

Modelling and synthesis of Alicyclic Bidentate N- and O chelating ligands.

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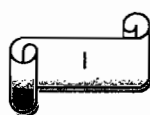
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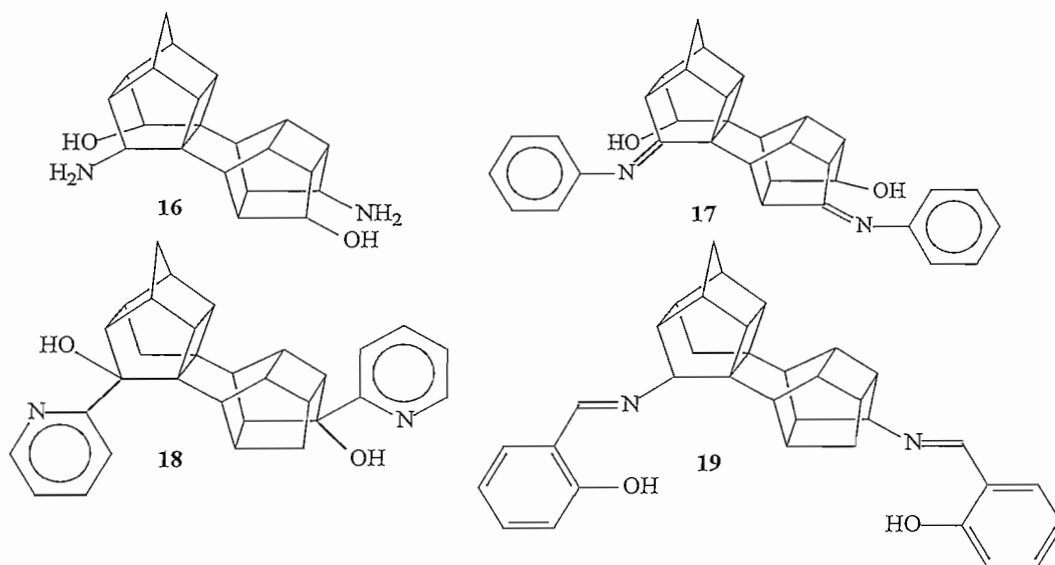
I give thanks to my Heavenly Father, without whom I could achieve nothing. I would also like to show my gratitude towards my parents, fiancé, friends and family for carrying me through the rough times.



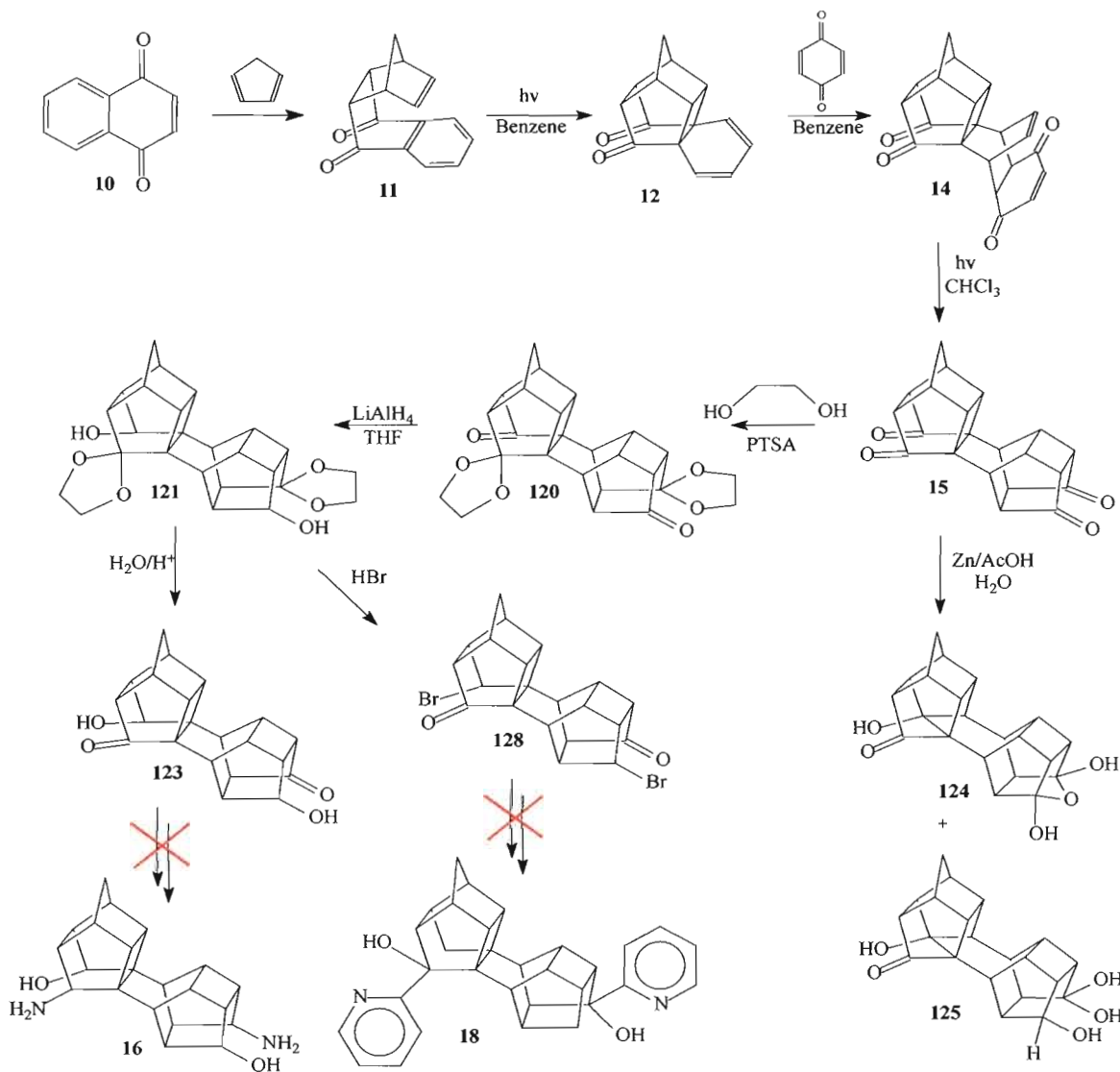
Abstract

The well-defined ruthenium-carbene complexes reported by Grubbs and co-workers were the first ruthenium catalysts to show good activity and selectivity in metathesis of acyclic and cyclic olefins. Unfortunately the use of the Grubbs type catalysts is limited to the small scale synthesis of polymers and essential organic reactions, due to cost and instability of the catalyst at elevated temperatures. Some of the most successful Grubbs-type catalysts included hemilabile ligands. By releasing a free coordination site (the so-called “on-demand-open-site”) for an incoming nucleophile, hemilabile ligands have the ability to increase the thermal stability and activity of a catalytic system, by stabilization of the transition metal centre. Previous studies indicated that the incorporation of a sterically hindered N and O chelating ligand increased the stability, activity and selectivity of Grubbs type complexes and increasing the electron density of the complex can influence the stability of a complex and therefore the catalytic performance.

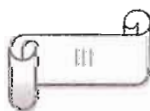
In this study alicyclic, bidentate N and O chelating ligands (**16-19**) were modelled in order to evaluate the hemilability of these ligands. The modelling was used as a corner stone from which the synthesis was conducted. Molecular modelling showed that of the four ligands identified only two (**16** and **18**) could potentially be hemilabile. **17** would rather form a transannular ether compound. The modelling results were inconclusive for ligand **19** and further investigation is necessary for this compound.



All attempts made to synthesize these compounds from the hexacyclo-pentadecane (**12**) compound unfortunately failed. All the products synthesized were thoroughly investigated with the use of spectrometric and other analytical techniques. The scheme below outlines the most important synthetic routes.



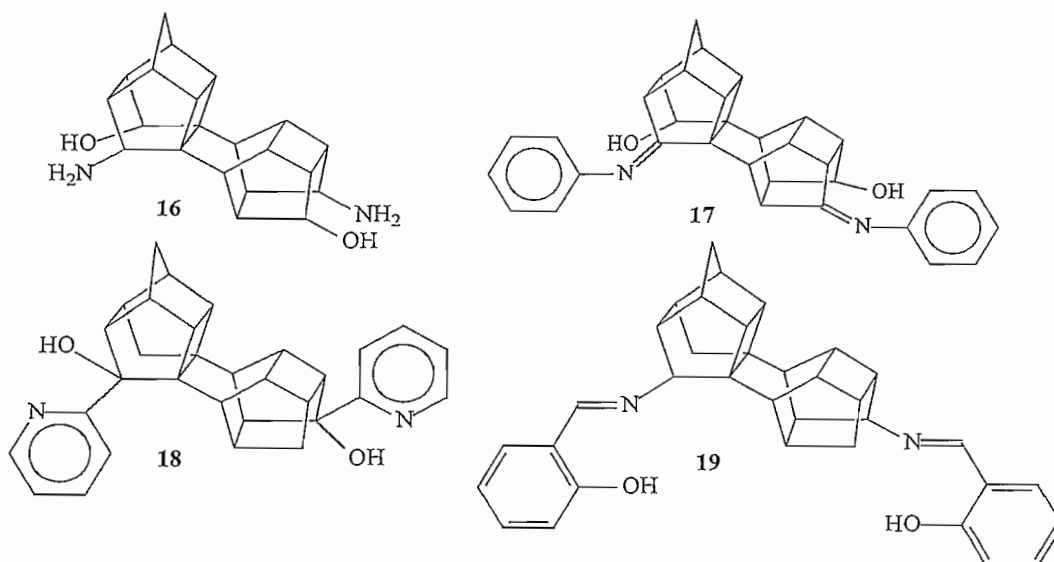
Keywords: ruthenium-carbene; Grubbs; hemilabile; alicyclic, bidentate; N and O chelating ligands; molecular modelling



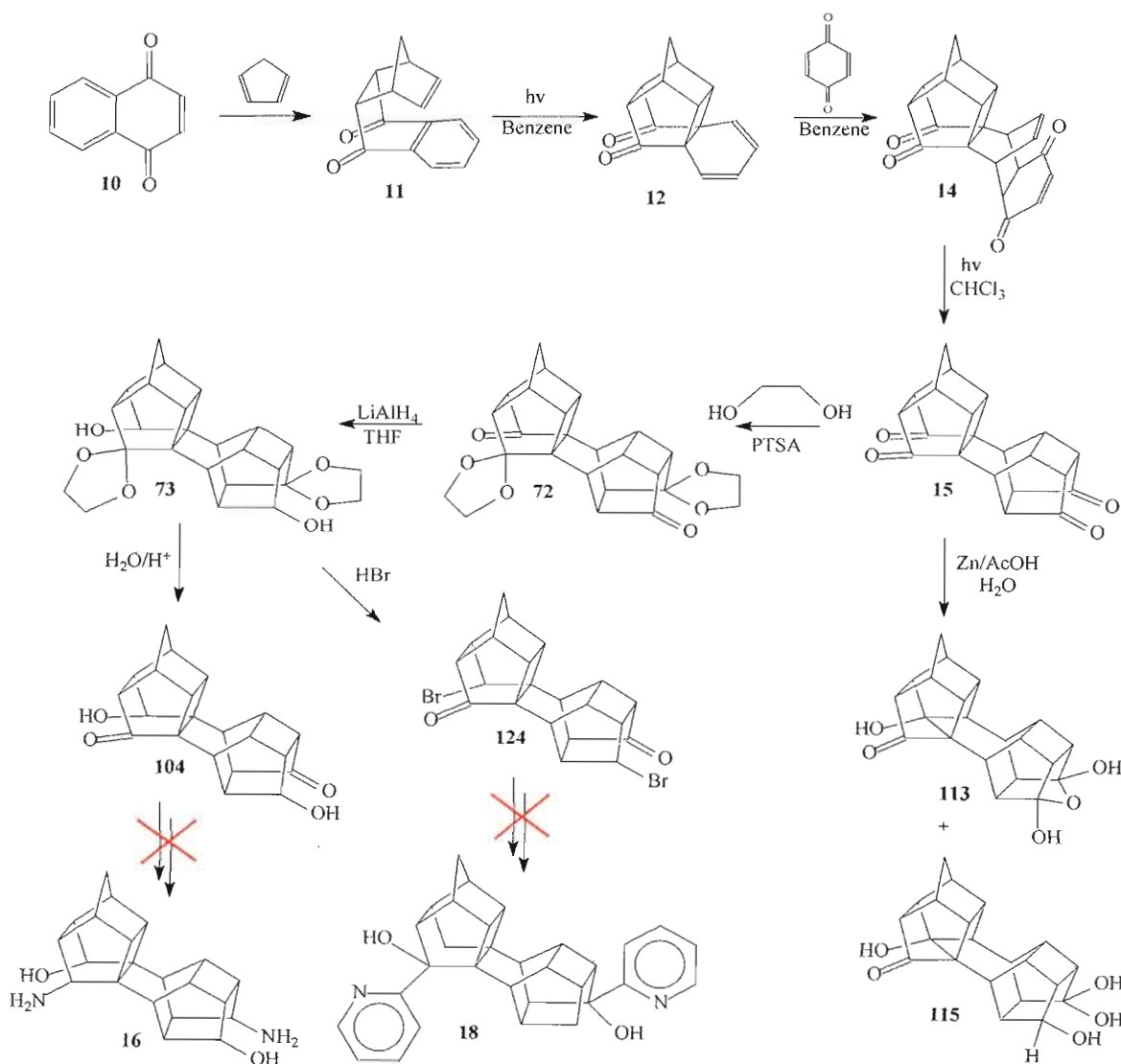
Opsomming

Die goed gedefinieerde rutenium-karbeenkomplekse wat deur Grubbs en mede-werkers gerapporteer is, was die eerste ruteniumkatalisator wat goeie aktiwiteit sowel as selektiwiteit tydens die metatiese van asikliese en sikliese olefiene getoon het. Ongelukkig is die gebruik van die Grubbs-tipe katalisator weens die koste en onstabiliteit by hoë temperatuur beperk tot kleinskaalse sintese van polimere en essensiële organiese reaksies. Van die mees suksesvolle Grubbs-tipe ligande sluit hemilabiele ligande in. Deur die beskikbaarstelling van 'n oop koördinasiepunt (die so-genaamde “on-demand-open-site”) vir 'n inkomende nukleofiel, het hemilabiele ligande deur die stabilisering van die oorgangsmetaal se kern die vermoë om die termiese stabiliteit en aktiwiteit van 'n katalitiese sisteem te verhoog. Vorige studies het aangetoon dat die insluiting van 'n steries gehinderde N- en O-ligand die stabiliteit, aktiwiteit en selektiwiteit van Grubbs-tipe komplekse kan verhoog en deur die elektrondigtheid van die kompleks te verhoog, die stabiliteit van 'n kompleks en dus die katalitiese vermoë kan beïnvloed.

In hierdie studie is alisikliese, bidentate N- en O-ligande (**16-19**) gemodelleer om die hemilabiliteit van hierdie ligande te evalueer. Die modellering is gebruik as fondament waarop die sintese gedoen is. Molekuulmodellering het aangetoon dat van die vier ligande, slegs twee (**16** en **18**) moontlik hemilabel kan wees. **17** sal eerder die *trans-annulêre* eterverbinding vorm. Die modelleringsresultate was nie beslissend vir **19** nie en verdere ondersoek is vir hierdie verbinding nodig.



Alle pogings om die verbindings vanaf die heksasiklo-pentadekaan (**12**) te sintetiseer het misluk. Alle produkte wat gesintetiseer is, is deeglik met behulp van spektrometriese en ander analitiese tegnieke ondersoek. Die skema hieronder lig die belangrikste sinteseroetes uit.



Sleuteltermen: rutenium-karbeen; Grubbs; hemilabiel; alisiklies; bidentate; N- en O-ligande; Molekuulmodelleering

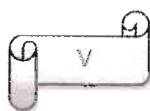


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Chapter 1: Introduction and Problem Statement

Olefin metathesis is a catalytic reaction in which two alkenes (the same or two different ones) rearrange to form new alkene products. The first metathesis reaction was observed in 1931 by Schneider and Frolich, during the conversion of propylene to ethene and butene at high temperatures.¹ The first metathesis experiment conducted after the observation of Schneider and Frolich, was in the 1950s at Du Pont.² This was the first reaction that was described as a metathesis reaction. The name “Olefin Metathesis” was given by Calderon³ in 1967 at the Goodyear Tyre and Rubber Company.

Olefin metathesis is a powerful tool, since it can initiate a wide range of different reactions and has some advantages over classical reactions. Advantages of olefin metathesis include: the use of inexpensive raw materials to produce valuable products, less CO₂ production and less toxic waste production.⁴ Thus olefin metathesis is a type of green chemistry which will be discussed in Chapter 2.

The well-defined ruthenium-carbene complexes reported by Grubbs and co-workers⁵ were the first ruthenium catalysts to show good activity and selectivity in metathesis of acyclic and cyclic olefins. Current interests in the chemistry of ruthenium revolve around the fascinating electron-transfer, photochemical and catalytic properties exhibited by the complexes of this metal.⁶ Unfortunately the use of the Grubbs type pre-catalysts is limited to the synthesis of polymers and essential organic reactions (see Chapter 2), due to cost and instability of the catalyst at elevated temperatures.^{4, 7}

Exhibiting high reactivity for a variety of metathesis processes under mild conditions and a remarkable tolerance towards many organic functional groups,⁵ ruthenium-carbene complexes has drawn a lot of interest, not only to the synthesis but also to the modelling of these types of systems. To date, the ruthenium-carbene catalyst has been widely used in a variety of olefin metathesis reactions with remarkable success.⁸ Olefin metathesis has thus emerged as a powerful tool for the formation of C-C bonds in chemistry.⁹

There currently exist four commercially available generations of the Grubbs catalysts (1-4), with a wide variety of derivatives. The use of the *N*-heterocyclic (NHC) ligand of the Grubbs 2 (2), instead of the normal PCy₃ ligand as in Grubbs 1 (1), has increased the stability, lifetime and activity of the catalyst.^{10, 11} The same phenomenon can be seen in the Hoveyda-Grubbs 2 (4) in comparison with Hoveyda-Grubbs 1 (3)³, where one of the phosphine ligands is replaced by an isopropoxy group attached to the benzene ring.¹² Sadly, most of these catalysts have a relative short life-time at elevated temperatures.^{7, 13} Another drawback of these catalysts are the fact that they are quite expensive. It is thus evident that this type of catalyst is impractical for the use on industrial scale synthesis.¹⁴ For these reasons the search for ligands with increased selectivity, lifetime and that can be produced in a more cost-effective manner for the use in olefin metathesis, has been the subject of discussion over the past two decades.

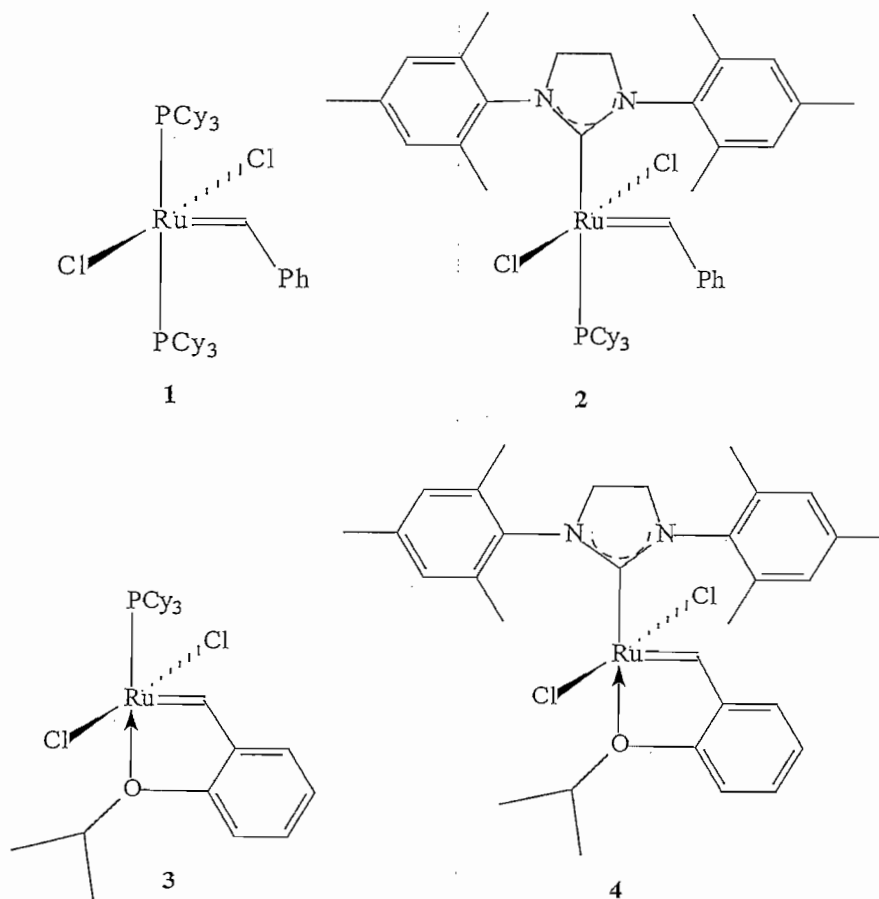


Figure 1.1: The existing commercially available Grubbs catalysts and Hoveyda-Grubbs pre-catalysts

The question that now arises is why ruthenium? Ruthenium has the widest range of oxidation states (from -2 in $\text{Ru}(\text{CO})_4^{-2}$ to $+8$ in RuO_4) of all the elements with a variety of coordination geometries in each electronic configuration, since ruthenium has a $4d^7 5s^1$ electronic configuration, which leads to a great potential for the exploitation in catalytic reactions.¹⁵ Ruthenium shows greater tolerance toward many functional groups and protic media. It has enhanced air and water stability relative to other popular single component catalytic systems based on molybdenum and tungsten. It is easy to handle and can initiate a variety of olefin metathesis reactions without the addition of a co-catalyst or promoter.¹⁶ Ruthenium carbenes are known to exhibit high rates of reactivity toward terminal olefins,¹⁷ it reacts preferentially with olefins in the presence of heteroatomic functionalities² and lastly ruthenium-based catalysts are robust and has a high activity to a wide range of substances.¹⁶ Therefore, it is clear why ruthenium based catalysts enjoy much more attention than any other transition metal used for olefin metathesis and why these metal-based catalysts will enjoy future interest.²

One of the most significant catalyst systems developed by Schrock and co-workers was the alkoxyimido molybdenum complex.¹⁸ This system is highly reactive towards a broad range of substrates. Vital drawbacks of Mo-based carbene complexes are the moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents, thermal instability on storage and expense of preparation. It is thus obvious why ruthenium-based catalysts have enjoyed more interest.

In recent years a new class of chelating ligands has become a popular topic of research due to their ability to place two or more donor atoms with distinct electronic properties close to the metal atom. This concept was known as hemilabile and the first hemilabile ligand was described in 1979 by Jeffrey and co-workers.¹⁹ A wide variety of different hemilabile ligands exists including $\text{P}^{\wedge}\text{N}$, $\text{P}^{\wedge}\text{X}$ ($\text{X} = \text{halide}$), $\text{O}^{\wedge}\text{O}$, $\text{O}^{\wedge}\text{S}$, $\text{O}^{\wedge}\text{P}$ and $\text{N}^{\wedge}\text{O}$,^{13, 20} For the purpose of this text, only $\text{N}^{\wedge}\text{O}$ ligands will be discussed briefly in this chapter (a detailed discussion with the focus on nitrogen and oxygen chelating ligands is given in Chapter 2). The development of $\text{N}^{\wedge}\text{O}$ ligands was due to the increased interest in chiral catalysts and catalysts which can control *cis/trans* selectivity.⁸ It was found that these ligands have an increased activity and stability when complexed with **1** and **2**.²¹

By releasing a free coordination site (the so-called “on-demand-open-site”) for an incoming nucleophile, hemilabile ligands have the ability to increase the thermal stability and activity of a catalytic system^{20, 22} by stabilization of the transition metal centre.²³ It was found that the incorporation of a sterically-hindered ligand of this type increased the stability, activity and selectivity of Grubbs-type complexes and increasing the electron density of the complex can influence the stability of a complex and therefore the catalytic performance.^{22, 24}

In recent years only a few catalytic systems (see Chapter 2) have been published that dealt with alicyclic cage compounds as ligands for olefin metathesis.^{21, 25, 26} Unfortunately none of these ligands showed any improvement in catalytic activity or stability. The fact that this pre-catalyst showed any activity at all is worth noting and for this reason it is worth investigation. Additionally the homobimetallic complexes synthesized by De Clercq²⁷ and Drozdak²⁸ show great promise in the development of a new catalytic system. Although none of these systems showed potential, alicyclic compounds have the prospective ability to further stabilize the Grubbs-type precatalyst, due to their thermal stability.²⁹

The synthesis of alicyclic cage compounds has increased tremendously over the past few decades.^{30, 31} This can be ascribed to the incredible versatility of these compounds for the use in polymer chemistry³² as well as in the pharmaceutical industry as potential drugs.³³⁻³⁶ It has been proven that alicyclic amines such as adamantane (**5**) and cyclic urea are inhibitors of HIV protease.³⁴ 8-benzylamino-8,11-oxapentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**6**) (NGP1-01) and a number of its derivatives (**7** and **8**) showed positive effects in neuroprotection studies,³⁶⁻³⁹ as well as potential as therapeutic agents in Parkinson’s and Huntington’s disease,³⁴ Alzheimer,³⁷ influenza and tuberculosis (**Figure 1.2**).³³

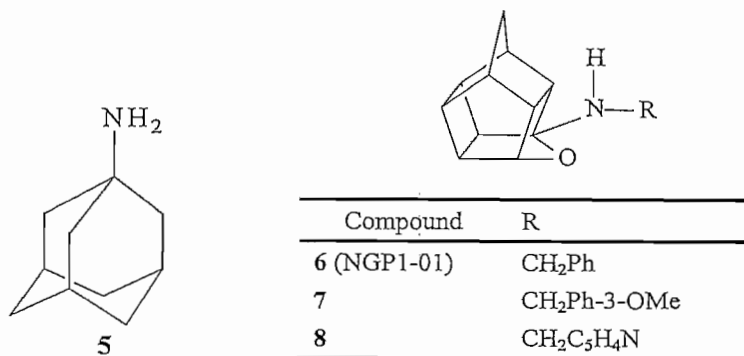
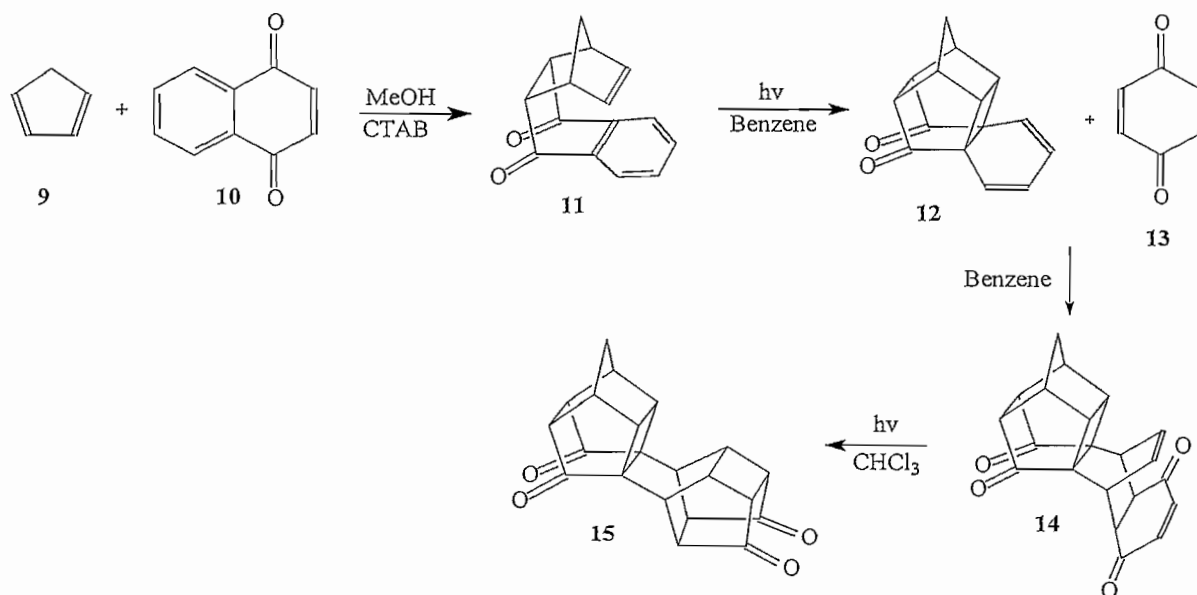


Figure 1.2: Adamantane (**5**), NGP1-01 (**6**) and other pharmaceutical important derivatives (**7** and **8**)

In 1971 Kusher *et al.*⁴⁰ synthesized the Diels-Alder adduct, hexacyclo-[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-dione (**11**) from the cycloaddition product of cyclopentadiene (**9**) and 1,4-naphthoquinone (**10**). The fascinating entity about this compound is that besides its thermal stability²⁹ it can also undergo further Diels-Alder reactions.⁴¹ The synthesis of **11** is an inexpensive and rather simple procedure.⁴⁰ **12** can then be reacted with p-benzoquinone (**13**) to produce a new Diels-Alder adduct (**14**), which after UV irradiation produces a tetrone (**15**, **Scheme 1.1**).⁴²



Scheme 1.1: Synthesis of the 1,4-naphthoquinone Diels-Alder product (**12**) and **15**

In this study alicyclic, bidentate N and O chelating ligands will be modelled in order to evaluate the hemilability of the ligands, after which these ligands will be synthesized. The main focus of this study will revolve around the synthesis of nitrogen containing derivatives (**16-19**, **Figure 1.3**) of the hexacyclo-pentadecane compound (**12**) and the molecular modelling of the substrates and products. The modelling will be used as a corner stone from which the synthesis will be conducted. It will also be used as a tool to explain some experimental observations. All the products synthesized will be thoroughly characterized with the use of spectrometric and other analytical techniques.

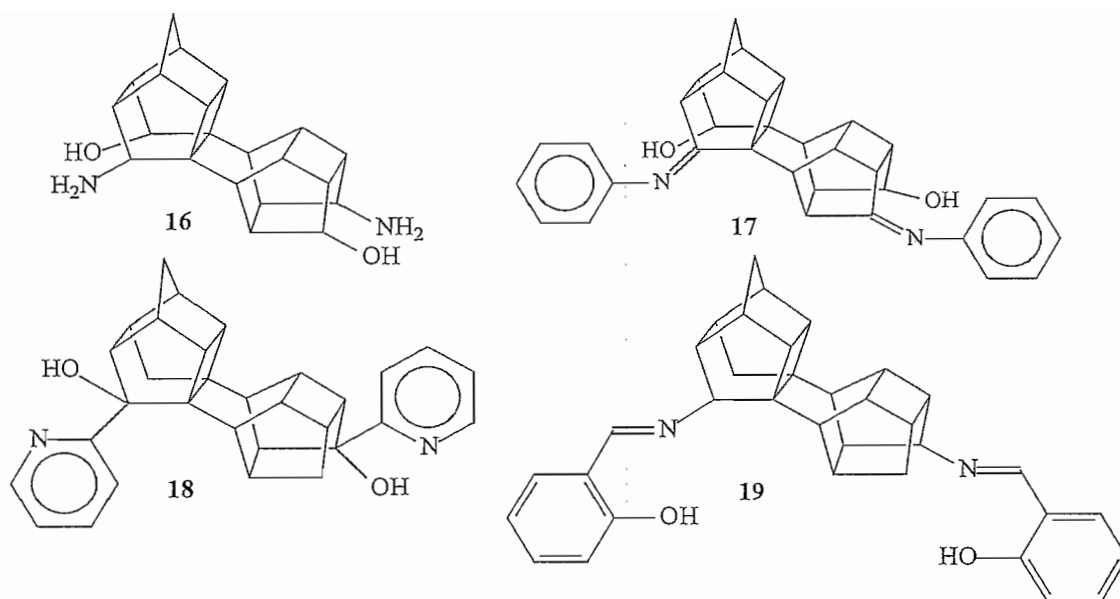


Figure 1.3: Possible nitrogen-containing derivatives of the hexacyclo-pentadecane compound (12) to be investigated in this study

Chapter 2: Literature Review

2.1. Introduction

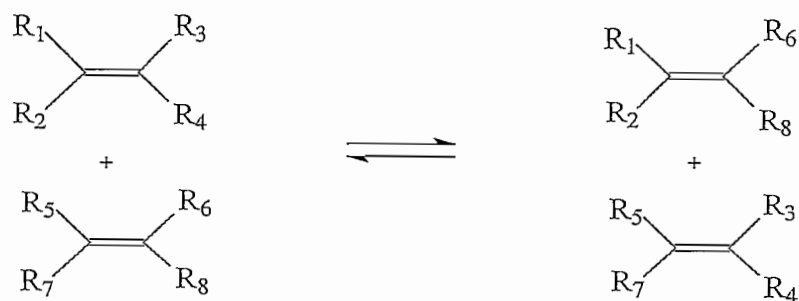
This chapter will be divided into three distinct themes. The first theme will shed light on:

- i. the development of olefin metathesis and the Grubbs-type pre-catalysts from a mysterious reaction to a powerful and vital tool in chemistry (this section will only highlight the most important events that contributed to the strength and development of olefin metathesis),
- ii. the discovery and development of the vast array of hemilabile ligands and the different types of hemilabile systems (since there are infinite possibilities to combine different atoms to form chelating ligands, only those that contain nitrogen and oxygen will be discussed) and
- iii. some advantages and applications of olefin metathesis.

The second theme will describe the most important fundamentals regarding alicyclic compounds; their applications and advantages. This chapter will then be concluded with the third theme consisting of a short review on molecular modelling that would be essential to the present study.

2.2. Development of Olefin Metathesis

As already mentioned in Chapter 1, olefin metathesis is a catalytic reaction in which two unsaturated organic molecules (the same or two different ones) rearrange to form new products. The etymology of the word metathesis comes from the Greek word μεταψεσις; meaning transposition.³ A typical example is shown in **Scheme 2.1**.



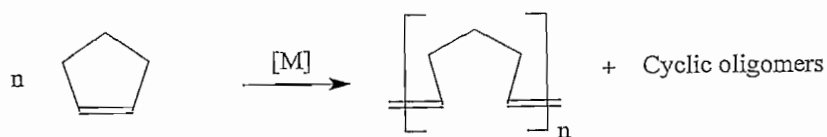
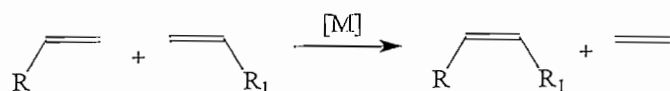
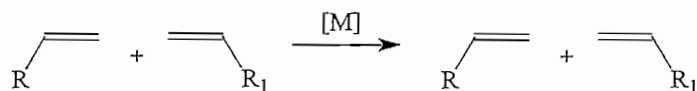
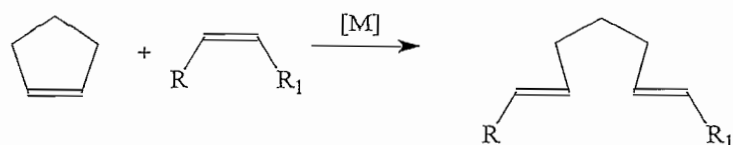
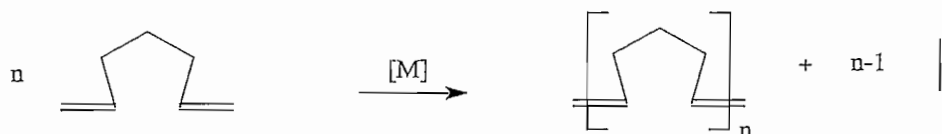
Scheme 2.1: A typical example of an olefin metathesis reaction

The first metathesis reaction was observed in 1931 by Schneider and Frolich, during the conversion of propylene to ethene and butene at high temperatures,¹ which was a non-catalytic system. The first metathesis experiment reported after the observation of Schneider and Frolich was only in the 1950s when industrial chemists at Du Pont reported that propene formed ethylene and 2-butene when heated with molybdenum in the form of the metal, metal-oxide or $[\text{Mo}(\text{CO})_6]$ on alumina.⁴³ This was the first reaction that was described as a metathesis reaction. The first polymerization of norbornene, by the system $\text{WCl}_6/\text{AlEt}_2\text{Cl}$, was independently reported in 1960 by Eleuterio and by Truett.³ The name “Olefin Metathesis” was given by Calderon⁴⁴ in 1967 at the Goodyear Tyre and Rubber Company.

At the end of the 1960s, although metathesis enjoyed some interest, the mechanism was poorly understood. Catalytic systems were either oxides, such as WO_3/SiO_2 used in the industry for the transformation of propene to ethylene and butenes, or Ziegler–Natta type systems, such as $\text{WCl}_6/\text{EtAlCl}_2/\text{EtOH}$. Due to the harsh conditions and strong Lewis acids that these catalysts require, they are incompatible with most functional groups.²

Numerous authors had mechanistic ideas, but none matched the results of some metathesis experiments.^{3, 43} In 1970 Chauvin and his student Jean-Louis Hérisson, not only proposed that olefin metathesis proceeds *via* metallacyclobutanes,⁴⁵ but also published several experiments confirming the mechanism, for the first time.⁴⁶ It is now generally accepted that both cyclic and acyclic olefin metathesis reactions proceed *via* metallacyclobutane and metal-carbene intermediates.⁴⁷

Over the past few decades olefin metathesis has emerged as a versatile tool for formation of carbon–carbon double bonds;^{48, 49} offering a wide range of reactions (**Scheme 2.2**) such as ring opening metathesis polymerization (ROMP), ring-opening metathesis (ROM), ring closing metathesis (RCM), cross metathesis (CM) and acyclic diene metathesis (ADMET).^{50–52} There are various other reactions such as atom transfer radical polymerization (ATRP),²⁷ epoxidation⁵³ hydrogenation, hydration, oxidation, isomerization, decarbonylation, cyclopropanation, Diels–Alder reaction, Kharasch addition, enol-ester synthesis²⁸ and many more, that will not be discussed.

ROMP:**RCM:****Productive CM:****Non-Productive CM:****ROM:****ADMET:****Scheme 2.2:** Some of the wide range of reactions offered by olefin metathesis

ROMP is a type of olefin metathesis polymerization that produces polymers from cyclic olefins. The driving force of the reaction is the relief of ring strain in cyclic olefins. RCM is simply an intramolecular olefin metathesis reaction with a Grubbs catalyst, yielding a cycloalkene and a volatile alkene; normally ethene. It is a useful method for the syntheses of

carbo- and heterocyclic ring-containing materials and has recently been utilized as key transformations in a number of impressive natural product syntheses. Another area of significant potential is selective CM, in which two different alkenes or the same one undergoes an intermolecular transformation to form two new olefinic products. CM can either be productive or non-productive. In the former case two new alkenes are formed and in the latter the same products as the starting alkenes are formed. A variation of cross-metathesis is ROM, where one of the olefin partners is a cyclic alkene and as the name suggests the cyclic alkene is opened up. In this reaction, a single product is obtained that incorporates the functionality of both starting olefins.⁵⁴ ROM is merely the reverse of RCM. Another variation of CM is ADMET, which is the cross metathesis of acyclic diolefins which results in polymers.⁵ The broad applicability of olefin metathesis has attracted attention from both academic and industrial scientists.⁵⁵

2.3. Advantages and Applications of Metathesis

Olefin metathesis opens up new industrial routes to important petrochemicals, oleochemicals, polymers and specialty chemicals. Olefin metathesis is very useful in the industry given the large quantities of hydrocarbons handled and the need for propylene,⁵⁶ produced by metathesis from ethylene and 2-butene. Propylene is used for the production of polypropylene, used for packaging and for the production of acetone and phenol through the cumene process. Propylene is also used during the production of many other chemical products such as isopropanol, acrylonitrile, and propylene oxide. Another example of practical use of metathesis is the Shell higher olefin process (SHOP) for the large-scale production of long-chain R-olefins.¹⁶

Olefin metathesis is also used for the synthesis of products that would otherwise not be possible. Some of these products includes: (R)-lasiodiplodin (**20**), a natural compound isolated from a culture broth of the fungus *Botrysdiplodia theobromae* and exhibits plant growth regulation properties and (±)-dactylol (**21**) which is a natural cyclooctenoid sesquiterpene product first isolated in 1978 from the mollusc *Aplysia dactylomela*. Olefin metathesis is also used for the synthesis of biologically active agents, such as Fluvirucin B₁ (**22**), that was discovered at Schering-Plough in 1990 and is an effective agent against the influenza A virus.⁵² These products (**Figure 2.1**) can all be synthesized employing RCM.

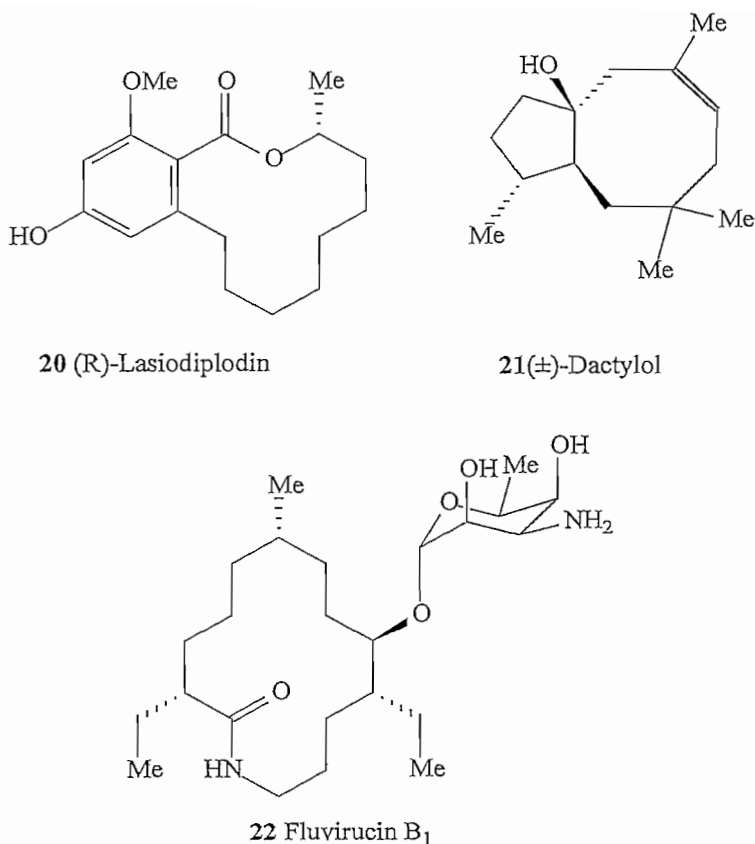


Figure 2.1: Some natural products (**20** and **21**) and a biologically active agent (**22**), synthesized by RCM

Olefin metathesis can also be applied to the metathesis of natural oils and fats⁵⁷ and their derivatives, which is a clean catalytic reaction that can be considered an example of green chemistry. As stated by Maureen Gorsen,⁵⁸ Director of the Department of Toxic Substances Control in the Californian Green Chemistry Initiative, Final Report for December 2008: “Green chemistry is a systematic scientific and engineering approach that seeks to reduce the use of hazardous chemicals and the generation of toxic wastes by changing how society designs, manufactures, and uses chemicals in processes and products, rather than managing wastes after end of product life. Green chemistry shifts our focus to designing chemicals, processes, and goods that have less or no adverse effects - throughout their lifecycle.”

Green chemistry seeks to reduce and prevent pollution at its source. Click chemistry,⁵⁹ often cited as a style of chemical synthesis that is consistent with the aims of green chemistry, is a chemical philosophy introduced by K. Barry Sharpless in 2001 and describes chemistry adapted to generate substances quickly and reliably by joining small units together, often with

the use of a catalyst. Although both green and click chemistry require the use of either no solvent or water as solvent and catalysis are usually conducted in chloroform,⁶⁰ many catalytic systems, especially ruthenium carbene based ones, are tolerant to a wide range of substances and even water. This in turn signifies that not only can olefin metathesis be used for the sustainable production of organic fuels at an industrial level from oleochemical feed stocks such as unsaturated fatty acid esters and oils, but it also complies with the aspirations of green and click chemistry.

Unlike petrochemicals, oleochemicals are derived from renewable resources, have good biodegradability and no net CO₂ production. Therefore, the use of renewable resources is an important component of green chemistry. The long-chain vegetable oils, such as soybean, sunflower, rapeseed and palm oil are the most important oils in oleochemicals. Short and medium chain vegetable oils, such as coconut, palm and kernel oil are important sources for the production of cosmetics, detergents, soaps, emulsifiers, etc. Linseed and soybean oil are valuable raw materials for the manufacturing of oil based paint, printing ink and synthetic resins. The advantage of using olefin metathesis, rather than traditional thermal polymerization for the process of molecular weight amplification, is that it does not involve the consumption of double bonds, but the equal amount of double bonds (or close to it) is formed in the product.⁴ This in turn results in a colossal arsenal of products, by the direct incorporation of functionality *via* the monomer.⁶¹

As already mentioned, over the past few decades olefin metathesis has emerged as a versatile tool for the formation of carbon-carbon double bonds. The number of catalytic systems that can initiate olefin metathesis is enormous. However, most early work in olefin metathesis was done using ill-defined multicomponent catalyst systems. It is only in the 1990s that well-defined single component metal carbene complexes have been prepared and employed in olefin metathesis.⁵⁵ This can be ascribed to all the researchers that developed and are still developing catalysts for the use in olefin metathesis.

In the following section some of the most important events that led to commercialization of catalysts specifically designed for the use in olefin metathesis will be highlighted. These catalysts, particularly Grubbs first and second generation pre-catalysts (**1** and **2**), laid the

foundation of most modern olefin metathesis catalysts, since catalytic design commence from the derivatives of these catalysts.

2.4. Development of Grubbs-type Catalysts

The ruthenium complex, $[\text{RuCp}\{\text{C}(\text{Me})\text{OMe}\}(\text{CO})(\text{PCy}_3)][\text{PF}_6]$, stabilized by a methoxy group on the carbene carbon atom, was synthesized by Green's group at Oxford in 1971, which was the first reported ruthenium-carbene complex.⁶² Drawing on earlier work by Michelotti and Keaveney on norbornene polymerization with hydrated trichlorides of ruthenium, osmium and iridium in alcoholic solvents,⁶³ the Grubbs group successfully polymerized the first ring-opening metathesis polymerization of a series of monomers based on the 7-oxabicyclo[2.2.1]hept-5-ene (7-oxanorbornene)⁶⁴ ring structure using RuCl_3 or $[\text{Ru}(\text{H}_2\text{O})_6](\text{Ots})_2$ (Ots = toluene sulfonate), in 1988. This system led to the first observed example of an organometallic complex formed from fully aqueous ruthenium(II) during the polymerization of 5,6-bis(methoxymethyl)-7-oxanorbornene.⁶⁵

In 1992, Grubbs⁶⁶ reported the first molecularly well-defined ruthenium-carbene complex, $[\text{RuCl}_2(\text{PPh}_3)(=\text{CH}-\text{CH}=\text{CPh}_2)]$ (**23**), which promoted the catalytic RCM of functionalized dienes^{67, 68} but is not an efficient catalyst for the ROMP of low-strain cyclic olefins or the metathesis of acyclic olefins.⁶⁰ In 1995, the Ru-complex $[\text{Ru}(=\text{CHPh})\text{Cl}_2(\text{PCy}_3)_2]$ (**1**), now known as the first generation Grubbs catalyst was commercialized⁶⁹ and is still the most used metathesis catalyst used by organic chemists.³ Unfortunately complex **1** displays a short lifetime and is intolerant to reaction temperatures above 50 °C.²²

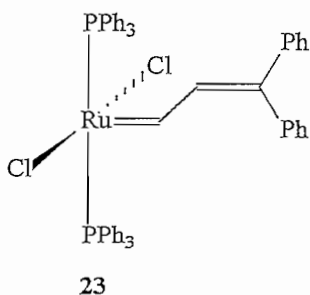


Figure 2.2: The first molecularly well-defined ruthenium-carbene complex

Early mechanistic studies of the catalysts with the general formula, $(\text{PR}_3)_2(\text{X})_2\text{Ru}=\text{CHR}$, established that a critical step in the olefin metathesis reaction was the dissociation of

phosphine and demonstrated that catalysts containing sterically bulky and electron-donating phosphine ligands display high catalytic activity.²⁴ This trend was explained on the basis of the increased *trans*-effect of larger and more basic phosphines, which was believed to accelerate dissociation of the second PR₃ ligand and to stabilize the ruthenium metallacyclobutane intermediate.⁷⁰

The ruthenium-carbene complex (which is penta-coordinated) adopts a distorted square pyramidal structure. These catalysts are used in a large variety of metathesis reactions, which proceed rapidly with high selectivity.^{12, 69} The catalytic activity of ruthenium carbene complexes originates from the liberation of one phosphine ligand and the coordination of the substrate at the empty coordination site. The C-C bond is then formed *via* a 14-electron metallacyclobutane intermediate. The stabilization of the intermediate catalytic species is favoured by the sterically demanding and highly donating phosphine ligands. Although catalysts bearing PCy₃ ligands are active toward many olefin reactions, it still suffers from a relatively low thermal stability as a consequence of phosphine loss and subsequent easily accessible bimolecular decomposition pathway which renders it only sparingly suitable for use at elevated temperatures. Nucleophilic carbene ligands of the imidazol-2-ylidene type have proven to be phosphine mimics.¹⁰

Experimental results of Grubbs and co-workers⁶⁰ suggest that electronic factors are more important than steric effects. This observation was made using two derivatives of **23**, one bearing P(*i*-Pr)₃ and one bearing PCy₃. Although these two ligands are sterically different, they are both electron rich compared to the phosphine group which is much less electron rich. This is in contrast to the catalysts developed from d⁰ early-transition-metals, where increasing the electron withdrawing ability of the ligands leads to increased turnover numbers. It appears that the d⁶ Ru^{II} metal centre requires electron-rich ligands for increased metathesis activity.

