Faculty of Applied Engineering
Research Group Bio-Chemical Green
Engineering & Materials (BioGEM)

Faculty of Science
Research Group Organic Synthesis (ORSY)

Functionalization of long chain olefins and fatty acid derivatives via boron intermediates

Thesis submitted in fulfilment of the requirements for the degree

of doctor in the Applied Engineering

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“The science of today

is the technology of tomorrow”

/Edward Teller/

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List of abbreviations

- 9-BBN: 9-Borabicyclo[3.3.1]nonane
- ACN: acetonitrile
- BHT: butylated hydroxytoluene
- CC: Column chromatography
- DEPT: Distortionless enhancement by polarization transfer
- DMC: Dimethyl carbonate
- DMS: Dimethyl sulfide
- DHP: 3,4-Dihydro-2H-pyran
- EI: Electron ionization
- FFA: Free fatty acids
- FID: Flame ionization detector
- GC: Gas chromatography
- GPC: Gel permeation chromatography
- HX: Hydrogen halide
- LAO: Linear alpha olefin
- LIO: Linear internal olefin
- m/z: mass-to-charge ratio
- MMS: Methyl methanesulfonate
- MS: Mass spectrometry
- MTBE: Methyl-*tert*-butylether
- n/a: not applicable
- OA: Oleyl alcohol
- PAA: Peracetic acid
- PE: Polyethylene
- PP: Polypropylene
- pTSA: *para*-Toluenesulfonic acid
- R_f: Retardation factor
- RRF: Relative response factor
- THF: Tetrahydrofuran

- TLC: Thin layer chromatography

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1. Summary

1.1. English version

This PhD work contributes to the valorization of unsaturated renewable materials into industrially relevant products. More specifically, the goal of this PhD work was to realize a sustainable method for the preparation of long carbon chain α,ω-bifunctionalized molecules starting from unsaturated long chain fatty acids and/or their derivatives. Two different methods to produce α – ω long chain building blocks were investigated: (1) the shift of mid-chain double bonds in derivatives of unsaturated (free) fatty acid esters by means of hydroboration-isomerization (the main method) and (2) the synthesis of long chain unsaturated dialkyl ethers followed by ozonolysis of the double bond.

The starting materials are easily available from renewable sources such as natural oils/fats. The envisioned end products on the other hand – α,ω-bifunctional molecules – are of high industrial value and as long molecules are not naturally occurring.

The first selected method, studied in depth in this work, was hydroboration-isomerization, which allows shifting of carbon-carbon double bond from an internal position to a terminal position. The feasibility of this first method for long chain molecules hinges on three different aspects: the double bond shift, the functionalization and the overall efficiency optimization. Aside from the shift of the double bond from its internal position to a more terminal position in the alkyl chain, also the introduction of molecular diversity by functionalization of the (shifted) double bond was investigated. As a third aspect, the study of this first method aims further optimization by reducing complexity and/or increasing the efficiency of the reactions and reducing the cost of the reagents.

The migration of substituted double bond to the terminal position is thermodynamically unfavorable. Shifting the double bond to the terminal position in a long aliphatic chain requires a molecule (or catalyst) with bulky ligands, which can induce steric hindrance. The latter causes the double bond to shift to less sterically encumbered positions, i.e. terminal.

Two approaches to realize the hydroboration-isomerization were examined:

Approach 1: internal dialkylborane

Approach 2: external dialkylborane

The results regarding hydroboration-isomerization can be summarized as follows:

Hydroboration-isomerization of model alkenes: Long chain alkenes can be considered as the most simple model case for hydroboration-isomerization. Thus far only data on shorter chain alkenes (max. 8 C atoms) have been reported, which render the preliminary study of long chain alkenes very important. Experimental work showed the influence of the carbon chain length on the isomerization of mid-chain double bonds and allowed to optimize the reaction conditions. It was observed that long chain olefins require other conditions (like solvent type or external dicycloalkyl borane) to improve the yield, as opposed to short chain analogues. A breakthrough in this research was the discovery that apolar (non-coordinating) solvents improve the conversion substantially and also improved the reaction kinetics. Moreover, isomerization of long chain molecules was only possible when using these solvents.

Hydroboration-isomerization of functionalized olefins: Functionalized olefins were subjected to hydroboration-isomerization using the conditions obtained in the alkene-study. In many instances, oxygen appears to have a significant influence on hydroboration-isomerization. More specifically, a carbonyl oxygen has an inhibiting effect on the hydroboration-isomerization. Fatty alcohol ethers were found to be suitable starting materials, because they do not interfere with the empty *p*-orbital on borane, unlike for example esters, and they are stable under the reaction conditions. This finding can be considered as a second breakthrough in this research.

The experimental data acquired allowed proposing a semi-theoretical understanding of hydroboration-isomerization. Steric hindrance of the alkyl chains attached to the boron atom plays an important role. The solvent influences the reaction strongly by changing the conformational structure of the chains. Polar solvents induce an increased steric hindrance, making hydroboration-isomerization more difficult, or even impossible. Solvents (but also functional groups in general) with a carbonyl oxygen inhibit the reaction by an additional interaction of free electrons from the oxygen atom with the empty *p*-orbital on the boron atoms.

A second selected method to synthesize α,ω-bifunctional compounds (i.e. not by the hydroboration-isomerization reaction) was conceptualized and tested. The synthesis of long chain unsaturated dialkyl ethers followed by ozonolysis of the double bond can also give long chain α,ω-bifunctional compounds. Such long ethers can successfully be synthesized by decarboxylation of their corresponding dialkyl

carbonates. This method involves dimethyl carbonate and hydrotalcite (as heterogeneous catalyst), which are both recognized as green materials.

Two methods were thus found that can realize the envisaged α,ω-bifunctional molecules. The borane-based approach has a high carbon atom economy, whereas the dialkylether approach implies a loss of half of the carbon chain of the starting alcohol. The borane chemistry involves however more steps and an additional ether cleavage to attain the desired product. First steps towards further optimization were explored by replacing methyl ether by benzyl ether. Nevertheless, further research is needed to conceive a complete economically viable process.

1.2. Dutch version:

Dit doctoraatswerk draagt bij tot de valorisatie van onverzadigde grondstoffen tot nieuwe, waardevolle producten. Het doel van dit doctoraatswerk was het vinden van een duurzame methode om onverzadigde vetzuren met lange koolstofketens en/of hun derivaten om te zetten naar α,ω bifunctionele moleculen. Tijdens het onderzoek werden twee verschillende methodes diepgaand onderzocht om deze α,ω lange keten bouwstenen te bekomen. De eerste is gebaseerd op het verschuiven van een interne (in het midden van de koolstofketen) dubbele binding in derivaten van onverzadigde vrije vetzuren door middel van hydroboratie – isomerisatie. De tweede methode vertrekt van de synthese van dialkyl ethers met lange onverzadigde koolstofketens, gevolgd door ozonolyse van de dubbele binding.

De beginproducten kunnen gemakkelijk verkregen worden vanuit hernieuwbare bronnen zoals natuurlijke oliën/vetten en zijn vlot beschikbaar op de markt. De beoogde eindproducten, α,ω bifunctionele moleculen, zijn van grote waarde voor de industrie maar komen zelf uiterst zelden voor in de natuur.

De eerste methode die uitgebreid werd bestudeerd, maakt gebruik van hydroboratie-isomerisatie, die toelaat om een interne koolstof-koolstof dubbele binding te verschuiven naar een externe positie. De toepasbaarheid van deze eerste methode op de beoogde lange moleculen hangt af van drie aspecten: de verschuiving, de functionalisering en procesoptimalisering. Naast het verschuiven van een dubbele binding van de interne naar de eindstandige positie, werd onderzocht hoe de verschoven dubbele binding kan omgezet worden in een functionele groep. Beide aspecten zijn van essentieel belang voor het uiteindelijke industriële proces. Gedurende het bestuderen van deze eerste methode, werd aandacht besteed aan de optimalisering van het proces door het verlagen van de complexiteit en/of het verhogen van de efficiëntie van de reactie, als derde aspect. Er werden tevens concepten gevonden die toelaten de kosten van de reagentia te reduceren (trialkylboraan benadering).

De migratie van de interne dubbele binding naar de eindstandige positie is thermodynamisch ongunstig. Om deze verschuiving van de dubbele binding in een lange alifatische keten toch te forceren, zijn moleculen (katalysatoren) nodig die omvangrijke structuren bezitten en zo sterische hinder veroorzaken. Door deze sterische effecten zal de dubbele binding de neiging vertonen om naar minder sterisch gehinderde posities te verschuiven, in dit geval de eindstandige.

De hydroboratie-isomerisatie werd op twee manieren benaderd:

Gebruik van interne dialkylboraan

Gebruik van externe dialkylboraan

De resultaten in verband met hydroboratie-isomerisatie kunnen in twee delen opgesplitst worden:

Hydroboratie-isomerisatie van modelalkenen: Alkenen met lange ketens deden dienst als de eenvoudigste modelmoleculen voor de hydroboratie-isomerisatiereactie. De studie van lange alkenen is van belang omdat momenteel enkel gegevens over kortere alkenen (max. 8 koolstofatomen) gerapporteerd zijn in de literatuur. Experimenteel werd aangetoond dat de lengte van de koolstofketen een invloed heeft op het verschuiven van een interne dubbele binding. Het bleek mogelijk om de reactieomstandigheden te optimaliseren. Olefinen met lange koolstofketens vereisen andere reactieomstandigheden (type solvent of externe dicycloalkylboranen) om de opbrengst te verhogen, in vergelijking met reacties met kortere ketens. Een eerste belangrijke doorbraak in het onderzoek was de vaststelling dat apolaire, niet-coördinatieve solventen de conversie aanzienlijk verhogen en ook een gunstige invloed hebben op de reactiekinetiek. Bovendien bleek dat de isomerisatie van moleculen met lange ketens enkel mogelijk was door gebruik van dergelijke solventen.

Hydroboratie-isomerisatie van gefunctionaliseerde olefinen: Gebruikmakend van optimale reactieomstandigheden, geselecteerd op basis van de bekomen gegevens in de studie van alkenen, werd hydroboratie-isomerisatie uitgevoerd op gefunctionaliseerde olefinen. In vele gevallen bleek dat een zuurstofatoom een sterke invloed heeft op hydroboratie-isomerisatiereactie. Meer bepaald hebben carbonyl zuurstofatomen een negatieve invloed en verhinderen de hydroboratie-isomerisatie volledig. Etherderivaten van vetzuren blijken geschikte startproducten te zijn omdat ze, in tegenstelling tot esters, niet interfereren met het lege *p*-orbitaal van boraan. Ze zijn bovendien stabiel in de gekozen reactieomstandigheden. Deze bevinding kan beschouwd worden als de tweede doorbraak in het onderzoek.

Het geheel aan experimentele data resulteerde in een semi-theoretisch inzicht in de hydroboratie-isomerisatiereactie. Sterische hinder veroorzaakt door alkylketens die gebonden zijn aan het booratoom, speelt een belangrijke rol. De reactie wordt sterk beïnvloed door het gekozen solvent, omdat dit laatste de conformationele structuur van de ketens verandert. Polaire solventen veroorzaken meer sterische hinder waardoor hydroboratie-isomerisatie zeer moeilijk (of zelfs onmogelijk) wordt. Bovendien verhinderen (solventen met) carbonyl zuurstofatomen de reactie door

bijkomende interactie van de vrije elektronen van het zuurstofatoom met het lege *p*-orbitaal van het booratoom.

Een tweede methode om α,ω bifunctionele moleculen te synthetiseren (dus niet via hydroboratie-isomerisatie) werd eveneens geconcipieerd en getest. De synthese van dialkyl ethers met lange, onverzadigde alkyl ketens, gevolgd door ozonolyse van de dubbele binding, biedt de mogelijkheid om α,ω bifunctionele moleculen te produceren. De lange ethers kunnen bereid worden via decarboxylatie van de overeenkomstige carbonaat esters. Tijdens deze synthese worden dimethylcarbonaat en hydrotalciet (heterogene katalysator) gebruikt. Beide zijn erkend als groene materialen.

Twee methoden zijn dus gevonden die het mogelijk maken om de beoogde α,ω bifunctionele moleculen te produceren. De methode gebaseerd op boraan is economischer op vlak van koolstofatomen. De aanpak via dialkylethers heeft tot gevolg dat de helft van de koolstofketen van het vetalcohol verloren gaat. De boraanchemie vereist echter meer stappen en een bijkomende splitsing van de etherbinding is nodig om het gewenste product te bekomen. Enkele eerste stappen naar verdere optimalisatie werden gezet door methyl ethers te vervangen door benzyl ethers. Desondanks is verder onderzoek noodzakelijk voor de ontwikkeling van een volledig economisch haalbaar proces.

2. Introduction

2.1. Goals

The chemical (related) industry is one of the largest industries in the world. At this moment this industry is mainly petrochemically based. Due to a rising shortage of petroleum and the stress between its function as fuel (source of energy) and its function as raw material (source of chemical building blocks), new strategies are deployed with respect to alternative raw materials that could lead to chemical building blocks.

Renewable, bio-based raw materials offer new possibilities since they fulfil the basic definition of a circular economy and a closed C-loop. Aside from countering future petroleum scarcity, they will also contribute to abating climate change as the carbon in bio-based chemical building blocks and materials is fixated from atmospheric CO_2.

Oleochemistry (centered on carbon containing molecules from natural oils and fats) seems an interesting way to obtain valuable chemical building blocks. A very interesting point is that it is a natural source of desirable long carbon-chain molecules, which can be further derivatized. The oleochemical approach has however also some disadvantages. A first important issue is the food versus fuel and/or food versus raw material discussion. The second issue is that there is a lack of long chain multifunctional, more specifically long chain α,ω-bifunctional molecules occurring in nature. Yet, such molecules can be used in high-value applications such as biopolymers and biolubricants.

Oils and fats offer an interesting stream of renewable and readily accessible starting molecules as they have: (1) a long carbon chain and (2) a terminal functional group (carboxylic group). However, in the chemical industry the use of said monofunctional molecules is limited. Biobased short chain α,ω-bifunctional compounds are known, some are produced directly by nature, e.g. succinic acid (butanedioic acid). The chain length of these compounds is however limited. Another approach to obtain similar short chain α,ω-bifunctional molecules uses scission of long chain unsaturated free fatty acids or derivatives. For example, the ozonolysis of oleic acid provides azelaic acid (α-ω bifunctional molecule) and pelargonic acid (monofunctional molecule). From this example it can be seen that this approach is however poor in value since (1) a rather short chain α,ω-bifunctional molecule is made (azelaic acid) and (2) a monofunctional (side) product is made (pelargonic acid).[116] As a conclusion can be

stated that there is at the moment a need for long chain α,ω-bifunctional molecules and processes to make them.

The greatest application of α,ω-bifunctional compounds (short as well as long type) can be situated in the production of biopolymers. Most of said biopolymers are based on polycondensation reactions (polyamides, polyesters, ...). Depending on the length of the chain the amount of polarity can be controlled in the biopolymer that has a polar repeating unit (e.g. ester group) that will be "diluted" with the long apolar hydrocarbon-chain. At the moment a lot of apolar (petro)polymers are used that are not biodegradable (PE, PP, etc.). From literature it is found that most of all produced apolar (petro)polymers are not recovered and thus induce environmental pressure. In case long chain α,ω-bifunctional molecules could be produced, polymers could be made that could mimic the apolar (petro)polymers. This polyester type "Pseudo-PE" would be degradable and hence will exert less environmental pressure.

As long chain bifunctional compounds, like α,ω-dicarboxylic acids are not provided by nature in sufficient amounts, it seems important to develop a process to obtain these compounds in an environmentally friendly and economically viable way. It is important to develop a process with an environmentally friendly catalyst and to optimize the process in such a way that not only edible clean fats/oils are used as starting material but also inedible fats/oils and maybe used oils/fats (used cooking oil).

2.2. Concept

This PhD research aims at developing a method for the preparation of long carbon chain α,ω-bifunctional molecules starting from mono- and polyunsaturated long chain fatty acids and/or their derivatives by using the double bond as a precursor for the introduction of the second functionality. As it is the intention to have the functionalities at the respective terminal positions, the double bond, occurring naturally at an internal position, has to be shifted. So the concept is to shift the double bond from its thermodynamically favored internal position to a more terminal position in the alkyl chain in a first step. In a second step, eventually occurring at the same stage as the isomerization, extra molecular diversity will be introduced by functionalization of the double bond. Both steps are essential in the final industrial application. A further substantial part of the research will be dedicated to unveil and understand the different reaction mechanisms and underlying principles. A last part of the research will cover further optimization to reduce complexity and/or increase the efficiency of the reaction and to reduce the cost of the reagents.

The starting material can be easily obtained from renewable resources such as natural oils/fats widely available on the market. On the other hand the envisioned α,ω-bifunctional molecules are of high industrial value and are almost not produced by nature. Also their production at this moment by chemical and biochemical means is tedious and expensive. The basic concept that was hypothesized at the beginning of this thesis work is shown in the following diagram (Fig. 2-1).

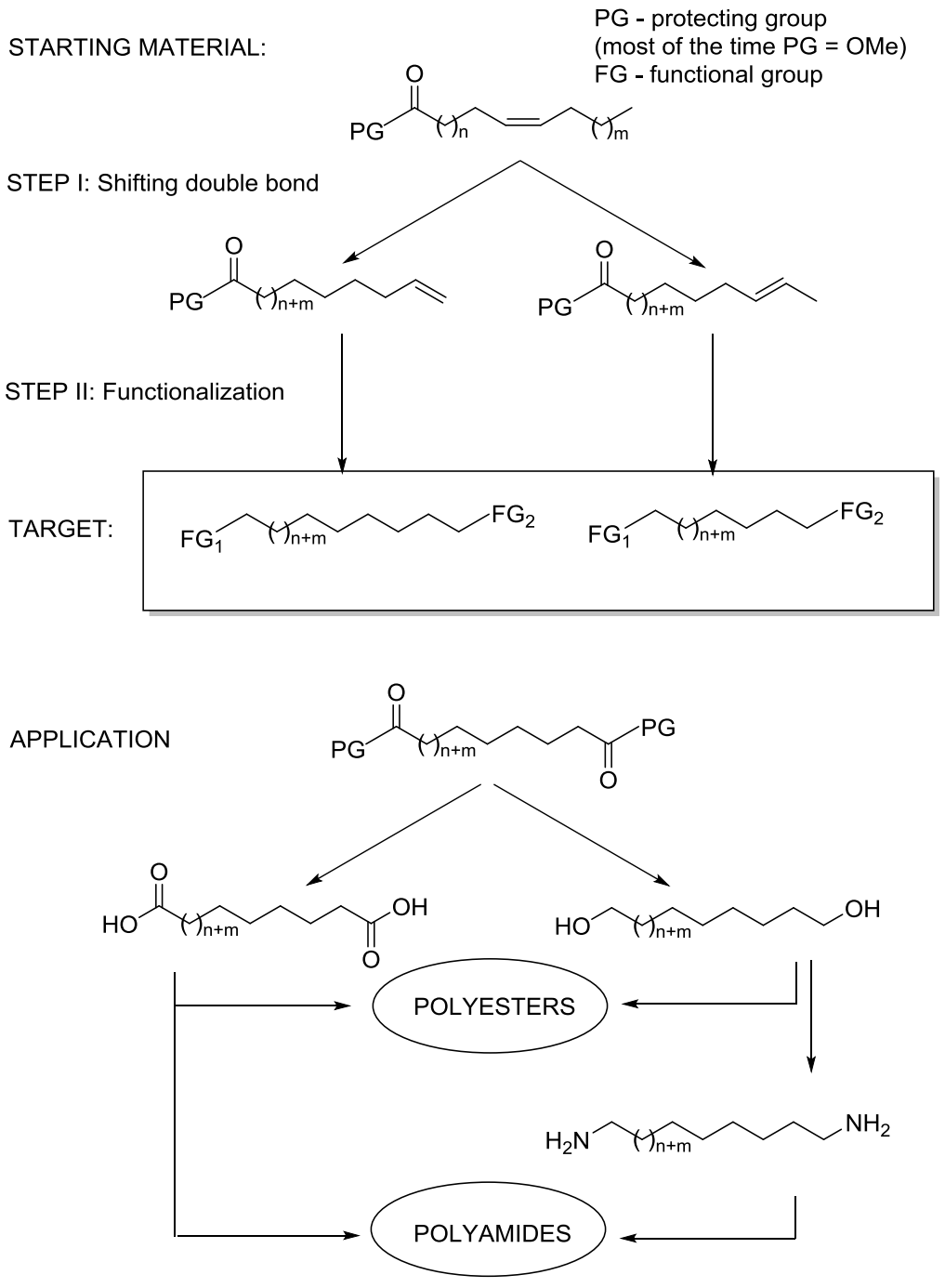

Figure 2-1 Generic concept description

2.3. Literature review

2.3.1. Isomerization of double bonds - background

Isomerization of olefinic and acetylenic compounds has received much attention during last decades in its theoretical and in practical aspects. The object of this chapter is to describe and discuss the known methods and related reactions used in isomerization of olefins (migration of the olefinic double bond). Acids and bases are the most important catalysts for double bond isomerization, and therefore the reactions involving these catalysts will be described first as a major part of the prior art. However, the more relevant prior art is related to new developments in recent years. They involve metal-, metal complex-, and boron compound-catalyzed isomerization. These methods will be presented in more detail in separate sections.

2.3.1.1. Base-catalyzed isomerization of olefins

The base-catalyzed isomerization of olefins is mechanistically closely related to the chemistry of carbanions. The reaction may be carried out in homogeneous solution or in the presence of a basic heterogeneous catalyst. The general overview of the mechanism is presented in Figure 2-2.

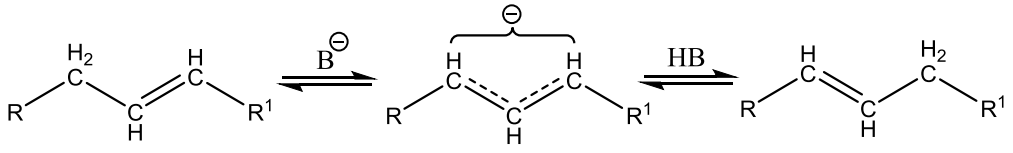

Figure 2-2 Base-catalyzed isomerization of olefins

In this type of catalysis a thermodynamically less-stable olefin is converted into a more stable form. In other words it means that terminal alkenes isomerize into internal alkenes, non-conjugated dienes into 1,3-dienes, and non-conjugated aryl-substituted olefins into corresponding styrenes.[1] A remarkable fact is that when more than two isomers are involved in the equilibria, the most stable one might be formed only slowly, therefore, the less stable isomer could be isolated after a short reaction time. For example 1-butene isomerizes readily to a mixture containing mainly *cis*-2-butene. Further prolonged heating leads eventually to the more stable *trans*-2-butene. In a case of long chain alkenes a double bond migration towards the middle of the chain is feasible, but slow.[2-3]

Base-catalyzed isomerization of olefins in homogeneous solution is mainly controlled by: (a) the thermodynamic stability of the isomeric alkenes, (b) the substituent effects upon the formation of carbanion from the olefins (polar effects, mesomeric

effects, steric inhibition, and steric hindrance), (c) solvent effects, (d) the collapse ratios $\frac{k_{-2}}{k_{-1}}$ or $\frac{k\prime_{-2}}{k\prime_{-1}}$ (Fig. 2-3)

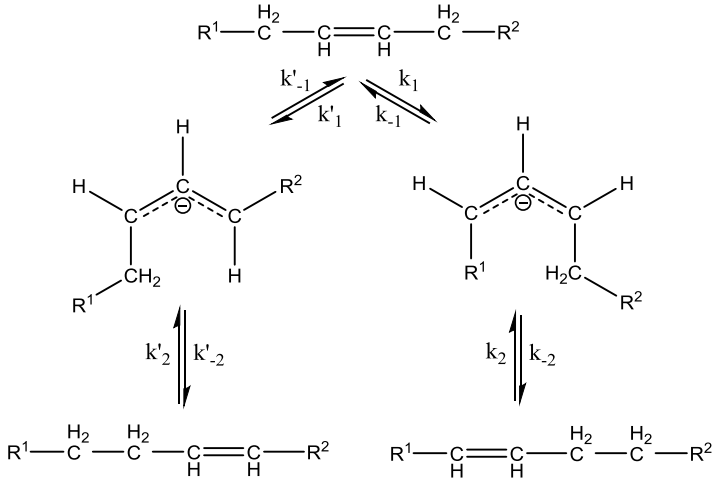

Figure 2-3 Equilibrium for isomerization reaction

It has been proven that 1,3-interactions in carbanions are more significant in determining its stability than 1,2-interactions (Fig. 2-4).[4]

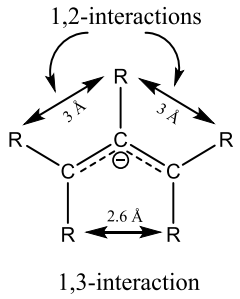

Figure 2-4 1,2- and 1,3-interaction in an allyl anion

The carbanion stability decreases as the 1,3 steric interaction increases with increasing size of the substituent. As an empirical rule, the rate of isomerization is enhanced by substituents in position 1 and 3 of the olefin in the following order:[5-6]

$$H_2C{=}CH \geq C_6H_5 > H > CH_3 > C_2H_5 > C_3H_7 > i\text{-}C_3H_7 > t\text{-}C_4H_9$$

Several solvents and solvent-base mixtures exist that allow isomerizing the olefinic double bond. The most widely used solvent that results in high reaction conversion and at low temperatures in homogeneous system is dimethyl sulfoxide (DMSO).[4, 6-9] Hexamethylphosphoric acid triamide possesses similar favorable properties as aforementioned DMSO.[10] Liquid ammonia has been extensively used as a solvent, but

its low boiling point is a serious disadvantage.[1] Lithium in ethylenediamine is a homogeneous system that is very attractive in promoting the migration of double bonds.[11] Sodium in isopropylamine with the addition of a small amount of allocimene was found to be effective in the isomerization of 1-octene into its internal isomers.[12] Dispersed sodium on alumina is an effective heterogeneous basic catalyst.[13] Sodium on γ-alumina with traces of ferric oxide added to the dispersed catalyst as a promoter is very active in the isomerization of allylbenzene and 1-phenyl-2-butene.[1] Potassium graphite also exhibits high catalytic activity in isomerization of terminal alkenes into *cis* and *trans* internal isomers.[14] Other interesting heterogeneous basic catalysts are sodium/anthracene,[13] fluorenyl/sodium, phenyl/sodium, various alkyl/sodium compounds.[15]

It has been demonstrated that dienes and aryl-substituted alkenes normally isomerize to yield predominantly the conjugated isomer. In the case of unsaturated aldehydes, ketones, carboxylic acids, esters, amides and nitriles, conjugation is likewise the most important factor in determining the equilibrium (Fig.2-5).[16]

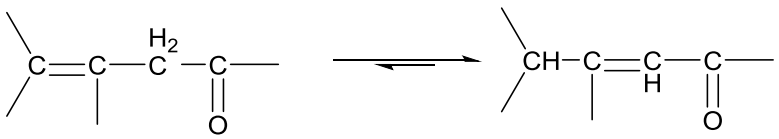

Figure 2-5 Conjugated isomer containing carbonyl group

In the base-catalyzed isomerization of long chain fatty acids, a fairly regular distribution of the double bond along the chain is observed; a slight preference for the α,β-position and ω-2,ω-1 may be noted.[17]

2.3.1.2. Acid-catalyzed isomerization of olefins

Whereas the base catalyzed isomerization of olefins proceeds through carbanions, the acid-catalyzed reaction takes place via carbenium ion as shown in Figure 2-6.

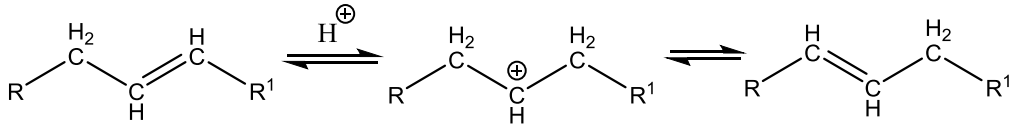

Figure 2-6 Acid-catalyzed isomerization of olefins

The order of carbocation stability is the reverse of that for carbanions:

tertiary > secondary > primary

Thus, it can be assumed that in acid-catalyzed and thermal isomerization, the olefins with the highest number of alkyl groups at the double bond are the most stable.[18]

To the most popular acid catalysts belong Brønsted–Lowry and Lewis acids as HF, HBF_4, $HClO_4$, H_2SO_4, *p*TSA, $AlCl_3$ and BF_3.[19] One of the most effective catalysts was found to be perchloric acid/acetic anhydride at 100 °C. The system sulfolane/methyl bromide/tetrafluoroboric acid and sulfolane/methyl bromide/4-nitrobenzenesulfonic acid are very convenient acidic catalysts for the isomerization of octenes.[3] Perchloric and phosphoric acids are the most frequently used acidic catalysts. The advantage of these catalysts is no oxidation activity toward olefins.[20]

2.3.2. Synthesis of linear α-olefins (LAOs)

As mentioned above, acids and bases are the most important catalysts for double bond isomerization of olefinic hydrocarbons. The base-catalyzed isomerization of olefins is mechanistically closely related to the chemistry of carbanions, whereas the acid–catalyzed reaction takes place via a carbocation intermediate.[21-22] These methods are used for shifting the double bond from terminal to more internal positions, yielding a more stable product.

More challenging is the isomerization from an internal position to the terminal position. Gee and Williams[23] presented interesting results on competitive double bond isomerization of terminal and internal alkenes. They showed that the internal double bond location for long chain olefins (C-22) has no measurable effect on the olefin's isomerization rate (Amberlyst® 15 at 90 °C); however the chain length of alkenes has an influence on the kinetics. Shorter chain internal alkenes isomerize about 1.35 faster than internal longer chain alkenes (comparison of C-12 and C-22). Moreover, the isomerization from a terminal to an internal position is almost twice as fast as the reverse reaction.

Linear α-olefins (LAOs) are linear hydrocarbons with a C=C double bond at the terminal position. These molecules find industrial use as chemical intermediates in the production of polyethylene-like polymers, surfactant alcohols, synthetic lubricants, and some specialty chemicals.[24-25] Most of the LAO production is based on ethylene oligomerization, two exceptions being the extractive processes of Sasol to recover 1-pentene, 1-hexene, and 1-octene from Fischer-Tropsch products and the recovery of 1-butene from refinery C_4-raffinate streams.[26] Despite most LAOs being produced from ethylene, the demand, application, and price of LAOs differ.

2.3.2.1. Ethylene-based LAOs production

Ethylene is widely used for the production of linear α-olefins. There are many processes to accomplish this reaction but one of the most known is the SHOP-process developed by Shell (The **S**hell **H**igher **O**lefin **P**rocess). The SHOP-process uses tree steps: oligomerization, isomerization and metathesis.

The oligomerization (Fig. 2-7) is the most important step, because it is the reaction that makes the hydrocarbon chain. The isomerization and metathesis are there to improve the yield of the desired products. This process uses a nickel-phosphine complex as a catalyst at high pressure and a temperature of approximately 100 °C. The ethylene will adsorb to the nickel. Other ethylene units will add to the ethylene that is already on the nickel. As a result the chain will grow with two methylene units per molecule of ethylene used. This will always result in a linear alpha-olefin but with

different chain lengths. The chains with more than 20 carbon atoms have low to no value on the market. These molecules undergo an isomerization step to form internal alkenes. The bonds in these alkenes are then broken in the metathesis step to create shorter length alkenes.[27-29]

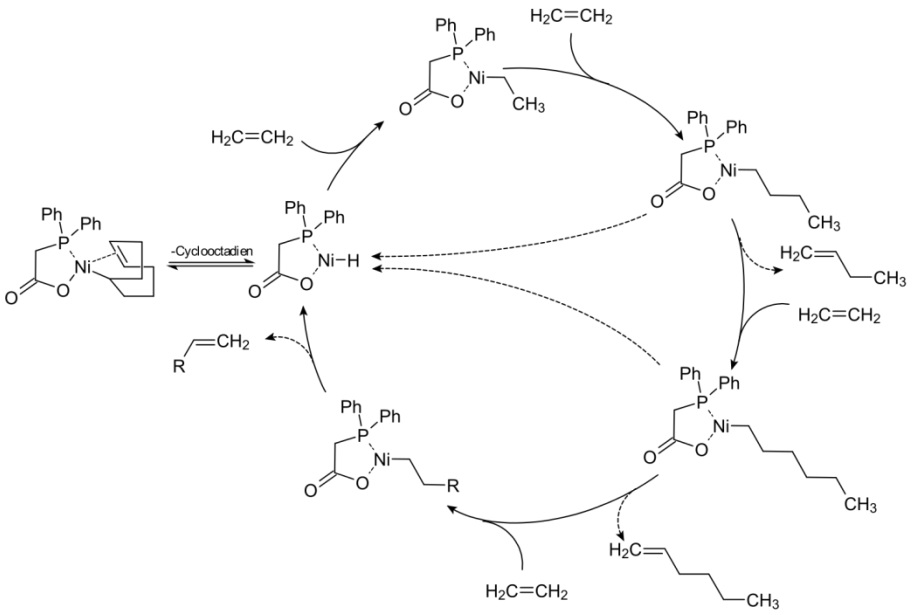

Figure 2-7 The oligomerization cycle of ethylene to produce LAOs

There are a several drawbacks associated with the production of LAOs by ethylene oligomerization. Firstly, the production cost is strongly dependent on the ethylene price. Secondly, only even-numbered LAOs can be produced, despite the fact that odd-numbered LAOs can produce interesting new materials.[26, 30-31] Moreover, most oligomerization processes yield a Poisson distribution of olefins in terms of chain length, which does not match the distribution required by the market.[32] To increase the proportion of LAOs in the desired range (typically C6-C18 based on price), further refining steps are required, such as isomerization and metathesis, increasing the production and total cost of such processes.

2.3.2.2. Organometallic catalysis

During recent years, the interest in metal- and metal complex-catalyzed isomerization of olefins has increased continuously, as a "contra-thermodynamic" isomerization is found to be possible aided by steric hindrance, which is extremely useful for the preparation of terminal olefins. The most popular catalysts are based on palladium. Cole-Hamilton and co-workers converted the internal double bond deep in the hydrocarbon chain very selectively to a terminal ester group by reaction with carbon monoxide and methanol in the presence of Pd(II) catalyst with bulky

electron-rich diphosphine ligands, like 1,2-bis[(di-*tert*-butylphosphino)-methyl]benzene (dtbpx).[33] The main force allowing shifting of the double bond is the presence of these bulky ligands. Whereas the migration of a double bond to the terminal position, in terms of traditional base/acid catalyzed reactions, is contra-thermodynamic, the migration of bulky ligands is a thermodynamically favorable reaction by the decrease of steric interactions. The development of organometallic catalysis has been a real success story in the past decades. These catalysts are based on complexes of some metals such as rhodium,[34-37] iridium,[38-40] titanium[41-42] and zirconium.[43] However, due to economic constraints, limited availability, and sometimes sensitivity and toxicity of noble metal complexes, other less expensive, bio-relevant metals were investigated e.g. iron.[44] All organometallic catalyzed reactions have however a major drawback – the catalyst recovery on industrial scale is difficult. Expensive catalysts must either be recovered or be sufficiently productive (i.e. the turnover number has to be higher than 10^4), in order to make the cost associated with their loss economically acceptable.[45]

2.3.2.3. Boron chemistry

Hydroboration (Fig. 2-8) is the addition of a boron-hydrogen bond across a carbon-carbon multiple bond to give an organoborane.[46]

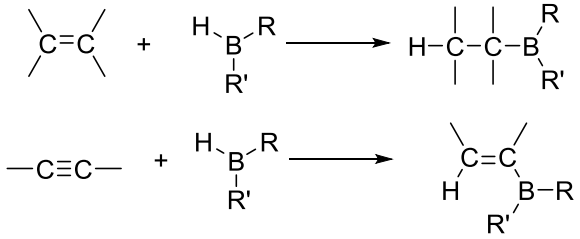

Figure 2-8 The general scheme of hydroboration

The addition of diborane is catalyzed by ethers. The catalytic effect can be attributed to the formation of weak readily dissociated borane-ether complexes (Fig. 2-9).[47]

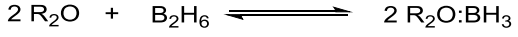

Figure 2-9 Formation of borane-ether complex

Borane adducts with other Lewis bases such as organic sulfides and certain hindered tertiary amines are also highly reactive. Stronger adducts with unhindered tertiary amines are less reactive. The hydroboration reaction proceeds in essentially complete yield under mild conditions, and many functional groups are tolerated.[46]

Hydroboration consists of the reaction of borane with an olefin or a derivative thereof. Borane reacts as a strong Lewis acid, meaning this molecule accepts electrons very easily. The presence of an empty *p*-orbital in the borane structure strongly attracts electrons. There are three hybridized sp^2 orbitals in borane (BH_3) which contain one electron and can form a sigma bond. One orbital stays unhybridized without any electrons. A schematic representation is shown in Figure 2-10.[48]

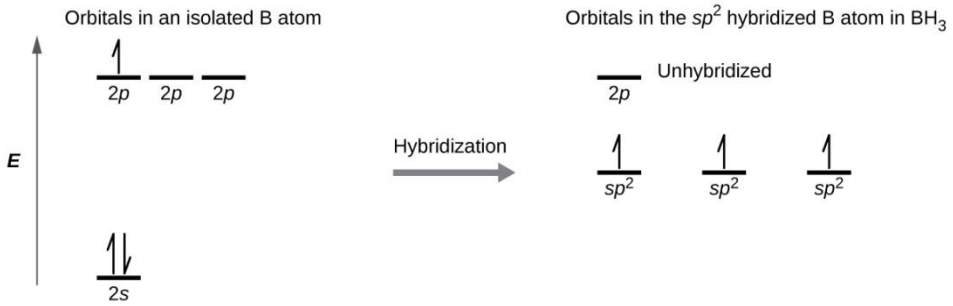

Figure 2-10 Orbital hybridization of boron

Borane is a toxic gas under standard conditions. The molecule is thermodynamically more stable when it reacts with itself forming a diborane complex (Figure 2-11). Thereby, two B-H-B bonds are formed which consist of three atoms but only two electrons, so called three-center-two-electron bond. This structure inhibits the borane reactivity which is not preferred if borane is applied as reagent.

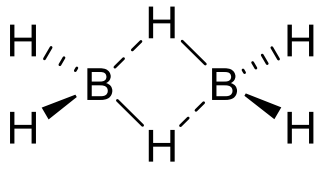

Figure 2-11 Structure of diborane complex

To prevent the molecule from reacting with itself, the borane is dissolved in ether-type solvent, mostly in tetrahydrofuran (THF). In this solvent, the bond BH_3-THF is strong enough to prevent the molecule to form diborane, yet sufficiently weak so that the borane is able to react with the substrate (Figure 2-12). THF is preferred at lab scale but when scaling up it can cause some problems such as recycling. Alternative carriers for the borane, instead of for THF, are SMe_2 and other sulfides[49].

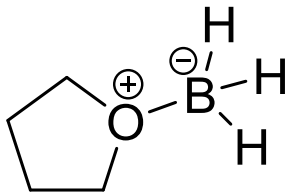

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Figure 2-12 Borane tetrahydrofuran complex (1)

Borane is consistently handled as a liquid borane-solvent complex like BH_3·THF (**1**). There are two hypotheses about the mechanism of reactions with the borane:THF complex. Either the borane-solvent complex dissociates completely according to an S_N1 reaction or borane is always bound and reacts with the substrate according to an S_N2 reaction.[50]

The rate of hydroboration depends on: (a) solvent – the type and concentration of the solvent determines the availability of free BH_3, (b) electron effect – the availability of the empty *p*-orbital of boron determines the reactivity. When derivatives of boron like for example *N*-derivatives are applied, the availability of the empty orbital and as a result the reactivity of boron can decrease, (c) steric effects: the steric properties of the olefin and the steric behavior of the borane molecule have a large influence on the reaction. Poor steric hindrance can lead to deactivation of the borane and excessive hindrance can prevent the borane from reacting with the double bond.[25]

The hydroboration reaction implicates a *syn*-addition of borane to the double bond on an olefin or a derivative. This means that the C-H and the C-B bonds are formed at the same side of the double bond of the alkene. In addition, the reaction involves a concerted transition state. In this transition state the C-C π bonds are broken and the C-B and C-H bonds are formed simultaneously.

The hydroboration reaction is based on an anti-Markovnikov mechanism. In a conventional Markovnikov reaction, the acid hydrogen of a hydrogen halide (HX) binds with the least substituted carbon of the substrate. The hydride of borane on the other hand reacts with the most substituted carbon, while boron reacts with the least substituted carbon of the substrate. This can be explained by the lower electronegativity of boron compared to the electronegativity of hydrogen. As a result, the boron atom will react with the most negative, least substituted carbon atom. The regioselective mechanism occurs clearly on terminal α olefins because the terminal carbon is less substituted than the internal carbon (Figure 2-13).

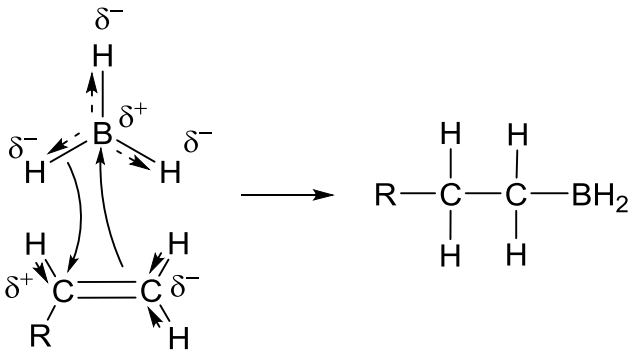


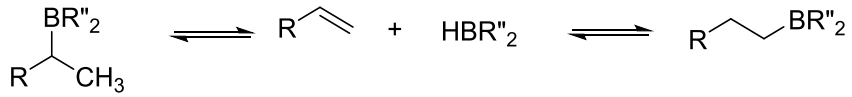
Figure 2-13 Mechanism of the hydroboration on a terminal olefin

When the double bond is located at an internal position, the hydroboration reaction is not very regioselective. This can be explained by the equal saturation of internal carbons, which both have only one bonded hydrogen atom.[46] Moreover, hydroboration of alkenes is a reversible process. This fact allows to use this reaction for double bond shifting.

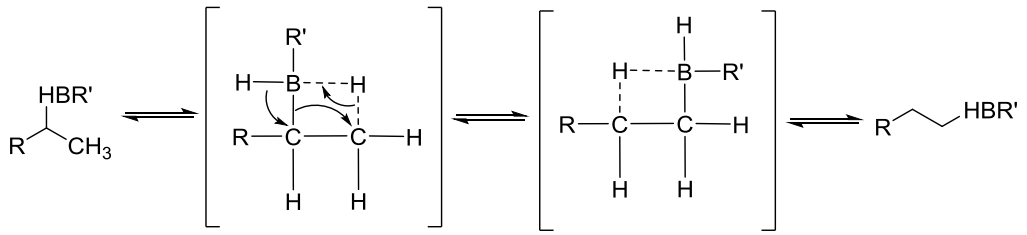
The hydroboration-isomerization reaction of alkenes is an attractive method for shifting a double bond from the internal position to the terminal position, which is also "contra-thermodynamic". This method could hence be an alternative to organometallic-catalyzed isomerization since it would avoid the problem associated with the cost and recycling of the metal based catalysts. By this approach less expensive LAO's[51] or directly functionalized hydrocarbons may be obtained.

Positioning on the terminal carbon atom is thermodynamically favored because the bond on a terminal position requires less energy than an internal bond due to partial negative charge of the less substituted, terminal carbon atom. Moreover, boryl at the terminal position possesses less steric interaction, which also makes this position more favorable. The internal B-C bond is hence shifted from an internal to the terminal position. This phenomenon is called regioselectivity. There is no clear understanding of the exact isomerization mechanism. Four different mechanisms have previously been suggested:

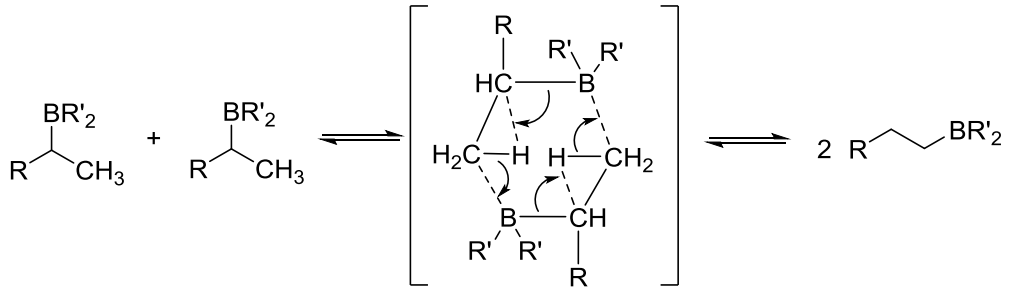
(a) successive dehydroboration-hydroboration:[52-53]



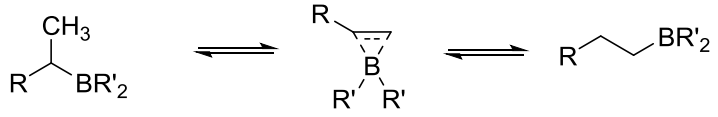
(b) rearrangement through a hydrogen bridge:[54]



(c) disproportionation going through a quasi-six-membered ring:[55]



(d) shifting via the π complex:[56]



It was hypothesized that at low temperatures (below 120 °C) isomerization occurs mainly by intramolecular rearrangement, while at higher temperatures the dehydroboration-hydroboration mechanism is dominant.[57]

The state of the art concerning the hydroboration reaction is based on the work of Brown.[58-59] The migration of an internal carbon-carbon double bond to the terminal position is thermodynamically not favored, as previously mentioned. In order to shift the double bond to the terminal position in a long aliphatic chain, a boron based molecule with bulky ligands has to be used. These bulky ligands induce the required steric hindrance and so the double bond can be shifted to the less sterically encumbered position. Most of the methods[60-64] involve (e.g. **3**) derived from cycloalkenes like **2**, which shift the double bond from an internal position to the terminal position by inducing steric hindrance (Fig. 2-14). The existing literature[47, 58, 60-61, 65-76] confirms high efficiencies of isomerization of alkenes to the corresponding terminal olefins within chains of at most 8 carbon atoms in length.

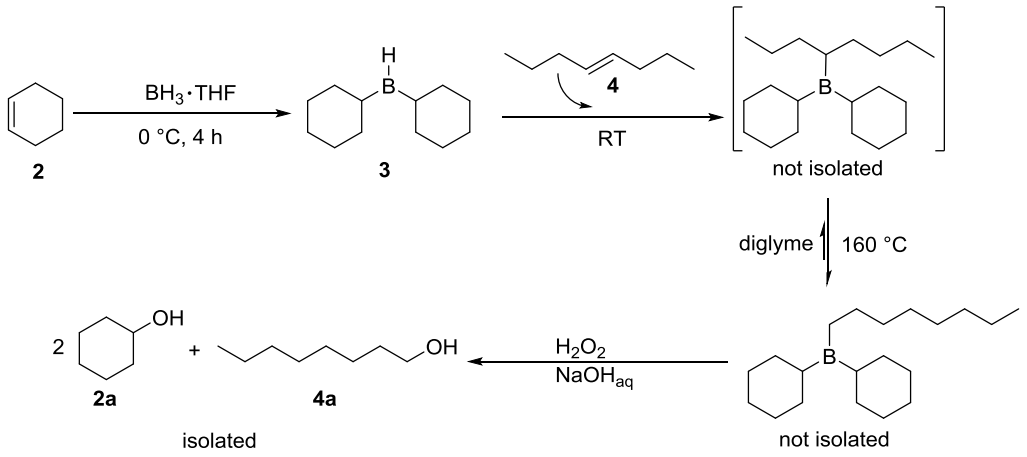


Figure 2-14 The state of the art concerning the hydroboration isomerization based on the work of Brown

The biggest advantage of the hydroboration-isomerization procedure is the possibility to convert the alkylborane intermediates into primary alcohols via an anti-Markovnikov reaction. Besides primary alcohols, also a broad range of other functional groups are accessible; linear internal olefins (LIOs) can be converted by a one-pot reaction into primary alcohols, carboxylic acids or amines.[77] Terminal fatty alcohols are nowadays mainly produced by hydrogenation of both fatty acids and their methyl esters.[78] The hydroboration-isomerization-oxidation of long chain LIOs can be a good alternative for the hydrogenation of fatty acids. Fatty alcohols find a huge application as surfactants,[79] lubricants[80-81] and coatings.[82]

To produce the target molecule with a functional alcohol group, the isomerized (tri)alkyl borane must be oxidized. Therefore, a reactive nucleophile is required which can react with the boron atom. Peroxide in basic conditions is applied to execute this reaction. Activation of peroxide occurs by the reaction with a strong base like NaOH. As a result, a strong nucleophilic peroxide anion is formed (Figure 2-15).

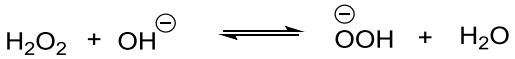


Figure 2-15 Formation of a peroxide anion

The boron atom has an empty *p*-orbital which makes the boron atom electron deficient. Due to this property, boron will easily create a bond with the peroxide anion, which has a free electron pair. An alkyl group will move to the neighboring oxygen atom. While migration of the alkyl group occurs, a hydroxide ion will be displaced. In the last step of the mechanism, hydrolysis of the borate will take place whereby the displaced hydroxyl group will bind to the boron atom and an alkoxide

group will be split off. Eventually a proton donor such as a strong acid can be introduced. The alkoxide ion will be protonated in order to form an alcohol. Also potential saponification products will be protonated. The complete mechanism is presented in Figure 2-16.

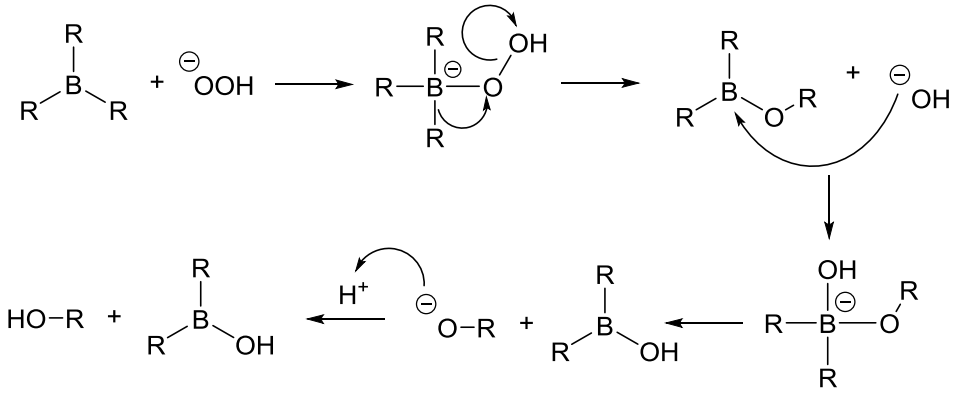


Figure 2-16 Oxidation of trialkylborane

The three alkyl groups that are present on the trialkylborane molecule can be oxidized if an excess of hydrogen peroxide is provided. The mechanism described above is identical for each alkyl group that is bound to borane. Eventually, three equivalents of alcohol will be formed in addition to one equivalent of boric acid.[83] Oxidation to the hydroxyl group is not the only one possibility. As mention above, trialkylborane can be oxidized or converted to other interesting groups like: hydroxyperoxides,[84-85] aldehydes,[86] ketones,[86-87] carboxylic acids,[88] amines,[89] alkyl halides[90] or organometallic compounds[91]. This feature opens the possibility to different functionalization and therefore extends the application potential of the whole process.

2.3.2.4. Aluminium chemistry

The addition of aluminium hydride (AlH_3) to olefins proceeds in a similar way to boron and yields a trialkylaluminium molecule. The reaction with internal olefins is about two times slower than with α-olefins, and isomerization of the branched trialkylaluminium to yield linear alkylalanes is slow.[92] Aluminium is also capable of alkyl exchange at room temperature,[93] making purification difficult. These properties lower the usefulness of aluminium as an isomerization agent. An alternative approach is to use the aluminium to convert LIOs to linear primary alcohols[25] and then dehydrate the primary alcohols to produce LAOs.

2.3.2.5. Silicon chemistry

Hydrosilylation is more difficult than hydroboration, especially in the absence of a catalyst, requiring temperatures of about 300 °C.[94] Liberation of olefins from alkylsilanes is also very difficult, and despite the reported liberation of ethylene from tetraethylsilane,[95] attempts at olefin liberation generally had little success. High temperature (580 °C) decomposition of alkylsilanes is possible, and it occurs by homolytic Si-C bond scission to produce alkyl radicals.[96] Consequently it is not viable to develop an isomerization process based on silicon chemistry.[25]

Table 2-1 presents the comparison of different methods to shift double bonds in linear internal olefins (LIOs) to terminal positions.

Table 2-1 Comparison of different method to synthesize LAOs

Method	Strengths	Weaknesses
Hydroboration	Conceptually simple, LIO to LAO conversion demonstrated	Cost and availability of large quantities of borane not known, isomerization is slow, potential for thermal borane loss
Hydroalumination	Conceptually simple, LIO to LAO conversion demonstrated	olefin insertion and chain growth tendency, isomerization is slow
Hydrosilylation	N/A	LIO to LAO conversion not yet shown, viable LAO liberation step doubtful
Organometallic	Tunable catalysts, widely studied chemistry, catalytic approach	LIO to LAO conversion not proven, potentially difficult catalyst scale-up, expensive, catalyst recovery and LAO separation difficult

2.3.3. Synthesis of α,ω-bifunctional compounds

For the synthesis of long-chain aliphatic polyesters and polyamides, polycondensation of monomers with an appropriate number of carbon atoms are required. Traditionally, these linear long-chain difunctional compounds are prepared via sequential build-up starting from shorter-chain building blocks. An interesting alternative to these multistep syntheses is a selective terminal functionalization of fatty acid derivatives, which already contain linear, long-chain crystallizable segments. A number of such straight-chain compounds actually also occur naturally. Aliphatic long-chain dicarboxylic acids as well as ω-hydroxycarboxylic acids naturally occur like cutin and suberin in cork.[97-98] Nevertheless, these natural resources are normally not used to recover these compounds, as their purity is often low and removal of other contaminants is extremely difficult. Hence, these polycondensation monomers have often been prepared via classical organic synthesis.[99]

2.3.3.1. Classical organic synthesis

Syntheses of long chain α,ω-bifunctional compounds can be achieved by the coupling of two shorter-chain fragments. For example, the synthesis of long chain terminal diols can be executed by means of monobromination of short chain diols followed by Wurtz coupling.[100-101] A useful coupling protocol to linear long-chain α,ω-functionalized compounds is Kolbe electrolysis. Starting from sodium ethyl sebacate, the linear long-chain aliphatic C34 diester can be obtained via two subsequent electrolysis steps.[99] Starting from aliphatic α,ω-dihalides (e.g. **5**), long-chain dicarboxylic acids with up to 22 carbon atoms (**6**) have been prepared by metal-catalyzed coupling reactions with short-chain α,ω-ester acid chlorides (Fig. 2-17).[102] On the basis of an iterative sequence involving a coupling step through Wittig olefination of an aldehyde, straight-chain aliphatic dicarboxylic acids containing from 48 up to 192 methylene groups were generated.[103-104]

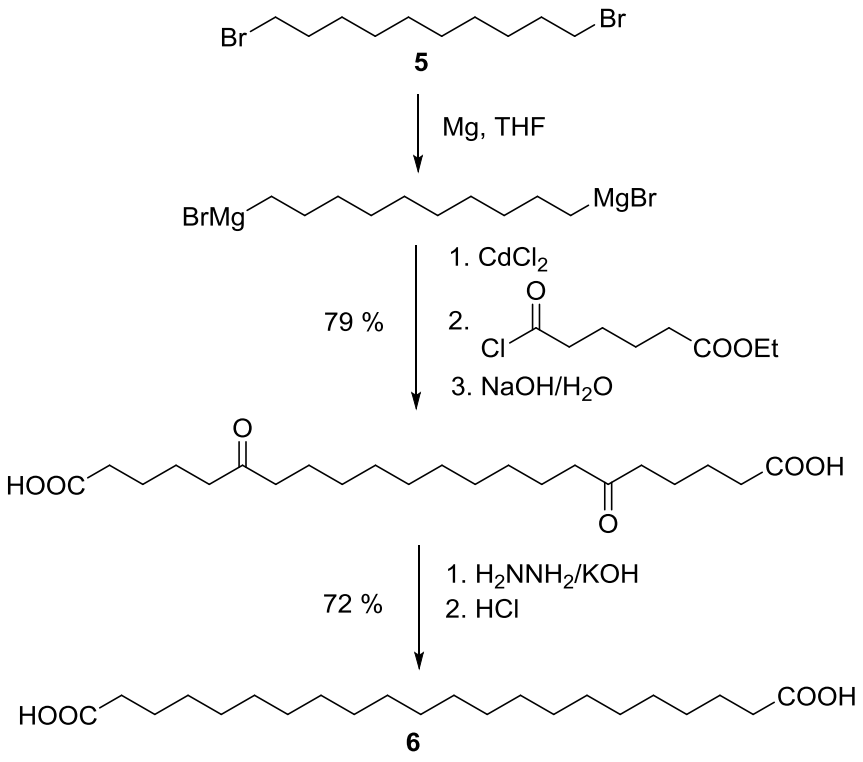


Figure 2-17 Chain extension of 1,10-dibromodecane via Grignard coupling[102]

Many further examples of such multistep approaches to long chain α,ω-bifunctional compounds have been reported.[105-108] Despite that they are able to even provide components with a very large number of carbon atoms precisely, they are very tedious and rather inefficient as a source of monomers for use at large industrial scale.

