New polymer building blocks from bio-based methyl vinyl glycolate

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June, 2019

"Pressure makes diamonds" General George S. Patton Jr.

Preface

This thesis describes the work I did during my three years at the Technical University of Denmark as a Ph.D. student from May 2016 - April 2019. The work comprises attempts to modify methyl vinyl glycolate into useful chemicals for industrial applications, such as monomers that are novel promising polymer building blocks. The work was performed under the supervision of professor Robert Madsen and co-supervision by R&D director Ph.D. Esben Taarning from Haldor Topsøe A/S. During a brief external stay at Perstorp AB in Perstorp, Sweden, the applications of the modified compounds from methyl vinyl glycolate were tested for possible commercial applications.

This marks the end of a three year trial from when I accepted the position as a Ph.D. student, a position I accepted as a challenge. It has been challenging and not without regrets, where making it through required a lot of "grit and grind." Nevertheless, it has been a learning experience. Standing at Trivium, I choose to finish this study. Not every goal set out to accomplish has been achieved.

Acknowledgements

First and foremost I would like convey my gratitude and thanks to my supervisor professor Robert Madsen for giving me the opportunity to write a Ph.D. in his research group, for his advice, support and trust during these three years of study. It has been a great learning experience to study in your group, which will help me in the future challenges. I also want to convey my thanks to my co-supervisor R&D director Esben Taarning. He has always been there with new ideas and checked in regularly to make sure the project has been on track. I appreciate it. Also a special thanks to Ph.D. Amanda Birgitte Sølvhøj. She started this project and helped lay the foundation of this research. She has always been prepared to help out with problems both theoretical and practical. I found your help invaluable, and indispensable. I would like to thank the students that worked on this project, B.Sc. Emma Springhorn Grønkjær, B.Sc. Emil Holm Kristiansen, and B.Sc. Thomas Wammen Sørensen. I have also been fortunate to collaborate with M.Sc. Irene Tosi and M.Sc. Samuel G. Elliot on this project, both of them fellow Ph.D. students in the Cat2BioChem project. Thank you for your collaboration and discussions. I would like to thank Dr. Sebastian Meier for collaboration, literature study, general discussion, and help at the end of the Ph.D. study. It has been great to discuss chemistry with someone that has realistic opinions similar to mine. I would like to thank Ph.D. Amalie E. Modvig for collaboration on the

cyclocarbonylation of methyl vinyl glycolate. I would like to thank the research group of Robert Madsen that made my stay easier and more enjoyable. I would like to thank the technicians Philip Charlie Johansen, Anne Hector, Brian Brylle Dideriksen, Johanne Marie Nielsen and Ph.D. Kasper Enemark-Rasmussen for keeping the equipment and instruments working at the institute and also for purchasing chemicals when needed. I would like to thank Lars Egede Bruhn and the service center employees. I would like to thank Andreas Graff Pedersen and the metal workshop employees. I would like to thank Perstorp AB for collaboration and accommodation at their "haunted house" Stensmölla during my external stay. I would like to thank the people that helped me during my stay at Perstorp AB. Special thank to Pia Wennerberg, thank you Stefan Lundmark, Matias Kangas, Pär Jörgensen, Rickard Martinsson, Niklas Persson, Mehrnoush Jowkar Deriss, Sara Andersson, Johan Raab, Snjezana Trupina Grönlund and the rest of the team, they were all helpful during my external stay at Perstorp AB.
I would like to thank the people working at Haldor Topsøe A/S, who have been working on similar projects. I would like to thank Marianne Johnson Henriksen. I would like to thank M.Sc. Bjarne Enrico Nielsen. I would like to thank my old fellow student during my studies at the University of Copenhagen, M.Sc. Morten Kristensen. He helped me by reading and correcting my thesis, catching many of my mistakes. I trust him over sea-level and under.

I have to thank associate professor M. Pittelkow, my former supervisor during my bachelor and master studies at the University of Copenhagen. He suggested that I undertake a Ph.D. study. He is also responsible for my habits in the laboratory. I am also thankful to him for making his LC-MS HRMS equipment available for me to perform analysis of compounds synthesised. I will not forget your early contributions to my education.

I am grateful for the financial support by the Danish Innovation Fund Denmark.

Finally I would like to thank friends and most importantly my family. My sister Lene for her support and my sweet little nephew Karl, my God child, whom I hope to inspire by completing this dissertation. I would like to thank my parents Anne Marie and Bjarne Jessen for giving me a strong foundation in life, and for always supporting my pursuits, from my deployment to choice of education.

Contents

Abstract

This thesis contains six individual chapters and an appendix. The first chapter contains the general background and plan of this project, research and why it was pursued. Chapter two to four describe the work performed during this project.

Chapter 1 Introduction is a general chapter, describing why this project was started, what has been performed previously, and what is prior art. The chapter covers some of the market for bio-chemicals, chemicals including lactic acid that can be considered an analogue to methyl vinyl glycolate (**MVG**) and is an established polymer building block on the current market. The chemistry of polymerisation and envisioned applications of the monomers modified from **MVG** are described.

Chapter 2 Methyl vinyl glycolate modifications covers most of the chemistry performed on **MVG** and the subsequent modifications. It describes the successes and failures of the project and how we envision some of the monomers can be used in polymerisation. It describes the scale of the monomers we were able to produce in relative amount, which were shipped out for testing.

Chapter 3 Allylic acetate rearrangement describes the work with the rearrangement of allylic moieties derived from **MVG**. We studied the rearrangement pathway and proposed a mechanism. In this chapter, possible conversion to produce new monomers from the rearrangement of **MVG** derived compounds is also described.

Chapter 4 Diels Alder reactions contains the Diels Alder reactions that the oxidised **MVG** (methyl 2-oxobut-3-enoate) is able to undergo. The compound is a good dienophile, which can produce a range of new undiscovered compounds through a pericyclic cycloaddition.

Chapter 5 Final remarks summarises the work performed and the achievements during this project. It shows the multiple compounds currently available from **MVG** as a platform.

Chapter 6 Experimental describes the procedures for synthesising all the compounds tested and uncovered during this project.

Appendix contains some of the data collected and the work performed at my external stay at Perstorp AB (Appendix C).

Resumé

Denne afhandling består af seks individuelle kapitler og et appendiks. Første kapitel indeholder generel baggrund og overvejelserne udført for retningen af dette projekt samt hvorfor projektet er blevet realiseret. Kapitel to til fire beskriver arbejdet udført under dette projekt.

Kapitel 1 Introduction er et generelt kapitel der beskriver tankerne bag hvorfor projektet blev startet og tankerne bag mulig anvendelse. Det beskriver hvad der tideligere er blevet udgivet i litteraturen og beskriver noget af markedet for biokemikalier. *Bulk* kemikalier der allerede har den status på markedet vi arbejder mod at få **MVG** til at opnå. Det inkluderer polymere konkurrenter allerede på markedet, samt yderligere omhandler den kemi de nye monomerer fra **MVG** skal kunne polymerisere ved. Det indeholder de specielle egenskaber af polymerer vi har ønsket at installere i modificerede produkter fra **MVG**.

Kapitel 2 Methyl vinyl glycolate modifications omhandler den kemi udført på **MVG** og den efterfølgende modificering. Det beskriver resultaterne fra disse forsøg og de muligheder de nye byggeblokke kan have i polymerisering. Kapitlet beskriver det omfang vi syntetiserede vores produkter i, der efterfølgende er videresendt til yderligere testning hos vores samarbejdspartnere.

Kapitel 3 Allylic acetate rearrangement beskriver arbejdet udført på omlejringen af allyl-derivater syntetiseret fra **MVG**. Vi har studeret reaktionsvejen og har foreslået en mulig mekanisme for omlejringen. Kapitlet omhandler og beskriver også nye byggeblokke fra omlejring af de syntetiserede **MVG** derivater.

Kapitel 4 Diels Alder reactions indeholder Diels Alder reaktionerne som den oxiderede **MVG** (Methyl 2-oxobut-3-enoate) danner med diener. Methyl 2-oxobut-3-enoate er en god dienofil der kan producere flere nye stoffer via en pericyklisk additionsreaktion.

Kapitel 5 Final remarks opsummerer arbejdet udført og opnået i dette projekt. Det viser de produkter der på nuværende tidspunkt er mulige at syntetisere med **MVG** som platform.

Kapitel 6 Experimental beskriver de eksperimentelle procedurer for syntese af de studerede stoffer samt nye produkter i dette projekt.

Appendix indeholder data indhentet og opsamlet fra dette projekt. Et afsnit beskriver også arbejdet der blev udført under mit eksterne ophold hos Perstorp AB (Appendix C).

CHAPTER 1

Introduction

1.1 Project aim

The aim of this project is to use methyl vinyl glycolate (**MVG**) as a renewable substrate for the synthesis of monomers to be used in polymer applications. This constitutes a new approach to prepare polymers from renewable sources and will serve to decrease the dependence on fossil fuels. Relevant monomers derived from **MVG** were studied for stability and the mechanistic pathways were elucidated for their formation.

1.2 Fossil fuels

Fossil fuels are defined as "an organic substance, such as coal, petroleum, etc., found underground in deposits formed in a previous geologic period and used as a source of energy".[1] Fossil fuels are anaerobic decomposition of trapped ancient organisms. A depletion of oxygen from a biological substance takes place through de-oxygenation.[2,3] The age of fossil fuel deposits is often millions of years. Selby et al. dated deposits in Canada to 112 ± 5.3 millions based on Re-Os isotope data.[4] Fossil fuels contain high percentages of carbons, which give them a high energy density and make them highly efficient.[5] Fossil fuels are composed of coal, petroleum, bitumen, kerogen, kerosene, natural gas mostly methane, but also ethane, propane, butanes, pentanes, and heavier hydrocarbons.[3] Even though fossil fuels are comprised of carbon based material, it is not considered to be a bio-renewable source, because of the extensive years required to produce these types of products. The discovery that fossil fuels consist of plant-remains is credited to M. Lomonosov in 1763.[6]
Fossil fuels have had a massive impact on human history. The use of them supported the development of our world.[5] The first use of fossil fuels dates back to small quantities used by ancient Babylonians, Egyptians, and the Chinese.[7,8] Marco Polo describes how

coal was used in China for heating.[9] Archaeological digs in Egypt and old Mesopotamia shows oil or bitumen was used for waterproofing ships and small storage containers. Other uses include mortars in construction, adhesives, glue, domestic artefacts, jewellery, sculptures, and mummification.[7] In the Middle Ages, oil was used as ingredient in medicine, perfumes, and cosmetics. Oil was also weaponized as Greek firer, popularized by the Byzantine Empire to reek havoc on their enemies.[10, 11] Some of the potential for fossil fuels was starting to be uncovered and become useful to the society of the late Middle Ages. Coal helped the industrial revolution in Britain during the 18th century.[12] The industrial revolution was immensely helped by the invention of the steam engine by Thomas Newcomen and the improvement of his technology by James Watt.[13] This engine was powered by coal. The engine could perform the work of a dozen horses. It also had the advantage of being cheaper than the equivalent horses needed to do the same amount of work. This paved the way for large scale production in mills, factories, and mines. Coal helped speeding up travel, with coal-derived inventions, such as railways for trains and ships powered by steam instead of wind-power.[13] Fossil fuels helped to facilitate lighting, heating, cooking, and transportation. Later, it also helped powering cars and planes.[14]

It is difficult to narrow down, where the first commercial oil well was drilled. The first commercial oil well in the U.S.A. was drilled with a steel pipe 11 meters into the ground in 1859 in Titusville, Pennsylvania.[15] It pumped out 20 barrels a day. This marked the beginning of the age of oil. Oil barrels output in 1861 was 2 million. In 2017, 92,649,000 barrels were pumped out every day.[16] This increased number has been achieved with help from the inventions of hydraulic fracturing, horizontal drilling and the discovery of new wells. The invention of auto-mobiles, which predominantly are relying on diesel and petrol, secured the success of oil. During World War One the demand for oil-powered ships instead of coal was stimulated. Oil could also power planes and tanks, which were a military advantage to possess and use in warfare.[17] The most prolific oil field-reserves are in the Middle East region. In the world, there are proven 239.3 billion tons of oil left (a number suggested in 2017).[16] Many projections exist on how long the world will have oil available. There is a lot of oil in the world, and humans will probably not exhaust their oil reserves. There is clearly a vast supply and new technology will help excavating more oil in the future, but gradually oil will become more expensive to excavate, which will lead to other energy alternatives becoming more cost efficient to use instead.[18] There is still an increase in consumption of oil.[16] A vast amount of commodity or bulk chemicals are derived from petroleum, which is a product of fossil fuels (mainly oil). These chemicals are referred to as petrochemicals.[19] Some of the valuable bulk chemicals are ethylene, propylene, and isobutylene. These have important polymer properties and are used for manufacturing materials. They are used for the production of polyethylene (**PE**), and polypropylene (**PP**). These two products are polyolefins, and they are a dominant part of the plastics produced and used by consumers in everyday life.[20] Isobutylene is used for polyisobutylene, which is synthetic rubber.[21] Polymers are important materials, and most polymers are made from petrochemicals.[22]

It is undeniable that the use of fossil fuels have had a high impact on our technological development, but it has also had an effect on emissions of carbon dioxide and other greenhouse-gasses. Such emissions have had an effect on our ecosystem.[23] Since the beginning of the industrial revolution, scientists have recorded a rise in tempera-

ture. Since the emission from fossil fuels first started, the temperature on the planet has seen an increase because carbon dioxide is a greenhouse-gas. Greenhouse-gases are gases that are in the atmosphere and adsorb infrared radiation. This creates a warming effect of the planet.[24] The gases are long living, which causes the effect of greenhouse-gases to be long-lived. The reason of the these climate changes have been widely debated. The general consensus is now that one effective cause is the burning of fossil fuels on a large scale, releasing greenhouse-gases.[25] Therefore the public opinion against the use of fossil fuels has seen an increase.[26] In the future, climate change globally will be a topic that will have to be addressed, but remains a politically charged topic.[27]

1.3 Polymers

1.3.1 History

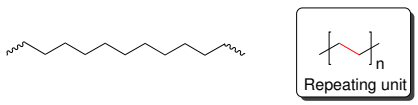


Figure 1.1: One of the simplest polymers, polyethylene (**PE**). Synthesised from the monomer ethylene.

Polymers are very important to our everyday life. The word "polymer" is derived from the Greek language, where *poly* means many, and *mer* means part. This means a polymer has many parts, as polymers are composed of many monomers. The word "monomers" is also a Greek term, *mono* meaning single.[28] Polymers are macromolecules that have a relatively high molecular mass. A polymer is made from large number of monomers, and if one monomer is removed from the polymer, it has a negligible effect due to the size of the polymer, unless the monomer has special properties in the polymer.[29] One of the better known commercial applications of polymers are the materials known as plastics, but polymers are also found in foods such as starch, proteins, in our clothes in the form of polyesters, and in Nylons. Humans also consist of polymers. Our DNA is a polymer, as are proteins and carbohydrates in the human body. Polymers are also used in elastomers, fibers, coating, adhesives, and composites. The term polymers was coined by J. J. Berzelius in 1833.[30] There have been many important contributions in the nineteenth century that helped lay the foundation for polymers in science. In 1820, T. Hancock had a factory for producing rubber commodities. C. MacIntosh made a discovery that would lead to the raincoat. He made a waterproof fabric by making a sandwich with two rubber cloths in 1823. H. V. Regnault prepared vinyl chloride in 1836 and observed polymerisation to a product commercially known as polyvinyl chloride (**PVC**). J. Bonastre prepared styrene in 1931. Polymers of styrene were observed prior to this by E. Simon in 1839, and the polymers are known as polystyrene (**PS**) now.[31] The potential of these polymers was not realised at the time of their first discovery, and their valuable uses had to be rediscovered later. M. Faraday showed that rubber consisted of C_5H_8 isoprene in 1840. C. Goodyear discov-

ered vulcanization of rubber and received a patent in the U.S. in 1844. C. F. Schonbein made nitrocellulose or gun cotton in 1836. In the twentieth century E. Fischer spearheaded research into natural polymers regarding polypeptides and polyesters. He is considered the father of polymer chemistry.[32] Staudinger sedimented the existence of macromolecules in the 1920s, which he later received the Nobel Prize for in 1953.[33,34] W. H. Carothers laid the foundation for the understanding of polymer properties that we have today.[35] He was also responsible for developing Nylon at DuPont and also helped lay the groundwork for the production of neoprene. Many other contributions to the field of polymers have been made since then.

1.3.2 Polymer properties

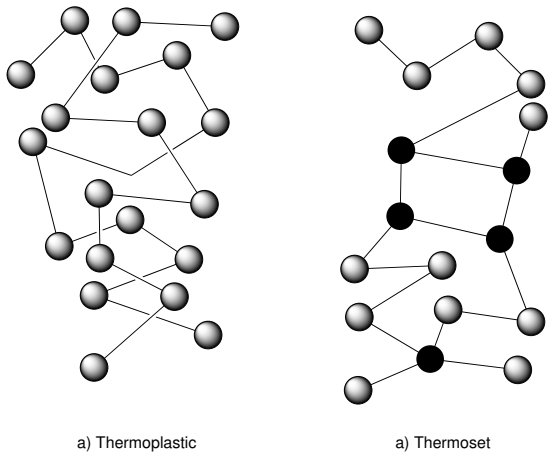


Figure 1.2: a) Thermoplastic. Plastic is of Greek origin and means to mould, form. b) Thermoset, a polymer with cross-linking.

Polymers can either be a thermoplastic polymer or a thermoset polymer material. Thermoplastic are individual chains with no connection between them (Figure 1.2a). Thermoset polymers are cross-linked (Figure 1.2b), connecting two polymers via a chemical bond. The thermoset polymer is viewed as the strongest polymer in regards to heat resistance and mechanical strength. The drawback of thermoset polymers are their inability to be remoulded after the cross-linking is performed. Thermoplastics, on the other hand can be reshaped.

Polymers have two different states. They can be amorphous (Figure 1.3a), and they can be semi-crystalline. Semi-crystalline is when some of the polymer has structured crystals (Figure 1.3b). The crystals are neatly aligned, unlike the amorphous polymer that is near-random (the amorphous polymer pattern is random). Polymers used are both semi-crystal and amorphous, and they both have valued specific properties. Polymers have two key transition states. The glass transition state (T_g) and the melting

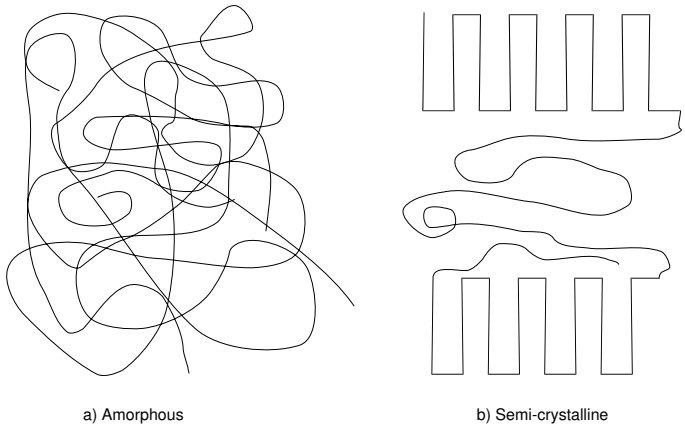


Figure 1.3: a) Amorphous. b) Semi-crystalline.

temperature (T_m). The amorphous regions of a polymer below T_g are frozen. When the temperature is heated above T_g, the amorphous regions starts flowing, making it possible to mould the polymer. When the temperature is above the T_m, the crystalline regions of a polymer starts to flow. The amorphous polymer only has a T_g, where the semi-crystalline polymer has a T_g and T_m because it has a crystalline region. The size of the polymer has an influence on the polymer entanglement and whether they are amorphous or semi-crystalline. If the polymers are long, they will start to form crystal regions.

Polymers can be linear, which favours crystalline properties. They can also be branched, which creates a more amorphous property in the polymer. Thermoset plastic are cross-linked. Cross-linked polymers can be achieved in various ways, e.g. di-thiols can form simple cross-linking, and if the compound has multiple thiol functionalities it will have equally as many positions to cross-link to. Cross-linking can also be achieved through metathesis. Grubbs catalyst can combine two olefins to create a new olefin and eliminate ethylene.[36]

There are different types of polymer composition. There are homopolymers, which are monomers of the same type. There are co-polymers that consist of two different monomers and ter-polymers that are three different monomers. Block polymers are polymers, where one block is made from the same monomer and then combined with a different block made from a different monomer. This is a co-polymer with two different monomers. If two monomers are random in a polymer-chain, then the polymer is considered a random co-polymer. If the monomers are alternating they are considered an alternating polymer. An example of this would be Nylon. Some polymers have the possibilities to attach macromolecules to them and thereby endow the polymers with new properties. These are graft polymers. In addition branched polymers can

be prepared with different topologies. If the polymer branches out, it can be a star or like a tree crown, i.e. polymers that are called dendrimers. They can also be ordered like a ladder. Another way to control and give polymers different properties is by controlling the stereochemistry.[29] All these different properties, create opportunities to mould polymers and give them desired properties through their design. In this project, we were trying to develop new monomers where the monomers had these specialised properties and multiple possibilities for modification.

Stereochemistry

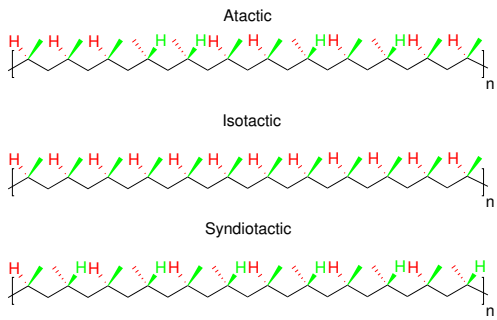


Figure 1.4: Tacticities of polypropylene.

In polymers, stereochemistry is involved if the monomer has a chiral center, and a simple example would be polypropylene (**PP**). When **PP** is polymerised, it has a repeating backbone of ethane, and one methyl group as substituent on the backbone for every monomer. This substituent can affect the polymer in two ways, positional and regional. If the substituent is randomly positioned on the left and the right side of the polymer, the term for this property is atactic (top, Figure 1.4). If the substituents are located on the same side, the term is isotactic (middle, Figure 1.4). If the substituents alternate between the right and the left-side, the term is syndiotactic (bottom, Figure 1.4). These three terms describe, where the substituents are positioned along the polymer chain, if the monomers are connected from head to tail. The monomers can also be connected from head to head or tail to tail which complicates the stereochemistry. These type of polymerisation are considered irregular and are seen as defects in a polymer.

1.3.3 Polymer additives

The desired polymer property can not always be achieved through design modification of the polymer or through synthesis. The polymer sometimes needs to be modified by adding compounds to it. Additives have been developed to modify the properties of the polymer in different ways. There is a long list of additives to add to a polymer that will change the polymer properties. Additives and the modification they provide to a polymer include:[37]

- Anti-blocking agents: Anti-blocking agents are used to block adhesion between two layers adjacent to each other.
- Anti-fogging agents: Anti-fogging agents are used to reduce fogging on the surface of a polymer.
- Antioxidants: Antioxidants are additives that prevent oxidation of the polymer.
- Blowing agents: Blowing agents are used for foaming in a polymer, which produces a cellular structure.
- Colourants: Colourants are used to give the polymers a specific colour
- Coupling agents: Coupling agents are used to functionalise a polymer further.
- Cross-linking agents: Cross-linking agents are used to make links between polymers.
- Curing agents: Curing agents are used to make cross-links via heat, radiation, electron beams, or chemical additives.
- Fillers: Fillers are particles added to a polymer to lower the consumption of the more expensive polymer.
- Retardants: Retardant additives are used to lower the flammability of a polymer.
- Heat stabilisers: Heat stabilisers are used to stabilise polymers so the polymer can be processed at higher temperature without degradation.
- Hydrolytic stabilisers: Hydrolytic stabilisers are to make polymers acid resistant.
- Impact modifiers: Impact modifiers are to enhance polymers resistance to mechanical stress impact.
- Lubricants: Lubricants are used for polymers that are subjected to friction. Lubrication enhances their durability.
- Pigments: Pigments are used for the colouring of polymers.
- Plasticisers: Plasticisers are to soften a polymer and enhance their plasticity or to decrease the viscosity of a polymer.
- Preservatives: Preservatives are to enhance the lifetime of a polymer, making the polymer resistant to the environment it is used in.
- Release agents: Release agents are used to prevent other materials bonding to the surface of the polymer.
- Thermal stabilisers: Thermal stabilisers are additives to increase the resistance to higher temperature of a polymer.
- UV stabilisers: UV stabilisers are to make the polymer more resistant to UV light, the sun.
- Viscosity depressants: Viscosity depressants are used to lower the viscosity of polymers.

1.3.4 Polymerisation types

There are different types of radical polymerisation to produce polymers. These types include free radical polymerisation (**FRP**), controlled radical polymerisation with atom transfer radical polymerisation (**ATRP**), nitroxide-mediated radical polymerisation (**NMP**), reversible addition-fragmentation chain-transfer polymerisation (**RAFT**), complex coordinated catalytic anionic polymerisation, and cationic polymerisation.

Free radical polymerisation (FRP)

One way to synthesise polymers is through **FRP**, an uncontrolled polymerisation. It is an addition polymerisation where a monomer is continuously added to a chain making the chain longer. A **FRP** starts with an initiation. **FRP** initiators can be peroxides and azo-compounds. These two initiators are thermally activated and are considered cheap.[38] The azo-compounds release nitrogen when the reaction starts. Initiators can also be photo-initiated and redox-initiated. The common feature for the initiators when they are cleaved into activated radicals is that they start the polymerisation (Figure 1.5). The radical reacts with a monomer and initiates the polymer formation. The polymer chain then starts to grow through propagation. The polymer chain with a free radical attacks the olefin and the chain grows longer. This propagation continues for as long as there are olefins present to react with. When the reaction is terminated, the growth of the polymer chain stops. Termination occurs if two radicals couple or combine and if a disproportionation occurs (Figure 1.5). **FRP** is used for polymerisation of low density polyethylene, acrylonitrile, butadiene, styrene, polystyrene, and poly(methyl methacrylate). The advantages of **FRP** are the simplicity of the reaction, since contaminants are not added to get the reaction started. One disadvantage is the need for solvents in these type of reactions, because without a solvent present the polymerisation terminates. **FRP** leads to high dispersion between the polymers.

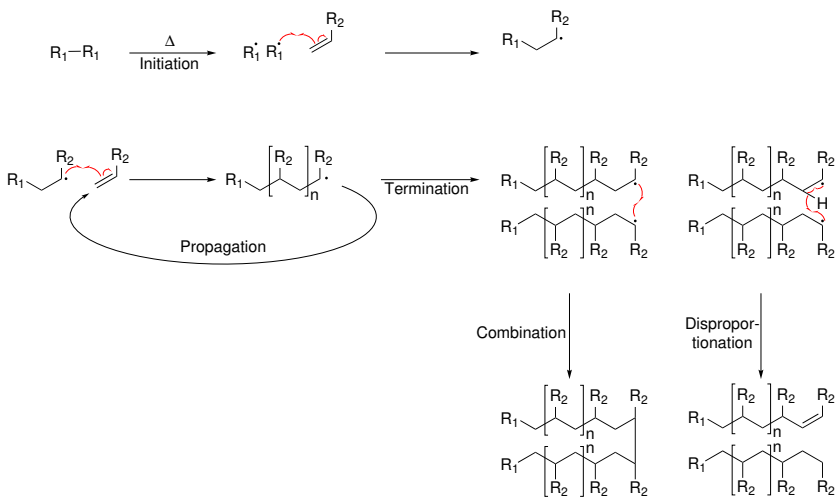


Figure 1.5: Radical mechanism for free radical addition polymerisation.[39]

Controlled radical polymerisation (CRP)

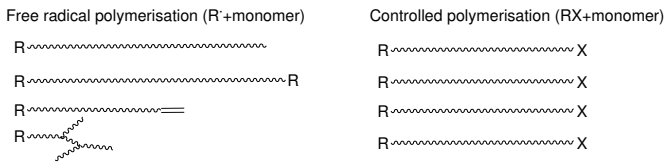


Figure 1.6: Free radical polymerisation versus controlled radical polymerisation.[40]

Polymerisation can also be achieved through controlled radical polymerisation (**CRP**). **CRP** is a reversible deactivation polymerisation. In **FRP**, the chain-lengths vary. The advantage of using **CRP** is the control of the polymer length. The polymer size dispersion with **CRP** is closer than in **FRP**. A **CRP** is an equilibrium between a compound and two radicals, with one reactive radical and one stable or persistent radical. The stable or persistent radical cannot initiate the reaction. The reactive radical initiates the reaction with a monomer and starts the propagation. The concentration of the reacting radical is very low. During propagation, the radical is in equilibrium with the dormant species. The polymerisation can terminate in a bimolecular fashion, but the termination is suppressed by excess reactant. For the propagation in **CRP** to start, the initiators need to be cleaved into the two radicals (Figure 1.7). This cleavage can be achieved through different chemical processes, where one process is a redox process. This type is called atom transfer radical polymerisation (**ATRP**). The transition is mediated by a metal, e.g. copper with a halide. This is a common metal used for this type of polymerisation with two ligands e.g. 2,2'-bipyridyl. This example is published work by Wang et al. in 1995.[41] The aryl or alkyl halide is the initiator and the foundation of the polymer. From the initiator, the polymer propagates (Figure 1.8). This method of polymerisation can be used to synthesise block polymers. First, one monomer is fed into the reaction mixture sequentially, followed by another monomer feed, making two blocks of polymers. The reaction speed can be adjusted by changing the halide. Chloride species are slower to react than bromide, intuitively similar to nucleophilic substitution reactions.

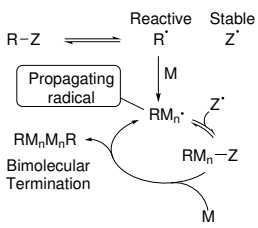


Figure 1.7: **CRP** mechanism.[42]

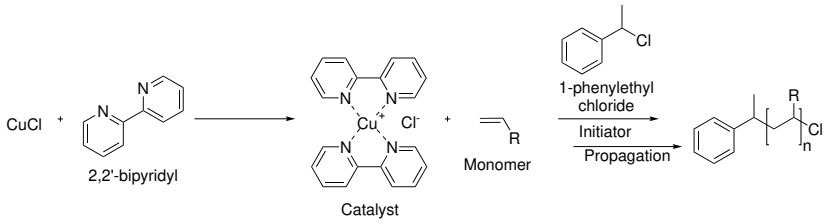


Figure 1.8: **ATRP** from Wang et al. 1995.[41]

A different approach to synthesise polymers through **CRP** would be to use nitroxide mediated controlled radical polymerisation (**NMP**). **NMP** is a thermal cleavage of a homolytic bond. An example of a nitroxide would be 2,2,6,6-tetramethyl-1-piperidinyl-*N*-oxy (**TEMPO**). The nitroxide is a stable radical, and can therefore help to control a polymerisation, which otherwise would be a **FRP**. The first example of this type of reaction was in a bimolecular process by George working at Xerox in 1983. Benzoyl peroxide and **TEMPO** in ratio of 1.3:1 at 130 °C successfully polymerised styrene in a controlled fashion (Figure 1.9). Uni-molecular initiators have also been developed, and one of them is depicted in Figure 1.9. One drawback of **NMP** is their lack of compatibility in a polymerisation with methacrylates, unless they are co-polymerised with another monomer. **NMP** can be used for block polymers, graft polymers, and random co-polymers.

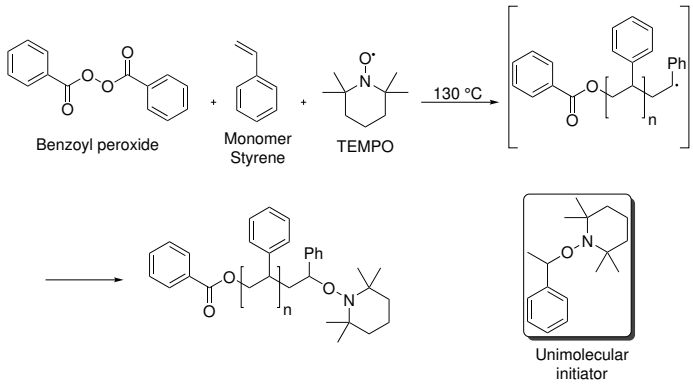


Figure 1.9: Nitroxide mediated polymerisation.[43]

A third alternative in a controlled radical polymerisation is reversible addition-fragmentation chain-transfer polymerisation (**RAFT**). **RAFT** involves sulphur containing compounds, which makes them unpleasant to work with due to their smell.

Vinyl polymerisation with complex coordination catalyst

Historically, the vinyl complex coordination catalysts were developed by Ziegler and Natta in the 1950s.[44] Transition metals and organometallic compounds can catalyse polymerisation at low temperature. E.g. Ziegler described that **PE** can be polymerised as high density **PE**, which has very little branching of its polymers. This is a different property from the outcome of **FRP**, where there is more branching. Natta showed that this could be achieved with propylene, synthesising the now-known polymer isotactic **PP**. Ziegler and Natta where awarded the Nobel Prize in chemistry in 1963 for their work.[45]

Classical Ziegler-Natta **(ZN)** catalysts are transition metals in group IV B to VI B of the periodic table, e.g. titanium, vanadium, chromium, molybdenum, and zirconium. The organometallic co-catalysts are from group I to III in the periodic table, e.g. aluminium, lithium, zinc, tin, cadmium, beryllium, and magnesium. **ZN** catalyst polymerisation is a heterogeneously localised polymerisation. The organometallic compound alkylates the metal on the surface of the metal. The monomer is then incorporated into the polymer by insertion between the terminal carbon of the polymer and the transition metal. There are two mechanisms: a mono-metallic mechanism that favours a heterogeneous process, and a bimetallic mechanism, which generally favours a soluble catalyst in solution. In a mono-metallic mechanism with titanium there is a vacant site on the metal (Figure 1.10). This site coordinates to the olefin, which is oxidatively inserted. Then, the alkyl group is inserted into the monomer and shifts from the current site. This re-establishes a vacant site, which can undergo further polymerisation. The bi-metallic mechanism is more advanced. There is a coordination between the metal and the alkyl group (Figure 1.11). Titanium coordinates to the olefin, which is oxidatively inserted. The alkyl moiety is then inserted from the organometallic-alkyls in a six-membered transition state. The metal and organometallic starting state is then re-established with a new alkyl group, where a new monomer can be incorporated. Metallocenes have later shown to work similar to **ZN** catalysts,

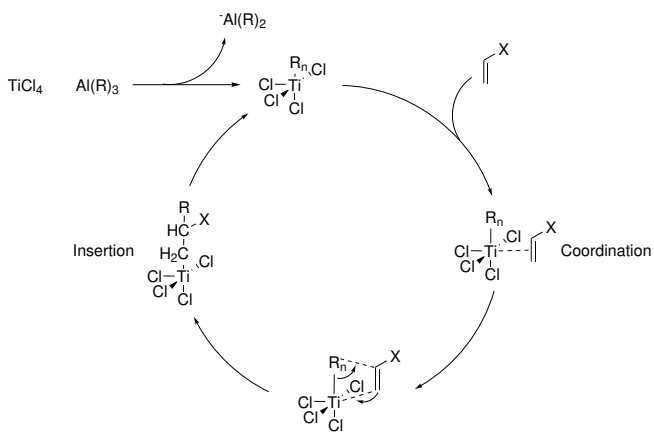


Figure 1.10: Ziegler-Natta uni-molecular mechanism.[44]

but they are homogeneous in solution.[32]

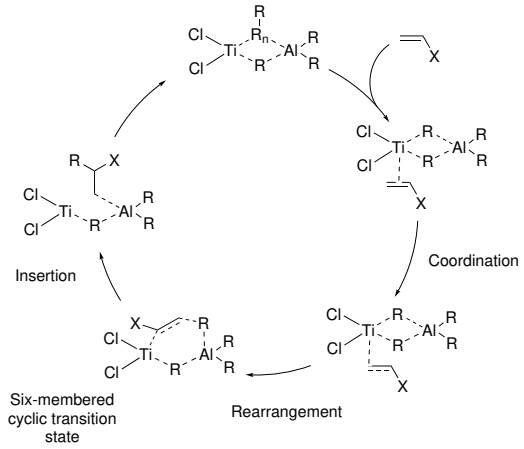


Figure 1.11: Ziegler-Natta bimolecular mechanism.

Anion polymerisation

Anion polymerisation is also a possibility in polymerisation. It can only be used for monomers that contain electron withdrawing groups, e.g. nitro, esters, and nitriles. The polymerisation is initiated when a nucleophile is produced or added to react with the monomer, e.g. 2-nitropropene with a base that can be potassium bicarbonate and butyl lithium. In the reaction, a nucleophile is produced and the initiation is started (Figure 1.12). The nucleophile attacks the olefin and an anion is created. The anion is stabilised through resonance. The anion can form a polymer chain by further propagation with monomers. The termination can proceed through a transfer of the anion to the monomer. The monomer can then undergo further polymerisation. Termination can also occur because of back-biting, e.g. methyl methacrylate can close in a six-membered ring through back-biting and terminate the polymerisation by creating a cyclohexanone. The polymerisation can also be terminated by quenching with an acid. Anion polymerisation is notably used for producing tires, footwear, and flooring.

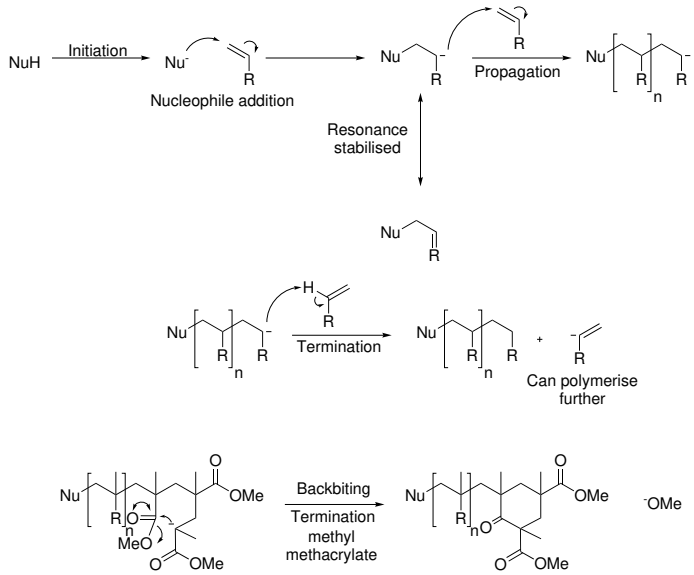


Figure 1.12: Anion polymerisation.

Cationic polymerisation

Cationic polymerisation needs donating groups unlike anion polymerisation, e.g. vinyl ethers. The initiators are mineral acids (sulphuric acid and phosphoric acid) or Lewis acids (aluminium trichloride, boron trifluoride, titanium tetrachloride, and tin tetrachloride). The Lewis acids require trace water, proton or cation source. The reaction is started by an initiation, to produce a cation (Figure 1.13). This cation attacks an olefin and creates a new cation that is stabilised through resonance. Termination occurs through transfer of the cation to the monomer. This monomer can then start a polymerisation again. The polymerisation can also be quenched with a base.

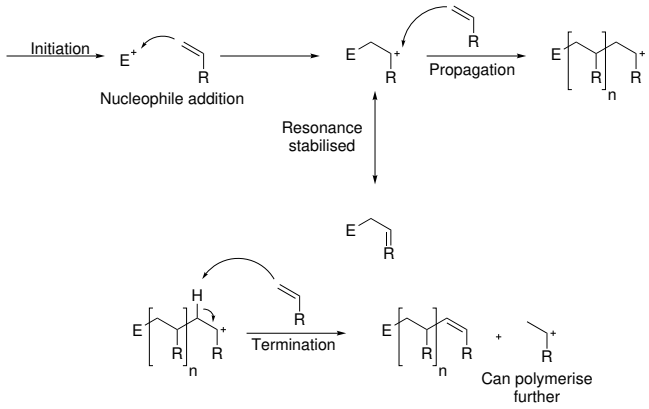


Figure 1.13: Cation polymerisation.

Ring opening polymerisation

Polymers can also be synthesised through ring opening polymerisation. Monomers that are useful for these type of reactions are lactones, lactams, ethers, and epoxides. The lactones and lactams are opened by a nucleophilic attack, which then initiate a polymerisation cycle by adding more of the monomer, growing a longer chain. The polymerisation can also be catalysed by an acid.

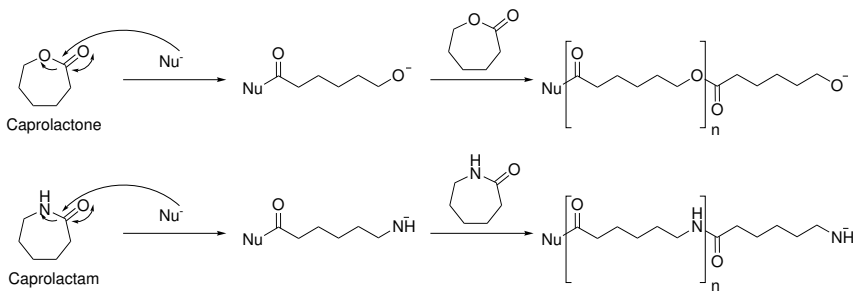


Figure 1.14: Ring opening polymerisation.

Step-growth polymerisation

Step-growth polymerisation is an important polymerisation type, as it is a means to produce Nylons. The reaction is simple, e.g. 1,6-hexanediamine and adipic acid react with each other and liberates water (Figure 1.15). This type of polymer is popularly known as Nylon 6,6 and is a co-polymer. This type of polymerisation can also be used to synthesise polyesters with carboxylic acids and diol monomers. The polymeri-

sation releases small molecules (hydrogen chloride, methanol, and water) through a condensation reaction.

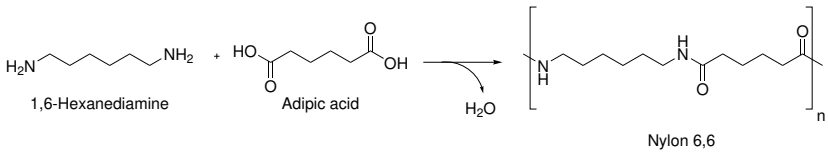
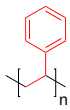
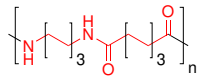
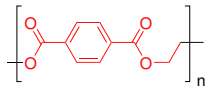
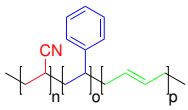
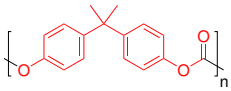


Figure 1.15: Step-growth polymerisation.

1.3.5 Important polymers

Some important polymers are polyethylene (**PE**), polypropylene (**PP**), polystyrene (**PS**), polyvinyl chloride (**PVC**), polyamide (**PA**), polyethylene terephthalate (**PET**), acrylonitrile butadiene styrene (**ABS**), and polycarbonate (**PC**). They are listed in Table 1.1.

Table 1.1: An overview of some of the important polymers and a few of their many uses.

Polymer	Monomer	Repeating unit	Commercial uses[37, 46]
Polyethylene (**PE**)	Ethylene[a,b]		Bottles, drums, pipe, sheet, films, wire cable insulation
Polyvinyl chloride (**PVC**)	Vinyl chloride[a]		Pipping, blood-bags, wire, cable-insulation
Polypropylene (**PP**)	Propylene[a]		Auto-mobile and appliance parts, rope, cordage, carpeting, film
Polystyrene (**PS**)	Styrene[a]		Cutlery (single-use) cups, toys, gardening pots, Styrofoam
Poly-hexamethylene adipamide (**Nylon 6,6**)[c]	1,6-Hexane-diamine,[a] adipic acid[a]		Textile, fibers, rope, hoses
Polyethylene terephthalate (**PET**)	Ethylene glycol[a,b], terephthalate[a]		Beverage bottles, furniture, diapers
Poly-acrylonitrile co-butadiene co-styrene (**ABS**)[d]	Acrylonitile,[a] butadiene,[a] styrene[a]		Waste drains, music instruments auto-mobiles, Lego[47]
Polycarbonate (**PC**)[c]	Bisphenol A,[a] phosgene[a]		Eye-wear lenses, cars

[a]Petrochemicals as a raw material. [b]Bioethanol as a raw material. [c]Co-polymer. [d]Ter-polymer.

Polyethylene

Polyethylene (**PE**) is a remarkable polymer. It is resistant and resilient.[48] It is one of the simplest polymers made from the monomer ethylene. It is cheap because the monomer is available in bulk as a petrochemical. Ethylene can also be produced from a bio-renewable source, since bioethanol can be dehydrated to ethylene.[49] **PE** is used

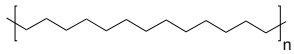


Figure 1.16: Polyethylene.

extensively as a materiel in containers and in packaging. It has two resin identification codes (**RIC**) for recycling: number 2, high density polyethylene and number 4, low density polyethylene. The two resins have different properties, which is why they have different numbers. **PE** low density is majorily synthesised by **FRP** under high pressure. High density polyethylene can be synthesised with a Ziegler-Natta catalyst.[44] Ethylene is also a starting material for glycolethylene, a component in the co-polymer **PET**.

Polyvinyl chloride

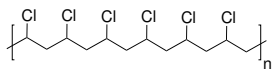


Figure 1.17: Polyvinyl chloride.

Polyvinyl chloride (**PVC**) is a very common polymer made from the monomer vinyl chloride. **PVC** is generally a stiff polymer unless plasticisers are added to the mixture. The polymers are thermally unstable, and if the polymer is heated too much, it releases water, and hydrochloric acid. Because of this property and the need for plasticisers to make it more flexible, it has been replaced for some use in commercial applications by other alternatives, but it is still used in large quantities as a polymer. The **RIC** for **PVC** is number 3. Commercial **PVC** is a atactic polymer.[50]

Polypropylene

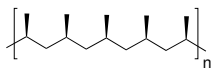


Figure 1.18: Isotactic polypropylene.

Polypropylene (**PP**) is a polymer used commercially in similar applications as **PE**, but has a lower percentage of crystallinity, which makes the polymer **PP** more rigid and stronger. In **PP** there is a side group to the backbone that has introduced stereochemistry into the polymer. The commercial tacticity is predominantly the isotactic polymer (Figure 1.18). The polymerisation of **PP** is achieved with a Ziegler-Natta catalyst. Like **PE**, it is a very resilient polymer and very cheap because it is made from a petrochemical. **PP** is made from the monomer propylene. Commercial uses for **PP** are the same as for **PE**. **PP** is notably used in containers. **PP** has the **RIC** number 3.

Polystyrene

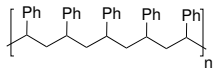


Figure 1.19: Polystyrene.

Polystyrene (**PS**) is a polymer used as a homo-polymer and in co-polymers. **PS** is polymerised by addition in **FRP**. **PS** is very heat-resistant and it can tolerate high temperatures without melting. **PS** is therefore a useful material for cups used for warm beverages. **PS** is a clear, rigid, and brittle polymer. It has its own **RIC** number 6. A popular use of polystyrene is in Styrofoam, which is used in containers to keep food cold or warm and as house insulation. **PS** is slow to degrade and is therefore an environmental concern with regards to pollution in nature.[51]

Polyamide

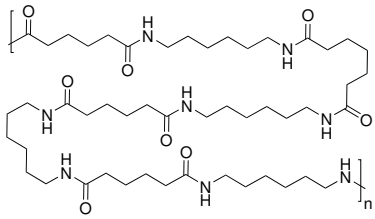


Figure 1.20: Polyamide, Nylon 6,6.

Polyamide synthesis is a condensation reaction. An amine and a carboxylic acid can liberate water by reacting together, which makes them a co-polymer. These types of polymers are popularly known as Nylons and were named by the company DuPont that developed the polymer. The polymer is hygroscopic and needs to be dried before processing, so the polymer does not degrade prior to use in desired applications.

Polyethylene terephthalate

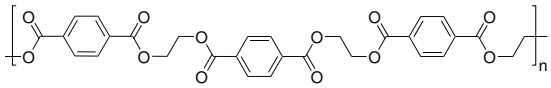


Figure 1.21: Polyethylene terephthalate.

Polyethylene terephthalate (**PET**) is another hygroscopic polymer. This polymer is also a co-polymer, but the bond between the two monomers is an ester bond unlike

the Nylons that have amide bonds. The two polymers in **PET** are ethylene glycol and terephthalate. The polymer is very cheap with raw materials derived from petrochemicals. Ethylene glycol can also be made from bioethanol, and some of the polymer composition can therefore be considered from a bio-renewable source. The **RIC** number for **PET** is 1.

Acrylonitrile butadiene styrene

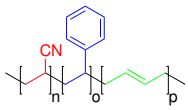


Figure 1.22: Acrylonitrile butadiene styrene **(ABS)**.

Acrylonitrile butadiene styrene **(ABS)** is prepared by a block addition polymerisation. It is a ter-polymer made from three different monomers: Acrylonitrile, butadiene, and styrene. The polymer is amorphous, and it is very lightweight with strong properties. Most Danes have played with this polymer when they were children. Many parts of the Danish founded toy-company Lego has **ABS** in the toys.[47]

Polycarbonate

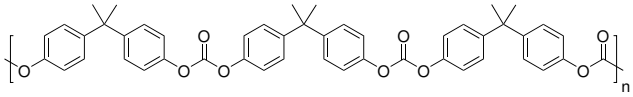


Figure 1.23: Polycarbonate from phosgene and bisphenol A.

Polycarbonate is a polymer with a carbonate functionality. The polymers are synthesised through a condensation polymerisation where sodium chloride and water are released. The polymer is a co-polymer that can consist of phosgene and bisphenol A.

