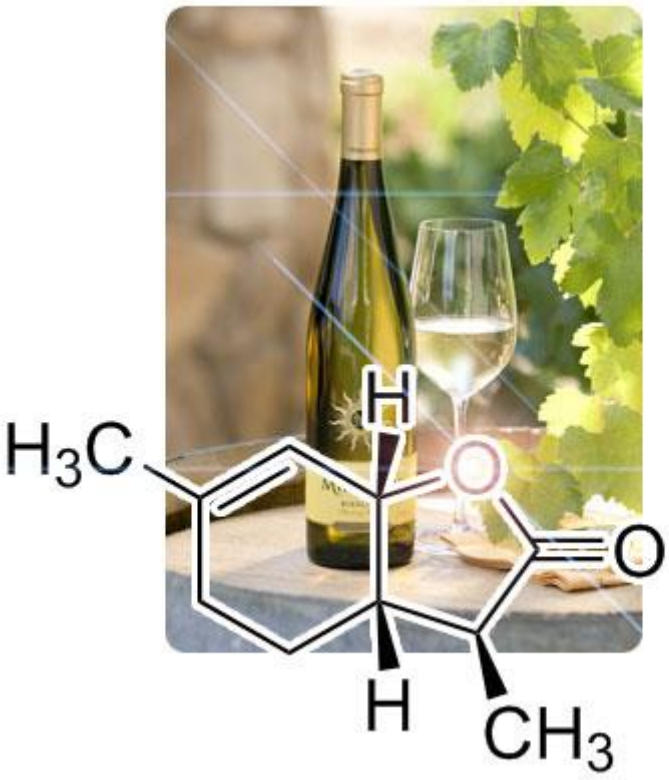
# Total synthesis of (±)-wine lactone using a novel Diels-Alder approach




A dissertation submitted in partial fulfilment
of the requirements for the degree of
Bachelor of Science (Honours)

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THE UNIVERSITY OF AUCKLAND
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Te Whare Wānanga o Tāmaki Makaurau

*Cover image courtesy of* http://www.mirassou.com/images/product-riesling.jpg

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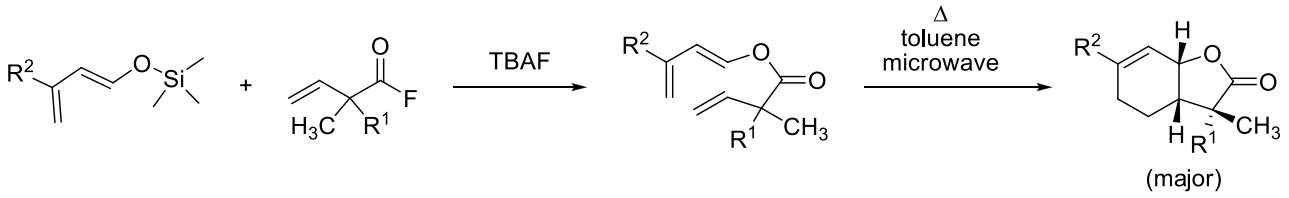
Finally I dedicate this work to my mother Kim Jong Soon (김종순) and my father Kim Young Sik (김영식). I love you and hope to make you proud.

U Bin Kim
November 200

**Abstract**

A novel route to 3,6-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7*aH*)-one (racemic wine lactone) involving a novel intramolecular Diels-Alder (IMDA) reaction has been realised. The required Diels-Alder precursor was made *via* convergent synthesis from tetra-*n*-butylammonium fluoride mediated acylation reaction between 2-methylbut-3-enoyl fluoride and trimethyl(3-methylbuta-1,3-dienyloxy)silane. Using a similar protocol, three other wine lactone analogues; 3,3,6-trimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7*aH*)-one, 3,3-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7*aH*)-one and 3-methyl-3,3a,4,5-tetrahydrobenzofuran-2(7*aH*)-one have been prepared. The diastereoselectivity of the Diels-Alder reactions were determined by gas chromatography-mass spectrometry (GC-MS) analysis and the cycloaddition was found to favour the formation of the natural wine lactone diastereomer. These findings were verified by computational analysis.



**Abbreviations**

| | |
|---|---|
| 9-BBN | 9-Borabicyclo[3.3.1]nonane |
| b. p. | boiling point |
| cat. | Catalytic |
| DBU | 1,8-Diazabicyclo[5.4.0]undex-7-ene |
| DFT | density functional theory |
| DMSO | dimethylsulfoxide |
| EI | electron impact |
| equiv. | equivalent |
| g | gram |
| GC | gas chromatography |
| GCMS | gas chromatography-mass spectrometry |
| h | hour |
| HOMO | highest occupied molecular orbital |
| HRMS | high resolution mass spectroscopy |
| TS | transition state |
| IBX | 2-Iodoxybenzoic acid |
| IMDA | Intramolecular Diels-Alder |
| IR | infra-red |
| *J* | NMR coupling constant (Hertz) |
| LDA | lithium diisopropylamide |
| lit | literature |
| LUMO | lowest unoccupied molecular orbital |
| Me | methyl |
| MHz | MegaHertz |
| mL | millimetre |
| mmol | millimole |
| MP2 | Møller-Plesset perturbation theory |
| NBS | *N*-Bromosuccinimide |
| NMR | nuclear magnetic resonance |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| r.t. | room temperature |
| TBAF | tetra-*n*-butylammonium fluoride |
| TEMPO | 2,2,6,6-Tetramethylpiperidine-1-oxyl |

| | |
|---|---|
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsulyl |
| VOC | volatile organic compounds |
| ZPVE | zero point vibrational energy |

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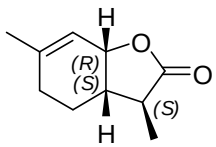
# Chapter 1. Introduction

## 1 Introduction



**1**

Wine lactone (**1**) is a sweet smelling organic compound first isolated as a Koala urine metabolite by Southwell in 1975.[1] Since its isolation it has been identified as a significant odorant in a variety of natural sources with a diversity ranging from black pepper to orange juice.[7,8,9,10,11,12] The natural product derives its name from the recognition of **1** as an important flavour constituent of Riesling wine.[13] Interestingly, wine lactone has an amazingly low odour detection threshold of 0.02 pg/L in air.[2] While the name wine lactone is reserved for the specific stereoisomer **1**, the term wine lactones generically refers to the eight possible stereoisomers corresponding to the three stereocentres of the bicyclic compound.

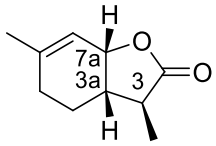
### 1.1 Discovery

The Australian Koala (*Phascolarctos cinerus*) favours feeding on the leaf of the Australian Grey Gum (*Eucalytpus punctata*). In 1975 a study of the essential oil composition of Grey Gum[14] and the composition of koala urine extract post-feeding[1] established wine lactone (**1**) as one of the Koala metabolites of Grey Gum.

### 1.2 Distribution

Studies aimed at identification of important odorants in commercially important commodities revealed the presence of wine lactone (**1**) in black pepper[7] (1999), grapefruit juices from American seedless White marsh grapes (1999),[8] hand-squeezed juices from Valencia late oranges (2001),[9] Cox-orange apple variety (2002),[10] orange essential oils (2003)[11] and freshly squeezed orange Juice (2008).[12] Given the widespread prevalence of wine lactone in nature, it is reasonable to speculate the future findings of these compounds elsewhere.

### 1.3 Odour characteristics

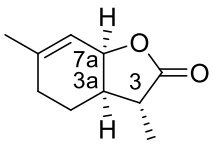



**1**

The odour of wine lactone is subjectively characterised as being sweetly scented with a coconut like odour.[2] During his investigation Guth[2] prepared and determined the odour detection threshold for all eight possible stereoisomers of wine lactone **1**. These are tabulated below (**Table 1**);

| Stereoisomer | Odour threshold (ng/l air) |
|---|---|
| (3*S*, 3*aS*, 7*aR*) wine lactone (**1**) | 0.00001-0.00004 |
| (3*R*, 3*aR*, 7*aS*) – ent-(**1**) | > 1000 |
| (3*R*, 3*aS*, 7*aR*) – (**2**) | > 1000 |
| (3*S*, 3*aR*, 7*aS*) – ent-(**2**) | 80–160 |
| (3*S*, 3*aS*, 7*aS*) – (**3**) | 0.007–0.014 |
| (3*R*, 3*aR*, 7*aR*) – ent-(**3**) | 14-29 |
| (3*R*, 3*aS*, 7*aS*) – (**4**) | 8-16 |
| (3*S*, 3*aR*, 7*aR*) – ent-(**4**) | 0.05-0.02 |

**Table 1.** *Odour thresholds of wine lactone stereoisomers.*

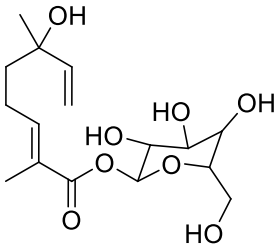



*ent*-**1**

The enormous variation in odour detection threshold for the different stereoisomers (from weakest being $10^6$ pg/l to the strongest being 0.04 pg/l) underline the importance of stereogenic configuration for odorants especially for natural wine lactone (**1**). Interestingly while wine lactone (**1**) is the most potent smelling isomer, its enantiomer *ent*-(**1**) has the weakest odor of the wine lactone family.

### 1.4 Importance in Wine

The aroma and flavour of wine is largely determined by volatile organic compounds (VOCs) and thus the chemical composition of wine is of paramount importance. With the advent of gas chromatography (GC), the investigation of the identity and prevalence of odoriferous flavour contributing compounds as an area of research has intensified and is now known as wine science. It is especially important for New Zealand to actively engage in such efforts as the New Zealand wine industry accounts for a significant fraction of New Zealand's export economy (estimated export revenue of 700 million dollars in 2007).[15]



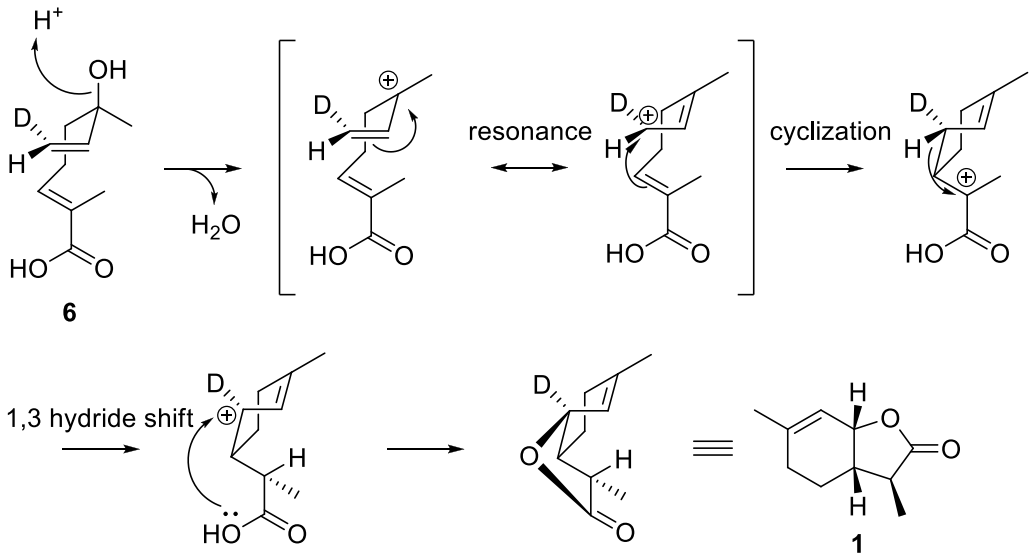

**5**

In 1997 Guth *et al.*[16] isolated wine lactone (**1**) in the Gewürztraminer and Scheurebe wine varieties. This was later followed by the total synthesis of wine lactone and all of its stereoisomers.[2] By demonstrating an extraordinarily low detection threshold, wine lactone (**1**) was identified as a major flavour component of white wines.

Following this work, Winterhalter *et al.*[13] isolated and characterised the novel terpenoid glycoside **5** from Riesling wine. The free acid form was also found[17] and under acidic conditions this was shown to be converted to wine lactone (**1**).[18] The prevalence of wine lactone is not limited to white wine varieties; detection of the wine lactone has been reported from wines made with Merlot, Cabernet Sauvignon and Grenache grapes.[19]

### 1.5 Biosynthesis

It is thought that oxidation of terpenoids *via* pathways common in grapes gives rise to glycoside **5** and the corresponding acid. Winterhalter *et al.*[13] noted the easy transformation of such odourless terpenoid glycoconjugates to volatile organic constituents. The mechanism of wine lactone formation from the free acid has been postulated by Laun *et al*.[18] Deuterium labelled analogue **6** was prepared and cyclized under acidic conditions. From this study, a non enzymatic stereoselective cationic cascade mechanism was proposed. This is outlined below (**Scheme 1**).




**Scheme 1**. *Proposed mechanism for the formation of wine lactone by Laun et al.*[18]

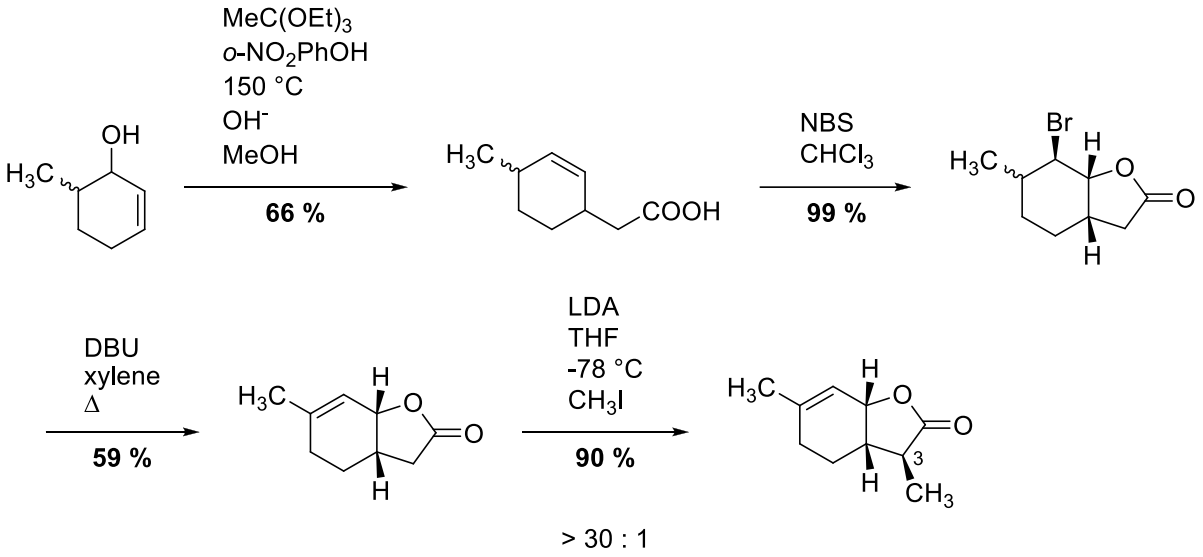
Variation of the fermentation yeast did not affect the amount of the wine lactone generated lending credibility to the simple acid mediated mechanism of formation.[12] As a koala metabolite the wine lactone is speculated to have been derived from metabolism of (+/-)-pinene *via* cyclization of hydroxylated 8-carboxy-pinene.[1]

### 1.6 Previous syntheses

To date there have been five reported syntheses of wine lactone. These will be detailed below.

### 1.6.1 Synthesis by Pizzo and Bartlett (1981)

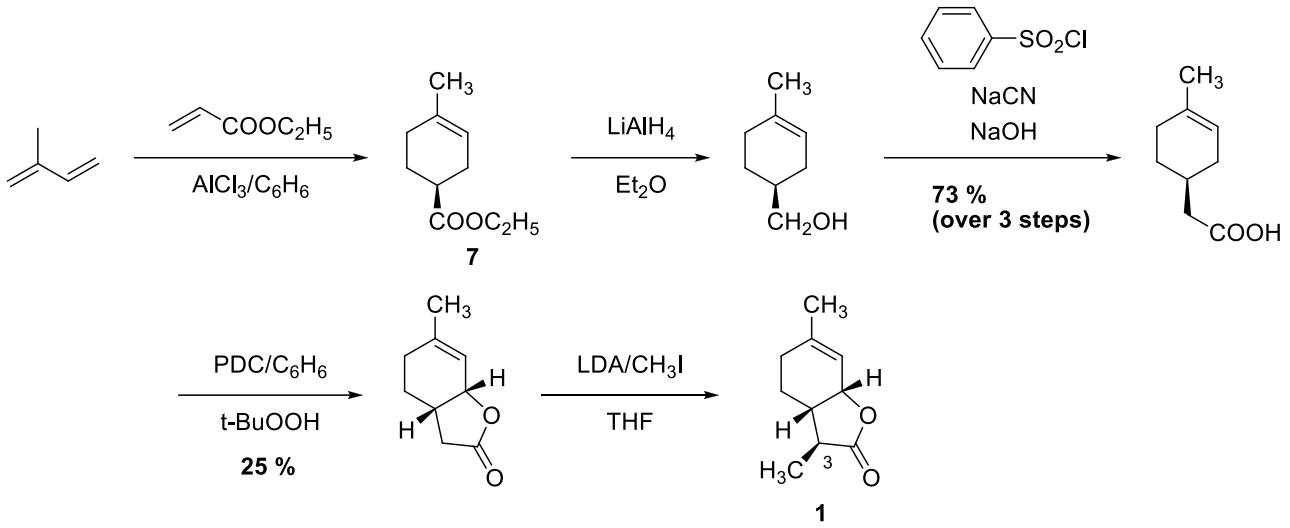
Wine lactone (**1**) was unknowingly prepared by Pizzo and Bartlett[4] using what is arguably the most elegant synthesis reported to date (**Scheme 2**). The key step of the synthesis involved an elegant Claisen rearrangement.[4] Following bromolactonisation, the C3-methyl function was installed from the convex face of the molecule by alkylation of an enolate.




**Scheme 2.** *Synthesis of racemic natural wine lactone by Pizzo and Bartlett.*[4]

### 1.6.2 Synthesis by Guth (1996)

In a comprehensive study Guth *et al.*[2] isolated, synthesised and established the absolute stereochemistry of all eight wine lactone isomers. The stereoselective synthesis of (racemic) natural wine lactone is outlined below **(Scheme 3)**.

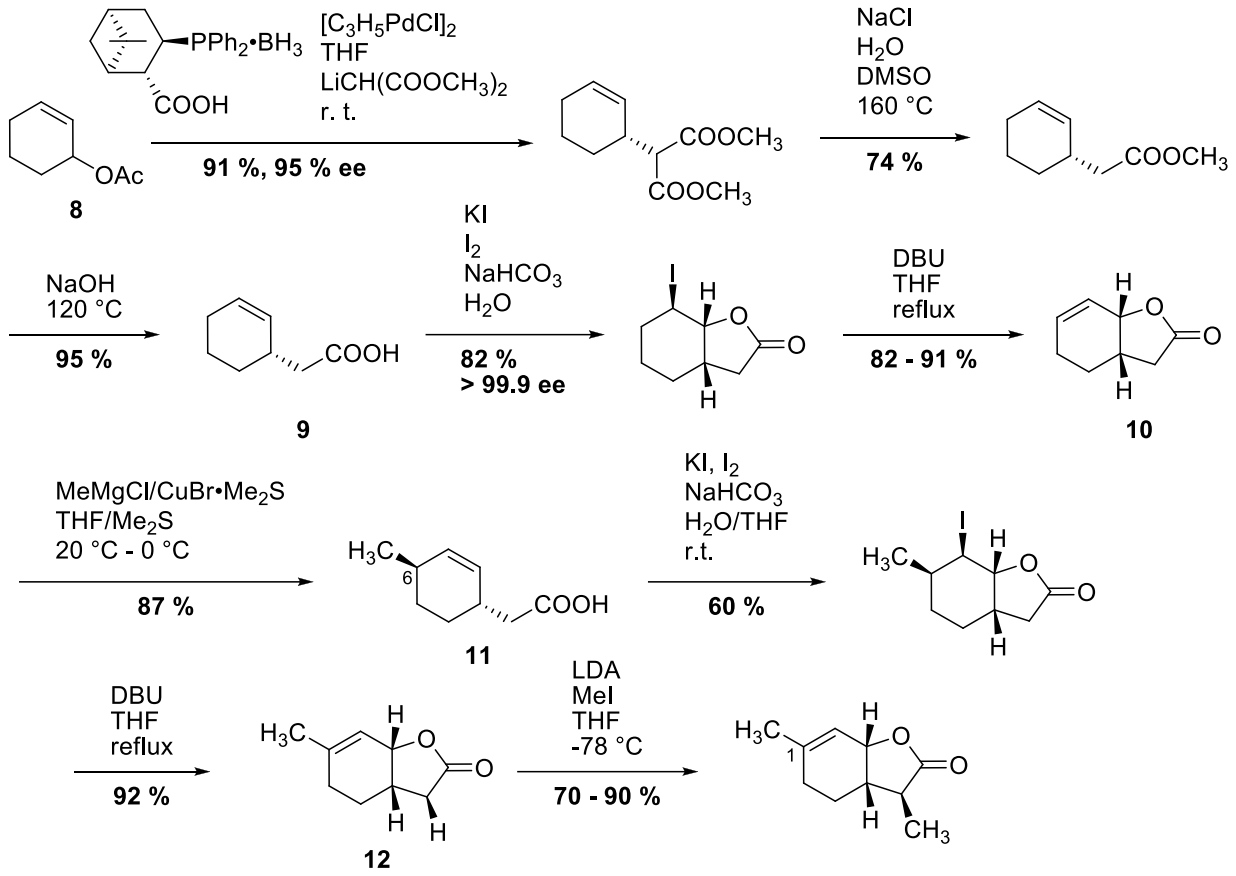



**Scheme 3**. *Synthesis of racemic natural wine lactone by Guth.*[2]

Racemic cyclohexene **7**, synthesised by Diels-Alder cycloaddition, was reduced and chain elongated by sequential $S_N2$ alkylation with cyanide followed by alkaline hydrolysis to give the carboxylic acid. Following lactonisation the lithium enolate was alkylated with iodomethane from the sterically undemanding face to afford the diastereomer with *syn* relationship the bridgehead between the methine proton and the C3-methyl group. Although this route is concise the synthesis does not allow for an asymmetric variant to be easily adapted other than by developing an asymmetric Diels-Alder reaction in the first step.

