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Synthetic studies towards one isomer of (-)-mucosin

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Acknowledgements

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Graphical abstract
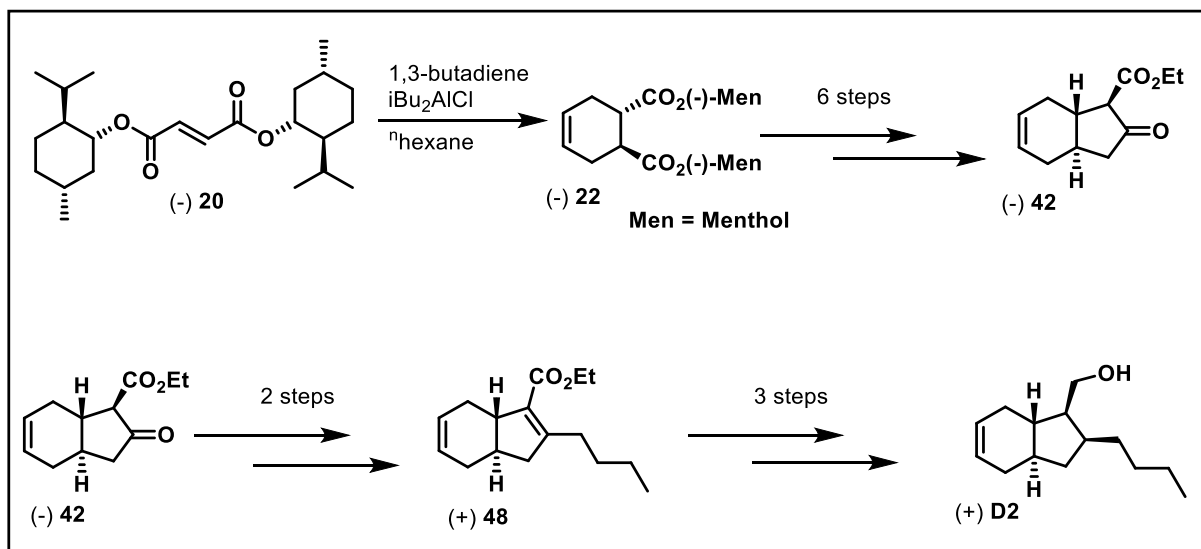
Abstract

This thesis describes synthetic work towards one isomer of (-)-mucosin, which is a bicyclic natural product isolated from a marine sponge. The focus of this project was to develop an enantioselective total synthesis of one *trans*-fused isomer of the suggested structure of the naturally occurring (-)-mucosin (**1**).

The synthesis was mainly divided into two parts, the synthesis of the bicyclic ketone *trans*-bicyclo[4.3.0]non-3-en-8-one (**35**) and the synthesis towards mucosin. Synthesis of the bicyclic ketone was previously reported in the literature, and was synthesized in this project by following the same protocols.

Regarding the synthesis towards *trans*-fused mucosin from ketone **35**, a change in synthetic strategy was made. After an asymmetric Diels-Alder reaction of (-)-dimenthyl fumarate (**20**) with 1,3-butadiene, the same literature protocols reported for synthesis of ketone **30** was followed to synthesize (-)-ethyl (1*R*,3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (**42**). From compound **42**, synthesis of ethyl (+)-(3a*S*,7a*R*)-2-((((trifluoromethyl)sulfonyl)oxy)-3a,4,7,7a-tetrahydro-1*H*-indene-3-carboxylate (**39**), ethyl (+)-(3a*S*,7a*R*)-2-butyl-3a,4,7,7a-tetrahydro-1*H*-indene-3-carboxylate (**48**), and ethyl (3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (**38a**) were accomplished. Reduction of **38a** to the corresponding alcohol ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methanol (**49**) gave separation of the diastereomers by column chromatography.

Derivatization of alcohol **49** to ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methyl 3,5-dinitrobenzoate (**50**) afforded crystals of one diastereomer obtained from **49**. The relative stereochemistry of this compound was determined by X-ray crystallography, and this isomer was named **D2**. Based on diastereoselective synthesis and comparison of the obtained data with literature values, stereochemical assignments were made of the synthesized compounds.

Unfortunately, synthesis of one isomer of *trans*-fused (-)-mucosin was not completed given the time of this project. However, the work accomplished can be used in later synthetic attempts of the compound, and there is suggested future work following this strategy presented at the end of this thesis.

Sammendrag

Denne oppgaven beskriver et forsøk på syntese av en isomer av (-)-mucosin, et bisyklisk naturprodukt isolert fra en marin svamp. Hovedfokuset i oppgaven var å utvikle en enantioselektiv totalsyntese basert på den foreslåtte strukturen (**1**) til naturproduktet, men med *trans* stereokjemi over 5/6-ring systemet.

Syntesen ble hovedsakelig delt inn i to: syntese av det bisykliske ketonet *trans*-bicyclo[4.3.0]non-3-en-8-one (**35**) og syntesen av mucosin. Keton **35** har tidligere blitt syntetisert og rapportert i litteraturen, og ble i dette prosjektet syntetisert ved å følge de samme protokollene.

I syntesen fra keton **35** mot en *trans*-fusjonert isomer av mucosin ble strategien endret. Etter en asymmetrisk Diels-Alder reaksjon mellom (-)-dimentyl fumarat (**20**) og 1,3-butadiene, ble de samme protokollene som er rapportert for syntesen av keton **35** fulgt til syntesen av (-)-(1*R*,3a*R*,7a*S*)-2-oks-2,3,3a,4,7,7a-heksahydro-1*H*-inden-1-karboksylat (**42**). Fra forbindelse **42**, ble synteser av etyl (+)-(3a*S*,7a*R*)-2-(((trifluorometyl)sulfonyl)oksy)-3a,4,7,7a-tetrahydro-1*H*-inden-3-karboksylat (**39**), etyl (+)-(3a*S*,7a*R*)-2-butyl-3a,4,7,7a-tetrahydro-1*H*-inden-3-karboksylat (**48**), og etyl (3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-heksahydro-1*H*-inden-1-karboksylat (**38a**) gjennomført. Reduksjon av forbindelse **38a** til ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-heksahydro-1*H*-inden-1-yl)metanol (**49**) ga seperasjon av den diastereomere blandingen ved hjelp av kolonne kromatografi.

Derivatisering av alkohol **49** til ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-heksahydro-1*H*-inden-1-yl)metyl 3,5-dinitrobenzoat (**50**) ga krystaller av den ene diastereomeren syntetisert fra **49**. Den relative stereokjemien til denne forbindelsen ble så bestemt ved røntgenkrystallografi og navngitt som **D2**. Via stereoselektiv syntese og sammenlikning av oppnådde data med litteraturverdier ble stereokjemien av de syntetiserte forbindelsene bestemt.

I løpet av tiden som ble gitt til dette prosjektet, ble dessverre ikke syntesen av en *trans*-fusjonert (-)-mucosin isomer gjennomført. Arbeidet som har blitt utført kan imidlertid bli brukt i senere forsøk på syntese av forbindelsen, og forslag til videre arbeid basert på strategien som har blitt benyttet er presentert i slutten av oppgaven.

Abbreviations

AA	Arachidonic acid
COX	Cyclooxygenase
DGLA	Dihomo-γ-linolenic acid
DHA	Docosahexaenoic acid
DIBAL-H	Diisobutylaluminium hydride
DMSO	Dimethyl sulfoxide
EPA	Eicosapentaenoic acid
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
LO/LOX	Lipoxygenase
LT	Leukotriene
LX	Lipoxin
MaR	Maresin
NSAID	Non-steriodal anti-inflammatory drug
PD	Protectin
PG	Prostaglandin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
PGI	Prostacyclin
p-Ts	*para*-toluenesulfonyl
PUFA	Polyunsaturated fatty acid
RT	Room temperature
Rv	Resolvin
SPM	Specialized pro-resolving mediator
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofurane
TLC	Thin layer chromatography

Table of contents

1   Introduction

In 1997, Casapullo et al.[1] reported the isolation of mucosin, a marine natural product from the Mediterranean sponge *Reniera mucosa.* The proposed structure (**1**) was elucidated as the optically active methyl ester (**2**) by using several analytical tools (MS, IR, and various NMR experiments), but the absolute configuration was not determined.

The suggested structure (**1**) contains a bicyclo[4.3.0]nonene moiety, with side chains on C-8 and C-16, as shown in figure 1.1.
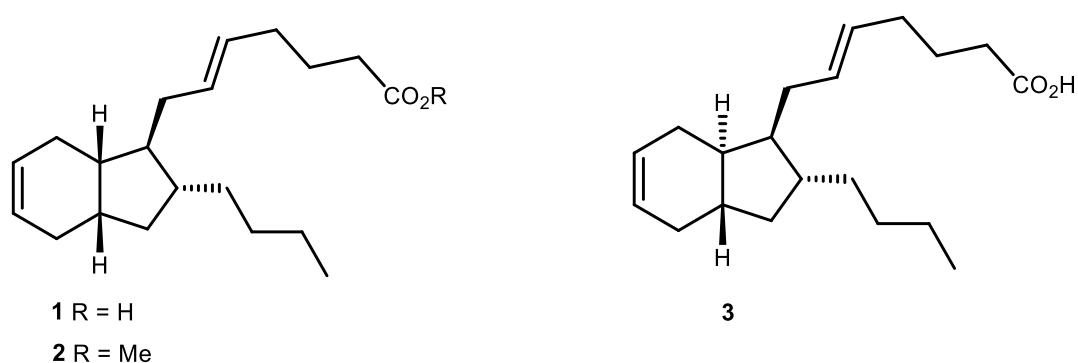

1 R = H
2 R = Me
               3

Figure 1.1: *The initial reported structure of mucosin (**1**), its methyl ester (**2**) and one putative isomer of trans-fused mucosin (**3**).*

In 2012, Whitby et al.[2] published a synthesis of the enantiomer of mucosin. The absolute configuration of the natural product was indirectly established by comparison of data, including optical rotation and NMR spectroscopy, with **2**.

However, the first total synthesis of the originally claimed structure of mucosin was recently reported by Gallantree-Smith et al.[3] Spectral data and optical rotation values obtained did not comply with that of the isolated natural product nor the synthetic isomer.

In addition, the same group has prepared one of several diastereoisomers of mucosin (**1**) with opposite *anti* configuration on C-8 and C-16.[4] The obtained spectroscopic data of this isomer was not in agreement with the data of the isolated natural product either.

The true structure of mucosin is thus still not established, and it is possible that the compound contains a *trans*-fused bicyclo[4.3.0]nonene ring system, depicted as one putative isomer (**3**) in figure 1.1. This remains to be verified by total synthesis.

1.1 Natural Products

Natural products are chemical compounds produced by living organisms, and can be divided into primary and secondary metabolites. Primary metabolites are produced in all living species and are involved in essential life processes to provide energy, normal growth, and reproduction. Examples include crucially important molecules such as carbohydrates, proteins, fats, and nucleic acids.[5]

Secondary metabolites, by contrast, are only found in specific organisms and only produced under certain conditions.[5-6] They are not biosynthesized by the general metabolic pathways and have no primary function directly involved in the normal physiological processes. Although these molecules are non-essential for life, they do seem to play an important role for the welfare of the producer, such as defense against predators or reproduction.[5]

Since ancient times, natural products have been a traditional source of medicines. As early as 7000 years ago, opium has been used to treat pain, and plants like turmeric and wild garlic have been used for treatment of blood clotting and circulatory problems, respectively.[7-8]

In modern time, the active ingredients have been isolated and characterized. A typical example include morphine isolated from the opium poppy. Numerous other natural products have been isolated and identified, with currently about one-third of clinically used drugs being of natural origin.[9]

1.2 Marine Natural Products

Secondary metabolites produced in the marine environment tend to exhibit greater chemical diversity compared with those from terrestrial organisms.[10] Research suggest that the harsh growth conditions in the marine environment has resulted in an array of natural products with unique structures and specific activities.[10-12]

Hence, the marine environment has attracted the interest of biologists and chemists worldwide for more than 50 years, which has led to the isolation of approximately 20,000 different compounds of marine origin. Many of these have proved to exhibit cytotoxic, anti-inflammatory, antiviral, antifungal and antibiotic activities among others.[10-13] However, by 2014, only eight drugs of marine origin were approved by the Food and Drug Administration

or the European Medicines Evaluation Agency, although a large number of compounds have entered the preclinical phase.[13]

One of the challenges of marine natural product discovery is accessibility to marine resources, and sustainable production for clinical trials and eventually marketing. Access to the ocean and its deepest areas is challenging, although resourceful equipment such as manned submersibles and remotely operated underwater vehicles has made selective sampling possible.[13]

Once an interesting compound is identified, the small amount available from its natural source usually does not provide sufficient material for structure elucidation, biological testing, and clinical trials. For instance to produce 300 mg of the anticancer compound halicondrin B (**4**), one ton of the scarce deep-water sponge *Lissodendoryx sp.* is required.[14-15] Commercialization of this compound by extraction from its natural source would clearly be devastating to the marine environment. One possible solution to this problem is chemical synthesis, which often represents its own challenges of making more complex molecules.[12-13] Other alternatives for commercial production are hemi-synthesis and/or synthesis of analogues.
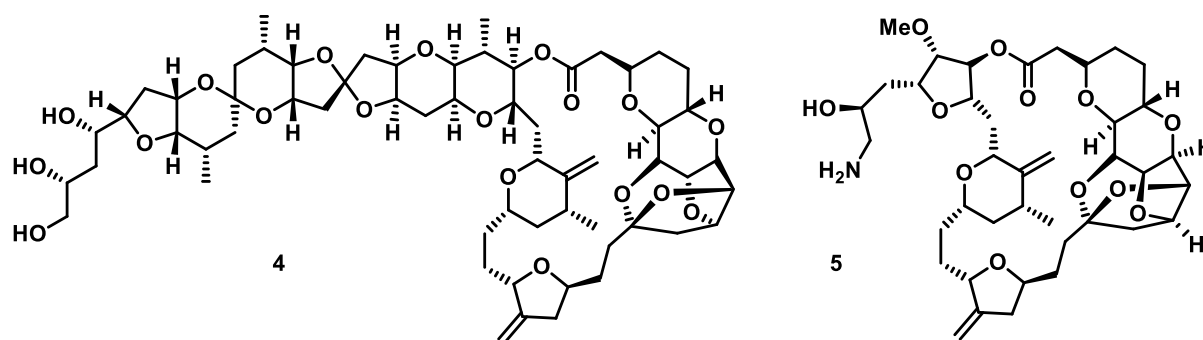

Figure 1.2: *Chemical structure of halicondrin B (**4**) and eribulin (**5**).[15]*

The complex marine natural product halicondrin B (**4**), was successfully synthesized by Kishi and coworkers in 1992.[16] The research resulted in the more potent and structurally simpler synthetic analogue eribulin (**5**), which has been used to treat patients with metastatic breast cancer.[12, 15, 17] Hence, this is an illustrative example of the importance and need for synthetic organic chemistry in medicinal research.

1.3 Fat and fatty acids

Fats are triesters of glycerol and fatty acids, which serve as long-term storage of energy for most organisms, and are very important components of cell membranes. In addition, fat insulate vital body organs and contributes to maintain body temperature.[18]

Fatty acids are carboxylic acids with a hydrocarbon chain. They are usually aliphatic with an even number of carbon atoms. Most commonly, the fatty acids are unbranched and can be saturated, mono – or polyunsaturated. If present, the double bonds are usually skipped with *cis*-geometry.[19-20]

Figure 1.3: Chemical structures of linoleic acid (6) and α-linoleic acid (7).

Mammals are only able to insert a *cis*-double bond between the carboxyl group and C-9, so the essential poly unsaturated fatty acids (PUFAs), such as linoleic acid (**6**) and α-linolenic acid (**7**), must be provided through the diet. The essential fatty acids are necessary for the biosynthesis of arachidonic acid (AA) and eicosapentaenoic acid (EPA), which are precursors for several other important molecules such as the prostaglandins and leukotrienes.[6, 19] Further chain extension and desaturation using EPA as the substrate, gives docosahexaenoic acid (DHA), an important precursor for metabolites active in the resolution phase of inflammation.[21-22]
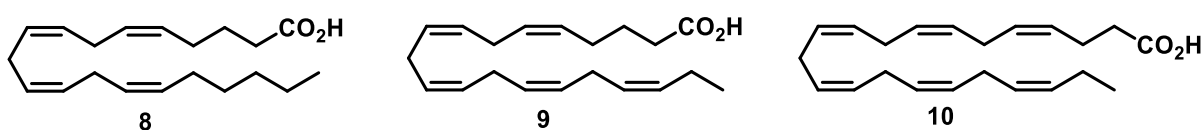

Figure 1.4: chemical structures of arachidonic acid (8), eicosapentaenoic acid (9), and docosahexaenoic acid (10).

1.4 Prostaglandins

Prostaglandins (PGs) are a class of biologically active PUFA derived compounds. PGs are formed by most cells in the mammalian tissue, and synthesized locally in response to sustain homeostatic functions. At very low concentrations, prostaglandins act as vasodilators, suppress blood platelet aggregation, inhibit gastric acid secretion, and regulate contractions of smooth muscle, in addition to play a key role in modulation of the inflammatory response.[19, 23-24]

Because of their ability to stimulate uterine smooth muscle, a major area for the application of prostaglandins are to induce abortion in the early stages of pregnancies, and to induce labor in mothers at term. They are also used to treat male impotence, and to reduce the risk of blood clotting during renal dialysis.[19, 25]

Prostaglandins are rapidly degraded with second to minute half-lives. Thus, synthetic analogues resistant to metabolism have been developed. Examples include misoprostol (**11**), used for treatment of peptic ulcers, and carboprost (**12**), used to induce both abortion and labor at term.[19]
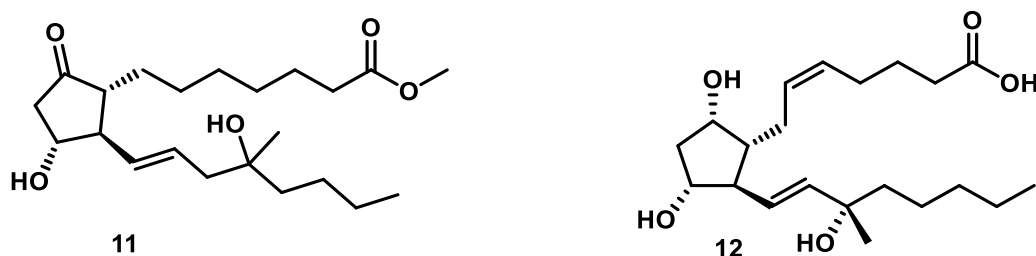

***Figure 1.5:*** *Chemical structure of misoprostol (**11**) and carboprost (**12**).*

The prostaglandin skeleton consist of a cyclopentane ring with two sidechains. One of the side chains is a seven-carbon carboxyl terminus, and the other an eight-carbon methyl terminus. PGs, together with the thromboxanes and leukotrienes, are all derived from three C-20 fatty acid precursors, and are therefore termed eicosanoids.[19, 23-24]

1.4.1 Biosynthesis of prostaglandins

AA (**8**) is considered to be the major prostaglandin precursor.[26] The biosynthetic pathway includes a number of steps and enzymes, but can be divided into a three-step sequence. First, the fatty acid is released from the membrane phospholipids. Second, the fatty acid is oxygenated by enzymes known as cyclooxygenase (COX). In this process, two molecules of molecular oxygen are incorporated, and a five membered ring is formed.[19] Finally, the resulting endoperoxide is transformed into a wide range of prostaglandins by specific enzymes; this is illustrated in scheme 1.1. [26-27]
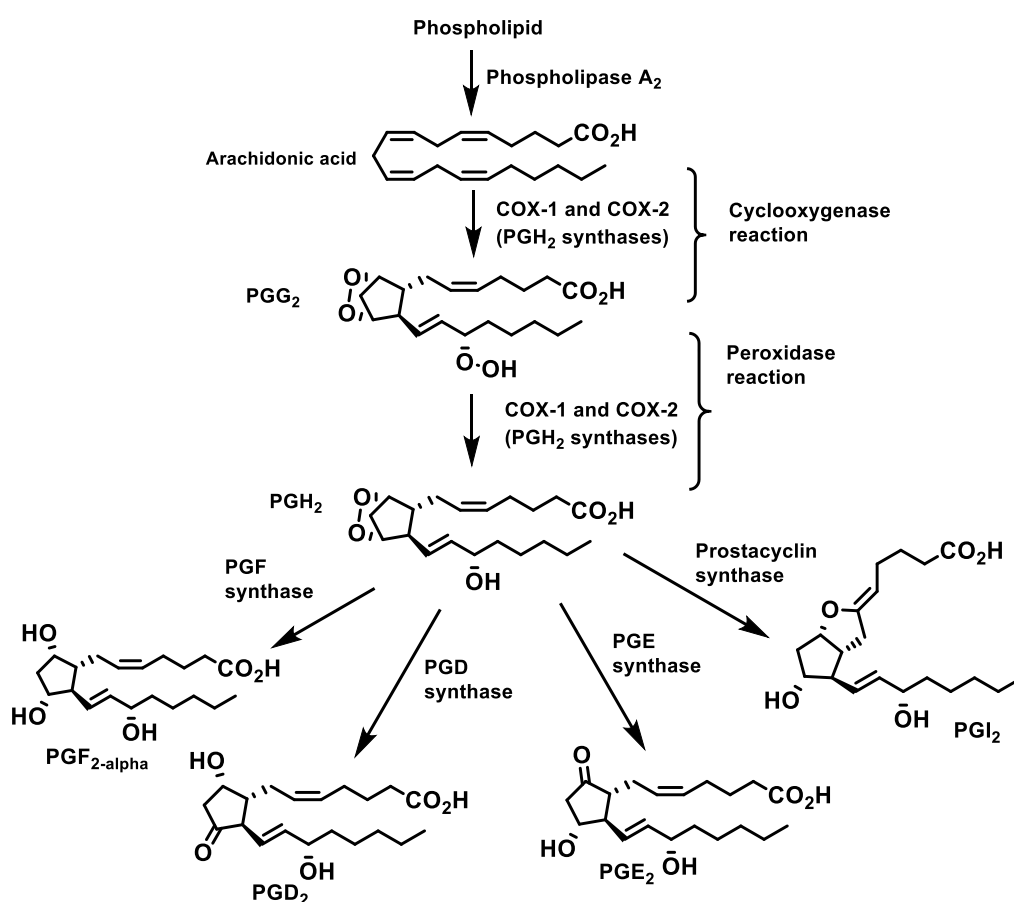
Scheme 1.1: Biosynthesis of prostaglandins.[27]

Dihomo-γ-linolenic acid (DGLA), in addition to AA (**8**) and EPA (**9**), serve as precursors for prostaglandins of the 1-, 2-, and 3-series respectively, and the different series are categorized according to the number of double bonds present in the side-chains of the products.[19]

1.5 Cyclooxygenases

Cyclooxygenase (COX) is an enzyme that participate in the prostaglandin synthesis. COX is a family of isozymes, but the two involved in the biosynthetic pathway are termed COX-1 and COX-2. COX-1, which is expressed in most cells, catalyze the formation of PGs that are important for normal cellular functions, whereas COX-2 is expressed as a response to inflammation.[24] These enzymes have two catalytic sites. In the cyclooxygenase active site, AA (**8**) is converted to the hydroperoxy-endoperoxide and a hydroperoxy group is added to C-15, giving PGG_2, shown in scheme 1.1. In the peroxidase active site, the hydroperoxy is reduced to the corresponding alcohol, namely PGH_2.[28]

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, inhibit the activity of COX and thereby the synthesis of PGs, which in turn reduce symptoms like fever and pain. Side effects, like gastrointestinal ulcers, have been associated with the inhibition of both. Since COX-2 is upregulated in influenced tissue, it is preferable for selective inhibition of this enzyme.[28-29] Although COX-2 is induced by inflammatory stimuli, recent studies show that the enzyme is also involved in the biosynthesis of novel potent anti-inflammatory and pro-resolving lipid mediators.[30-31]

1.6 Lipoxygenases

Lipoxygenase (LOX) is a class of enzymes that catalyze the stereoselective oxygenation of PUFAs to yield physiological important metabolites.[21, 32] There are several different LOXs expressed in humans: 5-LOX, 12-LOX, 12*R*-LOX, 12/15-LOX. The different LOX isoforms are named according to which carbon in the AA (**8**) chain the oxygen is added to.[32]

The first step of the catalytic cycle consist of stereoselective radical abstraction of a hydrogen, leading to a carbon centered radical between two skipped *Z*-double bonds in a PUFA, as shown in scheme 1.2. In the second step, one double bond migrates to yield an *E,Z*-conjugated diene. Then finally, insertion of molecular oxygen and hydrogen yields a hydroperoxy acid product. Very often the hydroperoxy products constructed by LOX enzymes are reduced to an alcohol. [32-33]
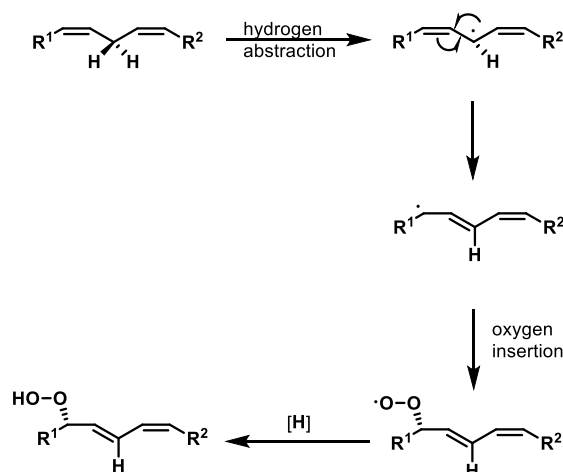
Scheme 1.2: *Mechanism for lipoxidation of a PUFA by lipoxygenase.*[32]

In addition to AA (**8**), other PUFAs such as EPA (**9**) and DHA (**10**), serve as substrates for lipoxygenases. The various hydroperoxy products are further transformed enzymatically to produce several biologically active lipid metabolites including leukotrienes, lipoxins, resolvins, protectins and maresins.[21]

1.7 Other oxylipins

In addition to the PGs, several other interesting PUFA metabolites have received attention because of their biological activity.

Inflammation is a protective mechanism by the body's immune system, which is caused by harmful stimuli or infections. The function of inflammation is to remove the cause of cell injury, followed by tissue repair and finally restore to normal cellular functions.[34]
The leukotrienes are produced from AA (**8**) by oxygenation via the 5-LOX pathway. These compounds, together with the PGs, are involved in allergic reactions and inflammatory processes by promoting inflammation (known as pro-inflammatory mediators).[22, 35] By contrast, AA (**8**) is also involved in the biosynthesis of lipoxins (LXs), which are known to inhibit the biosynthesis of pro-inflammatory lipid mediators, and to participate in the resolution phase of inflammation. LXs are biosynthesized by action of different LOXs in consecutive steps, as illustrated in figure 1.6. The products that results from the same pathway by oxygenation of the ω-3 fatty acids EPA (**9**) and DHA (**10**) produce several other anti-inflammatory and pro-resolving metabolites, such as the previous mentioned resolvins, protectins and maresins. [21-22] The chemically distinct families are collectively termed specialized pro-resolving mediators (SPMs), and have been identified and characterized by Serhan and coworkers in recent time.[21-22, 36]

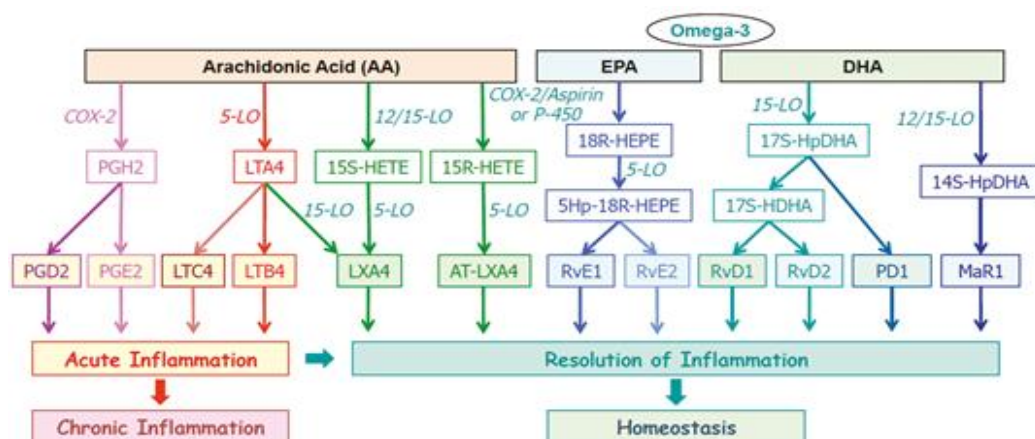

Figure 1.6: *Biosynthetic cascade of selected lipid mediators derived from AA (**8**), EPA (**9**) and DHA (**10**) and their role in inflammation. Adapted from reference 22.*

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1.8 Discussion of the biosynthesis of mucosin

Nothing is currently known regarding the biosynthesis of mucosin, but it is thought to be derived from AA (**8**) via an intramolecular cycloaddition, and isomerization of the *cis*-5,6-double bond. [1, 3]
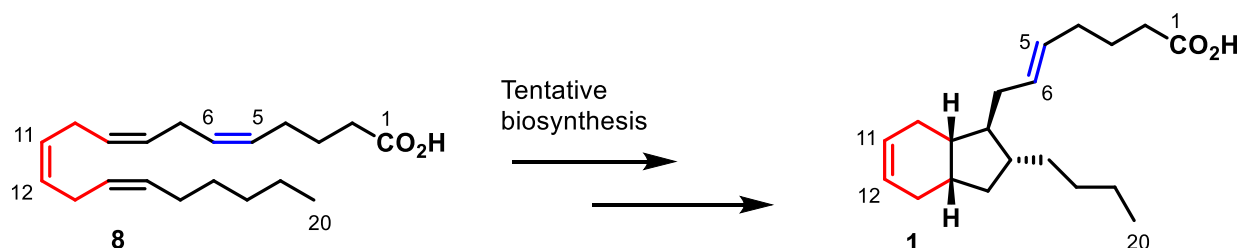
Scheme 1.3: *Illustrates the relationship between AA and the initial suggested structure of mucosin.*

An interesting proposal of the biosynthesis of a *trans*-fused mucosin isomer has been made by Professor Trond Vidar Hansen, which is outlined in scheme 1.4.
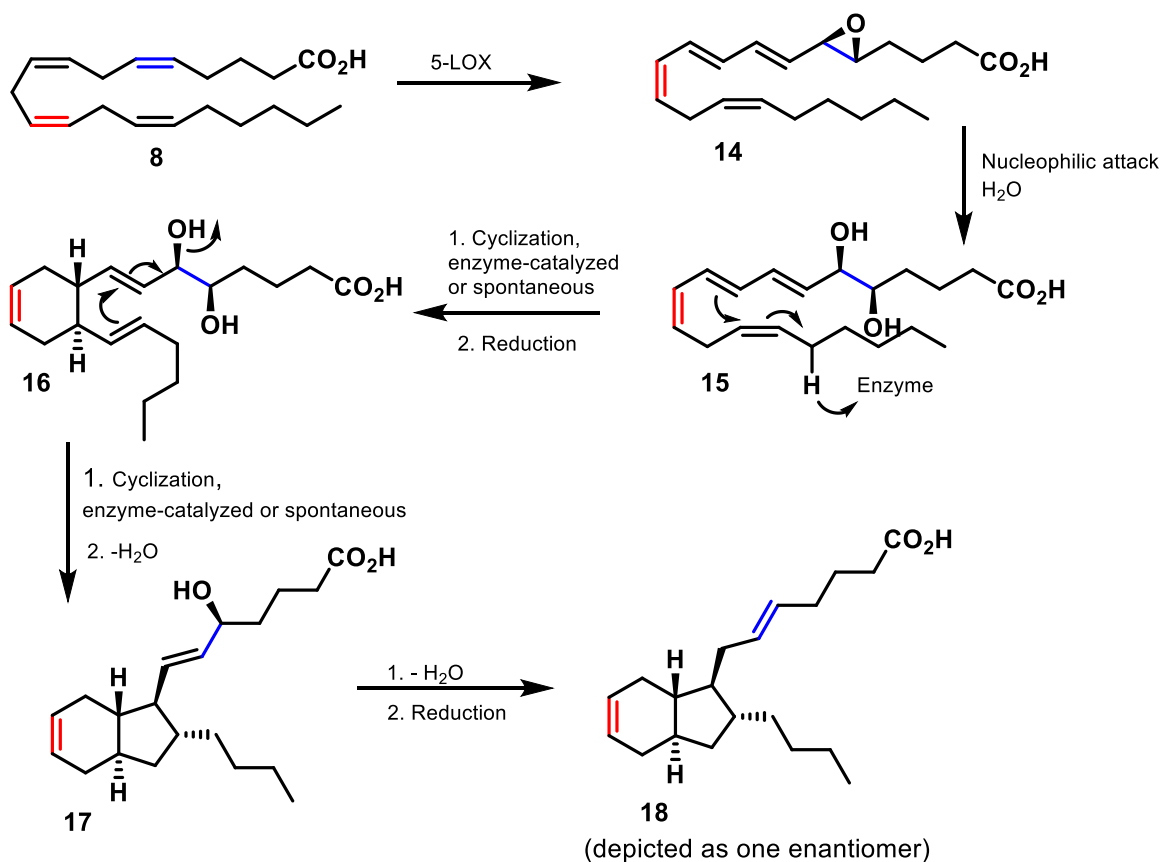
Scheme 1.4: *Postulated biosynthesis of one isomer of trans-fused mucosin.*

The suggested biosynthesis[1] starts with the synthesis of leukotriene A$_4$ (LTA$_4$) (**14**), which is known to be derived from AA (**8**) via the 5-LOX pathway.[37] LTA$_4$ is then subjected to a nucleophilic attack by water to form intermediate **15**. This intermediate, namely 5*S*,6*S*-diHETE, has been reported to be found in the marine environment.[38] Intermediate **15** then undergoes either a spontaneous or enzyme-catalyzed cyclization to form **16** with *trans*-related hydrogens on C-9 and C-14. Next, an additional enzyme-catalyzed or spontaneous cyclization occur to form intermediate **17**, which is followed by dehydration and migration to give *trans*-fused mucosin **18**.

It is also interesting to note that there are several studies of biosynthetic pathways where an enzyme are claimed to catalyze a [4+2] cycloaddition reaction, a so-called Diels-Alder-ase.[39] Several findings have been reported in the literature where these enzymes have been involved, and more recently, the first enzyme which specifically and alone catalyze a biological Diels-Alder reaction have been reported.[40] This could also be the case for mucosin, where a Diels-Alderase is involved in the biosynthetic pathway and the stereoselective formation of the cyclohexene moiety. However, the claimed structure of mucosin contains a *cis*-fused bicyclic ring system. For all the examples where a Diels-Alder-ase could be involved in the biosynthesis, the structure contain a *trans*-fused ring system.[39-42]

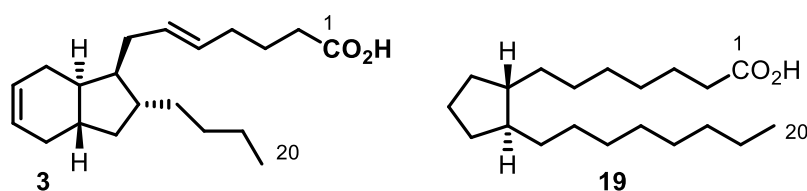### 1.8.1 Structural analysis of *trans*-fused mucosin

Figure 1.7: *Structure of one trans –fused isomer of mucosin and its relation to the carbon framework of prostaglandins.*

Mucosin is a C-20 compound with a carboxyl- and methyl terminus, which makes it likely to originate from a C-20 fatty acid such as AA (**8**).[1] However, no studies on the biosynthesis of the natural product have been reported.

By comparing the structure of mucosin with the basic carbon framework to the prostaglandins, figure 1.7 illustrates that the compounds share noteworthy structural similarities. Similarly, mucosin contains a cyclopentane moiety with two adjacent side-chains attached to it. One of the side-chains differs in length, but the C-7 side-chain with a carboxyl terminus is present in both. Although no biological testing has been carried out on the isolated natural product, or any of the synthetic isomers of mucosin, it is of interest to investigate if the compound will have prostaglandin-like properties.

Although mucosin apparently has structural similarities with the prostaglandin skeleton, it differs by having a bicyclo[4.3.0]non-3-ene system. As opposed to the *cis*-fused ring system, the *trans*-fused bicyclic system is more often encountered in nature.[3, 41, 43-44]

The same bicyclo[4.3.0]nonene skeleton is found in a marine natural product named dictyosphaerin,[45] shown in figure 1.8. This natural product also contain a secondary alcohol. When the structure of dictyosphaerin was elucidated, the authors of the published paper specified that neither the absolute nor the relative stereochemistry at any of the three stereogenic centers could be determined by spectrometric methods. The double bond in the side chain, however, was determined to be of *E*-configuration.
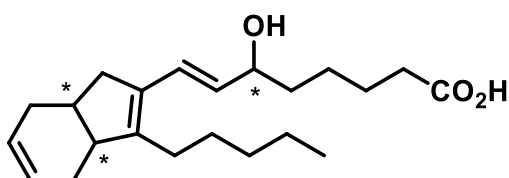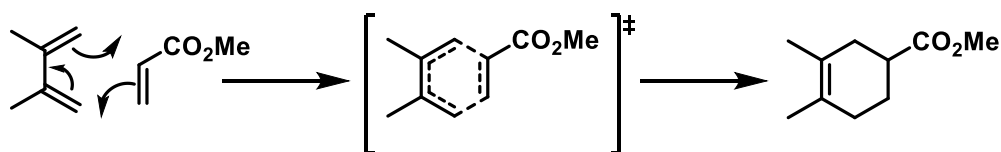

Figure 1.8: *Structure of dictyosphaerin.*

1.9 Chemical background

1.9.1 The Diels-Alder reaction

The Diels-Alder reaction is a [4+2] cycloaddition between a conjugated diene and a substituted alkene, often referred to as the dienophile.[46] The general reaction is outlined in scheme 1.5.


Scheme 1.5: *A Diels-Alder reaction with mechanism and concerted transition state.*

The reaction forms a cyclic product via a cyclic transition state. This process is concerted, meaning that the breaking and formation of new bonds occur simultaneously.[46]

Conjugated dienes participate in the Diels-Alder reaction provided that the two double bonds are able to exist in the s-*cis* conformation. For sterical reasons, compounds such as butadiene prefers to exist in the s-*trans* conformation – with the least interaction between the two double bonds. However, the rotation barrier around the sigma bond allows for rapid rotation to the reactive s-*cis* conformer so that the reaction can take place. The dienophile is commonly activated with at least one electron-withdrawing group conjugated to the alkene, whereas electron donating groups on the diene favors the reaction.[46-47]

Due to the concerted mechanism, the Diels-Alder reaction is stereospecific with respect to both the diene and the dienophile. When stereochemistry is present, it is consistently reproduced in the product. This is illustrated in scheme 1.6.[47]
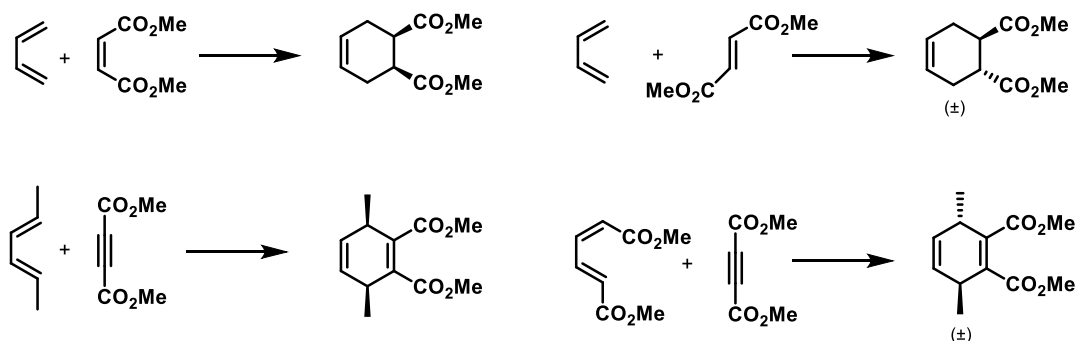
Scheme 1.6: *Diels-Alder reactions between various dienes and dienophiles.*

Cis and *trans* dienophiles give different diastereomers as the products. The substituents on the diene end up on the same face of the product if they have the same stereochemistry, and on the opposite face of the product if they have opposite stereochemistry. If the diene and dienophile are unsymmetrical, the major regiosisomers formed are so called "*ortho*" and "*para*" adducts. Moreover, cyclic dienes give stereoisomeric products where the *endo*-product usually is favored.[47]
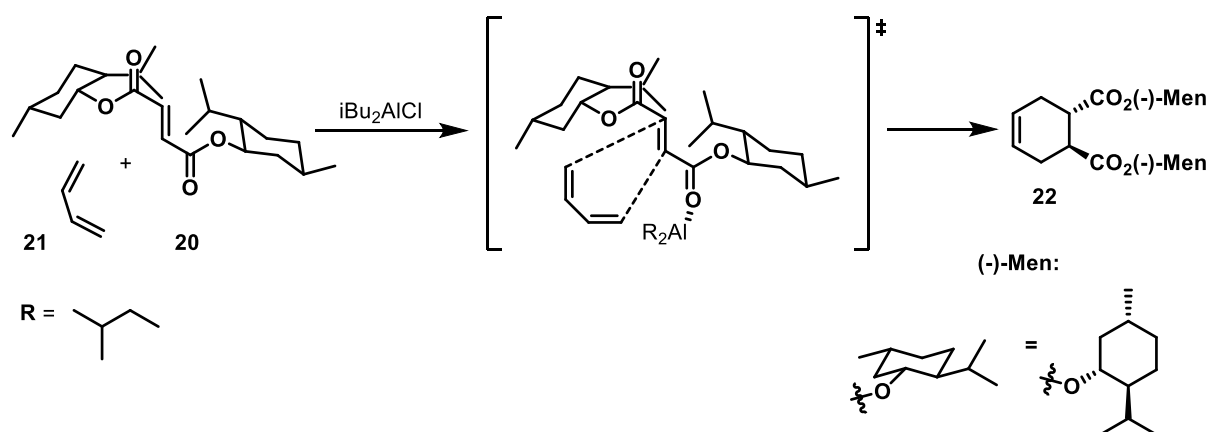
1.9.2 Asymmetric Diels-Alder reaction

Asymmetric synthesis involve stereoselective synthesis of chiral compounds. This can be achieved by several approaches: substrate control, reagent control (chiral reagent or catalyst), chiral pool and chiral auxiliaries.[48-49]

Asymmetric Diels-Alder reactions can be utilized for stereoselective synthesis. One way is the use of chiral auxiliaries.

The chiral auxiliary is an enantiomerically pure compound, which is temporarily attached to an achiral starting material. After a diastereoselective reaction, the directing group is removed.[48]

In asymmetric Diels-Alder reactions, the chiral auxiliaries are commonly located on the dienophile, which is generally an acrylate ester of an enantiomerically pure alcohol. The idea is to block one of the enantiotopic faces of the dienophile and thereby favor the addition of the diene to the opposite face. These reactions are nearly always performed with a Lewis acid catalyst because the complexed dienophile becomes more electrophilic and reactive towards the diene, and this allows the reaction to proceed at low temperature, which in turn increase the facial selectivity.[50] Scheme 1.7 illustrates the reaction between (-)-dimenthyl fumarate (**20**) and 1,3-butadiene (**21**) where an organoaluminium reagent is used.[51] This reagent, together with the chiral auxiliaries, blocks one face of the dienophile, which favors the addition if the diene to the more accessible face to yield product **22** in excess. In addition, the aluminium-carbonyl complex increase the reactivity of the dienophile by making it more electrophilic.

Scheme 1.7: *Asymmetric Diels-Alder reaction between (-)-dimenthyl fumarate (**20**) and 1,3-butadiene (**21**) to afford product **22** in excess.*

After the reaction, the chiral auxiliaries are removed, and an enantiomerically enriched product is obtained.[48] This specific reaction have been reported to give an adduct with 95% diastereomeric excess (% de).[51] Thus, the enantiomeric excess (% ee) after removal of the chiral auxiliaries will be 95% as well. The enantiomeric excess says something about how much of one enantiomer that is present over the other.[48]

1.9.3 Stereoselective acylation

One way to perform regioselective synthesis of β-keto esters from ketones is by direct addition of a cyanoformate ester onto a preformed enolate.[52]

Ketones can be converted into their corresponding enolate anions by treatment with a strong base. A hydrogen in the α-position to the carbonyl group is weakly acidic (pKa~19), so a base that has a corresponding acid with a pKa value above 19 must be employed for complete enolization.[53] For unsymmetrical ketones, two possible regioisomers can be formed, as illustrated in scheme 1.8. However, the regioselectivity can be controlled by the reaction conditions. The thermodynamic enolate (**23**) is favored due to formation of a more substituted double bond. However, a proton source, such as excess ketone, must be available for equilibration of enolate **24** to **23**, since both can be formed. The kinetic enolate (**24**) can be formed by working under lower temperatures and by using a bulky base for deprotonation of the more accessible α-proton. It is also important that the base do not react with the carbonyl carbon, and thus is a poor nucleophile, such as lithium diisopropylamide and potassium hydride.[53-54]
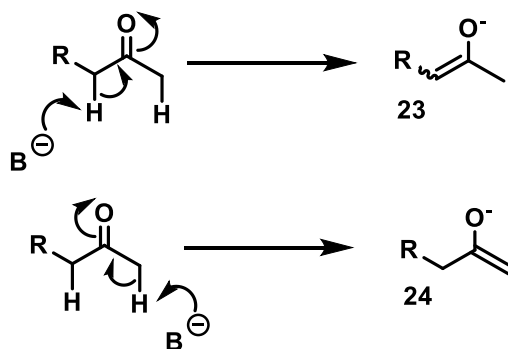
Scheme 1.8: *Formation of regioisomeric enolates by deprotonation.[53]*

In the bicyclic system depicted in scheme 1.9, an enolate anion can be formed by deprotonation by a base followed by acylation.[55] Deprotonation of either α-methylene groups to the ketone (**25**) will produce identical enolates.
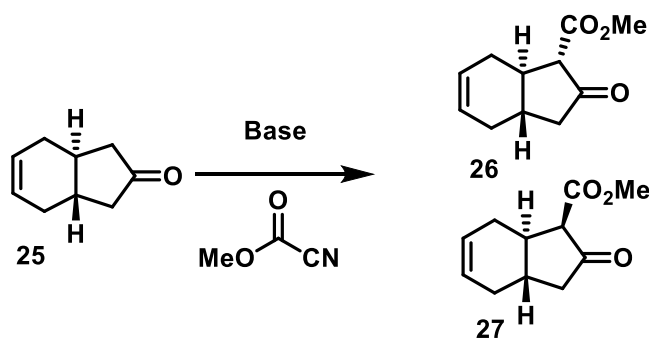
Scheme 1.9: *Illustrates the formation of an enolate followed by C-acylation.*

The acylation of pre-formed enolates with reactive acylating agents, such as acyl halides, usually gives a mixture of both C – and O – acylated products.[56] However, kinetic enolization followed by acylation with a cyanoformate ester is known to reliably perform C–acylation, and a commonly used acylating agent is methyl cyanoformate, often referred to as the Mander's reagent.[52]

A reaction of the corresponding enolate of the bicyclic ketone (**25**) in scheme 1.9 with a cyanoformate ester makes it possible for more than one isomer to be formed (by attack from either face of the enolate). It is not, however, given that the isomers **26** and **27** will be formed in equal amounts. That is, diastereomers, which have different physical properties, have diastereomeric transition states of different energy. Under kinetic control, the rates are influenced and the isomer generated via the lower energy transition state will predominate.[57]

1.10 Discussion of mucosin isomers

The initially proposed structure of mucosin (**1**) was made in 2016 by Galantree-Smith *et al*.[3] This work included the total synthesis of the originally claimed structure, with a *cis*-fused bicyclo[4.3.0]nonene skeleton, and later the diastereoisomer with opposite *anti* configuration on the C-8 and C-16 side groups.[4] X-ray analysis of a late stage intermediate of the former isomer provided support that the compound made was identical to the proposed structure of mucosin.

