NOVEL STUDIES ON THE CHEMOENZYMATIC SYNTHESIS OF POLYCHLORINATED BICYCLIC SYSTEMS AND THE SYNTHESIS OF C2 AND C3 SYMMETRIC CHIRAL LIGANDS

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Approval of the Graduate School of Natural and Applied Sciences.

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ABSTRACT

NOVEL STUDIES ON THE CHEMOENZYMATIC SYNTHESIS OF POLYCHLORINATED BICYCLIC SYSTEMS AND THE SYNTHESIS OF C_2 AND C_3 SYMMETRIC CHIRAL LIGANDS

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Optically active polychlorinated bicyclic systems are important starting materials for the synthesis of complex target molecules. In the first part of the study, the syntheses of several racemic and *meso* hexachloronorbornene derivatives were executed successfully, starting from hexachlorocyclopentadiene. The enantio-enriched acetoxymethyl derivative (-)-**2** and the hemiester (-)-**6** were synthesized in high e.e. values by using several hydrolase type enzymes. The absolute configuration of (-)-**2** was determined by transforming it to the corresponding norbornene derivative (-)-**7** with known absolute configuration.

In the second part of the study, C_2 symmetric chiral ligand (-)-**11** and C_3 symmetric chiral triamide derivative (-)-**12** were synthesized in high chemical yields starting from L-proline. In connection to these studies, the syntheses of the monoamide derivative (-)-**14** and the C_2 symmetric diamide derivative (-)-**15** were achieved by using appropriate amounts of L-proline.

Keywords: Hydrolases, hexachloronorbornene derivatives, C_2 and C_3 symmetric compounds.

ÖZ

POLİKLORLU BİSİKLİK SİSTEMLERİN KEMOENZİMATİK SENTEZİ VE C_2 VE C_3 SİMETRİK KİRAL LİGANDLARIN SENTEZİ ÜZERİNE ÖZGÜN ÇALIŞMALAR

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Optikçe aktif poliklorlu bisiklik sistemler, karmaşık hedef moleküllerin sentezi için önemli başlangıç maddeleridir. Çalışmanın birinci bölümünde, birçok rasemik ve *mezo* hekzakloronorbornen türevinin sentezi, hekzaklorosiklopentadienden başlanarak başarılı bir şekilde gerçekleştirilmiştir. Enantiyomerce zenginleştirilmiş asetoksimetil türevi (-)-**2** ve hemiester (-)-**6** birçok hidrolaz tipi enzim kullanılarak yüksek e.e. değerleriyle sentezlenmiştir. (-)-**2**'nin mutlak konfigürasyonu, mutlak konfigürasyonu literatürde mevcut olan (-)-**7**'ye dönüştürülerek belirlenmiştir.

Çalışmanın ikinci bölümünde, C_2 simetrik kiral ligand (-)-**11** ve C_3 simetrik kiral triamit türevi (-)-**12**, L-prolinden başlanarak yüksek kimyasal verimlerle sentezlenmiştir. Bu çalışmalarla bağlantılı olarak, monoamit türevi (-)-**14** ve C_2 simetrik diamit türevi (-)-**15**'in sentezleri, uygun miktarda L-prolin kullanılarak başarılmıştır.

Anahtar kelimeler: Hidrolazlar, hekzakloronorbornen türevleri, C_2 ve C_3 simetrik bileşikler.

To my dear parents and brother...

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LIST OF ABBREVIATIONS

THF: Tetrahydrofurane

DMSO: Dimethyl sulfoxide

DE: Diisopropyl ether

MTBE: Methyl *t*-butyl ether

CH: Cyclohexane

VA: Vinyl acetate

PB: Phosphate buffer

CCL: *Candida cylindricae lipase*

PPL: Porcine pancreas lipase

HLE: Horse liver esterase

PLE: Pig liver esterase

CAL-A: *Candida antarctica* lipase, type A

CAL-B: *Candida antarctica* lipase, type B

DCC: Dicyclohexylcarboxydiimide

DMAP: Dimethylaminopyridine

LAH: Lithium aluminum hydride

CHAPTER 1

A GENERAL INTRODUCTION TO ASYMMETRIC SYNTHESIS

1.1. Asymmetry In the Universe

Symmetry and asymmetry relations play an important role in almost all physical sciences, especially in chemistry and physics. According to the definition of Hermann Weyl, an object is symmetrical, if one can subject it to an operation and it appears exactly the same after the operation as before [1]. In that sense, a physicist is generally concerned with the symmmetry relations of the laws of nature under operations like translations in space and time, rotations around an axis, etc [2]. For example, laws of nature are symmetric under translations in space and time, whereas time, itself, is asymmetric with respect to directionality and there exists an *arrow of time* due to the Second Law of Thermodynamics [3]. On the other hand, a chemist usually deals with the symmetry of molecules with respect to chirality, or left and right handedness. An object is said to be chiral if it cannot be superimposed on its mirror image.

In 1848, Louis Pasteur achieved to resolve the ammonium sodium tartrate into its enantiomers [4] and it can safely be stated that the huge developments that occurred in the field of asymmetric synthesis during the 20th century raised *on the shoulders* of Pasteur's discoveries [5]. Now, with the help of the recent discoveries, the universe seems to possess asymmetry with respect to chirality at all levels [6] confirming Pasteur's famous statement, "*L'universe est dissymetrique*".

At the lowest level of this asymmetry hierarchy, electrons are present with the ability to possess chirality. In 1957, Chien-Shiung Wu and her colleagues from

Columbia University discovered the abundance of left-handed electrons over the right-handed ones during the beta decay of radioactive nuclei [7]. A mirror image situation is present in the beta decay of antimatter where right-handed positrons are emitted this time. All of these discoveries indicate that nature chooses one of the mirror-image forms over the other and this situation turned out to arise from the different effects of weak neutral currents on the right and left handed electrons [8]. As a result, the natural law distinguishes these mirror-image electrons and the law, itself, is asymmetric. Moreover, during the beta decay antineutrinos are also emitted besides electrons and they were found to be in the right-handed form while in the antimatter decay, neutrinos are emitted in their left-handed form. Hence, these particles can be assumed to produce an even lower level in the asymmetry hierarchy.

The chiral asymmetry at the level of elementary particles, mentioned above, causes a chiral asymmetry at an upper level, at the level of atoms. Again, as a consequence of the weak neutral currents, all atoms appear to be chiral and an atomic gas was calculated to rotate the plane polarized light by 10^{-5} degree which was also supported by experiments [9].

At the upper level, there exists molecules where nature again seems to choose one of the mirror-image forms. In living systems, this situation is conspicuous since proteins of all organisms except some bacteria are made of L-amino acids while their nucleic acids contain exclusively D-sugars. However, the asymmetry at the molecular level isn't restricted to living systems; any chiral molecule appears to exist in a lower or upper energy state than that of its enantiomer again due to the weak neutral currents, mentioned above. This energy difference is generally so small and according to the calculations of Mason and Tranter [10], in a statistical energy distribution, L-amino acids should outnumber D-amino acids by one part in 10^{17}. Nevertheless, this surprising fact forces us to review the general concept of enantiomers; according to the current view of the enantiomers of a chiral molecule, they appear to be mirror-images of each other with an energy difference and hence, the *real* enantiomer of a chiral molecule

should be defined as its mirror-image which is made up of exactly the anti-matter of all atomic and sub-atomic particles so that both of them will be in the same energy state.

At a slightly upper level, which can be considered as an intermediate level, biomolecular helices like DNA and α-helix of a protein are present. These macromolecules can form right and left handed helices and in nature, α-helices of proteins and B form of DNA exist only in the right-handed helix forms. In the light of the studies of the last decades, the connection has been revealed between the homochiral nature of the amino acids and sugars with the homochiral helicity of these macromolecules [11].

Next comes the organismal level where the chiral asymmetries are encountered even in daily life. Our heart is on the left of our body, the two lobes of our brains have different functions, most people are right-handed (i.e. use their right hands in manual work), etc. Examples can be extended to other organisms with more interesting features where helical seashells or some ivy species can either spiral in a right or left-handed manner [6]. A bacterium called *Bacillus subtilis* was found to form right-handed spiral colonies which undergoes a transition to the left-handed form with an increase in temperature that indicates clearly the energy difference between the two forms [12].

Finally, at the upmost level, there exist the galaxies whose chirality was investigated and it has been shown that different galaxy subclasses revealed a significant asymmetry whereas the whole system was symmetric [13].

After demonstrating clearly these asymmetries and homochirality at all levels, there comes the crucial question: *It is only natural to ask, how did these chiral asymmetries at various levels originate? Are they all independent of each other or are they some how related? It is entirely possible that they are all related and it is possible to formulate a general theory of spontaneous generation and*

propagation of chiral asymmetry from one level to another. Clues began to emerge that suggest connections between different levels and a general theory has been formulated whose expansions will probably be seen in very near future [14].

1.2. The Importance of Asymmetric Synthesis

Asymmetric synthesis can be accepted to be one of the most rapidly grown area of organic chemistry in the second half of the 20th century and asymmetric catalysis has made the greatest contribution to this situation especially within the last two decades. This fact can also be realized easily through a glimpse on the portion of the articles on this topic in many organic chemistry magazines. So what makes the asymmetric synthesis of organic (and organometallic and inorganic as well) compounds that important?

The answer of this important question is somehow more complicated than the question itself and includes contributions from both fundamental and applied sciences. From a fundamental point of view, elucidation of the mechanisms of asymmetric reactions has helped scientists to approach the problem of the origin of homochirality of biomolecules in living systems from a different perspective [15]. The explanation of the origin of homochirality in living systems has a great importance in the field of biomolecular evolution and the developments in absolute asymmetric synthesis [16], non-linear effects in asymmetric catalysis [17] and asymmetric autocatalysis [18] where no or little enantiomeric excesses can be amplified remarkably have caused a great progress in this area.

However, the real indispensability of asymmetric synthesis arises in the field of applied chemistry, particularly in the total synthesis of many drugs, biologically active compounds, food additives, etc. Since many components of the human body (or any living organism) including all the enzymes, DNA, RNA, receptors, etc. are homochiral (exist in their enantiopure forms), their interactions with chiral compounds have diastereomeric character although all the physical

properties of enantiomers are the same in the absence of any chiral influence. This situation results in different effects of enantiomers like different taste, smell, pharmacological effect, etc. upon their interactions with a human body [19].

The most well-known examples for the enantiomers that have different tastes and odors are limonene and carvone. Limonene is a chiral terpene molecule, that exists as the *R*-enantiomer in nature which has an orange-lemon odor. Unlike the *R*-enantiomer, the *S*-enantiomer has a piney, turpentine-like odor.

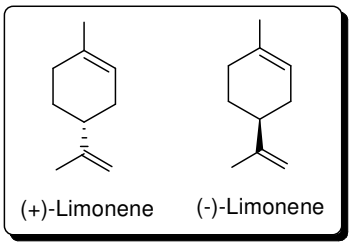


Figure 1. The structures of (+) and (-) Limonene

Limonene can be converted to carveol and carvone in plant metabolism and just like limonene, *R*- and *S*-carvone have different tastes: the former has the taste of spearmint, whereas the latter has the taste of caraway.

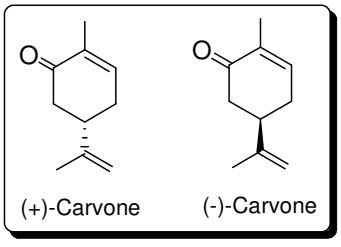


Figure 2. The structures of (+) and (-) Carvone

From a pharmacological point of view, the situation is very similar. More than half of all useful drugs appear to exist in enantiomeric forms and generally, one of these enantiomers is much more effective than its mirror image enantiomer, exhibiting a better fit to its receptor. For example, the *S* enantiomer of methacholine, a parasymphathomimetic drug, is over 250 times more potent than the *R* enantiomer. Penicillamine, ketamine, timolol and the well-known drug thalidomide, can be given as further examples to chiral drugs whose enantiomers exhibit different pharmacological effects (Figure 3). Furthermore, the more active enantiomer at any receptor type, may be less active at another type. Carvedilol, is such an example: Its *S* enantiomer is a potent beta receptor blocker, while the *R* enantiomer is 100-fold weaker at the beta receptor. However, both enantiomers are approximately equipotent as alpha receptor blockers [20].

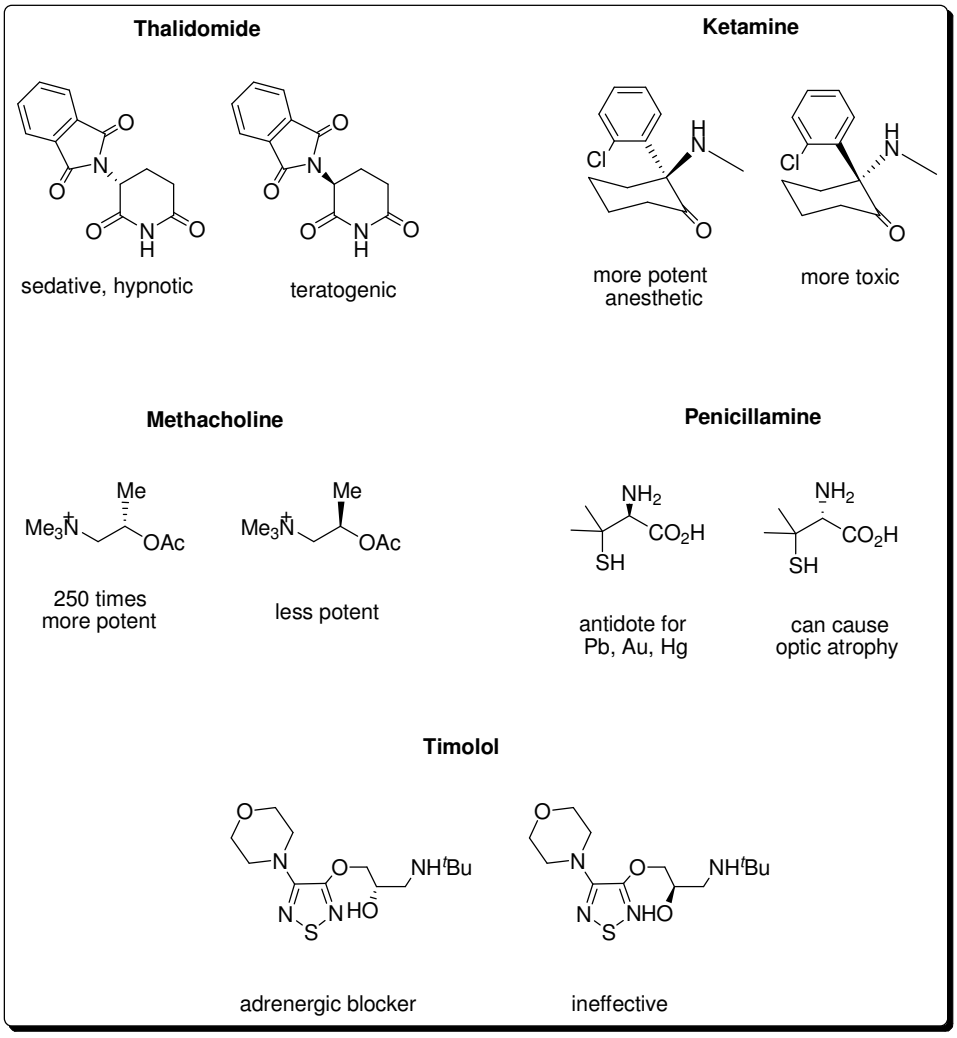


Figure 3. The structures and pharmacological effects of the enantiomers of some biologically active chiral molecules

CHAPTER 2

ENZYMATIC RESOLUTION AND DESYMMETRIZATION OF VARIOUS HEXACHLORONORBORNENE DERIVATIVES

2.1. Introduction

2.1.1. Enzymes in Organic Synthesis

2.1.1.1. General Properties of Enzymes

Enzymes are very efficient biocatalysts that catalyze most biological reactions *in vivo* and that can also act *in vitro* on both natural and unnatural substrates [21]. The variables that can be adjusted to increase the reaction rates such as temperature, pH and concentration are generally fixed within the biological system and despite all these constraints, enzymes can enhance the rate of reactions by factors of 10^8-10^{12} than those of the corresponding uncatalysed reactions [22].

The most important property of enzymes is that they work with great chemo-, regio- and stereoselectivity. Furthermore, they have a very broad substrate range, that is there is an enzyme-catalysed counterpart for any type of organic reaction except some rearrangement reactions and the Diels-Alder reaction [22]. Almost all enzymatic reactions within the body occur quantitatively and with great enantio- or diastereoselectivity, which means that among all possibilities, only one of the stereoisomers is formed at the end of the reaction.

This remarkable selectivity of enzymes can be explained by their complex 3-dimensional structures. The molecular recognition between the enzyme and its substrate occurs around a small region of the enzyme which is called its active

site. The electronic and steric properties of the enzyme's active site is rather important; the amino acids in this region can donate the active site with acidic, basic, nucleophilic or electrophilic properties and these properties play a crucial role in the reaction mechanism. In addition, most enzymes require coenzymes or cofactors in order to work effectively. Cofactors are metal cations like Mg^{2+}, Zn^{2+} and Fe^{2+} and make the active site of the enzyme electrophilic. Coenzymes are, however, organic molecules like NAD^{+} (Nicotinamide adenine dinucleotide), FAD (Flavin adenine dinucleotide) and vitamin B12 and they are responsible for the electron, atom or functional group exchange [23].

2.1.1.2. Models for the Enzyme-Substrate Interactions

In enzyme-catalyzed reactions, a reversible enzyme-substrate complex is formed first, either by covalent bonding or electrostatic, dipole-dipole interactions as well as hydrogen bonding. Two models were proposed to explain the high selectivity of enzymes: **Lock and key model** and **Induced-fit model**. Lock and key model was first proposed by Emil Fischer in 1894 [24] and according to this model, substrate binds to the enzyme just like how a key fits to its lock. This model depends on the assumption that enzymes have a rigid structure and when the shape of the substrate is exactly complementary to that of the enzyme's active site, the binding and hence, the reaction occurs. Although this model gained a wide acceptance in the first half of the 20^{th} century, a more expanded model was needed to be developed. This expanded model was the induced-fit model proposed by Koschland in 1968 [25]. It is based on the assumption that enzymes have more flexible structures than previously accepted. According to this model, when substrate interacts with the enzyme's active site, the enzyme changes its conformation such that it has a stronger binding to the substrate. This model is now widely accepted and able to explain several phenomena that cannot be explained by the lock and key model. The question of how enzymes can catalyze the transformations of unnatural compounds other than their own susbstrates is such a question.

2.1.1.3.Enzymes in Asymmetric Synthesis

The production of ethyl alcohol from the fermentation of sugar has been known for a long time. In 1948, Karklinsh and Skrastina developed a method to obtain citric acid from the microorganism *Aspergillus Niger* [26]. Despite these examples for the use of biocatalysts in chemical synthesis, it was only 15 years ago that enzymes gained a wide acceptance for their *in vitro* use in general organic synthesis. This is mostly due to the fact that they were started to be obtained more easily and increasingly from commercial sources, either in crude or purified forms. Moreover, recent developments in genetical engineering that allow to modify and modulate the enzyme activities by high performing methods like screening, recombination and oriented selection have played an important role in this situation [22].

Enzymes have several advantages and disadvantages when compared to ordinary catalysts in chemistry. Their first advantage is their effectiveness as catalysts which means that their turnover number is much higher than that of an ordinary catalyst. They are also elements of *green chemistry*; chemical catalysts generally require metal ions to function properly which cause a great environmental pollution. Their third advantage is that they function under mild conditions; generally in a pH range 5-8, temperature range 20-40 ^{o}C and at low salt concntrations which minimize possible side reactions. Finally, their biggest advantage is their enhanced stereoselectivity. All organisms except some bacteria, contain only L- amino acids and hence, due to the chiral nature of the active sites of enzymes, enzymatic reactions occur with % 100 enantioselectivity. This situation is the basic reason of the increase in the popularity of enzymes as biocatalysts in organic chemistry.

Despite all these benefits, enzymes possess some very important disadvantages, as well. First of all, since enzymes made up of D- amino acids aren't present in nature, only one of the enantiomer of a chiral molecule can be

synthesized by an enzyme-catalyzed reaction. Secondly, although most organic reactions are executed in organic solvents, water is the native environment of enzymes and this creates a controversy. However, it has been shown that enzymes can be stabilized even in pure organic solvents [27]. Another problem that is encountered with enzymes is their price. While some enzymes can be obtained in an inexpensive way, some of them are quite expensive due to the difficulties during their purifications. However, this problem has started to be overcome with the use of the enzyme immobilization technique. With this method, enzymes are bound to a polymeric material irreversibly and can be used more than once with little or no loss of activity.

In organic synthesis, hydrolases are the most widely used enzyme class with the portion of 65 %. The reason for this situation is that they are easily obtained, do nor require any cofactors or coenzymes to function and that they have a wide substrate range [23]. Within this enzyme class, proteases, esterases and lipases are the most common ones utilized in asymmetric synthesis and used in the hydrolysis and formation of ester and amide groups. Proteases hydrolyze peptide bonds in the body and enzymes such as α-chymotrypsin, papain, pepsin and trypsin belong to this subclass. On the other hand, esterases and lipases catalyze the hydrolysis of the ester groups of triglycerites and they are frequently used in asymmetric synthesis. The most commonly used esterases are PLE and HLE whereas PPL, *Candida sp. Lipases* (*Candida lipotyca,* CAL-A, CAL-B, CRL) and *Pseudomonas sp. Lipases* (*Pseudomonas fluorescens, Pseudomonas cepacia)* are typical lipases. Esterases have been found to be successful in the asymmetric hydrolysis reactions while lipases appear to be more effective in asymmetric acyl transfer reactions.

The early use of carboxylic acids as acyl donors in enzyme-catalyzed acyl transfer reactions was afterwards replaced by transacylation reactions since the stoichometric formation of water result in equilibrated reactions and poor control of the pH of the microaqueous environment. However, classical transesterification reactions generated new problems such that the alcohol generated as the side

product compete with the racemic alcohol to be resolved. Hence, enol esters like vinyl acetate and isopropenyl acetates are now the most widely used esters in lipase-catalysed transesterification reactions since the liberated enols as the side products isomerize immediately to either acetaldehyde or acetone, thus resulting in no competition. Alternatively, acid anhydrides have been occasionally employed in this type of reactions [22].

2.1.2. The Importance of Polychlorinated Norbornene Derivatives in Organic Synthesis

Synthesis and use of organochlorine compounds was very popular in 1950s for their function as pesticides and particularly as insecticides. DDT, DDE, aldrin, dieldrin, heptachlor, endosulfan and chlordane are the most well-known examples of these organochlorine compounds (Figure 4).

