(3+2) Cycloaddition Reactions of Carbohydrate-Derived Donor-Acceptor Cyclopropanes

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

by

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INDIA

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To

Appa, Amma,

And My family.

Contents

Statement

I here declare that, the overall material contained in this thesis is the outcome of research accomplished by me in the school of chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Prof. Perali Ramu Sridhar**.

In keeping with the general trend of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigations. Any omission, which might have occurred by oversight or error, is regretted.

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Certificate

This is to certify that the thesis entitled **"(3+2) Cycloaddition Reactions of Carbohydrate-Derived Donor-Acceptor Cyclopropanes"** submitted by **Ms. M V Kamala Lakshmi** bearing Regd. No. 17CHPH55 is a work carried out under my supervision and guidance. The thesis is plagiarism free and has not been submitted previously to this or any other University or Institution for the award of any degree or diploma.

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M V Kamala Lakshmi

Dec 2023

List of Publications

1. A Ring Expansion-Stereoselective Cycloaddition of Carbohydrate-Derived Donor-Acceptor Cyclopropanes: Synthesis of Bridged Oxepanone–Indole Hybrids.
   M V Kamala Lakshmi, Intzar Ali and Perali Ramu Sridhar *J. Org. Chem.* **2022**, *87*, 18, 12370– 12385; https://doi.org/10.1021/acs.joc.2c01652.

2. Synthesis of Hexenuloses and a Library of Disaccharides Possessing 3-oxo-glycal Unit.
   Perali Ramu Sridhar, Intzar Ali and **M V Kamala Lakshmi**. *J. Org. Chem.* **2022**, *87*, 14, 8939– 8955; https://doi.org/10.1021/acs.joc.2c00663.

3. A Short Route to the Synthesis of Digoxose Trisaccharide Glycal Donor via Mislow-Evans Rearrangement.
   Intzar Ali, **M V Kamala Lakshmi** and Ramu Sridhar Perali *J. Org. Chem.* **2023**, *88*, 16, 12105– 12114; https://doi.org/10.1021/acs.joc.3c01067.

4. (3+2) cycloaddition of spiro-cyclopropanecarboxylated sugars and nitriles: synthesis of tri-substituted pyrroles, THI derivatives and *C*-pyrrolyl furanosides. (Manuscript under preparation).

Conferences attended

1. Attended **International Carbohydrate Conference (CARBO-XXXIV)-2019,** organized by University of Lucknow in association with NIPER-R and ACCTI (Dec 2019).

2. **Oral presentation** at **ChemFest 2021** organised by School of Chemistry, University of Hyderabad (April 2021).

3. **Oral presentation** at **International Conference on Chemistry and Allied Sciences (ICCAS- 2022)** held at NIT Warangal (Aug 2022).

4. **Poster presentation** at **International Carbohydrate Conference CARBO XXXVI 2022** held in IIT Bombay (Dec 2022).

5. **Poster presentation** at **CHEMSCI2023:** LEADERS IN THE FIELD SYMPOSIUM in collaboration with RSC held at JNCASR, Bangalore (Jan 2023).

6. **Poster presentation** at the 2023 **XVIII J-NOST Conference for Young Researchers** at IISER Pune, (Oct 2023).

7. **Oral presentation** at the 12th Asian community for Glycoscience and Glycotechnology Conference (ACGGC) at SLS and SoC, University of Hyderabad. (Nov 2023).

Synopsis

The thesis entitled **"(3+2) Cycloaddition Reactions of Carbohydrate-Derived Donor-Acceptor Cyclopropanes"** is divided into three chapters.

Chapter 1

An Introduction to the Carbohydrate-Derived Donor-Acceptor Cyclopropanes and its Incorporation into (3+2) Cycloaddition reaction

Donor-acceptor cyclopropanes (DACs) are exclusive class of strained molecules that have been used as 3-carbon building block in various organic transformations. The 1,3-dipolar cycloaddition reaction is an important route to construct various hetero and carbocyclic scaffolds in regio-, stereo-selective manner. DACs are one among the synthons that undergo formal (3+2) cycloaddition very efficiently (Figure 1).

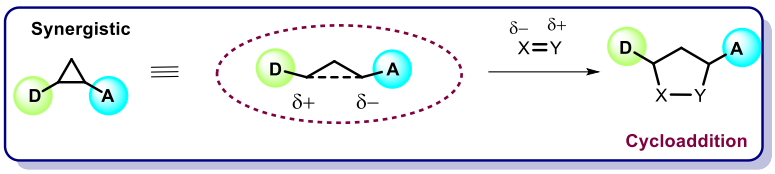


Figure 1: Effect of donor and acceptor substituents on the cyclopropane reactivity.

Cyclopropanated sugar substrates undergo various types of reactions and often utilized to construct diverse molecular scaffolds in a stereo-chemically pure form. Cyclopropanated carbohydrates are very important synthetic precursors in stereoselective total synthesis of natural products. Along with the endocyclic oxygen, when an electron withdrawing group is incorporated on the vicinal carbon, the sugar skeleton is susceptible to undergo unique bond

cleavages which is favorable for (3+2) cycloaddition reaction.

This chapter covers the types of unsaturated sugar derivatives required for the synthesis of various carbohydrate-derived DACs. Further, this chapter also describes the previous reports where carbohydrate-derived DACs are incorporated in formal (3+2) cycloaddition reaction. In this context, the important 1,2-dipolar synthons are also highlighted.

Overall, importance of carbohydrate-derived DACs in constructing multicyclic framework is explained and motivation to further develop biologically important skeletons is expressed.

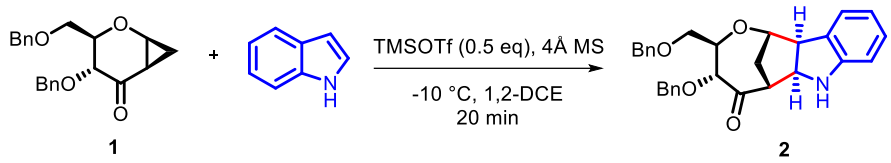
Chapter 2: Part A

A Ring Expansion Stereoselective Cycloaddition of Carbohydrate Derived Donor–Acceptor Cyclopropanes: Synthesis of Bridged Oxepenone–Indole Hybrids

Donor–acceptor cyclopropanes having a donor and an acceptor group on the vicinal carbon atoms of the cyclopropane, exhibits a synergistic effect. It forms a reactive 1,3-zwitter ion intermediate which is an excellent substrate for various (3+n) cycloaddition reactions. Till date, 3-oxo-1,2-cyclopropanated sugar derivates were used as glycosyl donors for ring expansion reactions. For the first time, this work exploits the inherent nature of 3-oxo-1,2-cyclopropanated sugar to form a 1,3-dipolar synthon. This chapter mainly describes the dearomative (3+2) cycloaddition of indole and 3-oxo-1,2-cyclopropanated sugar derivatives. A unique molecular scaffold, bridged oxepanone-indole, is formed as the cycloadduct. The methodology witnesses the alpha-selective cycloaddition reaction which forms four new stereogenic centers in a single transformation forming the chiral cycloadducts. The concept of molecular hybridization was effectively incorporated to construct interesting molecular hybrids which may contribute to the bioactivity.

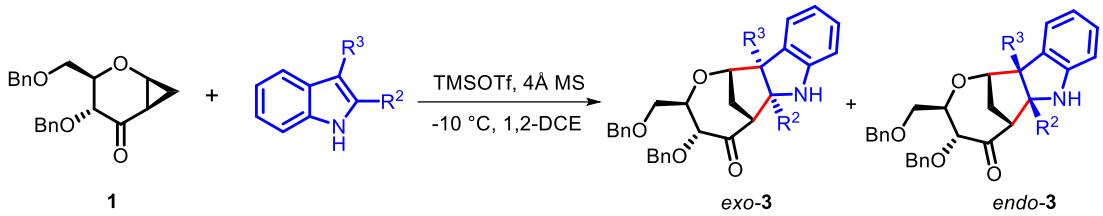
Glucose-derived 3-oxo-1,2-cyclopropanated sugar **1** and 1*H*-indole were used as model substrates. At -10 °C in 1,2-dichloroethane (1,2-DCE) solvent, TMSOTf as Lewis acid was used to activate the DAC. The dipolar substrates efficiently reacted to form the cycloadduct **2** in 70% yield

(Scheme 1). A high stereoselectivity was observed where only α-anomers were formed during the reaction.



Scheme 1: (3+2) Cycloaddition reaction between model substrates DAC**1** and 1*H*-Indole.

The developed methodology was successfully applied to a few indole substrates with variable substitution on the benzene ring as well as *N*-methyl indole. However, C2, C3 methylated indole substrates provided **3** as diastereomeric mixture of cycloadducts (*exo* & *endo*) with retention of α-stereochemistry (Scheme 2).



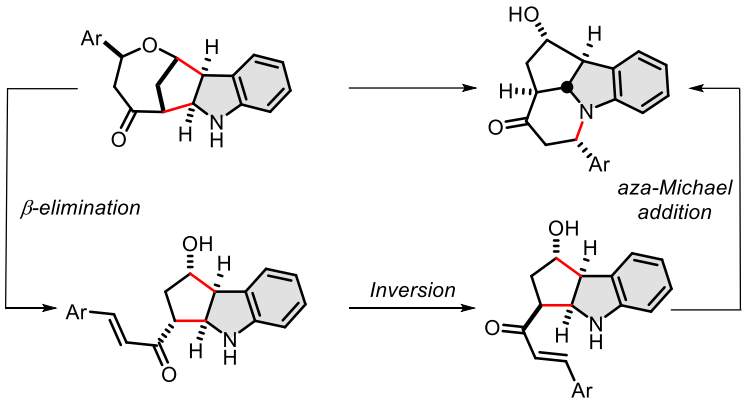
Scheme 2: (3+2) Cycloaddition of C2, C3 alkylated indole substrates.

Furthermore, we extended this work by employing different DACs from various sugar substrates and sugar analogues. The results were well in accordance with the model substrates.

Chapter 2: Part B

Post-synthetic Transformation: *En Route* to the Synthesis of A,B,E Tricyclic Core of Calyciphylline B-Type Alkaloids

Post synthetic transformations have become a necessary practice in the synthetic organic chemistry. The pre-existing molecules with specialized functional groups placed appropriately are exploited to construct a new molecular skeleton with biological or pharmacological significance different from the parent molecule.



Scheme 3: Transformation of (3+2) cycloadducts *via* the intramolecular aza-Michael addition reaction.

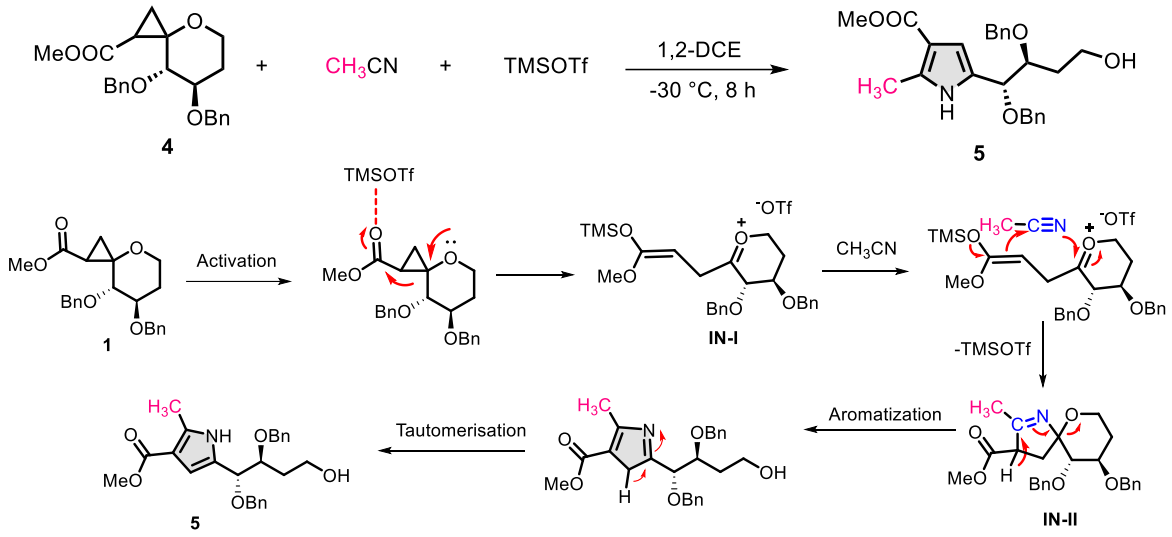
In this context, through a one-pot β-elimination, inversion of configuration, and an intramolecular aza-Michael addition reaction, the (3+2) cycloadducts of previous chapter, with suitably positioned ß-ketoethers were used to synthesize analogues of A,B,E tricyclic core of calyciphylline B-type alkaloids with a bowl-shaped architecture. The chapter mainly describes the base mediated ß-elimination of the suitable cycloadducts followed by an aza-Michael addition reaction with indole nitrogen led to the functionalized fused tetracyclic scaffolds in a single concerted step. This transformation witnessed the formation of a highly strained molecule and the beauty of the basket-shaped molecular construction, a skeleton analogous to naturally occurring alkaloid calyciphylline B (Scheme 3).

Chapter 3: Part A

(3+2) Cycloaddition Reaction of Spirocyclopropane Carboxylated Sugars and Nitriles: Synthesis of Highly Functionalized Pyrrole Derivatives

Heterocyclic molecules have always been a part of many natural and unnatural scaffolds with biological as well as pharmacological relevance. The synthesis of important heterocyclic skeletons in an effective way is of great interest and pyrrole derivatives is one such emerging class of molecular framework. Polyhydroxy alkyl substituted pyrrole derivatives are present in well-

known pharmaceuticals like — atorvastatin, isamoltane, aloracetam *etc*. The importance of these class of organic molecules motivated us to perform an application-oriented synthesis which is described in this chapter 2 that is further divided into three parts.



Scheme 4: (3+2) Cycloaddition reaction of spirocyclopropane carboxylated sugar **4** and acetonitrile.

Like 1,2-cyclopropanated sugar derivatives, spirocyclopropane carboxylated sugars are also unique class of donor-acceptor cyclopropanes which are used as a powerful tool in synthetic organic chemistry. The part A of this chapter mainly describes a unique (3+2) cycloaddition reaction between spirocyclopropane carboxylated sugars and various alkyl/aryl nitriles to efficiently construct 2,3,5-substituted pyrrole derivatives. TMSOTf- mediated activation of model substrate **4** formed a 1,3-dipolar intermediate **IN-I** and this underwent (3+2) cycloaddition reaction with acetonitrile to form a five-membered cyclic intermediate **IN-II.** Further, aromatization and tautomerization of this intermediate provided the 2,3,5-substituted pyrrole derivative **5** as the cycloadduct (Scheme 4).

The developed methodology was successfully applied to a several nitrile substrates which include alkyl, aryl, and substituted aryl nitriles. The established procedure was amenable to most of these substrates and products were formed in good to excellent yield. Further, we extended this protocol by employing a different DAC derived from D-glucal and subjected it for (3+2)

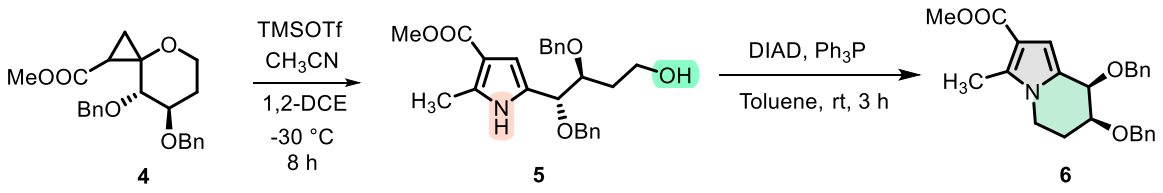
cycloaddition reactions with various substituted aryl nitriles. The results were well in accordance with the model substrates.

Chapter 3: Part B

Post-synthetic Transformation (Part 1): *En Route* to the Synthesis of Tetrahydroindolizines Based Scaffolds

Azabicyclic ring skeleton is the core unit of several secondary metabolites and bioactive compounds. Among them, several molecules are modified to form glycomimetics and exhibit the inhibitory activity on the glycosidase enzyme. Notably, the Tetrahydroindolizines (THIs) core is widely present in several bioactive natural products. Hence, synthesis of these core skeleton is much required area of research.

With this motivation, in this present chapter, we have attempted the synthesis of tetrahydroindolizines based scaffolds as a post synthetic application from the pyrrole cycloadducts obtained in the previous work. In this regard, the substituted pyrrole derivative **5** was subjected to Mitsunobu reaction condition using Ph_3P and DIAD to obtain the fused bicyclic THI derivative **6** (Scheme 5).



Scheme 5: Synthesis of THI derivative **6** from cycloadduct **5.**

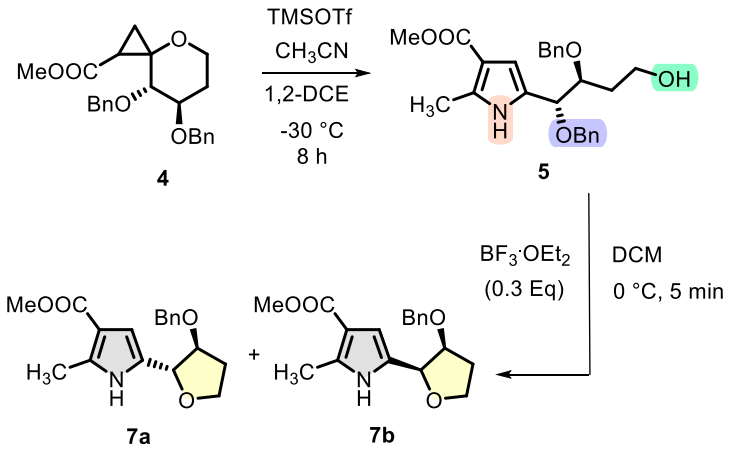
The reaction was performed on all the cycloadducts derived from spirocyclopropane carboxylated sugar substrate **4**. The fused bicyclic THI derivatives were obtained in excellent yield. The results were consistent with the model substrate.

However, a small anomaly was observed in the case of cycloadducts obtained from mono-benzyl spirocyclopropane carboxylated sugar substrate unlike substrate **4**. The details are further explained in this chapter.

Chapter 3: Part C

Post-synthetic Transformation (Part 2): *En Route* to the Synthesis of *C*-pyrrolyl Furanoside Derivatives

C-Glycosides have been employed as building blocks in the synthesis of several natural products and physiologically active compounds. They also could inhibit carbohydrate-interacting enzymes and one such example is the nucleoside inhibitors. Furanose sugar and nitrogenous base modifications are the preliminary chemical transformation made to produce these nucleoside inhibitors. In this regard, we report the synthesis of *C*-pyrrolyl furanoside derivatives through Lewis acid catalyzed intramolecular cyclization of the pyrrole cycloadducts obtained in previous work (part A).



Scheme 6: Synthesis of *C*-pyrrolyl furanoside derivative.

As a part of post-synthetic transformation, highly functionalized pyrrole derivative **5** obtained from spirocyclopropane carboxylated sugar substrate **4** is treated with catalytic amount of $BF_3{\cdot}OEt_2$ in dichloromethane solvent at 0 °C. Within 5 minutes, 1:1 diastereomeric mixture (**7a** &

7b) were formed (Scheme 6). The reaction was performed on all the cycloadducts derived from spirocyclopropane carboxylated sugar substrate **4**. The *C*-pyrrolyl furanoside derivatives were obtained in excellent yield with approximately 1:1 diastereomeric ratio. The results were consistent with the model substrate.

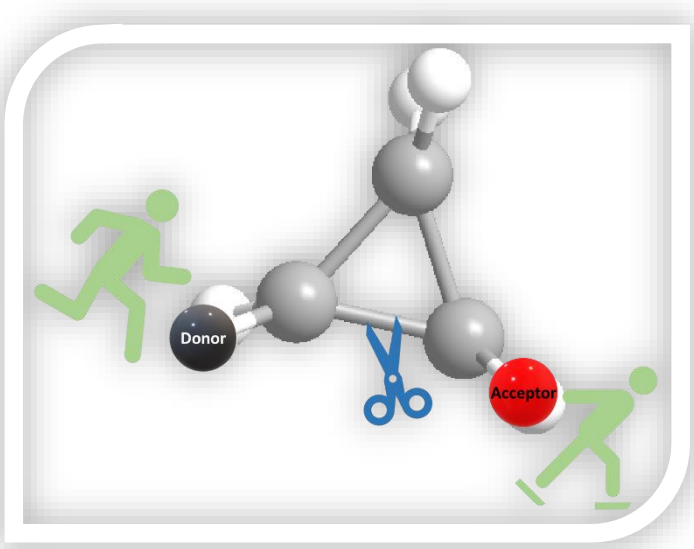
Abbreviations

α	alpha
Å	angstrom
β	beta
Bn	benzyl
Calcd	calculated
COSY	correlation spectroscopy
δ	delta
d	doublet
dd	doublet of doublet
DAC	donor-acceptor cyclopropane
DCE	dichloroethane
DCM	dichloromethane
DIAD	Diisopropyl azadicarboxylate
dt	doublet of triplet
EDA	ethyl diazo acetate
EtOAc	ethyl acetate
ESI	electrospray ionization
equiv.	equivalent
g	gram(s)
h/hr	hour(s)
HRMS	High resolution mass Spectrometry
HTIB	[hydroxy(tosyloxy)iodo]benzene
Hz	hertz
IR	infrared
J	coupling constant in Hz

m	multiplet
MHz	megahertz
mL	milliliter
mmol	millimolar
MS	molecular sieves
MeOH	methanol
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
Ppm	parts per million
Rf	retardation factor
s	singlet
t	triplet
THF	tetrahydrofuran
THI	tetrahydroindolizine
TLC	thin-layer chromatography
TMSOTf	trimethylsilyl trifluromethanesulfonate

Chapter 1

An Introduction to the Carbohydrate-Derived Donor-Acceptor Cyclopropanes and its Incorporation into (3+2) Cycloaddition reaction



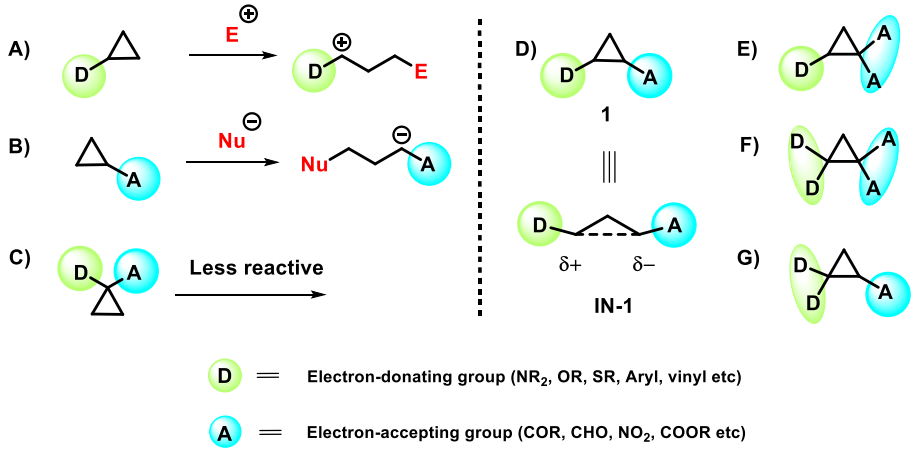
Abstract:

Carbohydrate-derived donor-acceptor cyclopropanes (DACs) acts as a unique chiral synthon. Like glycals, the new age chemistry is exhibiting these chiral DACs as the unique "transformation tool." As they undergo various type of reactions such as ring opening, ring expansion, ring contraction, annulations, and cycloaddition etc., these are one of the potential targets for the synthesis of biologically important frameworks. Especially, the (3+2) cycloaddition reactions using carbohydrate-derived DACs has opened the doors for the construction of significant multi-cyclic framework in a regiospecific and stereoselective manner.

1.1 Introduction to donor-acceptor cyclopropanes

Cyclopropane is a unique compound that exhibit features of both saturated and unsaturated hydrocarbons depending on the reaction partner(s) and circumstances used. One reason for the fascination for cyclopropane and its derivatives in organic synthesis is because many naturally occurring products and physiologically active substances have a three-carbon ring.[1] Also, the small size of the ring causes significant ring strain in the structure. Cyclopropanes, being members of the cycloalkane family, are known to engage in a wide range of reactions. The high strain energy of the three-membered ring allows it to participate in a variety of reactions. The discharge of this energy serves as a driving force for the ring to open. However, it is difficult to polarize the C-C bonds of cyclopropane and many of its derivatives by itself. As a result, the molecule requires reorganisation in terms of both electron distribution and geometry for elevated reactivity.

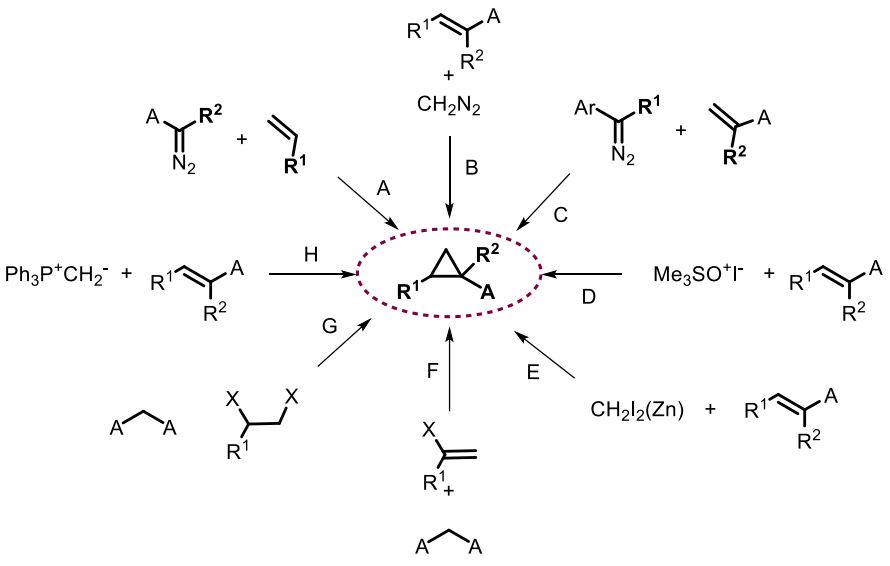
The usual strategy for activating cyclopropanes is the insertion of substituents that enhance a desirable action. One such example is the incorporation of donor or acceptor or both the groups on the cyclopropane (Scheme 1).[2]



Scheme 1: Types of donor and acceptor cyclopropanes and its reactivity.

The electron donating group stabilises the positive charge in the intermediate and allows the electrophilic ring opening by polarising the endocyclic C-C bonds (Scheme 1, A). The most

common electron-donating groups include heteroatom-based donor like R_2N-, RO-, RS- and aromatic, heteroaromatic, and alkenyl groups. These can stabilize the positive charge effectively. In contrast, the electron accepting groups, polarises the C-C bonds in the other direction, facilitating ring opening with nucleophiles (Scheme 1, B). Alkoxycarbonyl, carbonyl, nitrile, sulfonyl, and nitro groups are the frequently used electron-withdrawing functional groups, which stabilise the emerging negative charge. Next, when both donor and acceptor groups are present, the scenario becomes completely different with respect to the reactivity based on their relative attachment. When donor and acceptor groups have a geminal attachment (i.e., located on the same carbon atom of the ring), the electronic effect is nullified. Hence, the reactivity is drastically reduced (Scheme 1, C). Conversely, when donor and acceptor groups are located at the vicinal carbon atoms, like **1**, their combined effects cause significant polarisation of the C-C bond. They form a useful three carbon 1,3-zwitterion intermediate **IN-1**. As a result, these cyclopropanes react efficiently with both nucleophiles and electrophiles (Scheme 1, D). To emphasise their exceptional reactivity, it was termed as donor-acceptor (D-A) cyclopropanes by Reissig.[3] Apart from these, attachment of double electron donating and withdrawing groups is also reported which contributes to the diverse chemistry (Scheme 1, E-G).

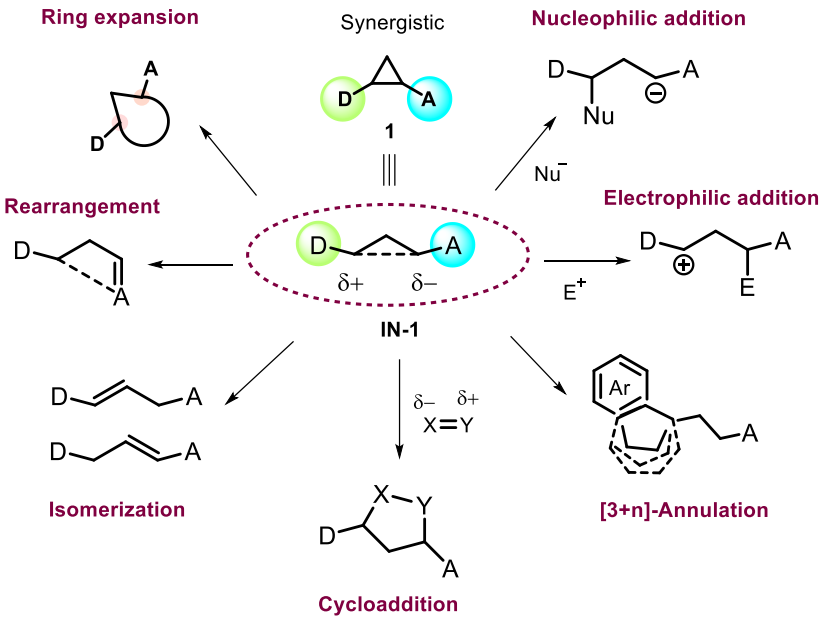


R^1 = H or **D**; R^2 = H or **A**; X = Hal, SO_2Ar

Scheme 2: General synthetic protocol for the synthesis of DACs.

Till date there is a huge library of donor-acceptor cyclopropanes (DACs) that are synthesized *via* a few general methods (Scheme 2).[4] Catalytic cyclopropanation of alkenes with diazo compounds *via* a metal-carbenoid formation is one of the most extensively used and accessible ways for the synthesis of DACs (Scheme 2; A, B, C). Another approach is the Corey-Chaykovsky reaction which has the most utility for the synthesis of DAC (Scheme 2, D). The sulfoxide ylides is used as the active reagent in this reaction. Apart from this, phosphorous ylides can also be used for the cyclopropanation reaction (Scheme 2; H). Next important protocol includes the use of organozinc reagents like Simmons-Smith reaction (Scheme 2; E). Another common method is the cycloalkylation of compounds with an activated methylene group (Scheme 2; F, G). The use of melanoates as the methylene source and addition over the haloalkenes or alkyl dihalides with suitable bases affords the appropriate cyclopropane.

In recent years, extensive studies have been done on these donor-acceptor cyclopropanes (DACs). The 1,3-zwitter ion intermediate **IN-1** is well exploited and this distinct three carbon ring is evolving as convenient three carbon building block for constructing various acyclic, alicyclic and heterocyclic molecules *via* numerous types of reactions such as cycloaddition and annulation reactions, ring-opening and ring expansions reactions, and rearrangement reactions etc (Scheme 3).[2]



Scheme 3: Type of reactions involving DACs.

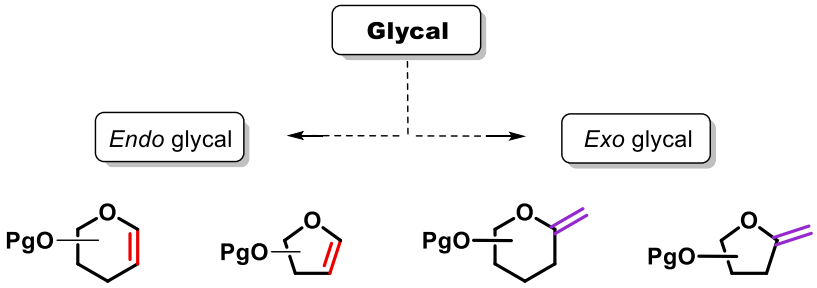
This chapter of the thesis focuses on the synthesis and diversity of carbohydrate-derived donor-acceptor cyclopropanes. Moreover, we give a short discussion on reactions involving carbohydrate-derived DACs especially in the (3+2) cycloaddition reaction.

1.2 Introduction to carbohydrates

Carbohydrates are optically active polyhydroxy aldehydes or ketones present in the form of pyranose or furanose cyclic system. They are omnipresent and components of many important natural products. Because of their potential biological and pharmacological utility, synthetic carbohydrate chemistry has recently shifted its focus to oligo- and polysaccharide synthesis and carbohydrate hybrids *via* conceptual alterations.[5] Carbohydrate derivatives as the chiral synthons has attained significant importance in the synthetic carbohydrate chemistry. Carbohydrate-derived donor-acceptor cyclopropanes which are in-turn derived from glycals, both are an efficient synthetic tool for the construction of various frameworks.

1.3 Glycals

Glycals are the unsaturated sugar derivative and structurally these are cyclic enol ethers.[6] Depending on the monosaccharide used, it can attain a pyranose form or furanose form. Based on the position of the double bond, the glycals are classified into *endo* and *exo*-glycals (Scheme 4). According to the stability, the pyranose glycals having *endo*-cyclic double bonds are more stable than *exo*-cyclic double bond whereas it is contrasting in case of furanose glycals. Several methods for the synthesis of both *exo*- and *endo* glycals are reported in the literature.[6]



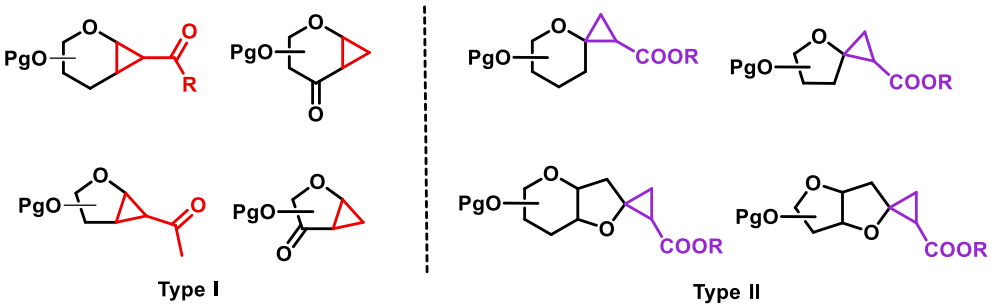
Scheme 4: Classification of glycals.

From past several decades, the glycals are widely recognised as one of the best precursors in synthetic sugar chemistry. The crucial components of glycals like the endo cyclic oxygen, the double bond and embedded chirality allows it to act as an efficient transformation tool. Some of the reactions such as epoxidation,[7] halogenation,[8] glycosylation,[9] dihydroxylation, addition, cyclopropanation,[10] etc can be performed using glycals.

Among these, the study of cyclopropanated glycals has gained more attention. Incorporating a three-membered ring into the glycal skeleton produces strained and reactive enantiopure building blocks for the synthesis of a wide range of structurally varied compounds and natural products. Further advancement in the synthetic chemistry has achieved the construction of carbohydrate-derived donor-acceptor cyclopropanes. Hence, glycals are the immediate precursors for the synthesis of cyclopropanated sugars.

1.4 Carbohydrate-derived donor-acceptor cyclopropanes

As discussed above, the exo- and endo-glycals are efficiently incorporated as the olefin source in the cyclopropanation reaction. Further transformation of the cyclopropanated sugar derivatives into a carbohydrate-derived donor-acceptor cyclopropane derivatives is also explored by several groups. However, there are reports for synthesis of few carbohydrate-derived DACs which follows the protocol without involving cyclopropanation reaction. Till date, there is a small library of these derivatives whose skeleton is represented in the scheme 5. It can be noticed that the endocyclic oxygen inherently acts as the electron donating group and further the electron withdrawing group can be modified according to requirement.

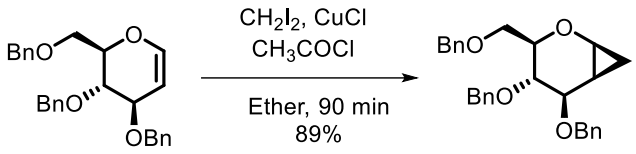


Scheme 5: Carbohydrate-derived donor-acceptor cyclopropane library.

Below are some of the reported synthetic routes for the synthesis of carbohydrate-derived DACs.

1.4.1 Using Simmon-Smidth cyclopropanation

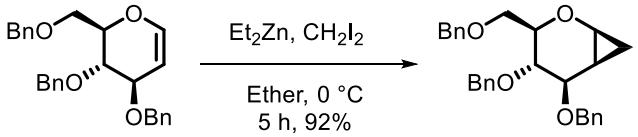
Simmon-Smith reaction was first incorporated on sugar substrates by Nagarajan and co-workers in 1995. In their report, 3,4,6-tri-*O*-benzyl-D-glucal **2** was treated with CH_2I_2/Zn/CuCl in presence of acetyl chloride to obtain the cyclopropane derivative **3** in 89% yield as a single diastereomer (Scheme 6).[11] The organozinc reagent plays an important role for deciding the stereochemical outcome.



2 **3**

Scheme 6: Simmons-Smith cyclopropanation of tri-*O*-benzyl D-glucal.

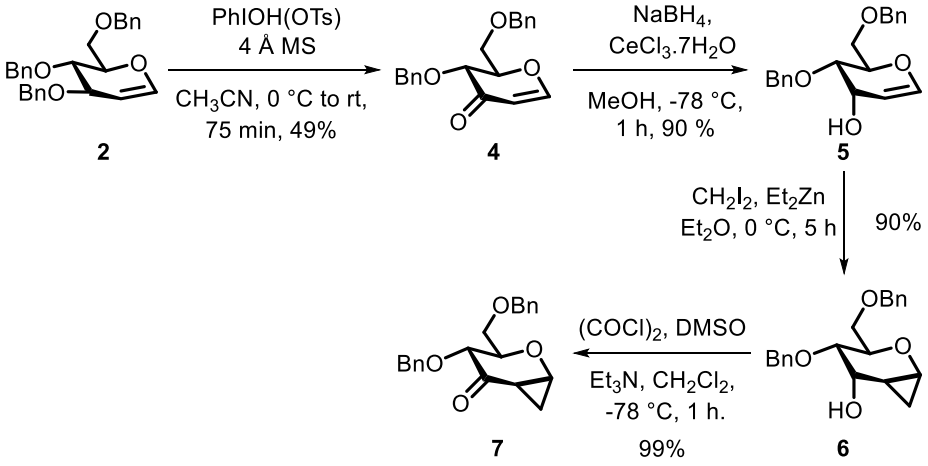
The previous version of reaction was modified by Hoberg and co-worker where diethyl zinc was used instead zinc-copper couple.[12] By adopting this improved approach, a wide range of protected glycals have been cyclopropanated with good selectivity and yields. The significance of this reaction is that it gives only *syn*-diastereomer, in which the cyclopropane ring is *syn* to the stereochemistry of C-3 position. For example, tri-*O*-benzyl-D-glucal **2** in ether when treated with diiodomethane and diethyl zinc at 0 °C, provided the *syn*-cyclopropanated product **3** in 92% yield (Scheme 7).



2 **3**

Scheme 7: Synthesis of cyclopropanes using the Furukawa's method.

This protocol was successfully adopted by our group, for the synthesis of carbohydrate-derived donor-acceptor cyclopropane.[13] The concept involved the incorporation of an electron-withdrawing property at the C-3 position of 1,2-cyclopropanated sugar derivatives to facilitate the access of cyclic donor-acceptor cyclopropanes. In this regard, by using [hydroxy(tosyloxy)iodo]benzene (HTIB, also known as Koser's reagent), 3,4,6-tri-*O*-benzyl-D-glucal **2** was oxidised in acetonitrile to generate the sugar-derived enone **4** in a reasonable yield. Further, a single diastereomer, **5**, was obtained *via* Luche reduction. Under Simmons-Smith reaction conditions, hydroxyl-directed cyclopropanation of **5** using CH_2I_2 and Et_2Zn generated the allose derived 1,2-cyclopropane **6**, which upon Swern oxidation provided the 1,2-cyclopropa-3-pyranone **7** in excellent yield (Scheme 8).[13]



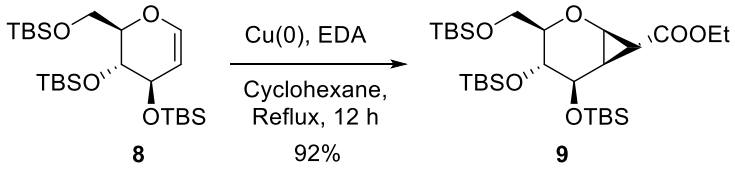
Scheme 8: Synthesis of D-glucose-derived 1,2-cyclopropanated donor.

1.4.2 Using Diazo-based Cyclopropanation

Transition-metal catalysed cyclopropanation using diazo compounds has been widely employed for stereoselective cyclopropanation of sugars. These cyclopropanated sugars have an ester functionality in the cyclopropane ring. In this construction, the endocyclic oxygen acts as the donor group and ester acts as the acceptor group. As a result, the carbohydrate-derived DACs is obtained and the type depends on the glycal used.

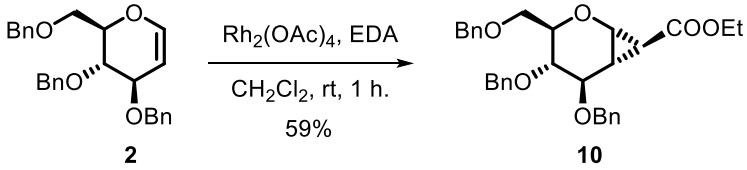
3,4,6-tri-*O*-acetyl-D-glucal was the first carbohydrate substrate to be cyclopropanated to give the sugar cyclopropane carboxylate, and this reaction was initially described in 1981.[14] Following that, Fraser-Reid *et al*, cyclopropanated the glycals using copper powder and ethyl

diazoacetate (EDA).[15] The D-glucose-derived *β*–1,2-cyclopropanecarboxylate **9** was obtained in 92% yield as a single by gradually adding EDA in cyclohexane to the combination of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-D-glucal **8** and copper powder in cyclohexane (Scheme 9).



Scheme 9: Copper-mediated diazo-based cyclopropanation of glycal.

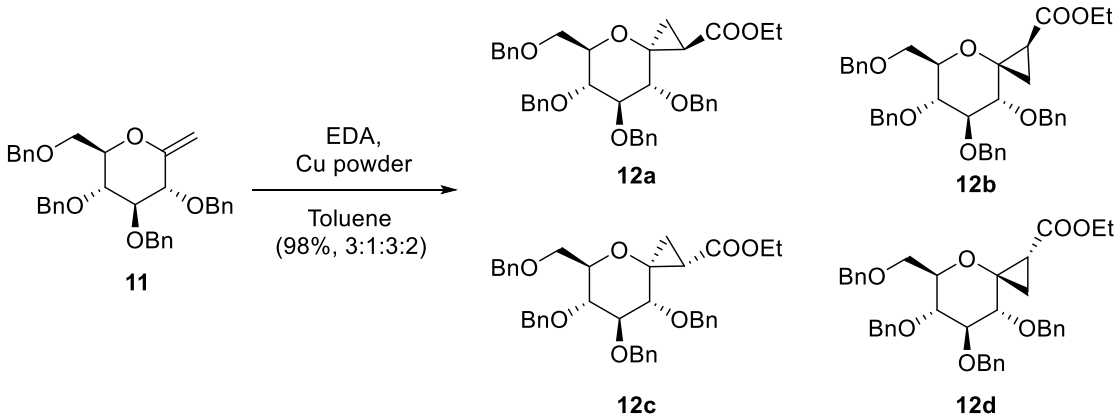
In contrast, Hoberg and coworker, used dirhodium tetraacetate in place of Cu(0) for the cyclopropanation using ethyl diazoacetate (EDA) to obtain *trans*-cyclopropanated glycal derivatives.[16] Using this synthetic procedure, variety of carbohydrate derived α-1,2-cyclopropanecarboxylated sugars were synthesized with excellent yield and stereoselectivity. This protocol is tolerable for variable protected glycals. The formation of α-selective products is explained based on the steric factors governed by C-3 position substituent. An example of this is depicted in scheme 10 where the 3,4,6-tri-*O*-benzyl-D-glucal **2** is transformed to α-1,2-cyclopropane carboxylate derivative **10** using EDA and $Rh_2(OAc)_4$.



Scheme 10: Ethyl diazoacetate-mediated cyclopropanation using catalytic $Rh_2(OAc)_4$.

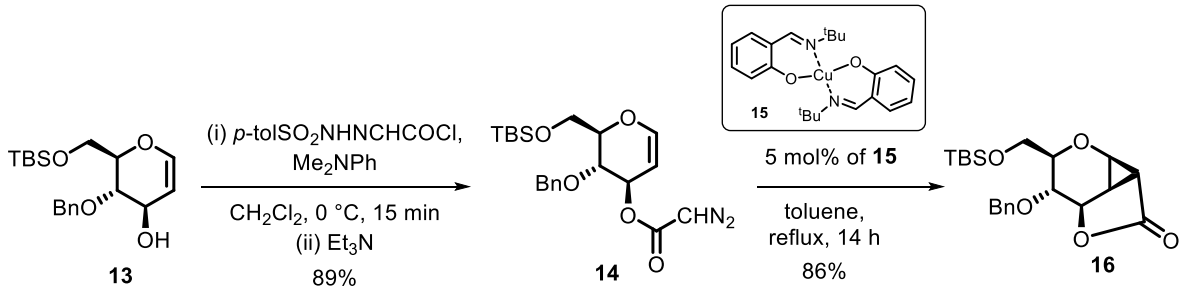
In a similar way, the *exo*-glycals can also be used for the cyclopropanation reaction using diazo-based reagent to provide a spiro-cylopropanated sugar derivatives. For the first time, Andrea Vasella and co-worker in 2003,[17] reported the synthesis of spiro-cylopropanated sugar derivatives from *exo*-glycal **11** using Cu powder under reflux conditions in toluene. The reaction provided a mixture of diastereomers (**12a-b**) with 93-98% yield (Scheme 11).

However, use of $Rh_2(OAc)_4$ catalyst did not provide satisfactory yields. Further development of this reaction was successfully applied on different sugars and worked well even with variable protecting groups.



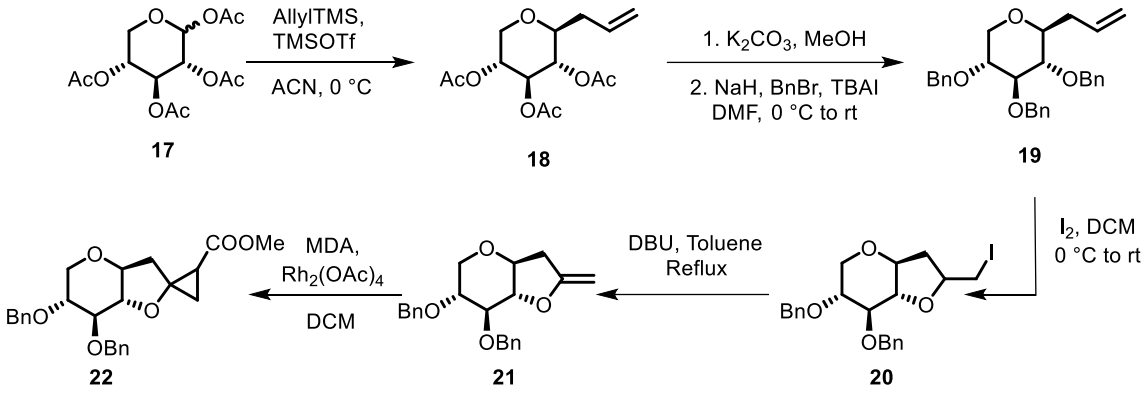
Scheme 11: Synthesis of glucose derived spiro-cyclopropanated sugar using *exo*-glycal sugar substrate.

In another work, Pagenkopf group reported a unique cyclopropane carboxylate sugar derivative using diazo sugar substrate, EDA and copper reagent *via* a intramolecular cyclopropanation.[18] Treating glycal **13** with a solution of glyoxylic acid chloride (*p*-toluenesulfonyl)hydrazone in CH_2Cl_2 and Et_3N provided the corresponding glycal diazo acetates **14** in excellent yield. The obtained glycal diazo acetates were transformed to *β*-1,2-cyclopropanecarboxylated sugar derivatives **16** under the catalysis of bis(*N*-*tert*-butylsalicylaldiminato)copper(II) [Cu(TBS)$_2$] (**15**) with 85% yield (Scheme 12).



Scheme 12: Synthesis of cyclic cyclopropanated sugar derivative 16.

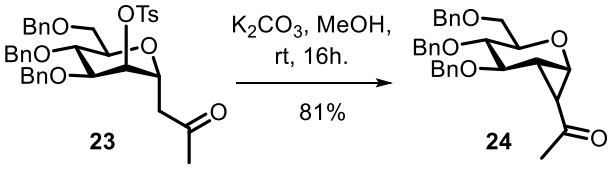
Our group also synthesized a unique and highly strained bicyclic spiro-cyclopropane carboxylated sugars which added into the library of carbohydrate-derived DACs.[19] Our synthesis started with peracetylated D-xylose **17** which was allylated to give the *C*-glycoside **18** in 80% yield. Base-mediated deacetylation followed by benzylation gave the perbenzylated product **19** in 85% yield. Iodine promoted cyclization of **19** resulted in the formation of bicyclic product **20** in 96% yield. DBU mediated dehydrohalogenation offered the *exo*-olefin **21** in 88% yield. Further, cyclopropanation of this vinyl ether **21** using methyl diazoacetate and rhodium acetate afforded the fused bicyclic spiro-cyclopropane carboxylated sugar **22** in 55% yield (Scheme 13). The synthetic method was tolerated by other pyranose and furanose sugar derivatives as well.



Scheme 13: Synthesis of fused bicyclic spiro-cyclopropane carboxylated sugar.

1.4.3 Miscellaneous protocol

Shao *et al.* in the year 2003, reported the base–mediated intramolecular S_N2 reaction of 2'-oxoalkyl-2-*O*-Ts-*α*-C-mannopyranoside **23** to obtain 1,2-cyclopropaneacetylated sugar derivative. D-Glucose-derived 1,2-cyclopropaneacetylate **24** was prepared by treating the 2'-ketone C-mannoside **23** with potassium carbonate in methanol over 81% yield (Scheme 14).[20]



Scheme 14: Base-mediated intramolecular cyclopropanation.

The chemistry of donor-acceptor cyclopropanes has shown numerous advances in the recent few decades, especially regarding their use in the synthesis of intriguing molecular structures. The intrinsic chirality of donor-acceptor cyclopropanated carbohydrates is thought to be even more fascinating since it can be transferred to the products with a high degree of stereocontrol. Further, application of the methodologies developed using sugar-derived DA cyclopropanes in construction of novel library of molecules and in the total synthesis of complex bioactive natural products remains open area of research.

Certainly, the carbohydrate-derived donor-acceptor cyclopropanes have been acting as one of the versatile synthons. Our group for more than a decade has pioneered in exhibiting various types of reaction that can possibly happen with some of the carbohydrate-derived DACs mentioned in scheme 5 such as ring opening, ring expansion, ring contraction reactions etc. [21] Apart from these, we were interested to unveil the interesting features played by carbohydrate-derived DACs in formal (3+2) cycloaddition reactions. In this regard, we did a brief study about the previous reports on the applications of carbohydrate-derived DAC in formal (3+2) cycloaddition. Further, part of this chapter explains the role played by the carbohydrate-derived DAC in formal (3+2) cycloaddition reactions.

1.5 Synthetic applications of carbohydrate-derived donor-acceptor cyclopropane in formal (3+2) cycloaddition reaction

Donor-acceptor cyclopropanes have been successfully introduced as a 1,3-dipolar species which is consider as synthetic equivalent of diene in the cycloaddition reaction.

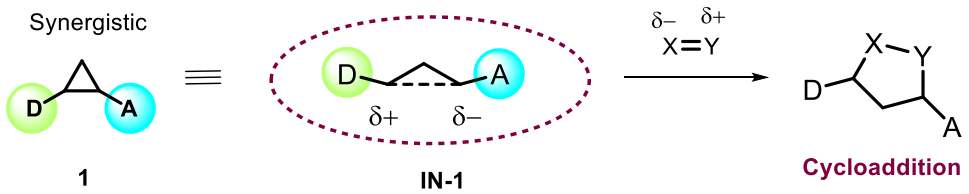
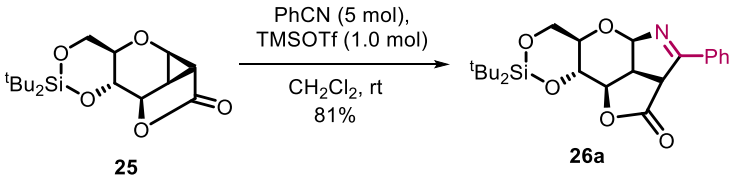


Figure 1: (3+2) cycloaddition of DACs.

The electronic effect of DAC **1** and synergistic effect of **IN-1** plays an important role in the (3+2) cycloaddition reaction (Figure 1). Moreover, under treatment with Lewis acid, donor-

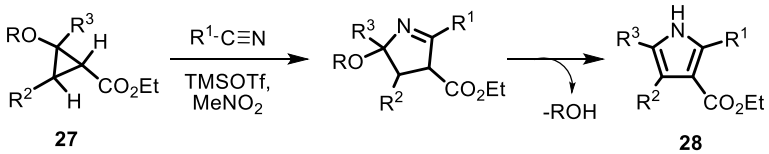
acceptor cyclopropanes can produce of diverse carbocycles and heterocycles. Also, the reacting dienophile or the 1,2-dipolar partner also plays an important role in molecular design outcome. The carbohydrate-derived DAC provides a mould for the synthesis of chiral cycloadducts *via* (3+2) cycloaddition. In an effort to extend the versatility of carbohydrate-derived DAC various groups have worked on the stereoselective (3+2) cycloaddition reactions with arrays of 1,2-dipolar synthons. Following are the reports in the literature till date.

In the year 2003, Pagenkopf and co-workers,[22] found that TMSOTf activation of glycal-derived cyclopropane **25** efficienty formed a dipolar species which in-turn reacted with benzonitrile present in the reaction medium to give the imine cycloadduct **26a** under the optimised reaction condition in 81% yield (Scheme 15). With this initial success, they further utilised a wide variety of nitriles and found that both aliphatic and α,β-unsaturated nitriles participated equally well in the cycloaddition reaction.

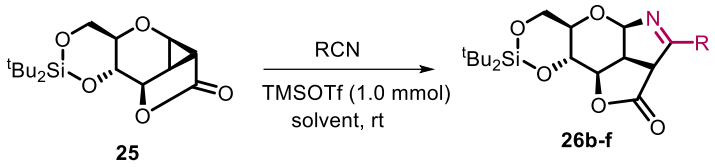


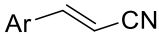
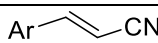
Scheme 15: Nitrile cycloaddition to sugar derived DAC.

The discovery of the nitrile cycloaddition with a unique sugar-derived template **25**, allowed them to further widen the sugar substrate scope. In their next study, a peculiar type of substrate **27** was taken as the model skeleton. In contrast to the preceding study, the pyrrole derivative was formed as a cycloadduct **28** by the removal of the alkoxy group and tautomerization (Scheme 16).[23]



Scheme 16: Pyrrole synthesis *via* (3+2) cycloaddition of DAC and nitrile.



Entry	Nitrile	Solvent	Cycloadduct	Yield[a]
1	MeCN	MeCN	**26b**, R = CH_3	81%
2	PrCN	CH_2Cl_2	**26c**, R = Pr	95%
3	^{t}BuCN	CH_2Cl_2	**26d**, R = ^{t}Bu	79%
4[b]		$MeNO_2$	**26e**, R = CHCHAr, X = H	60%
5[b]		$MeNO_2$	**26f**, R = CHCHAr, X = OMe	75%

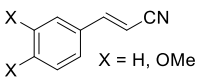
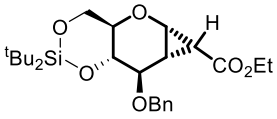
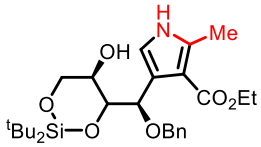
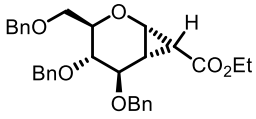
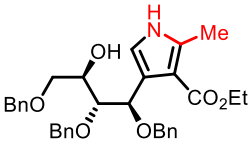
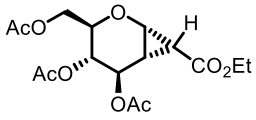
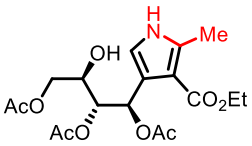
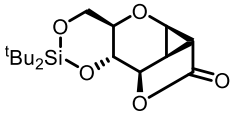
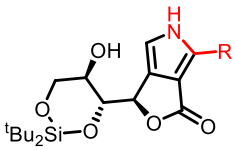
[a]isolated yield; [b]Nitrile = 

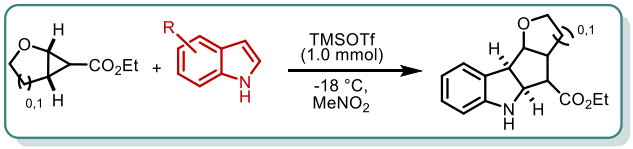
Table 1: Nitrle addition to cyclopropane 25.

Entry	Substrate	Nitrile	Pyrrole	Yield
1		MeCN		87%
2		MeCN		77%
3		MeCN		58%
4[a]		^{t}BuCN PhCN ArCN		R = ^{t}Bu; 87% Ph; 85% Ar; 93%

[a]Acid workup (1 M HCl). [b]ArCN = *p*-$MeOC_6H_4CN$.

Table 2: Nitrile Cycloadditions with carbohydrate-derived DACs.

The highlight of their work was on the results from cycloaddition reactions with glycal-derived 1,2-cyclopropane carboxylate and acetonitrile to form the highly functionalized pyrrole derivative with intact sugar fragment. These reactions showed that a range of protecting groups like di-tert-butylsilylenes (table 2, entries 1 & 4), benzyl ethers (table 2, entries 2) and acetates (table 2, entry 3) were compatible with the pyrrole synthesis. Alongside, the model DAC substrate **25** from previous work was also subjected to TMSOTf mediated (3+2) cycloaddition reaction with various nitriles (Table 2; entry 4).



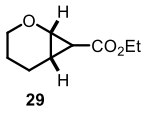
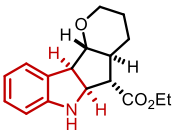
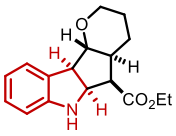
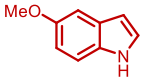
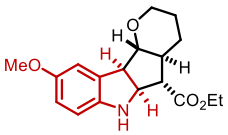
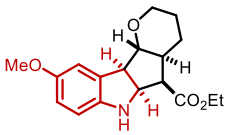
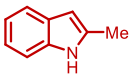
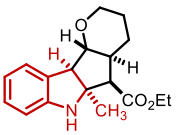
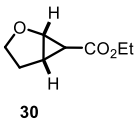
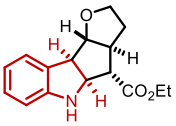
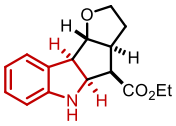
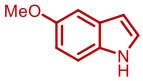
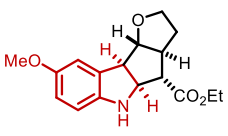
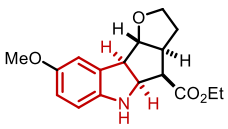
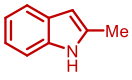
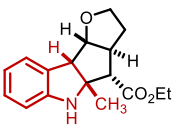
Entry	Substrate	Indole	Cycloadduct		Yield
1	 **29**				88% (1:1)
2	"				90%; (1:1)
3	"				74%
4	 **30**				58%; 1.3:1
5	"				70%; 1.4:1
6	"				72%

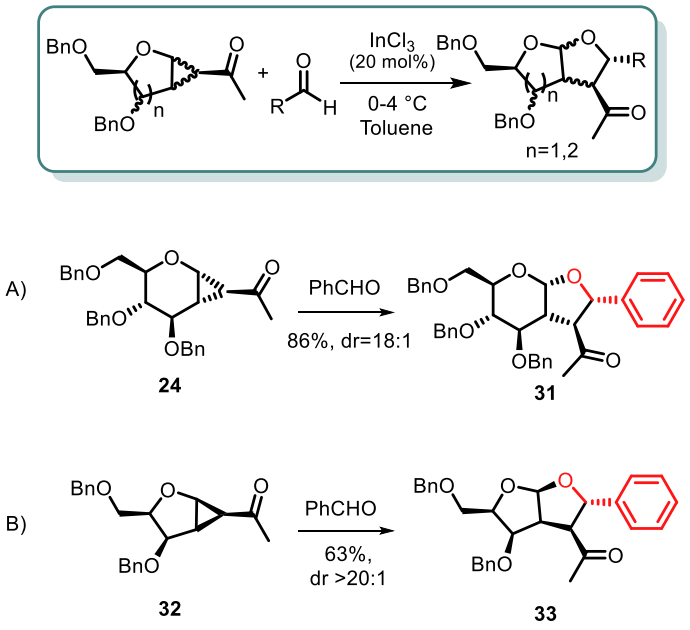
Table 3: Scope of cycloaddition of indoles with DA Cyclopropanes.

Unlike in the previous report, the acid work-up after the reaction provided ring opened and aromatized substituted pyrrole as the cycloadduct. Hence, even in this case they were successful in synthesizing the substituted pyrrole derivative with sugar fragment intact. This work sets a great illustration for the precise construction of pyrroles of increased complexity.

Pagenkopf and coworkers, however, further explored the opportunities of 1,2-dipolar synthons apart from nitriles. Expanding their research on DAC and its (3+2) cycloaddition reaction, in the year 2007, reported the dearomative addition of indoles on the 2-alkoxycyclopropanoate esters for the efficient construction of fused tricyclic ring skeleton.[24] Although, they did not directly involve a sugar derived DAC, they used a DACs derived from dihydropyran **(29)** and dihydrofuran **(30)**, as it structurally resembles the core skeleton of carbohydrate-derived 1,2-cyclopropane carboxylate. The table 3 is the evaluated results of the cycloaddition reaction with respected to DAC **29** and **30** and indoles with variable substitutions for the effective construction of tricyclic scaffolds. The products were characterized by NMR and X-ray studies.

Further reports by Huawu Shao group, showed the elegant application of 1,2-cyclopropyl ketones derived from sugars in (3+2) cycloaddition reaction. The meticulous construction of the fused tetrahydropyrans and furans ring skeleton was eased by their methodology. The first report in 2013,[25] showed the $InCl_3$ catalysed (3+2) cycloaddition reaction of 1,2-cyclopropanated sugars with aldehydes in a highly diastereoselective manner for the construction of bis-THFs and furo-pyran fused architectures. The model substrate **24** in toluene solvent and in the presence of 20 mol% of $InCl_3$, efficiently underwent cycloaddition reaction with benzaldehyde to give multisubstituted perhydrofuro-[2,3-b]pyran **31** in 86% yield with 18:1 diastereomeric ratio (Scheme 17, a). The reaction was screened for generality by incorporating various aryl, substituted aryl, and alkyl aldehydes as 1,2-dipolar substrates in the synthesis. The formation of 1,3-zwitter ion was highlighted as the key intermediate in the proposed mechanism. After the successful entries of the multi-substituted fused furo-pyran ring systems, the methodology was focused for the construction of bis-THFs. In this regard, the furanosyl 1,2-cyclopropanated ketone **32** was subjected to (3+2) cycloaddition reaction under standard conditions with benzaldehydes to obtain the cycloadduct bis-THF **33**

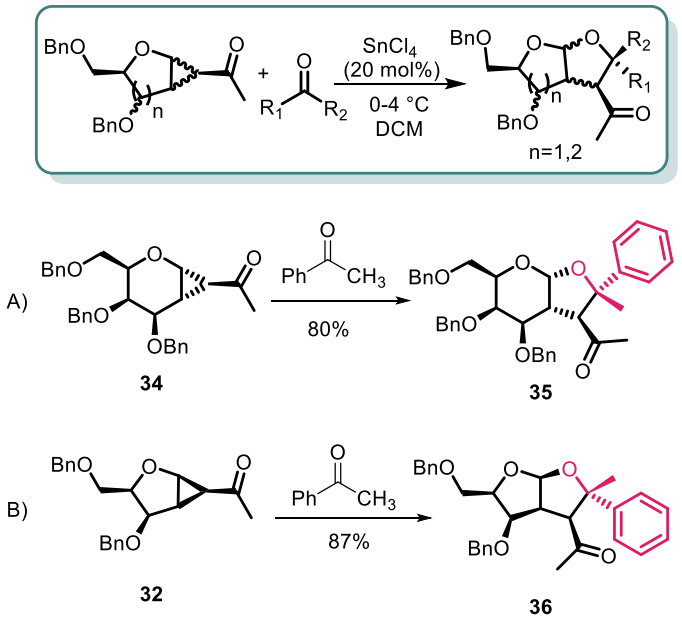
as the product. The results were as expected based on the proposed mechanism. Further the methodology was expanded by carrying out the cycloaddition reactions with various aryl, substituted aryl and alkyl aldehydes.



Scheme 17: $InCl_3$ catalyzed (3+2) cycloaddition reaction between 1,2-Cyclopropanated sugars and aldehydes.

Further efforts by Shao and co-workers showcased the stereospecific (3+2) cycloaddition of glycal-derived 1,2-cyclopropanes (**34 and 32)** and ketones under the lewis acid conditions.[26] $SnCl_4$ catalysed cycloaddition reaction offered multisubstituted bis-THFs and furo-pyran fused systems a quaternary carbon containing chiral centre in good to excellent yield. The methodology witnessed a high stereoselectivity and compatibility with wide range of functional groups in the formal (3+2) cycloaddition of cyclopropanes and ketones. Initial studies were performed with cyclopropanated sugar **34** and acetophenone as model substrates in presence of 20 mol% $SnCl_4$ in CH_2Cl_2 at 0-4 °C. In these circumstances, the cycloadduct **35** was obtained as a single diastereomer, in 80% yield (Scheme 18, a). Subsequently, scope of the methodology was evaluated for different aryl and alkyl ketones. The opportunity of the (3+2) cycloaddition of cyclopropanated sugar and ketones was further extended to furanosyl 1,2-cyclopropanated sugar **32**. Multi-substituted bis-THF

derivative **36** was obtained in 87% yield as a single diastereomer, when sugar **32** and acetophenone was treated under standard reaction condition. Consistent with the previous results, the sugar substrate **32** reacted very well different ketones and all the reactions offered a single diastereomer as the only cycloadduct.



Scheme 18: (3+2) cycloaddition of glycal-derived 1,2-cyclopropyl ketone and ketones.

1.6 Research Motivation

Following a thorough investigation, we were very interested in the utilisation of carbohydrate-derived donor-acceptor cyclopropanes in the (3+2) cycloaddition reaction to build significant skeletons with potential biological or therapeutic uses as well as for the synthesis of natural products. During our study we learnt that, two DAC skeleton **37** and **38** were still unused and unexplored in specific for (3+2) cycloaddition reaction (Figure 2).

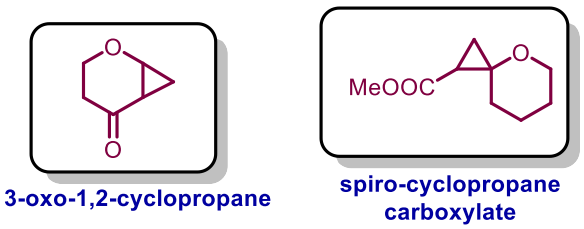


Figure 2: Structural skeleton of our model substrates of our study.

As our group had consistently been exploring the chemistry involving these carbohydrate-derived DAC skeleton, we were further motivated to take it forward and study its behaviour under cycloaddition reaction condition. Also, we were curious to build some important biological frameworks using this opportunity and contribute to the developments in synthetic carbohydrate chemistry area.

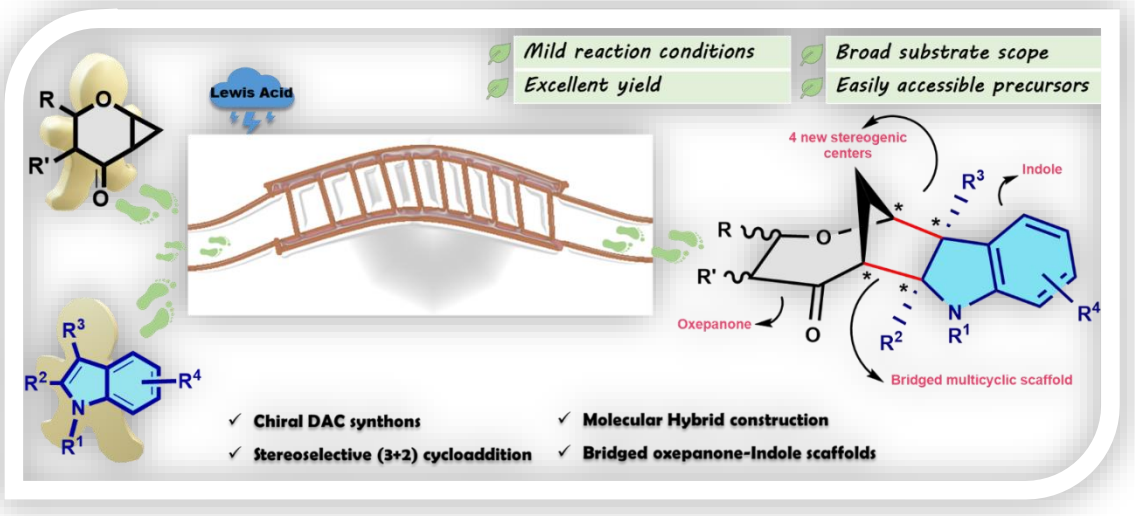
References

1) (a) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625-1647
   (b) Special issue on cyclopropanes and related rings: *Chem. Rev.* **2003**, *103(4)*.
   (c) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051-1070.
   (d) Kulinkovich, G. Cyclopropanes in Organic Synthesis. (Hoboken, NJ: Wiley, 2015).
   (e) Keglevich, P.; Keglevich, A.; Hazai, L.; Kalaus, G.; Szantay, C. *Curr. Org. Chem.* **2014**, *18*, 2037.
   (f) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603-1623.
2) (a) Schneider, T. F.; Kaschel, 1066 J.; Werz, D. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5504−5523.
   (b) Ivanova, O. A.; Trushkov, I. V. *Chem. Rec.* **2019**, *19*, 2189-2208.
3) Reissig, H.-U.; Hirsch, E. *Angew. Chem. Int. Ed.* **1980**, *19*, 813–814.
4) Tomilov, Yu. V.; Menchikov, L. G.; Novikov.; R. A. Ivanova, O. A.; Trushkov I. V. *Russ. Chem. Rev.* **2018**, *87*, 201-250.
5) Davis, B. G.; Fairbanks, A. J. *Carbohydrate Chemistry*; Oxford University Press Oxford, **2002**.
6) McNaught, A. D. Nomenclature of carbohydrates. *Carbohydr. Res.* **1997**, *297*, 1- 92.
7) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.
8) (a) Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1964**, *42*, 1473-80.
   (b) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1965**, *43*, 1460-1475.
9) (a) Gomez, A. M.; Lobo, F.; Uriel, C.; Lopez, J. C. *Eur. J. Org. Chem.* **2013**, 7221–7262.
   (b) Ansari, A. A.; Lahiri, R.; Vankar, Y. D. *ARKIVOC* **2013**, 316-362.

10) Harvey, J. E.; Hewitt, R. J.; Moore, P. W.; Somarathne, K. K. *Pure Appl. Chem.* **2014**, *86*, 1377–1399.
11) Ramana, C. V.; Murali, R.; Nagarajan. M. *J. Org. Chem.* **1997**, *62*, 7694–7703.
12) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831–6834.
13) Sridhar, P. R.; Venukumar. P. *Org. Lett.* **2012**, *14*, 5558-5561.
14) Baidzhigitova, E. A.; Afanasev, V. A.; Dolgii, I. E. *Izv. Akad. Nauk Kirg.* **1981**, 50–56.
15) Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901–8904.
16) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, 37, 2533–2536.
17) Blüchel, C.; Ramana, C. V.; Vasella, A. *Helv. Chim. Acta.* **2003**, *86*, 2998-3036.
18) Yu, M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563–2566.
19) Ramakrishna, B.; Sridhar, P. R. *Org. Lett.* **2013**, *15*, 4474–4477.
20) Shao, H.; Ekthawatchai, S.; Chen, C. S.; Wu, S. H.; Zou, W. *J. Org. Chem.* **2005**, *70*, 4726–4734.
21) V. Ganesh, P. R. Sridhar, S. Chandrasekaran, *Isr. J. Chem.* **2016**, *56*, 417-432.
22) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122-8123.
23) Yu, M.; Pagenkopf. *Org. Lett.* **2003**, *5*, 5099–510.
24) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631–9634
25) Ma, X.; Tang, Q.; Ke, J.; Zhang, J.; Wang, C.; Wang, H.; Li, Y.; Shao. *Org. Lett.* **2013**, *15*, 5170–5173.
26) Ma, X.; Zhang, J.; Tang, Q.; Ke, J.; Zou, W.; Shao, H. *Chem. Commun.* **2014**, **50**, 3505-3508.

Chapter 2 – Part A

A Ring Expansion Stereoselective Cycloaddition of Carbohydrate Derived Donor–Acceptor Cyclopropanes: Synthesis of Bridged Oxepenone–Indole Hybrids



Abstract:

An efficient method for the construction of sugar-derived chiral oxepanone–indole molecular hybrids is investigated. The reaction condition is optimized by monitoring the progress at various temperatures, with various solvents, and with different Lewis acid catalysts. Under optimized conditions, high stereoselectivity and efficiency are achieved in most of the formed cycloadducts. The accessibility of the strategy is evaluated by utilizing an array of carbohydrate-derived donor–acceptor cyclopropanes and variably substituted indole substrates. Additionally, quick access to the bridged indole–oxepanone framework is described by utilizing a diastereoselective (3+2) cycloaddition of aryl-substituted donor–acceptor cyclopropanes incorporated in a pyran ring.

2.1.1 Introduction

Oxepane, an important class of heterocycles, is a seven-membered cyclic ether, which is found as the core skeleton in various bio-active natural products. Interestingly, the oxepanone frame-work occurs in numerous marine natural products such as the sipholenol A scaffold, dahabinine A, raspacionin B, etc. (Figure 1A).[1] Moreover, these cyclic ethers display multipurpose and promising pharmacological properties like anti-bacterial, anticancer, and antifungal activities.[1] Additionally, oxepane forms the structural backbone of the biologically active target molecule, septanose sugar. Septanoses are homologues of pyranoses and are used as a "non-natural" surrogate in many biochemical investigations.[2] This has prompted a number of scientists to develop processes for the synthesis of the glycoconjugates containing oxepane and septanose sugar backbone.[3] The carbohydrate biomolecules play an inevitable role in all living systems. Carbohydrate-derived drug design is an emerging area of research in the field of medicine and therapeutics.[4]

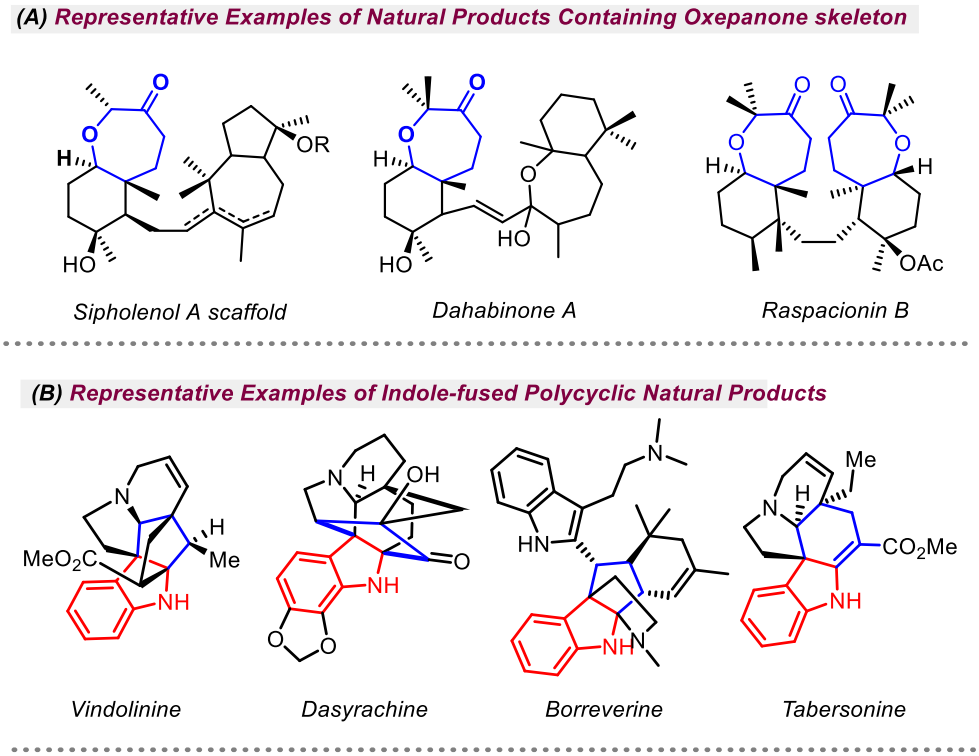


Figure 1. Representative examples of natural products accomplishing oxepanone and indole-fused polycyclic scaffolds.

The modern approach to fusing the active pharmacophores and biopotential carbohydrate scaffolds has created a new research direction for the construction of molecular hybrids.[5] The druggable properties of the carbohydrate mimics have been enhanced by employing the molecular hybridization(MH) strategy. Carbohydrate-derived donor–acceptor cyclopropanes (DACs) make up one such class of compounds that are being explored to exploit the potential to construct several biologically important carbohydrate mimics.[6] In recent research, DACs have become extremely valuable, highly strained, 1,3-dipolar synthon and as three-atom building blocks in synthetic organic chemistry.[7] Through a variety of (3+n) annulation and (3+n) cycloaddition, DACs are effectively employed to construct regio-and stereoselectively fused and bridged ring systems.[7] A member of the important pool of 1,2-dipolar synthons is indole, which efficiently undergoes the formal (3+2) cycloaddition reaction with the DAC.[8] Famous for its immortal role as an active pharmacophore, indole is used for the synthesis of indolines and indole-fused polycyclic scaffolds present in a variety of naturally occurring compounds such as vindolinine, dasyrachine, borreverine, tabersonine, etc. (Figure 1B), and pharmaceutically relevant molecules.[9]

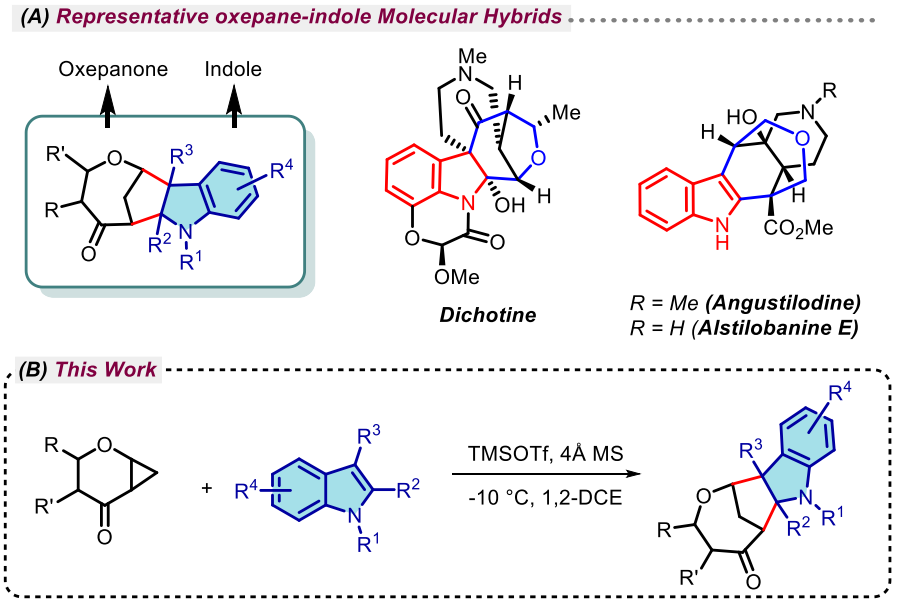
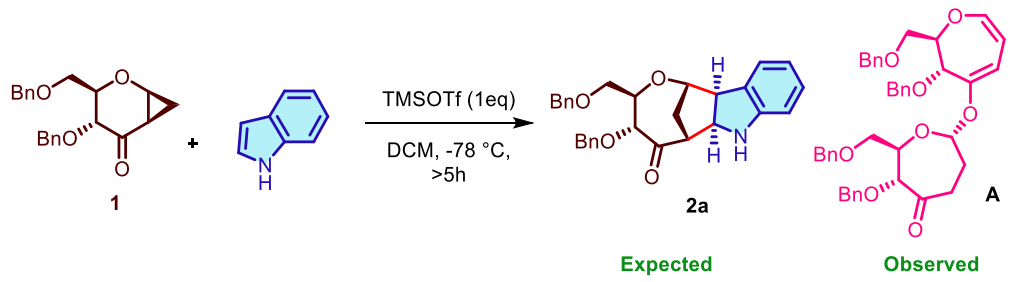


Figure 2. Outlook of present methodology.

