# Study program/ Specialization:
Environmental engineering/Water Science and Technology

<table>
<thead>
<tr>
<th>Spring semester, 2010</th>
<th>Open</th>
</tr>
</thead>
</table>

## Writer:
Joachim Hope Kyllingstad

(Writer’s signature)

## Faculty supervisor:
Prof. II Dr. Einar Bakstad

## External supervisor(s):

## Title of thesis:
Progress in the Total synthesis of Hazardiaadione

## Credits (ECTS): 30

## Key words:
- Total Synthesis
- Cyclopropanation
- Alkylation Reaction
- Aldol Cyclization

<table>
<thead>
<tr>
<th>Pages: 54</th>
<th>Stavanger,</th>
<th>Date/year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgments

I would like to offer thanks to Dr. Einar Bakstad (director of research, Biolink Group AS and Adj. Prof., University of Stavanger) for his support and guidance through my thesis. I am grateful for all the knowledge I have received this year in both theoretical and experimental organic chemistry.

I would also thank my fellow students Kristine Fagerstrand, Guro H. Rongnså and Siri Lunde for creating a good working atmosphere in the lab.

I would also like to thank the people which have assisted me in my work, engineer Jorma H. Kinnari at Ewos Innovation for 500 MHz NMR analysis, professor Kåre Jørgenses at the University of Stavanger for assisting me in NMR analysis and Dr. Tore Nordvik and Msc. Anders Grinrød for use of FT-IR at MI-SWACO.

I would also thank BIOLINK GROUP AS for inviting me to do practical work in their facilities.

Last but not least, I would thank my wonderful fiancée for supporting me.
Abstract

The total synthesis of Hazardiadione 1 was almost completed, but the time ran out. Figure 1 shows a graphical presentation of the abstract (figure 1).

Progress in the synthesis of Hazardiadione

The diketone 20 was synthesized in five steps from the starting material a cis/trans mixture of 2.6- dimethylcyclohexanone (9). The overall yield for the diketone 20 is currently low only 0.4 %. The yield in the fourth and fifth step can be improved dramatically. Hazardiadione can probably be synthesized from the diketone 20 with an aldol cyclization followed be a regioselective allylic oxidation.

The C₆ side chain was synthesized in two different ways.
The C₆ side chain was synthesized in 15 % using three steps and in 6 % using two steps.
# Table of Contents

1. **Introduction** 4  
2. **Background** 5  
   2.1. Hazardiadione, a Novel Sesquiterpene 5  
   2.2. Terpenoids 6  
      2.2.1 Biosynthetic pathways for IPP and DMAPP 8  
      2.2.2 Sesquiterpenes 11  
      2.2.3 Biologically activity of some important sesquiterpenes 14  
3. **Retrosynthetic analysis of Hazardiadione** 16  
4. **Results and discussion** 17  
   4.1 Earlier unpublished results from Dr. Bakstad research group 17  
      4.1.1 Results from Dr. Bakstad and Dr. Bonger 17  
      4.1.2 Results from Dr. Bakstad and guest scientist Josenne Mae R. Sanchez 20  
   4.2 Progress in the synthesis of Hazardiadione 20  
      4.2.1 Synthesis of the silyl enol ether 10 20  
      4.2.2 Alkylation reaction between the silyl enol ether 10 and nitroalkene 13 23  
      4.2.3 Aldol cyclization 29  
      4.2.4 Removal of halogen 30  
   4.3 Synthesis of the C₆ side chain 31  
      4.3.1 Synthesis of the nitroalkene 13 31  
      4.3.1 Synthesis of the α-bromoketone 6A 35  
5. **Conclusion and further work** 36  
6. **Experimental section** 37  
   6.1 Synthesis towards Hazardiadione (1) 37  
   6.2 Synthesis of the C₆ side chain  

References 48  
Appendix A 49  
Appendix B 51
1. Introduction

During my master thesis as a part of the master program environmental technology at the University of Stavanger I worked on the total synthesis of a novel sesquiterpene we called Hazardiadione 1. The duration of the work was from January to July 2010.

The structure of the sesquiterpene is proposed by prof. Fred Stevens at the Linus Pauling Institute, Oregon State University. The proposed structure has one stereogenic center and a double α,β-unsaturated carbonyl. The total synthesis of the sesquiterpene is of interest because of its possible biological activities and the compound is not described in the literature.

The plan was to synthesize the sesquiterpene first as a racemate and compare the spectral analysis of the synthesized compound to the spectral data of the isolated natural sample.

If the spectroscopic data of the synthesized molecule is in accordance with the naturally isolated compound, a strategy for stereoselective synthesis should be developed in order to synthesize both enantiomers of Hazardiadione.
2. Background

2.1 Hazardiadione, a novel sesquiterpene

A novel sesquiterpene has been isolated from a plant found in the desert of Arizona. The plant is called *Hazardia orcutti* and belongs to the sunflower family (*Asteraceae*).\(^1\) The proposed molecule structure was elucidated by various 2-D NMR techniques and high-resolution MS by prof. dr. Fred Stevens.\(^2\) A suggested name for the compound is hazardiadione 1. The proposed structure of hazardiadione 1 is described in figure 2.

![Figure 2. Proposed structure of Hazardiadione (1).](image)

This sesquiterpene has a double α,β- unsaturated carbonyl systems. The double α,β-unsaturated carbonyl systems gives 4 electrophilic centers, one on the β-position on the five membered ring and one on the seven membered ring and the two carbonyl carbons. These electrophilic centers are reactive towards attack from nucleophiles. (figure 3)

![Figure 3. Electrophilic centers reactive towards nucleophilic attack.](image)
A hard nucleophile will normally attack the carbonyl, while a soft nucleophile will normally attack the β-carbons in a Michael reaction. The soft nucleophile is expected to attack the β-position on the seven membered ring more easily because of the steric hindrance from the isopropyl side chain on the five membered ring. Hazardiadione has one stereogenic center and the compound was found to be optically active by measurements on optical rotation by Dr. Vidar Bjørnstad. This concludes that the molecule is not synthesized in the plant as racemate. Because the molecule has double α,β-unsaturated carbonyl systems and is optically active, it is probable that at least one of the enantiomers are biological active.

### 2.2 Terpenoids

Compounds isolated from nature are of interest because of their possible biological activity. Some of these compounds can be used for human purpose as medicine or health products. Many of the interesting compounds from nature are isolated from plants.

Compounds that are produced by plants can be divided into primary metabolites and secondary metabolites. Primary metabolites are compounds that are essential to life, the carbohydrates, amino acids, proteins and nucleic acids. Secondary metabolites are compounds known to be important for survival and propagation. There are three major classes of secondary metabolites alkaloids, terpenoids and phenolics. Terpenoids are the largest class of secondary metabolites.

Terpenoids have been known since antiquity as ingredients of flavors, soaps, drugs, perfumes and pigments. Terpenoids are natural compounds derived from isoprene C₅ units in a head to tail fashion. The structures contains carbon skeletons represented by (C₅)ₙ and are classified according to number of carbons. (table 1.)[3]

<table>
<thead>
<tr>
<th>Classification</th>
<th>#Carbons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiterpenes</td>
<td>C₅</td>
</tr>
<tr>
<td>Monoterpenes</td>
<td>C₁₀</td>
</tr>
<tr>
<td>Sesquiterpenes</td>
<td>C₁₅</td>
</tr>
<tr>
<td>Diterpenes</td>
<td>C₂₀</td>
</tr>
<tr>
<td>Sesterterpenes</td>
<td>C₂₅</td>
</tr>
<tr>
<td>Triterpenes</td>
<td>C₃₀</td>
</tr>
<tr>
<td>Tetraterpenes</td>
<td>C₄₀</td>
</tr>
</tbody>
</table>

Table 1. Classification of the terpenoids.

Few of the natural terpenoids have structures conformed exactly to the simple concept of linear head-to-tail combination of isoprene units. Most terpenoids are modified further by cyclization reactions. The terpenoids are all build up by isoprene units. The biochemically active isoprene units are dimethylallyl diphosphate (DMAPP) and isopentyl diphosphate (IPP) and these isoprene units are the building blocks for al terpenoids (figure 4.)[3]
DMAPP is a reactive electrophile, diposphate is a good leaving group and gives the allylic cation with is stabilized by charge delocalization in an $S_N1$ type reaction. (figure 5)$^{[3]}$
Figure 5. DMAPP reacts as a electrophile in $S_N^1$ type reaction

IPP act as a nucleophile especially towards the electrophilic DMAPP, and this is the basis of terpenoid biosyntheses. Figure 6 shows the generation of geranyl diposphosphate from DMAPP and IPP.$^{[3]}$