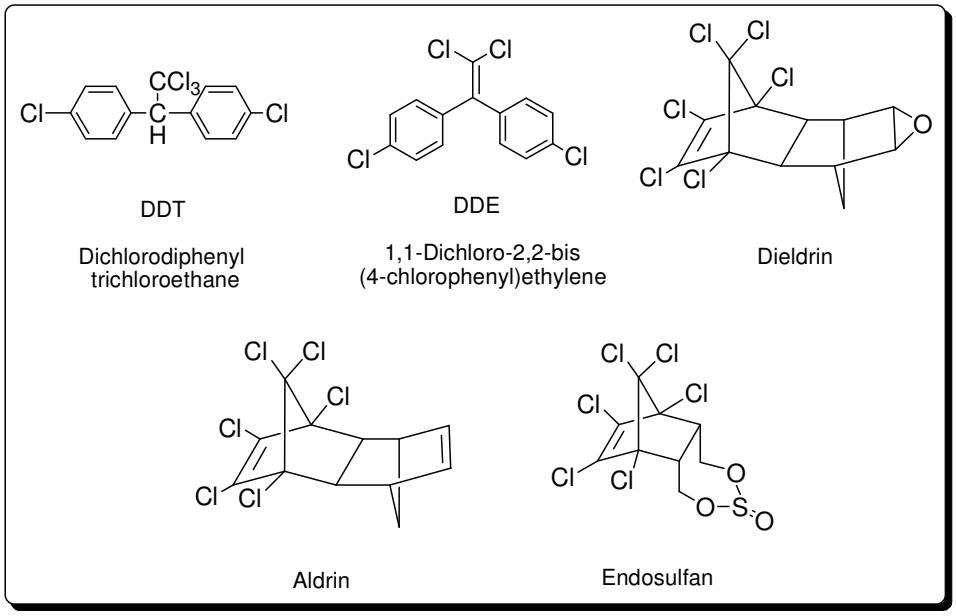


Figure 4. The structures of some well-known organochlorine pesticides

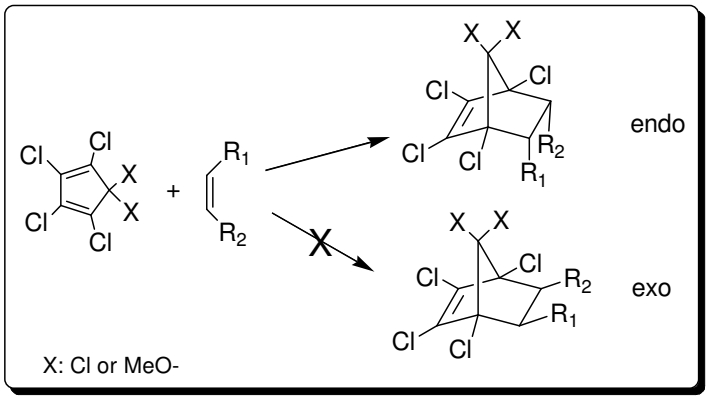
DDT was the first modern insecticide that was developed during the II. World War against mosquitoes spreading diseases like malaria and typhus. The Swiss chemist Paul Hermann Müller won the Nobel Prize in Physiology or Medicine in 1948 for "his discovery of the high efficiency of DDT as a contact poison against several arthropods''. However, after the publication of *Silent Spring* [28] book of Rachel Carson, an American biologist, in 1962 which argued the poisoning effects of DDT upon human health, debates started and the usage of DDT was banned in many countries after 1970s.

The common property of these organochlorine insecticides is that they are quite soluble in fat and organic solvents unlike water and they tend to accumulate in animal fat tissue. For example, DDE which isn't used as an insecticide is the breakdown product of DDT and it was encountered in human fat resulting from the presence of DDT.

After 1990s, organochlorine compounds, especially polychlorinated norbornene and norbornadiene derivatives started to attract organic chemists' attention once again, but this time due to their high functionality in organis synthesis [29]. These norbornene or norbornadiene derivatives can be obtained through the Diels-Alder reactions of hexachlorocyclopentadiene or 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene with various dienophiles. 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene, is prepared easily by the addition of KOH-MeOH [30] or NaOMe-MeOH [31] to hexachlorocyclopentadiene.

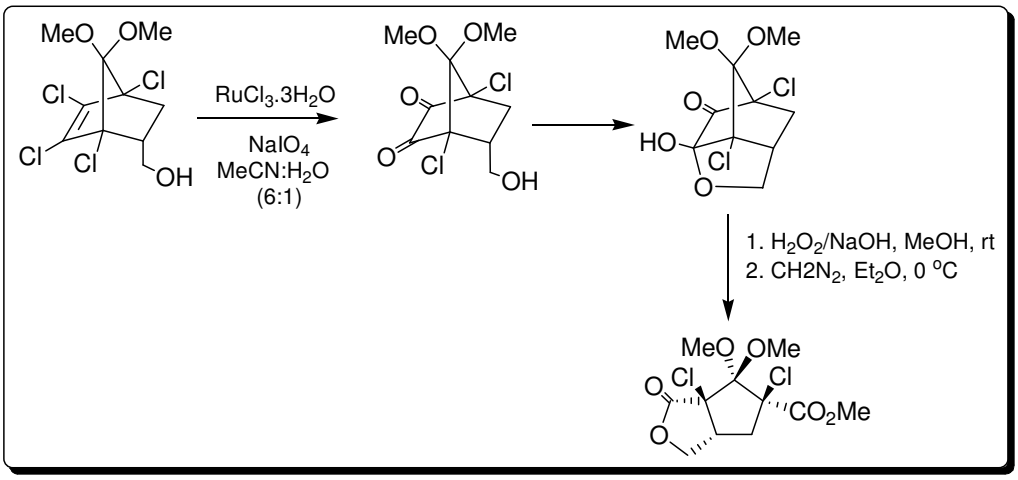
An important feature of these Diels-Alder reactions is that very high *endo* selectivity is obtained due to the steric repulsions of the Cl atoms or MeO- groups at the C-5 position (Scheme 1) [32]. Moreover, because of the great inductive effect its 6 Cl atoms, hexachlorocyclopentadiene has the ability to undergo *inverse* Diels-Alder reactions meaning that it can also react with electron rich dienophiles. Hence, these Diels-Alder reactions are executed generally at high temperatures, either under reflux in solvents with high boiling points or in sealed tubes with solvent-free conditions. The Diels-Alder reaction conditions of

hexachlorocyclopentadiene with several dienophiles have been investigated in detail [33].



Scheme 1. *Endo* selective synthesis of polychlorinated norbornene derivatives

Apart from the general aspects of the polychlorinated norbornene derivatives mentioned above, the vicinal olefinic chlorine atoms in the tetrachloro-dimethoxy norbornene derivatives can be utilized to form α-diketones with an efficient methodology employing catalytic $RuCl_3.3H_2O$ and stoichiometric $NaIO_4$ [34]. Subsequent to this functionalization, several important compound classes such as γ-lactone-fused cyclopentanoids (Scheme 2) [35], acyloins [36], highly symmetric, unnatural oxa-bridged compounds [37] and U-shaped polycyclic molecules with luminescence properties [38] can be obtained.

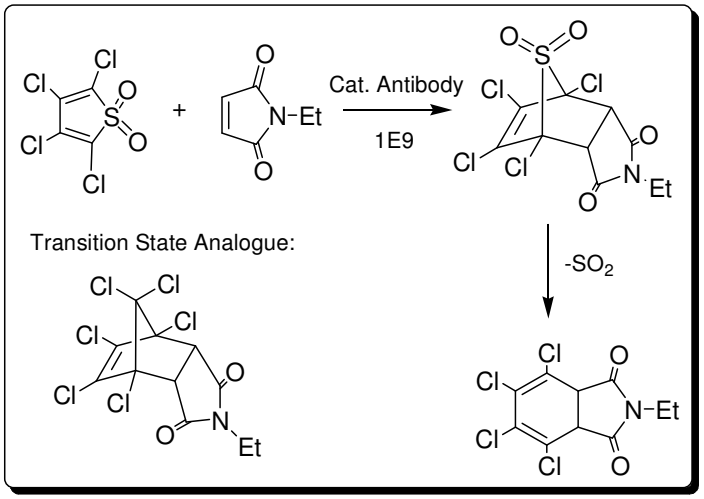


Scheme 2. The synthesis of a γ-lactone-fused cyclopentanoid

The vicinal halogen atoms are not the only groups that can be functionalized; in the case of starting with tetrabromo-dimethoxy norbornene derivatives, the bridge-head bromine atom at C-1 position can be utilized for the synthesis of *trans*-hydrindane ring systems [39]. Furthermore, the unwanted chlorine (and bromine as well) atoms can be eliminated by reductive dechlorination reactions in the presence of Na in liquid ammonia to afford ordinary norbornene and norbornadiene derivatives [40]. This approach has been utilized in many organic syntheses such as synthesis of five-membered rings [41] and in the Diels-Alder approach of Yadav et al. for the stereocontrolled construction of the C ring fragment of Taxol [42].

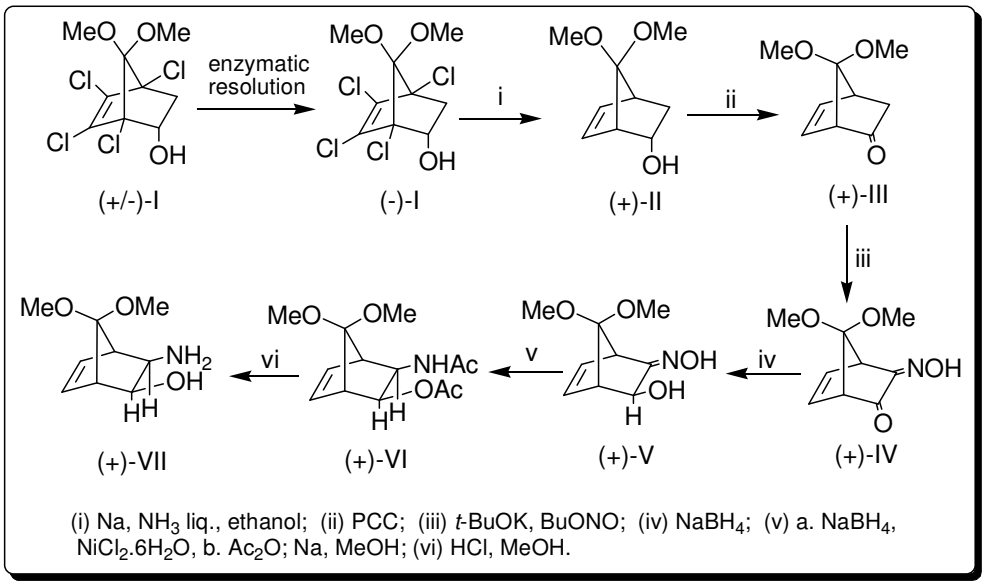
In another interesting research executed by Hilvert et al., a hexachloronorbornene derivative was used as a transition state analogue to raise the Diels-Alderase antibody 1E9 (Scheme 3) [43a]. Catalytic antibodies attracted great attention within the last two decades as biocatalysts [21] and have been proved to be able to catalyse a variety of chemical reactions like ester and amide hydrolysis [44], photochemical processes [45], sigmatropic rearrangement [46] and

β-elimination [47]. In this case, the Diels-Alderase antibody 1E9 was raised in the presence of the related hexachloronorbornene derivative and was found to catalyse the cycloaddition of tetrachlorothiophenedioxide and *N*-ethylmaleimide quite efficiently [43]. The optimization conditions of the catalytic antibody has been investigated in detail [43c].



Scheme 3. Use of the catalytic antibody 1E9 in the model Diels-Alder reaction

The asymmetric synthesis of these polychlorinated norbornene derivatives have further importance as they can easily be converted to biologically active molecule precursors [48] and chiral ligands [49]. A chiral hexachloronorbornene carboxylic acid derivative was found to be a suitable resolving agent of some optically active biological molecules in high performance liquid chromatography [50]. Scheme 4 is an example for the synthesis of a chiral ligand starting from a tetrachloro-dimethoxy norbornene derivative.



Scheme 4. The synthesis of a chiral ligand starting from a tetrachloro-dimethoxy norbornene derivative

2.1.3. The Aim of the Work

Despite the potential value of the optically active polychlorinated norbornene derivatives, described in the previous section, for the synthesis of complex target molecules, there are very few examples to their asymmetric synthesis in the literature [48, 49, 51]. Our group have previously reported the enzymatic resolution of **(±)-**2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hepta-2,5-diene, (±)-2-acetoxy methyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hepta-2,5-diene [52] and enzymatic desymmetrization of *meso*-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo [2.2.1] hepta-2,5-diene and *meso*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachloro bicyclo[2.2.1] hepta-2,5-diene [53]. The success of these studies prompted us to investigate the enzymatic asymmetric synthesis of various hexachloronorbornene derivatives. Norbornene derivatives possess more flexible structures than the corresponding norbornadiene derivatives and may exhibit different chemical

reactivities. The intramolecular cyclization reaction of the 2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene derivative to afford a tricyclic product [54] and the racemization of the hemiester (-)-**6** derivative which will be explained in Part 2.2.3.2. are such examples.

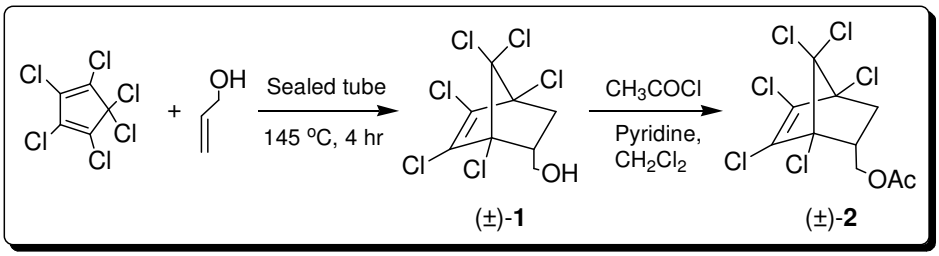
In this work, we describe the highly efficient resolution of (±)-2-*endo*-hydroxymethyl and acetoxymethyl substituted hexachloronorbornene derivatives [55] ((±)-**1**, (±)-**2)** and desymmetrization of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo [2.2.1] hept-5-ene (*meso*-**3**) using several lipases and esterases.

2.2. Results and Discussion

2.2.1. Synthesis of the Hexachloronorbornene Derivatives

(±)-2-*endo*-Hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**1** was synthesized through a Diels-Alder reaction by heating a mixture of hexachlorocyclopentadiene and allyl alcohol in a sealed tube. The reaction was carried out at 145 ^{o}C for 4 hours and the product was obtained in its pure *endo* form with 89 % chemical yield.

The racemic product (±)-**1** was subsequently acetylated with acetyl chloride in the presence of pyridine to afford the acetoxy product, (±)-2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**2**, in 81 % chemical yield (Scheme 5).



Scheme 5. The synthesis of (±)-**1** and (±)-**2**

Structure elucidations of the compounds **1** and **2** were done by ^{1}H-NMR and ^{13}C-NMR analysis.

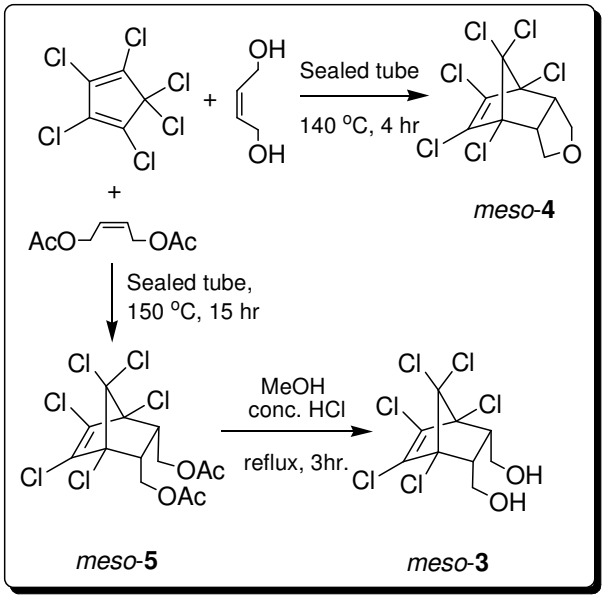
The ^{1}H-NMR spectrum of **1** shows a triplet at 1.43 ppm belonging to the O**H** proton. The proton at the *endo* position, H_c shows a doublet of doublet at 1.86 ppm, wheras the proton at the *exo* position, H_b shows a doublet of doublet at 2.59 ppm. H_a proton which is splitted with the four neighbouring protons gives a multiplet between 2.96-3.03 ppm. The diastereotopic C**H$_2$**O protons show two multiplets between 3.39-3.45 and 3.73-3.79 ppm (Figure A1). In the ^{13}C-NMR spectrum, there are 8 different signals confirming the structure of **1** (Figure A2).

In the ^{1}H-NMR spectrum of **2** the singlet at 1.99 ppm belongs to the methyl protons of the ester functionality. H_c proton at the *endo* position shows a doublet of doublet at 1.86 ppm and H_b proton at the *exo* position gives a doublet of doublet at 2.60 ppm. The multiplet between 3.00-3.13 ppm belongs to the H_a proton. Diastereotopic C**H$_2$**O protons give rise to two doublet of doublets at 3.92 and 4.08 ppm (Figure A3). In the ^{13}C-NMR spectrum, there are two additional signals when compared to that of **1**, belonging to the ester group. One of these signals appears at 170.8 ppm corresponding to the carbonyl carbon and the **C**H$_3$ carbon of the ester group gives a signal at 21.1 ppm (Figure A4).

In order to accomplish the synthesis of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene *meso*-**3**, a

mixture of hexachlorocyclopentadiene and cis-2-buten-1,4-diol was heated in a sealed tube. However, the hexachloro-tetrahydrofuran derivative *meso*-**4** was unexpectedly obtained, probably due to the elimination of water from the diol derivative at high temperature. The formation of *meso*-**4** rather than the diol derivative *meso*-**3** was confirmed by the absence of OH signal in the ^{1}H-NMR spectrum, absence of the broad OH band in IR spectrum and from their elemental analysis.

Hence, an indirect approach was followed for the synthesis of *meso*-**3** and *meso*-**5** (Scheme 6). First, bis(acetoxymethyl) derivative, *meso*-**5** was synthesized in its pure *endo* form by heating a mixture of hexachlorocyclopentadiene and cis-2-buten-1,4-diol diacetate in a sealed tube. The reaction was carried out at 150 ^{o}C for 15 hours and the product was obtained in 70 % yield. *Meso*-**5** was subsequently subjected to hydrolysis in methanol with catalytic amount of concentrated HCl to afford the bis(hydroxymethyl) derivative, *meso*-**3** in 95 % yield.



Scheme 6. The synthesis of *meso*-**3**, *meso*-**4** and *meso*-**5**

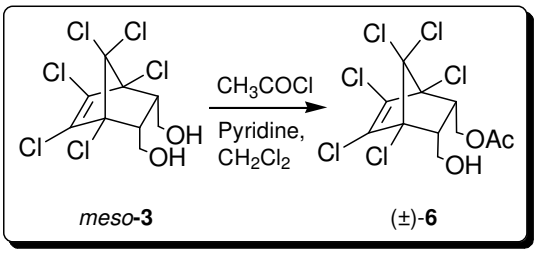
Structure elucidations of the compounds **3, 4** and **5** were done by ^{1}H-NMR and ^{13}C-NMR analysis.

The structure of *meso*-**3** is quite symmetrical bearing only four different protons. Its ^{1}H-NMR spectrum shows a singlet belonging to O**H** groups at 3.09 ppm.The multiplet between 3.23-3.29 ppm belongs to the *exo* protons, H_a. H_b and H_c give a triplet and a doublet at 3.68 and 4.02 ppm, respectively (Figure A5). The ^{13}C-NMR was taken in a solvent mixture d^6-DMSO:$CDCl_3$ = 2:1, because of the low solubility of the diol in pure $CDCl_3$. There are only 5 signals in the ^{13}C-NMR spectrum due to the symmetry plane of the molecule (Figure A6).

The ^{1}H-NMR and ^{13}C-NMR spectra of *meso*-**4** are very similar to those of *meso*-**3** except the O**H** signal which is apparently absent in the ^{1}H-NMR spectrum (Figures A7 and A8).

The ^{1}H-NMR spectrum of *meso*-**5** shows a singlet at 2.06 ppm belonging to the C$\mathbf{H_3}$ protons of the ester group. The multiplet between 3.24-3.30 ppm belongs to the H_a protons at the *exo* position. The diastereomeric H_b and H_c protons (C$\mathbf{H_2}$O) show two doublet of doublets at 4.17 and 4.31 ppm (Figure A9). In the ^{13}C-NMR spectrum, the signals at 20.7 ppm and 170.1 ppm indicate the presence of the ester functionality (Figure A10).

Finally, the bis(hydroxymethyl) derivative *meso*-**3** was acetylated with acetyl chloride in the presence of pyridine to afford (±)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**6** (Scheme 7). The purpose of synthesizing this racemic compound was both to determine the HPLC conditions for the determination of the enantiomeric excess and also to use it as a reference during the enzymatic reactions.



Scheme 7. The synthesis of (±)-**6**

Structure elucidation of the compound **6** was done by ^{1}H-NMR and ^{13}C-NMR analysis.

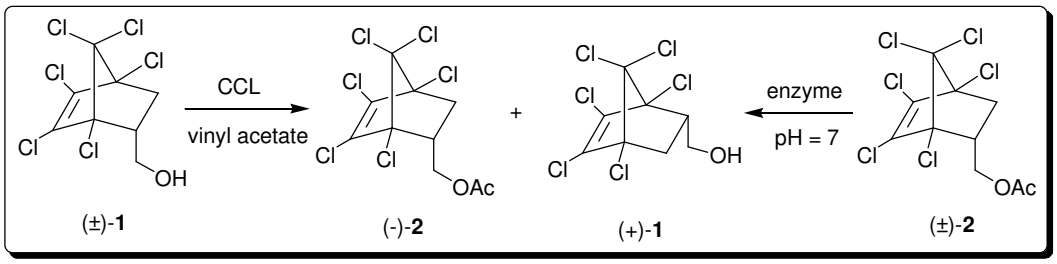
From both NMR spectra, it's apparently seen that the symmetry present in **3**, **4** and **5** has been broken in **6**. Its ^{1}H-NMR spectrum shows a singlet at 2.07 ppm belonging to the O**H** proton and a singlet at 2.09 ppm belonging to the C**H$_3$** protons. H_2 and H_3 protons show multiplets between 3.14-3.20 and 3.26-3.30 ppm. The multiplets between 3.64-3.70 and 3.93-3.95 ppm and the doublet of doublets at 4.27 and 4.37 ppm belong to four H_8 and H_9 protons (Figure A11). From the ^{13}C-NMR spectrum, the broken symmetry and the presence of an ester group can be easily understood (Figure A12).