1.4 Sustainable and environmentally friendly polymers

1.4.1 Terminology

When sustainable and environmentally friendly polymers are discussed, many different terms are being used. It is important to be precise in defining what these terms mean. For instance, a ”biodegradable” polymer can not be thrown in nature without repercussion, since it is still littering and pollution. Nature still takes a long time to break down the polymer without the right environment. The definition bio-degradation is defined as: ”Breakdown of a substance catalysed by enzymes in vitro or in vivo.”[52] Bio-polymers are defined as: ”Macromolecules (including proteins, nucleic acids and

polysaccharides) formed by living organisms."[53] Biomass is defined as: "Material produced by the growth of micro-organisms, plants or animals."[53] Bio-renewable resources are feedstock material obtained from a biological organism.[54]

1.4.2 Bio-renewable polymers

The need for renewable sources is recognised worldwide. The U.S.A. have initiatives to reduce the dependency on oil and increase the usage of biomass. This strategy was published in a report from 2016 by the National Renewable Energy Laboratory **(NREL)**, and is motivated by two factors, i.e. reducing dependency on oil and emission of greenhouse-gases.[55] The report lists 15 % of the entire oil barrel production is for chemical products. By replacing these petrochemicals with a bio-sustainable source, both dependency and emission from oil will be reduced significantly. It is projected that bio-based chemicals on the global market will go from 2 % in 2008 to 22 % in 2025.[56] This increase presents a huge potential for research and development of bio-renewable chemicals for bulk-usage. **NREL** released a list of twelve chemicals that have prospect as near-term deployments on the market. These twelve chemicals were selected from an earlier list of thirty-six chemicals that have been published in the literature with promising results (Figure 1.24). These chemicals were chosen with market consideration, feedstock flexibility, prices, growth potential, and near or midterm deployment into the market. They were expected to be close to being set into production on large scale. Technology readiness level **(TRL)** describes the bulk chemicals readiness for the market. **TRL** was originally used by N.A.S.A. TRL 1 means the technology is in the basic research stage. The technology then has to go through levels of research to prove feasibility, technology development, technology demonstration, system/subsystem development to reach system test, and launch of operation, which is level 9.

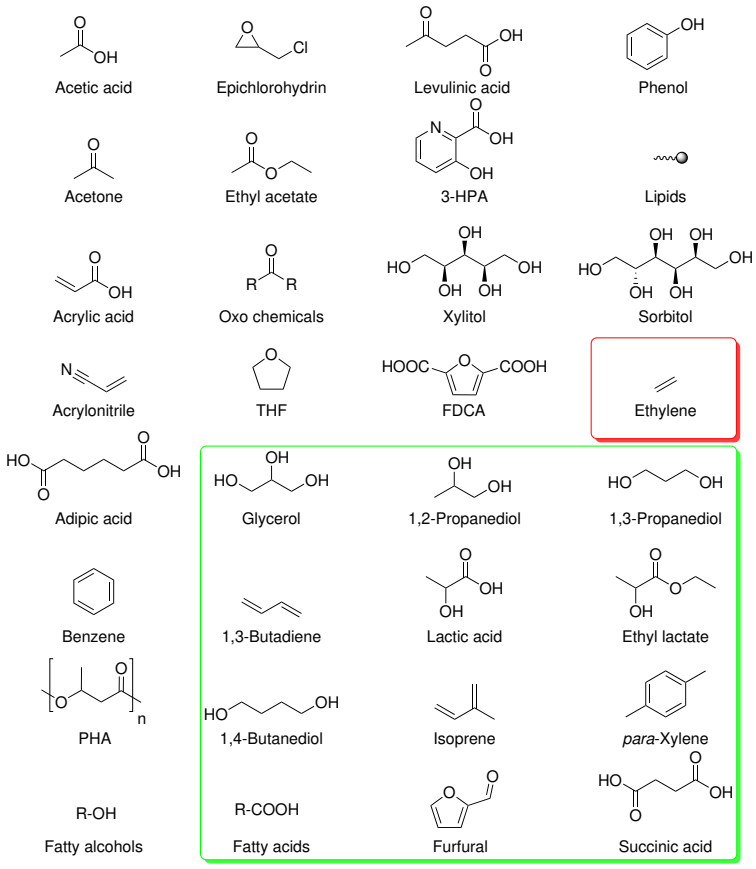


Figure 1.24: Potential bulk chemicals from bio-renewable sources. The chemicals in the green ring are twelve chosen chemicals that currently are described with the highest potential.[55] Ethylene in the red ring has already been developed as a bulk chemical and can be produced from a bio-renewable source.

Biomass-derived chemicals can replace petrochemicals in two ways on the market. They can supplement the current petrochemicals or they can compete with the petrochemicals that have similar properties. The biomass-derived chemicals that supplement petrochemicals can be referred to as "a drop in replacement chemical", the chemical is the same as what is produced from petrochemicals. The biomass-derived chemical has the advantage of being produced from a renewable source. Ethylene is an example of drop in replacement chemical. Ethylene can be produced from petrochemicals and a bio-renewable source. Then, there are the biomass-derived chemicals that are new and do not have the same structure or property as any petrochemicals. These chemicals are usually specialised with superior properties in certain applications in order to compete with petrochemicals. These chemicals can be referred to as "a functional replacement chemical." Biochemicals might be more expensive until oil prices

increase or the technologies to develop them become cheaper, possibly through the discovery of new technologies and research. The bio-products can be produced through different techniques: Biochemical **(BC)**, thermochemical **(TC)**, hybrid thermochemical/biochemical **(TC/BC)**, and algal routes (Table 1.2).[55] This implies that different branches of science are implemented to produce bio-renewable chemicals.

Table 1.2: An overview of the twelfth chosen focus chemicals by **NREL**. Table data from **NREL** report.[55]

Chemical	Type	Conversion pathway	TRL level
1,3-Butadiene	Drop-in	BC-biological, TC/BC gasification /fermentation.	6
1,4-Butanediol	Drop-in	BC-biological.	8
Ethyl lactate	Functional	BC-biological.	9
Fatty alcohols	Drop-in	TC-gasification, BC-biological, algae.	9
Furfural	Functional	TC-pyrolysis, BC-catalytic.	9
Glycerol	Functional	Algea.	9
Isoprene	Drop-in	BC-biological.	6
Lactic acid	Functional	BC-biological.	9
1,3-Propanediol	Functional	BC-biological.	9
1,2-Propanediol	Functional	BC-biological.	9
Succinic acid	Functional	BC-biological.	9
para-Xylene	Drop-in	BC-catalytic, TC-pyrolysis.	6

1,3-Butadiene

Figure 1.25: 1,3-Butadiene.

1,3-Butadiene is an important monomer for producing rubber. It is used to produce tires for everyday vehicles. The bulk chemical is currently produced from a petrochemical. The supply of 1,3-butadiene is constrained (on the market). 1,3-Butadiene is a by-product from the production of ethylene. Currently some of the ethylene production is manufactured from shale-gas, which does not yield the by-product 1,3-butadiene. This gives fluctuation in the price of 1,3-butadiene. For this reason, the bulk chemical has potential to be developed from renewable resources to compete with the petrochemical-derived source. There are multiple strategies to develop 1,3-butadiene from biomass. One strategy is from ethanol in the Lebedev or Russian process. Ethanol is mixed with

a MgO/SiO^2 catalyst.[57] Copper can further promote the conversion.[58] Companies with investments in this research include Braskem, INVISTA, Synthos, and Versalis.[55]

1,4-Butanediol

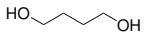


Figure 1.26: 1,4-Butanediol.

1,4-Butanediol is a chemical used as solvent and in polymerisation of polymers. The demand in 2016 was listed at 200 million metric tons. The chemical is used by Nike and INVISTA. Bio-derived 1,4-butanediol is produced by BASF. BASF use commodity sugars to produce the bulk chemical on a large scale. Genomatica with support from the Department of Energy (U.S.A.) is implementing lignocellulosic sugars as raw material to directly synthesise bulk 1,4-butanediol. Downstream chemicals include γ-butyrolactone through oxidation at high temperature, THF through dehydration with phosphoric acid, and polybutylene terephthalate polymerisation with terephthalate.[59] Currently, 1,4-butanediol is being researched as a downstream chemical from succinic acid produced at bio-refineries.[60]

Ethylene

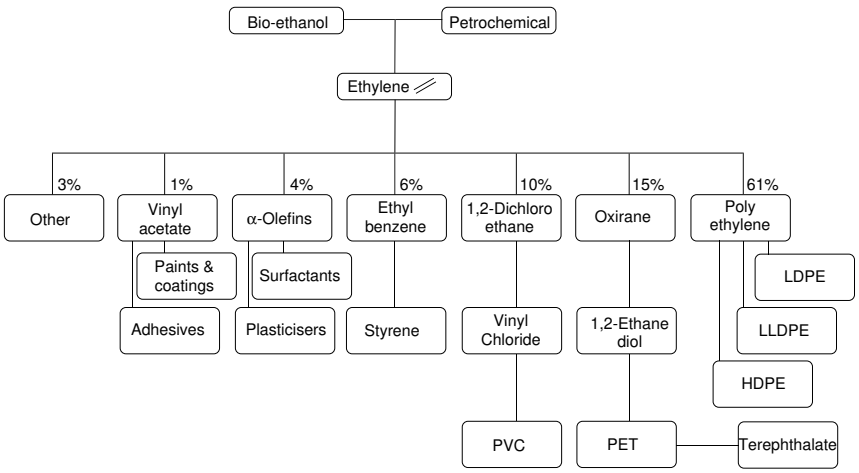


Figure 1.27: Ethylene value-chain.[55]

Ethylene (also known as ethene) is a very valuable bulk chemical. Some of its use has been covered in sub-subsection 1.3.5 Polyethylene. **PE** has 36 % market share, **PVC** 12 %, and PET <10 % in plastics.[61] These are three of the most important polymers to substitute or replace. They are valuable polymers and have a high profitable potential

to substitute with a sustainable source for the continued use in commodities on the market. Ethylene can be produced via dehydration of bioethanol.[62] Braskem has a large plant in Brazil that produces bioethanol and dehydrates it to ethylene. The value chain of ethylene is depicted in Figure 1.27.

Ethyl lactate

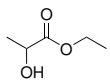


Figure 1.28: Ethyl lactate.

Ethyl lactate is used as a solvent and can be derived from lactic acid. Ethyl lactate is relatively benign as a solvent and is being implemented as a substitution for petrochemical-derived solvents. Ethyl lactate has shown similar or improved properties compared to the petrochemical-derived traditional solvents like toluene, methyl ethyl ketone, and *N*-methyl-pyrrolidone, when used in many applications. Ethyl lactate is expected to compete with these solvents on the market when the bulk material production has been fully incorporated into the market.[63]

Fatty alcohols

Fatty alcohols are used as detergents if the carbon-chains are longer than twelve. They are also used to produce surfactants for household cleaning items. Short chains can be used as plasticisers. They can be produced from tallow, vegetable oil, and petroleum. These three sources are competitors for the market. The production is therefore shifted from place to place, depending on the lowest price option. Finding a steady supply of feedstock from biomass that is price-competitive would be advantageous for the use of this bulk chemical.[64]

Furfural

Figure 1.29: Furfural.

Furfural is a heterocyclic aldehyde, which can be produced by dehydration of xylose.[65] Furfural can produce furfuryl alcohol by reduction of the aldehyde. This is the currently predominant pathway to furfuryl alcohol, which is an important foundry resin with anti-corrosive property,[66] and thus important in reinforcing pipes. Furfural has several other important applications and it is not produced by petrochemicals. This means it currently does not displace fossil fuels. Research shows potential to replace

jet fuel, which is an important field to reduce dependency on fossil fuels.[67] Currently viable substitution options for jet fuel have not been discovered.

Glycerol

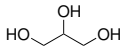


Figure 1.30: Glycerol.

Glycerin is a commercial term for glycerol. Glycerol is a polyhydric alcohol and the main component of triglycerides. It can be obtained from fat in animal and vegetable oil. Glycerol is a by-product from the production of bio-diesel in 10-20 %, a by-product in bioethanol at around 10 %, and a by-product from the production of soap. Synthetically, it is produced from propylene. Bio-derived glycerol is dependent on the production of soap, bioethanol and bio-diesel, as there are no other bio-derived pathways to glycerol. One commercial use for glycerol is as a deicing agent. Glycerol is a hygroscopic humectant used in food and personal care products. Bio-derived glycerol can compete with petrochemical-derived glycerol for the market.[68]

Isoprene

Figure 1.31: Isoprene.

Isoprene is used in rubber production. Isoprene production from petrochemicals fluctuates like 1,3-butadiene production and has the same competitive possibility on the market as 1,3-butadiene. Isoprene has been discovered to be derived from fermentation of sugars. Bio-derived isoprene can compete with petrochemical-derived isoprene for the market. Major tire-companies are investing in this research (Bridgestone, Goodyear, and Michelin), which is still in early stages. Some bacteria can synthesise isoprene, but only at 11 % yield. Further research is being performed to find better solutions with higher yields.[69]

1,3-Propanediol

Figure 1.32: 1,3-Propanediol.

1,3-Propanediol is a linear aliphatic diol and useful building block. It is used in polymers, personal care products, solvents, and lubricants.[70] 1,3-Propanediol is used

in polytrimethylene terephthalate, which is an important polymer in fibers, textiles with superior durability, and strain resistance compared to Nylons. DuPont Tate and Lyle Bio Products Company is a large producer of bio-based 1,3-propanediol. Bio-based 1,3-propanediol uses 40 % less energy than would be required in a petroleum-based route. This gives the bio-based route a preferable advantage over its petrol counterpart.[55]

1,2-Propanediol

Figure 1.33: 1,2-Propanediol.

1,2-Propanediol is a colourless, odourless, viscous substance, that does not evaporate at room temperature. It is a benign chemical and safe for human consumption. 1,2-Propanediol is used in antiperspirants, suntan lotions, flavourings, and drugs. 1,2-Propanediol is also used in polymer resins. It is used as a cooling agent and deicing agent. 1,2-Propanediol is produced from methyl oxirane by hydration. Bio-derived 1,2-propanediol is a by-product from bio-diesel. Companies with interest in bio-derived 1,2-propanediol include ADM, Ashland, and Cargill.[55]

Succinic acid

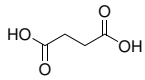


Figure 1.34: Succinic acid.

Succinic acid has a two-functional carboxylic acid moieties and is derived from biomass and petrochemicals. It has potential as a specialised bulk chemical. Succinic acid has potential value as a precursor to other commodity chemicals to produce polymers, surfactants, and solvents, and has high potential growth, because of the potential as a platform molecule for valuable downstream chemicals.[71]

para-Xylene

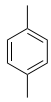


Figure 1.35: *para*-Xylene

para-Xylene is a high boiling solvent and it is a precursor for terephthalate, which is important for **PET** production. There are major interests in bio-derived **PET** from companies such as Coca Cola and PepsiCo. Research is also being focused on polyethylene furanoate as a replacement for **PET**.[55]

Itaconic acid

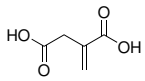


Figure 1.36: Itaconic acid.

Itaconic acid has three functional groups. It has two carboxylic acids and one double bond in conjugation with one of the carboxylic acids. This opens possibilities for polymerisation via poly-condensation and cross-linking via the double bond with other polymers in post-polymerisation modification. At room temperature itaconic acid is a white crystalline powder. In 1836 itaconic acid was discovered by Baup.[72] A itaconic acid metabolite was observed and published in the late 1920s from *Aspergillus terreus*.[73] Glucose and glycerol can be used as a feed in fermentation to produce itaconic acid.[74] Itaconic acid can be used in detergents, elastomers, coatings, composites, and adhesives. It has similar functionalities as methacrylic acid and acrylic acid, which means it has the potential to replace those two chemicals.[75] Itaconic acid has been successfully polymerised in a step-growth condensation with ethylene glycol in a co-polymer. This approach was published by Singh et al. in 1981.[76] Itaconic acid can also be co-polymerised with isocyanate and diols to produce polyurethane. Itaconic acid has shown potential as a co-polymer, but currently has some cost issues, as the cost to produce monomers of itaconic acid via fermentation is higher than its current petrochemical derived monomer competitors.[77]

Furan dicarboxylic acid

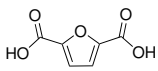


Figure 1.37: 2,5-Furan dicarboxylic acid.

2,5-Furan dicarboxylic acid (**FDCA**) is an aromatic compound with two carboxylic acid groups. It is similar to terephthalate, but is composed of a five-membered furan ring instead of a benzene ring. **FDCA** was discovered and published in 1876 via a synthesis from mucic acid.[78,79] Currently **FDCA** is synthesised by oxidation of 5-hydroxymethylfurfural (**HMF**) with a noble metal catalyst such as platinum or gold.[80] **HMF** can be synthesised with a feed of fructose, glucose, and C6-polysaccharide dehydration. **FDCA** has the potential to substitute terephthalate in polymerisation of

PET. The new polymer is called polyethylene furanoate (**PEF**). The **PEF** has similar properties as **PET** and is therefore ideal to replace terephthalate in polymerisation.[81] Large companies are interested in producing bottles completely from a bio-renewable sources and replace petrochemicals. Coca Cola is one of these companies with the PlantBottle^{TM}, where 30 % of the bottle is made from a plant source.[82] **PEF** also has potential as films, fibres, and packaging.[83] Furthermore **FDCA** has potential to replace adipic acid. **FDCA** was on the Department of Energy (U.S.A.) list of top twelve biochemicals in 2004.[77] A drawback for **FDCA** is the catalyst price for the noble metals to oxidate the feed **HMF** to **FDCA**.

3-Hydroxypropionic acid

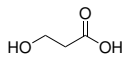


Figure 1.38: 3-Hydroxypropionic acid.

3-Hydroxypropionic acid has a primary alcohol and a carboxylic acid, that can be dehydrated to acrylic acid. 3-Hydroxypropionic acid can furthermore be used as a monomer for polymerisation in step-growth condensation. 3-Hydroxypropionic acid is bio-degradable and can be produced as a metabolite through fermentation of sugars with bacteria.[84, 85] It can be used for shampoo bottles, packaging, and because of the bio-degradable property it can also be used for medical applications, e.g. surgical sutures, bone plates or osteosynthetic materials.[86]

Lactic acid and polylactic acid

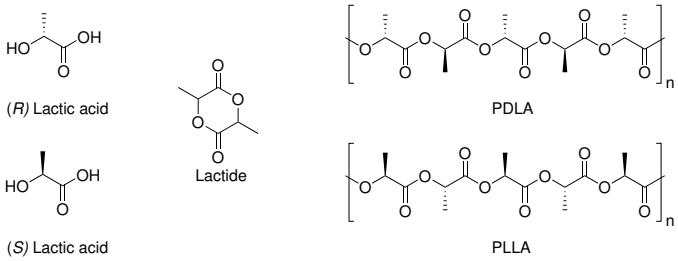


Figure 1.39: Lactic acid, lactide, **PLA**.

Lactic acid is an *alpha*-hydroxyester with one stereocenter. There are two enantiomers of lactic acid with (R) or (D) and (S) or (L) configuration (Figure 1.39). Lactic acid polymers are usually formed from the lactide to synthesise polylactic acid (**PLA**), which is a polyester that can be synthesised through removal of water, in a step-growth polymerisation. **PLA** is a polymer with both enantiomers incorporated in the polymer chain with no specification. **PLA** has specific preferable properties as a polymer. It

is made from a bio-renewable source and is bio-degradable.[87] If the polymer is made from enantiomerically pure lactic acid, it can be either poly-(D)-lactic acid **(PDLA)** or poly-(L)-lactic acid **(PLLA)**. *(S)* Lactic acid is produced in animals through pyruvate and the enzyme lactate dehydrogenase in a fermentation. Lactic acid is also produced by microbial degradation of sugars in nature. Lactic acid was first isolated by a Swedish chemist C.W. Schele in 1780.[88] He isolated it from sour milk. "Lact" means milk in Latin, which is why it was named lactic acid.[89] The IUPAC name is 2-hydroxypropanoic acid. Lactic acid is further used in applications in food (spoilage inhibitor, acidulant, and flavouring agent) and medical applications (sutures and tissue scaffolds). **PLA** polymers are also being used for 3D printing.

Lactic acid is commercially available. It can be produced in bulk from fermentation and a catalytic process. The fermentation to lactic acid can be achieved through pentoses, hexoses, and lactic acid bacteria.[88,90,91] Feed used for lactic acid production via fermentation include wheat, rice bran, corn cob, pretreated wood, cellulose, barley, cassava bagasse, wheat starch, whole wheat, and potato starch.[92,93] The fermentation produces gypsum and requires extensive downstream processing to purify the product. These are drawbacks in the production of lactic acid via fermentation. Lactic acid can also be produced by a catalytic process. Tin beta zeolites have shown promising results in producing methyl lactate, the methyl ester of lactic acid. Fructose was used as feed at 160 °C in methanol with the tin beta zeolite as a catalyst to produce methyl lactate in 60 % yield with low deactivation of the catalyst.[94,95] Glucose can also be used as feed.[96] Other catalysts have been reviewed (and are covered in a publication) by De Clercq et al. 2017.[97]

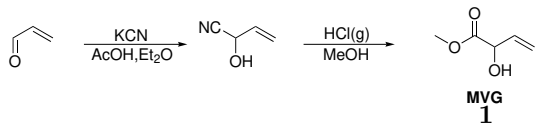
Lactic acid can further serve as platform for producing acrylic acid, pyruvic acid, 1,2- propanediol, and other alkyl lactates.[57] **PLA** is one of the most important downstream chemicals from lactic acid and was first produced in 1845. The importance of this discovery was not realised until the 1990s, when Cargill Inc. developed a route to high molecular **PLA**, and patented the process.[98,99] There are patents on **PLA** dating back to 1954, and even older publications on **PLA** with polymerisation from lactides.[100,101] **PLA** was considered useless, since the polymers were heat and water sensitive. Later this polymer property was taken advantage of 1960s where it was discovered that the polymer would be useful in sutures because of the bio-degradability.[102] It could be used for internal bone fracture fixation and the sutures would degrade in vivo. **PLA** can be co-polymerised with other monomers such as ϵ-caprolactone. Lactic acid derives from a bio-renewable source and ϵ-caprolactone is derived from a petrochemical and thus they are both bio-degradable. This property persists for the co-polymer as well.[103] This presents the possibility to make diblock-, multiblock-, star- and random polymers. There are many possibilities to modify the properties of polymers where lactic acid is incorporated. There are two enantiomers of lactic acid, which means the properties of a **PLA** polymer can be quite different depending on the composition of the stereoisomers in the polymer.[104] **PLLA** with the (S) stereoisomer of lactic acid in the polymer is a semi-crystalline polymer with T_m 160-180 °C and a T_g of 55-65°C. It has high tensile/modulus strength and low elongation. This makes **PLLA** ideal for load-bearing fixation and sutures in orthopaedics. A mixture of (R) and (S) **(PDLLA)** is an amorphous polymer, a random polymer. The ten-

sile strength is lower than the pure **PLLA**, but it has higher elongation and a very rapid degradation time. This makes **PDLLA** ideal in drug delivery systems. Compared to other petrochemical-based polymers, **PLLA** has a higher strength with 60 MPa modulus 3 GPa, where high density poly ethylene (**HDPE**) has 30 MPa and 1.5 GPa Modulus, but the drawback with **PLLA** is the brittleness of the polymer with a tensile strain of less than 6 %. **PLLA** research into toughening the polymer has received a lot of attention. Experimenting with co-polymerisation with other monomers such as ϵ-caprolactone (which is also bio-degradable) raised the tensile strain to 50 %. Trimethylene carbonate co-polymer raised the strength to 900 %, but for this strength to occur 50 % of the polymer is trimethylene carbonate.[37]

PLA has the potential to replace and mimic **PVC**, **LDPE**, **LLDPE**, and **PS**. Challenges for the **PLA** is the production cost, which is still an issue, but scale up of production should lower the price and make the polymer more competitive on the market. Barrier mechanical properties of **PLA** are still an issue compared to conventional petrochemical polymers. The balance of being bio-degradable and hydrophobic is a fine balance, that can be difficult to manage.

1.5 Methyl vinyl glycolate

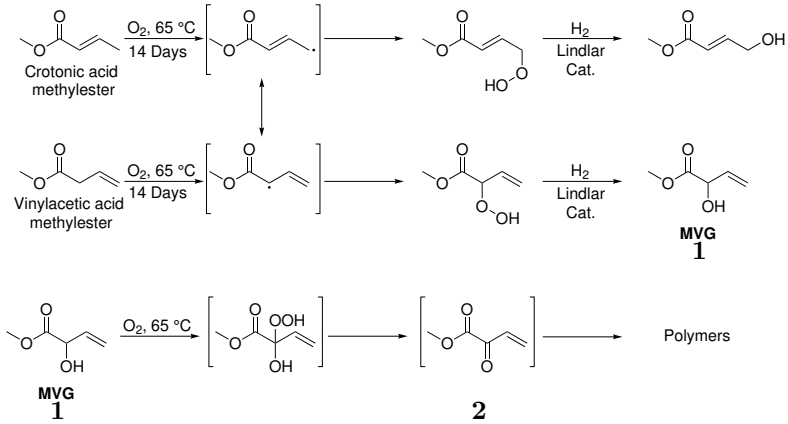
1.5.1 History



Scheme 1.1: First synthesis of methyl vinyl glycolate (**MVG**).[105]

Methyl vinyl glycolate **(MVG)** (**1**) is a chemical compound with three functional groups, i.e. a methyl ester, a secondary alcohol, and a vinyl group. The secondary alcohol and the vinyl group are an allylic alcohol. The IUPAC name of **MVG** is methyl 2-hydroxybut-3-enoate. **MVG** can be purchased at 460 € for 10 gram through Sigma-Aldrich (Jan. 2019). The first publication on **MVG** is in the french journal *Bulletin de la Societe Chimique de France, Memoires* from 1934 (R. Rambaud).[105] **MVG** was synthesised with acrylaldehyde and potassium cyanide in a nucleophilic attack on the aldehyde as shown in Scheme 1.1. The product from the reaction between these two compounds is 2-hydroxybut-3-enenitrile. The nitrile group can be converted into an ester with an alcohol and dry hydrochloric acid. For the synthesis of the methylester, methanol was used and gave roughly a 40 % yield. R. Rambaud also made vinyl glycolic acid through dilution with hydrochloric acid in water and published the formation of the dimerisation of vinyl glycolic acid into the lactide through heating of the monomer.

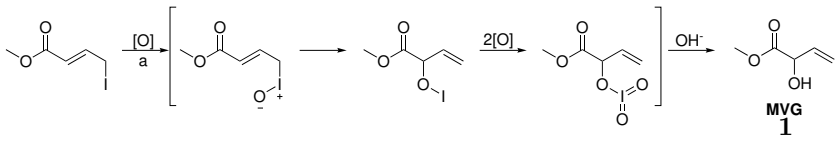
The first publication in a German journal was in 1962 by Rieche et al.[106] They were researching auto-oxidation of fatty acids. They mixed crotonic acid methyl ester and vinylacetic acid methyl ester in separate containers and shook the containers with



Scheme 1.2: Rieche et al. synthesis of **MVG**.[106]

oxygen at 65 °C (Scheme 1.2). This produced radicals at the α and γ positions to the methylester in both reactions. There is an equilibrium between the position of the radicals at the α or γ position. The radicals are attacked by oxygen, which leaves a peroxide at their respective positions. The peroxide products were isolated in roughly 4 % yields. The peroxide was cleaved by hydrogenation with the Lindlar catalyst.[107] This formed the two products, γ-hydroxycrotonic acid methylester and **MVG**. They also attempted to oxidise **MVG** further to vinylglyoxylic acid methylester (**2**). They could not isolate this compound, and they speculated this was due to polymerisation of vinylglyoxylic acid methylester.

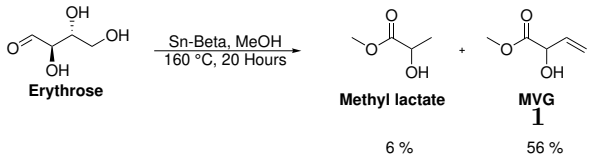
Rieche and Seyfarth published another article about γ-hydroxycrotonic acid methyl ester and **MVG** in 1966.[108] In this publication they covered the peroxydation of α,β-unsaturated alcohols (allylic alcohols). γ-Hydroxycrotonic acid methylester was oxidised to fumaraldehydic acid methylester. **MVG** oxidation led to the already previously mentioned polymerisation. They proved their hypothesis that vinylglyoxylic acid methylester is produced in situ and then polymerises. This was proven by using substrates similar to **MVG**, which then were oxidised to form α-ketoesters.



Scheme 1.3: Yamamoto et al. synthesis of **MVG**. a: *m*-CPBA, EtOAc or CH_2Cl_2 / aqueous Na_2CO_3, 5-20 °C, 1 hour.[109]

In 1983 Yamamoto et al. published the oxidation, rearrangement and hydrolysis

of allylic iodides into allylic alcohols.[109] One allylic iodide moiety tested was methyl *trans*-γ-iodocrotonate that afforded the rearranged alcohol **MVG** in 65-67 % yield. **MVG** could also be synthesised in a Mislow-Evans rearrangement through methyl γ-phenylthiocrotonate *S*-oxide with triphenylphosphine in methanol and benzene with refluxing for seven hours.



Scheme 1.4: Synthesis of **MVG** with erythrose as feed and tin beta as the catalyst.[110]

In 2010 Holm et al. published the conversion of sugars to lactic acid and derivatives using a heterogeneous zeotype catalyst.[111] A tin beta zeolite converted glucose, fructose, and sucrose into methyl lactate in methanol through a retro aldol mechanism reaction at 160 °C. The catalyst could be filtered off and reused. Methyl lactate had to be purified through distillation due to by-product formation. The by-product in the reaction consisted of levulinic acid, hydroxymethylfurfural, and alkyl vinyl glycolate. When erythrose was used as feed, 56 % of the formed product was **MVG** and only 6 % was methyl lactate (Scheme 1.4). Multiple publications subsequently, on the production of **MVG** have been published. In 2012 Holm et al. further published the use of other feeds for production of methyl lactate, and the publication also showed how different feeds could affect the production of **MVG**. The results are listed in Table 1.3.[110]

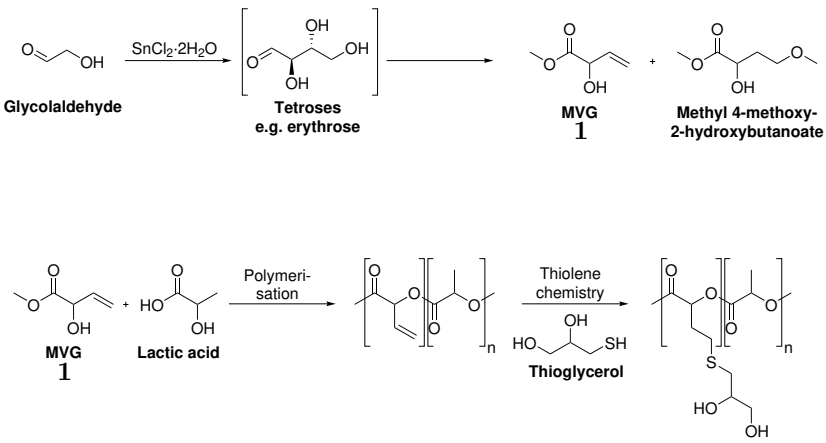


Figure 1.40: Synthesis of **MVG** and incorporation into a **PLA** polymer and further modification.[112, 113]

In 2013 Dusselier et al. published two papers on the synthesis of **MVG** and how

Table 1.3: An overview of the conversion of various sugars to **MVG** with tin-beta at 160 °C.

Feed	Reaction time [h]	**MVG** yield [%]
Xylose	16	7
Ribose	16	8
Arabinose	16	8
Lyxose	16	7
Glucose	16	10
Fructose	16	11
Mannose	16	9
Galactose	16	5
Sucrose	16	5
Lactose	16	2
Maltose	16	2
Cellobiose	44	2
Turanose	44	1
Melibiose	44	3
Trehalose	44	0
Glycolaldehyde	16	30[a]
Pseudo hemicellulose[b]	16	5

[a]Performed at 140 °C. [b]Pseudo hemicellulose is an equal mixture of the monosaccharides xylose, arabinose, ribose, glucose, mannose, and galactose on a weight basis.[110]

it could be to used in **PLA** to add functional moieties into the polymer and then post functionalise the polymer after the synthesis.[112,113] **PLA** was produced with a less hydrophilic property by incorporating **MVG** into the **PLA** polymer and then post-functionalising the polymer by performing thiolene chemistry on the olefin of **MVG** in the **PLA** polymer (Figure 1.40). **MVG** was incorporated into **PLA** via poly-condensation and azeotrope distillation to remove water. The thiols were attached through UV-initiated radicals. They successfully attached benzyl mercaptan and thio-glycerol. Their synthesis of **MVG** was with the homogeneous catalyst tin chloride instead of tin beta. The feed for producing **MVG** was glycolaldehyde. Glycolaldehyde was turned into threose and erythrose through an aldol condensation. These tetroses were subsequently converted into methyl 4-methoxy-2-hydroxybutanoate and **MVG** with the catalyst tin(II) chloride dihydrate with the optimum yield of 4 % **MVG** at 90 °C for 20 hours. Tin(IV) chloride pentahydrate produced 7 % of **MVG**. Changing the solvent from methanol to *iso*-propanol enhanced the yield further to 22 %, giving the product *iso*-propyl vinyl glycolate.[114]

In 2015 De Clercq et al. published a dealuminated tin beta catalyst that yielded 24 % of **MVG** using erythrulose as the feed at 120 °C for 5 hours.[115] When ethanol was used as a solvent with the tin beta catalyst for 20 hours at 90 °C, the yield increased to 33 % with the product being ethyl vinyl glycolate. Using the tin beta catalyst at 160 °C for 5 hours, the yield was further improved to 50 %.

In 2016 Tolborg et al. published a paper on the identification of a glycolytic pathway via 3-deoxyglucosone.[116] They also covered the effect of alkali ions by adding potassium carbonate to the reaction mixture with the tin beta zeolite catalyst present. This showed an increase in yield of both lactic acid and **MVG** when using the feed glucose. The highest **MVG** yield with potassium carbonate added was 18 %. They also discovered formation of methyl(*E*)-2,5,6-trihydroxyhex-3-enoate **(THM)** up to 18 %.

In 2017 Dusselier et al. published the synthesis of **MVG** in 6 % yield with tin(II) triflate as the catalyst and cellulose as the feed at 200 °C in methanol for 2 hours with 2 MPa of nitrogen pressure.[117] Cellulose is a cheaper feed, but it lowers the yield of **MVG** considerably and favours the formation of other α-hydroxyesters e.g. methyl lactate.

Multiple papers have also been published, covering the pathway to α-hydroxyesters, including **MVG**.[118, 119, 120] In Table 1.4, the various catalysts published for the synthesis of **MVG** are summarised.

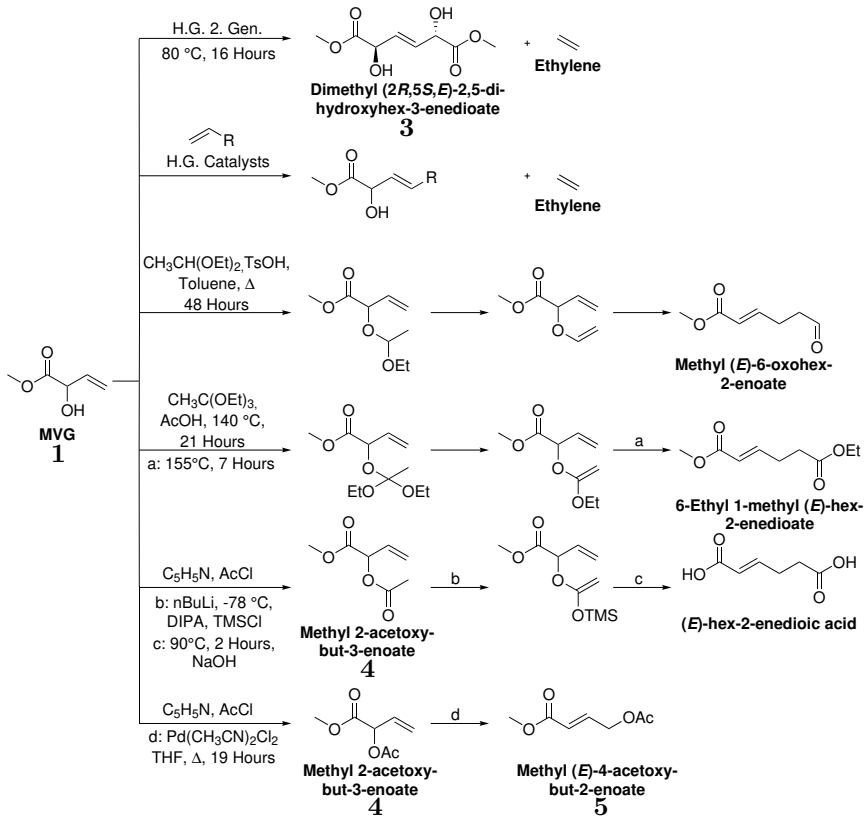
Table 1.4: An overview of the conversion of sugars to **MVG**.[111, 110, 112, 113, 115, 116, 117, 121, 122]

Entry	Catalyst	Feed	Additives	Yield
1	Sn-Beta	Erythrose	-	56 %[111]
2	Sn-Beta	Glycolaldehyde	-	30 %
3	$SnCl_2 \cdot 2\ H_2O$	Glycolaldehyde	-	4 %
4	$SnCl_2 \cdot 2\ H_2O$	Glycolaldehyde	-	22 %[a]
5	$SnCl_4 \cdot 5\ H_2O$	Glycolaldehyde	-	7 %
6	deAl[b] Sn-beta	Erythrulose	-	24 %
7	Sn-beta	Erythrulose	-	33 %[c]
8	Sn-beta	Erythrulose	-	50 %[115]
9	Sn-Beta	Glucose	K_2CO_3	18 %
10	$Sn^{(II)}(OTf)_2$	Cellulose	-	6 %

[a] *iso*-Propanol was used as solvent, synthesising *iso*-propyl vinyl glycolate instead. [b] Dealuminated catalyst. [c] Ethanol was used as solvent, synthesising ethyl vinyl glycolate instead.

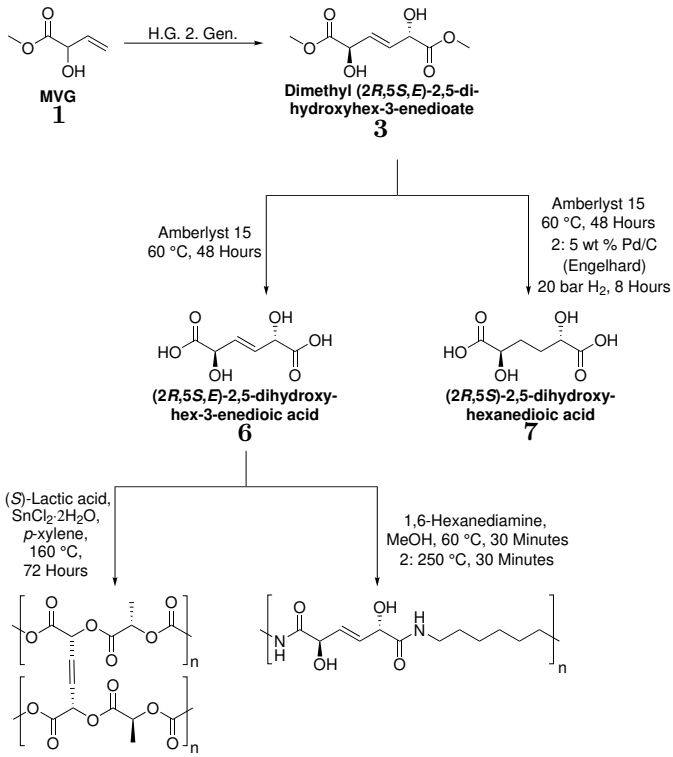
1.5.2 Methyl vinyl glycolate as a platform molecule

In 2016, Sølvhøj et al. published multiple conversions of **MVG**. **MVG** can be converted into the homo-dimer dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) through metathesis and release of ethylene.[123] This is patented for potential use as a new adipated derivative.[124] A typical Grubbs catalyst could be used to achieve this.[36] Hoveyda Grubbs second generation catalyst performed optimally with a published yield of 93 % with only the meso stereoisomer being formed.[125] Furthermore it was possible to perform cross metathesis between **MVG** and dodec-1-ene (68 % yield), dec-1-ene (63 % yield), and tetradec-1-ene (63 % yield) with the **MVG** homo dimer as a by-product. Small amounts of (*Z*) product was detected but not quantified. Methyl 6-



Scheme 1.5: **MVG** as a platform for metathesis reactions, Claisen, Johnson-Claisen, Ireland-Claisen rearrangement, and allylic acetate rearrangement.[123]

oxohex-2-enoate can be produced with acetaldehyde diethyl acetal and *p*-toluenesulfonic acid refluxing with a Dean Stark set-up in toluene. This approach resulted in a 46 % yield in a Claisen rearrangement (Scheme 1.5). Introducing other substituents at the five position of methyl 6-oxohex-2-enoate can be achieved by using a different aldehyde, and a ketone could also be used.[126, 127] 6-Ethyl 1-methyl (*E*)-hex-2-enedioate was synthesised in 74 % yield with triethyl orthoacetate, acetic acid at 140 °C for 21 hours, followed by heating to 155 °C for 7 hours in a Johnson-Claisen rearrangement (Scheme 1.5). Methyl 2-acetoxy-but-3-enoate (**4**) was synthesised with pyridine and acetyl chloride in near quantitative yield. Methyl 2-acetoxy-but-3-enoate was treated with butyl lithium, di-*iso*-propyl amine and trimethylsilyl chloride, with subsequent heating to 90 °C, for the rearrangement to occur. The silyl, as well as the methyl ester, were cleaved during work-up, synthesising (*E*)-hex-2-enedioic acid in 66 % yield in an Ireland-Claisen rearrangement (Scheme 1.5). Methyl 2-acetoxy-but-3-enoate (**4**) could be rearranged with bis(acetonitrile)dichloropalladium(II) in THF, refluxing for 19 hours to produce methyl (*E*)-4-acetoxy-but-2-enoate (**5**) in 59 % yield (Scheme 1.5).



Scheme 1.6: **MVG** as a platform for the metathesis reaction to dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate, (2*R*,5*S*,*E*)-2,5-dihydroxy-hex-3-enedioic acid, and (2*R*,5*S*)-2,5-dihydroxy-hexanedioic acid. Co-polymerisation of (2*R*,5*S*,*E*)-2,5-dihydroxy-hex-3-enedioic acid with (*S*)-lactic acid and 1,6-hexanediamine.[128]

In 2016 Dewaele et al. published the synthesis of **3** through metathesis in 96 % yield (Scheme 1.6) similar to the publication by Sølvhøj et al.[128] The two identical discoveries were made separately from each other. Dewaele et al. further published the hydrolysis of **3** to (2*R*,5*S*,*E*)-2,5-dihydroxy-hex-3-enedioic acid (**6**) in 93 % yield and the hydrogenation into (2*R*,5*S*)-2,5-dihydroxy-hexanedioic acid (**7**) in 92 % yield. Compound **7** could be co-polymerised with lactic acid and 1,6-hexanediamine. The co-polymerisation with a lactic acid polymer creates a point where the polymer can branch out. If compound **6** is incorporated in a polymer it can form a network in the polymer. The co-polymerisation with 1,6-hexanediamine is similar to Nylon 6,6, but with different properties with the internal double bond and extra hydroxy groups compared to the adipate used for the production of Nylon 6,6.

Other publications on modifications of **MVG** include formation of a lactide in 24 % yield with a shape selective zeolite catalyst (Figure 1.41), and the synthesis of maple furanone.[130, 131] **MVG** has also shown potential in polymerisation to either re-

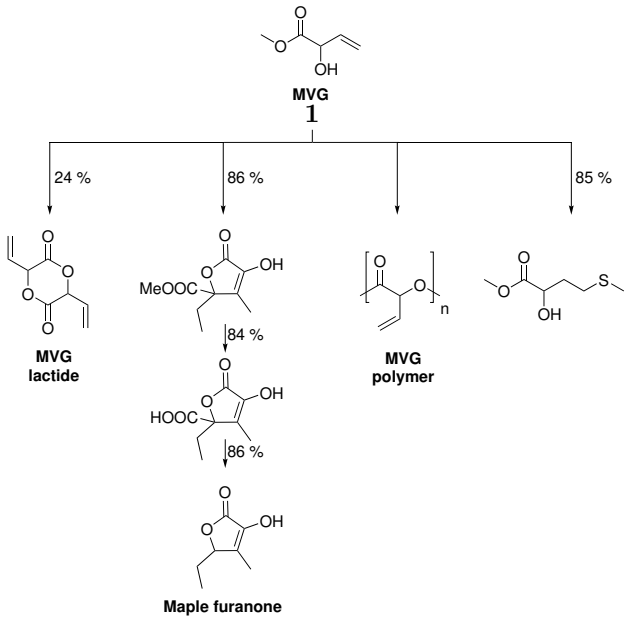


Figure 1.41: **MVG** as a platform for lactide, maple furanone, curing of a polymer with **MVG**, and methyl 2-hydroxy-4-(methylthio)butanoate.[129, 130, 131, 132, 133]

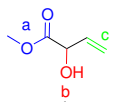
place or supplement acrylates. An **MVG** polymer was successfully cured with a photo initiator Irgacure® 500 and patented.[134] **MVG** can also be converted into methionine α-hydroxy analogues e.g. methyl 2-hydroxy-4-(methylthio)butanoate with methylthiol and a radical initiator in 85 % yield.[132, 133]

Given the extensive research into **MVG**, the potential of it is already recognised for polymer applications and as a possible substitution for some petrochemicals. Many patents on **MVG** have already been published. The compound, however, is still a new chemical, compared to some of the already established bio-renewable chemical platform molecules that are currently available on the market. **MVG** bulk production and new applications still need to be discovered and studied for the chemical to establish itself commercially and to be competitive.

CHAPTER 2

Methyl vinyl glycolate modifications

2.1 Methyl vinyl glycolate functional groups.



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Scheme 2.1: **MVG** functional groups for modifications.

MVG is a small molecule with many possibilities to alter through simple transformations. **MVG** has an ester (a) (blue) in Scheme 2.1, which can be altered through transesterification, hydrolysis or reduction. **MVG** also has a secondary hydroxy group (b) (red) in Scheme 2.1, which can undergo addition, esterification, methylation, and oxidation. The last functional group of **MVG** is the olefin (c) (green) in Scheme 2.1, which can be epoxidated, rearranged, and undergo metathesis. For a small molecule, **MVG** has many possible modifications to synthesise different new molecules. Most of these modifications are simple and can therefore possibly be performed on a large scale for industrial purposes.

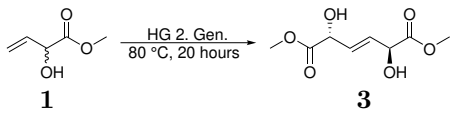
2.2 Aims for modifications of methyl vinyl glycolate

As noted in the introduction of chapter 1, our aim in this project was to use **MVG** as a platform to build new monomers for testing in commercial polymer applications. **MVG** was modified in multiple ways to change the way it can be polymerised and to modify its properties in polymers. Furthermore, studies were performed to synthesise

(E)-2,5-dihydroxy-3-pentenoic acid methyl ester and methyl (E)-2,5,6-trihydroxyhex-3-enoate following a subsequent purification with the goal to produce similar compounds as **MVG** on a relatively large scale.

2.3 Results and discussion

2.3.1 Dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate



Scheme 2.2: Synthesis of dimethyl (2R,5S,E)-2,5-dihydroxyhex-3-enedioate (**3**).

The synthesis of dimethyl (2R,5S,E)-2,5-dihydroxyhex-3-enedioate (**3**) (Scheme 2.2) has been described by A. Sølvhøj et al. and Dewaele et al.[123, 124, 128] Details are described in the subsection 1.5.2 on methyl vinyl glycolate as a platform molecule. It was attempted to synthesise 110 grams of **3**. While synthesising this amount, the reaction conditions were optimised. The mol percent of the catalyst for the reactions was optimised to a lower loading and reduced the price for production of **3**. The data from this optimisation can be seen in Table 2.1. The product **3** was interesting to test for application as a adipate moiety substitute to use in Nylons, and as a branching point in polymers. Application for **3** in curing with known polymers was also tested specifically, to change the properties of polymers cured with the addition of **3**. This task was addressed during my external stay at Perstorp AB. These tests can be seen in appendix C (External stay at Perstorp AB).

The metathesis reactions of **MVG** favours a homo dimerisation with the (E) stereoisomer over the (Z) stereoisomer with the Hoveyda-Grubbs second generation catalyst (**HG II**).[135] However not all catalysts favour the (E) stereoisomer. Chatterjee et al. developed a catalyst that is available commercially, i.e. a Grubbs Z-selective metathesis catalyst, which was tested.[36] This experiment showed very little to no conversion of **MVG**, and the small conversion was not the desired product. Other catalysts were not tested as it would require synthesis of known (Z) catalysts and in the interest of time this project was discarded. The 110 grams of **3** was shipped to our collaborators for testing. Product **3** was tested in blends and cured with discouraging results. Product **3** is very insoluble in the tested blends. One of the free hydroxy groups in **3** was successfully combined with ϵ-caprolactone that could grow in size with multiple ϵ-caprolactones. Unfortunately, it was not possible to attach ϵ-caprolactone at both hydroxy groups in **3**. One free hydroxy group in **3** ring opens one ϵ-caprolactone, which produced a primary hydroxy group on the ring opened ϵ-caprolactone. This primary hydroxy group is more reactive and prefers to react with a new ϵ-caprolactone. The product formed consists of one **3** with a polymer string of ϵ-caprolactones. Product **3** was also tested as a plasticiser via a small oligomer reacted with 1,6-hexanediol. The

Table 2.1: The experiments were performed in a Schlenk flask under inert atmosphere at 80 °C overnight.