It was demonstrated that the substitution of phosphine with stable *N*-heterocyclic carbenes (NHC) produced interesting changes in reactivity.⁵⁵ In 1998, Hermann and co-workers reported a complex in which both phosphines of **2** had been replaced by dialkylimidazolin-2-ylidene ligands, which showed only some activity. Due to the fact that NHC-ligands were less labile than the phosphines and that they showed any activity at all, suggested that they might be interesting ligands.⁵⁵ In order to accelerate the dissociation step of the phosphine,

Grubbs introduced a cyclic bis-amino-carbene ligand (imidazolylidene).³ These ligands are excellent σ -donors without π -acceptor properties, which increase the electron density at the ruthenium centre and their *trans* effect labilizes (break) the ruthenium-phosphine bond, favouring phosphine dissociation. Imidazolylidene is also sterically more bulky and more electron donating than dialkylimidazolin-2-ylidene, which was the missing ingredient for the production of a more active catalyst.²⁵ This was the birth of the Grubbs second generation catalyst (**2**) and its catalytic activity in cross-metathesis (CM) and ring-closing metathesis (RCM) reactions were successively proposed within a few months by the groups of Nolan, Fürstner⁷¹ and Grubbs.^{48, 72}

The development of *N*-heterocyclic carbenes (NHC) as ligands for ruthenium closed the gap between the molybdenum and ruthenium systems.⁷³ This new catalyst is more active and thermally more stable.^{3, 74} This is attributed to the high selectivity of the 14 electron active species to coordinate alkenes compared to the phosphine analogue.^{12, 75-77} In comparison to the corresponding phosphane complexes, NHC-ligands have a high dissociation energy, which shows promise for chiral modifications and catalyst immobilisation.⁷⁸

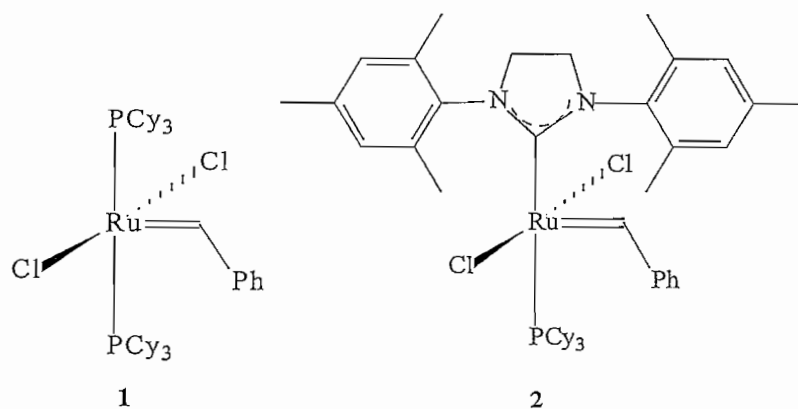


Figure 2.3: The commercially available Grubbs catalysts

The introduction of a chelating carbene ligand on **2** by Hoveyda *et al.*¹² has increased the stability towards air and moisture even more. The Hoveyda-Grubbs first generation catalyst (**3**) is derived from Grubbs first generation catalysts (**1**). It bears only one phosphine and one of the phosphine ligands is replaced by an isopropoxy group attached to the benzene ring. With the introduction of the isopropoxy group, it made it possible to recycle catalyst **3** and eliminate excessive catalytic activity loss by stabilisation of the active species in

RCM.⁷³ Despite the stability of this complex isolation from the substrate is problematic, the Ru-carbene **1** is substantially more reactive and it is mainly efficient for substrates that contain terminal alkenes.⁷⁵

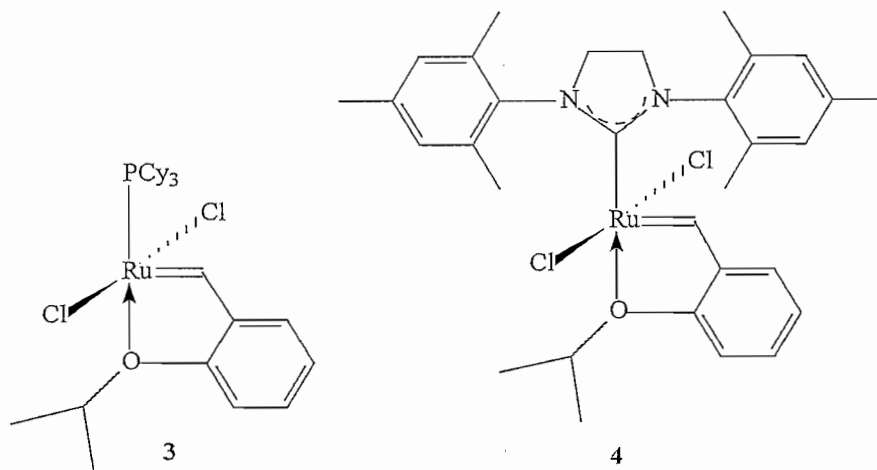


Figure 2.4: The commercially available Hoveyda-Grubbs catalysts

In 2000 two independent research groups both synthesized a catalyst containing one NHC ligand instead of the phosphine ligand.^{75, 76} This is known as the Hoveyda-Grubbs second generation catalyst (**4**). Catalysts bearing NHC-ligands leads to higher activity and thermal stability,⁷⁹ enabling the preparation of R-functionalized (functionalized aliphatic alkenes) di-, tri-, and tetra-substituted olefins.^{80, 81} Both **3** and **4** are now commercially available, although expensive. While the *N*-heterocyclic carbene (NHC) complexes **2** and **4** exhibit significantly enhanced activity and thermal stability relative to **1**, overall selectivity is often compromised by competing olefin isomerization,¹³ which can lead to the formation of undesirable secondary metathesis products (SMPs).²²

Due to double bond isomerization and subsequent secondary metathesis product formation, the second generation Grubbs catalyst (**2**) exhibit lower selectivities toward desired primary metathesis products.⁸² Further improvement is limited to the steric bulk and electronic properties of this system.²⁵ In an attempt to alleviate these concerns and to improve catalyst life time, Forman and co-workers⁸³ investigated a ruthenium alkylidene complex bearing cyclohexylphoban (“phobcat”) (**24-29**, **Figure 2.5**) as ligands, using Grubbs 1 (**1**), and it shows superior performance in CM and RCM with respect to improved catalyst stability and good selectivity to primary metathesis products, relative to that of the commercial PCy₃-based catalysts.⁸⁴ Up to 2007 there were about 15 different variations of the Grubbs catalyst,

all of which have slightly different features.⁸⁵ The latest, the third generation catalyst replaced one PCy₃ group of **2** with a pyridine group with an additional pyridine ligand to yield a six coordinated catalyst. This catalyst is more reactive, but has not been explored with many reactions.⁸⁶

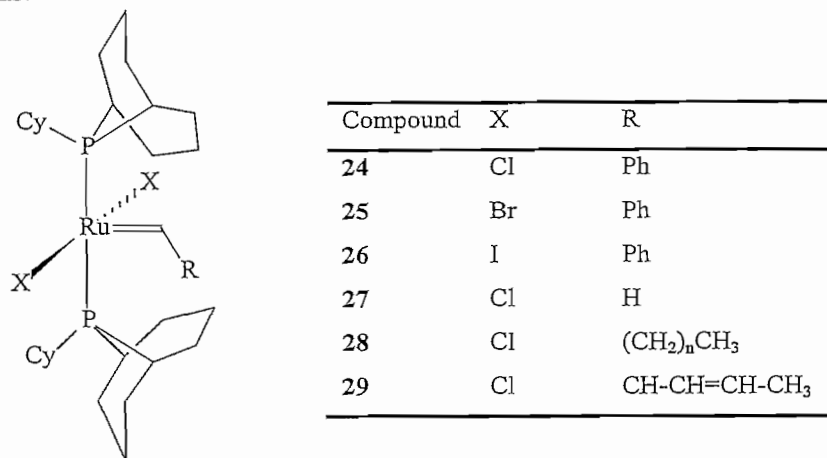


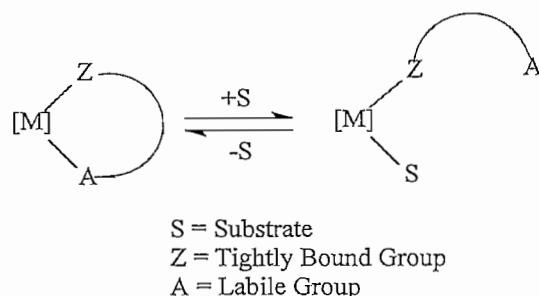
Figure 2.5: The phobcat derived catalysts

The quest for the search for more stable and more reactive catalysts is far from over. This is what inspires so many researchers to investigate ligands for the use in olefin metathesis, as can be seen from the previous example. In the following section, hemilability and only a few N-O chelating ligands will be discussed. It would be a daunting task to just even list all the different types of ligands synthesized up to this point, since practically every day a new paper is published which discuss olefin metathesis.

2.5. Hemilabile Ligands

Through the introduction of NHC ligands it was possible to achieve higher activities, compared to the original biphosphine systems.^{87, 88} Mechanistic and theoretical studies, showed that it was possible to further improve reaction rates, through combination of strongly binding NHC ligand and a labile ligand such as phosphines (in the case of Grubbs **2**),^{71, 78, 89} pyridine⁹⁰ (which is a Schiff base) or easy dissociating metal fragments. A concept that has been pursued in this context is the use of the so-called “on-demand-open-site” ligands or hemilabile ligands.⁹¹ These ligands are presumed to act as chelating ligands at room temperature and to open up one coordination site at elevated temperatures.⁹²

Recently this new class of chelated ligands has become a popular topic of research due to their ability to place two or more donor atoms with distinct electronic properties close to the metal atom. Such ligands possess different types of bonding groups (Z and A) where the labile group (A) can be displaced from the metal centre, although remaining available for recoordination (**Scheme 2.3**)²⁰ By releasing a free coordination site (the so-called “on-demand-open-site”) for an incoming nucleophile, hemilabile ligands have the ability to increase the thermal stability and activity of a catalytic system,²² by stabilization of the transition metal centre.²³



Scheme 2.3: The concept of hemilability²⁰

The term hemilabile can be divided into the prefix “hemi” meaning half or semi and “labile” meaning relatively unstable and transient chemical species or a relatively stable but reactive species or constantly undergoing change or something that is likely to undergo change. The first hemilabile ligand, *o*-(diphenylphosphino) anisole (**30**, **Figure 2.6**), was described in 1979 by Jeffrey and co-workers.¹⁹ Many studies have concentrated on the use of phosphorus/oxygen (P[^]O) ligands, including ketophosphines, phosphinoalcohols, phosphino-carboxylates and phosphine ethers.⁹³⁻¹⁰⁰ Other studies have shown that combination of other hard and soft atoms also show potential for hemilabile ligands such as nitrogen/phosphorus (N[^]P),^{101, 102} sulphur/phosphorus (S[^]P),¹⁰³ sulphur/oxygen (S[^]O),⁹¹ oxygen/oxygen (O[^]O),¹⁰⁴ phosphorus/halide (P[^]X) (X = halide), nitrogen/oxygen (N[^]O)¹³ and many other innovative approaches have been explored.^{105, 106} In this study nitrogen and oxygen containing ligands will be modelled and synthesized, for this reason only these ligands will be discussed.

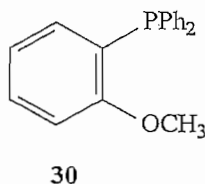


Figure 2.6: The first hemilabile ligand, *o*-(diphenylphosphino) anisole

Examples of N⁺O systems have been published by Grubbs,⁸ Allaert,⁴⁹ and De Clercq^{21, 107} that use chelating Schiff bases combined with alkylphosphine ligands (**31-41** with Grubbs 1 as parent molecule) and Schiff base ligands combined with NHC-ligands (**Figure 2.7, 42-45** with Grubbs 2 as parent molecule).

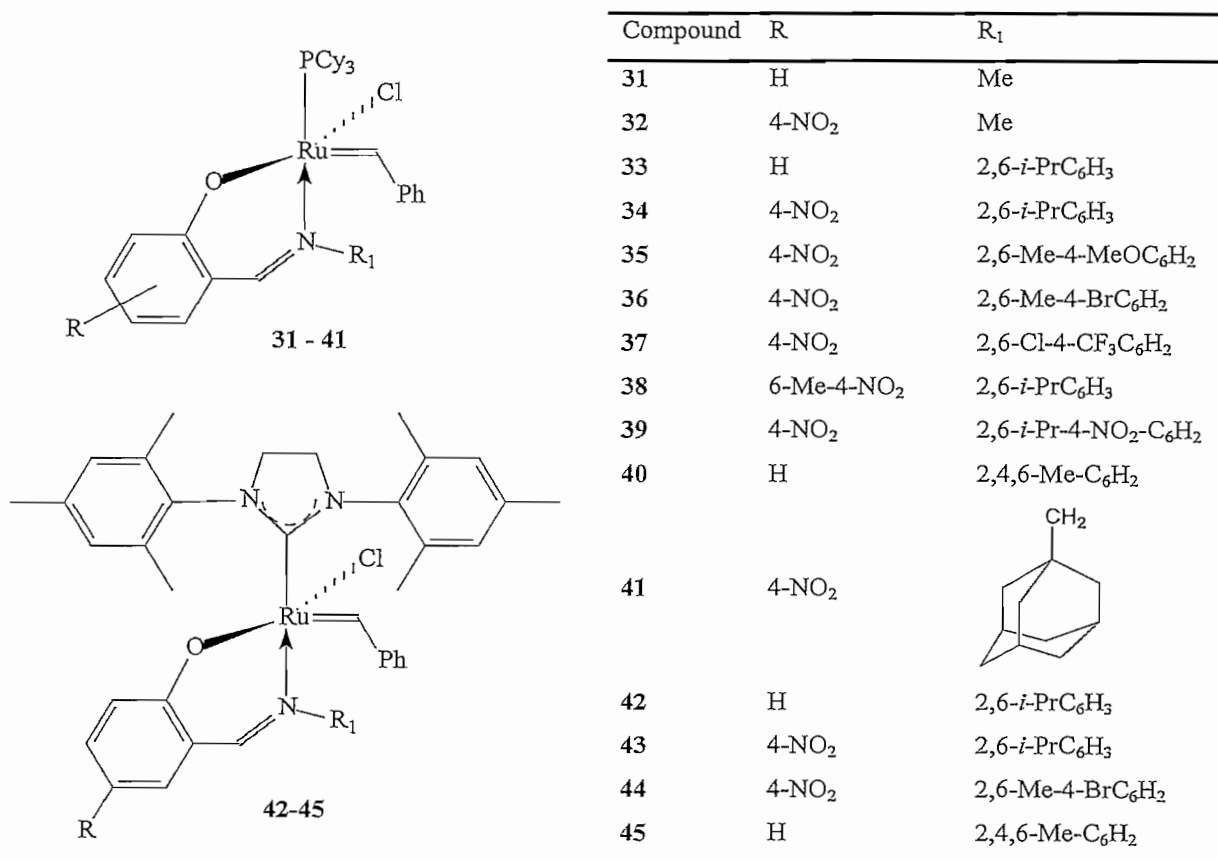


Figure 2.7: Some of the Schiff base complexes synthesized

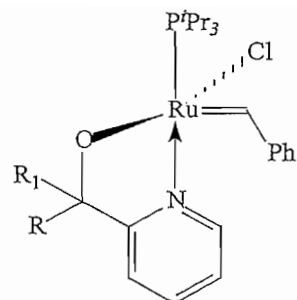
The use of bidentate Schiff-base ligands in organometallic chemistry has been extensive, because:

- i. they are easy to prepare,
- ii. they exert easily varied (or fine tuned) steric and/or electronic effects by the proper selection of bulky and/or electron withdrawing or donating substituents incorporated into the Schiff bases and
- iii. the two donor atoms, N and O, employ two opposite electronic effects: the phenolate oxygen is a hard donor known to stabilize the higher oxidation state of the ruthenium

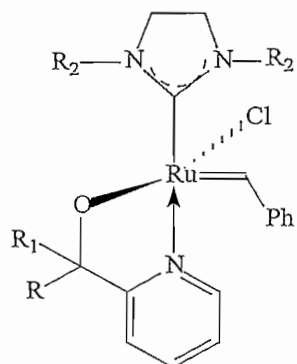
atom whereas the imine nitrogen is a softer donor and will stabilize the lower oxidation state of the ruthenium.²⁸

The development of N[^]O ligands was due to the increased interest in chiral catalysts and catalysts which can control *cis/trans* selectivity.⁸ It was found that the incorporation of a sterically hindered ligand of this type increased the stability, activity and selectivity of Grubbs type complexes and increasing the electron density of the complex can influence the stability of a complex and therefore the catalytic performance.^{21, 22, 24} Ruthenium complexes containing Schiff base ligands have been used in as much different reactions as olefin metathesis itself.^{53, 108-111} These complexes show improved thermal stability and high activity even in protic solvents.⁸ Schiff base substituted catalysts are less active than their phosphine analogues at lower temperatures,¹¹² but at elevated temperatures the energy of coordinated complexes increases; leading to a marginal favouring of the decoordinated form and consequently increasing activity.⁴⁹

Another N[^]O chelating ligand group that shows promise is the pyridinyl alcoholate ligands (46-51, **Figure 2.8**), synthesized by Hermann and co-workers, which have numerous advantages such as they are also easily accessible and it is possible to transfer chiral information to the metal centre by the quaternary carbon atom.¹¹³ At elevated temperatures these ligands can be compared to highly active mixed-substituted NHC phosphine systems, such as Grubbs 2.⁹²



46 - 47

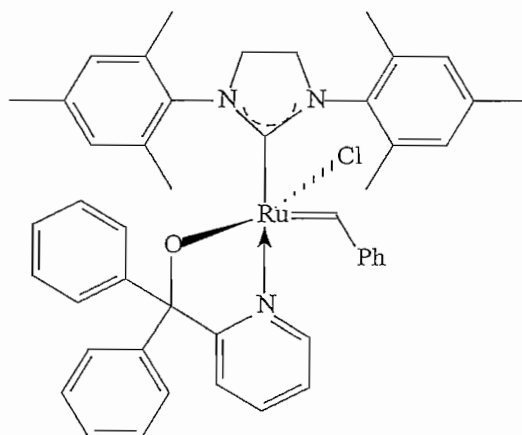


48 - 51

Compound	R	R ₁	R ₂
46	Me	Me	-
47	(CH ₂) ₅	(CH ₂) ₅	-
48	Me	Me	Cy
49	(CH ₂) ₅	(CH ₂) ₅	Cy
50	Me	Me	CH ₂ CH ₂ Ph
51	(CH ₂) ₅	(CH ₂) ₅	CH ₂ CH ₂ Ph

Figure 2.8: Pyridinyl alcoholate complexes synthesized

In 2007 Jordaan¹¹⁴ *et al.* synthesized a number of pyridinyl alcoholate ligands, of which the so called “Puk-Grubbs 2 pre-catalyst” (**52**), showed the most potential with regard to increased lifetime, stability, activity and selectivity during the metathesis of 1-octene.



52

Figure 2.9: Puk-Grubbs 2 pre-catalyst

Continuing on Jordaan’s work, Huijsmans *et al.*²⁶ in 2009 modelled over 200 different pyridinyl alcoholate ligands for their ability to be hemilabile ligands. Of these ligands, those

which showed the most promise from the preliminary results were chosen to be synthesized. Of the five that were chosen, three showed improvement in stability and the overall turnover number (**53-55**, **Figure 2.10**), as well as increased activity at elevated temperatures in comparison with **52**, at the cost of selectivity.

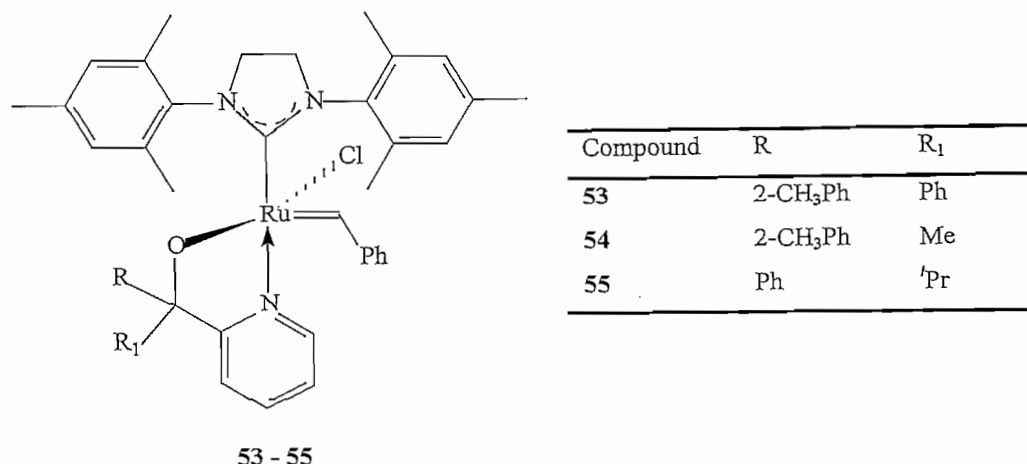


Figure 2.10: Three Grubbs-type pre-catalysts synthesized by Huijsmans²⁶

Attempts of Huijsmans²⁶ to synthesize two complexes containing bulky alicyclic ligands unfortunately failed (**56** and **57**). This was ascribed to the fact that according to modelling these ligands acts as monodentate ligands which does not stabilize the metal centre which results in decomposition. Although this might be true and can certainly play a role, it was shown by Dinger²⁵ and De Clercq²¹ that ligands containing too much steric bulk can be detrimental to the catalytic performance, despite the fact that in the case of Dinger's pre-catalyst (**58**) the 2,4,6-trimethyl group on the NHC of **2** was replaced by adamantane, it was too bulky for the catalyst to be synthesized. Given that NHC ligands have a greater steric demand in contrast to PCy₃ and taking into consideration the observations of Dinger and De Clercq, it can be concluded that both **56** and **57** could not be synthesized on the basis of steric hindrance rather than on account of the ligands being monodentate.

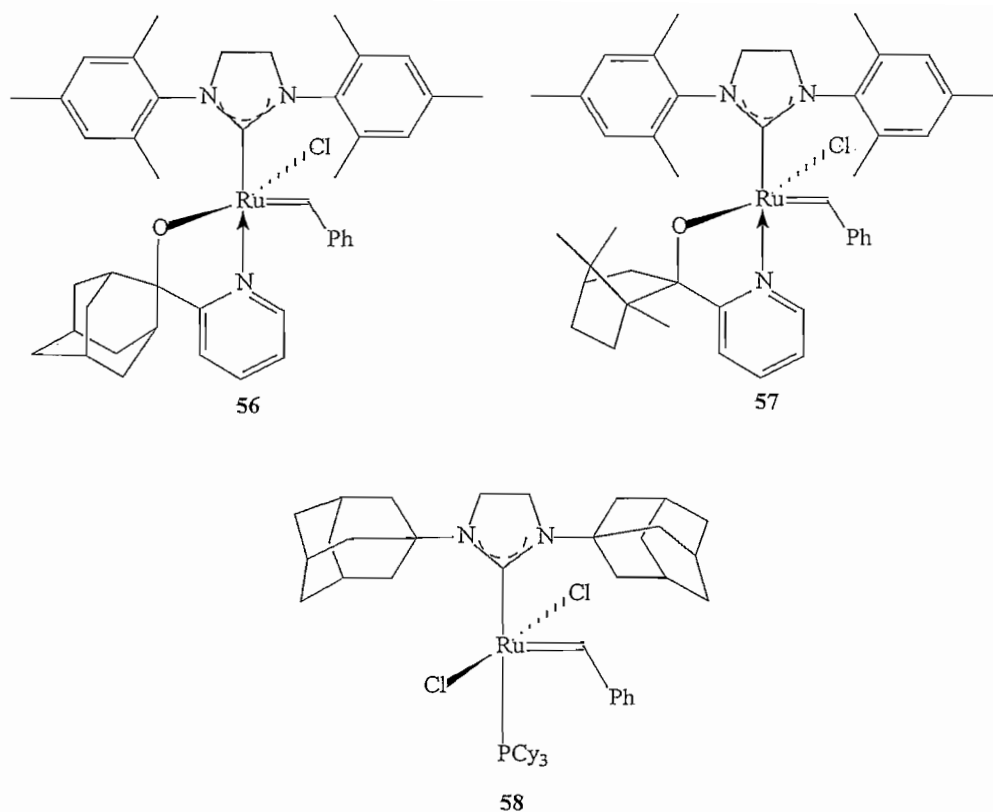


Figure 2.11: Potential alicyclic pre-catalysts

There are several complexes that are homobimetallic, but only a handful of these are Grubbs-type catalytic systems. De Clercq²⁷ and Drozdak²⁸ reported several of these complexes (**59-64**, **Figure 2.12**) for the use in atom transfer radical addition and polymerization, as well as RCM and ROMP. These complexes showed excellent activity and were quite robust.

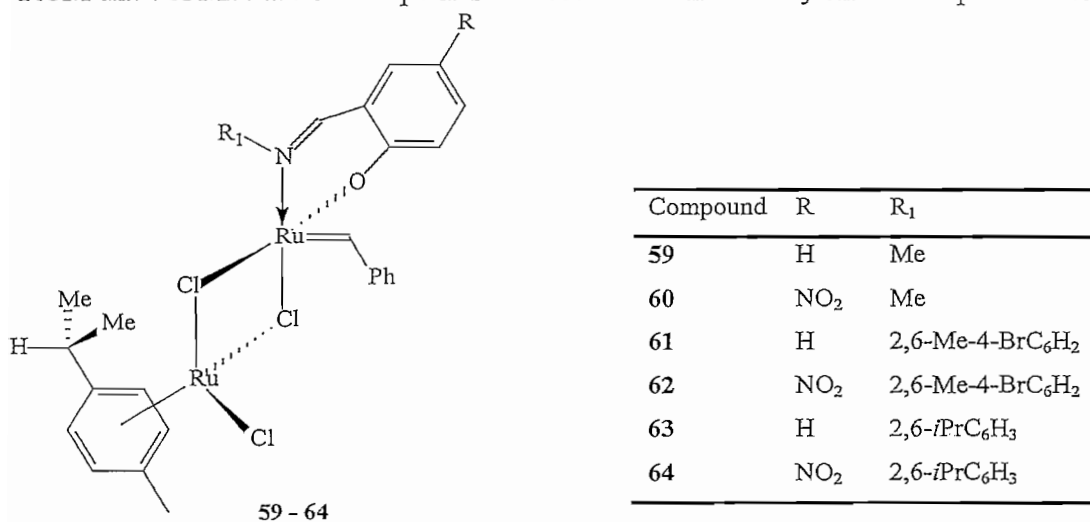


Figure 2.12: Homobimetallic complexes

2.6. Alicyclic Compounds

The word alicyclic is a collective of aliphatic and cyclic, i.e. a compound that consists of cyclic rings fused together, but has aliphatic reactivity. These compounds have been the subject of various interesting investigations over the past few decades.³⁰ With the exception of adamantane, most saturated alicyclic cage molecules contain considerable strain energy as evidenced by the fact that they:

- i. contain unusually long framework carbon-carbon σ -bonds,
- ii. contain unusual C-C-C bond angles that deviate significantly from 109.5° ,
- iii. possess unusually negative heats of combustion, and
- iv. possess unusually positive heats of formation when compared with nonstrained systems.³¹

These properties contribute to the unusual chemical reactivity and exceptional thermal stability²⁹ of these so-called “cage” or “bird-cage” compounds.

As already mentioned in Chapter 1, **12** can undergo further Diels-Alder reactions.⁴¹ Pandey and Coxon have shown that **12** can react exclusively either from the cyclobutane face or from the ketone face of the diene, depending on the nature of dienophiles.¹¹⁵ In 1987 Coxon *et al.*⁴¹ showed that due to the steric bulk of the *p*-benzoquinone, it reacts exclusively on the carbonyl face (Figure 2.13) to produce a new Diels-Alder adduct, that after UV irradiation produces a tetrone.⁴²

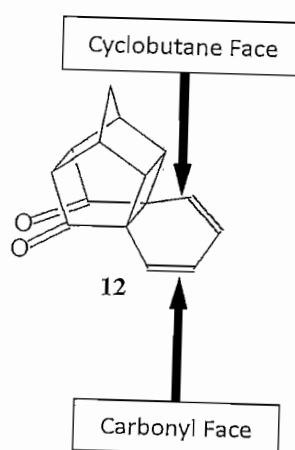


Figure 2.13: π -Facial selectivity of **12**

The Diels-Alder reaction is an intramolecular asymmetric, hetero and inverse electron demand reaction which is a highly useful synthetically reaction.¹¹⁶ This transannular cyclization reaction of appropriately functionalized molecules often provide a convenient method for preparation of heterocage compounds which are otherwise difficult to obtain.¹¹⁷ Diels-Alder reactions, a $[2 + 4\pi]$ -cycloaddition reaction,¹¹⁸ are among the most versatile and synthetically useful reactions in which four new contiguous stereogenic centers can be generated in a single laboratory operation.¹¹⁹ The synthesis of **12** is an inexpensive and rather simple procedure.⁴⁰ **12** has received considerable attention as a substrate for investigation of the factors which determined π -facial selectivity in Diels-Alder reactions.^{120, 121}

In this study alicyclic Grubbs-type pre-catalysts will be synthesized with **9** and **10** as starting material. Although there are several molybdenum¹²² and platinum¹²³ based alicyclic ligands (**65** and **66**) reported in literature, there is only one alicyclic ruthenium based pre-catalyst (**67**), reported by Dinger,²⁵ which could be successfully synthesized. Sadly this complex showed only limited activity in olefin metathesis due to immense sterical hindrance. As with **2**, the fact that this pre-catalyst showed any activity at all is worth noting and for this reason it is worth investigation.

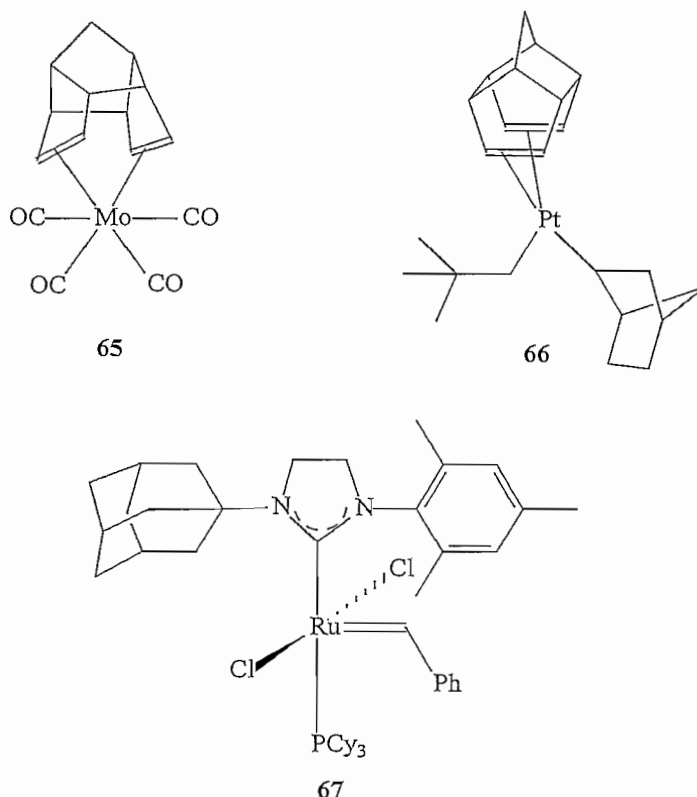


Figure 2.14: Literature catalysts containing alicyclic ligands

2.7. Molecular Modelling

The theoretical methods and computational techniques to model or mimic the behaviour of molecules are known collectively as molecular modelling. Molecular modelling is used in the fields of computational chemistry, computational biology and materials science for studying molecular systems. Computational chemistry is a branch of chemistry that uses computers to assist in solving chemical problems. It uses the results of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures and properties of molecules and solids. The term theoretical chemistry may be defined as a mathematical description of chemistry, whereas computational chemistry is usually used when a mathematical method is developed to a point where it can be automated for implementation on a computer.¹²⁴

Over the last decade considerable progress has been made in the computational chemistry field, which now allows for the calculation, at the full quantum mechanical level, of realistic structures of both homogeneous and heterogeneous catalysts.¹²⁵ This can be attributed to the development and quality improvement in computer hardware, software and theoretical method development. There are currently a variety of different methods available to answer chemical questions utilising computational chemistry such as *ab initio*, density functional theory (DFT), molecular mechanics, semi-empirical and empirical methods. Of these methods, DFT is a very popular method in the study of many electron systems in both chemistry and solid-state physics. The electrons are treated fully quantum mechanically with the nuclei being treated classically in most current programmes. The attractiveness of DFT in the study of chemical reactions lies in the fact that a chemical reaction inherently involves atoms moving, and the wave function changes upon reaction.¹²⁵ Unfortunately this method is a demanding method in terms of computational power, but with the advent of faster and better computers this obstacle is readily overcome.

DFT has become the method of choice for first principles quantum chemical calculations of the electronic structure and properties of many molecular and solid systems.¹²⁶ With the exact exchange correlation functional, DFT could take into account all complex many-body effects (three or more interactions). The generalized gradient approximation (GGA) includes the first-order gradient of the density. GGA significantly reduce the over-binding tendency of the

local density approximation (LDA), but generally remain inadequate for thermochemistry of molecules.¹²⁷

With reference to work done by Jordaan¹¹⁴ and Huijsmans²⁶, it was decided that all equilibrium geometry optimizations will be performed with the DMol³ DFT code^{128, 129} as implemented in the Materials Studio (Version 4.2) program package of Accelrys®, since it usually gives realistic geometries, relative energies and vibrational frequencies for transition metal compounds. The nonlocal generalized gradient approximation (GGA) exchange correlation functional by Perdew and Wang (PW91) will also be used for all calculations. DMol³ utilizes a basis set of numeric atomic functions, which are exact solutions of the Kohn-Sham equations for the atoms. These basis sets are generally more complete than a comparable set of linearly independent Gaussian functions and have been demonstrated to have small basis set superposition errors.¹³⁰ In this study a polarized split valence basis set, termed double numeric polarized (DNP) basis set will be used. All geometry optimisations employed highly efficient delocalised internal coordinates. The use of delocalized coordinates significantly reduces the number of geometry optimisation iterations needed to optimise larger molecules compared to the use of traditional Cartesian coordinates.¹¹⁴

Chapter 3: Results and Discussion

3.1. Introduction

As mentioned in Chapter 1, alicyclic compounds with the ability to incorporate two metals are promising substrates for the development of a new series of homobimetallic catalysts. In this chapter the results obtained in this study will be summarized after which it will be discussed. This chapter will be divided into two main divisions: Molecular Modelling and Experimental Results. The former will deal with the molecular modelling of the ligands and the pre-catalysts, while the latter will shed light on the experimental observations, problems encountered and mechanisms of some of the reactions with the aid of molecular modelling. This section will have the same layout as the experimental Chapter 5.

3.2. Molecular Modelling

3.2.1. Method Validation

In recent years a number of papers have been published concerning molecular modelling of Grubbs-type pre-catalysts that specifically used Materials Studio.^{14, 131, 132} As already mentioned in Chapter 2, it was decided that all geometry optimizations will be performed with the DMol³ module based DFT code^{128, 129} as implemented in the Materials Studio (Version 4.2) program package of Accelrys®. The GGA/DNP/PW91 functional will be used for all calculations. From the above mentioned papers^{14, 131, 132} it was found that this method is reliable for catalytic systems. In this study the same method will be used to model the ligands and the calculated results will also be used to explain some of the experimental observations. For this reason the method must be validated for organic compounds, specifically alicyclic cage compounds (68-71) similar to that used in this study. This can be done by the optimization of the geometry of these compounds and comparing the bond lengths and angles with crystallographic data.

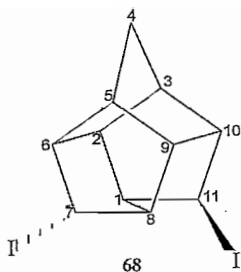


Figure 3.1: Structure of *syn*-4,*syn*-7-diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**68**)¹³³

Table 3.1: The calculated and experimental (crystallographic data) bond lengths (Å) for **68**

Bond	Calculated	Experimental	Difference
C1-C2	1.58	1.56	0.02
C2-C3	1.58		
C3-C4	1.53		
C4-C5	1.53	1.52	0.01
C5-C6	1.55	1.51	0.03
C6-C7	1.58	1.53	0.05
C7-C8	1.54	1.53	0.01
C8-C9	1.58	1.57	0.01
C9-C10	1.58		
C10-C11	1.52		
C1-C11	1.52		
C1-C8	1.54	1.53	0.01
C5-C9	1.58	1.56	0.02
C3-C10	1.55		
C2-C6	1.58	1.56	0.02
C7-I	2.22	2.15	0.07
Average			0.03

Table 3.2: The theoretical and experimental angles (deg) for **68**

Angle	Calculated	Experimental	Difference
C11-C1-C2	103	103	0.0
C8-C1-C2	99	100	1.2
C8-C1-C11	104	102	2.1
C1-C2-C3	104	104	0.0
C1-C2-C6	104	104	0.0
C3-C2-C6	104	103	0.5
C2-C3-C10	99	101	2.3
C4-C3-C10	103	103	0.3
C2-C3-C4	106	106	0.5
C3-C4-C5	95	93	1.6
C5-C6-C7	101	100	0.9
C9-C10-C3	99	99	0.1
C9-C10-C11	106	106	0.0
C1-C11-C10	96	96	0.0
I-C11-C10	115	115	0.0
I-C11-C10	115	116	1.1
Average			0.67

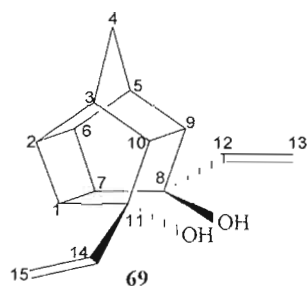


Figure 3.2: Structure of *exo-exo*-8,11-divinyl pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-*endo,endo*-8,11-diol (**69**)¹³⁴

Table 3.3: The calculated and experimental (crystallographic data) bond lengths (Å) for **69**

Bond	Calculated	Experimental	Difference
C1-C2	1.57	1.57	0.00
C2-C3	1.56	1.57	0.01
C3-C4	1.53	1.53	0.00
C4-C5	1.53	1.54	0.01
C5-C6	1.56	1.54	0.02
C6-C7	1.56	1.53	0.03
C7-C8	1.54	1.53	0.01
C8-C9	1.57	1.53	0.04
C9-C10	1.60	1.60	0.00
C10-C11	1.55	1.56	0.01
C1-C11	1.53	1.56	0.03
C1-C7	1.58	1.56	0.02
C5-C9	1.55	1.52	0.03
C3-C10	1.56	1.55	0.01
C2-C6	1.56	1.54	0.02
C8-O	1.42	1.45	0.03
C11-C14	1.51	1.50	0.01
C14-C15	1.33	1.28	0.05
C11-O	1.46	1.45	0.01
C8-C12	1.51	1.45	0.06
C12-C13	1.33	1.24	0.09
Average			0.03

Table 3.4: The calculated and experimental (crystallographic data) angles (deg) 69

Angle	Calculated	Experimental	Difference
C2-C1-C7	89.7	90.0	0.3
C7-C1-C11	116.1	112.5	3.6
C1-C2-C6	90.3	90.4	0.1
C2-C3-C4	103.7	104.4	0.7
C4-C3-C10	104.7	104.9	0.2
C4-C5-C6	103.6	103.0	0.6
C6-C5-C9	100.0	99.6	0.4
C2-C6-C7	90.5	90.4	0.1
C1-C7-C6	89.6	89.0	0.6
C6-C7-C8	103.8	100.7	3.1
O-C8-C9	116.7	112.4	4.3
C7-C8-C9	98.6	100.1	1.5
C9-C8-C12	109.1	111.0	1.9
C5-C9-C10	102.0	101.8	0.2
C3-C10-C9	102.4	101.8	0.6
C9-C10-C11	115.5	114.0	1.5
O-C11-C10	116.3	114.3	2.0
C1-C11-C10	100.5	100.7	0.2
C10-C11-C14	110.4	109.4	1.0
C11-C14-C15	127.6	131.0	3.4
C2-C1-C11	102.6	101.7	0.9
C1-C2-C3	107.4	110.3	2.9
C3-C2-C6	102.9	101.9	1.0
C2-C3-C10	99.9	98.8	1.1
C3-C4-C5	95.3	96.4	1.1
C4-C5-C9	105.2	105.4	0.2
C2-C6-C5	102.9	103.7	0.8
C5-C6-C7	107.4	108.5	1.1
C1-C7-C8	115.9	118.8	2.9
O-C8-C7	117.4	115.8	1.6
O-C8-C12	102.8	104.9	2.1
C7-C8-C12	112.5	117.4	4.9
C5-C9-C8	101.9	100.0	1.9
C8-C9-C10	114.9	116.6	1.7
C3-C10-C11	100.5	101.7	1.2
O-C11-C1	112.0	113.0	1.0
O-C11-C14	105.0	104.9	0.1
C1-C11-C14	113.6	112.3	1.3
C8-C12-C13	128.0	127.7	0.3
Average			1.40

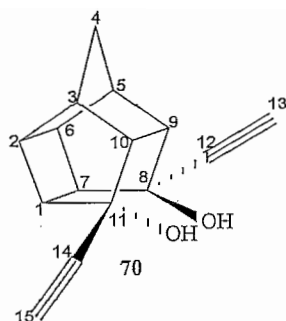


Figure 3.3: Structure of *exo-exo*-8,11-bis(ethynyl)-pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-*endo,endo*-8,11-diol (**70**)¹³⁴

Table 3.5: The calculated and experimental (crystallographic data) bond lengths (Å) for **70**

Bond	Calculated	Experimental	Difference
C1-C2	1.56	1.54	0.02
C2-C3	1.56	1.55	0.02
C3-C4	1.53	1.52	0.01
C4-C5	1.53	1.51	0.01
C5-C6	1.56	1.55	0.01
C6-C7	1.56	1.55	0.01
C7-C8	1.54	1.54	0.00
C8-C9	1.56	1.54	0.03
C9-C10	1.59	1.58	0.01
C10-C11	1.56	1.54	0.02
C1-C11	1.54	1.53	0.01
C1-C7	1.57	1.56	0.02
C5-C9	1.56	1.54	0.02
C3-C10	1.56	1.53	0.03
C2-C6	1.56	1.54	0.03
O-C8	1.43	1.43	0.00
C11-C12	1.47	1.48	0.00
C12-C13	1.21	1.17	0.04
O-C11	1.43	1.42	0.01
C8-C14	1.47	1.48	0.01
C14-C15	1.21	1.17	0.05
Average			0.02

Table 3.6: The calculated and experimental (crystallographic data) angles (deg) for **70**

Angle	Calculated	Experimental	Difference
C2-C1-C7	89.8	89.6	0.2
C7-C1-C11	116.0	115.0	1.0
C1-C2-C6	90.2	90.8	0.6
C2-C3-C4	103.6	104.2	0.6
C4-C3-C10	104.9	104.7	0.2
C4-C5-C6	103.6	103.9	0.3
C6-C5-C9	100.2	99.8	0.4
C2-C6-C7	90.2	89.9	0.3
C1-C7-C6	89.8	89.8	0.0
C6-C7-C8	103.1	102.3	0.8
O-C8-C9	117.8	111.7	6.1
C7-C8-C9	99.2	99.5	0.3
C9-C8-C14	109.2	111.8	2.6
C5-C9-C10	102.3	102.3	0.0
C3-C10-C9	102.3	102.1	0.2
C9-C10-C11	115.3	115.0	0.3
O-C11-C10	117.8	115.4	2.4
C1-C11-C10	99.2	99.5	0.3
C10-C11-C12	109.2	110.3	1.1
C11-C12-C13	175.8	178.3	2.5
C2-C1-C11	103.1	103.1	0.0
C1-C2-C3	107.6	107.6	0.0
C3-C2-C6	102.8	102.7	0.1
C2-C3-C10	100.2	100.3	0.1
C3-C4-C5	95.2	94.8	0.4
C4-C5-C9	104.9	104.7	0.2
C2-C6-C5	102.8	103.2	0.4
C5-C6-C7	107.6	108.0	0.4
C1-C7-C8	116.0	116.0	0.0
O-C8-C7	113.4	118.7	5.3
O-C8-C14	107.5	107.4	0.1
C7-C8-C14	109.4	107.6	1.8
C5-C9-C8	101.0	101.8	0.8
C8-C9-C10	115.3	114.8	0.5
C3-C10-C11	101.0	101.6	0.6
O-C11-C1	113.4	116.8	3.4
O-C11-C12	107.5	105.2	2.3
C1-C11-C12	99.2	109.7	10.5
C8-C14-C15	175.8	175.2	0.6
Average			1.22

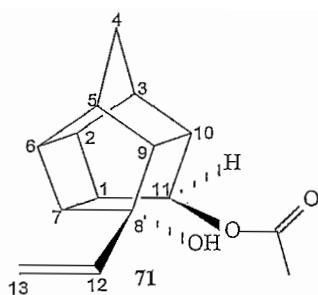


Figure 3.4: Structure of *endo*-11-acetoxy-*exo*-8-vinylpentacyclopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-*endo*-8-ol (**71**)¹³⁴

Table 3.7: The calculated and experimental (crystallographic data) bond lengths (Å) for **71**

Bond	Calculated	Experimental	Difference
C1-C2	1.57	1.54	0.03
C2-C3	1.55	1.55	0.00
C3-C4	1.53	1.51	0.02
C4-C5	1.53	1.52	0.01
C5-C6	1.56	1.55	0.01
C6-C7	1.56	1.55	0.02
C7-C8	1.53	1.53	0.00
C8-C9	1.55	1.54	0.01
C9-C10	1.59	1.58	0.01
C10-C11	1.54	1.51	0.03
C1-C11	1.52	1.51	0.02
C1-C7	1.57	1.56	0.01
C5-C9	1.56	1.53	0.03
C3-C10	1.56	1.54	0.02
C2-C6	1.56	1.54	0.03
O-C8	1.44	1.43	0.00
O-C12 (S)	1.36	1.35	0.01
C12-C13	1.50	1.48	0.03
O-C11	1.44	1.46	0.02
O=C12 (D)	1.22	1.19	0.03
C8-C14	1.52	1.51	0.01
C14-C15	1.33	1.29	0.05
Average			0.02

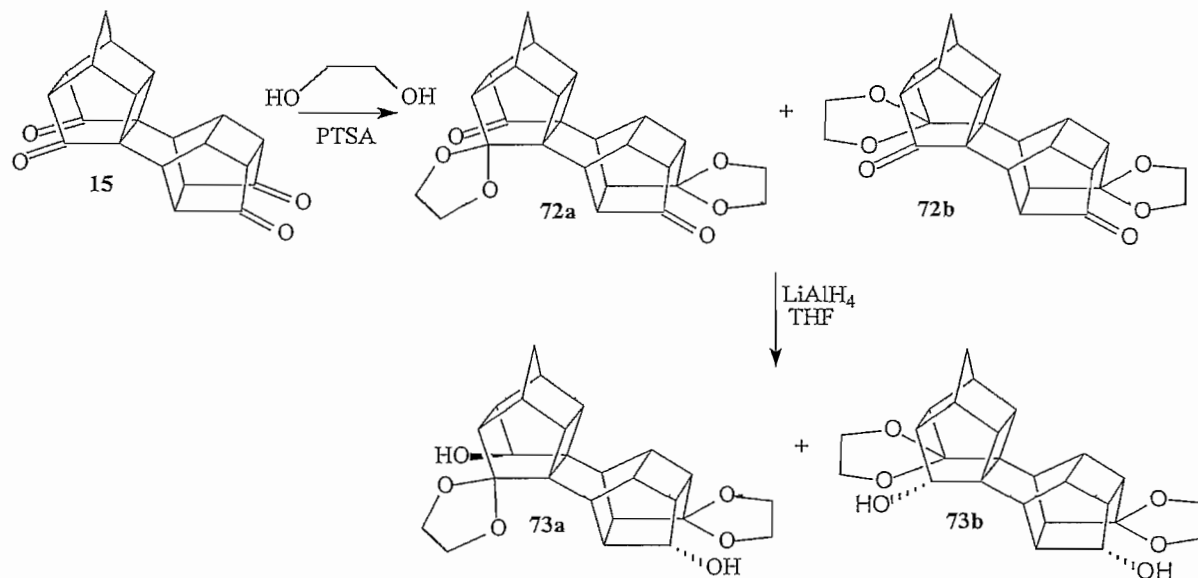
Table 3.8: The calculated and experimental (crystallographic data) angles (deg) for **71**

Angle	Calculated	Experimental	Difference
C11-O-C12	115.5	117.3	1.8
C2-C1-C11	101.0	101.7	0.7
C1-C2-C3	107.5	107.1	0.4
C3-C2-C6	102.8	102.9	0.1
C2-C3-C10	109.3	100.0	9.3
C3-C4-C5	95.2	95.0	0.2
C4-C5-C9	104.8	105.4	0.6
C2-C6-C5	102.9	102.9	0.0
C5-C6-C7	107.5	107.4	0.1
C1-C7-C8	115.2	115.5	0.3
O-C8-C7	111.3	116.8	5.5
O-C8-C14	106.7	102.9	3.8
C7-C8-C14	113.1	112.7	0.4
C5-C9-C8	101.5	102.0	0.5
C8-C9-C10	114.7	114.7	0.0
C3-C10-C11	98.9	99.4	0.5
O-C11-C1	114.6	115.8	1.2
C1-C11-C10	101.5	101.4	0.1
O-C12-C13	110.5	112.0	1.5
C8-C14-C15	127.9	128.7	0.8
C2-C1-C7	89.7	89.7	0.0
C7-C1-C11	116.6	116.1	0.5
C1-C2-C6	90.2	90.6	0.4
C2-C3-C4	103.6	103.4	0.2
C4-C3-C10	104.8	105.1	0.3
C4-C5-C6	103.7	103.4	0.3
C6-C5-C9	100.0	100.3	0.3
C2-C6-C7	90.2	90.4	0.2
C1-C7-C6	89.9	89.4	0.5
C6-C7-C8	103.5	103.2	0.3
O-C8-C9	116.2	115.8	0.4
C7-C8-C9	99.7	99.1	0.6
C9-C8-C14	109.9	109.7	0.2
C5-C9-C10	102.6	102.3	0.3
C3-C10-C9	102.2	102.2	0.0
C9-C10-C11	115.8	116.1	0.3
O-C11-C10	119.3	115.1	4.2
O-C12-O	124.5	122.4	2.1
O-C12-C13	125.0	125.6	0.6
Average			1.02

From these tables it can be seen that the overall average bond lengths differ with 0.02 Å and the overall bond angles differ with 1.08°. Taking these values into account it is clear that this method is suitable for the molecular modelling of alicyclic cage compounds.

3.2.2. Molecular Modelling of Ligands

The addition of ethylene glycol to **15**, forming **72**, is not regioselective (**Scheme 3.1**). This in turn means that the ligands (**16-19**) would also have more than one isomer. For this reason all the possible isomers were modelled in order to evaluate the stability of these isomers. The four ligands, **16-19**, with their respective isomers were modelled using the method described in Chapter 5. The number of isomers was decreased due to the fact that the reduction of **72** to form **73** is stereoselective (**Scheme 3.1**). The one side is blocked by the acetal which leads to an *exo* hydride attack, producing only the *endo* alcohols in **16** and **17**. **Tables 3.9-3.12** summarize the isomers together with their respective electronic energies.



Scheme 3.1: Synthesis and structures of **72** and **73**

The electronic energies obtained with the DFT calculations are very large in chemical terms, since they refer to the energy required to pull the molecule apart including the removal of electrons from the nuclei. This means that the reference for “zero” in the calculation is when the electrons and nuclei are separated in such a manner that they do not interact. For this reason the electronic energies give no indication of their real Gibbs free energies (ΔG). ΔG can only be calculated with a frequency calculation, but this is beyond the scope of this study. The electronic energies are only of value if the difference between the values (ΔE) is taken into account in comparison with a reference compound. For each ligand the reference ligand would be the one with the lowest energy within the same set of ligands. The ligands differ from each other in molecular mass which results in more energy required to separate the

additional atoms and thus only similar compounds can be compared. These values are summarized in the table below.

Table 3.9: Different isomers of **16** and their respective electronic energies

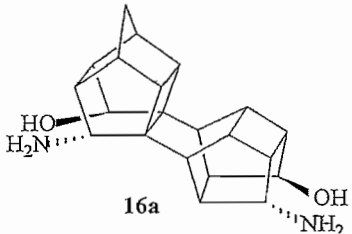
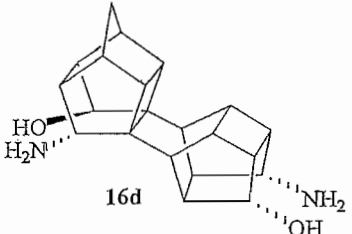
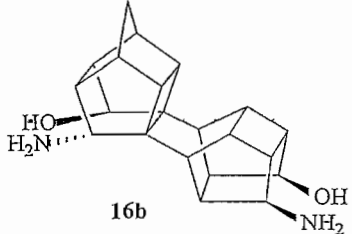
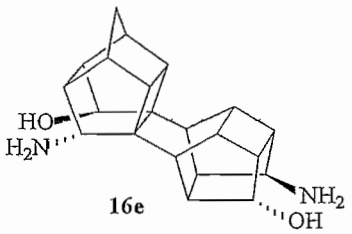
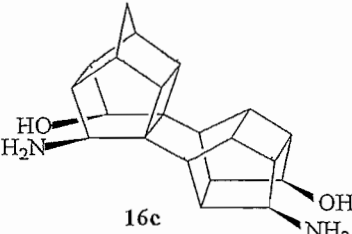
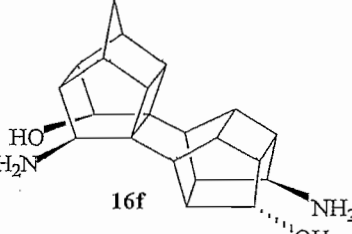
Structure	ΔE (kcal/mol)	Structure	ΔE (kcal/mol)
 16a	0	 16d	0
 16b	0	 16e	0
 16c	6	 16f	6

Table 3.10: Different isomers of **17** and their respective electronic energies

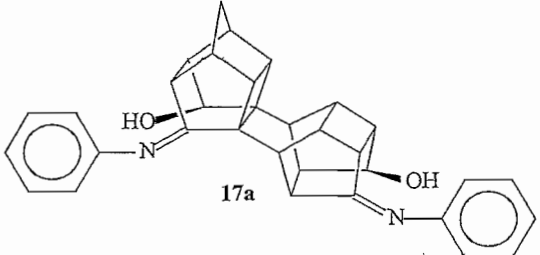
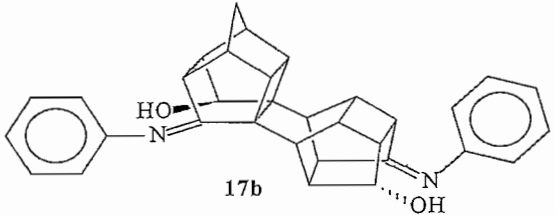
Structure	ΔE (kcal/mol)
 17a	0
 17b	0

Table 3.11: Different isomers of **18** and their respective electronic energies

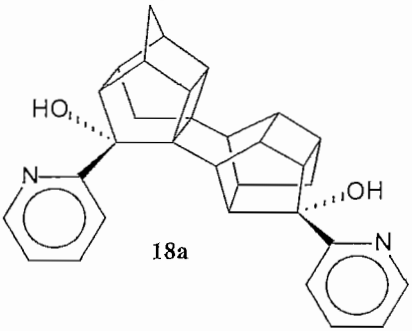
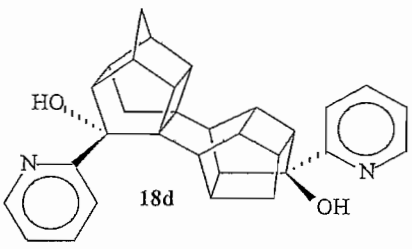
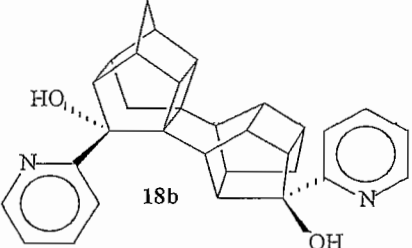
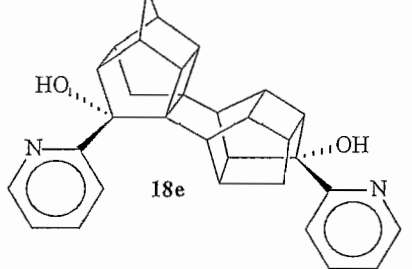
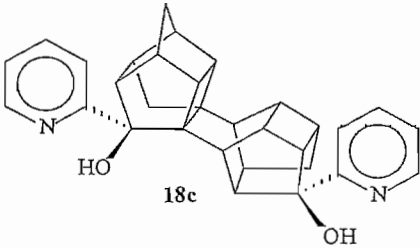
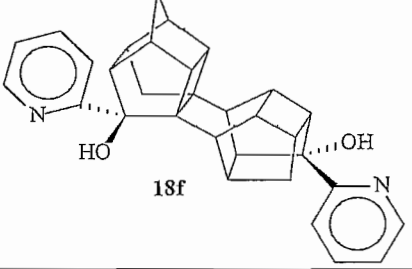
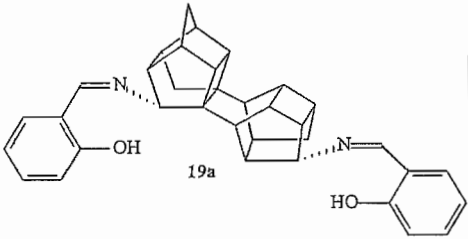
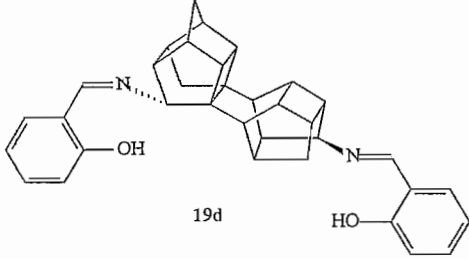
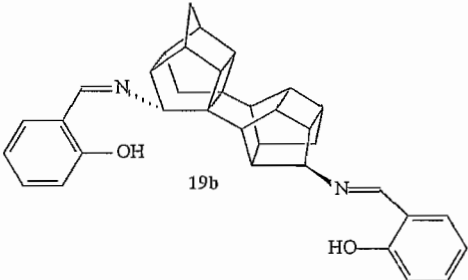
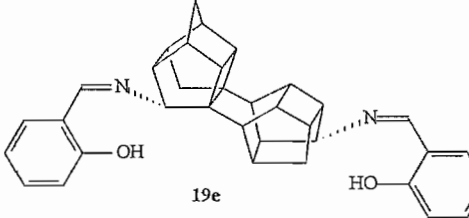
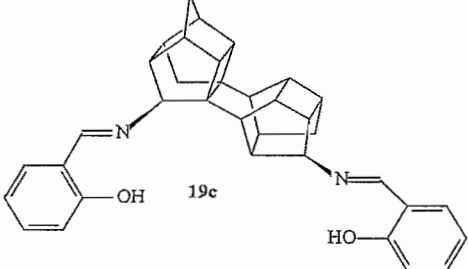
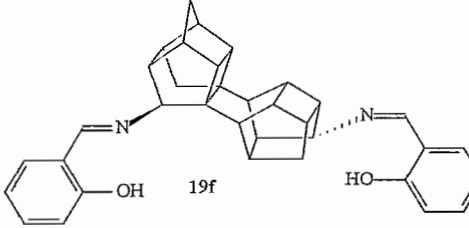
Structure	Δ_E (kcal/mol)	Structure	Δ_E (kcal/mol)
 18a	6	 18d	0
 18b	6	 18e	6
 18c	6	 18f	6

Table 3.12: Different isomers of **19** and their respective electronic energies

Structure	Δ_E (kcal/mol)	Structure	Δ_E (kcal/mol)
 19a	19	 19d	0
 19b	19	 19e	32
 19c	25	 19f	38

These tables unambiguously illustrate that the energy does not differ significantly between each isomer for each of the different ligands. This means that there are no discrepancies as to which isomer will form and thus all the isomers will form with the same probability.