2.2.2. Enzymatic Resolution of (±)-2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene and (±)-2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachloro bicyclo [2.2.1]hept-5-ene

2.2.2.1. Enzymatic Studies for the Resolution of (±)-1 and (±)-2

For the enantiomeric resolutions of these compunds, enzymatic resolution approach was followed and several hydrolases were tried during the screening tests. In order to achieve the enzymatic resolution of the hydroxymethyl derivative (±)-**1**, enzymatic acetylation process was performed and vinyl acetate was used as

the acetyl source, which is the most common reagent used for this purpose. On the other hand, for the resolution of the acetoxymethyl derivative (±)-**2**, enzymatic hydrolysis was performed in pH=7 phosphate buffer and prior to the enzymatic studies, (±)-**2** was proven to remain intact (i.e. it doesn't auto-hydrolyze) in pH=7 buffer in the absence of any enzyme. The enzymatic approach is summarized in Scheme 8.



Scheme 8. General strategy for the enzymatic resolution of (±)-**1** and (±)-**2**

The enzymatic acetyl transfer reaction to (±)-**1** was performed with catalytic amount of CCL (substrate:enzyme = 1:0.02) and vinyl acetate. No co-solvent was used during the reaction because of the high solubility of (±)-**1** in vinyl acetate. The reaction was followed by TLC monitoring and it was stopped at 50 % conversion. (-)-**2** was isolated with 97 % ee in 39 % chemical yield. All ee determinations during this study was done over the acetoxymethyl derivative **2**, since both the hydroxymethyl derivative **1** wasn't effectively resolved by HPLC and also the yields of this derivative were relatively low.

Alternatively, the acetoxymethyl derivative (±)-**2** was subjected to enzyme catalyzed hydrolysis in pH=7 buffer with the hydrolase type enzymes PLE, HLE and PPL. The results are shown in Table 1. All the enzymes gave quite successful results, but among them PLE and HLE appeared to be the most efficient in terms of enantioselectivity and the reaction durations. On the other hand, PPL showed the lowest enantioselectivity among all and longer duration when compared to PLE

and HLE. All of the enzymes including CCL, afforded the same configured acetoxymethyl derivative (-)-**2**.

Table 1. Results of the enzymatic studies for the resolution (±)-**1** and (±)-**2**

Substrate	Enzyme	Substrate:Enzyme Ratio (w/w)	Time (h)	Ester	Yield (%)[a]	$[\alpha]_D^{20}$	E.e. (%)
(±)-**1**	CCL	1:0.02	168	(-)-**2**	39	-1.5	97
(±)-**2**	PLE	500 mg:100μL	23	(-)-**2**	49	-1.5	98
(±)-**2**	HLE	1:0.08	20	(-)-**2**	40	-1.5	98
(±)-**2**	PPL	1:0.08	100	(-)-**2**	47	-1.4	94

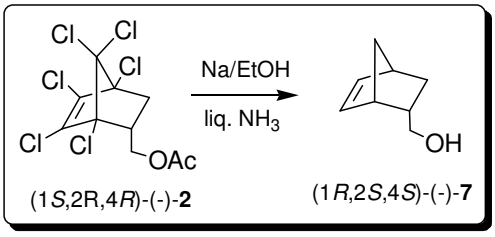
[a] Yields (%) are given as the isolated esters.

The enantiomeric excess values of the enantio-enriched (-)-**2** derivatives were determined by HPLC with the chiral column OD-H. The HPLC chromatograms of racemic (±)-**2** and enantio-enriched (-)-**2** are shown in Figure A13 and A14.

2.2.2.2. Determination of the Absolute Configuration of (-)-2

Single-crystal X-ray diffractometry is the most powerful and reliable method for the determination of the absolute configuration of chiral compounds but it still poses some problems since the product must be solid and be well crystallized. On the other hand, converting an enantiopure (or enantio-enriched) compound without affecting the stereogenic centers to another one with known absolute configuration and then comparing their optical rotation values, is still widely used for the absolute configuration determination of chiral compounds.

For the absolute configuration determination of (-)-**2**, it was transformed into the corresponding 2-*endo*-hydroxymethyl-bicyclo[2.2.1]hept-5-ene **7** derivative via the dechlorination reaction with Na in liquid NH_3 (Scheme 9) [40]. During the reductive dechlorination, acetyl group was hydrolyzed to the corresponding alcohol. The absolute configuration of compound (-)-**2** was assigned as (1*S*,2*R*,4*R*) by comparison of its specific rotation with the previously determined value for (1*R*,2*S*,4*S*)-(-)-2-*endo*-hydroxymethyl-bicyclo[2.2.1]hept-5-ene **7** [56].

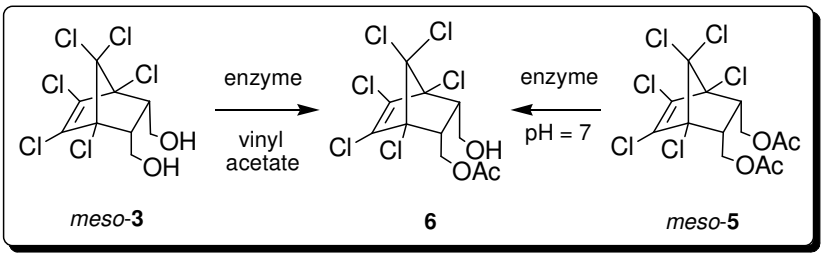


Scheme 9. Reductive dechlorination of (-)-**2**

2.2.3. Enzymatic Desymmetrization of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene

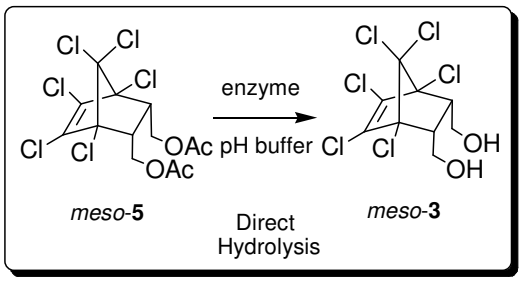
2.2.3.1. Enzymatic Studies for the Desymmetrization of *meso*-3 and *meso*-5

The same enzymatic approach mentioned in 2.2.2. was followed for the desymmetrization of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachloro bicyclo[2.2.1] hept-5-ene *meso*-**3** and *meso*-2,3-*endo*-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene *meso*-**5** and it's summarized in Scheme 10.



Scheme 10. General strategy for the enzymatic desymmetrization of *meso*-**3** and *meso*-**5**

Screening reactions were first executed with various hydrolases and among the hydrolases studied, CCL and CAL-B appeared to be suitable for the acetyl transfer reactions to *meso*-**3,** whereas all the esterases appeared to perform the direct hydrolysis of *meso*-**5** to *meso*-**3**, surprisingly (Scheme 11). The results are shown in Table 2.



Scheme 11. Enzymatic hydrolysis of *meso*-**5**

Table 2. Results of the enzymatic hydrolysis studies of *meso*-**5**

Enzyme	Substrate:Enzyme Ratio (w/w)	Time (h)	Solvent	Yield (%)[a]
PLE	150 mg:50μL	110	PB	-
PPL	1:0.33	360	PB	-
HLE	1:1	215	PB	-

[a] The hemiester, **7** couldn't be obtained in any attempts even in trace amounts. Either partial or full hydrolysis to *meso*-**3** was observed in all cases.

At this point, we concentrated our attention on the acetyl transfer reaction to *meso*-**3** and investigated several conditions for the optimization of the enantioselectivity. Since the reactions performed by using CAL-A, PS Amano and PPL gave either very slow or no conversion during the screening tests, CCL and CAL-B were used for the optimization studies. The variables that can be adjusted during the enzymatic reactions are temperature, pH, enzyme type, enzyme-substrate ratio, the acetyl source (in the case of acetyl transfer reactions) and the solvent. During our studies, temperature (25 ^{o}C), enzyme type (CCL and CAL-B) and the acetylating agent (vinyl acetate) were kept constant, while the effect of enzyme-substrate ratio and the co-solvent were investigated.

Because of the low-solubility of *meso*-**3** in vinyl acetate, various co-solvents such as THF, MTBE, diisopropyl ether and cyclohexane were used with the knowledge that lipases are stable in organic solvents [27] and the effect of the solvent polarity on the enzyme efficiency was examined.

When THF and MTBE were used as the co-solvents and CCL as the lipase in 1:0.25 substrate:enzyme ratio (w/w) the hemiester (-)-**6** was obtained in 49 % and 53 % enantiomeric excess, respectively (Table 3, entries 1,2). However, in the latter one, the reaction proceeded in a shorter duration (19 hours) and greater chemical yield (96%). When the substrate:enzyme ratio was decreased to 1:0.1 in MTBE, an increase in the ee value to 62 % was observed (Table 3, entry 3).

Since both THF and MTBE are relatively polar solvents, we wanted to examine how a decrease in polarity would affect the enantioselectivity. Cyclohexane was used as the non-polar component of the solvent and an increase in the enantioselectivity was observed up to 76 % ee (Table 3, entries 4,5). Finally, diisopropyl ether was used as the co-solvent with CCL in 1:0.1 substrate:enzyme ratio and the hemiester (-)-**6** was obtained in 81 % ee and in 87 % chemical yield. This is the maximum ee value that could be reached when CCL was used (Table 3, entry 6).

Table 3. Results of the studies of CCL catalyzed desymmetrization of *meso*-**3**

Entry	Substrate : Enzyme Ratio (w/w)	Solvent	Time (h)	Hemi-ester	Yield (%)	$[\alpha]_D^{25}$	E.e (%)
1	1:0.25	THF +VA	72	(-)-**6**	83	- 5.3	49
2	1:0.25	MTBE +VA	19	(-)-**6**	96	- 5.6	53
3	1:0.1	MTBE+VA	240	(-)-**6**	82	- 6.5	62
4	1:0.1	MTBE+CH+VA	47	(-)-**6**	91	- 7.6	76
5	1:0.05	MTBE+CH+VA	118	(-)-**6**	89	- 7.0	74
6	1:0.1	DE+VA	56	(-)-**6**	87	- 7.8	81

The above results, apparently indicate that the enzyme efficiency increased in non-polar medium in terms of enantioselectivity. As a result, reactions in which CAL-B was used as the lipase, were executed in these co-solvents (Table 4, entries 1,2 and 3). Among these, the best result was achieved when CAL-B was used in 1:0.2 substrate:enzyme ratio in diisopropyl ether and the product was obtained in 44 hours with 84 % ee and 86 chemical yield (Table 4, entry 2). Moreover, it should be stated that all of the conditions with both enzymes afforded the same configured hemiester, (-)-**6**.

Table 4. Results of the studies executed with other enzymes for the desymmetrization of *meso*-**3**

Entry	Enzyme	Substrate: Enzyme Ratio	Solvent	Time (h)	Hemi Ester	Yield (%)	$[\alpha]_D^{25}$	E.e. (%)
1	CAL-B	1:0.2	MTBE+ CH+ VA	56	(-)-**6**	98	- 8.5	83
2	CAL-B	1:0.2	DE+VA	44	(-)-**6**	86	- 8.8	84
3	CAL-B	1:0.05	DE+VA	120	(-)-**6**	75	- 7.7	79
4[a]	PS Amano	1:0.5	MTBE+ VA	216	-	-	-	-
5[a]	PPL	1:1	MTBE+ CH+ VA	430	-	-	-	-
6[a]	CAL-A	1:0.13	DE+VA	192	-	-	-	-

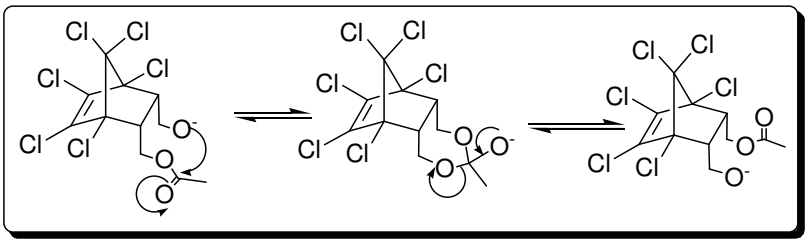
[a]Either no or very slow conversion were obtained in these cases.

The enantiomeric excess values of the enantio-enriched (-)-**6** derivatives were determined by HPLC with the chiral column OJ-H. The HPLC chromatograms of racemic (±)-**6** and enantio-enriched (-)-**6** are shown in Figure A15 and A16.

2.2.3.2. Racemization Studies of (-)-2-endo-acetoxymethyl-3-endo-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (-)-6

In the literature, such kind of hemiesters bearing an alcohol and and ester group are known to undergo racemization via intramolecular acetyl transfer [57]. Thus, we decided to investigate whether (-)-**6** would racemize in basic medium or not. LiH was added to a solution of (-)-**6** of 50 % ee in THF and after 2 hours of

stirring at room temperature, the mixture was neutralized with NH_4Cl. The resulting hemiester was found to be completely racemized which was confirmed both by HPLC analysis and its optical rotation value. The reason of using LiH as the base, was to maximize the solubility of the resulting alkoxide salt. The mechanism of the racemization process is depicted in Scheme 12.

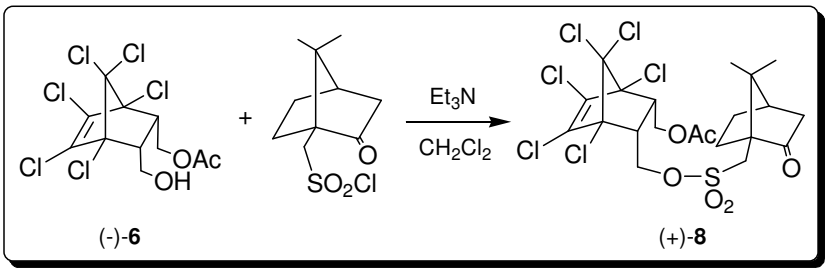


Scheme 12. Mechanism of the racemization of (-)-**6** in basic medium

Two important consequences can be deduced from this observation. First of all, the enantioenriched hemiester shouldn't be kept in basic or acidic media in order to avoid racemization. The more important implication is that this racemization process maybe the source of the relative low enantioselectivity (upto 84 % ee) throughout this study and also the direct hydrolysis of the bis(acetoxymethyl) derivative *meso*-**5** to the bis(hydroxymethyl) derivative *meso*-**3**.

2.2.3.3. Absolute Configuration Determination Studies

In order to determine the absolute configuration of (-)-**6** with the single-crystal X-ray diffractometry method, (-)-**6** of 83 % ee was reacted with (1*R*)-(+)-camphor-10-sulphonyl chloride in the presence of triethylamine to afford the sulphonate ester, (+)-**8** (Scheme 13).



Scheme 13. The synthesis of the sulphonate ester (+)-**8**

The major diastereomeric product, (+)-**8** was purified and characterized by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H-NMR spectrum, the two singlets at 0.88 and 1.10 ppm belong to the characteristic C**H**$_3$ protons of the camphor structure. The C**H**$_3$ protons of the ester group give rise to a singlet at 2.09 ppm (Figure A17). In the ^{13}C-NMR, the signals at 130.2 and 132.1 ppm correspond to the olefinic carbons. The carbonyl carbon of the ester group at 170.2 ppm and the ketone carbon at 214.2 ppm indicate unambiguously the correct structure (Figure A18). However, altough several crystallization techniques were tried, the product couldn't be crystallized and remained as an oil.

2.3. Conclusion and Perspectives

Polychlorinated norbornene derivatives are important starting materials for the synthesis of complex target molecules, including biologically active natural and aesthetically pleasing unnatural products.

In this study, various hydroxymethyl and acetoxymethyl substituted hexachloronorbornene derivatives were synthesized in good yields starting from commercially available hexachlorocyclopentadiene.

In the first part of the study, **(±)-**2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene and **(±)-**2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hept-5-ene were subjected to either enzymatic acetyl trasfer or hydrolysis with commercially available and inexpensive hydrolases CCL, PPL, HLE and PLE in catalytic amounts. All the enzymes afforded the the same configured acetoxymethyl derivative (-)-**2** with ees of 94-98 %. PLE and HLE gave the best results, among all, in terms of both enantioselectivity, reaction durations and chemical yields.

The absolute configuration of the enantioenriched product (-)-**2** was assigned as (1*S*,2*R*,4*R*) by comparison of its spesific rotation with the previously determined value for (1*R*,2*S*,4*S*)-(-)-2-*endo*-hydroxymethyl-bicyclo[2.2.1]hept-5-ene (-)-**7**. An unexpected deacetylation was observed during the reductive dechlorination reaction.

The same method was applied for the desymmetrization of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene and *meso*-2,3-*endo*-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo [2.2.1] hept-5-ene. Surprisingly, the bis(acetoxymethyl) derivative was observed to hydrolyze directly to the bis(hydroxymethyl) derivative bypassing the hemiester **6**. During the studies for the desymmetrization of the bis(hydroxymethyl) derivative by enzymatic acetyl transfer, the enantioenriched product (-)-**6** was obtained in good to excellent chemical yields (75-98 %) and in average to good ee values (50-84 %). Among all enzymes, CAL-B gave the best result affording the hemiester (-)-**6** in 84 % ee with 86 % chemical yield. In all studies, the same configured hemiester was obtained.

(-)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene was found to racemize in basic medium at room temperature in 2 hours via an intramolecular acetyl transfer mechanism. However, this situation which can be considered as a disadvantage, can be utilized in a

reverse, positive manner in other asymmetric transformations like dynamic kinetic resolution, etc.

For the absolute configuration determination of the (-)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene, its sulphonate ester was synthesized by its reaction with (1*R*)-(+)-camphor-10-sulphonyl chloride. However, attempts to produce its single-crystals failed.

All the enantioenriched products, synthesized in this part, can be used in the asymmetric synthesis of more complex molecules. For example, the $RuCl_3$ catalyzed oxidation procedure can be applied to convert the dichloroalkene moiety to α-diketone functionality. Furthermore, the possible danger of the deacetylation of the (-)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene (-)-**6** product during the dechlorination reaction can be surmounted by converting the acetoxy group to other functional groups by a simple nucleophilic substitution reaction with strong, non-basic nucleophiles. In this way, several chiral ligands with different heteroatoms can be synthesized.

2.4. Experimental

Determination of the structures and physical properties of the compunds synthesized in this study was done by the instruments mentioned below.

Nuclear magnetic resonans (^1H and ^{13}C NMR) spectra were recorded on Bruker Spectrospin Avance DPX 400 spectrometer in either $CDCl_3$ or d^6-DMSO. Chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard. Spin multiplicities are mentioned as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet).

Infrared spectra were obtained from KBr pellets on a Varian 1000 FT-IR spectrophotometer and were reported in cm^{-1}. Band intensities are indicated as: vs (very strong), s (strong), m (medium), w (weak) and br (broad).

Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III automatic polarimeter at 20 ^{o}C or 25 ^{o}C.

Mass spectra were recorded on a Varian MAT 212.

Melting points are uncorrected.

Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates. The relative proportion of solvents are in volume:volume ratio used in column chromatography as eluent.

Separations were carried out on Chiralcel OD-H or OJ-H analytical column (250 x 4.60 mm) with hexane/2-propanol as eluent. The conditions are specified in each case.

PLE (pig liver esterase) was purchased from Sigma as a suspension in ammonium sulfate solution (3.2 mol/L). CCL (lipase, Type VII, from *Candida rugosa*), HLE (horse liver acetone powder), PPL (lipase, Type II, from porcine pancreas), PS Amano (Amano Lipase PS-C II, immobilized on ceramic), CAL-A (Lipase A *Candida antarctica*, recombinant from *Aspergillus oryzae,* CAL-B (Lipase B *Candida antarctica*, Novozyme 435) were purchased from Aldrich.

Solvents were either in technical or high grade and when necessary they were dried with appropriate drying agents and purified by distillation. THF was distilled over benzophenone and metallic sodium, whereas DCM was distilled over phosphorus pentoxide. Pyridine was refluxed over KOH pellets for two hours prior to distillation and distilled over KOH.

2.4.1. Synthesis of (±)-2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene, (±)-1

A mixture of allyl alcohol (1.74 g, 30 mmol) and hexachlorocyclopentadiene (2.73 g, 10 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 145 ^{o}C for 4 h. The crude product was purified by flash column chromatography to afford (**±**) **1** (EtOAc:Hexane, 1:2) (2.94 g, 89% yield). Mp: 159-160 ^{o}C. ^{1}H NMR: δ 1.43 (t, 1H, OH, *J* = 5.0 Hz), 1.86 (dd, 1H, *endo* CH_2, *J*= 4.1 and 12.6 Hz), 2.59 (dd, 1H, *exo* CH_2, *J*= 8.8 Hz and 12.6 Hz), 2.96-3.03 (m, 1H, CH), 3.39-3.45 (m, 1H, CH_2O), 3.73-3.79 (m, 1H, CH_2O). ^{13}C NMR: δ 38.7 (C_3), 49.4 (C_2), 62.5 (C_8), 79.1 (C_4), 81.4 (C_1), 103.0 (C_7), 130.2 (C_5), 132.4 (C_6). IR (neat): 1599 (s), 3345 (br) cm^{-1}. HRMS: Calcd for $C_8H_6Cl_6O$ $(M+H)^+$, 328.8628. Found 328.8645.

2.4.2. Synthesis of (±)-2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene, (±)-2

To a stirred solution of (±)-**1** (1.50 g, 4.5 mmol) in CH_2Cl_2 (25 mL), dry prydine (0.72 g, 9.1 mmol) was added at 0 ^{o}C and the mixture was stirred for 30 min under inert atmosphere. Acetyl chloride (0.54 g, 6.8 mmol) was added dropwise. The resultant mixture was stirred for 17 h at rt. The organic phase was extracted with 0.1 N HCl (3x50 mL), saturated $NaHCO_3$ (3x50 mL) and brine (2x50 mL), dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford **(±)-2** (EtOAC:Hexane, 1:2) (1.38 g, 81%). ^{1}H NMR: δ 1.86 (dd, 1H, *endo* CH_2, *J*=4.2 and 12.6 Hz), 1.99 (s, 3H, CH_3), 2.60 (dd, 1H, *exo* CH_2, *J*= 8.9 and 12.6 Hz), 3.00-3.13 (m, 1H, CH), 3.92 (dd, 1H, CH_2O, *J*=6.7 and 11.7 Hz), 4.08 (dd, 1H, CH_2O, *J*=5.8 and 11.7 Hz). ^{13}C NMR: δ 21.1 (C_{10}), 38.6 (C_3), 46.4 (C_2), 62.7 (C_8), 79.0 (C_4), 81.3 (C_1), 102.9 (C_7), 130.5 (C_5), 132.3 (C_6), 170.8 (C_9). IR(neat): 1745 (s), 1585 (s) cm^{-1}. HRMS: Calcd for $C_{10}H_8Cl_6O_2$ $(M+H)^+$, 370.8734. Found 370.8717.