However, the specific optical rotation values of the synthesized isomers deviated from the value reported for the isolated natural product. In addition, a number of δ-values observed in ^{13}C-NMR were inconsistent with the ones reported for the natural product and the synthesized enantiomer as well. This is presented in table 1.1, and the notable differences are highlighted.

Table 1.1: Comparing methyl ester stereoisomers of (-)-mucosin (**1**) by the observed ^{13}C-NMR resonances (δ-values).

Casapullo *et al*.:[1]	Whitby *et al*.:[2]	Gallantree-Smith *et al*.:[3]	Antonsen *et al*.:[4]
174.2	174.2	174.2	174.2
130.0	130.3	130.4	**131.2**
129.8	129.8	129.9	**129.0**
127.0	127.3	**126.3**	125.3
127.0	127.1	**126.1**	125.1
52.1	52.2	**51.4**	**51.6**
51.4	51.4	51.0	51.4
47.1	47.2	**44.0**	**41.3**
42.1	42.3	**40.3**	37.2
39.9	40.1	**38.1**	36.2
36.7	37.0	**37.7**	35.5
36.5	36.7	**37.1**	35.4
36.4	36.7	**34.9**	33.4
33.2	33.4	33.4	33.0
32.0	32.4	31.9	31.9
31.7	31.9	**31.0**	**31.0**
31.5	31.6	**27.8**	26.9
30.7	30.7	**27.7**	24.7
24.5	24.7	24.8	**23.0**
22.6	22.9	22.9	**21.7**
13.8	14.1	14.1	14.1

The table contains ^{13}C-NMR data for the isolated natural product, the synthetic enantiomer, the synthetic isomer based on the originally claimed structure, and the later synthesized diastereomer of the latter compound respectively.

From the NMR data presented of the isolated methyl ester **2**, the C-8 and C-16 side-chains were suggested to be *trans* related and the bicyclic ring system was suggested to be *cis* fused. This was based on data obtained from both 1D- and 2D-NMR techniques. However, the coupling constants were not reported in terms of the four contiguous stereocenters, because the correlations appear in a restricted area of the aliphatic region (δ 1.12 – 1.59) with multiple signals.[1]

Moreover, the spectroscopic data of the natural product demonstrate that an *E*-alkene is present in the longer side chain towards the carboxylic acid, and the double bond in the ring is forced to be *cis*. The four stereogenic centres will then give rise to 16 different stereoisomers.

Previous work has constricted the target selection in the search for the true structure of mucosin. In this project, the target molecule will be mucosin with a *trans*-fused bicyclic carbon skeleton (**3**), depicted at one putative isomer in figure 1.1.

1.11 Synthetic Strategy

Mucosin is an optically active compound. When the natural product was identified and characterized, the optical activity of methyl ester **2** was measured ($[\alpha]_D$ = -35.5º).[1] The goal of this synthesis was to choose a synthetic strategy that would achieve the same optical purity in the product, and hopefully with a matching specific optical rotation value.

One possible method to accomplish this is to start the synthesis with racemic starting material and then later introduce a new chiral centre by a stereoselective reaction. The enantiomeric mixture is then converted into a pair of possibly separable diastereomers.

The synthetic work was based on the commercially available racemic starting material **28**, which has the correct relative stereochemistry present. Several syntheses of the bicyclic ketone bicyclo[4.3.0]non-3-en-8-one (**35**) have been reported in the literature, so a synthesis was designed following these protocols.[58-60] The synthetic strategy of ketone **35** is outlined in scheme 1.10.
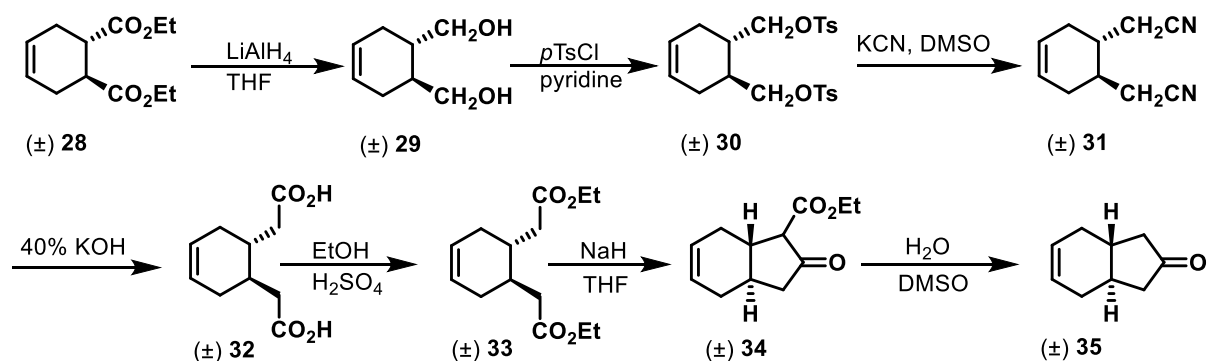
Scheme 1.10: *Suggested synthesis of ketone 35.*

Another method to produce the bicyclic ketone (**35**) would be through an asymmetric chiral auxiliary synthesis. Furuta *et al.*[51] have reported that remarkably high diastereoselectivity is observed in the organoaluminium catalyzed asymmetric Diels-Alder reaction of (-)-dimenthyl fumarate (**20**) with various dienes. The chiral auxiliary groups (menthol) achieve effectively diastereoface differentiation of the dienophile, and by employing an organoaluminium reagent instead of a simple Lewis acid catalyst, the diastereoselectivity of the reaction improves greatly.[51] After purification by column chromatography, the chiral auxiliaries can be removed by reduction to yield diol **29** as one enantiomer. By following the synthetic sequence in scheme 1.10, the bicyclic ketone **35** will be produced enantiomerically enriched as well.

In further planning of the synthesis towards the putative isomer of *trans*-fused mucosin, a retrosynthetic analysis was carried out. As several stereoisomers of mucosin have previously been prepared, we wanted to rely on some of the established chemistry.[3] The retrosynthetic analysis is outlined in scheme 1.11.
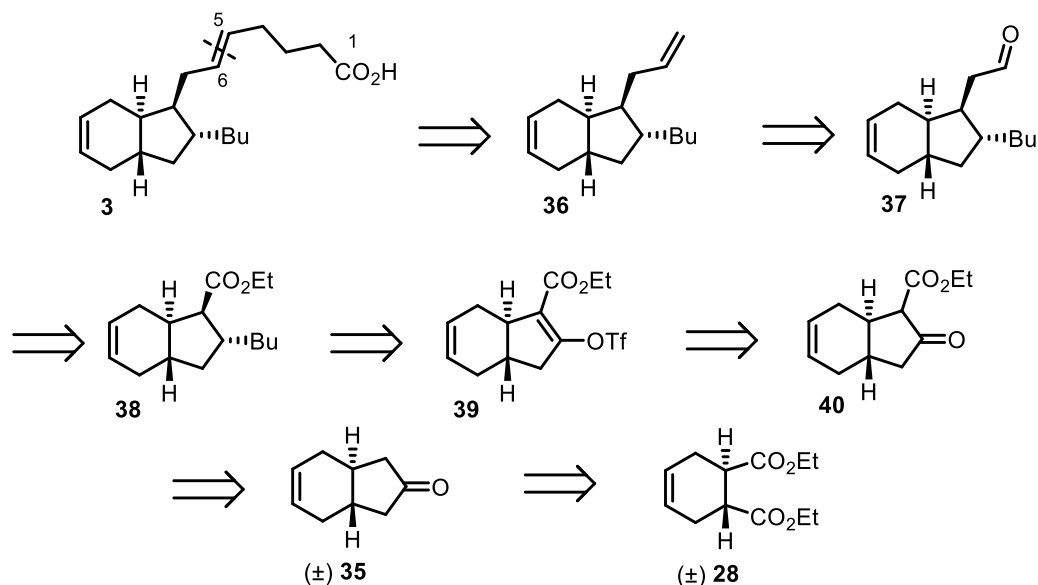
Scheme 1.11: *Retrosynthetic analysis of trans-fused mucosin (3).*

Formation of the *E*-olefin at C5-C6 can be performed by a cross-metathesis reaction with commercially available methyl 5-hexenoate, catalyzed by Grubbs catalyst, or by a *E*-selective Wittig reaction. This would lead back to alkene **36** which can be prepared by a Wittig reaction with aldehyde **37**. Then, the aldehyde **37** can be prepared from ethyl ester **38** by reduction to the corresponding aldehyde followed by a homologation reaction, as performed by Seiple *et al.*[61]

The next step would be to insert the butyl sidechain. The strategy chosen was a four step sequence, as performed by Gallantree-Smith *et al.:*[3] converting β-keto ester **40** to vinylic triflate **39**, which provides a good leaving group for a copper mediated cross coupling with ^nBuLi and Cu(I)CN. Chemoselective reduction of the conjugated double bond can then produce ethyl ester **38** as a mixture of *syn* and *anti* isomers. Magnesium in methanol is known to perform such a reduction.[62] The *syn* isomer can then be equilibrated via sodium ethoxide to the assumed more thermodynamically favored *anti* isomer **38** – with the least steric interaction between the two groups on C-2 and C-10. At this point, stereochemistry should be established in both the 5- and 6-membered ring by NMR and X-ray analyses.

It is, however, of vital importance to notice the *trans* relationship in the 5/6-membered ring system. Figure 1.9 illustrates the different conformations of compound **38** when the hydrogens at the ring system are *cis* and *trans* related.
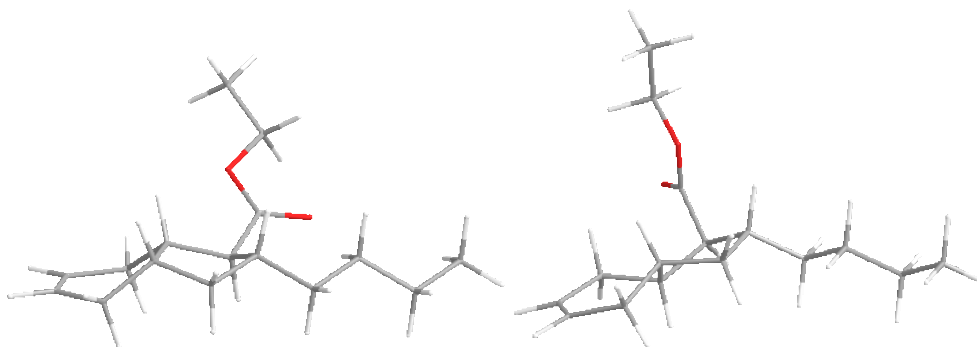
Figure 1.9: *Different conformations of ethyl ester **38**, with a cis-fused bicyclic system (to the left), and a trans-fused system (to the right). Generated by ChemDraw.*

Compared to the *cis*-fused system, which has a more accessible *exo* surface and a more hindered *endo* face, the *trans*-fused isomer is forced to have both of the bonds connected to the attachment points of the rings in equatorial position, which flattens out the molecule. This difference in conformation naturally makes the two compounds not directly comparable.

The two side groups on the cyclopentane ring of mucosin (**1**) are suggested to be *trans*.[1] However, nothing has currently been published regarding the absolute configuration of mucosin, so either *anti* isomer of **38** can be a match with the isolated natural product.

The β-keto ester **40** was envisioned to most easily be obtained by deprotonation, and diastereoselective acylation of ketone **35**, followed by separation of diastereomers by column chromatography.

1.12 Aims of study

The aim of this master thesis was to develop an enantioselective total synthesis of one *trans*-fused isomer of the suggested structure of the natural product (-)-mucosin. The synthetic approach was based on earlier work performed at NMBU. An interesting and important part of the work constituting this thesis was to investigate if the published protocols using *cis*-**1** were adaptable to *trans*-**3**.

2 Results and discussion

2.1 Synthesis of *trans*-bicyclo[4.3.0]non-3-en-8-one (35)

(±) **35**
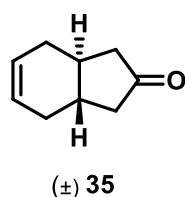
The first target molecule in this synthesis was the bicyclic ketone *trans*-bicyclo[4.3.0]non-3-en-8-one (**35**). Several syntheses of the ketone with both *cis* and *trans* fused rings have been reported in the literature.[3-4, 58-60, 63] The actual synthetic sequence of ketone **35** that was performed is shown in scheme 1.10, chapter 1.11.

2.1.1 Preparation of (cyclohex-4-ene-1,2-diyl)dimethanol alcohol (29)

The reaction was performed by following a procedure from Mundy and Theodore.[60]
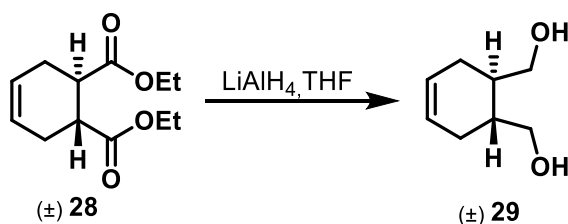
Scheme 2.1: *Reduction of diester (28)*

Reduction using LiAlH$_4$ gave **29** by using a workup procedure from Fieser & Fieser.[64] This procedure entails to add n mL of water, n mL of 15% (w/v) NaOH and 3n mL of water drop-wise to the solution containing n g LiAlH$_4$. A white precipitate was formed, and the solution turned into a thick suspension that could not be stirred. An appreciate amount of dry THF was then added so that the solution could be stirred and filtered to give a pale yellow oil.

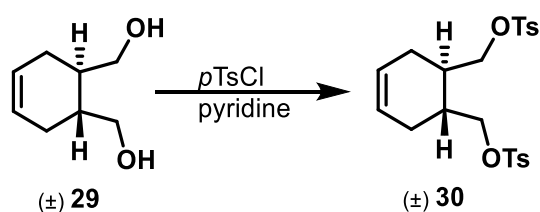The spectroscopic data obtained was in accordance with literature.[63]
The alkene carbons appear at 126.2 ppm in the ^{13}C-NMR-spectrum, and the methylene carbons next to the hydroxyl groups is confirmed by the signal at 66.4 ppm. In the ^{1}HNMR-spectrum the alkene hydrogens appear at 5.63 ppm. The spectra obtained by NMR analysis indicated that no further purification of the product was necessary.

The broad absorption peak at 3295 cm^{-1} in the IR spectrum confirms that the ester groups were reduced to the corresponding alcohols. In addition, the base peak in the recorded MS spectrum corresponds to the calculated molecular mass of the sodium adduct of **29** (*m/z* 165.089).

The reaction was repeated several times giving yields from 84-95%.

2.1.2 Preparation of (cyclohex-4-ene-1,2-diyl) *bis*(methylene)*bis*(4-methylbenzenesulfonate) (30)

The reaction was performed by following a procedure from Mundy and Theodore.[60]

*Scheme 2.2: Tosylation of diol (**29**)*

To provide a good leaving group for the next reaction, diol **29** was treated with tosyl chloride. Slow addition of **29** to the reaction mixture and temperature control was important in order to avoid unwanted side reactions, like cyclization. The reaction gave a white powder, which was recrystallized from methanol to give white crystals.

The spectroscopic data obtained was in accordance with literature.[63]
The five signals in the ^{13}C-NMR spectrum over 100 ppm confirms the alkene hydrogens in the cyclohexene ring and the aromatic carbons. The methylene carbons next to oxygen is observed at 71.4 ppm. The ^{1}H-NMR spectrum confirms the aromatic hydrogens as two doublets at 7.76 and 7.35 ppm in the spectrum. The alkene hydrogens appear as a signal at 5.51 ppm, and the four methylene hydrogens next to oxygen are observed at 3.87-3.99 ppm. The singlet at 2.46 ppm confirms the two methyl groups attached to the aromatic rings.

The base peak in the recorded MS spectrum corresponds to the calculated molecular mass of the sodium adduct of **30** (*m/z* 473.106).

The reaction was repeated several times giving yields from 77-90%.

2.1.3 Preparation of 2,2'-(cyclohex-4-ene-1,2-diyl)diacetonitrile (31)

This synthesis was performed by following two different methods: method 1 from Mundy and Theodore[60], and method 2 from Aubé *et al.*[58]

Method 1
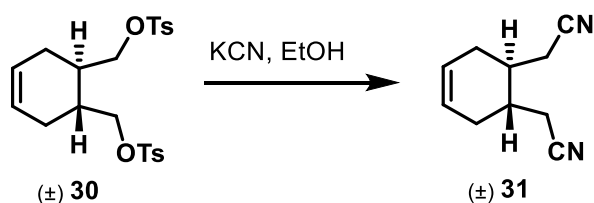
Scheme 2.3: S$_N$2 with cyanide, method 1

The reaction gave dinitrile **31** 79% yield, but the reaction time was relatively long (27 h). By changing the solvent from polar protic to polar aprotic, the reaction time can be reduced considerable, see method 2 for details. The spectroscopic data obtained was in accordance with literature.[63] In the IR spectrum, the stretch at 2248 cm^{-1} confirms that a nitrile group is present in the product. In the ^{13}C-NMR spectrum the alkene carbons are observed at 124.6 ppm and the nitrile carbon at 117.8 ppm. In the ^{1}H-NMR spectrum the alkene hydrogens are observed at 5.66 ppm, and the methylene hydrogens next to the nitrile groups are confirmed by the multiplet at 2.41-2.53 ppm integrating for four hydrogens. The two multiplets at 2.23-2.35 and 2.02-2.15 confirms the methine hydrogens on C-3 and C-8, and the hydrogens on C-4 and C-7 respectively.

Method 2
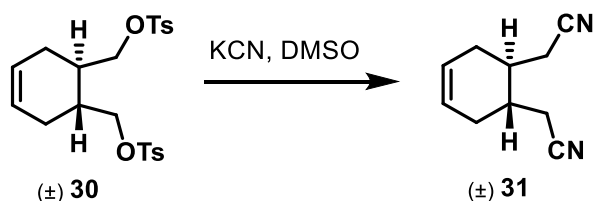
Scheme 2.4: S$_N$2 with cyanide

In this reaction, the solvent was changed from EtOH to dimethyl sulfoxide (DMSO), and the reaction was complete after 6 hours. This reaction was repeated several times giving yields from 15-95%. The low yield was obtained when the dinitrile was precipitated from the reaction mixture by adding it to ice water. However, by changing the workup to extraction with water and ethyl acetate, all yields were more than 80%. The spectroscopic data obtained was in accordance with literature,[63] and the base peak in the recorded MS spectrum corresponds to the calculated molecular mass of the sodium adduct of **31** (*m/z* 183.089).

2.1.4 Synthesis of diethyl 2,2'-(cyclohex-4-ene-1,2-diyl)diacetate (33)

These reactions were performed by following a procedure from Barret *et al.*[63]
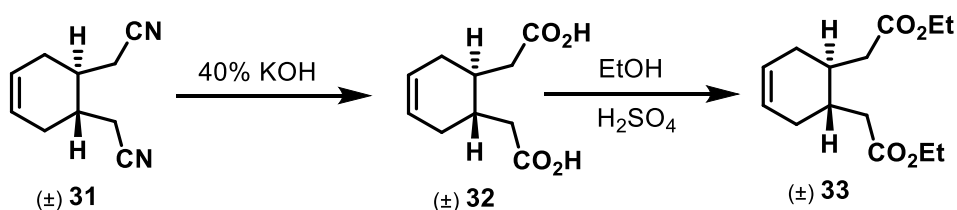
*Scheme 2.5: Hydrolysis of dinitrile and Fischer esterification*

Hydrolysis of **31** gave a yellow powder in 95% yield at the most. The crude diacid **32** was used as such without further purification to give diester **33** as a colorless oil. The reactions were repeated several times with the best overall yield of 78%.

The spectroscopic data obtained was in accordance with literature.[63] In the ^{13}C-NMR spectrum of diacid **32**, the carbonyl groups appear at 176.8 ppm, and the alkene carbons are confirmed at 126.0 ppm. The alkene hydrogens in this compound appear as a singlet at 5.60 in

the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum from diester **33** confirms the carbonyl and alkene carbons at 173.1 and 125.1 ppm respectively. In the ^{1}H-NMR spectrum, the alkene hydrogens appear at 5.59 ppm and the ethyl group of the esters is confirmed as a quartet at 4.13 ppm and triplet at 1.25 ppm. In addition, the strong absorption band at 1731 cm^{-1} in the IR spectrum of diester **33** confirms the ester functional groups, and the base peak in the recorded MS spectrum corresponds to the calculated molecular mass of the sodium adduct of **33** (*m/z* 277.141).

2.1.5 Preparation of ethyl 2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (34)

This reaction was performed by following a procedure from Barret *et al.*[63]

$(\pm)$ **33** $(\pm)$-*trans* **34**
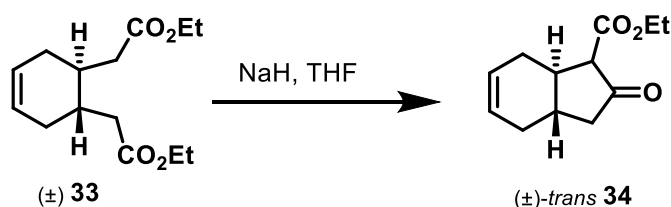
Scheme 2.6: Dieckman cyclization

The reaction gave β-keto ester **34** as a colorless oil. The reaction was performed several times with the highest yield of 90%.

The spectroscopic data was in accordance with literature.[63] From the ^{13}C-NMR spectrum the ketone carbon and ester carbon are confirmed at 209.9 ppm and 169.0 ppm respectively. The alkene carbons are observed at 126.7 and 126.4 ppm. The ethyl carbons can be observed at 62.0 ppm for the methylene- and at 14.3 for the adjacent methyl-C. The ^{1}H-NMR spectrum confirms the alkene hydrogens at 5.72 ppm, and the ethyl hydrogens connected to the ester group can be observed at 4.16-4.22 ppm for the methylene hydrogens, and at 1.22-1.30 ppm for the methyl hydrogens. The doublet at 2.66 ppm confirms the single hydrogen on the α-carbon to the ester functionality.

The IR spectrum obtained has two characteristic stretches. One at 1723 cm^{-1}, which confirms the ketone functionality, and one at 1756 cm^{-1}, which confirms the ester functionality present in the product. The base peak in the recorded MS spectrum corresponds to the calculated molecular mass of the sodium adduct of **34** (*m/z* 231.099).

26

2.1.6 Preparation of *trans*-bicyclo[4.3.0]non-3-en-8-one (35)

This reaction was performed by following a procedure from Barret *et al.*[63]
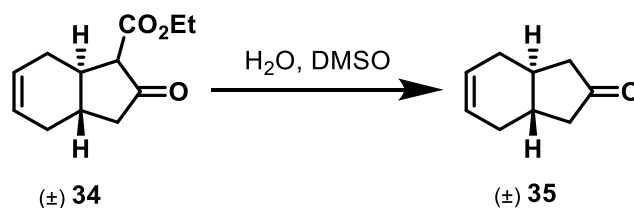
Scheme 2.7: Hydrolysis and decarboxylation

The reaction gave the bicyclic ketone **35** as a white solid. The reaction was performed several times with the highest yield of 94%.

The spectroscopic data obtained was in accordance with literature.[63]
The signal at 217.9 ppm in the ^{13}C-NMR spectrum confirms the ketone functionality, and the alkene carbons are observed at 126.8 ppm. In the ^{1}H-NMR spectrum the alkene hydrogens and are confirmed at 5.78 – 5.71. In the recorded MS spectrum, the base peak corresponds to the calculated molecular mass of the sodium adduct of **35** (*m/z* 159.078).

The ketone **35** was formed in 48% overall yield through a seven-step synthetic sequence from diester **28**.

2.1.7 Attempted synthesis of ethyl (1*R*,3a*S*,7a*R*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (41) and ethyl (1*R*,3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (42)

The reaction was performed following a procedure from Gallantree-Smith *et. al.*[3]
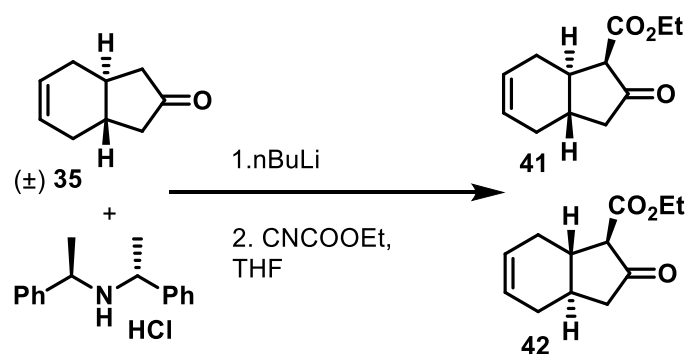
Scheme 2.8: Deprotonation and acylation

To a preformed enolate of **35**, by using chiral base formed by (+)-*bis*[*R*-1-phenylethyl]amine hydrochloride and ⁿBuLi, was added ethyl cyanoformate to acylate the alpha carbon on one side of the bicyclic ketone stereoselectively. The reaction gave a crude oil that showed five distinct spots on TLC. Tedious flash chromatography gave a pale yellow oil in 61% yield.

In the ^{1}HNMR-spectrum obtained, the more deshielded proton on the alpha carbon between the ester and keto functional groups appears as a doublet at 2.88 ppm. This proton has a coupling constant of 12.2 Hz, and its coupling partner is the proton sitting on the bridgehead carbon next to it. The large coupling constant suggests that the hydrogens has a *trans* relationship, which strongly indicates that diastereomer **42**, or its enantiomer is the one formed in excess. In addition, the spectroscopic data was in accordance with the literature for the suggested isomer.[63] Isomer **41** was not isolated in this reaction.

GC analysis of the purified product by using a chiral column resulted in two peaks with different areas. The analytical data indicates that a mixture of two enantiomers was obtained, and from this the % ee was suggested to be 60. However, without racemic material available for comparison, no conclusions could be made. The specific optical rotation value was measured to be + 16.7 (c = 2.1, CHCl₃), which is not a match with the reported value for ethyl ester **42** ($[\alpha]_D$ = -24.1 (c = 1.62, CHCl₃),[63] but suggests that the enantiomer of **42** is formed in excess in this reaction.

The recorded MS spectrum of the product gave a molecular formula and base peak which is in correspondence with the calculated sodium adduct of **42** (*m/z* 231.099).

This strategy worked well for the *cis*-fused 6,5-membered ring system by giving 83% yield of only one isomer. The conformation of the *trans*-isomer is more flat, so in this case the *exo*-selectivity is most likely decreased in comparison with the *cis*-fused ring system, which might be a rationale for the lower selectivity in this reaction.

For these reasons, we decided to abandon this strategy, and proceed by starting the synthesis with an enantiomerically pure starting material.

2.2 New strategy towards *trans*-fused mucosin (3)

The new synthetic strategy involved to start with an asymmetric Diels-Alder reaction by using commercially available (**-**)**-**dimenthyl fumarate (**20**), 1,3-butadiene (**21**), and diisobutylaluminium chloride. A procedure from Heathcock *et al.*[65] was followed. This afforded dimentyl (**-**)**-22**, that was reduced to diol (+)**-43**. The same literature protocols that were used for preparing racemic material were used to produce enantiomeric β-keto ester (**-**)**-42**. Of note, the Dieckman cyclization of (+)**-47** has been reported to be highly diastereoselective (R:S = 11:1)[63], so the formation of vinyl-triflate **39** could take place from this specie. The synthetic sequence that was performed in this project is outlined in scheme 2.9.
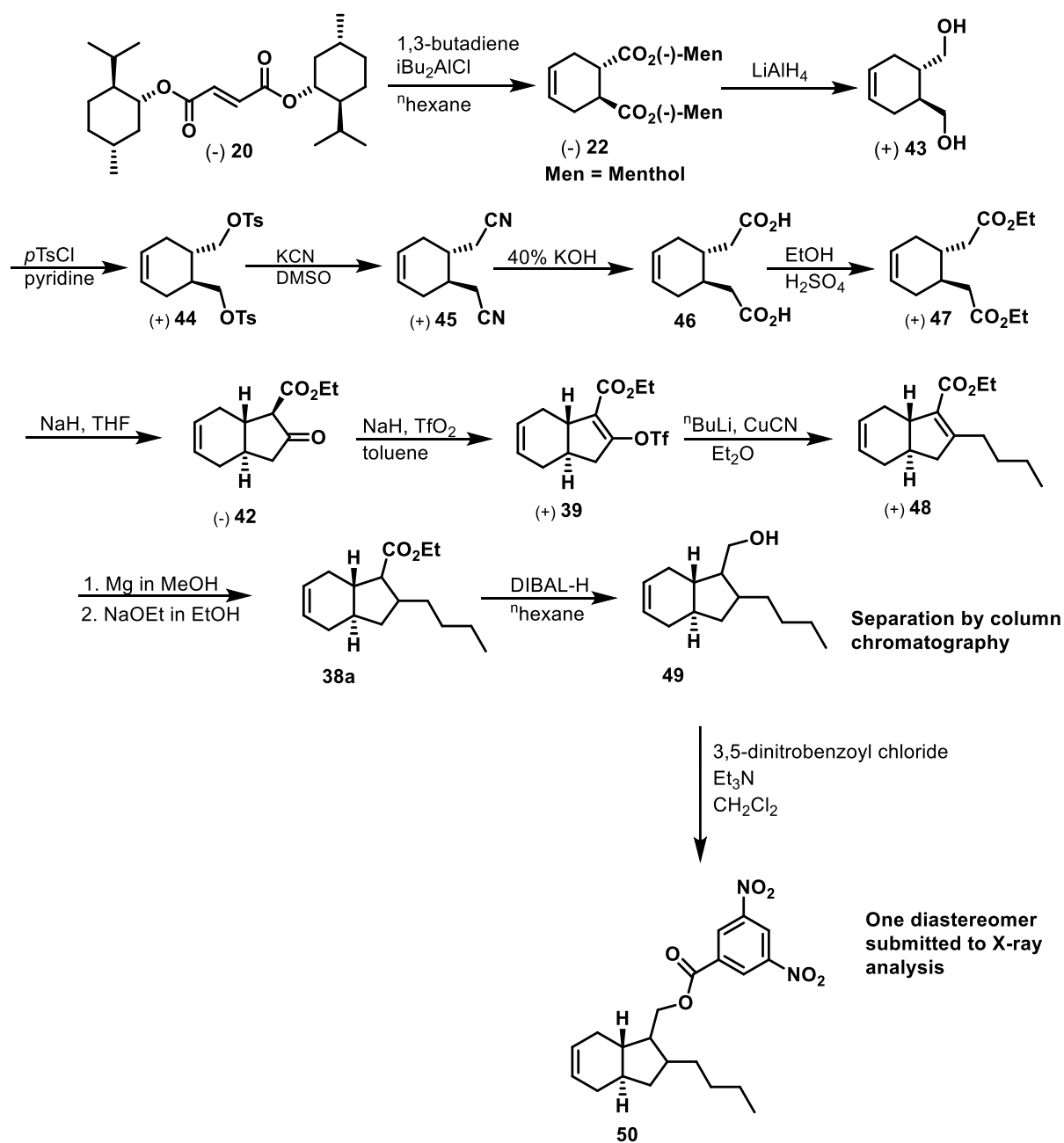
Scheme 2.9: *New synthetic strategy towards one putative isomer of (-)-mucosin.*

2.2.1 Preparation of (-)-(1S,2S)-di-(-)-menthyl cyclohex-4-ene-1,2-dicarboxylate (22)

This reaction was performed by following a procedure from Heathcock *et al.*[65]
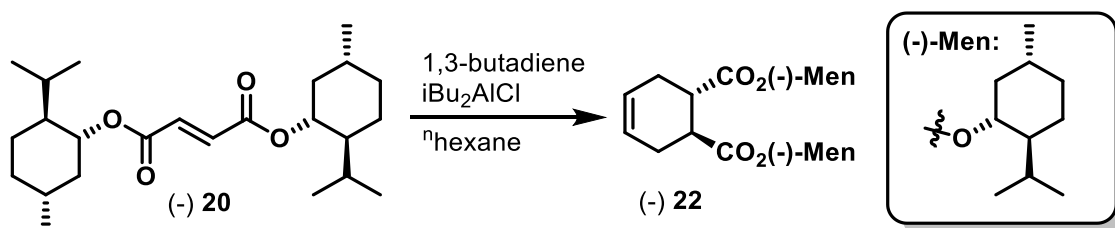
*Scheme 2.10: Asymmetric Diels-Alder reaction with diisobutylaluminium chloride*

This reaction was performed several times giving yields varying from 58-91%.

The 1,3-butadiene was condensed into a flask placed in an acetone/dry ice bath, then transferred into a mixture of (-)-20 and diisobutylaluminium chloride with a syringe and cannula that was kept in freezer over night. It does not take long for the syringe to heat to ambient temperature, so the transfer was performed quickly. When lower yields were obtained, it was suspected that butadiene had evaporated during addition, as these reactions did not go to completion. A larger excess of the reagent was therefore condensed directly into the reaction flask.

The data obtained from ^{13}C-NMR and ^{1}H-NMR spectra was in accordance with literature.[65] The recorded IR spectrum confirms the ester functional groups by the stretch at 1724 cm^{-1}. The specific optical rotation value was measured to be – 26.7 (c = 2.23, CHCl$_3$), which is close to the reported value of – 29.3 (c = 2.15, CHCl$_3$). The recorded MS spectrum show a base peak that corresponds to the calculated molecular mass of the sodium adduct of **22** (*m/z* 469.329). The analytical data suggest that dimenthyl **22** was successfully prepared in excess.

2.2.2 Synthesis of ethyl (-)-(1*R*,3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (42)

The synthetic sequence from **22** to **42** was performed by following the same literature protocols used to produce racemic material.[58, 60, 63]
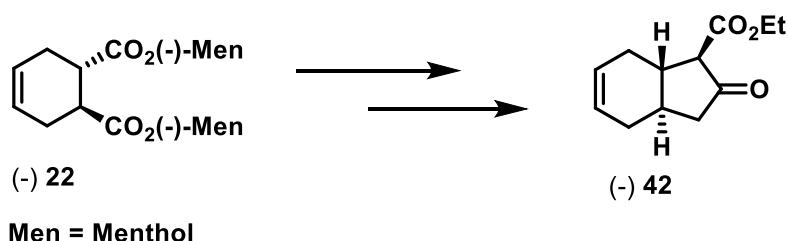
Scheme 2.11: *Synthesis of β-keto ester (-)-42*

All reactions gave the desired product, and the spectroscopic data obtained was nearly identical to the data obtained by synthesis of racemic material. Moreover, the specific optical rotation values of compounds **22 – 42** outlined in scheme 2.9, were close to the values reported in the literature.[63]

Compound (**-**)-**42** was synthesized with an overall yield of 46% through six synthetic steps from dimenthyl (**-**)-**22**. The specific optical rotation value was measured to be - 25.0 (c = 2.06, $CHCl_3$) compared to the reported value of - 24.1 (c = 1.62, $CHCl_3$).[63] The IR spectrum and NMR recordings were in agreement with literature. In the MS spectrum obtained, the base peak corresponds to the calculated molecular mass of the sodium adduct of **42** (*m/z* 231.099).

Stereochemical assignments were made by comparing with previously reported values, which include optical rotation and NMR spectroscopy.[63] Of most importance, the reported stereochemistry of β-keto ester **42** allow for assignment of the stereocenters connecting the two fused rings. The stereochemical assignment of the stereogenic center next to the ester functionality will be lost in the next reaction. The assignment is depicted in figure **2.1**.
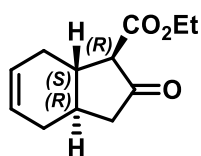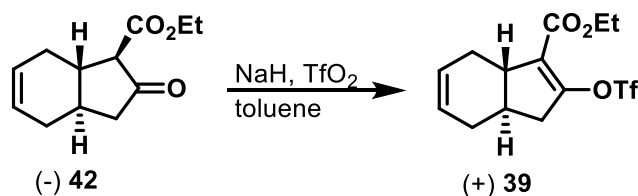

Figure 2.1: *Stereochemical assignment of (-)-42*

2.2.3 Preparation of ethyl (+)-(3a*S*,7a*R*)-2-(((trifluoromethyl)sulfonyl)oxy)-3a,4,7,7a-tetrahydro-1*H*-indene-3-carboxylate (39)

The reaction was performed by following a procedure form Gallantree-Smith *et al.*[3]

**Scheme 2.12:** *synthesis of vinyl-triflate (39)*

The reaction gave vinyl-triflate **39** as a colorless oil in 95% yield.

The spectroscopic data obtained was in agreement with the isolated product **39**. In the ^{13}C-NMR spectrum, the quartet observed at 118.2 ppm is characteristic for the presence of the CF$_3$ group due to coupling of the carbon with fluorine. Four signals in the alkene region are observed corresponding to the four alkene carbons, and the ester carbonyl is confirmed by the signal at 162.4 ppm. In the ^{1}H-NMR spectrum obtained, the methyl and ethyl hydrogens to the ester group are confirmed by the triplet at 1.32 ppm and the multiplet at 4.21-4-31 ppm respectively. The alkene hydrogens are observed at 5.69-5-7.5 ppm, and integration of all the signals in the spectrum are in agreement with the total number of hydrogens present in **39**.

The IR spectrum obtained confirms the conjugated ester functionality at 1715 cm^{-1}. In addition, the recorded HRMS spectrum provides a molecular formula and a base peak that corresponds to the calculated molecular mass of the sodium adduct of **39** (*m/z* 363.0484).

2.2.4 Preparation of ethyl (+)-(3aS,7aR)-2-butyl-3a,4,7,7a-tetrahydro-1H-indene-3-carboxylate (48)

The reaction was performed by following a procedure from Gallantree-Smith et al.[3]
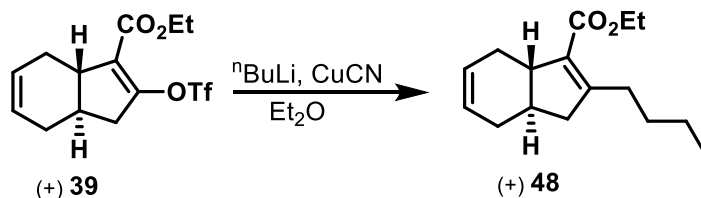

Scheme 2.13: Copper mediated cross-coupling

The α,β-unsaturated ethyl ester **48** was isolated as a colorless oil in 59% yield. A thick brown slurry was formed during the reaction that was filtered through celite. The celite filter was washed with organic solvent, but the poor yield might be due to product that was stuck in the filter.

The spectroscopic data obtained was in agreement with the isolated product **48**. In the ^{13}C-NMR spectrum, above 100 ppm, four signals correspond to the alkene carbons, and the carbonyl carbon is confirmed at 166.6 ppm. A total number of 16 signals corresponds to **48**. In the ^{1}H-NMR spectrum obtained, the alkene hydrogens are confirmed at 5.71 ppm, and the methylene hydrogens next to the ester oxygen are confirmed as two multiplets at 4.18-4.10 and 4.28-4.19 ppm respectively. The triplet at 0.91 ppm confirms the methyl hydrogens at the end of the butyl side-chain. Integration of all the signals in the spectrum are in agreement with the total number of hydrogens present in **48**. The IR spectrum show a stretch at 1697 cm^{-1}. This is likely to be the ester carbonyl, which might have a lower frequency than expected due to conjugation.

The recorded HRMS spectrum provides a molecular formula and a base peak that corresponds to the calculated molecular mass of the sodium adduct of **48** (*m/z* 271.1669).

2.2.5 Preparation of ethyl (3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (38a)

The reaction was performed by following a procedure from Gallantree-Smith *et al.*[3]
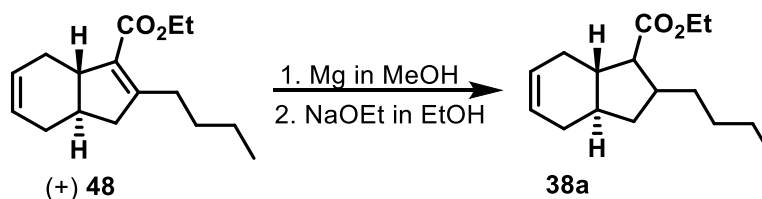


Scheme 2.14: *Selective reduction and equilibration*

The conjugated double bond in the α,β-unsaturated ester **48** proved to be successfully reduced without affecting the olefin moiety in the six-membered ring. The λ_{max} observed at 232 nm by UV analysis of the starting material (**48**) was absent in the UV spectrum of product **38a**, as shown in figure 2.2. Moreover, in the ^{13}C-NMR spectrum of **38a**, only two signals in the alkene region were observed.
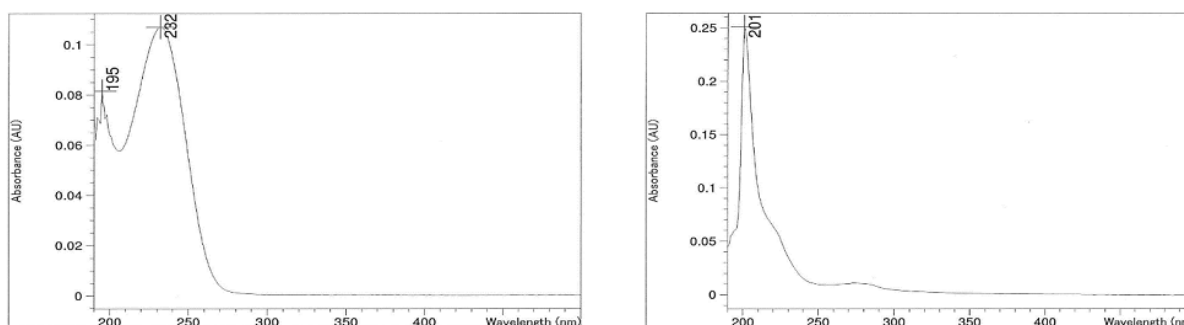
Figure 2.2: *UV analysis and λ_{max} of compound* **48** *(to the left), and compound* **38a** *(to the right).*

A mixture of diastereomers was formed according to NMR-analysis, both prior and post equilibration. The non-equilibrated and equilibrated diastereomic mixtures were analyzed by GC. The ratio between the diastereomers was determined to be 2:1 in both experiments, where the minor diastereomer switched to become the major isomer after equilibration. The ratio was then observed to be 1:2. The chromatograms obtained are shown in figure 2.3. Injection of equimolar amounts of the two mixtures produced a chromatogram with two peaks that were nearly identical. The equilibration was repeated for a longer period of time and analyzed by ^{13}C-NMR, but then a complex mixture was formed.
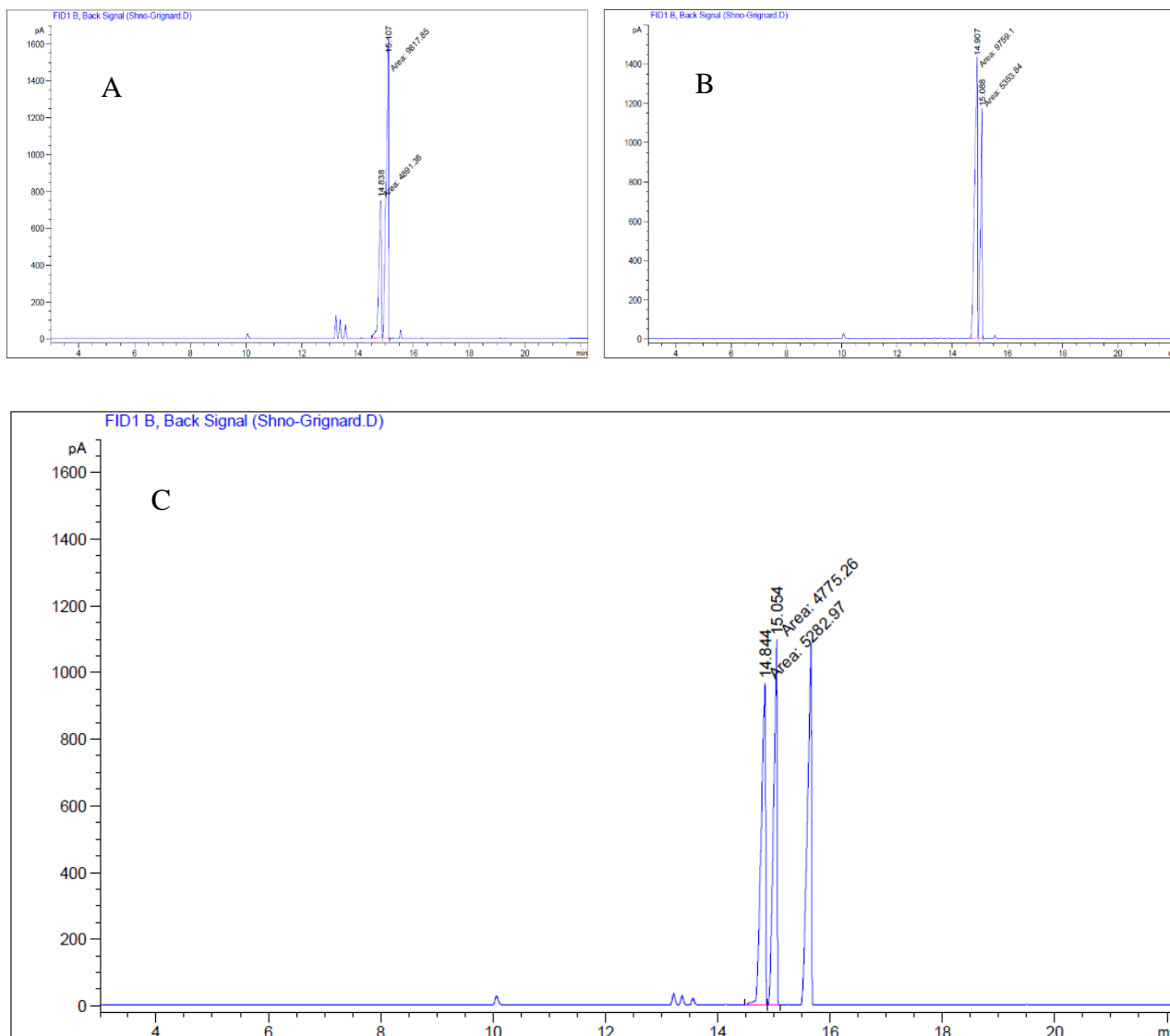
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.844	MM	0.0910	5282.96631	967.24506	52.52382
2	15.054	MM	0.0725	4775.26270	1097.69897	47.47618

Figure 2.3: *C: chromatogram of co-injection of A (prior to equilibration of **38a**) and B (post equilibration of **38a**) together with starting material **48**, in equimolar amounts.*

Much time was spent on TLC analysis trying to separate the diastereomers without success. Various mixtures of several solvents, including hexane, diethyl ether, ethyl acetate, dichloromethane and methanol were tested.

