STEREOSELECTIVE SYNTHESIS OF CYCLOPENTANOIDS AND CYCLITOL DERIVATIVES ORIGINATED FROM POLYCHLORINATED NORBORNENE SYSTEMS

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ABSTRACT

STEREOSELECTIVE SYNTHESIS OF CYCLOPENTANOIDS AND CYCLITOL DERIVATIVES ORIGINATED FROM POLYCHLORINATED NORBORNENE SYSTEMS

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Optically active polychlorinated norbornene systems are important starting compounds for the synthesis of many complex molecules. The synthetic strategy of this study mainly depends upon the enzymatic resolution of hydroxymethyl-substituted polychlorinated norbornene structures. The enantiomerically enriched acetoxymethyl derivatives were synthesized in high ee values by several lipases. The absolute configuration of tetrachlorinated norbornene system was determined by X-ray analysis.

The second part of the thesis involves the ruthenium and cerium-catalyzed oxidation reactions of various polychlorinated norbornene derivatives to afford α-diketones. The regioselectivity of ruthenium catalyst was tested in polychlorinated norbornadiene systems.

In the third part of the study, cyclopentanoid derivatives were synthesized in high chemical yield starting from enantio-enriched both tetra- and hexa-chlorinated norbornene derivatives.

In the last part of the study, stereo- and regioselective synthesis of carbasugar systems which are potential glycosidase inhibitors were performed. Starting from enantio-enriched acetoxymethyl substituted tetrachloro norbornene system both carbasugar by cleavage of C_1-C_7 bond and 'confused' carbasugar by cleavage of C_4-C_7 bond were synthesized.

Keywords: Enzymatic resolution, oxidation of dihaloalkenes, cyclopentanoids, cyclitol, carbasugar.

ÖZ

SİKLOPENTANOİD VE SİKLİTOL TÜREVLERİNİN POLİKLORLU NORBORNEN SİSTEMLERİNDEN STEREO SEÇİCİ SENTEZİ

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Optikçe aktif poliklorlu norbornen sistemleri, birçok karmaşık moleküllerin sentezi için önemli başlangıç maddeleridir. Bu çalışmanın sentetik stratejisi temel olarak hidroksimetil poliklorlu norbornen yapılarının enzimatik ayrıştırılmasına dayanmaktadır. Enantiyomerce zenginleştirilen asetoksimetil türevleri çeşitli lipazlarla yüksek ee değerleriyle sentezlenmiştir. Tetraklorlu norbornen sisteminin mutlak konfigürasyonu X-ışınları yöntemiyle tayin edilmiştir.

Tezin ikinci bölümü çeşitli poliklorlu norbornen türevlerinin rutenyum ve seryum katalizörlü yükseltgenme tepkimesiyle α-diketonların oluşmasını içermektedir.

Çalışmanın üçüncü bölümünde, enantiyomerce zengin tetra ve hekzaklorlu norbornen sistemlerinden başlanarak siklopentanoid türevleri yüksek kimyasal verimle sentezlenmiştir.

Çalışmanın son bölümünde, potansiyel glikosidaz inhibitör özelliğe sahip karbaşekerler stereyo- ve regio-seçici olarak sentezlenmiştir. Enantiyozengin asetoksimetil tetraklorlu norbornen sisteminden başlanarak,

C_1-C_7 bağının kırılmasıyla karbaşeker, C_4-C_7 bağının kırılmasıyla 'karmaşık' karbaşeker sentezlenmiştir.

Anahtar kelimeler: Enzimatik ayrıştırma, dihaloalkenlerin yükseltgenmesi, siklopentanoitler, siklitol, karbaşeker.

To My dear family

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LIST OF ABBREVIATIONS

Ac	Acyl
br s	broad singlet (spectral)
˚C	degrees Celcius
CRL	Candida rugosa lipase
CIP	Chan Ingold Prelog system
COSY	correlation spectroscopy
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
dd	doublet of doublets (spectral)
DMSO	dimethyl sulfoxide
dtd	doublet of triplet of doublet (spectral)
ee	enantiomeric excess
Et	ethyl
g	gram(s)
h	hour(s)
HMBC	heteronuclear multi bond coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
i-Pr	isopropyl
LAH	lithium aluminium hydride
m	multiplet (spectral)
MCPBA	*meta*-chloroperbenzoic acid

Me	methyl
min	minutes
mL	milliliter(s)
mmol	millimole(s)
M.p.	melting point
NMO	N-methyl morpholine N-oxide
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
PPL	porcine pancreatic lipase
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofurane
TLC	thin layer chromatography
t_R	retention time (in HPLC)

CHAPTER 1

INTRODUCTION

1.1. Biological importance of chiral compounds

All the major biochemical events taking place in an organism are governed by enzymes. Since the majority of these events are highly selective with respect to the chirality of a substrate, it is obvious that the enantiomers of a given bioactive compound such as a pharmaceutical or an agrochemical cause different biological effects [1]. Consequently, they must be regarded as two distinct species. The isomer with the highest activity is denoted as the 'eutomer' whereas its enantiomeric counterpart possessing less or even undesired activities is termed as the 'distomer'. The range of effects derived from the distomer can extend from lower (although positive) activity, no response or toxic events. Some representative examples of different biological effects are given in Figure 1.

Probably the most well-known and tragic example of a drug where the distomer causes serious side-effects is 'Thalidomide', which was administrated in 1960s. At that time it was not known that the sedative effect resides in the (*R*)-enantiomer but the (*S*)-counterpart is highly teratogenic [2].

As a consequence, racemates of pharmaceuticals and agrochemicals should be regarded with suspicion. Chiral purity of drug molecules is therefore warranted essential. Recently, asymmetric syntheses of these molecules have gained importance.

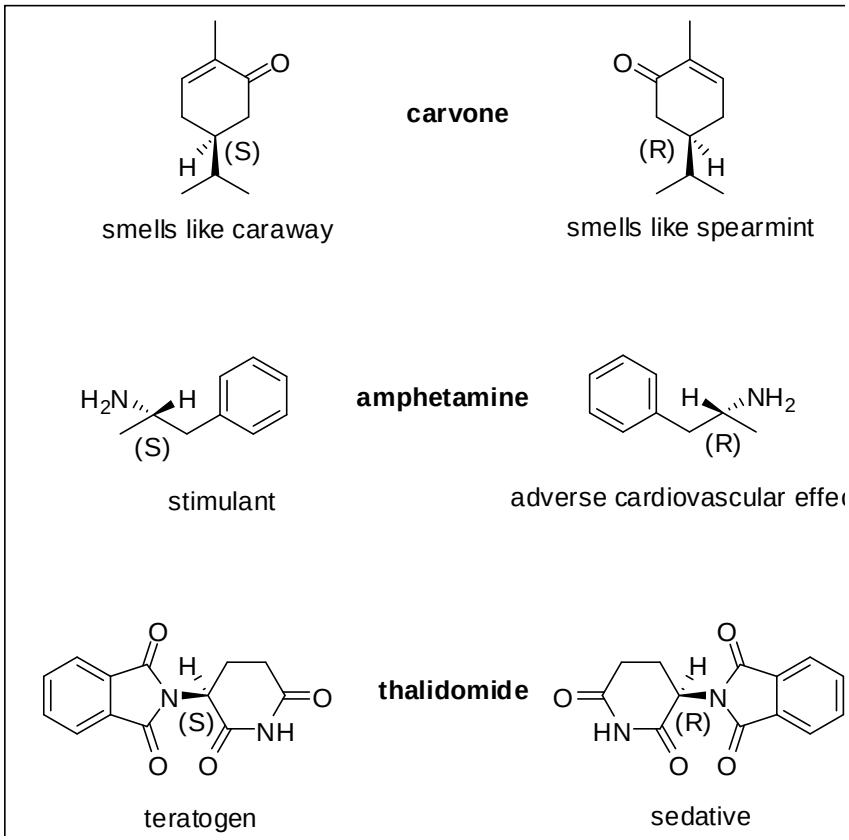


Figure 1. Biological effects of enantiomers

The principle of asymmetric synthesis [3] makes use of enantiomerically pure auxilary reagents which are used in catalytic or sometimes in stoichiometric amounts. They are often expensive and cannot be recovered in many cases. Likewise, starting a synthesis with an enantiomerically pure compound which has been selected from the large stock of enantiomerically pure natural compounds [4] such as carbohydrates, amino acids, terpenes or steroids (the so-called ‘chiral pool’) has its limitations. Considering the above mentioned problems with the alternative ways of obtaining enantiomerically pure compounds, it is obvious that enzymatic methods represent a valuable extra kit for the preexisting toolbox available for the asymmetric synthesis of fine chemicals [5].

1.2. Routes to enantiomerically pure compounds

The synthesis of optically active compounds is a subject that has fascinated chemists for more than a century. Since the pioneering work of Pasteur, van't Hoff and Le Bell [6] the area of stereochemistry began to evolve into the major field of research nowadays [7]. In recent years, the synthesis and isolation of enantiomerically pure compounds has gained new impetus, due to the realization that a chiral compound interacts with enantiomers in different ways as a result of a diastereomeric relationship [8].

The search for efficient syntheses of enantiomerically pure compounds is going on, largely stimulated by the requirements for new bioactive materials. In general there are three main routes to obtain pure enantiomers (Figure 2): resolution of a racemic mixture, synthesis with compounds from the chirality pool and asymmetric synthesis.

Figure 2. Routes to enantiomerically pure compounds

Although significant advances in other routes to obtain enantiomerically pure compounds have been reported, the classical resolution of racemates by diastereomeric crystallization still constitutes the most important method in industry [9]. However, the maximum theoretical yield of one enantiomer is 50%,

unless the unwanted enantiomer can be recycled. In a kinetic resolution the two enantiomers of a racemic mixture react at different rates with a chiral entity, preferably used in catalytic amounts [10].

Naturally occurring chiral compounds (referred to as the “chirality pool”) can be used as starting materials for enantiomerically pure compounds or may be employed as enantioselective agents (catalysts or ligands) in organic synthesis [11]. The lack of availability of both enantiomers of most natural compounds often is a limiting factor. Therefore many desired enantiomers have to be obtained by synthesis. In the early days, synthesis to enantiomerically pure compounds from prochiral precursors was considered possible only by using biochemical methods. Although powerful, those methods using enzymes, cell cultures, or (living) microorganisms are in most cases substrate specific.

Organic synthesis, on the other hand, has revealed a variety of versatile stereoselective reactions that complement biological processes [12]. Asymmetric synthesis is “a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate” [13]. Optically active compounds can be obtained using either a stoichiometric or a catalytic amount of chiral auxiliary. All stereoselective syntheses are based on the principle that the products are formed via diastereomeric transition states that differ in Gibbs free energy of activation. If this energy difference is sufficient (3 kcal/mol) one enantiomer will be formed, preferentially.

Asymmetric catalysis is the most promising and attractive form of stereoselective synthesis, since a small amount of enantiomerically pure material produces large quantities of enantiomerically enriched, or in the ideal situation, enantiomerically pure material. A wide variety of highly successful reactions with enantiomeric excesses (ee's) > 95% have been reported [14]. In most cases chiral transition metal complexes, often prepared in situ, are employed as the catalysts

[15]. The reactions involved are generally asymmetric reduction, asymmetric oxidation and asymmetric carbon-carbon bond formation.

1.3. Use of enzymes as catalysts

The development of synthetic organic chemistry has made possible the stereocontrolled synthesis of a very large number of complex molecules. As the field has developed, its targets and constraints have changed. Two problems now facing organic synthesis are the development of techniques for preparing complex, water-soluble biochemical, and the development of environmentally friendly synthetic processes that are also economically acceptable. Enzymes are able to contribute to the resolution of both of the issues, and they should be considered as one useful class of catalysts to be used, when appropriate, for organic synthesis.

Enzymes are proteins that catalyze most biological reactions *in vivo* and that can also act *in vitro* on both natural and unnatural substrates [16]. Enzymes have several advantages and disadvantages when compared to ordinary catalysts in chemistry:

Advantages:

- They accelerate the rate of reactions by a factor of 10^8-10^{10}.
- Enzymes are environmentally acceptable. Unlike heavy metals, for instance, biocatalysts are completely degraded in the environment.
- Enzymes act under mild conditions. This minimizes problems of undesired side-reactions such as decomposition, isomerization and racemization.
- Enzymes are compatible with each other. Since enzymes generally function under the same or similar conditions, several biocatalytic reactions can be carried out in one flask.
- Enzymes are not bound to their natural role. They exhibit a high substrate tolerance by accepting a large variety of man-made unnatural substances and often they are not required to work in water.

- Enzymes can catalyze a broad spectrum of reactions.

There is an enzyme-catalyzed process equivalent to almost every type of organic reaction [17]: for example;

➢ Hydrolysis-synthesis of esters [18], amides [19], lactones [20], lactams [21], ethers [22], acid anhydrides [23], epoxides [24], and nitriles [25].

➢ Oxidation-reduction of alkanes [26], alkenes [27], aromatics [28], alcohols [29], aldehydes and ketones [30, 31], sulfides and sulfoxides [32].

➢ Addition-elimination of water [33], ammonia [34], hydrogen cyanide [35].

➢ Halogenation and dehalogenation [36], alkylation and dealkylation [37], isomerization [38], acyloin- [39] and aldol reactions [40]. Even Michael-additions have been reported [41].

- Enzymes display three major types of selectivities:

Chemoselectivity

Since the purpose of an enzyme is to act on a single type of functional group, other sensitive functionalities, which would normally react to a certain extent under chemical catalysis, survive. As a result, reactions generally tend to be cleaner and purification of product(s) from impurities emerging through side-reactions can largely be omitted. For instance, enzymatic ester hydrolysis does not show any propensity for acetal cleavage.

Regioselectivity and Diastereoselectivity

Due to their complex three-dimensional structure, enzymes may distinguish between functional groups which are chemically situated in different regions of the same substrate molecule [42].

Enantioselectivity

Almost all enzymes are made from L-amino acids and thus are chiral catalysts [43]. As a consequence, any type of chirality present in the substrate molecule is recognized upon the formation of the enzyme-substrate complex. Thus a prochiral substrate may be transformed into an optically active product and

both enantiomers of a racemic substrate may react at different rates, affording a kinetic resolution. These properties collectively constitute the specificity of an enzyme and represent its most important feature for selective and asymmetric exploitation [44]. This key feature was recognized by E. Fischer as long ago as 1898 [45].

Disadvantages:

- Enzymes are provided by nature in only one enantiomeric form. Since there is no general way of creating mirror-image enzymes, it is impossible to invert the chiral induction of a given enzymatic reaction by choosing the other enantiomer of the biocatalyst, a strategy which is possible if chiral chemical catalysts are involved. To gain access to the other enantiomeric product, one has to follow a longer path in search of an enzyme with exactly the opposite stereochemical selectivity. However, this is sometimes possible.
- Enzymes require narrow operation parameters. The obvious advantage of working under mild reaction conditions sometimes turn into a drawback. If a reaction proceeds only slowly under given parameters of temperature or pH, there is only a narrow scope for alteration. Elevated temperatures as well as extreme pH lead to deactivation of the protein, as do high salt concentrations. The usual technique of lowering the reaction temperature in order to gain an increase in selectivity is of limited use with enzymatic transformations.
- Enzymes display their highest catalytic activity in water. Due to its high boiling point and high heat of vaporization, water is usually the least desired solvent of choice for most organic reactions. Furthermore, the majority of organic compounds are only poorly soluble in aqueous media. Thus shifting enzymatic reactions from an aqueous to an organic medium would be highly desired, but usually some loss of activity happens, which is often in the order of one magnitude.
- Enzymes are prone to inhibition phenomena. Many enzymatic reactions are prone to substrate or product inhibition, which causes the enzyme to cease to work at higher substrate and/or product concentrations, a factor which limits the

efficiency of the process. Whereas substrate inhibition can be circumvented comparatively easily by keeping the substrate concentration at a low level through continuous addition, product inhibition is a more complicated problem. The gradual removal of product by physical means is usually difficult as is the engagement of another step to the reaction sequence in order to effect chemical removal of the product.

- Enzymes may cause allergic reactions. However, this may be minimized if enzymes are regarded as chemicals and handled with the same care.

1.4. Mechanistic aspects

Among the numerous theories and rationales which have been developed in order to understand enzyme catalysis, the most illustrative models for the organic chemist will be briefly discussed.

1.4.1. Lock and key mechanism

The first proposal for a general mechanism of enzymatic action was developed by E. Fischer in 1894 [46]. It assumes that an enzyme and its substrate mechanistically interact like a lock and a key, respectively (Figure 3). Although this assumption was quite sophisticated at that time, it assumes a completely rigid enzyme structure.

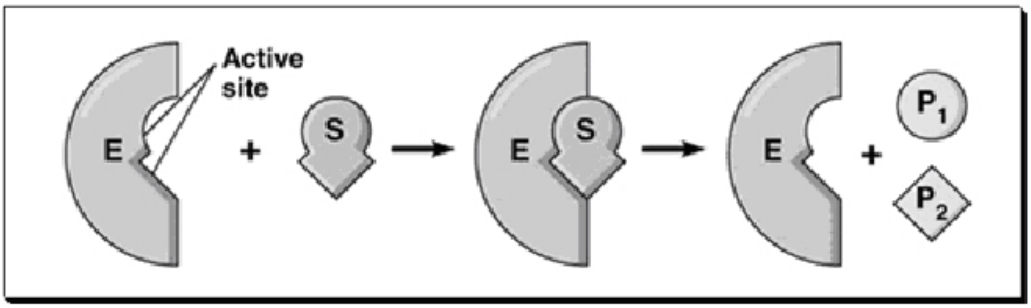


Figure 3. Representation of the Lock and Key mechanism

Thus, it cannot explain why many enzymes do act on large substrates, while they are inactive on smaller, similar counterparts. Given Fischer's rationale, small substrates should be transformed at even higher rates than larger substrates since the access to the active site would be easier. Furthermore, the hypothesis cannot explain why many enzymes can convert not only their natural substrates but also numerous non-natural compounds possessing different structural features. Thus, a more sophisticated model had to be developed.

1.4.2. Induced-fit mechanism

This rationale, which takes into account that enzymes are not entirely rigid but rather represent delicate and soft structures, was developed by Koshland Jr. in the late 1960s [47]. It assumes that upon approach of a substrate during the formation of the enzyme-substrate complex, the enzyme can change its conformation under the influence of the substrate structure so as to wrap around its guest (Figure 4). A similar picture is given by the interaction of a hand (the substrate) and a glove (the enzyme).

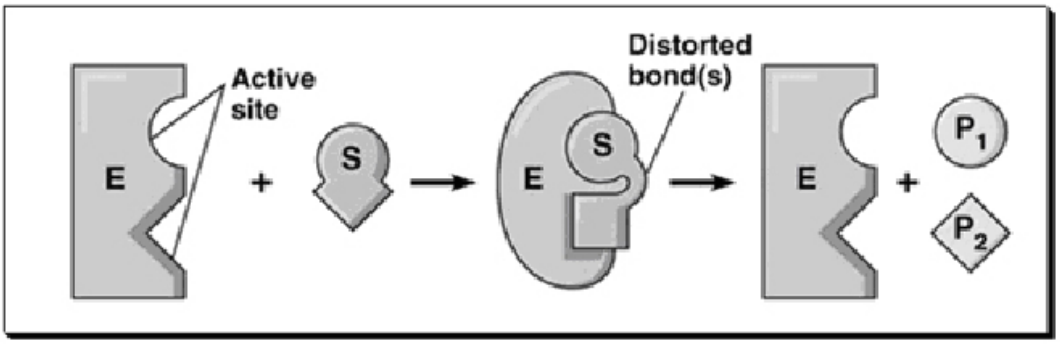


Figure 4. Representation of the induced-fit mechanism

This model can indeed explain why in many cases several structural features on a substrate are required. These structural features may be located quite a distance from the actual site of the reaction. The most typical 'induced-fit' enzymes are the lipases. They can convert an amazing large variety of artificial substrates which possess structures which do not have much in common with the natural substrates, triglycerides.

1.4.3. Desolvation and solvation-substitution theory

Quite recently, Dewar developed a different rationale [48] in attempting to explain the high conversion rates of enzymatic reactions, which are often faster than the chemically-catalyzed equivalent processes [49]. The theory (called the 'desolvation-theory') assumes that the kinetics of enzyme reactions have much incommon with those of gas-phase reactions. If a substrate enters the active site of the enzyme, it replaces all of the water molecules from the active site of the enzyme. Then, a formal gas phase reaction can take place which mimics two reaction partners interacting without disturbing solvent. In a solution, the water molecules impede the approach of the partners, hence the reaction rate is reduced. This theory would explain why small substrate molecules are often more slowly

converted than larger analogues, since the former are unable to replace all the water molecules from the active site. However, there is still much debate about this theory.

This desolvation theory has recently been extended by a solvation substitution theory [50]. It is based on the assumption that the enzyme would not be able to strip off the water which is surrounding the substrate to effect a desolvation, because this would be energetically unfavored. Instead, the solvent is displaced by another environment (provided by the active site of the enzyme) by a so-called ‘solvation substitution’. Thus the (often) hydrophobic substrates replace the water with the (often) hydrophobic site of the enzyme. In any case it is clear that a maximum change in entropy is only obtained upon a tight and close fit of a substrate into the pocket of an active site of an enzyme [51].

1.4.4. Three-point attachment rule

This widely used rationale to explain the enantioselectivity of enzymes was suggested by Ogston [52]. To get a high degree of enantioselection, a substrate must be held firmly in a three dimensional space. As a consequence, there must be at least three different points of attachment of the substrate onto the active site [53]. This is exemplified for the discrimination of the enantiomers of a racemic substrate (A and B, Figure 5) with its chirality located on a sp^3-carbon atom.

Case I: Enantiomer A is a good substrate by allowing an optimal interaction of its groups (A, B, C) with their complementary binding site areas of the enzyme (A´, B´, C´). It ensures an optimal orientation of the reactive group (D) towards the chemical operator which is required for a successful transformation.

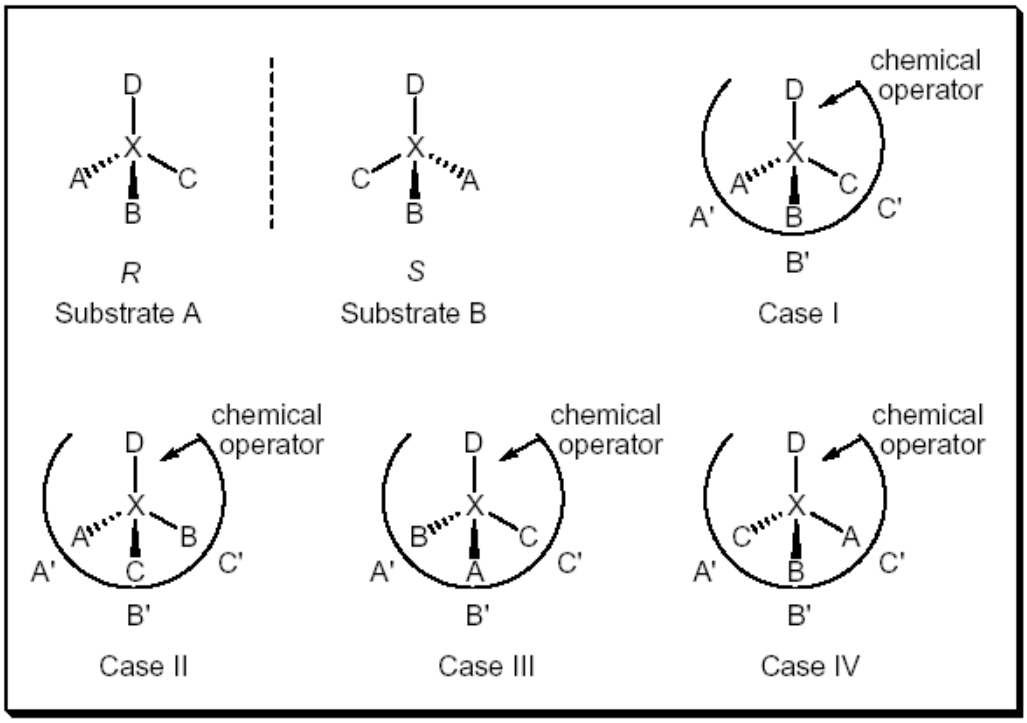


Figure 5. Enzymatic enantiomer discrimination

Cases II through IV: Regardless of its orientation in the active site, enantiomer B is a poor substrate because optimal binding and orientation of the reactive group D is not possible. Thus poor catalysis will be observed.

1.5. Classification of enzymes

International Union of Biochemistry has classified enzymes into six categories according to the type of reaction they can catalyze (Table 1).

Table 1. Classification of enzymes

Class	Enzyme	Number classified	available	Reaction type
1	Oxidoreductases	650	90	Oxidation-reduction: oxygenation of C-H, C-C, C=C bonds, or overall removal or addition of hydrogen atom equivalents.
2	Transferases	720	90	Transfer of groups: aldehydic, ketonic, acyl, sugar, phosphoryl or methyl.
3	Hydrolases	636	125	Hydrolysis-formation of esters, amides, lactones, lactams, epoxides, nitriles, anhydrides, glycosides.
4	Lyases	255	35	Addition-elimination of small molecules on C=C, C=N, C=O bonds.
5	Isomerases	120	6	Isomerizations such as racemization, epimerization.
6	Ligases	80	5	Formation-cleavage of C-O, C-S, C-N, C-C bonds with concomitant triphosphate cleavage.

1.6. Enzyme Sources

The large majority of enzymes used for biotransformations in organic chemistry are employed in a crude form and are relatively inexpensive. The preparations typically contain only about 1-30% of actual enzyme, the remainder

being inactive proteins, stabilizers, buffer salts or carbohydrates from the fermentation broth from which they have been isolated. It should be kept in mind that crude preparations are often more stable than purified enzymes.

The main sources for enzymes are as follows:

- The detergent industry produces many proteases and lipases in huge amounts. These are largely used as additives for detergents to affect the hydrolysis of proteinogenic and fatty impurities.
- The food industry uses proteases and lipases for meat and cheese processing and for the amelioration of fats and oils.
- Numerous enzymes can be isolated from slaughter waste or cheap mammalian organs such as kidney or liver. Alternatively, microbial sources can be utilized. Only a small fraction of enzymes is obtained from plant sources.
- Pure enzymes are usually very expensive and thus are mostly sold by the unit, while crude preparations are often shipped by the kg. Since the techniques for protein purification are becoming easier, thus making their isolation more economically feasible, the use of pure enzymes in biotransformations is steadly increasing.

1.7. Hydrolases

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 not require any cofactors or coenzymes to function and that they have a wide substrate range. 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 -chymotrypsin, papain, pepsin and trypsin belong to this subclass. On the other hand, esterases and lipases catalyze the hydrolysis of the ester groups of triglycerides 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

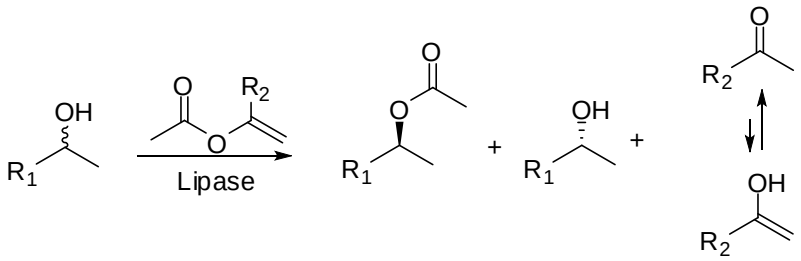
Pseudomonas sp. Lipases (*Pseudomonas fluorescens, Pseudomonas cepacia)* are typical lipases. Esterases have been found to be successful in the asymmetric hydrolysis reactions while lipases appear to be more effective in asymmetric acyl transfer reactions.

1.7.1. Acyl transfer

In contrast to hydrolytic reactions, where the nucleophile (water) is always in excess, the concentration of the foreign nucleophile in acyl transfer reactions (usually another alcohol or ester) is always limited. As a result, trans and interesterification reactions involving normal esters are generally reversible in contrast to the irreversible nature of a hydrolytic reaction. This leads to a slow reaction rate and can cause a severe depletion of the selectivity of the reaction. In order to avoid the undesired depletion of the optical purity of the remaining substrate during an enzymatic resolution under reversible reaction conditions, two tricks can be applied to shift the equilibrium of the reaction:

- use of an excess of acyl donor; this may be expensive and not always compatible to retain high enzyme activity,
- a better solution however, is the use of special acyl donors which ensure a more or less irreversible type of reaction.

Irreversible transesterification reagents such as oxime esters may also drive the equilibrium in the desired direction (i.e., ester formation) . The most widely accepted choice is the use of enol esters (vinyl or isopropenyl ester) and the unstable enols formed during hydrolysis tautomerizes to result in a carbonyl compound, and thus becoming unavailable for the reverse reaction (Scheme 1) [54].



Scheme 1. Irreversible acylation of alcohols with enol esters

Enzyme-catalyzed acylation in organic media is advantageous over hydrolytic reactions in particular due to the following reasons:

i) possible change of enantioselectivity,

ii) successful transformation of lipophilic substrates being poorly soluble in aqueous systems,

iii) better overall yields since loss-causing extractive workup is avoided,

iv) lack of undesired side-reactions requiring water such as racemisation,

v) no need for immobilization since enzymes can be recovered by simple filtration from the lipophilic media,

vi) enhanced stability of enzymes,

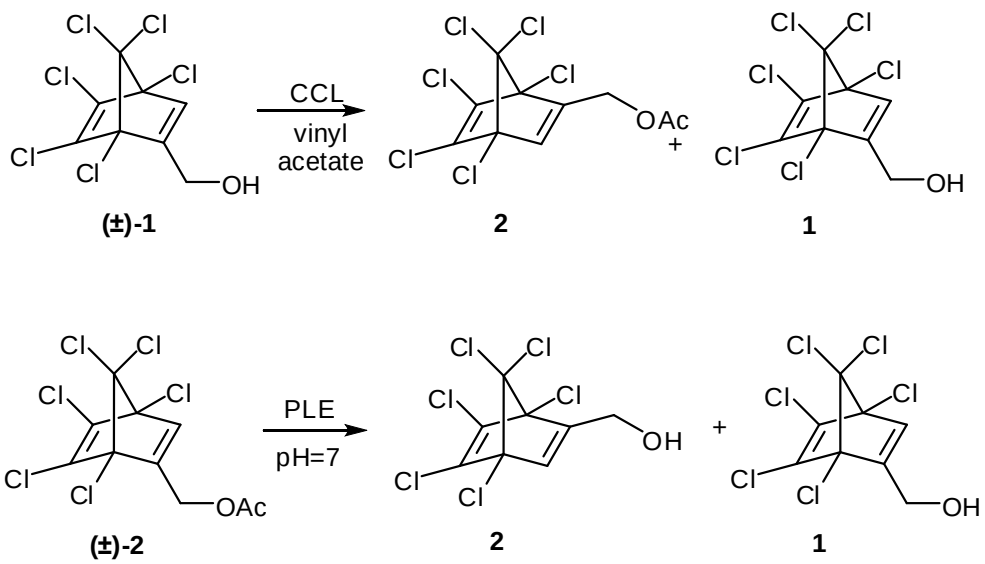
vii) a negligible risk of microbial contamination.

1.7.2. Kinetic resolution

In this approach a substrate is acted on by a chiral agent to produce one enantiomer or diastereomer of the product at a much faster rate than the other isomer. Kinetic resolution may be realized by chemical or enzymatic methods; in the former case the reaction may be either catalytic or stoichiometric with respect to the optically active auxiliary; from an economic standpoint catalysis is obviously preferred. Kinetic resolutions and high ee values are more commonly found with enzymic processes than chemical ones.

Despite its widespread use, kinetic resolution has several disadvantages for preparative applications, particularly on an industrial scale. After all, an ideal process should lead to a single enantiomer in 100 % chemical yield. The drawbacks are as follows: (i) the theoretical yield of each enantiomer is limited to 50 %. ii) Separation of the product from the remaining substrate may be laborious, in particular when simple extraction or distillation fails.

In the literature, there have been only a few examples of enzymatic resolution of hexa- and tetra-chlorinated norbornene derivatives. Tanyeli and coworkers have reported the lipase and esterase-catalyzed resolution of (±)-2-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hepta-2,5-diene (±)-**1** and (±)-2-acetoxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hepta-2,5-diene (±)-**2** (Scheme 2) which are key intermediates in the synthesis of biologically active analogues of the prostaglandin endoperoxides PGH_2 and PGG_2 [55] .



Scheme 2. Enzymatic resolution of alcohol and acetyl derivatives.

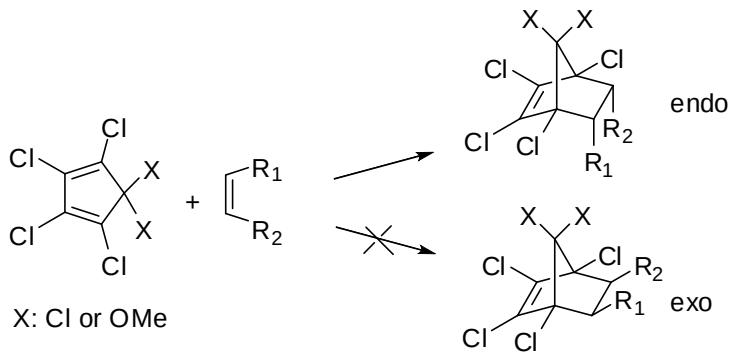
1.8. The Importance of Polychlorinated Norbornene Derivatives in Organic Synthesis

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 6).

Figure 6. The structures of some well-known organochlorine pesticides

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 organic synthesis.

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 3). 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.



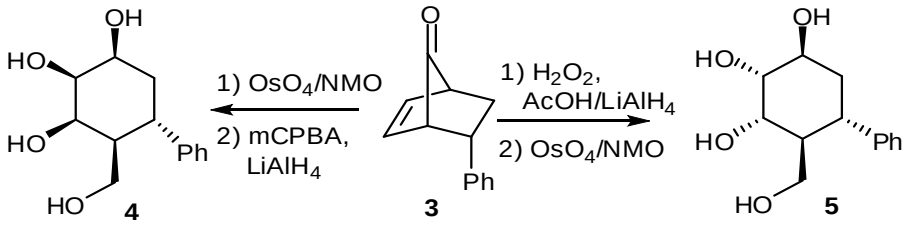
Scheme 3. *Endo* selective synthesis of polychlorinated norbornene derivatives

Apart from very high *endo*-selectivity associated with Diels-Alder reactions, there are several other fascinating features associated with these bicylic products which make them convenient entities in the synthesis of complex molecules.

1.8.1. Applications of norbornene derivatives in organic synthesis

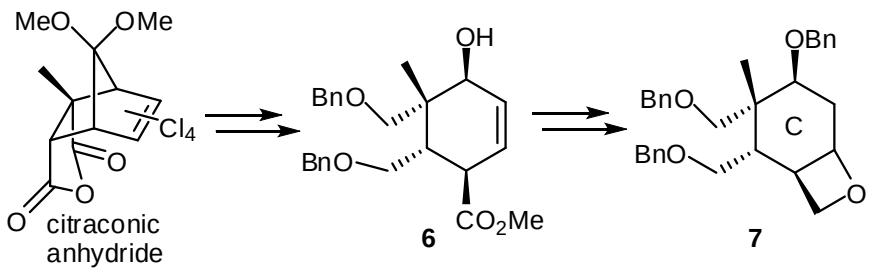
The norbornene skeleton acts as a powerful template for the regio- and stereoselective synthesis of complex molecules. For example, the bond between carbonyl carbon (C_7) and bridgehead carbon (C_1 or C_4) in **3** was broken by a two step procedure involving Baeyer-Villiger oxidation followed by $LiAlH_4$ reduction

to give cyclohexene derivatives **4** or **5** depending upon the sequence in which the two steps were executed, with as many as five stereocenters fixed (Scheme 4) [56].



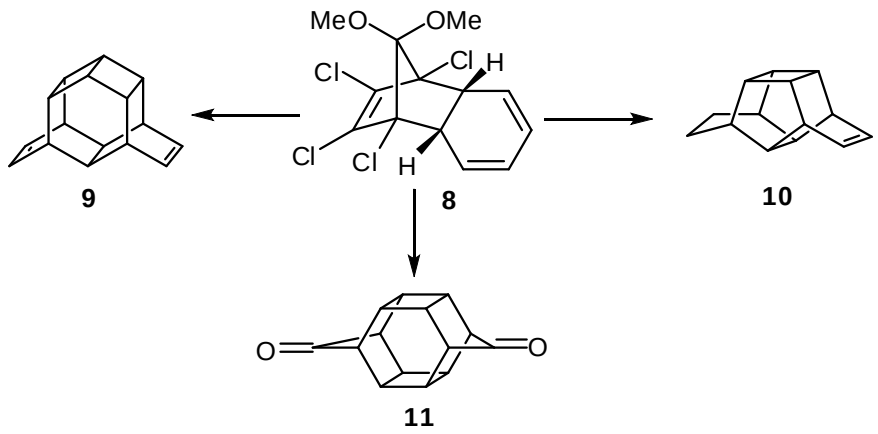
Scheme 4. Synthesis of cyclohexane derivatives **4** and **5**

The C-ring fragment **7** of the antitumour agent, Taxol was constructed in a stereocontrolled manner starting from citraconic anhydride adduct via the intermediate **6** (Scheme 5) [57].



Scheme 5. Synthesis of Taxol-C ring fragment.

There are many applications in the synthesis of unnatural products. The Diels-Alder adduct **8** serve as advantageous precursor for the construction of prismane analogues **9-11** (Scheme 6) [58].



Scheme 6. Synthesis of prismane analogues

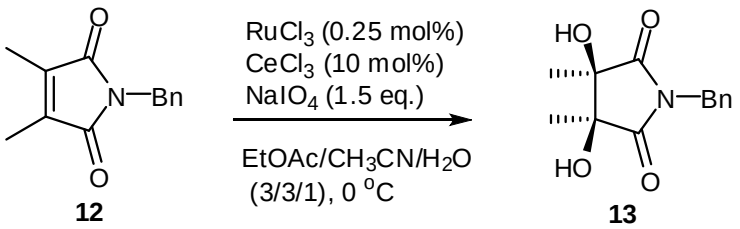
1.9 Ruthenium tetraoxide-catalyzed oxidations

The catalytic dihydroxylation of olefins represents a unique synthetic tool for the generation of two C-O bonds with defined relative configuration. The osmium-catalyzed dihydroxylation of C,C-double bonds belongs to the most successful catalytic transformations developed so far. The use of OsO_4, however, has several drawbacks. It is very expensive, volatile, and toxic. Hence, the search for a less expensive and toxic albeit comparably selective oxidation catalyst is still of current interest.

In 1981, the Sharpless group reported [59] an improved procedure for the cleavage of alkenes and oxidation of a range of functional groups with a catalytic amount of ruthenium tetraoxide and a stoichiometric amount (>2 equiv) of sodium metaperiodate in a two-phase solvent system (CCl_4, CH_3CN, H_2O in a ratio of 2:

2: 3). However, the dihydroxylation of olefins with RuO_4 has not been achieved in acceptable yields.

High catalyst loading and undesired side reactions were severe drawbacks in RuO_4-catalyzed oxidations of C,C-double bonds. Recently, Plietker's group were able to improve the RuO_4-catalyzed dihydroxylation by addition of Bronsted acids to the reaction mixture. The use of only 10 mol % of $CeCl_3$ allowed a further decrease in the catalyst concentration down to 0.25 mol % while broadening the scope of the reaction. Thus, the new bimetallic oxidation system of $RuCl_3/CeCl_3/NaIO_4$ represents an improved protocol for the preparation of *syn*-diols from unreactive or acid sensitive olefins in good to excellent yields [60]. A represantative example is shown in Scheme 7.



Scheme 7. $CeCl_3$-accelerated dihydroxylation

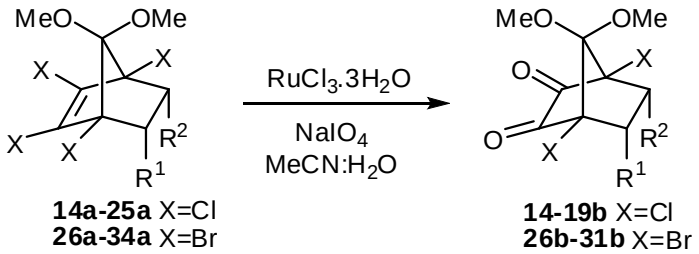
1.9.1. Conversion of vicinal dihaloalkenes to α-diketones

The α-diketones, a powerful assembly of two adjacent carbonyl groups, are of great interest because of their wide-ranging applications [61]. α-Diketones exhibit interesting photochemistry [62], are used as flavorants [63], serve as precursors for ligands in transition metal chemistry [64], and are used in the preparation of variety of heterocycles [65] and natural products [66]. α-Diketones also function as the key elements in the Weiss reaction [67] and in the construction of rigid molecular assemblies (molecular wires, rods, etc.) based on

“block” chemistry [68]. Some of the common methods to obtain α-diketones are the following: (i) oxidation of α-hydroxyketones [69], (ii) oxidation of alkynes [70] and (iii) oxidation of α-methylene ketones [71]. Although controlled oxidation of alkenes is difficult, $KMnO_4/Ac_2O$ was reported [72] to give low to moderate yields of α-diketone along with side products. However, the method is not suitable for small cyclic (below cyclooctene) and bicyclic systems.

Khan and coworkers have developed a novel, facile and extremely efficient methodology employing catalytic $RuCl_3.3H_2O$ and $NaIO_4$ as stoichiometric cooxidant for the conversion of vicinal dihaloalkenes to α-diketones [73]. The results are summarized in Table 2. In all cases the reaction proceeds smoothly and efficiently, providing good to excellent yield of α-diketones (entries 1-6, 13-18) or the interesting products derived from them (entries 7-12, 19-21) (Figure 7).

Table 2. Ruthenium-catalyzed oxidation of vicinal dihaloalkenes to α-diketones



entry	substrate	R^1, R^2	product	time	yield (%)
1	**14a**	CO_2Me	**14b**	13 h	95
2	**15a**	CO_2Me, H	**15b**	10 min	94
3	**16a**	$-CH_2OCH_2OCH_2-$	**16b**	6h	93
4	**17a**	$-(CH_2)_4-$	**17b**	6h	83
5	**18a**	Ph, H	**18b**	20 min	96
6	**19a**	OAc, H	**19b**	2 min	98
7	**20a**	CH_2OH	**20c,d,e**	38 h	21,30,34
8	**21a**	CH_2OH, H	**21b**	2 h	76
9	**22a**	CO_2H, H	**22b**	4 h	74
10	**23a**	$-CH_2OC(O)-$	**23b**	5.5 h	78
11	**24a**	$-C(O)-(CH_2)_3-$	**24b**	9 h	90
12	**25a**	$-C(O)-(CH_2)_2-C(O)-$	**25b**	6 h	94
13	**26a**	CO_2Me	**26b**	30 h	93
14	**27a**	CO_2Me, H	**27b**	2 h	89
15	**28a**	$-CH_2-O-CH_2-O-CH_2-$	**28b**	6 h	87
16	**29a**	Ph, H	**29b**	10 h	99
17	**30a**	OAc, H	**30b**	20 min	98
18	**31a**	CH_2OAc, H	**31b**	1 h	90
19	**32a**	CH_2OH	**32c,d,e**	34 h	55,30,10
20	**33a**	CH_2OH, H	**33b**	5 h	92
21	**34a**	CHO, H	**34b**	3 h	83

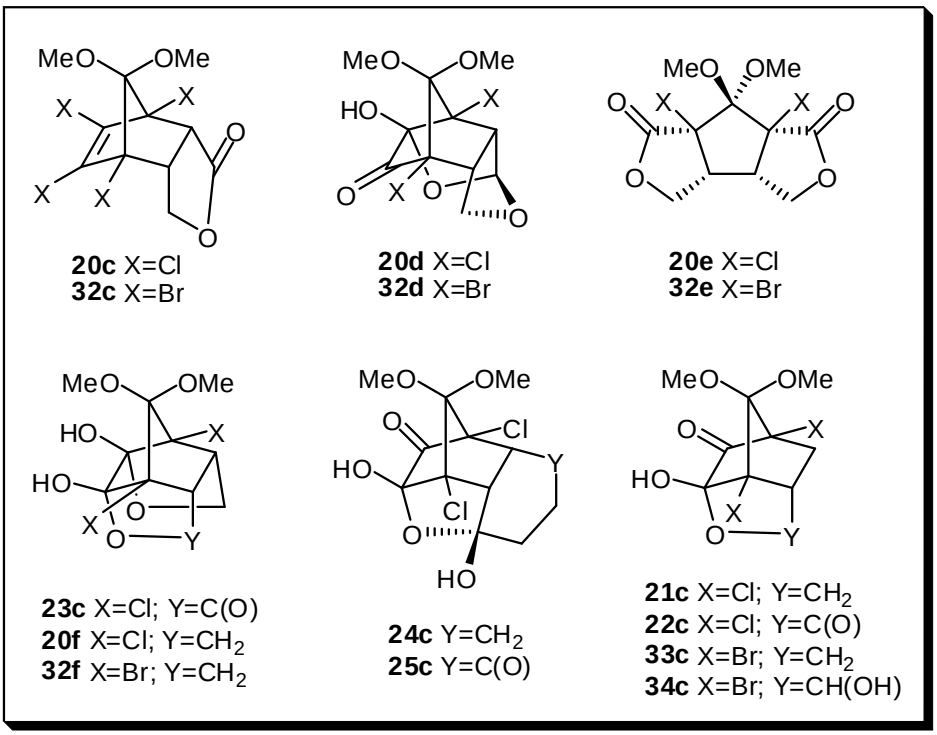
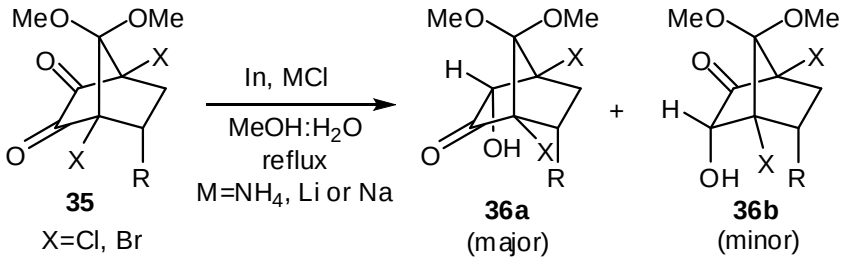


Figure 7. Interesting ruthenium tetroxide oxidation products

1.10. Regio- and diastereoselective reduction of norbornyl α-diketones

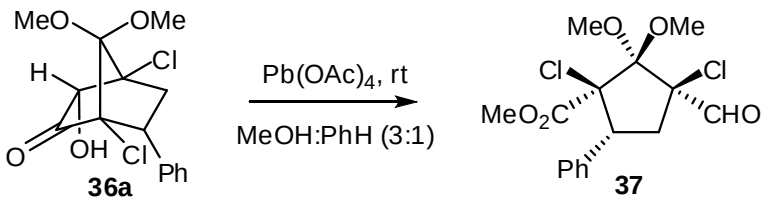
The acyloin (α-hydroxyketone) functional group plays an important role in organic synthesis and is widespread in compounds of natural origin as well as in advanced intermediates en route to several target molecules [74]. Conventionally, α-hydroxyketones are prepared by acyloin condensation reaction [75], oxidation of enolates [76], and reduction of α-diketones [77]. However, the problems of over-reduction to a diol or to an α-methylene ketone that are associated with reduction of α-diketones make this procedure less attractive. Indium-mediated reactions have gained considerable importance in the recent past due to their mild nature, functional group tolerance, high stereoselectivity, ease of handling and versatility of the reagent for a number of useful transformations that could be carried out even in water as solvent, without a need to rigorously exclude air [78].