2.4.3 CCL Acetylation of (±)-2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo [2.2.1]hept-5-ene, (±)-1

To a stirred solution of 500 mg (±)-**1** in 5 mL vinyl acetate, 10 mg CCL was added in one portion and the reaction mixture was stirred at 20 ^{o}C (TLC monitoring). The reaction mixture was filtered and vinyl acetate was evaporated under reduced pressure. The products (1*R*-2*S*-4*S*)-(+)-**1** and (1*S*-2*R*-4*R*)-(−)-**2** were purified by flash column chromatography (EtOAc:Hexane, 1:2). (1*R*-2*S*-4*S*)-(+)-**1**: (0.15 g, 30% yield). (1*S*-2*R*-4*R*)-(−)-**2: (**0.22 g, 39% yield). HPLC-analysis of (−)-**2**: Chiralcel OD-H at room temperature, *n*- hexane/2-propanol = 98:2, 1.0 mL/min, 254 nm, t_1 = 6.3 min (minor), t_2 = 6.8 min (major), $[\alpha]_D^{20}$= -1.5 (c 1.53, MeOH).

2.4.4 General Procedure for enzymatic hydrolysis of (±)-2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene, (±)-2

To a stirred solution of 500 mg **(±)-2** in 50 mL pH 7.00 phosphate buffer, 40 mg HLE (PPL or 100 μL PLE) was added in one portion and the reaction mixture was stirred at 20 ^{o}C in a pH stat unit. The conversion was monitored by TLC. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The products (1*R*-2*S*-4*S*)-(+)-**1** and (1*S*-2*R*-4*R*)-(−)-**2** were purified by flash column chromatography (EtOAc:Hexane, 1:2).

PLE hydrolysis products: (1*R*-2*S*-4*S*)-(+)-**1**: (98 mg, 22% yield). (1*S*-2*R*-4*R*)-(−)-**2: (**0.25 g, 49% yield). $[\alpha]_D^{20}$= -1.5 (c 1.53, MeOH).

HLE hydrolysis products: (1*R*-2*S*-4*S*)-(+)-**1**: (0.11 g, 25% yield). (1*S*-2*R*-4*R*)-(−)-**2: (**0.20 g, 40% yield). $[\alpha]_D^{20}$= -1.5 (c 0.97 MeOH).

PPL hydrolysis products: (1*R*-2*S*-4*S*)-(+)-**1**: (44 mg, 10% yield). (1*S*-2*R*-4*R*)-(−)-**2: (**0.24 g, 47% yield). $[\alpha]_D^{20}$=-1.5 (c 1.44, MeOH).

2.4.5 Dechlorination of (1*S*,2*R*,4*R*)-(-)-2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachloro bicyclo [2.2.1]hept-5-ene (1*S*,2*R*,4*R*)-(-)-2

To a stirred solution of metallic sodium (0.6 g, 26 mmol) in liquid NH_3 (30 mL), (1*S*,2*R*,4*R*)- (-)-**2** (0.51 g, 1.37 mmol) in absolute EtOH/ether (12 mL, 1:1 ratio) was added dropwise under argon atmosphere over 20 min. The resultant mixture was stirred for additional 20 min and then solid NH_4Cl was added in small portions until the solution became colourless. NH_3 was removed by passing N_2 through the mixture and ice-water was added. The resultant mixture was acidified with 2N HCl and extracted with ether (3x50 mL). Organic phase was washed with saturated $NaHCO_3$ (3x50 mL), brine (2x50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford (1*R*,2*S*,4*S*)-(-)-**7** (EtOAc:Hexane, 1:2). (0.12 g, 70% yield). $[\alpha]_D^{20}$= -72.0 (c 1.05 , 95% EtOH). All spectroscopic data and optical rotations are in accordance with the literature [56].

2.4.6. Synthesis of *meso*-4-oxa-1,4,5,6,7,7-hexachlorotricyclo[5.2.1.0]dec-8-ene, *meso*-**4**

A mixture of cis-2-buten-1,4-diol (1.32 g, 15 mmol) and hexachlorocyclopentadiene (2.73 g, 10 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 140 ^oC for 4 h. The crude product was recrystallized from heptane to afford *meso*-**4** as white crystals (2.23 g, 65% yield). Mp. 209-213 ^oC. ^1H NMR ($CDCl_3$): δ 3.36-3.41 (m, 2H, *exo* CH), 3.50-3.58 (m, 2H, CH_2O), 3.92 (d, 2H, CH_2O, J = 11.1 Hz). ^{13}C NMR ($CDCl_3$): δ 52.7 (C_2 and C_3), 65.9 (C_8 and C_9), 79.4 (C_1 and C_4), 102.6 (C_7), 128.7 (C_5 and C_6). IR (neat): 1466 (m), 1606 (s), 2880 (m), 2945 (w) cm^{-1}. Anal. calcd for $C_9H_6Cl_6O$ (342.86): C, 31.53; H, 1.76. Found: C, 32.03; H, 1.92.

2.4.7. Synthesis of *meso*-2,3-*endo*-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene, *meso*-5

A mixture of cis-2-buten-1,4-diol diacetate (4.90 g, 28.5 mmol) and hexachlorocyclopentadiene (4.85 g, 17.8 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 150 ^{o}C for 15 h. The crude product was recrystallized from heptane to afford *meso*-**5** as white crystals (5.50 g, 70% yield). Mp. 115-117 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 6H, CH_3), 3.24-3.30 (m, 2H, *exo* CH), 4.17 (dd, 2H, CH_2O, J = 5.8 and 12.1 Hz), 4.31 (dd, 2H, CH_2O, J = 3.7 and 12.0 Hz). ^{13}C NMR ($CDCl_3$): δ 20.7 (**C**H_3), 47.8 (C_2 and C_3), 59.8 (C_8 and C_9), 80.7 (C_1 and C_4), 102.8 (C_7), 131.1 (C_5 and C_6), 170.1 (**C**O). IR (neat): 1602 (w), 1745 (s) cm^{-1}. Anal. calcd for $C_{13}H_{12}Cl_6O_4$ (444.95): C, 35.09; H, 2.72. Found: C, 34.66; H, 2.70.

2.4.8. Synthesis of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo [2.2.1] hept-5-ene, *meso*-3

A mixture of *meso*-**5** (3.00 g, 6.7 mmol), concd HCl (0.3 mL) amd methanol (15 mL) was stirred for 3 h at reflux. The reaction vessel was cooled down to 25 ^{o}C and upon slow evaporation of MeOH white *meso*-**3** crystals were obtained and recrystallized (2.3 g, 95% yield). Mp. 216-217 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 3.09 (s, 2H, OH), 3.23-3.29 (m, 2H, *exo* CH), 3.68 (t, 2H, CH_2O, J = 10.0 Hz), 4.02 (d, 2H, CH_2O, J = 9.2 Hz). ^{13}C NMR (d^6-DMSO:$CDCl_3$ = 2:1): δ 51.0 (C_2 and C_3), 57.4 (C_8 and C_9), 81.1 (C_1 and C_4), 103.4 (C_7), 130.7 (C_5 and C_6). IR (neat): 1460 (m), 1604 (m), 2926 (w), 3236 (br) cm^{-1}. Anal. calcd for $C_9H_8Cl_6O_2$ (360.88): C, 29.95; H, 2.23. Found: C, 30.12; H, 2.34.

2.4.9. Synthesis of (±)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene (±)-6

To a stirred solution of *meso*-**3** (0.80 g, 2.2 mmol) in CH_2Cl_2 (25 mL), dry prydine (0.27 mL, 3.3 mmol) was added at 0 ^{o}C and the mixture was stirred for 30 min under inert atmosphere. Acetyl chloride (0.173 mL, 2.4 mmol) was added

dropwise. The resultant mixture was stirred for 24 h at rt. The organic phase was extracted with 0.1 N HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford **(±)-6** (3% MeOH/ 97% $CHCl_3$) (0.55 g, 62%). ^{1}H NMR: δ 2.07 (s, 1H, OH), 2.09 (s, 3H, CH_3), 3.14-3.20 (m, 1H, *exo* CH), 3.26-3.30 (m, 1H, *exo* CH), 3.64-3.70 (m, 1H, CH_2O), 3.92-3.95 (m, 1H, CH_2O), 4.27 (dd, 1H, CH_2O, J = 7.2 and 12.1 Hz), 4.37 (dd, 1H, CH_2O, J = 5.6 and 12.0 Hz). ^{13}C NMR: δ 20.9 (C_{11}), 47.9 (C_3), 51.1 (C_2), 58.5 (C_9), 60.2 (C_8), 80.7 (C_4), 80.9 (C_1), 102.8 (C_7), 130.8 (C_5), 131.0 (C_6), 170.4 (C_{10}). IR(neat): 1598 (m), 1739 (s), 3403 (br) cm^{-1}.

2.4.10. General Procedure for enzyme-catalyzed acetylation of *meso*-2,3-*endo*-bis (hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene, *meso*-3

To a solution of 200 mg *meso*-**3** in 4 mL vinyl acetate and 3 mL MTBE (Table 1, entry 3), 20 mg CCL was added in one portion and the reaction mixture was stirred in a shaker at 25 ^{o}C (TLC monitoring). The reaction mixture was filtered and vinyl acetate and MTBE were evaporated under reduced pressure. (−)-**6** was either obtained as pure product or purified by flash column chromatography (3% MeOH / 97% $CHCl_3$). (−)-**6:** (183 mg, 82% yield). HPLC-analysis of (−)-**6**: Chiralcel OJ-H at room temperature, *n*- hexane/2-propanol = 95:5, 1.0 mL/min, 254 nm, t_1 = 9.2 min (major), t_2 = 11.5 min (minor), $[\alpha]_D^{25}$= -6.5 (c 1.86, MeOH).

Table 3, entry 1: m(*meso*-**3**) = 200 mg, m(CCL) = 50 mg, Solvent: 4 mL vinyl acetate + 2 mL THF, (−)-**6:** (185 mg, 83% yield), $[\alpha]_D^{25}$= -5.3 (c 1.80, MeOH).

Table 3, entry 2: m(*meso*-**3**) = 200 mg, m(CCL) = 50 mg, Solvent: 4 mL vinyl acetate + 3 mL MTBE, (−)-**6:** (215 mg, 96% yield), $[\alpha]_D^{25}$= -5.6 (c 2.40, MeOH).

Table 3, entry 3: m(*meso*-**3**) = 200 mg, m(CCL) = 20 mg, Solvent: 4 mL vinyl acetate + 3 mL MTBE, (−)-**6:** (183 mg, 82% yield), $[\alpha]_D^{25}$= -6.5 (c 1.86, MeOH).

Table 3, entry 4: m(*meso*-**3**) = 200 mg, m(CCL) = 20 mg, Solvent: 4 mL vinyl acetate + 4 mL cyclohexane + 2 mL MTBE, (−)-**6: (**202 mg, 88% yield), $[\alpha]_D^{25}$= -7.6 (c 3.86, MeOH).

Table 3, entry 5: m(*meso*-**3**) = 200 mg, m(CCL) = 10 mg, Solvent: 4 mL vinyl acetate + 7 mL cyclohexane + 1 mL MTBE, (−)-**6: (**198 mg, 89% yield), $[\alpha]_D^{25}$= -7.0 (c 1.22, MeOH).

Table 3, entry 6: m(*meso*-**3**) = 200 mg, m(CCL) = 20 mg, Solvent: 2 mL vinyl acetate + 6 mL diisopropyl ether, (−)-**6: (**194 mg, 87% yield), $[\alpha]_D^{25}$= -7.8 (c 2.39, MeOH).

Table 4, entry 1: m(*meso*-**3**) = 100 mg, m(CAL-B) = 20 mg, Solvent: 2 mL vinyl acetate + 3 mL cyclohexane + 1.5 mL MTBE, (−)-**6: (**219 mg, 98% yield), $[\alpha]_D^{25}$= -8.5 (c 2.68, MeOH).

Table 4, entry 2: m(*meso*-**3**) = 100 mg, m(CAL-B) = 20 mg, Solvent: 1 mL vinyl acetate + 3 mL diisopropyl ether, (−)-**6: (**192 mg, 86% yield), $[\alpha]_D^{25}$= -8.8 (c 2.12, MeOH).

Table 4, entry 3: m(*meso*-**3**) = 300 mg, m(CAL-B) = 15 mg, Solvent: 3 mL vinyl acetate + 9 mL diisopropyl ether, (−)-**6: (**251 mg, 75% yield), $[\alpha]_D^{25}$= -7.7 (c 2.20, MeOH).

2.4.11. Racemization of (-)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene (-)-6

To a stirred solution of (-)-**6** (112 mg, 0.29 mmol) in freshly distilled THF (10 mL), LiH was added (6 mg, 0.75 mmol) at 0 ^oC under argon atmosphere. The mixture was stirred at room temperature for 2 hours, neutralized by NH_4Cl, filtered and solvent was evaporated under reduced pressure. Both HPLC analysis and optical rotation value showed that the final product was totally racemic.

2.4.12. Synthesis of the sulphonate ester (+)-8

To a stirred solution of (-)-**6** of 83% ee (180 mg, 0.45 mmol) in CH_2Cl_2 (15 mL), (1*R*)-(+)-camphor-10-sulphonyl chloride was added (225 mg, 0.90 mmol) at 0 ^oC under argon atmosphere and stirred for 20 min. Triethylamine (75 μL, 0.54 mmol) was added dropwise. The resultant mixture was stirred for 48 h at rt. The organic phase was extracted with 0.1 N HCl, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford **(+)-8** (66% hexane/ 33% EtOAc/ 1% HOAc) (138 mg, 49%). ^1H NMR ($CDCl_3$): δ 0.89 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.44-1.50 (m, 1H), 1.65-1.72 (m, 1H), 1.95-2.03 (m, 1H), 2.09 (s, 3H, $COCH_3$), 2.14 (t, 1H, *J* = 4.42 Hz), 2.35-2.46 (m, 2H), 3.01 (d, 1H, CH_2SO_2, *J* = 15 Hz), 3.26-3.31 (m, 1H, *exo* CH), 3.37-3.42 (m, 1H, *exo* CH), 3.58 (d, 1H, CH_2SO_2, *J* = 15 Hz), 4.19-4.26 (m, 1H, CH_2O), 4.29-4.39 (m, 2H, CH_2O), 4.58 (dd, 1H, CH_2O, *J* = 4.8 and 10.6 Hz). ^{13}C NMR ($CDCl_3$): δ 19.7, 20.8, 24.9, 26.9, 42.5, 42.8, 47.4, 47.8, 48.2, 48.7, 48.9, 57.9, 59.3, 65.2, 80.4, 80.8, 102.6, 130.2, 132.2, 170.2, 214.3.

CHAPTER 3

SYNTHESIS OF CHIRAL C_2 AND C_3 SYMMETRIC 1,2-DIAMINE LIGANDS

3.1. Introduction

3.1.1. Chiral Catalysts in Asymmetric Synthesis

Several methods for the synthesis of enantiopure compounds have been developed so far. If absolute asymmetric syntheses cases where enantiopure products can be obtained from totally achiral environment are excluded, any chiral information must be introduced into the system to obtain enantiopure products, either at the beginning, middle or at the end of the process. Hence, the asymmetric information can originate from either the starting material or the reagent.

When chiral starting materials are used, the intrinsic asymmetric information is transferred into the new chiral centers. This approach is generally named as *internal asymmetric induction*. The asymmetric induction during the production of the new chiral center is, in this case, a diastereoselective process. The utilization of chiral pool compounds such as amino acids, carbohydrates and terpenes, which are easily available from natural sources and hence, inexpensive, is the hallmark of this method and it's widely known as the chiron approach [58]. The synthesis of (+)-vincamine from aspartic acid [59] is an example to this approach (Figure 5).

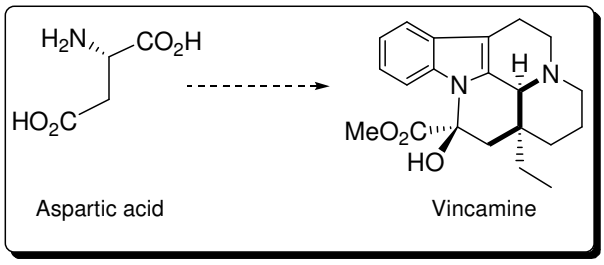


Figure 5. The structural relationship between (+)-vincamine and aspartic acid

The second type of asymmetric induction is called *relayed asymmetric induction*. In this approach, the asymmetric information, named as chiral auxiliary, is introduced into the system at a suitable stage before the chirality forming reaction and after the chirality is introduced, it's removed. A major drawback of this approach is that one usually needs two extra synthetic operations: introduction of the chiral auxiliary and then the removal of it, which lengthen the process [60].

Finally, the third type of asymmetric induction involves processes where chiral information is brought transiently into the system, generally through reversible and weak bond formation and finally released in its original form at the end of the reaction. This approach is called *external asymmetric induction* and is achieved with the use of chiral catalysts [60]. These processes are economically the best desired ones, since the chiral originator is used in catalytic amounts in contrast to the first two approaches where the chirality sources are used stoichometrically [61].

3.1.2. Previliged Chiral Ligands

Knowles, in 1968, synthesized the first chiral ligand bearing a chiral phosphine atom and further modifications led to the synthesis of the ligands CAMP and PAMP. The rhodium complex of the dimerized form of PAMP, which

he called DiPAMP, was used in an asymmetric hydrogenation reaction for the commercial production of L-Dopa (Figure 6) [62].

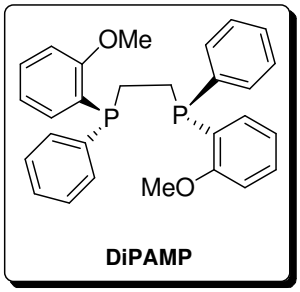


Figure 6. The structure of the chiral ligand DiPAMP

Following these developments, Kagan synthesized the first chiral C_2 symmetric diphosphine ligand, DIOP, in 1971 and used its rhodium complex again for asymmetric hydrogenation [63].

After three decades of the discovery of the first chiral catalyst, the situation is much different today. Thousands of chiral ligands have been synthesized so far and they can be utilized in almost all types of organic reactions like asymmetric epoxidation, cyclopropanation, borane reduction, alkylation, aldol reaction, aziridination, Diels-Alder reaction, etc. However, among this huge number of chiral catalysts, some of them exhibited greater success than the others. The term *previliged chiral catalysts* has been attributed for those catalysts that are highly efficient over a wide range of different reactions [64]. The most famous ones of these previliged chiral ligands are shown in Figure 7.

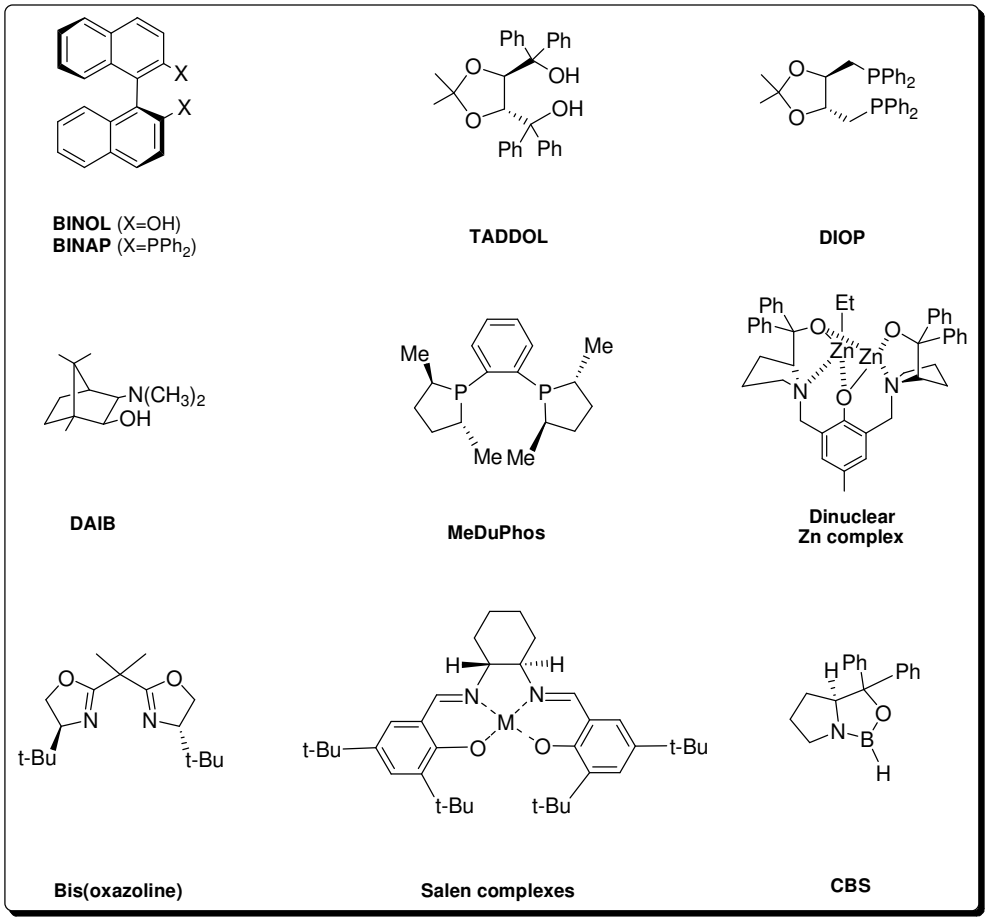


Figure 7. The structures of the most well-known *privileged* chiral ligands and catalysts

The chiral ligands or catalysts shown in Figure 7, have all been proved to work with high efficiencies in different asymmetric transformations. For example, TADDOL complexes, synthesized from tartaric acid, are used in asymetric Diels-Alder reactions, ester alcoholysis and iodolactonization [64]. The bis(oxazoline) (BOX) ligands were inspired by the ligand framework of vitamin B12 and were reported independently by research groups in 1990-91 [65]. A remarkable advantadge of this ligand type is that they are prepared from simple amino alcohols and they can be tailored in order to obtain maximum efficiency for a particular transformation.

The Corey-Bakshi-Shibata (CBS) catalyst is prepared from the amino acid proline and has been found to work quite effectively in the asymmetric borane reduction of prochiral ketones [66]. DAIB ligand was first synthesized by Noyori and gave excellent results in dialkylzinc additions to aldehydes [67]. Recently, Trost developed a dinuclear Zn complex, which has been used successfully in various asymmetric aldol reactions [68].

3.1.3. C_2 versus C_3 Symmetry in Chiral Ligands

C_2 symmetric chiral ligands are of great significance in asymmetric catalysis and most of the *previliged* chiral ligands or catalysts described in 3.1.2. such as the salen comlplexes, TADDOL, BINOL (BINAP) and BOX ligands possess a C_2 symmetry. It is because the twofold axis of symmetry reduces the number of diastereomeric intermediates and transition states in the stereo-determining step [69]. A nice comparison of the C_2 symmetric P-P and N- N ligands with C_1 symmetric P-N ligands has been done by Pfaltz and Drury shown that C_1 symmetric ligands may sometimes outperform the C_2 symmetric ones due to the different electronic effects of the different hetero-atoms [65].

In spite of the extensive work done on C_2 symmetric ligands, C_3 symmetry still remains as a mysterious, less investigated area. However, studies have shown the great potential of C_3 symmetric compounds in diverse fields like asymmetric catalsysis and molecular recognition [70]. Various crown-ethers, cyclotriveratrylenes, calixarenes, porphyrins and clathrands with C_3 or D_3 symmetry have been synthesized and proved to be successful in molecular recognition [70a].