### 1.6.3 Synthesis by Bergner and Helmchen (2000)

The Guth synthesis was followed by work by Helmchen and Bergner who reported an enantioselective syntheses of wine lactone (**Scheme 4**).[5]



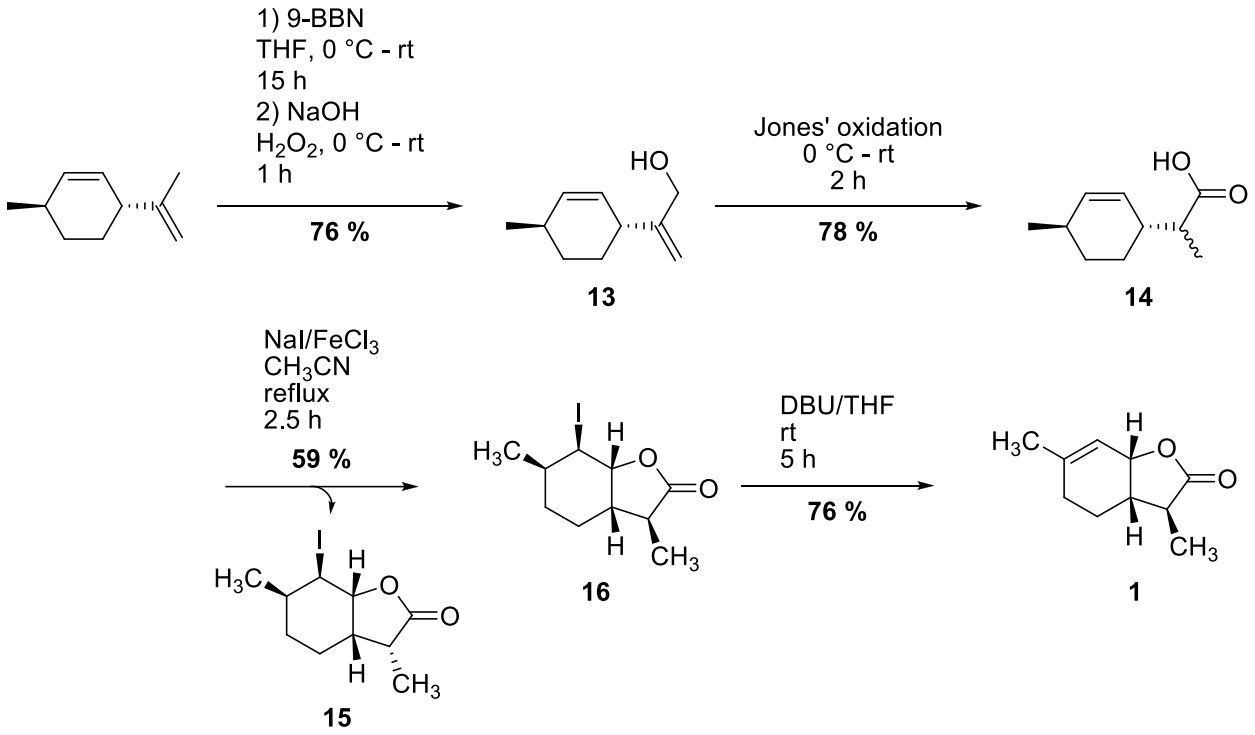

**Scheme 4.** *Synthesis of wine lactone by Bergner and Helmchen*.[5]

Desymmetrisation of *meso* cyclohex-2-enyl acetate **8** was accomplished by formation of a palladium π-allyl complex. A careful choice of chiral ligands on the palladium ensured alkylation of the enantiotopic faces by diethyl malonate occurred in a stereoselective manner. The product was converted to its ester *via* Krapcho decarbomethoxylation then saponified to yield acid **9**. The 5-membered lactone **10** was prepared by iodolactonization and subsequent DBU (1,8-diazabicycloundec-7-ene) induced elimination. $S_N2$ alkylation of the allylic ether moiety with the organocopper reagent prepared from MeMgCl and CuBr·$Me_2S$ yielded the carboxylic acid **11** with the required methyl group installed at C-6. Use of a second iodolactonisation and subsequent DBU induced dehydrohalogenation yielded lactone **12** which was alkylated according to the procedure of Bartlett and Pizzo[4] to give wine lactone **1**.

Though noteworthy as the first enantiomeric preparation of wine lactone, the protracted nature and the necessary destruction of the lactone following the first iodolactonization step encouraged further efforts in the search for an efficient route to wine lactone.

### 1.6.4 Synthesis by Chavan *et al.*[3] (2001)

Appreciating the importance of halolactonisation reactions, Chavan *et al.*[3] used an iodolactonisation reaction as the central step in their chiral pool synthesis of wine lactone (**Scheme 5**):

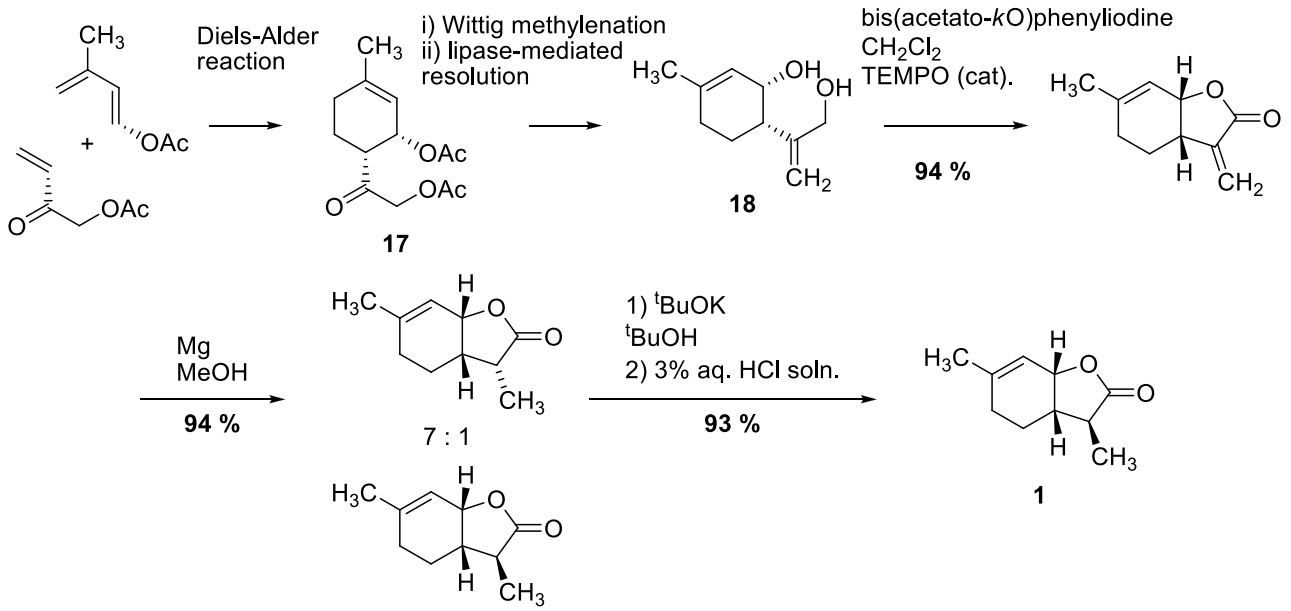



**Scheme 5**. *Synthesis of wine lactone by Chavan et al.*[3]

Starting from readily available (+)-isolimonene, regioselective hydroboration yielded alcohol **13**. Jones' oxidation provided the required acid **14** which was then subjected to the novel iodolactonisation protocol using $FeCl_3$/NaI to afford the iodolactones **15** and **16** in slightly higher yield (59%) compared to the aforementioned protocol using $I_2$ in saturated $NaHCO_3$ (52%). After separating the resultant iodolactone diastereomers, iodolactone **16** was subjected to dehydrohalogenation to furnish the natural wine lactone (**1**).

### 1.6.5 Synthesis by Fuganti and Serra (2004)

A resolution based synthesis by Fuganti and Serras[6] in 2004 offered marginal improvement in terms of scalability over previous syntheses. An *endo* selective Diels-Alder cycloaddition afforded *cis*-substituted cyclohexene **17** as a racemate which, following methylenation, was subjected to lipase resolution to give enantiopure allylic alcohol **18**. Further chemical manipulation yielded the natural wine lactone (**Scheme 6**):




**Scheme 6**. *Synthesis of wine lactone by Fuganti and Serra.*[6]

The enzymatic resolution facilitated an asymmetric synthesis without the need for catalysts or enantiopure starting materials. Adopting this route wine lactone **1** could be accessed in six steps.

In summary, the synthesis of wine lactone has improved consistently over the last 20+ years. This is depicted below (**Figure 1**).

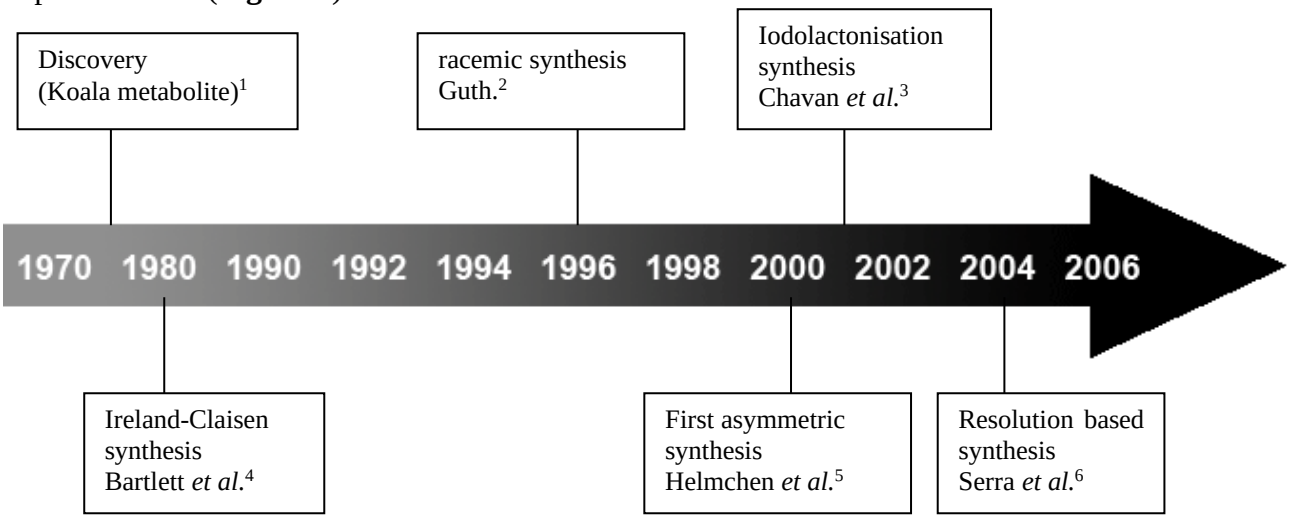



**Figure 1**. *Important developments for the synthesis of wine lactone.*

## 1.7 Proposed novel synthesis of wine lactone

### 1.7.1 The Diels-Alder reaction

The Diels-Alder cycloaddition between a diene and a dienophile is a powerful organic reaction which can involve the formation of up to four new stereogenic centres in one step. A striking feature of the wine lactone structure is the lactone fused cyclohexene moiety – thus hinting at a possible synthesis using an intramolecular Diels-Alder cycloaddition (IMDA). However, conventional wisdom dictates that this cyclohexene system is unattainable *via* cycloaddition chemistry because the necessary precursor (see retrosynthesis **Figure 2**) is not classically activated with an electron withdrawing group (EWG) on the dienophile.

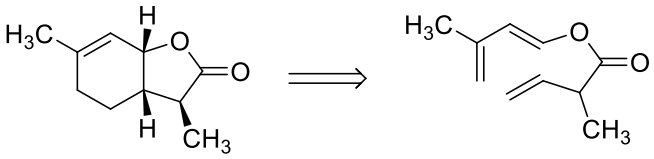



**Figure 2**. *Possible retrosynthesis of wine lactone*

In addition to lowering the energy of the dienophile $\pi^*$ orbital, a carbonyl EWG can $\pi$-$\pi$ interactions with the diene, this is known as secondary orbital overlap and has the effect of lowering the activation energy for the reaction making the cycloaddition kinetically favourable. Although the aforementioned synthesis by Serra *et al.*[20] (*vide supra*) reported the use of a Diels-Alder cycloaddition for the construction of wine lactone, the dienophile in this case did have a conjugated electron withdrawing group.

The IMDA cycloaddition is a reaction wherein a diene and the dienophile moiety present in the same molecule are induced to react. If the diene is joined *via* the terminus to the dienophile then the reaction is termed a Type I IMDA and results in a bicyclic system. Conversely, if the diene is joined *via* the middle to the dienophile then the reaction is termed a Type II IMDA and results in a bridged bicyclic system (**Figure 3**).[21]

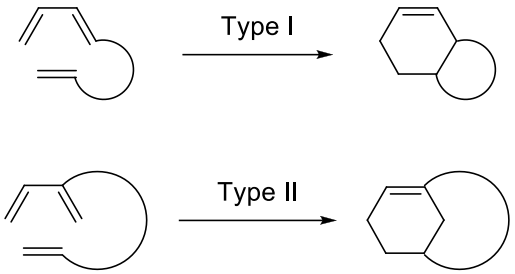
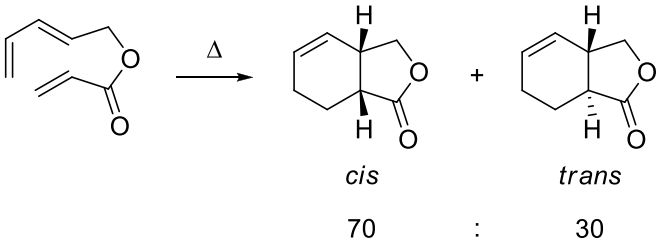



**Figure 3.** *The types of Intramolecular Diels-Alder reaction.*[21]

This simultaneous formation of two new rings allows the assembly of many complex structures. Despite the lack of classical activation we envisaged a Type I intramolecular Diels-Alder (IMDA) cycloaddition would simultaneously install the cyclohexene moiety and the fused five-membered lactone ring in wine lactone.

The formation of fused 5-membered lactones *via* an IMDA cycloaddition was first investigated by Sherburn *et al.*[22] using pentadienyl acrylates (**Scheme 7**). Note that in contrast to the trienes for the proposed wine lactone synthesis (**Scheme 8**), the trienes used in Sherburn's studies are in fact activated by the presence of a carbonyl group conjugated to the dienophile.

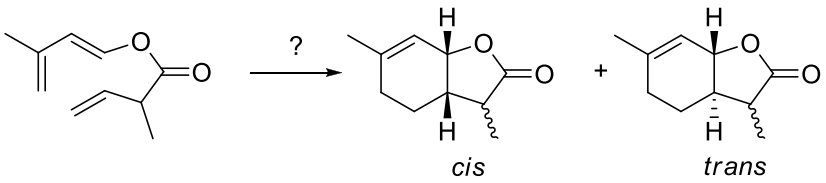



**Scheme 7**. *Sherburn's Lactone IMDA*

Sherburn noted that the above IMDA gave two products- a major *cis* product arising through an *endo* transition state and a minor *trans* product arising through an *exo* transition state. Two opposing effects were thought to influence the transition state energy and thereby govern the isomer distribution ratio. These effects can be summarised with reference to the *cis*-transition state. Firstly,

favourable secondary orbital interactions lead to transition state energy stabilisation, and secondly, torsional strain, specifically $A^{1,3}$- and $A^{1,2}$-strain, about the C4-C5 bond leads to transition state destabilisation.

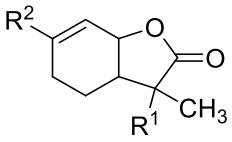
Application of IMDA methodology to the synthesis of wine lactone however, would not involve any form of secondary orbital overlap between the dienophile and the diene, and it was unclear from the outset whether such a reaction would even be feasible. It was anticipated that IMDA cycloaddition would be somewhat activated by the electron donating effect of the vinyl ether. It is noteworthy that such a reaction is thus far unreported in the literature.




**Scheme 8**. *IMDA synthesis of wine lactone*

Paddon-Row *et al.*[22] used the Gaussian 03 computational chemistry programme to calculate the transition state energy differences leading to Sherburn's kinetic Diels-Alder adducts. Paddon-Row's theoretical calculations were in good agreement with the experimentally determined diastereoselectivity indicating the level of theory and basis set RMP2/6-31+G(d)//RB3LYP/6-31+G(d) were well suited to analysis of this IMDA reaction. We hoped to similarly apply computational analysis to the four IMDA transition states leading to the four diastereoisomers comprising the wine lactone family in order to gain insight into the factors governing diastereoselectivity.

### 1.7.2 Proposed routes to the Diels-Alder precursor

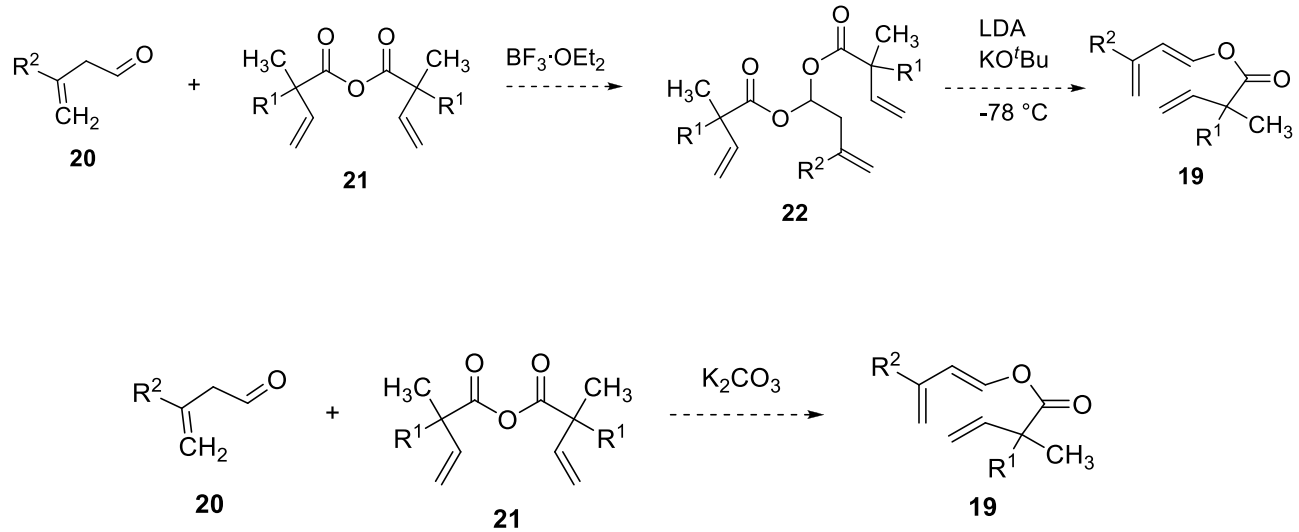


**19**

The investigation into the novel IMDA cycloaddition hinges on the ability to prepare conjugated enol ether **19**. A robust route to this Diels-Alder precursor which allows variation of the R groups should provide easy access to wine lactone and its analogues. Three convergent synthetic pathways were identified to prepare the linear triene precursors and through extensive testing two synthetic routes were found to be viable. These pathways will be described below.

#### 1.7.2.1 First Generation Approach – the Anhydride Route

We initially envisioned preparing the conjugated Diels-Alder precursor **19** by coupling unconjugated enal **20** with an anhydride **21**. Such reactions are reported to be catalysed by both Lewis acid[23] and Bronsted base[24] (**Scheme 9**). In the presence of Lewis acid an aldehyde and an anhydride can form a *gem*-diacyl acetal adduct **22** which was hoped would undergo $E_2$ elimination in the presence of a strong base, such as the Schlosser[25] base, to give the desired linear triene. An alternative and complementary approach relies on the base catalysed coupling of the aldehyde with the anhydride. The latter method is particularly attractive in that the desired acylated enol ether is formed in a single step.

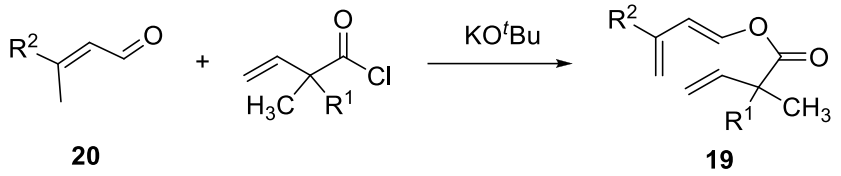



**Scheme 9**. *Acid (above) and Base (below) catalyzed coupling approaches*

Unfortunately, neither of the anhydride-enaldehyde couplings was successful in our model studies (*vide infra*).

### 1.7.2.2 Second generation approach - Acid chloride *O*-acylation

While investigating the preparation of enyne metathesis precursors, Beller *et al.*[26] reported a general method for *O*-acylation by coupling acid chlorides with aldehyde enolates, themselves generated *via* reaction with potassium *tert*-butoxide. Application of this method to the construction of wine lactone Diels-Alder precursors is illustrated **(Scheme 10)**.

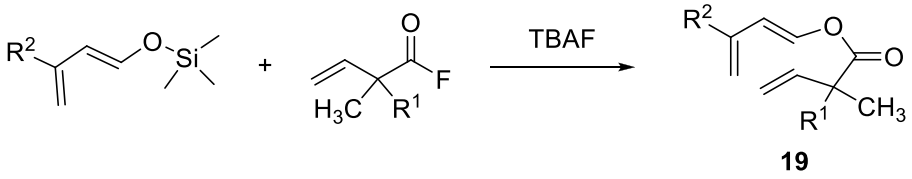



**20** **19**

**Scheme 10**. Putative potassium *tert*-butoxide mediated *O*-acylation

### 1.7.2.3 Third generation approach - Acid fluoride coupling

Schlosser and Limat[27] reported the *O*-acylation of acid fluorides by treatment of trimethylsilyl enol ethers with catalytic tetrabutylammonium fluoride. In this case, the fluoride mediated desilylation of the enol gives a charge separated enolate. The 'naked' enolate anion is preferentially *O*-acylated by the acyl fluoride which releases a fluoride anion in the process thereby propagating the catalytic cycle. This route, illustrated in **Scheme 11**, is advantageous in that the stereochemistry adjacent to the carbonyl group is preserved during the reaction. Due to the mild conditions and preservation of stereochemistry this method has found wide application in peptide synthesis.[28]



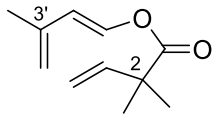

**19**

**Scheme 11**. *Putative TBAF mediated O-acylation*

It was envisioned that these routes would allow easy access to the bis-acyl enol-ether Diels-Alder precursors with different substitution patterns. Adoption of these synthetic routes would enable the synthesis of wine lactone and analogues thereof, using a novel intramolecular Diels-Alder reaction.

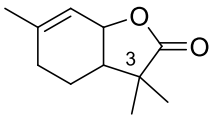
# Chapter 2. Results and Discussion; Diels-Alder precursor synthesis

### 2.1.1 Attempted preparation of model dimethyl lactone 25 *via* anhydride coupling




**24**

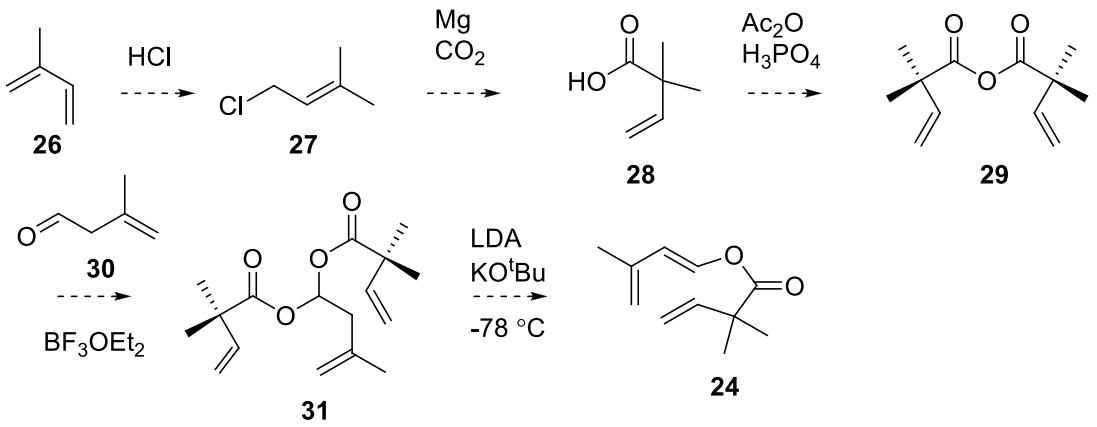
This section describes the efforts undertaken to synthesize *gem*-dimethyl wine lactone precursor **24** using an anhydride-aldehyde coupling as the key step. Although the required anhydride and aldehyde were prepared, the pivotal coupling reaction proved elusive and this approach was ultimately abandoned.