Although the end ligand would be a mixture of different isomers, the energies of the complexes formed from the different isomers would also have the same energy. In order to validate this statement, **16a-16d** attached to a simplified Grubbs 1 (to form **74a-74d** respectively), were also modelled. **Figure 3.5** provide the generic structure of the simplified Grubbs 1 used in the calculation. All of the calculated energies were the same (**Table 3.13**). Given that the energies of the ligands as well as the simplified complexes are the same for the various isomers, it was decided that only **16a**, **17a**, **18a** and **19a** will be modelled thus reducing computational time. For this reason **16** will imply **16a-16f** and so on, unless stated otherwise.

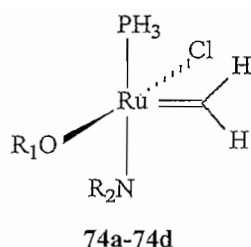


Figure 3.5: Generic structure of the simplified Grubbs 1 (**74a-74d**), with R₁ and R₂ attached to **16a-16d**

Table 3.13: Electronic energies of **74a-74d**

Complex	Δ_E (kcal/mol)
74a	0
74b	0
74c	0
74d	0

Throughout this study the assumption is made that the oxygen atom will form a hard bond and the nitrogen atom will form a soft bond with the ruthenium atom. In order for any ligand to coordinate with ruthenium, the HOMO of the ligand and the LUMO of the metal must be able to overlap, i.e. the energies must be in the same order. Before the ligands can be coordinated with **1**, the hydrogen on the OH-group must be removed to ensure that the oxygen atom has the ability to form a hard bond to the ruthenium. This can be conducted through the reaction of the ligand with a strong Lewis base such as TlOC₂H₅ (thallium ethoxide or TlOEt) or BuLi (butyllithium).

Normally BuLi will be used, due to lower toxicity compared to TlOEt. But for **16** BuLi will remove both a hydrogen on the nitrogen and on the oxygen, since the pK_a of the R-OH is ~ 16 and that of R-NH₂ is ~ 38, while that of BuLi is ~ 50. This will result in both the nitrogen and the oxygen forming hard bonds to the ruthenium and in a ligand that will not be hemilabile. For this reason **16** must be reacted with TlOEt, to ensure that only the oxygen reacts with ruthenium. The HOMO as well as the electrophilic Fukui functions of the ligands without a proton on the oxygen (**75-78**, i.e. **16a**, **17a**, **18a** and **19a** with the hydrogen removed from the oxygen) is summarized in **Table 3.15** and the two dimensional structures of these ligands are given in **Table 3.14** for clarity. The LUMO and nucleophilic Fukui function of **1** is presented in **Figure 3.6**.

Table 3.14: Two dimensional (2D) structures of ligands **75-78**

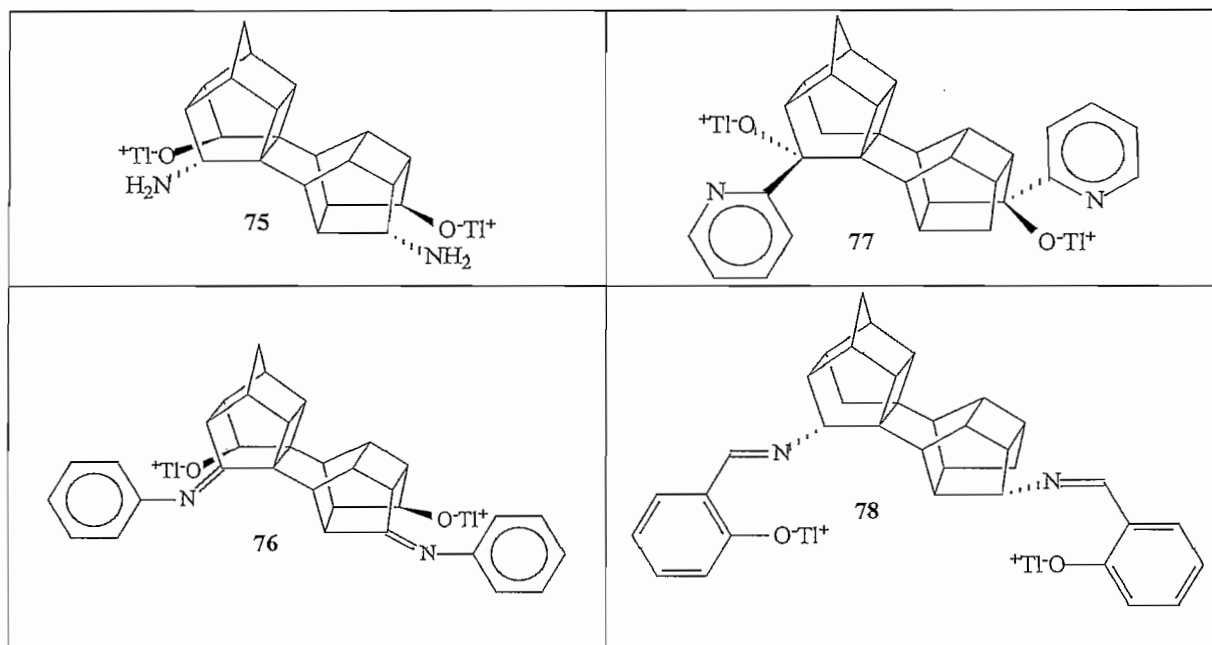
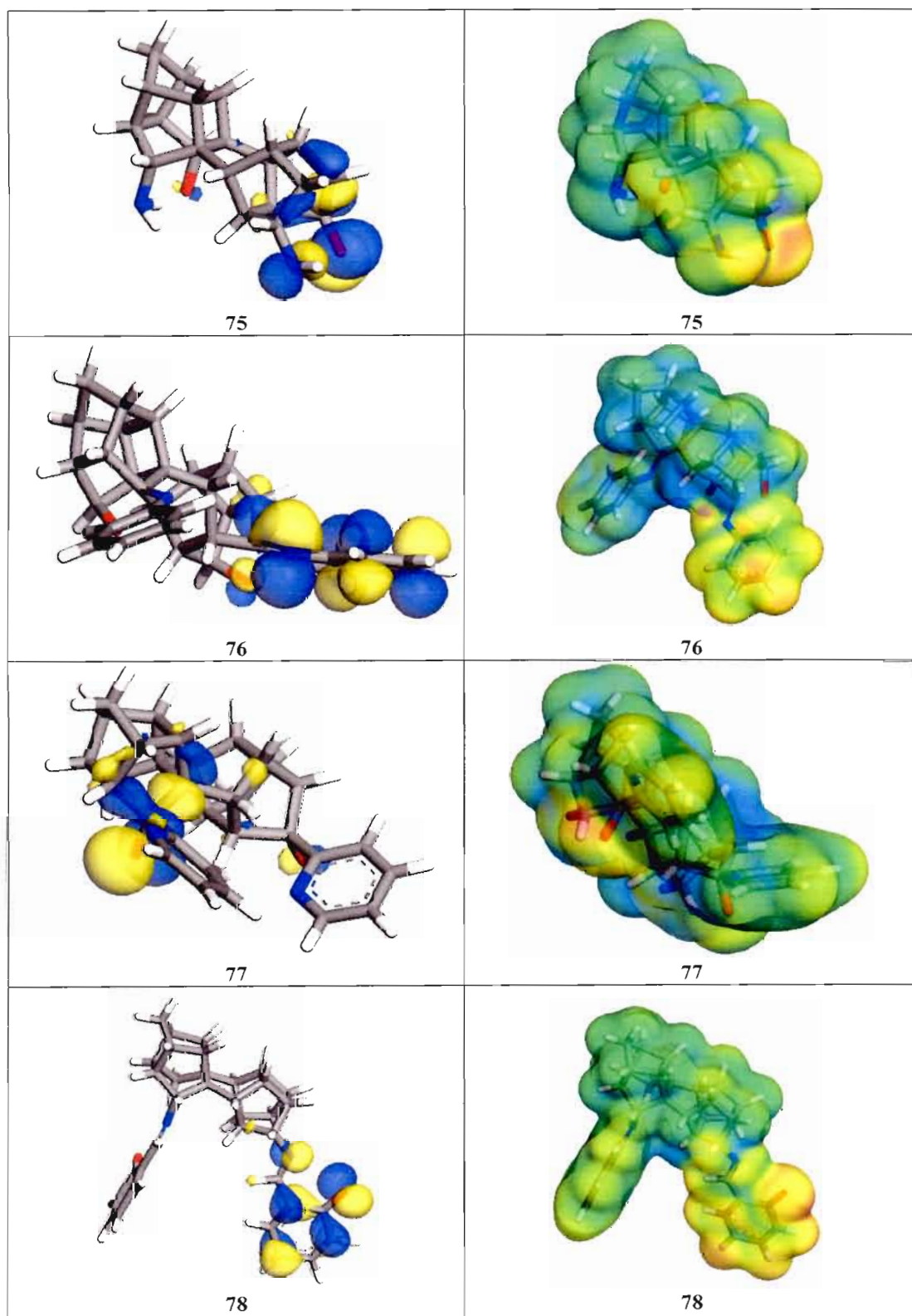


Table 3.15 demonstrates that for all the ligands except for **76**, the HOMO is mostly on the oxygen. This means that ligands **75**, **77** and **78** will preferably coordinate to the ruthenium with the oxygen on the side where the HOMO is. For **76** the HOMO is on nitrogen and the benzene ring. The hydroxy groups on this ligand are only *endo* (as already explained above), resulting in a hydroxy group in close proximity to a Schiff base. It has been demonstrated by various authors that in a situation like this, a transannular attack occurs (**Scheme 3.2**) on the Schiff base resulting in a cyclic ether.¹³⁵⁻¹³⁷ This in turns results in the HOMO being shifted to the more accessible and more reactive nitrogen, since the nitrogen is effectively only bound to two groups and will take up a hydrogen and thus the HOMO must be on the nitrogen for this attack to occur. It should also be noted that this attack will probably not occur simultaneously, but rather with a stepwise mechanism.

The electrophilic Fukui function illustrates the distribution of the electron rich parts of the different ligands. The red areas shows high electron density areas, whilst the lesser electron rich parts are yellow and the more positive areas are blue, green or slightly yellow. For the nucleophilic Fukui function this is *vice versa*, i.e. indicating low electron density with red. For **75**, **77** and **78** the electron rich parts are mostly around the oxygen with some electron density distributed around the carbons and nitrogen. This is consistent with the arrangement of the HOMO.

Table 3.15: The HOMO (left) and electrophilic Fukui function (right) of **75-78**



In **Figure 3.6** the LUMO and the nucleophilic Fukui function of **1** are illustrated. From this figure, one can see that the LUMO (area of low electron density) is around the ruthenium metal centre and the benzylidene group. This is understandable, since **1** is already an active metathesis catalyst which means that the LUMO should be around the metal centre in order for the HOMO of the olefin to overlap and undergo metathesis. Given that the LUMO is around the metal centre and the ligands (**75**, **77** and **78**) have HOMOs on the oxygen, coordination is possible. The data in **Table 3.15** suggest that for **75** and **78** if the first ruthenium is able to coordinate it will coordinate on the right hand side (where the HOMO of the ligand is) and for **77** on the left hand side.

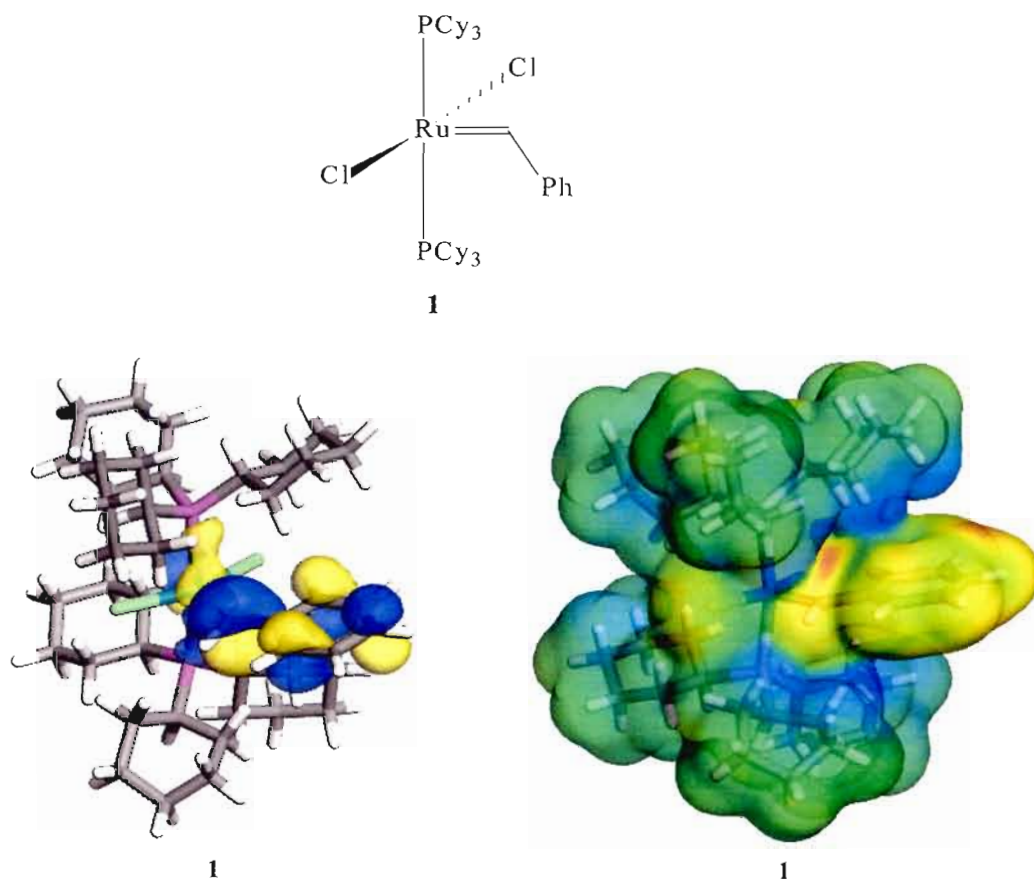
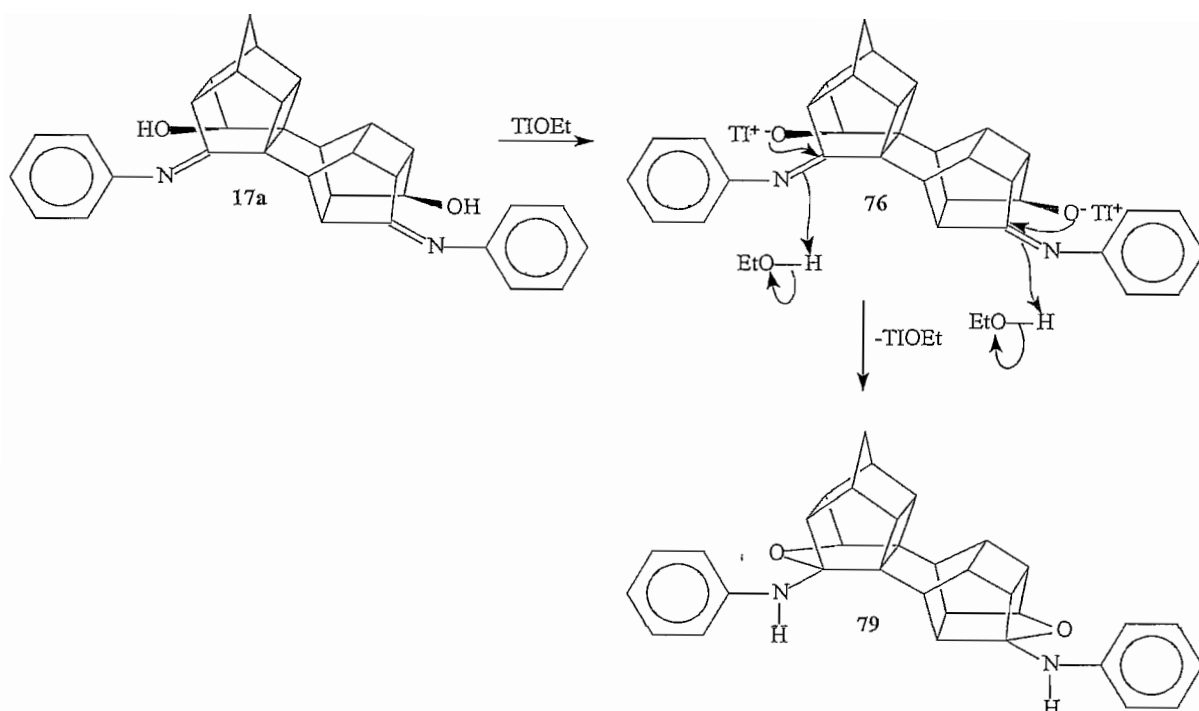


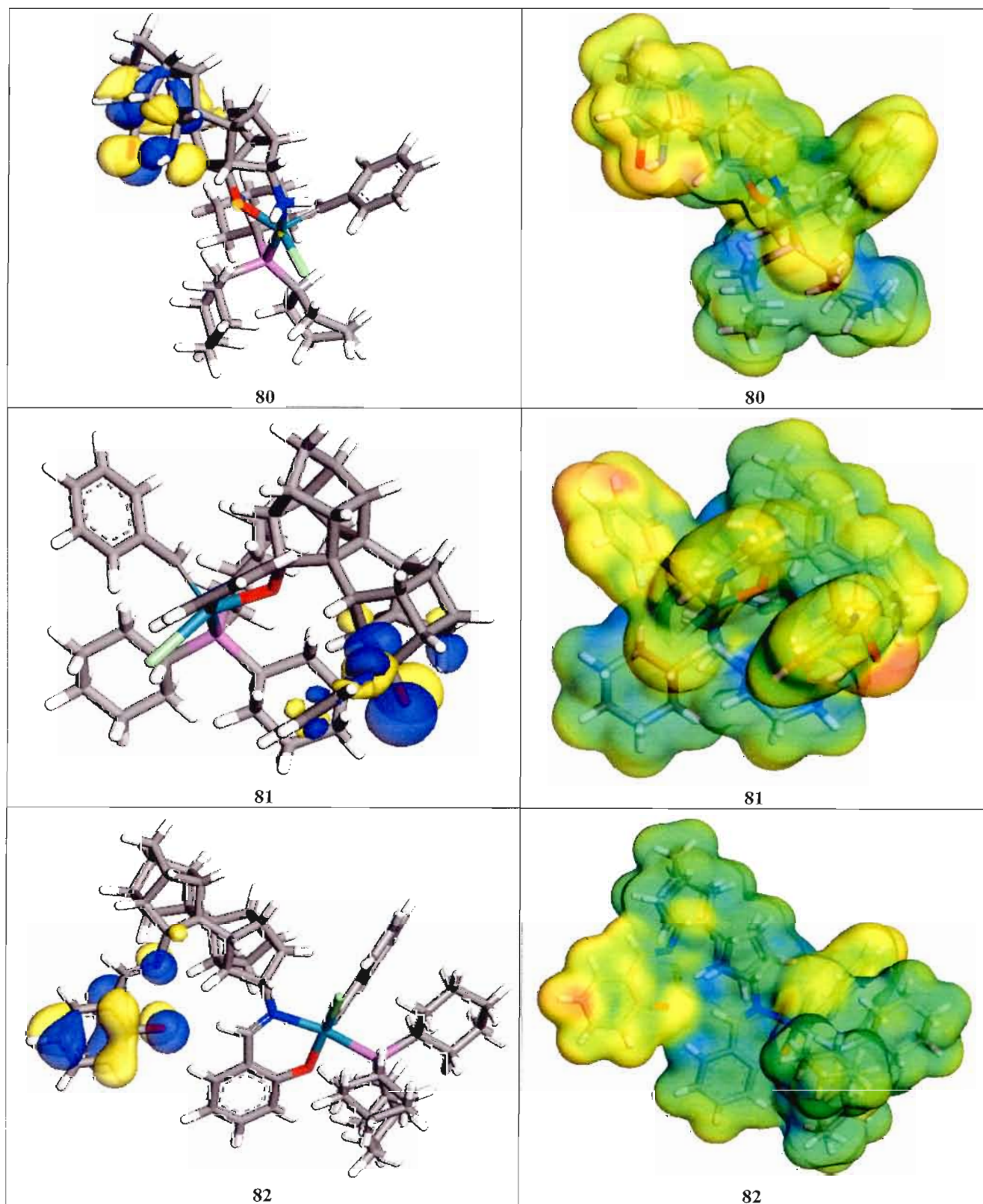
Figure 3.6: The 2D structure together with the LUMO and nucleophilic Fukui function of **1**



Scheme 3.2: The transannular ether formation of **76**

Table 3.16 illustrates the HOMO and electrophilic Fukui function of **80-82**, i.e. the bidentated ligands **75**, **77** and **78** with one ruthenium coordinated to both the oxygen and the nitrogen, with the oxygen forming a hard bond and the nitrogen a soft bond. This table illustrates, similar as in **Table 3.15**, that the HOMO is situated mostly around the oxygen. This means if the first ruthenium would be able to coordinate, the HOMO shifts to the other side of the ligand, which means that the ligand would be able to coordinate to a second ruthenium.

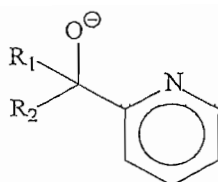
Table 3.16: The HOMO (left) and electrophilic Fukui function (right) of **80-82**



Although the visual illustration of the HOMO and LUMO above offers some idea of the size and position of the frontier orbitals, it does not give a tangible picture of whether or not the ligands will be able to coordinate to ruthenium. The coordination ability of the ligand to the ruthenium metal can be better illustrated with numeric values. It was already mentioned in the beginning of this section that in order for any ligand to coordinate with ruthenium, the HOMO of the ligand and the LUMO of the metal must be able to overlap and thus the energies must be in the same order. Accordingly the electronic energies of the frontier orbitals were calculated and the absolute difference of the energy ($|\Delta E|$) of the HOMO (E_{HOMO}) and the energy of the LUMO (E_{LUMO}), regarded as HOMO/LUMO gap energy,¹³⁸ are tabulated in **Table 3.17**. Even though a numeric value can be assigned to the frontier orbitals, a conclusion can still not be draw if these ligands would coordinate or not. In order to alleviate this problem, compounds **83-85** (**Figure 3.7**), which were successfully incorporated in Grubbs 1 and 2 in 2007 by Jordaan,¹¹⁴ were also modelled and the HOMO/LUMO gap energy was calculated. These values can now be compared to the reference compound, which can coordinate to **1**, and thus a more conceivable conclusion can be drawn.

Table 3.17: Calculated HOMO/LUMO gap energies (eV) of the HOMO of **75**, **77-78**, **80-85** and the LUMO of **1**

Compound	E_{HOMO} (eV)	$ \Delta E $ (eV)
75	3.80	6.80
77	3.05	6.04
78	1.95	4.94
80	-4.27	1.27
81	-0.89	2.10
82	-1.45	1.55
83	1.53	4.53
84	1.45	4.45
85	1.15	4.15
E_{LUMO} of 1	-2.99 eV	



83 $R_1=R_2=CH_3$

84 $R_1=R_2=Ph$

85 $R_1=R_2=C_6H_{11}$

Figure 3.7: The structures of **83-85**

Given that the HOMO/LUMO gap energy is approximately 4.5 eV for the reference compounds **83-85** and that of **75**, **77-78** are higher; it is not to say that these ligands would not be able to coordinate. This can be ascribed to the fact that the HOMO/LUMO gap energy for aluminium nitride (AlN) is 6.3 eV, which is higher than that of **77** and **78**. From this table it can be seen that if the first ruthenium coordinates the second ruthenium will coordinate even faster, since the band gap energy is much lower and thus the coordination of the first ruthenium is the rate determining step. It can be concluded that if the HOMO/LUMO gap energy can be overcome for **75**, coordination of the second ruthenium metal is possible. For **77** and **78** coordination will most probably take place, since the HOMO/LUMO gap energies are lower than that of known compounds with high HOMO/LUMO gap energies such as AlN.

It has been shown, from the above tables that ligands **16**, **18** and **19** all have the ability to coordinate to two ruthenium atoms, since the HOMO is found on the oxygen atom of all the ligands, the LUMO is on the ruthenium atom and the HOMO/LUMO gap energies are in the same order. **17** would probably not coordinate to ruthenium but rather form the transannular ether as illustrated in **Scheme 3.2**.

3.2.3. Molecular Modelling of the Pre-catalysts

As already mentioned above, the energies of the different isomers are the same (**Table 3.9-3.12**) and ligand **17** will probably not react with **1** in such a manner that the oxygen forms a hard bond and the nitrogen forms a soft bond. For this reason only **16**, **18** and **19** will be modelled with both sides coordinated to **1**, in order to determine if the pre-catalysts would be hemilabile and be able to metathesize 1-octene (**92**). The first step in the catalytic cycle of metathesis (with **1** as catalyst) is the dissociation of the PCy₃ group to produce a reactive

complex that is attacked by the substrate.¹³¹ An assumption that is made here is that, when coordination occurs, both the oxygen and the nitrogen will bind and only when an appropriate substrate is added then will the nitrogen or PCy_3 dissociate to form an open coordination site. In order for a reaction to take place the HOMO of the substrate (**92**) must overlap with the LUMO of the pre-catalyst (or activated complex) and thus the HOMO/LUMO gap energies must be in the same order. Thus this section will be divided into three subdivisions viz.

- i. Determination of dissociation energies of both the Ru-N bond and the Ru-P bond;
- ii. Determination if the ligands are hemilabile; and
- iii. Determination whether or not 1-octene would be able to bind to the pre-catalyst.

Before the dissociation energies can be calculated, one must first determine the active side of the pre-catalyst, since there are two possibilities. The assumption made is that the side where the LUMO is already situated on the pre-catalyst would probably react first with 1-octene. This can be ascribed to the fact that the HOMO of 1-octene must overlap with the LUMO of the pre-catalyst. **Table 3.18** illustrates the 2D structures as well as the LUMO of the pre-catalysts **86-88**, i.e. **16a**, **18a** and **19a** coordinated to two Grubbs 1 pre-catalysts.

Table 3.18 shows that for **86** and **88**, the LUMO is found on the right hand side of the molecule and for **87**, the LUMO is found on the left hand side. The dissociation energy of the N-Ru (E_d N-Ru) bond can be calculated by taking the absolute difference in energy between the bonded complex and the dissociated one. For the dissociation energy of the P-Ru (E_d P-Ru), one must incorporate a mass balance factor, i.e. the energy of the free PCy_3 must be added to the dissociated complex. The input structures for the calculation of the E_d N-Ru is where the C-C-O-Ru dihedral angle is turned away and optimized (**86**, **87** and **88** forms respectively **89**, **90** and **91** with the N-Ru dissociated). The same calculation will be used to determine the hemilability of the ligands and for this reason both will be discussed here. **Table 3.19** summarizes the E_d N-Ru and E_d P-Ru.

Table 3.18: The LUMO of 86-88

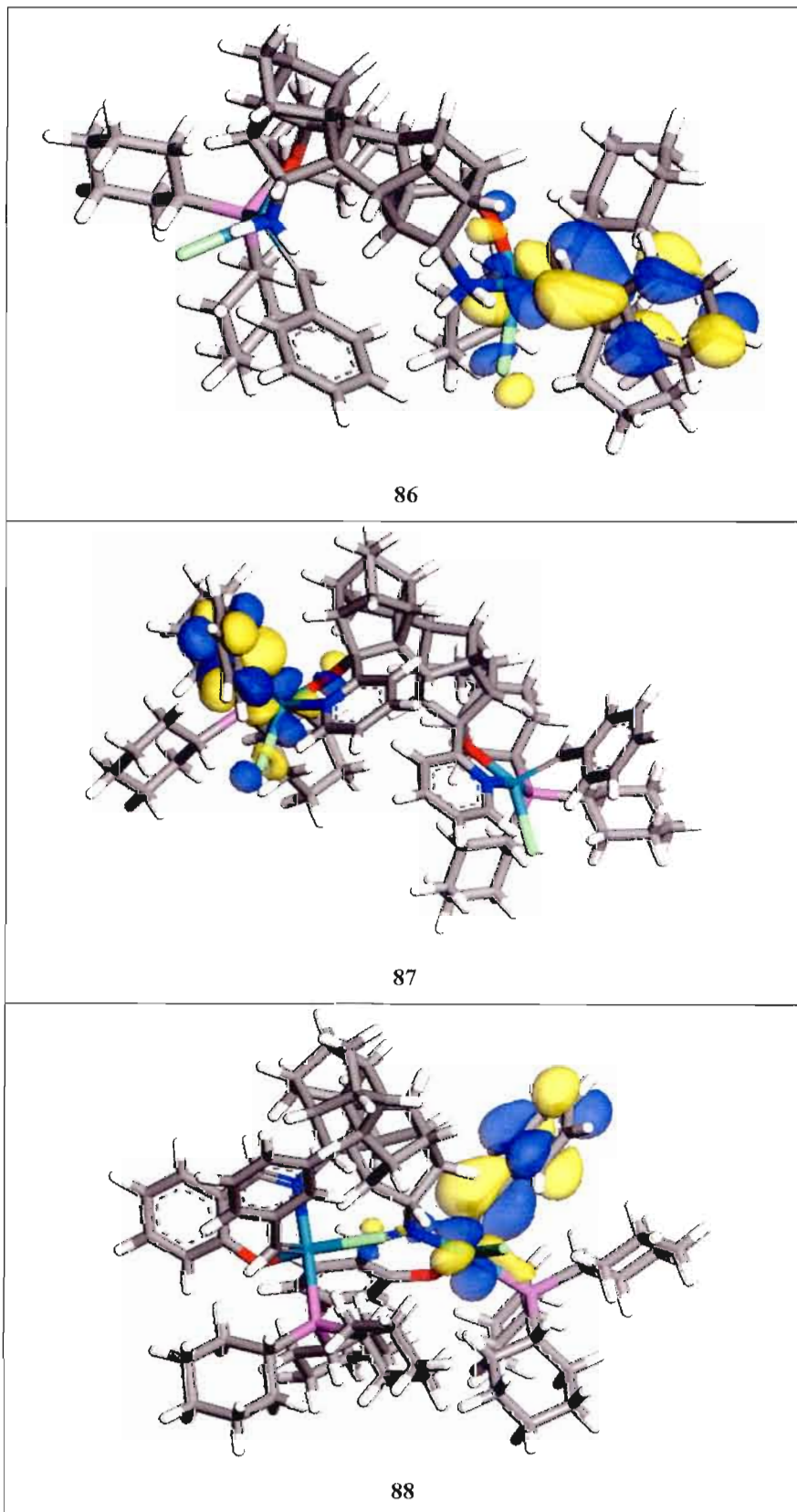


Table 3.19: Dissociation energies of N-Ru and P-Ru bonds

E (kcal/mol)							
Ligand	Grubbs on both sides	Ligand	N-dissociated and turned	PCy ₃ removed	PCy ₃	E _d N-Ru	E _d P-Ru
86	-8482907.24	89	-8482773.61	-7825687.91	-657061.52	133.63	157.80
87	-8723558.95	90	-8723533.91	-8066446.43		25.05	51.01
88	-8820719.62	91	-8820570.03	-8163615.81		149.58	42.29

From this table it seems that, although the E_d of the N-Ru bond is lower than that of the P-Ru bond for **86**, the dissociation energy is quite high and thus no dissociation would take place once coordination has occurred. This also indicates that this ligand would most probably not be hemilabile but rather be bidentate. But in view of the fact that the dissociation energy of both the N-Ru and P-Ru bonds are so high, it can be concluded that this type of ligand would not make an efficient catalyst, since no open coordination site can be generated at elevated temperature.

The principle of a hemilabile ligands is that these ligands are presumed to act as chelating ligands at room temperature and to open up one coordination site at elevated temperatures.⁹² Considering that the classical meaning of dissociation energy is defined as the standard enthalpy change when a bond is cleaved by homolysis, with reactants and products of the homolysis reaction at 0 K. This means that these energies are measured at 0 K. and that at elevated temperature, less energy have to be added in order to achieve bond dissociation. Thus, the dissociation of the N-Ru bond can be achieved by increasing the metathesis reaction temperature. This in turn can mean that although the E_d of N-Ru is high, it can be overcome and thus resulting in a hemilabile pre-catalyst (since the nitrogen have the ability to re-coordinate to the ruthenium during optimization of the dissociated form) that is active at very high reaction temperatures and thus can increase the reaction rate.

For **87** the N-Ru bond would dissociate first, since the E_d of N-Ru bond is about half of the E_d of P-Ru bond. During the geometric optimization of the complex, the ruthenium turns back to the nitrogen indicating that this ligand would be hemilabile. The pyridine alcolate complexes synthesized by Jordaan *et al.*¹¹⁴ in 2007 was not hemilabile but rather bidentate when coordinated to Grubbs 1 (**1**). For these complexes the PCy₃ would dissociate and not the Ru-N bond as was expected. This can be attributed to the insufficient steric and electronic influences of the R-groups (such as methyl, *i*-propyl and phenyl groups) to stimulate the

dissociation of the Ru-N bond. In the current study it seems that the pyridine alcolate complex (**87**) is hemilabile, indicating that the cage annulated compound provide the necessary steric and electronic influences for these complexes to be hemilabile.

For **88**, it seems that the P-Ru bond would dissociate first and not the N-Ru bond as expected. During the geometric optimization of **88**, the ruthenium turns away from the nitrogen and finds a lower minimum which effectively increases the E_d of the N-Ru bond. This can be credited to the fact that the dissociation energies are calculated by the absolute difference in the original complex and the dissociated complex. If the dissociated complex finds a lower minimum the dissociation energy must increase (like in the present case). In this case, **91** (dissociated form of **88**) was turned around the C-C-O-Ru dihedral from -176° to 61° (**Figure 3.8, 91a**). If **91** is turned around the C-C-O-Ru dihedral angle from -176° to 91° (30° difference between the two limiting cases) and optimized, the ruthenium turns back to the nitrogen (**Figure 3.8, 91b**) and the E_d of N-Ru calculates to be 0.1128 kcal/mol. This in turn means that this bond would be so weak that it would in effect not form, but rather be in a dissociated state. Consequently the nitrogen would give no stabilization to the ruthenium and the pre-catalyst would decompose, if it forms at all.

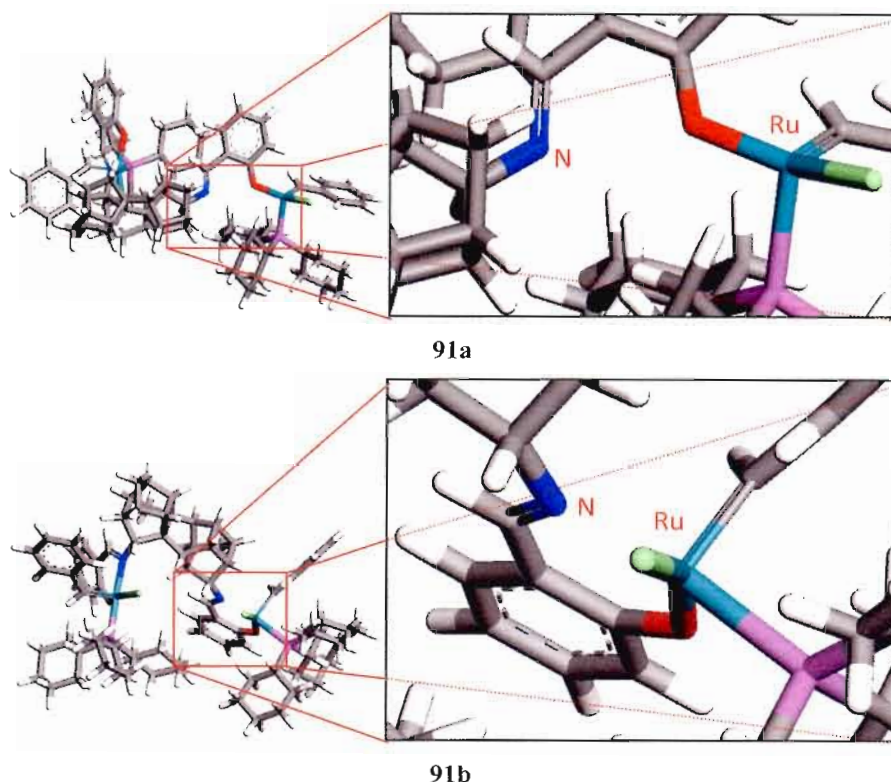


Figure 3.8: Explosive views of **91a**, ruthenium turned away from nitrogen and **91b**, ruthenium turned towards nitrogen

In order to investigate this complex (**87**) and make a conclusion, experimental data are required such as from X-Ray crystallography. In view of the fact that in this study attempts to synthesize this complex was futile, no experimental data are available for this complex and consequently no conclusion can be made about the coordination ability and hemilability of this complex. It seems that the specific model used to investigate this complex was inadequate to investigate these properties (coordination ability and hemilability). For this reason only **89** and **90**'s (dissociated forms of **86** and **87** respectively) coordination ability with 1-octene (**92**) will be investigated.

Before the coordination ability of **86** and **87** can be determined an important question arises, namely: when the N-Ru bond dissociates, will the other side also dissociate or will the catalytic cycle continue? **Table 3.20** shows that the LUMO of **89** and **90** is still found on the same side as the initial complex **86** and **87** respectively, which means that the catalytic cycle will continue with the attack of the substrate (if possible) on the ruthenium and that the simultaneous or random attack on both sides will not occur. Although, as the catalytic cycle

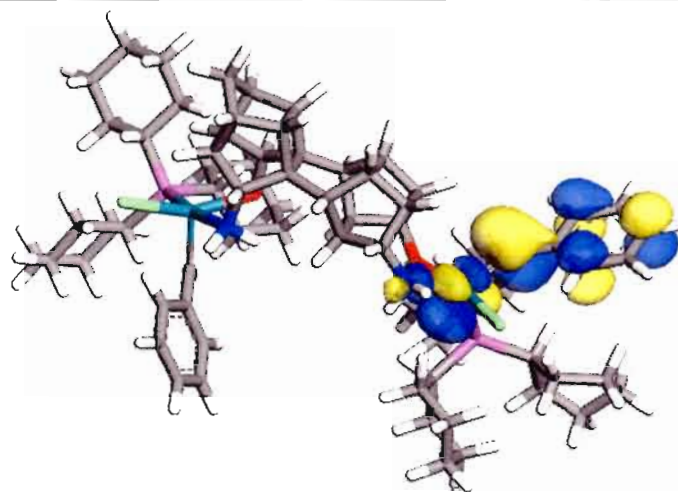
continues at the one side (right for **86** and left for **87**) it is not to say that the other side will not also be activated during the catalytic cycle, but this type of information is beyond the scope of this study, since some complex calculations and a catalytic cycle must be modelled and due to the size of these complexes it was not plausible within the time frame of this study.

The coordination ability of **89** and **90** can be determined by once again taking the absolute energy difference of the LUMO of the complex and the HOMO of **92**. **Table 3.20** shows the position of the HOMO of **92** and the position of the LUMO of **89** and **90**, while **Table 3.21** gives the calculated HOMO/LUMO gap energies (eV) of the LUMO of **89** and **90** and the HOMO of **92**.

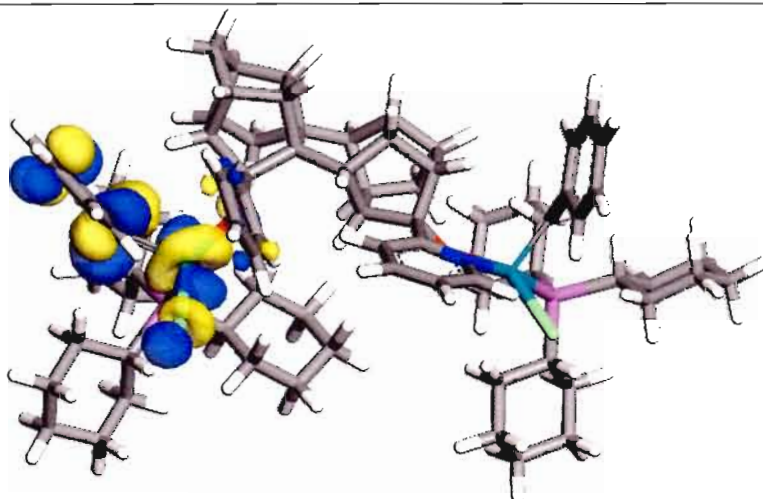
Table 3.20 indicates that the HOMO of **92** is located on the double bond, which is expected, since this is the only region that has high electron density. The LUMO of **89** is situated on the right hand side like in the non-dissociated complex **86** and for **90** on the left hand side, which is also the same side as in **87** as discussed above.

Table 3.21 indicates that the HOMO/LUMO gap energies for the two dissociated complexes are lower than that of the HOMO/LUMO gap energies of the oxygen with ruthenium (**Table 3.19**). Taking all the above information into account, a conclusion can be made that both **86** and **87** would have the ability to coordinate with 1-octene and thus most likely be able to undergo metathesis (if the complex can be synthesized). This can be ascribed to the fact both of these pre-catalysts are hemilabile, which means that sufficient space can be made for the incoming nucleophile (1-octene) and coordination to ruthenium are possible.

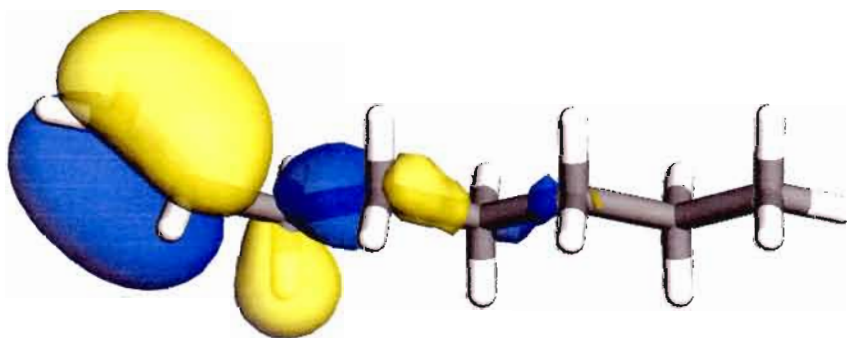
Table 3.20: The position of the LUMO of **89** and **90** and the HOMO of **92**



89



90



92

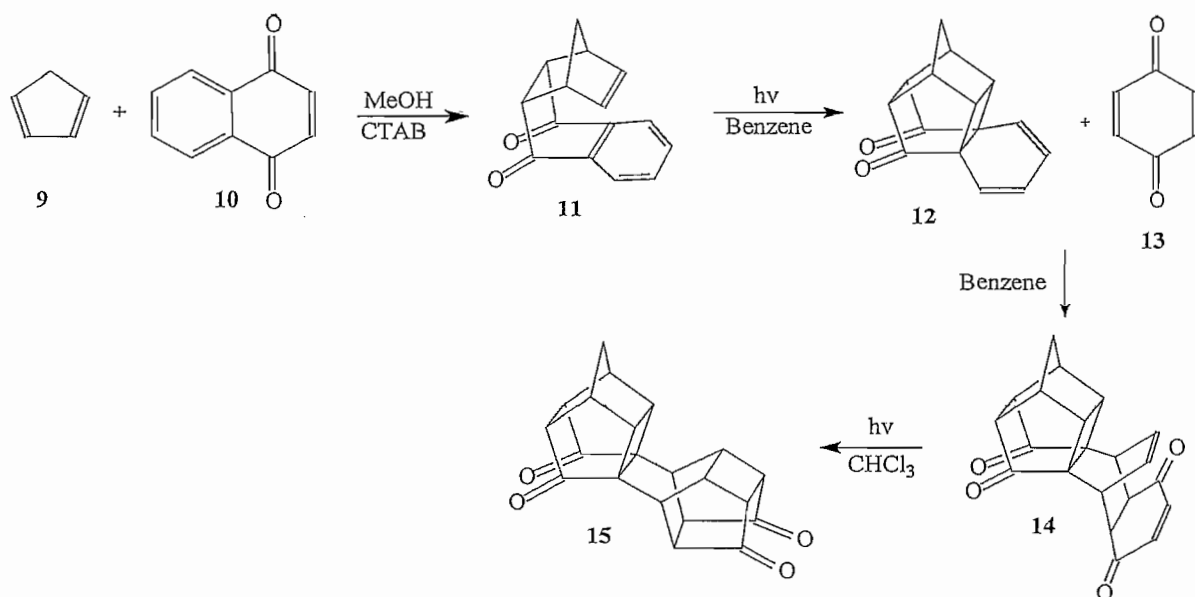
Table 3.21: Calculated HOMO/LUMO gap energies (eV) of the LUMO of **89** and **90** and the HOMO of **92**

Compound	E_{LUMO} (eV)	$ \Delta E $ (eV)
89	-2.58	3.33
90	-2.72	3.18
E_{HOMO} of 92	-5.91 eV	

As can be seen from all the above data, ligands **16** and **18** have the potential to incorporate two ruthenium metal centres as well as the ability to be hemilabile. For this reason attempts have been made to synthesize these compounds.

3.3. Experimental

In 1971 Kusher *et al.*⁴⁰ synthesized the Diels-Alder adduct hexacyclo-[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-dione (**11**) by the cyclo-addition of cyclopentadiene (**9**) and 1,4-naphthoquinone (**10**, **Scheme 3.3**). This reaction can be carried out with ease and high yields (up to 86%) with modified conditions developed by Beukes *et al.*¹³⁹ NMR data of this compound were identical to the authentic sample and will thus not be included in the Addendums.



Scheme 3.3: Synthesis of the 1,4-naphthoquinone Diels-Alder product (**12**) and **15**

12, **14** and **15** (**Scheme 3.3**) can all be synthesized with relative ease and high yields by UV irradiation of **11** in benzene, cycloaddition of *p*-benzoquinone (**13**) to **14** and lastly UV

irradiation of **14**, respectively to form **15**. All analyses were in accordance with literature data. The melting point of **15** is much higher than that published by Pandey *et al.*⁴² but this can be ascribed to the fact that the melting point apparatus used by this author were unable to reach temperatures as high as 371°C. ¹H-NMR spectra of the decacyclo-compounds (**15** and its derivatives) are exceptionally complex, besides a few H-H couplings that can be seen. For this reason not much attention will be given to the ¹H-NMR spectra of these compounds, but rather to the ¹³C-NMR spectra that give a much better indication on the structure of the product.

The addition of ethylene glycol to pentacycloundecane (**97**) compounds was introduced by Eaton *et al.*¹⁴⁰ in 1976. According to Eaton the steric bulk of the cage compound as well as the introduction of the first acetal group hinders the introduction of a second acetal group on the adjacent carbonyl. Although this reaction is chemoselective, it is not regioselective, resulting in the formation of four different isomers (**Figure 3.9**).

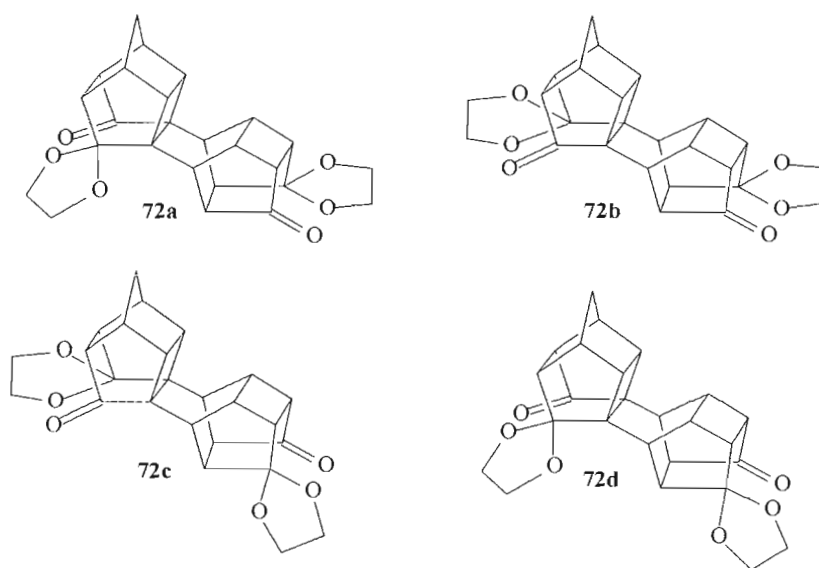


Figure 3.9: The four possible isomers that can form during the addition of ethylene glycol to **72**

From this figure it can be observed that **72a** and **72c** as well as **72b** and **72d** are in fact enantiomers which will result in only two isomers detected in the NMR spectrum. It is evident from the ¹³C-NMR of **15** that there are only two carbonyls present and only eleven signals are registered instead of the twenty one carbons present. This means that **15** is

symmetrical and that the adjacent carbonyls are equivalent. Thus any one of the carbonyls on each side can therefore form an acetal, but the formation of a second acetal on the same is blocked as indicated by Eaton *et al.*¹⁴⁰

Molecular modelling of **15** indicates that the HOMO (since the oxygen must be protonated in the first step of acetal formation and thus must have high electron density or available lone pair electrons) of **15** is situated around the oxygens of the carbonyls on the right hand side (**Figure 3.10**). Consequently the acetal will first form on either one of the carbonyls on the right and then on either one of the carbonyls on the other side. It is for this reason that the ^{13}C -NMR shows about double the number of peaks (44 versus 50 carbons in the two structures) for compound **72**. The discrepancy in the number of peaks is due to some carbons having the same chemical shift (being degenerate) in both structures, for example the DEPT shows only one CH_2 bridge carbon and only two quaternary carbons, while there are in fact two CH_2 bridge carbons and four quaternary carbons respectively.

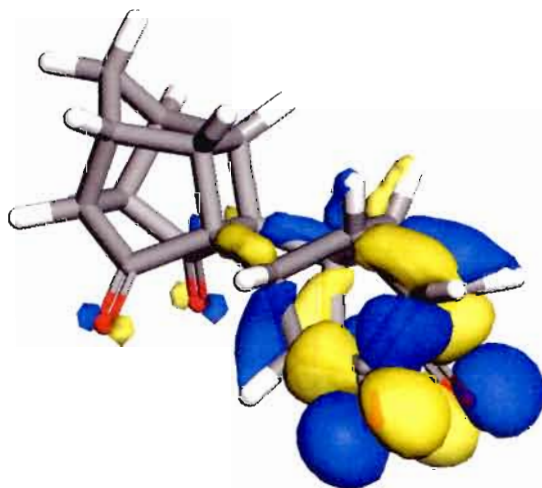


Figure 3.10: The HOMO of **15**

The ^{13}C -NMR of **72** shows four different carbonyl groups at δ_{C} 214.04, 213.94, 213.41 and 212.96 ppm, which can be explained by the spatial arrangement of the acetal group on the other side of the carbonyl. **Figure 3.11** illustrates the numeric numbering of **72a** and **72b** used in **Table 3.22**, that shows the calculated C-C-O bond angles (it should be noted that the numbering is for illustrative purposes only and not done by the conventional technique, this is done to simplify the discussion).

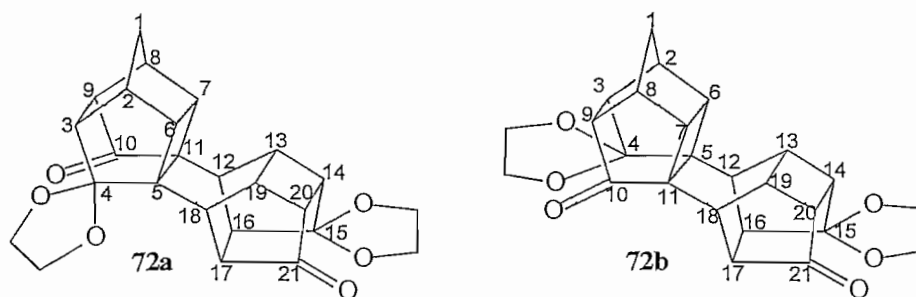


Figure 3.11: 72a and 72b showing the numeric numbering

Table 3.22: Calculated bond angles of the carbonyl groups

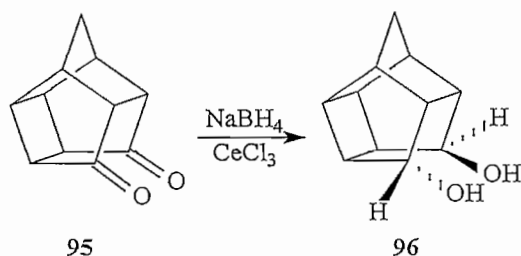
Angle	72a	72b
C9-C10-O	127.53	127.59
C11-C10-O	127.65	127.67
C17-C21-O	127.23	127.59
C20-C21-O	127.71	127.57

From this table it can be seen that although the angles do not differ significantly, that this could account for the slight chemical shift in the ^{13}C -NMR. The distance between the oxygen facing the carbonyl of the acetal and the carbonyl oxygen can also be measured. The carbonyl oxygen (on C10) and the acetal oxygen (on C4) distance is 3.26 Å and 3.23 Å for **72a** and **72b**, respectively, while the carbonyl oxygen (on C21) and the acetal oxygen (on C15) distance is 3.17 Å and 3.15 Å, respectively. The bond angles together with the slight difference in interatomic distances cause a minor change in the electronic environment around the carbonyls which causes the carbon atoms of **72a** to be deshielded and shifted downfield, while the carbon atoms of **72b** are more shielded and shifted upfield. This is commonly known as magnetic anisotropic and refers to the electron distribution of molecules with high electron density. This abnormal electron density affects the applied magnetic field and causes the observed chemical shift to change.