Figure 6. Generation of geranyl diposphate from DMAPP and IPP.$^{[3]}$

### 2.2.1 Biosynthetic pathways to IPP and DMAPP

There are two pathways leading to IPP and DMAPP, the mevalonate pathway and the recently discovered mevalonate independent pathway via deoxyxylulose phosphate also called the methlyerythriol phosphate pathway. The mevalonate pathway are described in figure 7.$^{[3]}$
The isomerisation is reversible but the equilibrium lies towards IPP. Perhaps ATP assists the loss of hydroxyl as shown in figure 7. The reduction involves the enzyme HMG-CoA reductase and nicotinamide adenine dinucleotide phosphate (NADPH) and is an irreversible and rate limiting transformation. MVA is transformed into the phosphorylated isoprene units IPP and DMAPP in two steps, beginning with phosphorylation of the primary alcohol group giving mevalonic acid diphosphate. The phosphorylation involves two different ATP dependent enzymes. The mevalonic acid diphosphate undergoes decarboxylation requiring an ATP molecule to give IPP. Perhaps ATP assists the loss of hydroxyl as shown in figure 7. IPP is formed in a stereospecific allylic isomerisation by the isomerisation enzyme isomerase. Isomerase removes the proton Hₐ and incorporates a proton from water on the terminal carbon. The isomerisation is reversible but the equilibrium lies towards DMAPP. The methylerythriol phosphate pathway is described in figure 8.
The diphosphate of vitamin B1 (thiamine), Thiamine diphosphate (TPP) reacts with pyruvate in an aldol type reaction followed by decarboxylation giving an acetaldehyde equivalent in the form of an enamine. The TPP/pyruvate-derived enamine reacts as a nucleophile with the aldehyde in glyceraldehyde 3-phosphate followed by release of the TPP anion to give 1-
Deoxy-D-xylulose 5-phosphate.\textsuperscript{[3]} Deoxy-D-xylulose 5-phosphate is transformed by a pinacol-like rearrangement reaction followed by a reduction by NADPH to give 2-C-methyl D-erythritol 4-P. A single enzyme catalyzes the rearrangement and reduction reaction without release of any intermediate.\textsuperscript{[3]} 2-C-methyl D-erythritol 4-P reacts with cytidine triphosphate (CTP) to give a cytidine diphospho derivative (4-(CDP)-2-C-methyl-D-erythritol). The cytidine diphospho derivative is phosphorylated by ATP to give the 2-phospho-(CDP)-2-C-methyl-D-erythritol, which is converted to a cyclic 2-C-methyl-D-erythritol-2,4-cyclophosphate by loss of cytidine phosphate.\textsuperscript{[3]} The cyclophosphate is converted to IPP and DMAPP by steps not yet elucidated. The reaction may occur as described in figure 8, an intermolecular elimination, and then enol-keto tautomerism followed by two sets of reduction with NADPH followed elimination of H\textsubscript{2}O to give IPP. DMAPP may be formed by an isomerism by the enzyme isomerase, or may be formed independently.\textsuperscript{[3]}

Whether a biosynthesis of a terpenoid is provided with isoprene units from the mevalonate pathway or the deoxyxylulose phosphate pathway must be established experimentally. The animal lacks the deoxyxylulose phosphate pathway so the mevalonate pathway is used exclusive for the generation of isoprene units for terpenoids production in animals. The steroids are formed via terpenoids precursors. Inhibition of the mevalonate pathway enzyme HMG-CoA reductase will downregulate the steroid production. This is of interest since the biosynthesis of cholesterol could be regulated by use such inhibitors.\textsuperscript{[3]} Plants and many other organisms are equipped with both pathways. In plants the pathways seem to be compartmentalized, the mevalonate pathway enzymes are located in cytoplasm and the deoxyxylulose phosphate pathway enzymes are located in the chloroplasts. Therefore triterpenes and steroids which are cytosolic products are formed by the mevalonate pathway, while most other terpenoids are formed in the chloroplast and are deoxyxylulose phosphate derived.\textsuperscript{[3]} Therefore the novel sequiterpene Hazardiadione is probably build up of isoprene units from the deoxyxylulose phosphate pathway.

\textbf{2.2.2 Sesquiterpenes}

Sesquiterpenes are the terpenoids containing a carbon skeleton of 15 carbons (C\textsubscript{15}). The fundamental sesquiterpene precursor is farnasyl diphosphate (FPP) (figure 9).\textsuperscript{[3]}
Figure 9. Biosynthesis of farnesyl diphosphate (FPP)

The FPP is generated by an addition of an IPP unit to GPP, which reacts in a $S_N^1$ type reaction with IPP followed by a stereospecific loss of proton to give FPP. FPP can give rise to linear and mono-, bi-, and tri-cyclic sesquiterpenes. The stereochemistry of the double bond nearest the diphosphate can adopt an $E$ configuration or a $Z$ configuration, giving the two stereochemical configuration $E,E$-Farnesyl PP and $E,Z$- Farnesyl PP (figure 10).
This allows different possibilities for folding the carbon chain. The folding reactions are dictated by the enzymes involved and cyclization by electrophilic attack on the double bonds. Reactions of carbocations explain most of the common skeletons of sesquiterpenes. The guaiane skeleton could be generated via $E,E$-farnesyl cation. (figure 11).\(^3\)

\[\text{E,E-farnesyl cation} \xrightarrow{\text{cyclization by electrophilic attack on double bond}} \text{germacryl cation} \xrightarrow{\text{protonation and cyclization (anti marcovnikov)}} \text{guaiyl cation}\]

\[\text{E,Z farnesyl PP} \xrightarrow{\text{OPP}} \text{nerolilyl PP}\]

Figure 10. Ionization of FPP

Figure 11. The guaiane skeleton could be generated via $E,E$-Farnesyl cation.\(^3\)

$E,E$-Farnesyl cation undergoes cyclization by electrophilic attack on the double bond to give germacryl cation. Then protonation at the most substituted end of the double bond followed by cyclization could give the guaiyl cation and the guaiane skeleton which has resemblances to the skeleton of Hazardiadiione, a seven membered ring fused with five membered ring. The skeleton of hazardiadiione is called isoduacane. (figure 12)\(^4\)

Figure 12. Isoduacane skeleton
2.2.4 Biological activity of some important sesquiterpenes

Tabel 2. Lists of some biological active sesquiterpenes

<table>
<thead>
<tr>
<th>Biological activity</th>
<th>Sesquiterpene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinflammatory</td>
<td>helenalin[^4], chamazulene[^4]</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>(+)-isivelleral[^4], Δ^6^-protoilludiene[^5], (-)illudine M[^4], (-)illudine S[^4], (-)-merulidial[^4], (+)-dihydroxy-γ-inoyldiene[^4], artemisic acid[^4]</td>
</tr>
<tr>
<td>Anticancer</td>
<td>helenalin[^4], (-)illudine M[^4], (-)illudine S[^4]</td>
</tr>
<tr>
<td>Antimalaria</td>
<td>artemisinin[^3]</td>
</tr>
<tr>
<td>Antihematic</td>
<td>helenalin[^4]</td>
</tr>
<tr>
<td>Antipyretic</td>
<td>helenalin[^4]</td>
</tr>
<tr>
<td>CNS and respiratory stimulant</td>
<td>(-)-picotoxinin[^4]</td>
</tr>
<tr>
<td>Antifungal</td>
<td>(+)-armillar[^4]</td>
</tr>
<tr>
<td>Antimycotic</td>
<td>(-)-merulidial[^4]</td>
</tr>
<tr>
<td>Antihelmithic</td>
<td>α-santonin[^3]</td>
</tr>
<tr>
<td>Antimigrane</td>
<td>parthenolide[^3]</td>
</tr>
</tbody>
</table>

One of the most interesting sesquiterpenes is the antimalaria compound artemisinin. Artemesinin is a lactone with a rare peroxide linkage which appears to be essential for the antimalaria activity (Figure 13).[^3]

![Figure 13. Artemisinin](image)

Artemisine is a sesquiterpene isolated from the plant *Artemisin annu* (compositae/Asteraceae). *Artemisin annu* has been used in Chinese traditional medicine for centuries for treatment of fewer and malaria. Artemisinin is the compound responsible for the antimalaria properties in the herbal medicine.[^3]

Malaria is a disease in tropical regions of the world caused by infection from varies spesies of protozoa in the genus *plasmodium*. The protozoon enters the blood system from the saliva from infected female (*anopheles*) mosquitos. There are four spesies of protozoa causing malaria, *plasmodium falciparum*, *plasmodium vivax*, *plasmodium ovale* and *plasmodium malariae*, of which *plasmodium falciparum* gives the most severe malaria.[^6] Artemisinin is an effective blood schizontocide in humans infected with malaria and the compound shows low toxicity.[^3] This is very interesting and there is effort to produce artemisinin or analogues as
new antimalaria drugs. Many of the currently used drugs have become less satisfactory due to resistant strains of protozoa *Plasmodium falciparum*. Artemisinin has proved effective toward these resistant strains.\[^3\] Reduction of artemisinin gives dihydroartemisinin which has been used to make a range of semi synthetic analogues to artemisinine, the acetals artemether and arteether and the water soluble sodium salt of artelinel acid and artesunic acid (figure 14)\[^3\]

![Chemical structures](image)

**Figure 14.** Semi synthetic analogues to artemisinin.

Artemether is effective against chloroquine resistant strains of *Plasmodium falciparum* and is currently being used in injection formulas. The artesunic acid is also used in injection form.\[^3\]
3. Retrosynthetic analysis of hazardiadione

The retrosynthetic analysis of Hazardiadione 1 is presented in figure 15.

![Diagram of the retrosynthetic analysis of Hazardiadione]

Figure 15. The retrosynthetic analysis of Hazardiadione.

The first step in the retrosynthetic analysis of Hazardiadione is a functional group addition (FGA), the addition of a halogen. This functionality can make it possible to make derivatives of the natural product. The removal of the halogen gives the target molecule 1. The removal of the halogen can probably be achieved by reduction with tributyltin hydride (BTH) or SmI₂. The next step is a functional group interconversion (FGI). The diketone 2 could be synthesised from the precursor 3 with a regioselective allylic oxidation. Regioselective oxidation must be preformed since there are several allylic carbons, and might be achieved by oxidation using pyridinium chlorochromate (PCC). Nicolaou et al. had a similar challenge in the synthesis of Taxol and used PCC to get the regioselectic allylic oxidation. The next step is disconnection between the α-carbon and the β-carbon in molecule 3. Molecule 3 can probably be regained by a intramolecular aldol cyclization of the diketone 4. The next step is a disconnection of the side chain, the diketone 4 can be regained in an alkylation reaction between the α,β unsaturated ketone 5 and the electrophile 6. The next step in the retrosynthetic analysis is a ring expansion. The ketone 5 can be synthesized from the enol ether 8 by using a cyclopropanation with concomitant ring expansion. The next step is a FGI, the enol ether 8 can be prepared from the corresponding ketone 9 in a standard reaction with trimethylsilyl chloride, sodium iodide and triethylamine. 2,6 Dimethylcyclohexanone (9) is commercially available as a mixture of cis and trans isomers.
4 Results and discussion

4.1 Earlier unpublished results from Dr. Bakstads research group

Dr. Bakstad and Dr. Bonger worked on the synthesis on Hazardiadione in 2001/2002 and Dr. Bakstad and guest research scientist Josenne Mae R. Sanchez worked on the project in 2007/2008, so the first part of this chapter presents the results in their work.