Khan's group reported a mild, efficient and stereoselective route to acyloins mediated by indium metal in MeOH and water in the presence of NH_4Cl, LiCl or NaCl [79]. They synthesized both chloro and bromo derivatives of acyloins in a regio- and stereoselective manner (Scheme 8).



Scheme 8. Indium-mediated reduction of monosubstituted α-diketones to acyloins

On the other hand, treatment of acyloin **36a** obtained via indium reduction furnished the aldehyde **37** in good yield upon treatment with $Pb(OAc)_4$ in MeOH-PhH (3:1), thus constituting an efficient and stereoselective route to highly functionalized cyclopentane carboxaldehydes which are potential building blocks in organic chemistry (Scheme 9).



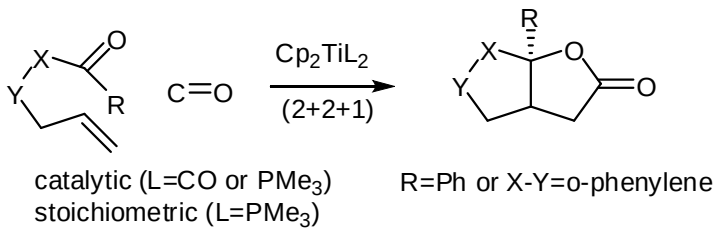
Scheme 9. Synthesis of cyclopentane carboxaldehyde

1.11. Importance of cyclopentane derivatives

Highly substituted cyclopentane rings are found within many biologically active natural and unnatural products such as prostaglandins, carbocyclic nucleosides, and carba-sugars. Specific examples include (+)-mannostatin A which inhibits Golgi from processing mannosidase II, sarkomycin an antibiotic, (-)-aristeromycin an antineoplasic antibiotic, and trehazolin an inhibitor of the enzyme trehalase which is involved in the control of insects and certain fungi [80].

A cyclopentane ring cis-fused at the α,β-bond of the γ-lactone is the basic structural unit of many complex and challenging biologically active natural products and also functions as the basic building block for the synthesis of a variety of cyclopentanoid natural products [81]. Various synthetic methods have been adopted in the literature to acquire this important ring system [82].

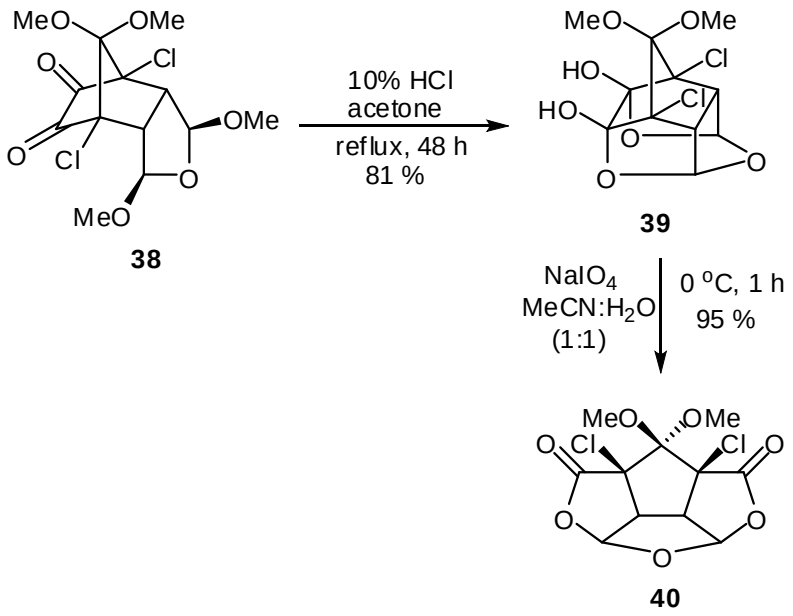
Crowe's group have developed a general catalytic protocol for the intramolecular Hetero-Pauson-Khand cyclization to convert unsaturated ketones and aldehydes to fused, bicyclic γ-butyrolactone products as shown in Scheme 10 [83].



Scheme 10. The Hetero-Phauson-Khand reaction

Khan and coworkers have reported the synthesis of bowl-like bis γ-lactone, symmetrical molecular architecture [84]. According to their strategy; the

hydrolysis of the cyclic ketal moiety **38** furnished caged bis-hemiacetal **39** and then oxidative cleavage of the glycolic bond employing $NaIO_4$ in 1:1 MeCN-H_2O gave the desired lactone **40** (Scheme 11).



Scheme 11. Synthesis of a novel, bowl-like bis lactone

1.12. Cyclitols

The word *cyclitol* refers to cyclic polyalcohols among which the great majority of work is dedicated to ones bearing cyclohexane skeleton, e.g. conduritols **41**, quercitols **42**, inositols **43**, carbasugars **44** and polycyclitols **45** (Figure 8). During the last era, chemists, as well as biologists and biochemists, have been captivated by the beauty of cyclitols, the attractiveness of which arises from their synthetic diversity and biological activities [85].

Conduritols, aminoconduritols, and their derivatives is of great interest due to their glycosidase inhibitory activity and antibiotic effects [86]. Quercitols constitute a large group of stereoisomeric family, some of which were isolated as

natural products. Inositols play a crucial role in signal transduction in living organisms, that is; they act as cell mediators.

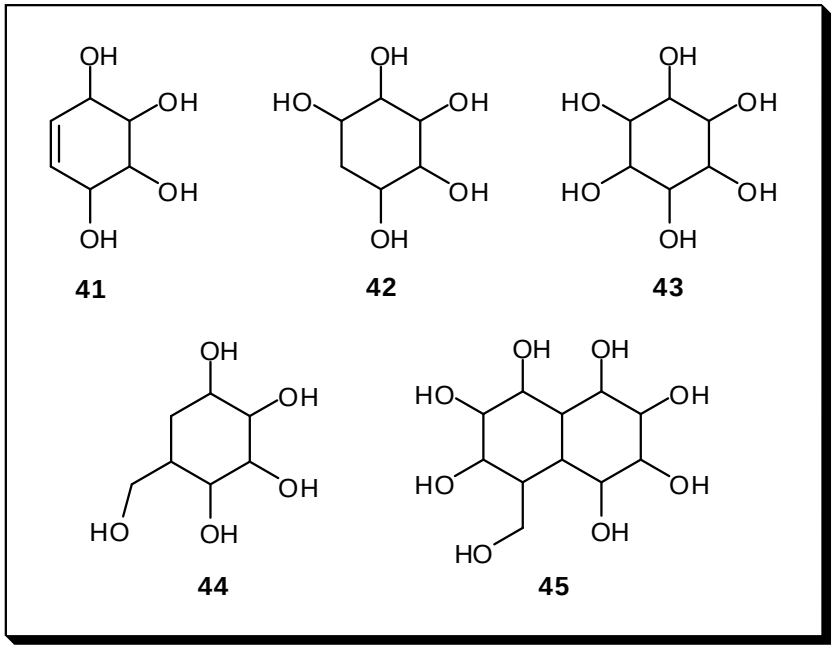


Figure 8. Important cyclitols

1.12.1 Conduritols

Conduritols are 1,2,3,4-cyclohexenetetrols having six diastereomers, theoretically. Two of these diastereomers are symmetrical and the others are found in four enantiomeric pairs. To avoid confusion, conduritols are named by letters A, B, C, D, E, and F in the order of their discovery (Figure 9). However, only two isomers A and F can be found in nature.

In 1908, Kübler isolated an alcohol from the bark of the vine *Marsdenia condurango* and he named it as "conduritol", which was optically inactive and later designated as Conduritol **A**. In 1962, Plouver discovered another conduritol isomer from *Crysanthemum Leucanthemum* and it was named as L-

Leucanthemitol (Conduritol **F**). Conduritol **F** can be found at least in traces in almost all green plants, while the abundance of conduritol **A** is limited to specific subfamilies of tropical plants.

Being an extensive subgroup of cyclitols, as it was mentioned before, conduritols are known to have some important biological activities, the most striking of which is that they are inhibitors of glycosidases. Moreover, they have antifeedant, antibiotic, antileukemic, and growth-regulating activity [87].

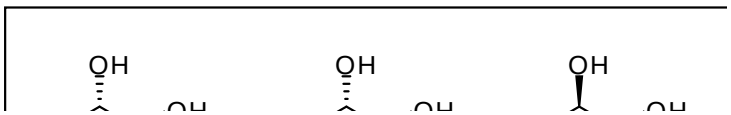
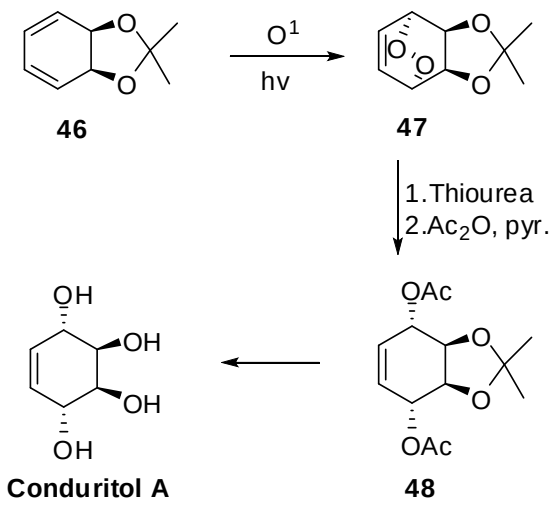


Figure 9. Conduritol isomers

In addition to their biological importance, conduritols and their derivatives involve in many reactions leading to the other interesting compounds like inositols, quercitols, deoxyinositols, aminoconduritols, conduritol epoxides, cyclophellitol, pseudo-sugars, amino sugar analogs, sugar amino acid analogs, etc. which make them synthetically valuable precursors [88].

In the literature, there are many examples for the synthesis of conduritols [89]. Balcı *et al.* added singlet oxygen to protected *cis*-benzenediol **46** and obtained only one *endo*-peroxide **47** with high yield. The selective cleavage of peroxide was achieved by thiourea. After hydrolysis of the ketal **48**, conduritol **A** was isolated (Scheme 12) [90].

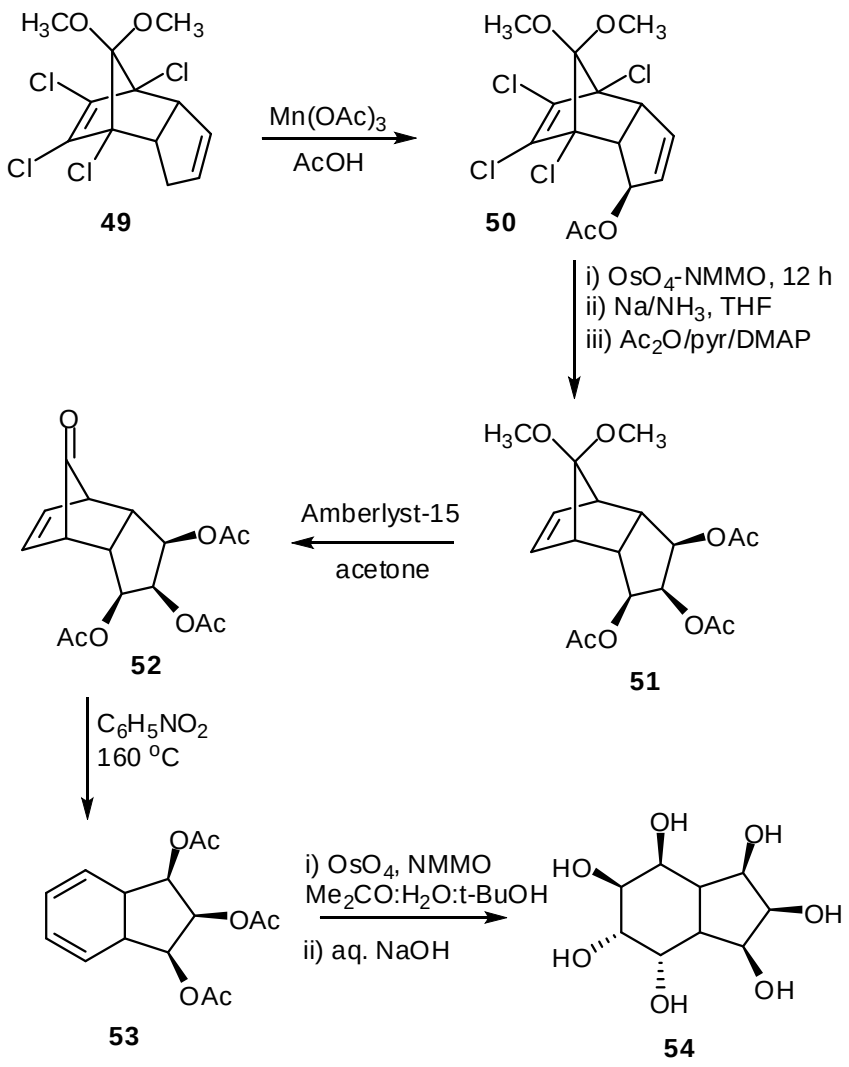


Scheme 12. Synthesis of conduritol A

1.12.2. Bicyclitols

Bicyclitols are fused polycarboxylic systems with dense hydroxyl functionalization. They can be regarded as annulated conduritol or carbasugars. Bicyclitols show potent and selective α-glucosidase inhibition at μM concentration [91].

Mehta et al. have described the synthesis of a new family of bicyclitols based on the hydrindane framework (Scheme 13). The bicyclitol **54** was screened against α- and β-glucosidases (from Bakers' yeast and almonds respectively) that accept corresponding p-nitrophenylglycosides as substrates. Moderate inhibition of α-glucosidase was observed, but not for β-glucosidase.



Scheme 13. Synthesis of bicyclitol **54**

1.12.3. Carbasugars

Carbasugars, also known as pseudosugars, are a family of carbohydrate mimics, which have attracted a great deal of attention among medicinal and organic chemists in recent years due to their potential biological properties as antibiotics, inhibitors of glucose-stimulated insulin release and more recently as inhibitors of various glycosidases. They are alicyclic cyclohexanes [2,3,4,5-tetrahydroxy-1-(hydroxymethyl)cyclohexanes] having structural features and substitution patterns similar to monosaccharides, in which the ring oxygen of the sugar moiety has been replaced by a methylene unit, Figure 10. These small molecules were initially postulated to exhibit similar biological properties to sugars and later work has confirmed this prediction. The ability of carbasugars to mimic the size and polarity of parent sugars and inertness towards glycosidases make them potential candidates for glycosidase inhibition.

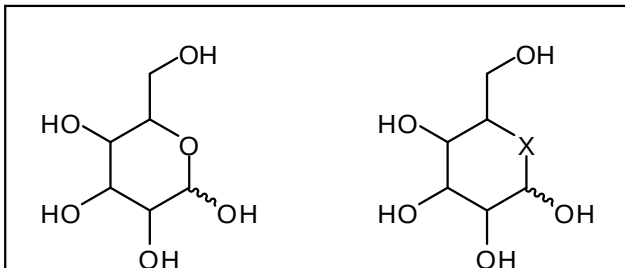
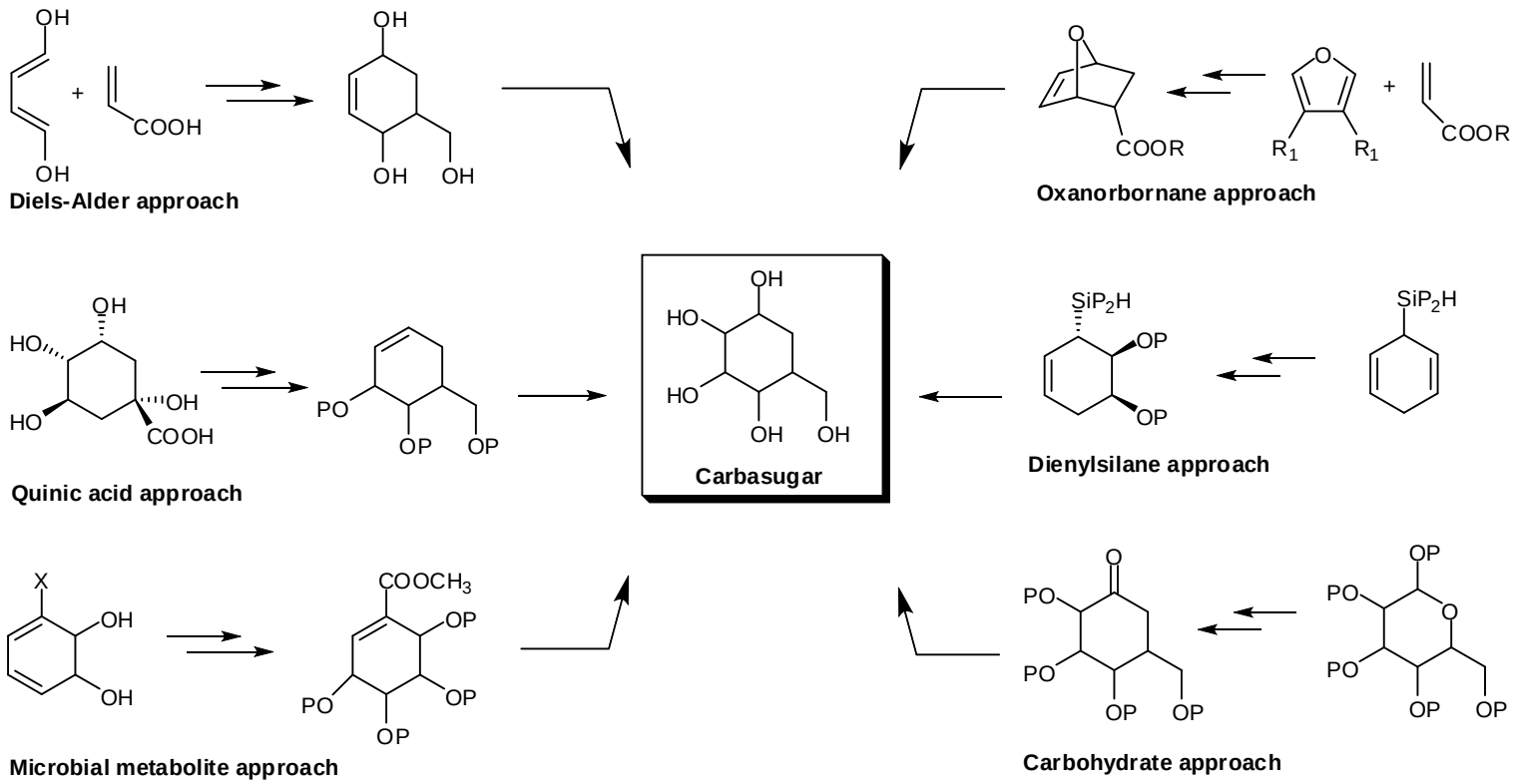


Figure 10. Sugar structures

Theoretically, there are 32 possible isomers of carbasugars and all the predicted carbasugars have been synthesized in racemic series [92]. The only naturally occurring carbasugar, pseudo-α-D-galactopyranose [93] was isolated

from the fermentation broth of *Streptomyces sp.* MA *4145* as an antibiotic against *Klebsibela pneumonia* MB-1264, almost seven years after its synthesis.

The biological significance of carbasugars has stimulated the scientific community to, synthesize them and their analogues either in racemic or in chiral form and several approaches have been used to accomplish their synthesis. Among the prominent ones are: transformation of natural sugars [94] , Diels-Alder reaction of cyclic dienes [95], modification of aromatics via microbial metabolism [96] or chemical oxidation [97], manipulations on quinic acid [98] and use of 7-oxanorbornanes as building blocks [99] Scheme 14**.**



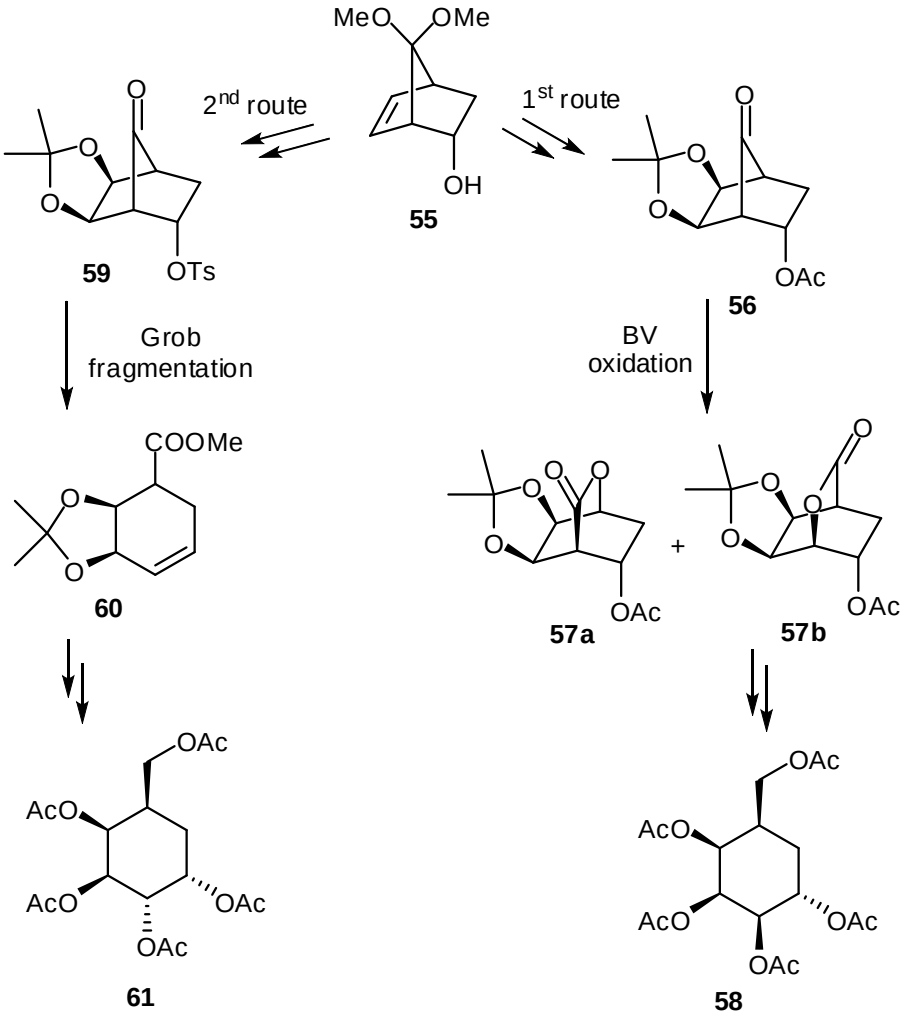
Scheme 14. Major synthetic approaches towards carbasugars

A novel approach towards the synthesis of several carbasugars emanating from norbornyl systems has been delineated by Mehta et al [100]. The key tactic involved in this strategy relied upon establishing the equivalence of a suitable norbornyl derivative with carbasugars. It was edvisaged that norbornyl system could be considered as an equivalent of the carbasugar because six carbons of the norbornane system (C1 to C6) can be considered as a carbasugar cyclohexane with bridgehead C7 being equivalent of the exo-hydroxymethyl group. This equivalence of the norbornane framework to a carbasugar could be established through the tactical cleavage of C4-C7 or C1-C7 bond in a suitably functionalized norbornyl derivative (Figure 11).

Figure 11. Carbasugar-norbornyl system equivalence

To execute this strategic cleavage, the first generation synthesis of carbasugars utilized Baeyer-Villiger (BV) oxidation in 7-ketonorbornyl derivative **56,** which was conveniently synthesized from the norbornyl system **55**, to furnish a regioisomeric mixture of lactone **57a** and **57b** in, 87:13 ratio (Scheme 15). Subsequently, the minor lactone **57b** obtained in BV oxidation was transformed to pseudo-α-talose **58**. The second-generation synthesis of carbasugars was affected through a novel Grob-type fragmentation reaction on a suitably orchestrated norbornyl ketone **59** thereby extracting the six-membered ring in the form of the cyclohexene ester **60** in a regioselective manner, Scheme 16. Further elaboration

of **60** furnished naturally occurring carbasugar pseudo-α-galactose **61** and other related sugars.



Scheme 15. First and second generation route to carbasugars

CHAPTER 2

RESULTS AND DISCUSSIONS

2.1. Aim of the study

Polychlorinated norbornene systems are important precursors for the synthesis of many chiral molecules since they can be resolved efficiently and they have flexible structures. In this study, we planned to resolve these polychlorinated norbornene systems with various lipases and obtain enantiomerically enriched starting compounds.

In the second part of the study, we planned to synthesize γ-lactone fused cyclopentanoids starting with enantiomerically enriched polychlorinated norbornene systems. The stereoselective synthesis of cyclopentanoids are of considerable interest as they can easily be converted into biologically active precursors and chiral ligands. The retrosynthetic approach is shown in Figure 12. Resolution studies will be performed with various lipases.

In the last part of the study, we aimed to synthesize two novel carbasugar derivatives which are good candidates for glycosidase inhibition. The starting compound is again enantiomerically enriched polychlorinated norbornene systems. The retrosynthetic analysis is shown in Figure 13.

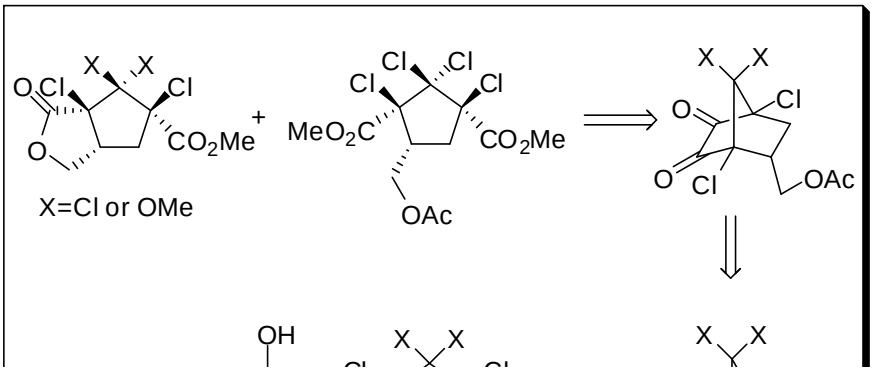


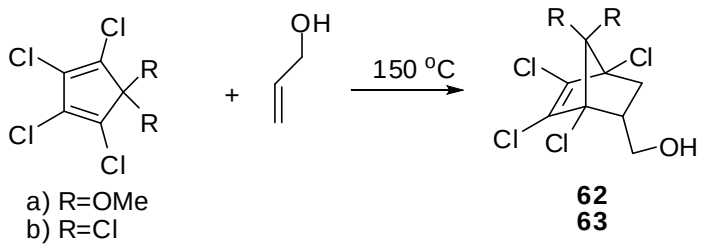
Figure 12. Retrosynthetic analysis of cyclopentanoids synthesis

Figure 13. Retrosynthetic analysis of carbasugar synthesis

2.2. Synthesis of racemic polychlorinated cycloadducts

Diels-Alder (D.A.) reaction is a well known method for the synthesis of various norbornene derivatives. Polychlorinated cyclopentadiene have emerged as an applicable and important diene system in D.A. reaction since they afforded only the *endo* product comparing with the nonchlorinated cyclopentadienes. The resultant polychlorinated *endo* norbornene adducts are valuable precursors due to their potential stereoselective nature and rigid structures. They can be resolved with very high ee% values compared to nonchlorinated norbornene systems. Moreover, they can easily be transformed to the corresponding norbornene derivatives via applicable dechlorination procedure.

In this study, (±)-2-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene **62** and (±)-2-hydroxymethylhexachloro bicyclo[2.2.1]hept-5-ene **63** were synthesized in their pure *endo* form, through Diels-Alder reaction by heating a mixture of 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene and hexachlorocyclopentadiene, and allyl alcohol in a sealed tube, respectively (Scheme 16).



Scheme 16. Synthesis of Diels-Alder adducts **62** and **63**

Structure elucidations of the compounds **62** and **63** were done by ^{1}H-NMR and ^{13}C NMR analysis.

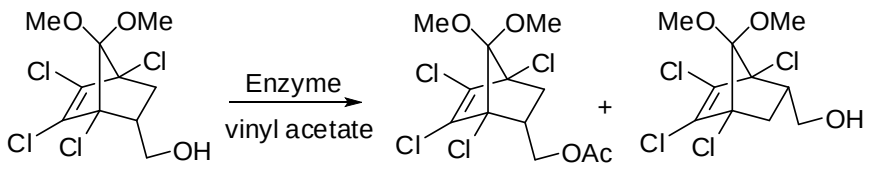
The ^{1}H NMR spectrum of **62** shows two multiplets at 3.70-3.66 and 3.32-3.27 ppm belonging to the diastereotopic CH_2O protons (Figure A1). CH proton which is splitted with four neighbouring protons gives a multiplet at 2.83-2.77 ppm. The *endo*-H_3 proton shows a doublet of doublets at 1.56 ppm, wheras the *exo* H_3 shows a doublet of doublets at 2.44 ppm. Since the dihedral angle between *exo*-H_3 and H_2 is 0˚ while it is 120˚ between *endo*-H_3 and H_2 ,coupling constant is greater in the former case (this numbering system is used as indicated in the experimental part). In the ^{13}C NMR spectrum, there are 10 different signals confirming the structure of **62** (Figure A1).

In the ^{1}H NMR spectrum of **63**, *endo* and *exo* methylene protons resonate at 1.85 and 2.59 ppm as doublet of doublets, respectively. The signals at 132.0 and 129.8 ppm in the ^{13}C NMR spectrum indicates the olefinic carbons (Figure A2).

2.3. Enzymatic resolution of (±)-2-Hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene and (±)-2-hydroxymethylhexachloro bicyclo[2.2.1]hept-5-ene

One of the most convenient method for obtaining enantiopure compounds is enzymatic resolution. In the literature, there are several examples for the resolution of chlorinated norbornene systems reported by our group [101]. In our study, first (±)-2-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo [2.2.1]hept-5-ene **62** was subjected to enzymatic resolution reaction with various lipases and vinyl acetate as acetyl source (Scheme 17).

During the course of our studies on the biotransformation of (±)-2-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene **62**, the screening reactions were first examined with various lipases (CRL, HLE, PPL and Novazyme 435) by the substrate:enzyme ratio which varied from 1:0.5 to 1:0.1. Among the lipases studied, CRL, PPL and Novazyme 435 proved suitable for the enantioselectice acetylation of this substrate.



Scheme 17. Resolution of **(±)-**2-Hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene, **62**

The first bioconversion was performed using PPL according to the following procedure. To a stirred solution of *rac*-**62** (500 mg) in vinyl acetate (5 mL), PPL (50 mg, 10% w/w) was added in one portion and the reaction mixture was shaked at 25 ˚C. The conversion was monitored by TLC and 50% conversion was obtained after 45 h. The products were separated by flash column chromatography and (+)-**64** was isolated with 64% ee in 45% yield. The next attempts involved the use of CRL (50 mg) and Novazyme 435 (100 mg) under the same conditions as given above. CRL appeared to be best enzyme tested, since (+)-(1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-en-2-yl) methyl acetate **64** was obtained with 88% ee in 45% isolated yield. HPLC chromatogram is given in Appendix part (Figure A39). In order to improve the enantiomeric excess value, the different experimental conditions have been applied and some experimental parameters have been changed. First, diisopropyl ether was used as co-solvent and then the experiments were performed by using the different amount of CRL, since it gives the best result in terms of enantioselectivity. Unfortunately, no increase in the enantioselectivity was observed. All ee determinations were done over acetylated derivative (+)-**64**, since it was effectively resolved by HPLC comparing the corresponding alcohol derivative (-)-**62**.

In order to determine the ee value of alcohol (-)-**62**, it was transformed into acetyl derivative (-)-**64** by chemical acetylation method. All of the enzymes

afforded the same configurated acetoxymethyl derivative (+)-**64**. The results are summarized in Table 3.

Table 3. Results of the enzyme catalyzed acetylation of **(±)-62**.

Entry	Enzyme	Ester	Substrate/Enzyme ratio (w/w)	Time (h)	Yield[a] (%)	$[\alpha]_D^{20}$	ee[b](%) of **64**
1	CRL	(+)-64	1:0.1	168	45	+10.7	88
2	Novazyme 435	(+)-64	1:0.2	20	49	+10.4	86
3	PPL	(+)-64	1:0.1	45	38	+7.6	64

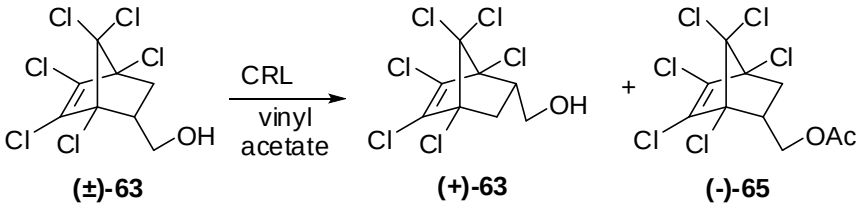
[a]Yiels (%) are given as the isolated esters.
[b]Enantiomeric excess values are determined by the Chiralcel OD-H chiral column HPLC-analysis

In the ^{1}H NMR spectrum of acetylated compound **64**, the characteristic acetyl protons resonate at 2.04 ppm. In the ^{13}C NMR spectrum, there are two additional signals when compared to that of **62**, belonging to the ester group. One of these signals appears at 170.6 ppm corresponding to the carbonyl carbon and the methyl carbon of the ester group gives a signal at 20.7 ppm (Figure A3).

Enzymatic resolution of **(±)-**2-hydroxymethyl-hexachloro[2.2.1]hept-5-ene **63** has been performed by our group (Scheme 18) [101]. The highest enantioselectivity was obtained by using catalytic CRL (substrate:enzyme=1:0.02) in vinyl acetate as 98% with 39% chemical yield. We followed the same procedure and got the same results. This enantiomerically enriched product was used as the starting compound in the synthesis of cyclopentanoids which will be discussed in the further parts.

In the ^{1}H NMR spectrum of acetylated compound **65**, the characteristic acetyl protons resonate at 1.99 ppm as singlet. In the ^{13}C NMR spectrum, there are

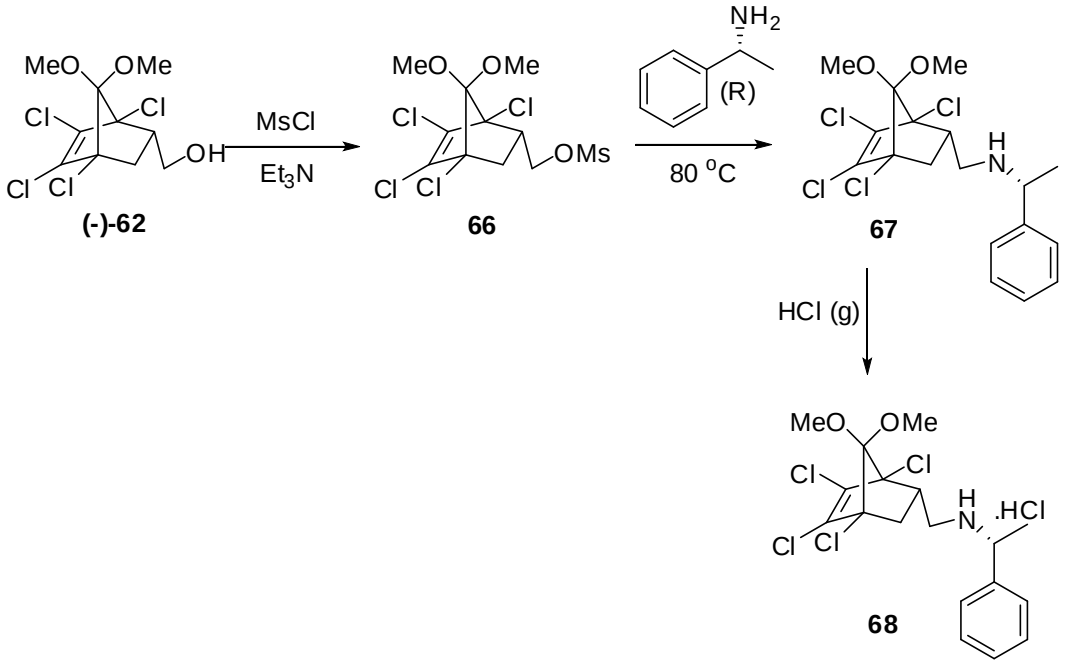
additional signals at 170.8 and 21.1 ppm indicating carbonyl carbon and the methyl carbon of the acetyl group, respectively (Figure A4).



Scheme 18. Resolution of **(±)**-2-hydroxymethyl-hexachloro[2.2.1]hept-5-ene, **63**

2.4. Absolute configuration determination of alcohol (-)-62 and (+)-63

The absolute configuration of the enantiomerically enriched alcohol **(-)-62** isolated with 80% ee from CRL-catalyzed acetylation was determined by transforming it into first corresponding mesylate derivative **66** and subsequent substitution with optically pure (+)-(*R*)-methyl-benzylamine afforded the corresponding amine compound **67**. Since it has not appropriate crystal structure for X-ray analysis, it was transformed into its HCl salt by passing HCl gas through the amine solution and the crystals of **68** were obtained (Scheme 19). Absolute configuration was determined by X-ray analysis.



Scheme 19. Synthesis of amine salt **68**

In ^{1}H NMR spectrum of mesylate **66**, the expected characteristic signals were observed as two doublets of doublets at 2.56 and 1.73 ppm belong to *exo* and *endo*-H_3 protons of methylene on norbornene skeleton, respectively. Diastereotopic protons of methylene group possessing mesylate unit are observed as two doublets of doublets at 4.29 and 3.91 ppm. The singlet at 3.03 ppm shows CH_3 protons of mesyl group. ^{13}C NMR spectrum is very similar to that of alcohol (-)-**62** except one additional peak at 37.6 ppm coming from mesyl moiety (Figure A5).

In ^{1}H-NMR spectrum of amine **67**, aromatic protons resonate at 7.26-7.15 ppm as a multiplet. The diastereotopic CH_2 protons show a multiplet at 3.65-3.60 ppm due to the neighboring NH proton. In the ^{13}C NMR spectrum, new six signals at 144.9, 129.4, 127.9, 127.7, 126.5 and 126.0 ppm which belong to aromatic carbons are observed (Figure A6).

The crystal structure analysis [102] of **68** confirmed the compound as N-(1-phenylethyl)-1,2,3,4-tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-2-ene-5-methan-amine hydrochloride (Figure 14). There are four ion-pairs (I to IV) in the asymmetric unit (this is the unit cell in the triclinic non-centrosymmetric space group P 1). In the crystal 84.1% of the cations (namely the cations I to III and 36.4(3)% of the cations IV) show the *R,S,S,R* configuration (related to the asymmetric C atoms at C1, C4, C5, and C17 in molecule I), and 15.9% (namely 63.6(3)% of the cations IV) show the *S,R,R,R* configuration (Figure 15). Due to this disorder two of the four chloride anions are disordered as well. Nevertheless each N atom has exactly two hydrogen bonds by each of its bonded H atoms to a chloride anion. By these hydrogen bonds an isolated tetrameric aggregate consisting of four Cl^- anions and of four almost coplanar NH_2^+ groups is formed.

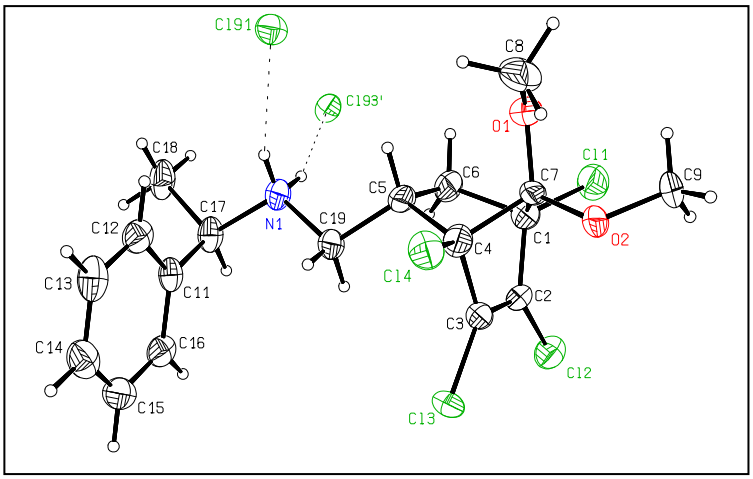


Figure 14. ORTEP plot of one cation of **68** together with its coordinating anions showing the atomic numbering scheme. The presumed hydrogen bonds are drawn with dotted lines.

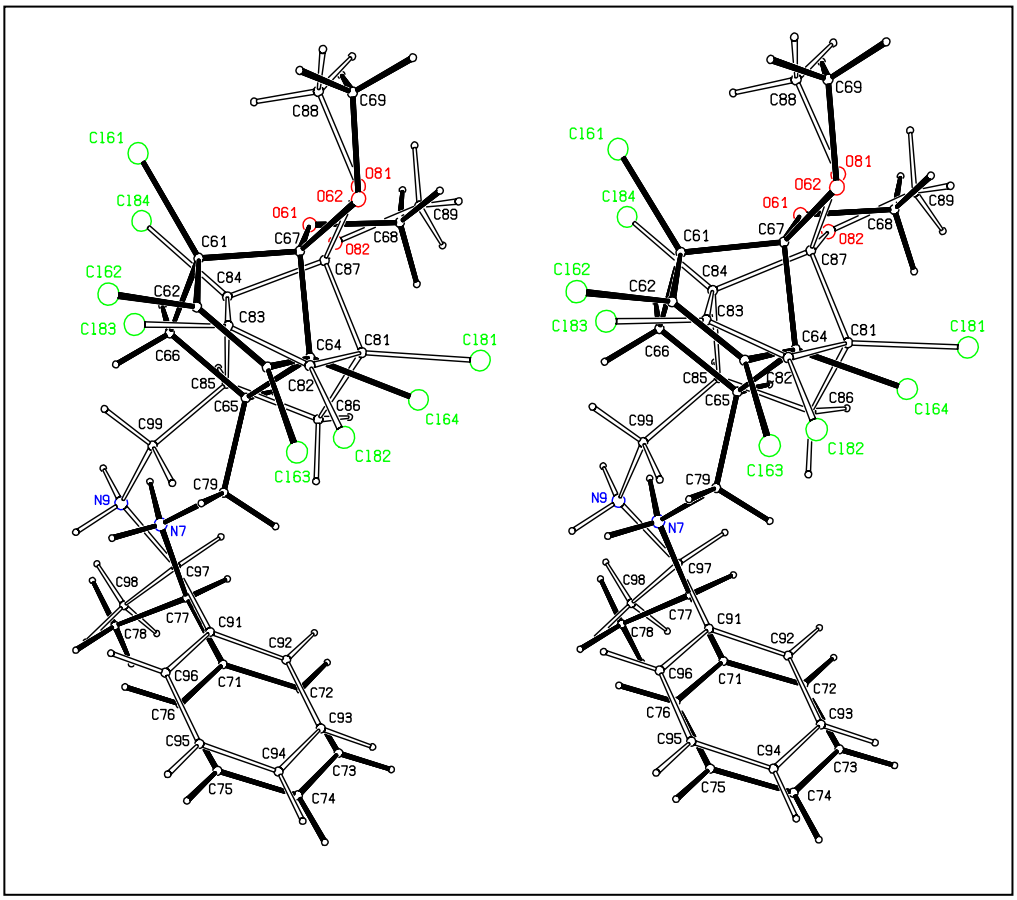


Figure 15. Stereoscopic ORTEP plot the disordered cation IV of **68**. The atoms are drawn with arbitrary radii. The cation having the S,R,R,R configuration [site occupation factors of 0.636(3)] is drawn with full bonds, the cation having the R,S,S,R configuration [site occupation factors of 0.364(3)] is drawn with open bonds.