2.3.3.2. Chemical modification of fatty acids

As the most prominent starting material, ricinoleic acid (12-hydroxy-9-*cis*-octadecenoic acid), the major component of castor oil, has been used for many years. 10-Undecenoic acid could be obtained via thermal rearrangement with chain cleavage.[109] Further addition of hydrobromic acid and reaction with ammonia yields 11-aminoundecanoic acid, the starting material for nylon-11. Likewise, sebacic acid, which is used for nylon-6,10 synthesis, can be generated by cleavage under strongly basic conditions.[110]

Castor oil is significantly more costly (ca. double the price) than other plant oils like soybean, palm, or rapeseed oil. Moreover, in the aforementioned transformations, only one side of the fatty acid chain with respect to the double bond is incorporated and stoichiometric amounts of less valuable byproducts are formed. These

arguments also apply to ozonolysis, which converts monounsaturated fatty acids (and/or derivatives) to α,ω-diacids. In this way, several thousand tonnes of the medium chain length diacids azelaic acid (**13**) and brassylic acid (tridecanedioic acid) are produced industrially by oxidative cleavage of oleic acid (**7**) and erucic acid ((Z)-docos-13-enoic acid), respectively, producing also pelargonic acid (**12**) as a byproduct. The advantage of ozonolysis is the fact that ozonide can be converted into different functional groups depending on work-up conditions (Figure 2-18).[111-116]

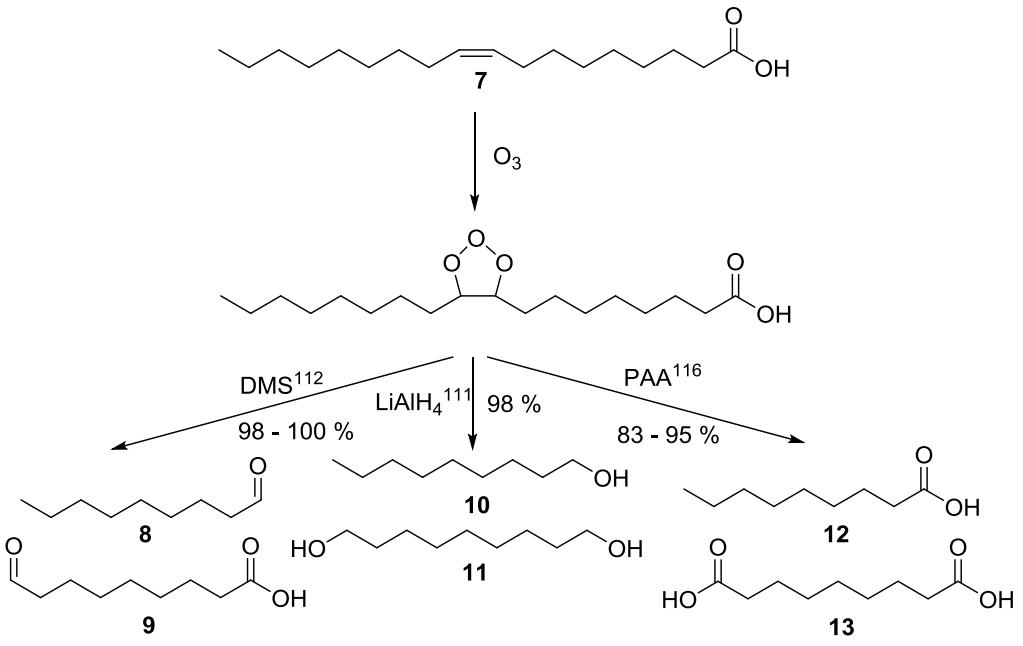


Figure 2-18 Ozonolysis of oleic acid with possible oxidation / reduction routes

2.3.3.3. Biochemical modification of fatty acids

To employ the potential of the linear long-chain hydrocarbon segments and also to utilize the feedstock most efficiently, a full incorporation of the entire fatty acid chain into linear long chain α,ω-bifunctional compounds is desirable. Biotechnological transformations provide a possible approach to this challenge.

Certain yeast strains, e.g., *Candida tropicalis*, *Candida maltosa*, and *Yarrowia lipolytica*, are able to oxidize terminal aliphatic carbons to carboxylic acids. This ω-oxidation enables the conversion of fatty acids (e.g. **14**) and their derivatives to long-chain dicarboxylic acids (e.g. **15**) (Figure 2-19).[117-119]

The first step of this biotechnological transformation is catalyzed by a hydroxylase complex and involves a terminal oxidation of the fatty acid to a primary alcohol. In a

second step the alcohol is oxidized by a fatty alcohol oxidase to the corresponding aldehyde, which is subsequently converted to the carboxyl group of the corresponding diacid.[120-122]

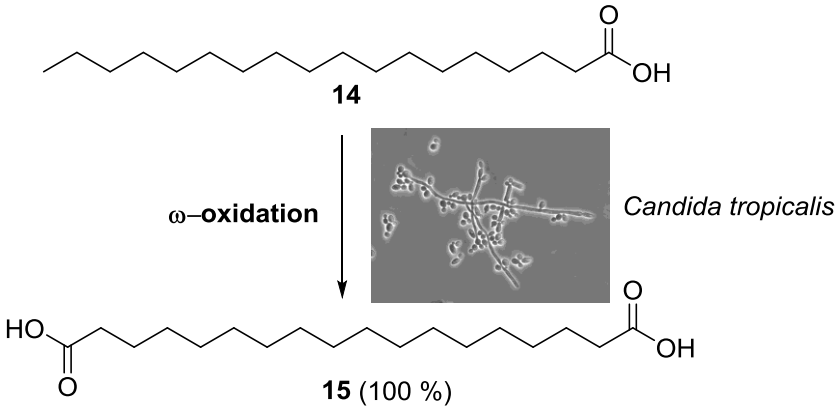


Figure 2-19 Enzymatic ω-oxidation of fatty acids

A crucial issue in the biotransformation is the downstream processing, i.e., separation and purification of the products from the fermentation broth. Mechanical, thermal, or chemical separation methods have to be adapted to the scaling up bioconversion process, just as much as to further utilization of the obtained compounds.[123]

2.3.3.4. Olefin metathesis

Since the pioneering work of Boelhouwer and co-workers in 1972,[124] olefin metathesis reactions with fatty acid derivatives have made considerable progress.[125-126] Particularly the last 10 years have brought about significant improvements, making olefin metathesis one of the most versatile tools in oleochemistry. One of the main reasons for this advance was the development of functional-group-tolerant metathesis catalysts by Grubbs and others,[127] thus allowing the reduction of the catalyst amounts as well as transformations with olefins containing functional groups.

Metathesis reactions can be divided into two types: (1) self-metathesis (Fig. 2-20) where only one olefin takes part in the reaction and (2) cross-metathesis (Fig. 2-21) where two olefins take part in the reaction exchanging their alkyl chains. Especially the synthesis of ω-functionalized fatty acids by cross-metathesis was heavily researched over the last few years.[128-133]

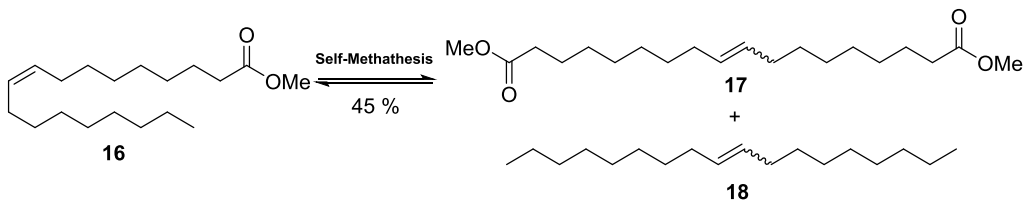


Figure 2-20 Self-metathesis of methyl oleate

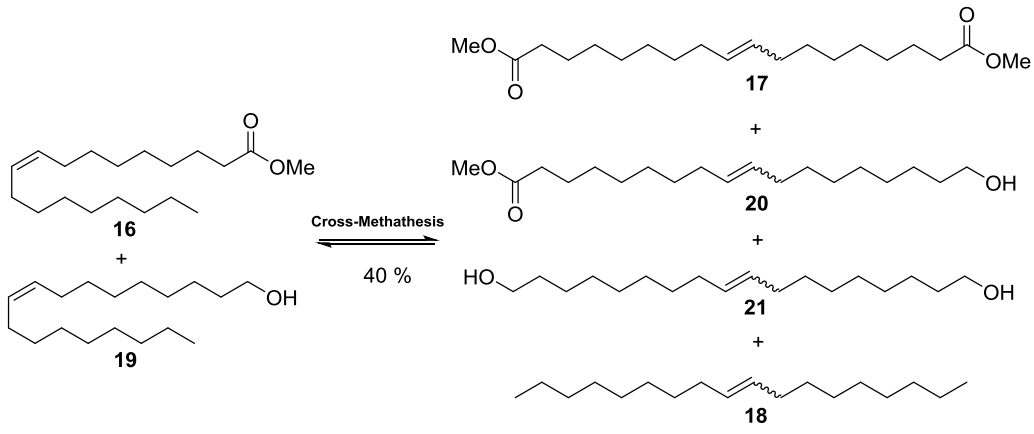


Figure 2-21 Cross-metathesis of methyl oleate with oleyl alcohol

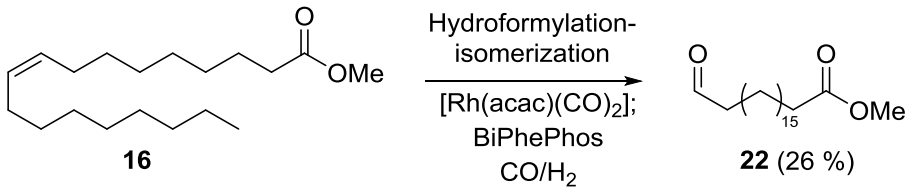
A significant number of new types of catalysts and conditions are reviewed[134-138] to improve the metathesis reaction, but still the carbon economy of this conversion is low, since a non-functionalized alkene is always formed in equivalent amounts. Moreover, the recovery of the expensive catalyst is difficult.

2.3.3.5. Isomerization of double bonds in functionalized olefins

The aforementioned metathesis reactions construct the α,ω dicarboxylic acid product from half of the unsaturated fatty acid derivatives. The other half of the substrate's chain yields stoichiometric amounts of hydrocarbons. A more efficient way would be using the vegetable oil starting materials and isomerize the double bond to the ω-position. To the most interesting methods belong:

Hydroformylation-isomerization:

An ω-aldehyde ester (**22**) was obtained by hydroformylation-isomerization of methyl oleate (**16**) (Fig. 2-22) and methyl linoleate using a rhodium-based catalyst system. Yields of 26 % and 34 % were obtained, respectively.[139] The disadvantage of this method is the relatively low yield and the high cost related to the catalyst and its recovery.

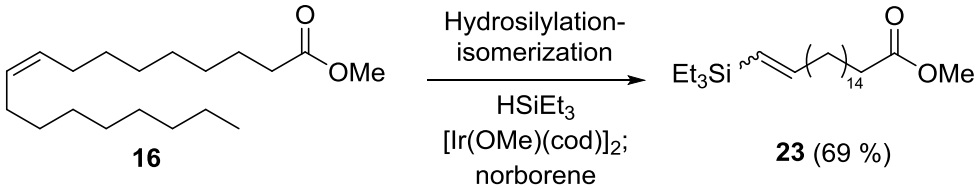


acac - acetylacetonate
BiPhePhos - 6,6'-[(3,3'-Di-tert-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diyl)bis(oxy)]bis(dibenzo[d,f][1,3,2]dioxaphosphepin)

Figure 2-22 Hydroformylation-isomerization of methyl oleate.

Hydrosilylation-isomerization

Riepl and co-workers reported[140] the selective addition of silane containing groups. Methyl oleate (**16**) was shown to undergo an iridium-catalyzed dehydrogenative silylation with triethylsilane to give the terminal vinylsilane (**23**) in 69 % yield.



cod - 1,5-cyclooctadiene

Figure 2-23 Hydrosilylation-isomerization of methyl oleate

Alkoxycarbonylation-isomerization

A promising approach to achieve α,ω-bifunctional compounds is the alkoxycarbonylation-isomerization (Fig. 2-24).[141-142] This reaction, first observed for fatty acid esters by Cole-Hamilton and co-workers,[33] converts the internal double bond deep in the hydrocarbon chain very selectively to a terminal ester group by reaction with carbon monoxide and methanol. The reaction is promoted by Pd(II) catalysts with bulky electron-rich diphosphine ligands, like 1,2-bis[(di-*tert*-butylphosphino)-methyl]benzene (dtbpx). Dimethyl nonadecane-1,19-dioate (**24**) (via carbonylation-isomerization of methyl oleate(**16**)) and diethyl tricosane-1,23-dioate (from ethyl erucate) were obtained in preparative scale with high yield (Y = 95 %) at high purity (>99 % by crystallization from the reaction solvents), enabling utilization for polycondensation reactions.[143]

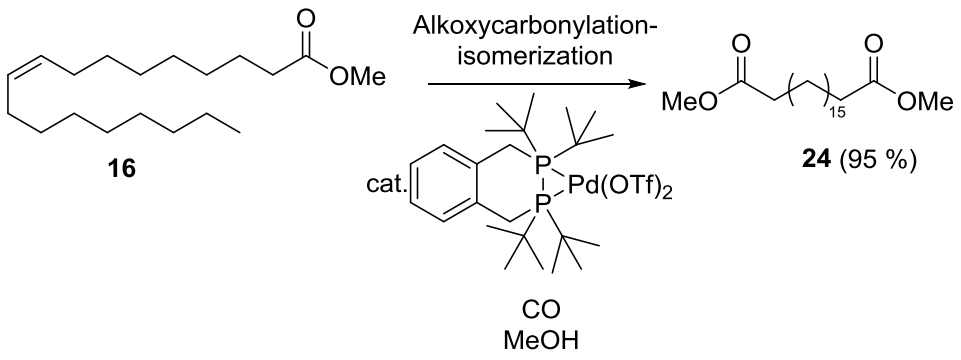


Figure 2-24 Alkoxycarbonylation-isomerization of methyl oleate

Hydroboration-isomerization

A significant increase in selectivity in the hydroboration-isomerization of methyl oleate (**16**) with pinacolborane was reported by Zhu and co-workers,[144] applying iridium nanoparticles in the presence of a bulky diphosphine ligand, yielding the desired terminal boronate ester in 78 % isolated yield. After a further oxidation step, terminally borylated fatty acids provide a promising access to long-chain ω-hydroxy esters (**25**). Despite the relatively high conversion, the high cost of the catalyst and pinacolborane is problematic.

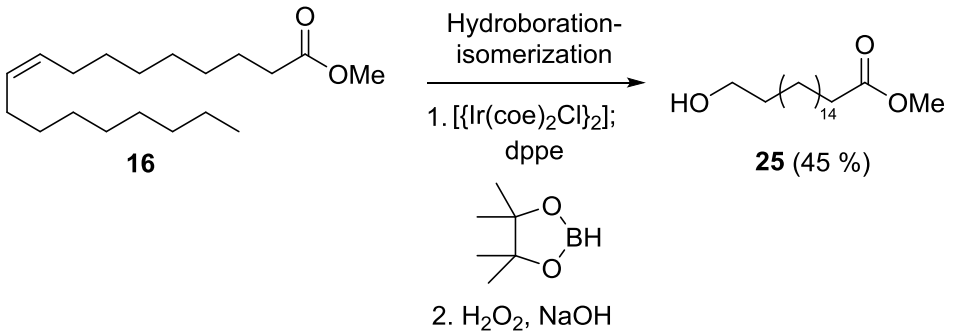


Figure 2-25 Hydroboration-isomerization of methyl oleate

2.4. Why α,ω-bifunctional compounds? – Applications

The synthesis of bio-based compounds from renewable resources is currently intensively studied by researchers from both academia and industry.[145-148] Unsaturated free fatty acids are a unique feedstock for the production of chemical building blocks for three reasons: (1) they contain a long sequence of methylene groups, (2) carboxylic groups are suitable functional groups for further modifications, (3) the presence of one or multiple double bonds enables their post modification and the generation of additional functional groups.[24, 149] The isomerization of a double bond to the ω-position opens new possibilities of applications. The full potential of the long methylene sequence of FFA to give useful properties such as hydrophobicity or crystallinity is not yet fully valorized, but gave already promising results.[99, 150] The conversion of unsaturated FFA into linear, long-chain α,ω-bifunctional compounds is of interest, for example, for the generation of semi-crystalline aliphatic polyesters and hydrophobic polyamides[151] as shown in Figure 2-26.

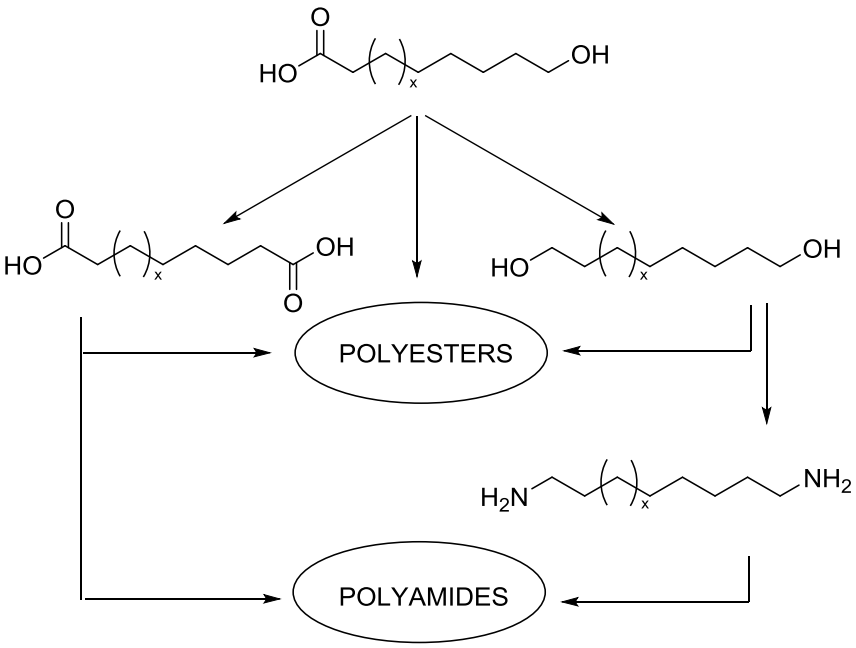


Figure 2-26 Long chain α,ω-bifunctional compounds as a starting material for biopolymer production

Organic oligomers and polymers constitute an indispensable category of materials, because of their low density, easy production, high versatility and usually high chemical resistivity. Yet, their ever increasing application causes environmental stress, because (1) they are mostly petroleum sourced, resulting in a high carbon footprint, (2) they may leak into waterways because of improper waste management, (3) they are often poorly recyclable as a result of extended blending and use of

additives. Specialty applications (water repellent coatings, surface modifiers, release agents, food and cosmetics, etc.) require a simultaneously highly versatile (fit-to-purpose), biobased and biodegradable material. Traditional plastics (PE, PP, PET, PA, etc.) often fall short with regard to at least one of those desirables.

Recently, long-chain aliphatic polymers gained attention to *bridge the gap*[99] between semi crystalline polyolefins and traditional polycondensates based on short-chain congeners. Whereas polyolefins are relatively easy to produce and process, they are not readily biodegradable. Additionally, increasing their versatility mostly occurs by blending, and using additives, impeding their recycling potential. Polycondensates are characterized by a usually high polarity (hence hydrophilicity), and higher susceptibility to various kinds of degradation. In short, the physical (macroscopic) properties of polycondensates, as well as their degradation susceptibility, are often dominated by their functional groups.[99] Indeed, most commercially available biodegradable plastics (e.g. PLA, PHA, PCL, and PBS) are polycondensates produced from short-chain congeners. Polycondensates with linear long-chain aliphatic repeating units differ from their shorter chain congeners like Nylon-6,6 or poly(butylene adipate) as their solid structure is dominated by interaction between adjacent stretched methylene sequences, that is, by their hydrocarbon nature. Therefore, these novel materials are often called “polyethylene mimics” or “polyethylene-like”.[108]

The pursued improvements could be: (1) better resistance against moisture/temperature regarding dimensional stability (15-45 °C /15-85 % RH), (2) lower water uptake (15-45 °C and 15-85 % RH), (3) better stability to acidic and alkaline conditions (by stronger non polar behavior), (4) better hydrophobicity/larger contact angle for water e.g. when applied as a coating, as fabric, (5) improved mechanical strength at ambient conditions (reduced brittleness, tougher response), (6) tunable melting point (Fig. 2-27).[99, 152-158]

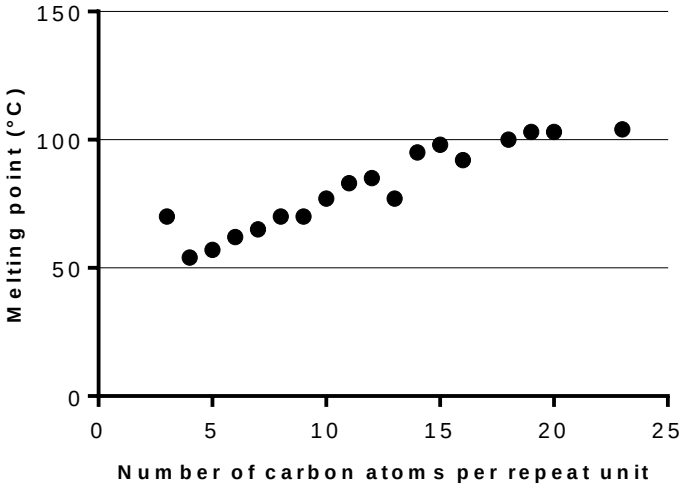


Figure 2-27 Melting points of different polyesters

Modern life relies on polymers, from the materials that are used to make clothing, houses, cars and airplanes to those in sophisticated applications in medicine, diagnostics and electronics.[159] A significant fact is that only about 6 % of the oil produced worldwide is used in the manufacture of polymers, yet there are environmental concerns associated with both the raw materials used to make them[160] and petrochemical based polymers.[161] Therefore, the development of more sustainable polymers is crucial. It is worth noticing that the potential for sustainable polymers is stimulated by policy, legislation and international agreements, including some negotiated at the 2015 United Nations Climate Change Conference (COP21) (ref. 3) in Paris on reducing CO_2 emissions.[159] Last but not least, is the fact that in 2014, for example, only 0.57 % of more than 300 megatons of polymers produced globally were bioderived, of which the three main products, by volume, were bioderived polyethylene terephthalate (PET), polyethylene and polylactide.[162-163]

3. Selected method in this thesis work for isomerization and functionalization of the double bond

The state of the art concerning reactions is based on the work of Brown.[58, 74] The migration of an internal carbon-carbon double bond to the terminal position is thermodynamically not favored, as previously mentioned. In order to shift the double bond to the terminal position in a long aliphatic chain, a boron based group (or catalyst) with bulky ligands has to be used. These bulky ligands induce the required steric hindrance so that the double bond can be shifted to a less sterically encumbered position.

The literature methods[58, 60] involve external cycloalkenes (e.g. **2**), resulting in dicycloalkylboranes (**3**), which shift the double bond from an internal position to the terminal position by inducing steric hindrance (Fig. 3-1). The existing literature confirms high efficiencies (>90 %) of isomerization of alkenes to the corresponding terminal olefins within chains of up to 8 carbon atoms (**4**) in length. Longer chains have not been studied.

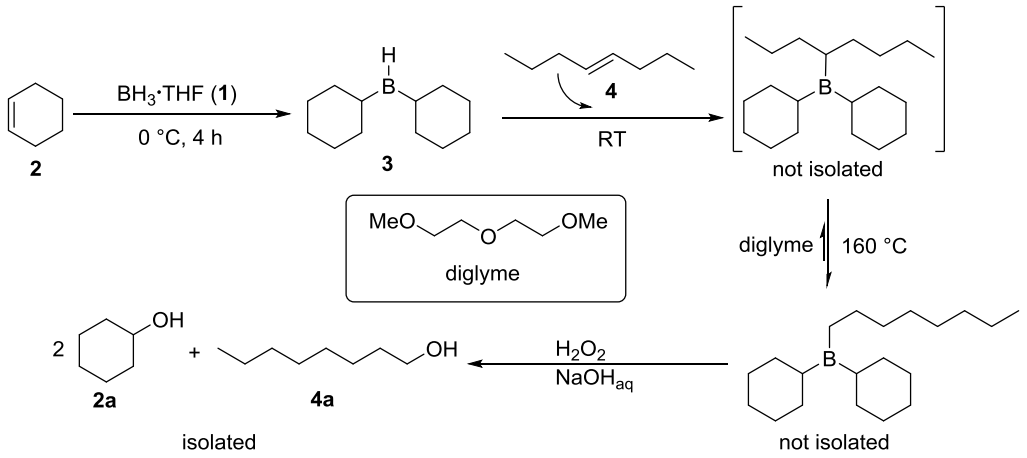


Figure 3-1 State of the art

Inspired by this seminal work, one objective of this thesis is to study the isomerization-functionalization of a non-terminal double bond in longer chain (> 8 carbon atoms) functionalized olefins. As already mentioned in the state of the art (in short chain non functionalized olefins) so-called "external dialkylboranes" (e.g. **3**), prepared from a cycloalkene are used to induce the steric hindrance. The drawbacks of this approach are (1) the necessity of using additional compounds (cycloalkene) and (2) low boron efficiency since one B atom is used per only only one isomerized

oflefin. Therefore we also explored the approach making use of a so-called “internal dialkylborane”, synthesized from the same linear alkene as the define to be isomerized olefin. In this case 1 eq of borane is consumed per 3 eq of isomerized olefins. This method is very attractive from an economical point of view, because it does not require use of any external dicycloalkylborane to induce the steric hindrance. This approach deliver three major advantages: (1) no external molecule is required which leads to easier purification and lower cost, (2) increased carbon economy (more isomerized olefins in one process), (3) increased boron efficiency (less borane is required). A further improvement that was realized with respect to the state of the art lies in the more efficient post oxidation of the boranes after the isomerization. Brown[49] suggests to use a 3 M NaOH aqueous solution in combination with H_2O_2. However this solution promotes the unwanted protodeborylation as a side reaction increasing the amount of alkanes formed (reducing the amount of the envisaged alcohols). It was found that switching to a methanol based system (3 M NaOH solution in methanol as a first solution and 50 % (w/w) H_2O_2 as a second solution), significantly suppresses this alkane formation, improving thereby significantly the yield with respect to the alcohols.

From now on, the new optimized approach will be called in this thesis “Approach 1: internal dialkylborane”. This approach is schematically shown in Figure 3-2.

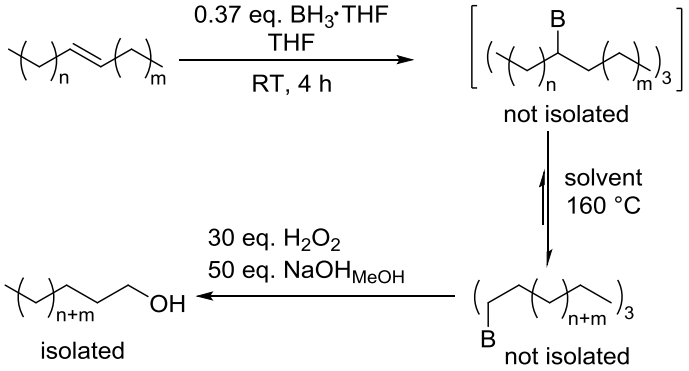


Figure 3-2 Approach 1: Internal dialkylborane

As will be shown further in this thesis, the first approach fails sometimes under specific conditions; hence it was necessary to introduce a second approach to induce the shift of the mid-chain double bond in long chain olefins (e.g. C-17). Figure 3-3 shows this alternative approach (based directly on the state of the art) that will be called further on “Approach 2: external dialkylborane”. An important issue in this

approach is a possibility to recycle the cycloalkanols (product of oxidation of external cycloalkenes) and secondary alcohols (the final product is an equilibrium of primary and secondary alcohols) into cycloalkenes and internal alkenes respectively, which can be reused.

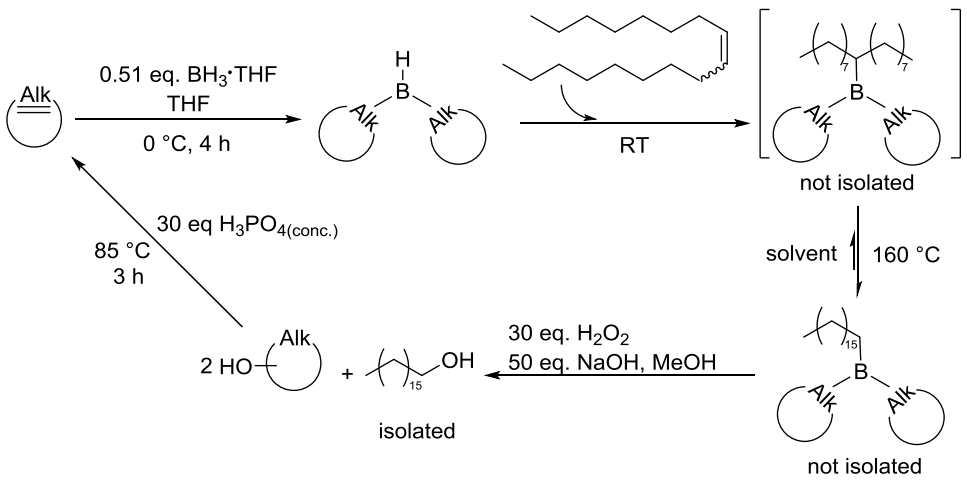


Figure 3-3 Approach 2: External dialkylborane

The main goal of this thesis work was to describe a novel method to synthesize long chain α,ω-bifunctional compounds by means of hydroboration-isomerization starting from unsaturated fatty acids derivatives. An important feature desired for this strategy is that it should be industrially applicable. For this reason, the approach 1 presented in Figure 3-2 (internal dialkylborane) is the more interesting.

Most of the publications which were cited up to now refer to the isomerization of a double bond in short chain alkenes (max. 8 C atoms) in presence of dicycloalkylborane (Fig. 3-1).

Table 3-1 summarizes the literature data in relation to the project expectations and possible problems.

Table 3-1 Literature data vs project requirements

What is known	What is needed
Hydroboration-isomerization of short chain alkenes (max. 8 C atoms)	Hydroboration-isomerization of long chain olefins
No functionality	Functionalized olefins
Non-economic approach (1 B atom per 1 eq of alkene, external cycloalkene)	Economic approach (1 B atom per 3 eq of olefins, without external cycloalkene)
Possible problems	
Influence of chain length Influence of functional group Reduced steric requirements in approach 1	

To summarize, the aim of this work is to investigate whether derivatives of unsaturated fatty acids can be converted to valuable chemicals – α,ω-bifunctional compounds using a hydroboration-isomerization reaction. To achieve this a more fundamental study about the influence of all of the following different factors (chain length, functional group, solvent type, temperature, concentration, position of double bond) on hydroboration-isomerization in general is required, as is checking for possible applications on industrial scale. Figure 3-4 presents the overview/lay-out of experiments and the reason/logic for selected reactions.

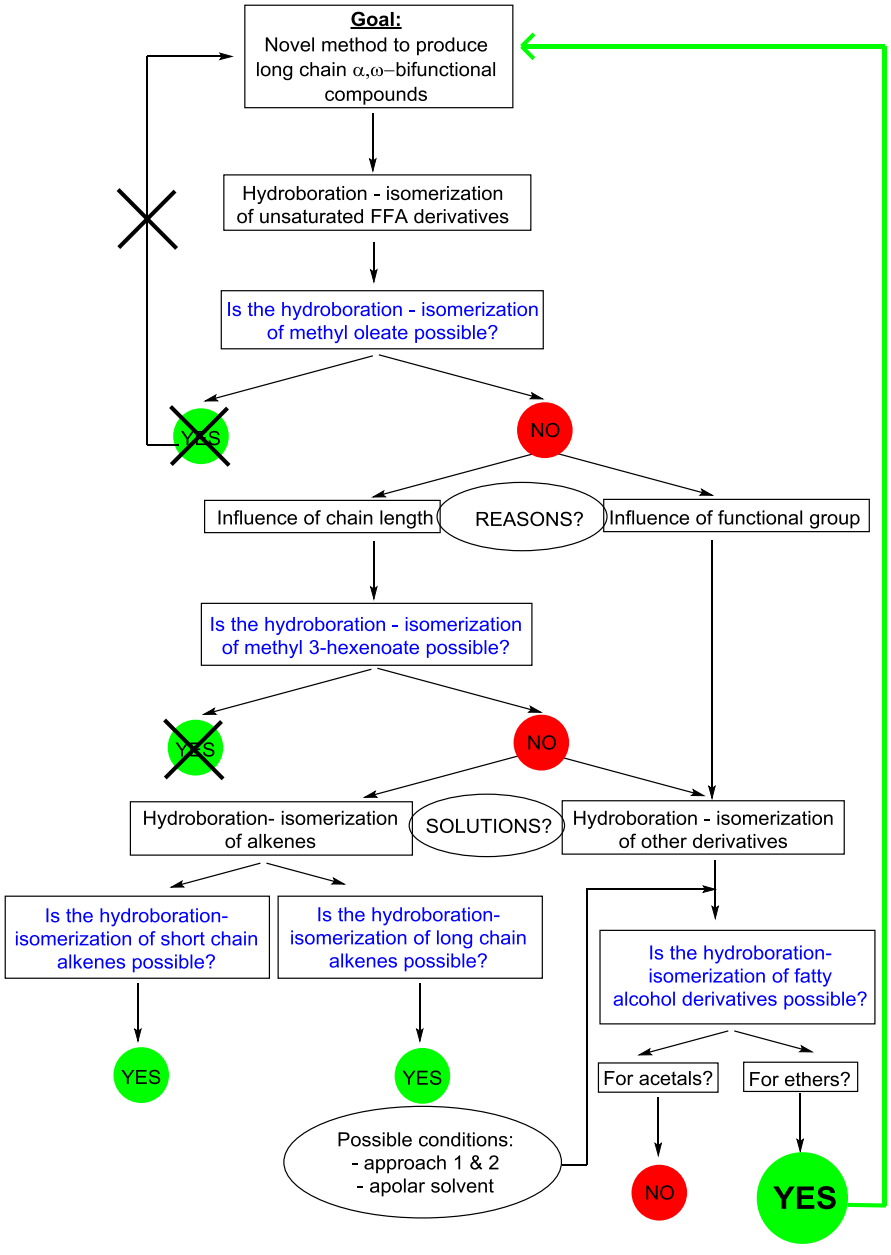


Figure 3-4 Generic overview of the PhD research

4. Results and discussion

As mentioned in previous chapters, unsaturated FA (and their derivatives) can serve as feedstock for α,ω-bifunctional compounds. Carboxylic acids (FFAs = free fatty acids) as such cannot be used for hydroboration reactions, since they will be reduced to the corresponding alcohols rapidly and completely, even under remarkably mild conditions (Fig. 4-1).

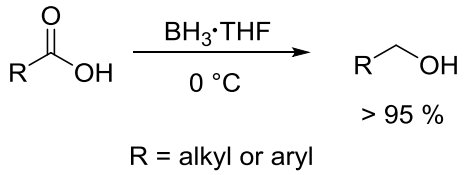


Figure 4-1 Reduction of carboxylic acid by borane

The reactivity of functional groups towards borane decreases in the order: carboxylic acid ≥ olefins > ketones > nitriles > epoxides > esters > acid chlorides[164]. Therefore protected and/or stable derivatives of FFA have to be used. The most simple protection form is an ester. Among all fatty acid esters, methyl esters are the cheapest and the easiest to synthesize. Methyl oleate (Fig. 4-2) was selected as a model compound for the isomerization of monounsaturated fatty acid derivatives.

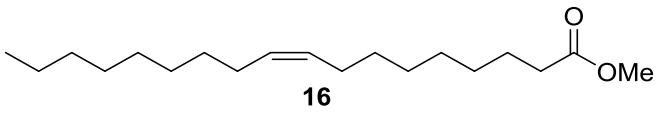


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Figure 4-2 Methyl oleate

The procedure for hydroboration-isomerization is the same for all reactions performed in this thesis. Only some changes were made in the optimization part, where the influence of solvent type, temperature and dilution were examined. The generic procedure and differences in two approaches are as following:

Hydroboration – approach 1:

Hydroboration in approach 1 is an one-step reaction where the 1.1 eq of BH_3·THF (**1**) is mixed with 3 eq of the olefin to be isomerized at room temperature for 4 hours. The resulting concentration of final trialkylborane is around 0.45 M.

Hydroboration – approach 2:

Hydroboration in approach 2 is an two-step reaction, where in the first step the external dialkylborane reagent is synthesized by mixing 1.1 eq of borane **1** with 2 eq of cycloalkene in a ice bath for 4 hours. In the second step, the ice bath is removed and 1 eq of the olefin to be isomerized is added at room temperature. The reaction mixture is stirred at room temperature overnight. The concentration of final trialkylborane is around 0.45 M.

Isomerization

THF is removed in vacuum and subsequently replaced by the desired solvent under constant argon flow. The concentration of the trialkylborane obtained in the previous hydroboration step was kept constant at 0.45 M. The reaction mixture was heated in a temperature controlled oil bath at 160 °C. In order to follow the progress of the isomerization, a sample of the reaction mixture (2 mL) was taken at 0 h, 1 h, 2 h, 3 h, 6 h, 24 h and 48 h.

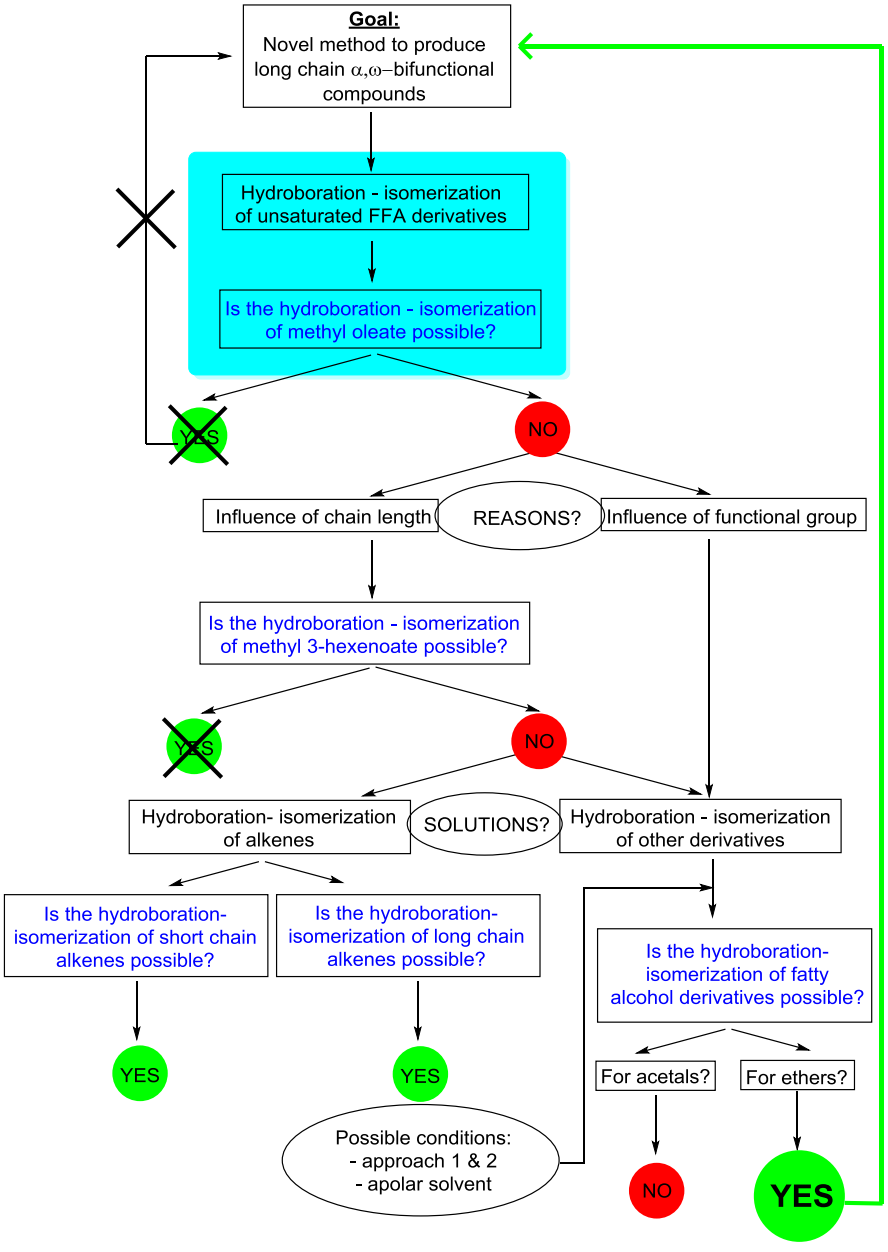
Oxidation

The samples were oxidized with a 50 w% aqueous H_2O_2 and a 3 M NaOH solution in methanol at room temperature for one hour. In a next step the solution was acidified with 12.5 M HCl (the pH was monitored by pH indicator paper, as exact control of the pH is not required). In the presence of a strong acid (in this case HCl) the produced sodium borate (poorly soluble in water) is converted into more soluble boric acid and sodium chloride, thereby facilitating the extraction with petroleum ether. The samples were analyzed qualitatively by means of GC-MS and quantitatively by means of GC-FID.

Important remark:

Protodeborylation is promoted by the presence of water during the oxidation step. In our first experiments on hydroboration a high amount of protodeborylation was observed (up to 30 %) due to the presence of water in the alkaline oxidizing solution used. The before mentioned alkaline oxidizing solution was selected as suggested from literature[58] (water solution of NaOH and 30 % H_2O_2). We found by experiments and tuning work that by replacing the water solution by a $NaOH_{MeOH}$ solution and by using a 50 % aqueous H_2O_2 solution, the amount of side product was significantly reduced (down to 5 – 8 %).

4.1. Hydroboration-isomerization of methyl oleate



Hydroboration-isomerization of methyl oleate was performed by means of both approaches: approach 1 and approach 2. Unfortunately, in both cases no shifting of the double bond to the terminal position was observed (any hydroxyl group connected to a primary carbon atom was detected by means of GC-MS). As will be shown further on, some isomerization occurred in the chain, so that non-mid chain positions were reached, but a complete shift towards the envisaged terminal position

was not realized. This first negative result indicated that the simple assumption that the chemistry described in literature regarding simple alkenes cannot be directly extrapolated to functionalized olefins. Other effects clearly come into play (Table 4-1). The absence of isomerization of the double bond to the ω-position could be due to two new factors influencing the reaction in comparison to literature data.

The first factor could be the chain length. The existing methods of hydroboration-isomerization were studied on short non-functional olefins (max. 8 carbon atoms). No literature data is available on reactions involving long chain alkenes.

The second factor could be the presence of the functional group. On the one hand, it is known that esters are stable towards borane even at relevant high temperature (160 °C). The reduction of ester group to the alcohol group is possible with trialkylborane only at very high temperature (300 °C) and in the presence of big excess of trialkylborane (4 eq).[192-193] This fact is in line with the hypothesis that during the isomerization step the lone pair from carbonyl oxygen is able to permanently occupy the empty *2p* orbital on borane (intra- and/or intermolecular) and thereby inhibit the isomerization activity of borane (Fig. 4-3), but because of the low temperature the reduction is not feasible.

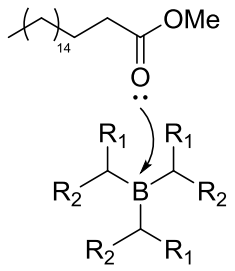


Figure 4-3 2*p*-orbital (constant) occupation in trialkylborane by carbonyl oxygen

Both effects were studied. The first important question to be addressed was whether the failure was due to the presence of the longer chain in methyl oleate or not. Therefore the hydroboration-isomerization reaction was performed on a short chain ester. The chain length was chosen within the range that was known from literature to give efficient isomerization of non-functional alkenes. As a model compound methyl *trans*-3-hexenoate was chosen (Fig. 4-4).

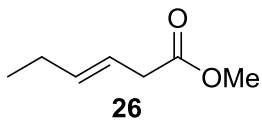


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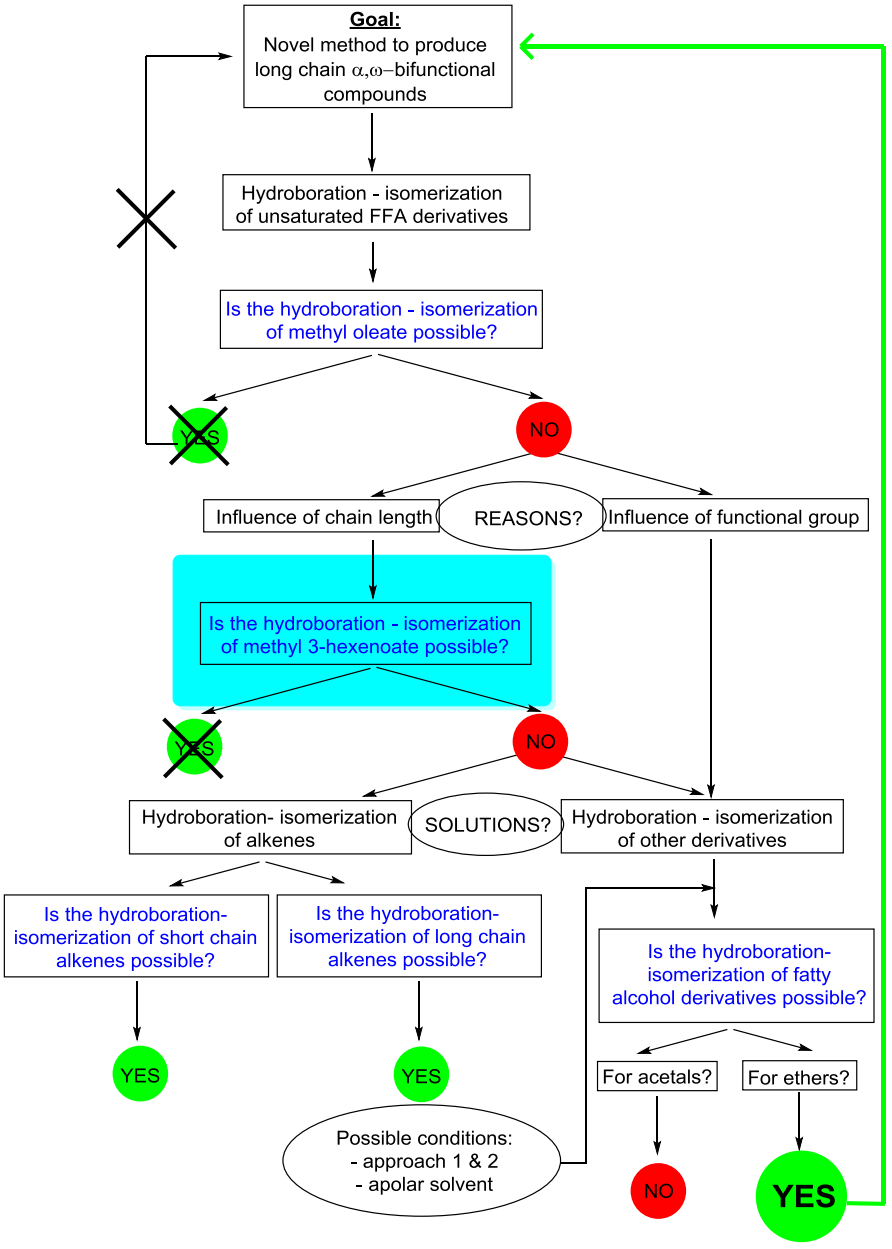
Figure 4-4 Methyl *trans*-3-hexenoate

In case the model compound would show isomerization, this would indicate that the failure of isomerization of methyl oleate was only due to the longer chain length. A persisting failure would indicate clearly that the presence of carbonyl oxygen inhibits the reactivity of borane, but it should be kept in mind that the influence of chain length could still be an additional effect.

4.2. Hydroboration-isomerization of methyl 3-hexenoate



Both approaches of hydroboration-isomerizations were examined: "internal dialkylborane" (Fig. 4-5 A) and the reaction which involved "external" dicyclohexylborane (Fig. 4-5 B). Before isomerization, sample "0 h" was taken and oxidized to analyze the non-isomerized products: methyl 3-hydroxyhexanoate (**26c**) and methyl 4-hydroxyhexanoate (**26b**) (Fig. 4-5 C). After replacing THF by diglyme (b.p. 162 °C) and heating the reaction mixture (160 °C) samples were taken after 1h, 2h, 3h, 6h, 24h and 48h (Fig. 4-5 D) and oxidized to analyze the isomerized products (Fig. 4-5 E).

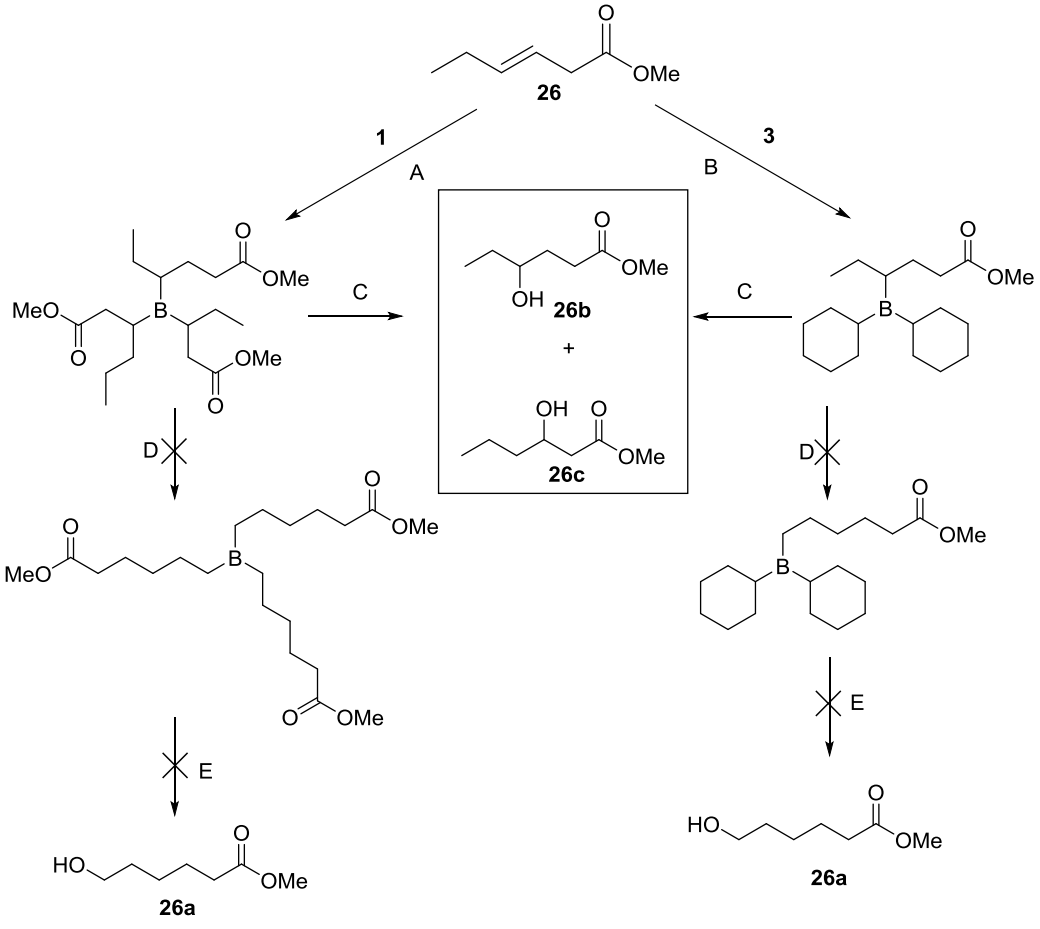


Figure 4-5 Hydroboration-isomerization of methyl *trans*-3-hexenoate

The GC analysis of the isomerized product showed no shifting towards the primary position since **26a** was not detected (GC chromatograms in the "Supporting information"). Further analysis (by means of dehydratation and ozonolysis method, *vide infra*, p. 50) of the hydroxyl group position showed the presence of two methyl hydroxyhexanoates most likely of **26b** and **26c**, the same as for the non-isomerized

sample “0 h”. The yield (determined by mass balance) after the oxidation is around 93 %.

Whereas some isomerization was observed (GC chromatograms in the “Supporting information”) in the case of long chain esters (although not all the way to the terminal position) no internal isomerization was observed at all with methyl 3-hexenoate. This fact is important as it demonstrates the complex nature of the processes. A possible explanation is that this effect might result from the starting position of the borane group with respect to the carbonyl oxygen. The position of the double bond implies that the borane has to be introduced at the 3rd of 4th position. In this position it can create a stable 5- or 6-membered ring (respectively) with the carbonyl oxygen (Fig. 4-6). This quite stable structure most likely prevents the borane group to shift.

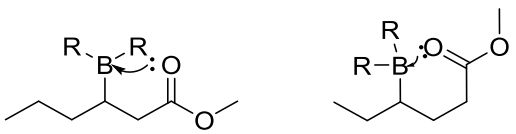
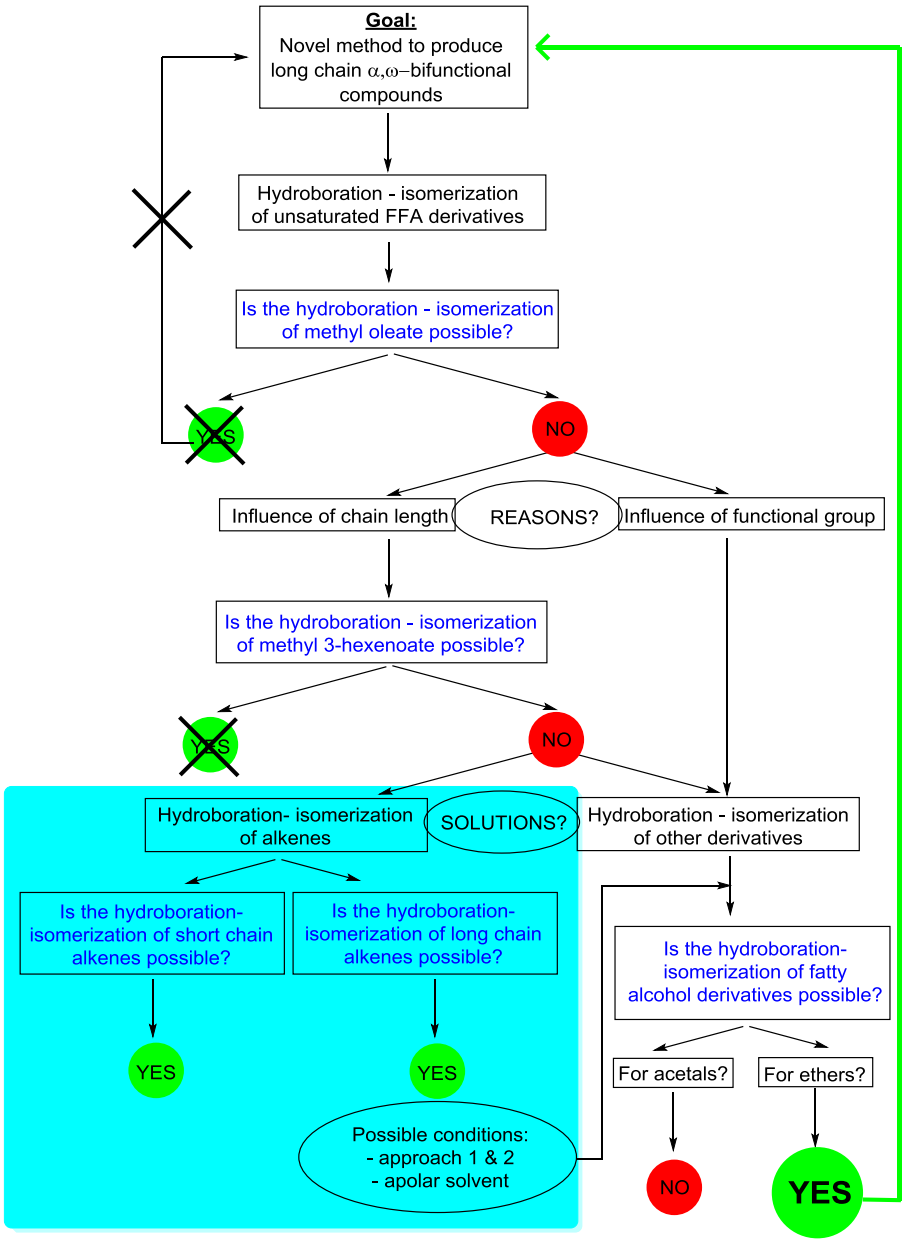


Figure 4-6 Intramolecular occupation of empty *p*-orbital on borane by the lone pair from the carbonyl oxygen

In methyl oleate the double bond is present between the 9th and 10th carbon atom. As a consequence, the borane is introduced at a position too far from the carbonyl oxygen to allow any intramolecular interaction, while only intermolecular interactions could inhibit the isomerization towards the ω-position.

