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Writer: Joachim Hope Kyllingstad	…… (Writer's signature)
Faculty supervisor: Prof. II Dr. Einar Bakstad External supervisor(s):	
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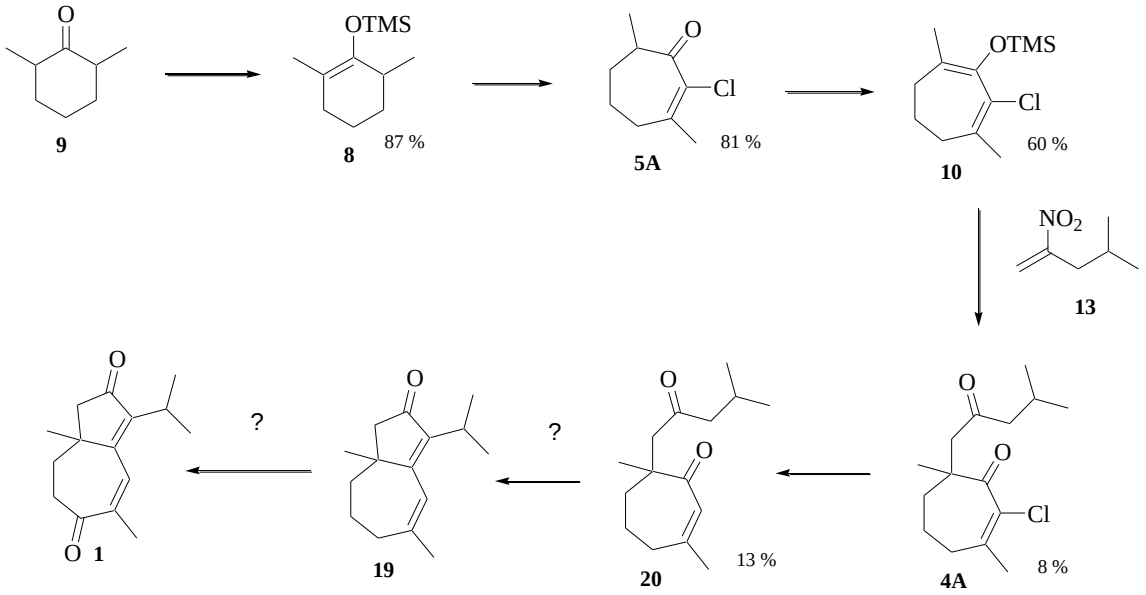
Last but not least, I would thank my wonderful fiancée for supporting me.

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 synthesis of the electrofile for the alkylation reaction in step 4.

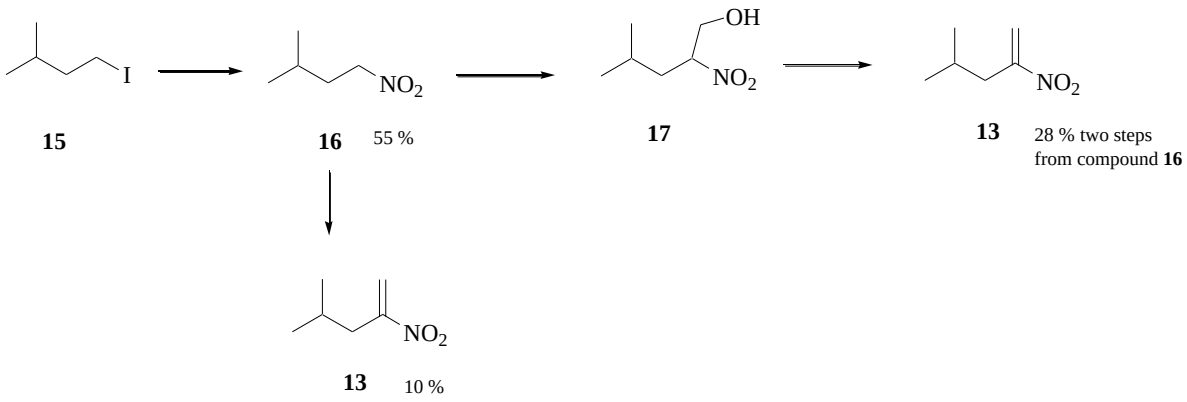


Figure 1. Graphical abstract

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 C_6 side chain was synthesized in two different ways.
The C_6 side chain was synthesized in 15 % using three steps and in 6 % using two steps.

Table of Contents

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 orcuttii* 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.

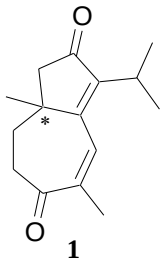


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Figure 2. Proposed structure of Hazardiadione **(1)**.

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)

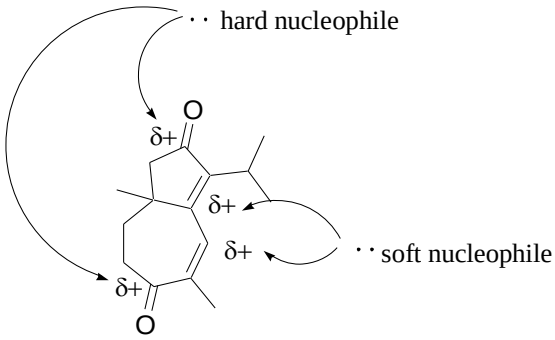


Figure 3. Electrophilic centers reactive towards nucleophilic attack.

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 entantiomers 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 C_5 units in a head to tail fashion. The structures contains carbon skeletons represented by $(C_5)_n$ and are classified according to number of carbons. (table 1.)[3]

Table 1. Classification of the terpenoids.

Classification	**#Carbons**
Hemiterpenes	C_5
Monoterpenes	C_{10}
Sesquiterpenes	C_{15}
Diterpenes	C_{20}
Sesterterpenes	C_{25}
Triterpenes	C_{30}
Tetraterpenes	C_{40}

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]

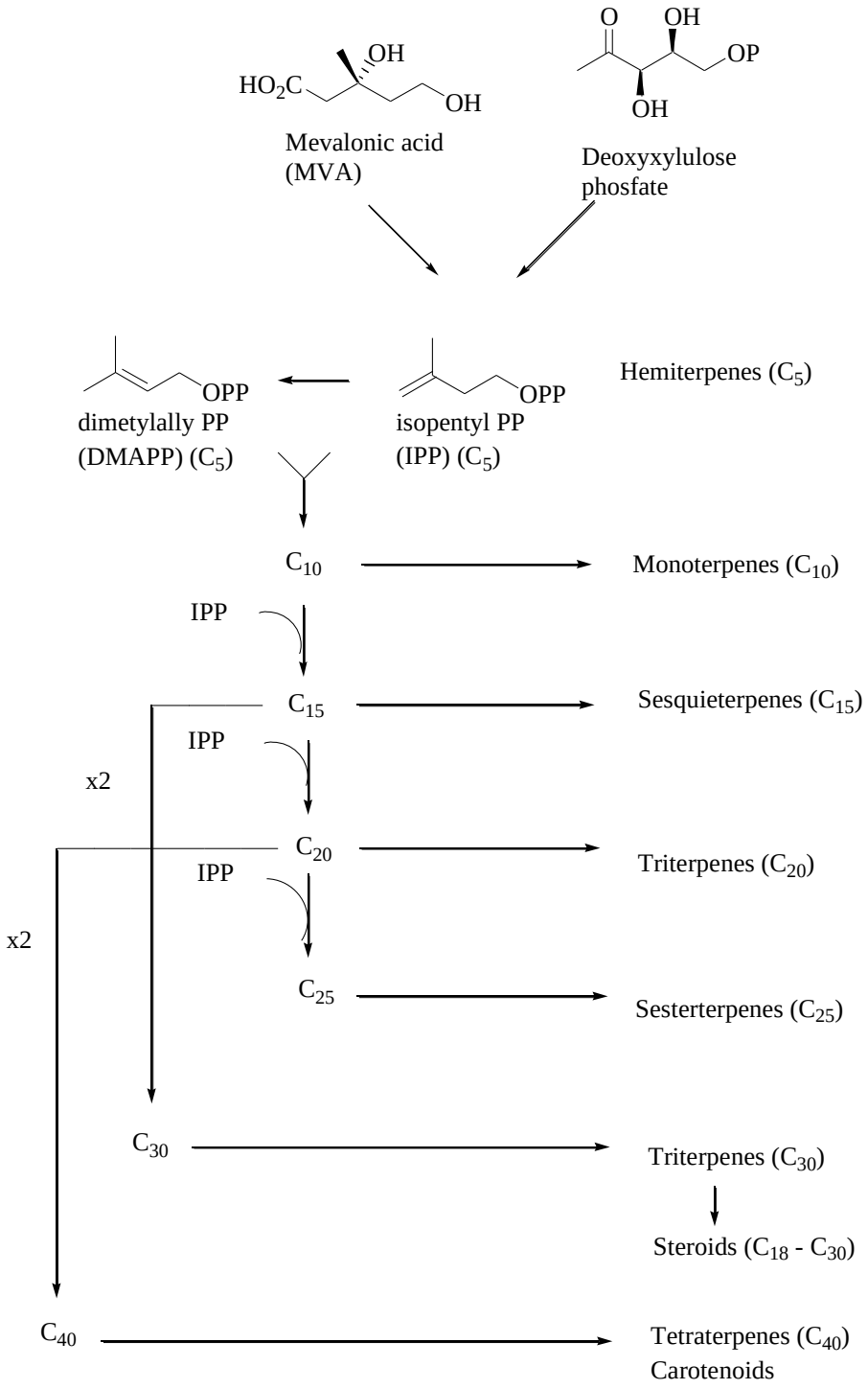


Figure 4. Biosynthesis of terpenoids

DMAPP is a reactive electrophile, diphosfate 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]

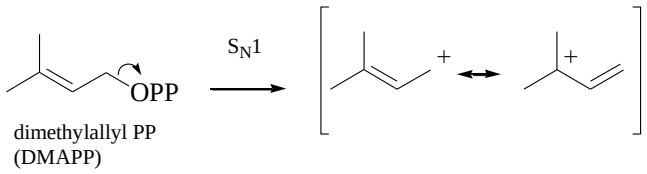


Figure 5. DMAPP reacts as a electrophile in S_N1 type reaction

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 diposphate from DMAPP and IPP.[3]

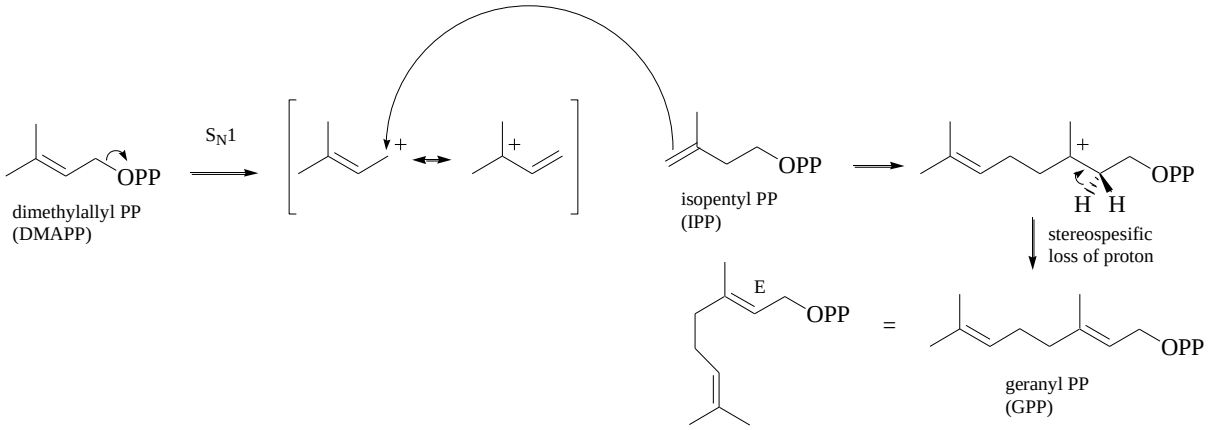


Figure 6. Generation of geranyl diposphate from DMAPP and IPP.[3]

2.2.1 Biosynthetic pathways to IPP and DMAPP

There are two pathways leading to IPP and DMAPP, the mevalonate patway and the recently discovered mevalonate independent pathway via deoxyxylulose phosphate also called the methylerythriol phosphate pathway. The mevalonate pathway are described in figure 7.[3]