The use of C_3 symmetric chiral ligands in asymmetric catalysis has been of growing interest within the last decade. For example, rhodium(I) complexes of enantiopure tripodal phosphanes with C_3 symmetry were used in asymmetric hydrogenation of dimethyl itachonate giving 94 % ee, while 90 % ee was observed when its C_2 symmetric analogue was used [71]. A C_3 symmetric diborate

complex was shown to be highly enantioselective in asymmetric Diels-Alder reaction of cyclopentadiene and methacrolein [72]. Katsuki and co-workers developed tridentate tris(oxazoline) ligands as chiral auxiliaries in the asymmetric allylic oxidation of cycloalkenes [73]. A C_3 symmetric tripodal ligand having a central mesitylene-drived core and three axially chiral biaryl subunits was shown to work effectively in the asymmetric dialkylzinc addition to aldehydes [74]. Du and co-workers developed a series of chiral C_3 symmetric tris(β-hydroxy amide) ligands for the asymmetric alkynylation of aldehydes in the present of diethylzinc and $Ti(O^iPr)_4$ [75]. The reduction of symmetry from C_3 to C_1 in chiral tris(oxazoline) ligands in asymmetric cyclopropanation reactions has been investigated in a modular way [76]. Examples to some C_3 symmetric chiral ligands are given in Figure 8.

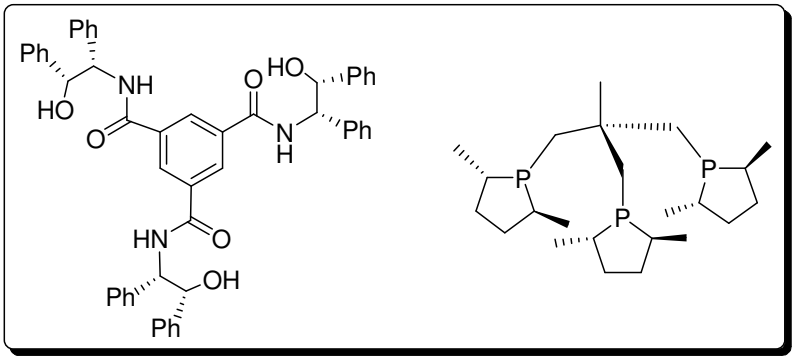


Figure 8. Examples to C_3 symmetric chiral ligands

3.1.4. Chiral Diamine Ligands in Asymmetric Catalysis

Utilization of nitrogen containing chiral ligands gained wide interest in recent years due to their high stability, easier preparation and promising results in asymmetric catalysis [77]. They can easily be prepared in enantiomerically pure forms from the nitrogen containing compounds in chiral pool and cheap industrial chemical intermediates. The second distinct advantage of these nitrogen-

containing ligands is the presence of several synthetic pathways for the possible transformations of these compounds which allow tailor-made modifications for the synthesis of specific target molecules.

Chiral diamines are important building blocks for the synthesis of pharmaceuticals and encountered frequently in natural products [78]. Moreover, they serve as strong synthetic tools, especially as chiral auxiliaries and catalysts [69a]. Chiral 1,2-diamine ligands have found a wide application in asymmetric transformations, including epoxidation, epoxide ring opening, Diels-Alder reactions and transfer hydrogenation [79].

The most widely applied 1,2-diamines are *trans*-1,2-diphenylethylene diamine and *trans*-1,2-diaminocyclohexane. However, several proline derived chiral diamine compounds have been synthesized in recent years either for use in metal complexation or for use as organocatalysts. These proline derived diamine (or amide) compounds have been utilized successfully in asymmetric aldol and borane reduction reactions [80]. Examples of some chiral diamine ligands are shown in Figure 9.

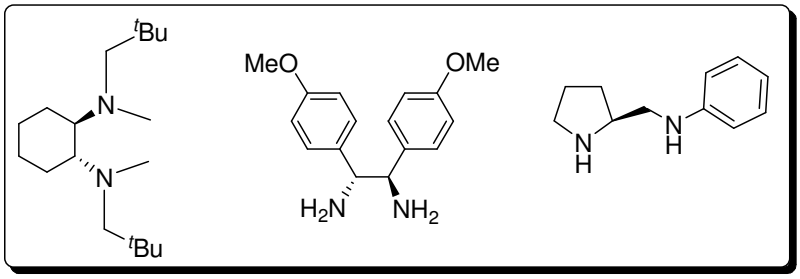


Figure 9. Examples to chiral 1,2-diamine ligands

3.1.5. Aim of the Work

In the literature, the synthesis of the tetradentate ligands *N,N'*-bis{[(*S*)-pyrrolydin-2-yl] methyl}phenylenediamine and *N,N'*-bis{[(*S*)-*N*-benzyl-pyrrolydin-2-yl]methyl}phenylene diamine is described starting from *L*-proline and 1,2-diaminobenzene [81b]. However, only limited applications of these ligands for the use of asymmetric catalysis have been reported (iridium and rhodium catalyzed hydrogenation and copper and manganese catalyzed cyclopropanation) and moderate enantioselectivities were obtained [81].

The C_2 symmetric diamine ligand (-)-**11** and the C_3 symmetric diamine ligand (-)-**12** were chosen as the target molecules for the use as chiral ligands (Figure 10). The general success of the C_2 and C_3 symmetric chiral ligands as well as chiral 1,2-diamine ligands was the starting point of this study. To the best of our knowledge, such a proline-derived C_3 symmetric ligand isn't described in the literature. The reason of choosing 1,3-diaminobenzene as the central core of the ligand (-)-**11** was to investigate the catalytic activity of the exact C_2 analogue of ligand (-)-**12**. Moreover, despite the general tetradentate coordination of such C_2 symmetric ligands, the formation of two distinct catalytic sites of C_1 symmetry with a total C_2 symmetry was planned.

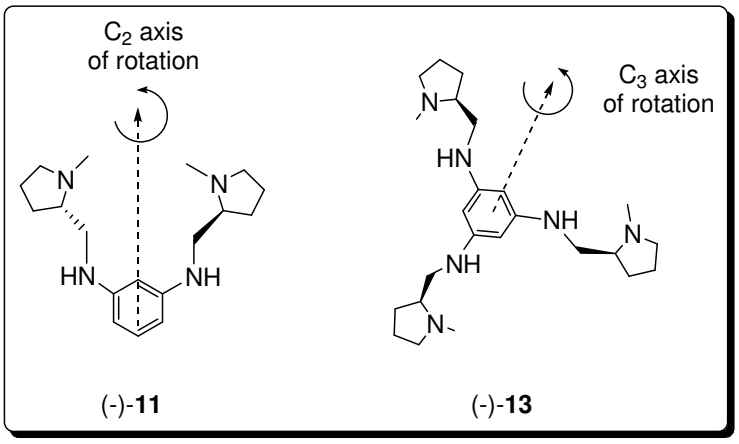
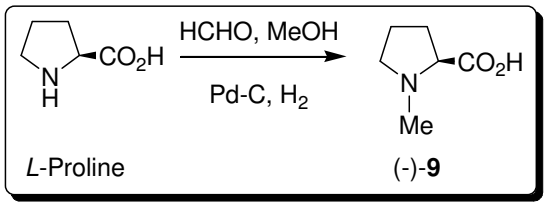


Figure 10. The structures of the target C_2 and C_3 ligands (-)-**11** and (-)-**13**

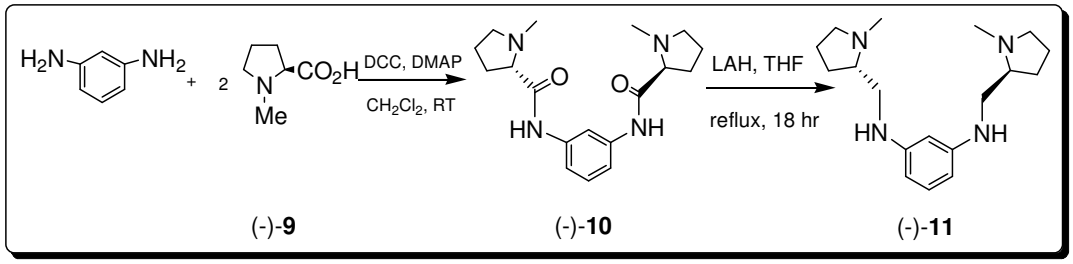
3.2. Results and Discussion

N-Methyl-L-proline was synthesized from commercially available L-proline according to the literature procedure [82]. Proline was treated with formaldehyde and hydrogen gas under palladium catalyst to afford *N*-methyl proline, (-)-**9** in 92 % chemical yield (Scheme 14):



Scheme 14. The synthesis of *N*-methyl L-proline from L-proline

Treatment of 1,3-diaminobenzene with *N*-Methyl-L-proline afforded the C_2 symmetric diamide (-)-**10** with 95 % chemical yield. DCC was used in order to activate the carboxylic acid functionality of (-)-**9** and catalytic amount of DMAP was used as the catalyst. The subsequent reduction of the diamide (-)-**10** with LAH in THF under reflux afforded the target C_2 symmetric chiral ligand (-)-**11** (Scheme 15).



Scheme 15. The synthesis of the chiral diamine ligand (-)-**11**

Structure elucidations of the compounds **10** and **11** were done by ^{1}H-NMR and ^{13}C-NMR analysis. In these types of compounds, the most valuable information is obtained from the aromatic region (the number of the different protons and carbons, their chemical shifts and relative integration values) and the amide group (whether present or not) signals in their NMR spectra.

The ^{1}H-NMR spectrum of (-)-**10** reveals that there are 3 different protons in the aromatic region: a singlet at 7.89 ppm belonging to H_1 proton; a doublet of doublet 7.43 ppm belonging to two H_3 protons and a triplet at 7.28 ppm belonging to H_4 proton. One of the splitting constants of the signal at 7.43 ppm is so small (1.7 Hz) that it's not observed in the singlet signal at 7.89 ppm. The broad signal at 9.36 ppm belongs to the amide proton, N**H**. The N-C**H$_3$** protons give a singlet at 2.44 ppm. (Figure A19).

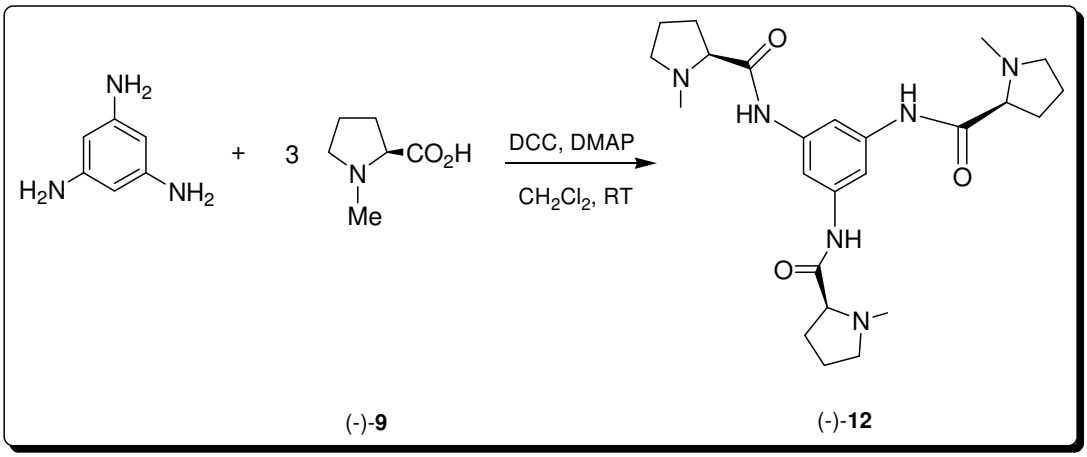
The ^{13}C-NMR of (-)-**10** is also very informative about the structure. In the aromatic region there are four different signals indicating four different carbon atoms: 109.0, 113.8, 128.5 and 137.5 ppm corresponding to C_1, C_2, C_3 and C_4. The carbonyl carbon of the amide group shows a signal at 172.0 ppm (Figure A20).

The ^{1}H-NMR spectrum of (-)-**11**, there appears again 3 different signals in the aromatic region: a triplet at 6.96 ppm belonging to H_4 proton; a doublet of doublet at 6.01 ppm belonging to two H_3 protons and a singlet at 5.91 ppm belonging to H_1 proton. The broad signal at 4.01 ppm belongs to the two N**H** protons. The N-C**H$_3$** protons give a singlet at 2.32 ppm (Figure A21). The ^{13}C-NMR show four signals in the aromatic region at 97.1, 102.5, 129.9 and 150.3 ppm corresponding to C_1, C_3, C_4 and C_2 carbons, respectively (Figure A22).

Comparison of the NMR spectra in Figures A19 and A20 with those in Figures A21 and A22, clearly indicate the structural differences of (-)-**10** and (-)-**11**. The general signal patterns in both spectra are quite similar which is expected due to the symmetrical relation (C_2 symmetry) in both molecules. However, disappearance of the carbonyl carbon of the amide group in Figure A20, the

transformation of the amide proton signal in Figure A19 to the amine proton signal in Figure A21 and the presence of an additional signal in the aliphatic region in Figure A22 are the most important clues for the approval of the reduction of (-)-**10** to (-)-**11**. Another very important but can be easily underestimated clue is the relative positions of the signals in the aromatic region in both ^{1}H-NMR and ^{13}C-NMR spectra. The greater inductive effect of the amide group and the greater mesomeric effect of the amine group totally influence both the relative positions and the chemical shifts of these signals.

In connection to the studies mentioned above, the triamide (-)-**12** was synthesized starting from 1,3,5-triaminobenzene and *N*-Methyl-L-proline. 1,3,5-Triaminobenzene was prepared according to the literature procedure from phloroglucinol (1,3,5-trihydroxybenzene) [83]. The amide formation reaction was carried out in the presence of DCC and catalytic amount of DMAP to afford the C_3 symmetric triamide (-)-**12** in 82 % chemical yield. (Scheme 16)

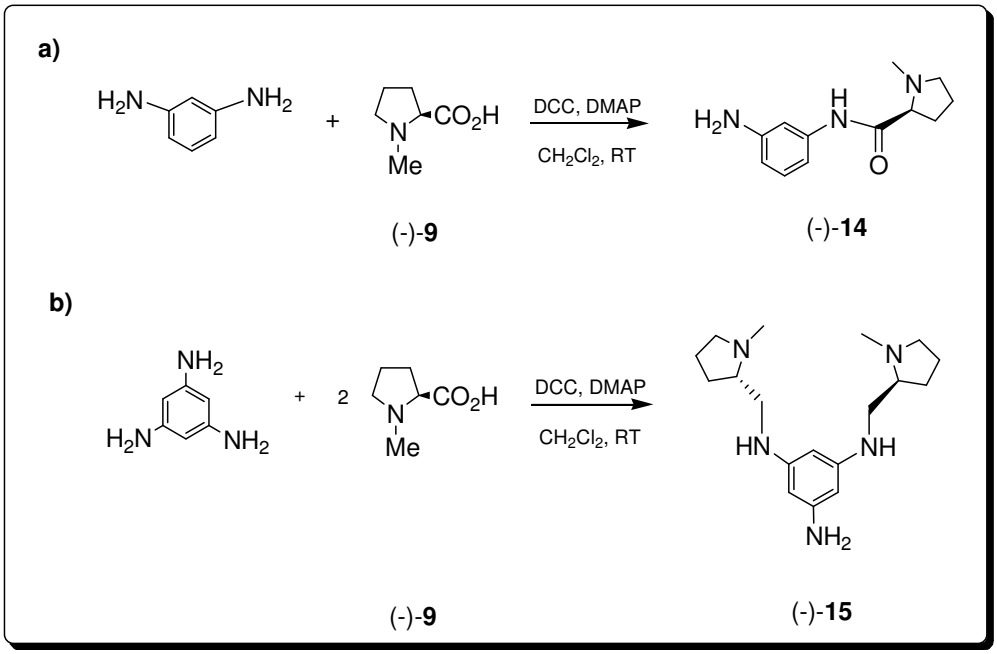


Scheme 16. The synthesis of the C_3 symmetric triamide (-)-**12**

The structure of (-)-**12** was determined by ^{1}H-NMR and ^{13}C-NMR analysis.

The ^{1}H-NMR spectrum of (-)-**12** shows a singlet 7.84 ppm belonging to the aromatic proton, H_1. The N**H** proton of the amide group gives a broad singlet at 9.42 ppm. The singlet at 2.44 ppm belongs to the N-C**H$_3$** protons (Figure A23). The ^{13}C-NMR spectrum of (-)-**12** is rather elegant due to the symmetry of the molecule. The signal at 105.3 and 138. 9 ppm correspond to C_1 and C_2, respectively. The carbonyl carbons of the three amide groups gives a signal at 173.4 ppm (Figure A24).

During the studies to synthesize the diamide (-)-**10** and the triamide (-)-**12** derivatives, the sequential attachment of *N*-methyl proline was observed which inspired us for the synthesis of the monoamide (-)-**14** and the diamide (-)-**15** derivatives. Both of these derivatives were synthesized with the same method starting from 1,3-diaminobenzene and 1,3,5-triaminobenzene, respectively, by just adjusting the equivalent of *N*-methyl proline. The approach followed is described in Scheme 17.



Scheme 17. The synthesis of the chiral monoamide derivative (-)-**14** and the diamide derivative (-)-**15**

Structure elucidations of the compounds **14** and **15** were done by ^{1}H-NMR and ^{13}C-NMR analysis.

The ^{1}H-NMR of (-)-**14** reveals that there are four different protons with equal integrations on the aromatic region belonging to the benzene ring protons and the splitting patterns are in accord withe the *meta* position of the amide and amine substituents: a singlet at 7.16 ppm, a triplet at 7.00 ppm, a doublet of doublet at 6.68 ppm and a doublet at 6.34 ppm. The broad signal at 9.13 ppm with an integration corresponding to a single proton is the indicator of only one amide group in the whole molecule. The N**H$_2$** protons give a very broad signal at 3.55 ppm whereas the N-C**H$_3$** proton show a singlet at 2.36 ppm (Figure A25).

In the ^{13}C-NMR spectrum, there are six signals in the aromatic region indicating the presence of six distinct aromatic carbons: 106.1, 109.4, 110.8, 129.6, 138.9 and 147.3 ppm. The carbonyl carbon of the amide group give a signal at 172.7 ppm. Both NMR spectra indicate unambiguously the presence of only one amide group and hence, the reduction of the symmetry in to C_1 (Figure A26).

In the ^{1}H-NMR spectrum of (-)-**15**, there are two different protons in the aromatic region with integration ratios: 2:1; a singlet at 7.12 ppm belonging to H_1 and a doublet at 6.92 ppm belonging to two H_3 protons. The amide proton N**H** shows a broad signal at 9.23 ppm with an integration value of two protons. The broad signal at 3.69 ppm belongs to the N**H$_2$** protons of the primary amine group. The N-**CH$_3$** protons give a sharp singlet at 2.42 ppm (Figure A27).

In the ^{13}C-NMR, the signal at 172.9 ppm corresponds to the amide carbon, C_5. The aromatic carbons, C_1 and C_3 give signals at 100.4 and 101.6 ppm while C_2 and C_4 give at 139.2 and 147.9 ppm (Figure A28).

The presence of both amide and amine protons, four different signals in the aromatic region and the relative signal intensities in the ^{1}H-NMR spectrum indicate unequivocally the C_2 symmetry of the molecule and the presence of (-)-**15**.

3.3. Conclusion and Perspectives

The C_2 symmetric chiral 1,2-diamine ligand (-)-**11** has been synthesized in 3 steps starting from commercially available and inexpensive L-proline and 1,3-diaminobenzene in 80% overall yield which is a quite successfull value for a ligand synthesis.

The C_3 symmmetric triamide (-)-**12** has been synthesized from L-proline and 1,3,5-triaminobenzene in 75% overall yield and characterized with the help of NMR spectra. As a next step of the study, the reduction of (-)-**12** will be executed to obtain the C_3 symmetric chiral diamine ligand (-)-**13**.

As an extension of the original study, the monoamide and diamide derivatives (-)-**14** and (-)-**15** were synthesized in moderate yields, 66% and 58% yields, respectively. These intermediate species, will be utilized in a future work to attach the corresponding C_1 and C_2 symmetric chiral ligands to a polymeric material in order to synthesize recoverable chiral ligands.

The effectiveness of these ligands will be tested in various asymmetric transformations such as asymmetric diethylzinc addition to aldehydes and asymmetric borane reduction of prochiral ketones.

3.4. Experimental

The same instrumental techniques which were described in 2.4. were used for the characterization and purification of the compounds synthesized in this part.

3.4.1. Synthesis of *N*-methyl-L-proline (-)-9

L-Proline (2.0 g, 17.4 mmol) was dissolved in methanol (20 mL) and to this solution 40 % aqueous solution was added (1.4 mL, 19.1 mmol). This was followed by the addition of 10 % palladium-on-charcoal catalyst (500 mg) and the

resulting slurry was stirred under hydrogen balloon overnight. The slurry was then filtered through a Celite pad to remove the catalyst. The pad was washed with methanol and the combined filtrates were concentrated undr reduced pressure. The residue was taken up in ethanol-benzene (1:1, 100 mL) and concentrated a second time to provide a solid, which was recrystallized from methanol-diethyl ether. (-)-**9** was isolated as fine, white needles (2.04 g, 91 %). All the spectroscopic data are in accord with the literature [82].

3.4.2. Synthesis of *N,N'*-(1,3-phenylene)bis[(*S*)-*N*-methyl-pyrrolidine-2-carboxamide] (-)-10

To a stirred suspension of *N*-methyl proline (0.8 g, 6.2 mmol) and 1,3-diaminobenzene (0.108 g, 2.07 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC under argon atmosphere, DCC (1.28 g, 6.2 mmol) and DMAP (0.126 g, 1.04 mmol) were added simultaneously. The mixture was stirred at room temperature for 72 h and DCC precipitated as dicyclohexylurea. The mixture was filtrated, concentrated under reduced pressure and purified by column chromatography (94% $CHCl_3$/ 5% MeOH/ 1% NH_4OH) to afford (-)-**10** as a white solid (0.649 g, 95% yield). Mp: 109-111 ^oC. ^1H NMR: δ 1.76-1.83 (m, 4H), 1.91-1.99 (m, 2H), 2.23-2.34 (m, 2H), 2.40-2.46 (m, 2H), 2.44 (s, 6H, N-CH_3), 3.01 (dd, 2H, *J* = 5.1 and 10.2 Hz), 3.17-3.22 (m, 2H), 7.28 (t, 1H, *J* = 8.1 Hz), 7.43 (dd, 2H, *J* = 8.1 and 1.7 Hz), 7.89 (s, 1H), 9.36 (s, 2H, CONH). ^{13}C NMR: δ 23.5 (C_8), 30.1 (C_7), 40.9 (C_{10}), 55.7 (C_9), 68.5 (C_6), 109.0 (C_1), 113.8 (C_3), 128.5 (C_4), 137.5 (C_2), 172.0 (C_5). IR (neat): 1411 (m), 1523 (s), 1685 (s), 2851 (m), 2939 (w), 3324 (br) cm^{-1}. $[\alpha]_D^{25}$= -119 (c 4.92, $CHCl_3$).