**25**

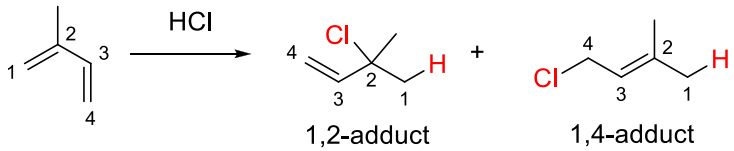
C3-Dimethyl wine lactone **25** was our first investigative target for synthetic efforts towards natural wine lactone **1**. It was thought the extra methyl group at C3 would render purification easier by raising the boiling point of the low molecular weight lactone. Enolisation of the lactone and potential formation of ketenes would also be avoided by incorporation of a *gem*-dimethyl group. *Gem*-dimethyl substituted triene **24** would also serve as a model compound to investigate the Intramolecular Diels-Alder reaction as cyclization would be kinetically favoured by the Thorpe Ingold (*gem*-dimethyl) effect.[29] The synthesis of **25** was therefore undertaken to serve as a guide for the key intramolecular Diels-Alder transformation thus initial attention focussed on the synthesis of model triene **24**.

It is known that anhydrides react with aldehydes under acidic[23] conditions to form symmetrical *gem*-diacyl acetals. It was hoped that E2 elimination of a suitable functionalised diacyl acetal catalyzed by Schlosser base[25] would generate the desired acyl enol ether. Towards that end, multi gram scale preparation of anhydride was initiated. Anhydride **29** could be derived from carboxylic acid **28** which in turn was prepared by Grignard reaction of prenyl magnesium chloride with $CO_2$. Prenyl chloride is prepared from isoprene (**26**) (**Scheme 12**).




**Scheme 12**. *Proposed synthetic route to model triene **24***

An initial attempt to convert isoprene **26** to prenyl chloride (**26**) *via* addition of dry hydrogen chloride gas as advocated by Chorley and Jones[30] only proceeded in poor yield (**Method A, Table 2**). However using concentrated hydrochloric acid with sodium chloride[31] the yield was significantly improved (**Method B**, **Table 2**). It was noted in the patent that fractional distillation of the crude product gave both prenyl chloride (1,4-adduct) and isomeric products. It was also noted that inclusion of the isomeric by-products in the reaction mixture resulted in a higher yield than would otherwise have been obtained. Therefore the reaction mixture from the failed Chorley and Jones attempt was added to the reaction vessel (**Method C, Table 2**) to afford a high yield of the desired 1,4-adduct (79%). These results are summarized below (**Table 2**).



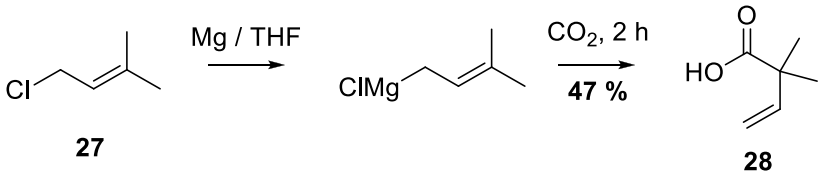

**26** **32** **27**

| Method | Reagents | Yield (1,4-adduct) |
|---|---|---|
| Chorley and Jones (**A**) | HCl (g) + isoprene | not determined |
| Levy *et al.*[31] (**B**) | HCl (aq) + NaCl | 43% |
| Levy *et al.*[31] (**C**) | HCl (aq) + NaCl + Fractional by-products | 79% |

**Table 2**. *Conversion of isoprene (**26**) to prenyl chloride (**27**)*

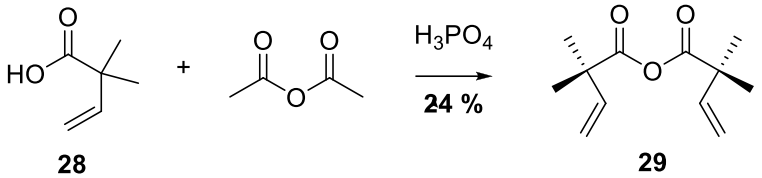
The high yield afforded by the batchwise patented procedure can be accounted for by three factors; firstly by the presence of unreacted isoprene in the fractionation by-products; secondly by the presence of the desired prenyl chloride in the reaction fractionation by-products and thirdly, by the presence of structural isomers and by-products such as dichloro-3-methylbutane in the reaction fractionation by-products. If the presence of undesired isomers from the fractional distillation of the previous batch increases the yield of subsequent batchs it would imply that prenyl chloride is the thermodynamic product of a reversible reaction.

With prenyl chloride in hand, the necessary Grignard reagent required to prepare acid **28** was next prepared.[32] Prenyl chloride (**27**) was reacted with activated magnesium in anhydrous tetrahydrofuran to afford the Grignard reagent. Due to the exothermic nature of the reaction prenyl chloride (**27**) was added in a slow controlled manner to maintain gentle reflux. The Grignard reagent was quenched with dry $CO_2$ with the $CO_2$ being passed through a calcium oxide drying tube prior to introduction to the reaction mixture. Workup of the crude material as described by Miller and Kwart[32] followed by distillation of the crude material yielded the desired carboxylic acid **28** in 47% yield **(Scheme 13)**.




**Scheme 13**. *Preparation of the carboxylic acid **28***

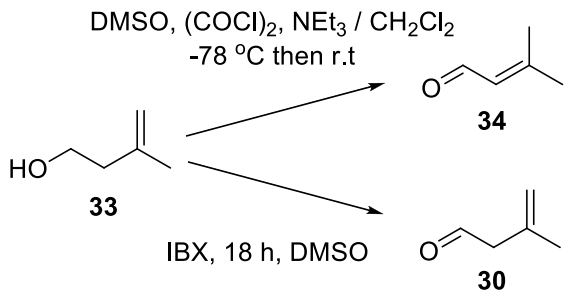
Treatment of the acid **28** with acetic anhydride (1.1 equiv) in the presence of catalytic phosphoric acid followed by immediate distillation afforded a modest yield (24%) of the desired anhydride **29**.[33]




**Scheme 14**. *Preparation of the anhydride **29***

With anhydride **29** in hand, attention next focused on the preparation of aldehyde **30**. Although it was envisioned that aldehyde **30** would be prepared by Swern oxidation of alcohol **33**, Swern oxidation unexpectedly yielded the conjugated alcohol **34** (**Scheme 15**). Presumably conjugation to the thermodynamically favoured $\alpha,\beta$-enal occurred due to *in situ* liberation of HCl.

Vederas and Scholte[34] noted this problem in their preparation of alcohol **30** using PCC. Following their suggestion, use of the milder IBX oxidant was adopted **(Scheme 15)**. Non-aqueous work-up as described by Vederas and Scholte yielded the desired aldehyde **30** which was used without further purification.

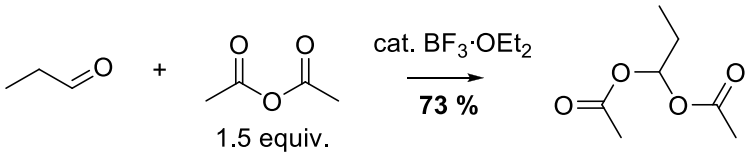



**Scheme 15**. *Oxidation of alcohol **33***

The successful preparation of anhydride **29** and aldehyde **30** allowed subsequent investigation of the critical coupling step to form the required Diels-Alder precursor.

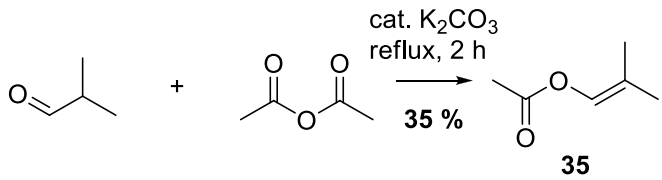
### 2.1.2 Attempted coupling of aldehyde 30 and anhydride 29.

Two different and complementary approaches for coupling aldehydes with anhydrides were appropriate for the present work. Hauser and Sanderson[23] described the Lewis acid catalyzed addition of aliphatic anhydrides to aldehydes to form bisacetylated acetals using propionaldehyde and acetic anhydride (**Scheme 16**).



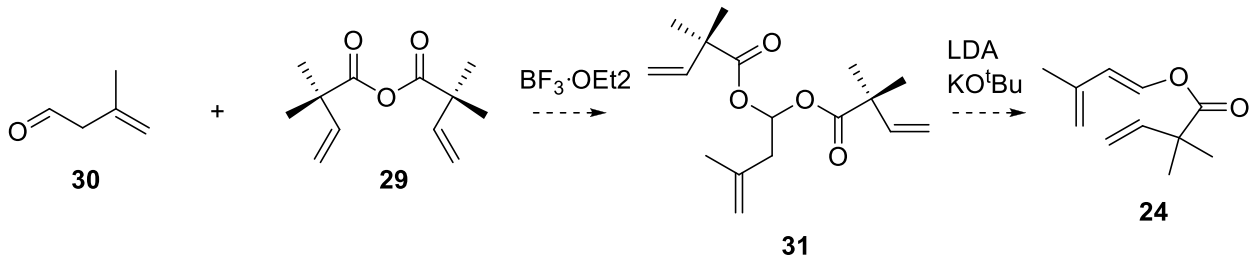

**Scheme 16**. *Acidic coupling protocol*

Benezra and Barbier[24] meanwhile reported coupling of isobutyraldehyde to acetic anhydride in the presence of a catalytic quantity of basic potassium carbonate to yield enol acetate **35** (**Scheme 17**). This method is particularly attractive as the desired acyl-enol ether is made in a single step.

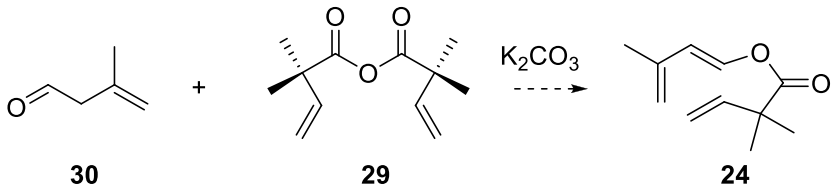



**Scheme 17**. *Basic coupling protocol*

By coupling prepared aldehyde **30** and anhydride **29** using the aforementioned $BF_3{\cdot}OEt_2$ approach *gem*-diacetate **31** would be accessed that could undergo $E_2$ elimination to give the desired triene (**Scheme 18**). If the $K_2CO_3$ approach were used, treatment of aldehyde **30** with $K_2CO_3$ and anhydride **29** would directly yield the desired triene **24** (**Scheme 19**).




**Scheme 18**. *Desired aldehyde anhydride coupling mediated by $BF_3{\cdot}OEt_2$ followed by E2 elimination*




**Scheme 19**. *Direct route to triene **24** via reaction mediated by $K_2CO_3$*

A summary of the attempts to couple of aldehyde **30** with anhydride **29** is presented in **Table 3**. Unfortunately, both the acidic ($BF_3{\cdot}OEt_2$) and basic ($K_2CO_3$) coupling protocols failed to deliver the desired adducts (**Entry 1, 2, Table 3**). Returning to the acid-mediated approach, efforts were made to establish a working model of the reaction. 2-Phenylacetic anhydride (**37**) was prepared to serve as the model anhydride and this was coupled with butyraldehyde (**36**) using 0.8 equivalents of $BF_3{\cdot}OEt_2$ (**Entry 3, Table 3**). This model reaction was also unsuccessful. A report by Hauser and Sanderson[23] noted using an excess of Lewis acid was not detrimental to the reaction and this prompted use of an increase in catalyst loading. Pleasingly, use of excess catalyst afforded the desired product in 30% yield (**Entry 4, Table 3**).

Having established a successful model, the same strategy was applied to the reaction of aldehyde **30** with anhydride **29** (**Entry 5, Table 3**). Disappointingly, this reaction was unsuccessful. Given the success of the model reaction (*vide infra*), we attributed the lack of reactivity to the steric hindrance of the carbonyl group of the anhydride due to the presence of the neighbouring geminal dimethyl group.

Base mediated acylation reactions using conjugated aldehyde **34** and acid chloride **38** catalyzed by triethylamine (**Entry 6, Table 3**) and LDA (**Entry 7, Table 3**) were next attempted. The acid

chloride was prepared by treatment of the carboxylic acid with phosphorus trichloride. Unfortunately, all attempts to effect these base-mediated reactions of aldehyde **34** with acid chloride **38** were unsuccessful.

It was originally postulated that use of an anhydride or an acid chloride as the acylating agent would promote the required *O*-acylation of the enol of aldehyde **30** or **34**. However failure of this key reaction prompted re-evaluation of this strategy. The anhydride route was therefore abandoned and a new approach was devised to prepare the model triene **24**.

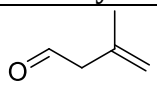
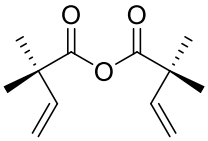
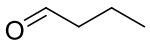
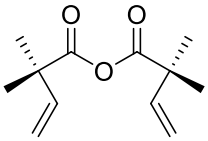
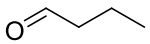
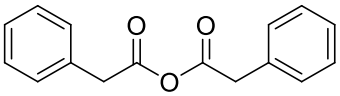
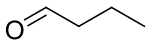
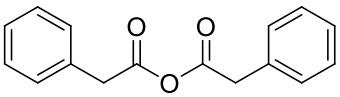
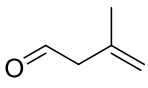
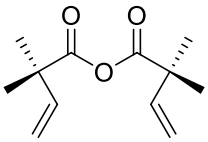
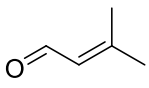
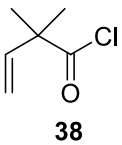
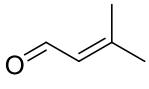
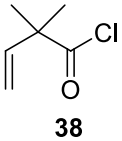
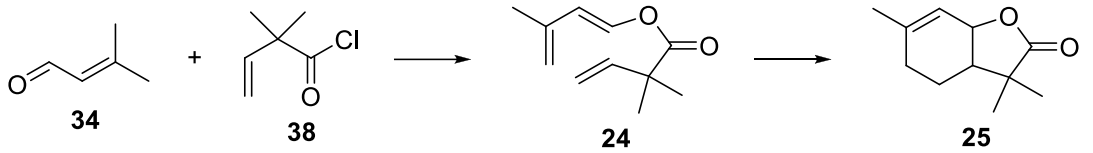
| Entry | Aldehyde | Anhydride or Acid chloride | Reaction Conditions | Yield (%) |
|---|---|---|---|---|
| 1 |  **30** |  **29** | $BF_3{\cdot}OEt_2$ (0.1 equiv)<br>-78 °C<br>$CH_2Cl_2$ | N.R |
| 2 |  **36** |  **29** | $K_2CO_3$<br>130 °C<br>neat | N.R |
| 3 |  **36** |  **37** | $BF_3{\cdot}OEt_2$ (0.8 equiv)<br>0 °C<br>$CH_2Cl_2$ | N.R |
| 4 |  **36** |  **37** | $BF_3{\cdot}OEt_2$ (excess)<br>-78 °C<br>$CH_2Cl_2$ | 30 |
| 5 |  **30** |  **29** | $BF_3{\cdot}OEt_2$ (excess)<br>-78 °C<br>$CH_2Cl_2$ | N.R |
| 6 |  **34** |  **38** | LDA (2 equiv.)<br>-78 °C<br>$CH_2Cl_2$ | N.R |
| 7 |  **34** |  **38** | $NEt_3$ (2 equiv)<br>$ZnCl_2$ (catalytic)<br>diethyl ether | N.R |

**Table 3**. *Attempted coupling reactions*

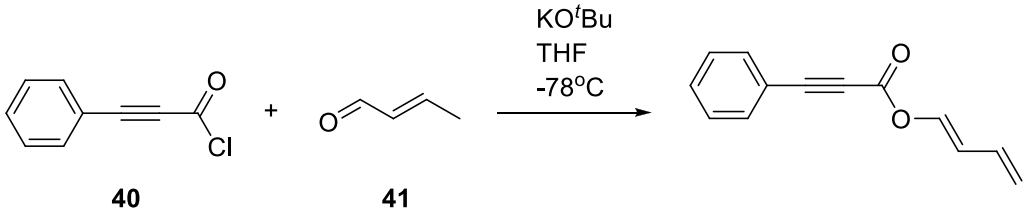
## 2.2 Preparation of model dimethyl lactone 25 *via* reaction with an acid chloride using potassium *tert*-butoxide




This section describes the successful efforts undertaken to prepare the geminal dimethyl linear triene **24** by *O*-acylation of an aldehyde with an acid chloride mediated by potassium *tert*-butoxide. From the linear triene **24** dimethyl wine lactone **25** was successfully prepared establishing that the novel intramolecular Diels-Alder reaction was indeed feasible.

### 2.2.1 Potassium *tert*-butoxide mediated acylation of aldehyde 34

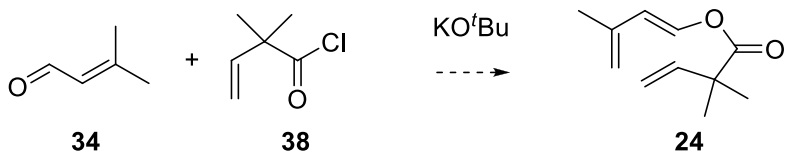
Conventional wisdom dictates that enolates predominantly undergo *C*-acylation with acid chlorides.[35] However, this trend can be reversed by the appropriate choice of enolate, electrophile, solvent and cation. Beller *et al.*[26] described the *O*-acylation of crotonaldehyde (**41**) by acid chloride **40** in a reaction mediated by potassium-*tert* butoxide with tetrahydrofuran as the solvent (**Scheme 25**).




**Scheme 25**. *Bellter et al. acylation of crotonaldehyde (**43**)*

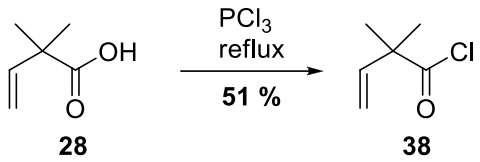
It is thought that use of an electropositive potassium cation gives the enolate more ionic character and this combined with use of a polar solvent such as tetrahydrofuran allows the enolate anion to exist separately from the potassium cation. This "naked" enolate anion with its negative charge localised on oxygen is free to react with the acylating agent giving rise to the desired *O*-acylated product.[35] The low temperature of the reaction also ensures that the kinetic *O*-acylation is favoured over the thermally favoured *C*-acylation.

Given the unsuccessful implementation of the original route to linear triene **24**, it was hoped that an alternative approach to prepare the Diels-Alder precursor by coupling an aldehyde enolate with an acid chloride would prove successful. By coupling aldehyde **34** and acid chloride **38** in presence of potassium *tert*-butoxide, linear triene **24** could be accessed (**Scheme 20**).



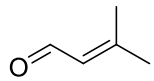

**Scheme 20**. *Foreseen route to linear triene **24** via Beller et al.*[26] *approach*

Acid chloride **38** was prepared by heating acid **28** under reflux with an excess of $PCl_3$. Subsequent distillation yielded the acid chloride in modest yield (**Scheme 21**).[26] Although phosphorus trichloride is relatively hazardous, the facile reaction procedure and the ready availability of this reagent rendered this approach more attractive than use of other chlorinating agents such as $SOCl_2$ which was unavailable at the time. Having the required acid chloride **38** in hand, methods to prepare aldehyde **34** were next investigated.



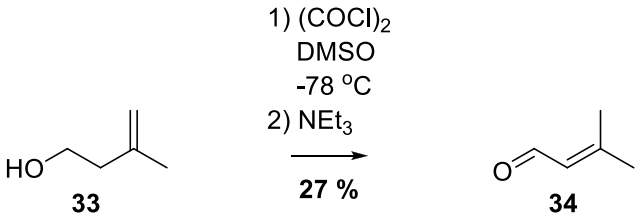

**Scheme 21**. *Preperation of acid chloride **38***

### 2.2.1 Preparation of 3-methylbut-2-enal



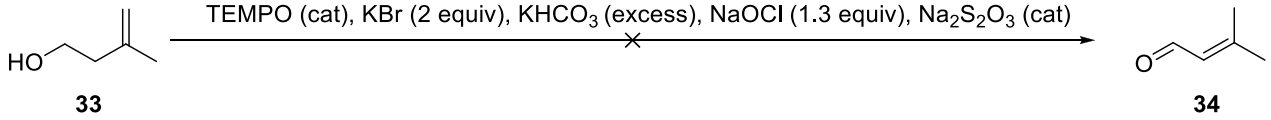
**34**

3-Methylbut-2-enal (**34**) was the other key starting material. It was previously noted that Swern oxidization of alcohol **33** yielded this conjugated aldehyde. Curiously a literature search using the Beilstein database did not reveal this Swern oxidation protocol as a method to achieve this transformation. Many examples of chromium mediated oxidations of alcohol **33** however, have been reported. Chromium reagents were not investigated due to safety and toxicity concerns. Despite several attempts the Swern oxidation of alcohol **33** only proceeded in low yield (**Scheme 22**).



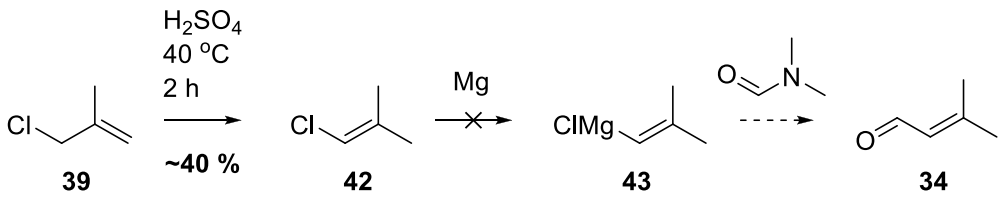

**Scheme 22**. *Swern oxidation of alcohol **33** to yield conjugated aldehyde **34***

Determined to find a high yielding route to conjugated aldehyde **34** TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) mediated hypochlorite oxidation was next attempted without success. **(Scheme 23)**




**Scheme 23**. *Attempted TEMPO mediated hypochlorite oxidation of alcohol **33***

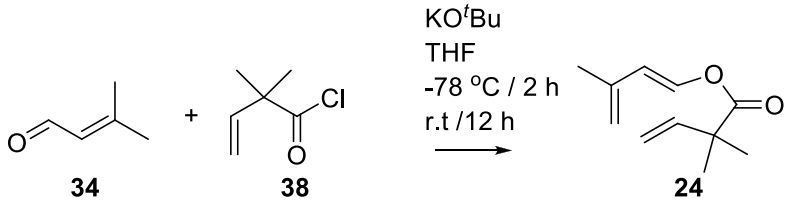
An alternative method relying on indirect carbonylation of an appropriate Grignard reagent **43** was also investigated in an effort to provide the necessary aldehyde. (**Scheme 24**).