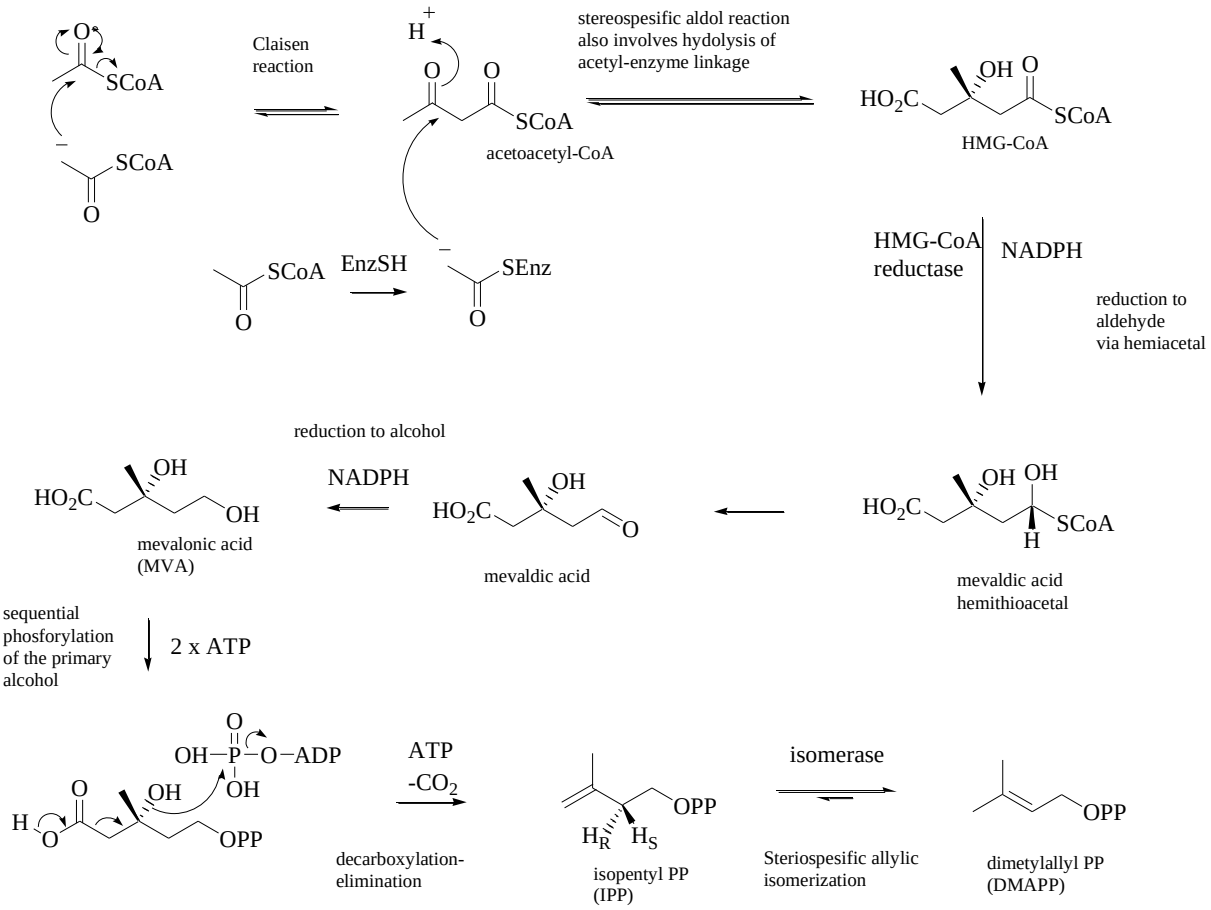


Figure 7. Mevalonic acid pathway.

Three molecules of acetyl-coenzyme A are starting materials in this pathway. Two of the acetyl-coenzyme A molecules reacts in a Claisen condensation to give acetoacetyl- coenzyme. The third acetyl- coenzyme molecule is bond to an enzyme thereafter reacting with the acetoacetyl- coenzyme in a stereospesific aldol reaction followed by hydrolysis of the enzyme linkage to give the β-hydroxy-β-methylglutaryl-CoA (HMG-CoA).[3] HMG-CoA is converted to mevalonic acid (MVA) by a two step reduction of the thioester group to a primary alcohol. The reduction involves the enzyme HMG-CoA reductase and nicotinamide adenine dinucleotide phosphate (NADPH) and is an irreversible and rate limiting transformation.[3] 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.[3] IPP is formed in a stereospesific allylic isomerisation by the isomerisation enzyme isomerase. Isomerase removes the proton H_R and incorporates a proton from water on the terminal carbon. The isomerisation is reversible but the equilibrium lies towards DMAPP.[3]

The methylerythriol phosphate pathway is described in figure 8.[3]

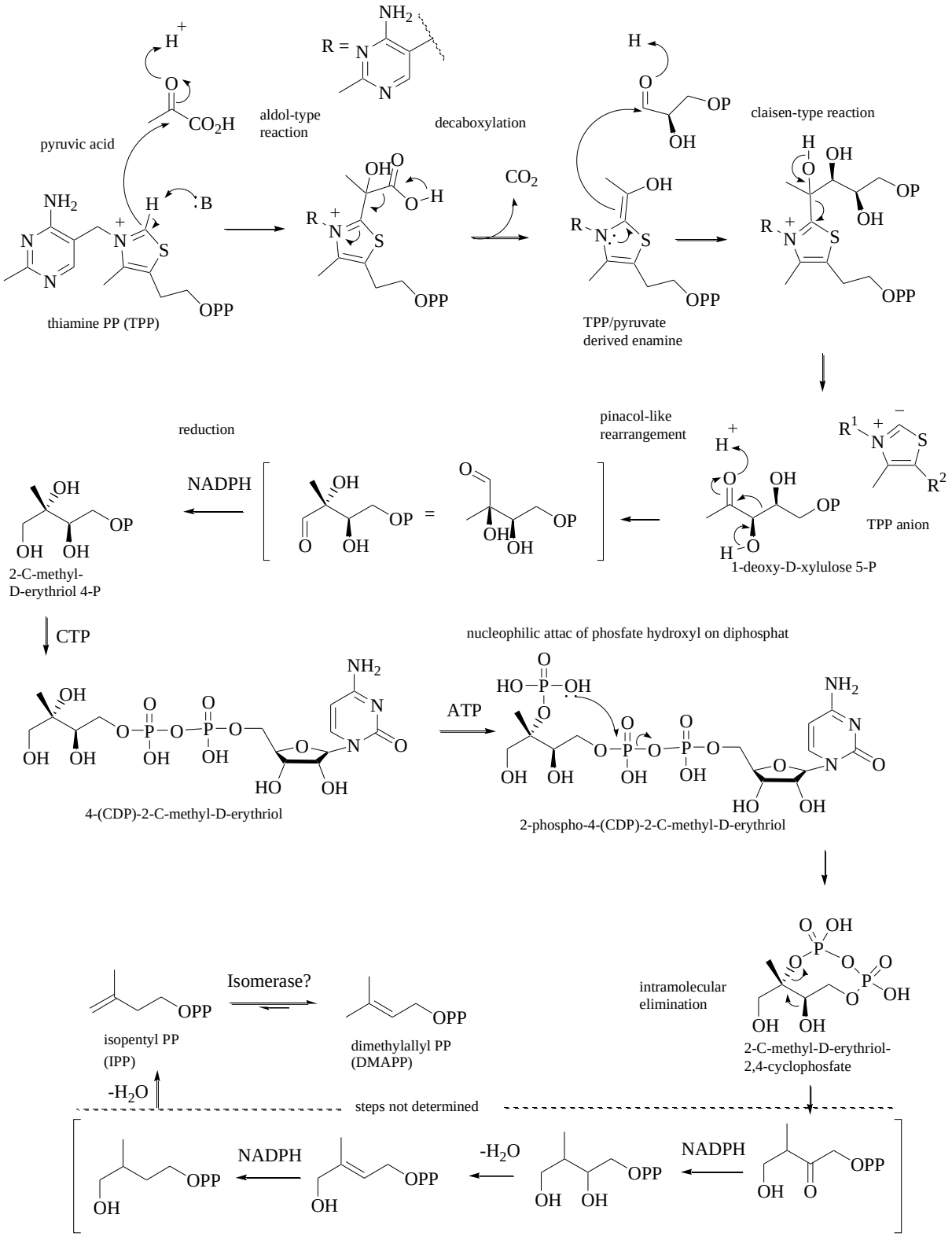


Figure 8. The methylerythriol phosphate pathway.

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 glyceralaldehyde 3- phosphate followed by release of the TPP anion to give 1-

deoxy-D-xylulose 5- phosphate.[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-erythriol 4-P. A single enzyme catalysis the rearrangement and reduction reaction without release of any intermediate.[3] 2-C-methyl D-erythriol 4-P reacts with cytidine triphosphate (CTP) to give a cytidine diphospho derivate (4-(CDP)-2-C-methyl-D-erythriol). The cytidine diphospho derivate is phosphorylated by ATP to give the 2-posph-4-(CDP)-2-C-methyl-D-erythirilol, which is converted to a cyclic 2-C-metyl-D-erythirol-2,4-cycloposphate by loss of cytidine phosphate.[3] The cyclophosphate is conversed 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_2O to give IPP. DMAPP may be formed by an isomerism by the enzyme isomerase, or may be formed independently.[3]

Whether a biosynthesis of a terpenoid is provided with isoprene units from the melavonate pathway or the deoxyxylulose phosphate pathway must be established experimentally. The animals lacks the deoxyxylulose phosphate pathway so the melovonate 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 down regulate the steroid production. This is of interest since the biosynthesis of cholesterol could be regulated by use such inhibitors.[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.[3] Therefore the novel sequiterpene Hazardiadione is probably build up of isoprene units from the deoxyxylulose phosphate pathway.

2.2.2 Sesquiterpenes

Sesquiterpenes are the terpenoids containing a carbon skeleton of 15 carbons (C_{15}). The fundamental sesquiterpene precursor is farnasyl diphosphate (FPP) (figure 9).[3]

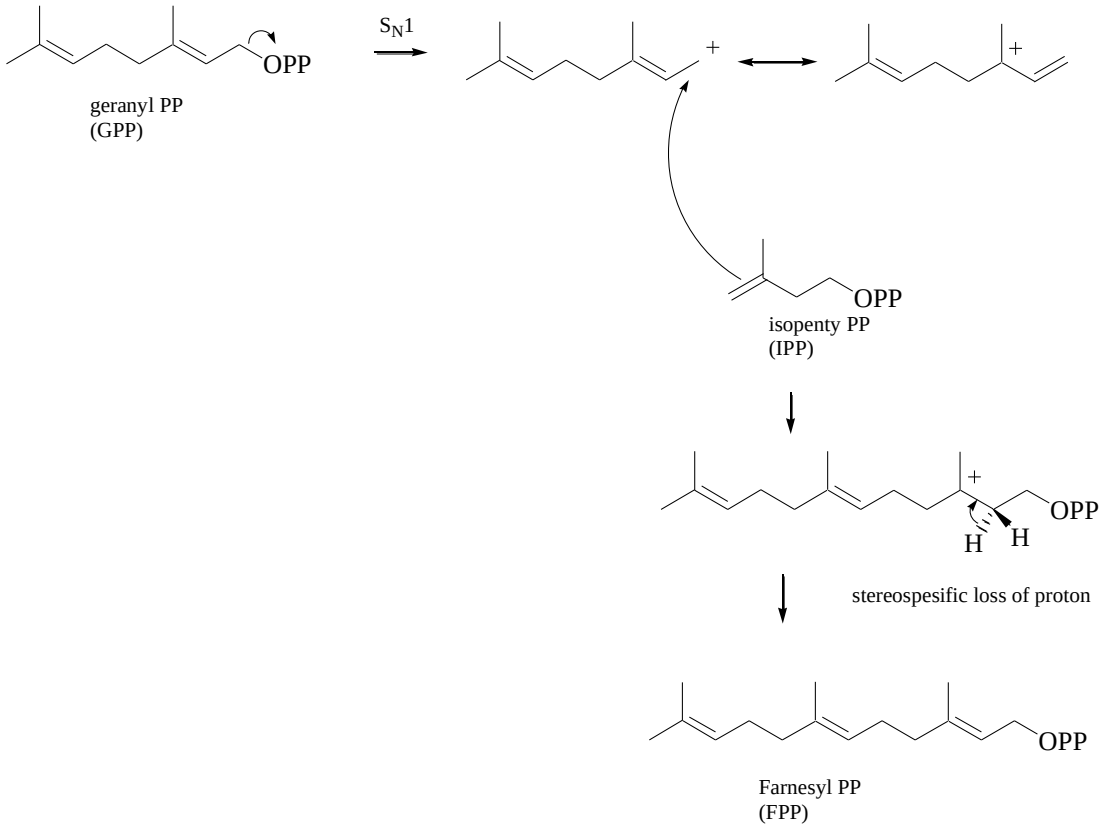


Figure 9. Biosynthesis of farnesyl diphosphate (FPP)

