UNIVERSITY OF KWAZULU-NATAL

SYNTHESIS OF CAMPHOR DERIVED LIGANDS FOR APPLICATIONS IN ASYMMETRIC CATALYSIS

2009

GRANT ALEXANDER BOYLE

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A thesis submitted to the School of Chemistry, Faculty of Science and Agriculture, University of KwaZulu-Natal, Westville, for the degree of Doctor of Philosophy.

This thesis has been prepared according to **Format 3** as outlined in the guidelines from the Faculty of Science and Agriculture which states:

> This is a thesis in which the chapters are written as a set of discrete research papers, with an Overall Introduction and a Final Discussion. These research papers would not be published yet, but at least one paper would have already been submitted for publication.

As the candidate's supervisor, I have approved this thesis for submission.

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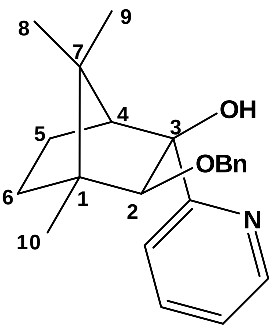
ABSTRACT

Chiral monoterpenes such as camphor have been widely used in the development of asymmetric catalysts with varying degrees of success. Pyridyl *N*-donor ligands derived from camphor have been extensively studied and have proven to be very successful. C3 pendant pyridyl alchol ligands have been neglected until this study. Herein the synthesis of a series of six novel C3 pendant ligands is described.



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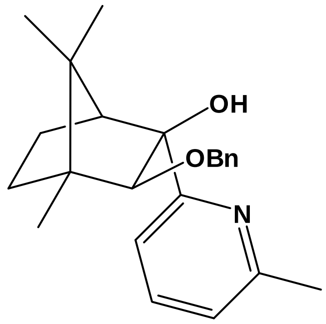

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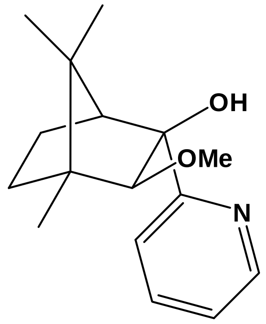

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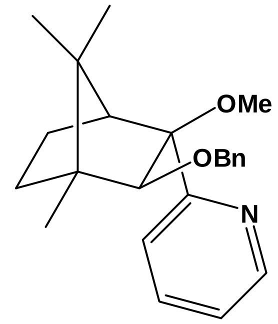

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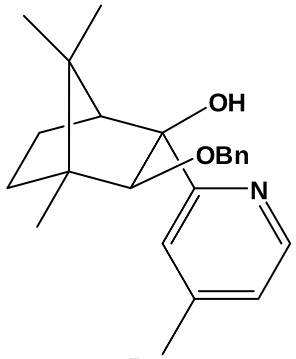

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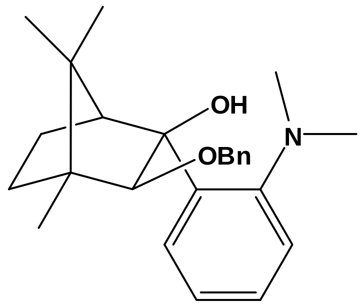

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The ligands were synthesised in six steps (seven for ligand **4**) using *R*-(+)-camphor as the starting material. Two alternative methods for the synthesis were investigated with the second method (Method B) proving to be superior. Several difficulties with regards to regioisomers and diastereomers were overcome in establishing the procedure for the synthesis of the ligands. The final compounds were successfully synthesised in moderate yields with absolute *regio*- and *stereo*-control.

The ligands were evaluated as chiral catalysts in a series of different reactions. The first of these was the alkylation of a series of aldehydes using diethylzinc. This reaction was investigated in order to compare the efficacy of the novel compounds to previous camphor derived pyridyl alcohol ligands. All previous molecules of this type have been evaluated as catalysts in this reaction with varying degrees of success. The novel ligands successfully catalysed this reaction with moderate to good enantioselectivity (up to 85% *ee*). The results obtained showed these compounds to be significantly superior to a previous analogous C2 pendant β-amino alcohol reported in literature. The results were

also comparable to other camphor derived pyridyl alcohol ligands reported previously. The synthesis of ligands **1-4** as well as their evaluation as catalysts in the alkylation of aldehydes with diethylzinc is discussed in detail in chapter 2 (Paper 1).

The second reaction in which the ligands were evaluated was the Henry (Nitroaldol) reaction. This reaction has not seen many camphor derived ligands applied as catalysts. Two additional derivatives (**5-6**) were synthesised and all the compounds were screened as catalysts in this reaction. The ligands successfully catalysed the reaction with good to excellent yields but only moderate selectivity (up to 56% *ee*). The details of this evaluation are discussed in chapter 3 (Paper 2).

The final reaction in which the ligands were evaluated was the Diels-Alder reaction of 2-acrolyloxazolidinone with cyclopentadiene. The reaction was again successfully catalysed in moderate to good yields with good *endo:exo* selectivity but fairly poor stereoselectivity (up to 43% *ee*). Computational models of the proposed complexes were developed in order to explain the poor observed selectivity. The details of this study are reported in chapter 4 (Paper 3).

Chapter 5 (Paper 4) involves a NMR and computational investigation of some of the ligands. Complete NMR elucidation using 2D NMR techniques were carried out for the selected ligands. Optimisation of the ligands using high level DFT calculations was carried out in order to aid in the visualisation of potential through space interactions within each molecule.

DECLARATIONS

DECLARATION 1 - PLAGIARISM

I, ………………………………………….………………………., declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons’ data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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DECLARATION 2 - PUBLICATIONS

DETAILS OF CONTRIBUTION TO PUBLICATIONS that form part and/or include research presented in this thesis (include publications in preparation, submitted, *in press* and published and give details of the contributions of each author to the experimental work and writing of each publication)

Publication 1

Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M., (1*R*,4*S*)-(-)-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007,** E63, (9), o3765.

Contributions: Synthesised crystal and wrote the paper. All other authors are supervisors.

Publication 2

Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M., Synthesis of novel 3-Hydroxy-3-pyridyl Camphor Derivatives, *S. Afr. J. Chem*, Accepted for publication **2009**.

Contributions: Synthesised all compounds, carried out all testing and wrote the paper. All other authors are supervisors.

Publication 3

Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M., The evaluation of novel camphor derived ligands as catalysts in the asymmetric Henry reaction, *S. Afr. J. Chem.*, Accepted for publication **2009**.

Contributions: Synthesised all compounds, carried out all testing and wrote the paper. All other authors are supervisors.

Publication 4

Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M.; Naicker, T., The evaluation of novel camphor derived pyridyl ligands as catalysts in the asymmetric Diels-Alder reaction of cyclopentadiene with 3-acryloyl-2-oxazolidinone, *S. Afr. J. Chem.*, Accepted for publication **2009**.

Contributions: Carried out testing with the assistance of T. Naicker. Carried out computations. Wrote the paper. All other authors are supervisors.

Publication 5

Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M., NMR Elucidation of novel ligands derived from (*R*)-(+)-Camphor, *Struct. Chem.*, Accepted for publication **2009**.

Contributions: Carried out all computations and elucidations. Wrote the paper. All other authors are supervisors.

Signed:

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LIST OF PUBLICATIONS

1. Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M., (1*R*,4*S*)-(-)-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007,** E63, (9), o3765.
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6. Boyle, G. A.; Govender, T.; Kruger, H. G.; Ndlovu, N. I., 8-Amino-11-hydroxypentacycloundecane-8,11-lactam. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007,** E63, (9), o3906.
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CHAPTER 1
INTRODUCTION

1.1 HISTORY OF CHIRALITY

The existence of optically active compounds has been known to scientists since the early 19th century. The first separation of a racemic mixture was achieved by Pasteur in 1848.[1] He succeeded in separating the two enantiomorphous crystal forms of racemic sodium ammonium tartrate salt using a pair of tweezers and a microscope.[1] These enantiomorphs had different crystal shapes and thus separation was achieved based on this physical property alone. It was found that these crystals rotated plain polarised light in opposite directions with equal intensity. The origin of this phenomenon was enantiomeric differences. Enantiomers are defined as non-superimposable mirror images (Figure 1). They have many identical physical (mp, TLC, NMR, IR) and chemical properties when acting in an achiral environment.[2-7] The difference is that they rotate plane polarised light in equal but opposite directions. There are many examples of chiral molecules in nature. In fact, some of the basic building blocks of biological systems, namely 19 of the 20 naturally occurring amino acids, are chiral.[2, 6] The only exception being glycine. Natural sugars found in biological systems are also chiral.

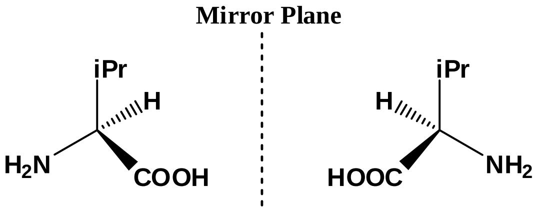


Figure 1: The enantiomers of the natural amino acid valine, the (*S*)-enantiomer on the left and the (*R*)-enantiomer on the right.

As a result of the inherent chirality of nature, much investigation into this phenomenon has been undertaken.[3] Major breakthroughs occurred in the 1960's when advancements in the analytical and synthetic tools utilised in organic chemistry were made. The harnessing of chiral catalysis, initially using enzymatic systems, saw the first industrial scale processes for the production of chiral molecules.[3, 4] Later in the 20th century, industrial processes began using metal catalysed asymmetric reactions for production of various pharmaceuticals and speciality chemicals.[3, 4]

1.2 THE IMPORTANCE OF ENANTIOMERICALLY PURE COMPOUNDS

It is known today that different enantiomers of a particular chiral molecule can have markedly different effects in their interaction with receptors in the biological system.[4] An example of this is the interaction of the different enantiomers of carvone with the olfactory sensor in the nose. The (*R*)-enantiomer has spearmint odour while the (*S*)-enantiomer has a caraway smell.[4] Perhaps the most tragic and well publicized example of the dramatic effects of different enantiomers occurred in the 1960's when the drug Thalidomide was prescribed in its racemic form to pregnant women for use as a sedative drug.[4] The resultant foetal deformities were later linked solely to the (*S*)-enantiomer, which shared little of the sedative effect of the (*R*)-enantiomer, but had the tragic teratogenic effect.

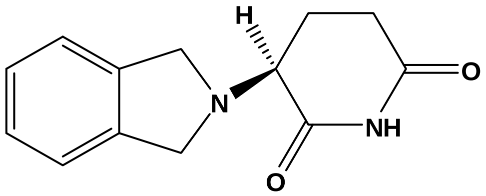


Figure 2: The teratogenic (*S*)-enantiomer of the drug Thalidomide.

This resulted in a massive drive to obtain optically active compounds in their enantiomerically pure form.[3, 5, 7] The safety of any potential drug made from chiral precursors is not the only concern however. There are also sound economic reasons. The production of only a single enantiomer may result in significant cost reduction. Smaller, selective processes would require less raw materials and solvents and also produce less waste. This would also negate the need for costly separation of enantiomers. Approximately 63% of all drugs on the market in 1983 were chiral. At this time, the majority (~60%) of these were racemic, the other ~40% of chiral drugs were mainly of natural origin. In only 19 years (2002) this had changed dramatically with only ~10% of all chiral drugs being racemic.[8] This is partly due to the fact that since 1992, the drug approval process requires all optically active drugs going through clinical trials to have each enantiomer screened separately.[8] It is also due in part to the advances in asymmetric synthesis and catalysis in the latter part of the 20th century which have made it possible to selectively synthesise only a single enantiomer of a particular optically active compound.

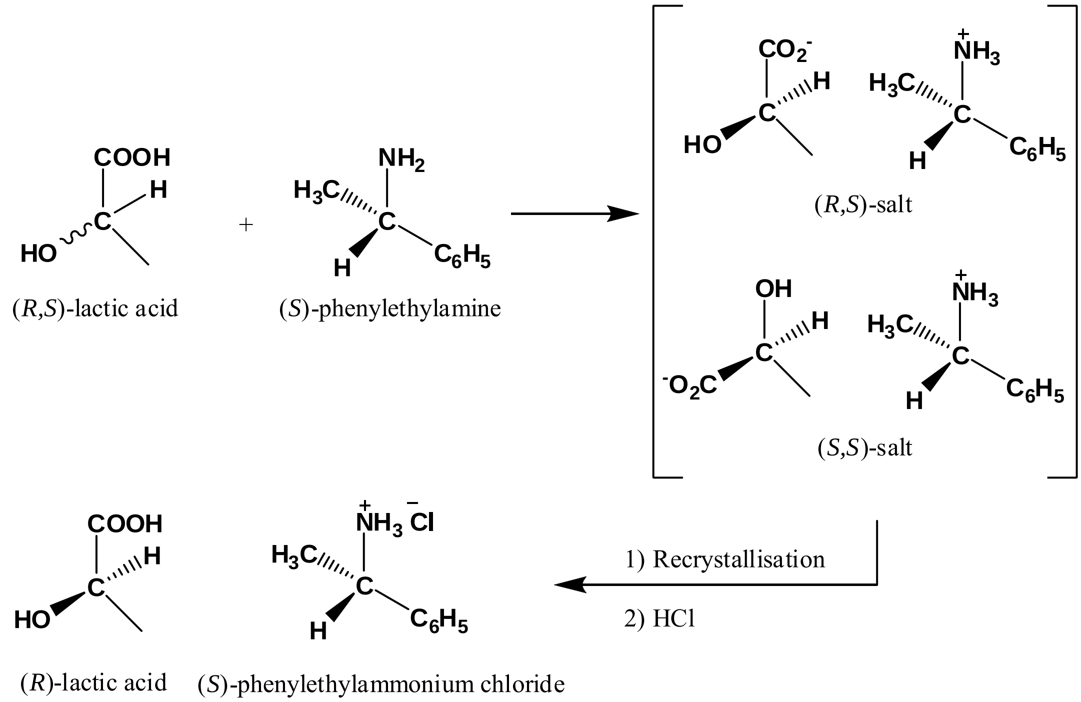
1.3 METHODS OF OBTAINING ENANTIOMERICALLY PURE SUBSTANCES

The basic strategies involved in obtaining optically active compounds as single enantiomers can be divided into three categories:[4]

1. Resolution of racemates.
2. Utilisation of naturally chiral compounds as starting materials.
3. Asymmetric synthesis including enzymatic methods.

1.3.1 RESOLUTION OF RACEMATES

This method is utilised, as the name suggests, in the separation of individual enantiomers from a racemic mixture. The most common and simple method is to convert the enantiomers into diastereomeric compounds. These diastereomers no longer have identical physical and chemical properties and thus can be separated using conventional techniques such as chromatography or even recrystallisation. The enantiomers are usually derivatised by reaction with an enzyme or another chiral molecule of natural origin; in other words, a covalent bond is formed with the chiral auxiliary. This results in the formation of diastereomers which can then be separated. Another method is to form an electrostatic (non-covalent) complex with an optically pure compound. The resulting complex could have different solubilities and therefore be separable by recrystallization. An example of this form of resolution is the separation of racemic lactic acid by (*S*)-phenylethylamine (Scheme 1).[6]

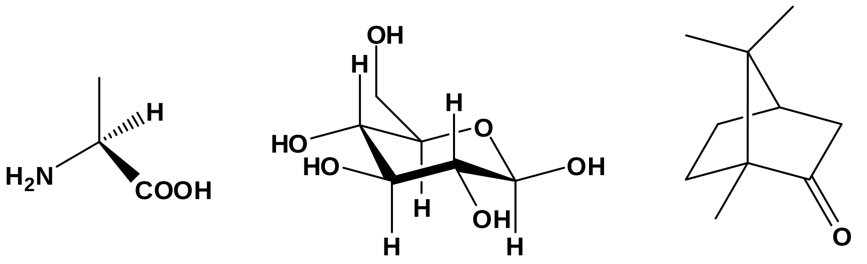


Scheme 1: Example of resolution of racemates.

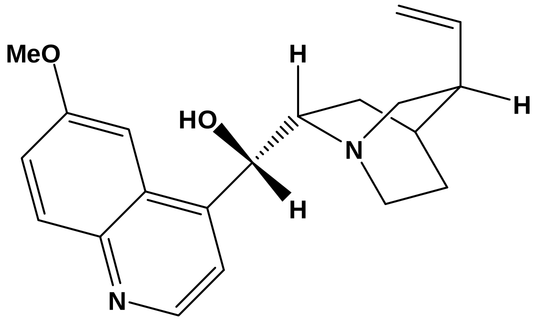
There are advantages and disadvantages to this method. The main disadvantage is the theoretical yield is at most 50 %. An advantage, however, is the fact that both enantiomers can be isolated in many cases.

1.3.2 UTILISATION OF NATURALLY CHIRAL COMPOUNDS

The "chiral pool" of naturally occurring, non-racemic chiral molecules provides a selection of molecules that can be used as enantiopure starting materials for a synthesis.[3-5, 7] Due to the inherently chiral nature of the world around us there is a variety of classes of compounds available to the synthetic chemist from which to choose. These include the previously stated amino acids, carbohydrates, terpenes and alkaloids to mention just a few (Figure 3).



(*S*)-valine (amino acid) *β*-(*D*)-Glucose (carbohydrate) *D*-Camphor (terpene)



Quinine (alkaloid)

Figure 3: Some examples of naturally occurring non-racemic chiral molecules.

Many compounds have been synthesised using these chiral molecules as starting materials. In fact, this thesis deals with the synthesis of derivatives of camphor.

1.3.3 ASYMMETRIC SYNTHESIS

Asymmetric synthesis has become the most common method for obtaining chiral compounds. It can be broken down into a series of sub-divisions. These include substrate controlled asymmetric synthesis, auxiliary controlled asymmetric synthesis, reagent controlled asymmetric synthesis and chiral catalysis. Chiral catalysis includes enzymatic methods, which will not be discussed here. Numerous books and reviews describing enzymatic synthesis are available.[4, 9-11]

It could be argued that substrate controlled asymmetric synthesis is similar to the 2nd category above, namely the use of natural chiral compounds as starting materials in asymmetric synthesis. Although this is true, this category is not limited to only naturally occurring substances. The formation of a new chiral centre is regulated by the existing chiral centre in the molecule.

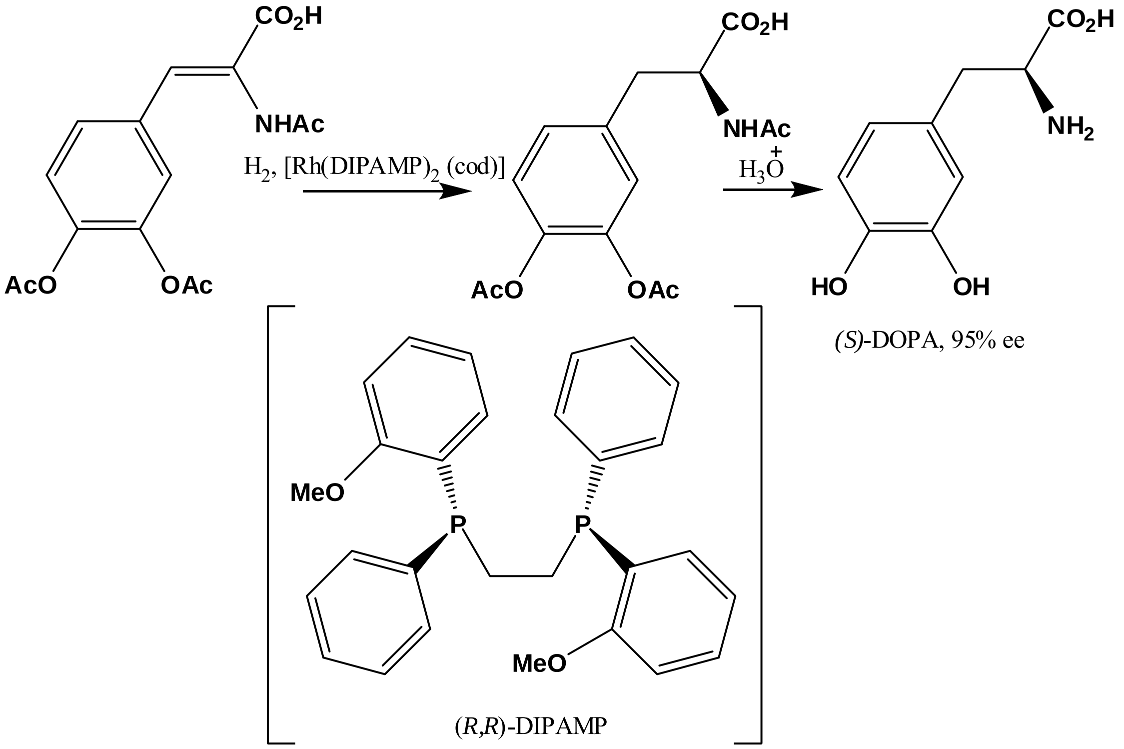
Auxiliary controlled synthesis occurs when a chiral compound is only temporarily attached to the non-chiral starting material. After the formation of the new chiral centre, this optically active material is removed.

In reagent controlled asymmetric synthesis the prochiral starting material is converted to a chiral product using a chiral reagent.

Chiral catalysis is probably the most common form of asymmetric synthesis. Here, a chiral catalyst is used to induce chirality in a prochiral substrate by reducing the activation energy of one of the diastereomeric transition states hence favouring the formation of one enantiomer over the other. This particular category is described in more detail in the next section.

1.4 ASYMMETRIC CATALYSIS

Asymmetric catalysis as a distinct field of organic chemistry has grown rapidly in the last few decades. The importance of synthesising chiral compounds from prochiral substrates has seen the rapid development of these catalysts. The first industrial application of asymmetric catalysis was in the production of the anti-Parkinson's drug (*S*)-DOPA, also known as *L*-DOPA (Scheme 2).[3, 12]



Scheme 2: Monsanto's (*S*)-DOPA synthesis, the first industrial application of asymmetric catalysis.

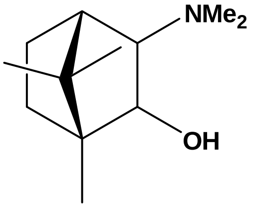
The catalyst was developed by William Knowles who, along with Ryoji Noyori and K. Barry Sharpless received the Nobel Prize for Chemistry in 2001.[13-15] Both Noyori and Sharpless developed their own successful catalysts which were also commercialised.[3, 7, 16-21] The development of new chiral catalysts continues today as one of the most active areas of organic synthesis.

1.5 DEVELOPMENT OF NEW CHIRAL CATALYSTS- OUTLINE OF RESEARCH CARRIED OUT IN THIS THESIS

The demand for new chiral catalysts is as strong as ever. The quest for ever more efficient catalysts for industrial applications in the fine chemicals and pharmaceutical industries is driving research in this field.[4] As such, it was decided to develop novel chiral catalysts based on the camphor skeleton.

1.5.1 HISTORY OF CAMPHOR IN ASYMMETRIC CATALYSIS

Camphor is a naturally occurring, non-racemic chiral molecule obtained from the camphor tree, *cinnamomum camphora*. It belongs to the group of compounds known as the monoterpenes. It has been the subject of much investigation over the years. Indeed, several successful chiral catalysts have been derived from this molecule.[22] Some examples of successful camphor-derived catalysts can be seen in Figure 4. These catalysts have been used to catalyse a wide variety of different reactions.[23-28] These include the addition of diethyl zinc to various aldehydes,[23, 25, 29, 30] hydrogenation reactions[27] and allylation of aldehydes.[28, 31]



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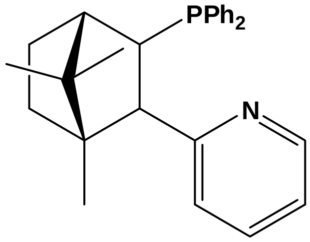
Diethylzinc to aldehyde, 99% *ee*



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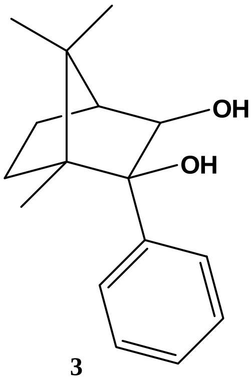
Hydrogenation, 97% *ee*



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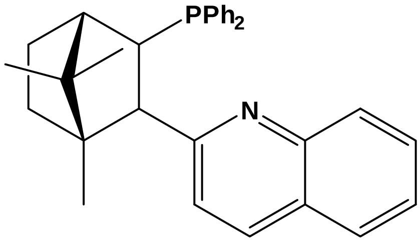
Allylboration of aldehydes, 98% *ee*



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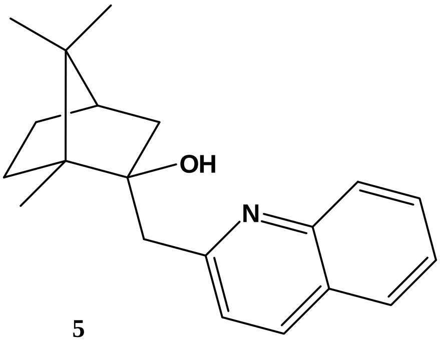
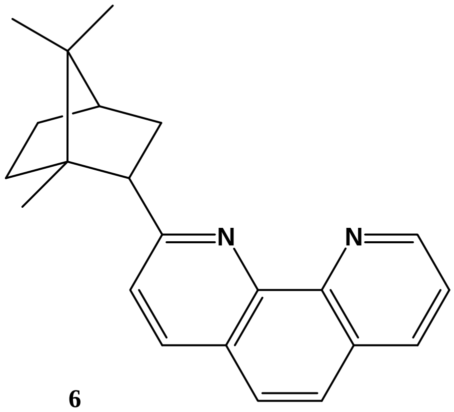
Hydrogenation, 95% *ee*



5

Diethylzinc to aldehyde, 95% *ee*



6

Allylic substitution, 92% *ee*

Figure 4: Some successful camphor-derived ligands.

Although there have been some very successful camphor derived ligands, the majority of ligands derived from this terpene have however only been moderately successful. This means there is much room for improvement for this family of catalysts.

1.5.2 RESEARCH CARRIED OUT IN THIS THESIS

As can be seen from Figure 4, the majority of the very successful ligands derived from camphor are pyridyl *N*-donor ligands. A review of the literature revealed that most camphor derived ligands to date fall into one of two categories. The first category is where one of the donor groups is pendant at C2 of the camphor skeleton while the other is at C3 such as compounds **1-4** in Figure 4. The second category is where the donor groups are pendant at the C2 position of the camphor skeleton such as ligands **5** and **6** in Figure 4. It was therefore decided to attempt to synthesise ligands pendant only at C3 of the camphor skeleton.

This thesis consists of a series of papers (1-4) dealing with the synthesis and evaluation of a series of ligands of the general structure shown in Figure 5. Due to the format adopted for the thesis, the numbering of the structures in each of the Chapters 2-5 will vary. Also, the referencing style will vary according to the style required for the journal. In order to ensure maximum continuity, the numbering of the structures in Chapter 6 will continue on from the numbering in Chapter 1.

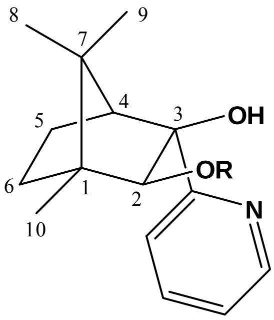


Figure 5: General structure of the synthesised ligands.

The ligands synthesised were evaluated as catalysts in three different reactions. The first reaction, the alkylation of various aldehydes using diethylzinc (Paper 1),[32] has seen a number of camphor derived ligands used as catalysts. Despite this, it was decided to catalyse this reaction in order to get a more direct comparison between the ligands synthesised in this study and the analogous C2 pendant example synthesised by Chelucci *et al.* (Figure 6).[33] The other two reactions, namely the Nitroaldol (Henry) reaction (Paper 2)[34] and the Diels-Alder reaction (Paper 3)[35] have not traditionally been catalysed by camphor derived ligands, with only a few examples appearing in the literature.

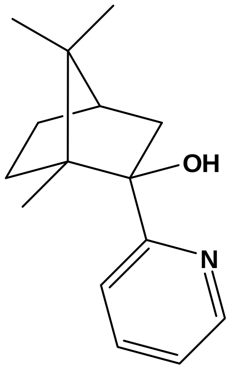


Figure 6: C2 pendant ligand.

The final paper (Paper 4)[36] is an NMR and computational study of some of the synthesised ligands carried out in order to get a better understanding of the structure and conformation of the compounds.

As mentioned earlier, the papers appear as distinct chapters in the format required by the journals to which they were submitted.

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CHAPTER 2

SYNTHESIS OF NOVEL 3-HYDROXY-3-PYRIDYLCAMPHOR DERIVATIVES

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ABSTRACT

The synthesis of a series of five novel precursor compounds derived from (R)-(+)-camphor is reported. From these precursors, a further four novel pyridyl alcohol ligands were synthesised. The molecules represent the first reported examples where the pyridyl and hydroxyl moeties are pendant on the C3 position of the camphor skeleton. The regioselective synthesis was investigated and an efficient method was identified. The final ligands are obtained in moderate yield with absolute regio- and stereoselective control. The molecules were screened as catalysts in the alkylation of aldehydes with diethylzinc in order to compare the new arrangement of donor groups with previously reported results obtained with C2 pendant ligands. The results demonstrated a significant improvement for the synthesised C3 pendant ligands over previous C2 examples with moderate yields and up to 85% ee being obtained.

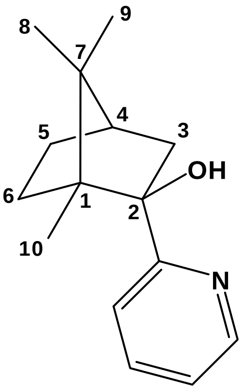
Keywords: Chiral; camphor ligands; pyridyl alcohols; asymmetric alkylation reactions.

INTRODUCTION

This is a second paper in a series of research results from our group in the field of asymmetric synthesis and catalytic applications. The first paper involved the synthesis of pentacycloundecane oxazolines and the application of the ligands in an asymmetric Diels-Alder reaction.[1] In the search for new ligands for asymmetric catalysis, the natural world has proven to be an invaluable source.[2, 3] A range of very effective homogeneous catalytic systems have been reported based on naturally occurring molecules.[4, 5] Chiral monoterpenes such as camphor have been widely used in the development of asymmetric catalysts with varying degrees of success in reactions such as the addition of diethylzinc to aldehydes,[6] hydrogenation and allylic substitution.[7] They afford a simple, inexpensive and inherently chiral scaffold around which to build the catalyst. The synthesis of pyridyl *N*-donor ligands derived from camphor has been extensively studied.[8-14] Several of these ligands have proven to be moderately to highly successful chiral catalysts for applications such as allylic oxidations,[11] addition of organozinc reagents to aldehydes[8, 10, 12, 13] and hydrogenation reactions.[14] Previous pyridyl alcohol ligands typically fall into one of two categories. First the pyridyl and hydroxyl groups are pendant at the C2 position of the camphor skeleton such as in **1.**[8, 13] This category has been much more prevalent with numerous examples in literature[8-11, 13] and have generally been used as catalysts in the addition of alkylzinc reagents to aldehydes. The results of these applications have varied from moderate[8] to good[10, 13] in terms of enantioselectivity. The second category is where the hydroxy group is at C2 and the pyridyl moiety is pendant at C3, such as in **2**.[12] This example (**2)** synthesised by Nevalainen *et al.*,[12] was also used as a catalyst for alkylzinc reactions with good results in terms of enantioselectivity. It thus appeared that there was a significant opportunity for investigation into ligands which are derivatised at the C3 position of camphor.

The reasons for this apparent lack of C3 pendant ligands could be due to the fact that camphor, which has a C2 ketone, is used as a convenient starting material. For analogous ligands pendant on C3, epicamphor, which is not easily synthesised, would have to be used as the starting material. This presents additional undesirable synthetic complications.[15] In order to expand the potential of camphor however, the synthesis of ligands **3-6** where both the pyridyl and hydroxyl groups are pendant on C3 of the skeleton was undertaken.

To the best of our knowledge, the molecules (**3-6**) represent the first examples of ligands with this arrangement of the donor groups. These compounds were compared directly to ligands such as **1** and **2** in the reaction of diethylzinc to aldehydes.[8]



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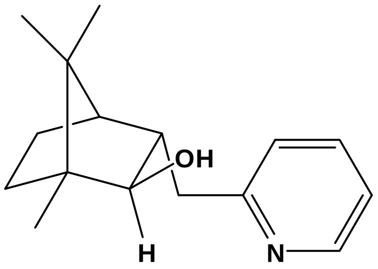

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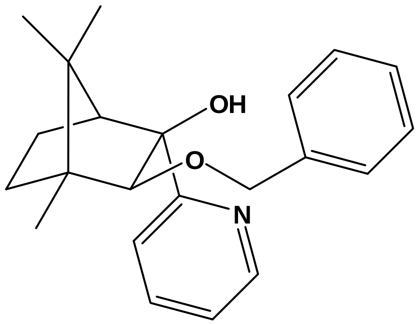

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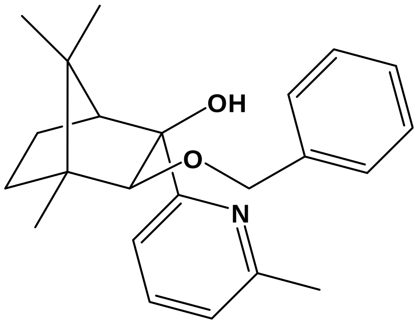

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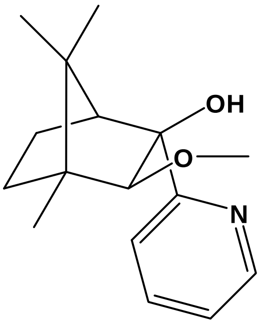

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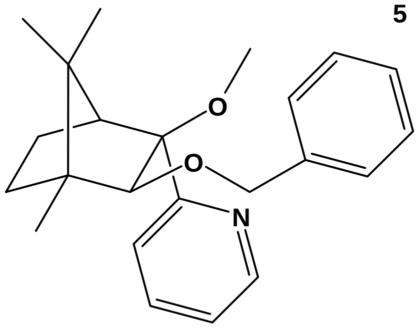

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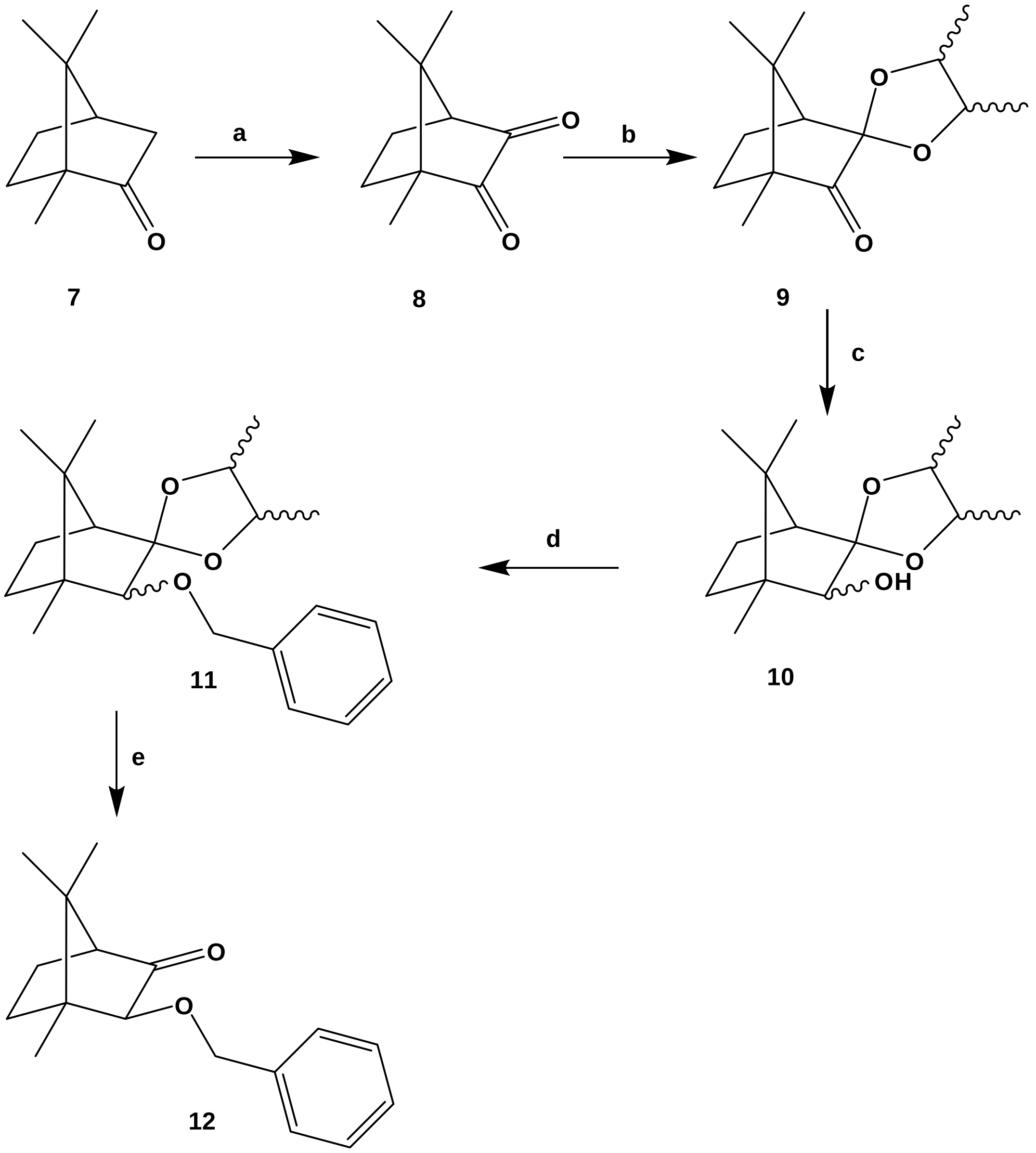
Figure 1: Camphor derived pyridyl alcohol ligands.

RESULTS AND DISCUSSION

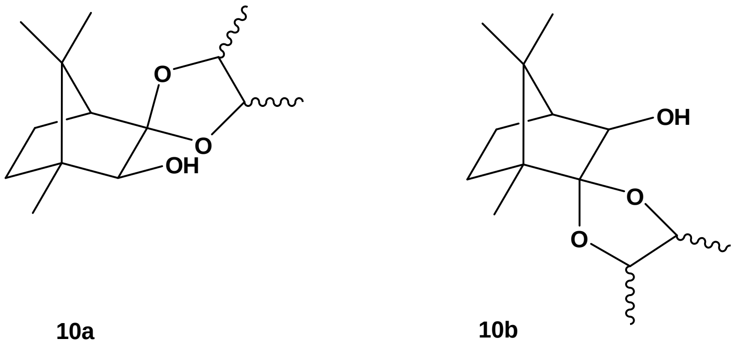
In the construction of these ligands, two approaches using similar methodologies were investigated in order to obtain the common precursor to the final target molecules. In both approaches, the (*R*)-(+)-camphor **7** starting material was converted to camphorquinone **8**, followed by ketalization with different diols. The synthesis of camphorquinone was carried out according to literature procedures to yield the yellow semi-crystalline product in good yields.[16] Method A (Scheme 1) involved the reaction of camphorquinone **8** with *meso*-2,3-butanediol *as per* the method adopted by Evans *et al.*[17-19] This particular diol was chosen for its steric bulk. The two methyl groups on the diol are sufficiently large so as to minimise reaction of the diol with the more sterically hindered C2 ketone (Figure 1). The selective protection of the C3 ketone should thus result. Method B (Scheme 2) utilised ethylene glycol as the protecting group. It is known from literature (Lachance *et al.*) that this method consistently results in a protection ratio of approximately 3:1 for the C3:C2 protected product.[20] Method A was attempted first.



Scheme 1: Method A (reaction, reagents and conditions). Key: a) SeO_2, Ac_2O, reflux 16hrs, 86 %, b) *meso*-2,3-butanediol, PTSA, benzene, reflux 12 hrs, 80 % c) $NaBH_4$, diethyl ether/MeOH (1:1), RT 2 hrs, 85 % d) benzyl bromide, NaH, dry THF, 12 hrs, 75 % e) conc. HCl/ THF (1:3), 2 hrs, 80 %.

The reaction of the quinone with the *meso*-2,3-butanediol using the methodology reported by Evans *et al.* yielded what appeared to be the monoprotected ketal **9**.[19] Although Evans *et al.* reported that the 3-substituted product **9** is obtained exclusively, we discovered that after reduction with sodium borohydride to obtain the hydroxy ketal **10**, we did in fact observe a small amount of the 2-substituted product **10b**. The approximate diasteriomeric ratio obtained was 9:1 for **10a**:**10b** (Figure 2). This ratio is determined by integration of the ^1H signal for the H-atom attached to C2 (3.34 ppm) or C3

(3.38 ppm). In our case it was not possible to determine this ratio before reduction nor was it possible to separate these regioisomers before the reduction point.

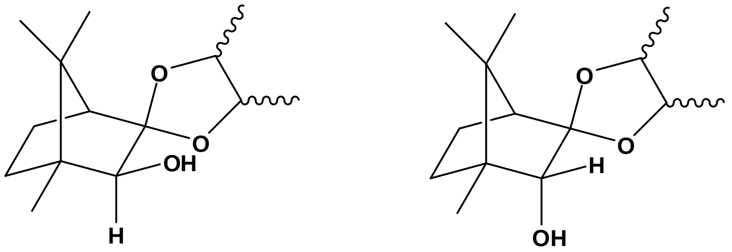


10a **10b**

Figure 2: Structural isomers **10a** and **10b**.

We managed to separate the predominant structural isomer (**10a**) from the minor isomer (**10b**) by simple column chromatography.

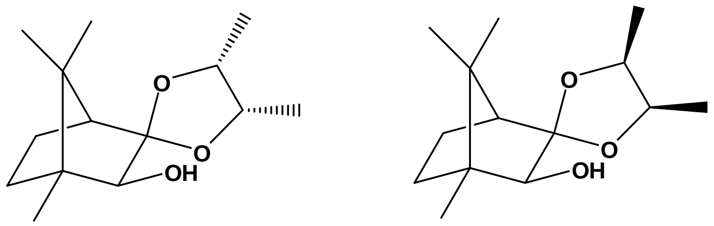
At this stage it was found that a small amount of the *endo*-OH product (**10a-2**) was present. This phenomenon was also observed and reported by Evans *et al.*[19] The isomeric ratio of the hydroxyl products **10a-1** and **10a-2** present was also determined by ^{1}H NMR *via* the integrating of the respective proton signals. The desired product (**10a-1**) has an *endo*-H at 3.34 ppm whilst the *exo*-H of **10a-2** appears at 3.67 ppm. The ratio was determined to be 11:1 *exo:endo*-OH (Figure 3).



10a-1 **10a-2**

Figure 3: The *exo*-OH and *endo*-OH diastereomers of compound **10a**.

Separation of these diastereomers was not achieved. Further investigation of the isolated mixture of diastereomers **10a-1** and **10a-2** revealed a further two structural isomers **10a-3** and **10a-4**. The orientation of the butanediol methyl groups (Figure 4) resulted in diastereomers which could be assigned by NMR. The isolated material consisted of a mixture of *exo*- and *endo*-OH diastereomers for each diastereomer (**10a-3** or **10a-4**) although the *exo*-OH diastereomer (as shown in Figure 4) was the predominant form with the *endo*-OH isomer present only in trace amounts (~5 %).



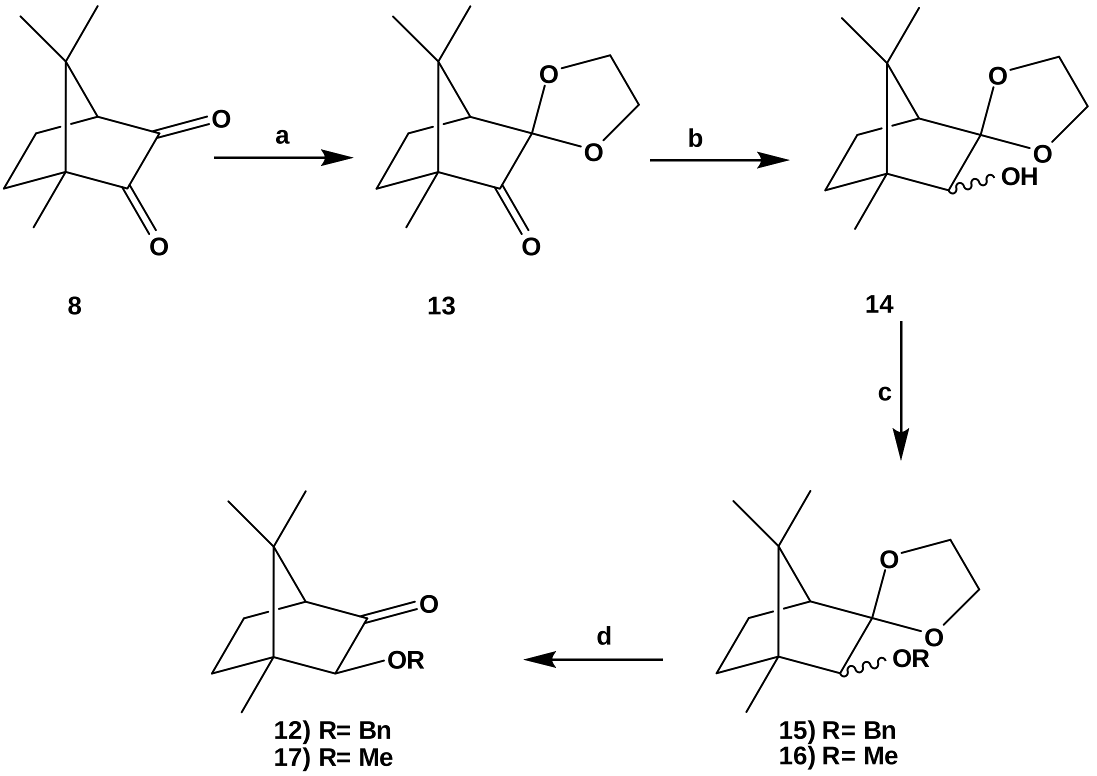
10a-3 **10a-4**

Figure 4: Diastereomers of compound **10a** where –OH group is in the *exo*-position.

NMR elucidation of the two diastereomers (**10a-3** and **10a-4**) was carried out. Reasonable separation was obtained, but the spectra still contain a slight mixture. The minor isomer **10a-3** showed no NOESy interactions between the methyl groups (1.11-1.15 ppm) on the butanediol with either the hydroxy proton (2.50 ppm) or the bridge methyl of the camphor (C9 – 1.03 ppm). The major product **10a-4** did in fact show through-space correlations with both of these groups. The orientation of these groups also results in a significant shift in the signal for the C2 *endo*-H proton. The signal appears at either 3.34 ppm (**10a-3**) or 3.19 ppm (**10a-4**) depending on the configuration. The orientation of these butane diol groups was not considered to be important due to the fact that the ketal was to be removed later on in the synthesis.

Protection of the hydroxyl group with benzyl bromide to yield **11** (Scheme 1) as well as the subsequent removal of the ketal to obtain **12** was carried out without difficulty. Although the yields obtained in the various steps of Method A were reasonable, the mixtures of diatereomers made this approach problematic. Indeed, even the final C3 ketone (**12)** exhibits significant doubling of the signals in the ^{13}C NMR spectrum. Thus, it was clear that an alternative method was necessary.

As such, Method B, involving a more traditional approach was explored. The ratio of approximately 3:1 for the C3 to C2 protected ketones was obtained as expected from literature. However, a literature survey revealed a synthesis of hydroxy epicamphor by Fleming *et al.*[21] in which the desired product **13** is crystallised from the crude reaction mixture with ethanol.



Scheme 2: Proposed reactions, reagents and conditions for Method B. Key: a) ethylene glycol, PTSA, benzene, reflux 12 hrs, 65 % b) $NaBH_4$, diethyl ether/MeOH (1:1), RT 2hrs, quant. c) benzyl bromide (**15**), MeI (**16**), NaH, dry THF, 12 hrs, 81 % (**15**), quant. (**16**) d) conc. HCl/ THF (1:3), 2 hrs, 80 % (**12**), 70 % (**17**).

Application of this procedure proved very successful in obtaining the desired C3 protected product **13**. Although the total yield of this reaction in terms of product isolated in the first step is not as high as the butanediol method, the average isomeric ratio of better than 100:1 is achieved for the alcohol **14** (according to NMR integration as described below). This makes method B much more attractive in terms of *regio*-selectivity. The relative configuration of **13** was confirmed by X-ray crystallography of the product obtained after recrystallisation (Figure 5).

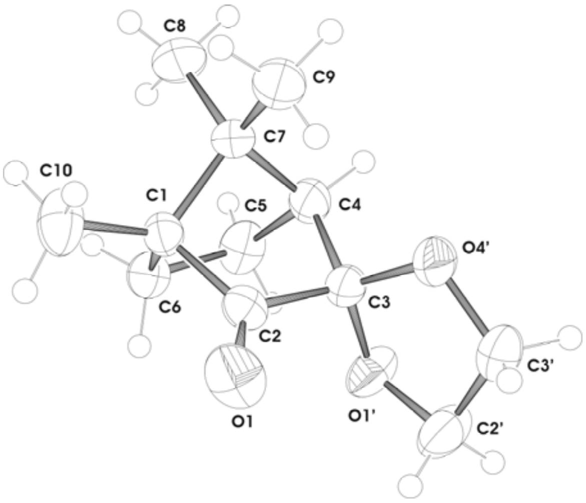
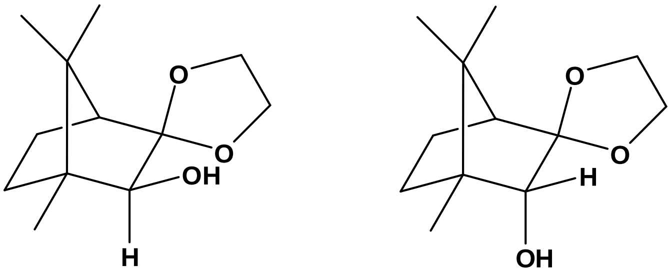


Figure 5: ORTEP diagram of compound **13** showing displacement ellipsoids at the 50 % probability level.[22]

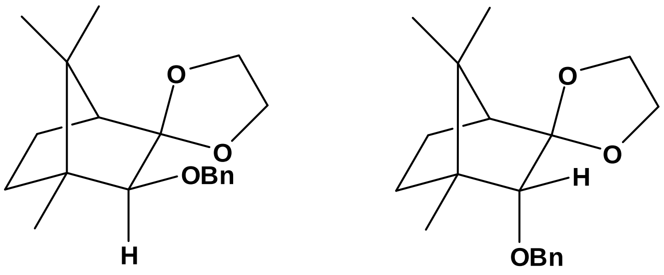
This breakthrough made it possible to proceed with the synthesis of the precursor ketone **12**. The ketal **13** was reduced using sodium borohydride to yield the hydroxy ketal **14** in quantitative yield. This also constitutes a vast improvement compared to the butanediol method where the yield of the isolated hydroxyl ketal **10a** was quite poor (~50 %). We determined the diastereomeric ratio by integration of the signal of the proton on C2. Once again it was discovered that a small amount of *endo*-OH was present (**14b**), the ratio of about 10:1 for **14a:14b** (determined by NMR –*exo*-H at 3.64 ppm and *endo*-H at 3.30 ppm).



14a **14b**

Figure 6: Diastereomers **14a** and **14b**.

We were unable to separate these diastereomers (Figure 6). Protection of the hydroxyl groups with benzyl bromide proceeded with good yields at room temperature to give the novel ketal ethers **15a** and **15b** (Figure 7).

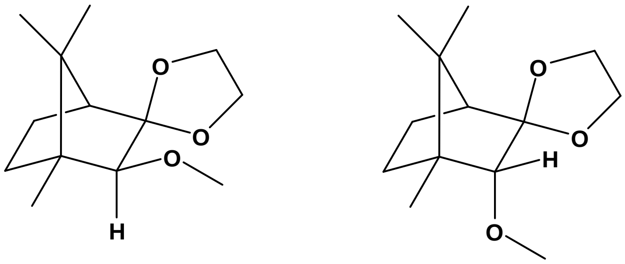


15a major **15b minor**

Figure 7: Inseparable diastereomers **15a** and **15b**.

It was discovered that the separation of the diastereomers improved significantly with each subsequent step. Removal of the ketal group was easily achieved using standard acid techniques to yield the precursor ketone **12** as almost exclusively the *exo* product in good yield.

Reaction of the same hydroxy ketal **14** with iodomethane afforded the methoxy derivative **16** in essentially quantitative yield. In isolating the product using simple column chromatography, it was discovered that the *exo*-OMe (**16a**) product could be easily separated from the *endo*-OMe product (**16b**). The concentration of latter isomer **16b** was so low that it could not be isolated.

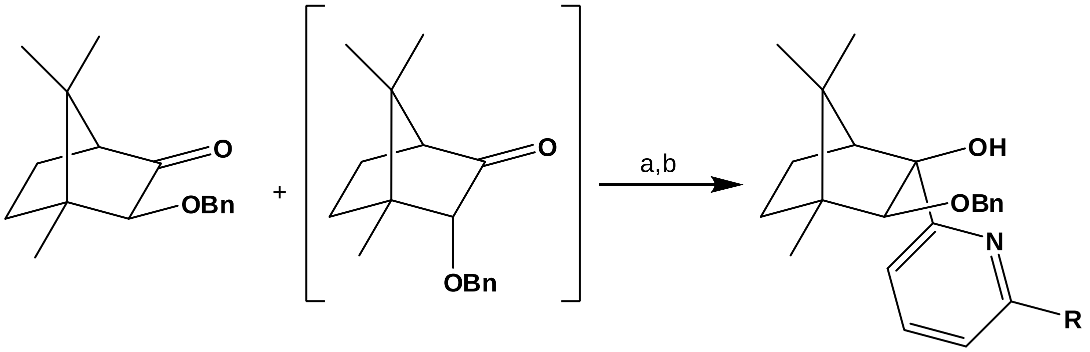


16a **16b**

Figure 8: Diastereomers **16a** and **16b**.

Removal of the ketal was carried out in the same way as before using hydrochloric acid in THF at room temperature to yield the methoxy ketone **17** in reasonable yield.

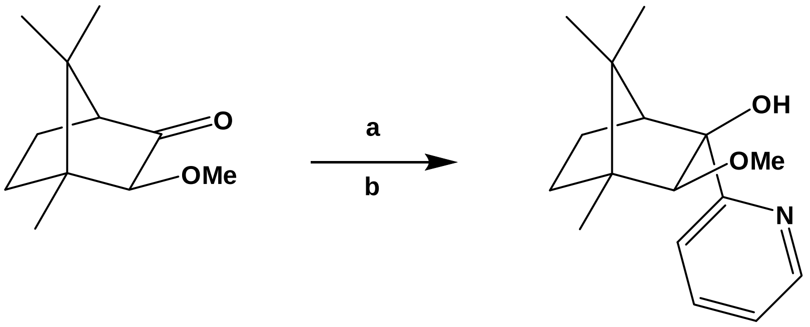
These precursor ketones **12** and **17** were to be reacted with pyridyllithium in order to afford the final ligands **3-5**. From literature, it is well documented that ketones derived from camphor are very unreactive and give poor yields unless activated by an additive such as $CeCl_3$.[7, 9, 20, 23] The commercially available cerium (III) chloride heptahydrate was dried using the method developed by Dimitrov *et al.*[24]



12a **12b (minor impurity)** **3) R= H**
4) R=CH$_3$

Scheme 3: Synthesis of Ligands **3** and **4**. Key: a) ketone **12**, CeCl$_3$, dry THF, RT b) pyridyllithium, -78°C 1 hr, RT overnight.

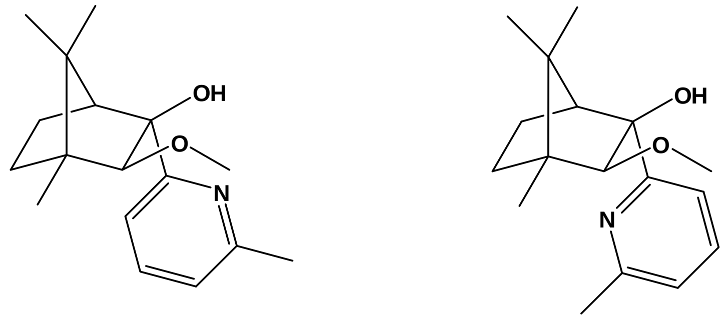
The lithiation reactions used to afford ligands **3** and **4** were carried out using the technique reported by Dimitrov *et al.*[9, 24] (Scheme 3). It was discovered upon isolation of the products that only the *exo*-ether ketone **12a** had reacted and that there was no indication of any *endo* product. It was assumed that the ketones with the ether group *endo* were too sterically hindered to allow nucleophillic attack by the pyridyllithium from the *endo* side, which is the only side from which it can attack since the steric bulk of the bridge methyl groups prevents *exo* attack. It is widely reported in literature that nucleophilic attack on ketones attached to the camphor skeleton is only possible from the *endo* side for this reason.[9, 20, 25] However, it was discovered that this final reaction step was extremely temperature sensitive. If the lithiation reaction was carried out at a temperature even slightly higher than -78°C, conformational isomers were obtained when the functionalised pyridines were used. Distinct doubling of several peaks in the ^{13}C NMR spectra was clearly observed. With the 6-methyl pyridine derivative **4** this problem was solved by carrying out the lithiation at -78°C or lower. The same procedure was used in the synthesis of ligand **5** (Scheme 4).



17 **5**

Scheme 4: Synthesis of Ligand **5**. Key a) CeCl$_3$, dry THF, RT b) pyridyllithium, -78°C 1hr, RT overnight.

Attempts were also made to synthesise the 6-methylpyridine derivative from the methoxy ketone **17**, but we could not resolve the isomers. This particular derivative formed conformational isomers **18a** and **18b** regardless of the temperature (Figure 9).

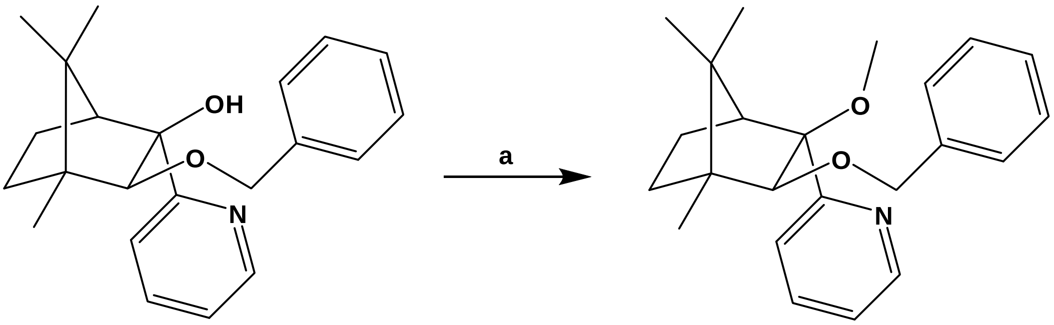


18a **18b**

Figure 9: Depiction of the proposed conformational isomers of compound **18**.

A variable temperature NMR study of this compound clearly showed that as the temperature of the sample was increased, the ^{13}C NMR signals for the conformers shifted closer together. However, even at a temperature of 100°C the signals are still distinct indicating that the pyridyl group was not free to rotate. It therefore seemed that for the signals of the conformers to be merged completely in order to yield only a single form, the mixture would have to be heated to a point at which decomposition of the sample would be possible. As a result, it was decided that further efforts with this derivative were not worth pursuing for our applications.