Experiment	**HG II** Loading (mol %)	**MVG** Scale (mmol)	Yield[a] (%)
1	0.5	60	63
2	0.052	172	69
3	0.050	171	67
4[b]	0.0129	172	-
5	0.10	171	79
6	0.10	169	82
7	0.15	172	81
8	0.11	168	84
9[c]	0.11	173	87

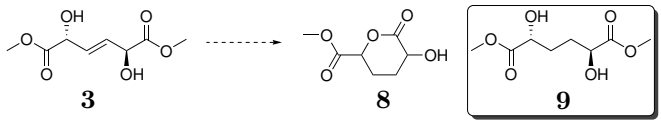
[a]Isolated yields are from washing of the precipitate before eventual purification through dry column vacuum chromatography (**DCVC**). [b]This experiment did not convert enough **MVG**. Product **3** did not precipitate, and more catalyst (43 mg) was added to yield more of **3** (41 %). [c]The synthesis was performed for one hour without heating. Toluene used for washing contained 6 % more of the desired compound, but it had a darkgrey colour.

result was discouraging. Product **3** was tested in cross-linking with trimethylolpropane tris(3-mercaptopropionate). The results were again discouraging.
The synthesis of **3** was achieved in a high yield at a low temperature, but requires an expensive ruthenium catalyst that is difficult to recover for reuse. The catalyst also changed colour and it seemed to be deactivated based on the observations that if the loading is too small it will not convert all **MVG** in the reaction. The catalyst might also be present in the product in low amounts. This has to be taken into account for applications downstream. The by-product from the synthesis of **3** is a release of ethylene for every two molecules of **MVG**. This is a large amount of ethylene that has to be handled if the product is synthesised at a larger scale. There will be safety concerns dealing with this amount of gas released. If the product **3** was to be set into production the ethylene released could be harvested and sold as ethylene from a bio-renewable source. The expensive catalyst and the amount of product formed in this reaction will not justify production of only ethylene in this way for sale as ethylene from a bio-derived source.

2.3.2 Dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate

It was attempted to synthesise methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate (**8**). This is a lactone that could be tested in a step-growth polymerisation. The ring-strain 39.7 kJ mol^{-1} of a six-membered lactone ring **8** might favour polymerisation.[136] Product **8** still has the same hydroxy functional group as **3**, which has potential to form branching in a polymer. It could also create a network through the two exposed hydroxy groups in the open form, after ring-opening of the lactone.

The synthesis of methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate (**8**) was thought to be straightforward (Scheme 2.3). Product **8** can be synthesised with a noble metal catalyst (palladium) in a hydrogen atmosphere, where hydrogen reduces the



Scheme 2.3: Reduction of **3** was thought to form a ring-closed lactone methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate (**8**). Instead of the formation of the ring-closed lactone **8**, the double ester from the starting material **3** remained, but with a reduction of the olefin, forming the compound dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**) in majority.

double bond and then the product **8** should be formed through release of methanol. Instead of the ring-closed lactone, the double ester from the starting material **3** remained, but with a reduction of the double bond, forming the compound dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**). Additionally the synthesis produced extra carbon signals (red dots, Figure 2.1). The ^{1}H-NMR (Figure A.2) and HRMS (Figure B.1) spectra support the synthesis of **9** from the reduction of **3**, but the by-product is not the ring-closed lactone. The by-product yielded chemical shifts close to the identified **9**. It was assumed these might be diastereomers of **9** (Scheme 2.4).[137] To avoid this by-product, multiple catalysts were tested with the same outcome. Experiments are depicted in the list seen in Table 2.2. To confirm the stereochemistry of **9** and verify the assumed by-product formed, **9** was reduced to the tetraol hexane-1,2,5,6-tetraol to compare with literature values of the different stereoisomers. Further tests were performed to uncover why the by-product was formed, and pollution with **HG II** in the reduction of **3** did not seem to have an effect. The reaction was tested without a metal using hydrazine and 2-nitrobenzenesulfonyl chloride. This was without success, since no product was formed. The reductions of (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioic acid (**6**) and dimethyl (2*R*,5*S*,*E*)-2,5-diacetoxyhex-3-enedioate (**10**) were tested, and they both showed the same issues as the reduction of **3**. Different solvents were also tested to avoid formation of diastereomers without success.

The reaction was then performed with a new catalyst, 5 % palladium on activated carbon in methanol at 60 bar of hydrogen pressure with fast assembling of the apparatus, and this seemed to limit the diastereomer formation to a negligible amount.[138] Therefore it seems that diastereomers are being formed when the reduction is performed under conditions that are slowed. An experiment in the laboratory at normal atmospheric pressure was performed with a balloon filled with hydrogen and a balloon filled with nitrogen. The nitrogen gas was mixed with hydrogen gas in the reaction, which retarded the reaction and formed more of the diastereomers. It was also attempted to follow the hydrogenation reaction with the conditions used at high pressure by taking out samples from a reaction and analyse them by NMR spectroscopy. The result of this can be seen in Figure 2.2. Full conversion to the product was fast. The conclusion from this experiment was that the reaction is completed in less than an hour. The NMR analysis did not yield any information on the diastereomer problem. It has been described in previous studies that palladium can form an allylic intermediate **11** (Scheme 2.4).[140, 141, 142, 143] It is suspected that an allylic complex is being

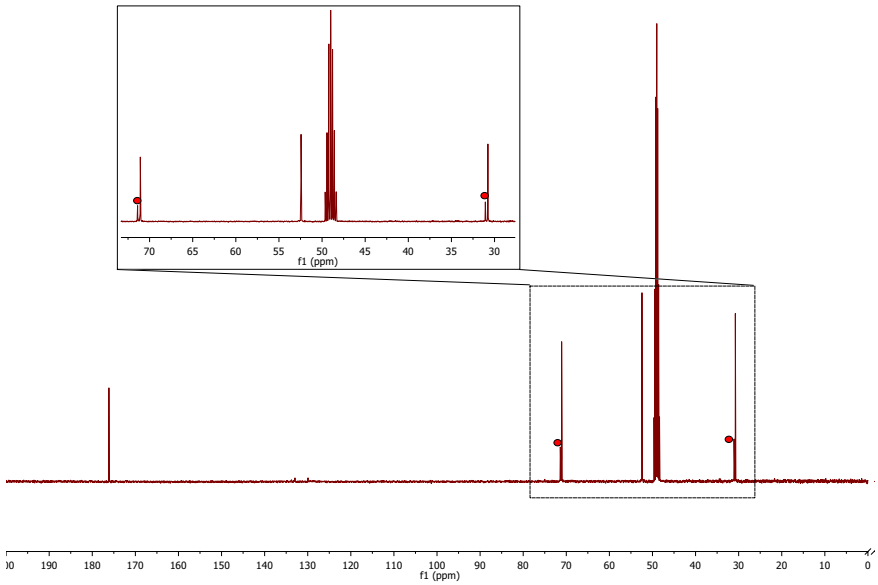


Figure 2.1: ^{13}C-NMR of the reduction of **3** to synthesise **9**. Red dots show extra carbon signals.

formed where the hydroxy group is expelled and reattached again.[144] This reattachment reforms both the (*R*) and the (*S*) configurations leading to diastereomers of the initial product. Ruthenium can also catalyse this reaction. It was later discovered that the by-product can be removed by recrystallisation of **9** in toluene.

The product **9** was synthesised in near quantitative yields (>98 %, 6.144 grams). Product **9** has potential as a substitute for adipate moieties in polymerisation with hydroxy groups for branching out. A possible application is in the production of Nylons.

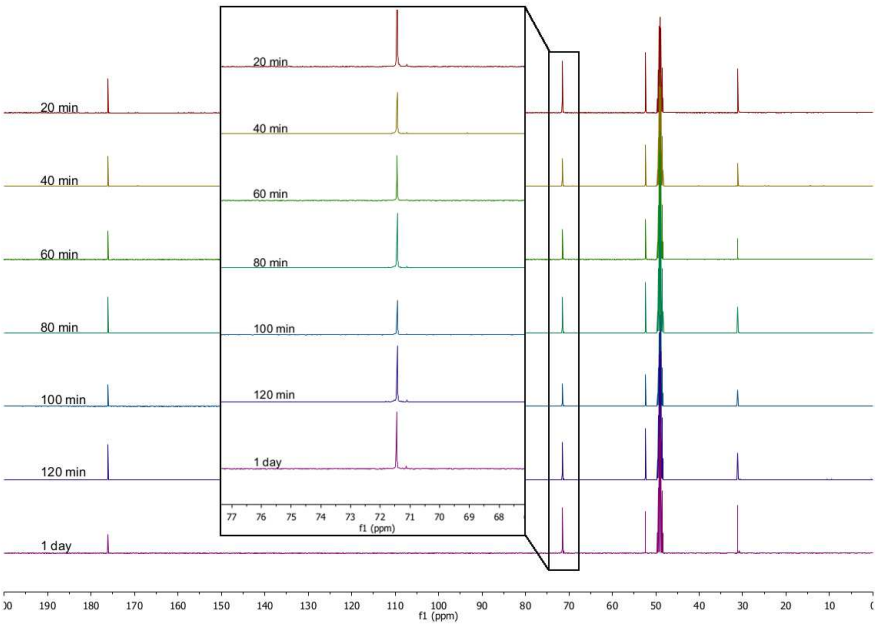
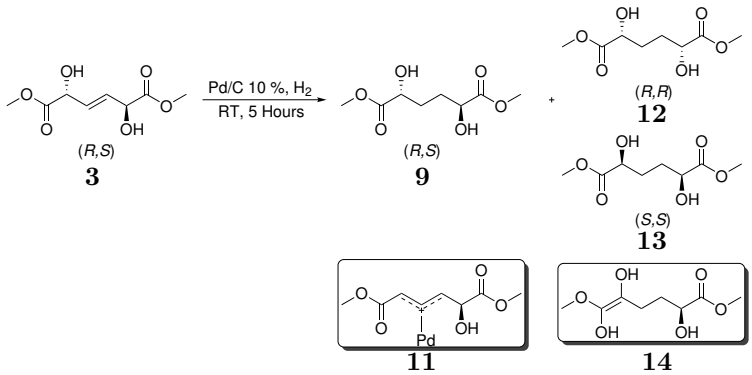
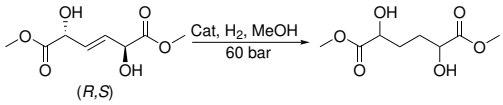


Figure 2.2: Hydrogenation over time of dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) at 60 bar of hydrogen at room temperature.



Scheme 2.4: Reduction of **3** forms diastereomers. The reaction yields by-products **12** and **13** with the main product being **9**. This can occur through either **11** or **14**, where the most plausible transformation is the first, also substantiated by similar reactions described in the literature.[140, 141, 142, 143]

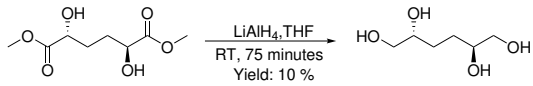
Table 2.2: List of catalysts tested to avoid the formation of diastereomers. Reactions were performed in methanol at room temperature with a high pressure of hydrogen.



Catalyst	Product
Pd/C 10 %	Diastereomers
Ru/C 5 %	Diastereomers
(*R*)-Ru(OAc)$_2$(T-BINAP)[138]	Diastereomers
(*S*)-Ru(OAc)$_2$(T-BINAP)[138]	Diastereomers
Wilkinsons Catalyst	Diastereomers
Pt/C 5 %	Diastereomers
Ru/Al 5 %	Diastereomers
Pd/C 5 %	Diastereomers
RaneyNi 2800(50 °C, H_2 90 bar)	Diastereomers
Pearlman's Catalyst	Diastereomers
H_2, No Catalyst	Minimal conversion
Pd/C 10 % without H_2	No conversion
Hydrazine[a]	No conversion

[a]Was performed with hydrazine(imide) and 2-nitrobenzene sulfonyl chloride in acetonitrile.[139]

2.3.3 Hexane-1,2,5,6-tetraol



9 **15**

Scheme 2.5: Reduction of **9** to hexane-1,2,5,6-tetraol (**15**).

The synthesis of hexane-1,2,5,6-tetraol (**15**) was straightforward once a new reducing agent was obtained. It was attempted to synthesise this compound from what was believed to be a mixture of diastereomers formed from the reduction of the double bond of **3** to verify the hypothesis that diastereomers were formed. Product **9** can be reduced with sodium borohydride and lithium aluminium hydride. Lithium aluminium hydride was preferred as the conversion and reduction were faster. The quenching and the subsequent work-up of the reaction presented a problem for this product. The product hexane-1,2,5,6-tetraol (**15**) is soluble in water, and as a result the reaction mixture can not be washed with water. The reaction was therefore quenched with water and then filtered through silica. The **DCVC** work-up method is believed not to be the most efficient and to be the cause of the low overall yield of 10 %, (31 milligrams). The reduction shows that the main product of the synthesis is **15** and it has the (*R,S*) configuration, while the enantiomeric compounds (*R,R*) and (*S,S*) are the by-products (Table 2.3). This confirms the suspicion that during the synthesis of **9**, the by-products are the formation of the (*R,R*) and (*S,S*) compounds, which are diastereomers to (*R,S*)-**15**. This was analysed by ^{13}C-NMR in deuterated water. The chemical shifts values obtained from the reduction of **9** to **15**, where diastereomers are present, are listed in the middle of Table 2.3. The chemical shifts values obtained from the reduction of enantiomerically pure **9** to **15** are listed on the right in Table 2.3. Experimental values of a diastereomeric mixture from the literature are listed in the left column of Table 2.3.[145]

Table 2.3: The ^{13}C-NMR values in deuterated water obtained from the reduction of **9** to **15**, where diastereomers are present, are listed in the middle. The chemical shifts values obtained from the reduction of enantiomerically pure **9** to **15** are listed on the right. Experimental chemical shifts values of a diastereomeric mixture from the literature are in the left column.[145]

Literature values (*S,S*, *R,R*, *R,S*)	Experimental values (*S,S*, *R,R*, *R,S*)	Experimental values (*R,S*)
29.60	29.60	-
29.83	29.83	29.83
66.63	66.61	66.61
66.69	66.68	-
72.87	72.88	-
73.19	73.21	73.20

2.3.4 Methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate

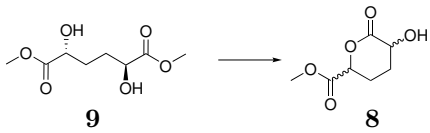


Figure 2.3: Synthesis of methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate (**8**) from **9**.

Experiments were performed to find a viable way to synthesise **8**. The way initially thought to be plausible to synthesise **8** was from the starting material **3**, through a hydrogenation with a subsequent closing of the ring by removing methanol. The ring-strain energy barrier might be too large to overcome under the conditions used and it synthesised **9** instead. The synthesis of the lactone **8** was still a target and it was decided to try synthesising **8** from **9**. Emphasis was on removing methanol through an intramolecular condensation reaction between one of the esters and one of the hydroxy groups. Various reactions were tested and some of them are listed in Table 2.4. An old publication in the literature by Le Sueur from 1908 describes (2*R*,5*S*)-2,5-dihydroxyhexanedioic acid **16** was closed into a lactone. It was also observed to close into a dilactone with reduced pressure and heating where the product sublimates on a cold-finger.[137,146] All our experiments showed no conversion or low conversion to the desired product **8**. From the experiments it was evident that the product was difficult to handle and a NMR analysis of the crude reaction mixture showed impurities with very low yield of the desired product. The yield was not quantified. Attempts to isolate **8** via **DCVC** were unsuccessful. NMR analysis of the product after purification seems to indicate a ring-opening, but that was not confirmed. Sublimation on a cold finger also proved unsuccessful. The most successful result was achieved in a solution of formic acid, based on NMR analysis. It was possible to perform a HRMS analysis, which showed the mass of the desired lactone (Figure B.2). These issues with the synthesis of **8** led to the discontinuation of this approach. The formation of the lactone and the problem it presented did not seem cost-effective enough to continue this route.

Table 2.4: Multiple reactions tested to synthesise **8** from **9**.

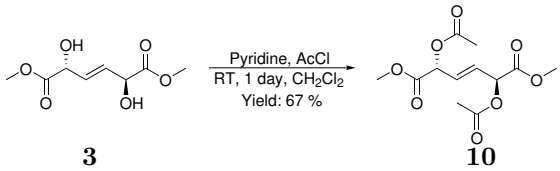
Catalyst	Result/product
p-Toluenesulfonic acid, sulfolane, 190 °C[147]	Decomposition
Dean Stark set-up, *o*-xylene, 144 °C	Decomposition
Molecular sieves, *o*-xylene, 144 °C	Decomposition
Nb_2O_5, molecular sieves, *o*-xylene, 144 °C	Decomposition
Formic acid, toluene, reflux	Low conversion
Formic acid, toluene, 100 °C	Very low conversion
Formic acid, toluene, 90 °C	Conversion with by-products
Formic acid, 90 °C	Low conversion
Formic acid, *o*-xylene, 130 °C	Low conversion[a]
Formic acid, toluene, MW 130 °C 45 min	Low conversion
Tin(II) 2-ethylhexanoate, toluene, 90 °C	Conversion with by-products
Tin(II) 2-ethylhexanoate, vacuum, 95 °C	No conversion
KO*t*-Bu, toluene, 90 °C	No conversion
HCl, THF, RT	Conversion with by-products
H_2SO_4, toluene, RT	Decomposition
$AlCl_3$, toluene, reflux	Very low conversion
$AlCl_3$, toluene, RT	Very low conversion
Dean Stark set-up $AlCl_3$, toluene, reflux	Low conversion
Vacuum, 100 °C[146]	Low conversion
Vacuum, 100 °C[b]	Very low conversion

[a]Purification through **DCVC** tested. [b]Equipment was not flamed before use.

2.3.5 Dimethyl (2*R*,5*S*,*E*)-2,5-diacetoxyhex-3-enedioate

It was also attractive to acetylate **3** since this would provide an allylic acetate, which is a good leaving group in a Tsuji-Trost type reaction.[148,149] It was also desirable to perform an allylic rearrangement of this compound. The recipe from the work published by Sølvhøj et al.[123] in 2016 was used. Acetyl chloride was added drop-wise (3 ml/h) to a reaction mixture with **3** and pyridine. It was not enough to purify the product by washing with a solution of hydrochloric acid and a saturated solution of sodium carbonate to remove pyridine and excess acetyl chloride, and the product dimethyl (2*R*,5*S*,*E*)-2,5-diacetoxyhex-3-enedioate (**10**) was therefore precipitated from ethyl acetate and heptane to yield a pure white powder in 67 % yield (0.483 grams).

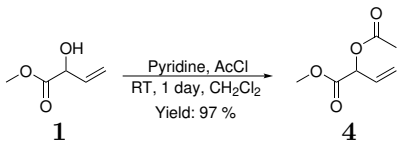
The synthesis of **10** was validated by B.Sc. E. S. Grønkjær and she further tested this compound for application in a Tsuji-Trost type reaction, using compound **10** in THF with the catalyst tetrakis(triphenylphosphine)palladium(0) and sodium hydride as base with dimethyl malonate as the nucleophile. The reaction proved problematic in practice.[150] After she finalised her project further NMR analysis on the reaction mixture from the Tsuji-Trost experiment was performed. The analysis showed that instead of a nucleophillic substitution, the product **10** underwent elimination of an acetate to form a conjugated diene dimethyl 2-acetoxyhexa-2,4-dienedioate. The product structure was determined only by 1D and 2D NMR spectroscopy. There is an uncertainty with regard to the stereochemistry of the product and there are unknown



Scheme 2.6: Acetylation of **3** with pyridine and acetyl chloride to synthesise dimethyl (2*R*,5*S*,*E*)-2,5-diacetoxyhex-3-enedioate (**10**).

by-products present. The product was not isolated and the reaction was not investigated any further. Diacetate **10** was also tested in an allylic rearrangement because it had an internal double bond. The compound did not show any rearrangement when tested. Other similar tests are described in chapter 3 Allylic acetate rearrangement.

2.3.6 Methyl 2-acetoxybut-3-enoate



Scheme 2.7: Synthesis of methyl 2-acetoxybut-3-enoate (**4**) with pyridine and acetyl chloride in dichloromethane stirred overnight.

Our collaborators at Perstorp AB tested **MVG** in radical polymerisations. They reported that it had been difficult to use **MVG** in polymerisations and the secondary allylic alcohol appears to be very stable. It was attempted to modify the allylic alcohol into an allylic acetate for experiments with the radical polymerisation of the double bond. It was also necessary to produce bulk quantities of methyl 2-acetoxybut-3-enoate (**4**) to perform further modifications and to synthesise downstream products.
In the work published by Sølvhøj et al. in 2016, **MVG** was acetylated to form **4**.[123] The procedure from this published work was followed to synthesise **4** in bulk quantities (Scheme 2.7). A total of 100 grams of **4** was produced. In Table 2.5, the yields of the nine experiments from the synthesis of **4** in bulk quantities are listed. The 100 grams of the synthesised **4** had a yellowish colouring. This undesirable trait is due small impurities not detected by NMR spectroscopy. These impurities can be removed via a distillation, yielding a clear liquid.

The acetylation with the acid chloride is a very effective method of synthesising **4**, but alternative methods for producing this compound was still attempted. One way to approach this differently would be to perform a Fischer esterification with the secondary alcohol of **MVG** and acetic acid (Scheme 2.8).[151] To catalyse this reaction, concentrated sulphuric acid was used for its hygroscopic property and acidic property. Both properties should help in the formation of **4**. The result from these experiments

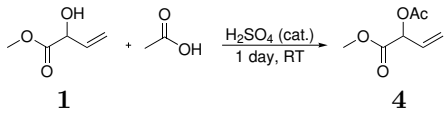
Table 2.5: Table of experiments to acetylate **MVG** in the synthesis of **4**. The synthesis was performed with 86 mmol of **MVG** in 300 ml of dichloromethane mixed with 1 equivalent of pyridine and 1.9 equivalent of acetyl chloride, which was added drop-wise (3 ml/h). The mixture was left to stir overnight. The mixture was then poured into ice and extracted with dichloromethane, then washed with 1 M hydrochloric acid and with a solution saturated with sodium carbonate. The dichloromethane phase was dried with magnesium sulphate, filtered, and evaporated off on a rotavapor.

Experiment	Yield [%]	Mass [g]
1	90	12.19
2	84[a]	11.41
3	92	12.49
4	93	12.64
5	93	12.66
6	96	13.04
7	97	13.15
8	93	12.58
9	93	12.62

[a]The product from the reaction had impurities and had to be distilled to reach acceptable purity.

showed that it was possible to synthesise the desired ester via a Fischer esterification between **MVG** and acetic acid, but it was difficult to reach full conversion of the substrates. The best results were experiments 5 and 6 (Table 2.7), where the reactions were performed in neat acetic acid with sulphuric acid as the catalyst and **MVG**. Isolating product **4**, from experiments 5 and 6 (Table 2.7) requires quenching with stoichiometric amount of base relative to the amount of acid present. It was therefore also tested to find other solvents where the reaction would occur, but use of heptane, tetrahydrofuran, and ethyl acetate gave low conversion and decomposition. The reaction seems to tolerate some dichloromethane, but the results are not consistent. IR 120 resin was tested as a catalyst, but yielded low conversion (experiment 19, Table 2.7). The yields were very low and were not determined. Hydrochloric acid did not give full conversion (experiment 4, Table 2.7). The amount of acid in these experiments were catalytic, and the results were not consistent. It seems the specific amount of acid plays a role, which should be investigated further.

MVG in neat acetic acid with sulphuric acid as the catalyst gave the best yield of **4**. It was attempted to isolate **4** from the reaction by quenching with a solution of saturated sodium carbonate and extracting with dichloromethane. The product **4** could be isolated this way in moderate yields, and the results are listed in Table 2.6. It was attempted to perform a direct distillation, but that led to decomposition of the product, probably due to the presence of sulphuric acid. The yield isolated from the Fischer esterification reaction was modest (Table 2.6) compared to the acetylation of **4** with acetyl chloride, leading to the conclusion that the acetylation is the better synthesis method to obtain **4** at a higher yield. The low yield of synthesising **4** from **MVG**, acetic acid, sulphuric acid, and the undesirable amount of base needed for purification, meant that further experiments through this synthesis pathway were abandoned.



Scheme 2.8: Synthesis of **4** through a Fischer esterification of **MVG** with acetic acid.

Table 2.6: Table of experiments for synthesising **4** via a Fischer esterification between **MVG** and acetic acid with isolated yield of the reactions. All reactions were performed in neat 1 ml acetic acid at room temperature overnight. Quenching of the reactions was achieved by pouring the reaction mixtures into a solution of saturated Na_2CO_3 and extracting the product **4** with dichloromethane.

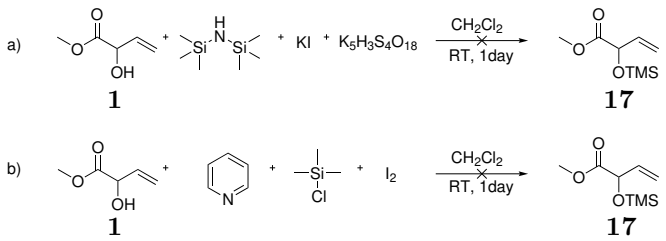
Experiment	**MVG** [mmol]	Catalyst	Work-up	Yield [%]
1	0.44	H_2SO_4	Quench & extraction	38
2	2.41	H_2SO_4	Quench & extraction	21
3	2.32	H_2SO_4	Quench & extraction	32
4	1.05	H_2SO_4	Quench & extraction	27
5	0.51	H_2SO_4	Quench & extraction	21

Table 2.7: Experiments for synthesising **4** via a Fischer esterification between **MVG** and acetic acid. Different solvents were tested: Neat acetic acid, heptane, tetrahydrofuran, ethyl acetate and dichloromethane at room temperature overnight. Different catalysts were also tested.

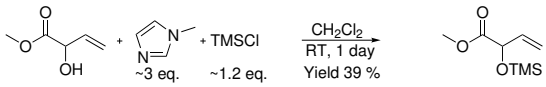
Ex.	**MVG** [mmol]	Acetic acid [mmol]	Solvent [mmol]	Catalyst cat. amount	Product
1	0.5	17.5	-	-	**1**
2	0.5	17.5	-	H_2SO_4	**4**
3	0.5	8.75	CH_2Cl_2 7.8	H_2SO_4	**4**
4	0.5	17.5	-	HCl	**1**, **4**
5	1	17.5	-	H_2SO_4	**4**
6	0.25	17.5	-	H_2SO_4	**4**
7	0.25	0.25	Heptane 6.8	H_2SO_4	**4**
8	0.25	0.25	EtOAc 10.2	H_2SO_4	**1**, **4**
9	0.25	0.25	CH_2Cl_2 15.6	H_2SO_4	**1**, **4**
10	0.25	0.25	THF 12.3	H_2SO_4	**1**
11	0.25	8.75	THF 6.15	H_2SO_4	Decomposition
12	0.25	8.75	Heptane 3.4	H_2SO_4	**1**, **4**
13	0.25	8.75	EtOAc 5.1	H_2SO_4	Decomposition
14	0.25	8.75	CH_2Cl_2 7.8	H_2SO_4	**1**, **4**
15	0.5	17.5	CH_2Cl_2 15.6	H_2SO_4	**4**
16	0.5	1	Heptane 6.8	H_2SO_4	Decomposition, **4**
17	2	2	Heptane 27.2	H_2SO_4	**1**, **4**
18	4.5	175	-	H_2SO_4	**1**, **4**
19	1	17.5	-	IR 120 Resin	**1**, **4** (low conversion)

2.3.7 Silylation of methyl vinyl glycolate

After successfully synthesising **4**, it was attempted to see if **MVG** could be silylated to test the properties when **MVG** is silylated. A recipe cited at Sigma Aldrich was tested. The experimental procedure of Kolvari et al. was followed.[152] **MVG** was mixed with hexamethyldisilazane, potassium iodide, and Oxone (potassium peroxymonosulphate) in dichloromethane at room temperature for one day. This reaction is depicted in Scheme 2.9a. The reaction gave unknown by-products. Scheme 2.9b shows a second attempt to silylate **MVG**. **MVG** was mixed with pyridine, chlorotrimethylsilane, and iodine at room temperature for one day. This reaction also gave unknown by-products. Following the two failed attempts, a third attempt was made, where **MVG** was mixed with methyl imidazole in dichloromethane and chlorotrimethylsilane was added in drops, followed by stirring the mixture at room temperature for one day (Scheme 2.10). This yielded the desired product in 39 % yield (1.278 grams). During the synthesis, it was noticed, the compound synthesised (methyl 2-((trimethylsilyl)oxy)but-3-enoate (**17**) was very susceptible to hydrolysis. If deuterated chloroform in the NMR analysis was not filtered through aluminium chloride before being used, it would hydrolyse **17** back to **MVG**. The silylation of **MVG** was also tested with *tert*-butyldimethylsilyl chloride under the same conditions that had been carried out with chlorotrimethylsilane. **MVG** was mixed with methyl imidazole in dichloromethane and *tert*-butyldimethylsilyl was added. The mixture was then stirred at room temperature for one day. This yielded the desired compound methyl 2-((*tert*-butyldimethylsilyl)oxy)but-3-enoate (**18**) in 51 % yield (0.520 grams) (Scheme 2.11).
It was possible to silylate **MVG** with both chlorotrimethylsilane and *tert*-butyldimethylsilyl chloride. The yield from both reactions were mediocre. The expensive silylating agents and the mediocre yields made it undesirable to produce the silylated **MVG** on a larger scale for testing. The labile silyl group of **17** was also a concern. This meant the project was discontinued.

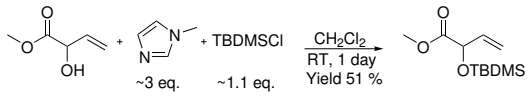


Scheme 2.9: a) First silylation attempt of **MVG** mixed with hexamethyldisilazane, potassium iodide and Oxone (potassium peroxymonosulphate) mixed in dichloromethane at room temperature for one day.[152] This gave unknown by-products. b) Shows the second attempt.[153] **MVG**, pyridine, chlorotrimethylsilane, and iodine were mixed in dichloromethane at room temperature for one day. This also gave unknown by-products.



1 **17**

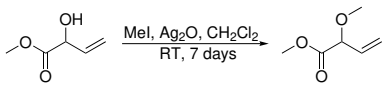
Scheme 2.10: **MVG** was mixed with methyl imidazole in dichloromethane and chlorotrimethylsilane was added in drops. The mixture was then stirred at room temperature for one day to give methyl 2-((trimethylsilyl)oxy)but-3-enoate (**17**) in 39 % yield.



1 **18**

Scheme 2.11: **MVG** and methyl imidazole were added to dichloromethane, *tert*-butyldimethylsilyl chloride was added and the reaction was stirred at room temperature for one day to give methyl 2-((*tert*-butyldimethylsilyl)oxy)but-3-enoate (**18**) in 51 % yield.

2.3.8 Methyl 2-methoxybut-3-enoate



1 **19**

Scheme 2.12: **MVG** can be methylated with methyl iodide and silver(I) oxide in dichloromethane for seven days to yield methyl 2-methoxybut-3-enoate (**19**).[154]

Alkylation of the **MVG** hydroxy group was a target of interest. Lebrasseur et al. methylated **MVG**, in order to use it as a building block toward synthesising aquayamycin.[154] They methylated **MVG** with methyl iodide and silver(I) oxide in chloroform with a yield of 95 %. The information published was revised and we could not find all the specific details on how the methylation was achieved. The methylation was therefore re-established, and the experiments showed that methylation was possible with methyl iodide in excess and silver(I) oxide in 1.25 equivalent in dichloromethane. This yielded the desired methylation of **MVG** to afford methyl 2-methoxybut-3-enoate (**19**). Silver(I) oxide was added in two steps, 0.75 equivalents in the first step, and 0.5 equivalents in the second step. The reaction also seems to be very slow. The mixture was left for five days before adding more silver(I) oxide, completing the reaction in seven days (Scheme 2.12). The reaction was analysed after one, five, six and seven days where ^{1}H-NMR analysis was performed, which showed that **MVG** had not been fully converted until the seventh day (Figure 2.4). After one day the conversion of

MVG to **19** was <30 %. The ^{1}H-NMR data after five days still showed incomplete conversion of **MVG**, which led to the addition of more silver(I) oxide. After six days the conversion was nearly complete, but **MVG** was still present in a small amount. On the seventh day the ^{1}H-NMR spectrum did not show any signals for **MVG**. The reaction was filtered and then distilled. The analysis after the filtration showed small impurities, which led us to further purify the product **19** via distillation. After the filtration a yield of 83 % was obtained. When the distillation was performed, the yield was lowered to 49 % (0.555 grams). It was then attempted to use propyl iodide as alkylating agent without success. It seemed the alkylation would only react with methyl iodide. The amount of silver(I) oxide was varied from 0.1 - 1.25 equivalent, to see if it was possible to see a linear correlation between the added silver(I) oxide and the conversion. The experiments showed that it was best to add close to 1 equivalent of silver(I) oxide and then add more after a few of days. Other methylating agents were also tested without success, and this included trimethyloxonium tetrafluoroborate, that did methylate, but not to full conversion nor with a better result than with silver(I) oxide and methyl iodide. It was possible to synthesise **19** in bulk quantities, but it required excess of both methyl iodide and silver(I) oxide. A more viable way to synthesise **19** was not discovered and focus was aimed at other targets.

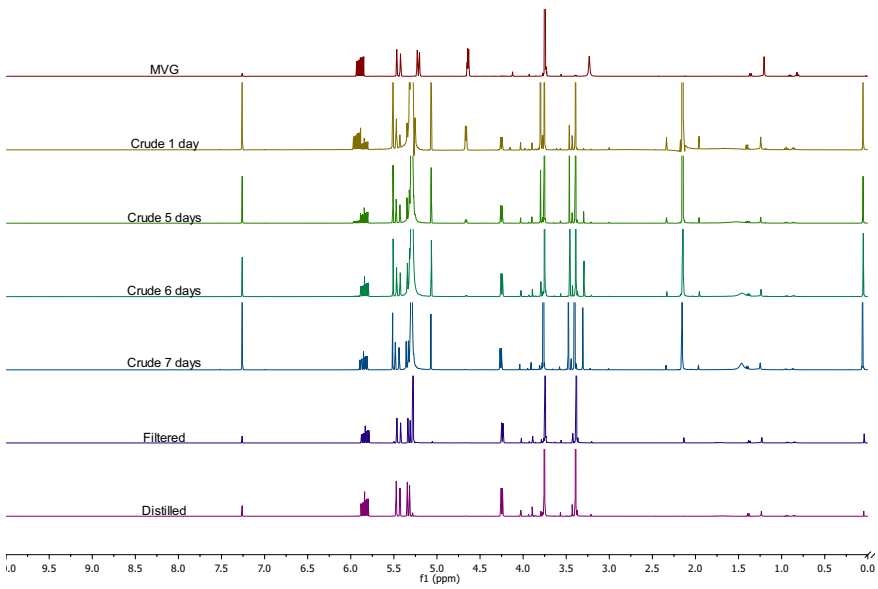
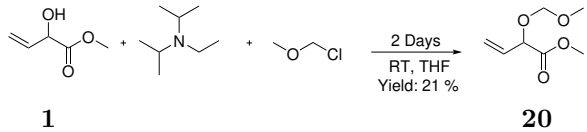


Figure 2.4: ^{1}H-NMR spectrum of methylation of **MVG** over time from the beginning at the top, to the completion of the reaction with the final product **19**, seven days later, and the purification.

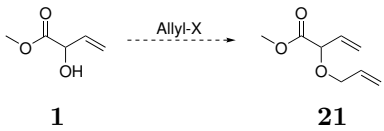


Scheme 2.13: **MVG** can be methoxy methylated with a base di-*iso*-propylethylamine and chloromethyl methyl ether in dichloromethane for two days to synthesise methyl 2-(methoxymethoxy)but-3-enoate (**20**).

2.3.9 Methyl 2-(methoxymethoxy)but-3-enoate

Alkylating **MVG** with chloromethyl methyl ether was another way to modify the allyl alcohol in **MVG**. Lebrasseur et al. also did an alkylation with chloromethyl methyl ether in 80 % yield in 2005.[154] It was possible to duplicate their synthesis, albeit at a lower yield. ^{1}H-NMR analysis yield with 1,3,5-trimethoxy benzene as reference showed 30 % yield. **MVG** was alkylated with excess chloromethyl methyl ether and di-*iso*-propylethylamine. It was possible to achieve 21 % isolated yield (0.057 grams). Chloromethyl methyl ether is a highly carcinogenic compound to work with and very reactive. In some of the initial experiments, it degraded a needle from which the nitrogen atmosphere was provided to keep the reaction inert. The degradation of this needle formed an undesired by-product difficult to separate from the desired compound. The by-product has a methylene methyl ether signal detectable in the ^{1}H-NMR spectrum, but the rest of the composition is not known. The carcinogenic issues with this reaction and the low yield meant that further research on this product was abandoned.

2.3.10 Methyl 2-(allyloxy)but-3-enoate



Scheme 2.14: Experiments to synthesise methyl 2-(allyloxy)but-3-enoate (**21**).

The difficulties in radical polymerisation of **MVG** led to the plan to allylate **MVG**. Adding another olefin in **MVG** might make the second olefin reactive towards radical polymerisation. Therefore, it was attempted to conduct allylation of **MVG**. The electrophiles tested for this reaction were the allyl halides allyl bromide and allyl chloride. Different solvents were tested, hoping a polar solvent would favour the transition state more. Solvents that were tested include THF, ethanol, methanol, and acetonitrile. Different bases were also tested to deprotonate **MVG** and make it react with an electrophile (allyl halide). The bases tested were *N*,*N*-di-*iso*-propylethylamine (DIPEA), sodium hydroxide, cesium carbonate, pyridine, calcium hydroxide, lithium bis(trimethylsilyl)amide (LiHDMS), and sodium hydride. Various temperatures were

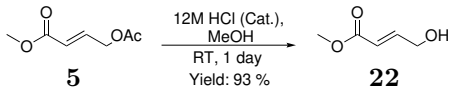
also tested, e.g. THF was refluxed in experiment 2, Table 2.8. It was also attempted to use higher temperatures than the refluxing temperature of THF using 150 °C in a microwave reactor in experiment 3 and 4, Table 2.8. The different allyl halide, solvent, base, and temperature combinations tested are listed in Table 2.8. All the experiments gave no conversion to the allylated **MVG**. The strongest base tested was sodium hydride in experiment 17 and 18, Table 2.8. In these experiments, bubbles were observed instantly when **MVG** was added to sodium hydride. This was presumably due to the formation of hydrogen gas. Gelation was also occurring in the reaction vial. It was presumed that some form of aldol reaction was occurring.[131] **MVG** can form the dimer maple furanone with sodium methoxide. In experiment 17 and 18 it is presumed that a longer chain is produced through an aldol reaction instead of a dimer product. The aldol pathway is described in the literature by Starch et al. in 1987.[131] The aldol reaction presumably occurs by deprotonating **MVG**, which then isomerises the double bond into a carbonyl group at the α position and an anion on the β position in regards to the ester functionality. This compound can then attack another α-keto-ester, thereby synthesising larger molecules.

Table 2.8: Experiments tested to allylate **MVG** with allyl halides allyl bromide and allyl chloride, with different solvents, temperatures and bases tested. The reactions were stirred overnight. Sodium hydride seems to catalyse the polymerisation of **MVG** with the release of hydrogen gas.

Ex.	Base	Electrophile	Solvent	Result
1	DIPEA	Allyl chloride	THF, RT	No conversion
2	DIPEA	Allyl chloride	THF (reflux)	No conversion
3	DIPEA	Allyl chloride	THF (MW 150 °C)[a]	No conversion
4	DIPEA	Allyl chloride	THF (MW 150 °C)[b]	No conversion
5	DIPEA	Allyl bromide	THF, RT	No conversion
6	NaOH	Allyl chloride	Ethanol (55°C)	Decomposition
7	Cs_2CO_3	Allyl chloride	THF, RT	No conversion
8	NaOH	Allyl bromide	Methanol (55°C)	No conversion
9	C_5H_5N	Allyl chloride	THF, RT	No conversion
10	C_5H_5N	Allyl chloride	CH_3CN, RT	No conversion
11	NaOH	Allyl chloride	THF, RT	No conversion
12	NaOH	Allyl chloride	CH_3CN, RT	No conversion
13	$Ca(OH)_2$	Allyl chloride	THF, RT	No conversion
14	$Ca(OH)_2$	Allyl chloride	CH_3CN, RT	No conversion
15	LiHMDS	Allyl chloride	THF, RT	No conversion
16	LiHMDS	Allyl chloride	CH_3CN, RT	No conversion
17	NaH	Allyl chloride	THF, RT	Polymerisation
18	NaH	-	Toluene, RT	Polymerisation
19	DIPEA	*tert*-Butyl chloride	THF, RT	No conversion
20	DIPEA	*tert*-Butyl bromide	THF, RT	No conversion

[a]Reaction stirred 15 minutes. [b]Reaction stirred 3 hours.

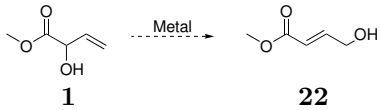
2.3.11 Methyl (*E*)-4-hydroxybut-2-enoate



Scheme 2.15: Compound **5** can be methanolysed with a catalytic amount of 12 M hydrochloric acid and methanol overnight to form methyl (*E*)-4-hydroxybut-2-enoate (**22**).

The methanolysis of **5** was achieved with a catalytic amount of 12 M hydrochloric and mixed in methanol and stirred overnight. 12 M Hydrochloric acid and methanol were evaporated, leaving the pure product methyl (*E*)-4-hydroxybut-2-enoate (**22**) in 93 % yield (0.064 grams). It is suspected that if the product is left under strong vacuum for too long, it will evaporate off. If the *cis* isomer of **5** is not removed before the methanolysis, it stays present and then forms the *cis* product of **22** in <5 %. Compound **22** was synthesised to show the feasibility of synthesising γ-butyrolactone (**23**), and 1,4-butanediol downstream. The compound **22** in itself was also an interesting monomer for applications in polymerisation.

2.3.12 Transposition of methyl vinyl glycolate



Scheme 2.16: Experiment for transposition of **MVG** to methyl (*E*)-4-hydroxybut-2-enoate (**22**).

It was achieved to synthesise **22** through acetylation of **MVG** and a subsequent allylic acetate rearrangement from the α-position to the γ-position and followed by methanolysis. This is three steps with an overall yield of 67 %. The three steps are time-consuming and the catalyst tetrakis(triphenylphosphine)palladium(0) is an expensive catalyst. It was attempted to test if this transformation could be achieved in one step with a better yield through an allylic transposition. In the literature transpositions of an allylic alcohols are known. This would offer the product methyl (*E*)-4-hydroxybut-2-enoate (**22**) in one step. Different catalysts have been published to achieve the transposition e.g. vanadium(IV)-oxy acetylacetonate, bis(acetylacetonato)-dioxomolybdenum(VI), trioxo(triphenylsilyloxy)rhenium(VII), dirhenium(VII) heptoxide.[155, 156, 157] All the catalysts did not convert **MVG** sufficiently to the desired target. Vanadium(IV)-oxy acetylacetonate (experiment 2, Table 2.9 with $(Me_3SiO)_2$) yielded a small conversion to methyl 2-oxobut-3-enoate (**2**) after one day. The catalyst $Ph_3SiOReO_3$ showed the same small conversion after two days (experiment 7, Table 2.9). The only catalyst that showed conversion to the desired product **22** was

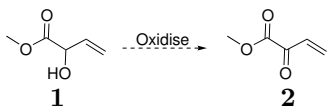
dirhenium(VII) heptoxide after eight days (experiment 10, Table 2.9). The conversion was very small, i.e. less than 4 % based on NMR analysis of the crude reaction mixture. Based on the data from the tests performed for allylic transposition of **MVG**, a viable pathway was not discovered and the synthesis of **22** on a larger scale was not altered from the three steps pathway that gave 67 % overall yield.

Table 2.9: Experiments for achieving transposition of **MVG** to methyl (*E*)-4-hydroxybut-2-enoate (**22**).

Ex.	Reagent	Solvent & temperature	Result
1	$C_{10}H_{14}O_5V^a$, $(Me_3SiO)_2$	CH_2Cl_2, RT	No conversion
2	$C_{10}H_{14}O_5V^a$, $(Me_3SiO)_2$	CH_2Cl_2, RT	Small conversion[g]
3	$C_{10}H_{14}O_5V^a$, $(Me_3SiO)_2$	CH_2Cl_2, MW 150 °C	Decomposition
4	$C_{10}H_{16}O_6Mo^b$, $(Me_3SiO)_2$	CH_2Cl_2, RT	No conversion
5	$C_{10}H_{16}O_6Mo^b$	CH_2Cl_2, RT	No conversion
6	$C_{10}H_{16}O_6Mo^b$	CH_2Cl_2, MW 150 °C	No conversion
7	$Ph_3SiOReO_3^c$	CH_2Cl_2, RT	Minimal conversion[g]
8	$Ph_3SiOReO_3^c$	CH_3CN, RT	No conversion
9	$Ph_3SiOReO_3^c$,[f]	Et_2O, 0 °C	No conversion
10	$Re_2O_7^d$	CH_2Cl_2, RT	Minimal conversion[e]

[a]Vanadium(IV)-oxy acetylacetonate. [b]Bis(acetylacetonato)dioxomolybdenum(VI). [c]Trioxo-(triphenylsilyloxy)rhenium(VII). [d]Dirhenium(VII) heptoxide. [e]Showed the desired conversion to **22** after eight days. [f]With trimethylsilyl (*E*)-*N*-(trimethylsilyl)acetimidate (BSA) & *N*-(trimethylsilyl)acetamide (TMSA). [g]Conversion to compound **2**.

2.3.13 Methyl 2-oxobut-3-enoate



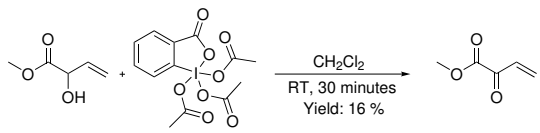
Scheme 2.17: **MVG** has a hydroxy group *alpha* to the ester group. This functionality can be oxidised with an oxidation agent to form an α-ketoester.

MVG has a α-hydroxy moiety. With an oxidation agent it should be possible to convert the hydroxy group into a carbonyl group, and transform **MVG** into an α-ketoester. Different oxidising agents were tested (Table 2.10), including manganese(IV)oxide, hydrogen peroxide, Burgess reagent, Parikh–Doering oxidation, Swern oxidation, and the Dess-Martin periodinane reagent. The Dess-Martin periodinane reagent successfully oxidised **MVG**, yielding the product methyl 2-oxobut-3-enoate (**2**) in 60 % yield based on ^{1}H-NMR analysis with an internal NMR standard. After purifying the product **2** the yield was only 16 %. The synthesis of **2** was achieved with **MVG** and a small excess of the Dess-Martin periodinane reagent in dichloromethane (Scheme 2.18). The reaction was finished after 30 minutes. If the reaction mixture was

not worked up immediately and was left to stir overnight the reagent would oxidise **MVG**, which then presumably would form a dimer and polymers. Two methods of purification were performed. One was **DCVC**, while the second method was a wash with a saturated sodium carbonate solution and then filtered through silica under reduced vacuum. The first method of purification seemed to give the best yield, however the method left some acetic acid, which was later discovered to be problematic for the stability of the product.

Table 2.10: Oxidation reagents tested to synthesise methyl 2-oxobut-3-enoate (**2**).

Ex.	Reagent	Solvent	Result
1	MnO_2	CH_2Cl_2	No conversion
2	H_2O_2	CH_2Cl_2	No conversion
3	Burgess Reagent	CH_2Cl_2/DMSO	No conversion
4	$C_5H_5NSO_3$, NEt_3	CH_2Cl_2/DMSO	No conversion
5	$(COCl)_2$, DMSO, NEt_3	CH_2Cl_2, 3 Å sieves	No conversion
6	Dess-Martin perodinane	CH_2Cl_2	Conversion to **2**

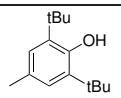
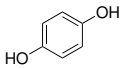
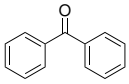


Scheme 2.18: Synthesis of methyl 2-oxobut-3-enoate (**2**).

The product **2** was very reactive. Removing all the solvent and keeping the product at room temperature made it prone to react in a hetero Diels Alder reaction. This was discovered over a long process. Initially, the compound was thought to polymerise as reported in the literature.[106] The initial experiments showed that **2** was not stable at room temperature. A ^{1}H-NMR spectrum of stored **2** was performed (Figure 2.5). New signals were appearing in the ^{1}H-NMR spectrum after one day at room temperature and increased over time (Red dots, Figure 2.5). After this discovery, multiple stabilising agents were tested with compound **2** in deuterated chloroform with the additives added. Compound **2** was mixed with antioxidants 2,6-di-*tert*-butyl-4-methylphenol (Ex. 1, Table 2.11) and hydroquinone (Ex. 2, Table 2.11), but both antioxidants did not stabilise **2**. Compound **2** was tested with a light stabiliser benzophenone (Ex. 3, Table 2.11), but this did not stabilise it either. An acid neutraliser aluminium oxide (Ex. 4, Table 2.11) was also added and tested, and this did not stabilise **2**. Compound **2** was stored in a freezer at - 18 °C to test if this would stabilise the product **2**. This gave a promising result and the method of storage was tested for sixteen days (Figure 2.6). At the beginning there was some of the undesired hetero Diels Alder product (marked with green dots, Figure 2.6). The product **2** was stable the first three days. Then in the analysis from day six to day eight, it started to show small formation of the hetero Diels Alder product, which at the time was assumed to be decomposition or polymerisation

(red dots, Figure 2.6). In the first eight days the formation of the new product was negligible. On day sixteen the new product was more noticeable. It was concluded that compound **2** would be stable for a week at - 18 °C. Another experiment was performed with storage of **2** at - 18 °C for ten days (Figure 2.7). This experiment verified that the compound would be stable and this batch seemed to be stable even longer with no new products being formed. After two days it seemed that the hetero Diels Alder product was starting to be formed (red dot, Figure 2.7), but when another spectrum was performed after ten days, this formation had stayed the same and negligible. Due to these observations the impact of removing acetic acid completely from product **2** was uncovered. The first test with sixteen days of storage of **2** had acetic acid present. The second test with ten days of storage had no acetic acid present. At this time it was discovered that if acetic acid was present, it seemed to catalyse the formation of the Diels Alder product. This underlines that the method for purification had to remove all the acetic acid. As a means of precaution, compound **2** was still stored in a freezer at - 18 °C if not used immediately after synthesis. It was attempted to find applications for **2**, and it was mixed with aniline to produce an imine (Ex. 1, Table 2.12). This resulted in decomposition. It was also mixed with *p*-toluenesulfonamide (Ex. 2, Table 2.12), but no reaction occurred. It was mixed with water (Ex. 3, Table 2.12), which had no effect and not even the hydrate could be detected. Furthermore, it was mixed with methanol (Ex. 1, Table 2.12), which seemed to result in a reaction based on NMR spectroscopy. It was surmised that the product being formed was methyl 2-hydroxy-4-methoxybut-2-enoate with a high degree of uncertainty of the stereomeric isomer. In the ^{1}H-NMR analysis there is a methoxy signal and one proton with a shift located where an olefin signal is expected to be located. The olefin signal has a triplet splitting. This proton has a neighbouring carbon with two protons that has a duplet splitting.
It was discovered that **2** could be used in a Diels Alder reaction, which is covered in chapter 4 (Diels Alder reactions). It was also interesting to test **2** in polymer applications, both in poly-condensation and radical polymerisation. The lack of stability of the monomer meant the product **2** was not produced in bulk quantities.