For the absolute configuration of compound (-)-**65**, it was transformed into the corresponding 2-endo-hydroxymethyl-bicyclo[2.2.1]hept-5-ene **65a** derivative via dechlorination with Na in liq. NH_3 (Scheme 20). The absolute configuration of compound (-)-**65** was assigned as (2R) by comparison of its specific rotation with the previously determined value for (2S)-(-)-2-endo-hydroxymethyl-bicyclo[2.2.1]hept-5-ene **65a** [101a].

Scheme 20. Absolute configuration determination of (-)-**65**

2.5. Oxidation of vicinal dihaloalkenes to α-diketones

The α-diketones, a powerful assembly of two adjacent carbonyl groups, are of great interest because of their wide-ranging applications [51]. Vicinal dihaloalkenes can serve as masked α-diketones (Figure 16). Khan et al. have developed a novel, facile and extremely efficient methodology employing catalytic $RuCl_3.3H_2O$ and $NaIO_4$ as stoichiometric cooxidant [73]. They have reported the oxidation of various tetrachloro norbornene derivatives. We particularly chose easily accessible tetra and hexachloro derivatives because they have been serving as exceptionally powerful templates for the synthesis of numerous complex natural as well as unnatural products.

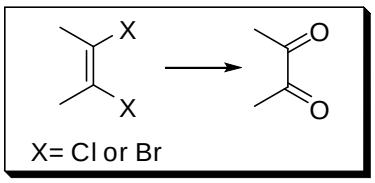
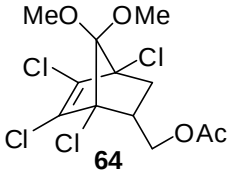
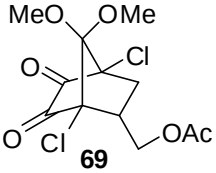
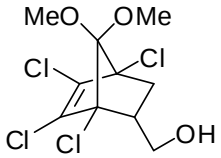
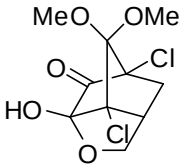
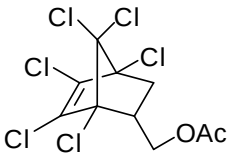
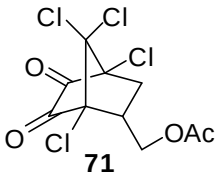
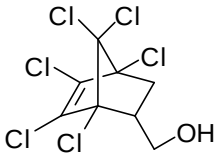
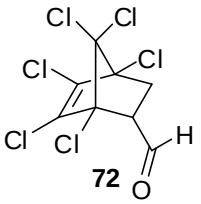


Figure 16. α-Diketone equivalency of dihaloalkenes.

Racemic tetra and hexachlorinated norbornene derivatives were subjected to ruthenium-tetroxide (generated in situ) oxidation employing $RuCl_3.3H_2O/NaIO_4$ in acetonitrile-water. The results are summarized in Table 4.

Table 4. Ruthenium-catalyzed oxidation of norbornene derivatives

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **64**	 **69**	3	98
2	 **62**	 **70**	5	96
3	 **65**	 **71**	20	90
4	 **63**	 **72**	24	82

In all cases the reaction proceeded smoothly and efficiently providing good yield of expected oxidation products except the substrate **63**. The oxidation of **63** yielded the corresponding aldehyde **72** without oxidation of dichloro alkene moeity. The duration of reactions varied considerably, but in general hexachlorinated derivatives required relatively longer reaction times compared with tetrachloro derivatives. However, we could not find any reasonable explanation for this difference. The oxidation of acetoxymethyl substituted compounds **64** and **65** afforded the normal α-diketone products **69** and **71**,

respectively. Hydroxymethyl substituted derivative **62** exclusively furnished the corresponding hemiacetal in high yield. The reason for this hemiacetal formation in this system was explained by Khan et al. He stated that " The α-diketone group in these rigid molecules is constrained into a cisoid conformation and therefore one of the carbonyls has a very high tendency to switch to a sp^3-hybridized carbon, preferably through intramolecular hemiacetal formation."

The tricyclic α-keto hemiacetals are important because of the occurrence of closely related substructure in some of the biologically active natural products [103] and also they can serve as potential building blocks in organic synthesis.

Structure elucidation of all products were done by ^1H and ^{13}C NMR spectroscopy.

In the ^1H NMR spectrum of α-diketone **69**, we observed just slight differences in chemical shift values for the peaks at 3.98 and 4.17 ppm (Figure A7). The presence of the characteristic carbonyl peaks at 187.5 and 186.3 and also the disappearance of olefinic carbon peaks at 128.3 and 130.2 ppm in ^{13}C NMR spectrum confirm the structure of α-diketone (Figure A7).

In ^1H NMR spectrum of hemiacetal **70**, two doublets of doublets at 1.86 and 2.66 ppm belong to *endo*-H_3 and *exo*-H_3 protons respectively. Since methine H_2 proton coming at 2.96-2.92 as multiplet is also in *exo* position, *exo*-H_3 couples with this H_2 proton much more than *endo*-H_3. The diastereotopic protons give one doublet at 3.72 ppm and one doublet of doublets at 4.37 ppm (Figure A8). In the ^{13}C NMR, two new peaks at 196.8 and 103.5 ppm belonging to ketone and the hemiacetal carbon respectively are observed while two peaks arising from the olefinic carbons at 129.3 and 127.1 disappeared as expected (Figure A8).

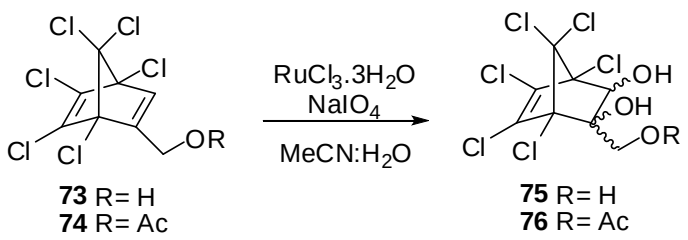
The ^1H NMR spectrum of tetrachloro α-diketone **71** is consistent with the structure. The *endo*-H_3 proton resonates as doublet of doublets at 2.36 ppm while the *exo*-H_3 appears as triplet at 2.84 ppm (Figure A9). The *exo*-H_2 proton gives multiplet at 3.14-3.09 ppm since it couples with diastereotopic methylene protons as well as H_3 protons. Two doublets of doublets at 4.12 and 4.31 ppm are arising from diastereotopic protons. The ^{13}C NMR spectrum consists of 10 lines each corresponding to a different carbon atom. Carbonyl carbons resonate at 185.2 (C_5)

and 184.3 (C_6) ppm. The signal at 169.3 indicates the acetyl carbonyl carbon. The bridge carbon has a chemical shift at 92.9 ppm being shifted to lower field by chlorine atoms.

In the ^{1}H NMR spectrum of aldehyde **72**, the absence of diastereotopic methylene protons and the presence of a broad signal at 9.60 ppm confirm the structure of the aldehyde. In ^{13}C NMR spectrum, carbonyl carbon resonates at 195.2 ppm. The two peaks at 133.3 and 128.6 ppm prove the presence of olefinic carbons (Figure A10).

2.6. The regioselectivity of ruthenium catalyst

Ruthenium-tetraoxide is well known as an efficient oxidation catalyst also for the dihydroxylation of olefins [60]. In order to observe the regioselectivity of this catalyst, we synthesized norbornadiene derivatives **73** and **74** by Diels-Alder reaction of hexachlorocyclopentadiene and propargyl alcohol and subsequent acetylation, respectively. These systems containing both dichloro and methylene substituted double bonds were subjected to oxidation by $RuCl_3.3H_2O$ and $NaIO_4$ (Scheme 21). From these reactions, it could be expected to be oxidized from both olefinic moieties. However, it was only observed the dihydroxylation on hydroxyl or acetoxymethylene substituted double bond. Depending upon these results, it can be concluded that ruthenium tetraoxide reacts regioselectively in the presence of different olefinic systems.



Scheme 21. Ruthenium-catalyzed oxidation of **73** and **74**

First of all, the structural elucidation of the starting norbornadiene systems **73** and **74** is being discussed in this part.

The ^{1}H NMR spectrum of **73** consists of three peaks. Alcohol proton resonates at 2.28 as singlet. The multiplet at 4.36-4.25 ppm indicates the diastereotopic CH_2 protons. The olefinic proton appears as singlet at 6.42 ppm. In ^{13}C NMR spectrum, there are four characteristic olefinic carbon peaks resonating at 151.2, 138.3, 137.0 and 133.9 ppm (Figure A11). Related to the structure elucidation of norbornadiene alcohol **73**, acetylated derivative **74** shows a singlet at 2.01 which belongs to methyl protons of acetyl group. In the ^{13}C NMR of **74** posseses a signal at 169.7 ppm due to the acetyl carbonyl group (Figure A12).

In the ^{1}H NMR spectrum of **75**, three alcohol protons are seen at 2.80, 4.20 and 4.27 ppm as three broad singlets. CH_2 protons resonate at 4.12 ppm as broad singlet. The singlet at 4.51 ppm indicates the CH proton connected to hydroxide. In ^{13}C NMR spectrum, it was observed that two peaks arising from dichlorinated olefin unit stay at 134.6 and 130.7 ppm while the other olefin carbons disappeared. Also other 6 lines in the spectrum clarifies the structure of dihydroxylated product (Figure A13).

The ^{1}H NMR spectrum of acetylated product **76** shows a doublet at 3.10 ppm for the OH proton due to the coupling with the methane proton of norbornene system. The second OH proton resonates as singlet at 4.35 ppm since it is connected to quaternary carbon. The peak at 4.56 ppm splitting as doublet with OH proton belongs to the methine proton on norbornene skeleton. The diastereotopic protons resonate at 4.64 and 4.75 ppm as AB system having a coupling constant of 12.6 Hz. In ^{13}C NMR spectrum, acetyl carbonyl resonates at 171.9 ppm. Two peaks at 133.6 and 129.5 ppm belong to the dichlorinated olefinic carbons. There is no other peak in the olefinic region which shows that other olefin was fully saturated by dihydroxylation (Figure A14).

The ^{1}H NMR of **76** was also taken in D_2O. Thus we could use the advantage of rapid OH exchange with the deuterium of heavy water to assign hydroxyl proton resonance signals. This removes the hydroxyl protons from the sample and their resonance signal in the ^{1}H NMR spectrum disappears.

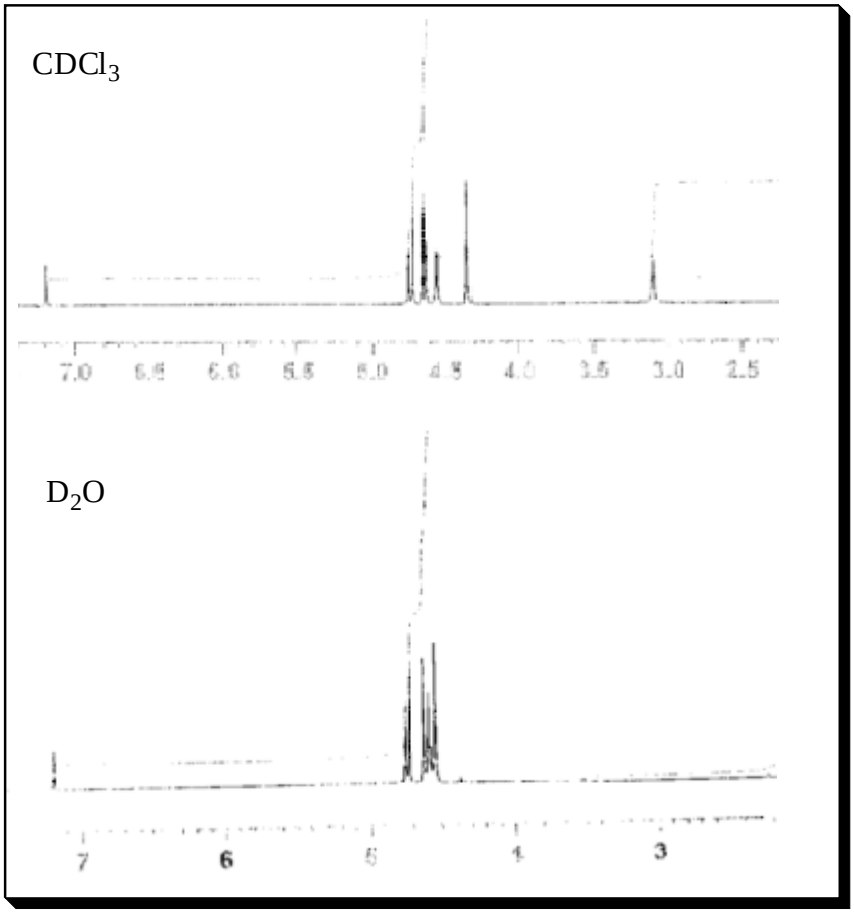


Figure 17. ^{1}H NMR spectra of **76** taken in $CDCl_3$ and D_2O, respectively

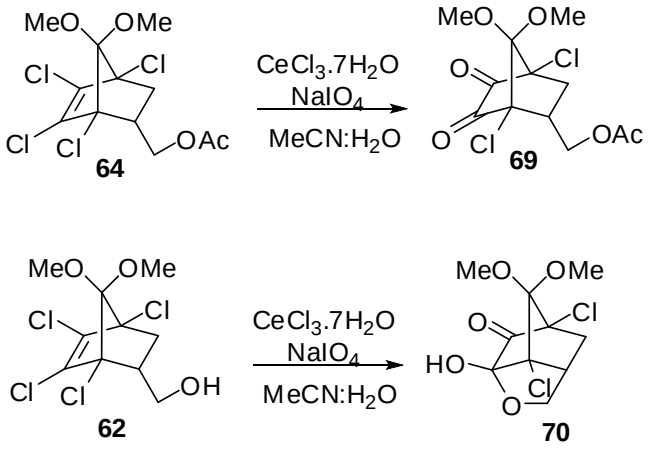
Experimentally, one simply adds a drop of D_2O to chloroform-d solution of the compound and runs the spectrum again. The result of this exchange is displayed in Figure 17. Two peaks at 3.10 and 4.35 ppm disappeared in the second spectrum taken in D_2O thus we can assign them as hydroxyl protons. Also, CH proton resonating at 4.56 ppm as doublet turned to singlet in the second spectrum since it does not couple with *gem*-OH proton anymore.

The exact structure of diol systems could be interpreted by ^{1}H NMR, ^{13}C NMR and full analysis. However, it is impossible to estimate the stereochemistry of the hydroxyl groups as *endo* or *exo*. Syn dihydroxylation can take place from both *endo* and exo faces but here it was represented as *exo*-diol. Since the

dihydroxylated products are semi crystals, the X-ray analysis could not be done for the stereochemistry determination.

2.7. Cerium chloride catalysis in the formation of α-diketones

Ruthenium chloride is very powerful and useful catalysts in the oxidation reactions. However, it is expensive and not applicable for very sensitive olefin systems. From this point of view, we attempted to search new catalysts as an alternative to ruthenium. The screening reactions were examined with $RhCl_3$ and $CeCl_3.7H_2O$ by the use of catalytic amount of 10 mole % and stoichiometric amount of $NaIO_4$ as oxidant in the oxidation of tetrachloro norbornene system **64**, separately. In the case of $RhCl_3$-catalyzed oxidation, no product was observed. Fortunately, the desired α-diketone **69** was obtained with 90% yield by the catalysis of $CeCl_3.7H_2O$. Subsequently, the same procedure was applied to the alcohol derivative **62** and the corresponding hemiacetal **70** has been afforded with 82% yield (Scheme 22). The yields of both cerium-catalyzed oxidations are comparable with the ruthenium-catalyzed oxidation of the same substrates as 90 to 98% and 82 to 90%, respectively. Plietker and co-workers have used $CeCl_3$ is used as cocatalyst in ruthenium-catalyzed dihydroxylation reaction of dehalogenated alkene systems [50]. To the best of our knowledge, this is the first application of cerium-periodato complexes in the oxidation of vicinal dihalo alkenes to α-diketones. It is possible to conclude that cerium chloride is mild, less toxic and environmentally convenient catalyst as compared to ruthenium.



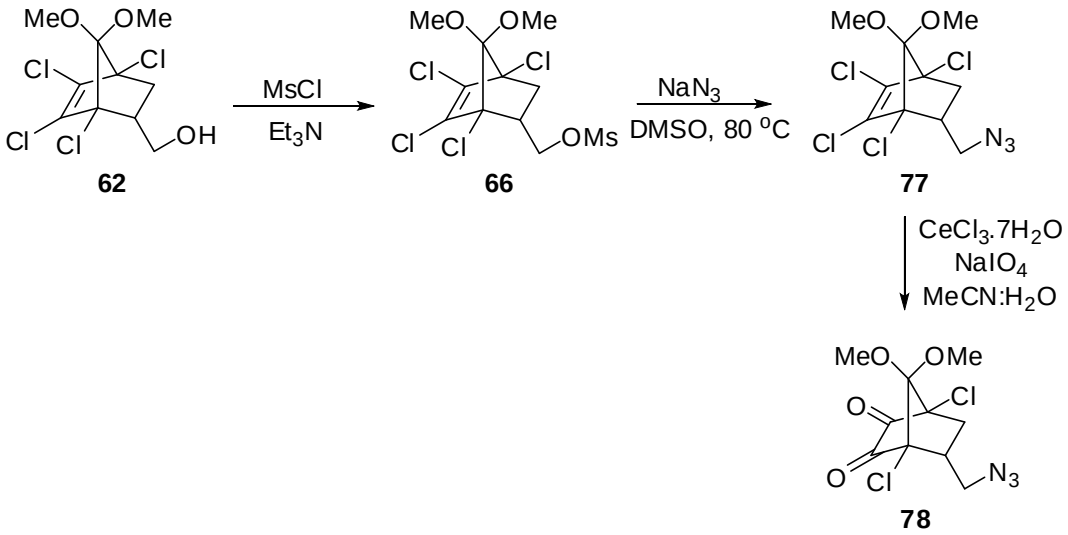
Scheme 22. Oxidation of **62** and **64** by the catalysis of cerium chloride

Cerium-catalyzed oxidation was applied also to the hexachloro-norbornene derivatives. However, no product was observed. Although the only difference arises from the bridge carbon substituents as dimethoxy and chloro, it could not be possible to give a reasonable explanation for the unsuccessful results with the dihalo derivative.

Second screening reactions were performed to test the activities of various oxidants (i.e. NaOCl, TEMPO and O_2) in the ruthenium-catalyzed oxidation reaction of the substrate **64**. However, all the oxidants other than $NaIO_4$ did not show any activity in the oxidations.

In the literature, there is no example for the oxidation of amine derivatives of polyhalogenated norbornene backbone to α-diketone. In order to see the versatility of the method, azide derivative **77** was synthesized starting from hydroxymethyl substituted norbornene system **62** and subsequently, oxidation reaction was performed by $CeCl_3$ catalyst system. In the synthetic pathway, first step was the mesylation of the alcohol derivative **62**. The mesylate **66** was transformed to azide derivative **77** by heating the reaction mixture with sodium azide in DMSO. Finally, oxidation of azidomethyl substituted norbornene **77** with cerium periodato complex afforded the desired azidomethyl substituted α-

diketone **78** (Scheme 23). The azide derivative can be a very good candidate for various amine synthesis.



Scheme 23. Synthesis of azidomethyl substituted α-diketone **78**

The structure elucidation of the azide **77** and α-diketone **78** were done by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

In the ^{1}H NMR spectrum of the azide **77**, the *endo*-H_3 proton splits into doublet of doublet at 1.54 ppm due to the interaction of the *exo*-H_3 and the methine proton of norbornene system. The other doublet of doublet at 2.46 ppm belongs to *exo*-H_3 proton. Methine H_2 proton gives a multiplet at 2.74-2.80 ppm due to the coupling with both diastereotopic protons next to azide and methylene protons. Diastereotopic methylene protons show one multiplet at 2.87-2.81 ppm and one doublet at 3.50 ppm. In the ^{13}C NMR spectrum, olefinic carbons resonate at 130.8 and 127.7 ppm as expected (Figure A15).

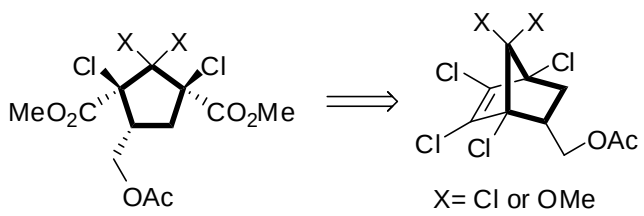
^{1}H NMR spectrum of α-diketone **78**, the splitting pattern shows similarities to that of azide **77** with slight differences in chemical shift values. The diastereotopic methylene protons next to the azide moiety resonate at 3.46 ppm.

The ^{13}C NMR spectrum strongly proves the formation of the desired α-diketone **78** with the signals at 187.5 and 186.6 ppm indicating the formation of two ketone carbonyl groups. The signals in the olefinic region disappeared as expected (Figure A16).

2.8. Stereoselective synthesis of γ-lactone-fused cyclopentanoids

Cyclopentanoids are a biologically important class of compounds. Several methodologies of asymmetric synthesis of the chiral building blocks with cyclopentane ring have been developed [80]. Khan et al. described an efficient synthetic methodology for the synthesis of α-diketones and the subsequent cleavage using $Pb(OAc)_4$ or alkaline H_2O_2 to give cyclopentanoids derivatives in their racemic form [103].

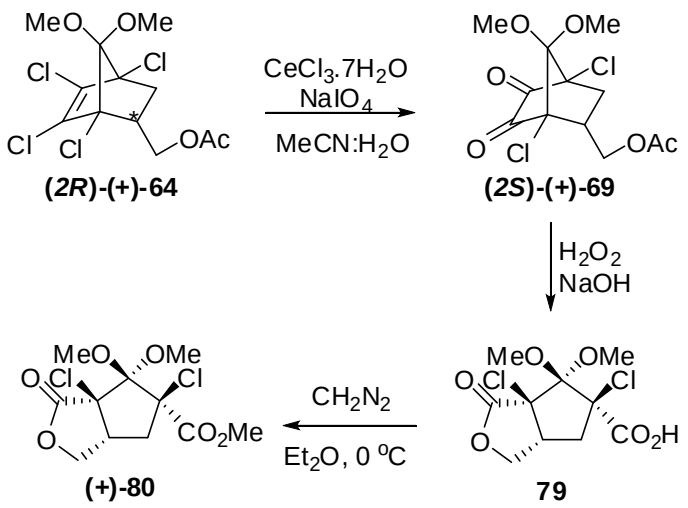
From this point of view, we planned to synthesize highly functionalized chiral cyclopentanoids making use of the persuasive advantages of the structural flexibility and stereochemical control offered by the polychlorinated norbornene derivatives. Norbornene skeleton can easily be converted to cyclopentane ring by the cleavage of the olefinic bond (Scheme 24). During the course of these transformations, the chiral information of the starting compound which has been already loaded by the enzymatic resolution was preserved.



Scheme 24. Cyclopentane equivalency of norbornene skeleton

The enantiomerically enriched acetate derivative (*2R*)-(+)-**64** resolved by CRL was subjected to oxidation reaction using a catalytic amount of $CeCl_3$

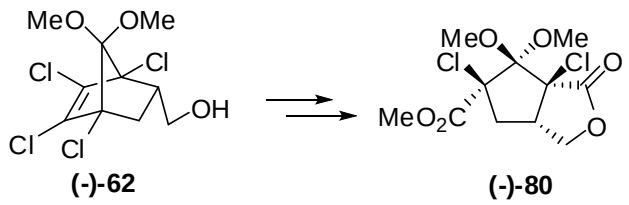
anhydrous in the presence of $NaIO_4$ to give α-diketone (*2R*)-(+)-**69** in excellent yield (Scheme 25). Subsequently, H_2O_2/NaOH mediated cleavage reaction was tested to afford the corresponding cyclopentane derivative. However, the α-diketone (*2R*)-(+)-**69** was transformed smoothly in a highly regio- and stereoselective manner to γ-lactone-fused cyclopentanoid (+)-**80** instead of the expected cyclopentane derivative. The reason for this lactone formation is due to the hydrolysis of acetyl group during the cleavage of double bond in alkaline medium. The carboxylic acid derivative **79** was directly converted to its methyl ester derivative (+)-**80** with diazomethane procedure.



Scheme 25. Synthesis of γ-lactone-fused cyclopentanoid (+)-**80**

γ-Lactone-fused cyclopentanoids are important intermediates in synthetic organic chemistry and are among the most abundant structures found in numerous naturally occurring molecules [81]. A cyclopentane ring cis-fused at the α,β-bond of the γ-lactone is the basic structural unit of many complex and challenging biologically active natural products [104] and also functions as the basic building block for the synthesis of a variety of cyclopentanoid natural products [105] .

By the same synthetic pathway, the other enantiomer of the γ-lactone-fused cyclopentanoid (-)-**80** was also synthesized starting from enantiomerically enriched alcohol derivative (*2S*)-(-)-**62** (Scheme 26).



Scheme 26. Synthesis of γ-lactone-fused cyclopentanoid (-)-**80**

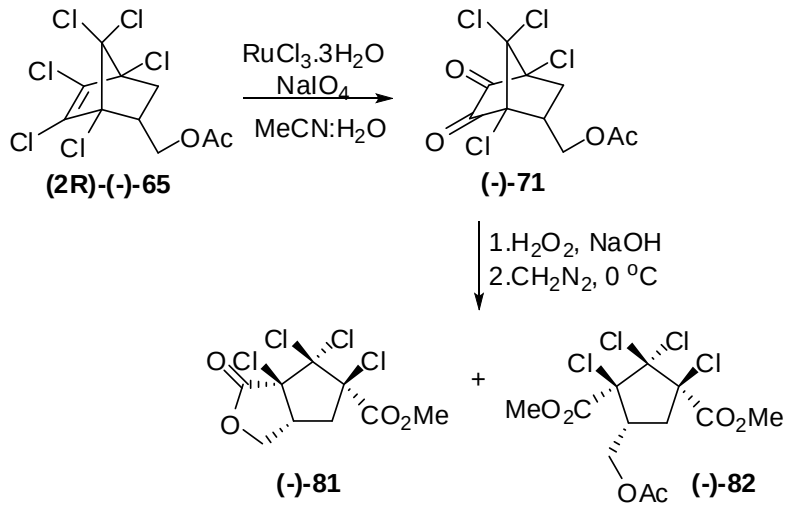
Thus, the stereo- and regioselective synthesis of both enantiomeric forms of the γ-lactone-fused cyclopentanoid **80** has been performed successfully.

The characterization of the γ-lactone-fused cyclopentanoid **80** was done by H-NMR, ^{13}C NMR and also the comparison with the literature data [103].

In the ^{1}H NMR spectrum of the compound (*2R*)-(+)-**80**, the diastereotopic methylene protons of cyclopentane ring resonate at 2.66 and 2.82 ppm as doublet of doublets, respectively. The methine proton of cyclopentane ring system splits into doublet of triplet of doublet at 3.49 ppm (Figure A17). The doublet of doublet with the chemical shift value of 4.14 ppm belongs to one of the diastereotopic CH_2 protons of lactone moiety. The other diastereotopic proton resonates at 4.61 ppm as triplet. In the ^{13}C NMR spectrum, carbonyl signals of lactone and acetyl group resonate at 171.1 and 167.7 ppm, respectively. The full NMR analysis results are given in experimental part (Figure A18, A19 and A20).

(*2R*)-**(-)**-2-Acetoxymethyl-hexachloro[2.2.1]hept-5-ene (*2R*)-(-)-**65** can also serve as potential precursor for the synthesis of enantiopure cyclopentane derivative. Two geminal chlorine atoms can easily be transformed to many functional groups. The hexachlorinated acetate (*2R*)-(-)-**65** resolved by CRL was exposed to the ruthenium-catalyzed oxidation since cerium did not perform this

oxidation. The resultant α-diketone (*2R*)-(-)-**71** was further subjected to cleavage by H_2O_2 followed by methylation with CH_2N_2 to afford the mixture of cyclopentanoid derivatives (-)-**81** and (-)-**82**. The mixture was separated by flash column chromatography furnishing cyclopentane (-)-**82** and γ-lactone-fused cyclopentane (-)-**81** in the ratio of 4:1 (Scheme 27).



Scheme 27. Synthesis of tetrachloro cyclopentane derivatives (-)-**81** and (-)-**82**

In the ^{1}H NMR spectrum of cyclopentane derivative **82**, the diastereotopic methylene protons of cyclopentane ring resonate at 2.68 ppm and 2.92 ppm as doublet of doublets, respectively. The multiplet at 3.57-3.49 ppm indicates the methane proton which couples with CH_2 protons of both neighbouring carbons. The diastereotopic CH_2 protons of acetoxymethylene group resonate at 4.48 and 4.71 ppm both splitting to doublet of doublet, respectively (Figure A22). In ^{13}C NMR spectrum, two methyl ester carbonyl carbons gave the signals at 165.8 and 165.3 ppm. In the ^{13}C NMR spectrum, This the acetate carbonyl carbon resonates at 170.5 ppm. The disappearance of ketone carbonyl signals of compound (-)-**71**

also justifies the cleavage of α-diketone unit. Full NMR analysis is given in experimental part (Figure A23, A24 and A25).

In the ^{1}H NMR spectrum of the compound **81**, the CH_2 protons on cyclopentane ring resonate at 2.98-3.00 ppm as a multiplet. CH proton splits into multiplet resonating at 3.70-3.79 ppm. The doublet of doublet at 4.15 ppm and the triplet at 4.72 ppm indicate the diastereotopic CH_2 protons on the lactone ring. In the ^{13}C NMR spectrum, two carbonyls of lactone and methyl ester group resonate at 168.3 and 165.4 ppm, respectively. Full NMR analysis is given in experimental part (Figure A21).

2.9. Stereoselective synthesis of novel carbasugar derivatives

In this study, we planned to synthesize novel enantiopure cyclitol derivatives starting with enantiomerically enriched (*2S*)-(-)-2-Hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene system (2S)-(-)-**62**. the structures of these cyclitols are very similar to carbasugars and quercitols. Since the structures are more similar to the carbasugars with only CH_2 difference we called them carbasugar derivatives (Figure 18).

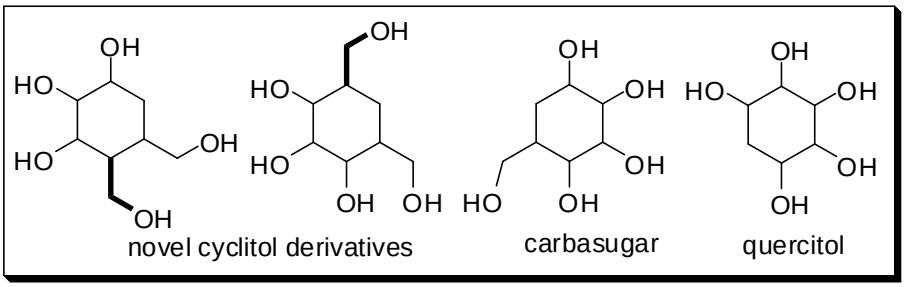
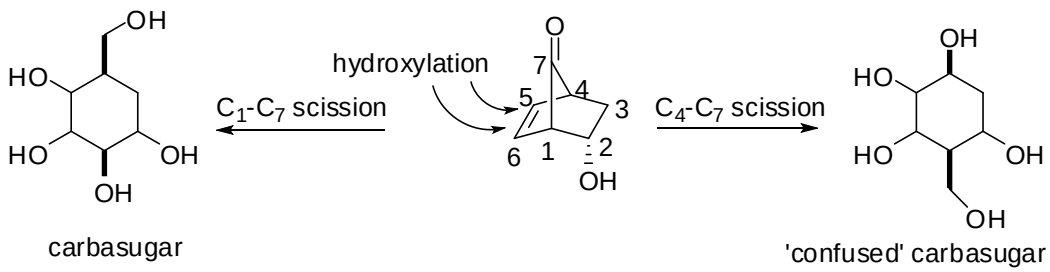


Figure 18. Structural relations of novel cyclitol derivatives with carbasugars and quercitols.

Carbasugars have attracted a great deal of attention among medicinal and organic chemists in the recent years due to their potential biological properties as antibiotics, inhibitors of glucose- stimulated insulin release and more recently as inhibitors of various glycosidases [86].

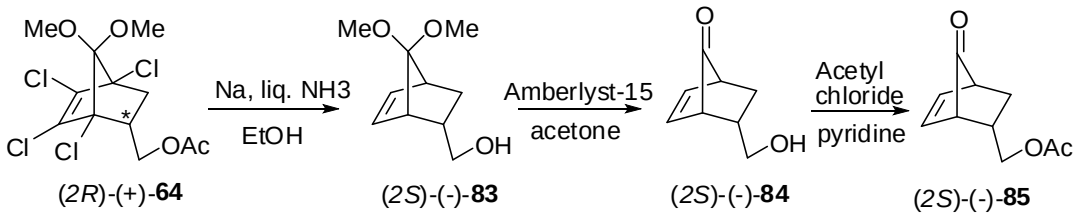
Mehta et al. has reported a general norbornyl based synthetic approach to carbasugars and ‘confused’ carbasugars. He stated that "C_7 framework of the norbornyl system has been recognized as simple ‘locked’ carbasugar from which the six-membered C_7-carbasugar skeleton can be easily retrieved through ‘unlocking’ involving C1-C7 or C4-C7 bond scission (Scheme 28). Thus, norbornenone derivative can be elaborated to carbasugars and also ‘confused’ carbasugars. The ‘confused’ carbasugars have the same level of oxygenation on the cyclohexanoid framework as the carbasugars, but the hydroxymethyl and the parahydroxy groups are interchanged."



Scheme 28. Formation of carbasugars and ‘confused’ carbasugars

By using this norbornyl approach, we planned to synthesize a novel carbasugar and a ‘confused’ carbasugar derivatives in a stereoselective manner. After the enantiomeric enrichment of tetrachloronorbornene derivative (2R)-(+)-**64** using its advantages in the enzymatic resolution over the nonchlorinated derivative, it was subjected to sodium/liq. NH_3 mediated reductive dehalogenation to afford the compound (2S)-(-)-**83**. Acetyl group was hydrolyzed under reaction

conditions. During this dehalogenation reaction, the absolute configuration of the norbornene skeleton was not changed but due to the priority the configuration of the compound (-)-**83** changed from (R) to (S) in CIP system. The resultant *endo*-hydroxymethyl-7-norbornenone ketal (-)-**83** was transformed to 7-ketonorbornene (2S)-(-)-**84** by Amberlyst-15 resin in acetone [107]. Subsequent acetylation of 7-ketonorbornene (-)-**84** afforded *endo*-acetoxymethyl-7-ketonorbornene (-)-**85** which is the key precursor required for the synthesis of target carbasugar and 'confused' carbasugar derivatives (Scheme 29).



Scheme 29. Synthesis of *endo*-acetoxymethyl-7-ketonorbornene (-)-**85**

All the products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

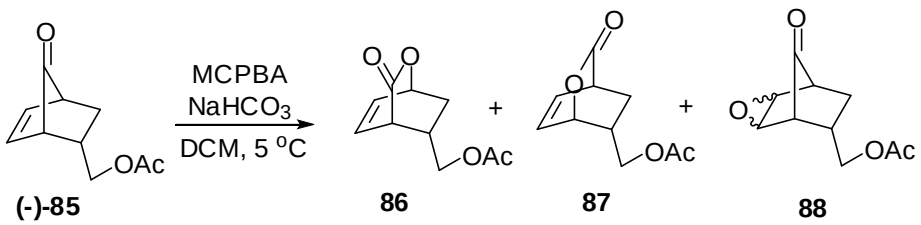
In the ^{1}H NMR spectrum of compound **83**, two peaks splitting to doublet of doublets in the olefinic region indicate the formation of dechlorinated compound. Other newly formed bridgehead protons H_4 and H_1 resonate at 2.96 and 2.79 ppm as multiplets, respectively. In the ^{13}C NMR spectrum, olefinic carbons shifted to lower field resonating at 134.1 and 130.6 ppm as compared to compound **64** (Figure A26).

In the ^{1}H NMR spectrum of compound **84**, the disappearance of two signals of methoxy protons at 3.15 and 3.22 ppm indicates the conversion of ketal **83** to ketone **84**. Also in ^{13}C NMR spectrum, three peaks belonging to bridge

carbon and two methoxy carbons in the spectrum of ketal **83** disappeared while a ketone peak at 204.7 ppm was observed (Figure A27).

In the ^{1}H NMR spectrum of compound **85**, acetyl protons resonate at 2.04 ppm and hydroxyl proton coming at 1.40 ppm disappeared as expected. In ^{13}C NMR spectrum, acetyl carbons resonate at 170.7 and 20.8 ppm (Figure A28).

Having synthesized the key precursor *endo*-acetoxymethyl-7-ketonorbornene (-)-**85**, the second attempt was Baeyer-Villiger oxidation reaction. *m*-Chloroperbenzoic acid mediated chemoselective BV oxidation of (-)-**85** yielded a regioisomeric mixture of lactones **86** and **87** with 87% yield and also epoxide **88** as a side product (5% yield) (Scheme 30).



Scheme 30. BV oxidation of *endo*-acetoxymethyl-7-ketonorbornene (-)-**85**

The mixture of lactones could not be separated by flash column chromatography. The epoxide was isolated and characterized by ^{1}H and C^{13} NMR spectroscopies. However, it is very hard to say about the absolute configuration of the epoxide **88** whether *endo* or *exo* by these data.

In the ^{1}H NMR spectrum of the epoxide **88**, the disappearance of the peaks in the olefinic region and the formation of two new signals resonating at 3.39 and 3.44 ppm and splitting as doublet of doublets indicate the formation of epoxide ring (Figure A29). Two bridgehead protons resonate together as a multiplet at 3.20-3.22 ppm. Also, when look at the COSY spectrum, correlation between all protons can easily be seen. The epoxide ring protons resonating at 3.39 and 3.44 ppm show a cross peak with only the bridge-head protons at 3.21 ppm (Figure

19). There are correlations between the bridge-head protons and all other protons on the norbornene skeleton which cause them appear as a multiplet in ^{1}H NMR spectrum.

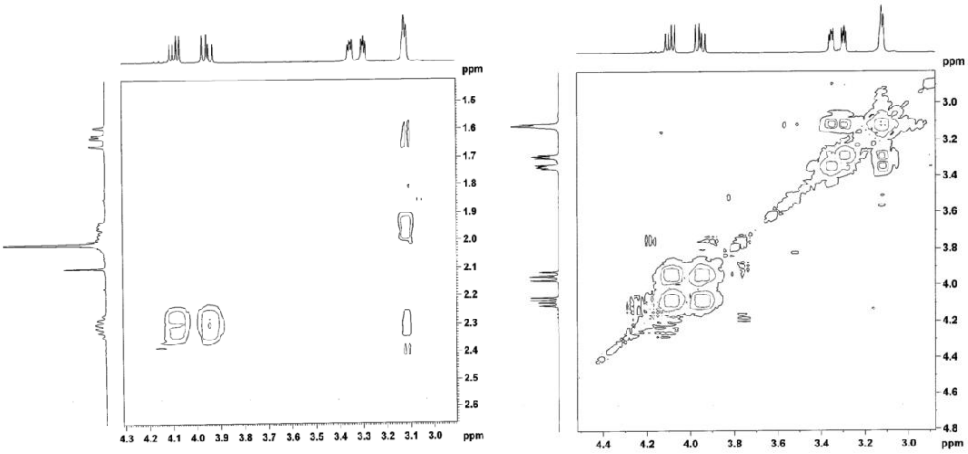
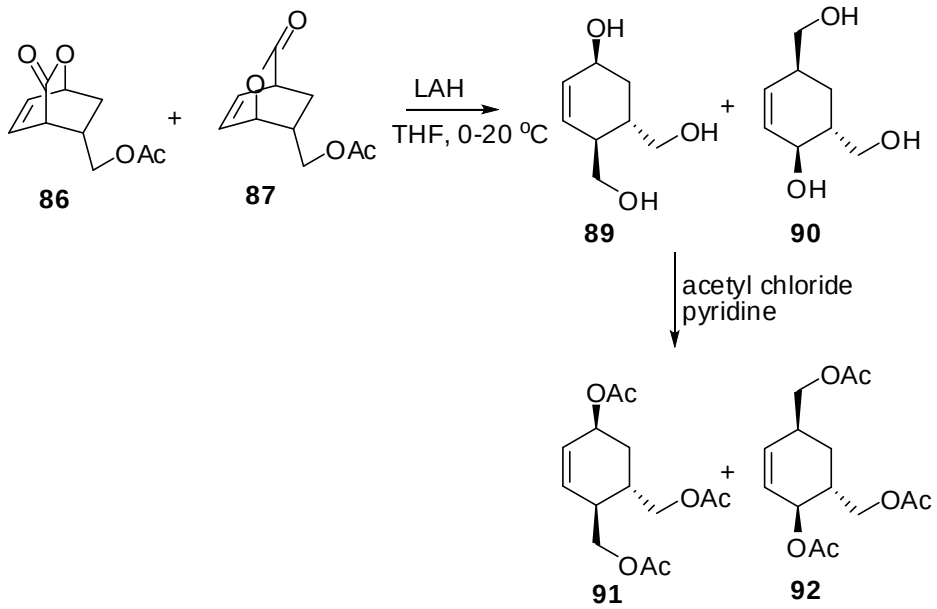


Figure 19. COSY spectra of epoxide **85**

In the ^{13}C NMR spectrum, the disappearance of olefinic peaks and formation of two new peaks 52.3 and 54.0 ppm indicates the epoxide structure.

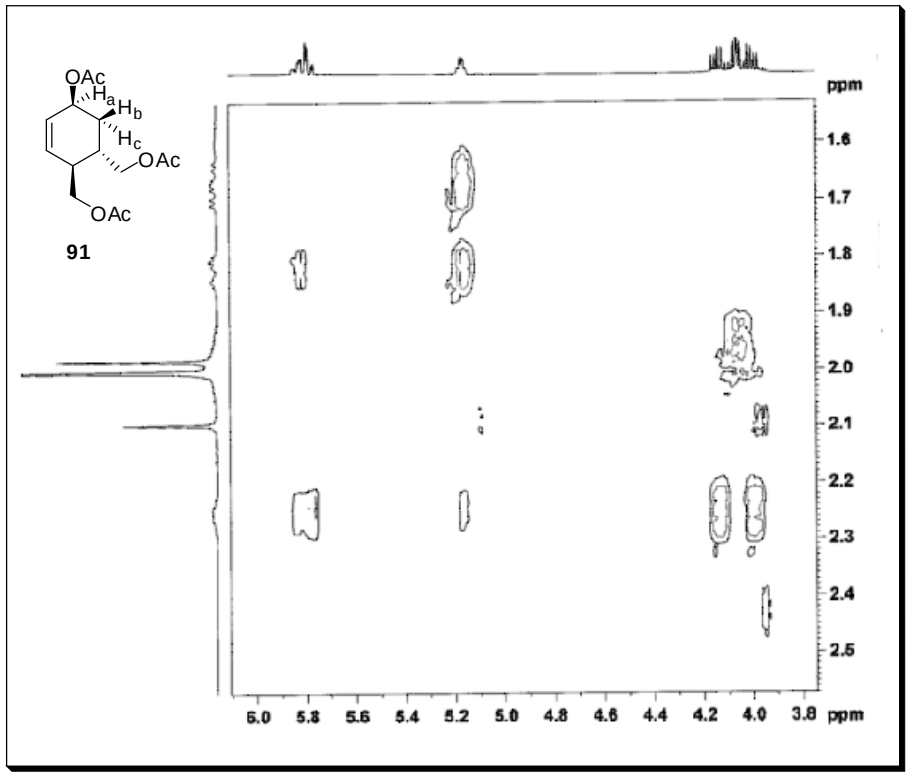
Lactone mixture **86** and **87** was subjected to LAH reduction to furnish the mixture of trihydroxylated cyclohexene **89** and **90** (Scheme 31). Thus, the free allylic hydroxyl groups formed which would direct the stereochemical outcome in the following dihydroxylation reaction. In order to prevent any side reaction and overcome the difficulties during the isolation, the mixture was acetylated and **91** and **92** were afforded. Both isomers were separated by flash column chromatography and fully characterized. Compound **92** was isolated as the major isomer (55:45).



Scheme 31. Reduction of lactone mixture and the formation of **91** and **92**

The structures of isomers were determined by their individual COSY spectral data. While H_a proton in isomer **91** resonating at 5.15 ppm showed strong cross peaks with H_b and H_c protons, $H_{a'}$ in isomer **92** resonating at 5.09 ppm did not show any cross peak with H_b and H_c protons (Figure 20).