As a conclusion, the isomerization of long chain olefins depends not only on the presence of a functional group, but also on other factors, such as the exact position of the functional group. This implies indirectly that the chain length should also be studied in detail. In this respect it was decided to study the effect of the chain length first. The extended study about the influence of a carbonyl group is presented in a separate section – “4.4.1. Hydroboration-isomerization of esters”.

4.3. Hydroboration-isomerization of model alkenes



The question whether it is possible to isomerize double bonds in long chain olefins is crucial in this thesis work. The reactions described to this point did not give any direct indication whether the isomerization of long chain olefins is feasible or not, but they could show the importance of the chain length and especially the position of functional groups with respect to each other. To understand in detail the hydroboration-isomerization of long chain functionalized olefins the hydroboration - isomerization of short and long chain alkenes has to be studied first. They can be

considered as a simplified model of the functionalized molecules that are considered as raw material (for example methyl oleate).

4.3.1. Hydroboration-isomerization in diglyme

Most of the methods described in literature with respect to hydroboration-isomerization involve external cycloalkenes, giving dicycloalkylboranes, which by inducing the steric hindrance shift the double bond from its internal position to the terminal position.[48, 58-61, 65-67] The most popular solvent in the isomerization step is diethylene glycol dimethyl ether (diglyme). As mentioned above, the high efficiency in isomerization of alkenes to the corresponding terminal olefins within chains with a maximum of 8 carbon atoms was proved. Therefore, inspired by this work, the isomerization –functionalization of a non-terminal double bond in longer chain alkenes was investigated in diglyme.

Another important point of investigation was to study whether instead of performing the isomerization – functionalization with an external dialkylborane (implying the use of one boron atom per isomerized alkene) it is also possible to do the isomerization – functionalization with the more economic approach – internal dialkylborane, were one boron is consumed per three isomerized alkenes. The hydroboration-isomerization of the olefinic bond in different long chain alkenes (from 8 carbon atoms up to 21 carbon atoms) was studied.

4.3.1.1. Approach 1: internal dialkylborane

To check the influence of the chain length on the hydroboration-isomerization, six different alkenes were examined with increasing numbers of carbon atoms: C-8, C-10, C-12, C-14, C-17, and C-21. In the alkenes with an even number of carbon atoms the double bond is located exactly in the middle of the molecule (symmetrically). In the last alkenes (C-17 and C-21) the double bond is located between the 8^{th} and 9^{th} carbon atom for 8-heptadecene and between the 9^{th} and 10^{th} carbon atom for 9-heneicosene. The overview of performed reactions is presented in Figure 3-2 (p. 36).

With the increase in number of carbon atoms, the presence of the corresponding primary alcohol decreases. For the alkenes with number of carbon atoms above 14, the isomerization (in these conditions) is low or even impossible. The conversions to primary alcohols for these six different hydroboration-isomerizations are presented in Figure 4-7.

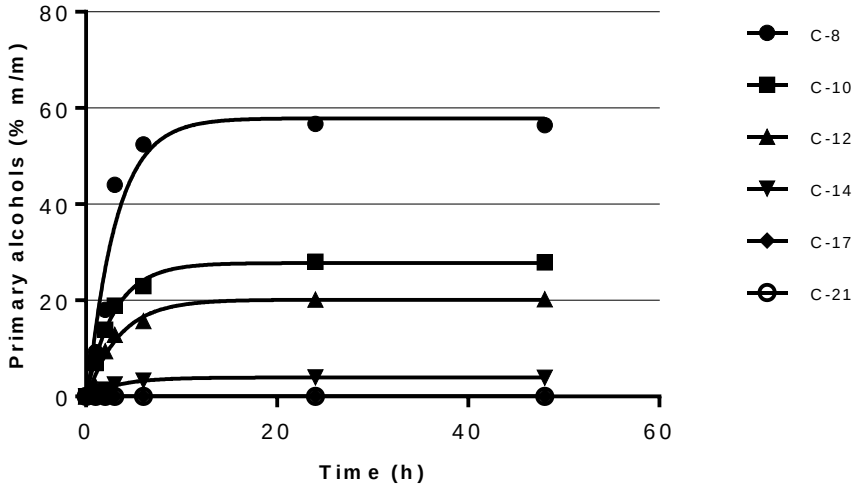


Figure 4-7 The conversions to primary alcohol in diglyme solvent system determined by GC-FID analysis

Table 4-1 presents the actual product distribution at equilibrium (after 24 h). The table includes the protodeborylation side products and the percentages of all secondary alcohols combined. The lower yield for shorter alkenes can be explained by the fact that corresponding alcohols are more polar and more volatile, therefore a bigger amount is lost during the extraction and evaporation.

Table 4-1 Products distribution for hydroboration-oxidation of different alkenes after 24 h

		Product distribution (%)[a]			
	Alkene	Primary alcohol	*Sec*.-alcohols	Alkane	Yield (%)[b]
1	4-octene	58	33	6	85
2	5-decene	28	65	7	88
3	6-dodecene	20	74	6	89
4	7-tetradecene	4	90	6	91
5	8-heptadecene	0	95	5	92
6	8-heneicosene	0	95	5	92

[a] Determined by GC-FID analysis, [b] Total yield determined after extraction

The carbon chain length has an influence on the hydroboration-isomerization of alkenes. Figure 4-8 shows the relation between the number of carbon atoms and the conversion to primary alcohols (determined by GC-FID analysis), using the approach 1. With an increasing number of carbon atoms the conversion drops significantly. The isomerization to other internal positions strongly depends on the chain length. When using 8-heptadecene and 8-henicosene, no primary alcohols were obtained, nor appreciable amounts of secondary alcohols at other positions than those corresponding to the initial double bond were found.

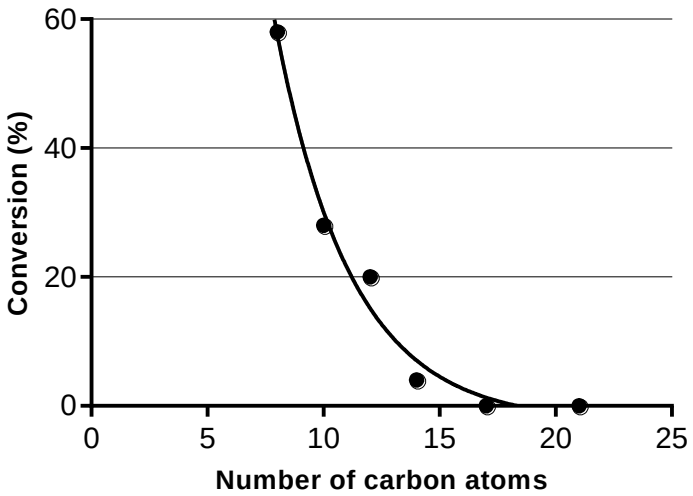


Figure 4-8 Number of carbon atoms versus the conversion to the primary alcohols determined by GC-FID analysis

The isomerization of double bonds to the primary position in long chain alkenes (C atoms > 14) following approach 1 was found to be impossible. An important question is whether or not internal isomerization occurred. In order to determine the position of the double bond, the products after isomerization of 8-heptadecene (**31**) and 8-henicosene (**32**) were dehydrated with phosphoric acid to recreate double bonds, which were subsequently ozonized and reduced (Fig. 4-9). The same procedure was repeated for the non-isomerized samples (samples at 0 h) and both results were compared by means of GC. The composition of the alcohol mixture was rather similar (GC chromatograms in the "Supporting information"). Small differences were observed in the amount of alcohols, but not in the type of the created alcohols. This means that no appreciable amounts of higher alcohols were found. The distribution of the synthesized alcohols was the following: 1-heptanol (**28a**) 12 %, 1-octanol 38 % (**4a**), 1-nonanol 42 % (**10a**), 1-decanol 8 % (**27a**). These results are rather comparable with the expected theoretical distribution, which is 12.5 %, 37.5 %, 37.5 %, 12.5 % (for **28a**, **4a**, **10a** and **27a** respectively). Based on these results it was concluded that only little, if any, isomerization occurred. The yield (determined by mass balance) after dehydration is 94 %, after ozonolysis 91 %. The total yield after determination of hydroxyl group position in secondary alcohols is 86 %.

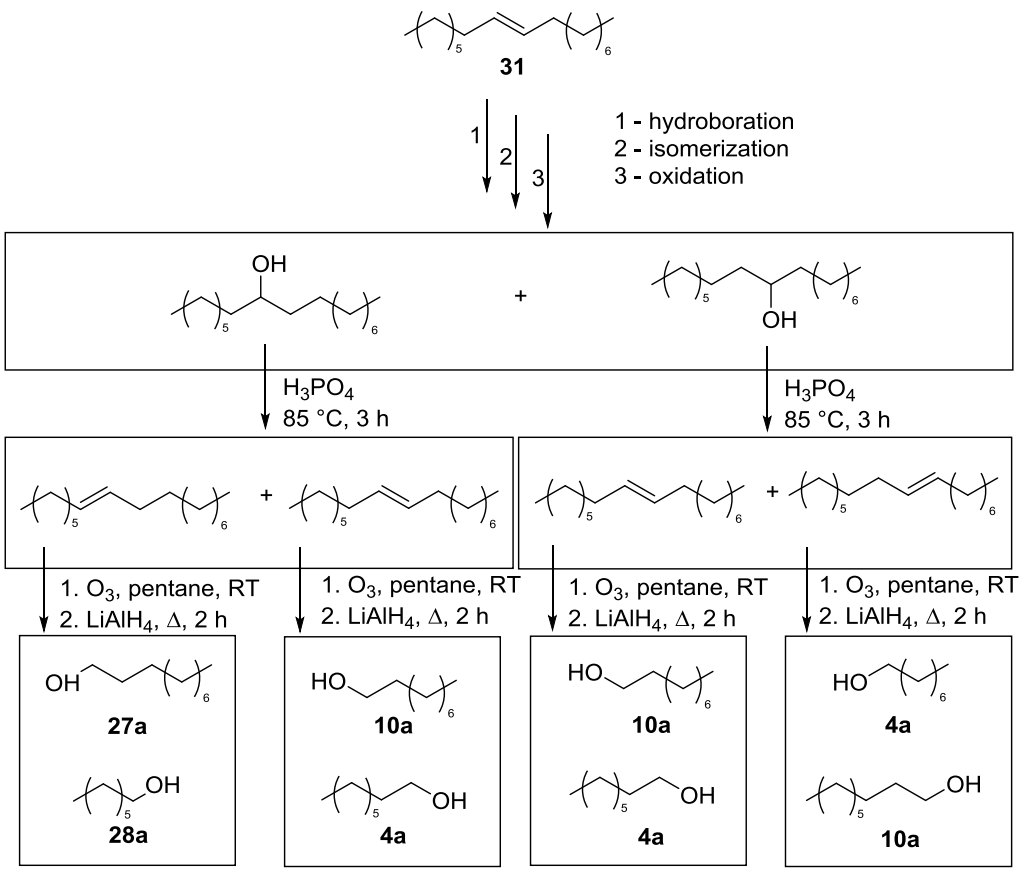


Figure 4-9 The overview of the determination of hydroxyl group position in secondary alcohols after hydroboration-isomerization of 8-heptadecene (31) following approach 1

During the oxidation step an unwanted protodeborylation side reaction occurs, leading to octane. The amount of this side product increases with the time of reaction (5 % after 1 h up to 15 % after 48 h). The increased amount of side product during the reaction can be explained by the fact that several samples were taken. Every time a small amount of water from the needle could penetrate into the reaction medium. A control test was prepared in which only one sample was taken after 48 h. The amount of side product found was around 6-7 %, confirming the above hypothesis.

Hydroboration-isomerization of 4-octene showed that the migration of the double bond to the terminal position is feasible by means of the economic approach 1 in short chain alkenes (Table 4-1). This reaction is clearly an equilibrium reaction. Also secondary alcohols are produced. Interestingly, all secondary alcohols could be distinguished on the GC column (Fig 4.10). For longer chain alkenes where the number of possible secondary alcohols is higher, the GC column is not able to distinguish all of the secondary alcohols (Fig. 4-11). Nevertheless, if necessary, the

aforementioned method (Fig. 4-9) can be used in order to determine the hydroxyl group position in the secondary alcohols.

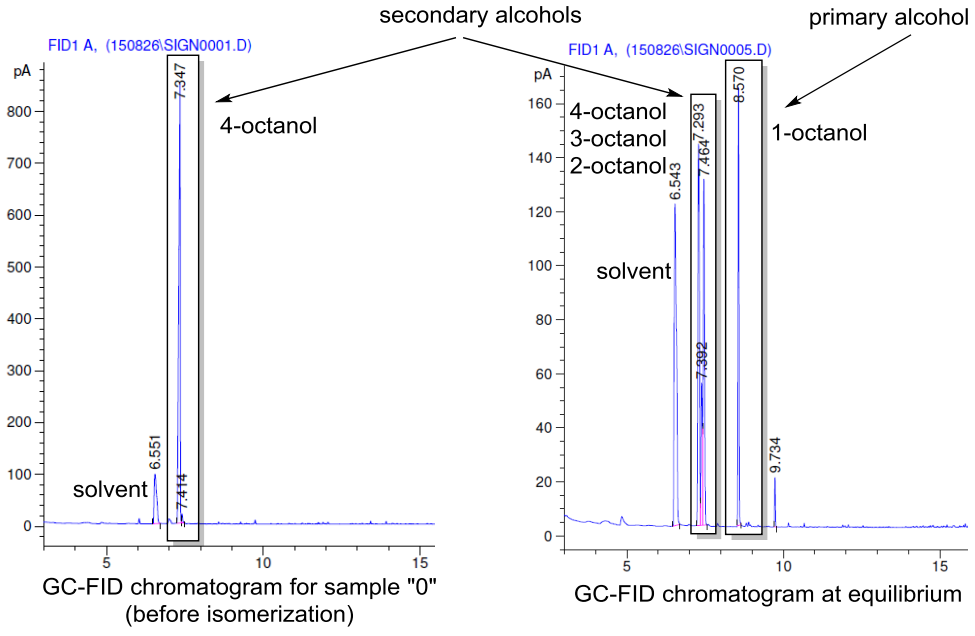


Figure 4-10 Separation of primary and secondary alcohols by means of GC-FID

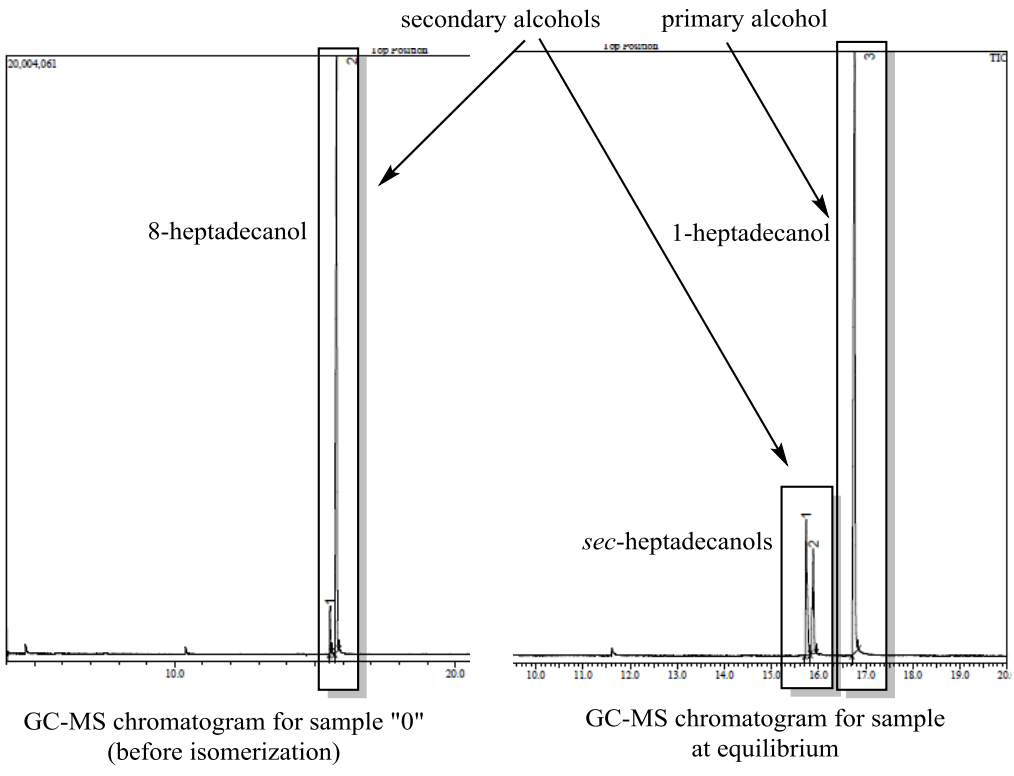


Figure 4-11 Separation of primary and secondary alcohols by means of GC-MS

GC-MS was mostly used for qualitative measurement. The molecular ion of an alcohol is usually undetectable especially in primary and secondary alcohols, but alcohols also frequently cleave to give resonance stabilized cations due to the breaking of the β bond. As a result of this cleavage, primary alcohols show a prominent peak at *m/z* 31 (Fig. 4-12).

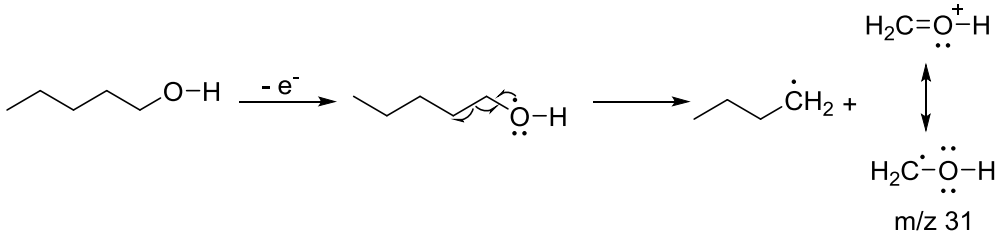


Figure 4-12 Creation of oxonium ion from primary alcohol

The presence of *m/z* 31 peak is not sufficient confirmation of a primary alcohol. It was always necessary for the peak to be relatively large in comparison to other peaks in the spectrum. This is because secondary alcohols can undergo a rearrangement resulting in a peak at *m/z* 31 as well. When diols were the final product the oxonium

ion was always large. As an example the mass spectrum 1-octadecanol and 1,18-octadecanediol is shown in Figure 4-13.

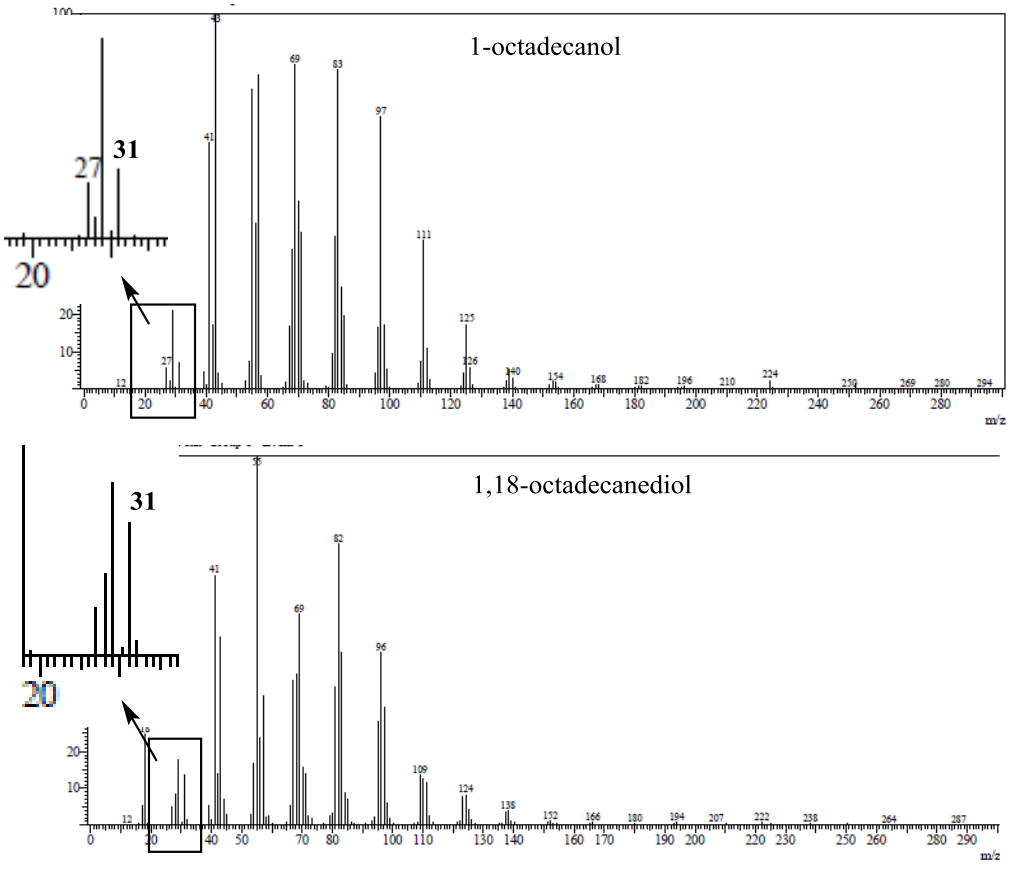


Figure 4-13 Comparison of MS spectrum for primary alcohol and diol

4.3.1.2. Approach 2: External dialkylboranes

The aforementioned isomerization by means of approach 1 is suitable for short chain alkenes, but was surprisingly unsuitable for long chain alkenes. Long chain alkenes did not undergo any isomerization in this trialkylborane system at all; hence approach 2 (Fig. 3-3) was applied to induce the desired far shift of the mid-chain double bond in long chain alkenes. As a model compound 8-heptadecene (**31**) was chosen. This approach uses "external" dialkylboranes – both linear and cyclic, of which more particularly six variants were investigated (Fig. 4-14).

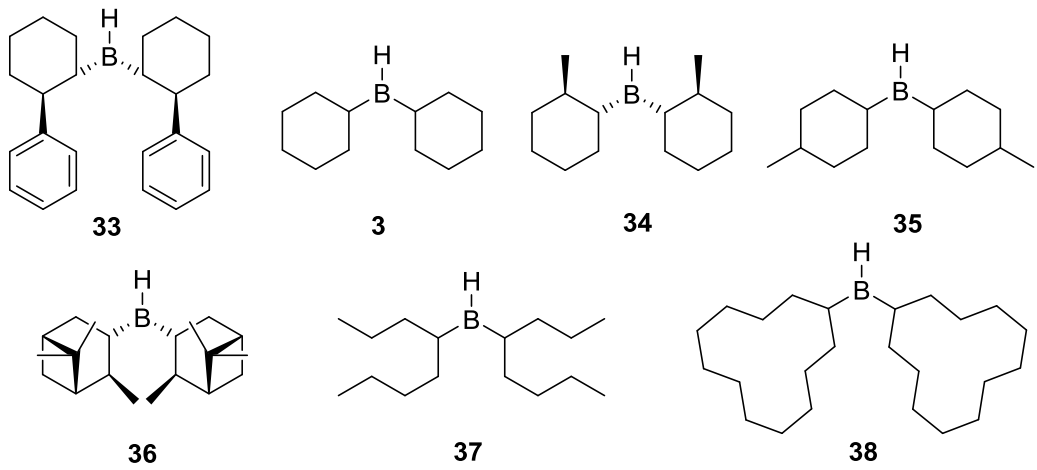


Figure 4-14 The examined dialkylboranes

Cyclohexene (**2**) is cited in literature[60] as a suitable cycloalkene for dicycloalkylborane synthesis. Brown *et al.* used dicyclohexylborane (**3**) to isomerize the double bond in *cis*-3-hexene with high conversion to the primary position (97 %) in diglyme. Dicycloalkylborane **3** is also suitable to shift the double bond in 8-heptadecene with relatively high yield (80 %).

As in the case of the trialkylborane approach, heptadecanols were not the only products. Protodeborylation occurs as well in this reaction, and heptadecane (6 %) is created as a side product. Cyclohexene is converted into cyclohexanol (majority) and cyclohexane. The actual product distribution is presented at the end of this chapter with all examined dialkylborane systems together (Table 4-2).

Di(2-phenylcyclohexyl)borane (**33**) is a unique example, as it contains an aromatic ring. The conversion is also very high (around 85 %). Moreover, the presence of the aromatic system has no negative influence on the hydroboration-isomerization.

Bis(α-pinyl)borane (**36**) gave a moderate conversion around 50 %. This result could be explained by the fact its structure is quite different from that of the aforementioned dicycloalkylboranes. Probably α-pinene induces excessive steric hindrance that could partially prevent the isomerization. This is consistent with the literature information that the steric properties of the olefin and the steric behavior of the borane molecule have a great influence on the reaction. Poor steric hindrance will not allow shifting the borane (ΔG is probably too low) and excessive hindrance can prevent the borane of reacting with the double bond.[25]

Dicyclododecylborane (**38**) is not suitable for isomerization of long chain alkenes. Cyclododecene, as a bigger molecule than α-pinene, induces the excessive steric hindrance that completely prevents the isomerization. The further study even showed the absence of internal isomerization.

In this experiment also a linear dialkylborane (**37**) was used. Since the long chain linear trialkylborane with three identical heptadecyl chains gave a negative result, it was the intention to check whether presence of some shorter alkyl chains would allow some isomerization. A surprising result was obtained. In this system the isomerization is feasible, although with a much lower conversion compared to dicycloalkyl systems (around 25 %).

Summarizing the results of the different reactions above, we conclude that by means of various dicycloalkylboranes the isomerization of mid-chain double bonds seems feasible, as opposed to the previously outlined approach 1. It can be seen that a short chain dialkylborane like **37** is also able induce a shift, but with lower conversion than the shift by cyclic dialkylboranes. Figure 4-15 shows the resulting amounts of primary alcohols. The percentage composition of the products at equilibrium (after 24 h) is presented in Table 4-2.

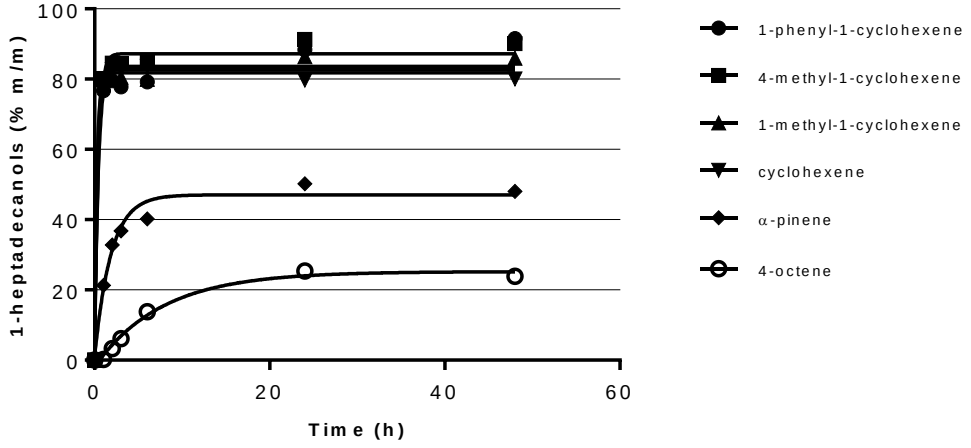


Figure 4-15 The comparison of the conversion to 1-heptadecanol for different dialkylboranes determined by GC-FID analysis

Table 4-2 Product distribution for hydroboration-oxidation of 8-heptadecene with several dialkylboranes (approach 2)

	Dialkylborane	Product distribution (%)[a]			Yield (%)[b]
		1-heheptadecanol	*Sec*.-heptadecanols	Alkane	
	35	85	10	5	94
2	**33**	83	10	7	93
3	**34**	82	11	7	94
4	**3**	80	13	6	88
5	**36**	46	46	8	93
6	**37**	24	70	6	82
7	**38**	0	95	5	96

[a] Determined by GC-FID analysis, [b] Determined after extraction

Kinetics discussion:

The question arises whether the different approaches and systems that were studied to this point show also some trend with respect to the kinetics of the isomerization reactions. In order to compare the kinetics of the different hydroboration-isomerization approaches, for each analyzed sample the amount of primary alcohol was plotted versus reaction time and a model nonlinear fit of these data was constructed and presents more an approximation of the kinetic.

The model equation of the fitted curve is given in Eq. 1.

$$n = n_0 + (n_{eq} - n_0) \times (1 - e^{-kt}) \qquad (1)$$

n is the molar amount at time t [mol x 10^{-2}], n_0 is the molar amount at time zero [mol x 10^{-2}], n_{eq} is the equilibrium amount [mol x 10^{-2}], k is a rate constant [min^{-1}], t is time [min]

From Eq. 1, half-time values ($t_{1/2}$) can be calculated, corresponding to the time needed for the amount of primary alcohol to reach 50 % of its maximum. Half-time values are indicative for the kinetics of the reaction. The half-time value for the primary alcohols and the correlation coefficient of the fitted curves are given in tables 4-3 and 4-4 below.

Table 4-3 Half-time values [h] and correlation coefficients after nonlinear fit of amount of primary alcohols for trialkylborane approach

	Alkene	$t_{1/2}$ (h)	R^2	Yield of primary alcohol (%)[a]
1	4-octene	2.06	0.9454	58
2	5-decene	2.03	0.9943	28
3	6-dodecene	2.34	0.9742	20
4	7-tetradecene	2.36	0.9250	4
5	8-heptadecene	-	-	0
6	8-henicosene	-	-	0

[a] Determined after extraction

From the data can be concluded that the half-time values are comparable for all trialkylborane approach 1 reactions (Table 4-3), so the chain length has no influence on the kinetics, in case all three alkenes attached to borane are identical. Contrarily, lower half-time values were observed when external dialkylboranes (approach 2) were used (Table 4-4). The lowest half-time values (quickest reaction) are associated with the use of dicycloalkylboranes. The difference is clear and amounts to a decade.

A hypothesis is formulated to explain this effect. In the case of systems with cyclic external dialkylboranes (approach 2), steric hindrance is more constant during the isomerization. On the other hand, when only linear trialkylboranes are used the steric hindrance is decreasing during the progress of shifting of the double bond towards a terminal position. This effect can be considered as a “zipper effect”: when the borane position is shifted more and more towards the external position the steric hindrance is lowering (Fig. 4-18). Therefore, the half-time values of trialkylboranes according to approach 1 are significantly higher than those in the dialkylborane approach when using a cyclic constituent in the dialkylborane. In the latter case, lower change of steric hindrance is found for the cyclic ring. In the case of using an external non-cyclic dialkylborane (approach 2), the systems will run more similar to how its runs in approach 1. This explains why $t_{1/2}$ is increasing for bis(α-pinyl)borane and di(octan-4-yl)borane.

Table 4-4 Half-time values [h] and correlation coefficients after nonlinear fit of amount of primary alcohols for external dialkylborane approach

	Dialkylborane	$t_{1/2}$ (h)	R^2	Yield of primary alcohol (%)[a]
1	**35**	0.29	0.9750	80
2	**33**	0.29	0.9933	77
3	**34**	0.21	0.9929	77
4	**3**	0.18	0.9978	70
5	**36**	1.29	0.9770	43
6	**37**	5.34	0.9839	20
7	**38**	0	0	0

[a] Determined after extraction

An interesting situation is obtained when an external short chain linear dialkylborane was examined. When dioctylborane was used to isomerize 8-heptadecene, the isomerization occurred on both 8-heptadecene and 4-octene. The isomerization of the 4-octene moieties was more efficient and occurred within a shorter time than when trioctylborane was used. This is logical in the sense that the heptadecyl induces higher steric hindrance. Figure 4-16 gives a comparison of the main products in three different hydroboration-isomerization processes involving only linear alkylboranes.

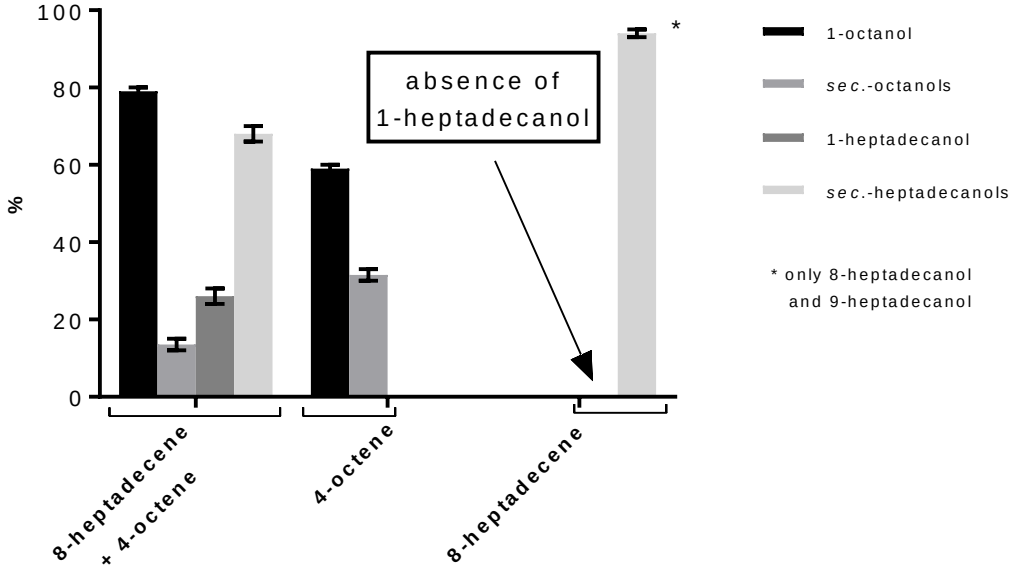


Figure 4-16 Correlation between different linear trialkylboranes and the conversion to the primary alcohols determined by GC-FID analysis

General conclusions:

The chain length of alkenes has a strong influence on isomerization reactions; the longer the chain, the more difficult the shifting of the double bond to the terminal position. Dicycloalkylboranes are still able to shift the double bond to the terminal position quite efficiently in long chain alkenes, even for those alkenes for which the linear trialkylborane approach 1 failed (triheptadecylborane – no shifting, dioctylborane with 8-heptadecene – 24 % of 1-heptadecanol, dicyclohexylborane with 8-heptadecene – 80 % of 1-heptadecanol).

These results led to a possible additional explanation that in linear long chain alkenes a high degree of disorder could lead to entanglement, preventing a shift of the double bond. In contrast, cyclic alkenes which possess less conformational flexibility but giving still a strong overall steric hindrance, direct the isomerization efficiently to the terminal position when used in dialkylboranes. The presented explanation, called “spaghetti effect”, based on our experimental findings, is visualized in figure 4-17.

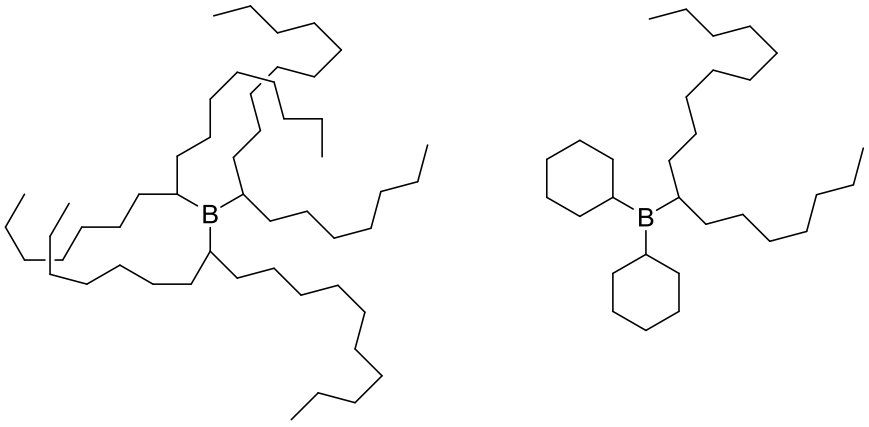


Figure 4-17 Visualization of explanation: "spaghetti effect"

An improved and interesting method to make long chain alkenes with a terminal position of the functional group was found using cyclic dialkylboranes. This opens new possibilities to produce specific functional molecules starting from internal alkenes. The dehydration with phosphoric acid is a selective reaction which allows removing water from secondary alcohols but not from primary alcohols. This feature is very useful for recovery of non-shifted alkenes. By means of this protocol cycloalkenes can be easily recovered from corresponding cycloalcohols, increasing the economic feasibility of the process. Additionally, this method offers the possibility to analyze the shifting process in detail (*vide supra*, p. 50).

A hypothesis derived from our research is the aforementioned “zipper effect” (visualized in Figure 4-18): when the borane position is shifted more to the more external position the steric hindrance is lowering.

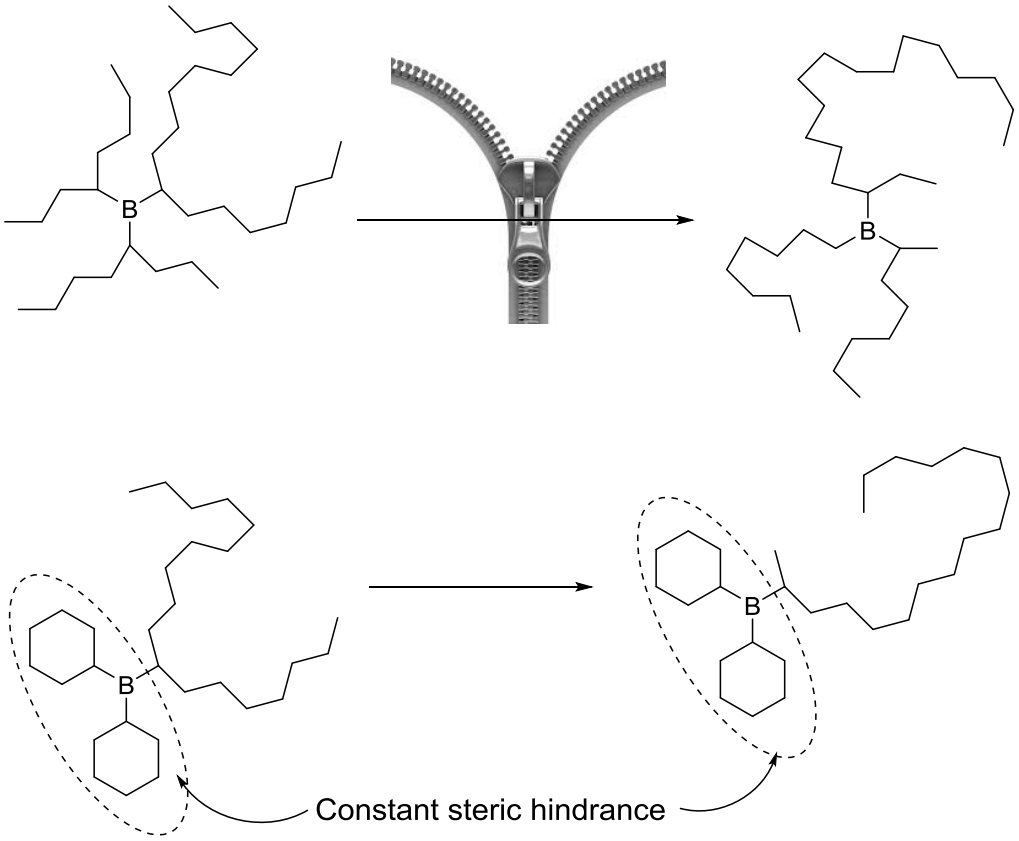


Figure 4-18 Visualization of hypothesis: "zipper effect"

4.3.2. Influence of solvent type

The economic approach 1 turned out to be ineffective for the isomerization of the double bond to a terminal position in long chain alkenes in the solvent diglyme. This solvent is a polar coordinating solvent in the sense that it may interact with the empty orbital in a borane. Therefore, additional research was needed to find a solution to this situation since the production of terminal unsaturated long chains is economically very important and approach 1 is certainly the more economically valuable method.

Three possible reasons why the reaction could not happen in this solvent system are considered. First reason could be too low a temperature, the second reason could be an inhibition effect, in this case maybe the solvent being the major source of

inhibition. The presence of a coordinating solvent stabilizes the borane compound (Fig. 4-19), but on the other hand the formed complex could inhibit the reactivity – a similar effect as for carbonyl oxygen, yet not that strong since the ether oxygen is a weaker Lewis base than carbonyl oxygen. The third reason could be the conformational changes in the structure of long alkyl chain which by increasing the steric interaction makes the isomerization more difficult. It is known from literature[165-166] that polar solvents promote the tendency to fold towards itself of long chain hydrocarbons.

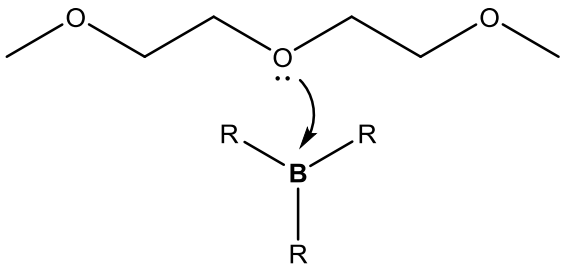


Figure 4-19 Possible stabilization of the empty *p*-orbital in borane by diglyme.

Accordingly we investigated solvents in the range of high boiling apolar solvents. Isododecane $C_{12}H_{26}$ was chosen as a possibly suitable solvent. To check which of both aforementioned factors (temperature or solvent) was the major driver, we decided to duplicate the diglyme study by changing the solvent to iso-C12 (b.p 182 °C).

The same alkenes as before (C-8, C-10, C-12, C-14, C-17, and C-21) were tested. In systems comprising isododecane as solvent, the isomerization of mid-chain double bonds was surprisingly found to be feasible in long chain alkenes, as opposed to the corresponding systems with the polar solvent diglyme. It can be seen that only for 9-heneicosene the conversion is significantly lower than for other alkenes. Figure 4-20 shows the resulting amounts of primary alcohols. The percentage composition of the products at equilibrium (after 24 h) is presented in Table 4-5.

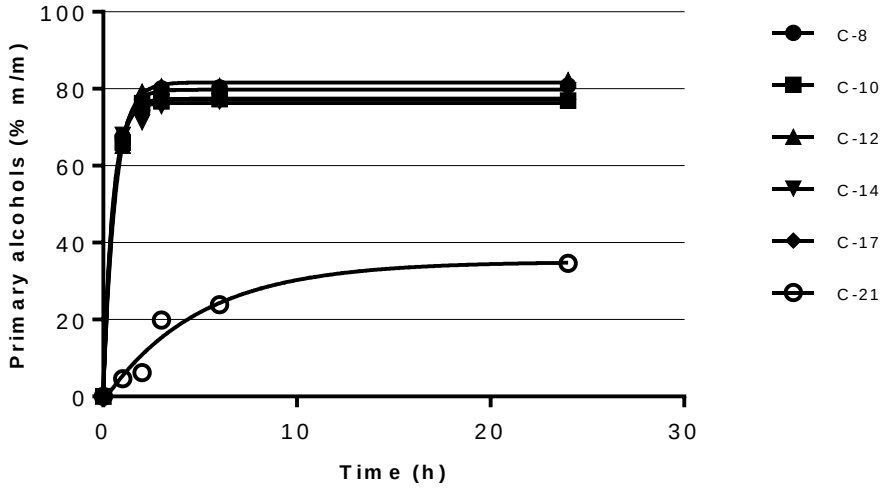


Figure 4-20 The conversions to primary alcohol in isododecane solvent system determined by GC-FID analysis

Table 4-5 Products distribution for hydroboration-isomerization of different alkenes after 24 h in isoodecane (approach 1)

	Alkene	Product distribution (%)[a]			Yield (%)[b]
		Primary alcohol	*Sec*.-alcohols	Alkane	
1	4-octene	83	13	4	84
2	5-decene	79	18	3	89
3	6-dodecene	84	13	3	94
4	7-tetradecene	80	16	4	93
5	8-heptadecene	79	17	4	92
6	8-henicosene	35	60	5	95

[a] Determined by GC-FID analysis, [b] Determined after extraction

The half-time values are comparable for all trialkylborane reactions (Table 4-6), except for the isomerization of 8-henicosene. The explanation could be that the C21 chain offers too much steric encumbrance. It is also found that the $t_{1/2}$ values are closer to those found in the approach 2 systems using diglyme as the solvent. The isomerization using approach 1 in isododecane is approximately 5-6 times faster than the isomerization in diglyme, but still slightly slower than isomerization by means of approach 2. This might again confirm the “zipper effect” hypothesis.

Table 4-6 Half-time values [h] and correlation coefficients after nonlinear fit of the amount of primary alcohols for the trialkylborane approach in isododecane

	Alkene	$t_{1/2}$ (h)	R^2	Yield of primary alcohol (%)[a]
1	4-octene	0.3868	0.9586	83
2	5-decene	0.3562	0.9884	79
3	6-dodecene	0.4282	0.9795	84
4	7-tetradecene	0.3288	0.9904	80
5	8-heptadecene	0.3537	0.9864	79
6	8-henicosene	3.417	0.9503	35

[a] Determined after extraction

Replacing the ether-type solvent by an apolar solvent has a significant influence on isomerization of the double bond. Therefore, the presence of a polar (coordinating) solvent inhibits the reaction, in contrast to the situation with an apolar (non-coordinating) solvent. The results were unexpected, because there are clear indications from literature[25] that the solvent has no effect on the isomerization. Moreover, it was reported by de Klerk *et al.*[25] that in systems using bulky alkylborane molecules, solvents are not able to coordinate the borane. If this statement is correct then another (more plausible) explanation, why diglyme is an insufficient solvent for isomerization of long chain alkenes could be the influence of polar solvent on the structure of alkyl chains according to the research of Sun *et al.*[165-166] The theoretical studies are presented in detail in the section "4.3.6. The complex nature of the isomerization reaction". Other apolar solvents were investigated to confirm this finding, as well as the isomerization without any solvent. These results are presented in the section "4.3.4. Influence of dilution".

Since the isomerization of the double bond in the long chain olefins (derivatives of unsaturated FFA) is the object of this thesis work all of the further optimization tests were performed on 8-heptadecene (C-17:1) as a model compound. The procedure for both the hydroboration and isomerization step was the same as described for economic approach 1. To make sure that differences in the results are due to the presence of different solvents, all other parameters (temperature, concentration, time, and oxidation) were kept identical.

Isomerization in decane

In order to check the influence of non-polar solvents on the isomerization step, decane was selected as high boiling (b.p. 174 °C) linear alkane (in contrast to branched high boiling isododecane). Decane, as a linear alkane, is also a suitable solvent for hydroboration-isomerization. The high conversion is comparable with

isododecane. The conversion rate is given in Figure 4-22 and the product distribution at equilibrium is presented in Table 4-7 (Entry 4).

Isomerization in octadecane

Octadecane (b.p. 317 °C) was selected as long chain linear alkane. By choosing this solvent it was the intention to check whether hydrophobic interaction of a long chain alkane with the alkyl chains (heptadecyl chain: C17) attached to borane would have an influence on the hydroboration-isomerization. The reference could be the reaction in the short decane system. When using octadecane, no significant improvement in conversion is observed. The conversion rate is given in Figure 4-22 and the product distribution at equilibrium is presented in Table 4-7 (Entry 3).

Isomerization in xylene

To check whether also non-alkane apolar systems would be beneficial to the hydroboration-isomerization reaction, also aromatic hydrocarbons were examined as a potential solvent. Xylene (mixture of isomers) was chosen as solvent with relatively high boiling point. Yet, a drawback of xylene is the boiling point (b.p. around 140 °C) being lower than the required 160 °C reaction temperature. Nevertheless the conversion to 1-heptadecanol is comparable to the conversion in aliphatic hydrocarbons. A small difference, as expected, is observed only in terms of the kinetics. The conversion rate is given in Figure 4-22 and the product distribution at equilibrium is presented in Table 4-7 (Entry 5).

Isomerization in silicone oil

To expand the system of apolar solvents to also non hydrocarbon solvents, an experiment was done using silicone oil as the solvent. The silicone oil is an interesting case as it has a non-carbon backbone, can have a high molecular weight and can comprise different substituents (alkyl and aryl). Polyphenyl-methylsiloxane (Fig. 4-21) was used as an “oxygen-containing” apolar solvent.

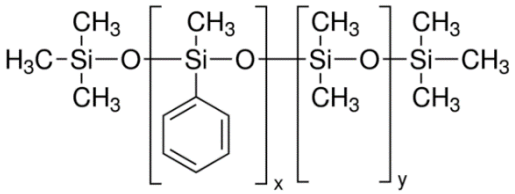


Figure 4-21 Polyphenyl-methylsiloxane

An interesting feature of the silicone oil under investigation was the presence of the siloxane bond, which is structurally similar to the ether bond. The Si–O bond is 1.64 Å

(vs Si–C distance of 1.92 Å)[167]. By way of comparison, the C–O distance in a typical dialkyl ether is much shorter; 1.414 Å[168]. Despite the presence of the "ether-like" groups, the isomerization in silicone oil gave the best results – approximately 90 % of conversion to 1-heptadecanol was found (Fig. 4-22 and Table 4-7 Entry 1). This remarkable result might be explained by the fact that the oxygens in the silicone oil are well shielded from possible interactions by the present methyl and phenyl groups. In this way they might not be able to interact with the empty *p*-orbital on borane.

General conclusions

Apolar solvents are suitable for hydroboration-isomerization of long chain alkenes. In contrast to polar (coordinating) solvent (diglyme), they are not able to interact with the trialkylborane (either by interaction with empty *p*-orbital on borane or by changing the conformational structure of alkyl chains) which is a desirable feature. Not only aliphatic hydrocarbons can be used, but also aromatic hydrocarbons and silicone oils. Figure 4-22 presents a comparison of the conversion of 8-heptadecene to 1-heptadecanol in different solvents. The hydrocarbons all gave similar yields (approximately 67 – 72 %), whereas silicone oil gave a yield around 90 %

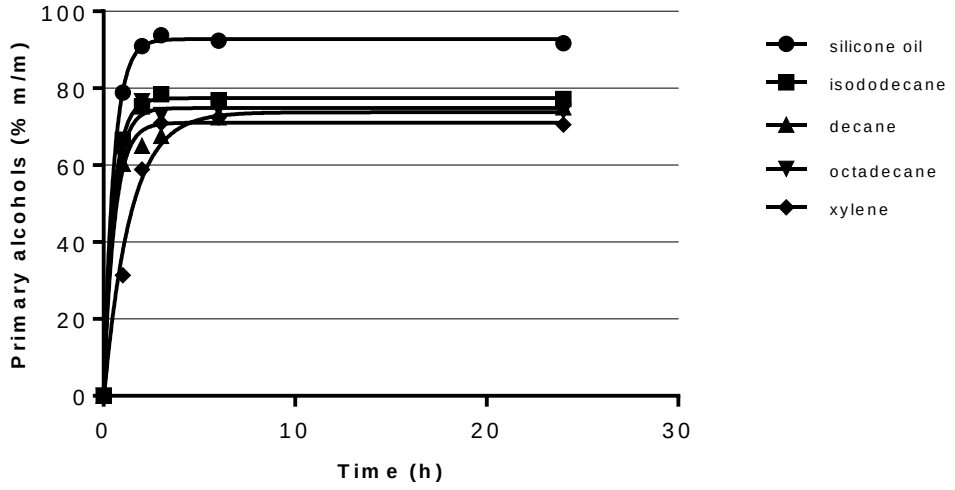


Figure 4-22 The conversions of 8-heptadecene to 1-heptadecanol in different non-polar solvents as determined by GC-FID analysis

The kinetics for all the reactions in these new solvents (carried out at 160 °C) are comparable (Table 4-7). The difference for the reaction in xylene is due to the lower reaction temperature. The influence of temperature on isomerization of the double bond is presented in the next section.

Table 4-7 Half-time values [h] and correlation coefficients after nonlinear fit of amount of 1-heptadecanol in different solvents

	Alkene	$t_{1/2}$ (h)	R^2	Yield of primary alcohol (%)[a]
1	silicone oil	0.3633	0.9994	89[*]
2	isododecane	0.3537	0.9772	70
3	octadecane	0.3960	0.9982	72[*]
4	decane	0.3708	0.9924	68
5	xylene	0.9441	0.9793	67

[a] Determined after extraction, [*] Determined after extraction and column chromatography

The finding that non-polar solvents are enhancing hydroboration-isomerization is without any doubt a major milestone. These solvents make the economic approach 1 viable. The results proved that apparently the polar diglyme disturbs the isomerization of long chain alkenes. The hydrocarbons can be more easily removed in the purification step than diglyme. Deep vacuum distillation is required for octadecane. Isododecane, decane and xylene can be removed on a rotary evaporator. Silicone oil can be removed by column chromatography with non-polar eluents (petroleum ether : ethyl acetate 9:1 v/v). Also low boiling point silicone oils exist. This might be an interesting approach to test in future work.

4.3.3. Influence of temperature

The next point of investigation was the study of the influence of temperature on hydroboration-isomerization. This study intrinsically allows getting an idea on the reaction thermodynamics. Both the position of the equilibria as well as the kinetics will unveil some thermodynamic aspects of the reactions involved. A similar kind of information can be obtained from a concentration dependence study as will be discussed in the next section.

In the literature[25, 46, 60], as was mentioned in the introduction, the suggested optimal temperature is 160 °C. Parametric variation was applied in this thesis to study the effect of temperature. By using xylene as solvent (see previous section) it was observed that the isomerization is also feasible around 140 °C with almost the same yield in comparison with the reaction at 160 °C. Even lower temperatures were tested (100 °C, 120 °C, 140 °C) as well higher temperatures (180 °C, 200 °C and 230 °C). For reactions at 100 °C, 120 °C, 140 °C and 160 °C, decane (b.p. 174 °C) was chosen as the solvent, for reactions at 180 °C, 200 °C and 230 °C, octadecane (b.p. 317 °C) was selected as solvent.

At 100 °C no shifting to the external position was observed. Further tests revealed that even internal isomerization did not occur. At 120 °C a small amount of isomerization is observed. The conversion of 8-heptadecene to 1-heptadecanol

amounted to approximately 30 % (Fig. 4-23). In the next reaction the applied temperature was 140 °C. A significant improvement in the conversion is observed. The conversion and kinetics are comparable with those in refluxing xylene (Fig. 4-23). Both reactions at 160 °C and 180 °C gave the same results for conversion and kinetics. No difference in kinetics indicates that the optimal temperature is situated around 160 °C. Further heating does not bring any improvement. At 200 °C and 230 °C no significant improvement is observed. Moreover more side products are formed which drastically decrease the total yield (Table 4-8, Entry 6 and 7).

Conclusions and hypothesis:

From the data at the different temperatures it can be seen that both the kinetics and the equilibria are temperature sensitive. The optimal temperature for the isomerization of mid-chain double bonds is between 140 and 180 °C. A lower temperature significantly reduces the conversion (Fig. 4-23). This effect is caused by the temperature sensitivity of the equilibria. From the strong temperature dependence it appears that probably steric effects play an important role in the reactions. Another important observation is the minimum temperature around 120 °C required to deliver enough energy to start shifting borane along the alkyl chain.

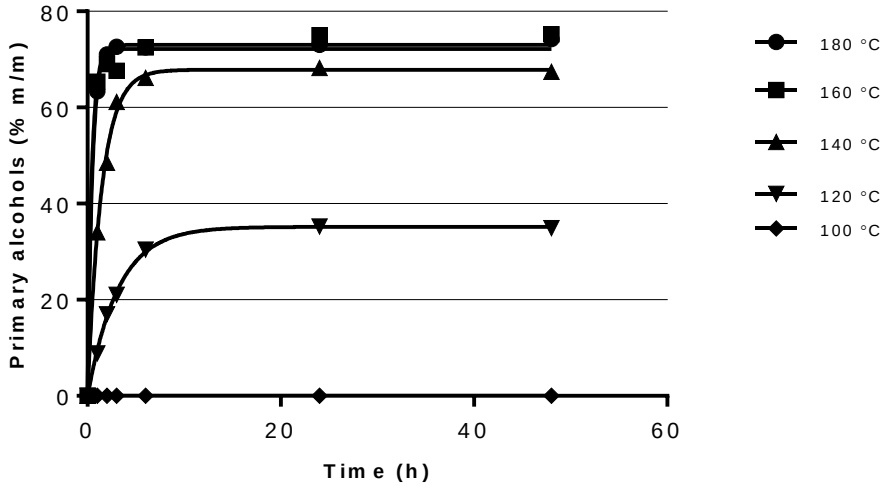


Figure 4-23 The conversions of 8-heptadecene to 1-heptadecanol at different temperatures as determined by GC-FID analysis

A comparison of all performed reactions at different temperatures is presented in Table 4-8. It can be concluded that the increasing amount of alkenes observed when isomerizing above 200 °C is probably due to the probable decomposition of trialkylborane during the heating. At these high temperatures this is probably a fast

side reaction as further tests confirmed that the observed alkenes are internal alkenes, which is in line with the hypothesis that the decomposition of trialkylborane takes place before isomerization.