**Scheme 24**. *Attempted preparation of aldehyde **34**.*

The literature procedure requires use of 1-bromo-2-methylprop-1-ene. However access to only 3-chloro-2-methylprop-1-ene (**39**) was available. Unfortunately the necessary organomagnesium reagent was unable to be formed using the less reactive chloride. In light of the inability to prepare the required Grignard reagent attempts to prepare aldehyde **34** were abandoned and the required aldehyde **34** was purchased from Sigma-Aldrich. 3-Methylbut-2-enal is prepared on an industrial scale by transition metal catalyzed direct carbonylation of olefin precursors at high temperatures and pressures.

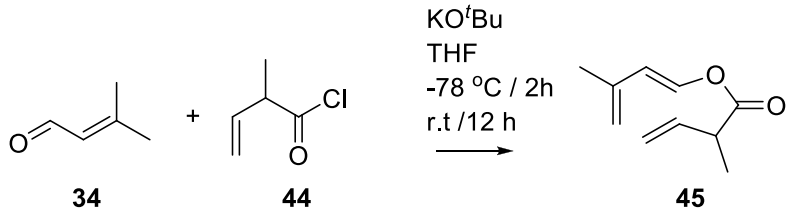
With the aldehyde **34** and acid chloride **38** at hand dimethyl linear triene **24** was synthesised. To prepare the aforementioned linear triene freshly sublimed potassium *tert*-butoxide was dissolved in tetrahydrofuran and cooled to – 78 °C. A solution of aldehyde **34** in tetrahydrofuran was then added *via cannula*. A separate solution of acid chloride **38** in tetrahydrofuran cooled to -78 °C was prepared and added to the aldehyde enolate solution *via cannula*. The reaction mixture was stirred at – 78 °C for 2 h and then warmed to room temperature and stirred for a further 12 h (**Scheme 26**). Work-up of the reaction mixture furnished the desired linear triene **24** containing several impurities.




**Scheme 26**. *Successful preparation of linear triene **24**. Yield not determined*

Although this reaction proceeds to give the desired product, purification of the mixture *via* flash chromatography was challenging due to the presence of numerous byproducts, the reactivity of the acyl-enol ether and the volatility of the product. The outcome of the reaction was thus determined over 2 steps by submission of the crude material to elevated temperatures thereby inducing the desired Diels-Alder cycloaddition (*vide infra*).

The potassium aldehyde enolate method was next applied to the synthesis of linear triene **45**, the precursor required to afford the natural wine lactone (**Scheme 27**). Although viable, this method was also complicated by the formation of side products. An improved method for the synthesis of linear trienes is described in the next section.

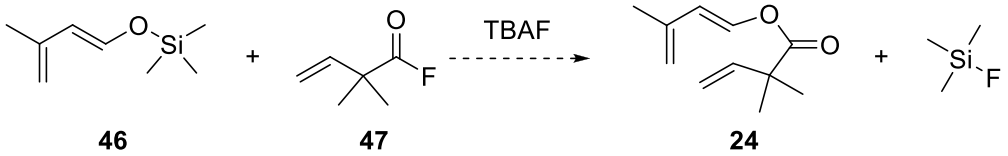



**Scheme 27**. *Successful preparation of a different linear triene **45**. Yield not determined*

## 2.3 Preparation of model dimethyl lactone 25 *via* coupling a silyloxydiene with an acid fluoride

This section describes the successful efforts undertaken to prepare the geminal dimethyl linear triene **24** by coupling an acid fluoride with a silyloxydiene catalyzed by tertrabutylammonium fluoride (TBAF). The ready access to linear triene **24** using this protocol facilitated the investigation of subsequent Diels-Alder adducts to furnish wine lactone and analogues thereof.

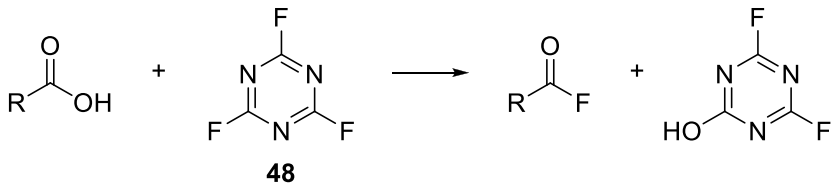
Schlosser and Limat[27] reported a method to generate "naked enolates" *via* deprotection of silyl enol ethers with catalytic amounts of tetrabutylammonium fluoride. Exclusive *O*-acylation was then effected by reaction of the naked enolates with acyl fluorides. It was thus envisioned that dimethyl model triene **24** could be prepared using this approach (**Scheme 28**).




**46** **47** **24**

**Scheme 28**. *Potential route to linear triene **24***

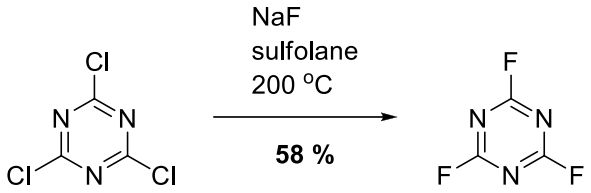
An efficient method to prepare the acid fluoride was the immediate concern. Having prepared carboxylic acid **28** a method to convert the acid to an acid fluoride was required. Cyanuric fluoride (**48**) has been described by Nubbemeyer[36] to be one of the most popular fluorinating agents used in organic synthesis. Indeed the relatively non-hazardous nature of cyanuric fluoride compared to conventional fluorinating agents such as hydrogen fluoride provided a convenient method to access acid fluorides obviating the need for specialised glassware (**Scheme 29**).




**48**

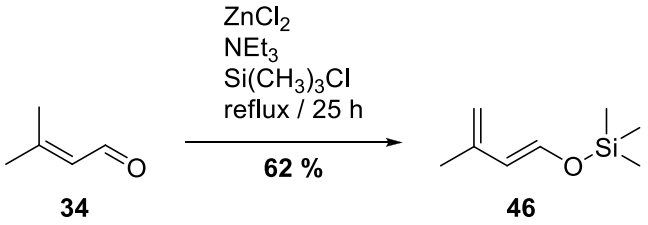
**Scheme 29**. *General preparation of acyl fluorides*

Following Nubbemeyer's procedure cyanuric fluoride was prepared from cyanuric chloride, sodium fluoride (6 equiv.) and sulfolane (8 equiv.) (**Scheme 30**). It was found that use of 8 molar equivalents of sulfolane as suggested by Nubbemeyer is critical for successful reaction. Use of 2 or less equivalents of sulfolane results in formation of a thick brown paste. It should also be noted that any glassware used in this preparation becomes etched.



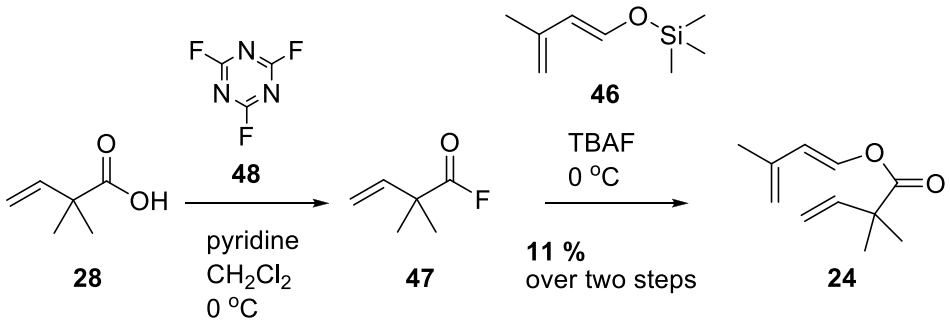

**Scheme 30**. *Preparation of cyanuric fluoride*

Having successfully obtained cyanuric fluoride it was decided to prepare the required trimethylsilyloxydiene. Aldehyde **34** was deprotonated using triethylamine catalyzed by zinc chloride. Careful addition of trimethylsilyl chloride afforded the trimethylsilyloxydiene in 62% yield (**Scheme 31**). This material was found decompose over several days at room temperature and was therefore stored in a fridge and used as soon as possible.




**Scheme 31**. *Preparation of TMS protected aldehyde **46***

With trimethylsilyloxydiene **46** and acid **28** in hand, investigation of the critical coupling reaction was possible. It was devised to generate the acid fluoride '*in situ*' and react it immediately with the trimethylsilyloxydiene to yield the linear triene **24 (Scheme 24)**. Pleasingly, both the coupling reaction and purification of the crude material were achievable and the desired triene **24** was afforded in modest unoptimised 11% yield. The yield for this transformation was considerably improved when preparing other analogues.

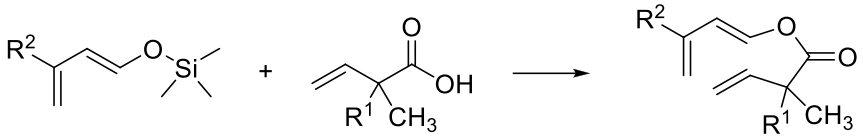



**Scheme 32.** *Preperation of linear triene **24***

Linear triene **24** was next heated in toluene at 250 ºC for 8 h thus effecting cycloaddition to lactone **25** (*vide infra*). Having established proof of concept for the intramolecular Diels-Alder cycloaddition and having established a facile method to prepare the Diels-Alder precursor, efforts were next turned to the synthesis of wine lactone precursor **45** and analogues thereof.

### 2.3.1 Facile synthesis of wine lactone and analogues thereof.

With a viable route to linear trienes in hand, the synthesis of analogues was next undertaken in order to investigate the subsequent novel intramolecular Diels-Alder cycloaddition. For the purposes of this investigation the scope of the study was limited to the synthesis of racemic analogues wherein $R^1$ = H or $CH_3$ and $R^2$ = H or $CH_3$ (**Scheme 33**) thus providing four racemic trienes. (**Table 4**).




**Scheme 33.** *Postulated synthesis of analogues*

As well as providing valuable insight into the diastereoselectivity and stereochemical factors governing the intramolecular Diels-Alder reaction, the analogues of wine lactone have potential to be novel odorants. Whilst incorporation of additional substituents would result in less volatile lactones small changes such as the addition, substitution or removal of a methyl or methylene group would likely retain the odour characteristics of the natural product, wine lactone **1**. **(Table 4)**;

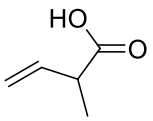
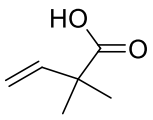
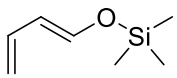
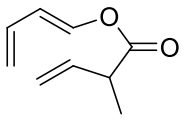
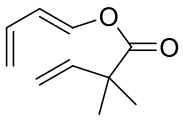
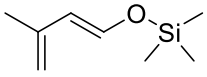
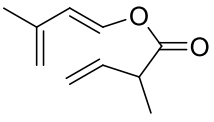
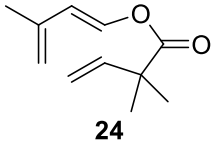
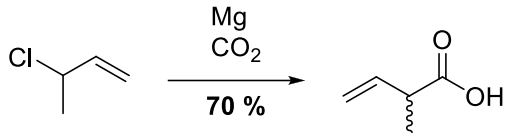
| silyl enol ether \ carboxylic acid |  **49** |  **28** |
|---|---|---|
|  **50** |  **51** |  **52** |
|  **46** |  **45** |  **24** |

**Table 4** *Punnet square illustration of the analogues accessible*

### 2.3.2 Preparation of 2-methylbut-3-enoic acid and 1-trimethylsilyloxybuta-1,3-diene

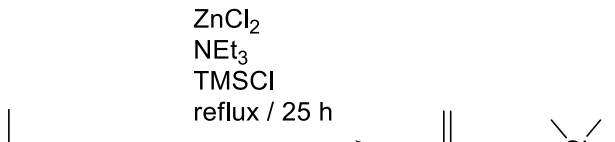
The required 2-methylbut-3-enoic acid (**49**) and 1-trimethylsilyloxybuta-1,3-diene (**50**) were prepared in large gram scale quantities. The acid was prepared by Grignard reaction of halide **53** with carbon dioxide (**Scheme 34**).[37]




**53** **49**

**Scheme 34**. *Gringard reaction of halide **53** in preparation of 2-methylbut-3-enoic acid*

1-trimethylsilyloxybuta-1,3-diene (**50**) was prepared by reaction of deprotonated crontonaldehyde with trimethylsilyl chloride (**Scheme 35**).[38]




**43** **50**

**Scheme 35**. *Preparation of silyl enol ether **50***

### 2.3.3 Versatile, efficient and swift; acid fluoride / silyloxydiene couplings

Having acquired the required starting materials for analogue production, the previously explored coupling approach was duly applied to the combination of acids and silyloxydienes mentioned (**Table 4**). The results are summarized below (**Table 5**).

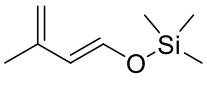
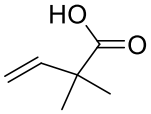
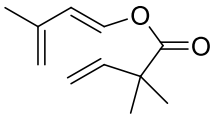
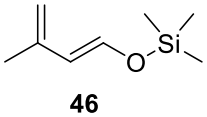
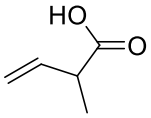
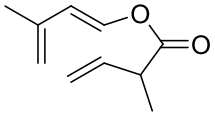
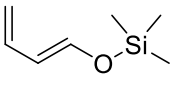
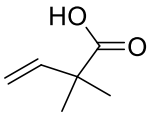
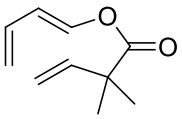
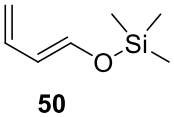
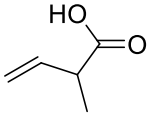
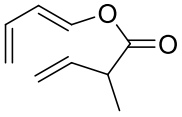
| Silyloxy diene | Acid | Reaction Conditions | Product | Yield |
|---|---|---|---|---|
|  **46** |  **28** | 1) **28**, pyridine, cyanuric fluoride, $CH_2Cl_2$, 0 ºC, 2 h 2) **46**, TBAF, 0 ºC, $CH_2Cl_2$, 2 h |  **24** | 11% |
|  **46** |  **49** | 1) **49**, pyridine, cyanuric fluoride, $CH_2Cl_2$, 0 ºC, 2.5 h 2) **46**, $CH_2Cl_2$, 0 ºC, 2 h |  **45** | 23 % |
|  **50** |  **28** | 1) **28**, pyridine, cyanuric fluoride, $CH_2Cl_2$, 0 ºC, 2 h 2) **50**, TBAF, 0 ºC, THF, 2 h |  **52** | 32 % |
|  **50** |  **49** | 1) **49**, pyridine, cyanuric fluoride, $CH_2Cl_2$, 0 ºC, 2 h 2) **50**, TBAF, 0 ºC, $CH_2Cl_2$, 2 h |  **51** | 70 % |

**Table 5**. *Acid fluoride & silyloxy diene coupling reactions*

The varying yields can be accounted for by two factors; firstly by the dimethyl group on acid **28** which resulted in modest yields due to the steric hindrance around the acidic group provided by the geminal dimethyl group. This is thought to render the acid resistant to fluorination by cyanuric fluoride. Second is by the slow destruction of cyanuric fluoride under storage. The resulting white precipitate is described by Nubbemeyer *et al.*[36] and redistillation was recommended to overcome this problem.

The striking feature of this protocol is the easy accessibility of the linear triene. No undue demands are placed in the set up, work-up, quench or purification procedures of the coupling reaction. Though synthesis of cyanuric fluoride is a demanding undertaking the reagent is readily available from commercial sources. With the appropriate acid and silyloxydiene at hand this approach allowed access to any linear triene and its corresponding lactone in a single extended laboratory session. If preparation of a library of wine lactone analogues is desired it is felt that the procedure described herein lends itself well to combinatorial chemistry methods.

In conclusion, following the identification of a viable method to synthesize the Diels-Alder precursor, the versatility and efficiency of this approach was confirmed through rapid synthesis of three other Diels-Alder precursors. This was invaluable in the study of the intramolecular Diels-Alder reaction described in the next section.

# Chapter 3. Results and Discussion; Intramolecular Diels-Alder reaction

## 3.1 The Intramolecular Diels-Alder reaction

This section begins by describing the optimisation of conditions used to facilitate the key cycloaddition. This section is followed by a review of the results which is discussed in three separate sections; The first part will deal with the assignment of the relative stereochemistry of the Diels-Alder adducts by $^{1}H$ NMR resonance, the second part discusses the diastereoselectivity of the Diels-Alder reaction as revealed by GC/MS analysis and the third part discusses the confirmation of the experimental findings and its implications aided by application of computational chemistry.

In a normal Diels-Alder reaction, cycloaddition is activated by raising the HOMO of the diene and lowering the LUMO of the dienophile; the latter often being accomplished by conjugation of a carbonyl group on the dienophile which has the added advantage of inducing secondary orbital interactions leading to *endo* diastereoselectivity. Because the wine lactone scaffold does not afford this possibility it was presumed that the Diels-Alder reaction would be difficult. Harsh thermal conditions were considered necessary and to supply the thermal energy it was decided to undertake the reactions in a microwave vessel at elevated temperature and pressure.

Microwave assisted reactions are advantageous as traditional application of heat involves exterior heating of the reaction vessel by an exterior heating device.[39] Although the existence of a "microwave effect" is debatable, it has been postulated that microwave irradiation can lead to rate enhancements through the formation of microscopic or macroscopic hotspots.[40] Sophisticated modern microwave reactors can carefully control and monitor the desired reaction temperature and if required pressurize the reaction vessel to allow higher reaction temperatures which would be traditionally unobtainable.

### 3.1.1 Optimisation of reaction conditions

Having decided to undertake a microwave-assisted reaction two parameters needed to be optimised, the temperature and reaction solvent. After several experiments the optimal solvent identified was toluene. The solubilizing properties of toluene and its high boiling point (110.6 °C) rendered it a ideal solvent. Other solvent systems and temperatures were inadequate. These are summarized below (**Table 6**).

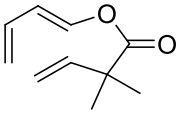
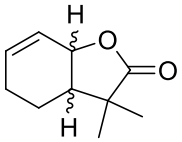
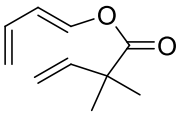
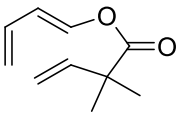
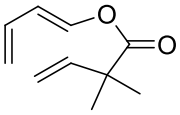
| D/A Precursor | Solvent | Boiling point of solvent (°C) | Temperature attained (°C) | Time (h) | Result |
|---|---|---|---|---|---|
|  | Toluene | 100.6 | 180 | 12 h |  (yield undetermined) |
|  | $CCl_4$ | 76.7 | 180 | 12 h | Complicated Mixture |
|  | *n*-Pentane | 36.1 | 150 | 12 h | No change, starting material isolated |
|  | *n*-Decane | 174.1 | 235 | 12 h | Complicated Mixture |

**Table 6.** *Optimisation of the conditions for the cycloaddition*

A significant drawback of toluene however is that its high boiling point hinders purification efforts. The high volatility of wine lactone and its analogues mean removing solvent *in vauco* is difficult. The devised protocol to address these challenges is described below.

### 3.1.2 Wine lactone purification protocol

The use of toluene as reaction solvent required development of a protocol to separate the toluene from the volatile lactones. The overriding elementary problem was that removal of toluene *in vauco* resulted in loss of the lactone. Separating the toluene entirely by flash chromatography proved to be unpractical due to the amount of silica and solvent needed. It was also determined that use of hexanes or ethyl acetate as eluent is undesirable due to its low volatility. Pentane and diethyl ether proved to be amendable eluents as they could be separated from the lactones at room temperature and pressure.

The optimised purification protocol firstly involves a careful distillation of the toluene at atmospheric pressure using the Kugelrohr distillation apparatus to concentrate the lactones. The resultant crude residue was then purified *via* flash column chromatography using pentane : diethyl ether as eluent. The residue is first flushed with pentane to remove the toluene. The fractions then can be collected with the appropriate eluent. For characterisation purposes the purified fractions were always left overnight for the eluent to evaporate away.

It is suspected that a significant amount of lactone is lost during the distillation process. The general difficulty associated with the diastereomeric separation and purification made determination of the yield challenging. For this reason the yields of the Diels-Alder reaction is not reported here.

### 3.1.3 Total synthesis of wine lactone and analogues

Model triene **24** was the first compound to be subjected to the intramolecular Diels-Alder reaction. As described it was hoped the presence of the *gem*-dimethyl group would help the cycloaddition to take place. 0.13 g of triene **24** was placed in the microwave and heated at 200 ºC for 6 h. Two diasteromers were isolated and purified (**Entry 1**, **Table 7**).

The wine lactone precursor **45** was subjected to same conditions. Significant amounts of the starting material could still be detected by thin liquid chromatography (TLC). It is suspected the absence of the *gem*-dimethyl group and the consequent absence of the Thorpe-Ingold *Effect* require longer reaction times. The reaction was therefore allowed to react for longer with satisfactory results (**Entry 2**, **Table 7**). Similar reaction conditions were required for the other wine lactone analogue **51** which is without the *gem*-dimethyl group. These account for the differing reaction times; analogues without the gem-dimethyl group were allowed to react longer. The abnormal reaction time allowed for linear triene **52** was due to microwave malfunction.

In some cases linear triene had to be prepared afresh; it is suspected the labile enol-ester linkage is exceptionally prone to hydrolytic cleavage. Owing to the easy accessibility to the linear triene this proved not to be a problem. The varying reaction temperatures are mostly due to limitations of the microwave. While 250 °C was the target temperature, the actual attained temperature was less (**Table 7**).

The successful intramolecular Diels-Alder reactions and the racemic lactones isolated by application of the optimised reaction conditions and purification protocols are tabulated below. The determination and proof of relative stereochemistry of the Diels-Alder adducts. The diastereoselectivity of the reaction is described in later sections (*Vide infra*).