3.4.3. Synthesis of *N,N'*-bis{[(*S*)-*N*-methyl-pyrrolidin-2-yl]methyl}benzene-1,3-diamine (-)-11

To a solution of (-)-**10** (200 mg, 0.61 mmol) in ice-cold THF (15 mL), $LiAlH_4$ (116 mg, 3.05 mmol) was added dropwise. When the addition was complete, the reaction mixture was stirred for 18 h under reflux and hydrolized by the cautious

addition of water. The mixture was filtered and the filtrate was concentrated to give the diamine (-)-**11** as an air sensitive yellow oil (170 mg, 92% yield). ^{1}H NMR: δ 1.66-1.78 (m, 6H), 1.84-1.94 (m, 2H), 2.19-2.27 (m, 2H), 2.32 (s, 6H, N-CH_3), 2.37-2.43 (m, 2H), 3.05-3.10 (m, 4H), 3.17-3.22 (m, 2H), 4.01 (broad, 2H, NH), 5.91 (s, 1H), 6.01 (dd, 2H, *J* = 7.8 and 1.8 Hz), 6.96 (t, 1H, *J* = 7.9 Hz). ^{13}C NMR: δ 22.6 (C_8), 28.7 (C_7), 40.5 (C_{10}), 45.3 (C_5), 57.4 (C_9), 64.6 (C_6), 97.1 (C_1), 102.5 (C_3), 129.9 (C_4), 150.3 (C_2). $[\alpha]_D^{25}$= -44 (c 1.07, $CHCl_3$).

3.4.4. Synthesis of *N,N',N''*-(benzene-1,3,5-triyl)tris[(*S*)-*N*-methyl-pyrrolidine-2-carboxamide] (-)-12

To a stirred suspension of *N*-methyl proline (1.04 g, 8.1 mmol) and 1,3,5-triaminobenzene (0.20 g, 1.62 mmol) in CH_2Cl_2 (30 mL) at 0 ^{o}C under argon atmosphere, DCC (1.67 g, 8.1 mmol) and DMAP (0.153 g, 1.25 mmol) were added simultaneously. The mixture was stirred at room temperature for 96 h and DCC precipitated as dicyclohexylurea. The mixture was filtrated, concentrated under reduced pressure and purified by column chromatography (94% $CHCl_3$/ 5% MeOH/ 1% NH_4OH) to afford (-)-**12** as a yellowish, white solid (0.612 g, 82% yield). Mp: 148-149 ^{o}C. ^{1}H NMR: δ 1.76-1.83 (m, 6H), 1.89-1.97 (m, 3H), 2.22-2.33 (m, 3H), 2.39-2.46 (m, 6H), 2.44 (s, 9H, N-CH_3), 3.01 (dd, 3H, *J* = 5.0 and 10.3 Hz), 3.17-3.21 (m, 3H), 7.84 (s, 3H), 9.42 (s, 3H, CONH). ^{13}C NMR: δ 24.5 (C_6), 31.2 (C_5), 41.9 (C_8), 56.7 (C_7), 69.6 (C_4), 105.3 (C_1), 138.9 (C_2), 173.4 (C_3). $[\alpha]_D^{25}$= -164 (c 1.82, $CHCl_3$).

3.4.5. Synthesis of the *N*-(3-aminophenyl)- (*S*)-*N*-methyl-pyrrolidine-2-carboxamide (-)-14

To a stirred suspension of *N*-methyl proline (0.700 g, 5.4 mmol) and 1,3-diaminobenzene (0.29 g, 2.7 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C under argon atmosphere, DCC (1.11 g, 5.4 mmol) and DMAP (0.083 g, 0.68 mmol) were added simultaneously. The mixture was stirred at room temperature for 60 h and DCC precipitated as dicyclohexylurea. The mixture was filtrated, concentrated

under reduced pressure and purified by column chromatography (94% $CHCl_3$/ 5% MeOH/ 1% NH_4OH) to afford (-)-**14** as a yellowish, white solid (0.39 g, 66% yield). Mp: 99-101 ^oC. ^1H NMR: δ 1.67-1.76 (m, 2H), 1.83-1.91 (m, 1H), 2.14-2.25 (m, 1H), 2.31-2.37 (m, 1H), 2.36 (s, 3H, N-CH_3), 2.90 (dd, 1H, *J* = 5.2 and 10.2 Hz), 3.08-3.12 (m, 1H), 3.55 (broad, 2H, NH_2), 6.34 (d, 1H, *J* = 7.3 Hz), 6.68 (t, 1H, *J* = 6.2 and 1.9 Hz), 7.00 (t, 1H, *J* = 7.9 Hz), 7.16 (s, 1H), 9.13 (s, 1H, CONH). ^{13}C NMR: δ 24.4 (C_{10}), 31.1 (C_9), 41.8 (C_{12}), 56.7 (C_{11}), 69.6 (C_8), 106.1 (C_1), 109.4 (C_5), 110.8 (C_3), 129.6 (C_4), 138.9 (C_6), 147.3 (C_2). IR (neat): 1448 (m), 1528 (s), 1624 (s), 1672 (s), 2849 (m), 2937 (m), 3363 (m), 3448 (m) cm^{-1}. $[\alpha]_D^{25}$= -121 (c 3.92, $CHCl_3$).

3.4.6. Synthesis of *N,N'*-(5-amino-1,3-phenylene)bis[(*S*)-*N*-methyl-pyrrolidine-2-carboxamide] (-)-15

To a stirred suspension of *N*-methyl proline (0.732 g, 5.7 mmol) and 1,3,5-triaminobenzene (0.20 g, 1.62 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC under argon atmosphere, DCC (1.17 g, 5.7 mmol) and DMAP (0.100 g, 0.81 mmol) were added simultaneously. The mixture was stirred at room temperature for 72 h and DCC precipitated as dicyclohexylurea. The mixture was filtrated, concentrated under reduced pressure and purified by column chromatography (94% $CHCl_3$/ 5% MeOH/ 1% NH_4OH) to afford (-)-**15** as a white solid (0.325 g, 58% yield). ^1H NMR: δ 1.74-1.83 (m, 4H), 1.89-1.98 (m, 2H), 2.22-2.29 (m, 2H), 2.38-2.45 (m, 2H), 2.42 (s, 6H, N-CH_3), 2.98 (dd, 2H, *J* = 5.2 and 10.3 Hz), 3.15-3.19 (m, 2H), 3.69 (broad, 2H, NH_2), 6.92 (d, 2H, *J* = 1.5 Hz), 7.12 (s, 1H), 9.23 (s, 2H, CONH). ^{13}C NMR: δ 24.4 (C_8), 31.1 (C_7), 41.8 (C_{10}), 56.7 (C_9), 69.6 (C_6), 100.4 (C_3), 101.6 (C_1), 139.2 (C_4), 147.9 (C_2), 172.9 (C_5). $[\alpha]_D^{25}$= -136 (c 3.10, $CHCl_3$).

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APPENDIX

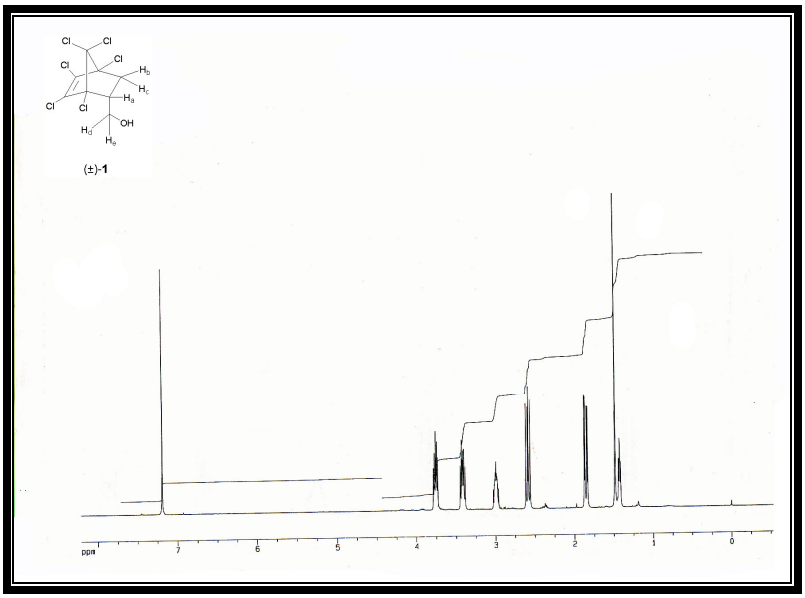

Figure A1. ^{1}H-NMR spectrum of **(±)-**2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**1**

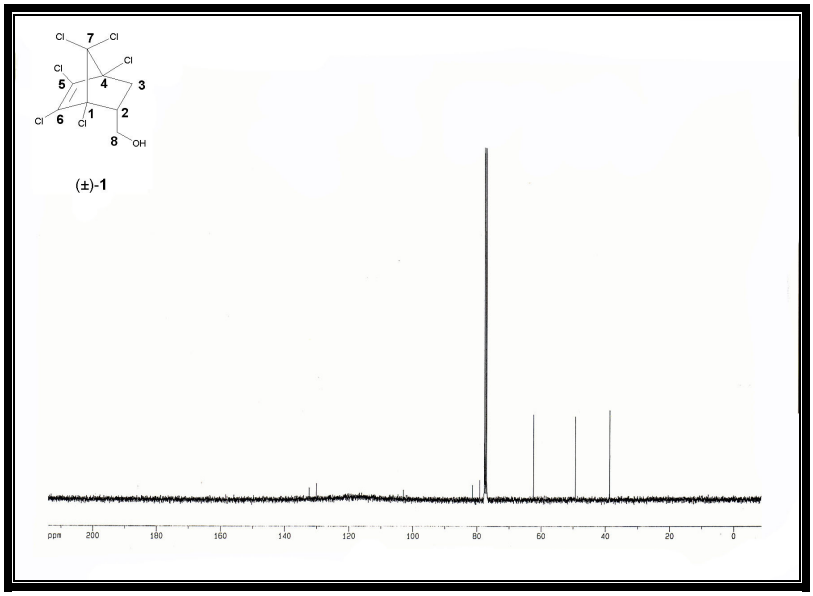

Figure A2. ^{1}H-NMR spectrum of **(±)-**2-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**1**

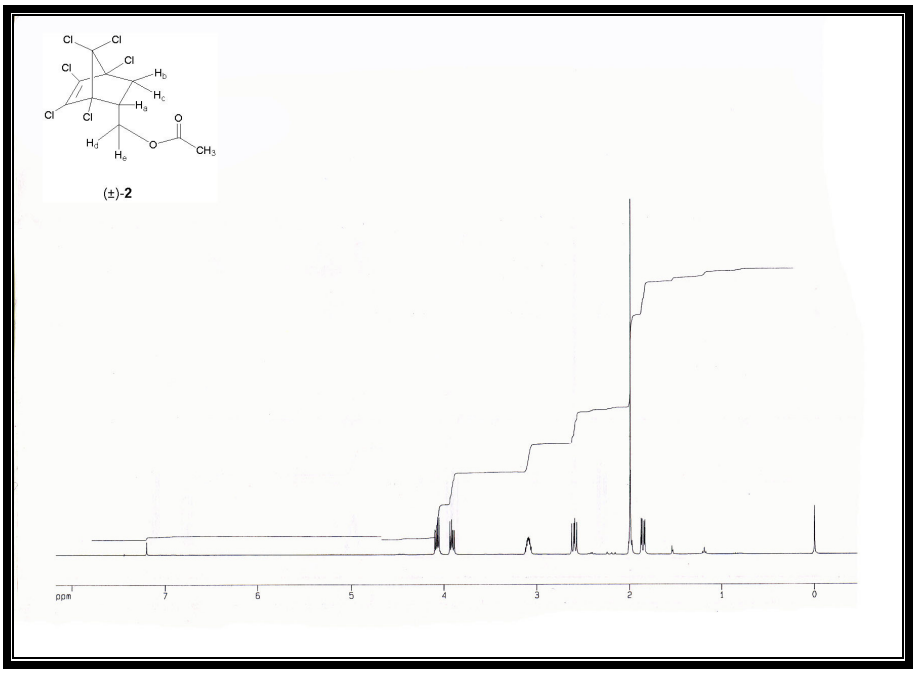

Figure A3. ^{1}H-NMR spectrum of **(±)-**2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**2**

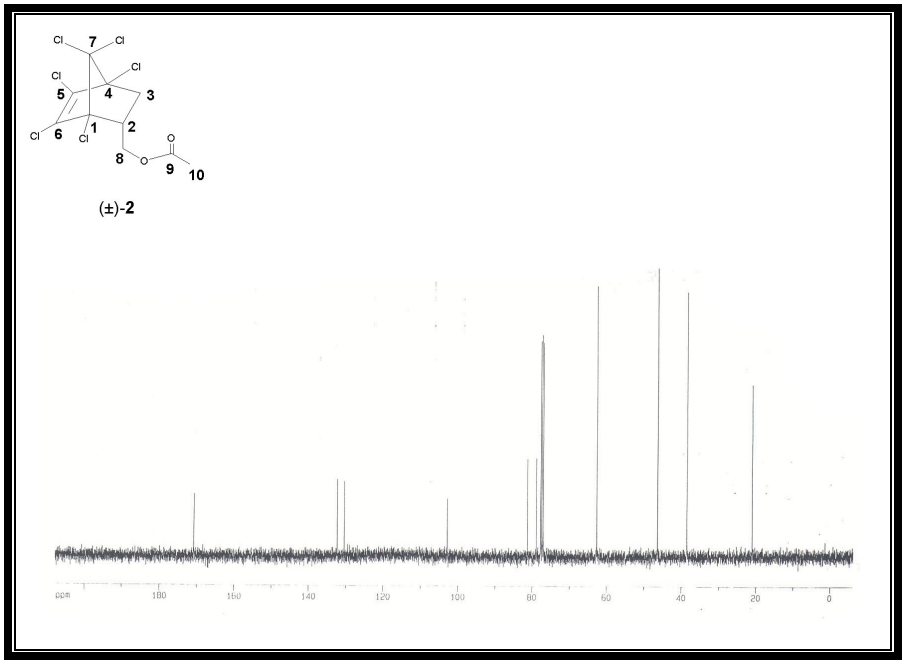

Figure A4. ^{13}C-NMR spectrum of **(±)-**2-*endo*-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**2**

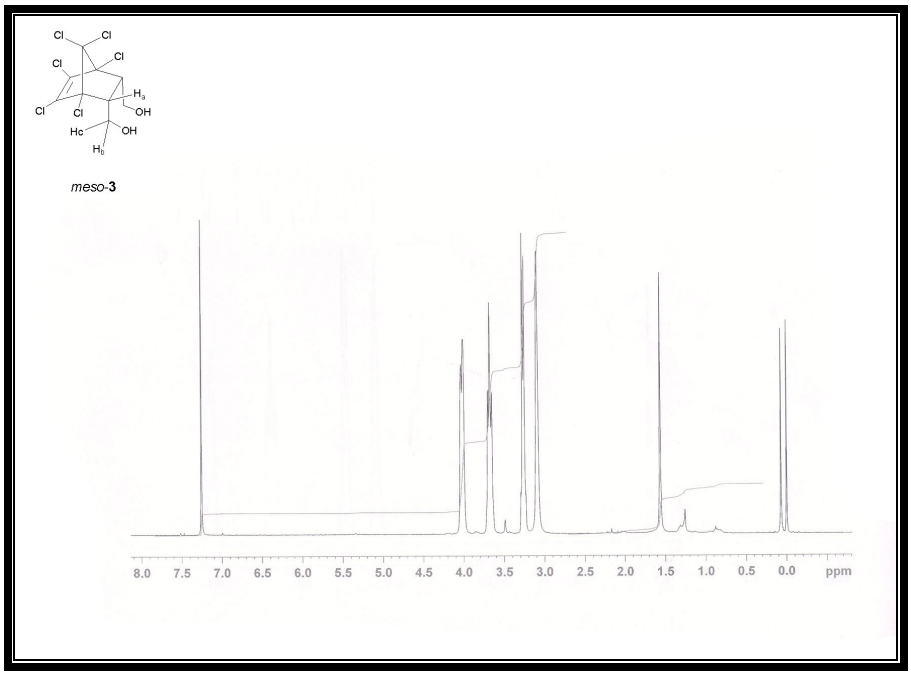

Figure A5. ^{1}H-NMR spectrum of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene *meso*-**3**

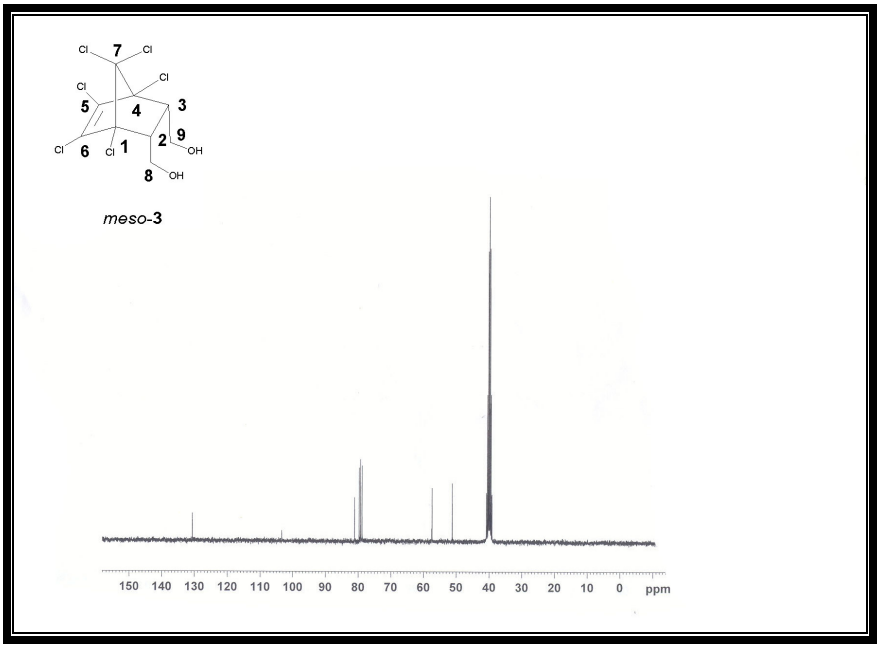

Figure A6. ^{13}C-NMR spectrum of *meso*-2,3-*endo*-bis(hydroxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene *meso*-**3**

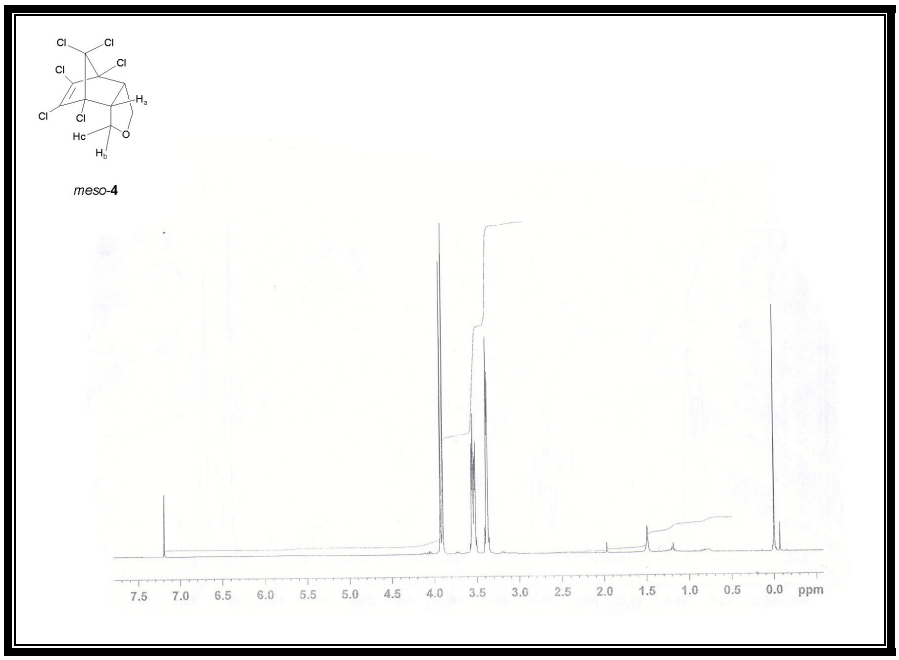

Figure A7. ^{1}H-NMR spectrum of *meso*-4-oxa-1,4,5,6,7,7-hexachlorotricyclo[5.2.1.0]dec-8-ene, *meso*-**4**

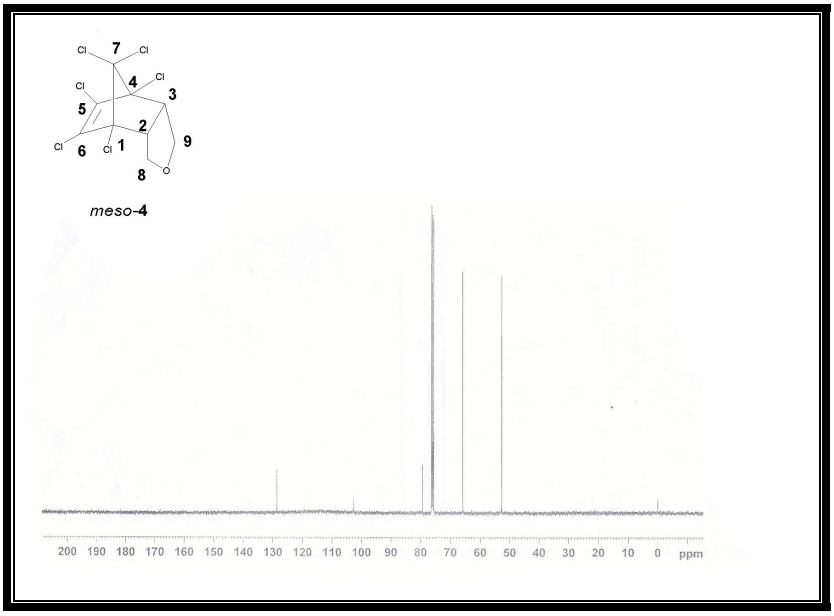

Figure A8. ^{13}C-NMR spectrum of *meso*-4-oxa-1,4,5,6,7,7-hexachlorotricyclo[5.2.1.0]dec-8-ene, *meso*-**4**