Interpretation of the ^{13}C-NMR spectrum confirms the ester carbonyl carbon at 176.1 ppm, and the two alkene carbons are confirmed at 127.1 and 126.8 ppm. The total number of signals are

in agreement with ethyl ester **38a**. The ^{1}H-NMR spectrum confirms the alkene hydrogens and the methylene group attached to the ester functionality at 5.57-5.71 and 4.05-4.20 ppm respectively. Integration of the signals in the spectrum are in agreement with **38a**. In addition, the recorded HRMS spectrum provides a molecular formula and a base peak that corresponds to the calculated molecular mass of the sodium adduct of **38a** (*m/z* 273.1825).

Although the ethyl ester diastereomers could not be separated, it was decided to proceed by reduction to the corresponding alcohol in aiming for separation after this step, or the next.

2.2.6 Preparation of ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methanol (49)

The reaction was performed by following a procedure from Gallantree-Smith *et al.*[3]
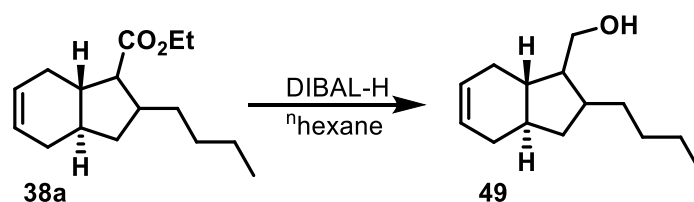
Scheme 2.15: Reduction of ester functionality

The reduction gave alcohol **49** with the best yield of 91%.

The ^{13}C-NMR spectrum shows that the reduction was done by the absence of any signals in the carbonyl region, and the alkene carbons appear at 127.5 and 127.1 ppm. The same is confirmed in the ^{1}H-NMR spectrum where the total number of hydrogens determined by integration are in agreement with **49**. The two multiplets at 3.79-3.73 and 3.71-3.35 confirms the methylene hydrogens next to the hydroxyl group.

TLC of the diastereomeric mixture gave separation on the silica plate, and a promising eluent system was found (hexane:Et$_2$O 8:2). After several rounds of column chromatography, the diastereomers were successfully separated. One isomer was obtained as a colorless oil and the other as a white solid. For simplification, the diastereomers were termed **D1** (eluting first from the column), and **D2** (eluting second from the column). The separation was done after reduction of non-equilibrated **38a**, and the diastereomer isolated in greater amount was **D2**, suggesting that this specie is the one converted to **D1** during equilibration (see figure 2.3).

The recorded HRMS spectrum provides a molecular formula and a base peak that corresponds to the calculated molecular mass of the sodium adduct of **49** (231.1719).

It was necessary to synthesize derivatives of **D1** and **D2** to obtain a crystalline solid of each isomer in order to determine the relative and/or absolute stereochemistry by X-ray analysis.

2.2.7 Preparation of ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methyl 3,5-dinitrobenzoate (50)

The reaction was performed by following a procedure from Gallantree-Smith *et al.*[3]
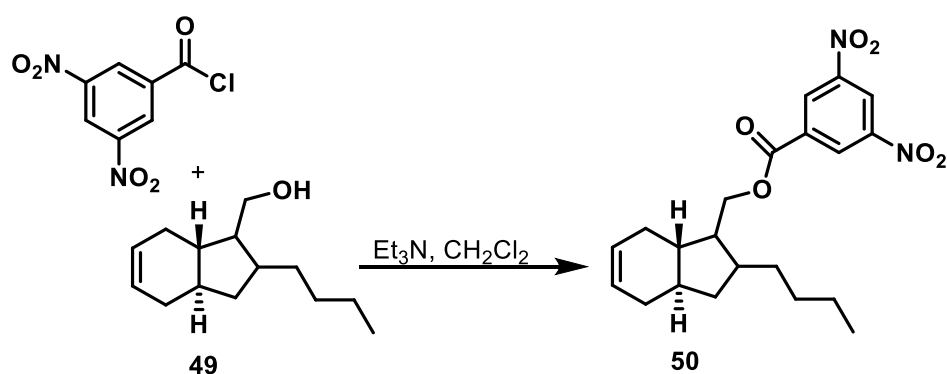
*Scheme 2.16: Acylation of alcohol **49** for X-ray crystal analysis*

This reaction was performed in order to obtain a crystalline product of the separated diastereomers of **49**. The reaction was performed several times with the highest yield of 97%, and the product was isolated as white needle forming crystals.

In the ^{13}C-NMR spectrum there are seven signals above 100 ppm, which confirms the ester carbonyl at 162.6 ppm. Two of the signals in this area confirms the alkene carbons and three of the signals confirms the aromatic carbons. The signal at 68.2 ppm confirms the methylene carbon next to the ester moiety. The number of signals are in agreement with compound **50**. In the ^{1}H-NMR spectrum, the three aromatic hydrogens appear at 9.23 and 9.15 ppm, and the alkene hydrogens are confirmed as a singlet at 5.69 ppm. The two double doublets at 4.58 and 4.57 ppm belongs to the methylene hydrogens next to the oxygen, which couples with each other and to the neighboring hydrogen. The number of hydrogens integrated in the spectrum are in agreement with **50**.

The recorded HRMS spectrum provides a molecular formula and a base peak that corresponds to the calculated molecular mass of the sodium adduct of **50** (*m/z* 231.1719).

The diasteromers were recrystallized with several different solvents and mixtures of solvents. After some experimentation, a mixture of THF and hexane was found successful to produce a suitable crystal of one diastereomer to be analyzed by X-ray crystallography. The crystal obtained was of the dinitro-diastereomer **50** derived from **D2** of alcohol **49**. The result gave the structure for the relative stereochemistry of **50** in figure 2.4.
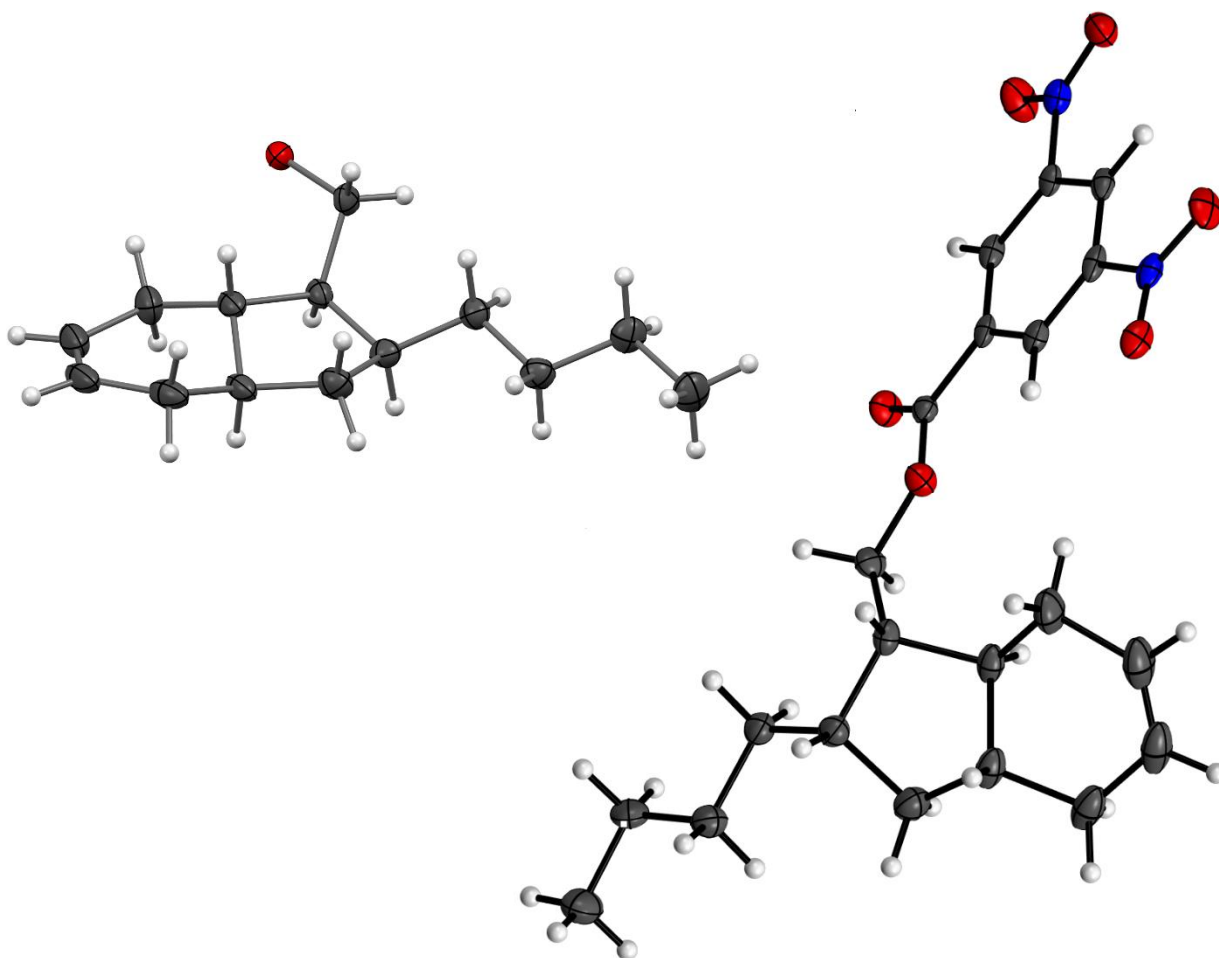

Figure 2.4: *Crystal structure of dinitro-ester **50** derived from **D2** (**51**).*

As seen in figure 2.4, the crystal structure of dinitro-ester **51** has a *trans*-fused 5/6-ring system. The groups attached to the cyclopentane moiety is pointing from the same side of the molecule and are thereby *syn* to each other. Based on the stereochemical assignment for β-keto ester **42**, the stereochemical configuration of this molecule can also be determined.

Moreover, when the methyl ester corresponding to **D2** is converted to **D1**, by equilibration in sodium ethoxide, only the stereocenter next to the ester group should be affected by removal of the more acidic α-proton. The enolate formed will then be protonated back to the *syn-*

diastereomer (**D2**) or to the *anti*-diastereomer, whereas the stereochemistry of the other three stereocenters remains unaltered. Based on this reasoning, it is likely that **D1** is the *anti*-isomer depicted in scheme 2.17. This scheme illustrates the opposite direction of that performed in the synthetic sequence, and reasons for the stereochemical assignment of **D2** and the suggested stereochemistry of **D1**.
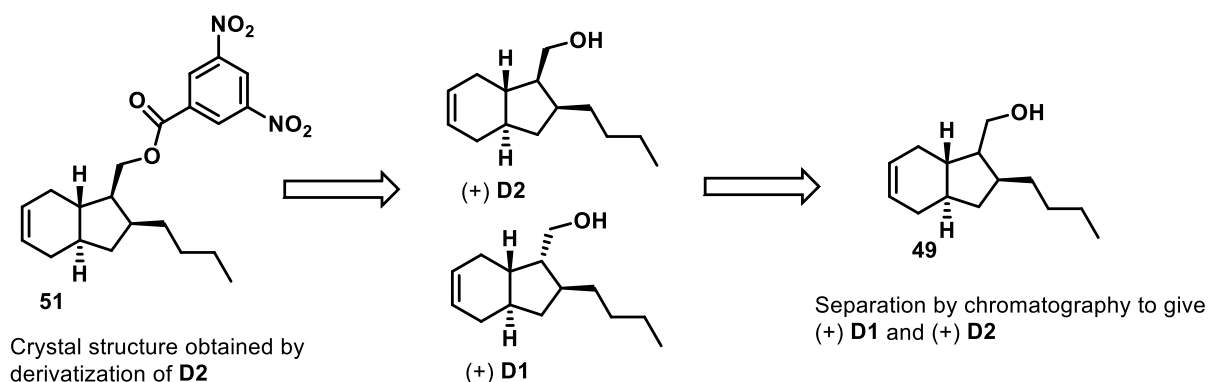
Scheme 2.17: *Proposed stereochemical assignment of synthesized isomers based on X-ray analysis of 51.*

Crystals of **D1** must be obtained and submitted to X-ray crystal analysis in order to confirm the relative and/or absolute stereochemistry of the four stereogenic centers. However, given the time on this project, this was not accomplished.

The best overall yield from (-)-dimenthyl fumarate **20** to alcohol **49** was 12% through 12 synthetic steps.

3 Summary and future work

In this project, several synthetic steps towards *trans*-fused mucosin have been performed successfully with high yields in most steps.

The first strategic pathway proved to be unsuccessful when diastereoselective acylation was attempted. When the synthetic strategy was changed, and the synthetic sequence was performed by starting with an enantiomerically enriched substrate, two separable diastereomers were formed. Equilibration of the diastereomers into the thermodynamic product seemed to be of little value for this system. However, in future perspective, the equilibration should be repeated, and followed by GC analysis to see if the reaction can be pushed to give the thermodynamic isomer in greater excess, and then terminate the reaction before a possible complex mixture is formed.

Alternatively, the isomers could be separated on a later stage. One attractive alternative is the separation of each of the synthetized isomers of the *trans*-fused mucosin. Access to as many as possible *trans* isomers over the 5/6-ring system will most likely aid the exact stereochemical assignment of the natural product.

With an enantiomerically enriched mixture of **52** in hand,[66] as discussed in chapter 2.1.7, a biocatalytic hydrolysis of the unwanted stereoisomer is of interest to try, as shown below:
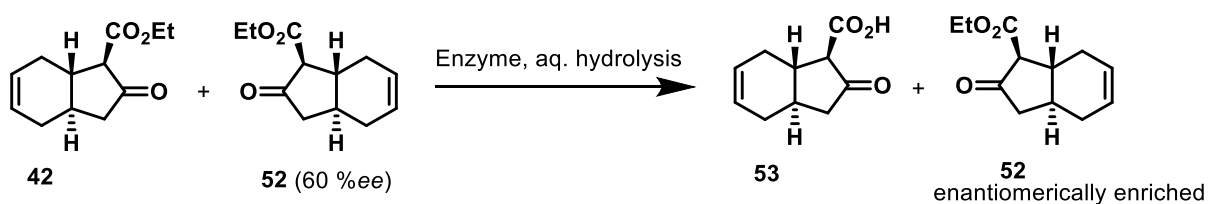
The acid could then be attempted removed using chromatography.

Based on diastereoselective synthesis and comparison of the obtained data with literature values, stereochemical assignment was made of all intermediates. Moreover, X-ray analysis provided information for further stereochemical assignment, as well as direct and indirect stereochemical assignment of the two diastereomers synthesized.

Future work in this project will be to repeat the equilibration procedure as described above, and to finish the planned synthesis as described in chapter 1.11 from the *anti*-diastereomer

synthesized so far. The four remaining steps involve oxidation, homologation, formation of a terminal alkene, and finally incorporation of the methyl ester sidechain to obtain an *E*-alkene.

When *trans*-mucosin is synthesized, spectroscopic data and optical rotation values can reveal if this is the true structure of the isolated natural product, or its enantiomer. In addition, the compound will be biologically tested.

4 Conclusion

Given the time on this project, synthetic studies towards of one putative isomer of *trans*-fused mucosin have been performed. The work accomplished in this project can be used in later synthetic attempts of the compound.

The two diastereomers, **D1** and **D2,** were successfully synthesized in a 12-step synthesis, with 12% overall yield. The stereochemistry were determined, which are of great importance for further synthetic studies. Moreover, with respect to β-keto ester **42**, high optical purity was achieved with this synthesis by starting with an asymmetric Diels-Alder reaction.

Equilibration of the *trans*-fused ring system by application of procedures performed when the *cis*-fused isomer was synthesized seemed to be inapplicable. However, further experimentation should be done before a conclusion about this can be made.

5 Experimental

5.1 General

All reactions were performed under nitrogen atmosphere. Solvents and reagents were of technical quality and used as purchased. Where specified, dry solvents of anhydrous quality were used under water-free reaction conditions.

Thin layer chromatography (TLC) was performed on silica plates of the type TLC Silica gel 60 F_{254} from Merck. Various visualizing reagents were used, depending on the reagents and products involved, including Potassium permanganate ($KMnO_4$), cerium-ammonium-molybdate (CAM), UV light, and vanillin.

Flash chromatography was the main method of purification.

The NMR spectra were recorded on a Bruker AVII400 at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR. Coupling constants (J) are reported in Hertz and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ^{1}H-NMR ($CDCl_3 = \delta$ 7.26, and MeOD-$d_4 = \delta$ 3.31) and the central carbon solvent resonance in ^{13}C-[1]NMR ($CDCl_3 = \delta$ 77.00 ppm, and MeOD-$d_4 = \delta$ 49.00).

IR spectra were recorded on a Perkin Elmer, FT-IR system.

Mass spectra were recorded at 70 eV on Micromass Prospec Q or Micromas QTOF 2W spectrometer using ESI as the method of ionization.

UV/Vis spectra from [1]90-900 nm were recorded using an Agilent Technologies Cary 8485 UV-VIS spectrophotometer using quartz cuvettes.

GC was performed on an Aglient Technologies 7820A GC instrument with split (1:30) injection and flame ionization detector, and equipped with an achiral column (Aglient J & W GC columns 19091J-413 HP-5) or a chiral column (Aglient CP-Chirasil DEX CB CP-7502).

Optical rotations were measured using a 0.7 mL cell with a 1.0 dm path length on an Anton Paar MCP 100 polarimeter using the stated solvents.

X-ray crystallography was performed on a Bruker D8 Venture diffractometer with InCoatec ImuS Microfocusradiation source and Photon 100 CMOS detector.

44

5.1.1 Preparation of (cyclohex-4-ene-1,2-diyl)dimethanol alcohol (29)

(±) **29**
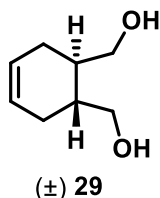
Procedure:[60]

To a stirring suspension of lithium aluminium hydride (389 mg, 10.3 mmol, 1.40 eq.) in dry tetrahydrofuran (THF) (2.3 mL), diester **28** (1.69 g, 7.50 mmol, 1 eq.) dissolved in dry THF (6.0 mL) was added dropwise by syringe through a septum. After complete addition, the reaction was refluxed until judged complete by TLC analysis (ca 24 h). The reaction mixture was allowed to cool to room temperature (RT) before water (0.40 mL) was *carefully* added to quench the reaction, all while maintaining vigorous stirring. After 15 minutes, 15 % (w/v) NaOH (aq) (0.40 mL) was added. Following an additional 15 minutes, water (1.2 mL) was added, and a fine precipitate soon resulted. A small portion of dry THF was added so the solids could be stirred, and then a small amount of $MgSO_4$ was added to ensure a dry organic solution. The reaction mixture was vacuum-filtered through a glass-sintered funnel, and the pad of salts washed with additional THF. The filtrate was concentrated in *vacuo* to give diol **29** as a pale yellow oil (1.01 g, 7.10 mmol, 95%).

R$_f$: 0.10 (60% EtOAc in heptane)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.63 (s, 2H), 3.78 – 3.64 (m, 4H), 3.58 – 3.47 (m, 2H), 2.08 – 1.92 (m, 2H), 1.89 – 1.76 (m, 2H), 1.74 – 1.58 (m, 2H)

^{13}C NMR (100 MHz, CDCl$_3$) δ 126.2, 66.4, 39.9, 28.7

IR: 2891, 3025, 3294 cm^{-1}

MS (TOF-ES$^+$): calculated for $C_8H_{14}O_2Na$ [M+Na]$^+$: 165.089, found 165.089

Compound **29** is known from the literature.[65]
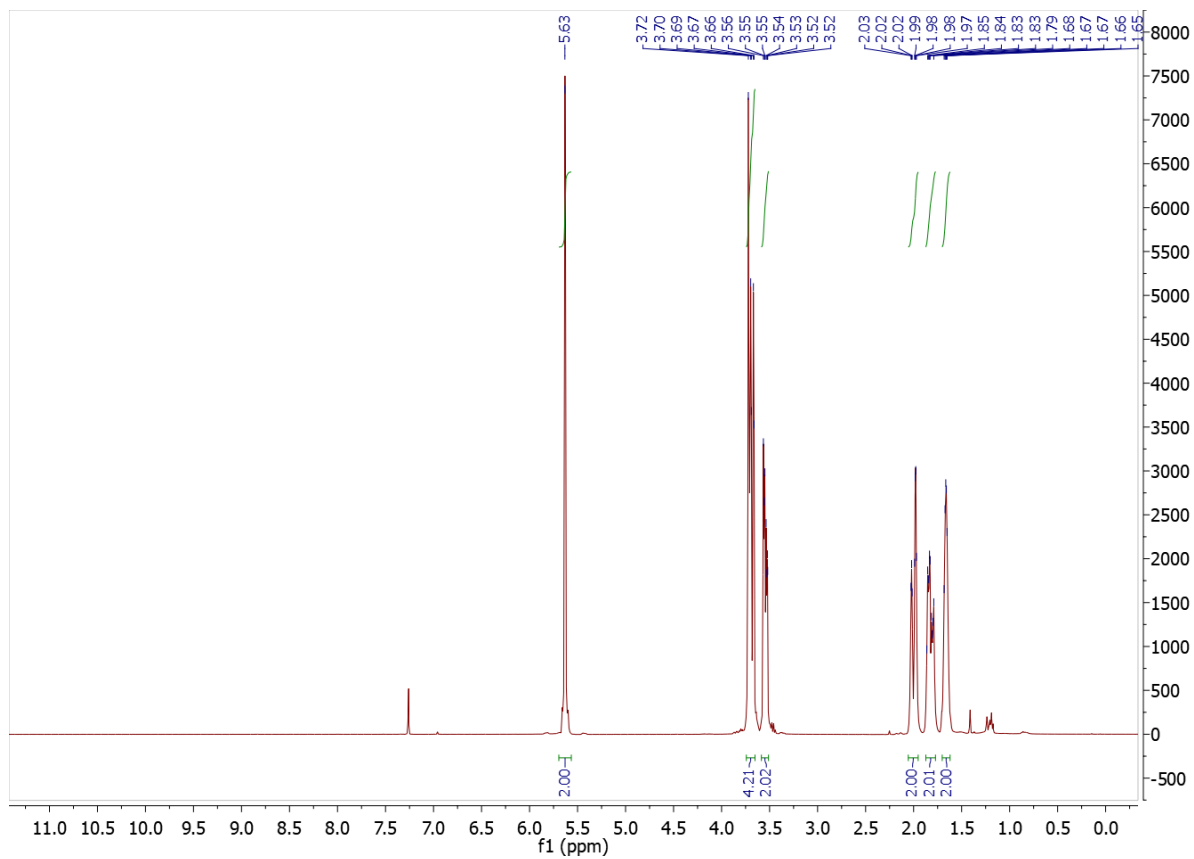
Spectrum 5.1: *^1H NMR spectrum of compound* ***29***.
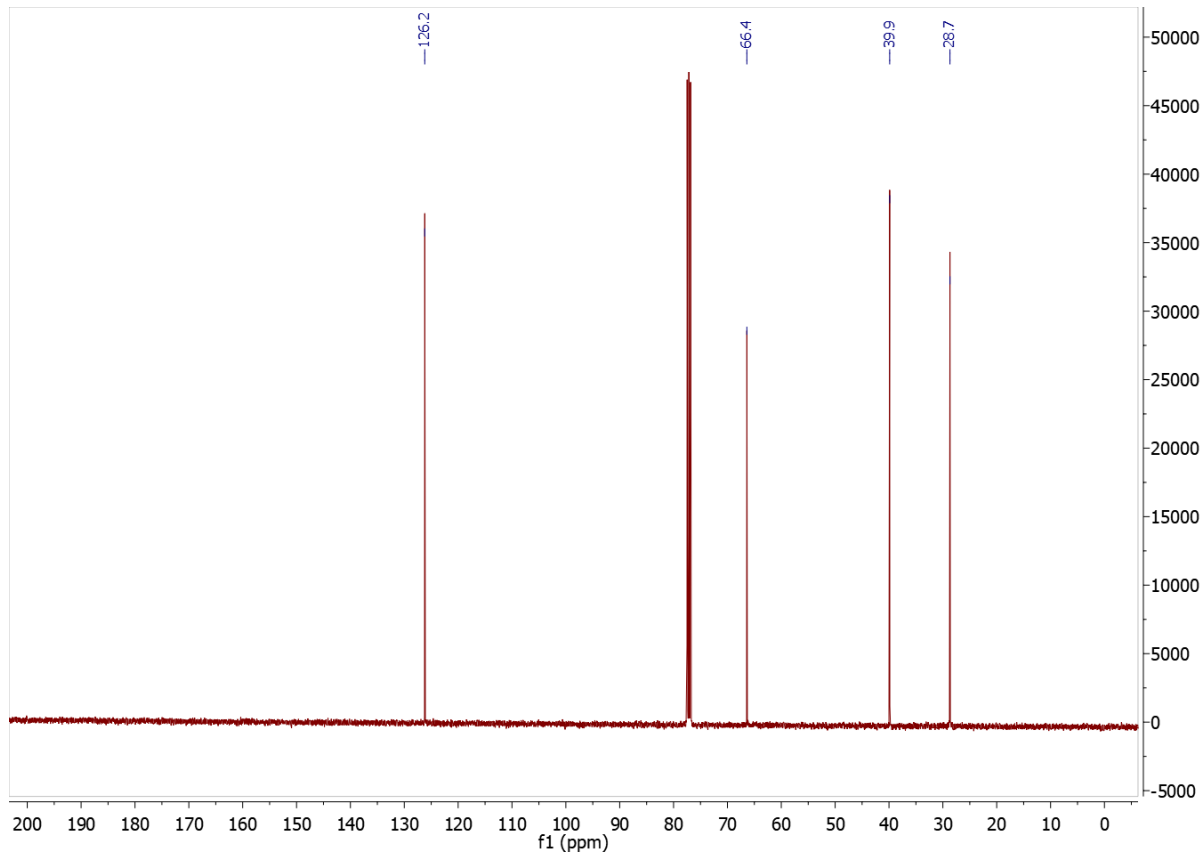
Spectrum 5.2: *^{13}C NMR spectrum of compound* ***29***.

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5.1.2 Preparation of (cyclohex-4-ene-1,2-diyl) *bis*(methylene)*bis*(4-methylbenzenesulfonate) (30)

(±) **30**
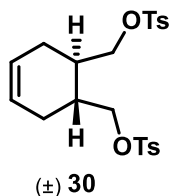
Procedure:[60]

p-Toluenesulfonyl chloride (11.4 g, 60.0 mmol, 3.00 eq.) was dissolved in pyridine (17 mL) at 0 ℃ followed by dropwise addition of a solution of **29** (2.66 g, 18.7 mmol, 1.00 eq.) in pyridine (8.5 mL). The flask containing the diol in pyridine were washed with a few drops of additional pyridine that were transferred to the reaction flask. The reaction mixture was stirred at 0 ℃ until judged complete by TLC analysis (ca 2.5 h).

The reaction mixture was poured into ice-water (50 mL) and a white precipitate was formed. The solvent was removed by vacuum filtration, and the crude product was recrystallized from methanol to yield white crystals of **30** (7.28 g, 16.2 mmol, 86%).

R$_f$: 0.52 (60% EtOAc in heptane)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.3 Hz, 4H), 7.35 (d, *J* = 8.3 Hz, 4H), 5.51 (s, 2H), 3.99 – 3.87 (m, 4H), 2.46 (s, 6H), 2.03 – 1.96 (m, 4H), 1.89 – 1.81 (m, 2H)

^{13}C NMR (100 MHz, CDCl$_3$) δ 145.1, 132.87, 130.1, 128.0, 124.8, 71.4, 33.2, 25.6, 21.8

Mp: 95-96 ℃ (lit.[63] mp 110-111 ℃)

MS (TOF-ES$^+$): calculated for C$_{22}$H$_{26}$S$_2$O$_6$Na [M+Na]$^+$: 473.106, found 473.106

Compound **30** is known from the literature.[63]
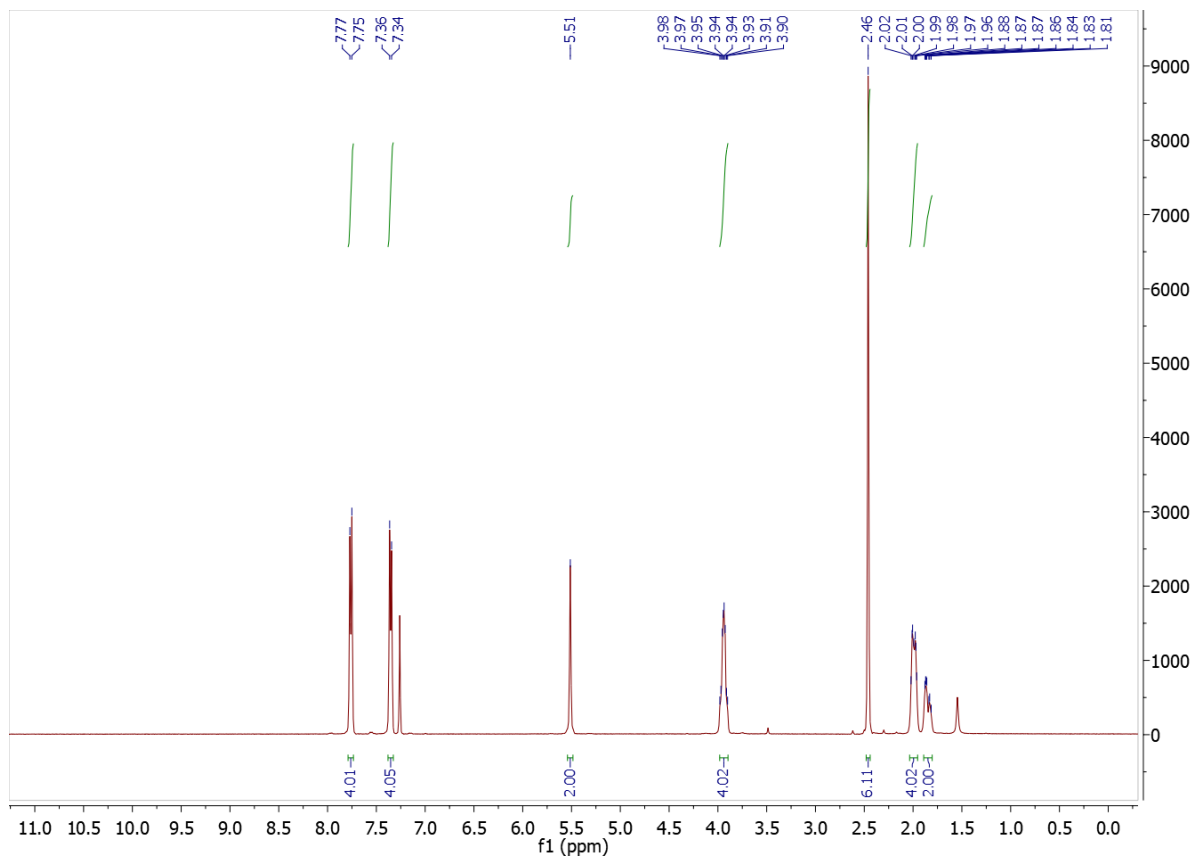
Spectrum 5.3: *^{1}H NMR spectrum of compound **30**.*
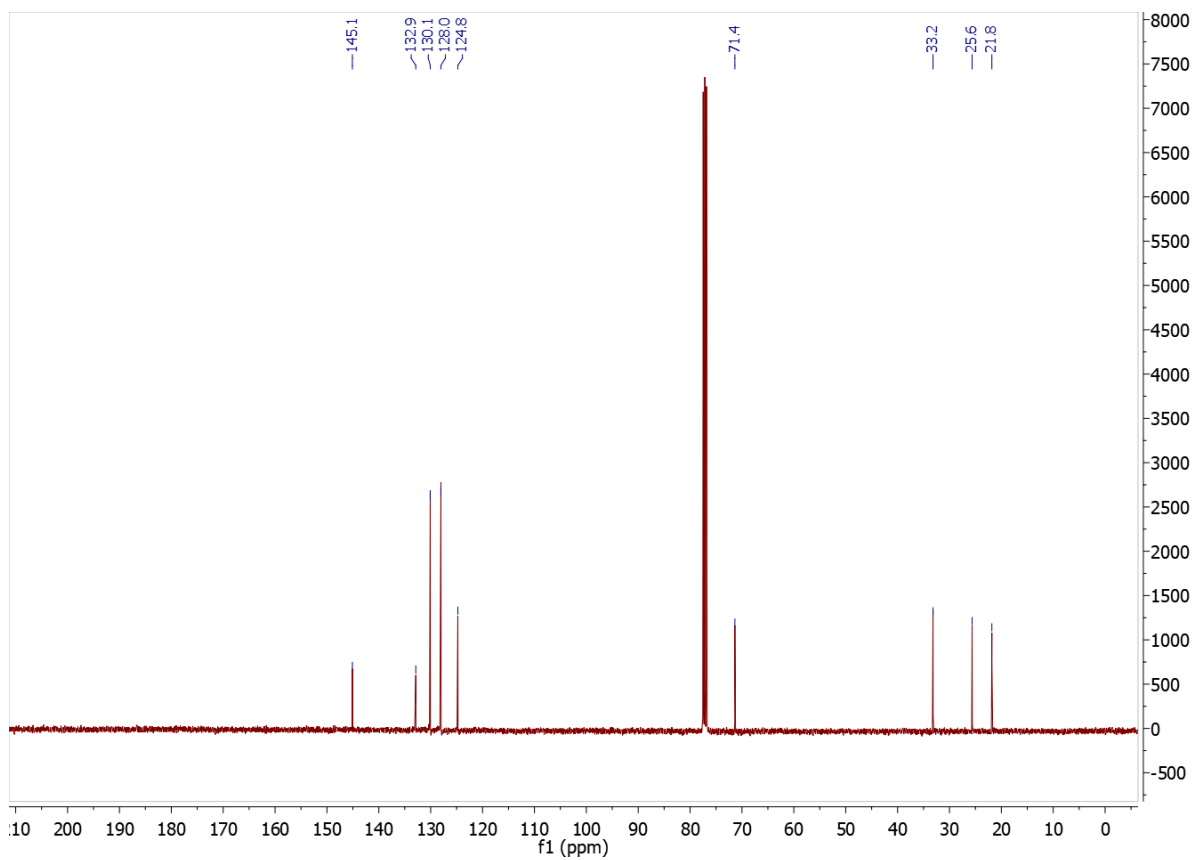
Spectrum 5.4: *^{13}C NMR spectrum of compound **30**.*

5.1.3 Preparation of 2,2'-(cyclohex-4-ene-1,2-diyl)diacetonitrile (31)

(±) **31**
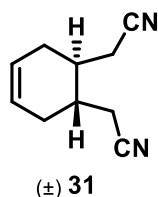
Procedure 1:[60] Ditosylate **30** (1.09 g, 2.40 mmol, 1.00 eq.) and KCN (360 mg, 7.40 mmol, 3.00 eq.) were dissolved in ethanol (7.0 mL) and refluxed until the reaction was judged complete by TLC analysis (ca 27 h). Approximately 5 mL of brine was poured into the reaction flask to dissolve the remaining salts. Then, the reaction mixture was poured into a separatory funnel and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL), dried (MgSO$_4$), filtered, and concentrated in *vacou* to give a brown solid of **31** (303 mg, 1.89 mmol, 79%).

Procedure 2:[58] Ditosylate **30** (477 mg, 1.06 mmol, 1.00 eq.) and KCN (224 mg, 3.44 mmol, 3.25 eq.) were dissolved in DMSO (1.7 mL) and heated to 100 ºC. The reaction mixture was stirred at this temperature until judged complete by TLC analysis (ca 6 h), then allowed to cool to ambient temperature. The resulting brown slurry was poured into water (20 mL), and the aqueous phase extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (15 x 10 mL), dried (MgSO$_4$), filtered, and concentrated in *vacuo* to give a cream-colored solid. This crude solid was purified by flash chromatography (30% EtOAc in heptane) to yield **31** as a white solid (151 mg, 0.943 mmol, 89%).

R$_f$: 0.42 (60% EtOAc in heptane)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.66 (s, 2H), 2.51 – 2.43 (m, 4H), 2.35 – 2.23 (m, 2H), 2.15 – 2.02 (m, 4H)

^{13}C NMR (100 MHz, CDCl$_3$) δ 124.6, 117.8, 32.9, 28.5, 21.3

Mp: 87-88 ºC (lit.[63] mp 97-99 ºC)

IR: 2247, 2919, 3056 cm^{-1}

MS (TOF-ES⁺): calculated for $C_9H_{12}N_2Na$ $[M+Na]^+$: 183.011, found 183.089

Compound **31** is known from the literature.[63]
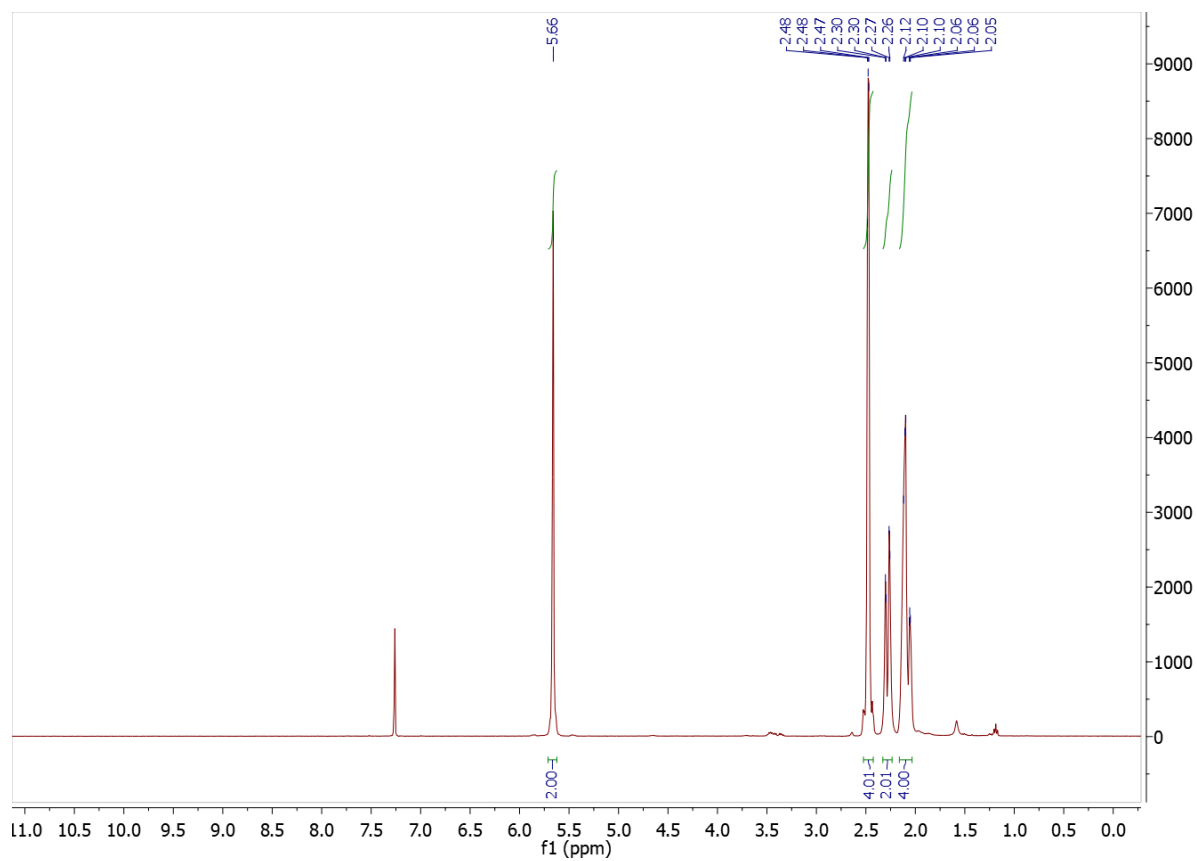
Spectrum 5.5: *¹H NMR spectrum of compound **31**.*
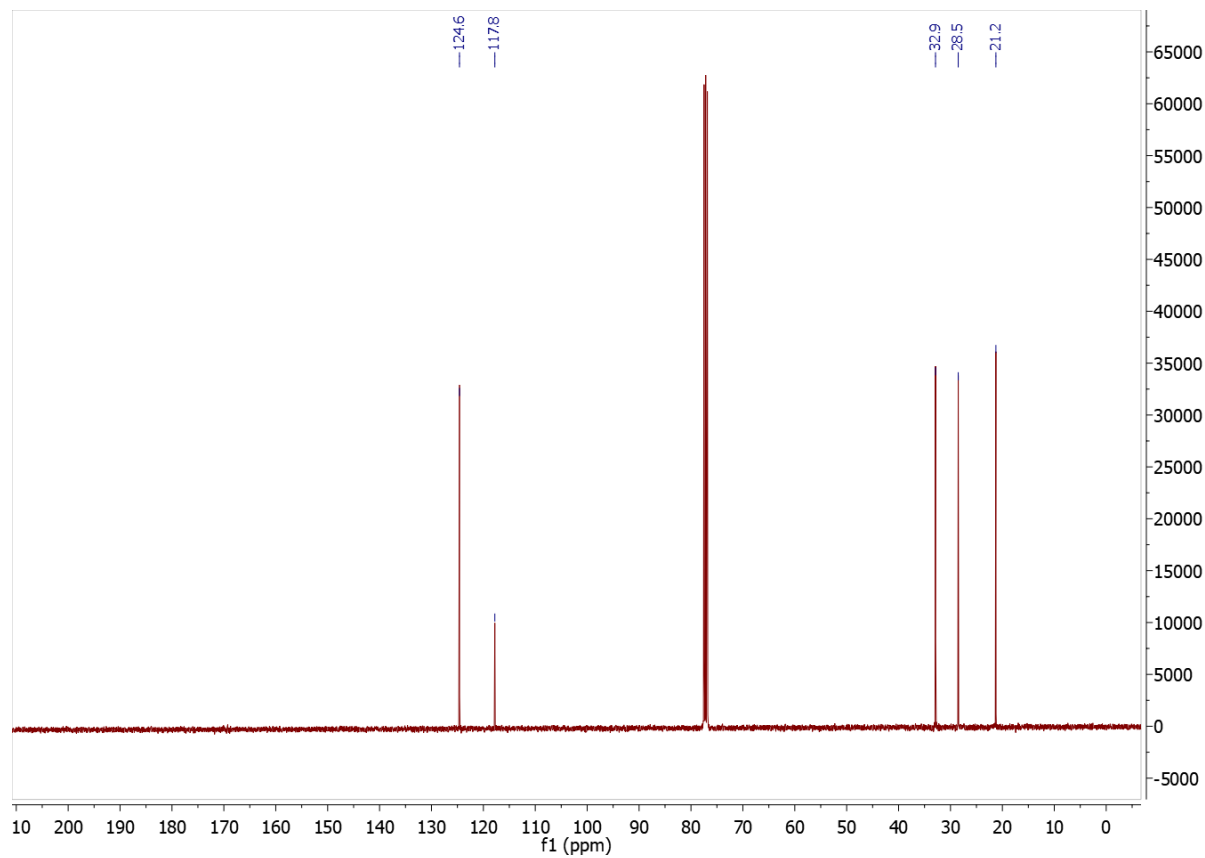
Spectrum 5.6: *¹³C NMR spectrum of compound **31**.*

5.1.4 Preparation of diethyl 2,2'-(cyclohex-4-ene-1,2-diyl)diacetate (33)
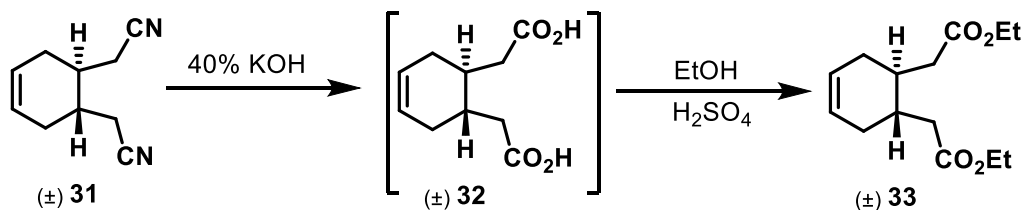
Scheme 5.1: Hydrolysis and esterification

Procedure:[63]

A solution of dinitrile **31** (4.82 g, 30.1 mmol) and aqueous KOH (40 %, 32 mL) were heated to reflux and monitored by TLC analysis. The reaction was judged complete when the starting material was no longer observable on the silica plate (ca 32 h). The resulting solution was cooled to 0 ℃ in an ice-bath, and aqueous H_3PO_4 (85%, 32 mL) was added dropwise with stirring. The resulting solid was isolated by vacuum filtration, washed with warm water, and dried under vacuum to give diacid **32** as a pale yellow powder (5.24 g, 26.5 mmol, 88%)

^{1}H NMR (400 MHz, Methanol-d_4) δ 5.62 (s, 2H), 2.51 – 2.39 (m, 2H), 2.31 – 2.18 (m, 4H), 2.06 (s, 2H), 1.86 (d, J = 17.8 Hz, 2H)

^{13}C NMR (100 MHz, CD$_3$OD) δ 176.8, 126.01, 39.3, 34.9, 29.6

The crude diacid **32** (5.23 g, 26.4 mmol) was taken up as a suspension in absolute EtOH (98 mL), and stirred with dropwise addition of H_2SO_4 (98%, 2.5 mL). After 48 h, the reaction was judged complete by TLC, and the reaction mixture was allowed to cool to ambient temperature before the EtOH was removed under vacuum to approximately ¼ of the volume. The mixture was added to water (200 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with water (1 x 50 mL), and saturated NaHCO$_3$ (aq) (1 x 50 mL), and the organic layer was dried (MgSO$_4$), filtered by vacuum, and concentrated in *vacuo* to give a yellow oil. This crude oil was purified by flash chromatography (hexane:Et$_2$O 2:1) to give diester **33** as a colorless oil (5.97 g, 23.5 mmol, 89%).