Table 2.11: Stability additives tested with **2**.

Ex.	Stabiliser	Property	Result
1		Antioxidant	No stabilisation
2		Antioxidant	No stabilisation
3		Light stabilisers	No stabilisation
4	Al_2O_3	Acid neutraliser	No stabilisation
5	Storage at - 18 °C	-	Stable short term

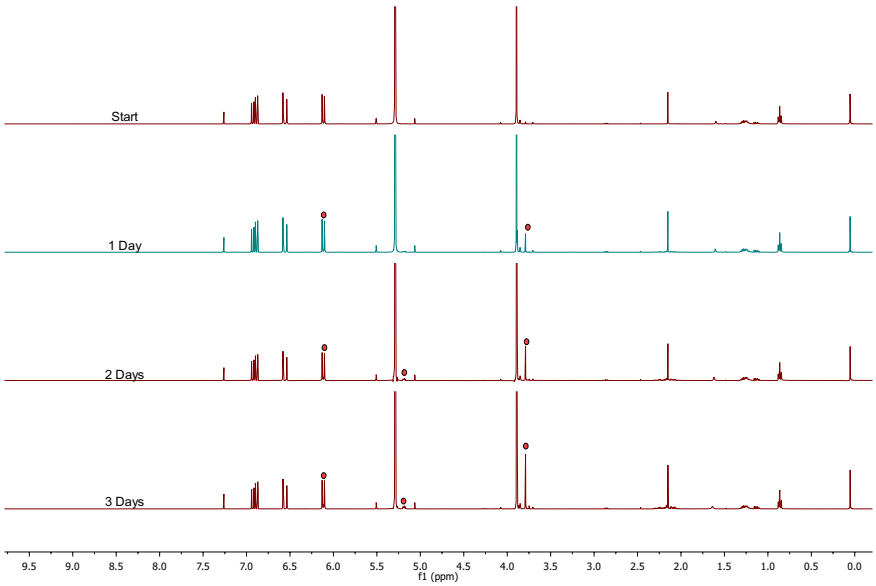


Figure 2.5: ^{1}H-NMR analysis on the stability of **2** in storage at 20 °C for three days.

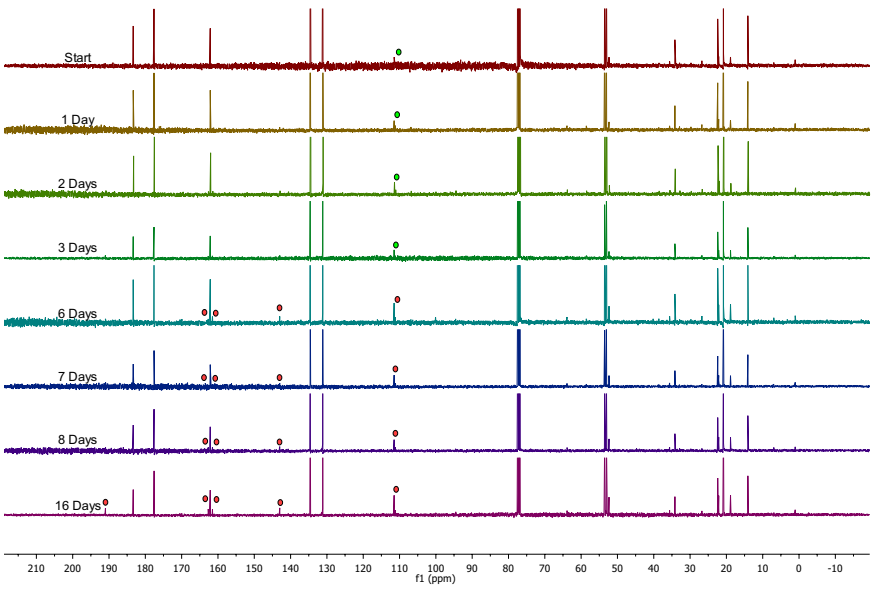


Figure 2.6: ^{13}C-NMR analysis on the stability of **2** in storage at - 18 °C for sixteen days.

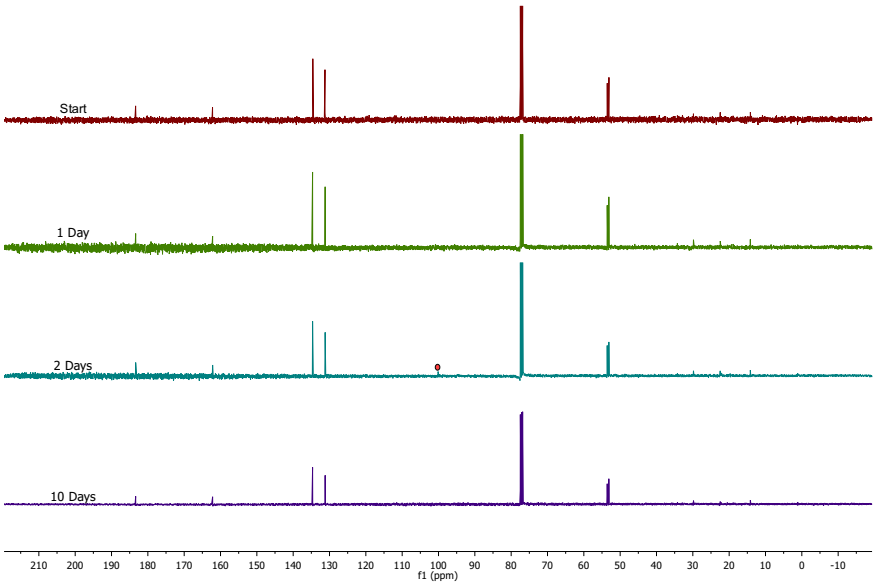
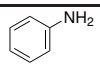
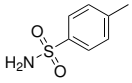
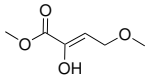


Figure 2.7: ^{13}C-NMR analysis on the stability of **2** in storage at - 18 °C for ten days.

Table 2.12: Compound **2** application experiments.

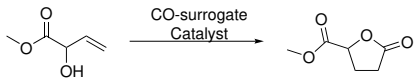
Ex.	Reactant	Result
1		Decomposition
2		No effect
3	H_2O	No effect
4	Methanol	

2.3.14 Methyl 5-oxotetrahydrofuran-2-carboxylate

Cyclo-carbonylation of **MVG** was a target, in order to yield methyl 5-oxotetrahydrofuran-2-carboxylate (**24**). In the literature, there are multiple ways to perform a carbonylation. Our laboratory was not setup with high pressure equipment, and it was therefore focussed initially on carbon monoxide surrogates for the carbonylation of **MVG**.[158, 159] The synthesis method described by Guatam et al. in 2017 with *N*-formylsaccharin as the carbon monoxide surrogate and 10 % Pd(0) on carbon as the catalyst was attempted to cyclo-carbonylate **MVG**.[160] The hydroformylation synthesis with catalyst $RhHCO(PPh_3)_3$ and formaldehyde as surrogate, a synthesis published by Ahn et al. in 1999, was investigated to synthesise **24**.[161] The synthesis path for hydroes-

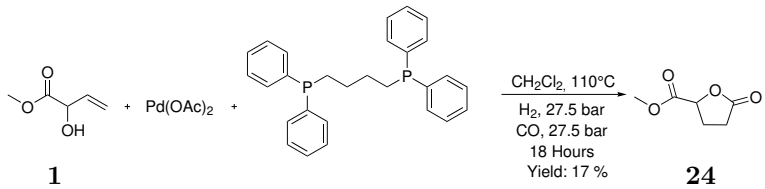
terification of **MVG** with phenyl formate as carbon monoxide source and $Pd(OAc)_2$ as the catalyst was attempted.[162] The synthesis of **24** with $Mo(CO)_6$ as the surrogate was tested with different palladium catalysts.[163,164,165] The synthesis of **24** with the catalysts $Pd(OAc)_2$ and $Rh(acac)(CO)_2$ were attempted with *para*-formaldehyde as surrogate, based on the work performed by Liu et al., in 2015.[166] All the experiments were performed by B.Sc. E. S. Grønkjær at atmospheric pressure, but did not yield the desired result. The experiments did not give the desired conversion and when the temperature in the reactions were raised to provide more energy to the system, it resulted in decomposition of the starting material. An overview of the experiments and results can be seen in Table 2.13.

Table 2.13: Experiments tested to achieve a cyclocarbonylation of **MVG** to methyl 5-oxotetrahydrofuran-2-carboxylate (**24**). All experiments were performed at atmospheric pressure. Different temperatures were tested.[150]



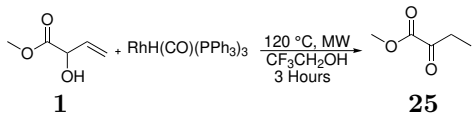
Ex.	CO Surrogate	Catalyst	Result
1	Phenyl formate	$Pd(OAc)_2$	Decomposition
2	$Mo(CO)_6$	Pd/C 10 %	Decomposition
3	$Mo(CO)_6$	$Pd(OAc)_2$	Decomposition
4	*para*-Formaldehyde	$Pd(OAc)_2$	No Conversion
5	*para*-Formaldehyde	$Rh(acac)(CO)_2$	Decomposition
6	*para*-Formaldehyde	$RhHCO(PPh_3)_3$	Decomposition
7	$Mo(CO)_6$	$Pd(OAc)_2$	Reduction of the double bond
8	*N*-Formylsaccharine	Pd/C 10 %	Decomposition

A final attempt to perform the cyclocarbonylation of **MVG** was conducted with a high pressure of carbon monoxide. This approach was based on the work by Brunner et al.[167] in 1997 using 27.5 bar of carbon monoxide and 27.5 bar of hydrogen in an autoclave with the catalyst palladium(II)acetate and the ligand 1,4-bis(diphenylphosphino)-butane (**dppb**) in dichloromethane. These conditions gave the desired product in 17 % yield (29 milligram) (Scheme 2.19). The impurities identified in the reaction were propionaldehyde, and a reduction of the double bond in **MVG**. The impurities were removed through **DCVC** with a 10 % gradient of heptane to ethyl acetate. With this promising result of a possible cyclo-carbonylation of **MVG**, the project was handed over to a PostDoc, who joined the project to perform further analysis on the reaction and to improve the yield.



Scheme 2.19: **MVG** can undergo a cyclo-carbonylation under high pressure of carbon monoxide (27.5 bar) and hydrogen (27.5 bar) with the catalyst palladium(II)acetate and ligand 1,4-bis(diphenylphosphino)butane (**dppb**) in dichloromethane to yield the product methyl 5-oxotetrahydrofuran-2-carboxylate (**24**).[167]

2.3.15 Methyl 2-oxobutanoate



Scheme 2.20: **MVG** can undergo isomerisation from an allylic alcohol to a carbonyl compound with $RhH(CO)(PPh_3)_3$ to form methyl 2-oxobutanoate (**25**). The reaction was performed in trifluoroethanol at a 120 °C in a microwave reactor for three hours.

An allylic alcohol can be converted to a carbonyl compound with a transition metal (Scheme 2.20). Diiron nonacarbonyl ($Fe_2(CO)_9$) was tested as a catalyst for the isomerisation of **MVG** to methyl 2-oxobutanoate (**25**).[168] The iron catalyst did not result in the desired isomerisation, since **MVG** was not converted. Tris(triphenylphosphine)-rhodium carbonyl hydride ($RhH(CO)(PPh_3)_3$) is also known to catalyse this form of isomerisation, with 0.01 equivalents of the catalyst $RhH(CO)(PPh_3)_3$ in trifluoroethanol (**TFE**) at 120 °C in a mirowave reactor. The conversion of **MVG** to **25** was detected in a ^{1}H-NMR analysis of the crude reaction mixture. Based on the ^{1}H-NMR analysis, it seems one of the undesired by-products is the reduction of the double bond, leaving the hydroxy group untouched and resulting in methyl 2-hydroxybutanoate (Figure 2.8).[169] By adding more of the catalyst up to 0.05 equivalents, the desired product formation was favoured in the conversion of **MVG**. Other solvents than trifluoroethanol were also tested. Toluene as a solvent allowed conversion of **MVG**, but with a low level of conversion. The best yield obtained and determined by ^{1}H-NMR analysis with 1,3,5-trimethoxy benzene as reference was roughly 60 % in **TFE** (Figure 2.8). Experiments to purify the product were performed. They showed that if a more viable synthesis pathway was uncovered and scaled up, the product could be purified and isolated through distillation. The synthesis method requires an expensive solvent and catalyst. The price for the product **25** (November 2018 from Sigma-Aldrich) is around 700 € for 500 grams i.e. 1.4 € per gram. The synthesis pathway from **MVG** is not competitive with the price. The lack of competitiveness of our synthesis pathway meant the at-

tempts to synthesise the target was discontinued. Unless a viable work-up method of **25**, and a cheaper catalyst could be discovered, it would be too expensive to synthesise **25** from this path. The synthesis of **25** was mainly performed to investigate possible downstream products.

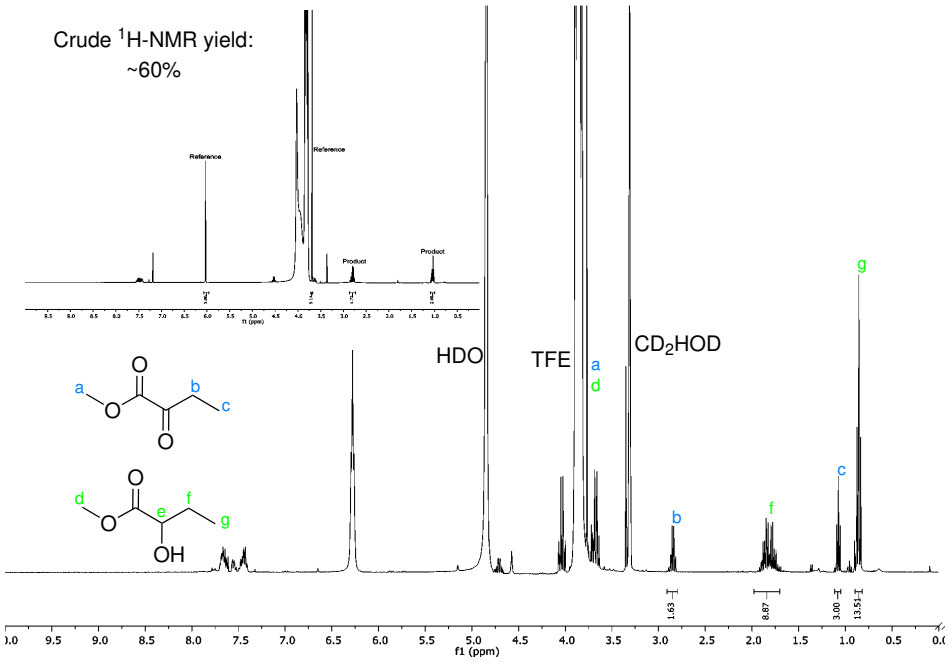
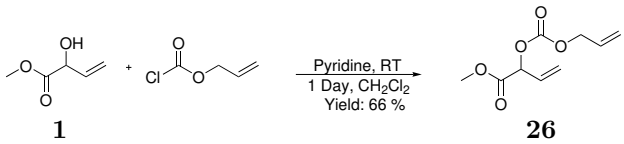


Figure 2.8: The ^{1}H-NMR analysis spectrum of the crude reaction mixture shows roughly 60 % yield of the desired isomerisation of **MVG** to methyl 2-oxobutanoate (**25**). The NMR reference used was 1,3,5-trimethoxy benzene. A by-product of the reaction is methyl 2-hydroxybutanoate (green: d, e, f, & g). The product is **25** and is shown in blue (a, b, & c).

2.3.16 Methyl 2-(((allyloxy)carbonyl)oxy)but-3-enoate

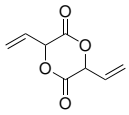


Scheme 2.21: Synthesis of methyl 2-(((allyloxy)carbonyl)oxy)but-3-enoate (**26**).

It was attempted again to add an olefin to **MVG**. This had been problematic

with an allyl electrophile, but **MVG** can be reacted with allyl chloroformate in a solution with pyridine and with dichloromethane as the solvent to synthesise methyl 2-(((allyloxy)carbonyl)oxy)but-3-enoate (**26**) (Scheme 2.21). The product can be purified by washing with 2 M hydrochloric acid and with a solution saturated with sodium carbonate, prior to being distilled to yield a pure product **26** in 66 % yield (11.36 grams). Compound **26** has one more olefin than **MVG**, which might make **26** more reactive in radical polymerisation. Product **26** was synthesised in 10 gram scale.

2.3.17 3,6-Divinyl-1,4-dioxane-2,5-dione

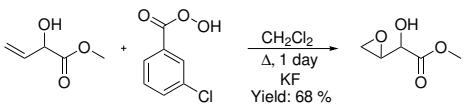


27

Figure 2.9: Lactide of **MVG** (**27**). The lactide is a dimer of **MVG**.

It was a target to synthesise the lactide of **MVG** (Figure 2.9). The lactide of lactic acid is used for polymerisation to prepare **PLA**. The lactide of **MVG** might react similar to the lactic acid lactide when used in polymerisation. The synthesis of this compound has been published in 2015 by Dusselier et al.[129] It was attempted to synthesise the lactide with tin(II) 2-ethylhexanoate, tin(IV) oxide, formic acid, H-beta Si/Al 12.5, sulphuric acid, hydrochloric acid, thionyl chloride, *para*-toluenesulfonic acid, amberlyst 15, and sodium methoxide. Set-ups where methanol could be removed from the reaction mixture were tested. The tests proved unsuccessful. The synthesis of the lactide was not achieved. The project was stopped because of the discouraging results and the lack of a novel pathway to produce bulk quantities of **27**.

2.3.18 Methyl 2-hydroxy-2-(oxiran-2-yl)acetate



1 **28**

Figure 2.10: **MVG** was epoxidated to methyl 2-hydroxy-2-(oxiran-2-yl)acetate (**28**) with *m*-CPBA. The purification was performed by precipitation of the by-product *m*-chlorobenzoic acid and the reactant *m*-CPBA with potassium fluoride and filtering it off.

The project involved B.Sc. student E. H. Kristiansen, who had some success in epoxidating **MVG**, but with no definitive result or purification method.[170] **MVG** was epoxidated with *m*-CPBA by stirring overnight under reflux conditions (Figure 2.10).

1,3,5 Trimethoxybenzene was added as a reference to the mixture in an equimolar amount to **MVG**, and then an NMR analysis was performed. The NMR sample showed that there was a 100 % conversion of **MVG** to the epoxidated methyl 2-hydroxy-2-(oxiran-2-yl)acetate (**28**). The reaction was performed with excess *m*-CPBA and *m*-chlorobenzoic acid was produced. Removal of the by-products was attempted by washing the mixture with an acid solution. There was a problem with the stability of **28**, once it was subjected to the acidic solution. The solution used to wash away the by-products, was therefore omitted. The next purification method tested was a column, but **DCVC** did not purify the epoxide.[171] It was suspected that the product oxiran group was opened and created new mixtures of undesired products. A 2D TLC plate was performed. This experiment yielded multiple spots, further supporting that compound **28** might not be feasible to purify via a column with silica. Purifying **28** via a column was then discarded. The last traditional purification method tested was a distillation. A clean NMR sample was produced from a small amount of the product condensed on a cold finger under vacuum and heating the mixture 5-10 °C above room temperature. When a distillation of a larger quantity of **28** was tested, inferior results were obtained compared to condensation on the cold finger, leading to excess of by-products and discolouration. The product **28** was reacting with itself, and purifying via distillation was abandoned. In an article from 1994, the by-product *m*-chlorobenzoic acid and the reactant *m*-CPBA were precipitated as a complex with potassium fluoride.[172] This purification method yielded an acceptable purity of **28** after repetitive precipitations, and the undesired by-products could be removed. The precipitation of the undesired by-products required pure *m*-CPBA. This was achieved following the procedure published in 1998 by Aggarwal et al.[173]
The epoxidation with *m*-CPBA is not stereoselective. The starting **MVG** is a racemic mixture and the enantiomers leads to a mixture of diastereomers and enantiomers (Figure 2.11). Based on ^{1}H-NMR analysis the diastereomeric distribution was 40/60. Diastereomers were not separated, and therefore it is not known which diastereomer is predominant. A crystal of a pure diastereomer was not possible to produce for determining the configuration. The pure epoxidated compounds could also not be purchased as references for determining the distribution of the diastereomers via GC analysis. The determination of the diastereomer distribution and use of the compound was also complicated by the stability of **28**. When the compound was left at room temperature for more than one day, it started to discolour from a clear liquid to a yellowish brown oil. It was discovered that this discolouring was due to decomposition, possible in a ring-opening polymerisation. The product **28** has to be stored at low temperature. A sample was stored in the freezer at -18 °C for 3 months and 26 days. The stability was then analysed by NMR spectroscopy, which showed it was stable during that period of time (Figure 2.12). It was also attempted to find other ways to prepare the epoxide of **MVG**. It was tested to synthesise **28** with TS-1 and hydrogen peroxide in dichloromethane.[174] This gave some of the desired product. The conversion although was less than 100 %. To deliver a pure compound **28** via this synthesis method would require purification. Given that previous trials had shown difficulties when purifying **28**, this synthesis method was abandoned. Vanadium(IV)-oxy acetylacetonate with *tert*-butyl hydroperoxide in dichloromethane was also tested with no epoxidation of **MVG**. A Sharpless epoxidation was also examined.[175] This method also did not epoxidate **MVG**, presumably because of the olefin in **MVG** is located terminally. The

Sharpless method is not reactive enough to epoxidate the terminal olefin with the conditions used. Compound **28** has been synthesised through a different pathway in 1991 by Tolstikov et al. The NMR spectroscopy data from this publication was used as a reference to verify the correct product.[176] The data in the literature do not provide any information on the stereoisomers (the publication is in Russian). The yield for the synthesis and isolation of **28** was moderate at 68 % yield (0.862 grams). Product **28** was produced in 20 grams. Compound **28** has an ester functionality and an epoxide that can be used in polymerisation. The epoxide group can ring-open with another nucleophile in a ring-opening polymerisation. Compound **28** needs to be further analysed to determine the distribution of the diastereomers from the epoxidation of **MVG**. Ph.D. students I. Tosi and S.G. Elliot from the Cat2BioChem project performed a test on **28** at their external stay with our collaborators at Perstorp AB. This test showed **28** has potential in UV curing of blends. They were able to produce a film with desirable properties, which is worthwhile of further investigation.

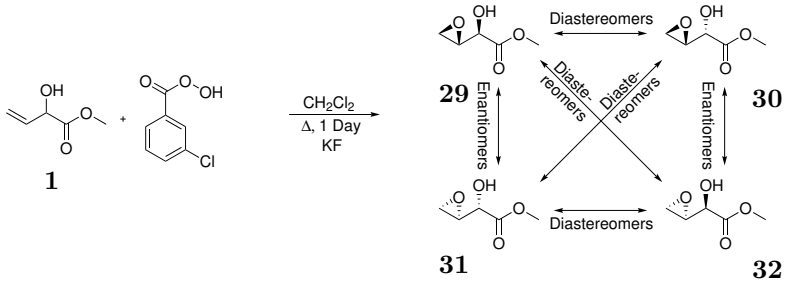


Figure 2.11: **MVG** was epoxidated to methyl 2-hydroxy-2-(oxiran-2-yl)acetate (**28**) with *m*-CPBA. The reaction yielded different stereoisomers. **MVG** is a racemic mixture and yielded methyl (*R*)-2-hydroxy-2-((*S*)-oxiran-2-yl)acetate (**29**), methyl (*S*)-2-hydroxy-2-((*S*)-oxiran-2-yl)acetate (**30**), methyl (*S*)-2-hydroxy-2-((*R*)-oxiran-2-yl)acetate (**31**) and methyl (*R*)-2-hydroxy-2-((*R*)-oxiran-2-yl)acetate (**32**).

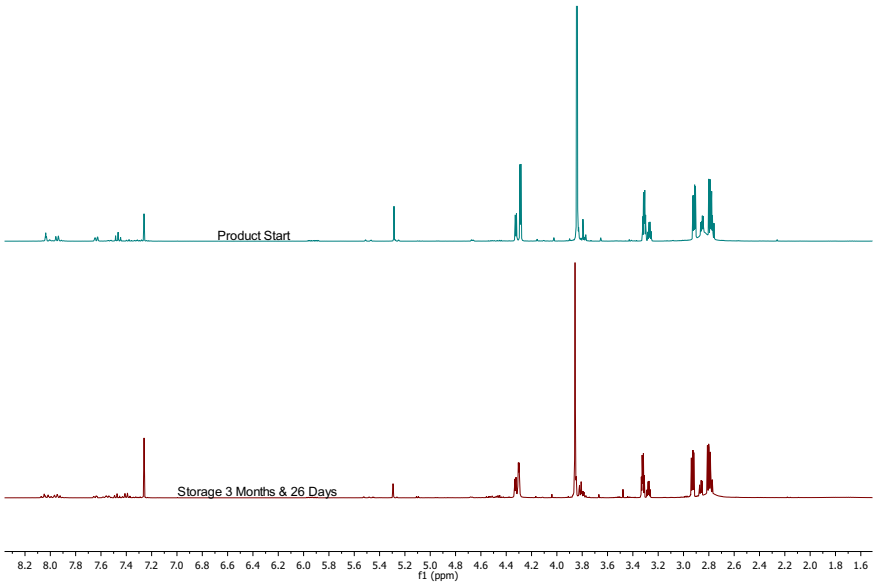
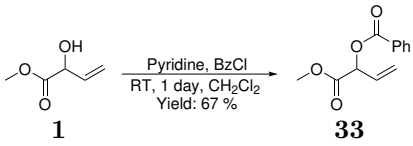


Figure 2.12: Methyl 2-hydroxy-2-(oxiran-2-yl)acetate (**28**) was stored for 3 months and 26 days in a freezer at -18 °C. The product was analysed by NMR spectroscopy, and the ^{1}H-NMR spectra are stacked.

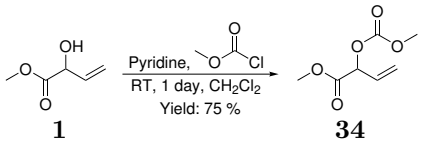
2.3.19 1-Methoxy-1-oxobut-3-en-2-yl benzoate



Scheme 2.22: Synthesis of 1-methoxy-1-oxobut-3-en-2-yl benzoate (**33**) by benzoylating **MVG** (**1**) with benzoyl chloride using pyridine as the base and dichloromethane as the solvent.

Benzoyl chloride can be reacted with **MVG** in the presence of pyridine as the base and dichloromethane as the solvent to synthesise 1-methoxy-1-oxobut-3-en-2-yl benzoate (**33**). The mixture was purified by quenching the reaction with 3-(dimethylamino)-1-propylamine and washing with a solution saturated with sodium carbonate.[177] The reaction was then further purified by **DCVC** resulting in a pure compound with an overall yield of 67 % (1.255 grams). If the solution was not quenched by 3-(dimethylamino)-1-propylamine, it was difficult to purify. This compound was synthesised to perform an allylic rearrangement.

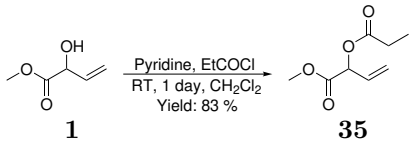
2.3.20 Methyl 2-((methoxycarbonyl)oxy)but-3-enoate



Scheme 2.23: Synthesis of methyl 2-((methoxycarbonyl)oxy)but-3-enoate (**34**).

MVG can be reacted with methyl chloroformate with pyridine present and dichloromethane as a solvent to synthesise methyl 2-((methoxycarbonyl)oxy)but-3-enoate (**34**) (Scheme 2.23). The product can be purified, first by washing with 1 M hydrochloric acid and a solution saturated with sodium carbonate, then by **DCVC** or distillation. The highest yield was obtained with distillation and was 75 % (11.22 grams). Product **34** was synthesised for testing in an allylic rearrangement. Product **34** was also an altered allylic alcohol worth testing in polymer applications. Such as **34** in radical polymerisation through the olefin. The product **34** was produced in 10 grams.

2.3.21 Methyl 2-(propionyloxy)but-3-enoate

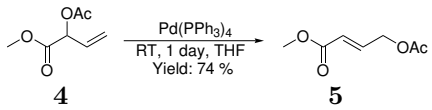


Scheme 2.24: Synthesis of methyl 2-(propionyloxy)but-3-enoate (**35**).

MVG can be reacted with propanoyl chloride with pyridine present and dichloromethane as a solvent to synthesise methyl 2-(propionyloxy)but-3-enoate (**35**) (Scheme 2.24). The product can be purified through a simple wash with 2 M hydrochloric acid and a solution saturated with sodium carbonate. Compound **35** was synthesised to be tested in an allylic rearrangement and for a mechanistic study. The best yield was 83 % (1.228 grams).

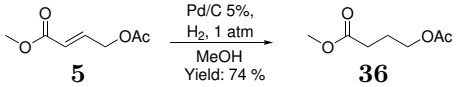
2.3.22 Methyl (*E*)-4-acetoxybut-2-enoate

Compound **4** can be rearranged through a palladium allyl complex. It was attempted to synthesise this in bulk quantities for testing in polymer applications and to perform further modifications to synthesise γ-butyrolactone downstream. The rearrangement was achieved in THF at room temperature with tetrakistriphenylphosphine palladium(0) (Scheme 2.25). The purification was performed through **DCVC** to yield the product **5** in 74 % (1.761 grams). The product **5** was produced in 10 grams.



Scheme 2.25: Synthesis of methyl (E)-4-acetoxybut-2-enoate (**5**).

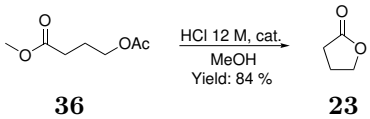
2.3.23 Methyl 4-acetoxybutanoate



Scheme 2.26: Synthesis of methyl 4-acetoxybutanoate (**36**).

It was attempted to synthesise methyl 4-acetoxybutanoate (**36**) in order to react **36** further to γ-butyrolactone. The synthesis of **36** was straightforward. Compound **5** was mixed with palladium 5 % on carbon in methanol. Hydrogen was supplied by two balloons filled with the gas. One balloon of hydrogen was bubbled through the reaction mixture (Scheme 2.26). A second balloon of hydrogen was then attached and the reaction was stirred overnight. The catalyst was then filtered off and the solvent was removed to produce a pure compound in 74 % yield (0.151 grams).

2.3.24 γ-Butyrolactone



Scheme 2.27: Synthesis of γ-butyrolactone (**23**).

The feasibility of synthesising γ-butyrolactone (**23**) from **MVG** was attempted. The product was synthesised with **36** mixed with methanol and a catalytic amount of concentrated hydrochloric acid (Scheme 2.27). The product **23** was purified by evaporating the solvent and the catalyst to give the product in 84 % yield (0.061 grams). Product **23** had small impurities from the open form methyl 4-hydroxybutanoate. Product **23** can be produced from **MVG**, but requires four steps and an expensive metal catalyst. To produce **23** in bulk quantities, a cheaper catalyst with a better yield needs to be uncovered.

2.3.25 Synthesis and purification (*E*)-2,5-dihydroxy-3-pentenoic acid methyl ester and methyl (*E*)-2,5,6-trihydroxyhex-3-enoate

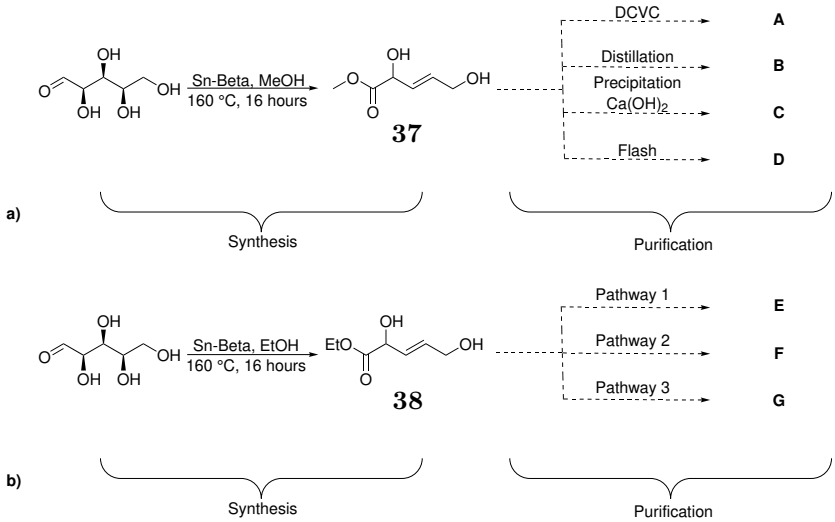


Figure 2.13: a) Compound **37** was synthesised from xylose and a Sn-beta catalyst at 160 °C with methanol as the solvent in an autoclave for sixteen hours.[178] Four pathways to purify larger quantities than a few milligrams were tested: **DCVC** (A), distillation (B), precipitation with $Ca(OH)_2$ (C) and flash column chromatography (D). b) DPE **38** was synthesised with xylose and a Sn-beta catalyst at 160 °C with ethanol as the solvent in an autoclave for sixteen hours. Compound **38** was synthesised to see if it was easier to purify. Three purification pathways were tested with multiple steps: Pathway one (E), three distillations followed by an automated column with a Combi Flash. Pathway two (F), kugelrohr distillation, two distillations followed by an automated column with a Combi Flash. Pathway three (G), one distillation.

(*E*)-2,5-Dihydroxy-3-pentenoic acid methyl ester (**DPM**) (**37**) was synthesised with xylose and a Sn-beta catalyst at 160 °C with methanol as the solvent in an autoclave for 16 hours cf. the published work in 2017 by Elliot et al.[178] Four pathways to purify larger quantities than a few milligrams were tested (Figure 2.13): **DCVC** (A), distillation (B), precipitation with $Ca(OH)_2$ (C), and flash column chromatography (D).
The compound **37** was supplied by Haldor Topsøe A/S, 85 % pure in a methanol solution. Haldor Topsøe had already attempted to purify this compound through a combination of distillation and columns. The task was to try improve the NMR purity up to 95 %. First, it was attempted to purify the compound through **DCVC** (A), but the impurities had a similar retention time as **37**. Therefore, a distillation was attempted instead of **DCVC**. This attempt presented the same issue. The product was difficult to separate from the impurities. It was therefore attempted to precipitate the product as the calcium salt by hydrolysing **DPM** with $Ca(OH)_2$ (C). The product

was not successfully precipitated. The purification method was switched to a flash column where the column was loaded and the product was flushed through the column with a 50/50 mixture of ethyl acetate/heptane, which made **37** run slowly through the column in multiple fractions. From these fractions, the middle fractions were isolated and the solvent was evaporated. This gave a pure product, but with an unsatisfactory yield. The column was performed using around 2 grams of **DPM**. From the middle fractions, around 500 milligrams of pure compound **37** were isolated, i.e. more than 75 % was lost. The ^{1}H-NMR spectrum of the isolated compound is shown in Figure 2.14. In collaboration with S. G. Elliot, it was tested to switch the solvent in the synthesis of **37** from methanol to ethanol. This produces the product ethyl (*E*)-2,5-dihydroxypent-3-enoate (**DPE**) (**38**) instead of **37**. Compound **38** has an ethyl ester instead of **37**'s methylester. The idea was to test if this product would be easier purified in a work-up process. Three purification pathways were tested with multiple steps: In the first pathway (E) (Figure 2.13) **38** was purified through three distillations followed by an automated column with a Combi Flash. This gave an acceptable purity analysed by NMR spectroscopy. The overall isolated yield was 600 milligrams, which corresponded to a 2 % yield from the overall reaction. The second pathway (F) (Figure 2.13) used one kugelrohr distillation and two distillations with a vigreux column, which gave 2.6 grams, 8 % yield, but with an unsatisfactory purity. The mixture was therefore purified through an automated Combi Flash, which yielded the desired purity with 760 milligrams, 2 % yield. This the same result as the first pathway. The third pathway (G) (Figure 2.13) was one distillation. The outcome after one single distillation was $<$ 15 % yield (5 grams), but the NMR analysis showed an unacceptable purity.
Thus, Compound **38** could be purified, but with a low overall yield. The research indicated the synthesis of **37** and **38** in bulk is too expensive to be feasible to produce for the market with the current methods used, including the applied purification methods. It was briefly also tested to produce methyl (*E*)-2,5,6-trihydroxyhex-3-enoate. This product had the same impurity issues as **37**. Because of the encountered issues during purification of **37** the project was discontinued.

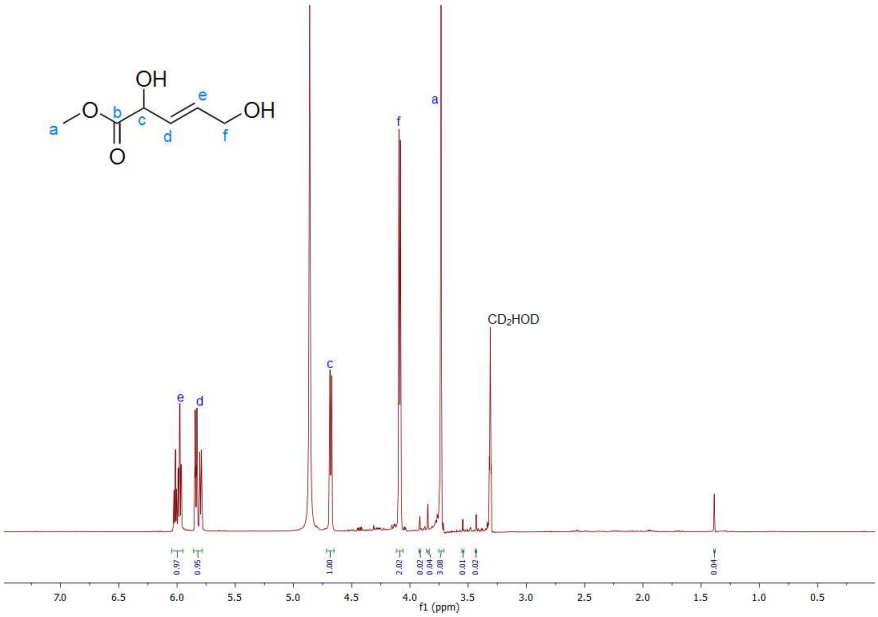


Figure 2.14: ^{1}H-NMR of purified (*E*)-2,5-dihydroxy-3-pentenoic acid methyl ester (**37**).

2.3.26 Reduction of (*E*)-2,5-dihydroxy-3-pentenoic acid methyl ester and methyl (*E*)-2,5,6-trihydroxyhex-3-enoate

Methyl 2,5-dihydroxypentanoate or the ring-closed lactone 3-hydroxytetrahydro-2*H*-pyran-2-one were targets in the project, but due to the problem with purifying **37** there was no large supply of **37** as reactant to perform the synthesis. Only a small amount of **37** was obtained, where it was attempted to reduce the olefin. The initial result showed that the reaction did not proceed quantitatively as hoped, indicating that there would be further purification problems similar to the ones encountered during the synthesis of **37**, which would require a large amount of the reactant to produce enough product for the purification. The ^{1}H-NMR analysis also showed that reducing the olefin in **37** gives the open linear form methyl 2,5-dihydroxypentanoate and not the ring-closed form 3-hydroxytetrahydro-2*H*-pyran-2-one, substantiated by a methyl ester signal visible in the NMR analysis.
It was further attempted to synthesise **37** and the subsequent reduction of the olefin without any purification between the two reactions. This approach yielded a brown mixture which was subjected to a distillation attempt. The main isolated fraction from the distillation showed multiple signals of impurities in the NMR spectra, which indicated that there would be issues when isolating the desired product (Figure 2.15). Synthesising the target methyl 2,5-dihydroxypentanoate (**39**) was therefore abandoned.

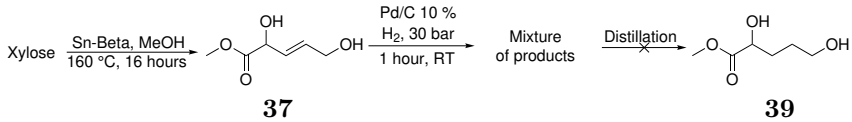
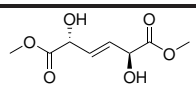
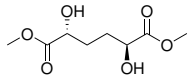


Figure 2.15: Direct synthesis of methyl 2,5-dihydroxypentanoate (**39**) without any work-up steps. The synthesis was performed with xylose and with a Sn-beta catalyst yielding **37**. The mixture was filtered and palladium 5 % on carbon was added to the solution. The mixture was then pressurised with hydrogen and stirred overnight to form **39**.

2.4 Summary

A wide array of molecules (Table 2.14) from **MVG** were successfully synthesised. Entries 1 and 2 are possible substitute for adipate moieties. They can be incorporated in poly-condensation and have hydroxy functional groups for branching in a polymer. Entry 1 can also be used for cross-linking via the double bond. Entry 3 can be used as a center of a polymer to branch out as a dendrimer. Entry 4 is also a substitute for adipate moieties, but without the hydroxy groups. Entries 5-9 and 16-18 are modified **MVG** moieties with alteration at the α-hydroxy group to change the reactivity of the olefin. These compounds were synthesised to test in radical reactions via the olefin. Entries 10 and 11 are interesting in both poly-condensation and radical polymerisation. Entry 11 has further shown to be capable of a cyclo-addition. Entry 12 is interesting in ring-opening polymerisation. When the ring is opened there is also a hydroxy group that can be used as a functional group for branching. Entry 13 can be used in poly-condensation, but was synthesised to make a enantiomerically pure α-hydroxy product in a subsequent step. This was never realised. Entry 14 was synthesised for radical polymerisation by introducing a new olefin into the **MVG** moiety. Entry 15 might be used in ring-opening polymerisation through the epoxide. Entry 19 might have possibilities in radical polymerisation and after methanolysis it might further be used in poly-condensation. Entry 20 was a synthesis step to synthesise γ-butyrolactone and might be used for the same applications as γ-butyrolactone in polymerisation. Entry 21, γ-butyrolactone is a bulk chemical that already is used for ring-opening polymerisation. Some of the synthesis paths uncovered were used to produce products on a larger scale. A larger portion of the compounds listed in Table 2.15 were synthesised. These chemicals were shipped to our collaborators at Perstorp AB for further testing.

Table 2.14: Synthesis yield and scale of modified **MVG**.

Entry	Product	Scale [mmol]	Yield[a] [%]
1		173	87
2		30.28	98

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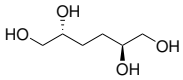
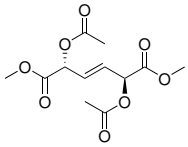
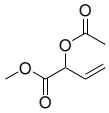
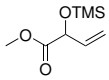
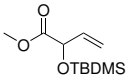
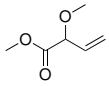
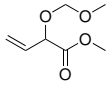
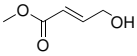
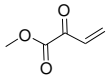
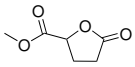
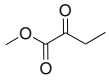
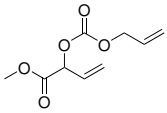
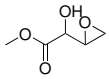
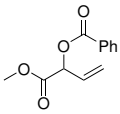
Entry	Product	Scale [mmol]	Yield[a] [%]
3		2.12	10
4		2.51	67
5		85.98	97
6		17.22	39
7		4.38	51
8		6.54	49
9		1.72	21
10		0.59	93
11		4.76	16[b]
12		1.15	17
13		0.47	60[c]
14		85.83	66
15		13.06	68
16		8.51	67

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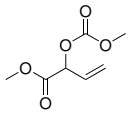
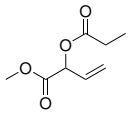
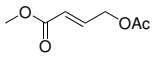
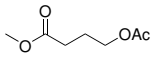
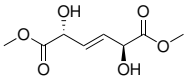
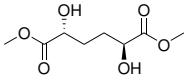
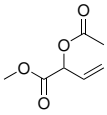
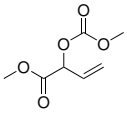
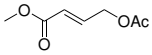
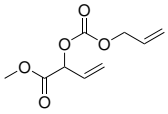
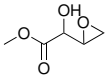
Entry	Product	Scale [mmol]	Yield[a] [%]
17		87.96	75
18		8.59	83
19		14.96	74
20		1.27	74
21		0.84	84

[a]Isolated yields. [b]Analysed yield with ^{1}H-NMR. [c]Crude mixture analysis with ^{1}H-NMR yield, the product was not isolated.

Table 2.15: Compounds synthesised on a larger scale and delivered to our collaborators for further testing.

Product	Scale [grams]
	110
	10
	100
	10
	10
	10
	20

CHAPTER 3

Allylic acetate rearrangement

3.1 Introduction

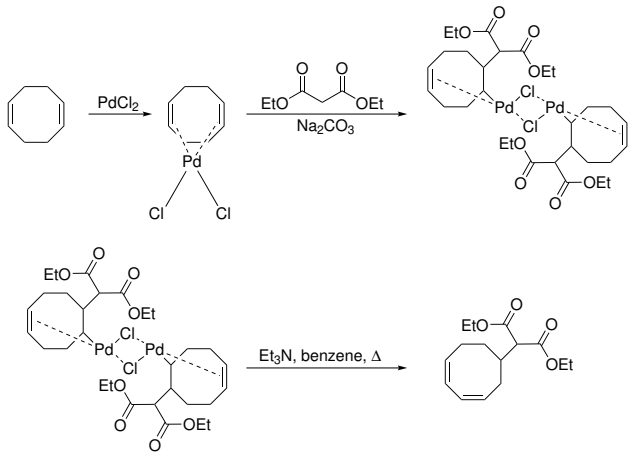
Palladium is an element in the periodic table with the atom number 46. It is a transition metal in group VIII B. The discovery of palladium involved a long discussion. There was a debate regarding whether palladium was an alloy or a pure element. R. Chenevix was the chemist that claimed it was an alloy and not an element based on his research. His steadfast claim would ruin his career in chemistry. The other chemist in the debate was W.H. Wollaston. The dispute between the two prominent chemists ended when W.H. Wollaston in 1805 presented his research paper, that he had published, to the Royal Chemical Society. The paper described the various tests applied to palladium, which proved that it was a metal. It was believed by R. Chenevix to be an alloy of mercury and platinum, but W.H. Wollaston could not obtain these metals from pure palladium and ended the debate.[179, 180]

Since the discovery of the pure element, many applications for palladium have been discovered. Palladium has unique properties in organic synthesis as a catalyst in transformations of compounds often at mild temperatures. One of the noteworthy use of palladium is in coupling chemistry. The Nobel Prize in 2010 was awarded for this research and discovery and the laureates were Negishi, Suzuki, and Heck.[181, 182] Their chemistry introduces a way to make new carbon-carbon bonds. Palladium also has numerous other applications. The element can also facilitate carbon-carbon bond formations through a palladium allyl complex. This complex has hence proven a very powerful tool in organic synthetic chemistry.