4.1.1 Results from Dr. Bakstad and Dr. Bonger

The α,β unsaturated ketone 5A was synthesised in good yield in (78 %) in two steps.[1] (Scheme 1)

![Scheme 1. Synthesis of the ketone 5A from 2,6-dimethylcyclohexanone (9).](image)

The most interesting with this synthesis is the cyclopropanation with the highly reactive titanium.[12]

The ketone 5A was also synthesised in good yield in (55 %) in four steps.[1] (Scheme 2)

![Scheme 2. Synthesis of the ketone 5A from 2,6-dimethylcyclohexanone](image)

The interesting with this synthesis was that the gem-dichoropropane 25 underwent ring opening to give the corresponding ketone 5A instead of the dimethylketal normally formed under these conditions.[13]

Problems arose under alkylation reactions between electrophiles and the ketone 5A. The main problem was that there is two possible enolates that can be formed in reactions with base.[1]

The two different enolates are shown in figure 15.
Figure 15. Abstraction of α- or γ-proton to generate different enolates.

Abstaction of the α-proton probably gives the kinetic enolate because $pK_a$ of the α-proton is expected to be lower than $pK_a$ of the γ-proton. It was observed that the γ-proton was abstracted giving the thermodynamic enolate. Dr. Bonger preformed alkylation reactions with many different electrophiles and the ketone 5A. None of these reactions gave the expected diketone 4A. The alkylation reactions are listed in table 3.

Table 3. Alkylation reactions on the ketone 5A studied by Dr. Bakstad and Dr. Bonger.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Electrophile</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA or NaHMDS</td>
<td></td>
<td>THF</td>
<td>Mainly starting material, traces of undefined products</td>
</tr>
<tr>
<td>2</td>
<td>KH</td>
<td></td>
<td>DMF</td>
<td>Starting material</td>
</tr>
<tr>
<td>3</td>
<td>KH</td>
<td></td>
<td>THF or DME</td>
<td>Starting material, Favorskii type reaction took place</td>
</tr>
<tr>
<td>4</td>
<td>KH</td>
<td></td>
<td>DMF</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>KH</td>
<td></td>
<td>DMF</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>KH</td>
<td></td>
<td>DMF</td>
<td></td>
</tr>
</tbody>
</table>
Dr. Bakstad and Dr. Bonger decided to study coupling reactions with specific enolate equivalents such as vinyl ether 11, silyl enol ether 10 or enamines 12 (figure 16).

![Figure 16 Equivalents for specific enolate](image)

The coupling reactions with the specific enolate equivalents can be done with electrophiles and Lewis acids. The reactions with specific enolate equivalents studied by Dr. Bakstad and Dr. Bonger are shown in table 4.\(^1\)

Table 4. Experiments preformed with specific enolate equivalents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Electrophile</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![O]Cl</td>
<td>![O]-[Br]</td>
<td>CH(_3)CN, reflux</td>
<td>Bromo ketone was unstable to heat</td>
</tr>
<tr>
<td>2</td>
<td>![OTMS]Cl</td>
<td>![O] or ![CH(_2)O]n</td>
<td>TiCl(_4),CH(_2)Cl(_2), -78(^\circ)C to RT</td>
<td>Undefined products and ketone 5A</td>
</tr>
<tr>
<td>3</td>
<td>![OTMS]Cl</td>
<td>![O]-[NR(_2)]</td>
<td>CAN, CH(_3)CN, RT</td>
<td>Undefined products and ketone 5A</td>
</tr>
</tbody>
</table>
4.1 Results from guest research scientist Josenne Mae R. Sanchez and Dr. Bakstad.

The research group synthesised the ketone 5A from the silyl enol ether 8 by the Doring – Hoffman conditions as described in scheme 4, and also worked on the synthesis of the nitroalkene 13 but didn’t complete it because of limiting time recourses.

4.2 Progresses in the total synthesis of Hazardiadione

Based on the earlier results by Dr Bakstad, Dr. Bonger and Josenne Mae R. Sanchez we decided to concentrate our studies on the alkylation reactions with the silyl enol ether 10 and suitable electrophiles. (Figure 17)

![Figure 17. Alkylation reaction with silyl enol ether 10 and a suitable electrophile in the presence of a lewis acid would probably give the desired diketone 4A.](image)

When the diketone 4A is obtained, an aldol cyclization should give the carbon skeleton of Hazardiadione. Changing the functionality by allylic oxidation using PCC and finally removal of the chloride with use of BTH should give the target molecule Hazardiadione as a racemate.

4.2.1 The synthesis of the silyl ether 10.

The synthesis of the silyl ether 10 is presented in scheme 4.

![Scheme 4. Synthesis of the silyl enol ether 10.](image)
The silyl enol ether 10 was synthesised from the starting material 2,6-dimethyl cyclohexanone (9) in 42% yield using three steps. In the first step the silyl enol ether 10 was synthesized from the starting material 9 in a reaction with trimethyl silyl chloride, triethylamine and sodium iodide.\[^{[11]}\] The strong affinity between oxygen and silicon results in an O-alkylation giving the silyl enol ether 10 in good yield (87% after distillation). Triethyl amine is a weak base with $pK_a = 10.75$ and on the $\alpha$-position on 2,6-dimethylcyclohexanone the $pK_a \approx 20$, so only catalytically amount of enolate can be generated and the strong affinity between silicon and oxygen is the driving force of the reaction.

Under distillation the silyl enol ether 10 was challenging because of uncontrolled boiling and foaming.

As an alternative cyclopropanation to the method used by Dr. Bakstad and Dr. Bonger we wanted to investigate the Doring-Hoffman reaction performed earlier by Josenne Mae R. Sanchez. The ketone 5A was synthesized from the silyl enol ether 8 using the Doring-Hoffman conditions in good yield (81%).\[^{[14]}\] Potassium tert-butoxide was used as base to abstract the proton on chloroform generating the dichlorocarbene. The dichlorocarbene reacts in a concerted reaction with the double bond on the silyl enol ether 10 to form the gem-dichlorocyclopropane 7A. The release of ring strain and donation of electrons from oxygen is the driving force of the ring expansion. A proposed mechanism for the ring expansion is shown in figure 18. In our case the gem-dichlorocyclopropane 9 was never tried isolated.

![Figure 18. Proposed mechanism of the synthesis of the ketone 5A](image)

Almassy *et al.* performed the Doring-Hoffman reaction on the same molecule.\[^{[14]}\] They managed to isolate the gem-dichlorocyclopropane as a mixture of the two diastereomers. (Figure 19)
They reported that the gem-dichlorocyclopropane 7A was very sensitive to ring opening and that it decomposed to a mixture of the seven membered ring ketone 5A and a silyl enol ether 22 in the ratio 2.1:1.0 at storage at deep freezer at -20°C. The crude product with gem-dichlorocyclopropane 7A was treated with TsOH in methanol for 20 hours giving (85% after distillation) of the seven membered ring ketone 5A.

We performed the same reaction that Almassy et al., but in our case we performed the reaction in 2 x scale using 10 eq. of CHCl₃ dissolved in DCM instead of 20 eq. of CHCl₃, and adding the CHCl₃ much faster 1.5 h compared to 4.5 h and we also kept the temperature colder between -30 and -50°C. We discovered that these conditions gave good yield (81%). It seems that the reactive dichlorocarbene reacts with the silyl enol ether 10 at colder temperature than -30°C.

The silyl enol ether 10 was synthesized from the ketone 5A using the same conditions as the synthesis of the six membered ring silyl enol ether 8.[11] The synthesis of the seven member ring silyl enol ether 10 was not as successful as the synthesis of the six member ring silyl enol ether 8. The reaction gave 60% of the seven membered ring silyl enol 10 after distillation. The reaction was challenging. It was difficult to get all of the ketone 5A consumed and some of the silyl enol ether 10 decomposed back to the ketone 5A under workup. Under workup saturated sodium bicarbonate was used and the crude product was distilled in presence of dry potassium carbonate so there should not be any acid present under the workup or distillation. This can conclude that silyl enol ether 10 is very sensitive towards decomposition.

As the six membered ring silyl enol ether 8 the silyl enol ether 10 was also challenging in distillation because of uncontrolled boiling and foaming.
4.2.2 Alkylation reaction with the silyl enol ether 13.

A less obvious electrophile is the nitroalkene 13. (Figure 20)

Figure 20. The nitroalkene 13, a suitable electrophile

The nitroalkene 13 is a reactive Michael acceptor and reacts in a Michael reaction with the silyl enol ether 10. The nitro group is a masked carbonyl which can be converted to a carbonyl. The conversion of nitro compounds into corresponding ketones is known as the Nef reaction. There are various methodologies developed, the standard method is with NaOH and H₂SO₄. (figure 21)

Figure 21. Nef reaction.

McMurry modification of the Neff reaction is a reductive method which leads to oximes, which can be hydrolyzed to the corresponding ketones. TiCl₃ in acidic conditions (pH < 1) is effective in this reaction (figure 22).[^15]

Figure 22. McMurry modification of the Nef reaction.