This effect can be seen especially for the bridge CH_2 , where the two protons are split up in two very distinct doublets. Normally the carbonyl peak of C10 is downfield of the carbonyl peak of C21 (this can be seen throughout the ^{13}C -NMR spectra of these compounds), which means that the chemical shift at δ_{C} 214.04 ppm, can be assigned to C10 in **72a**, 213.94 ppm can be assigned to C10 in **72b**, likewise, 213.41 ppm can be assigned to C21 in **72a** and 212.96 ppm can be assigned to C21 in **72b**. This phenomenon where there are more than one peaks for carbons that should be degenerate in the two isomers, is known as the isomer effect.

From the ^{13}C -NMR spectrum of **72a** and **72b**, there can also be distinguished between four different O-C-O groups (acetal), eight different $\text{CH}_2\text{-O-R}$ groups and about double the number of CH groups for one isomer. For the same reasons stated above the isomer effect can explain this observation. Since there are two isomers formed and conventional separation techniques, such as column chromatography, are unable to separate/purify these cage compounds, all the following products will have two or more isomers. Thus for simplicity the numeric value alone will imply all the isomers of a specific compound, while the alphabetical letter together with the numeric value will imply the specific isomer.

For the reduction of **72** to **73** four different methods were used, while only one gave the desired product. The first method used was the reduction of the ketone with NaBH_4 . This is a commonly used method to reduce aldehydes and ketones. Normally for the reduction of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**Scheme 3.4**, **95**),¹⁴¹ $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (known as the Luche reaction) will be added to assure that the diol formed would have an *endo-endo* conformation. Due to the fact that **72** is sterically blocked on the one side by the acetal group, only *exo* hydride attack can occur, producing the *endo* product and it was thus argued that the additional stereoselectivity was dispensable. This method was unable to reduce the carbonyls of **72** and only the starting compound could be extracted in high yields.



Scheme 3.4: Luche reduction of pentacyclo-undecane dione system

Due to the fact that NaBH_4 alone were incapable of reducing the ketone in **72**, the Luche reaction was attempted. The Luche reaction is a selective reduction method for the reduction of enones or ketones in the presence of aldehydes. This method is also widely used to produce specific stereoisomers (*endo-endo* products) from **95** (**Scheme 3.4**).¹⁴¹ The activity of the Luche reaction can be explained by the Hard and Soft Acid and Base (HSAB) theory. Carbonyl groups require hard nucleophiles for addition of a nucleophile to the carbonyl. The hardness of the borohydride is increased by replacing the hydride groups with alkoxide groups. This reaction is catalyzed by cerium salts by increasing the electrophilicity of the

carbonyl groups.¹⁴² Thus, a stronger reducing agent is produced and the cerium facilitates the reduction by binding to the oxygen, weakening the carbonyl bond and making it more susceptible to reduction (**Figure 3.12**). Even with the ketone being more susceptible to reduction no reaction took place.

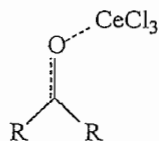
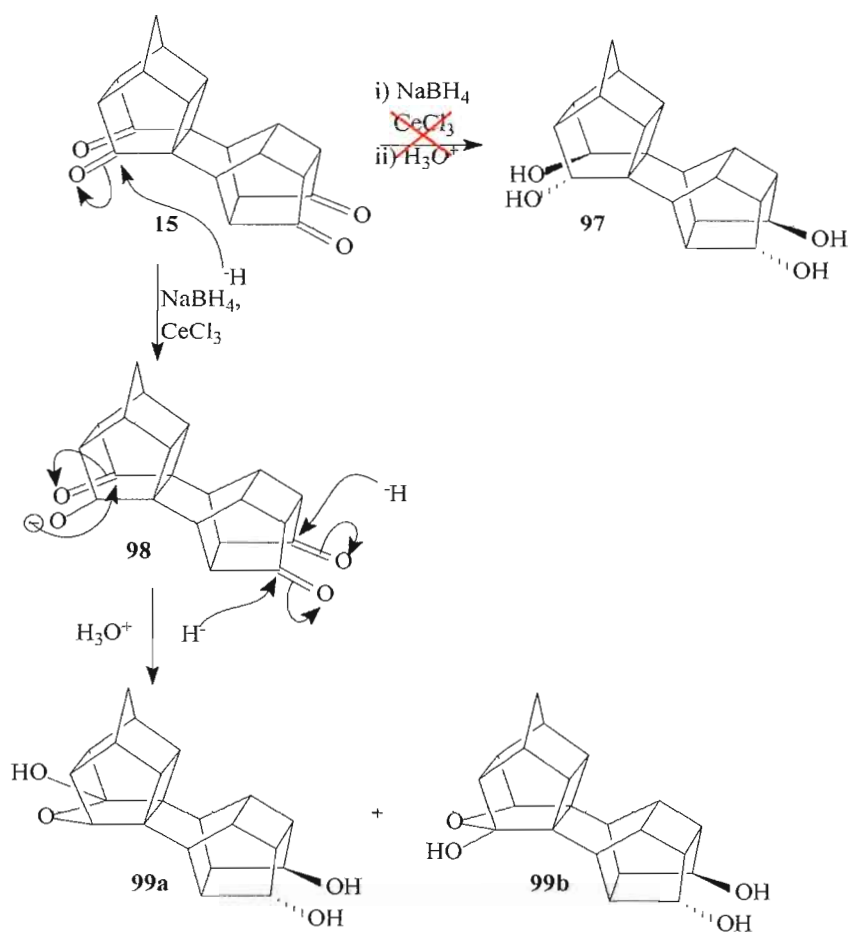


Figure 3.12: Binding of CeCl₃ to the oxygen and weakening the bond

The third method that was attempted was the Meerwein-Ponndorf-Verley reduction. This method, known for over 80 years, is a selective reduction of ketones and aldehydes. It generally uses inexpensive and environmentally friendly ⁱPrOH as a hydride source and aluminium alkoxides as catalysts and the reaction is chemoselective, easy to operate, and readily scalable.¹⁴³ For this reason this reaction looked attractive for the reduction of **72** to **73**. Unfortunately no reaction took place.

Up to this point it seemed that the ketone groups of **72** were resistant to reduction and thus inactive or the reagents used (NaBH₄) were inactive. Therefore, **15** was reduced using the Luche reaction. The expected product was the tetrol **97** (**Scheme 3.5**), but **99** rather formed. Molecular modelling indicates that the LUMO of **15** is concentrated on the left hand side of the molecule, the CH₂ bridge side (**Figure 3.13**), and this side will be reduced first.



Scheme 3.5: Reduction of **15** as well as a possible reaction mechanism

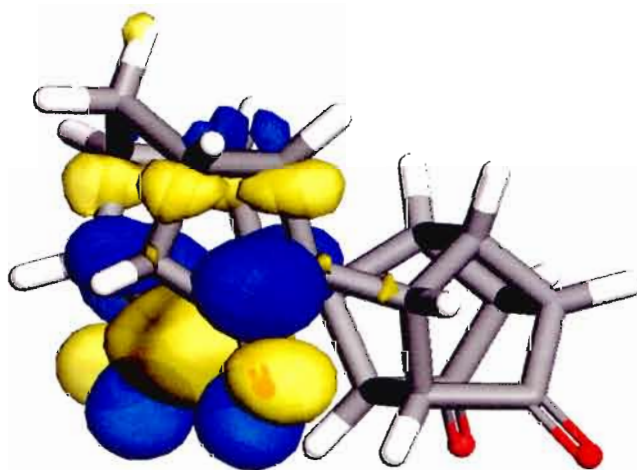
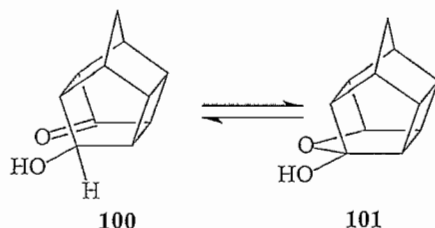


Figure 3.13: The LUMO of **15**

It has been reported by Mehta *et al.*¹⁴⁴ that for the pentacycloundecane (**95**) system this type of product (**101**) is only observed in equilibrium with the ketol **100** (Scheme 3.6, it should be

noted that the two carbonyl groups are equivalent and the reaction occurs without regiospecificity), although it was pointed out by Sasaki *et al.*¹⁴⁵ that **100** did not cyclise to **101**, even at 270 °C. Whether or not this cyclization occurs in **95**, it is evident from the ¹³C-NMR that only **99** is present (together with the contaminant **103**) in this case.



Scheme 3.6: The equilibrium reaction of the ketol **100** and **101**

The ¹³C-NMR of **99** shows four peaks at δ_C 117.39, 117.22, 111.00, 110.88 ppm (these peaks are also quaternary), of which the two at 117 ppm belongs to the contaminant **103** (**Scheme 3.5**), the reduced transannular hydrate of **15** formed during the addition of water at even room temperatures (the presence of the hydrate **102** within **15** can be confirmed with the occurrence of three carbonyls at δ_C 213.45, 212.46 and 210.91 ppm as well as the hydrate peak at δ_C 110.35 ppm in the ¹³C-NMR spectrum of **15** with DMSO-*d*₆ as solvent). The presence of this contaminant makes the complete assignment of all the atoms rather challenging.

Although physical evidence such as δ_C at 78.80 and 78.65 ppm are indications of a transannular ether bearing carbon with a hydrogen (instead of the normal hydroxyl group attached to this carbon). The DEPT indicates that there are also five quaternary carbons at δ_C 44.99, 44.51, 44.28, 43.90 and 43.80 ppm, four originating from **99** (of which two are for **99a** and two for **99b**, these peaks are split due to the isomer effect) and one for **103**. The ¹³C-NMR also showed signs that the sample was slightly contaminated with a compound consisting of a few CH₂ groups (this can be seen on the DEPT at δ_C 70–60 ppm). The peaks at δ_C 82.00, 69.96, 60.22, 31.29 and 18.80 ppm, are all credited to this compound and all of them are CH₂ groups. In order to obtain a pure sample, all the reactions up the **99** must be conducted in anhydrous conditions, which will also be quite difficult to perform, since some of the reactions are worked up in water.

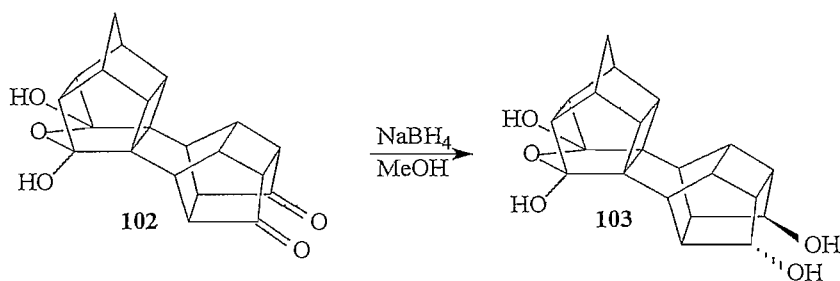


Figure 3.14: The side reaction that occurs during the reduction of **15** to **99**, producing the contaminant **103** from the hydrate **102**

From the reaction in **Scheme 3.5** it is clear that all four ketones seem to be active toward reduction. Thus, due to the steric hindrance around the ketones, they may be resistant to reduction. For this reason the reduction of **72** was attempted with the use of LiAlH_4 , a much stronger reducing agent than NaBH_4 .

With the use of LiAlH_4 , it was possible to reduce **72** to **73**, with relative ease and high yields (94%). This reaction was initially conducted with LiAlH_4 dissolved in THF and the ketone being added drop wise, over a period of 2 hours, to the stirred solution. It was argued that since the ketone is resistant to reduction this setup will result in a higher concentration of H^- (hydride) at any given time compared to the concentration of the ketone. The resulting product was an orange-brown oil. Although the IR showed a distinctive OH stretching band at 3427 cm^{-1} and the disappearance of the carbonyl peak at 1743 cm^{-1} , the NMR (^1H and ^{13}C), gave such a complex spectrum, with considerable background noise and contamination, making the identification of the product quite challenging. For this reason a ^{13}C -NMR study was launched to monitor the reaction.

The reaction was carried out the same as before, except that LiAlH_4 was added slowly to the stirred ketone (**72**) in THF over a period of 2 hours. A sample from the reaction mixture was taken at $t = 0, 30, 60, 90$ and 120 minutes, worked up and analyzed. The sample at $t=0$ was only taken to ensure that the solvent did not react with **72**. ^{13}C -NMR data showed that after only 30 minutes, the carbonyl peak disappeared completely with the appearance of the acetal peaks at δ_{C} 115.70, 115.69, 115.12 and 115.07 ppm. Once again the isomer effect can be seen for this compound with the splitting of degenerate peaks (since the reagent **72** was already a mixture of two isomers).

As with **72**, there are also eight different CH₂-O-R carbon peaks between δ_c 65 and 62 ppm. The DEPT also indicated two CH₂ bridge peaks that were degenerate in **72**. In comparison to **72**, **73** have four different quaternary carbons, indicating that the isomer effect is more significant in **73** than in **72**. This can be explained by taking into consideration that the hydroxyl group is spatially bigger than the ketone group, which causes a bigger disturbance in the electronic effect on the C4, C10, C15 and C21 of the two isomers (**Figure 3.15**, it should be noted that the numbering is for illustrative purposes only and not done by the conventional technique, this is done to simplify the discussion and to keep the numeric values of the different carbons the same). Consequently the quaternary C5 and C11 will thus split, due to very different electronic interaction experienced by these carbons in the two isomers.

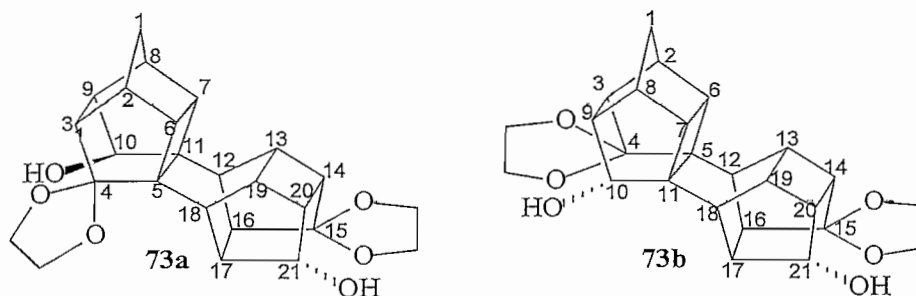
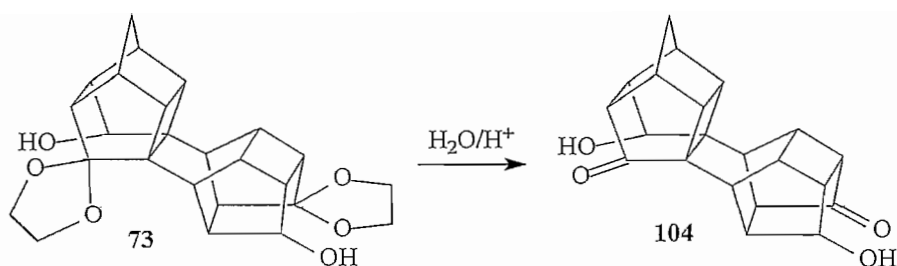


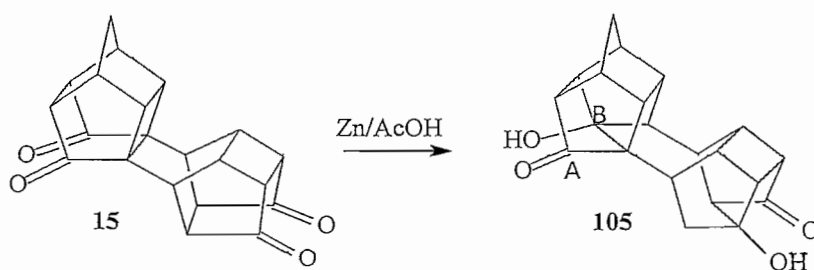
Figure 3.15: **73a** and **73b** showing the spatial difference between the two isomers (front and back of molecule if viewed from the current angle) and the numeric numbering

The following step in the synthesis of ligands **16** and **18** would be to remove the protecting acetal group of **73** in order to produce the hydroxy ketone **104** (**Scheme 3.7**). For the pentacyclo-undecane system, this can normally be accomplished by stirring the ketol in a 10% HCl solution for 2 hours and sometimes refluxing is necessary. For **73** this procedure is inadequate to remove the acetal group. Even when the solution was refluxed for 144 hours in a 25% HCl solution no reaction took place. The deprotection of **73** was achieved by refluxing this compound in a 24% HBr solution for 12 hours. IR and MS data confirms the presence of **104**, with a strong OH absorption band at 3423 and a carbonyl absorption band at 1720 cm⁻¹ as well as an *m/z* of 336. Unfortunately due to solubility problems, an efficient NMR data set could not be obtained and thus the structure of the product could not be confirmed. Additionally, due to the low yields alternative routes were followed for the synthesis of **16** and **18**.



Scheme 3.7: Synthesis of 104

In 1982, Beukes *et al.*¹³⁹ suggested that a hydroxy ketone (**105**) can be directly synthesized from **15** with the use of Zn and acetic acid (**Scheme 3.8**). This reaction offers a convenient way to generate the correct type of functionality in one single step. The oblique bond causes the carbonyl and the hydroxyl group to shift in toward each other, which causes the carbonyl and hydroxyl bearing carbons in close proximity. Molecular modelling shows that this can actually be advantageous, since it brings the carbonyl and the hydroxyl group closer together which will eventually lead to ruthenium and nitrogen coming closer together (in the dissociated state of the pre-catalyst), thus making it easier for the recoordination of the nitrogen to the ruthenium (**Figure 3.16**, the carbonyl will finally form the free amine in ligand **16**). The distance between A-B is 2.55 and 2.34 Å for the hydroxy ketone and the oblique hydroxy ketone, respectively.



Scheme 3.8: The synthesis of 105

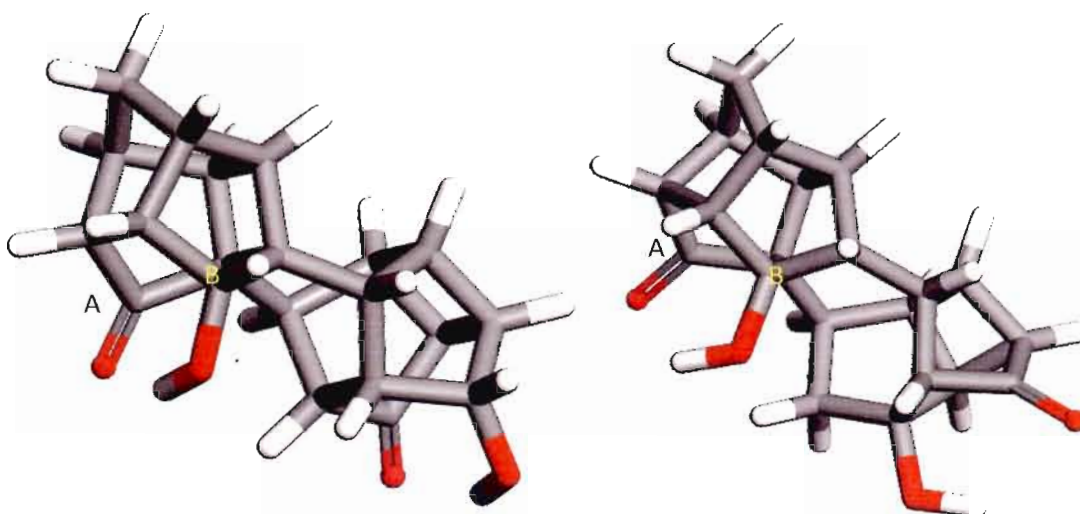
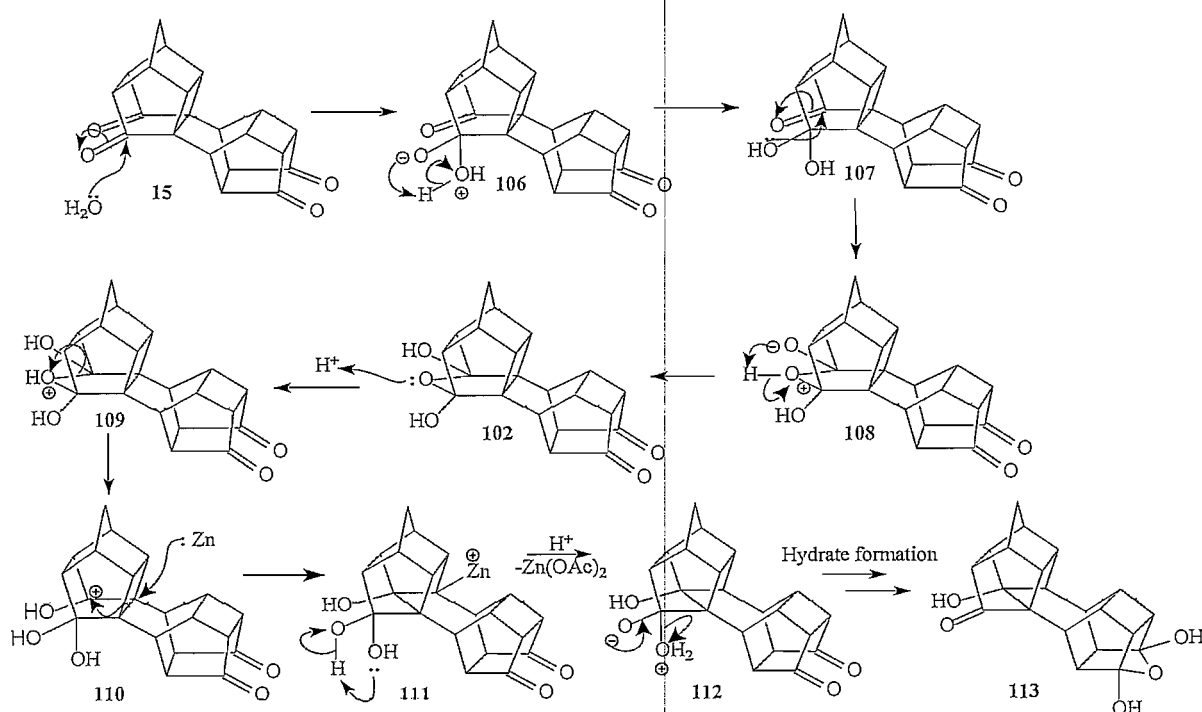


Figure 3.16: The hydroxy ketone (**104**) and the oblique hydroxy ketone (**105**)

Initially the reaction was carried out with the use of 99.9% acetic acid. But the ^{13}C -NMR spectrum showed the presence of only one carbonyl as well as the presence of a hydrate (O-C-O) group at δ_{C} 213.47 and at 110.37 ppm, respectively. **Scheme 3.9** shows a possible mechanism for the hydrate formation as well as the formation of the oblique hydroxy ketone. It was realized that in order for the reaction to occur a hydrate must first form and although the product produced in the previous reaction was a hydrate there is not enough water to solvate the acetic acid in order to release a proton that initiates the oblique hydroxy ketone formation. For this reason the reaction stops at **109**. The mechanism shown here are only for the one side where the LUMO of **15** is situated (**Figure 3.13**).



Scheme 3.9: Mechanism of hydrate and oblique hydroxyl ketone formation

When the reaction was repeated with an 80% acetic acid solution, the ¹³C-NMR showed a mixture of products which included three hydroxyl bearing carbons at δ_C 84.12, 84.25 and 84.20 ppm, which is consistent with a tertiary alcohol. ¹³C-NMR also shows three different carbonyl groups at δ_C 215.13, 215.10 and 215.04 ppm. The spectrum also indicated that there was still a hydrate present together with two geminal alcohol groups. These products were separated by means of their solubility. ¹³C-NMR of the product removed by filtration and washed with water (113) indicated only one carbonyl peak at δ_C 215.13 as well as the presence of a hydrate (O-C-O) at δ_C 109.5. Overall there were 21 peaks which indicates a non-symmetrical hydrate with a geminal diol on the other side. There are two possible oblique ketones that can form (**Figure 3.17**). The formation of 114 can be ruled out based on the fact that if this product formed at all, an additional CH₂ group would have been observed (**Figure 3.17** – red encircled carbon) which is not the case.

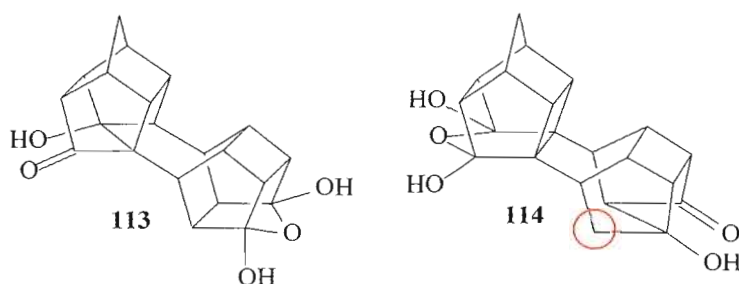
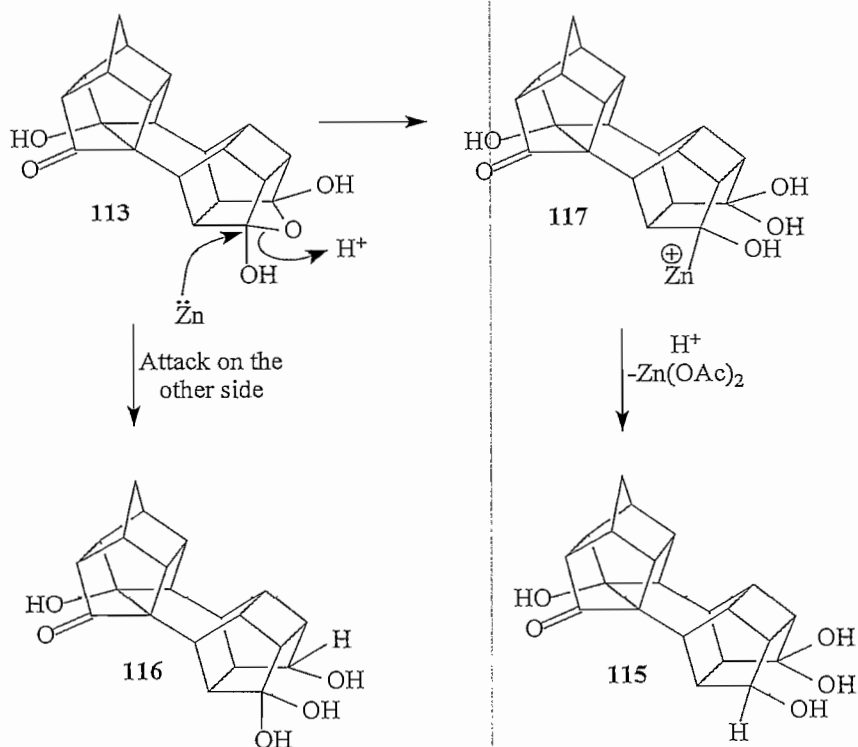


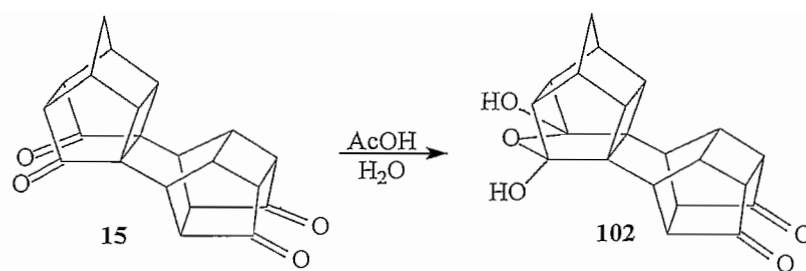
Figure 3.17: The two possible oblique hydroxy ketone that can form during the Zn/AcOH reduction of **15**

The ^{13}C -NMR of the other product isolated, signified that there were 42 resonance signals of which there were two carbonyl peaks at δ_{C} 215.1 and 215.04, two O-C-O peaks at δ_{C} 116.06 and 114.69, two different tertiary hydroxyl bearing carbon atoms at δ_{C} 84.25 and 84.20, two secondary hydroxyl bearing carbon atoms at δ_{C} 77.71 and 76.36, as well as two quaternary carbons at δ_{C} 55.31 and 55.25 ppm. This indicated that there were two isomers of which the degenerate peaks were split due to the isomer effect. Furthermore, the product contained a type of geminal alcohol together with an additional hydroxyl group. If the two different quaternary carbons are also taken into account only one structure is likely. A possible mechanism of product formation (**115** and **116**) is shown in **Scheme 3.10**. It should be noted that the hydrated carbons are equivalent and thus nucleophilic attack can occur on both sides to produce both **115** and **116** in a 1:1 ratio, as seen from the NMR.



Scheme 3.10: A possible mechanism for the formation 115 and 116

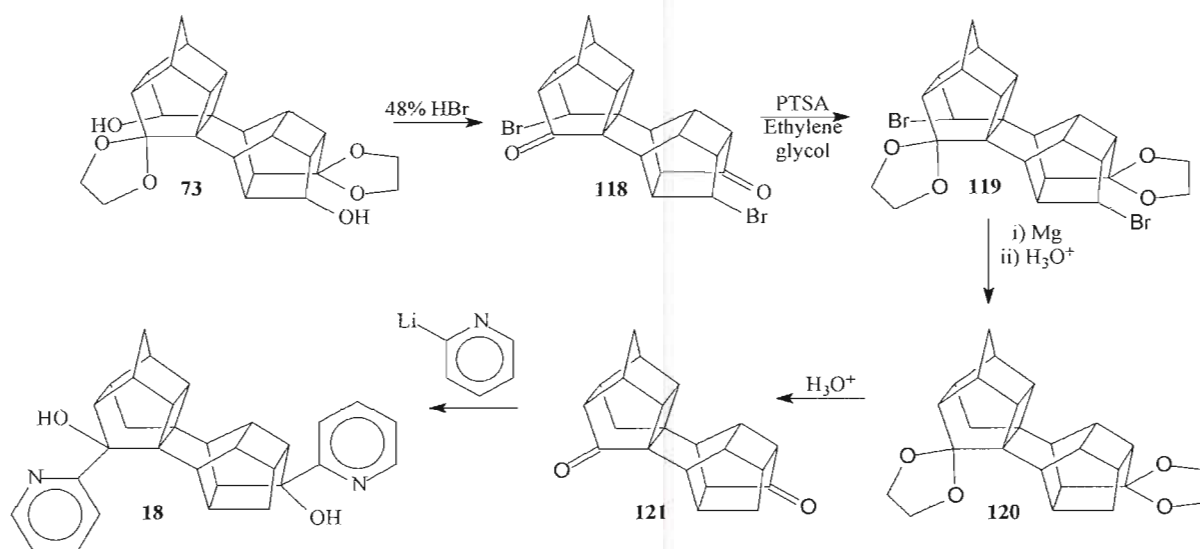
From these results above it seemed that the formation of **102** is chemoselective and that only one hydrate is formed during the reduction of **15** with Zn/AcOH (**Scheme 3.9**). The hydrate **102** was prepared to validate this statement (**Scheme 3.11**). ^{13}C -NMR of **102** showed only one carbonyl group, indicating that the transannular hydrate formation is chemoselective and consequently forms only one product (an interesting observation from the ^1H -NMR of this compound is the amount of singlet peaks. This can be ascribed to the fact that within some cage compounds 1, 2 and 3 bond coupling can be observed which results in extremely small coupling constants (J) which consequently results in the multiplet (that should have formed) to be displayed as singlets). Therefore it was argued that since the reaction in **Scheme 3.9** goes through a hydrate to form the oblique hydroxy ketone, that the side which initially formed the hydrate will be the side which will also form the oblique hydroxy ketone. Taking into consideration that the ^{13}C -NMR spectrum showed only two CH_2 groups due to the isomer effect (δ_{C} 37.03 and 37.01 ppm), the only products that can form is **113**, **115** and **116**.



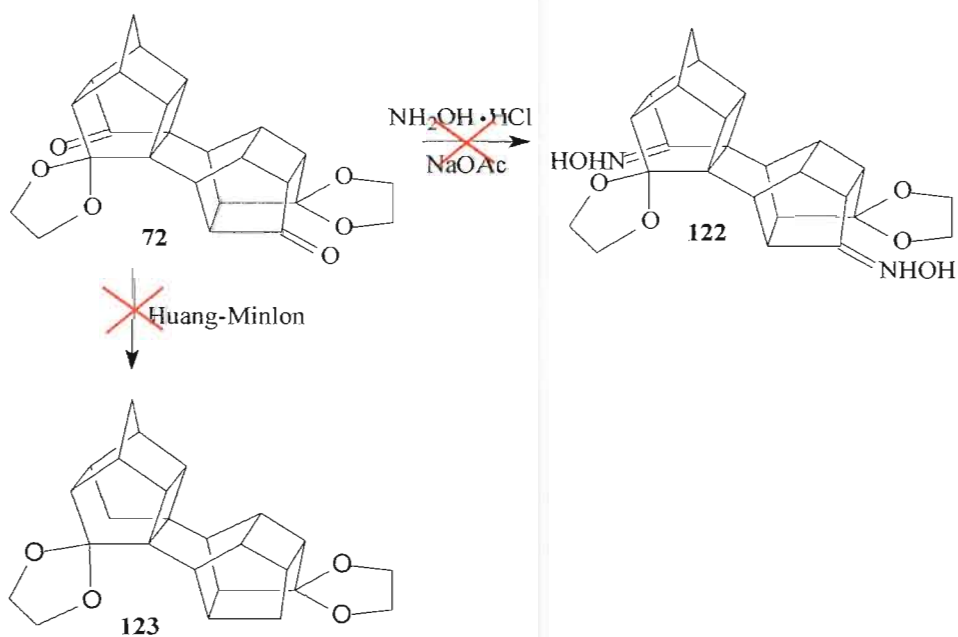
Scheme 3.11: Hydrate formation of **15**

The Zn/AcOH reduction reaction was carried out for 24 hours. This produced exclusively **115** and **116**, since **113** is the precursor for these compounds. Thus it is evident that the formation of **105** does not occur in the way that Beukes¹³⁹ stipulated, but rather through the formation of **102** and subsequent reduction of this compound to form **113**, **115** and **116** depending on the reaction time. As mentioned earlier, due to the low yields alternative routes were followed for the synthesis of **16** and **18**, it is thus obvious that this reaction cannot be used for this purpose.

In order to synthesize **18**, the reaction through the bromo ketone (**118**) looked quite attractive (**Scheme 3.12**). IR and MS confirmed the presence of this compound, but unfortunately solubility problems hindered the confirmation of the structure. Additionally, due to low yields this route is on this stage not feasible. Alternatively, two other routes were attempted to synthesize **16** and **18** (**Scheme 3.13**). The first reaction was the production of the imine from **72**, while the second one was through the use of the Huang-Minlon reaction. Unfortunately both of these reactions failed, yielding only unreacted **72**. This can be ascribed to the steric hindrance of the ketal as well as the cage structure.



Scheme 3.12: A possible route for the synthesis of **18**



Scheme 3.13: Alternative routes tested in order to synthesize **16** and **18**

Chapter 4: Conclusion and Recommendations

4.1. Introduction

In this study alicyclic, bidentate N and O chelating ligands were modelled (**16-19**, **Figure 1.3**) in order to evaluate the hemilability of the ligands, after which attempts have been made to synthesize these ligands. The main focus of this study revolved around the molecular modelling of the substrates and products and the synthesis of nitrogen containing derivatives (**16-19**, **Figure 1.3**) of the hexacyclo-pentadecane compound (**12**).

4.2. Molecular Modelling

The molecular modelling was conducted using the DMol³ module based DFT code^{128, 129} as implemented in the Materials Studio (Version 4.2) program package of Accelrys®, together with the GGA/DNP/PW91 functional was used for all calculations. It was shown by several authors that this configuration was suitable for the modelling of catalytic systems,^{14, 131, 132} but the method needed to be validated for pure organic systems. This was done by comparing crystallographic data with calculated data using the setup as mentioned above. It was found that this method was suitable for both organic and organometallic systems.

Initially it was realized that the proposed synthetic route of the ligands would yield different isomers and thus different isomeric pre-catalysts. For this reason a screening was done in order to evaluate the energy difference between each set of isomers. It was found that the energy difference between the same set of isomers were negligible as well as their respective simplified Grubbs 1 pre-catalysts (**Table 3.9-3.13**).

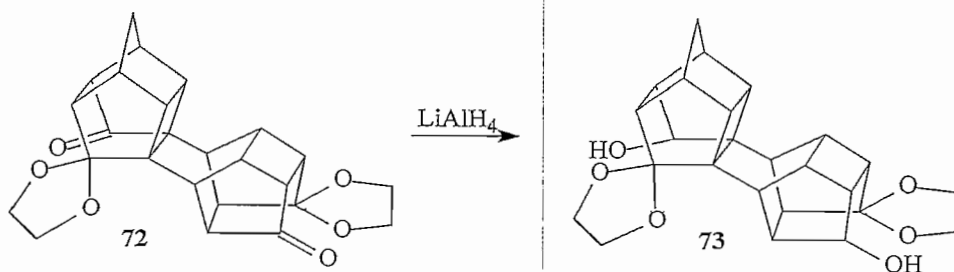
Preliminary modelling dismissed **17** as a possible hemilabile ligand, since it would rather form a transannular ether compound as indicated by **Scheme 3.2**. Additional modelling showed that ligands **16** and **18** could potentially be hemilabile, since the dissociation energies of the Ru-N bond would allow for efficient dissociation. Additionally after dissociation, if the Ru-O bond is turned away, the nitrogen could coordinate with the ruthenium again. The modelling results for ligand **19** were inconclusive and thus the recommendation is made that further investigation of this compound is necessary to evaluate this compound. In order to

investigate this complex (**91**) and make a conclusion, experimental data such as from X-ray crystallography are required. In view of the fact that in this study attempts to synthesize this complex was futile, no experimental data are available for this complex and consequently no conclusion can be made about the coordination ability and hemilability of this complex. It seems that the specific model used to investigate this complex was inadequate to study these properties (coordination ability and hemilability).

4.3. Experimental

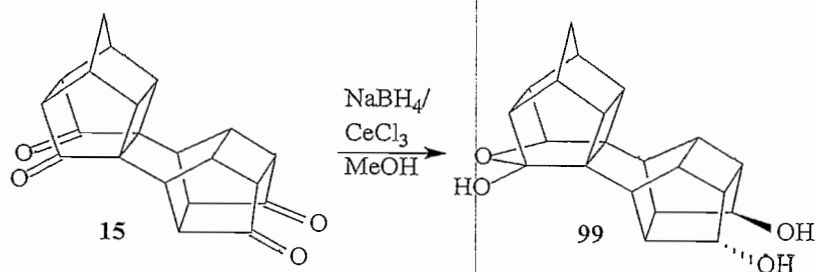
Although all attempts to synthesize ligands **16** and **18** from **12** have failed, a variety of valuable (and interesting) information about the chemistry and physical properties of the derivatives of this compound has been identified. Numerous new compounds have been prepared and characterized by means of IR, MS and NMR.

It was found that the ketones of compound **72** are sterically hindered and resistant to reduction. The reduction of **72** to **73** was achieved by LiAlH_4 (**Scheme 4.1**).



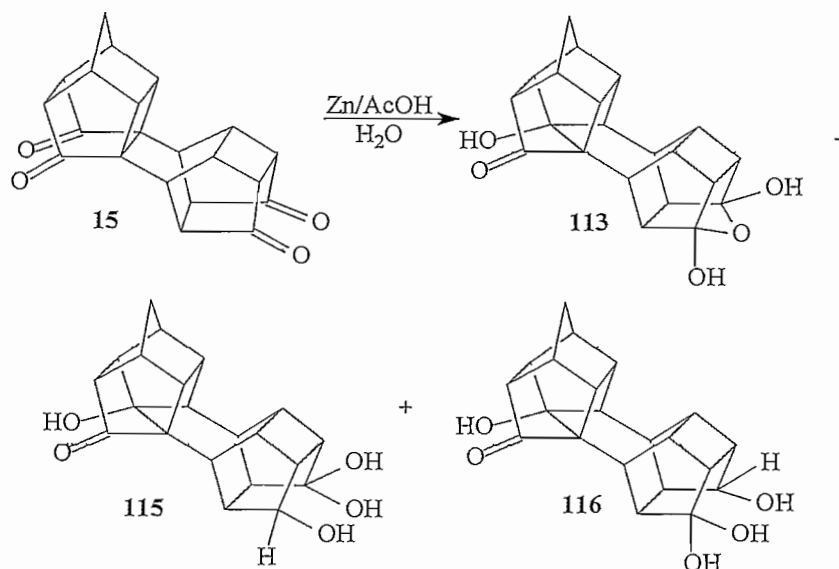
Scheme 4.1: Reduction of **72** with LiAlH_4

Unexpectedly, the reduction of **15** with $\text{NaBH}_4/\text{CeCl}_3$ (Luche reaction, **Scheme 4.2**) resulted in the formation of **99** and not the tetrol **97**. This reaction was done to confirm that all the carbonyl groups of **15** were active.



Scheme 4.2: Luche reduction of **15**

In 1982, Beukes *et al.*¹⁴⁰ suggested that a hydroxy ketone (**105**) can be directly synthesized from **15** by reduction of the one carbonyl group with the use of Zn and acetic acid (**Scheme 3.6**). It was shown that this reaction does not occur as claimed by Beukes, but rather the products **113**, **115** and **116** formed (**Scheme 4.3**). All additional attempts to synthesize **16** and **18** failed.



Scheme 4.3: Reaction of **15** with Zn/AcOH/H₂O

Additionally, the synthesis of **104** and **124** (**Figure 4.1**) must be optimized and in order to analyze these compounds; they can be derivatized to make them more soluble. For example the alcohols of **104** can be esterified. If the reactions of these compounds can be optimized, the next step can also be conducted and based on the analyses of the new products, confirmation of the structures of **104** and **124** can be obtained.

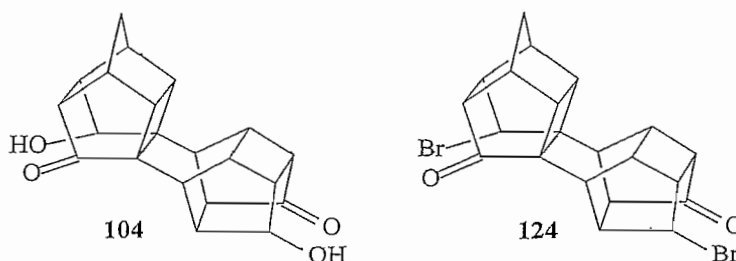


Figure 4.1: Structures of **104** and **124**

Chapter 5: Methodology

5.1. Molecular Modelling

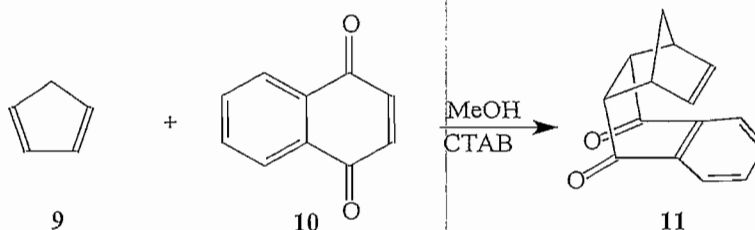
The quantum-chemical calculations were carried out by density functional theory (DFT) since it usually gives realistic geometries, relative energies and vibrational frequencies for transition metal compounds. All calculations were performed with the DMol³ DFT code as implemented in Accelrys Materials Studio[®] 4.2 using GGA/DNP/PW91 functional. The convergence criteria for these optimisations consisted of threshold values of 2×10^{-5} Ha, 0.004 Ha/Å and 0.005 Å for energy, gradient and displacement convergence, respectively; while a self-consistent field (SCF) density convergence threshold value of 1×10^{-5} Ha was specified. The electron density, frontier orbitals and Fukui-function was also calculated. Two computer systems were used for calculations, viz.

- HP Proliant CP4000 Linux Beowulf cluster, with 12 calculation nodes consisting of 4 HP DL145, 2 x 2.8 GHz AMD Opteron 64 CPU, 2 GB RAM, running Redhat Enterprise Linux 4
- HP Compaq dx2200 MT Intel® Core™2 Duo T7300 CPU @ 2.00 GHz, 3 GB RAM running Microsoft Windows XP Professional with service pack 2.

5.2. Synthesis

Experimental data were recorded using the following instruments: Infrared spectra (KBr discs) were recorded on a Bruker Tensor 27-IR spectrometer; EI mass spectra were obtained at 70 eV on a Micromass Autospec-TOF mass spectrometer and FAB mass spectra were obtained on a VG 70-SEQ magnetic sector analyser. NMR data were collected on a Varian Gemini-300 NMR spectrometer and a Bruker 600 MHz Avance Ultrashield. Melting points were determined using a Büchi Melting Point B-540 apparatus. Melting points are uncorrected.

5.2.1. Synthesis of Diels-Alder adduct of 1,4-naphthoquinone and cyclopentadiene (11)⁴⁰



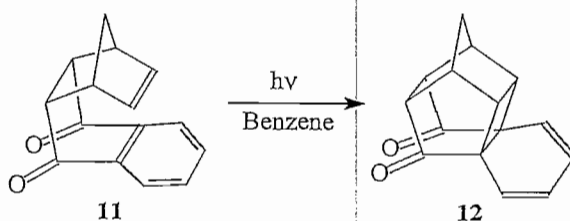
10 g 1,4-naphthoquinone (**10**) was dissolved in 800 ml methanol, after which 10 g of activated carbon was added and stirred for 10 minutes on a hot plate and filtered to yield a yellow solution of 1,4-naphthoquinone. To this solution 2.5 g cetyl trimethylammonium bromide (CTAB) was added, followed by the addition of 25 ml freshly distilled cyclopentadiene (**9**). After 3 hours of stirring in the dark at room temperature, the solution was concentrated to a small volume and was poured into 500 ml water, upon which a white to light-peach coloured precipitate formed. The precipitate was filtered and washed with cold water and a small amount of methanol, successively. The crystals were dried to yield 12.03 g (85 %) white crystals. Melting point: 101 °C.

IR (KBr): ν_{max} 3443, 2992, 1680, 1589 and 1270 cm^{-1} .

MS (EI): M^+ m/z 224.

NMR: data were identical to the authentic samples.

5.2.2. Synthesis of hexacyclo[7.4.2.0^{1,9}.0^{3,7}.0^{4,14}.0^{6,15}]pentadeca-10,12-diene-2,8-dione (**12**)^{40, 139}



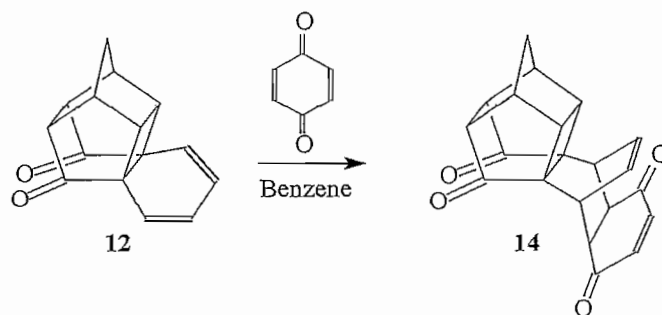
IR (KBr): $\nu_{\max}$ 3443, 2984, 1745, 1089 and 704 cm^{-1} .

MS (EI): M^+ m/z 224.

^{13}C -NMR [CDCl_3 , 75 MHz]: δ_{C} 210.33 (S, C=O), 124.67 (D, HC=CH), 119.73 (D, HC=CH), 54.538 (D), 51.57 (D), 50.10 (S), 44.16 (D), 38.91 (T, CH_2) ppm.

^1H NMR [CDCl_3 , 300MHz]: δ_{H} 5.96-5.90 (m, HC=CH), 5.38-5.31 (m, HC=CH), 3.31-3.0 (s), 2.98-2.93 (m), 2.77-2.76 (s), 1.98-1.93 (d) and 1.74-1.70 (d) ppm.

5.2.3. Synthesis of octacyclo[10.6.2.^{15,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,18}]heneicosa-15,19-diene-3,10,14,17-tetrone (14)⁴¹



4.8 g of **12** was dissolved in 350 ml benzene to which 2.32 g para-benzoquinone was added and refluxed for 20 h after which a yellow solid precipitated. The solid was filtered and washed with 40 ml 50% water/methanol solution to remove any unreacted para-benzoquinone and **12**. The yellow precipitate were dried to yield 6.79 g (95 %). Melting point: 265 °C, literature 265 – 267 °C.

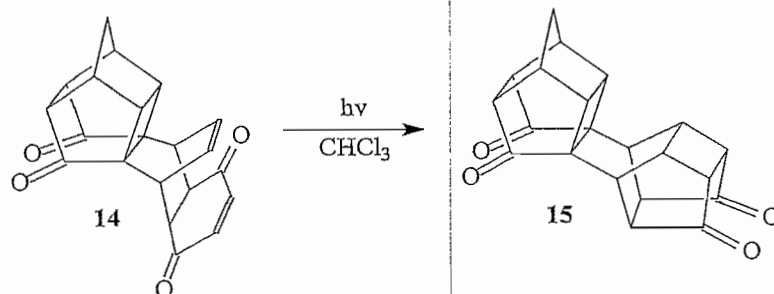
IR (KBr): $\nu_{\max}$ 2924, 1744, 1716, 1666, 1276 and 1062 cm^{-1} .

MS (EI): M^+ m/z 332.

^{13}C -NMR [CDCl_3 , 75 MHz]: δ_{C} 211.96 (S, C=O), 197.75 (S, C=O), 141.43 (D, HC=CH), 133.79 (D, HC=CH), 55.99 (D), 53.15 (S), 43.47 (D), 43.39 (D), 41.66 (D), 40.68 (T, CH_2), 34.28 (D) ppm.

^1H NMR [CDCl_3 , 300MHz]: δ_{H} 6.63 (s, HC=CH), 6.38-6.36 (m, HC=CH), 3.57-3.56 (s), 3.47-3.44 (m), 2.89-2.87 (t), 2.74-2.73 (d), 2.64-2.63 (d), 1.97-1.93 (d, CH_2), 1.84-1.80 (d, CH_2) ppm.

5.2.4. Synthesis of decacyclo[10.7.2.0^{1,2}.0^{2,6}.0^{3,10}.0^{4,9}.0^{7,11}.0^{14,20}.0^{15,21}]heneicosane-5,8,13,19-tetrone (15)⁴²



6 g of **14** was dissolved in 600 ml chloroform and irradiated with a medium pressure UV lamp for 3 hours in Pyrex vessels. After 3 h a white solid precipitated which was filtered and washed with chloroform to remove any unreacted reagents (4.31 g, 95 %). Melting point: 371°C.

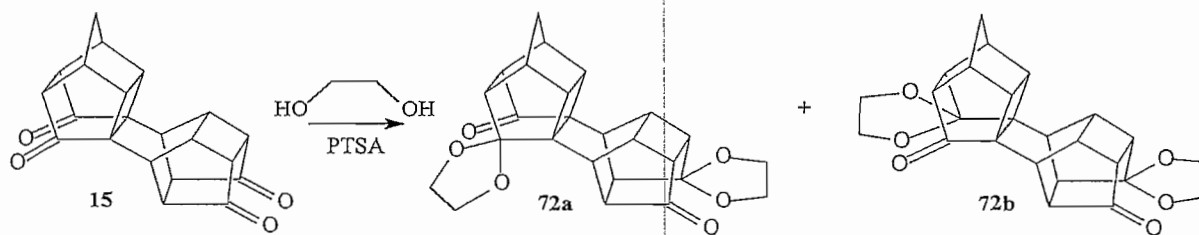
IR (KBr): $\nu_{\max}$ 2984, 1736, 1709, 1347, 1301, 1237, 1145 and 1095 cm^{-1} .

MS (EI): M^+ m/z 332.

¹³C-NMR [CDCl₃, 75 MHz]: δ_{C} 210.50 (S, C=O), 209.22 (S, C=O), 55.12 (D), 46.77 (S), 45.53 (D), 43.99 (D), 43.93 (D), 40.92 (D), 40.74 (T, CH₂), 33.12 (D), 31.81 (D) ppm.

¹H NMR [CDCl₃, 300MHz]: δ_{H} 3.38-3.34 (m), 3.15-3.13 (m), 3.14-2.96 (m), 2.86-2.84 (s), 2.80-2.79 (s), 2.23-2.20 (m), 2.08-2.07 (d, CH₂), 1.96-1.92 (d, CH₂) ppm.

5.2.5. Synthesis of oxa-ketal (72)^{140, 146}



5 g of **15**, 1.9 g (1.7 ml) ethylene glycol and 0.3 g *p*-toluenesulfonic acid (PTSA) was added in a conical flask equipped with a magnetic stirrer and a Dean-Stark apparatus, and refluxed in 300 ml toluene for 12 h. After this time, the toluene was removed under reduced pressure and a brown solid precipitated. The solid was washed with cold water and 10 ml cold methanol, to remove the unreacted ethylene glycol and PTSA, which liberated light brown -

white precipitate. The crystals were dried to yield 5.66 g (89 %) of **72**. Melting point: 253 °C.