In the ^{1}H NMR spectrum of **91**, olefinic protons resonate at 5.76-5.85 ppm as a multiplet. The doublet of doublet at 5.17 ppm indicates the CH proton on the cyclohexene ring attached to OAc group. The CH_2 protons connected to acetoxy groups resonate at 3.97-4.16 ppm as a multiplet. Two multiplets at 2.09-2.29 and 1.98 ppm shows methine protons connected to acetoxymethylene units. Three acetyl protons resonate at 2.00 and 1.98 ppm (Figure A31). Two multiplets at 1.80-1.85 and 1.67-1.78 ppm belong to methylene protons on the ring. In the ^{13}C NMR spectrum, three acetyl carbonyls resonate at 170.5, 170.4 and 170.1 ppm. Olefinic carbons resonate at 132.5 and 126.5 ppm. Two peaks at 66.0 and 65.5 ppm belong to methylene carbons connected to acetoxy groups. The CH proton connected to actoxy group resonate at 65.8 ppm. Two peaks at 37.2 and 31.5 ppm



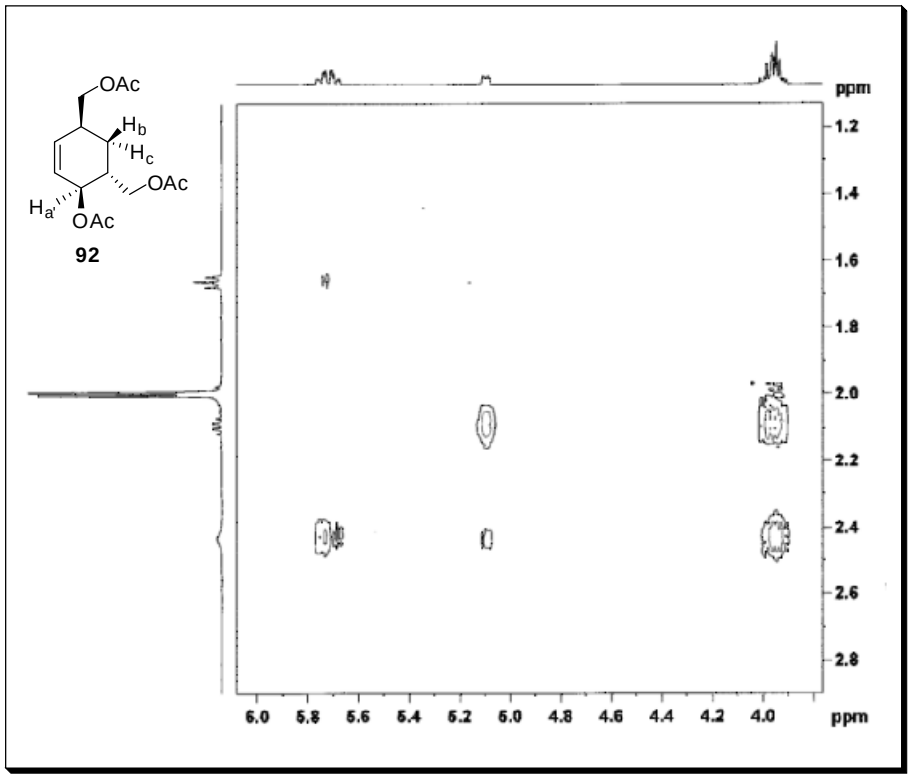
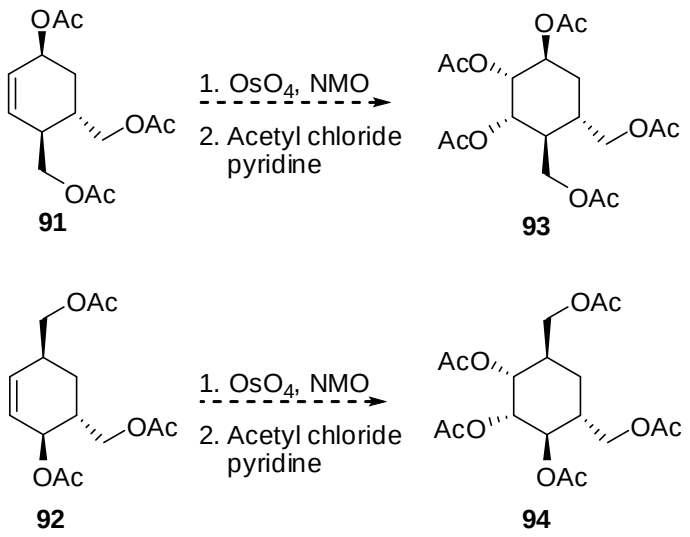


Figure 20. COSY spectra of isomers **91** and **92**

indicate the other CH carbons on the ring. The methylene carbon on the cyclohexene ring resonates at 30.2 ppm.

In the ^{1}H NMR spectrum of **92**, the olefinic protons resonate at 5.67-5.76 ppm as a multiplet. The multiplet at 5.08-5.10 ppm belongs to the methine proton attached to acetoxy group. Two methylene protons resonate at 3.90-4.01 ppm as a multiplet. Two similar methine protons on the cyclohexene ring can be differentiated by COSY spectrum. While the proton at 2.43 ppm correlates with olefinic proton, the other methine proton at 2.10 ppm does not give any cross peak with olefinic proton. We can conclude that the multiplet at 2.43 ppm belongs the methine next to double bond. The acetyl protons resonate at 2.1 ppm. The multiplet at 1.65-1.68 ppm indicates the methylene protons on the ring (Figure A32). In the ^{13}C NMR spectrum, three acetyl carbonyls resonate at 169.5, 169.4 and 169.2 ppm. The olefinic carbons resonate at 129.7 and 126.6 ppm. The peak at 67.6 ppm indicates the CH carbon attached to acetoxy group. Two methylene carbons of acetoxymethly units give peaks at 65.2 and 63.3 ppm. Two signals at 33.9 and 31.7 ppm belong to CH carbons on the cyclohexene ring. The methylene carbon on the ring resonates at 23.8 ppm and three acetyl carbons resonate at 20.0, 19.8 and 19.7 ppm.

These two isomers of triacetyl-substituted cyclohexene derivatives **91** and **92** are very important candidates for the formation of target carbasugar derivatives. OsO_4-mediated dihydroxylation of the olefins separately and subsequent acetylation can afford the target carbasugar **94** and 'confused' carbasugar derivatives **93** (Scheme 32).



Scheme 32. Synthesis of target carbasugar derivatives **93** and **94**

CHAPTER 3

CONCLUSION

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, hydroxymethyl-substituted polychlorinated norbornene derivatives were synthesized in good yields starting from commercially available cyclopentadiene derivatives.

In the first part of the study, (±)-2-endo-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene (±)-**62** was subjected to enzymatic acetylation with commercially available lipases CRL, PPL and Novazyme 435 in catalytic amounts. All the enzymes afforded the same configurated acetoxymethyl derivative (+)-**64** with ee's of 64-88%. CRL gave the best result in terms of enantioselectivity. The absolute configuration of enantiomerically enriched product (+)-**64** was assigned as (1S,2R,4R) by X-ray analysis.

The same method was applied for the enzymetic resolution of (±)-2-endo-hydroxymethyl-1,4,5,6,7,7-hexachloro bicyclo[2.2.1]hept-5-ene (±)-**63** and enantiomerically enriched acetyl derivative (-)-**65** was obtained with 98% ee by CRL catalyzed acetylation. The absolute configuration of (-)-**65** was assigned as (1S, 2R, 4R) by comparison of its specific rotation with the previously determined value in the literature.

In the second part of the study, various polychlorinated derivatives were subjected to ruthenium-catalyzed oxidation to afford α-diketone and hemiacetal derivatives. The oxidation of (±)-2-endo-hydroxymethyl-1,4,5,6,7,7-hexachloro

bicyclo[2.2.1]hept-5-ene (±)-**63** yielded the unexpected aldehyde derivative **72**. As an alternative to $RuCl_3.3H_2O$, $CeCl_3.7H_2O$ was used in these oxidations by using its advantages over ruthenium (e.g. cheap, mild, environmentally friendly) Cerium showed activity in the oxidations of tetrachlorinated norbornene derivatives.

In the oxidation studies, norbornadiene systems were also subjected to ruthenium-catalyzed oxidation to see the regioselectivity and it was only observed the dihydroxylation on hydroxyl or acetoxymethylene substituted double bond.

In the third part of the study, enantiomerically enriched acetoxymethyl substituted polychlorinated norbornene derivatives (+)-**64** and (-)-**65** were oxidized to the corresponding α-diketones and subsequent alkaline H_2O_2 cleavage afforded the cyclopentanoid derivatives. Thus, the stereoselective synthesis of biologically important cyclopentane derivatives was performed with good yields.

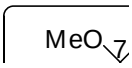
Carbasugars have very important biological properties as antibiotics, inhibitors of glucose- stimulated insulin release antibiotics. In the last part of the study, stereoselective synthesis of precursors for novel carbasugar derivatives has been performed starting from enantio-enriched acetoxymethyl substituted derivative (+)-**64**. Biological activity tests will be performed for glycosidase inhibition property after the dihydroxylation process.

CHAPTER 4

EXPERIMENTAL

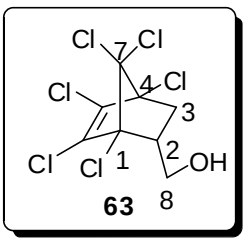
The ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX 400 spectrometer. ^{1}H NMR spectra were measured at 400 MHz and reported in ppm using TMS as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz and are reported in ppm with the residual solvent peak as internal standard ($CDCl_3$ at 76.9 ppm). Infrared spectra were obtained from KBr pellets on Varian 1000 FT-IR spectrophotometer and are reported in cm^{-1}. Optical rotations were measured a 1 dm cell using a Rudolph research analytical, Autopol III automatic polarimeter. HPLC measurements were performed with a Thermo Separation Products, Inc., P1500-SN-4000-UV2000 instrument using Chiralcel OD-H analytical column (250x4.60 mm). Flash column chromatography was performed on silica gel (60-mesh, Merck). The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. The reactions were monitored by thin layer chromatography using Merck 0.2 mm silica gel 60 F_{254} analytical aluminium plates. CRL, *candida rugosa lipase*, was purchased from Aldrich. Novazyme 435 was donated by Novo Nordisk AS, Bagsverd Denmark. All reactions were carried out in oven- or flame-dried glassware under argon atmosphere unless otherwise stated. CH_2Cl_2 was distilled from P_2O_5 and THF was dried over Na under argon.

4.1. Synthesis of (±)-2-Hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene, 62.



A mixture of allyl alcohol (2.62 g, 45.0 mmol) and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (10 g, 38.2 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 150 ºC for 70 h. The crude product was purified by flash column chromatography to afford **(±)-62** (EtOAc-hexane, 1:4) (9.47 g, 77% yield). White solid. Mp: 84 ºC (lit. [106] 83.5-84.5 ºC) ^{1}H NMR: δ 3.68 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, J=11.1 and 6.0 Hz), 3.54 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.32-3.27 (m, 1H, AB system diastereotopic H_8, CH$_a$$H_b$O), 2.83-2.77 (m, 1H, C$H$, H_2), 2.44 (dd, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$, J=11.8 and 4.1 Hz), 1.56 (dd, 1H, AB system diastereotopic *endo*-H_3, CH$_a$$H_b$, J=11.8 and 4.1 Hz), 1.60 (s, 1H, OH); ^{13}C NMR: δ 130.3, 128.1, 111.9, 77.2, 74.5, 62.3, 52.7, 51.6, 48.8, 39.4 (Figure A1).

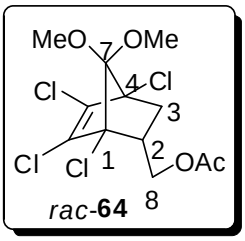
4.2. Synthesis of (±)-2-Hydroxymethyl-hexachlorobicyclo 2.2.1]hept-5-ene, 63.



63

A mixture of allyl alcohol (1.28 g, 22.0 mmol) and hexachlorocyclopentadiene (5 g, 18.3 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 150 ºC for 70 h. The crude product was purified by flash column chromatography to afford **(±)-63** (EtOAc-hexane, 1:4) (4.83 g, 80% yield). White solid. Mp: 159-160 ºC. ^{1}H NMR: δ 3.79-3.73 (m, 1H, AB system diastereotopic H_8, CH_aH$_b$O), 3.45-3.39 (m, 1H, , AB system diastereotopic H_8, CH$_a$$H_b$O), 3.03-2.96 (m, 1H, C$H$, H_2), 2.59 (dd, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$, J=12.6 and 8.9 Hz), 1.85 (dd, 1H, AB system diastereotopic *endo*-H$_3$, CH$_a$$H_b$, J=12.6 and 4.1 Hz), 1.43 (t, 1H, OH, J=4.9 Hz); ^{13}C NMR: δ 132.0, 129.8, 102.6, 80.9, 78.7, 62.0, 49.0, 38.3 (Figure A2).

4.3. Synthesis of (±)-2-Acetoxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo 2.2.1]hept-5-ene, 64.



rac-**64**

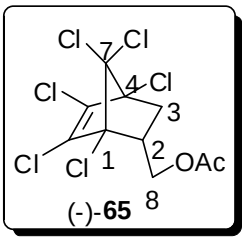
To a stirred solution of **62** (3 g, 9.3 mmol) in 50 mL CH_2Cl_2, dry pyridine (1.47 g, 18.6 mmol) was added at 0 ˚C and the mixture was stirred for 30 min under inert atmosphere. Acetyl chloride (1.12 g, 14.1 mmol) was added dropwise. The resultant mixture was stirred 3 h at rt. The reaction mixture was extracted with 0.1 N HCl (3x50 mL), saturated $NaHCO_3$ (3x50 mL) and brine (2x50 mL). The collected organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford the product *rac*-**64** (EtOAc-hexane, 1:3) (3.31 g, 98% yield). Colorless oil. ^{1}H NMR: δ 4.13 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, J=11.7 and 5.3 Hz), 3.86 (dd, 1H, AB system diastereotopic H_8,

CH_aH_bO, J=11.6 and 7.2 Hz), 3.61 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 2.99-2.92 (m, 1H, CH, H_2), 2.50 (dd, 1H, AB system *exo*-H_3, CH_aH_b, J=11.7 and 9.2 Hz), 2.04 (s, 3H, $COCH_3$), 1.67 (dd, 1H, AB system diastereotopic *endo*-H_3, CH_aH_b, J=11.9 and 4.1 Hz); ^{13}C NMR: δ 170.6, 130.2, 128.3, 111.9, 77.0, 74.4, 62.6, 52.7, 51.6, 45.8, 39.1, 20.7 (Figure A3).

4.4. Enzymatic resolution of (±)-2-acetoxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene, (2*R*)-(+)-64.

To a stirred solution of *rac*-**62** (500 mg) in vinyl acetate (5 mL), CRL (50 mg) was added in one portion and the reaction mixture stirred at 25 ºC (TLC monitoring). The reaction mixture was filtered and vinyl acetate was evaporated under reduced pressure. The products (2*S*)-(-)-**62** and (2*R*)-(+)-**64** were purified by flash column chromatography (EtOAc:hexane: 1:4). (2*S*)-(-)-**1**: (0.27 g, 54% yield), $[\alpha]_D^{20}$= -17.7 (*c* 1.8 , MeOH) for 80% ee and (*R*)-(+)-**2**: (0.25 g, 44% yield). HPLC-analysis of (2*R*)-(+)-**2**: Chiralcel OD-H at room temperature, n-hexane:2-propanol (99:1), 0.3 mL/min, 230 nm, t_1= 19.8 min (minor), t_2=21.3 min (major), $[\alpha]_D^{20}$= +10.7 (*c* 1.8 , MeOH) for 88 % ee.

4.5. Enzymatic resolution of (±)-2-acetoxymethyl-hexachlorobicyclo[2.2.1]hept-5-ene, (2*R*)-(-)-65.

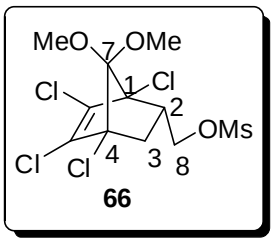


(-)-**65**

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 ^oC (TLC monitoring). The reaction mixture was filtered and vinyl acetate was evaporated

under reduced pressure. The products (2*S*)-(+)-**63** and (2*R*)-(-)-**65** were purified by flash column chromatography (EtOAc:Hexane, 1:2). (2*S*)-(+)-**63**: (0.15 g, 30% yield). (2*R*)-(-)-**65: (**0.22 g, 39% yield). HPLC-analysis of (-)-**65**: 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). ^{1}H NMR: δ 4.08 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, *J*=11.7 and 5.8 Hz), 3.92 (dd, 1H, dd, 1H, AB system diastereotopic H_8, CH$_a$$H_b$O, *J*=11.7 and 6.7 Hz), 3.00-3.13 (m, 1H, C*H*, H_2), 2.60 (dd, 1H, AB system *exo*-H_3, CH_aH$_b$, *J*= 12.6 and 8.9 Hz), 1.99 (s, 3H, COCH_3), 1.86 (dd, 1H, AB system *endo*-H_3, CH$_a$$H_b$, *J*=12.6 and 4.2 Hz); ^{13}C NMR: δ 170.8, 132.3, 130.5, 102.9, 81.3, 79.0, 62.7, 46.4, 38.6, 21.1 (Figure A4). IR(neat): 1745 (s), 1585 (s) cm^{-1}. HRMS: Calcd for $C_{10}H_8Cl_6O_2$ $(M+H)^+$, 370.8734. Found 370.8717.

4.6. Mesylation of (-)-2-hydroxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo[2.2.1]hept-5-ene, 66.



To a solution of alcohol (-)-**62** (1 g, 3.1 mmol) and Et_3N (0.87 mL, 6.2 mmol) in CH_2Cl_2 at 0 ˚C was slowly added methanesulfonyl chloride (0.36 mL, 4.6 mmol). After stirring for 10 min. The reaction mixture was diluted with water and the layers were separated. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated at room temperature under reduced pressure to afford the crude mesylate. The product **66** was purified by flash column chromatography (EtOAc-hexane: 1:3) (1.22 g, 98%). ^{1}H NMR: δ 4.29 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, *J*=10.3 and 5.2 Hz), 3.91 (dd, 1H, AB system diastereotopic H$_8$, CH$_a$$H_b$O, *J*=10.2 and 8.0 Hz), 3.61 (s, 3H,

OCH_3), 3.55 (s, 3H, OCH_3), 3.09-3.05 (m, 1H, C*H*, H_2), 3.03 (s, 3*H*, CH_3), 2.56 (dd, 1H, AB system *exo*-H_3, CH_aH$_b$, *J*=11.9 and 9.2 Hz), 1.73 (dd, 1H, AB system *endo*-H_3, CH$_a$$H_b$, *J*=12.1 and 4.1 Hz); ^{13}C NMR: δ 131.0, 127.7, 111.9, 77.4, 74.1, 67.4, 52.7, 51.7, 46.3, 39.3, 37.6 (Figure A5).

4.7. Synthesis of (1*R*)-1-phenyl-N-((1,4,5,6-tetrachloro-7,7-dimethoxybicyclo [2.2.1]hept-5-en-2-yl)methyl)ethanamine, 67.

The mesylate **66** (0.5 g, 1.25 mmol) and D-(+)-methylbenzyl amine (1.5 mL) were stirred at 90 ˚C under Ar atmosphere overnight. After the confirmation of the dissappearance of the mesylate by TLC, the reaction mixture was dissolved in CH_2Cl_2 and washed with aqueous sodium carbonate. The organic layer was separated, dried with $MgSO_4$, filtered and dried under reduced pressure. The crude product was purified by by flash column chromatography (EtOAc-hexane: 1:10 + 1% Et_3N) to afford **67**: (0.32 g, 60%). ^{1}H NMR: δ 7.26-7.15 (m, 5 H, *Ph*), 3.65-3.60 (m, 1H, NC*H*), 3.51 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 2.63-2.54 (m, 2H, CH_2N, H_8), 2.43-2.37 (m, 1H, C*H*, H_2), 2.10 (dd, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$, *J*=11.9 and 8.4 Hz), 1.42 (dd, 1H, AB system diastereotopic *endo*-H_3, CH$_a$$H_b$, *J*=11.5 and 9.0 Hz), 1.24 (d, 3H, CH_3, *J*=5.7 Hz); ^{13}C NMR: δ 144.9, 129.4, 127.9, 127.7, 126.5, 126.0, 111.3, 77.5, 74.1, 57.9, 52.3, 51.0, 47.7, 46.6, 40.6, 23.8 (Figure A6).

4.8. Amine salt formation of 67.

The amine **67** (0.32 g, 0.75 mmol) was dissolved in 15 mL ether. HCl gas produced from the reaction of NaCl with H_2SO_4 was passed through the amine solution. Amine salt precipitated as white crystals. For the X-ray analysis, (1*R*)-1-phenyl-N-((1,4,5,6-tetrachloro-7,7-dimethoxy- bicyclo[2.2.1]hept-5-en-2-yl)methyl)ethanamine **68** was recrystallized with EtOH.

4.9. X-ray diffraction data for 68.

All the measurements were performed using graphite-monochromatized Mo K_α radiation at 100K: $C_{18}H_{22}Cl_4NO_2^+Cl^-$, M_r 461.62, triclinic, space group *P*1, a = 12.6456(6)Å, b = 13.7775(6)Å, c = 14.1907(7)Å, α = 62.2039(15)°, β = 74.7209(17)°, γ = 88.2506(16)°, V = 2097.39(17)Å^3, Z = 4, d_{calc} = 1.462g cm^{-3}, μ = 0.705mm^{-1}. A total of 31320 reflections were collected (Θ_{max} = 26.0°), from which 14943 were unique (R_{int} = 0.0239), with 14465 having I > 2σ(I). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares techniques against F^2 (SHELXL-97) [107]. The absolute configuration was established by anomalous dispersion effects in the diffraction measurements on the crystal. Due to the enantiomeric impurity of the compound containing 15.9% of the S,R,R enantiomer besides 84.1% of the R,S,S enantiomer (related to the asymmetric C atoms at C1, C4, and C5 in molecule I) the molecule IV is disordered over two orientations and was refined with site occupation factors of 0.636(3) for the S,R,R enantiomer and of 0.364(3) for the R,S,S enantiomer, respectively. This disorder of the molecule IV has influences to the neighbouring

molecules, mainly to the phenyl ring of molecule II, and to two Cl^- anions (Cl93/Cl95 and Cl94/Cl96). A rigid bond restraint was applied to these disordered phenyl ring and to the molecules IVa/IVb and the equivalent bonds in the bicycle of the molecules IVa/IVb were restrained to have the same lengths. The C atoms of the disordered phenyl rings were fitted to a regular hexagon with C-C distances of 1.39Å. There is also a slight disorder observable in molecule I (the two largest peaks in a difference Fourier map are near this molecule), which could not be resolved. The entire molecules show R configuration at the asymmetric C atom bonded to the N atom (C17 in molecule I).

The other non-hydrogen atoms were refined with anisotropic displacement parameters without any constraints. The H atoms were refined with appropriate positional constraints and with common isotropic displacement parameters U_{iso} for equivalent H atoms. The H atoms of the methyl groups were refined with an idealized geometry with tetrahedral angles, enabling rotation around the X-C bond, and C-H distances of 0.98Å. Some H atoms showing U_{iso} smaller than the equivalent isotropic displacement parameters U_{eq} of the C atoms they are bonded to be included at calculated positions with their U_{iso} fixed to 1.2 times U_{eq} of the C atom they are bonded to. The C-H distances were fixed to 0.99, 1.00, and 0.95Å for the secondary, tertiary, and phenyl hydrogen atoms, respectively. The H atoms of the NH_2^+ groups were refined with common isotropic displacement parameters for the H atoms of the same group and idealized geometry with approximately tetrahedral angles and C-H distances of 0.92Å. For 1222 parameters final *R* indices of R1 = 0.0436 and wR^2 = 0.1165 (GOF = 1.049) were obtained. The largest peak in a difference Fourier map was 1.270eÅ^{-3} (Table 5). The structural data for **68** have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No. 739825).

Table 5. Hydrogen bonds for CLEM1 [Å, °]. The N-H distances were restrained to 0.92Å. The atoms Cl93, Cl94, N7, H701, H702 have site occupation factors of 0.636(3), the corresponding atoms Cl95, Cl96, N9, H901, H902 have site occupation factors of 0.364(3).

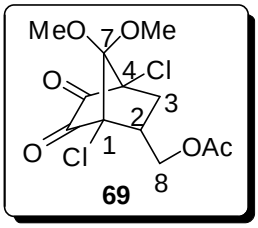
D-H···A	d(H···A)	d(D···A)	<(DHA)
N(1)-H(102)···Cl(91)	2.36	3.232(4)	158.0
N(1)-H(101)···Cl(93)$^{i)}$	2.40	3.291(6)	162.5
N(1)-H(101)···Cl(95)$^{i)}$	2.25	3.117(9)	156.1
N(3)-H(301)···Cl(91)$^{ii)}$	2.39	3.271(4)	160.6
N(3)-H(302)···Cl(93)	2.39	3.274(6)	161.6
N(3)-H(302)···Cl(95)	2.07	2.919(8)	152.2
N(5)-H(501)···Cl(92)	2.19	3.082(3)	163.8
N(5)-H(502)···Cl(91)$^{iii)}$	2.32	3.221(3)	167.0
N(7)-H(702)···Cl(93)	2.29	3.179(7)	161.3
N(7)-H(701)···Cl(94)	2.24	3.072(6)	150.2
N(9)-H(902)···Cl(95)	2.32	3.126(13)	146.5
N(9)-H(901)···Cl(96)	2.08	2.997(14)	171.1

Symmetry transformations used to generate equivalent atoms:
$^{i)}$ x, y, z-1 $^{ii)}$ x, y, z+1 $^{iii)}$ x, y+1, z

4.10. General procedure for ruthenium-catalyzed oxidation of dihaloalkene derivatives 62-65.

To a stirred solution of *rac*-dihaloalkene derivative (0.55 mmol) in acetonitrile (6 mL) at 0 ºC was added a solution of $RuCl_3.3H_2O$ (0.055 mmol) and $NaIO_4$ (0.17 g, 0.82 mmol) in water (1 mL). The mixture was stirred and monitored by TLC. The resulting suspension was filtered through a thin pad of silica gel followed by concentration of the filtrate. The crude product was purified by a short flash column chromatography (EtOAc-hexane:1:2).

4.10.1. (±)-(1,4-dichloro-7,7-dimethoxy-5,6-dioxobicyclo[2.2.1]heptan-2-yl) methyl acetate, (±)-69.



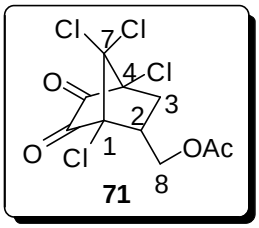
(0.17 g, 98%). Yellow liquid. ^{1}H NMR: δ 4.17 (dd, 1H, AB system dastereotopic H_8, CH_aH$_b$O, J=12.0 and 1.7 Hz), 3.98 (dd, 1H, AB system diastereotopic H_8, CH$_a$$H_b$O, J=12.1 and 3.1 Hz), 3.67 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.96-2.92 (m, 1H, CH, H_2), 2.68 (t, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$, J=12.6 Hz), 2.10 (dd, 1H, AB system diastereotopic *endo*-H$_3$, CH$_a$$H_b$, J=13.1 and 4.8 Hz), 1.84 (s, 3H, COCH_3); ^{13}C NMR: δ 187.5, 186.3, 168.6, 101.4, 77.5, 73.7, 58.7, 51.7, 50.6, 42.0, 32.8, 18.9 (Figure A7). IR (KBr) 2900, 1785, 1720, 1440, 1200 cm^{-1}.

4.10.2. (±)-Tricyclic α-keto hemiacetal, (±)-70.

(0.15 g, 96%). Colorless solid. ^{1}H NMR: δ 4.37 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, J=8.6 and 3.6 Hz), 3.72 (d, 1H, AB system diastereotopic H_8, CH$_a$$H_b$O, J=8.6 Hz), 3.60 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 2.96-2.92 (m, 1H, CH, H_2), 2.66 (dd, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$, J=12.7 and 11.1 Hz), 1.86 (dd, 1H, AB system diastereotopic *endo*-H$_3$,

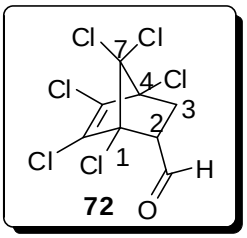
CH_aH_b, J=12.9 and 1.9 Hz); ^{13}C NMR: δ 196.8, 103.5, 102.3, 75.1, 74.1, 71.8, 52.4, 51.6, 46.5, 36.0 (Figure A8).

4.10.3. (±)-(1,4,7,7-tetrachloro-5,6-dioxobicyclo[2.2.1]heptan-2-yl)methyl acetate, (±)-71.



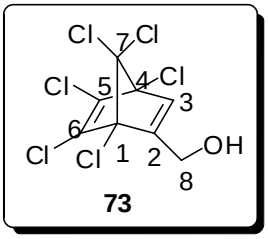
(0.16 g, 90%). Yellow liquid. ^1H NMR: δ 4.31 (dd, 1H, AB system diastereotopic H_8, CH_aH_bO, J=12.3 and 1.8 Hz), 4.12 (dd, 1H, AB system diastereotopic H_8, CH_aH_b, J=12.5 and 3.5 Hz), 3.14-3.09 (m, 1H, CH, H_2), 2.84 (t, 1H, AB system diastereotopic *exo*-H_3, CH_aH_b, J=12.7 Hz), 2.36 (dd, 1H, AB system diastereotopic *endo*-H_3, CH_aH_b, J=13.6 and 4.9 Hz), 1.93 (s, 3H, COCH_3); ^{13}C NMR: δ 185.2, 184.3, 169.3, 92.9, 82.5, 78.9, 59.2, 44.1, 34.4, 19.8 (Figure A9).

4.10.4. (±)-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene-2-carbaldehyde, (±)-72.



(0.15 g, 82%). Yellow oil. ^1H NMR: δ 9.60 (s, 1H, CHO), 3.59-3.56 (m, 1H, CH, H_2), 2.55 (dd, 1H, AB system diastereotopic *endo*-H_3, CH_aH_b, J=12.7 and 4.1 Hz), 2.45 (dd, 1H, AB system diastereotopic *exo*-H_3, CH_aH_b, J=12.6 and 8.6 Hz); ^{13}C NMR: δ 195.2, 133.3, 128.6, 102.1, 80.1, 78.6, 57.8, 34.8 (Figure A10).

4.11. Synthesis of 2-hydroxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-2,5-diene, (±)-73.



A mixture of propargyl alcohol (5.60 g, 100 mmol) and hexachlorocyclopentadiene (11.12 g, 40 mmol) containing a few crystals of hydroquinone was sealed under vacuum in a thick-walled Pyrex tube. The mixture was heated at 170 ˚C for 6 h. The crude product was purified by flash column chromatography (EtOAc:Hexane, 1:3) to afford (±)-**73**. (11.15, 85%). White solid. ^{1}H NMR: δ 6.42 (s, 1H, *olefinic*, H_3), 4.36-4.25 (m, 2H, CH_2O, H_8), 2.28 (s, 1H, O*H*); ^{13}C NMR: δ 151.2, 138.3, 137.0, 133.9, 115.0, 84.7, 82.8, 59.1 (Figure A11). mp: 86.5-87.5 ˚C. IR (neat): 3420, 1630, 750 cm^{-1}.

4.12. Synthesis of 2-acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-2,5-diene, (±)-74.

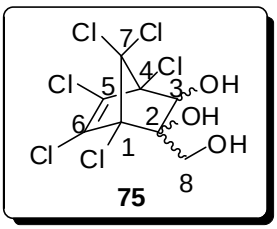
To a stirred solution of **73** (5 g, 15.2 mmol) in 100 mL CH_2Cl_2, dry pyridine (1.78 g, 22.5 mmol) was added at 0 ˚C and the mixture was stirred for 30 min under inert atmosphere. Acetyl chloride (1.77 g, 22.5 mmol) was added dropwise. The resultant mixture was stirred 5 h at rt. The organic phase 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 the product (±)-**74** (EtOAc-hexane, 1:6) (5.34 g, 96% yield). Colorless oil. ^{1}H NMR: δ 6.51 (s, 1H, *olefinic*, H_3), 4.72 (s, 2H, CH_2O, H_8), 2.01 (s, 3H, COCH_3); ^{13}C NMR: δ 169.7, 147.0, 137.9, 137.2, 136.6, 115.1, 84.8, 82.7, 59.0, 20.7 (Figure A12). IR (neat): 1728, 1680, 750 cm^1.

4.13. Ruthenium-catalyzed oxidation of hexachloronorbornadiene derivatives 73 and 74.

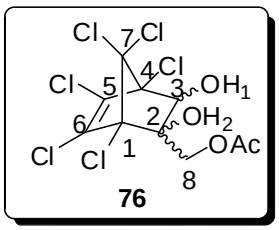
To a stirred solution of norbornadiene derivative (0.55 mmol) in acetonitrile (6 mL) at 0 ºC was added a solution of $RuCl_3.3H_2O$ (0.01 mmol) and $NaIO_4$ (0.17 g, 0.82 mmol) in water (1 mL). The mixture was stirred and monitored by TLC. The resulting suspension was filtered through a thin pad of silica gel followed by concentration of the filtrate. The crude product was purified by a short flash column chromatography (EtOAc-hexane:1:2).

4.13.1. 1,4,5,6,7,7-pentachloro-2-(hydroxymethyl)bicyclo[2.2.1]hept-5-ene-2,3-diol, 75.



(0.12 g, 65% yield). White solid. ^{1}H NMR: δ 4.51 (s, 1H, CH, H_3), 4.27 (bs, 1H, OH), 4.20 (bs, 1H, OH), 4.12 (s, 2H, CH_2, H_8), 2.80 (bs, 1H, OH); ^{13}C NMR: δ 134.6, 130.7, 98.1, 85.1, 81.8, 80.6, 78.0, 65.3 (Figure A13).

4.13.2. 1,4,5,6,7,7-pentachloro-2-(acetoxymethyl)bicyclo[2.2.1]hept-5-ene-2,3-diol, 75.

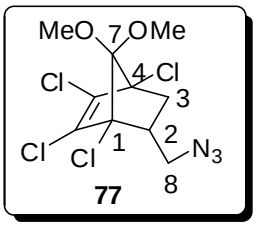


(0.19 g, 88% yield). White solid. ^{1}H NMR: δ 4.75 (d, 1H, AB system diastereotopic H_8, CH_aH$_b$, J=12.6 Hz), 4.64 (d, 1H, AB system diastereotopic H_8, CH$_a$$H_b$, J=12.6 Hz), 4.56 (d, 1H, CH, H_3, J=7.8 Hz), 4.35 (s, 1H, OH_2), 3.10 (d, 1H, OH_1, J=8.0 Hz), 2.08 (s, 3H, COCH_3); ^{13}C NMR: δ 171.9, 133.6, 129.5, 97.0, 83.6, 80.9, 79.3, 76.6, 67.2, 19.6 (Figure A14).

4.14. General procedure for cerium-catalyzed oxidations dihaloalkene derivatives 62, 64, 77.

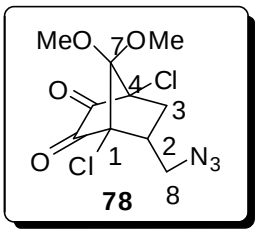
To a stirred solution of *rac*-dihaloalkene derivative (0.55 mmol) in acetonitrile (6 mL) at 0 ºC was added a solution of $CeCl_3.7H_2O$ (0.055 mmol) and $NaIO_4$ (0.17 g, 0.82 mmol) in water (1 mL). The mixture was stirred and monitored by TLC. The resulting suspension was filtered through a thin pad of silica gel followed by concentration of the filtrate. The crude product was purified by a short flash column chromatography (EtOAc-hexane:1:2).

4.15. Synthesis of 5-(azidomethyl)-1,2,3,4-tetrachloro-7,7-dimethoxybicyclo [2.2.1]hept-2-ene, 77.



To the solution of mesylate **66** (1 g, 2.5 mmol) in 4 mL dry DMSO, sodium azide (0.27 g, 4.25 mmol) was added. The reaction mixture was heated to 80 ˚C for 1 h and the mixture was poured into water (15 mL). Then it was extracted with CH_2Cl_2 (3x10 mL) and the organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solvent yielded the crude product which was purified by flash column chromatography (EtOAc-hexane:1:4). (0.81g, 94% yield). ^{1}H NMR: δ 3.54 (s, 3H, OCH_3), 3.51-3.50 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, J=13.6 and 9.2 Hz), 3.48 (s, 3H, OCH_3), 2.87-2.81 (m, 1H, AB system diastereotopic H_8, CH$_a$$H_b$O), 2.80-2.74 (m, 1H, C$H$, H_2), 2.46 (dd, 1H, AB system diastereotopic *exo*-H_2, CH_aH$_b$, J=12.0 and 8.0 Hz), 1.54 (dd, 1H, AB system diastereotopic *endo*-H$_2$, CH$_a$$H_b$, J=12.0, 4.0 Hz); ^{13}C NMR: δ 130.8, 127.7, 111.7, 74.3, 52.6, 51.6, 51.3, 46.8, 40.2 (Figure A15).

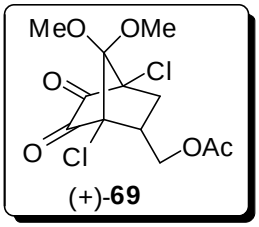
4.16. Synthesis of 5-(azidomethyl)-1,4-dichloro-7,7-dimethoxybicyclo[2.2.1] heptane-2,3-dione, 78.



78

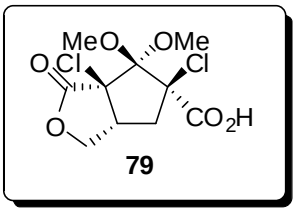
Cerium-catalyzed oxidation of the azide **77** (0.35 g, 1 mmol) was done according to the procedure 4.14. to afford **78**. (0.26 g, 85% yield). White crystals. ^{1}H NMR: δ 3.50 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.46 (d, 2H, CH_2, H_8, J=3.6 Hz), 2.86-2.80 (m, 1H, H_2), 2.58 (t, 1H, CH_2, *exo*-H_3, J=13.2 Hz), 2.10 (dd, 1H, CH_2, *endo*-H_3, J=13.2 and 5.2 Hz); ^{13}C NMR: δ 187.5, 186.6, 102.3, 78.8, 74.8, 52.6, 52.0, 48.5, 43.8, 33.9 (Figure A16).

4.17. Synthesis of (+)-(1,4-dichloro-7,7-dimethoxy-5,6-dioxobicyclo[2.2.1]heptan-2-yl) methyl acetate, (+)-69.



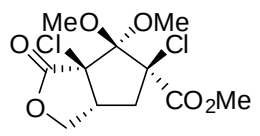
(+)-2-Acetoxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxybicyclo 2.2.1]hept-5-ene, (+)-**64** (1 g, 2.72 mmol) obtained from CRL catalyzed resolution was subjected to $CeCl_3$-oxidation reaction by the procedure 4.14 to afford (+)-**69**. (0.8 g, 90% yield). $[\alpha]_D^{20}$=+24.6 (*c* 3.7, MeOH).

4.18. Cleavage of α-diketone (+)-69.



To a stirred solution of α-diketone (+)-**69** (0.8 g, 2.4 mmol) in methanol (21 mL) was added 30% H_2O_2 (1.8 mL) followed by slow addition of 6 N NaOH (0.9 mL) solution. After the mixture stirred at room temperature for 2 h, 5% HCl was added and extracted with ethyl acetate. The combined organic layer was washed once with brine and dried over Na_2SO_4. The crude carboxylic acid **79** was obtained after concentration of EtOAc layer.

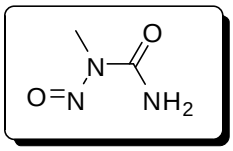
4.19. Esterificaton of carboxylic acid (+)-79.



(+)-**80**

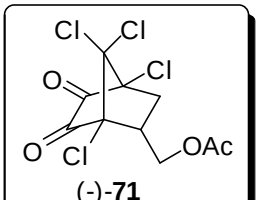
KOH (1.7 g, 30.3 mmol) was dissolved in 4 mL water and cooled in ice-salt bath. 25 mL Et_2O was cooled and added to the reaction mixture. When the temperature is 0 ˚C, N-methyl-N-nitroso urea (0.50 g, 4.8 mmol) was added slowly. After the gas evolution is completed, ether phase was separated and dried over KOH and filtered. To this solution cooled to 0 ˚C, carboxylic acid (0.71 g, 2.4 mmol) solution in ether was added dropwise. After the mixture come to 20 ˚C, ether was evaporated to afford crude methyl ester derivative. The crude product was purified by flash column chromatography (EtOAc-hexane, 1:3) to afford (+)-**80**. (0.68 g, 90 %). Colorless solid. $[\alpha]_D^{20}$= +7.2 (*c* 6.0, MeOH). Mp: 118-120 ºC; ^{1}H NMR: δ 4.61 (t, 1H, AB system CH_aH$_b$O, *J*=9.0 Hz), 4.14 (dd, 1H, AB system CH$_a$$H_b$O, *J*=9.3 and 3.6 Hz), 3.86 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.49 (dtd, 1H, C*H*, *J*=9.0, 9.0 and 3.6 Hz), 3.32 (s, 3H, CH_3), 2.82 (dd, 1H, AB system CH_aH$_b$, *J*=14.5 and 9.0 Hz), 2.66 (dd, 1H, AB system CH$_a$$H_b$, *J*=14.5 and 9.0 Hz); ^{13}C NMR: δ 171.1, 167.7, 110.0, 74.0, 73.8, 70.6, 54.3, 53.5, 51.6, 46.4, 41.9 (Figure A17); IR (KBr) 2850, 1740 (br), 1180 cm^{-1}. COSY, HMQC and HMBC spectra are given in Figure A18, A19 and A20, respectively.

4.20. Preparation of N-methyl-N-nitroso urea.



To a stirred solution of methylammonium chloride (10 g, 0.148 mol) KOCN (15 g) was added. The resultant solution was heated to boiling point and filtered after cooling. To this cold solution, $NaNO_2$ (10 g) solution in 20 mL water was added and then cooled to 0 ˚C. The mixture of 20 g of H_2SO_4 with 100 g ice was added dropwise during the mechanical stirring. N-methyl-N-nitroso urea was precipitated and filtered. The crude product was washed with water and methanol. The solid cake was dried to afford N-methyl-N-nitroso-urea.

4.21. Synthesis of (-)-(1,4,7,7-tetrachloro-5,6-dioxobicyclo[2.2.1]heptan-2-yl) methyl acetate, (-)-71.

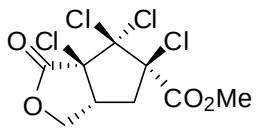


(-)-**71**

(-)-2-Acetoxymethyl-1,4,5,6,7,7-hexachlorobicyclo 2.2.1]hept-5-ene, (-)-**65** (1 g, 2.7 mmol) obtained from CRL catalyzed resolution was subjected to $RuCl_3$-catalyzed oxidation reaction by the procedure 4.10 to afford (-)-**71**. (0.8 g, 90% yield). $[\alpha]_D^{20}$=-46.0 (*c* 1, MeOH).

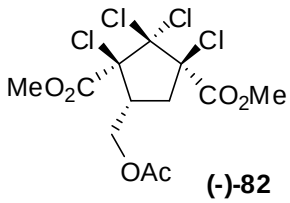
4.22. Synthesis of cyclopentanoid (-)-82 and γ-lactone fused cyclopentanoid, (-)-81.

(-)-(1,4,7,7-tetrachloro-5,6-dioxobicyclo[2.2.1]heptan-2-yl) methyl acetate (-)-**71** (0.8 g, 2.4 mmol) was subjected to H_2O_2-mediated cleavage and subsequently the methylation reaction to afford (-)-**81** and (-)-**82** following the same procedure for the synthesis of (+)-**80**.



(-)-81

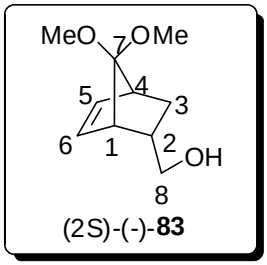
γ-lactone fused cyclopentanoid, (-)-**81**. (0.11 g, 15% yield). ^{1}H NMR: δ 4.72 (t, 1H, AB system CH_aH$_b$O, J=9.4 Hz), 4.15 (dd, 1H, AB system CH$_a$$H_b$O, J=9.4 and 4.6 Hz), 3.92 (s, 3H, CO_2CH_3), 3.79-3.70 (m, 1H, CH), 3.00-2.98 (m, 2H, CH_2); ^{13}C NMR: δ 168.3, 165.4, 92.8, 78.9, 70.9, 61.2, 54.0, 46.1, 42.5 (Figure A21). $[\alpha]_D^{20}$=-8.3 (c 0.6, MeOH).



(-)-82

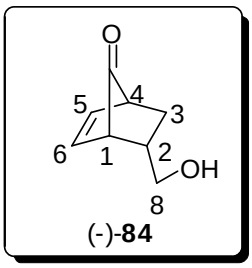
cyclopentanoid (-)-**82**. (0.58 g, 61% yield). ^{1}H NMR: δ 4.71 (dd, 1H, AB system CH_aH$_b$O, J=11.1 and 5.4 Hz), 4.48 (dd, 1H, AB system CH$_a$$H_b$O, J=11.1, 8.7 Hz), 3.90 (s, 3H, CO_2CH_3), 3.85 (s, 3H, CO_2CH_3), 3.57-3.49 (m, 1H, CH), 2.92 (dd, 1H, AB system CH_aH$_b$, J=15.0 and 11.8 Hz), 2.68 (dd, 1H, AB system CH$_a$$H_b$, J=15.0 and 8.0 Hz), 2.06 (s, 3H, $COCH_3$). ^{13}C NMR: δ 170.4, 165.8, 165.3, 95.0, 78.3, 76.5, 63.6, 53.6, 53.4, 49.3, 39.5, 20.7 (Figure A22). $[\alpha]_D^{20}$=-17.4 (c 2.5, MeOH). COSY, HMQC and HMBC spectra are given in Figure A23, A24 and A25, respectively.