There are also oxidative modifications of the Nef reaction, the procedure using the commercial reagent Oxone® is very interesting. The reaction mechanism for the Nef reaction using the strong oxidization agent Oxone® is described in figure 23.[^16]
Figure 23. Nef reaction with Oxone®

It has been reported in the litterature that reactions with silyl enol ethers and nitroalkenes with Lewis acids at -78 °C in DCM under N₂, followed by hydrolysis giving corresponding diketones in good yield.\[10\] These reactions were preformed for many molecules using the Lewis acids SnCl₄, TiCl₄ and AlCl₃ with generally best results with SnCl₄. Reaction scheme for the most similar to our compound is shown in scheme 5.\[10\]

Scheme 5. Alkylation reaction with nitroalkenes and a silyl enol ether similar to our molecules.

The Michael reaction described above was performed with the silyl enol ether 10 and the nitro alkene 13 with SnCl₄ followed by hydrolysis, the reaction was also performed with the Lewis acid TiCl₄. The desired diketone 4A was not observed in the crude product using these conditions (Scheme 6).
Scheme 6. Hydrolysis with these conditions did not give the diketone 4A.

We probably ended up with a compound with an oxidation state between the proposed intermediate and the diketone 4A.

Leo Paquette et al. performed a similar reaction.\textsuperscript{[17]} In their case the Michael addition of the silyl enol ether on the nitroalkene was followed by hydrolysis of the intermediate with 6M HCl and thereafter treatment with Oxone\textsuperscript{©}. The last maneuver converted the intermediate oxime into the diketone.\textsuperscript{[17]}

The reaction conditions from Leo Paquette et al. was performed on the silyl enol ether 10 and the nitroalkene 13.\textsuperscript{[17]} In the presence of SnCl\textsubscript{4} a Michael addition of the silyl enol ether 11 on the nitroalkene 13 followed by hydrolysis with 3M HCl followed by treatment with Oxone\textsuperscript{©} gave the diketone 4A. The diketone 4A was isolated after distillation in only 8\% yield. (scheme 7).

Scheme 7. Alkylation reaction between the silyl enol ether 10 and the nitroalkene 13 followed by Nef reaction with Oxone\textsuperscript{©}.

The yield is not representative to the reaction, the reaction went well and NMR analysis of the crude product indicated a good yield. The crude product was almost pure, but contained a small trace of the ketone 5A. The seven membered ring ketone 5A and the diketone 4A had similar R\textsubscript{f} values so purification with FC or DFC would be challenging, therefore the crude product was used in continuing experiments. Because of limiting time more of the diketone 4A couldn’t be made so one gram of the crude product was distilled under vacuum forcing over a pure sample for NMR and IR analysis. The conditions for the distillation were not
A possible mechanism for this reaction is described in figure 13.

Figure 24. Proposed mechanism of the alkylation reaction between the silyl enol ether 10 and the nitroalkene 13 followed by Nef reaction with Oxone®.

The diketone 4A has to are best knowledge never been synthesized before. The NMR analysis was in accordance to the structure of the diketone 4A. The C\textsuperscript{13} NMR specter contained 14 signals which is in accordance to the expected number of signals because the diketone has 15 carbons and the two methyl carbons on the side chain can appear as one signal. The specter contained the characteristic two carbonyl signals and two olefin carbon signals which are in accordance to the expected.  (Figure 25)
The $^1$H NMR specter was also in accordance to the structure of the diketone 4A. The integration of the signals was in accordance to the number of protons in the structure. Characteristic signals in the $^1$H NMR specter was two singlet's with chemical shifts 1.27- and 2.03 ppm and integrals of 3, these signal are from the two methyl group on the ring. The singlet with chemical shift 1.27 ppm is a strong indication that we have the correct structure, because if the side chain was not attached here the methyl group would show as a doublet.

The Michael reaction with the silyl enol ether 11 and nitroalkene 13 in presence of TBAF was also explored. The reaction with TBAF gave an undefined alkylation product. The undefined product was purified by flash chromatography. The NMR analyses informed that the compound consisted of fifteen carbons. Some characteristic signals in $^{13}$C NMR where one carbonyl signal with chemical shift of 208.2 ppm, and one signal with chemical shift of 203.7 ppm. Surprisingly there were no olefinic signals, meaning that the double bond was missing. The rest of the carbon signals were in the chemical shift region for saturated alkanes. The $^1$H NMR analysis informed that there were 20 protons on the compound. Characteristic signals where the two signals for the methyl groups on the seven membered ring. Both of these gave a singlet with integral 3. Since both the signals where singlets it is a strong indication that the side chain is connected on the $\alpha$- carbon on the seven membered ring. There where to doublets with coupling constant of 6.7 Hz and integral of 3 and chemical shifts 142.4 and 125.6 ppm, these signals probably represents the methyl groups on the side chain coupling with the methin proton. The rest of the specter was complex with multiplets and doublets of doublets.
indicating diastereotopic protons. A strong IR absorption at 1720 cm\(^{-1}\) is consistent with a ketone group but the IR absorptions at 1568- and 1371 cm\(^{-1}\) seems to be too weak to be consistent with the presence of a nitro group. Further structure elucidation of the compound is under investigation by x–Ray Crystallography.

The alkylation reaction was first performed with the α-bromoketone 6A (figure 27)

![Figure 27. α-bromoketone 6A](image)

Alkylation reactions with the the silyl enol ether 10 and the α-bromoketone 6A with TBAF was expected to give the desired diketone 4A. But NMR analysis of the crude products indicated that these alkylation reactions gave the O-alkylation product 14 instead of the desired C-alkylation product 4A. This is illustrated in figure 28.

![Figure 28. Alkylation reaction with α-bromoketone 6A in the presence of TBAF](image)

The reaction was performed in many different solvents to explore if a more unpolar solvent would give the desired C-alkylation. But only the O-alkylated product was formed and the reaction yield decreased with decreasing polarity of solvents. The performed experiments are listed in table 5.
Table 5. Alkylation reaction with α-bromoketone 6A in the presence of TBAF

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Electrofile</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="OTMS" alt="OTMS" /></td>
<td><img src="O" alt="O" /> <img src="6A" alt="6A" /></td>
<td>TBAF, THF, -78°C</td>
<td><img src="O" alt="O" /> <img src="14" alt="14" /> and traces of 7 membered ring ketone 5A</td>
</tr>
<tr>
<td>10</td>
<td><img src="OTMS" alt="OTMS" /></td>
<td><img src="O" alt="O" /> <img src="6A" alt="6A" /></td>
<td>TBAF, DCM, -78°C</td>
<td><img src="O" alt="O" /> <img src="14" alt="14" /> and traces of 7 membered ring ketone 5A</td>
</tr>
<tr>
<td>10</td>
<td><img src="OTMS" alt="OTMS" /></td>
<td><img src="O" alt="O" /> <img src="6A" alt="6A" /></td>
<td>TBAF, Methylcyclohexane, -78°C</td>
<td>Mixture of <img src="14" alt="14" /> And 7 membered ring ketone 5A</td>
</tr>
</tbody>
</table>

### 4.2.4 Aldol cyclization

The crude product from of the diketone 4A was treated with KOH in EtOH to force an aldol cyclization giving the Hazardiadiione skeleton 3. The NMR and TLC analysis of the crude product indicated that the diketone 4A reacted in an intermolecular aldol reaction instead of the intramolecular aldol cyclization. Reaction with KOH in EtOH have provided aldol cyclizaton for similar compounds\(^{[10]}\). A reason for the diketones 4A unwillingness towards aldol cyclization could be caused by steric hindrance from the halogen. The strategy was changed to remove the halogen before closing the five membered ring by aldol cyclization.
6.2.3 Removal of the halogen

The chlorine on the diketone 4A was removed in a reaction with tributyltin hydride (BTH) and azobisobutyronitrile (AIBN) in toluene.[7] The reaction gave the diketone 20 in 13% yield after purification on flash chromatography. (figure 29)

![Figure 29. Removal of halogen](image)

An interesting observation was that the reaction required 2 equivalents of BTH. When the reaction was performed with 1.2 equivalents of BTH the product was a mix of the diketone 4A and the diketone 20. When the reaction was performed with 2 equivalents of BTH the diketone 4A was not observed in the crude product.

The diketone 20 has to are best knowledge never been synthesized before. The NMR analysis was in accordance to the structure of the diketone 20. The carbonyl and olefinic signal had shifted compared to the NMR specter of the diketone 4A. There were signals with chemical shift of 128.1, 152.9, 206.9 ppm which is in accordance to the α-β unsaturated system. There was also a signal with chemical shift 209.1 ppm which is in accordance to the ketone group on the side chain. In the 1H NMR a singlet with integral of one and chemical shift of 5.89 ppm were a strong indication that the right compound had been made.

The AIBN decomposes under heating to form nitrogen gas and radicals figure 30.

![Figure 30. AIBN decomposed under heating to form nitrogen gas and radicals](image)

A proposed mechanism is described in figure 31.
Figure 31. Mechanism for the removal of the halogen

BTH in combination with AIBN under heating cleaves to give the tributyltinn radicals which reacts with the chlorine giving the vinyl radical. The vinyl radical reacts with toluene in a radical reaction giving the dikeketone 20.

Due to limiting time the following reactions to complete total synthesis where not performed.

6.3 Synthesis of the electrophilic side chain.

6.3.1 Synthesis of the nitroalkene 13

The nitroalkene 13 was synthesized from the commercially available 3-methyl-1-iodobutane (15) in 15% yield using tree steps. The reaction scheme is shown in scheme 8.

Scheme 8. The synthesis of the nitroalkene 13

The first step was first performed with 1-bromo-3-methylbutane (18), but 3-methyl-1-iodobutane (15) is commercial available and gave a better yield and gave a crude product
which was found to be essentially pure. 3-Methyl-1-iodobutane (15) is expensive so it was made from 3-methyl-1-bromobutane (18) in a Finkelstein reaction by reflux overnight in acetone in the presence of NaI.