R$_f$: 0.34 (Hexane:EtOAc 4:1)

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¹H NMR (400 MHz, Chloroform-*d*) δ 5.59 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 4H), 2.42 (dd, *J* = 14.9, 4.8 Hz, 2H), 2.29 – 2.20 (m, 3H), 2.18 – 2.15 (m, 1H), 2.09 – 2.02 (m, 2H), 1.88 – 1.80 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 6H)

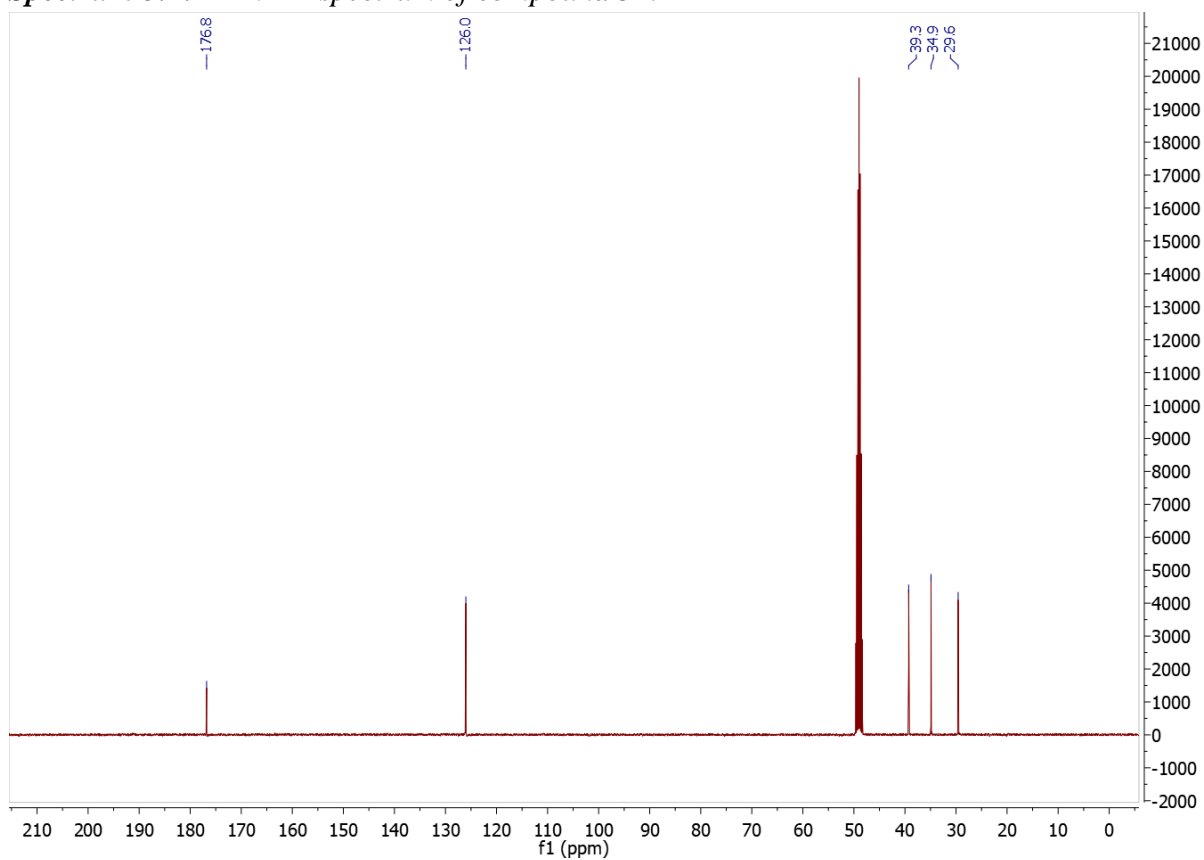**¹³C NMR** (100 MHz, CDCl₃) δ 173.1, 125.1, 60.5, 38.7, 33.7, 28.6, 14.4

IR: 1731, 2982, 3027 cm⁻¹

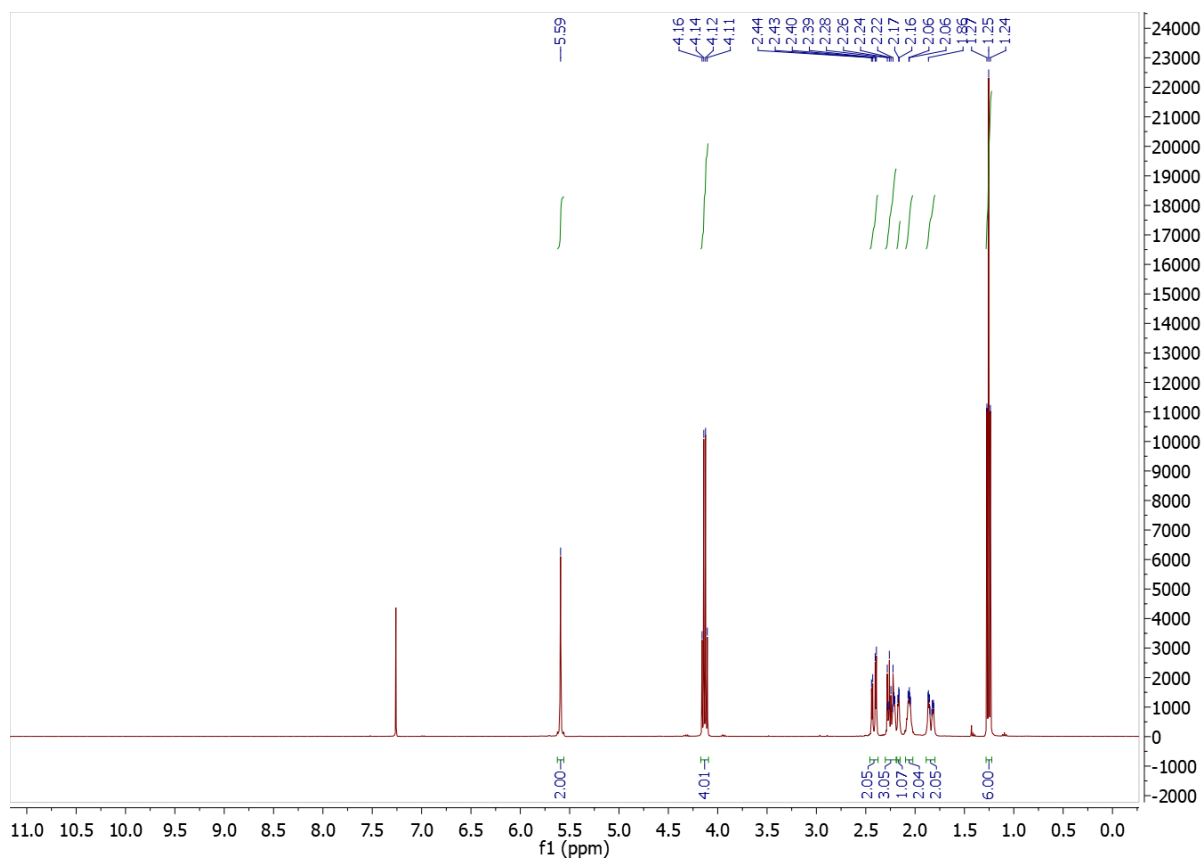**MS (TOF-ES⁺):** calculated for $C_{14}H_{22}O_4Na$ [M+Na]⁺: 277.141, found 277.141
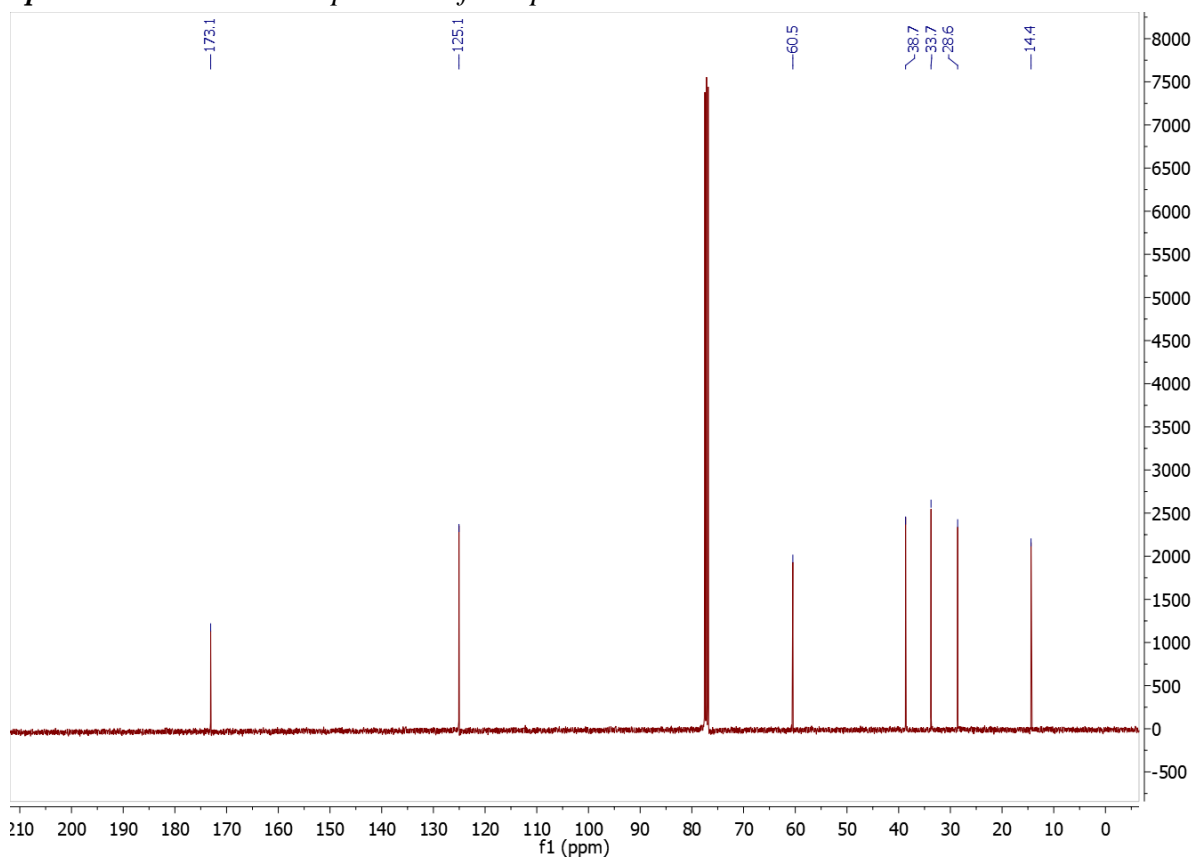
Compound **32** and **33** are known from the literature.[63]
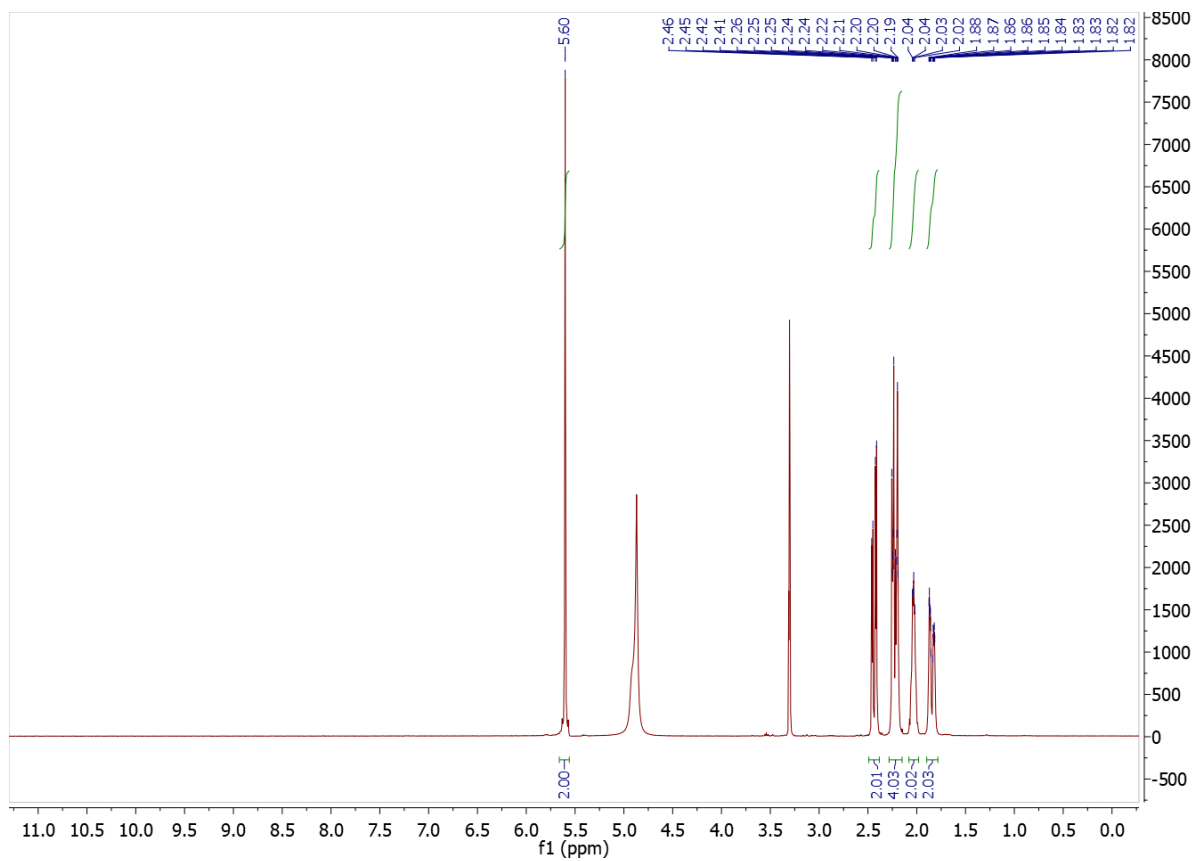
Spectrum 5.7: *^{1}H NMR spectrum of compound **32**.*

Spectrum 5.8: *^{13}C NMR spectrum of compound **32**.*

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Spectrum 5.9: *^{1}H NMR spectrum of compound **33**.*

Spectrum 5.10: *^{13}C NMR spectrum of compound **33**.*

5.1.5 Preparation of ethyl 2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (34)
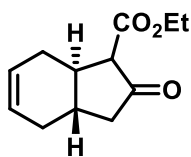
(±)-*trans* **34**

Procedure:[63]

NaH (60% dispersion in mineral oil, 527 mg, 13.2 mmol 1.00 eq.) was washed with dry hexane (2 x 10 mL), and then dry THF was added (12 mL). The mixture was heated to reflux followed by dropwise addition of a solution of diester **33** (3.38 g, 13.3 mmol, 1.00 eq.) in dry THF (5.3 mL) through septum. The mixture was subsequently refluxed until judged complete TLC analysis (1.5 h), and then allowed to cool to ambient temperature before glacial AcOH (0.84 mL, 14.6 mmol, 1.1 eq.) was added. The resulting gelatinous mixture was added to water (150 mL) and Et$_2$O (100 mL). The phases were separated, and the aqueous phase was extracted with Et$_2$O (3 x 50 mL). The combined organic extracts were washed with water (3 x 50 mL), saturated NaHCO$_3$ (aq) (50 mL), and brine (50 mL). The organic layer was dried (MgSO$_4$), filtered by vacuum, and concentrated in *vacuo* to give a crude oil that was purified by flash chromatography (30% EtOAc in heptane) to give a diastereomeric mixture of **34** as a colorless oil (2.48 g, 11.9 mmol, 90%).

R$_f$: 0.49 (hexane:EtOAc 4:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.72 (s, 2H), 4.22 – 4.16 (m, 2H), 2.86 (dd, *J* = 12.2, 2.2 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.42 – 2.26 (m, 3H), 2.06 – 1.83 (m, 4H), 1.30 – 1.22 (m, 3H)

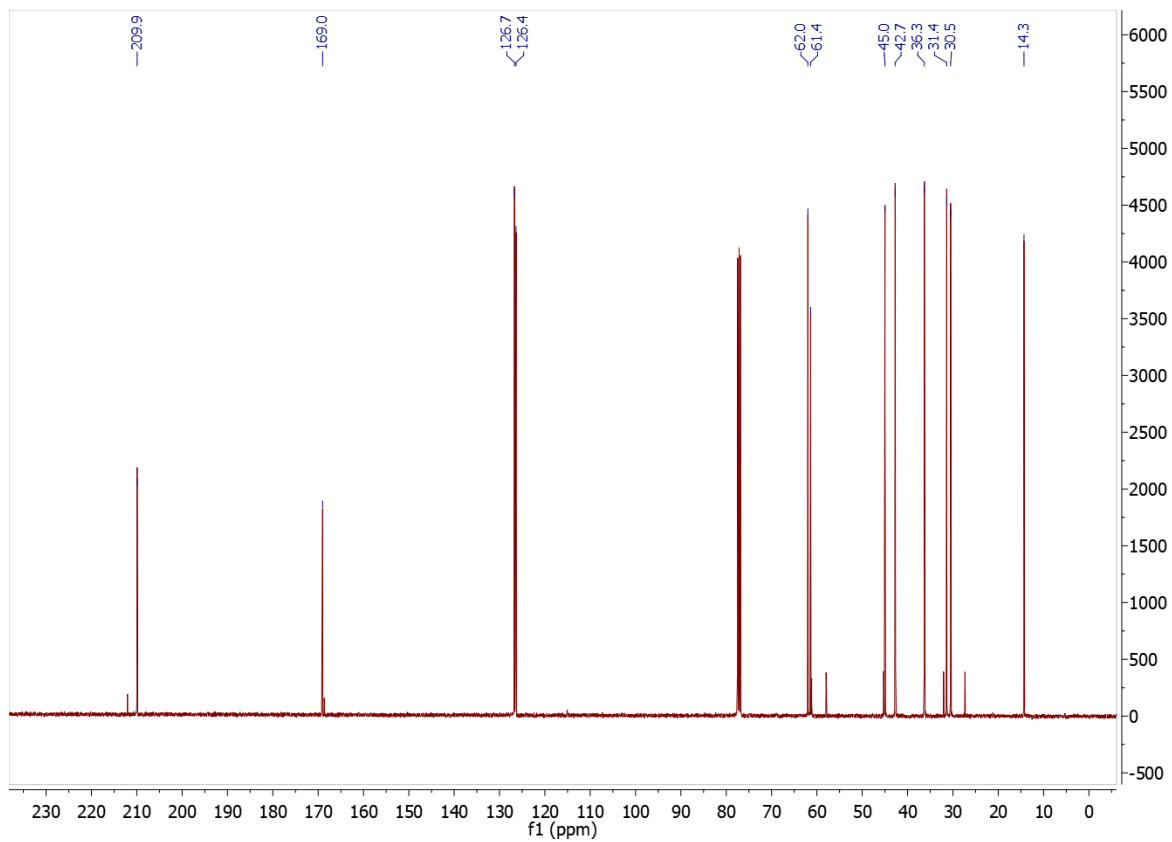**^{13}C NMR** (100 MHz, CDCl$_3$) δ 209.9, 169.0, 126.7, 126.4, 62.0, 61.4, 45.0, 42.7, 36.3, 31.4, 30.5, 14.3

IR: 1723, 1756, 2902, 3028 cm^{-1}

MS (TOF-ES$^+$): calculated for C$_{12}$H$_{16}$O$_3$Na [M+Na]$^+$: 231.09 **,** found 231.0

Compound **34** is known from the literature.[63]
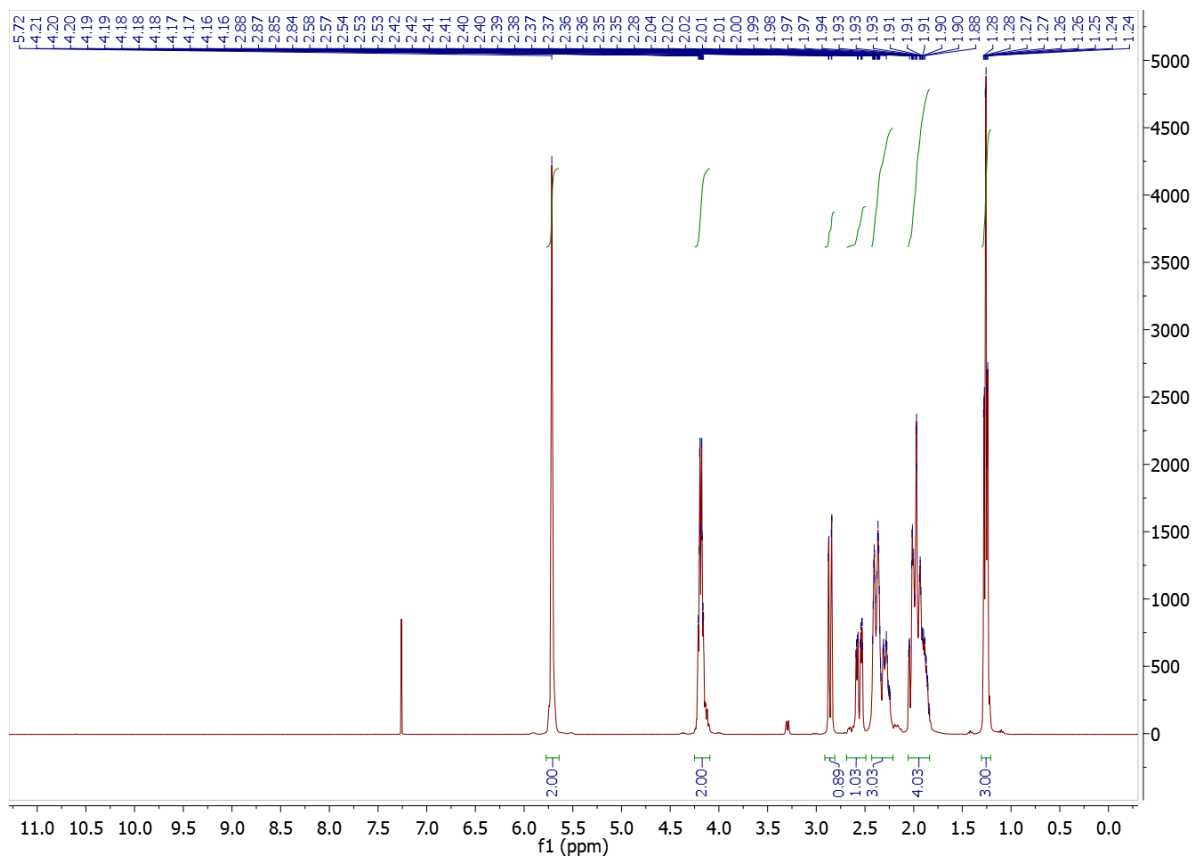
Spectrum 5.11: *^{1}H NMR spectrum of compound **34**.*

Spectrum 5.12: *^{13}C NMR spectrum of compound **34**.*

5.1.6 Preparation of (±)-*trans*-bicyclo[4.3.0]non-3-en-8-one (35)

(±) **35**
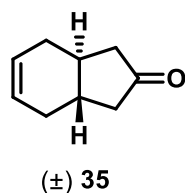
Procedure:[63]

A solution of **34** (1.27 g, 6.39 mmol, 1.00 eq.) in DMSO (7.9 mL) and water (0.5 mL) was heated to 155 ℃ and stirred at this temperature until judged complete by TLC analysis (ca 2 h). The mixture was allowed to cool to ambient temperature before it was added to water (100 mL), and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with water (10 x 30 mL), dried (MgSO$_4$), filtered by vacuum, and concentrated in *vacuo* to give a crude solid. This solid was purified by flash chromatography (hexane:Et$_2$O 4:1) to give **35** as a white solid (753 mg, 5.53 mmol, 94%).

R$_f$: 0.37 (20% EtOAc in heptane)

Mp: 68-69 ℃ (lit.[58] mp 66-67 ℃)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.75 – 5.73 (m, 2H), 2.48 (d, *J* = 10.8 Hz, 2H), 2.38 (d, *J* = 14.0 Hz, 2H), 2.01 – 1.81 (m, 6H)

^{13}C NMR (100 MHz, CDCl$_3$) δ 217.9, 126.8, 45.3, 39.0, 31.6

MS (TOF-ES$^+$): calculated for C$_9$H$_{12}$ONa [M+Na]$^+$: 159.078**,** found 159.078

Compound **35** is known from the literature.[63]
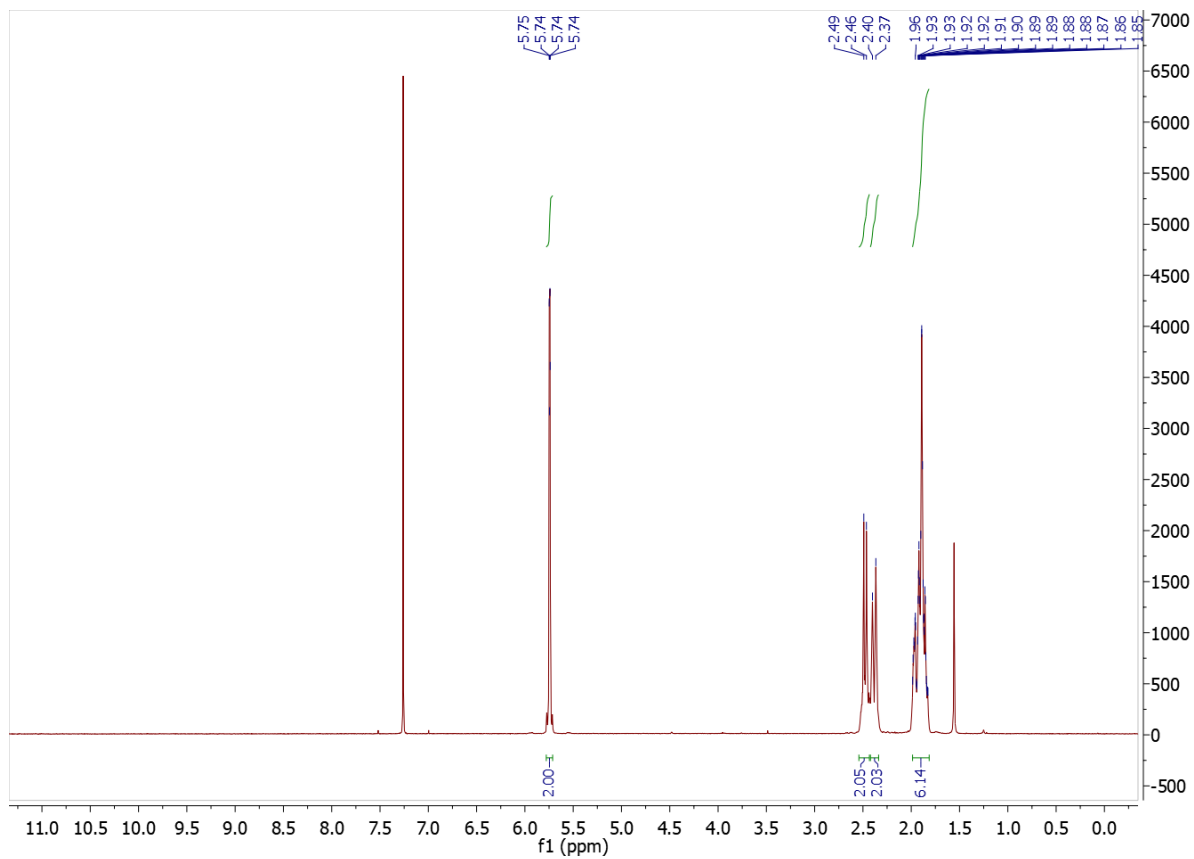
Spectrum 5.13: *^1H NMR spectrum of compound **35**.*
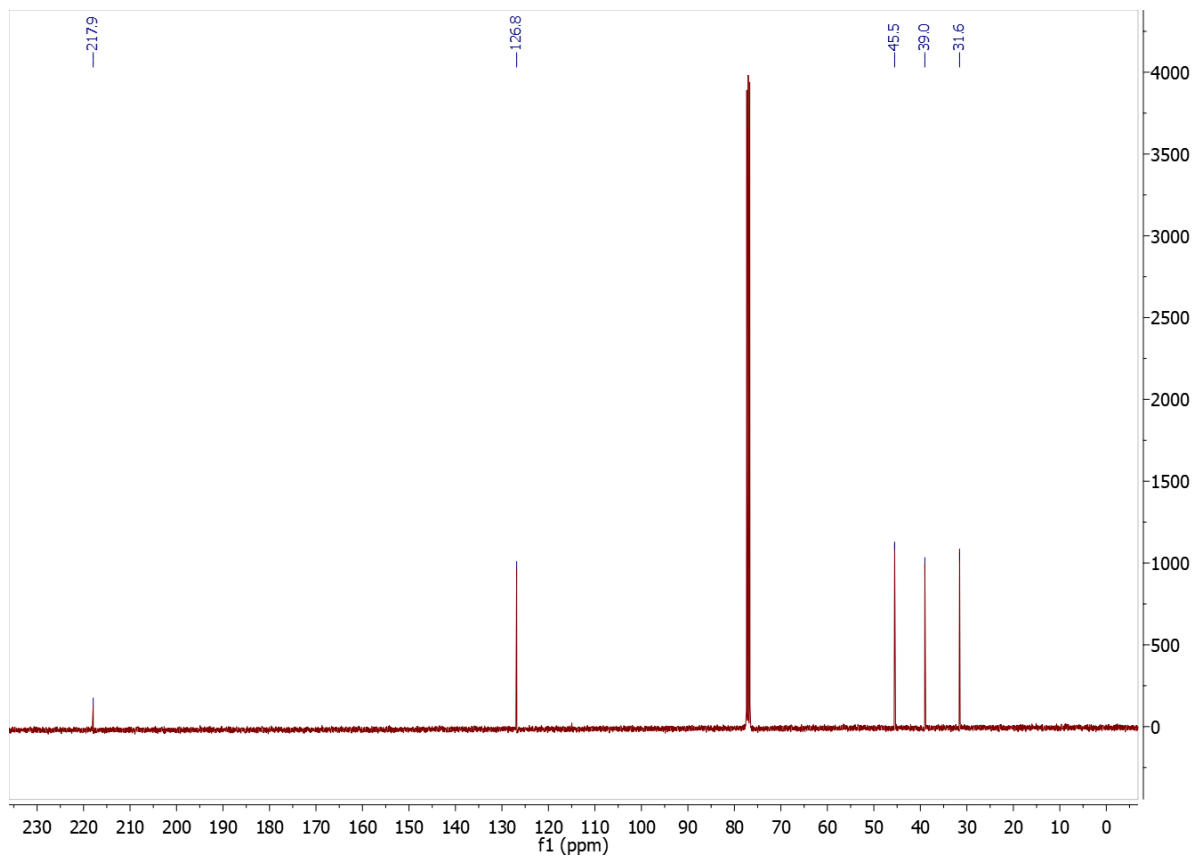
Spectrum 5.14: *^{13}C NMR spectrum of compound **35**.*

5.1.7 Preparation of ethyl (1*R*,3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (42) and ethyl (1*S*,3a*S*,7a*R*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (52)
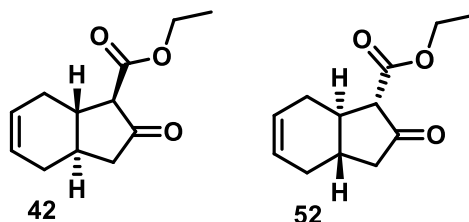
Procedure:[3]

(+)-*bis*[(*R*)-1-phenylethyl]amine hydrochloride (1.55 g, 5.92 mmol, 1.60 eq.) was added in one portion to dry THF (5.9 mL) at room temperature with stirring. After 5 minutes, the suspension was cooled to -78 °C and ^{n}BuLi (1.6 M in hexane, 7.5 mL, 11.7 mmol, 3.15 eq.) was added. After stirring at -78 °C for 15 min, the mixture was heated to room temperature, and then cooled to -78 °C again. Ketone (±)-**35** (506 mg, 3.72 mmol, 1.00 eq.) was added dropwise over 10 minutes, and the reaction mixture was subsequently stirred for 45 min whereby a purple color evolved. Ethyl cyanoformate (0.74 mL, 7.40 mmol, 2.00 eq.) was added over 5 min, and the reaction mixture was left to stir monitored by thin layer chromatography (TLC). After 3h, the reaction was judged complete, and quenched by the addition of water (1.2 mL) at -78 °C), followed by heating to room temperature. Next, the mixture was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with water (2 x 50 mL), aqueous HCl (0.5 M, 50 mL), and brine (1 x 50 mL), and dried over MgSO4, filtered and concentrated in *vacuo*. TLC of the crude product indicated that a mixture of 5 compounds, including residual starting material, was formed. The resulting mixture was purified with flash chromatography (hexane:Et$_2$O 4:1). One fraction was pure, and a quick ^{1}H-NMR analysis indicated that this was a product of interest. A new flash chromatography was prepared (hexane:Et$_2$O 5:1), to give a pale yellow oil (476 mg, 2.29 mmol, 61%). No other compounds were isolated. According to the specific optical rotation value measured, compound **52** is thought to be formed in excess by comparison with the literature of **42**.[63] GC analysis by using a chiral column provided a chromatogram with two peaks in~8:2 ratio.

$[\alpha]_D^{25}$ = + 16.7 (c = 2.1, CHCl₃), lit.[63] value for ethyl ester **42** ($[\alpha]_D$ = -24.1 (c = 1.62, CHCl₃)
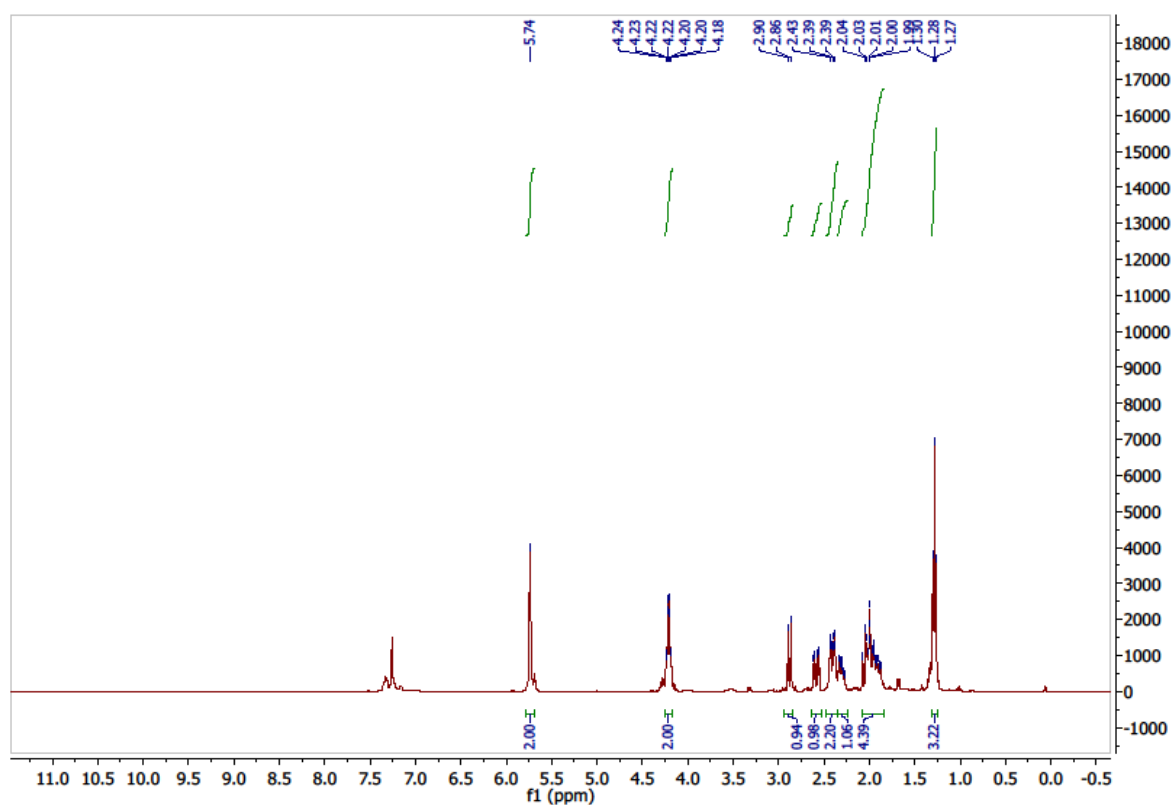
R_f: 0.18 (hexane:Et₂O 4:1)

¹H NMR (400 MHz, Chloroform-*d*) δ 5.74 (s, 2H), 4.24 – 4.18 (m, 2H), 2.88 (d, *J* = 12.2 Hz, 1H), 2.58 (dd, *J* = 17.8, 6.4 Hz, 1H), 2.45 – 2.36 (m, 2H), 2.35 – 2.27 (m, 1H), 2.09 – 1.88 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H)
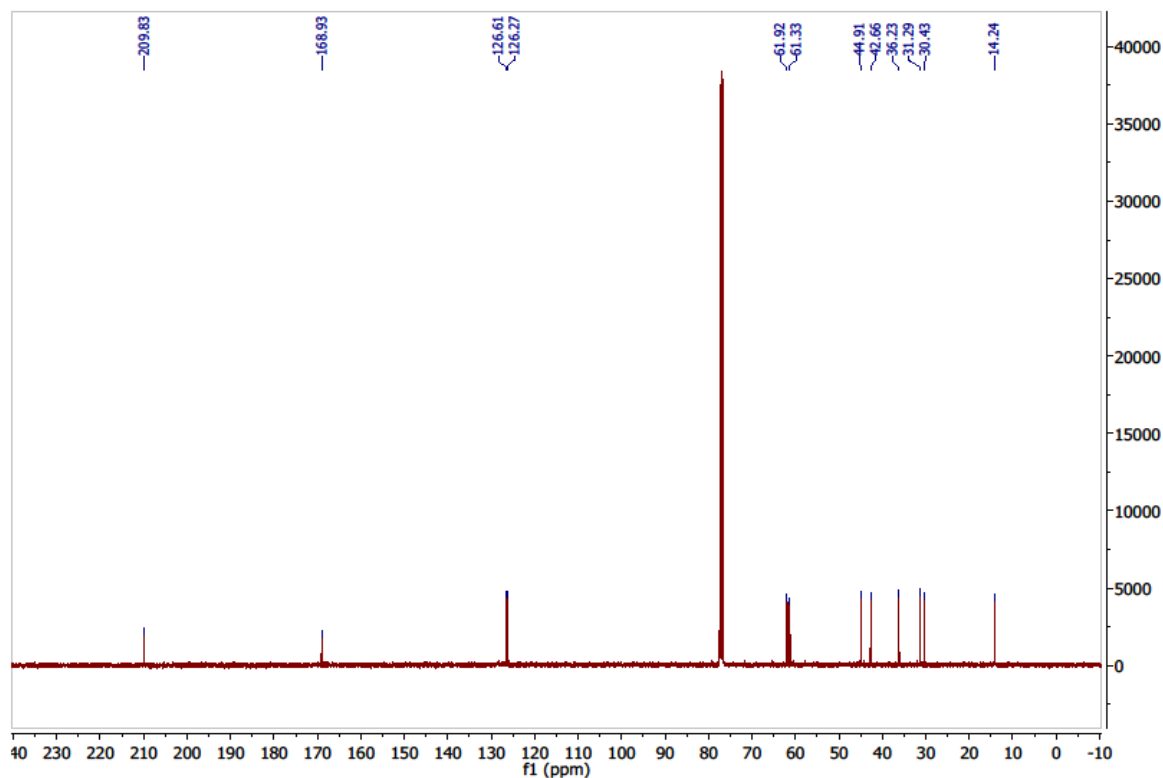
¹³C NMR (100 MHz, CDCl₃) δ 209.83, 168.93, 126.61, 126.27, 61.92, 61.33, 44.91, 42.66, 36.23, 31.29, 30.43, 14.24

MS (TOF-ES⁺): Exact mass calculated for $C_{12}H_{16}O_3Na$ [M+Na]⁺: 231.099, found 231.099

Compound **42** is known from the literature.[63]

Spectrum 5.15: *¹H NMR spectrum of compound **42** and **52**.*

Spectrum 5.16: *^{13}C NMR spectrum of compound **42** and **52**.*

5.1.8 Preparation of (-)-(1*S*,2*S*)-di-(-)-menthyl cyclohex-4ene-1,2-dicarboxylate (22)
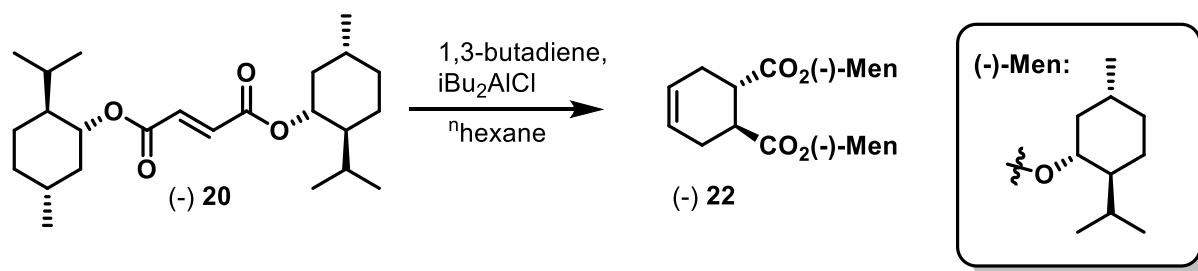
Scheme 5.2: *Asymmetric Diels-Alder reaction*

Procedure:[65]

(-)-dimenthyl fumarate (**20**) (1.71 g 4.36 mmol, 1.00 eq.) was stirred in dry hexane (26 mL) and cooled to -40 ℃ (acetone / dry ice bath). Diisobutylaluminium chloride (25% in hexane, 13 mL) was added by syringe through a septum, whereby an intense orange color was

produced. The solution was stirred at this temperature during which time 1,3-butadiene was condensed into a sealed flask cooled to -78 ºC, and then passed into the cooled reaction mixture (13 mL, 12.1 mmol, 2.04 eq.) by using a syringe that was pre-cooled in freezer overnight. The reaction was stirred at -40 ºC monitored by TLC analysis. After 5 hours, the reaction was not complete and kept at -18 ºC in freezer overnight. The next morning, the reaction was judged complete by TLC analysis and allowed to heat to ambient temperature. The reaction mixture was poured into HCl (aq) (0.5 M, 20 mL) and stirred with aqueous saturated rocelle salt (20 mL) for 1 h. The phases were separated, and the aqueous phase extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (aq) (1 x 30 mL), brine (1 x 30 mL), and dried ($MgSO_4$). Filtration and evaporation gave a crude oil that was purified by flash chromatography (Hexane:Et_2O 16:1) to give **22** as a colorless oil (1.76 g, 3.94 mmol, 91%).