Palladium allyl complex

The first palladium allyl complex published was by Slade and Jonassen in 1957. A palladium(II) complex with an allyl ligand was synthesised by mixing benzonitrile palladous chloride with a stream of butadiene added to the mixture. This turned the starting colour of the complex from red to yellow, producing the complex tetrachloro-μ-bis-(butadiene)-dipalladium(II).[183] The allyl complex was further substantiated by Smidt et al. in 1962, where ethylene was complexed to palladium(II) chloride and reacted with hydroxide, oxidating the olefin to the corresponding aldehyde ethanal.[184] With this knowledge, Tsuji and Takahashi published the carbon-carbon formation via a palladium(II) allyl complex in 1965.[148, 185] Tsuji and Takahashi synthesised a new complex from the 1,5-cyclooctadiene-palladium chloride complex with an excess of ethyl malonate in the presence of a base (sodium carbonate) at room temperature. This formed the new white complex μ,μ-dichlorobis(8-di(ethoxycarbonyl)methyl-4-cyclooctenyl)dipalladium. Decomposition of this compound was possible with a weak base, e.g. triethylamine in boiling benzene and led to the formation of diethyl 3,5-cyclooctadienylmalonate (Scheme 3.1). The reaction needs stoichiometric amounts of palladium(II) chloride to occur, which is a waste of palladium compared to a catalytic conversion. The active species in the formation of the palladium allyl complex in the reaction is palladium(0), which is generated in situ. The catalytic version was discovered later. Palladium(II) is reduced to palladium(0) before the formation of the complex occurs. This type of reaction is known as a classical Tsuji-Trost type reaction.[186]

Trost and Fullerton introduced the use of phosphor ligands in 1973.[149] It was later shown that a Tsuji-Trost type reaction can be achieved with reactants such as allylic arylethers, esters, aryls, and alcohols in substitution reactions with a suitable catalyst. Various palladium catalysts are able to catalyse the reaction, including palladium(II)acetate with triphenylphosphine, which forms tetrakistriphenylphosphinepalladium(0) as the active species.[187, 188, 189, 190, 191] Trost and Verhoeven pub-



Scheme 3.1: Tsuji and Takahashi synthesis of 3,5-cyclooctadienylmalonate.[148, 185]

lished palladium-catalysed allylic alkylations with retention of the stereocenter of the reactant.[192] Trost also published migration of allylic acetate with a palladium catalyst.[193] Tsuji-Trost type reactions have further been used in cyclisation reactions.[194]

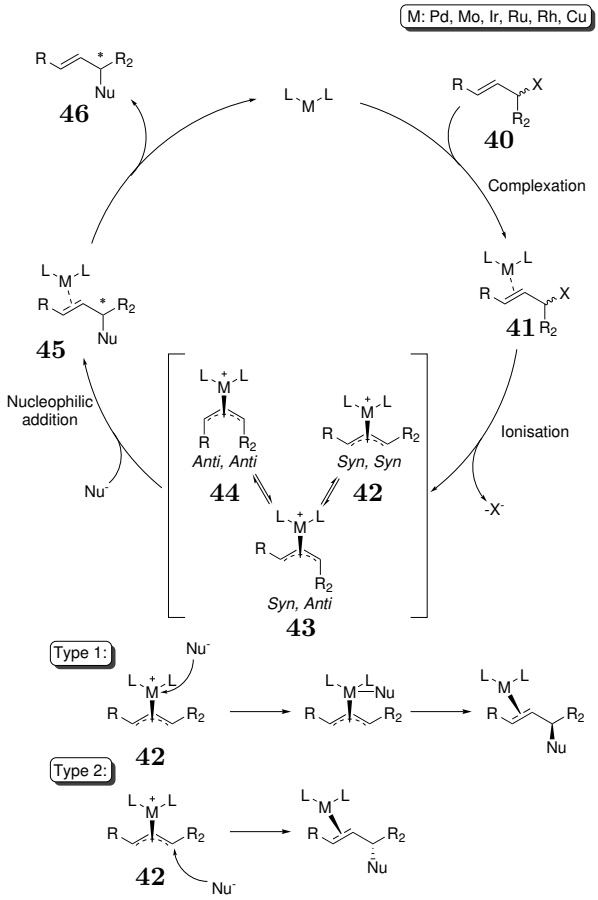
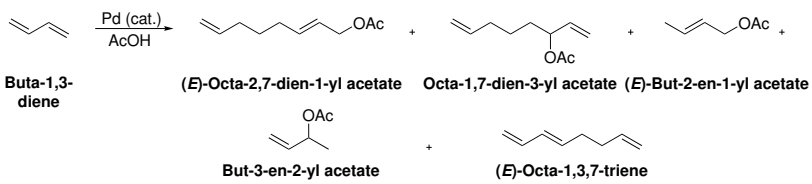


Figure 3.1: Tsuji-Trost reaction mechanism.[195]

The mechanisms of the allylic alkylation are fully discussed in multiple publications. The latest publications include the very comprehensive publications of Trost et al. in 2010.[195, 196, 197, 198] Different metals can be used as catalysts in the reaction, e.g. palladium, molybdenum, iridium, ruthenium, rhodium, and copper. All of the listed elements are transition metals. Ligands used for the reaction can be varied and include triphenylphosphine. X is the leaving group in Figure 3.1 and can be one of various functional groups, e.g. acetate. The mechanism then follows a complexation of **40** to form **41**. Then **41** is ionised and the leaving group is expelled to give **42**. The metal allyl complex is in equilibrium between **42**, **43**, and **44** through the π-σ-π bond formed. The most stable conformer is usually **42** unless the compound is locked

in a cyclic system and equilibration to the most stable conformer is inhibited. If a compound is in a cyclic locked system, then the reaction can go through *Syn, Anti* (**43**) or *Anti, Anti* (**44**). The nucleophile attacks the metal allyl complex and produces a new stereocenter in **45** in a nucleophilic substitution. The chirality of **45** is decided through two different mechanisms. The first mechanism, type 1 is a coordination to the metal and the insertion into the compound. The metal is then eliminated through reductive elimination. The nucleophile is inserted on the same side as the metal. In the second mechanism type 2, the metal allyl complex **42** is attacked by the nucleophile on the opposite side of the metal and then the complex undergoes reductive elimination. Type 1 is inversion of the reactant stereocenter, while the type 2 mechanism is retention of the stereocenter of the reactant. If the nucleophile is hard, the mechanism is often of type 1. If the nucleophile is soft, the mechanism often goes through the type 2 mechanism.
Palladium allyl complexes are electrophiles and they will react with nucleophiles at the less substituted site of the two termini of the allyl complex.[199] Decomposition of the complex will lead to diene formation. The palladium allyl complexes are stabilised by phosphor or nitrogen ligands. Typical reagents are tetrakistriphenylphosphine and bis(dibenzylideneacetone)palladium(0). The active palladium(0) in the allyl complex is often formed in situ from palladium(II) acetate or via a Wacker-type olefin oxidation.[200]

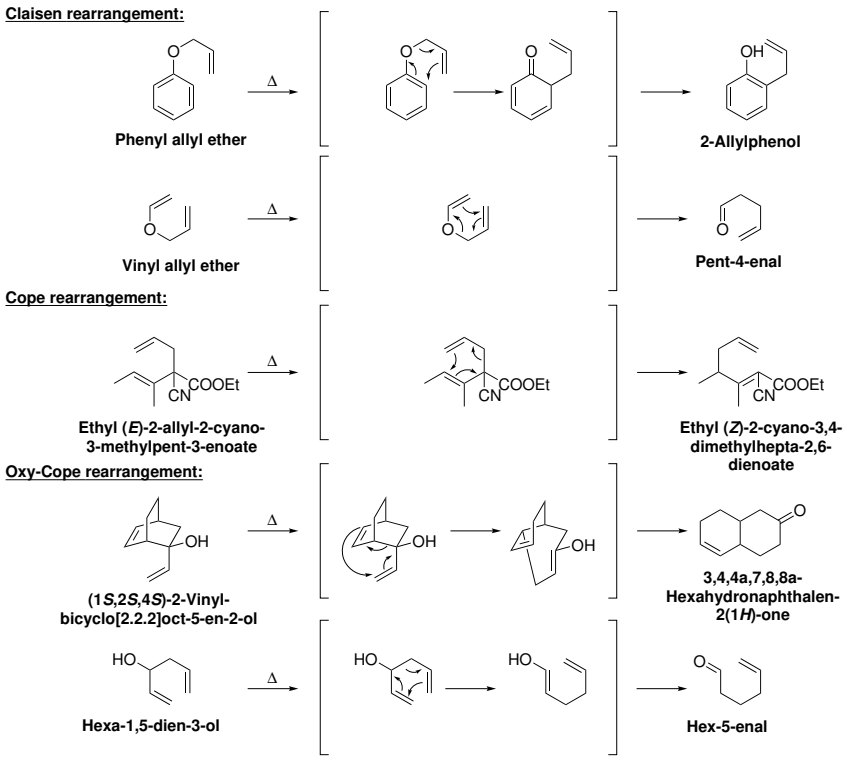


Scheme 3.2: Synthesis of 1,3,7-octatriene and butenyl esters.[189]

Allylic acetate transposition is also a possibility with palladium chemistry. A few examples of allylic acetate transposition have been observed in the literature. In 1970 Atkins et al. reported a low yield telomerization between two butadienes mixed with acetic acid, palladium(II)acetylacetonate, and triphenylphosphine as ligand.[189, 201, 202, 203] The reaction yielded a mixture of 1,3,7-octatriene, and butenyl esters (Scheme 3.2). During the synthesis, (*E*)-octa-2,7-dien-1-yl acetate undergoes transposition to octa-1,7-dien-3-yl acetate which causes multiple products to be formed. In 1976 Tsuji el al. reported the same observation.[204] In 1984 Overman reported [3,3]-sigmatropic rearrangement with a palladium catalyst.[205]

Claisen and sigmatropic [3,3] rearrangement

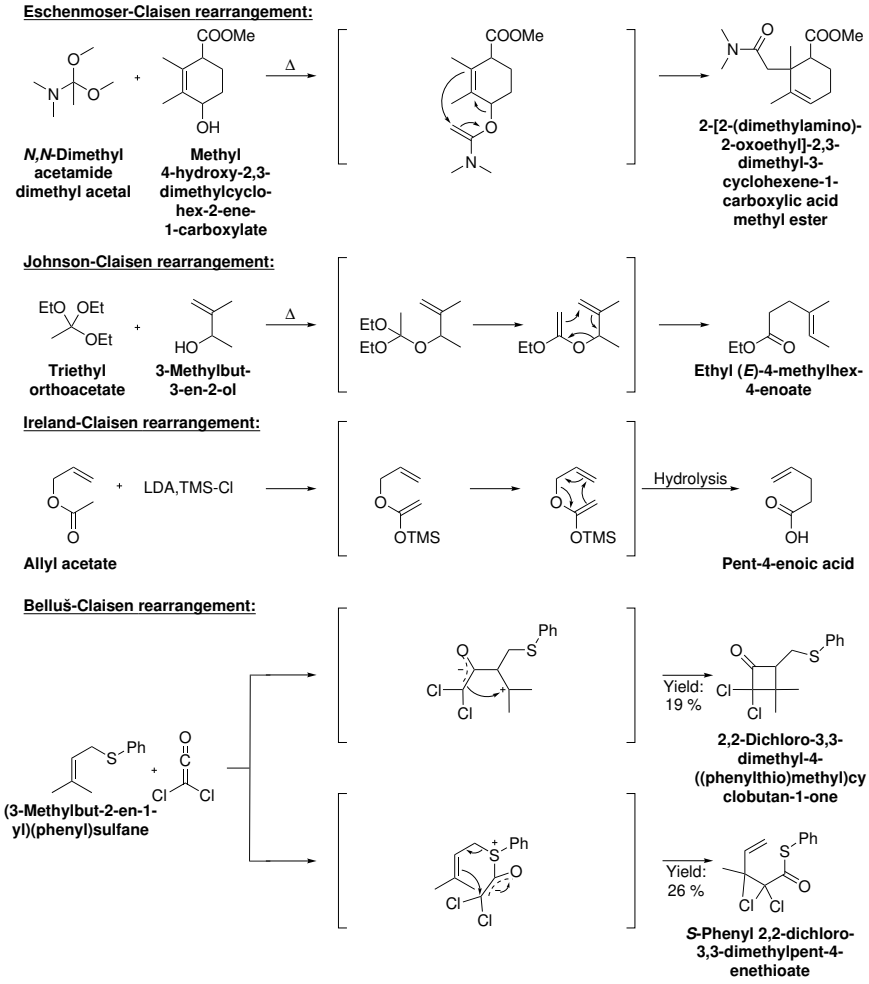
Other ways to alter molecules with the beneficial low atom economy is through rearrangement of compounds.[209] Many published rearrangements are sigmatropic [3,3] shifts. The Claisen rearrangement is an exothermic concerted reaction that occurs



Scheme 3.3: Claisen, Cope, and Oxy-Cope [3,3] sigmatropic rearrangements.[206, 207, 208]

intramolecularly with a sigmatropic [3,3] shift. This was proven by a crossover experiment, which showed no presence of the crossover product.[210] The first published Claisen rearrangement was described in 1912 where Claisen described the rearrangement of phenyl allyl ether to 2-allylphenol (Scheme 3.3) and rearrangement of similar compounds.[206] The most simple rearrangement without a hetero-atom in a sigmatropic [3,3] rearrangement is the Cope rearrangement (Scheme 3.3). This rearrangement was discovered and published by Cope et al. in 1940.[207] A variation of the Cope rearrangement with a hetero-atom was published in 1964 by Berson and Jones.[208] They named it the Oxy-Cope rearrangement. A secondary or tertiary alcohol is rearranged into an aldehyde and a ketone. Multiple variants of the Claisen rearrangement have been published. In 1964, a new Claisen type rearrangement was published by Wick et al., which was named the Eschenmoser–Claisen rearrangement.[211] Here, an allylic alcohol reacts with *N,N*-dimethylacetamide dimethyl acetal (Scheme 3.3). This made it possible to produce and rearrange methyl 4-hydroxy-2,3-dimethylcyclo-hex-2-ene-1-carboxylate into 3-cyclohexene-1-carboxylic acid, 2-[2-(dimethylamino)-2-oxoethyl]-2,3-dimethyl-, methyl ester. In 1970 Johnson et al. published the Johnson-Claisen rearrangement, a highly stereoselective reaction with excess triethyl orthoacetate reacting with an allylic alcohol with the *trans*-isomer being preferable.[212] This reaction rear-

ranges 3-methylbut-3-en-2-ol to ethyl (*E*)-4-methylhex-4-enoate (Scheme 3.4). A few years later in 1972 Ireland and Mueller published another Claisen type rearrangement, the Ireland-Claisen rearrangement.[213] In the reaction an allylic acetate is silylated with trimethylsilyl chloride (**TMS-Cl**) in the presence of lithium *iso*-propylcyclohexylamide (**LiICA**). The allylic acetate is rearranged into pent-4-enoic acid. In 1979 Malherbe and Belluš found a Claisen type reaction and named it Belluš-Claisen rearrangement.[214] A ketene is reacted with allylic ethers, amines, thioethers, and then rearranged. E.g. mixing (3-methylbut-2-en-1-yl)(phenyl)sulfane with in situ produced dichloroketene resulted in formation of 2,2-dichloro-3,3-dimethyl-4-((phenylthio)methyl)cyclobutan-1-one in 19 % yield and the rearranged product *S*-phenyl 2,2-dichloro-3,3-dimethylpent-4-enethioate in 26 % yield. Other hetero Claisen rearrangements have also been observed, including a rearrangement with nitrogen, phosphor and chromium.[215,216] **MVG** (**1**) is a scaffold able to undergo Claisen-, Johnsen-Claisen-, and Ireland-Claisen rearrangements. **MVG** can also undergo an allylic acetate rearrangement. Rearrangements with **MVG** have been published in the literature, an overview of the published rearrangements can be seen in Scheme 1.5 and is described in the subsection 1.5.2 (Methyl vinyl glycolate as a platform molecule).

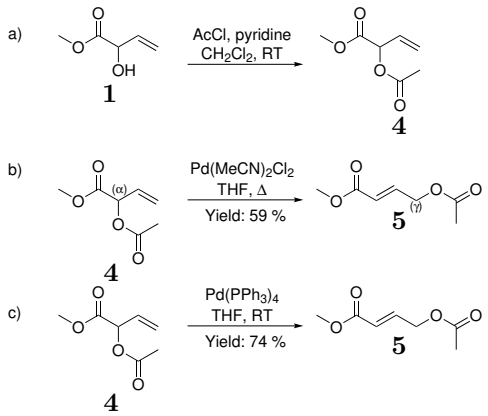


Scheme 3.4: Eschenmoser-, Johnson-, Ireland-Claisen [3,3] sigmatropic rearrangements and Belluš-Claisen rearrangement.[211, 212, 213, 214]

3.2 Results and discussion

Palladium(II) and palladium(0) complexes can rearrange allylic acetates and create regioisomers. Sølvhøj et al. published the rearrangement of acetylated **MVG**, methyl 2-acetoxy-but-3-enoate (**4**) with bis(acetonitrile)dichloropalladium(II) into methyl (*E*)-4-acetoxy-but-2-enoate (**5**). The allylic acetate moves from the α-position to the γ-position in 59 % yield.[123] This rearrangement was achieved through a palladium complex. This reaction led to the synthesis of methyl (*E*)-4-acetoxybut-2-enoate (**5**), methyl (*E*)-4-hydroxybut-2-enoate (**22**), methyl 4-acetoxybutanoate (**36**), and γ-butyrolactone (**23**). Compounds **5**, **22**, and **36** are interesting monomers for polymerisation

and polymer applications, since they can be polymerised through poly-esterification. The two monomers **5** and **22** also have a double bond that is worth testing in radical polymerisation. Compound **23** is a potential bulk chemical and the monomer can be used to synthesise polyesters. A Master student attempted to optimise the rearrangement of **4** to improve the yield and validate the production of **5**, **23**, and **36** with **MVG**. One of the optimised parameters was the preferred catalyst.



Scheme 3.5: a) Acetylation of **MVG**. b) The rearrangement of allylic acetate published by Sølvhøj et al.[123] c) The rearrangement of allylic acetate with tetrakis triphenylphosphine palladium(0).

As described, **MVG** can be acetylated with pyridine and acetyl chloride in dichloromethane (Scheme 3.5).[123, 148, 149] Allylic acetate transposition with palladium is known to be able to rearrange the acetate from the α-position to the γ-position. Sølvhøj et al. in 2016 achieved this by using bis(acetonitrile)dichloropalladium(II).[123, 217] The reaction was performed in THF at refluxing conditions in 59 % yield. Ondozabal's Master thesis research found that tetrakis triphenylphosphine palladium(0) can be used as a catalyst instead of bis(acetonitrile)dichloropalladium(II).[218] The yield improved from 59 % to 77 % yield of the isolated product. The reaction could also be performed at room temperature instead of refluxing conditions. This was the starting point where we picked up this research. In order to finish this project, the reaction conditions were tested on similar small allylic acetate substrates and a mechanistic study was performed of the reaction to elucidate the pathway.

First a selection of allylic alcohols was alkanoylated and then purified. The allylic alcohols successfully alkanoylated were purified via washing with 1-2 M hydrochloric acid and with a solution saturated with sodium carbonate. Products are depicted and listed in Figure 3.2 and include methyl 2-acetoxybut-3-enoate (**4**), 1-methoxy-1-oxobut-3-en-2-yl benzoate (**33**), methyl 2-((methoxycarbonyl)oxy)but-3-enoate (**34**), methyl 2-(propionyloxy)but-3-enoate (**35**), but-3-en-2-yl acetate (**47**), hex-1-en-3-yl acetate (**48**), 1-phenylallyl acetate (**49**) and (*E*)-hept-2-en-4-yl acetate (**50**). The yield and method of purification are listed in Table 2.5.

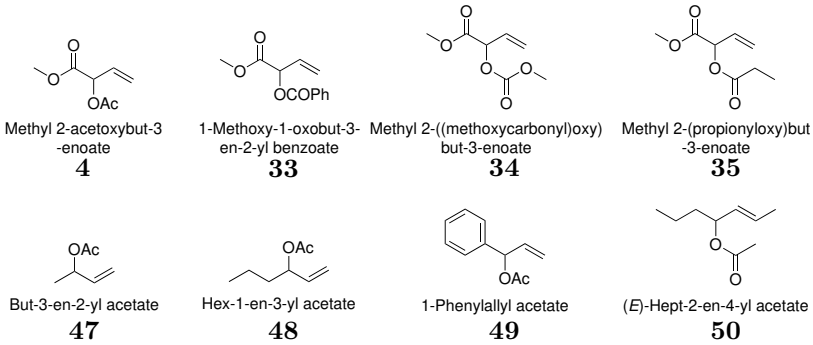


Figure 3.2: List of the successfully alkanoylated compounds: Methyl 2-acetoxybut-3-enoate (**4**), 1-methoxy-1-oxobut-3-en-2-yl benzoate (**33**), methyl 2-((methoxycarbonyl)oxy)but-3-enoate (**34**), methyl 2-(propionyloxy)but-3-enoate (**35**), but-3-en-2-yl acetate (**47**), hex-1-en-3-yl acetate (**48**), 1-phenylallyl acetate (**49**) and (E)-hept-2-en-4-yl acetate (**50**). All compounds were synthesised in dichloromethane at room temperature with acetyl chloride, propanoyl chloride or methyl chloroformate added drop-wise (3 ml/h).

Table 3.1: Alkanoylation of compounds **4**, **33**, **34**, **35**, **47**, **48**, **51**, **50** with yield and method of purification.

Compound	Yield [%]	Purification method
4	97	Wash
33	67	Wash and column
34	75	Wash and distillation or column
35	83	Wash
47	93	Wash
48	97	Wash
51	93	Wash
50	82	Wash

The compounds in Table 3.1 were tested for the rearrangement from the α-position to the γ-position, as depicted in Scheme 3.5c. All the compounds favour the (E) stereoisomer when rearranged, but a small percentage is converted into the (Z) stereoisomer in a negligible amount. The rearrangement to the (Z) stereoisomer has previously been observed to be slower, presumably due to a higher energy barrier in the pathway to this isomer.[215] The conformation of the allyl palladium complex favours the syn conformer, which produces the (E) stereoisomer (Figure 3.3) and further substantiates the favourable configuration of the stereochemistry as (E). When **4** was rearranged, roughly 5 % ends up as the (Z) isomer. The characterisation of the two isomers was based on the ^{1}H-NMR analysis of the products.

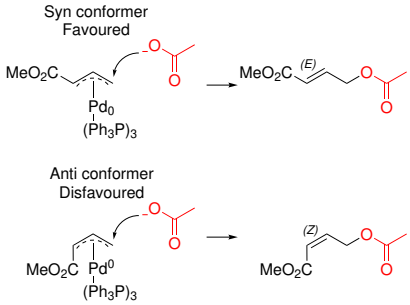


Figure 3.3: Favoured conformation of the allyl complex and the favourable stereochemical outcome of the nucleophilic attack. The rearrangement of **4** is depicted.

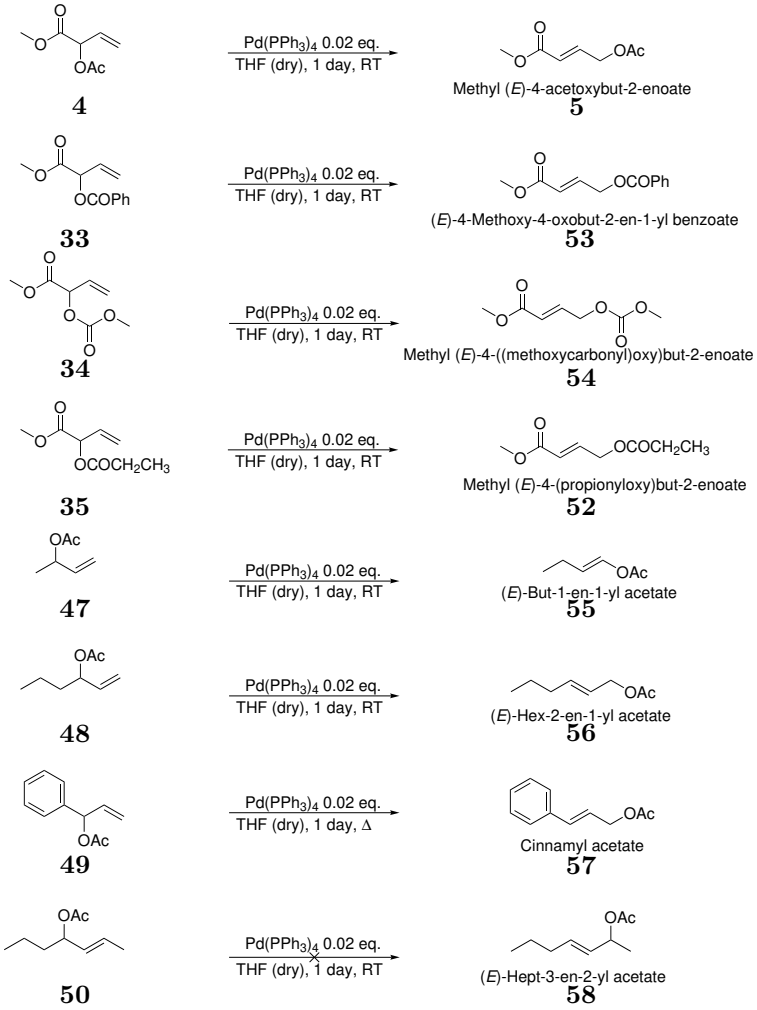


Figure 3.4: List of successfully rearranged compounds from the α- to the γ-position. The rearrangements were performed in THF with 0.02 equivalent of $Pd(PPh_3)_4$ under inert conditions and stirred overnight. The yields are listed later in Table 3.2.

The mechanism of the reaction was also studied. In an effort to understand whether this reaction goes through a concerted [3,3]-sigmatropic intramolecular mechanism or a Tsuji-Trost allyl complex involving a nucleophilic substitution in an intermolecular mechanism, two crossover experiments were performed to uncover the pathway.[219] The first was a rearrangement of **4** to **5** with 1 mmol of **4** and 0.02 eq. of tetrakistriphenylphosphine palladium(0) mixed in dry THF for one day. The crossover was tested with two equivalents of propanoate which was added to the mixture at the start of the reaction (Figure 3.5). If the reaction was intramolecular, the only product would be rearrangement of the acetate. In the reaction with propanoate, a mixture of rearranged products was observed, including methyl 2-(propionyloxy)but-3-enoate (**35**) a crossover product. Product **35** was observed through the retention time in GC-MS analysis (Figure 3.6) and ^{1}H-NMR analysis (Figure 3.7). The mechanism for the crossover product formation is drawn in Figure 3.9.

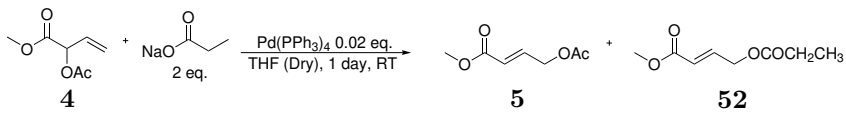


Figure 3.5: Mechanistic experiment with a rearrangement of **4** to **5**. A scale of 1 mmol of **4** with 0.02 eq. of tetrakistriphenylphosphine palladium(0) in dry THF for one day with two equivalents of sodium propanoate added to the mixture. Sodium propanoate was in a suspension in THF. The rearrangement gives both products **5** and **52**.[198]

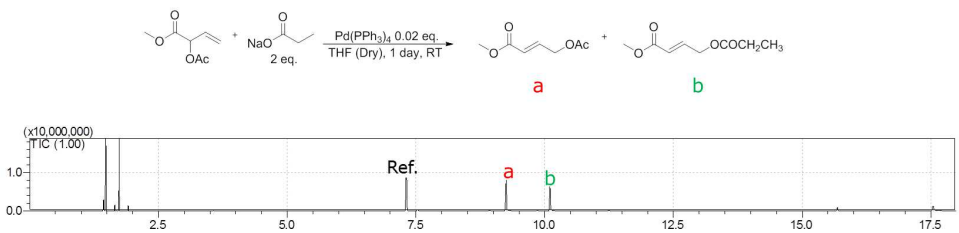


Figure 3.6: GC-MS trace for the intra- and the intermolecular mechanistic study. Both **5** (a) and **52** (b) are present, which supports that it is an intermolecular reaction mechanism.

The second crossover experiment performed was labelling **MVG** with deuterium. A transesterification of **MVG** was performed with deuterated methanol and with a catalytic amount of hydrochloric acid to synthesise methyl-d_3 2-hydroxybut-3-enoate (**59**) (Figure 3.8). Compound **59** was acetylated with the normal procedure to synthesise methyl-d_3 2-acetoxybut-3-enoate (**60**). The other labelling of **MVG** was an acetylation of **MVG** with acetyl chloride-d_3 to synthesise methyl 2-(acetoxy-d_3)but-3-enoate (**61**). Compounds **60** and **61** were then mixed and subjected to the normal procedure for the rearrangement of the acetate. This mixture was analysed by NMR spectroscopy to confirm the rearrangement was achieved. The mixture was also anal-

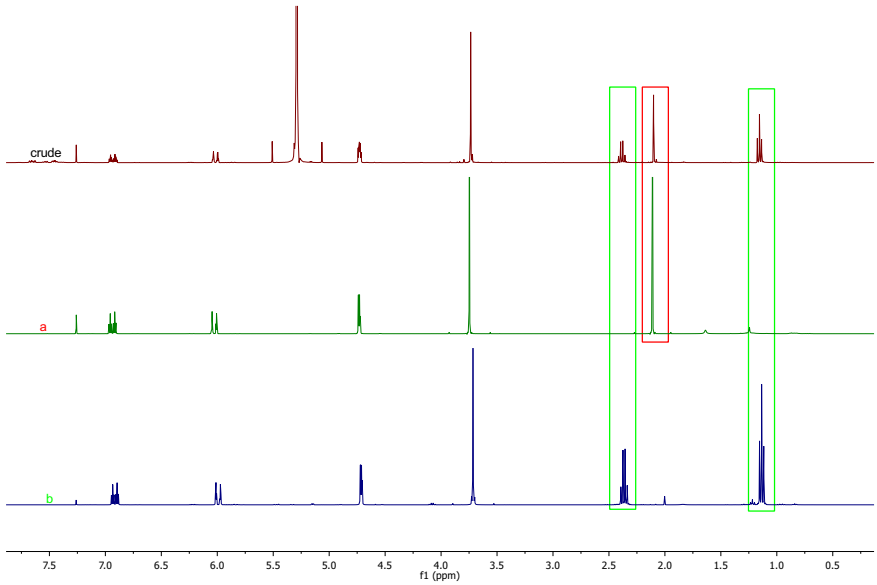


Figure 3.7: ^{1}H-NMR spectra of the crossover experiment. The top is the crude reaction mixture. The red coloured (a) spectrum is of the acetylated **MVG** (**5**) and the green coloured (b) spectrum is of the propanoylated **MVG** (**52**).

ysed by HRMS to confirm crossover products methyl (*E*)-4-acetoxybut-2-enoate (**5**) and methyl-d_3 (*E*)-4-(acetoxy-d_3)but-2-enoate (**62**). The HRMS analysis showed presence of crossover products **5** and **62** (Figure B.3). The first analysis of **62** had a large margin of error, and the data were therefore extracted from a second retention time (Figure B.4) to verify the presence of **62** in the mixture. The HRMS analysis of the mixture further substantiated the claim of an intermolecular reaction mechanism.

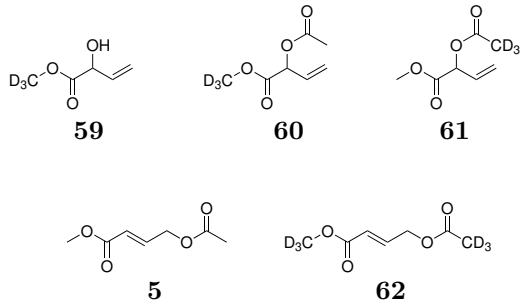


Figure 3.8: Compounds in the deuterium labelled experiment. Methyl-d_3 2-hydroxybut-3-enoate (**59**), methyl-d_3 2-acetoxybut-3-enoate (**60**), methyl 2-(acetoxy-d_3)but-3-enoate (**61**), methyl (E)-4-acetoxybut-2-enoate (**5**), and methyl-d_3 (E)-4-(acetoxy-d_3)but-2-enoate (**62**).

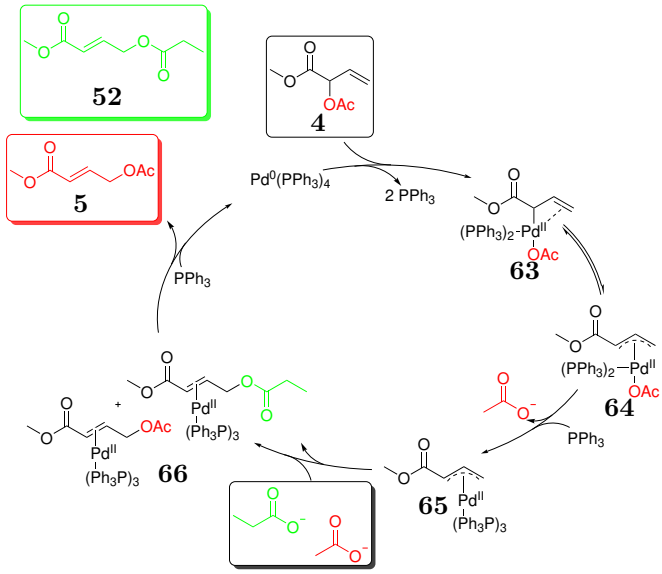


Figure 3.9: A crossover experiment was performed.[219] The experiment was performed to test if the mechanism involves an intramolecular or an intermolecular pathway. The result suggest that it is an intermolecular reaction. Both **5** and **52** are isolated from the experiment.

3.3 Summary

In summary, it was possible to synthesise 10 grams of each of the compounds **4**, **34**, and **5** and provided them for further testing in the application as monomers for polymerisation. A small substrate scope of rearranging acetylated allylic alcohols was performed.

Two crossover experiments were performed to uncover the mechanistic pathway of the allylic acetate rearrangement. The data support the mechanism to be intermolecular, similar to the Tsuji-Trost mechanism (Figure 3.10) with a nucleophilic attack on the palladium allyl complex. New moieties of **MVG** were synthesised and rearranged, including the synthesis of the molecules **33**, **34**, **35**, **52**, and **53** where it was possible to detect **54**, but it was not isolated. The **MVG** moieties except the carbonate showed high yields of rearrangement from the α-position to the γ-position. The yields of the rearrangements are listed in Table 3.2. It was downstream possible to synthesise methyl (E)-4-hydroxybut-2-enoate (**22**) in 93 % yield, methyl 4-acetoxybutanoate (**36**) in 74 % yield, and γ-butyrolactone (**23**) in 84 % yield. The synthesis of γ-butyrolactone contained some impurities from the open lactone methyl 4-hydroxybutanoate.

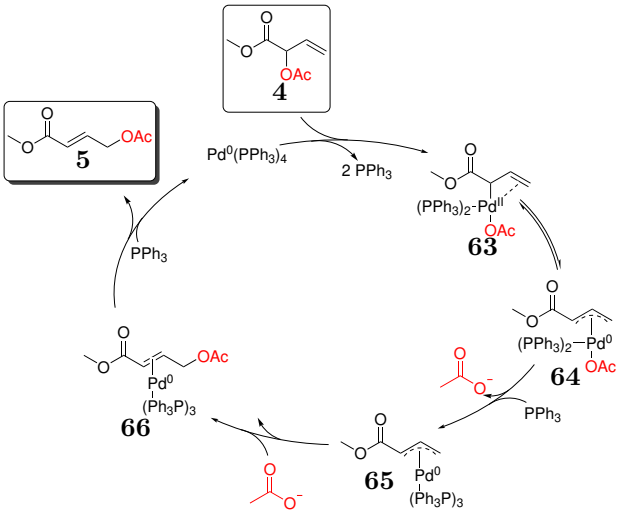
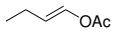
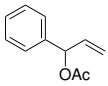
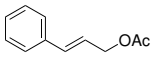
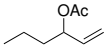
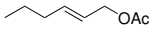
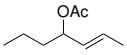
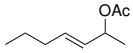
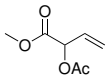
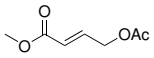
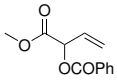
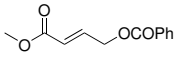
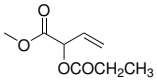
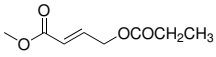
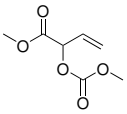
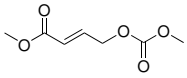


Figure 3.10: Rearrangement of **4** into **5** is believed to be similar to a Tsuji-Trost type reaction mechanism. First a complexation of palladium(0) to the olefin **63** through an oxidative insertion. Followed by an ionisation to the allyl complex **64** expelling acetate from the α-position to afford **65**. The nucleophile then attacks the more accessible γ-position and is attached at that position in a nucleophilic addition (**66**) to yield compound **5** through decomplexation in a reductive elimination.[195]

Table 3.2: Yield of the rearrangements.

Reactant	Product	GC/^{1}H-NMR yield^a	Isolated yield
		40 %	-
		52 %^{b}	-
		56 %	-
		-	-
		92 %	74 %
		89 %	90 %
		96 %	96 %
		40 %^{a}	-

^{a}Yield was quantified by NMR spectroscopy. ^{b}Conversion to the rearranged product was only achieved under refluxing conditions in THF.

CHAPTER 4

Diels Alder reactions

4.1 Introduction

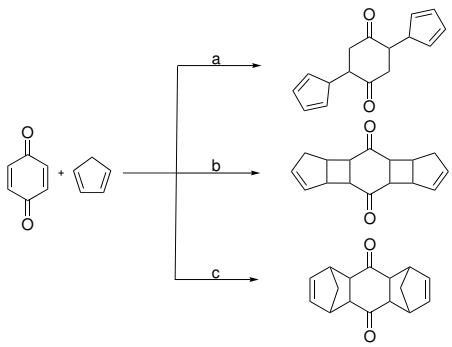


Figure 4.1: Incorrect pathways (a) and (b) were proposed routes when reacting quinone with cyclopentadiene before elucidation by Diels and Alder in 1928 (c).[220]

The pericyclic cycloaddition is a bimolecular reaction with a conserted mechanism. The Diels Alder reaction is an example of this type of reaction. The Diels Alder type reaction has been observed by others before publication by Diels and Alder in 1928, which elucidated the corrected structure. The proposed structures of the "diene reaction", as the reaction was known as at the time, were the di-cyclopentadiene quinone (a) and the cyclopentadiene quinone (b) (Figure 4.1). Diels and Alder proved that the reaction between an azoester and a cyclopentadiene yielded a bicyclic ring, and the product would be dimethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate. They further proved cyclopentadienequinone to react with two molecules of H_2. Figure 4.1

path (a) would require four equivalents of H_2 to react in the same fashion, while the correct molecule consumed two H_2 molecules. The path (b) in Figure 4.1 was disproved by the discovery of the synthesis of the bicyclic ring dimethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate with an azoester and cyclopentadiene as reactants. This led Diels and Alder to propose the correct pathway (c). Diels and Alder performed multiple studies of these systems, which led the reactions to be known as Diels Alder reactions.

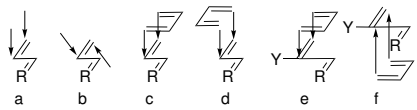


Figure 4.2: (a) Syn-addition. (b) Anti-addition. (c) Endo transition state. (d) Exo transition state. (e) Attack from the top. (f) Attack from below.[221]

In 1937, ten years after the elucidation of the Diels Alder reaction between quinone and cyclopentadiene, Alder and Stein published three observations regarding this type of reaction as questions and answers.[221] The first question was whether the reaction occurred via *cis* or *trans* addition to the double bond, known as syn-addition (a) or anti-addition (b) (Figure 4.2). The second question was, if the reaction occurred endo (c) or exo (d). The third question was if, the reaction occurred from the top (e) or from below (f). The last question was only relevant if a substituent (Y) produces asymmetry in the product. To the first question it was observed that the Diels Alder reactions occur on the same face in a syn addition (a) which Alder and Stein called *cis* addition. They called it the *cis* principle. Later it was shown that the vast majority the of Diels Alder reactions proceed through syn-addition with only a few exceptions. Regarding the second question, the observations showed the reactions occur mainly through the endo selectivity. This is known as the Alder endo rule. Structurally this is the unfavourable outcome when considering the stability the two products. The endo product is not the thermodynamically favourable product. Woodward and Hoffmann attributed this to occur because of secondary orbital effects.[222] It is the general consensus that secondary orbital effects play a role in the endo selectivity.[223] The transition state for the exo product and the exo reactant complex have higher energy barriers, which favours the formation of the kinetic endo product. Exceptions are furan, maleic anhydride, and maleimide because of redissociation in the reaction.[224] The third question proposed by Alder and Stein was left unanswered. There was no general observation to conclude if the reaction would occur selectively from the top or the bottom.

Woodward and Hoffmann introduced rules on how to explain the Diels Alder reaction with orbitals.[222] They proposed the Diels Alder reaction as a cycloaddition involving two molecules in a [4+2] cycloaddition where a new ring is formed. The π systems of the reactants form two new σ bonds. In the system the diene typically contain two double bonds with four p electrons and the dienophile is typically one double bond with two p electrons. The reaction occurs through orbital symmetry where there is overlap of the frontier orbitals. The reaction occurs face to face with a favourable

Figure 4.3: The favourable frontier orbital overlap in a [4+2] cyclo-addition Diels Alder reaction.

interaction between the HOMO and the LUMO (Figure 4.3) and the reaction mechanism is generally considered concerted. The Diels Alder reaction is susceptible to steric effects of the substituents on the dienophile and the termini of the diene. This can sterically hinder approach when they have large substituents, which affect the reaction rate. The reaction rate can also be affected by a preferable HOMO-LUMO gap. If the HOMO is raised by electron donating substituents and the LUMO is lowered by electron withdrawing substituents, a reaction is preferable. This can be applied to both the dienophile and the diene as long as the gap is shortened between the two. The regioselectivity of the reaction in general prefers *ortho* or *para* orientations, and the four examples are shown in Figure 4.4, where (C) and (D) are known as an inverse Diels Alder reaction. Diels Alder reactions are known to be catalysed by Lewis acids.[225]

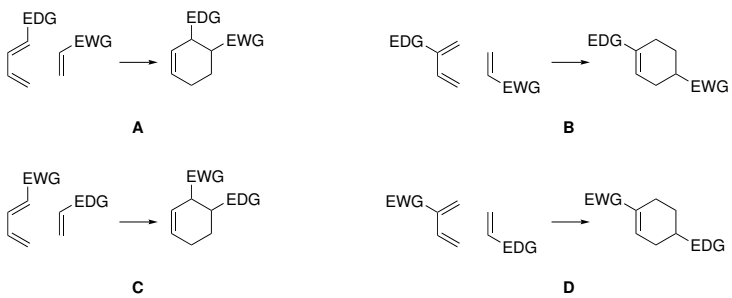


Figure 4.4: A and C favour *ortho*-orientations. B and D favour *para*-orientations. C and D are considered an inverse Diels Alder reaction.

4.2 Results and discussion

After isolation of **2** the compound was analysed. The initial suspicion was that **2** degraded at room temperature. The analysis proved that **2** dimerises via a hetero Diels Alder reaction resulting in a product methyl 2-(2-methoxy-2-oxoacetyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (**67**). In the hetero Diels Alder reaction, two structural stereoisomers are possible. Based on the 1D ^{1}H-NMR, integrals, and 2D HMBC analysis, only the depicted dimer **67** is detected (Figure 4.5). The reaction is not considered enantioselective and is therefore a racemic mixture. Eleven other dienes were tested: Furan, 2,3-dimethoxybuta-1,3-diene, cyclopentadiene (**68**), 1,2,3,4,5-pentamethylcyclopentadiene (**69**), cyclohexa-1,3-diene (**70**), 2,3-dimethylbuta-1,3-diene (**71**), isoprene

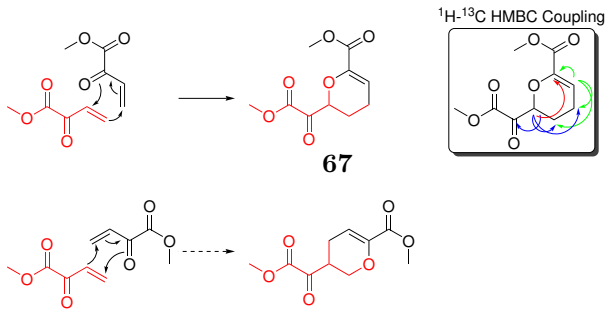


Figure 4.5: Compound **2** is very reactive and can undergo a hetero Diels Alder reaction with itself. This can occur in two ways, via the top and via the bottom pathway in the figure. Via 1D ^{1}H-NMR shifts, integrals and 2D HMBC analysis it was confirmed the reaction goes through the top path to produce compound **67**, which is what was expected with a preferable HOMO LUMO gap.

(**72**), 1-methoxycyclohexa-1,3-diene (**73**), (*E*)-buta-1,3-dien-1-yl acetate (**74**), (*E*)-1-methoxybuta-1,3-diene (**75**), and 2,3-dibenzyl-1,3-butadiene (**76**). These dienes were mixed with a known concentration of a solution of **2**, measured with 1,3,5-trimethoxy benzene as internal NMR standard. Furan and 2,3-dimethoxybuta-1,3-diene did not react as dienes at the tested conditions. They might react at elevated temperature, but this might also risk the formation of the easily produced **67**. The dienes **68**, **69**, **70**, **71**, and **76** are all symmetrical. They all create one stereocenter and go through the endo or exo transition state. Diels Alder reactions usually favour the endo transition state, which means these five dienes produce a racemic mixture. The five products synthesised were methyl 2-(bicyclo[2.2.1]hept-5-en-2-yl)-2-oxoacetate (**77**), methyl 2-oxo-2-(1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-en-2-yl)acetate (**78**), methyl 2-(bicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate (**79**), methyl 2-(3,4-dimethylcyclohex-3-en-1-yl)-2-oxoacetate (**71**), and methyl 2-(3,4-dibenzylcyclohex-3-en-1-yl)-2-oxoacetate (**80**) (Figure 4.6). The dienes **73**, **74**, and **75** all have electron donating groups that raise the HOMO in the reactions, which would favour a formation with *ortho*-orientation in the Diels Alder reaction. This was further confirmed by NMR spectroscopy. The three products synthesised were methyl 2-(1-methoxybicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate (**81**), methyl 2-(2-acetoxycyclohex-3-en-1-yl)-2-oxoacetate (**82**), methyl 2-(2-acetoxycyclohex-3-en-1-yl)-2-oxoacetate and (**83**) (Figure 4.6). The diene **72** gave orientations in both the *para*- and the *meta*-position, confirmed by ^{1}H-NMR analysis. The favoured product was 4 to 1 in favour of the structural isomer with the *para*-orientation. The methyl-group orientation in **72** is weakly electron withdrawing, which favours a *para*-orientation in the product. The product synthesised was methyl 2-(4-methylcyclohex-3-en-1-yl)-2-oxoacetate (**84**) (Figure 4.6).

Many of the Diels Alder reactions gave quantitative yields based on ^{1}H-NMR analysis with the internal standard 1,3,5-trimethoxy benzene (Table 4.1). Some impurities

from by-products and starting materials still need to be separated from the pure products. The reaction mixtures of the Diels Alder reactions were subjected to purification via **DCVC**. The products **77**, **80**, **81**, and **85** were successfully purified (Table 4.1). Compound **84** could be purified with **DCVC**, but it was not separated from its structural isomer. Compounds **78**, **79**, **82**, and **83** had some impurities of the starting material after **DCVC**, but could benefit from a lower gradient when purified, which might remove these impurities. All the columns were performed with a 4 % gradient from heptane to ethyl acetate. A smaller gradient at this scale would have been difficult and was not performed. Compound **67** has only been analysed in crude reaction mixtures, where it was the main product. This project was investigated and performed at the end of the Ph.D. study and could benefit from optimisation, which probably could help purifying the remaining products.

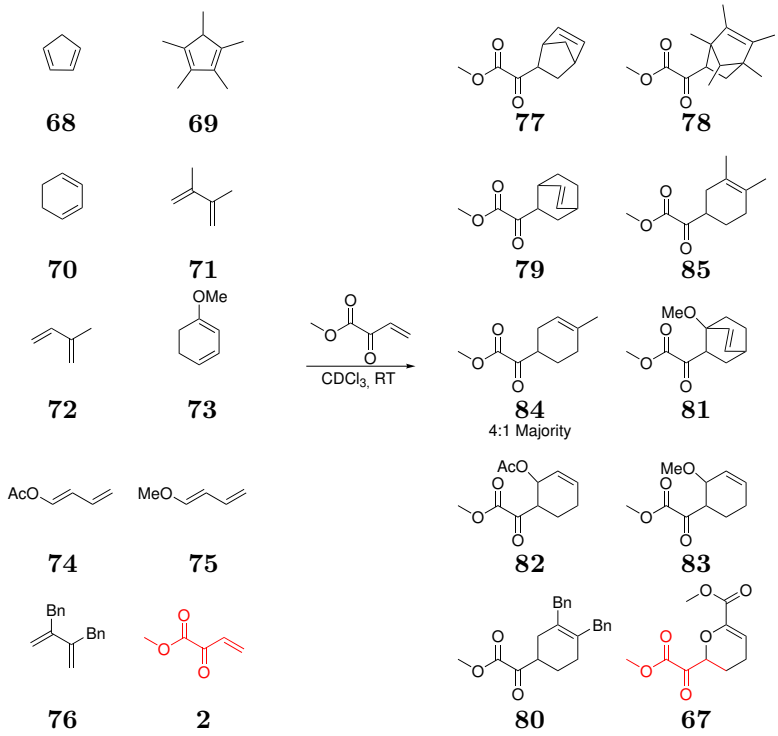
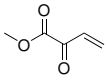
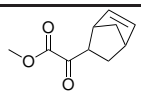
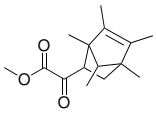
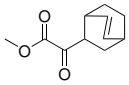
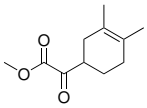
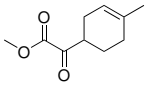
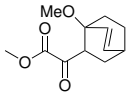
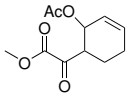
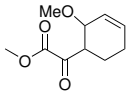
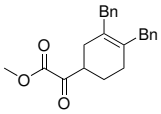
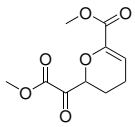


Figure 4.6: Compound **2** can be used as a dienophile for multiple dienes. Ten different dienes **68**, **69**, **70**, **71**, **72**, **73**, **74**, **75**, **76**, and **2** were successfully reacted with **2** to produce **77**, **78**, **79**, **85**, **84**, **81**, **82**, **83**, **80**, and **67**. Compound **67** was a possible by-product in all the Diels Alder reactions.

Table 4.1: Diels Alder experiments with **2** and various dienophiles were stirred overnight at room temperature.

Entry	 **2**	Dienophile [μmol]	Product	^{1}H-NMR yield[a]	Isolated yield[b]
1	11.5 mg 101 μmol	**68** 171 μmol		Quantitative	40 %
2	11.5 mg 101 μmol	**69** 122 μmol		75 %	-[e]
3	11.5 mg 101 μmol	**70** 205 μmol		80 %[c]	-[e]
4	11.5 mg 101 μmol	**71** 149 μmol		Quantitative	94 %
5	11.5 mg 101 μmol	**72** 228 μmol	 Majority 8:2	85 %[d]	39 %
6	11.5 mg 101 μmol	**73** 160 μmol		-	46 %
7	11.5 mg 101 μmol	**74** 165 μmol		85 %	-[e]
8	11.5 mg 101 μmol	**75** 117 μmol		75 %[d]	-[e]
9	11.5 mg 101 μmol	**76** 111 μmol		92 %[d]	67 %
10	11.5 mg 101 μmol	**2** 119 μmol		-	-

[a]The ^{1}H-NMR yield was determined by adding an internal standard 1,3,5-trimethoxy benzene. [b]Larger scale isolated by **DCVC**. [c]Stirred three days, [d]Stirred four days. [e]Impure after purification through **DCVC**.