4.23. Reductive dechlorination of (+)-2-Acetoxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo 2.2.1]hept-5-ene, (+)-64.



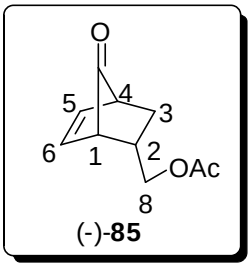
Liquid ammonia (150 mL) was distilled into a 250 mL three-necked round-bottomed flask equipped with a condenser. Small pieces of freshly cut sodium was added to the flask with stirring at -33 ˚C and dark blue color appeared. (+)-2-acetoxymethyl-1,4,5,6-tetrachloro-7,7-dimethoxy bicyclo 2.2.1]hept-5-ene, (+)-**64** (6 g, 16.5 mmol) was dissolved in dry ether-ethanol mixture (1:1, 40 mL) and introduced into the reaction mixture. The mixture was stirred at -33 ˚C for 30 min. During the reaction blue color should persist. If necessary, more Na pieces can be added. Then, solid NH_4Cl was added until the solution became colorless. The excess ammonia was allowed to evaporate and a cold aqueous saturated NH_4Cl solution and water were added to the resulting residue, which was subsequently extracted with ethyl acetate (3x100 mL). Removal of the solvent, followed by purification of the crude product by flash column chromatography (EtOAc-hexane, 1:3) afforded the dechlorinated product (-)-**83**. (2.4 g, 79% yield). Colorless oil. $[\alpha]_D^{20}$=-18.7 (c 1, MeOH). ^{1}H NMR: δ 6.04 (dd, 1H, olefinic proton, *J*=6.0 and 3.2 Hz), 6.18 (dd, 1H, olefinic proton, *J*=6.0 and 3.5 Hz), 3.38-3.28 (m, 2H, CH_2, H_8), 3.22 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 2.96 (m, 1H, C*H*, H_4), 2.79 (m, 1H, C*H*, H_1), 2.54-2.46 (m, 1H, C*H*, H_2), 2.05-1.99 (m, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$), 1.44 (bs, 1H, O*H*), 0.55 (dd, 1H, AB system diastereotopic *endo*-H_3, CH$_a$$H_b$, *J*=11.6 and 4.2 Hz); ^{13}C NMR: δ 134.2, 130.6, 119.3, 64.7, 51.8, 49.5, 46.3, 44.6, 38.8, 27.0 (Figure A26).

4.24. Synthesis of (-)-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-one, (-)-84.



To a stirred solution of (7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl)methanol (-)-**83** (2.4 g, 13 mmol) in acetone (50 mL) containing water (0.75 mL), Amberlyst-15 (0.52 g) was added. The reaction mixture was stirred overnight. The resin is filtered and the filtrate was evaporated to afford (-)-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-one, (-)-**84**. (1.78 g, 99% yield). Colorless oil. $[\alpha]_D^{20}$=-40.0 (c 1, MeOH). ^{1}H NMR: δ 6.59 (dd, 1H, olefinic proton, *J*=6.6 and 3.7 Hz), 6.44 (dd, 1H, olefinic proton, *J*=6.6 and 3.3 Hz), 3.46-3.41 (m, 1H, AB system diastereotopic H_8, CH_aH_bO), 3.38-3.32 (m, 1H, AB system diastereotopic H_8, CH_aH_bO), 3.07 (m, 1H, C*H*, H_4), 2.87 (m, 1H, C*H*, H_1), 2.56-2.48 (m, 1H, *CH*, H_2), 2.17-2.09 (m, 1H, AB system diastereotopic *exo*-H_3, CH_aH_b), 1.43 (bs, 1H, OH), 0.75 (dd, 1H, AB system diastereotopic *endo*-H_3, CH_aH_b, *J*=12.1 and 5.4 Hz); ^{13}C NMR: δ 204.6, 133.6, 130.0, 64.2, 48.5, 46.3, 36.1, 25.3 (Figure A27).

4.25. Acetylation of (-)-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-one (-)-84.



(-)-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-one (-)-**84** (2.4 g, 13.0 mmol) was subjected to acetylation reaction following the procedure in part 4.3 to afford (-)-5-(acetoxymethyl)bicyclo[2.2.1]hept-2-en-7-one (-)-**85**. (2.34 g, 98% yield). Colorless liquid. $[\alpha]_D^{20}$=-53.2 (c 1, MeOH). ^{1}H NMR: δ 6.60 (m, 1H, olefinic proton), 6.42 (m, 1H, olefinic proton), 3.90-3.84 (m, 1H, AB system CH_aH$_b$O, H_8), 3.77-3.71 (m, 1H, AB system CH$_a$$H_b$O, H_8), 2.99-2.98 (m, 1H, CH, H_4), 2.88-2.87 (m, 1H, CH, H_1), 2.63-2.59 (m, 1H, CH, H_2), 2.17-2.11 (m, 1H, AB system diastereotopic *exo*-H_3, CH_aH$_b$), 2.04 (s, 3H, COCH_3), 0.80-0.75 (m, 1H, AB system diastereotopic *endo*-H_3, CH$_a$$H_b$); ^{13}C NMR: δ 203.3, 170.7, 134.0, 130.0, 65.3, 48.6, 46.2, 32.7, 25.6, 20.8 (Figure A28).

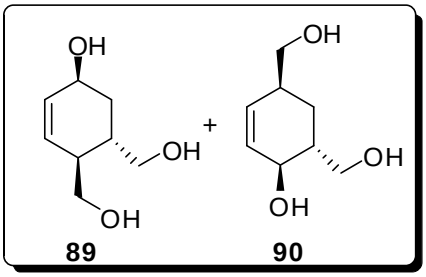
4.26. Baeyer-Villiger oxidation of *endo*-acetoxymethyl-7-ketonorbornene (-)-85

MCPBA (70%, 3.20 g, 13.0 mmol) was added to a stirred suspension of acetoxymethyl-7-ketonorbornene (-)-**85** (2.34 g, 13 mmol.) and Na_2C0_3 (1.38 g, 13.0 rnmol.) in DCM (50 rnL) at 0 ˚C . The reaction mixture was stirred for 6 h at *rt* before it was quenched with 10% aq. solution of $Na_2S_2O_5$ (25 mL). The organic layer was separated and aq. layer was extracted with DCM (2 x 50 mL). The combined organic extract was washed with saturated aq. $NaHCO_3$ solution (50 mL) followed by brine (50 mL), prior to drying over anhydrous Na_2SO_s. After filtration, the solution was concentrated in vacuum followed by column chromatography (ethyl acetate- hexane, 1:3) to afford the regioisomeric mixture of lactones, **86** and **87** and also epoxide **88** as side product.

The epoxide **88**. (0.12 g, 5% yield). ^{1}H NMR: δ 4.20-4.14 (dd, 1H, AB system diastereotopic H_8, CH_aH$_b$O, J=11.0 and 5.8 Hz), 4.04 (dd, 1H, AB system diastereotopic H_8, CH$_a$$H_b$O, J=11.0 and 7.3 Hz), 3.44-3.43 (m, 1H, CH, H_5), 3.39-3.38 (m, 1H, CH, H_6), 3.21 (s, 2H, CH, H_1 and H_4), 2.42-2.35 (m, 1H, CH, H_2), 2.08 (s, 3H, COCH_3), 2.03-2.01 (m, 1H, AB system diastereotopic exo-H$_3$, CH_aH$_b$), 1.70 (dd, 1H, AB system diastereotopic *endo*-H_3, CH$_a$$H_b$, J=14.6, 11.5 Hz). ^{13}C NMR: δ 170.8, 66.0, 54.0, 52.4, 50.7, 50.0, 30.8, 23.1, 21.0 (Figure A29).

Lactone mixture **86** and **87**. (1.91 g, 75% yield).
^{1}H NMR and ^{13}C NMR are shown in Figure A30.

4.27. LAH reduction of lactone mixture 86 and 87.

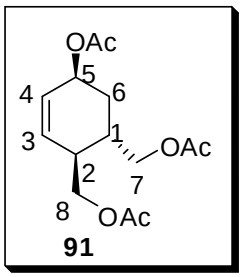


To a solution of **86** and **87** (1.91 g, 9.7 mmol) in dry THF (45 rnL), cooled at -15 'C, was added LAH (114 mg, 29 rnmol) and the reaction mixture stirred for ***2*** h at the same temperature. The reaction mixture was cautiously quenched with ethyl acetate (50 mL) followed by saturated Na_2S0_4 solution (25 rnL), to precipitate out

aluminium salts. After filtration, the filtrate was concentrated in vacuum to afford **89** and **90** and directly subjected to acetylation reaction.

4.28. Acetylation of trihydroxylated cyclohexene mixture of 89 and 90.

The mixture of compound **89** and **90** was acetylated following the procedure written in part 4.3. The isomers were separated by flash column chromatography (EtOAc:Hexane, 1:5) (70% yield).



((1S,2S,5S)-5-acetoxycyclohex-3-ene-1,2-diyl)bis (methylene) diacetate, **91**; colorless oil. $[\alpha]_D^{20}$=-22.0 (c 1, MeOH). ^{1}H NMR: δ 5.85-5.76 (m, 2H, olefinic protons), 5.17 (dd, 1H, C*H*OAc, *J*=3.6 and 7.2 Hz, H_5), 4.16-3.97 (m, 4H, CH_2Oac, H_7 and H_8), 2.29-2.09 (m, 1H, C*H*, H_2), 1.98 (m, 1H, C*H*, H_1), 2.00 (s, 6H, COCH_3), 1.98 (s, 3H, COCH_3) 1.85-1.80 (m, 1H, CH_2, H_6), 1.78-1.67 (m, 1H, CH_2, H_6) (Figure A31). ^{13}C NMR: δ 170.5, 170.4, 170.1, 132.5, 126.5, 66.0, 65.8, 65.5, 37.2, 31.5, 30.2, 21.2, 20.7.

((1R,3S,6S)-6-acetoxycyclohex-4-ene-1,3-diyl)bis (methylene) diacetate, **92**; colorless oil. $[\alpha]_D^{20}$=11.6 (c 1, MeOH). ^{1}H NMR: δ 5.76-5.67 (m, 2H, olefinic protons), 5.10-5.08 (m, 1H, C*H*OAc, H_6), 4.01-3.90 (m, 4H, CH_2Oac, H_7 and H_8), 2.43 (m, 1H, C*H*, H_3), 2.11-2.07 (m, 1H, C*H*, H_1), 2.02 (s, 9H, COCH_3), 1.68-1.65 (m, 2H, CH_2, H_2) (Figure A35). ^{13}C NMR: δ 169.5, 169.4, 169.1, 129.7, 126.6, 67.6, 65.2, 63.3, 33.9, 31.7, 23.8, 20.0, 19.8, 19.7.

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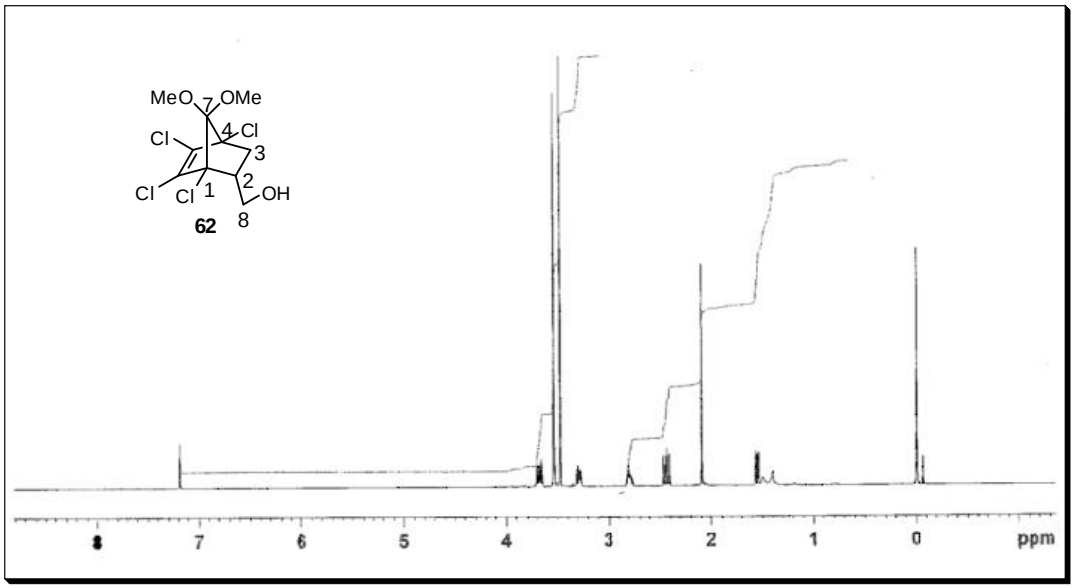
APPENDIX A



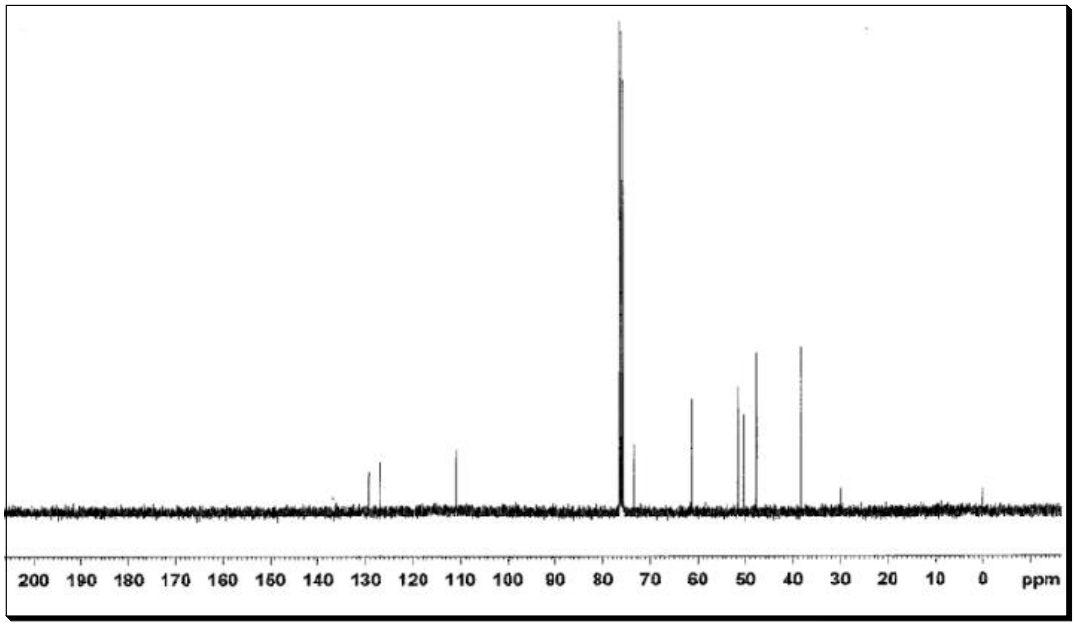
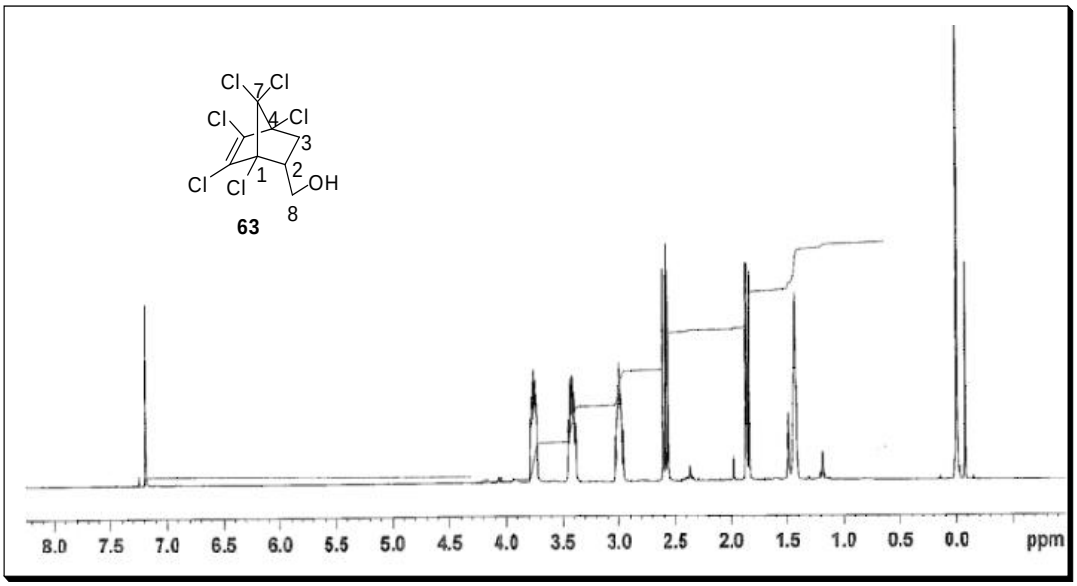


Figure A1. ^{1}H and ^{13}C NMR spectra of compound **62**.



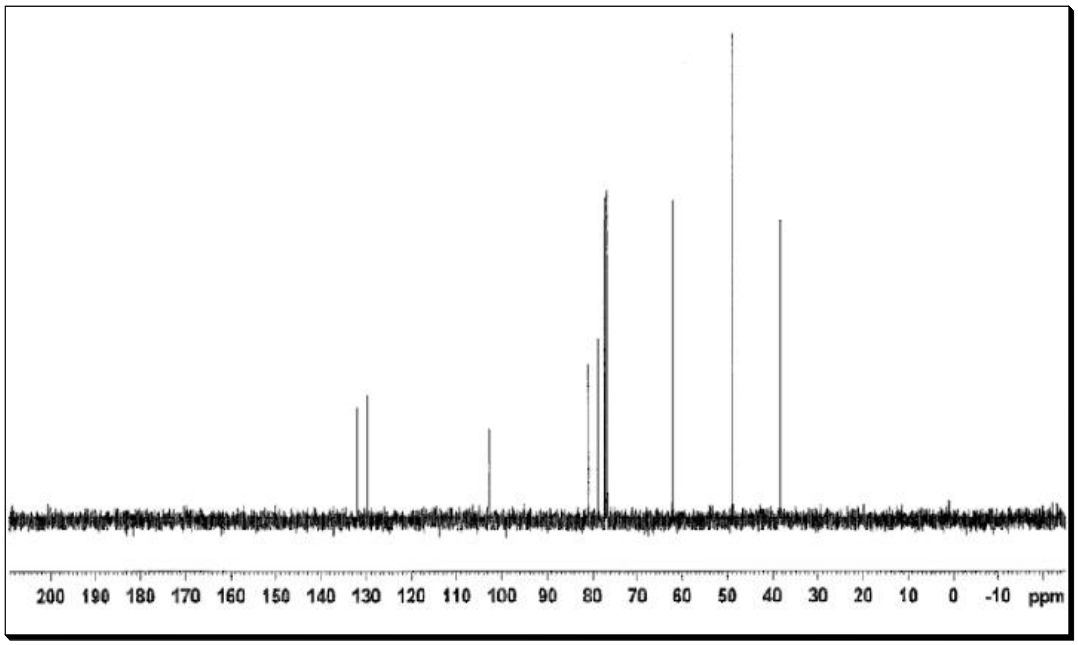
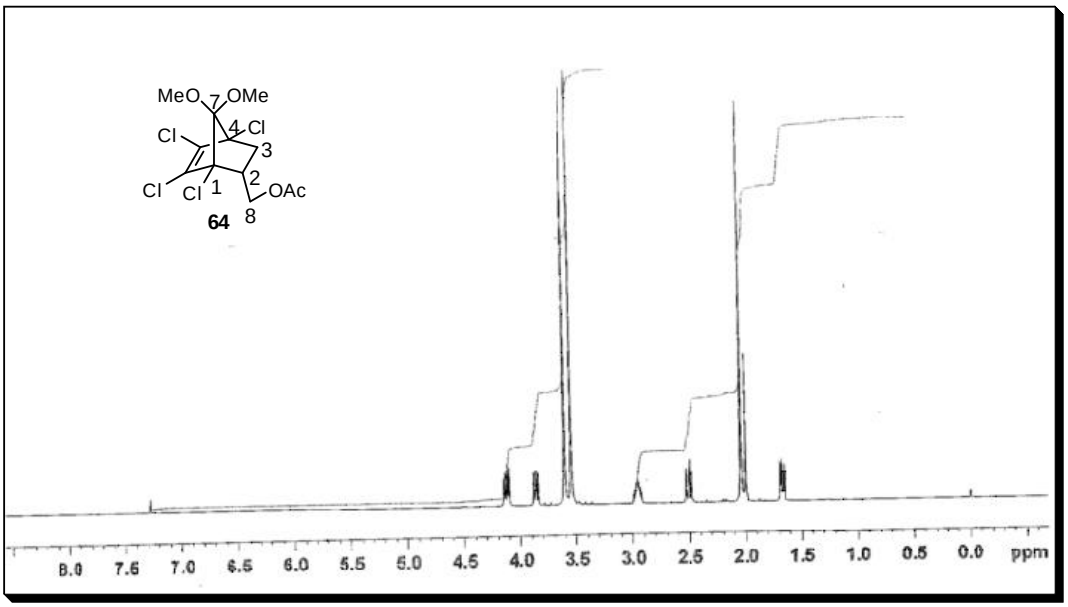


Figure A2. ^{1}H and ^{13}C NMR spectra of compound **63**.



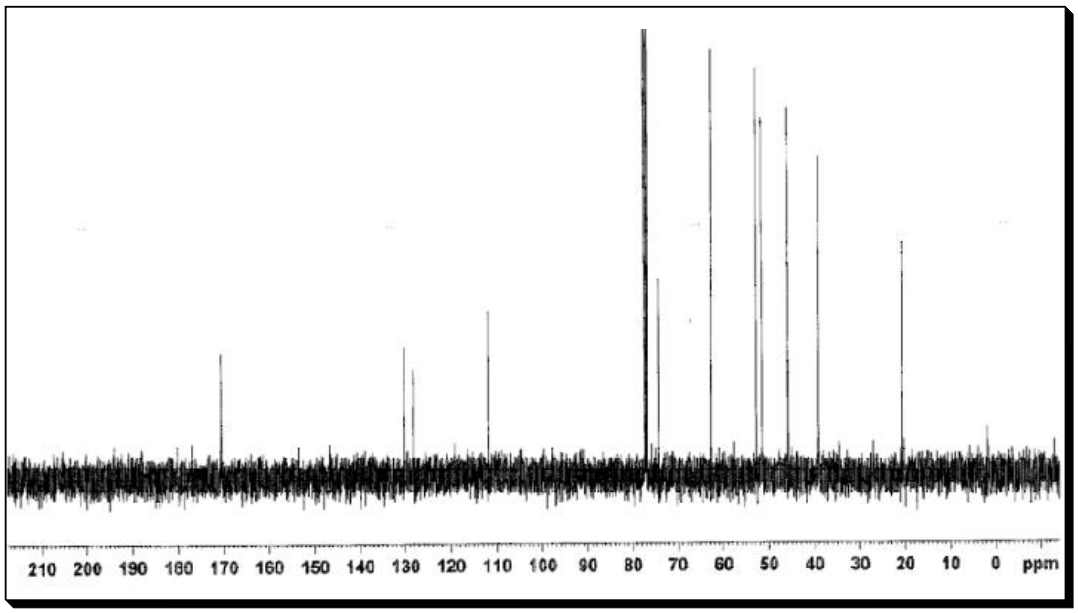
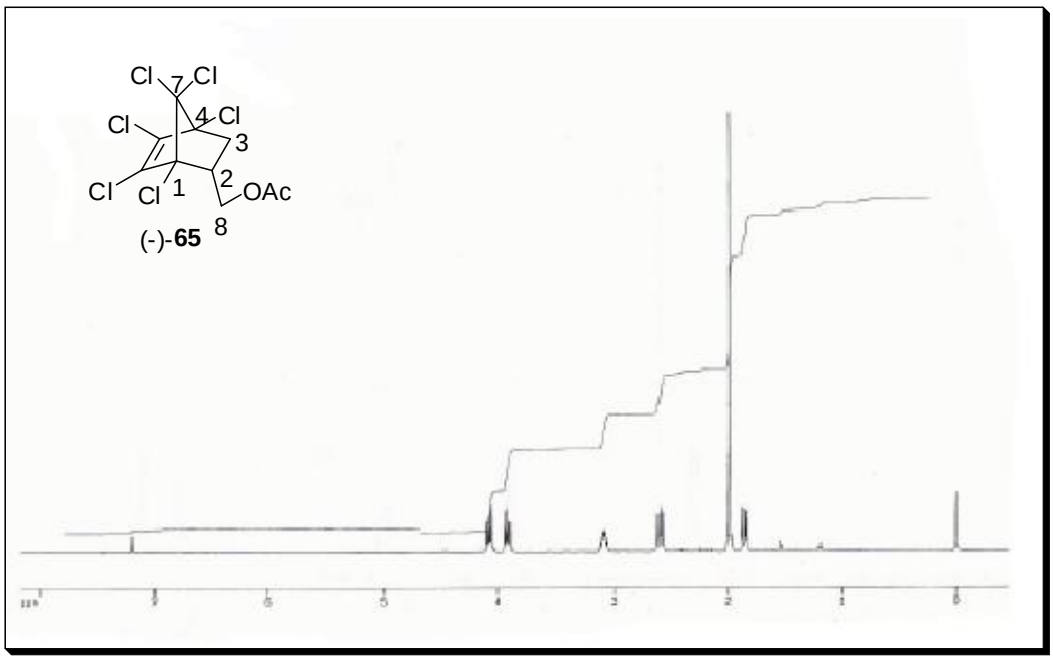


Figure A3. ^{1}H and ^{13}C NMR spectra of compound **64**.



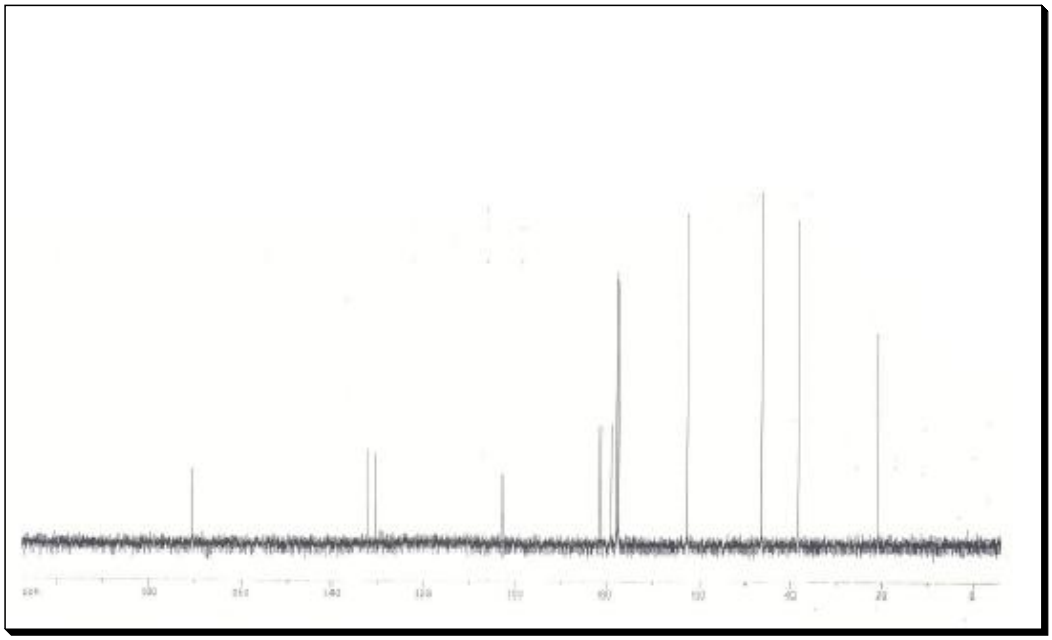
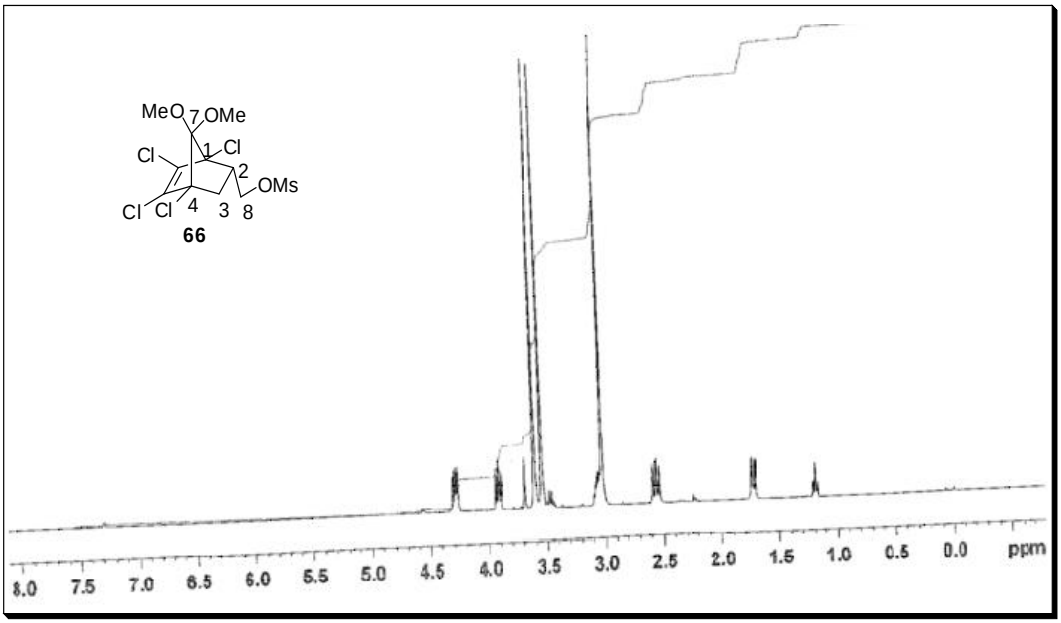


Figure A4. ^{1}H and ^{13}C NMR spectra of compound **65**.



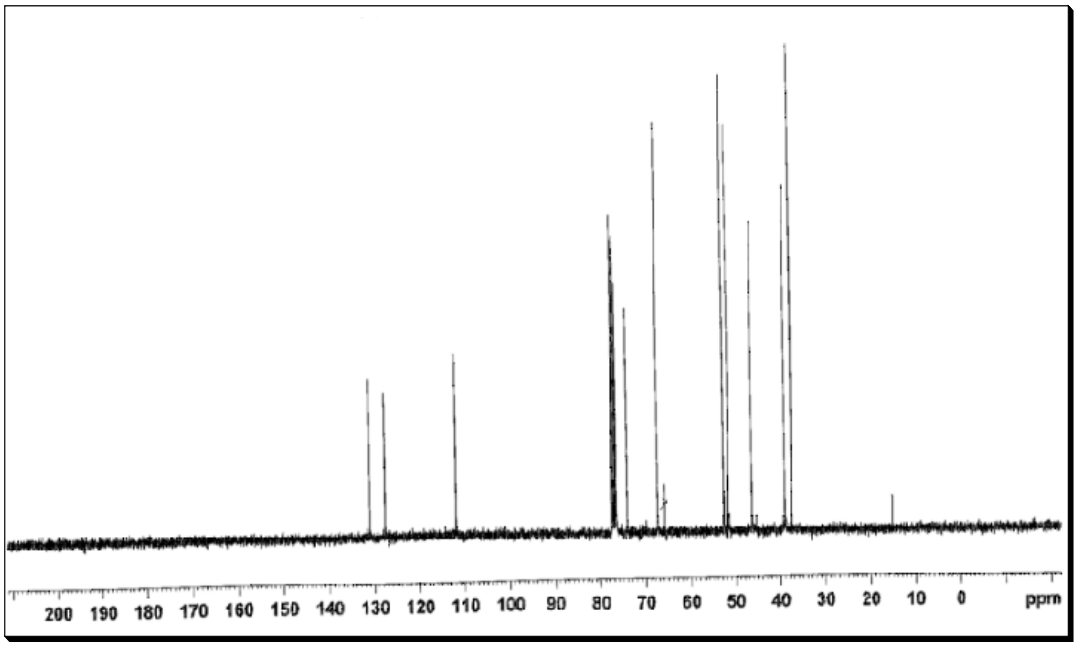
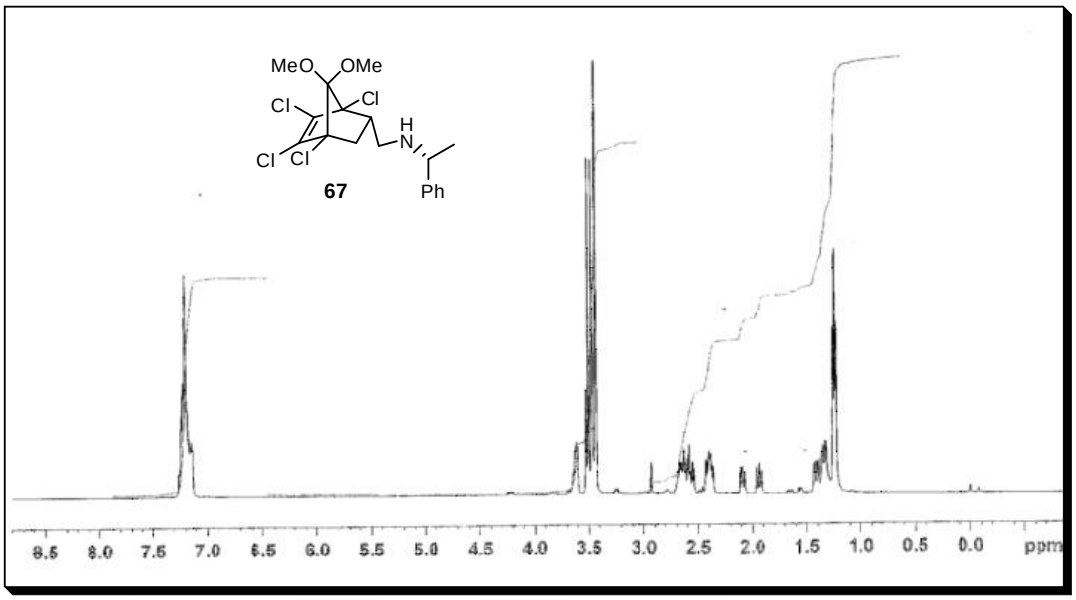


Figure A5. ^{1}H and ^{13}C NMR spectra of compound **66**.



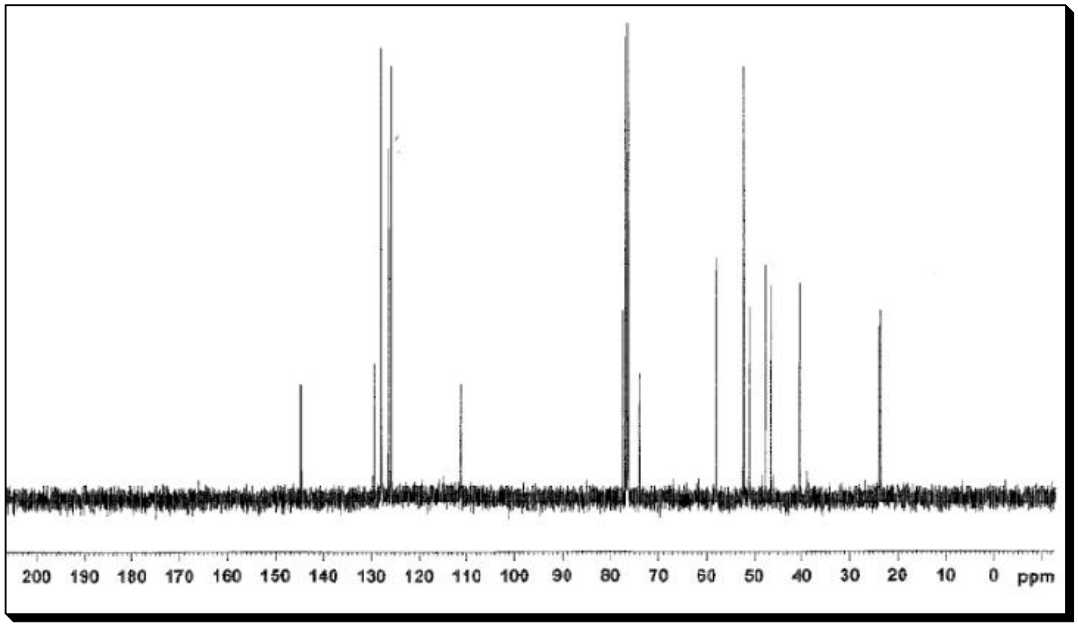


Figure A6. ^{1}H and ^{13}C NMR spectra of compound **67**.

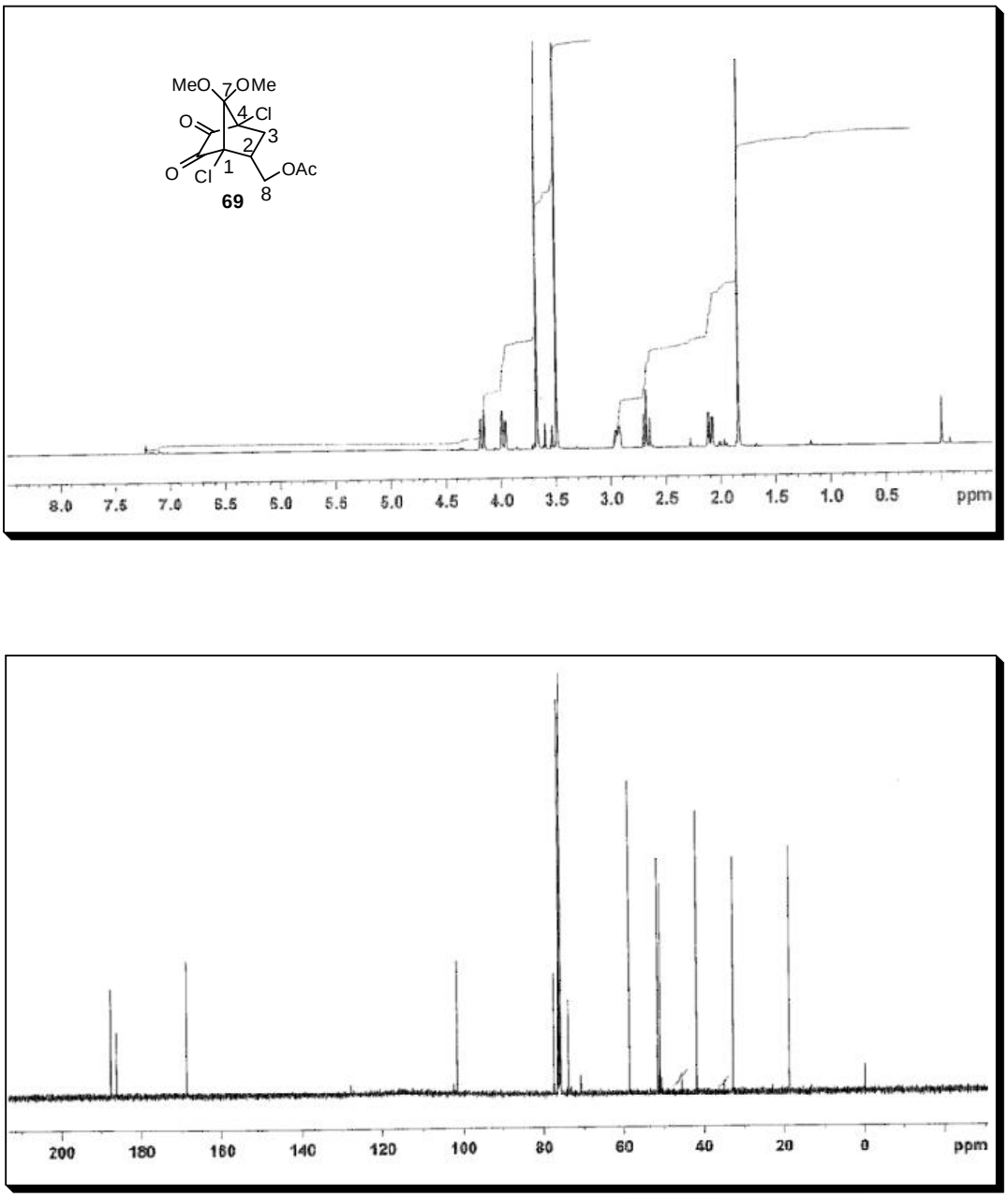
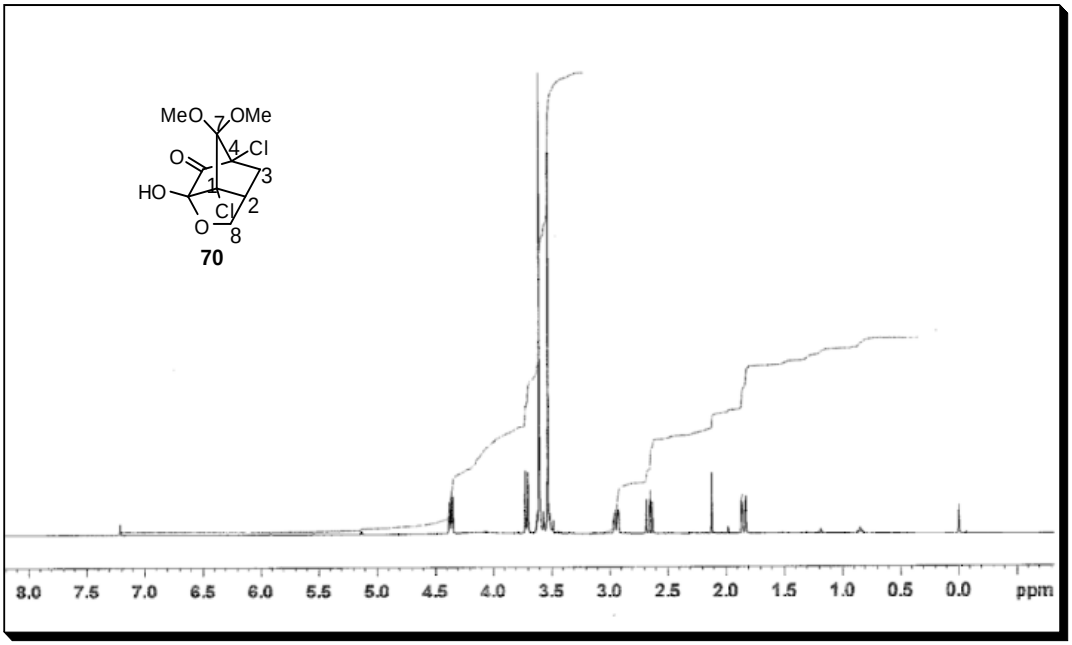


Figure A7. ^{1}H and ^{13}C NMR spectra of compound **69**.



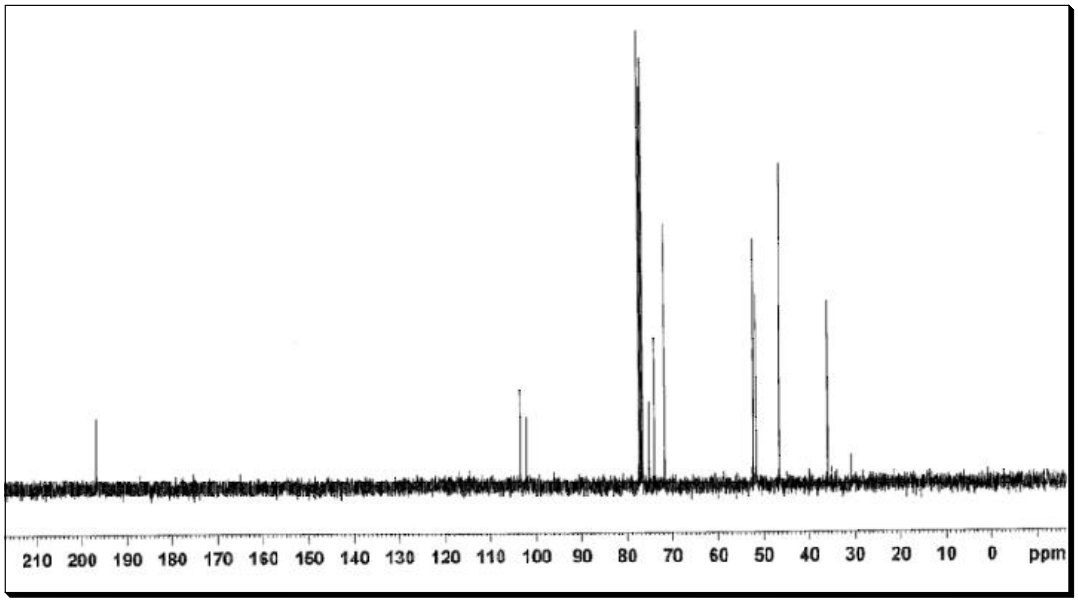
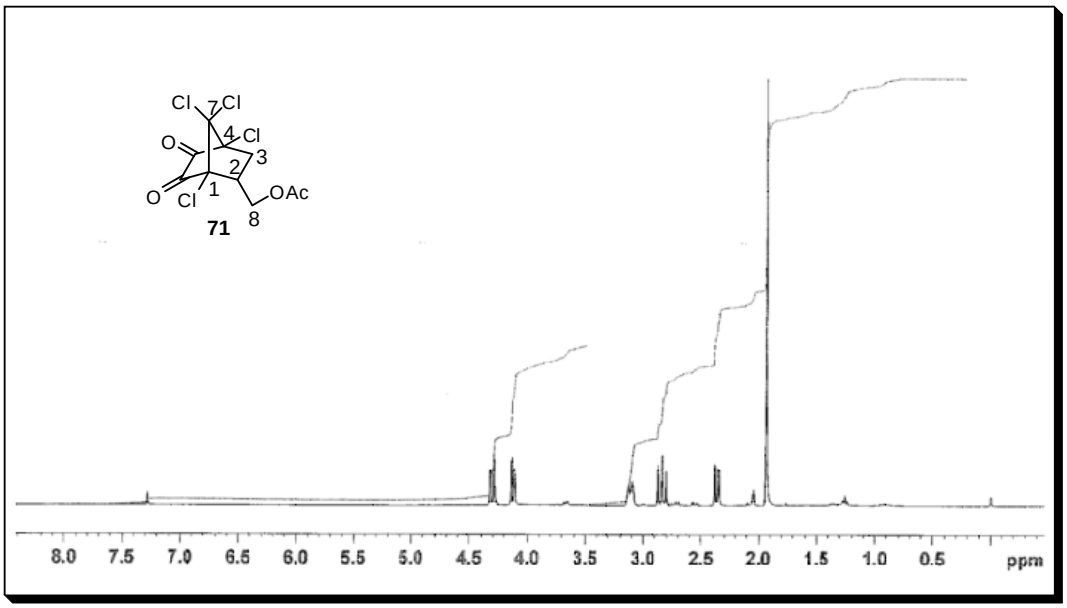


Figure A8. ^{1}H and ^{13}C NMR spectra of compound **70**.