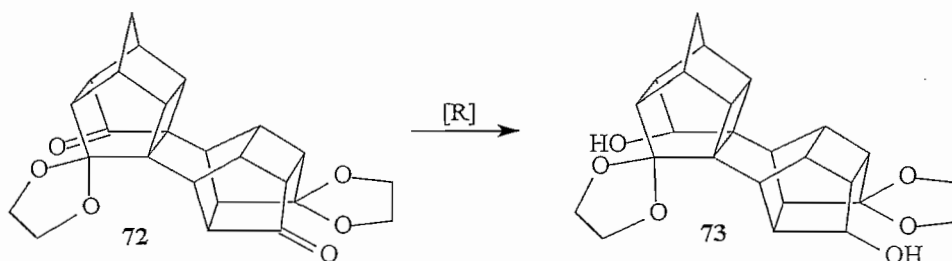
IR (KBr): $\nu_{\max}$ 2970, 1743, 1332, 1111 and 942 cm^{-1} .

MS (EI): M^+ m/z 420.

^{13}C -NMR [CDCl_3 , 150 MHz]: δ_{C} 214.04 (S, C=O), 213.94 (S, C=O), 213.41 (S, C=O), 212.96 (S, C=O), 113.55 (S, O-C-O), 113.31 (S, O-C-O), 113.04 (S, O-C-O), 112.94 (S, O-C-O), 65.81 (T, O-CH₂), 65.65 (T, O-CH₂), 65.43 (T, O-CH₂), 65.31 (T, O-CH₂), 65.26 (T, O-CH₂), 65.24 (T, O-CH₂), 64.56 (T, O-CH₂), 64.27 (T, O-CH₂), 54.23 (D), 54.11 (D), 51.18 (D), 46.84 (S), 46.74 (S), 44.49 (D), 44.44 (D), 44.19 (D), 43.86 (D), 43.41 (D), 43.36 (D), 42.88 (D), 42.64 (D), 42.55 (D), 42.45 (D), 42.38 (D), 42.20 (D), 41.86 (D), 39.03 (T, CH₂ of bridge), 38.98 (D), 38.19 (D), 35.59 (D), 35.24 (D), 32.79 (D), 32.04 (D), 31.47 (D), 31.10 (D), 30.33 (D) ppm.

^1H NMR: This spectrum consists of a series of multiples and thus will not be given here.

5.2.6. Synthesis of the hydroxy-ketal (**73**)



Method 1: 2 g of the diketal (**72**) was dissolved in 100 ml ethanol. The solution was cooled to 0 °C by means of an ice bath. 1.5 g sodium borohydride (NaBH_4) was added in small amounts so that the temperature did not rise above 5 °C. After addition, the reaction was stirred for 2 h in the ice bath, after which it was quenched with the addition of a solution of 50 ml water and 5 ml HCl. The resulting mixture was subjected to rotary evaporation in order to remove the excess ethanol. Subsequently, the solution was extracted three times with 50 ml CH_2Cl_2 . The combined organic layers were washed with a small amount of water and successively with brine. The organic layer was dried with MgSO_4 and filtered, after which the solvent was removed by rotary evaporation. IR and MS analysis showed no trace of a hydroxyl group, but rather the diketal (**72**) as the only compound present.

Method 2:¹⁴¹ (Luche reaction) 2 g of the diketal (72) was dissolved in a 0.4 M solution of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in ethanol. The solution was cooled to 0 °C by means of an ice bath. 1.5 g sodium borohydride (NaBH_4) was added in small amounts so that the temperature did not rise above 5 °C. After addition, the reaction was stirred for 2 h in the ice bath, after which it was quenched with the addition of a solution of 50 ml water and 5 ml HCl. The resulting mixture was subjected to rotary evaporation in order to remove the excess ethanol. Subsequently, the solution was extracted three times with 50 ml CH_2Cl_2 . The combined organic layers were washed with a small amount of water and successively with brine. The organic layer was dried with MgSO_4 and filtered, after which the solvent was removed by rotary evaporation. IR and MS analysis showed no trace of a hydroxyl group, but rather the diketal (72) as the only compound present.

Method 3:¹⁴³ (Meerwein-Ponndorf-Verley reduction) 3 g of 72 and 5 g of isopropanol was added to 100 ml toluene to which 0.3 g $\text{Al}(\text{O}^i\text{Pr})_3$ was added. The reaction mixture was refluxed at 60 °C for 96 h. The solution was cooled and extracted with 3x75 ml CH_2Cl_2 and the combined organic layers were washed with 100 ml water. The organic layer was dried with MgSO_4 and concentrated by means of rotary evaporation. IR and MS analysis showed no trace of a hydroxyl group, but rather the diketal (72) as the only compound present.

Method 4:^{146, 147} 1.2 g LiAlH_4 was added over a period of 30 minutes to a stirred solution of 4 g of 72 in 100 ml dry THF. After addition the solution was refluxed for 30 minutes, and left to cool to room temperature. 200 ml H_2O was added to decompose the reaction mixture. This solution was extracted with 3 x 50 ml dichloromethane, washed with water, dried over MgSO_4 and the solution was rotavaped. The brown oil that formed was dissolved in 2 ml dichloromethane and added to 20 ml petroleum ether. The milky solution was poured into a clean beaker and left to evaporate to yield 3.8 g (94%) of 73 as white solids. Melting point: 223°C.

IR (KBr): ν_{max} 3427, 2966, 2890, 1468, 1454, 1320, 1282, 1269, 1150, 1102, 1068, 1027, 1003, 956 and 581 cm^{-1} .

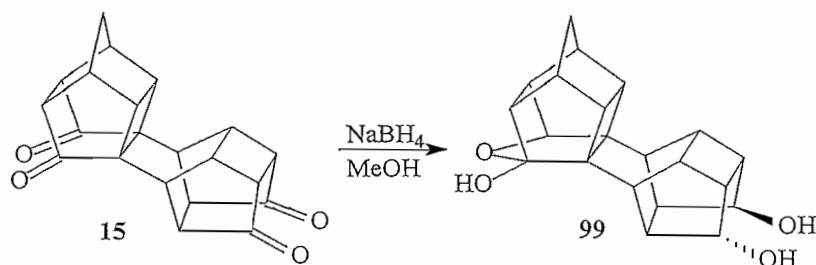
MS (EI): M^+ m/z 424.

^{13}C -NMR [CDCl_3 , 150 MHz]: δ_{C} 115.70 (S, O-C-O), 115.69 (S, O-C-O), 115.12 (S, O-C-O), 115.07 (S, O-C-O), 75.67 (D), 73.79 (D), 65.76 (T, O- CH_2 -R), 65.60 (T, O- CH_2 -R),

65.08(T, O-CH₂-R), 64.94 (T, O-CH₂-R), 64.06 (T, O-CH₂-R), 63.86 (T, O-CH₂-R), 62.34 (T, O-CH₂-R), 62.08(T, O-CH₂-R), 47.70 (D), 47.63 (D), 47.46 (D), 47.29 (D), 44.58 (S), 43.89 (S), 43.71 (S), 43.63 (D), 43.47 (D), 43.16 (S), 41.89 (D), 41.83 (D), 41.26 (D), 41.07 (D), 40.96 (D), 40.57 (D), 40.37 (D), 39.80 (D), 39.61 (D), 39.31 (D), 38.25 (D), 38.22 (D), 38.00 (D), 36.93 (D), 35.57 (D), 35.49 (D), 34.89 (T, CH₂ Bridge), 34.87 (T, CH₂ Bridge), 34.74 (D), 34.62 (D), 32.70 (D), 31.38 (D) ppm.

¹H NMR [CDCl₃, 600MHz]: Due the complexity of the spectrum no assignments were made, except at δ_H 6.13-6.00 (dd, OH) and 5.07-5.01 (dd, OH).

5.2.7. Reduction of 15



1.0 g of the tetrone (**15**) was dissolved in a 0.4 M solution of CeCl₃·7H₂O in methanol. The solution was cooled to 0 °C by means of an ice bath. 0.5 g sodium borohydride was added in small amounts, so that the temperature did not rise above 5 °C. After addition, the reaction was stirred for 3h and quenched with the addition of a solution of 50 ml water and 5 ml HCl. The resulting mixture was subjected to rotary evaporation in order to remove the excess methanol. Subsequently, the solution was extracted three times with CH₂Cl₂. The combined organic layers were washed with a small amount of water and successively with brine. The organic layer was dried with MgSO₄ and filtered, after which the solvent was removed by rotary evaporation which resulted in 0.92 g (91%) of **99** as a white precipitate. Melting point: 175 °C.

IR (KBr): ν_{max} 3375, 2958, 2871, 1445, 1404, 1351, 1309, 1236, 1147, 1119, 1103 and 1062 cm⁻¹.

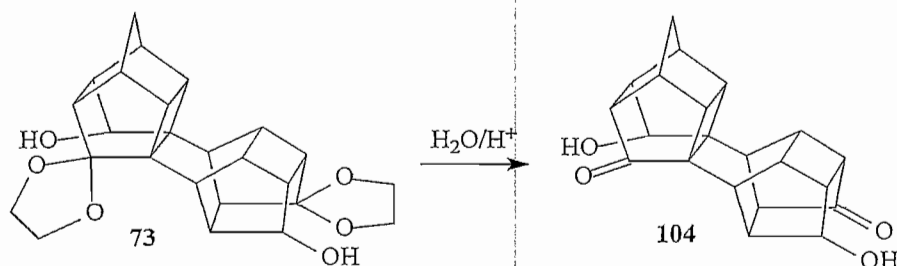
MS (FAB): [M+H]⁺ *m/z* 339.

¹³C-NMR [DMSO-*d*₆, 150 MHz]: δ_C 117.39 (S, O-C-O), 117.22 (S, O-C-O), 111.00 (S, O-C-O), 110.88 (S, O-C-O), 78.80 (D), 78.65 (D), 76.74 (D, C-OH), 76.72 (D, C-OH), 74.63 (D, C-OH), 74.62 (D, C-OH), 74.59 (D, C-OH), 46.81 (D), 46.73 (D), 46.67 (D), 46.43 (D),

46.42 (D), 46.35 (D), 46.30 (D), 44.61 (D), 44.62 (D), 44.99 (S), 44.51 (S), 44.28 (S), 43.90 (S), 43.81 (S), 42.80 (D), 42.78 (D), 42.48 (D), 42.41 (D), 41.65 (D), 41.62 (D), 41.49 (D), 41.47 (D), 40.97 (D), 40.72 (D), 40.03 (D), 38.46 (D), 37.69 (D), 37.24 (D), 36.73 (D), 36.65 (D), 36.51 (D), 36.46 (D), 36.45 (D), 36.43 (D), 36.28 (D), 35.42 (T, CH₂ – Bridge), 34.60 (T, CH₂ – Bridge), 31.30 (D) ppm.

¹H NMR: Due the complexity of the spectrum no assignments were made.

5.2.8. Synthesis of hydroxy-ketone (**104**)¹⁴⁸



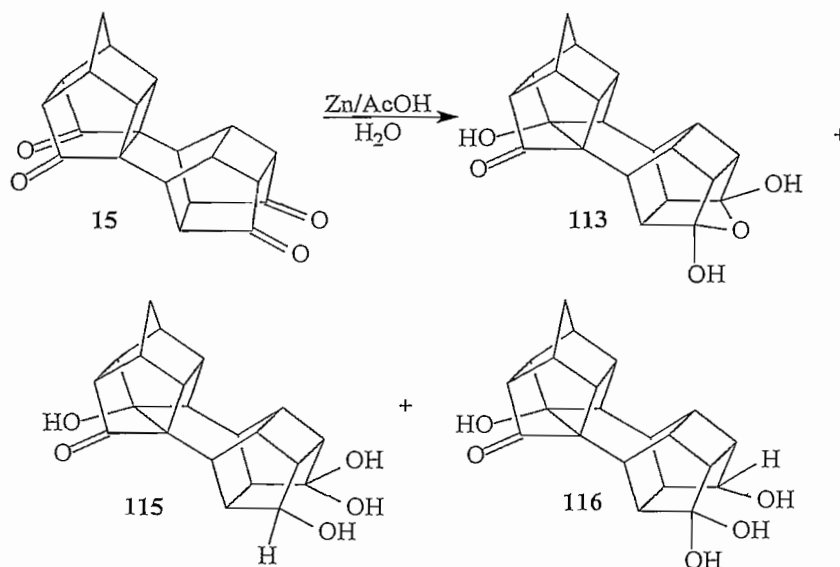
1 g of **73** was added to a stirring solution of a 24% HBr solution. This was refluxed for 12 hours after which the hot solution was poured over ice-water. The solution was extracted with 3 x 50 ml CH₂Cl₂, washed with water and dried over MgSO₄. The CH₂Cl₂ was concentrated on a rotary evaporator to yield a small amount of clear oil. The oil was dissolved in 1ml CH₂Cl₂ and poured into 20 ml petroleum ether. A white solid precipitated and was filtered off to yield 116 mg (14%) of **104**.

IR (KBr): ν_{max} 3423, 2964, 2867, 1720, 1333, 1304, 1276, 1150, 1131, 1076, 1056, 1004 and 923 cm⁻¹.

MS (EI): M⁺ m/z 336.

NMR data were inconclusive in identification of the product, due to solubility problems.

5.2.9. Reaction of 15 with Zn/AcOH/H₂O¹⁴⁹



20 g Zinc was activated with a small amount of hydrochloric acid (HCl), after which the Zn was washed with acetone and subsequently with water. The activated Zn was added to a stirred solution of 100 ml 80 % acetic acid/H₂O (AcOH) and 1 g of **15**. This solution was refluxed for 5 h, after which it was subjected to rotary evaporation, until only a small amount of acetic acid was left and a white solid precipitated. This solid was filtered off and water was added to the mother liquor after which **113** precipitated. The remaining filtrate was dissolved in water and extracted with 3x50 ml CH₂Cl₂. The combined organic layers were washed with water and dried over MgSO₄. The CH₂Cl₂ was concentrated on a rotary evaporator to yield **115** and **116** (558 mg) as a white solid.

Data for **113**:

Melting point: 281°C

IR (KBr): $\nu_{\max}$ 3400, 2961, 2874, 1741, 1355, 1296, 1226, 1196, 1134, 1071, 1013, 951, 908, 864, 643 and 499 cm⁻¹.

MS (FAB): [M]⁺ m/z 352.

¹³C-NMR [DMSO, 150 MHz]: δ_c 215.13 (S, C=O), 109.54 (S, O-C-O), 108.10 (S, O-C-O), 84.12 (S), 55.32 (D), 49.85 (D), 49.71 (D), 49.66 (D), 49.52 (D), 47.89 (D), 47.72 (D), 47.63 (S), 45.44 (D), 44.76 (D), 43.58 (D), 38.92 (D), 38.57 (D), 37.96 (D), 37.05 (D), 36.75 (D), 31.72 (D) ppm.

^1H NMR [DMSO, 300MHz]: δ_{H} 6.55 (s), 5.12 (s), 3.35 (s), 2.54-1.46 (a series of multiples), 1.48-1.46 (d, CH_2 – Bridge), 1.38-1.36 (d, CH_2 – Bridge) ppm.

Data for 115 and 116:

Melting point: 278°C

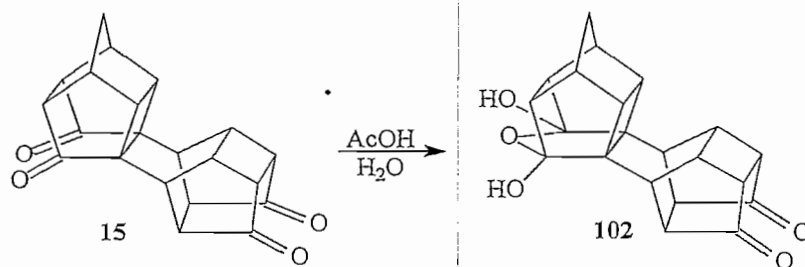
IR (KBr): ν_{max} 3307, 2969, 1740, 1332, 1273, 1228, 1156, 1066, 1013, 913, 850, 709 and 540 cm^{-1} .

MS (FAB): $[\text{M}-\text{H}_2\text{O}+\text{H}]^+ m/z$ 337.

^{13}C -NMR [DMSO, 150 MHz]: δ_{C} 215.10 (S, C=O), 215.04 (S, C=O), 116.06 (S, O-C-O), 114.69 (S, O-C-O), 84.25 (S), 84.20 (S), 77.71 (D), 76.36 (D), 55.31 (S), 55.25 (S), 49.88 (D), 49.86 (D), 49.70 (D), 49.66 (D), 48.11 (D), 47.93 (D), 47.91 (D), 47.78 (D), 47.70 (D), 47.66 (D), 45.50 (D), 45.42 (D), 45.25 (D), 45.08 (D), 44.74 (D), 44.70 (D), 42.77 (D), 41.45 (D), 40.73 (D), 40.04 (D), 38.74 (D), 38.67 (D), 38.56 (D), 38.53 (D), 38.03 (D), 37.53 (D), 37.48 (D), 37.03 (T, CH_2 – Bridge), 37.01 (T, CH_2 – Bridge), 35.52 (D), 32.54 (D), 30.33 (D) ppm.

^1H NMR [DMSO, 300MHz]: δ_{H} 6.66 (s), 5.22 (s), 4.35-4.33 (t), 4.26-4.24 (t), 3.33 (s), 2.72-2.71 (t), 2.67-2.66 (t), 2.61-2.56 (m), 2.52-2.40 (series of multiples), 2.36-2.34 (d), 2.26-2.22 (m), 2.14-1.88 (series of multiples), 1.75-1.72 (m), 1.48-1.46 (d, CH_2 – Bridge), 1.38-1.36 (d, CH_2 – Bridge) ppm.

5.2.10. Synthesis of the transannulated hydrate (102)



1g of 15 was added to a stirred solution of 80% AcOH/H₂O. After 24h of reflux, a white solid precipitated. The solution was cooled, filtered and dried to yield 1.01 g of 102 (96%).

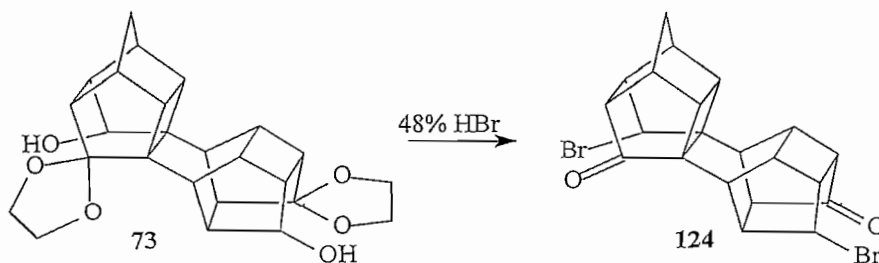
IR (KBr): ν_{max} 3412, 2984, 1736, 1709, 1348, 1302, 1237, 1201, 1146, 1096, 911 and 575 cm^{-1} .

MS (FAB): $[\text{M}+\text{H}]^+ m/z$ 351.

^{13}C -NMR [DMSO, 150 MHz]: δ_{C} 213.48 (S, C=O), 110.37 (S, O-C-O), 54.84 (D), 48.74 (S) 46.65 (D), 44.92 (D), 43.43 (D), 40.55 (T, CH_2 – Bridge) 40.25 (D), 34.67 (D), 31.91 (D) ppm.

^1H NMR [DMSO, 300MHz]: δ_{H} 6.82, 3.34, 2.93, 2.88, 2.74, 2.63, 2.49, 2.39, 2.20, 1.95, 1.93, 1.92, 1.81, 1.79 ppm.

5.2.11. Synthesis of the bromo ketone (**124**)¹⁴⁸



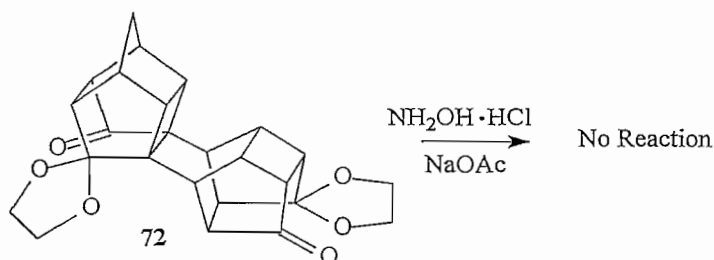
20 ml 48% HBr was added to 1 g of the hydroxy-ketal (**73**) and the solution was refluxed for 12 hours, upon which the solution turned black. The hot solution was then poured into ice-water and light-brown solids precipitated as well as black platelets, all of which were filtered off. The filtrate was washed with a small amount of CH_2Cl_2 , which removed **124**. The light-brown solution was left to dry to yield 368 mg (33%) of **124**.

IR (KBr): ν_{max} 3427, 2973, 1735, 1332, 1298, 1230, 1156 and 1017 cm^{-1} .

MS (EI): M^+ m/z 462.

NMR data were inconclusive in identification of the product, due to solubility problems.

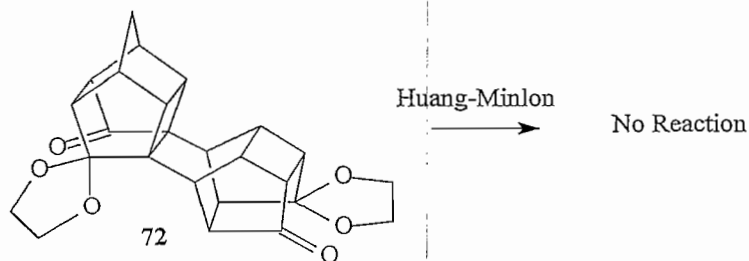
5.2.12. Imine synthesis from **72**



3 g of **72**, 2.2 g $\text{NH}_2\text{OH}\cdot\text{HCl}$ and 5.4 g NaOAc was added to 15 ml water and 35 ml ethanol. The solution was autoclaved at 110 $^{\circ}\text{C}$ for 20 h. After this time the solution was evaporated

on a steam bath to a small volume, after which a white solid precipitated. The precipitate was filtered off, but the IR spectrum was identical to that of **72**.

5.2.13. Huang-Minlon reduction of **72**^{146, 150}



4 g of **72** was dissolved in 100 ml ethylene glycol to which 7.0 g $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ was added and heated at 120 °C. After 90 min, 9 g KOH was added and the excess $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ and water was distilled off until the temperature reached 180 °C. The reaction mixture was refluxed for 3 h and the solution was distilled again to remove some of the excess ethylene glycol. The solution was extracted with 3x100 ml CH_2Cl_2 and the combined organic layers were washed with water. The organic phase was dried over MgSO_4 and concentrated under reduced pressure, but the IR spectrum was identical to that of **72**.

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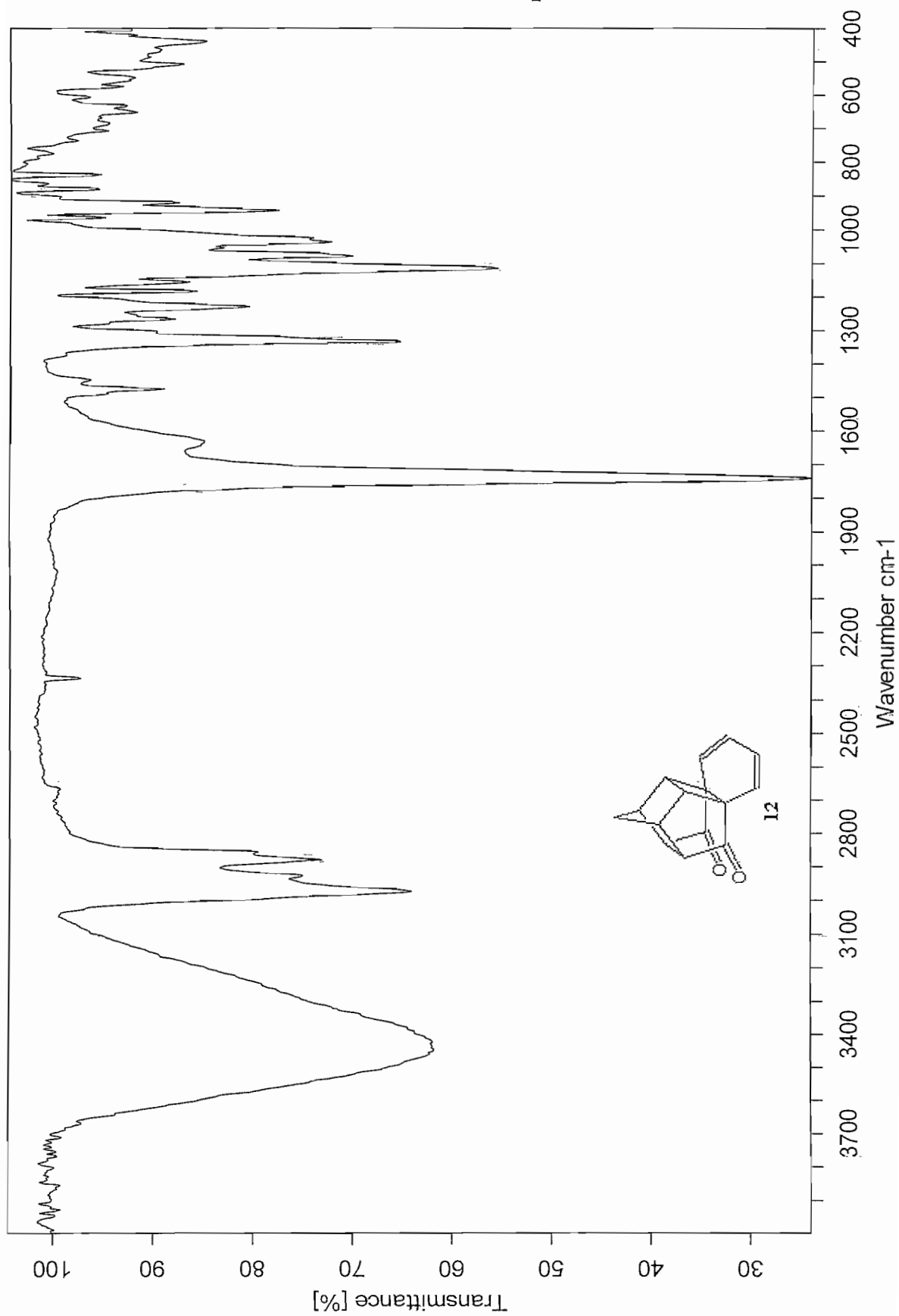
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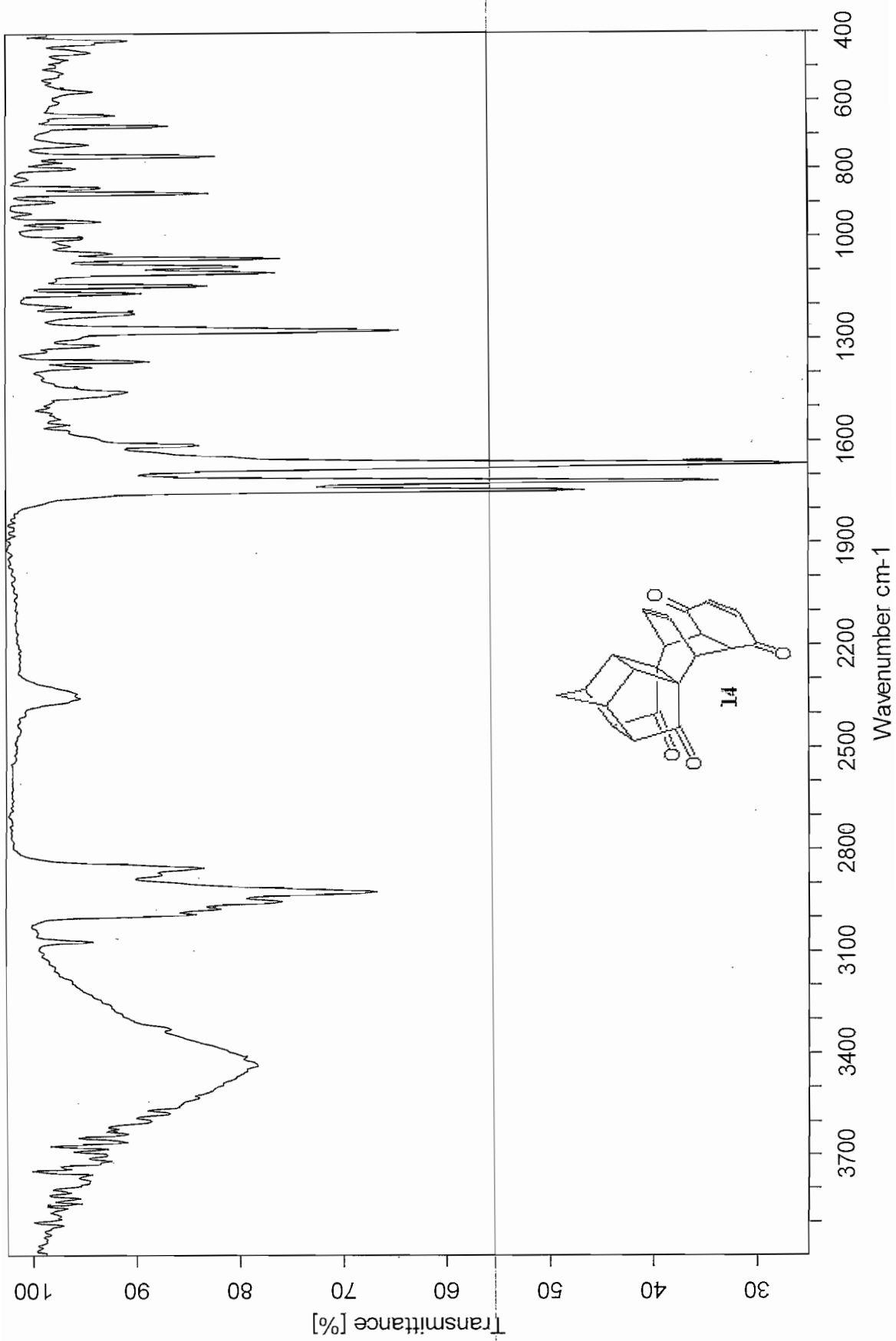
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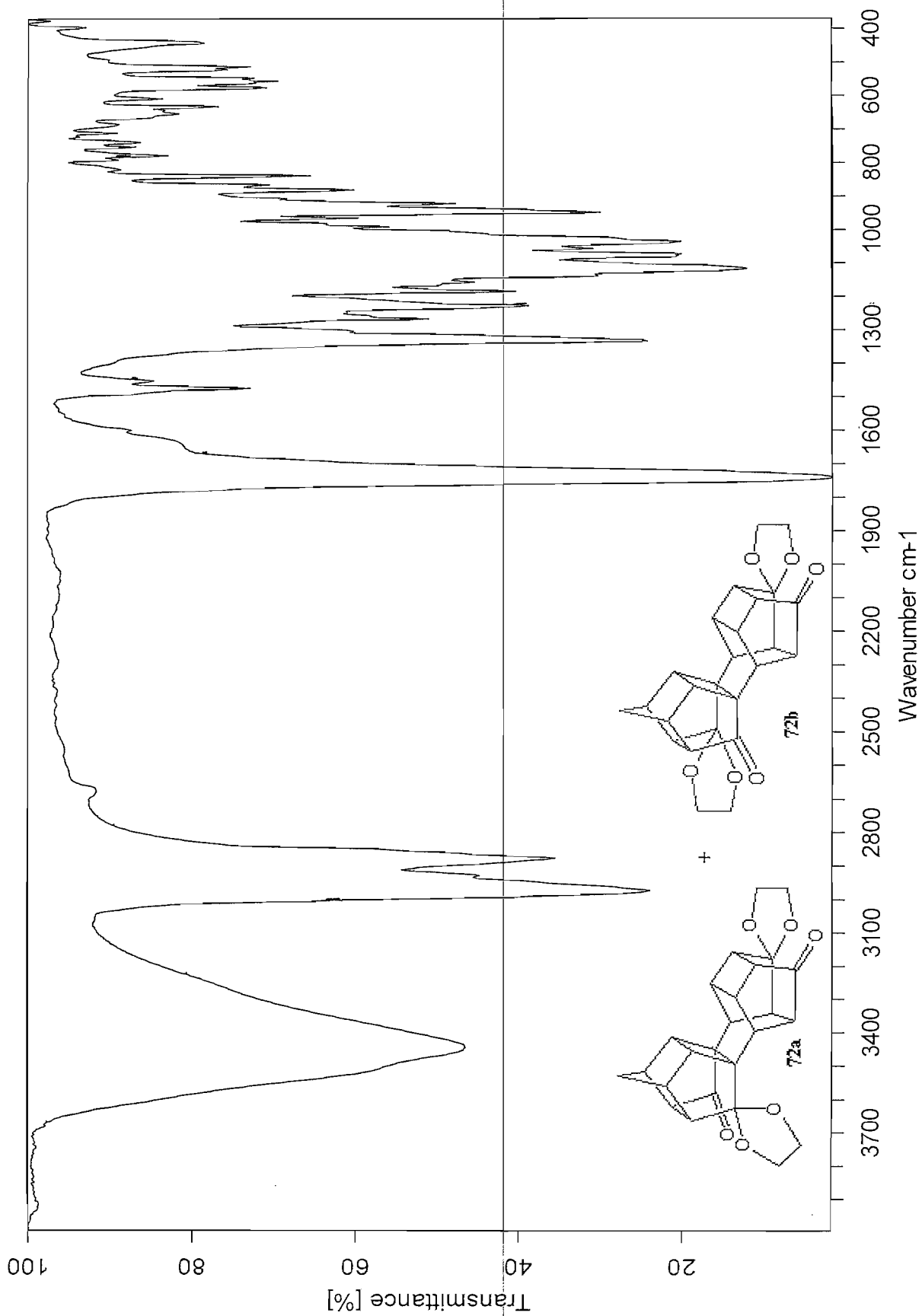
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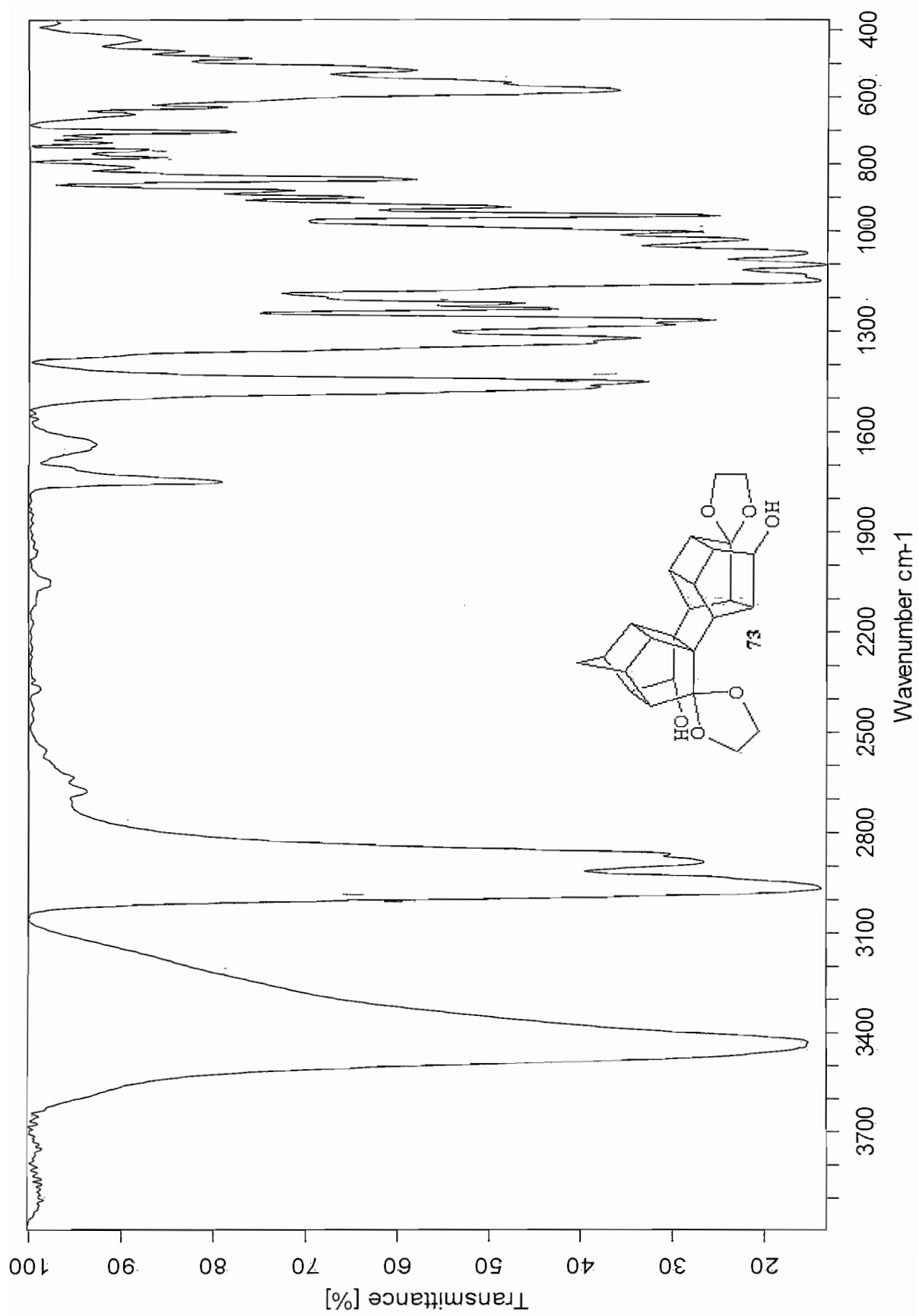
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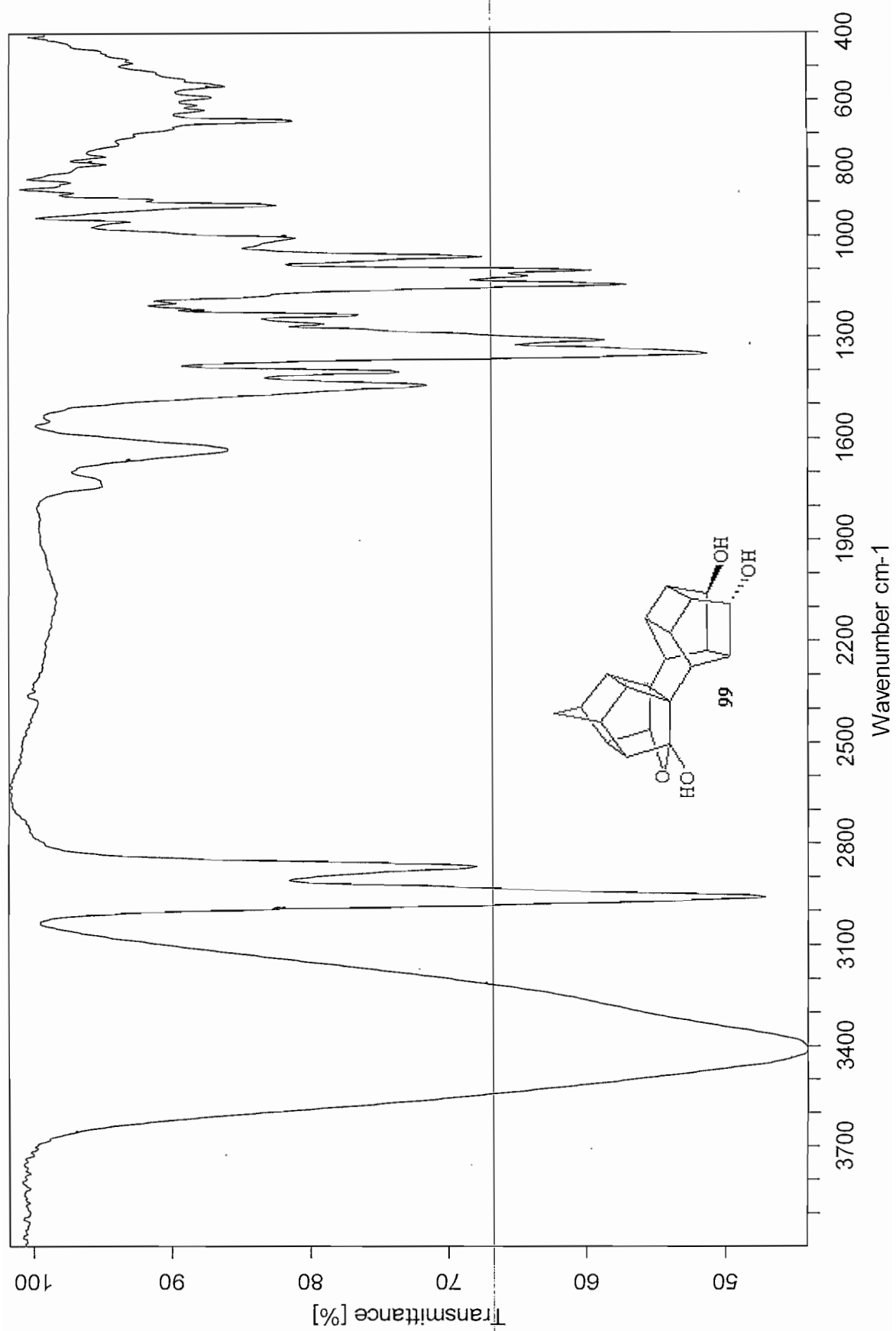
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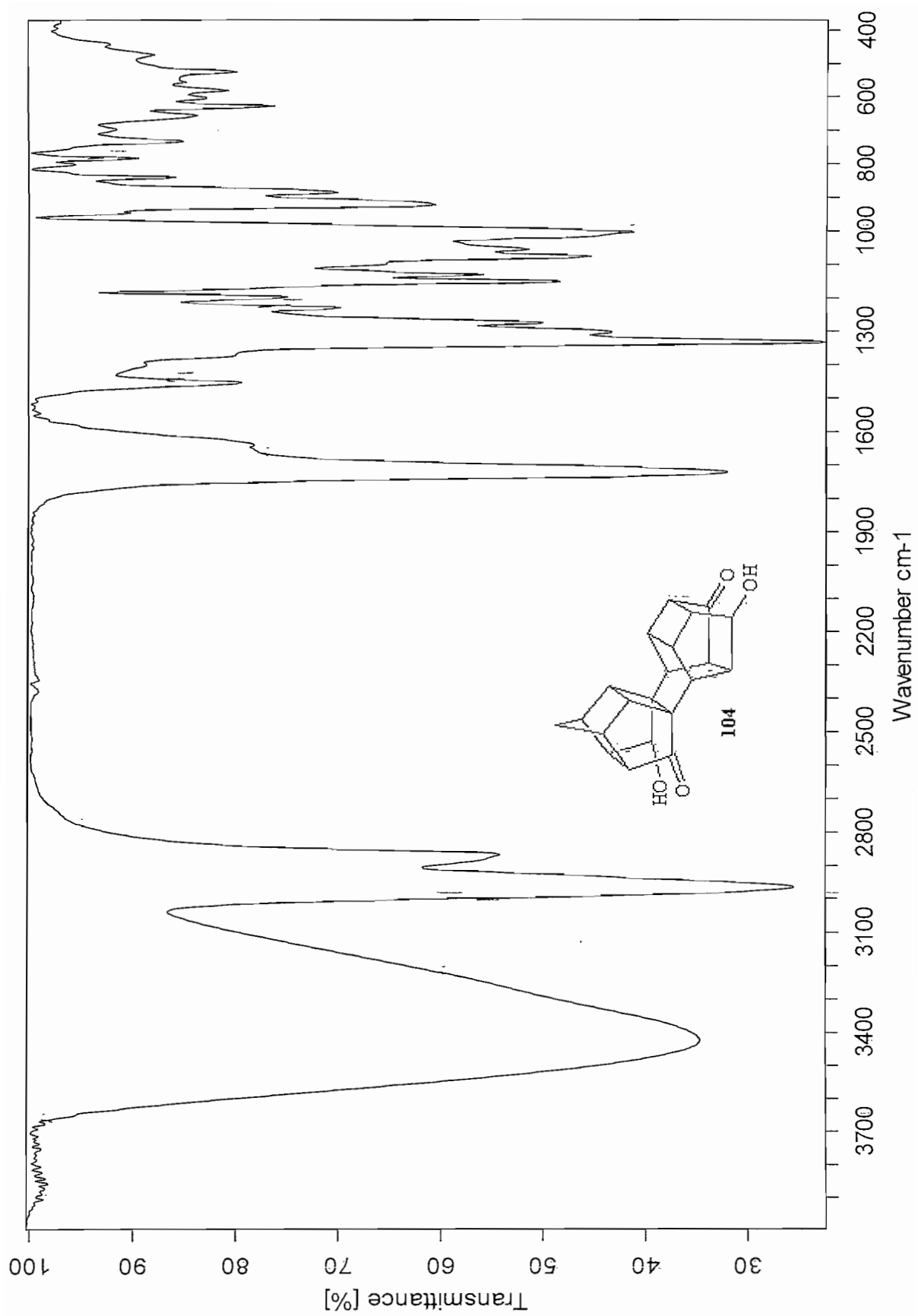