In the first step a Victor Meyer reaction gives the nitroalkane 16 in 55% yield.\(^{[18]}\) 3-Methyl-1-iodo-butane (15) reacts in a \(S_N2\) type reaction with NaNO\(_2\) in DMF under vigorously mechanically stirring. A proposed mechanism for the reaction is shown in figure 32.

![Figure 32. Proposed mechanism for the Meyer reaction.](image)

There can be a possible competition reaction. The lone pair electron on the negatively charged oxygen can attack as a nucleophile in a \(S_N2\) type reaction to give isoamyl nitrite 27. (Figure 33.)

![Figure 33. Possible competitive \(S_N2\) type reaction giving isoamyl nitrite 27.](image)

The yield of 55 % may be due to the possible competition reaction.

2-Nitroisohexanol (17) was made from the nitroalkane 16 in a Henry (nitro aldol) reaction.\(^{[19]}\) Triethylamine abstracted the proton on the \(\alpha\)-position on the nitroalkane 16 leading to an aldol reaction with paraformaldehyde giving the nitro aldol the 2-nitroisohexanol (17). A proposed mechanism is shown in figure 34.
The crude product from the Henry reaction was pure enough to use in the next step. The next step involved was performed in distillation set up. The crude product was mixed with phthalic anhydride and the nitroalkene 13 distilled over at 82 - 83 °C at 38 mmHg and redistilled (56 – 58 °C at 16 mmHg) to give the nitroalkene 13 in 28% yield. A proposed mechanism for the reaction is described in figure 35.

The nitroalkene 13 was also synthesized in 2 steps in overall 5.5 % yield. Instead of making the 2-nitroisohexanol (17), the nitroalkene 13 was made directly from the nitroalkane 16 in one step. (scheme 9)

The nitroalkane 16 was treated with paraformaldehyde and NaOH. The problem with this reaction was the poor yield, only 10% after purification with flash chromatography. The reaction was performed with the bases NaOH, KOH, LiOH with best results for NaOH. The NaOH also generates the base methoxide from methanol with also can help in the elimination of the nitro aldol adduct. A problem with this reaction was that an undefined byproduct was formed.

Elimination reactions with 2-nitroisohexanol (17) to provide the nitroalkene 13 was performed with potassium-tertbutoxide in DMSO, these conditions gave a mixture of the nitroalkene 13 and the undefined product mentioned above. Elimination was also tried in acidic conditions with TsOH without success.

The nitroalcohol 17 was also reacted with mesyl chloride and triethylamine in DCM to give the corresponding mesylate 28. The product gave a mix of the mesylate 28 and nitroalkene 13. Elimination of mesylate 28 in order to prepare the nitroalkene 13 with DBU was not successful. Joseenne Mae R. Sanchez synthesized the mesylate but the elimination using different bases was not successful. (Figure 36)

Figure 36. elimination reactons with the mesylate 28 was not successful
6.3.2 Synthesis of the α-bromoketone 5A

The α-bromoketone 6A was synthesized in three different ways (1[1], 2[20] and 3[21]) (Figure 37).

1. \[
\text{Br}_2, \text{H}_2\text{O} \quad \text{OH} \quad \text{Br} \rightarrow \text{Br} \quad \text{Br} \quad 3 \%
\]

2. \[
\text{OTMS} \quad \text{NBS} \quad \text{THF, -78} \quad \text{Br} \quad \text{Br} \quad 31 \%
\]

3. \[
\text{Br}_2, \text{Urea} \quad \text{acetic acid} \quad \text{Br} \quad \text{Br} \quad 24 \%
\]

Figure 37. Synthesis of α-bromoketone 6A, 1[1], 2[20] and 3[21]

The most interesting is the synthesis nr 2, where isobutyrimethylketone is treated with NaHMDS in the presence of TMSCl at -78 °C. The low temperature results in the kinetic enolate and the strong affinity between silicon and oxygen results in an O-alkylation giving the silyl enol ether 24. The silyl enol ether is thereafter treated with N-bromosuccinimide (NBS) to give the α-bromoketone 6A in 31% yield.
5. Conclusion and further work to complete the total synthesis of Hazardiadione

The diketone 20 can be synthesized in five steps from 2,6-dimethylcyclohexanone (9). The overall yield for the diketone 20 is currently low only 0.4 %. The yield in the fourth and fifth step can be improved dramatically. The C₆ side chain was synthesized in two different ways. The C₆ side chain was synthesized in 15 % using three steps and in 6 % using two steps.

The total synthesis of Hazardiadione could probably be completed by two reaction steps from the diketone 20. Based on similar molecules from literature the diketone 19 could be forced to undergo aldol cyclization in a reaction with KOH in EtOH to give the skeleton of Hazardiadione 20.¹⁰ (figure 38)

\[
\begin{array}{c}
\text{KOH} \\
\text{EtOH, } \Delta
\end{array}
\]

Figure 38. Aldol cyclization

An regioselective allylic oxidation on compound 19 using PCC should result in a regioselective allylic oxidation giving the Hazardiadione 1 as a racemate.⁹ (figure 39)

\[
\begin{array}{c}
PCC
\end{array}
\]

Figure 39. Regioselective allylic oxidation

The use of bromocarbene instead of gem-dichlorocarbene has to be investigated in step 2 in the synthesis of Hazardiadione. The bromocarbene can be generated with CH₂Br₂ and the strong base NaHMDS.¹² The bromocarbene would provide the seven membered ring ketone 21 without the halogen, this would reduce the total steps of the synthesis to 6 steps. (figure 40)

\[
\begin{array}{c}
\text{CH₂Br₂, NaHMDS}
\end{array}
\]

Figure 40. Reaction with bromocarbene
Experimental section

6.1 General

Commercially available chemicals were purchased from Sigma-Aldrich, Acros and Chiron.

Nuclear magnetic resonance 300 MHz $^1$H NMR spectra and 75 MHz $^{13}$C NMR spectra were recorded on a Varian 300 MHz spectrometer at the University of Stavanger. 500 MHz $^1$H NMR spectra and 125 MHz $^{13}$C NMR spectra were recorded on a Bruker Avance series Av II 500 MHz spectrometer located at Ewos Innovation, Dirdal. The chemical shift of $^1$H NMR spectra were reported relative to TMS ($\delta = 0.0$ ppm) $^{13}$C NMR spectra are referenced in ppm of deuterated chloroform ($\delta = 77.0$ ppm).

Flash chromatography (FC) and dry flash chromatography (DFC) performed on silica gel (Fluka: silica gel 60, particle size 0.040-0.063/230-400 mesh).

Thin layer chromatography (TLC) was performed by using silica gel plates from Fluka (silica gel / dc-alufolien-kiselgel with fluorescent indicator, prod. #60778). The molecules ran on TLC were detected by UV-light (extinction at $\gamma = 254$ nm or fluorescence at $\gamma = 366$ nm) in a UVP-UV-cabinet. The molecules invisible in UV- or fluorescence light had to be induced by staining with MOP ((molybdatophosphoric acid (14 g) in ethanol (125 mL)) and heat, or by CER-MOP (molybdatophosphoric acid (5 g), cerium (IV) sulfate (2 g) and 98% $\text{H}_2\text{SO}_4$ (16 mL) in water (180 mL) and heat.

Infrared spectroscopy was performed on Varian 1000 FT-IR spectrometer located at MI-SWACO.

Melting points (m.p.) were determined on Stuart Scientific SMP3 melting point apparatus. The melting point results were not corrected.

Vacuum was generated with water aspirator pump or an Edwards RV12 high vacuum pump.
6.2 Synthesis towards Hazardiadione 1

Synthesis of dimethylcyclohex-1-enyloxytrimethylsilane (8)

\[
\begin{align*}
\text{9} & \quad \text{i} \quad \text{8} \\
\text{(C}_3\text{H}_4\text{O)} & \quad \text{(C}_{11}\text{H}_{22}\text{OSi})
\end{align*}
\]

i) TMSCl, NaI, Et₃N, CH₃CN, Δ

Triethylamine (111.3 g, 1.10 mol) was added dropwise to a solution of 2.6 dimethylhexanone (9) (44.1 g, 350.0 mmol), TMSCl (76.1 g, 0.70 mol) and sodium iodide (108.8 g, 7.25 mol) in acetonitrile (350 mL) at 0°C. The solution was refluxed overnight. Saturated NaHCO₃ (aq) (600 mL) was added to the solution. The solution was extracted with petroleum ether (4 x 150 mL). The organic phase was washed with saturated NaHCO₃ (aq) (2 x 100 mL). The organic phase was dried with MgSO₄ then the solvent was removed under reduced pressure. Distillation gave 60.0 g (90%) of the silyl enol ether 8 (b.p. 80 - 82°C, 15 mm Hg).

Not visible on TLC. IR (neat) ν 2930, 2957, 1679, 1455, 1250, 1168, 924, 837, 751 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.17 (s, 9 H), 1.04 (d, J = 6.9 Hz, 3 H), 1.3-1.4 (m, 1 H), 1.41-1.51 (m, 1 H), 1.54 (s, 3 H), 1.57-1.68 (m, 1 H), 1.71-1.81 (m, 1 H) 1.94 (t, J = 6 Hz, 2 H), 2.04-2.18 (m, 1 H); ¹³C NMR (75MHz, CDCl₃) δ 0.6, 16.8, 18.9, 20.5, 30.8, 32.2, 34, 112, 147.