The final derivative **6** was synthesised in acceptable yield by simply reacting ligand **3** with excess iodomethane in the presence of NaH in dry THF at room temperature (Scheme 5). The product was easily isolated using column chromatography.



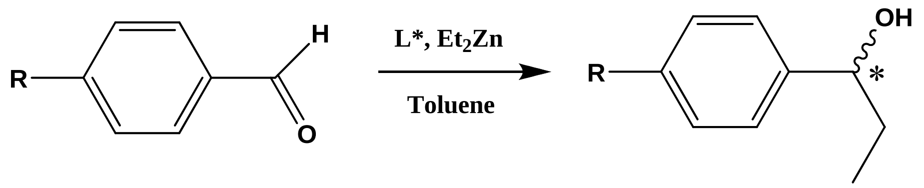
3 **6**

Scheme 5: Synthesis of ligand 6. Key: a) MeI, NaH, THF, Room temerature 12 hours.

Excess iodomethane could be used as any unreacted iodomethane was easily removed *in vacuo* during workup. Similar conditions were used in an attempt to synthesise a derivative using ligand **4** as starting material, but no product was obtained even after gentle heating and prolonged reaction times. It seems logical to believe that the hydroxyl group is too sterically hindered by the methyl on the pyridine ring for the reaction to proceed.

As mentioned previously, most C2 analogous ligands have been applied as catalysts in the addition of diethylzinc to various aldehydes. Previous results for the C2 pendant example **1** were mediocre for this reaction (44 % *ee*). In order to determine the efficacy of the synthesised ligands it was necessary to compare them in the same application used for close C2 pendant analogues. As such, the ligands were screened as catalysts in the reaction of diethylzinc with some selected aromatic aldehydes (Table 1). The reactions were carried out at room temperature with toluene as the solvent.

Table 1: Reaction of diethylzinc to various aldehydes at room temperature.



Ligand	Substrate	Time (hrs)	Yield (%)[a]	*Ee* (%)[b]	Configuration[c]
3	Benzaldehyde	48	65	68	R
4	Benzaldehyde	48	59	72	R
5	Benzaldehyde	48	76	50	R
6	Benzaldehyde	48	0	N/A	-
4	*p*-Nitrobenzaldehyde	48	73	2.5	R
4	*p*-Anisaldehyde	48	67	85	R
4	*p*-Tolualdehyde	48	71	58	R
4	*p*-Chlorobenzaldehyde	48	74	30	R

[a] Isolated yield after flash chromatography.
[b] Determined by HPLC (Diacel Chiralpak IB column).
[c] Determined by optical rotation and comparison to literature values.

On screening the ligands against benzaldehyde it was determined that ligand **4** was the most effective agent in terms of selectivity (72 % *ee*). This ligand was then applied in the reaction of a series of *para*-functionalised aldehydes. The selectivity obtained for the addition of diethylzinc to *p*-anisaldehyde proved to be the best with 85 % *ee* obtained. It was decided that as a result of the extended reaction times it would not be viable to attempt the reactions at low temperature.

These results compare very favourably with those obtained for the C2 pendant examples. If compared directly to the C2 analogue **1**, our equivalent C3 derivative **3** showed an improvement of more than 20 % (44 % *ee*[8] *vs* 68 % *ee*). These ligands perform better for the selected reaction than any other camphor pyridine β-amino alcohol derivatives in literature.

CONCLUSION

In summary, novel chiral ligands **3-6** were successfully synthesised in moderate yield and absolute *stereo-* and *regio*-selectivity using the second method, which proved superior to method A in terms of selectivity. In addition, several potentially useful novel precursors were also synthesised, some in good yield. The ligands reported are unique in that they are the first reported examples of pyridyl alcohols derived from camphor which are pendant on the C3 position of the camphor skeleton. In establishing the procedure to synthesise the ligands, it was found that it is possible using an established recrystallization technique to isolate the mono-protected ketal **13** as a single diastereomer in acceptable yield. This opens up many possibilities for *regio*-selective synthesis using camphorquinone as a starting material. The ligands (**3-6**) were screened as catalysts in the alkylation of aldehydes with diethylzinc. The results obtained indicated that the ligands were significantly better than the analogous C2 pendant ligands previously reported in literature with a best selectivity of 85 % *ee* obtained with ligand **4**. This demonstrates that the arrangement of the donor groups on the camphor skeleton can have a significant effect on their efficacy as chiral catalysts.

EXPERIMENTAL SECTION

All NMR spectra were recorded on Bruker AVANCE III 400 MHz or 600 MHz instruments with $CDCl_3$ as solvent unless otherwise stated. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 instrument equipped with a Universal ATR attachment. Optical rotation data was acquired on a Perkin Elmer Model 341 polarimeter using a 1 mL cell with a pathlength of 100 mm. Accurate mass measurements were obtained on a Bruker MicroTOF Q2 instrument using APCI and ESI ionisation methods. All solvents were dried using standard procedures prior to use. All reagents were purchased and used without further purification. Column chromatography was carried out on Silicagel 60 particle size 0.063-0.200 mm (230-400 mesh). All HPLC analysis was carried out on a Shimadzu Prominence system using a Diacel Chiralpak IB column with hexane/ isopropanol (97.5:2.5) as eluent.

(1*R*)-(-)-Camphorquinone (8)

Synthesis *as per* the method used by Lu *et al.*[16] (1*R*)-(+)-Camphor (30.42 g, 200 mmol), selenium dioxide (51.05 g, 460 mmol) in acetic anhydride (50.0 mL) was refluxed overnight. The black selenium residue was filtered off and the dark yellow filtrate solution was diluted with 50 mL of ice cold water. The resulting yellow precipitate was filtered and washed with ice cold water (3 x 20 mL). The yellow solid was dried on the filter paper under vacuum. NMR of the crude material indicated it was pure enough for further use without any additional purification (28.55 g, 86%). Mp. 201-205°C. Analytical data identical to authentic sample.

(1*R*, 4*S*)-(-)-3,3-(*meso*-2,3-Butanedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (9)[19]

A stirred solution of camphorquinone (5.00 g, 30.1 mmol), *p*-toluenesulphonic acid (1.00 g, 5.25 mmol) and *meso*-2,3-butanediol (2.70 g, 29.9 mmol) in benzene (350 mL) was heated under reflux using a Dean-Stark trap. The reaction was monitored using TLC (EtOAc:hexane- 25:75, $R_f = 0.56$). On completion, the solution was neutralised with aqueous sodium bicarbonate and washed with brine (2 x 100 mL), and water (3 x 100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified using column chromatography (EtOAc:hexane- 5:95, $R_f = 0.56$) to yield the product as a pale yellow oil (6.07g, 85 %). ^1H NMR [$CDCl_3$, 400 MHz]: δ_H 0.7-1.05 (m, 9H); 1.08-1.20 (m, 2H); 1.24-1.30 (m, 6H); 1.45-1.80 (m, 2H); 1.85-1.90 (m, 2H); 4.10-4.24 (m, 2H); 4.46-4.64 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 9.42 (q), 14.8 (q), 14.9 (q), 20.8 (t), 21.5 (q), 30.5 (t), 43.4 (s), 52.3 (d), 57.6 (s), 75.5 (d), 75.6 (d), 106.7 (s), 216.0 (s).

(1*R*, 2*S*, 4*S*)-(-)-3,3-(*meso*-2,3-Butanedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (10a)[19]

To a stirred solution of **9** (5.00 g, 20.9 mmol) in diethyl ether/ MeOH (1:1, 150 mL) was added $NaBH_4$ (3.78 g, 100 mmol) portion wise at *ca.* 0°C. The solution was allowed to gradually warm to room temperature and left to stir for 2 hours. The solvent was removed *in vacuo* and the white solid residue redissolved in water. The solution was extracted with dichloromethane (3 x 20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (EtOAc:hexane - 10:90, $R_f = 0.45$ on TLC EtOAc:hexane – 25:75) to yield the pure product as a clear oil (2.51 g, 49 %). ^1H NMR [$CDCl_3$, 400 MHz]: δ_H 0.79-0.88 (m, 6H); 1.03 (s, 3H); 1.11-1.15 (m, 8H); 1.47-1.67 (m, 3H); 2.61 (br s, OH); 3.30 (s, 1H); 4.06-4.08 (q, 1H); 4.18-4.20 (q, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 10.9 (q), 14.6 (q), 15.2 (q), 20.5 (t), 21.1 (q), 21.6 (q), 33.4 (t), 47.6 (s), 49.3 (s), 52.8 (d), 73.7 (d), 74.8 (d), 85.2 (d), 113.7 (s).

(1*R*, 2*S*, 4*S*)-(-)-2-Benzyloxy-3,3-(*meso*-2,3-butanedioxy)-1,7,7-trimethylbicyclo[2.2.1]heptan (11)

To a stirred suspension of NaH (1.92 g, 80 mmol) in dry THF (50 mL) was added a solution of **10** (4.0 g, 16.6 mmol) in dry THF (50 mL). The resulting solution was stirred at room temperature for 1hour before benzyl bromide (2.40 mL, 20.1 mmol) was added quantitatively. The mixture was stirred overnight at room temperature. The excess NaH was quenched by dropwise addition of water before the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane - 5:95, $R_f = 0.75$ on TLC EtOAc:hexane – 25:75) to yield the novel product as a clear oil (4.11 g, 75 %). $[\alpha]^{20}_D$ -35.4 (c = 1, $CHCl_3$); ^1H NMR [$CDCl_3$, 400 MHz]: (NB-Due to mixture of isomers, integration values may not be accurate) δ_H 0.80 (s, 3H); 0.88 (s, 3H); 1.07-1.26 (m, 9H); 1.45-1.74 (m, 4H); 3.29 (s, 1H); 4.07-4.24 (m, 2H); 4.42-4.45 (d, 1H); 4.84-4.87 (d, 1H), 7.21-7.38 (m, 5H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 11.7 (q), 15.6 (q), 15.8 (q), 20.4 (t), 21.3 (q), 34.3 (t), 47.9 (s), 49.5 (s), 51.9 (d), 72.6 (d), 73.1 (d), 73.5 (t), 92.1 (d), 114.3 (s), 127.0 (d), 127.3 (d), 128.1 (d), 139.6 (s),NB- only major product peaks reported; IR (ATR): $\nu_{\max}$ 2937(m), 2875(m), 1454(m), 1091(vs), 1029(m) cm^{-1}; HRMS calcd for $C_{21}H_{30}O_3$ ([M+H]$^+$) 331.2273, found 331.2234.

(1*R*, 2*S*, 4*S*)-(-)-2-Benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one (12)

To a stirred solution of THF:HCl (3:1, 100 mL) was added **11** (5.00 g, 15.1 mmol) in THF (30 mL). The solution was stirred at room temperature for 2 hours. The solvent was reduced *in vacuo* and the solution diluted with water before being neutralised with solid sodium bicarbonate. The neutralised solution was extracted with diethyl ether (3 x 30 mL). The organic layers were combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc: hexane - 10:90, $R_f = 0.65$ on TLC EtOAc:hexane – 25:75) to yield the pure product as a pale yellow oil (3.13 g, 80 %). $[\alpha]^{20}_D$ -120.7(c = 2, $CHCl_3$); ^1H NMR [$CDCl_3$, 400 MHz]: (NB-Due to mixture of isomers, integration values may not be accurate) δ_H 0.90 (s, 3H); 1.02 (s, 3H); 1.08 (s, 3H); 1.24-1.44 (m, 3H); 1.65 (m, 1H); 1.77-1.93 (m, 3H); 2.12 (m, 1H); 3.24 (s, 1H), 4.67-4.70 (d, 1H), 5.00-5.03 (d, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 10.9 (q), 18.6 (q), 20.8 (t), 21.5 (q), 33.9 (t), 46.3 (s), 49.9 (s), 59.3 (d), 73.6 (t), 85.1 (d), 127.4 (d), 127.5 (d), 128.2 (d), 138.5 (s); IR (ATR): $\nu_{\max}$ 2956(m), 2878(m), 1748(vs), 1110(s), 1094(s) cm^{-1}. HRMS calcd for $C_{17}H_{22}O_2$ ([M+H]$^+$) 259.1698, found 259.1647.

(1*R*, 4*S*)-(-)-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (13)[15, 16, 21]

A stirred solution of camphorquinone (5.00 g, 30.1 mmol), *p*-toluenesulphonic acid (1.00 g, 5.25 mmol) and ethylene glycol (1.90 g, 30.6 mmol) in benzene (100 mL) was heated under reflux using a Dean-Stark trap. The reaction was monitored using TLC. On completion, the solution was neutralised with aqueous sodium bicarbonate and washed with brine (2 x 100 mL), and water (3 x 100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified using column chromatography (EtOAc:hexane- 5:95, $R_f = 0.55$ on TLC EtOAc:hexane – 25:75) to yield the product as a pale yellow oil. This oil solidified on standing and was recrystallised from ethanol to yield the pure product as a white crystalline material (4.11 g, 65 %). ^1H NMR [$CDCl_3$, 400 MHz]: δ_H 0.91 (s, 3H); 0.98-1.02 (d, 6H); 1.45-1.70 (m, 2H); 1.75-1.82 (m, 1H); 1.85-2.02 (m, 2H); 3.85-4.02 (m, 2H); 4.20-4.32 (m, 1H); 4.35-4.45 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 9.18 (q), 19.0 (q), 21.4 (t), 21.5 (q), 30.9 (t), 43.6 (s), 51.5 (d), 58.2 (s), 64.5 (t), 66.1 (t), 106.9 (s), 217.4 (s).

(1*R*, 2*S*, 4*S*)-(-)-3,3-Ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (14)[15, 16, 21]

To a stirred solution of **13** (5.00 g, 23.8 mmol) in diethyl ether/ MeOH (1:1, 100 mL) was added $NaBH_4$ (3.78 g, 100 mmol) portion wise at *ca.* 0°C over a period of ten minutes. The solution was allowed to gradually warm to room temperature and left to stir for two hours. The solvent was removed *in vacuo* and the white solid residue redissolved in water. The solution was extracted with dichloromethane (3 x 20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The product was obtained as a clear oil (5.04 g, 100 %). NMR showed the product to be pure enough for further use without additional purification. ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.75-0.86 (m, 6H); 1.10 (s, 3H); 1.20-1.28 (m, 2H); 1.45-1.82 (m, 4H); 2.42 (d, OH); 3.31 (d, 1H); 3.76-4.12 (m, 4H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 10.3 (q), 20.1 (q), 20.4 (t), 20.6 (q), 32.8 (t), 46.8 (s), 48.9 (s), 51.9 (d), 62.9 (t), 64.9 (t), 84.8 (d), 114.6 (s).

(1*R*, 2*S*, 4*S*)-(-)-2-Benzyloxy-3,3-ethylenedioxy-1,7,7-trimethylbicyclo[2.2.1]heptan (15)

To a stirred suspension of NaH (1.92 g, 80.0 mmol) in dry THF (50 mL) was added a solution of **14** (4.41 g, 20.8 mmol) in dry THF (50 mL). The resulting solution was stirred at room temperature for 1hour before benzyl bromide (2.50 mL, 21.0 mmol) was added quantitatively. The mixture was stirred overnight at room temperature. The excess NaH was quenched by dropwise addition of water before the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane - 5:95, R_f = 0.80 on TLC EtOAc:hexane – 25:75) to yield the novel product as a clear oil (5.09 g, 81 %). $[\alpha]^{20}_D$ -35.9 (c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.82 (s, 3H); 0.90 (s, 3H); 1.21 (m, 4H); 1.53-1.65 (m, 4H); 3.18 (s, 1H); 3.76-3.97 (m, 4H); 4.44-4.46 (d, 1H); 4.65-4.67 (d, 1H), 7.24-7.34 (m, 5H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 11.8 (q), 20.6 (t), 20.9 (q), 21.3 (q), 34.3 (t), 47.9 (s), 50.2 (s), 52.9 (d), 63.4 (t), 65.1 (t), 73.5 (t), 92.9 (d), 116.1 (s), 127.2 (d), 127.3 (d), 128.2 (d), 139.3 (s); IR (ATR): ν_{max} 2946(m), 2875(m), 1096(vs), 1027(s), 1010(m) cm^{-1}; HRMS calcd for $C_{19}H_{26}O_3$ ($[M+H]^+$) 303.1960, found 303.1963.

(1*R*, 2*S*, 4*S*)-(-)-2-Benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one (12)

To a stirred solution of THF:HCl (3:1, 100 mL) was added **15** (5.00 g, 16.5 mmol) in THF (50 mL). The solution was stirred at room temperature for two hours. The solvent was reduced *in vacuo* and the solution diluted with water before being neutralised with solid sodium bicarbonate. The neutralised solution was extracted with diethyl ether (3 x 30 mL). The organic layers were combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane - 10:90, R_f = 0.65 on TLC EtOAc:hexane – 25:75) to yield the pure product as a pale yellow oil (3.42 g, 80 %). $[\alpha]^{20}_D$ -145.7(c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.90 (s, 3H); 1.02 (s, 3H); 1.08 (s, 3H); 1.24-1.44 (m, 2H); 1.77-1.93 (m, 2H); 2.12 (m, 1H); 3.24 (s, 1H), 4.67-4.70 (d, 1H), 5.00-5.03 (d, 1H), 7.25-7.34 (m, 5H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 10.9 (q), 18.6 (q), 20.8 (t), 21.5 (q), 33.9 (t), 46.3 (s), 49.9 (s), 59.3 (d), 73.6 (t), 85.1 (d), 127.4 (d), 127.5 (d), 128.2 (d), 138.5 (s), 218.3 (s); IR (ATR): ν_{max} 2956(m), 2878(m), 1748(vs), 1110(s), 1094(s) cm^{-1}; HRMS calcd for $C_{17}H_{22}O_2$ ($[M+H]^+$) 259.1698, found 259.1647.

(1*R*, 2*S*, 4*S*)-(-)-3,3-Ethylenedioxy 2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptan (16)

To a stirred suspension of NaH (1.92 g, 80 mmol) in dry THF (30 mL) under nitrogen was added a solution of **14** (5.00 g, 23.6 mmol) in dry THF (70 mL). The resulting solution was stirred at room temperature for one hour before methyl iodide (4.48 mL, 72.0 mmol) was added quantitatively. The mixture was stirred overnight at room temperature. The excess NaH was quenched by dropwise addition of water before the solvent was removed *in vacuo*. The residue was dissolved in diethyl ether and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane - 5:95, $R_f = 0.65$ on TLC EtOAc:hexane – 25:75) to yield the novel product as a clear oil (5,42 g, 100 %). $[\alpha]^{20}_D$ -16.9 (c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.77 (s, 3H), 0.84 (s, 3H), 1.09 (s, 3H), 1.16-1.18 (m, 1H), 1.47-1.66 (m, 4H), 2.89 (s, 1H); 3.36 (s, 3H); 3.79-3.81 (m, 2H), 3.87-3.90 (m, 1H), 3.96-3.99 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 11,5 (q), 20.6 (t), 20.8 (q), 21.1 (q), 34.3 (t), 47.8 (s), 50.1 (s), 52.9 (q), 60.3 (d), 63.2 (t), 65.2 (t), 95.7 (d), 115.9 (s); IR (ATR): ν_{max} 2945(s), 22876(s), 1115(vs), 1094(vs), 1044(s) cm^{-1}; HRMS calcd for $C_{13}H_{22}O_3$ ($[M+H]^+$) 227.1647, found 227.1594.

(1*R*, 2*S*, 4*S*)-(-)-2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-one (17)

To a stirred solution of THF:HCl (3:1, 100 mL) was added **16** (5.00 g, 22.1 mmol) in THF (50 mL). The solution was stirred at room temperature for two hours. The solvent was reduced *in vacuo* and the solution diluted with water before being neutralised with solid sodium bicarbonate. The neutralised solution was extracted with diethyl ether (3 x 30 mL). The organic layers were combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc:hexane - 10:90, $R_f = 0.60$ on TLC EtOAc:hexane – 25:75) to yield the pure product as a yellow oil (2.90 g, 72 %). $[\alpha]^{20}_D$ -155.8 (c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.84 (s, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.31-1.38 (m, 2H), 1.75-1.86 (m, 2H), 2.03 (s, 1H), 2.98 (s, 1H), 3.53 (s, 3H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 10.7 (q), 18.5 (q), 20.7 (t), 21.2 (q), 33.9 (t), 46.2 (s), 49.8 (s), 59.1 (q), 60.6 (d), 88.0 (d), 217.9 (s); IR (ATR): ν_{max} 2883(m), 2956(s), 1749(vs), 1110(vs), 1014(m) cm^{-1}; HRMS calcd for $C_{11}H_{18}O_2$ ($[M+H]^+$) 183.1385, found 183.1352.

General procedure for synthesis of Ligands 3-5 and 18

Anhydrous $CeCl_3$ (1.5 eq.) was weighed into a dry two-neck round bottom flask. The appropriate ketone (1 eq.) in dry THF (30 mL) was added and the mixture was stirred under nitrogen at room temperature until a homogeneous gel like mixture was obtained (usually about half an hour). The mixture was cooled to -78°C and the appropriate pyridyllithium solution (3 eq.) in THF (10 mL) was added quantitatively. The solution was stirred for *ca.* one hour at -78°C before being allowed to warm to room temperature. The mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 mL) and 2M HCl (20 mL) was added. The solution was then extracted with 2M HCl (2 x 30 mL) and the acidic extract retained. The acid layer was neutralised with solid sodium bicarbonate before being extracted with diethyl ether (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc: Hexane - 5:95) to yield the respective products as yellow oils.

(1*R*, 2*S*, 3*S*, 4*S*)-(+)-2-Benzyloxy-3-pyridyl-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (3): Pale yellow oil (46 %): R_f = 0.57 on TLC ETOAc:hexane – 25:75; $[\alpha]^{20}_D$ +73.3 (c = 3, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.52-0.57 (m, 1H), 0.85 (s, 3H), 0.99 (s, 3H), 1.18-1.30 (m, 4H), 1.38-1.43 (m, 2H), 1.63 (s, 1H), 2.01 (s, 1H), 3.81 (s, 1H), 4.59-4.68 (q, 2H), 4.79 (s, 1H), 7.11-7.14 (m, 1H), 7.23-7.34 (m, 4H), 7.52-7.55 (m, 1H), 7.64-7.67 (m, 1H), 8.45-8.47 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 12.0 (q), 22.2 (q), 22.4 (t), 22.5 (q), 33.1 (t), 49.9 (s), 50.4 (s), 56.3 (d), 74.4 (t), 83.5 (s), 88.1 (d), 121.8 (d), 122.6 (d), 127.6 (d), 127.7 (d), 128.3 (d), 136,4 (d), 138.4 (s), 147.0 (d) 164.8 (s); IR (ATR): ν_{max} 3495(br, m), 2954(m), 1590(m), 1064(vs), 735(vs) cm^{-1}; HRMS calcd for $C_{22}H_{27}NO_2$ ($[M+H]^+$) 338.2120, found 338.2191.

(1*R*, 2*S*, 3*S*, 4*S*)-(+)-2-Benzyloxy-3-(6-methylpyridine)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (4): Pale yellow waxy solid (57 %): R_f = 0.56 on TLC EtOAc:hexane – 25:75; $[\alpha]^{20}_D$ +40.4 (c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.61-0.66 (m, 1H), 0.86 (s, 3H), 0.97 (s, 3H), 1.14-1.47 (m, 6H), 1.61 (m, 1H), 2.02-2.03 (m, 1H), 2.52 (s, 3H), 3.86 (s, 1H), 4.62-4.70 (q, 2H), 4.77 (s, 1H), 7.00 (m, 1H), 7.26-7.36 (m, 5H), 7.52-7.55 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 12.0 (q), 22.2 (q), 22.5 (t), 22.6 (q), 22.4 (q), 33.2 (t), 49.8 (s), 50.3 (s), 55.9 (d), 74.0 (t), 83.6 (d), 88.0 (d), 119.0 (d), 120.8 (d), 127.5 (d), 127.9 (d), 128.2 (d), 136.5 (d), 138.5 (s) 155.7 (s), 163.8 (s); IR (ATR): ν_{max} 3498(br, m), 2941(m), 1453(s), 1063(vs), 696(s) cm^{-1}; HRMS calcd for $C_{23}H_{29}NO_2$ ($[M+H]^+$) 352.2277, found 352.2266.

(1*R*, 2*S*, 3*S*, 4*S*)-(+)-2-Methoxy-3-pyridyl-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (5): Yellow oil (48 %): R_f = 0.54 on TLC EtOAc:hexane – 25:75; $[\alpha]^{20}_D$ +35.3 (c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.53-0.55 (m, 1H), 0.86 (s, 3H), 1.01 (s, 3H), 1.23-1.45 (m, 5H), 2.04 (m, 2H), 3.48 (s, 3H), 3.84 (s, 1H), 4.52 (s, 1H), 7.12-7.15 (m, 1H), 7.56-7.58 (m, 1H), 7.65-7.67 (m, 1H), 8.45-8.67 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 11.7 (q), 22.2 (q), 22.3 (t), 22.3 (q), 33.1 (t), 49.9 (s), 50.3 (s), 56.2 (d), 60.7 (d), 83.3 (s), 89.9 (d), 121.7 (d), 122.6 (d), 136.4 (d), 146.9 (d), 164.9 (d); IR (ATR): ν_{max} 3491(br, m), 2938(s), 1590(m), 1101(m), 1073(m) cm^{-1}; HRMS calcd for $C_{16}H_{23}NO_2$ ($[M+H]^+$) 262.1807, found 262.1870.

(1*R*, 2*S*, 3*S*, 4*S*)-(+)-2-Methoxy-3-(6-methylpyridyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (18): Yellow oil (48 %): R_f = 0.54 on TLC EtOAc:hexane – 25:75; $[\alpha]^{20}_D$ +39.9 (c = 1, $CHCl_3$); ^{1}H NMR [DMSO, 600 MHz]: δ_H 0.43-0.46 (m, 1H), 0.77-0.91 (m, 4H), 1.08-1.64 (m, 7H), 1.86(s, 1H), 2.51 (s, 1H), 3.32 (s, 3H), 4.41 (s, 1H), 7.08-7.09 (m, 1H), 7.16-7.18 (m, 1H), 7.34-7.36 (m, 1H), 7.63-7.66 (m, 1H); ^{13}C NMR [DMSO, 150 MHz]: δ_C 11.9 (q), 13.8 (q), 21.8 (q), 22.3 (t), 21.9 (q), 22.1 (q), 22.5 (t), 24.3 (t), 29.3 (t), 32.8 (t), 34.9 (t), 49.1 (s), 49.8 (s), 55.9 (d), 59.8 (d), 84.7 (s), 89.5 (d), 119.2 (d), 120.6 (d), 121.1 (d), 122.6 (d), 127.1 (d), 128.1 (d), 136.0 (d) 136.6 (d), 149.0 (d), 154.8 (s), 164.6 (s); IR (ATR): ν_{max} 3501(br, m), 2936(m), 1576(m), 1100(s), 1075(s) cm^{-1}; HRMS calcd for $C_{17}H_{25}NO_2$ ($[M+H]^+$) 276.1964, found 276.2029.

(1*R*, 2*S*, 3*S*, 4*S*)-(+)-2-Benzyloxy-3-methoxy-1,7,7-trimethyl-3-pyridyl-bicyclo[2.2.1]heptan (6)

Ligand **3** (0.50 g, 1.48 mmol) was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in dry THF (50 mL). The solution was allowed to stir at room temperature under nitrogen for 30 minutes. MeI (excess) was added quantitatively and the solution was stirred at room temperature overnight. Excess NaH was quenched by dropwise addition of water and the solvent and excess MeI removed *in vacuo*. The crude residue was diluted with water and extracted with diethyl ether (3 x 30 ml). The organic layers were combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude product was purified using column chromatography (EtOAc:hexane - 5:95) to yield the pure product as a pale yellow oil (0.50 g, 95.9 %). R_f = 0.63 on TLC EtOAc:hexane – 25:75; $[\alpha]^{20}_D$ +53.1(c = 1, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ_H 0.52-0.57 (m, 1H), 0.85 (s, 3H), 0.99 (s, 3H), 1.18-1.30 (m, 6H), 1.38-1.43 (m, 2H), 1.63 (s, 1H), 2.01 (s, 1H), 3.81 (s, 1H), 4.59-4.68 (q, 2H), 4.79 (s, 1H), 7.11-7.14 (m, 1H), 7.23-7.34 (m, 4H), 7.52-7.55 (m, 1H), 7.64-7.67 (m, 1H), 8.45-8.47 (m, 1H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ_C 12.1 (q), 21.6 (q), 21.9 (q), 22.4 (t), 32.6 (t), 49.6 (s), 51.2 (s), 54.5 (d), 56.9 (q), 74.3 (t), 88.1 (d), 91.3 (s), 121.9 (d), 123.4 (d), 126.9 (d), 127.0 (d), 128.1 (d), 136.3 (d), 139.7 (s) 147.5 (d), 162.6 (s); IR (ATR): ν_{max} 2938(m), 2870(m), 1589(m), 1097(vs), 731(vs) cm^{-1}; HRMS calcd for $C_{23}H_{29}NO_2$ ($[M+H]^+$) 352.2277, found 352.2332.

General procedure for the addition of diethylzinc to aldehydes

To a solution of the ligand (20 mol % relative to aldehyde) in dry toluene (2 mL) under a nitrogen atmosphere at ambient temperature, was added a solution of $ZnEt_2$ in hexane (1.0M, 1.25 mL, 1.25 mmol). The mixture was stirred for 30 minutes, and then benzaldehyde (60 mg, 0.5 mmol) was added. The reaction was stirred at room temperature for 48 hours and then quenched by adding 10 % HCl and extracted with Et_2O and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude oil was purified via flash chromatography (hexane/ethyl acetate) and its enantiomeric excess determined by chiral HPLC.

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SUPPLEMENTARY INFORMATION

The proton and carbon NMR spectra of all novel compounds reported are available as supplementary material. The 2D NMR spectra of compounds **10a-3** and **10a-4** are also available as is the crystallographic data for structure **13**.

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CHAPTER 3

THE EVALUATION OF NOVEL CAMPHOR DERIVED LIGANDS AS CATALYSTS IN THE ASYMMETRIC HENRY REACTION

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ABSTRACT

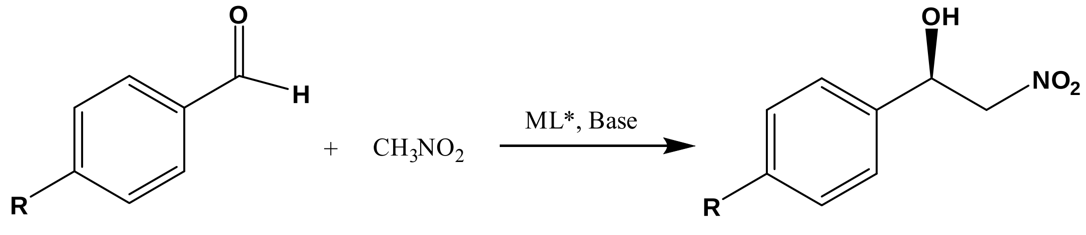
The evaluation of a series of camphor derived ligands as catalysts in the asymmetric Henry reaction is reported. The synthesis of two novel derivatives is detailed and these molecules are also screened as catalysts in this reaction. The single crystal X-ray structure of one of the novel compounds is reported. The reaction is catalysed with moderate to excellent yields and moderate enantioselectivity.

Keywords: Camphor; Asymmetric Catalysis, Henry reaction, Chiral Ligands

INTRODUCTION

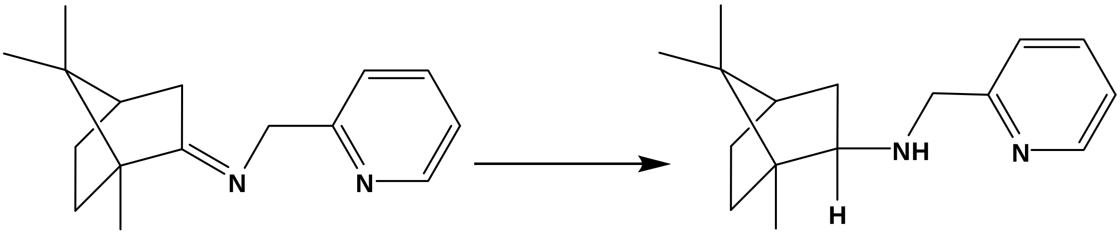
This is a third paper in a series of research results from our group in the field of chiral synthesis and catalytic applications. The first paper involved the synthesis of pentacycloundecane oxazolines and the application of the ligands in an asymmetric Diels-Alder reaction.[1] The second paper made use of camphor derived ligands in the chiral alkylation of aldehydes with diethylzinc.[2]

The nitro-aldol or Henry reaction is one of the classic named reactions in organic synthesis. Since it was discovered in 1895 it has been widely used to generate β-nitro-alcohols by coupling a nucleophile generated from a nitroalkane with a carbonyl electrophile.[3-5] These β-nitroalcohols are very versatile intermediates commonly used in the synthesis of a variety of biologically active compounds.[6, 7] It is as a result of this that much effort has been invested in the development of the asymmetric version of this carbon-carbon bond forming reaction (Scheme 1).


1 **2**

Scheme 1: The asymmetric Henry reaction.

Since the first reported incidence of the reaction being performed with a chiral catalyst more than sixteen years ago[8] a number of authors have reported ever improving selectivity from a range of chiral catalysts.[9-25] These catalysts are predominantly metal complexes using chiral ligands but several examples of organocatalysts[26, 27] have also emerged. Camphor derived ligands however have not been as widely investigated. Pedro *et al.* have reported the synthesis and evaluation of some very successful camphor derived C_1-symmetric iminopyridine ligands in this reaction.[7, 18, 24] One of these ligands has, after reduction to the corresponding aminopyridine derivative (Scheme 2), been used to synthesise a precursor β-nitroalcohol which was subsequently used in the synthesis of the antifungal agent miconazole.[7]


3 **4**

Scheme 2: Example of a previously successful camphor derived ligand.[7]

We have recently reported the synthesis of a series of camphor derived amino and pyridyl alcohol ligands **5-8** (Figure1).[2] These ligands differ from all other camphor ligands in that they are the first examples of molecules with the pyridyl alcohol moieties pendant at the C3 position of the camphor skeleton. Herein we report the synthesis of two additional derivatives (**9** and **10**) and the evaluation of these ligands as catalysts in the asymmetric Henry reaction of a series of aldehydes with nitromethane. This screening was carried out as part of an ongoing study to develop an overall picture of how successful these novel ligands are when applied as catalysts in different chiral reactions.

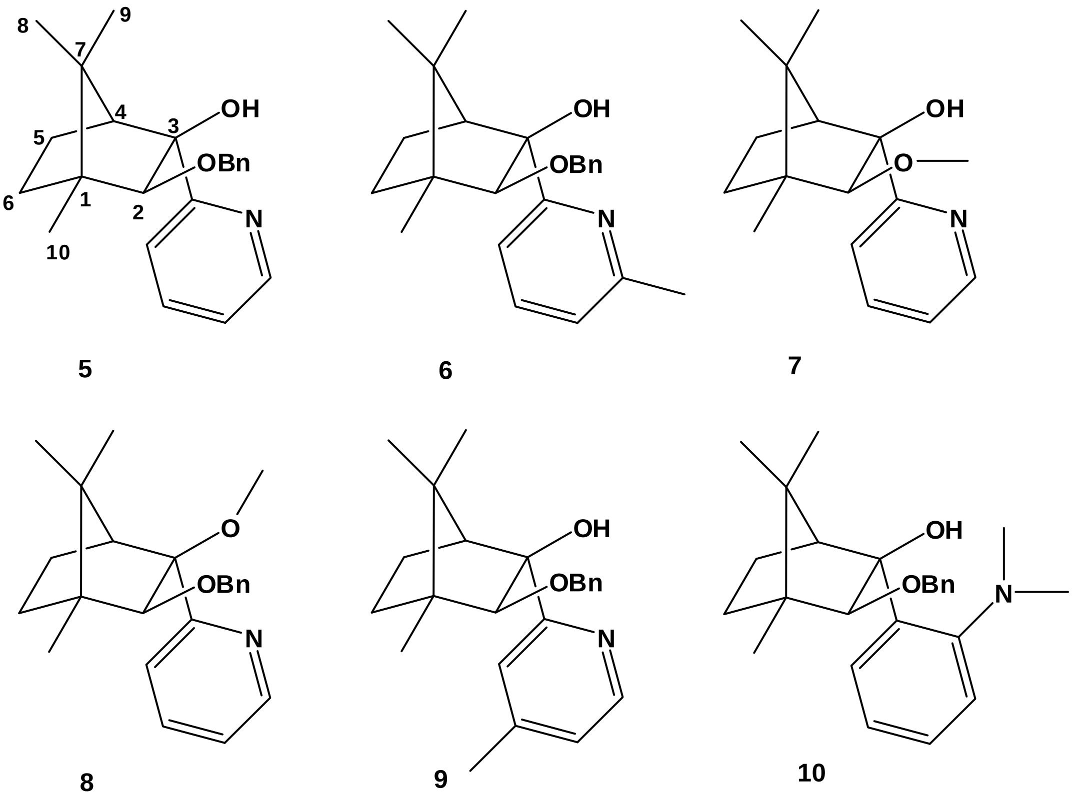
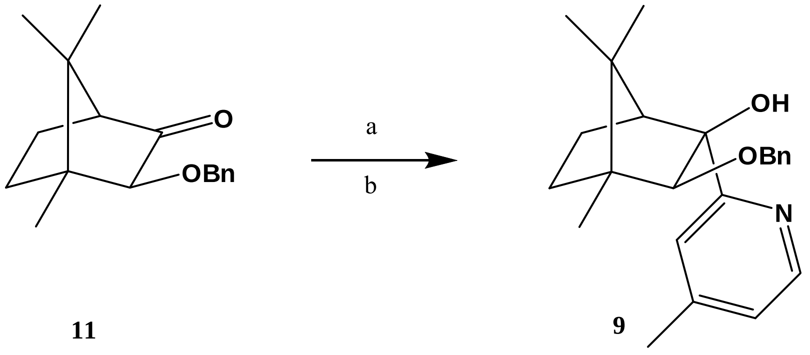


Figure 1: Novel camphor derived ligands.

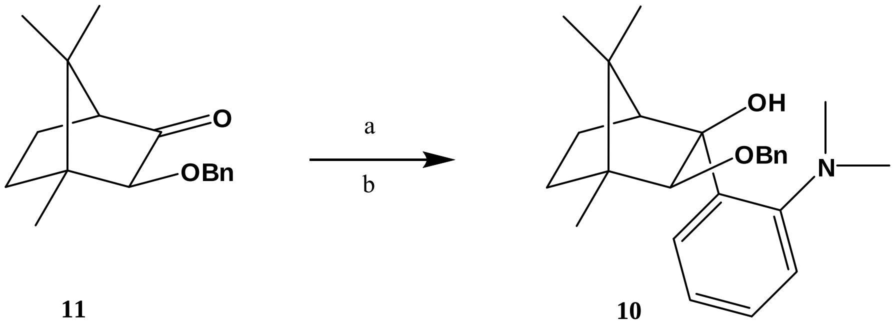
RESULTS AND DISCUSSION

The two new derivatives were synthesised according to similar procedures as reported previously.[2] For ligand **9** the benzyloxy ketone **11** was reacted with the pyridyllithium freshly prepared by reacting 2-bromo-4-methylpyridine with butyllithium at -78°C using the same procedure previously reported (Scheme 3).



Scheme 3: Synthesis of Ligand **9**. Key a) **11**, $CeCl_3$, RT, 30 min b) 4-methyl pyridyllithium, -78°C → RT, 12 hrs.

Ligand **10** was synthesised similarly except an aniline derivative (2-bromo-*N*,*N*-dimethylaniline) was used in place of the pyridine (Scheme 4).



11 10

Scheme 4: Synthesis of Ligand **10**. Key a) 11, $CeCl_3$, RT, 30 min b) 2-(dimethylamino)phenyllithium, -78°C → RT, 12 hrs.

On isolation of this compound it was discovered that it was possible to crystallize the free ligand from a chloroform/methanol solution to yield crystals of high enough quality for single crystal X-ray analysis. The analysis confirmed the structure of **10** (Figure 2).

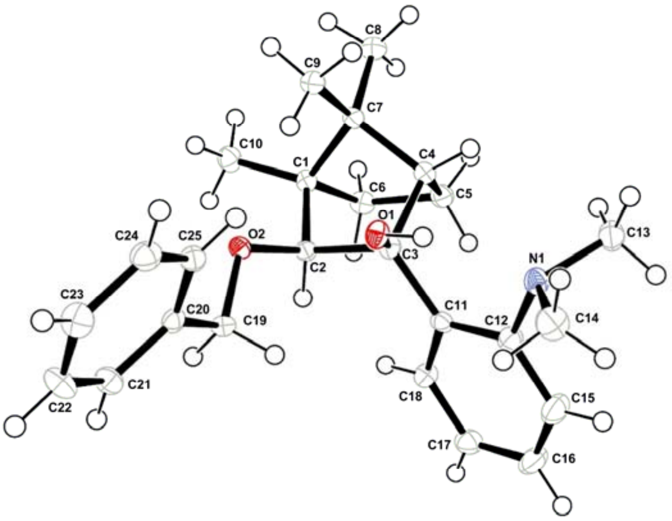


Figure 2: ORTEP diagram of novel ligand **10**. (The X-ray data is included as supplementary material)

A survey of the literature revealed that copper was a very successful metal for use in catalysing the Henry reaction.[10, 11, 15, 18, 19] The first step in screening the ligands was to determine which copper salt was the most effective in catalysing the reaction when combined with our ligands. A series of copper salts was screened in the Henry reaction of *p*-nitrobenzaldehyde with nitromethane (Table 1).

Table 1: Reaction of *p*-nitrobenzaldehyde with nitromethane catalysed by ligand **5** using various copper salts in ethanol.

Copper salt	**Time (hrs)**	**Yield (%)**	***ee* (%)**[a]	**Configuration**[a]
$Cu(OTf)_2$	96	10	rac	-
$Cu(OAc)_2.H_2O$	72	75	48	*S*
$CuCl_2$	96	4	rac	-
$Cu(ClO_4)_2$	96	12	44	*S*

[a] Determined by HPLC (Chiralpak IB)

Initially, ligand **5** (10 mol%) was used in the absence of base with ethanol as the solvent. No special precautions were taken for the exclusion of moisture or air. All reactions were carried out at room temperature. A control reaction without any ligand resulted in no product formation. Of the salts investigated, $Cu(OAc)_2.H_2O$ and $Cu(ClO_4)_2$ showed some selectivity. Due to the poor yield and long reaction time when $Cu(ClO_4)_2$ was used, this salt was not investigated further. The addition of organic bases has been shown to affect the rate of reaction as well as the selectivity.[28] This was investigated using a range of amine bases in ethanol as the solvent for the reaction (Table 2).

Table 2: Reaction of *p*-nitrobenzaldehyde with nitromethane catalysed by ligand **5** using various amine bases and $Cu(OAc)_2.H_2O$ in ethanol.

Base	**Time (hrs)**	**Yield (%)**	***ee* (%)**[a]	**Configuration**[a]
DIPEA	1	79	18	*R*
DBU	1	55	2	*R*
Et_3N	48	98	56	*S*
Piperidine	1	85	3	*R*
2,6-Lutidine	24	92	46	*S*

[a] Determined by HPLC (Chiralpak IB)

From the results it was determined that Et_3N was the most suitable base. This served to reduce the reaction time as compared to the reaction without base, as well as increase the selectivity slightly. The yield for the reaction also increased quite markedly from 75% to 98%. Consequently, it was decided that all subsequent reactions would be carried out with this combination of salt and base. Next, the effect of solvent was investigated. The reaction was carried out in a variety of protic and aprotic solvents. Ethanol was found to be the best solvent for the reaction (Table 3).

Table 3: Reaction of *p*-nitrobenzaldehyde with nitromethane catalysed by ligand **5** using various solvents and $Cu(OAc)_2.H_2O$ with Et_3N as base.

Solvent	Time (hrs)	Yield (%)	*ee* (%)[a]	Configuration[a]
Ethanol	48	98	56	*S*
Methanol	12	61	rac	-
Isopropanol	4	79	4	*R*
DCM	16	70	rac	-
THF	16	83	7	*R*
CH_3CN	12	58	3	*R*

[a] Determined by HPLC (Chiralpak IB)

Once we had determined the best combination of metal salt, solvent and base, it was decided to screen the remaining ligands in order to determine which would give the best selectivity in the reaction of *p*-nitrobenzaldehyde with nitromethane (Table 4).

Table 4: Screening of ligands **6-10** in the Henry reaction of *p*-nitrobenzaldehyde with nitromethane using ethanol, $Cu(OAc)_2.H_2O$ and Et_3N as base.

Ligand	Time (hrs)	Yield (%)	*ee* (%)[a]	Configuration[a]
6	72	96	23	S
7	1	88	rac	-
8	1	74	rac	-
9	1	94	4	R
10	72	78	3	R

[a] Determined by HPLC (Chiralpak IB)

Surprisingly, it was discovered that the initial ligand screened was in fact the most successful in terms of both yield and selectivity for the chosen reaction. All the other ligands showed little or no selectivity.

The next step was to investigate the ligand (**5**) with a variety of different substrates. The reactions were carried out using the optimised conditions at room temperature (Table 5).

Table 5: Screening of different substrates with nitromethane using ethanol, $Cu(OAc)_2.H_2O$ and Et_3N as base..

Substrate	Time (hrs)	Yield (%)	*ee* (%)[a]	Configuration[a]
o-Anisaldehyde	24	43	22	S
p-Anisaldehyde	24	44	15	S
Benzaldehyde	4	64	9	S
Cinnamaldehyde	4	68	6	S
o-Methoxycinnamaldehyde	4	41	14	S
o-Tolualdehyde	24	73	2	S
p-Tolualdehyde	12	50	2	S
o-Chlorobenzaldehyde	24	72	6	S
p-Chlorobenzaldehyde	12	67	2	S
Cyclohexanecarboxaldehyde	12	59	39	S

[a] Determined by HPLC (Chiralpak IB)

The results obtained from the substrate screening were disappointing. Only the cyclohexanecaboxaldehyde substrate resulted in any significant selectivity and even in this case the selectivity was considered poor.

CONCLUSION

Two novel ligands have been synthesised to add to the series of C3 pendant ligands synthesised previously. The ligands were screened as catalysts in the asymmetric Henry reaction with excellent yields but only moderate selectivity.

EXPERIMENTAL

4.1 General

All NMR spectra were recorded on Bruker (Karlsruhe, Germany) AVANCE III 400MHz or 600MHz instruments. Infrared spectra were recorded on a Perkin Elmer (Waltham, Massachusetts 02451, USA) Spectrum 100 instrument equipped with a Universal ATR attachment. Optical rotation data was acquired using a Perkin Elmer Model 341 polarimeter. Accurate mass measurements were obtained on a Bruker MicroTOF Q2 instrument with the ESI ionisation method. All solvents were dried using standard procedures prior to use. All reagents were purchased from Fluka or Sigma-Aldrich and used without further purification. Column chromatography was carried out on silicagel 60 particle size 0.063-0.200 mm (230-400 mesh). Full analytical data reported only for novel compounds.

4.2 Synthesis of ligands 5-8

The synthesis of all precursor compounds and ligands **5-8** was reported previously.[2]

4.3 General procedure for synthesis of Ligands 9 and 10

Anhydrous $CeCl_3$ (1.5 eq.) was weighed into a dry two-neck round bottom flask. The ketone **11** (1 eq.) in dry THF (20 mL) was added and the mixture was stirred under nitrogen at room temperature until a homogeneous gel like mixture was obtained (usually about half an hour). The mixture was cooled to -78°C and the appropriate pyridyllithium or lithioaniline solution (3 eq.) in THF was added. The solution was stirred for *ca.* 1hr at -78°C before being allowed to warm to room temperature. The mixture was stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 mL) and 2M HCl was added. The solution was then extracted with 2M HCl (2 x 30 mL) and the acidic extract retained. The acid layer was neutralised with solid sodium bicarbonate before being extracted with diethyl ether (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude residue was purified using column chromatography (EtOAc: hexane - 5:95).

4.3.1 (1*R*, 2*S*, 3*S*, 4*S*)-(+)-2-benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-(4-methylpyridine)-3-ol (9): Pale yellow waxy solid (59 %): Rf = 0.59 on TLC EtOAc:hexane – 25:75; $[\alpha]^{20}_D$ +20.7 (c = 1, $CHCl_3$); ^1H NMR [$CDCl_3$, 400MHz]: δ_H 0.54-0.59 (m, 1H), 0.86 (s, 3H), 1.01 (s, 3H), 1.21-1.59 (m, 6H), 2.01 (s, 1H), 2.34 (s, 3H), 3.82 (s, 1H), 4.60-4.68 (q, 2H), 4.81 (s, 1H), 6.96-6.98 (d, 1H), 7.25-7.37 (m, 6H), 8.32-8.34 (d, 1H); ^{13}C NMR [$CDCl_3$, 100MHz]: δ_C 12.0 (q), 21.1 (q), 22.2 (t), 22.4 (q), 22.5 (q), 33.1 (t), 49.8 (s), 50.4 (s), 56.4 (d), 74.4 (t), 83.4 (d), 87.9 (d), 122.9 (d), 123.2 (d), 127.6 (d), 127.7 (d), 128.3 (d), 138.4 (s), 146.8 (d) 164.6 (s); IR (ATR): ν_{max} 3499(br, m), 2945(m), 1603(s), 1065(vs), 695(s) cm^{-1}; HRMS calcd. for $C_{23}H_{29}NO_2$ ($[M+H]^+$) 352.2277, found 352.2309.

4.3.2 (1*R*, 2*S*, 3*S*, 4*S*)-(-)-2-benzyloxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-[(2-dimethylamino)phenyl]-3-ol (10): white solid (62 %): Rf = 0.57 on TLC EtOAc:hexane – 25:75; Mp 106-110°C; $[\alpha]^{20}_D$ -35.5 (c = 1, $CHCl_3$); ^1H NMR [$CDCl_3$, 400MHz]: δ_H 0.63-0.67 (m, 1H), 0.86 (s, 3H), 1.01 (s, 3H), 1.10-1.18 (m, 1H), 1.50-1.58 (m, 6H), 1.97 (s, 1H), 2.69 (s, 6H), 4.05 (s, 1H), 4.28-4.31 (d, 1H), 4.78-4.81 (d, 1H), 7.08-7.41 (m, 8H), 7.94 (s, 1H); ^{13}C NMR [$CDCl_3$, 100MHz]: δ_C 12.5 (q), 22.4 (q), 22.7 (t), 22.8 (q), 33.6 (q), 49.8 (s), 49.9 (s), 58.3 (s), 72.6 (d), 83.6 (d), 89.2 (t), 123.9 (d), 125.1 (d), 126.3 (d), 126.9 (d), 127.4 (d), 127.7 (d), 128.0 (d), 139.7 (s) 142.7 (s), 152.9 (s); IR (ATR): ν_{max} 2942(m), 1455(s), 1112(s), 736(vs), 559(s) cm^{-1}; HRMS calcd. for $C_{25}H_{33}NO_2$ ($[M+H]^+$) 380.2590, found 380.2606. Elemental Analysis: Calculated C= 79.11%, H= 8.76%, N= 3.695, O= 8.43%; Found C= 79.85%, H= 8.59%, N= 3.51%, O= 8.05%.

4.4 General procedure for asymmetric Henry reaction: The ligand (10 mol %) was dissolved in ethanol (2 mL) in a schlenk tube. The copper salt (1.2 mol equivalent relative to ligand) was added and the resulting blue solution was stirred at room temperature for one hour. Triethylamine (1 mol equivalent relative to substrate) was added followed by the substrate (50 mg). The mixture was stirred at room temperature until no starting material remained (TLC). The green solution was evaporated *in vacuo* and the product isolated using flash chromatography. The enantiomeric excess was determined by HPLC analysis [Daicel Chiralpak IB column (hexane: *i*-PrOH = 90:10) flow rate = 0.8 mL/min, *t*(*R*) 19.0 min, *t*(*S*) 21.0 min.] The configurations were assigned by comparison of HPLC elution order to literature values.[6, 28]

X-ray details: CCDC 721782 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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CHAPTER 4

THE EVALUATION OF NOVEL CAMPHOR DERIVED PYRIDYL LIGANDS AS CATALYSTS IN THE ASYMMETRIC DIELS-ALDER REACTION OF CYCLOPENTADIENE WITH 3-ACRYLOYL-2-OXAZOLIDINONE

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ABSTRACT

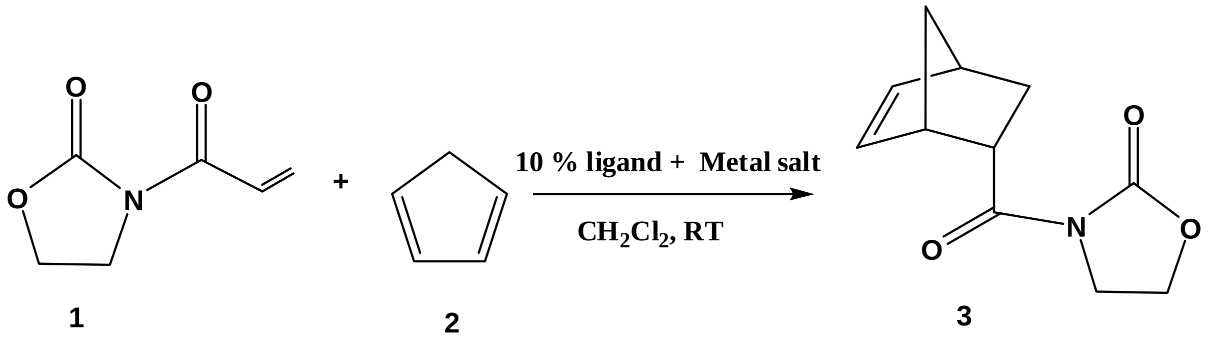
A series of camphor derived pyridyl ligands were evaluated in the Diels-Alder reaction of 3-acryloyl-2-oxazolidinone ***1*** *with cyclopentadiene* ***2****. High yields with good endo:exo selectivity, but only moderate enantioselectivities (43% ee), were obtained. The structures of the copper(II) complexes of the ligands were calculated using ONIOM density functional theory and the results suggest that chiral induction to the alkene functional group is indeed lacking. This explains the moderate experimental selectivities obtained.*

Keywords: Camphor Ligands, Asymmetric Catalysis, Diels-Alder cycloaddition, Computational modelling.

INTRODUCTION

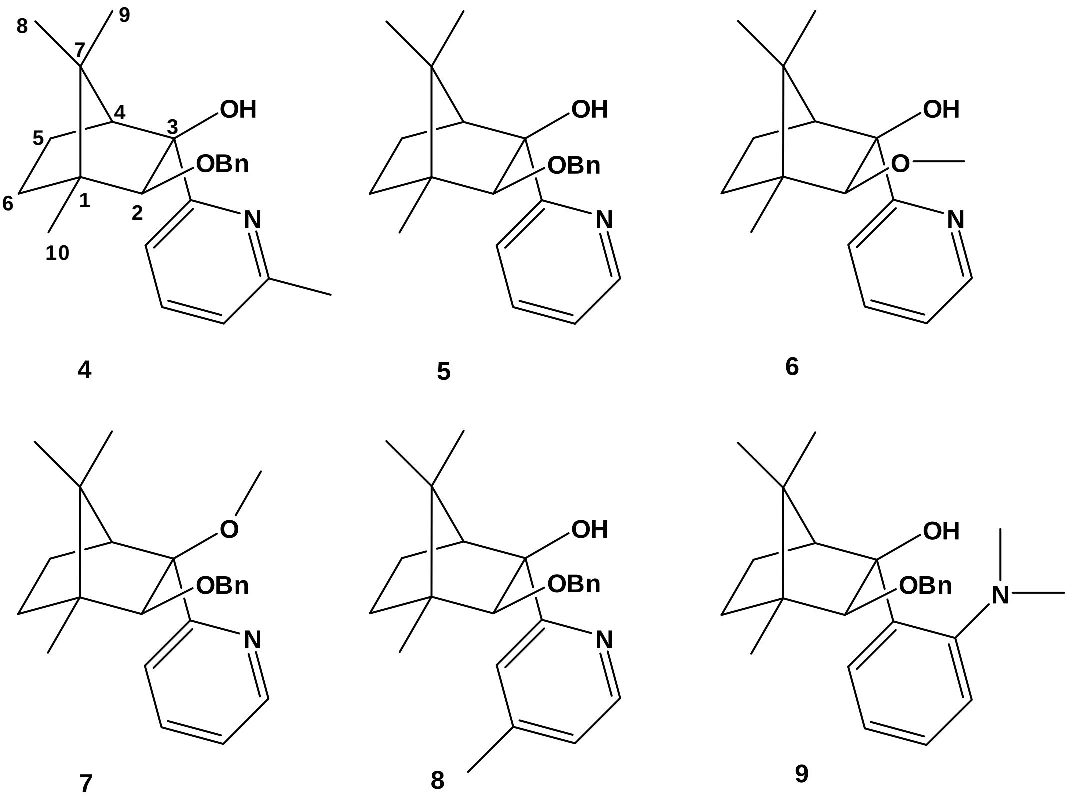
This is the fourth paper in a series of research results from our group in the field of chiral synthesis and catalytic applications. The first paper involved the synthesis of pentacycloundecane oxazolines and the application of the ligands in an asymmetric Diels-Alder reaction.[1] The second paper made use of camphor derived ligands in the chiral alkylation of aldehydes with diethylzinc,[2] while the third utilized these same camphor ligands, as well as two new derivatives, to catalyse the asymmetric Henry reaction.[3]

The Diels-Alder cycloaddition reaction is one of the classic named reactions in organic chemistry.[4] It is widely used in the regio- and stereo-selective construction of six membered rings.[4-8] The reaction has been the subject of much investigation since it was first reported in 1928.[9] In fact, more than 17000 papers have been published detailing research into this reaction, half of those in the last decade.[4] The first examples of the asymmetric Diels-Alder reaction were carried out more than 30 years ago in the late 1970's[10] and has since become an area of intense investigation. The discovery that the reaction is catalysed by Lewis acids under very mild conditions led to a number of researchers investigating the development of chiral ligands which could complex these Lewis acids hence leading to asymmetric products from the Diels-Alder reaction.[8] Certain "benchmark" reaction have emerged as standards for evaluation of chiral ligands as catalysts in the asymmetric Diels-Alder reaction.[11] One such reaction is the addition of 3-acryloyl-2-oxazolidinone **1** to cyclopentadiene **2** (Scheme 1).[11-18]



Scheme 1: Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**.