4.3 Summary

Compound **2** is a good dienophile that can react with itself in a hetero Diels Alder reaction. Nine other dienes were added to the dienophile to synthesise ten compounds (Table 4.1). Five of them were successfully isolated in moderate yields through **DCVC**. More optimisation is necessary to isolate the last five compounds in pure form. Compound **2** is isolated and purified in low yield and might benefit from synthesis in situ when synthesising the Diels Alder type reactions described in this chapter. This would yield more of **2** to be used for the Diels Alder reactions. An initial test has been performed and gives reason to believe that this method can be applied to produce higher yields. Isolation of the product (from this synthesis pathway) to determine the yield still has to be performed to support the hypothesis. The Diels Alder reactions between **2** and a diene are an effective way of producing a variety of new compounds.

CHAPTER 5

Final remarks

Since the discovery of fossil fuels, the prolific uses of fossil fuels have been surrounded by conflicts. Fossil fuels have sparked a technological revolution. Oil is not only used for powering of transportation and energy. It is used for providing chemicals for synthesis of a wide array of compounds from drugs to materials. The limited availability of oil and the uncertainty surrounding a continuous supply at a low cost are reasons for concerns. Today, the dependency on oil is full of danger. Countries are looking for ways to exchange oil for renewable energy and renewable chemicals, which will lead to less dependence on fossil fuels. Materials such as plastic developed from bio-renewable sources are being explored to replace plastic produced from petrochemicals to reduce the dependency on oil. Developing bio-renewable chemicals will lead to a more sustainable future with less dependency on, and lower emissions from fossil fuels and will extend the current supply of oil. This might finally be the inception of the end of dependency on fossil fuels.

In this project, the focus has been on investigating possible bulk chemicals, mainly monomers for potential commercial applications in industry. The focal point has been developing new products from **MVG** functioning as a platform. From this platform, new products were derived for possible commercial applications when developed further. We studied the synthesis and potential of molecules **2**, **3**, **4**, **5**, **6**, **9**, **10**, **15**, **17**, **18**, **19**, **20**, **22**, **23**, **24**, **26**, **28**, **33**, **34**, **35**, **36**, **52**, **53**, **54**, and **86** from **MVG** (**1**). The value tree of **MVG** can be seen in Figure 5.1. Large scale synthesis of **3**, **4**, **5**, **9**, **26**, **28**, and **34** were successful. The rearrangement of acetylated **MVG** (**4**) was investigated and a mechanistic pathway was proposed. The oxidation of **MVG** to methyl 2-oxobut-3-enoate (**2**) was investigated. Molecule **2** had potential as a dienophile in Diels Alder reactions, and it was possible to synthesise ten new compounds. **MVG** has potential as a bio-renewable source and bio-based chemical. There are many possible transformations of **MVG** to produce other chemicals. This diverse set of products may support the implementation of **MVG** on the marked as an alternative to petro-

chemicals.

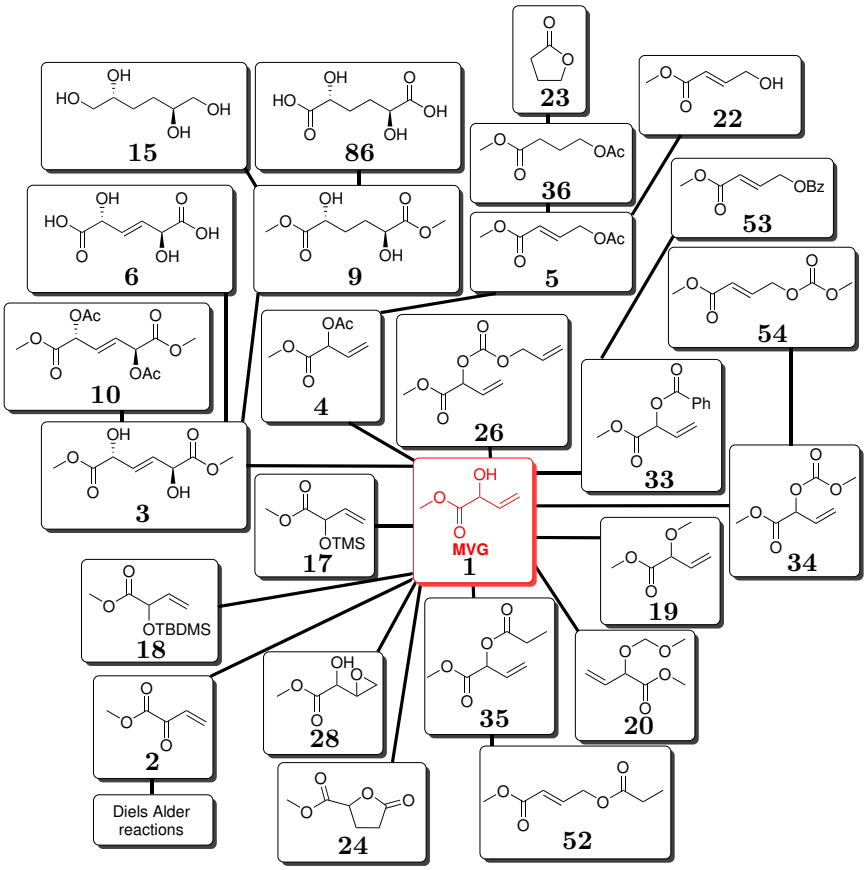


Figure 5.1: Downstream products from **MVG**, the value tree of **MVG**.

CHAPTER 6

Experimental

6.1 General methods and apparatus

NMR:
^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, APT, and HMBC spectra were recorded on two instruments. First instrument, Bruker AVANCE 400 MHz system, 5mm CryoProbe Prodigy: ^{15}N-^{31}P, ^{1}H, ^{19}F, SampleExpress sample changer for up to 60 samples, walk-up routine instrument. Second instrument, Bruker AVANCE 400 MHz system 5mm SmartProbe BB(F)-H-D: ^{15}N-^{31}P, ^{1}H, ^{19}F, B-ACS 60 sample changer for up to 60 samples, open access instrument. The spectra were all recorded at 298 K. Samples were prepared in deuterated solvents methanol-d_4, chloroform-d, dimethyl sulfoxide-d_6, and water-d_2. ^{1}H chemical shifts were referenced to the residual solvent signal at δ 3.310 (CD_2HOD), 7.260 ($CHCl_3$), 2.500 ($(CHD_2)SOCD_3$), and 4.790 (HDO). ^{13}C chemical shifts were referenced to the solvent resonance set to δ 49.000 (CD_3OD), 77.160 ($CDCl_3$), and 39.520 ($(CD_3)_2SO$). Bruker Topspin was used for data acquisition. MestReNova 10.0.2-15465 was used for processing the NMR data.

GC-MS & GC-FID:
Analysis was performed on two machines. First instrument used was a Shimadzu QP2010S GC/MS instrument with a column Supelco Equity 5, 30m x 0.25mm x 0.25µm film thickness. Second instrument used was a Agilent 7890A series GC-FID with a column Zebron ZB-5 (Phenomenex) 30 m x 250 um x 0.25 µm. The data were processed using GCMS solution version 4.11 SU2.

LC-MS:
Analysis was performed on two instruments. First instrument used was a Waters AQUITY UPLC system equipped with PDA and SQD electrospray MS detector. Column was a Thermo accucore C18 2.6µm, 2.1 x 50mm. Column temp: 50 ° C. Programs

used, flowrate: 0.6 ml/min, solvent A: 0.1 % formic acid in water, Solvent B: 0.1 % formic in acetonitrile. Gradient: 5 % B to 100 % B in 3 min, hold 1 min, total run time – 5 min. Second instrument used was a Waters AQUITY UPLC system equipped with PDA and SQD2 electrospray MS detector. Column thermo accucore C18 2.6µm, 2.1 x 50mm. Column temp: 50 ° C. Programs, flowrate: 0.6 ml/min solvent A: 0.1 % formic acid in water, Solvent B: 0.1 % formic acid in acetonitrile. Gradient: 5 % B to 100 % B in 3 min, hold 1 min, total run time – 5 min. The data were processed using MassLynx v. 4.1.

HRMS:
HRMS analysis was performed on a Dionex UltiMate 3000 system coupled to an UltiMate 3000 diode array UV/Vis detector. The sample was injected directly into the MS detector or through a column. The mobile phase solution was 0.1 % formic acid in H_2O and 0.1 % formic acid in acetonitrile. Water used as eluent was purified by a Millipore system. The MS analysis (HRMS) was carried out on a Bruker MicrOTOF-QII-system with an ESI-source with the following settings: nebulizer 1.2 bar, dry gas 8.0 L min^{-1}, dry temperature 200 °C, capillary 3500 V, end plate offset -500 V, funnel 1 RF 400.0 Vpp, ISCID energy 0.0 eV, funnel 2 RF 600.0 Vpp, hexapole RF 800.0 Vpp, quadrupole ion energy 5.0 eV, low mass 300.00 m/z, collision energy 10.0 eV, collision RF 1600.0 Vpp, transfer time 160.0 μs, and pre pulse storage 1.0 μs. The LC-MS data were processed using DataAnalysis v. 4.0 SP 5, and DataAnalysis v. 4.2 SR 2.
In the processing of HRMS measurements, a sodium formate calibrant solution eluting in the first part of the HRMS-run was used to calibrate the system before each measurement.

Microwave reactions:
Microwave reactions were performed on a Biotage Initiator 4.1.2., in microwave vials 2-5 ml.

Melting point apparatus:
Melting points were analysed with a Stuart melting point SMP 30. Serial R000100087. Not calibrated.

Automated columns:
Automated columns were performed with a Combi Flash Rf. Serial 207H20191.

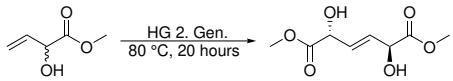
Chemicals:
Unless otherwise stated, all chemicals were purchased from commercial suppliers and used as received. Solvents used for reactions and columns were of HPLC grade and used as received. Chemicals and solvents were supplied mainly by Sigma-Aldrich, but also TCI Chemicals, Fluorochem, and ABCR. **MVG** was supplied from Haldor Topsøe A/S.

DCVC:
For purification through silica, mainly dry column vacuum chromatography was used with silica gel 60 (0.015-0.040 mm).[171]
TLC eluent used was 40/60, heptane/ethyl acetate unless stated otherwise. A potassium permanganate stain was used to enhance visualisation of the spots.

Diels Alder reactions: The Diels Alder reactions were performed with deuterated chloroform for easier analysis. For scale up of the reactions, it is recommended to switch to normal undeuterated chloroform.

6.2 Procedures

6.2.1 Dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate



1 **3**

Scheme 6.1: Synthesis of dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**).

The synthesis of dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) was based on the discoveries of former work in the research group by Sølvhøj et al.[123] The compound has also been published by Dewaele et al.[128] The synthesis has been optimised. A Schlenk tube with an outer and an inner joint was flamed. The outer joint was corked with a septum and connected to a Schlenk line via the inner joint. The tube was flushed with nitrogen. The tube was uncorked while continuing an excess flow of nitrogen stream in the tube. Hoveyda-Grubbs second generation catalyst was added (119 mg, 190 μmol) and the tube was corked. The tube was flushed with nitrogen and evacuated three times. Then, **MVG** (**1**) (20.09 g, 173 mmol) was added via a syringe. The solution started to bubble violently, releasing ethylene from the reaction mixture. The mixture bubbled ca. 5 min and then solidified. The mixture was left for 1 hour. After 1 hour, the mixture had a light brownish off-white colour in the precipitate. The product was removed and ground on a sintered glass filter tray. The precipitate was washed with toluene (40 ml). The white product **3** is a powder which was dried under vacuum.

Yield 15.37 g, 87 %.

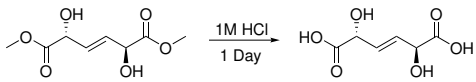
Melting point 131-133 °C. (Recrystallised from ethyl acetate)

^{1}H-NMR (400 MHz, Methanol-d_4) δ: 6.03 (dd, J = 2.5, 1.0 Hz, 2H), 4.72 (dd, J = 2.5, 1.0 Hz, 2H), 3.74 (s, 6H).

^{13}C-NMR (101 MHz, Methanol-d_4) δ: 174.25 (s, 2C), 130.43 (s, 2C), 71.91 (s, 2C), 52.70 (s, 2C).

HRMS (ESI+): m/z [M+Na]$^+$ calc. for $C_8H_{12}O_6Na$: 227.0526, found: 227.0533.

6.2.2 (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioic acid



3 **6**

Scheme 6.2: Synthesis of (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioic acid (**6**).

Dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) (1.018 g, 4.91 mmol) was added to 1 M hydrochloric acid (30 ml) and was stirred overnight. The solvent was evaporated on a rotary evaporator leaving a white solid compound **6**. This compound was dried under vacuum.

Yield 0.868 g, 99 %

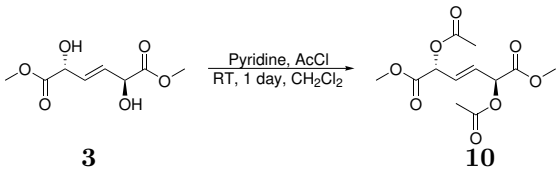
Melting point 176-178 °C. (Not Recrystallised) A slight discolouration is observed from 166 °C up until it starts melting. When the compound is melted it has the colour brown.

^{1}H-NMR (400 MHz, Dimethyl sulfoxide-d_6) δ: 5.88 (d, J = 2.2 Hz, 2H), 4.52 (d, J = 2.2 Hz, 2H).

^{13}C-NMR (101 MHz, Dimethyl sulfoxide-d_6) δ: 173.75 (s, 2C), 128.96 (s, 2C), 70.16 (s, 2C).

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_6H_8O_6Na$: 199.0213, found: 199.0216.

6.2.3 Dimethyl (2*R*,5*S*,*E*)-2,5-diacetoxyhex-3-enedioate



Scheme 6.3: Synthesis of dimethyl (2*R*,5*S*,*E*)-2,5-diacetoxyhex-3-enedioate (**10**).

Dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) (512 mg, 2.51 mmol) and pyridine (431 mg, 5.45 mmol) were added to dichloromethane (15 ml) in a Schlenk flask with an outer and an inner joint. The inner joint was connected to a Schlenk line and the outer joint was corked with a septum. The solution was degassed with nitrogen and the atmosphere in the flask was filled with nitrogen. To the septum a syringe pump was connected and set to pump at 3 ml/hour. The syringe was filled with acetyl chloride (1.765 g, 20.06 mmol). The pump was started and the reaction was stirred overnight. The following day the solution was poured into ice water (30 ml). More dichloromethane was added (ca. 10 ml) and the organic phase was separated. The organic phase was dried with $MgSO_4$, which was filtered off. The organic solution was evaporated on a rotary evaporator. The compound was dissolved in a small amount of ethyl acetate (ca. 10 ml), heptane was added (ca. 80 ml) and the mixture was stored in the fridge. In the mixture the product precipitated out and was filtered and washed with heptane (3 x 30 ml). The compound **10** was dried under vacuum.

Yield 0.483 g, 67 %.

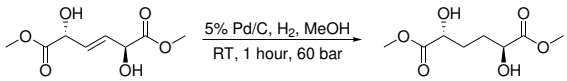
Melting point 122.0-124.1 °C.[150] (Recrystallised from ethyl acetate and heptane)

^{1}H-NMR (400 MHz, Chloroform-d) δ: 6.06 (dd, J = 2.9, 1.3 Hz, 2H), 5.55 (dd, J = 2.9, 1.3 Hz, 2H), 3.78 (s, 6H), 2.19 (s, 6H).

^{13}C-NMR (101 MHz, Chloroform-d) δ: 169.91, 168.43, 126.77, 71.72, 52.97, 20.75.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{12}H_{16}O_8Na$: 311.0737, found: 311.0733.

6.2.4 Dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate



3 **9**

Scheme 6.4: Synthesis of dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**).

Dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) (6.182 g, 30.28 mmol) was added to methanol (370 ml), creating a solution of 82 mM, which was added to a steel chamber with 5 % Pd/C active carbon (251 mg) and stirring was started. Then the chamber was closed tightly and flushed with nitrogen, then three times with hydrogen. The hydrogen pressure was set to 60 bar and the mixture was stirred for 1 hour. The solution was filtered through silica separating the palladium on carbon. Care needs to be taken that the palladium on carbon does not start a methanol fire, since it is not visible. The solvent from the mixture was evaporated and a white product **9** was collected. The powder was recrystallised from toluene if it was necessary to remove diastereomers. The powder was dried under vacuum.

Yield 6.144 g, 98 %.

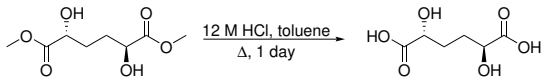
Melting point 89-91 °C. (Recrystallised from toluene)

^{1}H-NMR (400 MHz, Methanol-d_4) δ: 4.26 – 4.12 (m, 2H), 3.73 (s, 6H), 1.94 – 1.80 (m, 1H), 1.81 – 1.66 (m, 2H).

^{13}C-NMR (101 MHz, Methanol-d_4) δ: 176.12 (s, 2C), 71.46 (s, 2C), 52.40 (s, 2C), 31.13 (s, 2C).

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_8H_{14}NaO_6$: 229.0683, found: 229.0681.

6.2.5 (2*R*,5*S*)-2,5-dihydroxyhexanedioic acid



9 **86**

Scheme 6.5: Synthesis of (2*R*,5*S*)-2,5-dihydroxyhexanedioic acid (**86**).

Dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**) (307 mg, 1.49 mmol) was added to toluene (30 ml) with 12 M hydrochloric acid (0.3 ml) and refluxed for one day in a flask with a condenser attached. Toluene and hydrochloric acid were evaporated, leaving a white powder of **86**.

Yield 219 mg, 83 %.

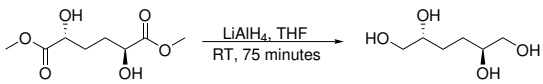
Melting point > 162 °C (decomposition).

^{1}H-NMR (400 MHz, Dimethyl sulfoxide-d_6) δ: 3.91 (dd, J = 6.2, 2.1 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.60 – 1.51 (m, 2H).

^{13}C-NMR (101 MHz, Dimethyl sulfoxide-d_6) δ: 175.69 (s, 2C), 69.60 (s, 2C), 30.06 (s, 2C).

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_6H_{10}O_6Na$: 201.0370, found: 201.0369.

6.2.6 Hexane-1,2,5,6-tetraol



9 **15**

Scheme 6.6: Synthesis of hexane-1,2,5,6-tetraol (**15**).

Dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**) (438 mg, 2.12 mmol) and $LiAlH_4$ (183 mg, 4.82 mmol) with a magnet for stirring were added in a Schlenk flask with an outer and an inner joint. The flask was flamed before use. The inner joint was connected to a Schlenk line. The outer joint was corked after addition of the two solids. The flask was flushed with nitrogen three times. Then dry (<10 ppm) THF (20 ml) was added via a syringe through the septum. The reaction reacts violently. The reaction mixture was stirred for 75 minutes. $LiAlH_4$ was quenched with water (1 ml) by adding it drop-wise for period over a couple of minutes. The reaction was stirred for 5 minutes and then more water (1 ml) was added. The mixture was evaporated on celite and purified via **DCVC** with a 8 % gradient of methanol from dichloromethane. Fraction 6-7 with the product **15** were isolated and the solvent was evaporated. The product was dried under vacuum.

Yield 31 mg, 10 %.

Melting point 88-89 °C. (Recrystallised from Ethanol)[226]

^{1}H-NMR (400 MHz, Methanol-d_4) δ: 3.63 – 3.54 (m, 2H), 3.52 – 3.40 (m, 4H), 1.77 – 1.67 (m, 2H), 1.44 – 1.34 (m, 2H).

^{13}C-NMR (101 MHz, Methanol-d_4) δ: 73.51 (s, 2C), 67.32 (s, 2C), 30.62 (s, 2C).

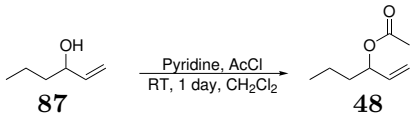
^{1}H-NMR (400 MHz, Water-d_2) δ: 3.75 – 3.65 (m, 2H), 3.60 (dd, J = 11.7, 3.9 Hz, 2H), 3.49 (dd, J = 11.7, 6.8 Hz, 2H), 1.72 – 1.61 (m, 2H), 1.49 – 1.36 (m, 2H).

^{13}C-NMR (101 MHz, Water-d_2) δ: 71.83 (s, 2C), 65.24 (s, 2C), 28.47 (s, 2C).

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_6H_{14}O_4Na$: 173.0784, found: 173.0788.

6.2.7 Hex-1-en-3-yl acetate

1-Hexen-3-ol (**87**) (0.996 g, 9.94 mmol) and pyridine (0.808 g, 10.21 mmol) were added to dry degassed dichloromethane (40 ml). Acetyl chloride (1.35 ml, 18.99 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was



Scheme 6.7: Synthesis of hex-1-en-3-yl acetate (**48**).

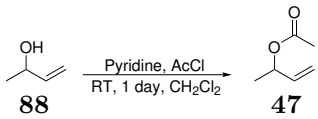
stirred overnight. The mixture was poured into ice water (50 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 2 M HCl (20 ml x 2 times) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **48**.

Yield 1.375 g, 97 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.83 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.34 – 5.19 (m, 3H), 2.12 (s, 3H), 1.76 – 1.55 (m, 2H), 1.49 – 1.35 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 170.47, 136.76, 116.56, 74.73, 36.41, 21.35, 18.45, 13.93. HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_8H_{14}O_2Na$: 165.0886, found: 165.0873.

6.2.8 But-3-en-2-yl acetate



Scheme 6.8: Synthesis of but-3-en-2-yl acetate (**47**).

3-Buten-2-ol (**88**) (1.006 g, 13.95 mmol) and pyridine (1.107 g, 13.99 mmol) were added to dry degassed dichloromethane (40 ml). Acetyl chloride (1.87 ml, 26.35 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (50 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 2 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **47**. The product was volatile.

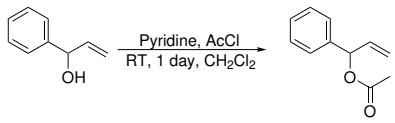
Yield 1.475 g, 93 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.83 (ddd, J = 17.3, 10.5, 5.9 Hz, 1H), 5.37 – 5.29 (m, 1H), 5.23 (ddd, J = 17.3, 1.3 Hz, 1H), 5.12 (ddd, J = 10.5, 1.3 Hz, 1H), 2.04 (s, 3H), 1.30 (d, J = 6.5 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 170.40, 137.81, 115.84, 71.10, 21.43, 20.02.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_6H_{10}O_2Na$: 137.0573, found: 137.0247.

6.2.9 1-Phenylallyl acetate



89 **49**

Scheme 6.9: Synthesis of 1-phenylallyl acetate (**49**).

α-Vinylbenzyl alcohol (**89**) (0.977 g, 7.28 mmol) and pyridine (0.581 g, 6.80 mmol) were added to dry degassed dichloromethane (40 ml). Acetyl chloride (1.87 ml, 26.35 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (50 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 1 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **49**. The product can be purified further by **DCVC**, if necessary.

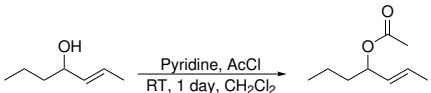
Yield 1.198 g, 93 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 7.34 – 7.15 (m, 5H), 6.18 (dd, J = 5.9, 1.4 Hz, 1H), 5.92 (ddd, J = 17.2, 10.4, 5.9 Hz, 1H), 5.27 – 5.11 (m, 2H), 2.01 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 169.99, 138.97, 136.36, 128.62, 128.23, 127.21, 116.96, 76.25, 21.30.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{11}H_{12}O_2Na$: 199.0730, found: 199.0741.

6.2.10 (*E*)-Hept-2-en-4-yl acetate



90 **50**

Scheme 6.10: Synthesis of (*E*)-hept-2-en-4-yl acetate (**91**).

(*E*)-Hept-2-en-4-ol (**90**) (0.984 g, 8.62 mmol) and pyridine (0.699 g, 8.84 mmol) were added to dry degassed dichloromethane (40 ml). Acetyl chloride (1.18 ml, 16.37 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (50 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 2 M HCl

(2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **50**. The product can be further purified by **DCVC** if necessary.

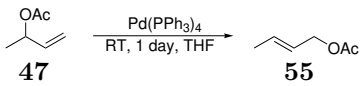
Yield 1.104 g, 82 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.76 – 5.63 (m, 1H), 5.44 – 5.34 (m, 1H), 5.18 (q, J = 7.0 Hz, 1H), 2.02 (d, J = 0.7 Hz, 3H), 1.71 – 1.65 (m, 3H), 1.64 – 1.55 (m, 1H), 1.53 – 1.45 (m, 1H), 1.36 – 1.23 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 170.58, 129.86, 129.15, 74.92, 36.75, 21.51, 18.59, 17.85, 13.96.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_9H_{16}O_2Na$: 179.1043, found: 179.0916.

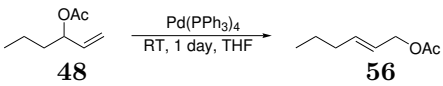
6.2.11 (*E*)-But-2-en-1-yl acetate



Scheme 6.11: Synthesis of (*E*)-but-2-en-1-yl acetate (**55**).

$Pd(PPh_3)_4$ (0.023 g, 0.020 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum. The tube was evacuated and flushed three times with nitrogen. Then dry degassed THF (3 ml, 23 ppm) was added through the septum using a syringe. The catalyst was stirred in the THF solution for a short period before but-3-en-2-yl acetate (**47**) (0.117 g, 1.03 mmol) was added through the septum using a syringe. Decane (88.3 mg) was added to the mixture as a reference. The reaction mixture was stirred overnight. A sample was drawn from the mixture for GC analysis and the GC yield of the product **55** was determined as 40 %. One reason for the low yield is unconverted starting material.

6.2.12 (*E*)-Hex-2-en-1-yl acetate

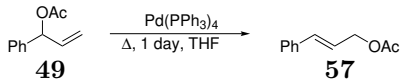


Scheme 6.12: Synthesis of (*E*)-hex-2-en-1-yl acetate (**56**).

$Pd(PPh_3)_4$ (0.024 g, 0.021 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum. The tube was flushed three times with nitrogen. Then, dry degassed THF (3 ml, 23 ppm) was added through the septum using a syringe. The catalyst was stirred in the THF solution for a short

period before hex-1-en-3-yl acetate (**48**) (0.141 g, 0.99 mmol) was added through the septum using a syringe. Decane (120.7 mg) was added to the mixture as a reference. The reaction mixture was stirred overnight. A sample was drawn from the mixture for GC analysis and the GC yield of the product **56** was determined as 56 %. One reason for the low yield is unconverted starting material.

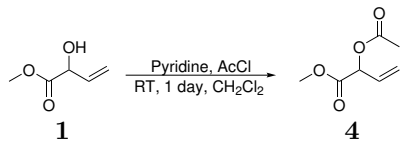
6.2.13 Cinnamyl acetate



Scheme 6.13: Synthesis of cinnamyl acetate (**57**).

$Pd(PPh_3)_4$ (0.025 g, 0.021 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum and a cold-finger, used as a condenser. The tube was flushed three times with nitrogen. Then dry degassed THF (3 ml, 41 ppm) was added through the septum using a syringe. The catalyst was stirred in the THF solution for a short period, before 1-phenylallyl acetate (**49**) (0.177 g, 1.00 mmol) was added through the septum using a syringe. Decane (147.4 mg) was added to the mixture as a reference. The reaction mixture was refluxed overnight. A sample was drawn from the mixture for GC analysis and the GC yield of the product **57**. GC yield 52 %. One reason for the low yield is unconverted starting material.

6.2.14 Methyl 2-acetoxybut-3-enoate



Scheme 6.14: Synthesis of methyl 2-acetoxybut-3-enoate (**4**).

The procedure published by Sølvhøj et al. was followed.[123] **MVG** (**1**) (9.984 g, 85.98 mmol) and pyridine (6.760 g, 85.46 mmol) were added to dry degassed dichloromethane (300 ml). Acetyl chloride (11.63 ml, 163.57 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (300 ml) and extracted with dichloromethane (2 x 30 ml). The dichloromethane phase was washed with 2 M HCl (2 x 50 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 50 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was subsequently removed with

a rotary evaporator, yielding a liquid product **4**, which can be further purified by distillation.

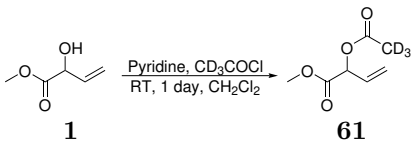
Yield 13.146 g, 97 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.94 (ddd, J = 16.9, 10.4, 6.4 Hz, 1H), 5.57 – 5.47 (m, 2H), 5.37 (ddd, J = 10.4, 1.3, 0.8 Hz, 1H), 3.76 (s, 3H), 2.17 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 170.13, 169.06, 130.10, 119.96, 73.14, 52.75, 20.79.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_7H_{10}O_4Na$: 181.0471, found: 181.0479.

6.2.15 Methyl 2-(acetoxy-d_3)but-3-enoate



Scheme 6.15: Synthesis of methyl 2-(acetoxy-d_3)but-3-enoate (**61**).

MVG (**1**) (0.974 g, 8.39 mmol) and pyridine (0.692 g, 8.75 mmol) were added to dry degassed dichloromethane (40 ml). Deuterated acetyl chloride (1.143 g, 14.02 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (50 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 2 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **61**. The product can be further purified by **DCVC** if necessary.

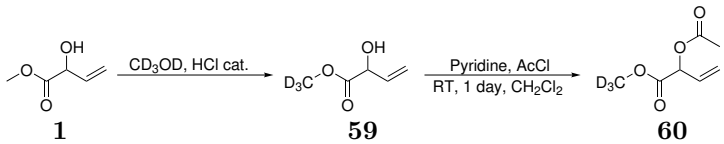
Yield 1.306 g, 97 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.91 (ddd, J = 16.9, 10.6, 6.3 Hz, 1H), 5.55 – 5.42 (m, 2H), 5.34 (ddd, J = 10.4, 1.1 Hz, 1H), 3.73 (s, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 170.04, 168.97, 130.05, 119.85, 73.03, 52.65, 20.02 (p, J 19.5 Hz, 1 C).

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_7H_7D_3O_4Na$: 184.0660, found: 184.0653.

6.2.16 Methyl-d_3 2-acetoxybut-3-enoate



Scheme 6.16: Synthesis of methyl-d_3 2-acetoxybut-3-enoate (**60**).

MVG (**1**) was labelled with deuterium at the methylester group via a transesterification with CD_3OD and a catalytic amount of hydrochloric acid to produce methyl-d_3 2-hydroxybut-3-enoate (**59**). The solvent was evaporated off. Compound **59** (0.505 g, 4.24 mmol) was mixed with pyridine (0.340 g, 4.30 mmol) in dry degassed dichloromethane (20 ml). Acetyl chloride (0.567 ml, 8.05 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (30 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 2 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **60**. The product can be further purified by **DCVC**, if necessary.

Yield 0.459 g, 67 %.

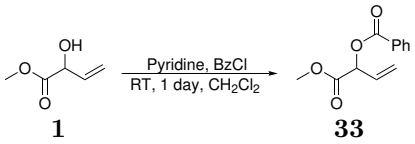
^{1}H-NMR (400 MHz, Chloroform-d) δ: 5.93 (ddd, J = 16.9, 10.5, 6.3 Hz, 1H), 5.54 – 5.46 (m, 2H), 5.43 – 5.31 (m, 1H), 2.16 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-d) δ: 170.09, 169.04, 130.07, 119.91, 73.11, 51.86 (p, J = 22.6 Hz), 19.5 Hz), 20.73.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_7H_7D_3O_4Na$: 184.0660, found: 184.0652.

HRMS (**MVG** labelled with deuterium) (ESI+): m/z $[M+Na]^+$ calc. for $C_5H_5D_3O_3$-Na: 142.0554, found: 142.0550.

6.2.17 1-Methoxy-1-oxobut-3-en-2-yl benzoate



Scheme 6.17: Synthesis of 1-methoxy-1-oxobut-3-en-2-yl benzoate (**33**).

MVG (**1**) (0.988 g, 8.51 mmol) and pyridine (0.684 g, 8.65 mmol) were added to dry degassed dichloromethane (40 ml). Benzoyl chloride (1.26 ml, 16.31 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight.

The mixture was quenched with 3-(dimethylamino)-1-propylamine (1.1 ml, 8.74 mmol) and stirred for 20 minutes.[177] Then, the mixture was poured into ice water (40 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 1 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **33**. The product was purified further by **DCVC** with a 4 % gradient from heptane to ethyl acetate.

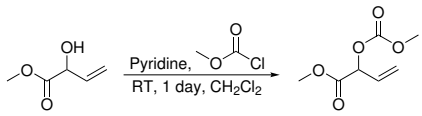
Yield 1.255 g, 67 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 8.15 – 8.09 (m, 1H), 7.65 – 7.56 (m, 1H), 7.52 – 7.39 (m, 1H), 6.09 (ddd, J = 17.2, 10.5, 6.0 Hz, 1H), 5.74 (ddd, J = 6.0, 1.6 Hz, 1H), 5.62 (ddd, J = 17.2, 1.6, 0.9 Hz, 1H), 5.44 (ddd, J = 10.5, 1.6, 0.9 Hz, 1H), 3.79 (s, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 169.00, 165.65, 133.59, 130.25, 130.04, 129.35, 128.57, 119.92, 73.47, 52.77.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{12}H_{12}O_4Na$: 243.0628, found: 243.0640.

6.2.18 Methyl 2-((methoxycarbonyl)oxy)but-3-enoate



1 **34**

Scheme 6.18: Synthesis of methyl 2-((methoxycarbonyl)oxy)but-3-enoate (**34**).

MVG (**1**) (0.962 g, 8.28 mmol) and pyridine (0.685 g, 8.66 mmol) were added to dry degassed dichloromethane (50 ml). Methyl chloroformate (1.5 ml, 12.91 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight. The mixture was poured into ice water (40 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 1 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **34**. The product was purified further by **DCVC** with a 4 % gradient from heptane to ethyl acetate. TLC eluent was 50/50, heptane/ethyl acetate.

Yield 0.421 g, 29 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.91 (ddd, J = 17.0, 10.5, 6.1 Hz, 1H), 5.51 (ddd, J = 17.0, 1.5, 0.7 Hz, 1H), 5.45 – 5.34 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 168.52, 154.79, 129.41, 120.13, 75.72, 55.24, 52.69.

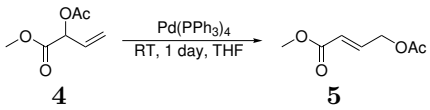
HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_7H_{10}O_5Na$: 197.0420, found: 197.0450.

Methyl 2-((methoxycarbonyl)oxy)but-3-enoate, large scale

MVG (**1**) (9.962 g, 86.09 mmol) and pyridine (6.958 g, 87.96 mmol) were added to dry degassed dichloromethane (300 ml). Methyl chloroformate (12.64 ml, 163.56 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was left to stir overnight. The mixture was poured into ice water (300 ml) and extracted with dichloromethane (2 x 30 ml). The dichloromethane phase was washed with 1 M HCl (2 x 50 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 50 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product. The product was purified further by distillation. The product was collected at 82 - 84 °C at 17 mbar

Yield 11.22 g, 75 %.

6.2.19 Methyl (*E*)-4-acetoxybut-2-enoate



Scheme 6.19: Synthesis of methyl (*E*)-4-acetoxybut-2-enoate (**5**).

$Pd(PPh_3)_4$ (0.350 g, 0.30 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum. The tube was flushed three times with nitrogen. Then dry degassed THF (45 ml, 21 ppm) was added through the septum using a syringe. The catalyst was stirred in the THF solution for a short period before methyl 2-acetoxybut-3-enoate (**4**) (2.366 g, 14.96 mmol) was added through the septum using a syringe. The reaction mixture was stirred overnight. The mixture was evaporated with celite on a rotary evaporator. The product **5** was separated using **DCVC** with a 4 % gradient from heptane to ethyl acetate. TLC eluent was 80/20, heptane/ethyl acetate. The procedure yielded a liquid product.

Yield 1.761 g, 74 %.

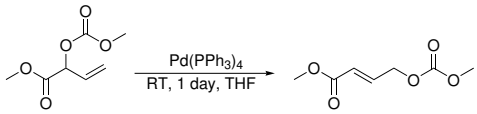
^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.94 (dt, J = 15.8, 4.6 Hz, 1H), 6.03 (dt, J = 15.8, 2.0 Hz, 1H), 4.73 (dd, J = 4.6, 2.0 Hz, 2H), 3.75 (s, 3H), 2.11 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 170.41, 166.36, 141.55, 121.93, 62.66, 51.88, 20.84.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_7H_{10}O_4Na$: 181.0471, found: 181.0472.

6.2.20 Methyl (*E*)-4-((methoxycarbonyl)oxy)but-2-enoate

$Pd(PPh_3)_4$ (0.027 g, 0.023 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum. The tube was evacuated and flushed three times with nitrogen. Then dry degassed THF (3 ml, 26 ppm) was added through the septum using a syringe. The catalyst was stirred in the THF solution



34 **54**

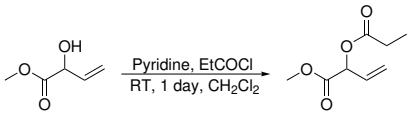
Scheme 6.20: Synthesis of methyl (*E*)-4-((methoxycarbonyl)oxy)but-2-enoate (**54**).

for a short period before methyl 2-((methoxycarbonyl)oxy)but-3-enoate (**34**) (0.180 g, 1.03 mmol) was added through the septum using a syringe. The reaction mixture was stirred overnight. DMSO (83.3 mg, 1.07 mmol) was added to the reaction mixture as a reference. A sample was drawn from the mixture for analysis with NMR for crude ^{1}H-NMR yields.

^{1}H-NMR yield 40 %.

HRMS not obtained.

6.2.21 Methyl 2-(propionyloxy)but-3-enoate



1 **35**

Scheme 6.21: Synthesis of methyl 2-(propionyloxy)but-3-enoate (**35**).

MVG (**1**) (0.997 g, 8.59 mmol) and pyridine (0.685 g, 8.66 mmol) were added to dry (35 ppm) degassed dichloromethane (40 ml). Propanoyl chloride (1.43 ml, 16.36 mmol) was added drop-wise (3 ml/hour) to the mixture. The reaction mixture was stirred overnight and was then poured into ice water (50 ml) and extracted with dichloromethane (2 x 15 ml). The dichloromethane phase was washed with 2 M HCl (2 x 20 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 20 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product. The product **35** is volatile.

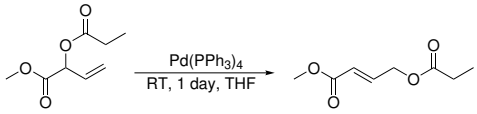
Yield 1.228 g, 83 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.95 (ddd, J = 17.5, 10.4, 5.7 Hz, 1H), 5.57 – 5.48 (m, 2H), 5.37 (ddd, J = 10.4, 1.3, 0.8 Hz, 1H), 3.76 (s, 3H), 2.47 (qd, J = 7.6, 4.7 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 173.60, 169.15, 130.22, 119.84, 72.96, 52.72, 27.42, 9.06.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_8H_{12}O_4Na$: 195.0628, found: 195.0629.

6.2.22 Methyl (*E*)-4-(propionyloxy)but-2-enoate



35 **52**

Scheme 6.22: Synthesis of methyl (*E*)-4-(propionyloxy)but-2-enoate (**52**).

$Pd(PPh_3)_4$ (0.023 g, 0.020 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum. The tube was evacuated and flushed three times with nitrogen. Then dry degassed THF (3 ml) was added through the septum using a syringe. The catalyst was stirred in the THF solution for a short period before methyl 2-(propionyloxy)but-3-enoate (**35**) (0.175 g, 1.02 mmol) was added through the septum using a syringe. The reaction mixture was stirred overnight. The solvent from the mixture was evaporated with celite added on a rotary evaporator. The product **52** was separated using **DCVC** with a 4 % gradient from heptane to ethyl acetate. TLC eluent was 80/20, heptane/ethyl acetate. The procedure yielded a liquid product.

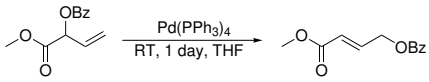
Yield 0.135 g, 77 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.91 (dt, J = 15.8, 4.6 Hz, 1H), 5.99 (dt, J = 15.8, 2.0 Hz, 1H), 4.71 (dd, J = 4.6, 2.0 Hz, 2H), 3.71 (s, 3H), 2.37 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 173.73, 166.29, 141.70, 121.73, 62.43, 51.77, 27.42, 9.09.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_8H_{12}O_4Na$: 195.0628, found: 195.0635.

6.2.23 (*E*)-4-Methoxy-4-oxobut-2-en-1-yl benzoate



33 **53**

Scheme 6.23: Synthesis of (*E*)-4-methoxy-4-oxobut-2-en-1-yl benzoate (**53**).

$Pd(PPh_3)_4$ (0.025 g, 0.022 mmol) was measured in a Schlenk tube. The Schlenk tube was then fitted to a Schlenk line and corked with a septum. The tube was evacuated and flushed three times with nitrogen. Then dry degassed THF (3 ml, 74.2 ppm) was added through the septum using a syringe. The catalyst was stirred in the THF solution for a short period before 1-methoxy-1-oxobut-3-en-2-yl benzoate (**33**) (0.221 g, 1.00 mmol) was added through the septum using a syringe. The reaction mixture was stirred overnight. The solvent from the mixture was evaporated with celite added on a

rotary evaporator. The product **53** was separated using **DCVC** with a 4 % gradient from heptane to ethyl acetate. TLC eluent was 80/20, heptane/ethyl acetate.

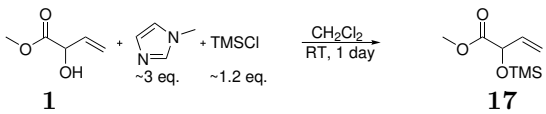
Yield 0.199 g, 90 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 8.14 – 8.00 (m, 2H), 7.63 – 7.56 (m, 1H), 7.53 – 7.39 (m, 2H), 7.07 (dt, J = 15.8, 4.5 Hz, 1H), 6.14 (dt, J = 15.8, 2.0 Hz, 1H), 4.99 (dd, J = 4.5, 2.0 Hz, 2H), 3.76 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 166.35, 165.93, 141.67, 133.47, 129.83, 129.63, 128.62, 121.92, 63.06, 51.88.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{12}H_{12}O_4Na$: 243.0628, found: 243.0633.

6.2.24 Methyl 2-((trimethylsilyl)oxy)but-3-enoate



Scheme 6.24: Synthesis of methyl 2-((trimethylsilyl)oxy)but-3-enoate (**17**).

MVG (**1**) (1.997 g, 17.22 mmol) and 1-methyl-1*H*-imidazole (4.316 g, 52.57 mmol) were added to dry degassed dichloromethane (60 ml, 8 ppm) in a flask with stirring. Chlorotrimethylsilane (2.618 ml, 20.63 mmol) was added drop-wise (3 ml/h) to the reaction mixture with a syringe pump. After 140 minutes, the reaction mixture was poured into ice water and extracted with dichloromethane (2 x 20 ml). The dichloromethane phase was washed with a saturated aqueous solution of NH_4Cl (3 x 80 ml). The mixture was not pure and was washed further with NH_4Cl (2 x 40 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. The solvent from the mixture was evaporated with celite added on a rotary evaporator. The product was separated using **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding a liquid product **17**. TLC eluent was 80/20, heptane/ethyl acetate. The product is prone to hydrolysis.

Yield 1.278 g, 39 %.

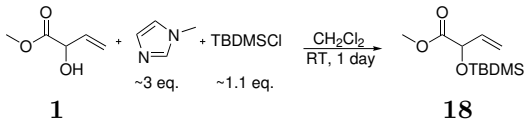
^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.97 (ddd, J = 17.1, 10.3, 5.2 Hz, 1H), 5.44 (ddd, J = 17.1, 1.6 Hz, 1H), 5.23 (dd, J = 10.3, 1.6 Hz, 1H), 4.70 (dd, J = 5.2, 1.6 Hz, 1H), 3.74 (s, 3H), 0.15 (s, 9H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 172.24, 135.19, 116.96, 73.15, 52.38, -0.02.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_8H_{16}O_3SiNa$: 211.0761, found: 211.0768.

6.2.25 Methyl 2-((*tert*-butyldimethylsilyl)oxy)but-3-enoate

MVG (**1**) (0.509 g, 4.38 mmol) and 1-methyl-1*H*-imidazole (1.115 g, 13.58 mmol) were added to dry degassed dichloromethane (15 ml) in a flask with stirring. *tert*-Butyldimethylsilyl chloride (0.716 mg, 4.75 mmol) was added to the mixture. After 140 minutes, the reaction mixture was poured into ice water and extracted with dichloromethane (2 x 20 ml). The dichloromethane phase was washed with 1 M HCl (2



Scheme 6.25: Synthesis of methyl 2-((*tert*-butyldimethylsilyl)oxy)but-3-enoate (**18**).

x 15 ml) and then with an aqueous solution saturated with Na_2CO_3 (2 x 15 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. The solvent was evaporated with celite added on a rotary evaporator. The product was separated using **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding a liquid product **18**. TLC eluent was 80/20, heptane/ethyl acetate.

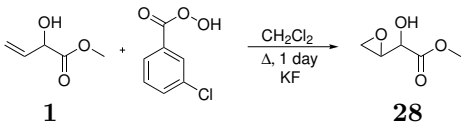
Yield 0.520 g, 51 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.96 (ddd, J = 17.0, 10.4, 4.8 Hz, 1H), 5.45 (ddd, J = 17.0, 1.8 Hz, 1H), 5.21 (ddd, J = 10.4, 1.8 Hz, 1H), 4.71 (ddd, J= 4.8, 1.8 Hz, 1H), 3.72 (s, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 172.29, 135.17, 116.46, 73.33, 52.24, 25.80, 18.55, -5.02.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{11}H_{22}O_3SiNa$: 253.1230, found: 253.1231.

6.2.26 Methyl 2-hydroxy-2-(oxiran-2-yl)acetate



Scheme 6.26: Synthesis of methyl 2-hydroxy-2-(oxiran-2-yl)acetate (**28**).

Purified *m*-CPBA (2.254 g, 13.06 mmol) was added to dry degassed dichloromethane (60 ml) in a flask with magnetic stirring and a condenser fitted.[173] When the *m*-CPBA was dissolved the **MVG** (**1**) (0.980 g, 4.44 mmol) was added to the mixture and stirred overnight at refluxing temperature. The heat source was removed and KF (0.946 g, 16.28 mmol) was added and left to stir overnight. KF was filtered off. The mixture still contained impurities and subsequently more KF (0.236 g, 4.06 mmol) was added prior to stirring, and then filtered off. This yielded 77 % of the product with roughly 10 % impurities. KF (0.336 g, 5.78 mmol) was added again and filtered off. Dichloromethane was evaporated, yielding a solid product **28** that was on the verge of turning into a liquid. The product is highly reactive and has to be stored in the freezer (-18 °C). The product was unsuccessfully purified through distillation and **DCVC**, hence only precipitation with KF worked out, so far.

Yield 0.862 g, 68 %.

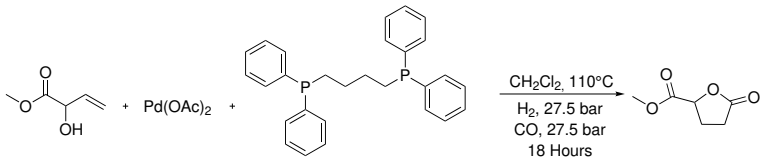
NMR Solvent was filtered through basic alumina to remove any acidity.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 4.31 (d, J = 3.7 Hz, 0.3 H), 4.26 (d, J = 2.9 Hz, 0.7 H), 3.81 (s, 2H), 3.81 (s, 1H), 3.30 – 3.24 (m, 1H), 2.89 (dd, J = 5.2, 2.6 Hz, 0.7 H), 2.83 (dd, J = 5.0, 2.6 Hz, 0.3 H), 2.79 – 2.73 (m, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 172.56, 172.22, 69.41, 69.09, 52.98, 52.96, 52.50, 52.05, 43.77, 43.71.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_5H_9O_4$: 133.0495, found: 133.0492.

6.2.27 Methyl 5-oxotetrahydrofuran-2-carboxylate



Scheme 6.27: Synthesis of methyl 5-oxotetrahydrofuran-2-carboxylate (**24**).

MVG (**1**) (0.134 g, 1.15 mmol), $Pd(OAc)_2$ (0.013 g, 0.057 mmol) and 1,4-bis-(diphenylphospino)butane (0.020 g, 0.047 mmol) were added to dry degassed dichloromethane (10 ml) in an autoclave with 50 ml volume.[167] The autoclave was sealed and flushed with CO. Then, the autoclave was pressurised with CO (27.5 bar) and H_2 (27.5 bar). The mixture was stirred for 20 hours at 110 °C. The solvent from the mixture was evaporated with celite added on a rotary evaporator. The product was separated using **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding a liquid product **24**. TLC eluent was 40/60, heptane/ethyl acetate.

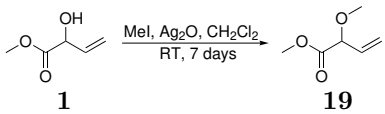
Yield 0.029 g, 17 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.04 – 4.89 (m, 1H), 3.79 (s, 3H), 2.72 – 2.44 (m, 3H), 2.40 – 2.21 (m, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 176.05, 170.41, 75.75, 52.87, 26.80, 25.90.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_6H_8O_4Na$: 167.0315, found: 167.0319.

6.2.28 Methyl 2-methoxybut-3-enoate



Scheme 6.28: Synthesis of methyl 2-methoxybut-3-enoate (**19**).[154]

Silver(I)oxide (1.505 g, 6.54 mmol) and methyl iodide (6.16 g, 43.41 mmol) were mixed in dry dichloromethane (30 ml) in a Schlenk tube attached to a Schlenk line.

