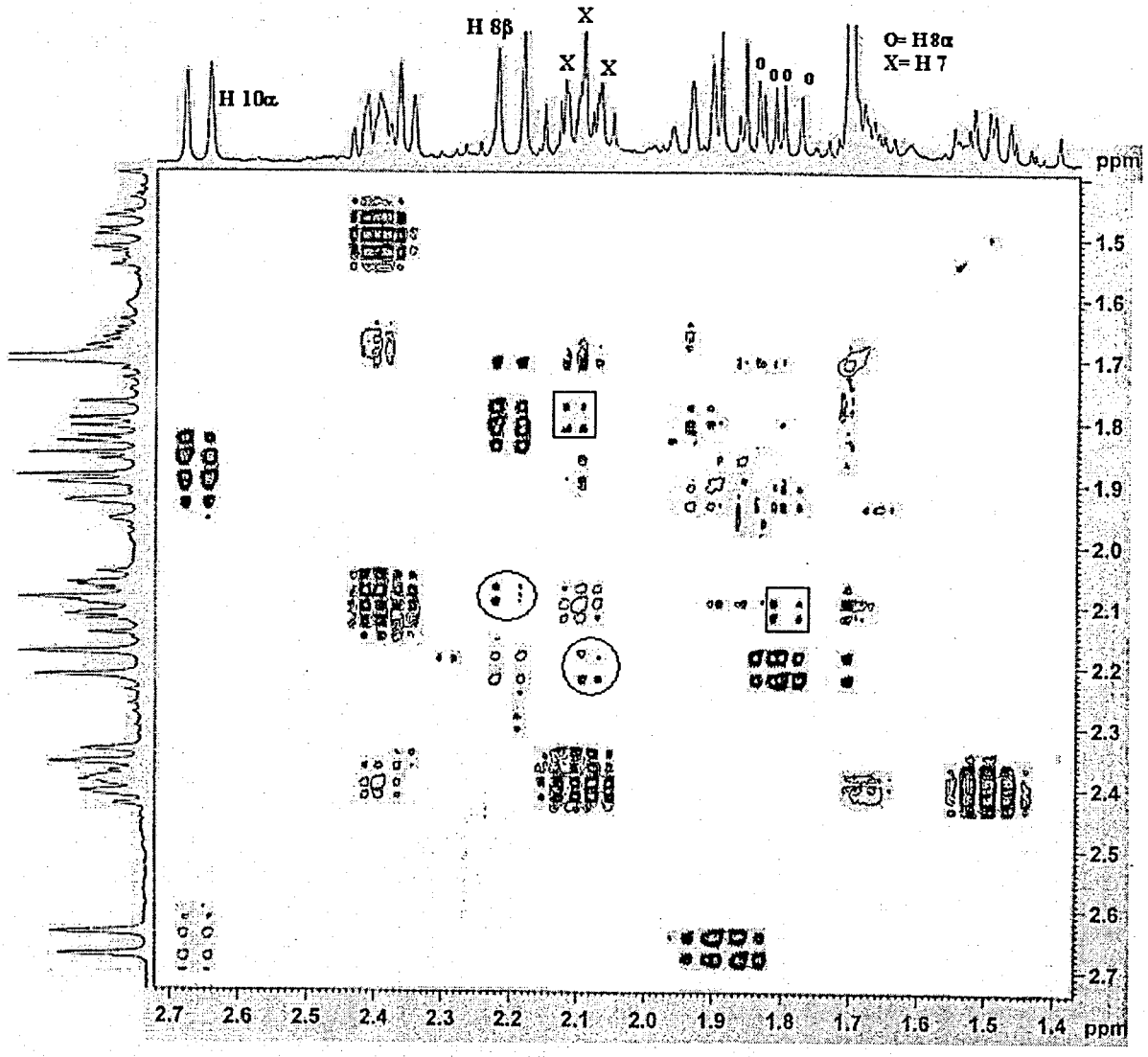
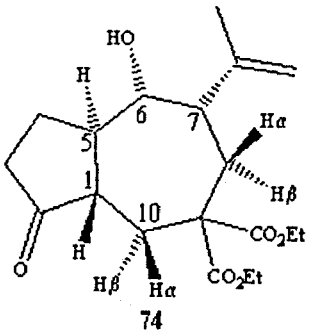
8.3





74

□= H 7- H 8α

○= H 7--H 8β

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8.4