The FPP is generated by an addition of an IPP unit to GPP, which reacts in a S_N1 type reaction with IPP followed by a stereospesific 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 a *E* configuration or an *Z* configuration, giving the two stereochemical configuration *E*,*E*-Farnesyl PP and *E*,*Z*- Farnesyl PP (figure 10).[3]

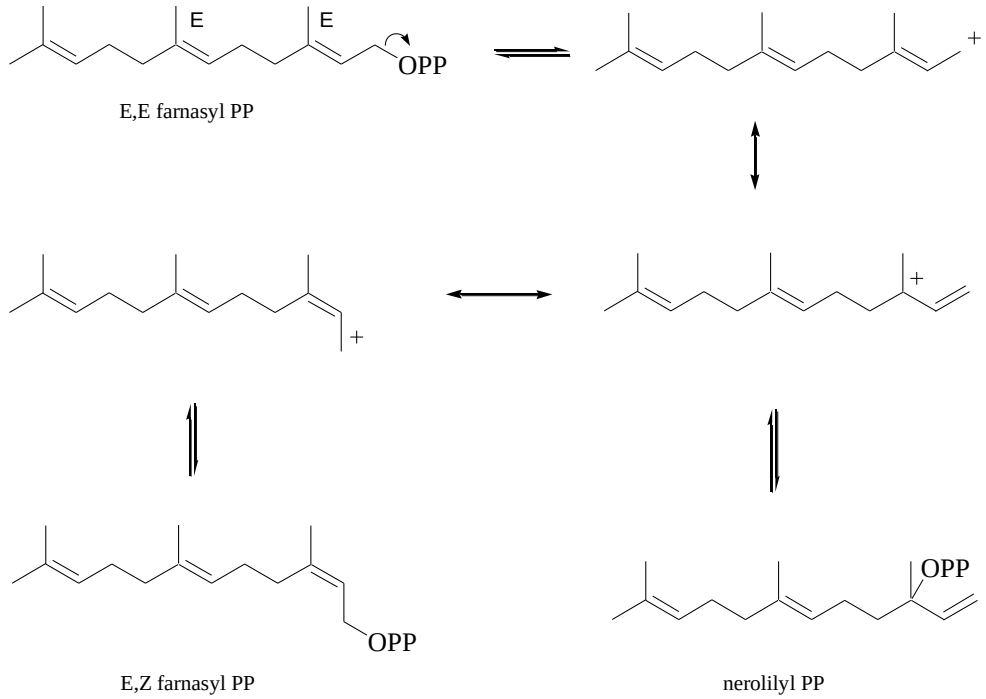


Figure 10. Ionization of FPP

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]

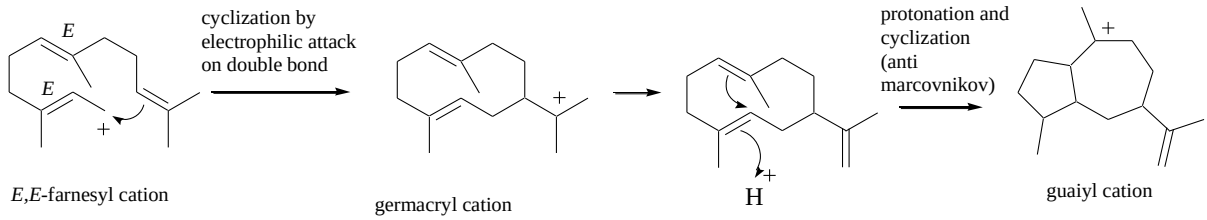


Figure 11. The guaiane skeleton could be generated via *E*,*E*-Farnesyl cation.[3]

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 Hazardiadione, a seven membered ring fused with five membered ring. The skeleton of hazardiadione is called isoduacane. (figure 12)[4]

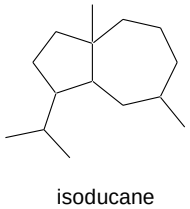


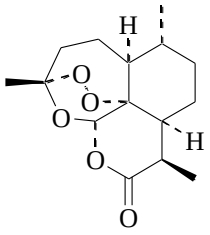
Figure 12. Isoduacane skeleton

2.2.4 Biological activity of some important sesquiterpenes

Tabel 2. Lists of some biological active sesquiterpenes

Biological activity	**Sesquiterpene**
Antiinflammatory	helenalin[4], chamazulene[4]
Antibacterial	(+)-isivelleral[4] , Δ^6-protoilludiene[5], (-)illudine M[4], (-)illudine S[4], (-)-merulidial[4], (+)-dihydroxy-γ-inoylidine[4], artemisic acid[4]
Anticancer	helenalin[4] , (-)illudine M[4], (-)illudine S[4]
Antimalaria	artemisinin[3]
Antirhematic	helenalin[4]
Antipyretic	helenalin[4]
CNS and respiratory stimulant	(-)-picotoxinin[4]
Antifungal	(+)-armillarin[4]
Antimycotic	(-)-merulidial[4]
Antihelmithic	α-santonin[3]
Antimigrane	parthenolide[3]

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]



artemisinin

Figure 13. Artemisinin

Artemisine is a sesquiterpene isoloated 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 reagions 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 arthemisinin gives dihydroathemisinin 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 artelinec acid and artesunic acid (figure 14)[3]

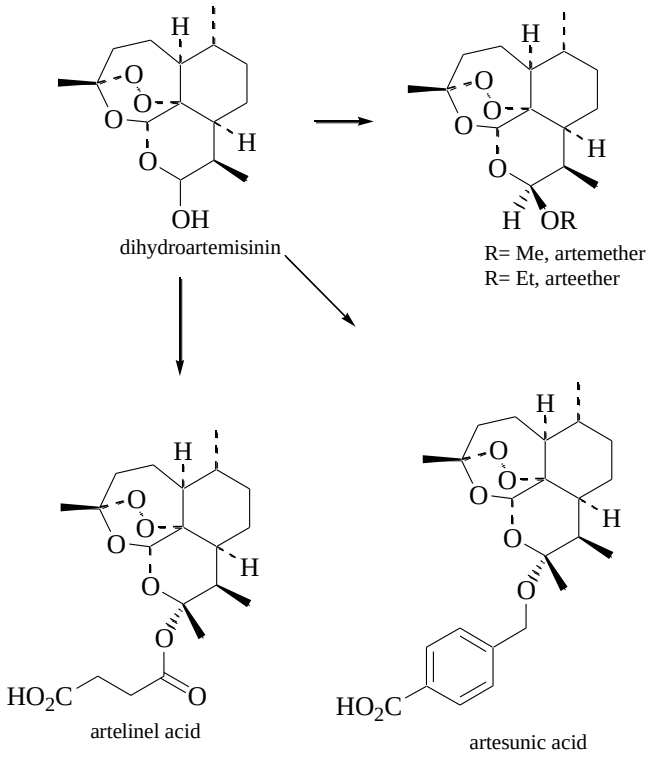
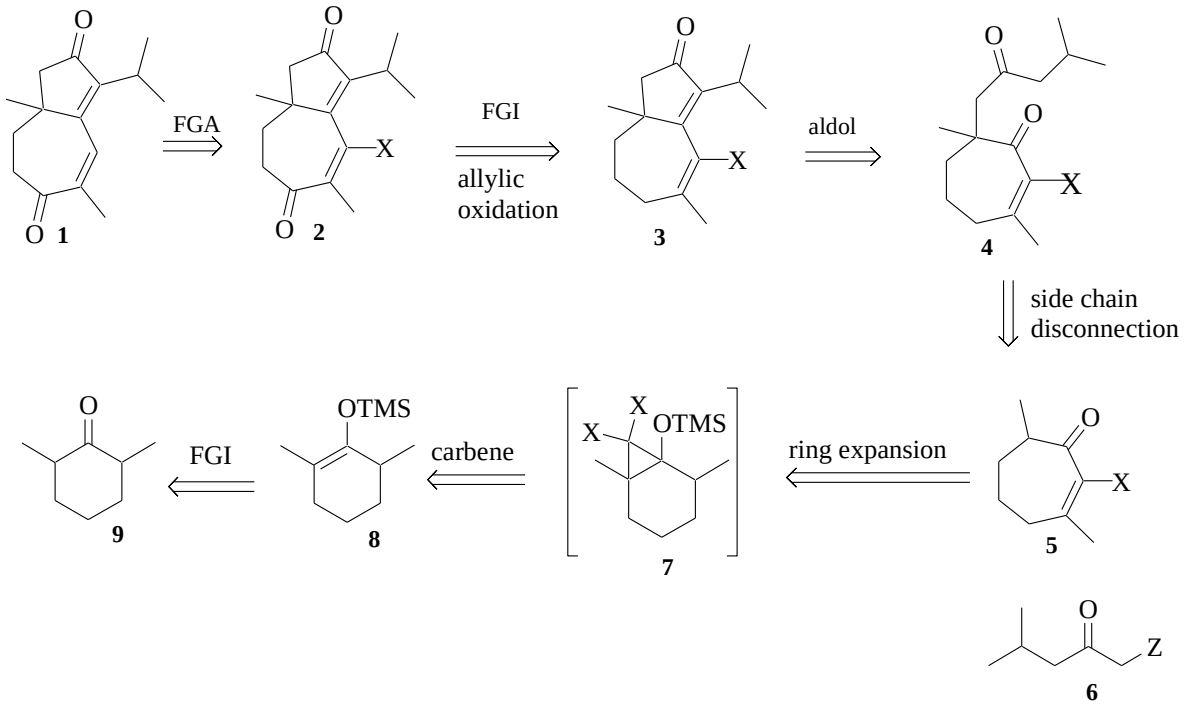


Figure 14. Semi synthetic analogues to artemisinin.

Artemether is effective against chloroquinine 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.



X = Cl, Br
Z = Br,I, OTs, OMs

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 SmI_2.[7, 8] 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).[9] Nicolaou *et al*. had a similar challenge in the synthesis of Taxol and used PCC to get the regioselictiv 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.**[10] 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.[11] 2,6 Dimethylcyclohexanone **(9)** is commercially available as a mixture of cis and trans isomers.

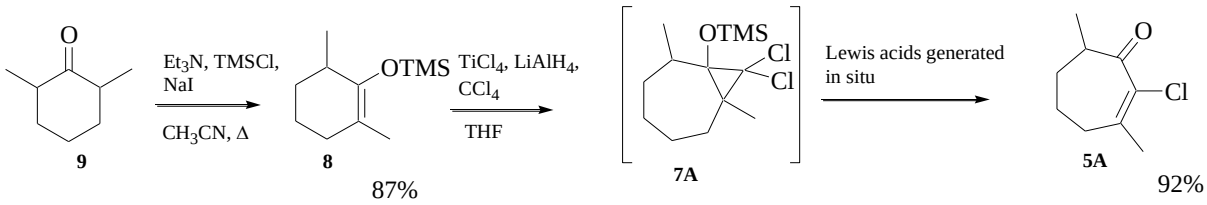
4 Results and discussion

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

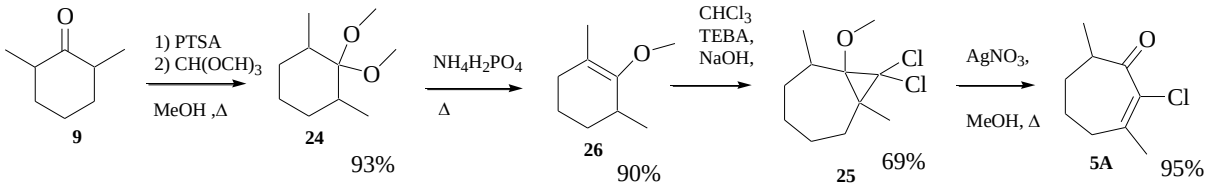
The α,β unsaturated ketone **5A** was synthesised in good yield in (78 %) in two steps.[1] (Scheme 1)



Scheme 1. Synthesis of the ketone **5A** from 2,6-dimethylcyclohexanone **(9).**

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

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.