MVG (**1**) (1.016 g, 8.72 mmol) was added drop-wise to the mixture. The reaction mixture was stirred for five days. After five days, NMR analysis of the reaction showed the reaction was incomplete. More silver(I)oxide (0.492 g, 2.12 mmol) was added to the mixture. NMR analysis showed the reaction was complete after two more days. The silver(I)oxide was filtered off. Dichloromethane was evaporated. To further purify the product it was distilled under vacuum (3 mbar) at 140-145 °C yielding a colourless liquid **19**.

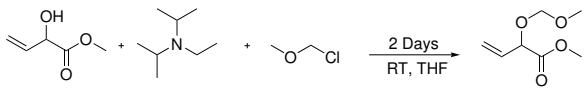
Yield 0.555 g, 49 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.84 (ddd, J = 17.1, 10.4, 6.4 Hz, 1H), 5.45 (ddd, J = 17.1, 1.3 Hz, 1H), 5.33 (ddd, J = 10.4, 1.3 Hz, 1H), 4.25 (ddd, J= 6.4, 1.3 Hz, 1H), 3.75 (s, 3H), 3.39 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 171.02, 132.63, 119.55, 81.60, 57.47, 52.38.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_6H_{10}O_3Na$: 153.0522, found: 153.0516.

6.2.29 Methyl 2-(methoxymethoxy)but-3-enoate



1 **20**

Scheme 6.29: Synthesis of methyl 2-(methoxymethoxy)but-3-enoate (**20**).

MVG 1 (0.200 g, 1.72 mmol) was mixed with di-*iso*-propylethyl amine (0.425 g, 3.29 mmol) in dry THF (3 ml) in a Schlenk tube with an inert nitrogen atmosphere and kept at 0 °C in an ice bath. Chloromethyl methyl ether (0.436 g, 5.42 mmol) was added to the mixture drop-wise with a syringe. After chloromethyl methyl ether had been added, the ice bath was removed and the mixture was left to stir for two days. Ether (10 ml) was added to the mixture. The organic phase was washed with 1 M hydrochloric acid (2 x 10 ml) and then with an aqueous solution saturated with Na_2CO_3 (2 x 10 ml). The organic phase was dried with $MgSO_4$, which was filtered off. The organic solvent was evaporated to yield the product **20**.

Yield 0.057 g, 21 %.

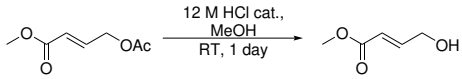
^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.91 (ddd, J = 17.1, 10.4, 6.3 Hz, 1H), 5.49 (dd, J = 17.1, 1.3 Hz, 1H), 5.35 (dd, J = 10.4, 1.3 Hz, 1H), 4.78 – 4.69 (m, 2H), 4.67 (dd, J = 6.3, 1.3 Hz, 1H), 3.77 (s, 3H), 3.40 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 171.13, 132.46, 119.39, 95.17, 75.94, 56.10, 52.48.

HRMS not obtained.

6.2.30 Methyl (*E*)-4-hydroxybut-2-enoate

Methyl (*E*)-4-acetoxybut-2-enoate (**4**) (0.094 g, 0.59 mmol) and a few drops of 12 M HCl in methanol (3 ml) were added in a small tube and was stirred overnight. The



Scheme 6.30: Synthesis of methyl (E)-4-hydroxybut-2-enoate (**22**).

mixture was concentrated on a rotary evaporator to yield a liquid product **22**. It is suspected some of the product can be lost, if left to evaporate for too long.

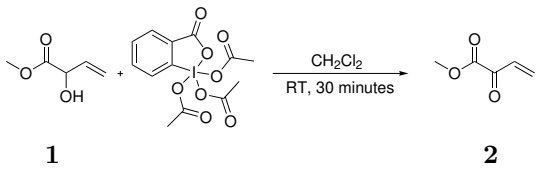
Yield 0.064 g, 93 %.

^{1}H-NMR (400 MHz, Chloroform-d) δ: 7.00 (ddd, J = 15.7, 3.9 Hz, 1H), 6.07 (ddd, J = 15.7, 2.2 Hz, 1H), 4.30 (dd, J = 3.9, 2.2 Hz, 2H), 3.71 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-d) δ: 167.23, 147.61, 119.62, 61.71, 51.77.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_5H_9O_3$: 117.0546, found: 117.0553.

6.2.31 Methyl 2-oxobut-3-enoate



Scheme 6.31: Synthesis of methyl 2-oxobut-3-enoate (**2**).

Dess-Martin periodinane (2.019 g, 4.76 mmol) was weighed in a 25 ml Schlenk tube with a magnet for stirring. The tube was flushed with nitrogen. Dry dichloromethane (15 ml) was added to the tube via a syringe. The flask was cooled in an ice bath. **MVG** (**1**) (502 mg, 4.32 mmol) was added drop-wise with a syringe. The cooling bath was removed. The reaction mixture was left to stir for 30 minutes. The mixture was poured into a separatory funnel and dichloromethane was added (35 ml). The organic phase was washed with an aqueous solution saturated with Na_2CO_3 (3 x 20 ml). The organic phase was evaporated until only a few millilitres remained. A mixture of 50 % pentane and 50 % dichloromethane was added (25 ml). The mixture was filtered through a dry column with 300 mbar of pressure vacuum. Increments of the mixture 50 % pentane and 50 % dichloromethane (25 ml) were poured through the column until all of the product was filtered through. RF value was 0.58, TLC eluent was 40/60, heptane/ethyl acetate. Solvents from the fractions with product were evaporated off at 300 mbar of vacuum. If the reaction is left too long the product will undergo a hetero Diels Alder reaction. The product should be stored at -18 °C to avoid the same reaction.

^{1}H-NMR Yield 16 %.

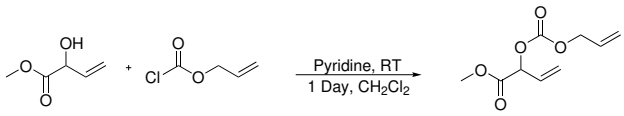
^{1}H-NMR (400 MHz, Chloroform-d) δ: 6.91 (dd, J = 17.6, 10.7 Hz, 1H), 6.56 (dd,

J = 17.6, 1.0 Hz, 1H), 6.12 (dd, J = 10.7, 1.0 Hz, 1H), 3.90 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-d) δ: 183.37, 162.20, 134.59, 131.25, 53.09.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_5H_6O_3Na$: 137.0209, found: 137.0218.

6.2.32 Methyl 2-(((allyloxy)carbonyl)oxy)but-3-enoate



Scheme 6.32: Synthesis of methyl 2-(((allyloxy)carbonyl)oxy)but-3-enoate (**26**).

MVG (**1**) (9.966 g, 85.83 mmol) and pyridine (6.950 g, 87.86 mmol) were added to dry degassed dichloromethane (300 ml). Allyl chloroformate (10.07 ml, 94.74 mmol) was added drop-wise (3 ml/hour) at 0 °C cooled with an ice bath. When the addition of allyl chloroformate was completed the ice bath was removed. The reaction mixture was stirred overnight. The mixture was poured into ice water (150 ml). The dichloromethane phase was washed with 1 M HCl (2 x 50 ml) and with an aqueous solution saturated with Na_2CO_3 (2 x 50 ml). The dichloromethane phase was dried with $MgSO_4$, which was filtered off. Dichloromethane was removed with a rotary evaporator, yielding a liquid product **26**, which was further purified by distillation. The pure fraction was collected at 103 - 104 °C at 10 mbar.

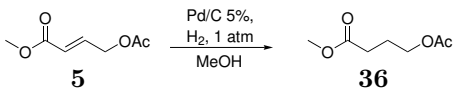
Yield 11.36 g, 66 %.

^{1}H-NMR (400 MHz, Chloroform-d) δ: 6.02 – 5.85 (m, 2H), 5.61 – 5.48 (m, 1H), 5.44 – 5.35 (m, 3H), 5.31 – 5.25 (m, 1H), 4.74 – 4.60 (m, 2H), 3.78 (s, 3H).

^{13}C-NMR (101 MHz, Chloroform-d) δ: 168.67, 154.18, 131.25, 129.52, 120.37, 119.31, 75.90, 69.15, 52.85.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_9H_{12}O_5Na$: 223.0575, found: 223.0575.

6.2.33 Methyl 4-acetoxybutanoate



Scheme 6.33: Synthesis of methyl 4-acetoxybutanoate (**36**).

5 % palladium on carbon (12 mg) was added to methanol (12 ml) in a flask with a septum. The flask was flushed with nitrogen. Methyl (E)-4-acetoxybut-2-enoate (**5**) (0.201 g, 1.27 mmol) was added to the mixture via a syringe. A balloon was filled with

hydrogen and was bobbled through the mixture. A second balloon was connected on the flask and the mixture was stirred overnight. The palladium catalyst was filtered off and methanol was evaporated using a rotary evaporator, leaving a liquid compound methyl 4-acetoxybutanoate (**36**).

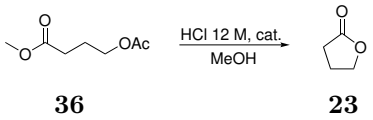
Yield 0.151 g, 74 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 4.01 (t, J = 6.4 Hz, 2H), 3.59 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 1.95 (s, 3H), 1.92 – 1.82 (m, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 173.17, 170.84, 63.33, 51.55, 30.46, 23.96, 20.7.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_7H_{12}O_4Na$: 183.0628, found: 183.0633.

6.2.34 γ-Butyrolactone



Scheme 6.34: Synthesis of γ-butyrolactone (**23**).

Methanol (3 ml) and three drops of 12 M hydrochloric acid were mixed in a flask. Methyl 4-acetoxybutanoate (**36**) (0.135 g, 0.84 mmol) was added to the mixture and the mixture was stirred overnight. The solvent was evaporated using a rotary evaporator, leaving the liquid compound γ-butyrolactone (**23**).

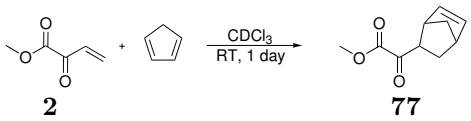
Yield 0.061 g, 84 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 4.30 (t, J = 7.0 Hz, 2H), 2.44 (t, J = 8.1 Hz, 2H), 2.27 – 2.17 (m, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 177.93, 68.60, 27.79, 22.15.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_4H_7O_2$: 87.0441, found: 87.0441.

6.2.35 Methyl 2-(bicyclo[2.2.1]hept-5-en-2-yl)-2-oxoacetate



Scheme 6.35: Synthesis of methyl 2-(bicyclo[2.2.1]hept-5-en-2-yl)-2-oxoacetate (**77**).

Methyl 2-oxobut-3-enoate (**2**) (0.024 g, 0.21 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with cyclopentadiene (0.035 g, 0.53 mmol), which was stirred overnight. The solvent was evaporated with celite

added and purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-(bicyclo[2.2.1]hept-5-en-2-yl)-2-oxoacetate (**77**).

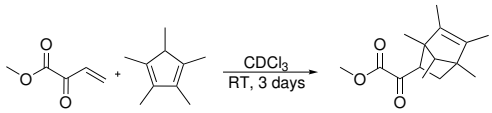
Yield 0.015 g, 40 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.18 (dd, J = 5.8, 3.1 Hz, 1H), 5.82 (dd, J = 5.8, 2.8 Hz, 1H), 3.86 (s, 3H), 3.63 (dt, J = 8.9, 3.9 Hz, 1H), 3.40 – 3.28 (m, 1H), 3.02 – 2.91 (m, 1H), 1.86 (ddd, J = 12.3, 8.9, 3.6 Hz, 1H), 1.54 – 1.47 (m, 2H), 1.43 – 1.34 (m, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 194.93, 162.60, 138.33, 131.31, 52.91, 50.14, 48.70, 46.32, 42.98, 27.86.

HRMS (ESI+): m/z [M+Na]$^{+}$ calc. for $C_{10}H_{12}O_3Na$: 203.0679, found: 203.0679.

6.2.36 Methyl 2-oxo-2-(1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-en-2-yl)acetate



2 **78**

Scheme 6.36: Synthesis of methyl 2-oxo-2-(1,4,5,6,7-pentamethylbicyclo[2.2.1]hept-5-en-2-yl)acetate (**78**).

Methyl 2-oxobut-3-enoate (**2**) (0.032 g, 0.28 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with 1,2,3,4,5-pentamethylcyclopentadiene (0.090 g, 0.66 mmol) and left to stir for three days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-oxo-2-(1,4,5,6,7-pentamethylbicyclo-[2.2.1]hept-5-en-2-yl)acetate (**78**). The product still contained impurities.

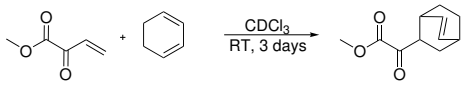
^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 3.83 (s, 3H), 3.54 (dd, J = 8.5, 5.2 Hz, 1H), 1.60 – 1.57 (m, 2H), 1.54 – 1.50 (m, 3H), 1.45 – 1.41 (m, 1H), 1.39 – 1.38 (m, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 0.54 (d, J = 6.5 Hz, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 196.37, 163.72, 136.66, 130.57, 62.58, 60.67, 56.12, 53.23, 52.79, 37.76, 15.20, 15.10, 11.46, 9.87, 7.98.

HRMS (ESI+): m/z [M+H]$^{+}$ calc. for $C_{15}H_{23}O_3$: 251.1642, found: 251.1652.

6.2.37 Methyl 2-(bicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate

Methyl 2-oxobut-3-enoate (**2**) (0.025 g, 0.22 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with cyclohexa-1,3-diene (0.048 g, 0.59 mmol) and left to stir for three days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-(bicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate (**79**). The



2 **79**

Scheme 6.37: Synthesis of methyl 2-(bicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate (**79**).

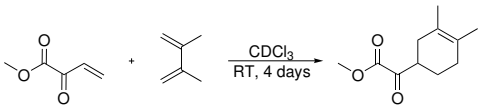
purification was unsuccessful.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.28 (ddd, J = 8.0, 6.6, 1.2 Hz, 1H), 6.03 (ddd, J = 8.0, 6.4, 1.2 Hz, 1H), 3.84 (s, 3H), 3.33 (ddd, J = 9.4, 6.0, 2.1 Hz, 1H), 2.96 – 2.87 (m, 1H), 2.71 – 2.54 (m, 1H), 1.76 – 1.63 (m, 3H), 1.58 – 1.49 (m, 1H), 1.38 – 1.20 (m, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 195.01, 162.71, 135.70, 130.68, 52.83, 47.03, 31.50, 29.47, 27.93, 25.70, 24.50.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_{11}H_{15}O_3$: 195.1016, found: 195.1020.

6.2.38 Methyl 2-(3,4-dimethylcyclohex-3-en-1-yl)-2-oxoacetate



2 **85**

Scheme 6.38: Synthesis of methyl 2-(3,4-dimethylcyclohex-3-en-1-yl)-2-oxoacetate (**85**).

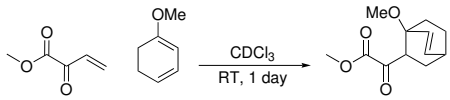
Methyl 2-oxobut-3-enoate (**2**) (0.027 g, 0.23 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with 2,3-dimethylbuta-1,3-diene (0.048 g, 0.58 mmol) and left to stir for four days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-(3,4-dimethylcyclohex-3-en-1-yl)-2-oxoacetate (**85**).

Yield 0.043 g, 94 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 3.85 (s, 3H), 3.24 (dddd, J = 11.1, 9.7, 5.6, 2.9 Hz, 1H), 2.22 – 2.02 (m, 3H), 2.00 – 1.89 (m, 1H), 1.61 (s, 3H), 1.60 (s, 3H), 1.59 – 1.43 (m, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 197.08, 162.22, 125.53, 123.57, 52.86, 43.67, 32.10, 30.92, 24.66, 19.09, 18.93.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_{11}H_{17}O_3$: 197.1172, found: 197.1166.



2 **81**

Scheme 6.39: Synthesis of methyl 2-(1-methoxybicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate (**81**).

6.2.39 Methyl 2-(1-methoxybicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate

Methyl 2-oxobut-3-enoate (**2**) (0.067 g, 0.58 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (2.5 ml) with 1-methoxycyclohexa-1,3-diene (0.113 g, 1.03 mmol) and was stirred overnight. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding a liquid product methyl 2-(1-methoxybicyclo[2.2.2]oct-5-en-2-yl)-2-oxoacetate (**81**).

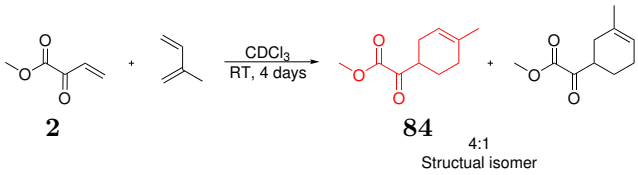
Yield 0.060 g, 46%.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.28 (dd, J = 8.8, 6.5 Hz, 1H), 6.07 (d, J = 8.8 Hz, 1H), 3.89 – 3.75 (m, 4H), 3.28 (s, 3H), 2.64 – 2.54 (m, 1H), 1.85 – 1.77 (m, 1H), 1.68 – 1.56 (m, 4H), 1.43 – 1.32 (m, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 197.17, 163.90, 134.39, 130.59, 81.44, 52.66, 51.31, 48.61, 29.45, 29.04, 28.42, 25.23.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_{12}H_{17}O_4$: 225.1121, found: 225.1145.

6.2.40 Methyl 2-(4-methylcyclohex-3-en-1-yl)-2-oxoacetate



2 **84**

Scheme 6.40: Synthesis of methyl 2-(4-methylcyclohex-3-en-1-yl)-2-oxoacetate (**84**).

Methyl 2-oxobut-3-enoate (**2**) (0.024 g, 0.21 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with isoprene (0.026 g, 0.37 mmol) and left to stir for four days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding a methyl 2-(4-methylcyclohex-3-en-1-yl)-2-oxoacetate (**84**), with a selectivity between the structual isomers of 4:1.

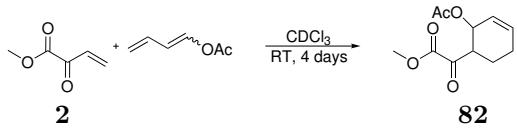
Yield 0.015 g, 39 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 5.46 – 5.34 (m, 1H), 3.86 (s, 3H), 3.22 (dddd, J = 11.0, 8.7, 6.0, 2.6 Hz, 1H), 2.26 – 1.93 (m, 5H), 1.66 (s, 3H), 1.63 – 1.57 (m, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 197.18, 162.21, 133.96, 118.80, 52.93, 42.69, 29.25, 26.20, 24.34, 23.54.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{10}H_{14}O_3Na$: 205.0835, found: 205.0812.

6.2.41 Methyl 2-(2-acetoxycyclohex-3-en-1-yl)-2-oxoacetate



Scheme 6.41: Synthesis of methyl 2-(2-acetoxycyclohex-3-en-1-yl)-2-oxoacetate (**82**).

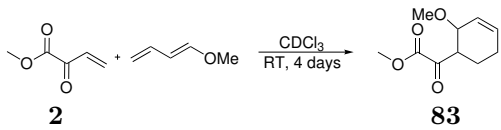
Methyl 2-oxobut-3-enoate (**2**) (0.024 g, 0.21 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with (*E*)-buta-1,3-dien-1-yl acetate (0.047 g, 0.42 mmol) and left to stir for four days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-(2-acetoxycyclohex-3-en-1-yl)-2-oxoacetate (**82**). The product still contained impurities.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.06 (ddd, J = 9.7, 5.2, 2.2 Hz, 1H), 5.81 (dddd, J = 9.7, 5.2, 2.7, 1.7 Hz, 1H), 5.67 – 5.62 (m, 1H), 3.45 (ddd, J = 12.1, 3.7 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.11 – 2.03 (m, 1H), 1.93 (s, 3H), 1.92 – 1.77 (m, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 193.07, 170.82, 161.20, 134.00, 123.36, 65.93, 53.08, 47.19, 24.52, 20.90, 17.70.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{11}H_{14}O_5Na$: 249.0733, found: 249.0732.

6.2.42 Methyl 2-(2-methoxycyclohex-3-en-1-yl)-2-oxoacetate



Scheme 6.42: Synthesis of methyl 2-(2-methoxycyclohex-3-en-1-yl)-2-oxoacetate (**83**).

Methyl 2-oxobut-3-enoate (**2**) (0.024 g, 0.21 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with (*E*)-1-methoxybuta-1,3-diene (0.031 g, 0.36 mmol) and left to stir for four days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-(2-methoxycyclohex-3-en-1-yl)-2-oxoacetate

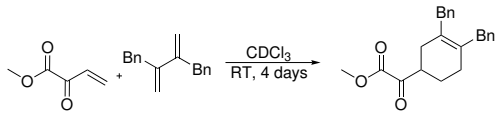
(**83**). The product still contained impurities.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.09 – 5.99 (m, 1H), 5.99 – 5.86 (m, 1H), 4.31 (dd, J = 4.5, 1.4 Hz, 1H), 3.86 (s, 3H), 3.25 (s, 3H), 3.22 – 3.10 (m, 1H), 2.28 – 2.18 (m, 1H), 2.04 – 1.91 (m, 1H), 1.87 – 1.70 (m, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 194.09, 161.94, 132.96, 123.74, 71.98, 56.32, 52.77, 48.23, 24.53, 17.90.

HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{10}H_{14}O_4Na$: 221.0784, found: 221.0786.

6.2.43 Methyl 2-(3,4-dibenzylcyclohex-3-en-1-yl)-2-oxoacetate



2 **80**

Scheme 6.43: Synthesis of methyl 2-(3,4-dibenzylcyclohex-3-en-1-yl)-2-oxoacetate (**80**).

Methyl 2-oxobut-3-enoate (**2**) (0.027 g, 0.23 mmol (measured with internal NMR standard)) was mixed in deuterated chloroform (1.0 ml) with 2,3-dibenzyl-1,3-butadiene (0.109 g, 0.46 mmol) and left to stir for four days. The solvent was evaporated with celite added and the product was purified with **DCVC** with a 4 % gradient from heptane to ethyl acetate, yielding methyl 2-(3,4-dibenzylcyclohex-3-en-1-yl)-2-oxoacetate (**80**).

Yield 0.056 g, 69 %.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 7.28 – 6.99 (m, 10H), 3.72 (s, 3H), 3.54 – 3.32 (m, 4H), 3.26 – 3.14 (m, 1H), 2.25 – 1.96 (m, 4H), 1.93 – 1.81 (m, 1H), 1.49 (dddd, J = 12.8, 10.8, 9.5, 6.4 Hz, 1H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 196.69, 161.96, 140.08, 139.90, 130.61, 128.83, 128.58 (s, 2C), 128.54, 128.52, 126.16, 126.12, 52.90, 43.31, 39.04, 38.93, 30.09, 28.83, 24.70.

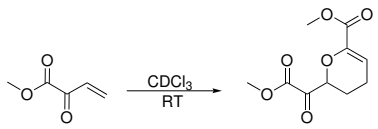
HRMS (ESI+): m/z $[M+Na]^+$ calc. for $C_{23}H_{24}O_3Na$: 371.1618, found: 371.1622.

6.2.44 Methyl 2-(2-methoxy-2-oxoacetyl)-3,4-dihydro-2*H*-pyran-6-carboxylate

The product methyl 2-(2-methoxy-2-oxoacetyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (**67**) was not isolated, but was observed as a product when synthesising methyl 2-oxobut-3-enoate (**2**). When the reaction mixture with **2** was stored/stirred too long, the main product becomes **67**. Compound **67** is a possible by-product in all Diels Alder reactions, where the dienophile is **2**.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ: 6.09 – 6.03 (m, 1H), 5.18 – 5.09 (m, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 2.28 – 1.97 (m, 4H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ: 190.91, 162.52, 161.42, 142.90, 111.37, 77.16,



2 **67**

Scheme 6.44: Synthesis of methyl 2-(2-methoxy-2-oxoacetyl)-3,4-dihydro-2*H*-pyran-6-carboxylate (**67**).

53.08, 52.21, 22.02, 18.76.

HRMS (ESI+): m/z $[M+H]^+$ calc. for $C_{10}H_{13}O_6$: 229.0707, found: 229.0723.

Appendix

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APPENDIX A

NMR spectra

Dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate

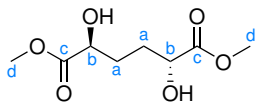


Figure A.1: Schematic representation of dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**).

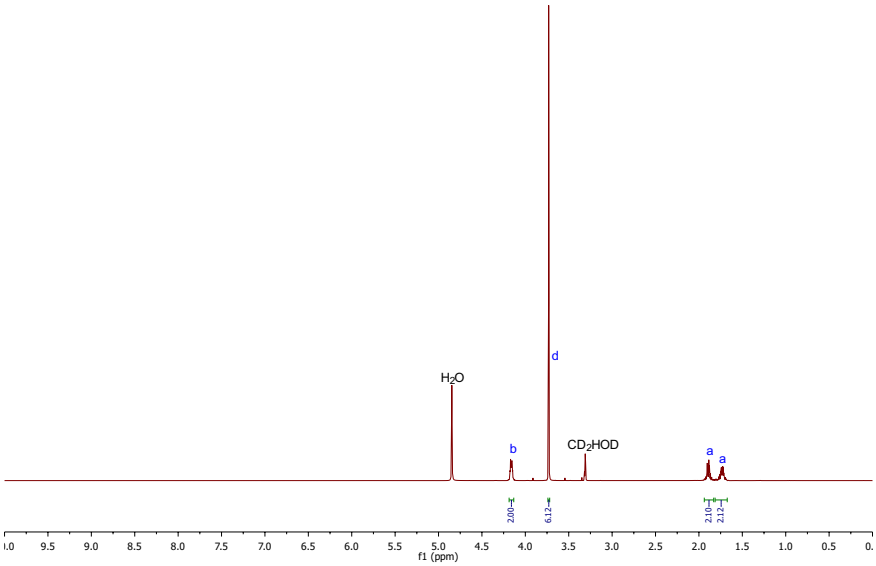


Figure A.2: 1D-NMR ^{1}H-NMR (400 MHz, Methanol-d_4) δ: 4.26 – 4.12 (m, 2H), 3.73 (s, 6H), 1.94 – 1.80 (m, 2H), 1.81 – 1.66 (m, 2H).

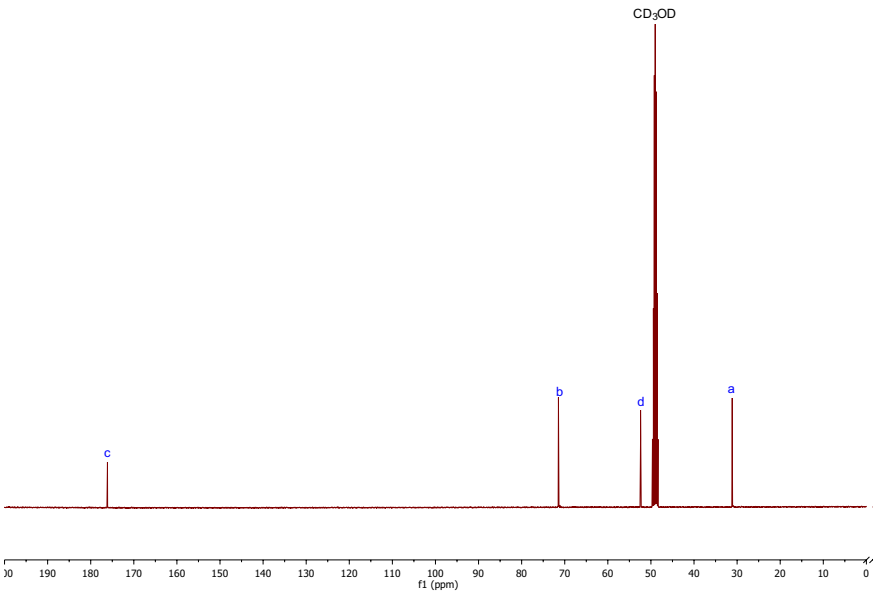


Figure A.3: 1D-NMR ^{13}C-NMR (101 MHz, Methanol-d_4) δ: 176.12, 71.46, 52.40, 31.13.

APPENDIX B

HRMS spectra

Dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate

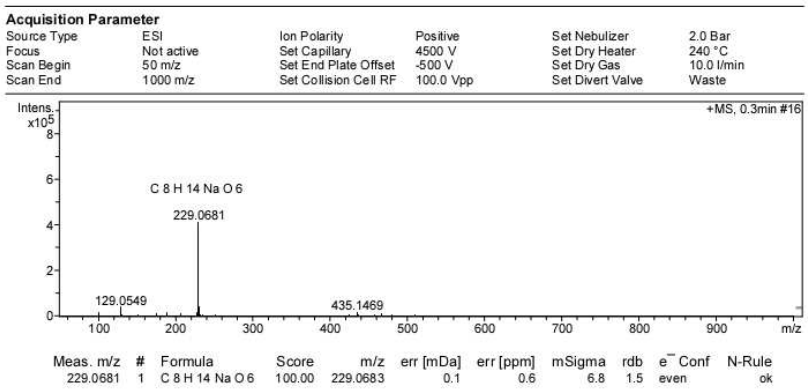


Figure B.1: HRMS: Mass spectrum smart formula report of dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**).

Methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate

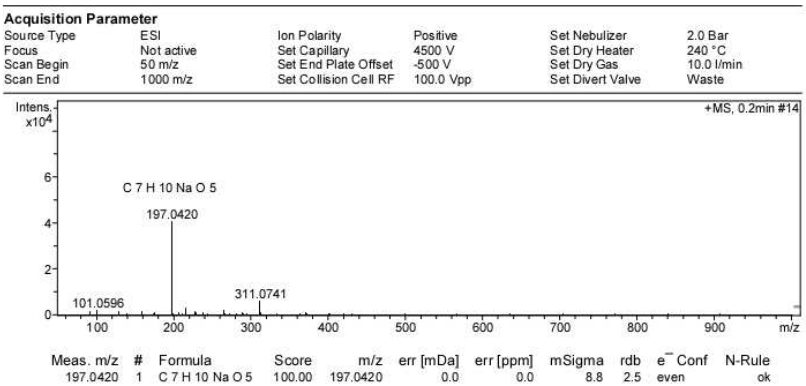


Figure B.2: HRMS: Mass spectrum smart formula report of methyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2-carboxylate (**8**).

Deuterium experiment

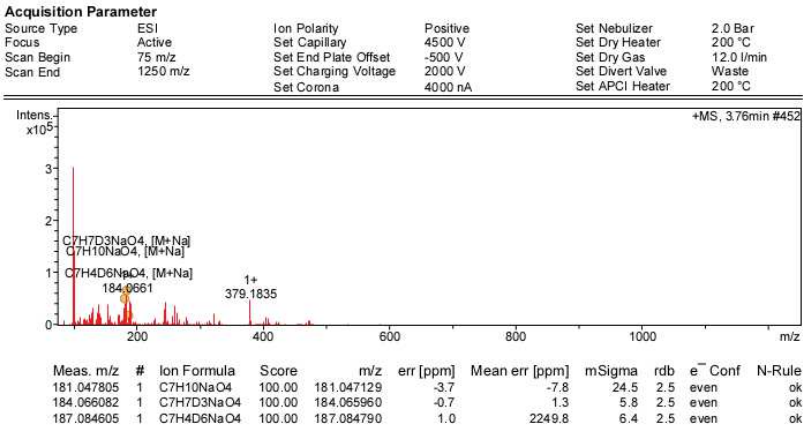


Figure B.3: HRMS: Mass spectrum smart formula report of methyl (*E*)-4-acetoxybut-2-enoate (**5**) [181.0478], methyl-d_3 (*E*)-4-acetoxybut-2-enoate [184.0661], methyl (*E*)-4-(acetoxy-d_3)but-2-enoate [184.0661], and methyl-d_3 (*E*)-4-(acetoxy-d_3)but-2-enoate (**62**) [187.0846].

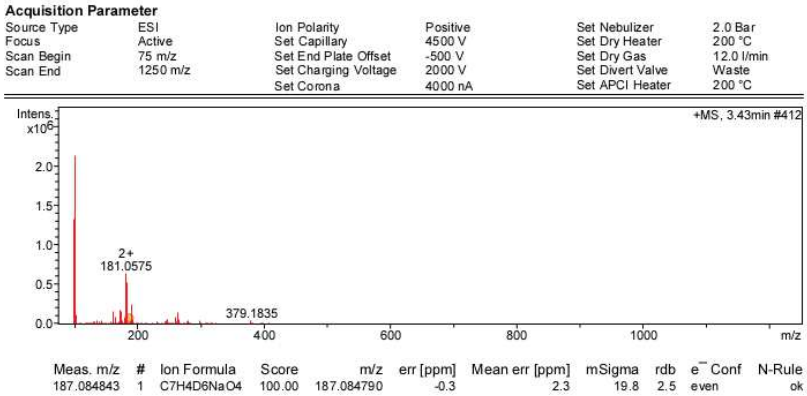


Figure B.4: HRMS: Mass spectrum smart formula report of methyl-d_3 (E)-4-(acetoxy-d_3)but-2-enoate (**62**) [187.0846].

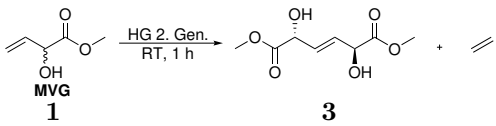
APPENDIX C

External stay at Perstorp AB

This is the work performed and the subsequent report from my external stay at Perstorp AB.

Background

In the project Cat2BioChem, new monomer building blocks were being synthesised. Ph.D. A. B. Sølvhøj discovered that methyl vinyl glycolate (**MVG**) could perform a homo metathesis. This reaction connects two **MVG** moieties and releases ethylene (Scheme C.1). The compound is crystalline and has a melting point around 130 °C. This molecule is dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**) and has two ester groups, two hydroxyl groups and a olefin moiety. With these functional groups, there are many opportunities to polymerise the molecule with itself and other compounds.



Scheme C.1: Reaction scheme for synthesis of dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate (**3**).

To test this molecule an external stay was planned at Perstorp AB. Perstorp AB is a collaborator in the project Cat2BioChem. Perstorp AB has experience with synthesising oligomers and polymers. Compound **3** was polymerised with limited success. It was possible to dimerise compound **3**. It was also tested to co-oligomerise and UV cure the molecule via the double bond with limited success. A synthesis of a polyurethane polymer with compound **3** was also tested.

MVG has a terminal double bond that supposedly is more reactive than compound **3**. It was also attempted to synthesise a polyurethane, polymerise, and UV cure with **MVG**, but the main focus remained compound **3**. It was tested if the double bond could be cross-linked in polymers via thiolene chemistry.

In addition it was tested if a cross-linking could be performed via a Diels Alder reaction between the project compounds that have double bonds (**MVG**, **3**). Specifically it was tested to cross-link them with the furan dicarboxylic acid (**FDCA**).

Compound **3** shows resemblance to adipate. Adipate is used as a plasticiser.[227] It was tested if **3** could be used as a successful plasticiser.

One of the products Perstorp AB produces is ϵ-caprolactone (**CAPA**). Perstorp AB uses **CAPA** for many different applications and they produce different polymers as well as the monomer from it. It was tested if it was possible to incorporate **CAPA** into a copolymer with **MVG** and **3**. Cyclohexanol was used as a surrogate for **MVG** and **3** to evaluate the reactivity of the secondary alcohol. Then with experience from that experiment, **MVG** and **3** were reacted with **CAPA**.
It was attempted to perform cross-linking between a diene and a dienophile in a Diels Alder reaction. Compound **3** and **MVG** were selected as the dienophiles. The two compounds have electron withdrawing substituents as neighbours to the double bond. This makes them poor dienophiles in a Diels Alder reaction, but they could react in an inverse Diels Alder reaction. **FDCA** was chosen as a diene. **FDCA** has already been used successfully in Diels Alder reactions in the literature. The Group of Pro-

fessor Picchioni succeeded in performing a Diels Alder reaction between a furan and a bismaleimide. The polymer was then cross-linked when subjected to high temperatures. The cross-linking was reversible and could be reversed when subjected to lower temperatures.[228, 229] **FDCA** is a possible substitution for terephthalic acid and can be synthesised via bio-renewable sources.[79] If a polymer is consisting of **3** or **MVG** along with **FDCA** it could give an interesting polymer. The polymer could be cured and might have self-healing properties.[230, 231]

Results

Compound **3** and dimethyl (2*R*,5*S*)-2,5-dihydroxyhexanedioate (**9**) resemble the adipate moiety with more functional groups. Compound **3** has two secondary alcohols and a olefin. Compound **9** has two secondary alcohols. Compound **3** is easily produced and more of the compound had been synthesised for testing as a plasticiser. Using **3** as the monomer would be difficult. It did not mix well with a polymer as compound **3** remained very crystalline and insoluble. Plasticisers are usually a liquid at room temperature and blend with molecules used for polymerisation.[232] It was attempted to make **3** more soluble in a polymer, by making adducts of **3** with 1,6-hexanediol (**HDO**) and adipate. Then, these adducts would be tested as a plasticiser.

It was attempted to incorporate **3** and **MVG** in a polyurethane. If this incorporation could be performed, the polymer would have double bonds. The polymer could then be cured after it was synthesised so the properties of the polymer could be modified post polymerisation.

Thiolene chemistry can also be used to cross-link polymers. Unlike adipate and lactic acid, **3** and **MVG** can be cross-linked. Professor Sels' group has already shown that **MVG** can be cross-linked.[128] It was attempted to cross-link **3**. Trimethylolpropane tris(3-mercaptopropionate) (**TMPTMPA**) was tested as a cross-linker.

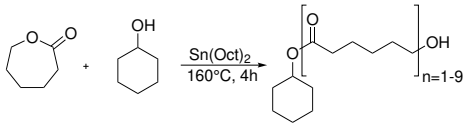
Perstorp AB had also attempted to incorporate **3** in UV curing without success, but further tests were performed with compound **3**, attempting to incorporate it as an additive to acrylate to change the properties by mixing the two compounds.

Oligomerisation with ϵ-caprolactone

Cyclohexanol

Cyclohexanol was mixed with **CAPA** in a 1:1 ratio with tin octanoate as the catalyst, and gave different oligomers. Cyclohexanol has a secondary alcohol. When the secondary alcohol has reacted, it ring-opens **CAPA**, creating an ester and a primary alcohol. The primary alcohol is then a strong competitor for the ring-opening of another **CAPA**. The reaction was analysed for monomer composition with LC and LC-MS. It gave a distribution of oligomers from one cyclohexanol to a dimer and to a nonamer

(Scheme C.2), consuming more than 99 % of the monomers. The LC-MS analysis is shown in Figure C.1.



Scheme C.2: Polymerisation of cyclohexanol with **CAPA** with tin octanoate as the catalyst.

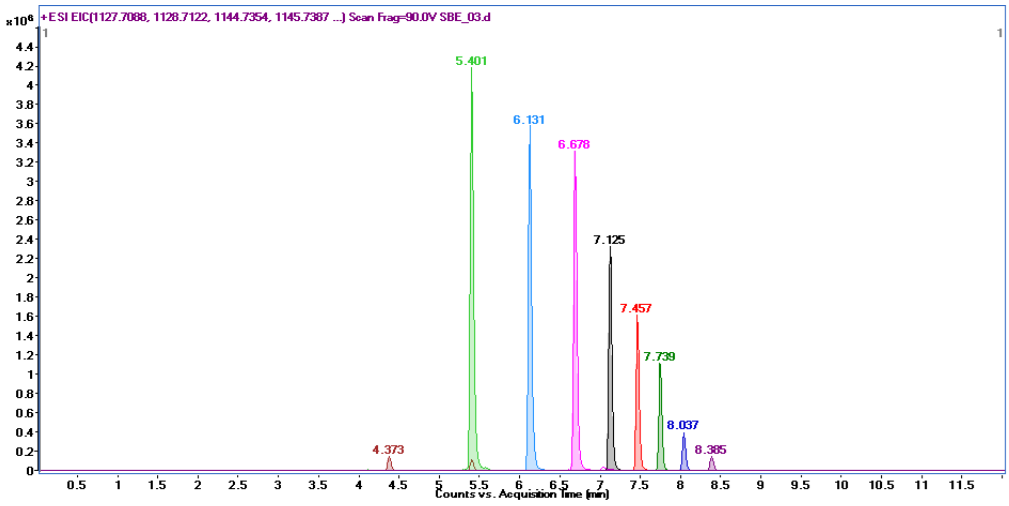
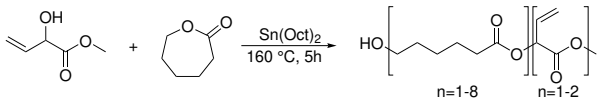


Figure C.1: LC-MS chromatogram (EIC:s Cyclohexanol + 1→9 **CAPA**) of sample after 4 hours.

Methyl vinyl glycolate

MVG was mixed with **CAPA** in a 1:1 ratio with tin octanoate as the catalyst (Scheme C.3), and gave different oligomers. **MVG** has a secondary alcohol, as is also found in cyclohexanol. When the secondary alcohol has reacted, it ring-opens **CAPA** creating an ester and a primary alcohol. The primary alcohols are then strong competitors for the ring-opening of another **CAPA**, the same case as with cyclohexanol. The experiment consumed the monomers and left less than 1 % of **CAPA** and about 7 % of **MVG**. The reason for **MVG** not being consumed completely is likely due to the secondary alcohol. If an excess of **CAPA** was used, then the **MVG** monomers would probably be consumed. The mixtures consisted of **MVG** with 1-7 **CAPA** and a **MVG** dimer with 1-8 **CAPA**'s, and the different oligomer composition can be seen in Table C.2.



Scheme C.3: Oligomerisation of **MVG** and **CAPA** with tin octanoate as the catalyst.

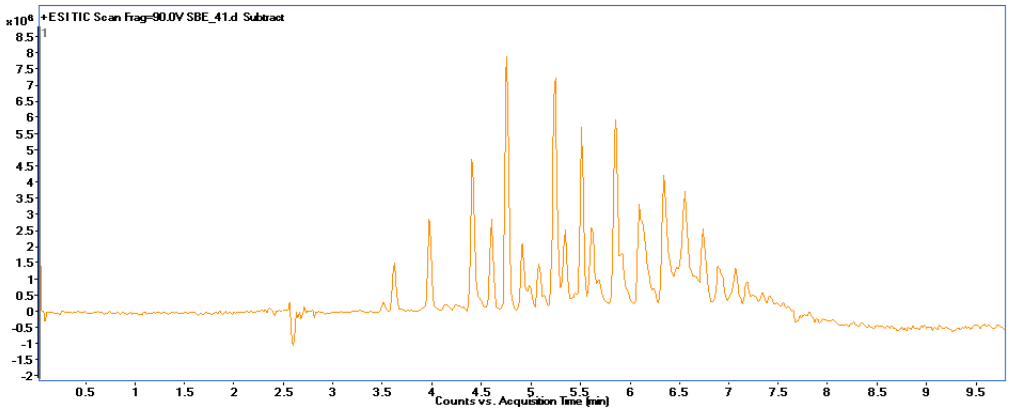


Figure C.2: LC-MS chromatogram (TIC).

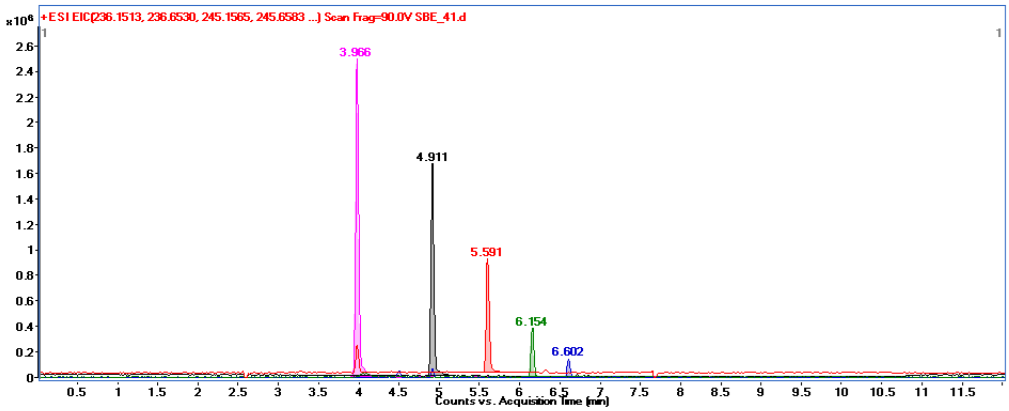


Figure C.3: LC-MS chromatogram (EIC:s, methylated **CAPA** homopolymer + 2→6 **CAPA**)

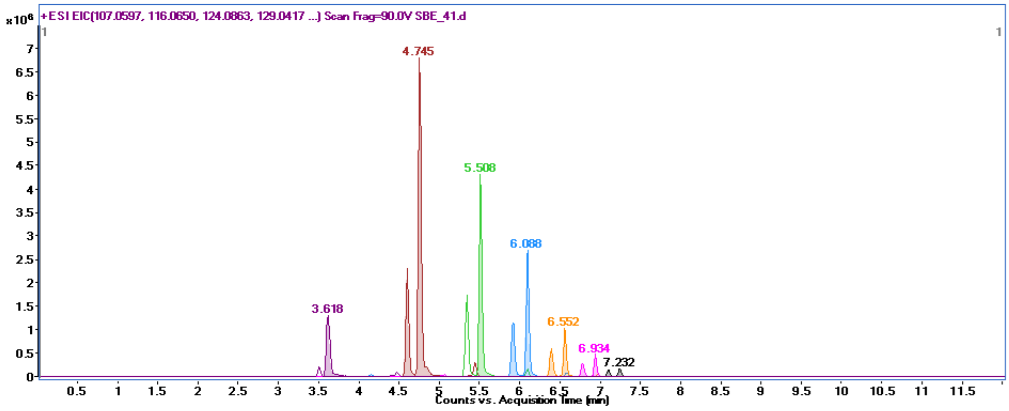


Figure C.4: LC-MS chromatogram (EIC:s, **MVG-CAPA** co-polymer + 1→7 **CAPA**).

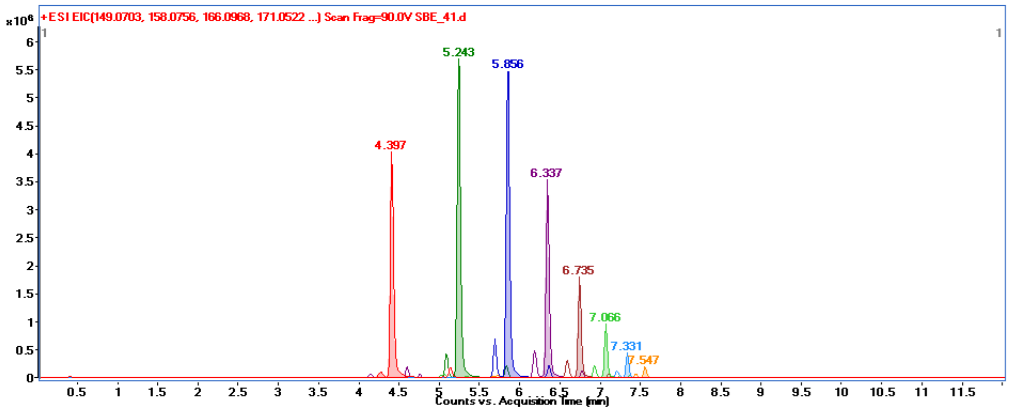
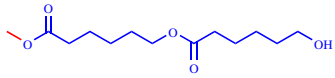
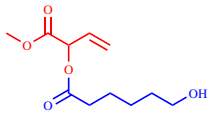
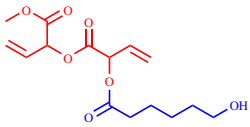


Figure C.5: LC-MS chromatogram (EIC:s, **MVG**-dimer-**CAPA** co-polymer + 1→8 **CAPA**).

Table C.1: Composition, LC-MS (EIC:s).

Oligomer	RT (min)	Composition area % PAB_CAPA_Sample 10
Cyclohexanol + 1 **CAPA**	4.4	1
Cyclohexanol + 2 **CAPA**	5.4	26
Cyclohexanol + 3 **CAPA**	6.1	22
Cyclohexanol + 4 **CAPA**	6.7	20
Cyclohexanol + 5 **CAPA**	7.1	14
Cyclohexanol + 6 **CAPA**	7.5	9
Cyclohexanol + 7 **CAPA**	7.7	6
Cyclohexanol + 8 **CAPA**	8.0	2
Cyclohexanol + 9 **CAPA**	8.4	1

Table C.2: Composition, LC-MS (EIC:s).

Identity	RT (min)	Area % (from EIC:s)
 Chemical Formula: $C_{13}H_{24}O_5$ Exact Mass: 260.1624 Molecular Weight: 260.3300	4.0	5
Methylated **CAPA** homoplymer, n=2		
Methylated **CAPA** homoplymer, n=3	4.9	3
Methylated **CAPA** homoplymer, n=4	5.6	2
Methylated **CAPA** homoplymer, n=5	6.1	1
Methylated **CAPA** homoplymer, n=6	6.6	0.5
 Chemical Formula: $C_{11}H_{18}O_5$ Exact Mass: 230.1154 Molecular Weight: 230.2600	3.8	3
MVG + 1 **CAPA**		
MVG + 2 **CAPA**	5.5	18
MVG + 3 **CAPA**	6.1	9
MVG + 4 **CAPA**	6.5	7
MVG + 5 **CAPA**	6.9	3
MVG + 6 **CAPA**	7.2	1
MVG + 7 **CAPA**	7.5	0.5
 Chemical Formula: $C_{15}H_{22}O_7$ Exact Mass: 314.1366 Molecular Weight: 314.3340	4.4	9
MVG dimer + 1 **CAPA***		
MVG dimer + 2 **CAPA**	5.2	12
MVG dimer + 3 **CAPA**	5.8	12
MVG dimer + 4 **CAPA**	6.3	7
MVG dimer + 5 **CAPA**	6.7	4
MVG dimer + 6 **CAPA**	7.1	2
MVG dimer + 7 **CAPA**	7.3	1
MVG dimer + 8 **CAPA**	7.6	0.5

*MS indicates molecular formula of $C_{15}H_{22}O_7$.