Camphor derived complexes have not been widely evaluated as a catalyst for this reaction. Only a few examples of camphor derived ligands appear in the literature as being applied as catalysts in the asymmetric Diels-Alder reaction.[19-21] These ligands have proven to be reasonably successful in terms of selectivity with enantiomeric excesses in the 80 and low 90 percent range. Herein we report the evaluation of a series of recently reported[2, 3] camphor derived pyridyl ligands **4-9** (Figure 1) as catalysts in the Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**. These molecules are unique in that they represent the only examples of camphor derived ligands which have pendant donor groups on the C3 position of the camphor alone. Most other existing camphor derived ligands have the donor groups pendant on the C2 position or have one donor group at C2 with the other at C3.[22]



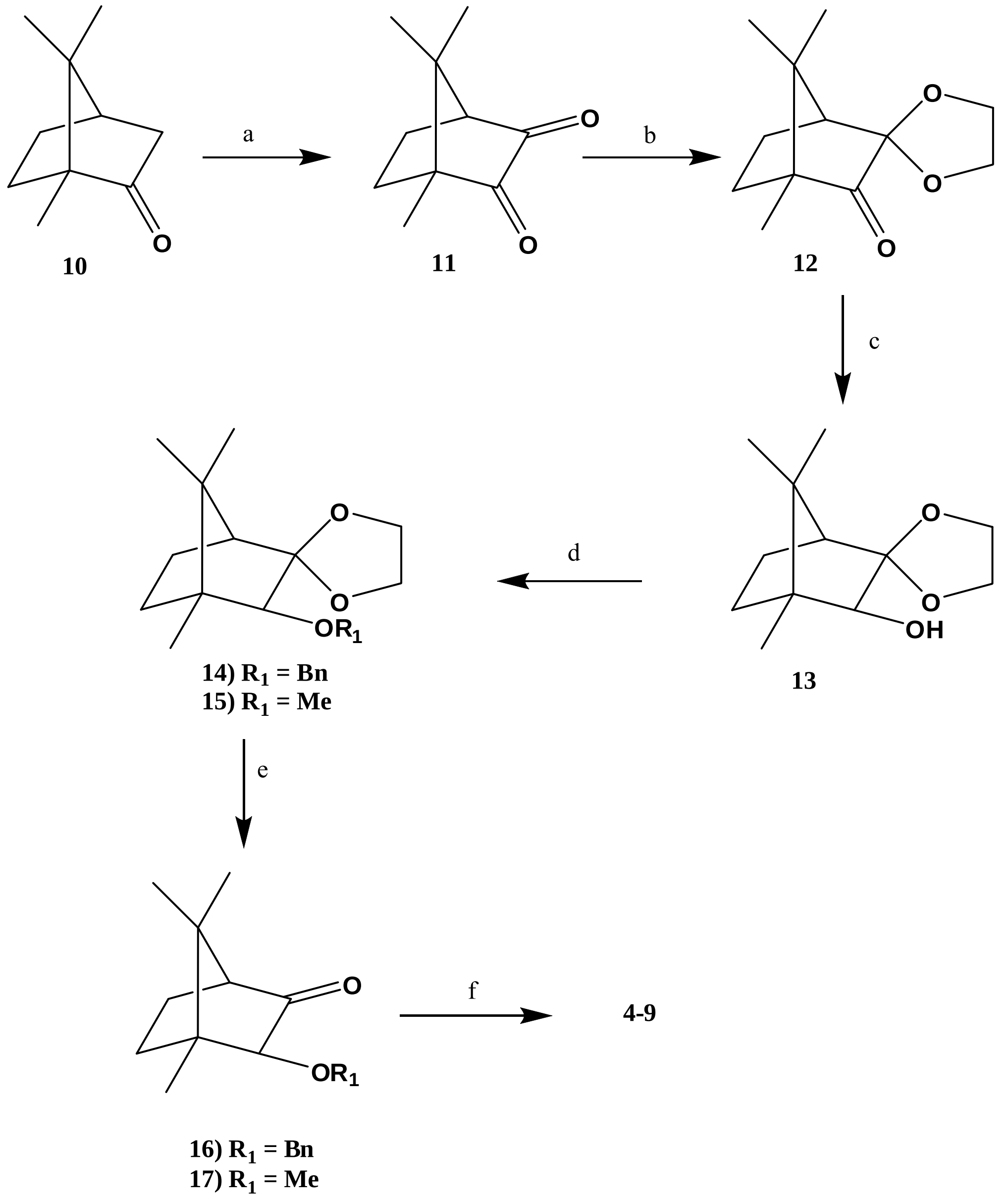
4 5 6

7 8 9

Figure 1: Ligands **4-9**

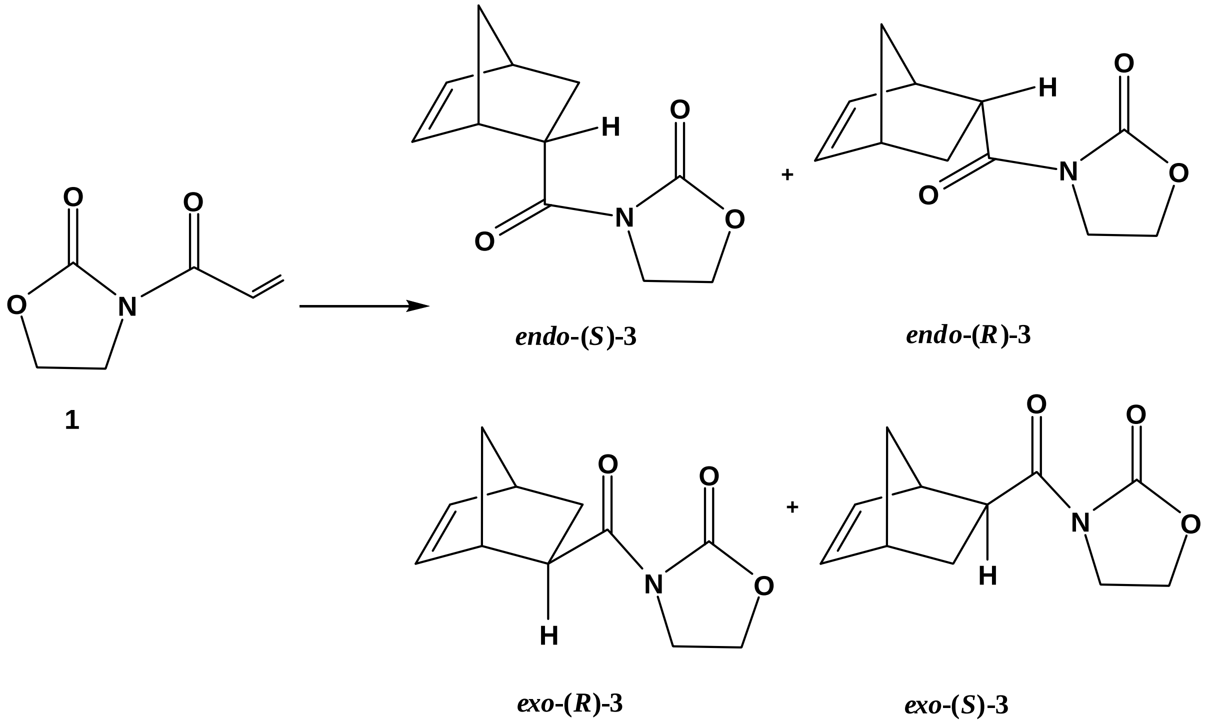
RESULTS AND DISCUSSION

Ligands **4-9** were synthesised according to the procedure outlined in previous studies (Scheme 2).[2, 3] The compounds were complexed to a series of metal salts and screened as catalysts in the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**.



Scheme 2: The synthetic scheme for Ligands **3**-**6**. Key: a) SeO_2, Ac_2O, reflux 16 hrs, 86%, b) ethylene glycol, PTSA, benzene, reflux 12 hrs, 80% c) $NaBH_4$, Diethyl ether/MeOH (1:1), RT 2 hrs, 85% d) benzyl bromide or methyl iodide, NaH, dry THF, 12 hrs, 75% (**14**) 95% (**15**) e) HCl/ THF (1:3), 2 hrs, 80% f) ketone **16** or **17**, $CeCl_3$, pyridyllithium or lithioaniline, -78°C → RT, 12 hrs.

There are four different ways the diene **2** can approach the dienophile **1**. Firstly, the dienophile **1** can either attack from above the plane of the paper and secondly from below the plane of the paper. (*R*)-**3** is formed *via* attack of the diene **2** from above the plane of the paper and (*S*)- **3** is the result of the diene attacking from below the plane of the paper. The chiral catalyst is supposed to limit the formation of one enantiomer over the other.[23] During the reaction of the substrates (**1** and **2**) in the presence of the chiral catalyst, the top side of attack is blocked or hindered to such an extent that *endo*-(*S*)-**3** is almost exclusively observed. Note that in both these cases the diene **2** approaches the dienophile **1** with the CH_2-group pointing away from the carbonyl oxygen of **1**. This is the more kinetically preferred approach and leads to what is called the *endo*-product.



Scheme 3: The four different potential products for the Diels-Alder reaction.

The last two possibilities are both the result of the diene **2** attacking the dienophile **1** with the CH_2-group pointing towards the carbonyl carbon of **1**. Again, two products are possible (i.e attack of the diene from either above or below the plane of the paper). *Exo*-(*S*)-**3** forms when attack is from below the plane of the paper and *exo*-(*R*)-**3** forms when attack occurs from above the plane of the paper. This approach is the less kinetically preferred and leads to what is called the *exo*-product.[24]

An equimolar amount of the metal salt was added to a solution of ligand **4** in dichloromethane.[18] The resultant catalyst complex was used to promote the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** and cyclopentadiene **2** to yield the cycloadduct **3** as illustrated in Scheme 1. The results for this preliminary screening of the metal salts is summarised in Table 1.

Table 1: Results obtained for the reaction between 3-acryloyloxazolidin-2-one **1** and cyclopentadiene **2** catalyzed by ligand **4** complexed to various metal salts with CH_2Cl_2 as the solvent at room temperature.

Entry	**Metal Salt**	**Time /min**	**% Yield**	***Endo:exo***[a]	**% (*S*)-*Endo ee***[b]
1	Blank	240	80	96:4	0
2	$Ni(ClO_4)_2$	30	71	83:17	4
3	$Zn(ClO_4)_2$	5	74	81:19	3
4	$Mg(ClO_4)_2$	>30	71	-	0
5	$Mn(ClO_4)_2$	5	61	88:12	3
6	$CoBr_2$	>30	71	-	0
7	ZnI_2	10	83	-	0
8	$MnBr_2$	>30	70	87:13	2
9	$NiBr_2$	>30	75	-	0
11	$FeCl_2$	>30	62	-	0
12	$NiBr_2$	>30	78	-	0
13	$Cu(OTf)_2$	5	55	92:8	43
14	$Sc(OTf)_2$	10	62	86:14	5

[a] Determined by ^1H NMR, [b] Determined by HPLC (Chiralpak IB).

From this initial screening it was determined that $Cu(OTf)_2$ was the most successful metal salt in terms of selectivity, albeit very moderate. Different copper salts were investigated to determine the effect of the counterion on the catalyst in the reaction (Table 2).

Table 2: Effect of different counterion on reaction between 3-acryloyloxazolidin-2-one **1** and cyclopentadiene **2** catalyzed by ligand **4** and Cu with CH_2Cl_2 as the solvent at room temperature.

Metal salt	**Time /min**	**% Yield**	***Endo:exo***	**% (*S*)-*Endo ee***
$Cu(OTf)_2$	5	55	92:8	43
$CuCl_2$	>30	73	-	0
$Cu(ClO_4)_2$	5	74	87:13	23
$Cu(OAc)_2.H_2O$	>30	75	-	0

$Cu(OTf)_2$ emerged as the best counterion and the next step was the screening of the remaining ligands in the hope of obtaining a higher selectivity. The results of this screening process is summarised in Table 3.

Table 3: Screening of ligands **5-9** in the reaction of 3-acryloyloxazolidin-2-one **1** and cyclopentadiene **2** catalyzed by ligand **4** and Cu(OTf)$_2$ with CH$_2$Cl$_2$ as the solvent at room temperature.

Entry	Ligand	Time /min	% Yield	*Endo:exo*[a]	% (*S*)-*Endo ee*[b]
1	5	5	81	87:13	4
2	6	5	93	87:13	4
3	7	5	81	80:20	5
4	8	5	80	86:14	5
5	9	5	92	88:12	27

[a] Determined by ^{1}H NMR, [b] Determined by HPLC (Chiralpak IB).

From this table it can be seen that ligands **5-9** gave poor selectivity. Only the aniline derivative (**9**) gave any significant selectivity. The only similarity between ligand **4** and ligand **9** is the fact that both of these compounds have sterically hindered *N*-donor atoms. They also form different chelate ring sizes, with ligand **4** forming a 5-membered chelate and ligand **9** forming a 6-membered chelate. All the other ligands have little or no steric bulk around the nitrogen atom.

In order to determine a possible reason for the observed selectivity obtained for this reaction with these ligands, a computational evaluation of the ligand **4**/ metal complex with the substrate in two possible orientations was carried out (Figure 2). The complex was modelled in the square planar arrangement for copper as this is known to be the preferred conformation in the +2 oxidation state. The basis set used for this evaluation is reported in literature to give accurate estimates of the structure under investigation.[25-27]

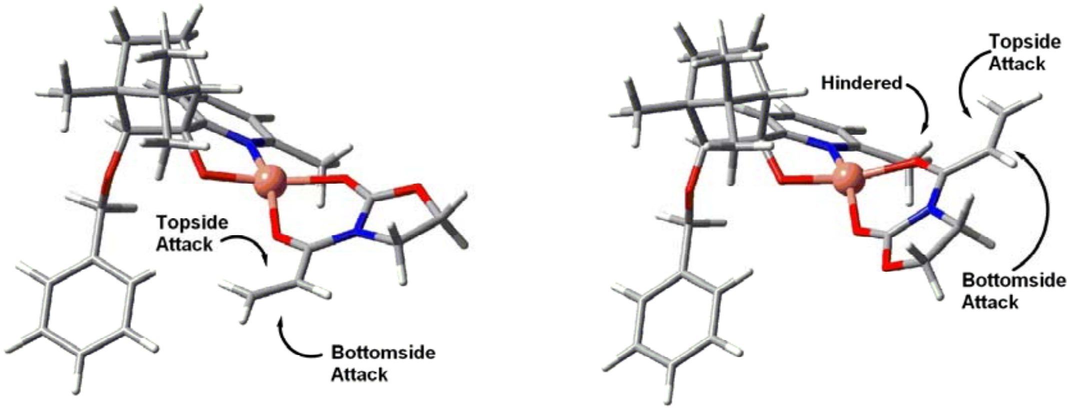


Figure 2: DFT Oniom optimised model of the ligand **4**/metal complex with substrate in two different conformations, **18a** (left) and **18b** (right). (Cartesian Coordinates of these optimized structures are available as supplementary material.)

The optimised structures revealed some interesting facts about the complex. First, the substrate is likely to complex to the metal in one orientation preferentially i.e. **18a**. This is determined by considering that the energy of the one orientation (**18a**, Fig.2) is lower (by 4.58 kcal/mol) than that of the other (**18b**, Fig.2) due to steric factors. The observation that **18b** is higher in energy can be practically deduced from the fact that the geometry of the "square planar" copper ion is of **18b** much more distorted than for **18a**. This is the result of steric hinderance between the substrate alkene group and the nearby methyl group on the pyridine ring. In **18a** the alkene group is positioned away from the pyridine ring and as a result the square planar geometry around the copper ion is much less distorted out of the plane. Second, the complexed alkene in **18a** (the low energy catalytic complex) is open to attack by cyclopentadiene (see Scheme 3) from both sides (top and bottom), thus resulting in the observed low selectivity.

Several computational studies have been carried out into the selectivity of the Diels-Alder reaction.[28, 29] From these it is apparent that for good enantioselectivity to be obtained the one side of the alkene should be completely blocked from attack by cyclopentadiene and the other side should partially block the vertical approach of cyclopentadiene so that the CH_2-group on the cyclopentadiene ring is pointing away due to the partial steric hinderance. Inspection of the 3D structure of **18a** clearly indicates a lack of steric hinderance on both sides of the alkene group.

CONCLUSION

In summary, a series of novel camphor derived pyridyl and aniline compounds have been screened in the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone **1** with cyclopentadiene **2**. The reaction proved to be very sensitive to both ligand and metal salt used, with only the combination of ligand **4**/$Cu(OTf)_2$ giving any significant selectivity. Although the results were only mediocre, the screening of this class of ligands in this reaction was necessary in order to develop an overall picture of how active the compounds are when used in varying catalytic applications. Further studies using computational models could potentially lead to the modification and design of more selective camphor ligands for this application.

EXPERIMENTAL

All NMR spectra were recorded on Bruker (Karlsruhe, Germany) AVANCE III 400MHz or 600MHz instruments. All HPLC analysis was carried out on a Shimadzu Prominence (Tokyo, Japan) system using a Diacel Chiralpak IB column with hexane/ isopropanol (95:5) as eluent. All solvents were dried using standard procedures prior to use. All reagents were purchased from Fluka or Sigma-Aldrich (St Louis, USA) and used without further purification. Column chromatography was carried out on silicagel 60 particle size 0.063-0.200 mm (230-400 mesh).

General procedure for the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone 1 with cyclopentadiene 2.

A mixture of ligand (1 mol eq.) and anhydrous metal salt (1 mol eq.) in dry CH_2Cl_2 (5 ml) was stirred under dry nitrogen at ambient temperature for three hours. The resulting complex was used for the Diels-Alder reactions as follows: 3-acryloyl-2-oxazolidinone **1** (50 mg, 0.4 mmol) and freshly distilled cyclopentadiene **2** (0.3 ml, 4.0 mmol) were added. The reaction was performed at room temperature and monitored by TLC. After the completion of the reaction, saturated aqueous ammonium chloride was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by flash column chromatography (hexane/EtOAc = 70:30) to give a mixture of *endo* and *exo* isomers of cycloadduct **3** (60 mg, 85 %). The *endo:exo* ratio was evaluated on the basis of the ^1H NMR spectrum (2.94 ppm and 3.02 ppm) and the enantiomeric excess determined by HPLC with a Daicel Chiralpak IB column (hexane: *i*PrOH = 95:5) flow rate = 1 L/min, *t*(*R*) 24.0 min, *t*(*S*) 22.6 min. Other anhydrous complexes were prepared *in situ* according to a similar procedure by using anhydrous metal halides such as $NiBr_2$, $CaBr_2$, $MnBr_2$, $FeCl_2$, $CoBr_2$, $CuCl_2$, and ZnI_2 and complexation time was three hours.

3-(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone 3

Colourless solid; enantiomeric purity was estimated on the basis of HPLC using a chiral column as described above and the *endo:exo* ratio was evaluated on the basis of the ^1H NMR spectrum; ^1H NMR ($CDCl_3$) δ_H 1.3-1.7 (m, 3H), 1.9-2.1 (m, 1H), 2.94 (m, 1H), 3.31 (m, 1H), 3.8-4.1(m, 3H), 4.40 (t, 2H), 5.88 (dd, 1H), and 6.25 (dd, 1H).

Details of the DFT-optimised structures

The complexes were optimized using Gaussian 03 utilizing the multilayer ONIOM (UPBEPBE/genecp: B3LYP: UFF) function. For this model the low level incorporated the entire complex, the mid level comprised the entire dienophile substrate, the pyridine moiety as well as the C3 carbon of the camphor skeleton and the attached hydroxyl group. The high level comprised the copper atom. An initial single point energy calculation was carried out in order to provide a starting point for the subsequent high level optimisation. For this initial calculation the low level of the onium was optimised using the UFF molecular mechanics forcefield while the mid and high levels used the 3-21G forcefield at the HF level of theory. For the high level multistep optimisation calculation the low level once again used the UFF molecular mechanics forcefield, the mid level calculation was carried out using the 6.31 + g(d) basis set at the B3LYP level of theory while the high level was carried out using the UPBEPBE/genecp basis set. The copper atom was modelled using the LAN2DZ basis set. The charge on the copper atom was left at +1 with doublet spin multiplicity. The Cartesian coordinates are available as supplementary material. The copper complex is quite rigid and the benzyl side chain was manually rotated to find the lowest energy structure.

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CHAPTER 5
NMR ELUCIDATION OF NOVEL LIGANDS DERIVED FROM (*R*)-(+)-CAMPHOR

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ABSTRACT

The complete NMR elucidation of five camphor derived ligands is reported. 2D NMR techniques such as NOESY are used to assist in the determination of the orientation of the donor groups in space. The compounds were synthesized as ligands to be used in asymmetric catalysis. They represent the first instance where both donor groups are pendant on the C3 position of the camphor skeleton. The single crystal X-ray structure of one of the ligands was obtained and was helpful in determining the potential NOESY interactions within the molecule. For the other ligands a high level Density Functional Theory (DFT) optimization was performed [B3LYP/6-31+g(d)] in order to visualize possible NOE interactions.

INTRODUCTION

Chiral monoterpenes such as camphor have been widely used in the development of asymmetric catalysts.[1-7] They afford a simple, inexpensive scaffold around which to build a chiral catalyst.[2, 5] The NMR elucidation of camphor derived compounds has not been widely reported, with only a few examples in the literature.[8, 9] NMR is also a useful method for determining the orientation of the donor groups of the synthesised ligand. Herein we report the full elucidation of a series of novel camphor derived ligands (**1-5**) recently synthesised as part of an ongoing effort to develop novel molecules for applications in asymmetric catalysis.[10, 11] These ligands represent the first examples where both donor groups are pendant on the C3 position of the camphor skeleton.

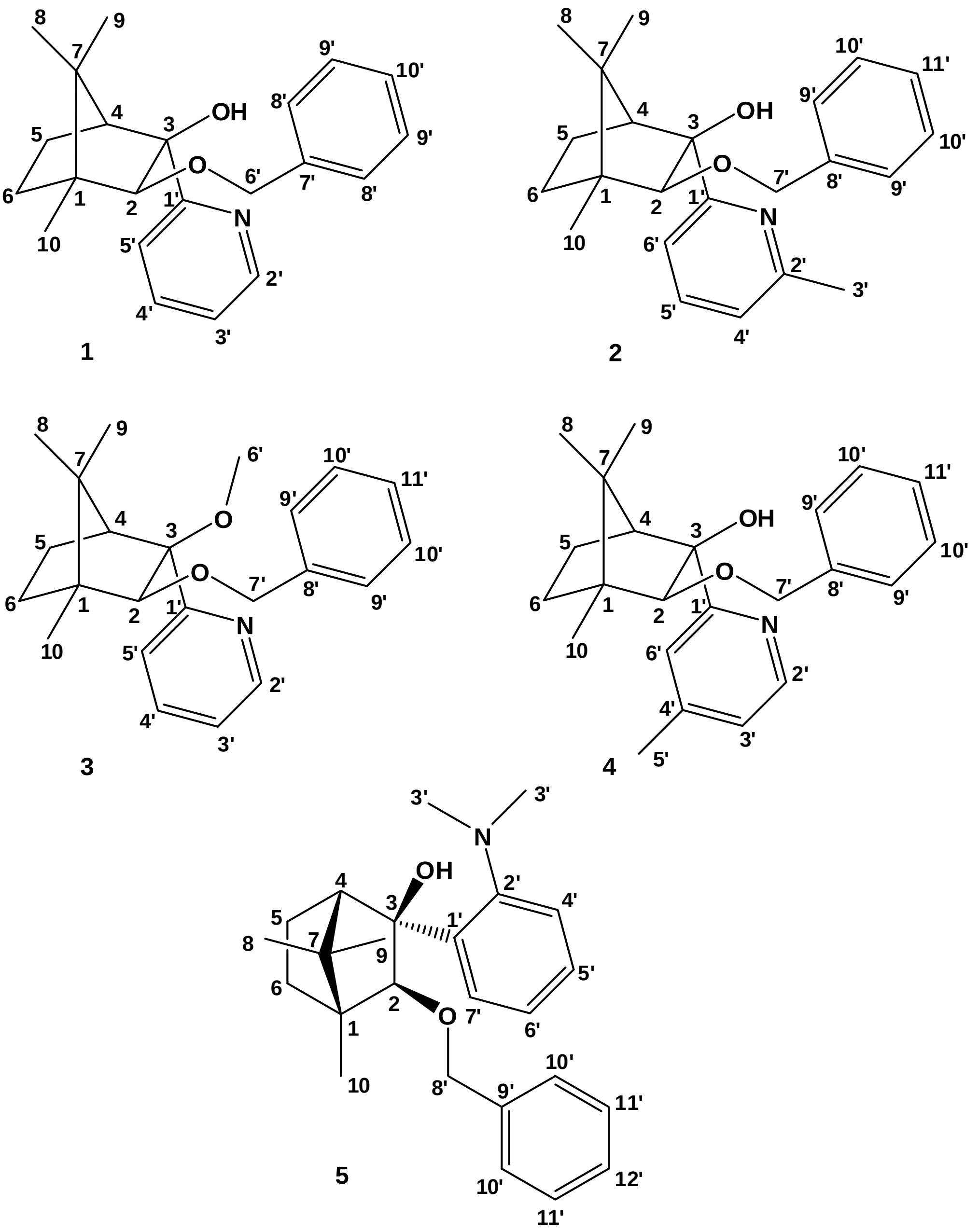
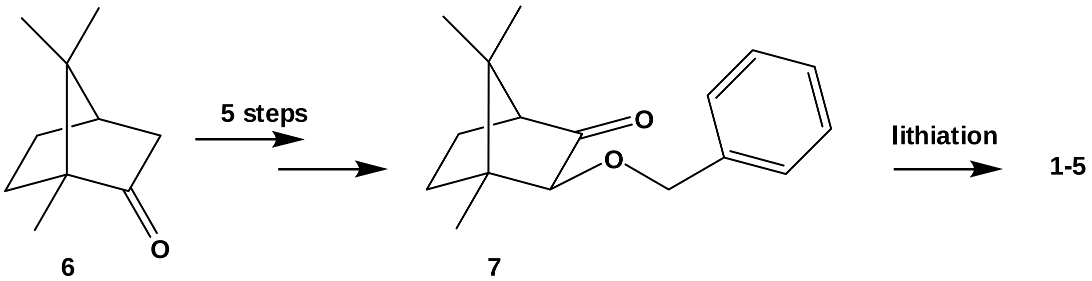


Figure 1: Structure of ligands **1**-**5**.

The starting material for all the ligands is (*R*)-(+)-Camphor **6**. This was converted *via* five steps to the benzyl ether protected ketone **7**. This ketone was then reacted with organolithium reagents to afford the novel ligands **1-5** (Scheme 1). The synthetic details involved in these reactions have recently been reported.[10, 11]



Scheme 1: Synthesis of ligands **1-5**.

RESULTS AND DISCUSSION

The assignment of signals for the camphor skeleton itself does not present significant difficulties. The only signals which pose a challenge are those belonging to the non-equivalent protons on C5 and C6 of the skeleton. The equatorial protons on both these carbons would be expected to have through space interactions with the 8-methyl group. The axial protons on C6 would potentially exhibit NOESY interactions with the methyl protons on C10. In order to assist with the visualisation of the various through space interactions that could be expected for the molecules, a high level Density Functional Theory (DFT) optimisation using density functional theory (B3LYP) with the 6-31+g(d) basis set was carried out for each of the ligands (**1-4**). This approach has been carried out to good effect in our group for other NMR elucidation efforts.[12-14]

Ligand **1** has recently demonstrated the ability to catalyse the asymmetric Henry reaction with moderate selectivity.[11] The ligand comprises a bornane skeleton with a 2-benzyloxy group, a 3-*endo*-pyridyl group and a 3-*exo*-hydroxy group. C3 is a quaternary carbon with an *endo*-pyridyl group and an *exo*-hydroxyl group. The DFT optimised structure is shown in Figure 2.

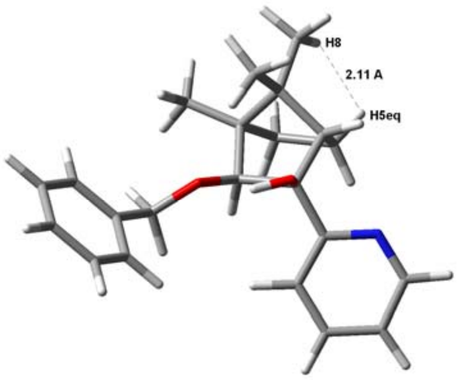


Figure 2: DFT optimised structure of ligand **1** [Cartesian coordinates available as supplementary material – B3LYP/6-31+g(d)].

The camphor skeleton was elucidated first. The *endo* proton on C2 was assigned to the downfield signal at 4.83 ppm due to the NOESY correlation between H2 and endo-H6. This assignment was confirmed with HMBC interactions with C6, C1 and C6'. The OH signal was assigned to the peak at 3.85 ppm (exchanges with D_2O). This signal shows some through space interactions with a methyl signal at 1.34 ppm. This signal was assigned to the methyl group protons H9. The methyl group protons H8 would be expected to interact with the equatorial protons H5 and H6 as discussed earlier. Interactions between a methyl proton signal at 0.89 ppm and signals at 0.59 ppm and 1.24 ppm are observed in the NOESY spectrum. These signals were therefore assigned to H8, $H5_{eq}$ and $H6_{ax}$ respectively. COSY interactions between the proton signals at 0.59 ppm and 1.43 ppm as well as with the signals at 1.24 ppm and 1.45 ppm saw the signal at 1.43 ppm assigned to $H5_{ax}$ and the signal at 1.45 ppm assigned to $H6_{eq}$. Another COSY interaction between $H5_{ax}$ and the signal at 2.04 ppm was noted. This signal was assigned to H4. The methyl signal at 1.03 ppm was assigned by elimination to the H10 protons. With all the camphor skeleton signals assigned, it was decided to assign the protons on the pyridine ring next. The far downfield doublet at 8.49 ppm was assigned to H2' due to the deshielding effect of the adjacent pyridyl nitrogen. The remaining protons on the pyridyl group were assigned using COSY interactions and are recorded in Table 1.

The methylene signal at 74.4 ppm on the ^{13}C spectrum was assigned to C6'. This signal shows HSQC interactions with the quartet signal between 4.63 ppm and 4.71 ppm. This signal represents the non-equivalent protons on C6'. These protons (H6') show a HMBC interaction with a quaternary carbon signal at 138.4 ppm which was assigned to C7'. This signal in turn shows a HMBC interaction with a proton signal at 7.32 ppm which was assigned to H9'. The remaining proton signals on the benzene moiety were assigned by COSY interactions. All signals for this molecule were confirmed using other 2D techniques and are summarised in Table 1.

Ligand **2** has recently been used to catalyse the asymmetric Diels Alder reaction of 3-acryloyl-2-oxazolidinone with cyclopentadiene with moderate selectivity.[15] It has also been used to catalyse the alkylation of various aldehydes with diethylzinc with good selectivity.[10] The molecule differs from ligand **1** in that it has a methyl group on the *ortho* position of the pyridine ring. The DFT optimisation of this structure revealed two possible structures. These structures are shown in Figure 3.

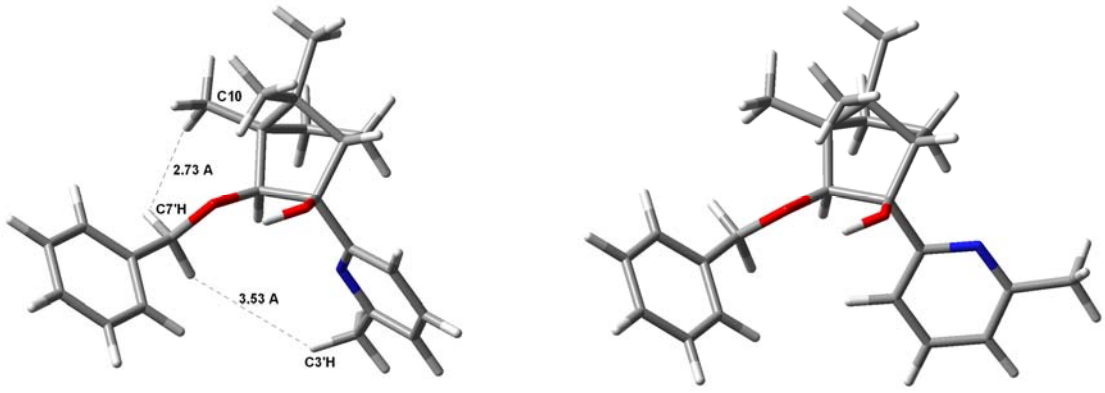


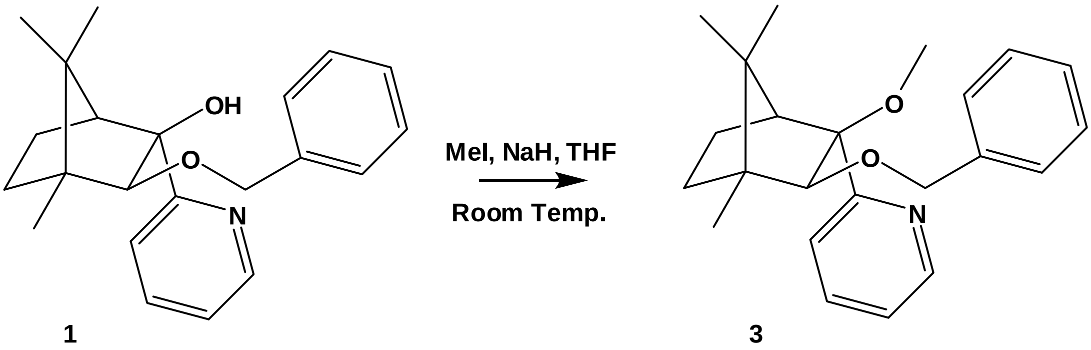
Figure 3: DFT optimised structures of ligand **2**, **2a** (left) and **2b** (right) [Cartesian coordinates available as supplementary material – B3LYP/6-31+g(d)].

We have previously observed conformational isomers with a similar ligand in solution. In that case the pyridyl moiety was not free to rotate and both conformations could be observed in the NMR spectrum.[10] In the present case we only observed a single conformer, but it was not immediately clear which of the two structures the free ligand was assuming in solution. The results of the optimisation indicate that the structure **2a** is the more stable of the two potential structures. The second structure, **2b**, has a minimum energy that is 4.31 kcal/mol higher in energy than **2a**. It therefore seems logical to assume that this molecule (**2b**) will not be the observed conformation in solution. The NMR elucidation was carried out in order to evaluate this conclusion.

The camphor skeleton protons were assigned as previously with clear NOESY correlations between the C8 protons with the $H5_{eq}$ and $H6_{eq}$. These and all other camphor skeleton assignment are summarised in Table 1. In order to determine the conformation of the pyridine ring, we looked for any through space correlations between the methyl group (C3') on the ring with any of the skeleton protons. Interestingly, a clear correlation between this group and the endo H6 proton on C6 was observed. Looking at the optimised structure it can be seen that this proton is marginally closer (3.8 Å) than the corresponding proton on C5 (3.9 Å). This appears to answer the question as to the conformation of the ring in space. It is believed that in this case the pyridyl moiety is free to rotate, hence only a single conformation is seen in solution. The other protons on the pyridine ring were assigned by considering the COSY correlations and are summarised in Table 1.

The protons of the benzyl group were assigned as previously. A clear NOESY interaction between the methylene protons H7' and the protons on C10 can be seen. A weak through space interaction between these protons (H7') and the protons on C3' (3.53Å) can also be seen hence confirming the orientation of the pyridyl group. The remaining protons on the benzene ring were assigned by looking at the COSY correlations. All assignments on the ligand were confirmed by HMBC and HSQC spectra and are summarised in Table 1.

Ligand **3** is a derivative of ligand **1**. The molecule comprises of the basic structure as seen for ligand **1** with the exception of the methyl ether on C3. This was obtained by simply reacting ligand **1** with methyl iodide as shown in Scheme 2.



Scheme 2: Synthesis of ligand **3**.

The optimised structure of this ligand can be seen in Figure 4.

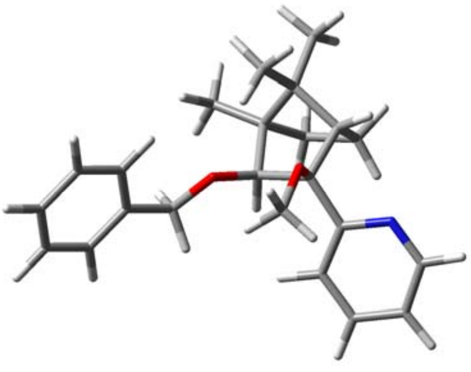
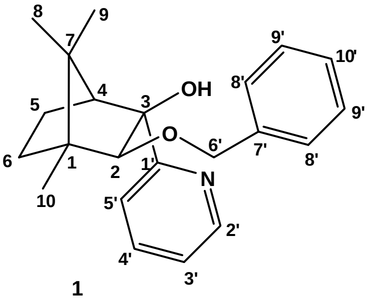


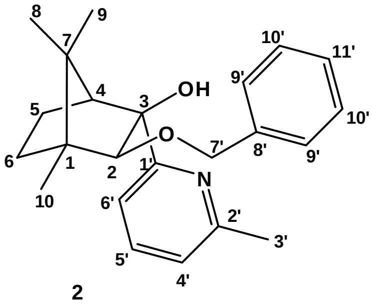
Figure 4: DFT optimised structure ligand **3** [Cartesian coordinates available as supplementary material – B3LYP/6-31+g(d)].

The assignment of all signals was carried out as described previously and are summarised in Table 1.

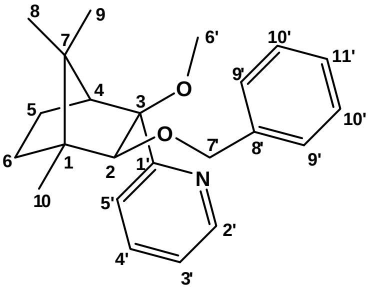
Table 1: NMR assignments for ligands **1-3**.



1



2



3

	Ligand 1			**Ligand 2**			**Ligand 3**		
Atom No.	**^{1}H (ppm)^{a,b}**	***J* (Hz)**	**^{13}C (ppm)^{a,b}**	**^{1}H (ppm)^{a,b}**	***J* (Hz)**	**^{13}C (ppm)^{a,b}**	**^{1}H (ppm)^{a,b}**	***J* (Hz)**	**^{13}C (ppm)^{a,b}**
1	-		50.4	-		50.3	-		51.2
2	4.83		88.0	4.79		88.0	4.92		88.1
3	-		83.5	-		83.5	-		91.3
4	2.04		56.3	2.04		55.9	2.05		56.9
5_{ax}	1.43		22.4	1.42		22.4	1.39		22.0
5_{eq}	0.59		-	0.66		-	0.39		-
6_{ax}	1.24		33.1	1.19		33.2	1.12		32.6
6_{eq}	1.45		-	1.44		-	1.40		-
7	-		49.9	-		49.8	-		49.6
8	0.89		22.2	0.88		22.1	0.86		21.6
9	1.34		22.5	1.33		22.5	1.49		22.4
10	1.03		12.0	0.99		12.0	1.02		12.1
1’	-		164.8	-		163.8	-		162.6
2’	8.49		147.0	-		155.7	8.59		147.5
3’	7.16		121.8	2.55		24.6	7.19		121.9
4’	7.69		136.4	7.01		120.8	7.70		136.3
5’	7.57		122.6	7.57		136.5	7.48		123.4
6’	4.63-4.71	11.6	74.4	7.31		119.0	2.99		54.5
7’	-		138.4	4.65-4.72	11.8	74.0	4.75-4.84	11.8	74.3
8’	7.34		128.3	-		138.5	-		139.7
9’	7.31		127.7	7.30		127.9	7.43		128.1
10’	7.27		127.6	7.33		128.2	7.31		127.0
11’	-	-	-	7.28		127.5	7.21		126.9
OH	3.85	-	-	3.88	-	-	-	-	-

[a] 600MHz for ^{1}H and 150MHz for ^{13}C
[b] Solvent $CDCl_3$

Ligand **4** is another example with a functionalised pyridine ring. In this case the methyl group is in the *para* position of the pyridine ring. The optimised structure is shown in Figure 5.

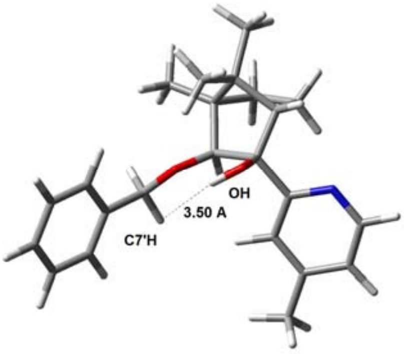


Figure 5: DFT optimised structure of ligand **4** [Cartesian coordinates available as supplementary material – B3LYP/6-31+g(d)].

On investigation of the various spectra, it was once again noted that the through space interactions between the protons on C5 and C6 with the protons on C8. NOESY interactions between H2 and $H6_{ax}$ and H10 were also observed. Other through space interactions include an interesting correlation between the OH and the methyl group on the pyridine ring (C5') as well as with the methylene protons (H7') of the benzyl group. The assignments of the signals were confirmed by other 2D techniques and are summarised in Table 2.

Ligand **5** is different from the other ligands in that it is an aniline derivative instead of a pyridine derivative. The ligand was prepared in the same way as the other ligands. This ligand was crystalline and a crystal suitable for single crystal X-ray analysis was obtained (Figure 6).[11] As a result of this, no DFT optimisation was carried out for this molecule.

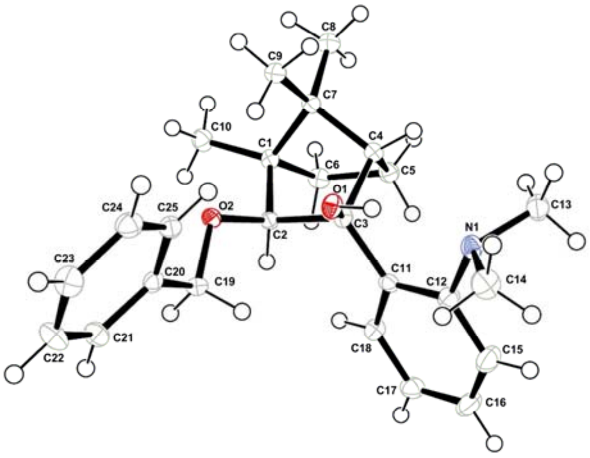
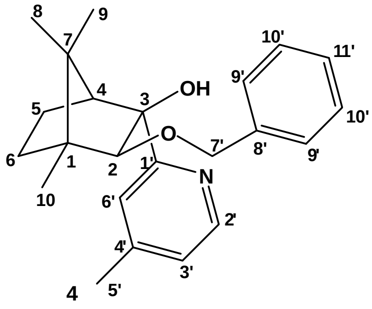


Figure 6: ORTEP diagram of ligand **5** showing displacement ellipsoids at 50% probability level (numbering the same as in the CIF file – see supplementary information).

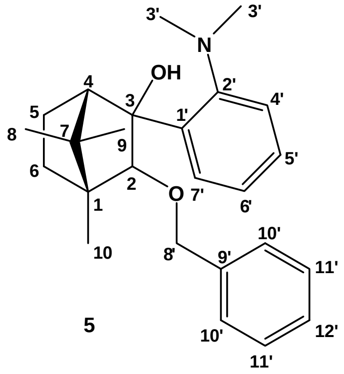
The NMR elucidation of the aromatic part of the molecule proved to be challenging. The signals for the camphor skeleton were assigned as before and are summarised in Table 2. The methyl groups 3' attached to the aniline nitrogen atom appear in the ^1H spectrum as a broad singlet at 2.72 ppm integrating to six protons. Unusually, there is no corresponding carbon signal for these groups. We cannot explain this phenomenon. The signal for the OH group is also missing. This might be explained by the fact that the hydroxyl group is involved in hydrogen bonding with the nitrogen on the aniline moiety. The remaining proton signals on the aniline could not be assigned unambiguously due to the complex nature of the multiplet in the aromatic region. Consequently, the aromatic signals of the benzyl group were also not assigned as they too fell into this multiplet region.

The signal for the benzyl methylene carbon gave rise to an interesting signal. The two protons are diastereotopic, showing an AB splitting pattern. Looking at the X-ray structure one would expect the proton facing towards the aniline moiety to experience a much larger deshielding effect from the nitrogen and oxygen atoms than the proton facing away. Thus the proton facing toward would result in a signal further downfield than the other. Consequently it was assigned to the signal at 4.82 ppm while the other was assigned to the signal at 4.32 ppm. All results are summarised in Table 2.

Table 2: NMR assignments for ligands **4** and **5**.



4



5

	Ligand 4			**Ligand 5**		
No.	**^{1}H (ppm)**	***J* (Hz)**	**^{13}C (ppm)**	**^{1}H (ppm)**	***J* (Hz)**	**^{13}C (ppm)**
1	-		50.4	-		49.9
2	4.84		87.9	4.08		89.2
3	-		83.4	-		83.6
4	2.04		56.4	2.01		58.3
5_{ax}	1.43		22.4	1.44		22.7
5_{eq}	0.59		-	0.67		-
6_{ax}	1.25		33.1	1.11		33.6
6_{eq}	1.44		-	1.50		-
7	-		49.8	-		49.8
8	0.89		22.2	0.89		22.4
9	1.33		22.5	1.54		22.8
10	1.04		12.0	1.04		12.5
1’	-		164.6	-		142.7
2’	8.35		146.8	-		152
3’	6.99		122.9	2.72		c
4’	-		147.4	d		d
5’	2.37		21.2	d		d
6’	7.40		123.2	d		d
7’	4.63-4.70	11.6	74.4	d		d
8’	-		138.4	4.32 and 4.82	12.5	72.6
9’	7.35		128.3	-		139.8
10’	7.33		127.7	d		d
11’	7.28		127.6	d		
12’	-	-	-	d		
OH	3.84			c		-

[a] 600MHz for ^{1}H and 150MHz for ^{13}C.

[b] Solvent $CDCl_3$.

[c] No signal present.

[d] Signal not assigned due to overlapping.

CONCLUSION

In summary, the complete elucidation of ligands **1-4** was successfully carried out. The elucidation of ligand **5** was partially carried out but due to major overlapping of the aromatic proton signals the complete assignment could not be achieved. This problem was negated by the fact that an X-ray structure of the molecule was obtained thus revealing the orientation of the donor groups in space. The orientation of the donor groups of the remaining ligands were determined from high level DFT calculations and confirmed by the elucidations.

SUPPLEMENTARY MATERIAL

All NMR spectra are available as supplementary material. CCDC 721782 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. The optimized coordinates for the DFT calculated structures are available as supplementary materials.

EXPERIMENTAL

All ^{1}H, ^{13}C and 2D NMR spectra were recorded on a Bruker AVANCE III-600MHz spectrometer using approximately 50 mg of sample per 0.5 ml of solvent.

The synthetic details for the all ligands have been previously reported.[10, 11]

Details of the DFT-optimised structures 1-4

The compounds were optimized by using Gaussian 03 utilizing density functional theory (DFT) at the B3LYP level of theory and the 6–31 + g(d) basis set. Diffuse functions are typically used for more accurate descriptions where π-electron delocalization is involved, while polarization functions remove some limitations of the basis set by expansion of the virtual space. Solvation effects were not considered in order to simplify the model. The second-derivative analytical vibrational frequency calculation utilizing the same methodology employed in the location of stationary points showed no negative frequencies, indicating that the structures were minimum energy structures. Cartesian coordinates of the optimized structures for **1-4** are available as supplementary material.

ACKNOWLEDGEMENTS

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14. H. G. Kruger and R. Ramdhani, *S. Afr. J. Chem.*, 2006, **59**, 71.
15. G. A. Boyle, T. Govender, H. G. Kruger, G. E. M. Maguire and T. Naicker, *S. Afr. J. Chem.*, 2009c, **Accepted for publication**.

CHAPTER 6
SUMMARY AND CONCLUSIONS

6.1 SUMMARY

Chiral monoterpenes such as camphor have seen wide use in the development of asymmetric catalysts with varying degrees of success. They afford a simple, inexpensive and inherently chiral scaffold around which to build a catalyst. The synthesis of pyridyl *N*-donor ligands derived from camphor has been extensively studied. Several of these ligands have proven to be successful chiral catalysts. All previous camphor derived pyridyl *N*-donor ligands have fallen into one of two categories. The first is where the donor groups are pendant at the C2 position of the camphor skeleton, the second is where one donor group is pendant at C2 with the other at C3. As such, an opportunity to expand the study into these types of compounds by synthesising the first examples of C3 pendant molecules was seized and the synthesis of a series of novel molecules was achieved with absolute *stereo* and *regio*-control.

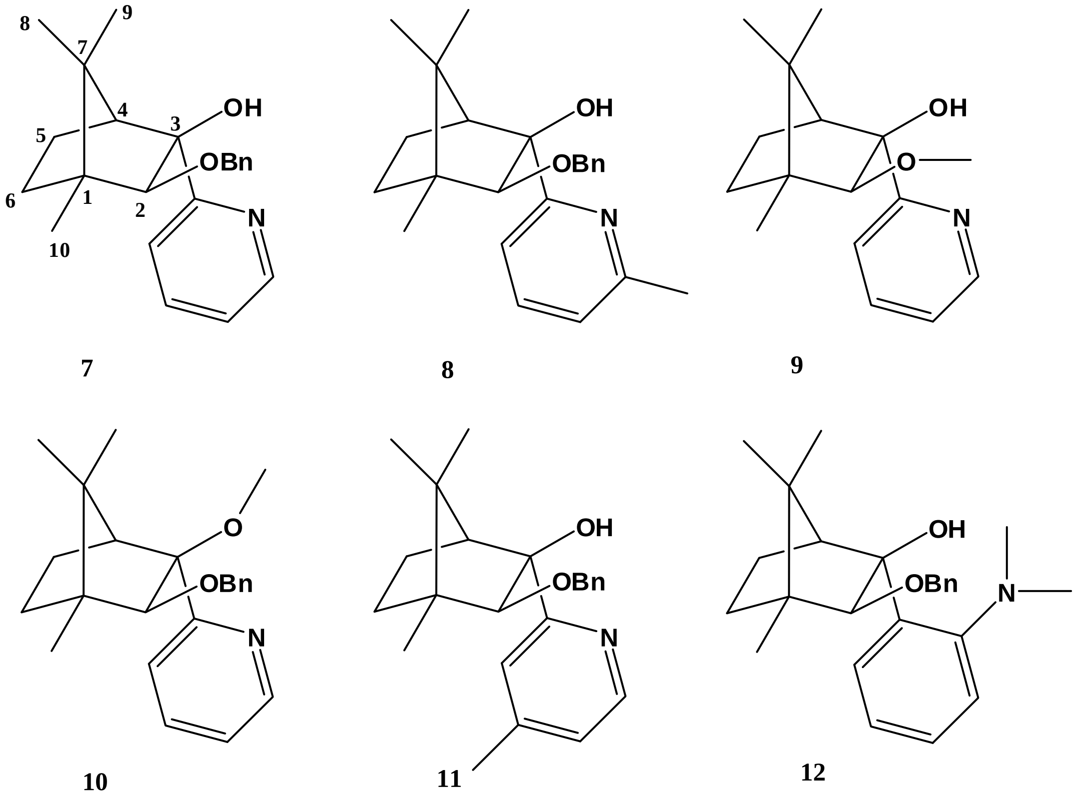
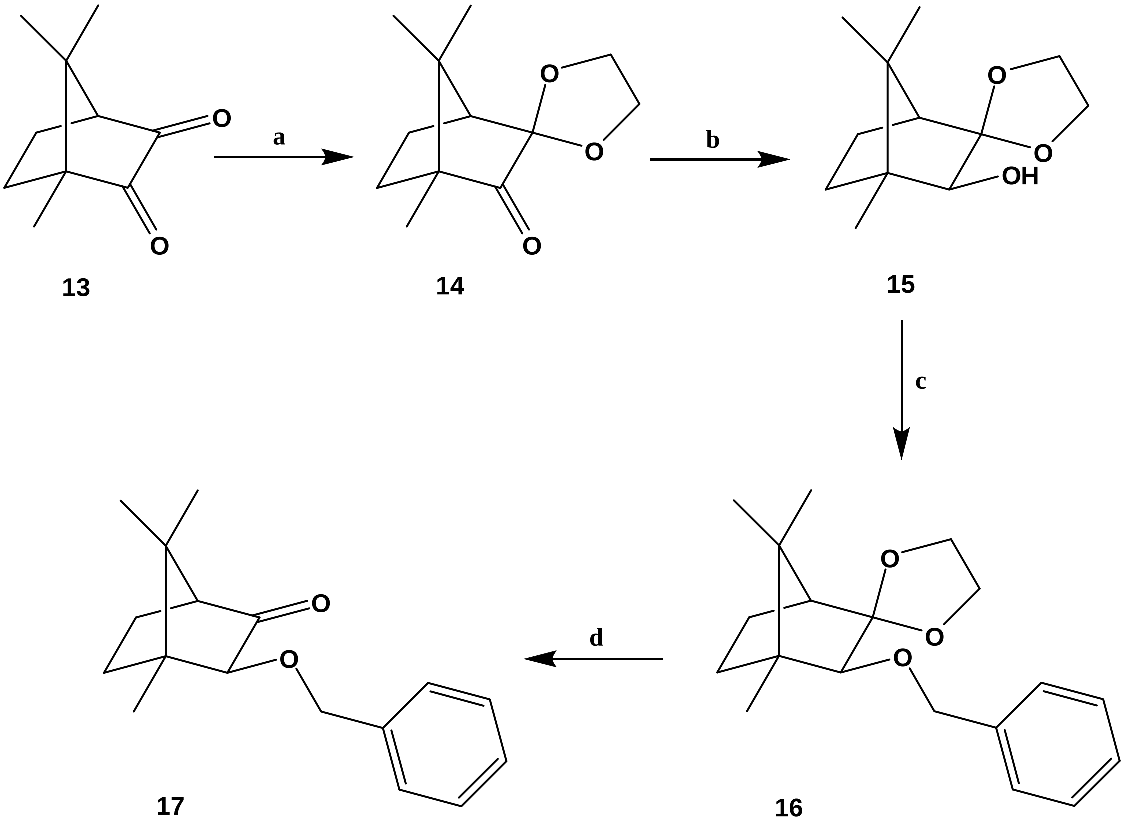


Figure 7: Synthesised ligands.

Most of the ligands shown in Figure 7 were synthesised in six steps (seven steps for ligand **10**) using *R*-(+)-camphor as the starting material. Two alternative methods for the synthesis were investigated with the second method (Method B, Scheme 3) proving to be superior.



Scheme 3: Successful synthetic route to final ligand precursor **17**. Key: a) ethylene glycol, PTSA, benzene, reflux 12 hrs, 65 % b) $NaBH_4$, diethyl ether/MeOH (1:1), RT 2hrs, quant. c) benzyl bromide, NaH, dry THF, 12 hrs, 81 % d) conc. HCl/ THF (1:3), 2 hrs, 80 %.

Several difficulties with regards to regioisomers and diastereomers were overcome in establishing the procedure for the synthesis of the ligands. The method adopted to synthesise the molecules made use of a rarely cited procedure which allows for the isolation of the regioisomerically pure C3-protected ketal **14**. The single crystal X-ray structure of this compound (Figure 8) was obtained and confirmed the regioisomeric purity of the compound.

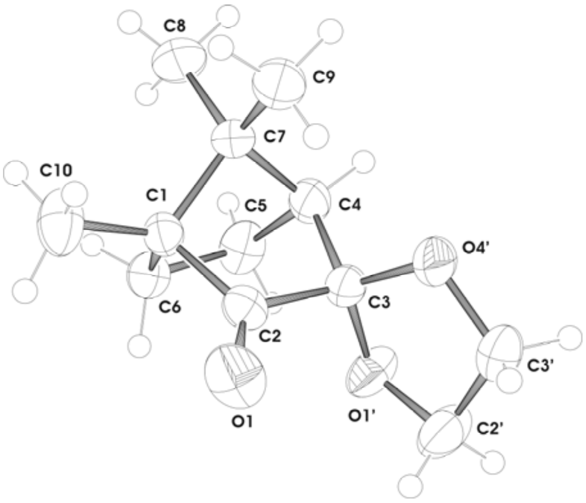


Figure 8: ORTEP diagram of compound **14**.

This provided the breakthrough that was required in order to eliminate any *regio*-isomer difficulties and allowed total *regio*-control for the remaining synthetic steps. The diastereomers that resulted after the reduction of the ketal-ketone **14** were addressed in the steps which followed. On isolation of the subsequent products it was discovered that the required *exo*-product eluted from the chromatography column ahead of the *endo*-product and hence this product could be obtained in a diastereomerically pure state using this standard laboratory technique. The final ligands were obtained in yields of between 45-60 % for the amino alcohol ligands (**7-9**, **11** and **12**) and essentially quantitative yield for the di-ether ligand **10**. The aniline derivative **12** was obtained as a crystalline solid which allowed for single crystal X-ray analysis (Figure 9).

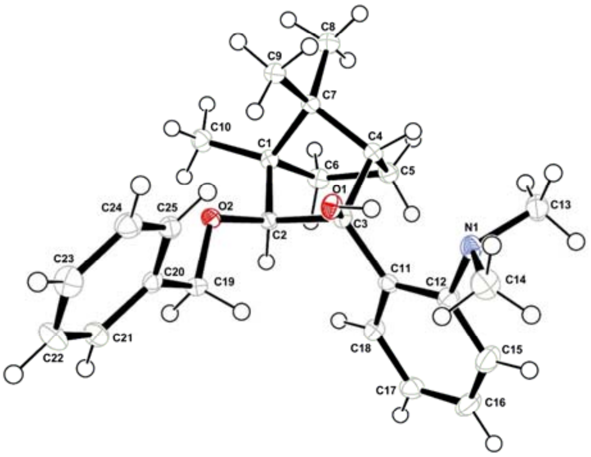
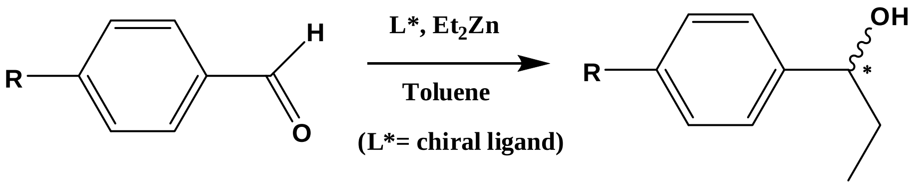


Figure 9: ORTEP diagram of ligand **12**.

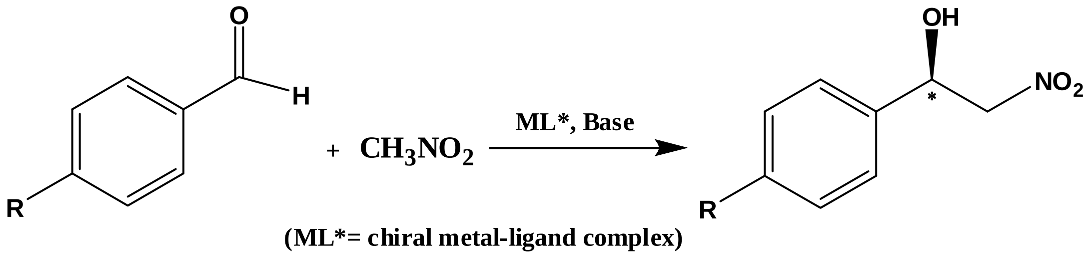
All the compounds were applied as chiral catalysts in a series of different reactions. The first of these reactions was the alkylation of various aldehydes using diethylzinc (Scheme 4).



Scheme 4: Alkylation of aldehydes using diethylzinc.

This reaction has been investigated with a very wide variety of different chiral catalysts. All previous camphor derived pyridyl alcohol ligands have been applied in the catalysis of this reaction. The previously reported C2 analogue of ligand **7** returned only moderate enantioselectivity when applied as a catalyst in this reaction. In order to obtain an idea of the efficacy of our C3 analogues it was necessary to compare them directly in this application. The results obtained from the screening of the molecules as catalyst in this reaction were comparable with most previous camphor derived pyridyl analogues. Ligand **7** proved to be significantly better than its closest C2 analogue in the alkylation of benzaldehyde (68 % *ee* compared to 44 % *ee* for C2 analogue). The most successful ligand, **8**, catalysed the alkylation of benzaldehyde with 72 % *ee*. This ligand was further screened against a series of other functionalised aromatic aldehydes to yield a highest enantioselectivity of 85 % when *p*-anisaldehyde was used as the substrate.