Our research group has developed various methodologies using a carbohydrate-derived DAC for the synthesis of several potential carbohydrate frameworks and biomimetics.[10] Adding to this account, our group reported the ring opening of carbohydrate-derived DACs for the synthesis of various carbohydrate-based oxepane scaffolds.[11] To date, only one natural product, dichotine,[12] possessing an oxpanone-fused indole scaffold has been reported in the literature, while oxepane-fused indole is a characteristic frame work embedded in several natural products like angustalodine,[13] alstilobanine E,[14] etc. (Figure2A). Considering our prior achievements in developing innovative methodologies using carbohydrate-derived DACs,[10,11] we envisioned that (3+2) cycloaddition reactions of 3-oxo-1,2-cyclopropanated sugar derivatives with indoles would lead to new carbohydrate-based molecular hybrids with probable biological and pharmacological applications. To the best of our knowledge, there are no reports of cycloaddition reactions of 3-oxo-1,2-cycloproponated sugars. In this view, we thought that 3-oxo-1,2-cycloproponated sugars would serve as extraordinary assets in formal (3+2) cycloaddition. Herein, we report the first (3+2) cycloaddition of a 3-oxo-1,2-cycloproponated sugar and indole under Lewis acid conditions (Figure2B). This methodology is the first example to offer a bridged oxepanone–indole hybrid, an elegant amalgamate of carbohydrate and indole, with high regio- and stereospecificity.

2.1.2 Results and discussion

At the onset of our approach, we chose carbohydrate-derived DAC **1**[11] and 1*H*-indole as our model substrates. Initially, DAC **1** (1.0 equiv) and 1*H*-indole (2.0 equiv) were treated with TMSOTf (1.0 equiv) at−78°C in dichloromethane as a solvent. We predictable a ring expansion followed by dearomative (3+2) cycloaddition.



Scheme 1. Initial attempt for (3+2) cycloaddition reaction between model substrates DAC 1 and 1*H*-indole.

However, we observed a dimerized product **A** which formed *via* a self-condensation reaction of sugar substrate **1** through a ring expansion mechanism (Scheme1). This indicates the reluctance of indole to participate in the reaction at lower temperatures while DAC **1** is reacting as expected under Lewis acid conditions. This encouraged us to conduct the optimization studies (Table1) to determine if indole participates in the reaction at higher temperature.

Entry	Solvent	Temperature	Time	Lewis Acid (Equiv.)	Yield % of 2a
1	DCM	-78 °C	>5 h	TMSOTf (1.0)	Nil
2	DCM	-40 °C	2 h	TMSOTf (1.0)	Nil
3	DCM	-20 °C	1 h	TMSOTf (1.0)	trace[a]
4	DCM	-10 °C	30 min	TMSOTf (1.0)	10%[b]
5	DCM	0 °C & rt	20 min	TMSOTf (1.0)	decomposed
6	CH_3NO_2	-20 °C	1 h	TMSOTf (1.0)	30%[b]
7	CH_3NO_2	-10 °C	30 min	TMSOTf (1.0)	50%[b]
8	CH_3NO_2	rt	10 min	TMSOTf (1.0)	decomposed
9	1,2-DCE	-30 °C	30 min	TMSOTf (1.0)	30%[b]
10	1,2-DCE	-20 °C	30 min	TMSOTf (1.0)	50%[b]
11	1,2-DCE	-10 °C	20 min	TMSOTf (1.0)	65%[b]
12	1,2-DCE	-10 °C	20 min	$Sc(OTf)_3$ (1.0)	10%[b]
13	1,2-DCE	-10 °C	20 min	$Cu(OTf)_2$ (1.0)	15%[b]
14	1,2-DCE	-10 °C	20 min	$Yb(OTf)_3$ (1.0)	trace[a]
15	1,2-DCE	-10 °C	20 min	$Bf_3.OEt_2$ (1.0)	40%[b]
16	1,2-DCE + 4Å MS	-10 °C	20 min	TMSOTf (0.5)	70%[b]

[a]HRMS analysis. [b]Isolated yield.

Table 1. Optimization details of cycloaddition of DAC 1 and 1*H*-indole.

While the cycloaddition product was not observed at −40°C, to our delight, a trace amount of product formation was observed when the reaction was carried out at −20°C with 1 equiv of TMSOTf for 3 h, as observed in the HRMS analysis. A prolonged reaction time did not improve product formation. However, when the reaction was conducted at −10°C in dichloromethane, the desired cycloadduct **2a** was isolated in 10% yield and the major product isolated was identified as an indole-dimerized product. In addition, reaction at 0 and 25°C resulted in the complete decomposition of DAC **1**. Encouraged by the results at−10°C, we performed further optimization as highlighted in Table 1. A brief solvent screen at−10°C indicated that 1,2-dichloroethane is a suitable solvent as it provided the desired cycloadduct in 65% yield. Further running the reaction in the presence of 4 Å molecular sieves by using 0.5 equiv of TMSOTf resulted in a slightly better yield of cycloadduct **2a** (70%). With the fruitful result in hand, we further explored the role of Lewis acids. However, different Lewis acids such as Sc(OTf)3, Cu(OTf)2, Yb(OTf)3, and $BF_3{\cdot}OEt_2$ at −10°C in 1,2-dichloroethane as a solvent resulted in inferior results. Ultimately, the reliable reaction condition was found to be DAC **1** and 1*H*-indole (1:2 molar ratio) stirred in 1,2-dichloroethane as a solvent and in the presence of 0.5 equiv of TMSOTfat−10°C, which provided cycloadduct **2a** in 70% yield (Table1, entry 16).

Screening and Scope of 1,2 and 1,3-Dipolar Partners.

With the optimized conditions in hand, we proceeded to test the generality of our methodology. Several indoles with different substitution patterns, such as electron-withdrawing (-CN and-NO_2), electron-donating (-OMe and -Br), and alkylated (3-methyl, 2,3-dimethyl, and N-methyl) functional groups (Tables 2 and 3) were screened. It is worth noting that substituents on the phenyl ring of indole, either -OMe or -Br, did not affect the expected results and anticipated cycloadducts **2b** and **2c** were obtained in 88% and 65% yields, respectively. In a similar way, highly electron withdrawing groups like -CN and -NO_2 substituents were also found to be tolerable and gave the cycloadducts **2d** (85%) and **2e** (80%) in good yields. In addition, while all of the indoles with substituents on the phenyl ring of the indole participated equally well in the reaction, the substitution on the pyrrole part also resulted in the cycloadducts in good yields despite steric

hindrance. DAC **1** successfully reacted with 3-methyl indole to give the cycloadducts instead of the alkylated products[8d] (Table3).

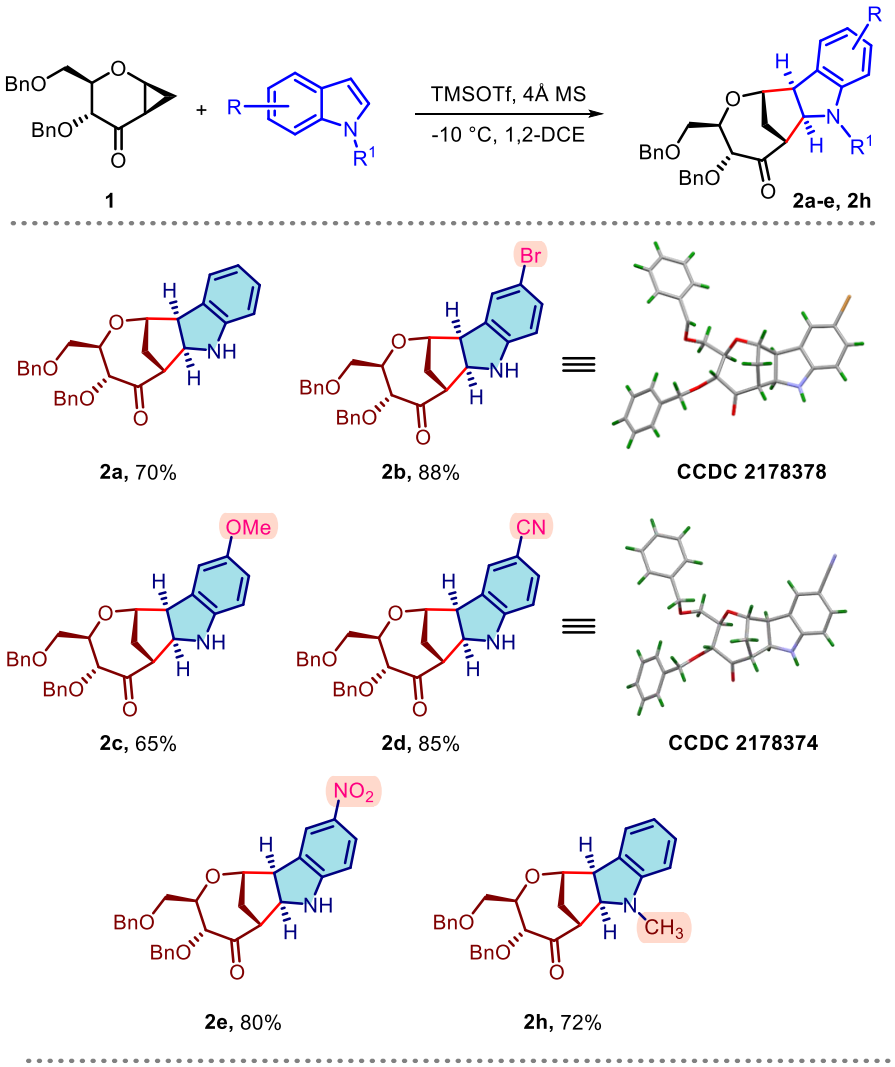
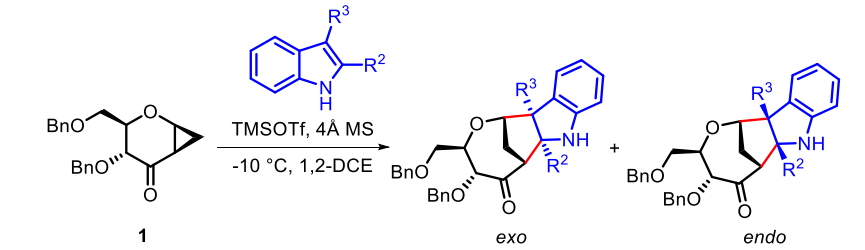


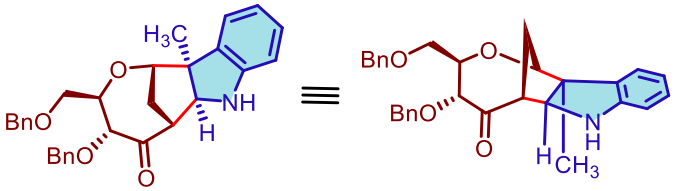
Table 2. Screening of functionalized indoles.

Interestingly, the indoles with alkyl-substituted functionalities over the pyrrole ring at positions C2 and C3 provided two diastereomers, and the products were identified as the *exo* and *endo* isomers on the basis of the structural arrangements. First, when 3-methyl-1*H*-indole and DAC **1** were subjected to cycloaddition under the optimized reaction conditions at −10 °C using 1,2-dichloroethane as a solvent and 0.5 equiv of TMSOTf, diastereomeric cycloadducts *exo*-**2f** (60%) and *endo*-**2f** (31%) were obtained in 91% overall yield. The reaction was also found to be efficient

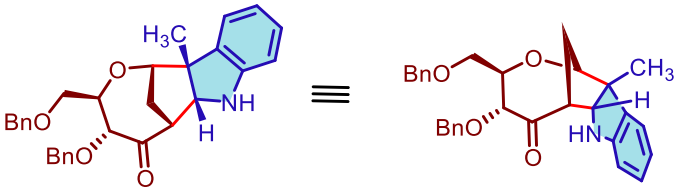
in providing the desired products *exo*-**2g** (58%) and *endo*-**2g** (35%) with an overall yield of 93%, when 2,3-dimethyl-1*H*-indole and DAC **1** were subjected to TMSOTf-catalyzed (3+2)cycloaddition. Lastly, the *N*-methyl indole participated equally well in the cycloaddition reaction and provided cycloadduct **2h** in 72% yield as a single diastereomer.



with 3-Methyl Indole

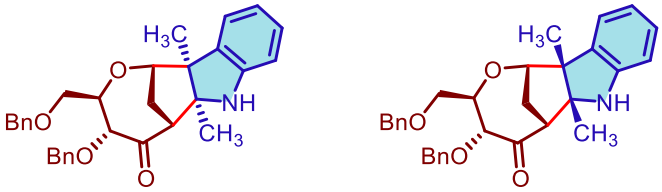


exo-**2f**, 60%



endo-**2f**, 31%

with 2,3-Dimethyl Indole



exo-**2g**, 58%

endo-**2g**, 35%

Table 3. (3+2) cycloaddition of C2, C3 alkylated indole substrates.

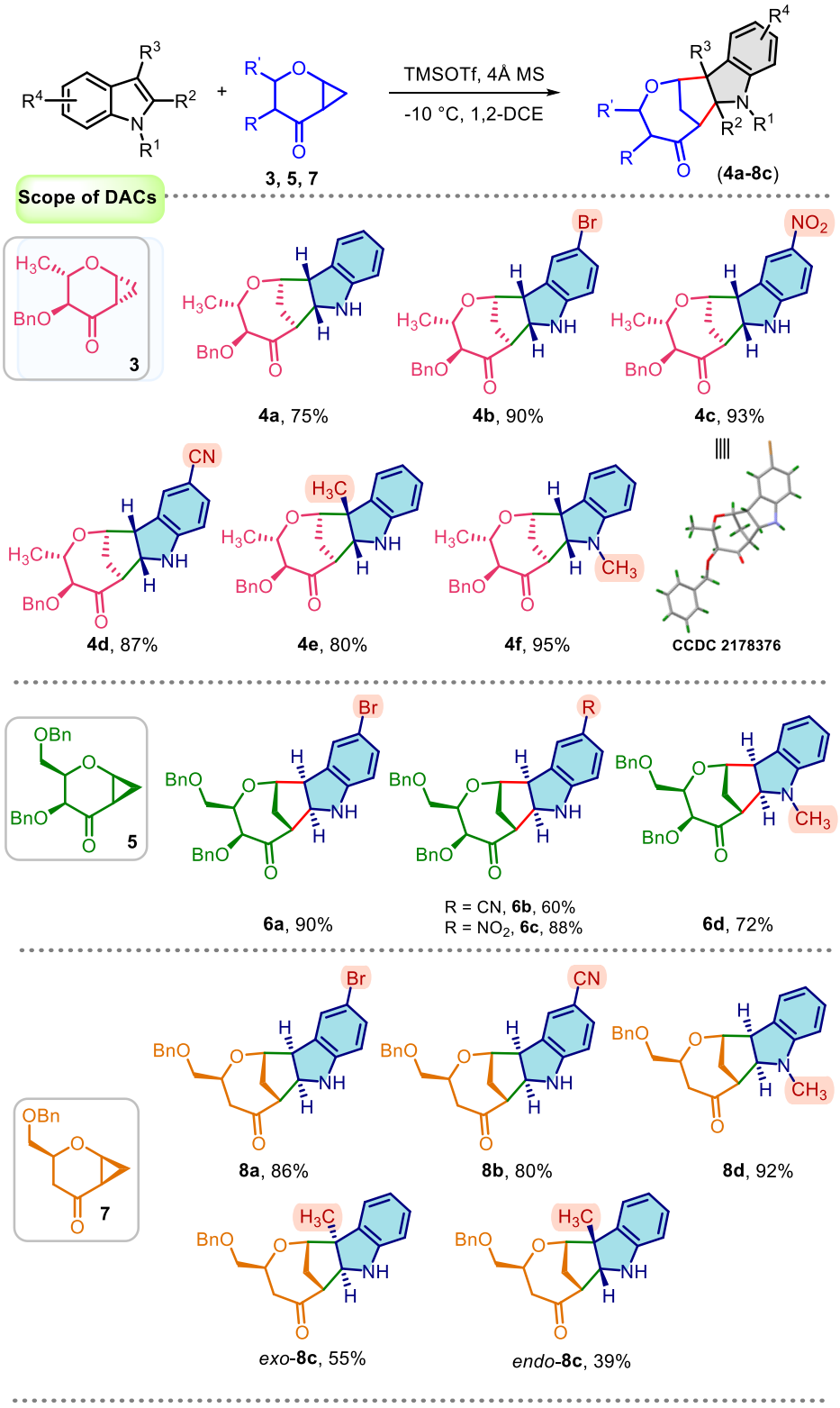


Table 4. Screening of various carbohydrate derived DACs

Then, we focused to extend the scope of the methodology further. We chose stereochemically diverse DACs and few selected indole substrates for (3+2) cycloaddition under optimized reaction conditions (Table 4). When L-rhamnose-derived DAC **3**[11] was subjected to (3+2) cycloaddition reaction with 1*H*-indole, cycloadduct **4a** was obtained in 75% yield. In addition, DAC **3** reacted with a range of indole (5-bromo,5-nitro,5-cyano,3-methyl, and *N*-methyl) substrates, which resulted in the exclusive formation of *exo*-cycloadducts (**4b–f**, respectively) in excellent yields. We further extended the investigation by choosing D-galactose-derived DAC **5**,[11] which again resulted in the exclusive formation of exo-cycloadducts **6a–d** in excellent yields. When D-glucose-derived 4-deoxy sugar DAC **7**[15] was subjected to (3+2) cycloaddition reaction with selected indole substrates (5-bromo, 5-cyano, and *N*-methyl), exo-cycloadducts (**8a, 8b,** and **8d**, respectively) were formed as single diastereomers. It is worth noting that the presence of the α-methylene group in DAC **7** did not hamper the formation of the cycloadducts. However, the reaction of DAC**7** and 3-methyl-1*H*-indole provided diastereomeric cycloadducts exo-**8c** (55%) and endo-**8c** (39%) in an overall yield of 94%. Following the success with the previous carbohydrate-derived DACs, we further chose aryl-substituted pyranoses possessing donor–acceptor cyclopropane functionalities. Hence, phenyl- and p-methoxy phenyl-substituted pyran-derived DAC **9**[16] and DAC 11, respectively, in racemic form were synthesized by the (4+2) cycloaddition of Danishefsky's diene and the corresponding aldehyde. As expected, DAC **9** and DAC **11** underwent (3+2) cycloaddition reaction efficiently with a number of substituted indole substrates. The electronic effects of indoles containing bromo substituents (5-bromoand 6-bromo) over the phenyl ring did not affect the cycloaddition, and in all cases, we observed that exo-cycloadducts (**10a**, **10b**, **12a**, and **12b**) formed in good to excellent yields (79−92%) (Table5). As previously observed, the 2- and 3-alkyl-substituted indoles provided the diastereomeric exo- and endo-cycloadducts **10c** and **10d** and **12c** in excellent yields, establishing the generality of the methodology. Finally, the *N*-methyl indole also reacted efficiently to give cycloadduct **10e** as a single diastereomer in 85% yield.

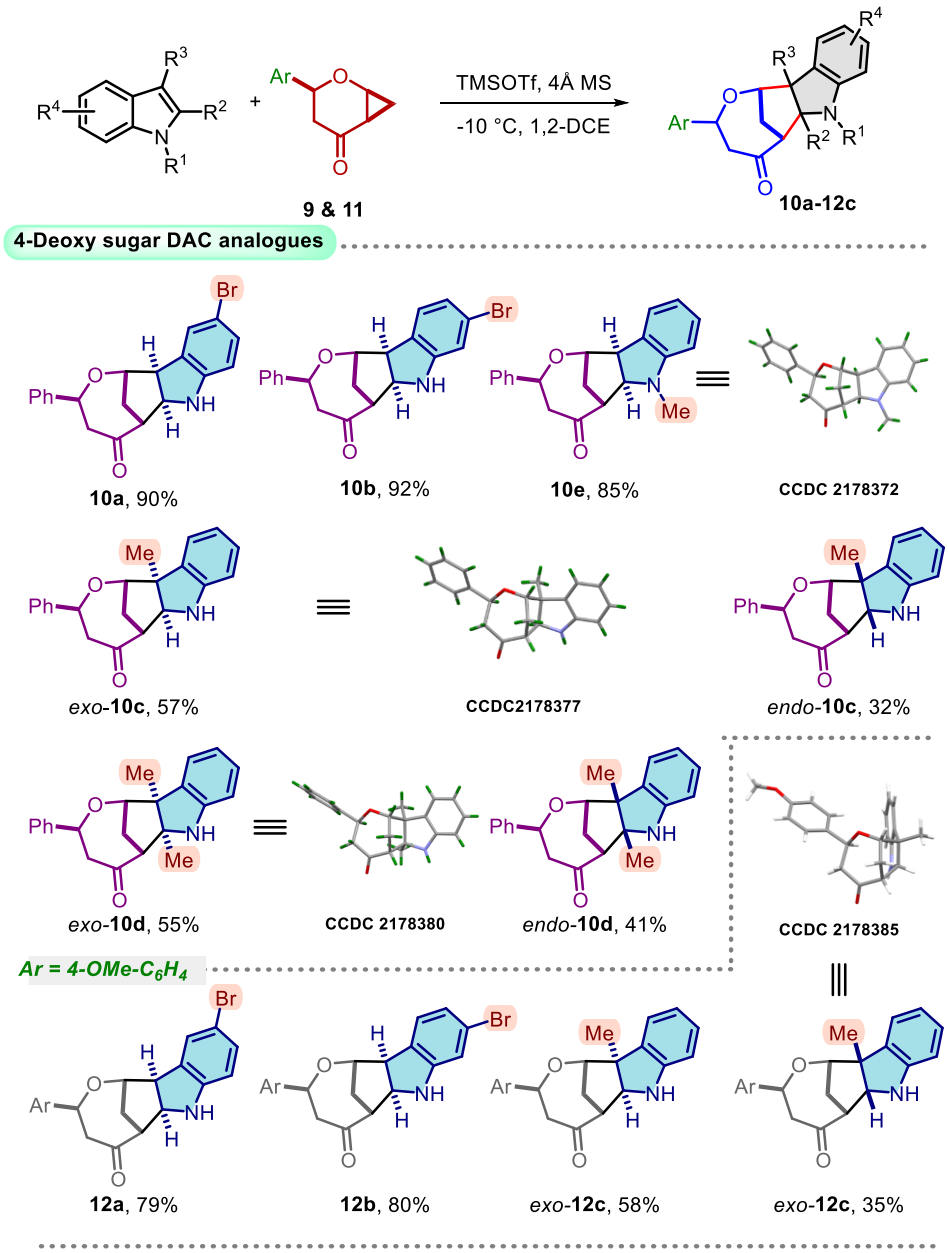


Table 5. 4-Deoxy sugar analogues cycloadducts.

Possible Mechanism.

We propose the following possible mechanism for the stereoselective formation of (3+2) cycloadducts. We expected that TMSOTf activates the 3-oxo functionality on the DAC that induces

the cleavage of the C1−C2 bond, leading to the formation of oxocarbeniumenolate intermediate (**IN-A**), which acts as a 1,3-dipolar species or the 1,3-zwitterion (Figure3).

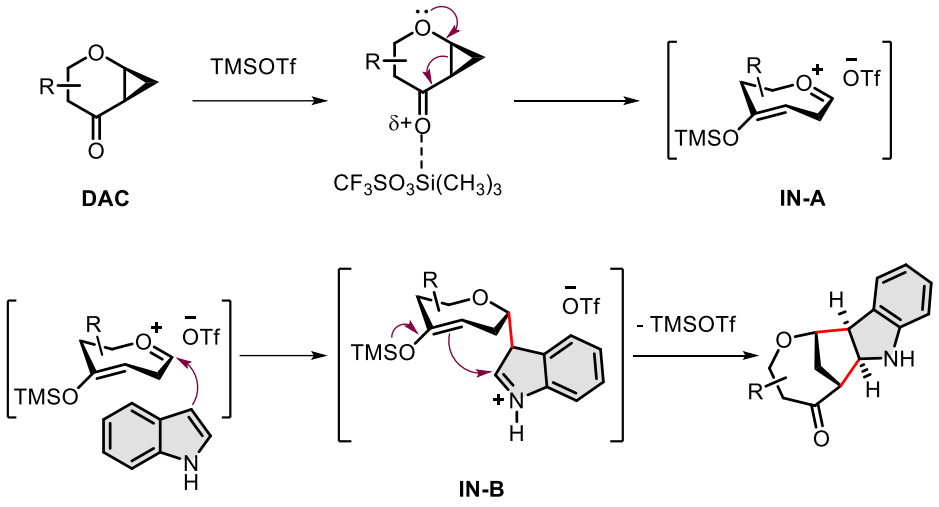


Figure 3. A Possible mechanism for the formation of cycloadducts.

Additionally, the preferential attack of the nucleophile along an axial trajectory toward this intermediate would provide the α-selective cycloadduct as the only product (**IN-B**). However, in the case of 2- or 3-substituted indoles, possible steric hindrance between the substituents on indole and the axial hydrogen on C6 of oxocarbeniumenolate restricts the formation of the *exo*-adduct and hence a substantial amount of the *endo*-product was observed. The structural arrangement of all of the formed cycloadducts (**2a–h**, **4a–f**, **6a–d**, **8a–d**, **10a–e**, and **12a–c**) was confirmed by ^{1}H and ^{13}C NMR analysis. Among them, a few (3+2) cycloadducts were studied in detail using two-dimensional (2D) NMR techniques. Through a thorough NMR correlation studies, the *exo*- and *endo*-products were also distinguished (Figure4). As shown in Figure 4, in *exo*-**2f**, a strong NOE was observed between the 3-CH_3 of the indole system and the 7′-H of the oxepanone ring. On the contrary, in the case of *endo*-**2f** correlation was observed between the 3-CH_3 of the indole and one of the bridged methylene CH groups, which indicates the *s-syn* arrangement of the methylene bridge and the methyl group. Encouragingly, we obtained the crystal structures of **2b**, **2d**, **4b**, exo-**10c**, exo-**10d**, **10e**, and endo-**12c**, which further authenticated the structural assignment of the (3+2) cyclo-addition products.

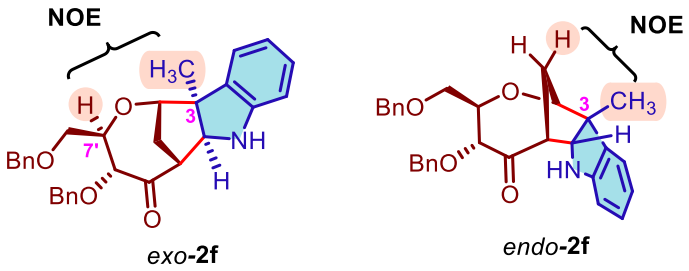


Figure 4. Correlation studies: Observed NOE in *exo*- and *endo*-cycloadducts.

2.1.3 Conclusion

In conclusion, an efficient and general method was developed for the construction of bridged oxepanone−indole molecular hybrids. The methodology utilizes the stereo electronic effects of endocyclic oxygen atom to afford the diastereomerically pure cycloadducts despite four stereocenters being formed in the (3+2) cycloaddition reaction. The generality and scope of the reaction were evaluated by applying the methodology to a number of monosaccharide-derived 3-oxo-1,2-cyclopropane derivatives (chiral) as well as simple aryl-substituted DACs (racemic). The reactivities of various indole substrates possessing electron-releasing and -withdrawing functional groups and *N*-alkyl indoles have been investigated. Thus, this methodology sets an example for the product's unique molecular construction, diastereoselectivity, metal-free synthesis, and wide substrate scope with possible biological activity.

2.1.4 References

1) Barbero, H.; Díez-Poza, C.; Barbero, A. *Mar. Drugs.* **2017**, *15,* 361-395.
2) *Pote, A. R.; Pascual, S.; Planas, A.; Peczuh, M. W. Int. J. Mol. Sci.* **2021**, *22*, 4497-4510.
3) (a) Saha, J.; Peczuh, M. W. *Chem. Eur. J.* **2011**, *17*, 7357 – 7365.
   (b) Vannam, R.; Peczuh, M. W. *Eur. J. Org. Chem*. **2016**, *2016,* 1800–1812.
4) (a) Thorson, J. S.; Vogt T. in Carbohydrate-Based Drug Discovery (Ed.: C.-H. Wong), Wiley-VCH, Wein-heim, **2003**, pp. 685–707.

(b) Mishra, S.; Upadhya, K.; Mishra K. B.; Shukla, A. K.; Tripathi, R. P.; Tiwari, V. K. Carbohydrate-based therapeutics: A Frontier in Drug Discovery and Development. *In Studies in Natural Products Chemistry*, Elsevier, **2016**; pp. 307–361.

(c) Seeberger, P. H.; Werz, D. B. *Nat Rev Drug Discov.* **2005**, *4*, 751-763.

5) (a) Langenhan, J. M.; Griffith, B. R.; Thorson, J. S. *J. Nat. Prod.* **2005**, *68*, 1696–1711.

(b) Toshima, K.; Takano, R.; Ozawa, T.; Matsumura, S. *Chem. Commun*. **2002**, 212-213.

(c) Shajahan, S. Parashar, S. Goswami, S. M. Ahmed, P. Nagarajan, S. G. Sampathkumar. *J. Am. Chem. Soc.* **2017**, *139*, 2, 693–700.

(d) Kumari, P.; Mishra, V. S.; Narayana, C. Khanna, A.; Chakrabarty, A.; Sagar, R. *Sci Rep*. **2020,** *10*, 6660-6676.

(e) Awan, S. I.; Werz, D. B. *Bioorg. Med. Chem.* **2012**, *20*, 1846-1856.

6) (a) Reissig, H-U.; Zimmer. R. *Chem. Rev.* **2003**, *103*, 4, 1151–1196.

(b) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, 53, 5504 – 5523.

(c) Ganesh, V. Sridhar, P. R. Chandrasekaran, S. *Isr. J. Chem.* **2016**, 56, 417.

7) Ivanova, O. A.; Trushkov, I. V. *Chem. Rec.* **2019**, 19, 2189 – 2208.

8) (a) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851–7854.

(b) Laugeois, M.; Ling, J.; Férard, C.; Michelet, V.; Ratovelomanana-Vidal, V.; Vitale, M. R. *Org. Lett.* **2017**, *19*, 2266–2269.

(c) Pirenne, V.; Robert, E. G. L.; Waser, J. *Chem. Sci.* **2021**, *12*, 8706–8712.

(d) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631–9634.

9) (a) Liu, H. K.; Wang, S. R.; Song, X. Y.; Zhao, L. P.; Wang, L.; Tang, Y. *Angew. Chem. Int. Ed.* **2019***, 58*, 4345-4349.

(b) Norwood, V. M.; Huigens, R. W. *ChemBioChem*, **2019**, *20*, 2273-2297.

10) (a) Sridhar, P. R.; Kumar, P. V.; Seshadri, K.; Satyavathi, R. *Chem. Eur. J.* **2009**, *15*, 7526-7529.

(b) Sridhar, P. R.; Seshadri, K.; Reddy, G. M. *Chem. Commun.* **2012**, *48*, 756-758.

(c) Ramakrishna, B.; Sridhar, P. R. *Org. Lett.* **2013**, *15*, 4474–4477.

11) a) Sridhar, P. R.; Kumar, P. V. *Org. Lett.* **2012**, *14*, 5558–5561.

(b) Kumar, P. V.; Sudharani, C.; Sridhar, P. R. *Chem. Commun*. **2014**, *50*, 2218-2221.

12) Ling, N. C.; Djerassi, C.; Simpson, P. G. *J. Am. Chem. Soc.* **1970**, *92*, 222-223.

13) Kam, T.-S.; Choo, Y.-M. *Helv. Chim. Acta.* **2004**, *87*, 366-369.

14) Koyama, K.; Hirasawa, Y.; Zaima, K.; ChinHoe, T.; Chan, K-L.; Morita, H. *Bioorg. Med. Chem.* **2008**, *16*, 6483-6488.

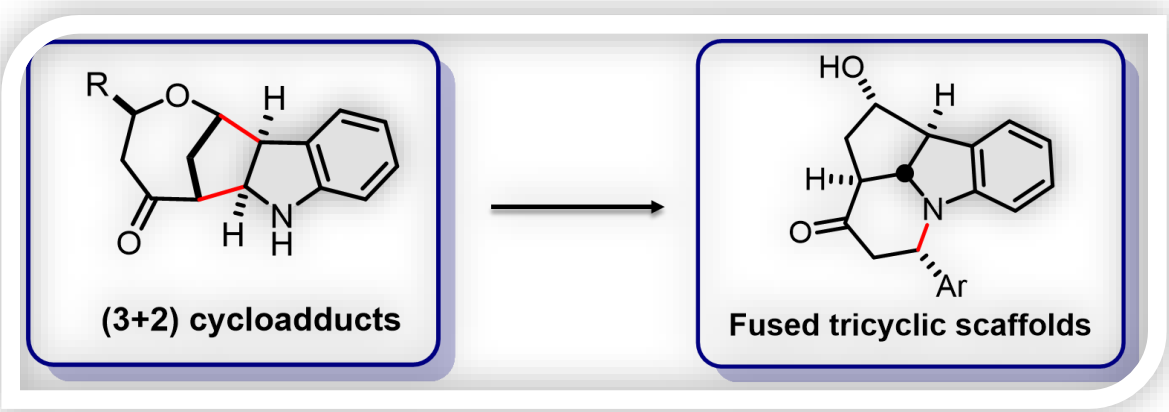
15) Sugita, Y.; Kimura, C.; Hosoya, H.; Yamado, S.; Yokoe, I. *Tetrahedron Lett.* **2001**, *42*, 1095-1098.

16) Sugita, Y.; Kimura, C.; Yokoe, I. *Heterocycles.* **2001**, *55*, 855-859.

17) Jaber, D. M.; Burgin, R. N.; Hepler, M.; Zavalija, P.; Doyle, M. P. ***Chem. Commun.*** **2011**, ***47***, 7623-7625.

Chapter 2– Part B

En route to the synthesis of A,B,E tricyclic core of calyciphylline B-Type alkaloids



Abstract:

An appropriately constructed tricyclic skeleton containing the common A,B,E rings present in calyciphylline B-type alkaloids was synthesized. In this regard, an efficient post synthetic transformation was performed on the bridged oxepanone-indole cycloadducts. The key features of the transformation is one-pot β-elimination, inversion of configuration, and an intramolecular aza-Michael addition reaction. The transformation is carried out via a three step one pot reaction which exploits the distinctive properties of the oxepanone ring of cycloadducts.

2.2.1 Introduction

Daphniphyllum alkaloids are a unique class of polycyclic natural products, exhibiting potent biological activities such as anticancer, antiviral, anti-HIV, antioxidant etc.[1] Among the 320 known *Daphniphyllum* alkaloids, calyciphylline B-type compounds belong to a small subclass, featuring a unique hexacyclic framework (ring A-F) encompassing 8-9 stereogenic centres (Calyciphylline B, Deoxycalyciphylline B etc.) (**Figure 1**). The central core of calyciphylline B-type alkaloids include a fused tricyclic skeleton (rings A,B,E) with nitrogen atom centrally located to form a convex shaped structure. Often this type of architechtures is synthesized *via* RCM, metal-catalyzed annulation coupling reactions, intramolecular cyclization, multi-step total synthesis, *etc*., which are complex and challenging synthetic routes.[2]

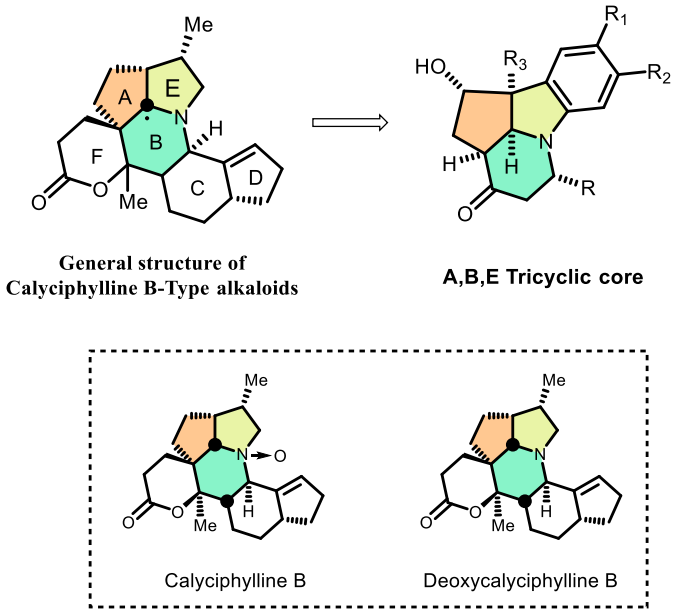


Figure 1. Calyciphylline B–Type alkaloids

With the successful synthesis of bridged bicyclic cycloadducts, we hypothesized that the (3+2) cycloadducts with suitably positioned ß-ketoethers, would be susceptible to ß-elimination, on deprotonation with base. These ß-eliminated products would then potentially undergo an aza-Michael addition reaction with indole nitrogen leading to the functionalized fused tetracyclic scaffolds in a single concerted step. This transformation would witness the formation of a highly

strained molecule and the beauty of the basket-shaped molecular construction, a skeleton analogous to naturally occurring alkaloid calyciphylline B. (**Figure 2**).[1]

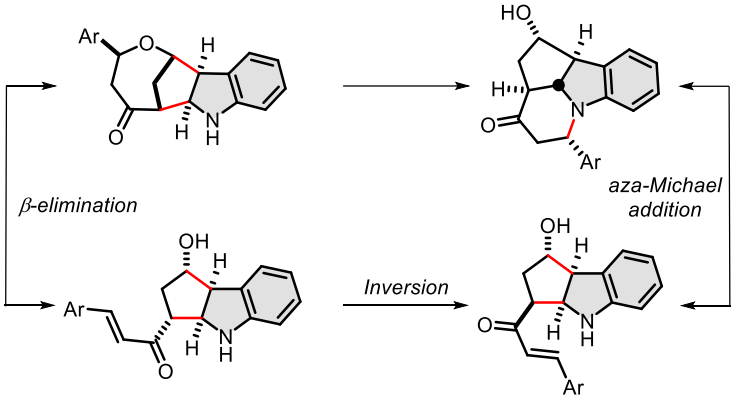


Figure 2. A Possible mechanism for the intramolecular aza-Michael addition reaction

2.2.2 Results and discussion

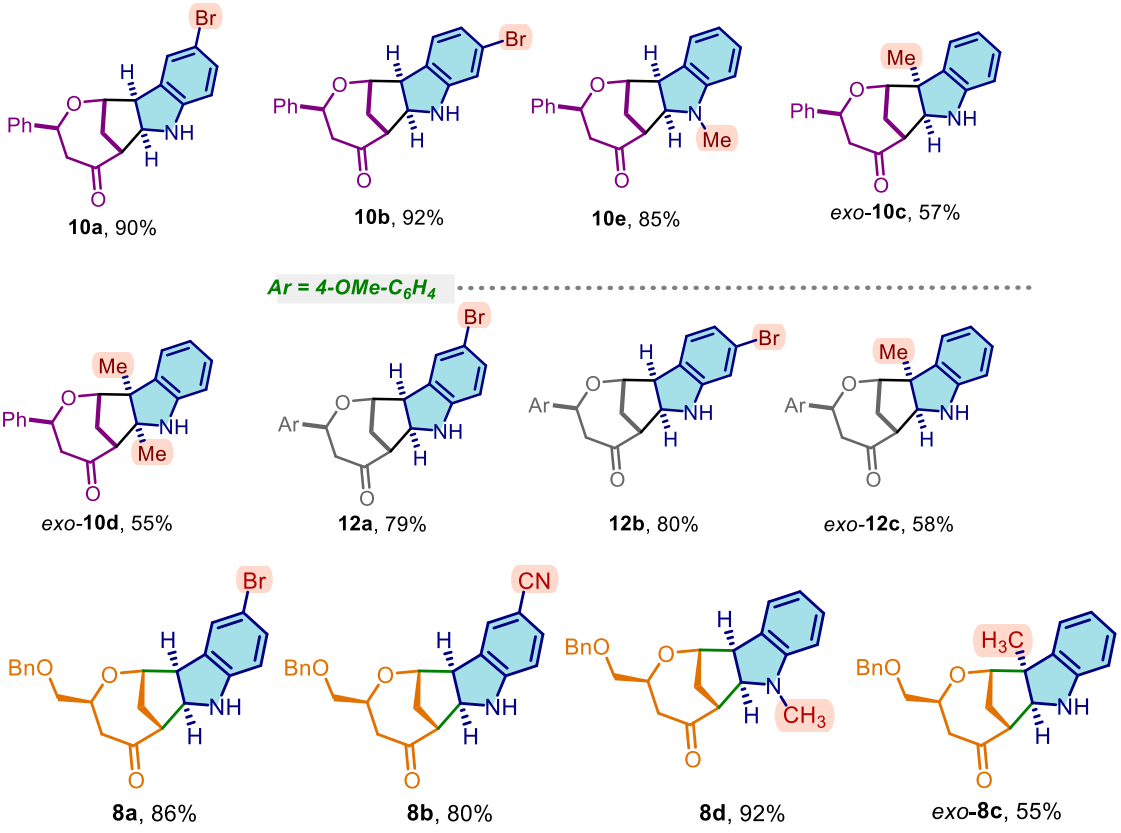


Table 1. (3+2) cycloadducts employed in post synthetic transformation

Gratifyingly, when a methanolic solution of cyclo-adduct **10a** was treated with K_2CO_3, ß-elimination followed by aza-Michael addition resulted in the formation of functionalized fused tretracyclic system **13** in 98% yield (Table 2).

With the successful formation of rearranged product **13**, we subjected some of the cycloadducts (**8a-8d**, **10b-10e**, and **12a-c;** Table 1) having active methylene groups to ß-elimination followed by aza-Michael reaction. The cycloadducts **10b** and *exo*-**10c** successfully underwent the ß-elimination followed intramolecular aza-Michael addition to give fused tetracyclic system **15** and **16** in 95% and 99% yield, respectively. However, it is interesting to note that compound **8a**-**8d** did not undergo the above rearrangement reaction, indicates the importance of an aryl group at C7 postion of the oxepanone ring which may assist the facile ß elimination reaction. Subjecting cycloadduct *exo*-**10d** to the rearrangement reaction condition resulted in an intractable reaction mixture. However, cycloadduct **10e** formed ring-opened *α,β*-unsaturated ketone product **20** and was isolated in 97% yield. Hence, the formation of compound **20** confirmed that the reaction underwent via ß elimination followed by aza-Michael addition. Further cycloadducts **12a-c** successfully underwent the rearrangement reaction resulting in the tetracyclic scaffolds (**17-19**) in excellent yields. The products obtained through the rearrangement of cycloadducts are the A,B,E tricyclic analogues of calyciphylline B-type alkaloids establishing a potential route for the synthesis of the same.

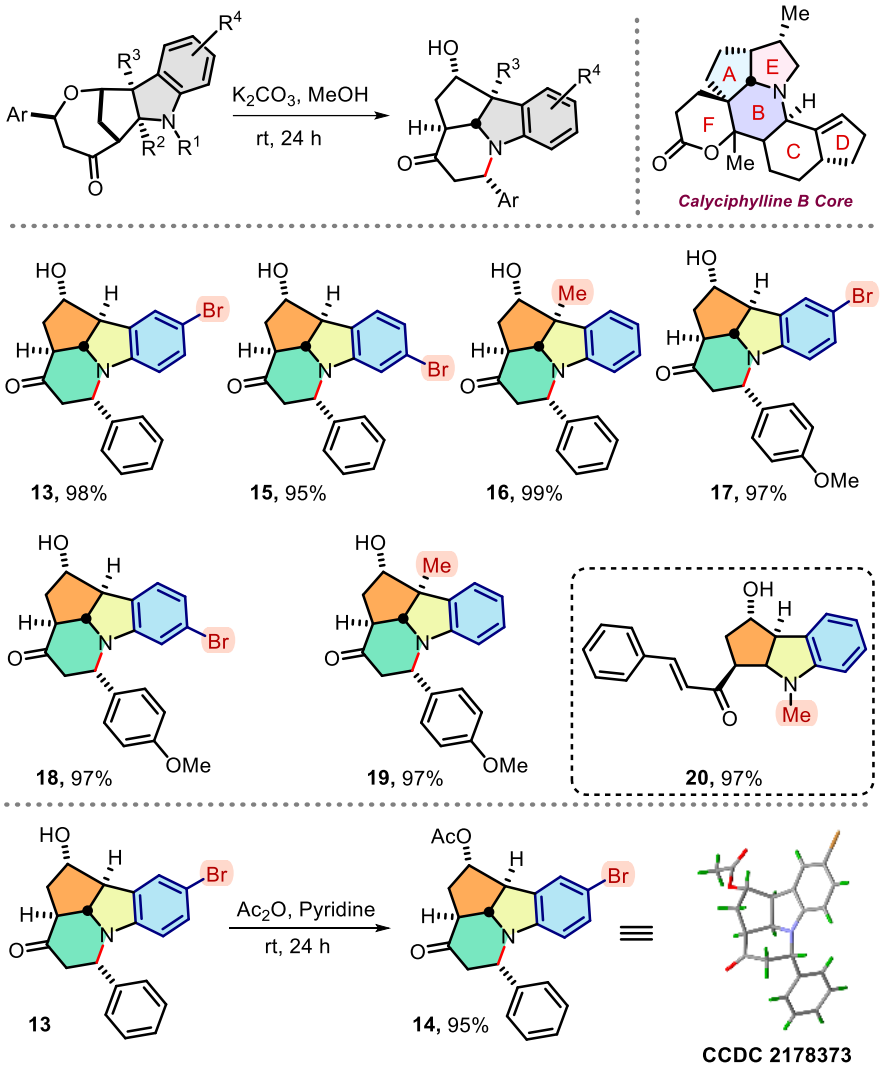


Table 2. Transformation of (3+2)-cycloadducts

To establish the relative configuration of the rearranged analogues, 1D and 2D NMR (COSY, NOESY) data of compound **13** was studied in detail. There were characteristic changes in the chemical shift values in ^{13}C NMR of **13** when compared to **10a**. Acetylation of compound **13** to form **14** guaranteed the presence of alcohol functionality as we could see an ester chemical shift value (170.23 ppm) and not an amide chemical shift value in the ^{13}C NMR. Known stereocenters of the bridged oxepanone-indole cycloadducts and NOESY experiments of the bowl-shaped product **13** guided us to assign the exact stereochemistry of the aza-Michael addition product. For example, in compound **13** there was a strong NOE between the two methylene groups that

are close enough to show NOE **(Figure 7)**. Similarly, for the β-elimination product **20**, one of the methylene proton showed NOE with α-hydrogen of α,β-unsaturated system, as well as the N-CH_3 had shown NOE with the β-hydrogen of α,β-unsaturated system. This implies the inversion of the configuration at the α-sp^3 carbon centre to the carbonyl group (**Figure 7**). Finally, the single-crystal X-ray diffraction studies of compound **14**, un-equivocally established the product structure and stereochemistry. Thus, our methodology through its single key concerted step allowed the construction of tricyclic core of calyciphylline B-type from the bridged bicyclic oxepenone scaffolds. We strongly believe that this methodology would pave a general way for the synthesis of a variety of calyciphylline alkaloids.

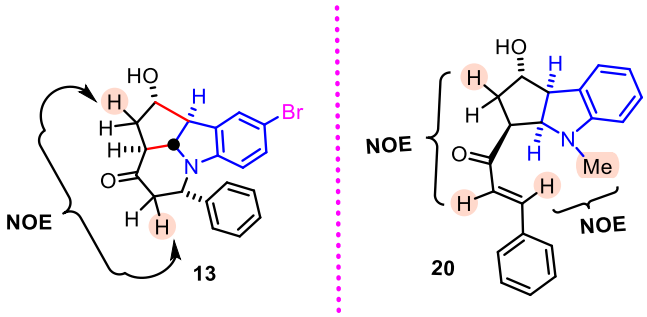


Figure 7. Representation of observed NOE in compounds 13 and 20.

2.2.3 Conclusion

In conclusion, an efficient post synthetic transformation was performed on the cycloadducts The bridged oxepane-indole scaffolds are further converted to a variety of calyciphylline B-type alkaloid analogues of A,B, E ring framework. Thus, this methodology sets an example for the product's unique molecular construction, diastereoselectivity, metal-free synthesis and wide substrate scope.

2.2.4 References

1. Chattopadhyay, A. K.; Hanessian, S. *Chem. Rev.* **2017**, *117*, 4104–4146

2. (a) Boissarie, P.; Belanger, G. *Org. Lett.* **2017**, *19*, 3739–3742.

(b) Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Org. Chem.* **2019**, *84*, 14069–14091.

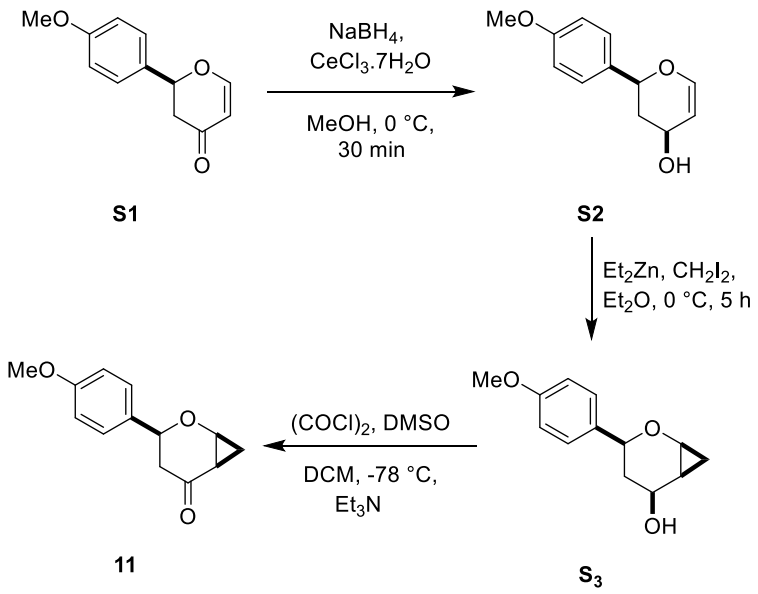
(c) Du, C.; Fang, J.; Chen, J.; Liu, Z.; Li, H.; Wang, X.; Xie, X.; She, X. *Org. Lett.* **2019**, *21*, 8718–8721.

Experimental Details

Chapter 2 - Part A: A Ring Expansion–Stereoselective Cycloaddition of Carbohydrate-Derived Donor–Acceptor Cyclopropanes: Synthesis of Bridged Oxepanone–Indole Hybrids.

Synthesis of DAC 11

(1*S*,3*S*,6*R*)-3-(4-methoxyphenyl)-2-oxabicyclo[4.1.0]heptan-5-one (DAC 11):



(2*S*,4*S*)-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-ol (S2): To a solution of enone **S1**[17] (2 g, 9.8 mmol) and $CeCl_3.7H_2O$ (5.4 g, 14.7 mmol) in MeOH (30 mL) at -78 °C was added $NaBH_4$ (557.6 mg, 14.7 mmol) in 5 portions. The solution was stirred for 1 h at -78 °C, then quenched with saturated NH_4Cl. The reaction mixture was extracted twice with ethyl acetate (100 mL x 2) and combined organic layers were washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). The solution was concentrated under vacuum and the crude residue was purified by silica-gel column chromatography with ethyl acetate/hexane to provide Compound **S2** (1.96 g, 9.48 mmol) as a yellow solid. Yield: 98%; R_f: 0.4 (30% EtOAc/hexane); **IR (neat):** 3342, 3065, 2954, 2916, 2836, 1640 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.61-7.64 (m, 2H), 7.22-7.25 (m, 2H), 6.83 (dd, 1H, *J* = 1.0 Hz, 6.5 Hz), 5.27 (dd, 1H, *J* = 2.0 Hz, *J* = 12.0 Hz), 5.18 (dt, 1H, *J* = 2.0 Hz, 6.0 Hz), 4.93 (bs, 1H), 4.14 (d, 3H), 2.66-2.71 (m, 1H), 2.32-2.37 (m, 1H), 1.85 (bs, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 159.45, 145.5, 132.4, 127.4, 114.0, 105.7, 76.5, 63.6, 55.3, 39.8.

HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{14}O_3Na$ $[M+Na]^+$: 229.0841, found: 229.0839.

(1*S*,3*S*,5*S*,6*S*)-3-(4-methoxyphenyl)-2-oxabicyclo[4.1.0]heptan-5-ol (S3): To a solution of **S2** (1.8 g, 8.7 mmol) in ether (30 mL) at 0 °C was added 1 M Et_2Zn in hexane (26.1 mL, 26.1 mmol) and CH_2I_2 (2.08 mL 26.1 mmol). The reaction mixture was stirred for 5 hours at same temperature, then quenched with saturated NH_4Cl solution (150 mL) and extracted with ether (100 mL x 2). The organic layers were washed with water (100 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo* and purified by silica gel column chromatography to obtain cyclopropane **S3** (1.86 g, 8.4 mmol) as a colourless oil. Yield: 97%; R_f: 0.4 (40% EtOAc/hexane); **IR (neat):** 3372, 3081, 3003, 2926, 2836 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.21-7.24 (m, 2H), 6.86-6.86 (m, 2H), 4.54-4.59 (m, 1H), 4.30 (d, 1H, *J* = 11.5 Hz), 3.88-3.91 (m, 1H), 3.80 (s, 3H), 2.05 (dd, 1H, *J* = 7.0 Hz, *J* = 23.5 Hz), 1.69-1.75 (m, 1H), 1.42-1.47 (m, 2H), 0.83-0.87 (m, 1H), 0.76-0.80 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 159.2, 133.5, 127.3, 113.8, 76.6, 65.6, 55.4, 54.8, 39.2, 17.9, 10.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{16}O_3$ $[M+Na]^+$: 243.0997, found: 243.0994.

(1*S*,3*S*,6*R*)-3-(4-methoxyphenyl)-2-oxabicyclo[4.1.0]heptan-5-one (11): To a solution of $(COCl)_2$ (1.04 mL, 12.1 mmol) in CH_2Cl_2 (25 mL) at -78 °C was added DMSO (1.4 mL, 20.2 mmol) dropwise. After 10 min, cyclopropropyl alcohol **S3** (1.8 g, 8.1 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the above mixture at same temperature for a period of 15 min. After stirring for 30 min at -78 °C, Et_3N (4.0 mL, 40.5 mmol) was added and allowed to warm to room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with water (70 mL x 2), brine (70 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo* and purified by silica gel

column chromatography to obtain compound **11** (1.69 g, 7.7 mmol) as a yellow solid. Yield: 95%; R_f: 0.6 (40% EtOAc/hexane); **IR (neat):** 3018, 2960, 2836, 2359, 2198, 1692cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.22-7.25 (m, 2H), 6.87-6.90 (m, 2H), 4.88 (dd, 1H, *J* = 2.0 Hz, *J* = 11.5 Hz), 4.22-4.25 (m, 1H), 3.80 (s, 3H), 2.55 (dd, 1H, *J* = 11.5 Hz, *J* = 16.0 Hz), 2.45 (dt, 1H, *J* = 1.5 Hz, *J* = 16.0 Hz), 1.82-1.87 (m, 1H), 1.42 (td, 1H, *J* = 3.5 Hz, *J* = 6.5 Hz), 1.35-1.39 (m, 1H).

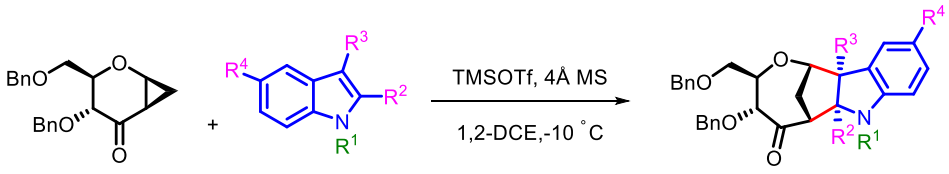
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ 205.4, 159.6, 131.7, 127.2, 114.0, 80.3, 57.5, 55.3, 47.1, 24.4, 19.6.

HRMS (ESI-TOF) *m/z*: calcd for $C_{13}H_{14}O_3$ $[M+H]^+$: 219.1021, found: 219.1025.

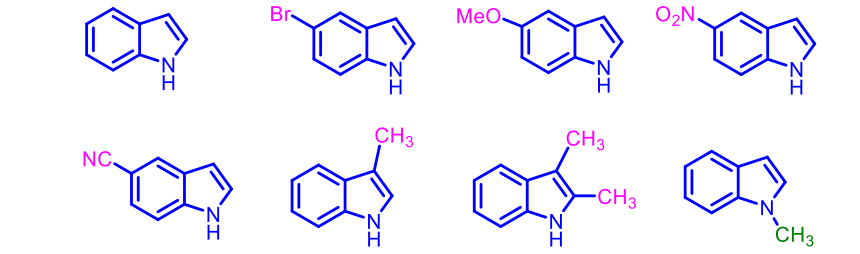
General procedure A for Lewis acid catalysed (3+2) cycloaddition:

To a solution of keto-cyclopropane (1 mmol) and respective indole (2 mmol) in 1,2-DCE (8 mL) was added 4 Å molecular sieves (50 mg) and stirred for 30 minutes at room temperature under argon atmosphere. The reaction mixture was then cooled to -10 °C to which TMSOTf (0.5 Eq) was added dropwise. The reaction was monitored by TLC until the completion. The reaction mixture was quenched by adding saturated solution of $NaHCO_3$ and extracted with DCM, dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified using silica gel column chromatography to obtain the desired product.

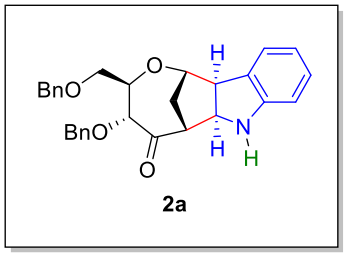
Compound Characterization:



1 **2a-h**



(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (2a):



2a

Compound **2a** was synthesised from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 1*H*-indole (138.50 mg, 1.18 mmol) by following **general procedure A.** Yield: 188 mg, 70%; R_f: 0.5 (40% EtOAc/hexane); Red oil.

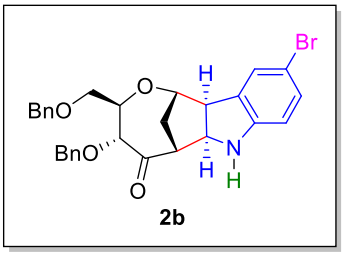
IR (neat): 3455, 3025, 2968, 2944, 1732 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.23-7.30 (m, 11H), 7.01 (t, 1H, *J* = 7.5 Hz), 6.67 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.47 (d, 1H, *J* = 8.0 Hz), 5.01 (dd, 1H, *J* = 5.0 Hz, 6.0 Hz), 4.73-4.77 (m, 2H), 4.40 (d, 1H, *J* = 11.0 Hz), 4.38 (d, 1H, *J* = 9.5 Hz), 4.23-4.34 (m, 3H), 4.01 (dd, 1H, *J* = 6.5 Hz, 12.0 Hz), 3.45-3.49 (m, 2H), 3.27-3.32 (m, 2H), 2.42 (d, 1H, *J* = 14.5 Hz), 1.97-2.02 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 209.6, 151.7, 138.4, 137.6, 128.6, 128.4, 128.3, 128.1, 127.7, 127.5, 127.3, 125.9, 124.5, 118.7, 109.3, 83.9, 80.1, 73.9, 73.0, 72.3, 70.8, 66.4, 54.2, 52.5, 37.1 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{29}H_{30}NO_4$ $[M+H]^+$: 456.2175, found: 456.2175.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-10-bromo-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (2b):



2b

Compound **2b** was synthesised from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 5-bromo-1*H*-indole (231.32 mg, 1.18 mmol) by following **general procedure A.** Yield: 276.79 mg, 88%, R_f: 0.6 (30% EtOAc/hexane); white solid; m.p. 116-118 ˚C.

Crystallization: Compound **2b** (100 mg) was dissolved in 10 ml 10% EtOAc/hexane. The solution was slightly warmed to 50 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.

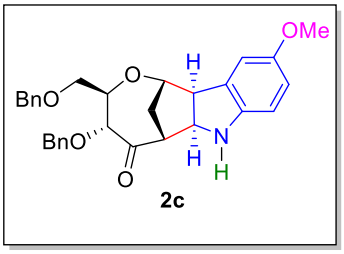
IR (neat): 3454, 3015, 2968, 2947, 1738, 1660 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.33 (m, 10H), 7.21 (s, 1H), 7.09 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.37 (d, 1H, *J*= 8.0 Hz), 4.76 (d, 1H, *J* = 11.0 Hz), 4.68 (d, 1H, *J* = 4.5 Hz), 4.60 (d, 1H, *J* = 12.0 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.52 (d, 1H, *J* = 8.5 Hz), 4.39 (d, 1H, *J* = 5.0 Hz), 4.37 (d, 1H, *J* = 3.0 Hz), 4.12 (bs, 1H), 3.87 (d, 1H, *J* = 8.5 Hz), 3.79 (dd, 1H, *J* = 5.0 Hz, 10.5 Hz), 3.75 (dd, 1H, *J* = 2.0 Hz, 10.0 Hz), 3.70-3.73 (m, 1H), 2.91 (d, 1H, *J* = 7.0 Hz), 2.28 (d, 1H, *J* = 14.5 Hz), 1.90-1.96 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 209.6, 149.5, 138.0, 137.3, 131.0, 129.8, 128.4, 128.4, 128.1, 127.9, 127.8, 127.7, 109.8, 109.6, 85.9, 83.9, 73.9, 73.8, 73.8, 70.6, 68.6, 59.9, 52.1, 32.8 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{29}H_{29}BrNO_4$ $[M+H]^+$: 534.1280, found: 534.1282.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-10-methoxy-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (2c):



2c

Compound **2c** was synthesised from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 5-methoxy-1*H*-indole (173.66 mg, 1.18 mmol) by following **general procedure A.** Yield: 187.23 mg, 65%, R_f: 0.4 (50% EtOAc/hexane); red oil.

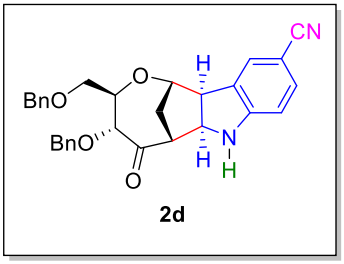
IR (neat): 3455, 3003, 2968, 2945, 2134, 1738 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.15-7.20 (m, 10H), 6.75 (d, 1H, *J* = 2.0 Hz), 6.51 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.33 (d, 1H, *J* = 8.5 Hz), 4.90 (dd, 1H, *J* = 5.0 Hz, 6.0 Hz), 4.67 (d, 1H, *J* = 10.5 Hz), 4.65 (dd, 1H, *J* = 9.0 Hz, 11.5 Hz), 4.31 (d, 1H, *J* = 10.5 Hz), 4.27 (d, 1H, *J* = 9.0 Hz), 4.24 (d, 1H, *J* = 12.5 Hz), 4.16 (d, 1H, *J* = 12.0 Hz), 3.90 (dd, 1H, *J* = 6.5 Hz, 12.0 Hz) 3.59 (s, 3H), 3.43-3.46 (m, 1H), 3.40 (dd, 1H, *J* = 4.5 Hz, 10.5 Hz), 3.24 (dd, 1H, *J* = 2.0 Hz, 10.5 Hz), 3.19 (dd, 1H, *J* = 7.5 Hz, 9.0 Hz), 2.33 (d, 1H, *J* = 15.0 Hz), 1.87-1.92 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 209.6, 153.4, 145.7, 138.4, ,137.7, 128.3, 128.1, 128.1, 127.7, 127.5, 127.3, 126.1, 114.1, 112.1, 110.2, 83.9, 80.0, 73.9, 73.0, 72.3, 70.9, 67.0, 55.9, 54.1, 53.0, 37.2.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{32}NO_5$ $[M+H]^+$: 486.2280, found: 486.2279.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-5-oxo-1,3,4,5,6,6a,7,11b-octahydro-1,6-methanooxocino[4,3-*b*]indole-10-carbonitrile (2d):



2d

Compound **2d** was synthesised from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 1*H*-indole-5-carbonitrile (167.74 mg, 1.18 mmol) by following **general procedure A.** Yield: 240.82 mg, 85%, R_f: 0.4 (30% EtOAc/hexane); white solid, m.p. 154-156 ˚C.

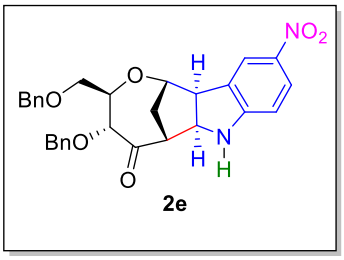
Crystallization: Compound **2d** (100 mg) was dissolved in 10 ml 10% EtOAc/Toluene. The solution was slightly heated to 70 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.**IR (neat):** 3353, 3013, 2968, 2945, 2209, 1738, 1609 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.33 (m, 12H), 6.44 (d, 1H, *J* = 8.0 Hz), 4.75 (d, 1H, *J* = 10.5 Hz), 4.67 (d, 1H, *J* = 4.5 Hz), 4.55-4.61 (m, 4H), 4.40 (d, 1H, *J* = 5.5 Hz), 4.38 (d, 1H, *J* = 7.5 Hz), 3.86 (d, 1H, *J* = 8.5 Hz), 3.79 (dd, 1H, *J* = 4.5 Hz, 10.0 Hz), 3.75 (dd, 1H, *J* = 2.0 Hz, *J* = 10.0 Hz), 3.70-3.73 (m, 1H), 2.91 (d, 1H, *J* = 7.0 Hz), 2.34 (d, 1H, *J* = 15.0 Hz), 1.86-1.91 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 209.2, 153.7, 137.9, 137.2, 134.0, 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 120.2, 107.2, 99.9, 85.7, 83.7, 74.2, 73.8, 73.8, 70.4, 68.4, 59.2, 51.3, 32.6.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{29}N_2O_4$ $[M+H]^+$: 481.2127, found: 481.2160.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-10-nitro-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (2e):



2e

Compound **2e** was synthesised from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 5-nitro-1*H*-indole (191.33 mg, 1.18 mmol) by following **general procedure A.** Yield: 236.09 mg, 80%, R_f: 0.4 (30% EtOAc/hexane); yellow solid, m.p. 157-159 ˚C.

IR (neat): 3341, 3014, 2968, 2943, 2132, 1738, 1609 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H), 7.96 (d, 1H, *J* = 2.0 Hz), 7.28-7.33 (m, 10H), 6.36 (d, 1H, *J* = 7.6 Hz), 5.07 (bs, 1H), 4.75 (d, 1H, *J* = 8.4 Hz), 4.71 (d, 1H, *J* = 3.6 Hz), 4.64 (d, 1H, *J* = 6.8 Hz), 4.60 (d, 1H, *J* = 9.6 Hz), 4.57 (d, 1H, *J* =9.6 Hz), 4.42 (d, 1H, *J* = 6.8 Hz), 4.40 (d, 1H, *J* = 8.8 Hz),

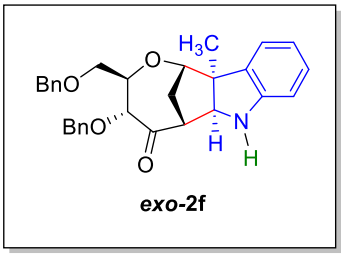
3.87 (d, 1H, *J* = 6.8 Hz), 3.72-3.82 (m, 3H), 2.93 (d, 1H, *J* = 5.6 Hz), 2.37 (d, 1H, *J* = 12.0 Hz), 1.86-1.91 (m, 1H).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 209.1, 155.8, 139.0, 137.8, 137.1, 128.4, 128.1, 128.0, 127.8, 127.7, 127.5, 126.9, 121.6, 105.5, 85.5, 83.7, 74.3, 73.8, 73.7, 70.4, 68.9, 58.8, 51.1, 32.5.

HRMS (ESI-TOF) *m/z*: calcd for $C_{29}H_{29}N_2O_6$ $[M+H]^+$: 501.2026, found: 501.2026.

Compound ***exo*-2f** and ***endo*-2f** was synthesized from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 3-methyl-1*H*-indole (154.78 mg, 1.18 mmol) by following **general procedure A.** Overall Yield: 251.92 mg, 91%.

(1*S*,3*R*,4*R*,6*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-11b-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*exo*-2f):



***exo*-2f**

Yield: 166.10 mg, 60%, R_f: 0.6 (30% EtOAc/hexane); red oil.

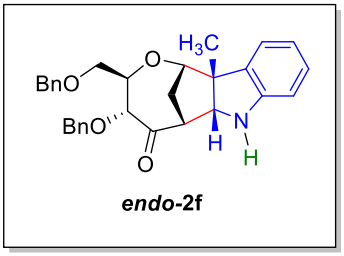
IR (neat): 3381, 3025, 2968, 1738, 1604 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.34 (m, 10H), 7.01 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.95 (dd, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.69 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.54 (d, 1H, *J* = 8.0 Hz), 4.76 (d, 1H, *J* = 11.5 Hz), 4.59 (s, 2H), 4.50-4.52 (m, 2H), 4.34 (d, 1H, *J* = 11.0 Hz), 4.05-4.08 (m, 1H), 4.03 (bs, 1H), 3.82 (dd, 1H, *J* = 5.5 Hz, 10.5 Hz), 3.78 (dd, 1H, *J* = 3.0 Hz, 10.5 Hz), 2.70 (d, 1H, *J* = 7.0 Hz), 2.37 (d, 1H, *J* = 15.0 Hz), 1.85-1.90 (m, 1H), 1.40 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 209.4, 149.4, 137.9, 137.4, 134.3, 128.4, 128.3, 128.1, 128.1, 127.9, 127.7, 127.6, 123.0, 118.5, 108.4, 84.6, 82.4, 76.2, 73.6, 73.3, 73.2, 70.3, 60.6, 58.8, 32.9, 21.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{32}NO_4$ $[M+H]^+$: 470.2331, found: 470.2331.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*R*)-4-(benzyloxy)-3-((benzyloxy)methyl)-11b-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*endo*-2f):



endo-2f

Yield: 85.81 mg, 31%, R_f: 0.3 (30% EtOAc/hexane); red oil.

IR (neat): 3377, 3029, 2932, 2864, 2358, 1707cm^{-1}.

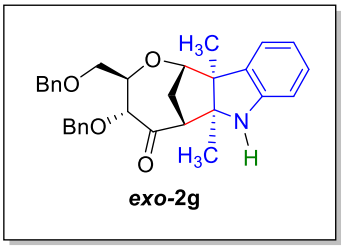
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.20-7.27 (m, 10H), 7.15 (dd, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.99 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.66 (td, 1H, *J* = 0.5 Hz, *J* = 7.0 Hz), 6.46 (d, 1H, *J* = 8.0 Hz), 4.68 (d, 1H, *J* = 11.0 Hz), 4.61 (d, 1H, *J* = 5.0 Hz), 4.34-4.38 (m, 3H), 4.24-4.29 (m, 2H), 4.11 (d, 1H, *J* = 9.0 Hz), 3.43 (dd, 1H, *J* = 4.0 Hz, *J* = 10.5 Hz), 3.26 (t, 1H, *J* = 8.0 Hz), 3.22 (dd, 1H, *J* = 2.0 Hz, *J* = 10.5 Hz), 3.09-3.12 (m, 1H), 2.36 (d, 1H, *J* = 15.0 Hz), 2.16-2.22 (m, 1H), 1.40 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 209.7, 150.4, 138.4, 137.6, 129.5, 128.4, 128.3, 128.1, 128.1, 127.7, 127.5, 127.3, 124.8, 118.6, 109.3, 86.6, 83.5, 73.8, 73.7, 73.2, 72.4, 70.8, 57.8, 55.0, 34.6, 30.0.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{32}NO_4$ $[M+H]^+$: 470.2331, found: 470.2330.

Compound ***exo*-2g** and ***endo*-2g** was synthesized from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 2,3-dimethyl-1H-indole (171.33 mg, 1.18 mmol) by following **general procedure A.** Overall Yield: 265.15 mg, 93%.

(1*S*,3*R*,4*R*,6*R*,6a*S*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-6a,11b-dimethyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*exo*-2g):



exo-2g

Yield: 165.36 mg, 58%, R_f: 0.7 (30% EtOAc/hexane); red oil.

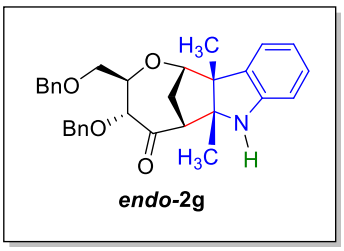
IR (neat): 3380, 3368, 3025, 2968, 1738, 1604 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.33 (m, 10H), 6.99 (td, 1H, *J* = 1.0 Hz, 9.0 Hz), 6.95 (d, 1H, *J* = 7.5 Hz), 6.66 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.44 (d, 1H, *J* = 8.0 Hz), 4.79 (d, 1H, *J* = 11.0 Hz), 4.57 (s, 1H), 4.45 (d, 1H, *J* = 3.5 Hz), 4.43 (d, 1H, *J* = 8.5 Hz), 4.34 (d, 1H, *J* = 11.5 Hz), 4.02-4.06 (m, 1H), 3.89 (bs, 1H), 3.74-3.80 (m, 2H), 2.83 (d, 1H, *J* = 6.5 Hz), 2.35 (d, 1H, *J* = 12.0 Hz), 2.26 (d, 1H, *J* = 14.5 Hz), 1.94-1.99 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 208.3, 148.4, 138.0, 137.5, 134.8, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 123.6, 118.2, 107.5, 87.0, 82.8, 75.8, 74.6, 73.6 (2), 70.6, 64.0, 60.1, 31.4, 21.5, 18.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{31}H_{34}NO_4$ $[M+H]^+$: 484.2488, found: 484.2487.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*R*)-4-(benzyloxy)-3-((benzyloxy)methyl)-6a,11b-dimethyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*endo*-2g):



endo-2g

Yield: 99.70 mg, 35%, R_f: 0.5 (30% EtOAc/hexane); red oil.

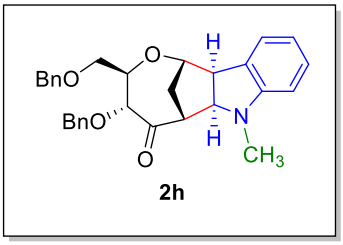
IR (neat): 3350, 3029, 2935, 2865, 2359, 1705 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.21-7.29 (m, 10H), 7.14-7.15 (m, 1H), 7.01 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.69 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.44 (d, 1H, *J* = 7.5 Hz), 4.73 (d, 1H, *J* = 11.0 Hz), 4.61 (d, 1H, *J* = 4.5 Hz), 4.35-4.40 (m, 3H), 4.26 (d, 1H, *J* = 12.0 Hz), 4.07 (s, 1H), 3.47 (dd, 1H, *J* = 4.0 Hz, *J* = 10.5 Hz), 3.38-3.41 (m, 1H), 3.26 (dd, 1H, *J* = 2.0 Hz, *J* = 10.0 Hz), 2.97 (d, 1H, *J* = 7.5 Hz), 2.32 (d, 1H, *J* = 15.0 Hz), 2.22-2.27 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 209.2, 148.9, 138.4, 137.7, 129.8, 128.4, 128.2, 128.1, 127.7, 127.5, 127.3, 125.0, 118.4, 108.8, 89.0, 83.2, 77.2, 76.3, 73.8, 73.0, 72.3, 71.0, 62.6, 59.9, 33.5, 27.3, 24.0.

HRMS (ESI-TOF) *m/z*: calcd for $C_{31}H_{34}NO_4$ $[M+H]^+$: 484.2488, found: 484.2485.

(1*S*,3*R*,4*R*,6*R*,6a*R*,11b*S*)-4-(benzyloxy)-3-((benzyloxy)methyl)-7-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (2h):



2h

Compound **2h** was synthesised from keto-cyclopropane **1** (200 mg, 0.59 mmol) and 1-methyl-1*H*-indole (171.33 mg, 1.18 mmol) by following **general procedure A.** Yield: 199.32 mg, 72%, R_f: 0.5 (20% EtOAc/hexane); red oil.

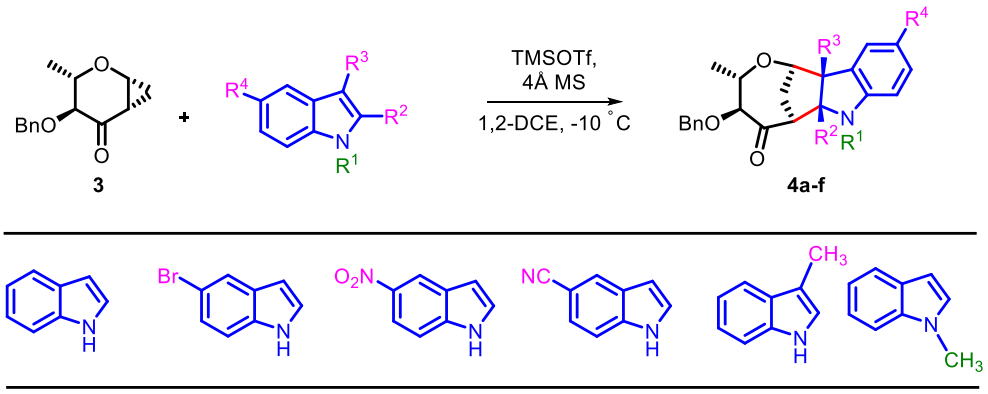
IR (neat): 3014, 2968, 2944, 2143,1738 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.27-7.35 (m, 10H), 7.10 (d, 1H, *J* = 7.0 Hz), 7.07 (t, 1H, *J* = 8.0 Hz), 6.61 (t, 1H, *J* = 7.5 Hz), 6.30 (d, 1H, *J* = 8.0 Hz), 4.76 (d, 1H, *J* = 10.5 Hz), 4.73 (d, 1H, *J* = 4.5 Hz), 4.61 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1H, *J* = 7.5 Hz), 4.40 (d, 1H, *J* = 9.0 Hz), 4.13 (d, 1H, *J* = 9.0 Hz), 3.85 (d, 1H, *J* = 11.5 Hz), 3.82 (dd, 1H, *J* = 4.0 Hz, 10.0 Hz), 3.78 (d, 1H, *J* =

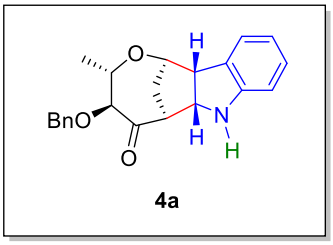
2.0 Hz), 3.72-3.76 (m, 1H), 3.02 (d, 1H, *J* = 7.0 Hz), 2.87 (s, 3H), 2.27 (d, 1H, *J* = 15.0 Hz), 1.86-1.91 (m, 1H).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 210.0, 151.6, 138.0, 137.4, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6, 124.5, 117.1, 105.3, 86.3, 84.1, 76.2, 73.8, 73.8, 73.5, 70.6, 55.8, 50.5, 33.1, 32.9

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{32}NO_4$ $[M+H]^+$: 470.2331, found: 470.2332.



(1*R*,3*S*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (4a):



Compound **4a** was synthesised from keto-cyclopropane **3** (100 mg, 0.43 mmol) and 1*H*-indole (100.87 mg, 0.86 mmol) by following **general procedure A.** Yield: 112.60 mg, 75%, R_f: 0.4 (40% EtOAc/hexane), colourless oil.

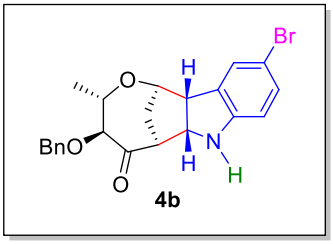
IR (neat):3380, 2967, 2924, 2850, 2142, 1709 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.31 (m, 5H), 7.16 (d, 1H, *J* = 7.0 Hz), 7.00 (dd, 1H, *J* = 7.5 Hz, 8.0 Hz), 6.68 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.45 (d, 1H, *J* = 8.0 Hz), 4.84 (t, 1H, *J* = 5.5 Hz), 4.79 (d, 1H, *J* = 11.5 Hz), 4.70 (dd, 1H, *J* = 9.0 Hz, 12.0 Hz), 4.35 (d, 1H, *J* = 11.5 Hz), 4.21 (bs, 1H), 4.00 (d, 1H, *J* = 9.0 Hz), 3.97 (dd, 1H, *J* = 6.5 Hz, *J* = 11.5 Hz), 3.34-3.40 (m, 1H), 3.25 (dd, 1H, *J* = 7.5 Hz, 8.5 Hz), 2.1 (d, 1H, *J* = 14.5 Hz), 1.91-1.97 (m, 1H), 0.91 (d, 3H, *J* = 6.5 Hz).

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 209.5, 151.7, 137.5, 128.3, 128.2, 127.8, 125.6, 124.4, 118.5, 109.3, 86.5, 79.9, 73.4, 69.9, 66.3, 54.1, 52.5, 37.2, 29.7, 19.2.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1756, found: 350.1751.