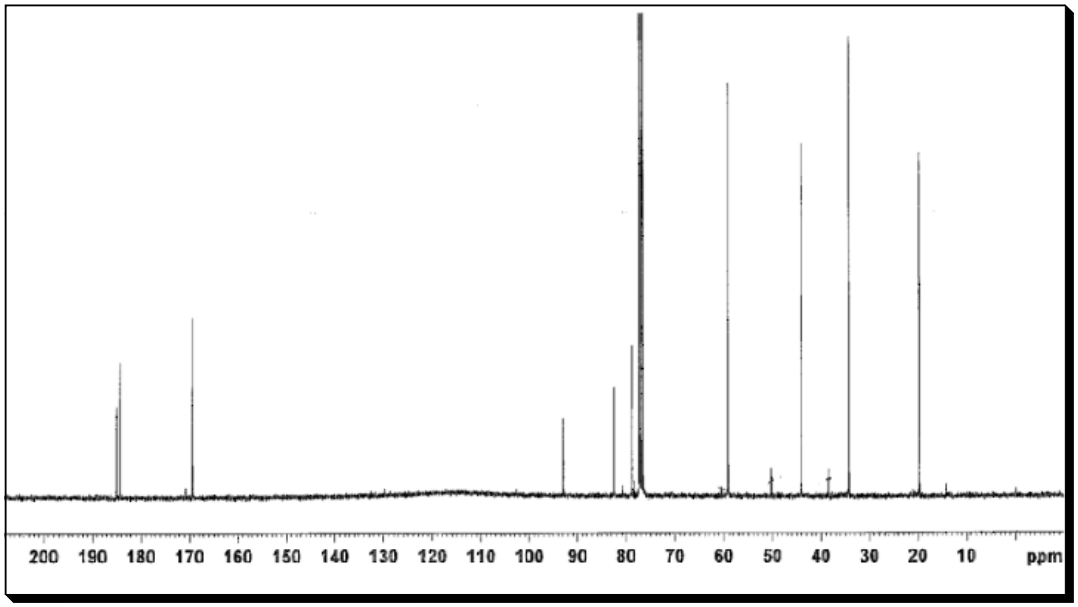
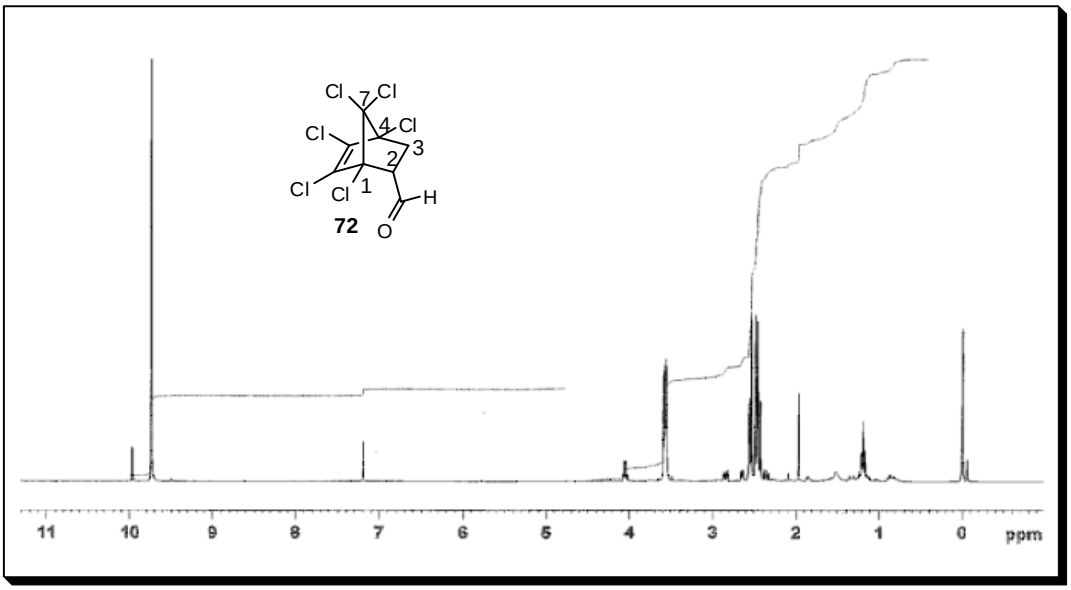


Figure A9. ^{1}H and ^{13}C NMR spectra of compound **71**.



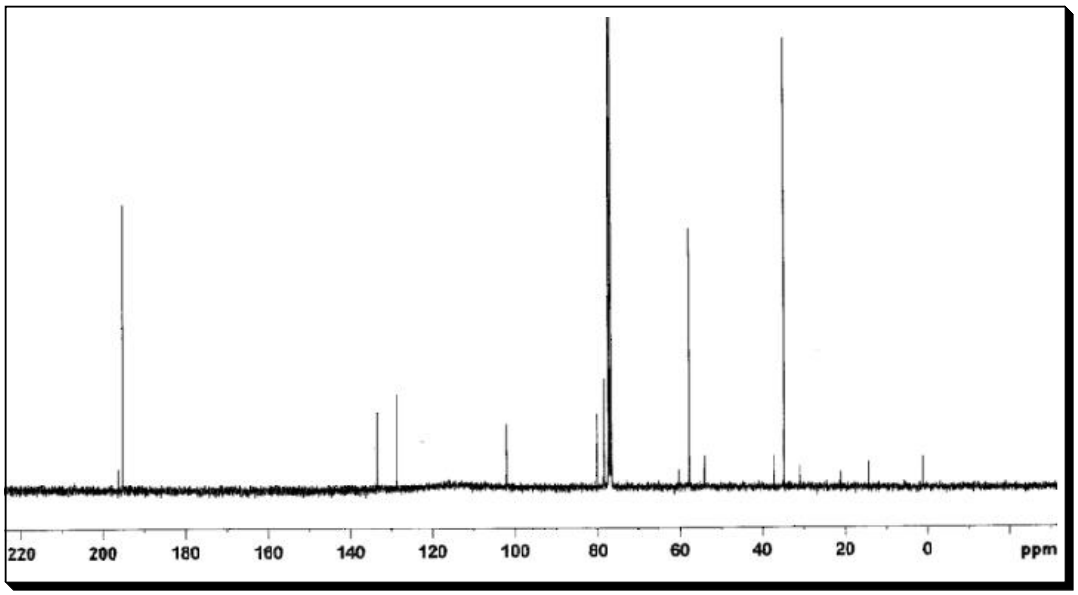
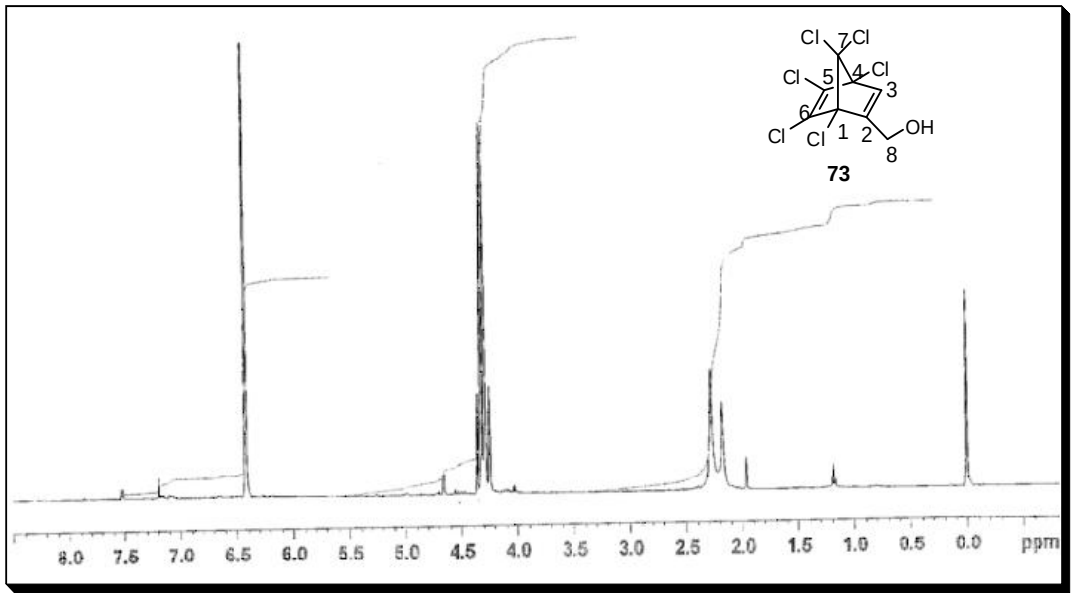


Figure A10. ^{1}H and ^{13}C NMR spectra of compound **72**.



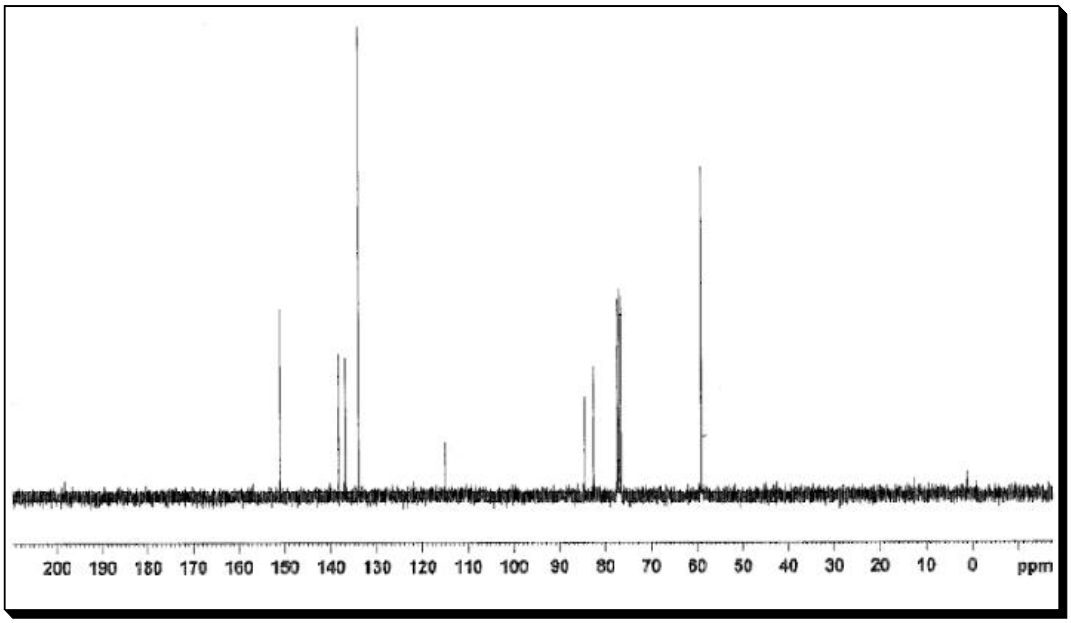
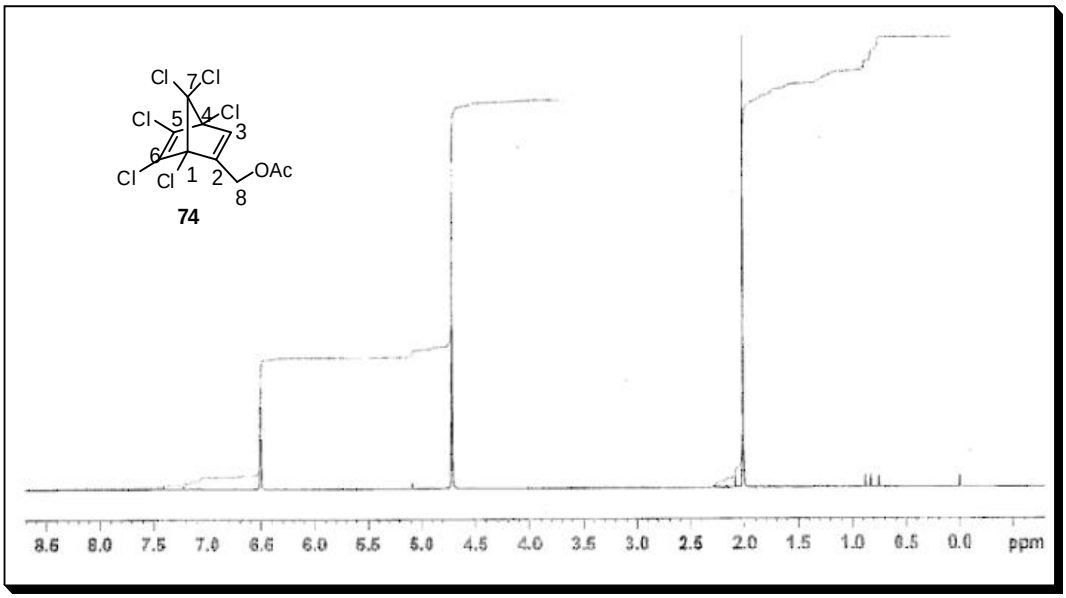


Figure A11. ^{1}H and ^{13}C NMR spectra of compound **73**.



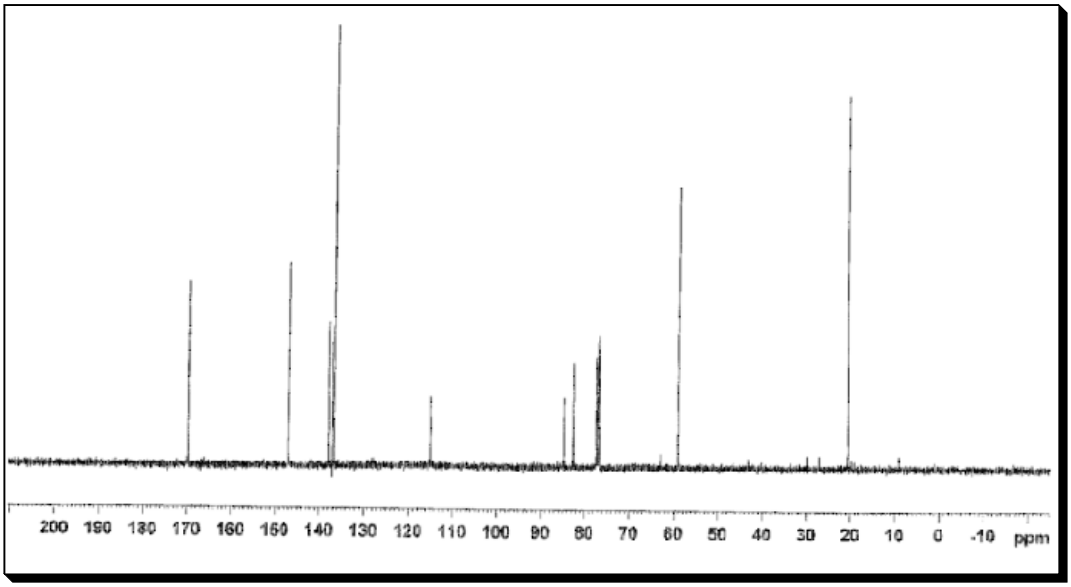
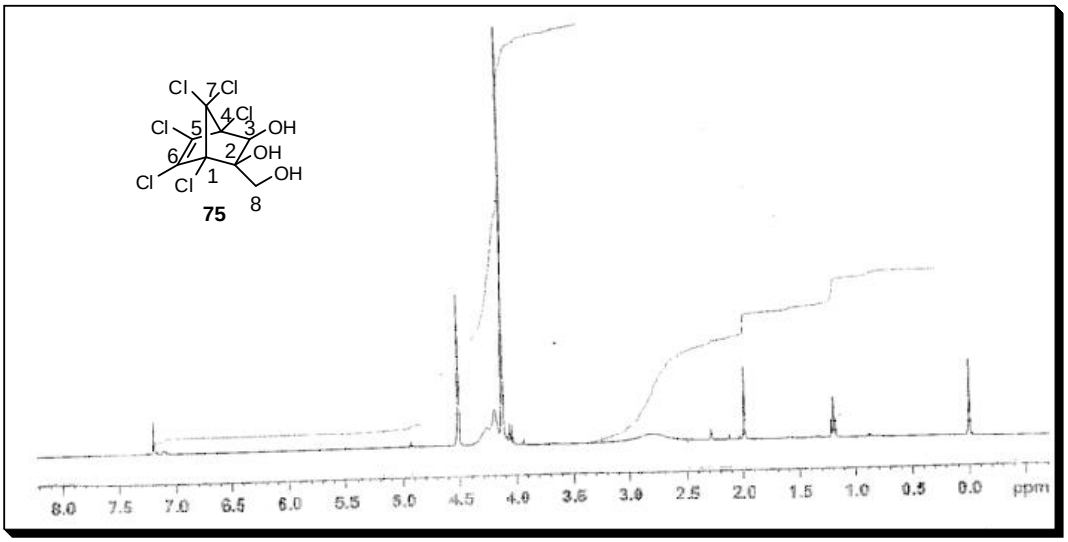


Figure A12. ^{1}H and ^{13}C NMR spectra of compound **74**.



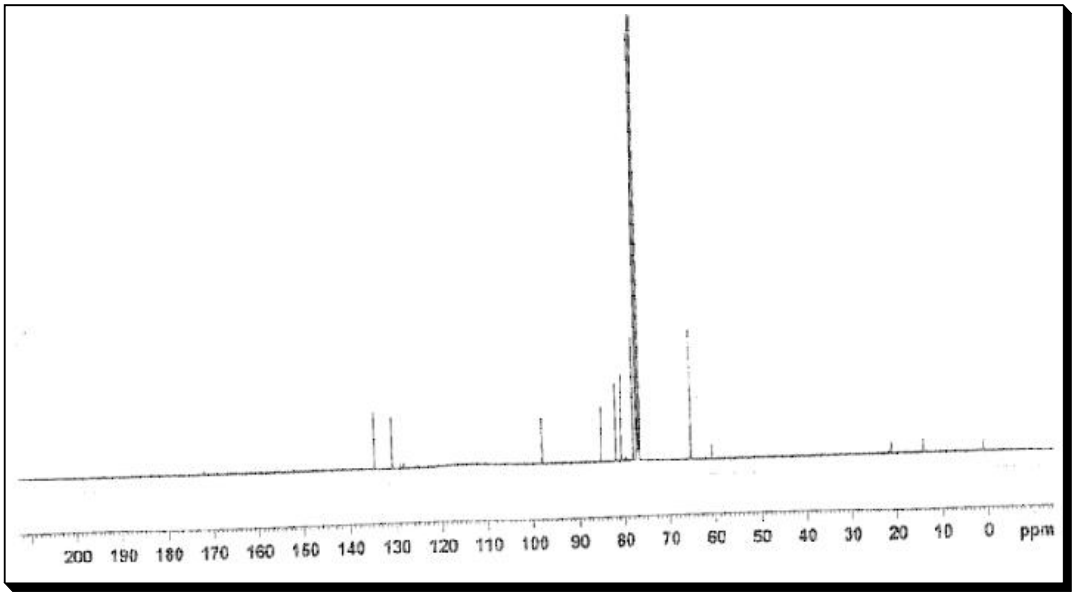
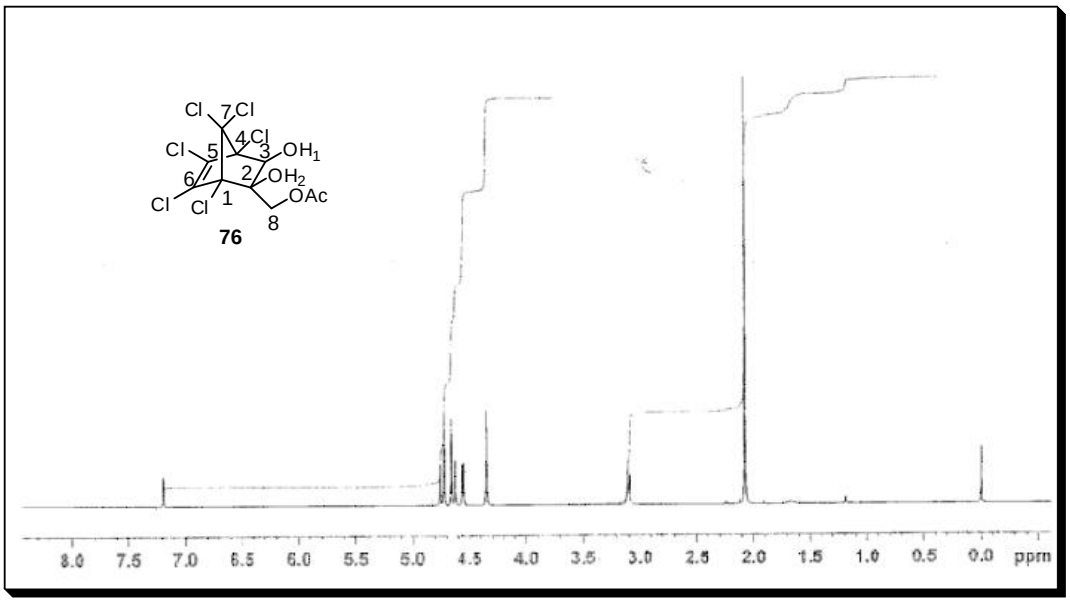


Figure A13. ^{1}H and ^{13}C NMR spectra of compound **75**.



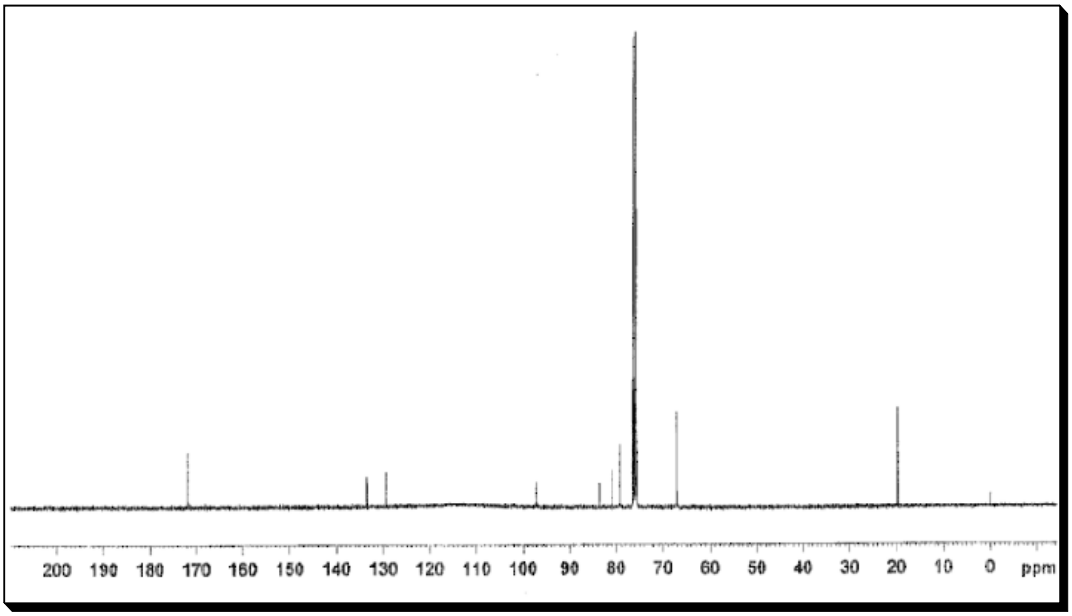
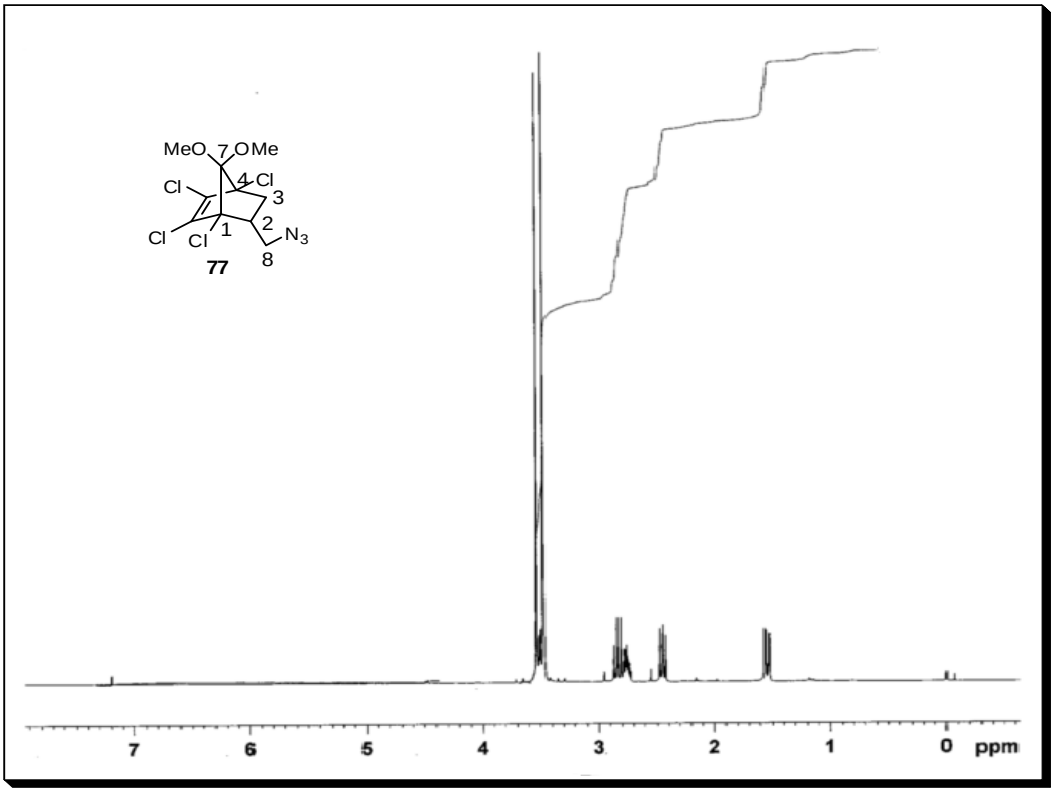


Figure A14. ^{1}H and ^{13}C NMR spectra of compound **76**.



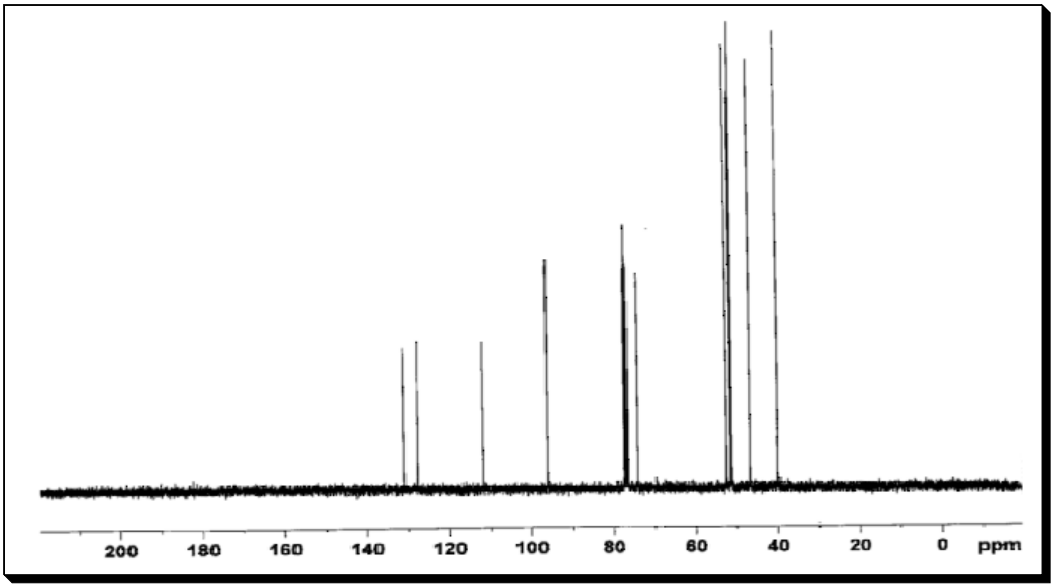
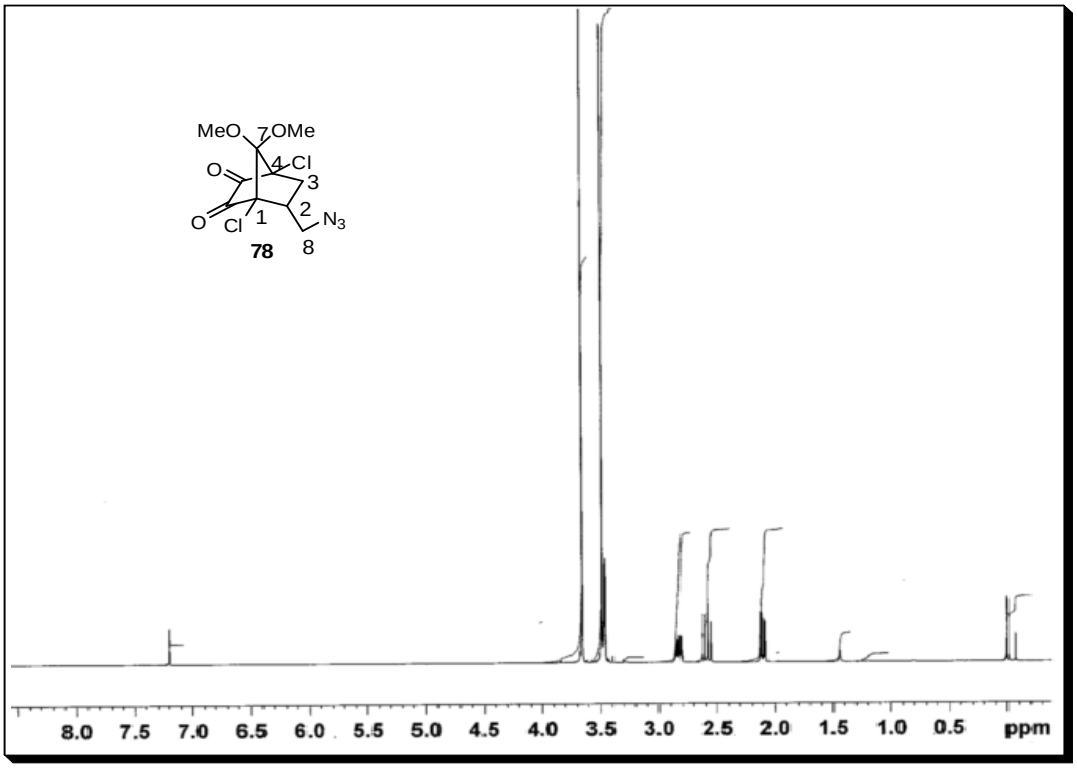


Figure A15. ^{1}H and ^{13}C NMR spectra of compound **77**.



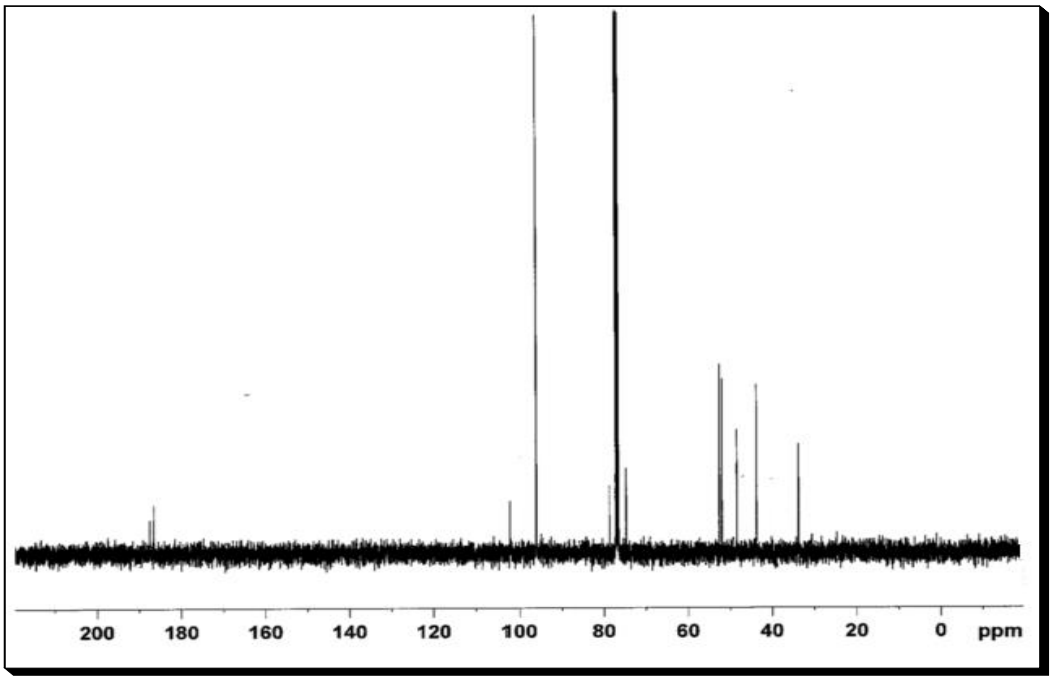
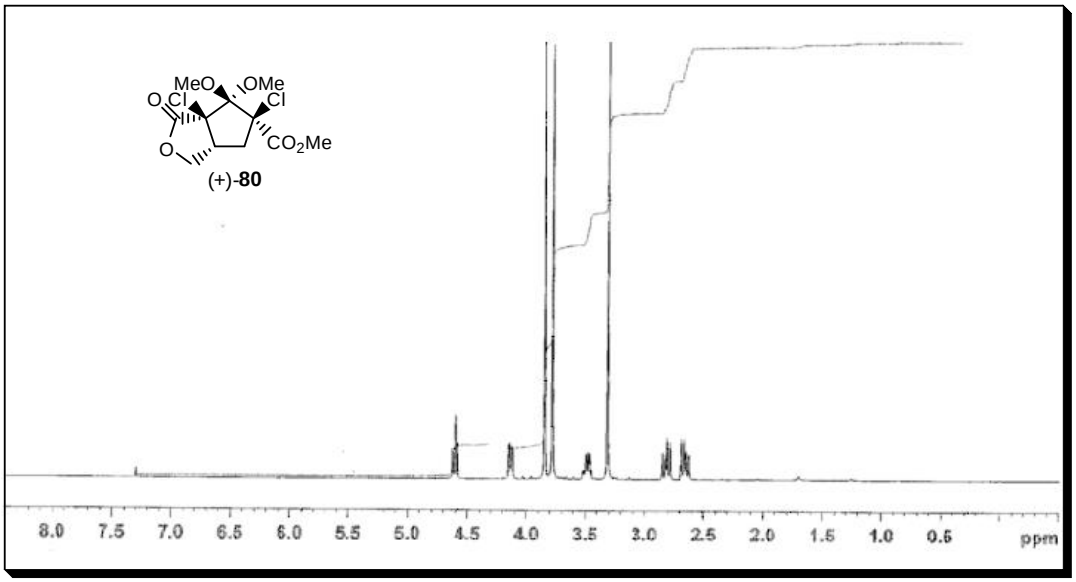


Figure A16. ^{1}H and ^{13}C NMR spectra of compound **78**.



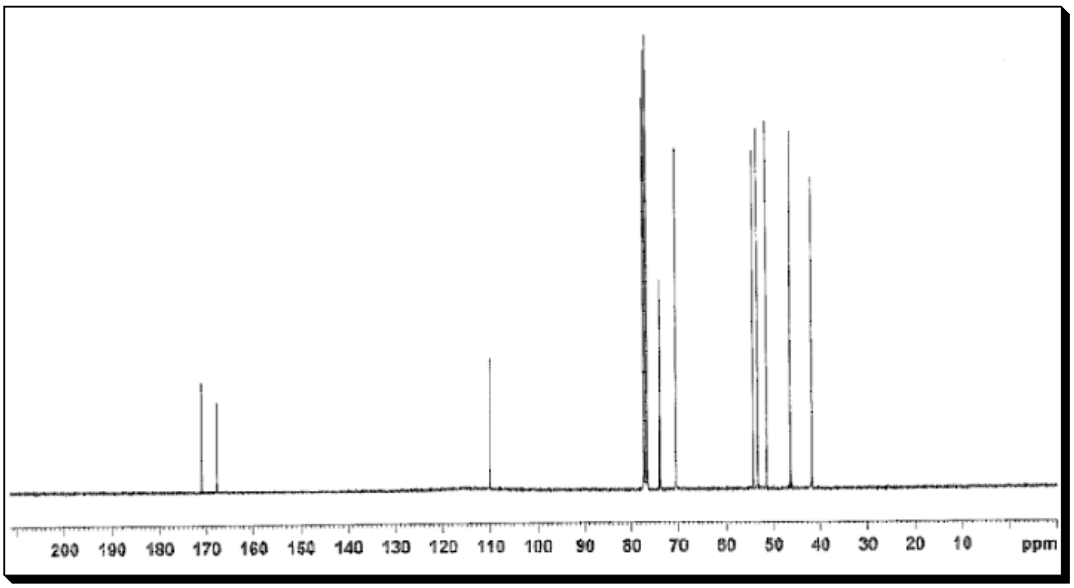


Figure A17. ^{1}H and ^{13}C NMR spectra of compound (+)-**80**.

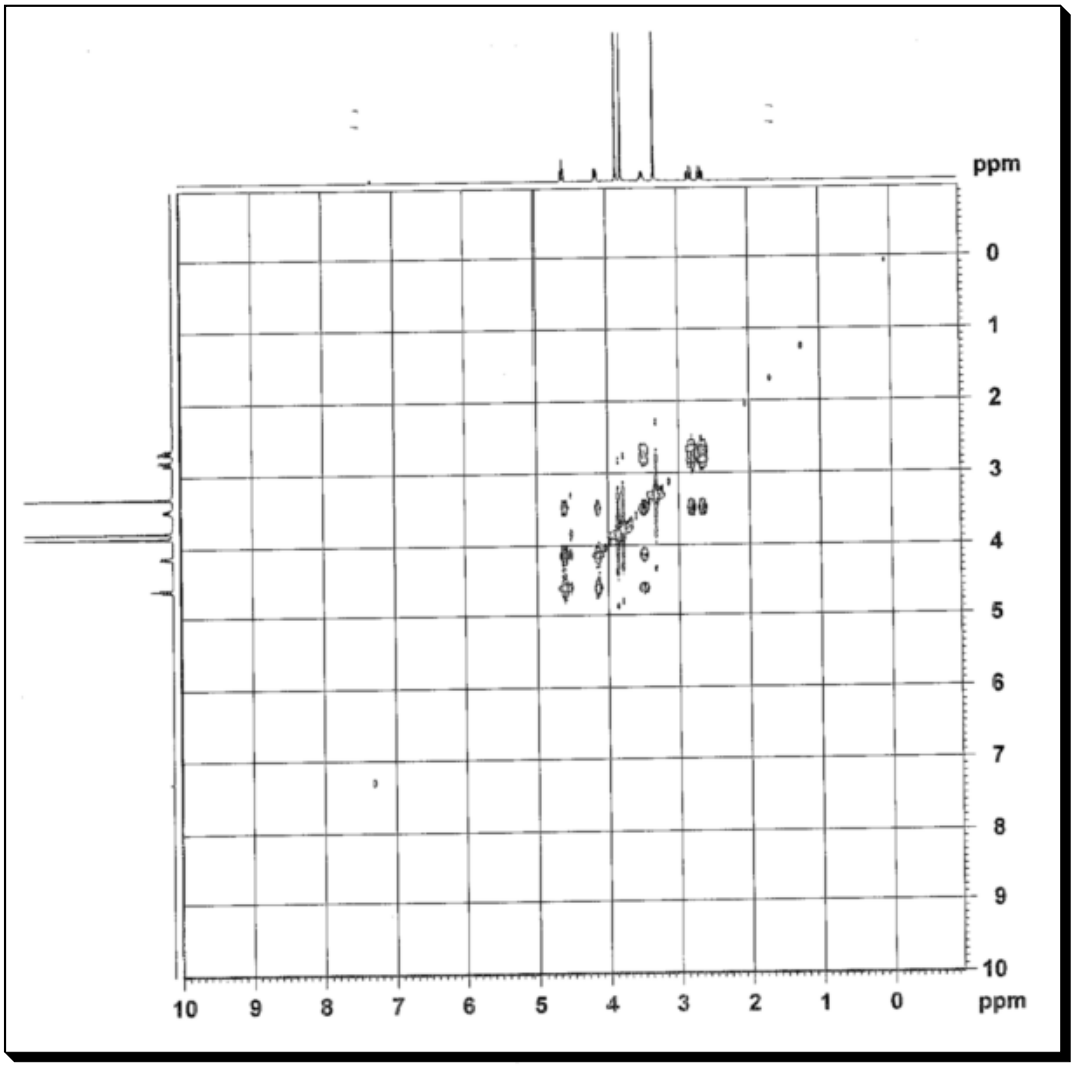


Figure A18. COSY spectra of compound (+)-**80**.

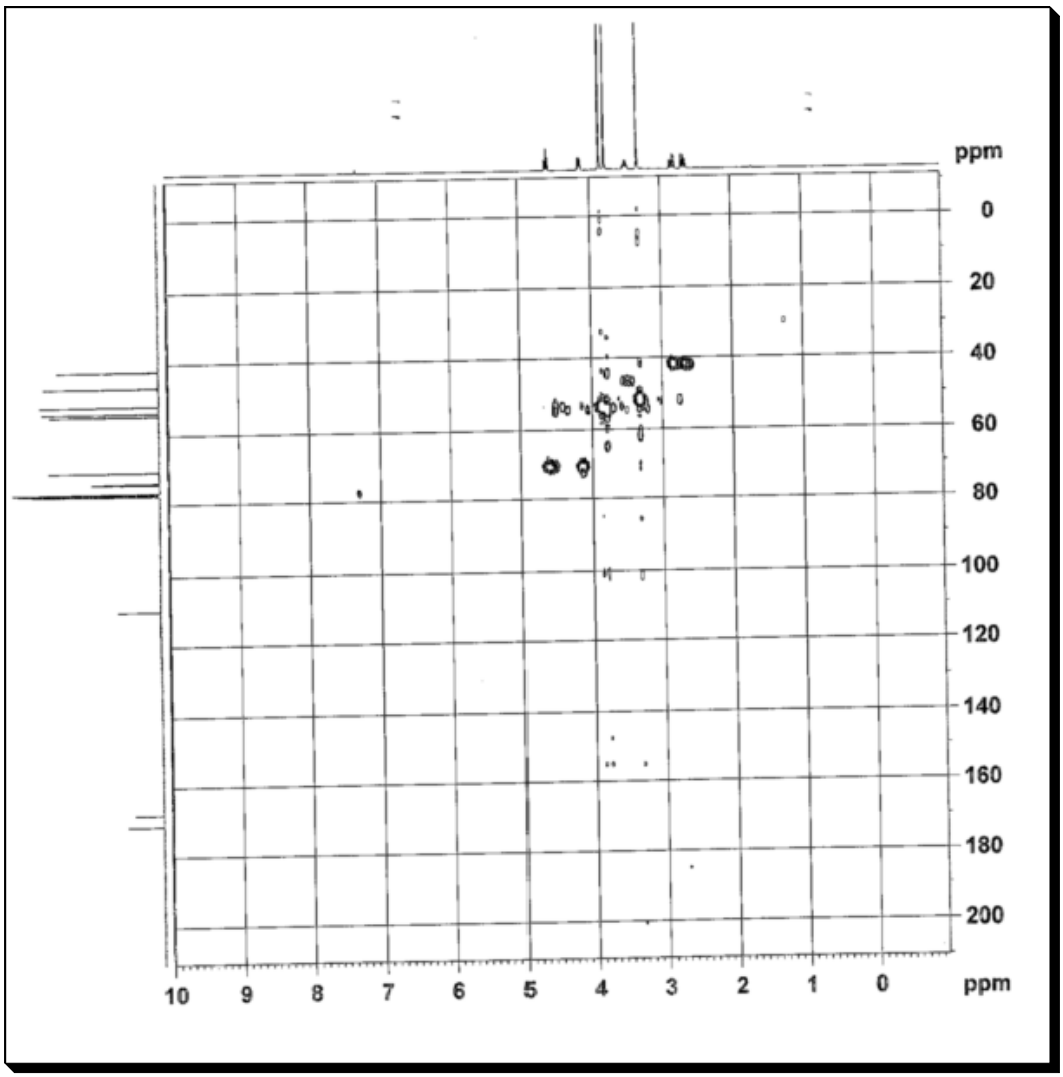


Figure A19. HMQC spectra of compound (+)-**80**.