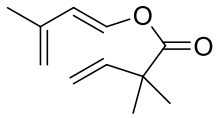
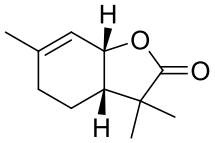
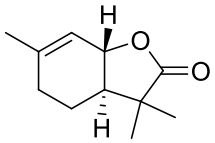
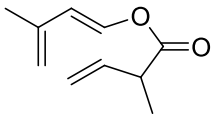
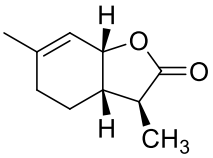
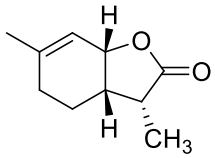
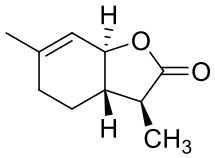
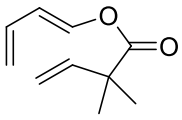
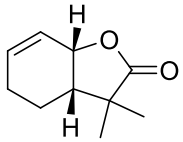
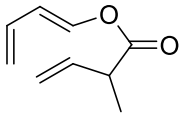
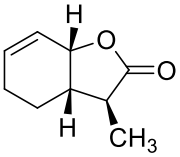
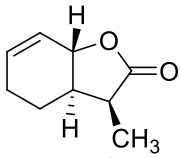
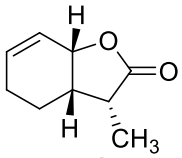
| Diels-Alder precursor | Reaction conditions | Products isolated (racemic) | | |
|---|---|---|---|---|
|  **24** | **24** (0.13 g)<br>200 °C<br>6 h<br>toluene | |  **25a** |  **25b** |
|  **45** | **45** (0.28 g)<br>250 °C<br>16 h<br>toluene |  **1** |  **2** |  **3** |
|  **52** | **52** (0.1 g)<br>180 °C<br>~18 h<br>toluene | | |  **54a** |
|  **51** | **51** (0.18 g)<br>218 °C<br>15 h<br>toluene |  **55a** |  **55d** |  **55b** |

**Table 7**. *Reaction conditions of successful IMDA*

### 3.2 Establishment of relative stereochemistry

#### 3.2.1 $^{1}$H NMR analysis

The pleasant smell of the isolated compounds from the intramolecular Diels-Alder reaction allowed preliminary insight into the successful outcome. However to establish the diastereoselectivity of the Diels-Alder reaction the stereochemical relationship of each isolated lactone needed to be determined. Once was stereochemistry established the lactones could be subjected to GC/MS analysis to determine the retention times of specific diastereomers. Armed with this information the Diels-Alder reaction mixture itself can be subjected to GC/MS analysis to yield the ratio of different diastereomers in the reaction mixture providing valuable insight into the diastereoselectivity of the Diels-Alder reaction.

Because different diastereomers of wine lactone family have dihedral angles between the methine protons H-3a and H-3 (**Figure 4**) different coupling constants are expected to be observed.

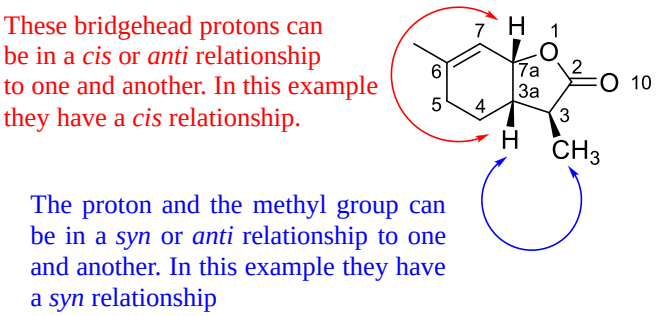



**Figure 4**. *The two possible relationships arising from thee different stereocenters. Natural wine lactone **1** can be described as having cis-syn relationship*

Guth in his comprehensive work have reported the coupling constants for the different relationships by examination of different stereoisomers of wine lactone.[2] This is tabulated below (**Table 8**).

| Wine lactone stereoisomer | Relationship *cis*/*trans*, *syn*/*anti* | *J* (7a, 3a) | *J* (3, 3a) |
|---|---|---|---|
| (3*R*, 3*aR*, 7*aS*) – ent-(**1**) | *cis, syn* | 6.5 | 8.9 |
| (3*R*, 3*aS*, 7*aR*) – (**2**) | *cis, anti* | 4.4 | 7.6 |
| (3*S*, 3*aS*, 7*aS*) – (**3**) | *trans, syn* | 9.7 | 13.1 |
| (3*R*, 3*aS*, 7*aS*) – (**4**) | *trans, anti* | 10.2 | 7.5 |

**Table 8**. *Coupling constants reported by Guth.*[2]

It is seen that having a *cis* relationship across the double bond result in relatively small couplings (*J*(7a, 3a) = 4.4 – 6.5 Hz) as opposed to *trans* relationships which display an opposite trend (*J*(7a, 3a) = 9.7 – 10.2 Hz). Having a *syn* relationship between methine proton 3a and methyl group on C-3 result in relatively large coupling (*J*(3, 3a) = 8.9 – 13.1 Hz) while an *anti* relationship give rise to a smaller coupling (*J*(3, 3a) = 7.6 – 7.5 Hz).

These coupling trends should also be valid for the structurally similar wine lactone analogues. Examination of the proton peak corresponding to proton 7a and its coupling constant across the ring junction to proton 3a reveals the *cis* or *trans* nature of the ring junction character. Similarly, examination of the proton peak 3 and its coupling to proton 3a should reveal a *syn* or *trans* relationship between the methine proton 3a and the methyl group at C-3. Below is the superimposed expanded proton spectra for three different isolated diasteromers of wine lactone analogue **55**. The diagnostic peak at 7a and its coupling constant are highlighted (**Figure 5**).

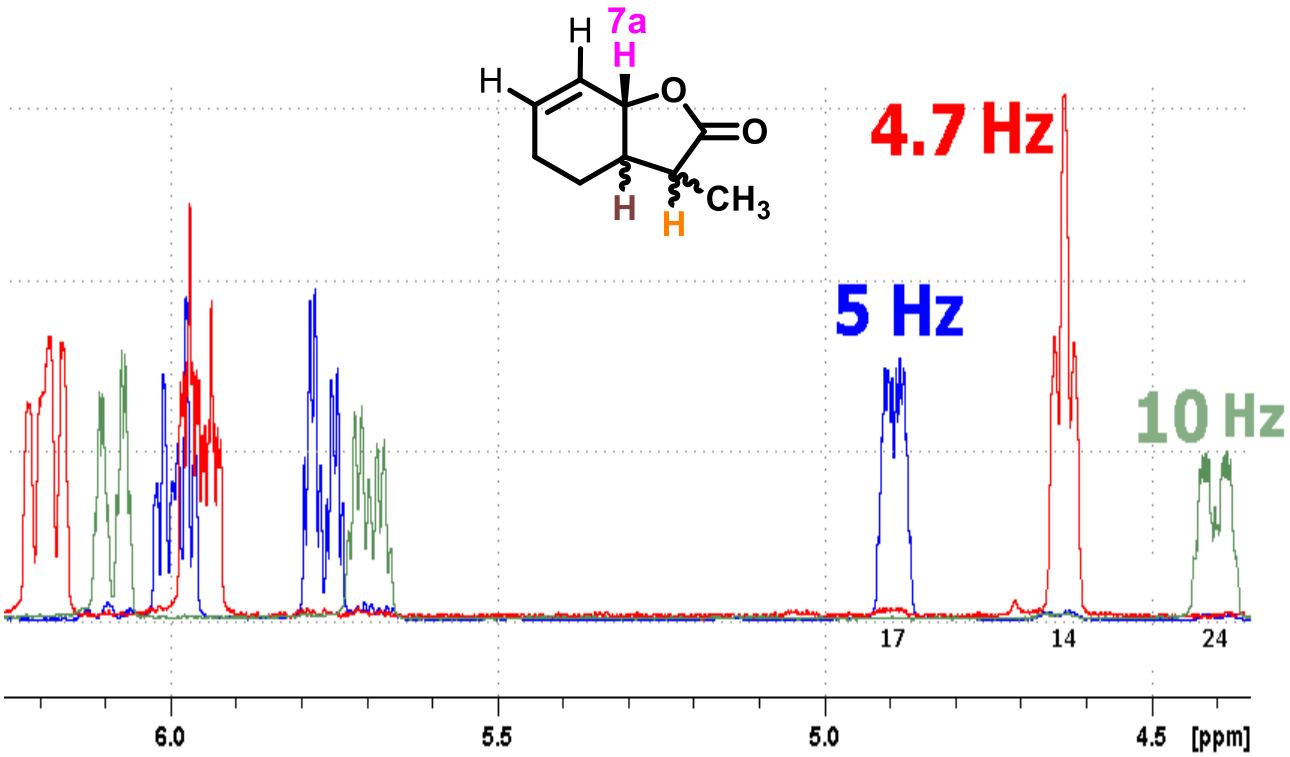



**Figure 5.** *Expanded $^{1}H$ NMR spectra showing the diagnostic peaks of three superimposed monomethyl wine lactone analogue **55** diastereomers. The three coloured peaks to the right represent proton 7a*

The protons of diastereomers coloured red and blue can be seen to have a coupling constant of around 5 Hz and from the aforementioned coupling constant analysis[2] a *cis* relationship across the ring junction can be deduced. In contrast the green 7a proton shows a much larger coupling constant of 10 Hz, indicative of a *trans* relationship. Similar analysis can be performed on other analogues of wine lactone to establish the bridgehead proton stereochemical relationship. The second relationship can be analyzed in a similar manner; on lactones lacking a *gem*-dimethyl group a large coupling on the methine proton H-3 is indicative of a *syn* relationship beween bridgehead proton 3a and the methyl group at C-3 while a small coupling is indicative of an *anti* relationship. The results of this analysis is tabulated below (**Table 9**).

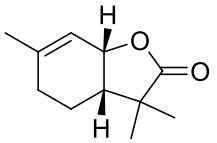
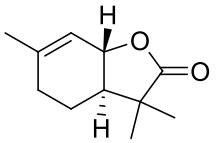
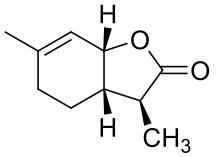
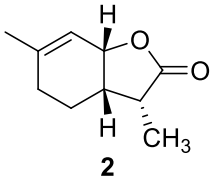
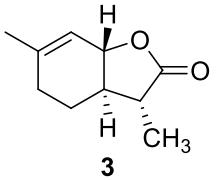
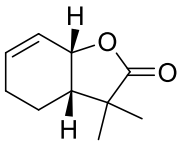
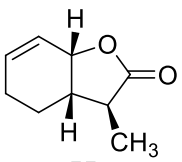
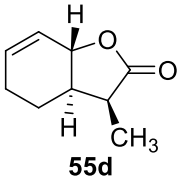
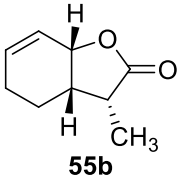
| Chemical shifts δ H–C(7a) | *J* (7a, 3a) | Chemical shifts δ H–C(3) | *J* (3, 3a) | *Deduced relationship* | *Deduced Stereoisomer (racemic)* |
|---|---|---|---|---|---|
| 4.82 – 4.78 | 5.08 | N/A | N/A | *cis* |  **25a** |
| 4.56 – 4.50 | 9.85 | N/A | N/A | *trans* |  **25b** |
| 4.92 – 4.87 | 5.45 | 2.47 – 2.35 | 8.55 | *cis, syn* |  **1** |
| 4.65 – 4.62 | 4.66 | 2.95 – 2.86 | 7.17 | *cis, anti* |  **2** |
| 4.40 – 4.33 | 10.56 | 2.37 – 2.25 | 12.5 | *trans, syn* |  **3** |
| 4.82 – 4.79 | 4.52 | N/A | N/A | *cis* |  **54a** |
| 4.92 – 4.87 | 5.47 | 2.50 – 2.40 | 9.10 | *cis, syn* |  **55a** |
| 5.72 – 5.66 | 9.99 | 2.38 – 2.24 | 6.78 | *trans, anti* |  **55d** |
| 4.65 – 4.62 | 4.67 | 2.96 – 2.86 | 7.34 | *cis, anti* |  **55b** |

**Table 9.** *Assignment of stereochemistry by $^{1}H$ NMR*

Despite our best efforts isomers **55c**, **4** and **54b** were not isolable (**Figure 6**). It was later revealed by GC/MS analysis **4** does not form in significant quantities by the Diels-Alder reaction while **55c** and **54b** forms but only in small amounts.

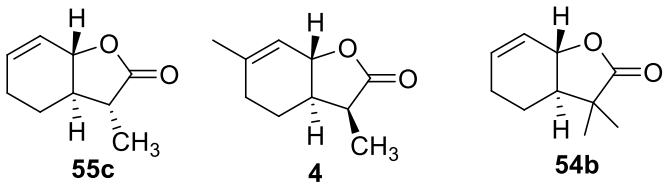



**Figure 6.** *Diastereomers not isolated*

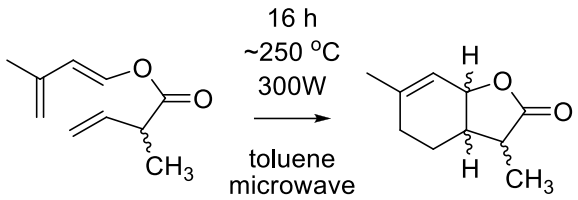
### 3.2.2 GC/MS analysis

Having determined the stereochemistry of lactones, each pure sample of the lactone was analyzed by gas chromatography-mass spectrometry (GC/MS) to find the respective retention times. It was hoped that with this information the reaction mixture could be analyzed and presence of each diastereomer quantified to give the ratio and therefore the diastereoselectivity of the reaction.

Diethyl ether was used as the carrier solvent. In some cases trace amounts of Butylated hydroxytoluene, a peroxide inhibitor from the diethyl ether caused problems, having retention times similar to some of the lactones. This problem was eliminated by distilling diethyl ether prior to GC/MS analysis. The compounds purified were all shown to have the correct mass. The relative retention times of isolated stereoisomers correlated with its respective polarity. The retention times of the lactones along with diastereomeric ratios are presented in the next section.

### 3.2.3 GC/MS analysis; diastereoselectivity of the Diels-Alder reaction

In order to determine the diastereoselectivity of the Diels-Alder reaction the reaction mixture had to be subjected for GC/MS analysis. The crude reaction mixture could not be used owing to the non-volatile nature of toluene. A very small amount of the reaction mixture therefore was loaded onto silica and toluene was flushed with pentane. The lactones were then recovered from silica with neat diethyl ether and lactone-ether mixture was analyzed. In some cases there was an additional peak in the mixture corresponding to a lactone which was not isolated *via* flash chromatography (**Figure 10**, **9**). These lactones were present in small amounts and stereochemistry was deduced from negation from other stereochemical relationships already claimed by lactones isolated. These results are outlined in the following pages; each page will feature the reaction scheme, expanded GC/MS spectrum and a relevant data table.




**Scheme 36**. *IMDA of wine lactone precursor **45***

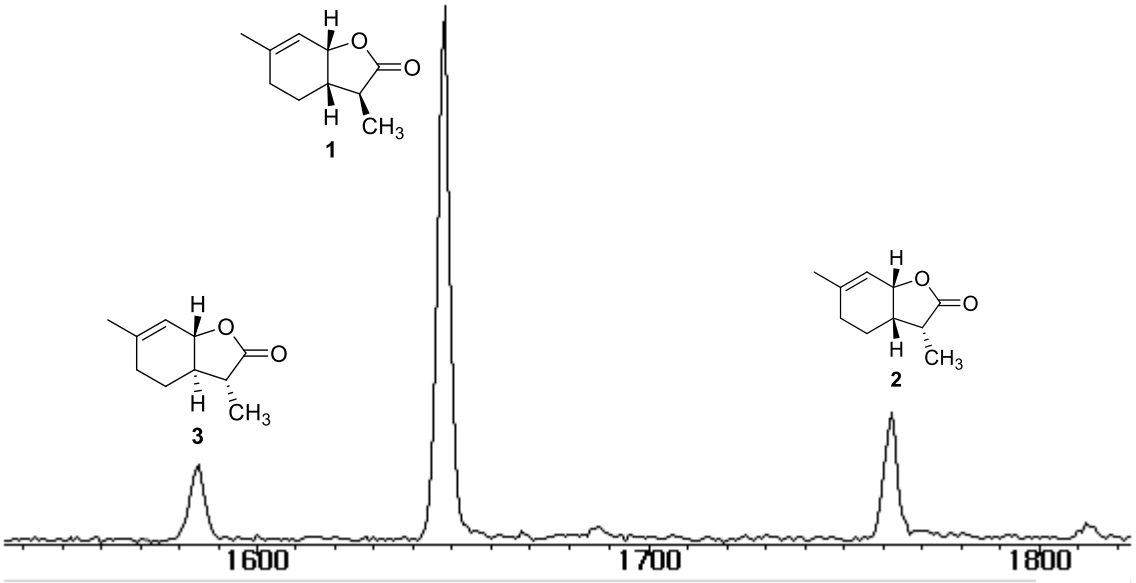



**Figure 7**. *Separation of 3,6-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one isomers by GC/MS*

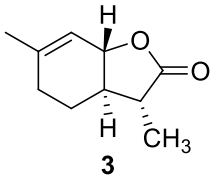
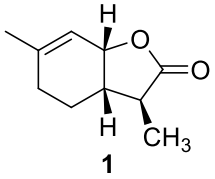
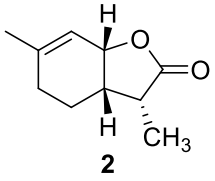
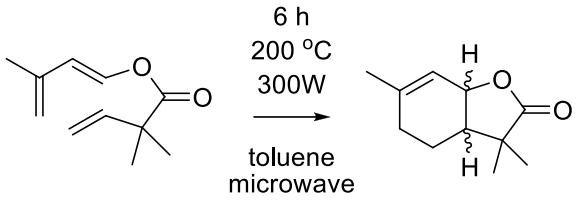
| Structure (+ enatiomers) | Retention time (m.s) | Area | Ratio | Ratio (%) |
|---|---|---|---|---|
|  **3** | 17.32 | 31273 | 1 | 12.1 % |
|  **1** | 18.41 | 180069 | 5.8 | 69.6 % |
|  **2** | 19.21 | 47290 | 1.51 | 18.3 % |

***Table 10***. *Retention time, area and area ratio of wine lactone isomers*




**Scheme 37**. *IMDA of dimethyl wine lactone precursor **24***

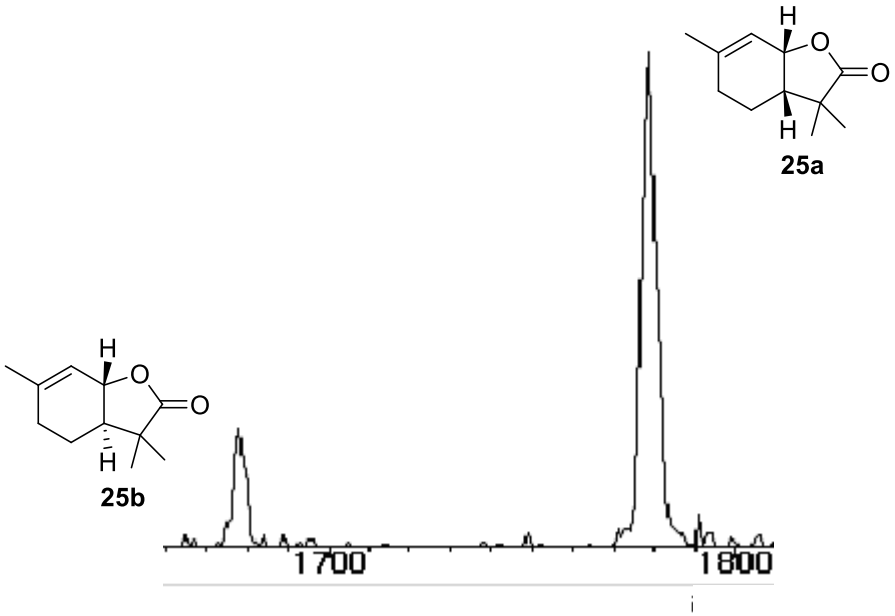



**Figure 8**. *Separation of 3,3,6-trimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one isomers by GC/MS*

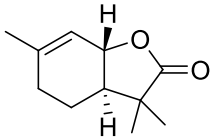
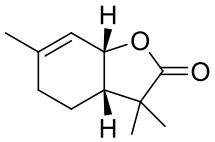
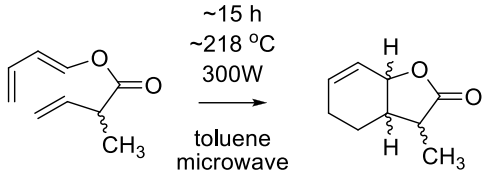
| Structure (+ enatiomers) | Retention time (m.s) | Area | Ratio | Ratio (%) |
|---|---|---|---|---|
|  **25b** | 18.21 | 3658 | 1 | 12.0 % |
|  **25a** | 19.10 | 26755 | 7.3 | 88.0 % |

***Table 11***. *Retention time, area and area ratio of dimethyl wine lactone isomer*




**Scheme 38**. *IMDA of monomethyl wine lactone analogue precursor **51***

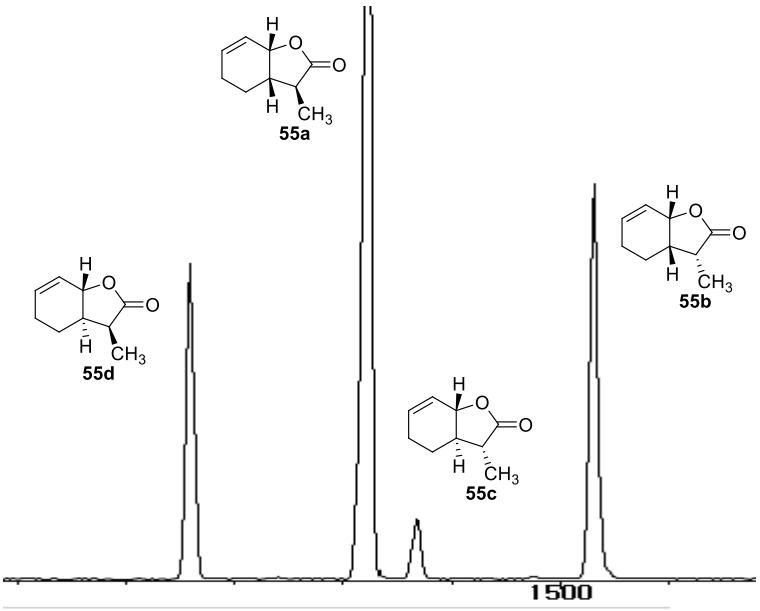
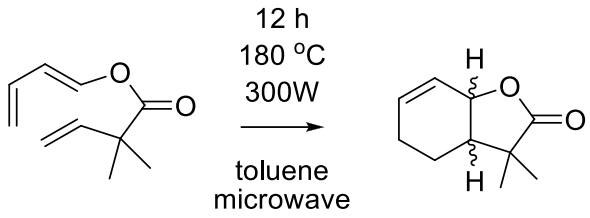



**Figure 9**. *Separation of 3 3-methyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one isomers by GC/MS*

| Structure (+ enatiomers) | Retention time (m.s) | Area | Ratio | Ratio (%) |
|---|---|---|---|---|
| **55d** | 15:25 | 1835547 | 1 | 16.9 % |
| **55a** | 16:81 | 6127101 | 3.3 | 56.4 % |
| **55c** | 16:14 | 384397 | 0.21 | 3.5 % |
| **55b** | 16:59 | 2519239 | 1.37 | 23.2 % |