(1*R*,3*S*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-10-bromo-3-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (4b):



4b

Compound **4b** was synthesised from keto-cyclopropane **3** (100 mg, 0.43 mmol) and 5-bromo-1*H*-indole (168.59 mg, 0.86 mmol) by following **general procedure A.** Yield: 165.27 mg, 90%, R_f: 0.4 (20% EtOAc/hexane), white solid, m.p. 176-178 ˚C.

Crystallization: Compound **4b** (100 mg) was dissolved in 10 ml 10% EtOAc/hexane. The solution was slightly warmed to 50 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.

IR (neat): 3375, 2928, 1708, 1602 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.30-7.37 (m, 5H), 7.21 (s, 1H), 7.09 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz), 6.37 (d, 1H, *J* = 8.5 Hz), 4.82 (d, 1H, *J* = 11.5 Hz), 4.58 (d, 1H, *J* = 4.5 Hz), 4.53 (d, 1H, *J* = 8.5 Hz), 4.37 (d, 1H, *J* = 11.5 Hz), 4.12 (bs, 1H), 4.06 (d, 1H, *J* = 8.5 Hz), 3.88 (d, 1H, *J* = 8.5 Hz), 3.68-3.74 (m, 1H), 2.91 (d, 1H, *J* = 7.0 Hz), 2.19 (d, 1H, *J* = 14.5 Hz), 1.91-1.95 (m, 1H), 1.36 (d, 3H, *J* = 6.5 Hz).

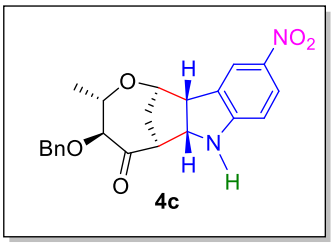
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 209.6, 149.5, 137.4, 131.0, 130.1, 128.4, 128.2, 128.0, 127.8, 109.8, 109.6, 86.9, 85.7, 73.5, 71.0, 68.9, 59.8, 52.2, 32.9, 19.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{23}BrNO_3$ $[M+H]^+$: 428.0861, found: 428.0858.

Gram scale synthesis of compound 4b: The keto-cyclopropane **3** (1.0 g, 4.3 mmol) and 5-bromo-1*H*-indole (1.6 g, 8.6 mmol) was dissolved in 1,2-DCE (25 mL). To this solution, 4 Å molecular sieves (200 mg) was added and stirred for 30 minutes at room temperature under argon atmosphere. The reaction mixture was then cooled to -10 °C to which TMSOTf (0.5 Eq) was added dropwise. The reaction was monitored by TLC until the completion. The reaction mixture was quenched by adding saturated solution of $NaHCO_3$ (30 mL) and extracted with DCM (2 X 50 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified using silica gel

column chromatography to obtain the desired product **4b** (1.5 g, 3.57 mmol) as a white solid. Yield: 83%; R_f: 0.4 (20% EtOAc/hexane).

(1*R*,3*S*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-methyl-10-nitro-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (4c):



Compound **4c** was synthesised from keto-cyclopropane **3** (100 mg, 0.43 mmol) and 5-nitro-1*H*-indole (139.44 mg, 0.86 mmol) by following **general procedure A.** Yield: 157.62 mg, 93%, R_f: 0.5 (30% EtOAc/hexane), yellow oil.

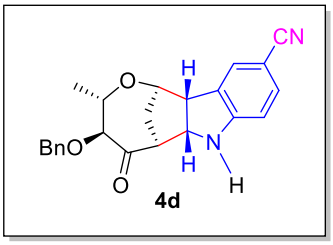
IR (neat): 3455, 3014, 2969, 1738 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1H), 7.99 (d, 1H, *J* = 2.5 Hz), 7.29-7.36 (m, 5H), 6.40 (d, 1H, *J* = 8.0 Hz), 4.87 (bs, 1H), 4.81 (d, 1H, *J* = 11.0 Hz), 4.66 (d, 1H, *J* = 8.5 Hz), 4.63 (d, 1H, *J* = 4.5 Hz), 4.38 (d, 1H, *J* = 11.5 Hz), 4.10 (d, 1H, *J* = 8.5 Hz), 3.91 (d, 1H, *J* = 8.5 Hz), 3.70-3.75 (m, 1H), 2.93 (d, 1H, *J* = 7.0 Hz), 2.27 (d, 1H, *J* = 15.0 Hz), 1.87-1.93 (m, 1H), 1.39 (d, 3H, *J* = 6.0 Hz).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 208.9, 155.6, 139.4, 137.2, 128.5, 128.2, 128.1, 127.8, 126.9, 121.6, 105.6, 86.9, 85.4, 73.6, 71.5, 69.2, 59.0, 51.3, 32.7, 19.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{23}N_2O_5$ $[M+H]^+$: 395.1607, found: 395.1606.

(1*R*,3*S*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-methyl-5-oxo-1,3,4,5,6,6a,7,11b-octahydro-1,6-methanooxocino[4,3-*b*]indole-10-carbonitrile (4d):



Compound **4d** was synthesised from keto-cyclopropane **3** (100 mg, 0.43 mmol) and 1*H*-indole-5-carbonitrile (122.25 mg, 0.86 mmol) by following **general procedure A.** Yield: 139.97 mg, 87%, R_f: 0.5 (40% EtOAc/hexane); pale yellow solid, m.p. 156-158 °C.

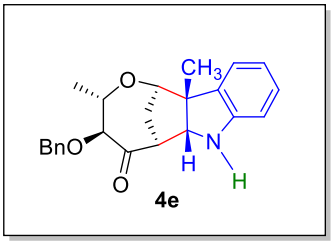
IR (neat): 3453, 2968, 2923, 2852, 2212, 1738 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.36 (m, 7H), 6.44 (d, 1H, *J* = 8.0 Hz), 4.81 (d, 1H, *J* = 11.5 Hz)., 4.64 (bs, 1H), 4.57-4.60 (m, 2H), 4.37 (d, 1H, *J* = 11.5 Hz), 4.08 (d, 1H, *J* = 8.5 Hz), 3.87 (d, 1H, *J* = 8.5 Hz), 3.69 – 3.74 (m, 1H), 2.92 (d, 1H, *J* = 7.0 Hz), 2.24 (d, 1H, *J* = 15.0 Hz), 1.86-1.91 (m, 1H), 1.38 (d, 3H, *J* = 6.5 Hz).

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 209.2, 153.7, 134.0, 128.5, 128.5, 128.1, 128.0, 120.2, 107.2, 99.9, 86.8, 85.6, 73.5, 71.2, 68.6, 59.2, 51.4, 32.8, 29.6, 19.3, 14.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{23}N_2O_3$ $[M+H]^+$: 375.1709, found: 375.1710.

(1*R*,3*S*,4*S*,6*S*,6a*R*,11b*R*)-4-(benzyloxy)-3,11b-dimethyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (4e):



4e

Compound **4e** was synthesised from keto-cyclopropane **3** (100 mg, 0.43 mmol) and 3-methyl-1*H*-indole (112.80 mg, 0.86 mmol) by following **general procedure A.** Yield: 124.93 mg, 80%, R_f: 0.5 (20% EtOAc/hexane); white gel.

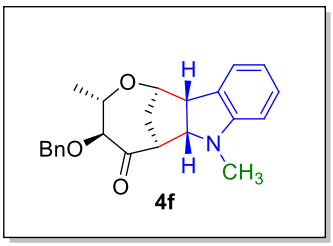
IR (neat): 3378, 2925, 2910, 2143, 1712, 1605 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.30-7.38 (m, 5H), 7.01 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.95 (d, 1H, *J* = 7.0 Hz), 6.68 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.54 (d, 1H, *J* = 7.5 Hz), 4.81 (d, 1H, *J* = 11.5 Hz), 4.40 (d, 1H, *J* = 3.0 Hz), 4.34 (d, 1H, *J* = 11.5 Hz), 4.23 (d, 1H, *J* = 7.5 Hz), 3.99-4.05 (m, 2H), 3.80 (bs, 1H), 2.69 (d, 1H, *J* = 7.0 Hz), 2.23 (d, 1H, *J* = 14.5 Hz), 1.86-1.91 (m, 1H), 1.43 (d, 3H, *J* = 7.0 Hz), 1.37 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 209.2, 149.4, 137.5, 134.3, 128.4, 128.2, 128.1, 127.9, 122.9, 118.6, 108.5, 86.1, 83.9, 73.4 (2), 73.1, 60.7, 58.8, 33.1, 21.0, 18.8.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1909, found: 364.1913.

(1*R*,3*S*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3,7-dimethyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (4f):



4f

Compound **4f** was synthesised from keto-cyclopropane **3** (100 mg, 0.43 mmol) and 1-methyl-1*H*-indole (112.80 mg, 0.86 mmol) by following **general procedure A.** Yield: 148.35 mg, 95%, R_f: 0.7 (20% EtOAc/hexane), colourless oil.

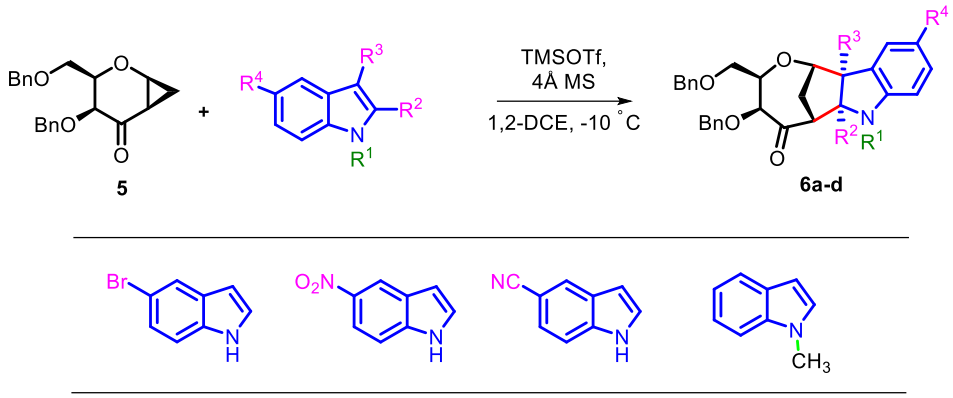
IR (neat): 2930, 2872, 2363, 1708, 1604 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.38 (m, 5H), 7.09 (d, 1H, *J* = 7.0 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.61 (t, 1H, *J* = 7.5 Hz), 6.31 (d, 1H, *J* = 7.5 Hz), 4.83 (d, 1H, *J* = 11.5 Hz), 4.61 (d, 1H, *J* = 4.5 Hz), 4.39 (d, 1H, *J* = 11.0 Hz), 4.13 (d, 1H, *J* = 8.5 Hz), 4.10 (d, 1H, *J* = 8.5 Hz), 3.85 (d, 1H, *J* = 9.0 Hz),

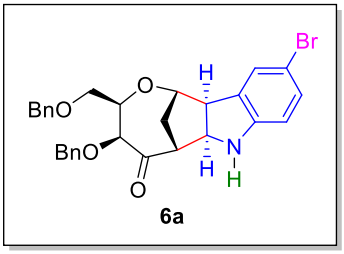
3.71-3.76 (m, 1H), 3.01 (d, 1H, *J* = 7.0 Hz), 2.88 (s, 3H), 2.18 (d, 1H, *J* = 15.0 Hz), 1.84-1.90 (m, 1H), 1.38 (d, 3H, *J* = 6.5 Hz).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 209.8, 151.7, 137.4, 128.5 (2), 128.4, 128.2, 127.9, 124.4, 117.0, 105.3, 87.1, 86.2, 76.3, 73.5, 70.7, 55.8, 50.7, 33.2, 32.9, 19.5.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1908, found: 364.1913.



(1*R*,3*R*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-((benzyloxy)methyl)-10-bromo-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (6a):



Compound **6a** was synthesised from keto-cyclopropane **5** (100 mg, 0.29 mmol) and 5-bromo-1*H*-indole (173.92 mg, 0.88 mmol) by following **general procedure A.** Yield: 139.14 mg, 90%, R_f: 0.5 (20% EtOAc/hexane); yellow gel.

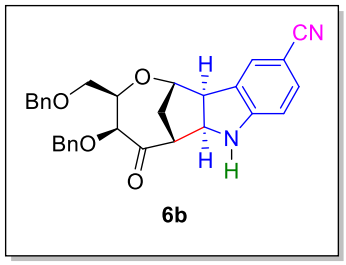
IR (neat): 3378, 3026, 2922, 2862, 2360, 1696 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.33 (m, 8H), 7.20-7.22 (m, 3H), 7.09 (dd, 1H, *J* = 1.5 Hz, 8.5 Hz), 6.37 (d, 1H, *J* = 8.5 Hz), 4.65-4.67 (m, 2H), 4.47 (d, 1H, *J* = 8.5 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 4.28 (d, 1H, *J* = 11.5 Hz), 4.05 (bs, 1H), 3.98 (d, 1H, *J* = 8.5 Hz), 3.82 (s, 1H), 3.65 (dd, 1H, *J* = 5.0 Hz, 7.5 Hz), 3.53 (dd, 1H, *J* = 5.0 Hz, 9.0 Hz), 3.47 (dd, 1H, *J* = 8.0 Hz, *J* = 9.0 Hz), 2.89 (d, 1H, *J* = 14.5 Hz), 2.85 (d, 1H, *J* = 7.0 Hz), 1.76-1.81 (m, 1H).

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 208.9, 149.3, 137.7, 136.7, 131.0, 130.3, 128.8, 128.4, 128.4, 128.2, 127.9, 127.8, 127.8, 109.9, 109.6, 87.3, 83.5, 73.4, 72.8, 70.4, 69.4, 69.0, 62.1, 51.8, 31.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{29}H_{29}BrNO_4$ $[M+H]^+$: 534.1280, found: 534.1280.

(1*R*,3*R*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-((benzyloxy)methyl)-5-oxo-1,3,4,5,6,6a,7,11b-octahydro-1,6-methanooxocino[4,3-*b*]indole-10-carbonitrile (6b):



6b

Compound **6b** was synthesised from keto-cyclopropane **5** (100 mg, 0.29 mmol) and 1*H*-indole-5-carbonitrile (125.10 mg, 0.88 mmol) by following **general procedure A.** Yield: 83.55 mg, 60%, R_f: 0.4 (20% EtOAc/hexane); colourless gel.

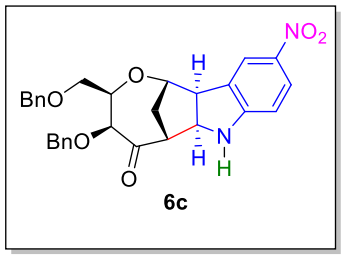
IR (neat): 3357, 3025, 2988, 2922, 2862, 2210, 1696, 1609 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.39 (m, 5H), 4.94-4.96 (m, 0.5H), 4.79-4.81 (m, 0.5H), 4.67-4.69 (m, 1.5H), 4.55 (d, 0.5H, *J* = 12.0 Hz), 3.95-3.98 (m, 1H), 3.52-3.55 (m, 1.5H), 3.27-3.29 (m, 0.5H), 2.05-2.08 (m, 0.5H), 1.95-2.00 (m, 0.5H), 1.60-1.81 (m, 2H), 1.49-1.55 (m, 1H);

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 208.4, 153.4, 137.6, 136.6, 133.9, 128.8, 128.5, 128.4, 128.4, 128.3, 127.9, 127.8, 120.2, 107.2, 100.0, 87. 3, 83.4, 73.4, 72.8, 70.5, 69.2, 68.9, 61.5, 51.0, 31.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{29}N_2O_4$ $[M+H]^+$: 481.2127, found: 481.2126.

(1*R*,3*R*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-((benzyloxy)methyl)-10-nitro-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (6c):



6c

Compound **6c** was synthesised from keto-cyclopropane **1** (100 mg, 0.29 mMol) and 5-nitro-1*H*-indole (142.69 mg, 0.88 mMol) by following **general procedure A.** Yield: 127.64, 88%, R_f: 0.6 (30% EtOAc/hexane); yellow oil.

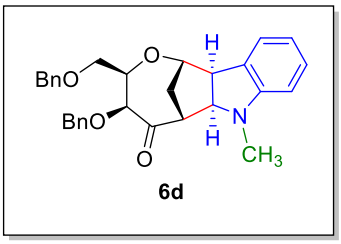
IR (neat): 3356, 3031, 2921, 2865, 1699, 1609 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.02 (bs, 1H), 8.00 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 7.28-7.34 (m, 8H), 7.20-7.22 (m, 2H), 6.41 (d, 1H, *J* = 8.5 Hz), 4.78 (bs, 1H), 4.70 (d, 1H, *J* = 4.5 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 4.60 (d, 1H, *J* = 8.5 Hz), 4.41 (d, 1H, *J* = 11.5 Hz), 4.38 (d, 1H, *J* = 11.5 Hz), 4.29 (d, 1H, *J* = 11.5 Hz), 4.01 (d, 1H, *J* = 8.5 Hz), 3.85 (d, 1H, *J* = 1.0 Hz), 3.64 (dd, 1H, *J* = 5.0 Hz, 8.0 Hz), 3.55 (dd, 1H, *J* = 4.5 Hz, 9.0 Hz), 3.48 (dd, 1H, *J* = 7.5 Hz, 9.0 Hz), 2.97 (d, 1H, *J* = 14.5 Hz), 2.87 (d, 1H, *J* = 7.0 Hz), 1.73-1.78 (m, 1H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 208.2, 155.3, 139.4, 137.6, 136.5, 128.8, 128.4, 128.3, 128.1, 127.9, 127.6, 126.8, 121.6, 105.6, 87.2, 83.3, 73.4, 72.8, 70.5, 69.5, 69.2, 61.2, 50.7, 31.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{29}H_{29}N_2O_6$ $[M+H]^+$: 501.2026, found: 501.2026.

(1*R*,3*R*,4*S*,6*S*,6a*S*,11b*R*)-4-(benzyloxy)-3-((benzyloxy)methyl)-7-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (6d):



6d

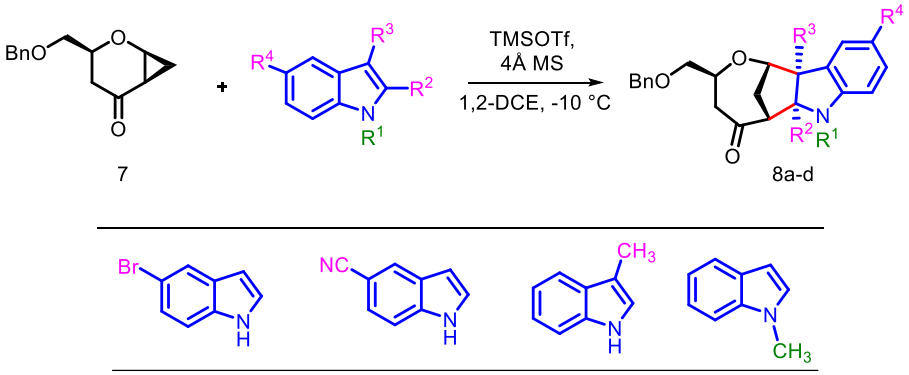
Compound **6d** was synthesised from keto-cyclopropane **1** (100 mg, 0.29 mmol) and 1-methyl-1*H*-indole (115.42 mg, 0.88 mmol) by following **general procedure A.** Yield: 97.98 mg, 72%, R_f: 0.7 (20% EtOAc/hexane); colourless oil.

IR (neat): 3028, 2917, 2866, 2360, 2320, 1695 cm^{-1}.

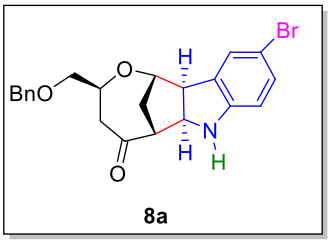
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.34 (m, 8H), 7.22-7.23 (m, 2H), 7.11 (d, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.61 (t, 1H, *J* = 7.5 Hz), 6.30 (d, 1H, *J* = 8.0 Hz), 4.69 (d, 1H, *J* = 4.5 Hz), 4.67 (d, 1H, *J* = 12. 0 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.31 (d, 1H, *J* = 11.5 Hz), 4.10 (d, 1H, *J* = 8.5 Hz), 3.97 (d, 1H, *J* = 9.0 Hz), 3.86 (d, 1H, *J* = 1.0 Hz), 3.71 (dd, 1H, *J* = 5.0 Hz, 8.0 Hz), 3.56 (dd, 1H, *J* = 5.0 Hz, 9.0 Hz), 3.50 (dd, 1H, *J* = 8.0 Hz, *J* = 9.0 Hz), 2.97 (d, 1H, *J* = 7.0 Hz), 2.92 (d, 1H, *J* = 14.5 Hz), 2.85 (s, 3H), 1.70-1.75 (m, 1H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 209.3, 151.5, 137.7, 136.7, 128.7, 128.4, 128.4, 128.2, 128.1, 127.8, 127.8, 124.5, 117.0, 105. 3, 87.5, 83.8, 77.3, 76.5, 73.4, 72.7, 70.2, 69.4, 57.8, 50.3, 32.8, 31.5.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{32}NO_4$ $[M+H]^+$: 470.2331, found: 470.2333.



(1*S*,3*S*,6*R*,6a*R*,11b*S*)-3-((benzyloxy)methyl)-10-bromo-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (8a):



8a

Compound **8a** was synthesised from keto-cyclopropane **7** (100 mg, 0.43 mmol) and 5-bromo-1*H*-indole (168.91 mg, 0.86 mmol) by following **general procedure A.** Yield: 157.93, 86%, R_f: 0.4 (20% EtOAc/hexane), yellow oil.

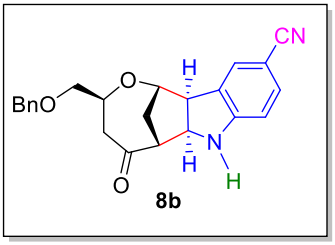
IR (neat): 3360, 3029, 2922, 2861, 1696 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.37 (m, 5H), 7.23-7.34 (m, 1H), 7.10 (dd, 1H, *J* = 0.5 Hz, 2.0 Hz), 6.38 (d, 1H, *J* = 8.5 Hz), 4.73 (d, 1H, *J* = 5.0 Hz), 4.60 (d, 1H, *J* = 12.5 Hz), 4.54 (d, 1H, *J* = 12.0 Hz), 4.51 (d, 1H, *J* = 9.5 Hz), 4.05 (bs, 1H), 3.99 (d, 1H, *J* = 8.5 Hz), 3.78-3.82 (m, 1H), 3.52 (dd, 1H, *J* = 5.0 Hz, *J* = 9.5 Hz), 3.44 (dd, 1H, *J* = 5.0, *J* = 10 Hz), 2.86-2.93 (m, 2H), 2.54, (d, 1H, *J* = 16.0), 2.25 (d, 1H, *J* = 14.5 Hz), 1.92-1.97 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.5, 149.2, 137.7, 131.0, 130.1, 128.5, 127.9, 127.8, 127.7, 109.8, 109.6, 87.1, 73.6, 73.2, 69.0, 68.3, 63.3, 52.5, 48.7, 34.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{23}BrNO_3$ $[M+H]^+$: 428.0861, found: 428.0862.

(1*S*,3*S*,6*R*,6a*R*,11b*S*)-3-((benzyloxy)methyl)-5-oxo-1,3,4,5,6,6a,7,11b-octahydro-1,6-methanooxocino[4,3-*b*]indole-10-carbonitrile (8b):



8b

Compound **8b** was synthesised from keto-cyclopropane **7** (100 mg, 0.43 mmol) and 1*H*-indole-5-carbonitrile (122.28 mg, 0.86 mmol) by following **general procedure A.** Yield: 128.71 mg, 80%, R_f: 0.5 (40% EtOAc/hexane), colourless oil.

IR (neat): 3357, 3015, 2923, 2862, 2359, 2211, 1698 cm^{-1}.

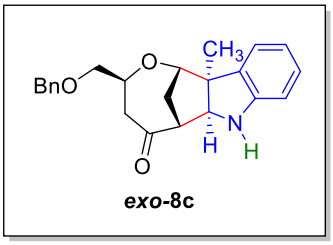
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.37 (m, 7H), 6.45 (d, 1H, *J* = 8.0 Hz), 4.72 (d, 1H, *J* = 5.0 Hz), 4.54-4.61 (m, 4H), 3.99 (d, 1H, *J* = 8.5 Hz), 3.76-3.80 (m, 1H), 3.54 (dd, 1H, *J* = 5.0 Hz, *J* = 9.5 Hz), 3.44 (dd, 1H, *J* = 5.0 Hz, *J* = 9.5 Hz), 2.87-2.94 (m, 2H), 2.56 (d, 1H, *J* = 15.5 Hz), 2.30 (d, 1H, *J* = 15.0 Hz), 1.88-1.94 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.0, 153.4, 137.7, 134.0, 128.5, 128.5, 128.2, 127.9, 127.8, 120.2, 107.2, 100.0, 87.1, 73.7, 73.2, 69.1, 68.2, 62.7, 51.7, 48.7, 34.0.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{23}N_2O_3$ $[M+H]^+$: 375.1709, found: 375.1714.

Compound ***exo*-8c** and ***endo*-8c** was synthesised from keto-cyclopropane **7** (100 mg, 0.43 mmol) and 3-methyl-1*H*-indole (112.80 mg, 0.86 mmol) by following **general procedure A.** Overall Yield: 146.79 mg, 94%.

(1*S*,3*S*,6*R*,6a*S*,11b*S*)-11b-methyl-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*exo*-8c):



***exo*-8c**

Yield: 85.88 mg, 55%, R_f: 0.6 (30% EtOAc/hexane), yellow oil.

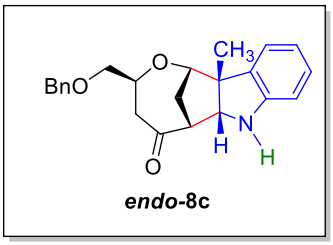
IR (neat): 3361, 3040, 2964, 2927, 2862, 1698 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.37 (m, 5H), 7.02 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.98 (d 1H, *J* = 7.5 Hz), 6.71 (td, 1H, *J* = 0.5 Hz, *J* = 7.5 Hz), 6.58 (d, 1H, *J* = 7.5 Hz), 4.65 (d, 1H, *J* = 7.5 Hz), 4.56-4.62 (m, 2H), 4.02-4.07 (m, 1H), 3.97 (bs, 1H), 3.55 (dd, 1H, *J* = 5.5 Hz, *J* = 10.0 Hz), 3.45-3.48 (m, 1H), 2.96 (dd, 1H, *J* = 11.0 Hz, *J* = 16.0 Hz), 2.75 (d, 1H, *J* = 8.0 Hz), 2.50 (d, 1H, *J* = 16.0 Hz), 2.50 (d, 1H, *J* = 16.0 Hz), 2.19 (d, 1H, *J* = 15.0 Hz), 1.90-1.96 (m, 1H), 1.46 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.4, 148.2, 137.8, 134.9, 128.4, 128.2, 127.8, 127.7, 122.7, 119.0, 108.8, 87.2, 73.6, 73.4, 73.4, 69.1, 64.8, 58.6, 47.0, 35.8, 20.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1913, found: 364.1910

(1*S*,3*S*,6*R*,6a*R*,11b*R*)-3-((benzyloxy)methyl)-11b-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*endo*-8c):



***endo*-8c**

Yield: 72.39 mg, 41%, R_f: 0.3 (30% EtOAc/hexane), yellow gel.

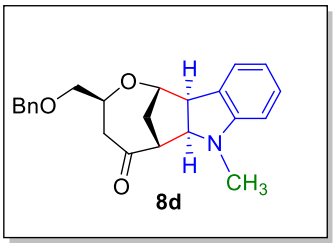
IR (neat): 3373, 3030, 2954, 2863, 1695 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.21-7.31 (m, 3H), 7.19 (dd, 1H, *J* = 0.5 Hz, *J* = 7.5 Hz), 7.14-7.16 (m, 2H), 7.05 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.73 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.51 (d, 1H, *J* = 8.0 Hz), 4.59 (d, 1H, *J* = 5.0 Hz), 4.17-4.25 (m, 3H), 4.08 (d, 1H, *J* = 12.0 Hz), 3.43-3.42 (m, 1H), 3.24 (t, 1H, *J* = 8.0 Hz), 3.01-3.07 (m, 2H), 2.90 (dd, 1H, *J* = 11.0 Hz, *J* = 15.5 Hz), 2.39 (d, 1H, *J* = 15.0 Hz), 2.19-224 (m, 2H), 1.41 (s, 3H).

$^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 212.6, 150.7, 138.1, 130.2, 128.4, 128.2, 127.4, 127.4, 125.0, 118.9, 109.1, 87.4, 73.9, 73.1, 72.3, 67.3, 58.4, 57.9, 48.5, 35.8, 30.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1913, found: 364.1942

(1*S*,3*S*,6*R*,6a*R*,11b*S*)-3-((benzyloxy)methyl)-7-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (8d):



8d

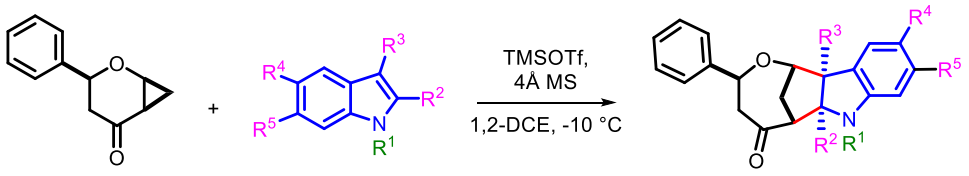
Compound **8d** was synthesised from keto-cyclopropane **7** (100 mg, 0.43 mmol) and 1-methyl-1*H*-indole (112.08 mg, 0.86 mmol) by following **general procedure A.** Yield: 143.66 mg, 92%, R_f: 0.6 (20% EtOAc/hexane), yellow oil.

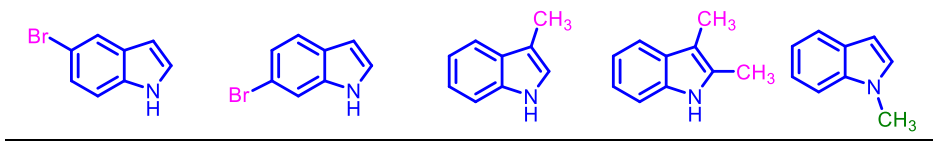
IR (neat): 3030, 2932, 2862, 2798, 1697, 1603 cm^{-1}.

^1H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.32 (m, 5H), 7.11 (d, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.61 (td, 1H, *J* = 0.5 Hz, *J* = 7.5 Hz), 6.30 (d, 1H, *J* = 7.5 Hz), 4.76 (d, 1H, *J* = 5.0 Hz), 4.61 (d, 1H, *J* = 12.0 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 4.16 (d, 1H, *J* = 8.5 Hz), 3.98 (d, 1H, *J* = 8.5 Hz), 3.81-3.85 (m, 1H), 3.54 (dd, 1H, *J* = 5.0 Hz, *J* = 10.0 Hz), 3.45 (dd, 1H, *J* = 4.5 Hz, *J* = 9.5 Hz), 2.92-2.98 (m, 2H), 2.85 (s, 3H), 2.54 (d, 1H, 15.5 Hz), 2.26 (d, 1H, 14.5 Hz), 1.85-1.90 (m, 1H).

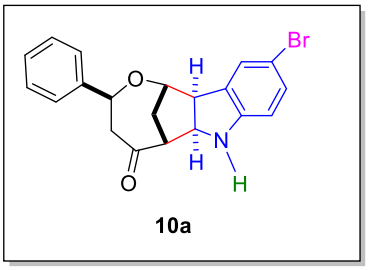
$^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 212.0, 151.3, 137.7, 128.4, 128.0, 127.8, 124.4, 116.9, 105.2, 87.4, 75.7, 73.5, 73.3, 68.9, 58.6, 51.1, 49.0, 34.2, 32.6.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1913, found: 364.1914.





(1*S*,3*S*,6*R*,6a*R*,11b*S*)-10-bromo-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (10a):



10a

Compound **10a** was synthesised from keto-cyclopropane **9** (100 mg, 0.53 mmol) and 5-bromo-1*H*-indole (208.46 mg, 1.06 mmol) by following **general procedure A.** Yield: 182.71 mg, 90%, R_f: 0.4 (20% EtOAc/hexane), yellow oil.

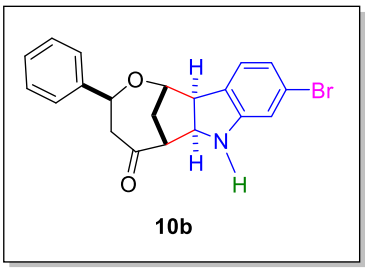
IR (neat): 3365, 3029, 2940, 2128, 1696 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.39 (m, 5H), 7.21 (bs, 1H), 7.11 (dd, 1H, *J* = 2.0 Hz, 8.0 Hz), 6.41 (d, 1H, *J* = 8.5 Hz), 4.84 (d, 1H, *J* = 5.5 Hz), 4.68-4.72 (m, 2H), 4.15 (d, 1H, *J* = 8.5 Hz), 4.12 (bs, 1H), 3.22 (dd, 1H, *J* = 10.5 Hz, 15.5 Hz), 2.95 (d, 1H, *J* = 7.0 Hz), 2.63 (d, 1H, *J* = 15.5 Hz), 2.39 (d, 1H, *J* = 14.5 Hz), 2.02-2.07 (m, 1H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.3, 149.2, 141.7, 131.1, 130.2, 128.7, 128.1, 127.7, 125.8, 109.9, 109.6, 87.4, 72.3, 68.6, 63.1, 54.2, 52.5, 34.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{19}BrNO_2$ $[M+H]^+$: 384.0599, found: 384.0598.

(1*S*,3*S*,6*R*,6a*R*,11b*S*)-9-bromo-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (10b):



10b

Compound **10b** was synthesised from keto-cyclopropane **9** (100 mg, 0.53 mmol) and 6-bromo-1*H*-indole (208.46 mg, 1.06 mmol) by following **general procedure A.** Yield: 186.76 mg, 92%, R_f: 0.6 (20% EtOAc/hexane), yellow solid.

IR (neat): 3390, 3028, 2925, 1695 cm^{-1}.

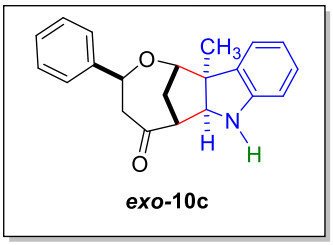
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.39 (m, 5H) 6.95(dd, 1H, *J* = 1.0 Hz, *J* = 8.0 Hz) 6.79 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.66 (d, 1H, *J* = 2.0 Hz), 4.82 (d, 1H, *J* = 5.0 Hz), 4.69-4.72 (m, 2H), 4.19 (s, 1H), 4.11 (d, 1H, *J* = 8.5 Hz), 3.23 (dd, 1H, *J* = 10.5 Hz, *J* = 15.0 Hz), 2.95 (d, 1H, *J* = 7.0 Hz), 2.63 (d, 1H, *J* = 16.0 Hz), 2.39 (d, 1H, *J* = 15.0 Hz), 2.02-2.07 (m, 1H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 211.3, 151.5, 141.7, 128.8, 128.1, 126.9, 125.9, 125.8, 122.0, 121.3, 111.2, 87.4, 72.3, 68.6, 63.0, 54.1, 52.0, 34.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{19}BrNO_2$ $[M+H]^+$: 384.0599, found: 384.0591.

Compound ***exo*-10c** and ***endo*-10c** was synthesised from keto-cyclopropane **9** (100 mg, 0.53 mmol) and 3-methyl-1*H*-indole (139.04 mg, 1.06 mmol) by following **general procedure A.** Overall Yield: 169.51 mg, 96%.

(1*S*,3*S*,6*R*,6a*S*,11b*S*)-11b-methyl-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*exo*-10c):



***exo*-10c**

Yield: 96.41 mg, 57%, R_f: 0.6 (30% EtOAc/hexane), yellow solid.

Crystallization: Compound *exo*-**10c** (80 mg) was dissolved in 5 ml 10% EtOAc/hexane. The solution was slightly warmed to 50 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.

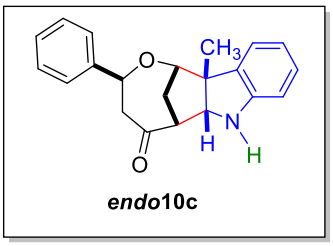
IR (neat): 3369, 2935, 2929, 2360, 1696 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.30-7.39 (m, 5H), 7.04 (td, 1H, *J* = 1.5 Hz, 7.5 Hz), 6.98 (d, 1H, *J* = 7.5 Hz), 6.72 (td, 1H, *J* = 1.5 Hz, 7.5 Hz), 6.60 (d, 1H, *J* = 7.5 Hz), 4.93 (d, 1H, *J* = 11.0 Hz), 4.76 (d, 1H, *J* = 4.5 Hz), 4.15 (bm, 2H), 3.32 (dd, 1H, *J* = 11.0 Hz, 16.0 Hz), 2.84 (d, 1H, *J* = 7.5 Hz), 2.59 (d, 1H, *J* = 16.0 Hz), 2.33 (d, 1H, *J* = 14.5 Hz), 1.99-2.05 (m, 1H), 1.53 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.2, 148.4, 142.0, 134.9, 128.8, 128.2, 128.1, 125.8, 122.7, 119.0, 108.8, 87.6, 73.7, 72.4, 64.7, 58.6, 52.0, 35.7, 20.7.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1651, found: 320.1655.

(1*S*,3*S*,6*R*,6a*R*,11b*R*)-11b-methyl-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*endo*-10c):



***endo*10c**

Yield: 60.81 mg, 32%, R_f: 0.6 (30% EtOAc/hexane), yellow oil.

IR (neat): 3377, 3030, 2957, 2359, 1694 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.15-7.20 (m, 5H), 6.79 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.74-6.76 (m, 2H), 6.62 (d, 1H, *J* = 8.0 Hz), 4.65 (d, 1H, *J* = 5.0 Hz), 4.36 (bs, 1H), 4.24 (d, 1H, *J* = 9.0 Hz), 4.20 (d, 1H, *J* = 11.5

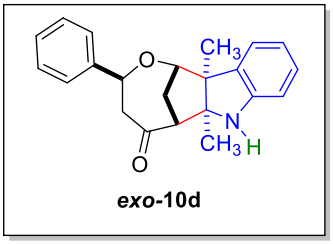
Hz), 3.31-3.34 (m, 1H), 3.27 (dd, 1H, *J* = 11.5 Hz, *J* = 15.0 Hz), 2.52 (d, 1H, *J* = 14.5 Hz), 2.33-2.37 (m, 1H), 2.26-2.31 (m, 1H), 1.45 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 212.1, 150.8, 141.7, 130.3, 128.5, 128.4, 127.8, 126.2, 125.1, 118.9, 109.2, 87.8, 73.9, 71.3, 58.3, 58.0, 52.2, 35.8, 30.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1651, found: 320.1652.

Compound ***exo*-10d** and ***endo*-10d** was synthesised from keto-cyclopropane **9** (100 mg, 0.53 mmol) and 2,3-dimethyl-1*H*-indole (153.79 mg, 1.06 mmol) by following **general procedure A.** Overall Yield: 169.51 mg, 96%.

(1*S*,3*S*,6*R*,6a*S*,11b*S*)-6a,11b-dimethyl-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*exo*-10d):



***exo*-10d**

Yield: 97.11 mg, 55%, R_f: 0.5 (20% EtOAc/hexane), yellow solid.

Crystallization: Compound *exo*-**10d** (80 mg) was dissolved in 5 ml 10% EtOAc/hexane. The solution was slightly warmed to 50 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.

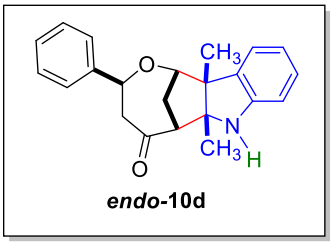
IR (neat): 3386, 2983, 2943, 1691 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.38 (m, 5H), 7.00 (td, 1H, *J*= 1.0 Hz, *J* = 7.5 Hz), 6.96 (dd, 1H, *J* = 0.5 Hz, *J* = 7.5 Hz), 6.67 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.46 (d, 1H, *J* = 8.0 Hz), 5.01 (d, 1H, *J* = 11.0 Hz), 4.66 (d, 1H, *J* = 4.5 Hz), 3.96 (bs, 1H), 3.31 (dd, 1H, *J* = 11.5 Hz, *J* = 16 Hz), 2.99 (d, 1H, *J* = 7.5 Hz), 2.59 (d, 1H, *J* = 16.0 Hz), 2.32 (d, 1H, *J* = 15.0 Hz) 2.07-2.12 (m, 1H), 1.52 (s, 3H), 1.50 (s, 3H).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 210.5, 147.9, 142.1, 135.6, 128.8, 128.6, 128.2, 128.1, 125.8, 123.7, 118.4, 107.3, 89.8, 74.5, 73.0, 68.5, 60.3, 52.4, 33.3, 21.6, 18.6.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1807, found: 334.1804.

(1*S*,3*S*,6*R*,6a*R*,11b*R*)-6a,11b-dimethyl-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*endo*-10d):



endo-10d

Yield: 72.39 mg, 41%, R_f: 0.3 (20% EtOAc/hexane), yellow oil.

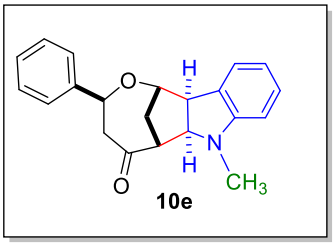
IR (neat): 3361, 2959, 2359, 1692 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.14-7.18 (m, 5H), 6.78 (td, 1H, *J*= 0.5 Hz, *J* = 7.5 Hz), 6.74-6.76 (m, 2H), 6.58 (d, 1H, *J* = 7.5 Hz), 4.64 (d, 1H, *J* = 5.0 Hz), 4.40 (d, 1H, *J* = 11.5 Hz), 4.10 (bs, 1H), 3.22 (d, 1H, *J* = 11.5 Hz, *J* = 11.5 Hz), 3.00 (dd, 1H, *J* = 7.0 Hz), 2.44 (d, 1H, *J* = 15.0 Hz), 2.37 (d, 1H, *J* = 15.5 Hz), 2.26-2.31 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.3, 149.3, 142.0, 130.4, 128.6, 128.4, 127.7, 126.2, 125.4, 118.8, 108.8, 90.3, 76.5, 71.2, 65.9, 60.3, 52.0, 34.6, 27.3, 24.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{24}NO_2$ $[M+H]^+$: 334.1807, found: 334.1806.

(1*R*,3*S*,6*S*,6a*S*,11b*R*)-7-methyl-3-phenyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (10e):



10e

Compound **10e** was synthesised from keto-cyclopropane **9** (100 mg, 0.53 mmol) and 1-methyl-1*H*-indole (139.04 mg, 1.06 mmol) by following **general procedure A.** Yield: 143.77 mg, 85%, R_f: 0.5 (10% EtOAc/hexane), yellow solid.

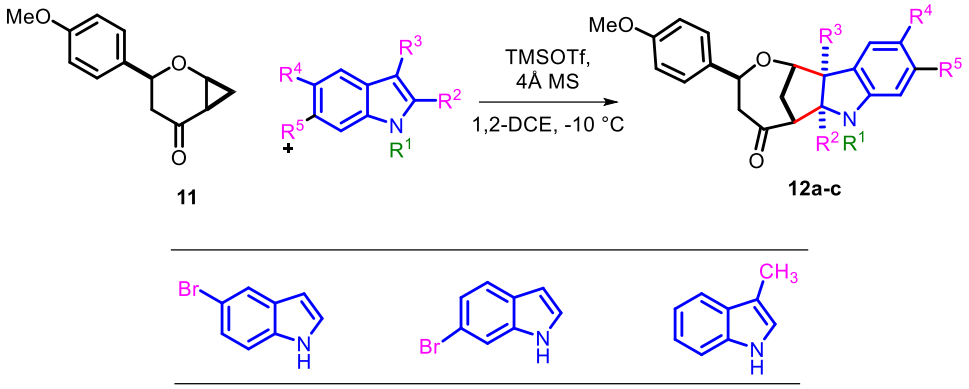
Crystallization: Compound **10e** (100 mg) was dissolved in 10 ml 2% EtOAc/hexane. The solution was slightly warmed to 50 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.

IR (neat): 3050, 2936, 2881, 2359, 1692 cm^{-1}.

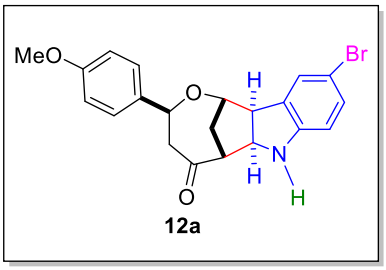
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.38 (m, 5H), 7.07-7.11 (m, 2H), 6.62 (td, 1H, *J* = 1.0 Hz, 7.5 Hz), 6.33 (d, 1H, *J* = 7.5 Hz), 4.86 (d, 1H, *J* = 5.0 Hz), 4.73 (d, 1H, *J* = 11.0 Hz), 4.31 (d, 1H, *J* = 8.5 Hz), 4.13 (d, 1H, *J* = 8.5 Hz), 3.26 (dd, 1H, *J* = 11.0 Hz, 15.5 Hz), 3.06 (d, 1H, *J* = 7.0 Hz), 2.90 (s, 3H), 2.63 (d, 1H, *J* = 15.5 Hz), 2.41 (d, 1H, *J* = 14.5 Hz), 1.96-2.01 (m, 1H).

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 211.6, 151.4, 141.9, 128.7, 128.5, 128.1, 128.0, 125.8, 124.5, 117.1, 105.3, 87.6, 76.0, 72.3, 58.6, 54.4, 51.0, 34.2, 32.8.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$: 320.1651, found: 320.1651.



(1*S*,3*S*,6*R*,6a*R*,11b*S*)-10-bromo-3-(4-methoxyphenyl)-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (12a):



Compound **12a** was synthesised from keto-cyclopropane **11** (100 mg, 0.45 mmol) and 5-bromo-1*H*-indole (179.79 mg, 0.91 mmol) by following **general procedure A.** Yield: 149.45 mg, 79%, R_f: 0.4 (30% EtOAc/hexane), white powder.

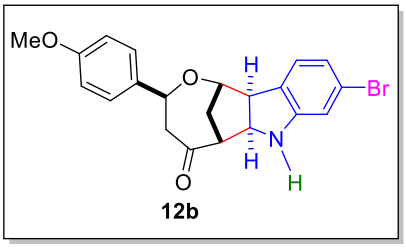
IR (neat): 3398, 2958, 2837, 2360, 1695 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.28 (m, 2H), 7.21-7.22 (m, 1H), 7.11 (dd, 1H, *J* = 1.0 Hz, *J* = 2.0 Hz), 6.88-6.91 (m, 2H), 6.41 (d, 1H, *J* = 8.0 Hz), 4.82 (d, 1H, *J* = 5.0 Hz), 4.65-4.69 (m, 2H) 4.09-4.15 (m, 2H), 3.80 (s, 3H), 3.23 (dd, 1H, *J* = 11.0 Hz, *J* = 16.0 Hz), 2.95 (d, 1H, *J* = 7.0 Hz), 2.61 (d, 1H, *J* = 15.5 Hz), 2.38 (d, 1H, *J* = 14.5 Hz), 2.00-2.06 (m, 1H).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 211.4, 159.4, 149.2, 134.0, 131.1, 130.2, 127.7, 127.0, 114.1, 109.9, 109.6, 87.3, 71.9, 68.6, 63.1, 55.3, 54.1, 52.5, 34.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{21}BrNO_3$ $[M+H]^+$: 414.0705, found: 414.0705.

(1*S*,3*S*,6*R*,6a*R*,11b*S*)-9-bromo-3-(4-methoxyphenyl)-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (12b):



12b

Compound **12b** was synthesised from keto-cyclopropane **11** (100 mg, 0.45 mmol) and 6-bromo-1*H*-indole (179.79 mg, 0.91 mmol) by following **general procedure A.** Yield: 148.70 mg, 80%, R_f: 0.6 (30% EtOAc/hexane), white powder.

IR (neat): 3399, 2960, 2934, 2835, 1694 cm^{-1}.

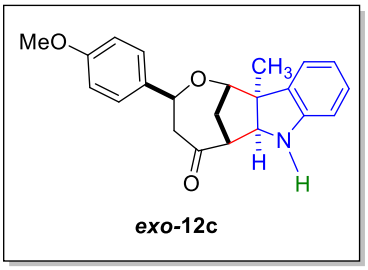
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.28 (m, 2H), 6.95 (d, 1H, *J* = 8.0 Hz), 6.88-6.90 (m, 2H), 6.78 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.65 (d, 1H, *J* = 1.5 Hz), 4.79 (d, 1H, *J* = 5.0 Hz), 4.65-4.69 (m, 2H), 4.18 (s, 1H), 4.09 (d, 1H, *J* = 9.0 Hz), 3.80 (s, 3H), 3.23 (dd, 1H, *J* = 11.0 Hz, *J* = 15.5 Hz), 2.94 (d, 1H, *J* = 7.0 Hz), 2.60 (d, 1H, *J* = 15.5 Hz), 2.38 (d, 1H, *J* = 14.5 Hz), 2.00-2.06 (m, 1H).

^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 211.4, 159.3, 151.5, 134.0, 127.0, 126.9, 125.9, 122.0, 121.3, 114.1, 111.2, 87.3, 71.9, 68.6, 63.0, 55.3, 54.1, 52.0, 34.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{21}BrNO_3$ $[M+H]^+$: 414.0705, found: 414.0702.

Compound ***exo*-12c** and ***endo*-12c** was synthesised from keto-cyclopropane **11** (100 mg, 0.45 mmol) and 3-methyl-1*H*-indole (119.36 mg, 0.91 mmol) by following **general procedure A.** Overall Yield: 148.71 mg, 93%.

(1*S*,3*S*,6*R*,6a*S*,11b*S*)-3-(4-methoxyphenyl)-11b-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*exo*-12c):



***exo*-12c**

Yield: 92.74 mg, 58%, R_f: 0.6 (40% EtOAc/hexane), white powder.

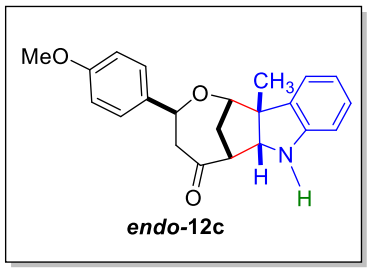
IR (neat): 3373, 3040, 2931, 2833, 2359, 1695 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.32 (m, 2H), 7.04 (td, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.98 (dd, 1H, *J* = 7.5 Hz), 6.89-6.92 (m, 2H), 6.72 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.60 (d, 1H, *J* = 8.0 Hz), 4.88 (d, 1H, *J* = 11.0 Hz), 4.73 (d, 1H, *J* = 4.5 Hz), 4.14 (s, 2H), 3.81 (s, 3H), 3.32 (dd, 1H, *J* = 11.0 Hz, *J* = 16.0 Hz), 2.83 (d, 1H, *J* = 8.0 Hz), 2.58 (d, 1H, *J* = 15.5 Hz), 2.32 (d, 1H, *J* = 15.0 Hz), 1.99-2.03 (m, 1H), 1.53 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 211.3, 159.4, 148.4, 134.9, 134.3, 128.2, 127.0, 122.7, 119.0, 114.1, 108.8, 87.5, 73.7, 71.9, 64.7, 58.6, 55.3, 51.9, 35.6, 20.7.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1756, found: 350.1759.

(1*S*,3*S*,6*R*,6a*R*,11b*R*)-3-(4-methoxyphenyl)-11b-methyl-3,4,6,6a,7,11b-hexahydro-1,6-methanooxocino[4,3-*b*]indol-5(1*H*)-one (*endo*-12c):



endo-12c

Yield: 55.90 mg, 35%, R_f: 0.4 (30% EtOAc/hexane), brown solid.

Crystallization: Compound *endo*-**12c** (50 mg) was dissolved in 5 ml 10% EtOAc/hexane. The solution was slightly warmed to 50 °C in an open container, allowed to cool to room temperature and kept without disturbing for slow evaporation of solvent. Crystals were found to be accumulating slowing. After complete evaporation of solvents, crystals were filtered, washed with hexane and dried.

IR (neat): 3377, 3049, 2955, 2067, 1695 cm^{-1}.

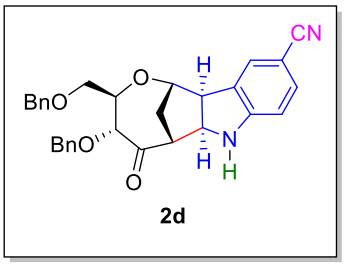
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.18 (dd, 1H, *J* = 0.5 Hz, *J* = 7.5 Hz), 7.15 (td, 1H, *J* = 1.5 Hz, *J* = 8.0 Hz), 6.79 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.69-6.71 (m, 2H), 6.63-6.65 (m, 2H), 6.60 (d, 1H, *J* = 7.5 Hz), 4.61 (d, 1H, *J* = 5.0 Hz), 4.31 (bs, 1H), 4.23 (d, 1H, *J* = 9.5 Hz), 4.13 (d, 1H, *J* = 11.5 Hz), 3.72 (s, 3H), 3.31 (t, 1H, *J* = 8.0 Hz), 3.26 (dd, 1H, *J* = 11.5 Hz, *J* = 15.5 Hz), 2.50 (d, 1H, *J* = 15.0 Hz), 2.31-2.51 (m, 1H), 2.24-2.29 (m, 1H), 1.43 (s, 3H).

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 212.3, 159.1, 150.8, 134.2, 130.4, 128.5, 127.5, 125.2, 118.9, 113.8, 109.2, 87.8, 73.9, 70.8, 58.4, 58.0, 55.2, 52.2, 35.8, 30.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1756, found: 350.1746.

Single Crystal X-ray data

Crystal data and structure refinement for **2d**: CCDC: **2178374**



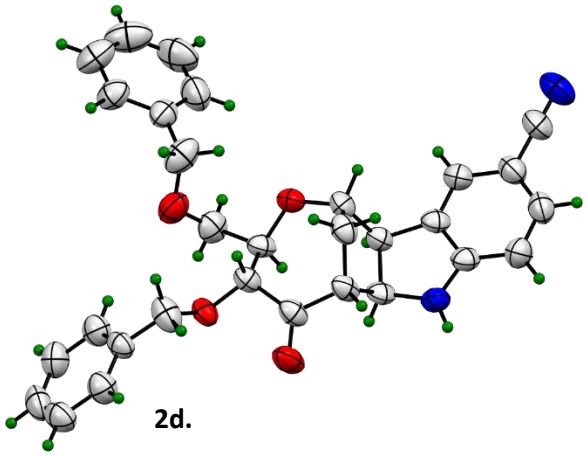


Figure **S3**: ORTEP representation of compound **2d.**

The ellipsoid contour % probability levels in the caption for the image of **2d** was 50%.

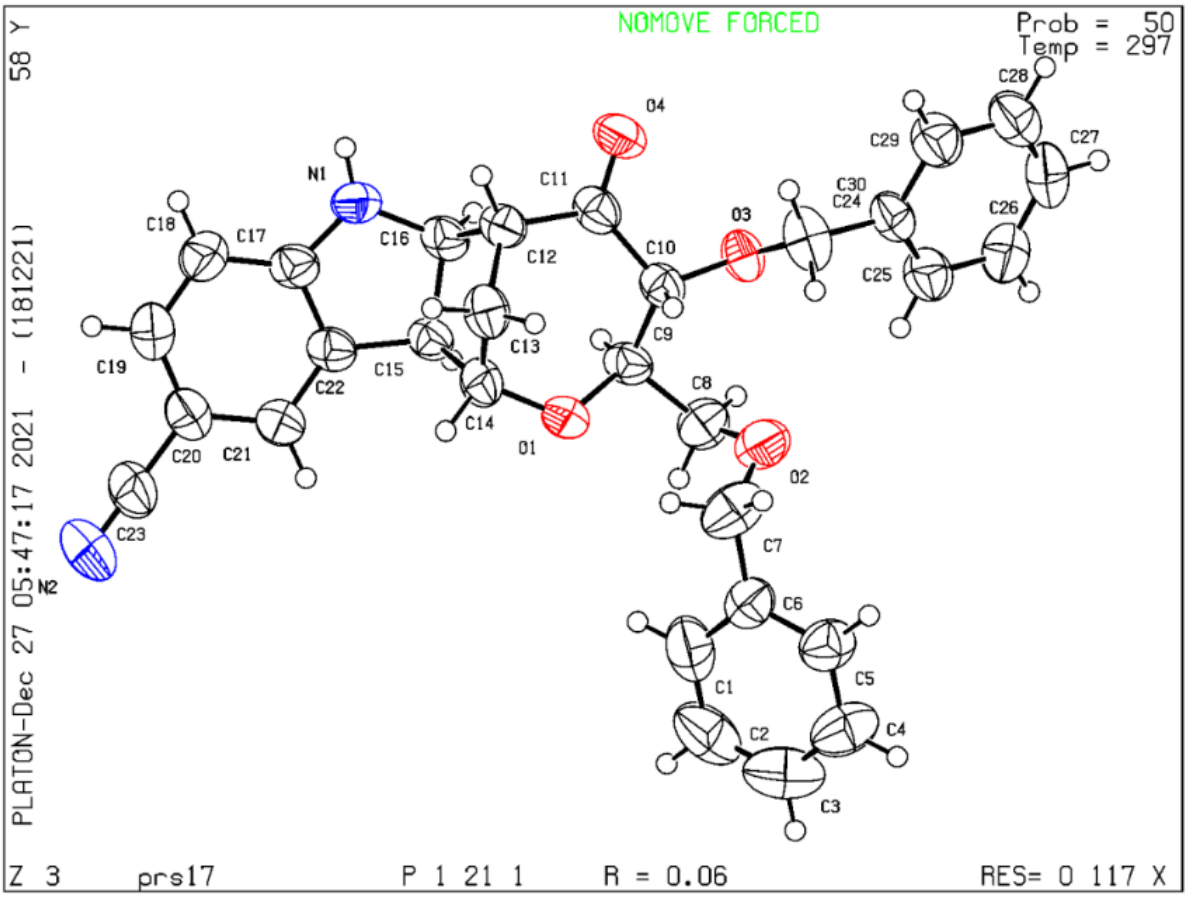


Table 1 Crystal data and structure refinement for PRS17.

Identification code	PRS17
Empirical formula	$C_{30}H_{28}N_2O_4$
Formula weight	480.54
Temperature/K	297(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.1136(4)
b/Å	8.4706(3)
c/Å	14.8635(6)
α/°	90
β/°	98.341(4)
γ/°	90
Volume/Å^3	1259.86(8)
Z	2
ρ_{calc}g/cm^3	1.267
μ/mm^{-1}	0.084
F(000)	508.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.07 to 50.046
Index ranges	-12 ≤ h ≤ 12, -10 ≤ k ≤ 8, -17 ≤ l ≤ 17
Reflections collected	9720
Independent reflections	3653 [R_{int} = 0.0680, R_{sigma} = 0.0812]
Data/restraints/parameters	3653/1/325
Goodness-of-fit on F^2	0.957
Final R indexes [I>=2σ (I)]	R_1 = 0.0560, wR_2 = 0.1199
Final R indexes [all data]	R_1 = 0.0893, wR_2 = 0.1435
Largest diff. peak/hole / e Å^{-3}	0.18/-0.18

Crystal data and structure refinement for **2b**: CCDC: **2178378**

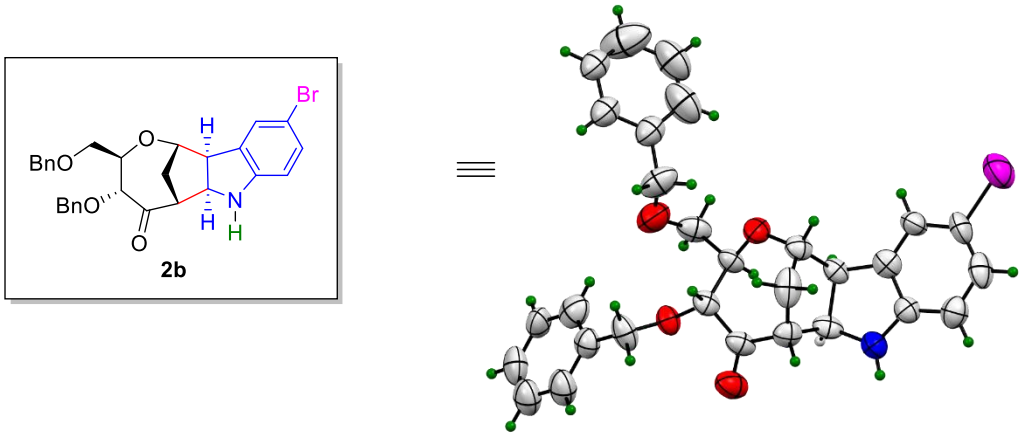


Figure **S4**: ORTEP representation of compound **2b.**

The ellipsoid contour % probability levels in the caption for the image of **2b** was 50%.

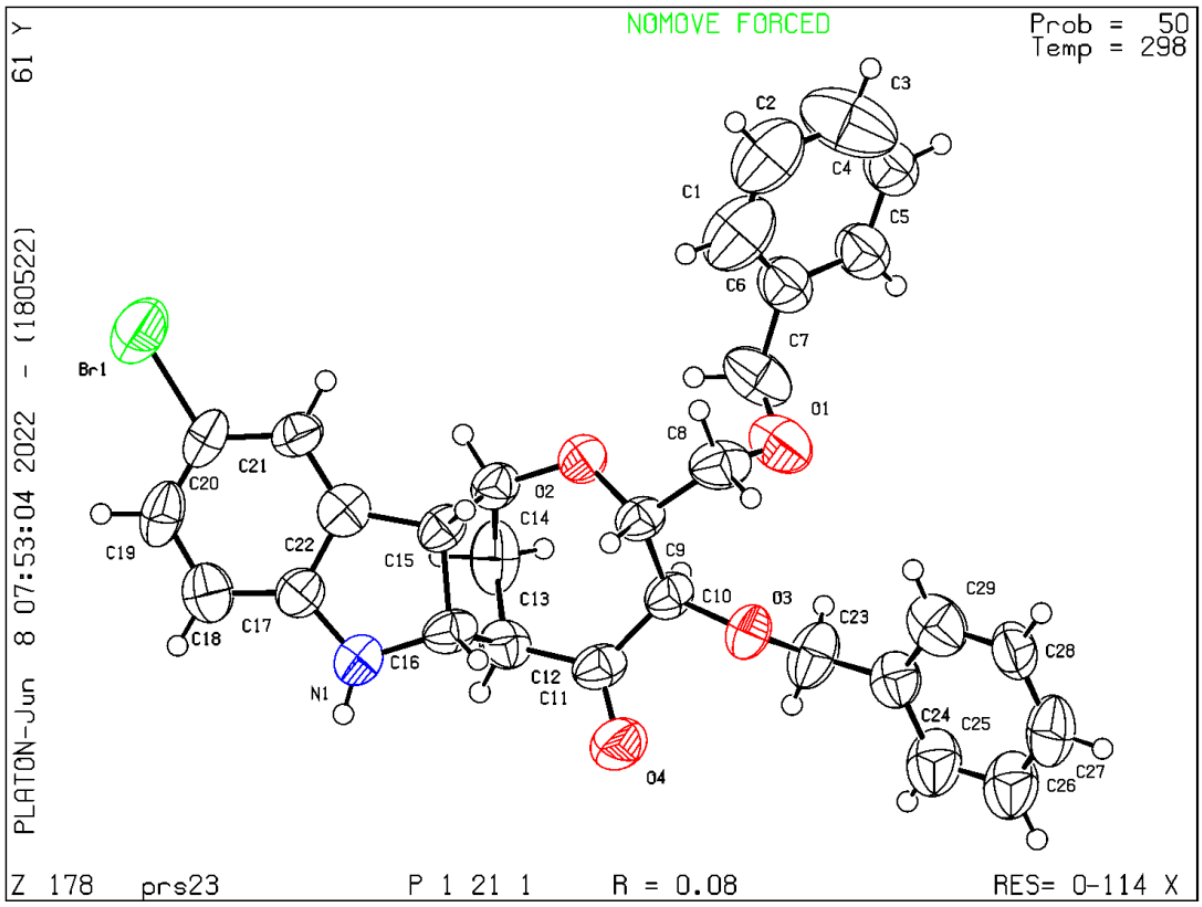


Table 2 Crystal data and structure refinement for PRS23.

Identification code	PRS23
Empirical formula	$C_{29}H_{28}BrNO_4$
Formula weight	534.43
Temperature/K	298.0(9)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.9708(7)
b/Å	8.7860(5)
c/Å	14.8105(12)
α/°	90
β/°	101.265(6)
γ/°	90
Volume/Å^3	1272.45(16)
Z	2
ρ_{calc}g/cm^3	1.395
μ/mm^{-1}	1.650
F(000)	552.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.166 to 50.05
Index ranges	-11 ≤ h ≤ 11, -10 ≤ k ≤ 10, -17 ≤ l ≤ 16
Reflections collected	11923
Independent reflections	4294 [R_{int} = 0.1708, R_{sigma} = 0.1542]
Data/restraints/parameters	4294/1/292
Goodness-of-fit on F^2	0.927
Final R indexes [I>=2σ (I)]	R_1 = 0.0838, wR_2 = 0.1848
Final R indexes [all data]	R_1 = 0.1670, wR_2 = 0.2434
Largest diff. peak/hole / e Å^{-3}	0.62/-0.82
Flack parameter	-0.019(12)

Crystal data and structure refinement for **4b**: CCDC: **2178376**

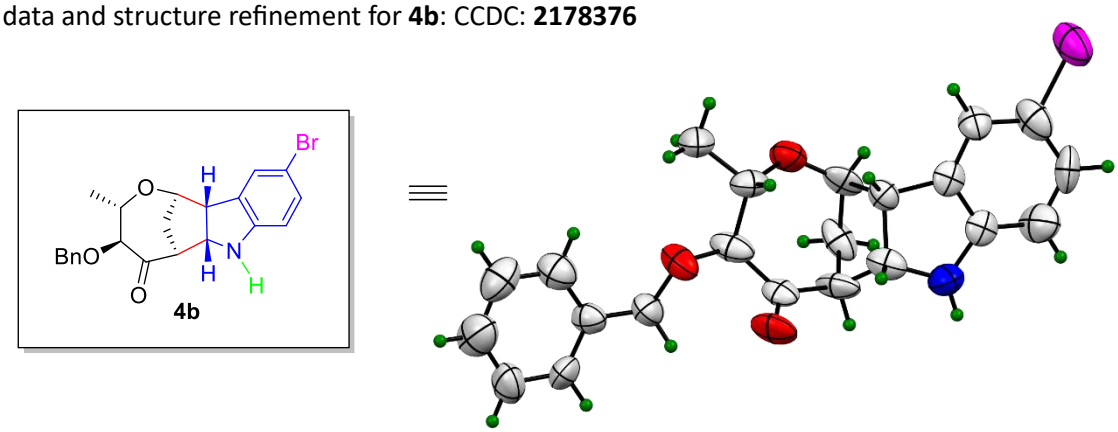


Figure S5: ORTEP representation of compound **4b.**

The ellipsoid contour % probability levels in the caption for the image of **4b** was 50%.

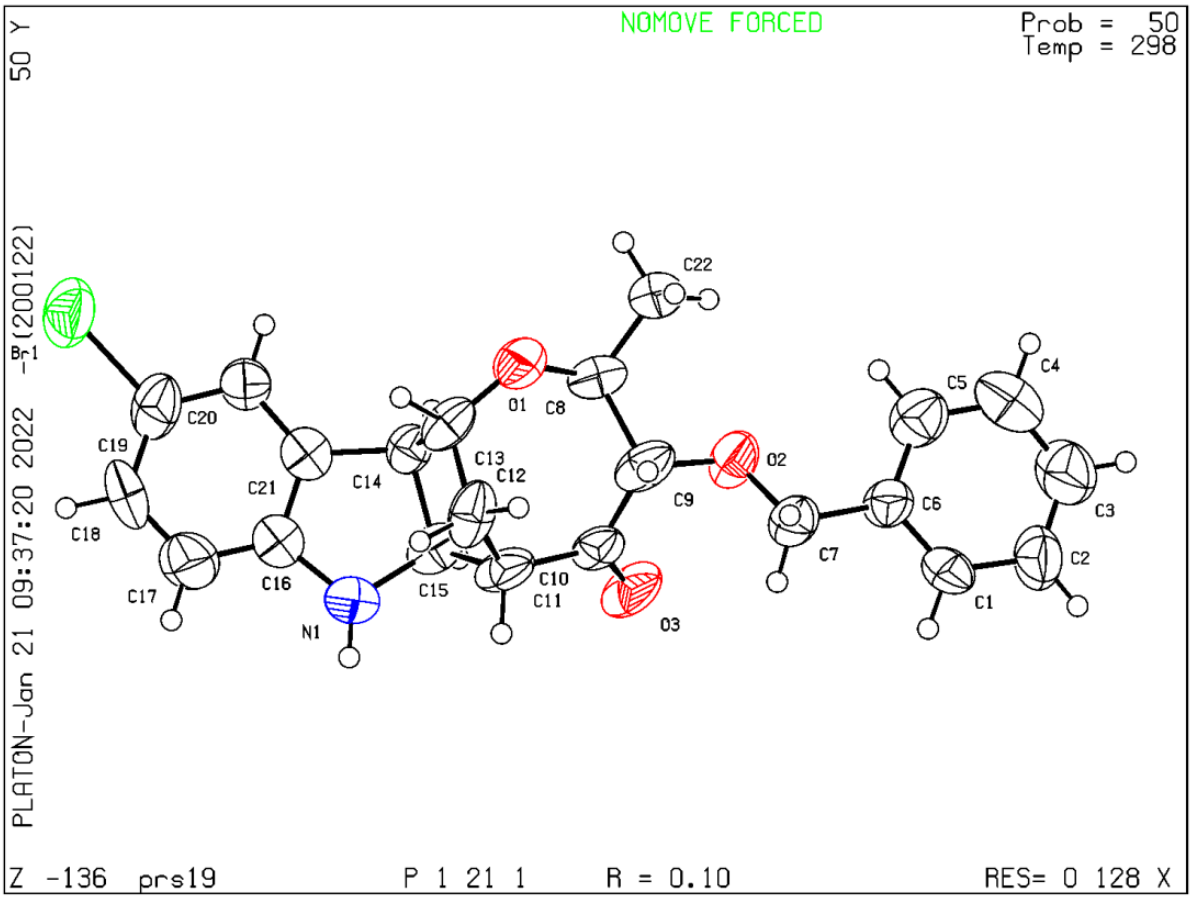


Table 3 Crystal data and structure refinement for PRS19.

Identification code	PRS19
Empirical formula	$C_{22}H_{22}BrNO_3$
Formula weight	428.31
Temperature/K	298(5)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.6317(8)
b/Å	6.1462(4)
c/Å	14.7221(13)
α/°	90
β/°	91.228(7)
γ/°	90
Volume/Å^3	961.79(13)
Z	2
ρ_{calc}g/cm^3	1.479
μ/mm^{-1}	2.159
F(000)	440.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.678 to 50.05
Index ranges	-12 ≤ h ≤ 12, -7 ≤ k ≤ 7, -17 ≤ l ≤ 17
Reflections collected	9629
Independent reflections	3100 [R_{int} = 0.2214, R_{sigma} = 0.1731]
Data/restraints/parameters	3100/1/239
Goodness-of-fit on F^2	1.064
Final R indexes [I>=2σ (I)]	R_1 = 0.0959, wR_2 = 0.2133
Final R indexes [all data]	R_1 = 0.1792, wR_2 = 0.2707
Largest diff. peak/hole / e Å^{-3}	0.38/-0.67

Crystal data and structure refinement for ***exo*-10c** CCDC: **2178377**

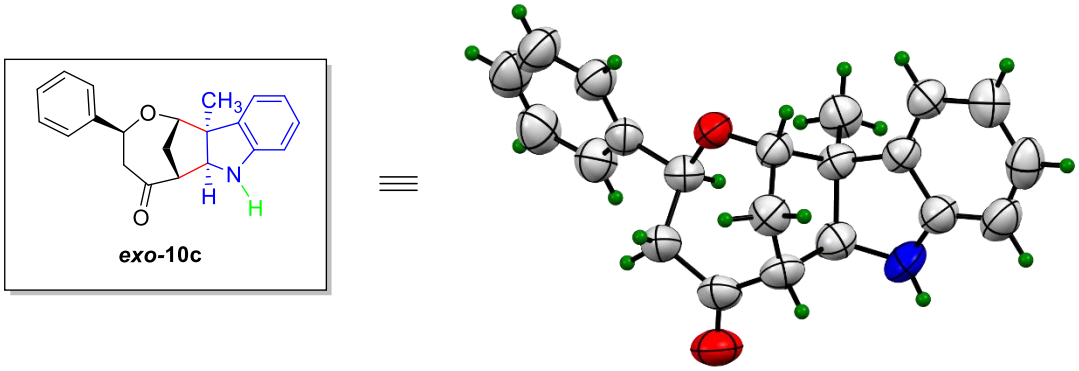
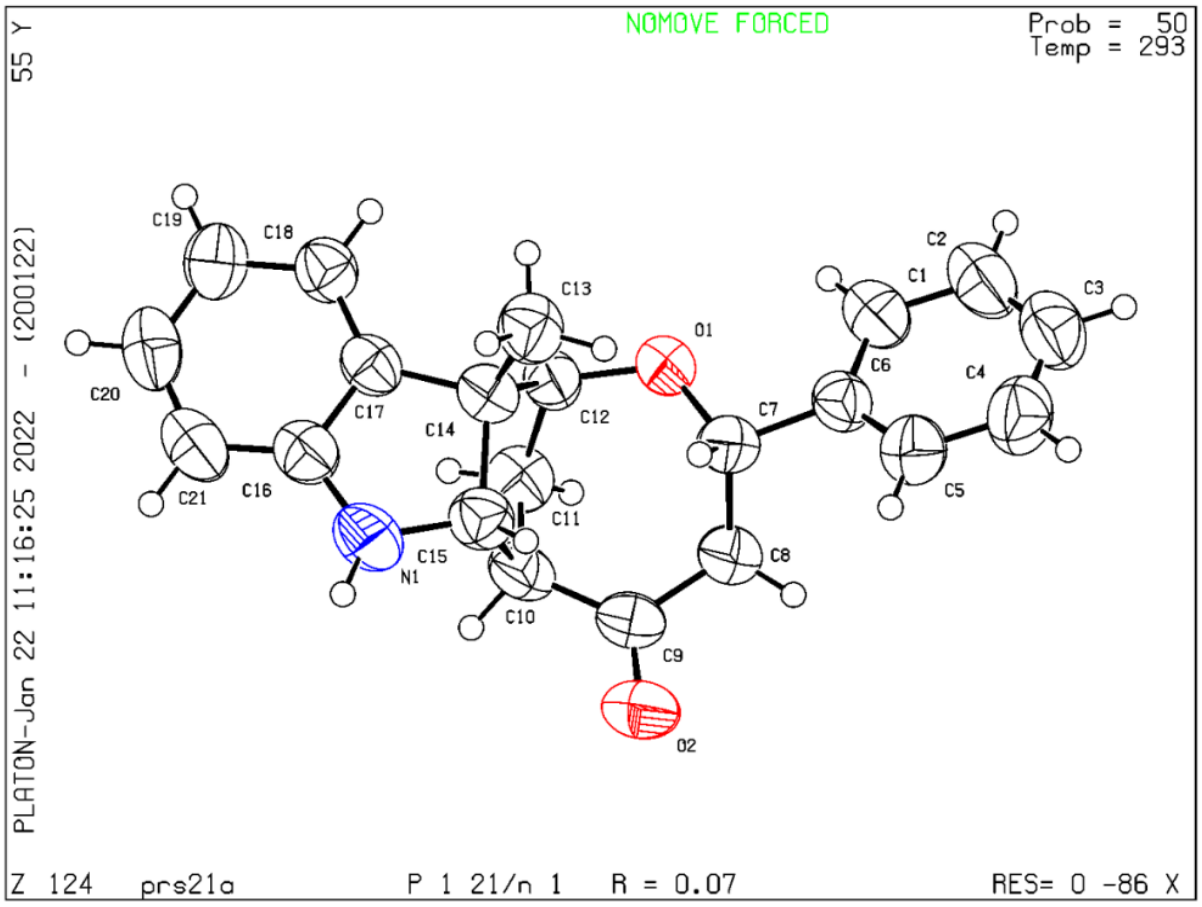


Figure S6: ORTEP representation of compound ***exo*-10c.**



The ellipsoid contour % probability levels in the caption for the image of ***exo*-10c** was 50%.

Table 4 Crystal data and structure refinement for PRS21A.

Identification code	PRS21A
Empirical formula	$C_{21}H_{21}NO_2$
Formula weight	319.39
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	13.2190(13)
b/Å	7.2388(5)
c/Å	17.8617(17)
α/°	90
β/°	97.632(9)
γ/°	90
Volume/Å^3	1694.0(3)
Z	4
ρ_{calc}g/cm^3	1.252
μ/mm^{-1}	0.080
F(000)	680.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.106 to 54.324
Index ranges	-16 ≤ h ≤ 16, -9 ≤ k ≤ 8, -22 ≤ l ≤ 22
Reflections collected	20210
Independent reflections	3586 [R_{int} = 0.1355, R_{sigma} = 0.1243]
Data/restraints/parameters	3586/0/218
Goodness-of-fit on F^2	0.961
Final R indexes [I>=2σ (I)]	R_1 = 0.0691, wR_2 = 0.1444
Final R indexes [all data]	R_1 = 0.1795, wR_2 = 0.1900
Largest diff. peak/hole / e Å^{-3}	0.18/-0.21

Crystal data and structure refinement for ***exo*-10d:** CCDC: **2178380**

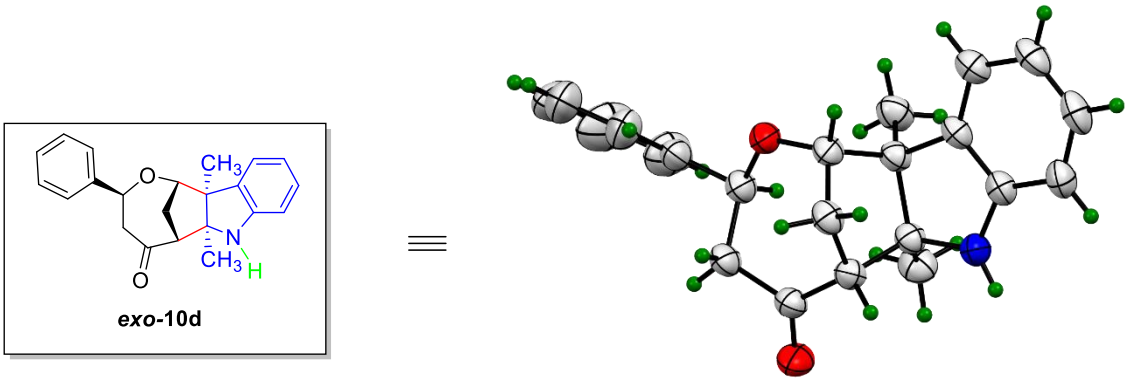
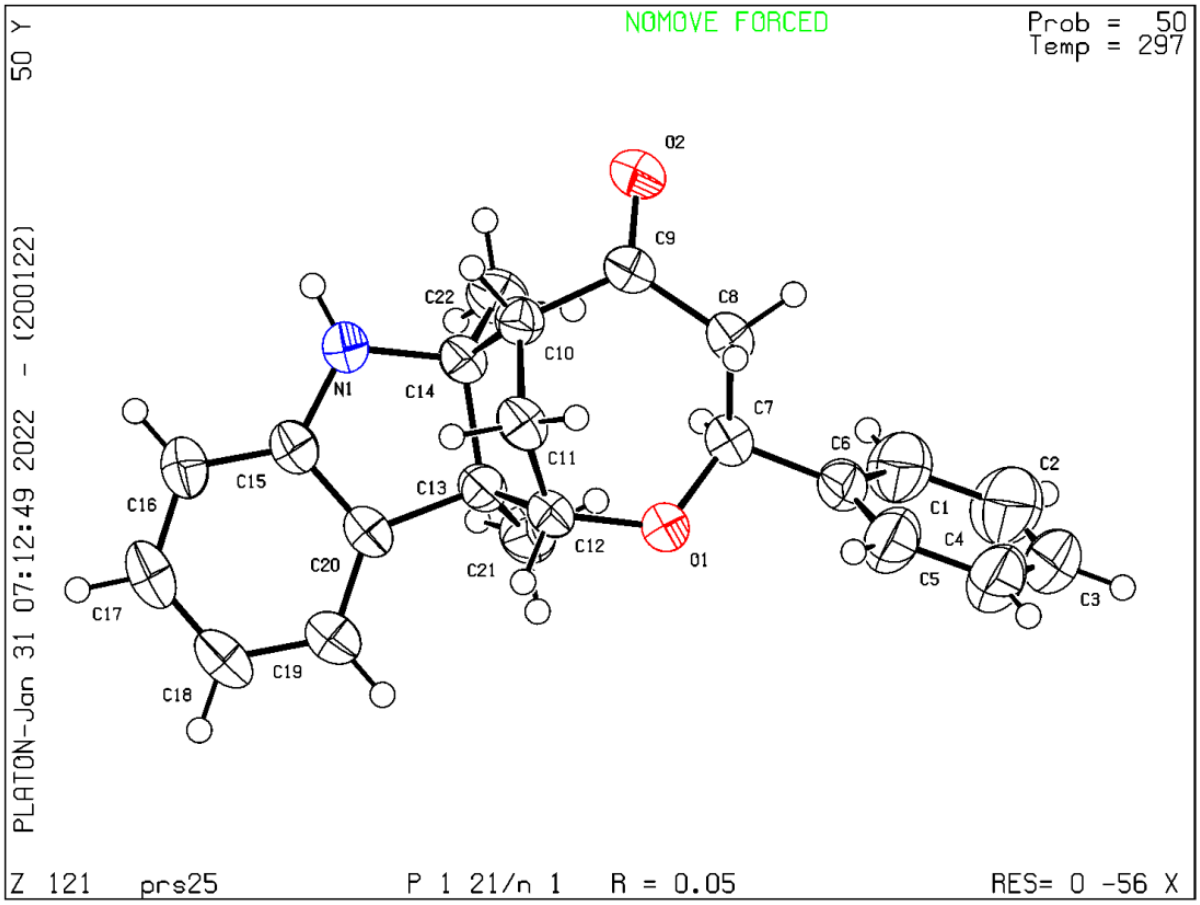


Figure S7: ORTEP representation of compound ***exo*-10d.**



The ellipsoid contour % probability levels in the caption for the image of ***exo*-10d** was 50%.