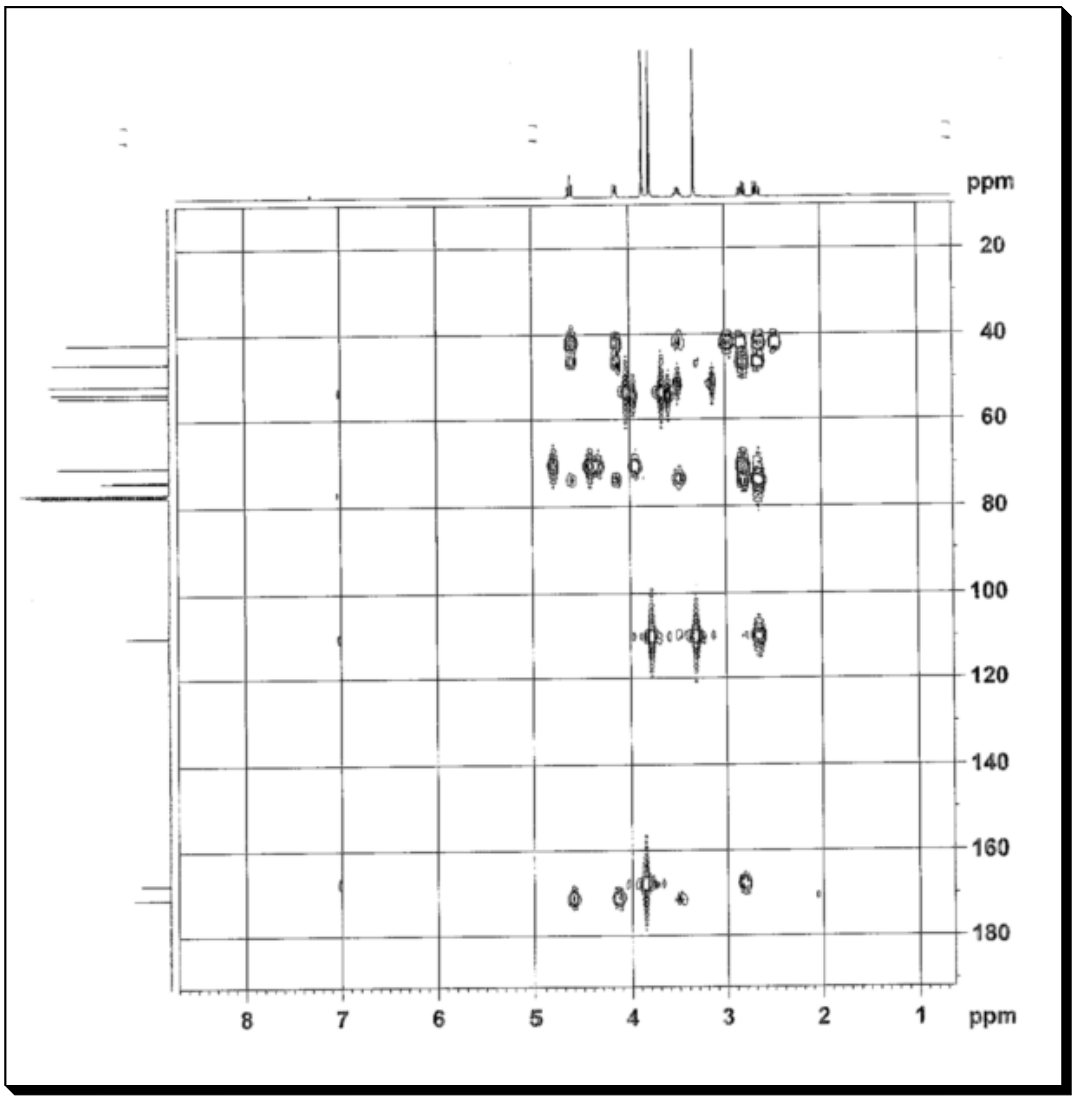
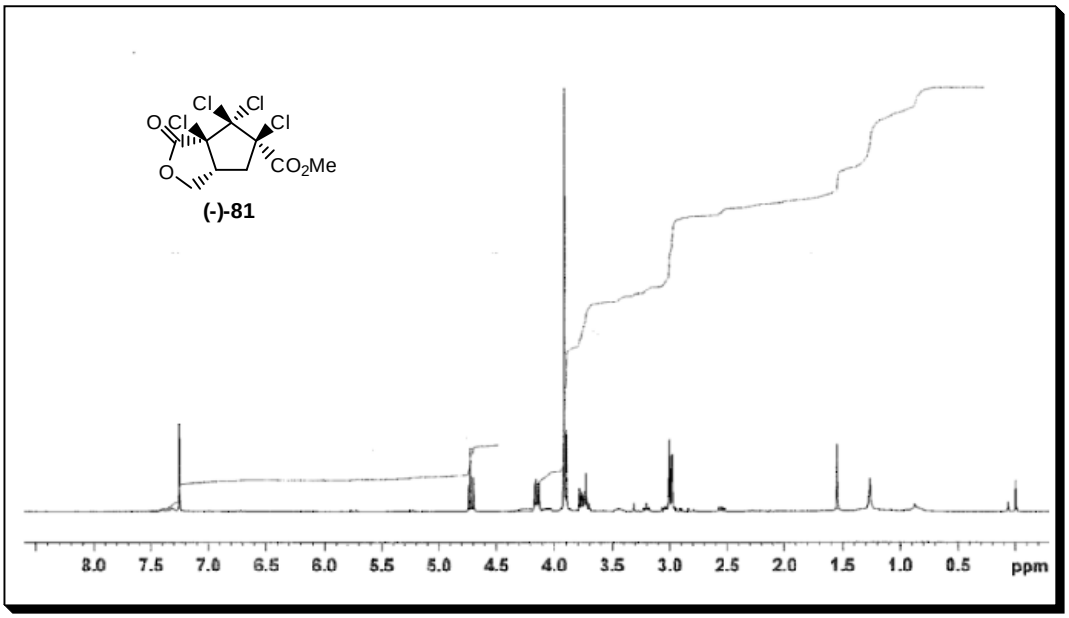


Figure A20. HMBC spectra of compound (+)-**80**.



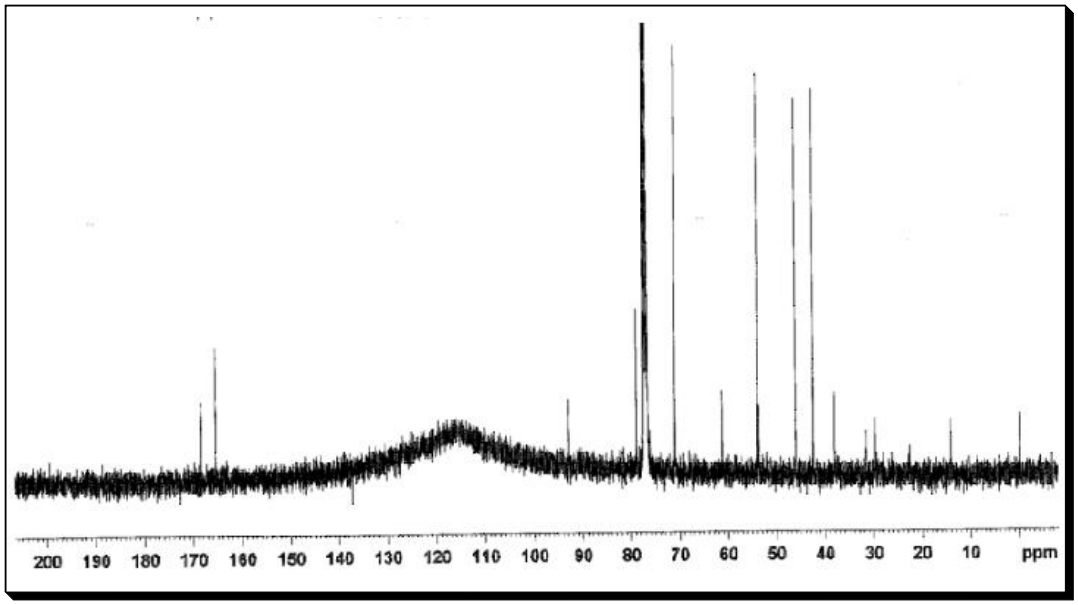
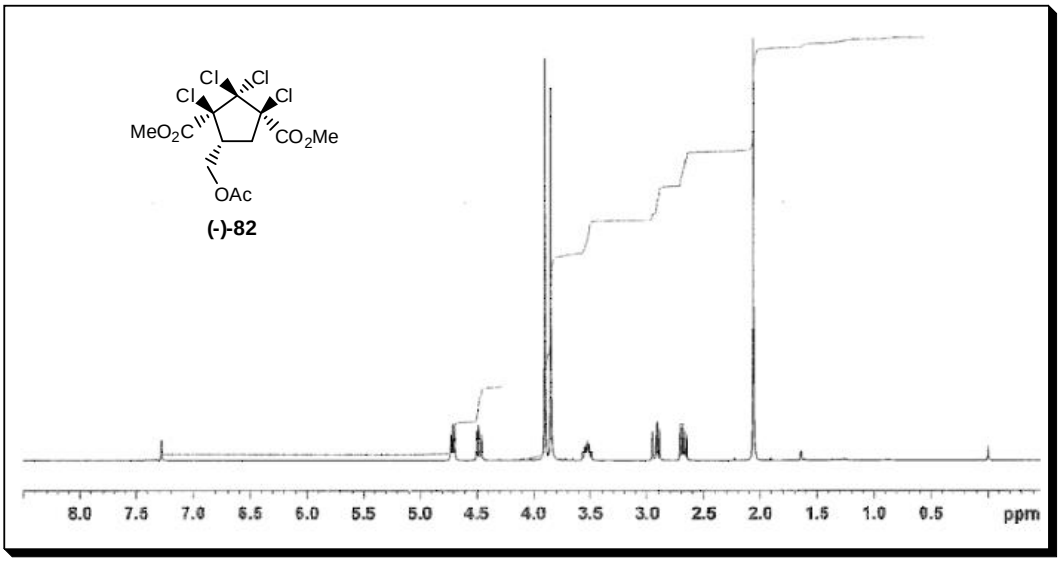


Figure A21. ^{1}H and ^{13}C NMR spectra of compound (-)-**81**.



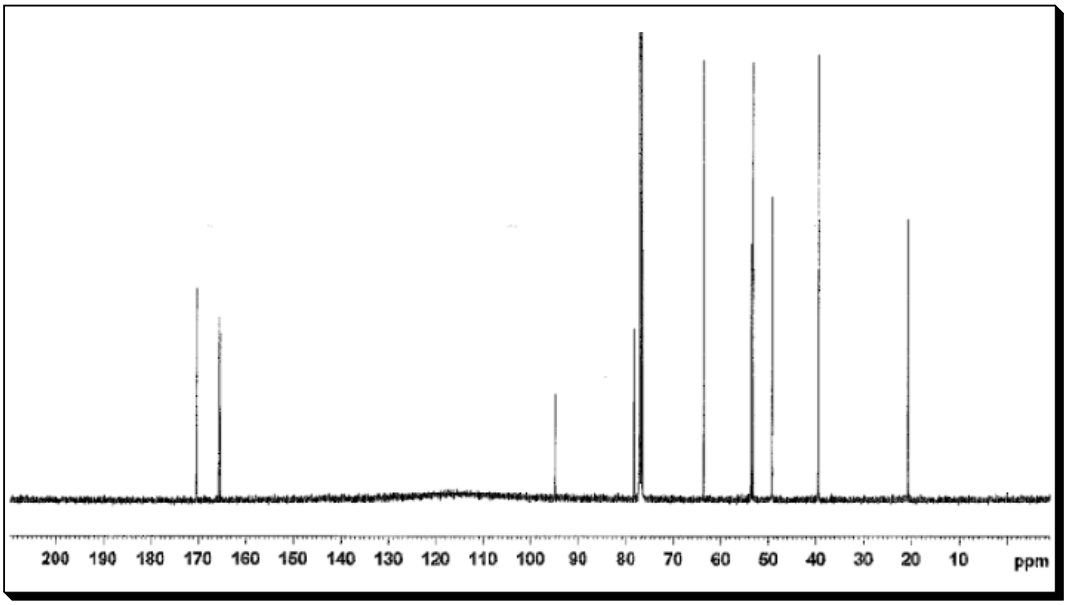


Figure A22. ^{1}H and ^{13}C NMR spectra of compound (-)-**82**.

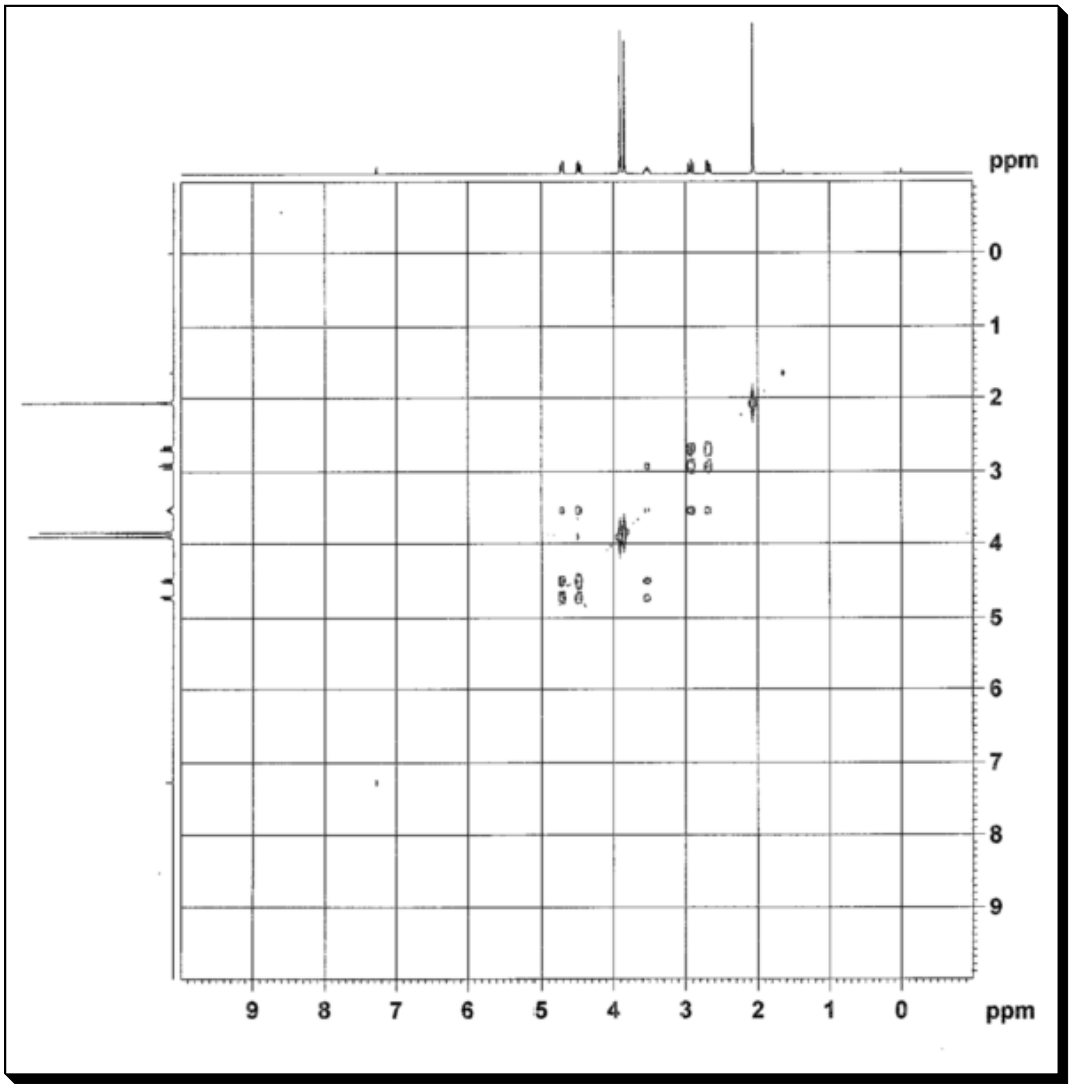


Figure A23. COSY spectra of compound (-)-**82**.

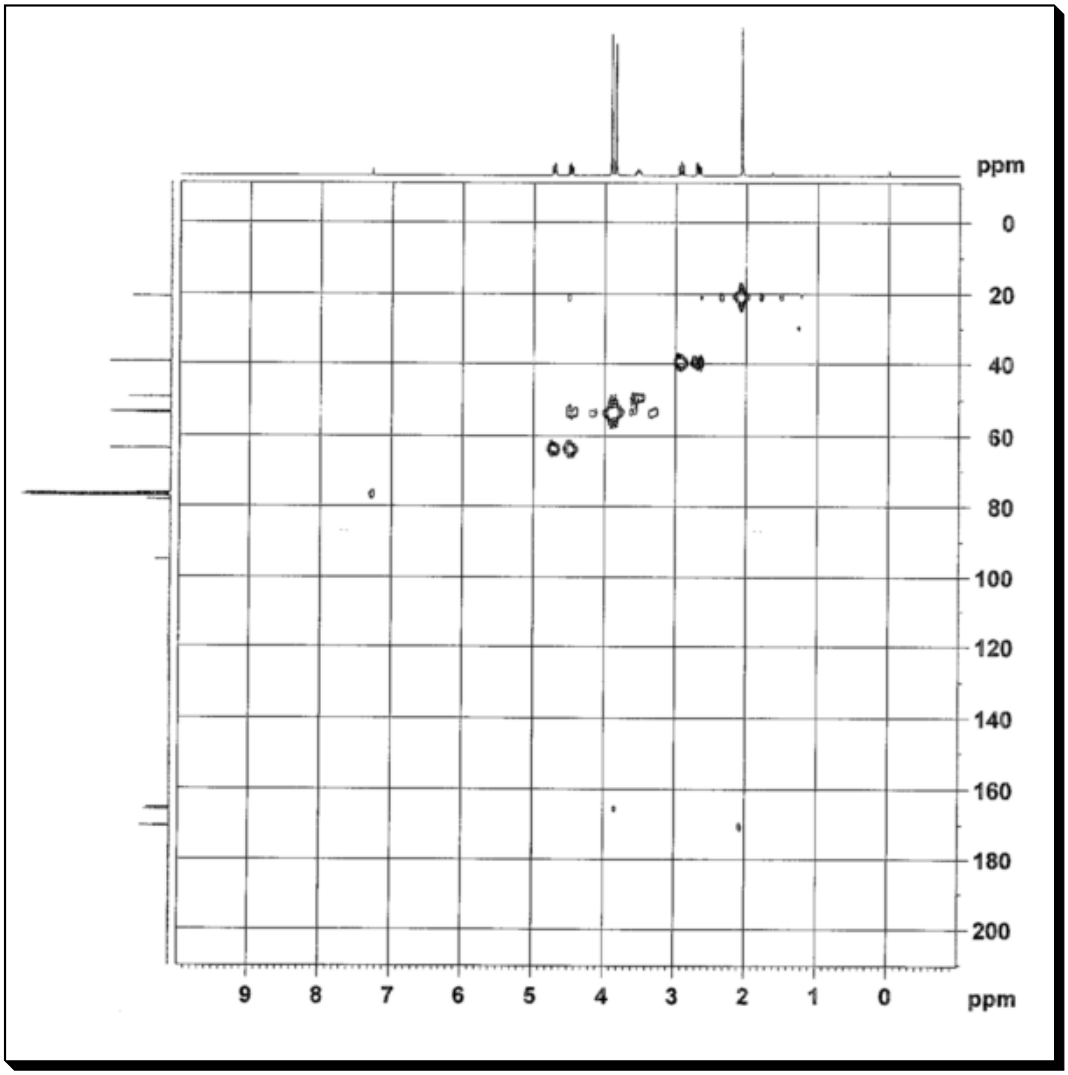


Figure A24. HMQC spectra of compound (-)-**82**.

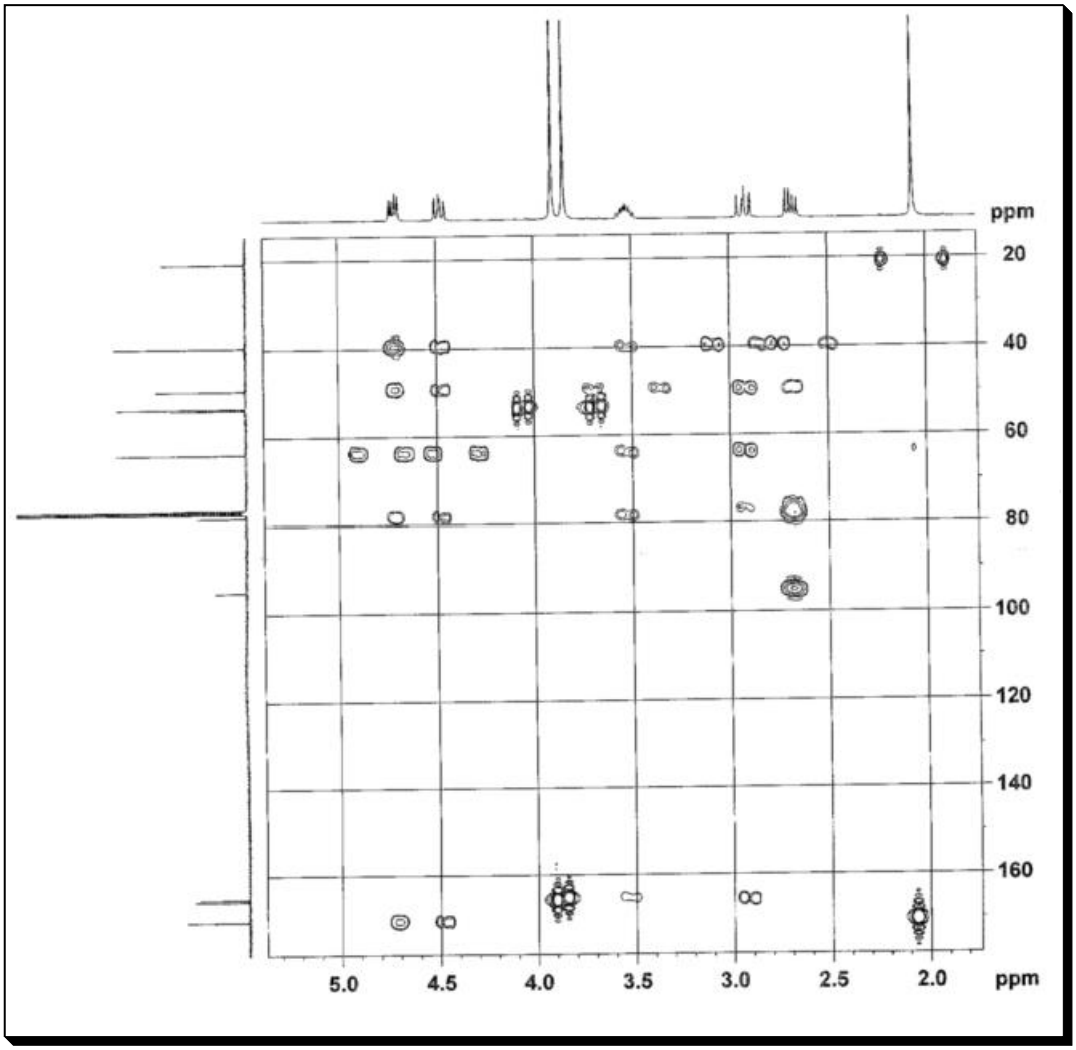
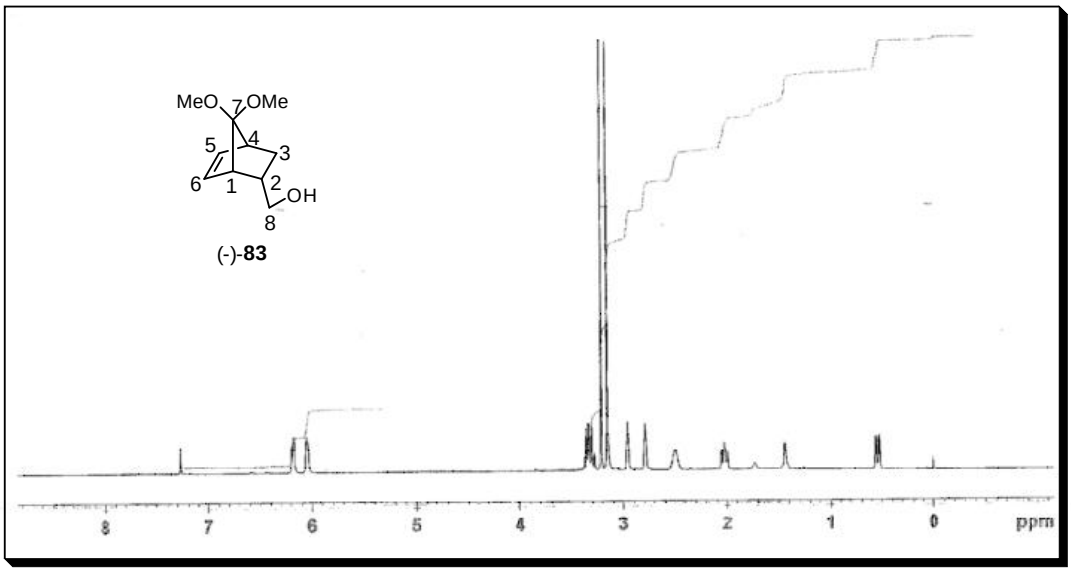


Figure A25. HMBC spectra of compound (-)-**82**.



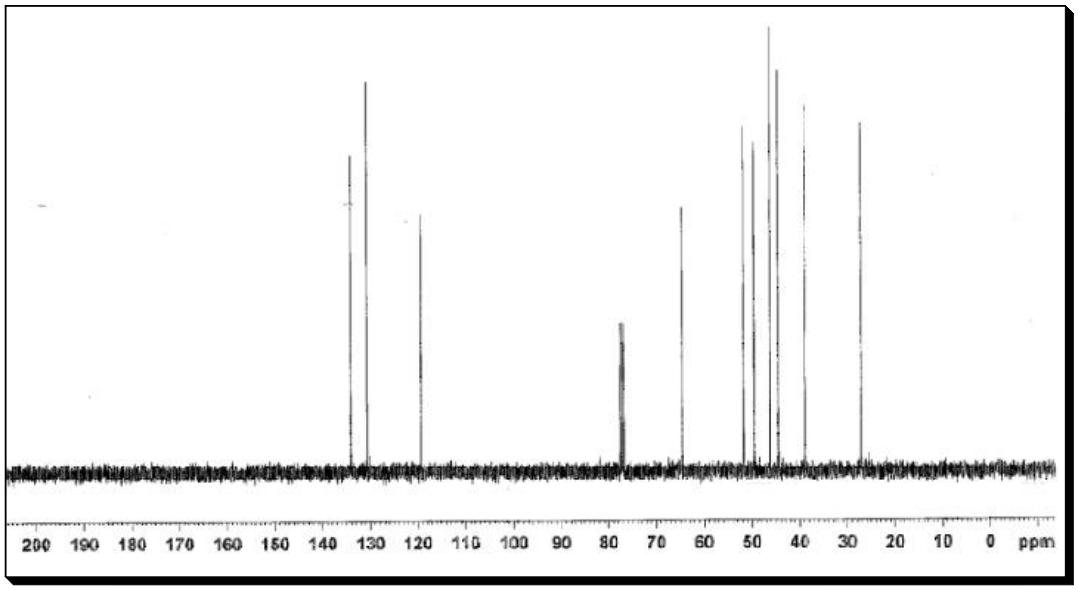
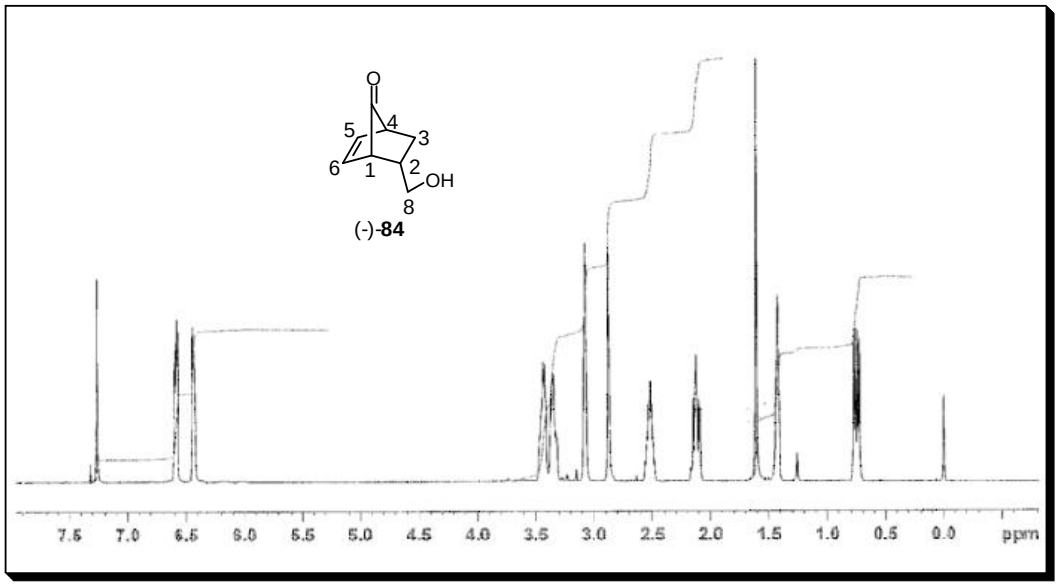


Figure A26. ^{1}H and ^{13}C NMR spectra of compound (-)-**83**.



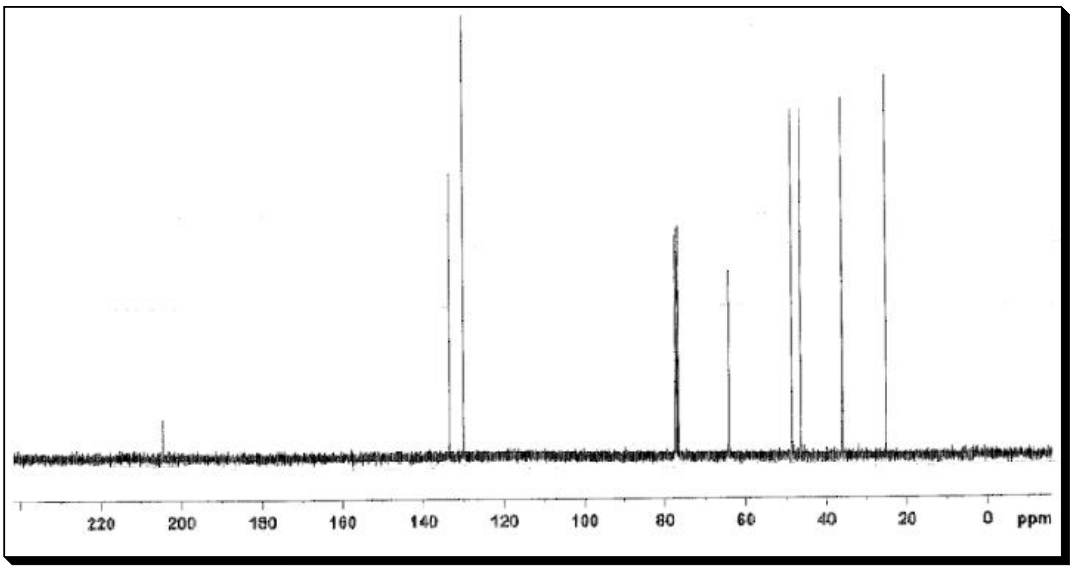
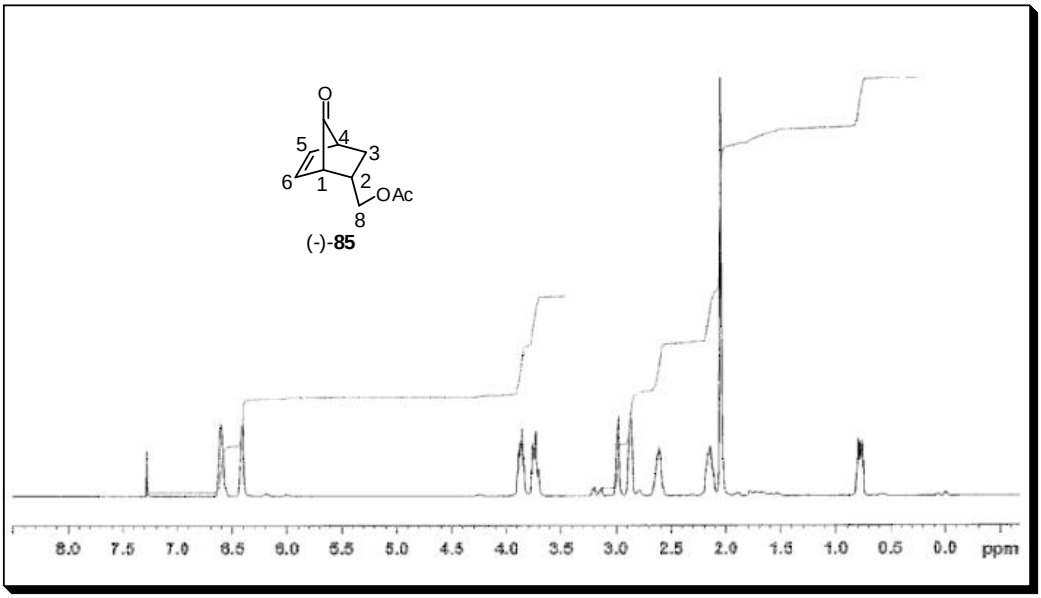


Figure A27. ^{1}H and ^{13}C NMR spectra of compound (-)-**84**.



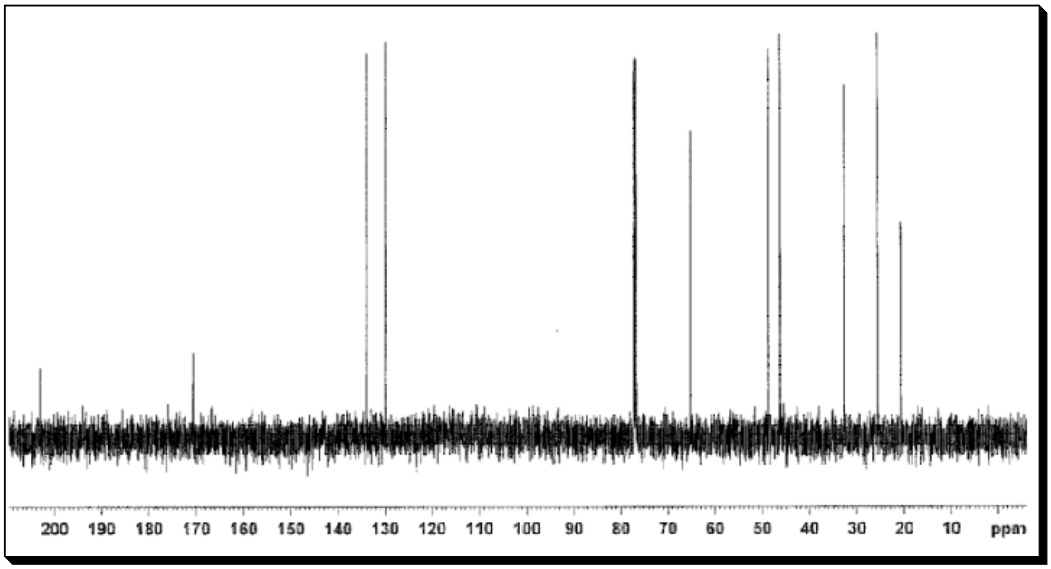
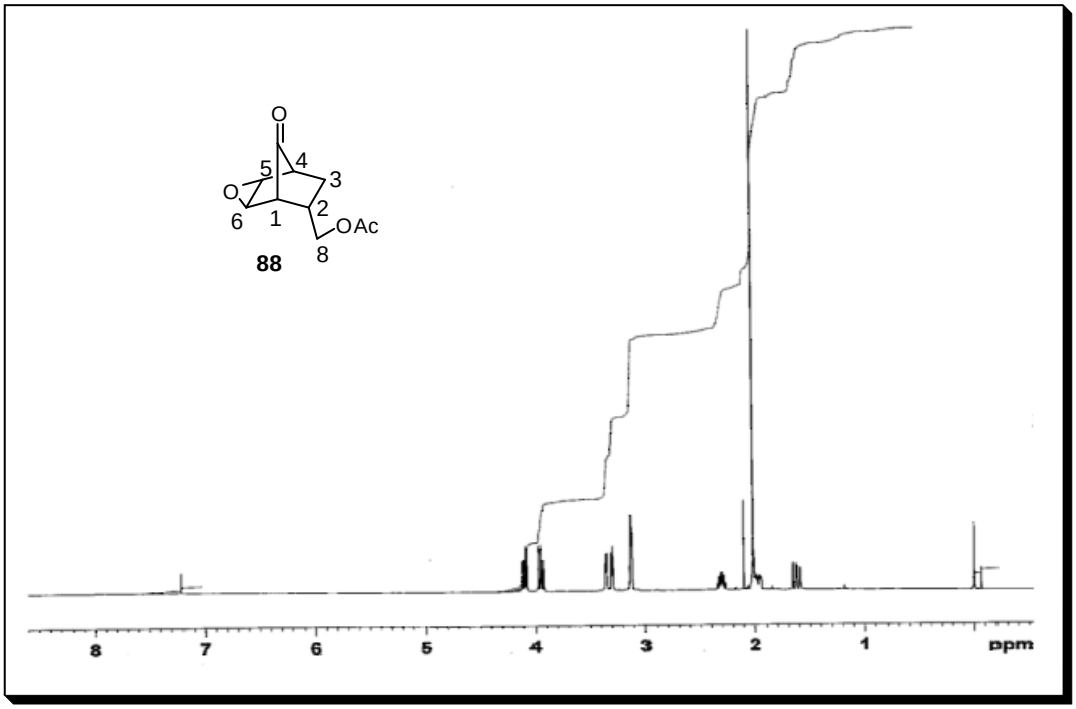


Figure A28. ^{1}H and ^{13}C NMR spectra of compound (-)-**85**.



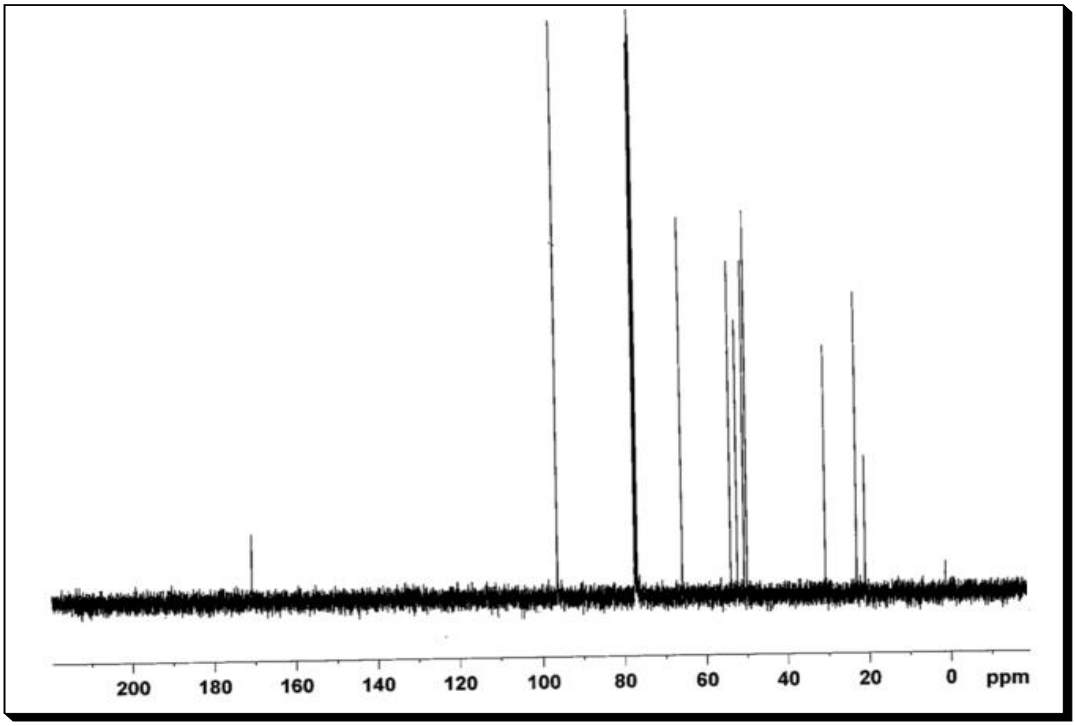
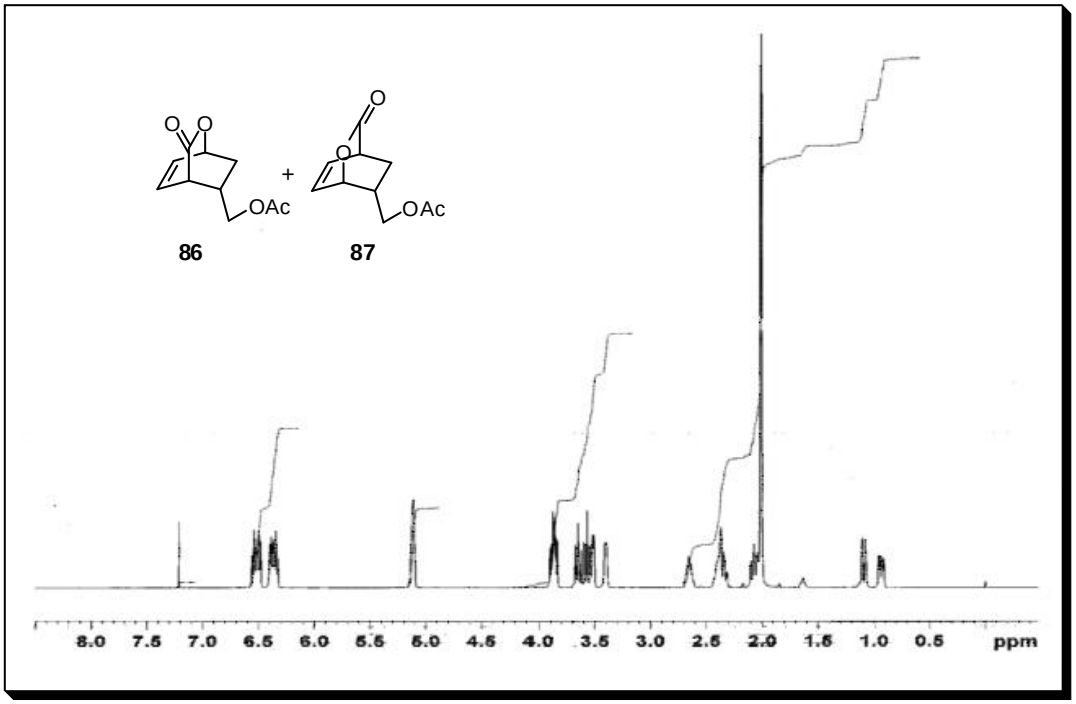


Figure A29. ^{1}H and ^{13}C NMR spectra of compound (-)-**85**.