Table 4-8 Product distribution for hydroboration-isomerization of 8-heptadecene at different temperature

	Temp. °C	half time (h)	Product distribution (%)[a]				Yield (%)[b]
			1-hepta-decanol	*sec*.-hepta-decanols	side products		
					hepta-decane	hepta-decene	
1	100	-	0	96	4	0	95
2	120	2.178	35	60	5	0	92
3	140	1.017	68	25	7	0	93
4	160	0.3057	72	21	7	0	95
5	180	0.3465	73	21	6	0	94*
6	200	0.2915	60	20	5	15	95*
7	230	0.2981	48	15	8	29	89*

[a] Determined by GC-FID analysis, [b] Determined after extraction, * Determined after extraction and column chromatography

4.3.4. Influence of dilution

An important parameter to get an idea on the thermodynamics of the reactions is the influence of the concentration. In all previous reactions, the same concentration was used (approximately 0.45 M). In this optimization study the isomerization without any solvent as well as in much more diluted systems was investigated.

Solvent-free reaction:

It was shown earlier in this thesis that the characteristics of the solvent have a major influence on the isomerization of long chain olefins. On the one hand, polar (coordinating) solvents suppress the migration of the borane, on the other hand the type of an apolar (non-coordinating) solvent does not significantly change the equilibrium. From this observation we could conclude that a solvent-free reaction should also be suitable for isomerization.

The hydroboration-isomerization of 8-heptadecene was performed in solvent-free conditions (during the isomerization step) at 160 °C. The high conversion (Fig. 4-20 and Table 4-9 Entry 1)) confirms our hypothesis about the role of solvent.

Solvent-assisted reaction:

The hydroboration-isomerization was also investigated at different concentrations. The standard concentration is 0.45 M (Table 4-9 Entry 3), but a 1 M (Table 4-9 Entry

2) solution was also examined. The presence of an apolar solvent has an influence on neither the kinetics nor the equilibria and runs similar to the reaction in the solvent-free state. Figure 4-24 shows in comparison the solvent-free and solvent-assisted reactions. This supports the hypothesis that all related reactions are intramolecular in nature and not intermolecular (at least in apolar (non-coordinating) conditions).

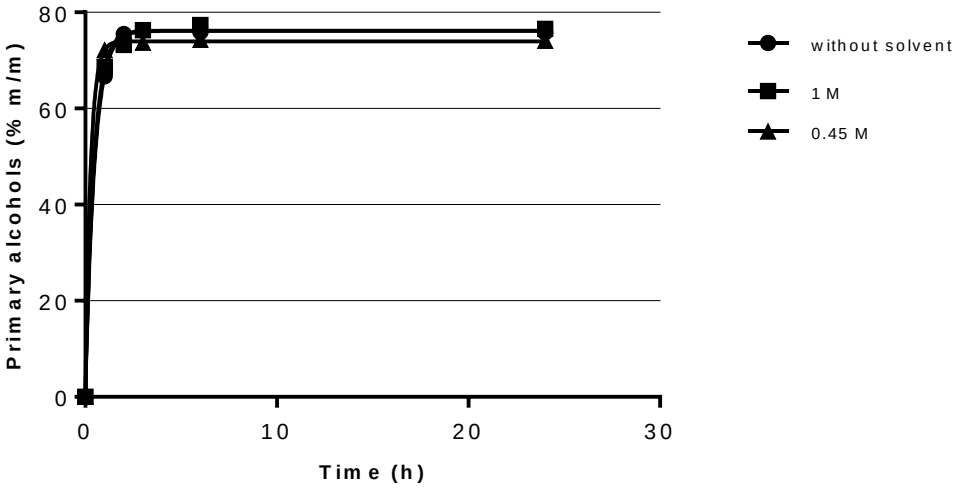


Figure 4-24 The conversions of 8-heptadecene to 1-heptadecanol at different dilutions determined by GC-FID analysis

Table 4-9 Half-time values [h] and correlation coefficients after nonlinear fit of amount of 1-heptadecanol in different dilutions

Entry	dilution	$t_{1/2}$ (h)	R^2	Yield of primary alcohol (%)[a]
1	without solvent	0.3933	0.9994	72
2	1 M	0.3537	0.9772	70
3	0.45 M	0.3560	0.9982	70

[a] Determined after extraction

4.3.5. Influence of the position of double bond

In most of the hydroboration-isomerization of internal alkenes, a final equilibrium was reached where approximately 80 % of the alcohols are primary in nature (shifted to the terminal position) and 20 % are secondary alcohols. To confirm that this ratio of alcohols is indeed the result of equilibrium, a control experiment was designed. A hydroboration-isomerization was performed on 1-heptadecene.

Isomerization of 1-heptadecene

Simple 1-alkenes react with borane-tetrahydrofuran in such way that 94 % of the borane is bonded on the terminal position and 6 % on the 2nd position[46]. Our experimental data confirmed that a trialkylborane is created for 92 % on the terminal position and for 8 % at the 2nd position. After isomerization, the distribution between primary and secondary alcohols equal approximately 80 % and 20 %, respectively. This result is consistent with the equilibrium hypothesis for isomerization, as the result is similar to the ratio found in the isomerization of 8-heptadecene (Fig. 4-25)

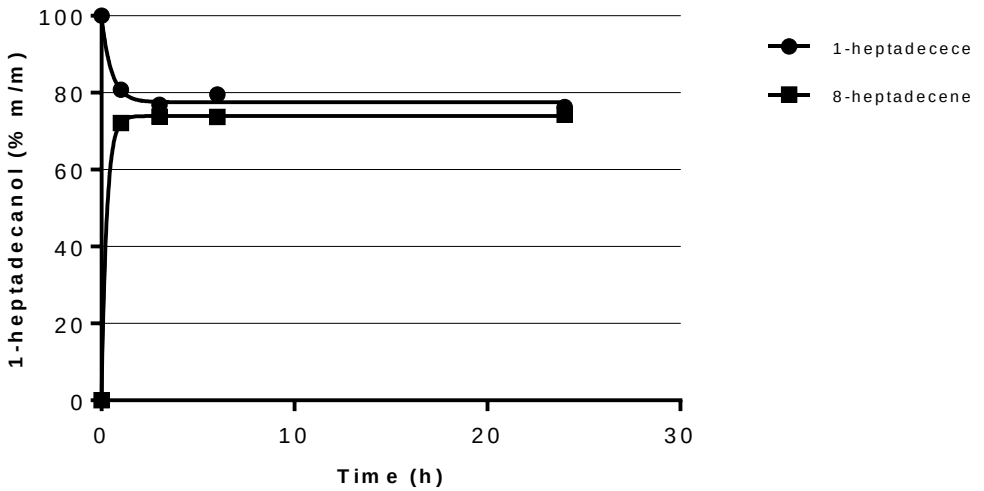


Figure 4-25 The percentage of 1-heptadecanol after hydroboration-isomerization of 1-heptadecene and 8-heptadecene determined by GC-FID analysis

4.3.6. The complex nature of the isomerization reaction

The isomerization is an intramolecular reaction. This can be concluded from the observation that the concentration of the reacting species does not have a major effect on the reaction equilibrium and the kinetics (Table 4-9). The intramolecular reaction is complex since a shift can occur statistically on each alkyl chain (each neighboring carbon atom sequentially) attached to the boron atom (Fig 4-26).

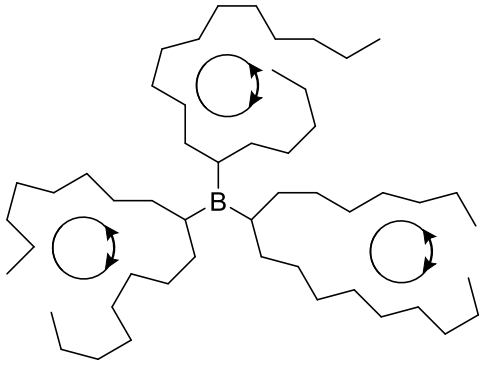


Figure 4-26 The visualization of isomerized trialkylborane

To illustrate this complexity but also in order to simplify the reasoning it is proposed to consider all shifts as taking place consecutively, but the shifts can take place on different alkyl chains. Under this assumption the reaction can then be considered as a sequence of internal shifts in the different chains up to their end. In a further approximation it is assumed that all internal shifts show a similar energy-reaction path profile and that only the terminal steps have a different (but identical to each other) energy-reaction path profile. This assumption may be not correct as the pre-terminal step might have a different energy – reaction path profile, lying somewhere between the internal and terminal steps. Also the terminal steps may be different from each other as the environment changes when 1, 2 or 3 terminal positions are realized.

Taking into account all these assumptions, the reaction of the total "entity" (i.e. the three alkyl chains connected to the boron atom) can be represented by an energy diagram (Figure 4-27), showing a reaction sequence from fully internal positions up to the three terminal positions. The activation energy for each step is indicated. From literature[46] it is known that in the case of hydroboration-isomerization the energy level of the terminal position should be lower than that in the internal positons. It is claimed in the literature that this is due to the reducing steric interaction at the end of the alkyl chain. This is shown in Figure 4-27 by the energy differences ΔG_i.

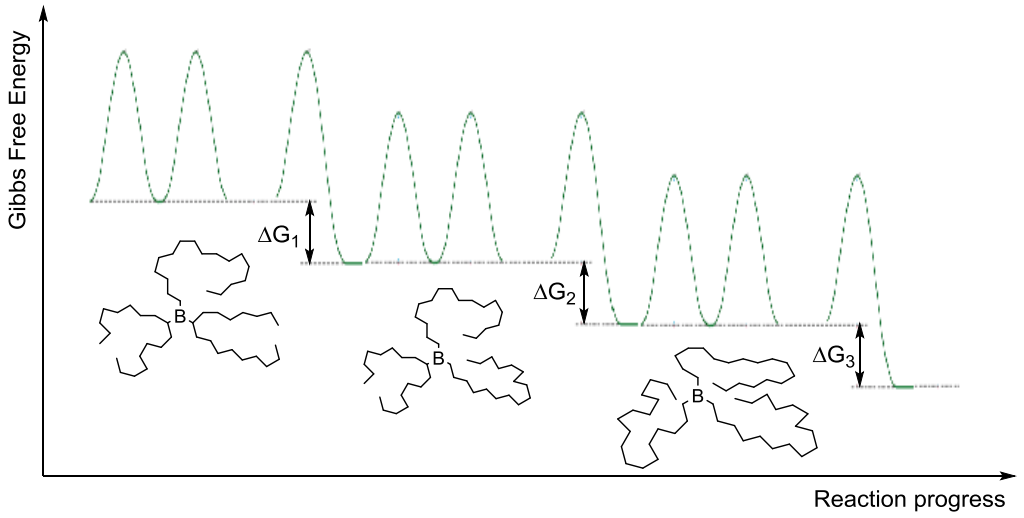


Figure 4-27 Energy – reaction pathway profile for the proposed reaction sequence in Hydroboration-isomerization for trialkylborane, with internal steps and three terminal steps.

The real complex situation is more similar as presented in Figure 4-28, showing a part of the "energy-reaction pathway profile" with slightly decreasing trend towards the end of the alkyl chain, an intermediate decrease in energy in the pre-terminal step and a large decrease in the terminal step. This pathway can be explained by fact that the alkyl chains shift simultaneously during isomerization, not as presented on Figure 4-27 first one alkyl chain, then the second one and the third alkyl chain at the end.

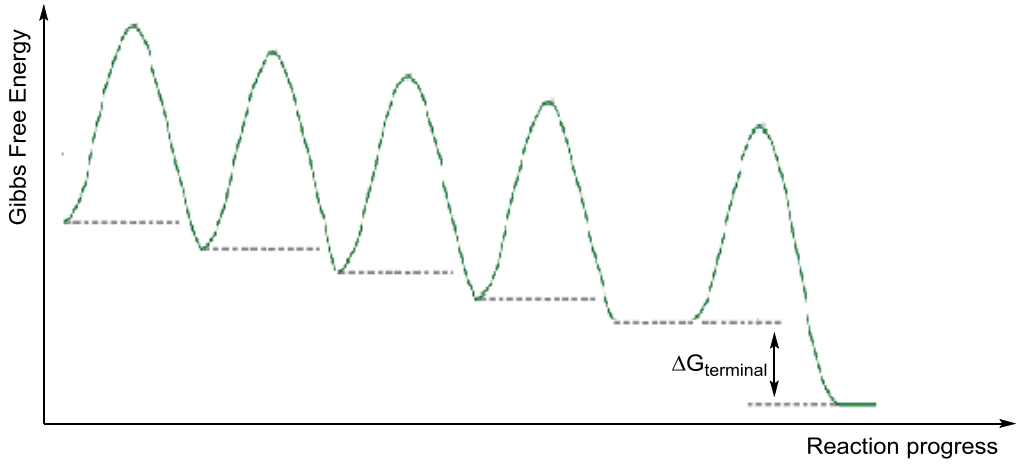


Figure 4-28 Energy – reaction pathway profile for approach 1

This situation is typical for approach 1. In case of approach 2, a simpler diagram can be made, especially when the borane comprises one long alkene and two identical cyclic alkenes, e.g. cyclohexene. Since a shift in the cyclohexene unit will not change

the thermodynamic state (sterically nor energetically), the internal shifts in the alkyl chain are rather identical and only the final step will be different. In this case the simplified profile in Figure 4-29 corresponds to the real situation.

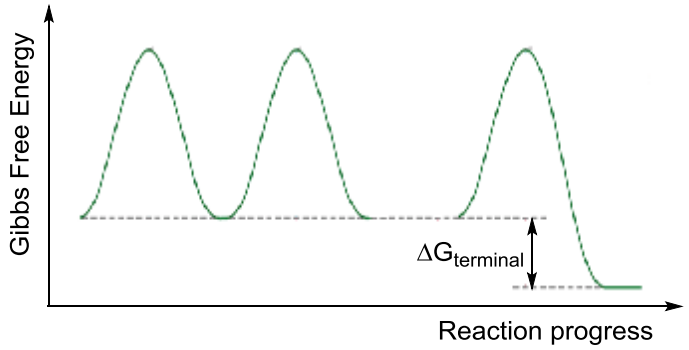


Figure 4-29 Energy – reaction pathway profile for approach 2

A first factor determining whether isomerization will take place is the height of the activation energy barrier. Looking into the diglyme system it is observed that in approach 1 borane systems with short alkyl chain isomerization occurs, thus implying that the activation barrier is not high. However, by increasing the carbon length chain, the overall rate of reaction is clearly decreasing (Table 4-10). This means that the activation barrier is becoming larger.

Table 4-10 The overall reaction rates during 1st hour for approach 1 in diglyme where C is the molar concentration of primary alcohols after 1 h.

number of carbon atom	$\frac{\Delta_C}{\Delta_{t_{1h}}}$
8	9.25
10	7.00
12	2.05
14	0.89

In long alkyl chains it was experimentally verified that no shifts occurred (Table 4-1). This means that when using long chain olefins the activation barrier is too high to allow for a shift. Therefore it can be concluded that in the diglyme system the activation barrier increases in following trend: the longer the alkyl chains are, the higher activation energy occurs to allow reaction, even when approach 2 is used, the bulky dicycloalkylboranes prevent the isomerization (moderate yield for α-pinene and no isomerization with cyclododecene). Increasing the temperature helps to activate the system, however it has to be noticed that the reaction is studied at

160 °C. The further temperature increase has no significant effect on the conversion, moreover above 200 °C the decomposition of trialkylborane is observed.

The increase in activation energy could be explained by the increased steric hindrance towards the empty *p*-orbital of the boron atom. When this empty orbital is hindered too much, it cannot easily accept the electrons needed to recreate the double bond and allow the shift. This effect is shown schematically in Figure 4-30.

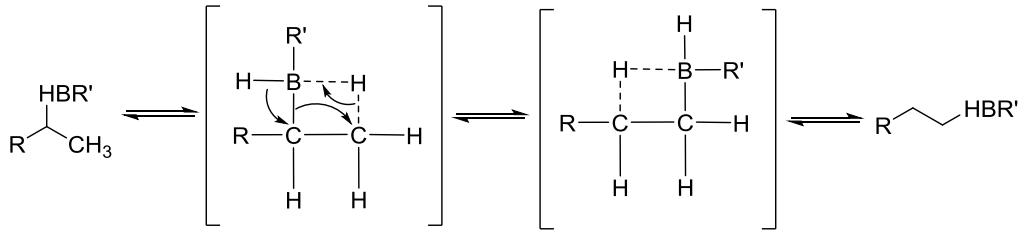


Figure 4-30 One of the proposed in the literature mechanism of hydroboration-isomerization

By taking shorter alkenes or by combining long alkenes with cyclic or short alkenes less steric hindrance is present, the activation barrier lowers and the shift occurs (Table 4-2). The effect of the activation barrier does not affect the conversion but only the rate of conversion, allowing for quick to infinitely slow reactions.

In apolar solvents and also in the solvent-free system isomerization occurs for approach 1, both for short and long alkyl chains, which is not the case for the isomerization in diglyme. This would imply that the steric hindrance induced by the long chain is influenced by the type of solvent. Two different reasons can be proposed: (1) the solvent interacts directly with the empty *p*-orbital of the boron atom making the electrons-acceptance more difficult, or (2) the solvent induces indirectly an effect through the shape changing of alkyl chain which subsequently increases or decreases the steric hindrance caused by the alkyl chains. The first effect is less likely as this would imply that with short alkyl chains the solvent could interact more strongly with the *p*-orbital and thus would block the H-acceptance more efficiently. This is however not the case for short alkenes, of which the isomerization is better than that for long alkenes. Hence it is concluded that the solvent has an influence on the amount of steric hindrance exerted by the linear alkyl chains.

This could be verified by doing conformation calculations of long hydrocarbon chains in force fields of different solvating environments. Sun *et al*.[165-166] studied the conformation distribution of octadecane in solvents of different polarity and found that the chain was showing an increasing tendency to fold towards itself if the more polar the environment was. Said folded conformation is shown in Figure 4-31.

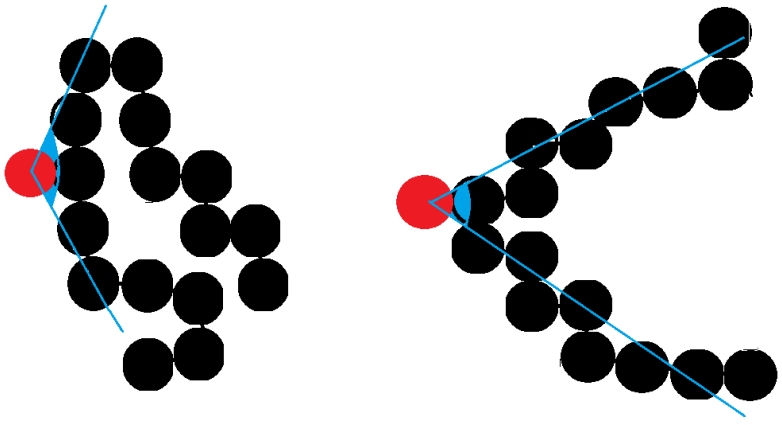


Figure 4-31 The behavior of long alkyl chain (in trialkylborane) in different solvents. On the left side – in a polar solvent, on the right side – in an apolar solvent.

The calculations of Sun *et al*. [165-166] are consistent with our suggestion that diglyme could induce the long alkyl chains to cluster and to fold towards themselves and each other, thus increasing the steric hindrance close to the boron atom. An apolar solvent such as isododecane would on the other hand unfold the alkyl chains to long stretched chains thus reducing the steric hindrance close to the boron atom. This will facilitate the accessibility of the empty *p*-orbital. A lower energy barrier is realized allowing for a shift. This could explain the significant improvement in the isomerization of long alkyl chains in isododecane. In this way the apolar nature of the solvent is the most important factor facilitating isomerization of long chain olefins. It has to be noted that this tendency to "fold towards itself" increases the longer the carbon chain is, as more rotatable bonds are present.

When the required conditions are accomplished isomerization can occur (see above) and the shift will proceed until a certain conversion is reached. Conversion is defined as the ratio of terminal positions realized versus the theoretical amount that could be realized when a total shift would take place. Experiments clearly indicate differences in conversion depending on carbon chain length, type of solvent, approach 1 versus approach 2 systems as well as temperature and functionality present in the olefins.

In case the energy barrier is low enough to allow shifting, the conversion will depend on ΔG, the difference in energy of terminal positions versus internal positions but also on the amount of terminal positions (2) versus internal positions (n-2), where n is the number of carbon atoms in the alkyl chain.

In case there would be no energy difference between all states, the conversion would be dictated by this ratio and follow equation 1:

$$Conversion = \frac{2}{n}\, x\, 100\ \% \qquad (1)$$

In Figure 4-32 this calculated conversion is compared to the observed conversion in the diglyme system. The trend is similar but the observed conversion show a steeper decrease indicating that an additional effect with dependence on alkyl chain length is present. This effect has to be attributed to differences in ΔG as a function of carbon chain length; in a way ΔG is becoming smaller the longer the alkyl chains are. This could be explained by the same steric effect discussed in the section on activation energy.

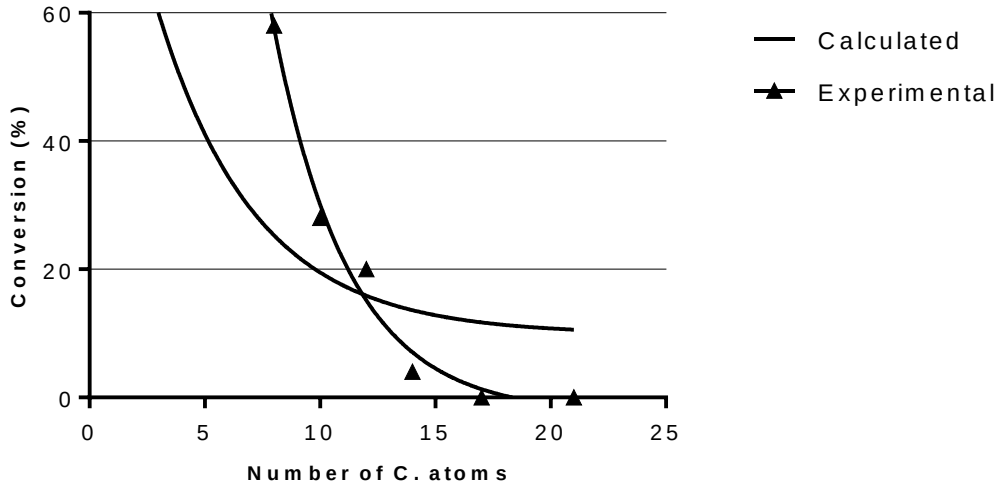


Figure 4-32 The experimental conversion in diglyme (approach 1) vs calculated conversion

The long alkyl chains have a tendency to fold back on themselves. In case of long carbon chain this will lead to an increasing steric hindrance at the terminal position. As shown in Figure 4-34, the long molecules have a tendency to create a quasi-cyclic structure. In such molecule the difference in steric hindrance on internal and terminal positions is not so large. The consequence is that the ΔG, the energy difference between the terminal and internal positions, is decreasing. This will lead in turn to a lower equilibrium constant K (2), and hence a lower concentration of terminal versus internal positions. A trend towards lower conversions for longer alkyl chains is found experimentally.

$$K = \frac{C_\omega}{C_{\omega-1}} = e^{-\frac{\Delta G}{RT}} \qquad (2)$$

The ΔG in a short alkyl chains in diglyme system and a long chain alkyl chains in diglyme system are shown schematically in Figure 4-33 A and B, respectively.

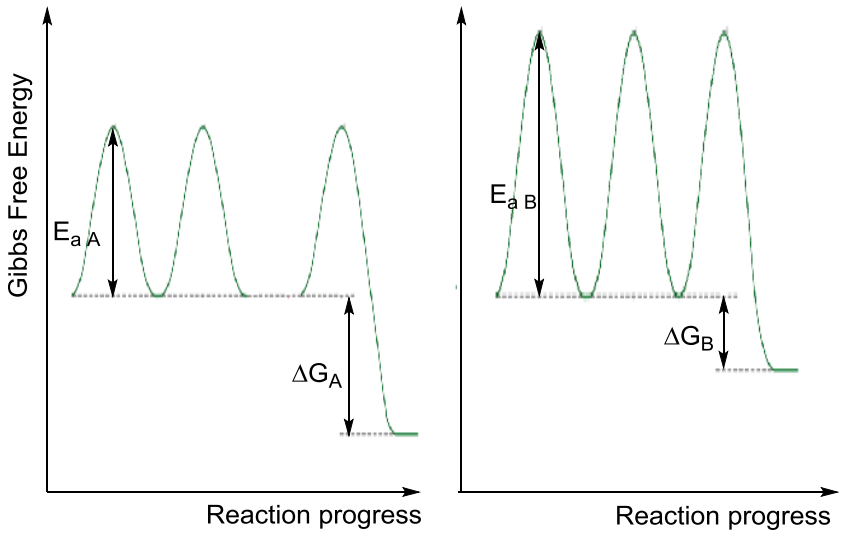


Figure 4-33 The suggested energetic diagrams for reaction in diglyme (A – short chain alkenes, B – long chain alkenes)

The activation energy (E_a) is higher in the long alkyl chain system. There is more steric hindrance in the internal position, but the steric hindrance is proportionally even higher in the terminal position.

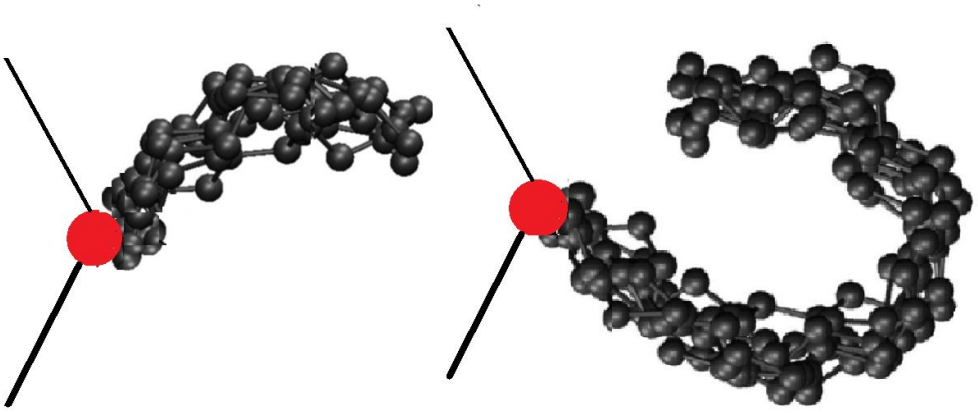


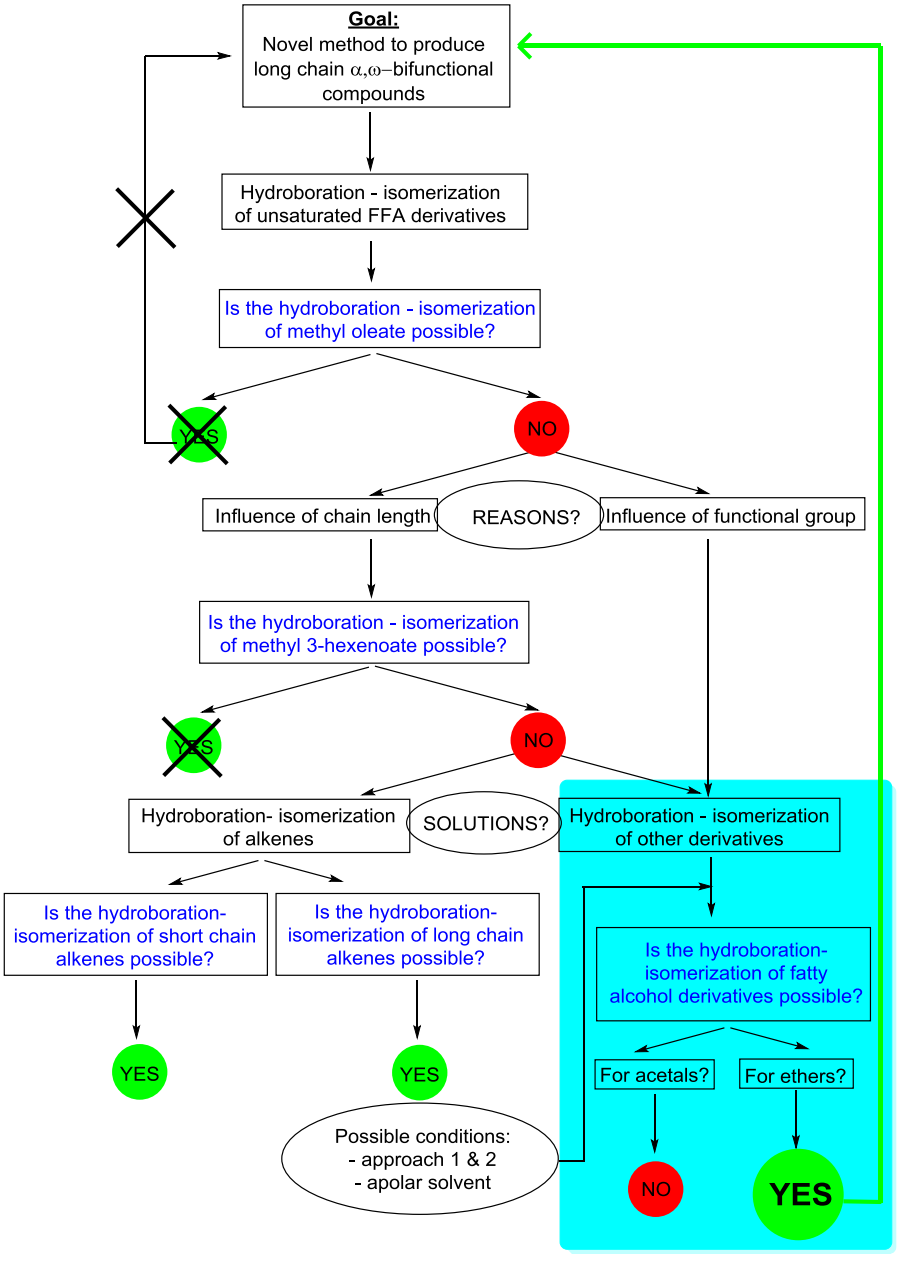
Figure 4-34 The folding effect in short and long alkyl chain

In diglyme the solvent will induce the folding effect in a more pronounced way due to its polar character, whereas in isododecane this is not the case. As a consequence, the conversion is lower in diglyme, compared with the conversions in isododecane. Also the decrease of the conversion as a function of chain length will be smaller. Long chains show good conversion in an apolar solvent, except the very long ones. A

possible explanation of lower conversion for C-21 alkene is that even in apolar solvent a tendency for the folding effect exists. The better conversions in isododecane are also seen in other apolar systems. This is consistent with the proposed explanation.

Without pretending to having proposed an all-comprising theory, it is argued that a rationalization can be made using the principle of steric hindrance due to the specific conformation distribution of the alkyl chains. This is dependent on chain length and solvent type. That way it is possible to explain a large number of observed trends and effects. It is however suggested to do additional experiments to obtain a complete theory.

4.4. Hydroboration-isomerization of functionalized olefins



Hydroboration-isomerization of model alkenes, as discussed in the previous chapter, revealed crucial information on the mechanisms involved, especially when long chain alkenes were used. The most important finding is the role of the solvent. It became obvious that polar (coordinating) solvents will not be useful for long chain functionalized olefins. It is necessary to use apolar (non-coordinating) solvents or run the reaction in solvent-free conditions. However, the same finding might imply that

the presence of a functional group in the long chain molecule also has an adverse effect on the isomerization. An important issue is hence to understand which type of functional groups are compatible with the hydroboration-isomerization conditions. A second important issue is whether such non-suppressing group can easily be introduced and removed so that after the isomerization the envisaged α,ω-bifunctional molecule is obtained.

4.4.1. Hydroboration-isomerization of esters

The first hydroboration-isomerizations performed on methyl oleate and methyl 3-hexenoate in diglyme gave negative results for approaches 1 and 2. Since it was found that isomerization for long chain alkenes in diglyme is feasible using approach 2 (external dialkylborane), the negative result appears to be due to the presence of carbonyl oxygen (*vide supra*, p. 42). In order to understand this process, several additional reactions were performed to further support this statement.

The reactions with methyl oleate and methyl-3-hexenoate were repeated in the isododecane solvent system. As expected, no isomerization to the terminal position was observed. A further analysis of the position of the hydroxyl group in the reaction product proved no internal isomerization of methyl 3-hexenoate and a partial internal isomerization for both the α and ω direction of methyl oleate. As it was mentioned above, for longer chain olefins where the number of possible secondary alcohols is higher, the GC column is not able to distinguish all of the secondary alcohols, therefore it was necessary to use the method to determine the hydroxyl group position in the secondary alcohols (Fig. 4-9). To decrease the complexity of the analysis, first the ester group was reduced to the alcohol group and subsequently the product was treated with concentrated phosphoric acid in order to dehydrate the secondary alcohols. The selectivity of this method is important and very useful. Firstly, only secondary alcohols are dehydrated. Secondly, the obtained alkenes can be reused again in the hydroboration-isomerization. The last step is the ozonolysis of synthesized olefins followed by reduction. The products in this approach are only alcohols and diols. An example of the cascade of reactions to determine the position of the hydroxyl group in the reaction product(s) is shown schematically in Figure 4-35.

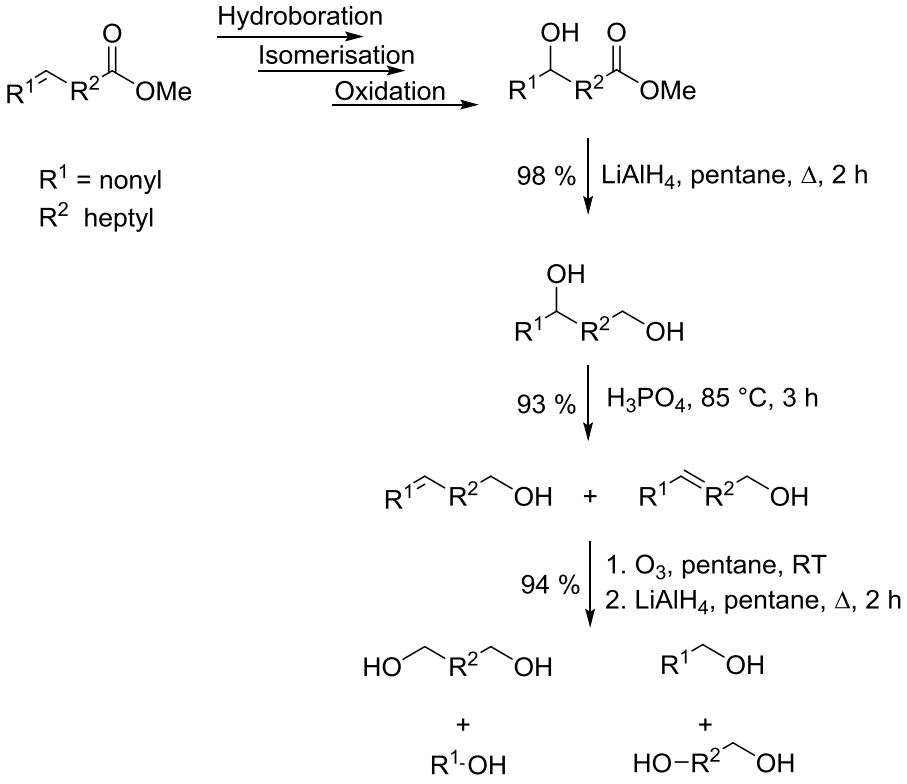


Figure 4-35 Determination of the hydroxyl group position after hydroboration-isomerization of methyl oleate

Applying this procedure on the isomerized methyl oleate, it was found that the migration of borane along an alkyl chain was only possible over a distance of three carbon atoms, as shown in Figure 4-36. The analysis of alcohols formed by using the dehydration - ozonolysis method showed a distribution of alcohols ranging from hexanol up to tridecanol. Analogous results were obtained for diols (Fig. 4-37). The maximum isomerization is three bonds from position 9 to "9 – 3" and "9 + 3".

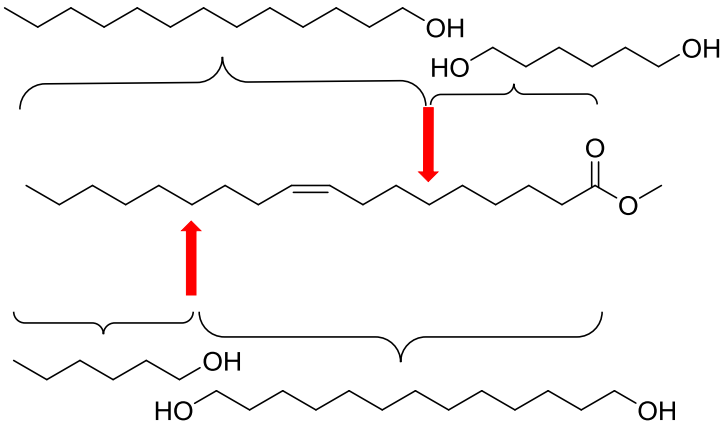


Figure 4-36 The maximum migration of borane on methyl oleate

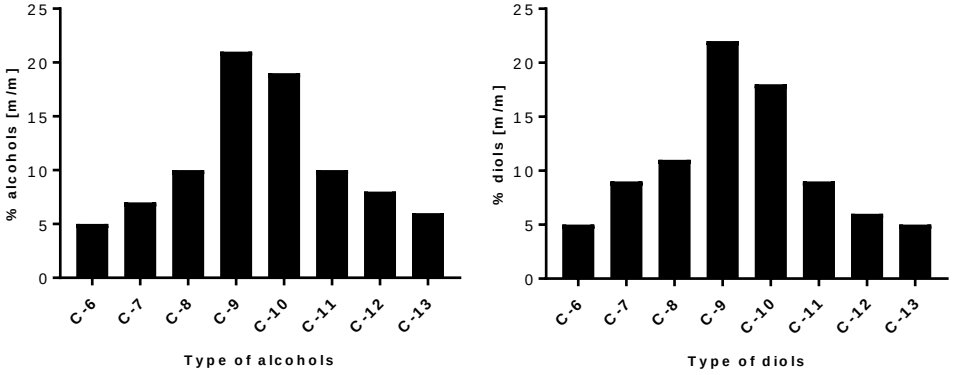


Figure 4-37 The percentage distribution of alcohols and diols after hydroboration-isomerization of methyl oleate determined by GC-FID analysis

As additional proof for the possibility of short range migration of the boryl group in long chain esters, methyl oleate was combined with 4-octene in a trialkylborane according to approach 2 and subsequently isomerized in isododecane as shown in Figure 4-38.

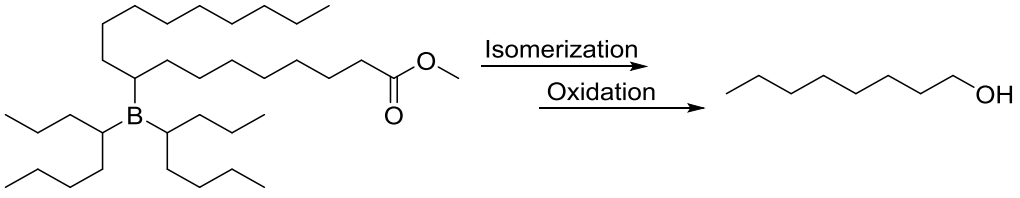


Figure 4-38 The isomerization of 4-octene with methyl oleate

This experiment confirmed the isomerization of the 4-octene coupled with methyl oleate with moderate conversion (approximately 45 %) (Fig. 4-39).

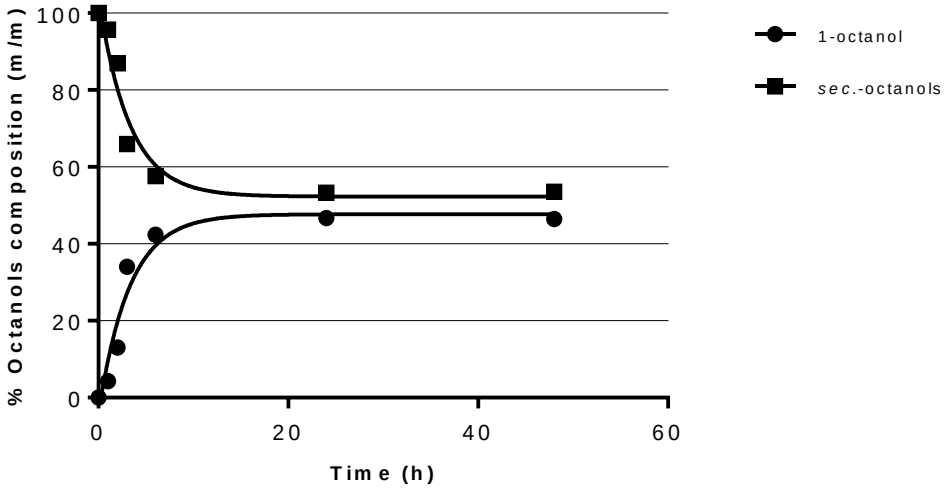


Figure 4-39 Percentage composition of octanols determined by GC-FID analysis

The isomerization to the terminal position is lower than for trioctylborane (see experimental results in the previous section). The high amount of 4-octanol indicates that part of the borane was blocked in this position. Nevertheless, this reaction gave higher conversion to the third position (referenced with respect to the initial position of the double bond) in the methyl oleate. When only methyl oleate is used, the borane migrates for 10 % to this position. When 4-octene (2 eq) is combined with methyl oleate (1 eq), the borane migrates for 45 % to the third position in the methyl oleate, where it can form a stable complex between the borane and the ester. The higher conversion might be explained by the fact that in the reaction with the 4-octene the total number of carbonyl oxygens is three times less compared to the situation with only methyl oleate.

A control reaction, identical to the 4-octene reaction discussed above, was designed. The only difference was the use of longer alkenes (8-heptadecene) instead of the short alkene (4-octene). The system is shown in Figure 4-40.

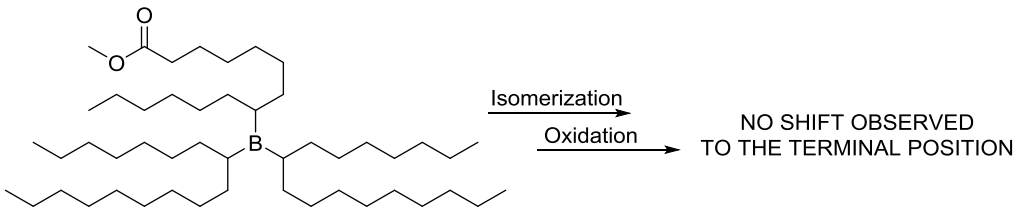


Figure 4-40 The isomerization of 8-heptadecene with methyl oleate

As expected, again no shift was observed to the terminal position in either of the long chains. Nevertheless, the partial internal isomerisation was found – simillar as presented in Figure 4-36. Another control reaction was the hydroboration-isomerization of methyl 3-hexenoate with 4-octene as shown in Figure 4-41.

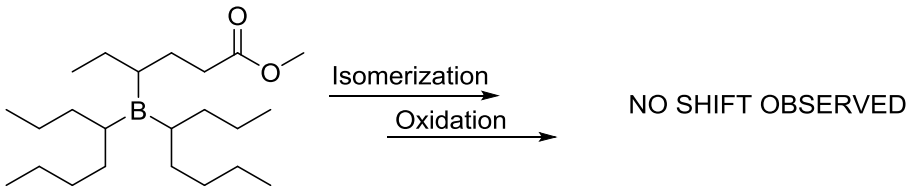


Figure 4-41 The isomerization of 4-octene with methyl 3-hexenoate

This reaction provides additional proof that if the borane is already initially close to the carbonyl group, it is intramolecular blocked by the carbonyl oxygen and internal isomerization does not occur at all. This becomes evident when the result of the reaction with methyl 3-hexanoate with the reaction with methyl oleate. In the latter case the carbonyl group in the methyl oleate is much further away from the initial active region for the isomerization.

A final verification experiment was performed to support the effect of the carbonyl group on the borane. In this verification experiment the influence of the carbonyl oxygen was investigated by a solvent spiking method. Two experiments were designed as shown in picture 4-42. In the first experiment 8-heptadecene together with the (assumed) inhibiting methyl octanoate (1.1 eq) was kept in the reaction mixture for 48 h, whereas in the second reaction this presumably inhibitor was removed after 6 h of heating.

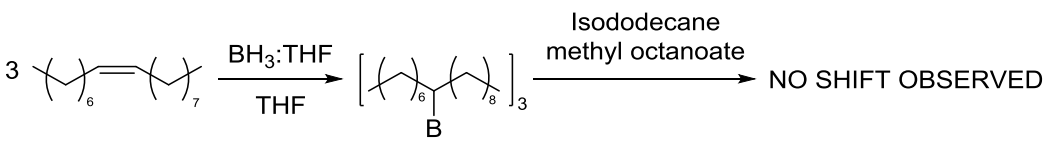


Figure 4-42 Hydroboration-isomerization of 8-heptadecene in isododecane spiking with methyl octanoate

In the first reaction, as expected, no isomerization to the terminal position occurred. In the second reaction also no isomerization was observed during the first 6 h of reaction, but after removal of the ester spike (by distillation), borane was seen to shift to the terminal position with a 40 % conversion (Fig. 4-43).

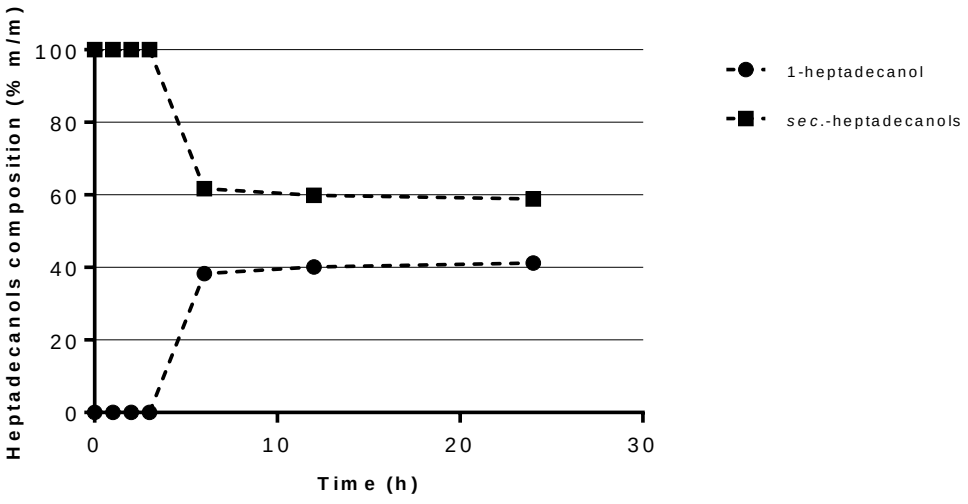
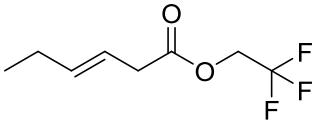
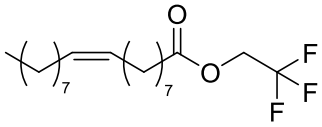
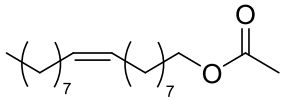
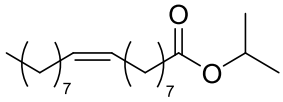
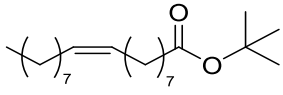


Figure 4-43 Percentage composition of heptadecanols (determined by GC-FID analysis) in a solvent spiking method

Also other types of esters were examined using both approaches 1 and 2, in isododecane, but neither of them led to isomerization to the terminal position (Table 4-11).

Table 4-11 Other examined esters

Examined ester		Isomerization	
		Internal	To the terminal position
Esters with electron withdrawing group		X	X
		V	X
"reverse ester"		V	X
Esters with bulky group		V	X
		V	X

General conclusions:

The series of aforementioned experiments supports and confirms the following hypothesis: during the isomerization step the carbonyl oxygen is able to complex with the borane (intra- and/or intermolecular), thereby suppressing/inhibiting the isomerization activity of borane. The interaction is depicted schematically in Figure 4-44.

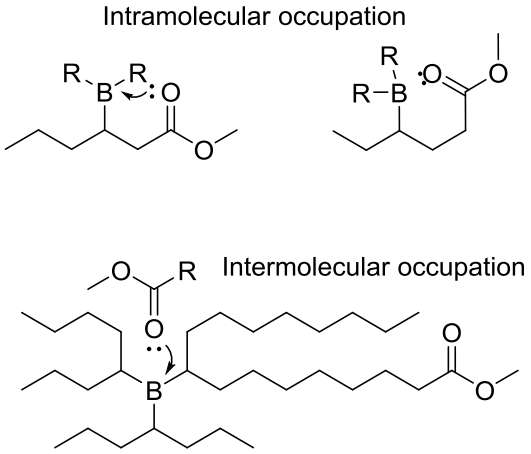


Figure 4-44 Intra- and intermolecular occupation of empty *p*-orbital on borane by free electrons from carbonyl oxygen

Intramolecular occupation occurs only if borane is close enough to the carbonyl oxygen, as this allows a stable 5- or 6-membered ring to be formed. If the carbonyl oxygen is remote enough from the borane, some intermolecular occupation is possible, but it is less effective. A partial internal isomerization is observed. The bonding of oxygen to boron is a reversible process. The carbonyl group can be decoupled, as evidenced by the possibility to distill off the carbonyl group comprising spike compound. By removal of the ester the activity of the borane can be restored.

4.4.2. Hydroboration-isomerization of acetals

It was found in the previous chapter(s) that carbonyl compounds induce problems for the hydroboration-isomerization mechanism. Therefore, a different derivative of fatty acid that would not induce the negative effects has to be found. Apart from the carboxylic acids also the corresponding fatty alcohols were considered. Oleyl alcohol (**19**) was taken as a representative. The saturated form of oleyl alcohol is stearyl alcohol (**39**) (Fig. 4-45).

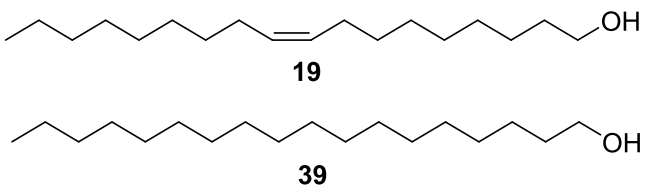


Figure 4-45 Oleyl and stearyl alcohol

Alcohols as such are unsuitable substrates for hydroboration-isomerization reactions due to their reactivity towards boranes. They can create an acid-base adduct, which in a second step is converted into alkoxyborane (Fig 4-46)[169]. Therefore, it is necessary to protect the hydroxyl group.

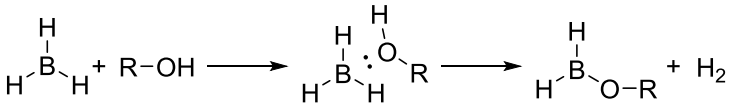
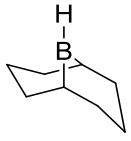


Figure 4-46 Synthesis of monoalkoxyborane from alcohol

For the sake of completeness three additional experiments were performed. In the first one 3 eq of oleyl alcohol (**19**) was mixed with 1 eq of BH_3·THF (**1**). These experiments proved the similar affinity of borane toward double bonds and hydroxyl groups. After alkali hydrolysis both **19** and **39** were observed. An important observation is the changing of the physical state of the reaction mixture – from the liquid at the beginning into gel after few minutes. This phenomenon can be explained by the fact of network formation during the two parallel reactions – making an alkoxyborane and hydroboration. In the second reaction instead of **1**, 1 eq of 9-BBN (**40**) and 3 eq of **19** were used. By using of **40** there is no possibility of network system formation. Again, after alkali hydrolysis both **19** and **39** were observed. In the third reaction 2 eq of **40** were used per 1 eq of **19** and the standard procedure of hydroboration-isomerization was followed. After 24 h of heating no isomerization to the terminal position was observed. The further analysis of hydroxyl group position showed also no internal isomerization. These experiments confirmed the necessity of using a protected form of fatty alcohols.



40

Figure 4-47 9-Borabicyclo[3.3.1]nonane (9-BBN)

The protected form of alcohols that was investigated first is an acetal. Two different acetals were tested: oleyl tetrahydropyranyl acetal and benzaldehyde dioleyl acetal. Since these compounds are not available commercially, they had to be synthesized. The synthesis is described in the chapter “6. Starting materials for hydroboration-isomerization”.

The hydroboration-isomerization of oleyl tetrahydropyranyl acetal is shown schematically in Figure 4-48. Both approaches, approach 1 and 2, were used in the presence of isododecane and in solvent-free conditions as well.

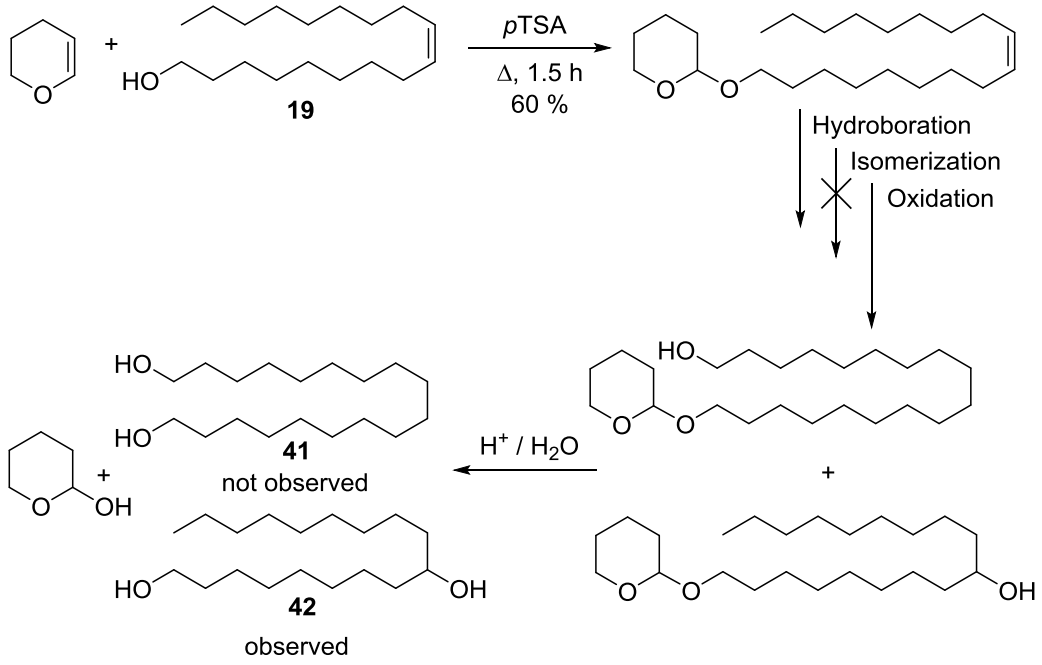


Figure 4-48 The overview of using oleyl tetrahydropyranyl acetal in hydroboration-isomerization

Tetrahydropyranyl acetal seems to be not suitable for hydroboration-isomerization. The isomerization to the primary position (**41**) was not accomplished, nevertheless the hydroxyl group was introduced in the position of the double bond (**42**), which proved the hydroboration. It is known from literature[170] that acetals in the presence of borane can undergo reductive cleavage leading to ethers. Interesting is the fact that no ethers are observed. This experiment showed higher affinity of borane towards double bond than to acetal.

Another examined protected alcohol was the benzaldehyde derived acetal. This acetal was synthesized as shown in Figure 4-49 and subsequently used in hydroboration-isomerization using approach 2 (with dicyclohexylborane) in both the solvent-free condition and in a solvent-assisted condition (isododecane). Due to the presence of two double bonds on the acetal, approach 1 makes no sense, as this would lead to network formation.