***Table 12**. Retention time, area and area ratio of monomethyl wine lactone analogue isomers*




**Scheme 39**. *IMDA of dimethyl wine lactone analogue precursor **52***

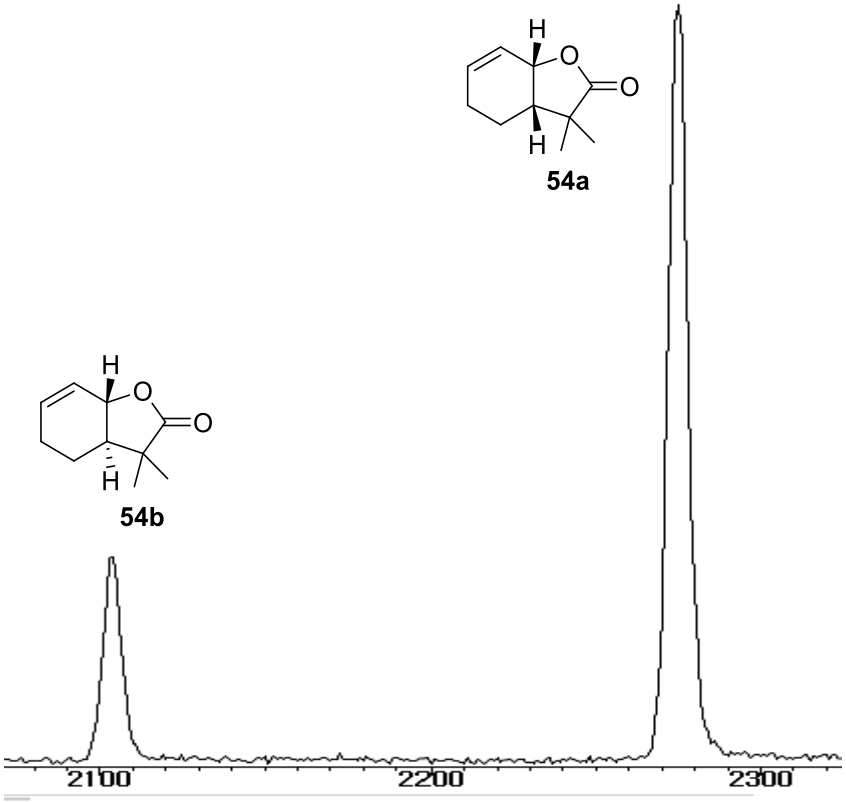



**Figure 10**. *Separation of 3,3-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one isomers by GC/MS*

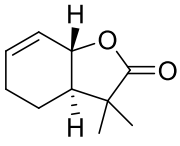
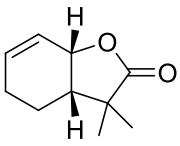
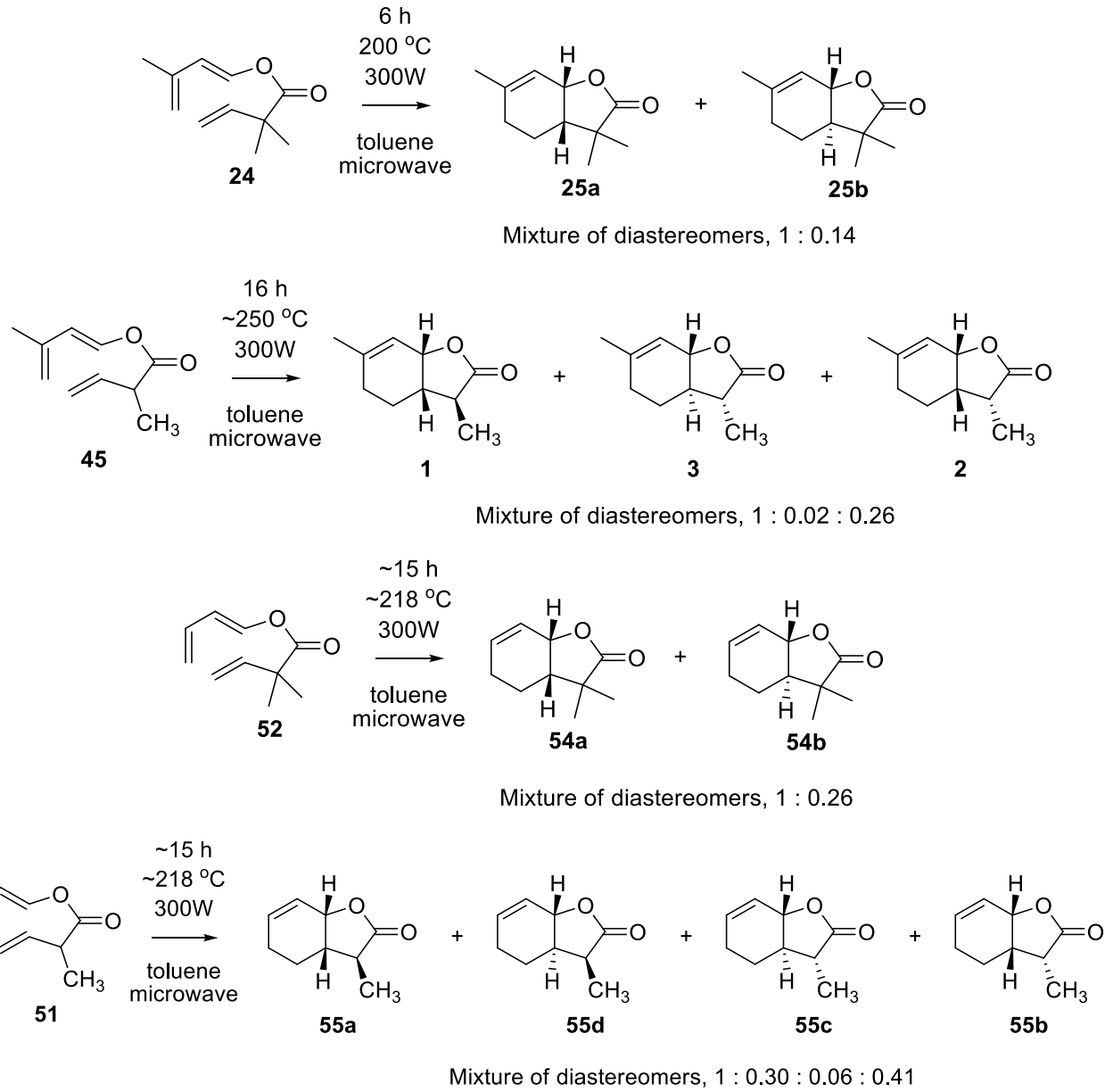
| Structure (+ enatiomers) | Retention time (m.s) | Area | Ratio | Ratio (%) |
|---|---|---|---|---|
|  **54b** | 16:22 | 111764 | 1 | 20.9 % |
|  **54a** | 17:12 | 422064 | 3.8 | 79.1 % |

***Table 13***. *Retention time, area and area ratio of dimethyl wine lactone analogue isomers*

In all cases the formation of lactones with a *cis* relationship across the ring junction was favoured. Where appropriate *syn* relationship between H-3a and the 3-$CH_3$ was also predominant. The diastereoselectivity of the Diels-Alder reaction therefore can be described as favouring the generation of *cis-syn* isomer where appropriate. Significantly, the natural wine lactone **1** exhibits this *cis-syn* relationship. The diastereoselectivity of the intramolecular Diels-Alder additions are summarized below (**Scheme 40**).




**Scheme 40.** *Diastereoselective ratios of respective IMDA reactions*

In the absence of a X-ray structure to confirm the stereochemical assignments, these results are only based on analysis of $^1$H NMR. To validate, compliment and gather further insight into these findings a computational study of the intramolecular Diels-Alder reaction similar to that carried out by Sherburn *et al*.[22,41] was undertaken.

### 3.3 Computational analysis

This section describes the computational analysis undertaken by Dr. Patrick D O'Connor and is based on work by Paddon-Row *et al*.[22] A combination of Density Functional Theory (DFT) and second order Møller-Plesset perturbation theory (MP2) were used to calculate the zero point vibrational energy (ZPVE) corrected transition state electronic energies. Boltzmann population analysis of the transition state energies gave a theoretical product distribution which bore a very close releationship to the experimental ratios. Interestingly, the product distributions in no way correlated with the Boltzmann ratios of the product energies. These results in combination with the transition state data indicated that the Intramolecular Diels-Alder reaction described herein is taking place under kinetic rather than thermodynamic control in despite of the high reaction temperature used.

To complement the experimental findings and gain further insight into the IMDA cycloaddition, computational analysis of the reactions was undertaken. Molecular structures were optimized to transition states using a B3LYP hybrid functional and 6-31+G(d) basis set. It has been shown by Sherburn *et al.*[22] that the level of theory and basis set were acceptable and correlated well with experimental findings for a similar Diels-Alder cycloaddition. Sherburn's pentadienyl acrylate can be considered a reverse ester of the wine lactone scaffold and moreover the similar reaction conditions were used to execute the pentadienyl acrylate IMDA reactions.[41] Though the computational study was performed assuming the molecules to be in the gas phase, Sherburn *et al.*[22] noted that the *cis*/*trans* selectivity was likely due to electronic effects, torsional strain and steric effects which could be adequately accounted for using a gas phase calculation.

In the present work there are two main transition states possible for the intramolecular Diels-Alder reaction. The dienophile substituent can be *end*o or *exo* with respect to the diene moeity. These possibilities are illustrated below using dimethyl wine lactone **25** as an example (**Figure 11**).

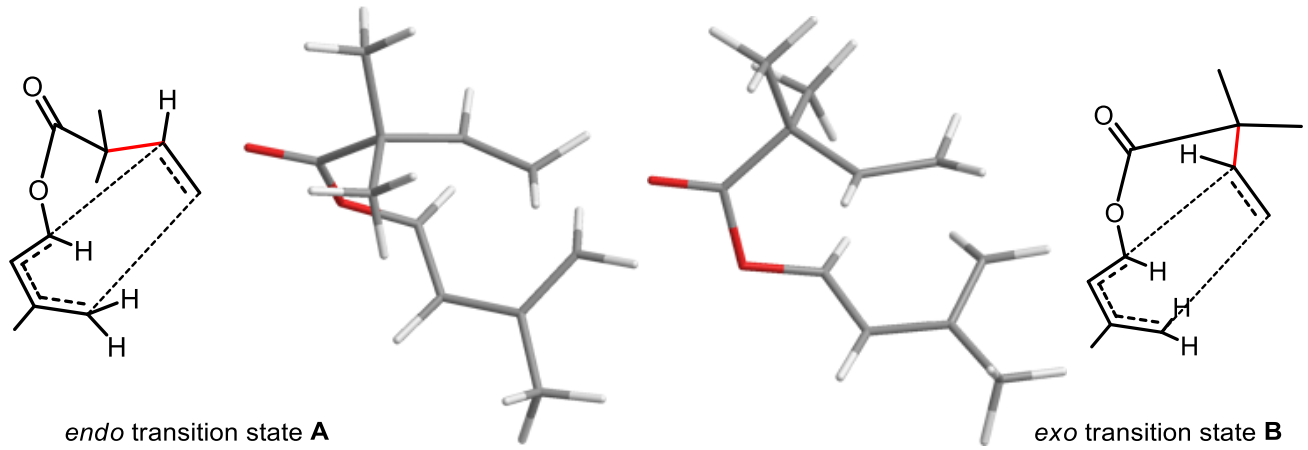
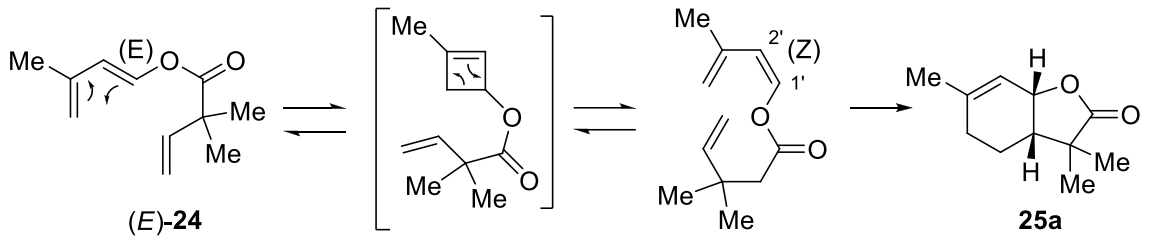



**Figure 11**. *The endo and exo transition states of dimethyl wine lactone **25***

From the transition states depicted it can be seen that an *endo* **TS A** would lead to a *cis* relationship for the protons across the ring junction while *exo* **TS B** would yield a *trans* relationship. The diastereoselectivity of the IMDA therefore depends on the population of transition states **A** and **B**.

An interesting point to note about this reaction that is not mentioned in the Sherburn publication is that the C1'-C2' olefin can interconvert an (*E*)- and a (*Z*)- isomers *via* two sequential conrotatory electrocyclic reactions (**Scheme 41**). This (*Z*)- isomer can then undergo IMDA cycloaddition, but only through an *exo* transition state (**Figure 12**) to yield a *cis* lactone.




**Scheme 41**. *Formation of (Z) isomer by sequential electrocyclic ring closing ring opening reactions, which can undergo IMDA to yield cis lactone*

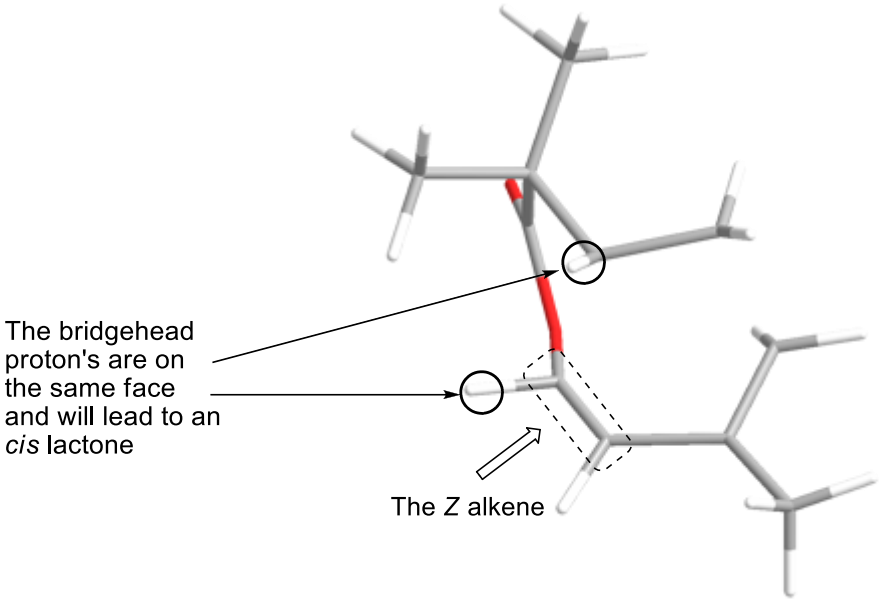
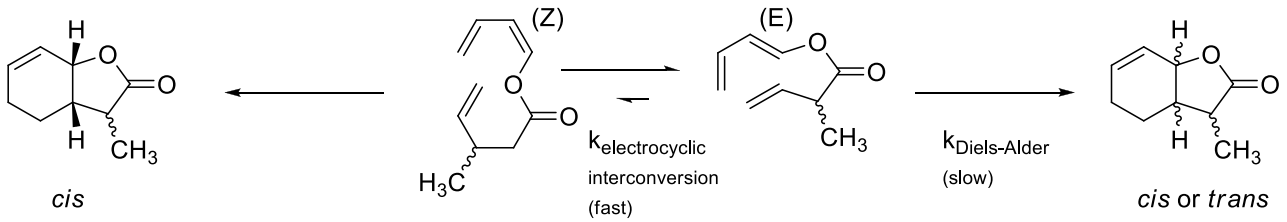



**Figure 12**. *The exo transiton state of the Z isomer*

Although the equilibrium would strongly favour the *E*-isomer, the Curtin-Hammett[42] principle dictates that provided the electrocyclic reaction is faster than the Diels-Alder ($k_{electrocyclic} >> k_{Diels-Alder}$) the product distribution will be based on the activation energy of the Diels-Alder pathway rather than the starting material isomer distribution. If $k_{electrocyclic} << k_{Diels-Alder}$ then the converse is true (**Scheme 42**).




**Scheme 42**. *Two alternative pathways.*

Quantification of transition state energy for the (*Z*)- isomer was thought to be important. The predicted ratios for the diastereomers based on Boltzmann distributions based on the calculated transition state energy differences are tabulated below together with the experimental result. The percentages shown in parenthesis include a contribution from (*Z*)-configured transition states. (**Table 14**, **15**).

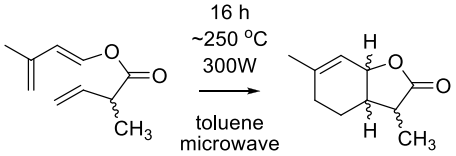
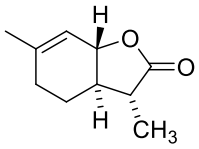
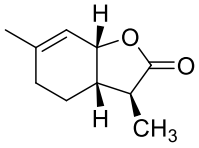
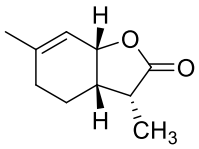
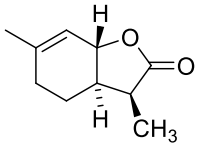
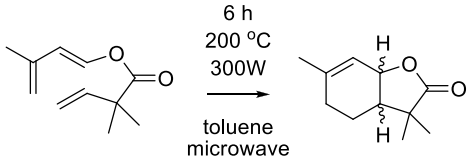
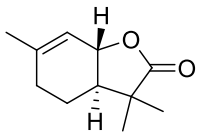
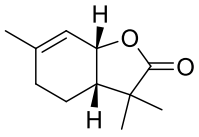
| MP2/6-31+G(d)//B3LYP/6-31+G(d) + B3LYP/6-31+G(d) ZPVE | | |
|---|---|---|
|   | | |
| Compound | Theoretical (%)* | Experimental (%) |
|  **3** | 14.4<br>(11.5) | 12.1 |
|  **1** | 66.6<br>(60.7) | 69.6 |
|  **2** | 16.7<br>(25.9) | 18.3 |
|  **4** | 2.4<br>(1.9) | not observed |
|   | | |
|  **25b** | 19.2<br>(17.4) | 12.0 |
|  **25a** | 80.8<br>(82.6) | 88.0 |

**Table 14.** *Theoretical product distribution based on transition state (ts) energy differences vs experimentally observed ratios*

* Percentages shown in parenthesis include a contribution from *z*-configured transition states.

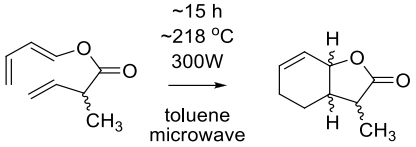
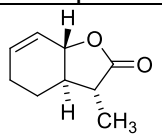
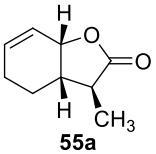
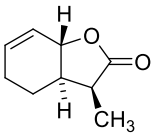
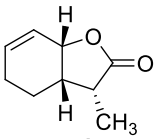
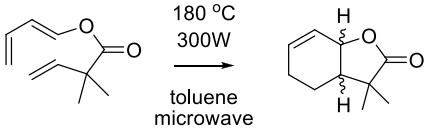
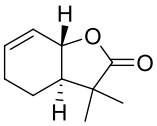
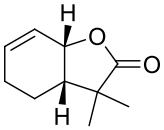
| MP2/6-31+G(d)//B3LYP/6-31+G(d) + B3LYP/6-31+G(d) ZPVE | | |
|---|---|---|
|   | | |
| Compound | Theoretical (%)† | Experimental (%) |
|  **55c** | 5.0<br>(0.3) | 3.5 |
|  **55a** | 52.9<br>(37.7) | 56.4 |
|  **55d** | 22.0<br>(1.2) | 16.9 |
|  **55b** | 20.1<br>(60.9) | 23.2 |
|   | | |
|  **54b** | 24.9 | 20.9 |
|  **54a** | 75.1 | 79.1 |

**Table 15**. *Theoretical product distribution based on ts energy differences vs experimentally observed ratios*

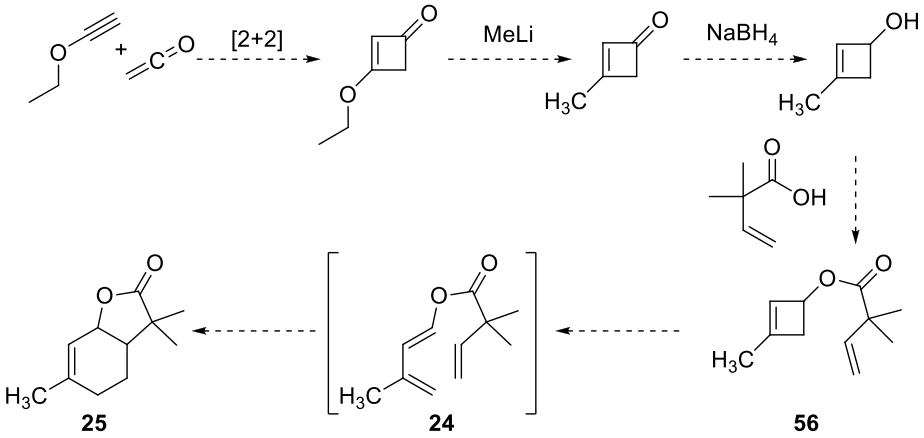
It can be seen that the calculated diastereoselectivity based on the transition state energies are in excellent agreement with the experimentally observed values (**Table 14, 15**), (**Appendix 1,2**). Similar analysis based on Boltzmann ratios of the Diels-Alder product energies were in poor agreement with the experimentally observed ratio (**Appendix 3**). These results established that Intramolecular Diels-Alder reaction takes place under kinetic control rather than thermodynamic control. Other theoretical aspects of this reaction are currently under investigation.

† Percentages shown in parenthesis include a contribution from *z*-configured transition states.

### 3.4 Future Work

In this section the possibility that wine lactone could be alternatively made by a cascade of pericyclic reactions is explored. We also explore the possibility of extension of the work to an asymmetric synthesis.

The majority of this dissertation deals with the synthesis of the hydrolytically unstable acyl enol ether moiety. Although a successful route was developed shortcomings were identified; in the preparation of dimethyl wine lactone the starting aldehyde was only obtained in poor yield *via* Swern oxidation. A new synthetic method avoiding the use of 3-methylbut-2-enal and the need to isolate the unstable linear triene is proposed. For future work it is anticipated that wine lactone analogues could be made from substituted cyclobutenes, as shown in **Scheme 43**.




**Scheme 43**. *Novel approach to dimethyl wine lactone **25***

In this case the reaction would proceed *via* a cascade electrocyclic ring opening followed by a Diels-Alder cycloaddition. This would remove the need to handle the acyl enol ether **24** in favour of handling the less sensitive cyclobutene ester **56**.

Another interesting undertaking would be to introduce asymmetry into the synthesis. If an enantiopure Diels-Alder precursor were employed the novel Diels-Alder approach would be enantioselective. Due to the scaffold of linear triene and the concise nature of our method stereogenicity can only be introduced at C-2 to effect an asymmetric Diels-Alder reaction (**Figure 13**).

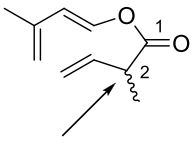



**Figure 13**. *The potential stereocentre*

It is reported that cyanuric fluoride mediated coupling preserves the stereocentre and is therefore used routinely in peptide synthesis.[28] The required stereocentre would be derived from classical resolution of racemic acid **49** (**Scheme 44**).