Table 5 Crystal data and structure refinement for prs25.

Identification code	prs25
Empirical formula	$C_{22}H_{23}NO_2$
Formula weight	333.41
Temperature/K	297.3(3)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	6.6818(2)
b/Å	8.9385(3)
c/Å	29.8319(8)
α/°	90
β/°	92.498(3)
γ/°	90
Volume/Å^3	1780.03(9)
Z	4
ρ_{calc}g/cm^3	1.244
μ/mm^{-1}	0.079
F(000)	712.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.758 to 50.048
Index ranges	-7 ≤ h ≤ 7, -10 ≤ k ≤ 9, -35 ≤ l ≤ 35
Reflections collected	15057
Independent reflections	3135 [R_{int} = 0.0373, R_{sigma} = 0.0333]
Data/restraints/parameters	3135/0/228
Goodness-of-fit on F^2	1.090
Final R indexes [I>=2σ (I)]	R_1 = 0.0463, wR_2 = 0.1216
Final R indexes [all data]	R_1 = 0.0621, wR_2 = 0.1302
Largest diff. peak/hole / e Å^{-3}	0.29/-0.31

Crystal data and structure refinement for **10e:** CCDC: **2178372**

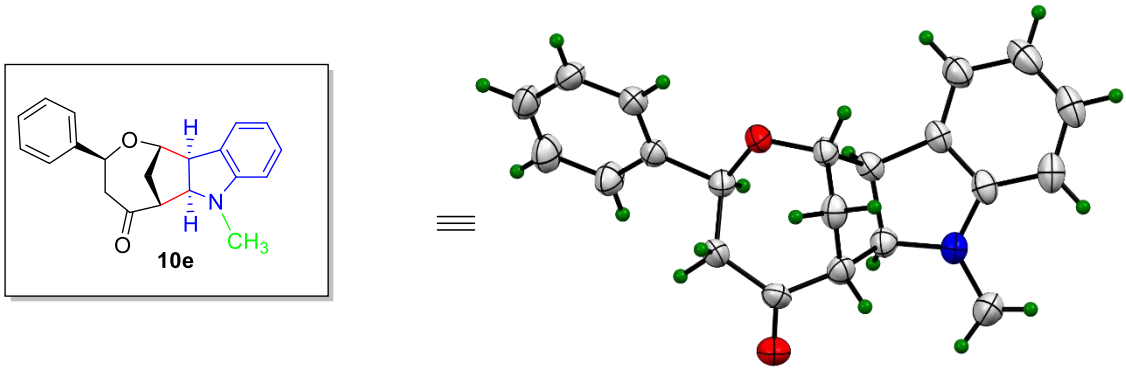


Figure S8: Figure S9: ORTEP representation of compound **10e.**

The ellipsoid contour % probability levels in the caption for the image of **10e** was 50%.

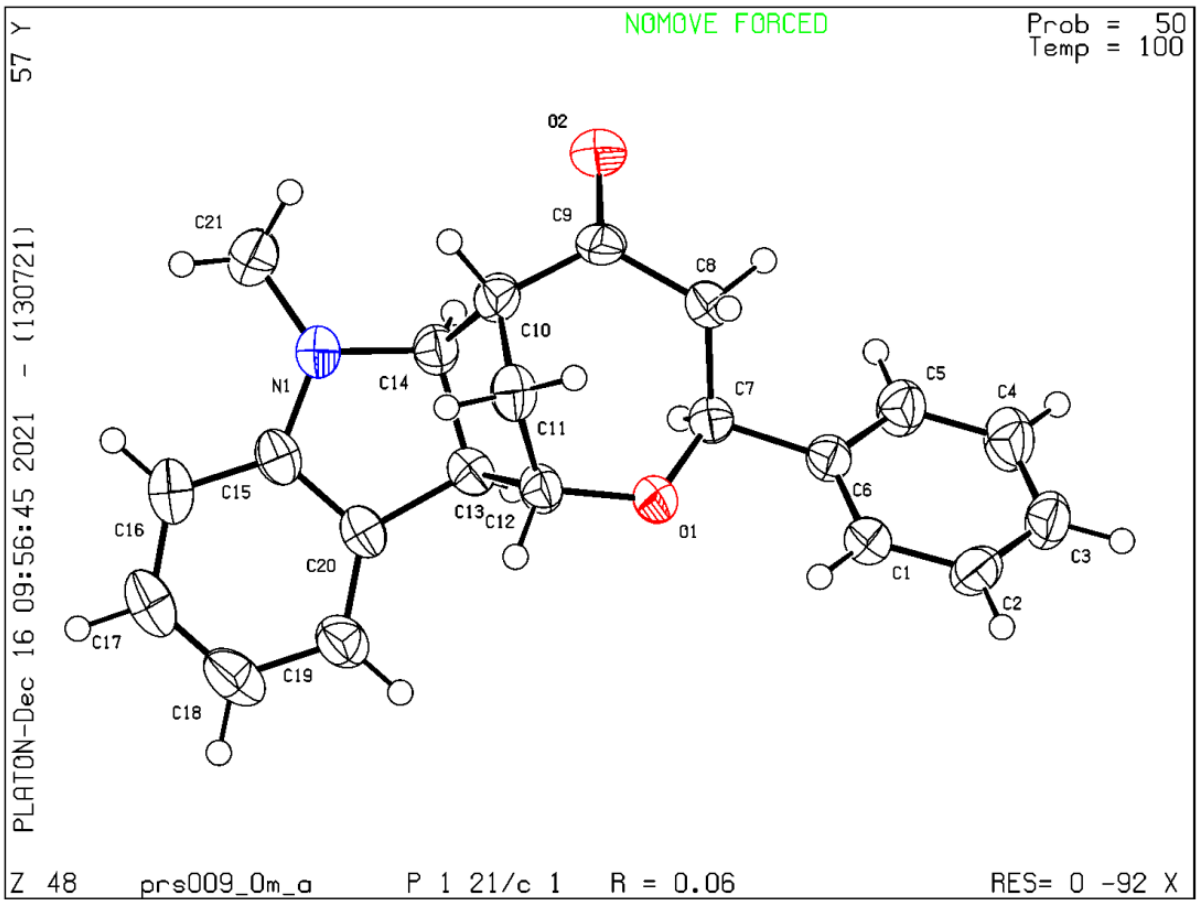


Table 6 Crystal data and structure refinement for PRS009_0m_a.

Identification code	PRS009_0m_a
Empirical formula	$C_{21}H_{21}NO_2$
Formula weight	319.39
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.0756(9)
b/Å	15.5049(16)
c/Å	11.4337(11)
α/°	90
β/°	94.894(4)
γ/°	90
Volume/Å^3	1603.0(3)
Z	4
ρ_{calc}g/cm^3	1.323
μ/mm^{-1}	0.085
F(000)	680.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.436 to 50.052
Index ranges	-10 ≤ h ≤ 10, -18 ≤ k ≤ 18, -13 ≤ l ≤ 13
Reflections collected	40159
Independent reflections	2837 [R_{int} = 0.1681, R_{sigma} = 0.1043]
Data/restraints/parameters	2837/0/218
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0559, wR_2 = 0.1439
Final R indexes [all data]	R_1 = 0.0803, wR_2 = 0.1551
Largest diff. peak/hole / e Å^{-3}	0.17/-0.20

Crystal data and structure refinement for ***endo*-12c:** CCDC: **2178385**

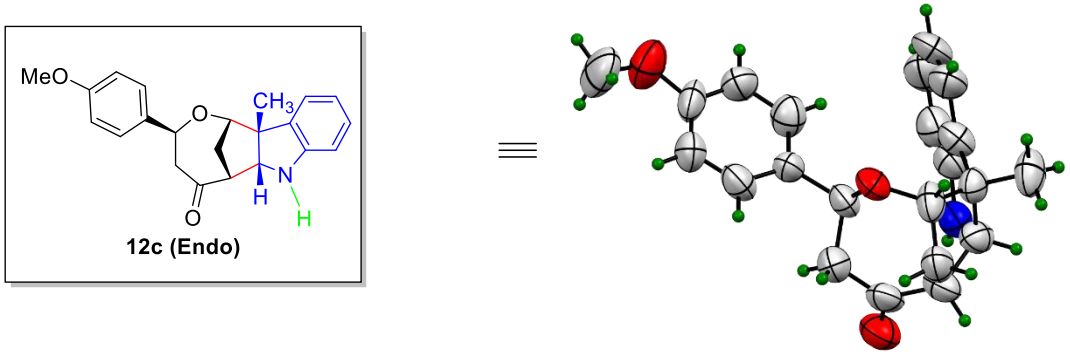


Figure S9: ORTEP representation of compound ***endo*-12c.**

The ellipsoid contour % probability levels in the caption for the image of ***endo*-12c** was 50%.

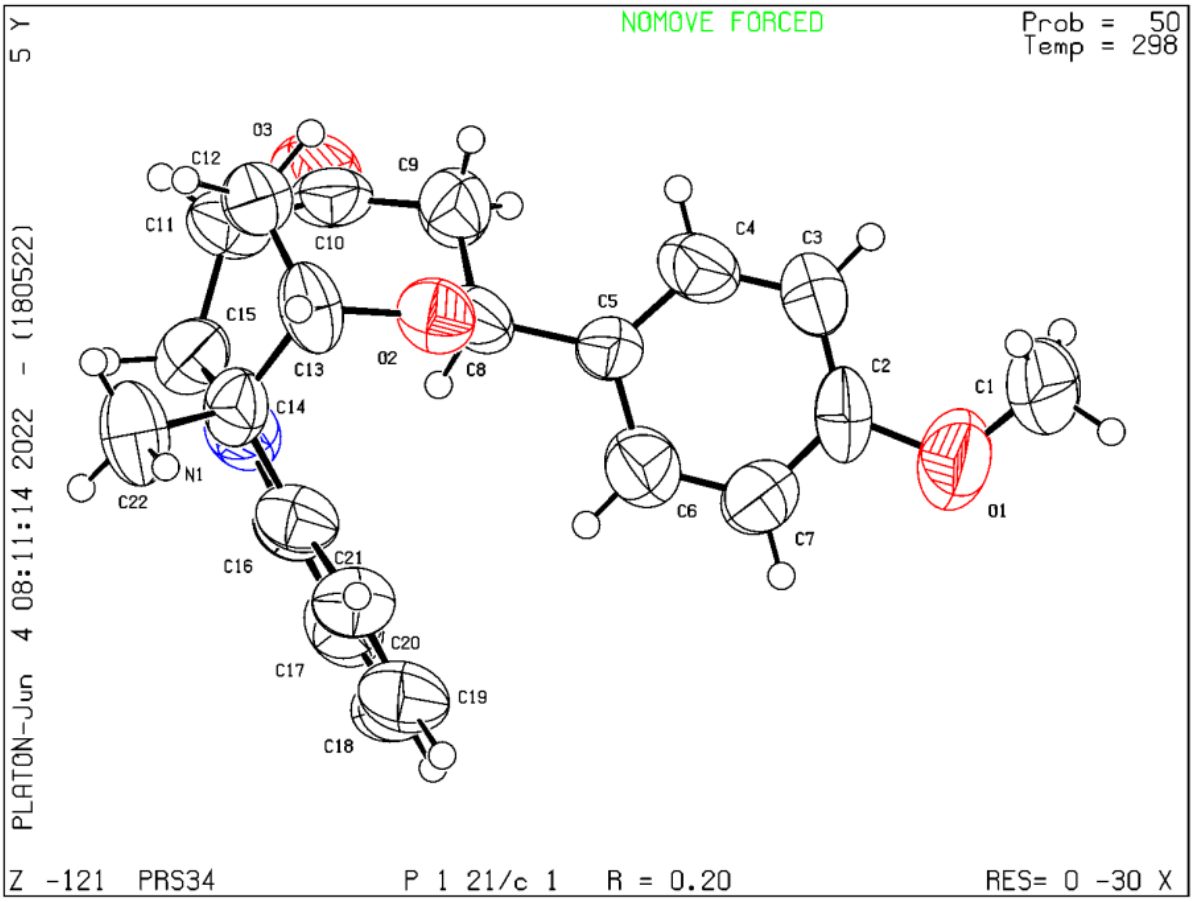


Table 7 Crystal data and structure refinement for PRS34.

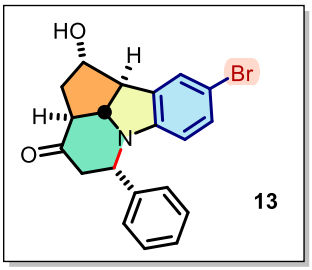
Identification code	PRS34
Empirical formula	$C_{22}H_{23}NO_3$
Formula weight	349.433
Temperature/K	298.4(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.8805(17)
b/Å	9.3053(8)
c/Å	12.5679(12)
α/°	90
β/°	105.167(10)
γ/°	90
Volume/Å^3	1792.5(3)
Z	4
ρ_{calc}g/cm^3	1.295
μ/mm^{-1}	0.086
F(000)	744.5
Crystal size/mm^3	0.6 × 0.4 × 0.2
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.12 to 53.98
Index ranges	-19 ≤ h ≤ 20, -11 ≤ k ≤ 11, -15 ≤ l ≤ 15
Reflections collected	20521
Independent reflections	3754 [R_{int} = 0.5022, R_{sigma} = 0.3022]
Data/restraints/parameters	3754/0/237
Goodness-of-fit on F^2	1.081
Final R indexes [I>=2σ (I)]	R_1 = 0.1963, wR_2 = 0.4376
Final R indexes [all data]	R_1 = 0.3863, wR_2 = 0.5547
Largest diff. peak/hole / e Å^{-3}	1.14/-0.96

Chapter 2 - Part B: Post-synthetic transformation: en route to the synthesis of A,B,E tricyclic core of calyciphylline B-Type alkaloids.

General Procedure B:

To a solution of (3+2) cycloadduct (1 Eq) in dry MeOH was added K_2CO_3 (2 Eq) at room temperature and stirred for 24 hours. After complete conversion of starting material, the reaction mixture was concentrated *in vaco* and the crude product was purified using silica gel column chromatography to obtain the desired product.

(1*R*,2a*S*,5*S*,10b*S*)-9-bromo-1-hydroxy-5-phenyl-2,2a,2a1,4,5,10b hexahydrobenzo[*b*]cyclopenta[*hi*]indolizin-3(1*H*)-one (13):



Compound **13** was synthesized from (3+2) cycloadduct **8a** (60 mg, 0.15 mmol) by following **general procedure B.** Yield: 58.8 mg, 98%, R_f: 0.5 (40% EtOAc/hexane), yellow Oil.

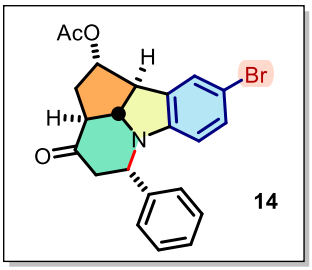
IR (neat): 3365, 2925, 2360, 2243, 1704 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.39 (m, 5H), 7.17-7.19 (m, 1H), 7.08 (ddd, 1H, *J* = 0.5 Hz, *J* = 2.0 Hz, *J* = 8.5 Hz), 6.10 (d, 1H, *J* = 8.5 Hz), 4.93 (dd, 1H, *J* = 6.5 Hz, *J* = 8.0 Hz), 4.85 (dd, 1H, *J* = 5.5 Hz, *J* = 8.0 Hz), 4.38 (d, 1H, *J* = 3.5 Hz), 3.88 (d, 1H, *J* = 8.5 Hz), 3.21-3.26 (m, 1H), 2.98 (dd, 1H *J* = 8.0 Hz, *J* = 14.0 Hz), 2.38 (dd, 1H, *J* = 6.0 Hz, *J* = 14.5 Hz), 2.08-2.12 (m, 1H), 1.69 (td, 2H, *J* = 3.5 Hz, *J* = 13.0 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 210.2, 149.7, 140.6, 131.2, 130.5, 129.0, 127.8, 127.6, 126.0, 108.8, 106.8, 79.6, 65.3, 57.2, 56.2, 53.0, 44.7, 36.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{19}BrNO_2$ $[M+H]^+$: 384.0599, found: 384.0599.

(1*R*,2a*S*,5*S*,10b*S*)-9-bromo-3-oxo-5-phenyl-1,2,2a,2a1,3,4,5,10b-octahydrobenzo[*b*]cyclopenta[*hi*]indolizin-1-yl acetate (14):



Compound **14** was synthesized by dissolving compound **13** (50 mg, 0.15 mmol) in 1ml pyridine, adding Ac_2O (3 Eq) dropwise at 0 °C and continued stirring for 8 hours at room temperature. After completion of reaction, pyridine was removed under reduced pressure and the crude was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase. Yield: 63.05 mg, 95%, R_f: 0.5 (40% EtOAc/hexane), yellow solid.

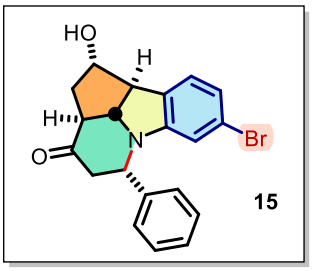
IR (neat): 3365, 2925, 2360, 2243, 1704 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.38 (m, 5H), 7.11 (ddd, 1H, *J* = 0.5 Hz, *J* = 2.0 Hz, *J* = 8.5 Hz), 6.12 (d, 1H, *J* = 8.5 Hz), 5.16 (d, 1H, *J* = 4.0 Hz), 4.86-4.92 (m, 2H), 3.92 (d, 1H, *J* = 8.5 Hz), 3.09-3.15 (m, 1H), 2.98 (dd, 1H, *J* = 8.0 Hz, *J* = 14.5 Hz), 2.85 (dd, 1H, 6.0 Hz, *J* = 14.5 Hz), 1.09 (m, 1H), 2.06 (s, 3H), 1.77 (td, 2H, *J* = 4.0 Hz, *J* = 14.0 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 209.2, 170.2, 149.5, 140.3, 131.5, 129.7, 129.1, 128.1, 127.8, 126.1, 109.2, 106.8, 81.7, 65.1, 56.9, 53.9, 53.4, 44.3, 33.3, 21.2.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{21}BrNO_3$ $[M+H]^+$: 426.0705, found: 426.0702.

(1*R*,2a*S*,5*S*,10b*S*)-8-bromo-1-hydroxy-5-phenyl-2,2a,2a1,4,5,10b-hexahydrobenzo[*b*]cyclopenta[*hi*]indolizin-3(1*H*)-one (15):



Compound **15** was synthesized from (3+2) cycloadduct **10b** (50 mg, 0.13 mmol) by following **general procedure B.** Yield: 47.5 mg, 95%, R_f: 0.5 (40% EtOAc/hexane), yellow oil.

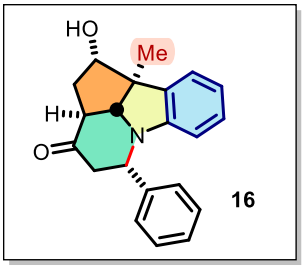
IR (neat): 3403, 2920, 2851, 1706 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.30-7.40 (m, 5H), 6.93 (dd, 1H, *J* = 1.0 Hz, *J* = 8.0 Hz), 6.74 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 6.36 (d, 1H, *J* = 1.5 Hz), 4.87-4.92 (m, 2H), 4.36 (d, 1H, *J* = 3.0 Hz), 3.83 (d, 1H, *J* = 8.0 Hz), 3.20-3.25 (m, 1H), 2.98 (dd, 1H, *J* = 8.0 Hz, *J* = 14.5 Hz), 2.85 (dd, 1H, *J* = 6 Hz, *J*= 14.5 Hz), 2.09 (dd, 1H, *J* = 7.0 Hz, *J* = 13.5 Hz), 1.70 (td, 2H, *J* = 3.5 Hz, *J* = 13.0 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.0, 152.0, 140.3, 129.1, 127.8, 127.4, 126.1, 125.7, 122.5, 120.3, 108.6, 79.7, 65.5, 56.9, 56.0, 53.0, 44.4, 36.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{19}BrNO_2$ $[M+H]^+$: 384.0599, found: 384.0592.

(1*R*,2a*S*,5*S*,10b*S*)-1-hydroxy-10b-methyl-5-phenyl-2,2a,2a1,4,5,10b-hexahydrobenzo[*b*]cyclopenta[*hi*]indolizin-3(1*H*)-one (16):



Compound **16** was synthesized from (3+2) cycloadduct **10c** (50 mg, 0.15 mmol) by following **general procedure B.** Yield: 49.5 mg, 99%, R_f: 0.5 (40% EtOAc/hexane), yellow oil.

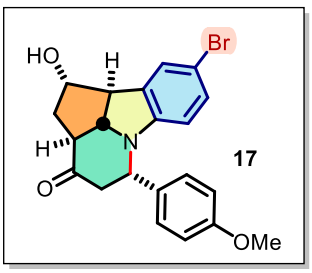
IR (neat): 3444, 3028, 2924, 1702 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.35-7.40 (m, 4H), 7.28-7.31 (m, 1H), 7.05 (td, 1H, *J* = 1.5 Hz, *J* = 8.0 Hz), 7.01 (d, 1H, *J* = 7.5 Hz), 6.68 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.36 (d ,1H, *J* = 8.0 Hz), 5.02 (t, 1H, *J* = 6.5 Hz), 4.24 (d, 1H, *J* = 7.0 Hz), 4.21 (d, 1H, *J* = 3.0 Hz), 3.14-3.19 (m, 1H), 2.96 (dd, 1H, *J* = 7.0 Hz, *J* = 14.5 Hz), 2.87 (dd, 1H, *J* = 6.0 Hz, *J* = 14.0 Hz), 2.01-2.05 (m, 1H), 1.71 (td, 2H, *J* = 3.5 Hz, *J* = 13.0 Hz), 1.49 (s, 3H).

^{3}C-NMR (125 MHz, $CDCl_3$): δ = 210.8, 150.3, 140.8, 134.9, 128.9, 128.5, 127.6, 126.3, 123.1, 118.0, 105.8, 80.3, 71.9, 58.7, 58.0, 52.8, 43.4, 37.2, 20.9

HRMS (ESI-TOF) *m/z*: $[M+H]^+$: calcd for $C_{21}H_{22}NO_2$ 320.1651, found: 320.1649.

(1*R*,2a*S*,5*S*,10b*S*)-9-bromo-1-hydroxy-5-(4-methoxyphenyl)-2,2a,2a1,4,5,10b-hexahydrobenzo[*b*]cyclopenta[*hi*]indolizin-3(1*H*)-one (17):



Compound **17** was synthesized from (3+2) cycloadduct **12a** (30 mg, 0.072 mmol) by following **general procedure B.** Yield: 29.4 mg, 98%, R_f: 0.4 (30% EtOAc/hexane), yellow Oil.

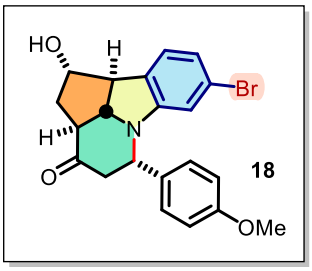
IR (neat): 3397, 2960, 2924, 2852, 1703 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.28 (m, 2H), 7.17 (bs, 1H), 7.10 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz), 6.88-6.90 (m, 2H), 6.14 (d, 1H, *J* = 8.5 Hz), 4.83-4.88 (m, 2H), 4.80 (d, 1H, *J* = 3.5 Hz), 3.86 (d, 1H, *J* = 8.5 Hz), 3.80 (s, 3H), 3.17-3.23 (m, 1H), 2.95 (dd, 1H *J* = 7.5 Hz, *J* = 14.5 Hz), 2.80 (dd, 1H, *J* = 6.0 Hz, *J* = 14.5 Hz), 2.08 (dd, 1H, *J* = 7.0 Hz, *J* = 13.5 Hz), 1.68 (td, 2H, *J* = 3.5 Hz, *J* = 13.0 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.1, 159.2, 149.8, 132.4, 131.2, 130.6, 127.7, 127.3, 114.4, 108.7, 106.9, 79.7, 65.2, 56.6, 56.2, 55.3, 52.8, 44.4, 36.5.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{21}BrNO_3$ $[M+H]^+$: 414.0705, found: 414.0684.

(1*R*,2a*S*,5*S*,10b*S*)-8-bromo-1-hydroxy-5-(4-methoxyphenyl)-2,2a,2a1,4,5,10b-hexahydrobenzo[*b*]cyclopenta[*hi*]indolizin-3(1*H*)-one (18):



Compound **18** was synthesized from (3+2) cycloadduct **12b** (30 mg, 0.072 mmol) by following **general procedure B.** Yield: 29.1 mg, 97%, R_f: 0.4 (30% EtOAc/hexane), yellow gel.

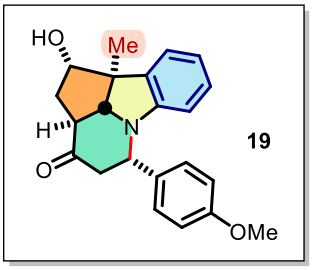
IR (neat): 3397, 2966, 2924, 2835, 1702 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.28 (m, 2H), 6.89-6.93 (m, 3H), 6.74 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.40 (d, 1H, *J* = 1.5 Hz), 4.83-4.89 (m, 2H), 4.30 (d, 1H, *J* = 3.0 Hz), 3.81-3.82 (m, 4H), 3.17-3.22 (m, 1H), 2.96 (dd, 1H, *J* = 7.0 Hz, *J* = 14.0 Hz), 2.82 (dd, 1H, *J* = 6.0 Hz, *J* = 14.5 Hz), 2.74 (s, 1H), 2.05-2.09 (m, 1H), 1.68 (td, 1H, *J* = 3.5 Hz, *J* = 13.5 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.1, 159.2, 152.1, 132.1, 127.5, 127.4, 125.7, 122.5, 120.2, 114.4, 108.6, 79.7, 65.3, 56.3, 55.9, 55.3, 52.9, 44.2, 36.4.

HRMS (ESI-TOF) *m/z*: calcd for $C_{21}H_{21}BrNO_3$ $[M+H]^+$: 414.0705, found: 414.0698.

(1*R*,2a*S*,5*S*,10b*S*)-1-hydroxy-5-(4-methoxyphenyl)-10b-methyl-2,2a,2a1,4,5,10b-hexahydrobenzo[*b*]cyclopenta[*hi*]indolizin-3(1*H*)-one (19):



Compound **19** was synthesized from (3+2) cycloadduct **12c** (50 mg, 0.14 mmol) by following **general procedure B.** Yield: 48.5 mg, 97%, R_f: 0.4 (30% EtOAc/hexane), yellow Oil.

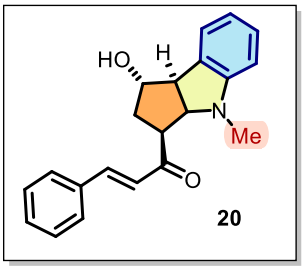
IR (neat): 3438, 2963, 2922, 2857, 1699 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29-7.32 (m, 2H), 7.06 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 7.00 (dd, 1H, *J* = 0.5 Hz, *J* = 7.0 Hz), 6.88-6.91 (m, 2H), 6.68 (td, 1H, 1.0 Hz, *J* = 7.5 Hz), 6.39 (d, 1H, *J* = 7.5 Hz), 5.01 (t, 1H, *J* = 6.0 Hz), 8.40 (d, 1H, *J* = 3.5 Hz), 4.16 (d, 1H, *J* = 7.0 Hz), 3.80 (s, 3H), 3.10-3.15 (m, 1H), 2.94 (dd, 1H, *J* = 6.0 Hz, *J* = 14.0 Hz), 2.84 (dd, 1H, *J* = 5.5 Hz, *J* = 14.5 Hz), 2.01 (dd, 1H, *J* = 7.5 Hz, *J* = 13.5 Hz), 1.70 (td, 2H, *J* = 3.5 Hz, *J* = 13.0Hz), 1.47 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.9, 158.9, 150.3, 135.1, 132.5, 128.5, 127.6, 123.1, 118.0, 114.2, 105.9, 80.4, 71.8, 58.6, 56.3, 55.3, 52.6, 43.0, 37.4, 20.8.

HRMS (ESI-TOF) *m/z*: calcd for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1756, found: 350.1759.

(*E*)-1-((1*S*,3*R*,3a*R*,8b*S*)-1-hydroxy-4-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-yl)-3-phenylprop-2-en-1-one (20):



Compound **20** was synthesized from (3+2) cycloadduct **10e** (50 mg, 0.15 mmol) by following **general procedure B.** Yield: 38.8 mg, 97%, R_f: 0.5 (40% EtOAc/hexane), yellow oil.

IR (neat): 3398, 3052, 2926, 1680, 1603 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, 1H, *J* = 16.0 Hz), 7.60-7.61 (m, 2H), 7.43-7.45 (m, 3H), 7.16 (d, 1H, *J* = 70 Hz), 7.09 (t, 1H, *J* = 7.5 Hz), 6.93 (d, 1H, *J* = 16.0 Hz), 6.66 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.38 (d, 1H, *J* = 8.0 Hz), 4.30-4.33 (m, 2H), 4.13 (d, 1H, *J* = 9.0 Hz), 3.85 (d, 1H, *J*= 9.0 Hz), 3.57-3.59 (m, 1H), 2.88 (s, 3H), 2.11-2.17 (m, 1H), 2.06-2.09 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 203.8, 151.3, 145.1, 134.1, 131.1, 129.4, 129.1, 128.6, 128.2, 124.5, 124.4, 117.6, 106.1, 80.7, 74.6, 57.7, 55.1, 36.8, 33.8.

HRMS (ESI-TOF) *m/z*: $[M+H]^+$: calcd for $C_{21}H_{22}NO_2$ 320.1651, found: 320.1653.

Single crystal data:

Crystal data and structure refinement for **14:** CCDC: **2178373**

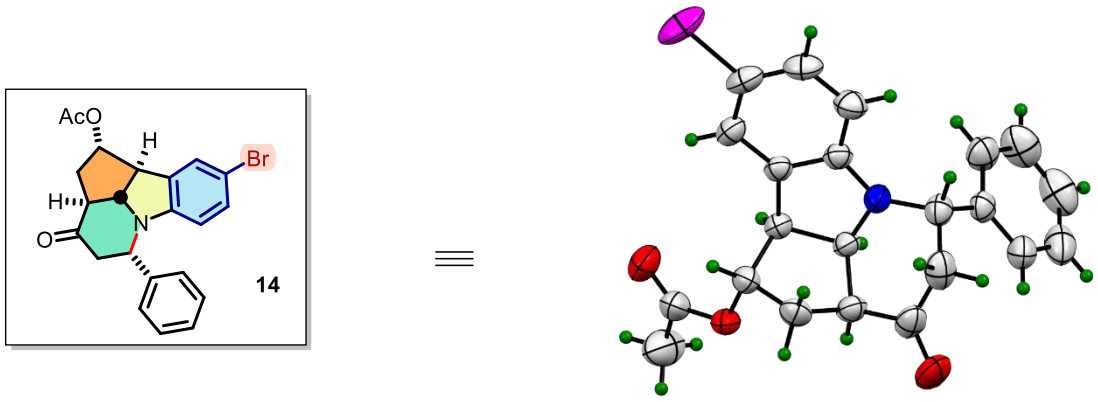


Figure S10: ORTEP representation of compound **14.**

The ellipsoid contour % probability levels in the caption for the image of **14** was 50%.

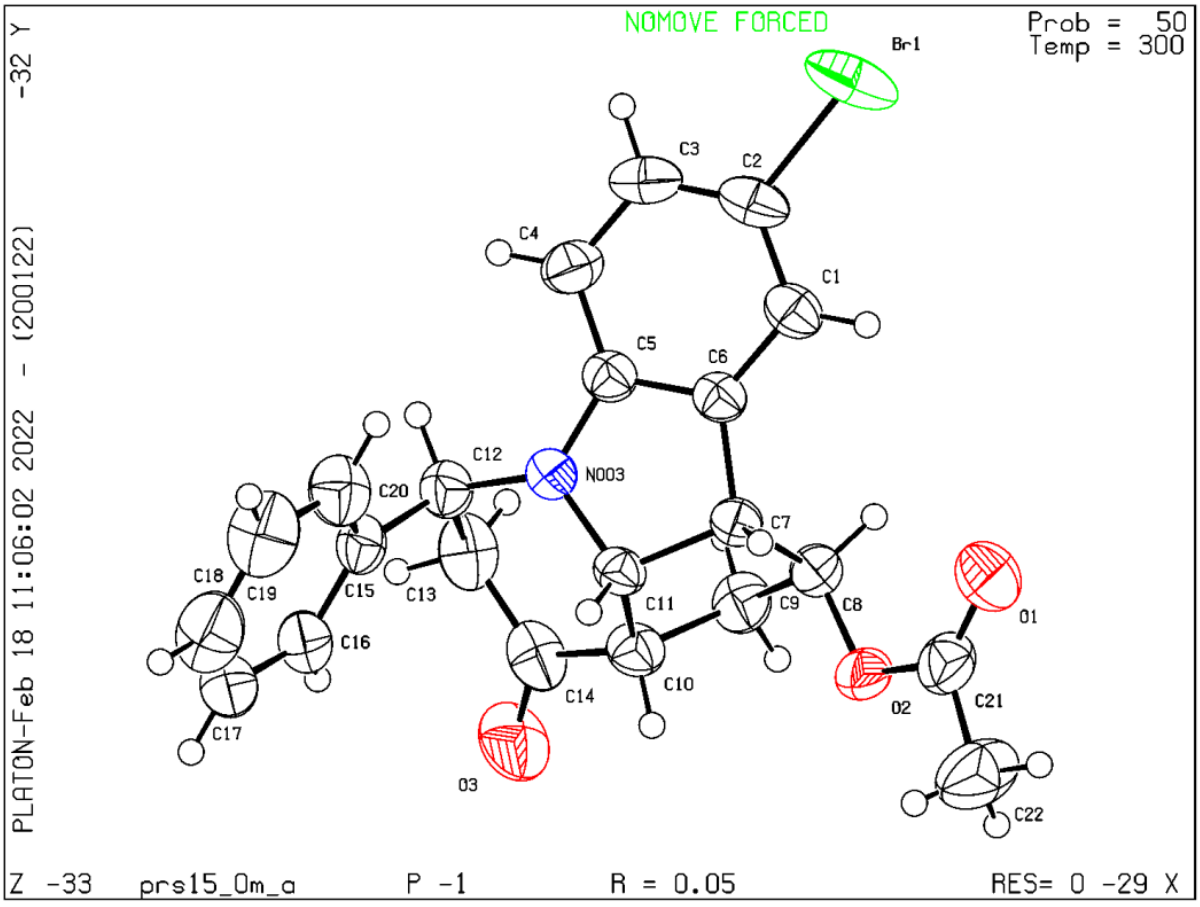


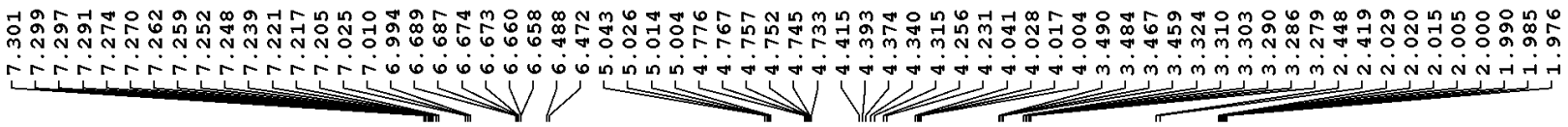
Table 1 Crystal data and structure refinement for PRS15_0m_a.

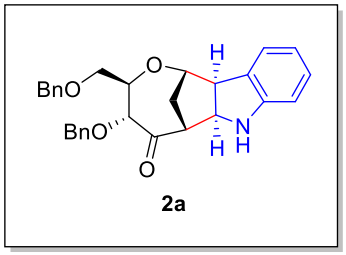
Identification code	PRS15_0m_a
Empirical formula	$C_{22}H_{20}BrNO_3$
Formula weight	426.30
Temperature/K	300.0
Crystal system	triclinic
Space group	P-1
a/Å	9.5761(12)
b/Å	10.4768(12)
c/Å	11.0552(13)
α/°	87.039(5)
β/°	67.724(4)
γ/°	69.434(4)
Volume/Å^3	956.7(2)
Z	2
ρ_{calc}g/cm^3	1.480
μ/mm^{-1}	2.171
F(000)	436.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4 to 50.042
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -13 ≤ l ≤ 13
Reflections collected	21477
Independent reflections	3393 [R_{int} = 0.0579, R_{sigma} = 0.0324]
Data/restraints/parameters	3393/0/245
Goodness-of-fit on F^2	1.093
Final R indexes [I>=2σ (I)]	R_1 = 0.0525, wR_2 = 0.1358
Final R indexes [all data]	R_1 = 0.0623, wR_2 = 0.1428
Largest diff. peak/hole / e Å^{-3}	0.96/-0.79

Compound Characterization: ^{1}H, ^{13}C, DEPT 135 NMR data

Chapter 2 - Part A: A Ring Expansion–Stereoselective Cycloaddition of Carbohydrate-Derived Donor–Acceptor Cyclopropanes: Synthesis of Bridged Oxepanone–Indole Hybrids.

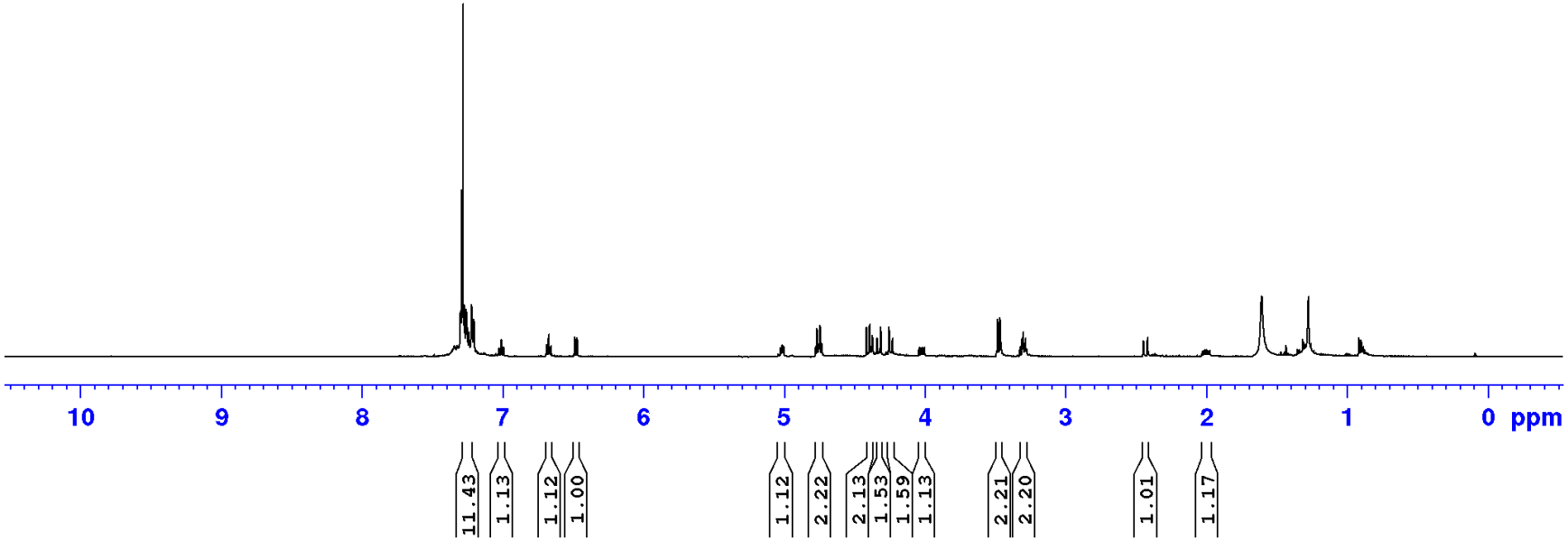
Chapter 2 - Part B: Post-synthetic transformation: en route to the synthesis of A,B,E tricyclic core of calyciphylline B-Type alkaloids.

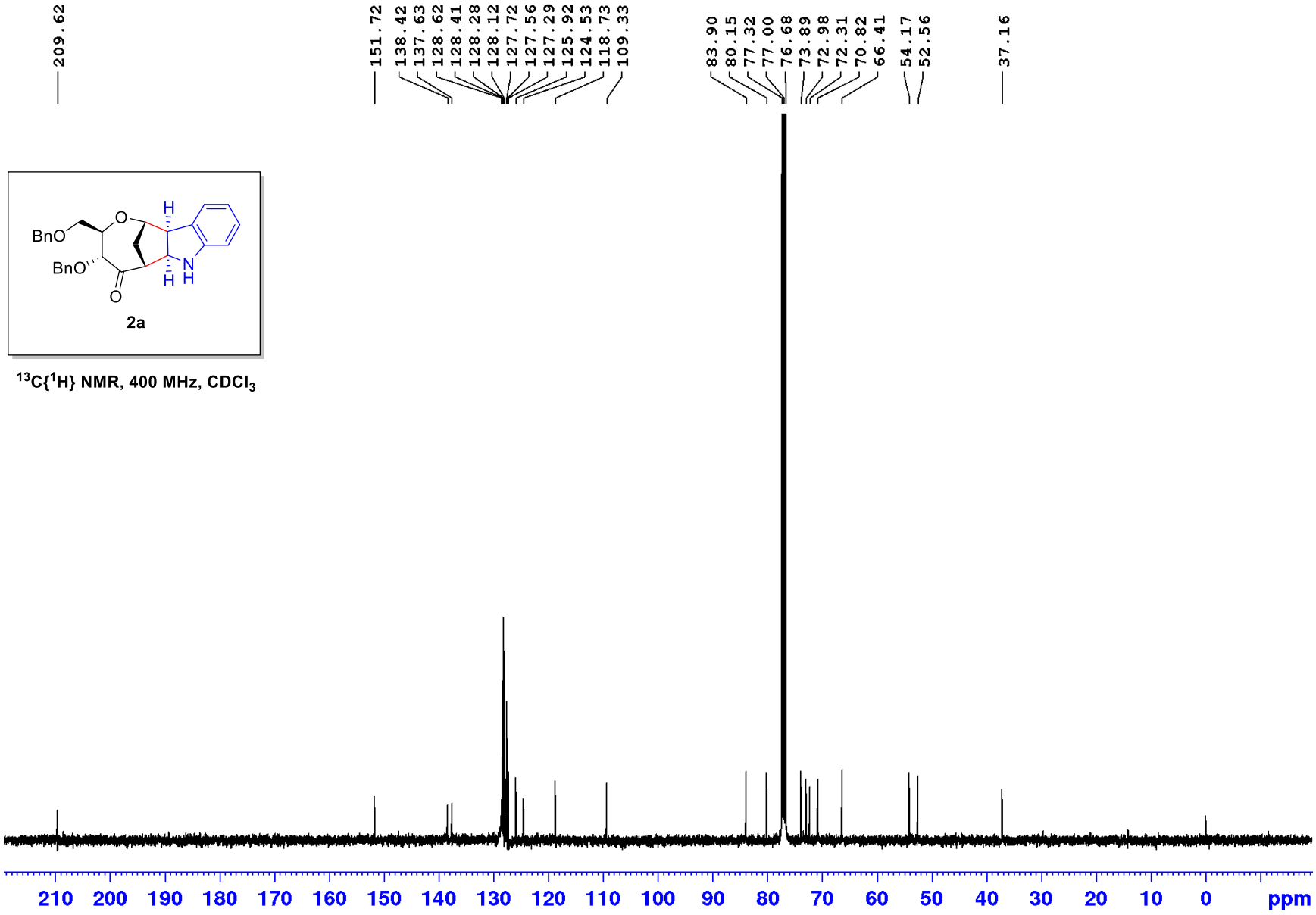




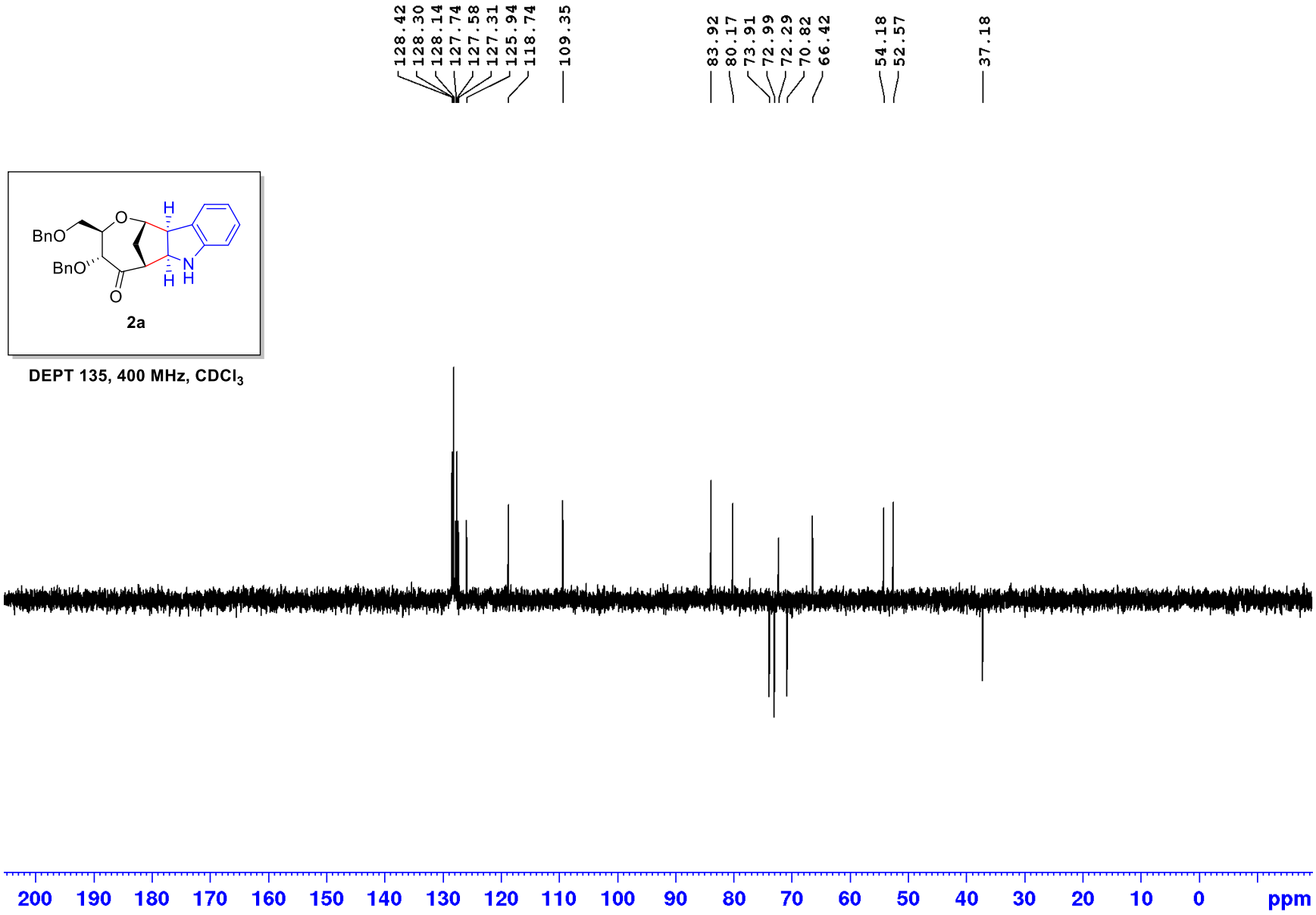
2a

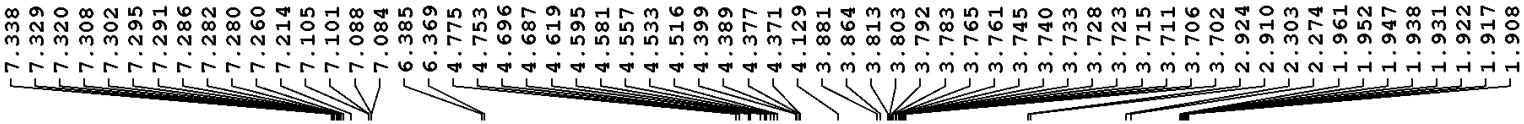
^{1}H NMR, 500 MHz, $CDCl_3$

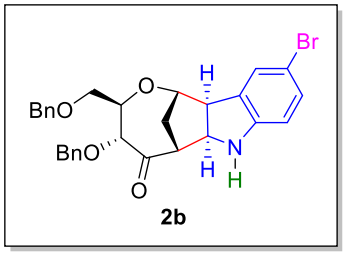




$^{13}C\{^{1}H\}$ NMR, 400 MHz, $CDCl_3$

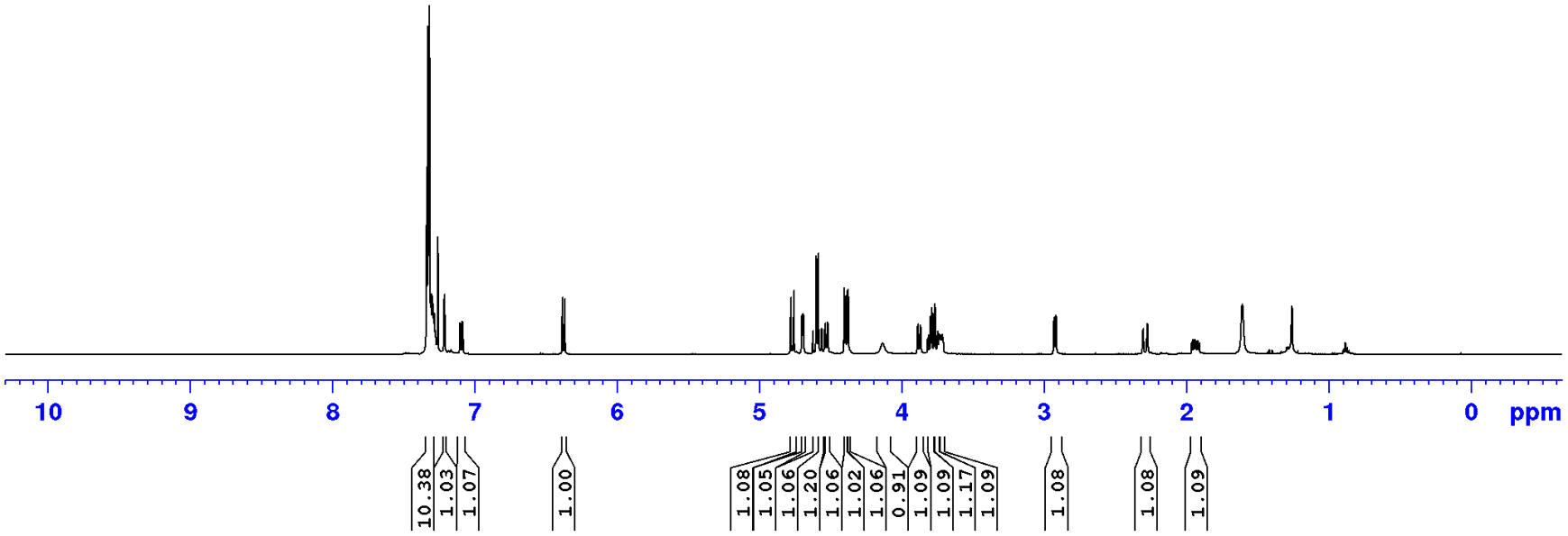

128.42
128.30
128.14
127.74
127.58
127.31
125.94
118.74
109.35
83.92
80.17
73.91
72.99
72.29
70.82
66.42
54.18
52.57
37.18
BnO
BnO
O
H
N
H
O
2a
DEPT 135, 400 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

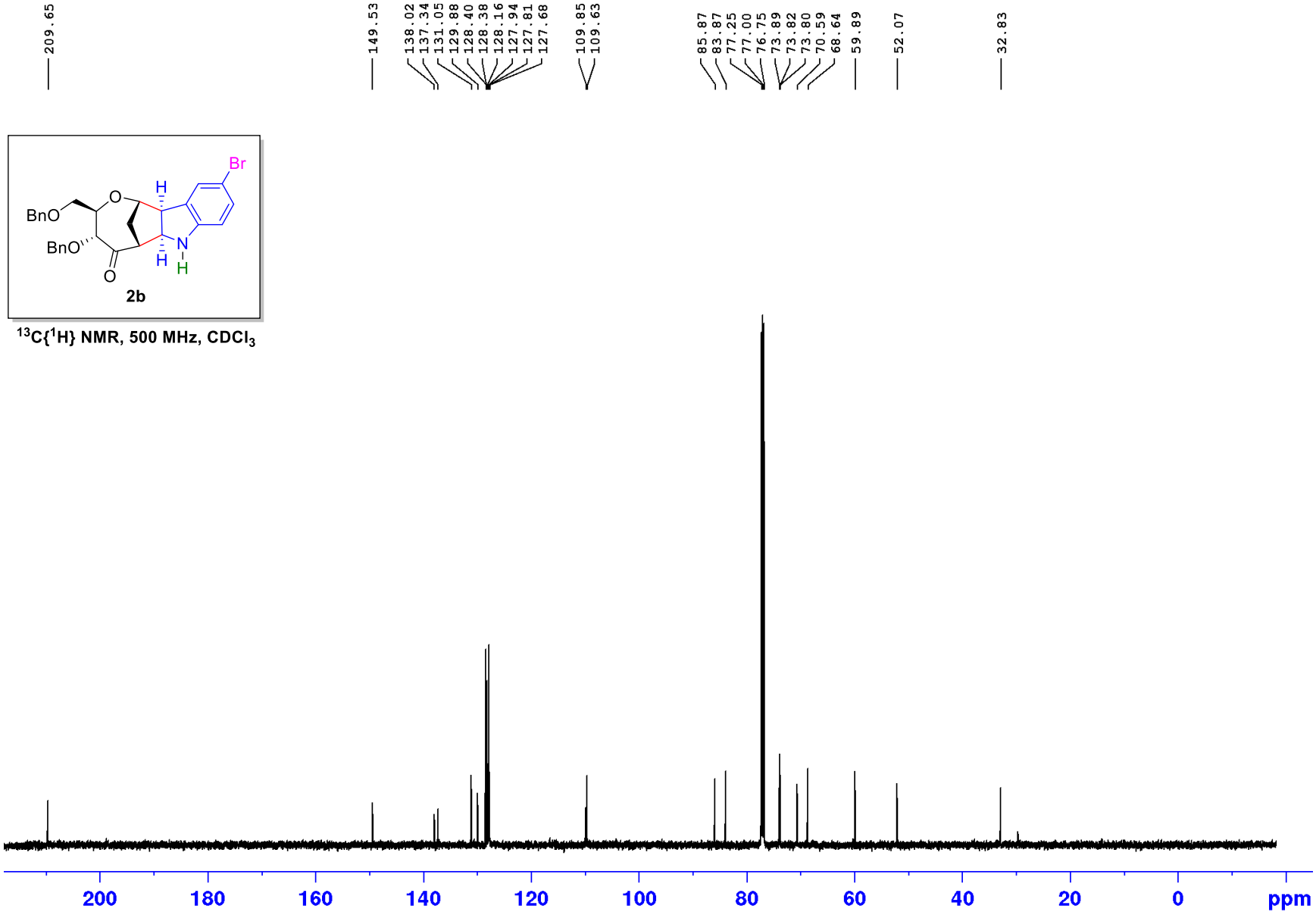




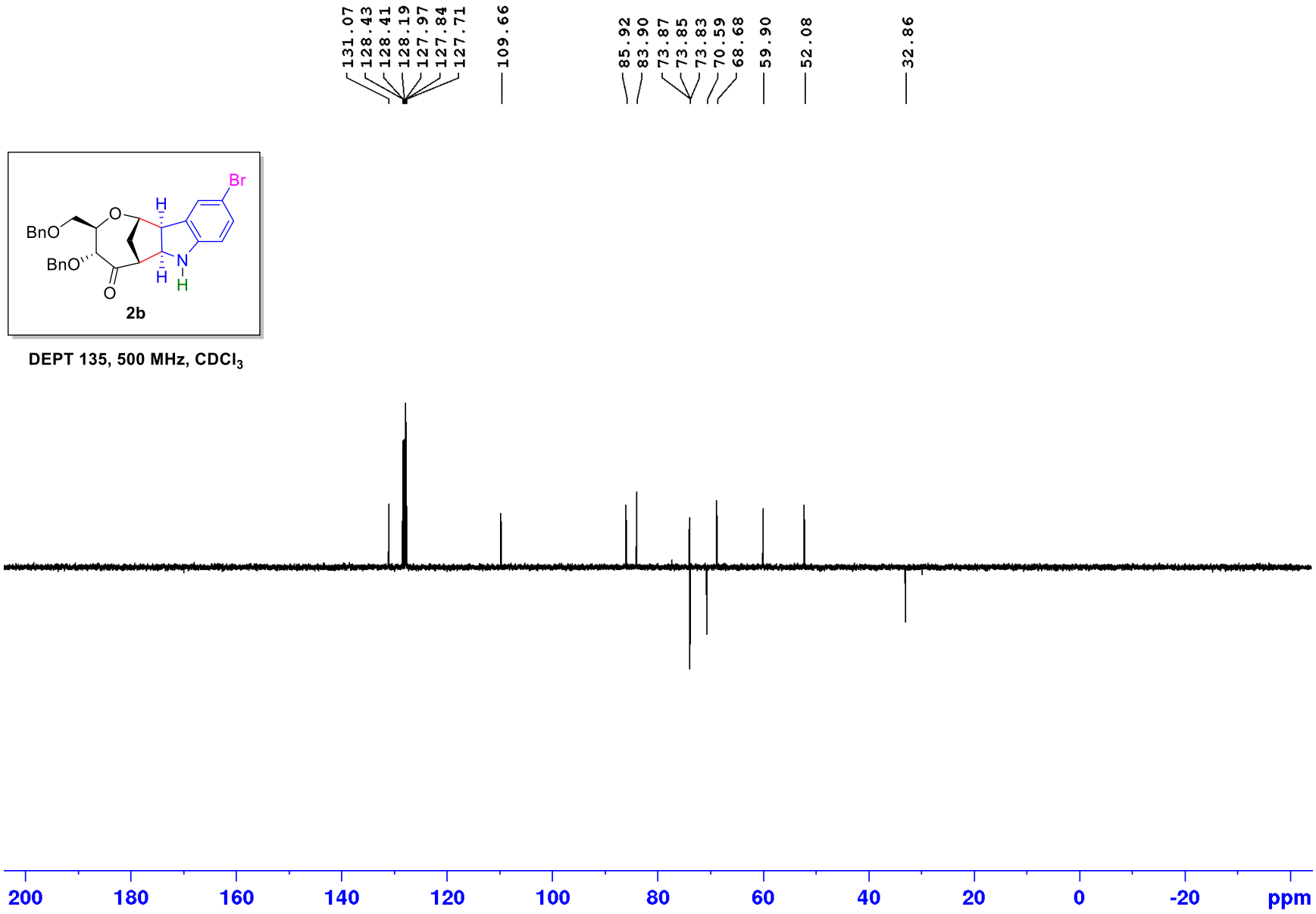
2b

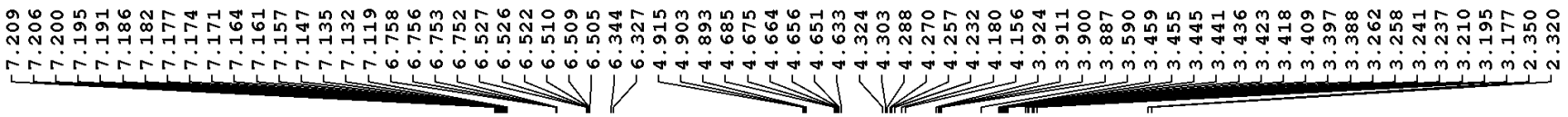
^{1}H NMR, 500 MHz, $CDCl_3$

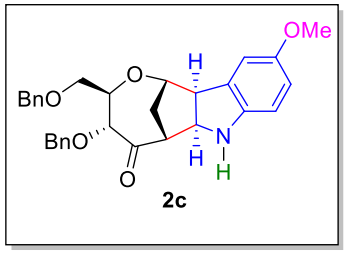




$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

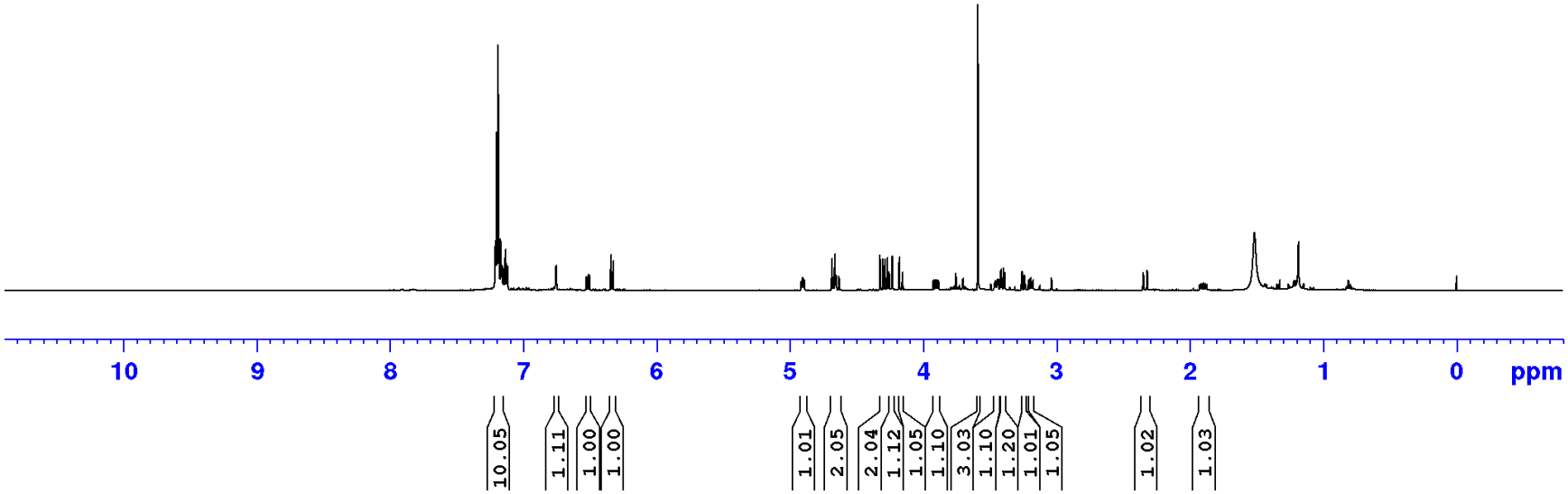

131.07
128.43
128.41
128.19
127.97
127.84
127.71
109.66
85.92
83.90
73.87
73.85
73.83
70.59
68.68
59.90
52.08
32.86
Br
H
O
BnO
BnO
N
H
H
O
2b
DEPT 135, 500 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

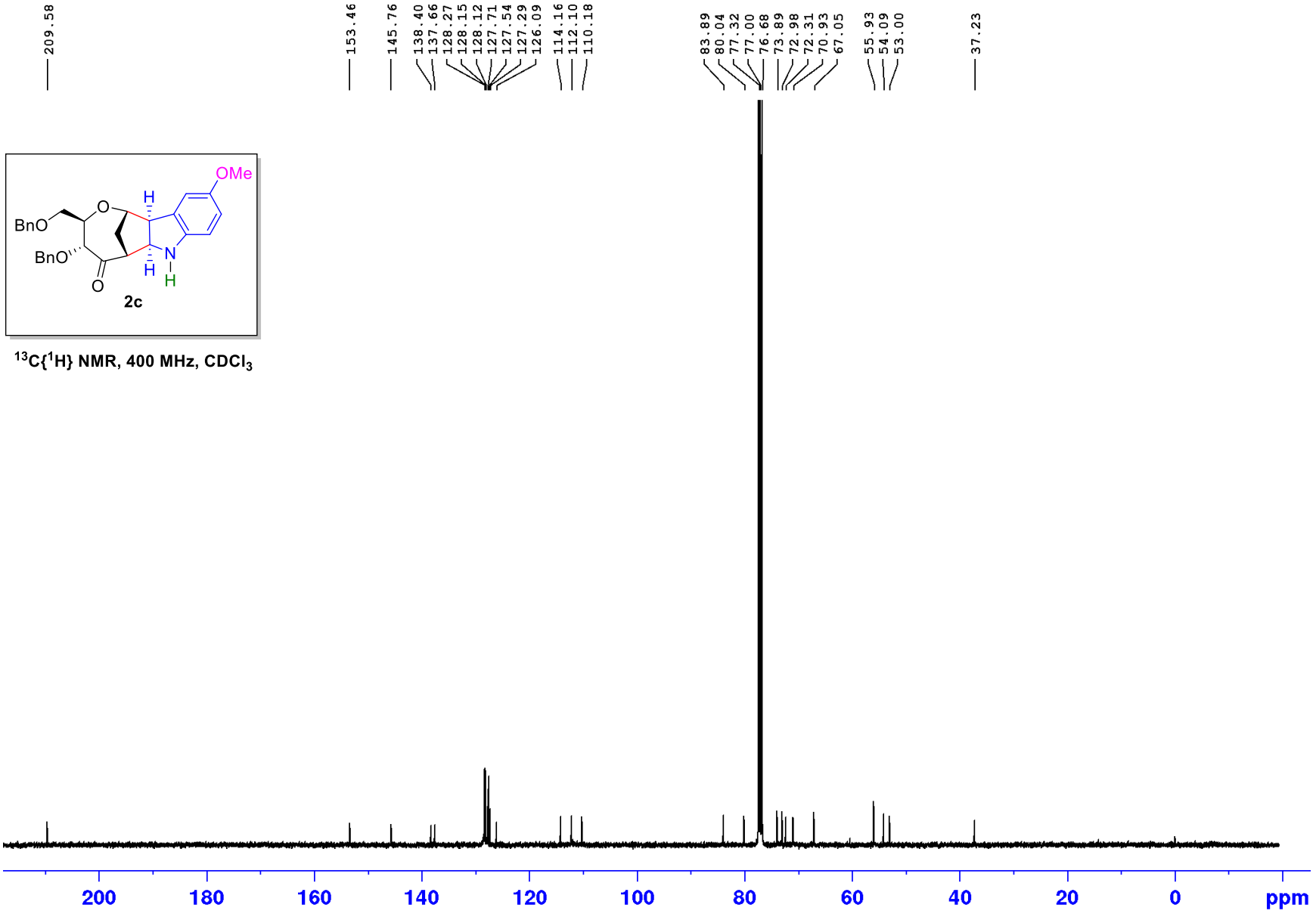




2c

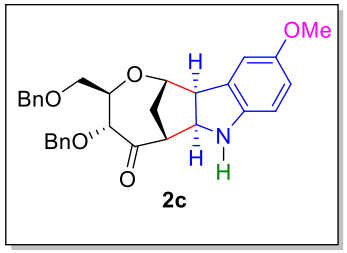
^{1}H NMR, 500 MHz, $CDCl_3$





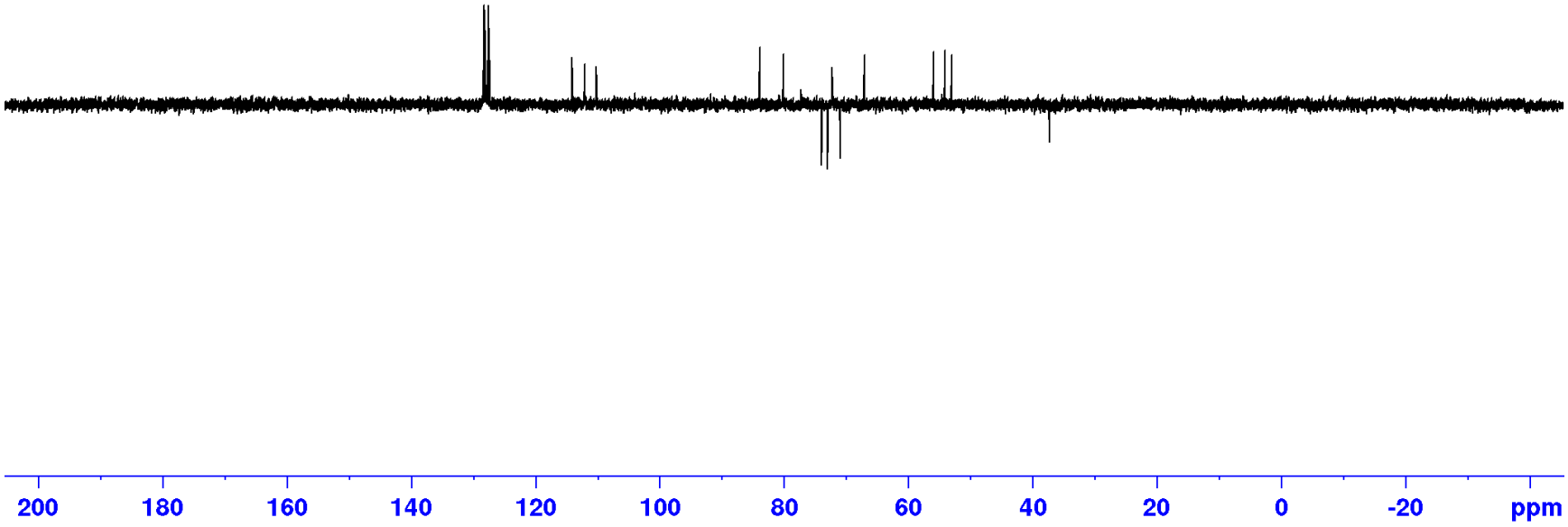
$^{13}C\{^{1}H\}$ NMR, 400 MHz, $CDCl_3$

128.29
128.17
128.14
127.74
127.57
127.32
114.15
112.08
110.21
83.91
80.06
73.92
72.99
72.27
70.93
67.06
55.93
54.10
53.01
37.26

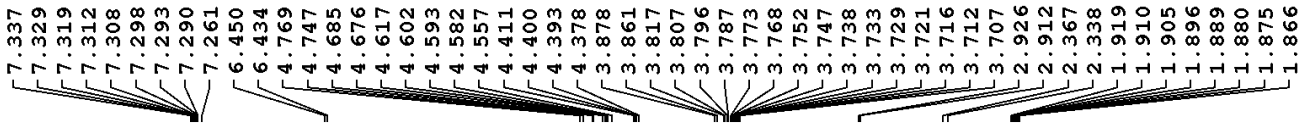


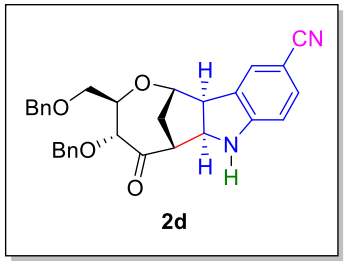
2c

DEPT 135, 400 MHz, $CDCl_3$



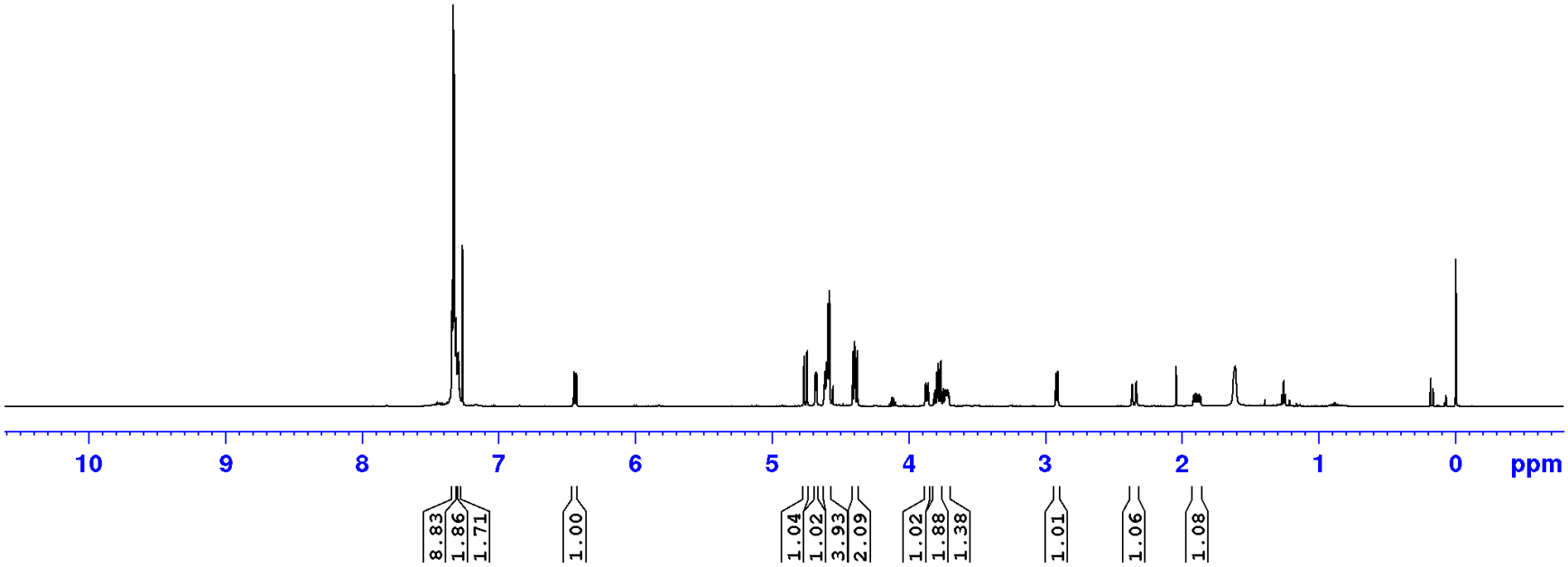
200 180 160 140 120 100 80 60 40 20 0 -20 ppm