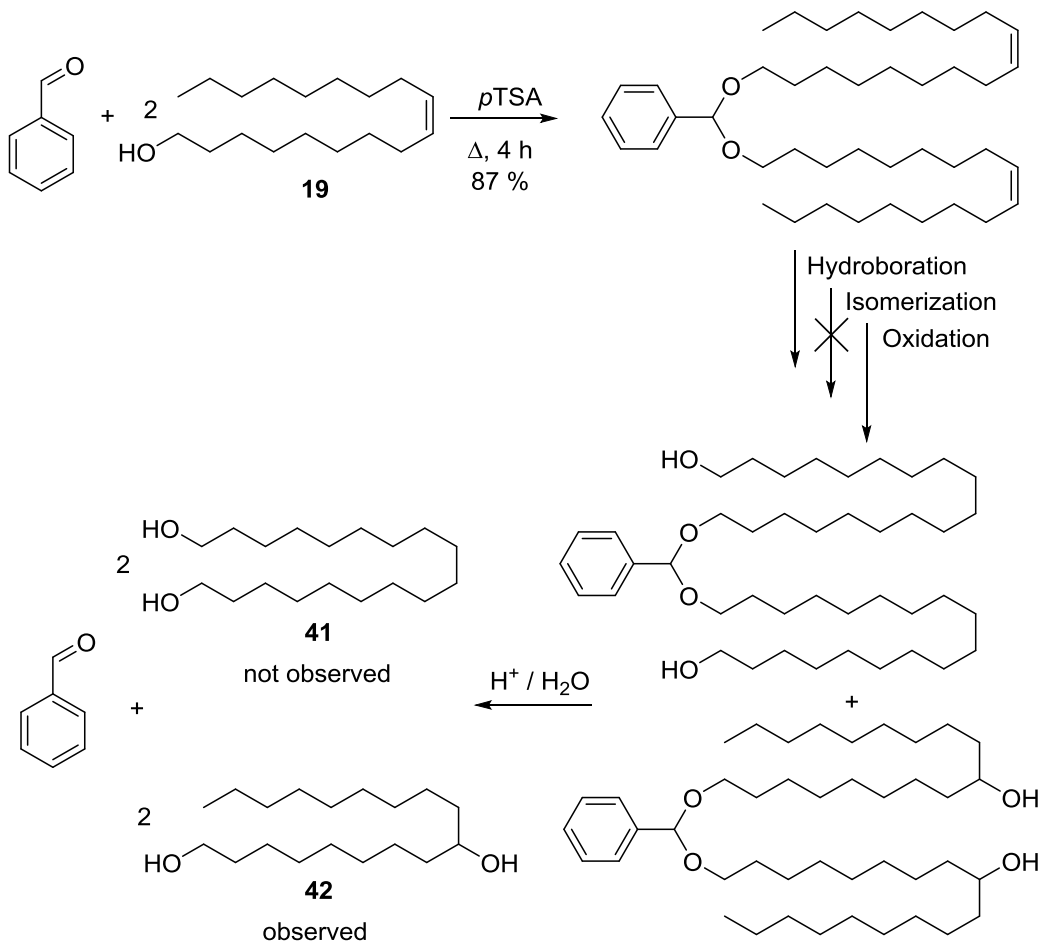


Figure 4-49 The overview of using benzaldehyde dioleyl acetal in hydroboration-isomerization

Similar to the previous experiments the isomerization to the primary position was not achieved – **41** was not detected, but instead, hydroboration of the double bond was observed, giving **42** as the only product. Any benzyl ether was found in the products mixture, which once again confirmed higher affinity of borane towards double bond than acetal.

The lack of isomerization could be explained by the possible interaction of acetal oxygen and empty *p*-orbital on borane and obstruct the migration. Moreover, benzaldehyde dioleyl acetal is a large molecule which could lead to entanglements, preventing an easy shift of the double bond. No further attempts were made using the acetal concept.

4.4.3. Hydroboration-isomerization of ethers

The negative results from hydroboration-isomerization of acetals, pointed at the necessity to expand the search for more stable protected alcohol molecules. Simultaneously a potential disadvantage does however a rise: the difficulty to deprotect the molecule after the hydroboration-isomerization step. The cleavage and recovery of the alcohol functionality on the α-position is crucial for a future industrial application.

Linear ethers are certainly stable under hydroboration-isomerization conditions (diglyme used in the classical reaction is an ether-type molecule). Two types of ether were investigated. The first is methyl oleyl ether, being the simplest linear ether possible derived from oleyl alcohol, and the second is benzyl oleyl ether. The selection of benzyl ether was not accidental, but was intended to overcome a serious disadvantage related to methyl ether. In order to remove the ether protection a strong (not green) reagent is required – mostly boron tribromide. It was found on the contrary that the benzyl alkyl ether can be easily cleaved by ozone and that by a subsequent methanolysis the hydroxyl group can be recovered. Additional information regarding the synthesis, stability, cleavage and identification are presented in the chapter “6. Starting materials for hydroboration-isomerization”.

4.4.3.1. Methyl oleyl ether

The first examined ether was methyl oleyl ether, which with respect to its structure is quite similar to linear alkenes. The total number of carbon atoms is 19 and the additional oxygen places this ether close to 9-henicosene with respect to its chain length. The similarity is also present with respect to the position of the double bond – situated between the 9^{th} and the 10^{th} carbon atom. The general overview of the sequence of experiments is presented on Figure 4-50. As a few molecules made during these reactions are new the points of analysis are also presented. The structure of a crucial molecule are confirmed by means of ^{1}H and ^{13}C NMR. Methyl oleyl ether used in the research was synthesized by means of Williamson method (*vide infra*, p. 212).

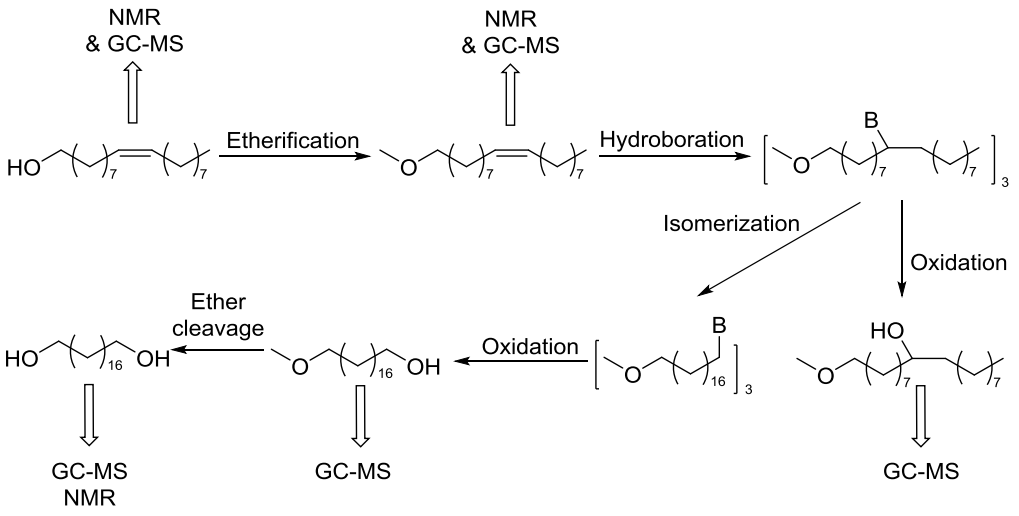


Figure 4-50 Sequence of experiments and point of analysis

Hydroboration-isomerization in solvent-free conditions

The high conversion of alkenes in solvent free conditions (Fig. 4-24) suggested exploring the hydroboration-isomerization without additional solvent. Both approaches (1 and 2) were used. As the external dialkylborane, dicyclohexylborane (**3**), was used (as well as for all other hydroboration-isomerization of unsaturated ethers). The percentage of 18-methoxyoctadecan-1-ol (**46**) (the isomerized product) for both approaches is given in Figure 4-51.

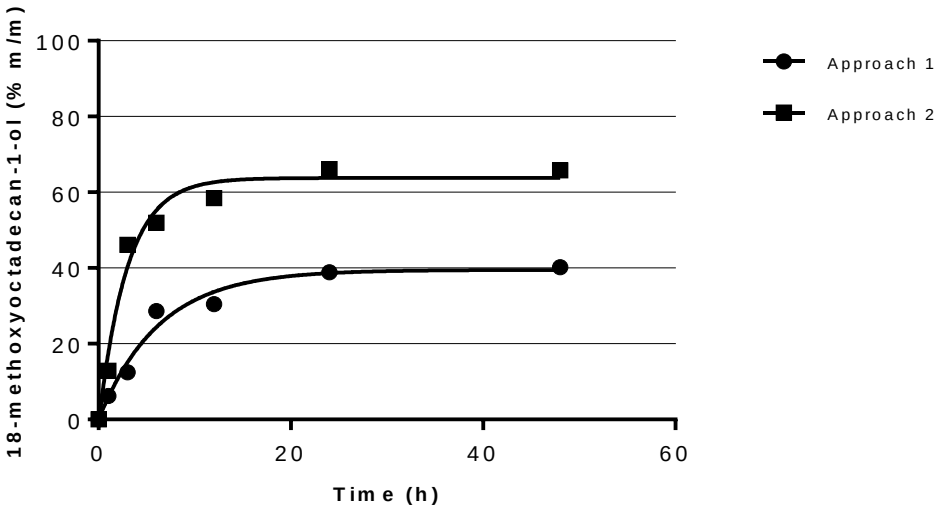


Figure 4-51 The content of isomerized product during hydroboration-isomerization of methyl oleyl ether in solvent-free condition determined by GC-FID analysis

The hydroboration-isomerization in solvent-free conditions gave a relatively high conversion when using approach 2 (72 %) and a moderate but still interesting conversion using the economic approach 1 (40 %). Another difference is observed with respect to the kinetics. The isomerization with dicyclohexylborane (approach 2) is two times faster than the isomerization with three identical alkyl ether chains (approach 1). The conversion for tri(18-methoxyoctadecyl)borane is comparable to that of triheneicosylborane (Fig. 4-20) – 40 % and 35 % respectively. This is supporting our statement that the ether is similar in behavior to the C21 alkene (see above).

Hydroboration-isomerization in isododecane

As an example of a solvent-assisted reaction, the reaction in isododecane was examined. The conversion for the economic approach 1 is the same for the solvent-free reaction. A small improvement is observed when using approach 2. No significant difference in kinetics is noticed in comparison with the reaction without solvent. The percentage of isomerized product is given in Figure 4-52.

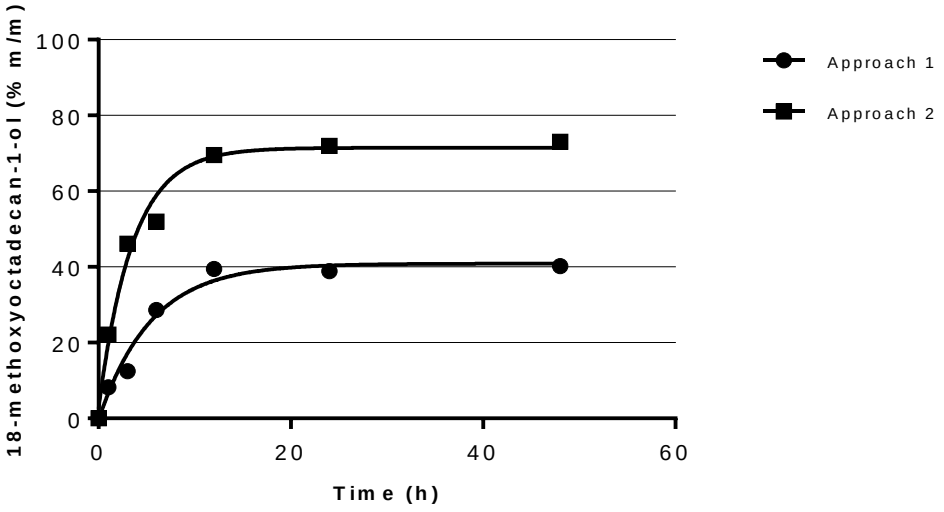


Figure 4-52 The content of isomerized product during hydroboration-isomerization of methyl oleyl ether in isododecane determined by GC-FID analysis

Hydroboration-isomerization in xylene

Xylene was also tested as a potential solvent for the hydroboration-isomerization reaction. Unexpected results were obtained in this solvent system. No isomerization was observed when using approach 1, and only a moderate isomerization when

approach 2 was used. Xylene does not seem to be a good solvent for isomerization. The much higher half time value for the reaction in xylene might be explained (as before) by the lower refluxing temperature (140 °C instead of 160 °C). The conversion is presented in Figure 4-53.

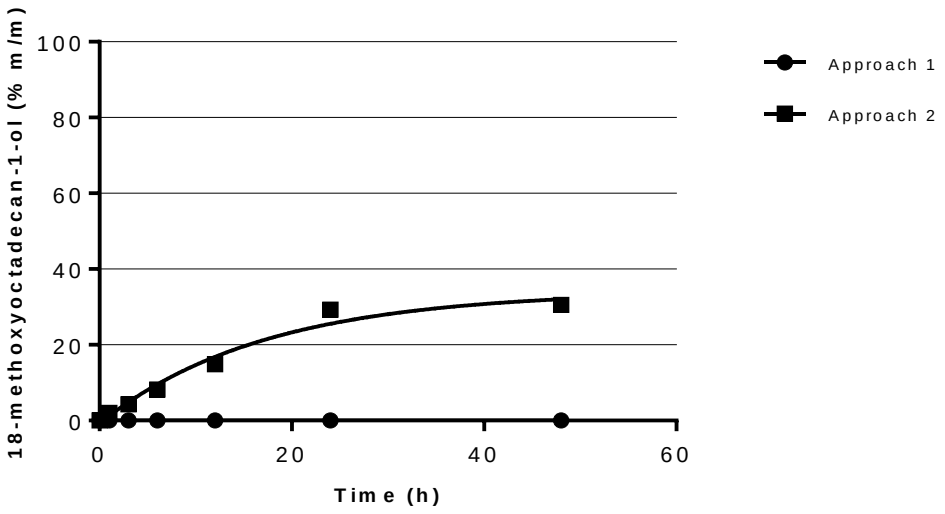


Figure 4-53 The content of isomerized product during hydroboration-isomerization of methyl oleyl ether in xylene determined by GC-FID analysis

Hydroboration-isomerization in silicone oil.

As a last solvent, silicone oil was used. Similar to xylene it contains also an aromatic functionality, since the silicone oil is $[polyphenyl]_x$-$[polymethyl]_y$ based. The conversion for approach 2 was somewhat higher compared to the xylene case (from 30 % to 43 %) (Fig. 4-54). This solvent does however not seem to be ideal and for example approach 2 does not give isomerization.

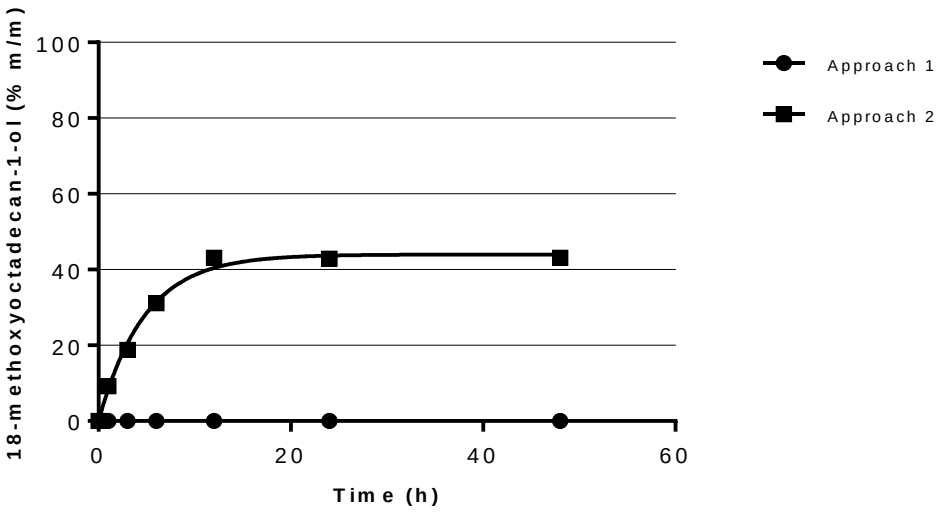


Figure 4-54 The content of isomerized product during hydroboration-isomerization of methyl oleyl ether in silicone oil determined by GC-FID analysis

In the hydroboration-isomerization of methyl oleate the less economic approach 2 is more efficient. The best results were obtained under solvent-free conditions and in isododecane. Only these two systems are suitable for the economic approach 1, but the maximum yield is limited to around 40 %. In those systems approach 2 gives more interesting yields (63-70 %).Table 4-12 shows an overview of the yields and kinetics of all performed reactions on methyl oleate.

Table 4-12 Half-time values [h] and the yield for hydroboration-isomerization of methyl oleyl ether

	solvent	Approach 1		Approach 2	
		Yield[a] [%]	$t_{1/2}$ (h)	Yield[a] [%]	$t_{1/2}$ (h)
1	solvent-free	38	4.34	63	2.05
2	isododecane	36	3.76	69	2.45
3	xylene	0	-	28	11.90
4	silicone oil	0	-	38*	3.31

[a] The yield of isomerized product **46** determined after extraction, * Determined after extraction and column chromatography

Based on these experiments only it is difficult to propose a solid explanation of why the aromatic-type solvent turned out to be inefficient in approach 1. Probably isododecane, by its hydrophobic nature, can better stabilize long alkyl chains.

4.4.3.2. Benzyl oleyl ether

The second investigated ether was benzyl oleyl ether, which seems to be more economically interesting, as the benzyl group can be more easily removed than

methyl group. To make a clear comparison with hydroboration-isomerization of methyl oleate, exactly the same reactions were executed.

Contrary to the case with methyl oleyl ether, the hydroboration-isomerization of benzyl oleyl ether gave negative results in solvent-free condition, isododecane and xylene. No isomerization occurred when using approach 1 and only up to 10 % of 18-(benzyloxy)octadecan-1-ol (**45**) (isomerized product) was obtained when using approach 2.

Unexpected results were also obtained in silicone oil. The conversion in approach 2 was substantially improved, from 10 % in all other systems to 55 % (Fig. 4-55). Comparing the methyl ether system with the benzyl ether system, the lower performance of the benzyl ether system might be due to the more polar nature of the ether oxygen (due to the aromatic nature of the benzyl group). This more polar oxygen will act similarly to the ether oxygen in diglyme. The fact that the benzyl ether did after all work in the silicone oil system might be due to the presence of more aromatic rings close to each other (the silicone oil is phenyl-methyl silicone oil), shielding sterically the ether oxygen from interacting with the borane.

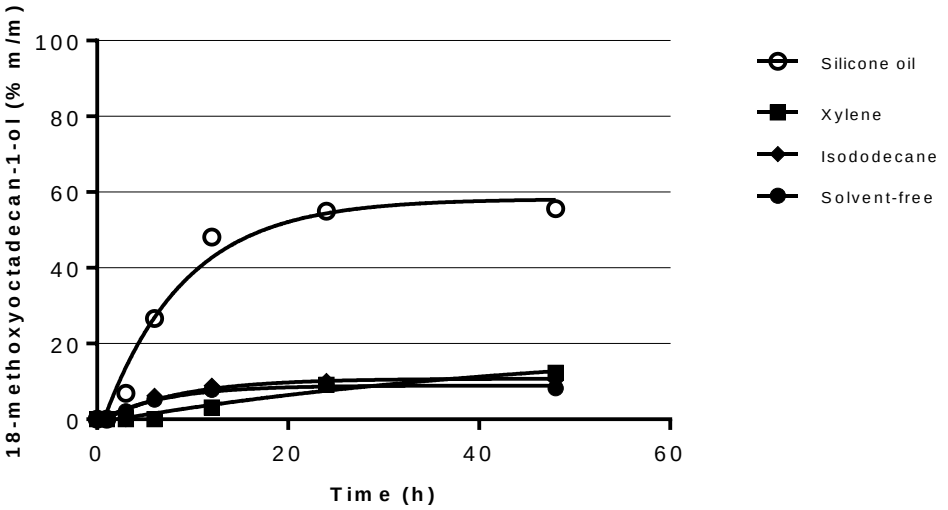


Figure 4-55 The content of isomerized product during hydroboration-isomerization of benzyl oleyl ether in different solvents determined by GC-FID analysis

Benzyl oleyl ether (at the moment) can only be used for hydroboration-isomerization using approach 2. Table 4-13 shows an overview of the yields and kinetics for all performed reactions.

Table 4-13 Half-time values [h] and the yield for hydroboration-isomerization of benzyl oleyl ether

	solvent	Approach 1		Approach 2	
		Yield[a] [%]	$t_{1/2}$ (h)	Yield[a] [%]	$t_{1/2}$ (h)
1	solvent-free	0	-	8	4.61
2	isododecane	0	-	10	6.643
3	xylene	0	-	10	21.08
4	silicone oil	0	-	55*	5.91

[a] The yield of isomerized product **45** determined after extraction, * Determined after extraction and column chromatography

Conclusions

Hydroboration-isomerization is possible on unsaturated ethers. Methyl oleyl ether gave better results than benzyl oleyl ether during the hydroboration-isomerization. The less economic approach 2 is more effective for both ethers. The total yield for product **41** via benzyl ether is higher than via methyl ether and equals around 52 % and 21 % respectively. The lower yield in hydroboration-izomerization of benzyl ether is compensate by high yield of ether formation (Y = 100 %) and benzyl group removal (Y = 93 %) (Fig. 4-56).

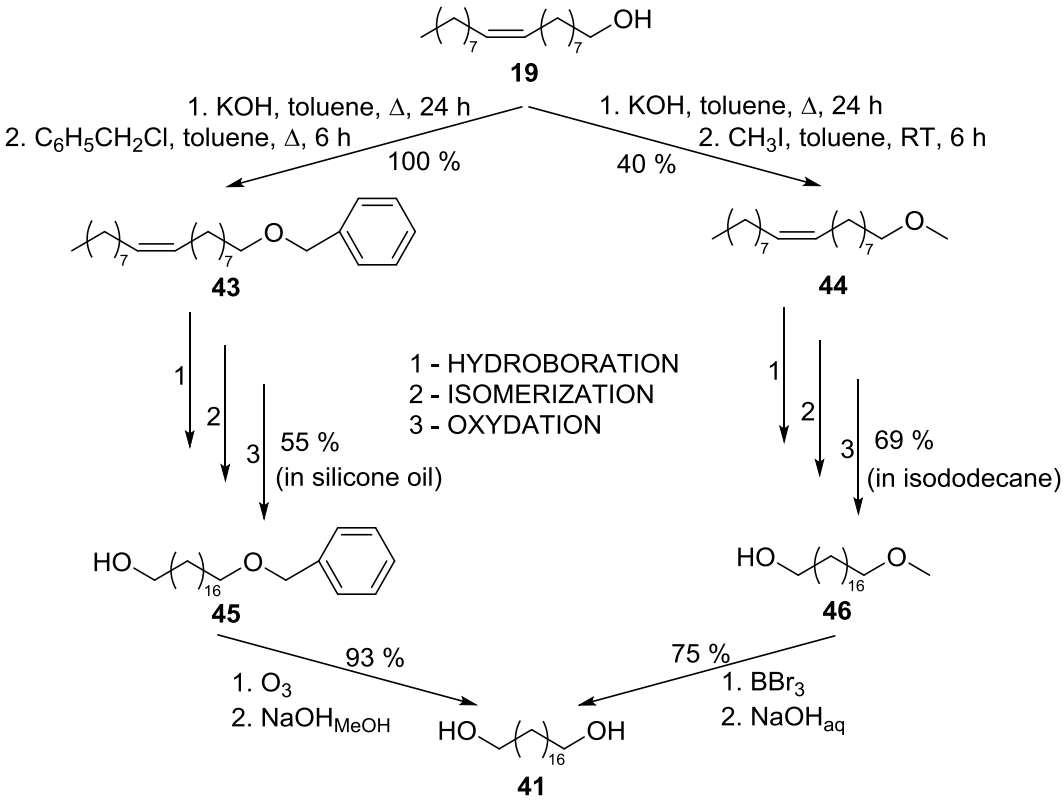


Figure 4-56 The overview of ether application in hydroboration-isomerization

4.4.4. The effect of the functional group in the chain.

The discussion above relates to functionalized olefin systems. In case a functional group is present more interaction takes place during hydroboration-isomerization. The influence of chain length and solvents type are not only one which occur during the reaction. Also a direct interaction of functional groups with the empty *p*-orbital of the borane could occur. This would lead to a very strong inhibition of any shift, what was proven during the reactions with esters. Especially free electrons on an atom can lead to strong interactions. This would imply that oxygen containing functional groups are inhibiting. The higher the electron density on the oxygen, the more inhibiting the oxygen would act. This correlates with the observation that a decrease in inhibition is observed in the series:

Carbonyl > benzyl ether > methyl ether > no function (=alkene)

As a consequence the best results are obtained for alkyl-ether functional groups. Another consequence is that the presence of molecules (solvent) containing strongly interacting groups blocks the isomerization. This is experimentally verified. The presence of even small amounts of ester blocks isomerization. Upon removal of this molecule by distillation, the isomerization initiates.

To study the interaction of functional groups and the empty *p*-orbital more in depth it is suggested to use boron-NMR. This can be part of further research.

4.5. Additional valorization potential for unsaturated fatty alcohols

Hydroboration-isomerization was selected at the start of this research to obtain long chain α,ω-bifunctional compounds. The possibility to shift, using borane, the double bond in long chain unsaturated mono-functional molecules has been proven. In this way is possible to obtain the envisaged molecules. Nevertheless, the whole process became more complicated than anticipated. Fatty acids cannot be used as such in hydroboration-isomerization. The same holds for the related fatty acid esters. Better starting materials are derivatives of fatty alcohols.

In this research also a second green method to synthesize alkyl and aryl ethers of fatty alcohols was found and optimized. The method is an extension of earlier work cited in the literature.[171-172] The less effective Williamson method to make ethers can be replaced by decarboxylation of dialkyl (or aryl alkyl) carbonates in the presence of a heterogeneous catalyst (hydrotalcite KW2000 ($Mg_{0.7}Al_{0.3}O_{1.15}$). As is well known that hydrotalcite is a synthetic aluminium-magnesium-hydroxycarbonate. Hydrotalcite-like anionic clays are a family of interesting materials with many practical applications as catalysts, catalyst supports, ion exchangers, and composite materials. Natural hydrotalcite, $Mg_6Al_2(OH)_{16}CO_3X4H_2O$, structurally similar to brucite ($Mg(OH)_2$) is composed of sheets of edge-sharing $Mg(OH)_6$ and $Al(OH)_6$ octahedrons. Due to isomorphous substitution of Al^{3+} for Mg^{2+}, the sheets are positively charged and stacked on top of each other and held together by charge-balancing anions, normally CO_3^{2-}, and/or hydrogen bonding. The Mg^{2+} and Al^{3+} in the sheets can also be isomorphously substituted by other metal ions having two or three positive charges and the CO_3^{2-} in the interlayer space by other inorganic and organic anions, forming new hydrotalcite-like materials. The general formula can be described as $[M_{1-x}^{2+}M_x^{3+}(OH)_2]^{x+}A_{x/n}^{n-}XmH_2O$, where M denotes metal ions, A denotes exchangeable anions with valence n, and x is within 0.17 – 0.33.[171-172] Hybrotalcite before being used in the reaction has to be calcinated at 800 °C. The calcination at lower temperature like 500 °C, decreases the catalytic activity of hydrotalcite.

Based on these findings, a new alternative concept to the upgrade of oleyl alcohol (**19**) was conceptualized. The decarboxylation of carbonates allows synthesizing long chain symmetrical unsaturated dialkyl ethers, such as for example dioleyl ether (**47**). Such unsaturated long molecules can then on their turn be subsequently ozonized and reduced to obtain long chain α,ω-bifunctional dialkyl ethers **48** with high yield (84 %) (Fig. 4-57). As a conclusion, a new method to obtain α,ω-bifunctional molecules is proposed.

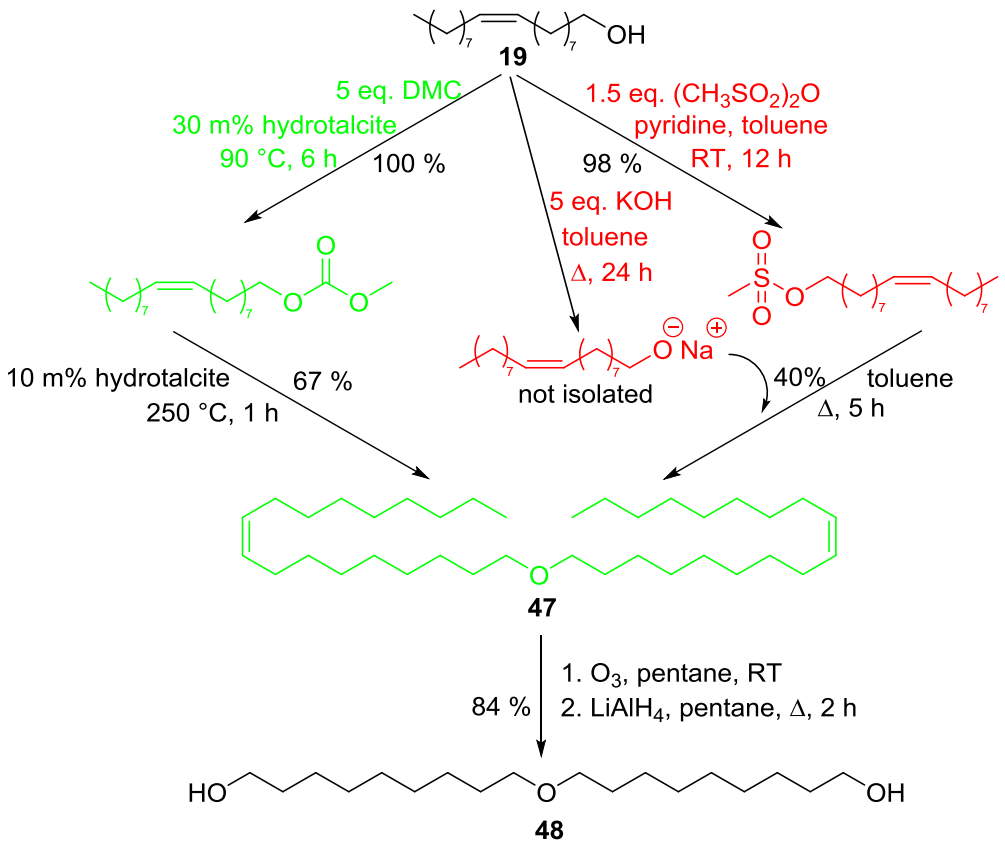


Figure 4-57 Synthesis of long chain α,ω-bifunctional dialkyl ether

Dioleyl ether (**47**) can be synthesized via a decarboxylation of a dialkyl carbonate in two ways. As presented in Figure 4-58, route A requires only two steps: (1) synthesis of methyl oleyl carbonate and (2) decarboxylation. The total yield of this approach is 67 % (of isolated product). Route B gave better yield (Y = 92 %), but requires three steps: (1) synthesis of methyl oleyl carbonate, (2) synthesis of dioleyl carbonate and (3) decarboxylation.

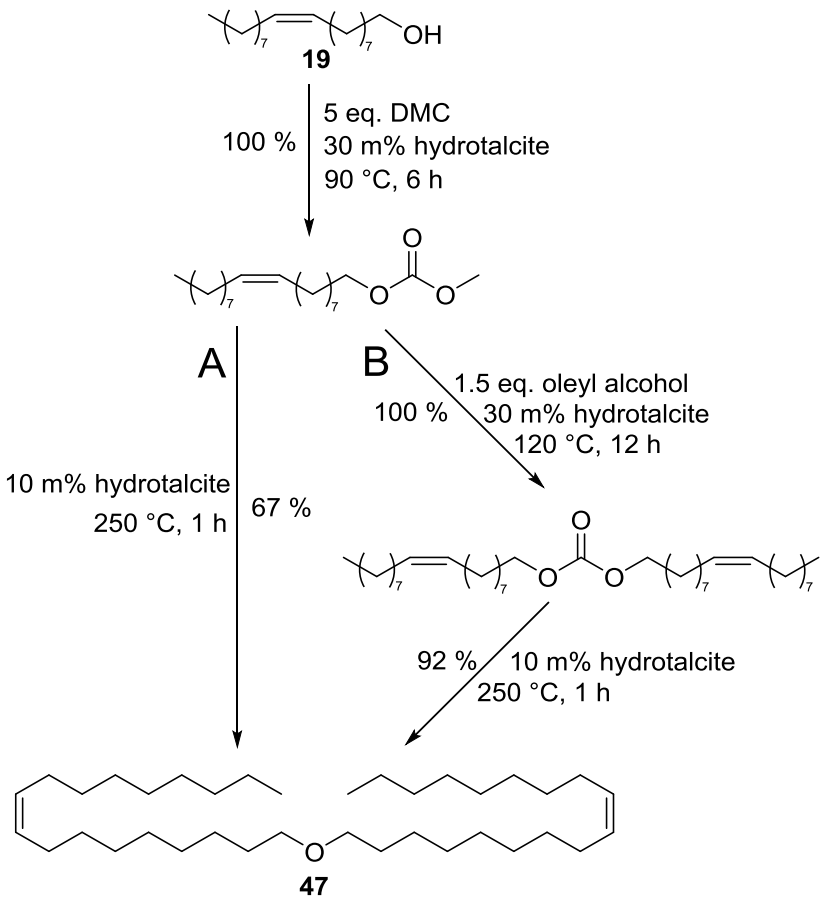


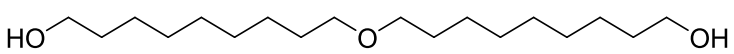
Figure 4-58 Synthesis of dioleyl ether by decarboxylation of carbonate ester

Both methods have strengths and drawbacks. In route A less steps are required to obtain the target molecule, but as side products methyl oleyl ether (25 %) and oleyl alcohol (8 %) are produced. In route B more steps are required, but the total yield is higher and as side product only oleyl alcohol is produced (8 %), which can be reused. After each step in the carbonate synthesis sequence a separation is required. After synthesis of methyl oleyl carbonate, the excess of DMC needs to be removed – this can be done on a rotary evaporator (b.p. of DMC: 90 °C). After synthesis of dioleyl carbonate, the excess of oleyl alcohol needs to be removed. This process can be done by distillation under reduced pressure (180 °C to 190 °C / 1 mbar). The removal of the alcohol is very important in order to reduce the amount of side product after decarboxylation. The comparison of both routes is given in Table 4-14.

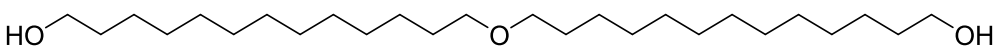
Table 4-14 The comparison of two routes to synthesize dioleyl ether by decarboxylation of dialkyl carbonate

	Factors	Route A	Route B
1	Yield	67 %	92 %
2	# steps	2	3
3	Required purification	Yes, after 2nd step	Yes, after 2nd and 3rd step
4	Time	1st step 3 h 2nd step 30 minutes	1st step 3 h 2nd step 12 h 3rd step 30 minutes
5	Recycle of side products	No – mixture of oleyl alcohol and methyl oleyl ether	Yes – only oleyl alcohol as side product

By combining the decarboxylation method and ozonolysis, long chain α,ω-bifunctional compounds can be obtained with high yields in a sustainable way. The overall yield of 9,9'-oxybis(nonan-1-ol) (Fig. 4-59) is 63 % when route A is used. Using route B, a yield of 86.5 % was obtained. When using a Williamson-based method (involving sulfonate as leaving group) to synthesize dioleyl ether and subsequently ozonizing the unsaturated ether, the total yield was found to be 38 %. As a conclusion, it can be stated that the decarboxylation/ozonolysis method B is superior in overall conversion. In the same way erucyl alcohol can give the interesting 13,13'-oxybis(tridecan-1-ol) (Fig 4-59).



9,9'-oxybis(nonan-1-ol) **48**



13,13'-oxybis(tridecan-1-ol) **49**

Figure 4-59 Interesting long chain diols obtained in alternative valorization of fatty alcohols

Especially the synthesis of asymmetrical α,ω bifunctional long chain compounds seems possible. Dioleyl ether and benzyl oleyl ether could find also additional applications in the synthesis of other long chain α,ω-bifunctional compounds. In the chapter "5. Conclusions and outlook" novel routes are presented using a combination of hydroboration-isomerization, decarboxylation and hydrogenation.

5. Conclusions and outlook

In this PhD work new routes for the valorization of unsaturated raw materials into valuable products were conceptualized and tested. More specifically, the aim of realizing a sustainable method for the preparation of long carbon chain α,ω-bifunctional molecules, starting from unsaturated long chain fatty acids and/or their derivatives, was satisfied by a new and comprehensive array of potential reactions, tailored at said long chain unsaturated molecules.

The experimental work performed proved that α,ω-bifunctional compounds can be synthesized in two different methods. The first method, based on boron chemistry, allows obtaining long chain terminal diols from unsaturated fatty ethers. The second method, based on long chain dialkyl ethers, allows obtaining terminal diols or diacids by ozonolysis of long chain unsaturated dialkyl ethers. Both methods, for the first time tailored at these long chain materials, have their strengths and weaknesses. The borane-based approach has a high carbon atom economy, whereas the dialkylether approach implies a loss of half a carbon chain of the starting alcohol. However, the borane chemistry involves more steps; inter alia the conversion of the fatty acids to the alcohols and subsequently to an ether. Additionally, it also involves cleavage of the ether to realize the desired products (diols). In this work also first steps toward optimization were taken, potentially leading to an overall economically viable process.

Several major (re)activity issues were encountered and resolved: (1) the influence of polar (coordinating) solvents on hydroboration-isomerization, (2) the inhibiting effect of carbonyl oxygen, (3) the isomerization of long chain alkenes, and (4) the difficulties with the removal of protecting groups (ether). Eventually, a comprehensive “toolbox” was generated, to be used in the conception and design of several possible conversion schemes.

The main novel findings of this doctoral research are: (1) hydroboration-isomerization of long chain alkenes is possible, (2) apolar solvents emphasize the conversion and kinetics of hydroboration-isomerization, (3) an improved economic process is possible by lowering the amount of boron necessary for reaction by incorporating the approach 1 – trialkyl borane with identical linear alkyl chains, (4) hydroboration-isomerization of functionalized olefins (unsaturated ethers) is possible, and (5) an alternative approach can lead to the similar α,ω-bifunctional

molecules via a sustainable synthesis of long chain dialkyl ethers with subsequent ozonolysis.

More specific, strategic conclusions leading to these general findings outlined above, can be summarized as follows:

- The chain length has an influence on the migration of boron along carbon chains. The longer the chain, the lower the conversion. This relation is observed very well in approach 1 (trialkylborane with identical alkyl chain) and allowed us to formulate a possible explanation called the “spaghetti effect”: in trialkylborane with linear long chain alkenes a high degree of disorder could lead to entanglement, preventing a shift of the double bond. In contrast, cyclic alkenes which possess less conformational flexibility but will still give a strong overall steric hindrance and direct the isomerization efficiently to the terminal position.
- The lower conversion in approach 1 can also be explained by an additional effect, confirmed by a series of experiments and called the “zipper effect”: when the boron position is shifted more and more towards the external position, the steric hindrance is lowering. This happens much faster in approach 1 than in approach 2, explaining the experimental observation that approach 1 leads to lower isomerization compared to approach 2.
- The type of solvent plays a major role in the isomerization process and two possible explanations can be presented. (1) The polar (coordinating) solvent interacts directly with the empty *p*-orbital of the boron atom making the H-acceptance more difficult or (2) the polar solvent induces indirectly an effect through the change in conformation of alkyl chains which subsequently has an effect on steric hindrance executed by the alkyl chains. By replacing the polar solvent by an apolar (non-coordinating) solvent the conversion can be significantly increased.
- Typical apolar (non-coordinating) solvent that can be used are: linear and branched saturated hydrocarbons, aromatic hydrocarbons, silicone oils.
- The hydroboration-isomerization reaction is a temperature dependent reaction. The minimum temperature for isomerization of long chain olefins is 120 °C. Moreover, the temperature has an influence not only on the kinetics, but also on the conversion.
- The average equilibrium for hydroboration-isomerization of long chain alkenes is 80 % : 20 % (terminal : internal). This equilibrium was confirmed also by a control hydroboration – isomerization reaction applied on an alkene with a terminal double bond.

- Carbonyl compounds are not suitable for hydroboration-isomerization. A hypothesis was formulated and confirmed by series of experiments: during the isomerization step carbonyl oxygen is able to permanently occupy the empty *2p* orbital of boron (intra- and/or intermolecular) thereby suppressing to even inhibiting the isomerization activity of the borane.
- Acetals, as a protected form of alcohols, are not stable under hydroboration-isomerization conditions. Therefore they cannot be used as a protection group
- Ethers are stable under hydroboration-isomerization conditions and hence are useful as protection group.
- Methyl oleyl ether gave better isomerization results than benzyl oleyl ether. This might be due to the fact that the aromatic moiety in the benzyl group induces a larger polarity to the ether oxygen. This could in turn give a stronger interaction with the borane, suppressing to some extent the hydroboration-isomerization. Further experiments are however necessary to confirm this hypothesis.
- Alkyl and aryl ethers of unsaturated fatty alcohols can be synthesized in a sustainable way with high yield.
- Unsaturated dialkyl or aryl alkyl ethers could allow for an additional valorization path of unsaturated fatty alcohols by ozonolysis.

Outlook and perspectives

Based on the performed experiments it is unclear whether only chain length has an influence on the conversion. A series of experiments with different methyl alkyl ethers could be examined as shown in Figure 5-1 (left) in a similar way as was done for alkenes. The influence of the chain length in unsaturated fatty ethers could be examined also by a series of experiments where different alkyl oleyl ethers would be tested (both linear and branched) (Fig. 5-1 right).

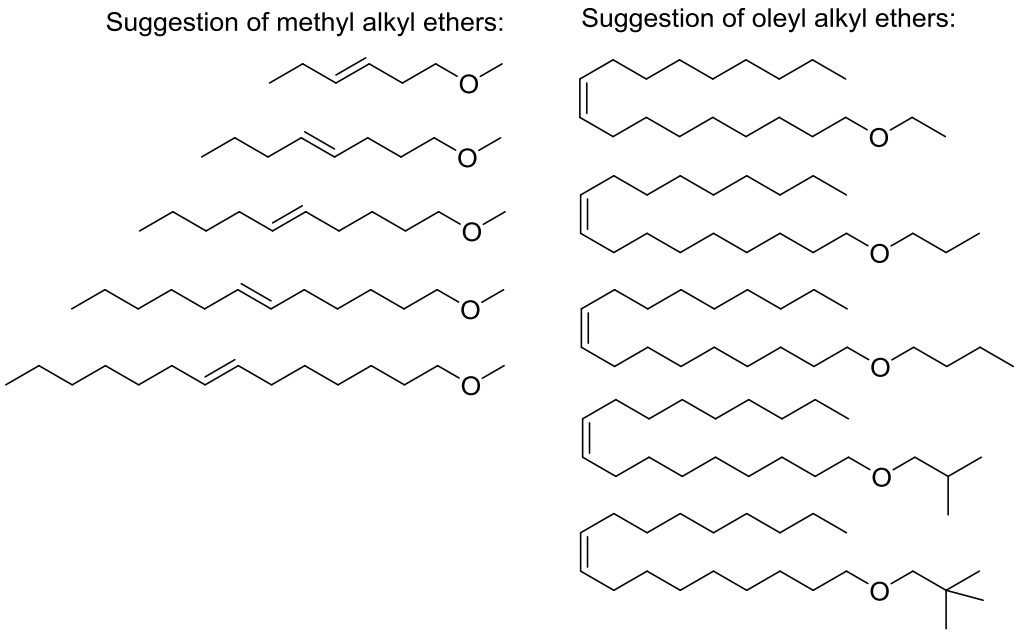


Figure 5-1 The suggestion of interesting unsaturated methyl alkyl ethers (left) and dialkyl ethers (right) for further development in hydroboration-isomerization

An interesting perspective could also be the hydroboration-isomerization of long chain dioleyl ether. This molecule could yield a very long chain α,ω-bifunctional compound as presented in Figure 5-2. In this molecule a chain of up to 35 atoms could be constructed. This is however to be experimentally validated.

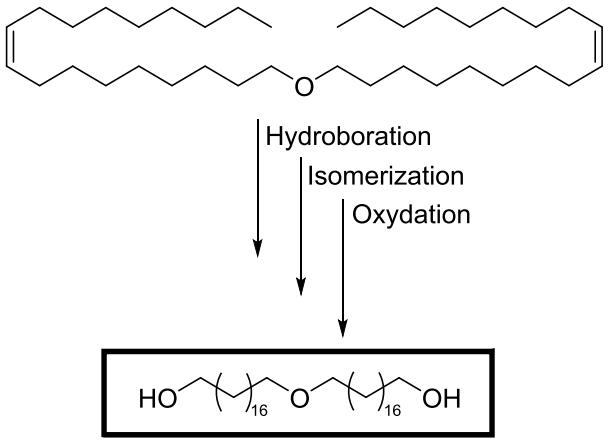


Figure 5-2 Highly interesting very long α,ω-bifunctional molecule

The envisioned new, innovative etherification methods are of high importance to develop industrially feasible routes for the production of long chain α,ω-bifunctional ether monomers from unsaturated free fatty acids. Such materials would yield cheap versatile oligomeric and polymeric materials with unprecedented physico-chemical

and mechanical properties. One highly desired characteristic of this new class of materials would be their biodegradability.

Possible strategic objectives for further research

1. Reduce unsaturated free fatty acids in a selective way to the corresponding unsaturated alcohols, in a robust, green and cost effective way. This implies finding an alternative method to the standard $LiAlH_4$ reduction. The method should be selective towards the carboxylic acid, without reducing the double bond. This because the double bond is crucial for the α,ω-functionalization of the ether monomer product. The method has to work on a variety of common FFAs.

2. Understand the decarboxylation mechanism under influence of calcined hydrotalcite catalyst, formulate alternative catalysts, and check whether the process would be suitable for other FFAs. Additionally, similar decarboxylation reactions could be explored for the production of asymmetrical α,ω-bifunctional monomers, allowing larger bifunctional monomer versatility. One potential strategy could be to produce the asymmetrical benzyl oleyl carbonate, in which the benzyl protects the alcohol during hydroboration-isomerization of the unsaturated chain.

3. In a quantitative way, make tradeoffs and selections in each reaction step based on the environmental impact and cost of various alternatives.

4. Design asymmetric α,ω bifunctional materials (as shown and elucidated in Figure 6-3: acid/acid – alcohol/alcohol – alcohol/acid.

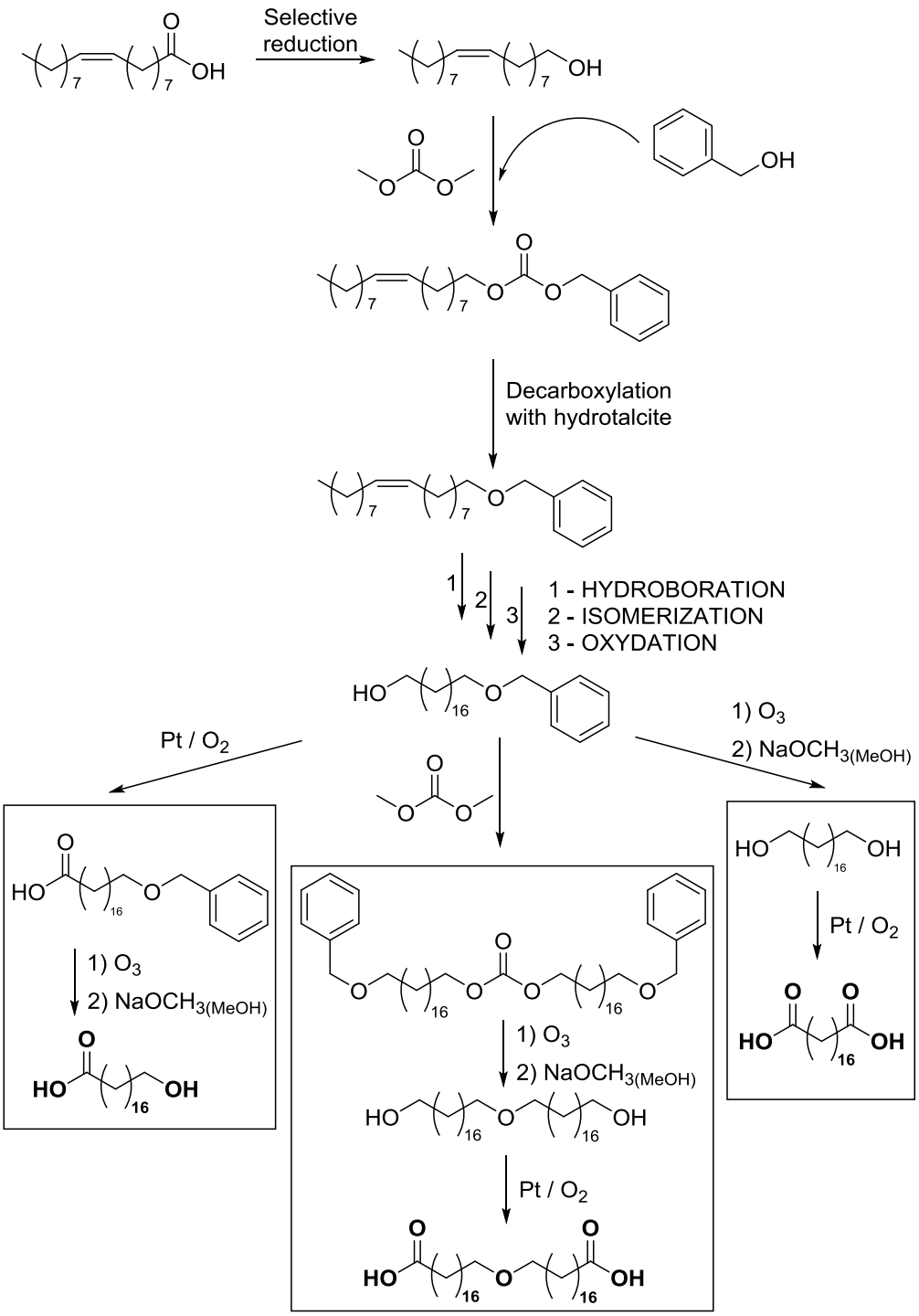


Figure 5-3 Reactive sequence for the production of (a)symmetric α,ω-bifunctional compounds

6. Starting materials for hydroboration-isomerization

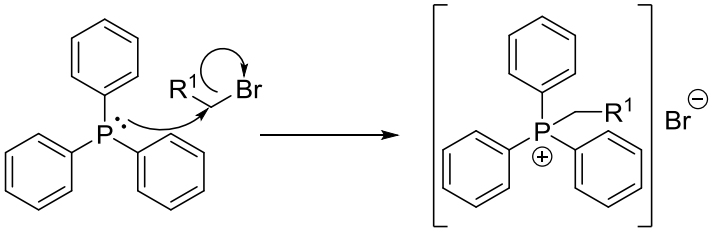
6.1. Long chain alkenes

Because of the lack of long chain alkenes (with internal double bond) on the market, these alkenes were synthesized in-house. Two different methods were applied. (Z)-5-decene, (Z)-6-dodecene and (Z)-7-tetradecene were obtained by means of the Wittig reaction. 8-Heptadecene and 9-heneicosene were synthesized via oxidative decarboxylation of related fatty acids.

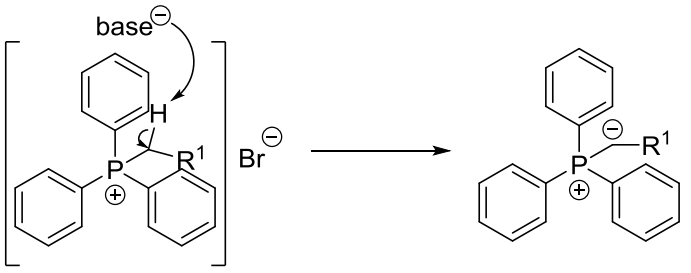
6.1.1. Wittig reaction

Three long chain alkenes were synthesized by the Wittig reaction. The synthesis procedure was taken from a literature source[173], but some significant parameters were optimized – temperature and dilution. Benzene as a solvent was replaced by less toxic toluene. A typical Wittig reaction starts with a phosphonium salt, which is treated with a strong base and then with a carbonyl (aldehyde or ketone only) compound. This reaction is water and oxygen sensitive, therefore it was always performed under argon atmosphere and under anhydrous conditions (by means of a Schlenk Line). The mechanism begins with an attack of the ylide on the carbonyl group. This reaction generates negatively charged oxygen that attacks the positively charged phosphorus and gives a four-membered ring called an oxaphosphetane. Now, this four - membered ring is unstable, and it can collapse in a way that forms two double bonds. The overview of this 4-step mechanism is given below[16].

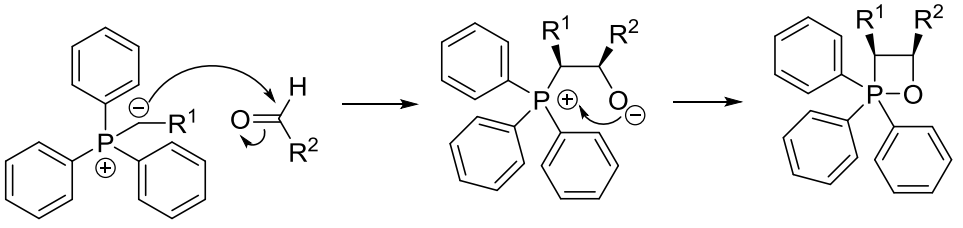
STEP 1: Formation of phosphonium salt – nucleophilic substitution:



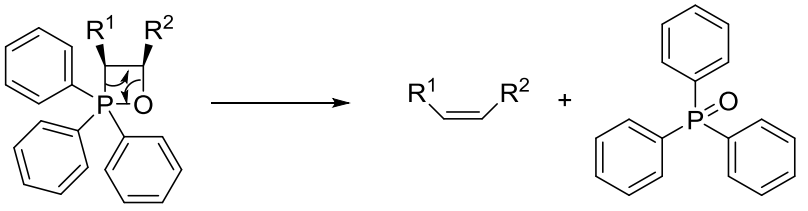
STEP 2: Formation of ylide – deprotonation (betaine formation):



STEP 3: Nucleophilic attack on the carbonyl group:



STEP 4: Decomposition of the four - membered ring:



Optimization of the Arbuzov reaction

The low yield of the reaction carried out under the same conditions as they are described in Vogel's text book[173] required optimization. The crucial part of the whole process is the synthesis of the phosphonium salt (Fig. 6-1). Below, the influence of different parameters is described. The optimization was performed during the synthesis (1-hexyl)triphenylphosphonium bromide. The best conditions were selected and used during the synthesis of other salts.

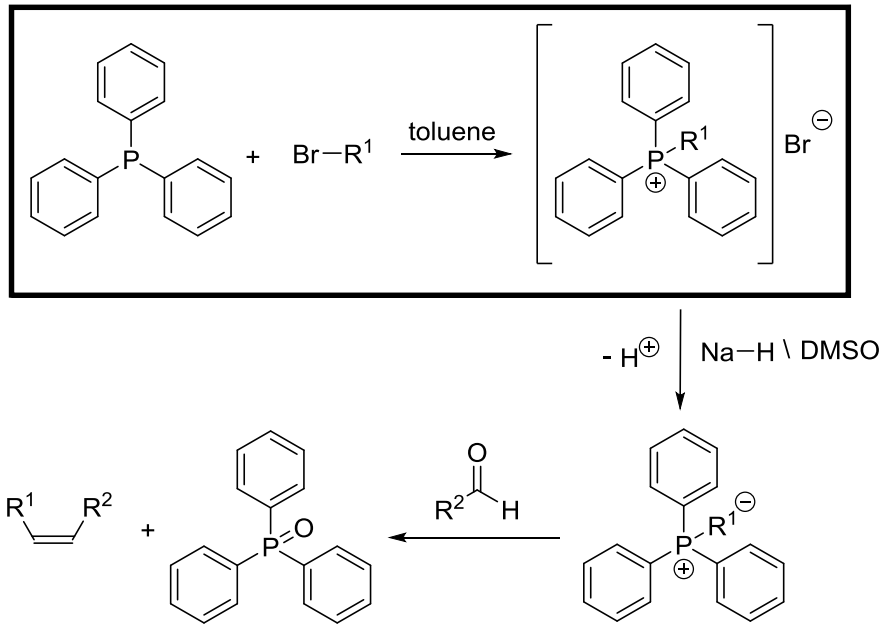


Figure 6-1 The overview of Wittig reaction. Step 1 - synthesis of phosphonium salt

Vogel's method:

In Vogel's method 1 eq of triphenylphosphine is dissolved in dry toluene and mixed with 1.33 eq of 1-bromoalkane. The amount of solvent (toluene) should be equal by volume to the amount of alkylbromide. The reaction mixture is stirred overnight at room temperature. After several hours a precipitate was observed. This was filtered under reduced pressure and the resulting white crystals of phosphonium salt were washed with toluene and dried. Unfortunately this approach brings low yield for longer chain alkylbromide (0.43 % of isolated yield from 1-bromohexane)

Influence of temperature:

By increasing the temperature from room temperature to reflux temperature (approximately 110 °C) 61.5 % of yield was achieved. The concentration and time was exactly the same as for procedure above.

Influence of dilution:

In the next step of the optimization a larger amount of solvent was used. According to Vogel's procedure, the amount of solvent should be equal by volume to the amount of bromoalkane. During the first reactions it was observed that the produced amount of phosphonium salt prevented good mixing. Therefore, double and triple of the amount of solvent was tested. With a double amount of solvent 93.2 % of

isolated yield was obtained, whereas with triple amount of solvent 80.5 % was obtained (for 1-bromohexane).

The aforementioned results showed that the high temperature and stronger dilution are required in order to obtain high yield of phosphonium salt. In Vogel's method a short chain salt was synthesized (ethyltriphenylphosphonium bromide). In the research longer bromoalkanes were used. This could explain why higher temperature and bigger dilution are necessary. The longer bromoalkanes are less reactive and more sterically hindered. Undoubtedly reflux and dilution help to create the phosphonium salt.