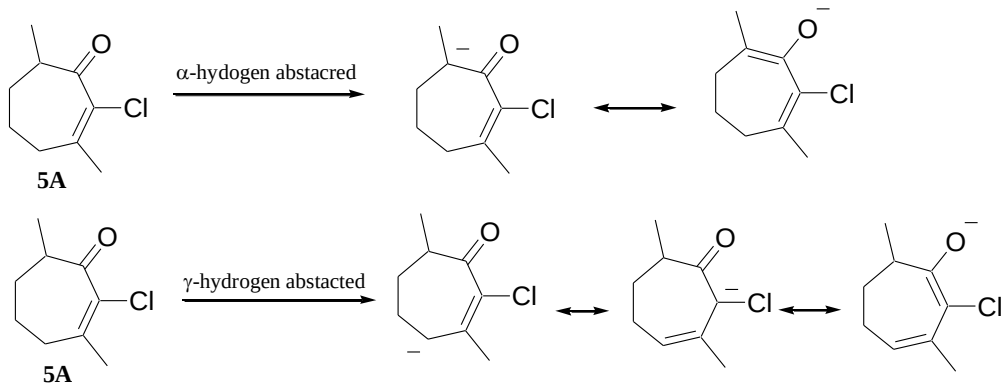
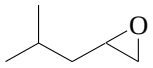
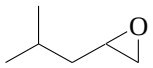
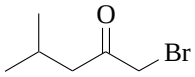
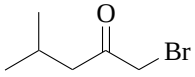
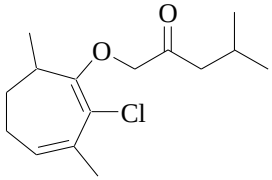
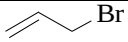
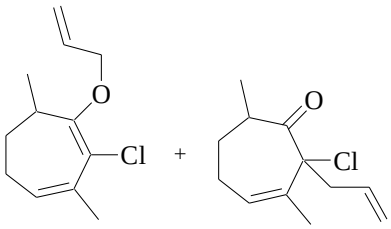
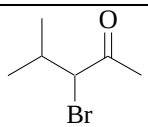
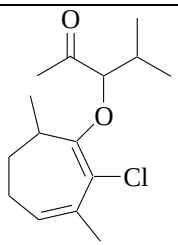


Figure 15. Abstraction of α- or γ-proton to generate different enolates.

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.

Entry	Base	Electrophile	Solvent	Results
1	LDA or NaHMDS		THF	Mainly starting material, traces of undefined products
2	KH		DMF	Starting material
3	KH		THF or DME	Starting material, Favorskii type reaction took place
4	KH		DMF	
5	KH		DMF	
6	KH		DMF	

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).

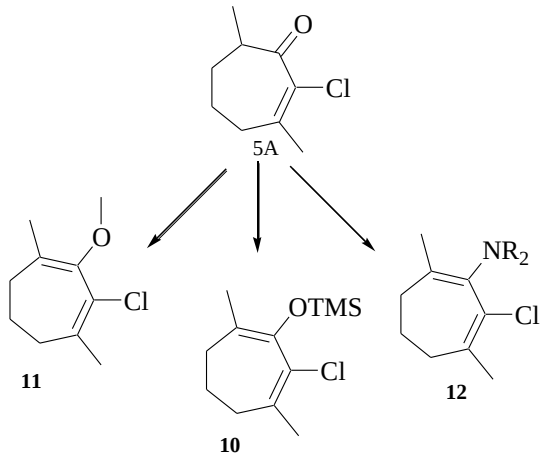
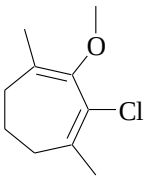
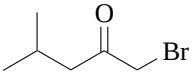
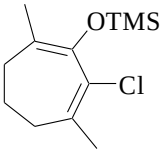
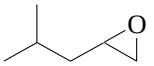
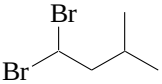
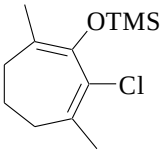
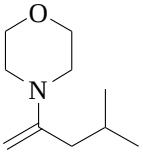


Figure 16 Equivalents for specific enolate

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.

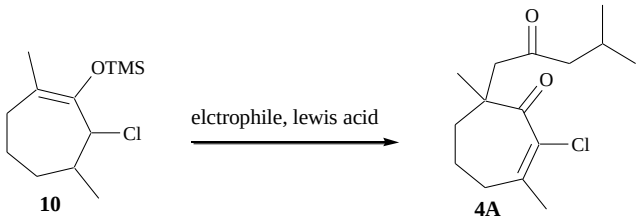
Entry	Nucleofile	Elecrtophile	Conditions	Products
1			CH_3CN, reflux	Bromo ketone was unstable to heat
2		 or $(CH_2O)_n$ or 	$TiCl_4$,CH_2Cl_2, -78°C to RT	Undefined products and ketone **5A**
3			CAN, CH_3CN, RT	Undefined products and ketone **5A**

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)



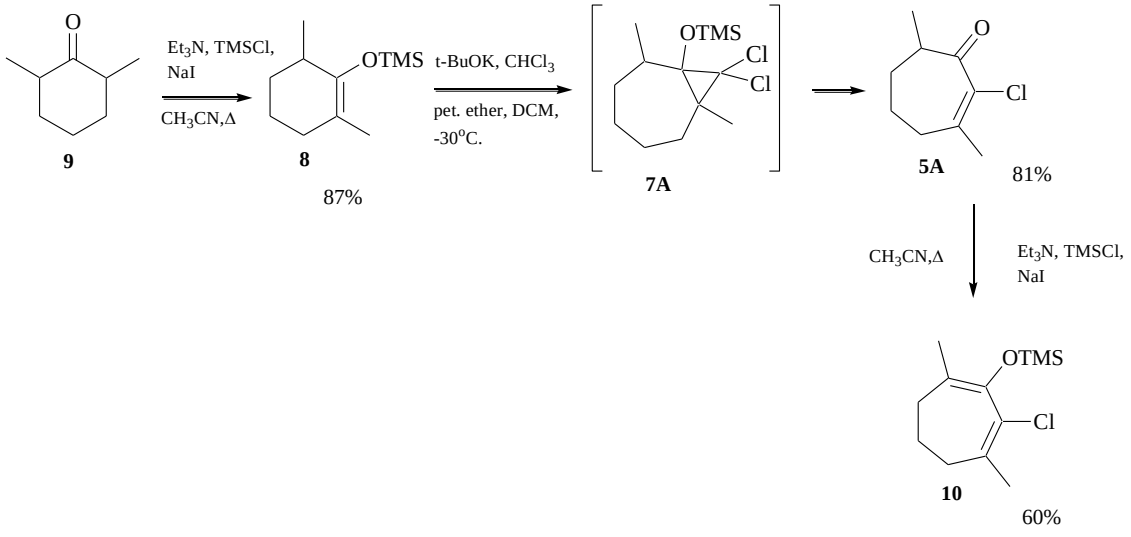
10 **4A**

Figure 17. Alkylation reaction with silyl enol ether **10** and a suitable electrofile in the presence of a lewis acid would probably give the desired diketone **4A**.

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.



9 **8** 87% **7A** **5A** 81% **10** 60%

Scheme 4. Synthesis of the silyl enol ether **10.**

The silyl enol ether **10** was synthesised from the starting material 2,6- dimethyl cyclohexanone **(9)** in 42% yield using tree 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 α-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 synthesises from the silyl enol ether **8** using the Doring-Hoffman conditions in good yield (81 %).[14] Potasium 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.

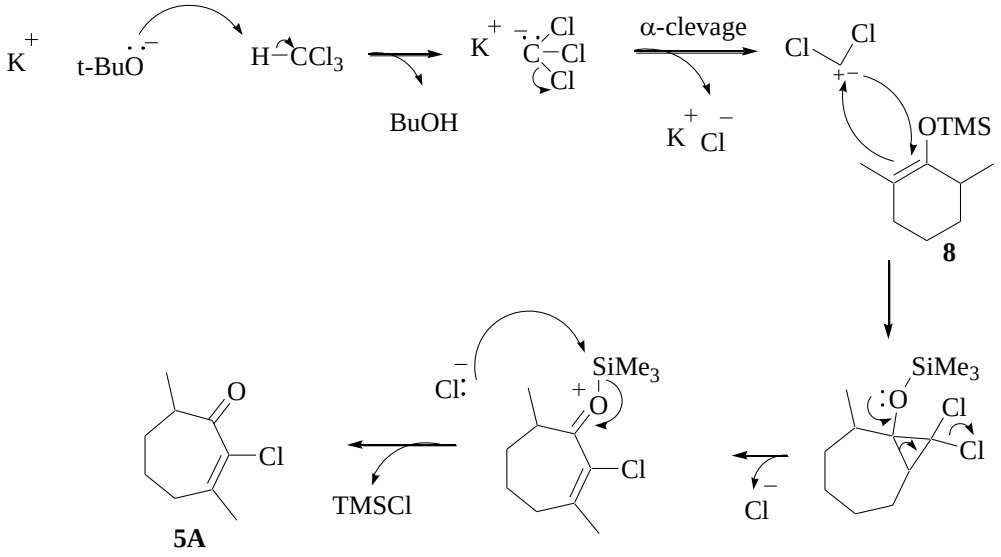


Figure 18. Proposed mechanism of the synthesis of the ketone **5A**

Almassy *et al*. preformed 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)

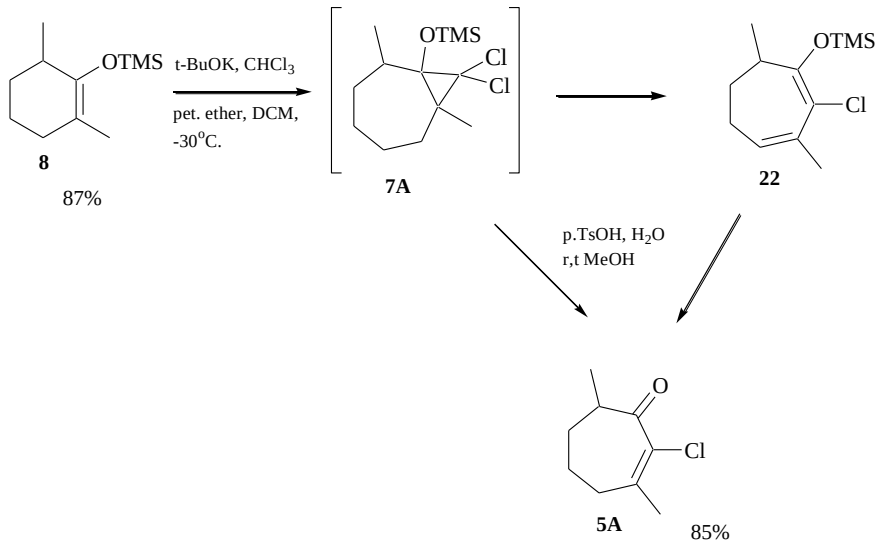


Figure 19. Almassy *et al*. synthesis of the ketone **5A**

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 it with TsOH in methanol for 20 hours giving (85% after distillation) of the seven membered ring ketone **5A.**

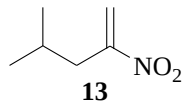
We performed the same reaction that Almmasy *et al*, but in our case we performed the reaction in 2 x scale using 10 eq. of $CHCl_3$ dissolved in DCM instead of 20 eq. of $CHCl_3$, and adding the $CHCl_3$ much faster 1.5 h compared to 4.5 h and we also kept the temperature colder between -30 and -50°C. 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 electophile is the nitroalkene **13. (**Figure 20)



13

Figure 20. The nitroalkene **13**, a suitable electrophile

The nitro alkene **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 H_2SO_4. (figure 21)

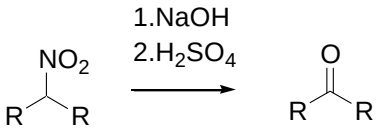


Figure 21. Nef reaction.