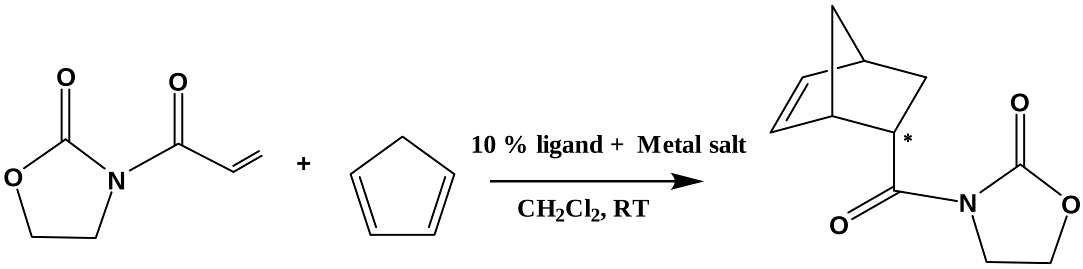
The next reaction that was investigated was the asymmetric Henry reaction (Scheme 5).



Scheme 5: Asymmetric Henry reaction.

This reaction is one of the classic named reactions. It has been widely used to generate β-nitroalcohols by coupling a nucleophile generated from a nitroalkane with a carbonyl electrophile. These β-nitroalcohols are very versatile intermediates commonly used in the synthesis of a variety of biologically active compounds. The reaction has seen much investigation with a number of different chiral catalysts. Camphor derived catalysts have not been widely applied in the catalysis of this reaction. Only a few previous camphor examples have been applied, these proving highly successful. Our ligands were applied as catalysts in the reaction of *p*-nitrobenzaldehyde with nitromethane using copper (II) as the metal ion. The results obtained showed that ligand **7** was the most successful compound. A variety of different conditions were investigated in which the solvent, base, substrate and metal counterion were varied. Ultimately, the best result obtained was 56 % enantioselectivity with *p*-nitrobenzaldehyde as the substrate in ethanol with triethylamine as the base.

The final reaction investigate was the asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone with cyclopentadiene (Scheme 6).



Scheme 6: Asymmetric Diels-Alder reaction of 3-acryloyl-2-oxazolidinone with cyclopentadiene.

This reaction has not seen camphor derived pyridyl alcohol derivatives used as catalysts. The ligands were screened and once again ligand **8** emerged as the most successful agent. Various conditions were varied including the metal ion and the counterion. It was discovered that copper (II) triflate was the best metal for catalysing the reaction. Ultimately however, the selectivity obtained proved to be low at 43 % *ee*. A series of computations were carried out in order to investigate the possible reason for such poor selectivity. From these calculations it could be inferred that probably the steric bulk of the ligand was insufficient for significant chiral induction (Figure 10).

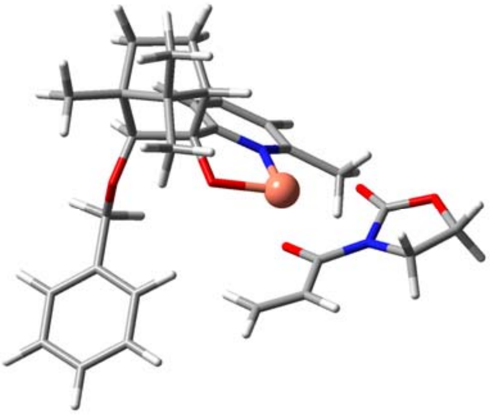


Figure 10: Computed structure of the Diels-Alder intermediate- ONIUM [UPBEPBE/genecp: B3LYP: UFF] (Cartesian Coordinates available as supplementary information).

The complete NMR elucidation of a number of the ligands was carried out in order to confirm the structure of the ligands. The structures of each of the ligands, with the exception of ligand **12** for which a single crystal X-ray structure was obtained, were optimised using high level DFT calculations. These optimisations were carried out in order to assist with the identification of potential through-space correlations in the 2D NMR spectra. The expected correlations were observed in the spectra.

6.2 CONCLUSIONS

This study opened a new route to C3 functionalised camphor ligands. A total of twelve novel compounds were synthesised. Six of these chiral ligands were used in various chiral model reactions with moderate success. Computational studies of the ligand attached to metal ions used in the chiral reaction suggest that further investigation of C3 pendant ligands is warranted. The use of a more extensive computational model (including transition states) is required for the logical design of any future chiral ligands. This approach would enable the ligands to be designed in such a way that they could be more reaction specific.

The regioselective synthesis carried out could potentially be applied to the development of a variety of other C3 ligands. Potentially, any ligand derived from camphor could be reinvented at the C3 position and evaluated as a chiral catalyst. It is therefore likely that this study could lead to the design of many more chiral camphor derived ligands.

APPENDICES

Appendix 1- Supporting information for Paper 1-NMR Spectra

Appendix 2- Suppporting information for Paper 4-NMR Spectra

CD- This contains all Cartesian Coordinates for the calculations carried out for Paper 3 and Paper 4. Also, all CIF files for the X-ray structures can be found in the respective directories on the disk.

APPENDIX 1
SUPPLEMENTARY INFORMATION
SYNTHESIS OF NOVEL 3-HYDROXY-3-PYRIDYLCAMPHOR DERIVATIVES

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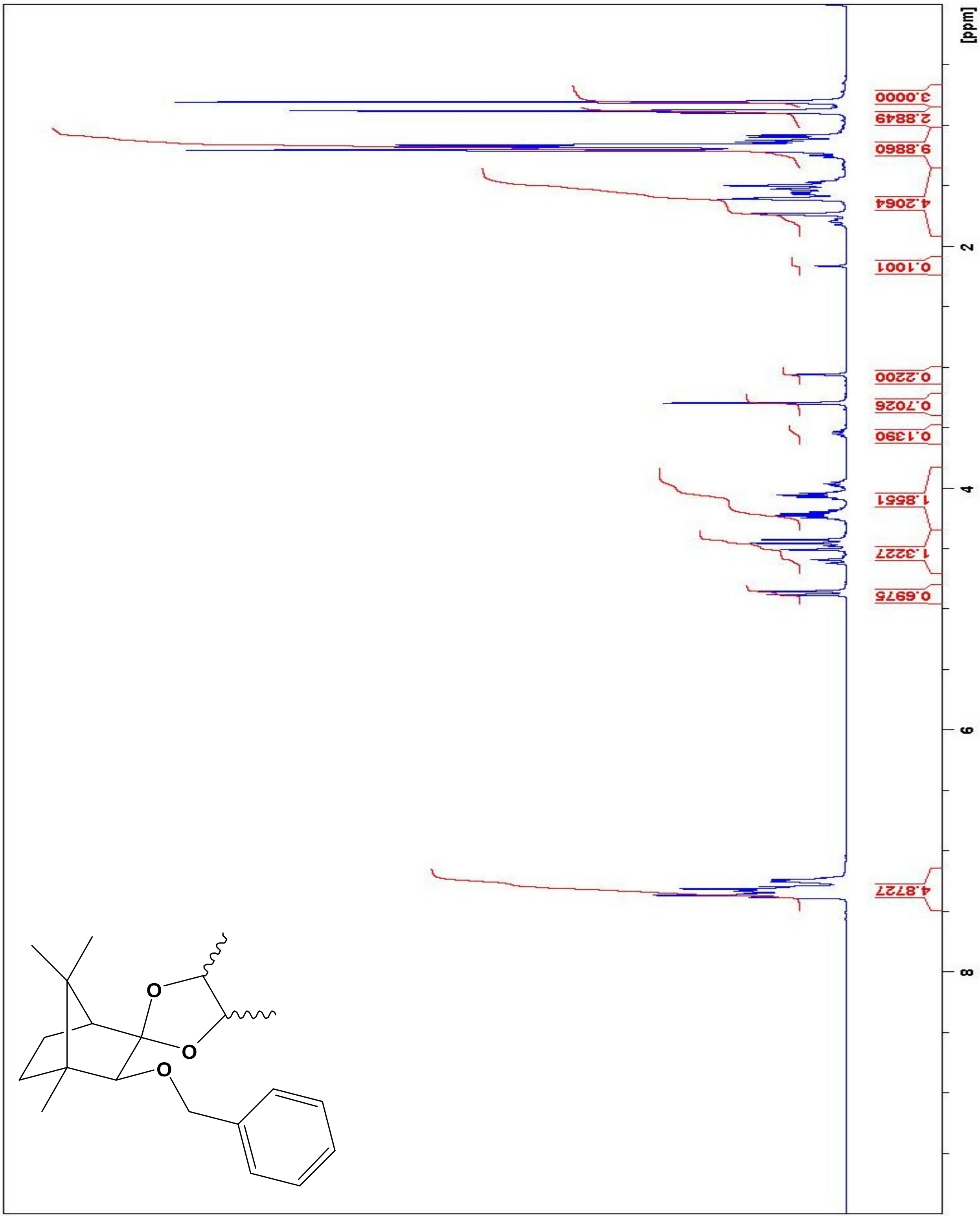
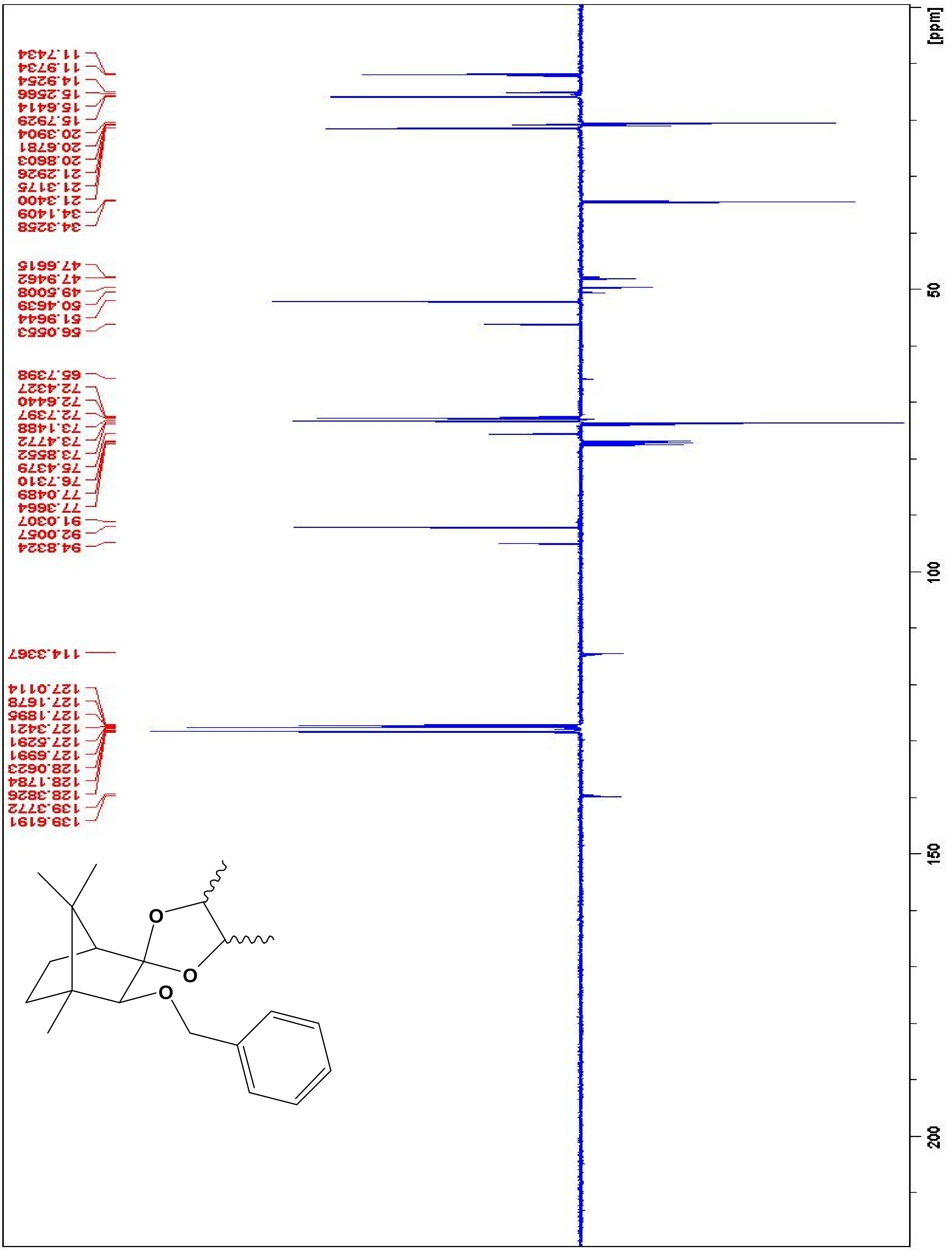
SECTION 1: ^{1}H AND ^{13}C APT NMR SPECTRA OF NOVEL COMPOUNDS



^{1}H NMR Spectrum (400 MHz) of Compound **11**



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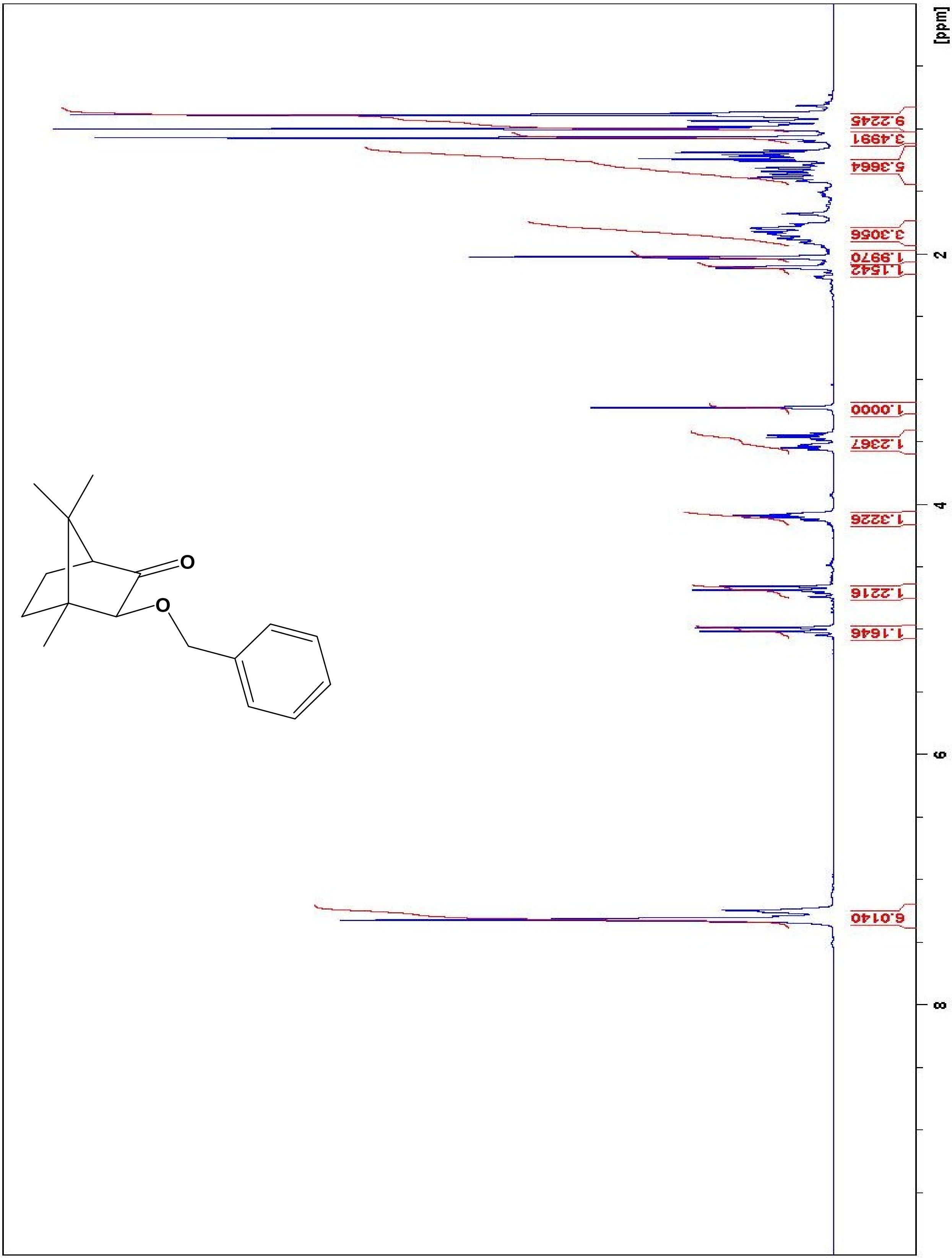

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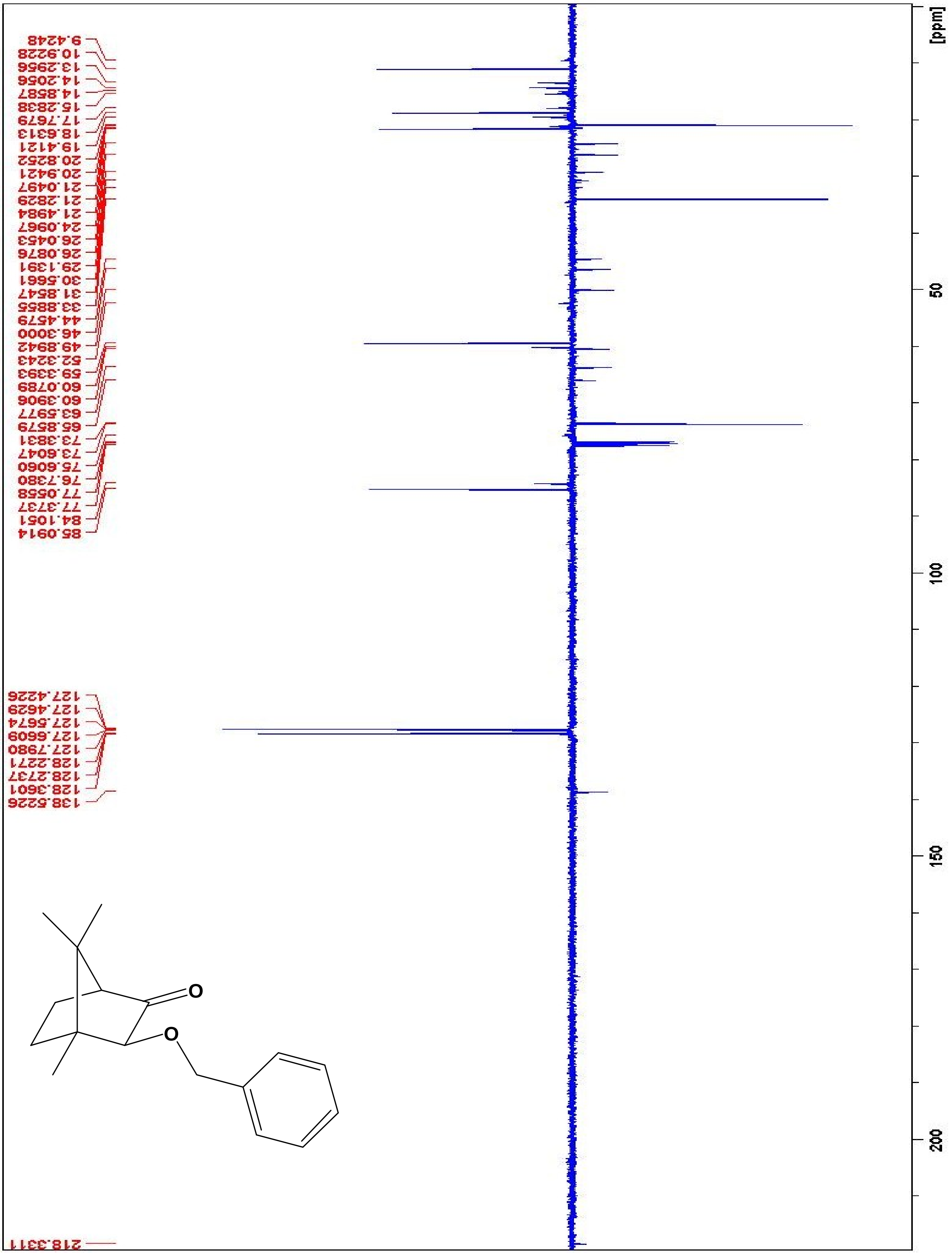

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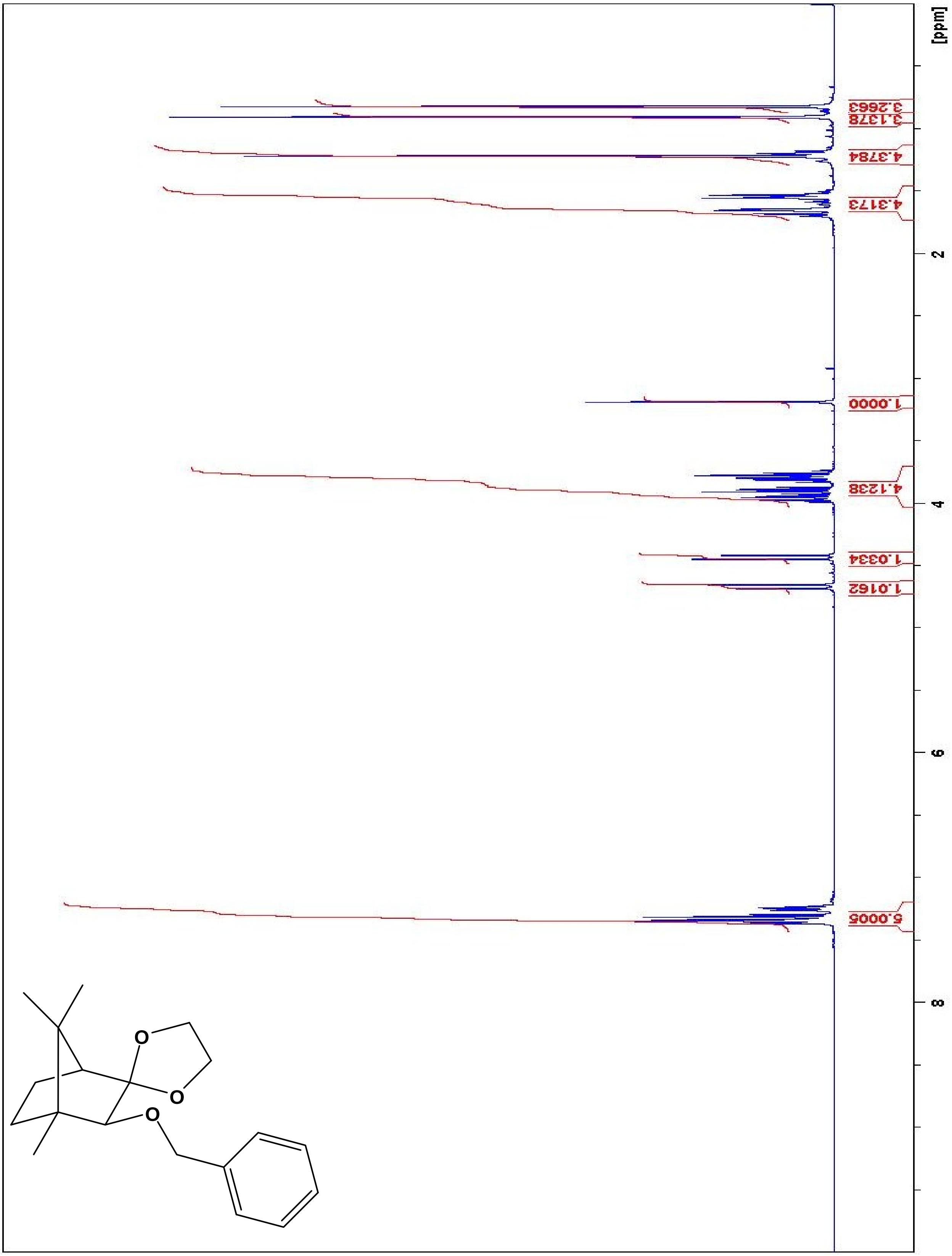

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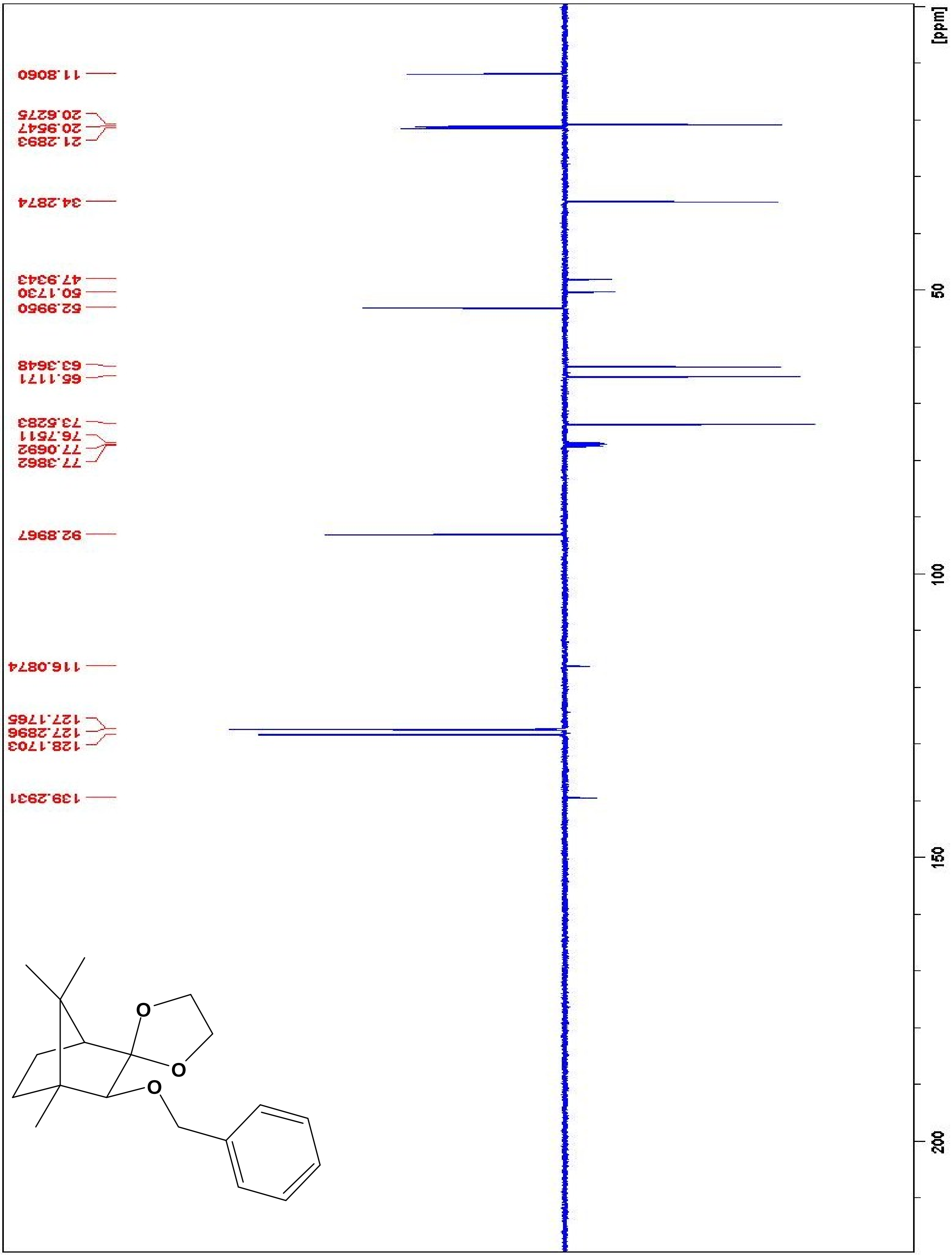

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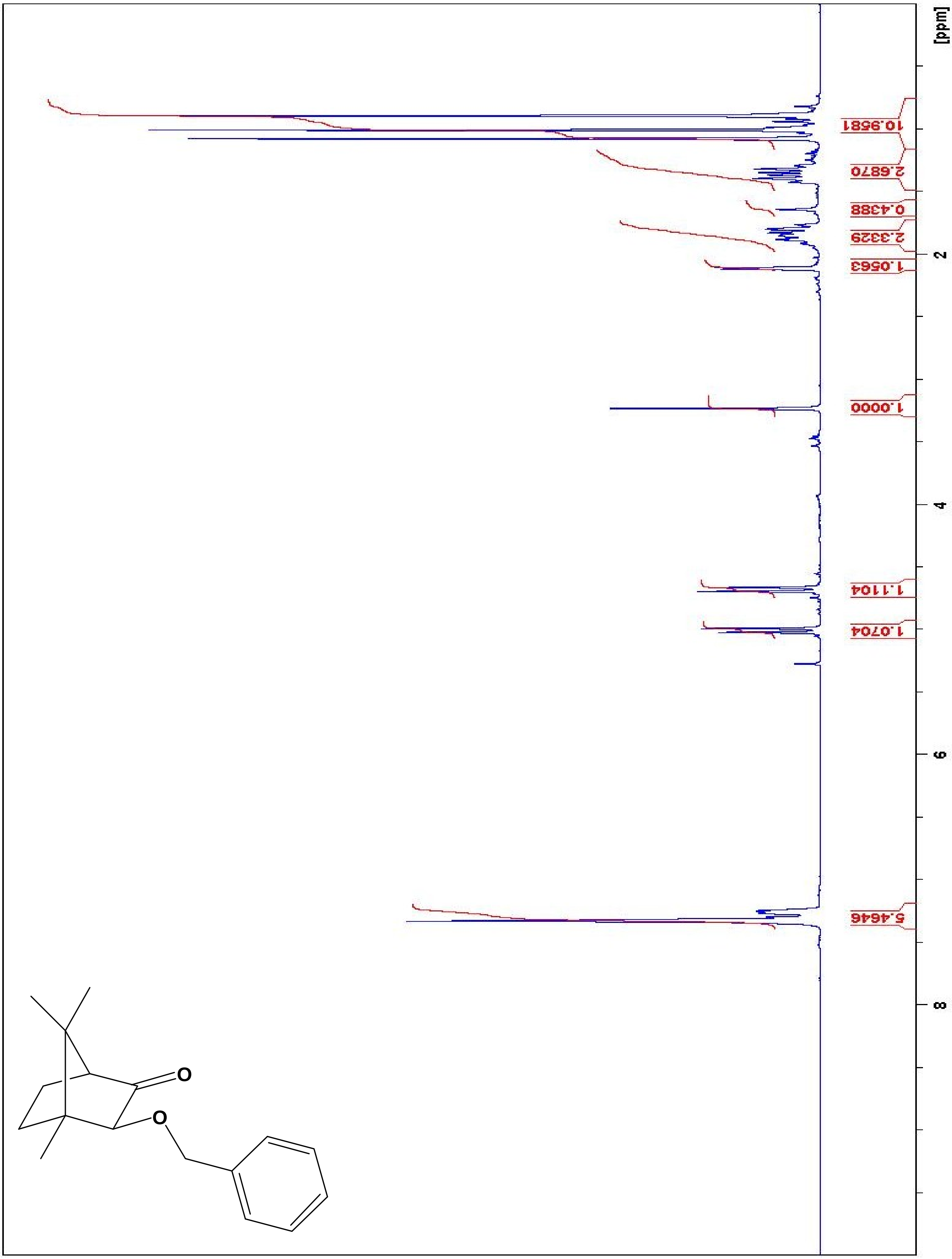

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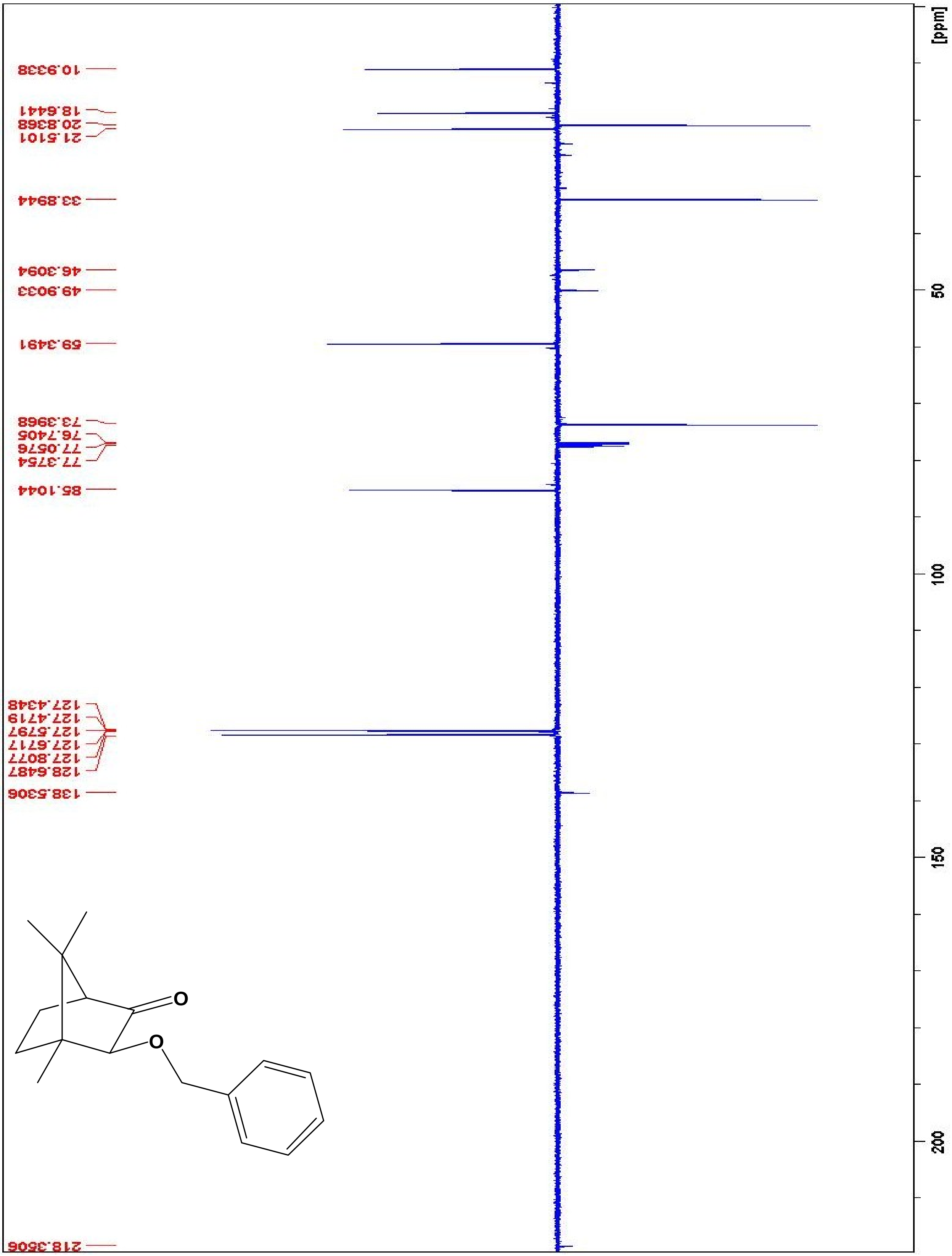

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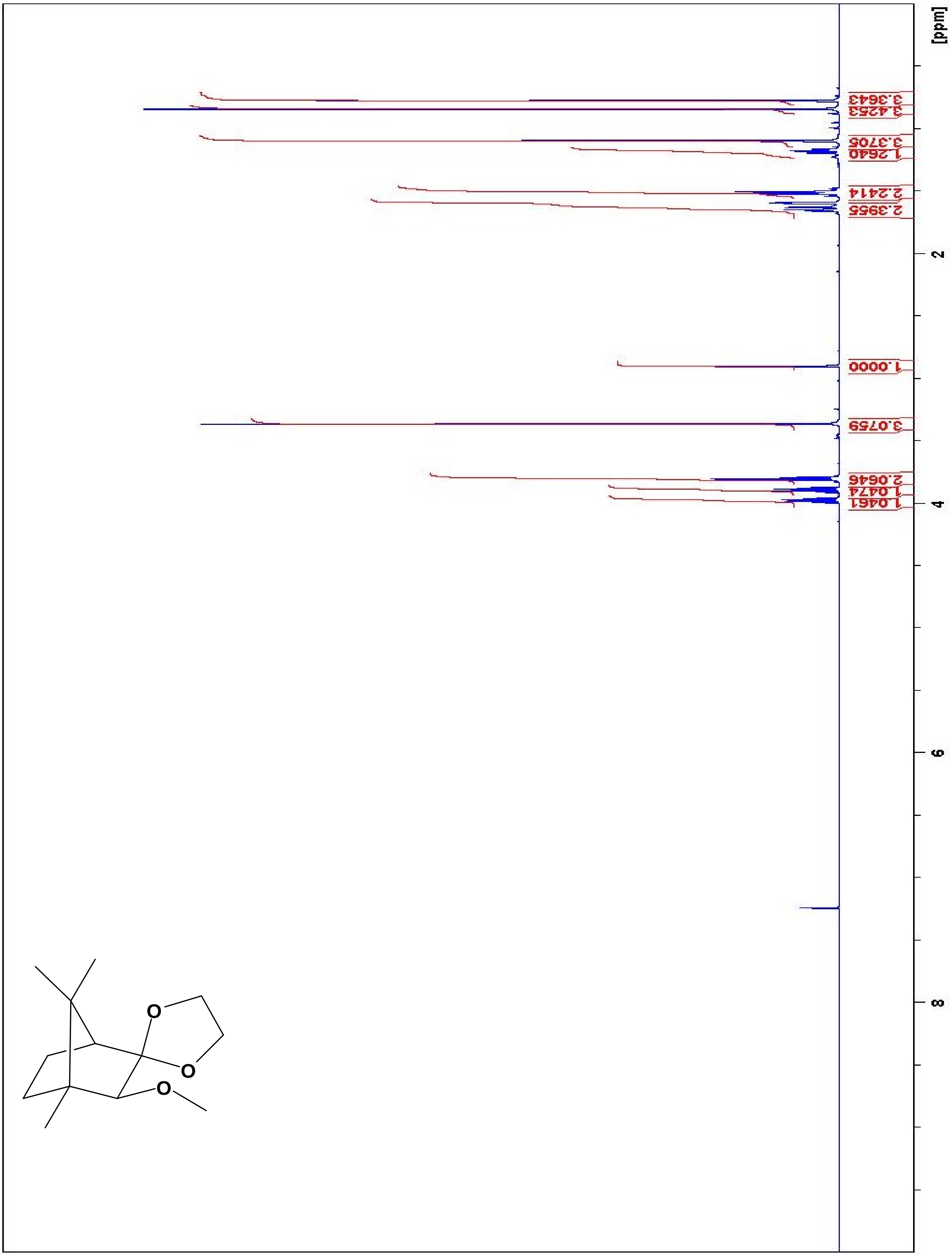

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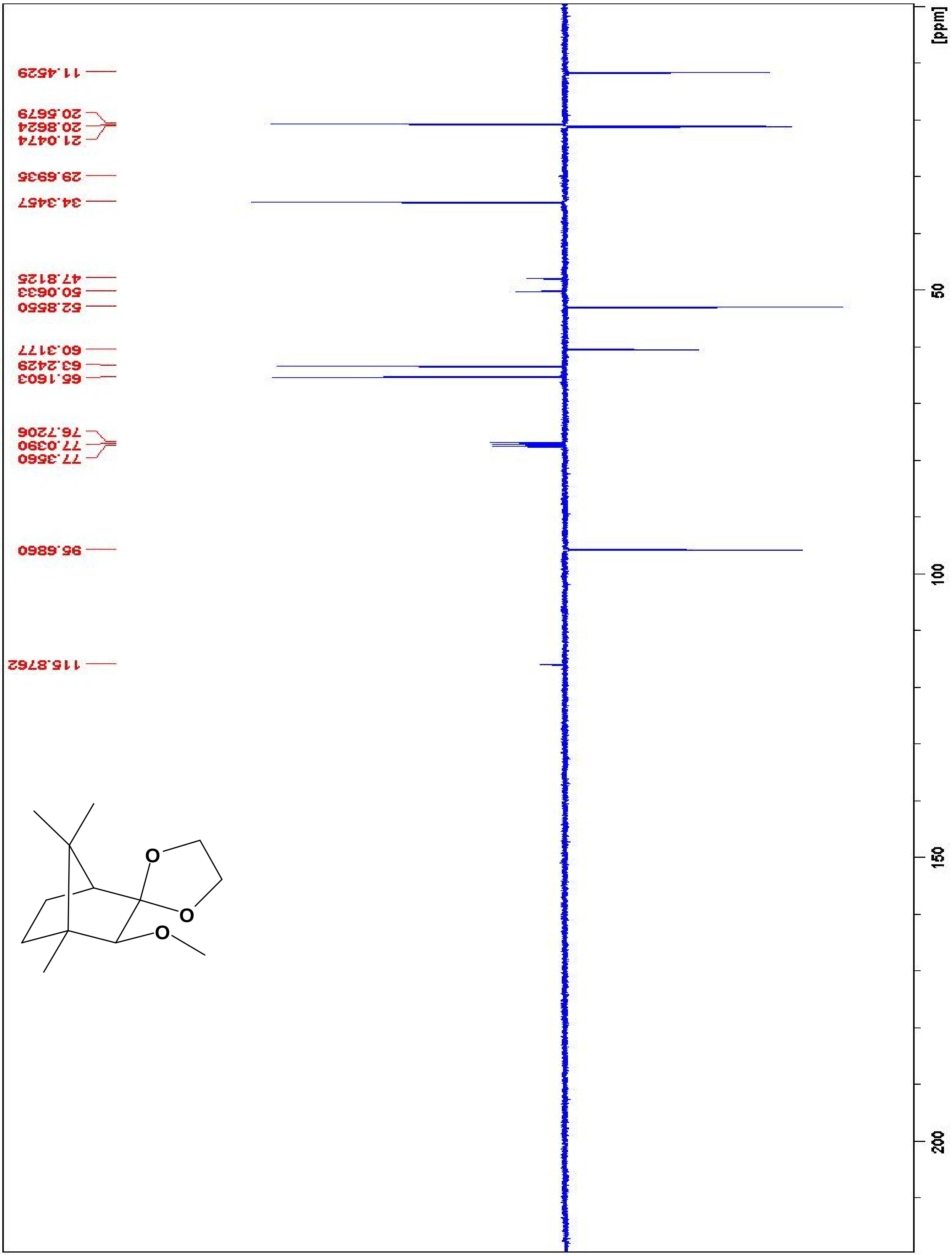

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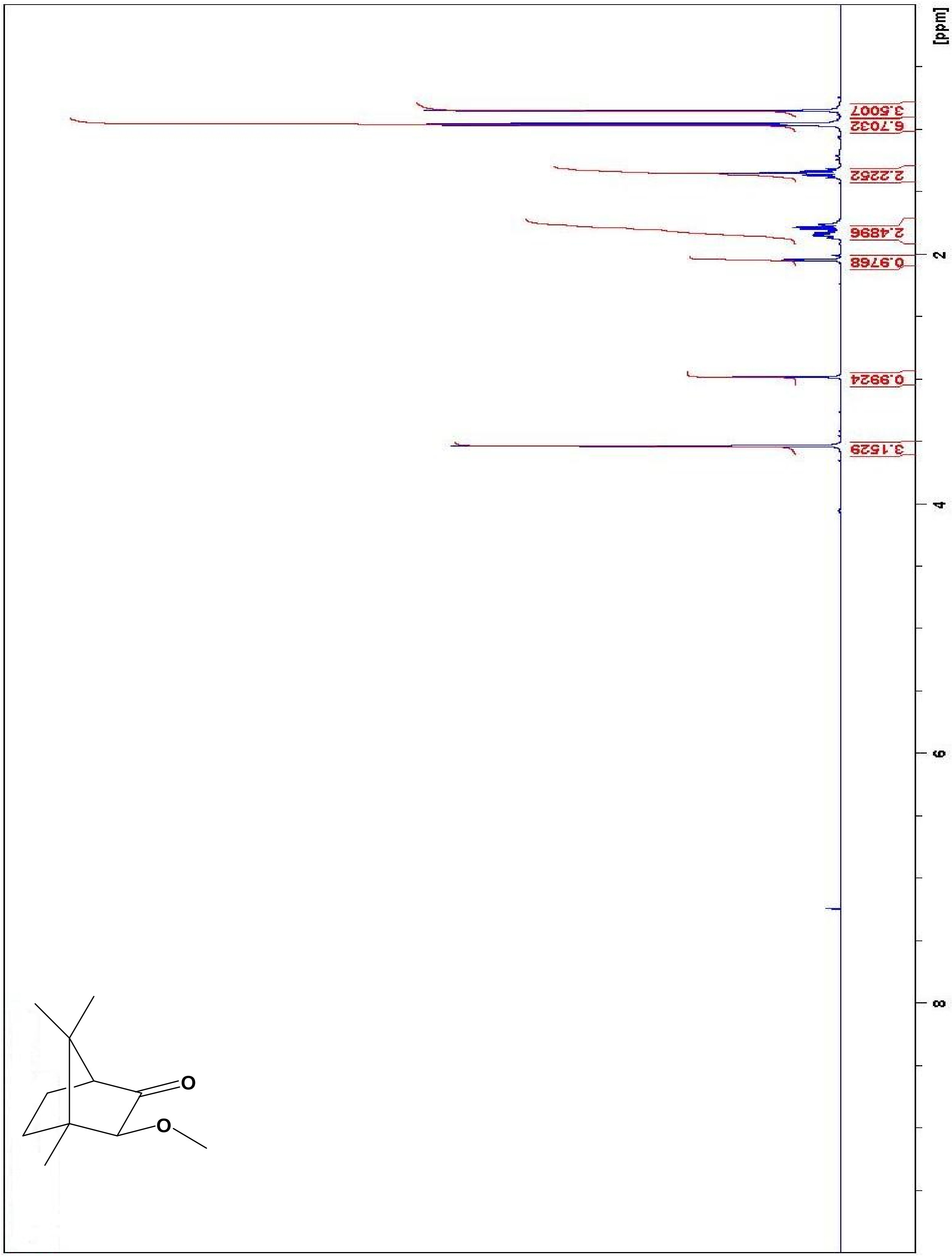

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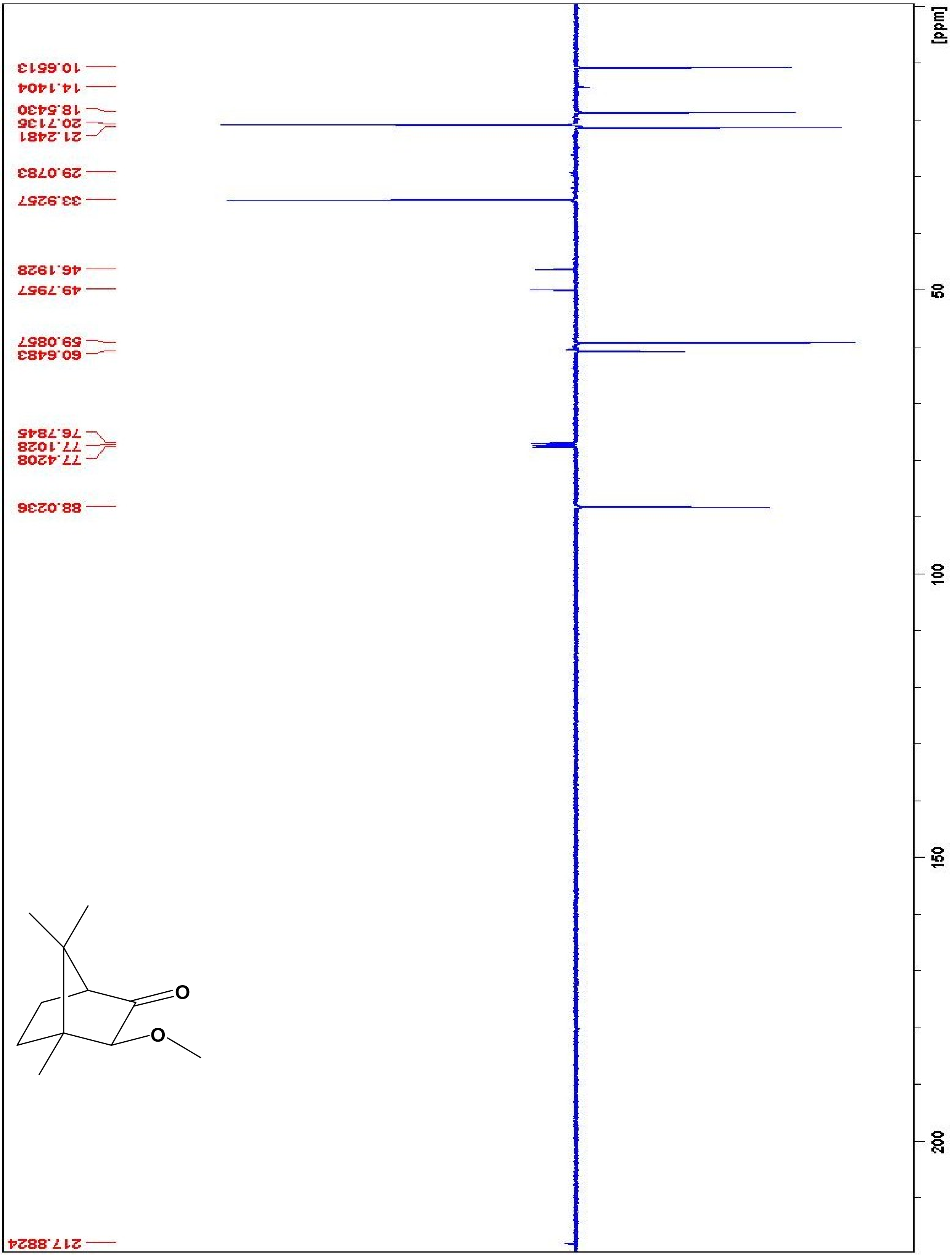

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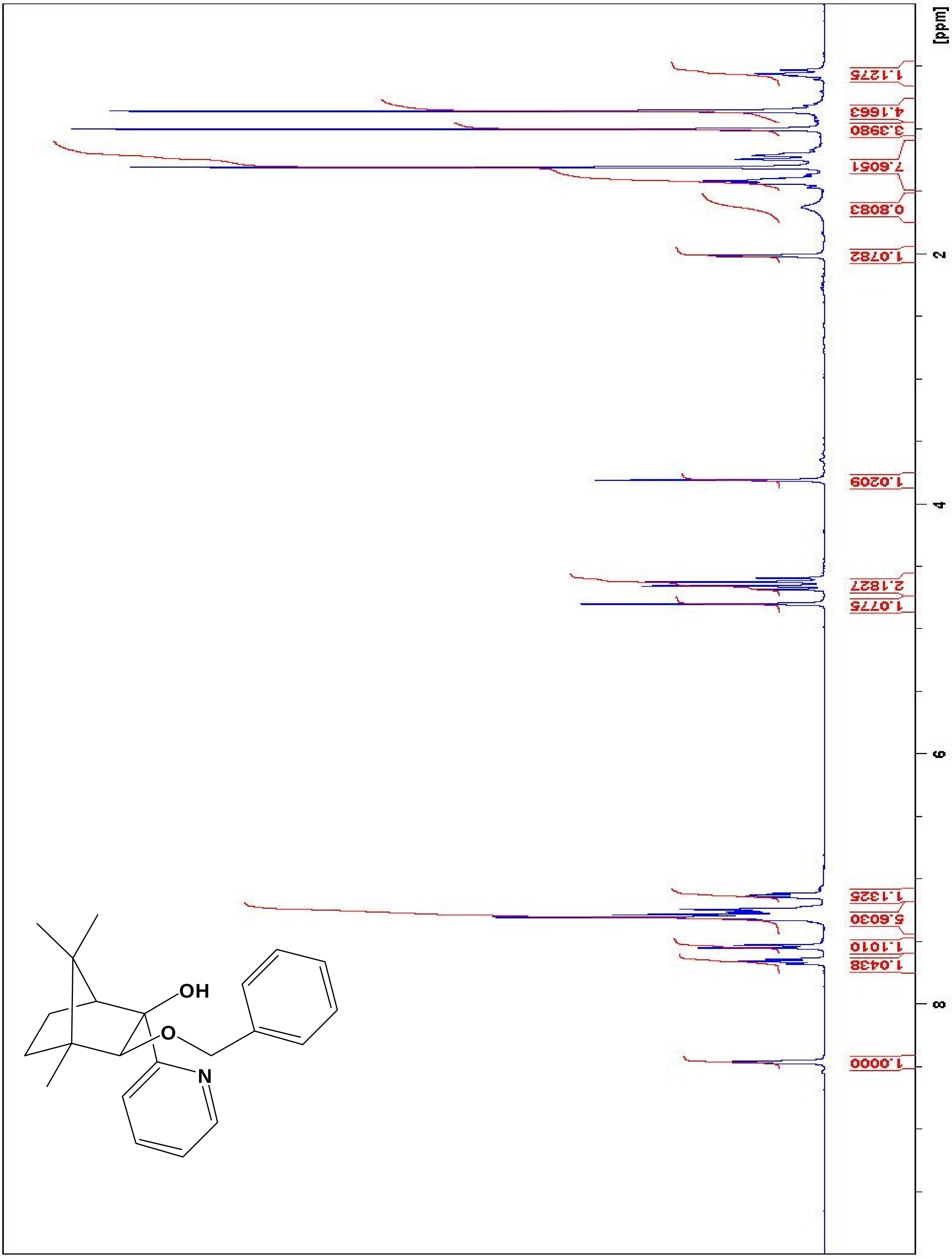

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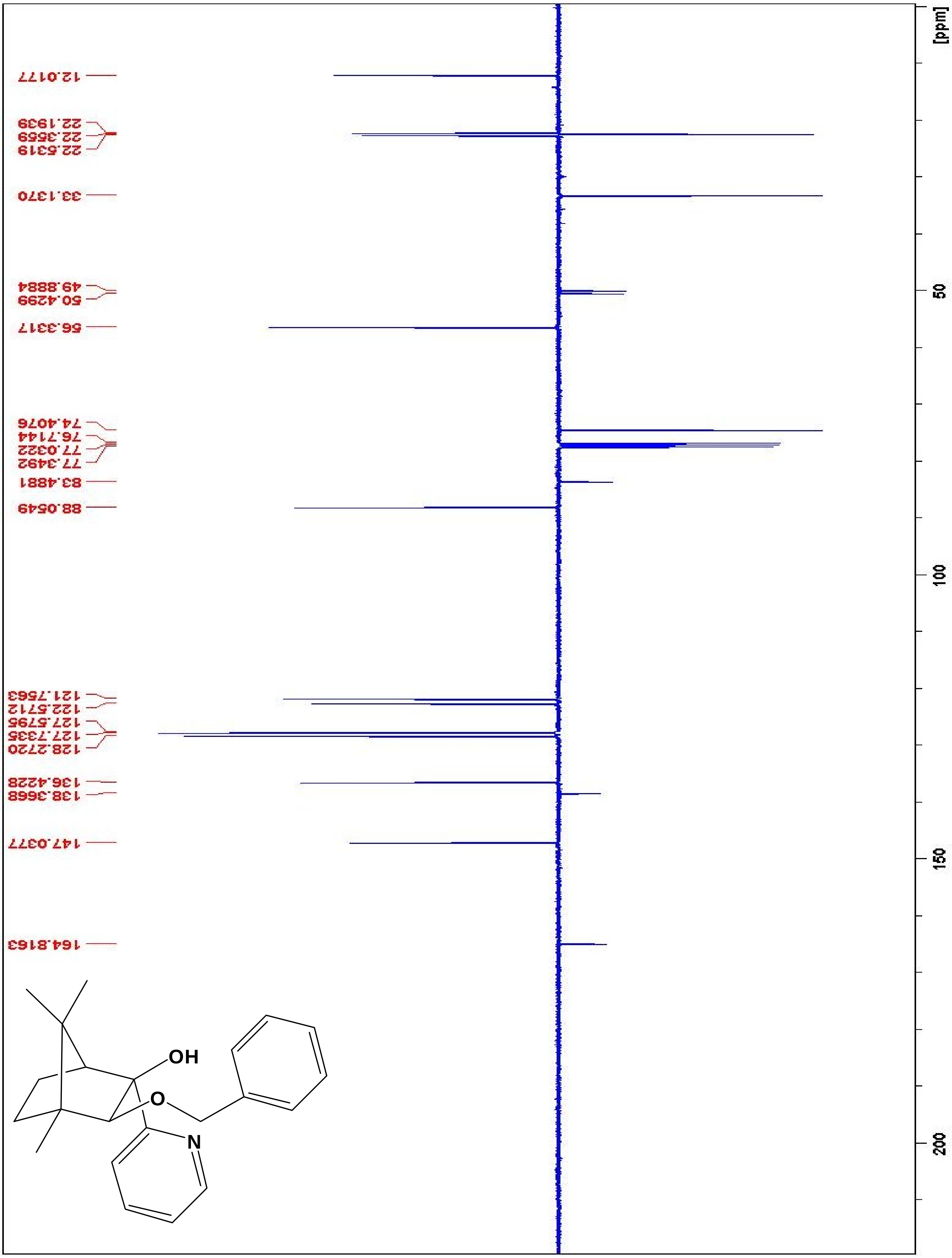

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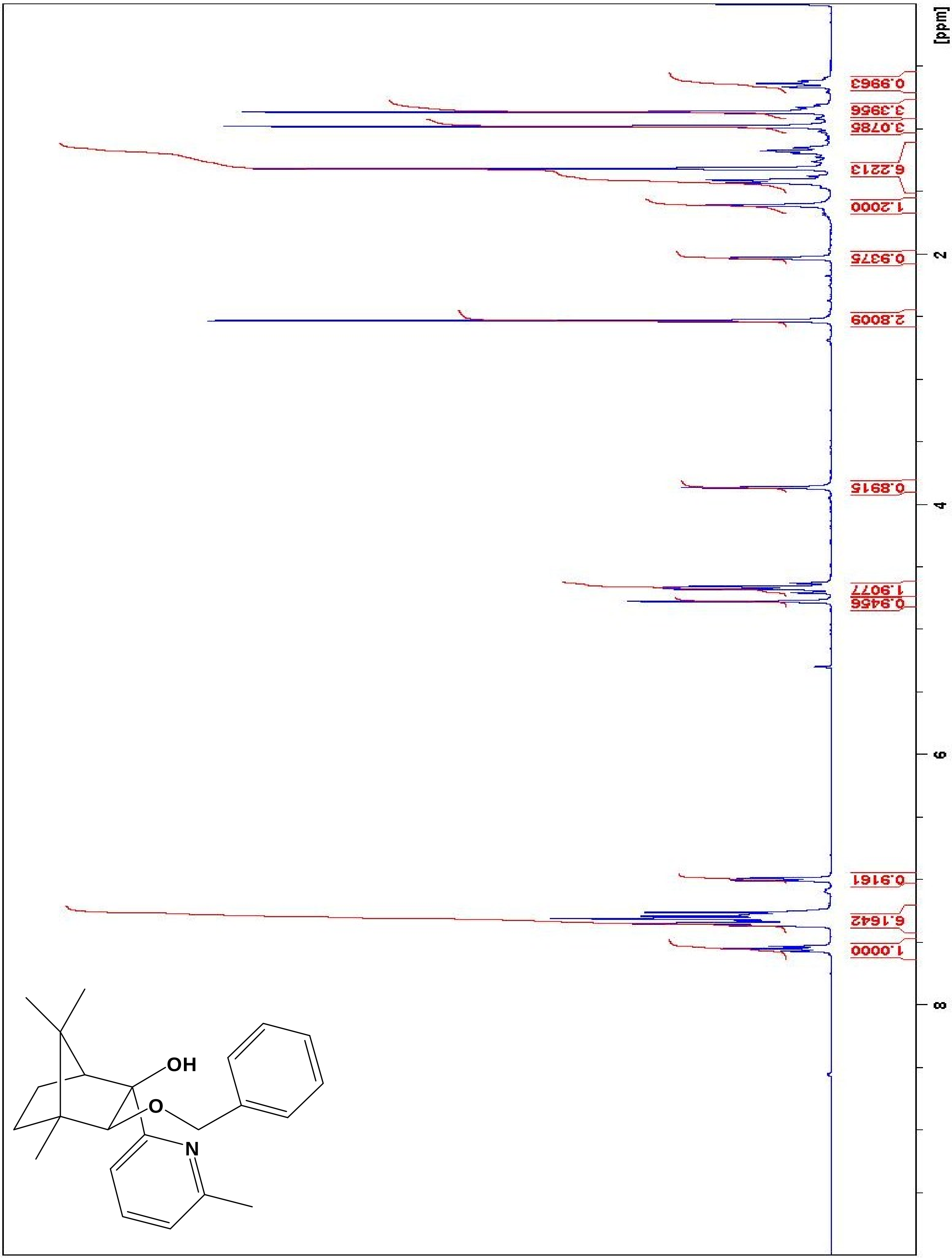