R_f: 0.53 (Hexane:Et_2O 10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.68 (d, *J* = 2.5 Hz, 2H), 4.66 (td, *J* = 10.9, 4.3 Hz, 2H), 2.88 – 2.83 (m, 2H), 2.46 – 2.38 (m, 2H), 2.21 – 2.11 (m, 2H), 2.04 – 1.96 (m, 2H), 1.92 – 1.83 (m, 2H), 1.71 – 1.63 (m, 4H), 1.54 – 1.44 (m, 2H), 1.43 – 1.36 (m, 2H), 1.31 – 1.24 (m, 2H), 1.10 – 0.96 (m, 4H), 0.91 – 0.86 (m, 16H), 0.73 (d, *J* = 7.0 Hz, 6H)
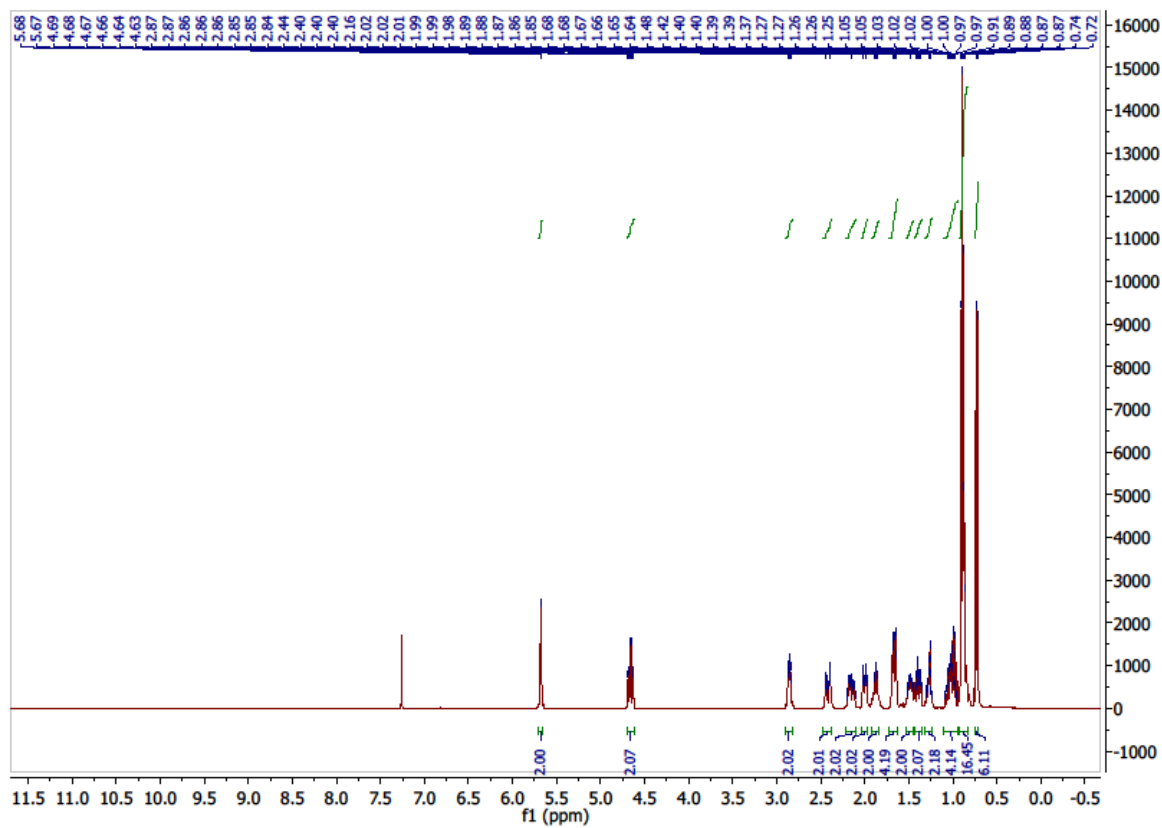
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 125.2, 74.5, 47.2, 41.4, 40.9, 34.5, 31.6, 28.0, 26.1, 23.3, 22.2, 21.0, 16.1
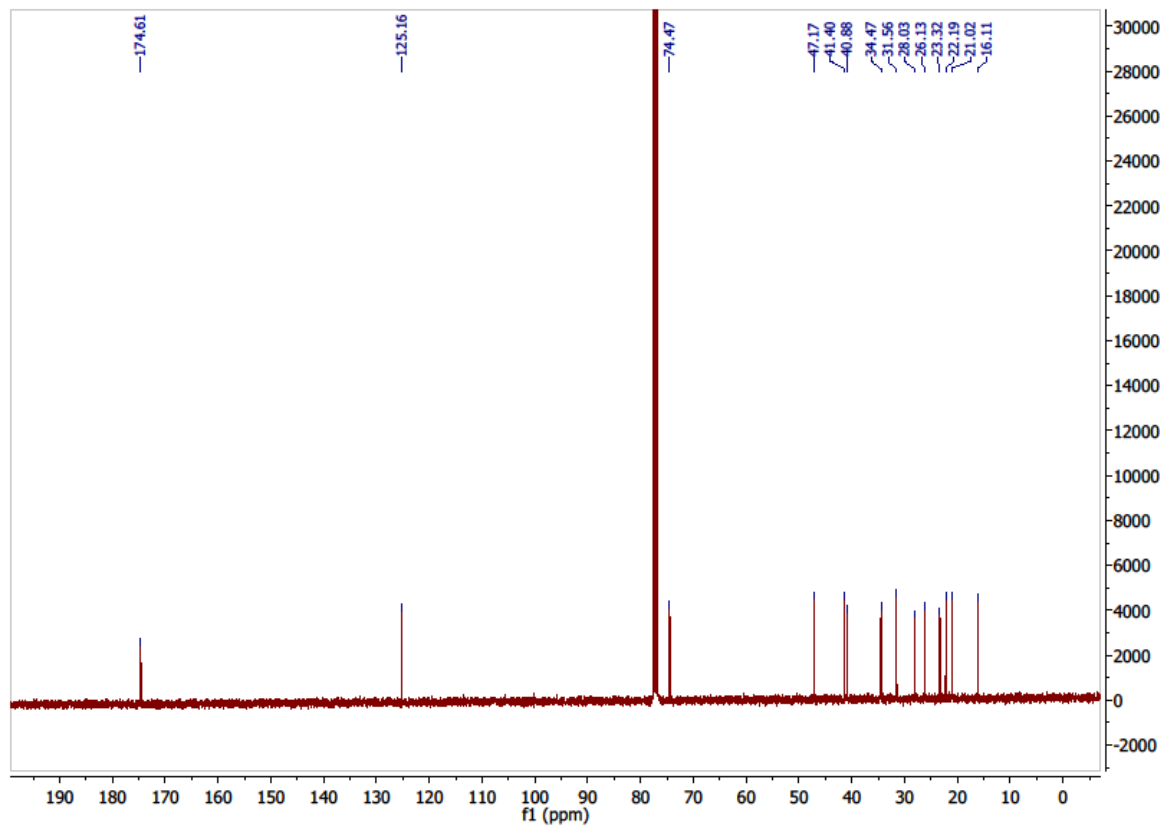
IR: 1724, 2957, 3033 cm^{-1}

MS (TOF-ES$^+$): Exact mass calculated for $C_{28}H_{46}O_4Na$ [M+Na]$^+$**:** 469.329**,** found 469.329

$[\alpha]_D^{20}$ = - 26.7 (c = 2.23, $CHCl_3$) ((lit.[65] $[\alpha]_D$ = - 29.3 (c = 2.15, $CHCl_3$))
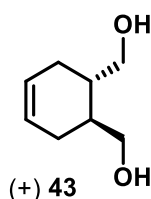
Compound **22** is known from the literature.[65]

Spectrum 5.17: *^{1}H NMR spectrum of compound **22**.*

Spectrum 5.18: *^{13}C NMR spectrum of compound **22**.*

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5.1.9 Preparation of (+)-((1*S*,2*S*)-cyclohex-4-ene-1,2-diyl)dimethanol (43)

(+) **43**

Procedure:[60]

To a stirring suspension of LiAlH$_4$ (448 mg, 11.8 mmol, 1.57 eq.) in dry THF (2.2 mL), dimenthyl **22** (3.38 g, 7.47 mmol, 1.00 eq.) dissolved in dry THF (6.0 mL) was added dropwise by syringe through a septum. After complete addition, the reaction was refluxed until judged complete by TLC analysis (ca 72 h). The reaction mixture was allowed to cool to RT before water (4.5 mL) was *carefully* added to quench the reaction, all while maintaining vigorous stirring. After 15 minutes, 15 % (w/v) NaOH (aq) (4.5 mL) was added. Following an additional 15 minutes, water (13.5 mL) was added, and a fine precipitate soon resulted. A portion of dry THF was added so the solids could be stirred, and then a small amount of MgSO$_4$ was added to ensure a dry organic solution. The reaction mixture was vacuum-filtered through a glass-sintered funnel, and the pad of salts washed with additional THF. The filtrate was concentrated in *vacuo* to give a crude oil that was purified by flash chromatography (Hexane:EtOAc 1:1) to give diol **43** as a colorless oil (902 mg, 6.34 mmol, 85%).

R$_f$: 0.10 (60% EtOAc in heptane)

^{1}H NMR ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.64 (s, 2H), 3.71 (dd, *J* = 11.1, 3.1 Hz, 2H), 3.57 (dd, *J* = 11.1, 6.4 Hz, 2H), 3.23 (s, 2H), 2.04 – 1.98 (m, 2H), 1.88 – 1.81 (m, 2H), 1.71 – 1.65 (m, 2H)
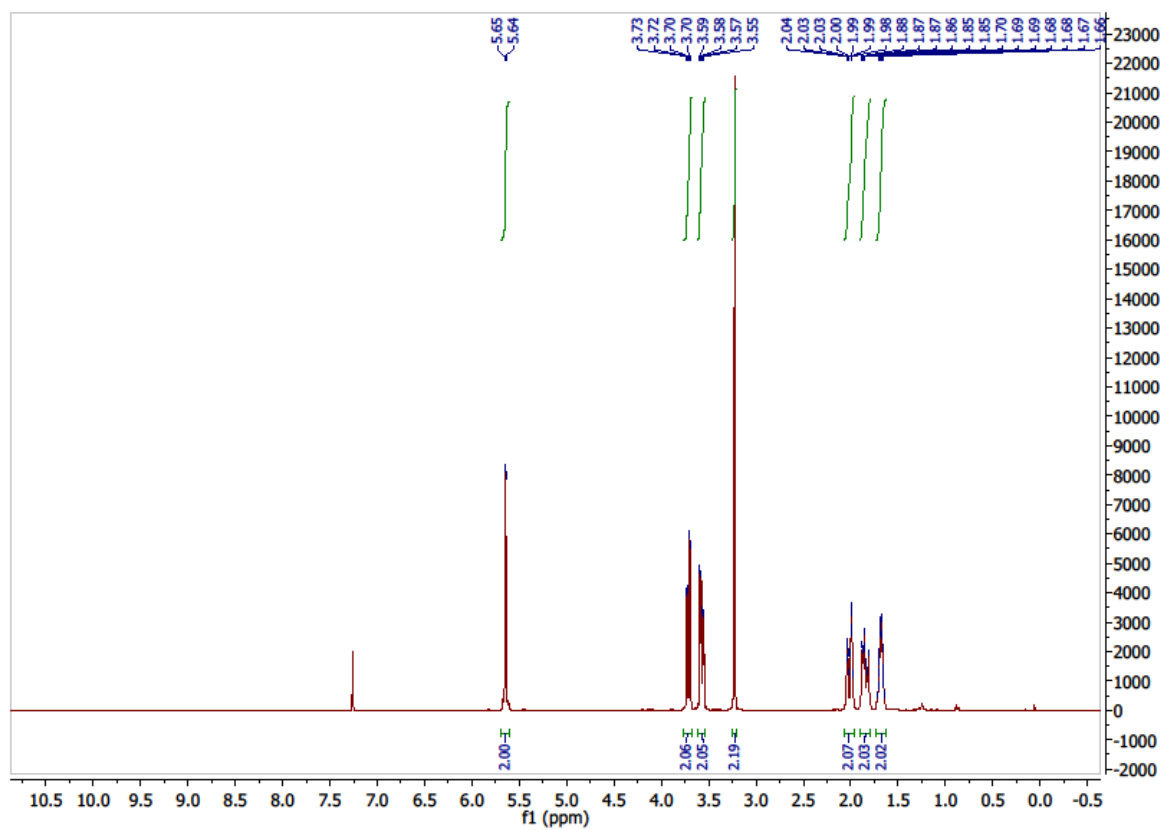
^{13}C NMR (100 MHz, CDCl$_3$) δ 126.2, 66.4, 39.9, 28.7
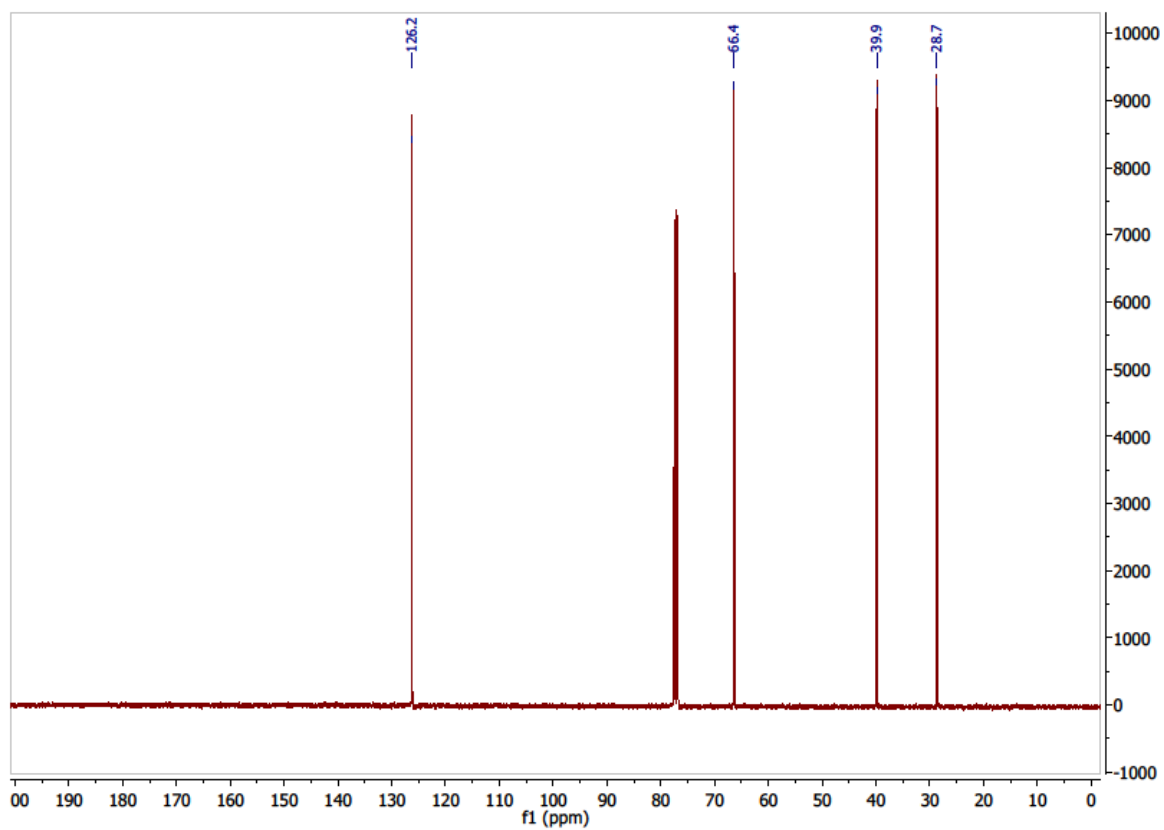
IR: 2891, 3025, 3294 cm^{-1}

MS (TOF-ES$^+$): calculated for C$_8$H$_{14}$O$_2$Na [M+Na]$^+$**:** 165.089**,** found 165.089

$[\alpha]_D^{20} = + 66.0$ (c = 1.39, CHCl$_3$) ((lit.[65] $[\alpha]_D$ = + 73.0 (c = 1.40, CHCl$_3$))

Compound **43** is known from the literature.[65]
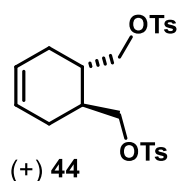
Spectrum 5.19: *^1H NMR spectrum of compound **43**.*

Spectrum 5.20: *^{13}C NMR spectrum of compound **43**.*

5.1.10 Preparation of (+)-((1*S*,2*S*)-cyclohex-4-ene-1,2-diyl)*bis*(methylene) *bis*(4-methylbenzenesulfonate) (44)

(+) **44**

Procedure:[60]

p-Toluenesulfonyl chloride (3.40 g, 17.5 mmol, 3.00 eq.) was dissolved in pyridine (5.3 mL) at 0 ℃ followed by dropwise addition of a solution of diol **43** (830 mg, 5.83 mmol, 1.00 eq.) in pyridine (2.3 mL). The flask containing the diol in pyridine were washed with a few drops of additional pyridine that were transferred to the reaction flask. The reaction mixture was stirred at 0 ℃ until judged complete by TLC analysis (ca 6 h).

The reaction mixture was poured into ice-water (20 mL) and a white precipitate was formed. The solvent was removed by vacuum filtration, and the crude product was recrystallized from methanol to yield white crystals of **44** (2.20 g, 4.88 mmol, 84%).

R$_f$: 0.52 (60% EtOAc in heptane)

^{1}H NMR ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.3 Hz, 4H), 7.35 (d, *J* = 8.3 Hz, 4H), 5.51 (s, 2H), 3.99 – 3.90 (m, 4H), 2.46 (s, 6H), 2.02 – 1.96 (m, 4H), 1.88 – 1.81 (m, 2H)
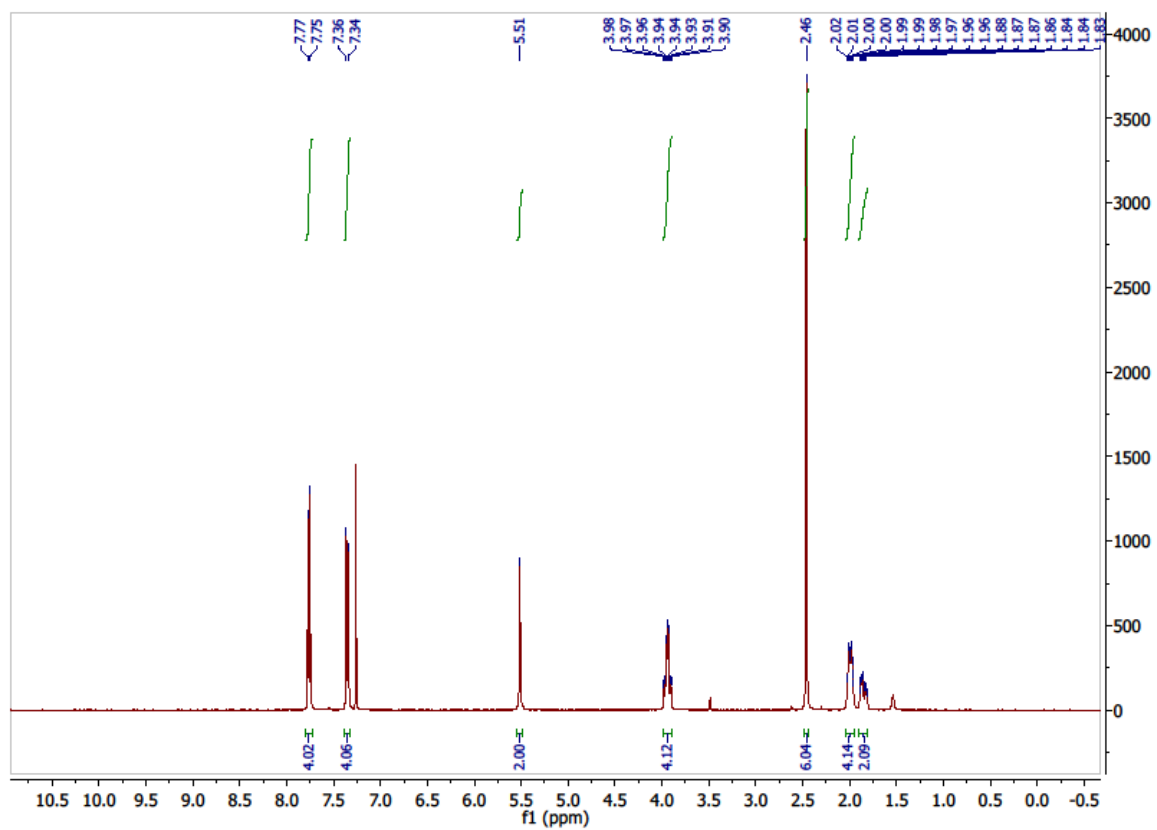
^{13}C NMR (100 MHz, CDCl$_3$) δ 145.1, 132.9, 130.1, 128.0, 124.8, 71.4, 33.2, 25.7, 21.8
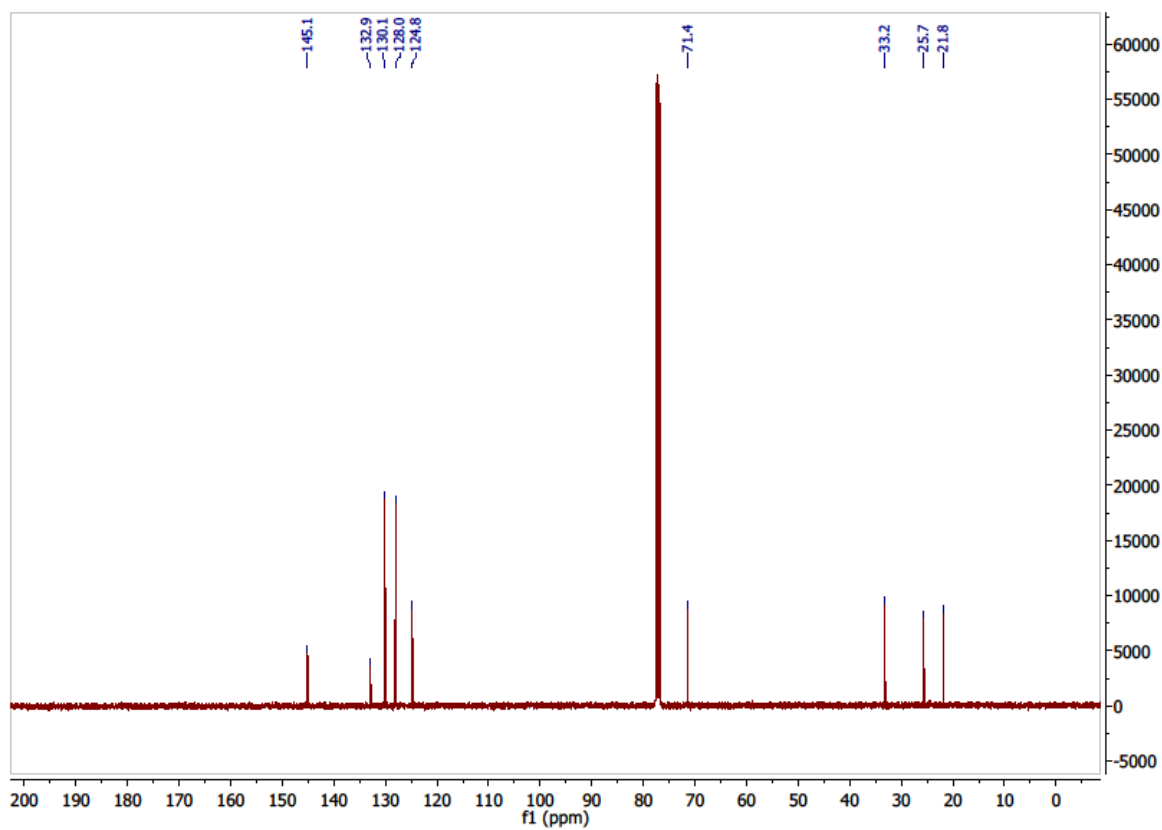
Mp: 111-113 ℃ (lit.[63] mp 110-111 ℃)

MS (TOF-ES$^+$): calculated for C$_{22}$H$_{26}$O$_6$S$_2$Na [M+Na]$^+$: 473.106, found 473.106

$[\alpha]_D^{25}$ = + 42.8 (c = 1.28, CHCl$_3$) ((lit.[63] $[\alpha]_D$ = + 43.4 (c = 1.52, CHCl$_3$))

Compound **44** is known from the literature.[63]

Spectrum 5.21: *^{1}H NMR spectrum of compound **44**.*

Spectrum 5.22: *^{13}C NMR spectrum of compound **44**.*

5.1.11   Preparation of (+)-2,2'-((1*R*,2*R*)-cyclohex-4-ene-1,2-diyl)diacetonitrile (45)

(+) **45**
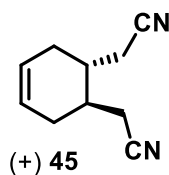
Procedure:[58] Ditosylate **44** (2.15 g, 4.78 mmol, 1.00 eq.) and NaCN (1.31 g, 20.1 mmol, 4.20 eq.) were dissolved in DMSO (7.7 mL) and heated to 100 ℃. The reaction mixture was stirred at this temperature until judged complete by TLC analysis (ca 6 h), then allowed to cool to ambient temperature. The resulting brown slurry was poured into water (70 mL), and the aqueous phase extracted with EtOAc (3 x 35 mL). The combined organic extracts were washed with water (15 x 20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo* to give a cream-colored solid of **45** (701 mg, 4.30 mmol, 92%), that was used such without further purification.

R$_f$: 0.35 (hex:Et$_2$O 2:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.66 (s, 2H), 2.52 – 2.42 (m, 4H), 2.31 – 2.23 (m, 2H), 2.13 – 2.02 (m, 4H)
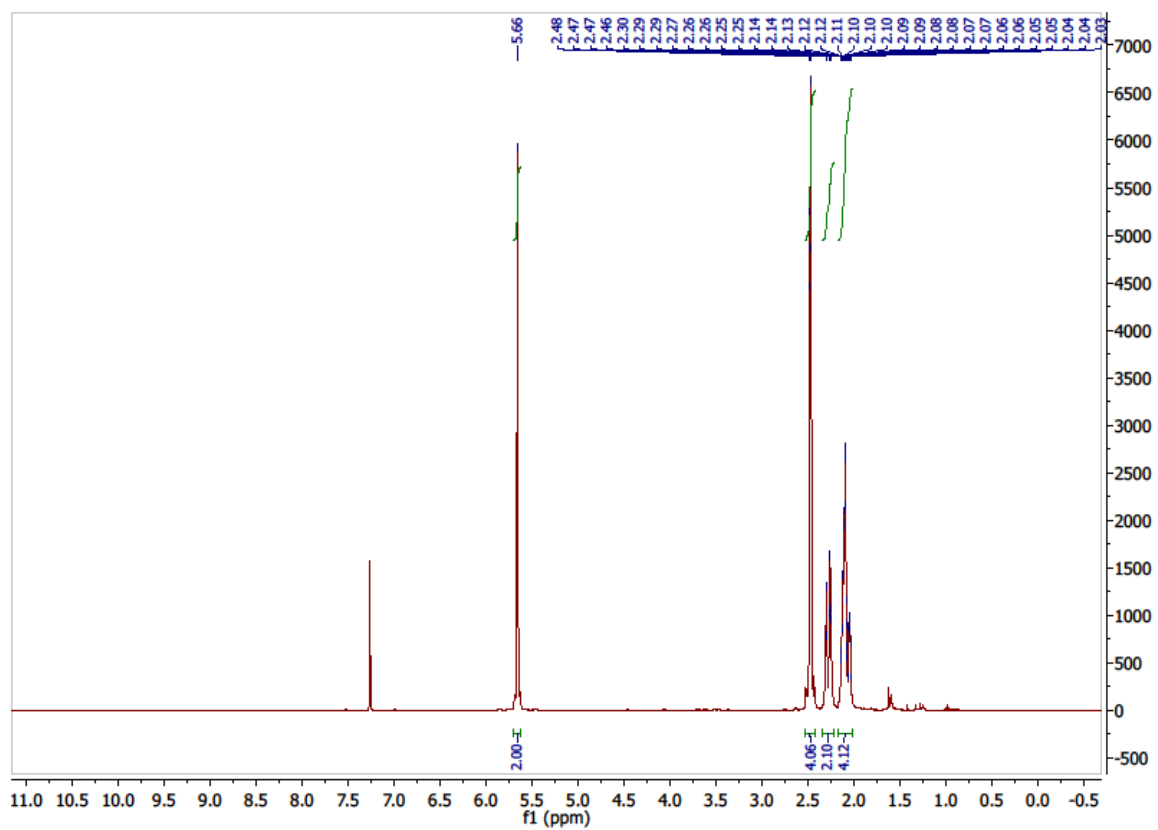
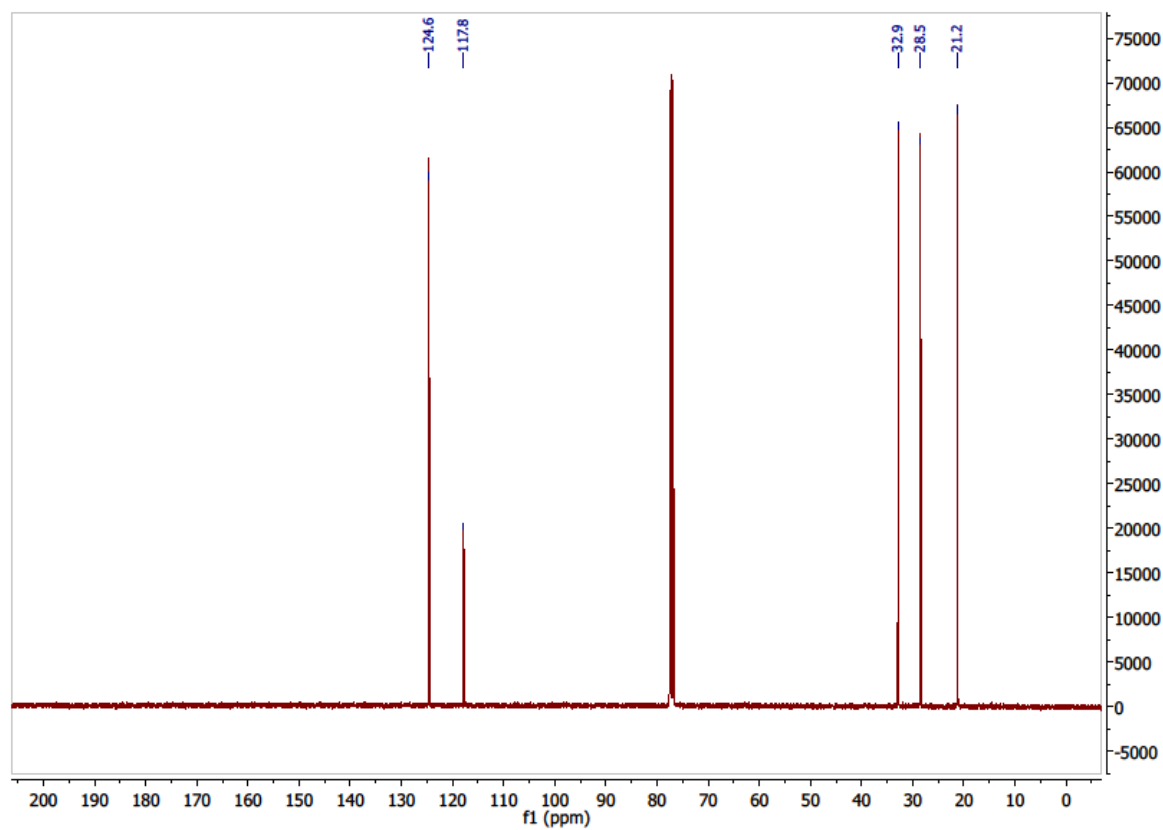**^{13}C NMR** (100 MHz, CDCl$_3$) δ 124.6, 117.8, 32.9, 28.5, 21.3

IR: 2247, 2919, 3056 cm^{-1}

MS (TOF-ES$^+$): calculated for $C_{10}H_{12}N_2Na$ [M+Na]$^+$: 183.090**,** found 183.089

$[\alpha]_D^{25} = + 107.8$ (c = 1.45, CHCl$_3$) ((lit.[63] $[\alpha]_D = + 111.0$ (c = 1.40, CHCl$_3$))

Compound **45** is known from the literature.[63]

Spectrum 5.23: *^{1}H NMR spectrum of compound **45**.*

Spectrum 5.24: *^{13}C NMR spectrum of compound **45**.*

70

5.1.12　Preparation of (+)-diethyl 2,2'-((1R,2R)-cyclohex-4-ene-1,2-diyl)diacetate (47)
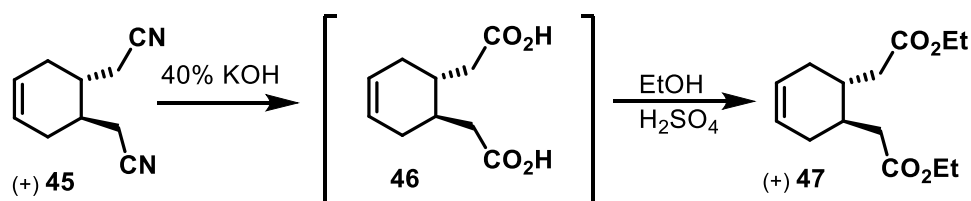
Scheme 5.3: *Hydrolysis and esterification*

Procedure:[63]

A solution of dinitrile **45** (2.15 g, 13.4 mmol, 1.00 eq.) and aqueous KOH (40%, 14.5 mL) were heated to reflux and monitored by TLC analysis. The reaction was judged complete when the starting material was no longer observable on the silica plate (ca 32 h). The resulting solution was cooled to 0 ℃ in an ice-bath, and aqueous H_3PO_4 (85%, 14.2 mL) was added dropwise with stirring. The resulting solid was isolated by vacuum filtration, washed with warm water, and dried under vacuum to give diacid **46** as a pale yellow powder (2.39 g, 12.1 mmol, 90%).

The crude diacid was taken up as a suspension in absolute EtOH (98 mL), and stirred with dropwise addition of H_2SO_4 (98%, 1.2 mL). After 48 h, the reaction was judged complete by TLC, and the reaction mixture was allowed to cool to ambient temperature before the EtOH was removed under vacuum to approximately ¼ of the volume. The mixture was added to water (200 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with water (1 x 50 mL), and saturated $NaHCO_3$ (aq) (1 x 50 mL), and the organic layer was dried ($MgSO_4$), filtered by vacuum, and concentrated in *vacuo* to give a yellow oil. This crude oil was purified by flash chromatography (hexane:Et_2O 2:1) to afford diester **47** as a colorless oil (2.79 g, 11.0 mmol, 91%). Overall yield of the reactions were 82%.

R$_f$: 0.34 (Hexane:EtOAc 4:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.59 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 4H), 2.41 (dd, *J* = 14.8, 4.7 Hz, 2H), 2.29 – 2.20 (m, 3H), 2.18 – 2.15 (m, 1H), 2.09 – 2.02 (m, 2H), 1.88 – 1.84 (m, 1H), 1.83 – 1.80 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 6H).
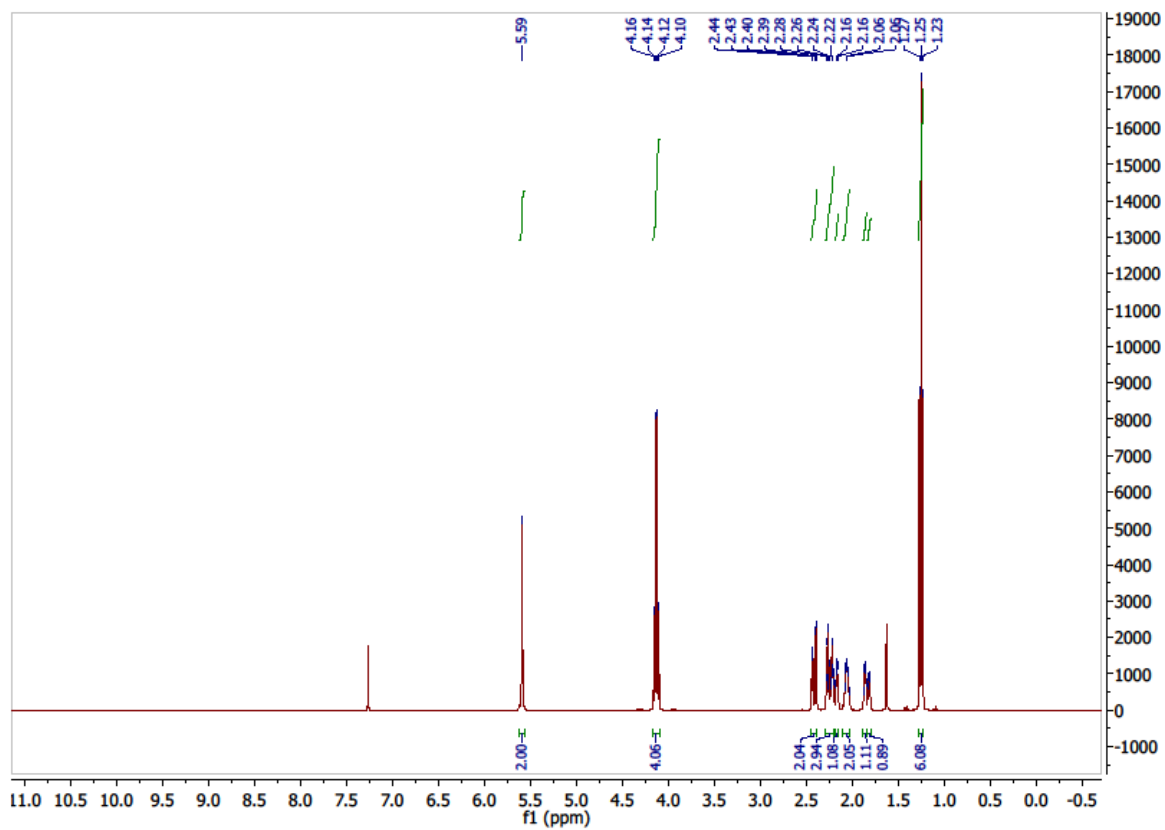
¹³C NMR (100 MHz, CDCl₃) δ 173.1, 125.1, 60.5, 38.7, 33.7, 28.6, 14.4
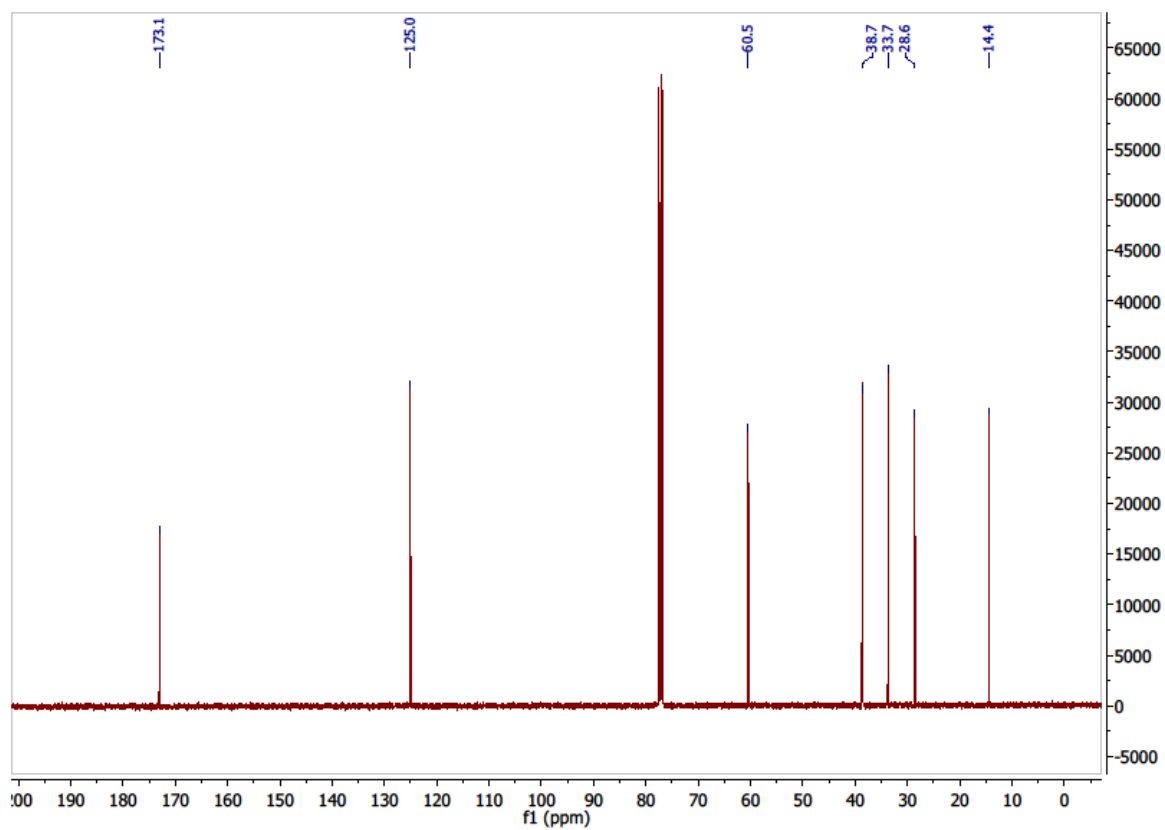
IR: 1731, 2982, 3027 cm^{-1}

MS (TOF-ES⁺): calculated for $C_{14}H_{22}O_4Na$ [M+Na]⁺**:** 277.141**,** found 277.141

$[\alpha]_D^{20}$ = + 50.3 (c = 1.84, CHCl₃) ((lit.[63] $[\alpha]_D$ = + 49.3 (c = 1.52, CHCl₃))

Compound **46** and **47** are known from the literature.[63]

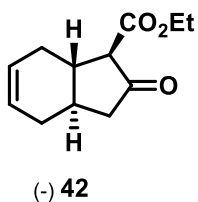**Spectrum 5.25:** *^{1}H NMR spectrum of compound **47**.*

Spectrum 5.26: *^{13}C NMR spectrum of compound **47**.*

5.1.13 Preparation of (-)-ethyl (1*R*,3a*R*,7a*S*)-2-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (42)

(-) **42**

Procedure:[63]

NaH (60% dispersion in mineral oil, 518 mg, 13.0 mmol 1.20 eq.) was washed with dry hexane (2 x 5 mL), and then dry THF was added (7.0 mL). The mixture was heated to reflux followed by dropwise addition of a solution of diester **47** (2.79 g, 11.0 mmol 1.00 eq.) in dry THF (4.5 mL) through septum. The mixture was subsequently refluxed until judged complete TLC analysis (1.5 h), and then allowed to cool to ambient temperature before glacial AcOH (0.70 mL, 12.1 mmol, 1.10 eq.) was added. The resulting gelatinous mixture was added to water (100 mL) and Et_2O (50 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with water (3 x 50 mL), saturated $NaHCO_3$ (aq) (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered by vacuum, and concentrated in *vacuo* to give a crude oil that was purified by flash chromatography (hexane:EtOAc 4:1) to give **42** as a colorless oil (1.99 g, 9.60 mmol, 87%).

R$_f$: 0.30 (hexane:EtOAc 4:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.75 – 5.73 (m, 2H), 4.25 – 4.17 (m, 2H), 2.88 (d, *J* = 12.1 Hz, 1H), 2.59 (dd, *J* = 17.8, 6.5 Hz, 1H), 2.45 – 2.37 (m, 2H), 2.35 – 2.27 (m, 1H), 2.05 – 1.86 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H)
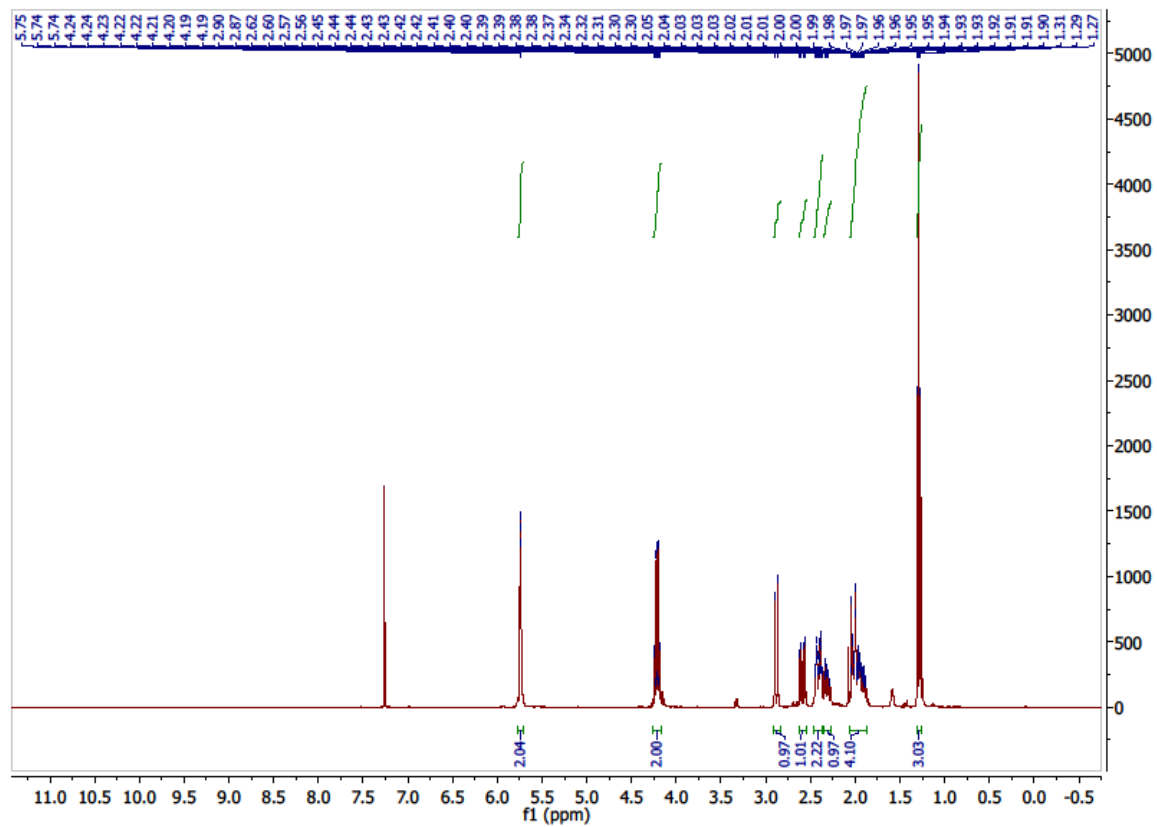
^{13}C NMR (100 MHz, CDCl$_3$) δ 210.0, 169.1, 126.8, 126.4, 62.1, 61.5, 45.1, 42.8, 36.4, 31.4, 30.6, 14.4
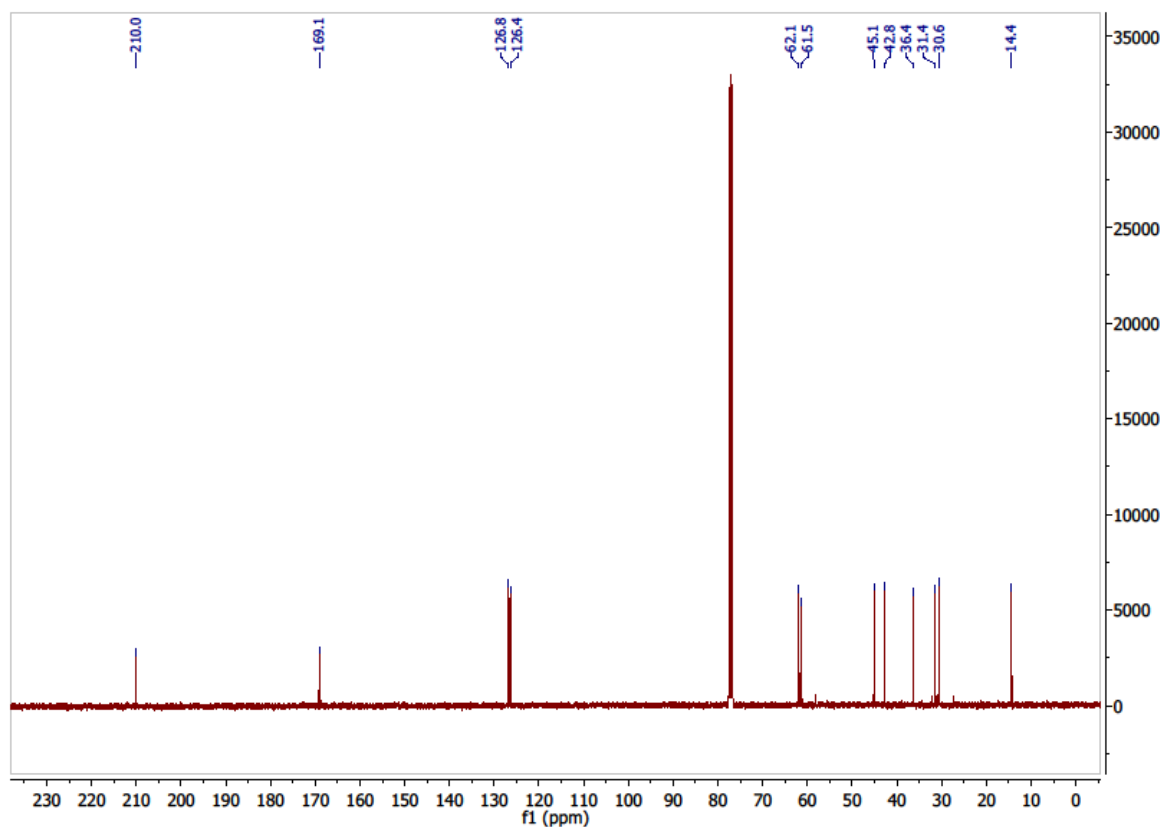
IR: 1723, 1756, 2902, 3028 cm^{-1}

MS (TOF-ES$^+$): calculated for $C_{12}H_{16}O_3Na$ [M+Na]$^+$: 231.099 **,** found 231.099

$[\alpha]_D^{20}$ = - 25.0 (c = 2.06, CHCl$_3$) ((lit.[63] $[\alpha]_D$ = - 24.1 (c = 1.62, CHCl$_3$))

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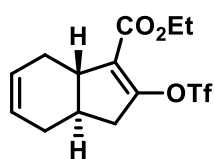Compound **42** is known from the literature.[63]

Spectrum 5.27: *¹H NMR spectrum of compound **42**.*

Spectrum 5.28: ^{13}C NMR spectrum of compound 42.