McMurry modification of the Neff reaction is a reductive method which leads to oximes, which can be hydrolyzed to the corresponding ketones. $TiCl_3$ in acidic conditions (pH < 1) is effective in this reaction (figure 22).[15]

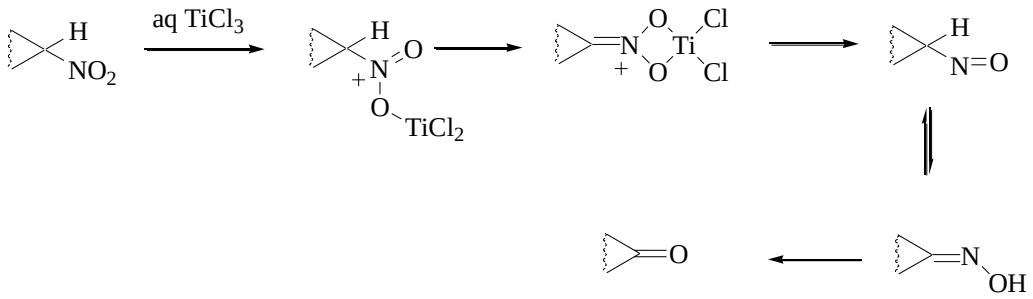


Figure 22. McMurry modification of the Nef reaction.

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]

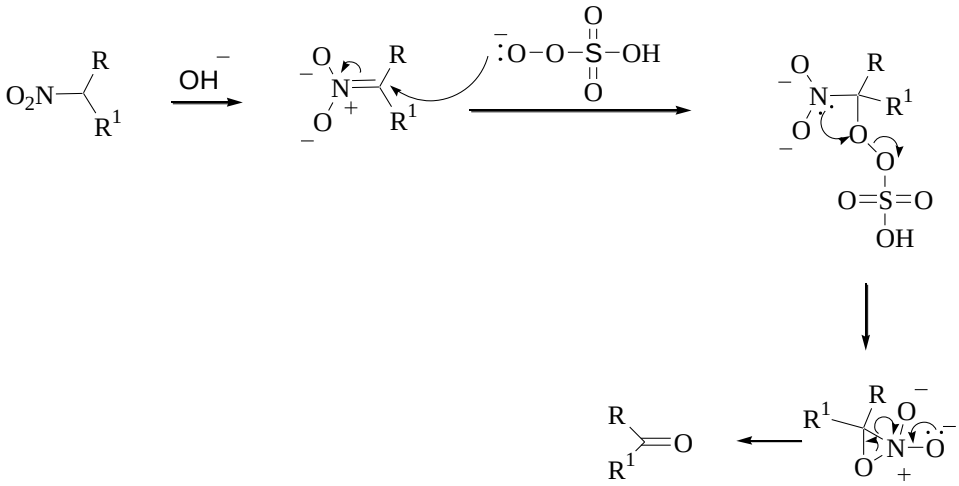
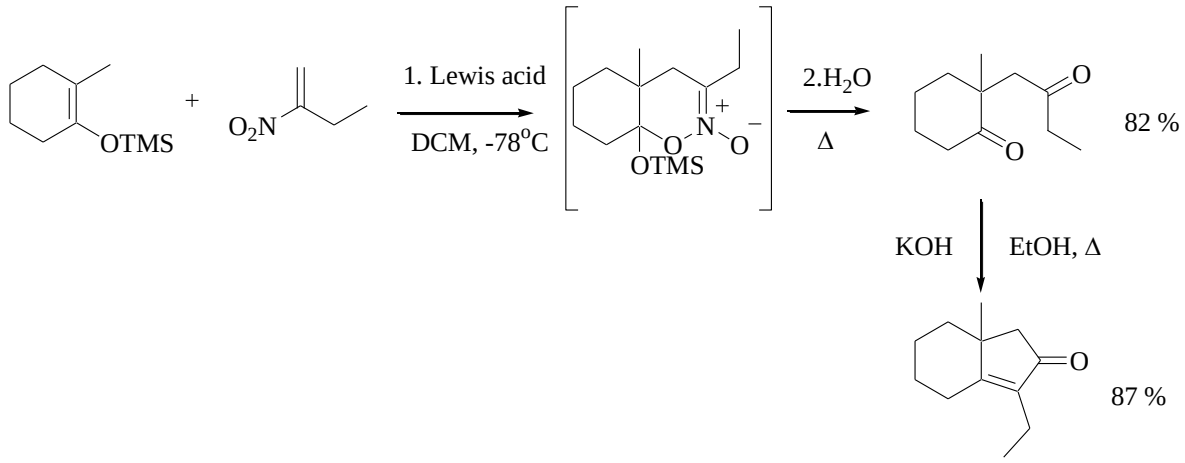


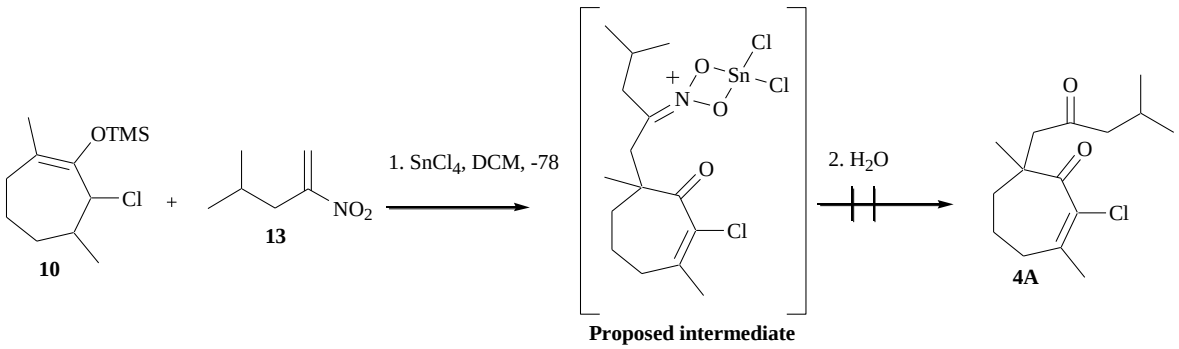
Figure 23. Nef reaction with Oxone®

It has been reported in the litterateure that reactions with silyl enol ethers and nitroalkenes with Lewis acids at -78 °C in DCM under N_2, followed by hydrolysis giving corresponding diketones in good yield.[10] These reactions were preformed for many molecules using the Lewis acids $SnCl_4$, $TiCl_4$ and $AlCl_3$ with generally best results with $SnCl_4$. 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 $SnCl_4$ followed by hydrolysis, the reaction was also performed with the Lewis acid $TiCl_4$. The desired diketone **4A** was not observed in the crude product using these conditions (Scheme 6).

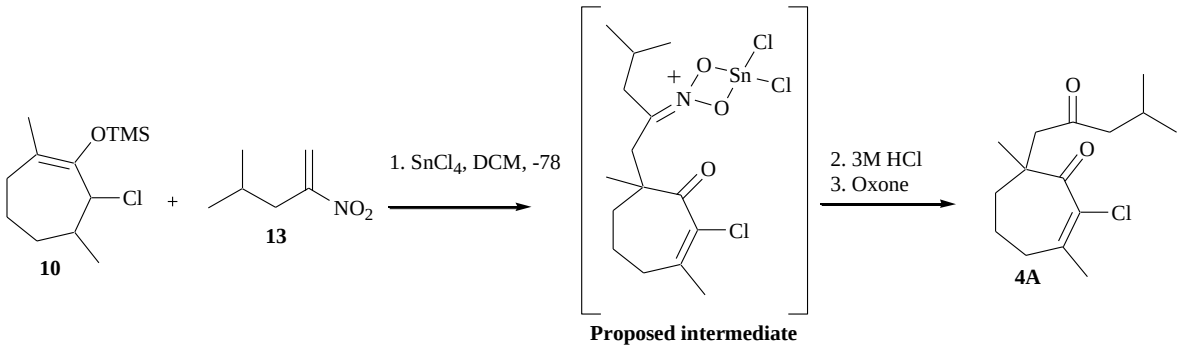


Shceme 6. Hydrolysis with these conditions did not give the diketone **4A.**

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.[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®. The last maneuver converted the intermediate oxime into the diketone.[17]

The reaction conditions from Leo Paquette *et al*. was performed on the silyl enol ether **10** and the nitroalkene **13.**[17] In the presence of $SnCl_4$ a Micheal addition of the silyl enol ether **11** on the nitroalkene **13** followed by hydrolysis with 3M HCl followed by treatment with Oxone® 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®.

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_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

good, it was to small amount of liquid for the distillation set up. Distillation with larger scale would probably provide the diketone **4A** in good yield.

A possible mechanism for this reaction is described in figure **13.**

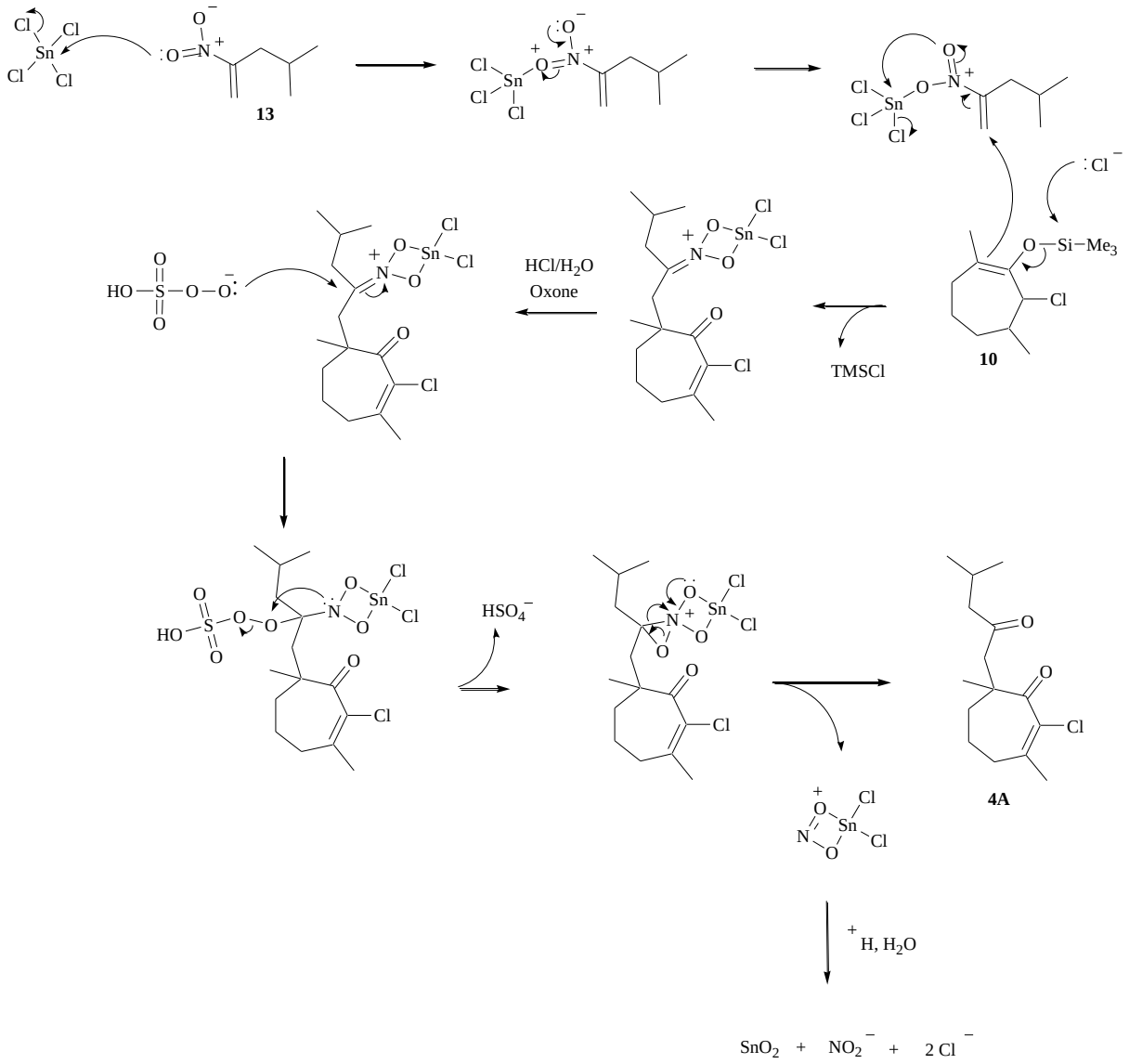


Figure 24. Proposed mechanism of the alkylation reaction between the silyl enol ether **10** and the nitroalkene **13** followed by Nef reaction with Oxone®.