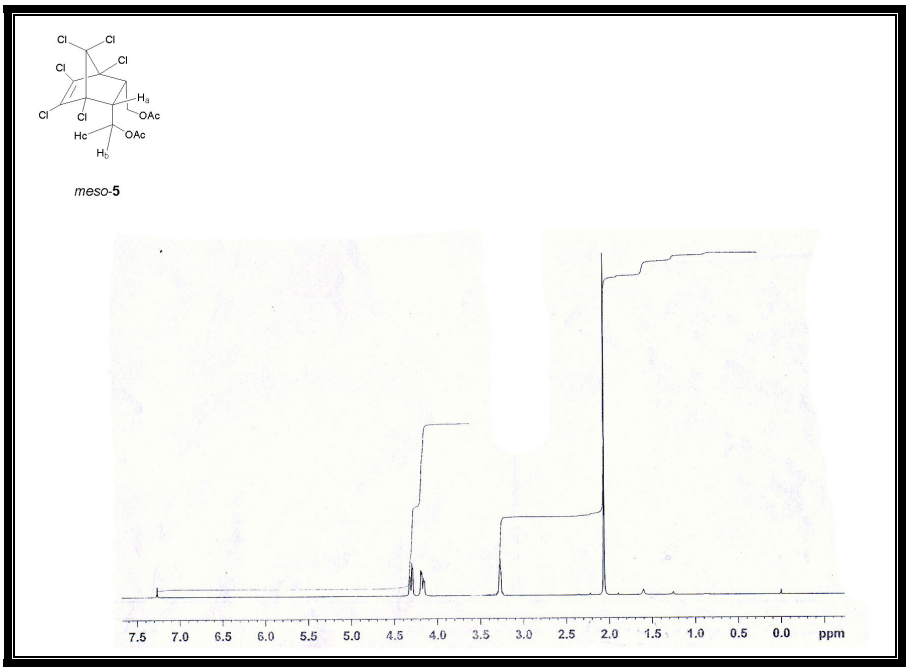

Figure A9. ^{1}H-NMR spectrum of *meso*-2,3-*endo*-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene *meso*-**5**

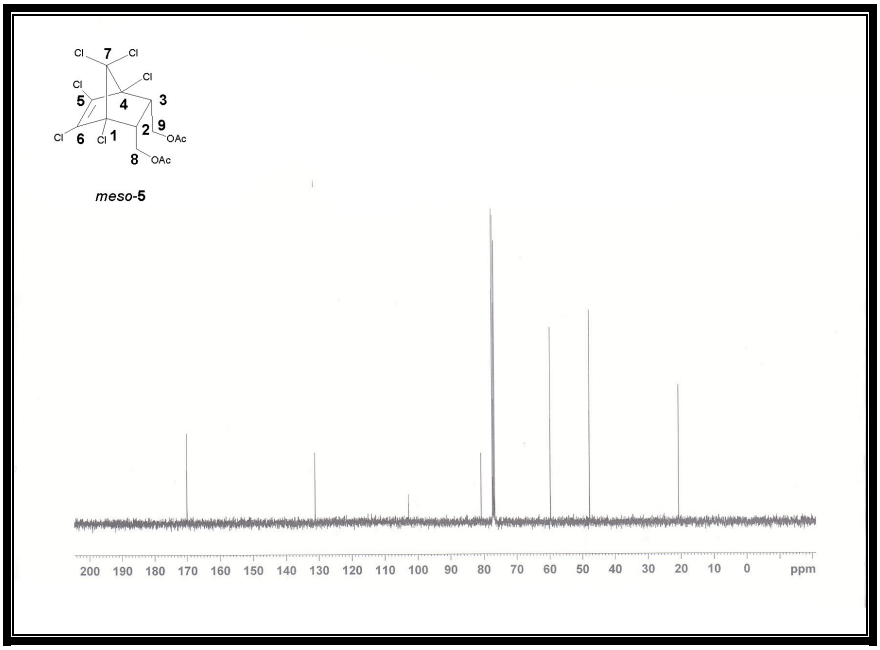

Figure A10. ^{13}C-NMR spectrum of *meso*-2,3-*endo*-bis(acetoxymethyl)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1] hept-5-ene *meso*-**5**

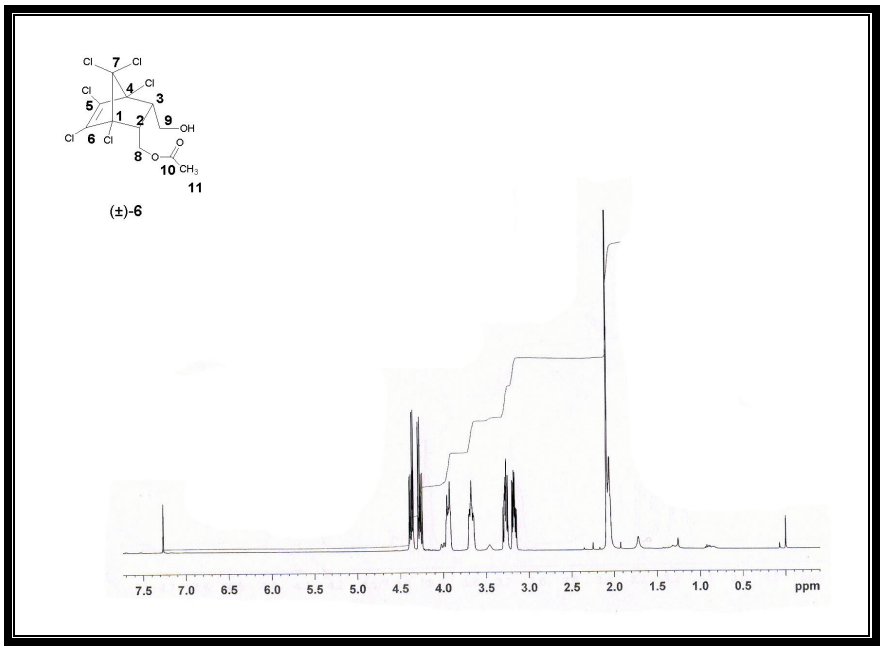

Figure A11. ^{1}H-NMR spectrum of (±)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**6**

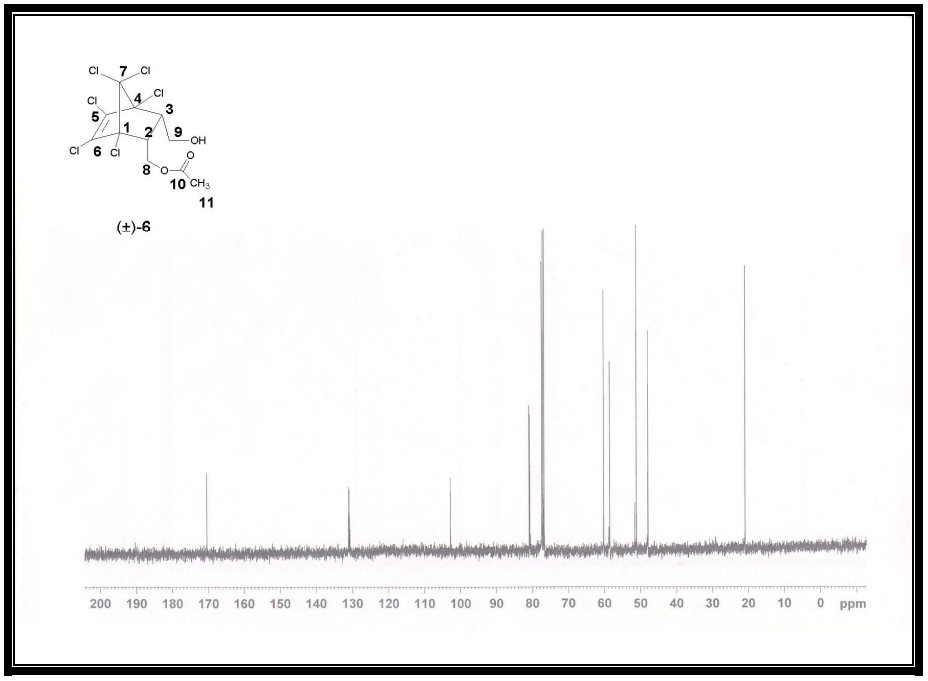

Figure A12. ^{13}C-NMR spectrum of (±)-2-*endo*-acetoxymethyl-3-*endo*-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene (±)-**6**

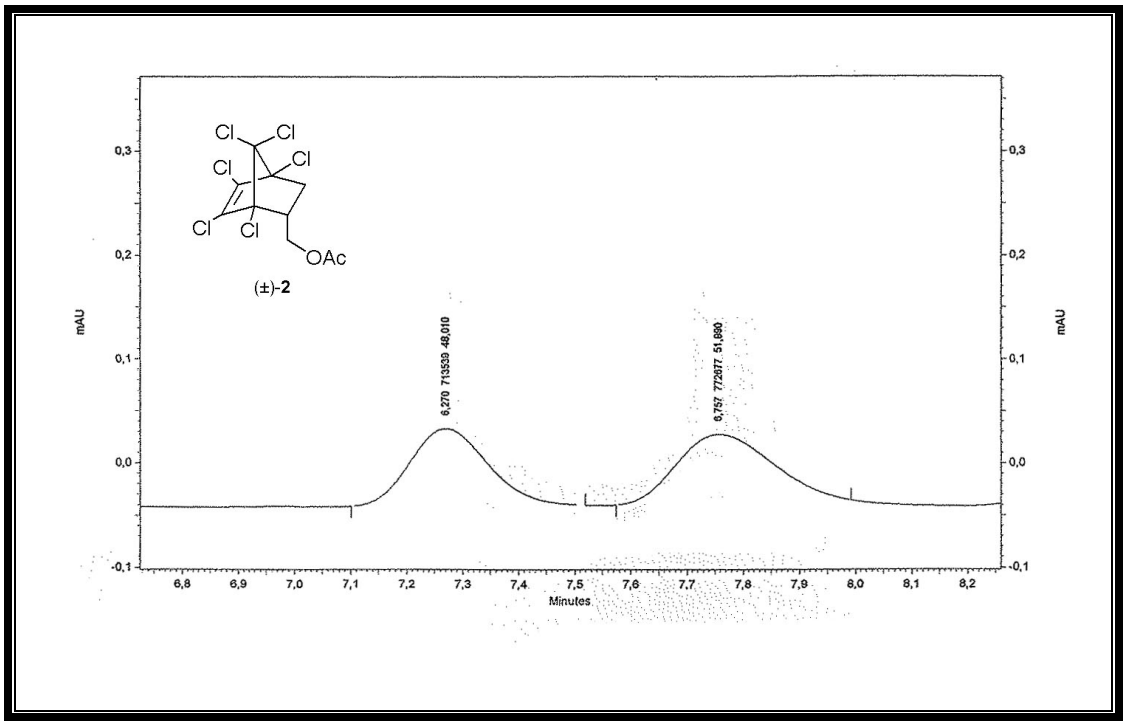

Figure A13. HPLC chromatogram of racemic acetoxymethyl derivative (±)-**2**

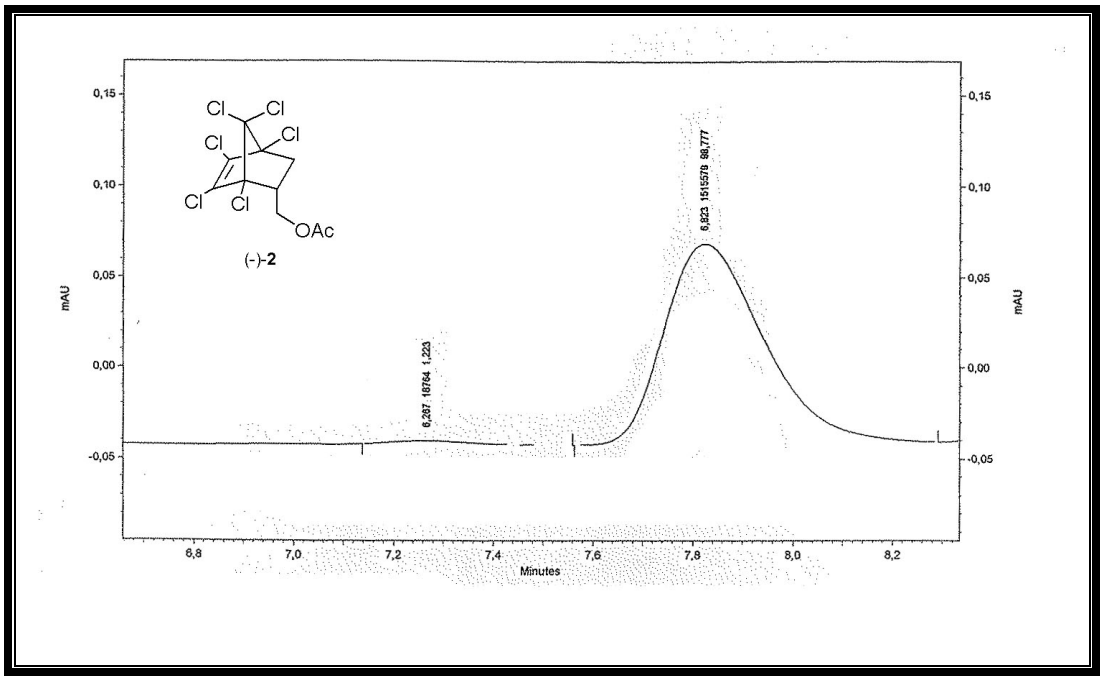

Figure A14. HPLC chromatogram of enantio-enriched acetoxymethyl derivative (-)-**2**

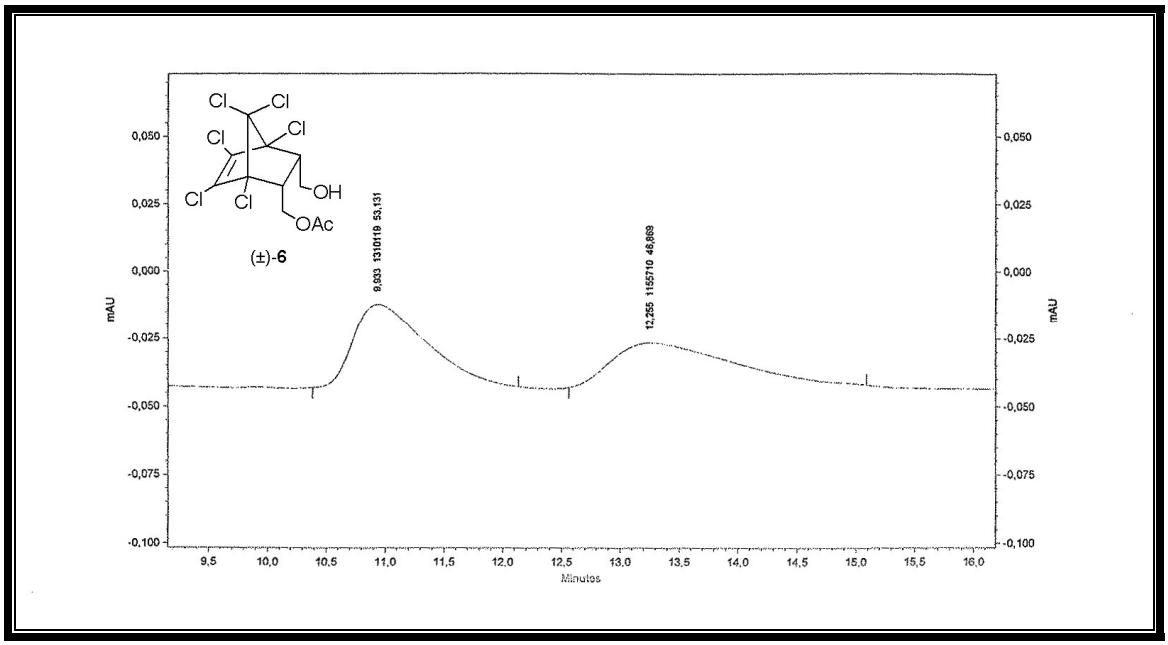

Figure A15. HPLC chromatogram of racemic hemiester derivative (±)-**6**

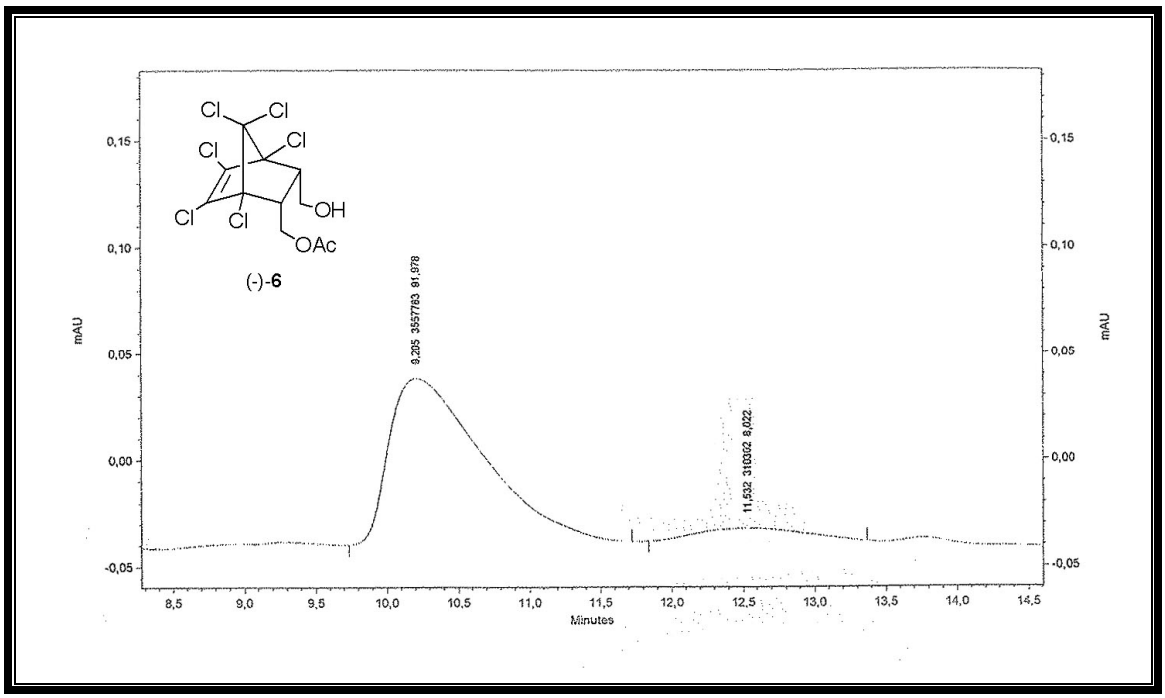

Figure A16. HPLC chromatogram of enantio-enriched hemiester derivative (-)-**6**

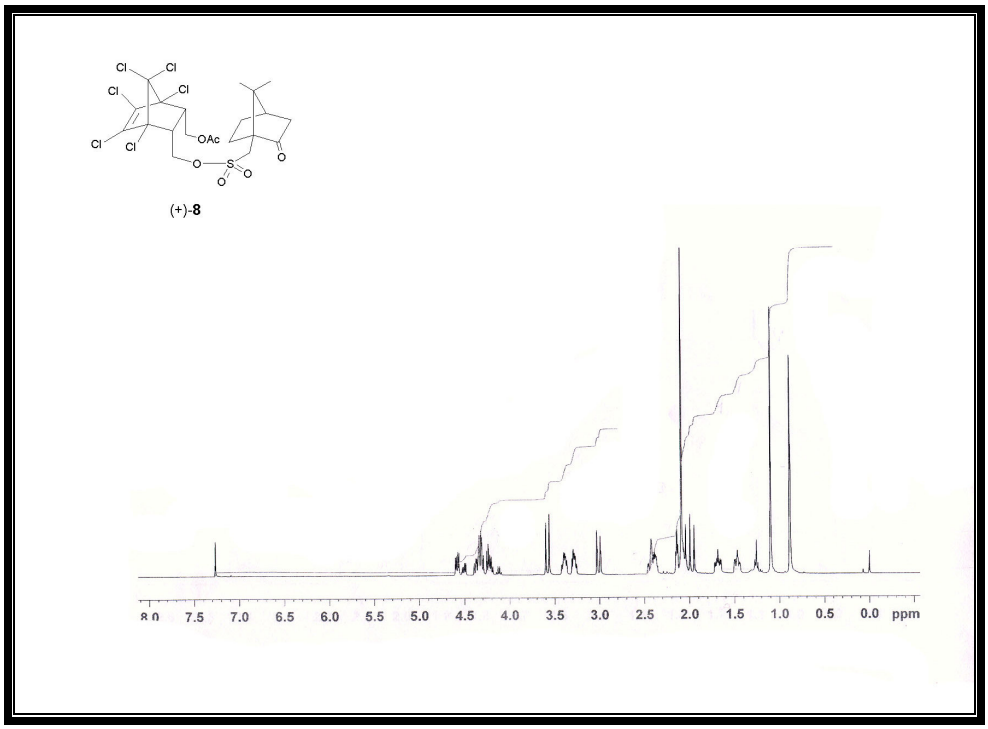

Figure A17. ^{1}H-NMR spectrum of the suphonate ester (+)-**8**.

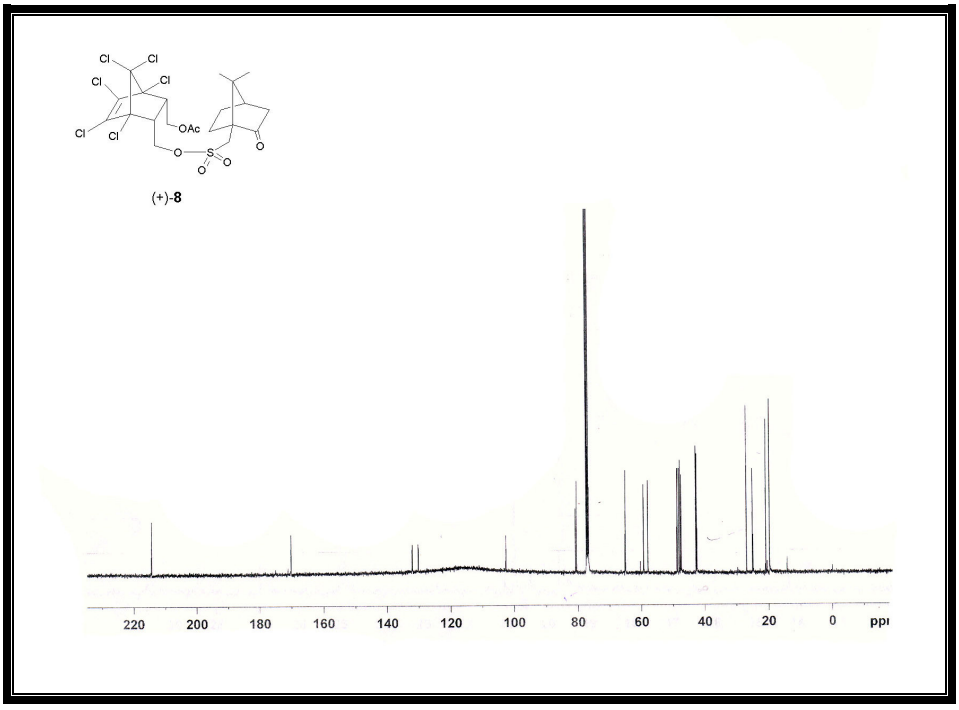

Figure A18. ^{13}C-NMR spectrum of the suphonate ester (+)-**8**.