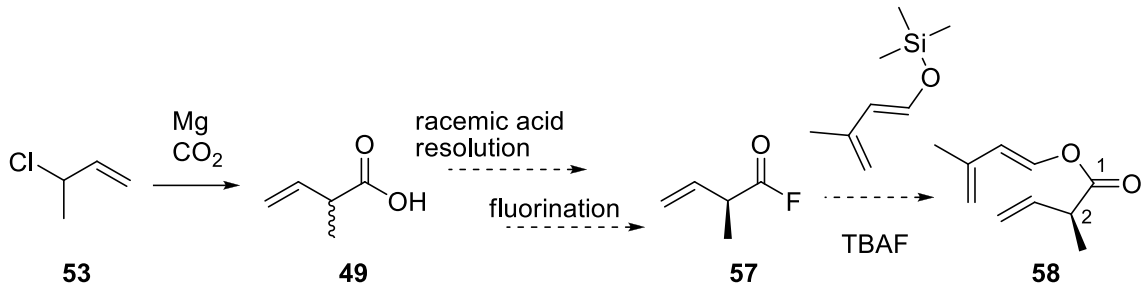



**Figure 14.** *Proposed synthesis of asymmetric triene **58***

Given the procurement of asymmetric triene **58**, an asymmetric variant of the intramolecular Diels-Alder reaction could be explored. Presumably, the steric bulk at C-2 would shield the dienophile from approaching the diene from one face thus leading to a degree of enantioselectivity.

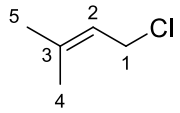
# Chapter 4. Experimental

**General Details**

All reactions were carried out in flame or oven dried glassware under a dry nitrogen or argon atmosphere. Tetrahydrofuran and diethyl ether were dried over sodium wire, toluene was dried over sodium lumps, pyridine, triethylamine were dried over calcium hydride. Acetic acid was glacial with no further purification. Flash column chromatography was carried out using 0.063-0.1 mm silica gel with the desired solvent. Thin layer chromatography (TLC) was performed using UV fluorescene and/or staining with: vanillin in ethanolic sulphuric acid or iodine. High resolution mass spectra were recorded at a nominal resolution of 5000 to 10000. Infrared spectra were recorded on a Perkin Elmer Spectrum One Fourier Transform infrared Spectrometer and were reported as wavenumbers ($\nu$, $cm^{-1}$). GC-MS analyses were performed by means of Agilent 6890N Gas Chromatograph equipped with Agilent 122-5532 30 m x 0.25 mm column

NMR spectra were recorded on either the Bruker DRX300 spectrometer operating at 300 MHz for $^{1}H$ nuclei and 75 MHz for $^{13}C$ nuclei or using the Bruker DRX400 spectrometer operating at 400 MHz for $^{1}H$ nuclei and 100 MHz for $^{13}C$ nuclei. All chemical shifts are reported in parts per million (ppm) releative to $CDCl_3$. $^{1}H$ NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; dq, doublet of quartets; t, triplet; m, multiplet), coupling constant (*J* Hz) and assignment.

## 1-chloro-3-methylbut-2-ene[31]



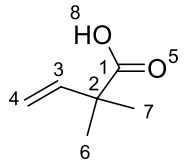

**27**

A three neck 250 mL round bottom flask containing isoprene (30.9 g, 454 mmol) was cooled in an ice salt bath. Sodium chloride (13.6 g, 234 mmol) was added with stirring at a rate not exceeding 2 g per 15 min. Concentrated hydrochloric acid (96 mL, 3.10 mol) was added at the same time at a rate not exceeding 1 mL per min. The reaction mixture was warmed to 15 °C and stirred for 3 h. The organic layer was separated and dried over anhydrous sodium carbonate. Distillation (b. p. 57~66 °C / 145~152 Torr, lit.,[31] 73 – 75 °C / 224 Torr) to give the *title compound* (33.6 g, 70%) as a colourless oil.

$\delta_H$ (300 MHz; $CDCl_3$) 1.73 (3H, s, 4-H), 1.78 (3H, s, 5-H), 4.09 (2H, d, *J* 8.1, 1-H), 5.45 (1H, t, *J* 8.1, 2-H); $\delta_C$ (75 MHz; $CDCl_3$) 17.6 ($CH_3$, 4-C), 25.7 ($CH_3$, 5-C), 41.2 ($CH_2$, 1-C), 120.5 (CH, 2-C), 139.3 (quart., 3-C).

The $^1H$ and $^{13}C$ NMR data were in agreement with that reported in the literature.[31]

## 2,2-dimethylbut-3-enoic acid[32]



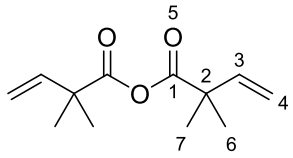

**28**

Prenyl chloride (13.8 mL, 95.6 mmol) was dissolved in anhydrous tetrahydrofuran (55 mL) and added to a suspension of activated magnesium (12 g, 82.3 mmol) in anhydrous tetrahydrofuran (38 mL) at a rate sufficient to maintain a gentle reflux. An excess of dry carbon dioxide was bubbled through the reaction mixture for 2 h followed by direct addition of solid dry ice (two pieces). Upon evaporation of excess dry ice the reaction mixture was hydrolyzed by the addition of concentrated hydrochloric acid (14 mL) in water (23.8 mL). After addition of sufficient NaCl to separate the remaining aqueous layer, the organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined organic solutions were dried over sodium sulphate and the solvent evaporated *in vacuo*. The crude product was distilled at reduced pressure (b. p. 85~90 °C / 37~39 Torr, lit.,[32] 187 °C / atmospheric pressure) to give the *title compound* (5.1 g, 47%) as a colourless liquid.

$\delta_H$ (300 MHz; $CDCl_3$) 1.32 (6H, s, 6,7-H), 5.11 (2H, m, 4-H), 6.05 (1H, dd, *J* 17.5 and 10.6, 3-H), 11.60 (1H, s, 8-H); $\delta_C$ (75 MHz; $CDCl_3$) 24.3 ($CH_3$, 6,7-C), 44.6 (quart., 2-C), 113.3 ($CH_2$, 4-C), 141.9 (CH, 3-C), 183.0 (quart., 1-C).

The $^1H$ and $^{13}C$ NMR data were in agreement with that reported in the literature.[32]

## 2,2-dimethylbut-3-enoic anhydride[33]



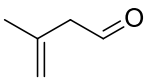

**29**

2,2-Dimethylbut-3-enoic acid (5.10 g, 44.7 mmol) was added to acetic anhydride (5.47 g, 53.2 mmol) and stirred for 1 h. The mixture was fractionally distilled (b. p. 80~110 °C / 18 Torr) to give the *title compound* (5.1 g, 46%).

$\delta_H$ (400 MHz; $CDCl_3$) 1.36 (H12, s, 6,7-H), 5.17 (H4, m, 4-H), δ 5.97 (2H, dd, *J* 17.4 and 10.6, 3-H); $\delta_C$ (100 MHz; $CDCl_3$) 24.0 ($CH_3$, 6,7-C), 46.2 (quart., 2-C), 114.5 ($CH_2$, 4-C), 140.6 (CH, 3-C), 171.3 (quart., 1-C).

The $^1H$ and $^{13}C$ NMR data were in agreement with that reported in the literature.[33]

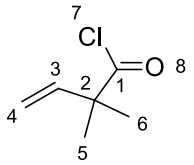
## 3-methylbut-3-enal[34]




**30**

To a stirred solution of 2-idoxybenzoic acid (0.76 g, 34.9 mmol) in dimethyl sulfoxide (~35 mL) was added 3-methylbuten-1-ol (1 mL, 11.6 mmol) and the mixture stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite® and the filtrate extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford aldehyde **30** as a yellow oil (2.2 g, 227%). The NMR of the product indicated that the product contained solvent.

## 2,2-Dimethylbut-3-enoyl chloride[43]



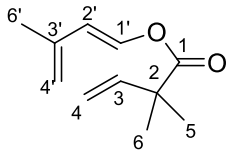

**38**

2,2-Dimethylbut-3-enoic acid (4.82 g, 42.2 mmol) and redistilled $PCl_3$ (1.5 mL, 17.2 mmol) were heated under reflux for 1.5 h. The mixture was cooled and the upper layer was decanted and distilled (b. p. 50 ºC / 47 Torr) to give the *title compound* (2.1 g, 37 %) as a colourless liquid.

$\delta_H$ (400 MHz; $CDCl_3$) 1.43 (6H, s, 5,6-H), 5.23 – 5.28 (2H, m, 4-H), 6.01 (1H, dd, *J* 17.4 and 10.4, 3-H); $\delta_C$ (100 MHz; $CDCl_3$) 24.9 ($CH_3$, 5,6-C), 54.7 (quart., 2-C), 119.3 ($CH_2$, 4-C), 140.9 (CH, 3-C), 178.3 (quart., 1-C).

The $^1H$ and $^{13}C$ NMR data and the boiling point were in agreement with that reported in the literature.[43]

## 3-methylbuta-1,3-dienyl 2,2-dimethylbut-3-enoate




**24**

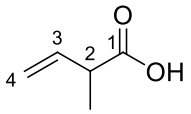
***Method A***[26]: A solution of aldehyde **34** (0.20 g, 2.38 mmol) in anhydrous tetrahydrofuran (~3 mL) was added to a mixture of potassium *tert*-butoxide (0.27 g, 2.38 mmol) and anhydrous tetrahydrofuran (3 mL) cooled to -78 ºC. To this mixture was added a solution of acid chloride **38** (0.32 g, 2.38 mmol) in anhydrous tetrahydrofuran (3 mL) and the reaction stirred for 2 h at -78 ºC then warmed to room temperature and stirred overnight. The crude product was purified by flash chromatography using hexane as eluent to yield the title compound.

***Method B***[44]: A solution of acid **28** (1.5 g, 13.1 mmol) and dry dichloromethane (25 mL) was cooled to 0 °C. Pyridine (0.53 mL, 6.57 mmol) was added followed by dropwise addition of cyanuric fluoride (0.6 mL, 6.96 mmol) and to resulting white milky mixture was stirred for 2.5 h. Silyl enol ether **46** (2.04 g, 13.05 mmol) was then added dropwise at 0 °C. To the resultant yellow mixture was added solid tetra-*n*-butylammonium fluoride (0.15 g, 0.57 mmol) and mixture stirred for 2.5 h. The mixture was warmed to room temperature and then pentane (200 mL) was added. The reaction mixture was dried over $MgSO_4$, filtered through Celite® and the solvent removed *in vacuo*. The yellow oily residue was purified *via* flash chromatography using 150:1 *n*-pentane-diethyl ether as

eluent to afford the *title compound* (0.26 g, 11 %) as a colourless liquid.

IR ($CDCl_3$) $\nu_{max}$: 2922, 2174, 1749, 1253, 1132. $\delta_H$ (400 MHz; $CDCl_3$) 1.20 – 1.35‡ (6H, m, 6,5-H), 4.89 – 4.96 (2H, m, 4-H), 5.21 – 5.23 (2H, m, 4-H), 6.01 – 6.02 (1H, m, 3-H), 6.18 (1H, d, *J* 12.6 2'-H), 7.37 (1H, d, *J* 12.8, 1'-H); $\delta_C$ (100 MHz; $CDCl_3$) 18.6 ($CH_3$, 6'-C), 23.9 ($CH_3$, 6,5-C), 115.4 ($CH_2$, 4'-C), 116.2 ($CH_2$, 4-C), 118.4 (CH, 2'-C), 136.8 (CH, 1'-C), 139.4 (CH, 3-C), 173.3 (quart., 1-C); HRMS (EI+) 180.11513 ($M^+$. $C_{11}H_{16}O_2$ requires 180.11503).

## 2-methylbut-3-enoic acid[37]




**49**

To a stirred suspension of activated§ magnesium (20 g, 0.82 mol) in dry tetrahydrofuran (200 mL), was added a single iodine crystal. The mixture was heated to reflux and a mixture of 3-chlorobut-1-ene (30 g, 0.33 mol) in tetrahydrofuran (30 mL) was slowly added at a rate sufficient to maintain a gentle reflux. The mixture was cooled to -78 °C and dry $CO_2$ was bubbled through the mixture for 1 h. The reaction mixture was than cooled to room temperature and filtered though Celite®. Water (200 mL) was added and the pH adjusted to 12 *via* addition of 1 M sodium hydroxide. The organic layer was discarded and the pH was re-adjusted to 2 by addition of 1 M HCl. Following extraction of the aqueous layer with $Et_2O$ (3 x 100 mL) the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the yellow, oily residue was distilled (b. p. 75 ~ 80 °C / 14 Torr, lit,[45] 80 °C / 14 Torr) to afford the *title compound* (23.4 g, 70%) as a colourless liquid.

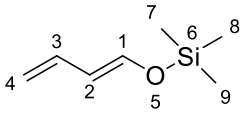
$\delta_H$ (300 MHz; $CDCl_3$) 1.31 (3H, d, *J* 6.9, 5-H), 3.16 (1H, m, 2-H), 5.22 – 5.13 (2H, m, 4-H), 5.88 – 6.00 (1H, m, 3-H), 11.8 (1H, s, 6-H); $\delta_C$ (75 MHz; $CDCl_3$) 16.4 ($CH_3$, 5-C), 43.5 (CH, 2-C), 116.5 ($CH_2$, 4-C), 136.4 (CH, 3-C), 181.2 (quart., 1-C).

The $^1H$ and $^{13}C$ NMR data and the boiling point were in agreement with that reported in the literature.[37,45]

‡ The sharp singlet expected around δ 1.33 was obscured by peaks attributed to *n*-pentane. The assignment is therefore made based on buta-1,3-dienyl 2,2-dimethylbut-3-enoate (#).

§ Magnesium turnings (20 g) were activated by dry stirring overnight under an argon atmosphere.

## 1-trimethylsilyloxybuta-1,3-diene[38]



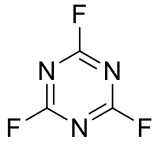

**50**

A dry 200 mL round bottom flask under an atmosphere of argon was charged with crotonaldehyde (24 mL, 0.29 mol), diethyl ether (60 mL), triethylamine (62 mL, 0.45 mol) and zinc chloride (0.34 g). Trimethylsilyl chloride (40 mL, 0.31 mol) was then added dropwise and the resultant brown-red mixture was heated to reflux for 25 h. Pentane (250 mL) was added to the mixture and the resultant precipitate was filtered through a pad of silica. The eluent was collected, the solvent removed *in vacuo* and the crude product distilled (b. p. 66 °C / 65 Torr, lit.,[38] 71 – 73 °C / 65 Torr) to afford the *title compound* (14.5 g, 36%) as colourless oil.

$\delta_H$ (300 MHz; $CDCl_3$) 0.20 (9H, s, 7,8,9-H), 4.81 (1H, dd, *J* 10.4 and 1.9, 4-H), 5.02 – 4.95 (1H, m, 4-H), 5.71 (1H, dd, *J* 11.7 and 11.0, 1-H), 6.28 – 6.15 (1H, m, 3-H), 6.53 (1H, d, *J* 11.8 2-H); $\delta_C$ (75 MHz; $CDCl_3$) 16.4 ($CH_3$, 7,8,9-C), 43.5 (CH, 2-C), 116.5 ($CH_2$, 4-C), 136.4 (CH, 3-C), 181.2 (CH, 1-C).

The $^1H$ and $^{13}C$ NMR data and the boiling point were in agreement with that reported in the literature.[38]

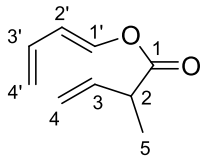
## Cyanuric fluoride[36]




**48**

A dry 500 mL round bottom flask was charged with cyanuric chloride (50.4 g), sodium fluoride (68.3 g) and warm sulfolane (217 mL) and the mixture heated and stirred vigorously (+250 °C). A white liquid was distilled (62 °C) which was distilled again (71 °C. lit.,[36] 72 – 73 °C) to yield the *title compound* (21.3 g, 58%) as a colourless liquid. Boiling point was in agreement with that reported in the literature.

## (*E*)-buta-1,3-dienyl 2-methylbut-3-enoate[44]

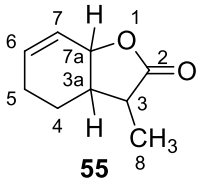



**51**

To a stirred solution of acid **49** (0.3 g, 3.0 mmol) and pyridine (0.113 mL, 1.4 mmol) in dry dichloromethane (10 mL) at 0 °C was added dropwise a solution of cyanuric fluoride (0.12 mL, 1.40 mmol). The resulting white milky mixture was stirred for 2 h. Silyl enol ether **50** (0.4 g, 2.8 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and added to the reaction mixture dropwise at 0 °C. To the resultant yellow solution was added solid tetra-*n*-butylammonium fluoride (0.03 g) and the mixture stirred for 2 h. The reaction was warmed to room temperature and pentane (120 mL) was added. The solution was dried over $MgSO_4$, filtered through Celite® and the solvent removed *in vacuo*. The yellow oily residue was purified *via* flash chromatography using 100:1 pentane-diethyl ether as eluent to afford the *title compound* (0.3 g, 70%) as a colourless liquid.

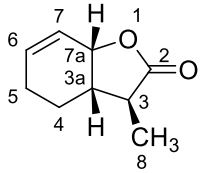
IR ($CDCl_3$) $\nu_{max}$: 1729, 1161, 1088, 994, 926, 830. $\delta_H$ (300 MHz; $CDCl_3$) 1.31 (3H, d, *J* 6.91, 5-H), 3.23 (1H, dq *J* 7.2, 1.2, 2-H), 5.06 – 5.24 (4H, m, 4,4'-H), 5.82 – 5.97 (1H, m, 3-H), 6.08 (1H, d, *J* 11.7 Hz, 2-H), 6.21 – 6.33 (1H, m, 3'-H), δ 7.39 (1H, d, *J* 12.4, 1'-H); $\delta_C$ (75 MHz; $CDCl_3$) 16.5 ($CH_3$, 5-C), 43.4 (CH, 2-C), 116.3 ($CH_2$, 4-C), 116.7 ($CH_2$, 4'-C), 117.3 (CH, 2'-C), 131.6 (CH, 3'-C), 136.1 (CH, 1'-C), 138.8 (CH, 3-C), 162.1 (quart., 1-C); HRMS (EI+) 153.09186 ($M^+$. $C_9H_{13}O_2$ requires 153.09155)**.**

## 3-methyl-3,3a,4,5-tetrahydrobenzofuran-2(7aH)-one




**55**

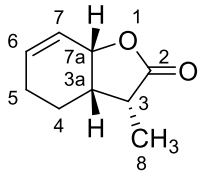
A mixture of triene **51** (0.18 g, 1.18 mmol) in toluene (4 mL) was stirred in a microwave reactor at 218 °C for 15 h. The solvent was removed by careful distillation at atmospheric pressure and the resultant dark yellow oily residue was purified *via* flash chromatography using 5:1 pentane-diethyl ether as eluent to afford the *title compound* (yield not determined, three diastereomers) as a sweet smelling colourless liquid.



**55a**

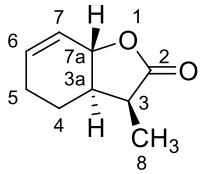
IR ($CDCl_3$) $\nu_{max}$: 2933, 1765, 1172, 1161, 994. $\delta_H$ (300 MHz; $CDCl_3$) 1.23 (3H, d, *J* 7.3 8-H), 1.68 – 1.89 (2H, m, 4-H), 2.05 – 2.10 (2H, m, 5-H), 2.28 – 2.37 (1H, m, 3a-H), 2.45 (1H, dq, *J* 9.1 and 7.0 3-H), 4.87 – 4.91 (1H, m, 7a-H), 5.77 (1H, dq, *J* 2.6 and 10.2 7-H), 5.99 (1H, dt, *J* 10.3 and 3.6, 6-H); $\delta_C$ (75 MHz; $CDCl_3$) 14.0 ($CH_3$, 8-C), 20.7 ($CH_2$, 5-C), 21.8 ($CH_2$, 4-C), 37.2 (CH, 3-C), 41.1 (CH, 3a-C), 74.3 (CH, 7a-C), 124.3 (CH, 7-C), 132.4 (CH, 6-C), 179.6 (quart., 2-C); HRMS (EI+) 152.08326 ($M^+$. $C_9H_{12}O_2$ requires 152.08373).

H' NMR values were in agreement with that reported in the literature.[36]



**55b**

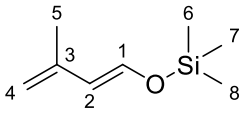
IR ($CDCl_3$) $\nu_{max}$: 1672, 1171, 949, 883. $\delta_H$ (300 MHz; $CDCl_3$) 1.20 (3H, d, *J* 6.7, 8-H), 1.55 – 1.72 (2H, m, 4-H), 1.94 – 2.24 (2H, m, 5-H), 2.40 – 2.47 (1H, m, 3a-H), 2.91 (1H, dq, *J* 7.32 and 7.32, 3-H), 4.61 – 4.64 (1H, m, 7a-H), 5.92 – 5.98 (1H, m, 7-H), 6.16 – 6.21 (1H, m, 6-H); $\delta_C$ (75 MHz; $CDCl_3$) 9.16 ($CH_3$, 8-C), 19.3 ($CH_2$, 5-C), 23.8 ($CH_2$, 4-C), 38.4 (CH, 3-C), 40.2 (CH, 3a-C), 73.4 (CH, 7a-C), 122.6 (CH, 7-C), 135.3 (CH, 6-C), 178.8 (quart., 2-C); HRMS (EI+) 152.08429 ($M^+$. $C_9H_{12}O_2$ requires 152.08373).



**55d**

IR ($CDCl_3$) $\nu_{max}$: 2934, 1774, 1648, 1134, 1016. $\delta_H$ (300 MHz; $CDCl_3$) 1.25 (3H, d, *J* 6.92, 8-H), 1.53 – 1.88 (2H, m, 4-H), 1.99 – 2.07 (1H, m, 3a-H), 2.24 – 2.38 (3H, m, 5-H), 4.37 – 4.44 (1H, m, 7a-H), 5.70 (1H, dq, *J* 10.24 and 3.33, 7-H), 6.09 (1H, dq, *J* 10.28 and 2.18 Hz, 1H, 6-H); $\delta_C$ (75 MHz; $CDCl_3$) 12.4 ($CH_3$, 8-C), 22.9 ($CH_2$, 5-C), 25.8 ($CH_2$, 4-C), 41.4 (CH, 3-C), 48.8 (CH, 3a-C), 79.4 (CH, 7a-C), 125.6 (CH, 7-C), 129.5 (CH, 6-C), 179.3 (quart., 2-C); HRMS (EI+) 152.08355. ($M^+$. $C_9H_{12}O_2$ requires 152.08373).