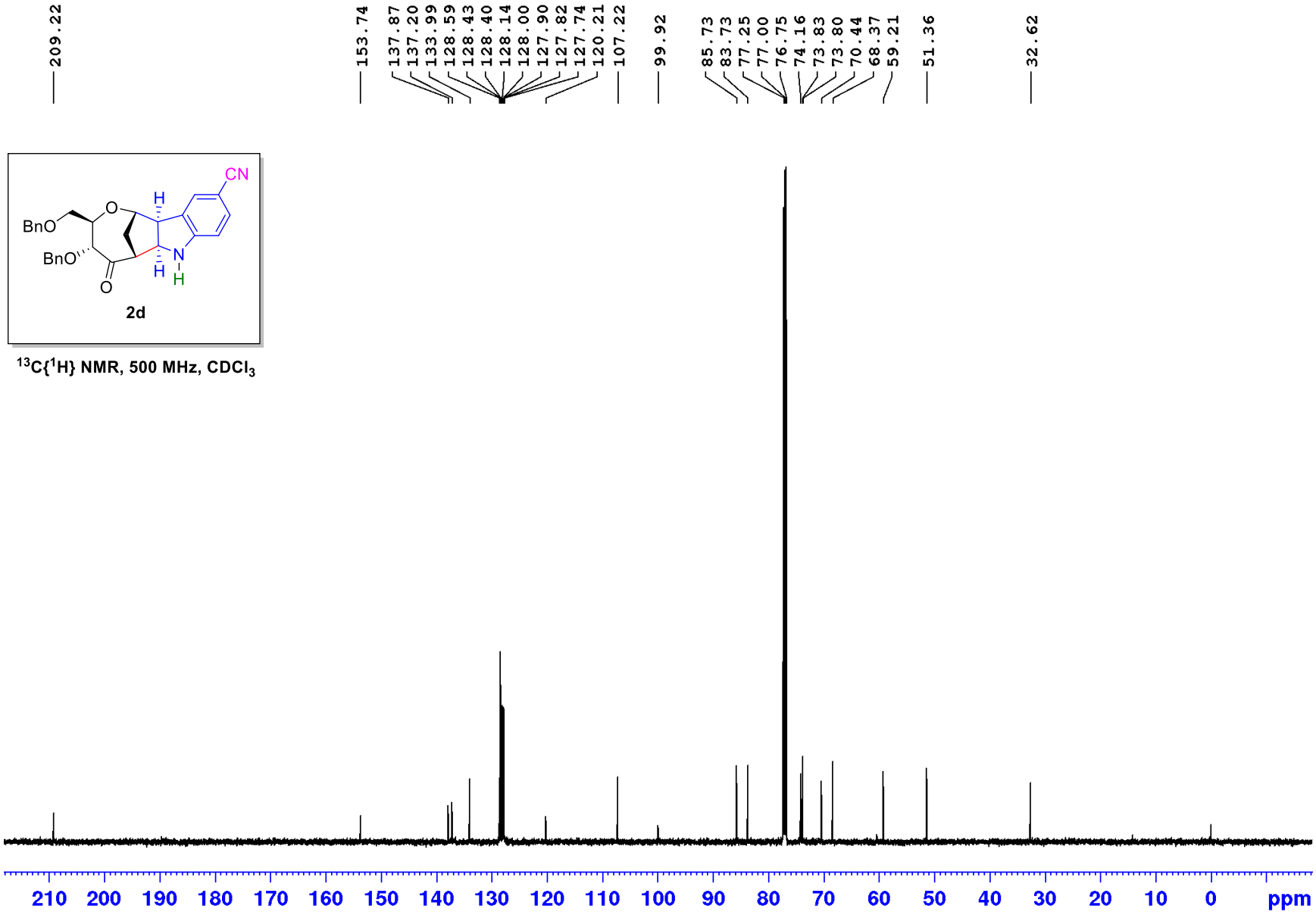




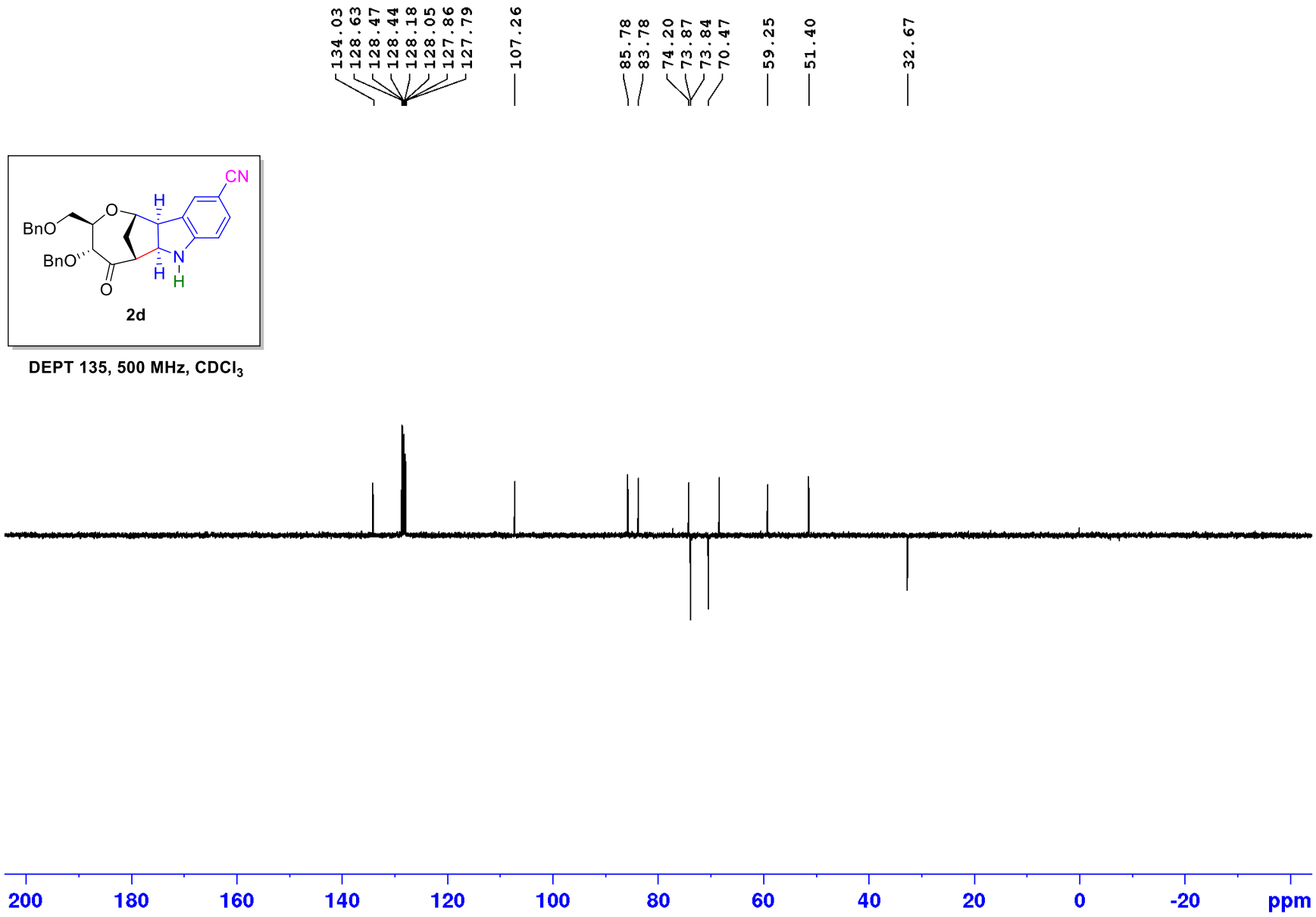
2d

^{1}H NMR, 500 Mz, $CDCl_3$

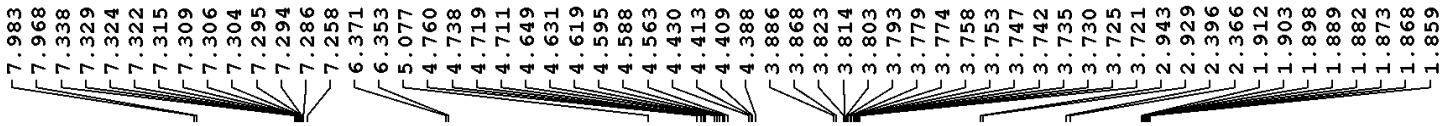


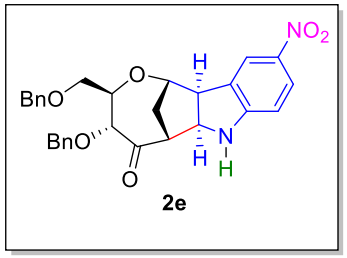


$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

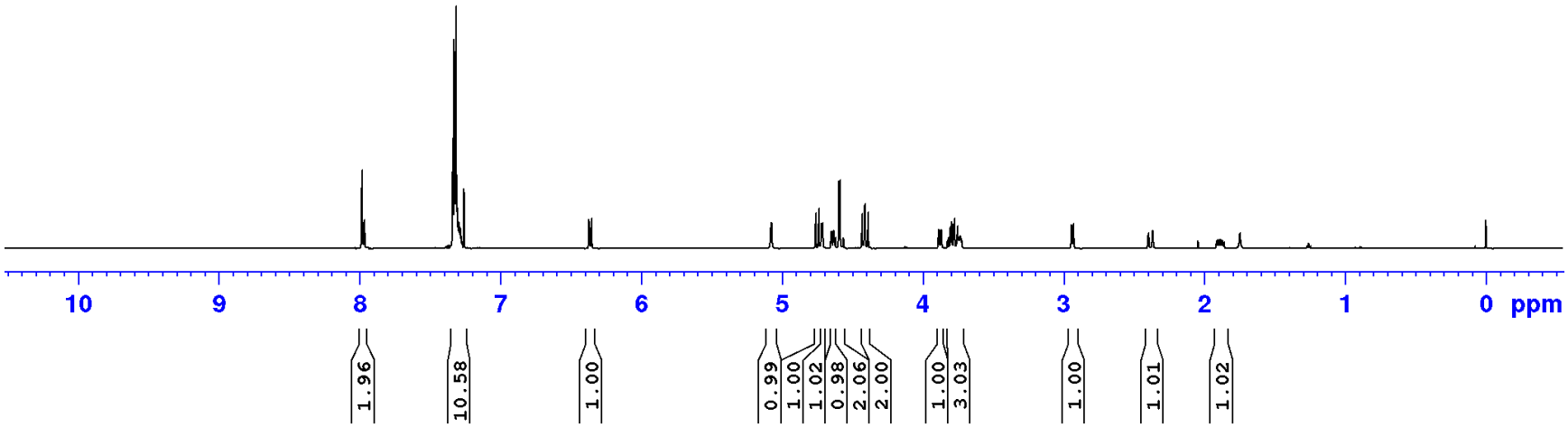


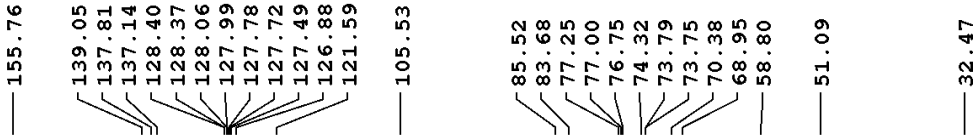
DEPT 135, 500 MHz, $CDCl_3$

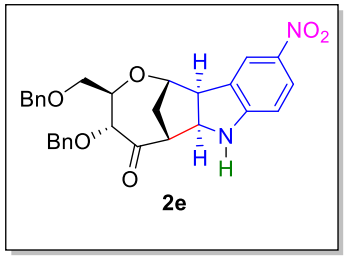




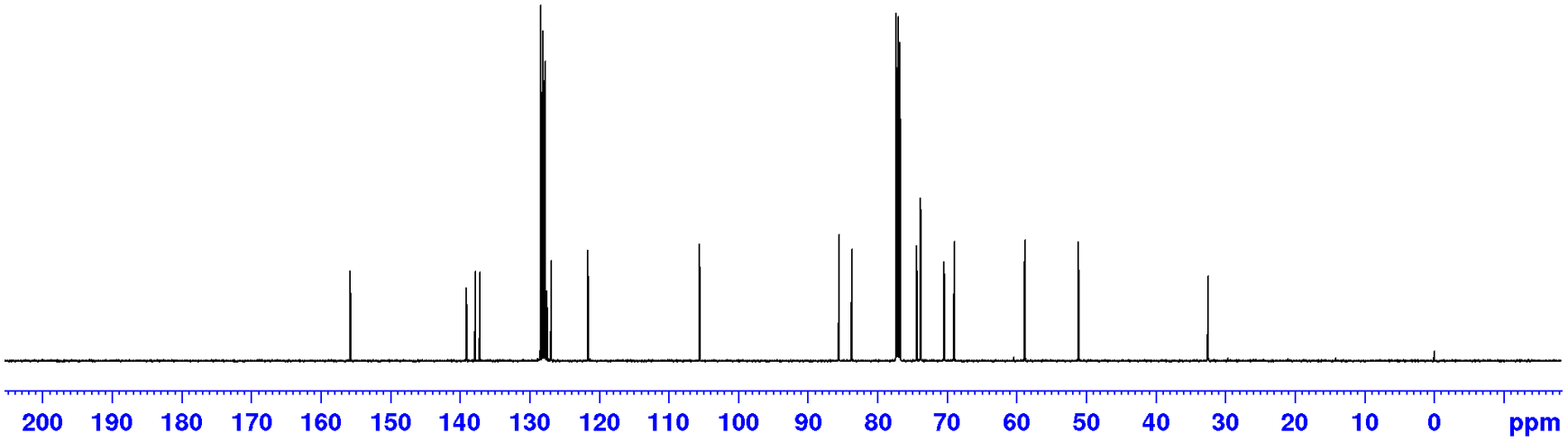
^{1}H NMR, 500 Mz, $CDCl_3$

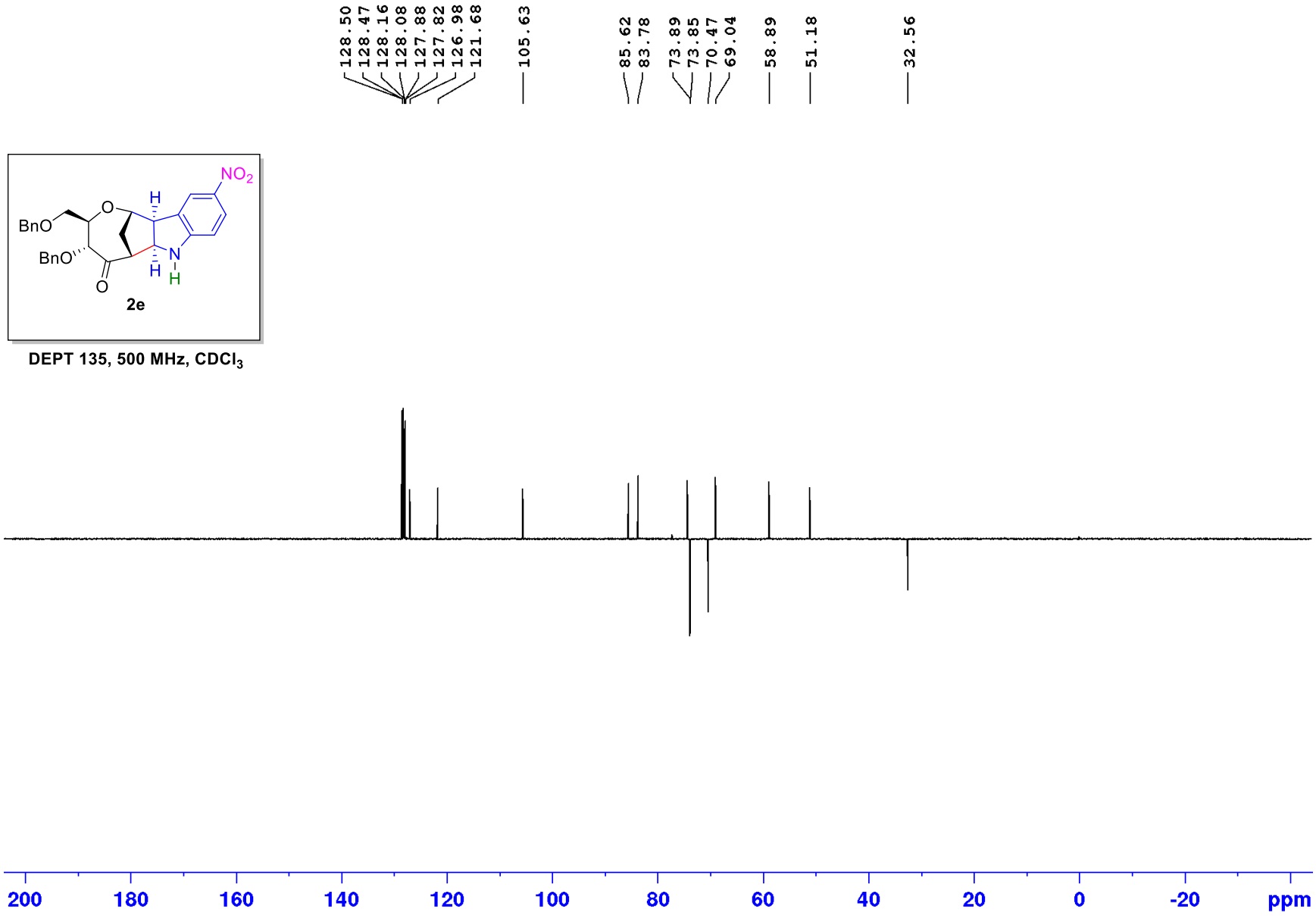




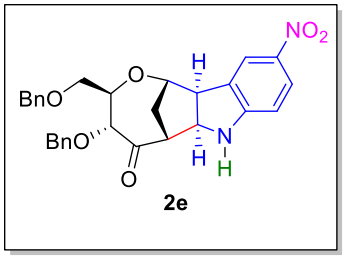


$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

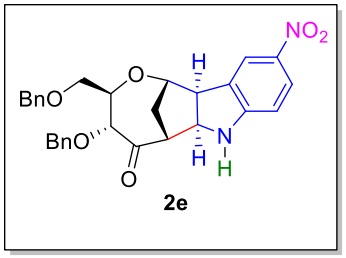




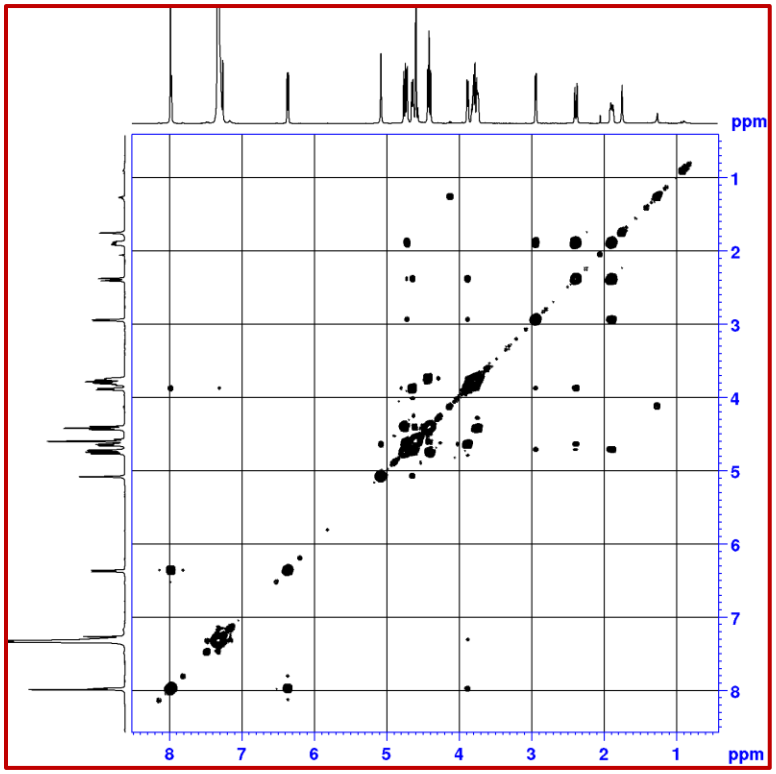
DEPT 135, 500 MHz, $CDCl_3$

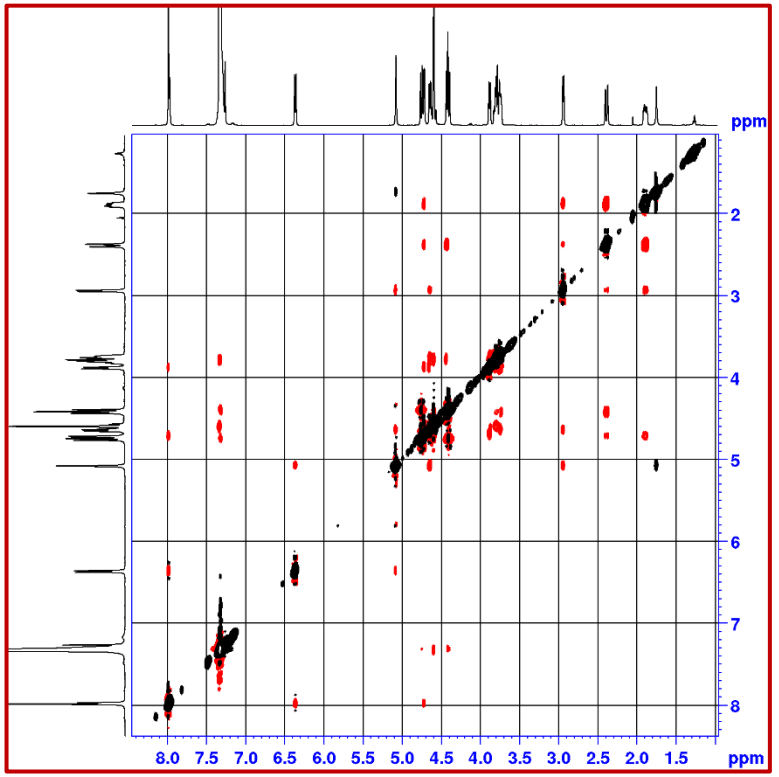


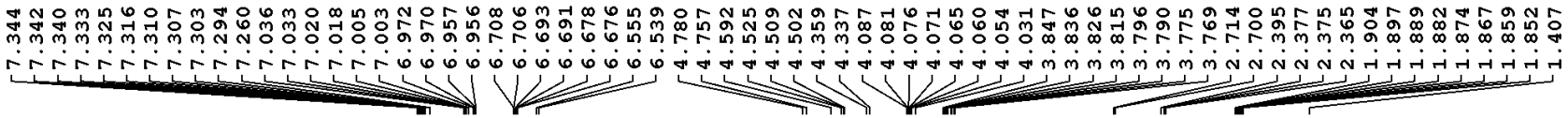
(COSY, 500 MHz)

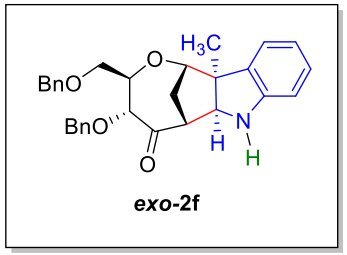


(NOESY, 500 MHz)



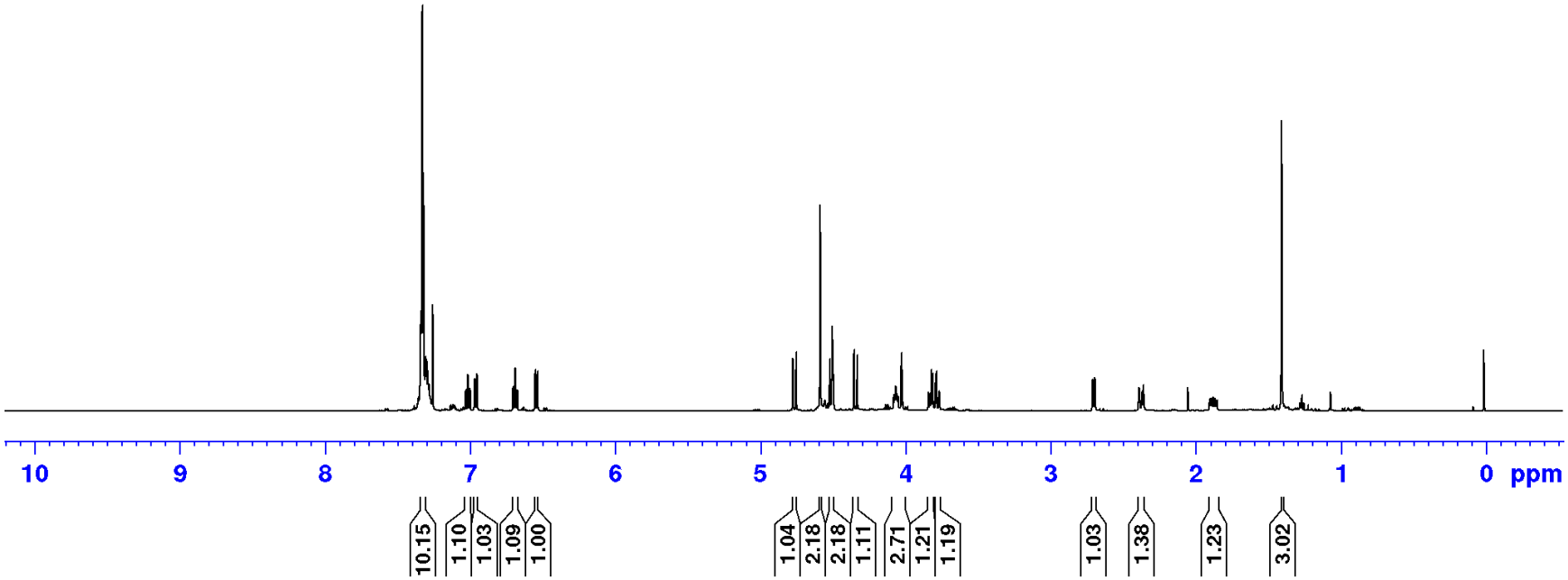






***exo*-2f**

^{1}H NMR, 500 Mz, $CDCl_3$



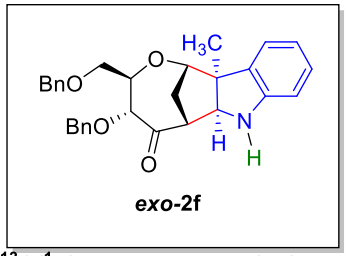
209.37

149.36
137.95
137.39
134.31
128.37
128.36
128.13
128.08
127.88
127.69
127.66
122.96
118.55
108.45

84.58
82.45
77.26
77.00
76.75
76.17
73.57
73.33
73.24
70.29
60.66
58.86

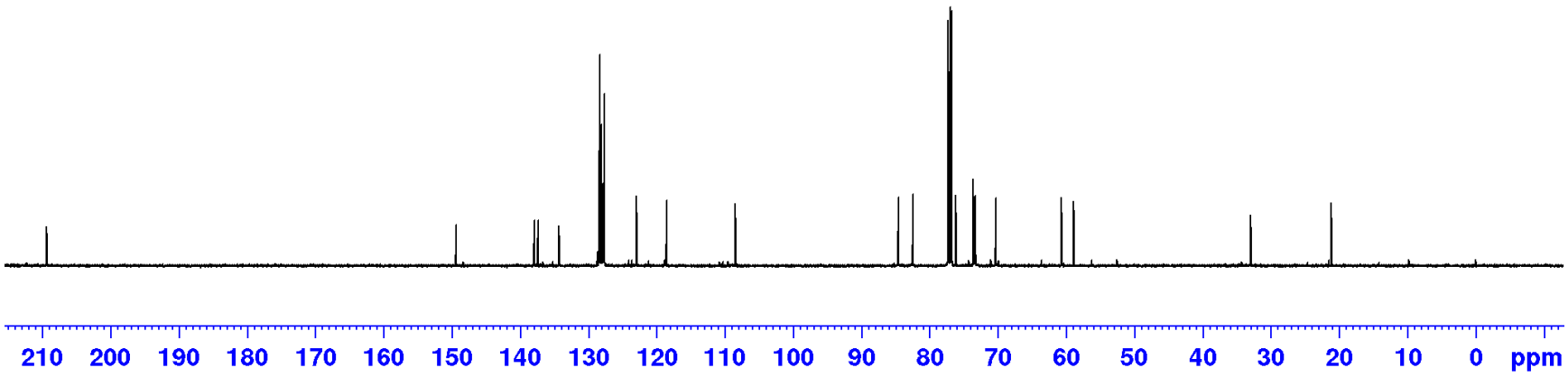
32.96

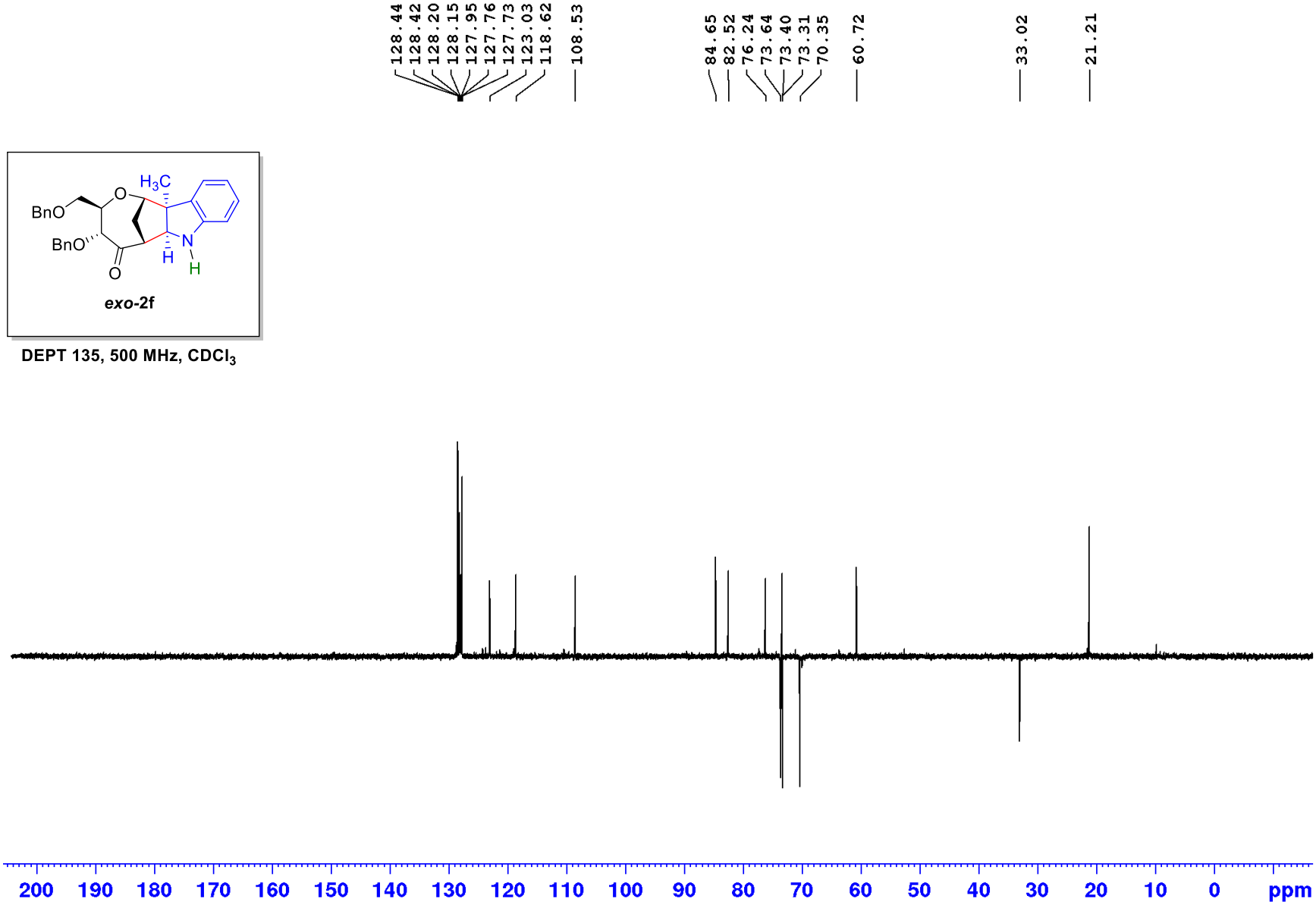
21.14



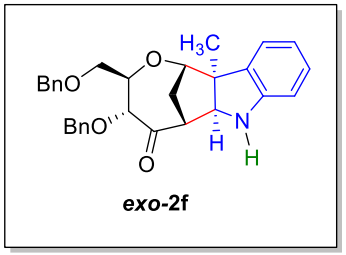
exo-2f

$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$



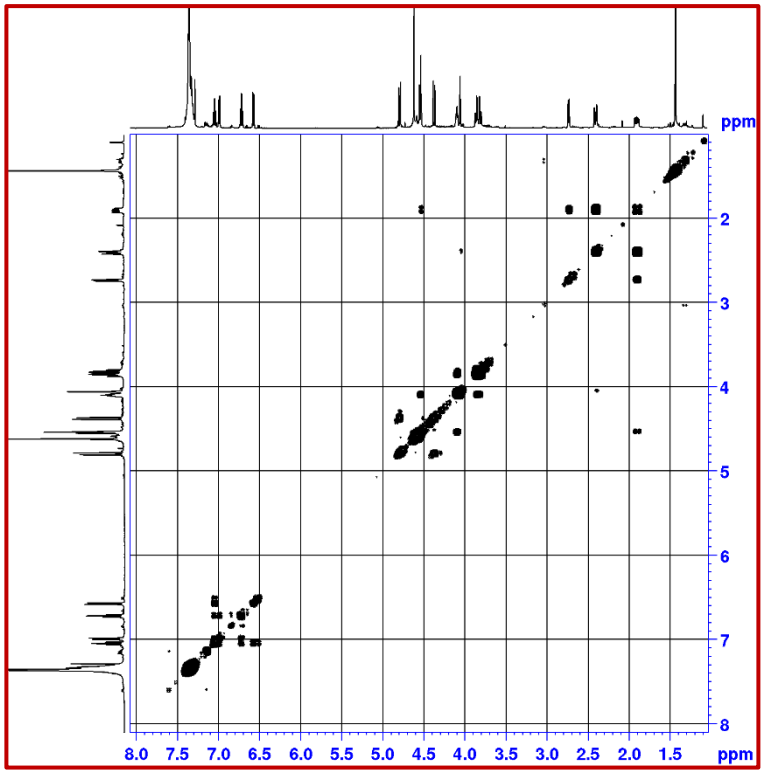


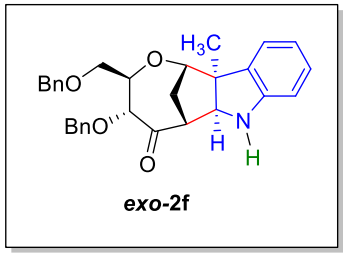
DEPT 135, 500 MHz, $CDCl_3$



***exo*-2f**

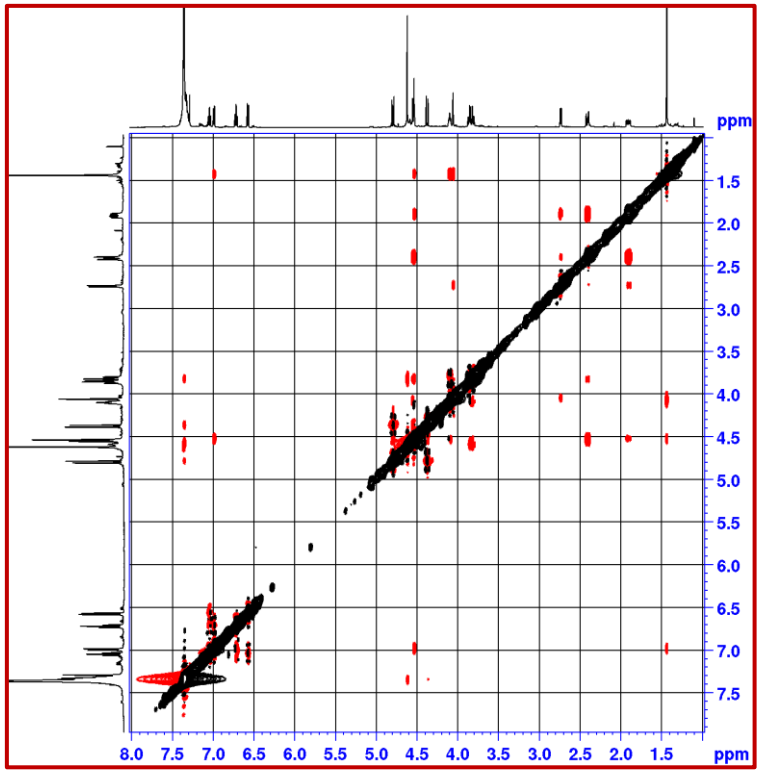
(COSY, 500 MHz)

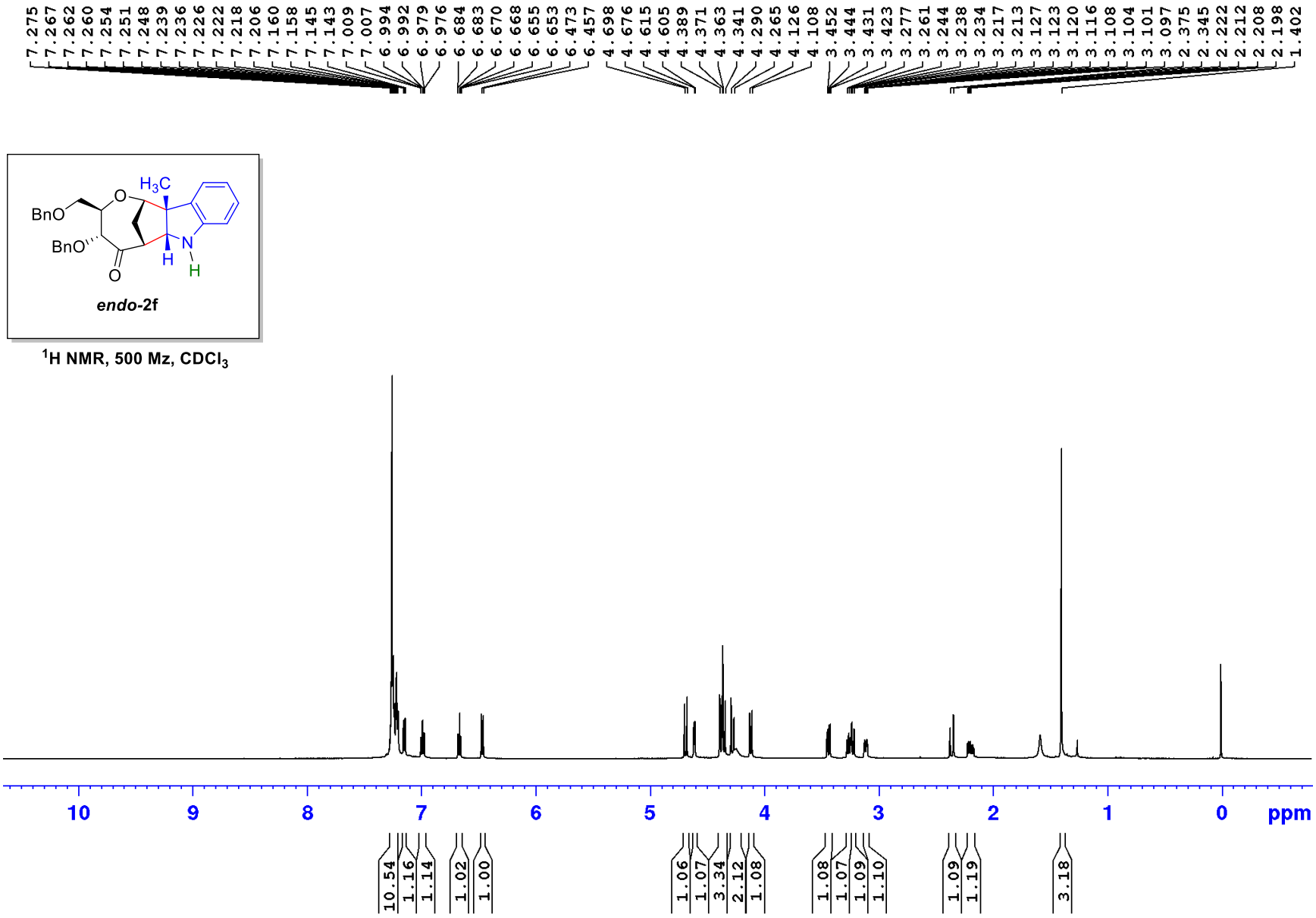


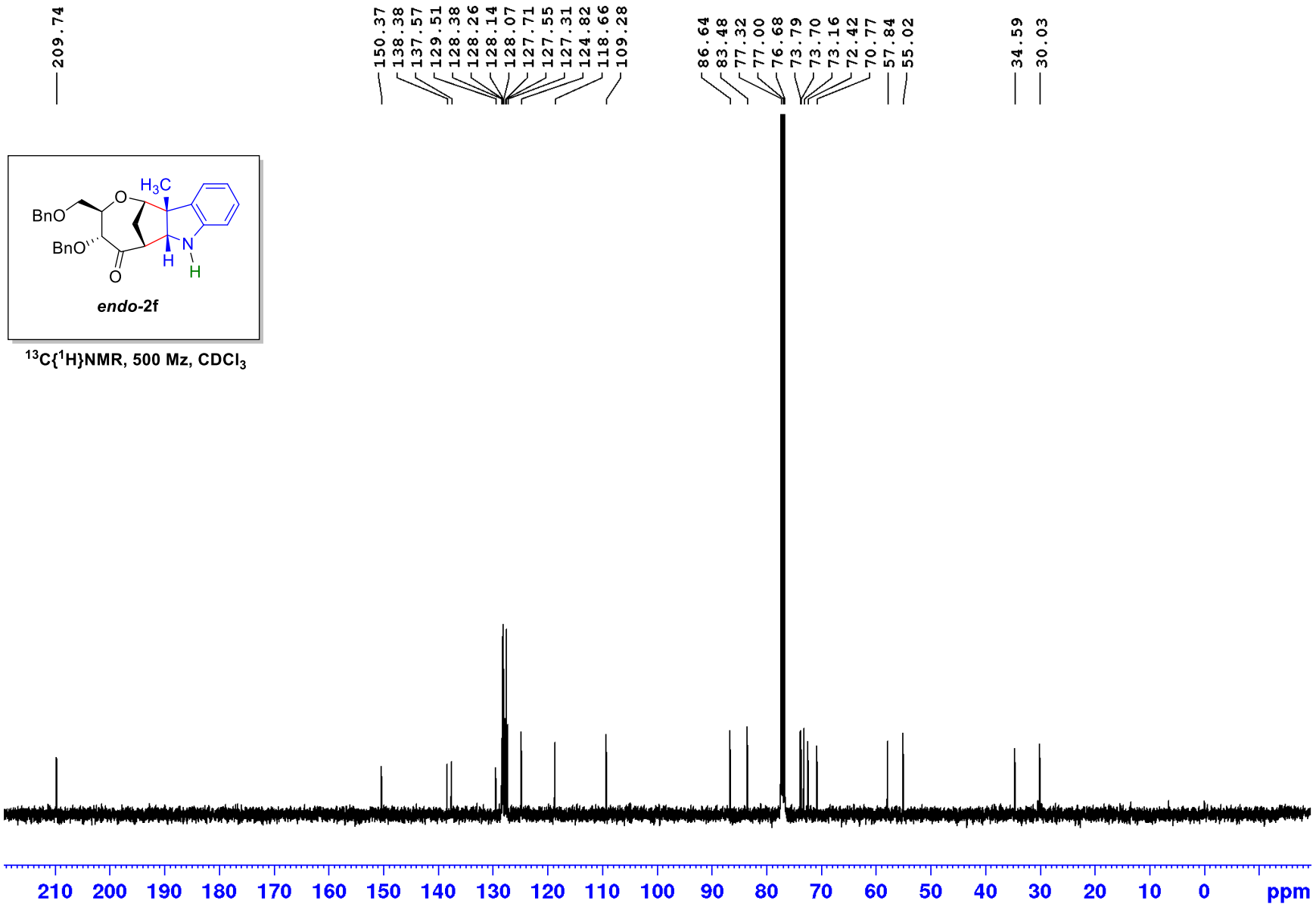


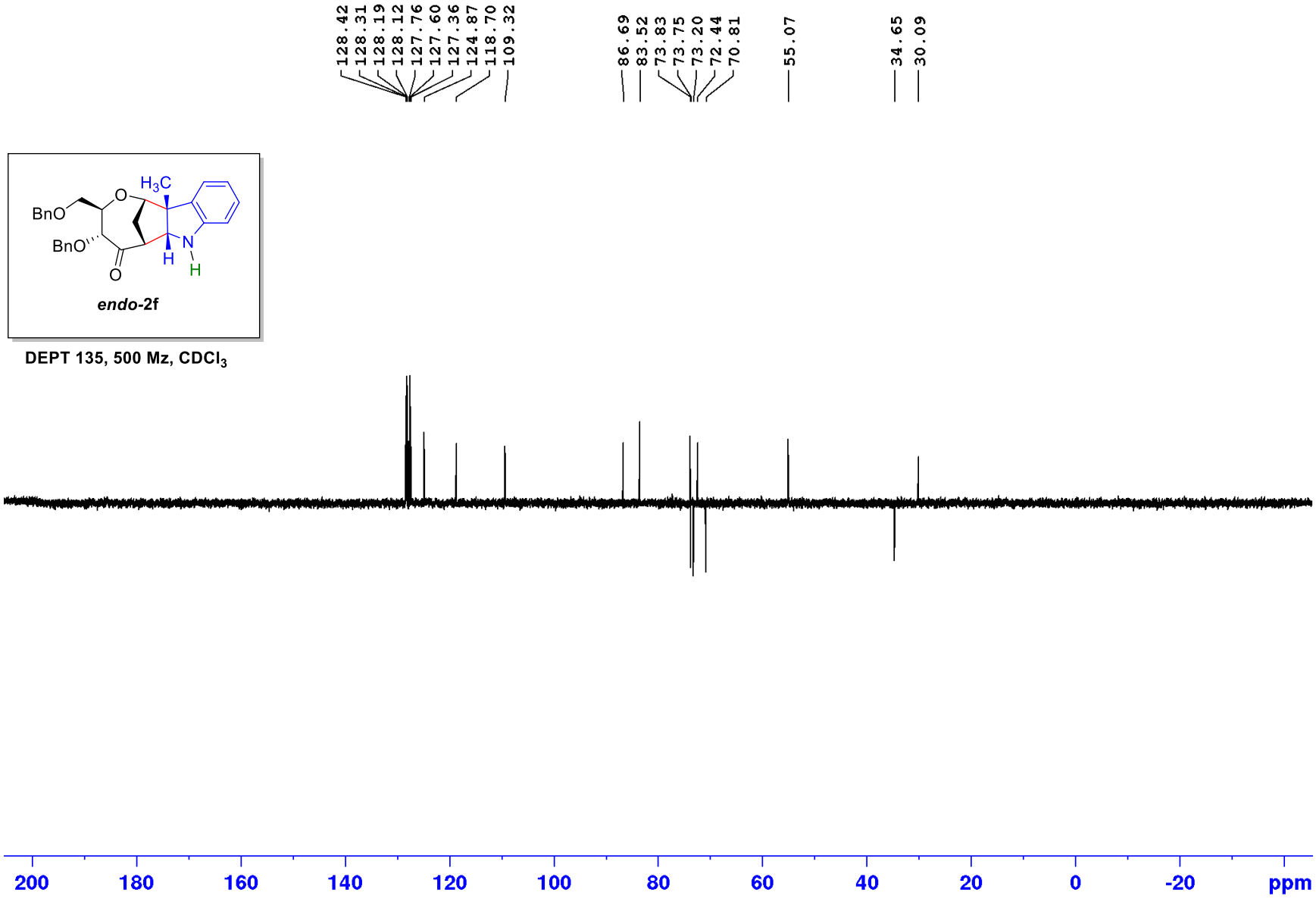
***exo*-2f**

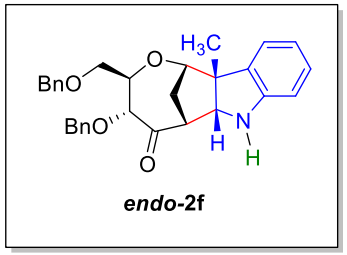
(NOESY, 500 MHz)




7.275
7.267
7.262
7.260
7.254
7.251
7.248
7.239
7.236
7.226
7.222
7.218
7.206
7.160
7.158
7.145
7.143
7.009
7.007
6.994
6.992
6.979
6.976
6.684
6.683
6.670
6.668
6.655
6.653
6.473
6.457
4.698
4.676
4.615
4.605
4.389
4.371
4.363
4.341
4.290
4.265
4.126
4.108
3.452
3.444
3.431
3.423
3.277
3.261
3.244
3.238
3.234
3.217
3.213
3.127
3.123
3.120
3.116
3.108
3.104
3.101
3.097
2.375
2.345
2.222
2.212
2.208
2.198
1.402
H3C
O
BnO
BnO
N
H
H
O
endo-2f
1H NMR, 500 Mz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
10.54
1.16
1.14
1.02
1.00
1.06
1.07
3.34
2.12
1.08
1.08
1.07
1.09
1.10
1.09
1.19
3.18

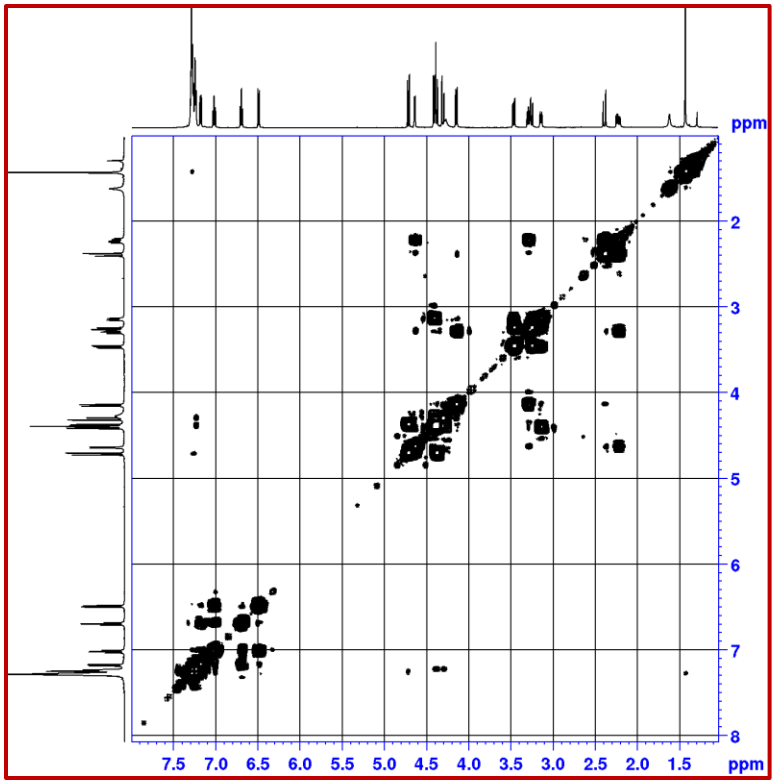

209.74
150.37
138.38
137.57
129.51
128.38
128.26
128.14
128.07
127.71
127.55
127.31
124.82
118.66
109.28
86.64
83.48
77.32
77.00
76.68
73.79
73.70
73.16
72.42
70.77
57.84
55.02
34.59
30.03
BnO
BnO
O
H3C
N
H
H
O
endo-2f
13C{1H}NMR, 500 Mz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

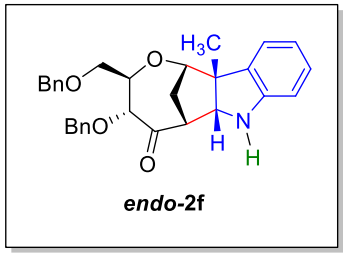

128.42
128.31
128.19
128.12
127.76
127.60
127.36
124.87
118.70
109.32
86.69
83.52
73.83
73.75
73.20
72.44
70.81
55.07
34.65
30.09
H3C
O
BnO
BnO
O
N
H
H
endo-2f
DEPT 135, 500 Mz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



endo-2f

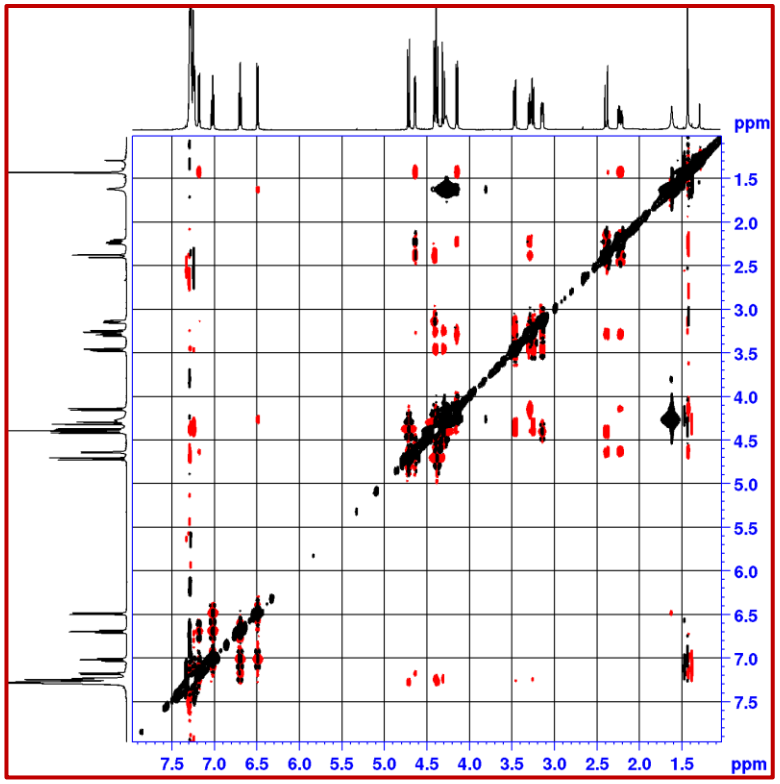
(COSY, 500 MHz)

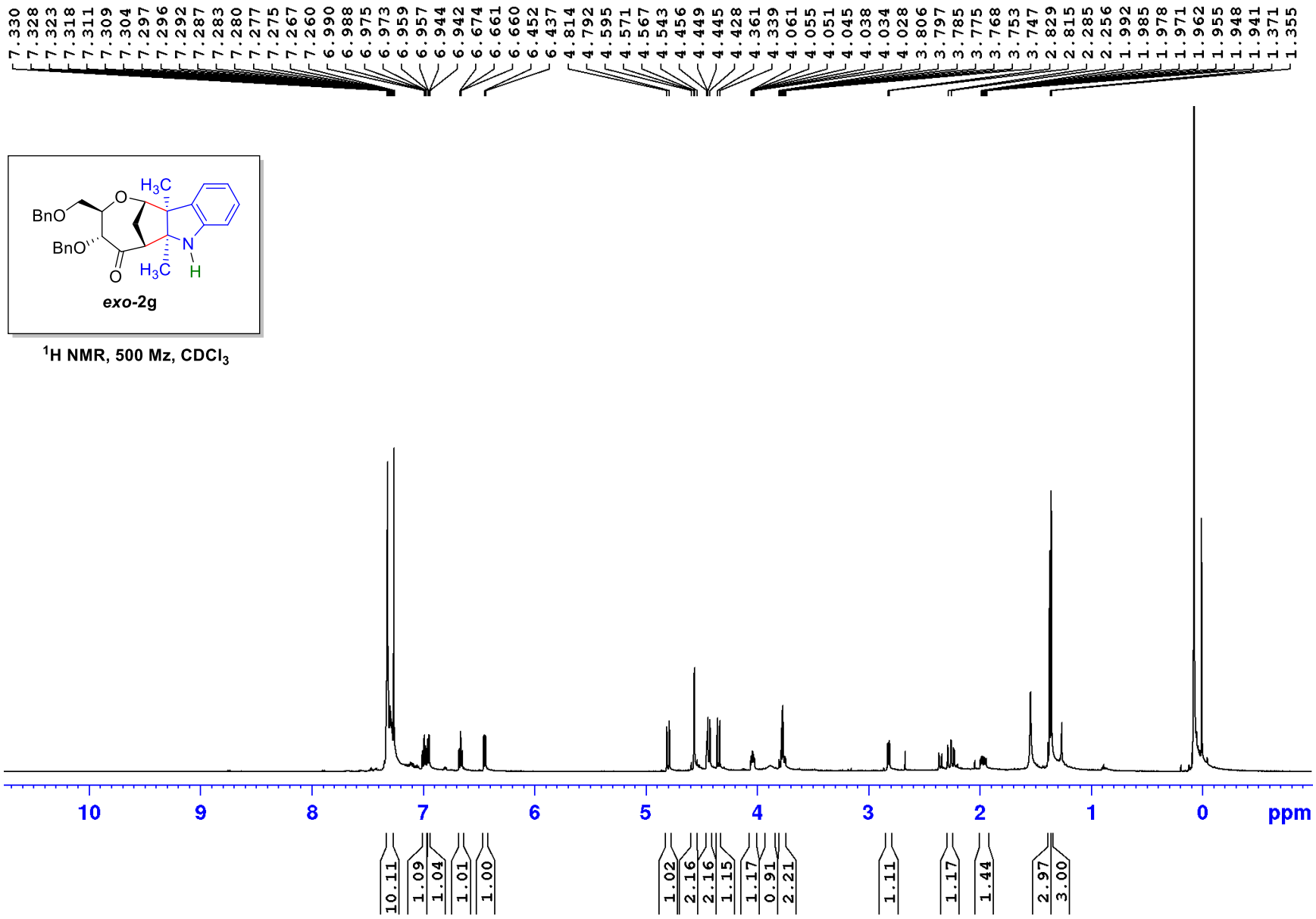




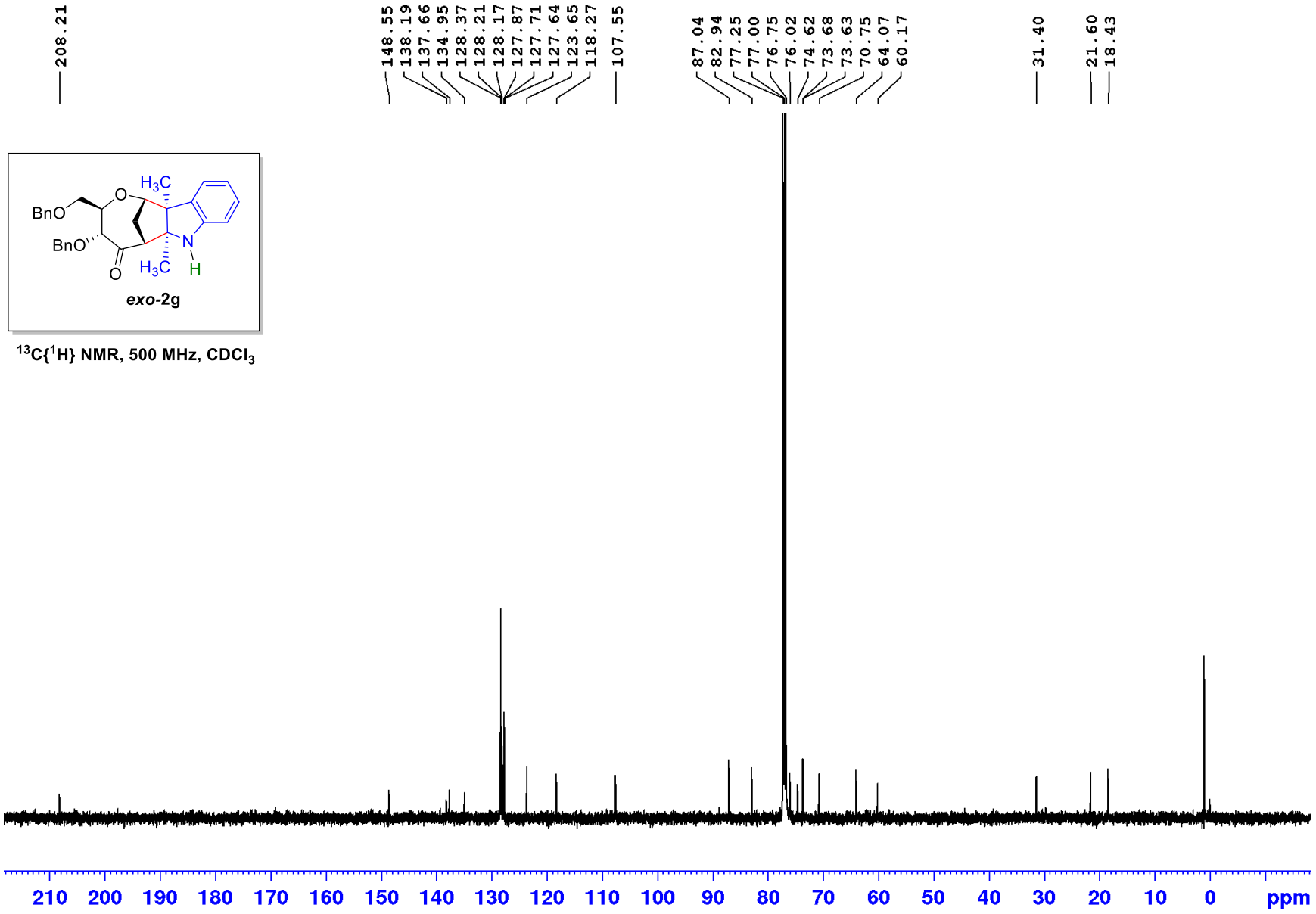
endo-2f

(NOESY, 500 MHz)



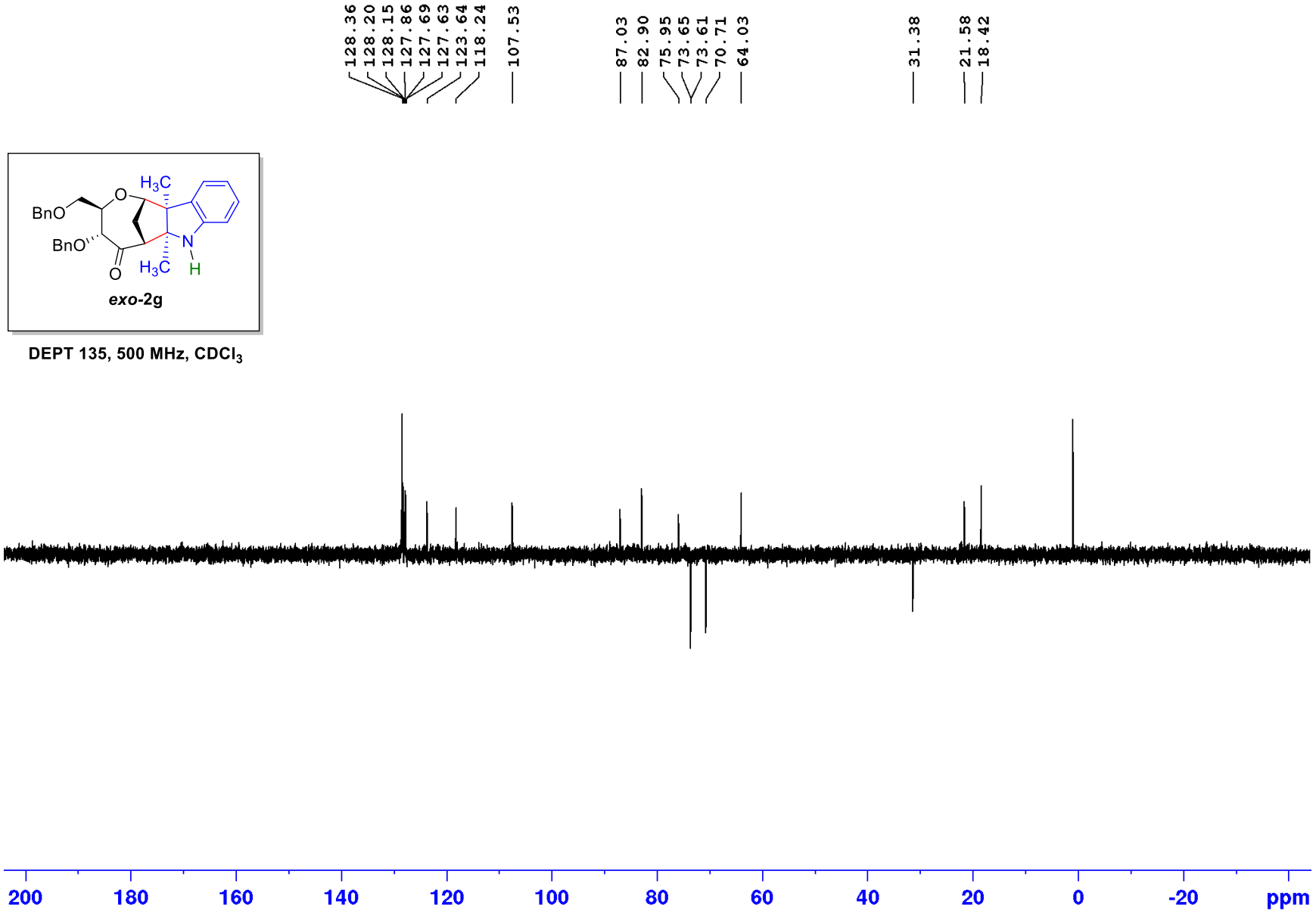


^{1}H NMR, 500 Mz, $CDCl_3$

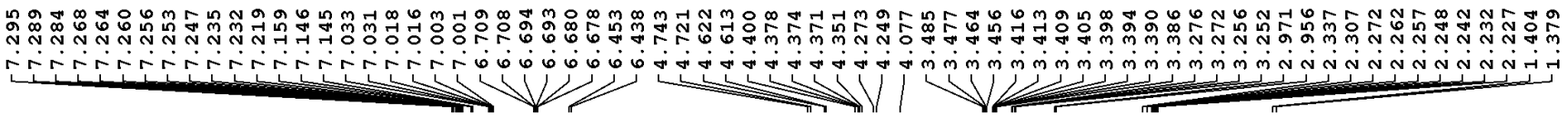


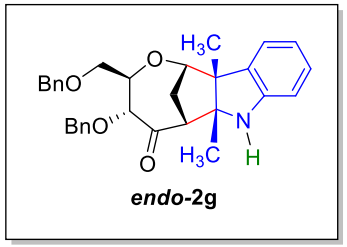
***exo*-2g**

$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$



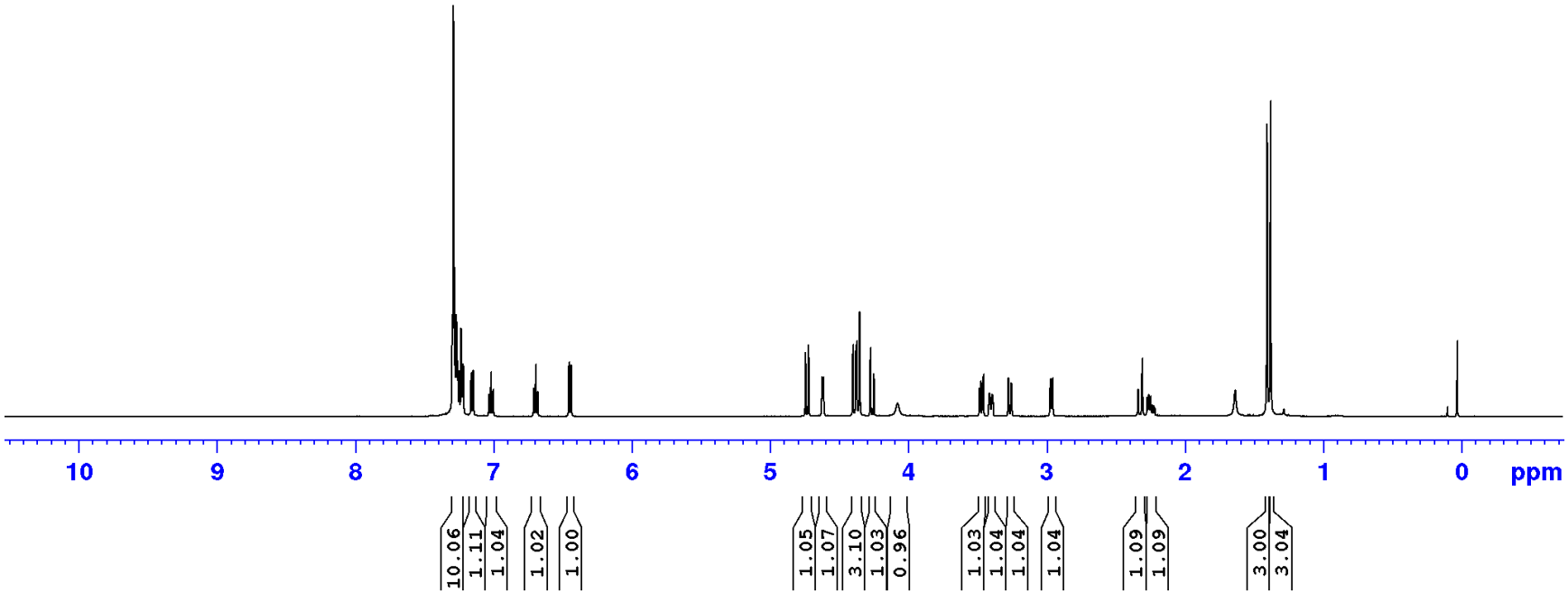
DEPT 135, 500 MHz, $CDCl_3$

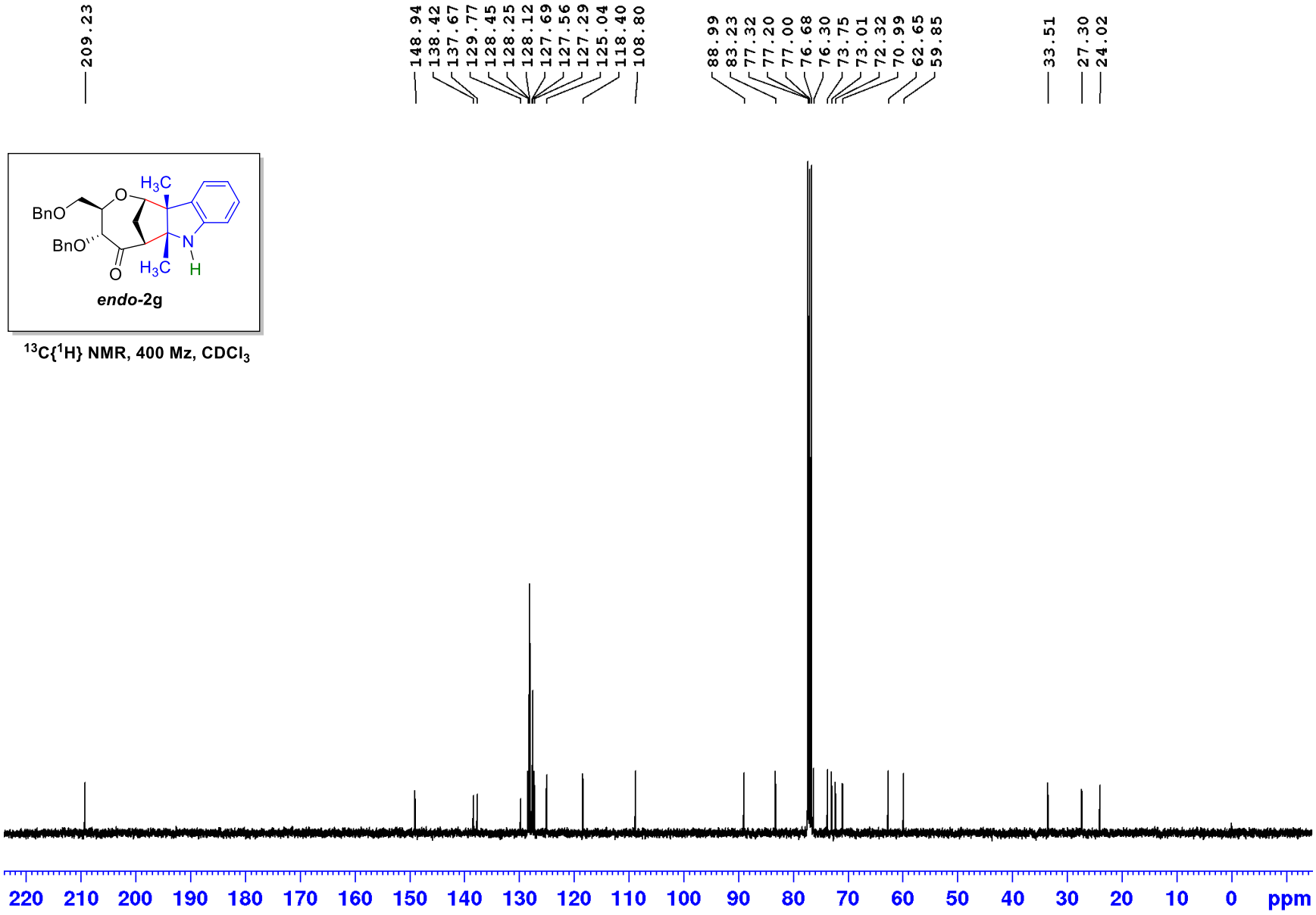


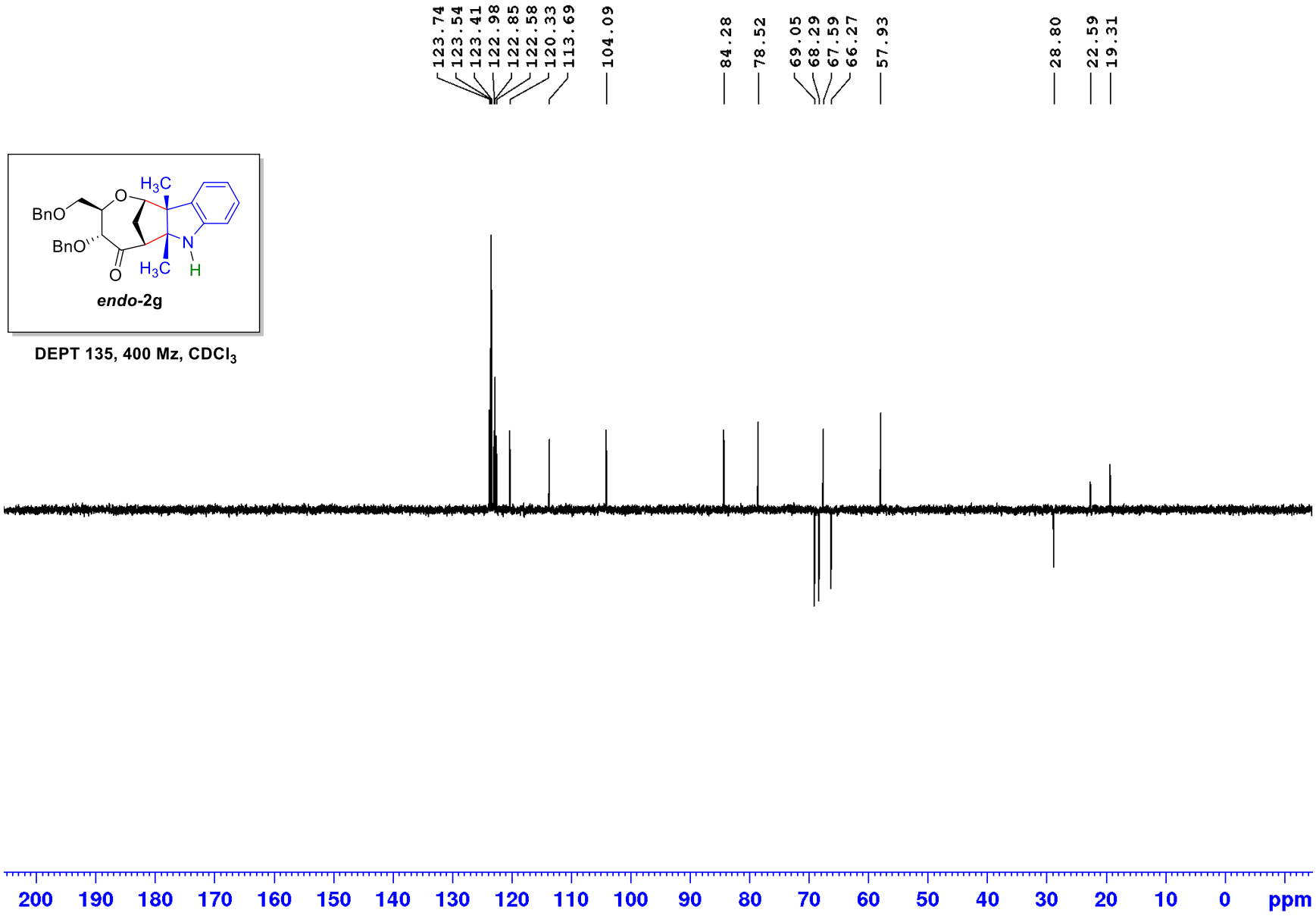


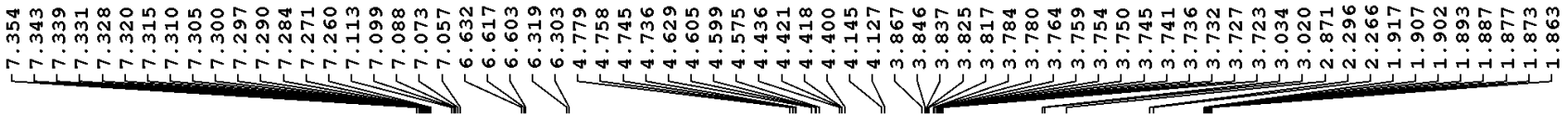
***endo*-2g**

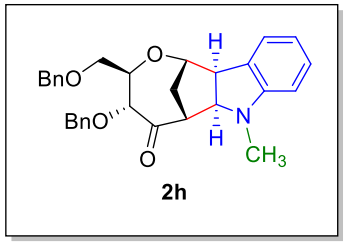
^{1}H NMR, 500 Mz, $CDCl_3$




209.23
148.94
138.42
137.67
129.77
128.45
128.25
128.12
127.69
127.56
127.29
125.04
118.40
108.80
88.99
83.23
77.32
77.20
77.00
76.68
76.30
73.75
73.01
72.32
70.99
62.65
59.85
33.51
27.30
24.02
BnO
BnO
O
H3C
N
H
H3C
O
endo-2g
13C{1H} NMR, 400 Mz, CDCl3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

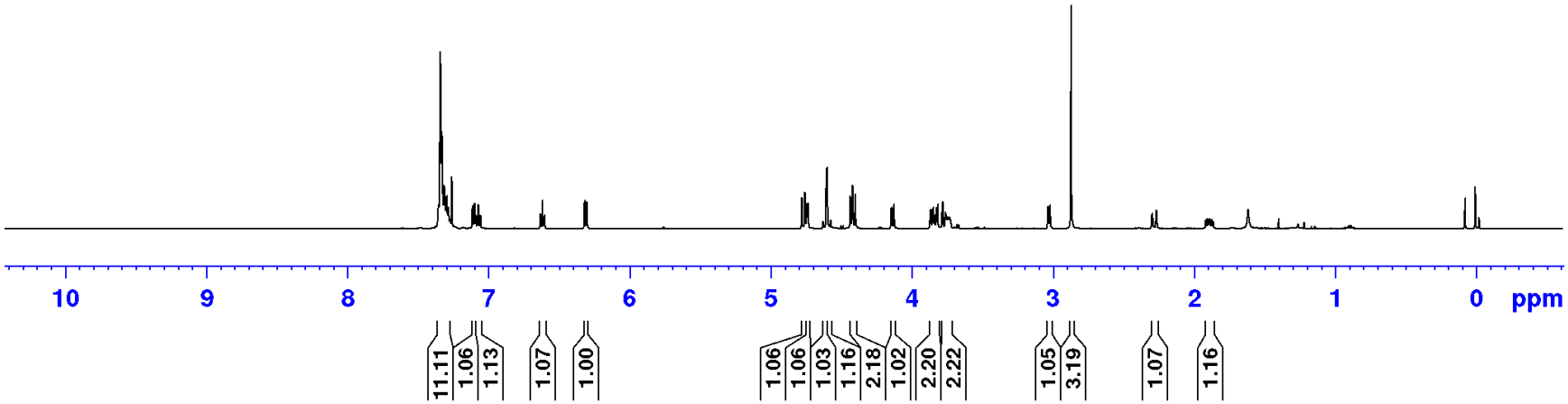

123.74
123.54
123.41
122.98
122.85
122.58
120.33
113.69
104.09
84.28
78.52
69.05
68.29
67.59
66.27
57.93
28.80
22.59
19.31
BnO
BnO
O
H3C
N
H
H3C
O
endo-2g
DEPT 135, 400 Mz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm





2h

^{1}H NMR, 500 Mz, $CDCl_3$



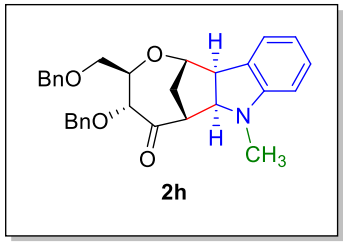
210.00

151.65
138.02
137.41
128.51
128.38
128.34
128.19
127.89
127.81
127.78
127.63
124.54
117.06
105.35

86.33
84.13
77.25
77.00
76.75
76.18
73.79
73.78
73.46
70.66

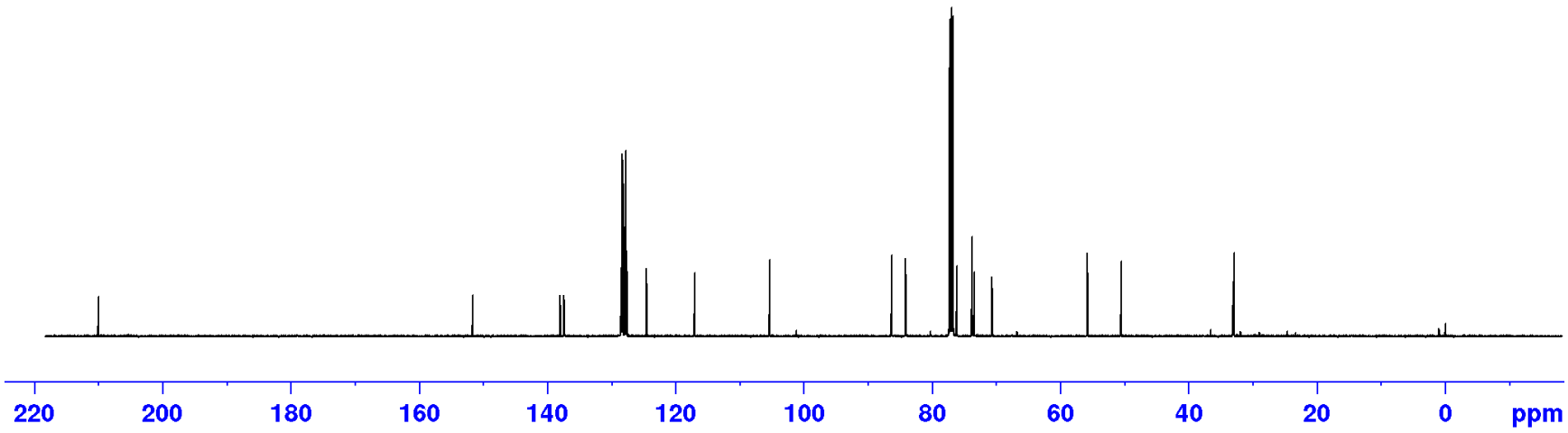
55.81
50.53

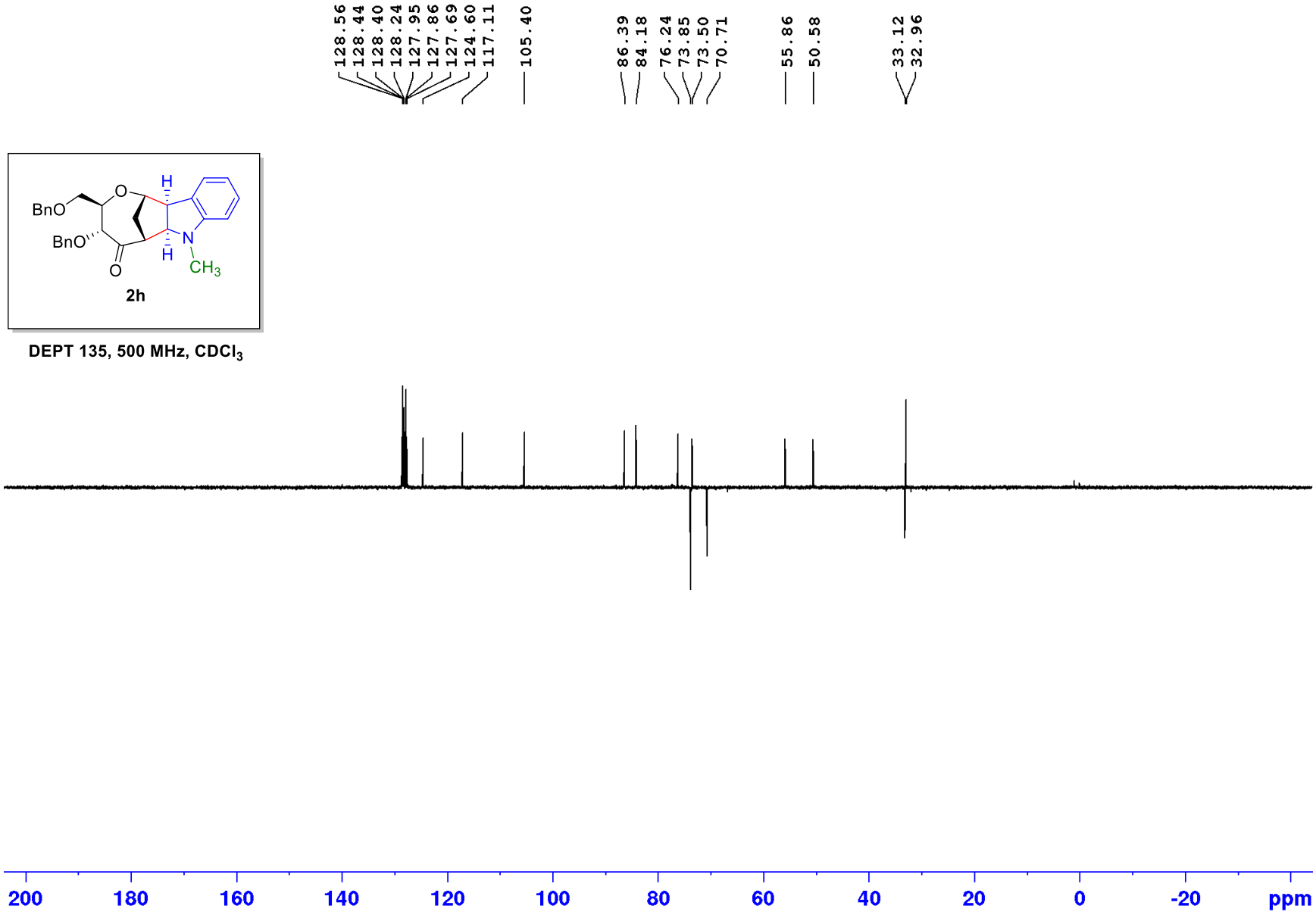
33.06
32.90

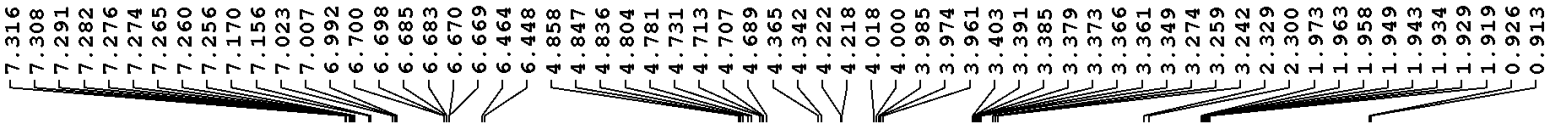


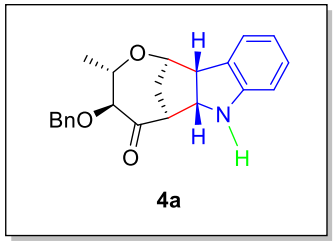
2h

$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$



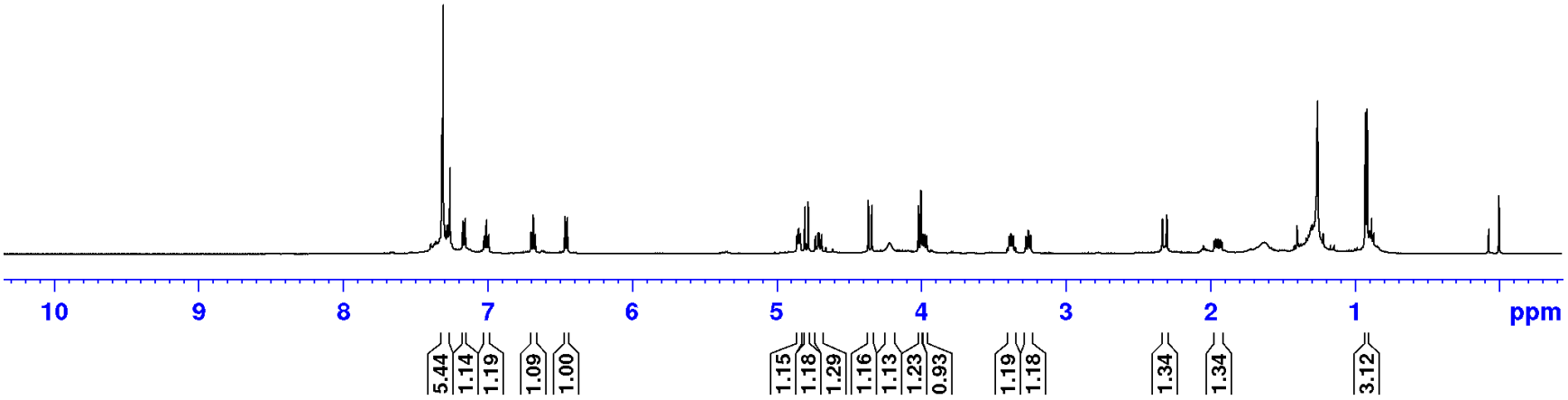

128.56
128.44
128.40
128.24
127.95
127.86
127.69
124.60
117.11
105.40
86.39
84.18
76.24
73.85
73.50
70.71
55.86
50.58
33.12
32.96
BnO
BnO
O
O
H
N
H
CH3
2h
DEPT 135, 500 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