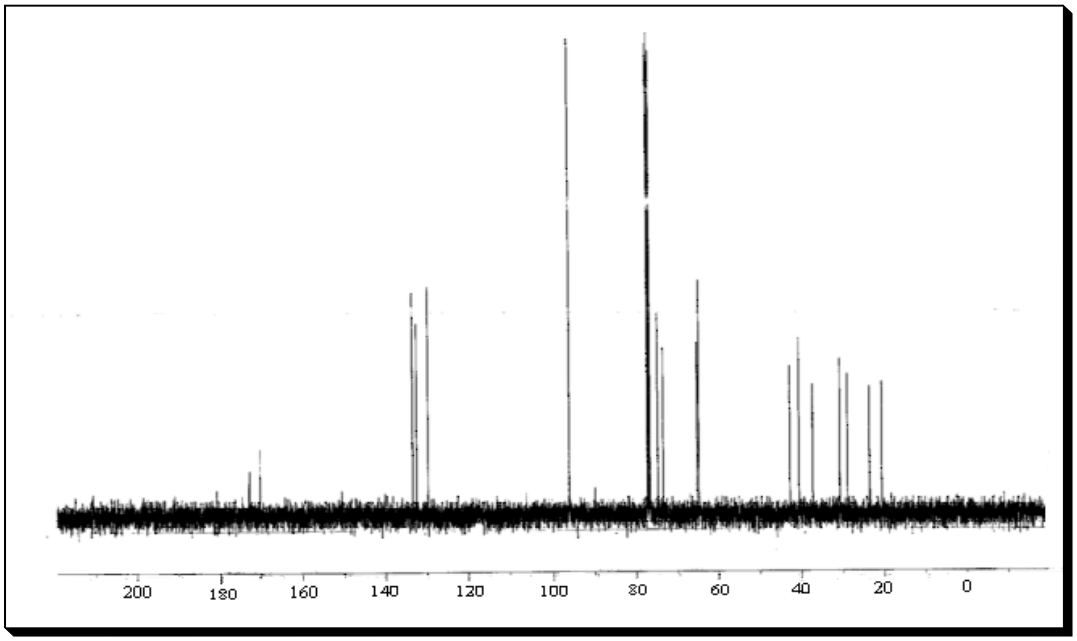
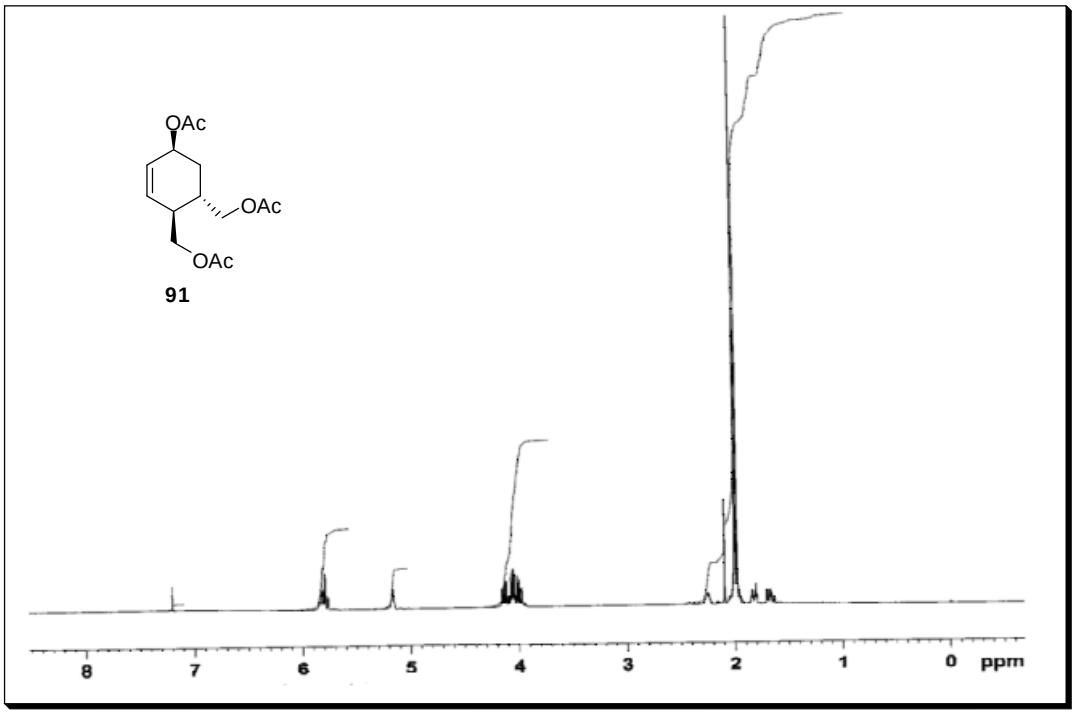


Figure A30. ^{1}H and ^{13}C NMR spectra of mixture **86** and **87**.



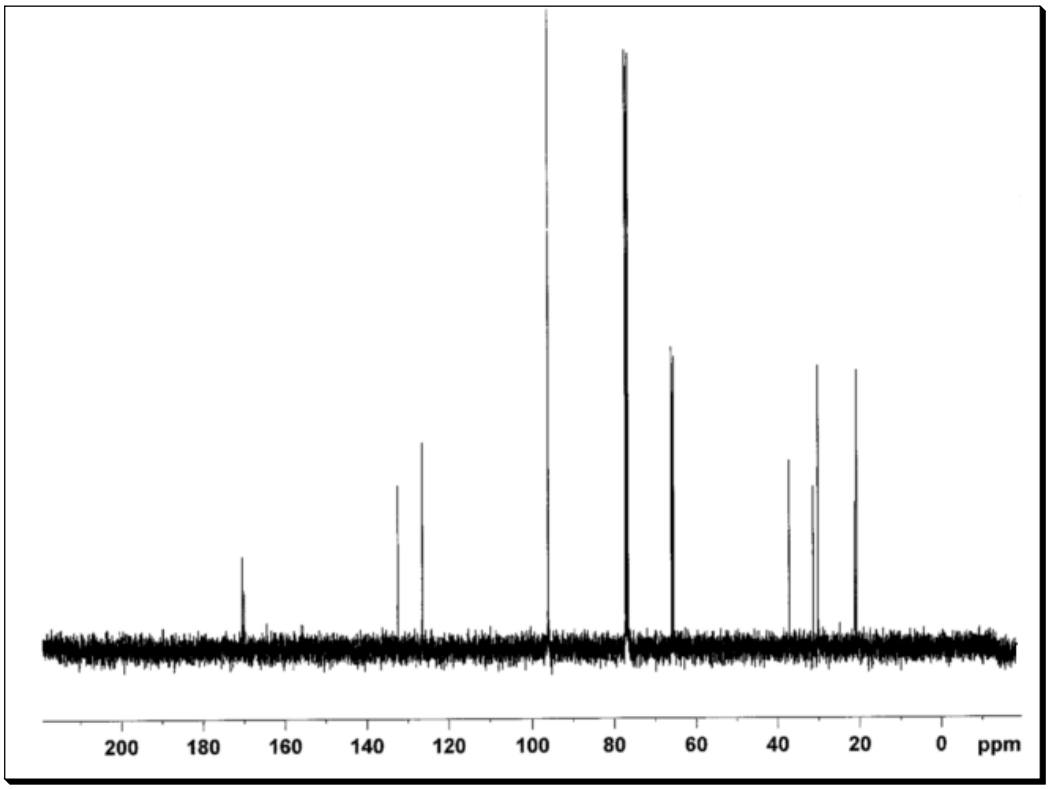
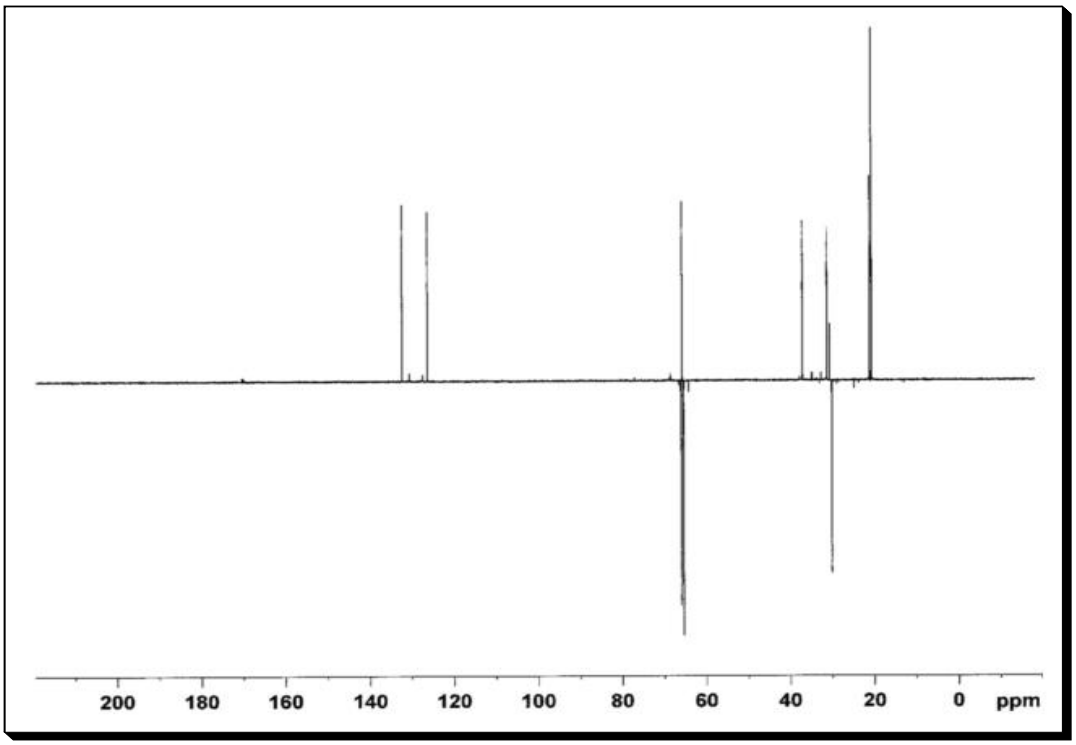


Figure A31. ^{1}H and ^{13}C NMR spectra of compound **91**.



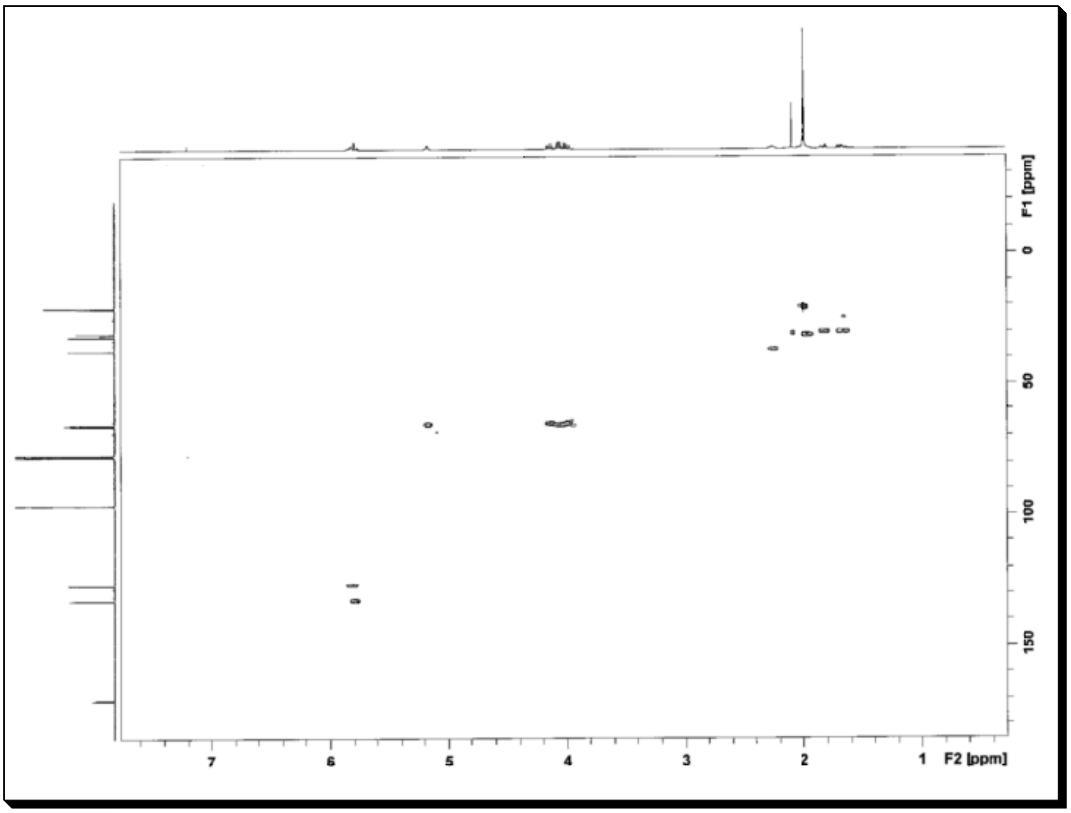


Figure A32. DEPT 135 and HSQC spectra of **91**, respectively.

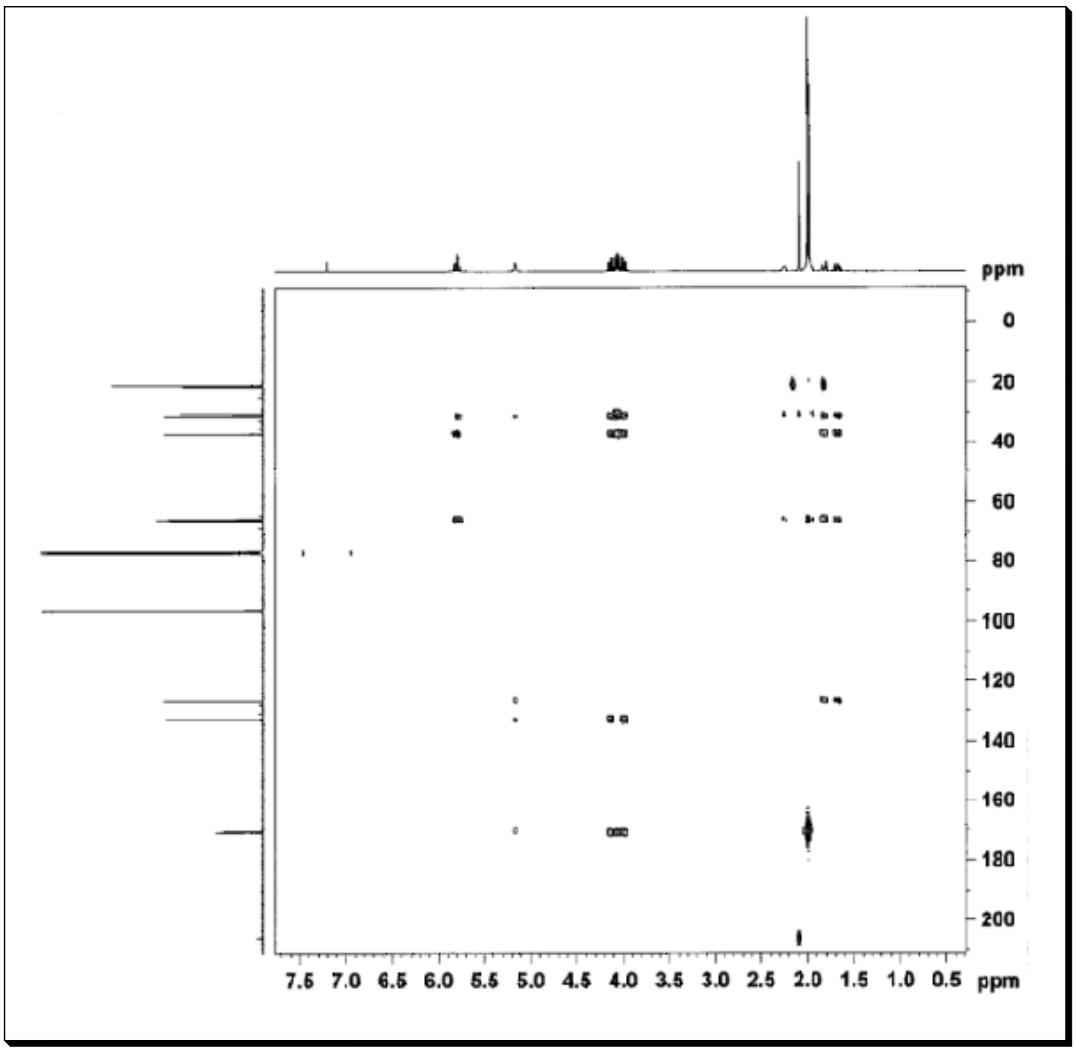


Figure A33. HMBC spectrum of **91**.

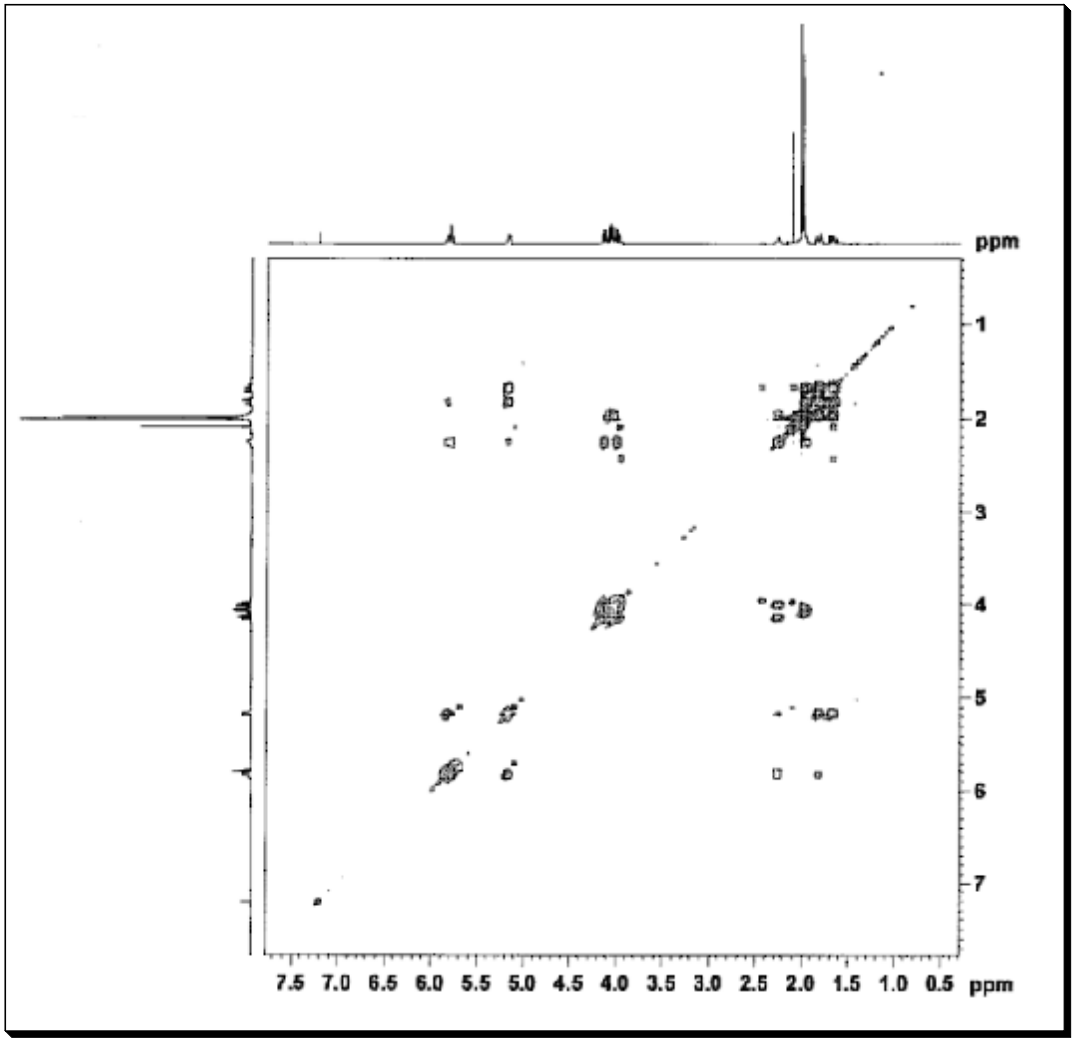
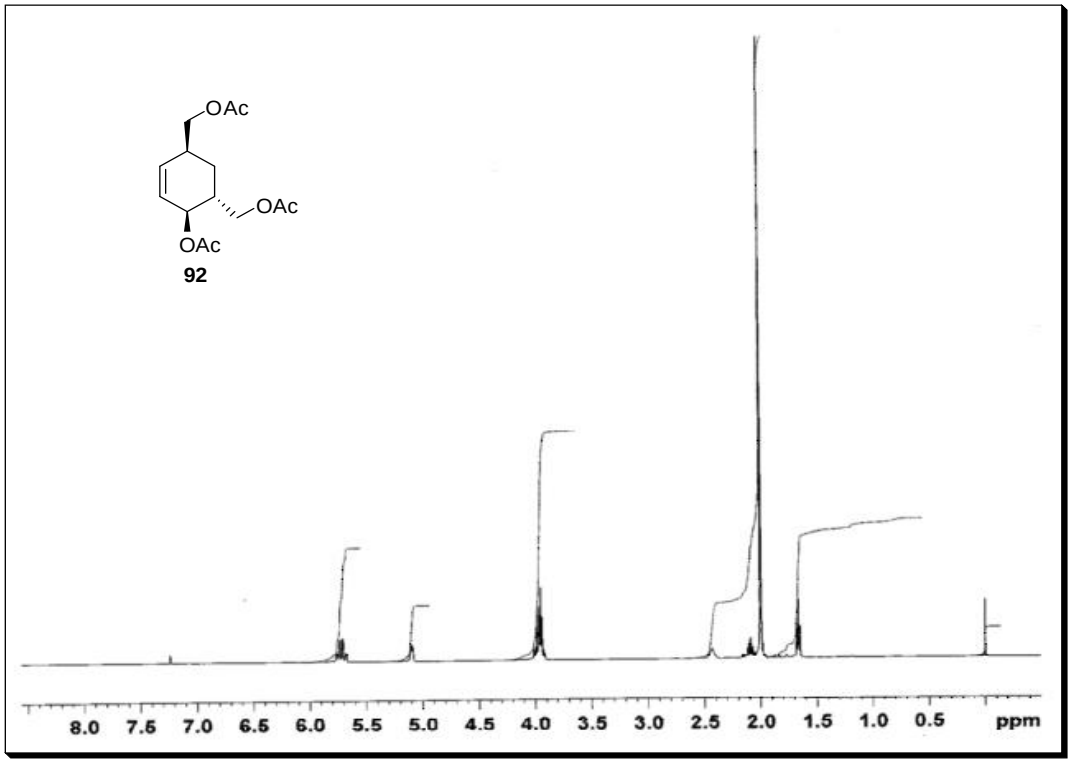


Figure A34. COSY spectrum of **91**.



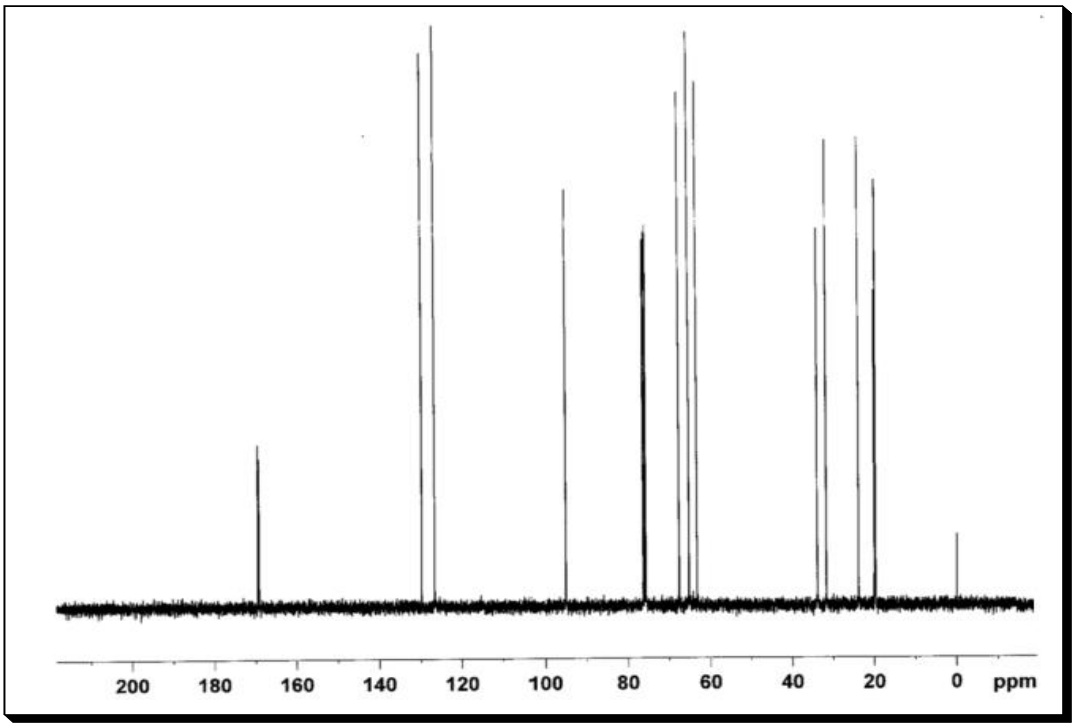
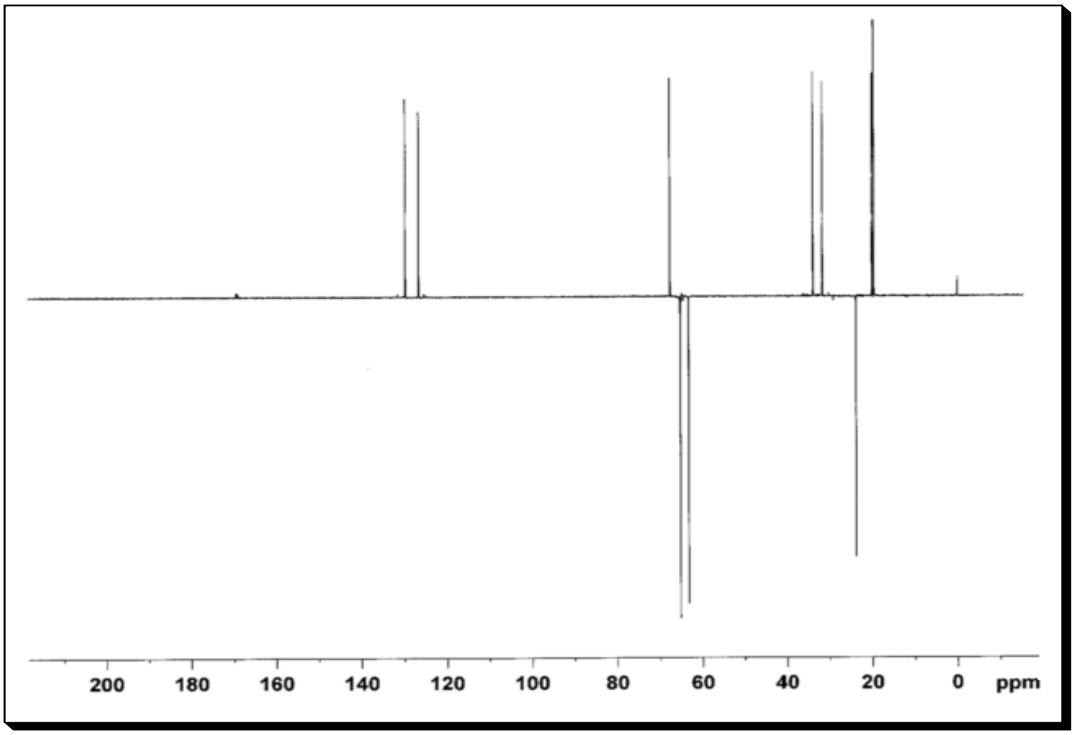


Figure A35. ^{1}H and ^{13}C NMR spectra of **92**.



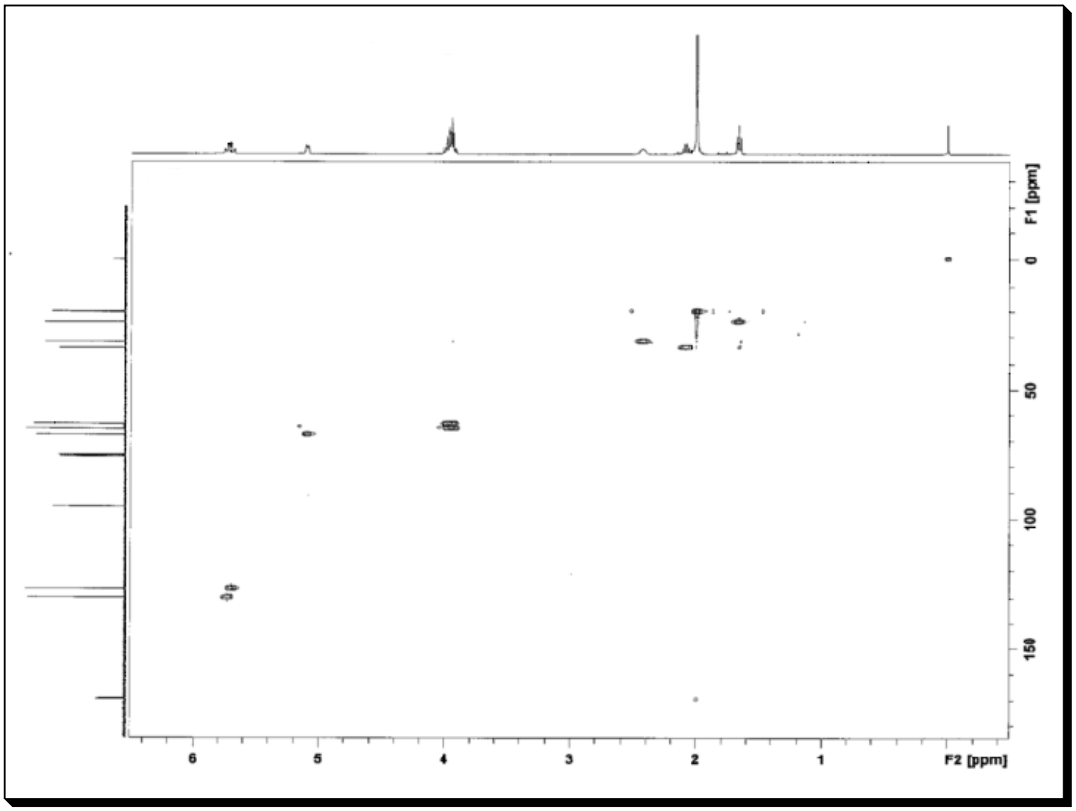


Figure A36. DEPT 135 and HSQC spectra of **92**, respectively.

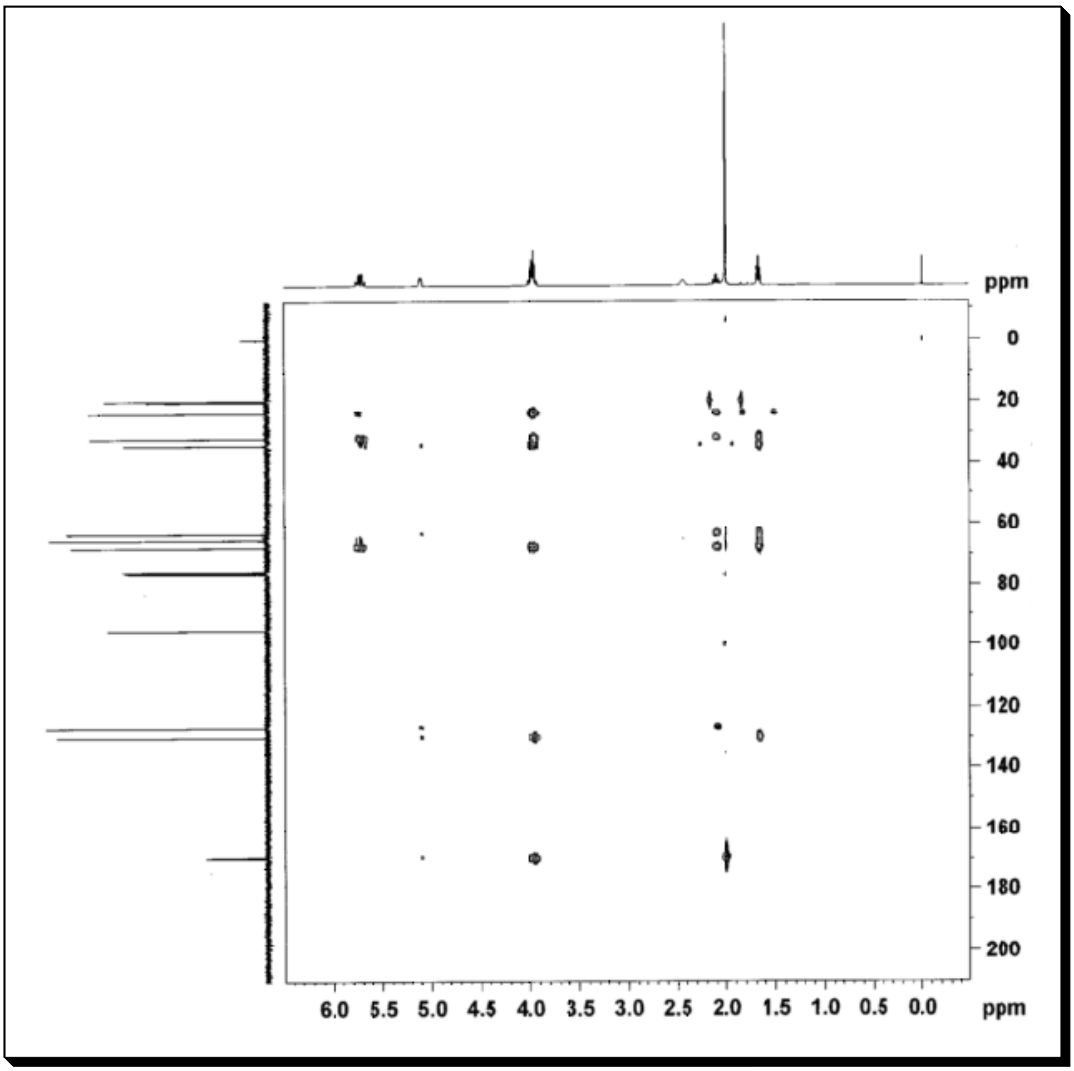


Figure A37. HMBC spectrum of **92**.

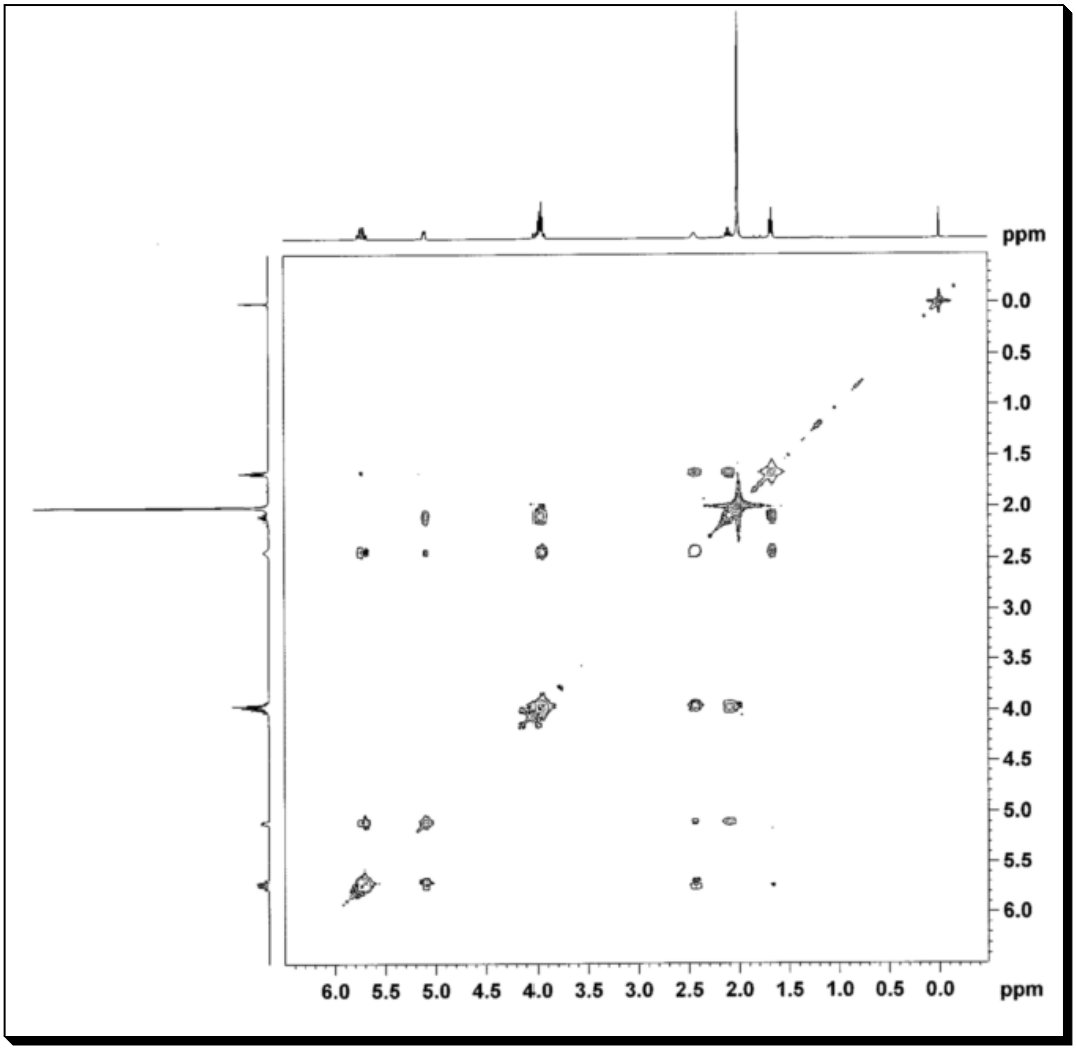
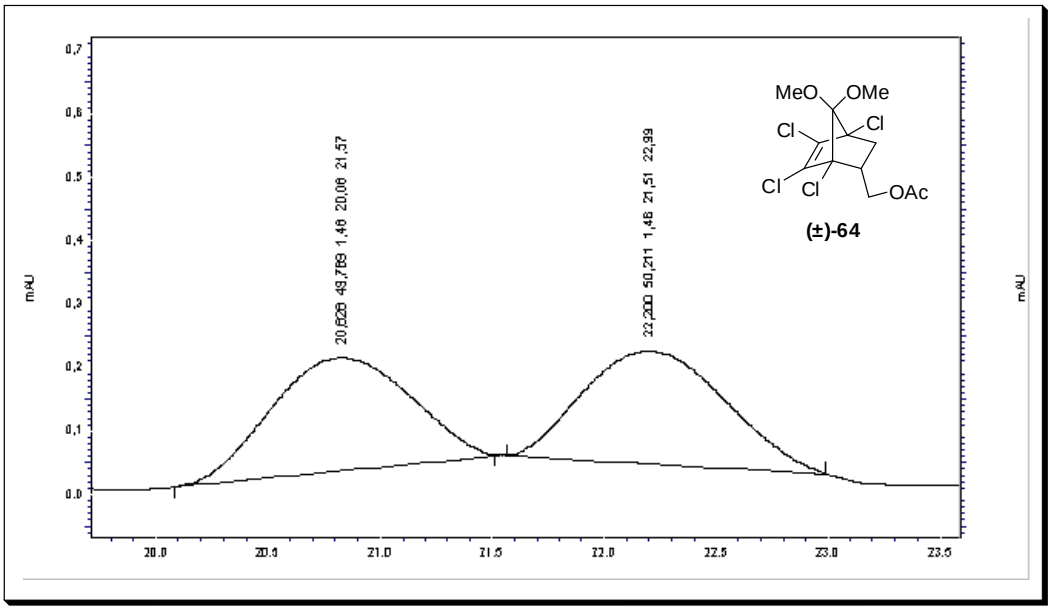


Figure A38. COSY spectrum of **92**.



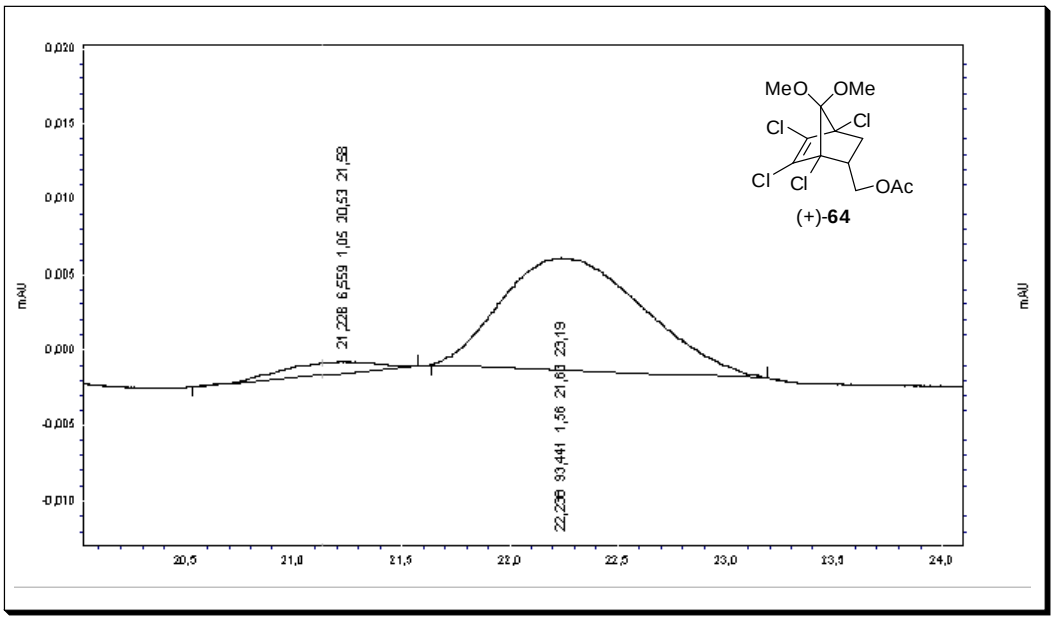
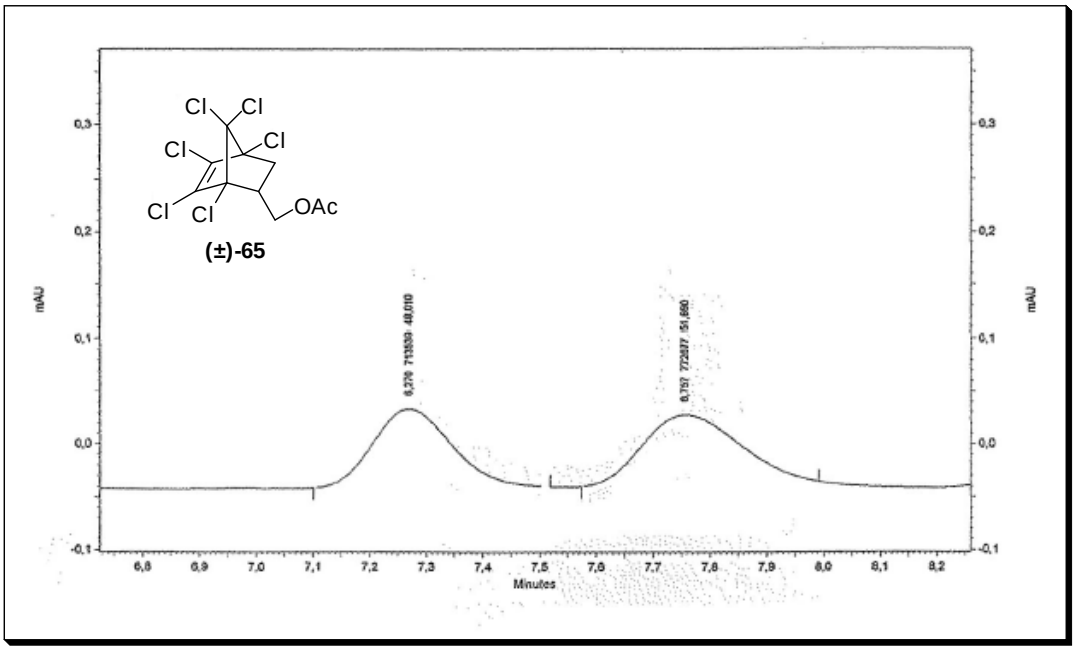


Figure A39. HPLC chromatograms of racemic (±)-**64** and enantio-enriched (+)-**65**.



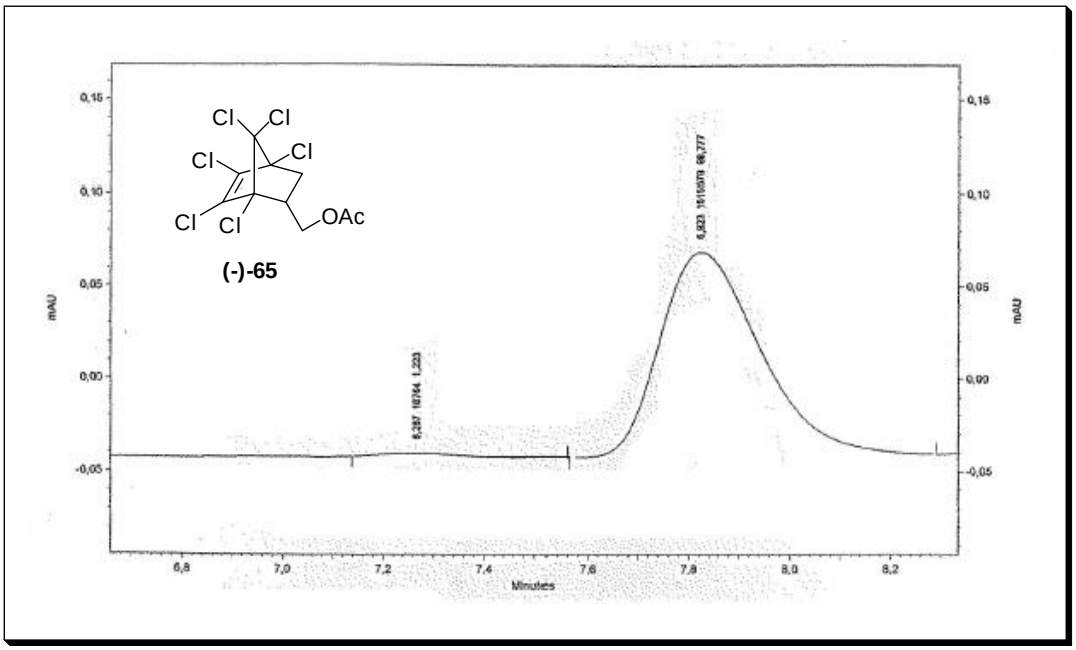


Figure A40. HPLC chromatograms of racemic (±)-**65** and enantio-enriched (-)-**65**.

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FOREIGN LANGUAGES

Fluent English

PUBLICATIONS

1. Tanyeli, C., Gümüş, A. Synthesis of polymer-supported TEMPO catalysts and their application in the oxidation of various alcohols. Tetrahedron Letters 44 (2003) 1639.
2. Tanyeli, C., Tosun (Gümüş), A., Turkut, E., Sezen, B. Manganese(III) acetate promoted acetoxylation of various α,β-unsaturated cyclopentanones. Tetrahedron 59 (2003) 1055.