Dimethyl (2*R*,5*S*,*E*)-2,5-dihydroxyhex-3-enedioate

Compound **3** was mixed with **CAPA** in a 1:2 ratio with tin octanoate as the catalyst (Figure C.6). Compound **3** has two secondary alcohols. It was desired to add **CAPA** on both of the alcohols. The reaction consumed 99 % of **3**, and gave oligomers with **3** and containing 1 to 6 **CAPA** monomers. All the different oligomers are shown in Table C.3.

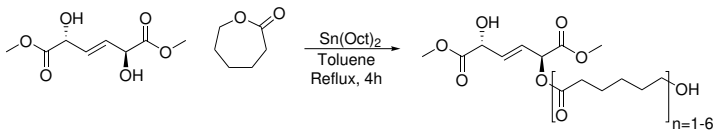


Figure C.6: Oligomerisation of **3** and **CAPA** with tin octanoate as the catalyst.

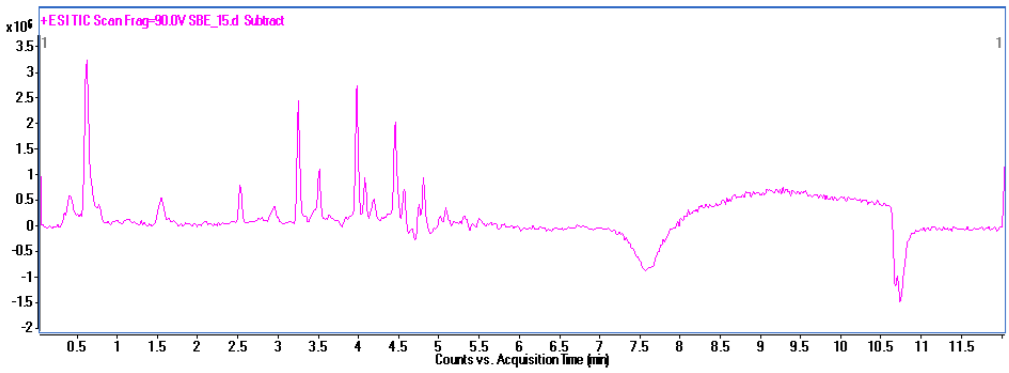


Figure C.7: LC-MS chromatogram (TIC).

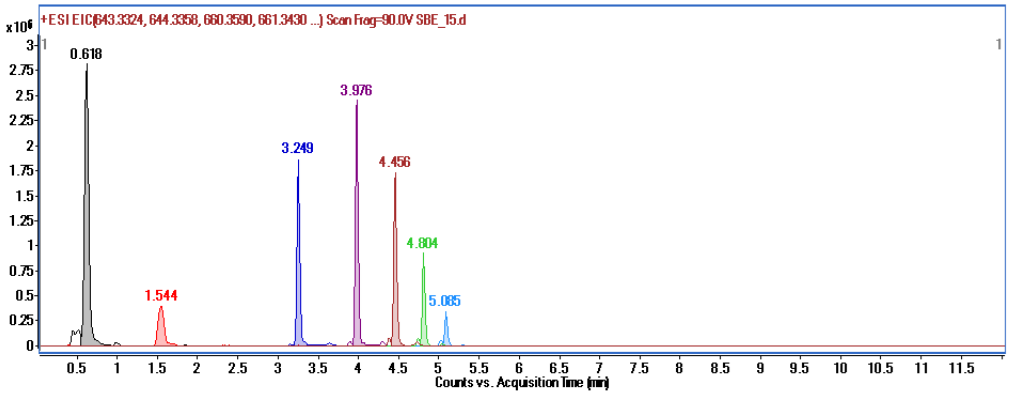


Figure C.8: LC-MS chromatogram (EIC:s, compound **3** + 0→6 CAPA).

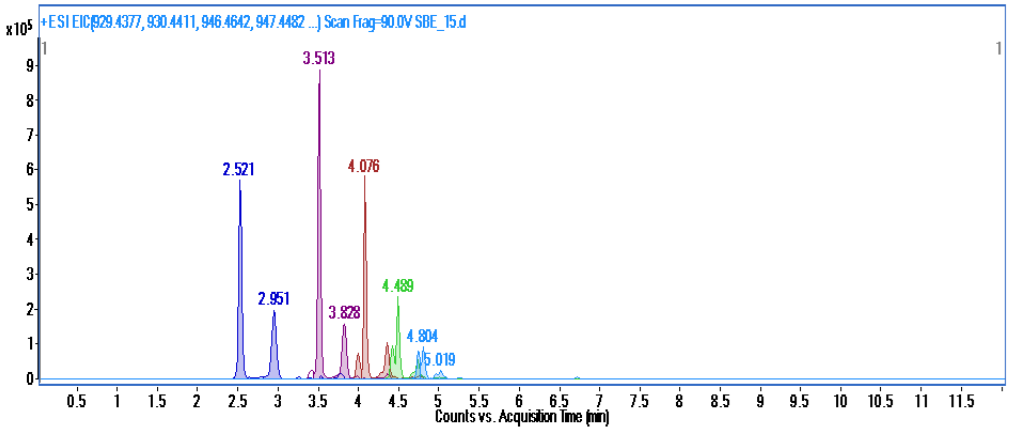
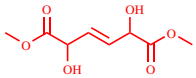
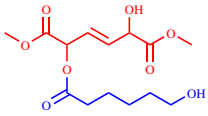


Figure C.9: LC-MS chromatogram (EIC:s, compound **3** dimer + 1→5 **CAPA**).

Table C.3: Composition, LC-MS (EIC:s).

Identity	RT (min)	Area % (from EIC:s)
 Chemical Formula: $C_8H_{12}O_6$ Exact Mass: 204.0634 Molecular Weight: 204.1780	0.6	27
Compound **3**		
 Chemical Formula: $C_{14}H_{22}O_8$ Exact Mass: 318.1315 Molecular Weight: 318.3220	1.5	6
Compound **3** + 1 **CAPA**		
Compound **3** + 2 **CAPA**	3.2	12
Compound **3** + 3 **CAPA**	4.0	15
Compound **3** + 4 **CAPA**	4.5	11
Compound **3** + 5 **CAPA**	4.8	6
Compound **3** + 5 **CAPA**	5.1	2
 Chemical Formula: $C_{21}H_{30}O_{13}$ Exact Mass: 490.1686 Molecular Weight: 490.4580	2.5-3.0	6
Compound **3** dimer* + 1 **CAPA**		
Compound **3** dimer + 2 **CAPA**	3.5-3.9	7
Compound **3** dimer + 3 **CAPA**	3.9-4.4	4
Compound **3** dimer + 4 **CAPA**	4.4-4.8	3
Compound **3** dimer + 5 **CAPA**	4.6-5.2	2

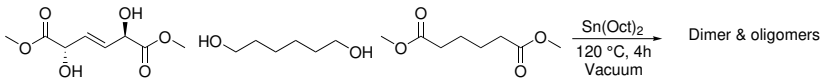
*MS indicates molecular formula of $C_{21}H_{30}O_{13}$.

Furan dicarboxylic acid

Before attempting to synthesise polymers with **FDCA**, the Diels Alder reaction between the monomers **MVG** and **3** with **FDCA** were tested. **FDCA** is very insoluble in many common organic solvents, but it can be dissolved in water and DMSO. Water was avoided because it might react with the methylesters of **MVG** and **3**. **FDCA** was mixed with both **MVG** and **3** in a 1:1 ratio. At room temperature no reaction was observed. The temperature in the mixtures were raised up to 200 °C. The Diels Alder reaction did not occur, and the result of this intense heating was decomposition, where the mixtures turned black and were difficult to analyse, but it was clear from the NMR spectra that the desired Diels Alder reaction did not occur.

Plasticiser

Compound **3** was mixed with **HDO** and dimethyl adipate (**DMA**) in a ratio close to 1:4:2 with tin octanoate as the catalyst. In order to favour an oligomer with a terminal **HDO** group. The excess of **HDO** is used to ensure that **HDO** are positioned on the ends of the oligomer. The reaction did not create the desired oligomer, but a lot of different smaller molecules. The main oligomers from the reaction can be seen in Table C.4. The mixture was a fluid and was tested as a plasticiser. Due to the quantities necessary to make a trial experiment, it had to be diluted further. This was achieved by synthesising an oligomer from **DMA** and **HDO** in a 1:2 ratio. This oligomer was then used as a diluent in a 1:1 dilution. To make sure that it was not the pure **DMA** and **HDO** that was the main plasticising agent, two samples were prepared and tested, where one was the reference, only containing the pure **DMA** and **HDO**. The other one was a mixture of **3**, **DMA** and **HDO**. This reaction gave the oligomers seen in Table C.5. All the analyses of the two mixtures are shown in Figure C.10 to Figure C.13. The two mixtures were mixed with **PVC** at approximately 80 °C in a Brabender mixer, where a plastogram analysis was used to determine when the mixing was good enough. When it was mixed properly, the resistance measured would decline. Then, the **PVC** mixture was mixed with a stabiliser Baerostab NT 340, which is a Calcium Zink stabiliser. The mixing of the two samples with **PVC** with the stabiliser was troubled by static electricity preventing homogeneous mixing. The reference mixture in the end had a white colour. The mixture with **3** had a faint yellowish colour which is attributed to **3** being in the mixture. The reference mixture was then added to the thermos-moulding mixer, moulding it into a **PVC** plastic film that could be tested. The mixer was from LabTech Engineering company LTD model LRM 150. This created a clear film of **PVC** out of **HDO** and **DMA**. The film was somewhat greasy, which was not desirable. The mixture with **3** was also treated with the same machine. When tested in the machine, it would not melt and created problems. A green colour appeared on the machine which indicated an acid attack on the machine was occurring. The experiment was immediately terminated to prevent damage to the machine. The machine operates at 160 °C. To investigate why the experiment had failed it was attempted to heat up the **PVC** mixture more to see if the **PVC** mixture could be made into a film. It seemed that in a small scale lab test, making a film could be achieved by raising the temperature to 175 °C. A thermo-moulding press machine from Collin model no 6208-12-02 was used in an attempt to mould a film at 190 °C. The first trial was left for too long, and the mould of the **PVC** was scorched. Another test was conducted that gave a white beige unclear film seen in Figure C.14. The film also leached. A sample was prepared and showed that it was the monomer of **3** and **DMA** with two **HDO** that leached out mainly. It was confirmed by LC-MS (Figure C.15 and Figure C.16).



Scheme C.4: Oligomerisation of **3**, **HDO** and **DMA** with tin octanoate as the catalyst.

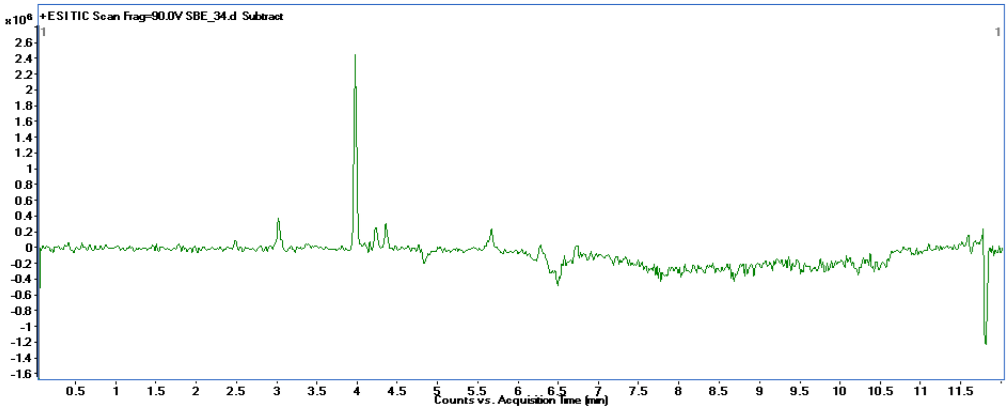


Figure C.10: LC-MS chromatogram (TIC) of **3**, **HDO** and **DMA**.

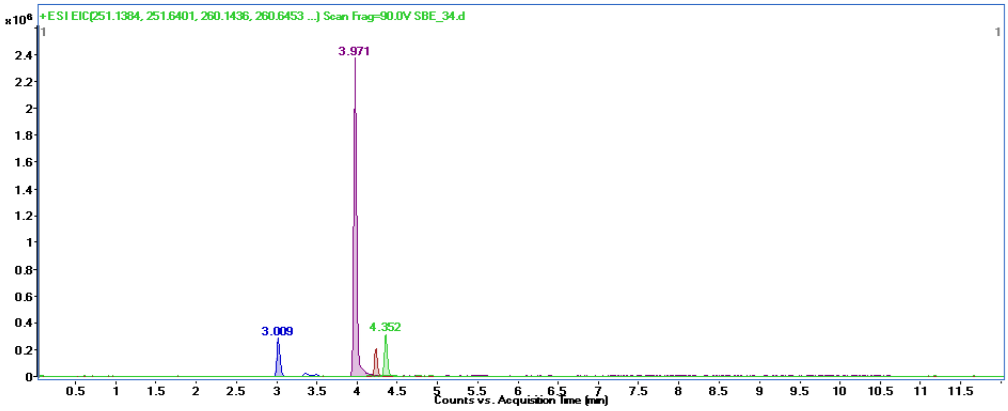
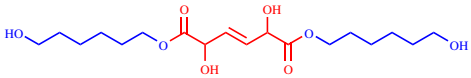
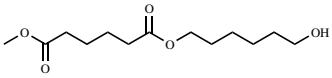
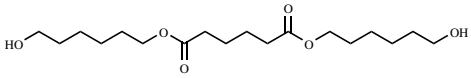
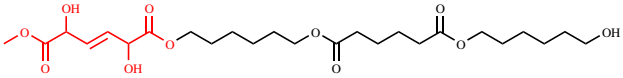


Figure C.11: LC-MS chromatogram (EIC:s) of **3**, **HDO**, **DMA**.

Table C.4: Composition, LC-MS (EIC:s).

Identity	RT (min)	Area % (from EIC:s)
 Chemical Formula: $C_{18}H_{32}O_8$ Exact Mass: 376.2097 Molecular Weight: 376.4460 Compound **3**:**HDO** 1:2	3.0	9
 Chemical Formula: $C_{13}H_{24}O_5$ Exact Mass: 260.1624 Molecular Weight: 260.3300 **DMA**:**HDO** 1:1	4.0	74
 Chemical Formula: $C_{18}H_{34}O_6$ Exact Mass: 346.2355 Molecular Weight: 346.4640 **DMA**:**HDO** 1:2	4.2	7
 Chemical Formula: $C_{25}H_{42}O_{11}$ Exact Mass: 518.2727 Molecular Weight: 518.6000 Compound **3**:**DMA**:**HDO** 1:1:2	4.4	10

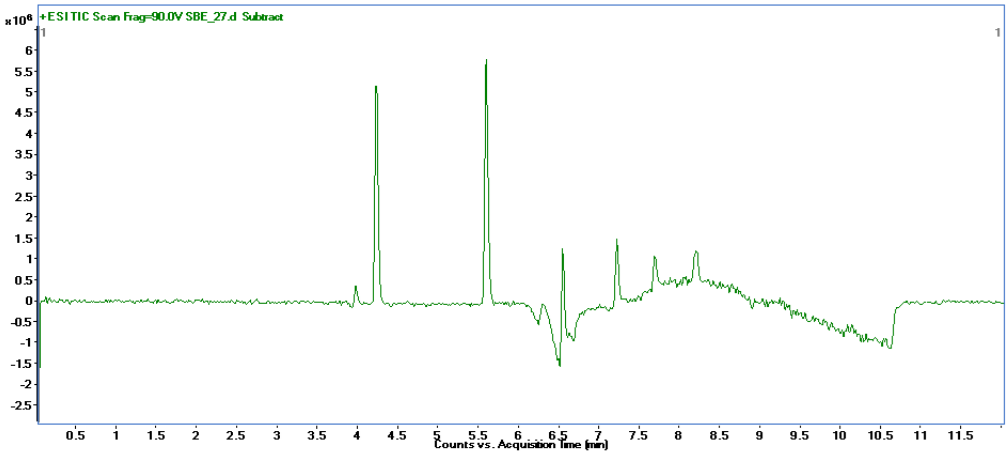


Figure C.12: LC-MS chromatogram (TIC) **HDO** and **DMA**.

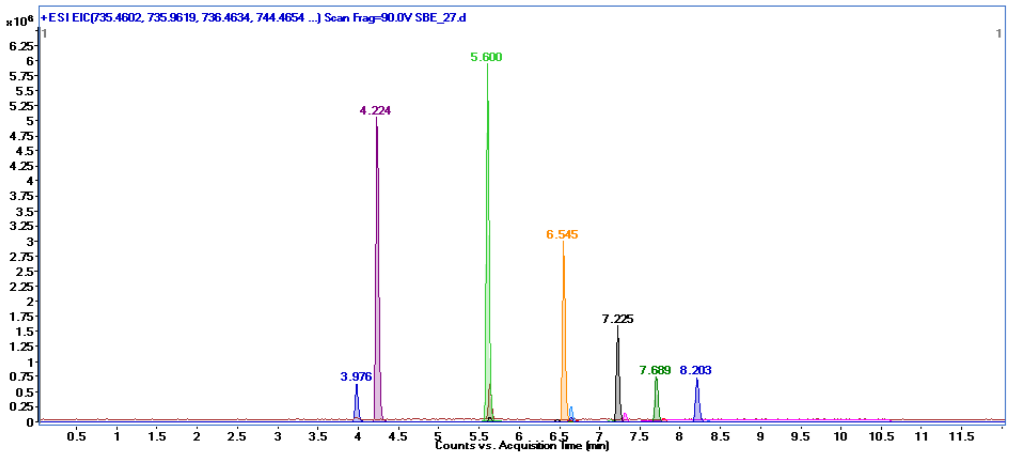
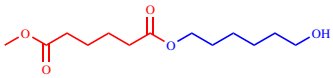


Figure C.13: LC-MS chromatogram (EIC:s, **DMA-HDO** oligomers).

Table C.5: Composition, LC-MS (EIC:s).

Identity	RT (min)	Area % (from EIC:s)
 Chemical Formula: $C_{13}H_{24}O_5$ Exact Mass: 260.1624 Molecular Weight: 260.3300	4.0	27
DMA:**HDO** 1:1		
DMA:**HDO** 1:2	4.2	6
DMA:**HDO** 2:2	5.6	12
DMA:**HDO** 2:3	5.6	15
DMA:**HDO** 3:3	6.6	11
DMA:**HDO** 3:4	6.5	6
DMA:**HDO** 4:4	7.3	2
DMA:**HDO** 4:5	7.2	6
DMA:**HDO** 5:5	7.8	7
DMA:**HDO** 5:6	7.7	4
DMA:**HDO** 6:7	8.2	3

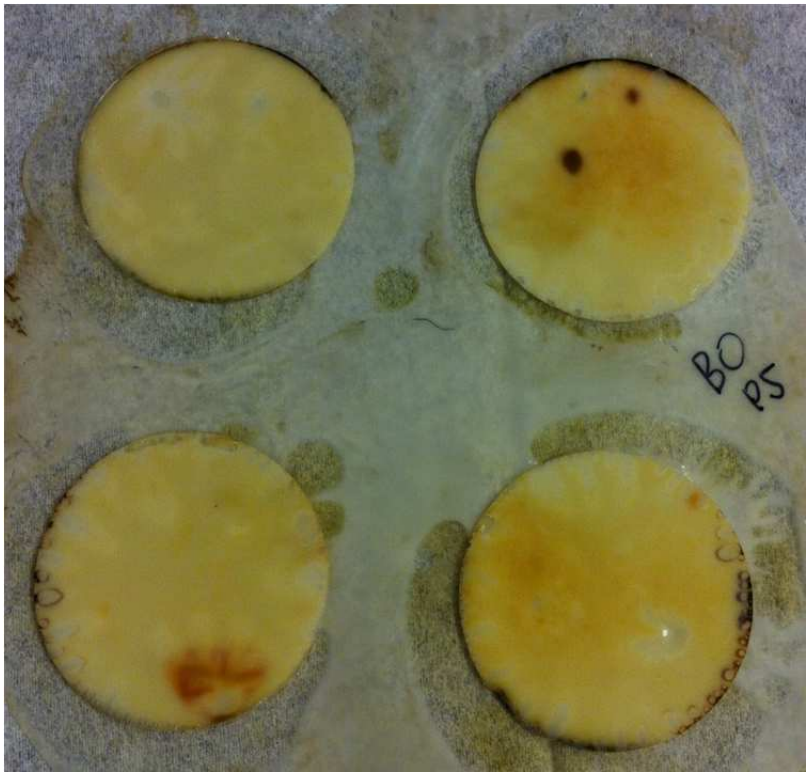


Figure C.14: Moulded plastic pressed from the **PVC** mixed with the mixture of **3**, **DMA** and **HDO** as a plasticiser.

Polyurethane

To test, if the compounds **3** and **MVG** could be incorporated into a polyurethanes, **MVG** was first mixed with Tolonate HDB 75B. There was an excess of 22 % monomer of **MVG** so all the isocyanate groups were converted into carbamate functional groups. The mixture was then attempted to cure with a drop of Irgacure 500 photoinitiator under a UV-lamp from fusion UV model 1000M and a moving belt from Efsen Engineering. This gave a promising result (Figure C.17). Four different plates with a film of the synthesised mixture of **MVG** and Tolonate HDB 75B were created to test hardness, flexibility and resistance to water, acetone and methylethylketone (**MEK**) rubs. The UV curing lamb was tested and gave the data seen in Table C.6 and the plates were created. One glass plate (20 curing turns) and one aluminium plate was made with 40 μm groves (10 curing turns). Two aluminium plates were made with 12 μm groves (5 curing turns). The plates were then tested. Before testing, the plates were stored in a room at 23 °C 50 % humidity.

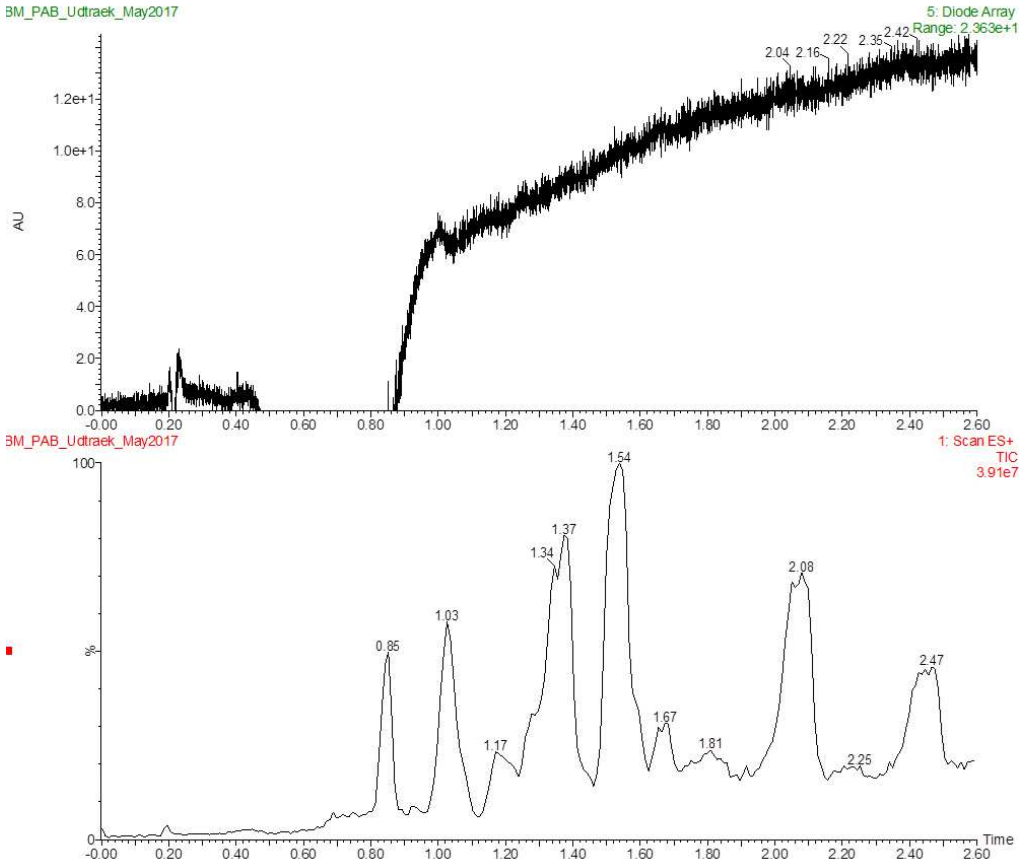


Figure C.15: LC-MS of the compounds leaching from the film. The main top on the TIC 1.54 is the monomer of **DMA** and two **HDO**.

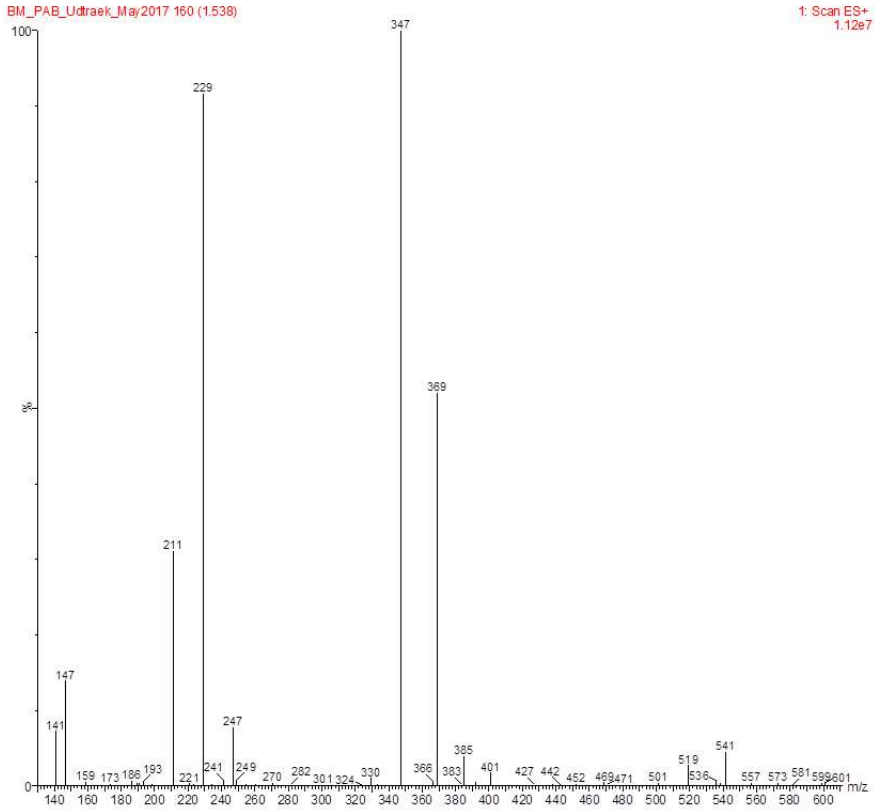


Figure C.16: MS trace 1.54 of the leaching compounds, shows the main composition is **3** monomer and **DMA** and two **HDO**.

Table C.6: UV lamb data, belt speed 5 m/min.

Type	J/cm^2
UV B	0.859
UV C	0.228
UV V	1.057
UV A	0.898

Figure C.17: Film synthesised from a mixture of **MVG** and Tolonate HDB 75B.

Hardness

One way to test hardness was on the glass plate with a König pendulum and the ASTM D4366 – 16 standard. This test was performed 3 times and gave the following results:

Test	Counts
1	27
2	23
3	23

Flexibility

The flexibility was tested on Erichsen model 202C. The 40 μm grooved aluminium plate was tested in the machine and the metal sphere was pushed up through the aluminium plate until the film on the aluminium plate cracked. This test was performed twice and gave the following results:

Test	mm
1	3.5-5
2	3.4-5

MEK double rub

The **MEK** double rub method is to determine the rub resistance. Cotton sticks were soaked in **MEK** and rubbed on an aluminium plate with 12 μm groves with 500 gram of pressure per cm^2.(ASTM D4752 Standard Test Method for Measuring **MEK** Resistance of Ethyl Silicate (Inorganic) Zinc-Rich Primers by Solvent Rub.) The test was performed twice and gave the following results:

Test	Rubs
1	4
2	7

Resistance to water and acetone

One aluminium plate with 12 μm groves was also tested for resistance to acetone and water. The solvent was added to a small beaker with an even rim and pressed against the surface. The film was broken in less than two minutes when subjected to acetone. When subjected to water, the film was changed after 6 hours, but looked intact when it was dried. After 27 hours the film was irreparably changed. The film had watermarks, where it had been in contact with water.

Thiolene cross-linking

To test if it was possible to cross-link **3** in a polymer, it was first tested if the thiols on **TMPTMPA** would react with **3**. **TMPTMPA** has three thiols, and the ratio of **TMPTMPA** to **3** was 1:3 with a radical initiator benzoyl peroxide. The product mixture was difficult to dissolve afterwards, which indicated a polymeriastion had occured, but when the product was dissolved in deuterated TFA, the ^{1}H-NMR spectra showed the reaction had not cross-linked, and the starting materials were still present (Figure C.18). The ^{1}H-NMR spectra also show that the double bond still persists. It seems the double bond is difficult to access.

UV curing of compound 3 mixed with acrylates

Compound **3** in itself did not UV cure. It was attempted dissolve it in an acrylate and then UV cure that film with a Irgacure 500 photoinitiator. 1,6-Hexanediol diacrylate was chosen to mix with **3**. Compound **3** is not very soluble in the acrylate. Adding more than a few milligrams to the acrylate would require heating. The acrylate needed to be heated to around 100 °C in an oven for a few hours, which dissolved **3** up to around 50 mg per millilitre acrylate, but the acrylate in some cases started to polymerise in the oven or as soon as the photo-initiator was added. The test, where it was possible to coat a film with the mixture on an aluminium plate and then UV cure it, resulted in the film cracking. Compound **3** precipitates in the film instead of being incorporated. One film was successfully cured, but it had a rough surface, which was created by **3**. This was confirmed by scratching some of the film off and dissolving it in deuterated chloroform. ^{1}H-NMR showed that **3** was not incorporated into the mixture (Figure C.19). It was also attempted to use methanol to help dissolve **3** in the early stage and then evaporate

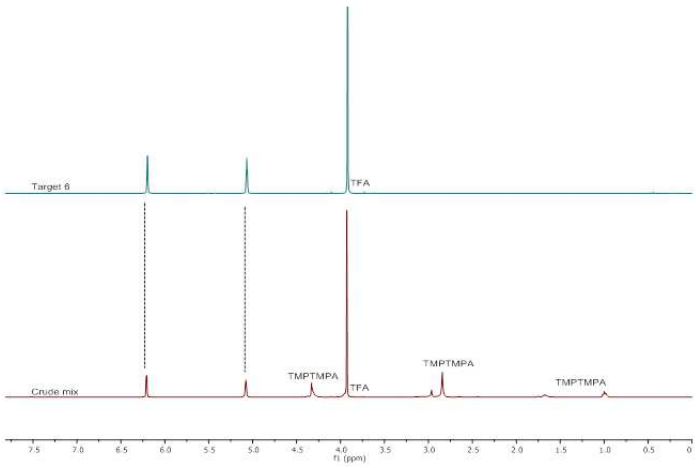


Figure C.18: 1D ^{1}H-NMR stacked with **3** and with the crude mixture from the attempt to cross-link it with **TMPTMPA**.

it later. This had a damaging effect on the films, and they cracked when cured. Many experiments were performed without success and Figure C.20 shows some of the failed attempts.

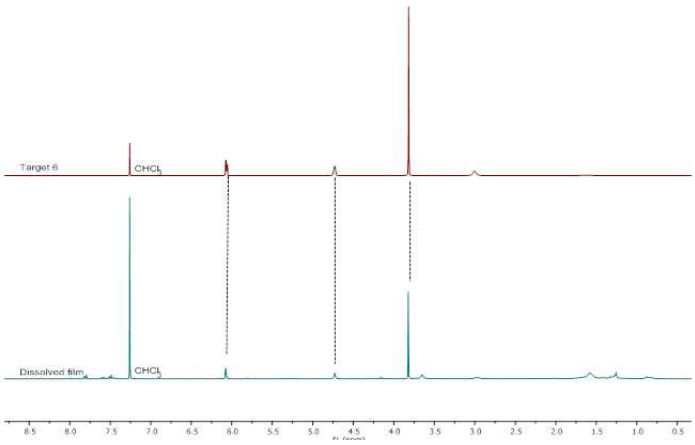


Figure C.19: 1D ^{1}H-NMR of **3** and the film dissolved in chloroform.

Figure C.20: Failed attempts at curing films with acrylate mixed with **3**.

Conclusion

The main tests in all experiments concerned the reactivity of **3**. It seems that the reactivity is low. Compound **3** is insoluble in many organic solvents at room temperature and this may contribute to the low reactivity. It has been attempted to access the double bond in **3** via radical chemistry and thiolene chemistry. Both pathways have been unsuccessful so far. It might be an advantage to try another radical initiator than benzoylperoxide and a different thiol as reactant, since **TMPTMPA** might be too large. A smaller compound might react better, but in these tests a commercial thiol was tested for industrial relevance. This compound did not react, but from an academic view it might be useful to understand the reactivity of **3** better and test smaller thiols. It was also attempted to incorporate **3** in a solution of another acrylate and thereafter UV cure it. This was performed to see, if it would change the property of the acrylate mixture, but **3** was difficult to dissolve and have a tendency to precipitate out of the solution during or before the UV curing. Oligomerization of **3** with **HDO** and **DMA** was performed to use it in a mixture as a plasticiser, which failed. The mixture leached and had problems with being dissolved into **PVC** plastic. When it was attempted to mould the **PVC** mixture at higher temperature, it burned and did not blend together to any useful material. The last attempt to try and find useful applications for these building blocks was to experiment with **MVG** as a building block in a polyurethane. **MVG** can be polymerised with **CAPA**. It was attempted to react **MVG** monomer with isocyanate with success, resulting in a film that could be used as a coating. The coating was synthesised, but it did not seem to have superior properties compared to other established films. It would be useful to see if there is potential for this material as a component in coatings.

Experimental

MVG reaction with isocyanate

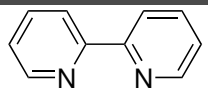
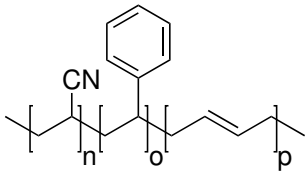
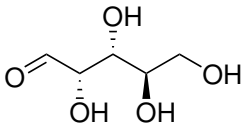
MVG (10 g) was mixed with Tolonate HDB 75B (7.28 g), 4-methoxyphenol (11 mg) and tin octanoate (35 mg) in a flask with a magnetic stirrer and a nitrogen atmosphere. The mixture was heated to 80 °C for 4 hours. A sample of 1 gram was taken out to UV cure.

Notes

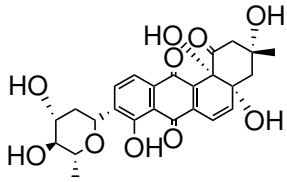
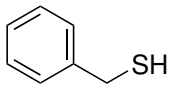
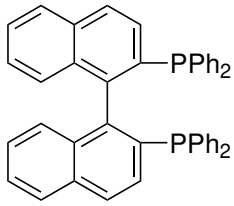
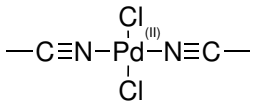
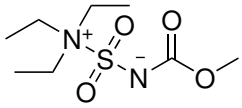
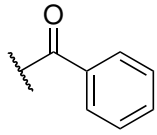
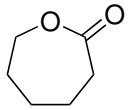
All analysis were performed by Perstorps AB's analysis department, by Sara Andersson (LC), Johan Raab (LC-MS) and Snjezana Trupina Grönlund (NMR). The exceptions are the leaching test of the plasticiser experiment and thiolene cross-linking attempt with **TMPTMPA** analysed by NMR.

APPENDIX D

Abbreviations, acronyms, definitions and descriptions

Abbreviation/ Name	Definitions/Description	Structure/Comment
2,2'-bipyridyl		
ABS	Acrylonitrile butadiene styrene	
Amberlite® IR120	Strongly acidic gel-type resin with sulfonic acid functionality	-
Arabinose	-	
ATRP	Atom transfer radical polymerisation	-

continued on the following page...

Abbreviation/ Name	Definitions/Description	Structure/Comment
Aquayamycin	(3*R*,4a*R*,12b*S*)-9-[(2*R*,4*R*,5*S*,6*R*)-4,5-dihydroxy-6-methyloxan-2-yl]-3,4a,8,12b-tetrahydroxy-3-methyl-2,4-dihydrobenzo[*a*]anthracene-1,7,12-trione	
BC	Biochemical	-
Benzyl Mercaptan	-	
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl	
Bio-degradation	Breakdown of a substance catalysed by enzymes in vitro or in vivo	-
Bio-renewable	Chemicals that are created by biological organisms that provide feedstocks for the chemical industry	-
Bitumen	Sticky, black, and highly viscous liquid or semi-solid form of petroleum	-
Bis(acetonitrile)-dichloro-palladium(II)	-	
Burgess reagent	Methyl *N*-(triethylammonio-sulfonyl)carbamate	
Bz	Benzoyl	
CAPA	ϵ-Caprolactone	
Cat.	Catalyst	-

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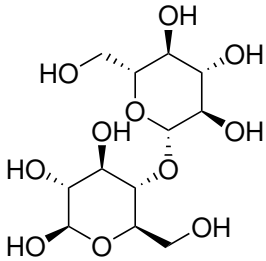
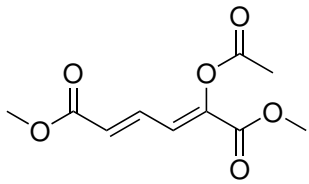
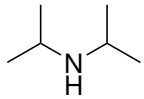
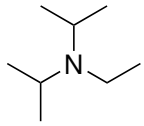
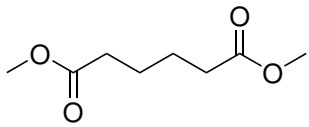
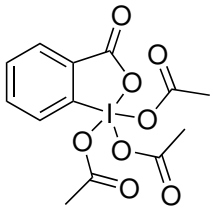
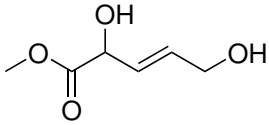
Abbreviation/ Name	Definitions/Description	Structure/Comment
Cellobiose	-	
COSY	Correlation spectroscopy	-
CRP	Controlled radical polymerisation	-
DCVC	Dry column vacuum chromatography	-
Dimethyl-2-acetoxyhexa-2,4-dienedioate	-	
DIPA	Di-*iso*-propylamine	
DIPEA	*N*,*N*-Di-*iso*-propylethylamine	
DMA	Dimethyl adipate	
DMP	Dess-Martin perodinane	
DPM	Methyl (*E*)-2,5-dihydroxypent-3-enoate	

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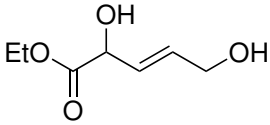
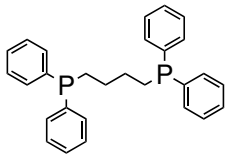
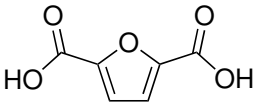
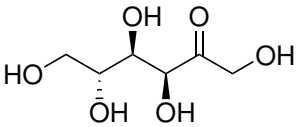
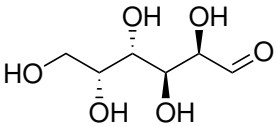
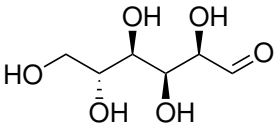
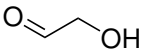
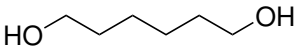
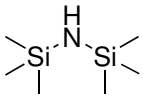
Abbreviation/ Name	Definitions/Description	Structure/Comment
DPE	Ethyl (*E*)-2,5-dihydroxypent-3-enoate	
dppb	1,4-Bis(diphenylphosphino)butane	
EDG	Electron donating group	-
EWG	Electron withdrawing group	-
Ex.	Experiment	-
FDCA	2,5-Furandicarboxylic acid	
FRP	Free radical polymerisation	-
Fructose	-	
Galactose	-	
Glucose	-	
Glycolaldehyde	-	
HDO	1,6-Hexanediol	
HDPE	High density polyethylene	-
Hexamethyldisilazane	-	

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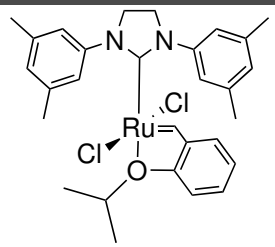
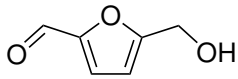
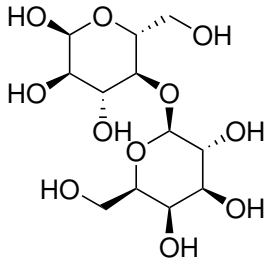
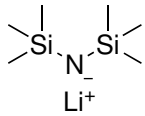
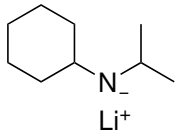
Abbreviation/ Name	Definitions/Description	Structure/Comment
HG II	Hoveyda Grubbs 2nd generation catalyst	
HMBC	Heteronuclear multiple bond correlation	-
HMF	5-(Hydroxymethyl)furfural	
HRMS	High resolution mass spectrometry	-
HSQC	Heteronuclear single quantum coherence	-
Irgacure 500	A liquid mixture of two photoinitiators 1-hydroxy-cyclohexyl-phenyl-ketone and benzophenone	-
Kerogen	Is a solid organic matter in sedimentary rocks	-
Kerosene	Is a combustible hydrocarbon liquid, which is derived from petroleum	-
Lactose	-	
LDPE	Low density polyethylene	-
LLDPE	Linear low density polyethylene	-
LiHMDS	Lithium bis(trimethylsilyl)amide	
LiICA	Lithium *iso*-propylcyclohexylamide	

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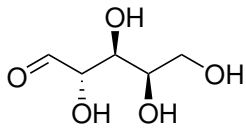
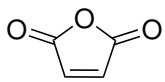
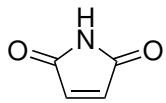
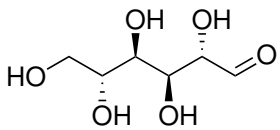
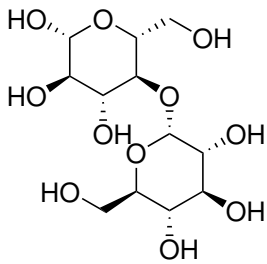
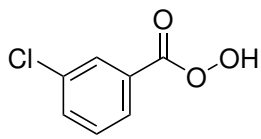
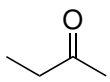
Abbreviation/ Name	Definitions/Description	Structure/Comment
Lindlar Cat.	Palladium deposited on calcium carbonate, poisoned with various forms of lead or sulphur. Best known for hydrogenation of alkynes to alkenes	-
Lyxose	-	
NMP	Nitroxide mediated polymerisation	-
NREL	National Renewable Energy Laboratory	-
Maleic anhydride	-	
Maleimide	-	
Mannose	-	
Maltose	-	
m-CPBA	*m*-Chloroperoxybenzoic acid	
MEK	Methyl ethyl ketone	
MW	Microwave	-

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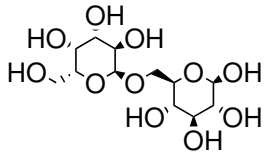
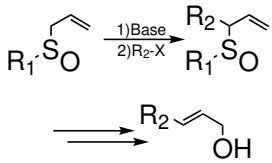
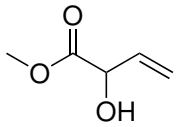
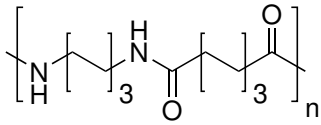
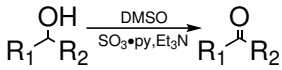
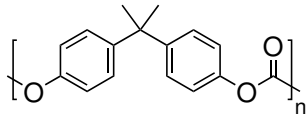
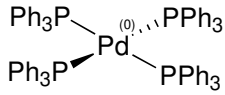
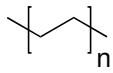
Abbreviation/ Name	Definitions/Description	Structure/Comment
Melibiose	-	
Mislow-Evans rearrangement	-	
Modulus	Resistance to deformation measurement	$\frac{Strain}{Stress}$
MVG	Methyl vinyl glycolate	
Oxone	Potassium peroxymonosulphate triple salt	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
Pa	Pascal	Unit $\frac{1 Newton}{m^2}$
PA	Polyamide e.g. Nylon 6,6	
Parikh–Doering oxidation	-	
PC	Polycarbonate	
$Pd(PPh_3)_4$	Tetrakistriphenylphosphine palladium(0)	
PE	Polyethylene	
Pearlman's Catalyst	-	$Pd(OH)_2$

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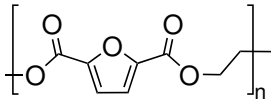
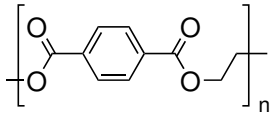
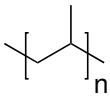
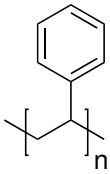
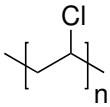
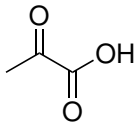
Abbreviation/ Name	Definitions/Description	Structure/Comment
PEF	Polyethylene furanoate	
PET	Polyethylene terephthalate	
PDLA	Poly(D)-lactic acid	See Figure 1.39
PDLLA	Poly(D,L)-lactic acid	-
PHA	Polyhydroxyalkanoate	-
PLA	Poly lactic acid	See Figure 1.39
PLLA	Poly(L)-lactic acid	See Figure 1.39
Plastic definition	A material consisting of synthetic or semi-synthetic organic compounds that are malleable and can be moulded into objects	-
Polydispersion	Measure of heterogeneous size of polymers in a mixture	
PP	Polypropylene	
PS	Polystyrene	
PVC	Polyvinyl chloride	
Pyruvate	-	
RAFT	Reversible addition fragmentation chain transfer	-
Resin	Polymer material made from monomer feed	-

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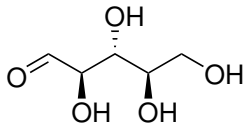
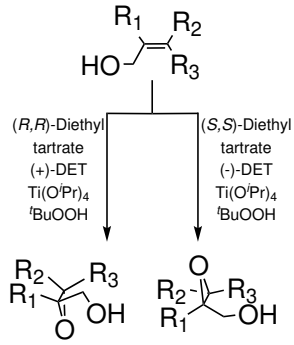
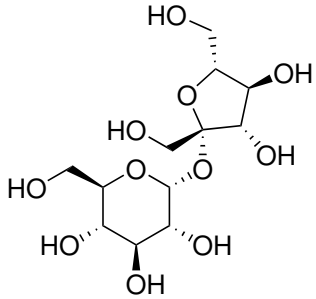
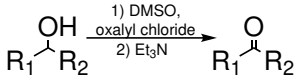
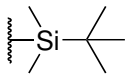
Abbreviation/ Name	Definitions/Description	Structure/Comment
Ribose	-	
RIC	Resin identification codes	-
RT	Room temperature	-
Shale-gas	Natural gas that is found trapped within fine-grained, clastic sedimentary rock composed of mud, a mix of flakes of clay minerals and tiny fragments of other minerals	-
Sharpless epoxidation	-	
Sucrose	-	
Swern oxidation	-	
TBDMS	*tert*-Butyldimethylsilyl	
TC	Thermochemical	-
TC/BC	Thermochemical/biochemical	-

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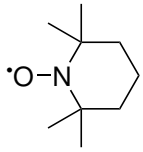
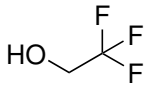
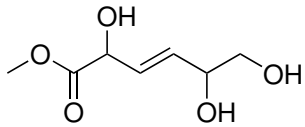
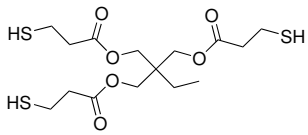
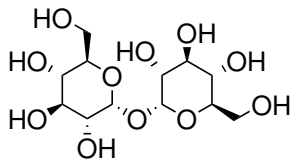
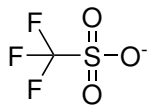
Abbreviation/ Name	Definitions/Description	Structure/Comment
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl	
Tensile strain breaking	$Strain = \frac{Extension}{Lenght}$	-
Tensile strain stress	$Strain = \frac{Force}{Area}$	-
TFE	Trifluoroethanol	
T_g	Glass transition temperature	-
THF	Tetrahydrofuran	
THM	Methyl (E)-2,5,6-trihydroxyhex-3-enoate	
TIC	Total ion current	-
TLC	Thin layer chromatography	-
T_m	Melting point	-
TMPTMPA	Trimethylolpropane tris(3-mercaptopropionate)	
TMS-Cl	Trimethylsilyl chloride	
Tolonate HDB 75B	An aliphatic polyisocyanate	-
Trehalose	-	
Triflate (OTf)	Trifluoromethanesulfonate	

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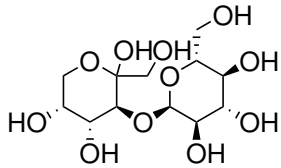
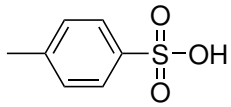
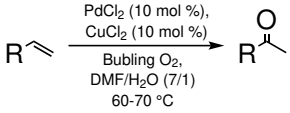
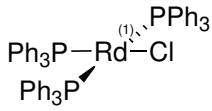
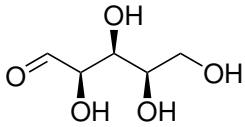
Abbreviation/ Name	Definitions/Description	Structure/Comment
Turanose	-	
TS-1	Titanium silicalite-1	-
TsOH	*p*-Toluenesulfonic acid	
Wacker-type olefin oxidation	-	
Wilkinsons Catalyst	Chloridotris(triphenylphosphane)-rhodium(I)	
Xylose	-	
ZN	Ziegler-Natta	-

"Success is not final, failure is not fatal: It is the courage to continue that counts." Sir Winston S. Churchill.