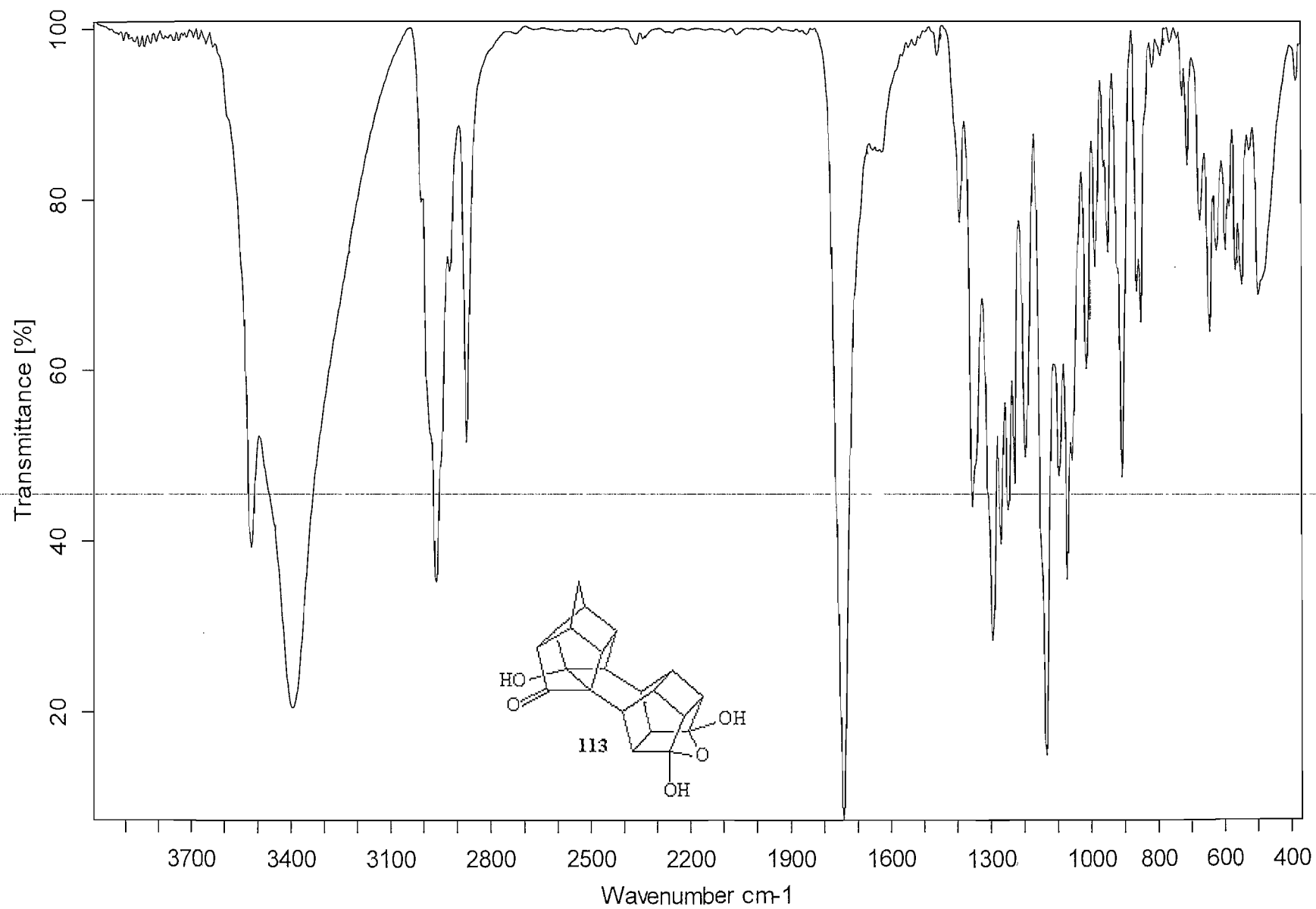


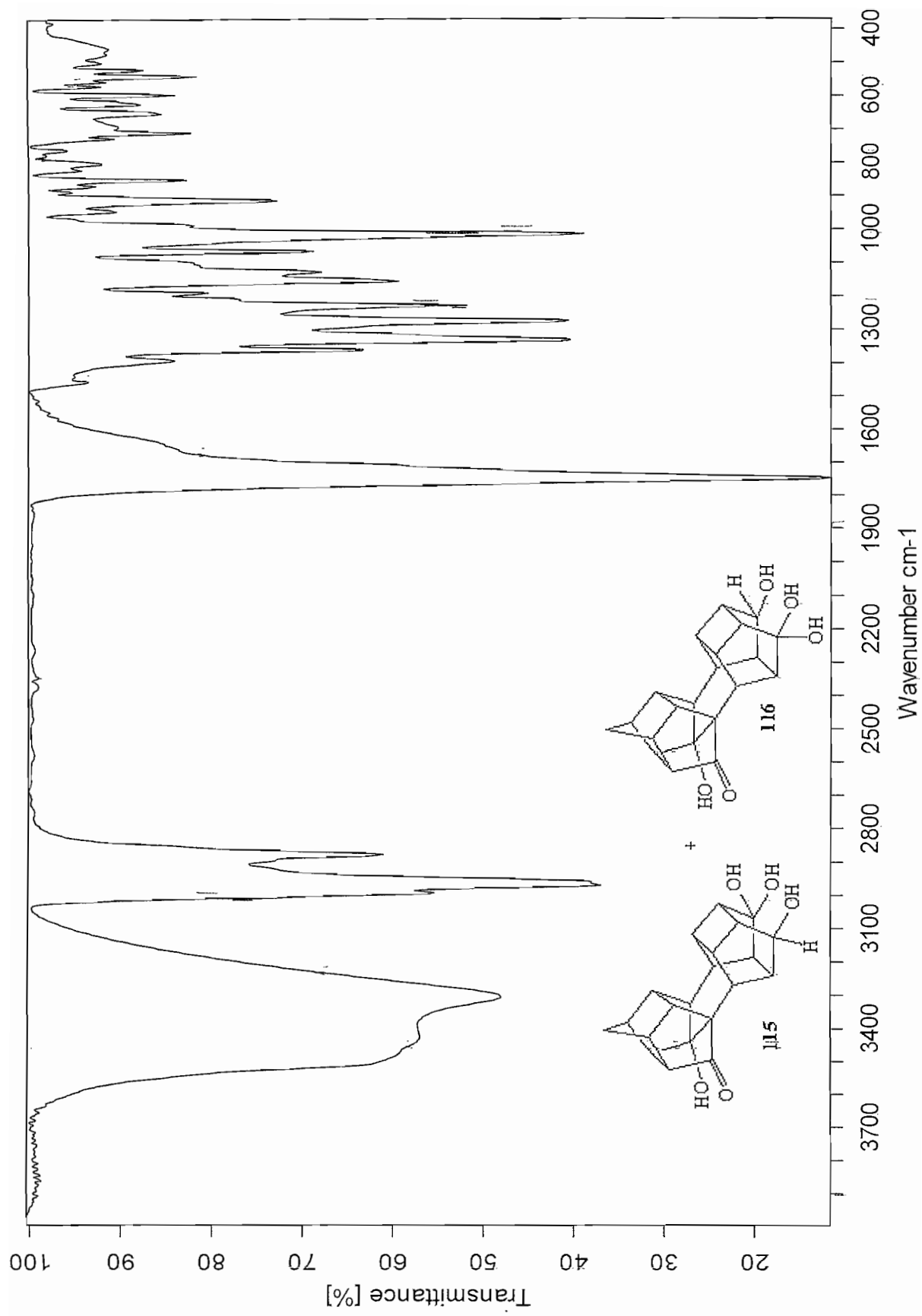


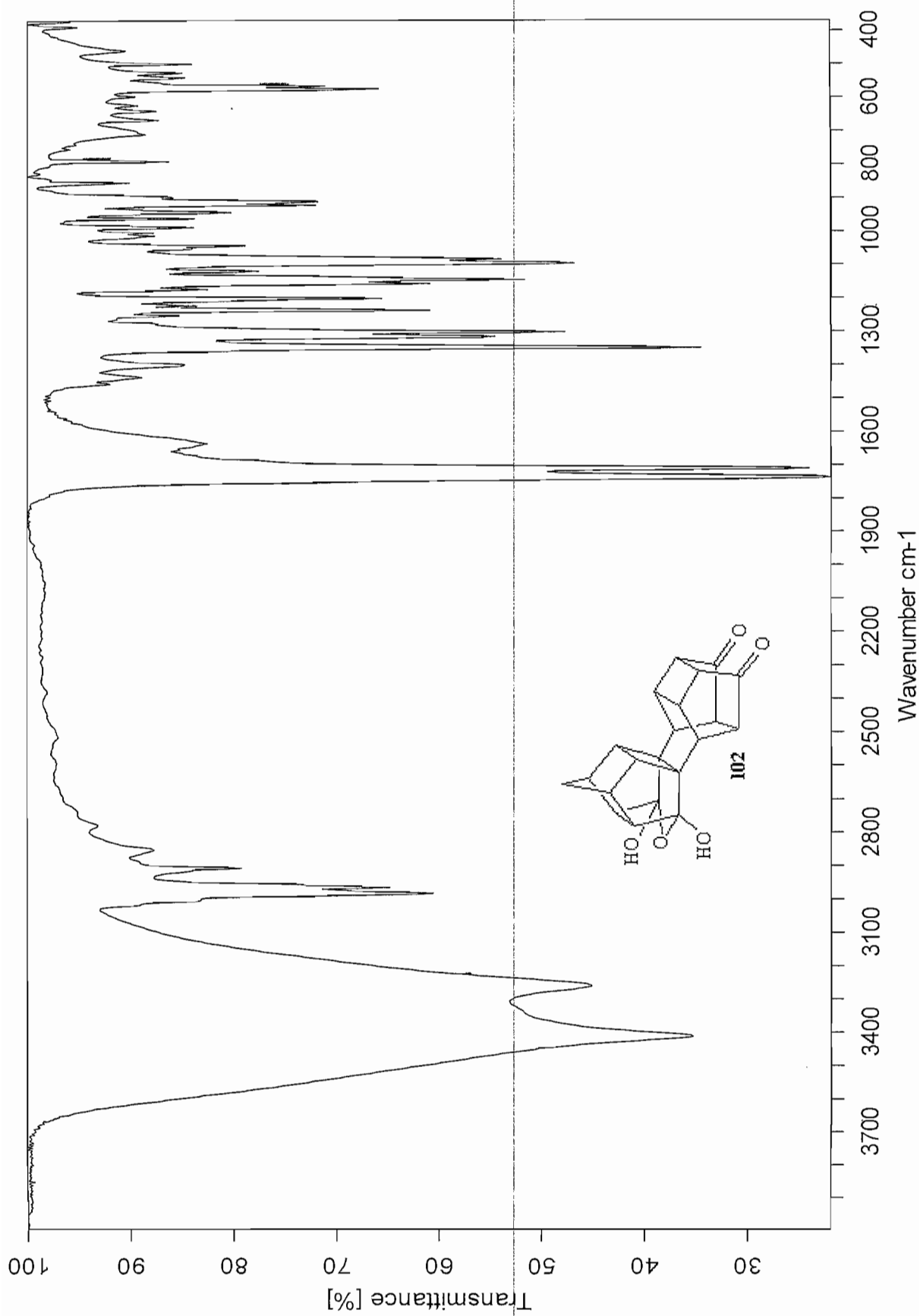


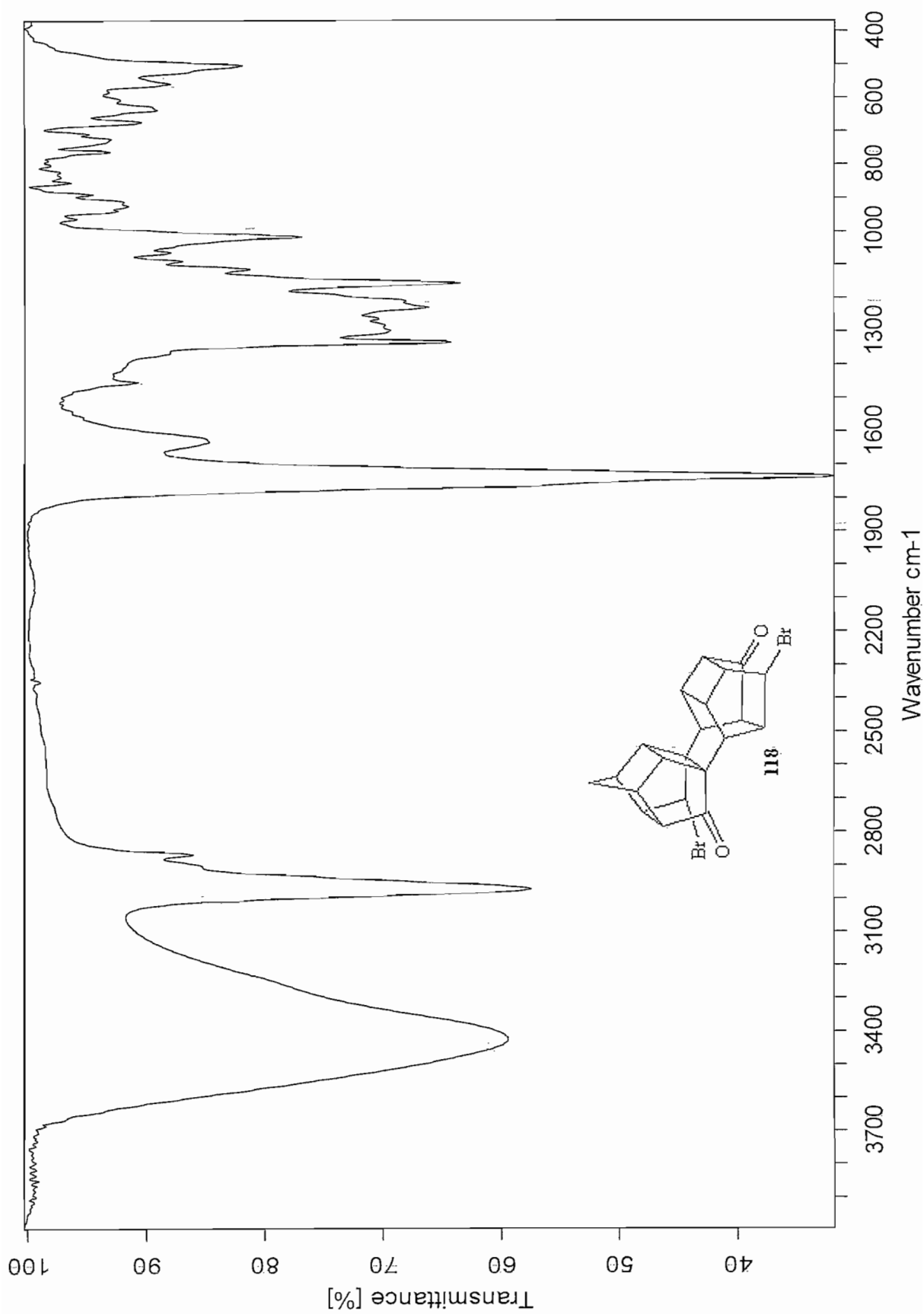




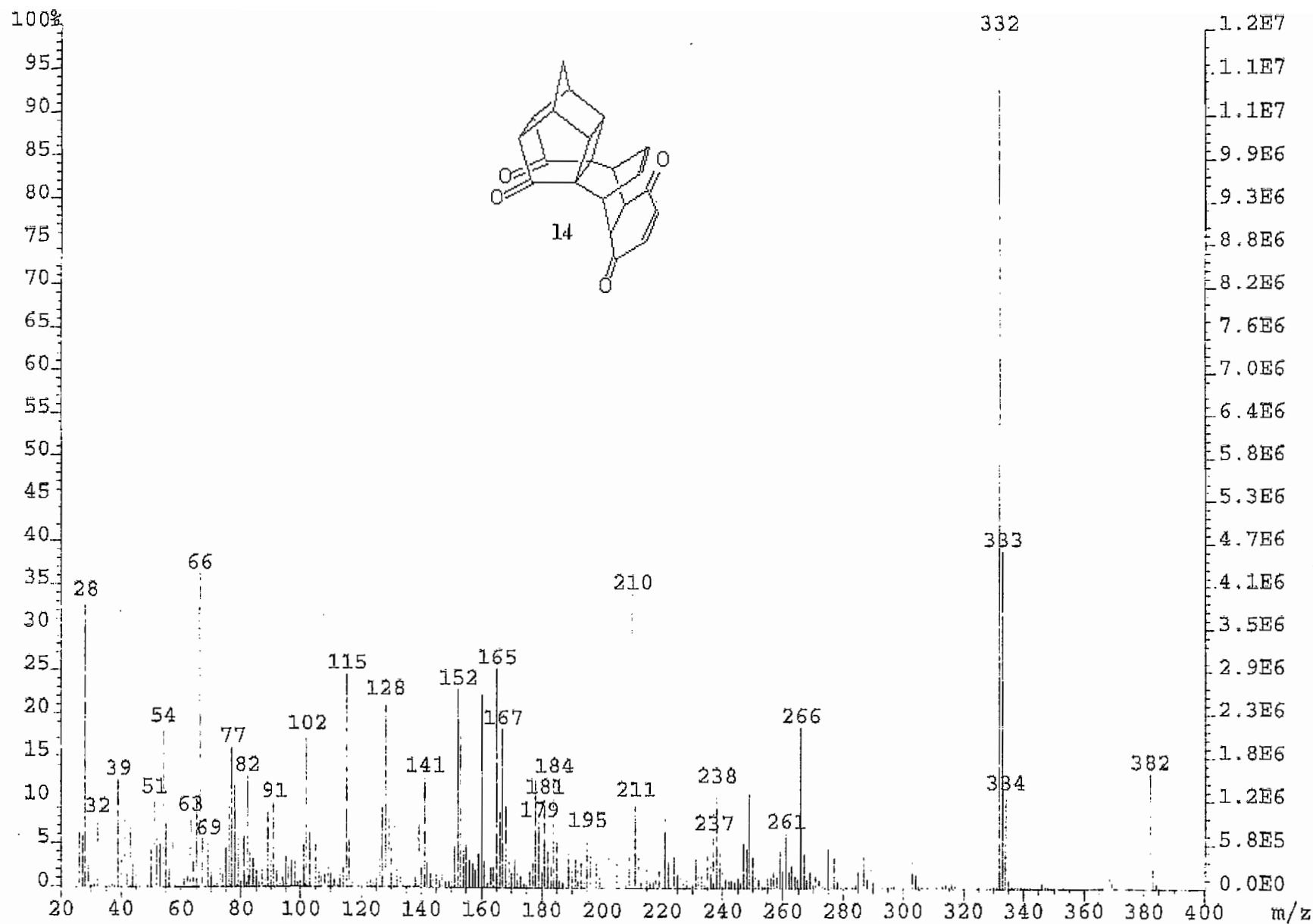




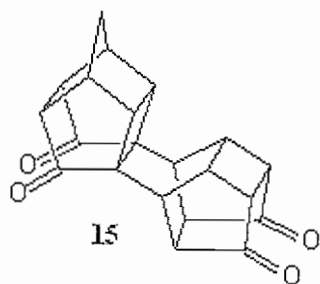




Addendum B: MS Spectra



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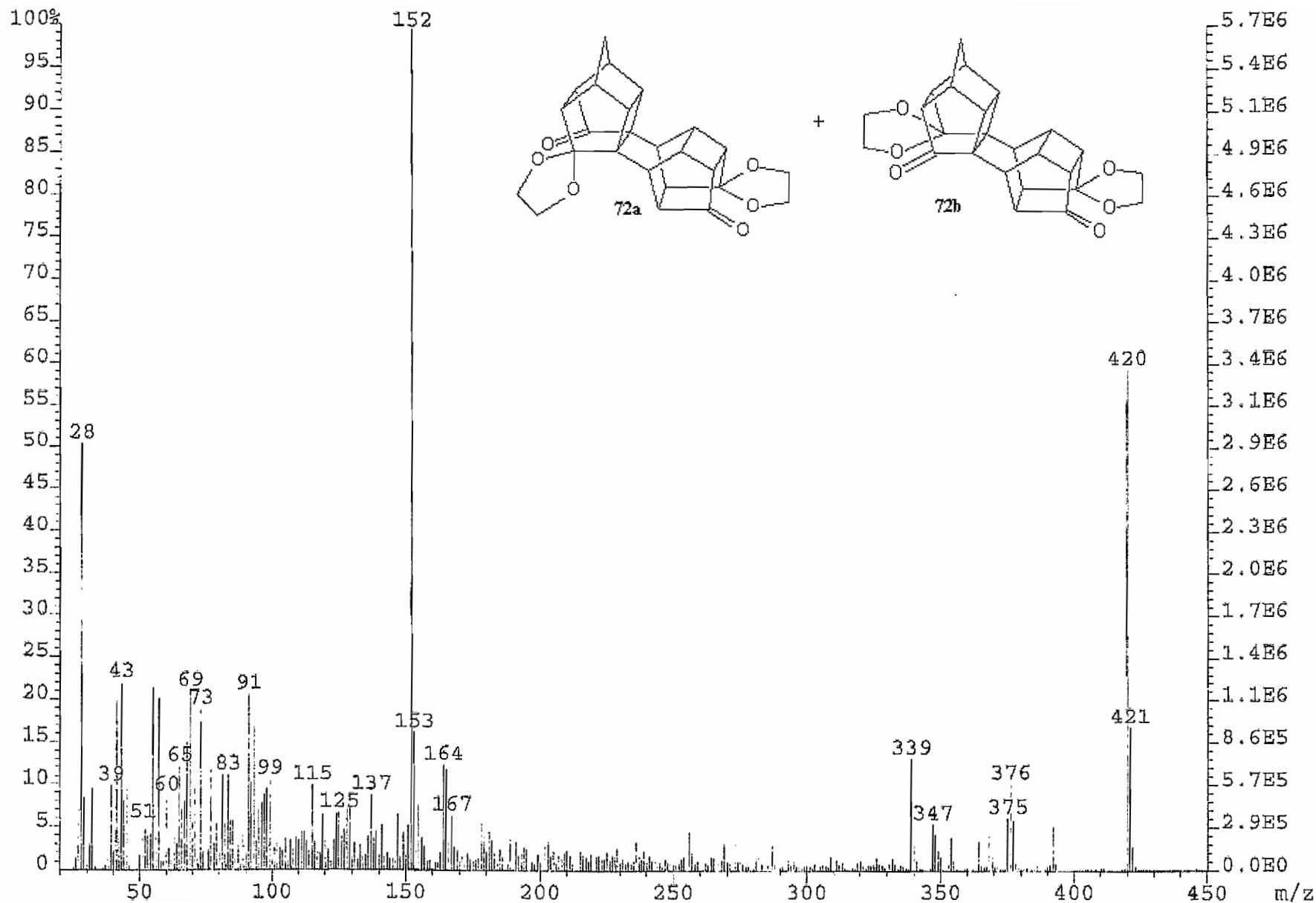
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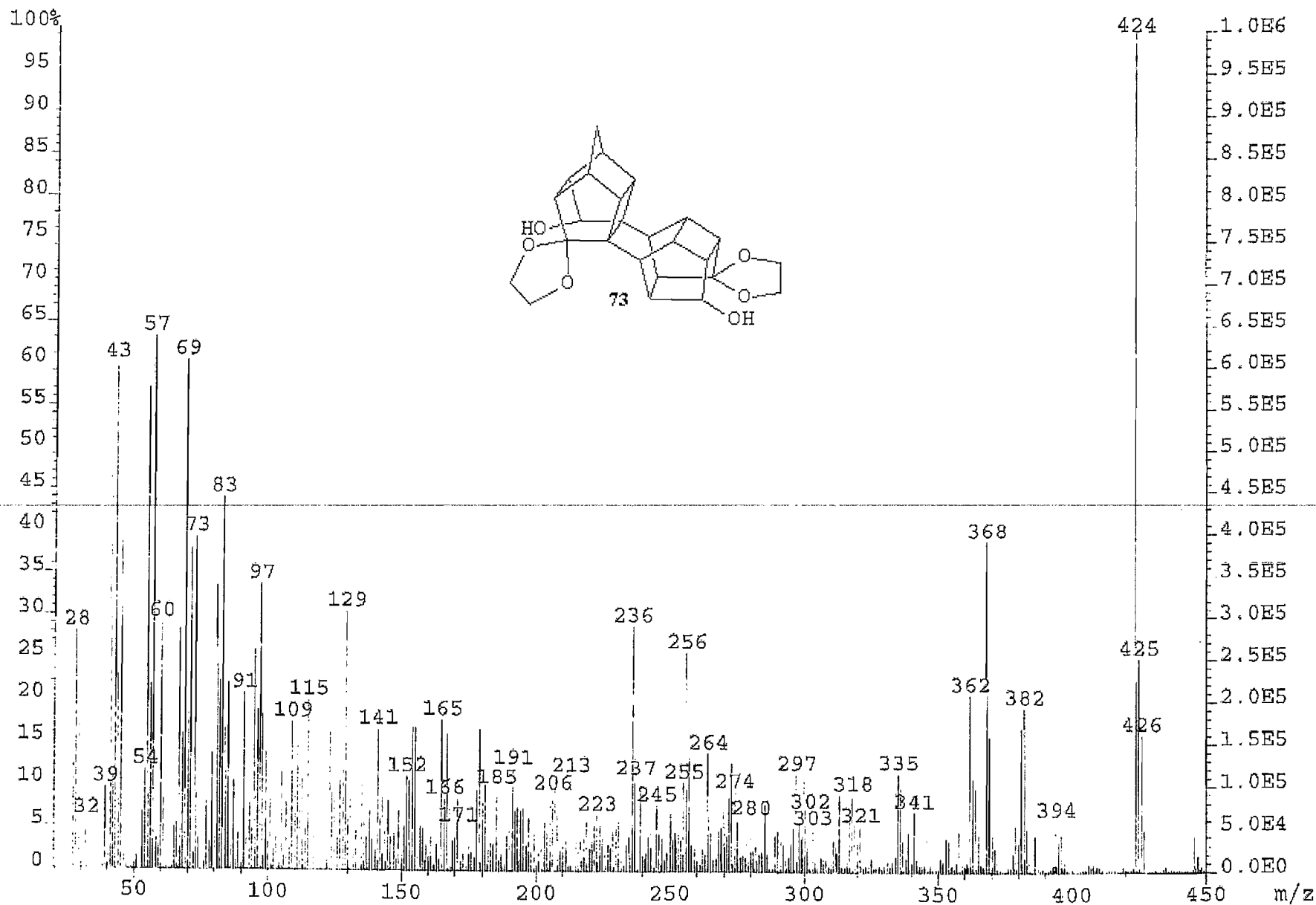
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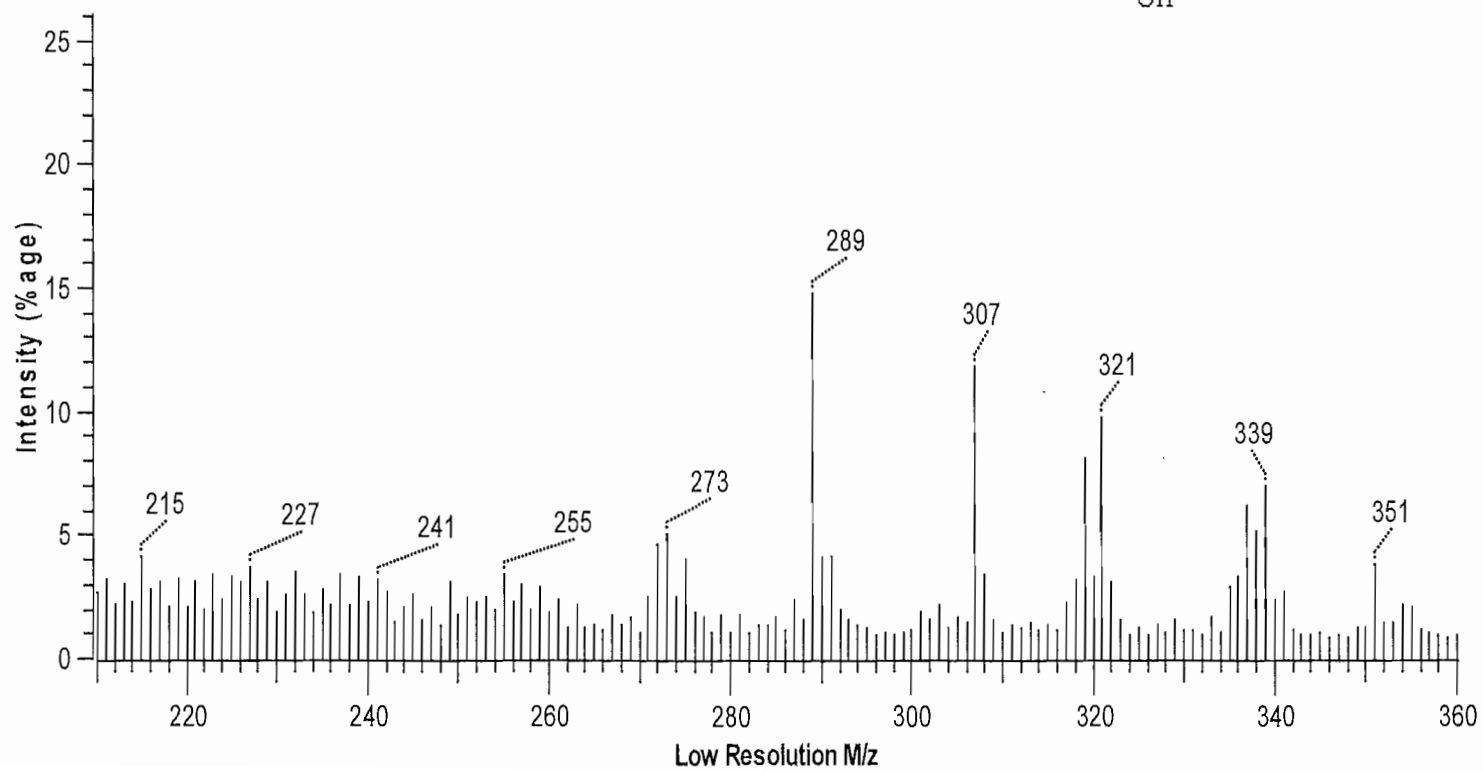
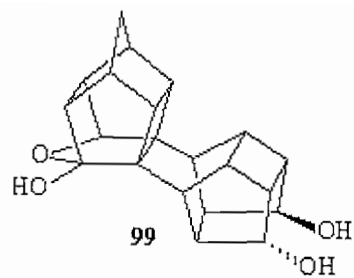
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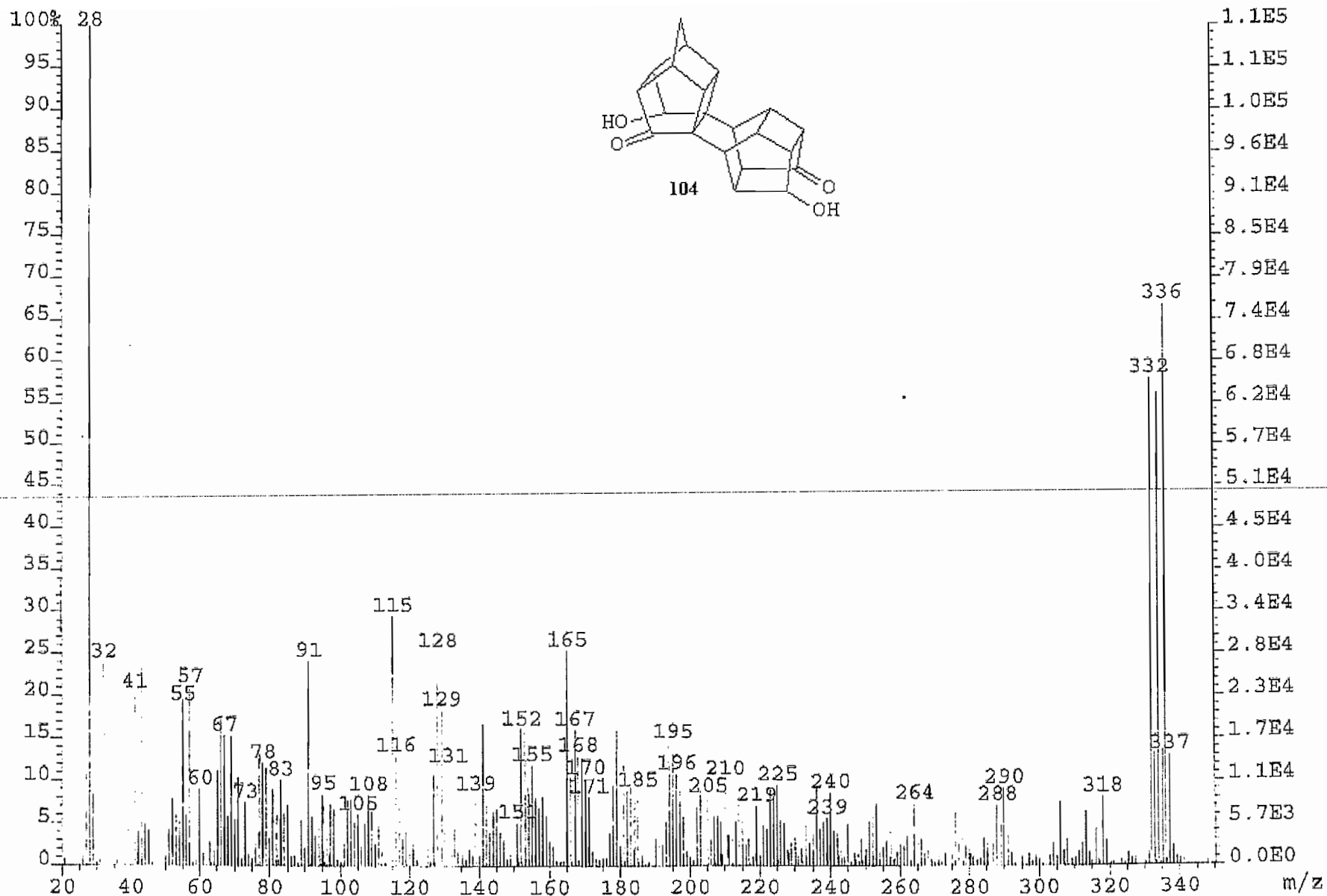
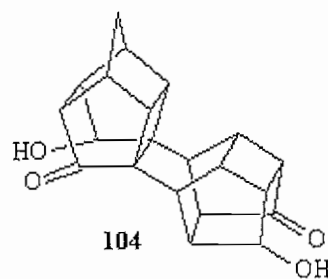
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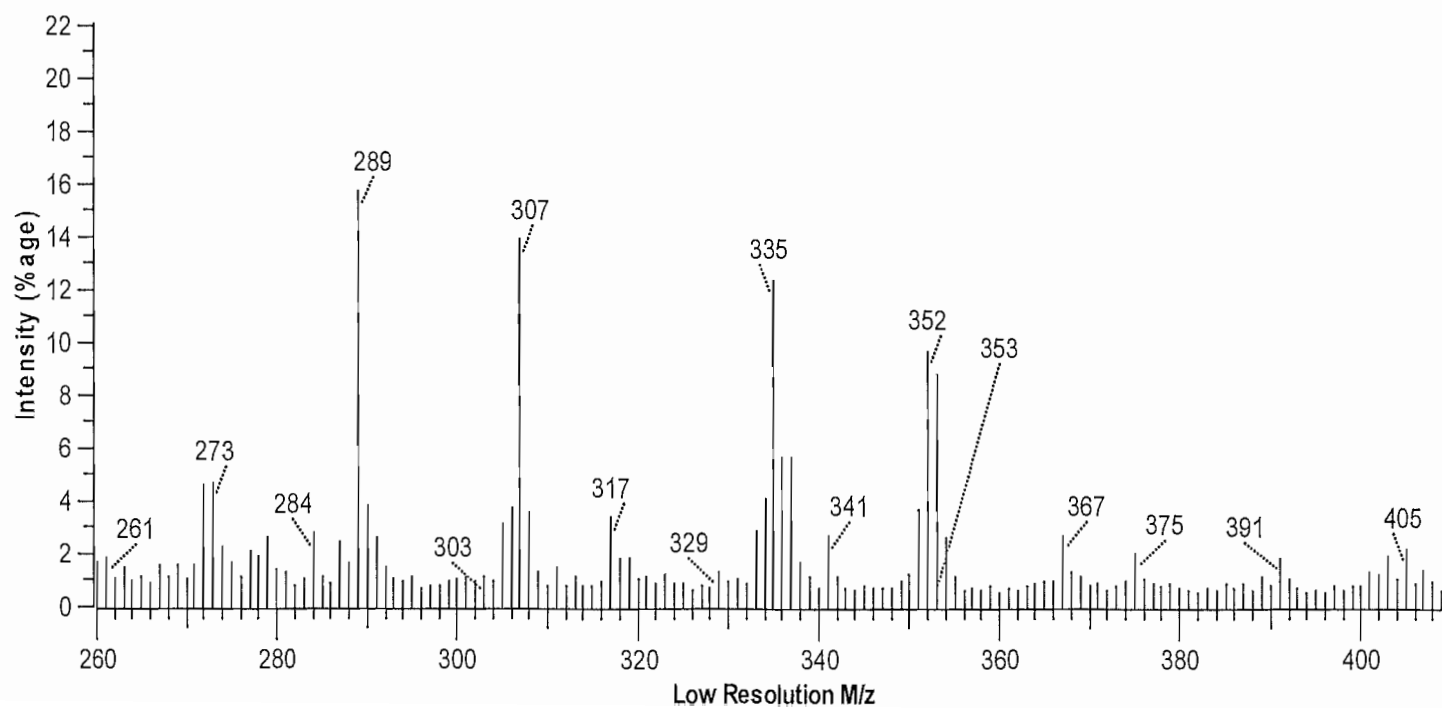
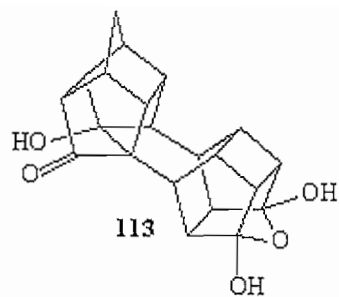


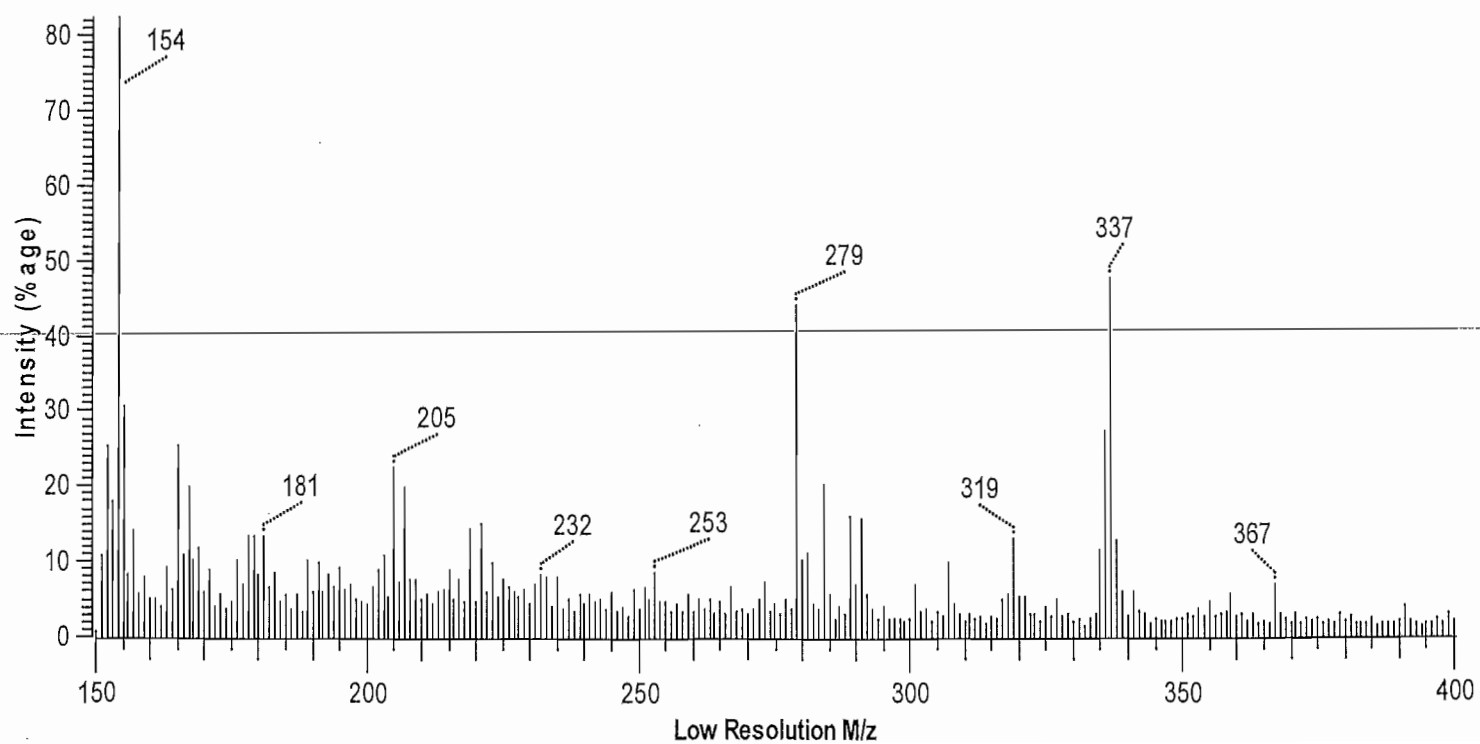
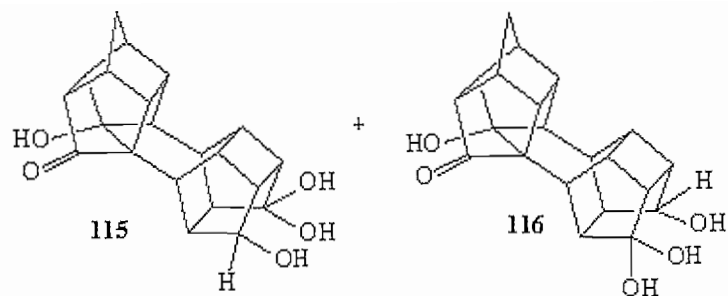


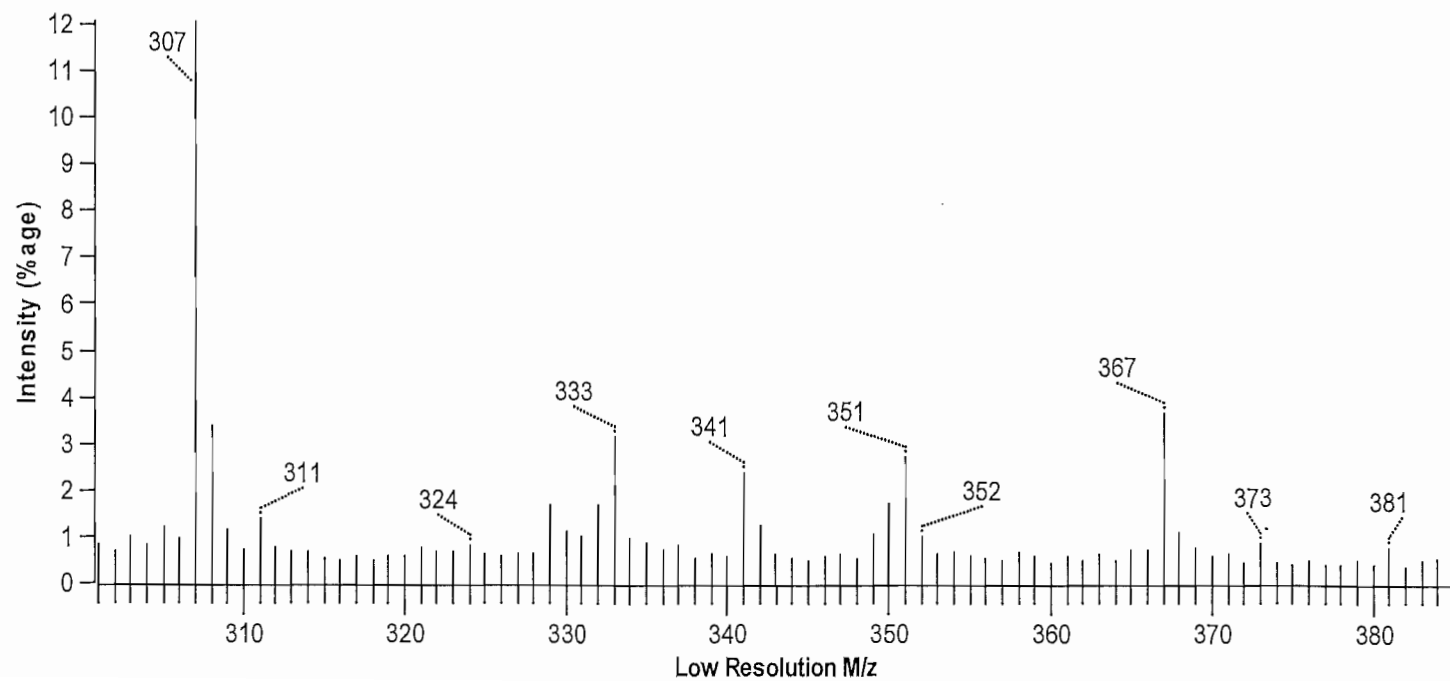
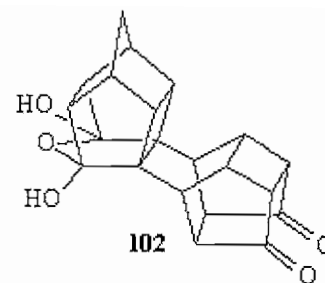




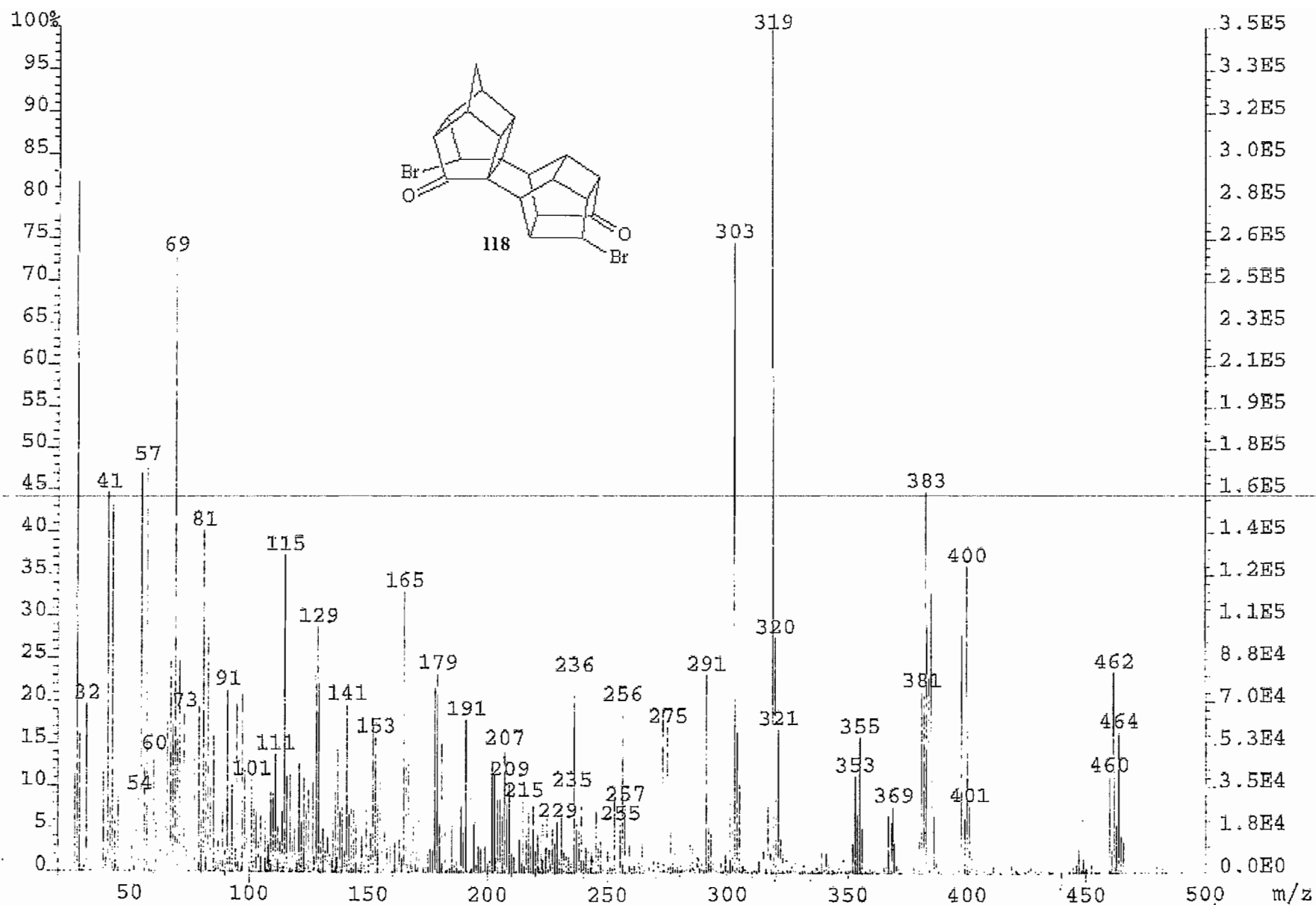
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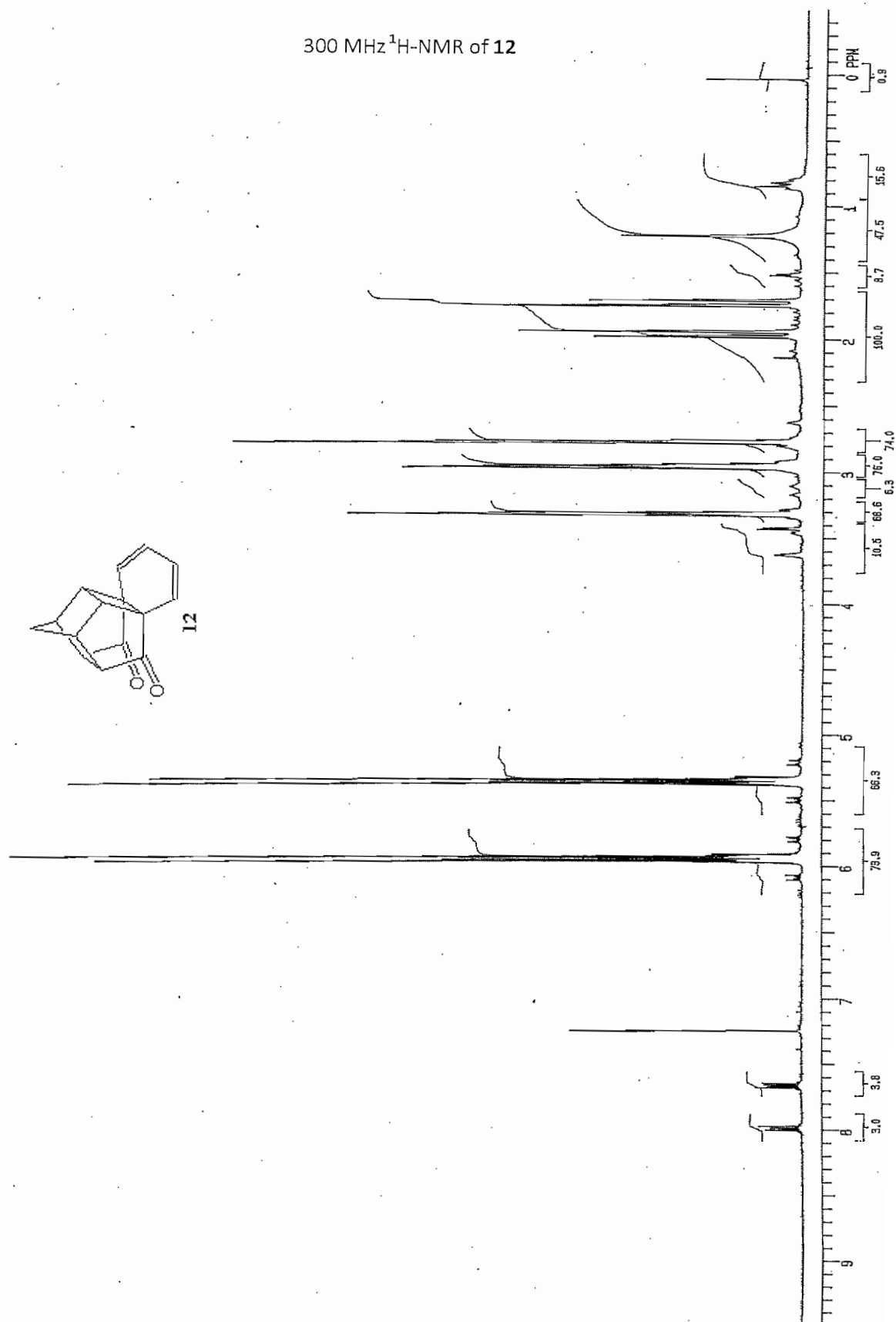


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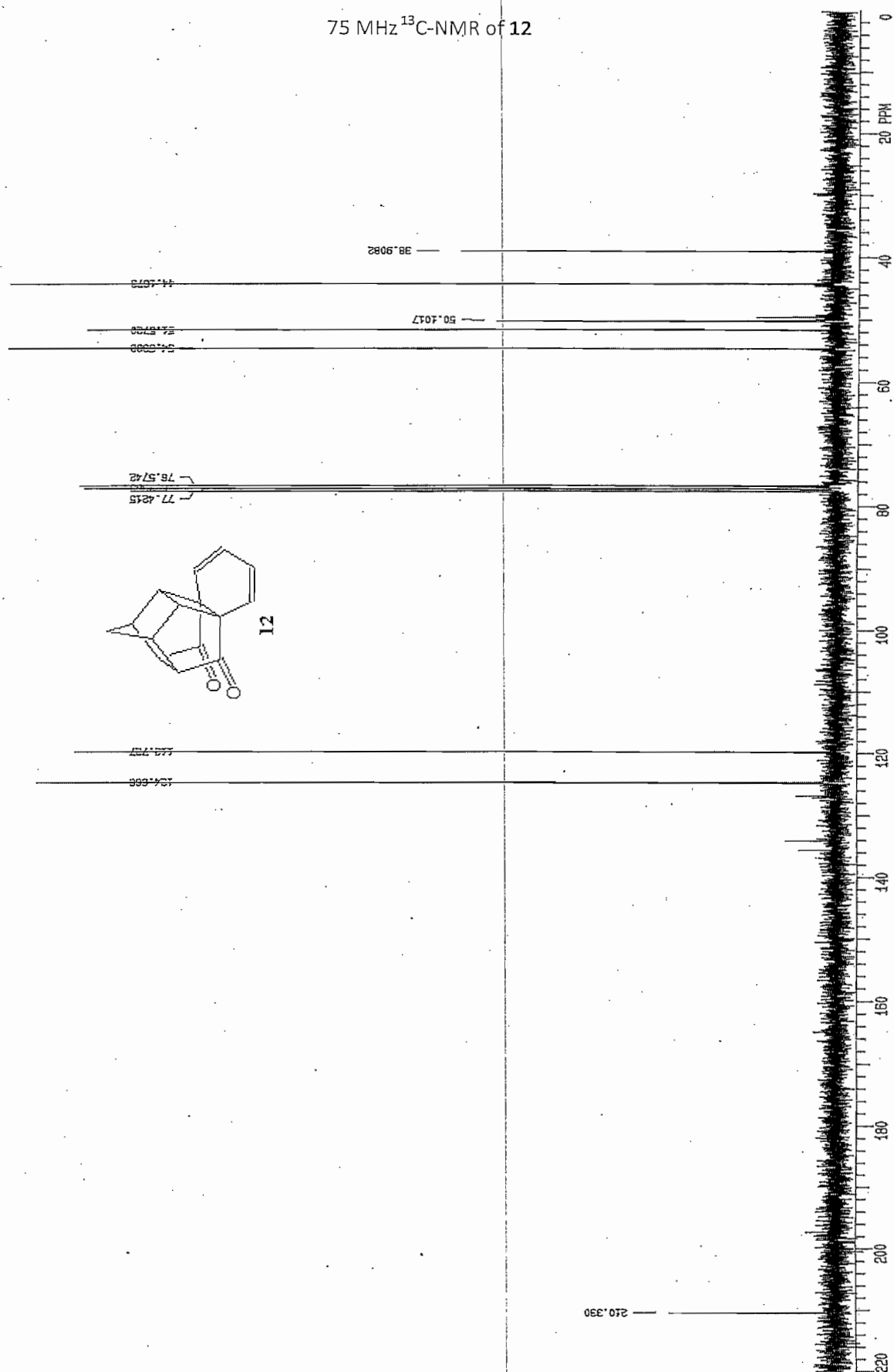


Addendum C: NMR Spectra

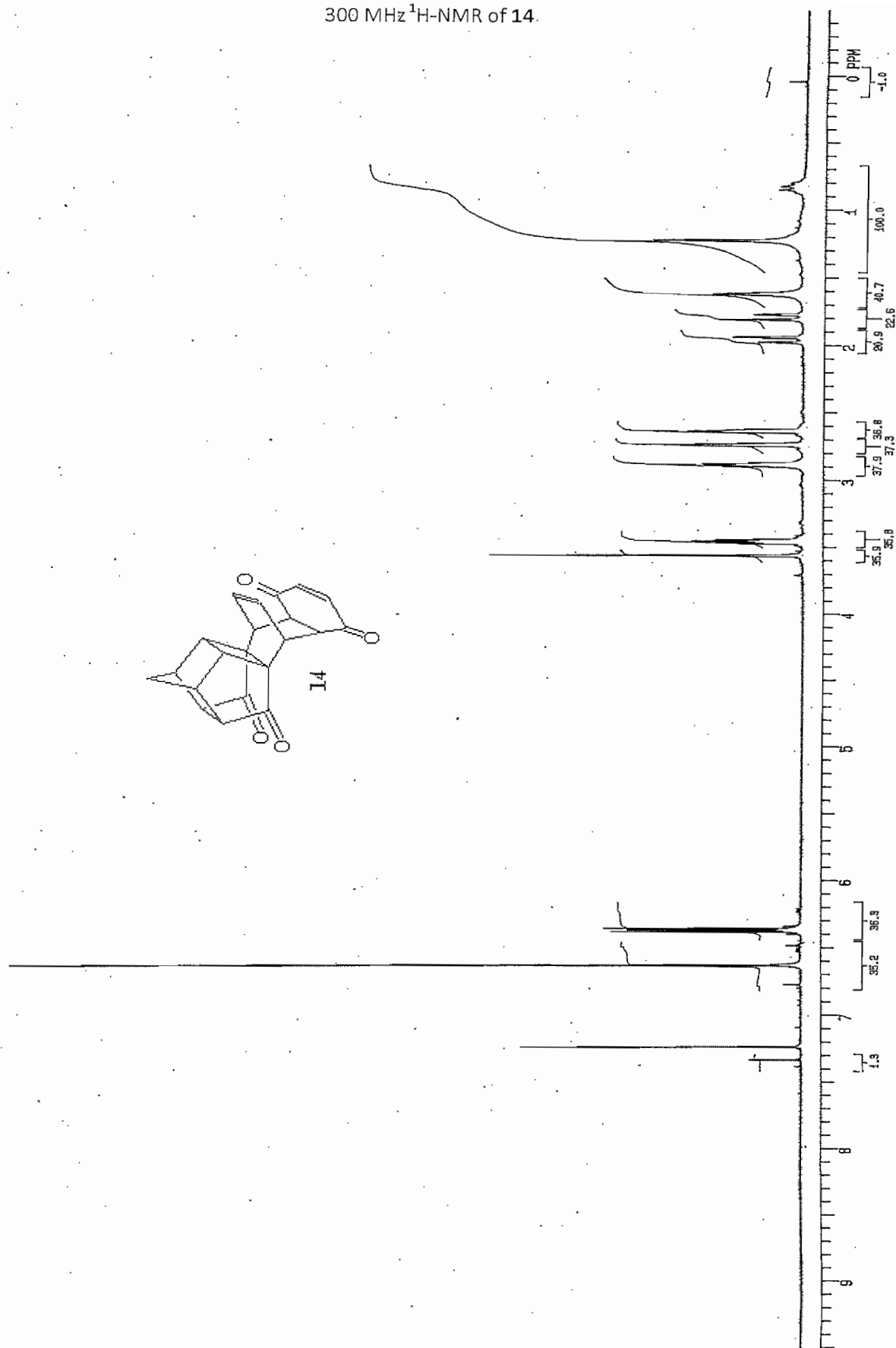
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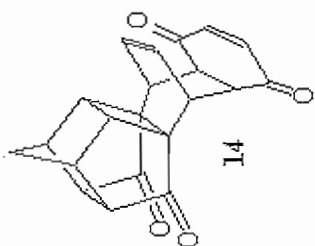
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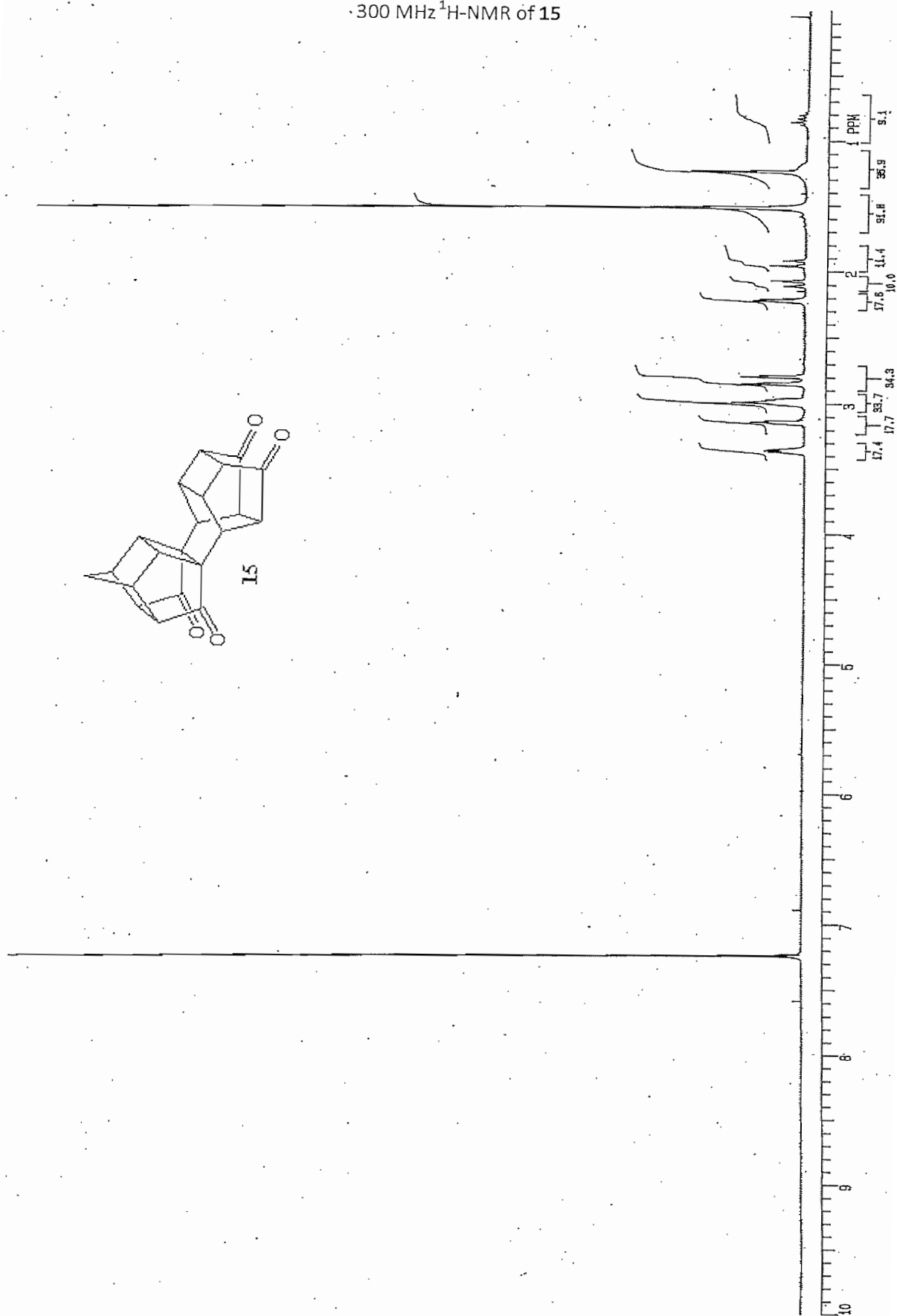
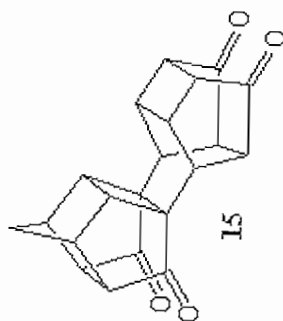
300 MHz ^1H -NMR of **14**.