Symmetrical Z-alkenes

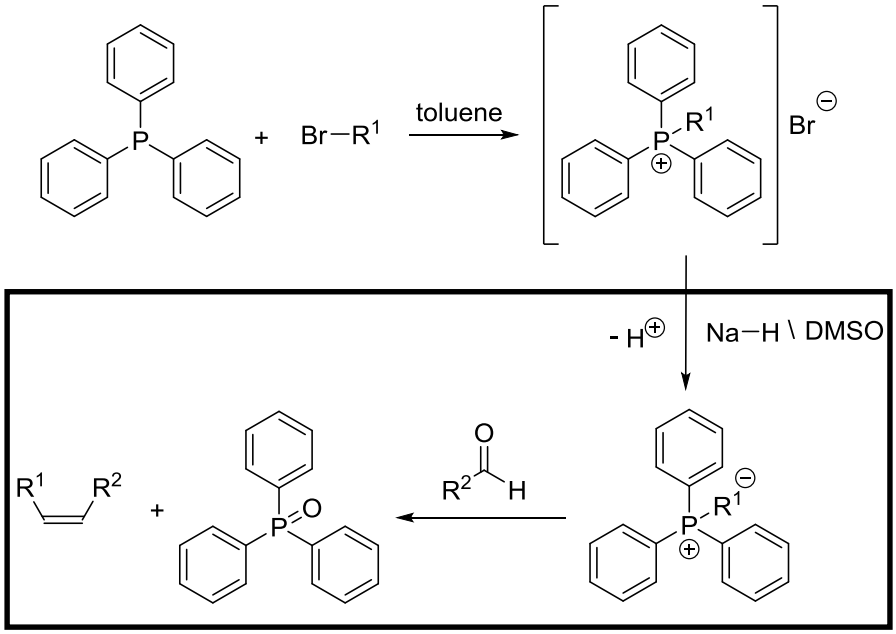


Figure 6-2 The overview of Wittig reaction. Step 2 - synthesis of symmetrical (*Z*)-alkenes

Synthesis of symmetrical (*Z*)-alkenes involves a two-step reaction (Fig. 6-2). The first step is formation of ylide (**49**) by the reaction of phosphonium salt (**48**) with sodium hydride, which in second step reacts with aldehyde giving (Z)-alkenes (**50**) and triphenylphosphine oxide (Fig. 7-3). The usage of unstabilized phosphine ylide leads to formation of (Z)-alkenes, in contrast to stabilized phosphine ylide which, gives (E)-alkenes.

The yields of each crucial step for all three synthesized alkenes are presented in Table 6-1.

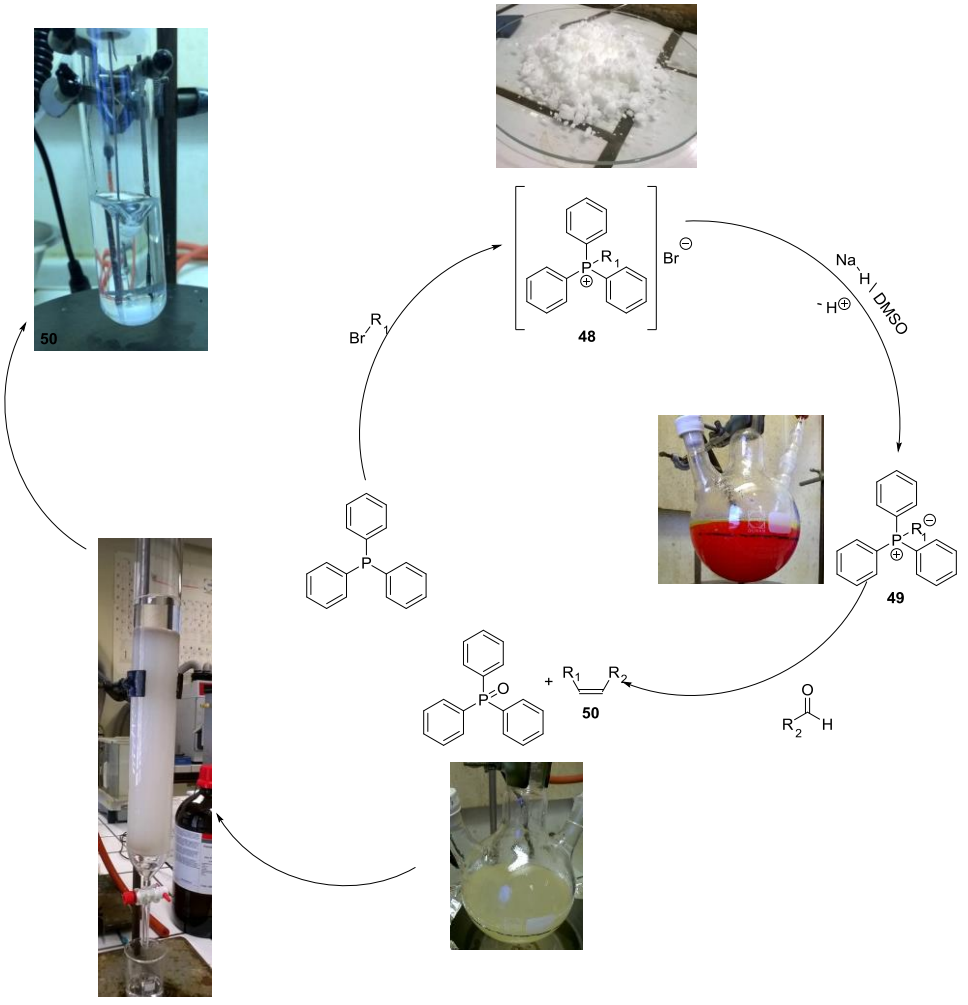


Figure 6-3 Overview of the synthesis of (*Z*)-5-decene

Table 6-1 The yields of each crucial steps during the synthesis alkenes

	Yield after Arbuzov reaction [%][a]	Yield after Wittig reaction [%][a]	Total yield [%][a]
5-decene	89	33	29
6-dodecene	93	33	30
7-tetradecene	93	41	38

[a] Determined by mass balance

Conclusions:

The alkenes synthesis method discovered by Wittig worked well during the research. As expected, the first step, in which the phosphonium salt is created, was the most problematic. That is why this process was scrutinized in view of optimization. It has been proven that the most efficient way to synthesize triphenylphosphonium bromide is using a double amount of toluene with reference to the amount of alkyl bromide and heating the reaction mixture at reflux temperature for at least several hours. Unfortunately, in one case this method failed. During the research, the reaction of obtaining (1-octyl)triphenylphosphonium bromide did not give the product, so this leaves the question why in this case the salt was not obtained. In this step the temperature has a large impact, and probably the reaction with 1-bromooctane needs higher temperature. It has been proven, that for methyl bromide 25 °C is enough to obtain the corresponding phosphonium salt. For the reactions with 1-bromopentane, 1-bromohexane and 1-bromoheptane the reflux temperature of toluene (111 °C) was necessary. Thus, probably the solution for the problem in reaction with 1-bromooctane, lies in changing the solvent for another one with higher boiling point, which allows carrying out the reactions at higher temperature or more polar solvent. Promising results have been obtained with ionic-liquid-promoted Arbuzov reaction[174] and microwave-assisted reaction Arbuzov reaction[175-176].

Considering the results obtained from the synthesis of alkenes, it can be concluded that steric hindrance further increases the yield of alkenes. Probably, the larger size of reacting aldehyde with ylide favors cutting the two bonds in four-membered-ring oxaphosphetane and results in more molecules of alkenes. That is an explanation why higher yields were obtained in reactions in which the compounds having a greater number of carbon atoms in the molecule were used.

6.1.2. Oxidative decarboxylation

Two alkenes that have been used in the research were synthesized by oxidative decarboxylation of the corresponding fatty acids. These fatty acids are carboxylic acids with a long unsaturated aliphatic chain. In this research oleic acid (C18:1) and erucic acid (C22:1) were used. Both 8-heptadecene and 9-heneicosene were prepared by a silver(II)-catalyzed oxidative decarboxylation (catalytic silver(I) was oxidized in situ to silver(II) by sodium peroxydisulfate), following a procedure described in the literature.[177] Starting from a saturated or unsaturated carboxylic acid, the carboxylic group was removed and an alkene was obtained. As described by van der Klis *et al*.,[177] the presence of copper(II) determined whether a new carbon-

carbon double bound was created. As shown in Figure 6-4, this reaction can be used to prepare internal and external alkenes.

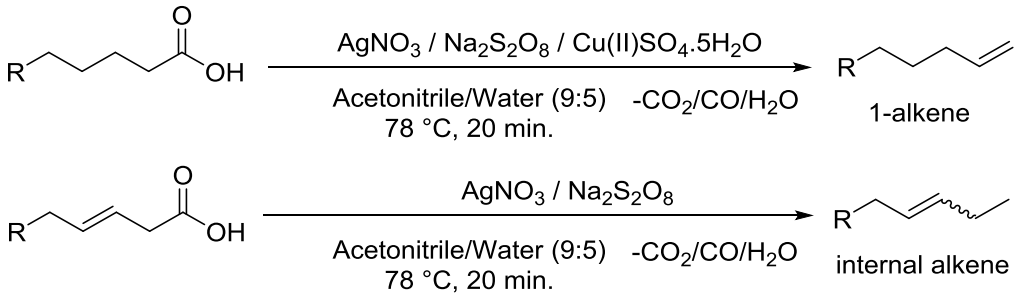


Figure 6-4 Oxidative decarboxylation

The reaction mechanism is not completely understood. Nevertheless the proposed reaction cascade and potential mechanism for competitive oxidant consumption is described in the literature by various authors.[178-179] Figure 6-5 gives a view at the assumed mechanism and consecutive reactions.

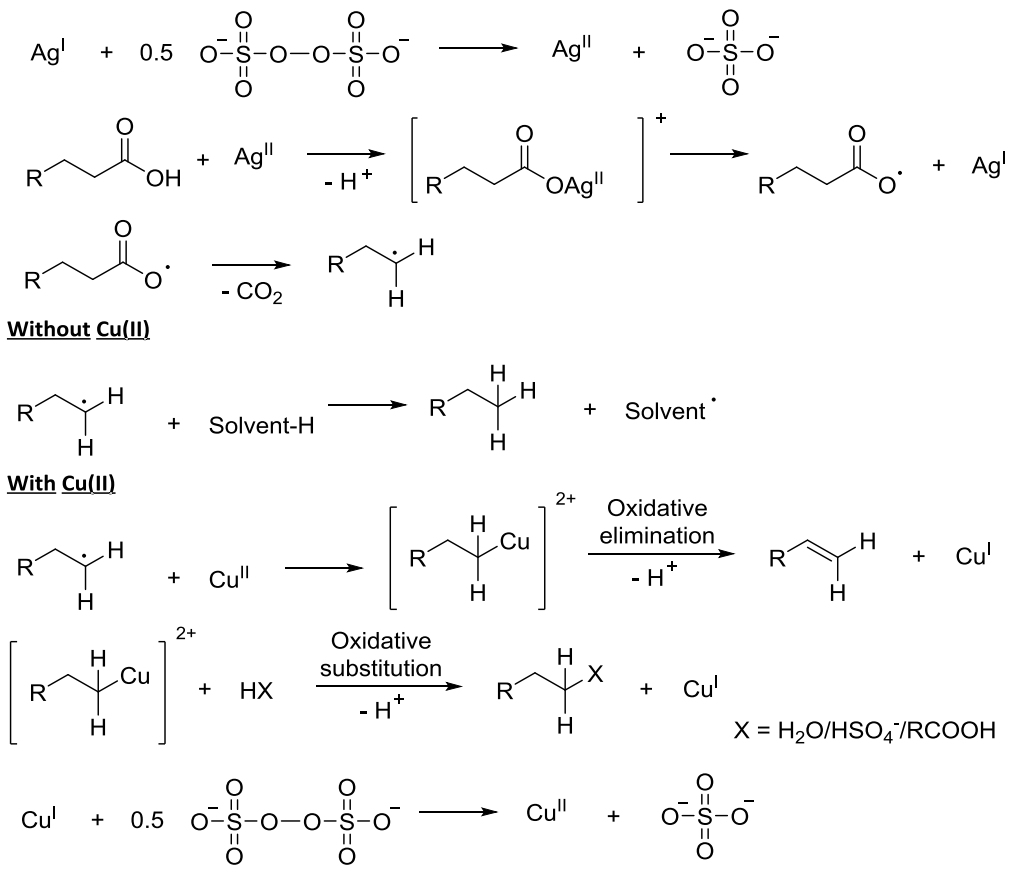
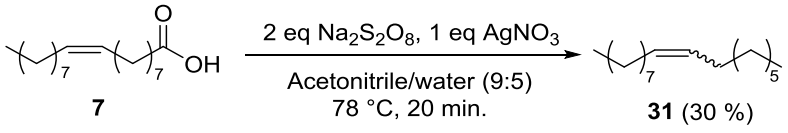


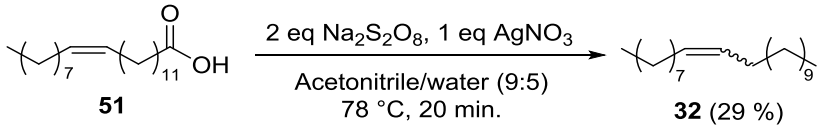
Figure 6-5 Suggested mechanism of oxidative decarboxylation

Decarboxylation of oleic and erucic acid



7 **31** (30 %)

Figure 6-6 Synthesis of 8-heptadecene



51 **32** (29 %)

Figure 6-7 Synthesis of 9-heneicosene

8-heptadecene (**31**) was obtained by oxidative decarboxylation of oleic acid (**7**) (Fig. 6-6) with silver nitrate and sodium peroxydisulfate. The isolated yield is 30 %. 9-henicosene (**32**) was synthesized analogous to the alkene **31** from erucic acid (**51**) (Fig. 6-7). The yield of the reaction was 29 %.

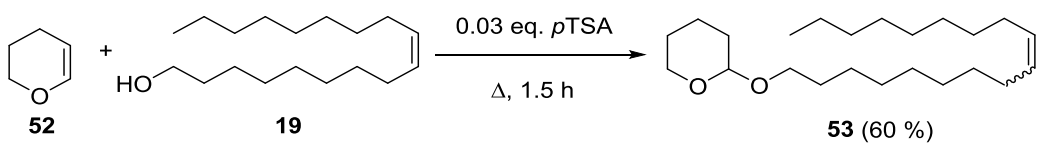
Conclusions:

Oxidative decarboxylation of unsaturated fatty acids is an easy method to obtain long chain internal (or external) alkenes. In comparison to other methods (e.g. thermal decarboxylation in supercritical condition) it does not require a very high temperature and pressure. The time (20 minutes) required is much shorter than for other methods. The yield and type of side products (mostly oligomers and polymers, due to the presence of double bond) is comparable with other methods.

6.2. Acetals

Oleyl tetrahydropyranyl acetal

One of the protecting groups was tetrahydropyranyl ether (THP-OR). This protective group is extensively used in chemical synthesis. The low cost, easy reaction method, stability to most non-acidic reagents and the easy deprotection are the greatest advantages. The formation can be done with dihyropyran and *p*-toluenesulfonic acid (*p*TSA) monohydrate as a catalyst[180] (Fig. 6-8)



52 **19** **53** (60 %)

Figure 6-8 Synthesis of oleyl tetrahydropyranyl acetal

Oleyl tetrahydropyranyl acetal (**53**) was obtained by reaction of 3,4-dihydro-2*H*-pyran (**52**) with oleyl alcohol (**19**). In order to obtain the final pure product flash chromatography was performed, using silica gel and petroleum ether / ethyl acetate (9.5 : 0.5 v/v) as eluent. The pure acetal is eluted as the first fraction. The used eluent was optimized by TLC (Fig. 6-19). Oleyl tetrahydropyranyl acetal was obtained with 60 % of yield.

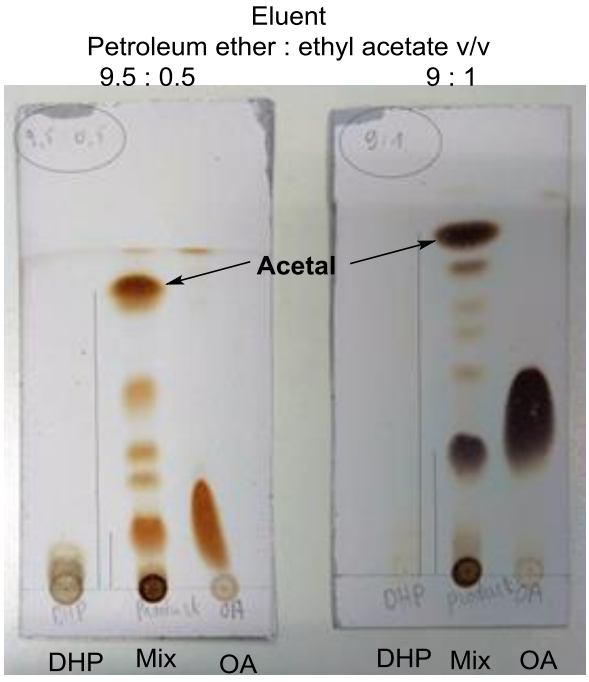


Figure 6-9 The separation of crude product on TLC with different eluents

Benzaldehyde dioleyl acetal

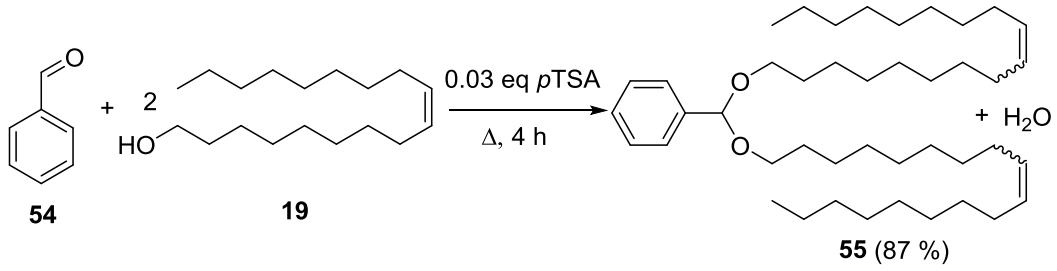


Figure 6-10 Synthesis of benzaldehyde dioleyl acetal

In the analogous way to the compound **53** benzaldehyde dioleyl acetal (**55**) was synthesized (Fig. 6-10). Instead of dihydropyran (**52**) benzaldehyde (**54**) was used as protective molecule. The purity of the product was determined by means of gel permeation chromatography (GPC) (Fig. 6-11) which is a useful technique to distinguish the molecules with big difference of molecular weight. The isolated yield of compound **55** is 87 %.

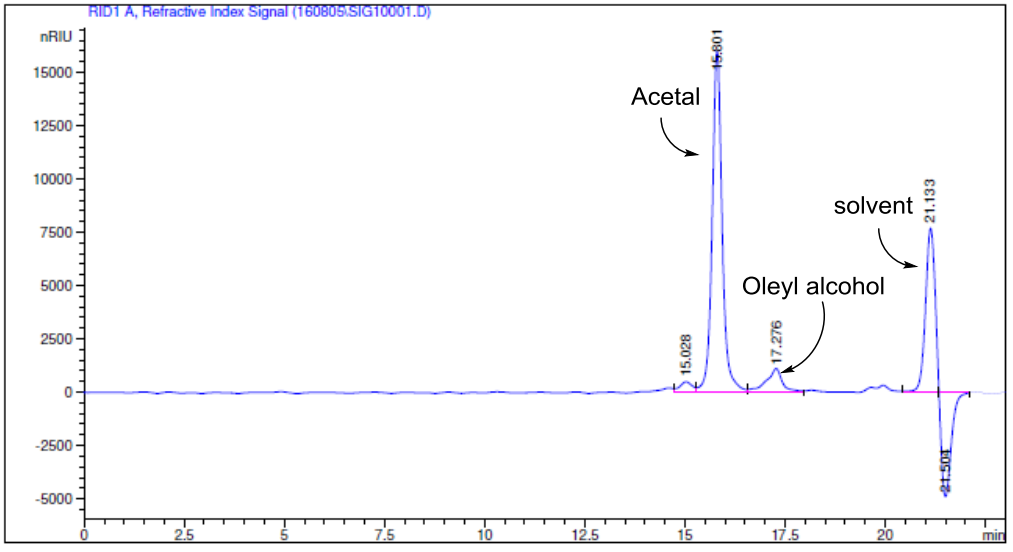


Figure 6-11 GPC chromatogram for final product

6.3. Ethers

6.3.1. Methyl oleyl ether

Methyl oleyl ether (**44**) was synthesized via three different approaches (Fig. 6-12). The first method is the classical Williamson synthesis which is the conventional and most common reaction for ether syntheses. The synthesis was first described by Alexander Williamson in 1850. The second method is the modified Williamson synthesis where organohalide is replaced by methyl methanesulphonate (MMS).[181] The third method involves decarboxylation of dialkyl carbonate (in this case methyl oleyl carbonate) in the presence of a heterogeneous catalyst (hydrotalcite).[172] In this approach methyl oleyl ether is the side product of synthesis of another valuable molecule – dioleyl ether (see section 4.5.)

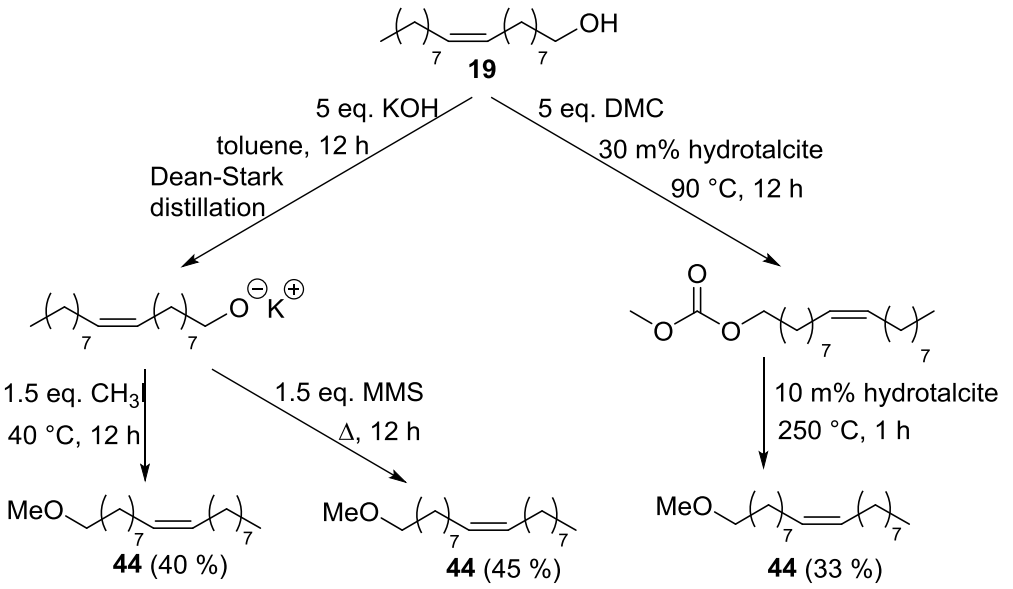


Figure 6-12 Different methods of methyl oleyl ether synthesis

Two first methods which base on Williamson synthesis of ether gave similar yields – 40 % and 45 %. Decarboxylation of methyl oleyl carbonate gave lower yield – 33 %, but it is more green and economic valuable methods. The further optimization is required. The hypothesis is that by decreasing the temperature of decarboxylation more methyl oleyl ether can be obtained as opposed to dioleyl ether.

6.3.2. Benzyl oleyl ether

In similar way to methyl oleyl ether, benzyl oleyl ether (**43**) was synthesized (Fig. 6-13). The first method is the conventional Williamson synthesis with benzyl bromide which gave 100 % yield. The second more sustainable method is decarboxylation of benzyl oleyl carbonate with hydrotalcite. In this method the yield is much lower – around 40 % and as side products dibenzyl and dioleyl ethers were obtained.

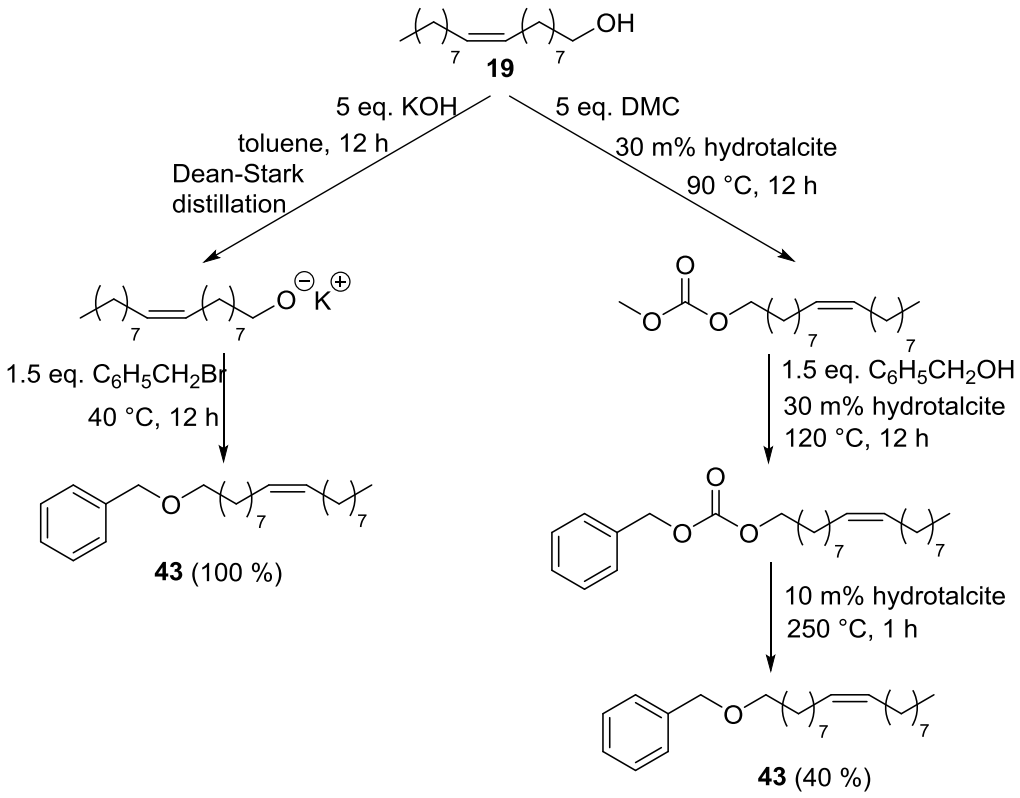


Figure 6-13 Different methods of benzyl oleyl ether synthesis

The stability of both methyl and benzyl ether was checked by the treatment of saturated version of these ethers (cetyl methyl ether and benzyl cetyl ether) with the hydroboration-isomerization condition (with dicyclohexylborane). After 24 h of heating at 160 °C only 6 % of benzyl cetyl ether and 2 % of cetyl methyl ether were degraded to the cetyl alcohol.

7. Deprotection methods

7.1. Ether cleavage with boron tribromide

The first purpose ether cleavage is the deprotection of the hydroxyl group and as the consequence creation of bifunctional molecules. The second target is the cleavage of the long ether containing 36 carbons (only for analytical purpose). The synthesized products have to be measured on the GC to identify the structures. Unfortunately the molecules are too long. A way to cut the products in 2 parts has to be found. The GPC doesn't give enough information about the specific structures.

Boron tribromide is an excellent Lewis acid which can be used for the cleavage of an ether bond, as a very good demethylating or dealkylating agent. It is a toxic fuming liquid. The solvent used in the experiments is dichloromethane because boron tribromide reacts violently with protic solvents. The great advantage is that the reaction can occur under mild conditions.

The reaction proceeds via a complex formed between the reagent and the ethereal oxygen atom. The formation of a dibromo(organo)borane is very important. The cleavage occurs via a bimolecular mechanism (S_N2). Afterwards the dibromo(organo)borane undergoes a hydrolysis to give a hydroxyl group (Fig. 7-1).

Boron tribromide as a strong Lewis acid can accept a pair of free electrons from the ether oxygen.

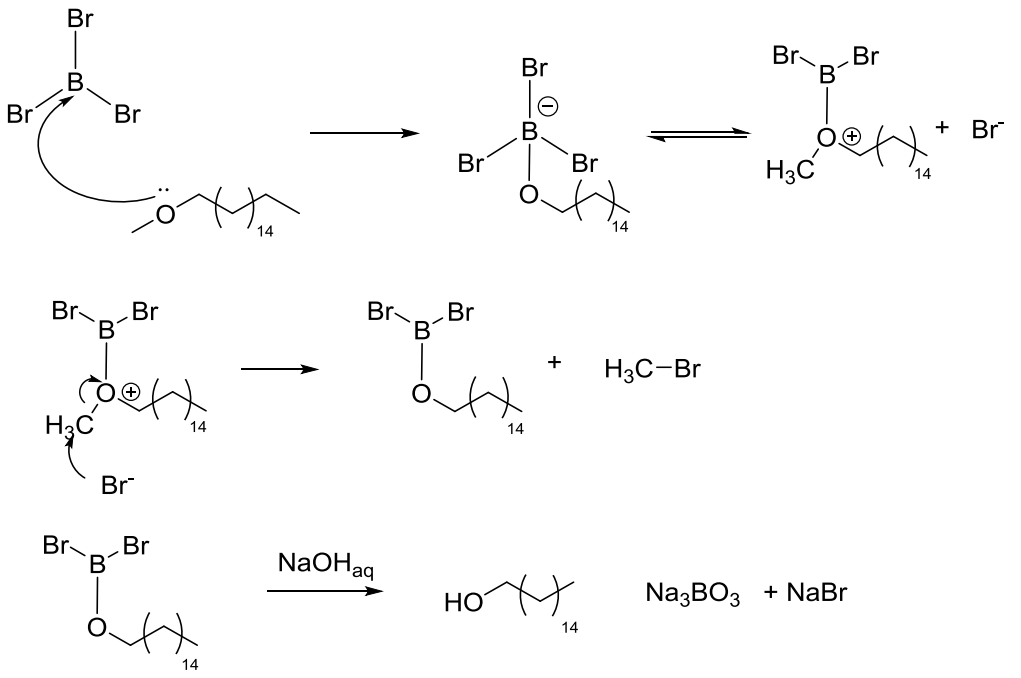


Figure 7-1 Ether cleavage with boron tribromide

7.2. Ozonolysis

Benzyl ethers provide a good protection and allow the deprotection to occur in mild conditions. Several methods for cleavage of benzyl ether are described in literature including hydrogenolysis[182] or transfer hydrogenation[183] where an alternative hydrogen transfer source is used, acetolysis[184] and Lewis acid[185] systems. These methods can cause complications of selectivity and reaction kinetics when multiple functionality is present in the molecule.

Deprotection can also be realized through oxidative techniques. [186] Oxidation with ozone is a commonly applied method that provides mild deprotection of the ether group. This method is called ozonolysis and has the advantage that ozone can be generated from oxygen in air. The deprotection with ozone consists of two steps. In the first step the concerned benzyl cetyl ether (**56**) is oxidized by the ozone into cetyl benzoate (**57**) which is subsequently hydrolyzed into cetyl alcohol (**58**) and benzoic acid (**59**) (Fig. 7-2).

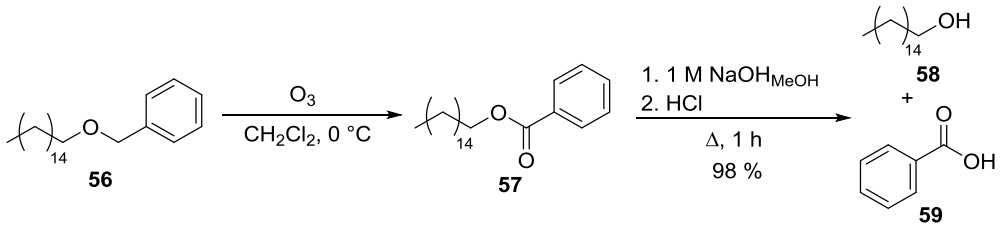


Figure 7-2 Ozonolysis and subsequent hydrolysis of benzyl cetyl ether

8. Experimental part

8.1. Analytical methods

8.1.1. GC-MS

GC-MS was performed on Shimadzu GCMS-QP2010S equipped with a Phenomenex ZB-5MS capillary column (L = 30 m, ID = 0,25 mm, df = 0,25µm), heating method: 50 °C (2') – 10 °C/min – 220 °C (5') – 10 °C/min – 300 °C, inert gas: helium, flow: 1.5 mL/min). Type of ionization: Electron ionization (EI). Front inlet (S/SL): Mode: split (ratio 5), temperature: 250 °C, inert gas: helium.

8.1.2. GC-FID

GC-FID was performed on Agilent Technologies 6890N Network GS-System equipped with the same capillary column, operated with the same parameters as GC-MS. Front inlet (S/SL).Mode: splitless, temperature: 250 °C, Pressure: 1.13 Bar (16.4 psi). Front detector (Flame ionization detector), temperature: 300 °C, H_2 flow: 30 mL/minute, air flow: 400 mL/minute

GC-FID and GC-MS were used complementary, therefore in both instruments the same columns were installed. The heating method is exactly the same. The flow of carrier gas is identical. GC-FID was mostly used for quantitative measurement. The response factors for different alcohols (Fig. 8-1) were examined (Table 8-1).

Relative response factors are derived from the reference solution results as shown (as example) in Table 8-1, in which the weight and area data are from experimental data and the response column data are obtained by dividing areas by weights.

Table 8-1 The reference solution

Compound	Mass (mg)	Area	Response	Relative response
Active X	39.4	480105	12185	1.05
Active Y	40.2	438002	10896	0.94
Internal standard	35.8	450119	11601	1.00

Relative responses are obtained by dividing responses by the response of the internal standard. The experimentally determined data and the calculated response for the internal standard are shown entered in Table 8-4.

Table 8-2 Measured data for the sample solution

Compound	Mass (mg)	Area	Response	Relative response
Active X	-	497423	-	1.05
Active Y	-	438002	-	0.94
Internal standard	40.5	450119	10746	1.00

Responses for the actives can be obtained by multiplying the internal standard response by the appropriate relative response factors, and the weights of the actives are calculated, remembering that response is area/weight. The completed calculation is shown as Table 8-3.

Table 8-3 Measured and calculated data for the sample solution

Compound	Mass (mg)	Area	Response	Relative response
Active X	44.1	497423	11203	1.05
Active Y	40.9	438002	10101	0.94
Internal standard	40.5	450119	10746	1.00

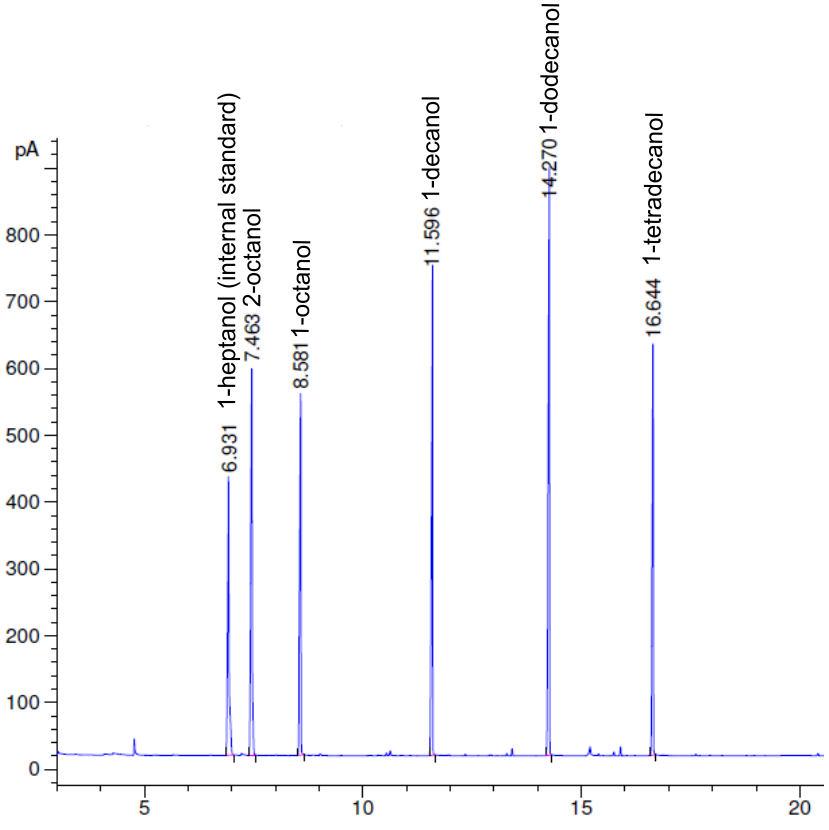


Figure 8-1 Analysis of different alcohols by means of GC-FID

Table 8-4 Relative response factors for different alcohols

	Alcohol	Relative response factor
1	1-heptanol (internal standard)	1
2	1-octanol	1.0018
3	2-octanol	1.0032
4	1-decanol	1.0075
5	1-dodecanol	1.0668
6	1-tetradecanol	1.0822
7	1-heptadecanol	1.1089
8	8-heptadecanol	1.1074

With an increasing number of carbon atoms, the response factor increases also. A significant observation is that relative response factor (RRF) is different only for different chain lengths. When primary and secondary alcohols with the same number of carbon atom are analyzed, the RRF for both is almost the same.

A linear relation between number of carbon atoms in primary alcohols and retention time on GC column was shown. This method allows estimating of retention time for newly synthesized alcohol. The same relation exists also for terminal diols (Fig. 8-2)

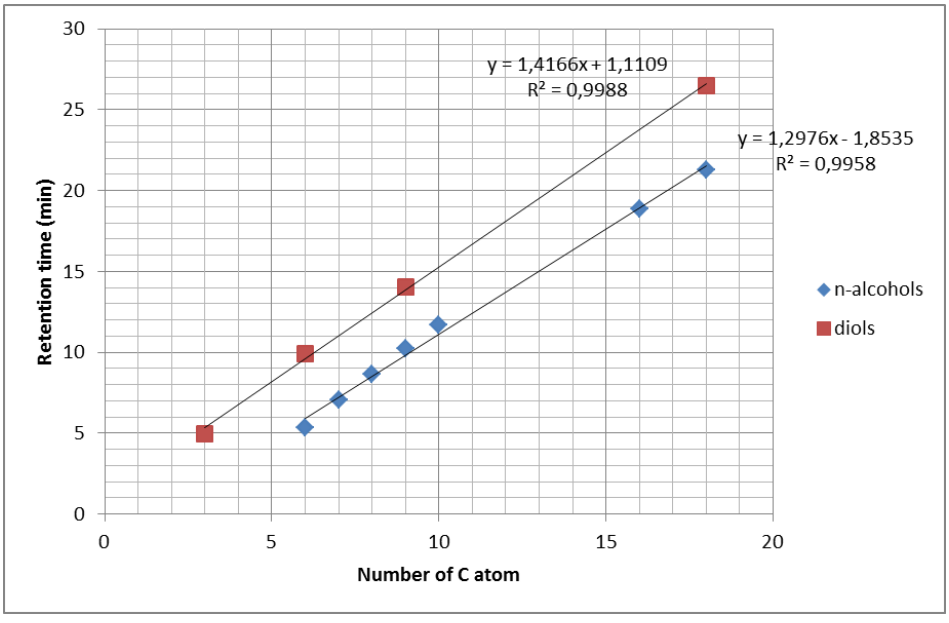


Figure 8-2 A linear relation between number of carbon atoms and retention time for primary alcohols and terminal diols

8.1.3. GPC

GPC (gel permeation chromatography) was performed on: Agilent Technologies 1100 series. Runtime: 23 min, injection loop: 20 µL, Eluent: THF, stabilized with 0.025 % BHT. First column: Phenogel, 5 u, 500 Å, dimensions: 300 x 7.8 mm. Second column: Phenogel, 5 u, 100 Å, dimensions: 300 x 7.8 mm Detector: Refractive index

GPC was used to analyze large molecules that cannot be analyzed directly on GC-MS and GC-FID. It gives an indication about the size of the molecule. This technique was used to follow the progress of synthesis of dioleyl ether and benzaldehyde dioleyl acetal. The combination of two columns allowed also separating mixture like oleyl alcohol and benzyl oleyl ether, oleyl alcohol and oleyl tetrahydropyranyl acetal. This possibility was very useful to quickly check the progress of reaction, the purity of collected samples from column chromatography and to make sure that during reactions no polymerization occurred, which was possible due to the presence of double bond in the molecule.

8.1.4. DEPT NMR

By using a variation on the technique called DEPT (distortionless enhancement by polarization transfer) NMR, different types of carbon atoms can be distinguished.

Table 8-5 The visibility of the peaks on the chromatogram for different scanning DEPT

	DEPT 45	DEPT 90	DEPT 135
CH	+	+	+
CH_2	+	0	-
CH_3	+	0	+

Table 8-5 shows which types of carbon atoms can be seen by scanning on a certain DEPT NMR. The + marks are positive peaks on the spectrum and the – marks are negative peaks. The 0 mark means that there will be no peak on the spectrum. On DEPT NMR only primary, secondary and tertiary carbon atoms are detected (Fig. 8-3). The quaternary carbon atoms can be detected on standard ^{13}C NMR.

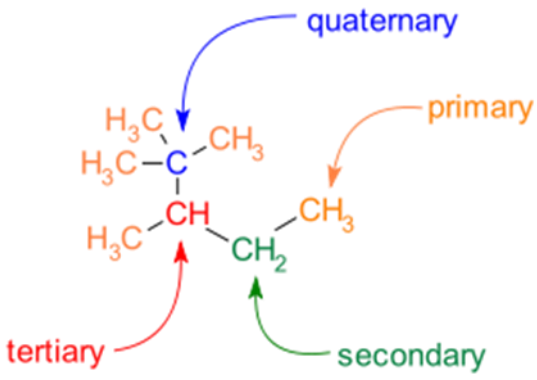


Figure 8-3 The different types of carbon atom that can be seen using ^{13}C NMR

8.2. Experimental procedures

8.2.1. Hydroboration via approach 1

A three-necked round bottomed flask, equipped with a magnetic stirrer and septa, was dried on a Schlenk line. Under argon flow, dry THF and the appropriate amount (1.1 eq) of 1 M BH_3·THF were placed into the dry flask and stirred vigorously. Next, the olefin to be isomerized (3 eq) was slowly added to this mixture at room temperature. Afterwards, the argon flow was replaced by a balloon with argon and the reaction mixture was left to stir at room temperature for at least 4 hours. The resulting concentration of trialkylborane was around 0.45 M.

8.2.2. Hydroboration via approach 2

A three-necked-round bottomed flask, equipped with a magnetic stirrer and septa was dried on the Schlenk line. Under argon flow, dry THF and the appropriate amount (1.1 eq) of 1 M BH_3·THF were placed into the dry flask and stirred vigorously in an ice bath. Next, (cyclo)alkene (2 eq) was slowly added to this mixture. The argon flow was replaced by a balloon with argon and the reaction mixture was stirred in the ice bath for 4 hours. Afterwards, the ice bath was removed and the olefin to be isomerized (1 eq) was added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. The concentration of trialkylborane was around 0.45 M.

8.2.3. Isomerization and oxidation

THF was removed completely and subsequently replaced by the desired solvent under constant argon flow. The concentration of the trialkylborane obtained in the previous hydroboration step was kept constant at 0.45 M. The reaction mixture was heated in a temperature controlled oil bath at 160 °C. In order to follow the progress of the isomerization, a sample of the reaction mixture was taken at 0 h, 1 h, 2 h, 3 h, 6 h, 24 h and 48h. The samples were taken with a syringe (2 mL) and added dropwise, while still warm, to a vial containing 10 mL of a 3 M NaOH solution in methanol. Simultaneously approximately 9 mL of a 50 w% aqueous H_2O_2 solution was added dropwise. When all the components were added, the vial was stirred vigorously at room temperature for one hour. In a next step the solution was acidified, by adding 37 % HCl_{aq} (the pH was monitored by pH indicator paper, as exact control of the pH is not required). In the presence of a strong acid (in this case HCl) the produced sodium borate (poorly soluble in water) is converted into more soluble boric acid and sodium chloride, thereby facilitating the extraction. The product was subsequently extracted with petroleum ether (three times 10 mL) and excess of solvent was removed on a rotary evaporator. The samples were analyzed qualitatively by means of GC-MS and quantitatively by means of GC-FID.

8.2.4. Dehydration of secondary alcohols

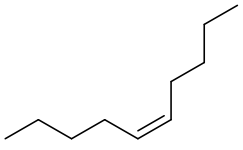
20mL of 85% phosphoric acid solution was added to a round-bottom flask, containing 2 g of mixture (1-heptadecanol and *sec*.-heptadecanols). The flask was then equipped with a magnetic stirrer and placed into an oil bath. Next, the mixture was heated to a temperature of 120 °C and left to react for 1 hour. Afterwards, the mixture was cooled down, neutralized and extracted 2 times with 10mL of n-hexane. The solvent was removed by means of the rotary evaporator. The product was analyzed by means of GC-MS which confirmed the selective dehydration of secondary heptadecanols to heptadecene and lack of dehydration of 1-heptadecanol. The isolated yield is 95 %.

8.2.5. Reduction of ester

15mL of 4M $LiAlH_4$ in diethyl ether (4 eq) and 300 mL of dry diethyl ether were placed into a, dried on the Schlenk line, 500 mL three-neck round-bottom flask. The flask was placed into ice bath and 31 g of methyl oleate (1 eq) was mixed with 120 mL of dry diethyl ether and was slowly added. When the mixture starts foaming, the addition of methyl erucate was stopped until the foam is disappeared. If necessary, an extra amount of dry diethyl ether can be added. After addition of $LiAlH_4$ the reaction mixture was refluxed for 10 minutes. Then, the mixture was cooled down in ice bath and 12 mL of cold water was added dropwise to neutralize the excess of $LiAlH_4$. In purification step 200 mL of 20 w% sulfuric acid was added. After dissolving the solid part, the mixture was transferred to a separator funnel and extract three times with MTBE (3 x 50 mL). The organic fractions were firstly added together and afterwards dried over $MgSO_4$ and the solvent was removed on the rotavapor. Oleyl alcohol was obtained in 95 % isolated yield.

8.2.6. Wittig reactions

(*Z*)-5-decene (**27**)



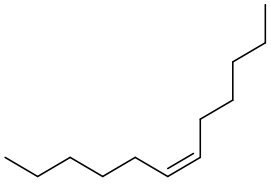
27

1st step (synthesis of (1-pentyl)triphenylphosphonium bromide): 23.91 g of triphenylphosphine (1 eq) was placed in a one-necked, round bottom flask that was dried on the Schlenk Line, and dissolved with 21 mL of toluene dried over molecular sieves. Then, 20.0g (1.33 eq) of 1-bromohexane was added. The amount of solvent should be double by volume to the amount of alkylbromide. Afterwards a balloon

filled with argon was attached to the top of the condenser in order to equalize the pressure and assure an inert atmosphere. The reaction mixture was stirred and refluxed for 18 h. After the reaction was completed, the contents of the flask were cooled down to room temperature. Solid phase was filtered under reduced pressure and white crystals of phosphonium salt were washed with toluene and dried into the oven for 3h at 110 °C.

2nd step (synthesis of 5-decene): In the three-necked, round bottom flask, closed with a septum and dried on the Schlenk line, 332 mL of dry DMSO (dimethyl sulfoxide) was placed. Then, 10.58 g (1.1 eq) of 60 % sodium hydride dispersion in mineral oil was added in one portion. The reaction mixture was heated at 65 °C until the hydride was dissolved. Afterwards, sodium methylsulfinylmethylide was cooled down to room temperature and 99.38g (1 eq) of (1-pentyl)triphenylphosphonium bromide was slowly added. The mixture was stirred for 45 min at 25 °C (Fig. 7-3 B). In the last step pentanal was added, 20.71 g (1 eq). Then the reaction mixture was heated overnight (approximately 18 h) at 50 °C . The product was extracted with petroleum ether and the residue after evaporation was analyzed by means of GC-MS. The crude product was purified by means of wet column chromatography by using petroleum ether as eluent. The total yield of the synthesis of (*Z*)-5-decene was 29 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (2H, t, J = 4.6 Hz), 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.35 (8H, m), 0.86 (6H, t, J = 7.0 Hz). Known compound. NMR spectra in accordance with literature data[187]. The mass spectrum and ^{1}H NMR are shown in the Supporting information".

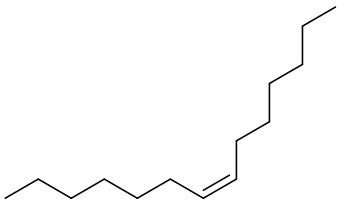
(*Z*)-6-dodecene (**29**)



29

The same procedure as for alkene **27** was followed. The product **29** was isolated in 30 % yield. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (2H, t, J = 4.6 Hz), 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.35 (12H, m), 0.86 (6H, t, J = 7.0 Hz). Known compound. NMR spectra in accordance with literature data[188]. The mass spectrum and ^{1}H NMR are shown in "Supporting information".

(*Z*)-7-tetradecene (**30**)

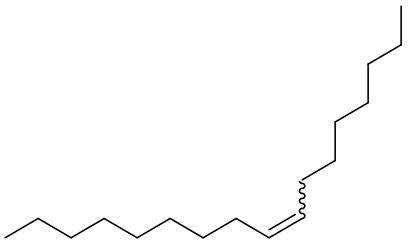


30

The same procedure as for alkene **27** was followed. The product **30** was isolated in 38 % yield. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (2H, t, J = 4.6 Hz), 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.35 (16H, m), 0.86 (6H, t, J = 7.0 Hz). Known compound. NMR spectra in accordance with literature data[187]. The mass spectrum and ^{1}H NMR are shown in "Supporting information".

8.2.7. Oxidative decarboxylation

8-heptadecene (**31**)

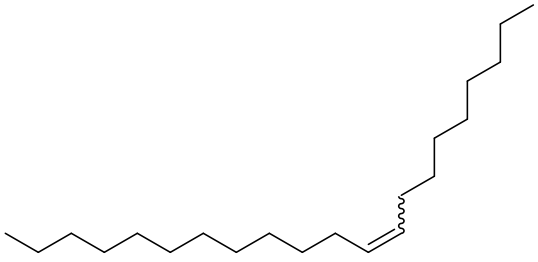


31

40 g of oleic acid (1 eq) was added to 360mL of acetonitrile in a three-necked-round-bottom flask (or a regular flask with Claisen adapter). This mixture was stirred vigorously and heated up to dissolve the oleic acid in the acetonitrile (ACN). After dissolving the oleic acid, the mixture was cooled down to room temperature and a 27.88 g of silver nitrate (1 eq) dissolved in 260 mL of distilled water was added. The reaction mixture was then heated up again until reflux temperature (approximately 78 °C). When the reaction mixture started refluxing, 67.44 g of sodium peroxydisulfate (2 eq) dissolved in 100 mL of distilled water was slowly added over approximately 10 minutes. Afterwards, the mixture was left to react for another 10 minutes at reflux temperature, before cooling it down to room temperature, using an ice bath. The total volume ratio between ACN and water should be 9:5. The purification was continued by filtering the reaction mixture and extracting with petroleum ether. The extracted organic layer was then washed with saturated sodium bicarbonate solution. To prevent the formation of an emulsion the brine was

added. In order to obtain the final pure product a dry column chromatography was performed, using silica gel and petroleum ether as eluent. The product **31** was isolated in 38 % yield. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (2H, t, J = 4.6 Hz), 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.35 (22H, m), 0.86 (6H, t, J = 7.0 Hz). Known compound. NMR spectra in accordance with literature data[189]. The mass spectrum and ^{1}H NMR are shown in "Supporting information".

9-heneicosene (**32**)

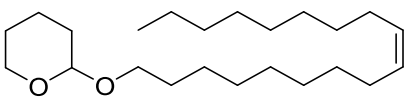


32

The same procedure as for alkene **31** was followed. The product **32** was isolated in 29 % yield. Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (2H, t, J = 4.6 Hz), 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.35 (30H, m), 0.86 (6H, t, J = 7.0 Hz). Known compound. NMR spectra in accordance with literature data[190]. The mass spectrum and ^{1}H NMR are shown in "Supporting information".

8.2.8. Synthesis of acetals

Oleyl tetrahydropyranyl acetal (**53**)

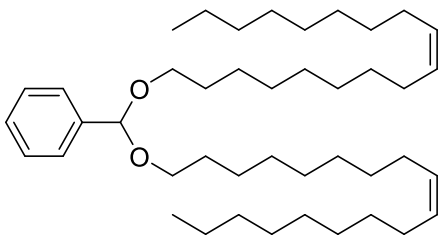


53

10 mg (0.03 eq) of *p*TSA are added to 12.3 mL (1.2 eq) of warm 3,4-Dihydro-2H-pyran (60 °C) in a three necked, round-bottom flask equipped with a magnetic stirrer. When the dihydropyran and the catalyst are mixed completely, 35.7 mL (1 eq) of oleyl alcohol was added dropwise. External cooling can also be necessary because the reaction is mildly exothermic. The reaction mixture is stirred for 1.5 hours after the addition is completed. Then a small amount of sodium bicarbonate is added for the neutralization. The reaction mixture is stirred for another hour. In order to obtain the

final pure product flash chromatography was performed, using silica gel and petroleum ether / ethyl acetate (9.5 : 0.5 v/v) as eluent. The pure acetal is eluted as the first fraction. Oleyl tetrahydropyranyl acetal was isolated with 60 % of yield. Colorless liquid. The pure product was analyzed by means of DEPT ^{13}C-NMR, which is shown in "Supporting information".

Benzaldehyde dioleyl acetal (**55**)

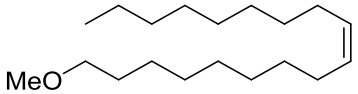


55

Around 10 mg (0.03 eq) of pTSA were dissolved in dry toluene (by volume 5 times more than oleyl alcohol) in round-bottom flask equipped with a Dean – Stark head. 20 mL (2.2 eq) of oleyl alcohol and 3.37 ml (1 eq) benzaldehyde was added. Dean – Stark distillation was continued by 24 hours. Then the reaction mixture was cooled down to room temperature and small amount of sodium bicarbonate was added to neutralize pTSA. The crude product was filtered and excess of toluene and benzaldehyde were removed on a rotary evaporator. In order to obtain the final pure product flash chromatography was performed, using silica gel and petroleum ether ethyl acetate (9.5 : 0.5 v/v) as eluent. The pure acetal is eluted as the first fraction. The purity of the product was determined by means of gel permeation chromatography (GPC). The product **55** was isolated in 87 % yield. Colorless liquid.

8.2.9. Synthesis of ethers

Methyl oleyl ether (**44**)



44

Via Williamson method:

20 ml (1 eq) of oleyl alcohol and toluene were added to a three-necked round bottom flask, fitted with a Dean Stark separator and condenser. Then, 16 g of KOH (well crushed) (5 eq) was added and the flask was closed by silicone septa. The

mixture was stirred and heated to reflux for 12 h. After formation of the oleyl alkoxide, the mixture was cooled down to room temperature and 6.11 ml of methyl iodide (1.1 eq) was added through the septum with a syringe. The mixture was then mixed at 40 °C for 12 h (b.p. 42.3 °C). When the reaction was completed, the mixture was cooled down to room temperature and neutralized with HCl, water was added to the mixture and the two formed layers were separated. The water layer was extracted two more times with petroleum ether. The organic layers were combined, dried with $MgSO_4$, filtered and evaporated by rotary evaporation. The crude product was purified by means of column chromatography. Methyl oleyl ether is eluted in first fraction with eluent: petroleum ether ethyl acetate (9 : 1 v/v). The product **44** was isolated in 40 % yield. Colorless liquid.

Via sulfonate method:

The procedure is analogous to the procedure of the Williamson method to synthesize methyl ether, but instead of organohalide, the methanesulphonate ester is used and the reaction is carried out under reflux. The yield is a bit better compared with Williamson method: Y = 45 %.

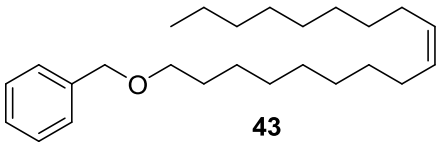
Via decarboxylation

1st step: 400 g (1 eq) of oleyl alcohol and 628 mL (5 eq) of DMC was mixed at 90 °C for. After mixing, 120 g of hydrotalcite (30 m% regarding to the mass of alcohol) (calcinated at 800 °C for 5 h) was added and reaction was left for six hours. After reaction, the catalyst was centrifuged and the excess of DMC was removed with the use of rotavapor. Methyl oleyl carbonate was obtained in 100 % yield.