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^{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)

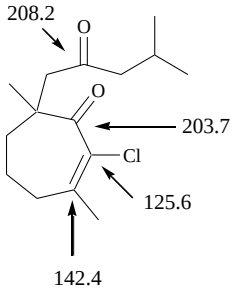


Figure 25. Characteristic carbon signals from NMR analysis

The H^1 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 H^1 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 shift1.27 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. (figure 26)

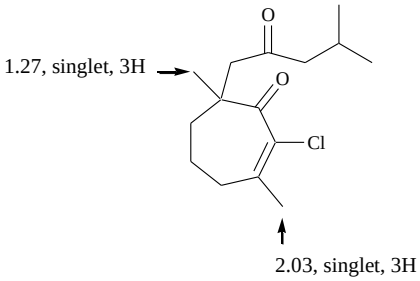


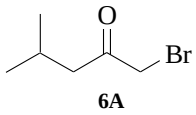
Figure 26. Characteristic proton signals from NMR analysis

The IR analysis of the diketone **4A** was also in accordance to the structure. The two strong IR absorptions at 1708 and 1690 cm^{-1} are consistent with the two carbonyl groups and a absorption at 1622 cm^{-1} is consistent with the C-C double bond.

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 C^{13} NMR where one carbonyl signal with chemical shift of 210.1 ppm, and one singnal with chemical shift of 64.1 ppm. Surprisingly there were no olefinic signals, meaning that the double bound was missing. The rest of the carbon signals were in the chemical shift region for saturated alkanes. The H^1 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 α- carbon on the seven membered ring. There where to doublets with coupling constant of 6.7 Hz and integral of 3 and chemical shifts 0.91 and 0.96 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)



6A

Figure 27. α-bromoketone **6A**

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.

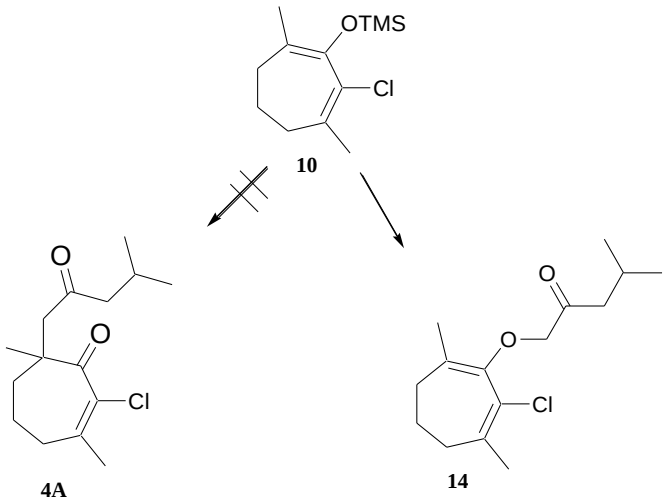
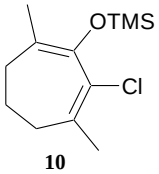
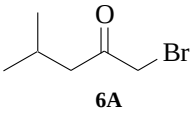
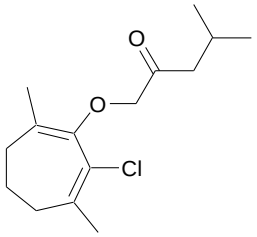
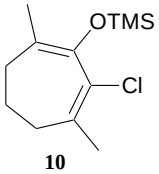
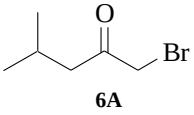
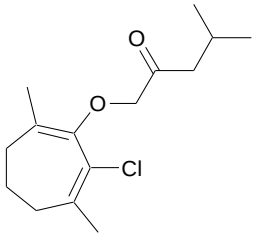
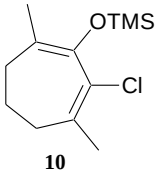
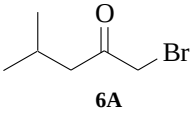
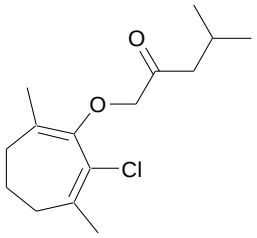


Figure 28. Alkylation reaction with α-bromoketone **6A** in the presence of TBAF

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

Entery	Nucleofile	Electrofile	Conditions	Products
	 **10**	 **6A**	TBAF, THF, -78°C	 **14** and traces of 7 membered ring ketone **5A**
	 **10**	 **6A**	TBAF, DCM, -78°C	 **14** and traces of 7 membered ring ketone **5A**
	 **10**	 **6A**	TBAF, Methyl-cyclohexane, -78°C	Mixture of  **14** And 7 membered ring ketone **5A**

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 Hazardiadione 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 similarl compounds.[10] A reason for the diketones **4A** unwillingness towards aldol cylization 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)

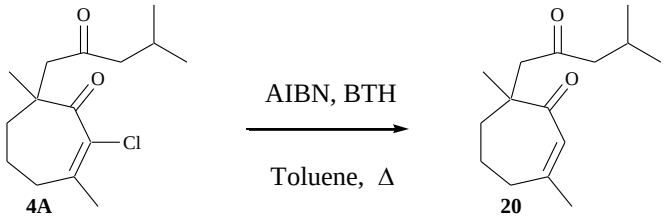


Figure 29. Removal of halogen

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 evivalents 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 the α-β unsaturated system. There was also a signal with chemical shift 209.1 ppm with is in accordance to the ketone group on the side chain. In the ^{1}H 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.

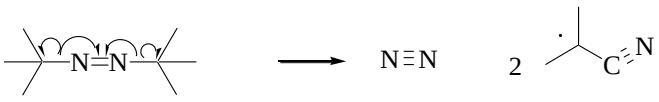


Figure 30 AIBN decomposed under heating to form nitrogen gas and radicals.

A proposed mechanism is described in figure 31.

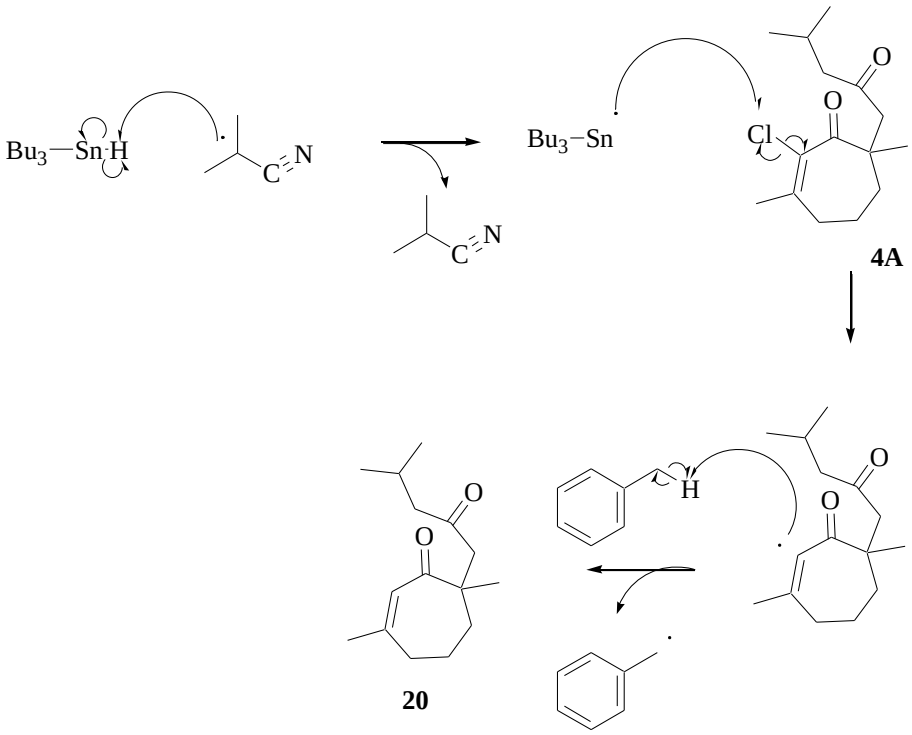


Figure 31. Mechanism for the removal of the halogen

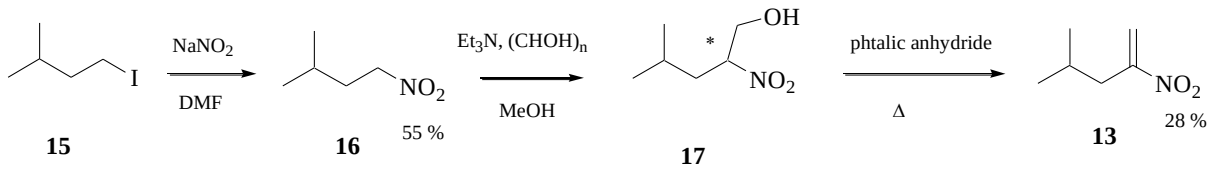
BTH in combination with AIBN under heating cleaves to give the tributyltinn radicals which reacts with the chlorine giving the vinyl radical. The vinyl radiacal reacts with toluene in a radical reaction giving the dikeketone **20**.

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

6.3 Synthesis of the electrofilic 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.

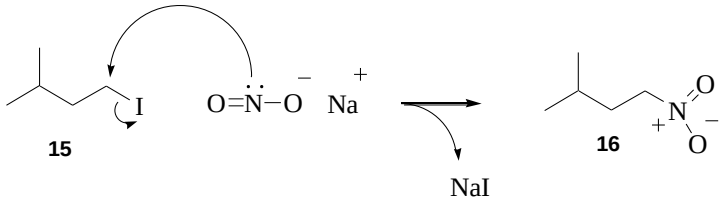


Figure 32. Proposed mechanism for the Meyer reaction.

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.)

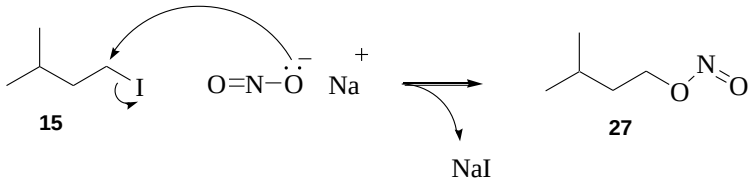


Figure 33. Possible competitive S_N2 type reaction giving isoamyl nitrite **27.**

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 α-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.

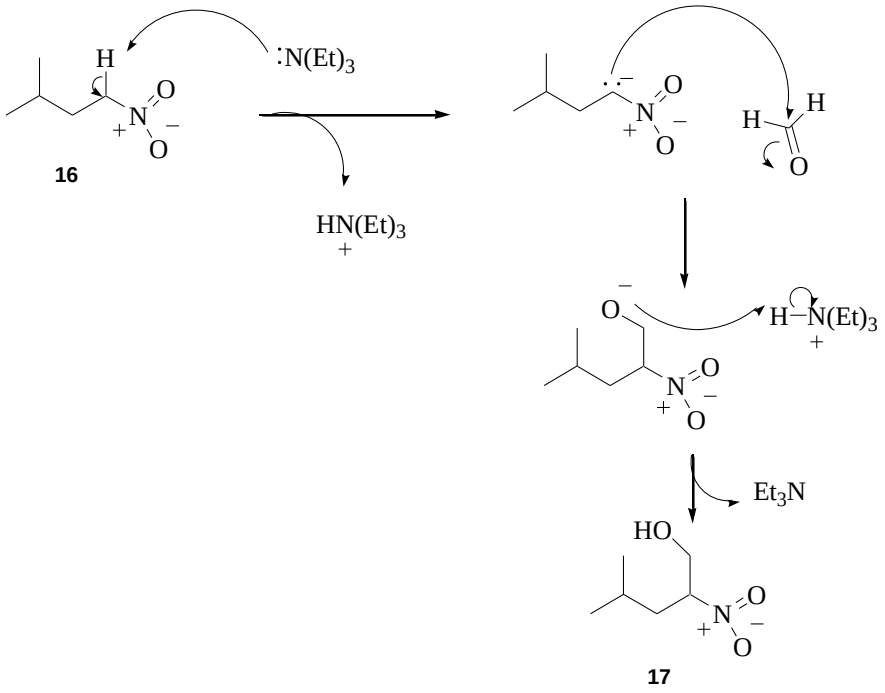


Figure 34. Proposed mechanism of Henry reaction.

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.