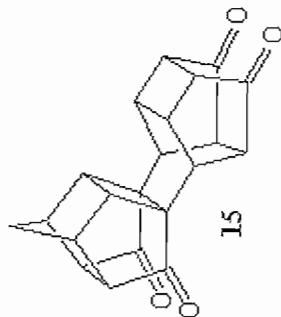
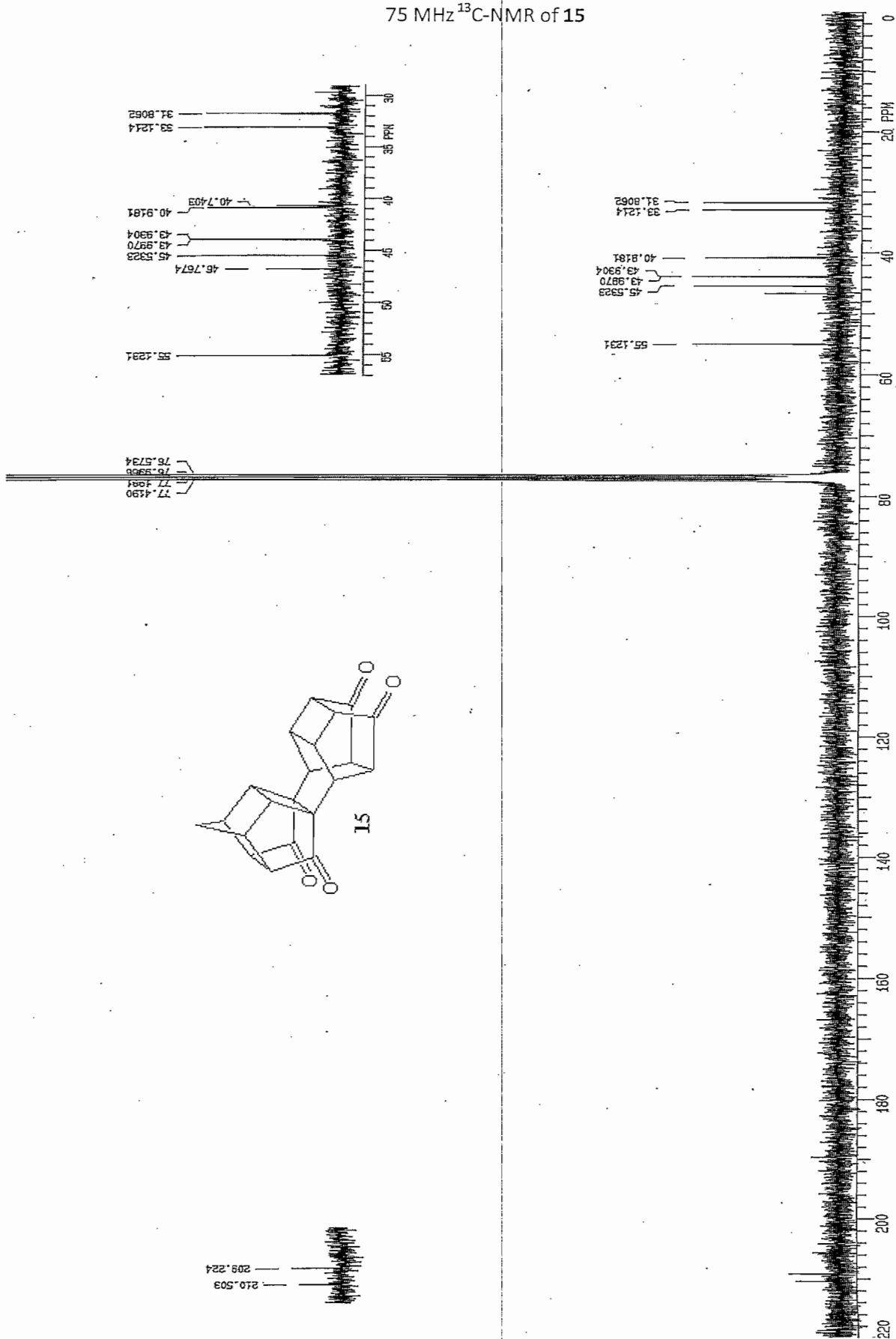
75 MHz ^{13}C -NMR of **14**



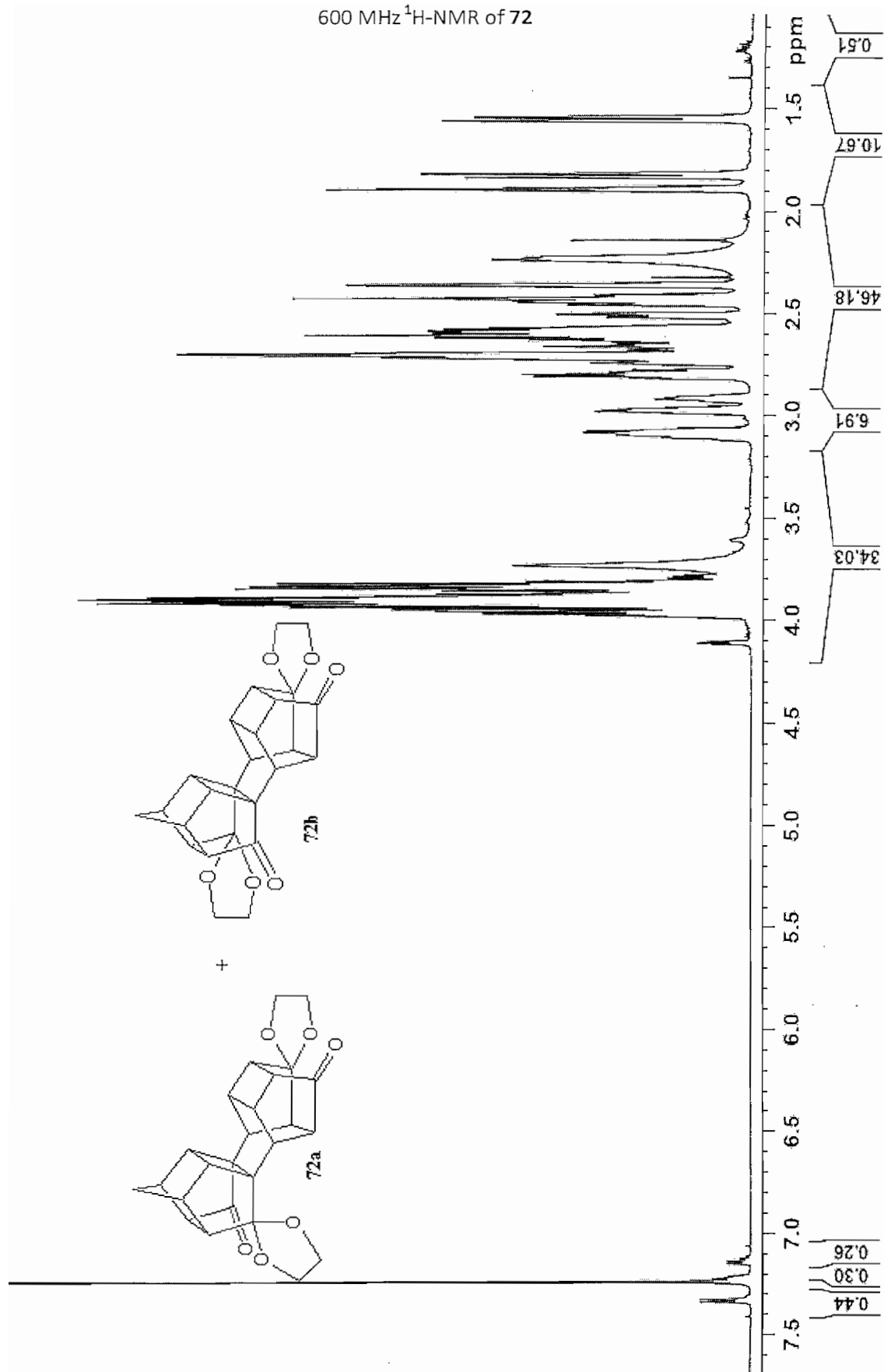
300 MHz ^1H -NMR of 15



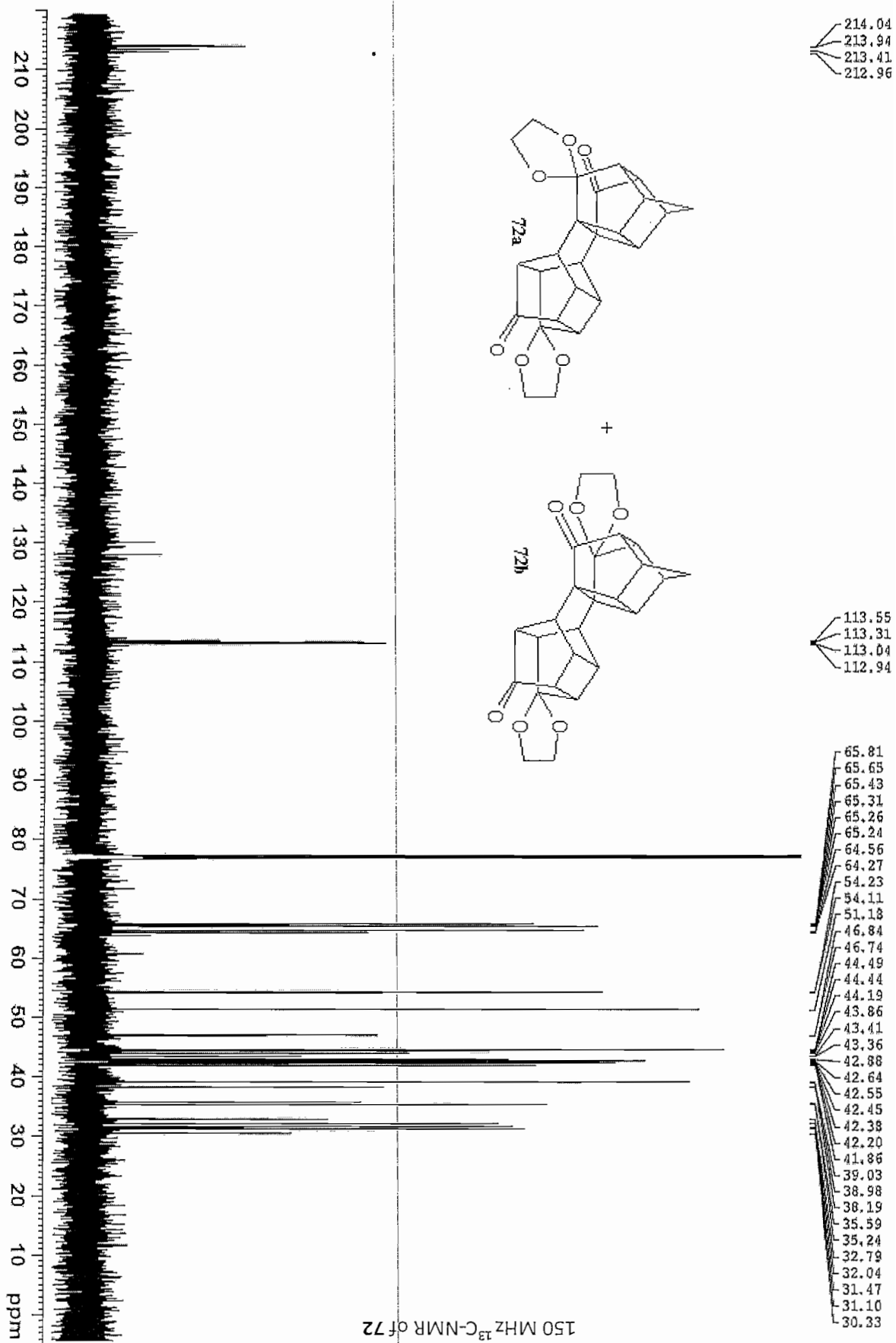
75 MHz ^{13}C -NMR of **15**

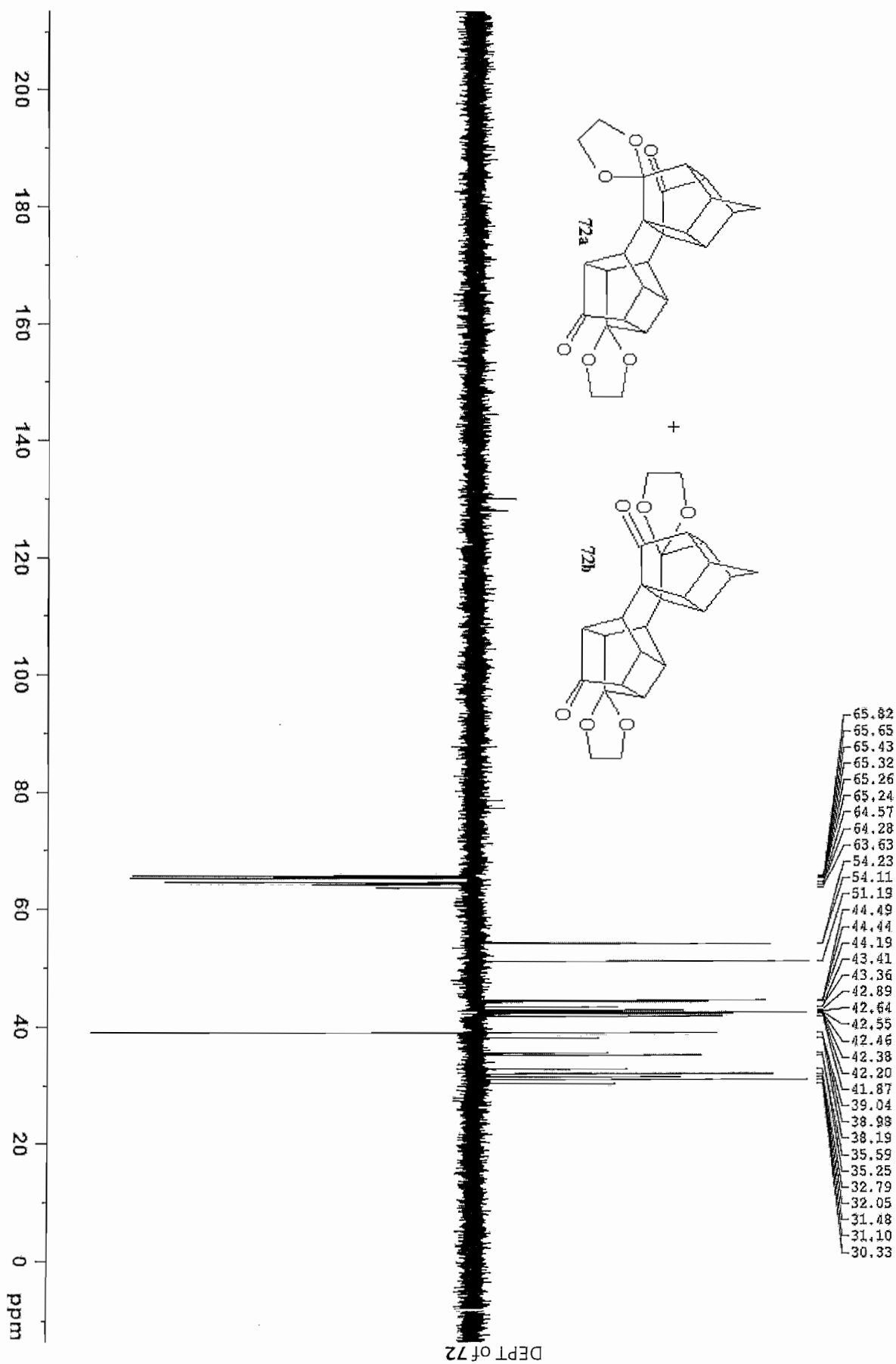


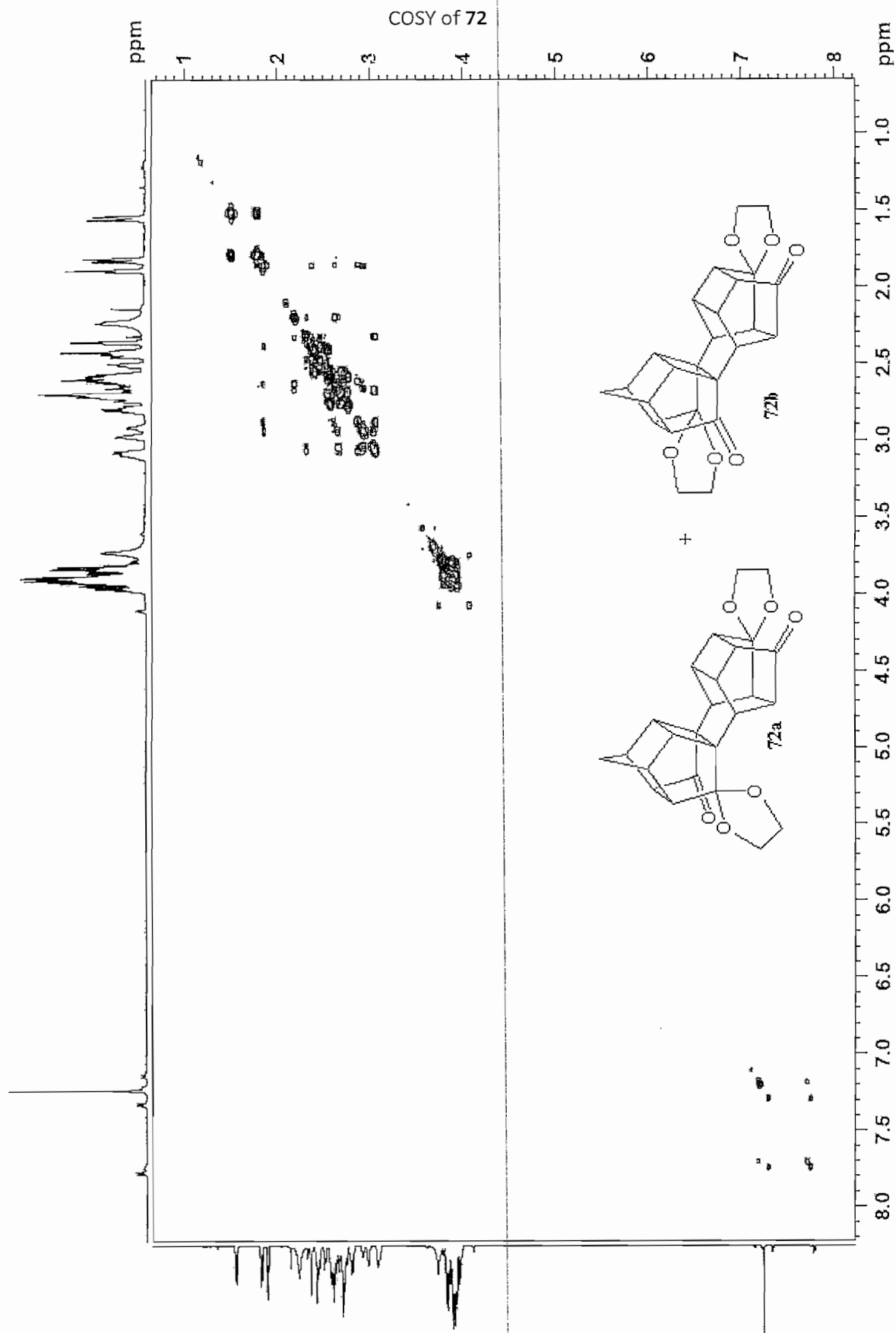
600 MHz ^1H -NMR of 72

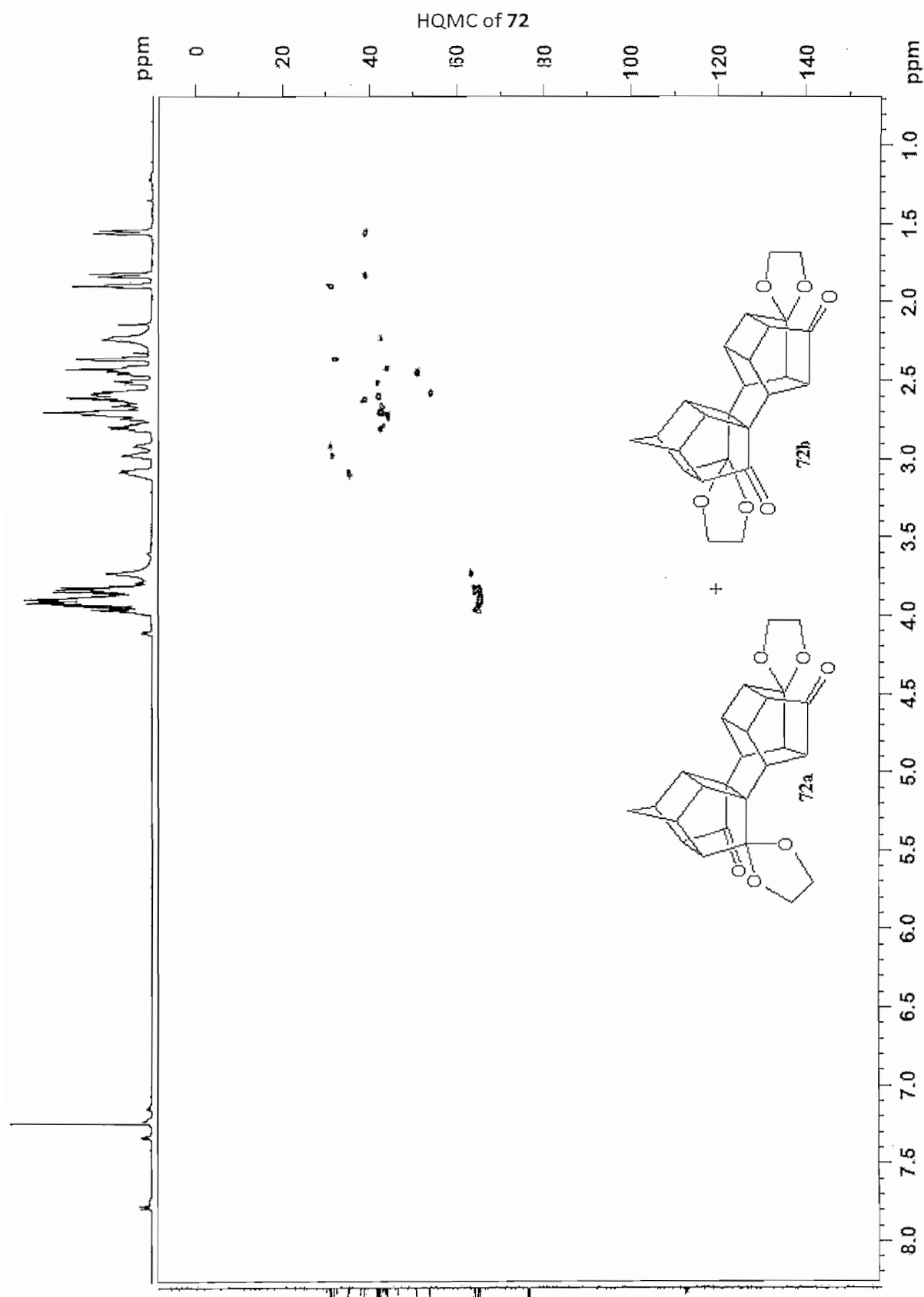


150 MHz ^{13}C -NMR of 72

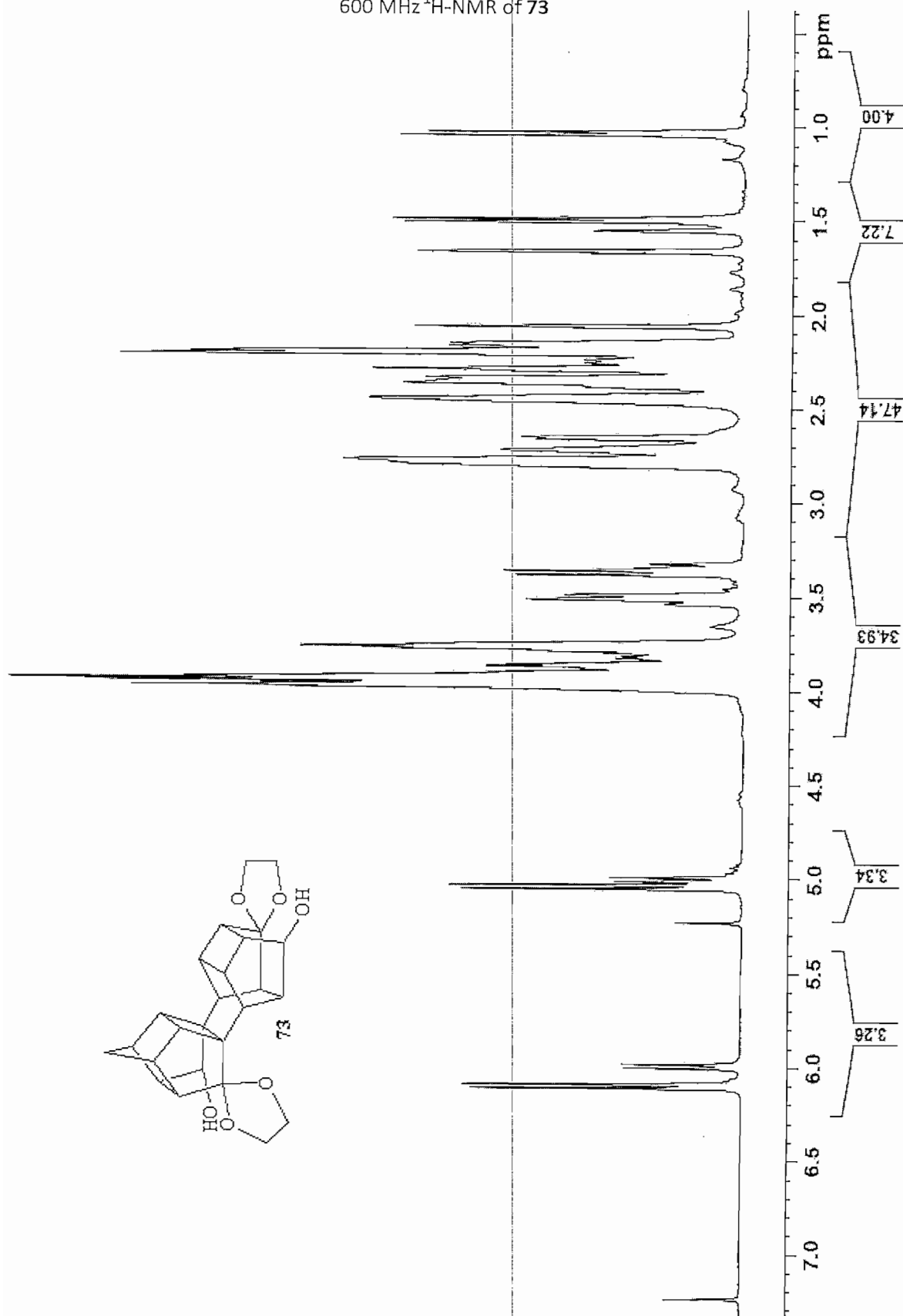


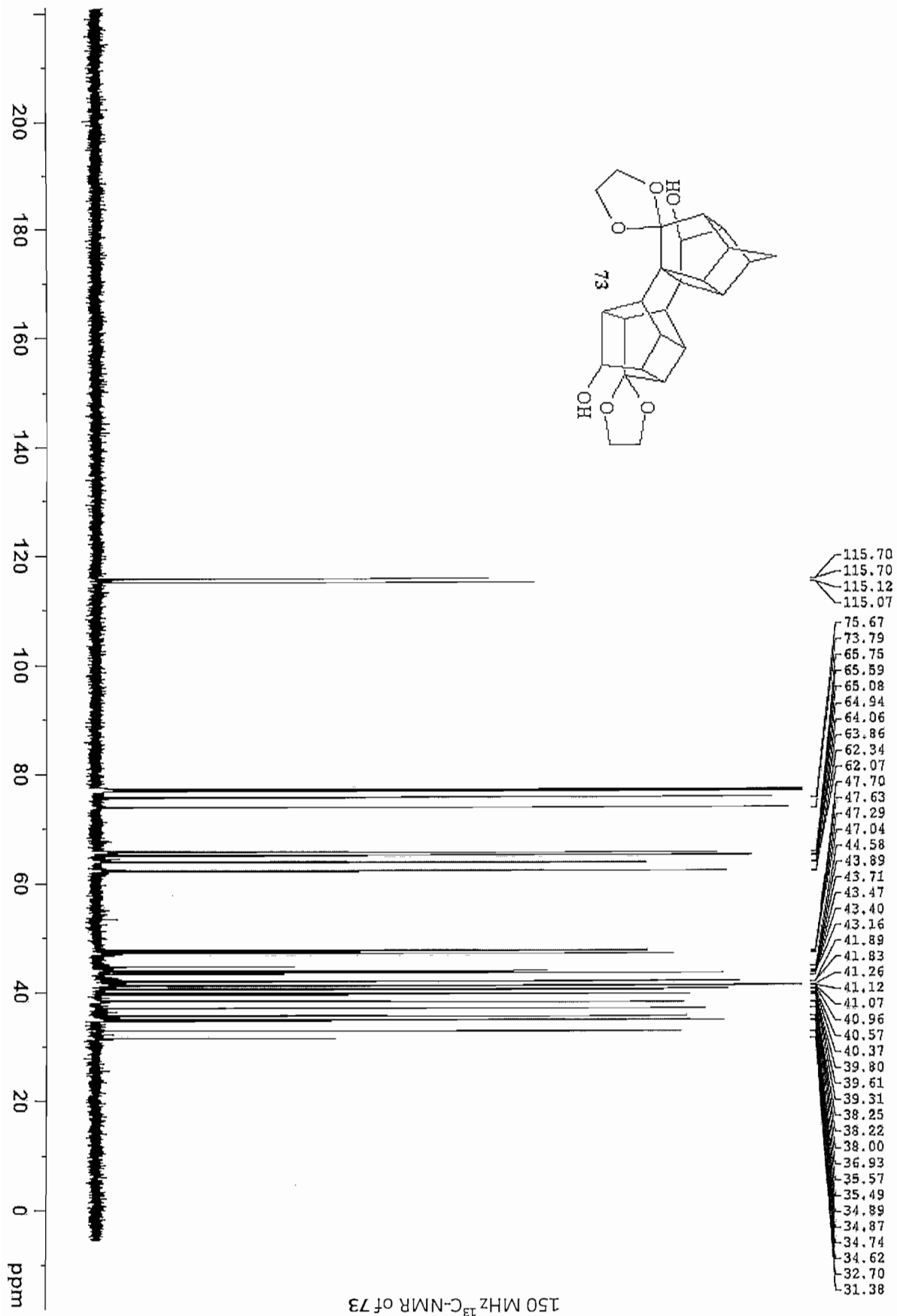


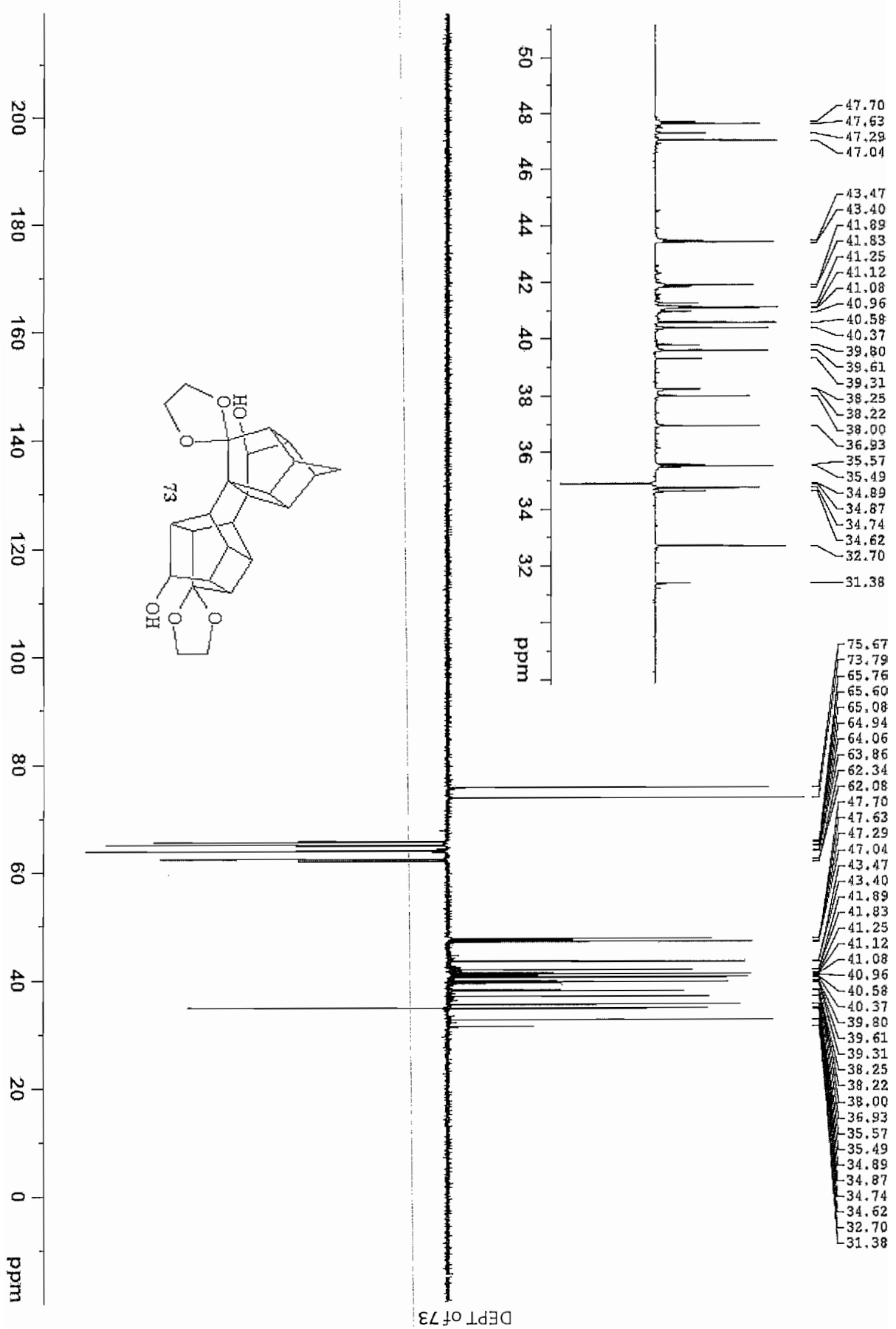


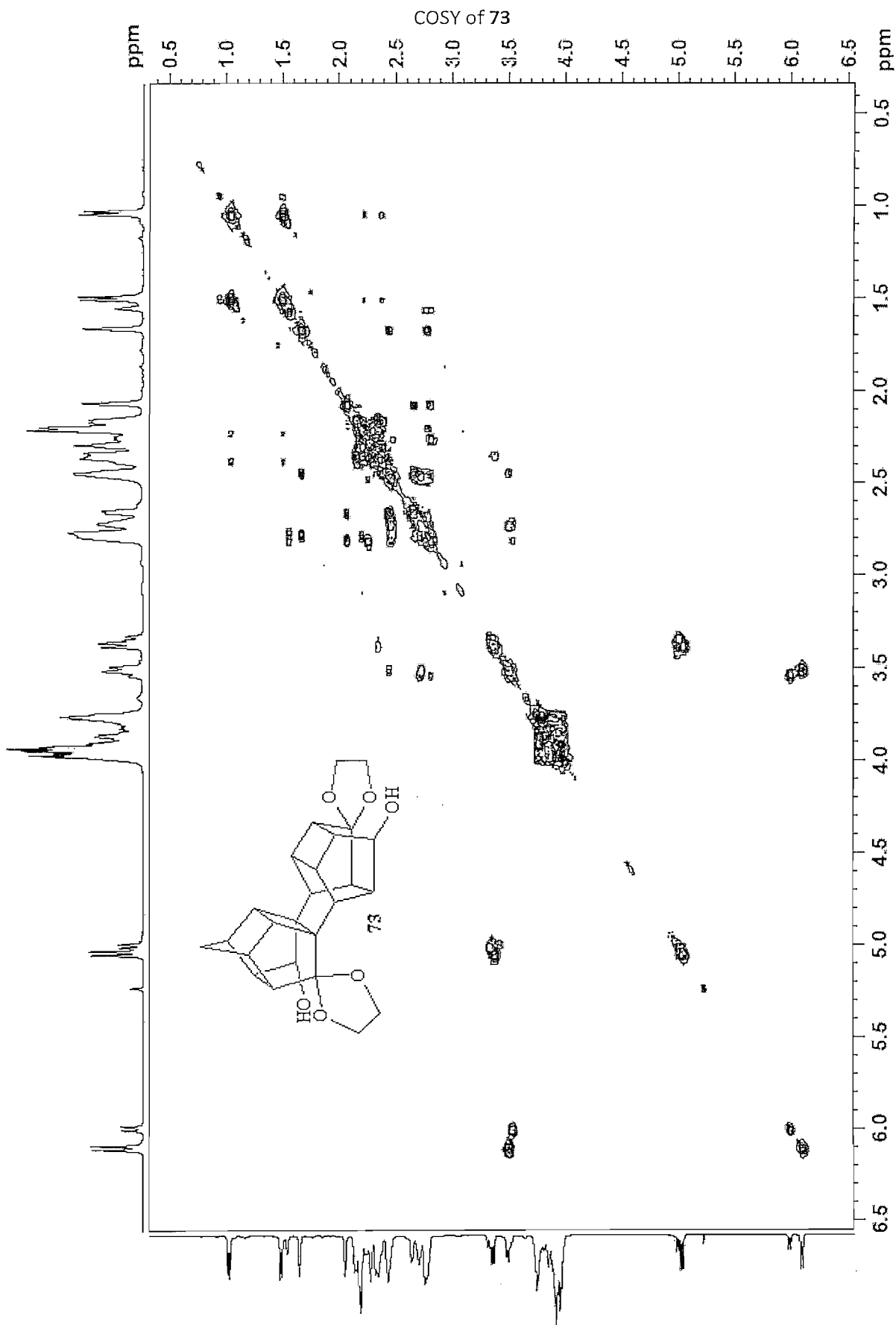


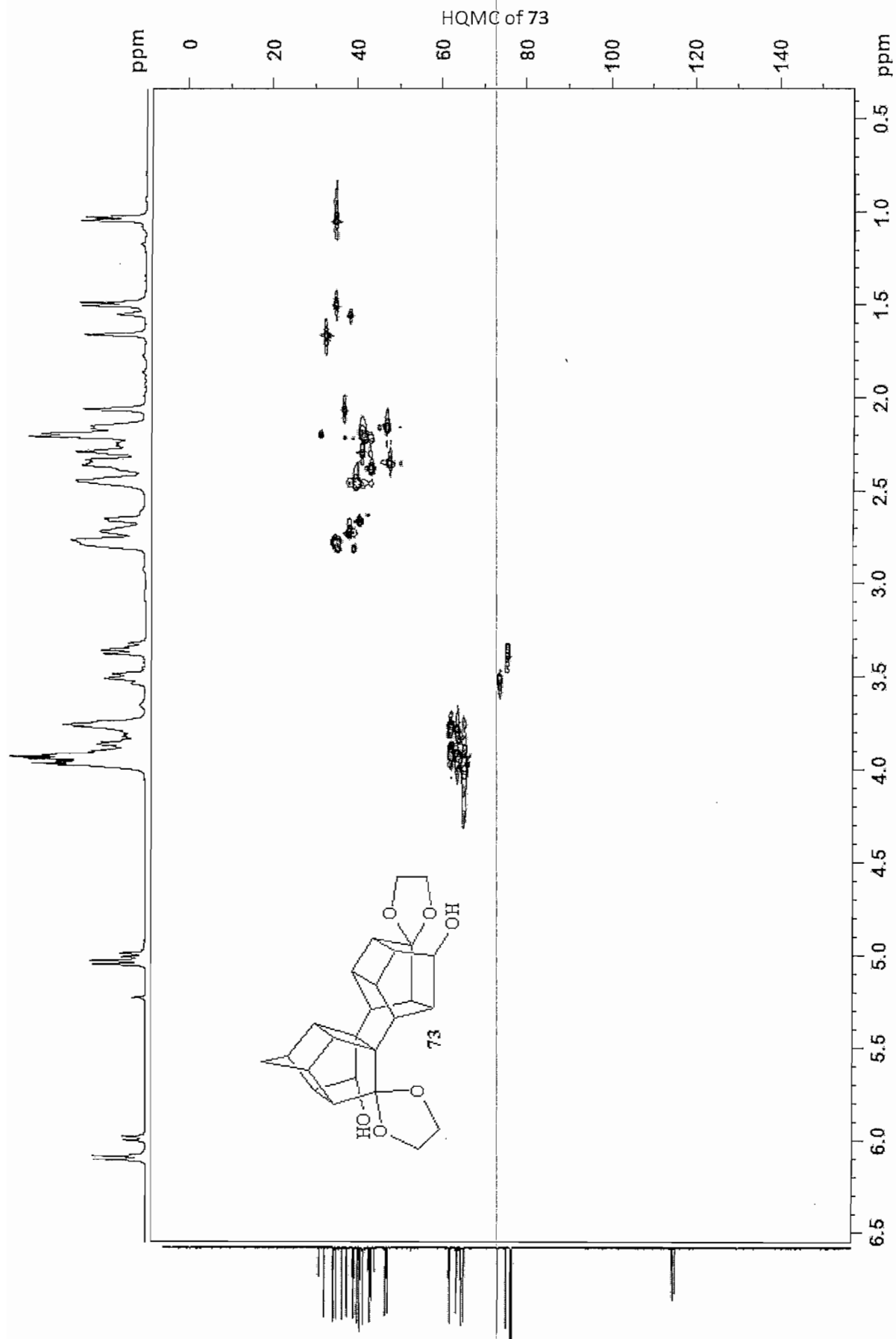
600 MHz ^1H -NMR of 73



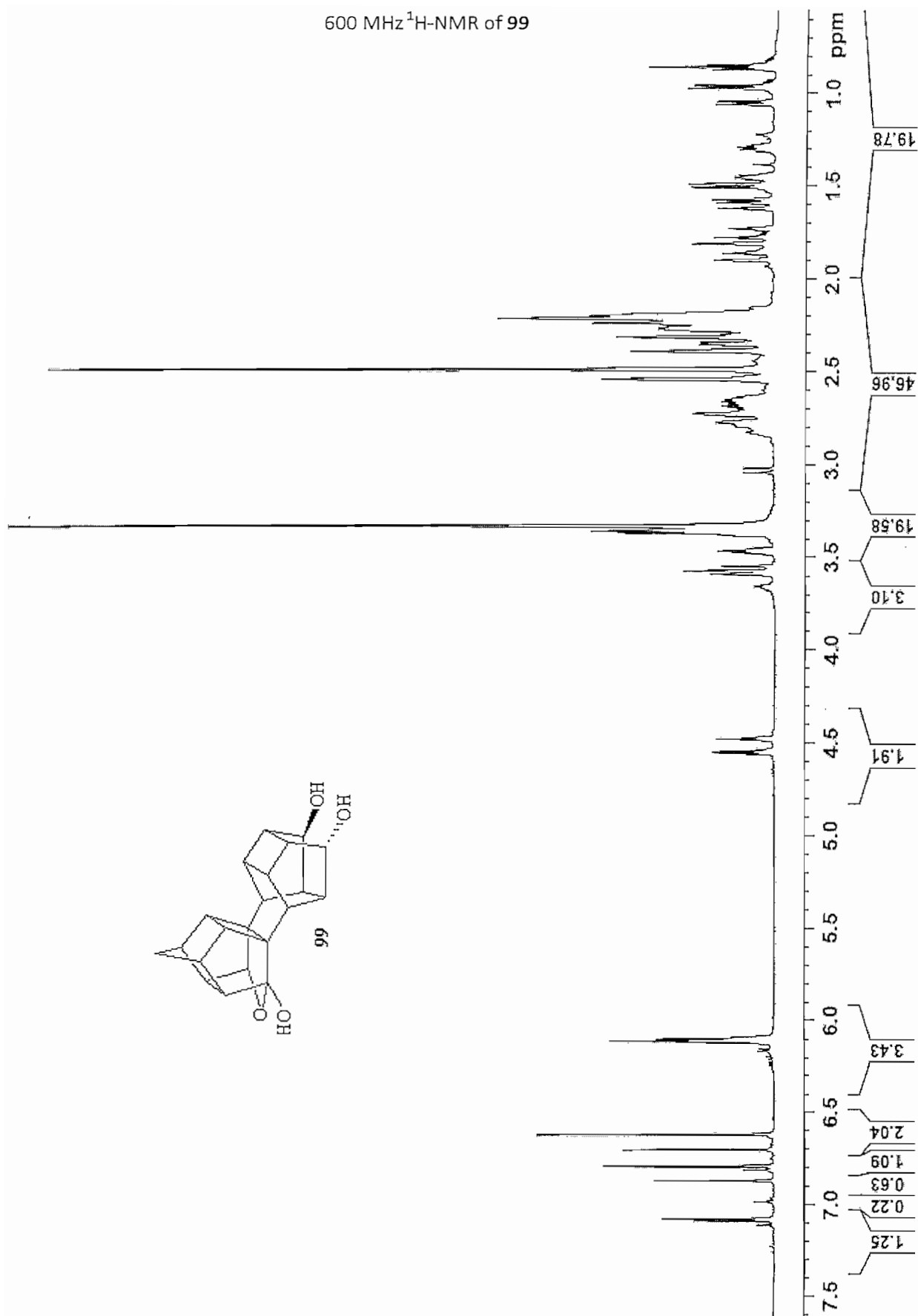


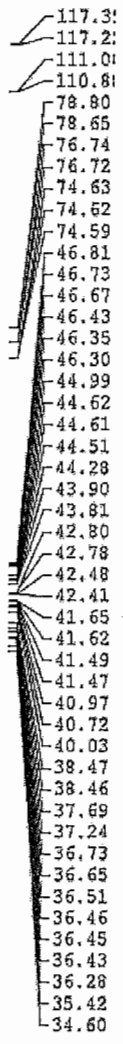
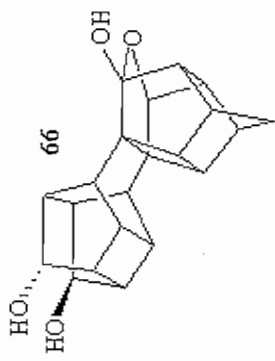
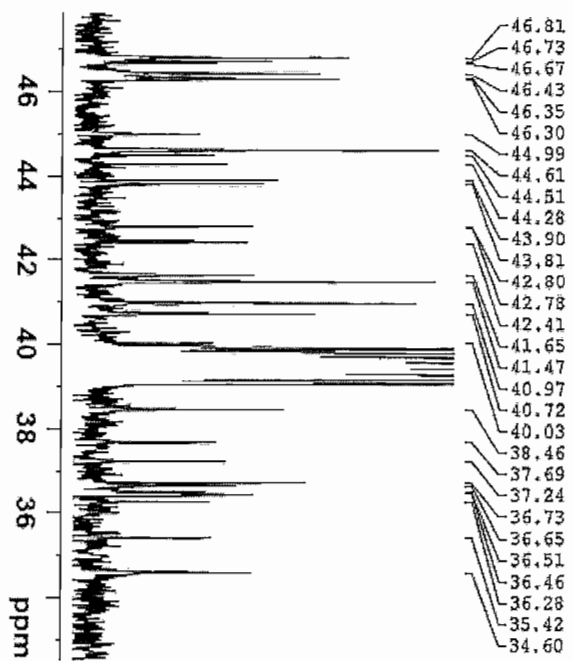
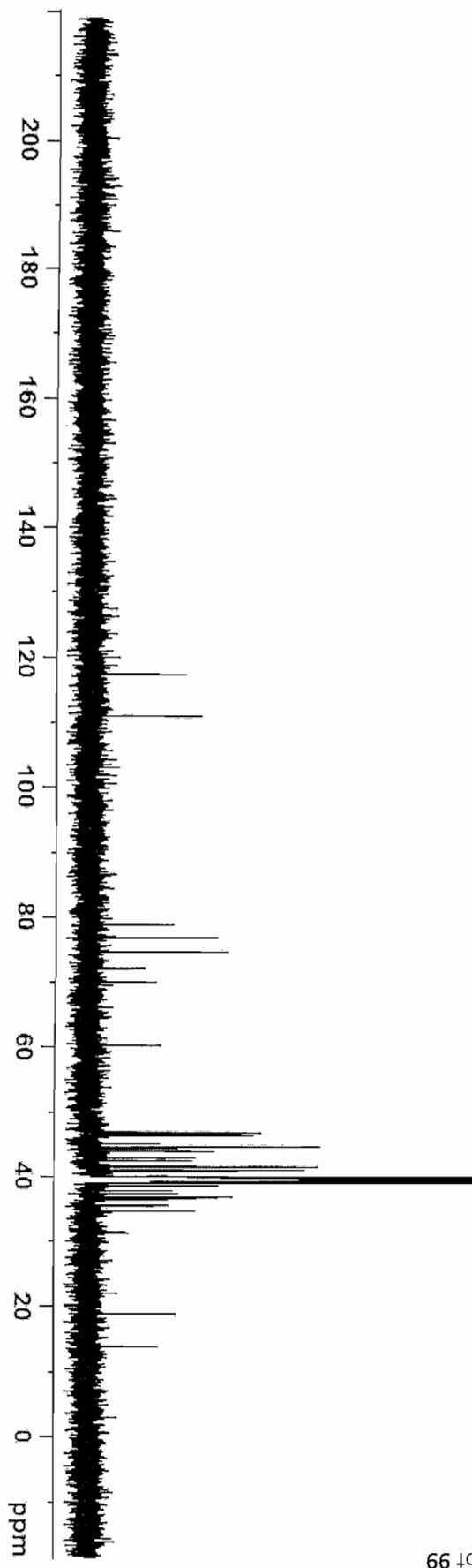