5.1.14 Preparation of (+)-ethyl (3a*S*,7a*R*)-2-(((trifluoromethyl)sulfonyl)oxy)-3a,4,7,7a-tetrahydro-1*H*-indene-3-carboxylate (39)

(+) **39**

Procedure:[3]

NaH (60% dispersion in mineral oil, 323 mg, 13.5 mmol 1.90 eq.) was added to dry toluene (35 mL) and stirred for 10 min, followed by dropwise addition of β-keto ester **42** (1.50 g, 7.20 mmol, 1.00 eq.) over 10 min. Bubbles were observed. After complete addition, the reaction mixture was heated to 85 ℃ for 1.5 h. Next, the reaction mixture was cooled to 0 ℃, and triflic anhydride (1.8 mL, 10.7 mmol, 1.50 eq.) was added by dropwise addition and stirred at 0 ℃ until judged complete by TLC analysis (ca 1h). The reaction was quenched by careful

addition of water (35 mL), and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with water (1 x 150 mL), brine (1 x 150 mL), and dried over MgSO4, filtered, and concentrated in *vacuo* to give a brown oil. The crude oil was purified by flash chromatography to afford triflate **39** as a colorless oil (2.33 g, 11.2 mmol, 95%).

R$_f$: 0.46 (Hexane:Et$_2$O 4:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.75 – 5.69 (m, 2H), 4.31 – 4.21 (m, 2H), 2.74 – 2.61 (m, 3H), 2.54 – 2.45 (m, 1H), 2.27 – 2.20 (m, 1H), 2.11 – 1.97 (m, 3H), 1.32 (t, *J* = 7.2 Hz, 3H)
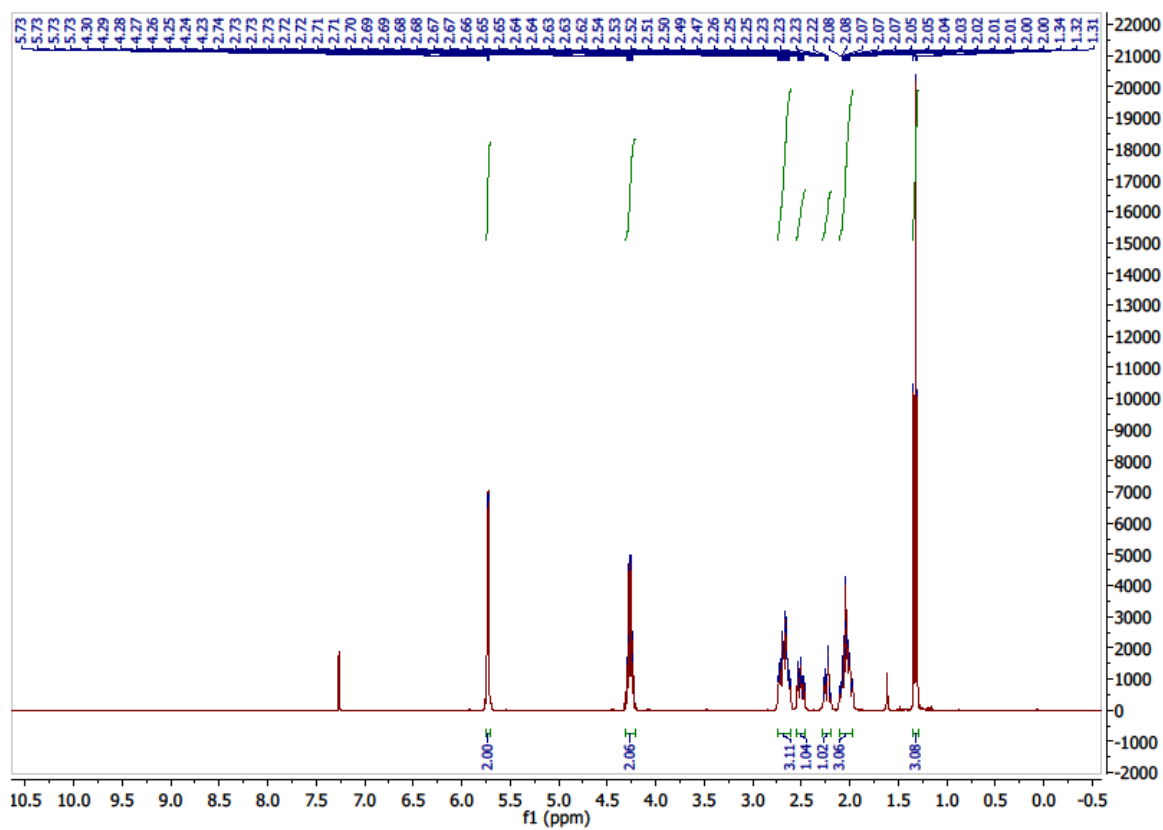
^{13}C NMR (100 MHz, CDCl$_3$) δ 162.4, 155.1, 126.9, 126.9, 126.3, 118.5 (q, $1J_{CF}$ = 320.1 Hz), 61.2, 44.47, 40.9, 37.6, 29.9, 29.9, 14.1
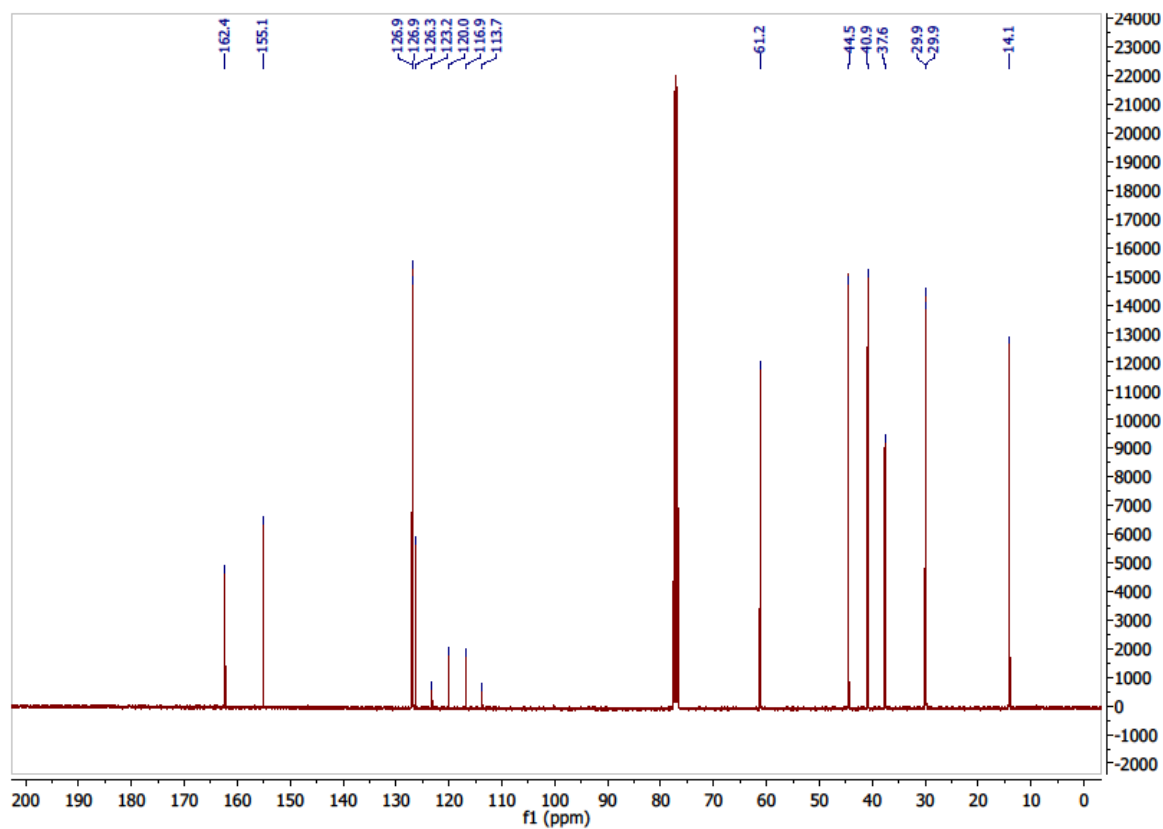
IR: 1715, 2986, 3054 cm^{-1}

HRMS (TOF-ES$^+$): Exact mass calculated for C$_{13}$H$_{15}$F$_3$O$_5$SNa [M+Na]$^+$**:** 363.0489**,** found 363.0485

$[\alpha]_D^{20}$ = + 143.2 (c = 1.71, MeOH)

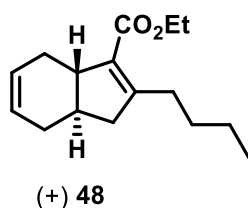Compound **39** is not known from the literature.

Spectrum 5.29: *¹H NMR spectrum of compound 39.*

Spectrum 5.30: *¹³C NMR spectrum of compound 39.*

5.1.15 Preparation of ethyl (+)-(3aS,7aR)-2-butyl-3a,4,7,7a-tetrahydro-1H-indene-3-carboxylate (48)

(+) **48**

Procedure:[3]

Solid Cu(I)CN (2.14 g, 23.9 mmol, 2.60 eq.) was added dry Et_2O (7.2 mL) under inert atmosphere. The suspension was stirred for 5 min, and then cooled to -50 ℃, followed by dropwise addition of ^nBuLi (2.5 M in hexane, 9.2 mL, 2.50 eq.) over 10 min. The mixture was stirred for 1 h before vinylic-triflate **39** (1.9 g, 9.21 mmol, 1.00 eq.) in dry Et_2O (7.2 mL) was added via cannula, and the reaction mixture was subsequently stirred at -50 ℃ monitored by TLC analysis. When the reaction was judged complete (ca 1 h), sat. NH_4Cl (aq) was added (7.2 mL) and the solution was left to warm to ambient temperature. The dark colored slurry was then filtered through celite, and the celite filter was washed with EtOAc (3 x 20 mL). Water (20 mL) was added to the filtrate, and the phases separated. The aqueous phase was extracted with EtOAc (2 x 20 mL), and the combined organic extracts were washed with water (1 x 100 mL), brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. This gave a crude oil, which was purified by flash chromatography (hexane:EtOAc 98:2) to afford the unsaturated ethyl ester **48** as a colorless oil (1.36 g, 5.48 mmol, 59%).

R_f: 0.72 (Hexane:EtOAc 9:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.71 (s, 2H), 4.28 – 4.19 (m, 1H), 4.18 – 4.10 (m, 1H), 2.73 – 2.63 (m, 1H), 2.60 – 2.54 (m, 2H), 2.51 – 2.43 (m, 2H), 2.28 – 2.15 (m, 1H), 2.11 – 1.97 (m, 2H), 1.96 – 1.85 (m, 1H), 1.75 – 1.64 (m, 1H), 1.50 – 1.38 (m, 2H), 1.35 – 1.27 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H)

^{13}C NMR (100 MHz, CDCl$_3$) δ 166.6, 160.9, 130.9, 127.8, 127.5, 59.7, 47.6, 42.5, 42.0, 31.2, 30.9, 30.4, 30.3, 22.9, 14.5, 14.1.
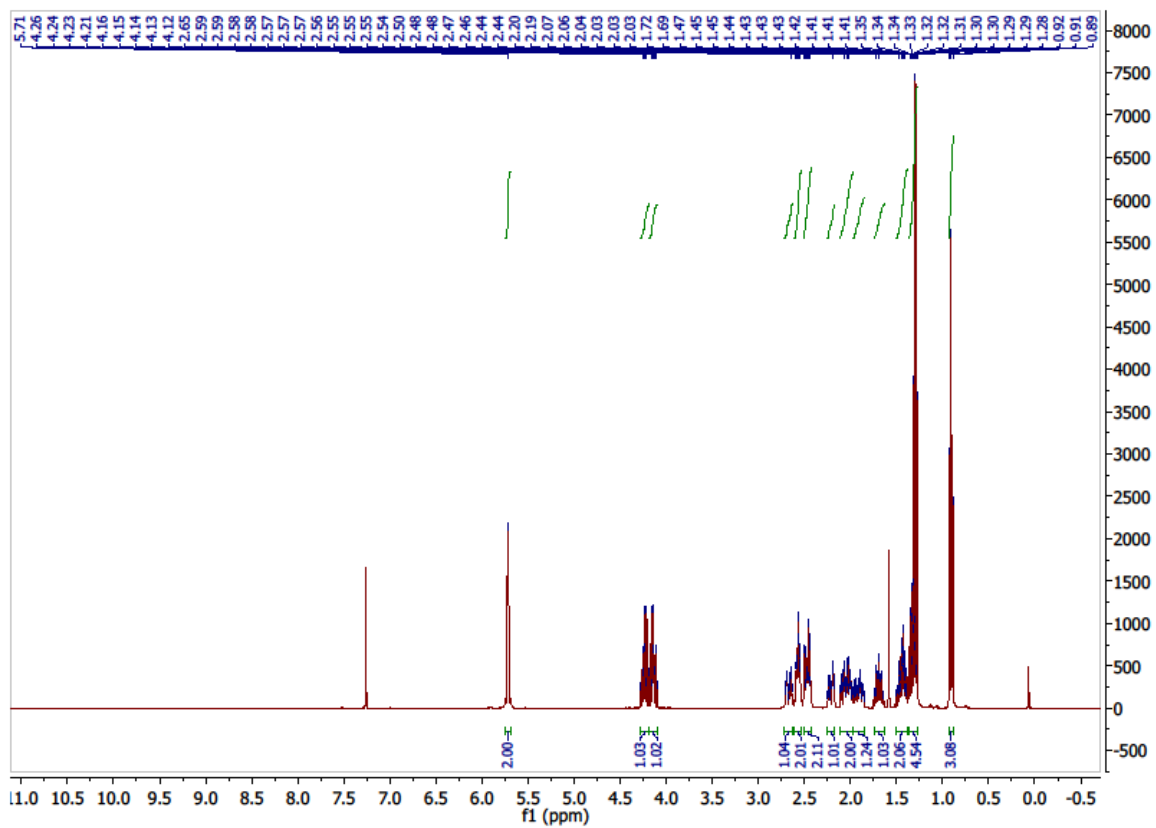
IR: 1697, 2986, 3054 cm^{-1}

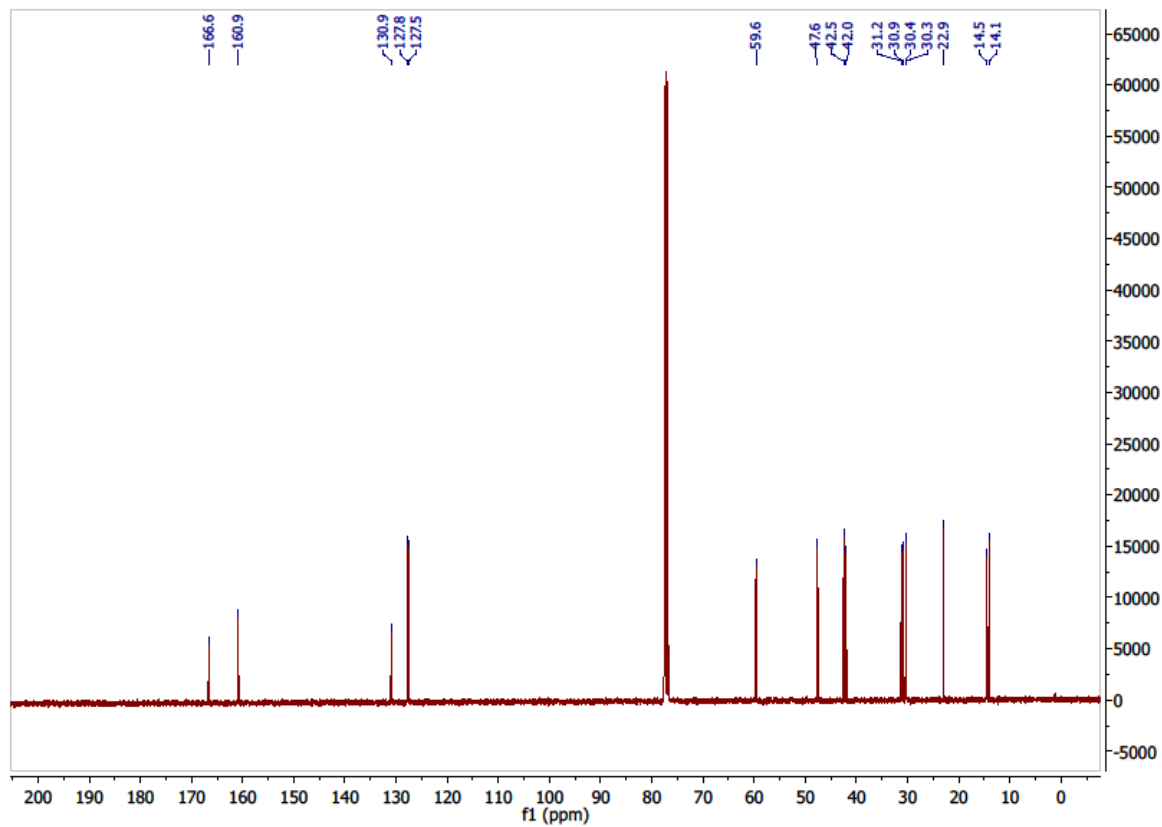**HRMS (TOF-ES⁺):** Exact mass calculated for $C_{16}H_{24}O_2Na$ [M+Na]⁺: 271.1674**,** found 271.1669

$[\alpha]_D^{20} = + 57.5$ (c = 0.61, MeOH)

UV (MeOH) $\lambda_{max} = 195, 232$ nm

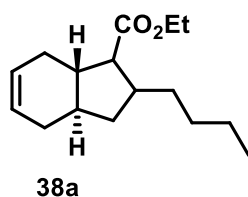Compound **48** is not known from the literature.

$[\alpha]_D^{20} = + 57.5$ (c = 0.61, MeOH)

Spectrum 5.31: *^{1}H NMR spectrum of compound* **48**.

Spectrum 5.32: *^{13}C NMR spectrum of compound* **48**.

5.1.16   Preparation of ethyl (3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene-1-carboxylate (38a)

38a

Procedure:[3]

Unsaturated ester **48** (610 mg, 2.50 mmol, 1.00 eq.) was dissolved in methanol (2.3 mL) and stirred at room temperature for 5 min during which time magnesium turnings (1.28 g, 52.8 mmol, 45.6 eq.) was heated by Bunsen burner and cooled under inert atm. in two separate portions. One portion was then added to the stirring solution, and the mixture was heated to 40 ℃. A violent reaction occurred with lots of bubbling. A grey-colored solid was formed during the reaction, and additional methanol was added as the reaction mixture was stirred at all time. When all the magnesium turnings were consumed, a second portion of turnings was added, and the reaction was followed by UV-analysis. When the absorbance at 232 nm was absent in the spectrum, the reaction was judge complete (ca 3 h). The reaction mixture was allowed to cool to ambient temperature before glacial acetic acid (4 mL) was added dropwise until all solids were dissolved. This solution was concentrated in *vacuo* to give a white slurry that was added to EtOAc (50 mL) and water (50 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (aq) (3 x 50 mL), brine (1 x 50 mL), and dried over $MgSO_4$. Filtration and concentration in *vacuo* gave a crude oil. This crude oil was analyzed by ^{13}C-NMR, and it appeared that mixture of diastereomers was formed in approximately a 2:1 ratio.

Without further purification, the crude diastereomeric mixture was dissolved in in dry ethanol (2.3 mL), and then added dropwise to a solution of sodium metal (350 mg, 14.7 mmol, 6.00 eq.) dissolved in dry ethanol (4.5 mL). The reaction mixture was heated to 70 ℃ for 4 h, then cooled to room temperature and concentrated in *vacuo*, but not to dryness. The mixture was then added to Et_2O (30 mL), and water (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with water (1 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated

in *vacuo* to afford a crude yellow oil (342 mg, mmol, 56%) . The crude oil was analyzed by ^{13}C-NMR.

The equilibration was repeated for a longer period of time and analyzed by ^{13}C-NMR, but then a complex mixture was formed.

The non-equilibrated and equilibrated diastereomic mixture was analyzed by GC. The ratio between the diastereomers was determined to be 2:1 in both experiments, where the minor diastereomer switched to become the major isomer after equilibration. The isomers was not separable according to TLC analysis by employing various eluent systems.

R$_f$: 0.53 (hexane:EtOAc 9:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.71 – 5.57 (m, 2H), 4.20 – 4.05 (m, 2H), 2.61 – 2.46 (m, 1H), 2.41 – 2.22 (m, 2H), 2.17 – 2.08 (m, 1H), 1.95 – 1.71 (m, 4H), 1.54 – 1.34 (m, 2H), 1.31 – 1.11 (m, 8H), 1.00 – 0.79 (m, 4H)
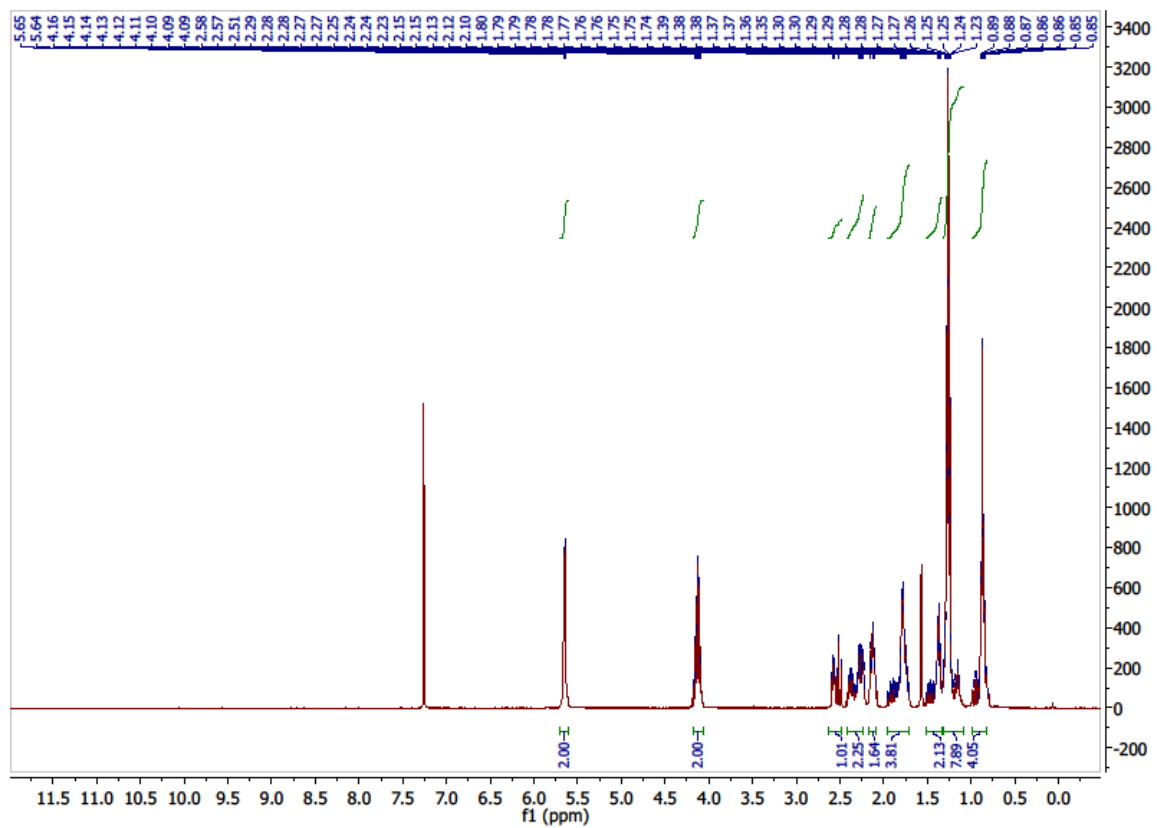
^{13}C NMR (100 MHz, CDCl$_3$) δ 176.1, 127.1, 126.8, 60.1, 52.7, 44.3, 42.3, 40.2, 40.1, 36.6, 32.3, 30.6, 28.5, 22.9, 14.6, 14.2
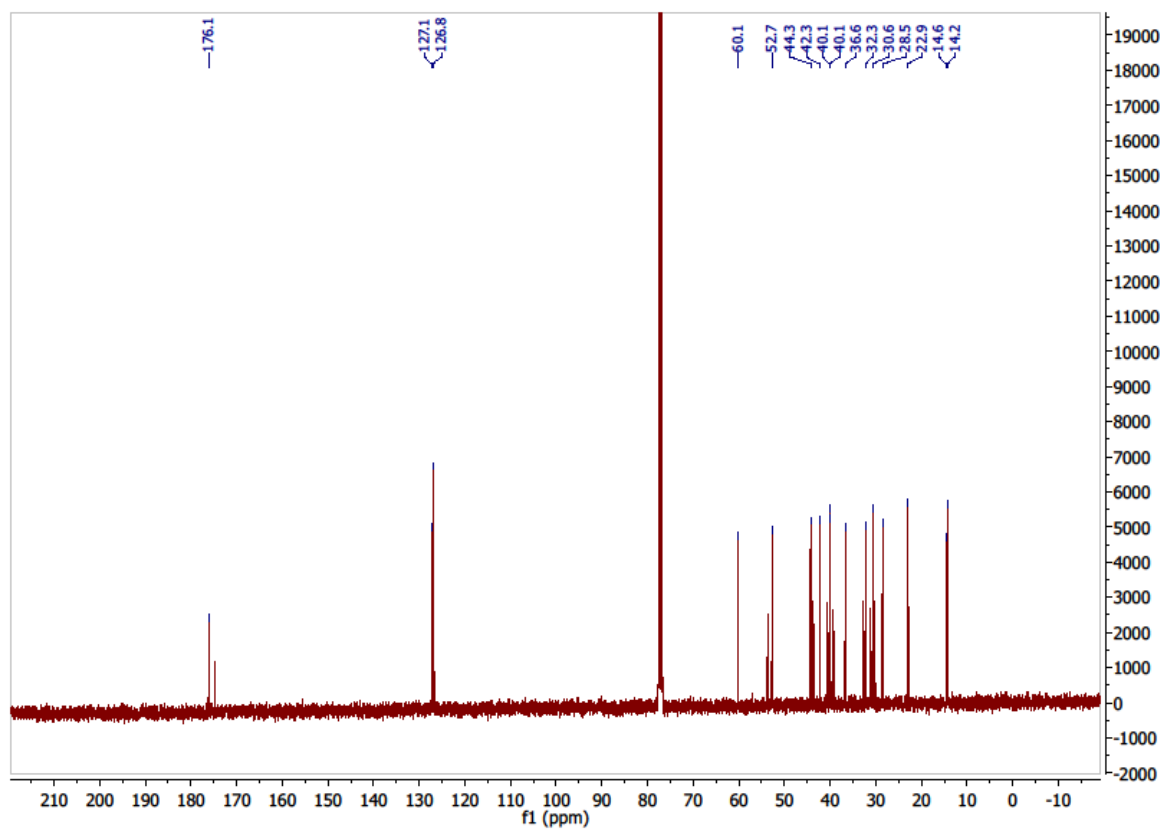
IR: 1720, 2986, 3054 cm^{-1}

HRMS (TOF-ES$^+$): Exact mass calculated for C$_{16}$H$_{26}$O$_2$Na [M+Na]$^+$: 273.1831, found 273.1825

UV (MeOH) λ$_{max}$ = 201 nm

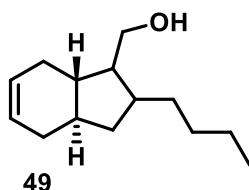Compound **38a** is not known from the literature.

Spectrum 5.33: *¹H NMR spectrum of compound **38a**.*

Spectrum 5.34: *¹³C NMR spectrum of compound **38a**.*

5.1.17 Preparation of ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methanol (49)

Procedure:[3]

Ethyl ester **38a** (310 mg, 1.24 mmol, 1.00 eq.) was dissolved in hexane (4.6 mL) and stirred for 5 min. at room temperature. Next, the solution was cooled to 0 ℃ before DIBAL-H (1.00 M in heptane, 3.6 mL, 3.00 eq.) was added dropwise over 5 min. After complete addition, the reaction mixture was slowly cooled to ambient temperature while monitored by TLC analysis. The reaction was judged complete after 1.5 h, and then cooled to 0 ℃. The suspension was added to saturated NH_4Cl (aq) (3.5 mL) to quench the reaction, and then aqueous saturated Rocelle salt was added followed by vigorous stirring for 1 h. The organic layer was separated, and the aqueous layer extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL) brine (1 x 10 mL) and dried ($MgSO_4$). Filtration and concentration in *vacuo* afforded a crude product that was purified by flash chromatography (hexane:Et_2O 7:3) to give a colorless oil (240 mg, 1.16 mmol, 91%). A mixture of diastereomers was confirmed by NMR- analysis. These were successfully separated by several rounds of column chromatography (hexane:Et_2O 8:2). The two diastereomers were termed **D1** (eluting first from column) and **D2** (eluting second from column), and were isolated as a colorless oil and as a white solid respectively.

Rf$_{D1}$: 0.31 (hexane: Et_2O 6:4)

Rf$_{D2}$: 0.29 (hexane: Et_2O 6:4)

^{1}H NMR$_{D1}$ (400 MHz, Chloroform-*d*) δ 5.75 – 5.60 (m, 2H), 3.64 (dd, *J* = 10.7, 7.4 Hz, 1H), 3.47 (dd, *J* = 10.7, 5.9 Hz, 1H), 2.32 – 2.13 (m, 2H), 2.13 – 2.00 (m, 2H), 1.87 – 1.72 (m, 2H), 1.70 – 1.43 (m, 4H), 1.40 – 1.24 (m, 6H), 0.95 – 0.85 (m, 3H), 0.83 – 0.73 (m, 1H)

^{13}C NMR$_{D1}$ (100 MHz, CDCl$_3$) δ 127.5, 127.0, 64.9, 48.9, 42.8, 41.8, 40.0, 39.9, 37.4, 32.7, 30.8, 27.7, 23.1, 14.3

¹H NMR_{D2} (400 MHz, Chloroform-*d*) δ 5.67 (s, 2H), 3.79 – 3.73 (m, 1H), 3.71 – 3.65 (m, 1H), 2.32 – 2.20 (m, 2H), 2.16 – 2.06 (m, 2H), 1.89 – 1.71 (m, 3H), 1.65 – 1.56 (m, 1H), 1.53 – 1.41 (m, 1H), 1.39 – 1.22 (m, 5H), 1.20 – 1.06 (m, 2H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.82 (dd, *J* = 11.3, 3.9 Hz, 1H)

¹³C NMR_{D2} (100 MHz, CDCl₃) δ 127.5, 127.1, 63.6, 50.1, 44.0, 41.2, 39.3, 38.8, 32.4, 32.1, 31.7, 30.9, 23.1, 14.4
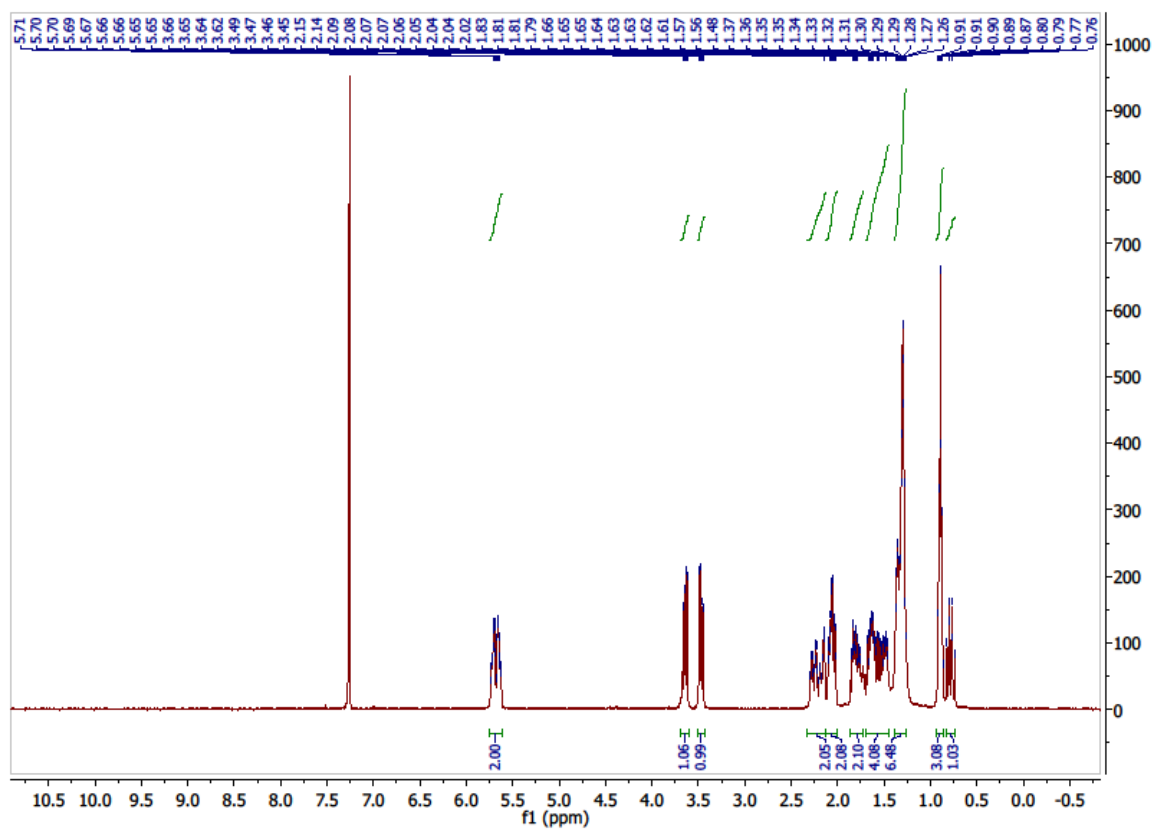
IR: 2927, 3054, 3619 cm⁻¹
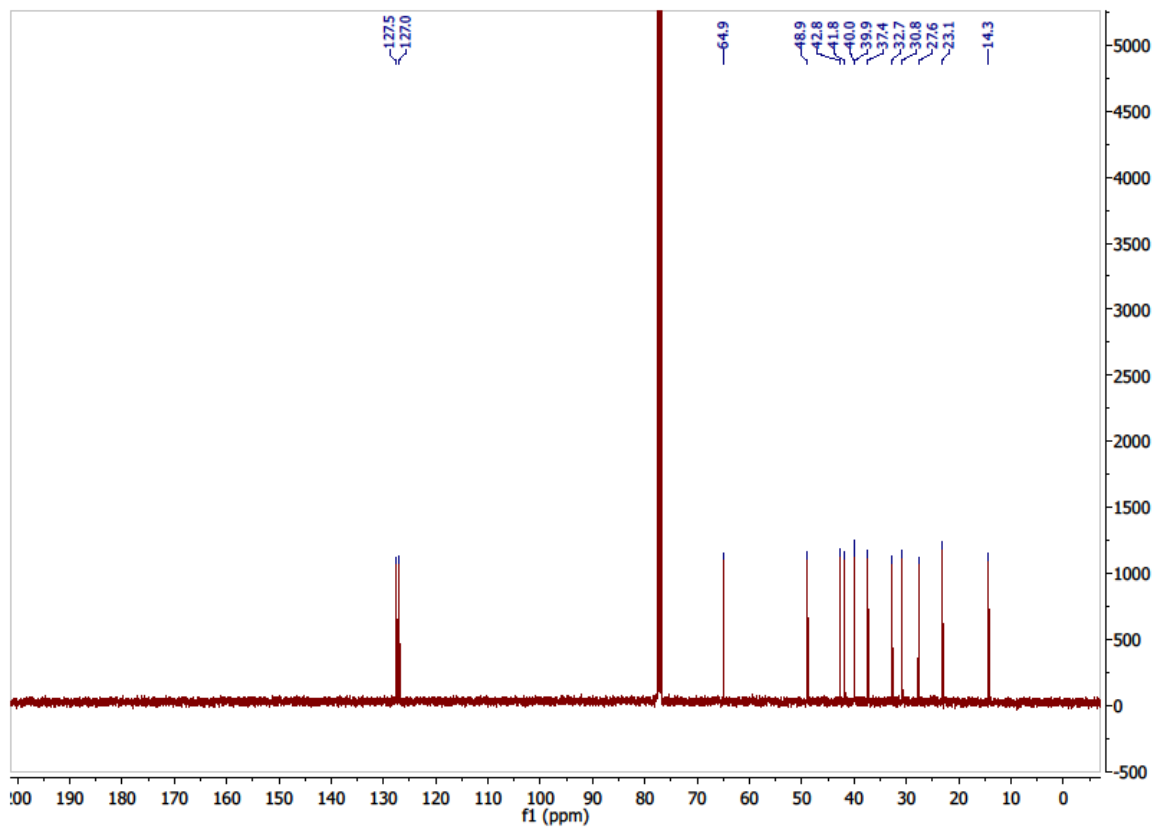
D1 $[\alpha]_D^{20}$ = + 88.9 (c = 0.53, CHCl₃)   **D2** $[\alpha]_D^{20}$ = + 180.9 (c = 0.86, CHCl₃)

HRMS (TOF-ES⁺): Exact mass calculated for $C_{14}H_{24}ONa$ [M+Na]⁺: 231.1725, found 231.1720
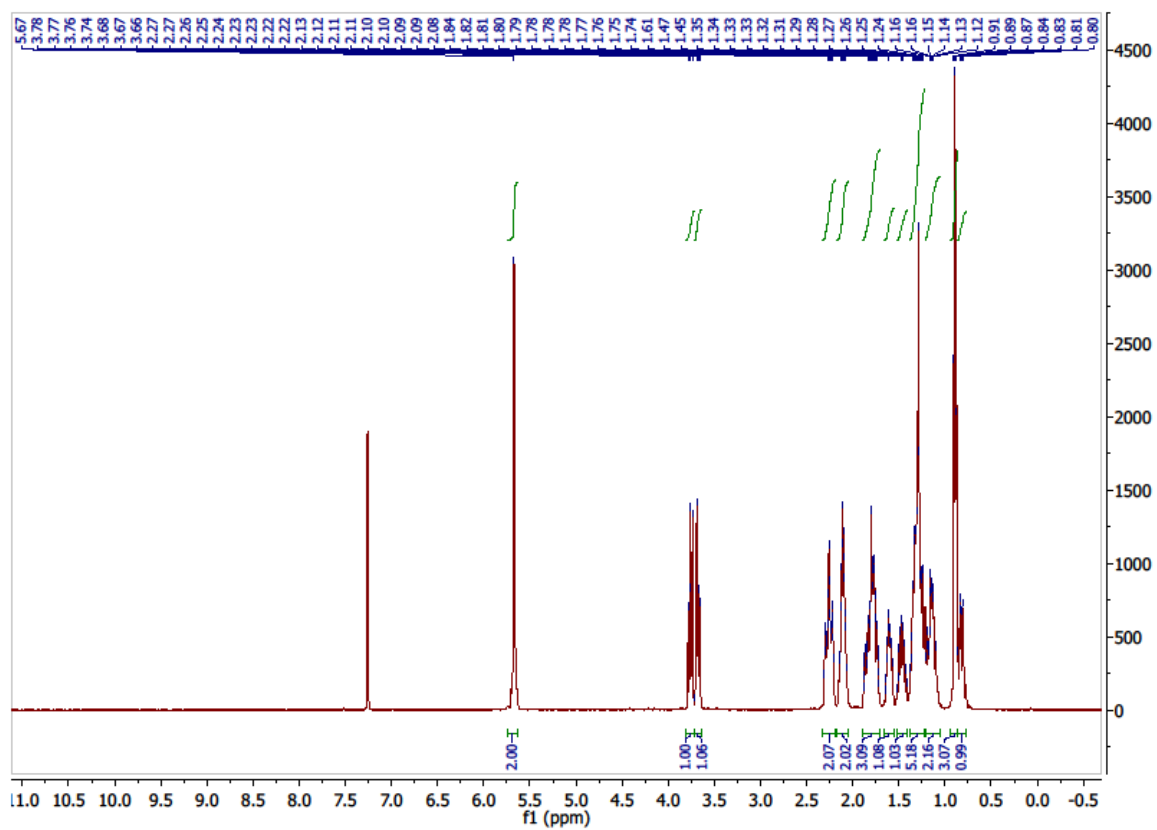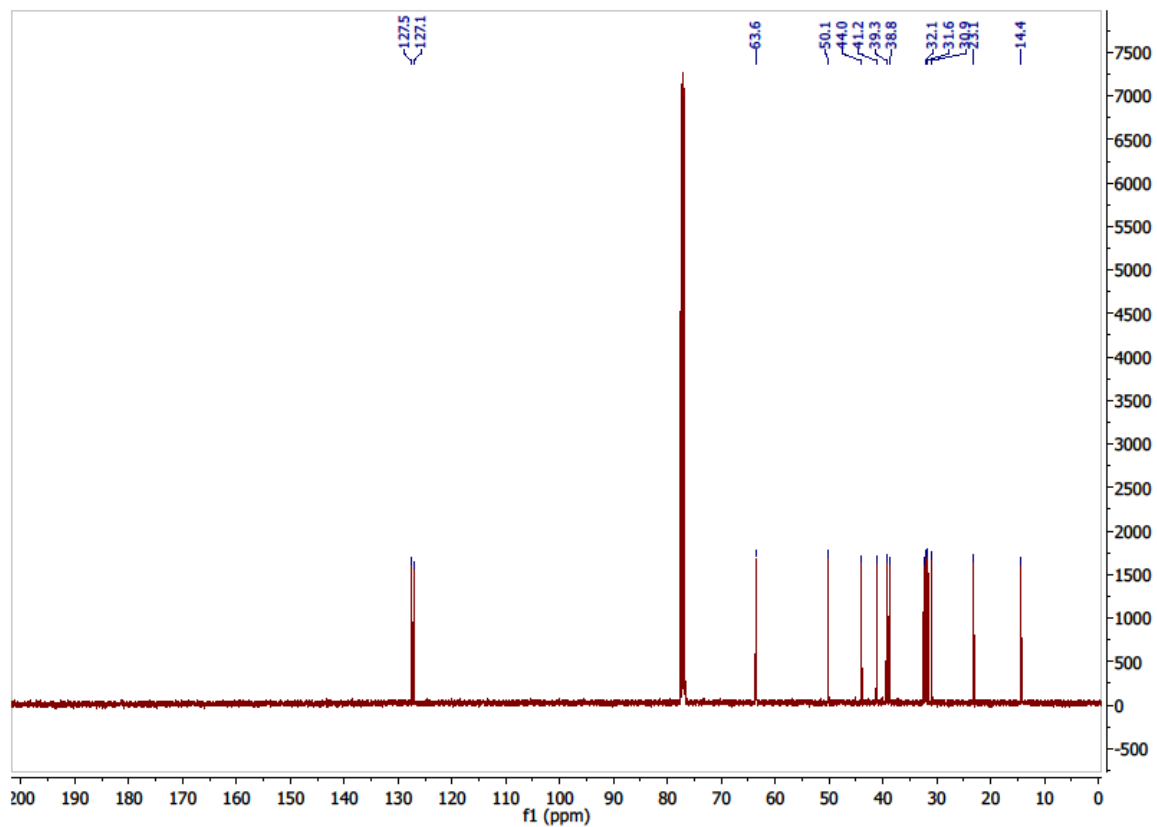
Compound **49** is not known from the literature.