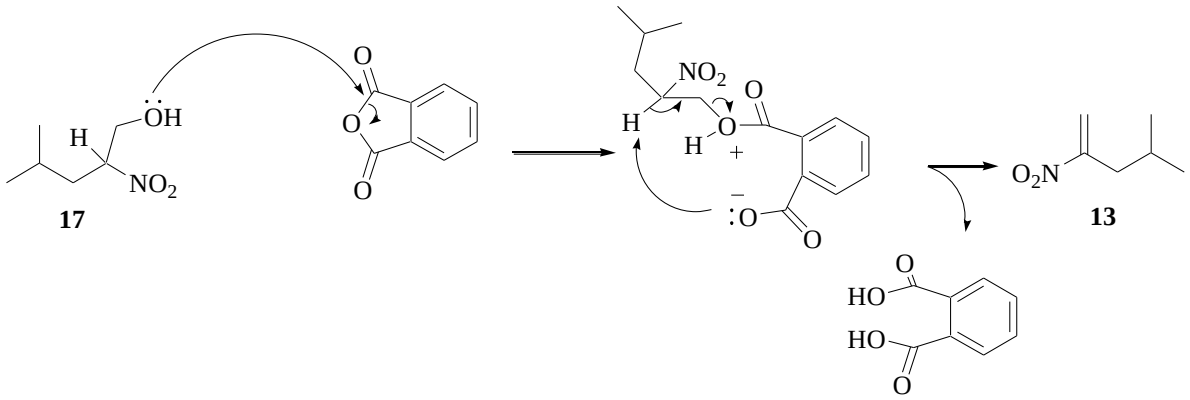
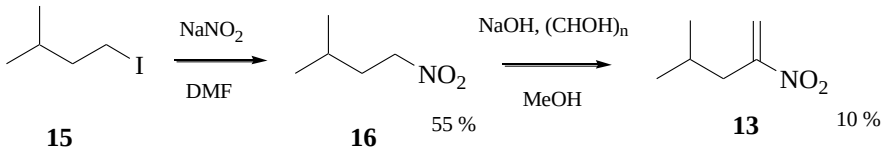


Figure 35. Mechanism of the reaction between phthalic anhydride and 2-nitroisohexanol (**17).**

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



Scheme 9. Synthesis of the nitroalkene **13.**

The nitroalkane **16** was treated with parafomaldahyde 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 nitro alkene **13** and the undefined product mentioned above. Elimination was also tried in acidic conditions with TsOH without success.

The nitroalohol **17** was also reacted with mesylchloride 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)

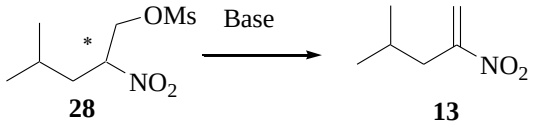


Figure 36. elimination reactons with the mesylate **28** was not successful

6.3.2 Syntesis of the α-bromoketone 5A

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

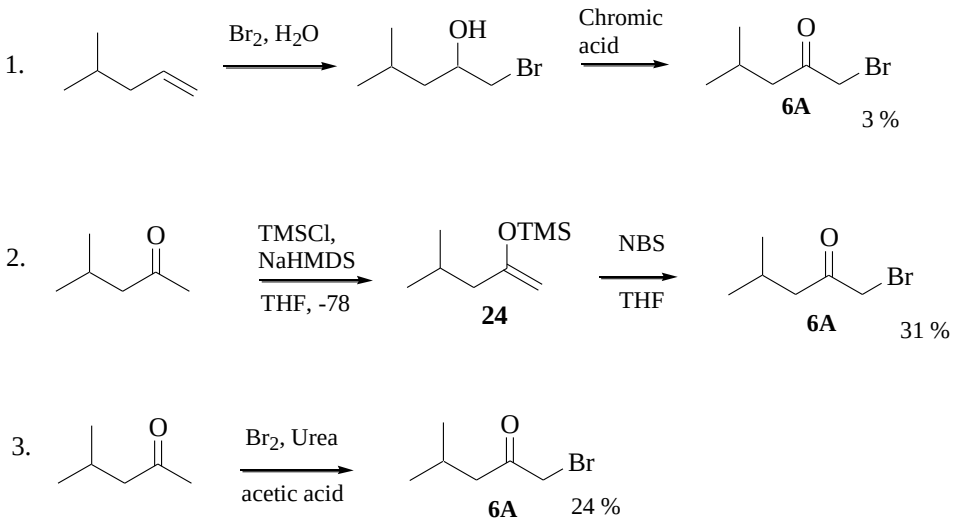


Figure 37. Synthesis of α-bromoketone **6A**, 1[1], 2[20] and 3 [21]

The most interesting is the synthesis nr 2, where isobytylmethylketone 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-bromosuccsinimide (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-dimethylcyclohaxanone **(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 C_6 side chain was synthesized in two different ways. The C_6 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)

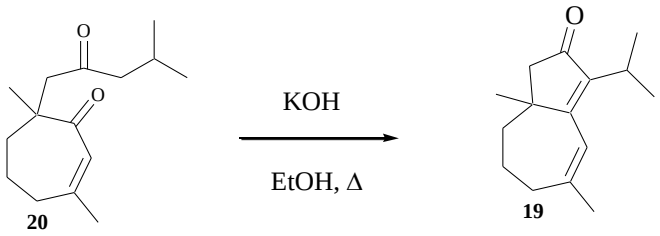


Figure 38. Aldol cyclization

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)

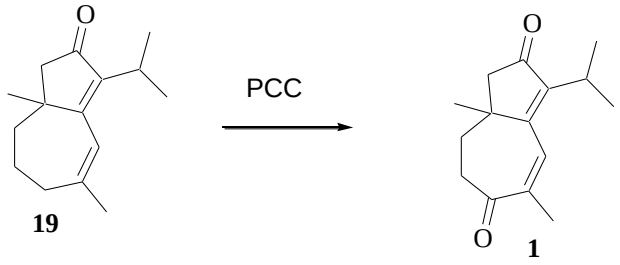


Figure 39. Regioselective allylic oxidation

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 CH_2Br_2 and the strong base NaHMDS.[22] The bomocarbene 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)

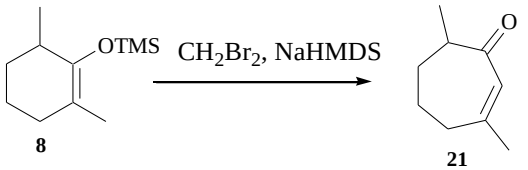


Figure 40. Reaction with bromocarbene

6 Experimental section

6.1 genaral

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 (δ 0.0 ppm) ^{13}C NMR spectra are referenced in ppm of deutero chloroform (δ 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 dedected by UV-light (extinction at γ = 254 nm or fluorescence at γ = 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% H_2SO_4 (16 mL) in water (180 mL) and heat.

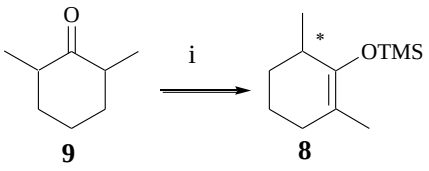
Infrared spectroscopy was performed on Varian 1000 FT-IR spectrometer located at MI-SWACO

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)



9 **8**

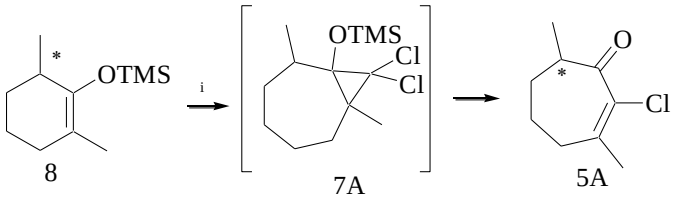
($C_8H_{14}O$) **($C_{11}H_{22}OSi$)**

i) TMSCl, NaI, Et_3N, CH_3CN, 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 $NaHCO_3$ (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 $NaHCO_3$ (aq) (2 x 100 mL). The organic phase was dried with $MgSO_4$ 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, $CDCl_3$) 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); ^{13}C NMR (75MHz, $CDCl_3$) 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).



8 7A 5A

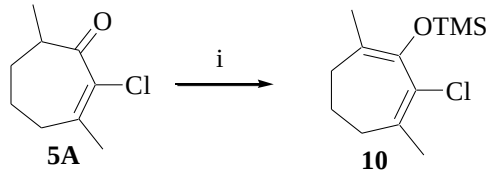
($C_{11}H_{22}OSi$) **($C_9H_{13}OCl$)**

i) tBuOK, $CHCl_3$, 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) ν 2933, 2864, 1682, 1604, 1458, 1375, 1224, 1200, 1088, 1032, 906, 846, 781, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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).



5A **10**

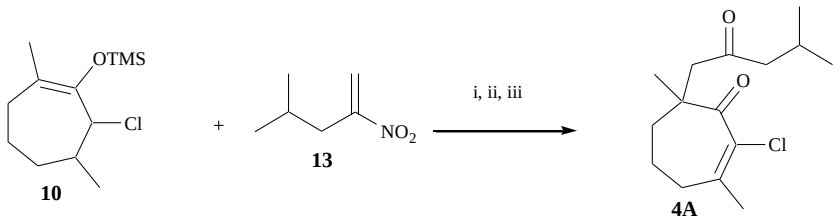
($C_9H_{13}OCl$) **($C_{12}H_{21}OClSi$)**

i) TMSCl, NaI, Et_3N, CH_3CN, Δ

Et_3N (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 $NaHCO_3$ (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 $NaHCO_3$ (aq) (2 x50ml). The organic phase was dried with $MgSO_4$ 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) ν 2932, 2857, 1634, 1449, 1286, 1251, 1209, 1163, 1097, 1063, 1020, 964, 895, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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)



10 **13** **4A**

($C_9H_{13}OCl$) ($C_6H_{11}NO_2$) ($C_{15}H_{23}O_2Cl$)

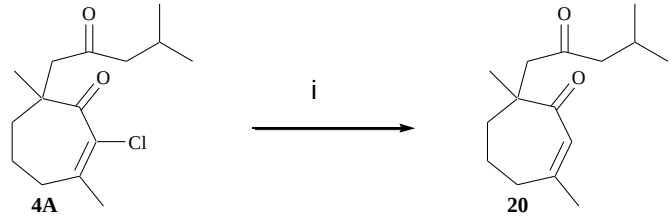
i) $SnCl_4$, DCM, - 78 °C
ii) 3M HCl
iii) Oxone

$SnCl_4$ (1.0 mL, 8.50 mmol) was added dropwise over a period of 15 min. to a solution of nitro alkene **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_2O (150 mL) was added and the water phase was extracted with Et_2O (50 mL x 4). The organic phase was washed with water (25 mL x 2) and dried with Na_2SO_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, 2071, 1708, 1690, 1622, 1455, 1367, 1225, 1148, 1104, 1048, 922, 893, 814 cm^{-1}. ^1H 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* = 17.1Hz, 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)



4A ($C_{15}H_{23}O_2Cl$) **20** ($C_{15}H_{24}O_2Cl$)

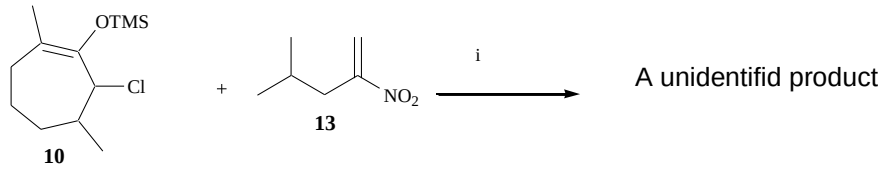
i) BTH, AIBN, Δ

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_2O (4 x 25 mL). The organic phase was washed with water (4 x 25 mL). The organic phase was dried with Na_2SO_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. ^{1}H 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). ^{13}C 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



10 **13**

($C_9H_{13}OCl$) ($C_6H_{11}NO_2$)

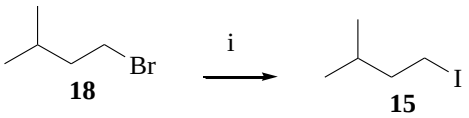
i) TBAF, - 78 °C

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} .^{1}H 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). ^{13}C 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)



18 **15**

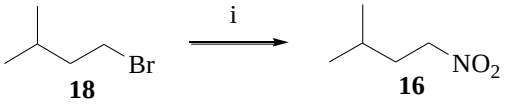
($C_5H_{11}Br$) **($C_5H_{11}I$)**

i) NaI, acetone

Bromo-3-methylbutane (**18)** (30.2 g, 0.20 mol) was added dropwise to a mixture of NaI (44.97g, 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.^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 5.2, 21.7, 29.0, 42.5

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



18 **16**

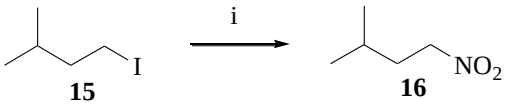
($C_5H_{11}Br$) **($C_5H_{11}NO_2$)**

i) $NaNO_2$, DMF

Isopentyl bromide (**18)** (120.84 g, 0.80 mol) was added dropwise to a mechanical stirred solution of sodium nitrite (110.39g, 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 Na_2SO_4 then the solvent was evaporated under reduced pressure. Distillation under vacuum gave 30.2g (32%) of the colorless nitroalkane **16** (b.p. 58 - 60 °C 21 mmHg)

Not visible on TLC IR (neat) ν 2962, 1549, 1470, 1434, 1434, 1381, 1211, 1133, 851 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.9, 25.5, 35.9, 74.2

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



15 **16**

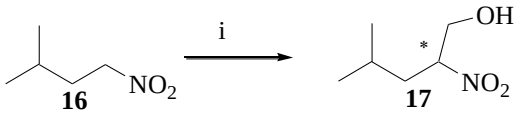
($C_5H_{11}I$) **($C_5H_{11}NO_2$)**

i) $NaNO_2$, 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 Na_2SO_4 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).