Synthesis of 2-chloro-3,7-dimethylcyclohept-2-enone (5A).

\[
\begin{align*}
\text{8} & \quad \text{i} \quad \text{5A} \\
\text{(C}_{11}\text{H}_{22}\text{OSi)} & \quad \text{(C}_9\text{H}_{15}\text{OCl})
\end{align*}
\]

i) tBuOK, CHCl₃, DCM, pet. ether.-30°C

A solution of silyl enol ether 8 (29.76 g, 150.0 mmol) in petroleum ether (20 mL) was added to a suspension of potassium tert-butoxide (168.31 g, 1.50 mol) in petroleum ether (500 mL) at r.t. Chloroform (179.02 g, 1.5 mol) in DCM (100 mL) was added over a period of 1.5 h at -30 °C. After addition the mixture was stirred 4 h at -30 °C the cooling was removed and the mixture was stirred overnight. The mixture was filtrated through celite and the filter cake was washed with petroleum ether (2 x 100 mL). The solvent was removed under reduced pressure. Distillation under vacuum gave 21.0 g (81%) of the ketone 5A (b.p. 124 - 126 °C, 12 mmHg).
R_f = 0.30 (15% EtOAc in Hexanes). IR (neat) v 2933, 2864, 1682, 1604, 1458, 1375, 1224, 1200, 1088, 1032, 906, 846, 781, 733 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.17 (d, J = 6.3 Hz; 3 H), 1.42 - 1.64 (m, 2 H), 1.8 - 2.0 (m, 2 H), 2.15 (s, 3 H), 2.45 - 2.64 (m, 2 H), 2.76 - 2.88 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 16.6, 24.8, 25.2, 31.4, 35.3, 44.5, 131, 152.5, 198.8.

Synthesis of 7-chloro-2,6-dimethylcyclohepta-1,6-dienyloxy trimethylsilane (10).

\[ \begin{array}{c}
\text{C₉H₁₃OCI} \\
\text{5A} \quad \text{i} \\
\text{C₁₂H₂₁OCiSi} \quad \text{10}
\end{array} \]

i) TMSCl, NaI, Et₃N, CH₃CN, Δ

Et₃N (15.18 g, 150.0 mmol) was added dropwise to a vigorously stirred solution of the ketone 5A (8.58 g, 50.0 mmol), TMSCl (10.86 g, 100.0 mmol), NaI (16.48 g, 110.0 mmol) in acetonitrile (200 mL). The mixture was stirred and refluxed overnight. Saturated NaHCO₃ (aq) (400 mL) was added to the mixture. The mixture was extracted with petroleum ether (4 x 80 mL) the organic phase was washed with NaHCO₃ (aq) (2 x 50 ml). The organic phase was dried with MgSO₄ and the solvent was removed under reduced pressure. Distillation under vacuum gave 7.43 g (60%) of the enol ether 11 (b.p. 104-108 °C, 9 mmHg).

R_f = 0.66 (15% EtOAc in Hexanes). IR (neat) v 2932, 2857, 1634, 1449, 1286, 1251, 1209, 1163, 1097, 1063, 1020, 964, 895, 839 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.18 (s, 9 H), 1.79 (s, 3 H), 1.87 - 1.94 (m, 2 H), 1.98 (s, 3 H), 2.00 - 2.06 (m, 4 H). ¹³C NMR (75 MHz, CDCl₃) δ 0.3, 17.3, 20.6, 30.5, 33.1, 34.1, 121.5, 124.3, 137.2, 140.9

Synthesis of 2-Chloro-3,7-dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone (4A)

\[ \begin{array}{c}
\text{C₉H₁₃OCI} \\
\text{10} \quad \text{Cl} \\
\text{CₖH₁₁NO₂} \quad \text{13} \\
\text{C₁₅H₂₃O₂Cl} \quad \text{4A}
\end{array} \]

i) SnCl₄, DCM, -78 °C
ii) 3M HCl
iii) Oxone
SnCl$_4$ (1.0 mL, 8.50 mmol) was added dropwise over a period of 15 min. to a solution of nitroalkene 13 (1.54 g, 11.90 mmol) in dry DCM (60 mL) under N$_2$ at -78 °C. Enol ether 10 (1.96 g, 8.0 mmol) solved in DCM (10 mL) was added dropwise to the solution over a period of 30 min. at -78 °C. The solution was stirred for three hours at -78°C. 3M HCl (15 mL) was added and the solution was refluxed overnight. The solution was treated with oxone (9.84 g, 16.0 mmol) over a period of 15 min. at 0 °C then the solution was refluxed for three hours. Water (200 mL) and Et$_2$O (150 mL) was added and the water phase was extracted with Et$_2$O (50 mL x 4). The organic phase was washed with water (25 mL x 2) and dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure giving a crude product (2.82 g) of viscous yellow oil. Some of the oil (2.53 g) was filtrated trough a short column giving 1.93 g of viscous yellow oil containing the diketone 4A and traces of ketone 5A. 1.0 g of the crude product was distilled under vacuum to give 166 mg (9%) of the diketone 5A (b.p. 140 °C, 0.2 mmHg).

$R_f = 0.28$ (15% EtOAc in Hexanes)

IR (neat) ν 2957, 2932, 2971, 2071, 1708, 1690, 1622, 1455, 1367, 1225, 1148, 1104, 1048, 922, 893, 814 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) δ 0.90 (d, $J = 6.9$ Hz, 6 H), 1.27 (s, 3 H), 1.55 - 1.64 (m, 1 H) 1.70 - 1.79 (m, 2 H), 2.03 (s, 3 H), 2.06 - 2.18 (m, 2 H), 2.26 (d, $J = 6.9$ Hz, 2 H), 2.38 - 2.43 (m, 2 H), 2.67 (d, $J = 17.1$ Hz, 1 H), 2.79 (d, $J = 17.1$Hz, 1 H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ , 22.1, 22.4, 23.0, 23.4, 24.5, 35.1, 35.9, 50.1, 52.3, 53.2, 125.6, 142.4, 203.7, 208.2.

**Synthesis of 3,7-dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone (20)**

![Chemical structure](image)

i) BTH, AIBN, Δ

Catalytically amounts of AIBN was added to a solution of the diketone 4A (270 mg, 1.0 mmol) and BTH (582 mg, 2.0 mmol) in toluene (40 mL) under N$_2$. The solution was stirred overnight at reflux. Water (100 mL) was added and the solution was extracted with Et$_2$O (4 x 25 mL). The organic phase was washed with water (4 x 25 mL). The organic phase was dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure. The crude product was first purified with a short column (10% EtOAc in Hexanes). The product was not pure so the
product was purified again by flash chromatography (5% EtOAc in Hexanes) to give (30 mg, 13%) of the diketone 20.

R_f = 0.58 (30% EtOAc in Hexanes). IR data is not yet available. ^1H NMR (300 MHz, CDCl_3) δ 0.89 (d, J = 6.3, 6 H), 1.92 (s, 3 H), 1.50 - 1.62 (m, 1 H), 1.73 - 1.89 (m, 2 H), 1.90 (s, 3 H), 2.05 - 2.17 (m, 2 H), 2.23 (d, J = 6.3, 2H), 2.34 (m, 2H), 2.50 (d, J = 17.1 Hz, 1 H), 2.94 (d, J = 17.1 Hz, 1 H), 5.89 (s, 1 H).

13C NMR (75 MHz, CDCl_3) δ 22.0, 22.5, 24.6, 25.6, 27.2, 35.3, 37.5, 49.7, 52.6, 54.1, 128.1, 152.9, 206.9, 209.1.

Synthesis of unidentified alkylation product

```
      OTMS
   |  C Cl
  13  |   |
  NO2  |  i
(C_9H_{13}OCl)   (C_6H_{11}NO_2)       A unidentified product
```
i) TBAF, - 78 °C

Tetra-n-butylammonium fluoride (TBAF) (2.37 g, 7.50 mmol) was added to a solution of the nitroalkene 13 (1.84 g, 11.0 mmol) and silyl enol ether 10 (1.84 g, 7.50 mmol) in DME (50 mL) at -78 °C under N_2. The reaction was stirred for 4 h at -78 °C than stirred overnight at room temperature. Water (100 mL) was added and the solution was extracted with pet. ether (2 x 50 mL), DCM (2 x 50 mL) and EtOAc (2 x 50 mL). The organic phase was washed with water (2 x 50 mL). The organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure giving 2.5 g crude product. The crude product was purified by DFC (1% EtOAc in Hexanes) giving 750 mg of an unknown compound, m.p. = 60 – 61 °C R_f = 0.46 (15% EtOAc in Hexanes).

IR(neat) ν 2955, 2931, 2868, 1720, 1568, 1450 1371, 1292, 1219, 1141,1111, 1050, 940, 890, 872, 826, 783 cm\(^{-1}\). ^1H NMR IR (500 MHz, CDCl_3) δ 1.81 (d, J = 6.7 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 3 H), 1.15 (s, 3 H), 1.30 (s, 3 H), 1.39 (dd, J = 9.4, 14.2 Hz, 1 H), 1.45 - 1.49 (m, 1 H), 1.55 (dd, J = 5.6, 14.2 Hz, 1 H), 1.66 - 1.72 (m, 1 H), 1.80 - 1.83 (m, 1 H), 1.95 - 2.00 (m, 2 H), 2.16 (d, J = 13.5 Hz, 1 H). ^13C NMR (125 MHz, CDCl_3) δ 21.9, 22.5, 23.2, 23.8, 25.2, 25.5, 32.1, 36.8, 38.0, 40.6, 42.4, 44.9, 64.2, 210.1

6.3 Synthesis of C_6 side chain

Synthesis of 3-methyl-1-iodo-butane (15)
Bromo-3-methylbutane (18) (30.2 g, 0.20 mol) was added dropwise to a mixture of NaI (44.97 g, 0.30 mol) and acetone (500 mL). The mixture was refluxed overnight. The mixture was filtrated and the filter cake was washed with (2 x 50 mL) acetone. The acetone was evaporated under reduced pressure. The compound was distilled under vacuum to give 13.8 g (35%) (b.p. 25 - 35 °C, 15 mmHg).