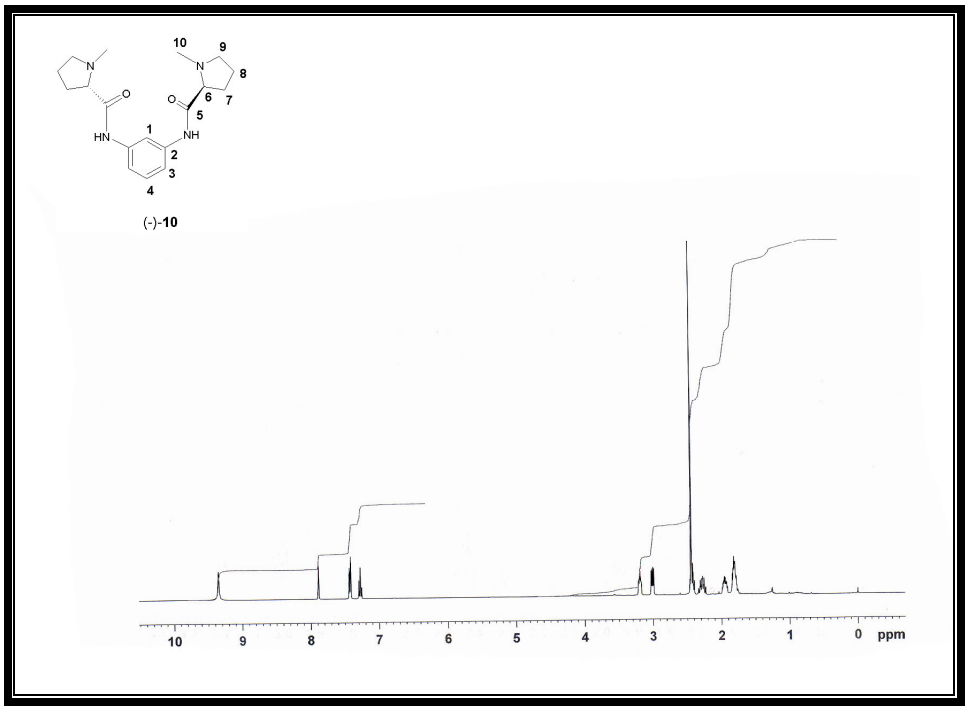

Figure A19. ^{1}H-NMR spectrum of the diamide derivative (-)-**10**

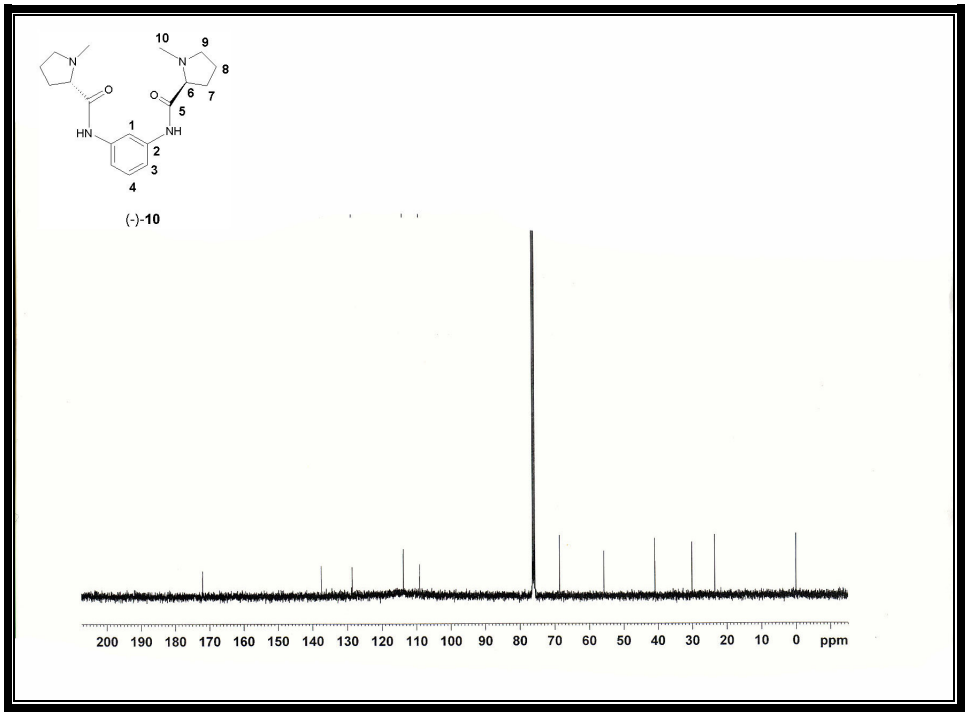

Figure A20. ^{13}C-NMR spectrum of the diamide derivative (-)-**10**

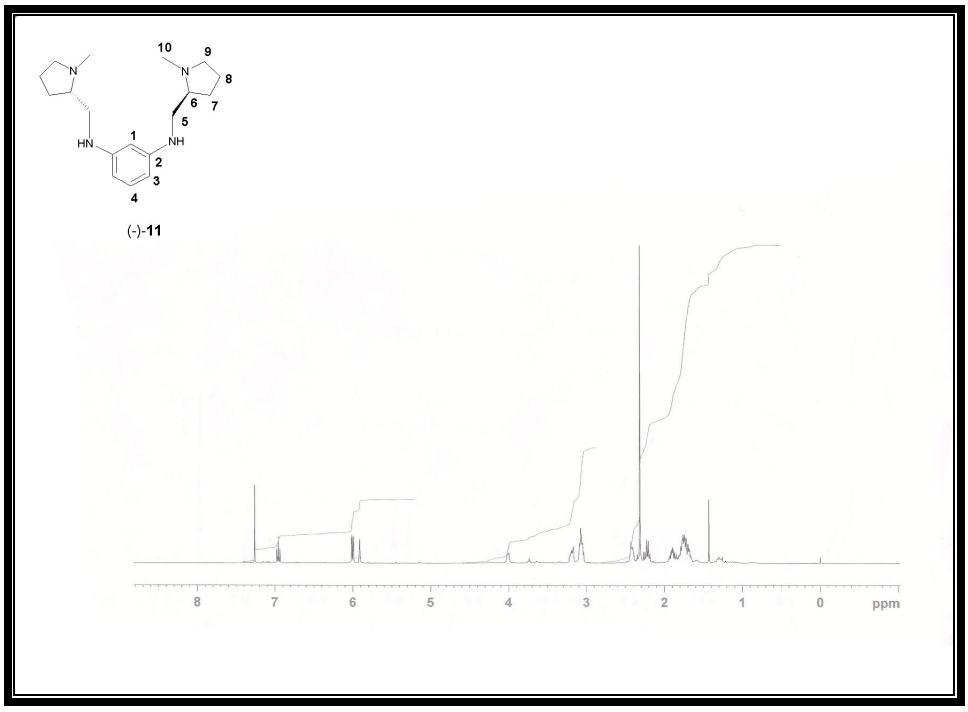

Figure A21. ^{1}H-NMR spectrum of the chiral diamine derivative (-)-**11**

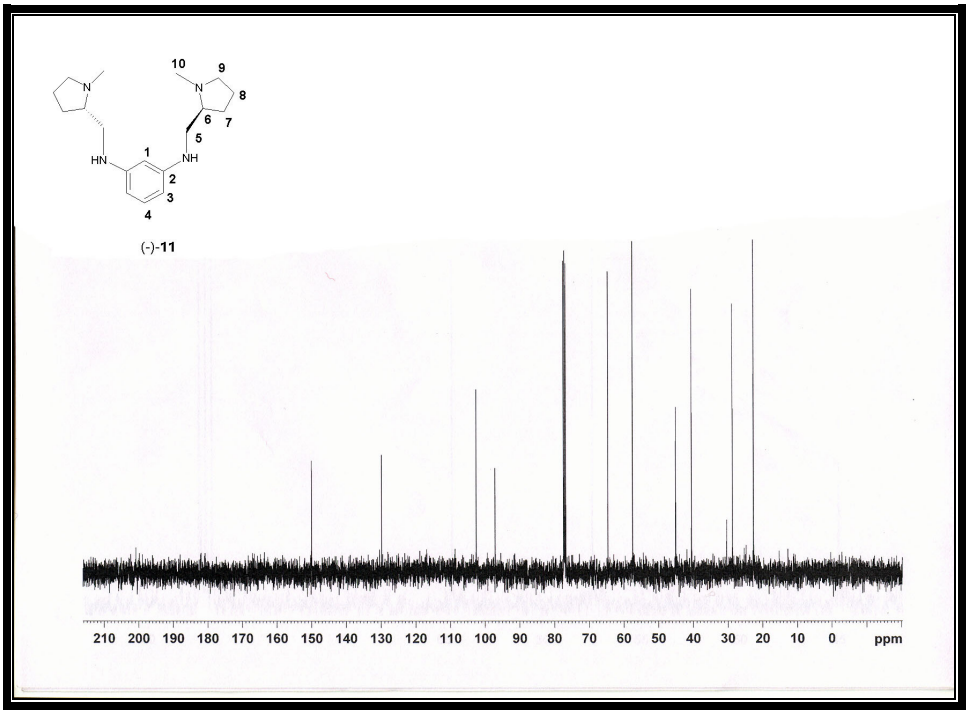

Figure A22. ^{13}C-NMR spectrum of the chiral diamine derivative (-)-**11**

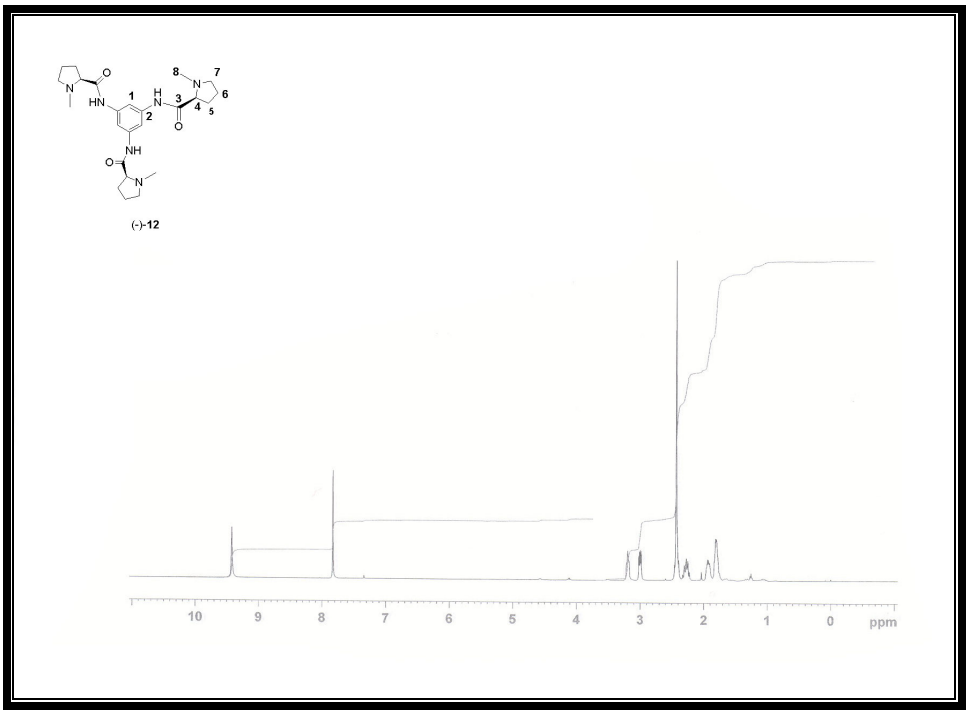

Figure A23. ^{1}H-NMR spectrum of the triamide derivative (-)-**12**

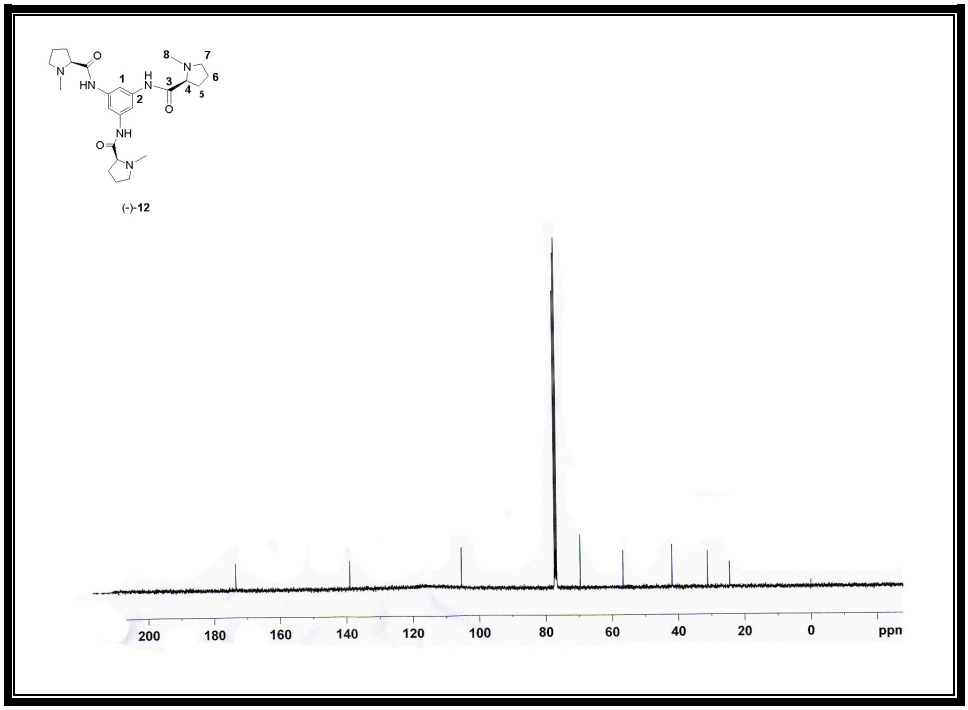

Figure A24. ^{13}C-NMR spectrum of the triamide derivative (-)-**12**

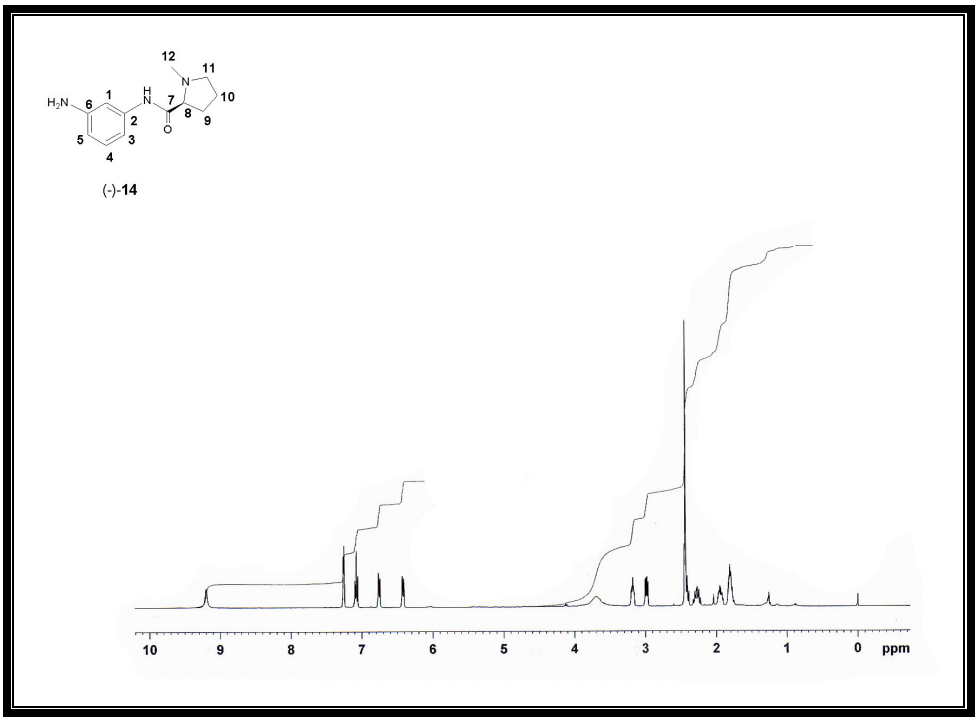

Figure A25. ^{1}H-NMR spectrum of the monoamide derivative (-)-**14**

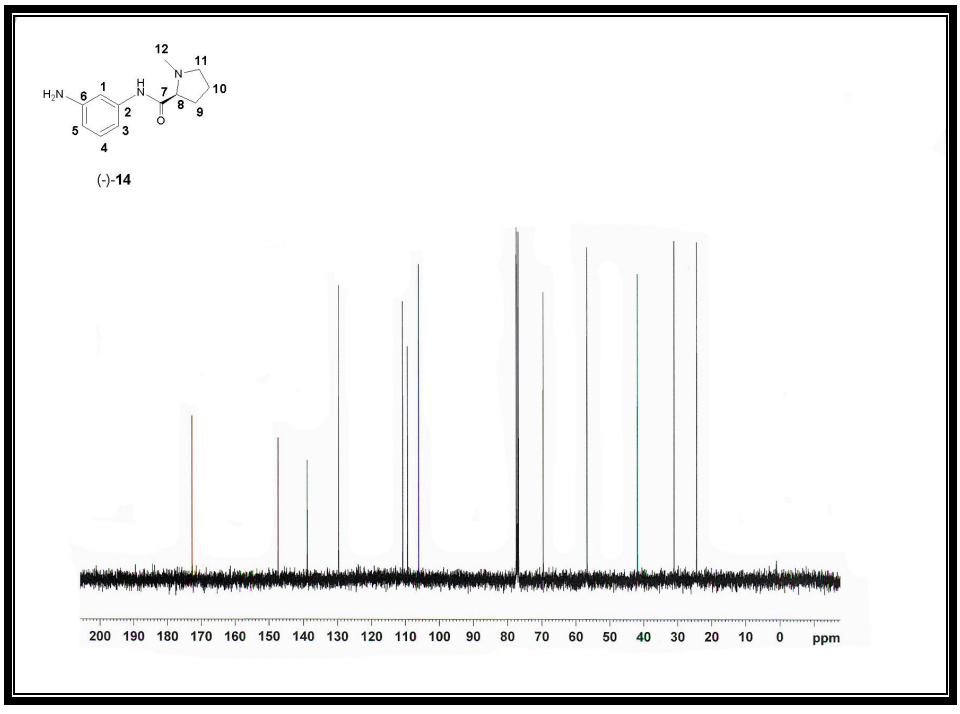

Figure A26. ^{13}C-NMR spectrum of the monoamide derivative (-)-**14**

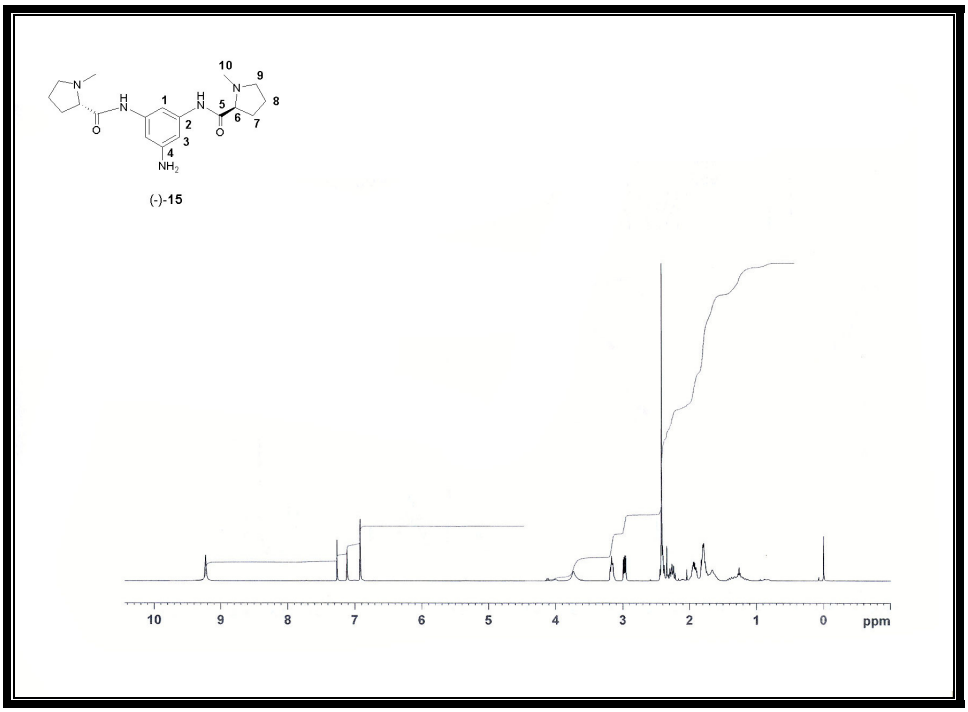

Figure A27. ^{1}H-NMR spectrum of the diamide derivative (-)-**15**

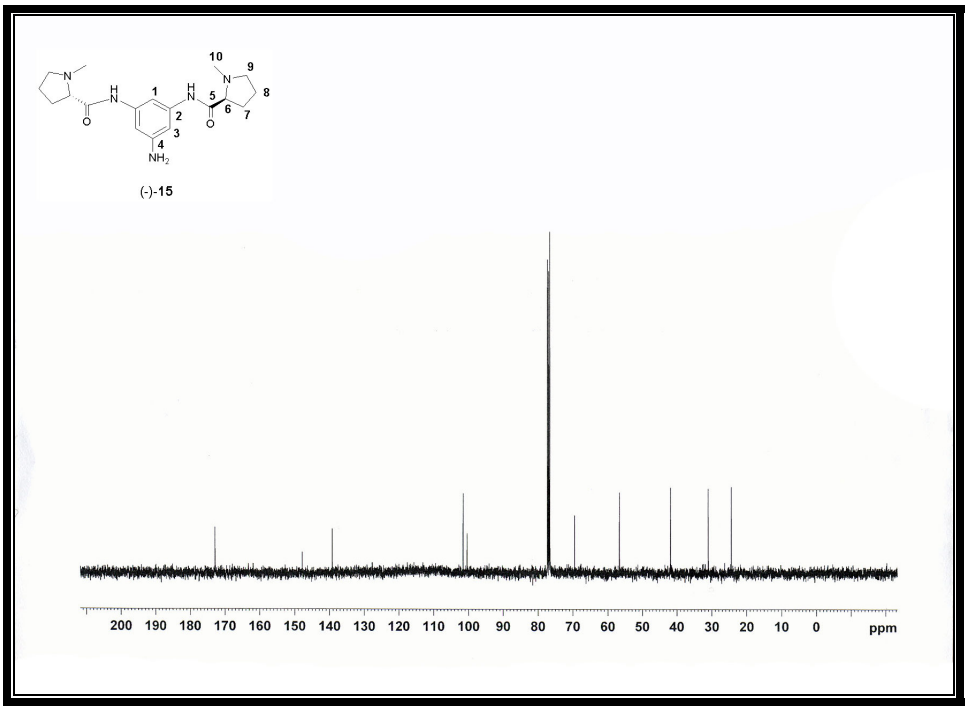

Figure A28. ^{13}C-NMR spectrum of the diamide derivative (-)-**15**