16 **17**

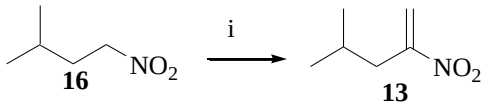
($C_5H_{11}NO_2$) **($C_6H_{13}NO_3$)**

i) $(CH_2O)_n$, Et_3N, 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 Na_2SO_4 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}. ^{1}H 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).^{13}C 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)



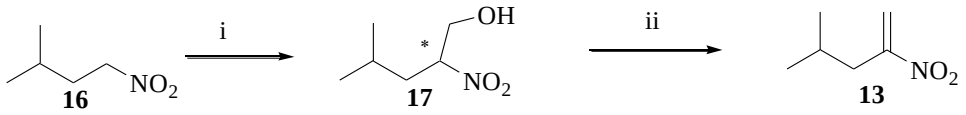
($C_5H_{11}NO_2$) **($C_6H_{11}NO_2$)**

i) $(CH_2O)_n$, NaOH, MeOH

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 H_2SO_4. 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 Na_2SO_4. 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%).

R_f = 0.50 (15% EtOAc in Hexanes ^{1}H) IR (neat) ν 2962, 1524, 1467, 1343, 1168, 1090, 942, 853, 823 cm^{-1}. ^{1}NMR (300 MHz, $CDCl_3$) 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). C^{13} NMR (75 MHz, $CDCl_3$): δ 21.9, 26.3, 39.1, 118, 157.2

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



($C_5H_{11}NO_2$) **($C_6H_{13}NO_3$)** **($C_6H_{11}NO_2$)**

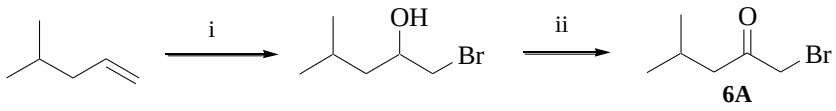
i) $(CH_2O)_n$, Et_3N, MeOH
ii) Phtalic anhydride, Δ

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 Na_2SO_4 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.

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



(C_6H_{11}) **($C_6H_{13}OBr$)** **6A** **($C_6H_{11}OBr$)**

i) Br_2 / H_2O
ii) Chromic acid

4-Methylpentene (10.1 g, 120.0 mmmol) was mixed with water (500 mL) at 0 °C. 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]

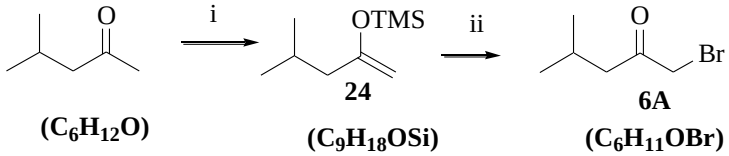
Chromic acid solution was prepared (500 mL)[23]:

$Na_2Cr_2O_7$ x H_2O (100 g, 0.33 mol) was dissolved in 300 mL of water. 97 % H_2SO_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} MNR (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)



24

6A

($C_6H_{12}O$) **($C_9H_{18}OSi$)** **($C_6H_{11}OBr$)**

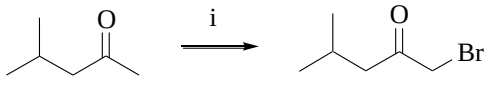
i) NaHMDS, TMSCl, THF, -78

ii) NBS, THF

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_2SO_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_2SO_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)



6A

($C_6H_{12}O$) **($C_6H_{11}OBr$)**

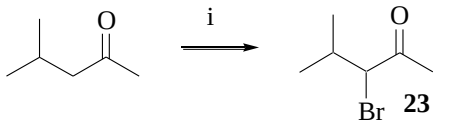
i) Br_2 , Urea, acetic acid

(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)



23

($C_6H_{12}O$) **($C_6H_{11}OBr$)**

i) Br_2 , acetic acid

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, 12mmHg).

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}. ^1H 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.

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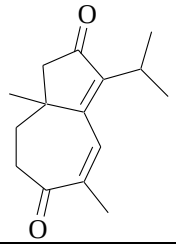
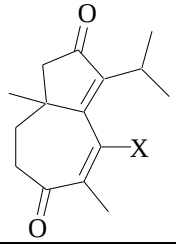
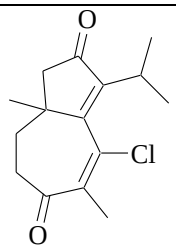
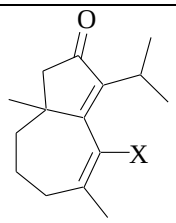
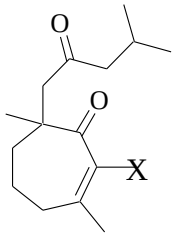
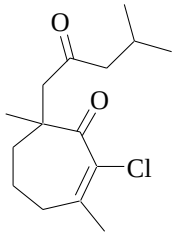
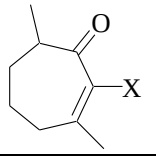
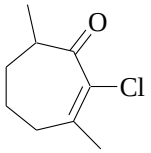
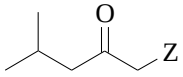
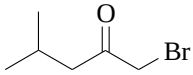
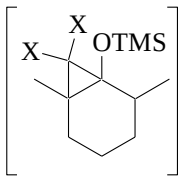
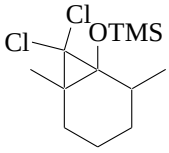
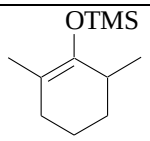
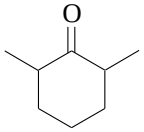
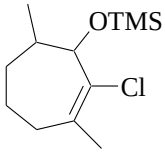
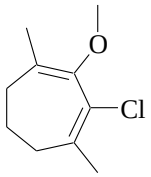
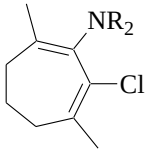
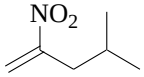
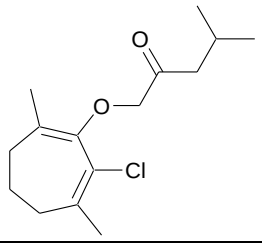
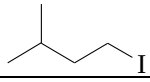
Apendix A Abbreviations:

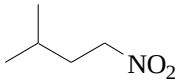
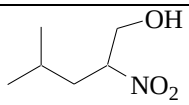
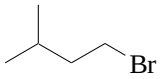
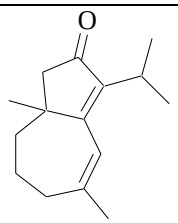
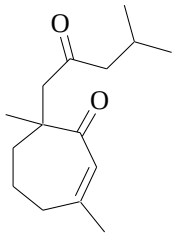
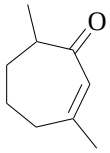
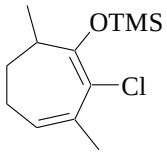
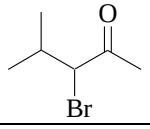
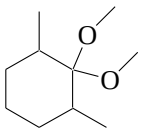
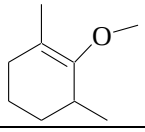
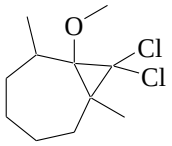
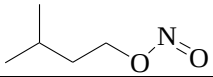
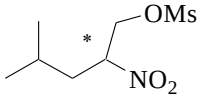
Ac	Acetyl
AIBN	Azobis(isobutyronitrile)
ATP	Adenosin triphosphate
BTH	Tributyltin hydride
CTP	Cytidine triphosphate
CBP	Cytidine diphosphate
d	doublet (NMR)
dd	doublet of doublets (NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichlormethane
DMAPP	Dimethylallyl diphosphate
DME	1,2,-dimethoxymethane
DMF	*N*,*N*-dimethylformamide
DFC	Dry flash chromatography
et al.	And others
FC	Flash chromatography
FGA	Functional group addition
FGI	Functional group interconversion
FPP	Farnesyl diphosphate
FT-IR	Fourier Transform Infrared Spectroscopy
Et	Ethyl
GPP	Geranyl diphosphate
h	heptet (NMR)
HMG-COA	β-hydroxy-β-methylglutaryl-Coenzyme A

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

Number	Compound	Name
1		3-Isopropyl-5,8a-dimethyl-1,7,8,8a-tetrahydro-azulene-2,6-dione
2		4-Halo-3-isopropyl-5,8a-dimethyl-1,7,8,8a-tetrahydro-azulene-2,6-dione
2B		4-Chloro-3-isopropyl-5,8a-dimethyl-1,7,8,8a-tetrahydro-azulene-2,6-dione
3		4-Halo-3-isopropyl-5,8a-dimethyl-6,7,8,8a-tetrahydro-1H-azulen-2-one
4		2-Halo-3,7-dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone
4A		2-Chloro-3,7-dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone
5		2-Halo-3,7-dimethyl-cyclohept-2-enone

5A		2-Chloro-3,7-dimethyl-cyclohept-2-enone
6		1-Z-4-methyl-pentan-2-one
6A		1-Bromo-4-methyl-pentan-2-one
7		(7,7-Dihalo-2,6-dimethyl-bicyclo[4.1.0]hept-1-yloxy)-trimethyl-silane
7A		(7,7-Dichloro-2,6-dimethyl-bicyclo[4.1.0]hept-1-yloxy)-trimethyl-silane
8		(2,6-Dimethyl-cyclohex-1-enyloxy)-trimethyl-silane
9		2,6-Dimethyl-cyclohexanone
10		(2-Chloro-3,7-dimethyl-cyclohept-2-enyloxy)-trimethyl-silane
11		2-Chloro-3-methoxy-1,4-dimethyl-cyclohepta-1,3-diene
12		Enamine
13		4-Methyl-2-nitro-pent-1-ene
14		1-(7-Chloro-2,6-dimethyl-cyclohepta-1,6-dienyloxy)-4-methyl-pentan-2-one
15		1-Iodo-3-methyl-butane

16		3-Methyl-1-nitro-butane
17		4-Methyl-2-nitro-pentan-1-ol
18		1-Bromo-3-methyl-butane
19		3-Isopropyl-5,8a-dimethyl-6,7,8,8a-tetrahydro-1H-azulen-2-one
20		3,7-Dimethyl-7-(4-methyl-2-oxo-pentyl)-cyclohept-2-enone
21		3,7-Dimethyl-cyclohept-2-enone
22		(2-Chloro-3,7-dimethyl-cyclohepta-1,3-dienyloxy)-trimethyl-silane
23		3-Bromo-4-methyl-pentan-2-one
24		1,1-Dimethoxy-2,6-dimethylcyclohexane
25		2-Methoxy-1,3-dimethylcyclohexene
26		8,8-Dichloro-1-methoxy-2,7-dimethyl-bicyclo[5.1.0]octane
27		Isoamyl nitritt
28		4-methyl-2-nitropentyl methansulfonate