Not visible on TLC. IR (neat) ν 2957, 2928, 2870, 1467, 1357, 1293, 1249, 1178, 1019, 870. 1H NMR (500 MHz, CDCl3) δ = 0.91 (d, J = 6.4 Hz, 6 H), 1.70 - 1.74 (m, 3 H), 3.20 (t, J = 7.2 Hz, 2 H). 13C NMR (125 MHz, CDCl3) δ = 5.2, 21.7, 29.0, 42.5

**Synthesis of 3-methyl-1-nitrobutane (16).**

Isopentyl bromide (18) (120.84 g, 0.80 mol) was added dropwise to a mechanical stirred solution of sodium nitrite (110.39 g, 1.60 mol) in DMF (500 mL) at 0°C. The reaction mixture was mechanically stirred overnight at room temperature. Water (1 L) was added to the mixture. The mixture was extracted with pet. ether (4 x 150 mL). The combined organic phases were washed with water (2 x 150 mL). The organic phase was dried with Na2SO4 then the solvent was evaporated under reduced pressure. Distillation under vacuum gave 30.2 g (32%) of the colorless nitroalkane 16 (b.p. 58 - 60 °C 21 mmHg)

Not visible on TLC IR (neat) ν 2962, 1549, 1470, 1434, 1381, 1211, 1133, 851 cm⁻¹. 1H NMR (500 MHz, CDCl3) δ 0.96 (d, J = 6.7 Hz, 6 H), 1.69 (h, J = 6.7Hz, 1 H), 1.91 (q, J = 7.2 Hz, 2 H), 4.41 (t, J = 7.3 Hz, 2 H). 13C NMR (125 MHz, CDCl3) δ = 21.9, 25.5, 35.9, 74.2

**Synthesis of 3-methyl-1-nitrobutane (16).**
I
(C₅H₁₁I)
NO₂
(C₅H₁₁NO₂)
i
NaNO₂, DMF

Isopentyl iodide (15) (9.90 g, 50.0 mmol) dissolved in DMF (40 mL) was added dropwise to a mechanical stirred solution of DMF (150 mL) and sodium nitrite (6.90 g, 100.0 mmol) at 0°C. The reaction mixture was mechanically stirred overnight at room temperature at r.t. Water (500 mL) was added to the mixture. The mixture was extracted with pet. ether (4 x 70 mL). The combined organic phases were washed with water (2 x 50 mL). The organic phase was dried with Na₂SO₄ then the solvent was evaporated under reduced pressure to give 3.2g (55%) of the nitroalkane 16. The crude product proved to be pure by NMR.

Spectral data was in accordance to previously reported results.

**Synthesis of 4-methyl-2-nitropentanol (17).**

(C₅H₁₁NO₂)

i)

(CH₂O)n, Et₃N, MeOH

Triethylamine (26.11g, 258.0 mmol) was added dropwise to a solution of vigorously stirred paraformaldehyde (7.30 g, 243.0 mmol) and the nitroalkane 16 (24.95 g, 213.0 mmol) in methanol (250 mL) at 0 °C. The mixture was stirred overnight at r.t. Water (500 mL) was added and the solution was brought to neutral with 2 M sulfuric acid. The solution was extracted with DCM (4 x 80 mL) and the organic phase was washed with water (2 x 50 mL). The organic phase was dried with Na₂SO₄ then the solvent was evaporated under reduced pressure to give 27.5 g of light brown oil. The nitro alcohol was distilled under vacuum to give 14.40 g (46%) of the nitro alcohol 17 (b.p. 70 - 72 °C, 1.5 x 10⁻² mmHg).

Not visible on TLC. IR (neat) ν 3395, 2962, 1549, 1469, 1371, 1241, 1081, 1046, 853 cm⁻¹. 

¹H NMR (500 MHz) δ 0.94 (d, J = 6.3 Hz, 3 H), 0.98 (d, J = 6.3 Hz, 3 H), 1.46 - 1.52 (m, 1 H), 1.58 - 1.64 (m, 1 H), 1.88 - 1.93 (m, 1 H), 2.9 (s, 1 H), 3.85 (dd, J = 12.3, 3.3 Hz, 1 H), 3.99 (dd, J = 8.6 Hz, 13 Hz, 1 H), δ 4.69 - 4.74 (m, 1 H). ¹³C NMR (125 MHz) δ 21.6, 22.5, 25.0, 38.4, 63.6, 88.1

**Syntesis of 4-methyl-2-nitro pent-1-ene (13)**
NaOH (5 g, 125.0 mmol) was added portion wise over a period of 15 min. to a solution of nitroalkane 18 (5.85 g, 50.0 mmol) and paraformaldehyde (1.51 g, 50.0 mmol) in methanol (200 mL) at 0 °C. The solution was stirred for 1h at 0°C then the cooling was removed and the solution was stirred overnight at r.t. Water 400 mL was added and the solution was brought to pH 4 with 2M H₂SO₄. The solution was extracted with pet. ether (75 mL x 6). The organic phase was washed with water (50 mL x 2). The organic phase was dried with Na₂SO₄. The solvent was removed under reduced pressure. The crude product was made pure by DFC (1% EtOAc in Hexanes) and gave 1.7 g (10%).

Rₗ = 0.50 (15% EtOAc in Hexanes) IR (neat) ν 2962, 1524, 1467, 1343, 1168, 1090, 942, 853, 823 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 0.95 (d, J = 6.9 Hz, 6 H), 1.88 (h, J = 6.3 Hz, 1 H), 2.48 (d, J = 6.9 Hz, 2 H), 5.53 (s, 1 H) 6.44 (d, J = 1.5, 1 H). C¹³ NMR (75 MHz, CDCl₃): δ 21.9, 26.3, 39.1, 118, 157.2

Synthesis of 4-methyl-2-nitro pent-1-ene (13)

Triethylamine (32.38 g, 320.0 mmol) was added dropwise to a solution of vigorously stirred paraformaldehyde (6.50 g, 216.5 mmol) and the nitroalkane 16 (22.01 g, 187.9 mmol) in methanol (250 mL) at 0 °C. The mixture was stirred overnight at room temperature. Water (500 mL) was added and the solution was brought to neutral with sulfuric acid (2M). The solution was extracted with DCM (4 x 80 mL) and the organic phase was washed with water (2 x 50mL). The organic phase was dried with Na₂SO₄ then the solvent was evaporated under reduced pressure to give 25.75 g of light brown oil. The crude product was mixed with phathalic anhydride (25.92 g, 17.05 mmol) in a distillation set up. The nitro alkene 13 (10.98
g) was distilled over at (82 - 83 °C, 38 mmHg). The compound was redistilled to give (6.88 g, 28 %) of the nitro alkene 13 (56 - 58 °C, 16 mmHg).

Spectral data was in accordance to previously reported results.

Sythesis of 1-Bromo-4-methyl-pentan-2-one (6A)

\[ \text{(C}_6\text{H}_{11}) \rightarrow \text{OH} \text{Br} \rightarrow \text{O} \text{Br} \]

i) \( \text{Br}_2 / \text{H}_2\text{O} \)

ii) Chromic acid

4-Methylpentene (10.1 g, 120.0 mmol) was mixed with water (500 mL) at 0 °C. \( \text{Br}_2 \) (19.2 g, 120.0 mmol) was added dropwise and the mixture was stirred overnight at r.t. The mixture was extracted with pet. ether (4 x 75 mL). The organic phase was dried with MgSO\(_4\) and the solvent was evaporated under reduced pressure giving the crude product (19.15 g, brown oil). The crude product contained a mixture of 1,2 dibromo-4-methylpentane and 1-bromo-4-methylpentan-2-ol and 2-bromo-4-methylpentanol. The crude product was separated on DFC using the eluent (10% EtOAc in Hexanes) giving 1,2 dibromo-4-methylpentane (11.3 g) and a mixture of 1-bromo-4-methylpentan-2-ol and 2-bromo-4-methylpentanol (1.9 g). Chromic acid solution (12.3 mL) was added to the mixture of 1bromo-4-methylpentan-2-ol and 2-bromo-4-methylpentanol (1.9 g) was dissolved in diethyl ether (50 mL) and the mixture was stirred overnight at r.t. Saturated NaHCO\(_3\) (aq) (200 mL) was added and the mixture was extracted with pet. ether (4 x 75 mL). The organic phase was dried with MgSO\(_4\) and the solvent was evaporated under reduced pressure giving the 1-bromo-4-methylpentan-2-one (0.72 g, brown oil, 3.3 %). The yield of this reaction was poor, but the same reaction is reported in 28% yield.[1]

Chromic acid solution was prepared (500 mL)[23]:

\[ \text{Na}_2\text{Cr}_2\text{O}_7 \times \text{H}_2\text{O} \] (100 g, 0.33 mol) was dissolved in 300 mL of water. 97 % H\(_2\)SO\(_4\) (136 g, 1. 34 mol) was then added. The solution was then diluted to 500 mL total volume. This solution will oxidize 1.00 mol of secondary alcohol.

\( R_f = 0.44 \) (15% EtOAc in Hexanes)
IR (neat) ν 2960, 2873, 1713, 1467, 1367, 1391, 1294, 1169, 1038, 950, 835 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 0.95 (d, \(J = 6.3\) Hz, 6 H), 2.18 (h, \(J = 6.9\) Hz, 1 H), 2.54 (d, \(J = 6.9\) Hz, 2 H), 3.38 (s, 2 H). C\(^{13}\) NMR (75 MHz, CDCl\(_3\)) δ 22.3, 24.6, 24.7, 48.5, 201.5

### Synthesis of 1-bromo-4-methyl-pentan-2-one (6A)

\[
\begin{align*}
\text{O} & \quad \text{i) NaHMDS, TMSCl, THF, -78} \\
\text{C}_6\text{H}_{12}\text{O} & \quad \text{ii) NBS, THF} \\
\text{O} & \quad \text{6A} \\
\text{C}_6\text{H}_{11}\text{OBr} & 
\end{align*}
\]

NaHMDS (15 mL, 30.0 mmol, 2M) was added dropwise to a solution of isobutylmethylketone (3.00 g, 30.0 mmol) and TMSCl (4.25 g, 40.0 mmol) in dry THF (100 mL) at -78 °C under N\(_2\). The solution was stirred for 2 h. at -78 °C then stirred overnight at r.t. Water (200 mL) was added and the solution was extracted with pet ether (4 x 50 mL) and washed with water (2 x 25 mL). The organic phase was dried with Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure giving the crude product (6.99 g). The crude product was dissolved in THF (100 ml) and NBS (5.80 g, 33.0 mmol) was added portionwise. The solution was stirred overnight at r.t. Water 200 mL was added and the solution was extracted with DCM (4 x 50 mL). The organic phase was washed with water (2 x 25 mL). The organic phase was dried with Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure giving the crude product (3.97 g) brown oil. Distillation gave 1.7 g (31%) of the colorless bromoketone \(6A\) (b.p. 65 - 66°C, 13 mmHg).