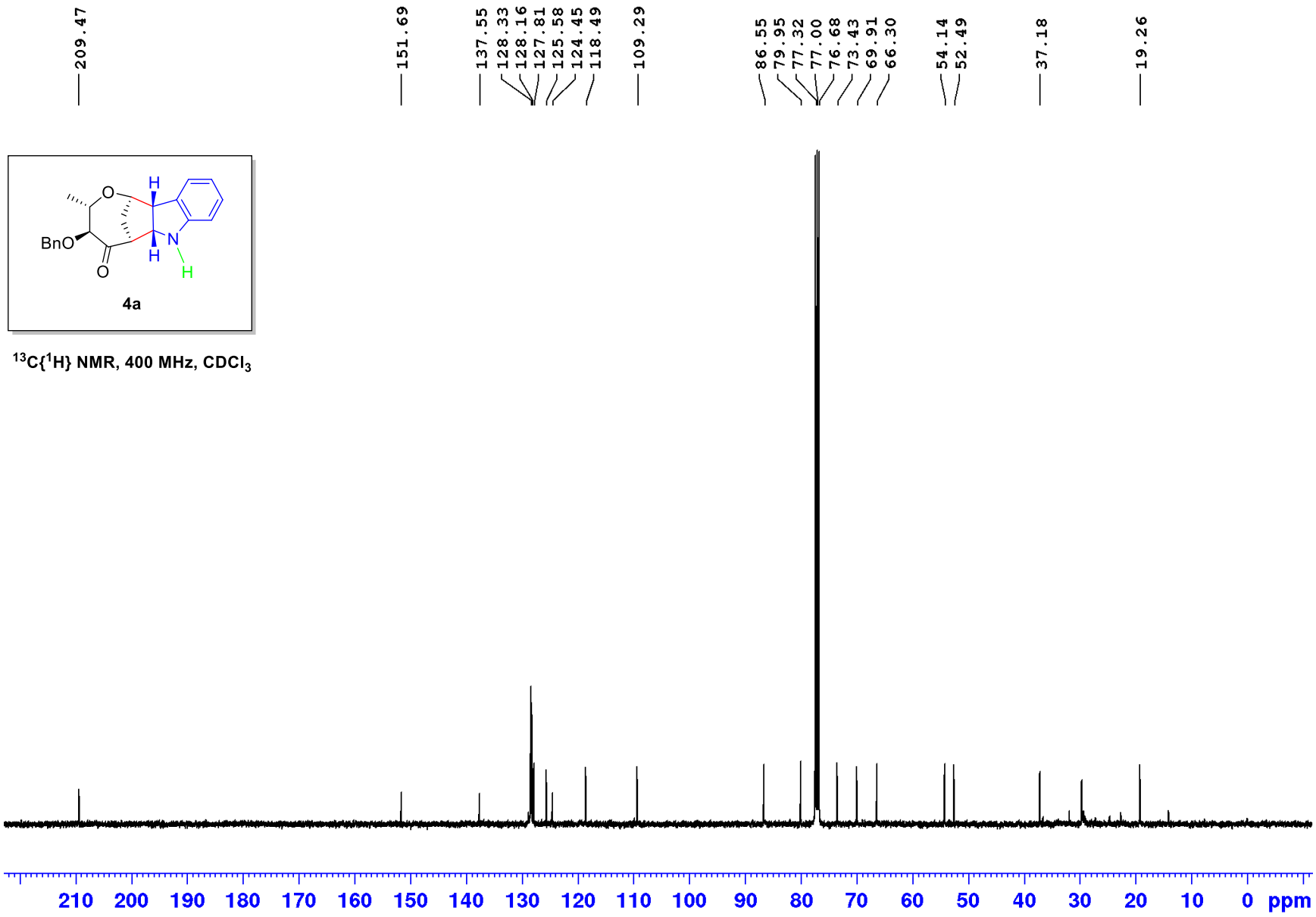




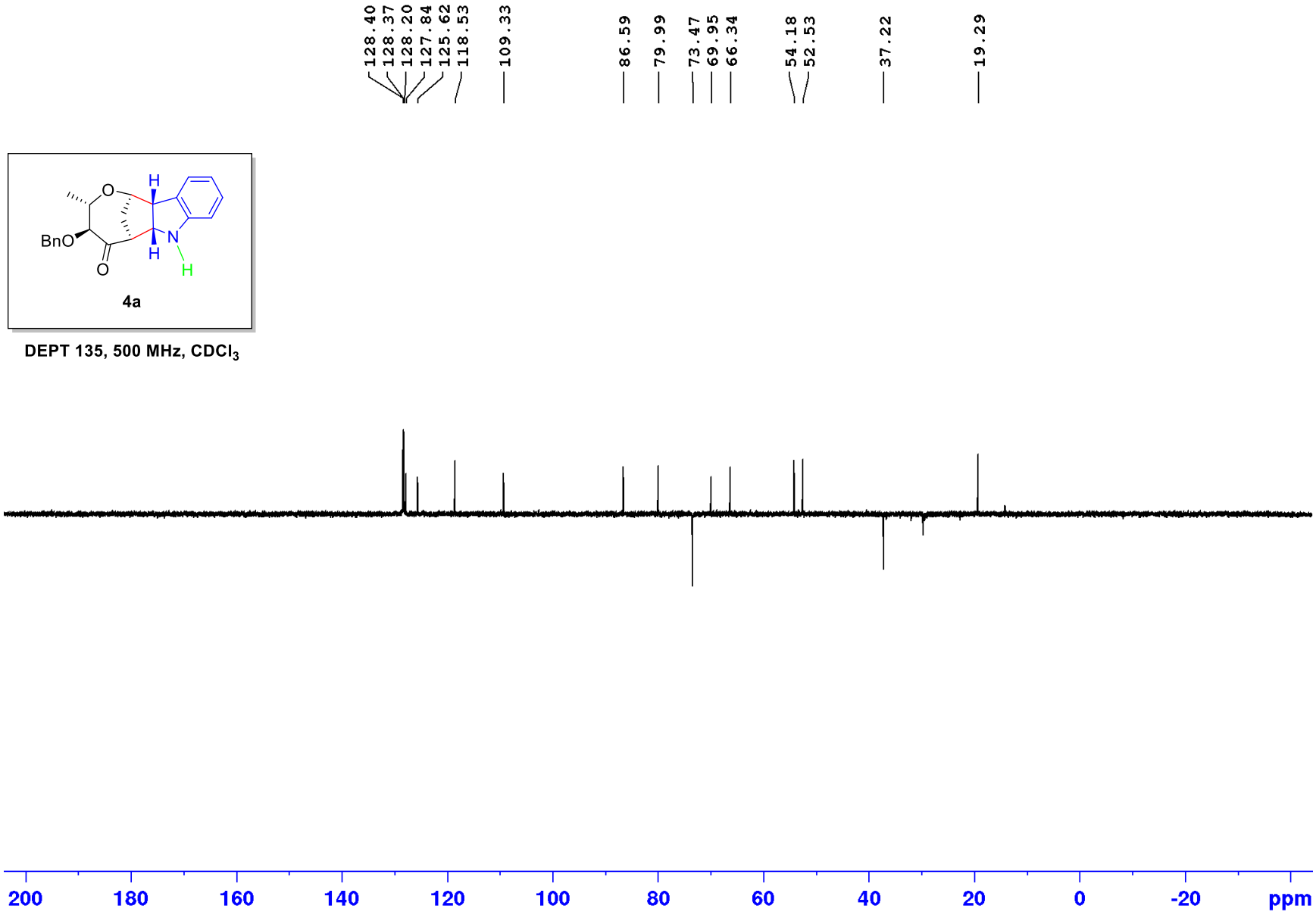
4a

^{1}H NMR, 500 Mz, $CDCl_3$

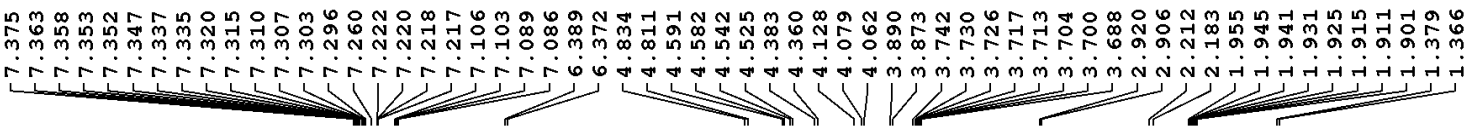


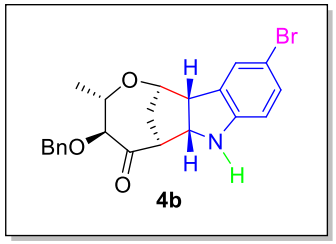


$^{13}C\{^{1}H\}$ NMR, 400 MHz, $CDCl_3$



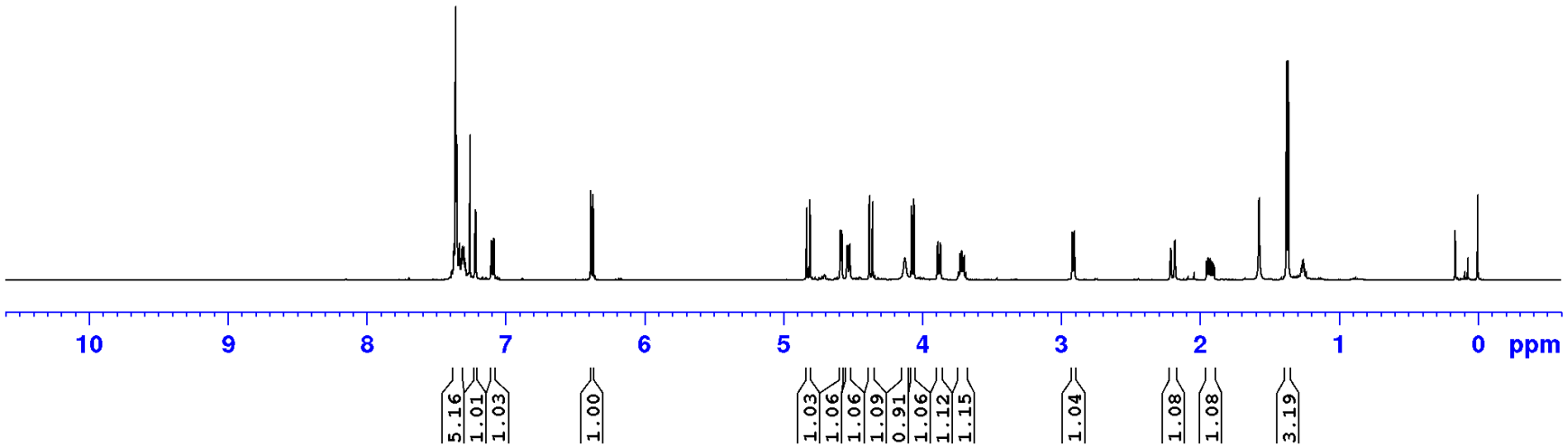
DEPT 135, 500 MHz, $CDCl_3$

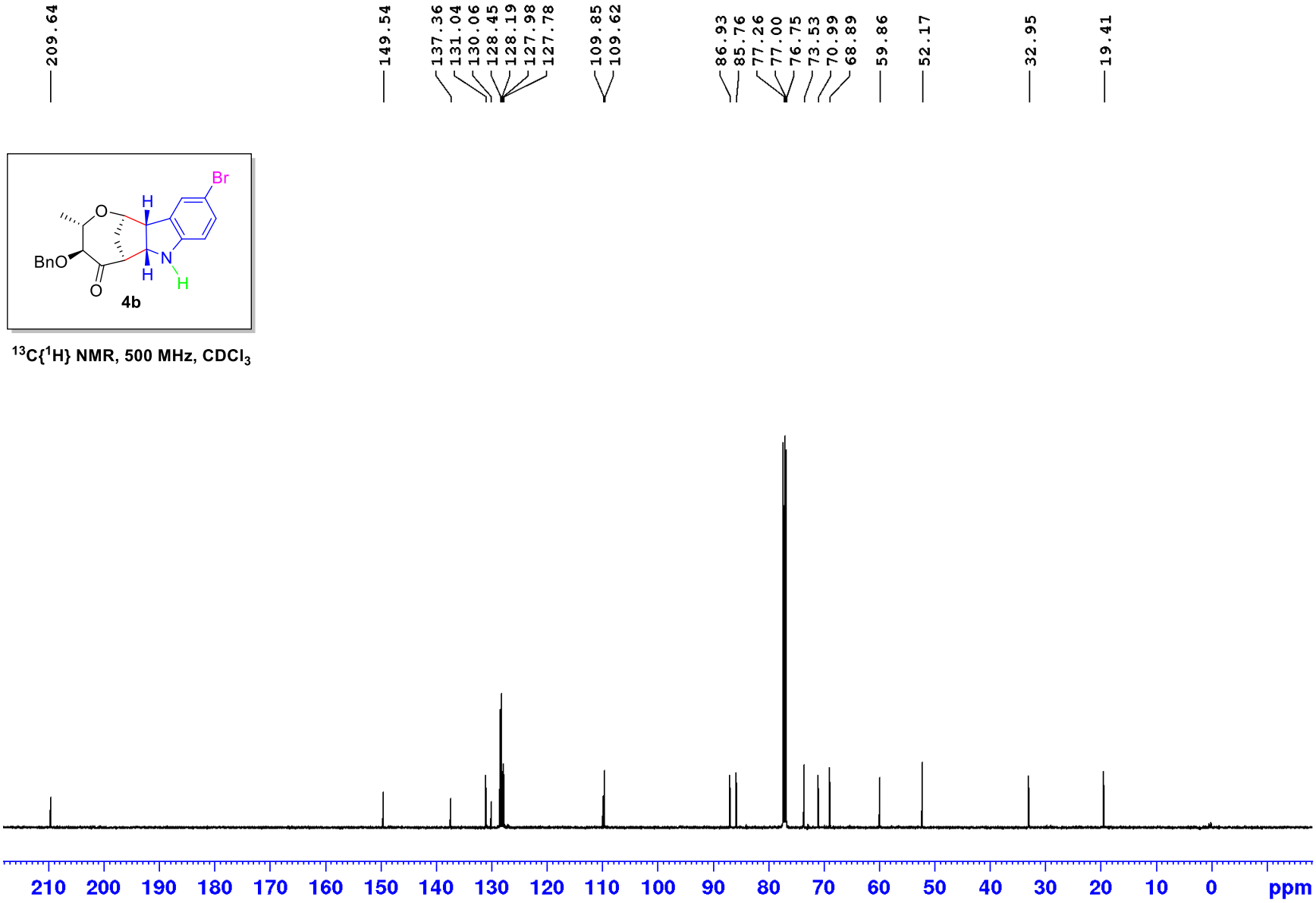




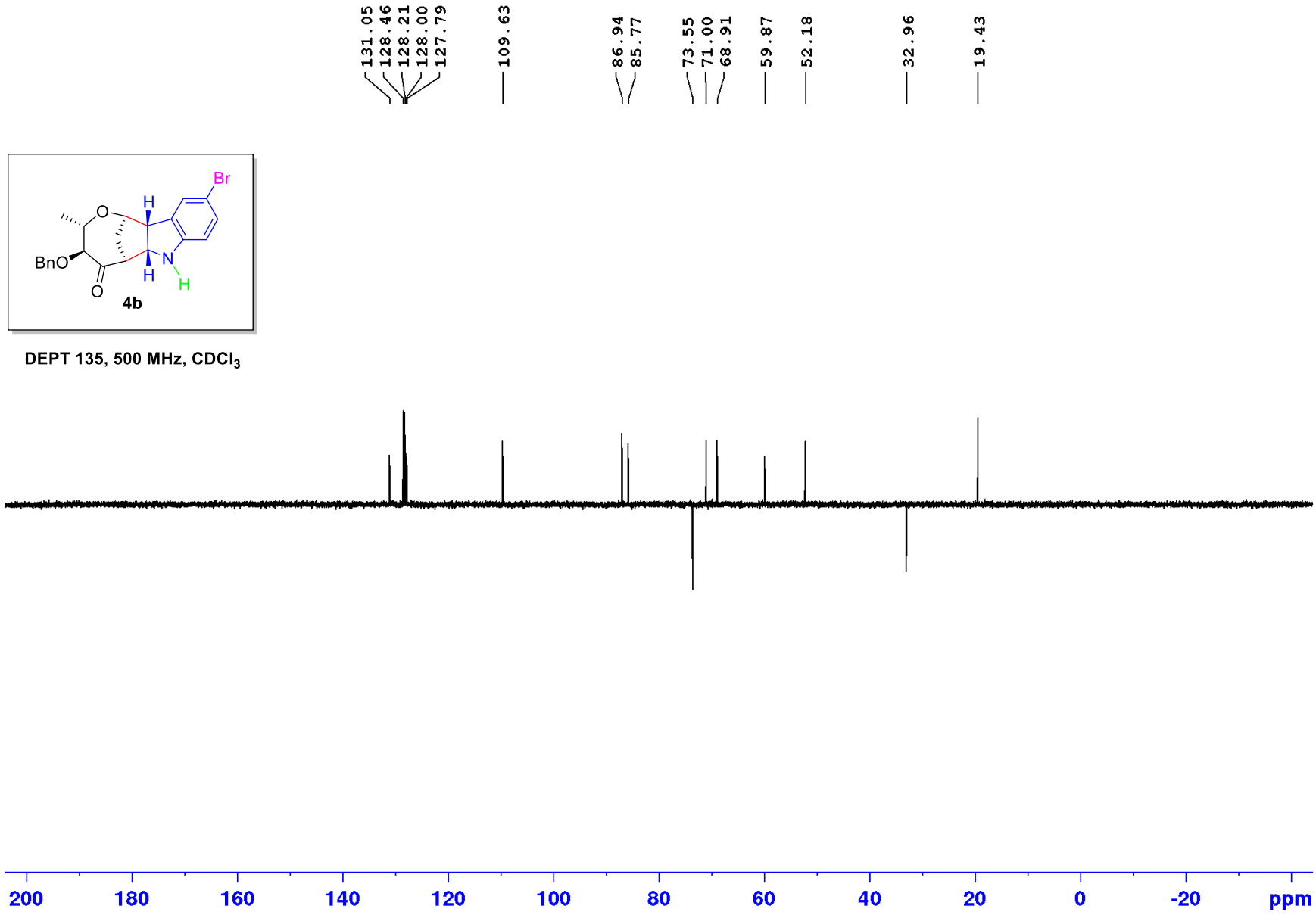
4b

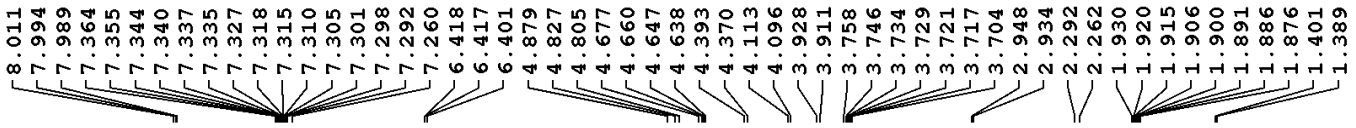
^{1}H NMR, 500 Mz, $CDCl_3$

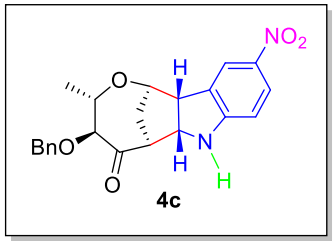




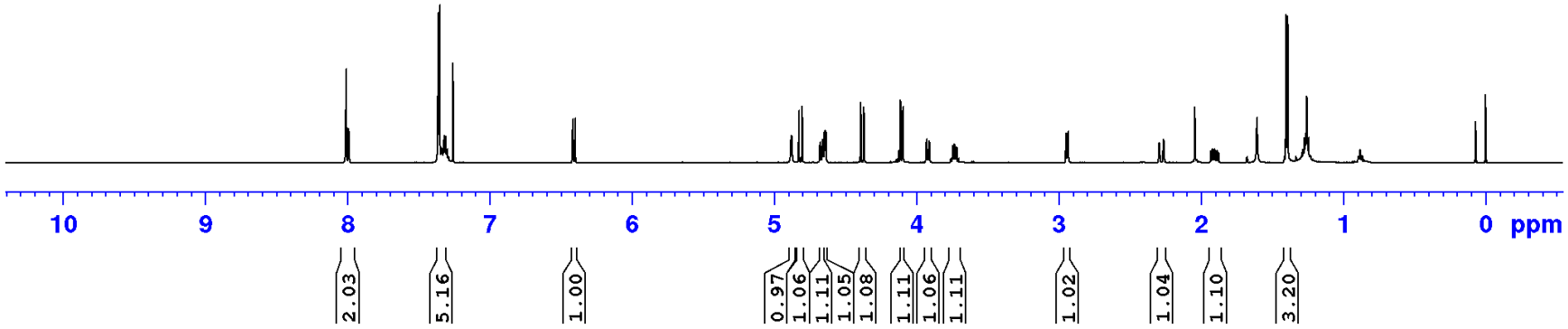
$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

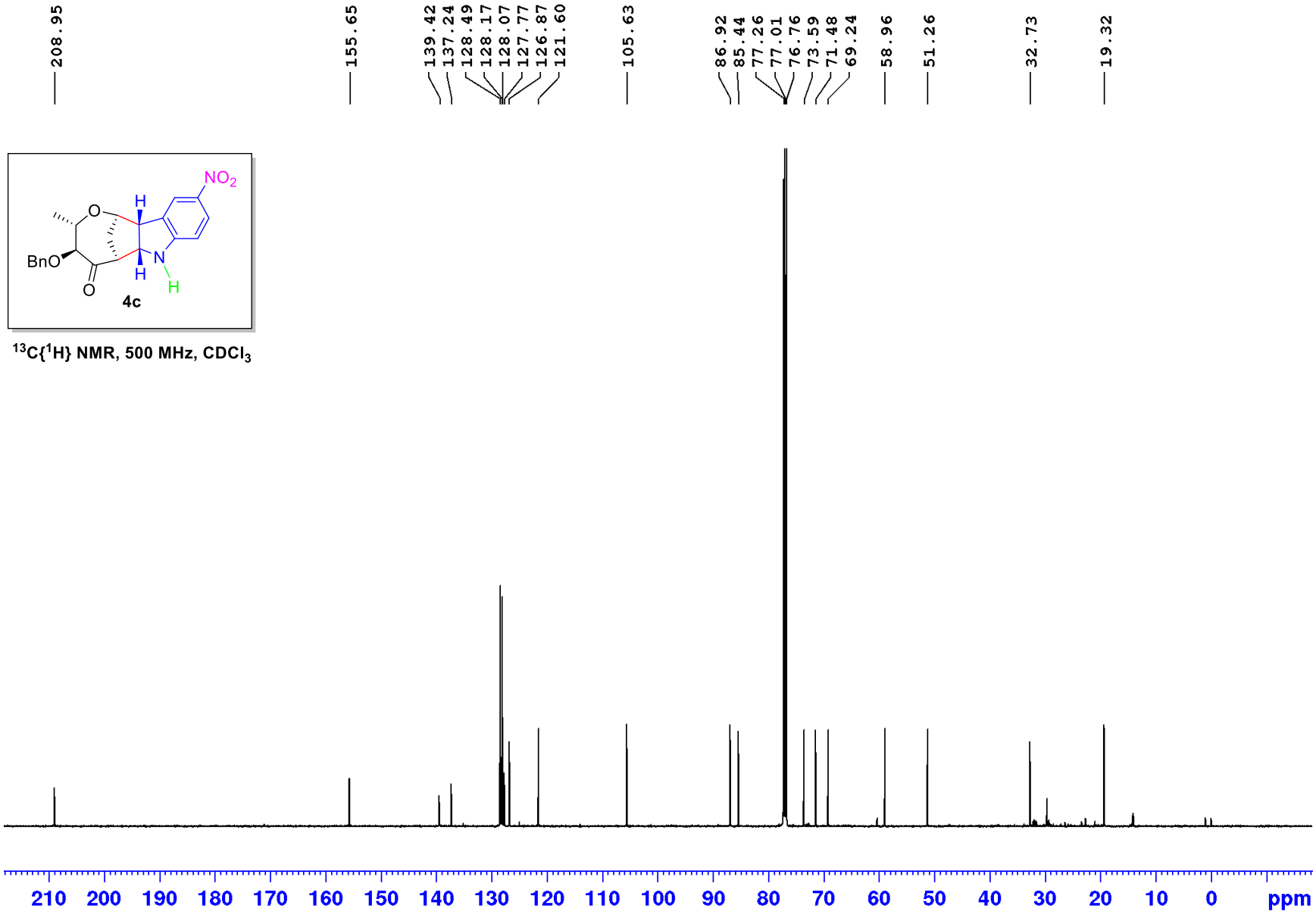

131.05
128.46
128.21
128.00
127.79
109.63
86.94
85.77
73.55
71.00
68.91
59.87
52.18
32.96
19.43
Br
H
O
BnO
N
H
H
O
4b
DEPT 135, 500 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



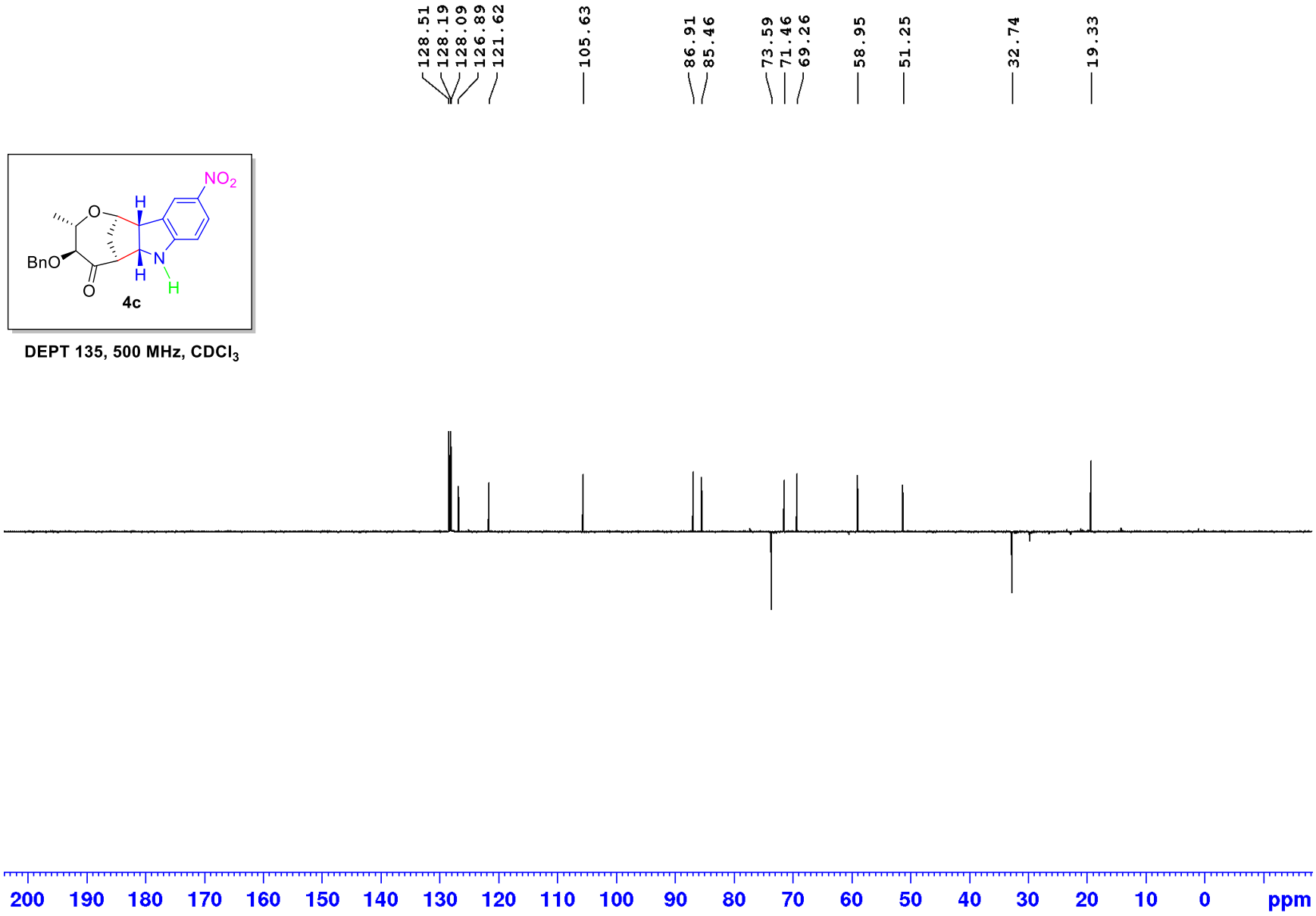


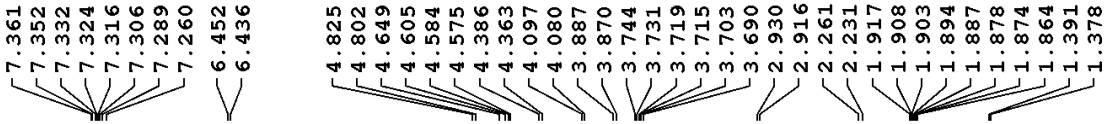
^{1}H NMR, 500 Mz, $CDCl_3$

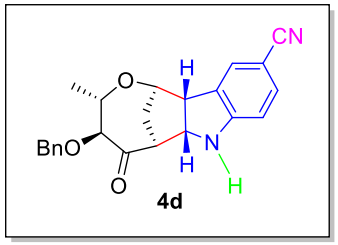




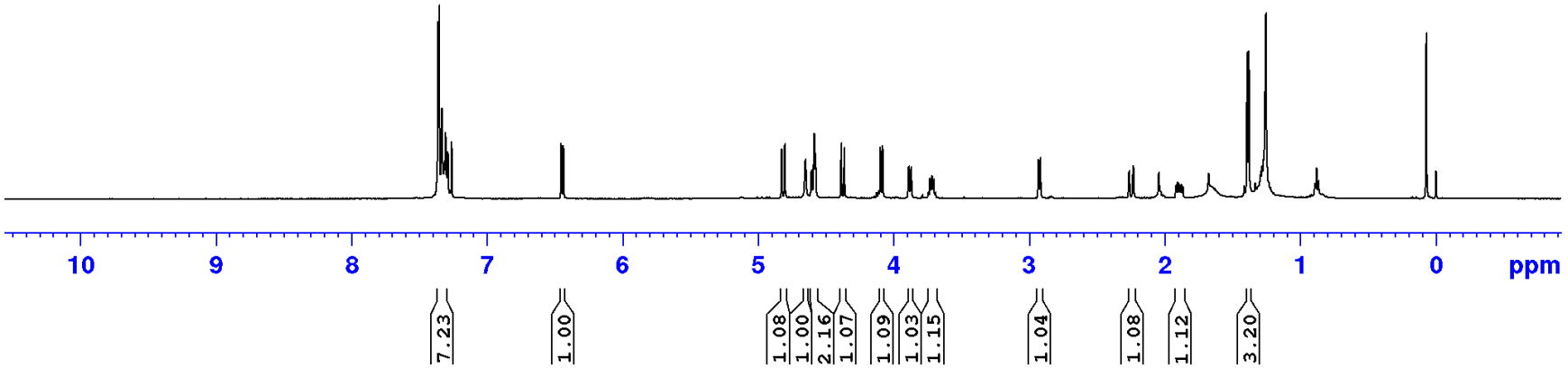
$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

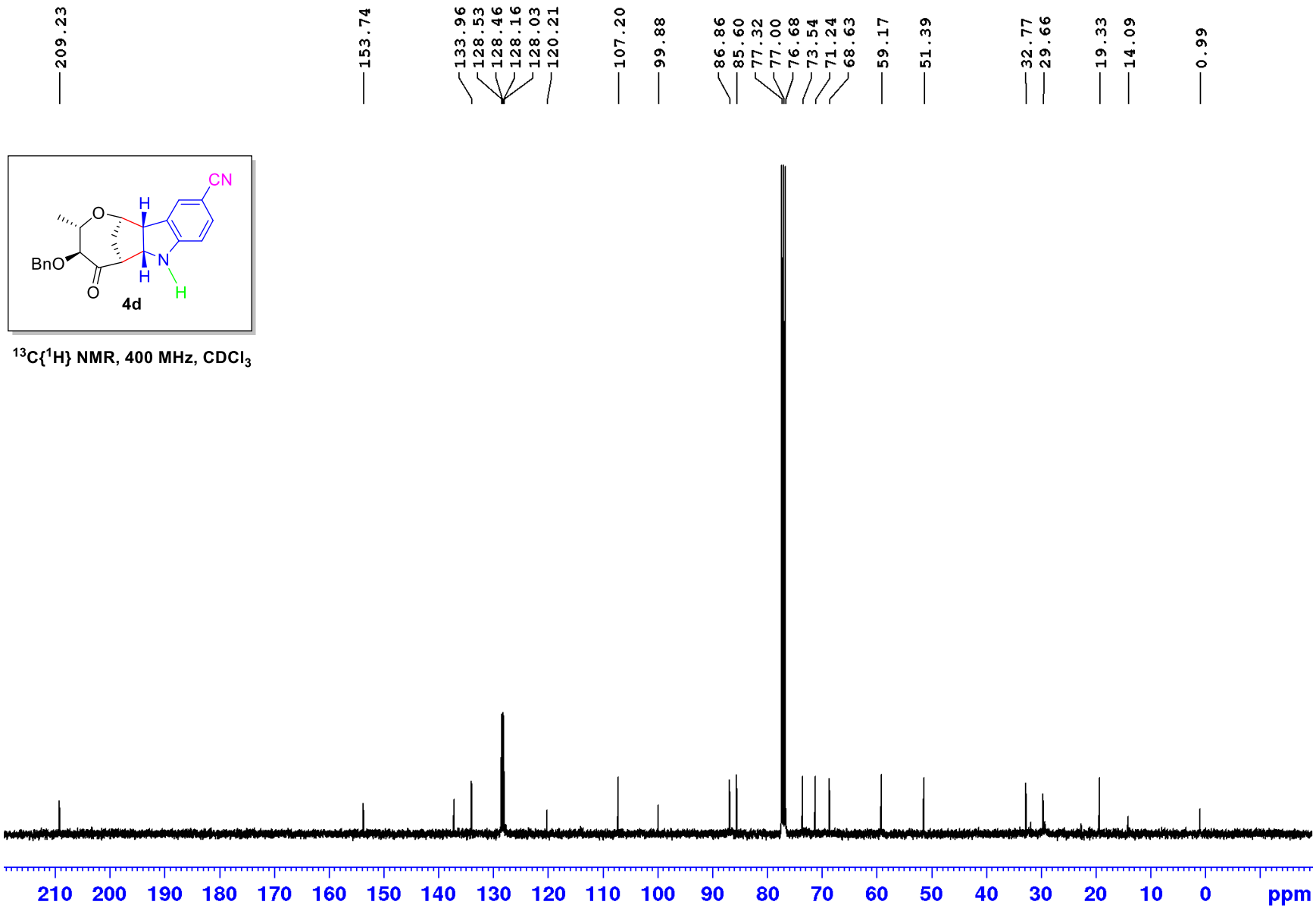

128.51
128.19
128.09
126.89
121.62
105.63
86.91
85.46
73.59
71.46
69.26
58.95
51.25
32.74
19.33
NO2
H
O
BnO
N
H
O
H
4c
DEPT 135, 500 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



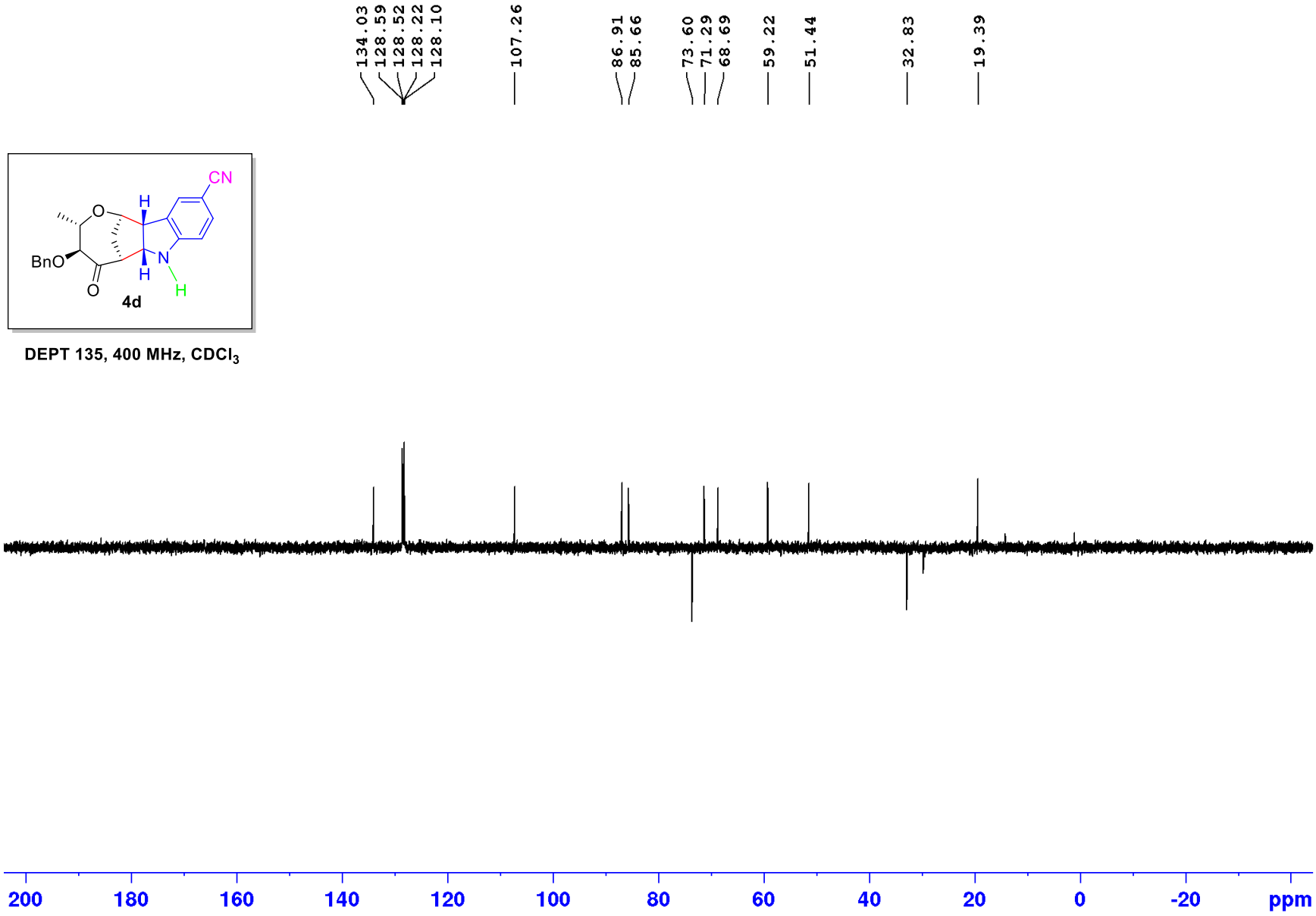


^{1}H NMR, 500 Mz, $CDCl_3$

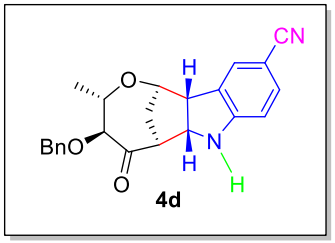




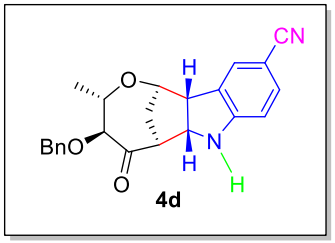
$^{13}C\{^{1}H\}$ NMR, 400 MHz, $CDCl_3$



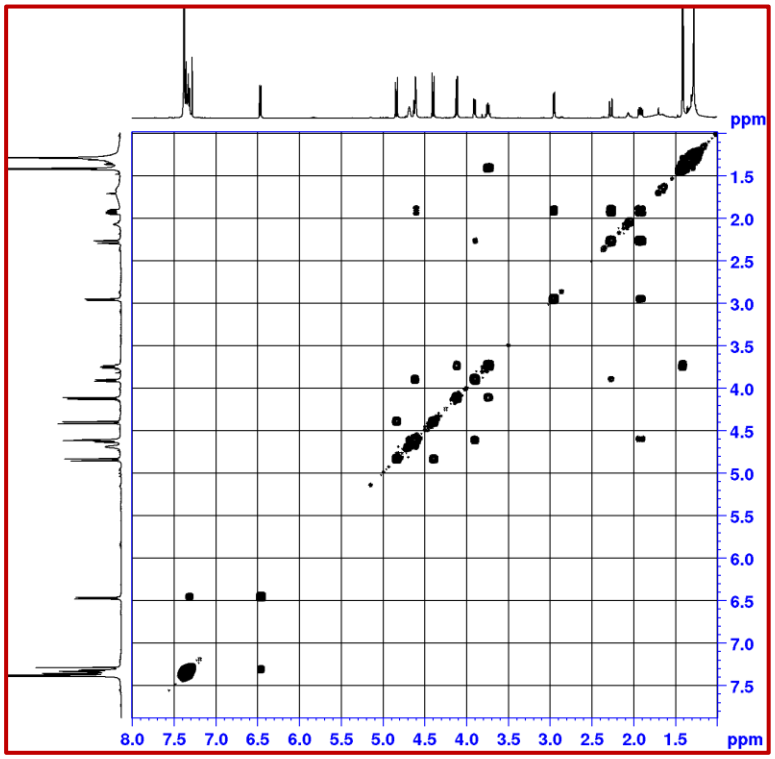
DEPT 135, 400 MHz, $CDCl_3$

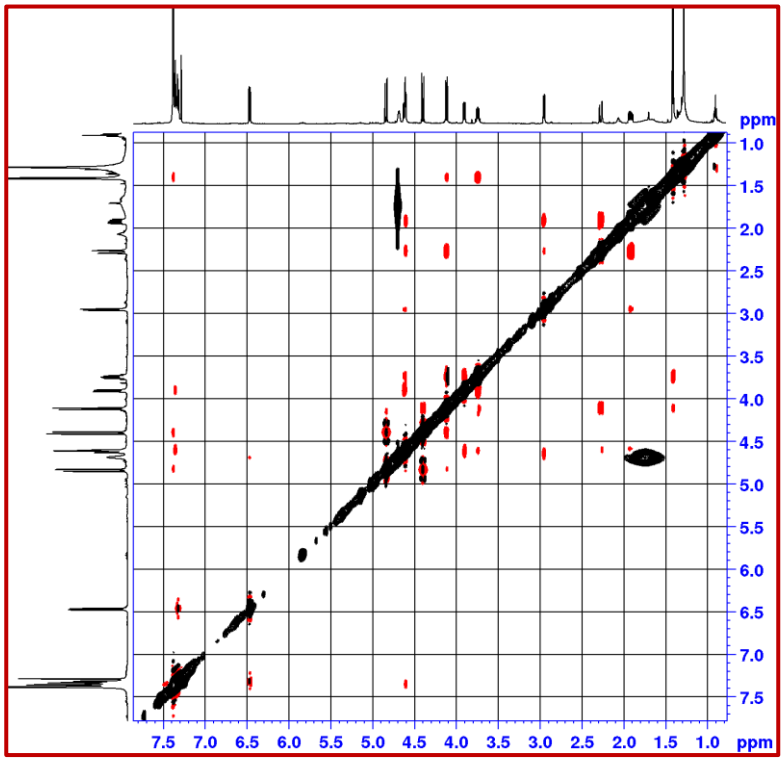


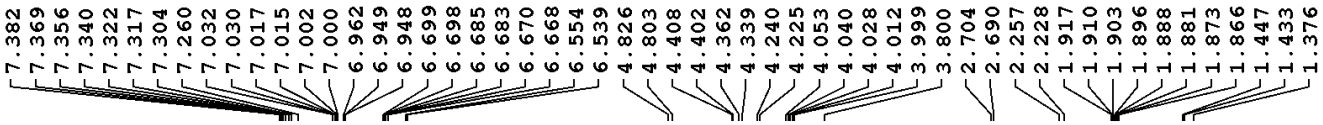
(COSY, 500 MHz)

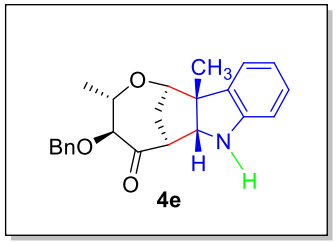


(NOESY, 500 MHz)

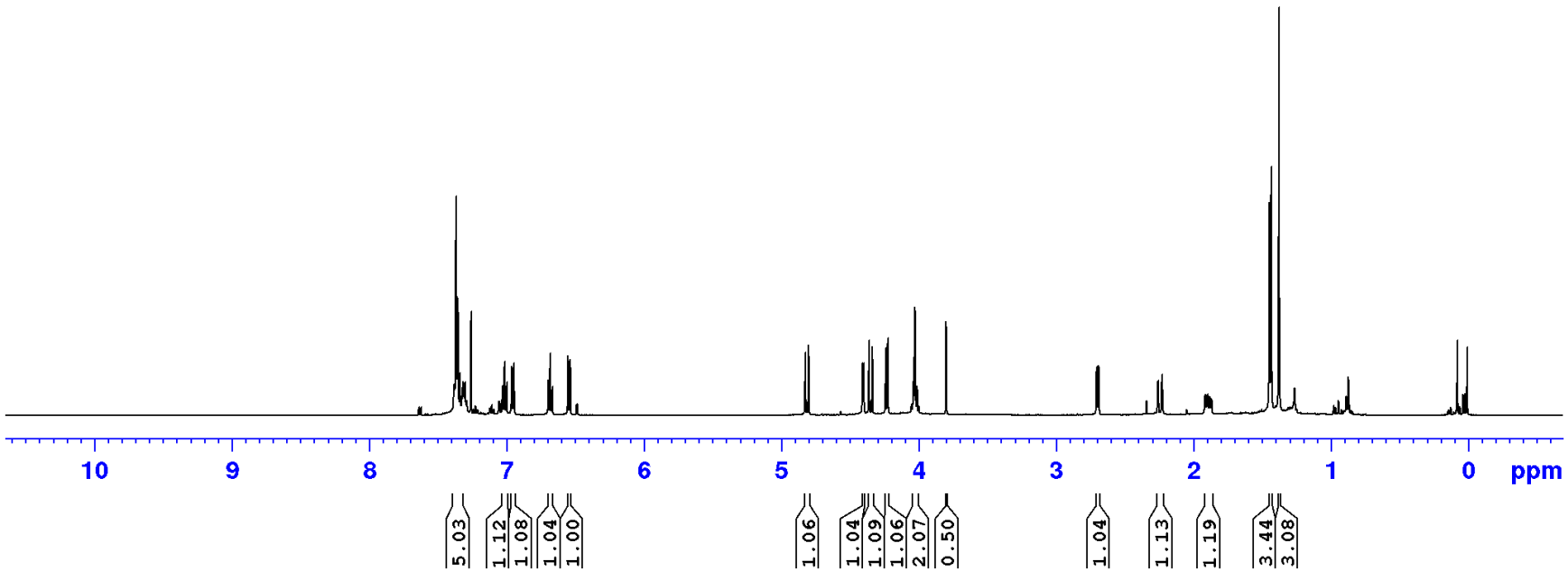




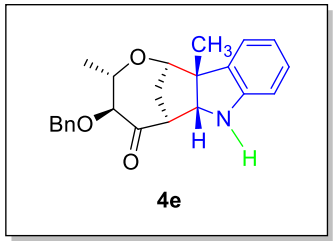




^{1}H NMR, 500 Mz, $CDCl_3$

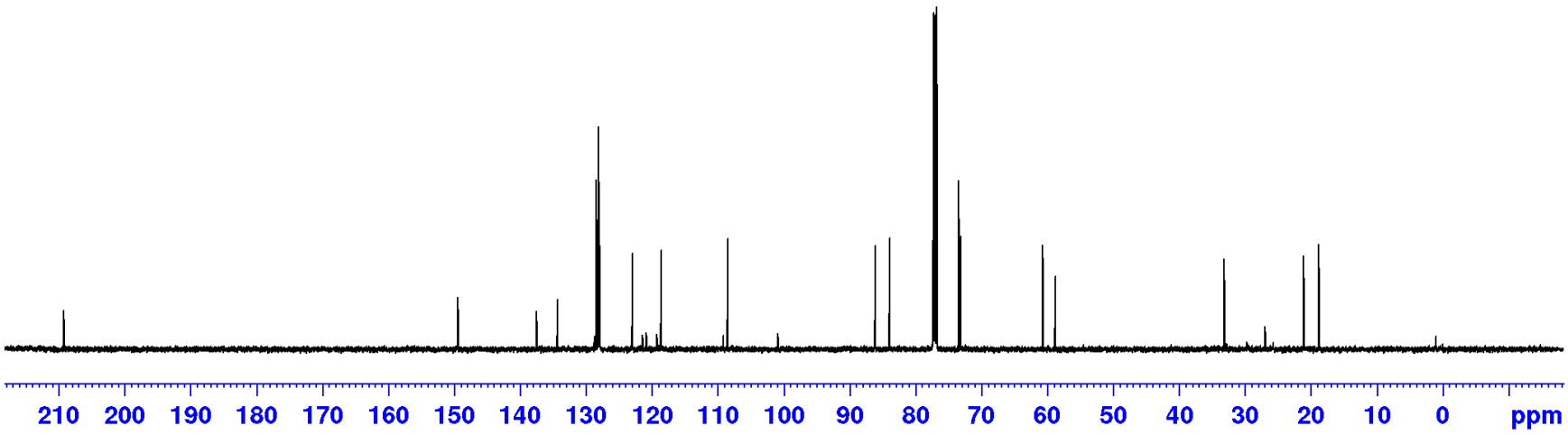


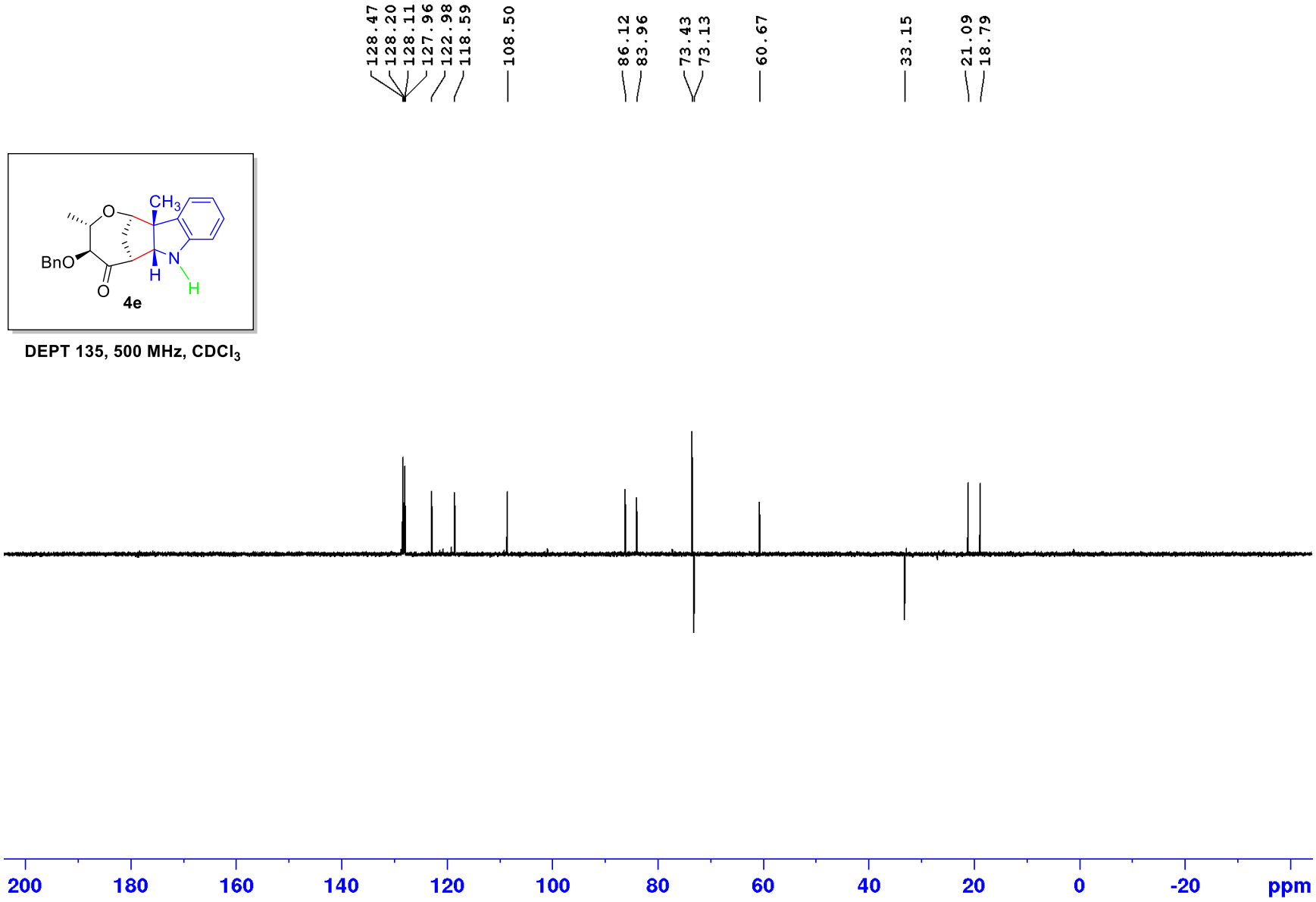
209.24
149.44
137.51
134.31
128.43
128.17
128.07
127.92
122.94
118.57
108.47
86.10
83.94
77.26
77.00
76.75
73.41
73.10
60.65
58.76
33.13
21.06
18.76



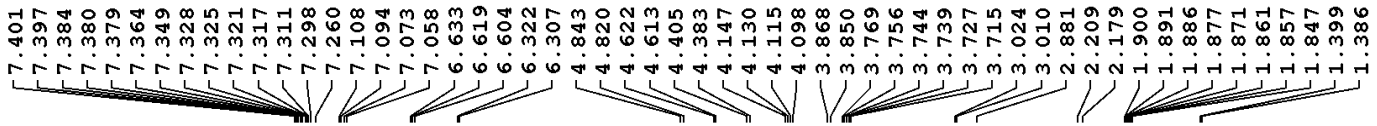
4e

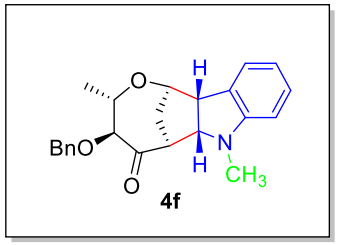
$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$



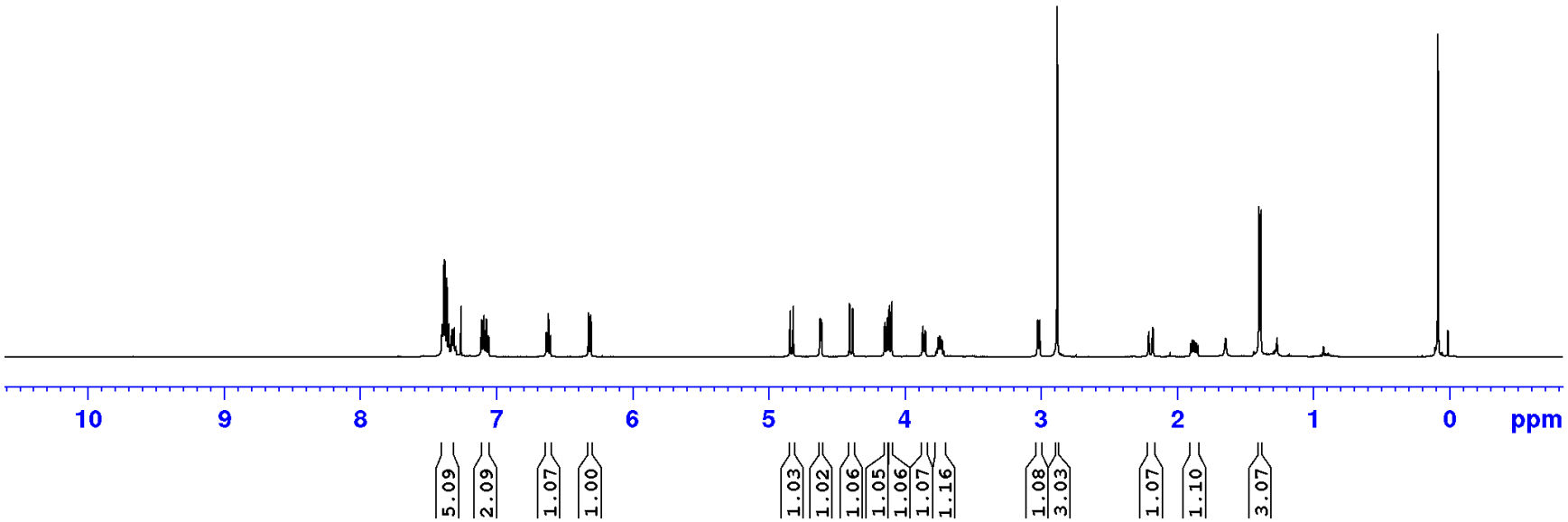


DEPT 135, 500 MHz, $CDCl_3$

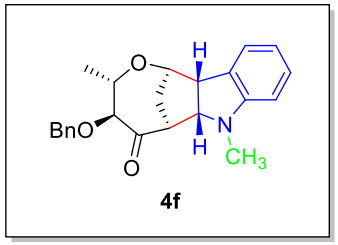




^{1}H NMR, 500 Mz, $CDCl_3$

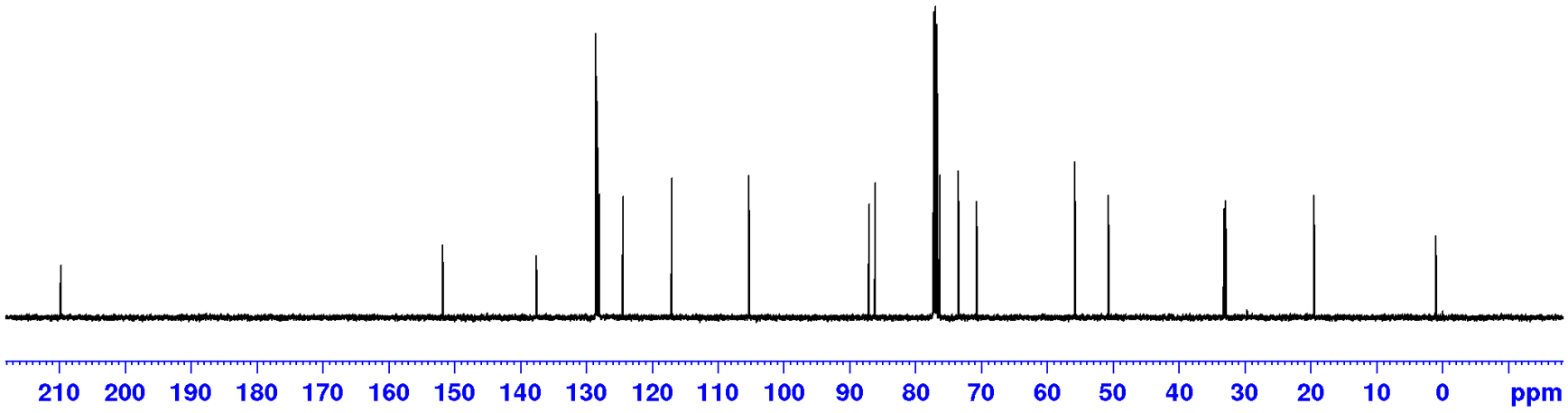


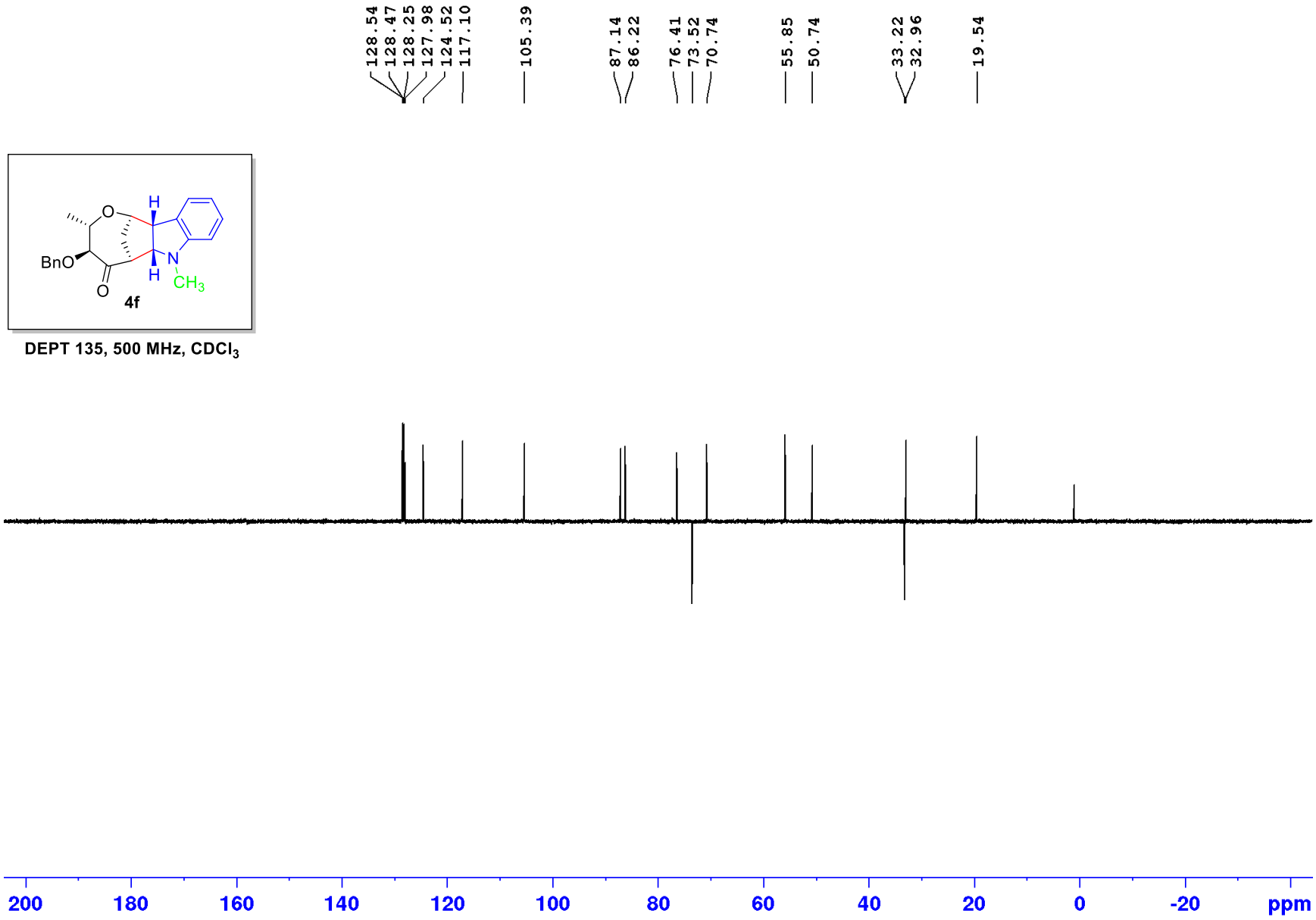
209.82
151.68
137.46
128.48
128.41
128.19
127.91
124.46
117.05
105.34
87.10
86.16
77.26
77.00
76.75
76.35
73.47
70.70
55.81
50.71
33.16
32.90
19.48
0.99

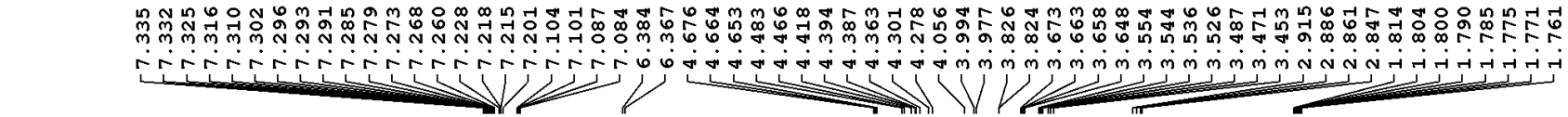


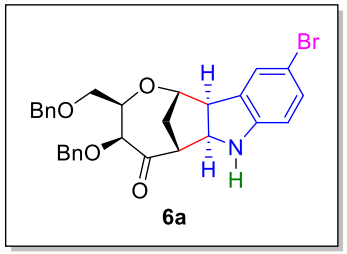
4f

$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$



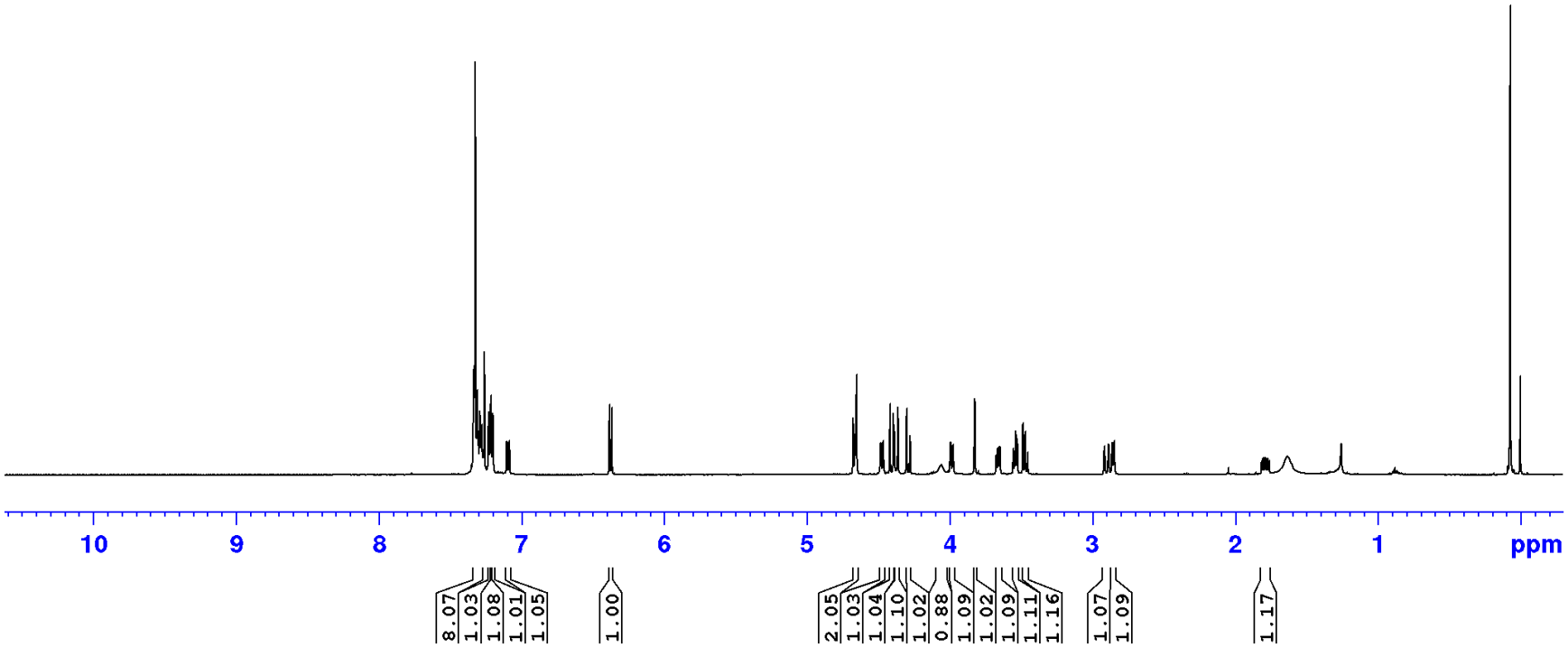

128.54
128.47
128.25
127.98
124.52
117.10
105.39
87.14
86.22
76.41
73.52
70.74
55.85
50.74
33.22
32.96
19.54
BnO
O
H
N
H
CH3
O
4f
DEPT 135, 500 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

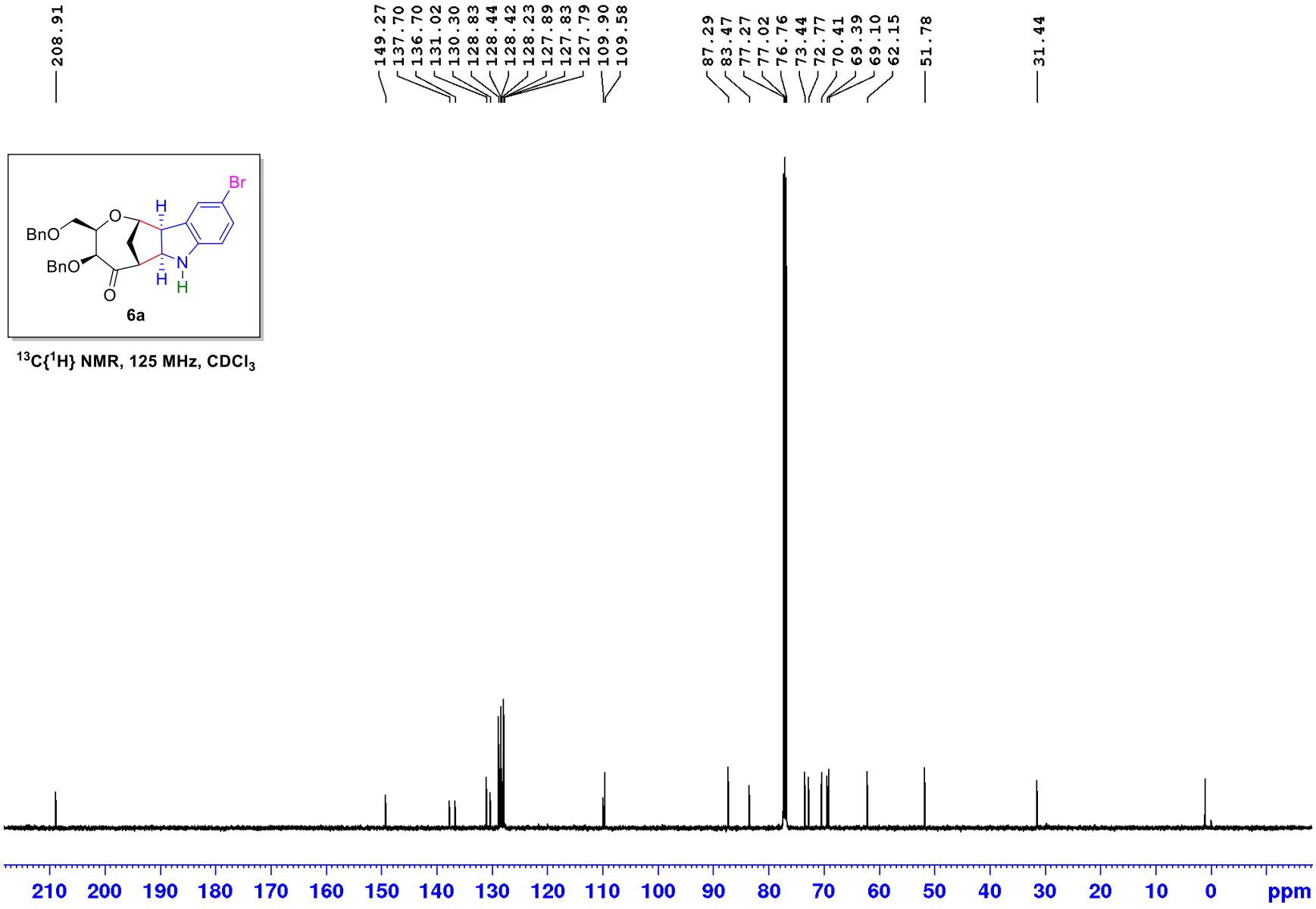




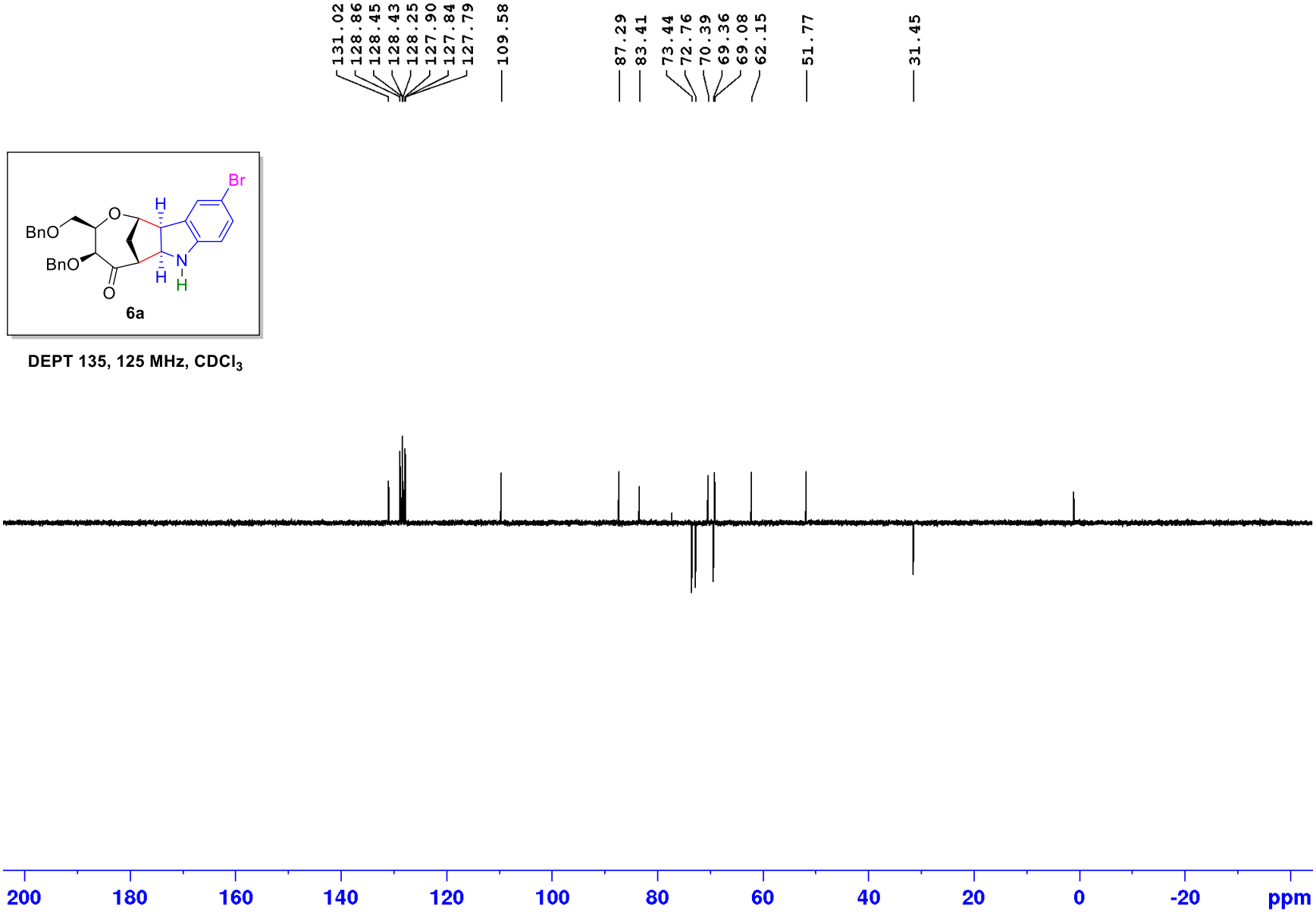
6a

^{1}H NMR, 500 Mz, $CDCl_3$

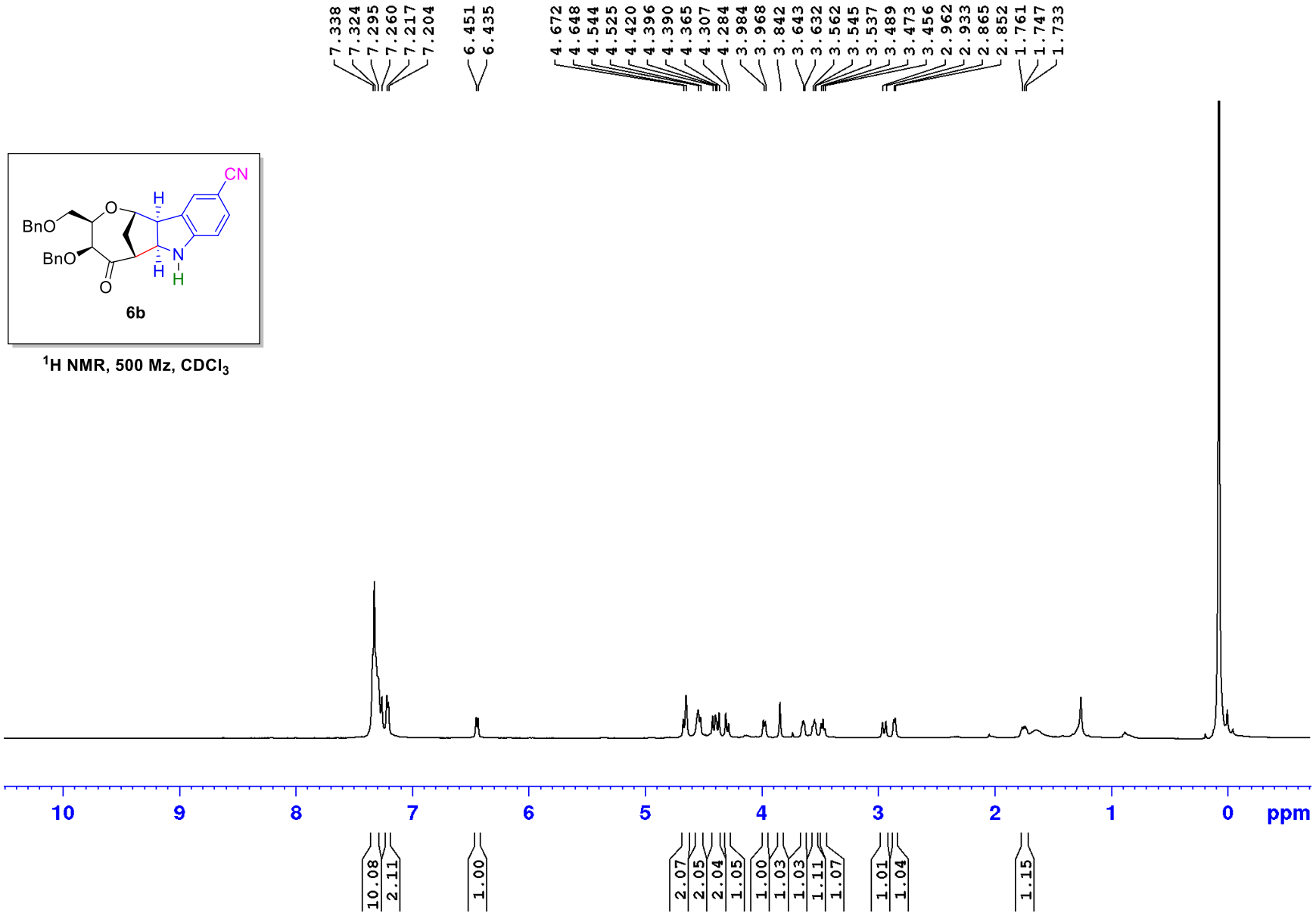




$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$

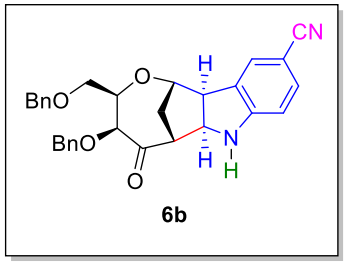


DEPT 135, 125 MHz, $CDCl_3$



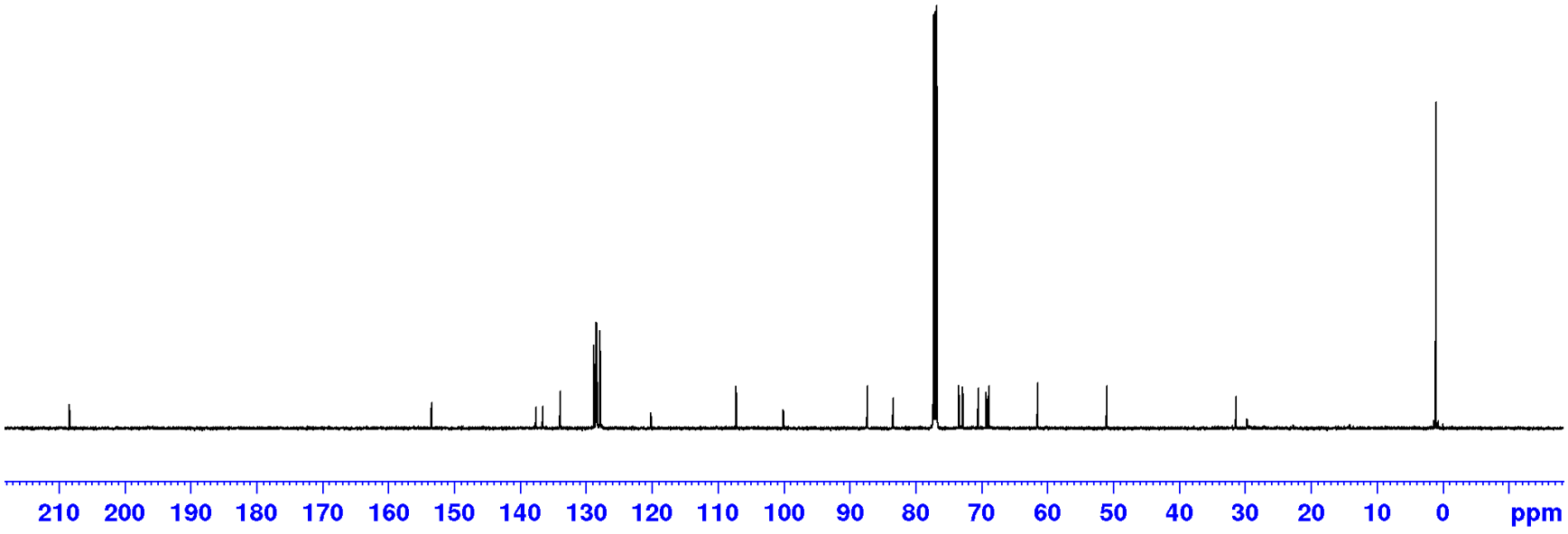
^{1}H NMR, 500 Mz, $CDCl_3$

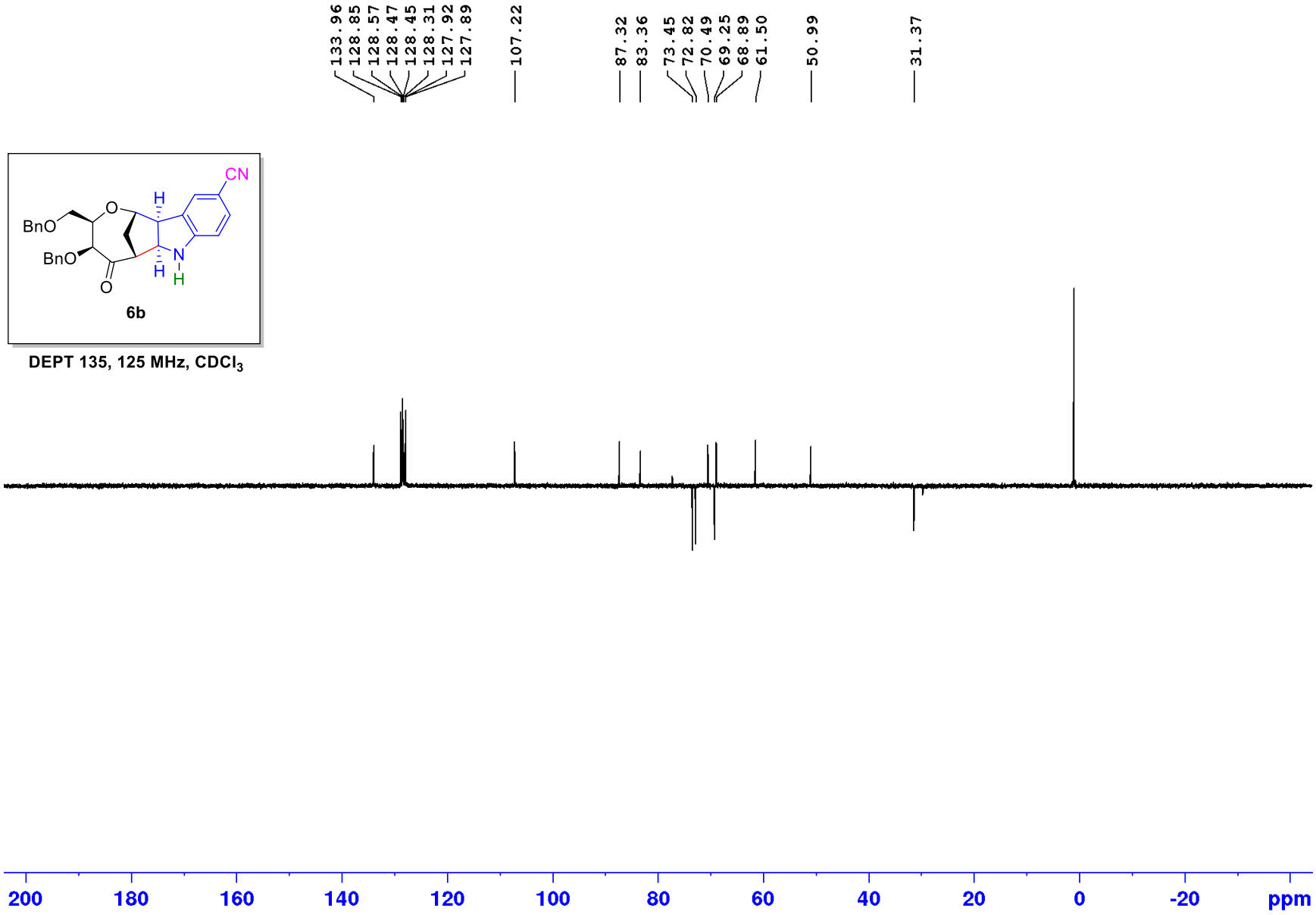
208.41
153.45
137.60
136.58
133.93
128.79
128.54
128.44
128.41
128.27
127.88
127.85
120.16
107.20
100.03
87.29
83.40
77.26
77.00
76.75
73.44
72.82
70.49
69.25
68.88
61.47
50.97
31.33