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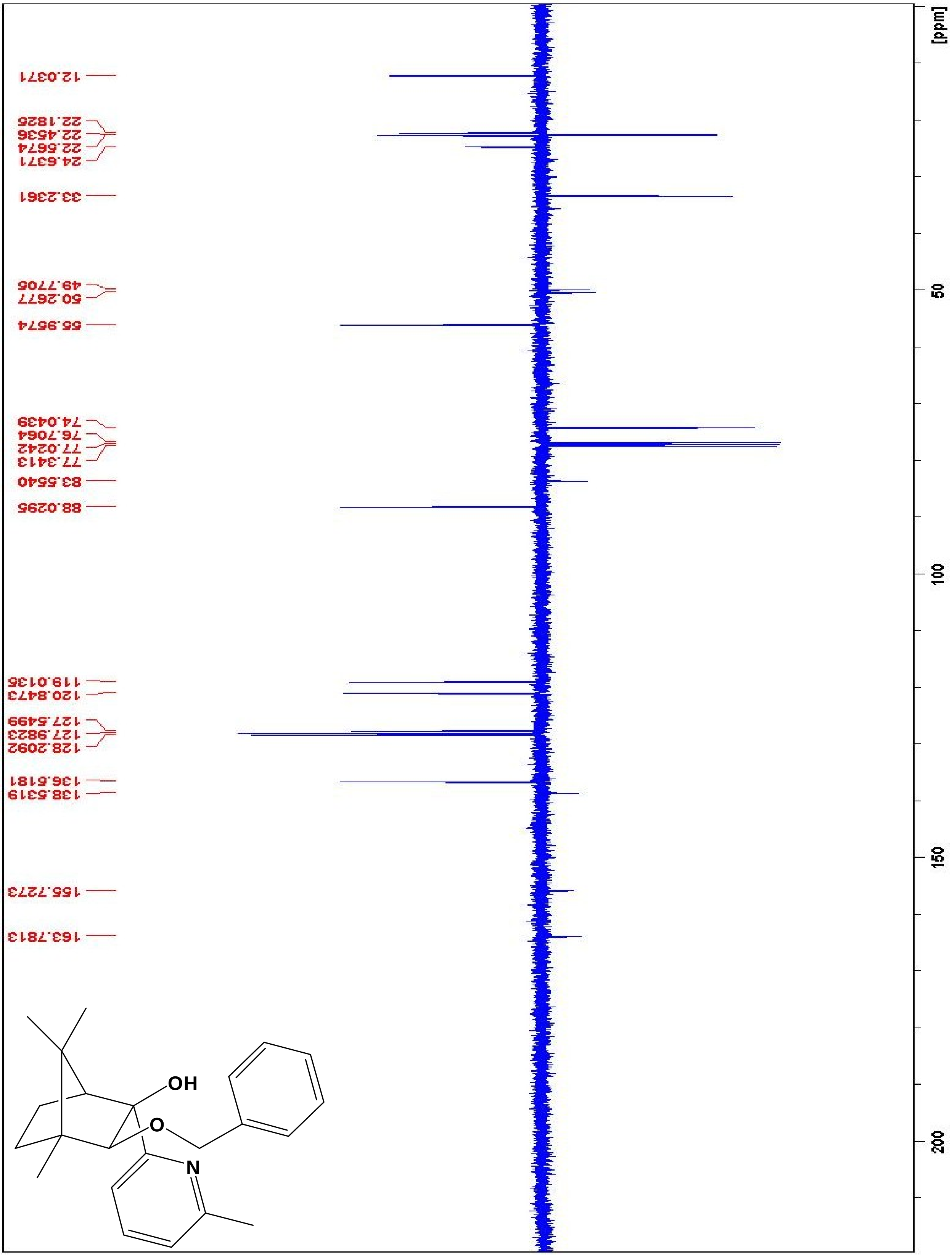

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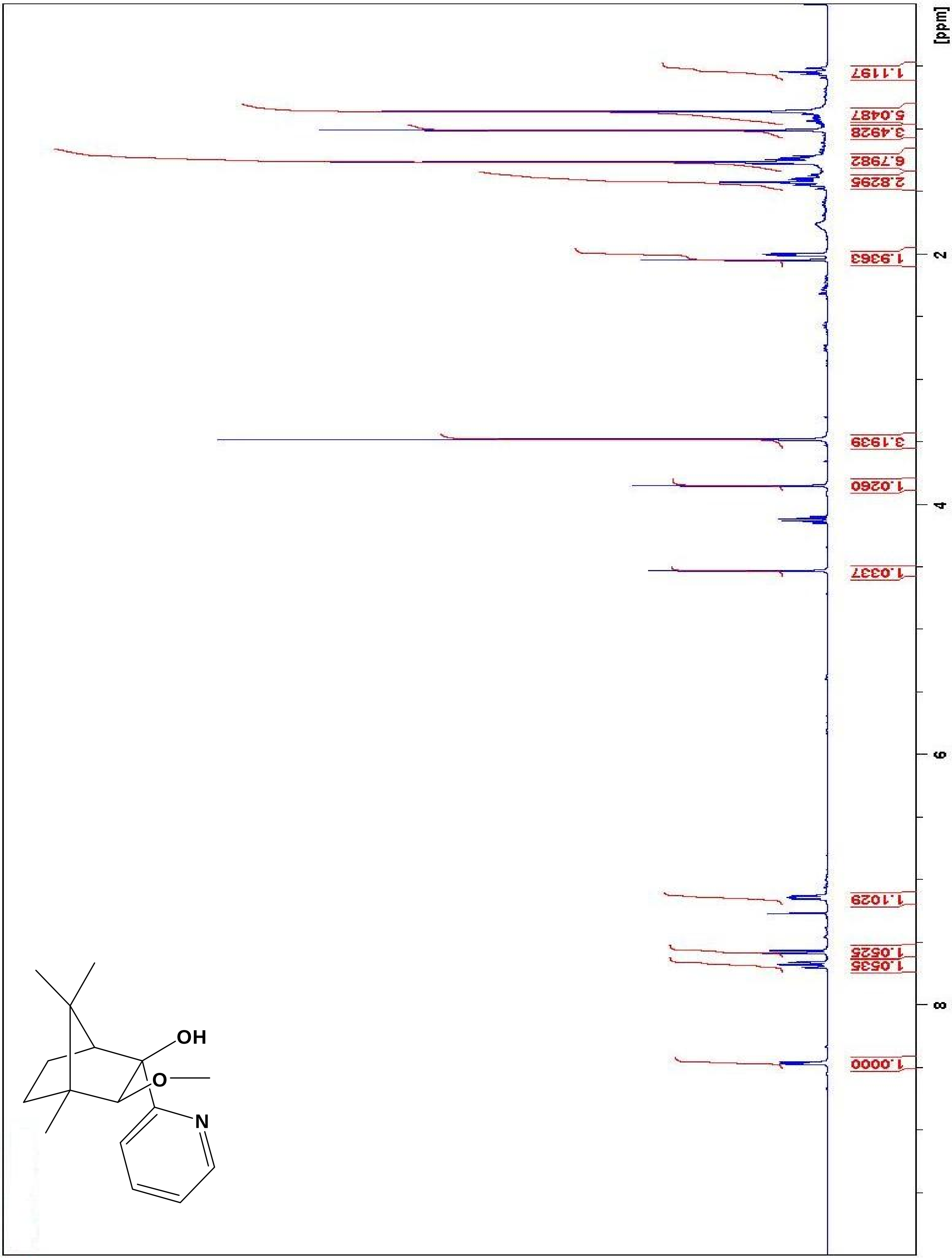

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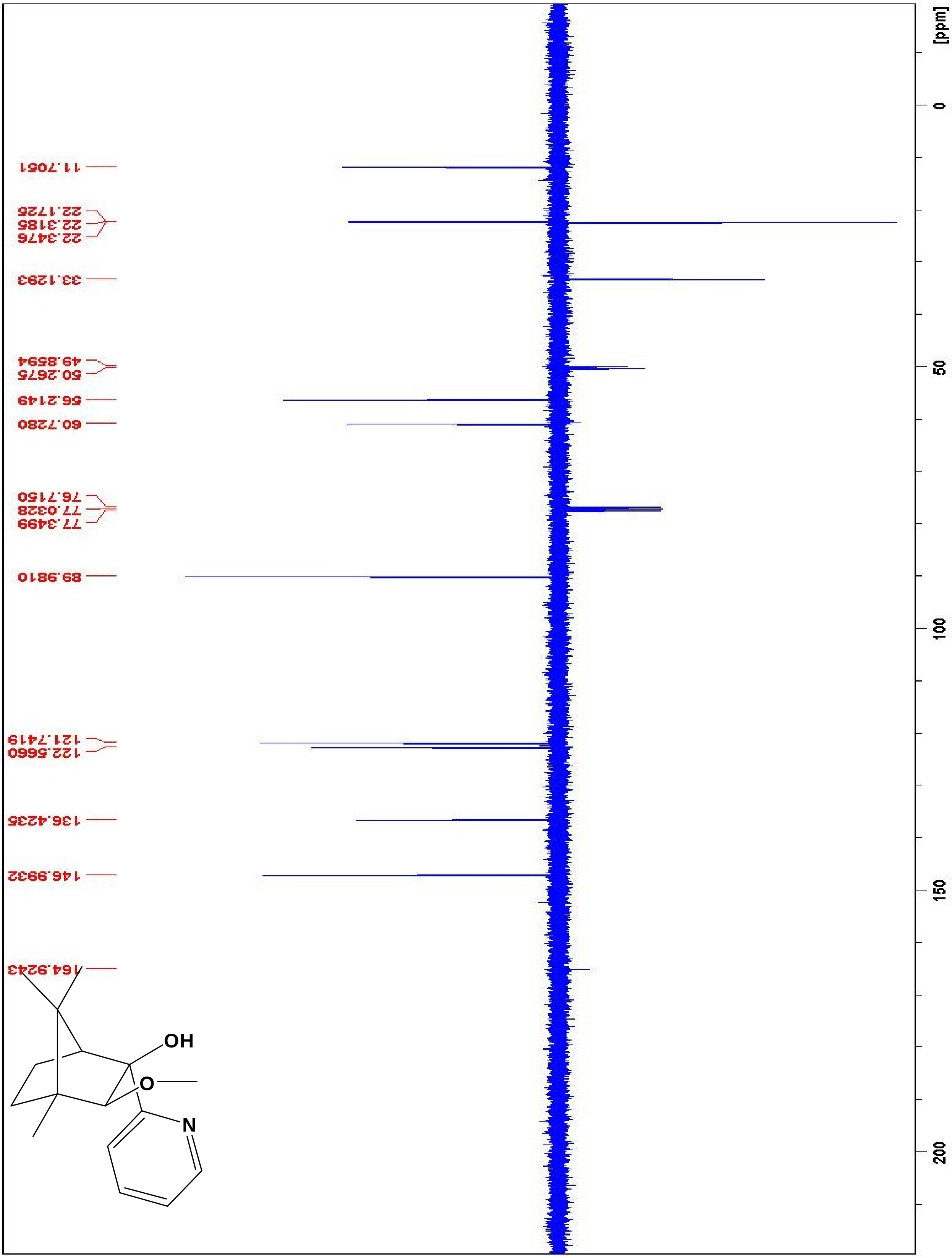

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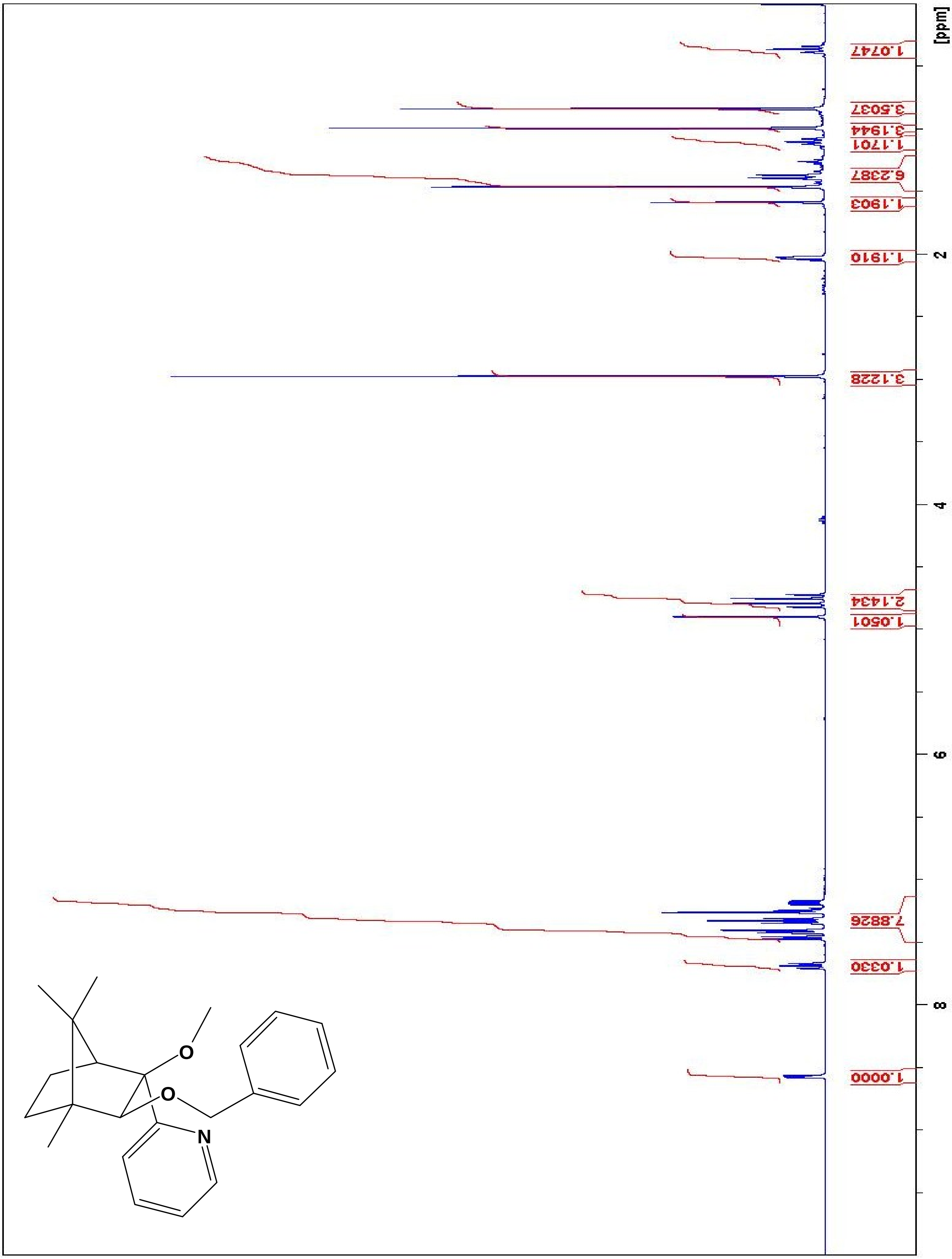

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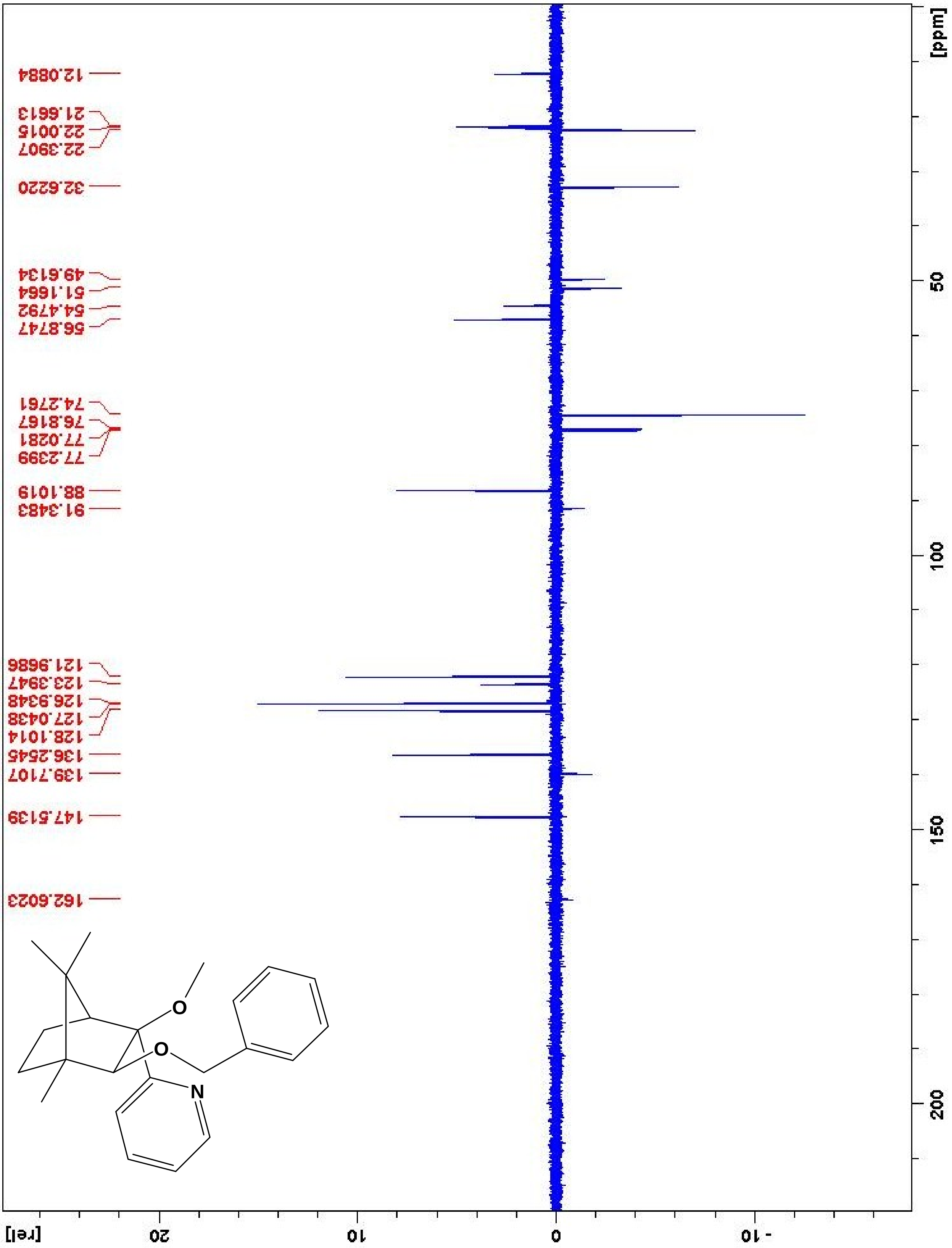

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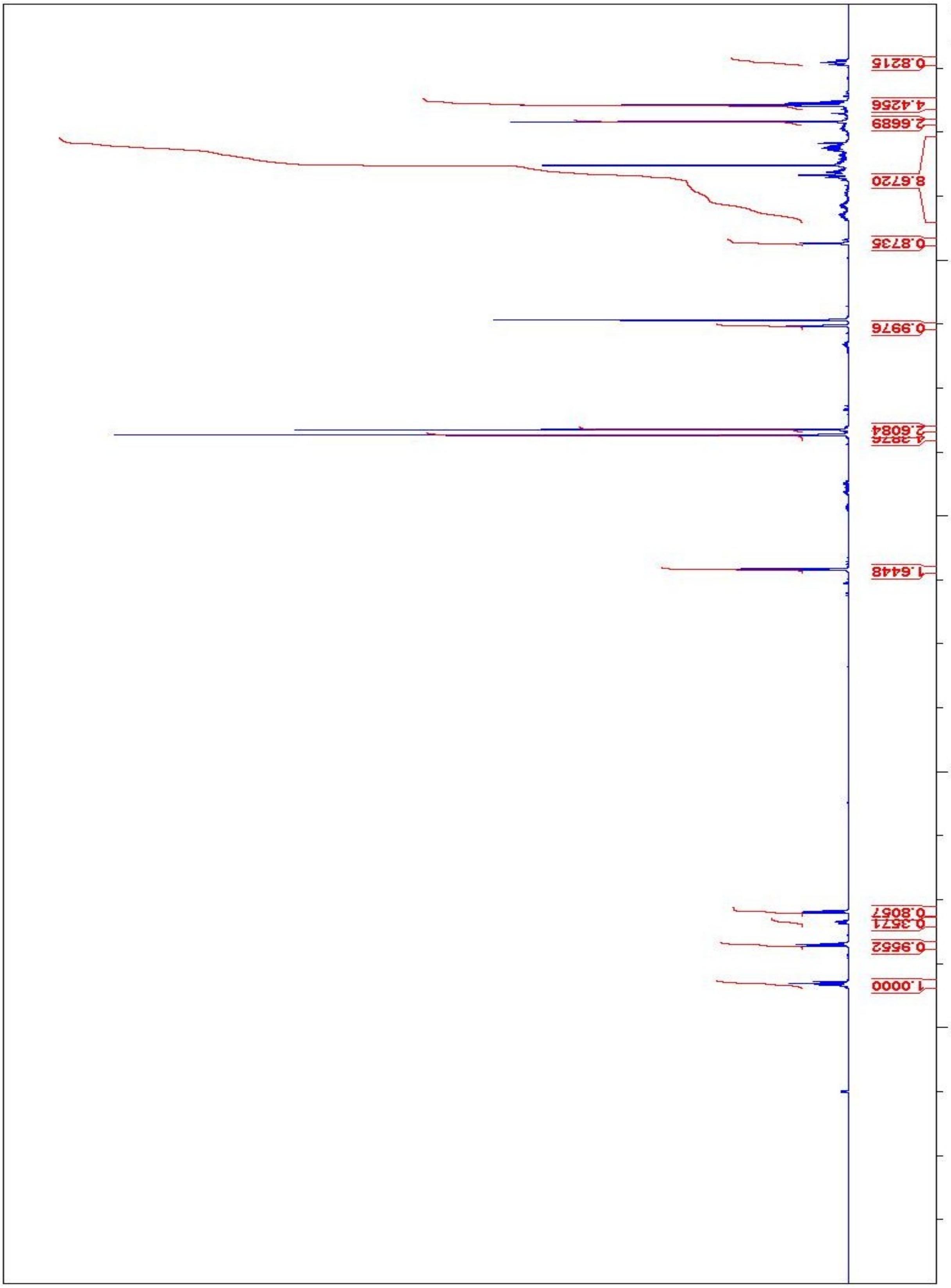
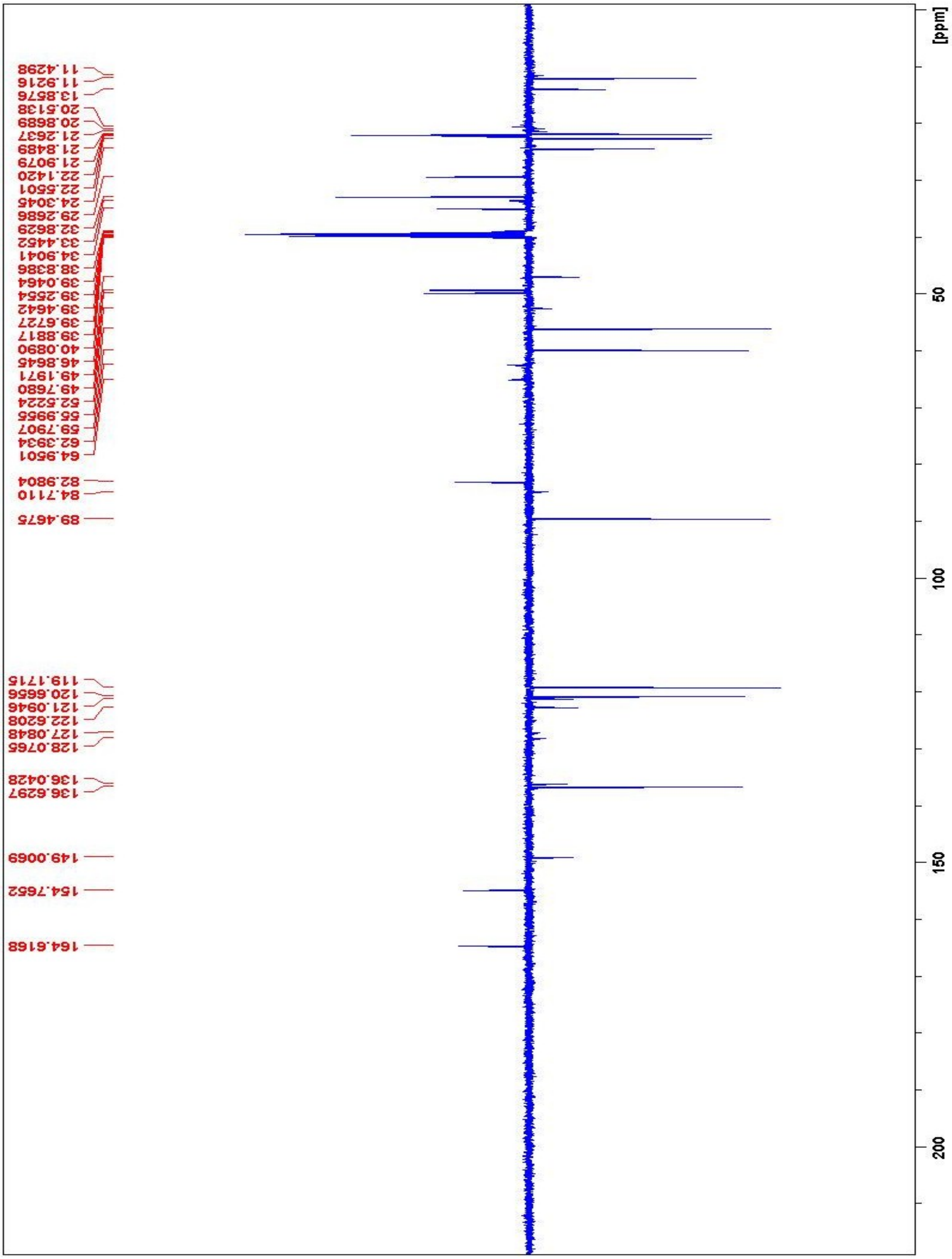


^{1}H NMR Spectrum (600 MHz) of Compound **18** in DMSO-D6



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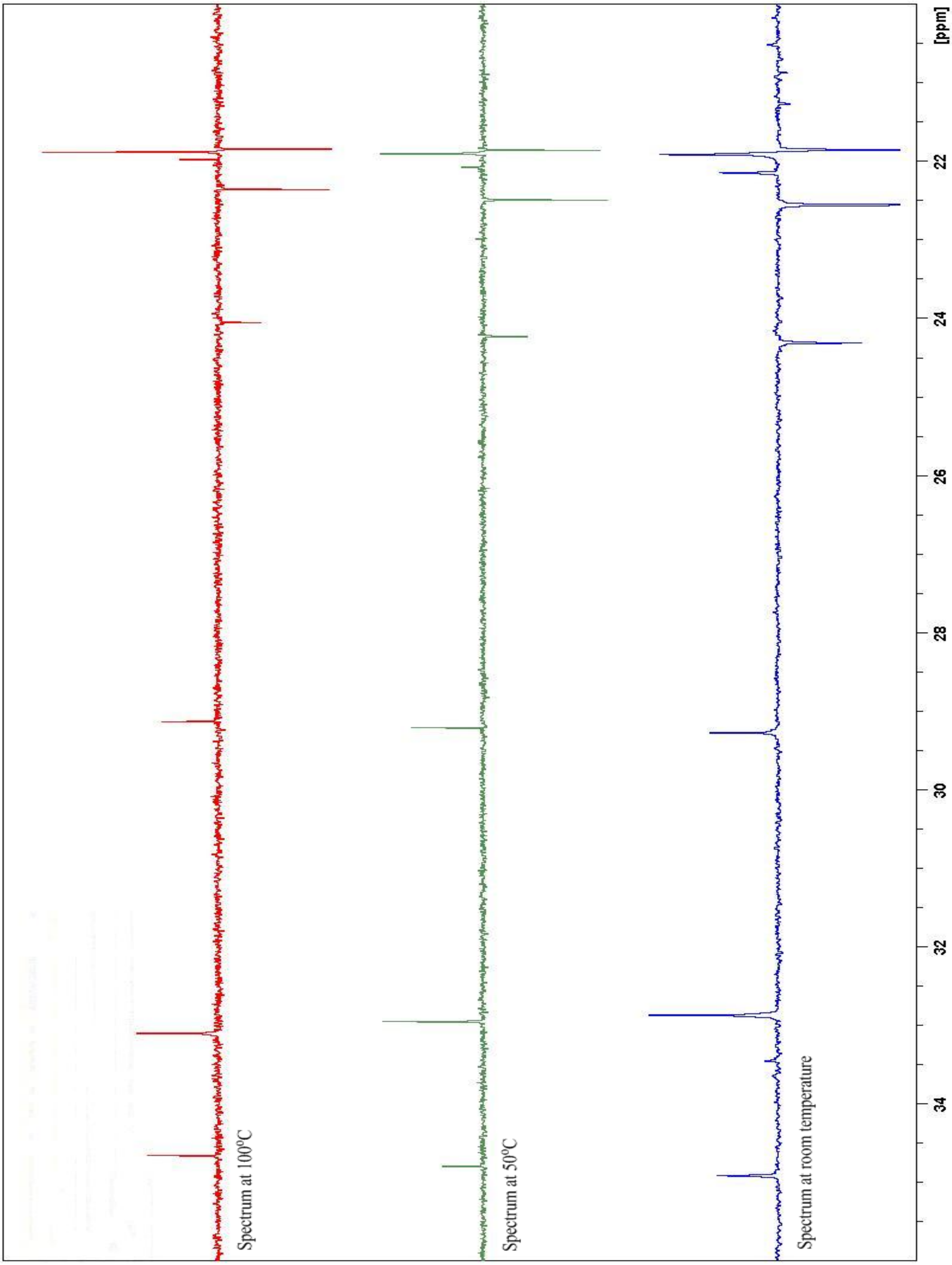
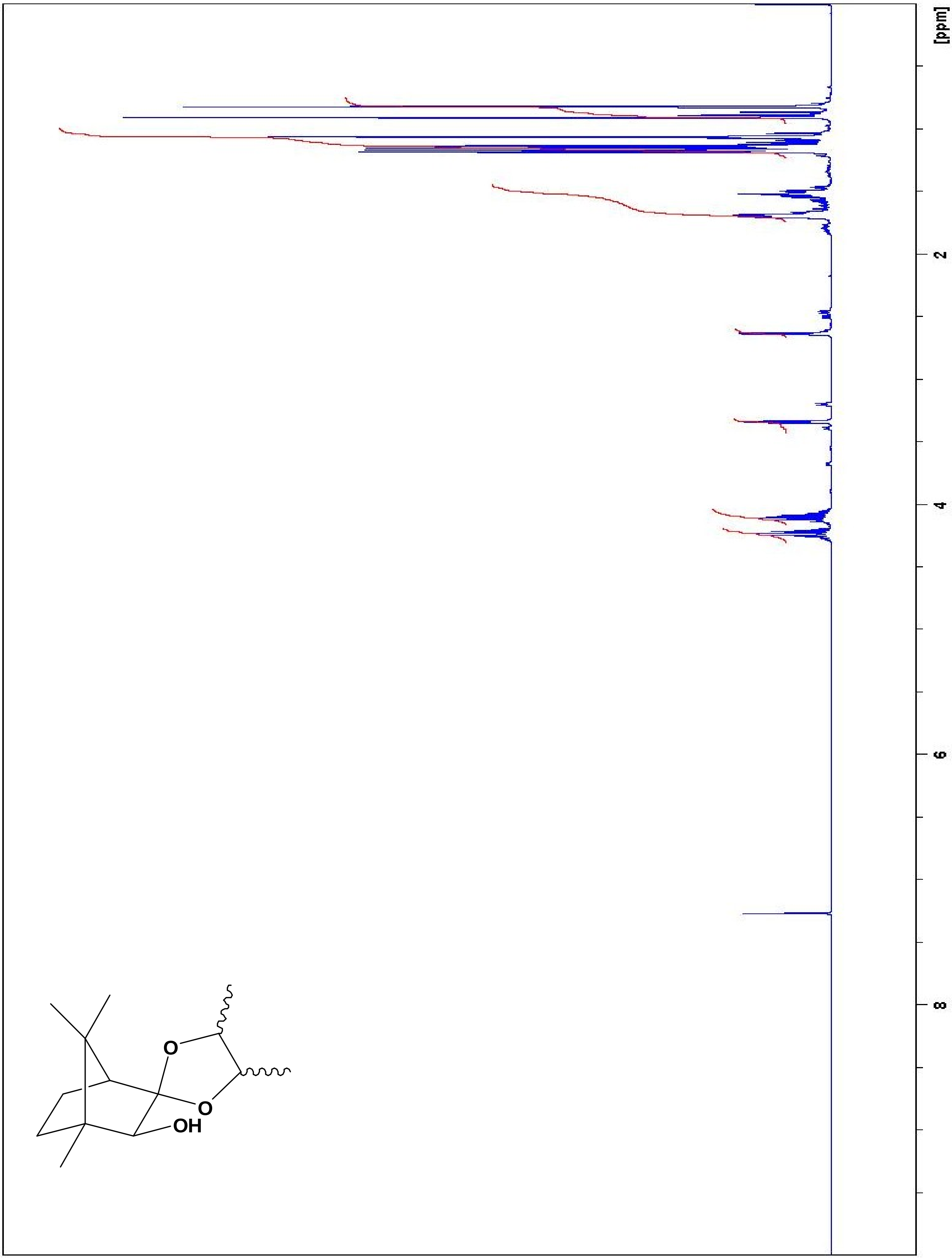


High temperature ^{13}C APT NMR Spectrum (400 MHz) of Compound **18** in DMSO-D6 expanded

SECTION 2: DIASTEREOMERIC RATIO DETERMINATIONS



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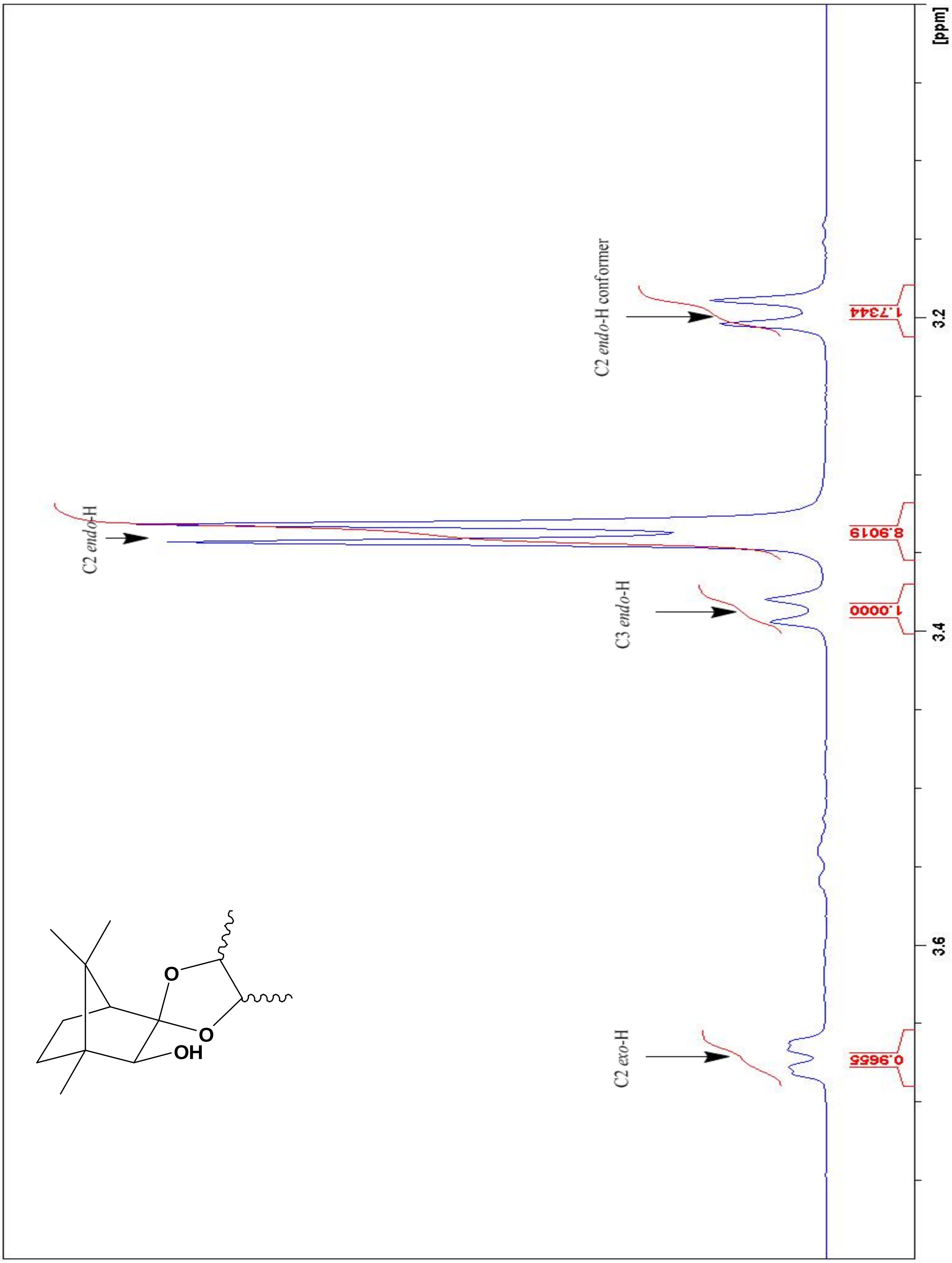

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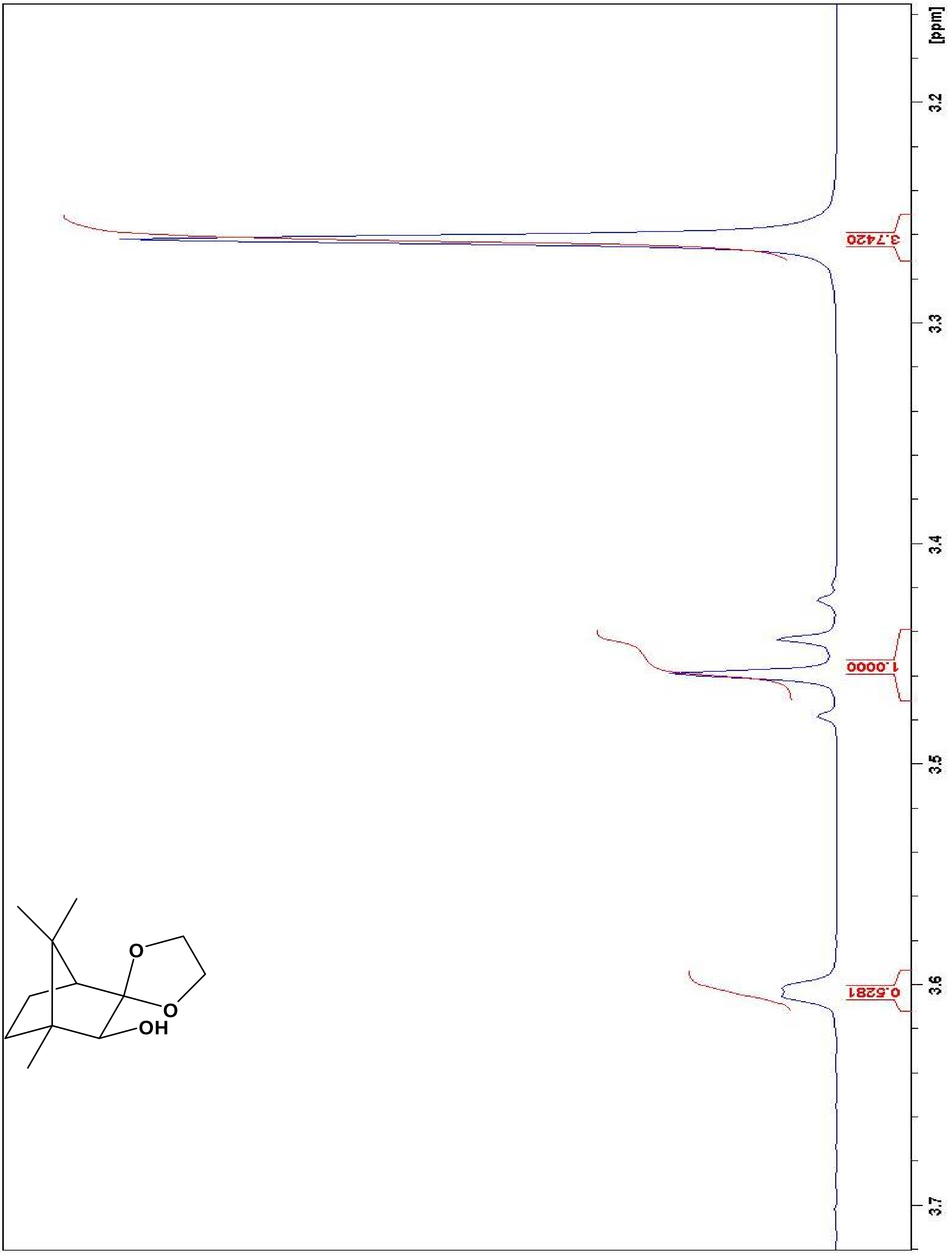
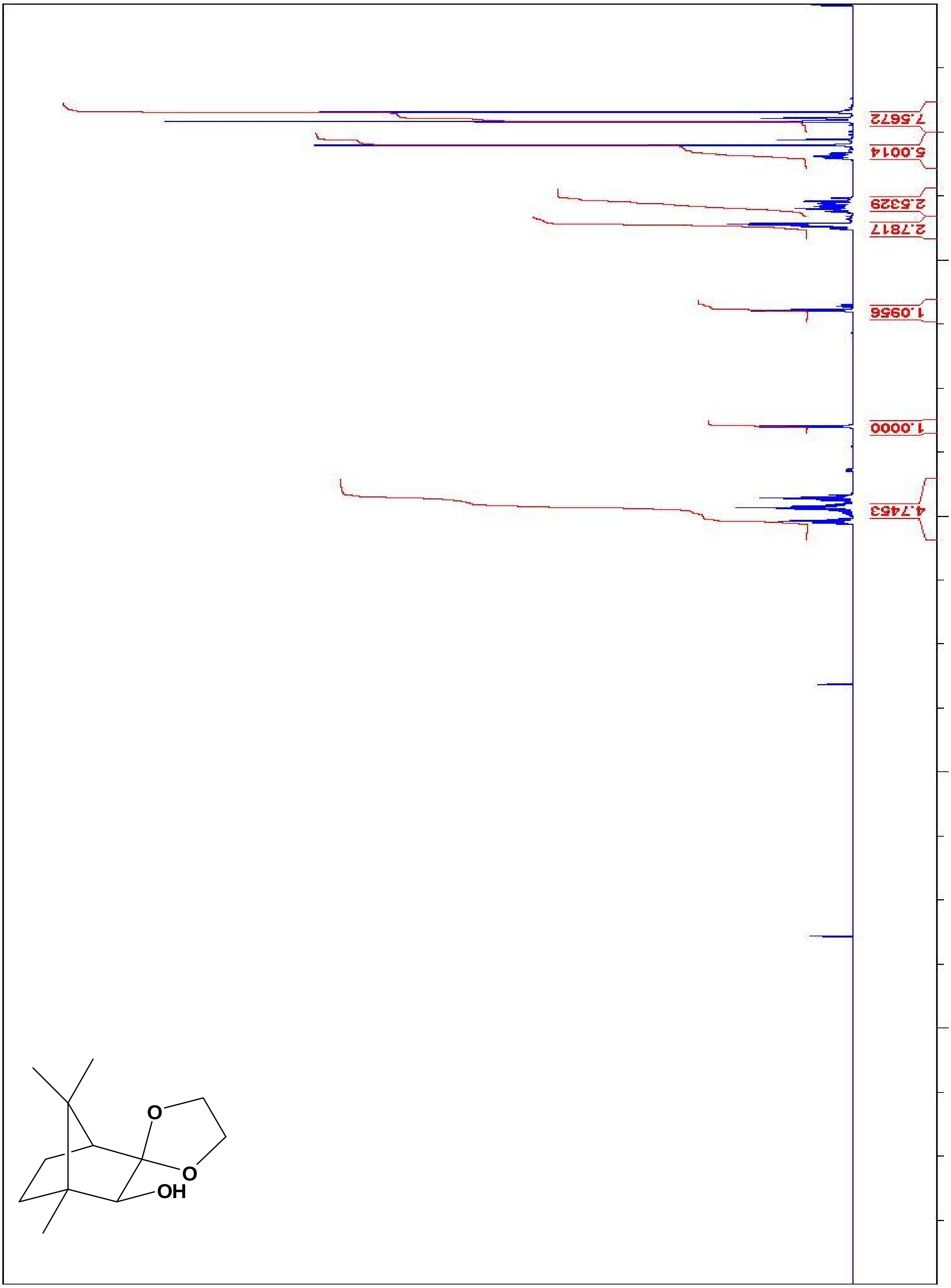
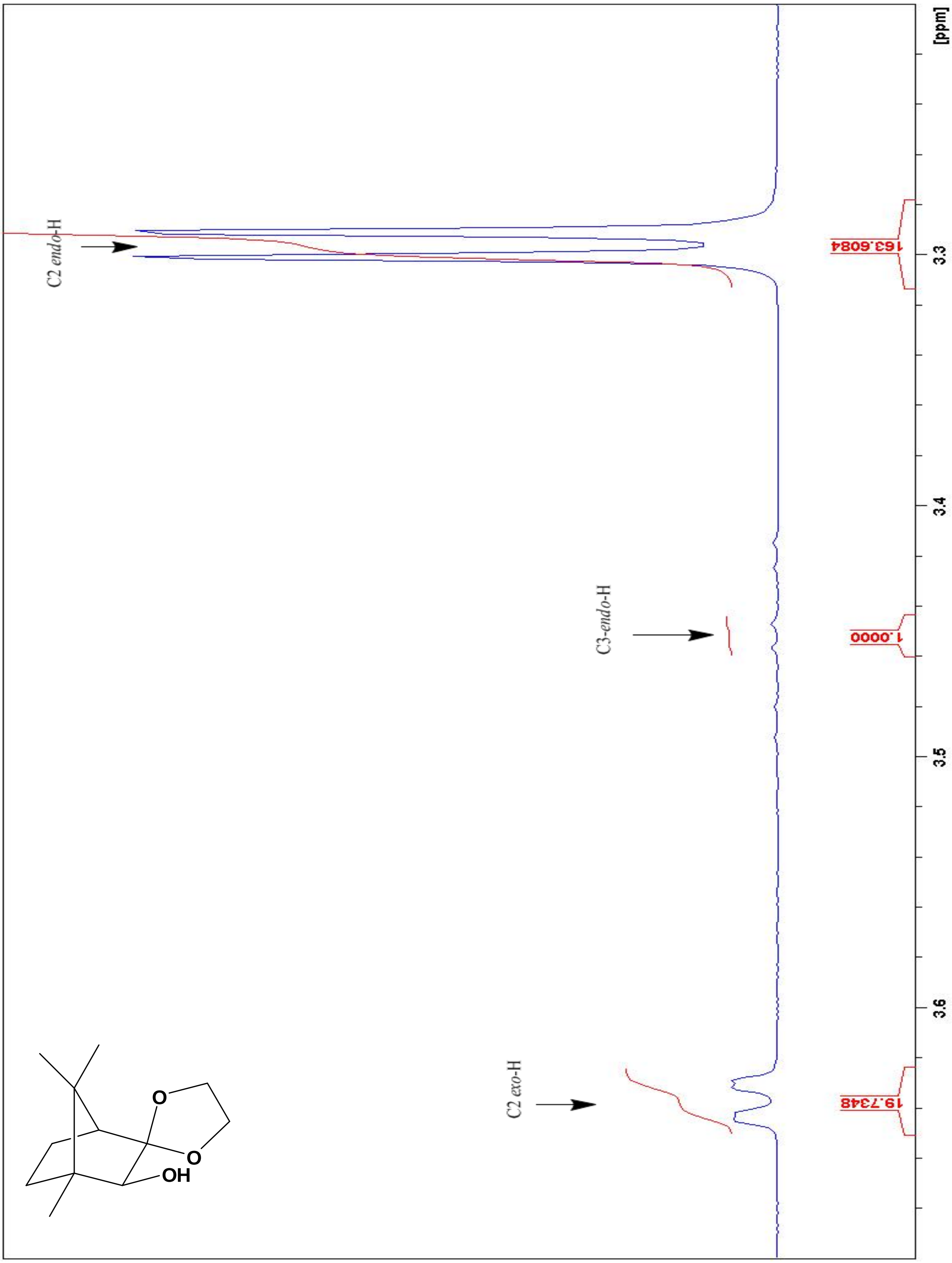


^{1}H NMR Spectrum (400 MHz) of Compound **14** before recrystallisation of preceding compound **13**(1:3 ratio)

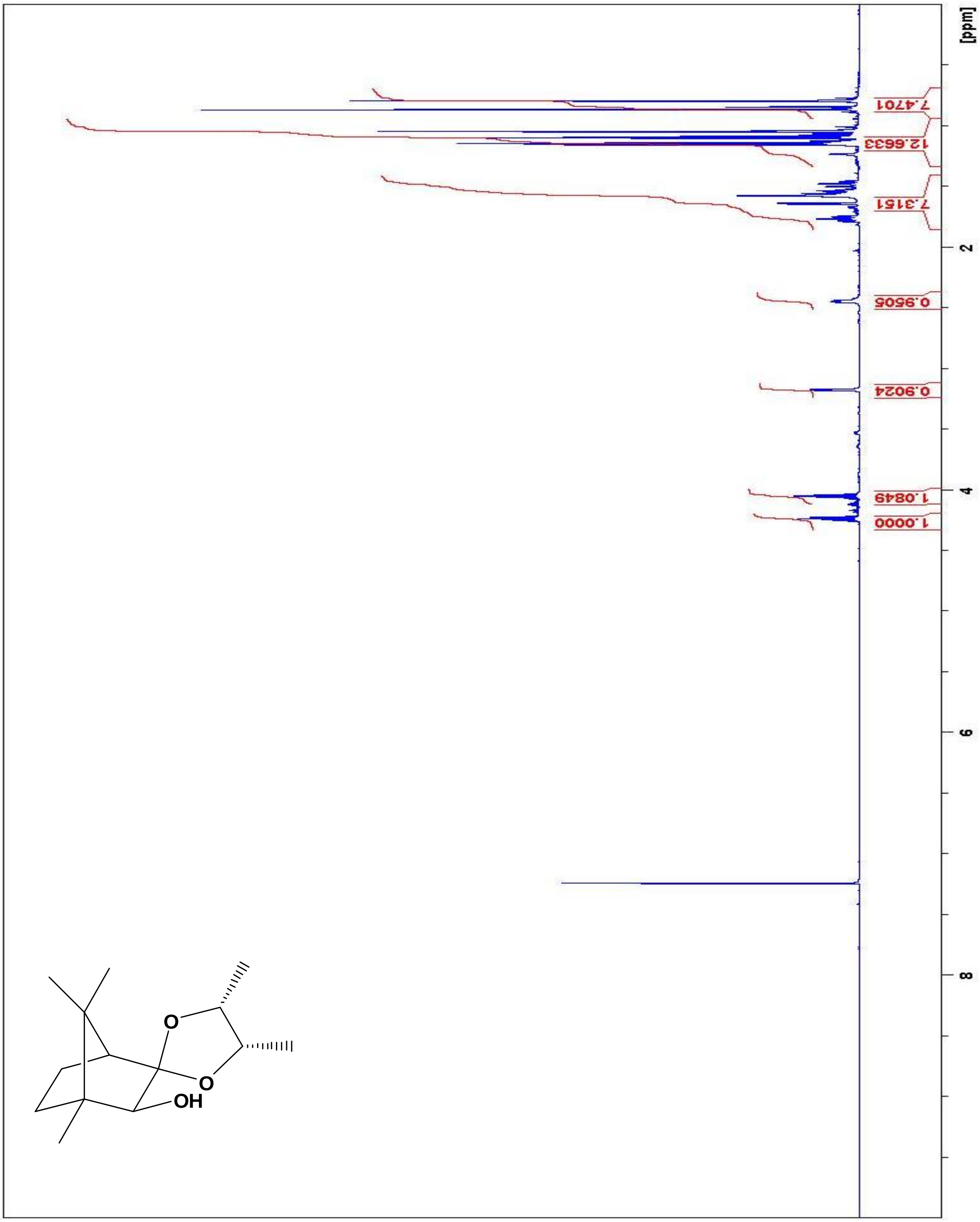


^{1}H NMR Spectrum (600 MHz) of Compound **14** after recrystallisation of preceding compound **13**

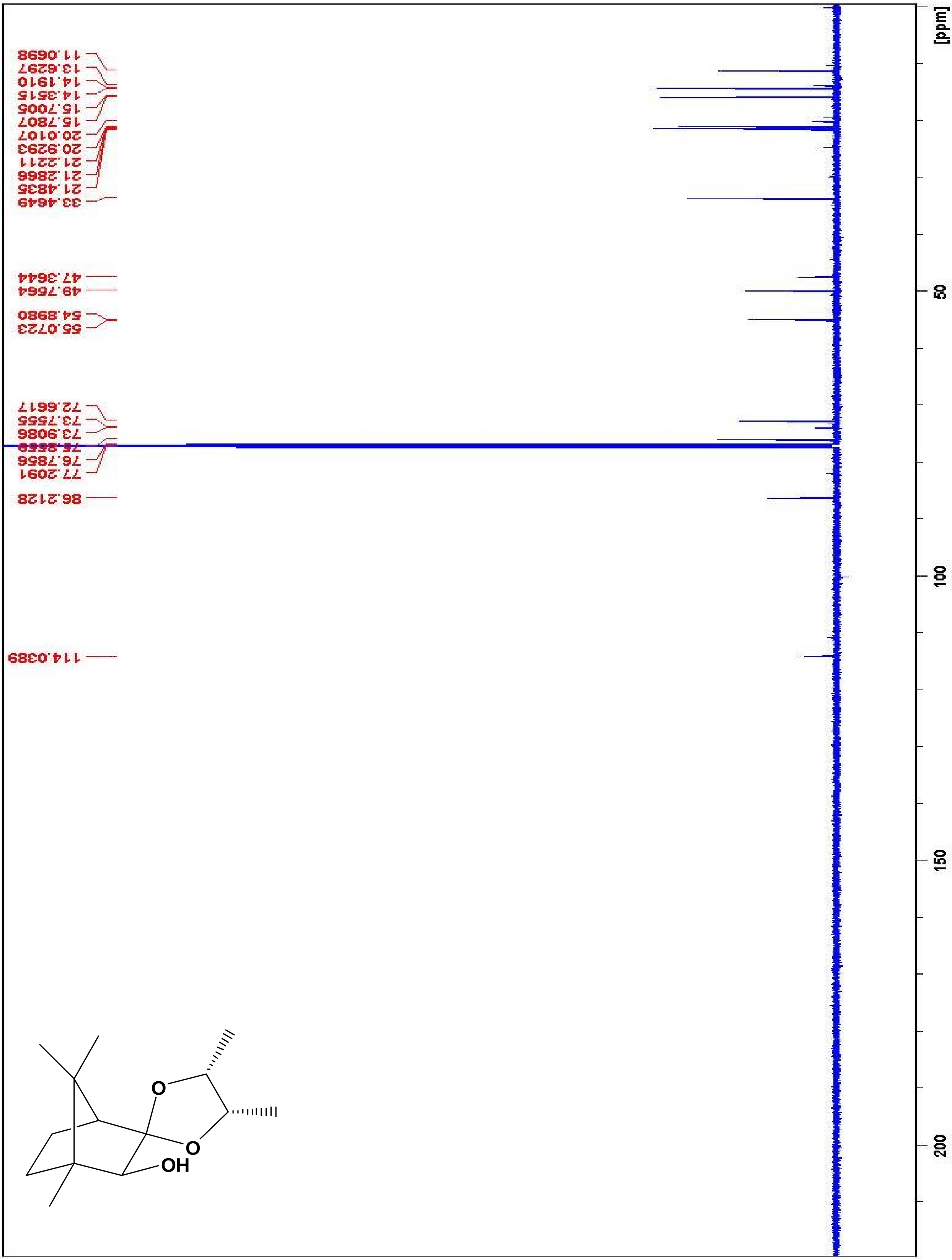


^{1}H NMR Spectrum (600 MHz) of Compound **14** (expanded) showing diastereomeric ratio after recrystallisation of preceding compound **13**

2D NMR Spectra



^{1}H NMR Spectrum (600 MHz) of Compound **10a-3**



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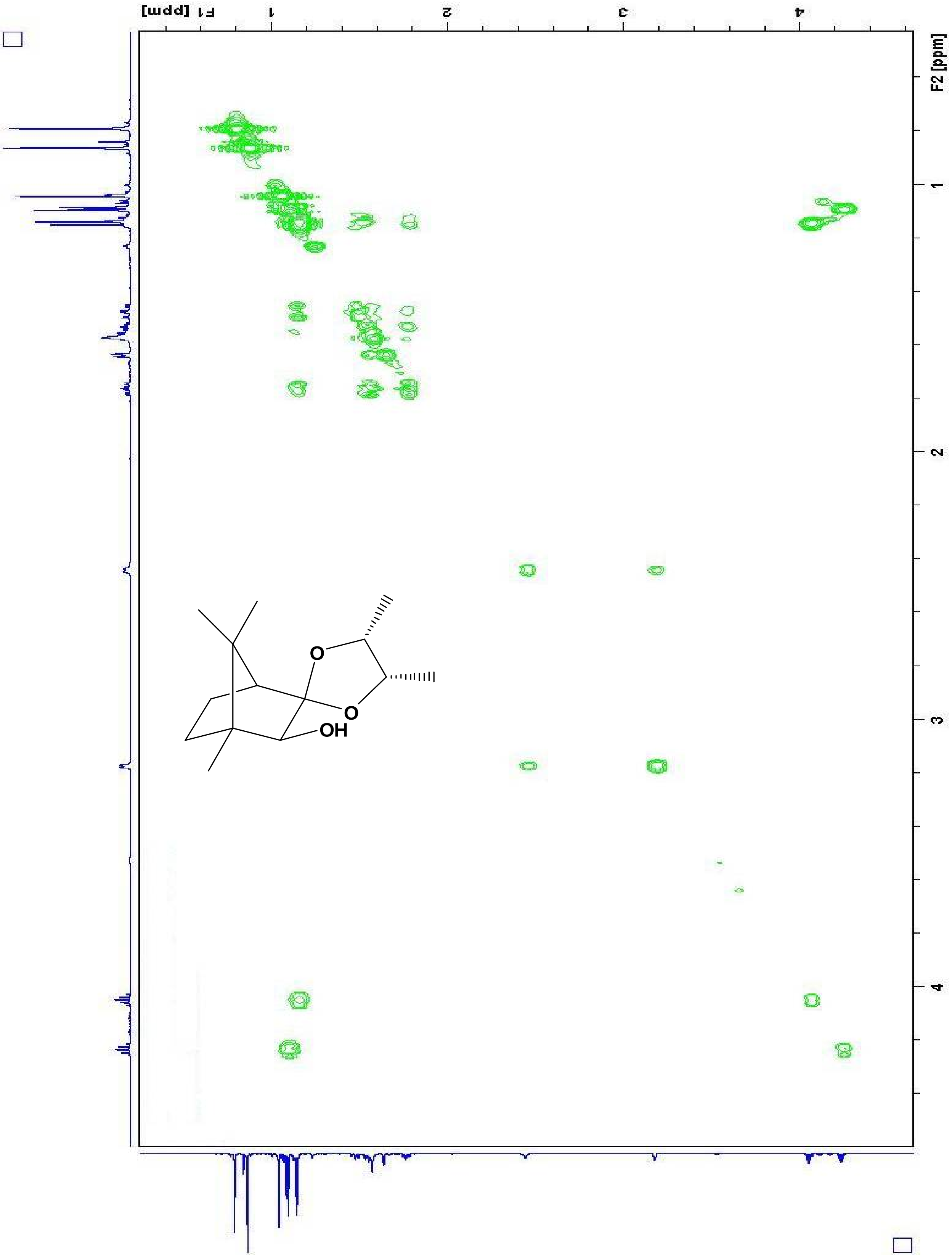