Spectral data was in accordance to previously reported results.

### Synthesis of 1-bromo-4-methyl-pentan-2-one (6A)

\[
\begin{align*}
\text{O} & \quad \text{i) Br}_2, \text{Urea, acetic acid} \\
\text{C}_6\text{H}_{12}\text{O} & \quad \text{6A} \\
\text{C}_6\text{H}_{11}\text{OBr} & 
\end{align*}
\]

(43.95 g, 275.0 mmol) dissolved in acetic acid (40 mL) was added dropwise to a solution of isobutylmethylketone (25.04 g, 250.0 mmol) and urea (24.02 g, 400.0 mmol) dissolved in
acetic acid (125 mL) at 0 °C. The cooling was removed and the solution was stirred overnight at r.t. Water (400 mL) was added and the solution was extracted with DCM (4 x 80 mL). The organic phase was washed with saturated NaHCO$_3$ (aq) (2 x 50 mL) and water (2 x 50 mL). The solvent was removed under reduced pressure giving the crude product (44.29 g) brown oil. Distillation gave 10.7 g (24 %) of the colorless bromoketone 15 (b.p. 65 - 68 °C, 11 mmHg).

Spectral data was in accordance to previously reported results.

**Synthesis of 3-bromo-4-methyl-pentan-2-one (23)**

\[
\begin{align*}
\text{(C}_6\text{H}_{12}\text{O}) & \quad \overset{i}{\longrightarrow} \quad \text{(C}_6\text{H}_{11}\text{OBr)} \\
\text{(C}_6\text{H}_{12}\text{O}) & \quad \text{Br}_2, \text{ acetic acid}
\end{align*}
\]

Br$_2$ (16.14 g, 101.0 mmol) dissolved in acetic acid (10 mL) was added dropwise to a solution of isobuthylmethylketone (10.01 g, 100.0 mmol) dissolved in acetic acid (200 mL) at r.t. The solution was stirred overnight at r.t. Water (400 mL) was added and the solution was extracted with DCM (4 x 80 mL). The organic phase was washed with NaHCO$_3$ (aq) (2 x 50 mL) and water (2 x 50 mL). The solvent was removed under reduced pressure giving the crude product (18.0 g) brown oil. Distillation gave 4.3 g (24 %) of the bromoketone 23 (b.p. 60 – 62 °C, 12 mmHg).

Rf 0.48 in 15% EtOAc in Hexanes. IR (neat) ν 2967, 2874, 1721, 1467, 1389, 1370, 1289, 1190, 1148, 1041, 948, 827 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) δ 0.96 (d, $J = 6.3$ Hz, 3 H), 1.11 (d, $J = 6.6$ Hz, 3 H), 2.14 - 2.30 (m, 1 H), 2.35 (s, 3 H), 4.03 (d, $J = 8$ Hz, 2 H). C$^{13}$ NMR (75 MHz, CDCl$_3$) δ 20.1, 26.3, 31.1, 63.0, 202.1.
References

### Apendix A Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobis(isobutynitrile)</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosin triphosphate</td>
</tr>
<tr>
<td>BTH</td>
<td>Tributyltin hydride</td>
</tr>
<tr>
<td>CTP</td>
<td>Cytidine triphosphate</td>
</tr>
<tr>
<td>CBP</td>
<td>Cytidine diphosphate</td>
</tr>
<tr>
<td>d</td>
<td>doublet (NMR)</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets (NMR)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichlormethane</td>
</tr>
<tr>
<td>DMAPP</td>
<td>Dimethylallyl diphosphate</td>
</tr>
<tr>
<td>DME</td>
<td>1,2,-dimethoxymethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DFC</td>
<td>Dry flash chromatography</td>
</tr>
<tr>
<td>et al.</td>
<td>And others</td>
</tr>
<tr>
<td>FC</td>
<td>Flash chromatography</td>
</tr>
<tr>
<td>FGA</td>
<td>Functional group addition</td>
</tr>
<tr>
<td>FGI</td>
<td>Functional group interconversion</td>
</tr>
<tr>
<td>FPP</td>
<td>Farnesyl diphosphate</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier Transform Infrared Spectroscopy</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>GPP</td>
<td>Geranyl diphosphate</td>
</tr>
<tr>
<td>h</td>
<td>heptet (NMR)</td>
</tr>
<tr>
<td>HMG-COA</td>
<td>β-hydroxy-β-methylglutaryl-Coenzyme A</td>
</tr>
</tbody>
</table>
Me    Methyl
m.p.  Melting point
Ms    Methanesulfonyl
MS    Mass spectroscopy
MVA   Mevalonic acid
NADPH Nicotinamide Adenine Dinucleotide Phosphate
NaHMDS Sodium Hexamethyldisilazide
NBS   N-bromosuccinimide
NMR   Nuclear Magnetic Resonance
r.t.  Room Temperature
s     singlet (NMR)
TBAF  Tetra-n-butylammonium fluoride
THF   Tetrahydrofuran
TPP   Thiamine diphosphate
TMS   Tetramethylsilane
Ts    Tosyl
t     triplet (NMR)
Δ     Heating
δ     Chemical shifts
Appendix B: Compounds

<table>
<thead>
<tr>
<th>Number</th>
<th>Compound</th>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>3-Isopropyl-5,8a-dimethyl-1,7,8,8a-tetrahydro-azulene-2,6-dione</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>4-Halo-3-isopropyl-5,8a-dimethyl-1,7,8,8a-tetrahydro-azulene-2,6-dione</td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td><img src="image3.png" alt="Compound 2B" /></td>
<td>4-Chloro-3-isopropyl-5,8a-dimethyl-1,7,8,8a-tetrahydro-azulene-2,6-dione</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image4.png" alt="Compound 3" /></td>
<td>4-Halo-3-isopropyl-5,8a-dimethyl-6,7,8,8a-tetrahydro-1H-azulen-2-one</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image5.png" alt="Compound 4" /></td>
<td>2-Halo-3,7-dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone</td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td><img src="image6.png" alt="Compound 4A" /></td>
<td>2-Chloro-3,7-dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image7.png" alt="Compound 5" /></td>
<td>2-Halo-3,7-dimethyl-cyclohept-2-enone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>---------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>5A</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>2-Chloro-3,7-dimethyl-cyclohept-2-enone</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>1-Z-4-methyl-pentan-2-one</td>
<td></td>
</tr>
<tr>
<td>6A</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>1-Bromo-4-methyl-pentan-2-one</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>(7,7-Dihalo-2,6-dimethyl-bicyclo[4.1.0]hept-1-yloxy)-trimethyl-silane</td>
<td></td>
</tr>
<tr>
<td>7A</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>(7,7-Dichloro-2,6-dimethyl-bicyclo[4.1.0]hept-1-yloxy)-trimethyl-silane</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>(2,6-Dimethyl-cyclohex-1-enyloxy)-trimethyl-silane</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>2,6-Dimethyl-cyclohexanone</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="image8.png" alt="Structure" /></td>
<td>(2-Chloro-3,7-dimethyl-cyclohept-2-enyloxy)-trimethyl-silane</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="image9.png" alt="Structure" /></td>
<td>2-Chloro-3-methoxy-1,4-dimethyl-cyclohepta-1,3-diene</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><img src="image10.png" alt="Structure" /></td>
<td>Enamine</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td><img src="image11.png" alt="Structure" /></td>
<td>4-Methyl-2-nitro-pent-1-ene</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td><img src="image12.png" alt="Structure" /></td>
<td>1-(7-Chloro-2,6-dimethyl-cyclohepta-1,6-dienyloxy)-4-methyl-pentan-2-one</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="image13.png" alt="Structure" /></td>
<td>1-Iodo-3-methyl-butane</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>![image]</td>
<td>3-Methyl-1-nitro-butane</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>![image]</td>
<td>4-Methyl-2-nitro-pentan-1-ol</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>![image]</td>
<td>1-Bromo-3-methyl-butane</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>![image]</td>
<td>3-Isopropyl-5,8a-dimethyl-6,7,8,8a-tetrahydro-1H-azulen-2-one</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>![image]</td>
<td>3,7-Dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>![image]</td>
<td>3,7-Dimethyl-cyclohept-2-enone</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>![image]</td>
<td>(2-Chloro-3,7-dimethyl-cyclohepta-1,3-dienyloxy)-trimethyl-silane</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>![image]</td>
<td>3-Bromo-4-methyl-pentan-2-one</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>![image]</td>
<td>1,1-Dimethoxy-2,6-dimethylcyclohexane</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>![image]</td>
<td>2-Methoxy-1,3-dimethylcyclohexene</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>![image]</td>
<td>8,8-Dichloro-1-methoxy-2,7-dimethyl-bicyclo[5.1.0]octane</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>![image]</td>
<td>Isoamyl nitritte</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>![image]</td>
<td>4-methyl-2-nitropentyl methansulfonate</td>
<td></td>
</tr>
</tbody>
</table>