2nd step: 33.2 g (10 m%) of hydrotalcite was placed into the Parr reactor and then heated to temperature 250 °C. During the heating, the Parr reactor was flushed with argon. When reactor reached the temperature about 250 °C the balloon with argon was removed and the 332 g of methyl oleyl carbonate was added. The reaction was carried out about 1 h. After reaction, the mixture was centrifuged in order to remove the catalyst. In the last step the mixture of dioleyl ether and methyl oleyl ether was separated by vacuum distillation in 200 °C (around 1 mbar). Methyl oleyl ether consist the distillated fraction and it is isolated in 33 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (2H, t, J = 4.7 Hz), 3.36 (2H, t, J = 6.6 Hz), 3.33 (3H, s) 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.58 (2H, m) 1.35 (24H, m), 0.86 (3H, t, J = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 130.05, 73.25, 58.63, 32.00, 29.70, 27.29, 26.22, 22.75, 14.14. Known compound. NMR spectra in accordance with literature data.[195] The mass spectrum, ^{1}H and ^{13}C NMR are shown in “Supporting information”.

Benzyl oleyl ether (**43**)



43

Via Williamson method

The procedure is analogous to the procedure of the Williamson method to synthesize methyl ether, as organohalide benzyl chloride was used and the reaction is carried out under reflux. The excess of toluene and benzyl chloride was removed by means of a rotary evaporator. The side product – dibenzyl ether was removed by vacuum distillation at 120 °C (1 mbar). The product **43** was isolated in 100 % yield. Colorless liquid.

Via decarboxylation:

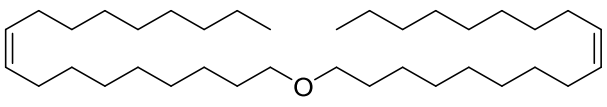
1st step: 400 g (1 eq) of oleyl alcohol and 628 mL (5 eq) of DMC was mixed at 90 °C. After mixing, 120 g of hydrotalcite (30 m%) was added and reaction was stirred for six hours. After reaction, the catalyst was centrifuged and the excess of DMC was removed with the use of rotavapor. Methyl oleyl carbonate was obtained in 100 % yield.

2nd step: 20 g of methyl oleyl carbonate was placed in a 250 mL three-neck round bottom flask and argon was bubbled through. Next, 6.8 mL (1.2 eq) of benzyl alcohol was added and the temperature was at 120 °C. The catalyst was centrifuged and the catalyst was rinsed with MTBE. The organic fractions were firstly added together and afterwards dried over $MgSO_4$ and the solvent and the excess of benzyl alcohol were removed with the use of a rotavapor. Benzyl methyl carbonate was obtained in 100 % yield.

3rd step: 3 g (10 m%) of hydrotalcite was placed into the Parr reactor and then heated to temperature 250 °C. During the heating, the Parr reactor was flushed with argon. When reactor reached the temperature about 250 °C the balloon with Ar was removed and the 30 g of benzyl methyl carbonate was added. The reaction was carried out about 1 h. After reaction, the mixture was centrifuged in order to remove the catalyst. In the last step the mixture of dioleyl ether, benzyl oleyl ether and dibenzyl ether were separated by vacuum distillation at 120 °C (around 1 mbar) for dibenzyl ether and 210 °C for benzyl oleyl ether. Dioleyl ether is the residue after distillation. Benzyl oleyl ether was isolated in 40 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (5H, m), 5.35 (2H, t, J = 4.7 Hz), 4.50 (2H, s), 3.45 (2H, t, J = 6.7 Hz), 2.00 (4H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.58 (2H, m) 1.35 (22H, m), 0.86 (3H, t, J = 7 Hz). ^{13}C NMR (400 MHz, $CDCl_3$). Known compound. NMR spectra in accordance with literature data.[194] The mass spectrum, ^{1}H and ^{13}C NMR are shown in "Supporting information".

Dioleyl ether (**47**)



47

Via Sulfonate method

1st step synthesis of oleyl methanesulphonate: First a flask is dried on the Schlenk line. Then 170 mL of toluene is added to the flask and stirred. While the toluene is stirring, 13.12 g (1.5 eq) of methanesulfonic anhydride was added to the flask. The anhydride is allowed to dissolve in the toluene, if the anhydride is not dissolved after 30 min the flask has to be heated for a few minutes until all anhydride is dissolved. Then in a small vial 13.5 g (1 eq) of oleyl alcohol is dissolved in 20 mL of pyridine (pyridine is an activator of anhydride in esterification). The toluene anhydride mixture is cooled down in an ice bath and the oleyl alcohol in pyridine is added very slowly and left overnight. 150 mL of O_2-free water is added to the reaction mixture for extraction. Then the water phase and organic phase are separated. The water phase is placed in an ice bath. The ether phase is extracted five times with different solvents. It is extracted first with 50 mL of water, then with 50 mL of 1M of sulfuric acid, then again with 50 mL of water, then with 50 mL of a 1 % potassium carbonate solution in water and finally again with 50 mL of water. All these extracts where combined and kept. Afterwards the original water phase is extracted with 200 mL of methyl *tert*-butylether (MTBE). Then the MTBE layer is again extracted with the 5 different solvents. It is extracted first with 50 mL of water, then with 50 mL of 1 M of sulfuric acid, then again with 50 mL of water, then with 50 mL of a 1 % potassium carbonate solution in water and finally again with 50 mL of water. These organic extracts are combined and dried and filtered over magnesium sulphate. The dried extraction phases are then evaporated on the rotary evaporator. Yield after 1st step is 98 %.

2nd step synthesis of dioleyl ether: The procedure is analogous to the procedure of the Williamson method to synthesize methyl ether, but instead of organohalide, the

methanesulphonate ester synthesized in 1st step is used and the reaction is carried out under reflux. The product **47** was isolated in 43 % yield. Colorless liquid.

Via decarboxylation

The same procedure as for ether **44** was followed. The product **47** was isolated in 67 % yield, as a residue after distillation. Colorless liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.35 (4H, t, J = 4.6 Hz), 3.45 (4H, t, J = 6.7 Hz), 2.00 (8H, dd, J = 6.4 Hz, J = 5.6 Hz), 1.58 (4H, m) 1.35 (44H, m), 0.86 (6H, t, J = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 130.01, 71.07, 32.06, 29.62, 27.37, 26.30, 22.78, 14.17. Known compound. Spectral data not available. The mass spectrum, ^{1}H and ^{13}C NMR are shown in "Supporting information".

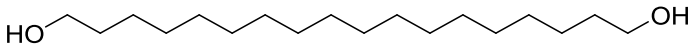
8.2.10. Cleavage of methyl ether

1.02 g (3 eq) of cetyl methyl ether and 10 mL of dichloromethane are placed in the first vial in an oil or water bath at 35 °C. One vial is equipped with a magnetic stirrer. A second vial is used to mix 0.255 mL (2 eq) of boron tribromide with 10 mL of the solvent (dichloromethane). The content of the second vial is added dropwise to the first one. The mixture is stirred for 1.5 hours. An aqueous sodium hydroxide solution is used to quench the reaction. Cetyl alcohol was isolated with 80 % yield (the remaining 20 % is cetyl bromide).

8.2.11. Cleavage of benzyl ether

1 g of benzyl cetyl ether and 100 mL dichloromethane were added to the flask and placed in an ice bath and the mixture was set to stir. The oxygen bottle was opened and flowed through the ozone generator. Ozone was bubbled softly through a nozzle, immersed in the mixture and the tap of the flask was opened. A small amount of Sudan III, as the indicator of the reaction progress (red -> yellow). After ozonolysis, the mixture was transferred to a single-neck round bottom flask and dichloromethane was removed by means of rotary evaporation. In order to execute the methanolysis, 10 mL of 1M NaOH solution in methanol was added and the mixture was heated to reflux for 1 hour. Afterwards, the mixture was cooled down and MTBE was added. Brine solution (saturated NaCl in water) was added to help with separation. Two layers were separated with a separation funnel and the methanol-water layer was extracted two more times with MTBE. The organic layers were collected, dried with $MgSO_4$, filtered and MTBE was removed on the rotary evaporator. Cetyl alcohol was isolated in 98 % yield.

8.2.12. Synthesis of 1,18-octadecanediol (41)



41

Via methyl ether

1st step synthesis of methyl oleyl ether: The procedure for ether **44** was followed (via sulfonate ester). The product was isolated in 45 % yield.

2nd step hydroboration-isomerization-oxidation: The standard procedure was followed with external dialkylborane and isododecane as solvent. The product was isolated in 69 % yield.

3rd step ether cleavage: The procedure for the cleavage of methyl ether was followed. The product **41** was isolated after this step in 75 % yield. White powder. The total yield of 1,18-octadecanediol synthesis is 23 %.

Via benzyl ether:

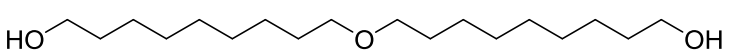
1st step synthesis of benzyl oleyl ether: The procedure for ether **43** was followed (via Williamson method). The product was isolated in 100 % yield.

2nd step hydroboration-isomerization-oxidation: The standard procedure was followed with external dialkylborane and silicone oil as solvent. The product was isolated in 55 % yield.

3rd step ether cleavage: The procedure for cleavage of benzyl ether was followed. The product **41** was isolated after this step in 93 % yield. White powder. The total yield of 1,18-octadecanediol synthesis is 51 %.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.6 (4H, t, J = 6.6 Hz), 1.58 (4H, m), 1.4 (30H, m). Known compound. NMR spectra in accordance with literature data[191]. The mass spectrum and ^{1}H NMR are shown in “Supporting information”.

8.2.13. Synthesis of 9,9'-oxybis(nonan-1-ol) (48)



48

55,1 g of dioleyl ether (1 eq) and about 150,0 mL of pentane was mixed with magnetic stirrer. A small amount of Sudan III, as the indicator of the reaction progress (red -> yellow). The reaction was carried out sixteen hours with ozone until mixture had changed color to yellow.

55,1 g (1 eq) of the product after ozonolysis and about 300 mL of dry pentane were mixed in three-neck bottom flask which was placed in ice bath. After mixing, 12,6 g (1,5 eq) of $LiAlH_4$ was added. During the reaction the flask was flushed with argon. The reaction was carried out about 2h with reflux at 40 ^{o}C. Next, the reaction mixture was cooled down in ice bath and 10 mL of cold water was dropwise added to neutralize not reacted $LiAlH_4$. In next step 250 mL of 20 m% sulphuric acid was added to dissolve the solid part (LiOH and $Al(OH)_3$). Mixture was left over night and two layers were separated. The water layer was extracted with MTBE (2 x 150 mL). The organic layers were combined, dried with magnesium sulfate, filtrated and evaporated. The oil in the flask was mixed with petroleum ether and left over night in the freezer for crystallization. After night mixture was centrifuged – the supernatant was moved to another flask and the solid phase was mixed with fresh cold petroleum ether and after 1 hour in fridge centrifuged again. The white powder was filtrated and rinse a few times with cold petroleum ether. The product **48** was isolated in 84 % yield. White powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.65 (4H, t, J = 6.6 Hz), 3.45 (4H, t, J = 6.7 Hz), 1.60 (8H, m), 1.35 (20H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 70.94, 63.04, 32.82, 29.73, 26.20, 25.76. Known compound. Spectral data not available. The mass spectrum, ^{1}H and ^{13}C NMR are shown in “Supporting information”.

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Personal information

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L. Pazdur, J. de Nys, J. Geuens, H. Sels, S. Tavernier, *New approach for low cost synthesis of high purity 1-monoglycerides*, 14th Euro Fed Lipid Congress, Gent, 2016.

Congresses, conferences, seminars

Participation at Summer School on Organic Synthesis, Gargnano (Italy), 14-18 June 2015 with poster presentation: *Low-temperature chemical synthesis of high-purity diacylglycerols (DAG) from monoacylglycerols (MAG)*.

Participation at “Chemistry Conference for Young Scientists”, Blankenberge (Belgium), 16 – 18 March 2016 with oral presentation: *Influence of carbon chain length on the isomerization of n-alkenes*.

Participation at 4th International Conference on Methods and Materials for Separation Processes, Brunow (Poland), 4 – 8 September 2016 with oral

presentation: *Separation of primary and secondary fatty alcohols and their derivatives and subsequent determination of the position of hydroxyl group in secondary alcohols*.

Participation at 14th Euro Fed Lipid Congress, Gent (Belgium), 18 - 21 September 2016 with oral presentation: *New approaches for low cost synthesis of high purity 1-monoglycerides*.

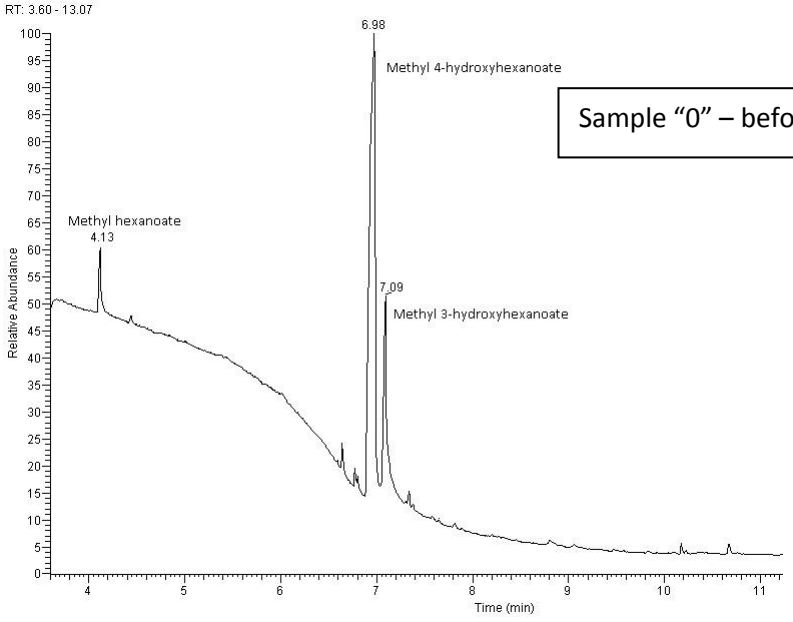
Granted projects

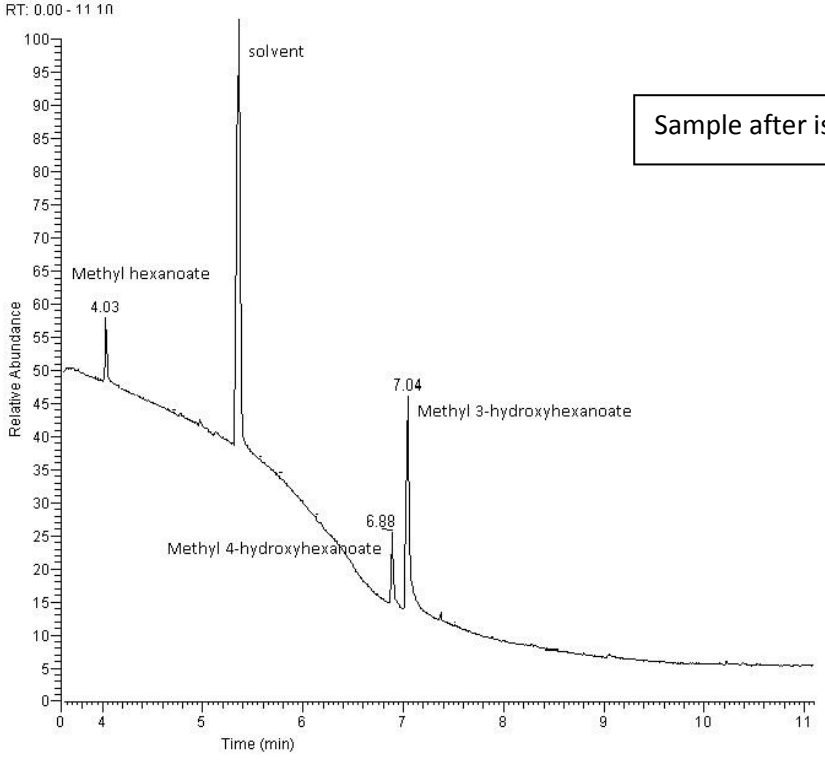
OZC – STRATINVEST-KP: oproep 2015: S. Tavernier, L. Pazdur (draftsman), “Efficient quantitative separation of BioGEM compounds e.g. free fatty acids and/or derivatives by means of BUCHI Glass Oven B-585 (Kugelrohr and Drying)”, total grant - 8 122,25 euro.

OZC – STRATINVEST-KP: oproep 2016, S. Tavernier, L. Pazdur (draftsman), "StarFish™: Multiexperiment work station to improve the productivity of the research", total grant - 9 327,08 euro.

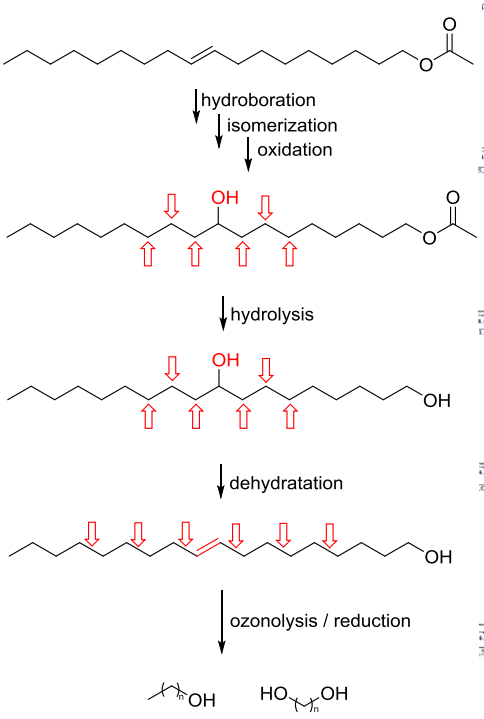
Supporting information

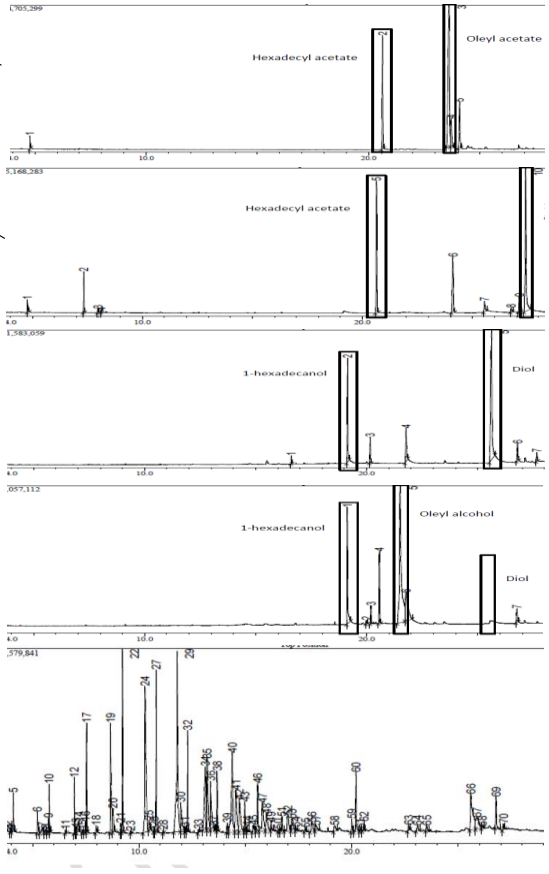
GC chromatogram for hydroboration-isomerization of methyl trans-3-hexenoate.



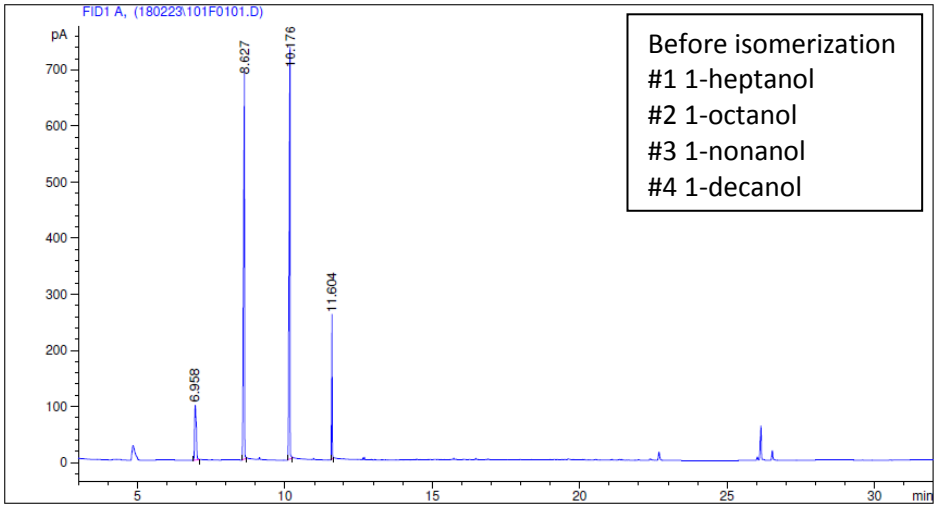


Internal isomerization of oleyl acetate

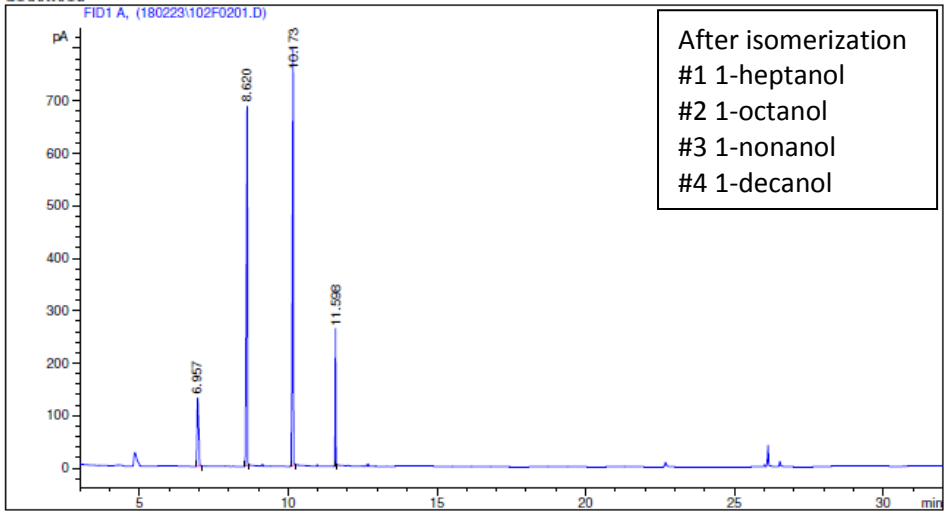




GC chromatogram of alcohols mixture after determination of double bond position

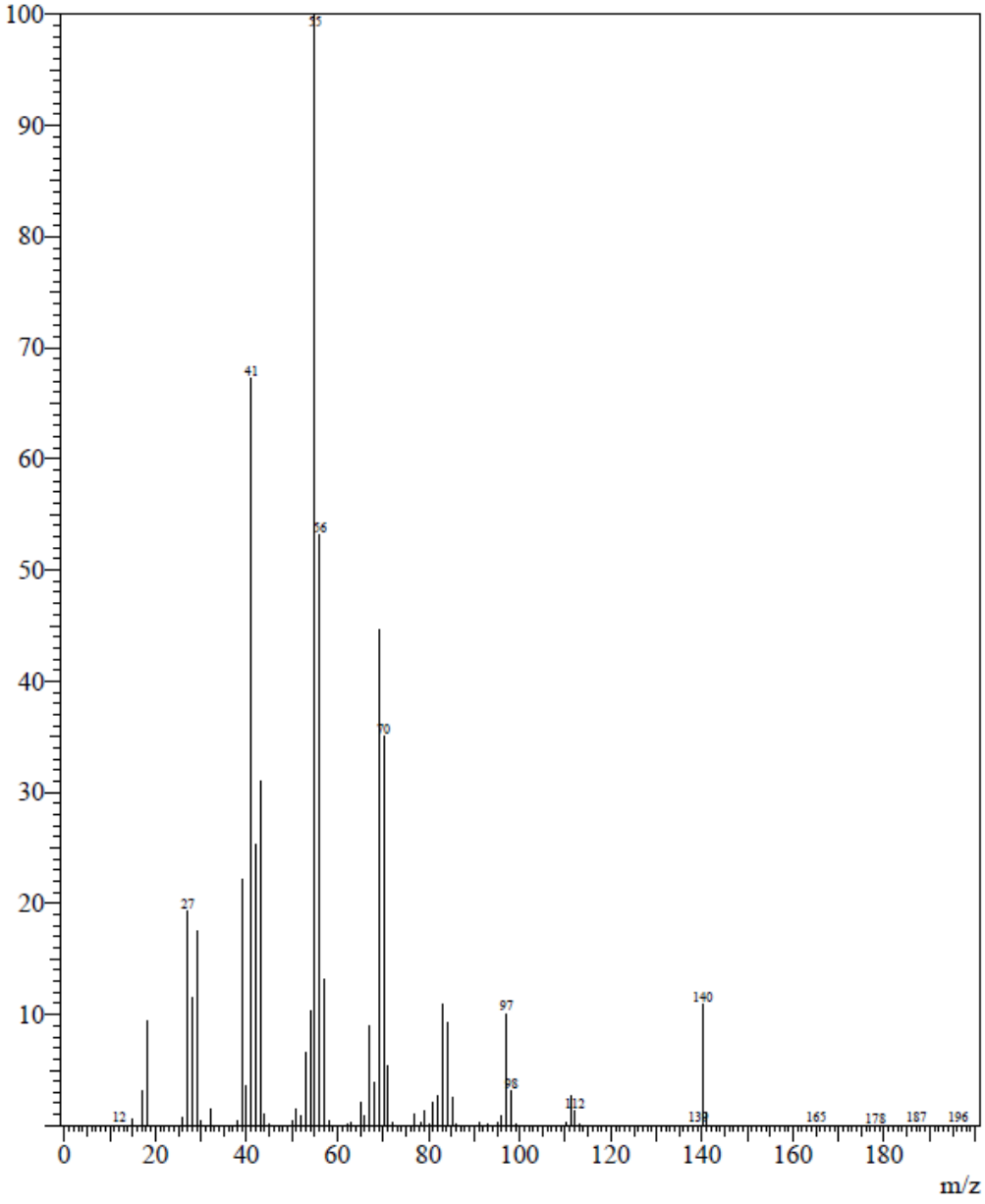


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.958	PB	0.0696	394.10754	96.68951	9.35969
2	8.627	PB	0.0352	1761.57324	680.74799	41.83574
3	10.176	PB	0.0345	1693.36646	717.78052	40.21589
4	11.604	PB	0.0216	361.64288	253.62112	8.58868



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	6.957	PB	0.0673	514.39215	129.68198	11.65557
2	8.620	BB	0.0349	1698.16663	685.52930	38.47861
3	10.173	BB	0.0316	1832.49463	775.30646	41.52233
4	11.598	PB	0.0225	368.22131	259.95969	8.34349

(*Z*)-5-decene (**27**)


100
90
80
70
60
50
40
30
20
10
0
20
40
60
80
100
120
140
160
180
m/z
55
41
56
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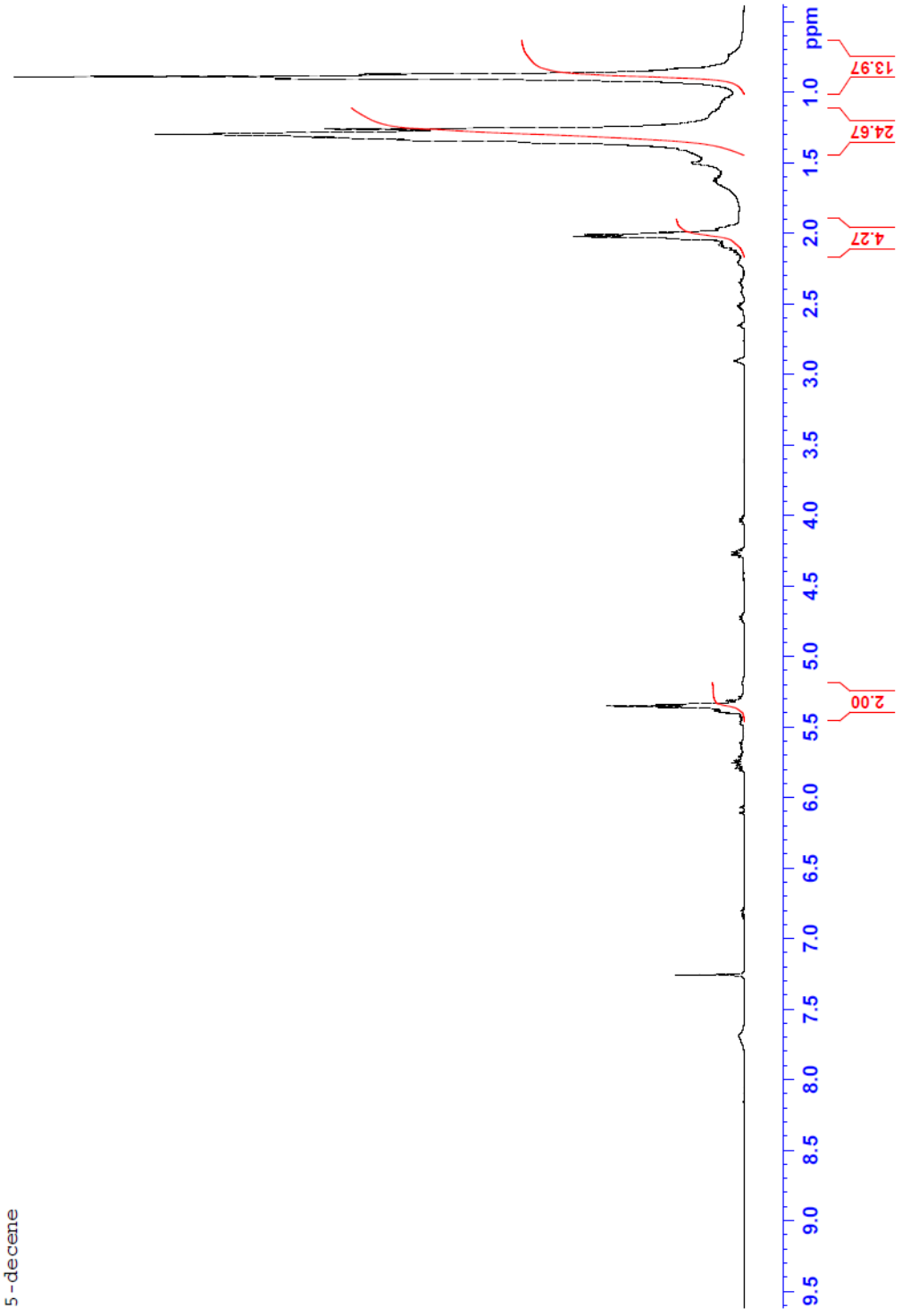
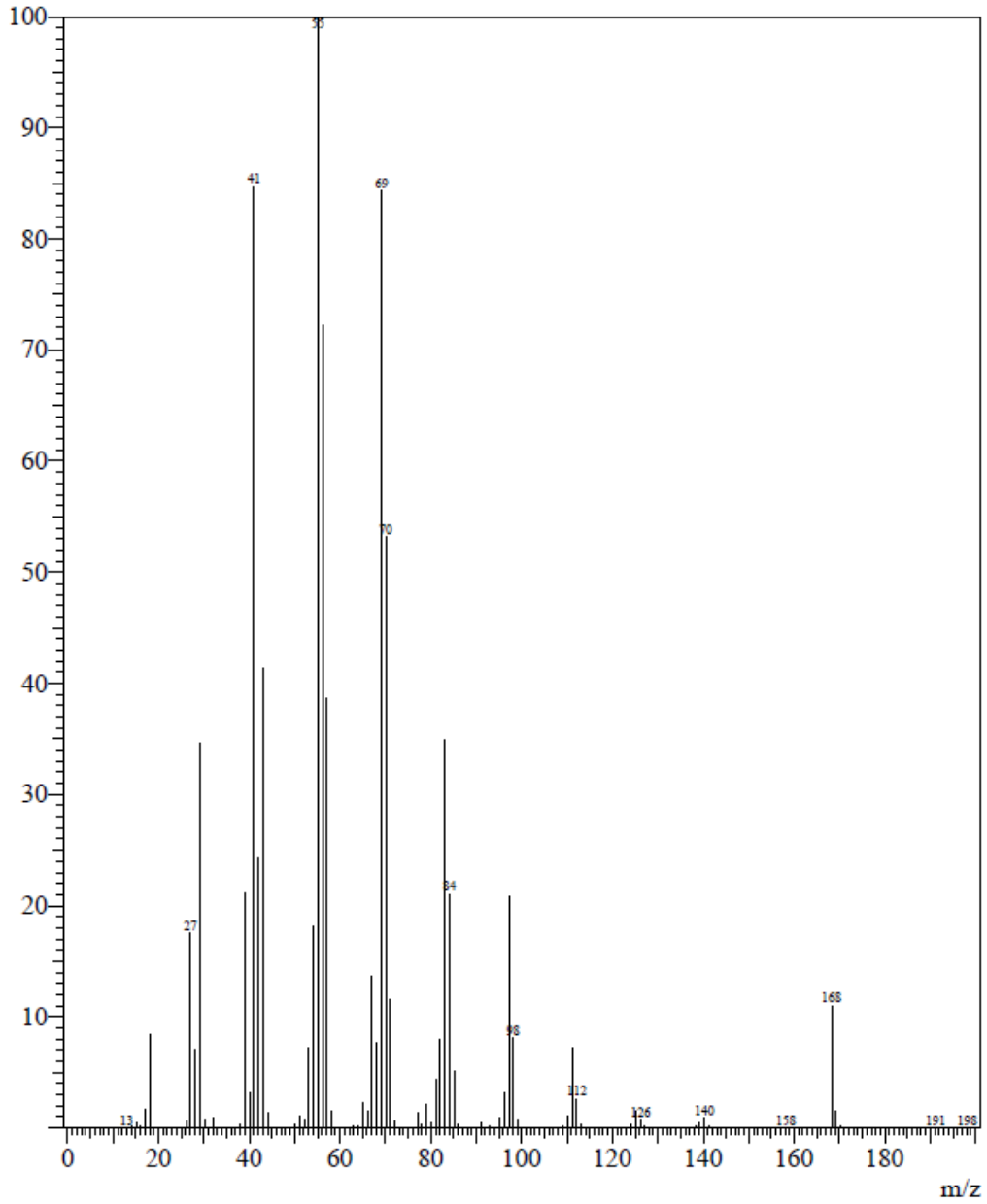
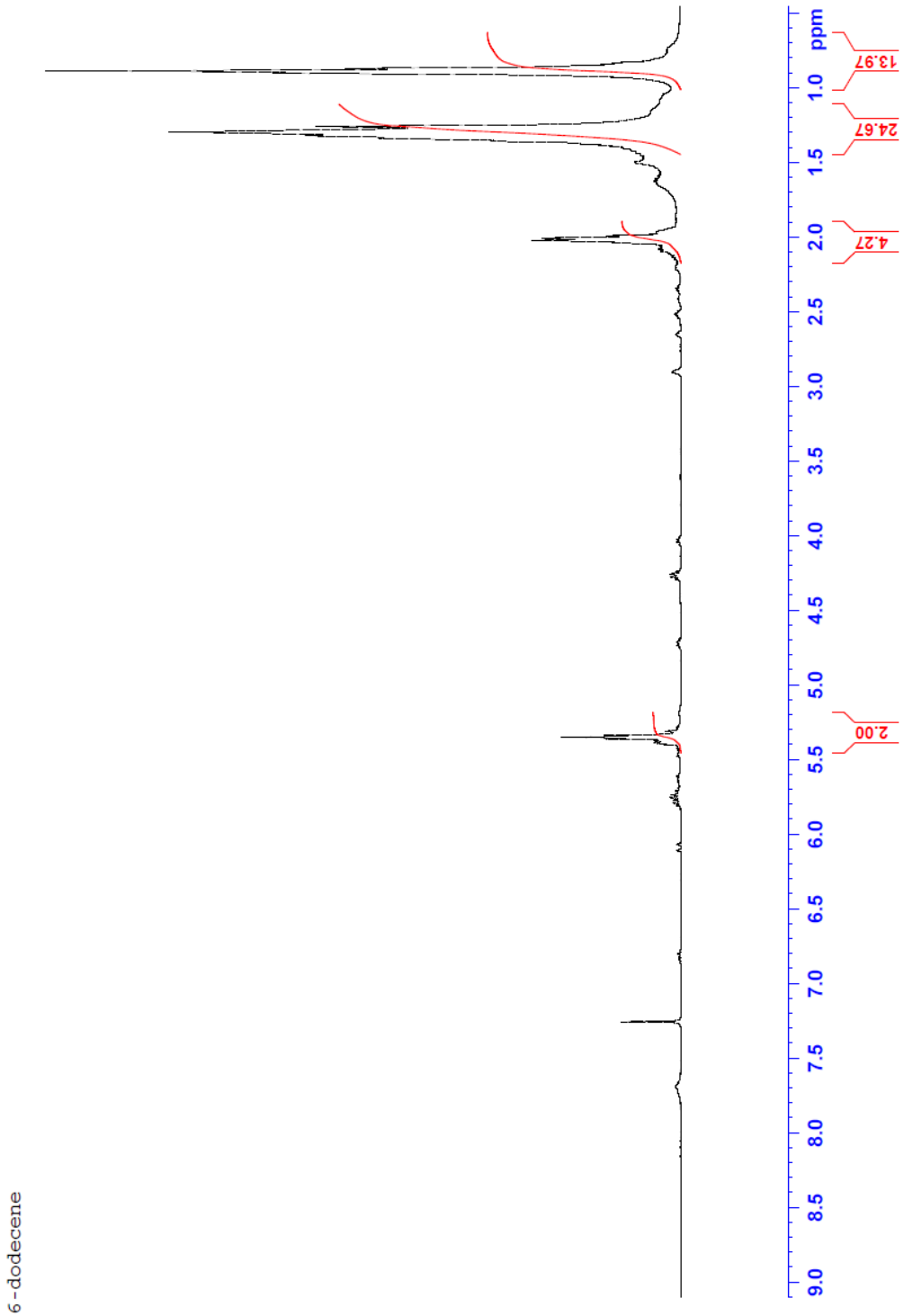
27
97
140
98
112
12
139
165
178
187
196

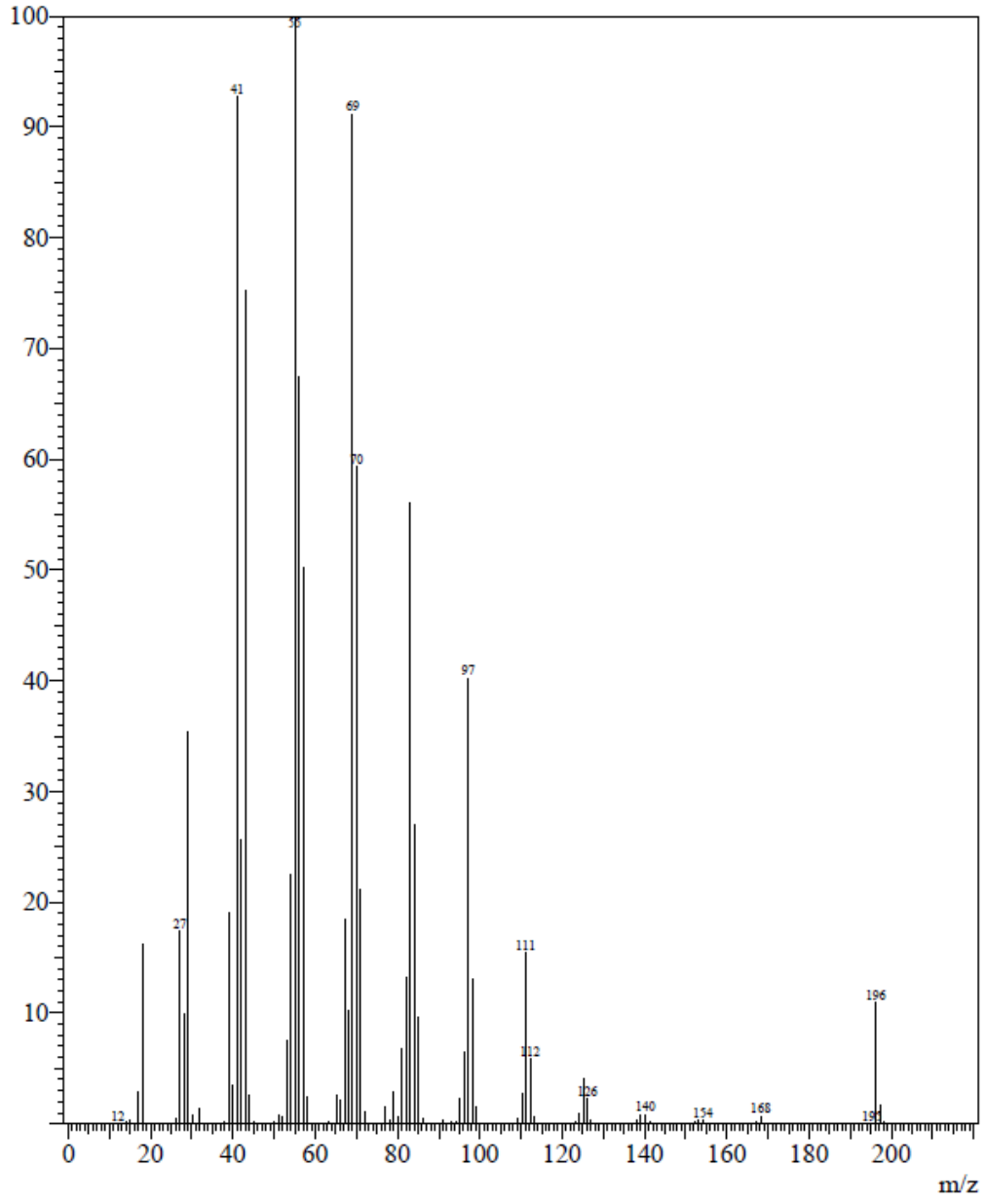

5-decene
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
2.00
4.27
24.67
13.97

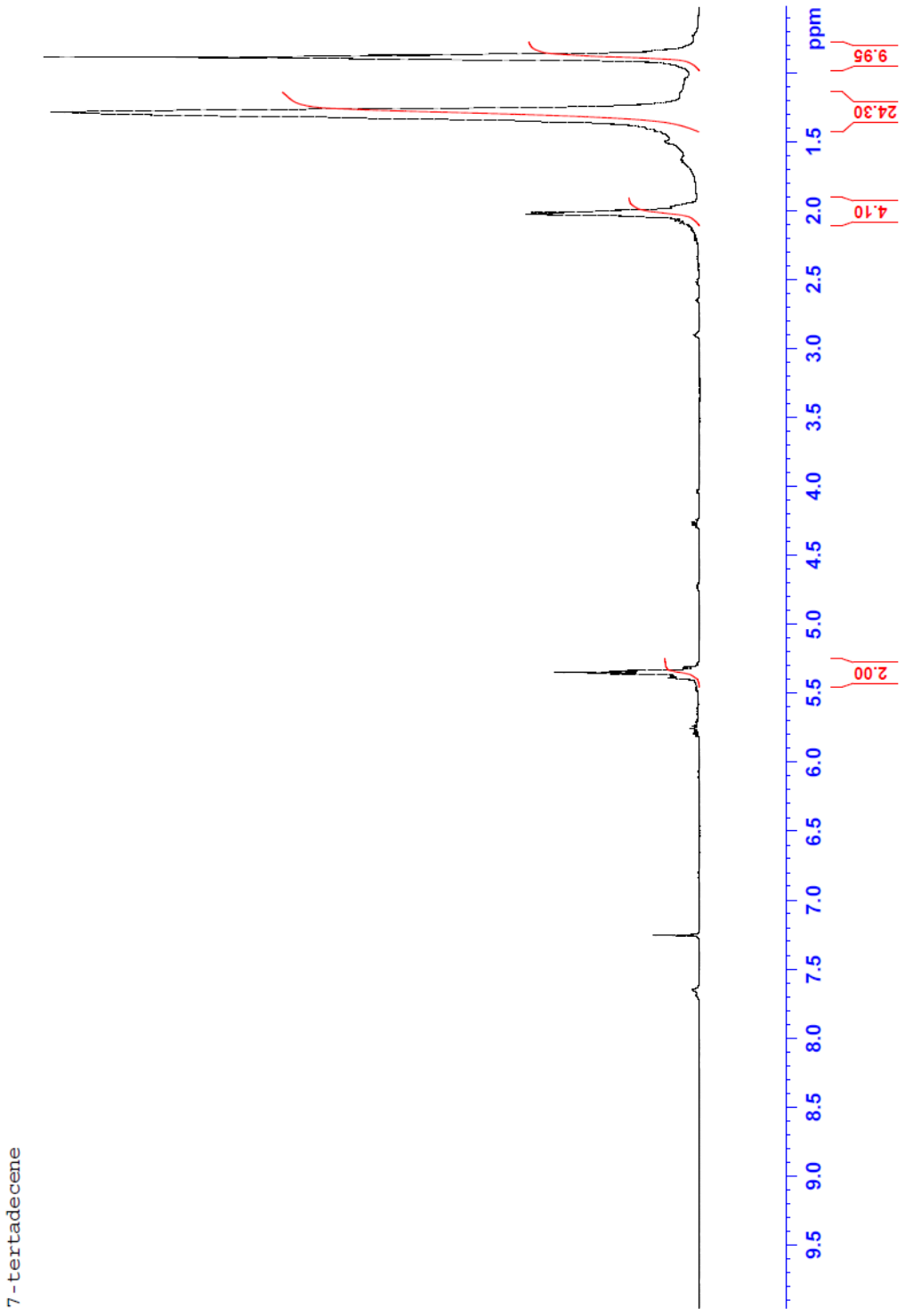
(*Z*)-6-dodecene (**29**)



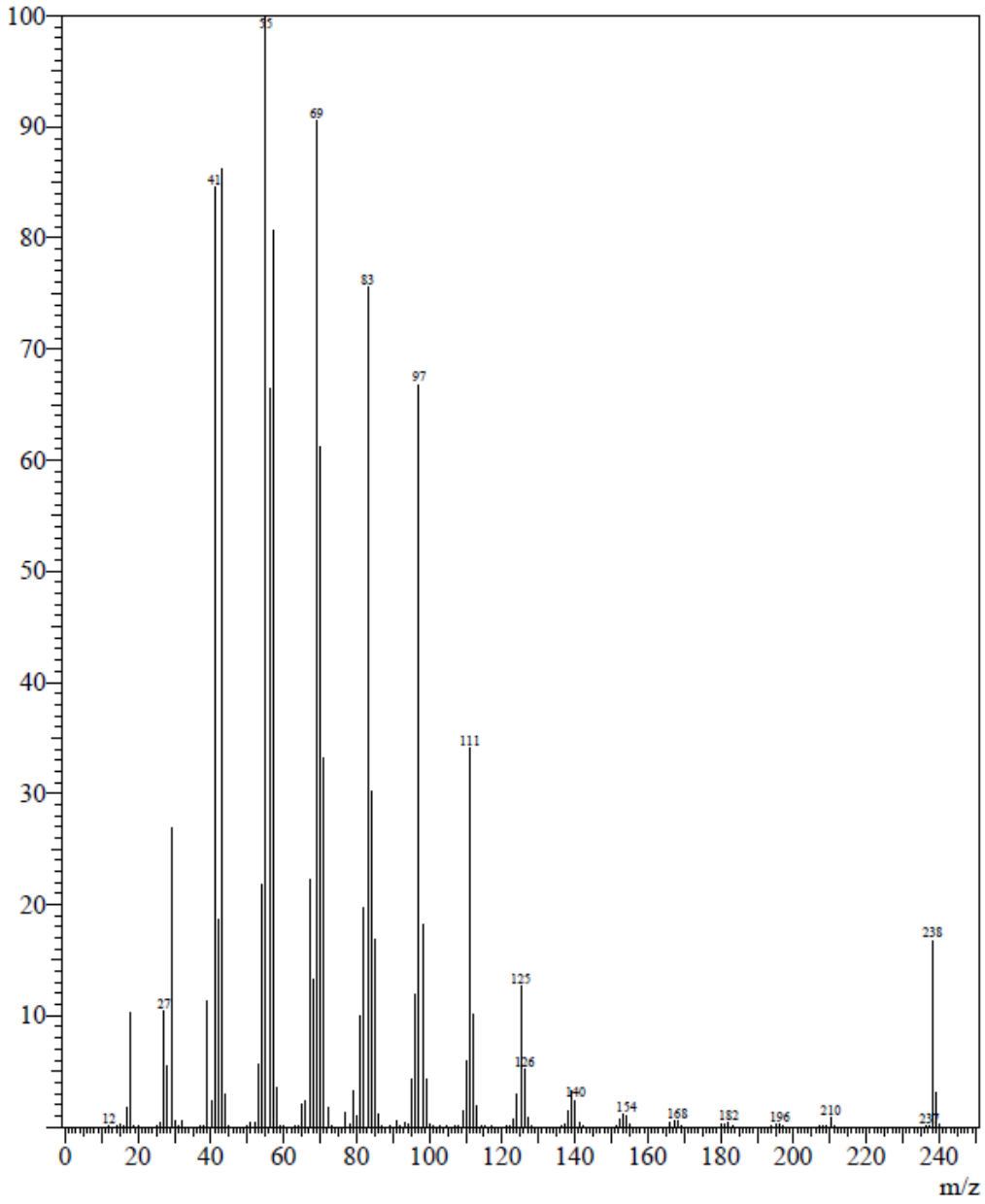

6-dodecene
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
13.97
24.67
4.27
2.00

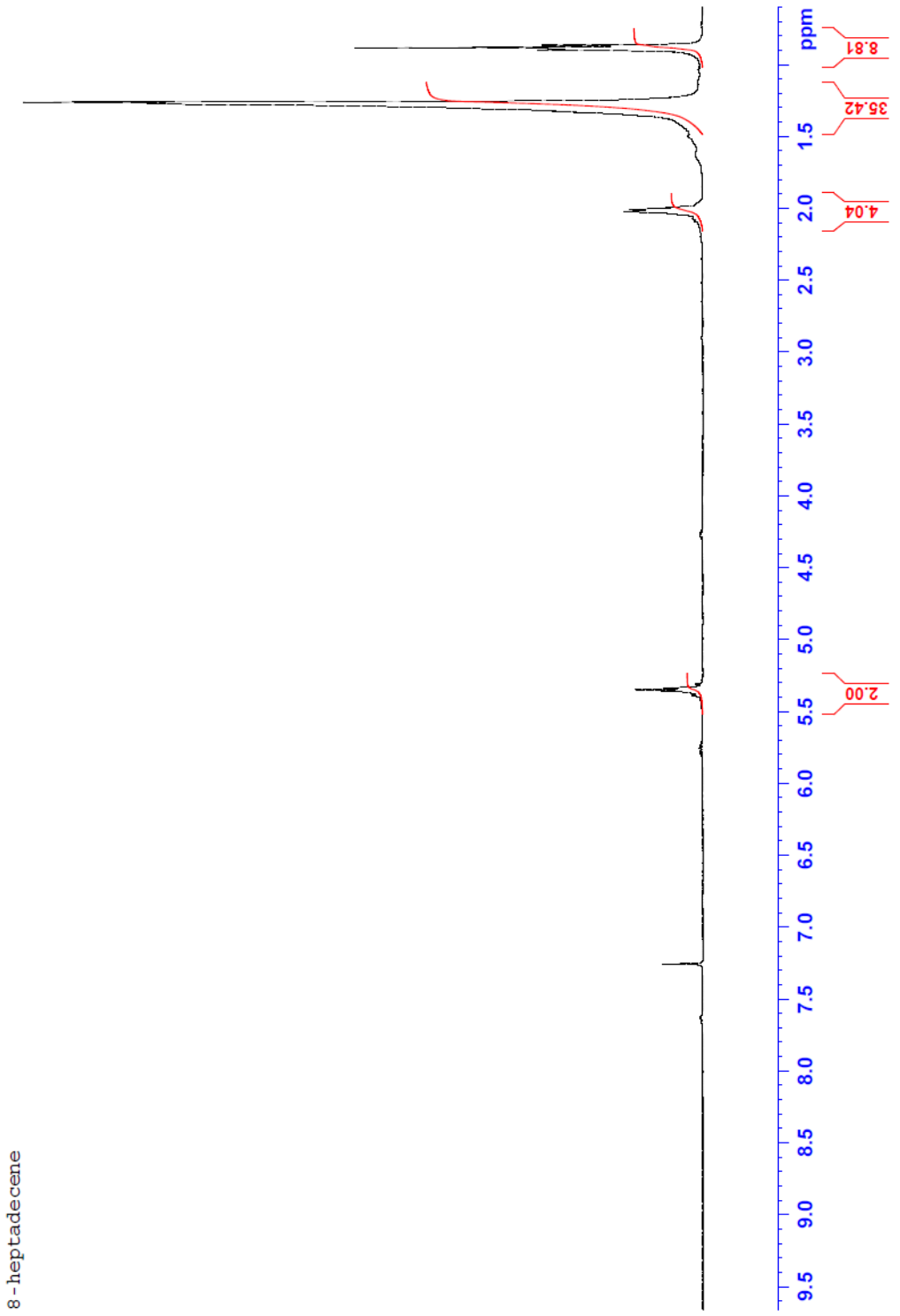
(*Z*)-7-tetradecene (**30**)



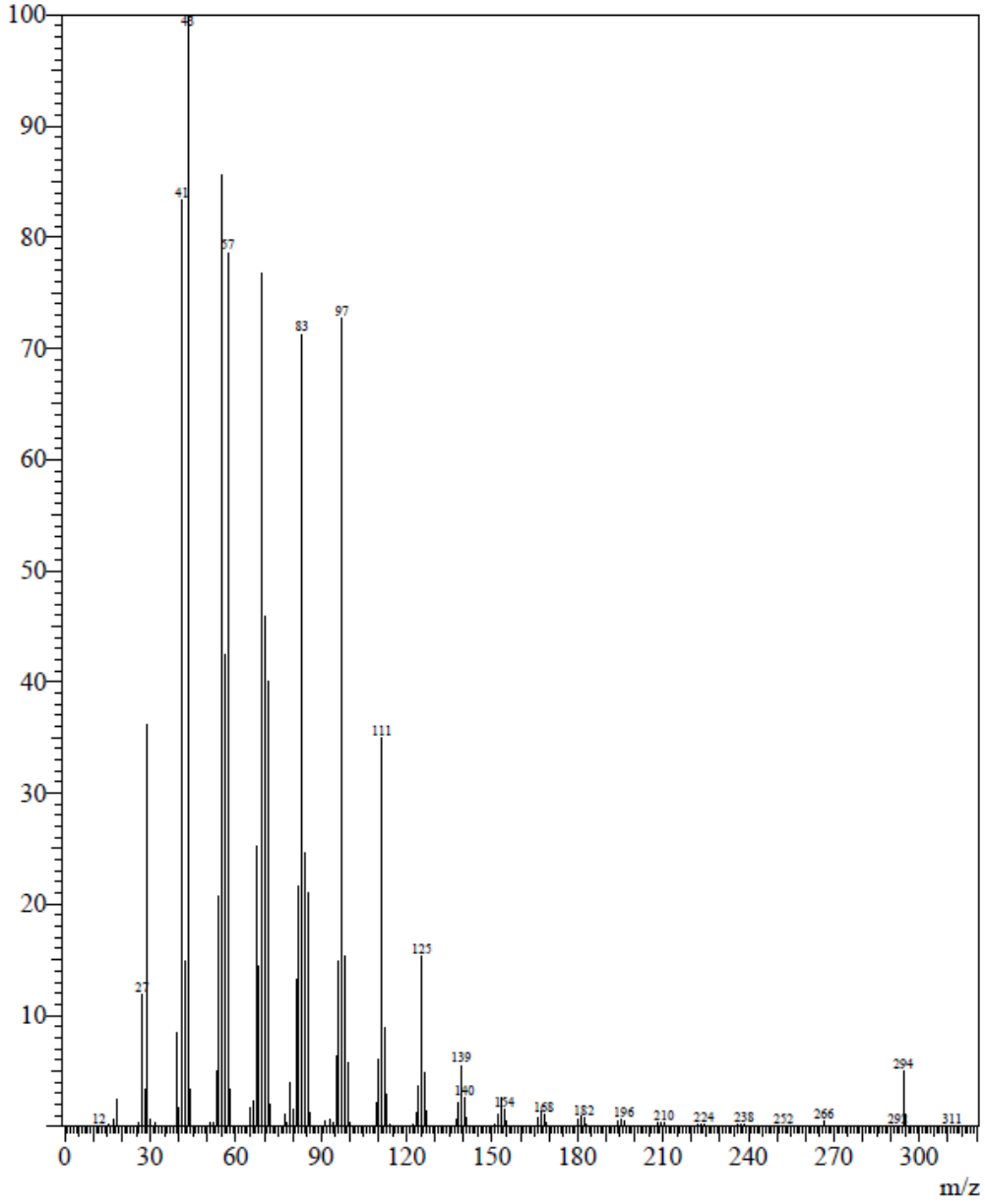

7-tertadecene
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
9.95
24.30
4.10
2.00