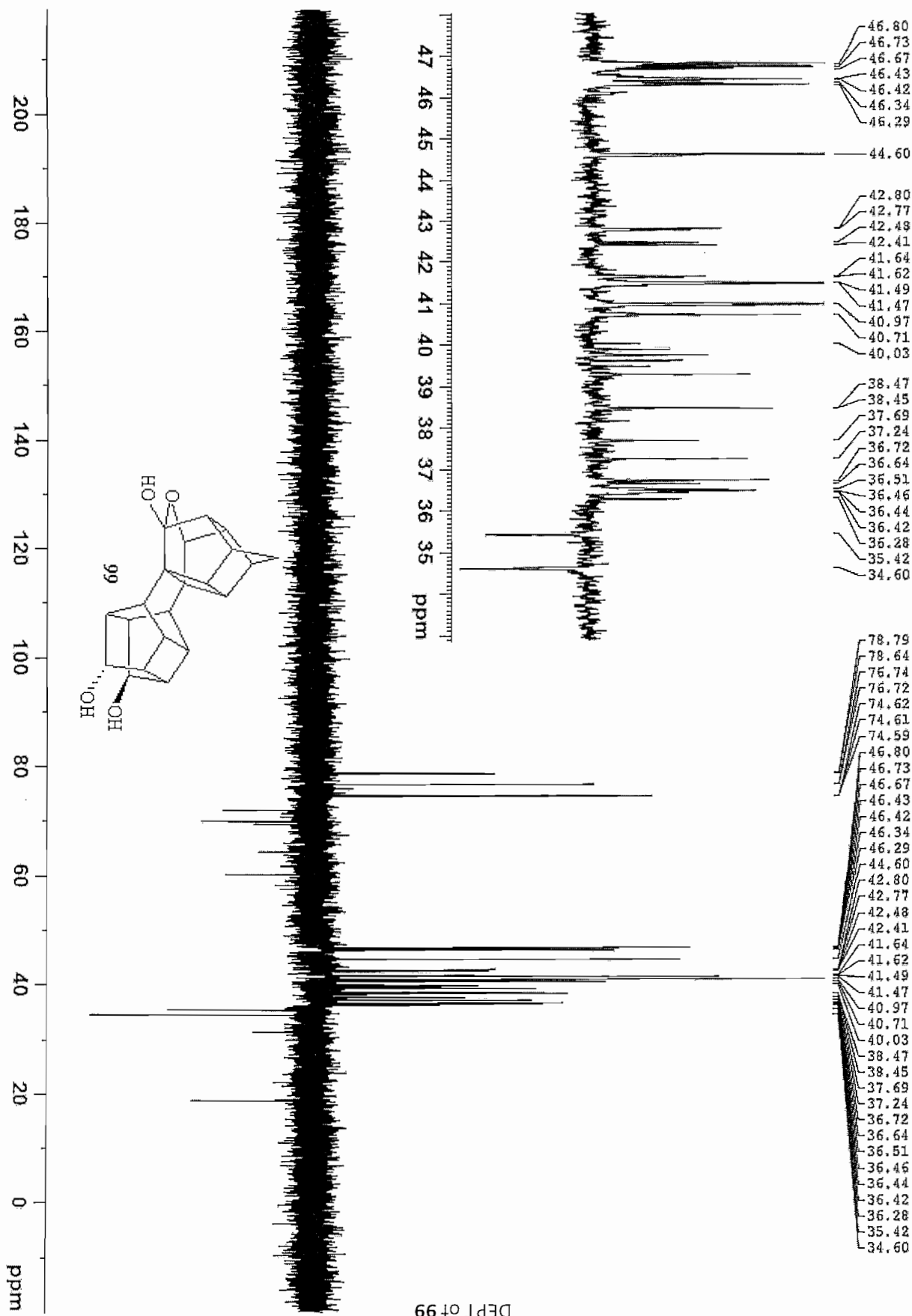


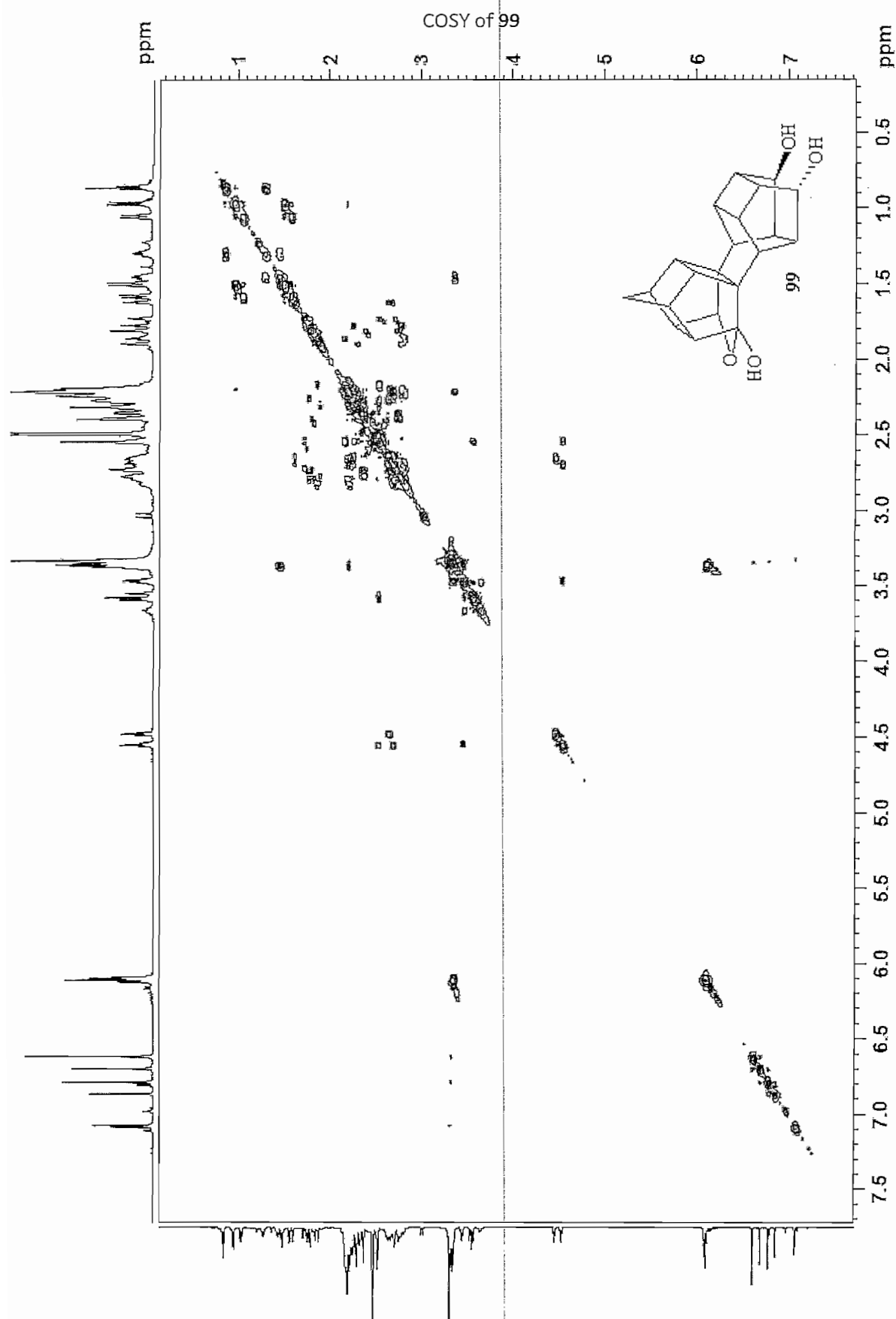
600 MHz ^1H -NMR of 99



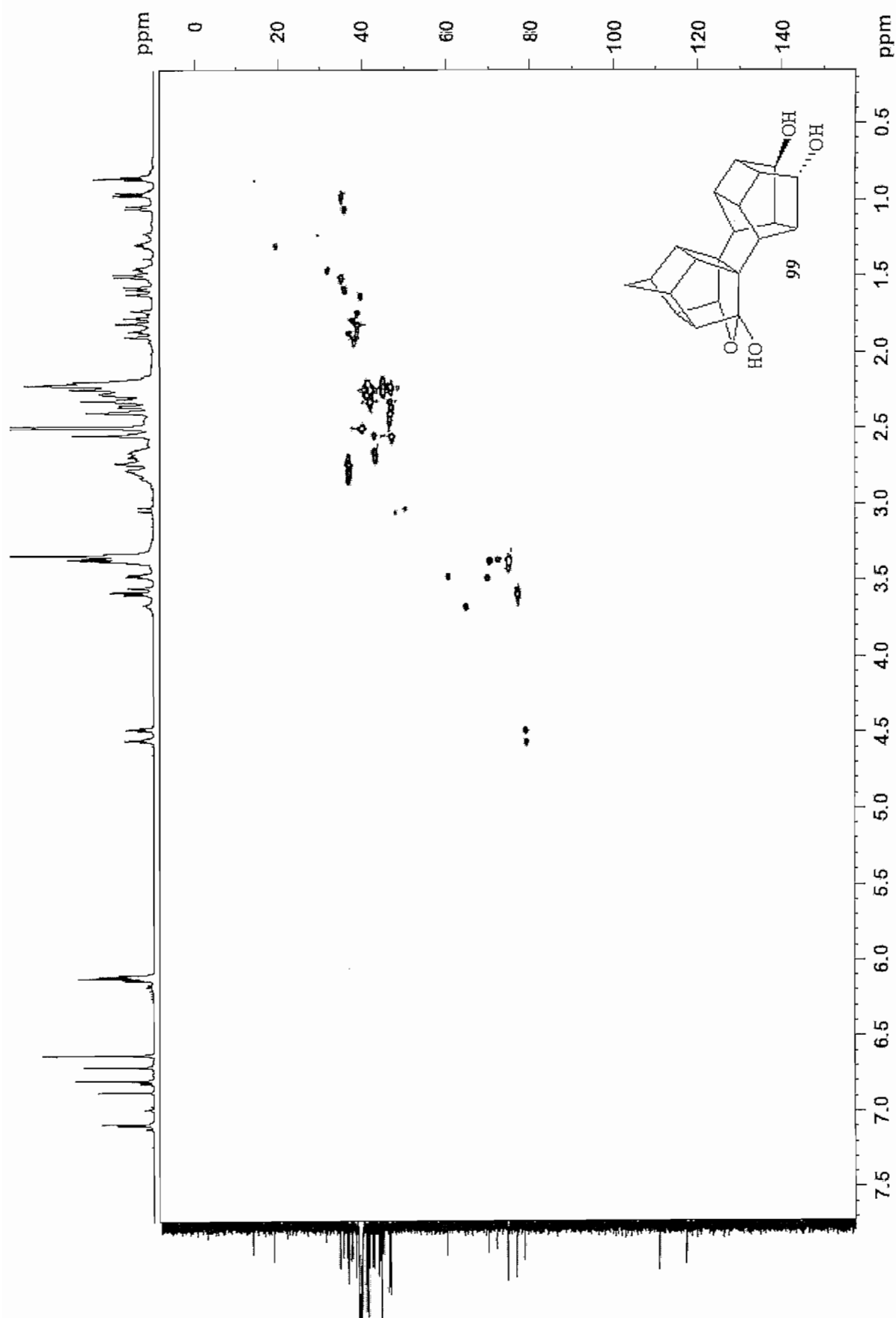


150 MHz ^{13}C -NMR of 99

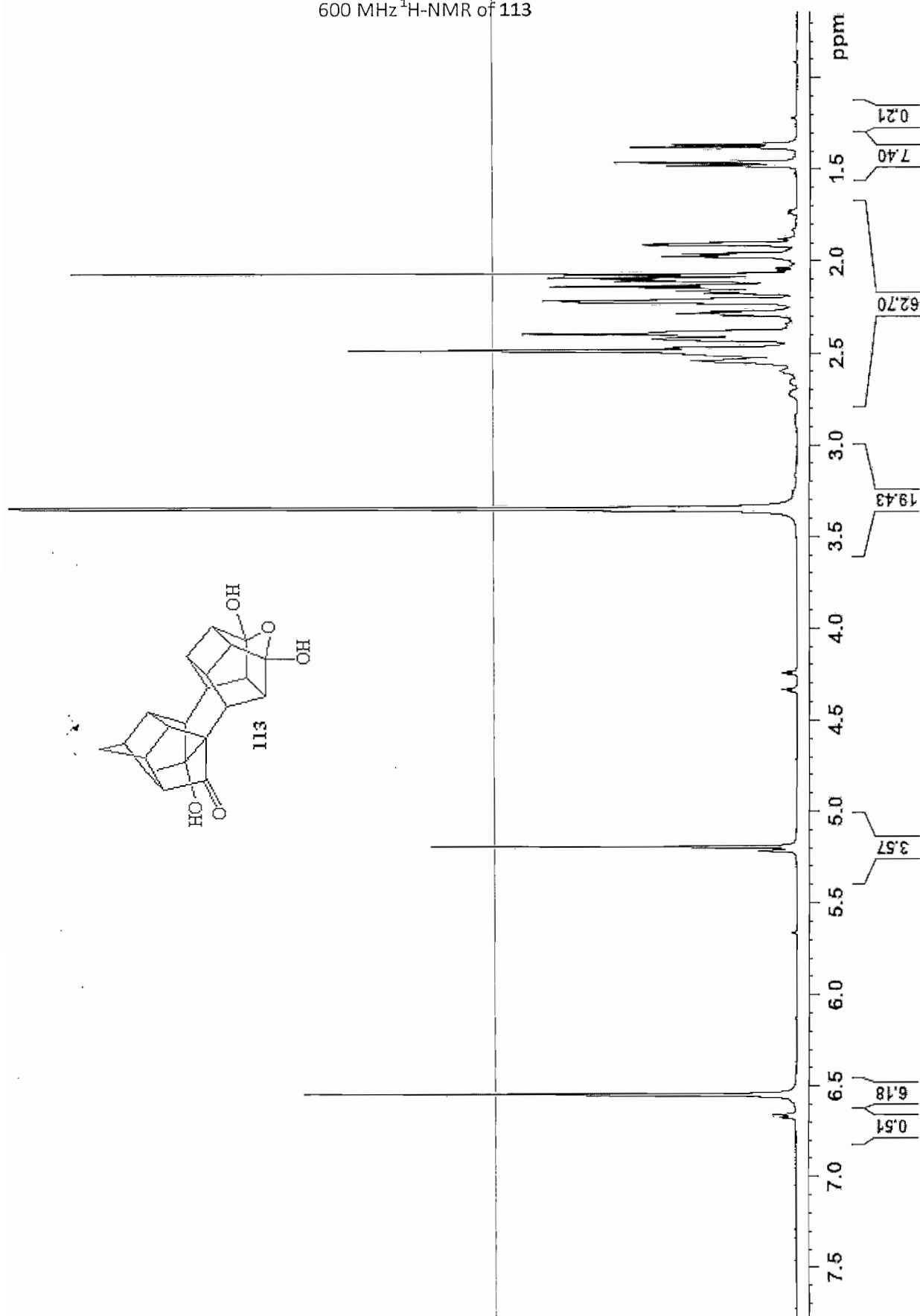


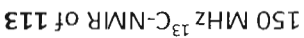


HQMC of 99

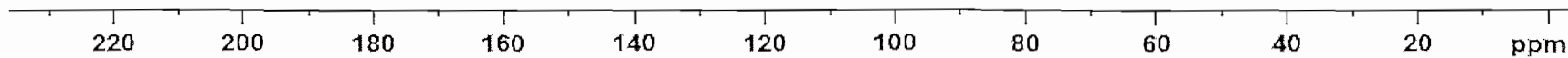
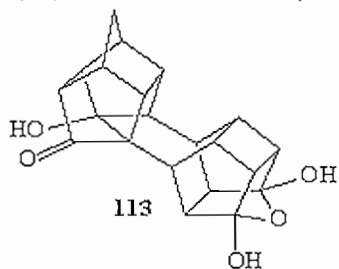
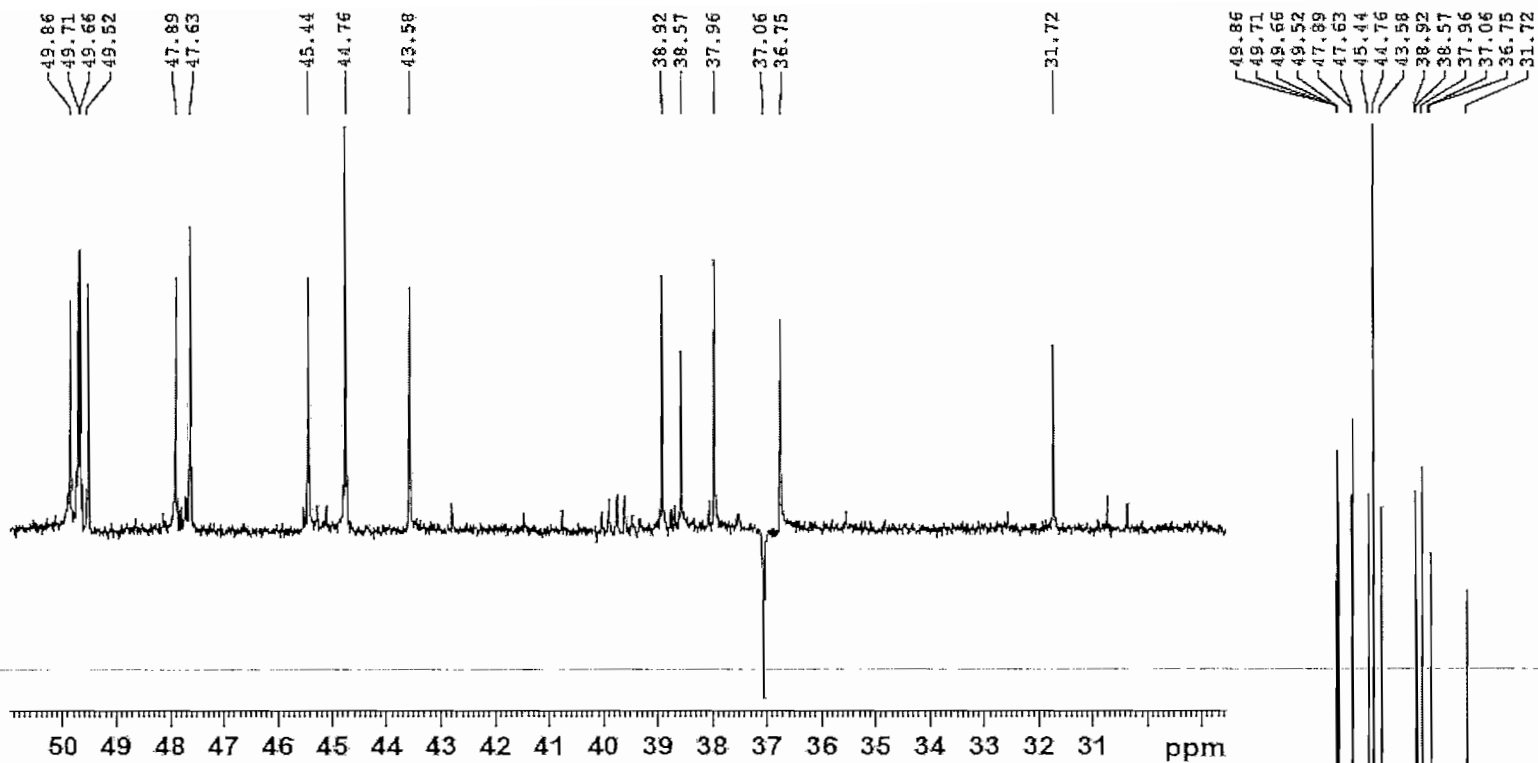


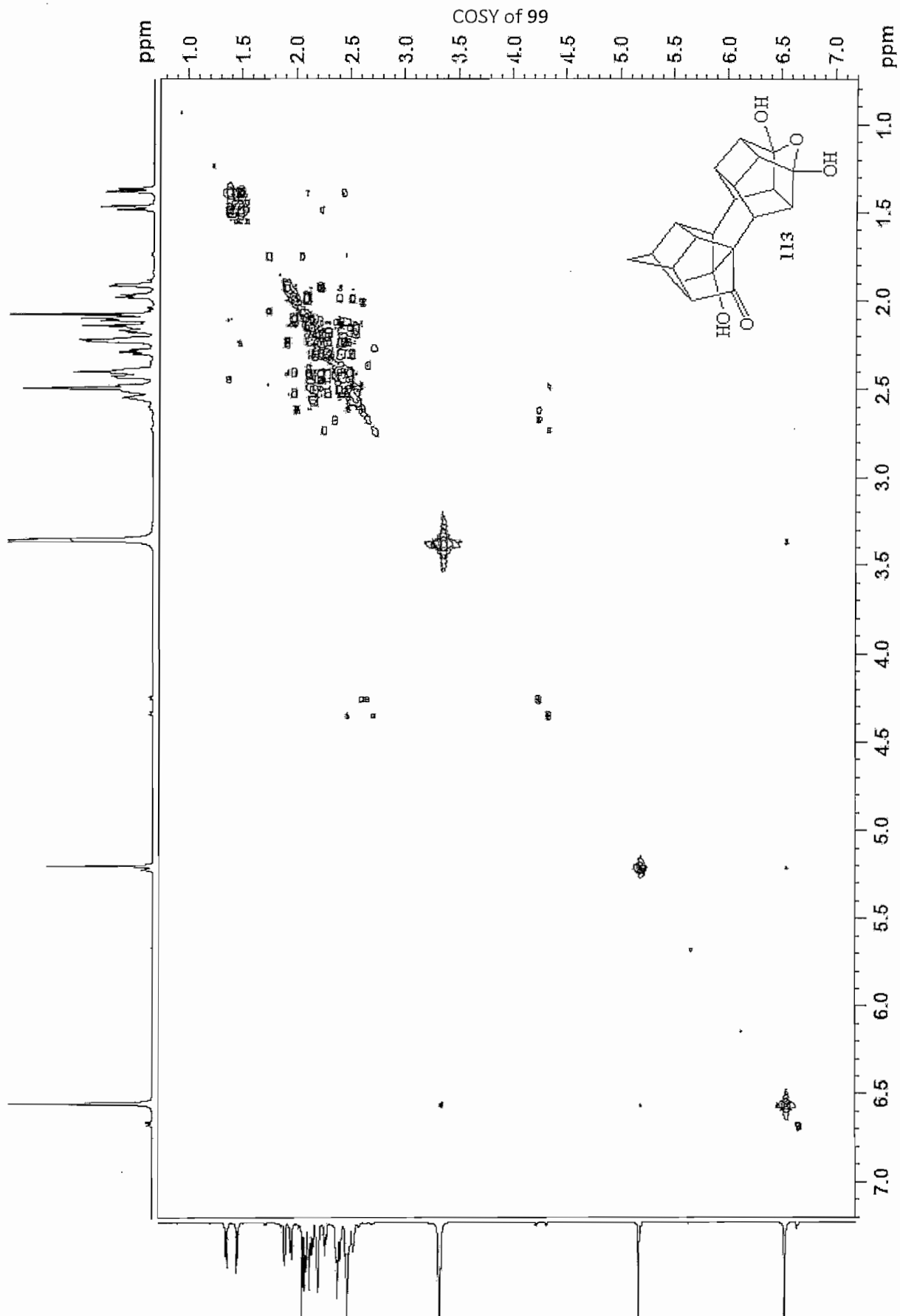
600 MHz ^1H -NMR of 113



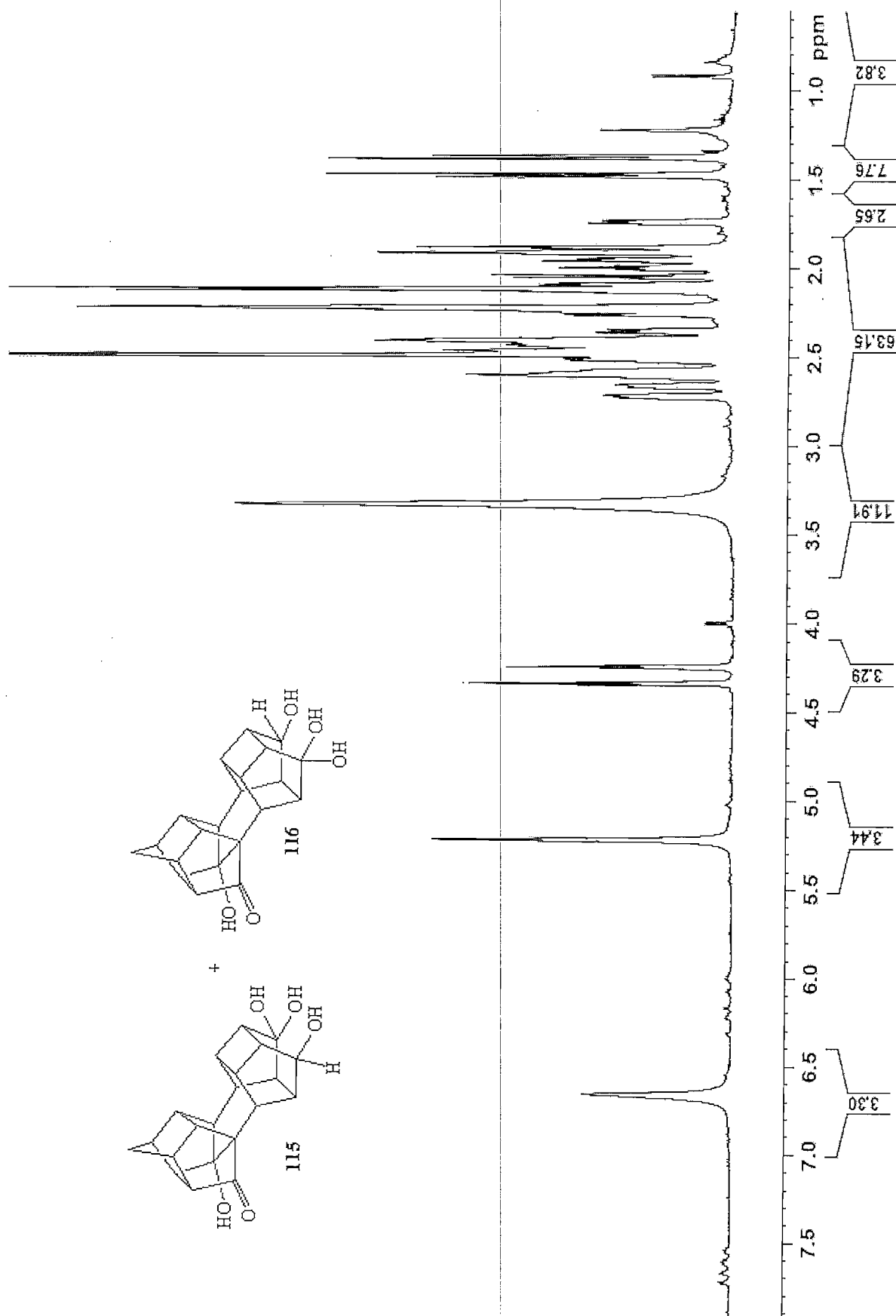


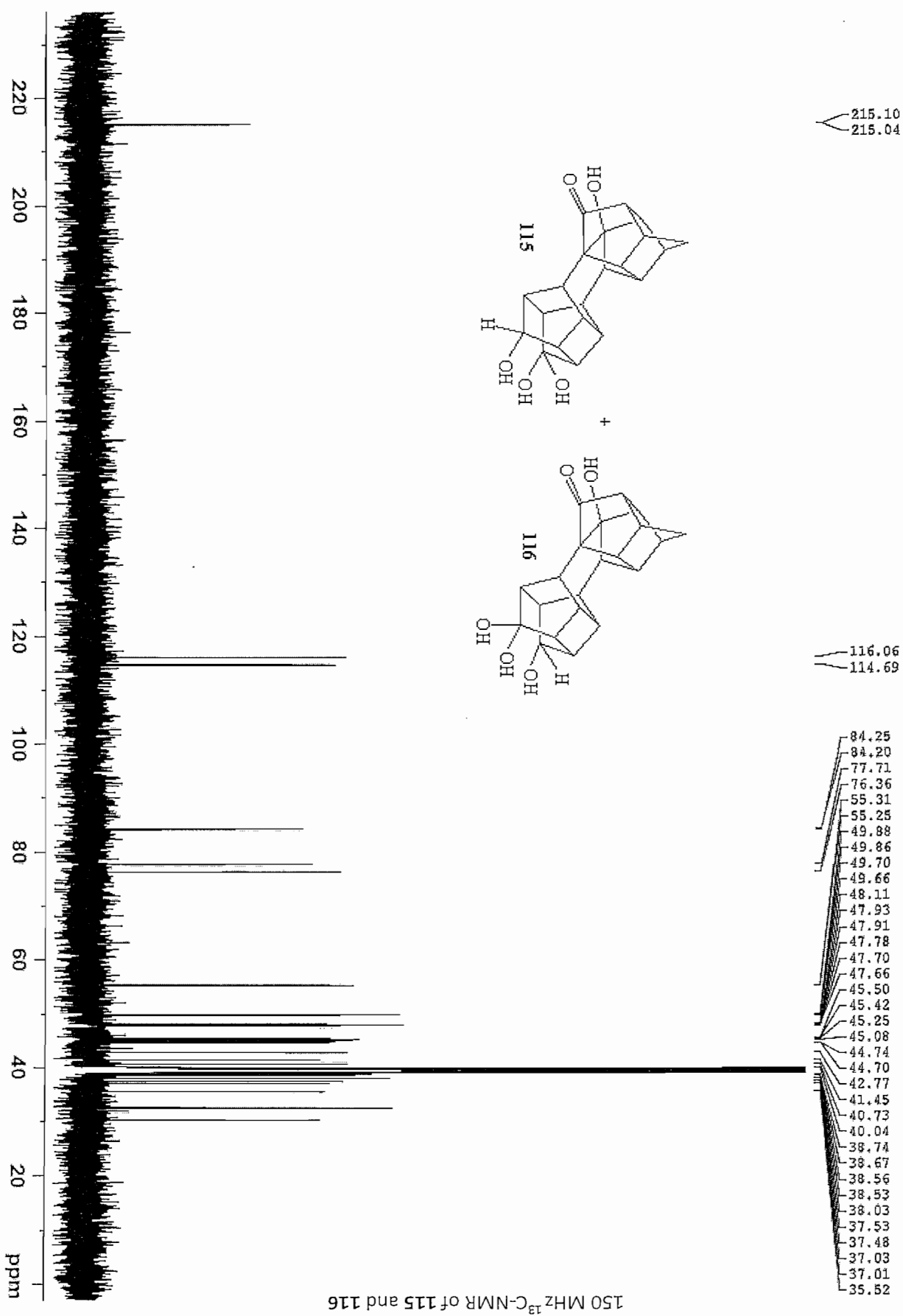
DEPT of 113

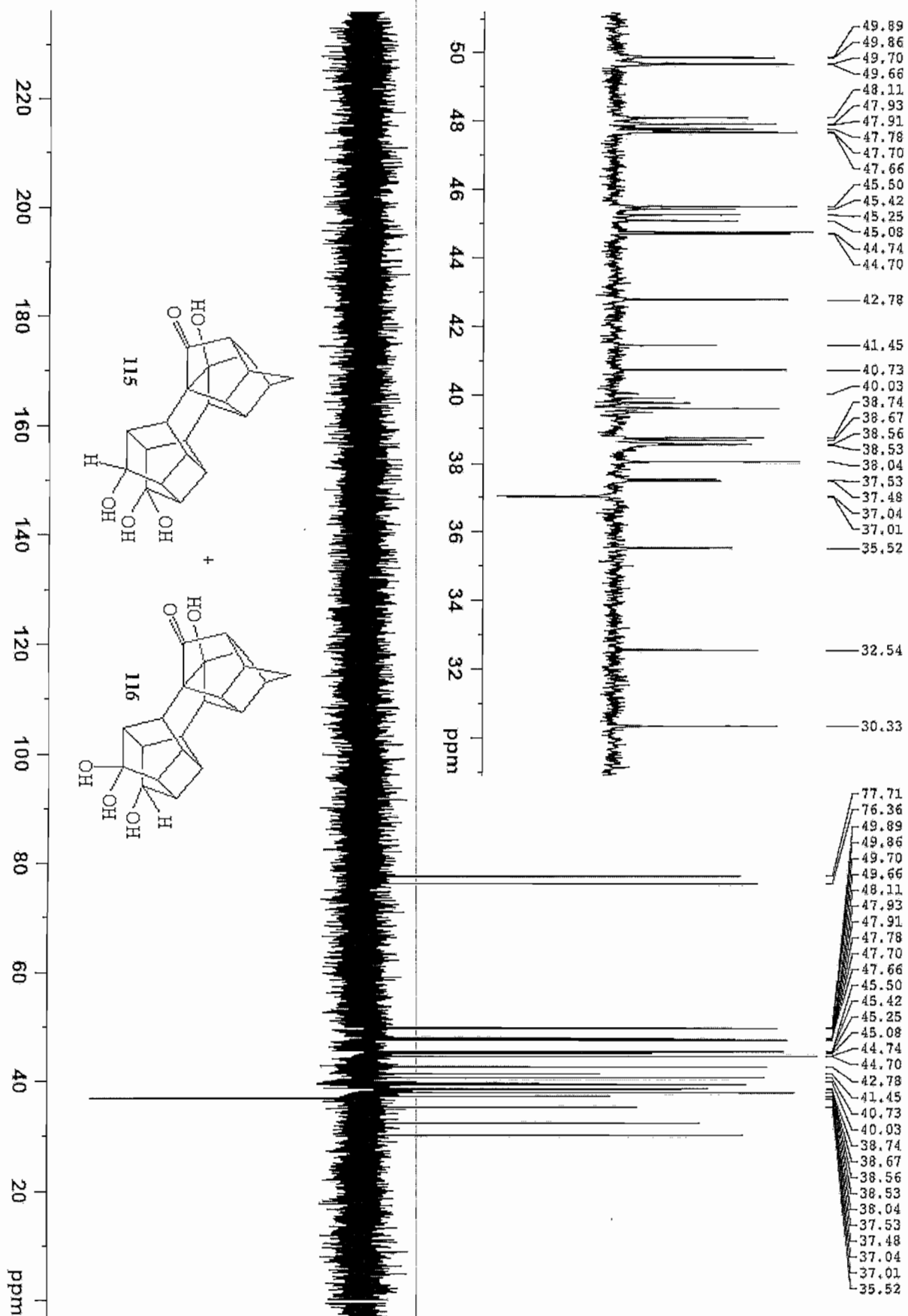




600 MHz ^1H -NMR of **115** and **116**

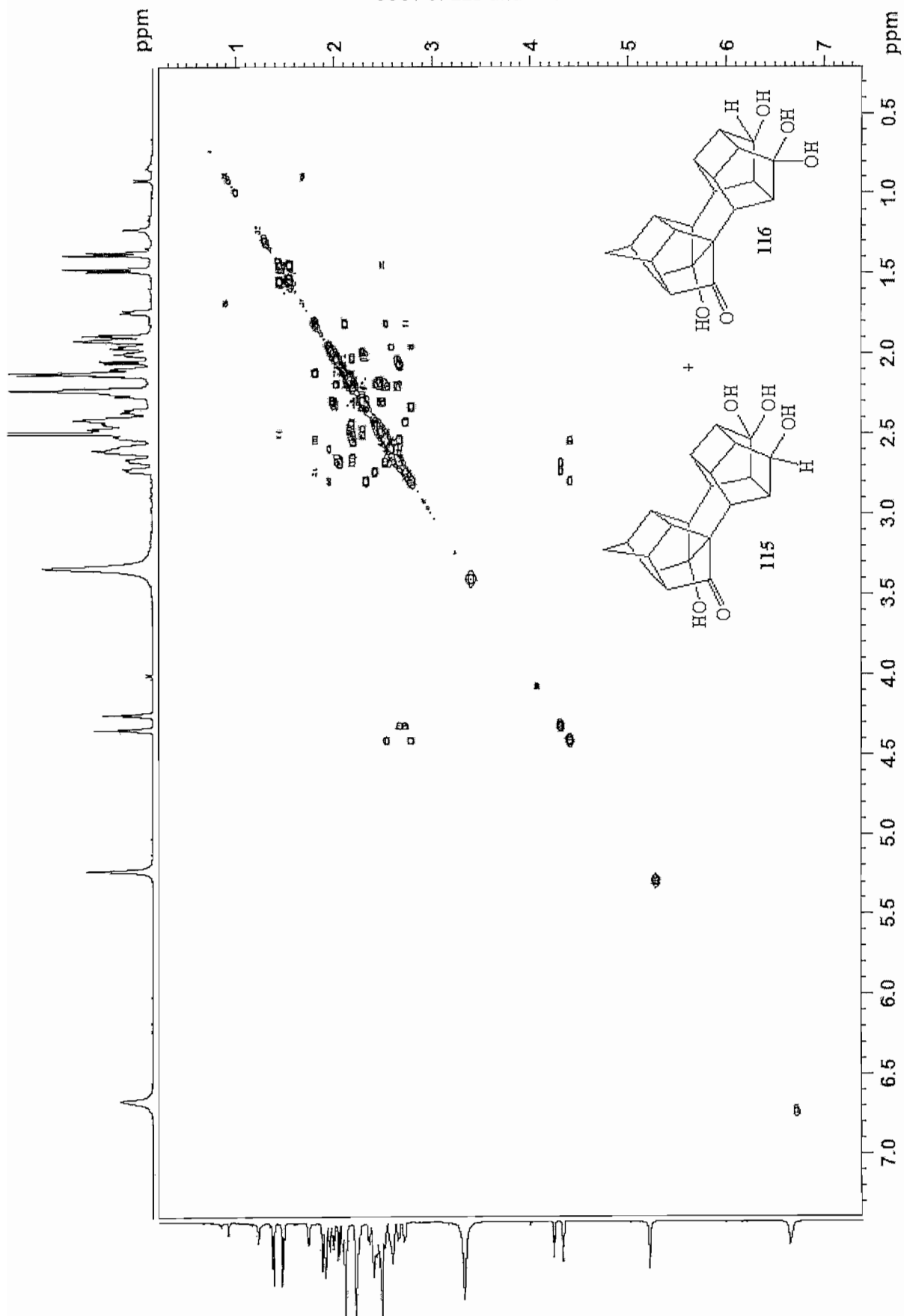




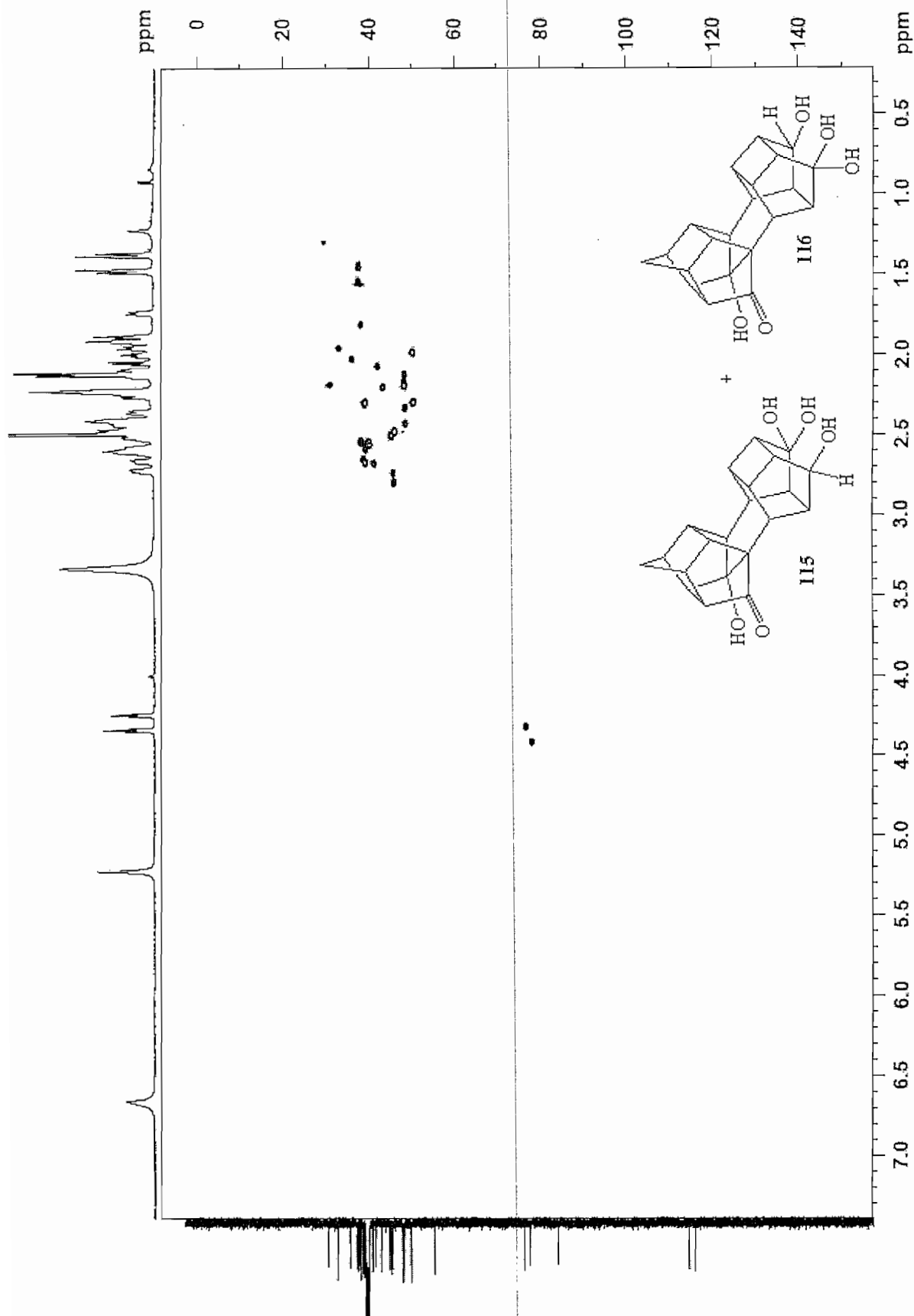


DEPT of 115 and 116

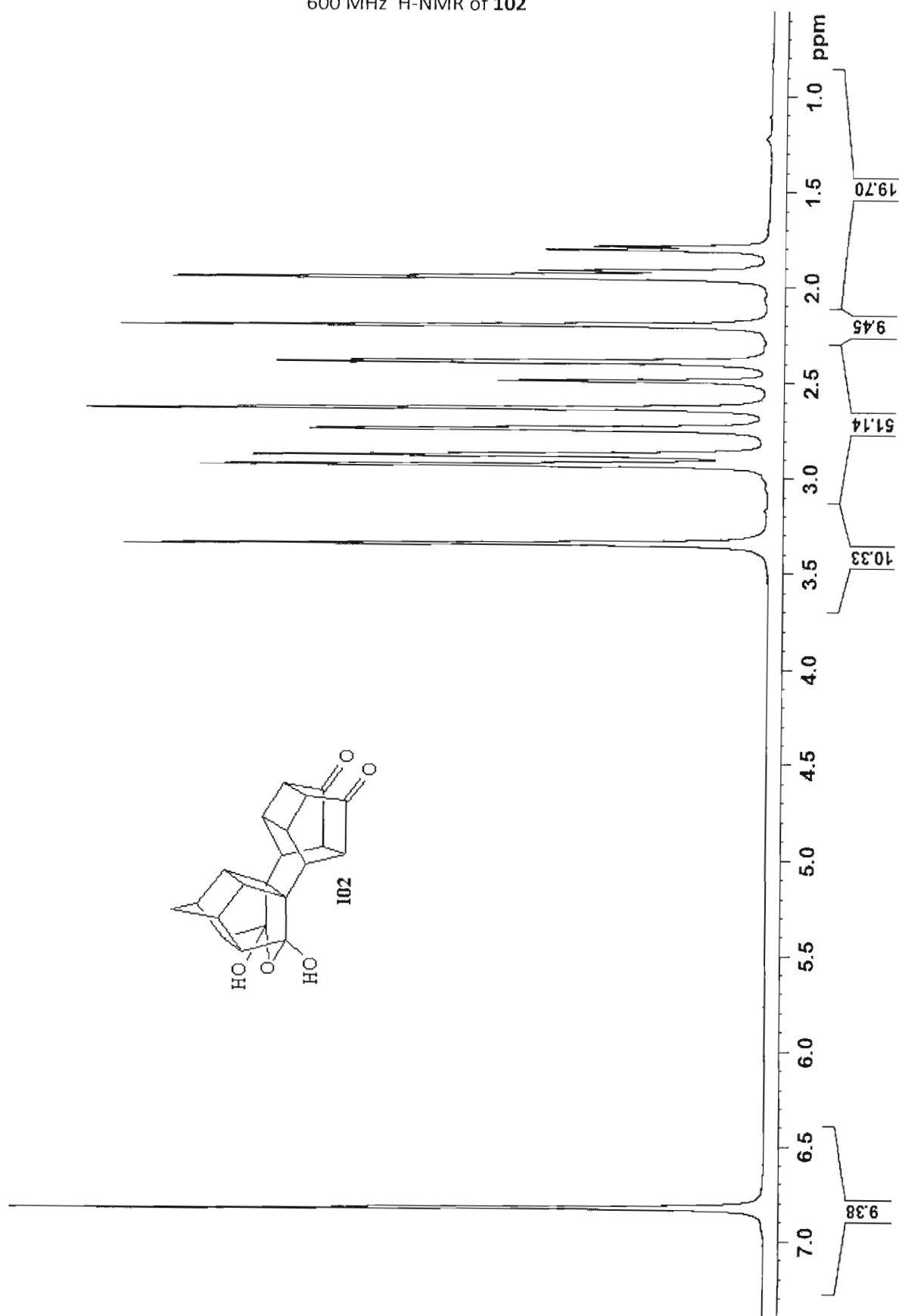
COSY of 115 and 116



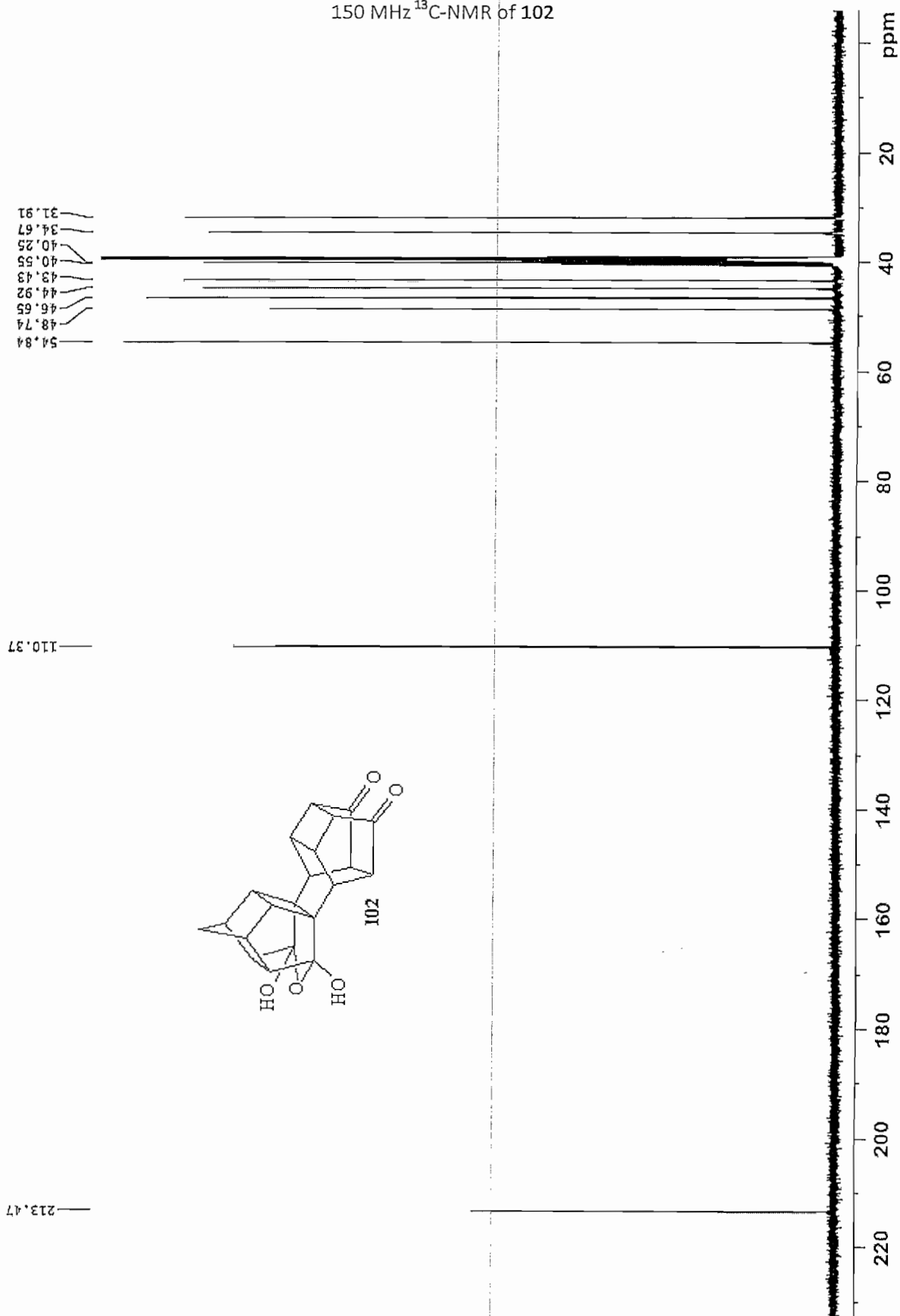
HQMC of 115 and 116



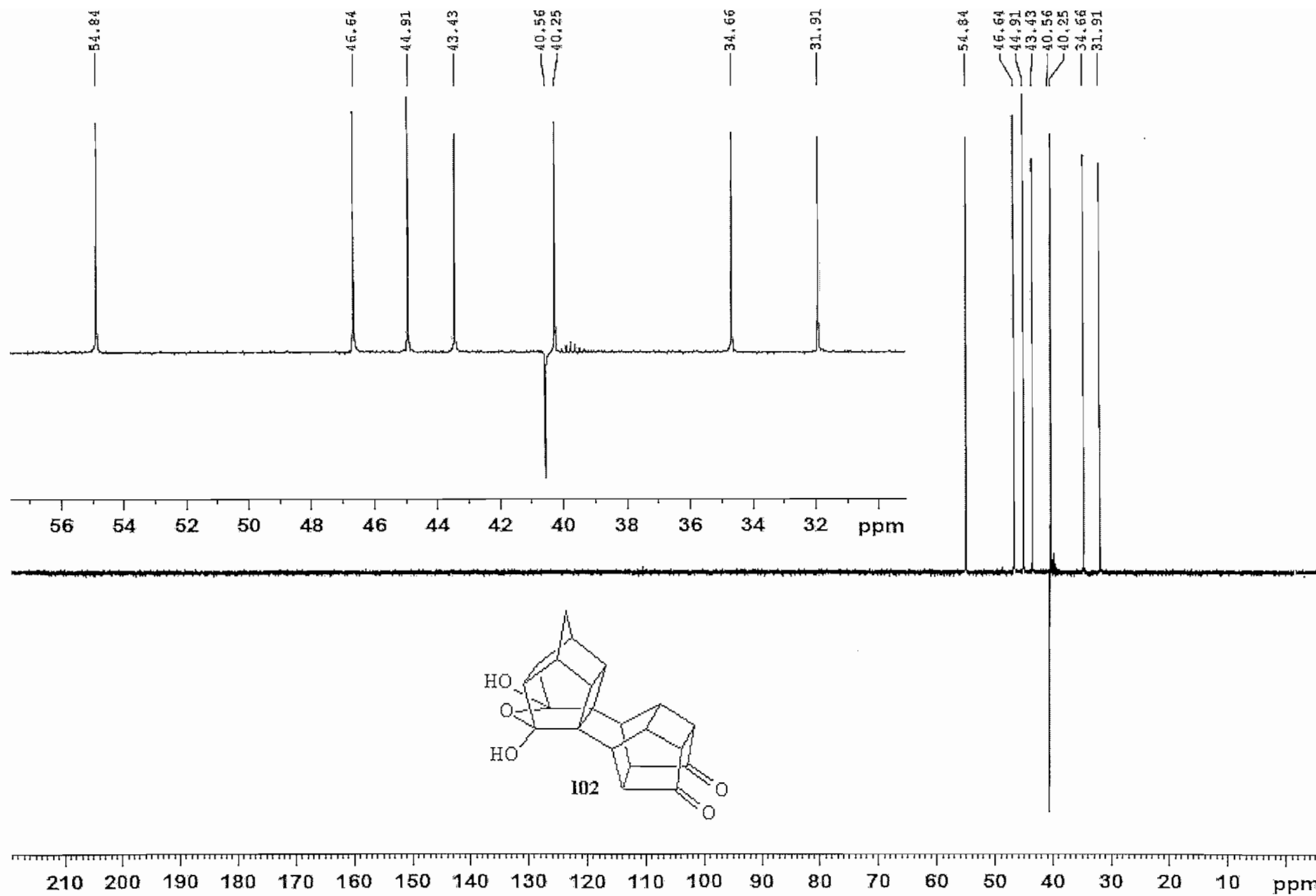
600 MHz ^1H -NMR of **102**



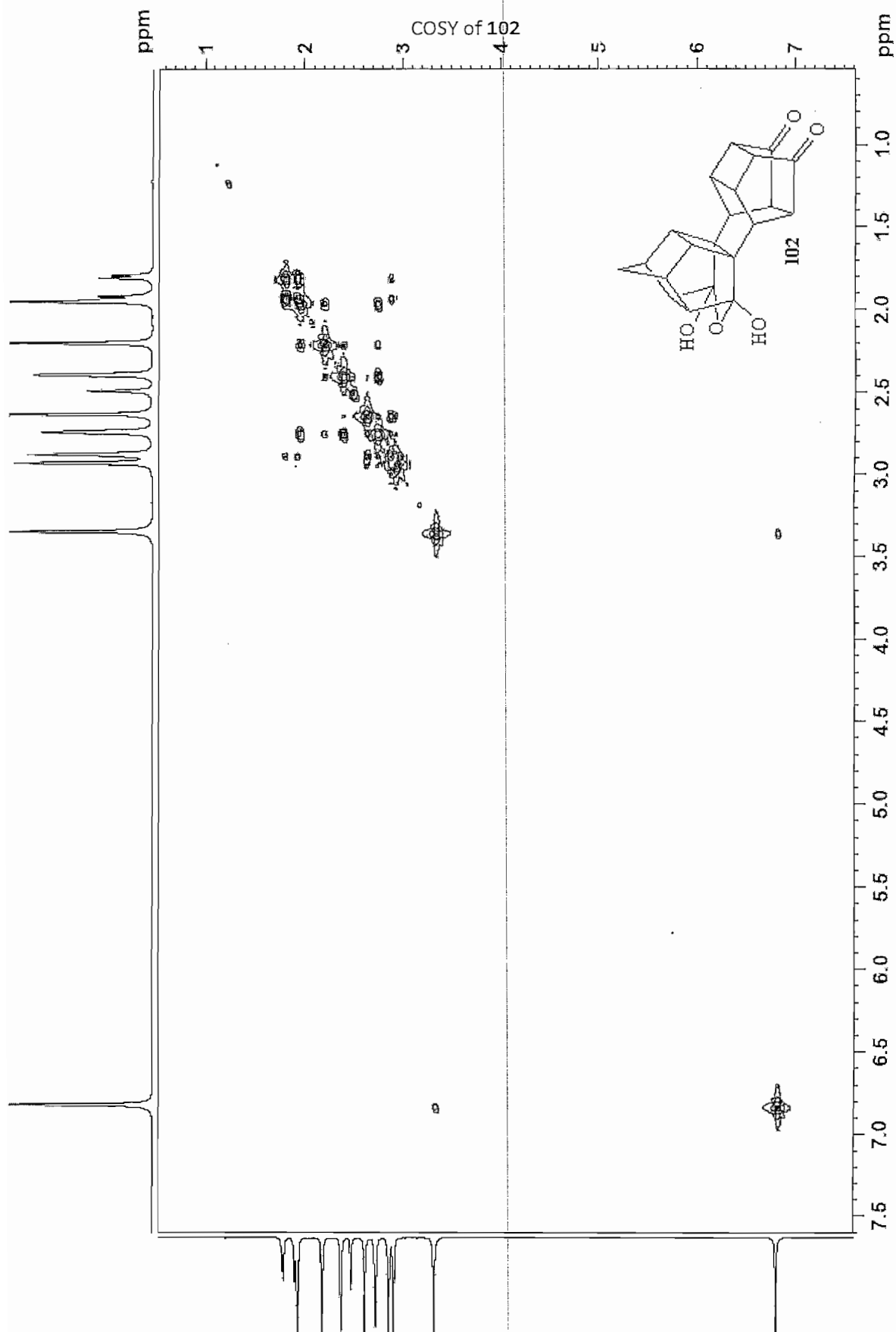
150 MHz ^{13}C -NMR of 102



DEPT of 102



0 145



HQMC of 102