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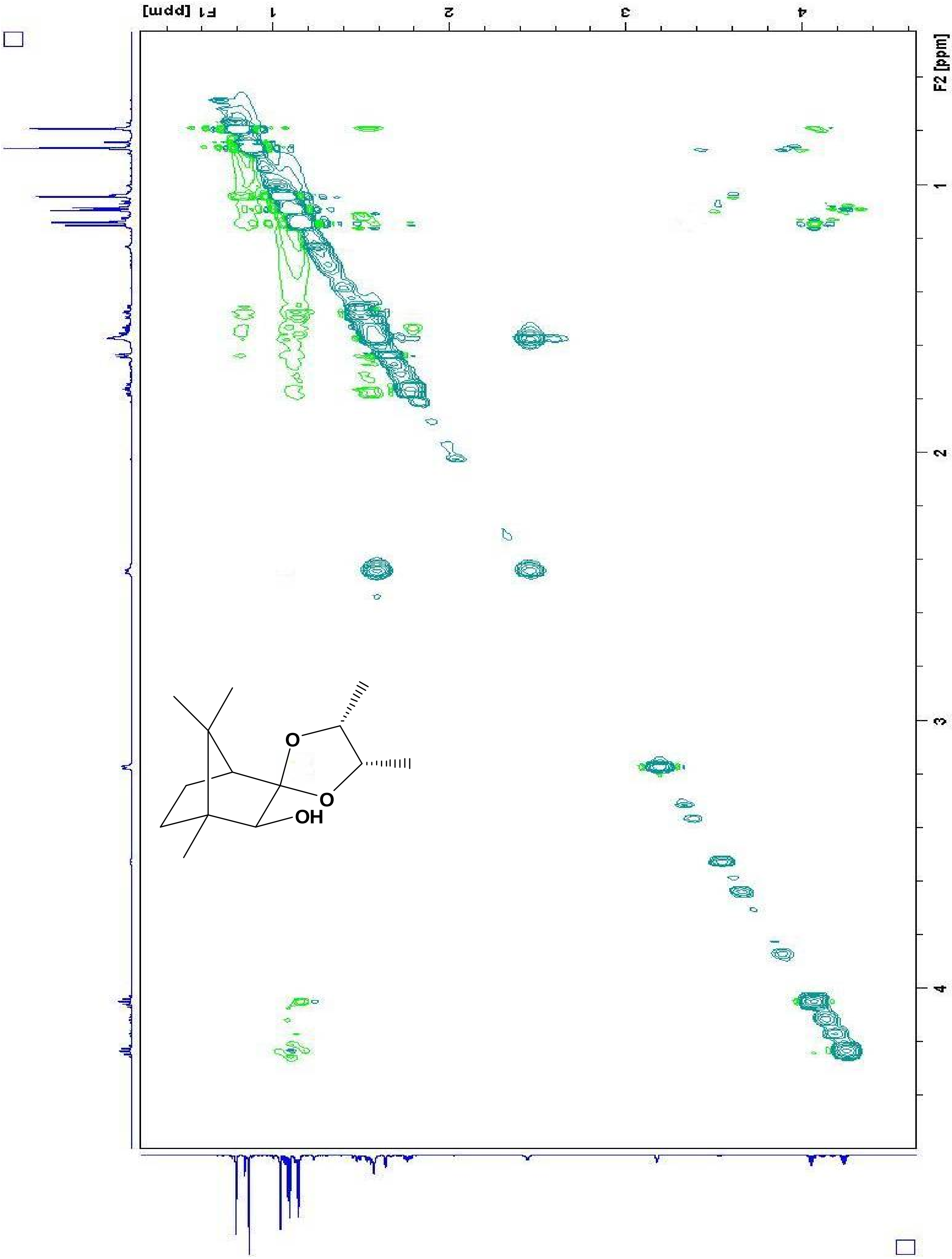

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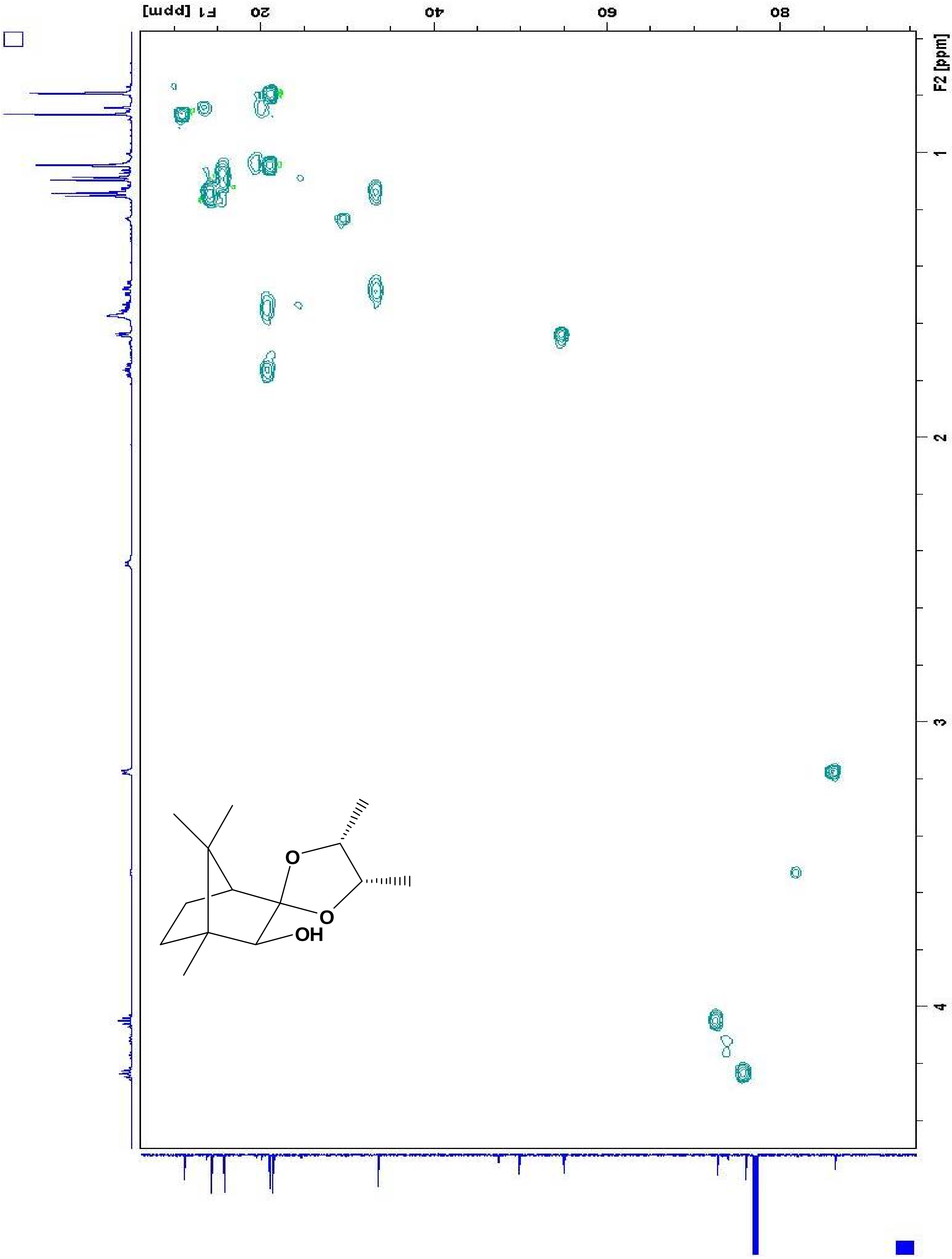
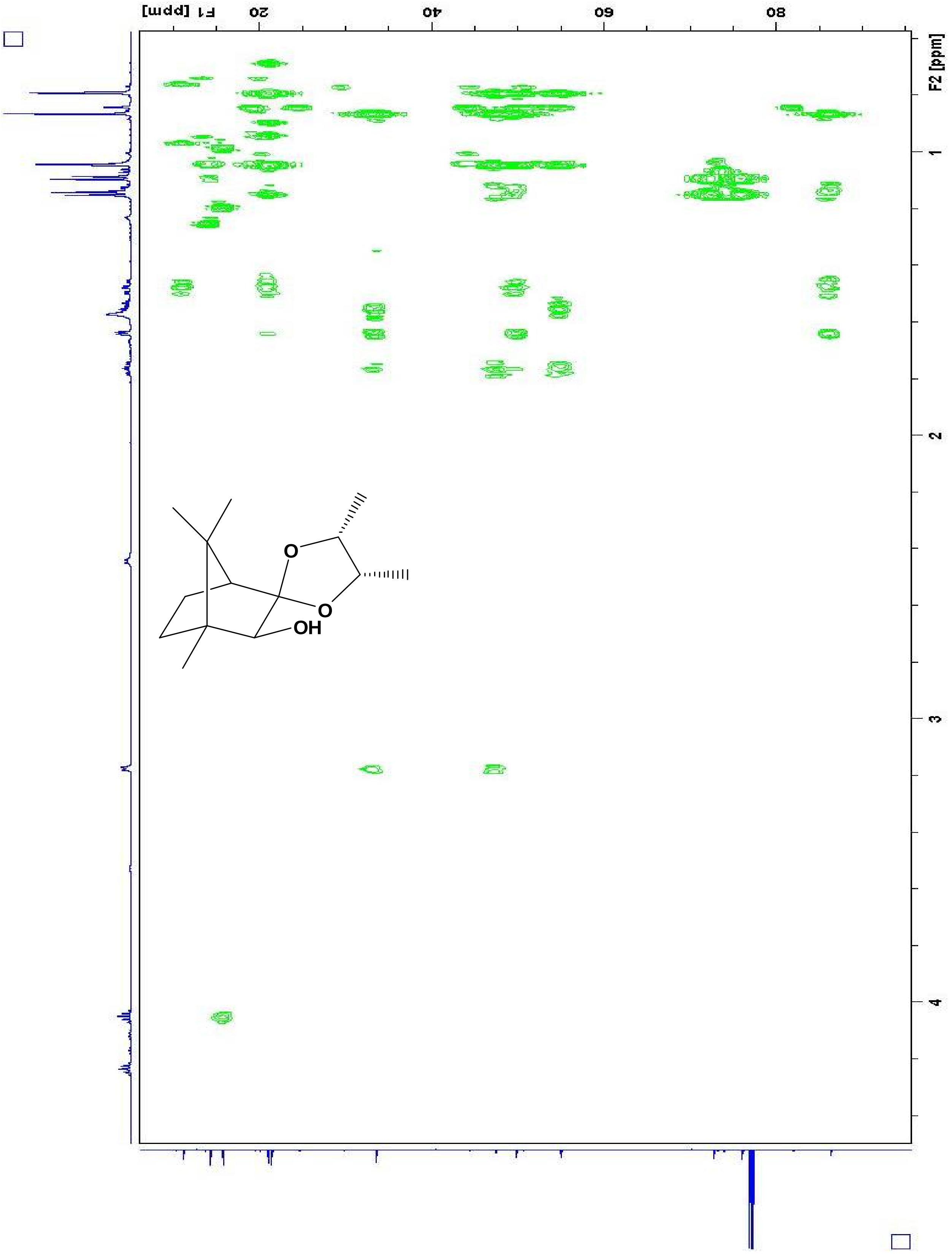
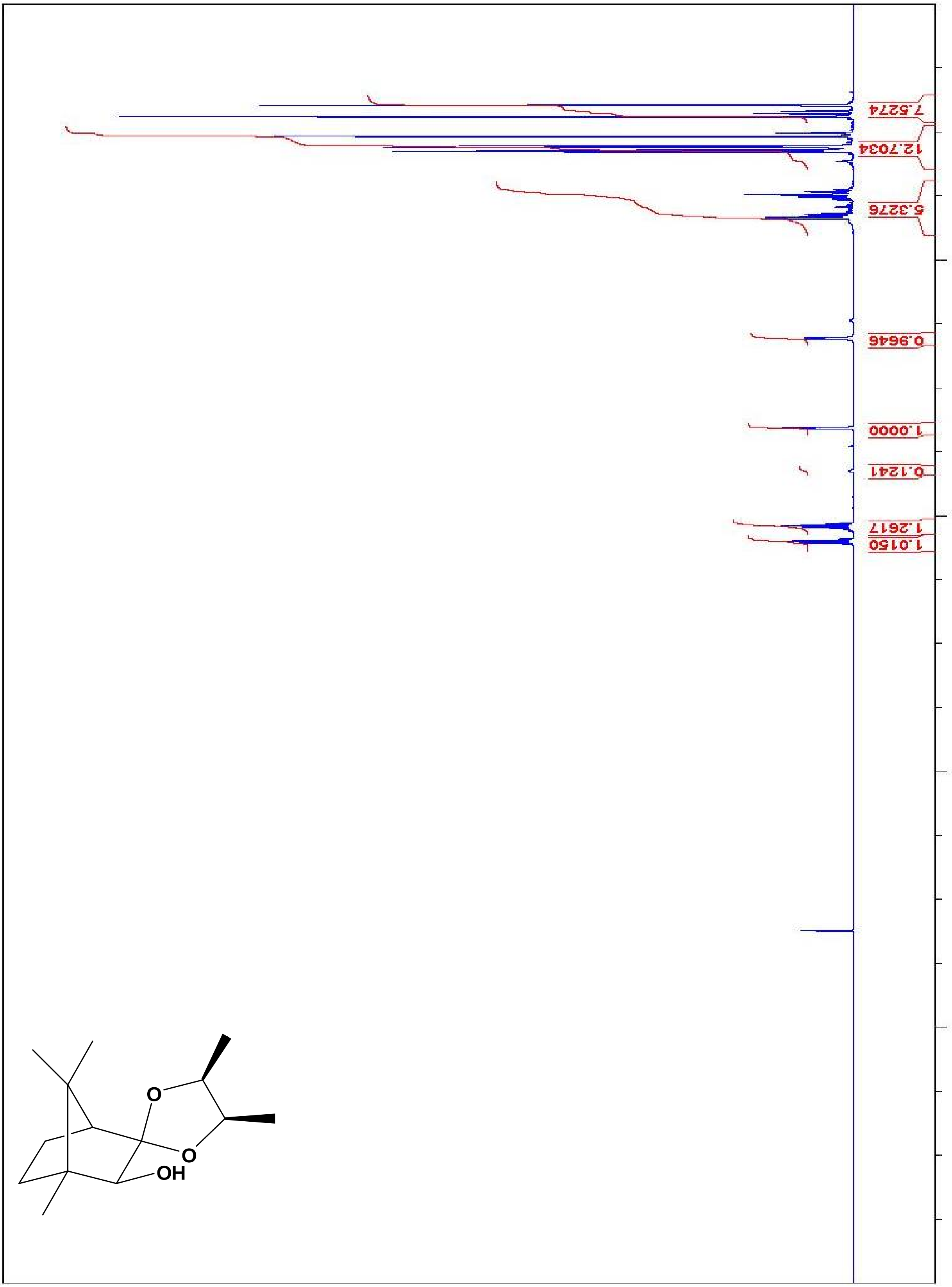


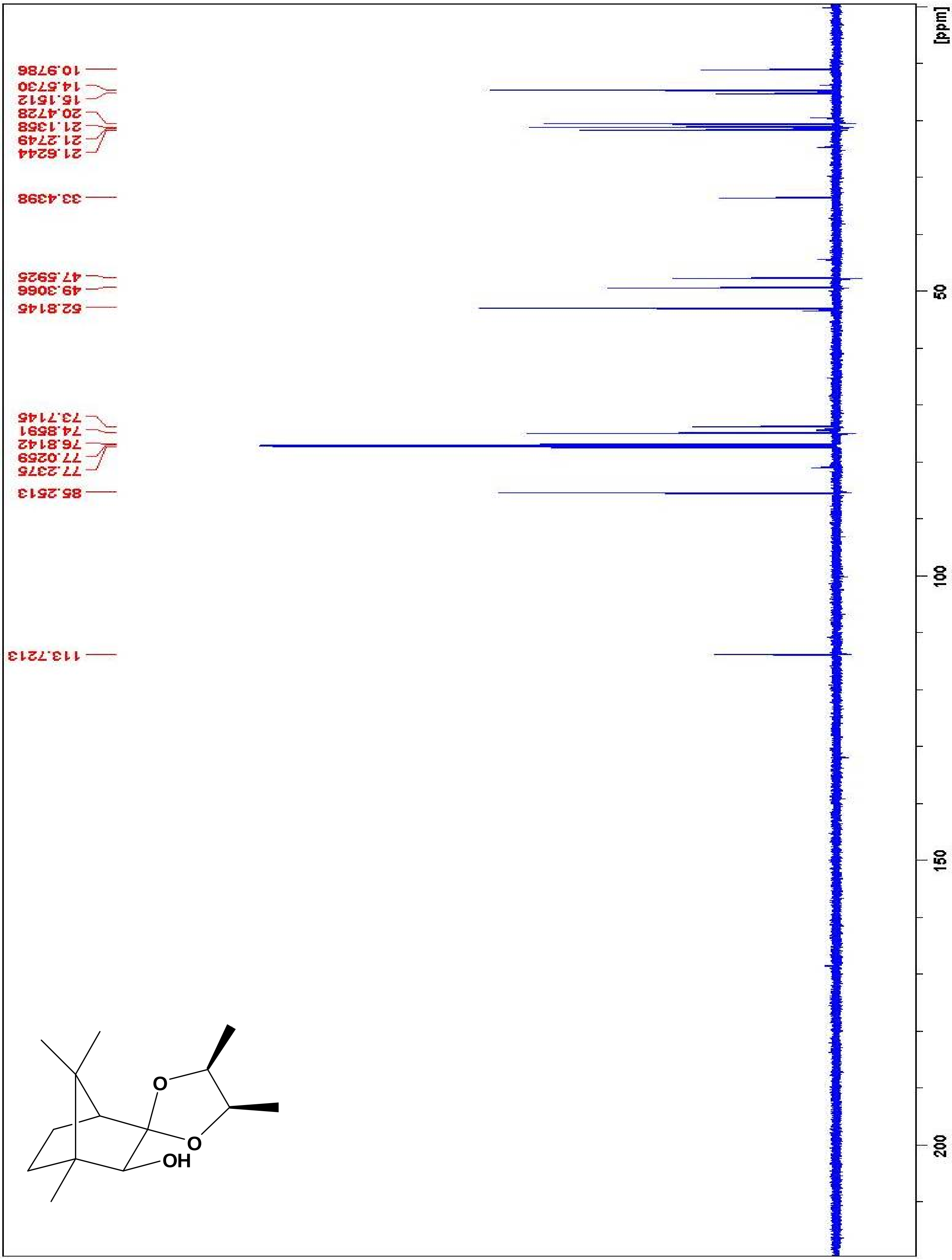
HSQC Spectrum (600MHz) of Compound **10a-3**



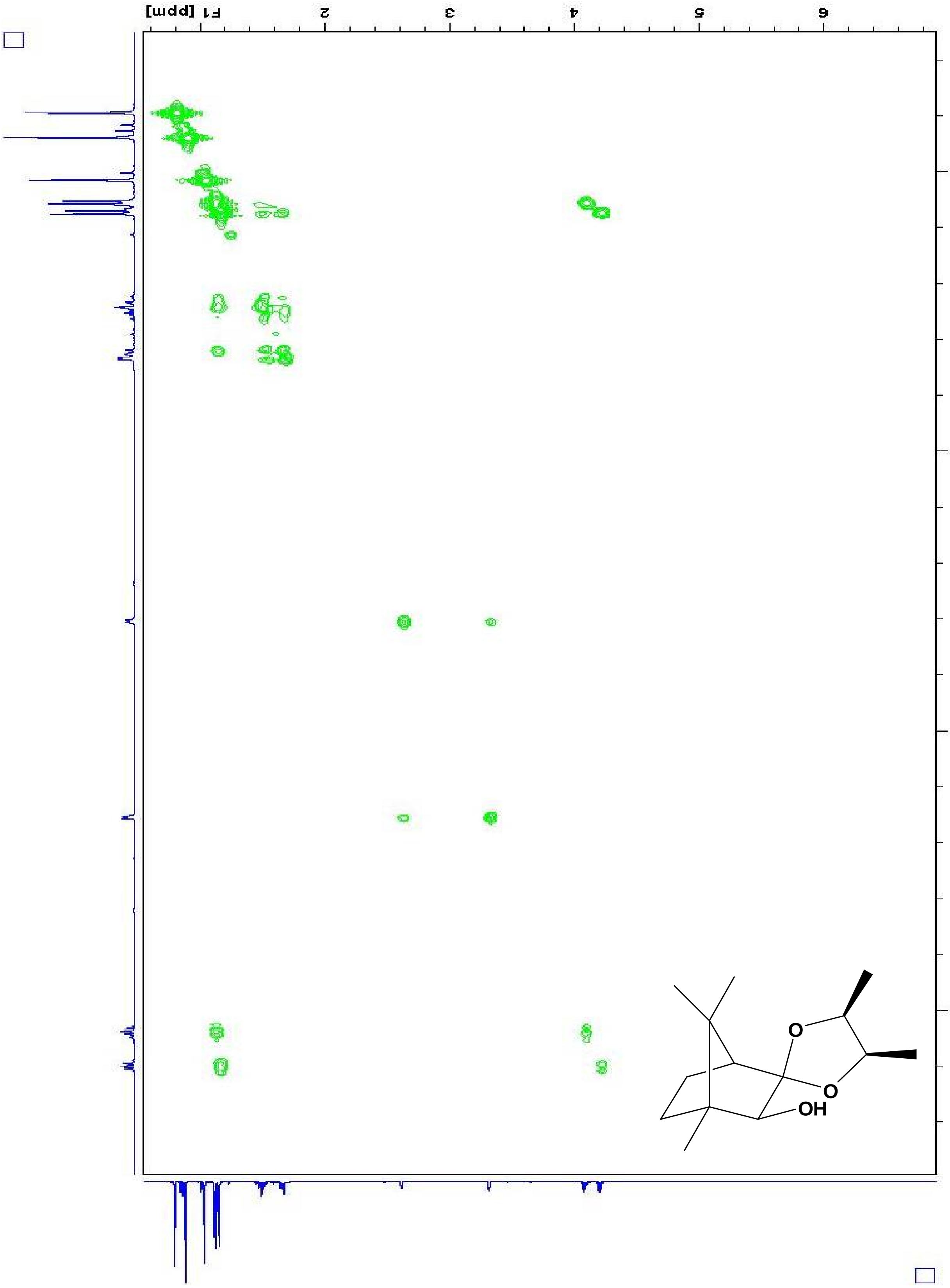
HMBC Spectrum (600MHz) of Compound **10a-3**



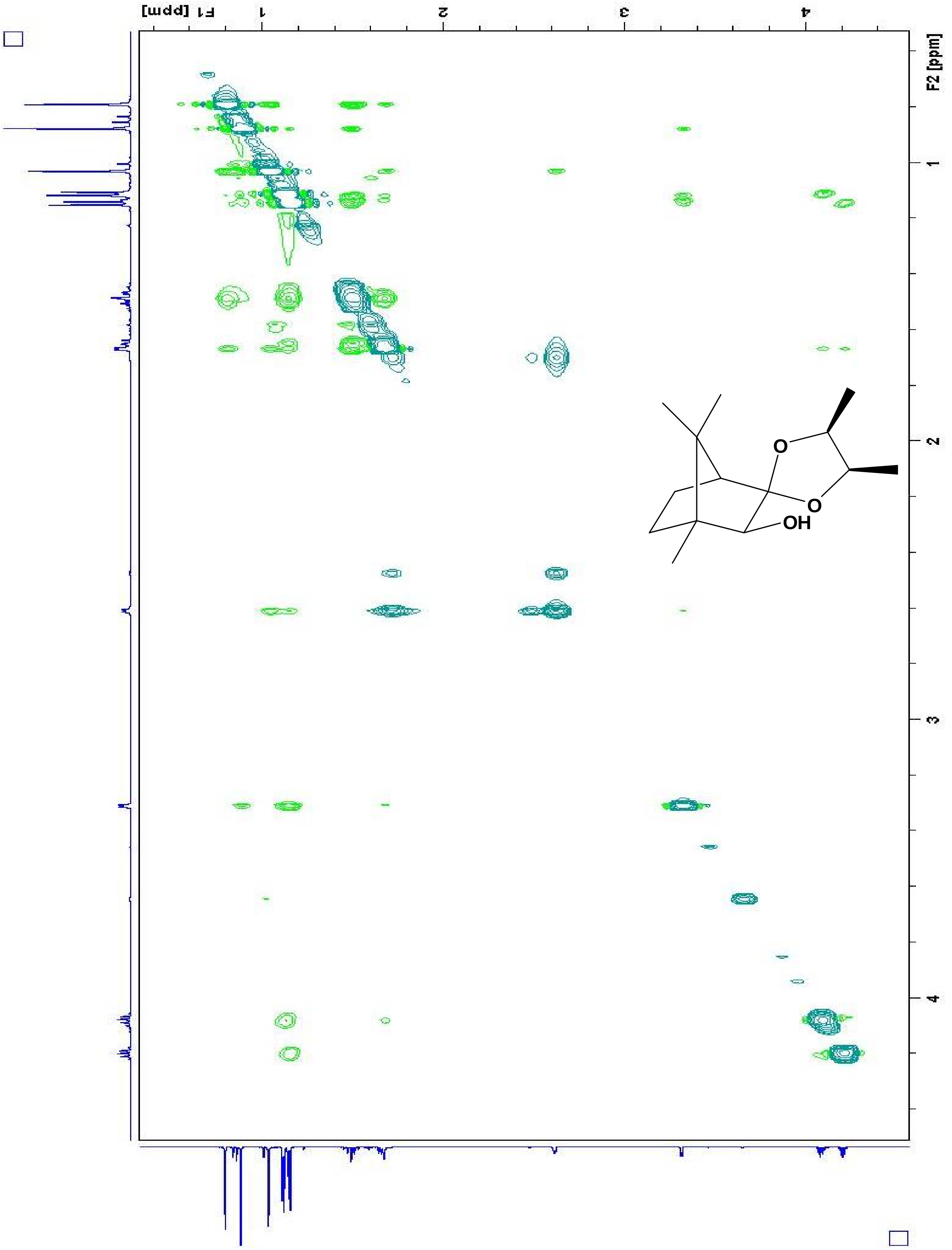
^{1}H NMR Spectrum (600 MHz) of Compound **10a-4**



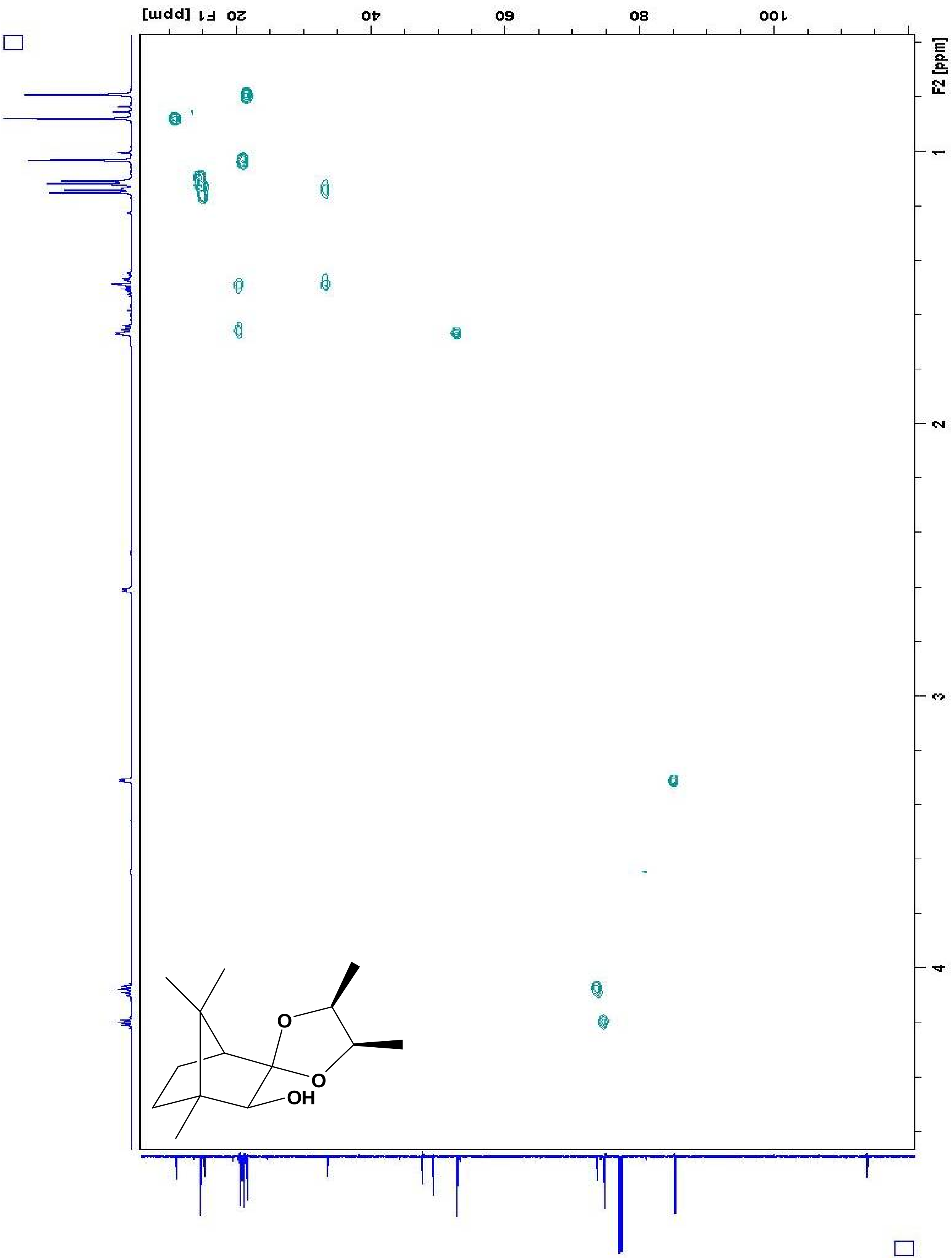
^{13}C NMR Spectrum (600 MHz) of Compound **10a-4**



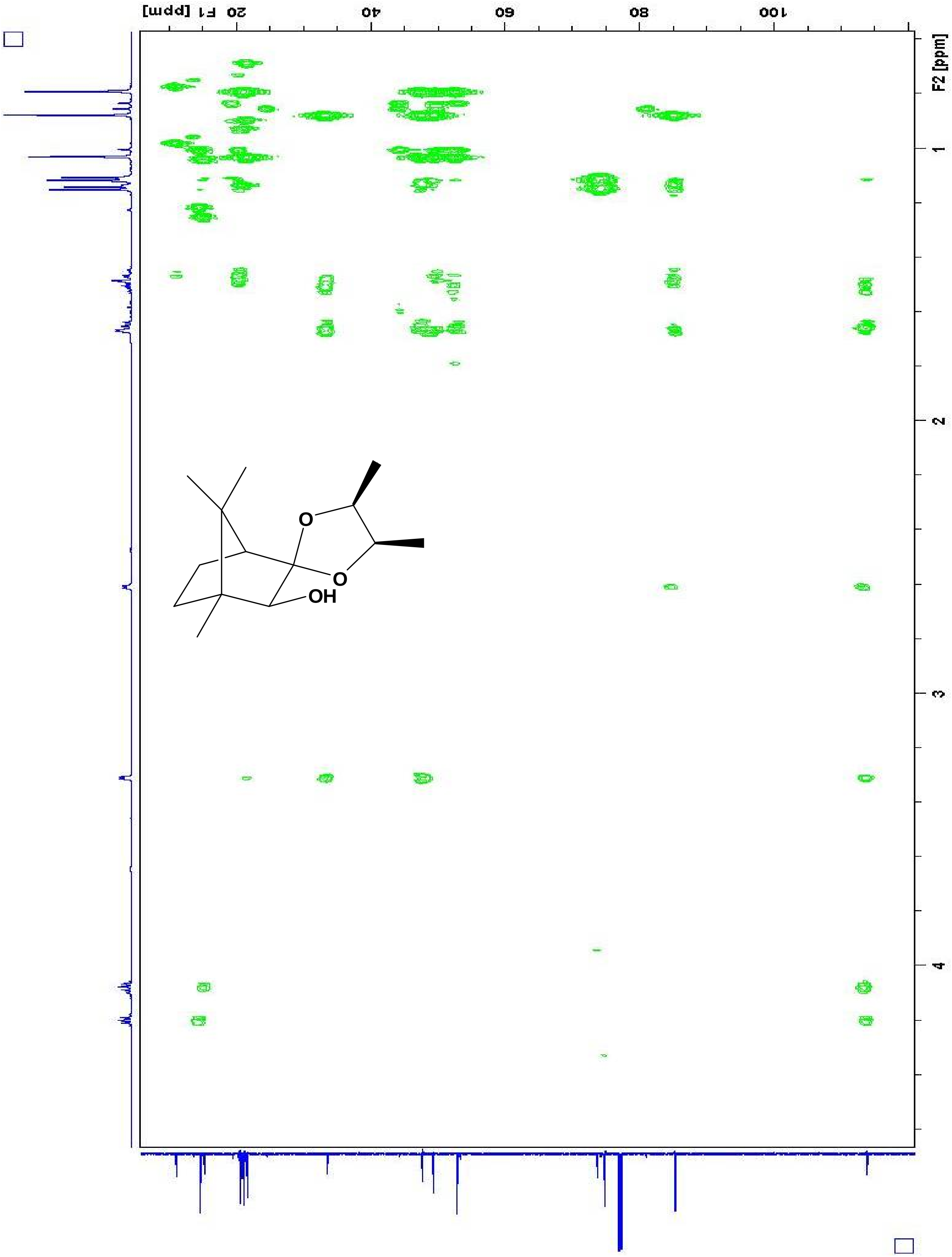
COSY Spectrum (600MHz) of Compound **10a-4**



NOESY Spectrum (600MHz) of Compound **10a-4**

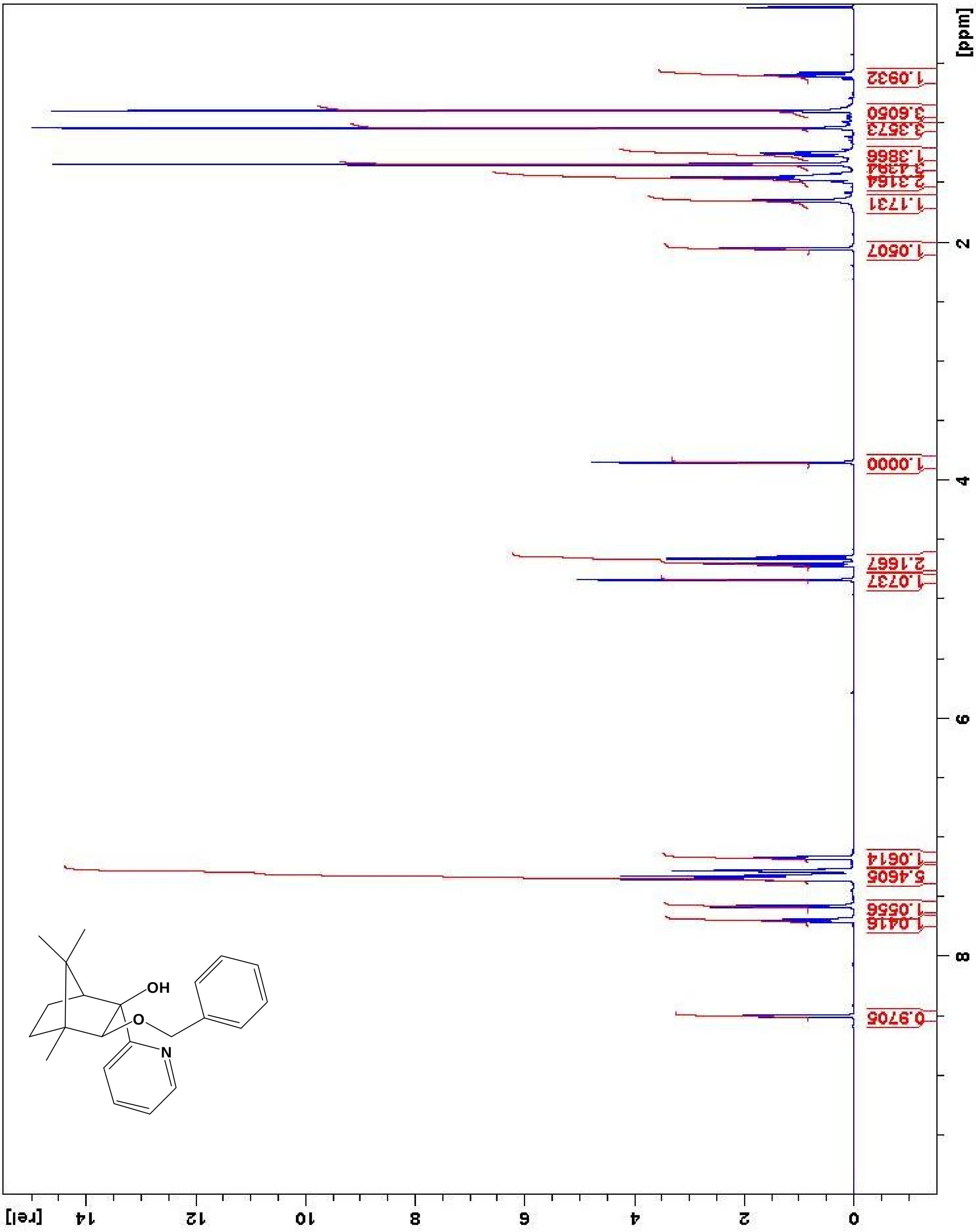


HSQC Spectrum (600MHz) of Compound **10a-4**

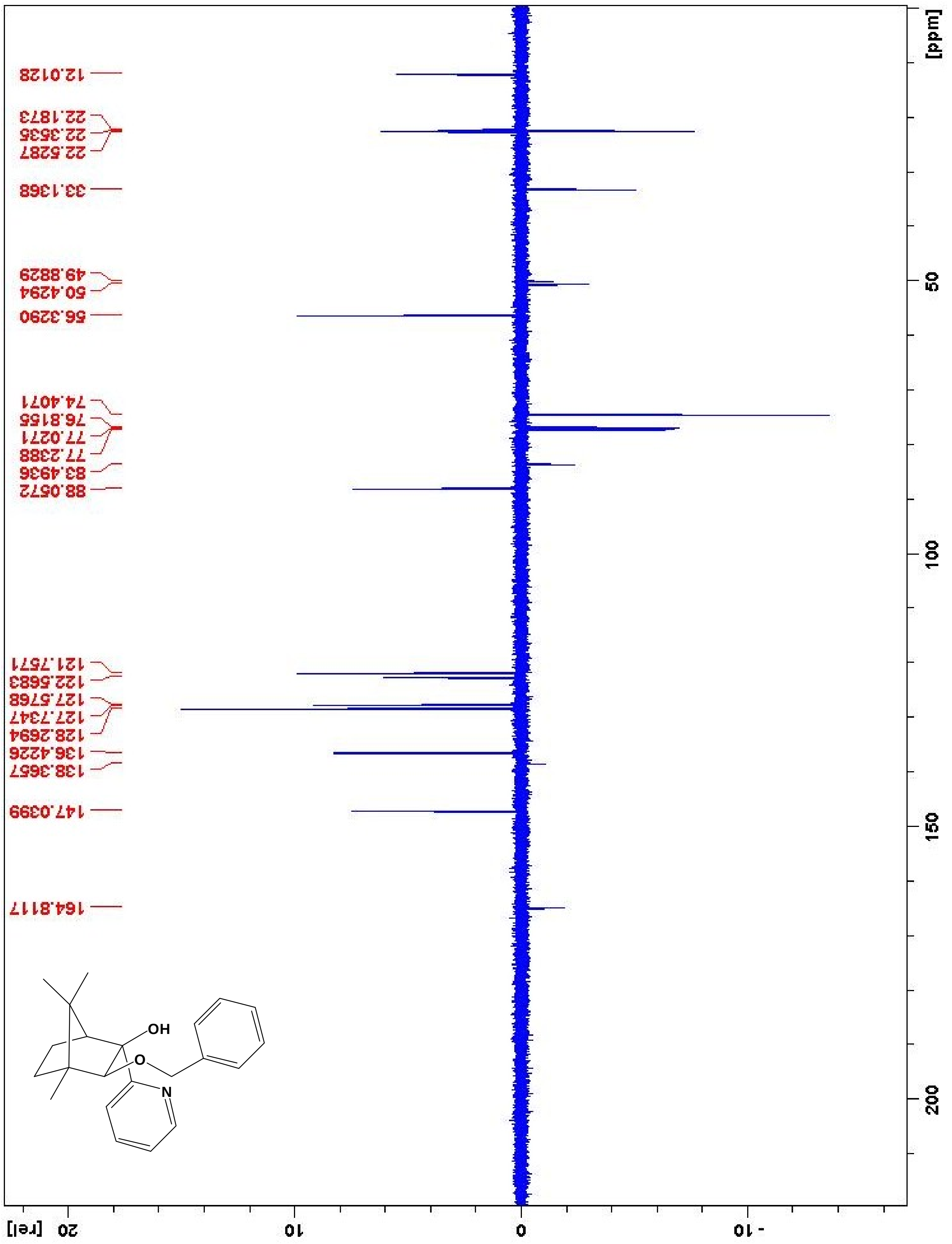


HMBC Spectrum (600MHz) of Compound **10a-4**

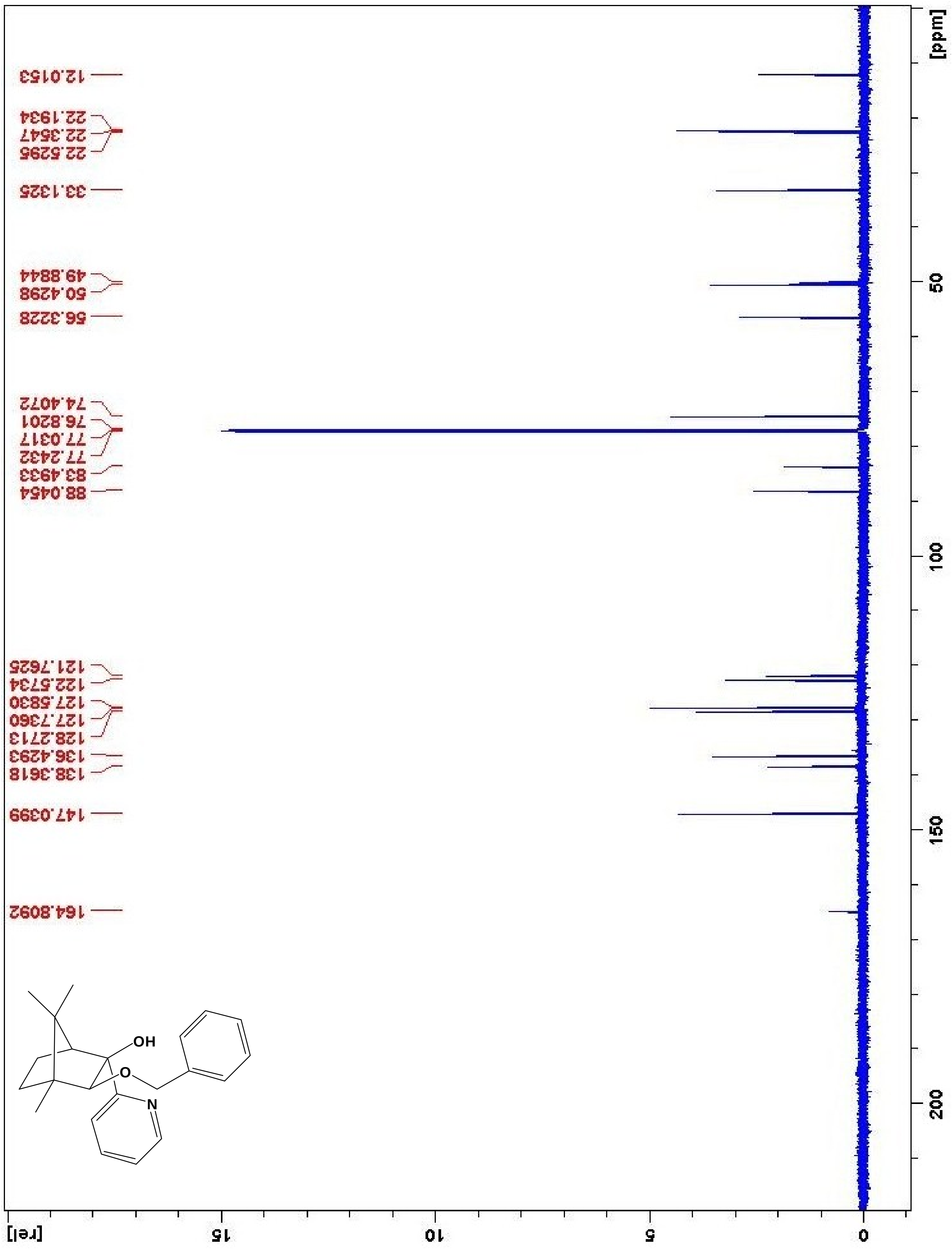
APPENDIX 2-NMR SPECTRA FOR CHAPTER 5



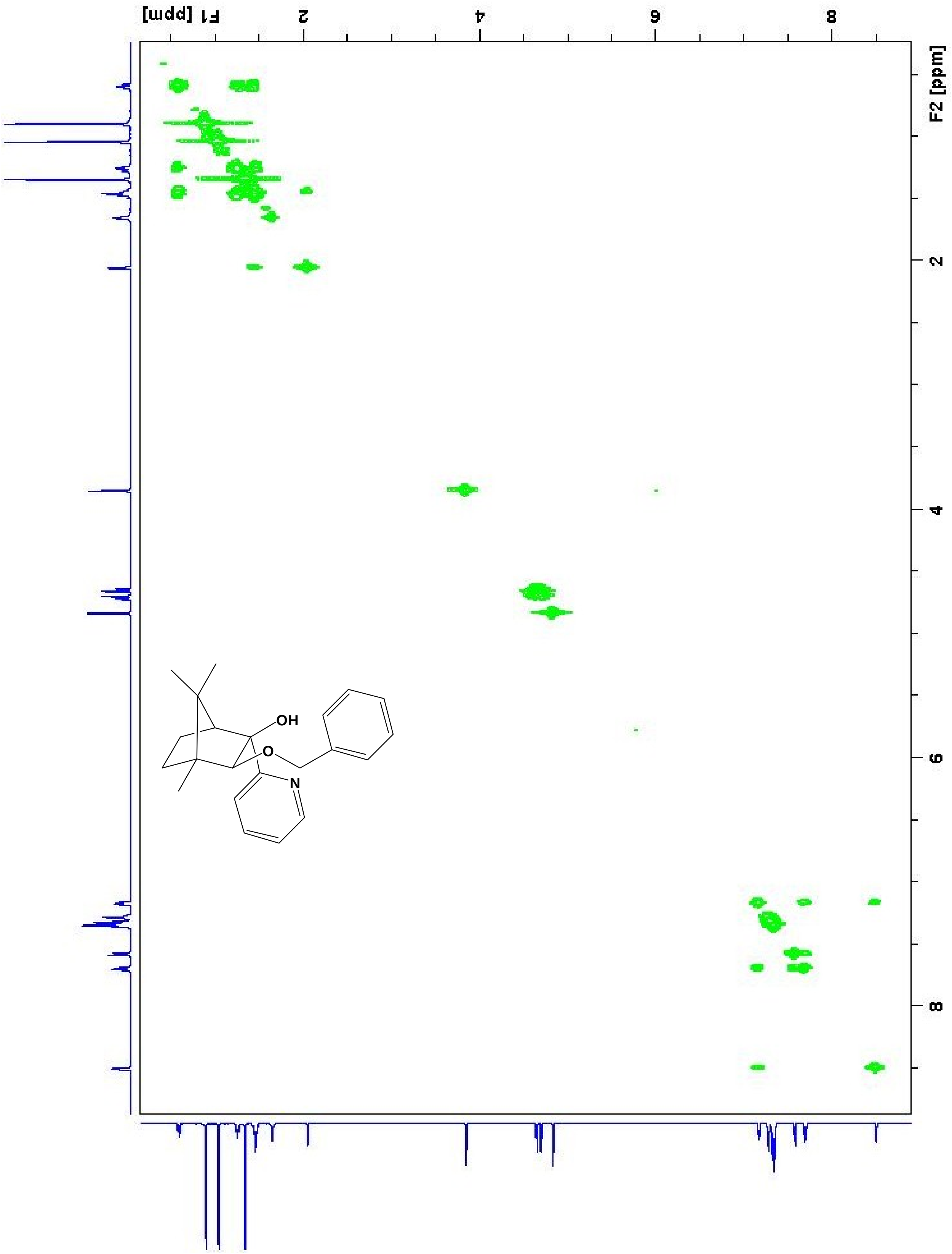
^{1}H NMR (600 MHz) Spectrum of Ligand **1** in $CDCl_3$



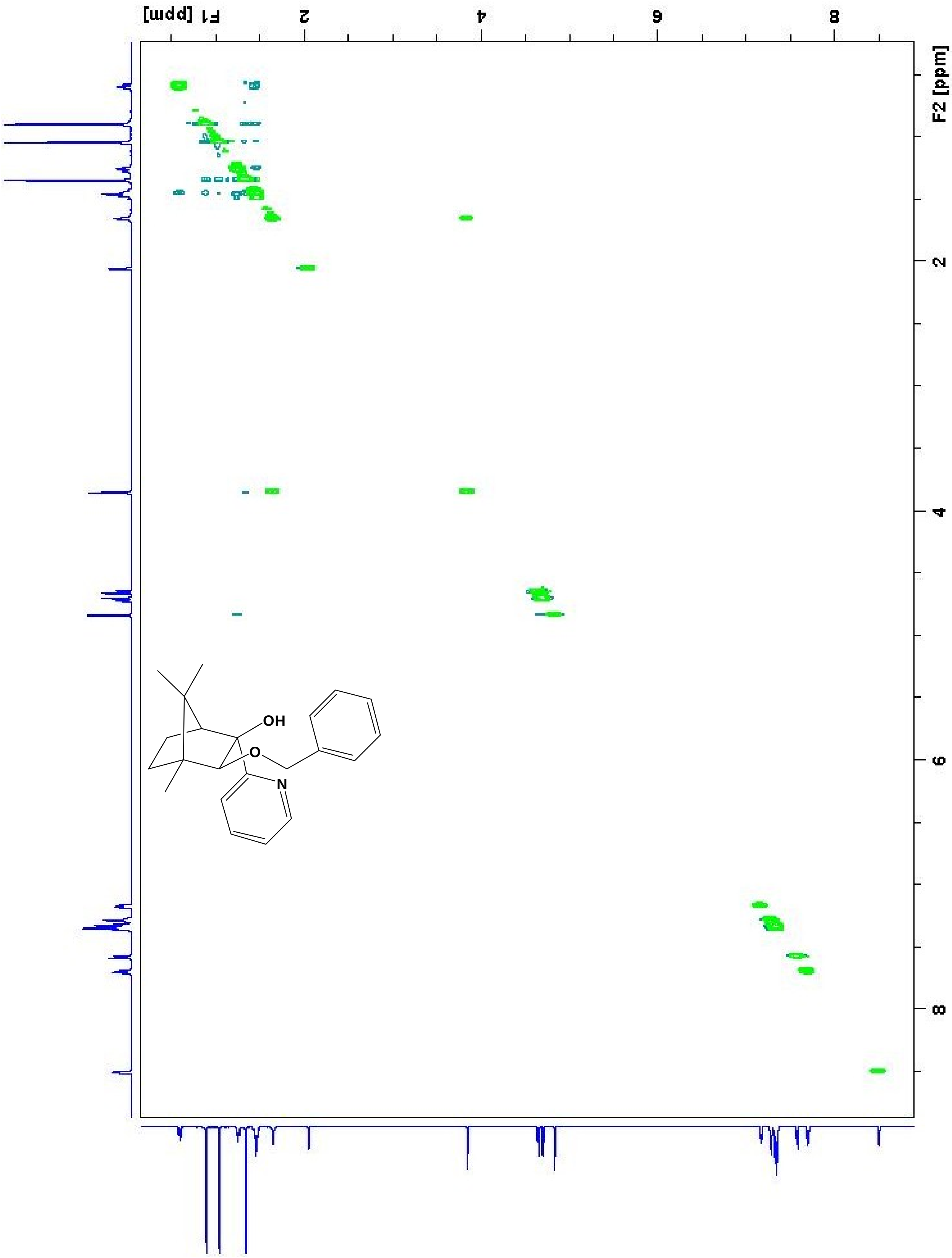
^{13}C APT NMR Spectrum (600 MHz) of Ligand **1** in $CDCl_3$



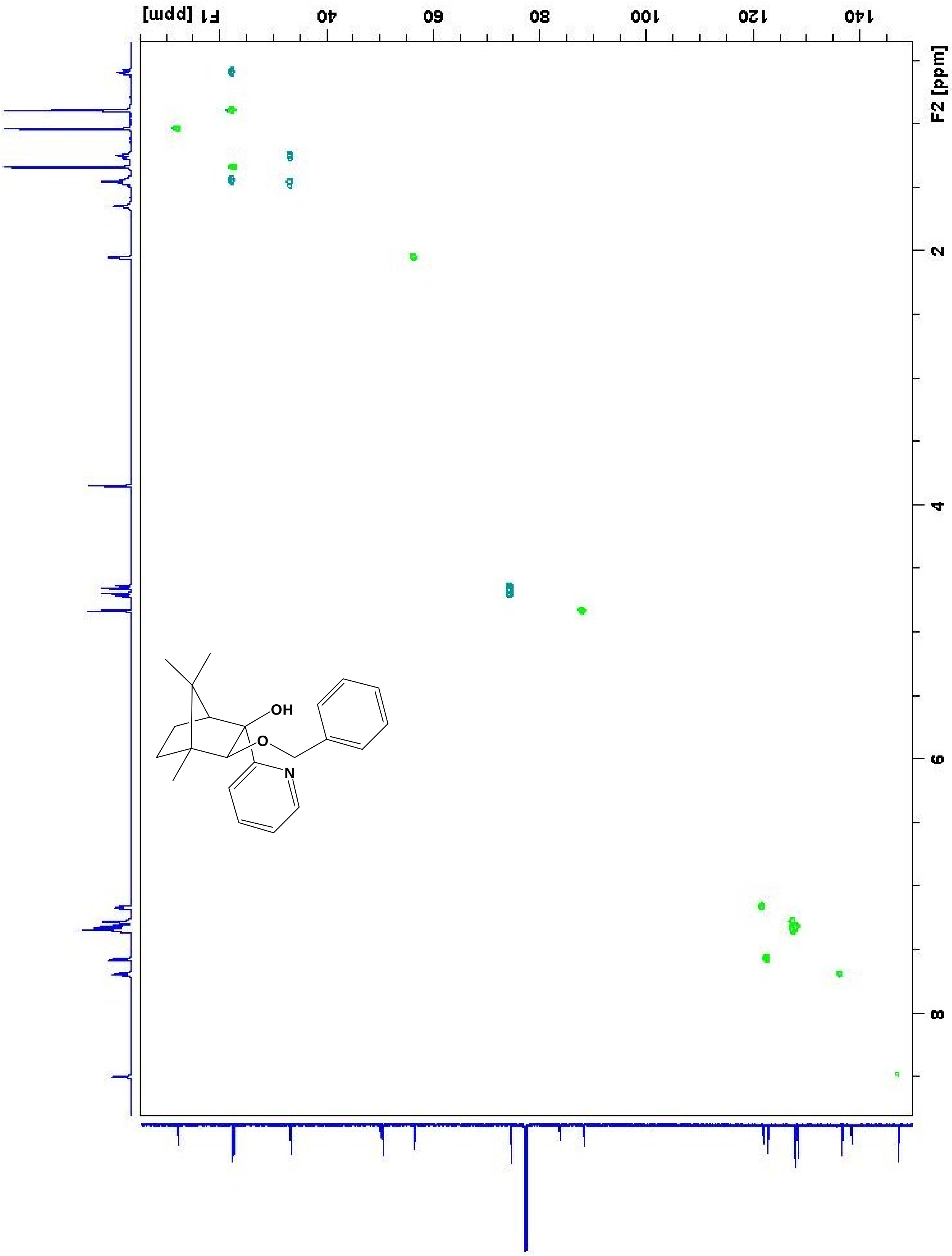
^{13}C NMR Spectrum (600 MHz) of Ligand **1** in $CDCl_3$