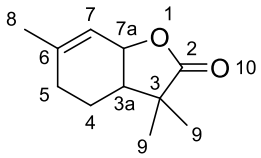
## (*E*)-trimethyl(3-methylbuta-1,3-dienyloxy)silane[38]




**46**

In a dry 100 mL round bottom flask charged with argon were added 3-methylbut-2-enal (13.7 mL, 0.143 mol), diethyl ether (25 mL) and triethylamine (22 mL, 0.160 mol), zinc chloride (0.2 g). Trimethylsilyl chloride (20 mL, 0.157 mol) was then added dropwise and the resulting brown-red mixture was heated under refluxed for 25 h. *n*-pentane (150 mL) was added and the precipitate filtered through silica. The solvent was removed *in vacuo* then distillation (b. p. 54 °C/ 15 Torr, lit., [38] 50 °C / 15 Torr) afforded the *title compound* (13.8 g, 62%) as colourless oil. Boiling point was in agreement with that reported in the literature.[38]

## 3,3,6-trimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7*aH*)-one



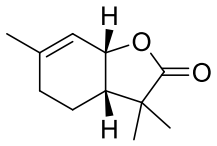

**25**

***Method A***:

A mixture of triene **24** (0.13 g, 0.72 mmol) in toluene (4 mL) was stirred in a microwave reactor at 200 °C for 6 h. The solvent was removed *in vacuo* and the resultant residue was purified *via* flash chromatography using 10:2 hexanes-diethyl ether as eluent to afford the *title compound* (yield not determined, two diastereomers) as a sweet smelling colourless liquid.

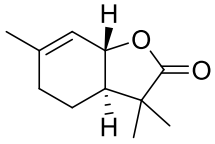
***Method B***:

A mixture of triene **24** (0.18 g , 1.00 mmol) in toluene (6 mL) was stirred in the microwave reactor at 250 °C for 5 h. The solvent was removed *in vacuo* and the residue purified *via* flash chromatography using 5:1 hexanes-diethyl ether as eluent to afford the *title compound* (yield not determined, two diastereomers) as a sweet smelling colourless liquid.



**25a**

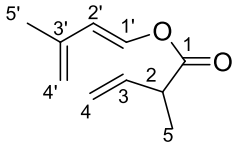
IR ($CDCl_3$) $\nu_{max}$: 1773, 1107. $\delta_H$ (300 MHz; $CDCl_3$) 1.19 (6H, s, 9-H), 1.18 – 1.73 (4H, m, 4,5-H), 1.79 (3H, s, 8-H), 1.92 – 1.99 (1H, m, 3a-H), 4.78 (1H, d, *J* 4.95, 7a-H), 5.66 (1H, m, 7-H); $\delta_C$ (75 MHz; $CDCl_3$) 19.2 ($CH_3$, 8-C), 21.5 ($CH_2$, 4-C), 23.8 ($CH_3$, 9-C), 24.8 ($CH_2$, 5-C), 43.3 (CH, 3a-C), 73.5 (CH, 7a-C), 117.3 (CH, 7-C), 143.7 (quart., 6-C), 181.4 (quart., 2-C); HRMS (EI+) 180.11476 ($M^+$. $C_{11}H_{16}O_2$ requires 180.11503).



**25b**

IR ($CDCl_3$) $\nu_{max}$: 2932, 1774, 1107. $\delta_H$ (300 MHz; $CDCl_3$) 1.24 (6H, s, 9-H), 1.47 – 1.60 (2H, m, 4-H), 1.69 (3H, s, 8-H), 1.78 – 1.91 (2H, m, 5-H), 2.14 – 2.27 (1H, m, 3a-H), 4.51 – 4.55 (1H, d, *J* 9.89, 7a-H), 5.82 – 5.85 (1H, m, 7-H); $\delta_C$ (75 MHz; $CDCl_3$) 19.5 ($CH_3$, 8-C), 22.9 ($CH_2$, 4-C), 23.5 ($CH_3$, 9-C), 30.9 ($CH_2$, 5-C), 42.4 (CH, 3a-C), 51.4 (quart., 3-C), 77.7 (CH, 7a-C), 120.8 (CH, 7-C), 137.6 (quart., 6-C), 182.5 (quart., 2-C); HRMS (EI+) 180.11515 ($M^+$. $C_{11}H_{16}O_2$ requires 180.11503).

## (*E*)-3-methylbuta-1,3-dienyl 2-methylbut-3-enoate[44**]



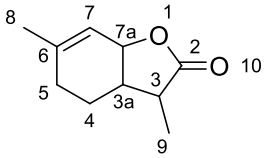
**45**

A solution of acid **49** (0.7 g, 7.00 mmol) and dry dichloromethane (20 mL) was cooled to 0 °C. Pyridine (0.28 mL, 3.48 mmol) was added followed by dropwise addition of cyanuric fluoride (0.3 mL, 3.5 mmol) and the resulting white milky mixture was stirred for 2.5 h. A solution of silyl enol ether **46** (1.2 g, 7.68 mmol) in dichloromethane (10 mL) was added to the reaction mixture dropwise at 0 °C. To the resultant yellow mixture was added solid tetra-*n*-butylammonium fluoride (0.05 g, 0.19 mmol) and the mixture was stirred for 2 h. After warming to room temperature *n*-pentane (150 mL) was added. The mixture was dried over $MgSO_4$, filtered through Celite® and the solvent removed *in vacuo*. The red residue was purified *via* flash chromatography using 150:1 pentane-diethyl ether as eluent to afford the *title compound* (0.28 g, 23%) as a colourless liquid.

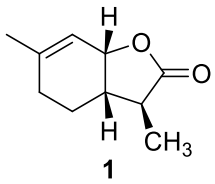
** The peaks corresponding to two methyl groups (5-C, 5-H) could not be adequately assigned due to solvent (*n*-pentane) contamination.

IR ($CDCl_3$) $\nu_{max}$: 2984, 1736, 1140, 918, 734. $\delta_H$ (300 MHz; $CDCl_3$) 3.19 – 3.27 (1H, m, 2-H), 4.93 – 4.96 (2H, m, 4-H), 5.14 – 5.19 (2H, m, 4-H), 5.87 – 6.00 (1H, m, 3-H), 6.18 (1H, d *J* 12.9, 2-H), 7.28 (1H, d *J* 12.9, 1-H); $\delta_C$ (75 MHz; $CDCl_3$) 43.1 (CH, 2-C), 115.8 ($CH_2$, 4-C), 116.5 ($CH_2$, 4'-C), 118.6 (CH, 2'-C), 136.2 (CH, 1'-C), 136.5 (CH, 3-C), 137.3 (quart., 3'-C), 161.5 (quart., 1-C); HRMS (EI+) 166.09876 ($M^+$. $C_{10}H_{14}O_2$ requires 166.09938).

## 3,6-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one



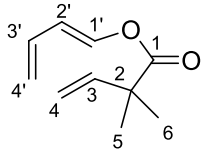

A mixture of triene **45** (0.28 g, 1.68 mmol) in toluene (4 mL) was stirred in a microwave reactor at 250 °C for ~16 h. The solvent was removed by careful distillation at atmospheric pressure and the resultant dark yellow oily residue was purified *via* flash chromatography using 6:1 pentane-diethyl ether as eluent to afford the *title compound* (yield not determined) as a sweet smelling liquid. The $^1H$ and $^{13}C$ NMR data were in agreement with that reported in the literature.[36]




**1**

IR ($CDCl_3$) $\nu_{max}$: 2916, 1981, 1769, 1016, 802. $\delta_H$ (400 MHz; $CDCl_3$) 1.21 (3H, d *J* 5.57, 9-H), 1.74 (3H, s, 8-H), 1.94 – 2.03 (4H, m, 4,5-H), 2.22 – 2.31 (1H, m, 3a-H), 2.35 – 2.47 (1H, m, 3-H), 4.88 – 4.91 (1H, m, 7a-H), 5.47 – 5.51 (1H, m, 7-H); $\delta_C$ (100 MHz; $CDCl_3$) 14.0 ($CH_3$, 9-C), 22.3 ($CH_2$, 4-C), 23.6 ($CH_3$, 8-C), 26.0 ($CH_2$, 5-C), 37.6 (CH, 3-C), 40.4 (CH, 3a-C), 75.4 (CH, 7a-C), 118.9 (CH, 7-C), 141.4 (quart. 6-C), 179.4 (quart., 2-C); HRMS (EI+) 166.09880 ($M^+$. $C_{10}H_{14}O_2$ requires 166.09938).

## (*E*)-buta-1,3-dienyl 2,2-dimethylbut-3-enoate[44]

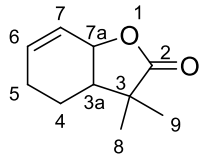



**52**

A solution of acid **28** (1.2 g, 10.5 mmol) and dry dichloromethane (20 mL) was cooled to 0 °C. Pyridine (0.4 mL, 4.97 mmol) was added followed by dropwise addition of cyanuric fluoride (0.4 mL, 4.66 mmol) and the resulting white milky mixture was stirred for 2 h. Silyl enol ether **50** (1.5g, 10.6 mmol) was then added dropwise at 0 °C. To the resultant yellow mixture was added anhydrous tetrahydrofuran (30 mL) followed by 1M tetra-*n*-butylammonium fluoride (1.8 mL, 1.8 mmol) and the mixture was stirred for 2 h. The mixture was warmed to room temperature and the pentane (150 mL) was added. The mixture was dried over $MgSO_4$ and filtered through Celite® and solvent removed *in vacuo*. The red residue was purified *via* flash chromatography using 100:1 hexane-ethyl acetate as eluent to afford the *title compound* (0.8 g, 32%) as a colourless liquid.

IR ($CDCl_3$) $\nu_{max}$: 1743, 1658, 1638, 1125. $\delta_H$ (400 MHz; $CDCl_3$) 1.35 (6H, s, 5,6-H), 5.07 – 5.24 (4H, m, 4',4-H), 5.99 – 6.11 (2H, m, 3,2'-H), δ 6.24 – 6.34 (1H, m, 3'-H), δ 7.39 (1H, d, *J* 12, 1-H); $\delta_C$ (100 MHz; $CDCl_3$) 24.3 ($CH_3$, 5,6-C) , 45.0 (quat., 2-C) , 113.6 ($CH_2$, 4-C) , 116.2 (CH, 2'-C) , 117.2 ($CH_2$, 4'-C) , 131.7 (CH, 3'-C) , 139.0 (CH, 1'-C) , 141.5 (CH, 3-C), 173.1 (quat., 1-C); HRMS (EI+) 167.10640 ($M^+$. $C_{10}H_{15}O_2$ requires 167.10720).

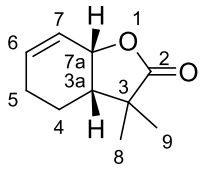
## 3,3-dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one††




**54**

A mixture of triene **52** (0.1 g, 0.6 mmol) in toluene (2.5 mL) was stirred in a microwave reactor at 190 °C for ~18 h. The solvent was removed by careful distillation at atmospheric pressure and the resultant dark yellow oily residue was purified *via* flash chromatography using 10:1 pentane-diethyl ether as eluent to afford the *title compound* (yield not determined, one diastereomer) as a sweet smelling colourless liquid.

†† The peaks corresponding to two methyl groups (8,9-H) could not be adequately assigned due to solvent (*n*-pentane) contamination.




**54a**

IR ($CDCl_3$) $\nu_{max}$: 2924, 1768, 1219, 1135, 772. $\delta_H$ (300 MHz; $CDCl_3$) 1.47 – 2.10 (4H, m, 4,5-H), 2.15 – 2.24 (1H, m, 3a-H), 4.80 (1H, t, *J* 9.35 and 4.67, 7a-H), 5.93 – 5.99 (1H, m, 7-H), 6.15 – 6.20 (1H, m, 6-H); $\delta_C$ (75 MHz; $CDCl_3$) 19.3 ($CH_3$, 8,9-C), 24.1 ($CH_2$, 5-C), 24.8 ($CH_2$, 4-C), 44.9 (CH, 3a-C), 72.0 (CH, 7a-C), 122.9 (CH, 7-C), 134.8 (CH, 6-C), 179.93 (quart., 2-C); HRMS (EI+) 167.10793 ($M^+$. $C_{10}H_{15}O_2$ requires 167.10720).

**References**


1. Southwell, I. A., *Tetrahedron Letters* **1975,** 16, (24), 1885-1888.
2. Guth, H., *Helv. Chim. Acta* **1996,** 79, (6), 1559-1571.
3. Chavan, S. P.; Kharul, R. K.; Sharma, A. K., *Tetrahedron: Asymmetry* **2001,** 12, 2985-2988.
4. Bartlett, P. A.; Pizzo, C. F., *J. Org. Chem.* **1981,** 46, (19), 3896-3900.
5. Bergner, E. J.; Helmchen, G., *Eur. J. Org. Chem.* **2000,** 2000, (3), 419-423.
6. Stefano, S.; Claudio, F., *Helvetica Chimica Acta* **2004,** 87, (8), 2100-2109.
7. Jagella, T.; Grosch, W., *Eur. Food Res. Technol.* **1999,** 209, (1), 16-21.
8. Buettner, A.; Schieberle, P., *J. Agric. Food. Chem.* **1999,** 47, (12), 5189-5193.
9. Buettner, A.; Schieberle, P., *J. Agric. Food. Chem.* **2001,** 49, (5), 2387-2394.
10. E. Fuhrmann, W. G., *Nahrung/Food* **2002,** 46, (3), 187-193.
11. Hognadottir, A.; Rouseff, R. L., *J. Chromatogr. A* **2003,** 998, (1-2), 201-211.
12. Perez-Cacho; Pilar, R.; Rouseff, R., *Crit. Rev. Food. Sci. Nutr.* **2008,** 48, 681-695.
13. Bonnlander, B.; Baderschneider, B.; Messerer, M.; Winterhalter, P., *J. Agric. Food. Chem.* **1998,** 46, (4), 1474-1478.
14. Southwell, I. A., *Phytochemistry* **1973,** 12, (6), 1341-1343.
15. *New Zealand Wine Growers Annual Report*; Auckland, 2007.
16. Guth, H., *J. Agric. Food. Chem.* **1997,** 45, (8), 3022-3026.
17. Winterhalter, P.; Buettner, A., *ACS Symp. Ser.* **2001,** 794, 21-32.
18. Luan, F.; Degenhardt, A.; Mosandl, A.; Wust, M., *J. Agric. Food. Chem.* **2006,** 54, (26), 10245-10252.
19. Lopez, R.; Ferreira, V.; Hernandez, P.; Cacho, J. F., *J. Sci. Food Agric.* **1999,** 79, (11), 1461-1467.
20. Stefano Serra, C. F., *Helvetica Chimica Acta* **2004,** 87, (8), 2100-2109.
21. Bear, B. R.; Sparks, M. S.; Shea, J. K., *Angew. Chem. Int. Ed.* **2001,** 40, (5), 820-849.
22. Paddon-Row, M. N.; Moran, D.; Jones, G. A.; Sherburn, M. S., *J. Org. Chem.* **2005,** 70, (26), 10841-10853.
23. Man, E. H.; Sanderson, J. J.; Hauser, C. R., *J. Am. Chem. Soc.* **1950,** 72, (2), 847-848.
24. Barbier, P.; Benezra, C., *J. Org. Chem.* **1983,** 48, (16), 2705-2709.
25. Tilly, D.; Castanet, A.-S.; Mortier, J., *Chem. Lett.* **2005,** 34, (3), 446-447.
26. Strubing, D.; Neumann, H.; Klaus, S.; Hubner, S.; Beller, M., *Tetrahedron* **2005,** 61, (48), 11333-11344.
27. Schlosser, M.; Limat, D., *Tetrahedron* **1995,** 51, 5807-5812.
28. Carpino, L. A.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; El-Faham, A.; Riemer, C.; Warrass, R., *J. Org. Chem.* **1999,** 64, (12), 4324-4338.
29. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F., *J. Chem. Soc., Trans.* **1915,** 107, 1080-1106.
30. Jones, W. J.; Chorley, H. W. T., *J. Chem. Soc.* **1946**.
31. Levy, J.; Christensen, N. J. Synthesis of prenyl chloride. 4036899, 1976.
32. Kwart, H.; Miller, R. K., *J. Am. Chem. Soc.* **1954,** 76, (21), 5403-5405.
33. Clarke, H. T.; Rahrs, E. J., *Organic Syntheses* **1941,** 1, 91.
34. Scholte, A. A.; Vederas, J. C., *Org. Biomol. Chem.* **2006,** 4, (4), 730-742.
35. House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P., *J. Org. Chem.* **1973,** 38, (3), 514-522.
36. GroB, S.; Laabs, S.; Scherrmann, A.; Sudau, A.; Zhang, N.; Nubbemeyer, U., *J. Prakt. Chem.* **2000,** 342, (7), 711-714.
37. Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G., *Org. Lett.* **2002,** 4, (22), 3875-3878.
38. Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L., *J. Org. Chem.* **1991,** 56, (12), 4045-4048.
39. Kappe, C. O., *Angew. Chem. Int. Ed.* **2004,** 43, (46), 6250-6284.
40. Hajek, M., *Microwaves in Organic Synthesis*. Wiley-VCH, Weinheim: 2002.
41. Cayzer, T. N.; Paddon-Row, M. N.; Moran, D.; Payne, A. D.; Sherburn, M. S.; Turner, P., *J. Org. Chem.* **2005,** 70, (14), 5561-5570.

42. Roth, M.; Damm, W.; Giese, B., *Tetrahedron Letters* **1996,** 37, (3), 351-354.
43. Russell, R. A., *Aust. J. Chem.* **1975,** 28, 2535-2538.
44. Limat, D.; Schlosser, M., *Tetrahedron* **1995,** 51, (20), 5799-5806.
45. Rossi, R.; Ingrosso, G., *Gazz. Chim. Ital.* **1968,** 98, 866-883.

**Appendix 1**.

| Compound | SCF energy RB3LYP/6-31+G(d) Hartree | ZPVE RB3LYP/6-31+G(d) Hartree | MP2 energy RMP2/6-31+G(d) Hartree | MP2 ZPVE corrected kJ/Mol | MP2 Normal kJ/mol | partition fcn | Boltzmann Population (%) |
|---|---|---|---|---|---|---|---|
| **55a** | -500.5511407 | 0.190544 | -498.9596871 | -1309518.385 | 0.000 | 1.000 | 52.9 |
| **55b** | -500.5487265 | 0.1909715 | -498.9587259 | -1309514.739 | 3.646 | 0.380 | 20.1 |
| **55d** | -500.5469644 | 0.1909837 | -498.9588674 | -1309515.079 | 3.307 | 0.416 | 22.0 |
| **55c** | -500.5493512 | 0.1906137 | -498.9563575 | -1309509.46 | 8.925 | 0.094 | 5.0 |
| **1** | -539.86894 | 0.2181806 | -538.1384985 | -1412309.795 | 0.000 | 1.000 | 66.6 |
| **2** | -539.8665581 | 0.2185697 | -538.1369 | -1412304.576 | 5.218 | 0.250 | 16.7 |
| **3** | -539.8645431 | 0.2185492 | -538.134105 | -1412297.292 | 12.503 | 0.036 | 2.4 |
| **4** | -539.8669604 | 0.2181737 | -538.1362934 | -1412304.023 | 5.771 | 0.216 | 14.4 |
| **54a** | -539.8631127 | 0.2187309 | -538.1375447 | -1412305.846 | 0.000 | 1.000 | 75.1 |
| **54b** | -539.8619322 | 0.2186908 | -538.1359214 | -1412301.689 | 4.157 | 0.332 | 24.9 |
| **25a** | -579.1809103 | 0.2463183 | -577.3103206 | -1515081.538 | 0.000 | 1.000 | 80.8 |
| **25b** | -579.1795078 | 0.2462418 | -577.308182 | -1515076.124 | 5.414 | 0.238 | 19.2 |

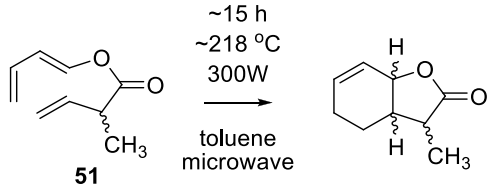
**Appendix 1**. *Calculations of transition state energies and the consequent Boltzmann distributions not taking account of the z-isomer TS arising from electrocyclic ring closing/ring opening reactions*

**Appendix 2**.

| Compound | SCF energy RB3LYP/6-31+G(d) Hartree | ZPVE energy RB3LYP/6-31+G(d) Hartree | MP2 energy RMP2/6-31+G(d) Hartree | MP2 ZPVE corrected kJ/mol | MP2 normal k/J/mol | partition fcn | Boltzmann Population (%) |
|---|---|---|---|---|---|---|---|
| **55a** | -500.5475629<br>-500.5511407 | 0.1910019<br>0.190544 | -498.963735<br>-498.9596871 | -1309527.811<br>-1309518.385 | 2.033<br>11.459 | 0.583<br>0.048 | 37.7 |
| **55b** | -500.5475781<br>-500.5487265 | 0.1910364<br>0.1909715 | -498.964544<br>-498.9587259 | -1309529.844<br>-1309514.739 | 0.000<br>15.105 | 1.000<br>0.018 | 60.9 |
| **55d** | -500.5469644 | 0.1909837 | -498.9588674 | -1309515.079 | 14.766 | 0.020 | 1.2 |
| **55c** | -500.5493512 | 0.1906137 | -498.9563575 | -1309509.46 | 20.384 | 0.004<br>1.673 | 0.3 |
| **1** | αββ<br>β,α,α | -539.8655366<br>-539.86894 | 0.218583<br>0.2181806 | -538.1360997<br>-538.1384985 | -1412302.44<br>-1412309.795 | 7.355<br>0.000 | 60.7 |
| **2** | βββ<br>α,α,α | -539.8655048<br>-539.8665581 | 0.218598<br>0.2185697 | -538.1368556<br>-538.1369 | -1412304.385<br>-1412304.576 | 5.409<br>5.218 | 25.9 |
| **4** | β,β,α | -539.8645431 | 0.2185492 | -538.134105 | -1412297.292 | 12.503 | 1.9 |
| **3** | α,β,α | -539.8669604 | 0.2181737 | -538.1362934 | -1412304.023 | 5.771 | 11.5 |
| **25a** | -579.1809103<br>-579.1778463 | 0.2463183<br>0.2465163 | -577.3103206<br>-577.3075615 | -1515081.538<br>-1515073.774 | 0.000<br>7.764 | 1.000<br>0.127 | 82.6 |
| **25b** | -579.1795078 | 0.2462418 | -577.308182 | -1515076.124 | 5.414 | 0.238 | 17.4 |

**Appendix 2**. *Calculations of transition state energies and the consequent Boltzmann distributions taking account of the z-isomer TS arising from electrocyclic ring closing/ring opening reactions*

**Appendix 3**




**51**

**Reaction 1.**

| Compound # | Relative energy kJ/mol | Theoretical (%) | Experimental (%) |
|---|---|---|---|
| **55d** | 25.80 | 0.08 | 16.9 |
| **55a** | 0.00 | 56.82 | 56.4 |
| **55c** | 32.70 | 0.01 | 3.5 |
| **55b** | 1.07 | 43.3 | 23.2 |

**Appendix 3**. *Calculation of the relative energies of the products to the Diels-Alder* ***Reaction 1*** *and subsequent deduction of theoretical product distribution. The poor correlation to the experimental findings can be seen indicating that the reaction is under kinetic rather than thermodynamic control*