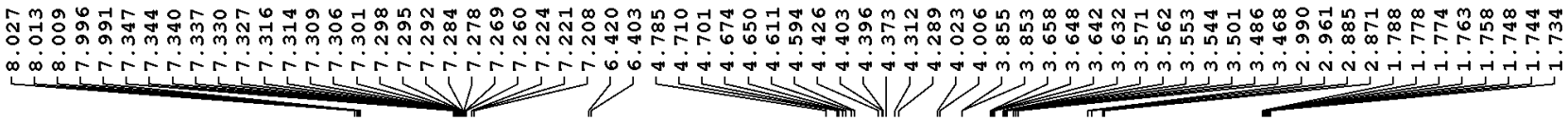


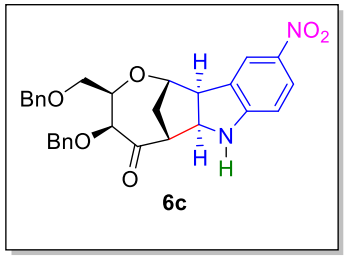
6b

$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$



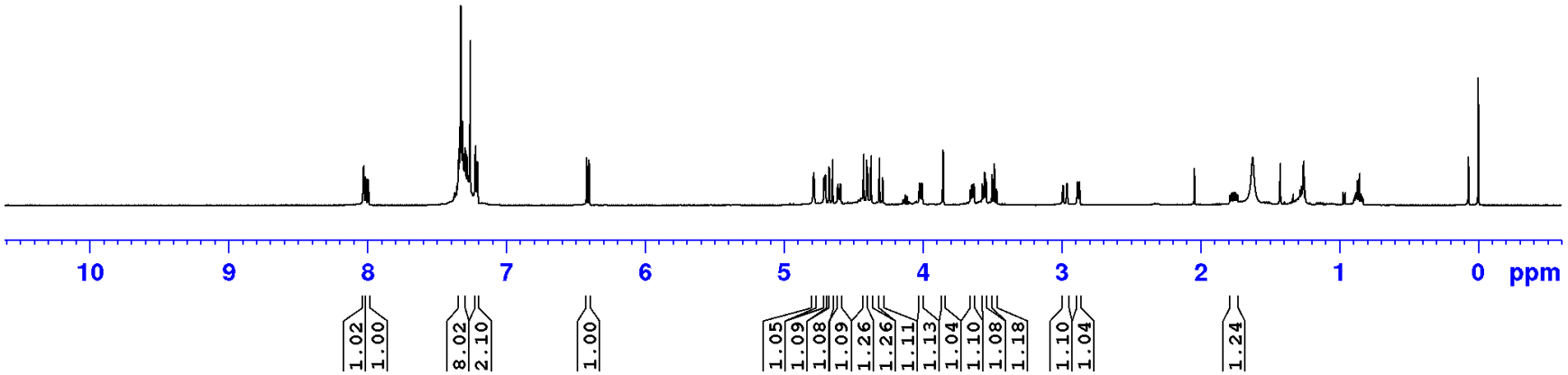

133.96
128.85
128.57
128.47
128.45
128.31
127.92
127.89
107.22
87.32
83.36
73.45
72.82
70.49
69.25
68.89
61.50
50.99
31.37
CN
BnO
BnO
O
H
N
H
O
6b
DEPT 135, 125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

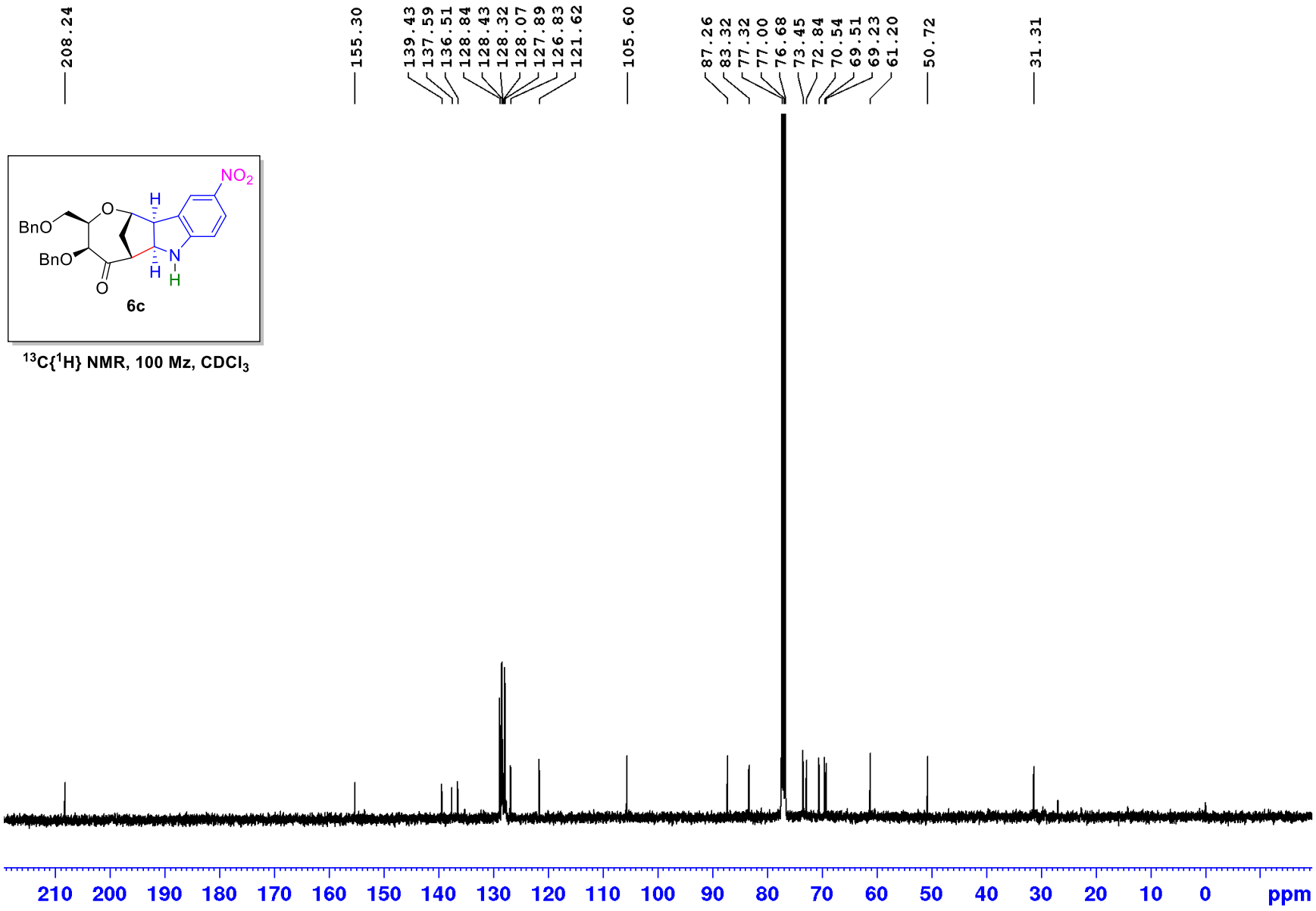




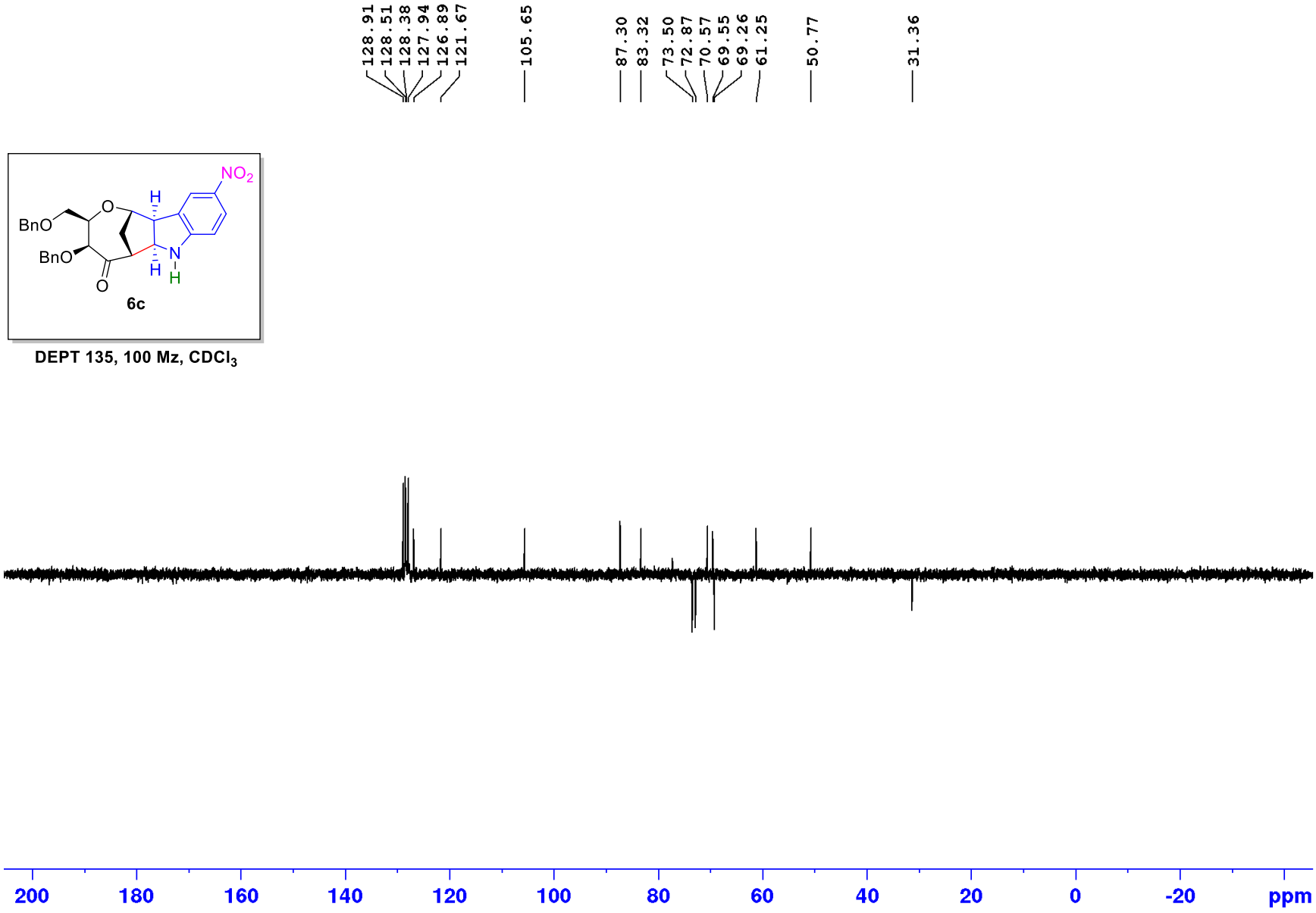
6c

^{1}H NMR, 500 Mz, $CDCl_3$

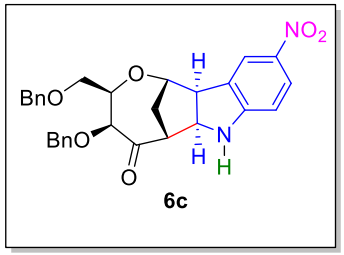




$^{13}C\{^{1}H\}$ NMR, 100 Mz, $CDCl_3$

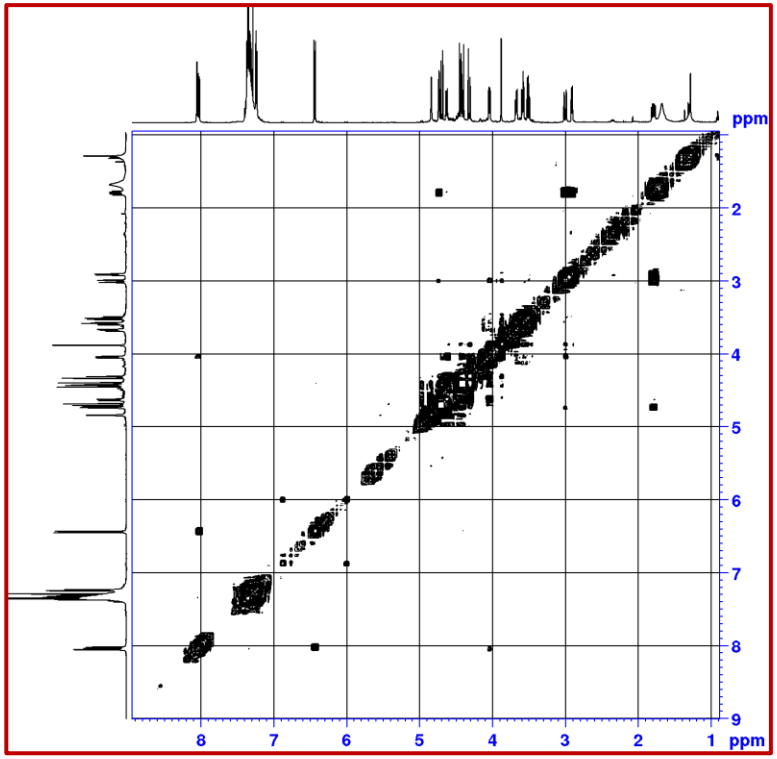


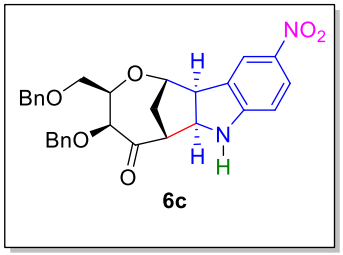
DEPT 135, 100 Mz, $CDCl_3$



6c

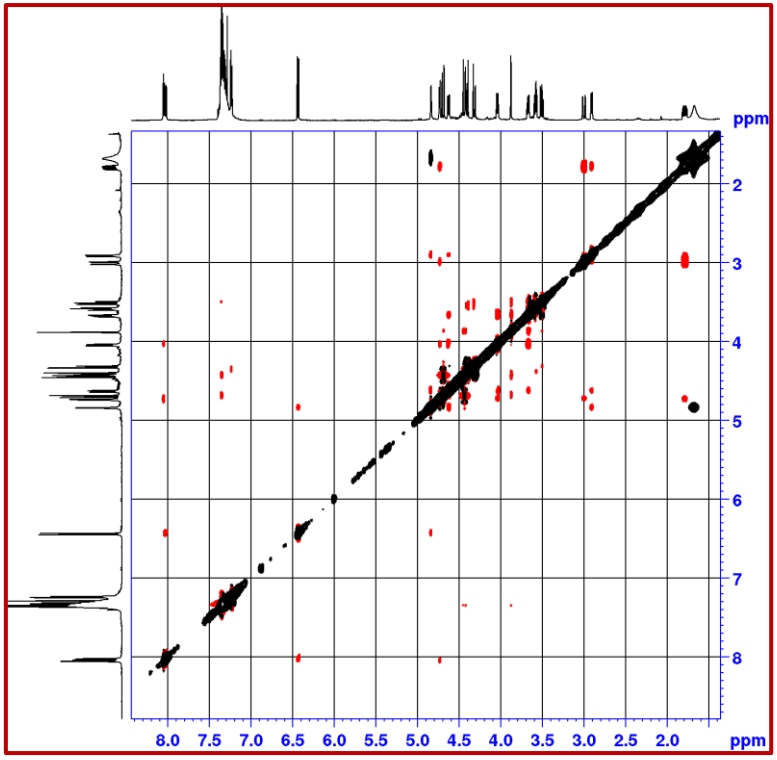
(COSY, 500 MHz)

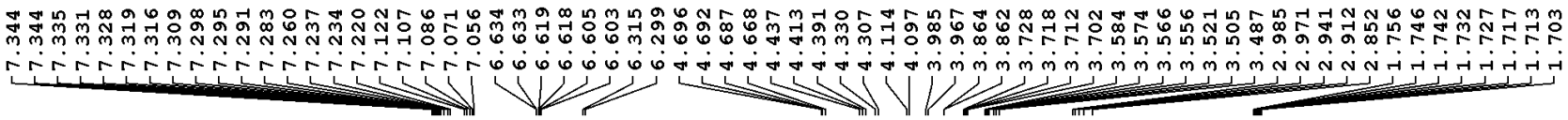


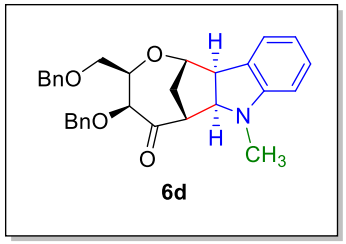


6c

(NOESY, 500 MHz)

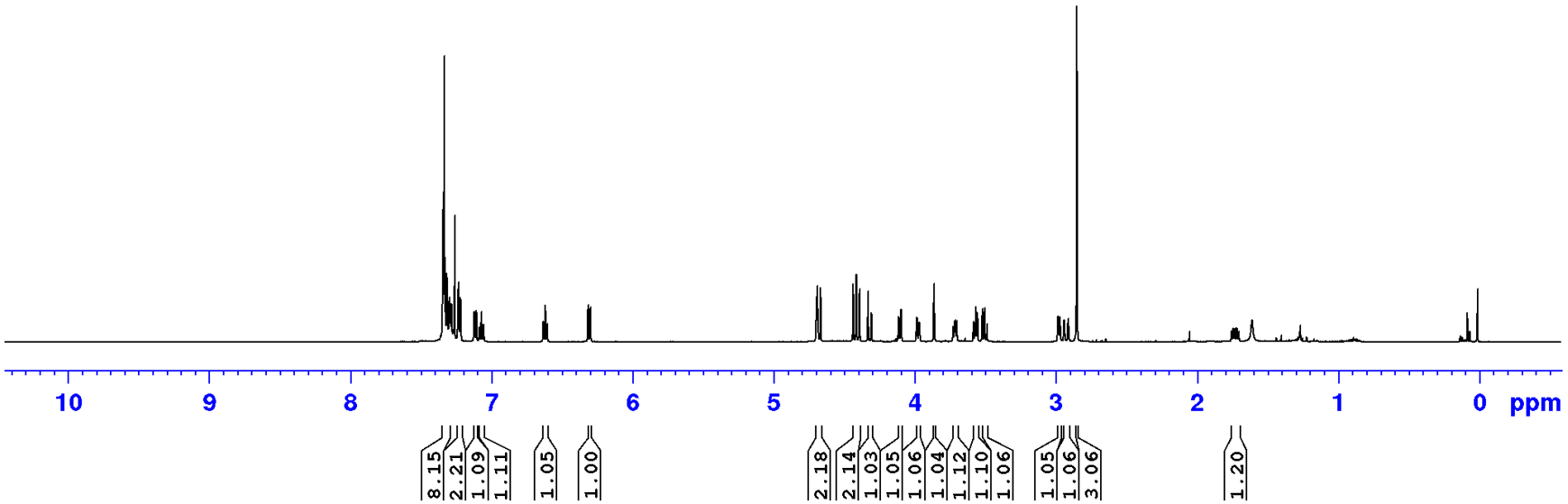




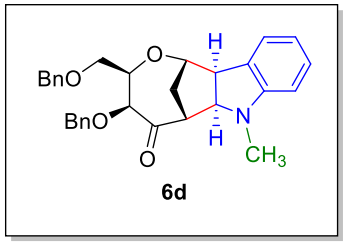


6d

^{1}H NMR, 500 Mz, $CDCl_3$

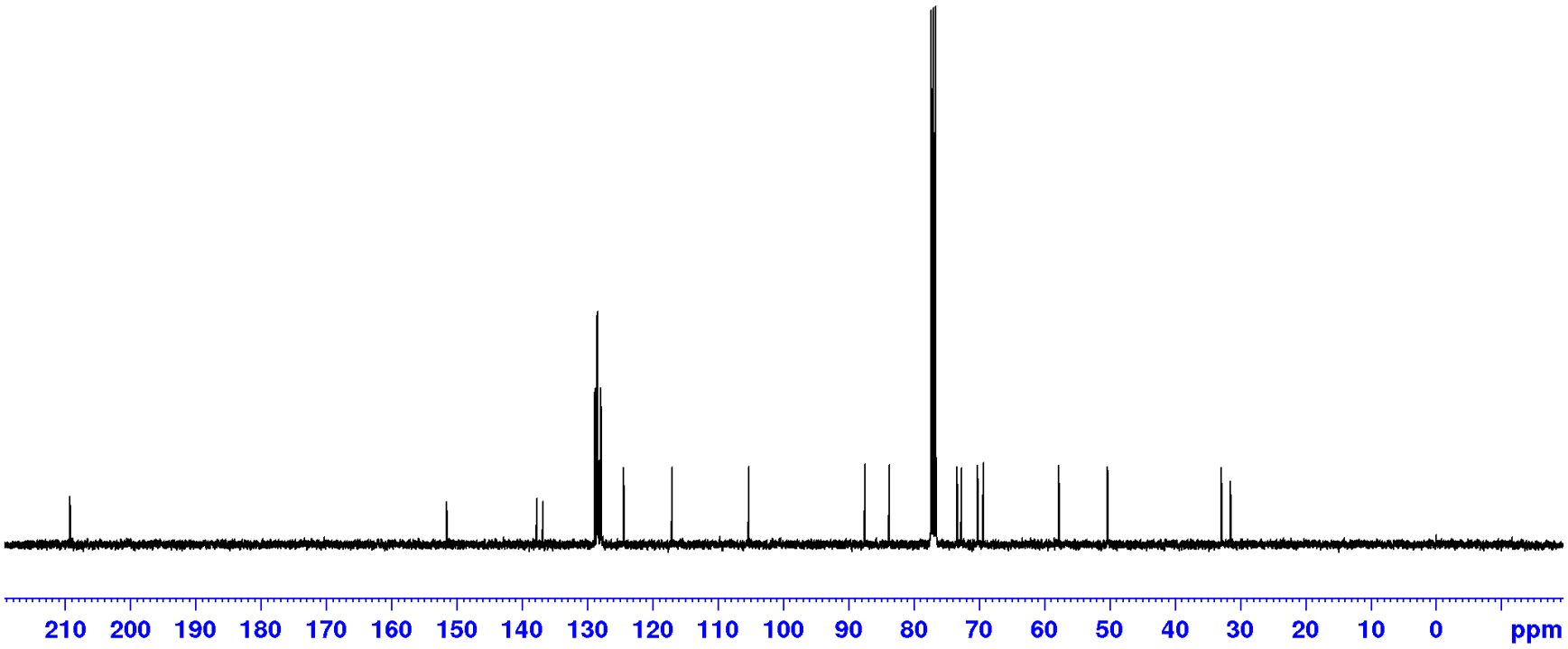


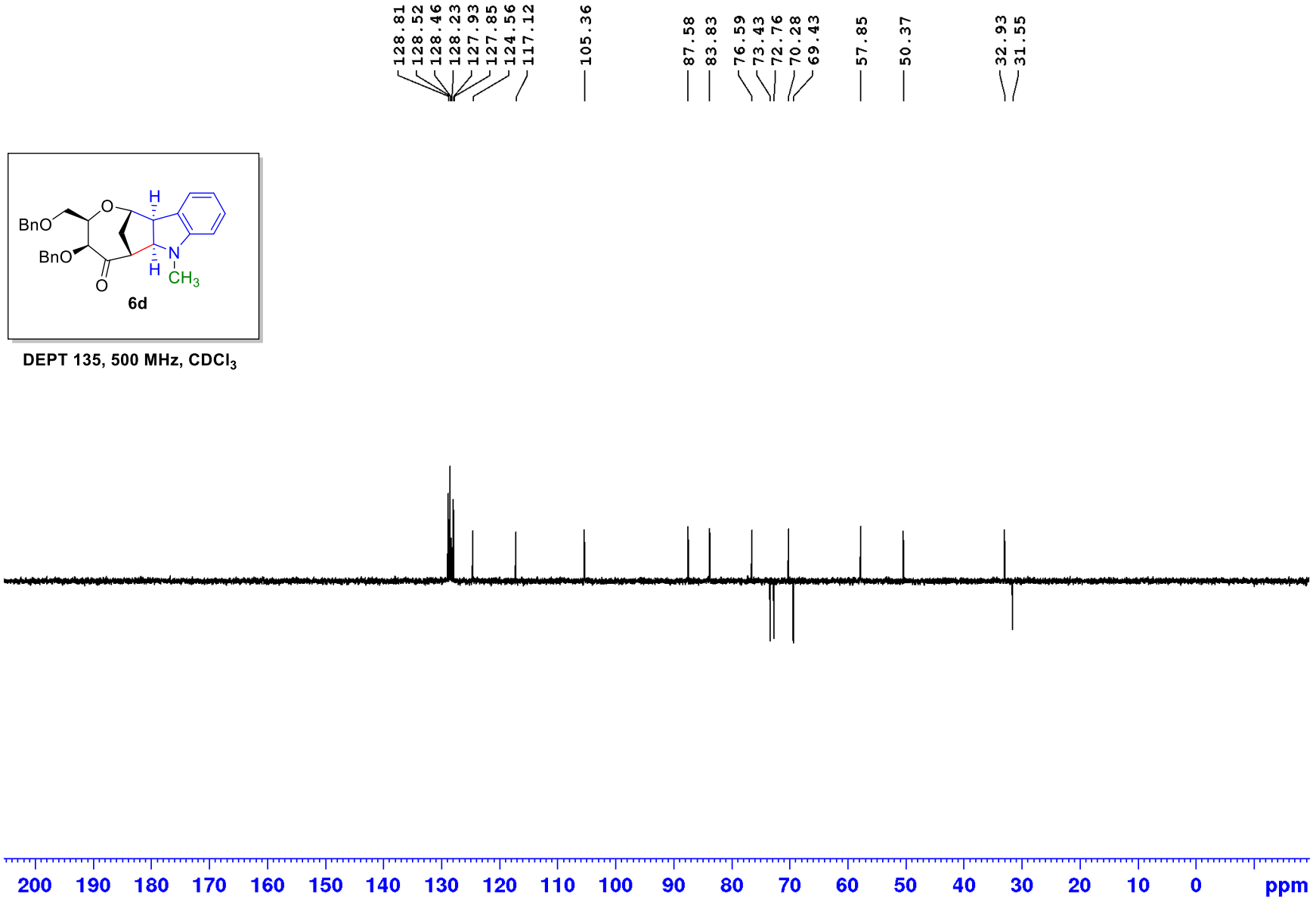
209.30
151.46
137.68
136.75
128.74
128.45
128.38
128.20
128.15
127.85
127.78
124.49
117.05
105.29
87.52
83.78
77.32
77.21
77.00
76.68
76.53
73.37
72.70
70.22
69.37
57.78
50.30
32.86
31.48



6d

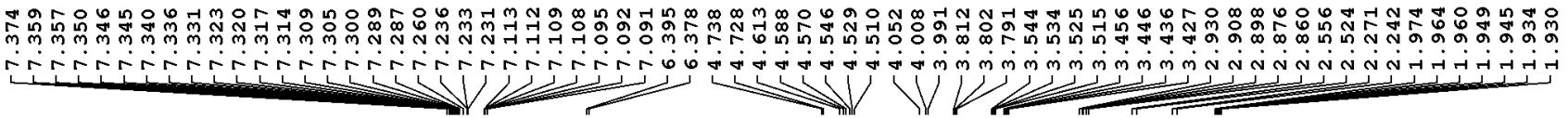
$^{13}C\{^{1}H\}$ NMR, 100 MHz, $CDCl_3$

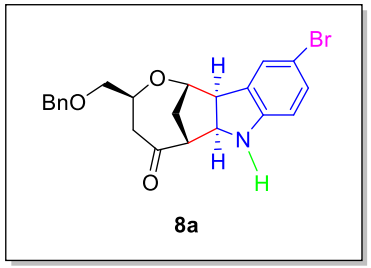




6d

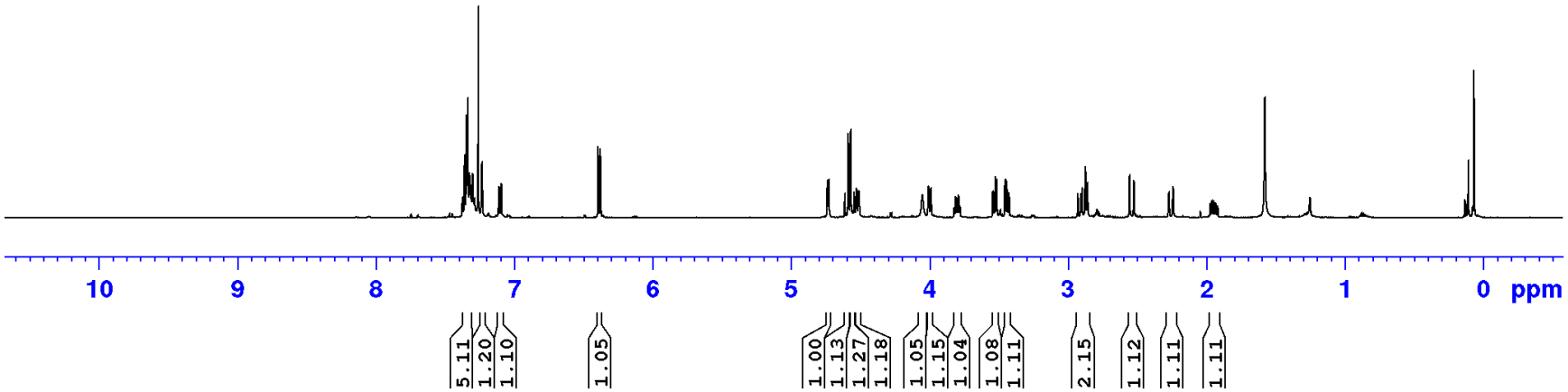
DEPT 135, 500 MHz, $CDCl_3$

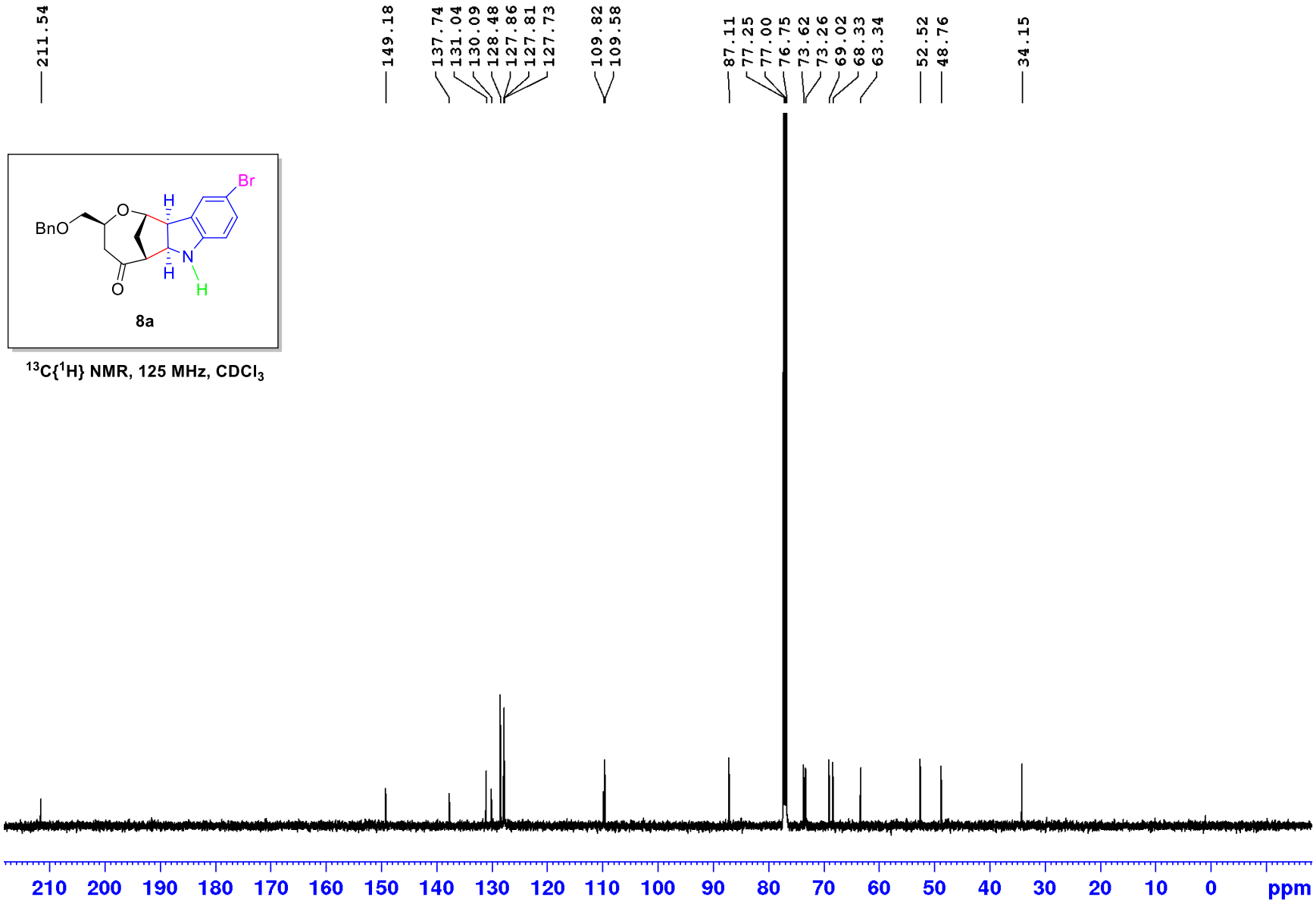




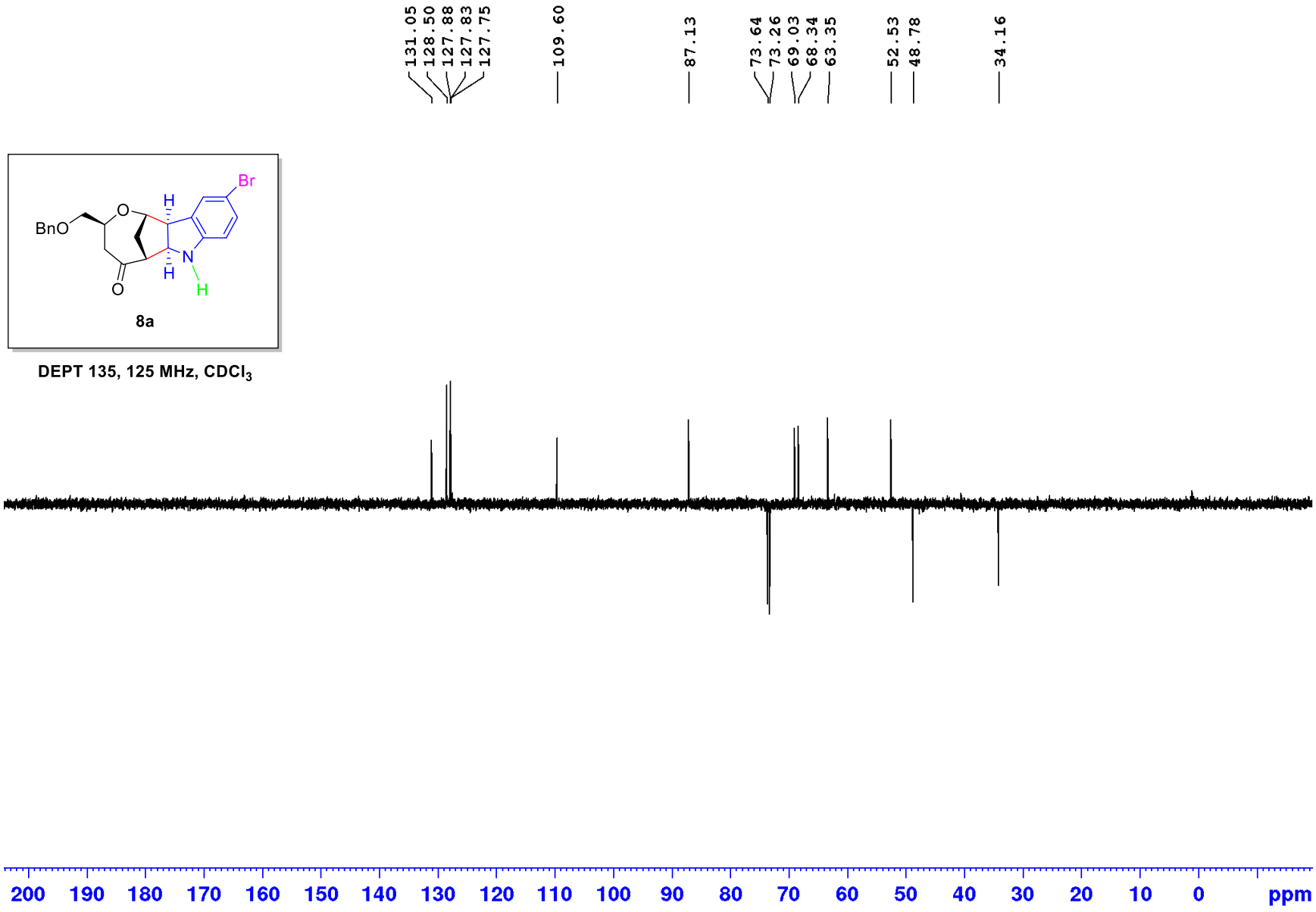
8a

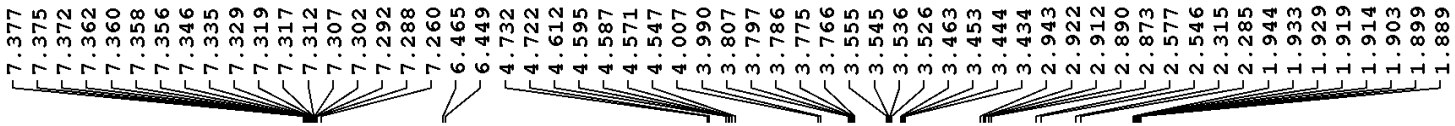
^{1}H NMR, 500 MHz, $CDCl_3$

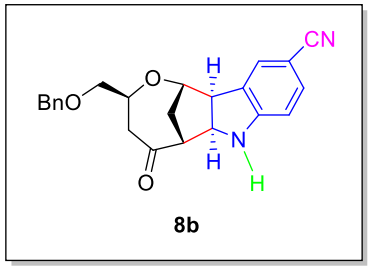




$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$

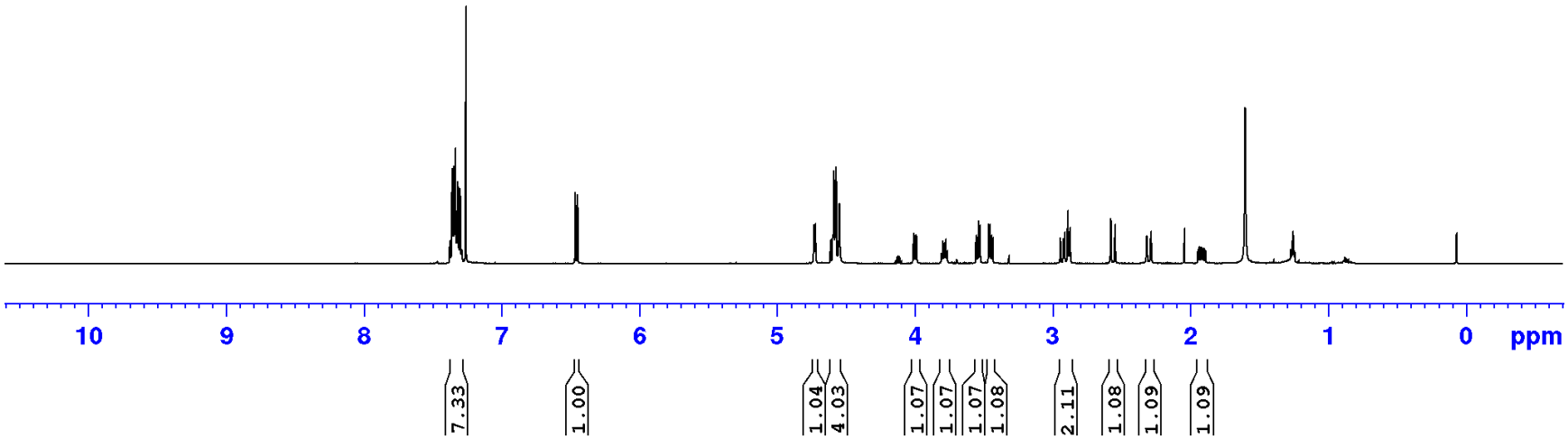

131.05
128.50
127.88
127.83
127.75
109.60
87.13
73.64
73.26
69.03
68.34
63.35
52.53
48.78
34.16
Br
BnO
O
H
N
H
O
H
8a
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

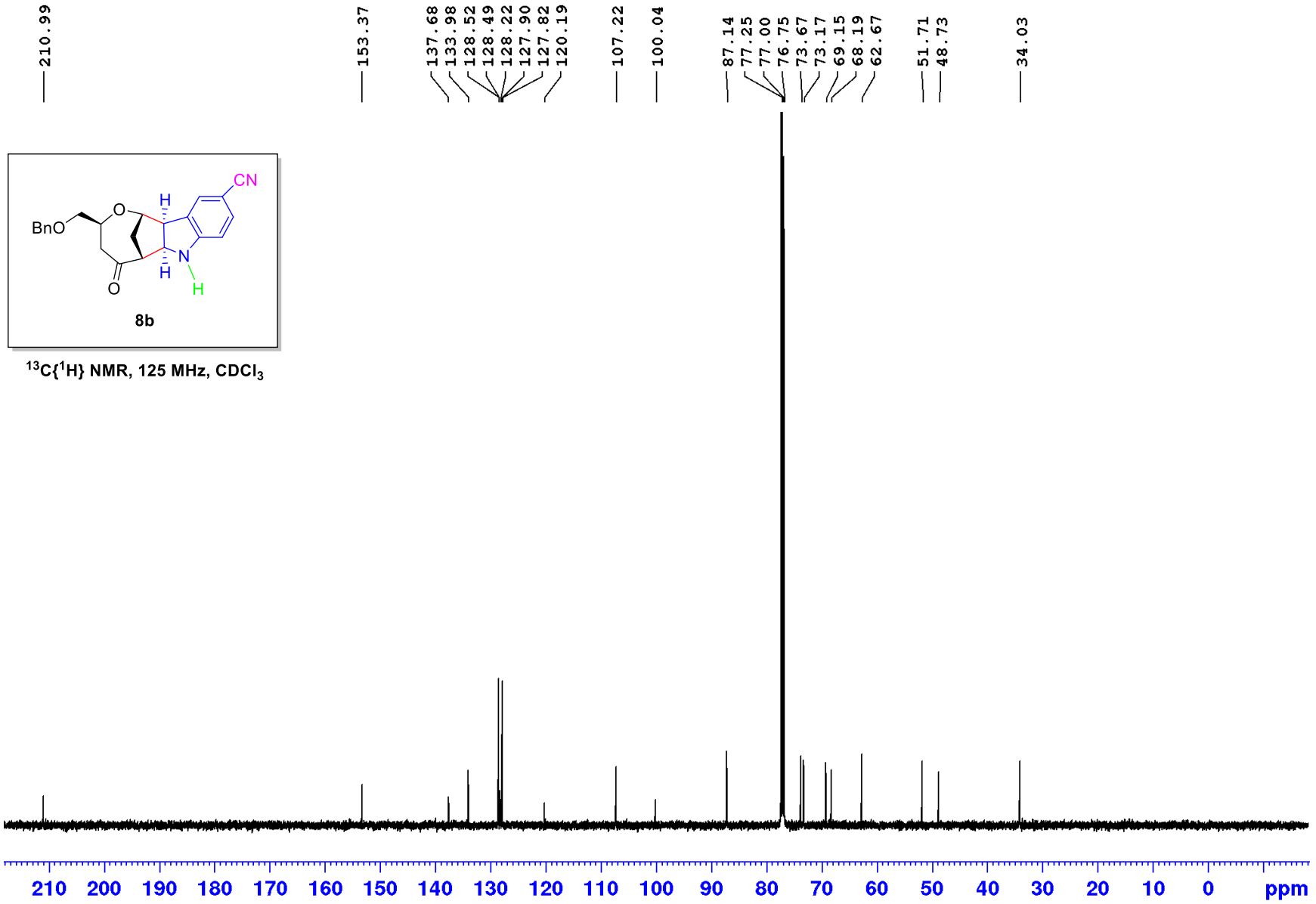




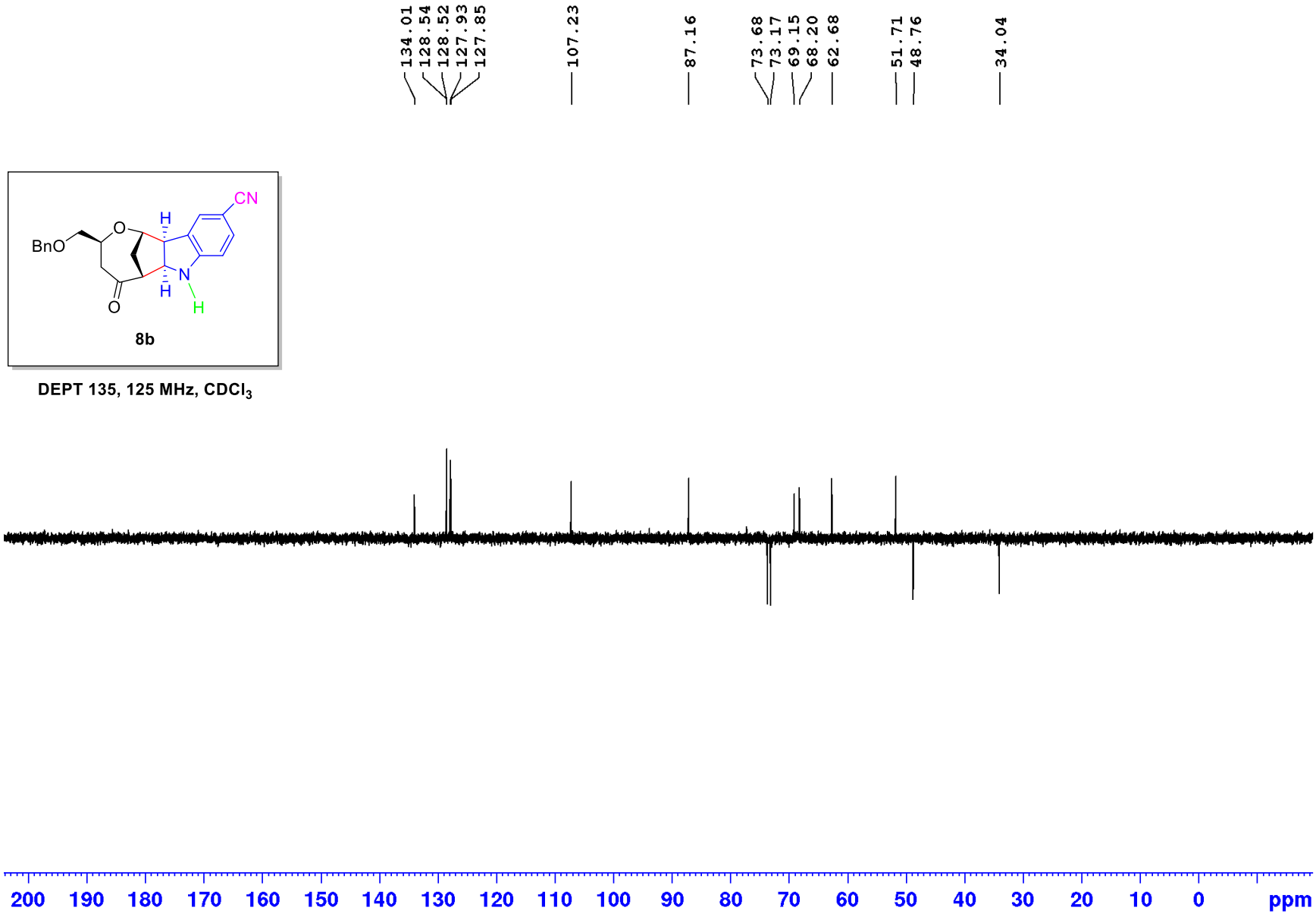
8b

^{1}H NMR, 500 MHz, $CDCl_3$

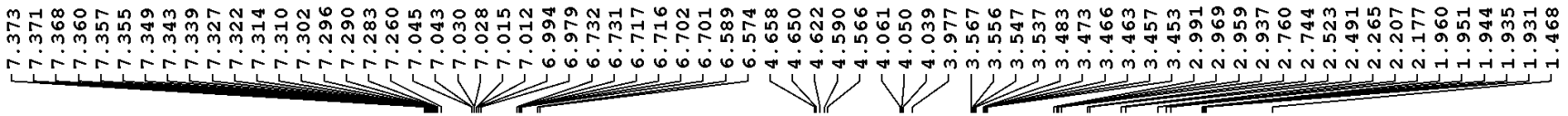


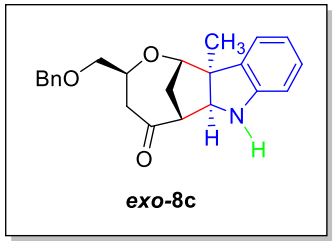


$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$



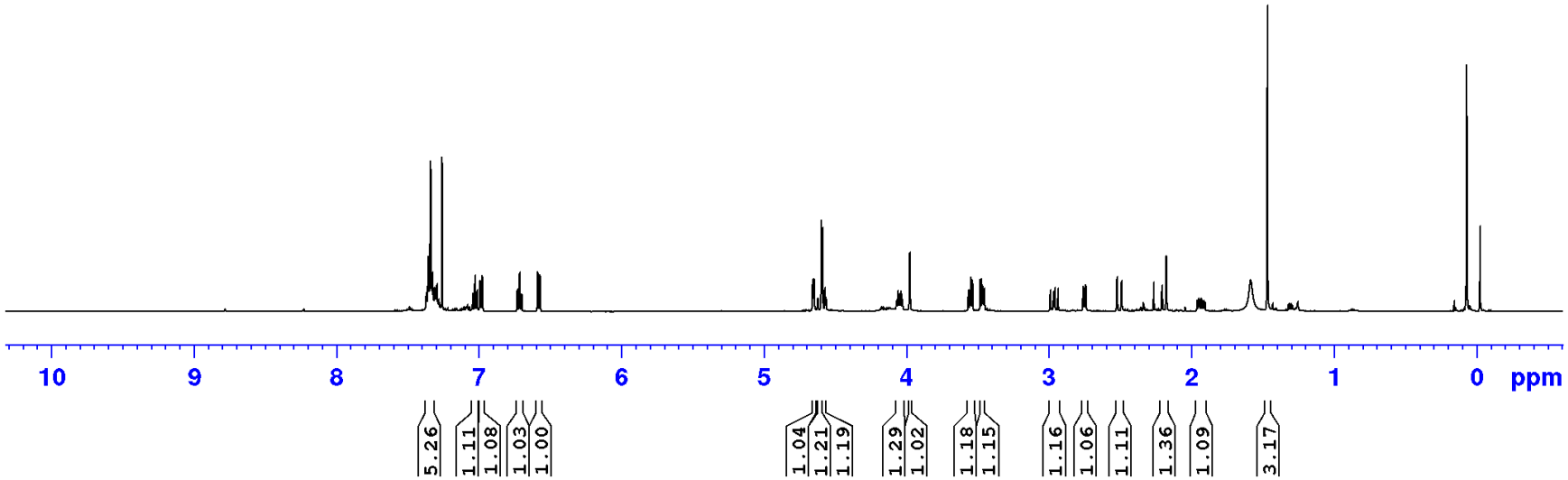
DEPT 135, 125 MHz, $CDCl_3$

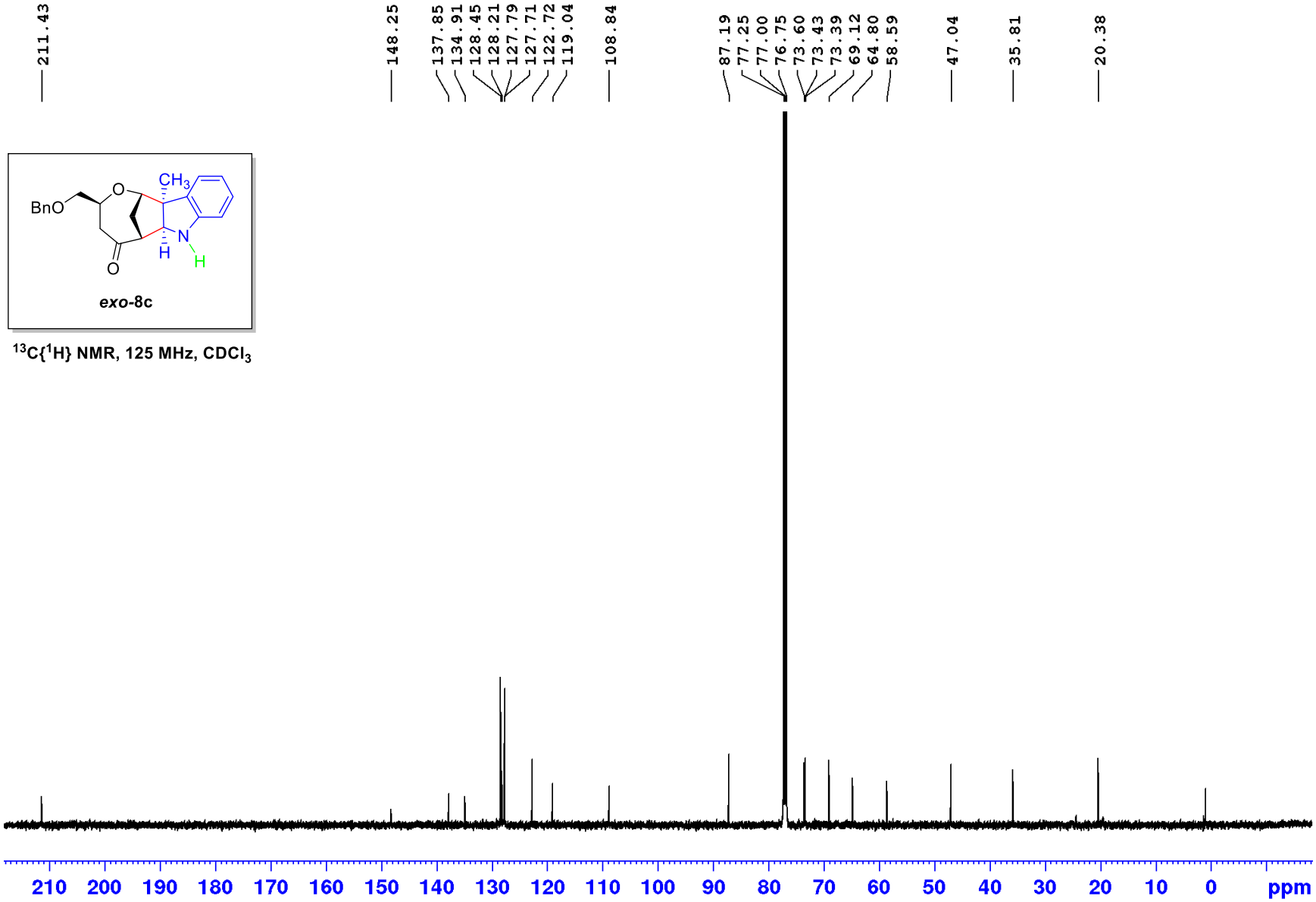




***exo*-8c**

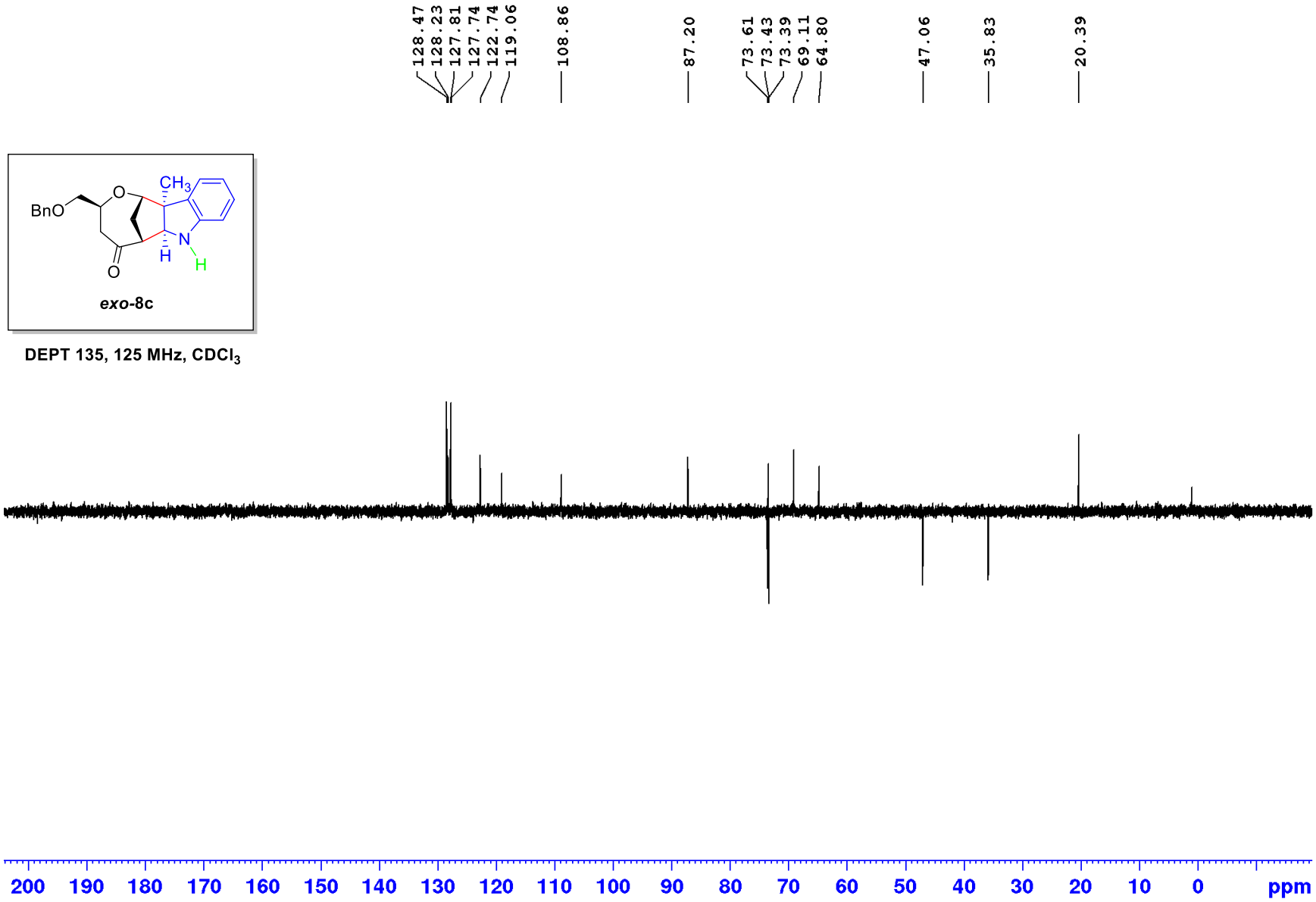
^{1}H NMR, 500 MHz, $CDCl_3$

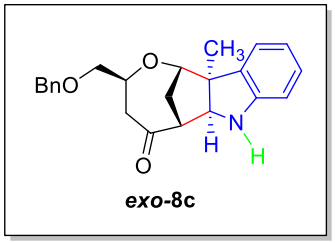




***exo*-8c**

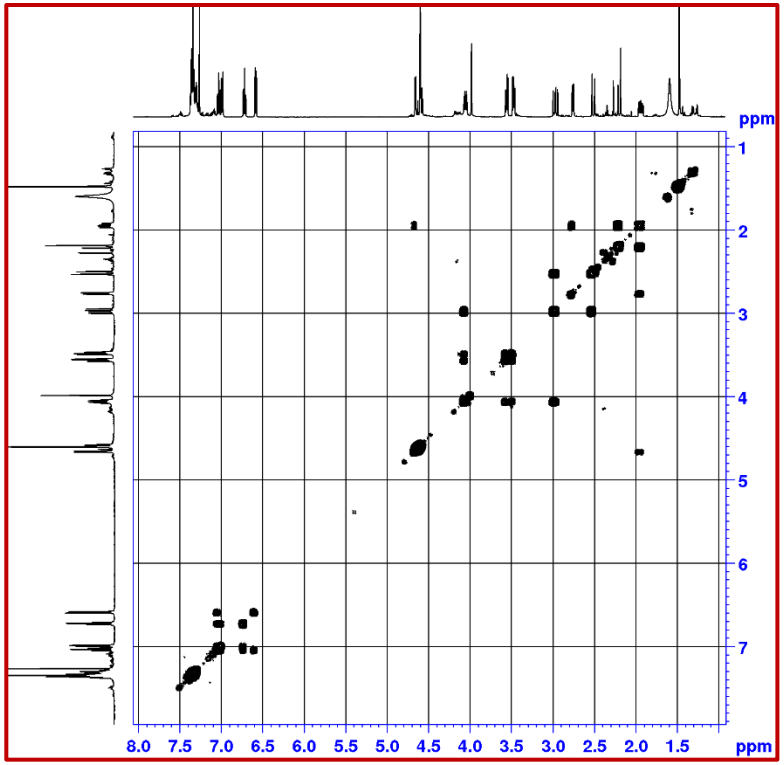
$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$

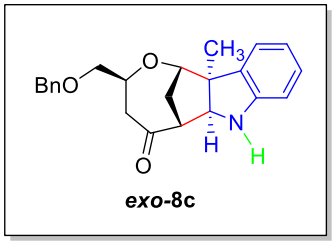

128.47
128.23
127.81
127.74
122.74
119.06
108.86
87.20
73.61
73.43
73.39
69.11
64.80
47.06
35.83
20.39
BnO
O
CH3
N
H
H
O
exo-8c
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



***exo*-8c**

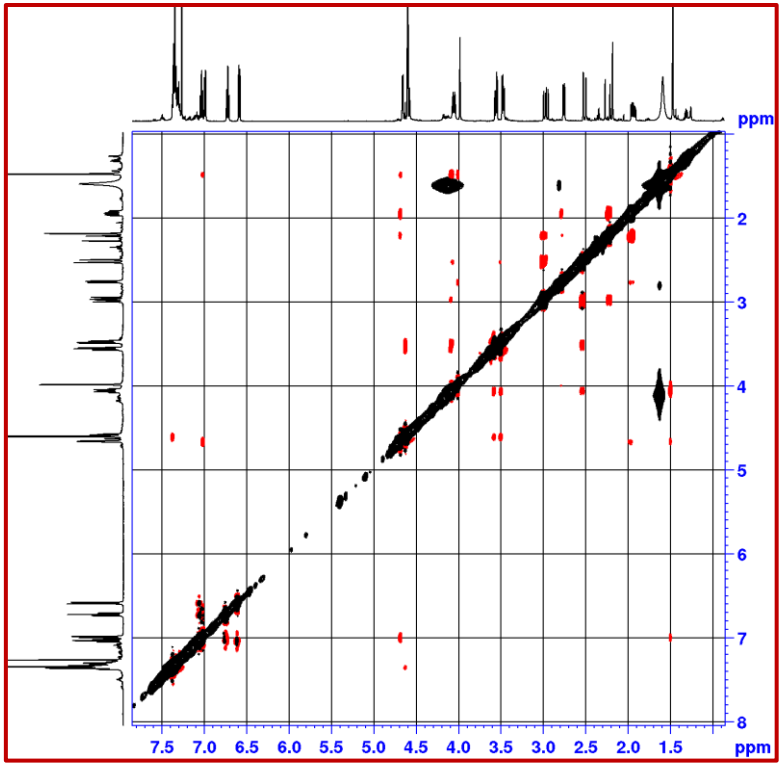
(COSY, 500 MHz)

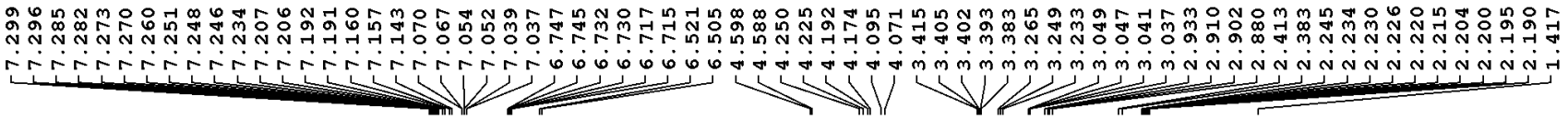


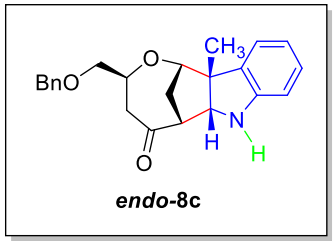


***exo*-8c**

(NOESY, 500 MHz)

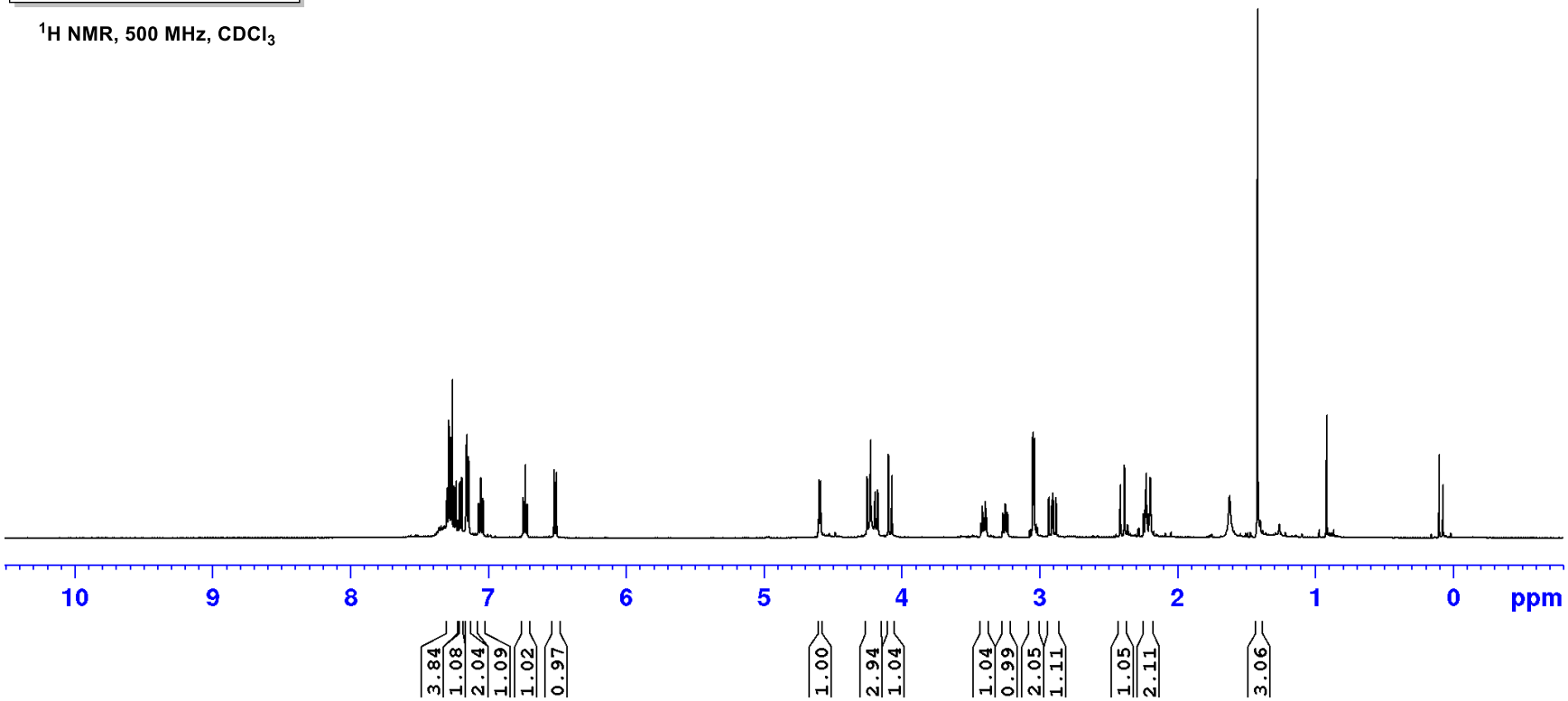


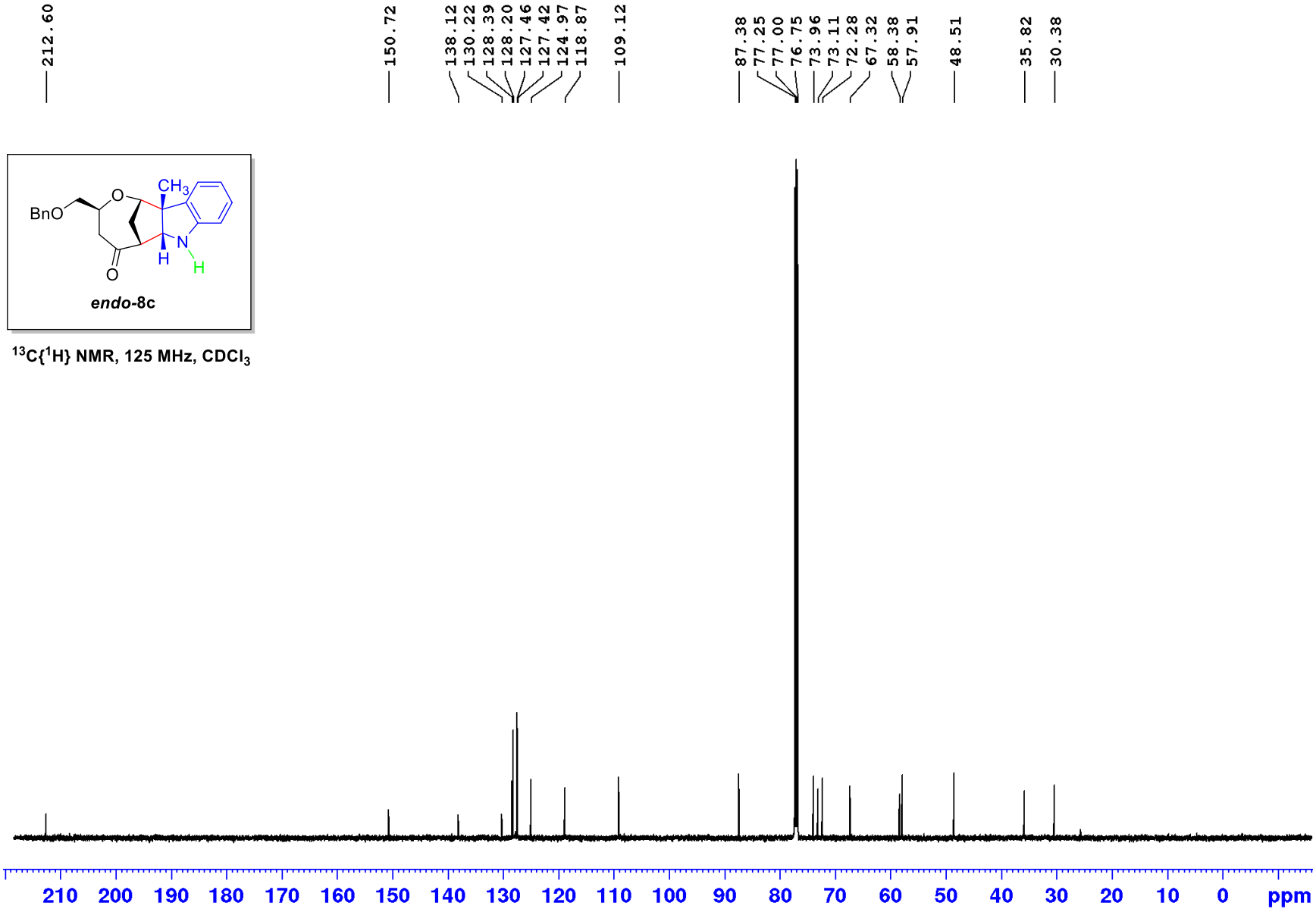




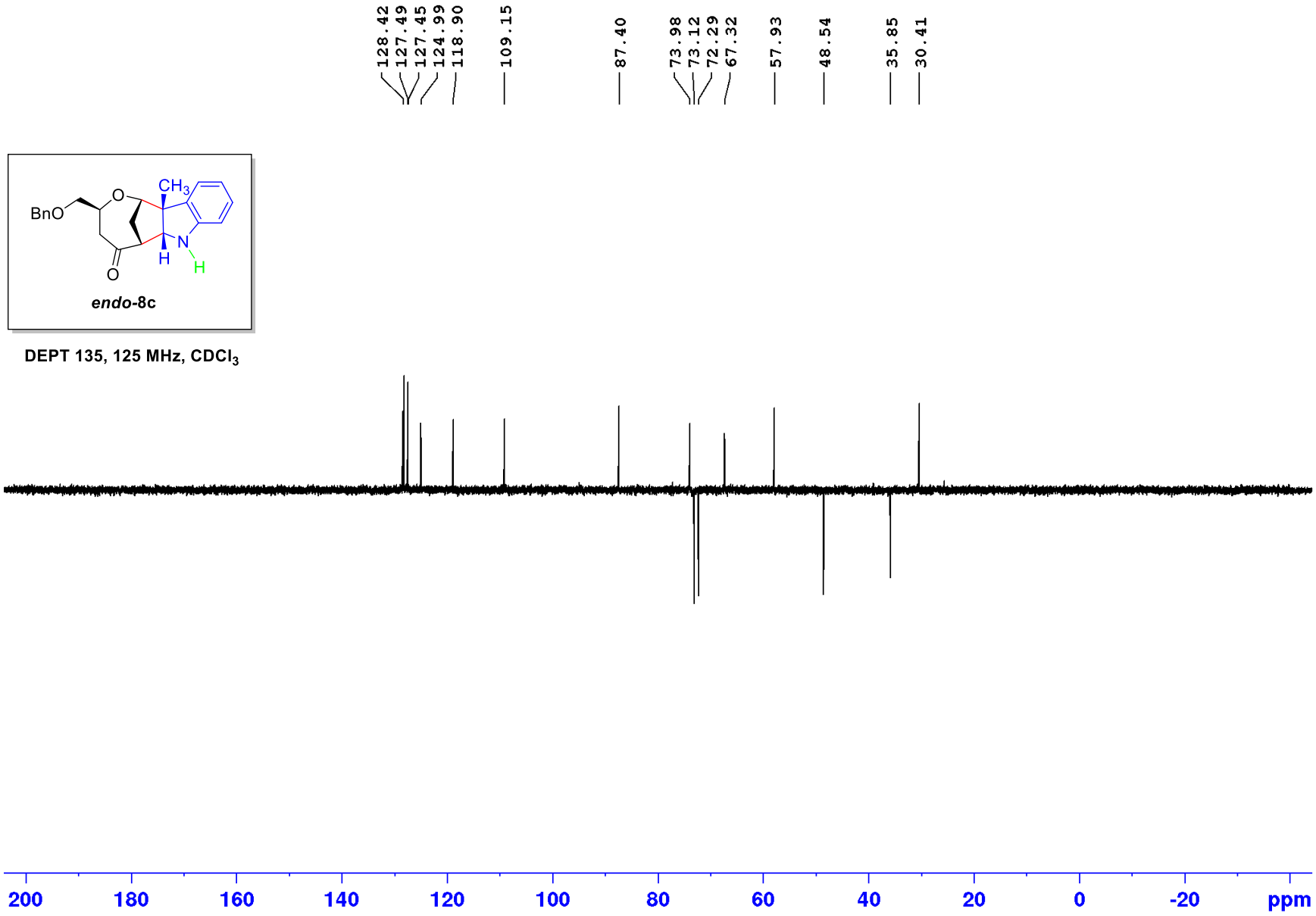
***endo*-8c**

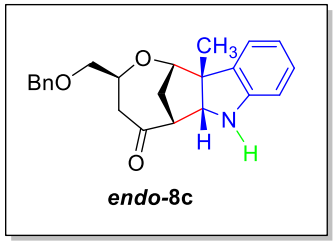
^{1}H NMR, 500 MHz, $CDCl_3$





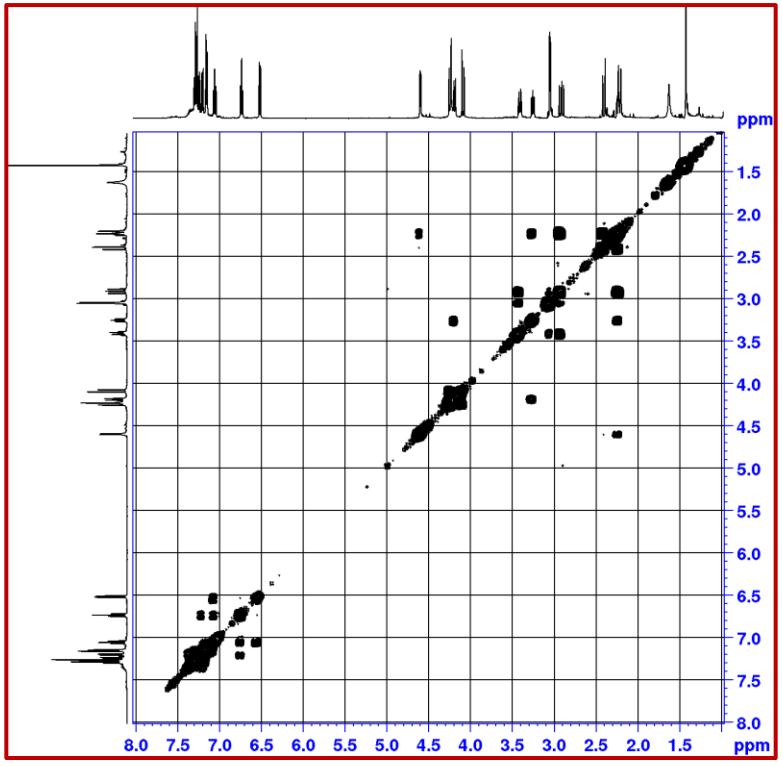
$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$