Spectrum 5.35: *¹H NMR spectrum of **D1** of compound **49**.*

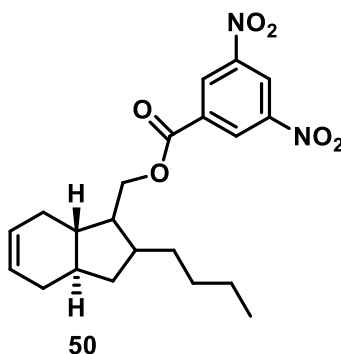***Spectrum 5.36:*** *¹³C NMR spectrum of **D1** of compound **49**.*

Spectrum 5.37: *¹H NMR spectrum of **D2** of compound **49**.*

Spectrum 5.38: *¹³C NMR spectrum of **D2** of compound **49**.*

5.1.18 Preparation of ((3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methyl 3,5-dinitrobenzoate (50)

50

Procedure:[3]

A stirring solution of alcohol **49** (69.6 mg, 0.334 mmol, 1.00 eq.) in dry dichloromethane (5.8 mL) was added triethylamine (0.15 mL, 102 mg, 1.00 mmol, 3.00 eq.) dropwise. The solution was cooled to 0 ℃ before 3,5-dinitrobenzoyl chloride (131 mg, 0.568 mmol, 1.70 eq.) was added. The color of the mixture changed from clear to orange immediately. The reaction mixture was slowly warmed to room temperature monitored by TLC analysis, and judged complete after 1.5 h. The mixture was poured over water (10 mL), the phases separated, and the aqueous phase extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (1 x 30 mL), brine (1 x 30 mL), and dried (MgSO$_4$). Filtration and concentration in *vacuo* gave a brown solid that was purified by flash chromatography (hexane:EtOAc 9:1) to afford **50** as white crystals (132 mg, 0.328 mmol, 97%). Compound **50** (4.00 mg) was recrystallized from a 1:1 mixture of THF and hexane (2.5 mL) in a 2 mL vial by vapor diffusion (MeOH as anti-solvent) to give crystals.[67]

R$_f$: 0.29 (hexane:EtOAc 9:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.23 (t, *J* = 2.2 Hz, 1H), 9.15 (d, *J* = 2.2 Hz, 2H), 5.69 (s, 2H), 4.58 (dd, *J* = 11.0, 7.0 Hz, 1H), 4.47 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.36 – 2.10 (m, 5H), 1.99 – 1.89 (m, 1H), 1.86 – 1.76 (m, 1H), 1.61 – 1.50 (m, 3H), 1.40 – 1.18 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H)
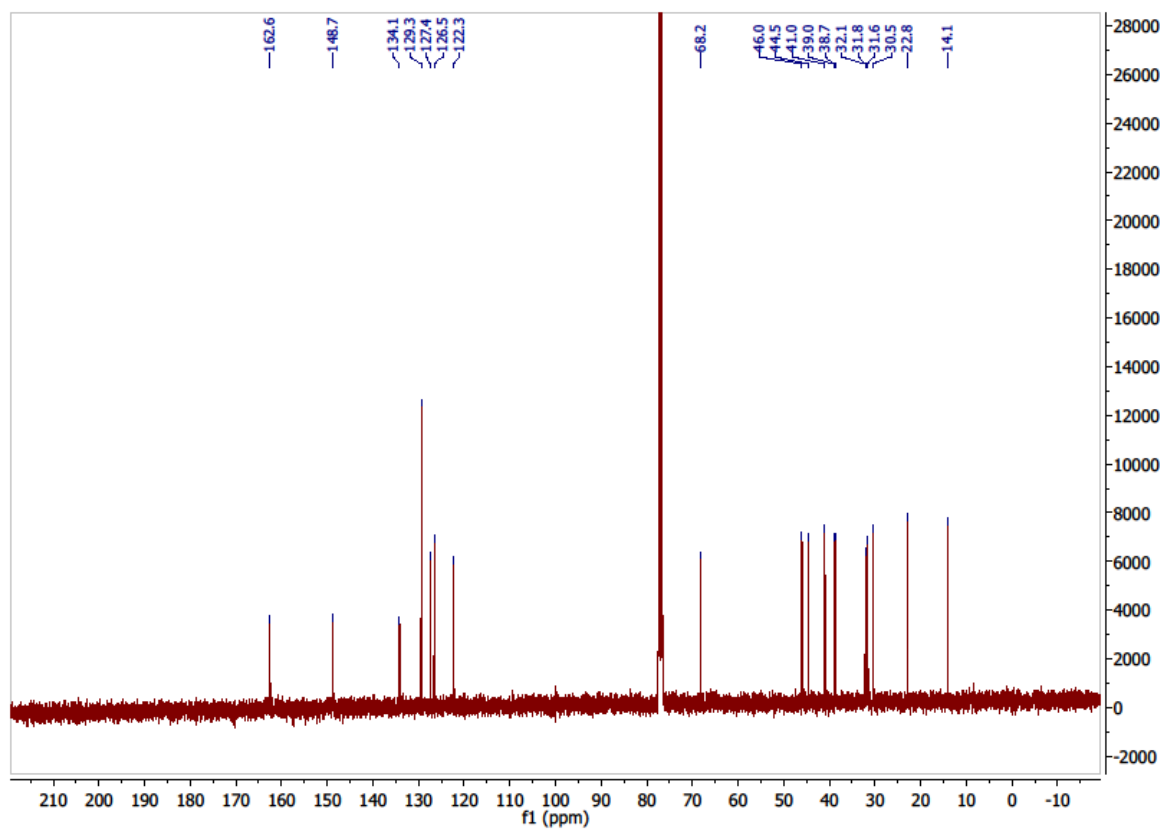
^{13}C NMR (100 MHz, CDCl$_3$) δ 162.6, 148.7, 134.2, 129.3, 127.4, 126.5, 122.3, 68.2, 46.0, 44.5, 41.0, 39.0, 38.7, 32.1, 31.8, 31.6, 30.5, 22.8, 14.1

HRMS (TOF-ES⁺): Exact mass calculated for $C_{21}H_{26}N_2O_6Na$ [M+Na]⁺: 425.1689, found 425.1683

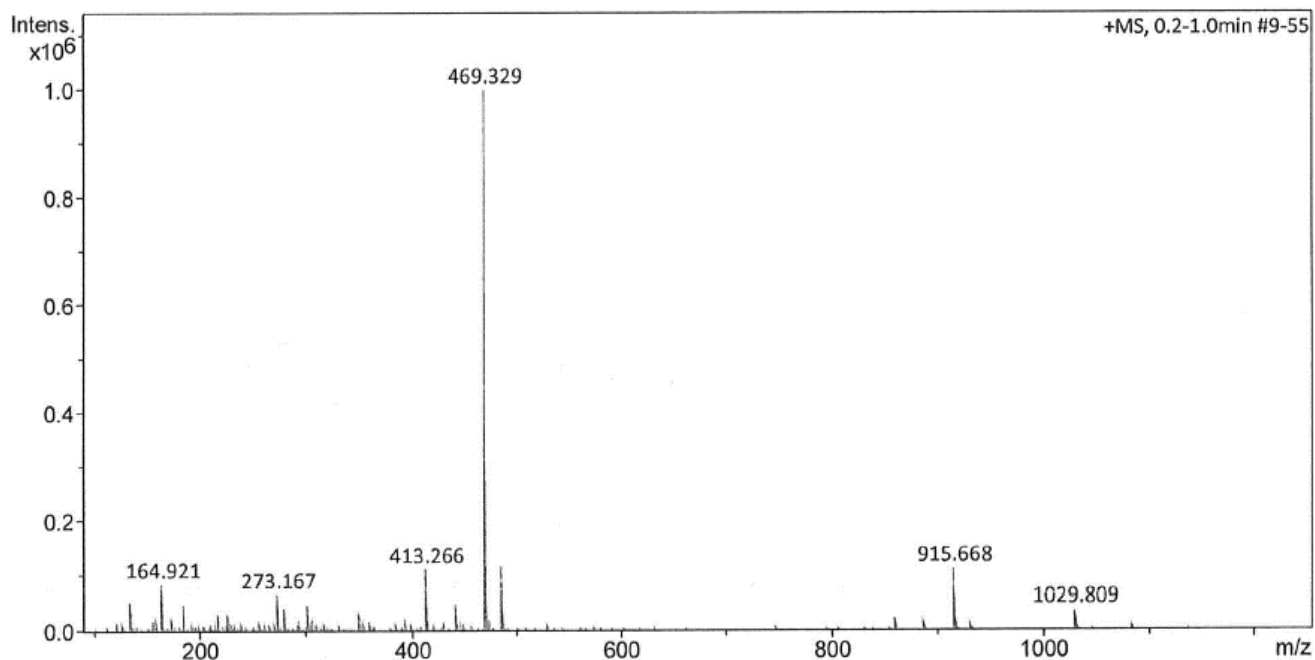Compound **50** is not known from the literature.
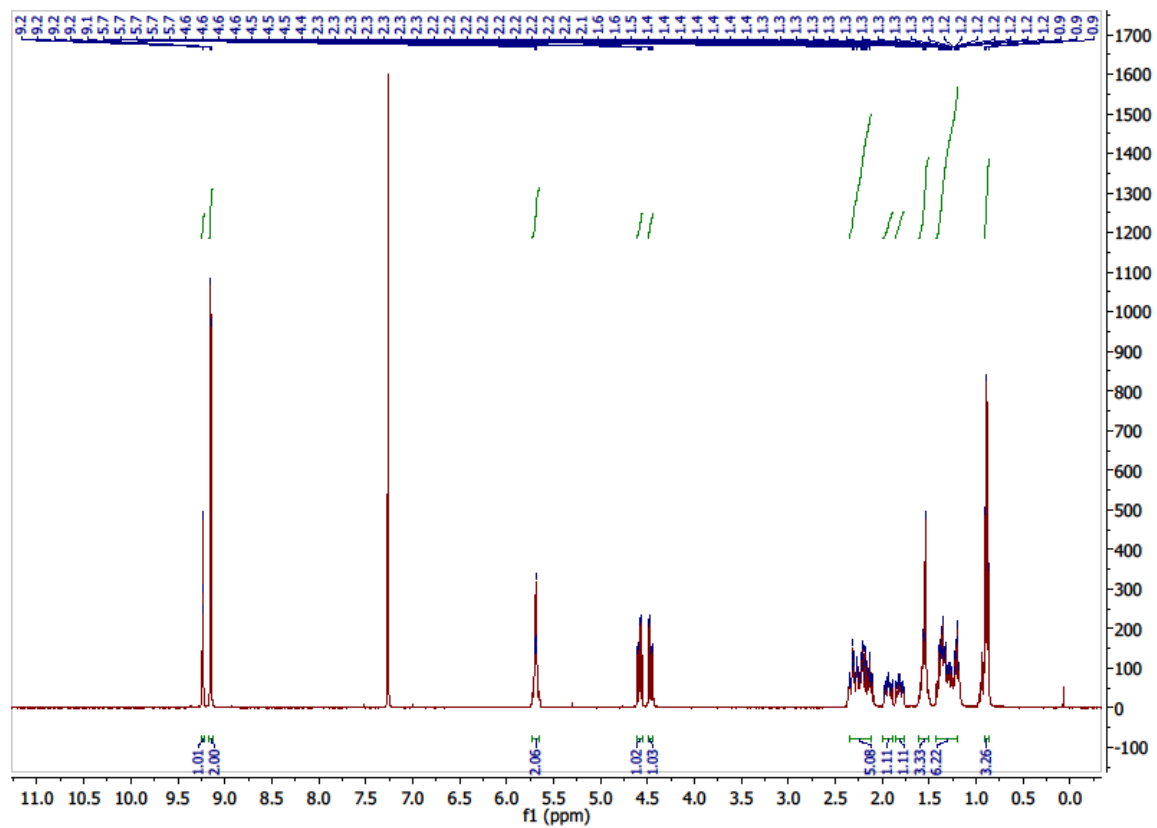
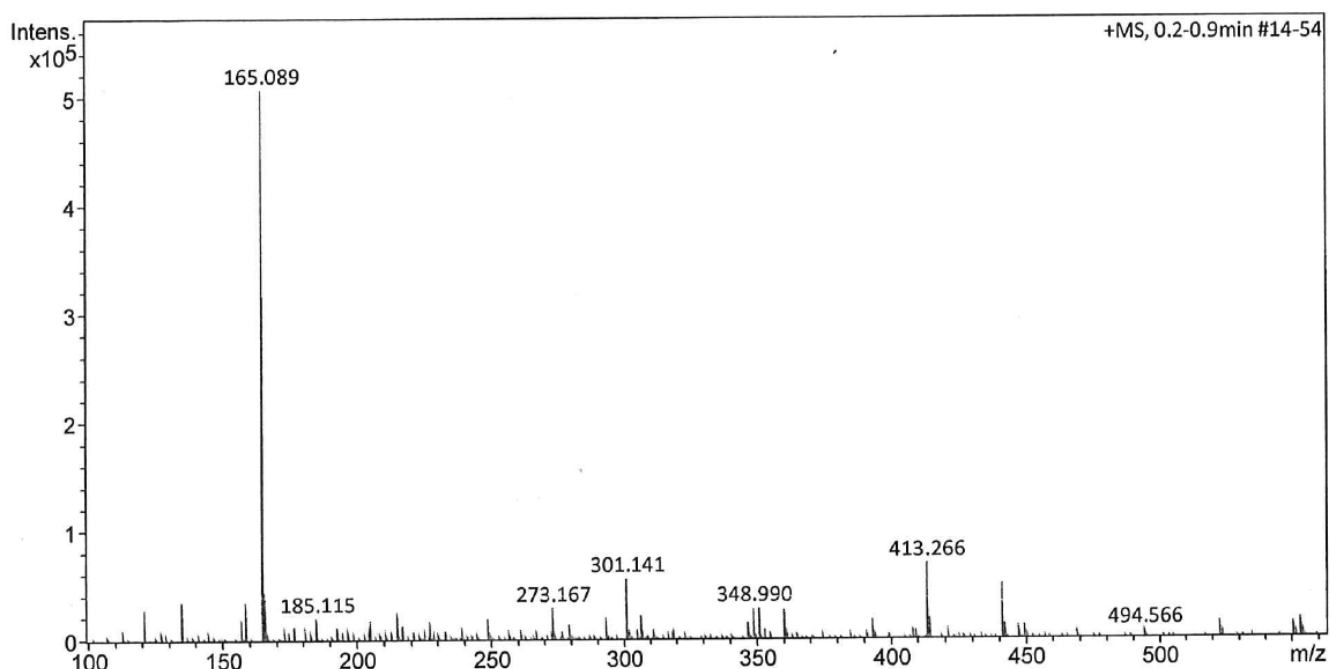***Spectrum 5.39:*** *¹H NMR spectrum of compound **50** derived from **D2** (**51**).*

Spectrum 5.40: *^{13}C NMR spectrum of compound **50** derived from **D2** (**51**).*
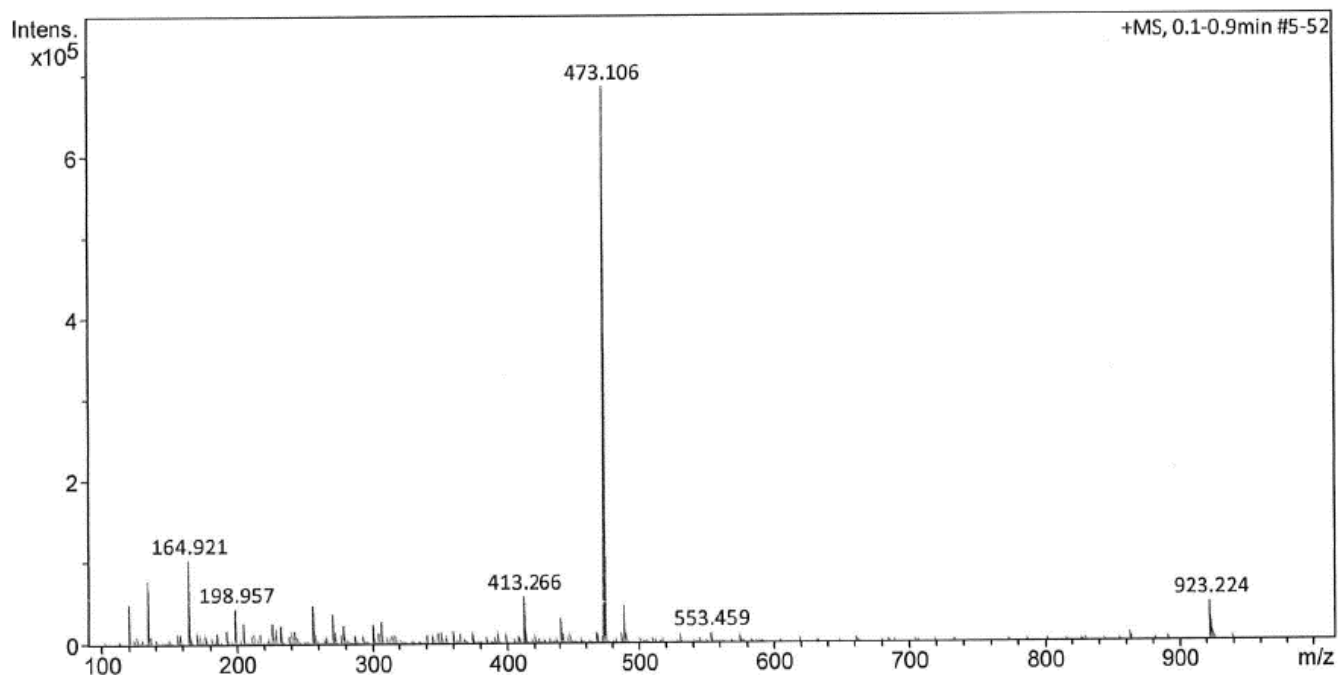
6 Appendix

6.1 MS and HRMS spectrum.

Spectrum 6.1: *MS-spectrum of compound 22.*

Spectrum 6.2: *MS-spectrum of compound 43.*

Spectrum 6.3: *MS-spectrum of compound **44**.*
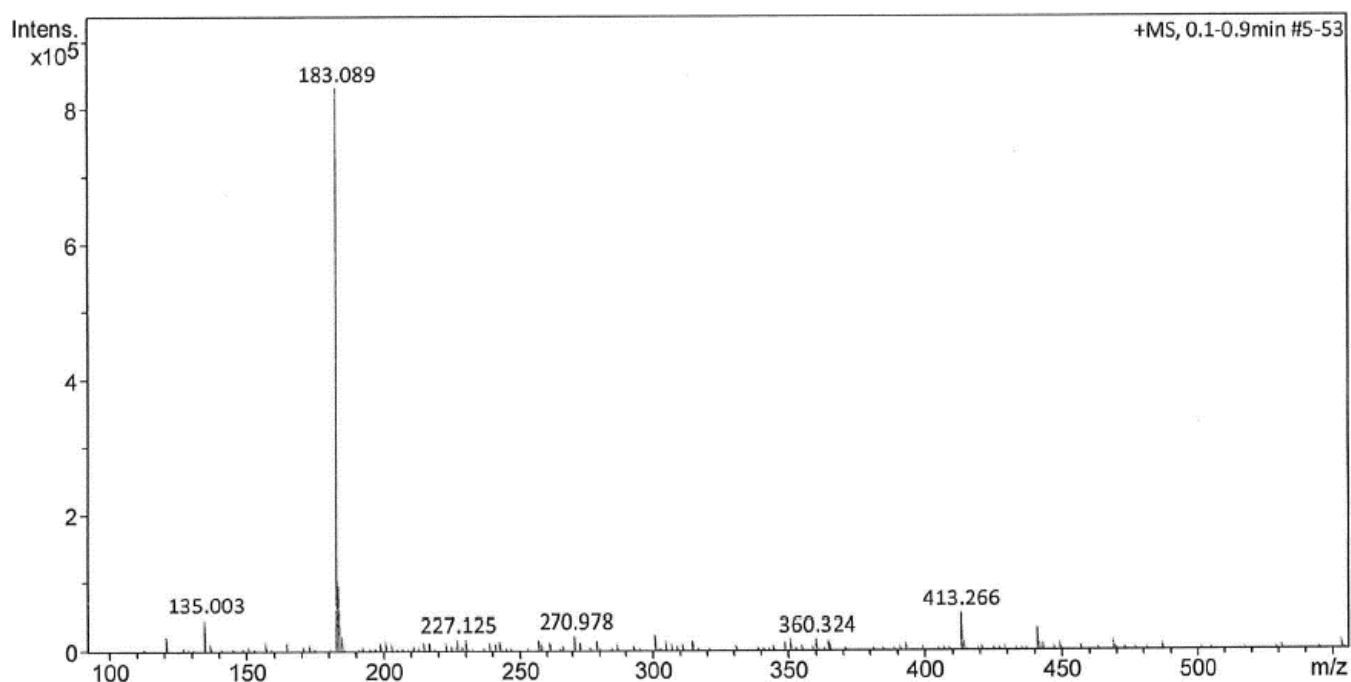
Spectrum 6.4: *MS-spectrum of compound **45**.*
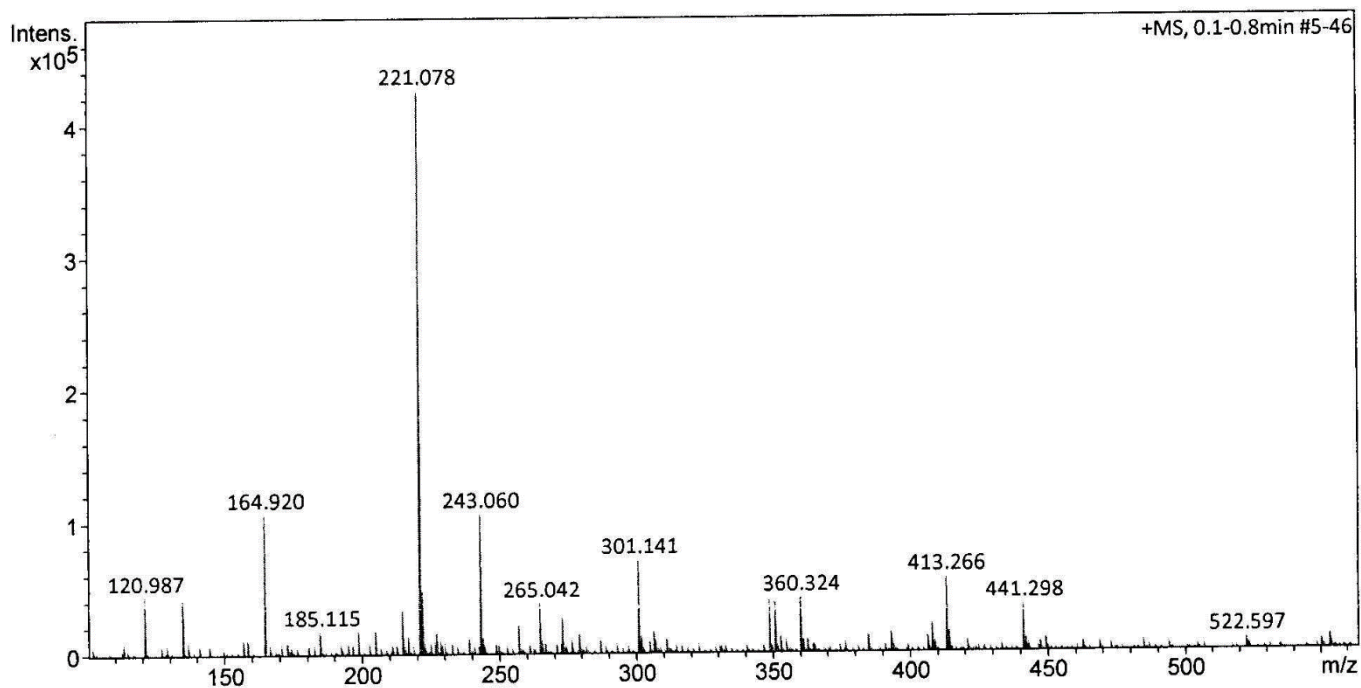
Spectrum 6.5: *MS-spectrum of compound **46**.*
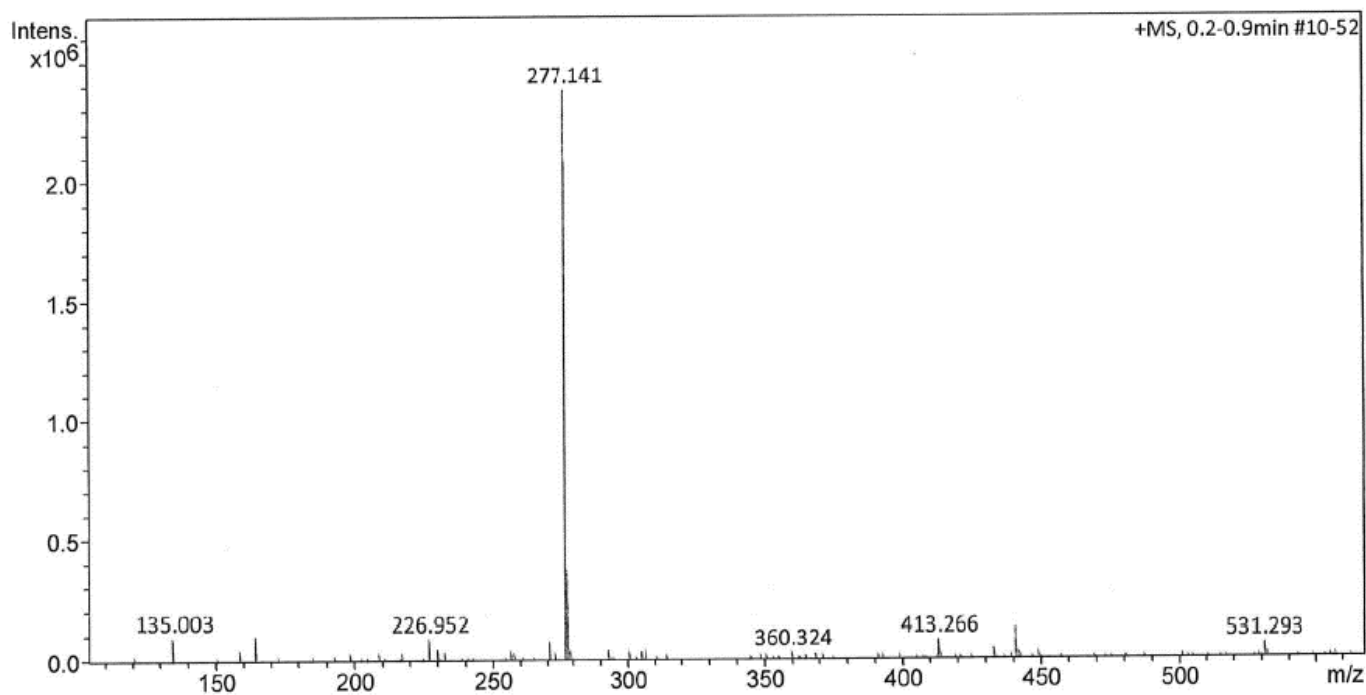
Spectrum 6.6: *MS-spectrum of compound **47**.*
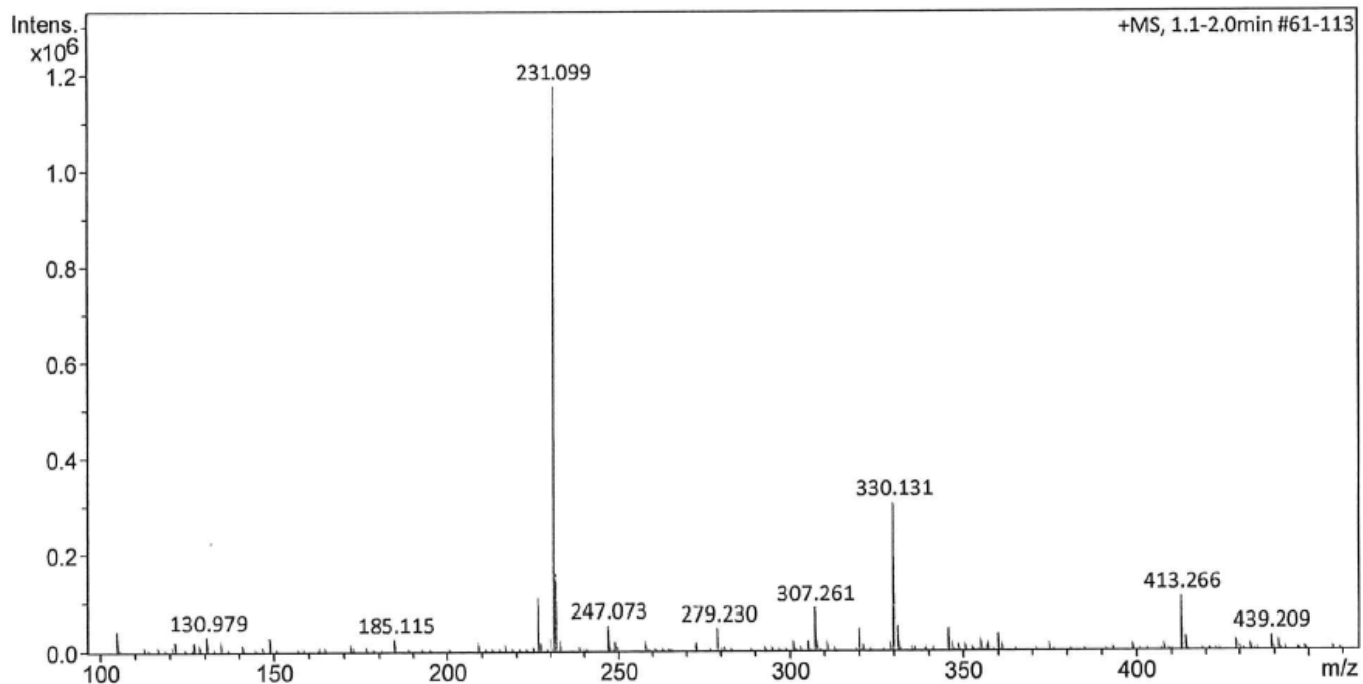
Spectrum 6.7: *MS-spectrum of compound **42**.*
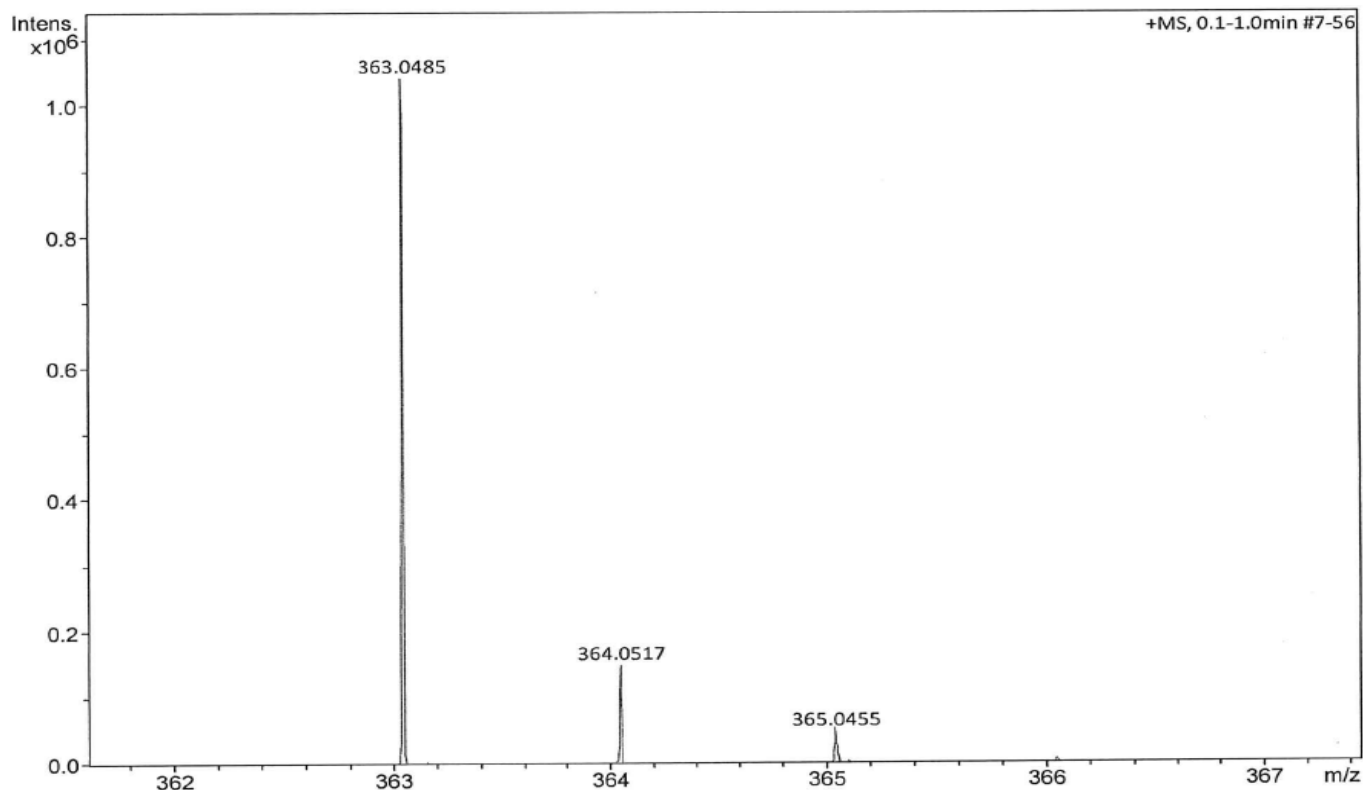
Spectrum 6.8: *HRMS-spectrum of compound **39**.*
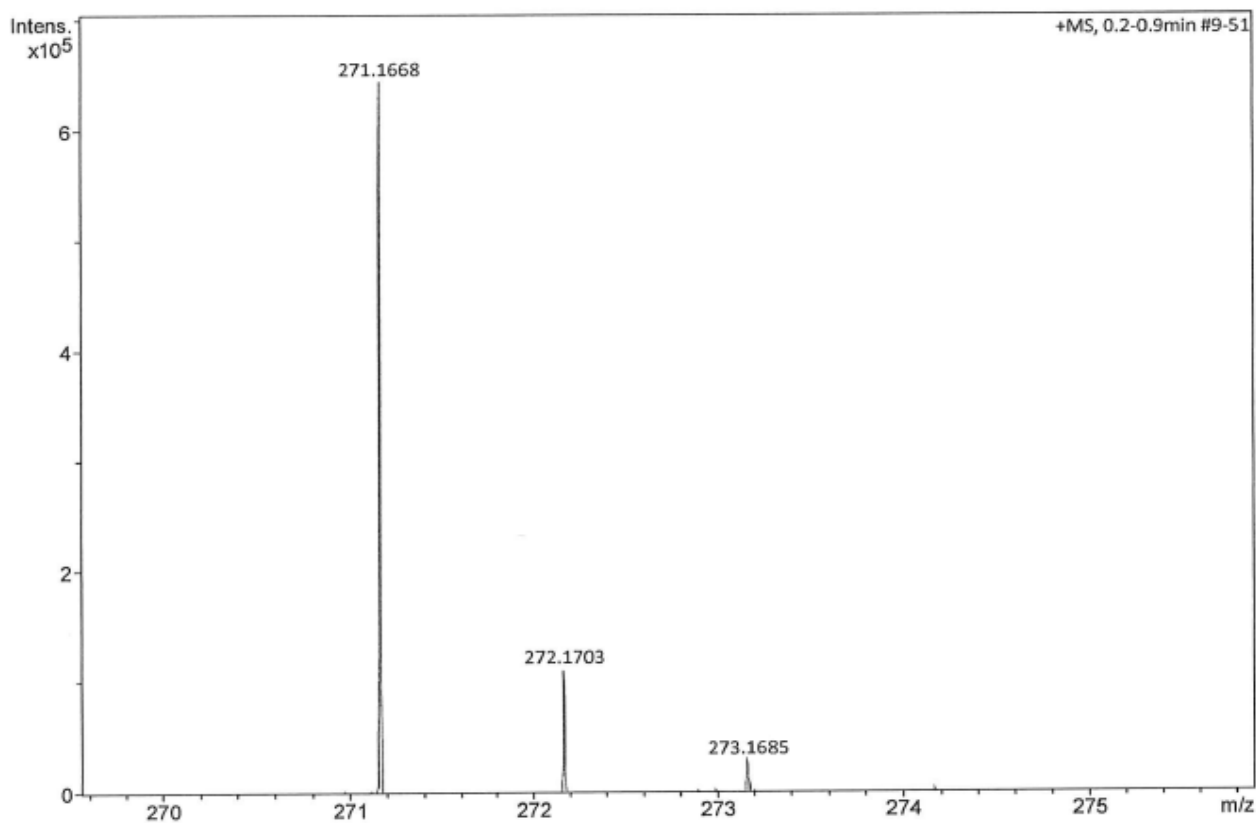
Spectrum 6.9: *HRMS-spectrum of compound **48***.
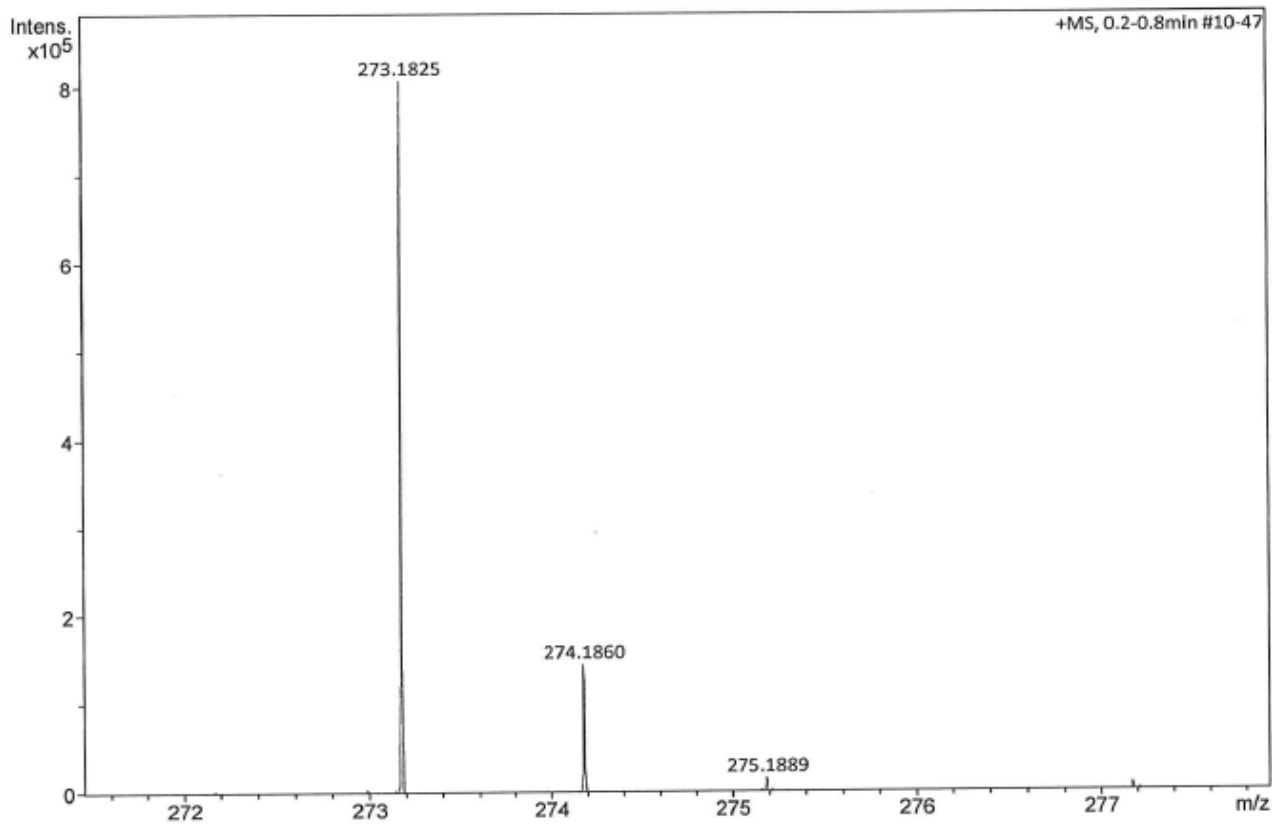
Spectrum 6.10: *HRMS-spectrum of compound **38a***.

96
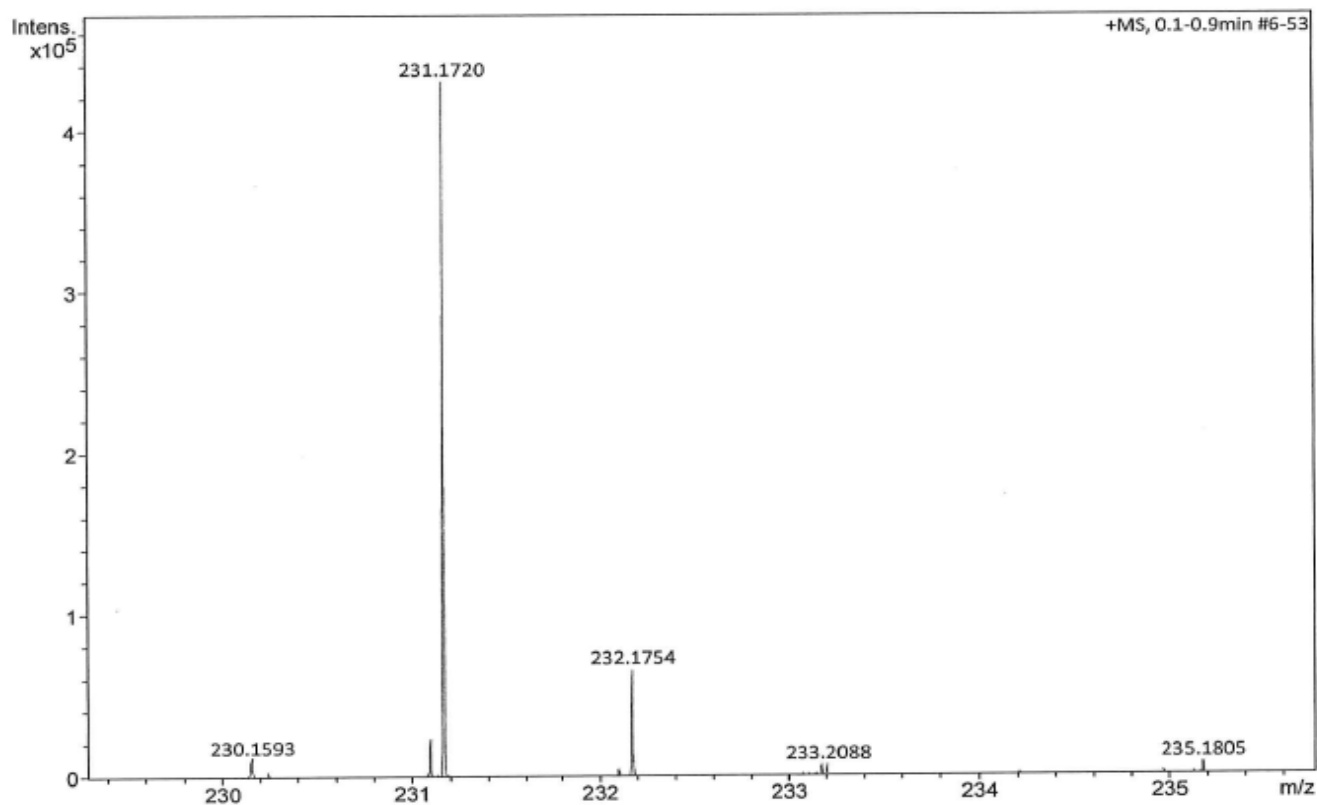
Spectrum 6.11: *HRMS-spectrum of compound **39**.*
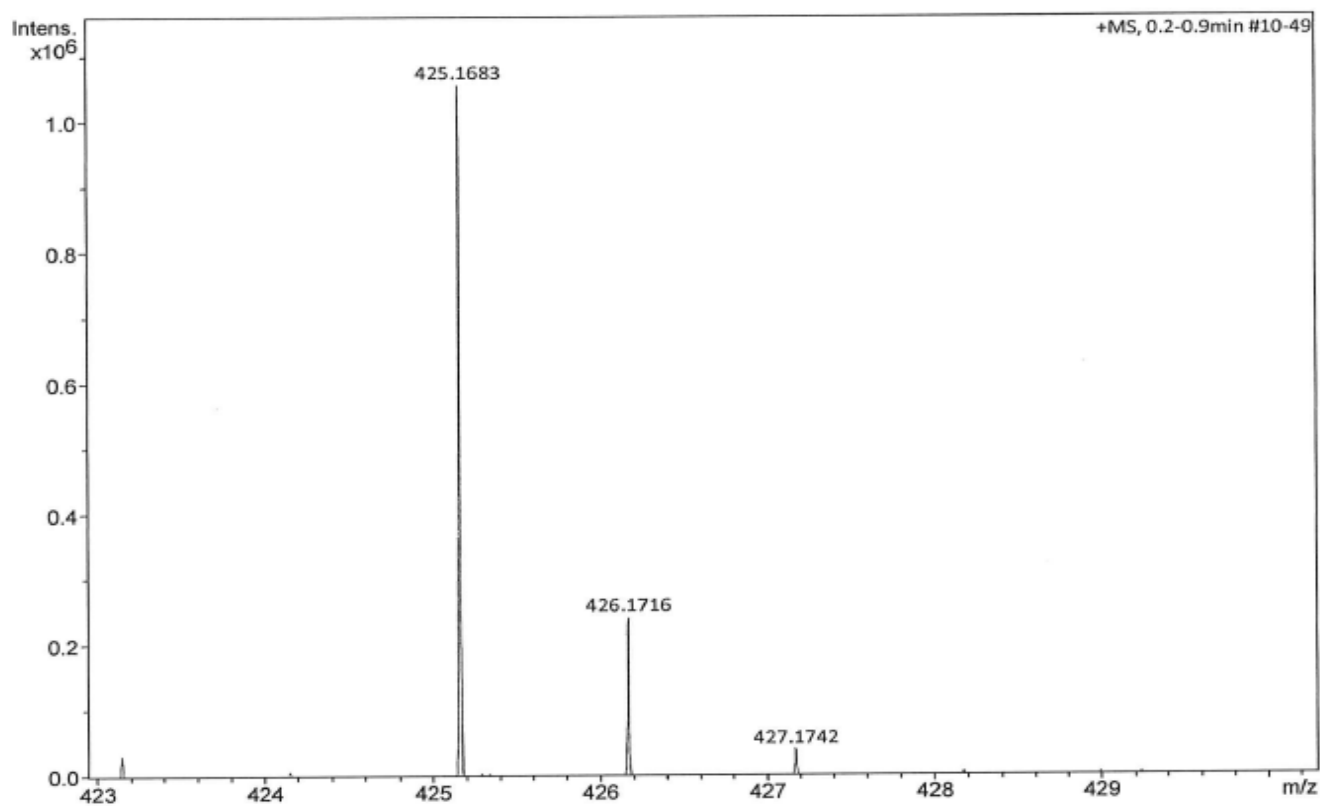
Spectrum 6.12: *HRMS-spectrum of compound **50**.*

6.2 Chromatograms

```
Data File C:\CHEM32\1\DATA\TEST\2017-10-24H.D
Sample Name: Jannicke Chiral 9

==================================================================
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : 7820 GC                    Location : Vial 1
Injection Date  : 10/24/2017 14:19:56
                                             Inj Volume : Manually
Acq. Method     : C:\CHEM32\1\METHODS\CP7502\CP7502.M
Last changed    : 3/16/2017 13:57:30 by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\CP7502\STANDBY KIRAL.M
Last changed    : 10/24/2017 16:26:41 by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```
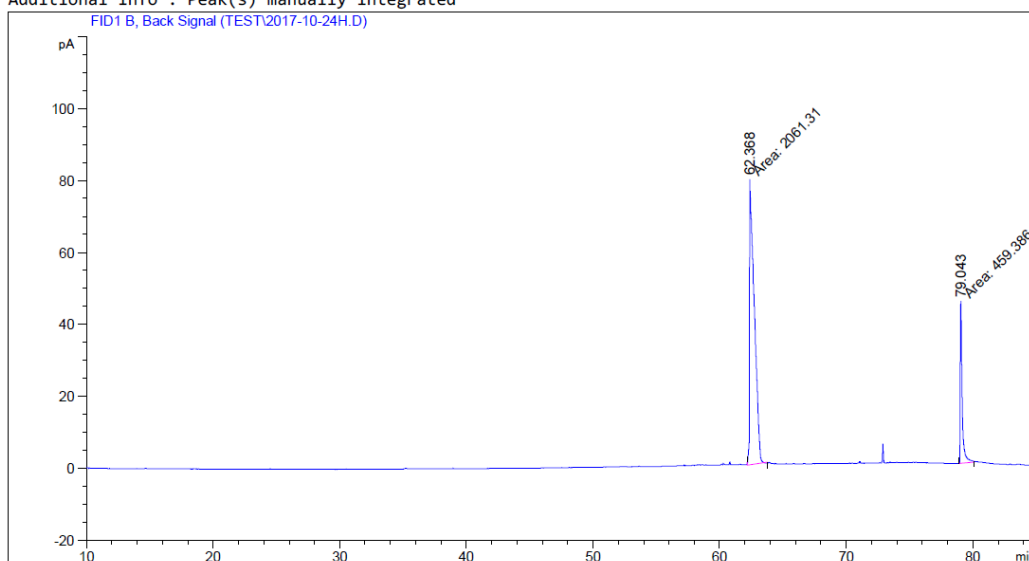
```
==================================================================
                    Area Percent Report
==================================================================