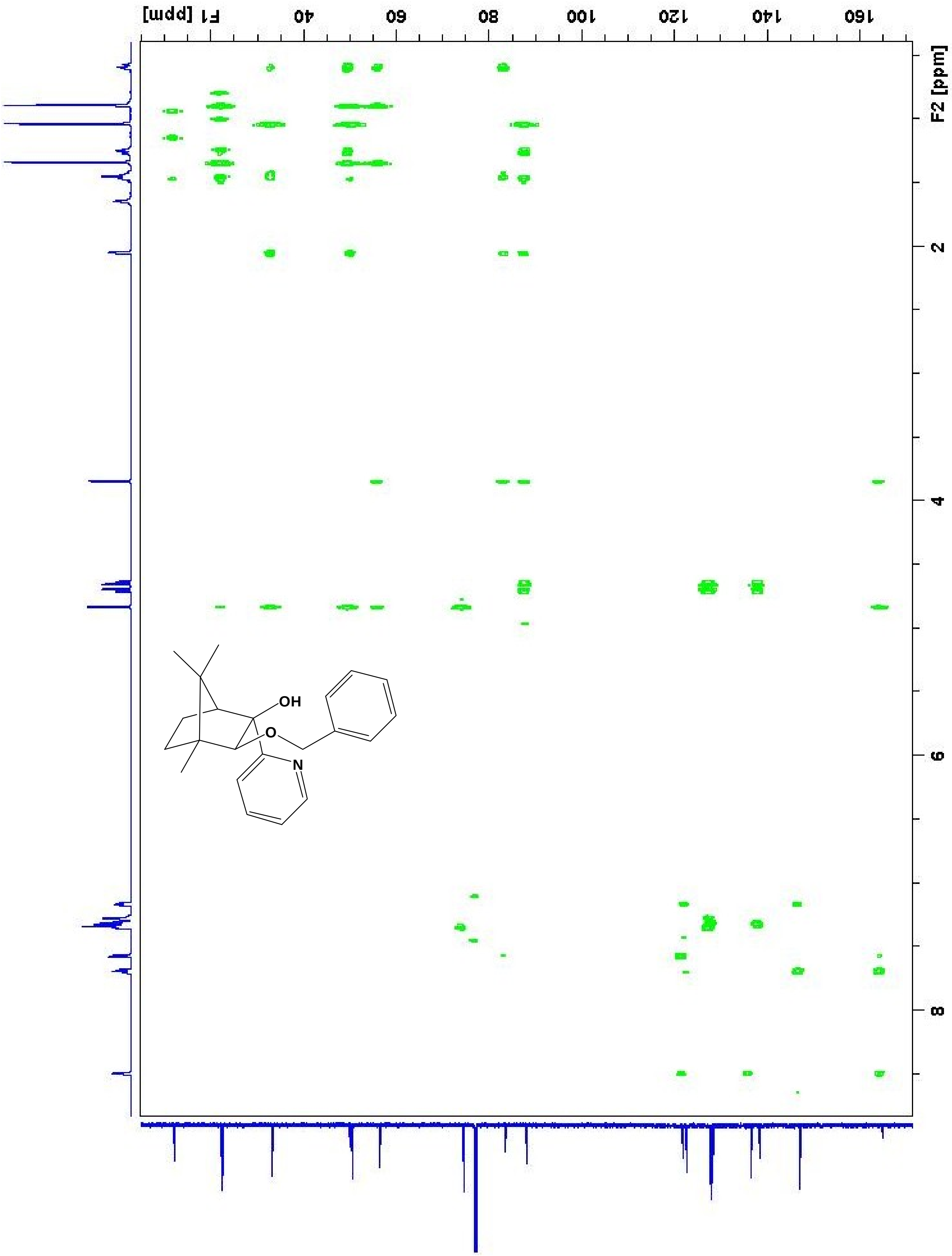
COSY Spectrum (600 MHz) of Ligand **1** in $CDCl_3$



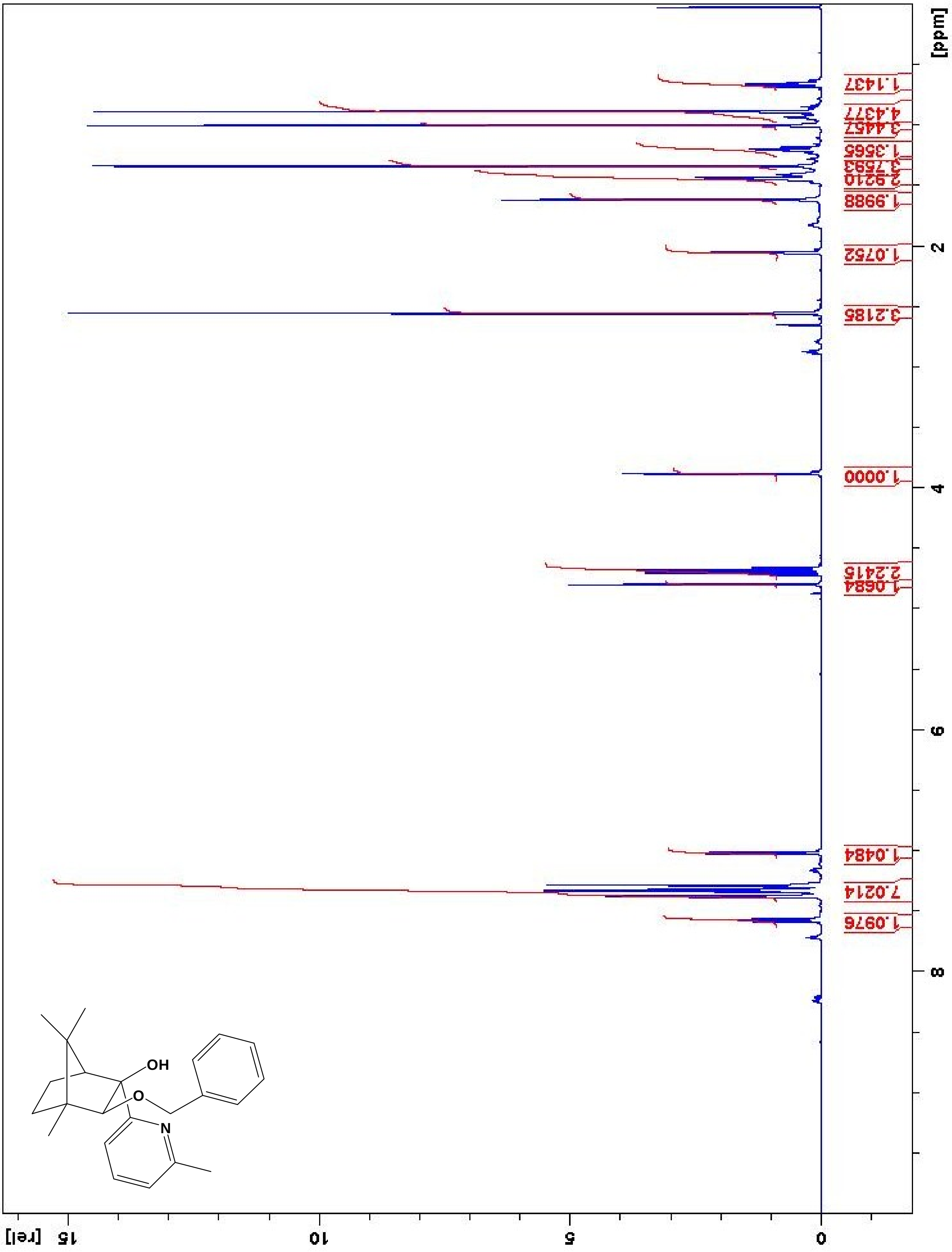
NOESY Spectrum (600 MHZ) of Ligand **1** in $CDCl_3$



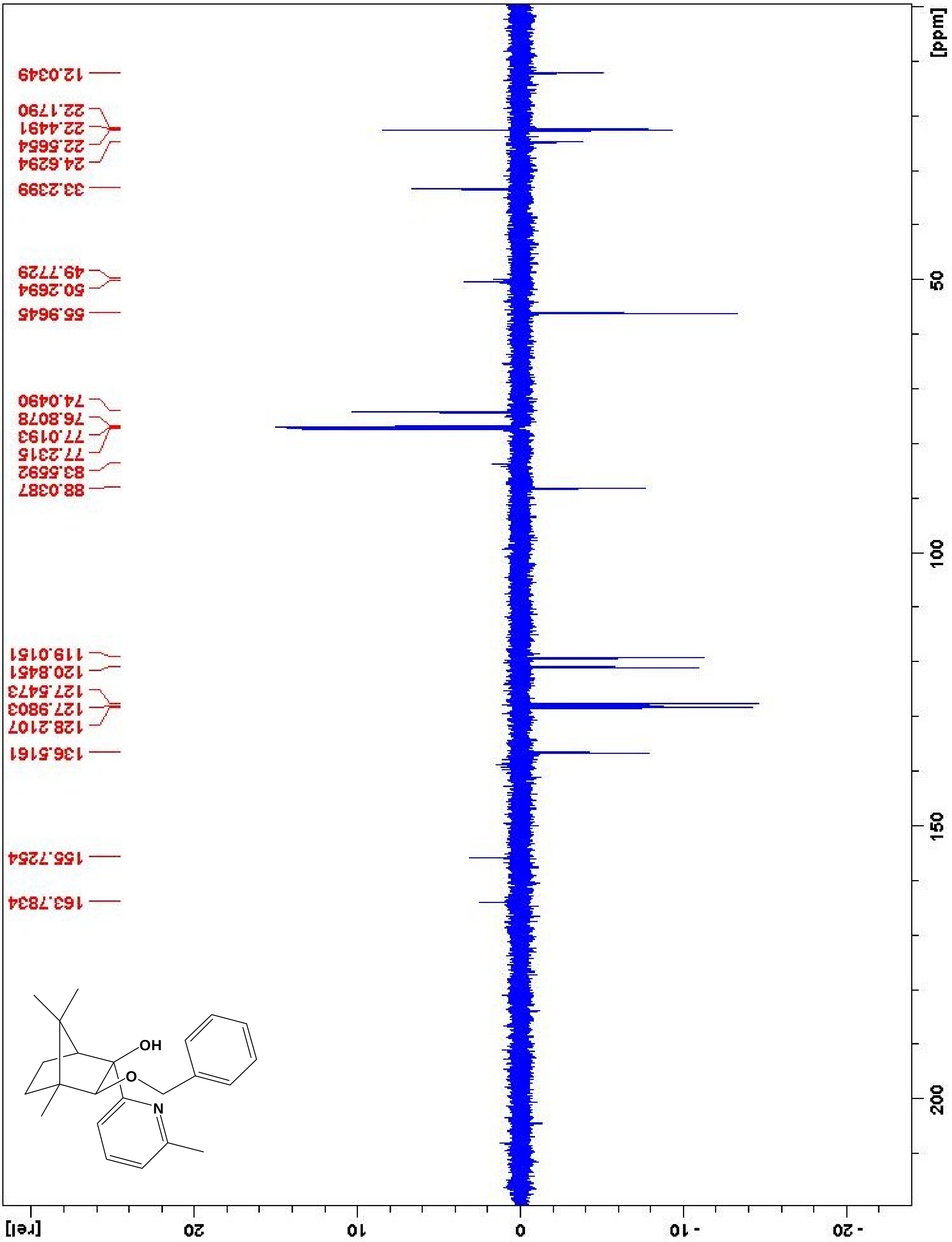
HSQC Spectrum (600 MHz) of Ligand **1** in $CDCl_3$



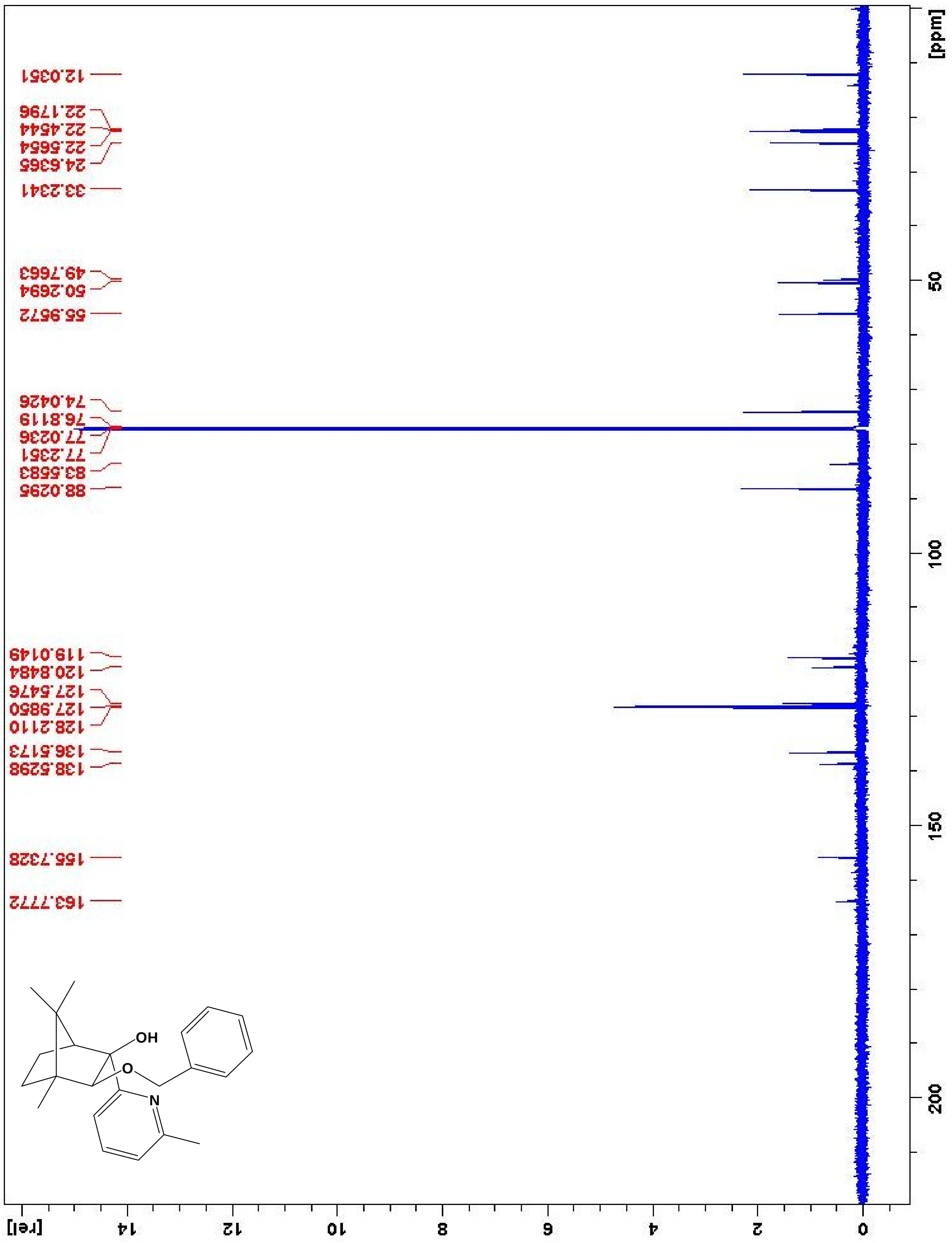
HMBC Spectrum (600 MHz) of Ligand **1** in $CDCl_3$



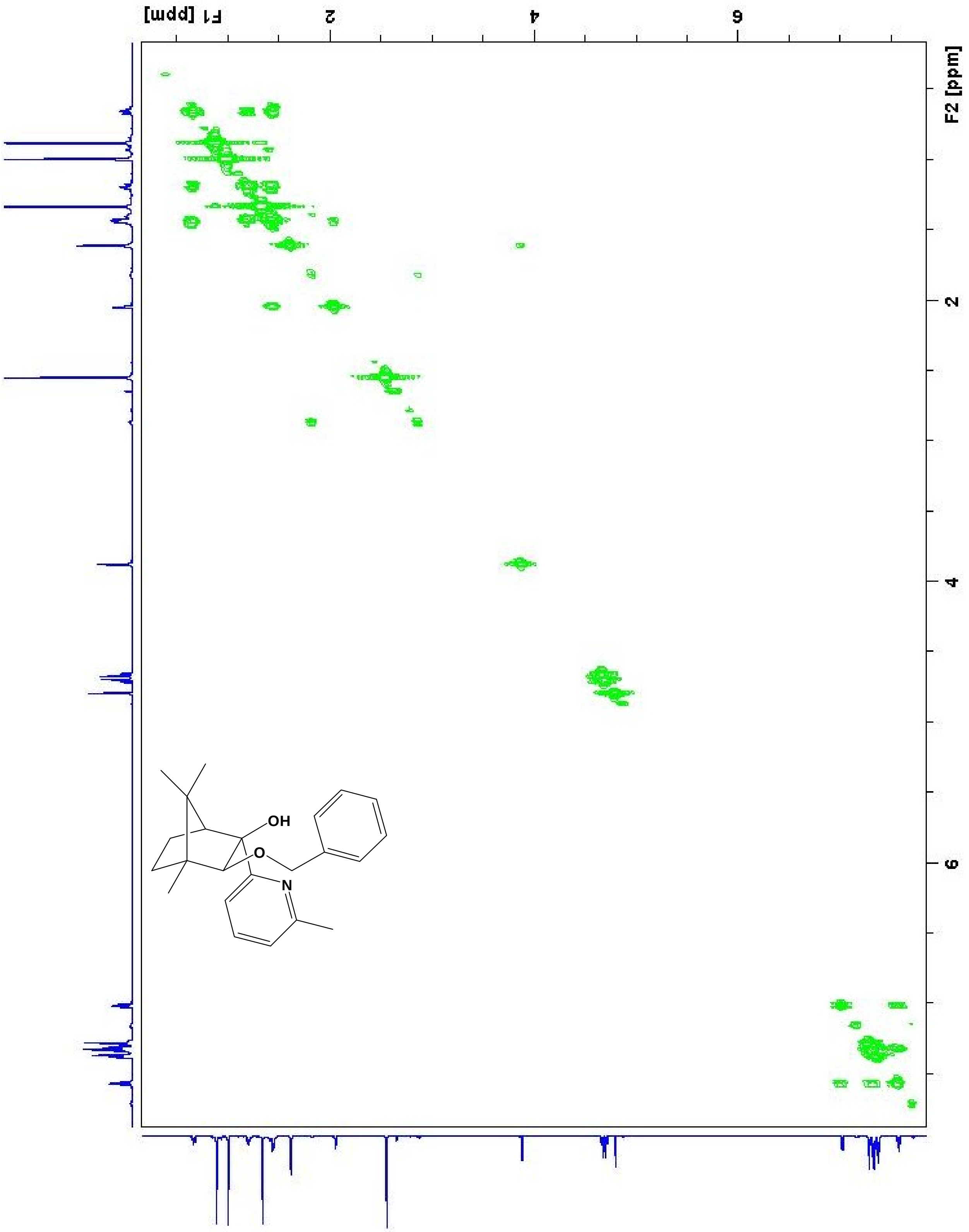
^{1}H NMR (600 MHz) Spectrum of Ligand **2** in $CDCl_3$



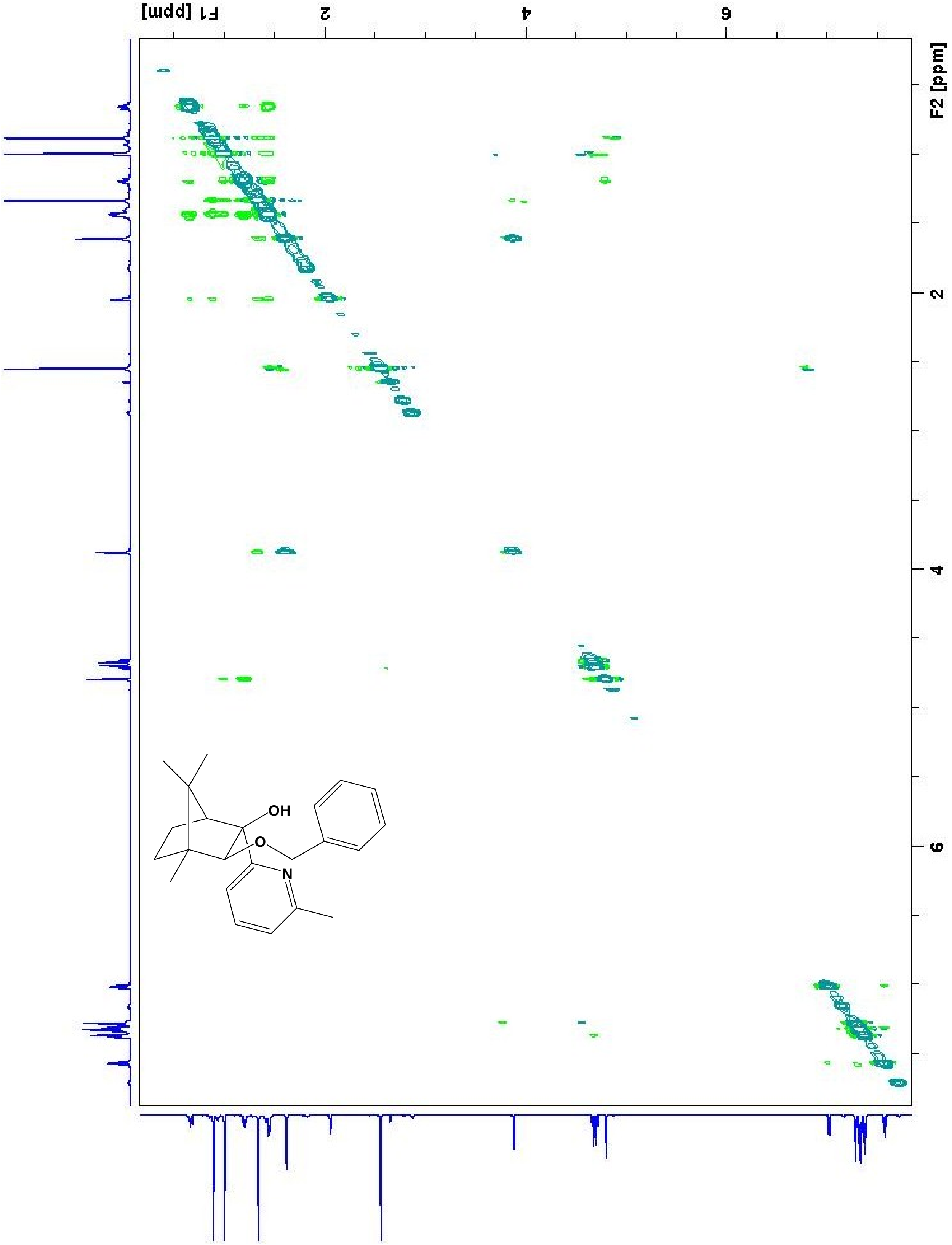
^{13}C APT NMR Spectrum (600 MHz) of Ligand **2** in $CDCl_3$



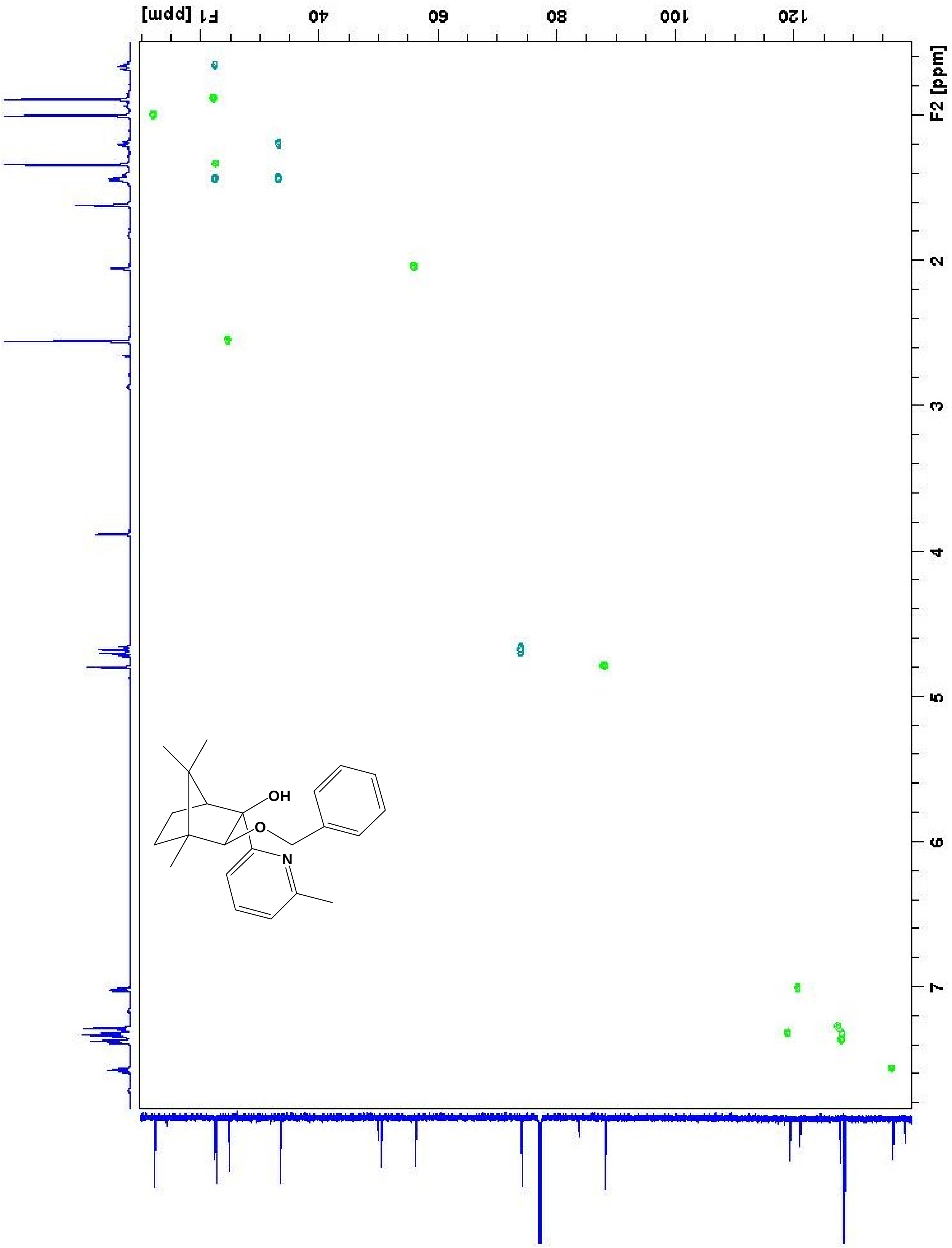
^{13}C NMR Spectrum (600 MHz) of Ligand **2** in $CDCl_3$



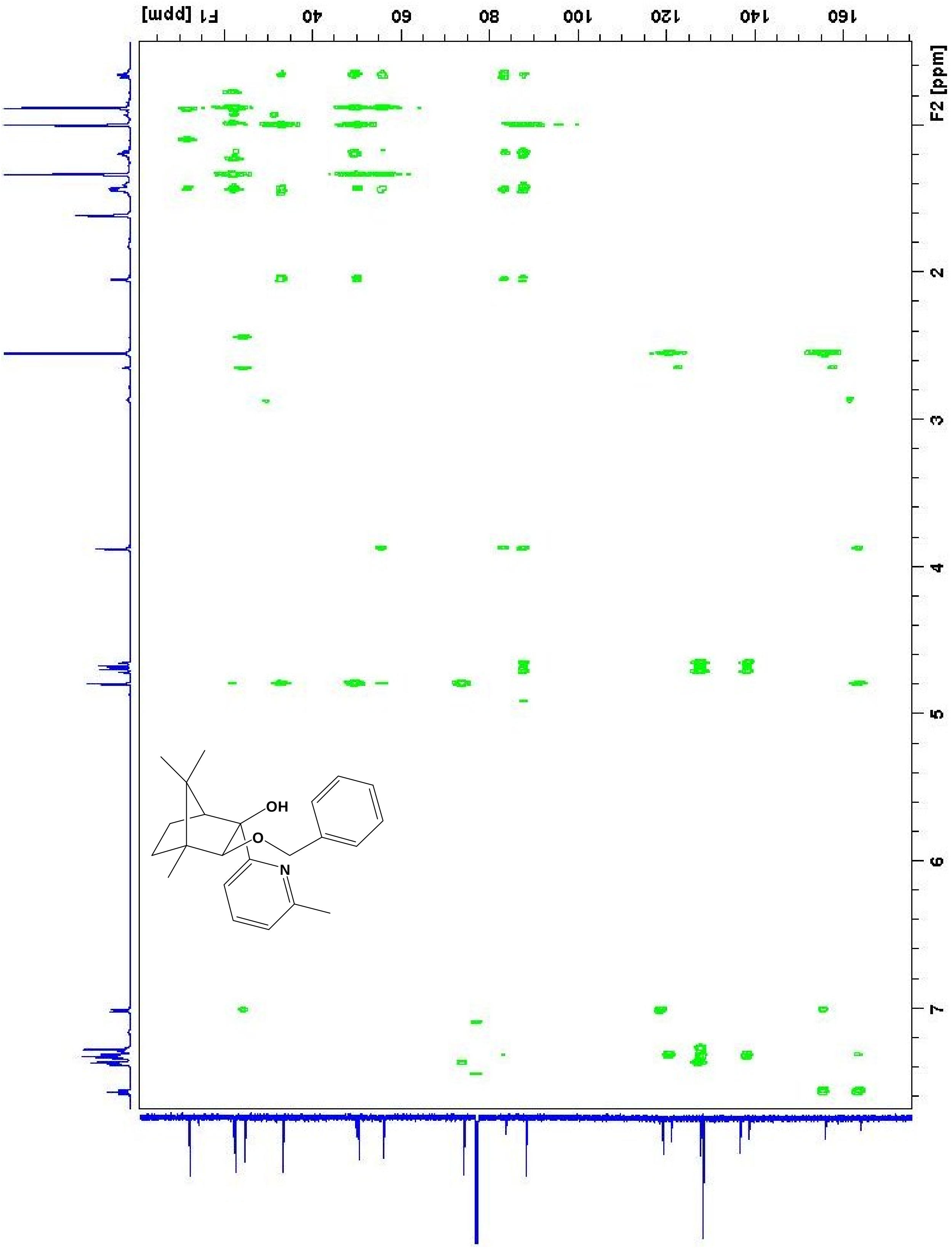
COSY Spectrum (600 MHz) of Ligand **2** in $CDCl_3$



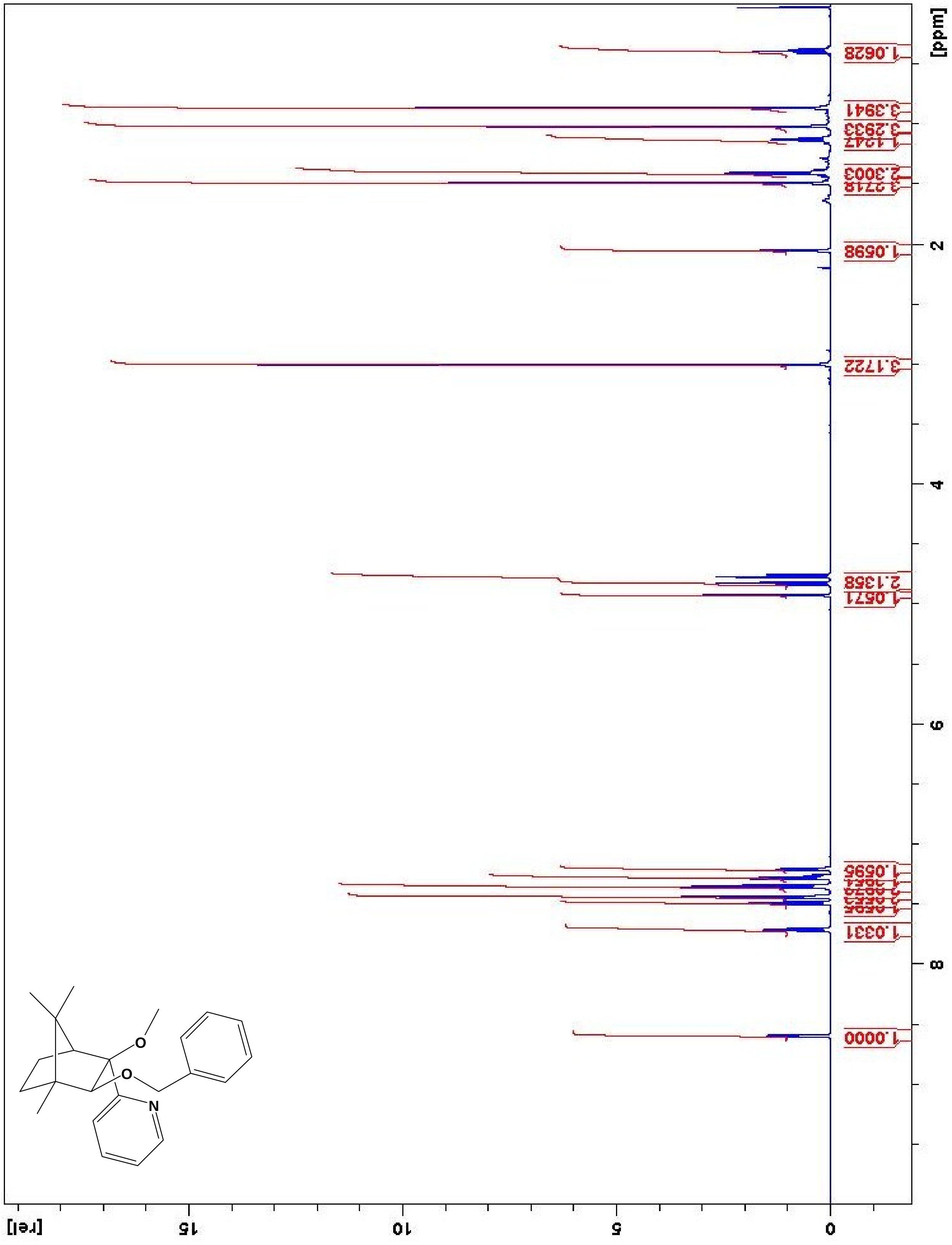
NOESY Spectrum (600 MHz) of Ligand **2** in $CDCl_3$



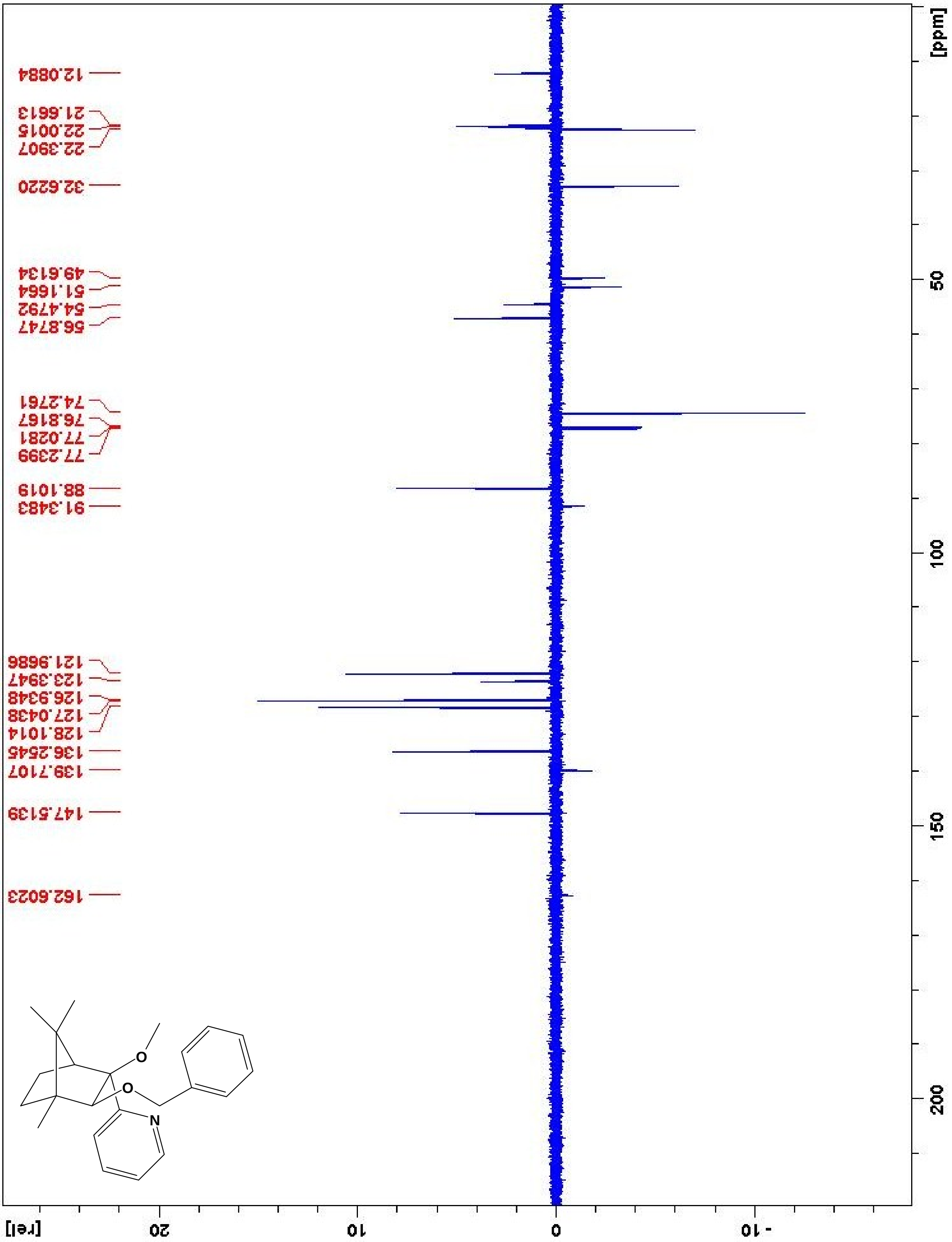
HSQC Spectrum (600 MHz) of Ligand **2** in $CDCl_3$



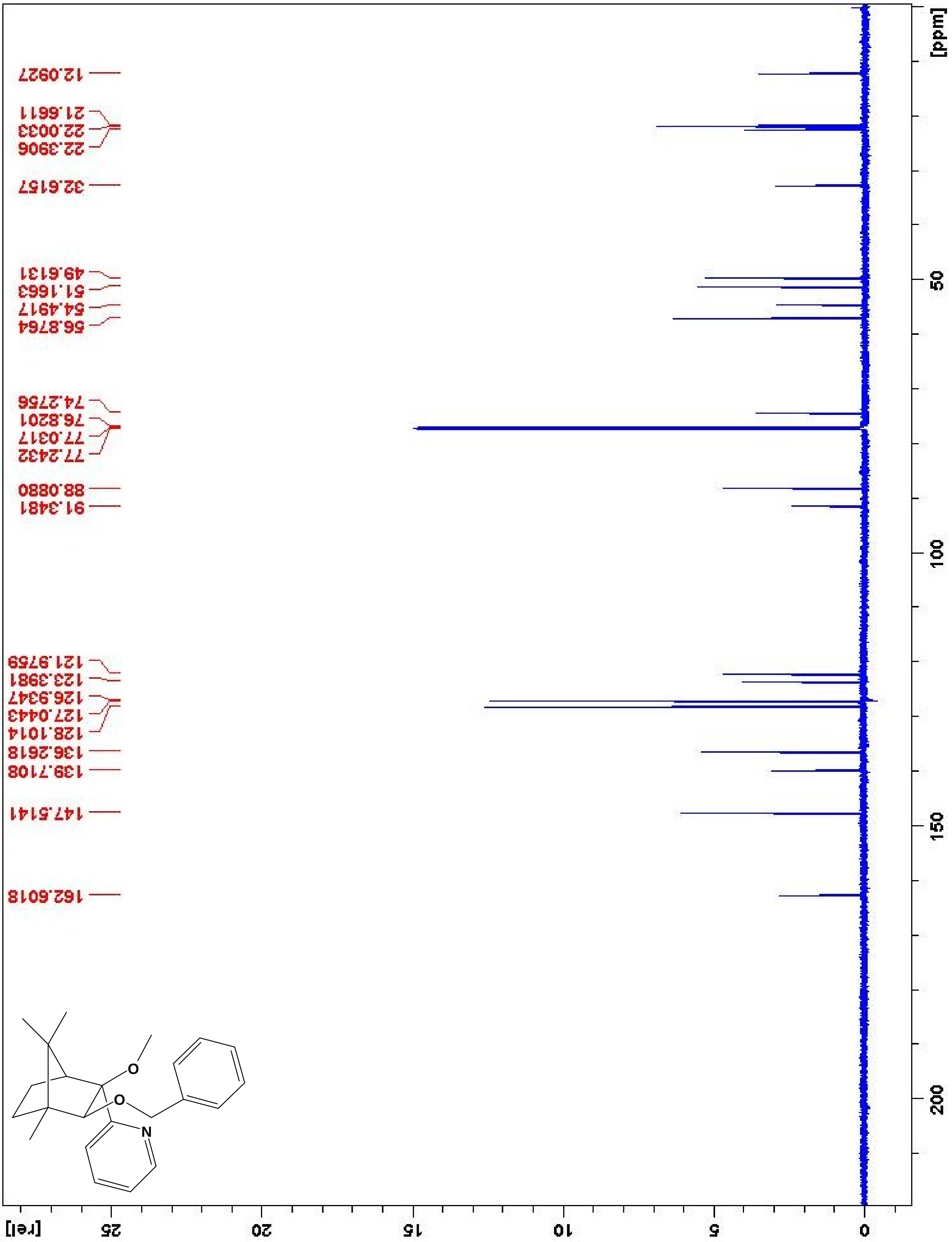
HMBC Spectrum (600 MHz) of Ligand **2** in $CDCl_3$



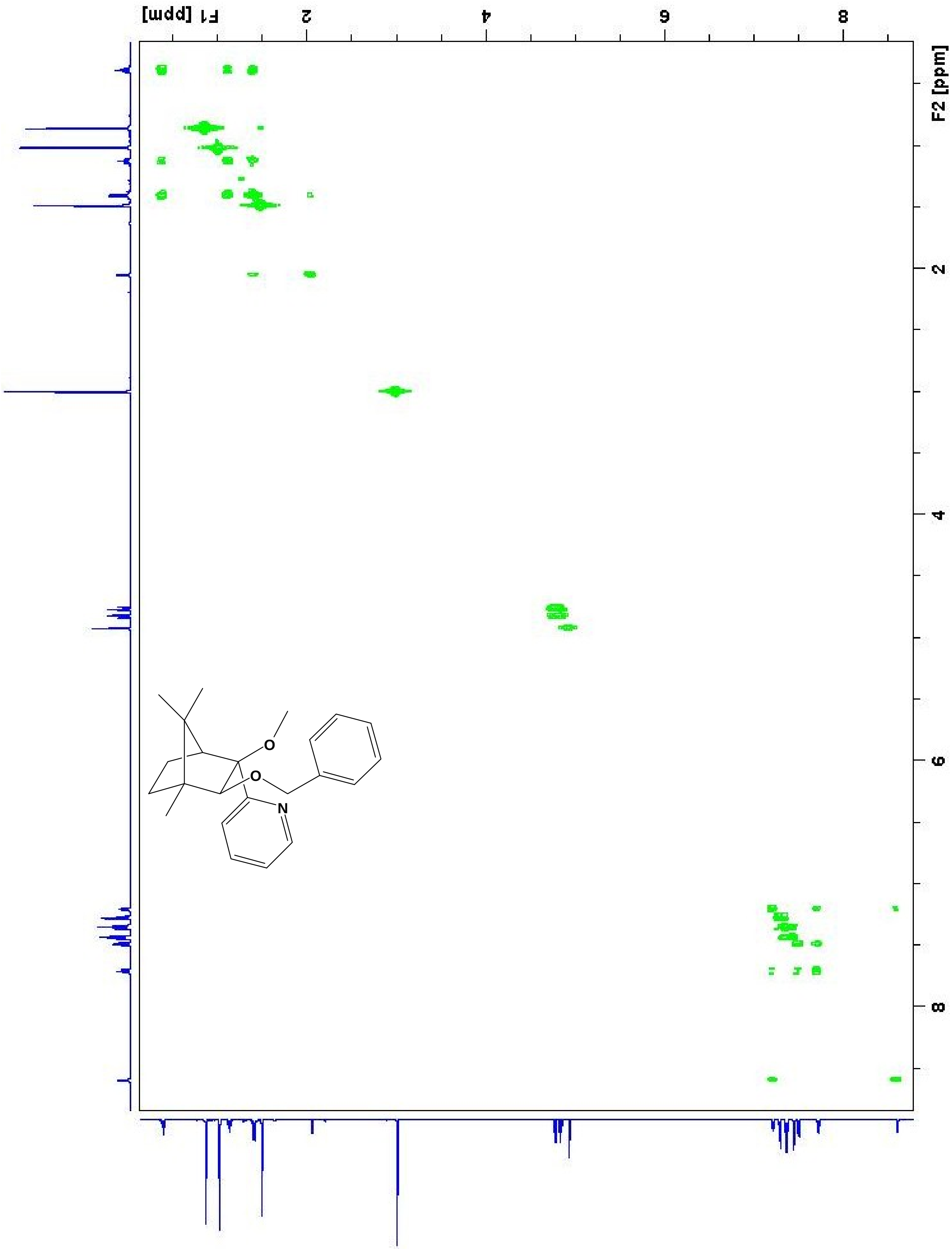
^{1}H NMR Spectrum (600 MHz) of Ligand **3** in $CDCl_3$



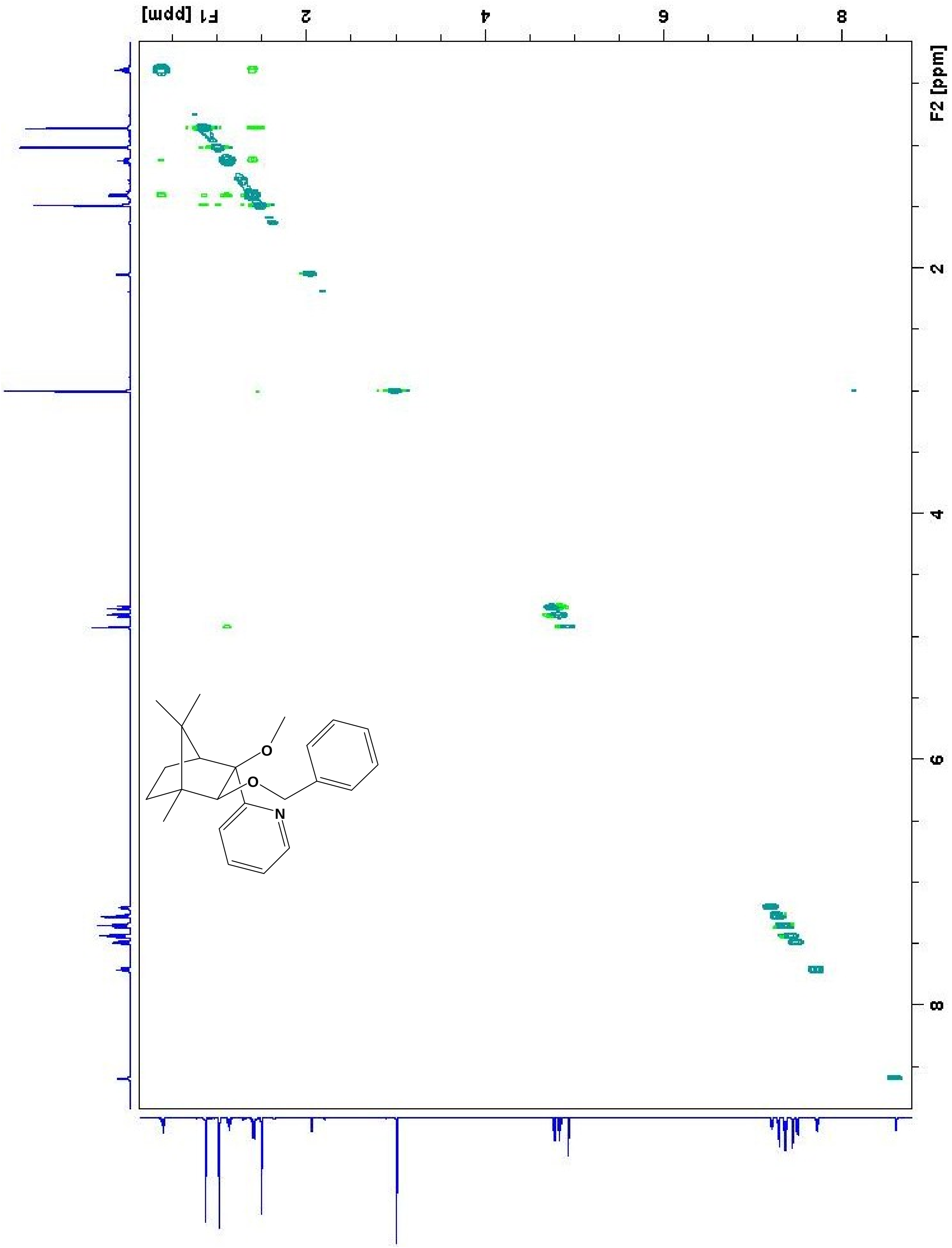
^{13}C APT NMR Spectrum (600 MHz) of Ligand **3** in CDCl$_3$



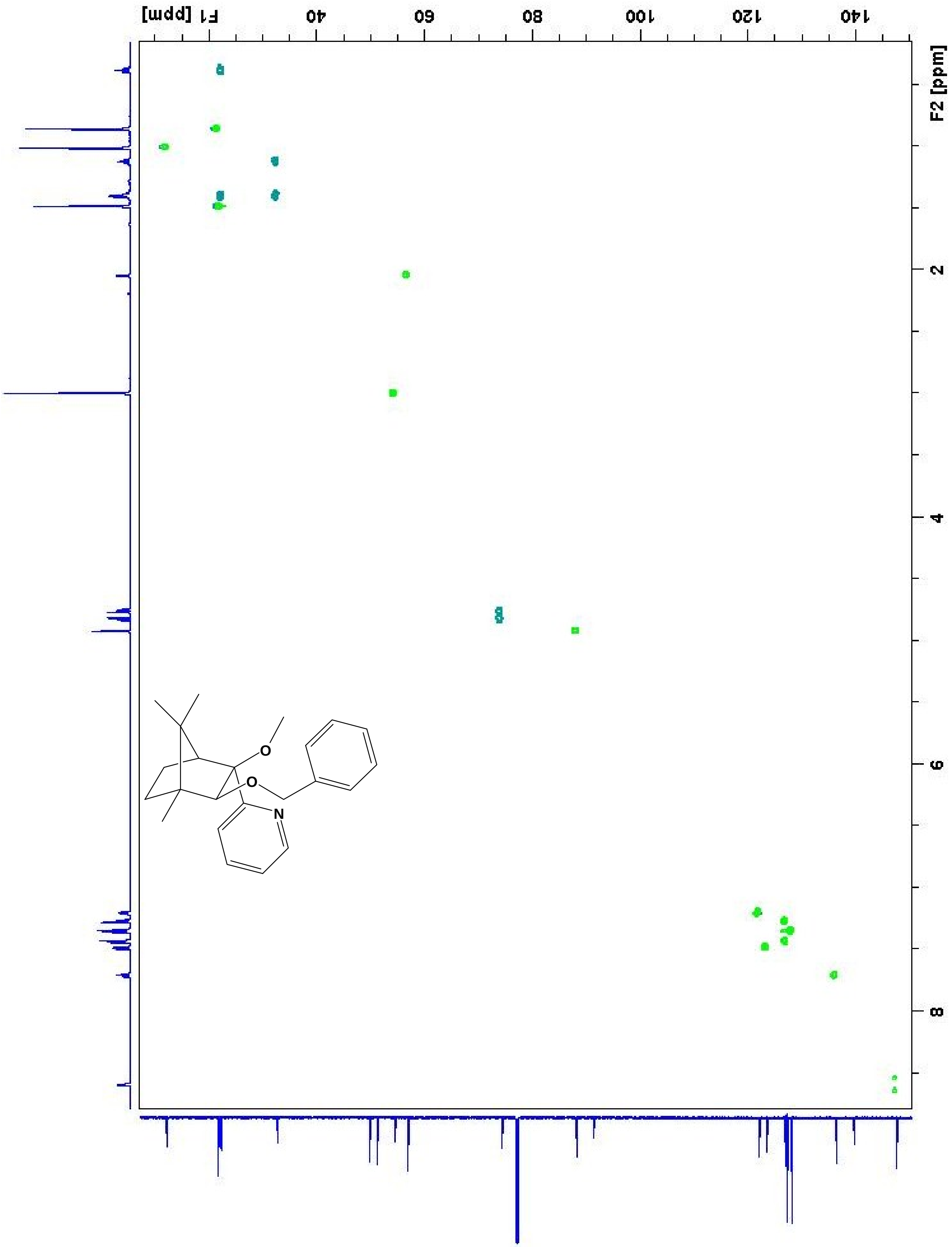
^{13}C NMR Spectrum (600 MHz) of Ligand **3** in $CDCl_3$



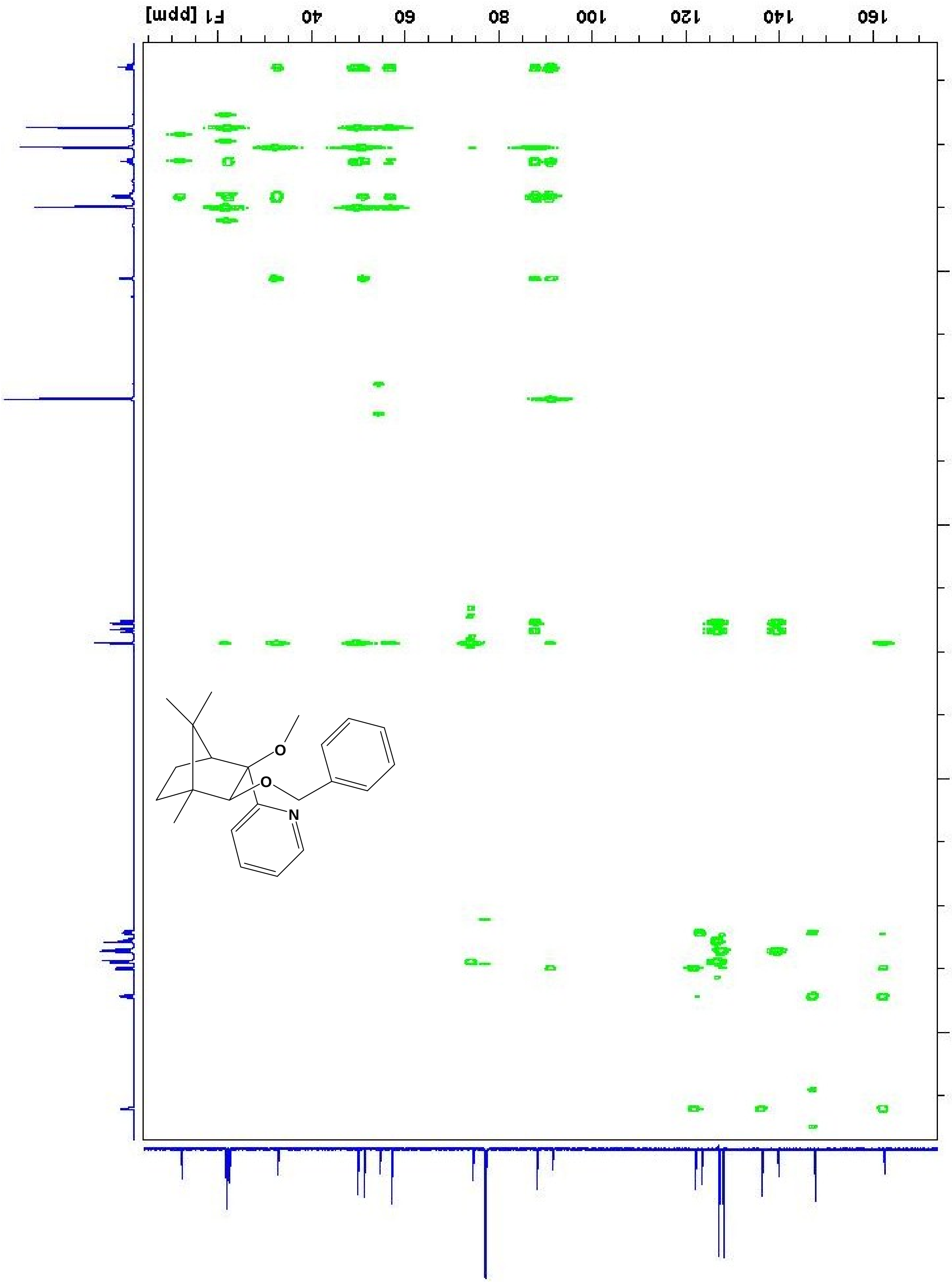
COSY Spectrum (600 MHz) of Ligand **3** in $CDCl_3$



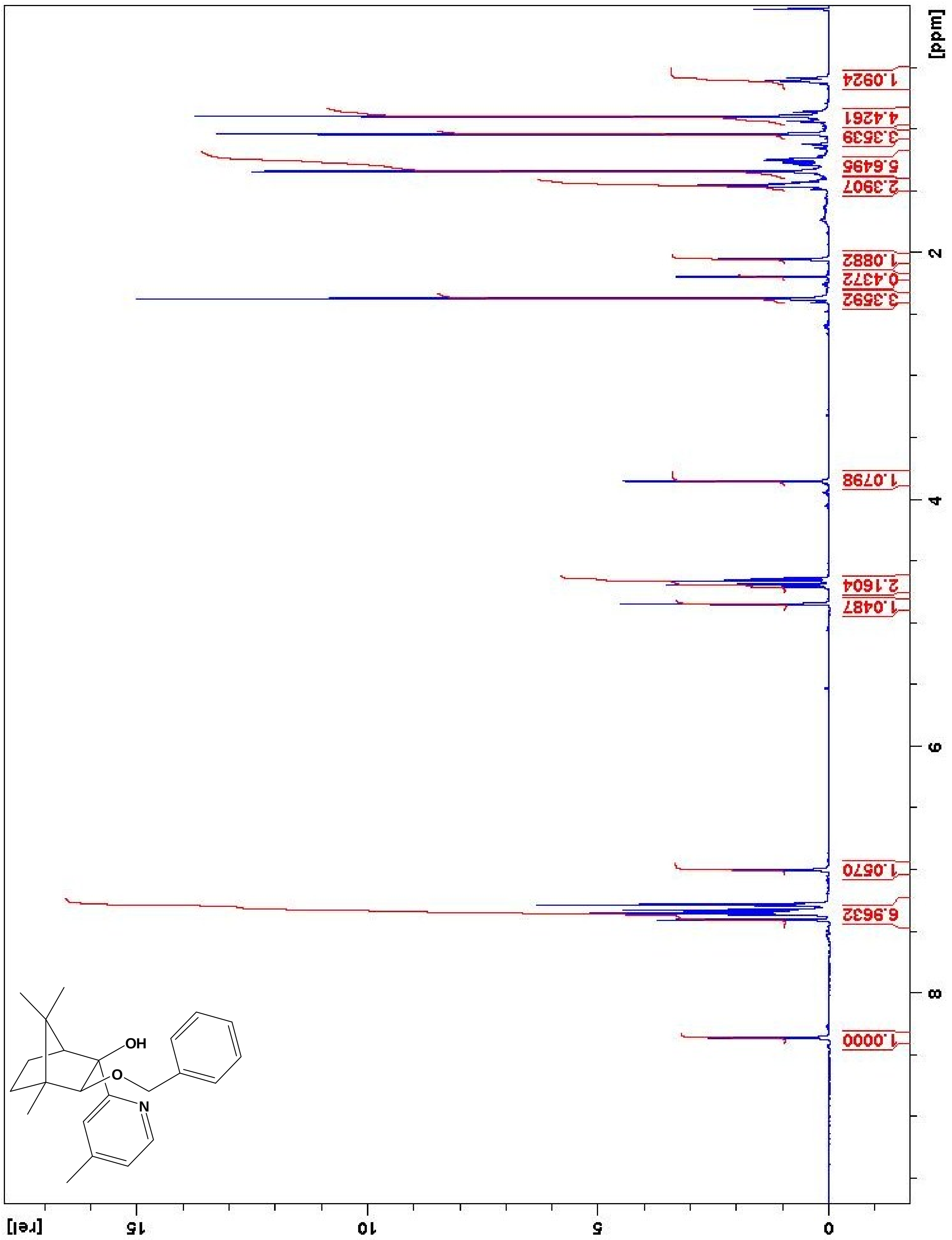
NOESY Spectrum (600 MHz) of Ligand **3** in $CDCl_3$