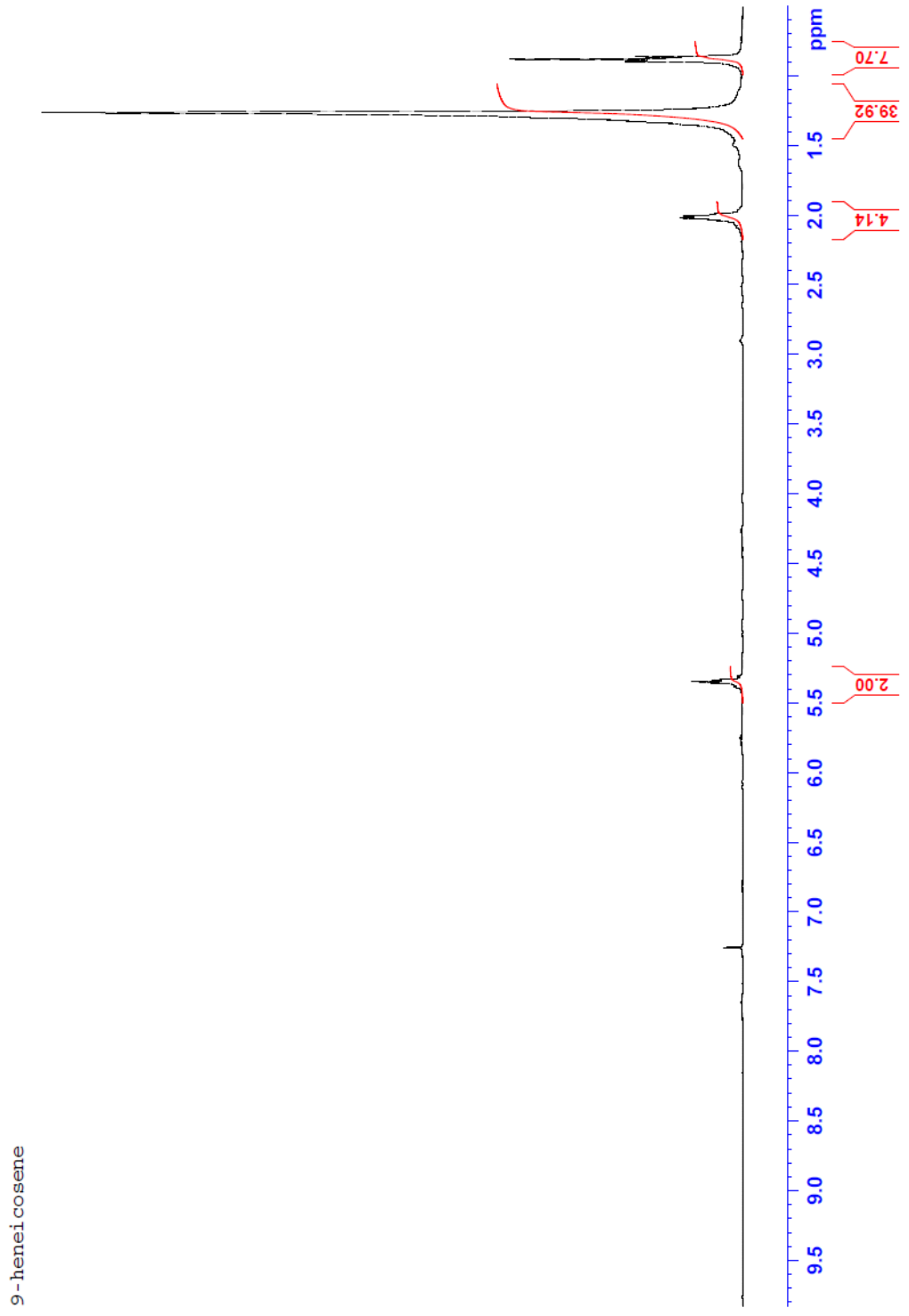
8-heptadecene (**31**)



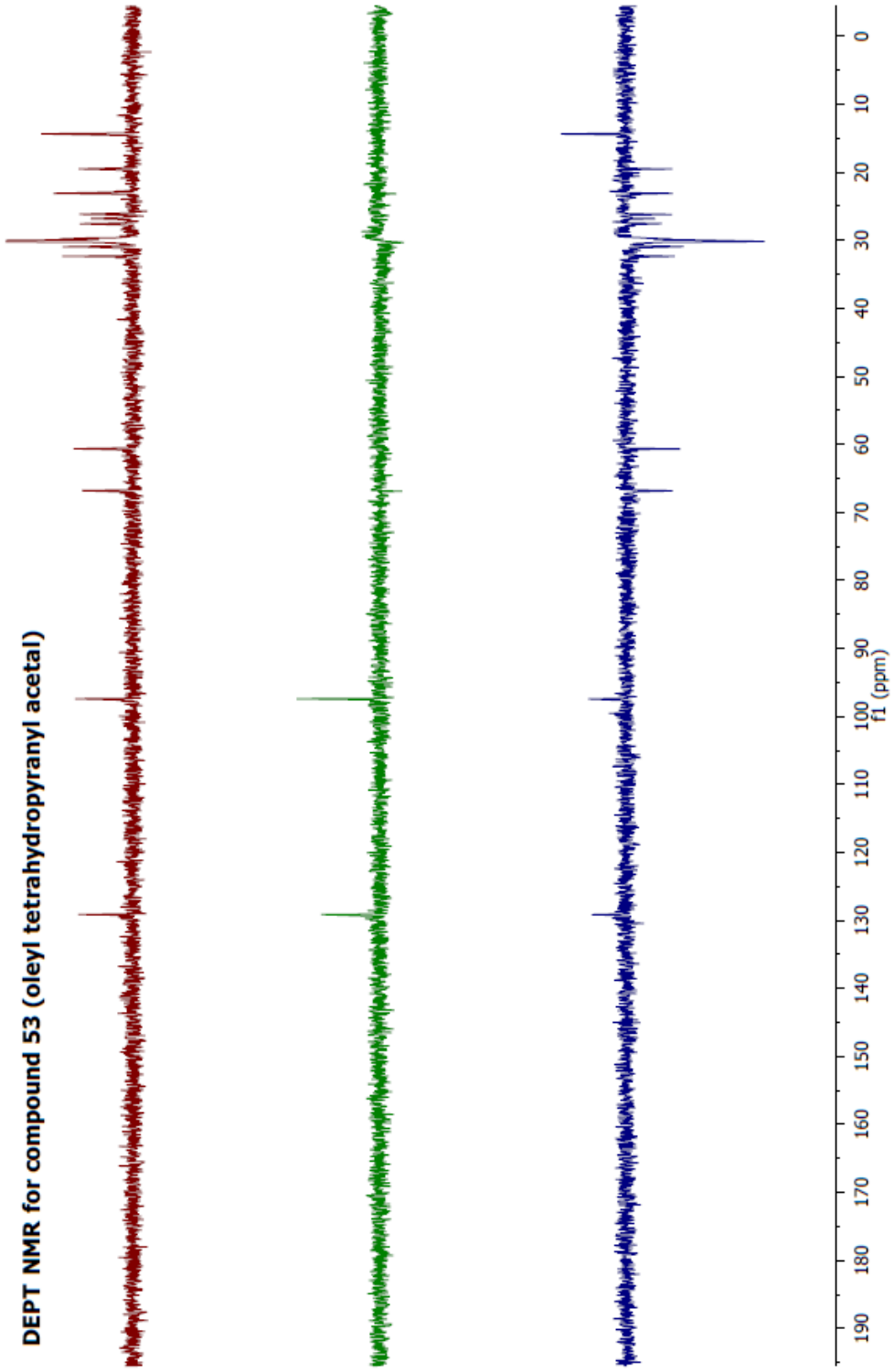

8-heptadecene
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
8.81
35.42
4.04
2.00

9-heneicosene (**32**)

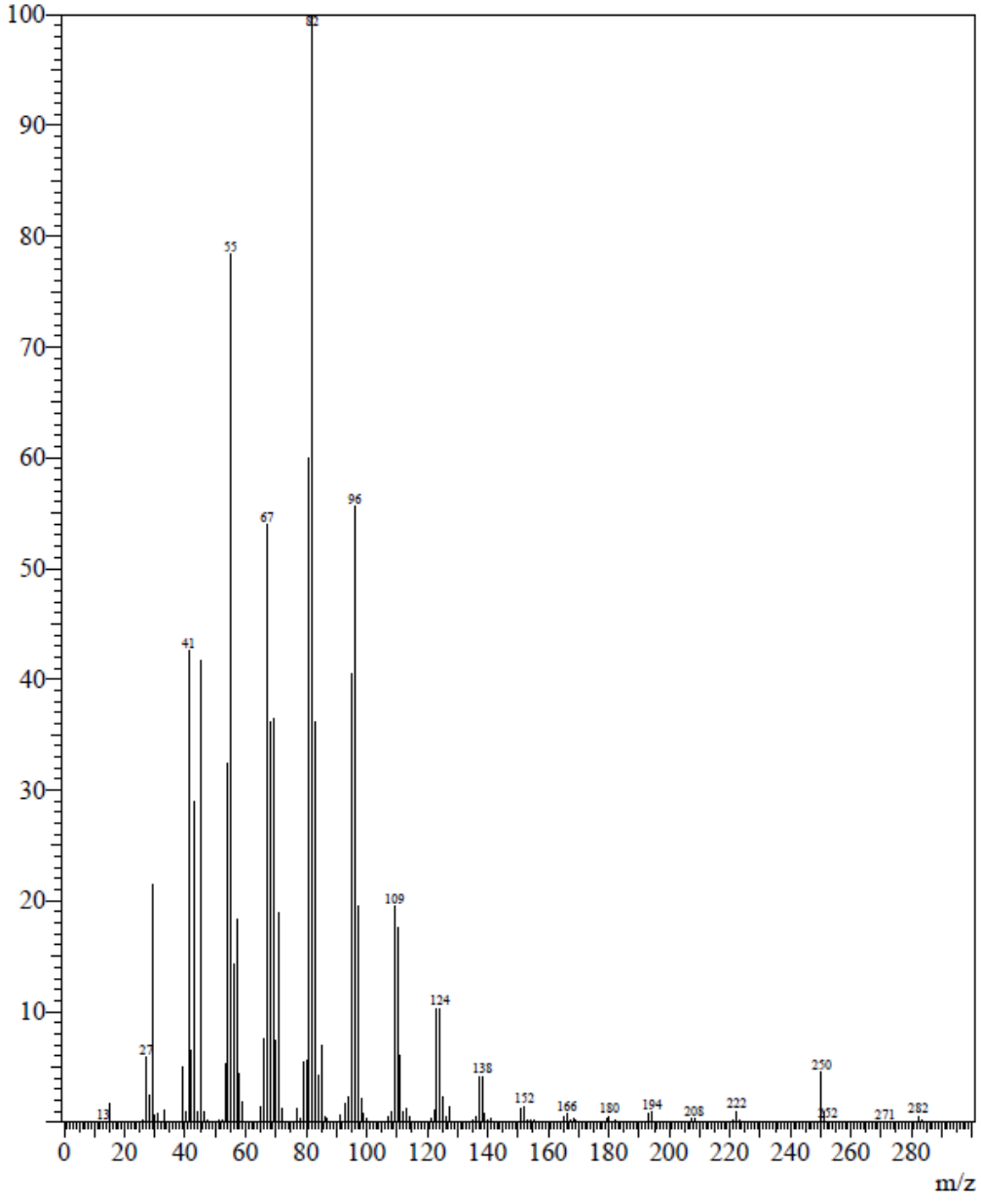


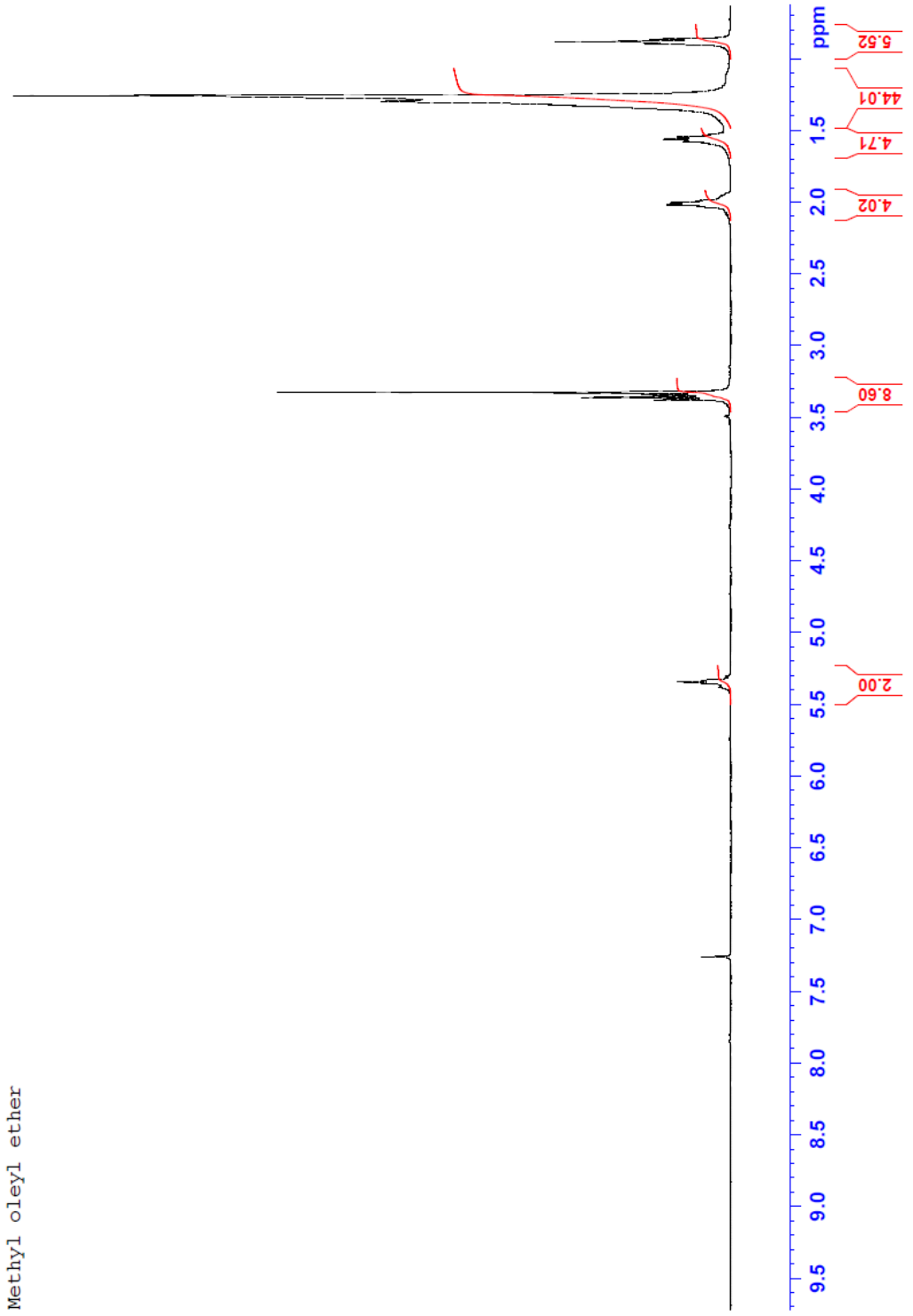

9-heneicosene
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
7.70
39.92
4.14
2.00

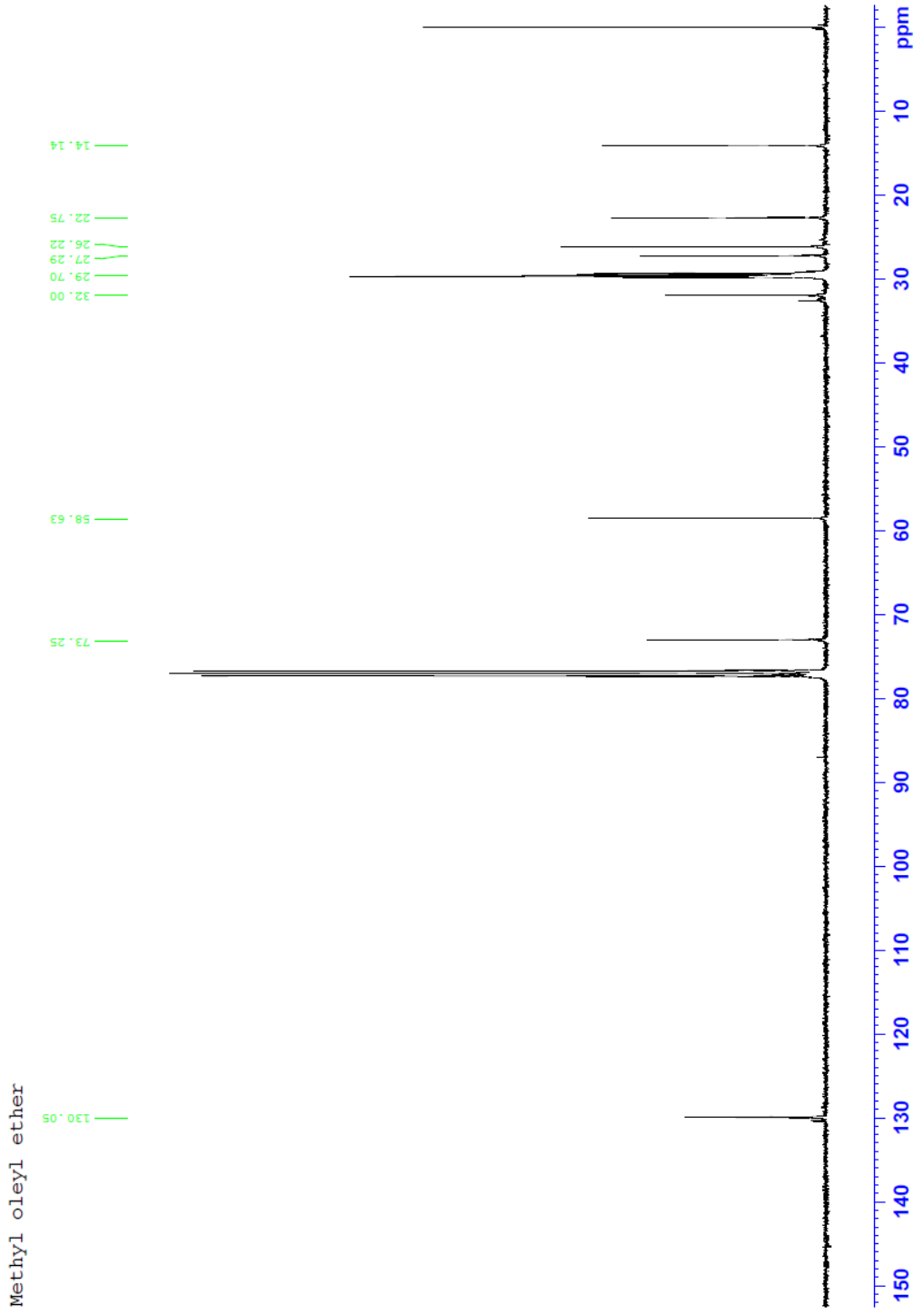
Oleyl tetrahydropyranyl acetal (**53**)



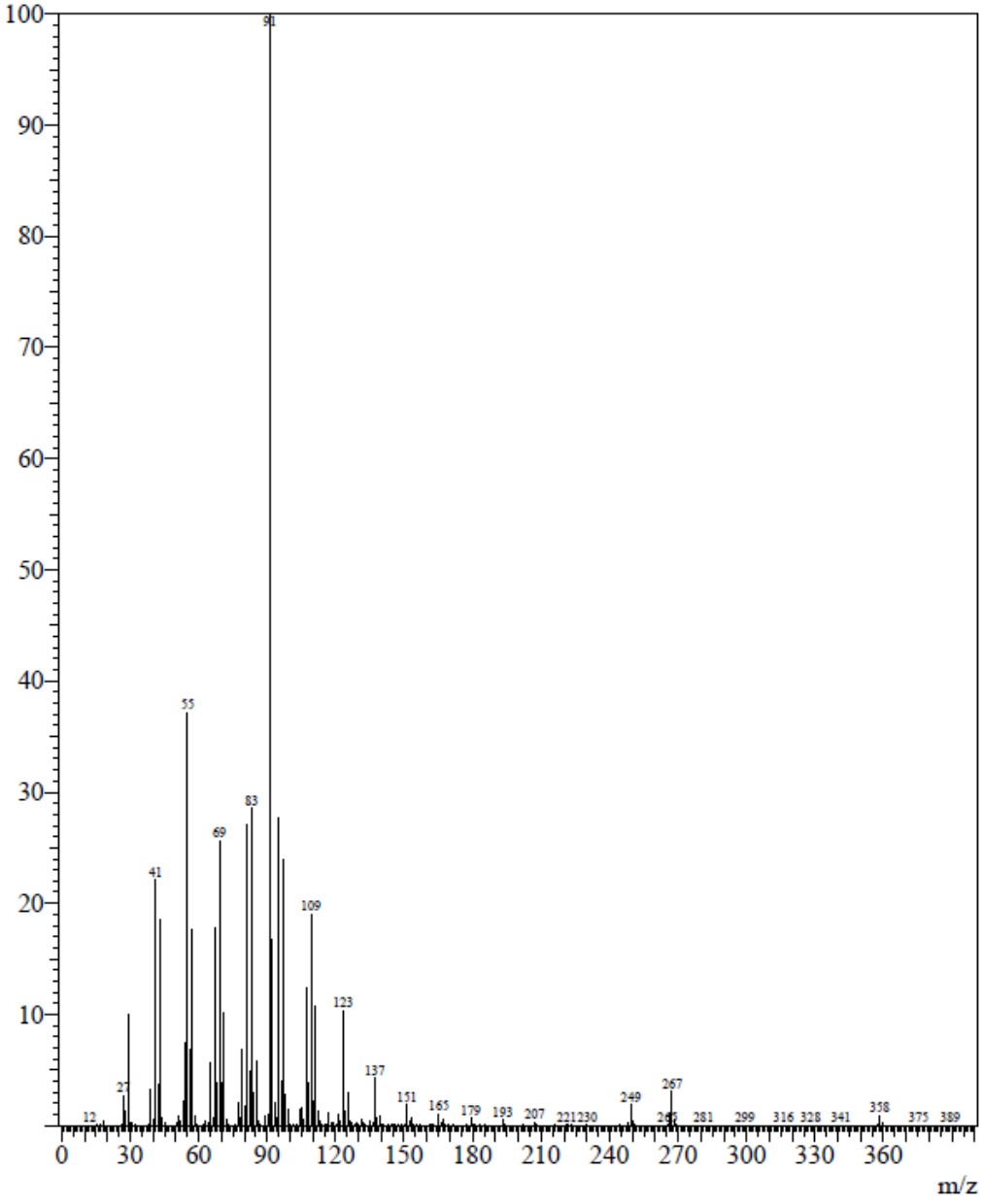
Methyl oleyl ether (**44**)

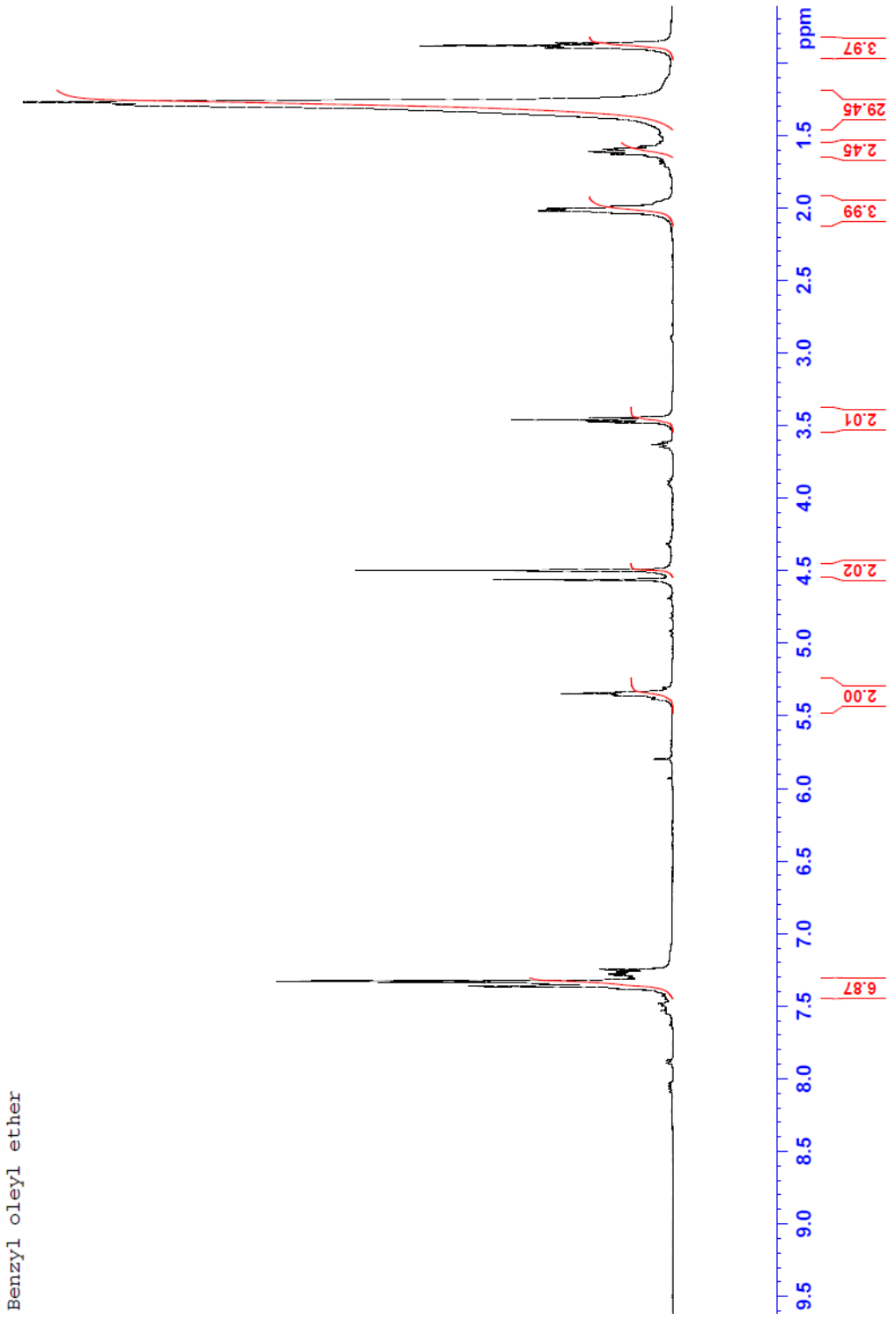



Methyl oleyl ether
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
5.62
44.01
4.71
4.02
8.60
2.00

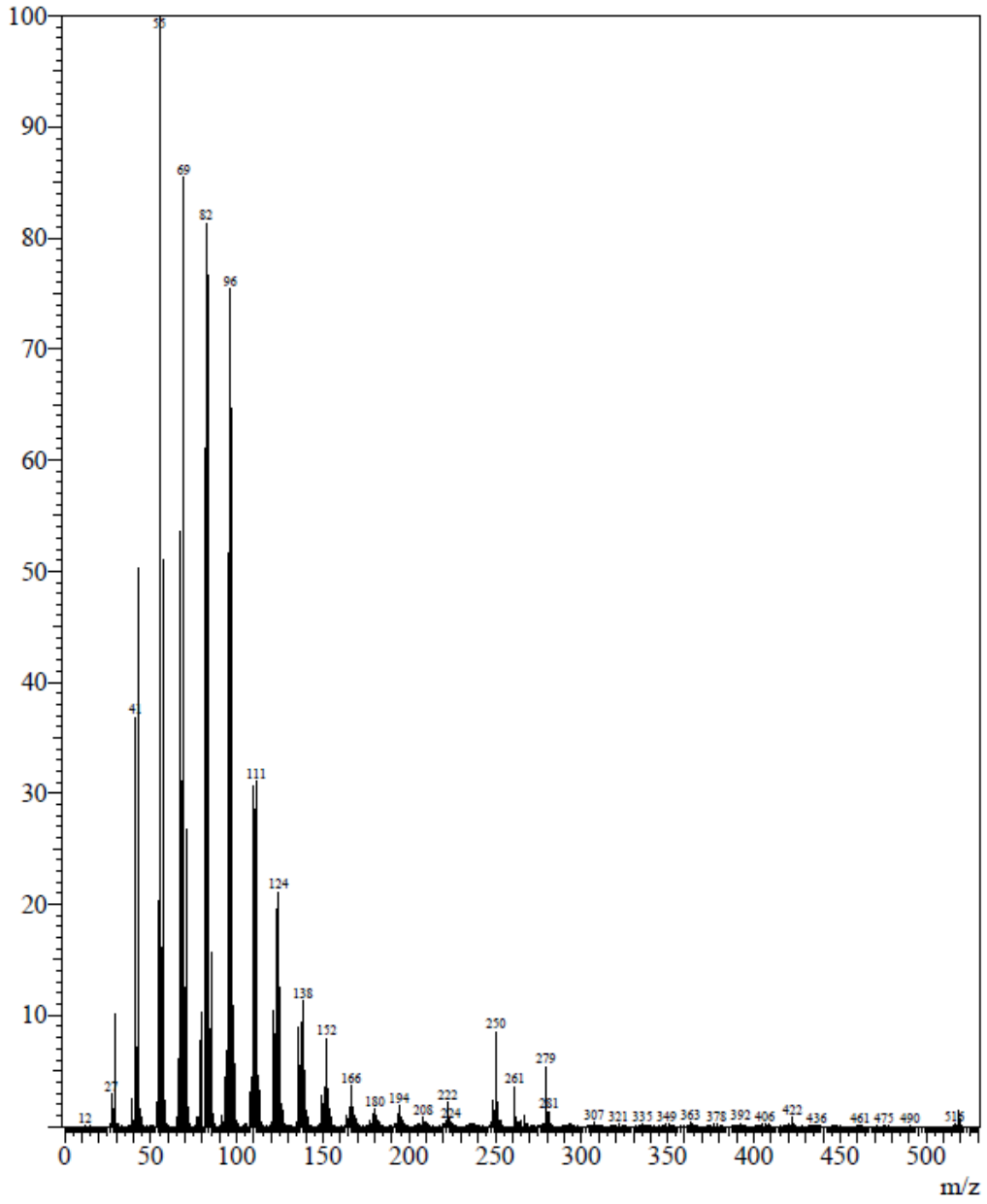

Methyl oleyl ether
14.14
22.75
26.22
27.29
29.70
32.00
58.63
73.25
130.05
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

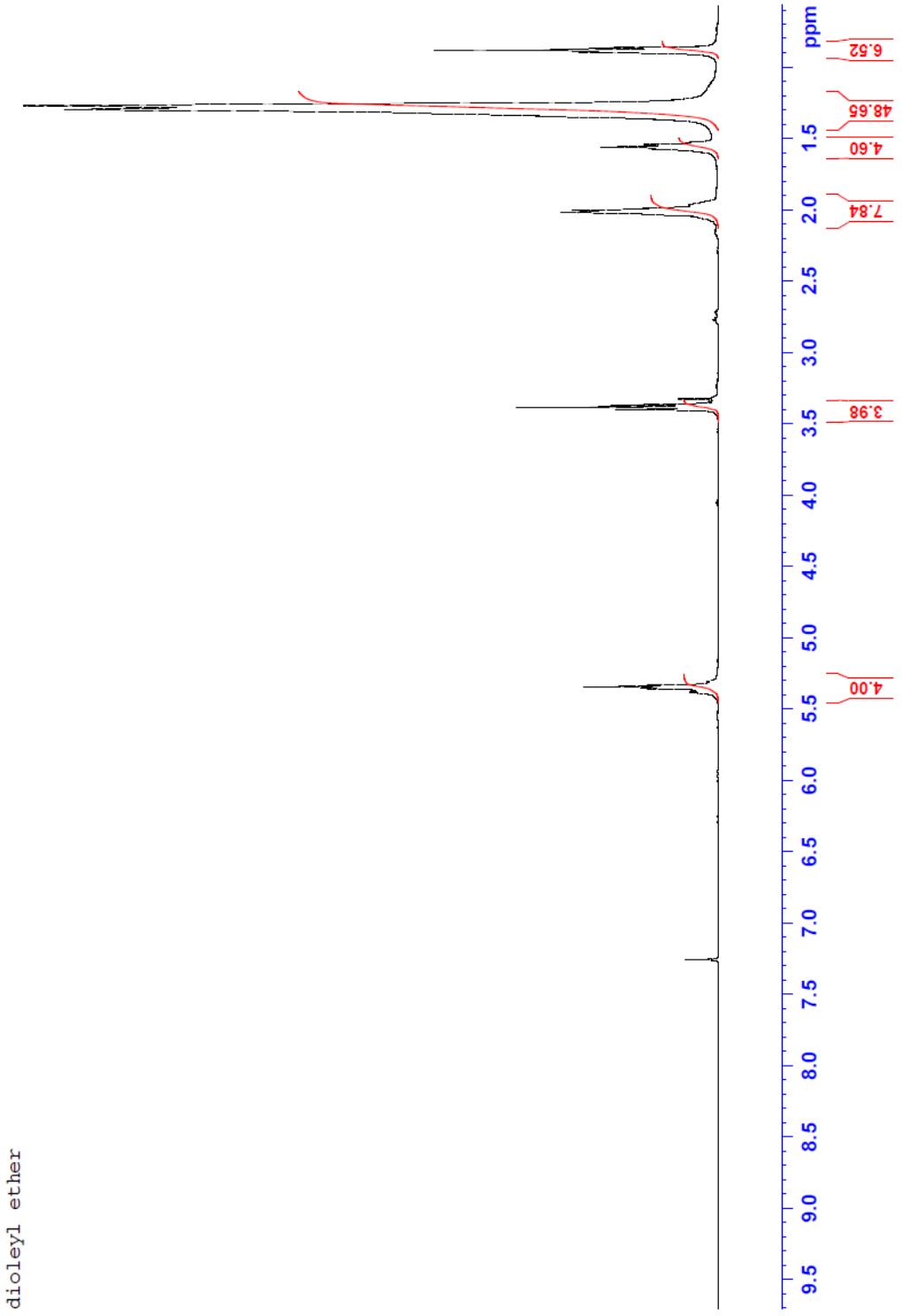
Benzyl oleyl ether (**43**)

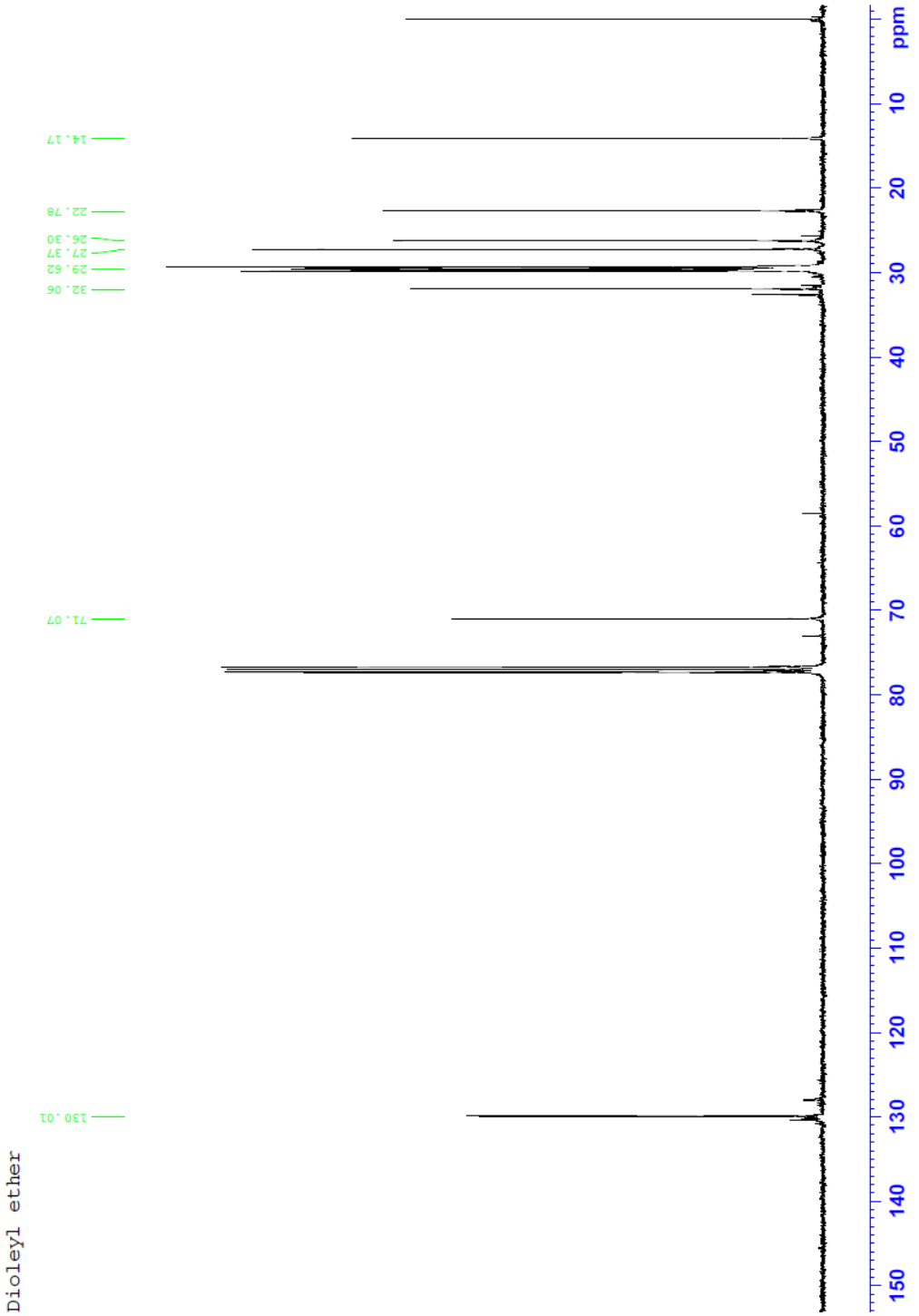



Benzyl oleyl ether
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
6.87
2.00
2.02
2.01
3.99
2.45
29.45
3.97

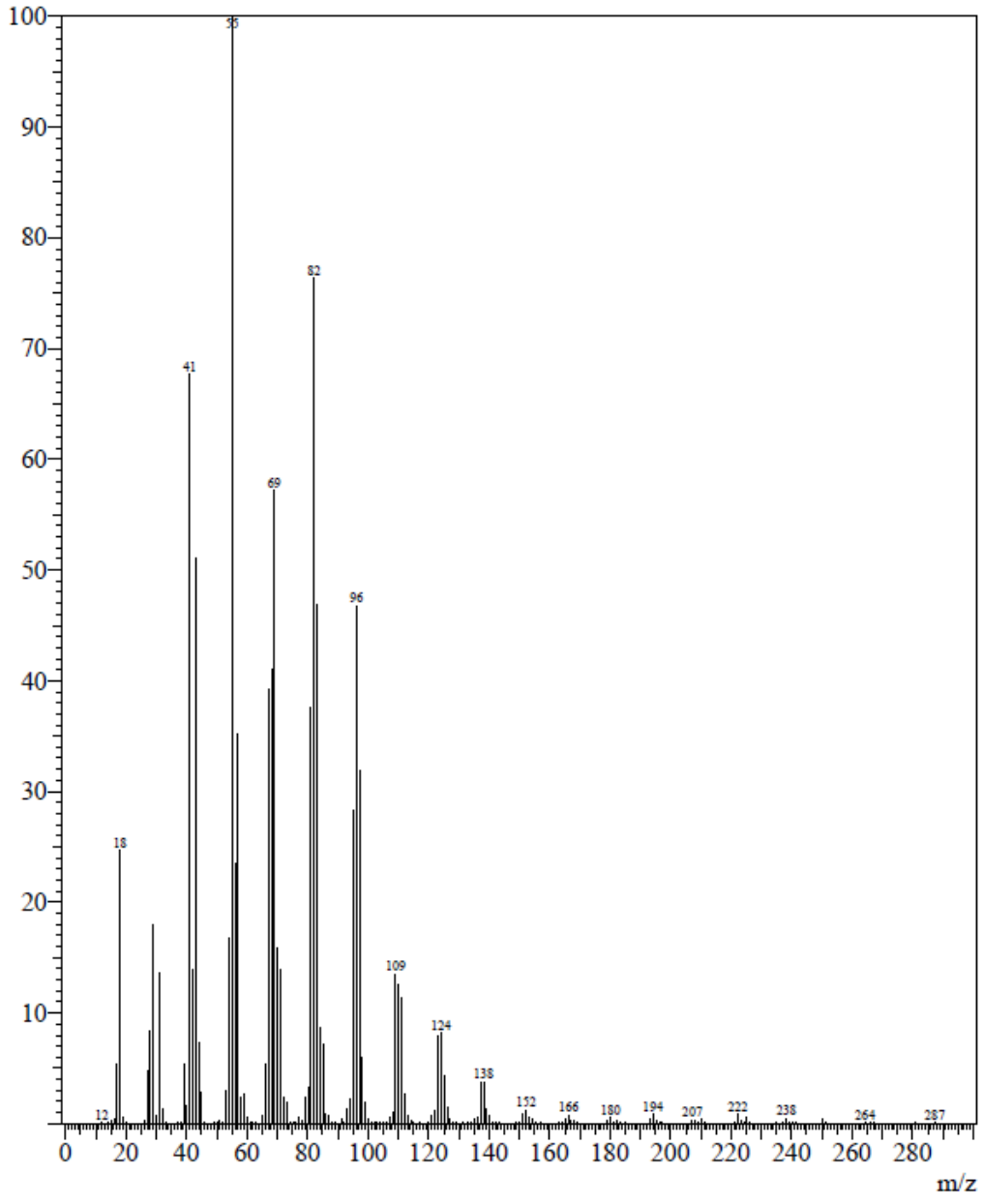
Dioleyl ether (**47**)

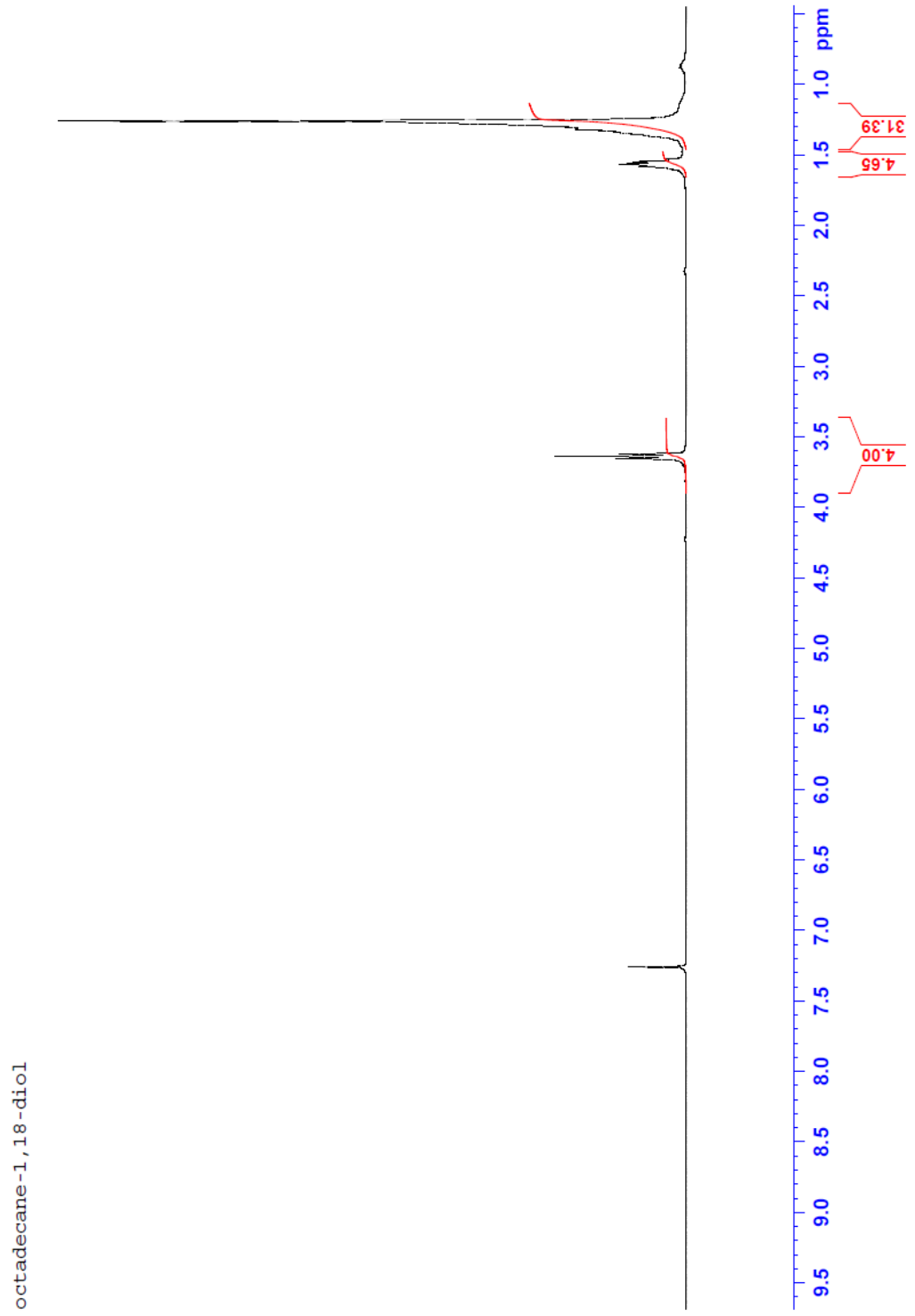



dioleyl ether
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
6.52
48.65
4.60
7.84
3.98
4.00

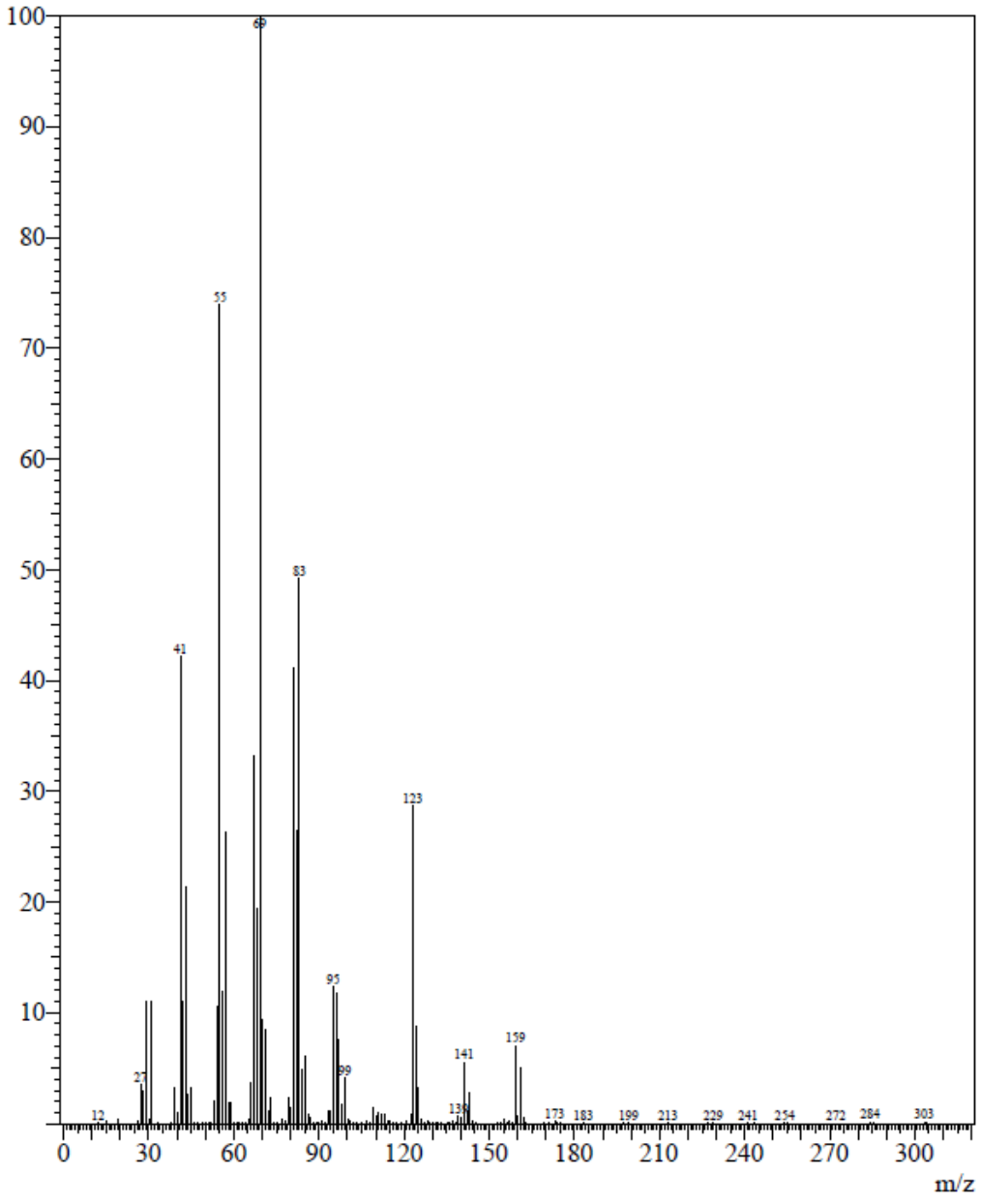

Dioleyl ether
14.17
22.78
26.30
27.37
29.62
32.06
71.07
130.01
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

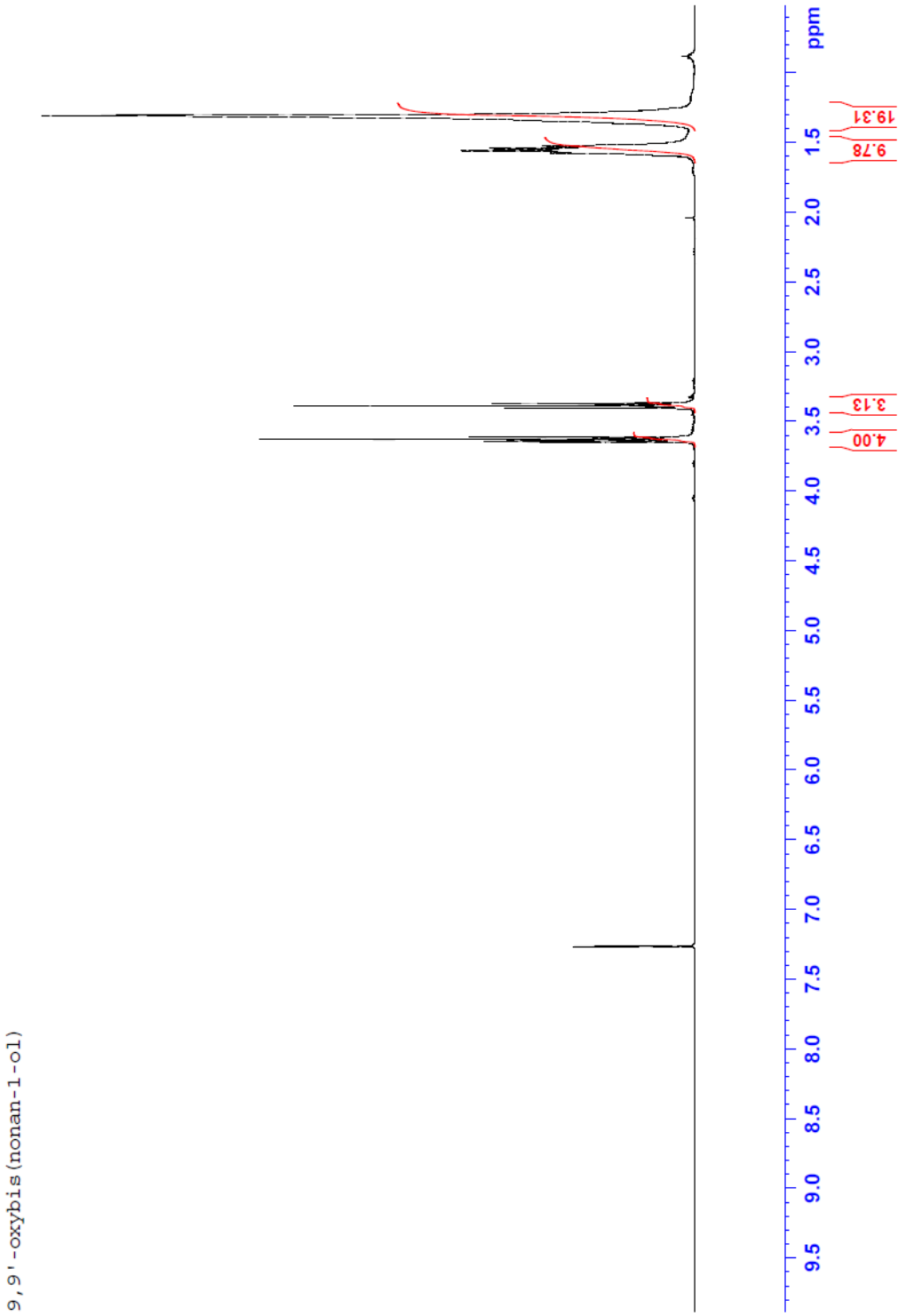
1,18-octadecanediol (**41**)

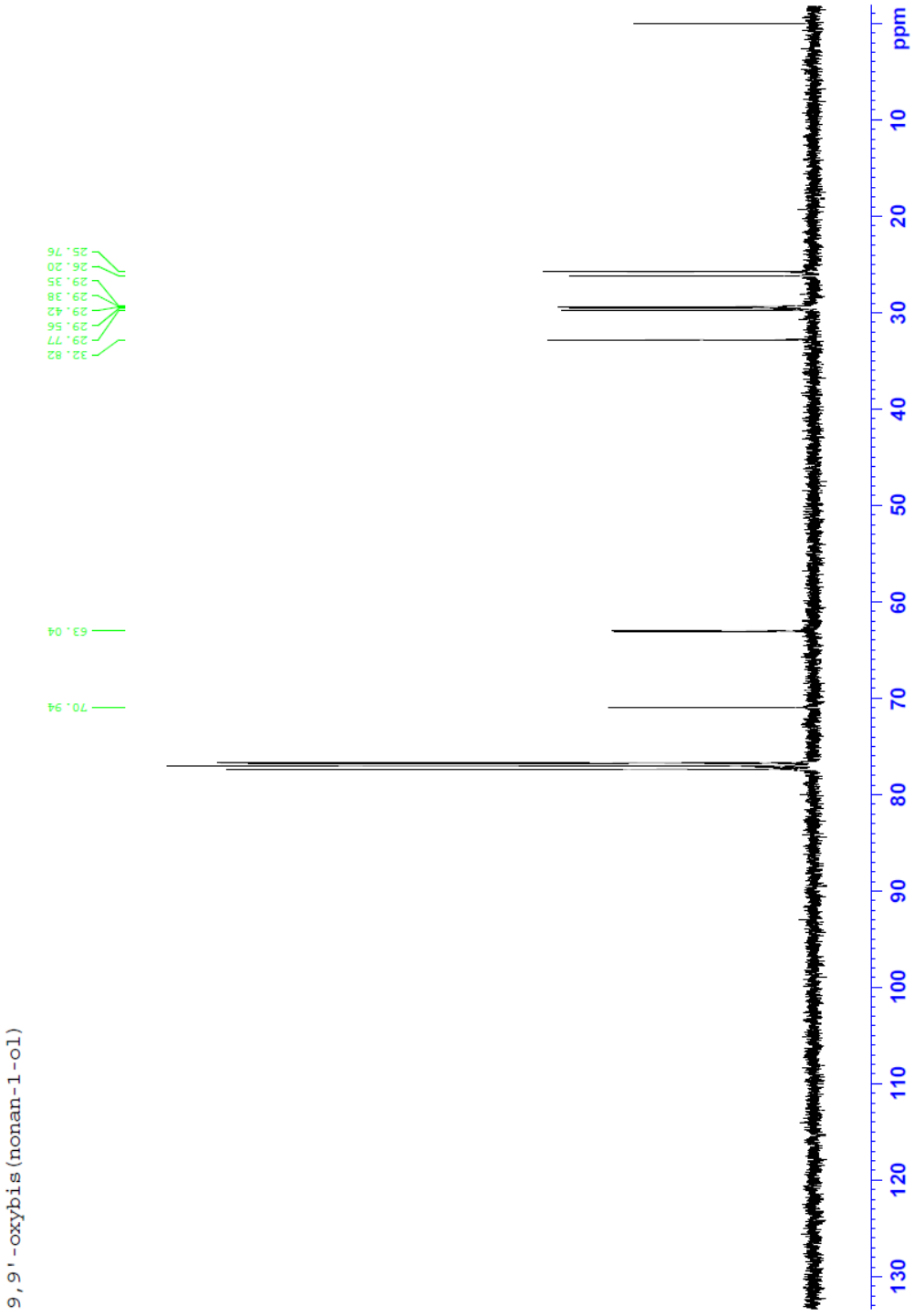



octadecane-1,18-diol
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
31.39
4.65
4.00

9,9'-oxybis(nonan-1-ol) (**48**)




9,9'-oxybis(nonan-1-ol)
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
19.31
9.78
3.13
4.00


9,9'-oxybis(nonan-1-ol)
32.82
29.77
29.56
29.42
29.38
29.35
26.20
25.76
63.04
70.94
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130