Sorted By           :      Signal
Multiplier          :      1.0000
Dilution            :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area       Height      Area
 #   [min]        [min]    [pA*s]       [pA]         %
----|-------|----|-------|----------|----------|--------|
  1  62.368 MM   0.4323 2061.30981   79.46215 81.77542
  2  79.043 MM   0.1694  459.38617   45.20096 18.22458

Totals :                 2520.69598  124.66311
```

Chromatogram 6.2.1: *GC-chromatogram of ethyl ester **42** and **52**.*

```
Data File C:\Chem32\1\Data\Shno-Grignard.D
Sample Name: Oppgave 4 FRM 4030

    ====================================================================
    Acq. Operator   : SYSTEM
    Sample Operator : SYSTEM
    Acq. Instrument : GC7820A                      Location :   1   (F)
    Injection Date  : 12.09.2017 14:55:01
                                                   Inj Volume : Manually
    Acq. Method     : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
    Last changed    : 12.09.2017 14:49:37 by SYSTEM
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
    Last changed    : 12.09.2017 15:57:47 by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```



```
    ====================================================================
                          Area Percent Report
    ====================================================================


    Sorted By          :        Signal
    Multiplier         :        1.0000
    Dilution           :        1.0000
    Do not use Multiplier & Dilution Factor with ISTDs



    Signal 1: FID1 B, Back Signal

    Peak RetTime Type  Width     Area        Height      Area
     #    [min]        [min]    [pA*s]        [pA]         %
    ----|-------|----|-------|----------|----------|--------|
      1  15.763 MM   0.1349 1.60244e4  1979.59985 1.000e2

    Totals :                  1.60244e4  1979.59985
```
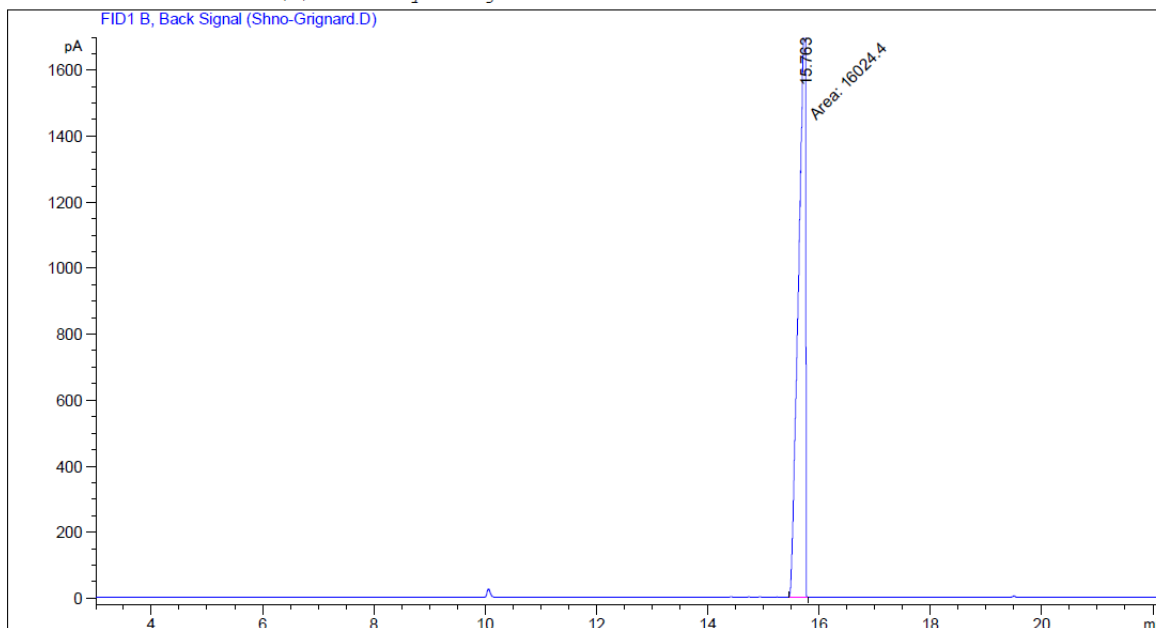
Chromatogram 6.2.2: *GC-chromatogram of unsaturated ethyl ester **48**.*

Data File C:\Chem32\1\Data\Shno-Grignard.D
Sample Name: Oppgave 4 FRM 4030

===
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : GC7820A   Location :   1 (F)
Injection Date : 12.09.2017 12:42:59
                                             Inj Volume : Manually
Acq. Method   : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
Last changed   : 07.09.2017 19:18:02 by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
Last changed   : 12.09.2017 13:44:19 by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated

===
                    Area Percent Report
===

Sorted By   :   Signal
Multiplier   :   1.0000
Dilution   :   1.0000
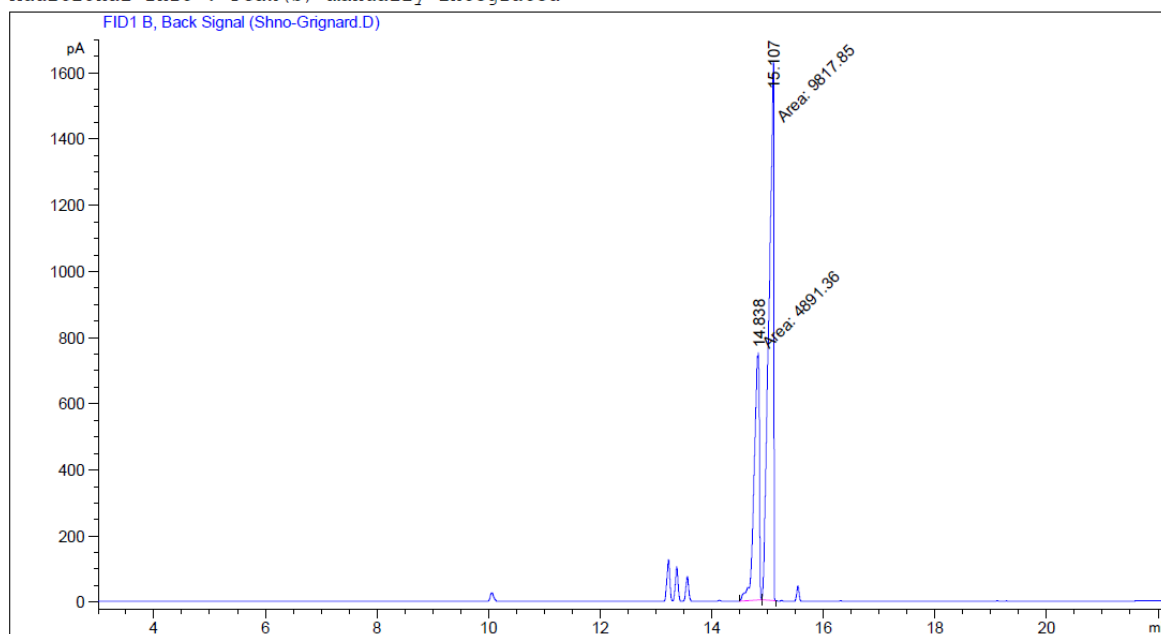Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 B, Back Signal

Peak RetTime Type Width   Area   Height   Area
  #   [min]   [min]   [pA*s]   [pA]   %
----|-------|----|-------|----------|----------|--------|
  1 14.838 MM   0.1088 4891.36377 749.18091 33.25373
  2 15.107 MM   0.1006 9817.85352 1625.90173 66.74627

Totals :   1.47092e4 2375.08264

Chromatogram 6.2.3: *GC-chromatogram of non-equilibrated ethyl ester **38a**.*

100

```
Data File C:\Chem32\1\Data\Shno-Grignard.D
Sample Name: Oppgave 4 FRM 4030

====================================================================
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : GC7820A                    Location :   1  (F)
Injection Date  : 12.09.2017 10:19:14
                                            Inj Volume : Manually
Acq. Method     : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
Last changed    : 07.09.2017 19:18:02 by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
Last changed    : 12.09.2017 12:34:28 by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```



```
====================================================================
                    Area Percent Report
====================================================================


Sorted By           :       Signal
Multiplier          :       1.0000
Dilution            :       1.0000
Do not use Multiplier & Dilution Factor with ISTDs



Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area        Height      Area
  #   [min]        [min]   [pA*s]        [pA]         %
----|-------|----|-------|----------|----------|--------|
  1  14.907 MM    0.1139 9759.10059 1427.54114 64.57448
  2  15.088 MM    0.0762 5353.83691 1171.39087 35.42552

Totals :                 1.51129e4   2598.93201
```
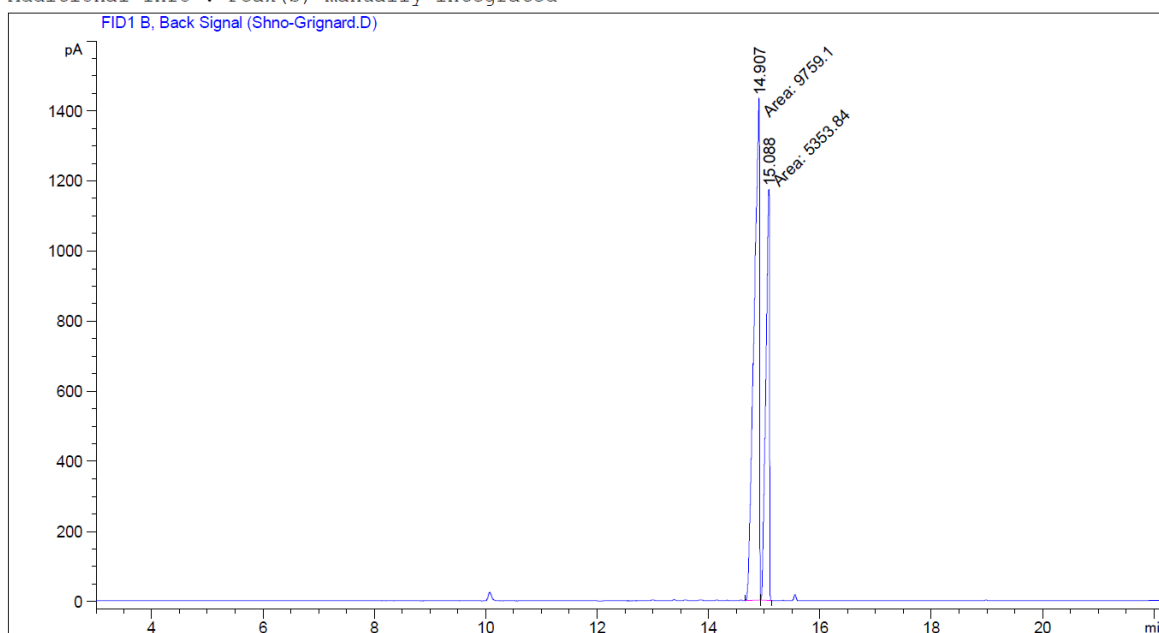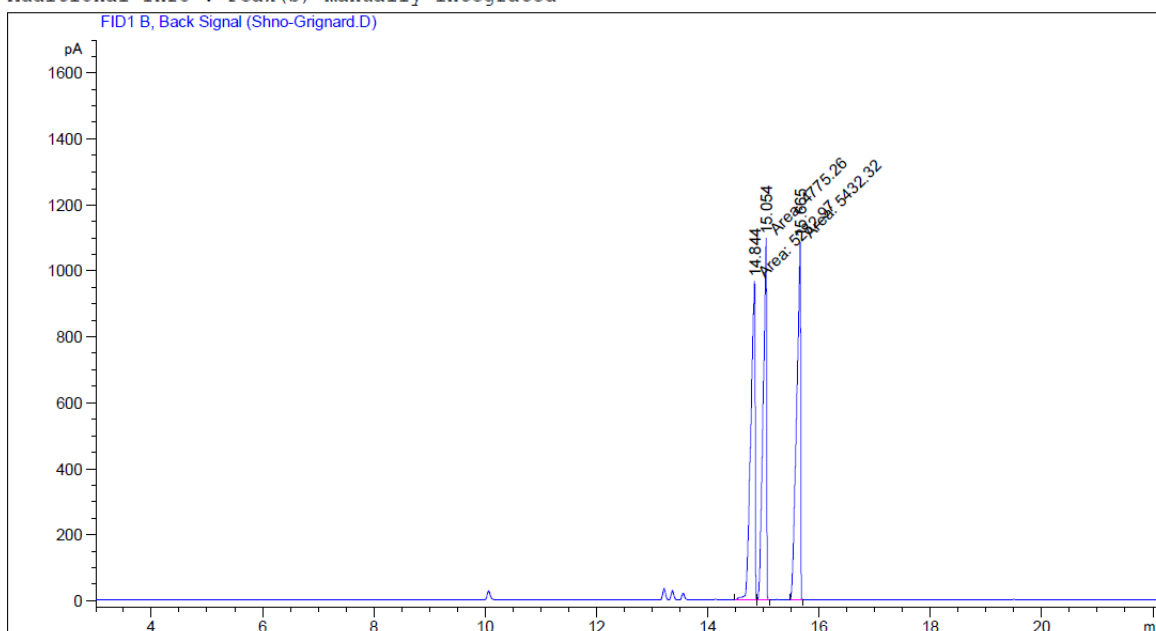
Chromatogram 6.2.4: *GC-chromatogram of equilibrated ethyl ester **38a**.*

```
Data File C:\Chem32\1\Data\Shno-Grignard.D
Sample Name: Oppgave 4 FRM 4030

    =================================================================
    Acq. Operator   : SYSTEM
    Sample Operator : SYSTEM
    Acq. Instrument : GC7820A                    Location :  1  (F)
    Injection Date  : 12.09.2017 13:53:10
                                                 Inj Volume : Manually
    Acq. Method     : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
    Last changed    : 12.09.2017 13:44:19 by SYSTEM
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\ANDERS METODER\Jannicke1.M
    Last changed    : 12.09.2017 14:49:37 by SYSTEM
                      (modified after loading)
    Additional Info : Peak(s) manually integrated
```



```
    =================================================================
                        Area Percent Report
    =================================================================


    Sorted By            :       Signal
    Multiplier           :       1.0000
    Dilution             :       1.0000
    Do not use Multiplier & Dilution Factor with ISTDs



    Signal 1: FID1 B, Back Signal

    Peak RetTime Type  Width     Area        Height      Area
     #   [min]        [min]    [pA*s]       [pA]         %
    ----|-------|----|-------|----------|----------|--------|
       1  14.844 MM   0.0910 5282.96631  967.24506 34.10444
       2  15.054 MM   0.0725 4775.26270 1097.69897 30.82694
       3  15.665 MM   0.0832 5432.32324 1088.41248 35.06862

    Totals :                  1.54906e4  3153.35651
```
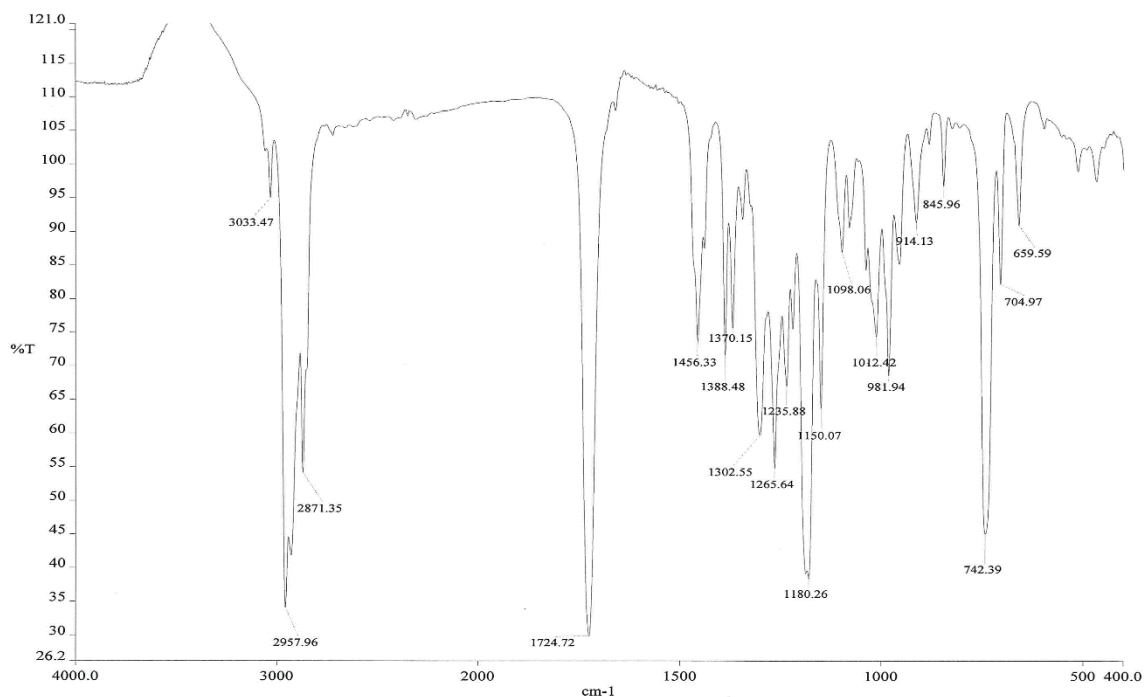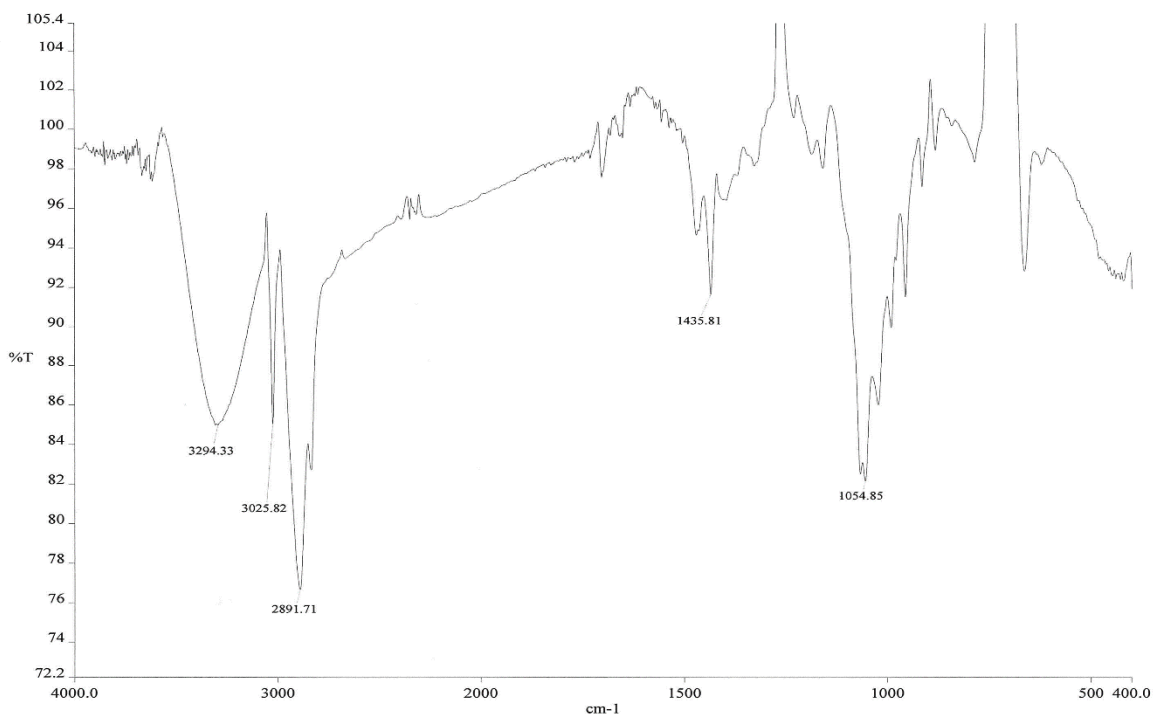
Chromatogram 6.2.5: GC-chromatogram obtained by co-injected unsaturated ethyl ester **48**, non-eqilibrated ethyl ester **38a** and equilibrated ethyl ester **38a** in equal concentrations.
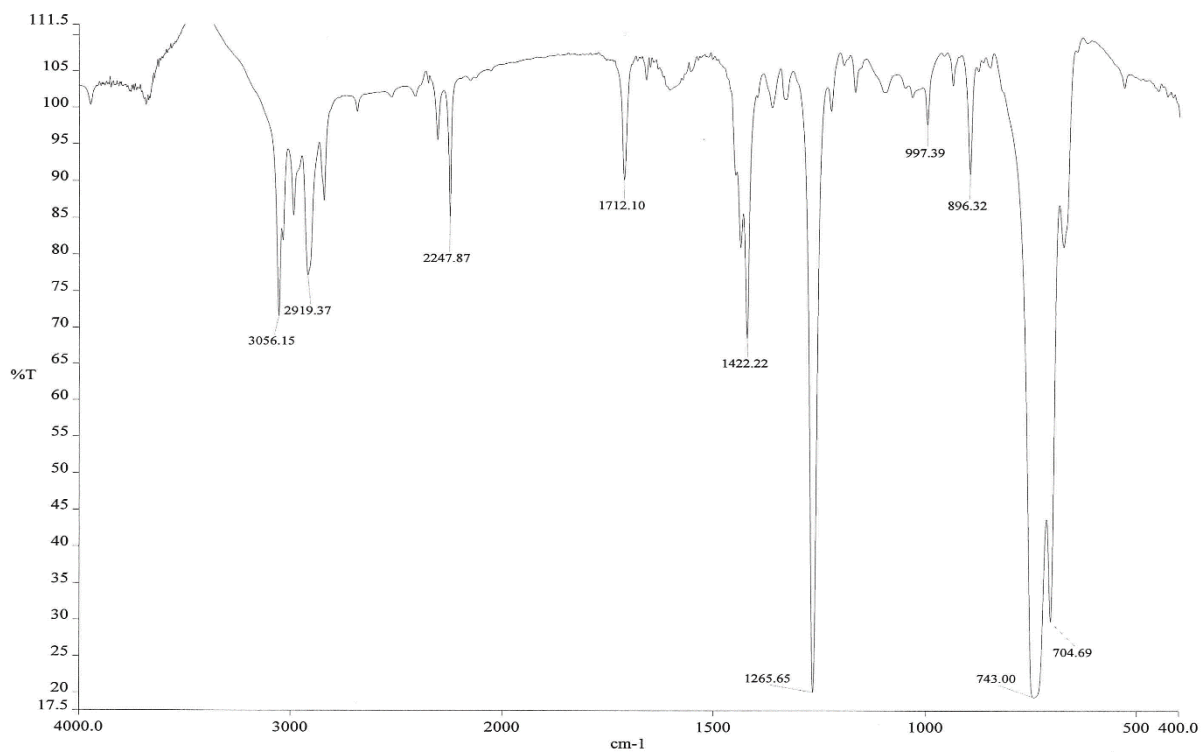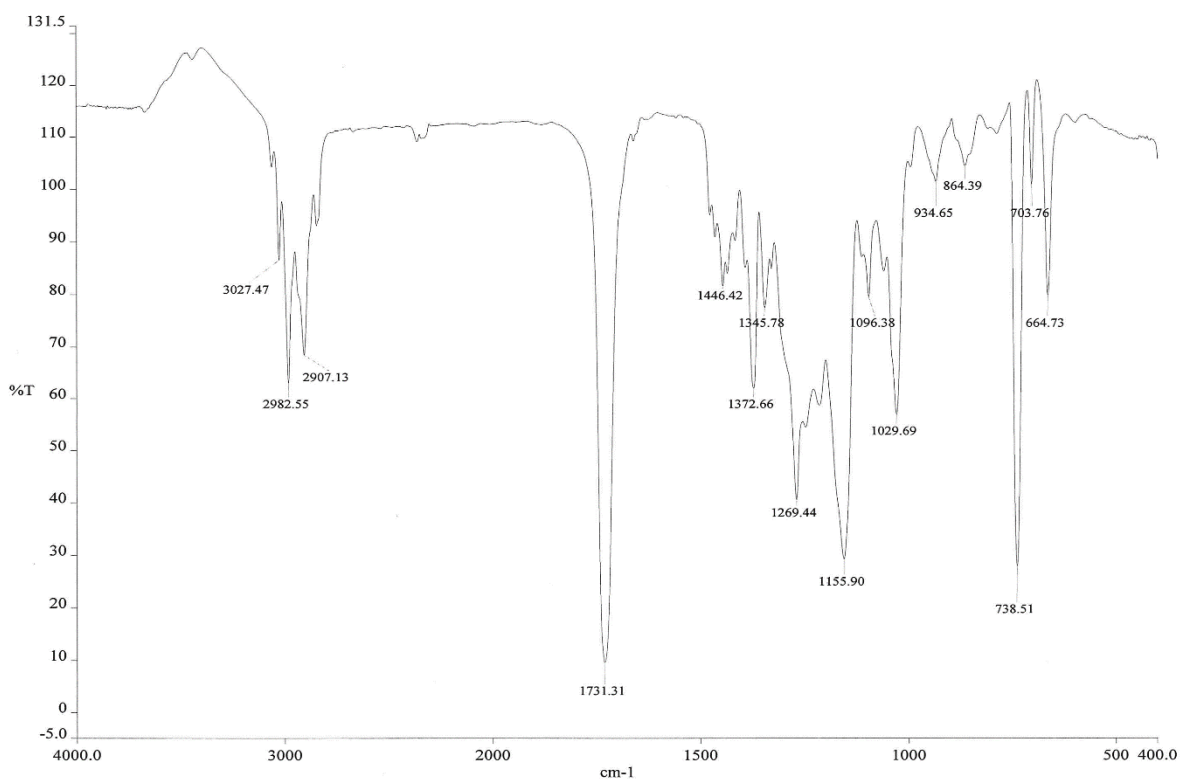
6.3 IR spectrum

Spectrum 6.3.1: *IR-spectrum of dimenthyl **22**.*

Spectrum 6.3.2: *IR-spectrum of diol **43**.*

Spectrum 6.3.3: *IR-spectrum of dinitrile **45**.*

Spectrum 6.3.4: *IR-spectrum of diester **47**.*
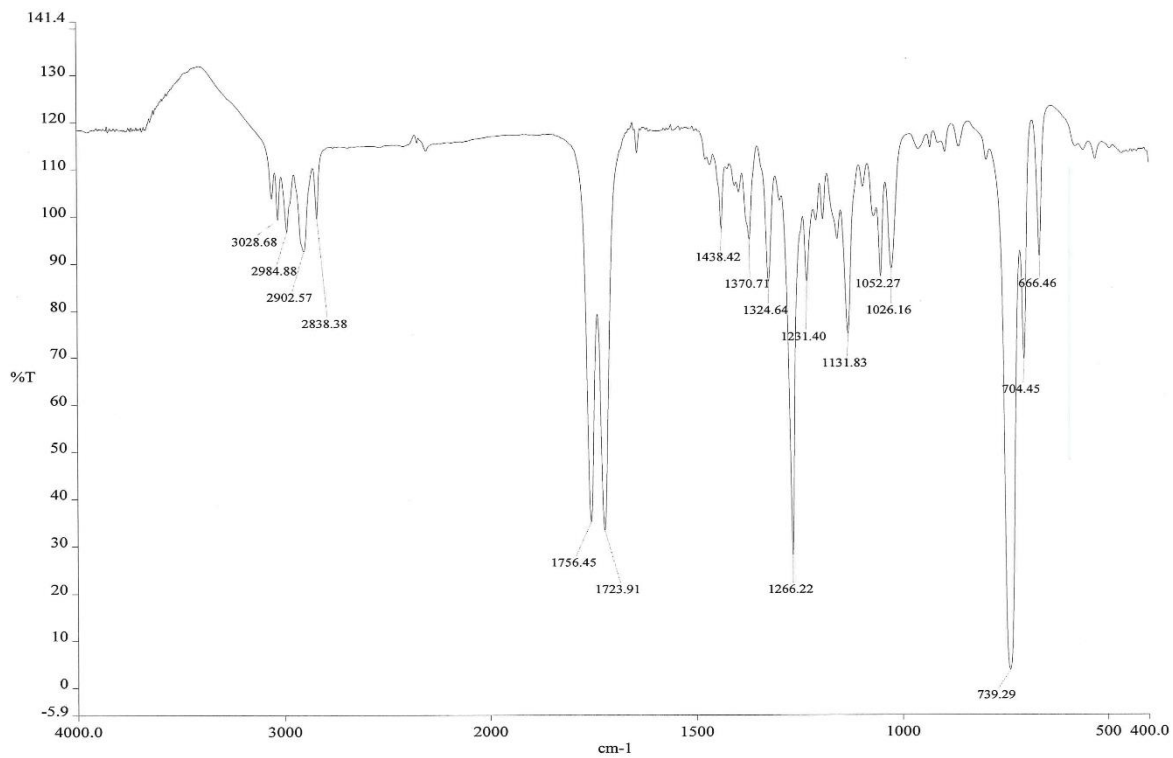
Spectrum 6.3.5: *IR-spectrum of β-keto ester* **42**.
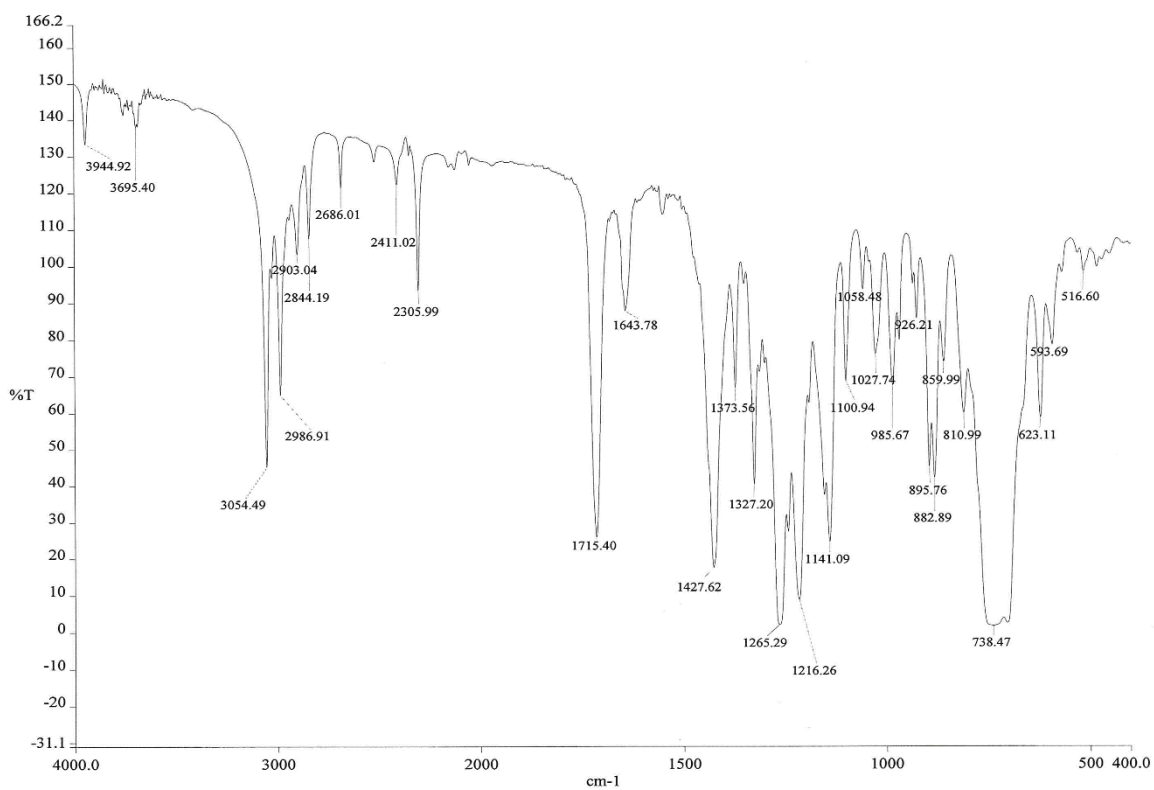
Spectrum 6.3.6: *IR-spectrum of triflate* **39**.
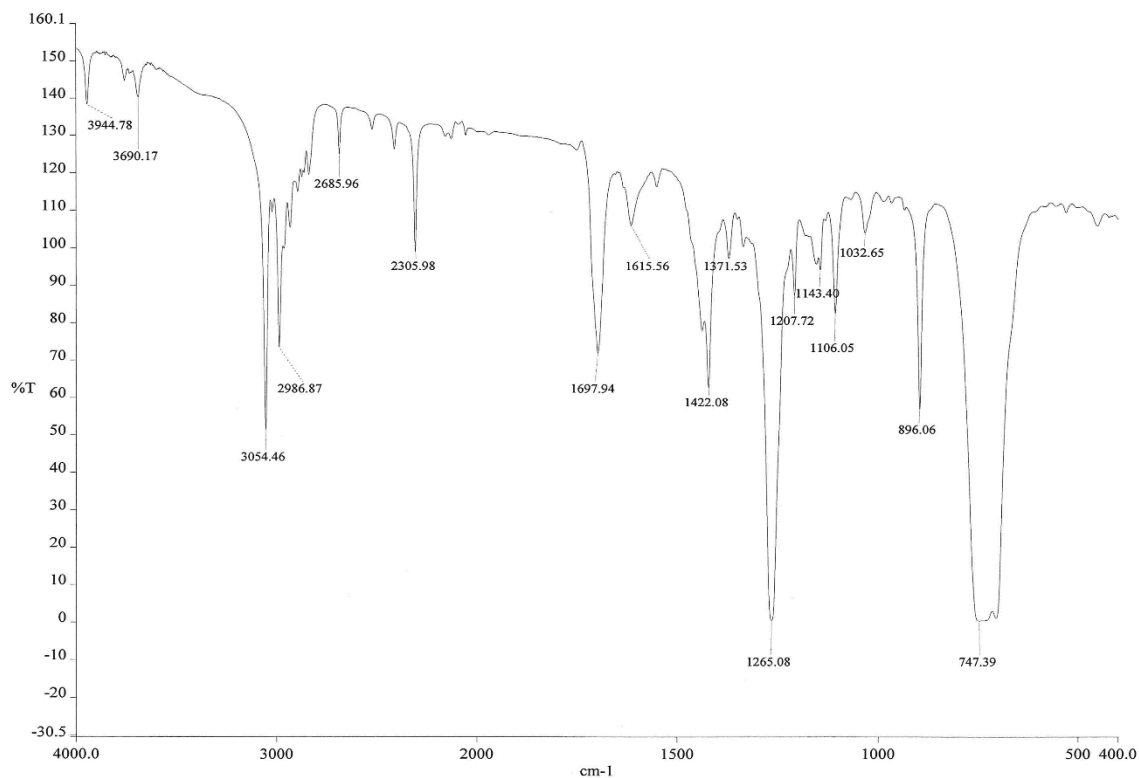
Spectrum 6.3.7: *IR-spectrum of α,β unsaturated ethyl ester **48**.*
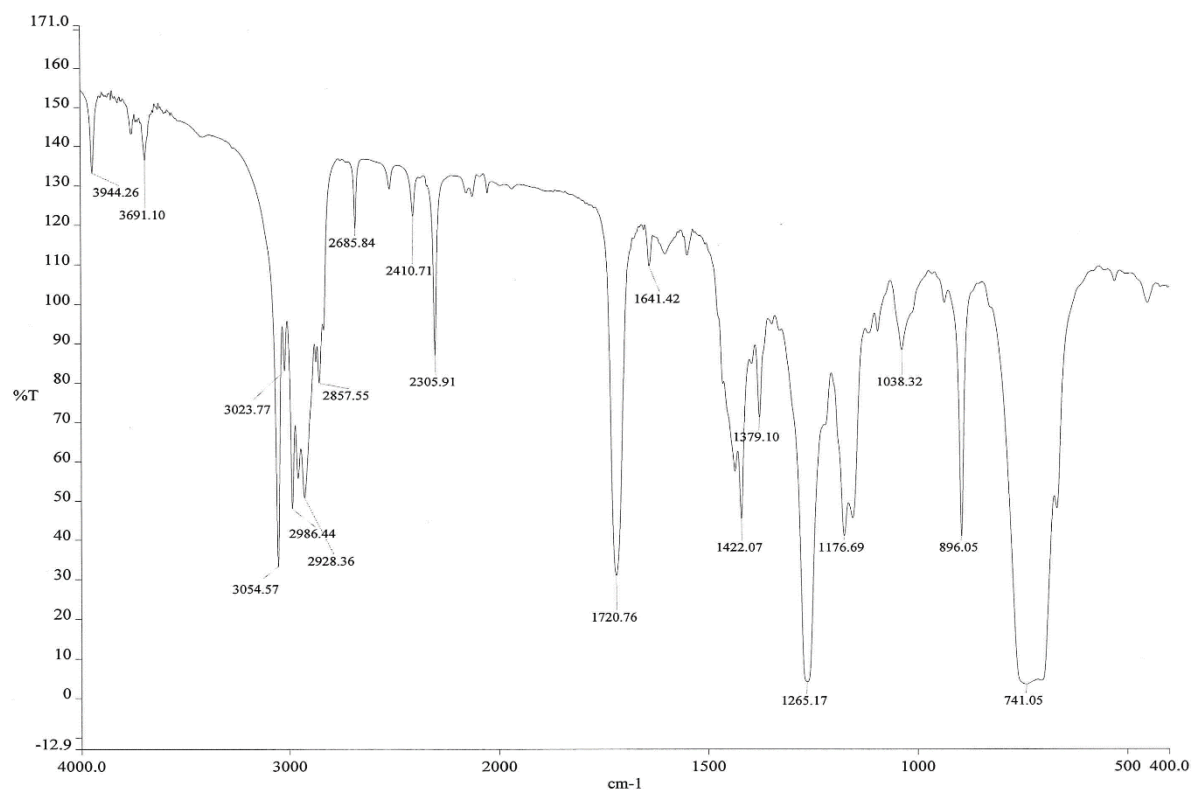
Spectrum 6.3.8: *IR-spectrum of ethyl ester **38a**.*

6.4 UV spectrum
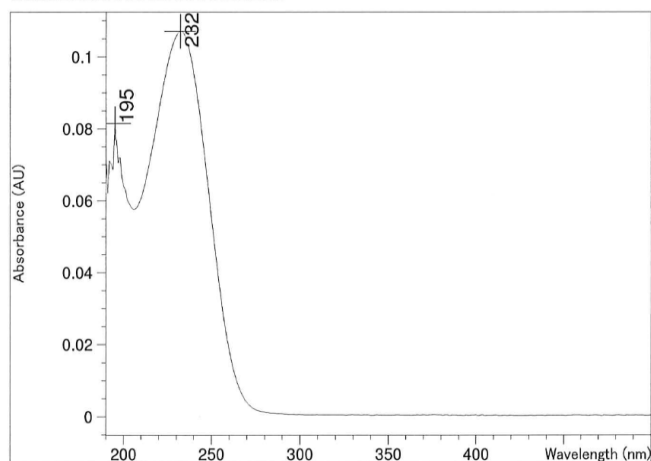
Spectrum 7.4.1: *UV-spectrum of α,β-unsaturated ethyl ester **48**.*
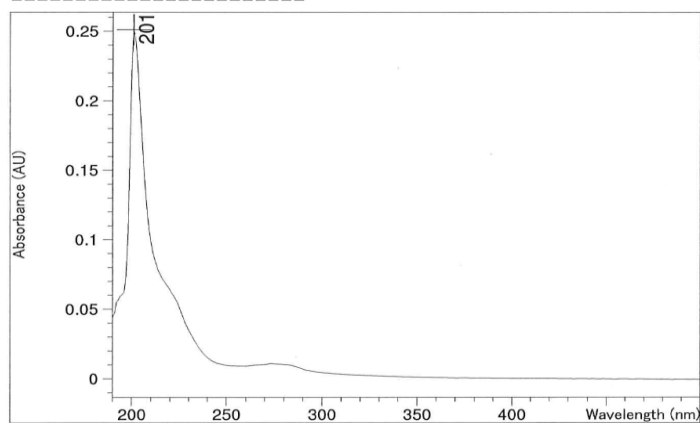
Spectrum: 6.4.2: *UV-spectrum of ethyl ester **38a**.*

6.5 X-ray crystallography
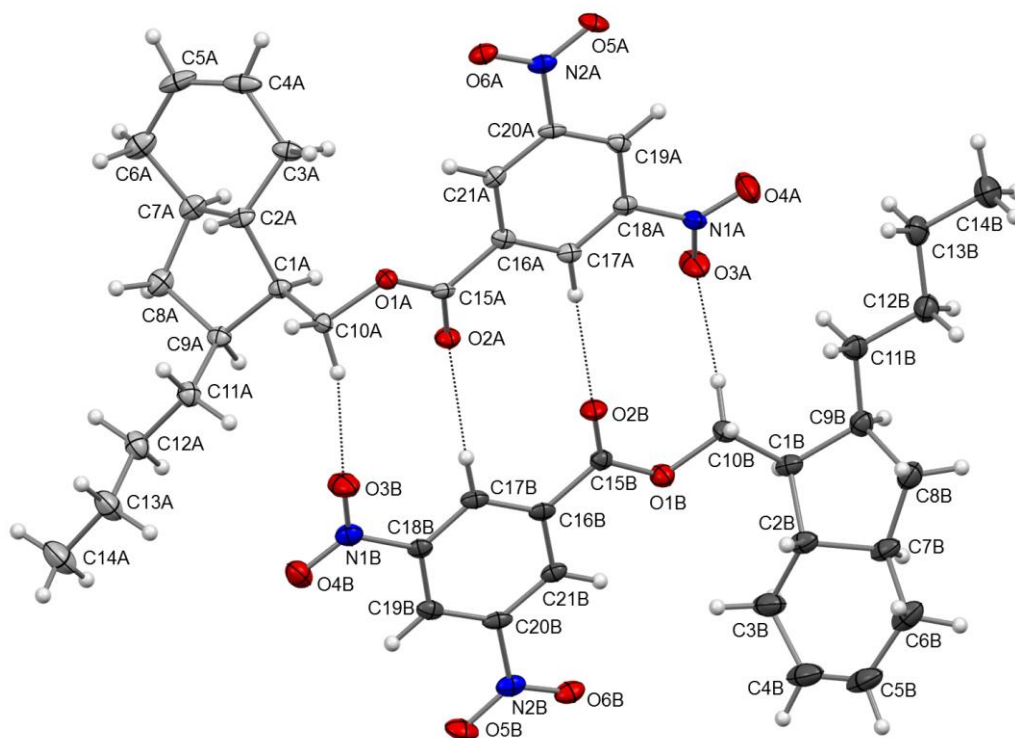
Figure 6.5.1: *X-ray structures of 3,5-dinitrobenzoate **51**, which differs by the conformation of the cyclopentane ring.*
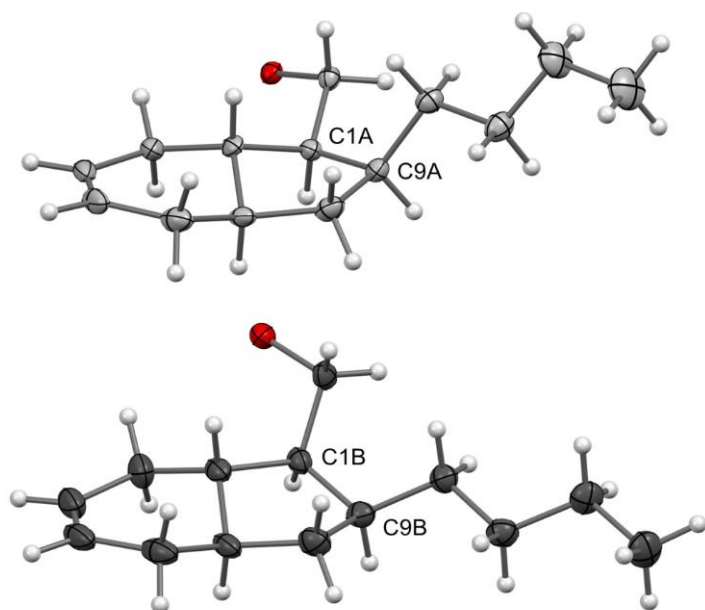
Figure 6.5.2: *X-ray structures of 3,5-dinitrobenzoate **51**.*
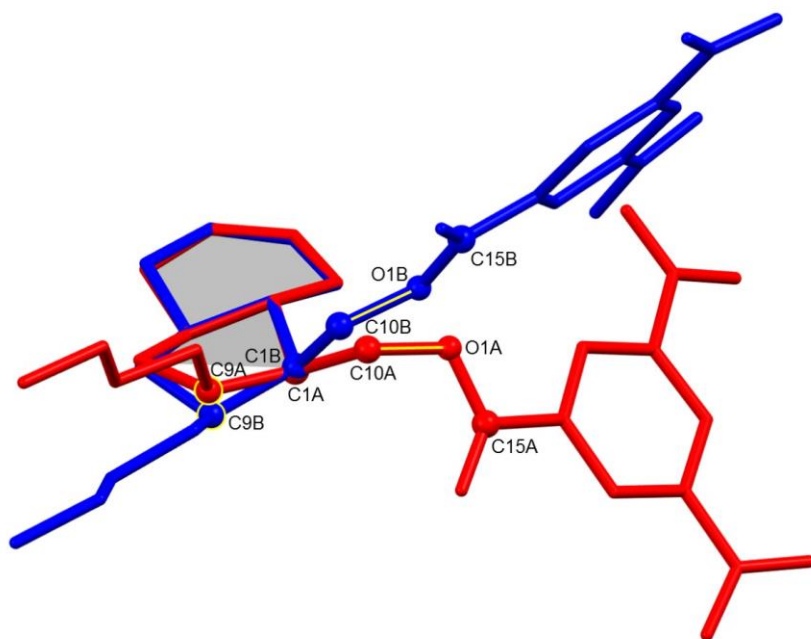
Figure 6.5.3: *Capped sticks presentation of compound **51** in relation with the other conformer of **51**.*

Table 7.5.1: Crystal data for ((1*S*,2*S*,3a*R*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)methyl 3,5-dinitrobenzoate (**51**).

Chemical formula	$C_{21}H_{26}N_2O_6$
M_r	402.44
crystal system, space group	monoclinic, *C*2
a	38.246(3) Å
b	5.6970(5) Å
c	19.5490(15) Å
β	108.032(2)°
Z	8
Radiation	Mo *K*α
Temperature	100 K
Crystal size	$0.028 \times 0.020 \times 0.018$ mm
Instrument	Bruker D8 Venture diffractometer
$N_{observed}$	7935
N_{par}	525
$R[F^2 > 2\alpha\ (F^2)]$	0.0482
$wR(F^2)$	0.1145

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