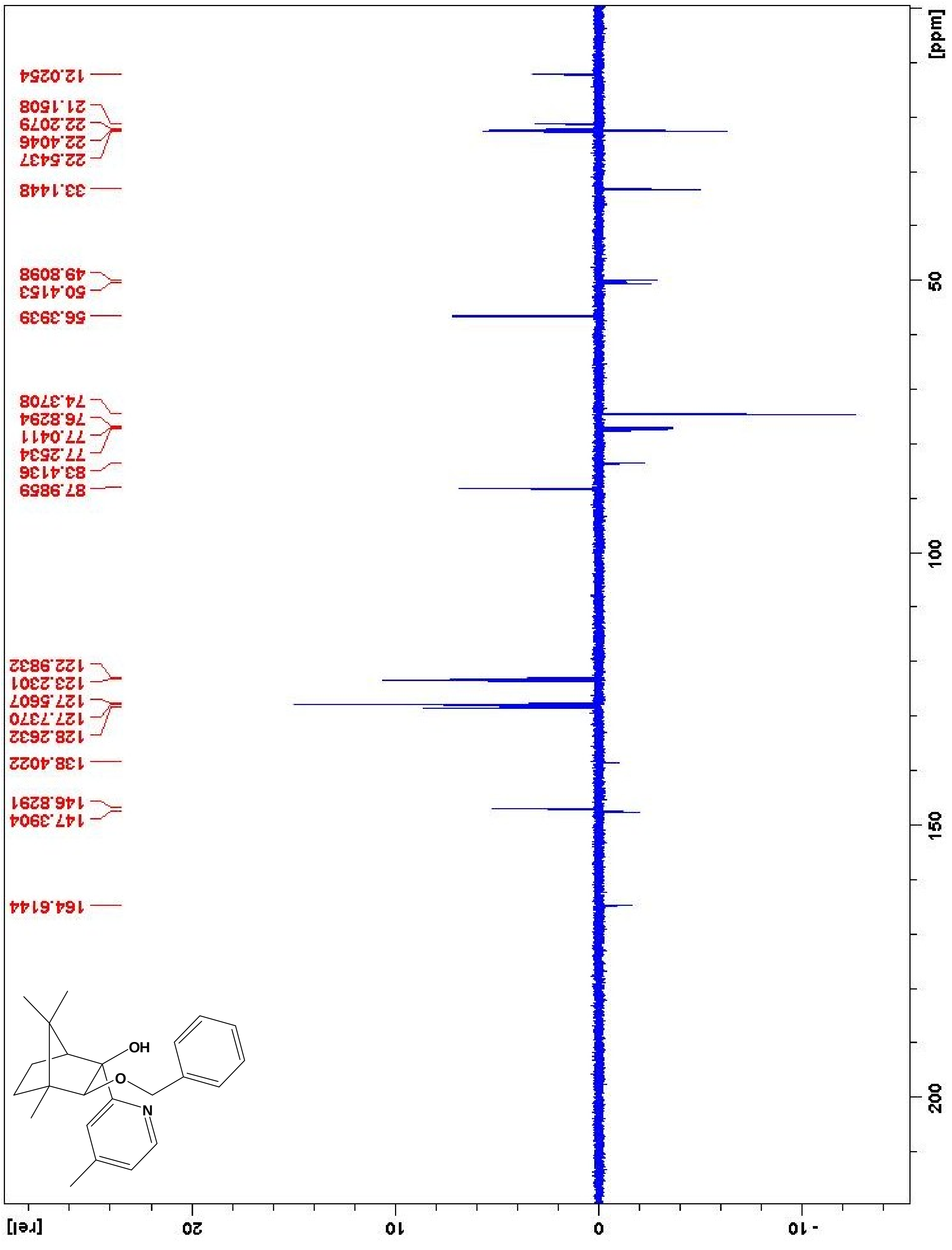
HSQC Spectrum (600 MHz) of Ligand **3** in $CDCl_3$



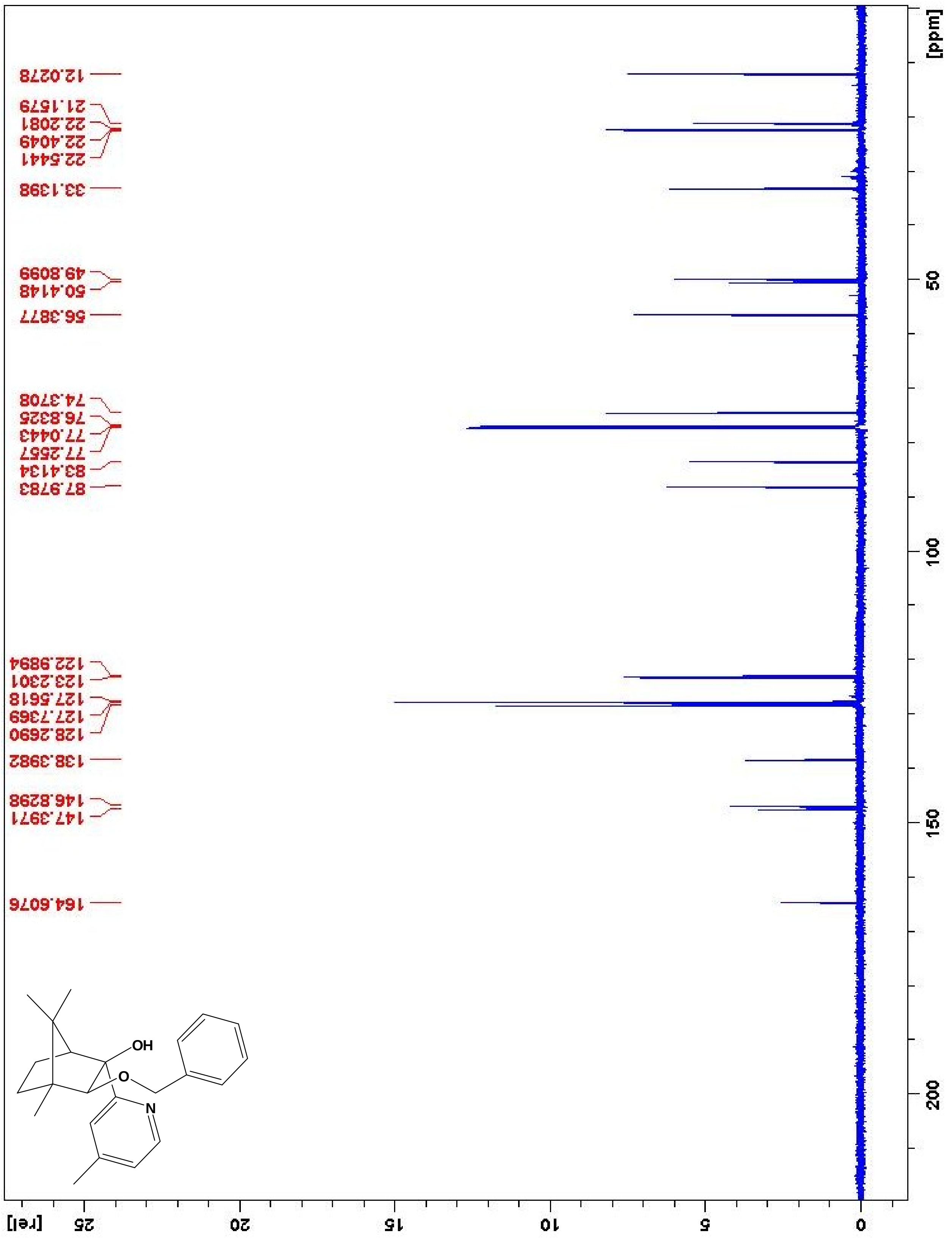
HMBC Spectrum (600 MHz) of Ligand **3** in $CDCl_3$



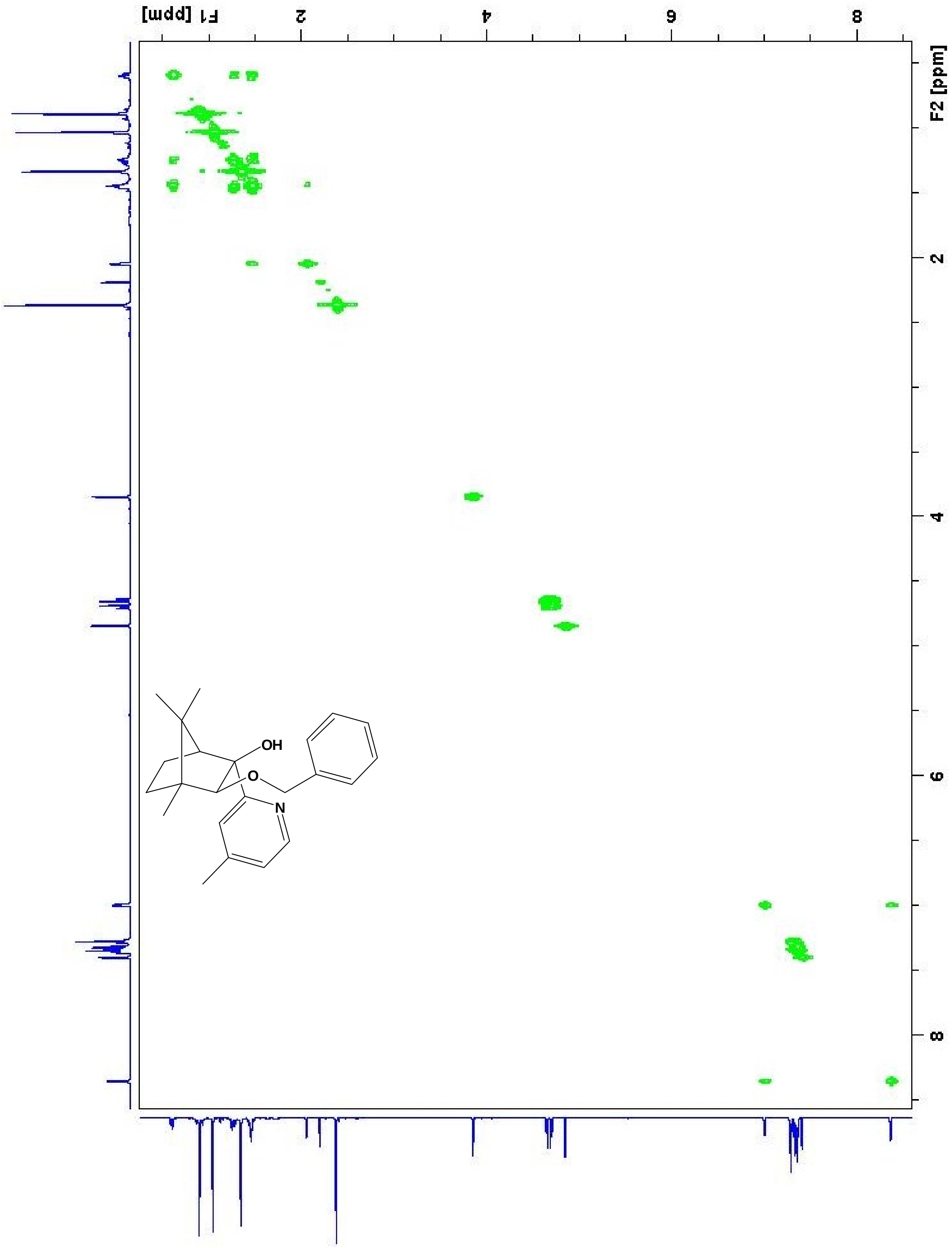
^{1}H NMR Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



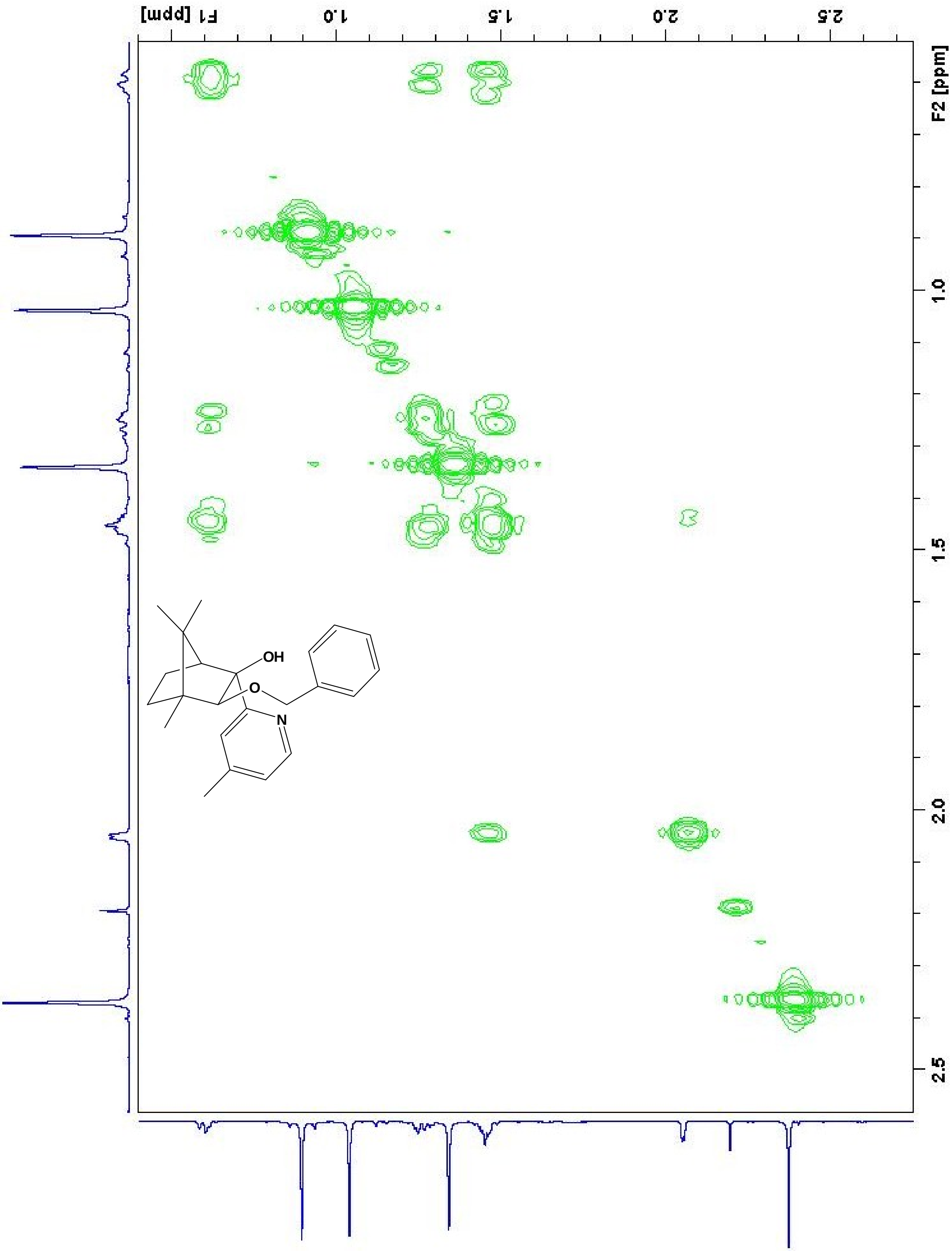
^{13}C APT NMR Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



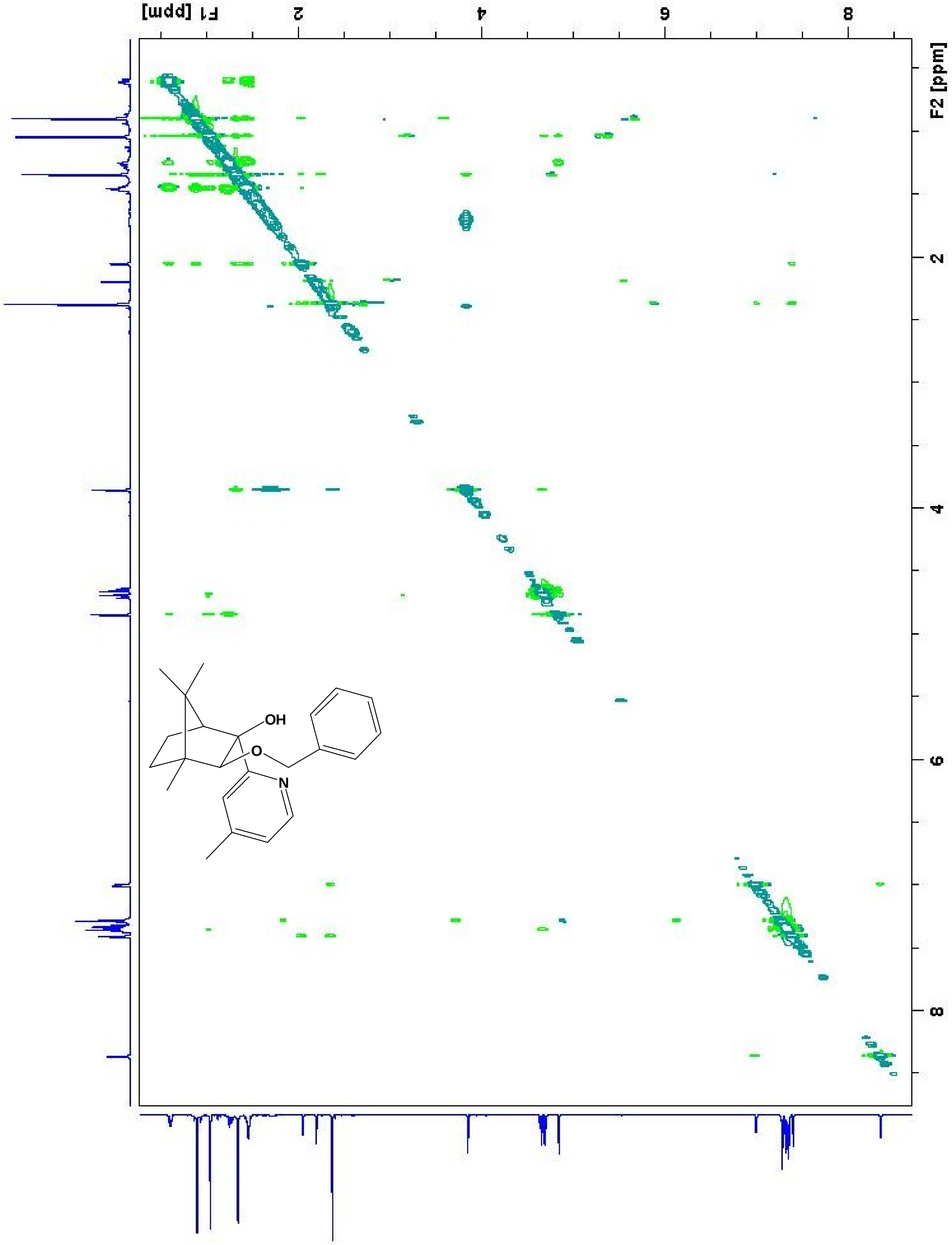
^{13}C NMR Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



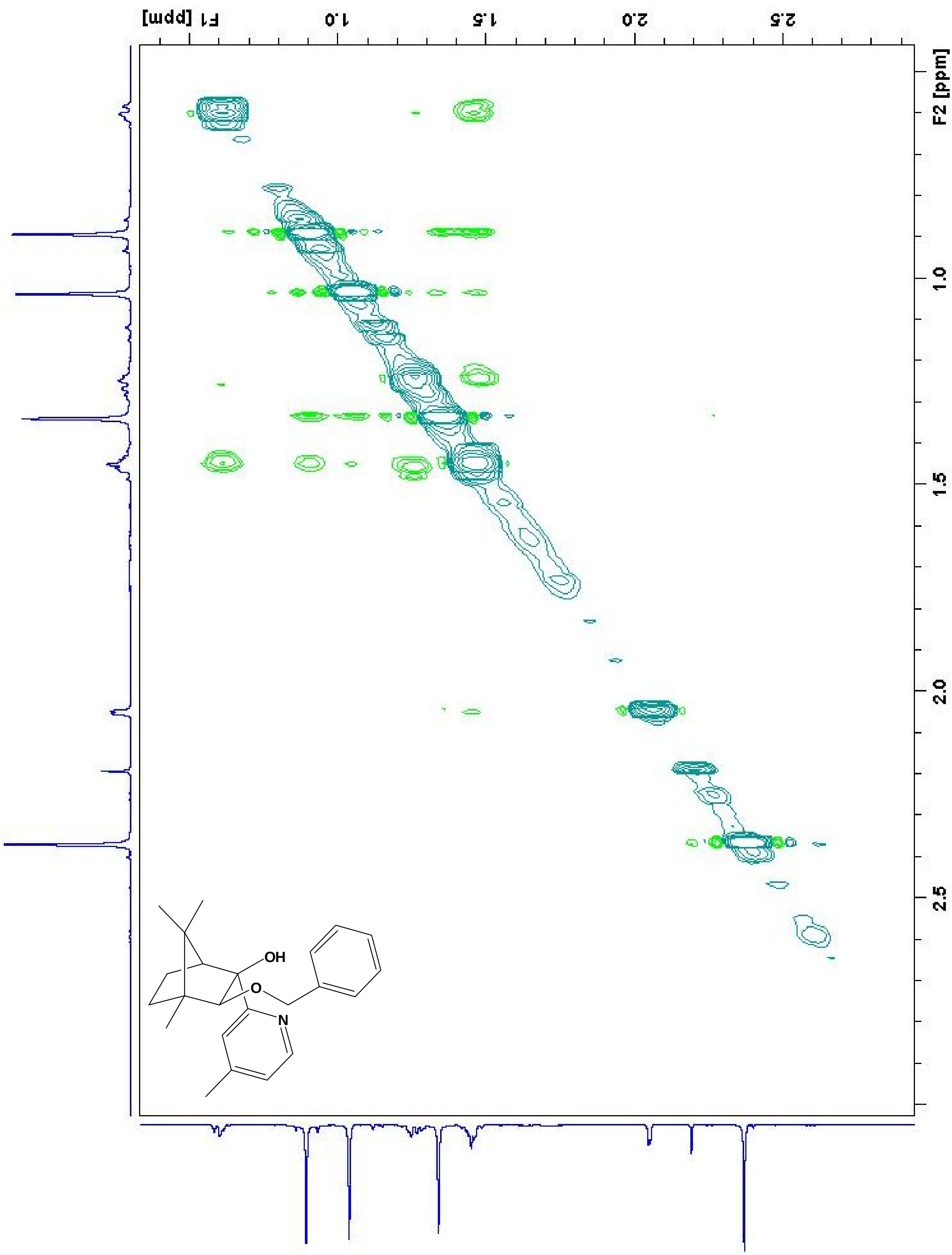
COSY Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



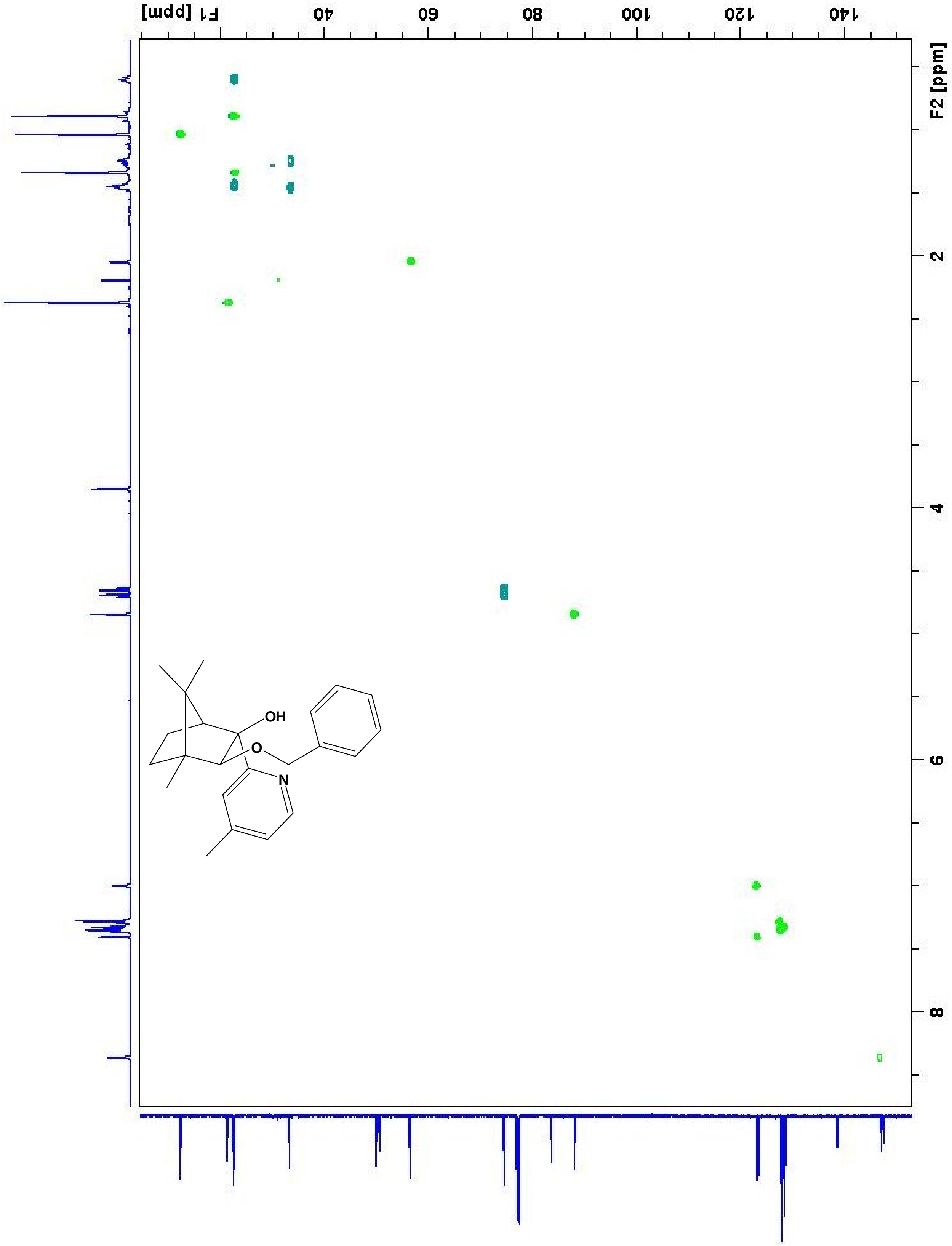
COSY Spectrum (600 MHz) of Ligand **4** in $CDCl_3$ expanded



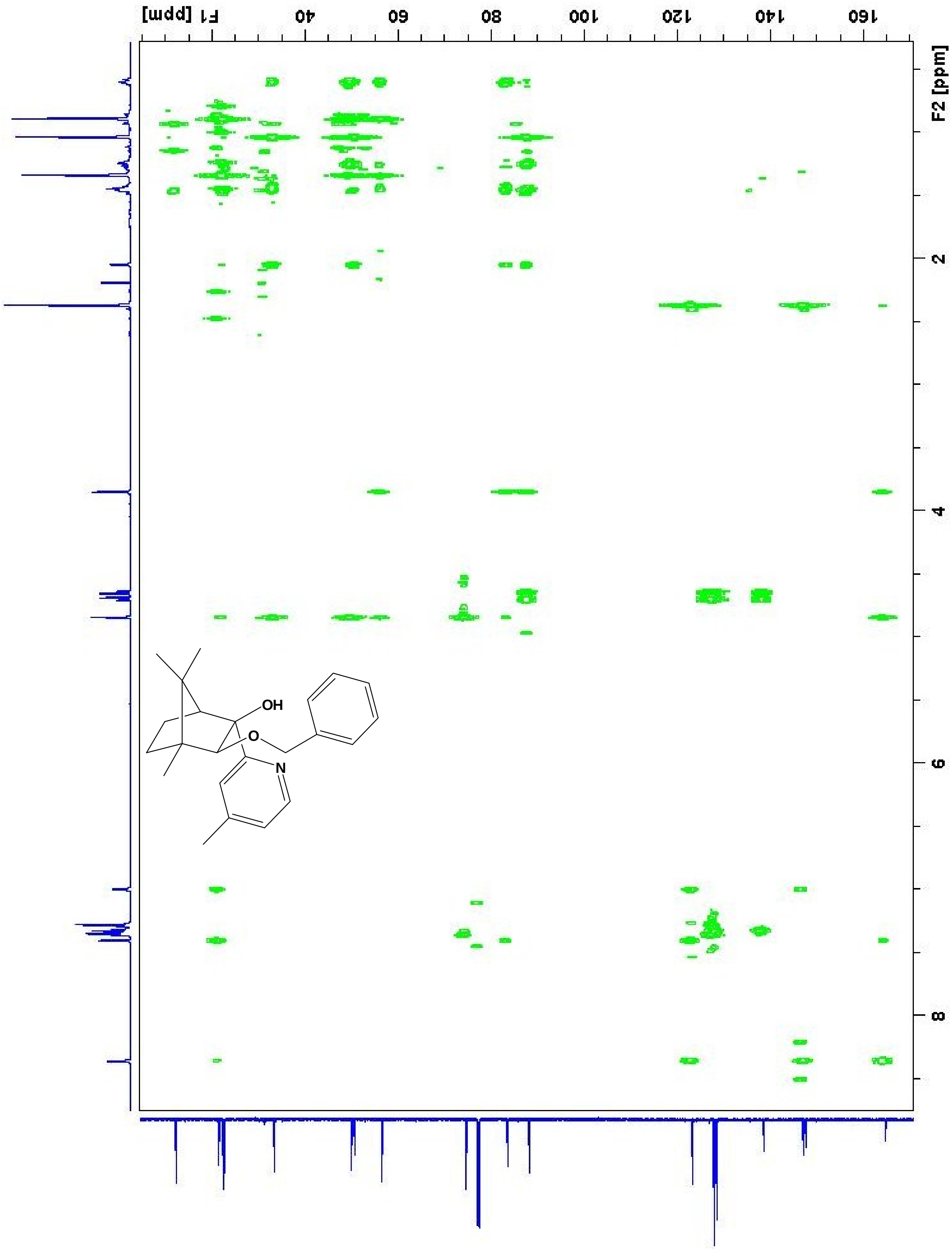
NOESY Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



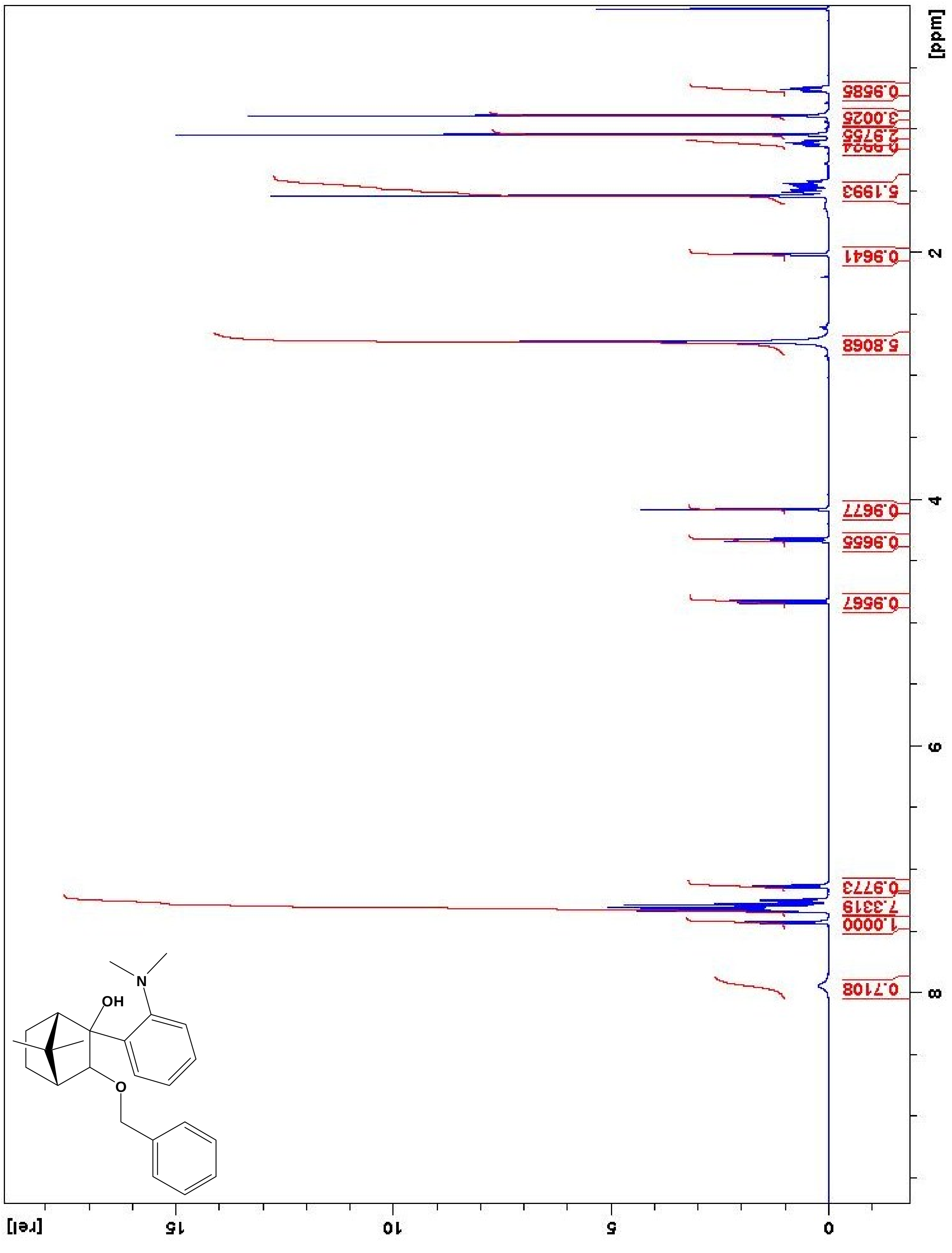
NOESY Spectrum (600 MHz) of Ligand **4** in $CDCl_3$ expanded



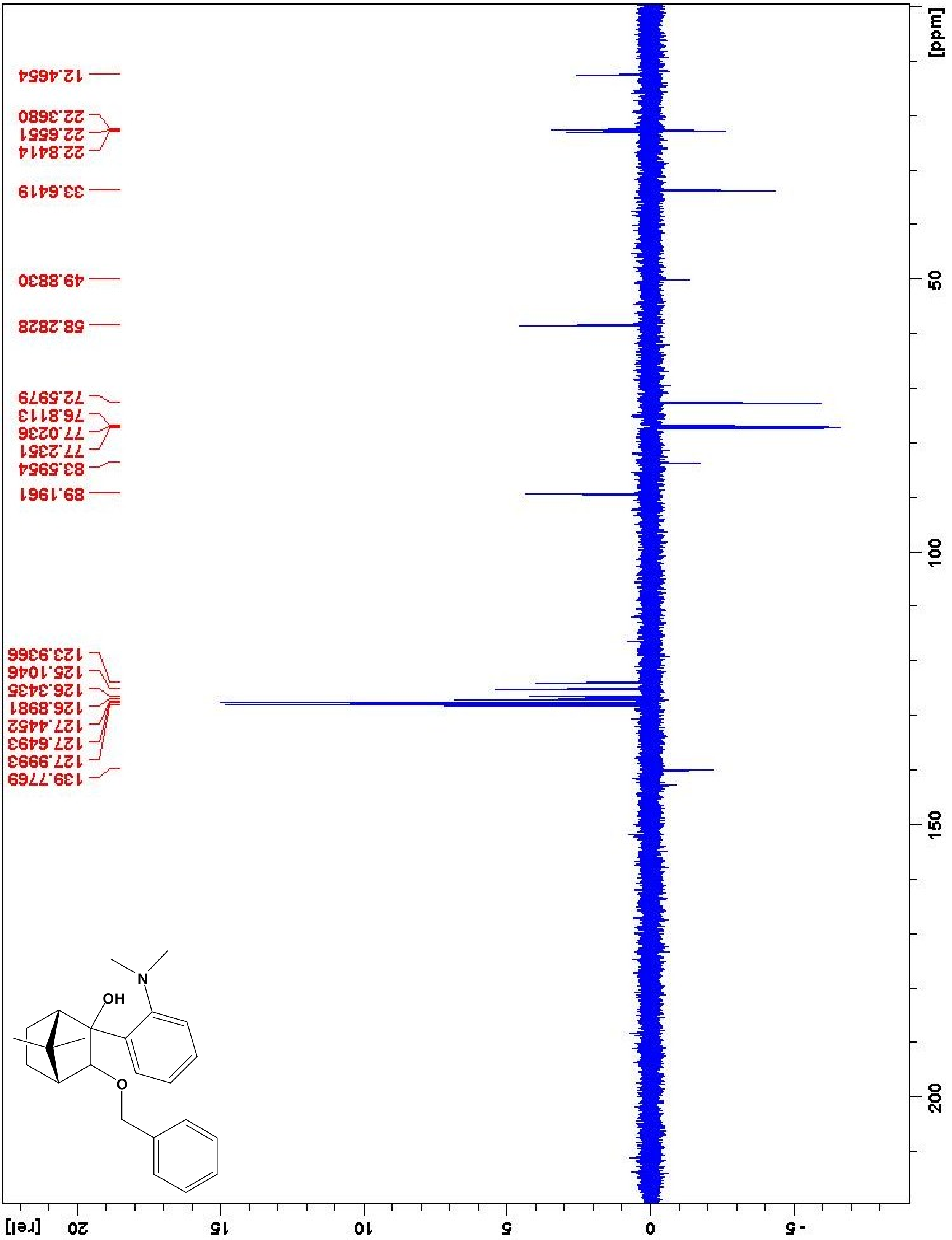
HSQC Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



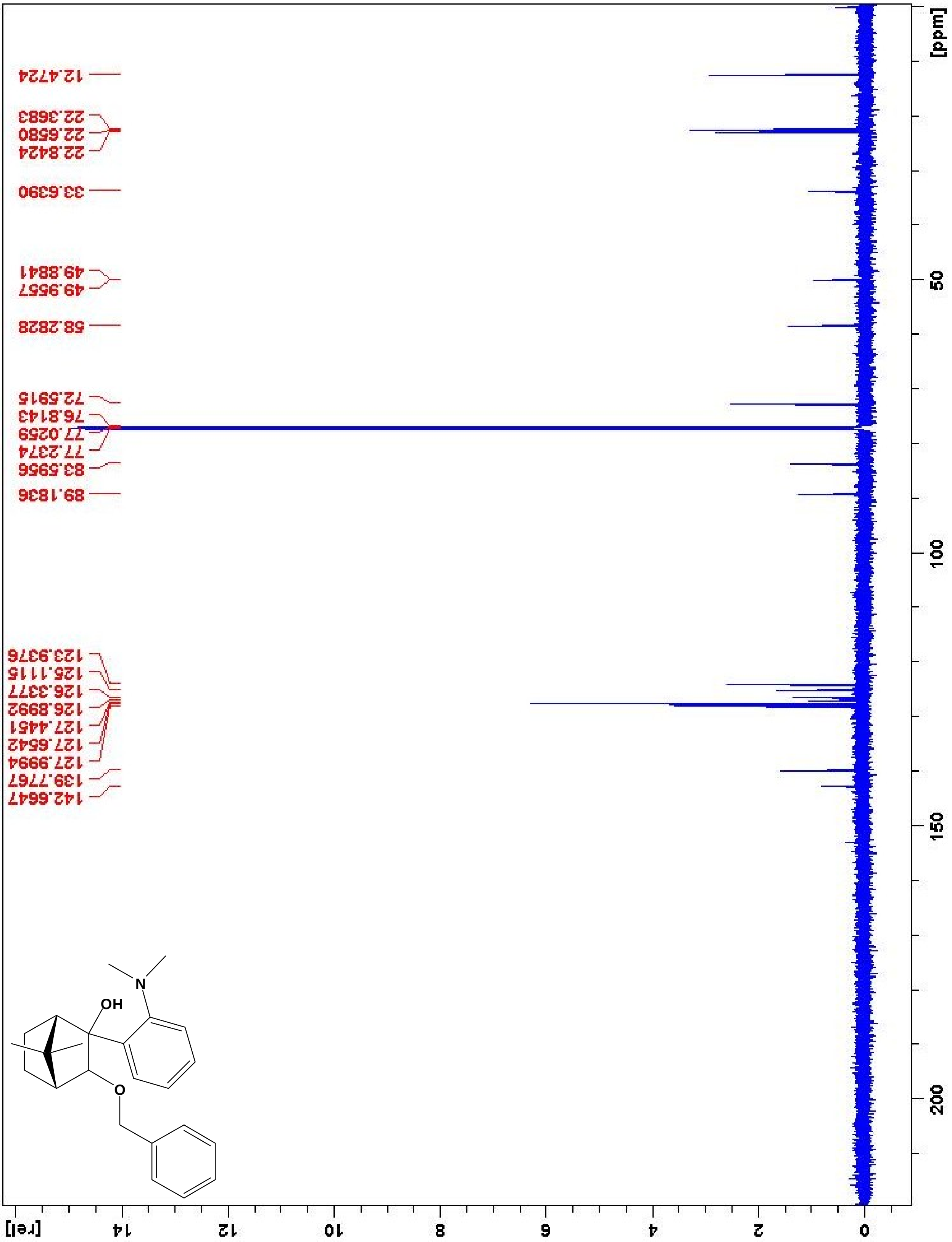
HMBC Spectrum (600 MHz) of Ligand **4** in $CDCl_3$



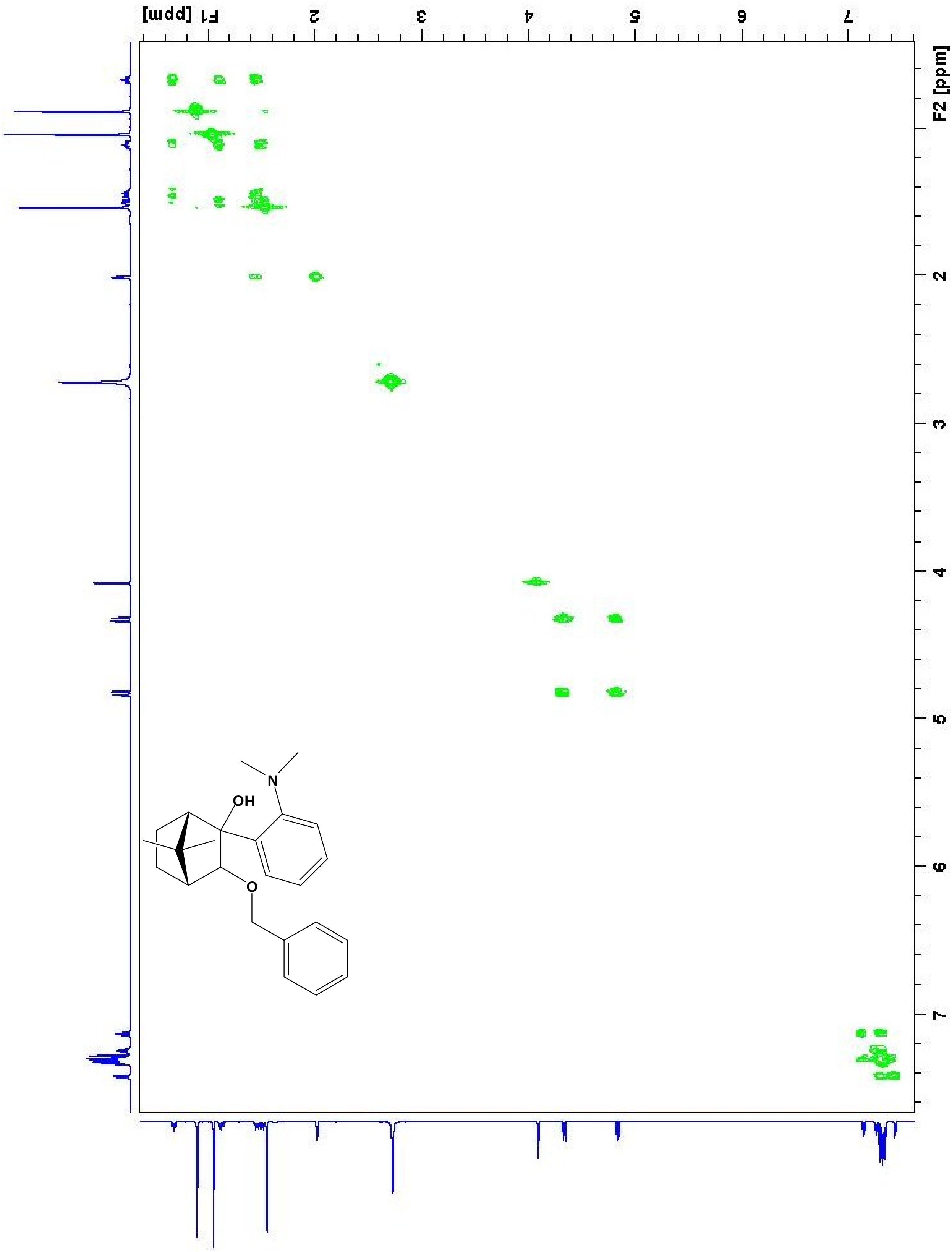
^{1}H NMR Spectrum (600 MHz) of Ligand **5** in $CDCl_3$



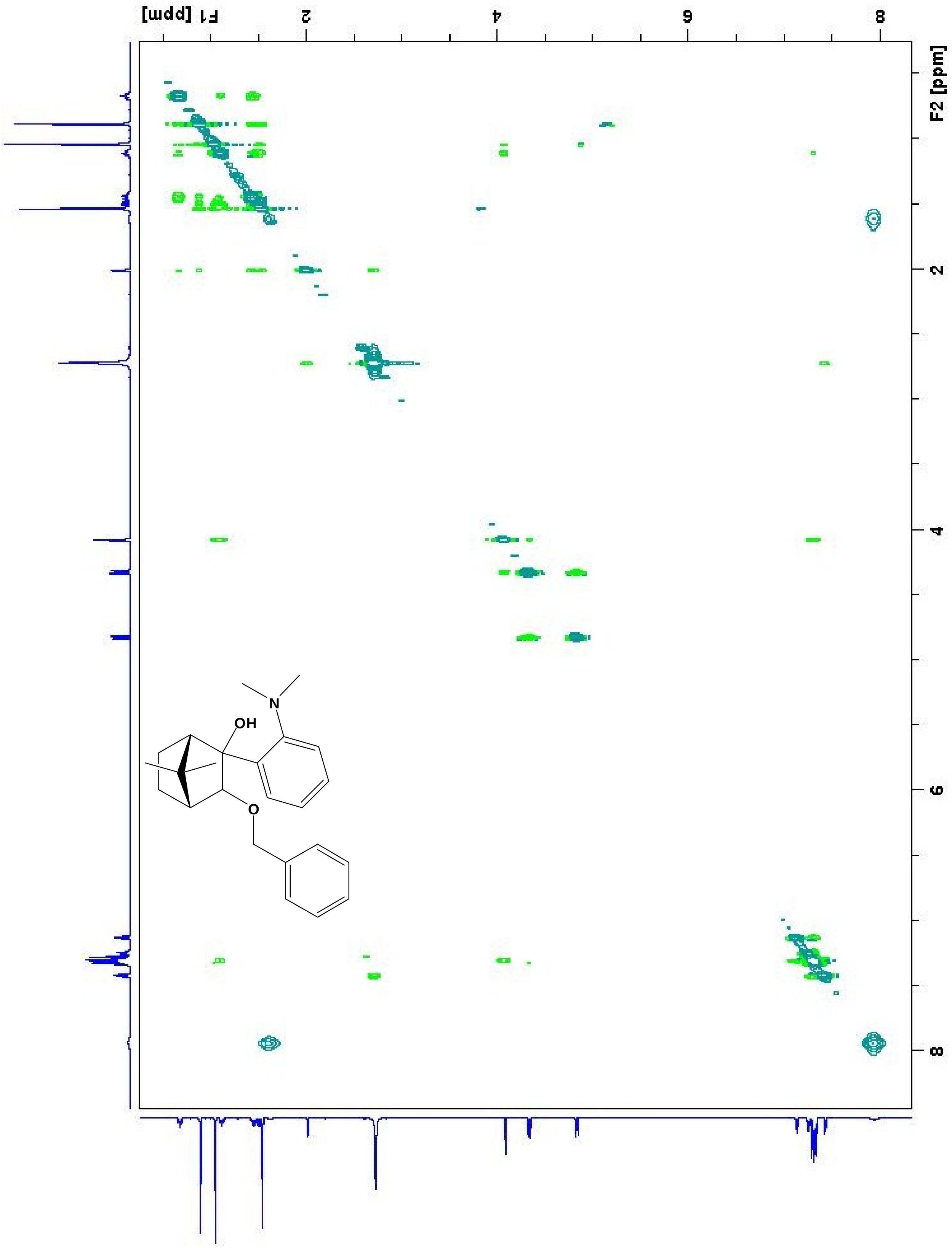
^{13}C APT NMR Spectrum (600 MHz) of Ligand **5** in $CDCl_3$



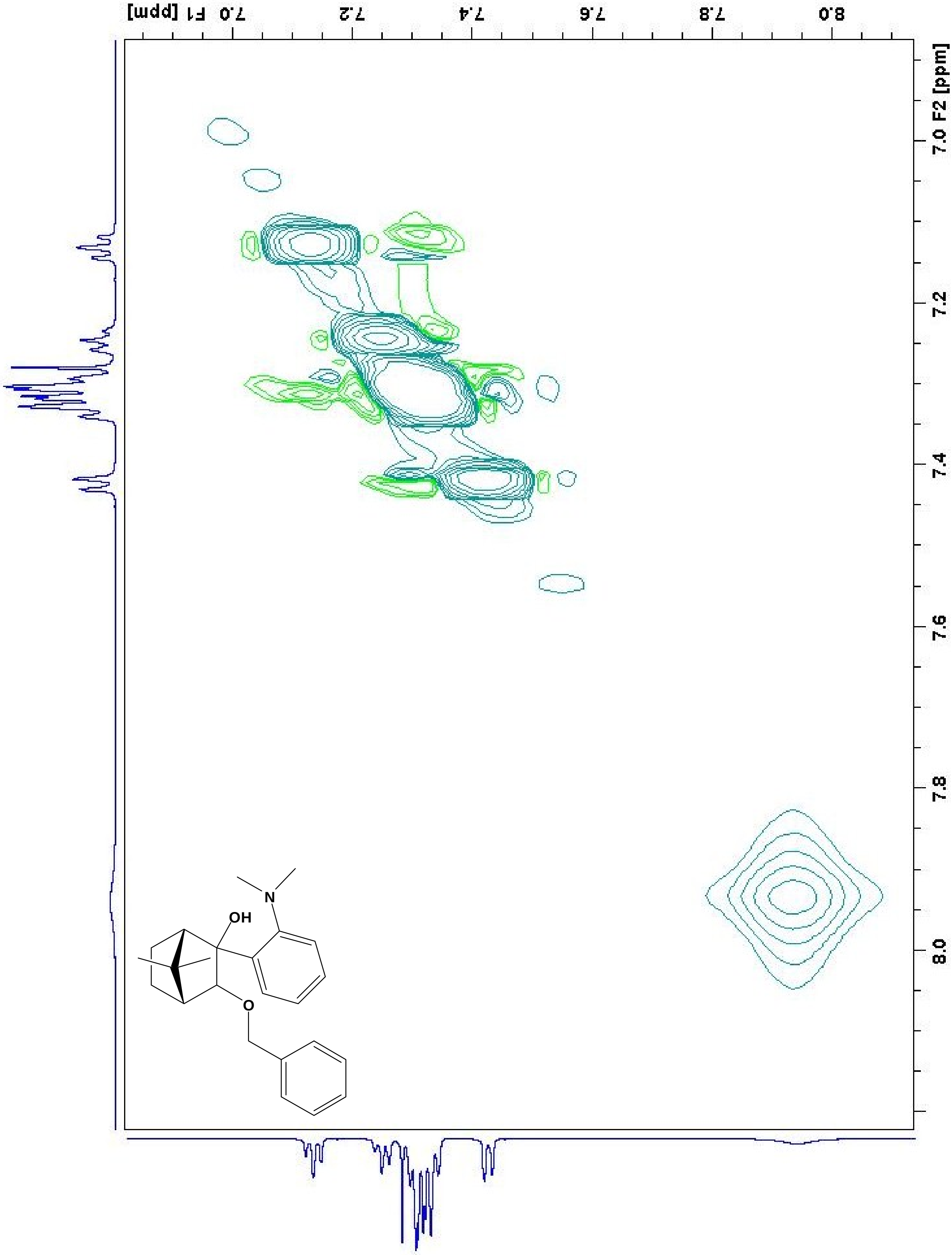
^{13}C NMR Spectrum (600 MHz) of Ligand **5** in $CDCl_3$



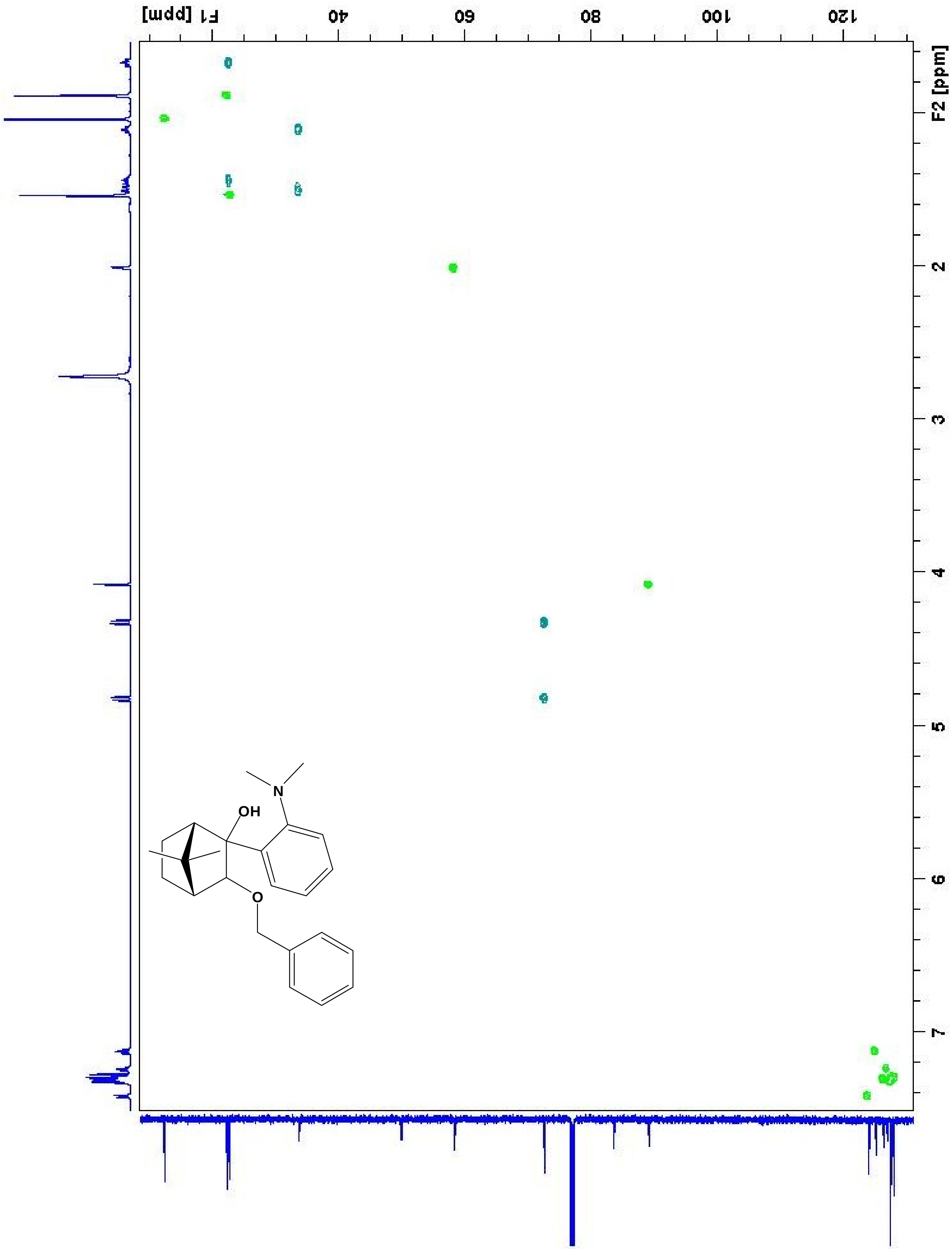
COSY Spectrum (600 MHz) of Ligand **5** in $CDCl_3$



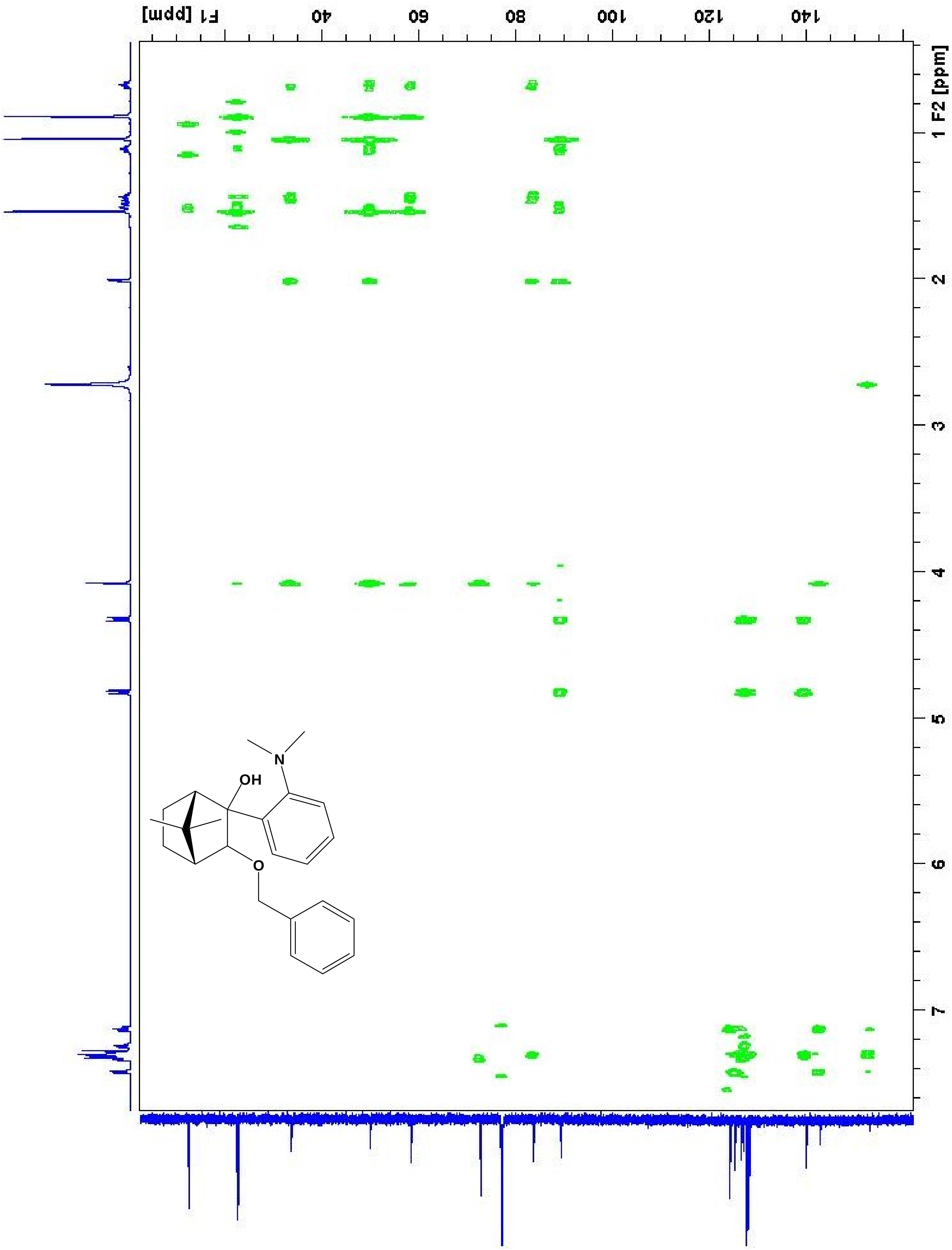
NOESY Spectrum (600 MHz) of Ligand **5** in $CDCl_3$



NOESY Spectrum (600 MHz) of Ligand **5** in $CDCl_3$ expanded



HSQC Spectrum (600 MHz) of Ligand **5** in $CDCl_3$



HMBC Spectrum (600 MHz) of Ligand **5** in $CDCl_3$