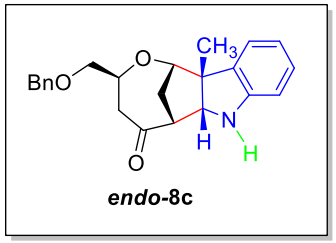

128.42
127.49
127.45
124.99
118.90
109.15
87.40
73.98
73.12
72.29
67.32
57.93
48.54
35.85
30.41
BnO
O
CH3
N
H
H
O
endo-8c
DEPT 135, 125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



endo-8c

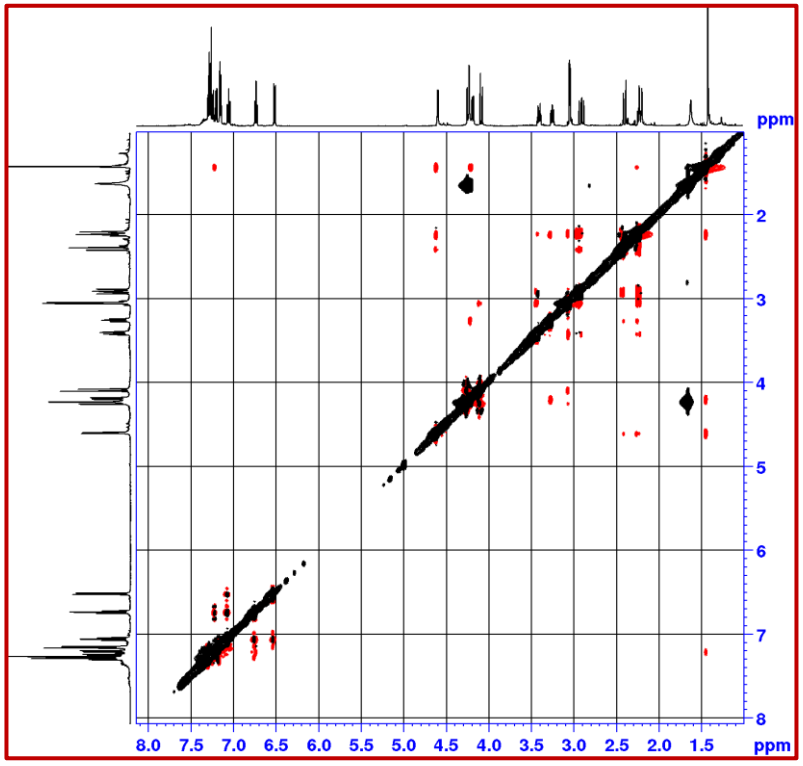
(COSY, 500 MHz)

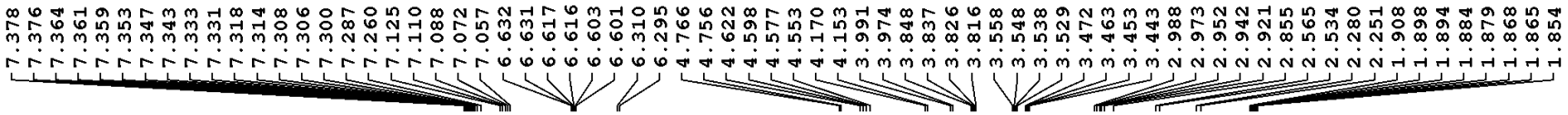


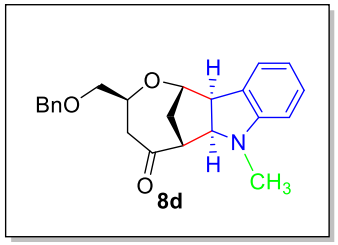


endo-8c

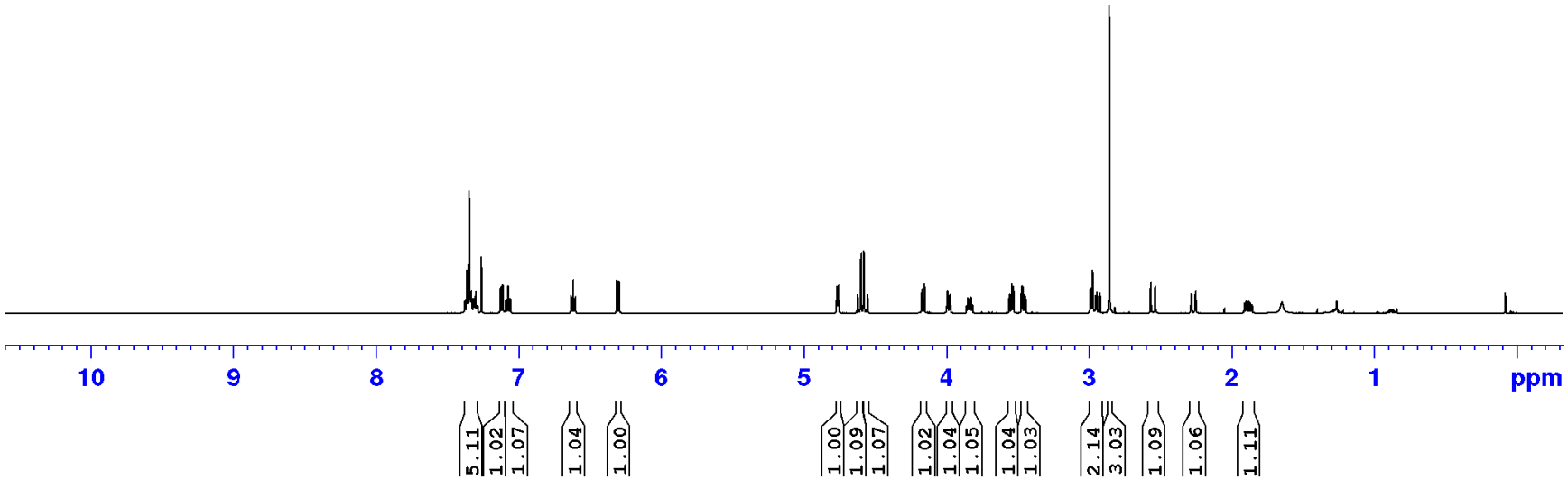
(NOESY, 500 MHz)

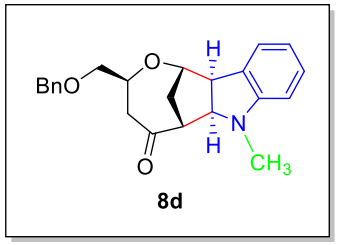






^{1}H NMR, 500 MHz, $CDCl_3$

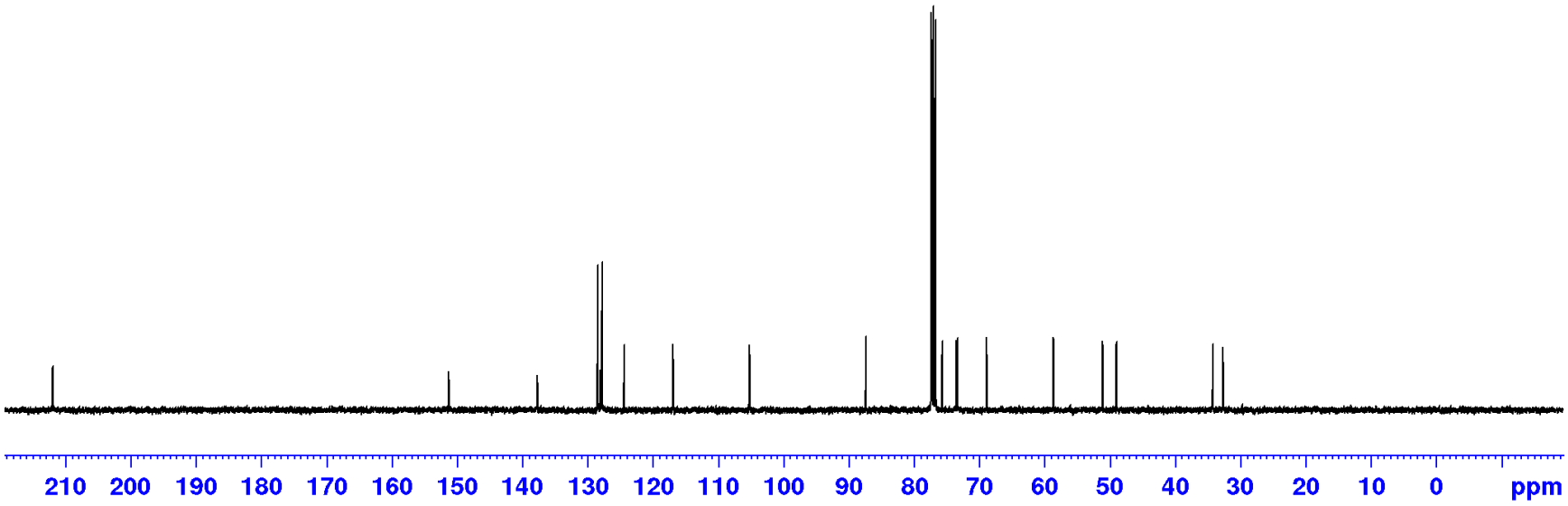


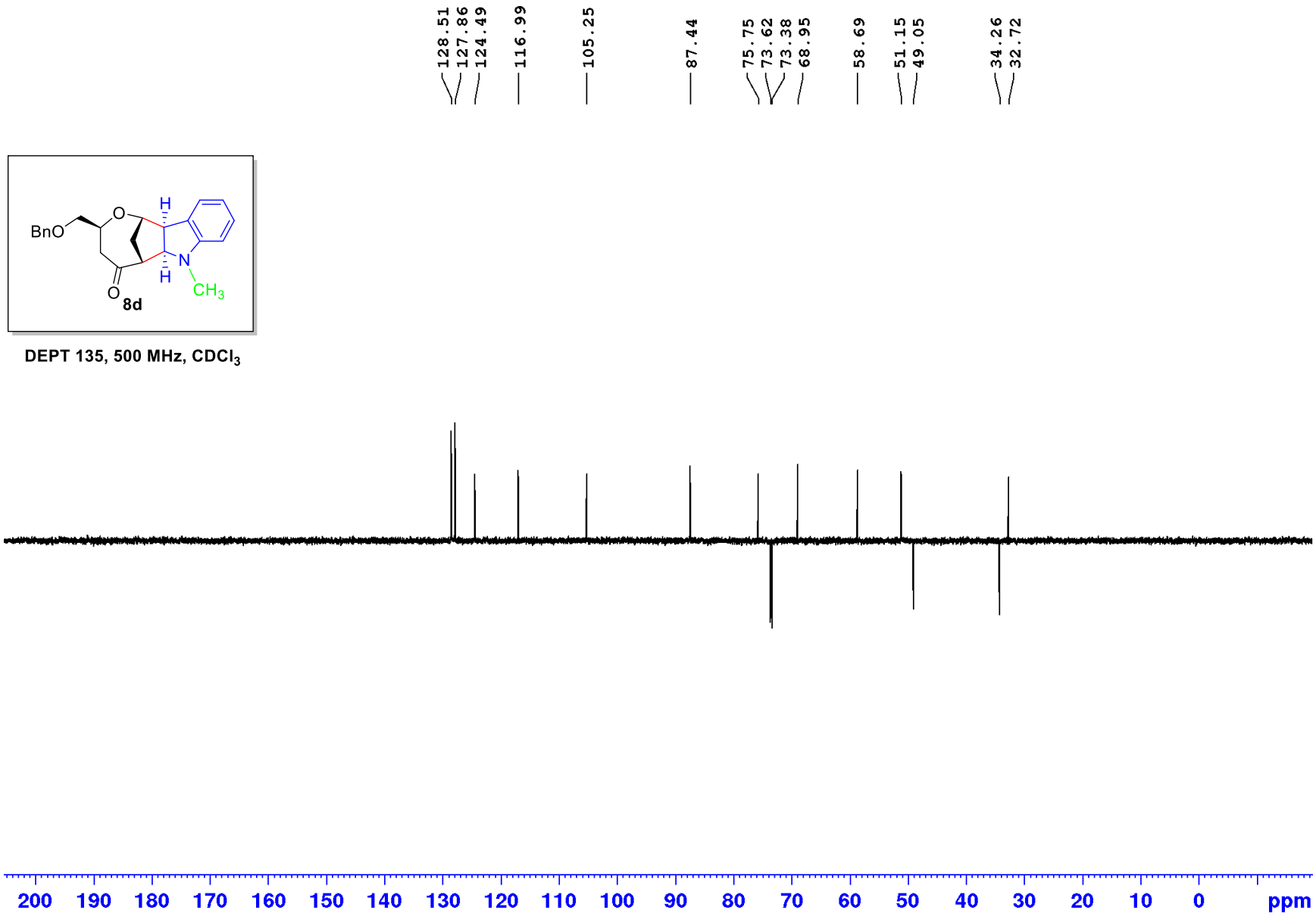


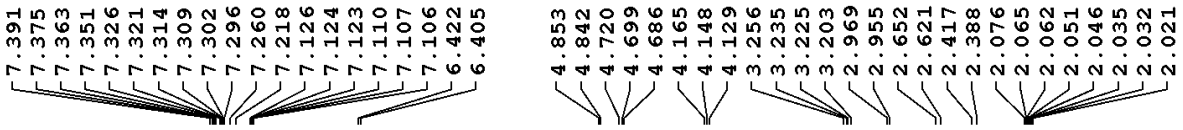
8d

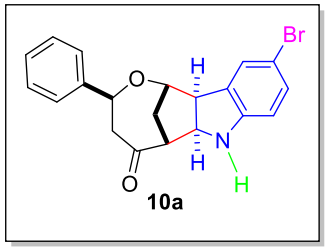
$^{13}C\{^{1}H\}$ NMR, 100 MHz, $CDCl_3$

211.97
151.32
137.73
128.44
128.04
127.78
124.42
116.92
105.18
87.36
77.32
77.00
76.68
75.68
73.55
73.31
68.88
58.62
51.08
48.98
34.19
32.64



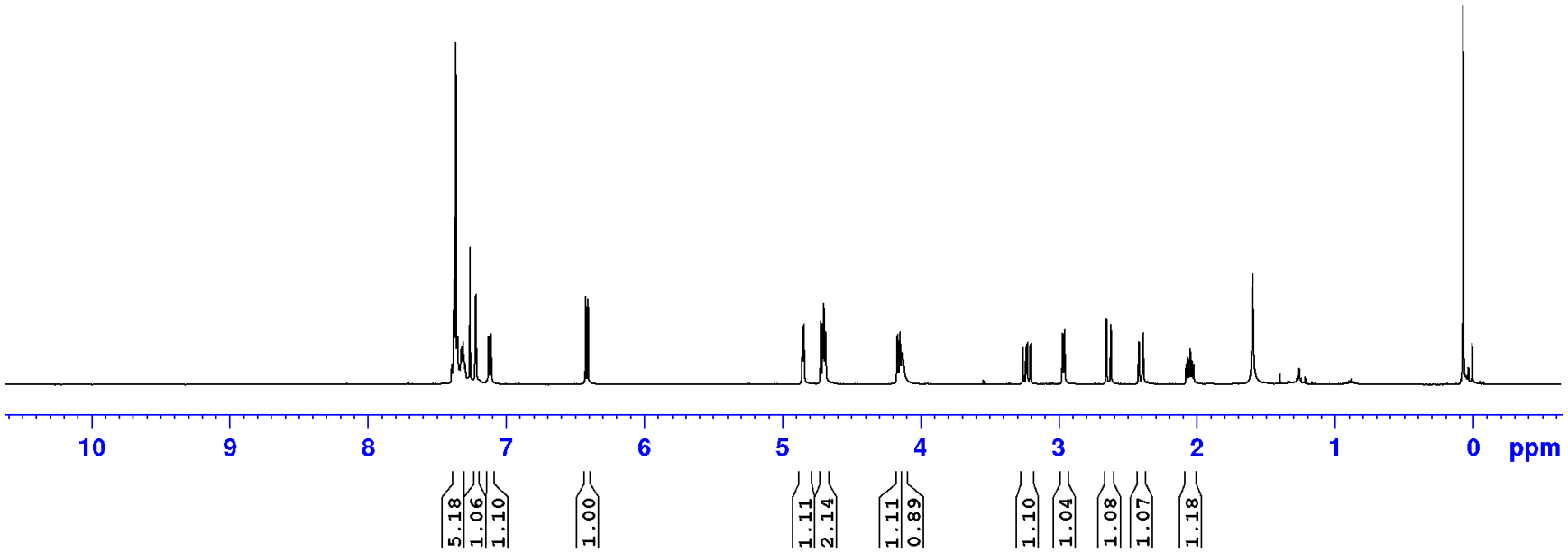

128.51
127.86
124.49
116.99
105.25
87.44
75.75
73.62
73.38
68.95
58.69
51.15
49.05
34.26
32.72
BnO
O
H
N
H
CH3
O
8d
DEPT 135, 500 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



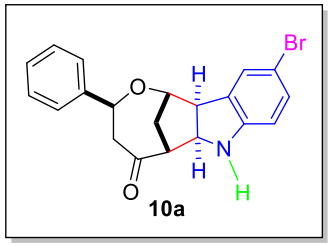


10a

^{1}H NMR, 500 Mz, $CDCl_3$

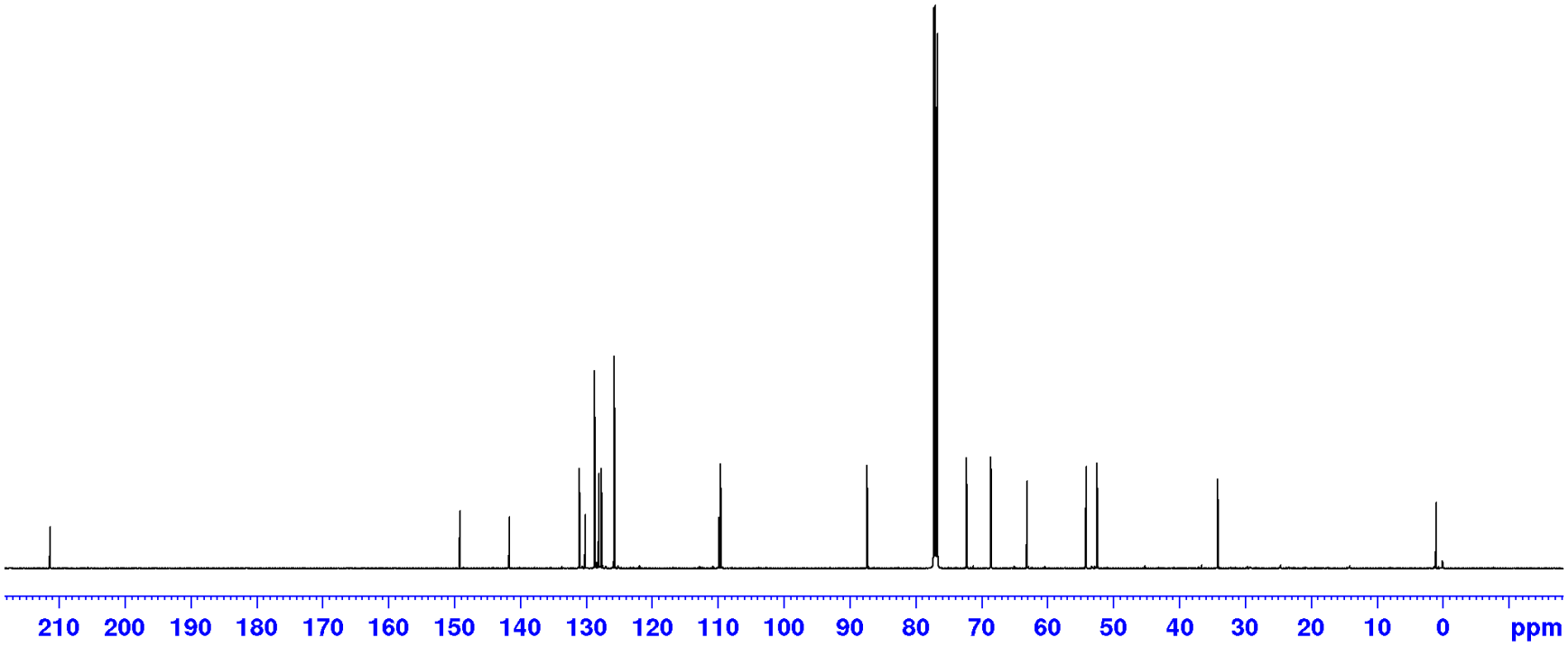


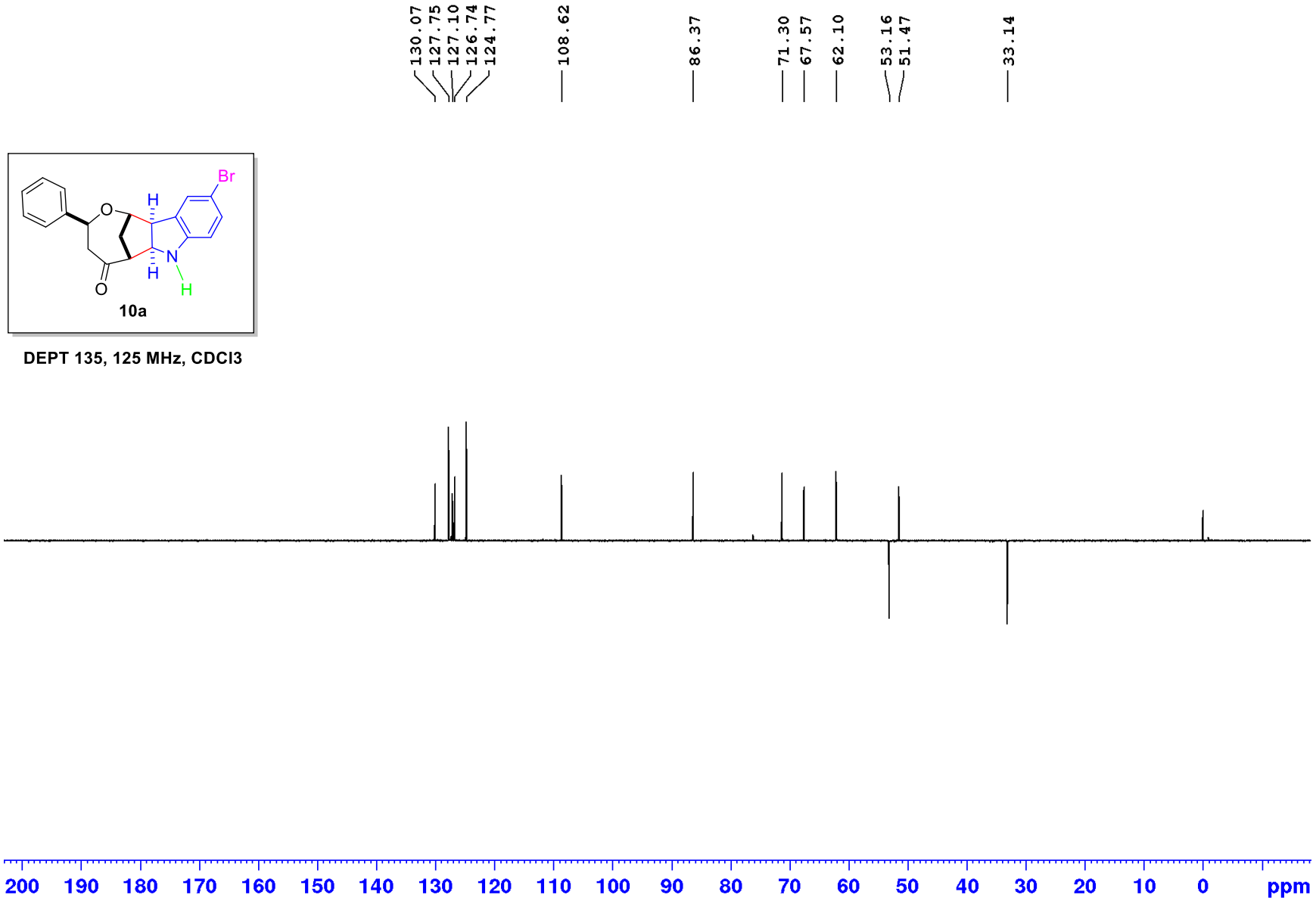
211.30
149.22
141.70
131.07
130.17
128.75
128.10
127.75
125.77
109.88
109.62
87.37
77.25
77.00
76.75
72.30
68.58
63.11
54.16
52.48
34.14

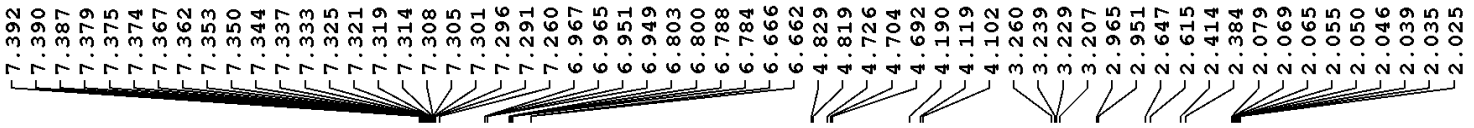


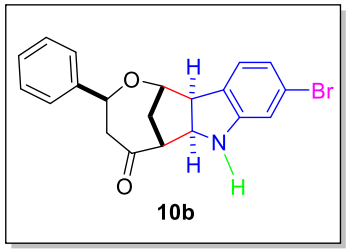
10a

$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$



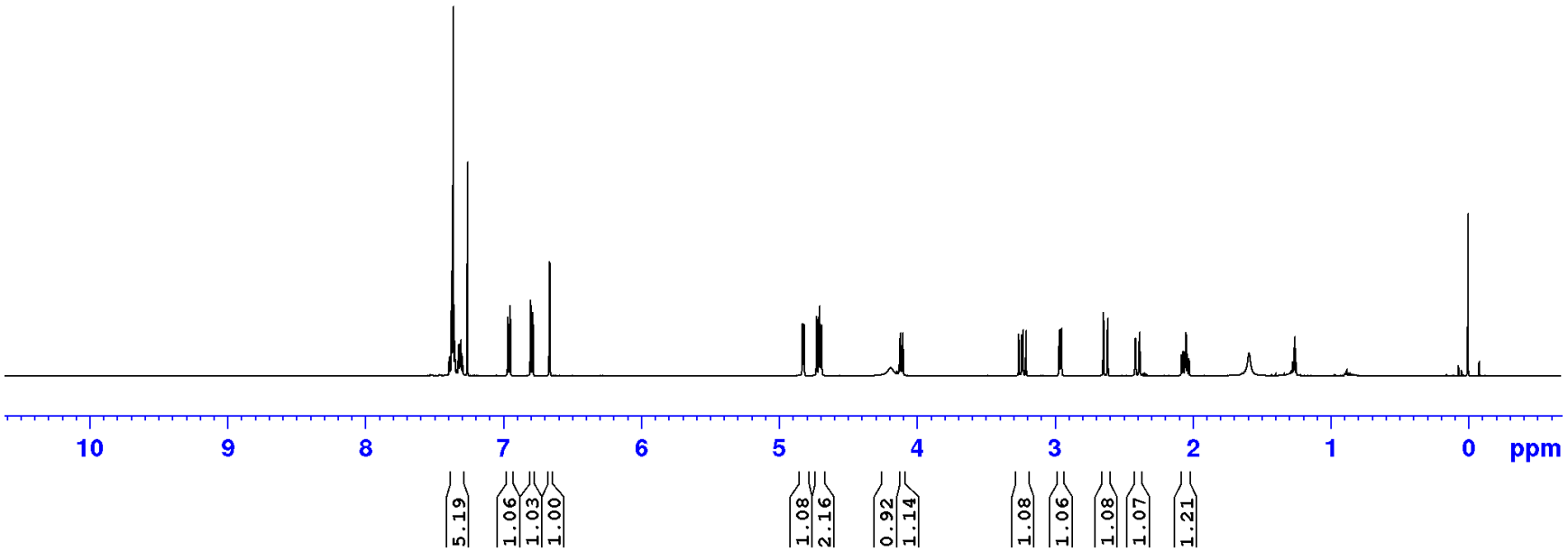

130.07
127.75
127.10
126.74
124.77
108.62
86.37
71.30
67.57
62.10
53.16
51.47
33.14
Br
O
H
N
H
H
O
10a
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

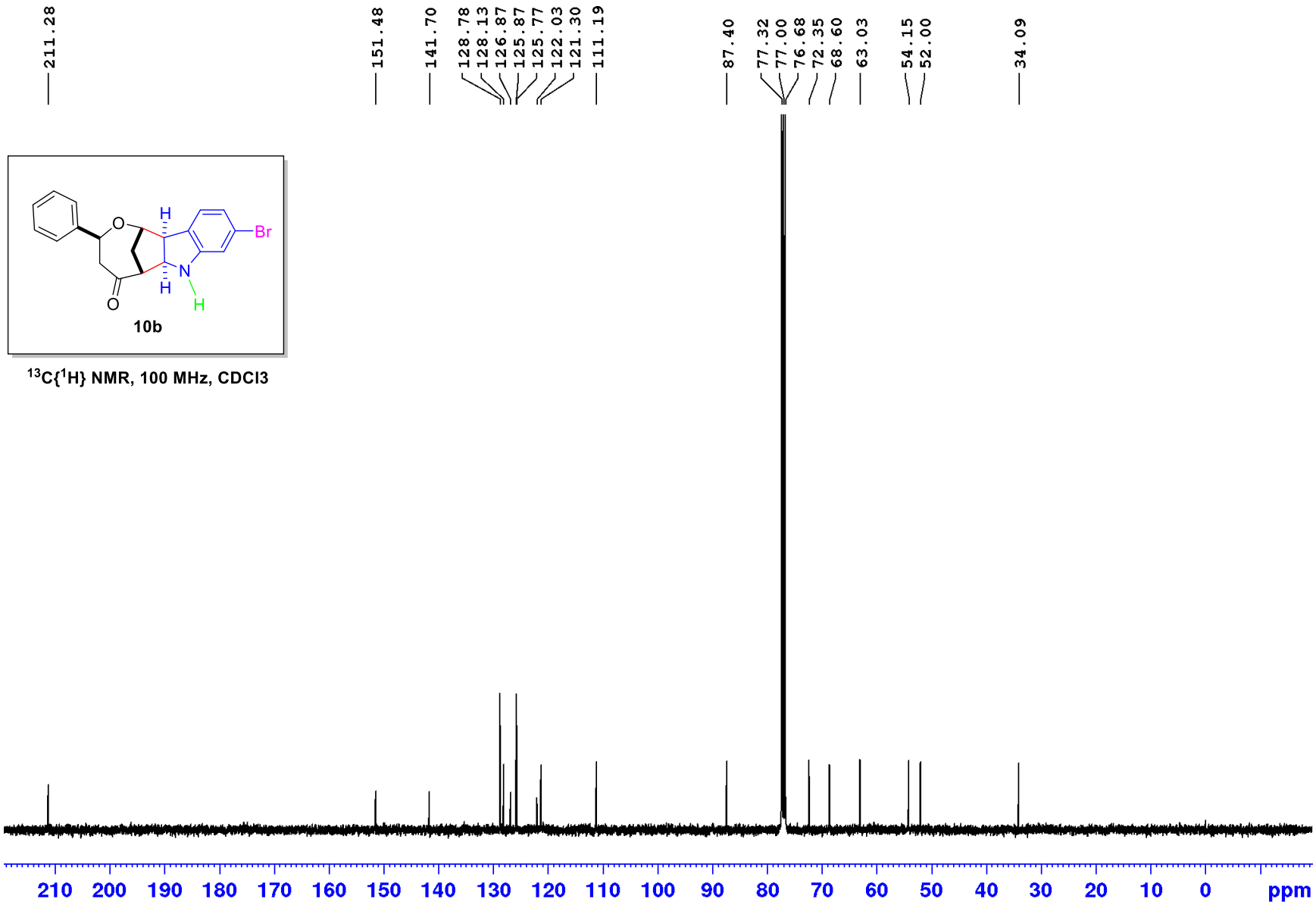




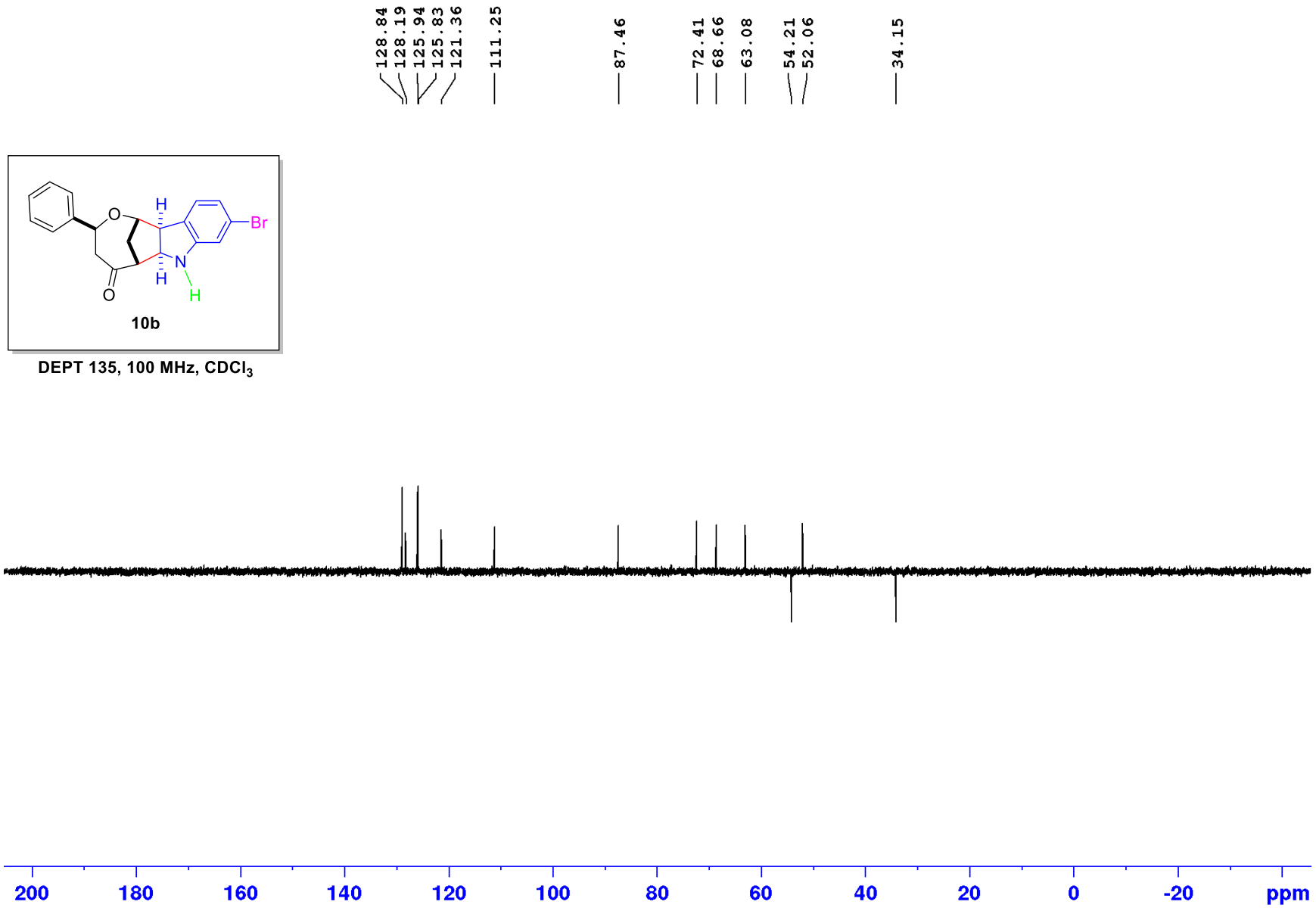
10b

^{1}H NMR, 500 MHz, CDCl3

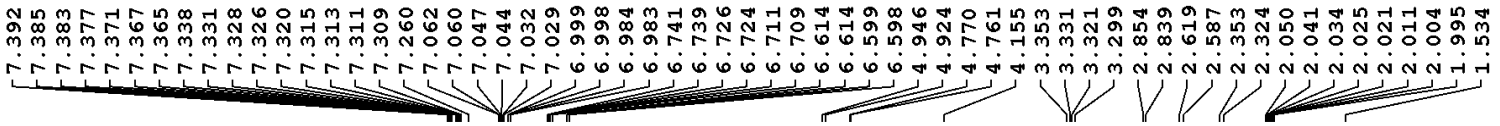


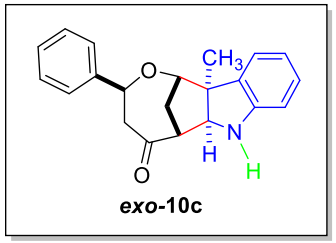


$^{13}C\{^{1}H\}$ NMR, 100 MHz, CDCl3



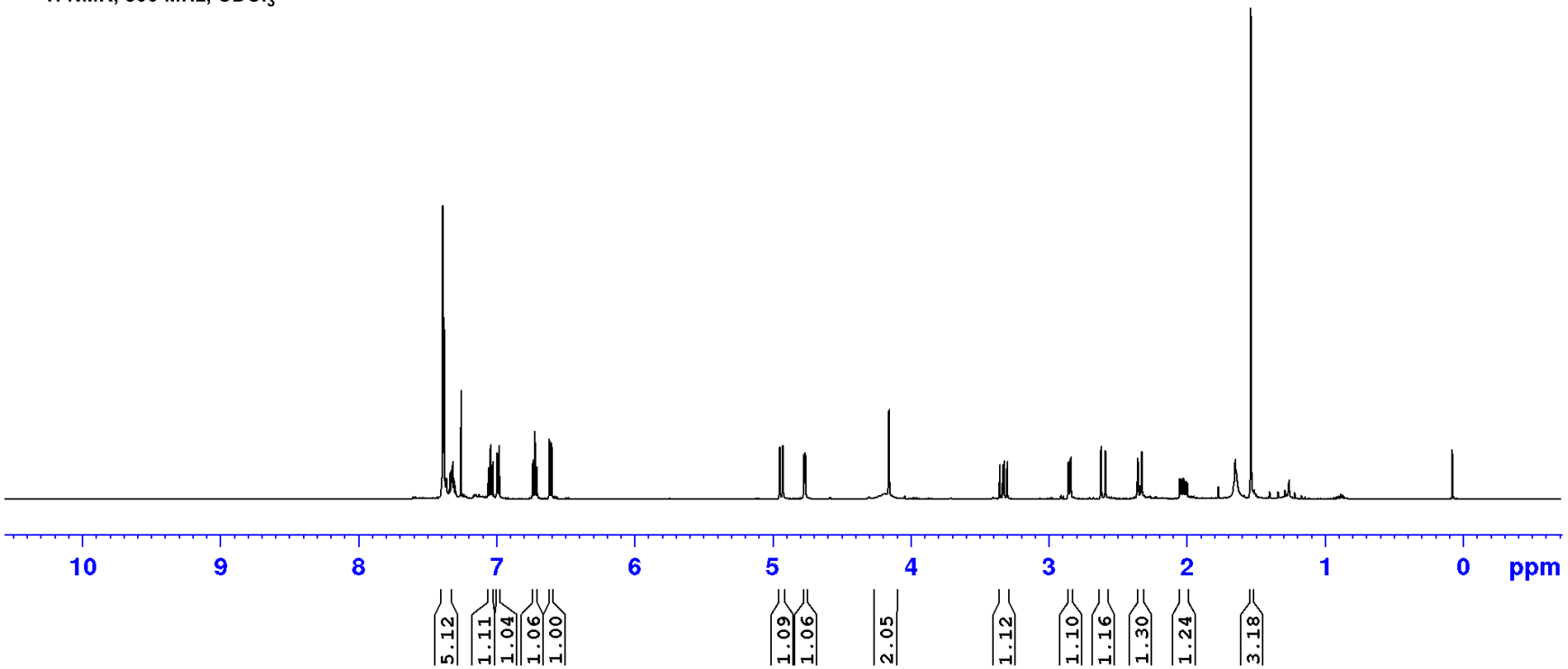
DEPT 135, 100 MHz, $CDCl_3$



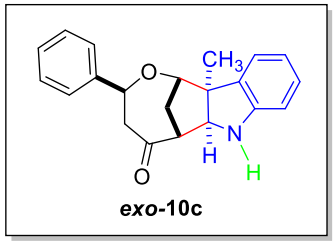


***exo*-10c**

^{1}H NMR, 500 MHz, $CDCl_3$

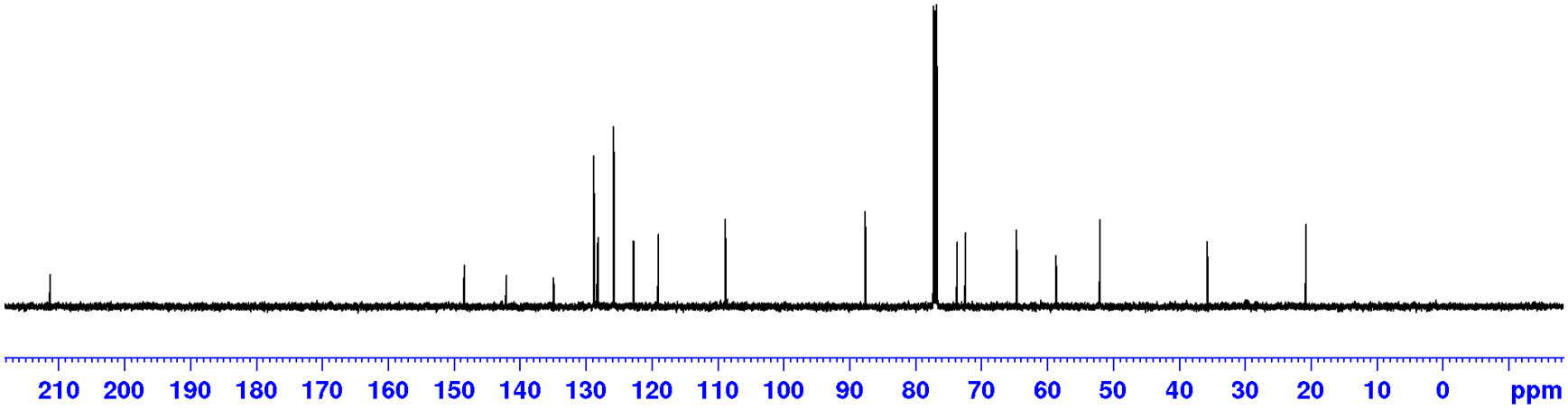


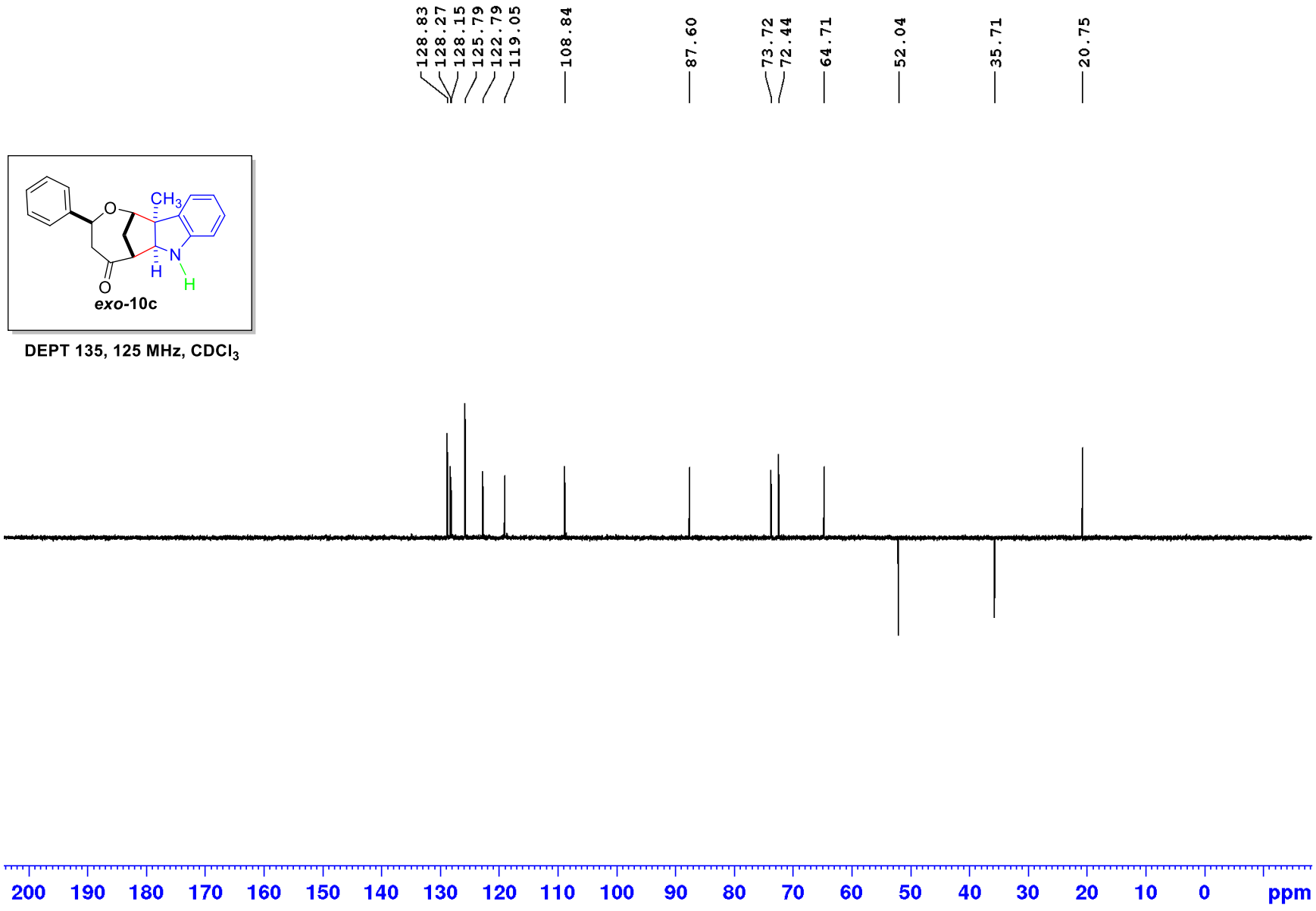
211.22
148.37
141.99
134.89
128.79
128.24
128.11
125.76
122.76
119.02
108.81
87.58
77.26
77.00
76.75
73.70
72.41
64.68
58.62
52.01
35.68
20.72

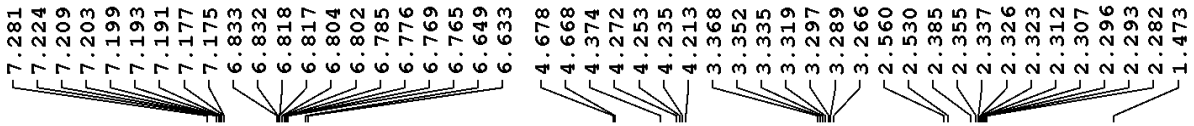


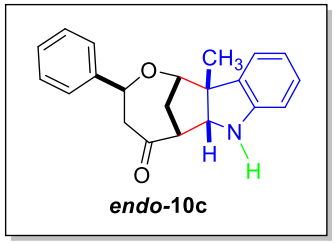
exo-10c

$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$



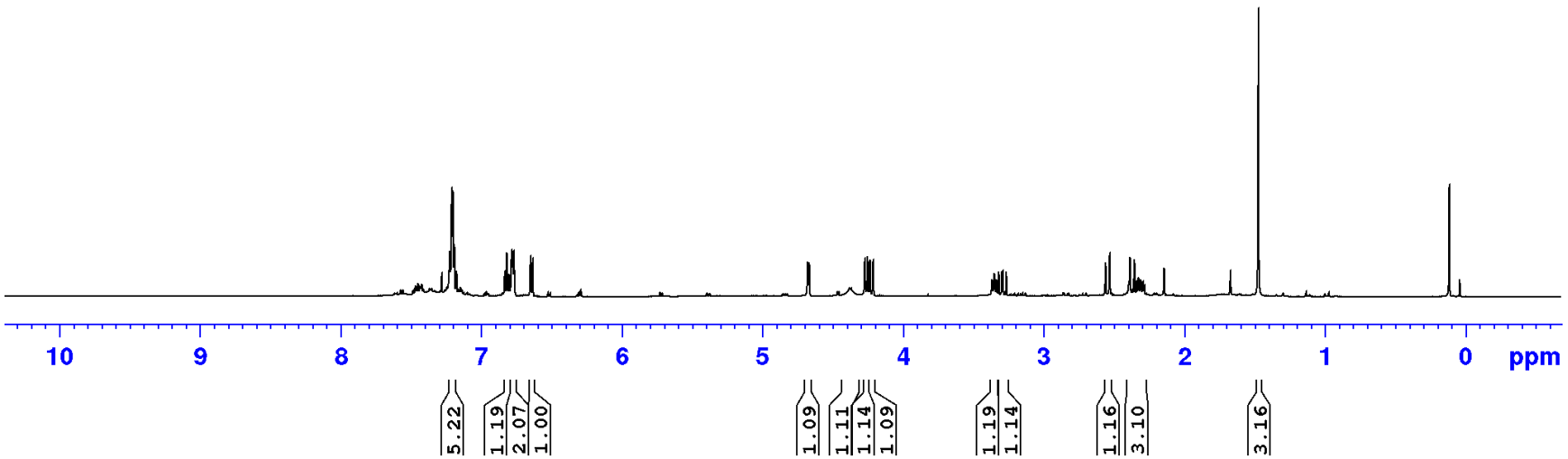

128.83
128.27
128.15
125.79
122.79
119.05
108.84
87.60
73.72
72.44
64.71
52.04
35.71
20.75
CH3
O
N
H
H
O
exo-10c
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



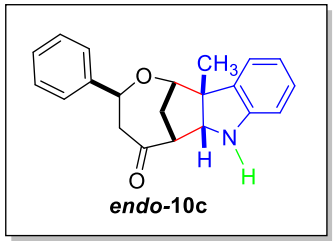


endo-10c

^{1}H NMR, 500 MHz, $CDCl_3$

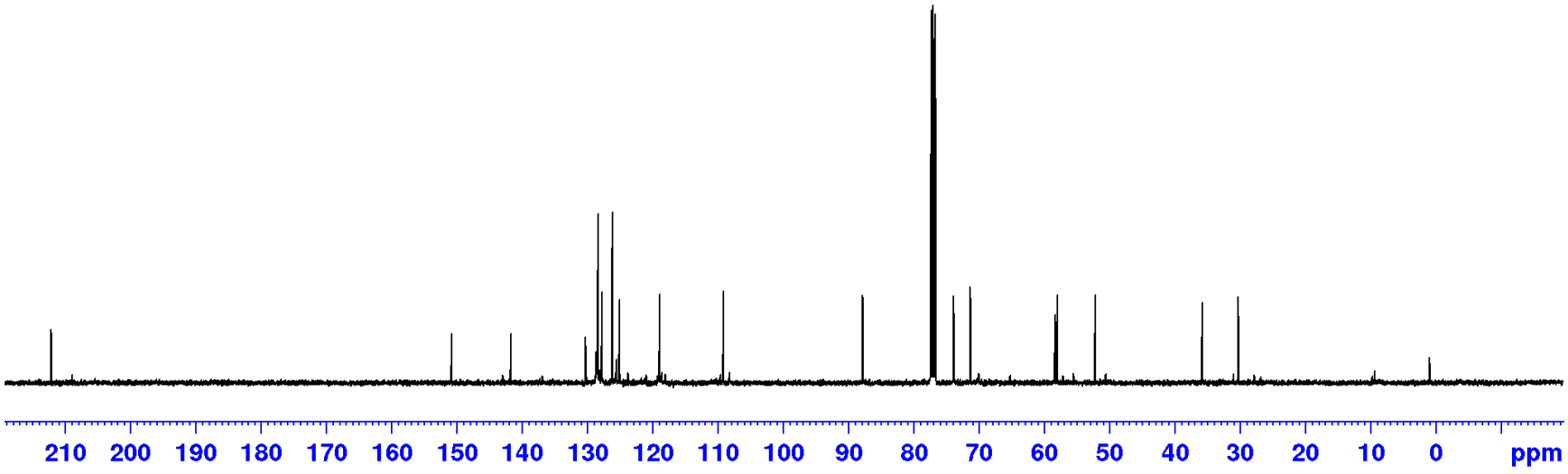


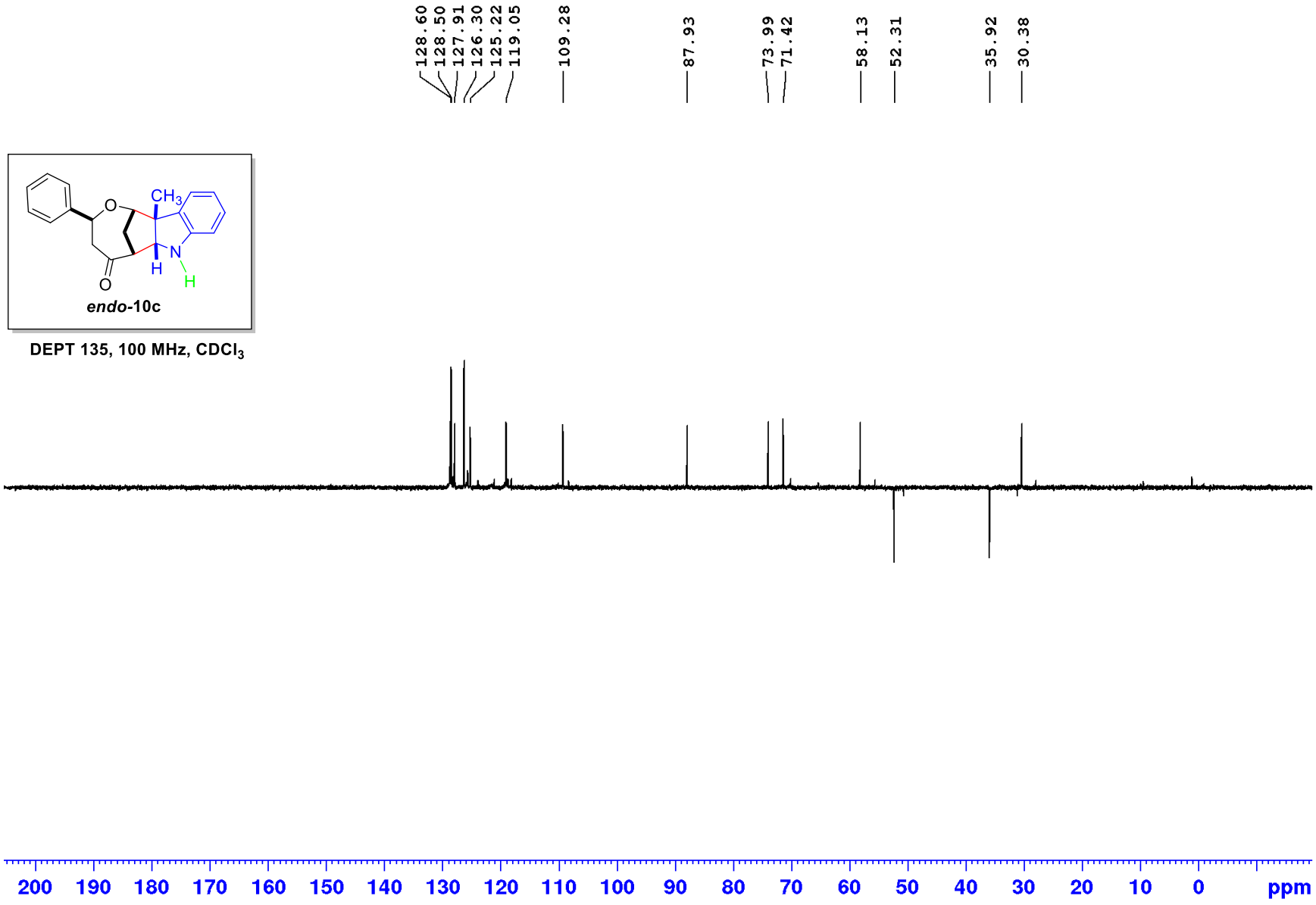
212.15
150.79
141.71
130.29
128.49
128.38
127.79
126.18
125.11
118.94
109.17
87.81
77.32
77.00
76.68
73.88
71.31
58.36
58.02
52.20
35.80
30.27

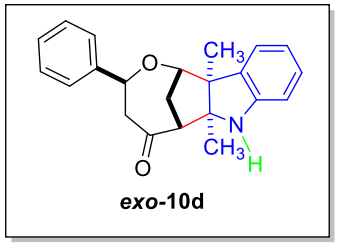


endo-10c

$^{13}C\{^{1}H\}$ NMR, 100 MHz, $CDCl_3$

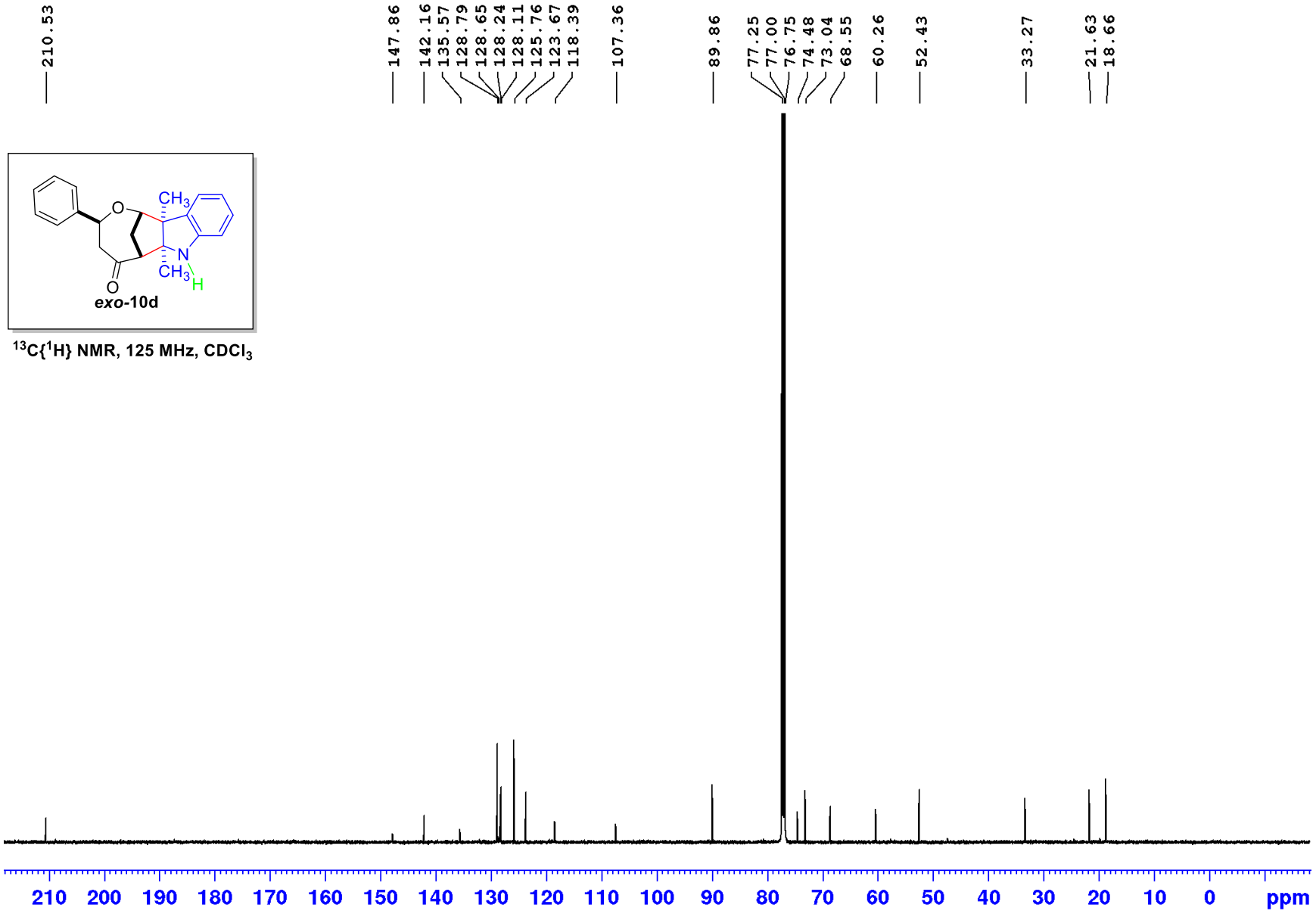



128.60
128.50
127.91
126.30
125.22
119.05
109.28
87.93
73.99
71.42
58.13
52.31
35.92
30.38
CH3
O
N
H
H
O
endo-10c
DEPT 135, 100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

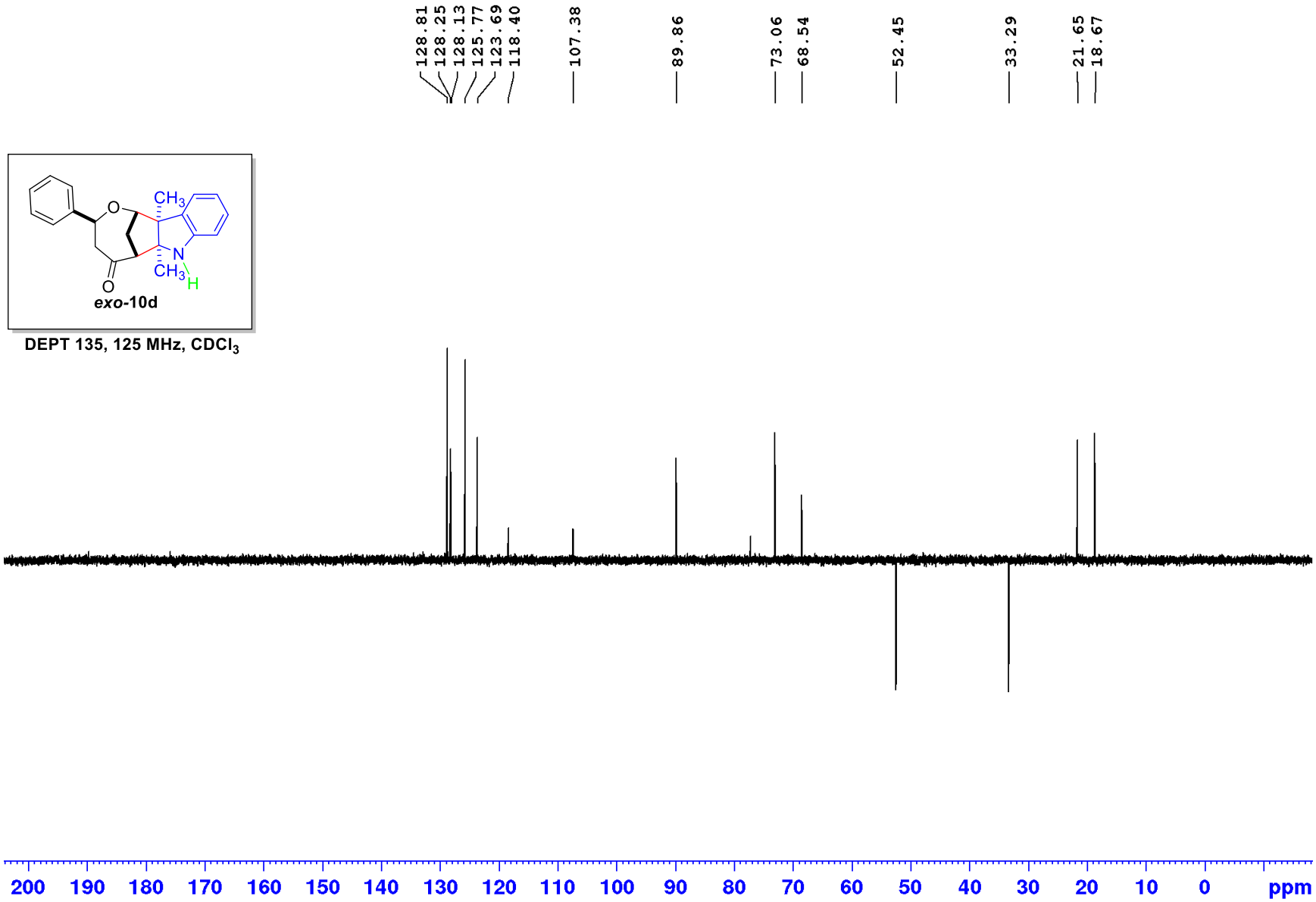


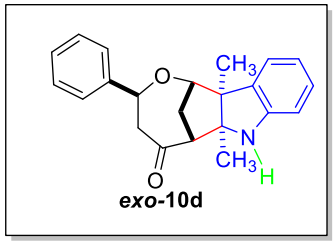
***exo*-10d**

^{1}H NMR, 500 MHz, $CDCl_3$

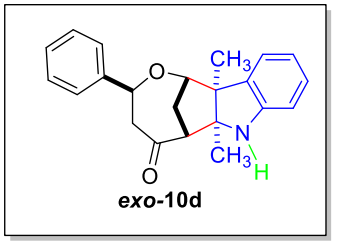


$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$

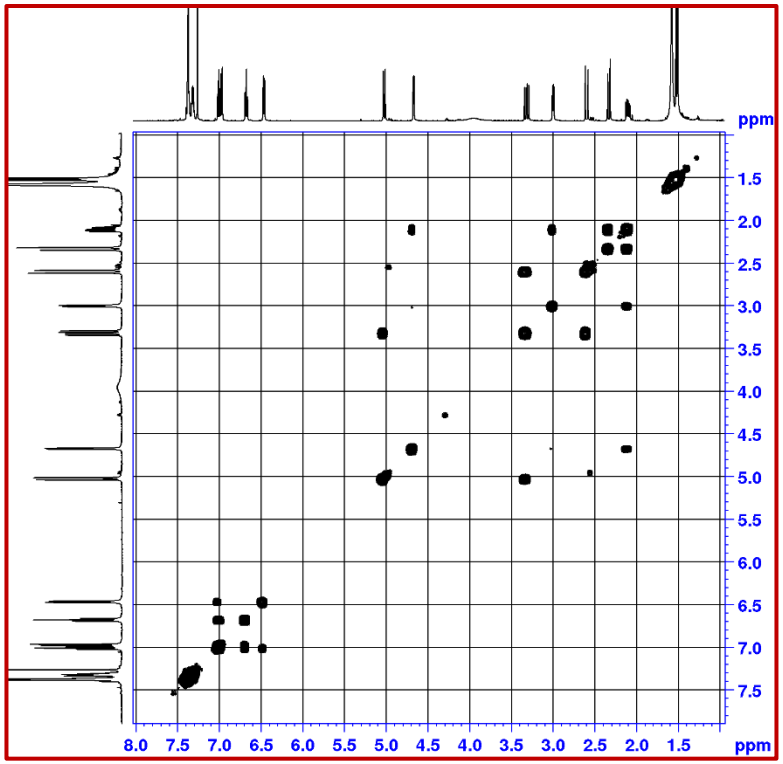

128.81
128.25
128.13
125.77
123.69
118.40
107.38
89.86
73.06
68.54
52.45
33.29
21.65
18.67
CH3
O
N
CH3
H
O
exo-10d
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

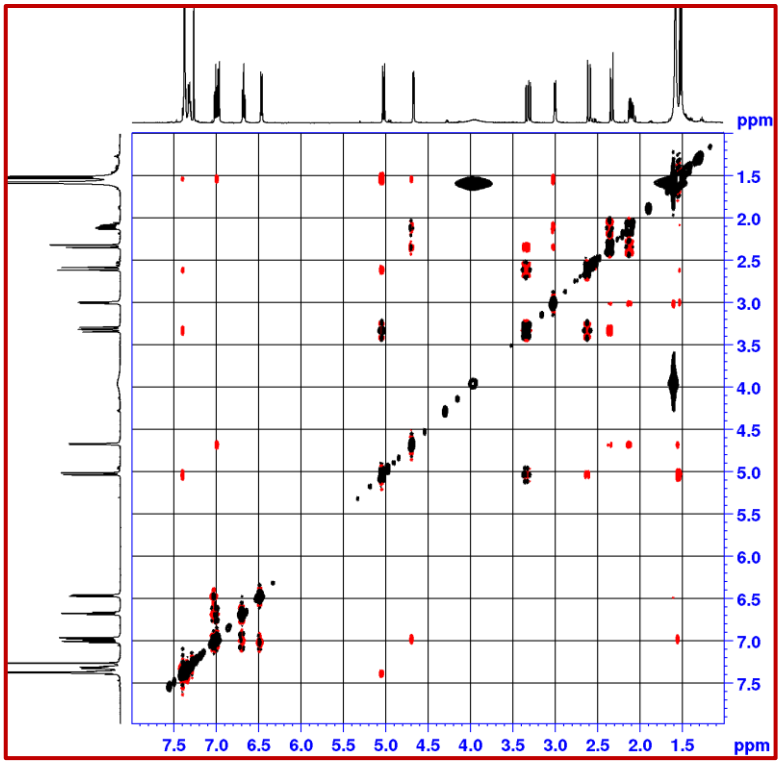


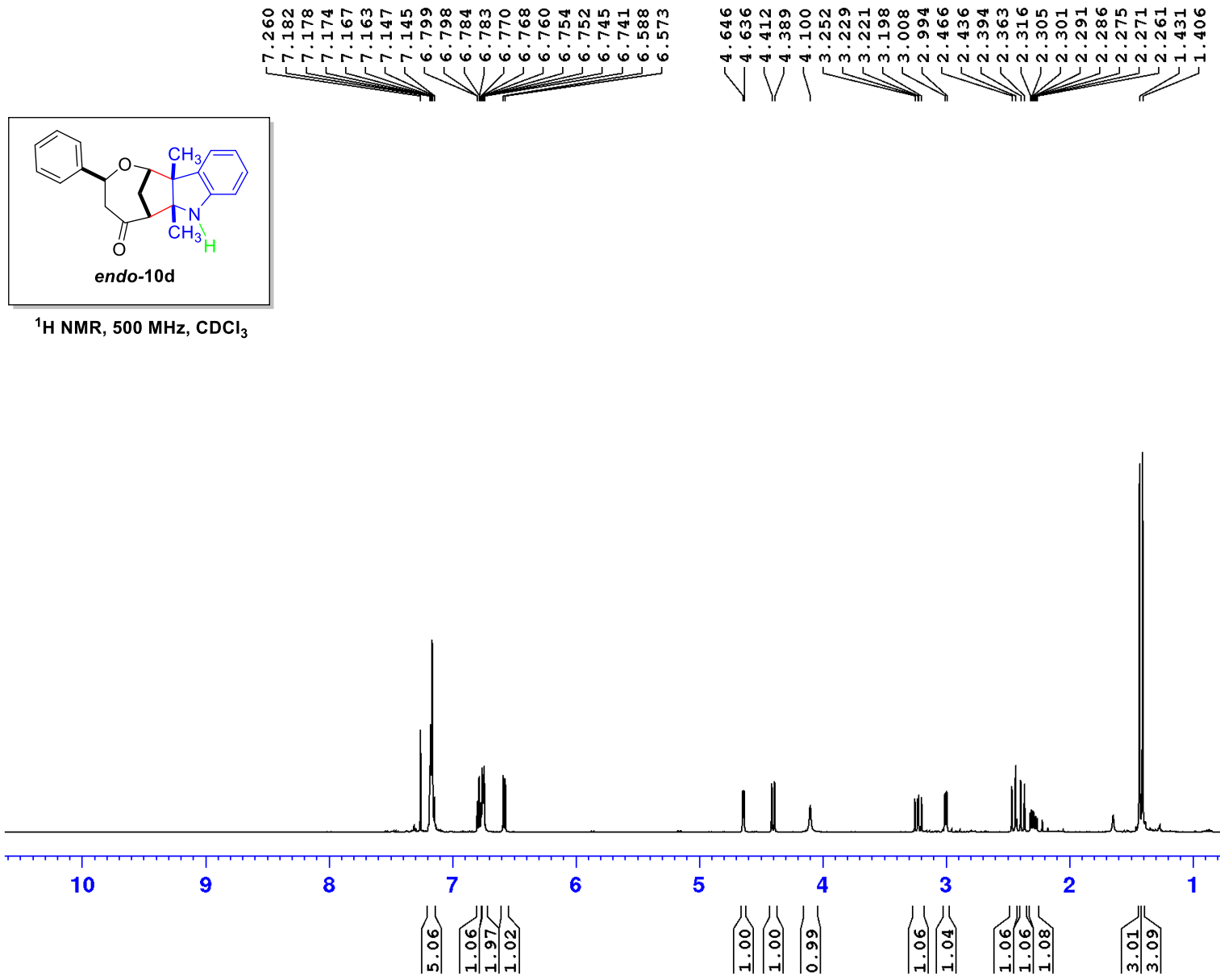
(COSY, 500 MHz)



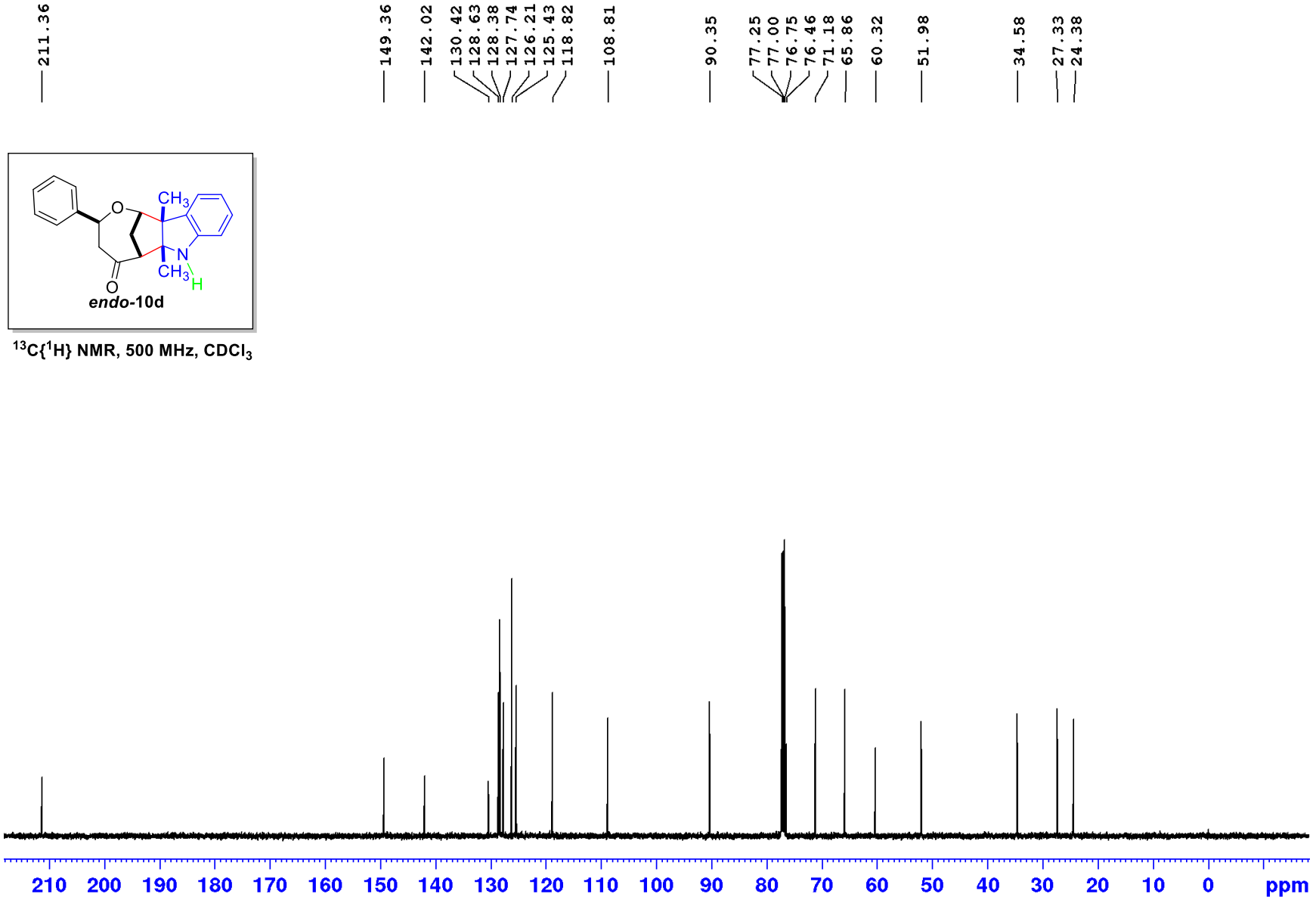
(NOESY, 500 MHz)



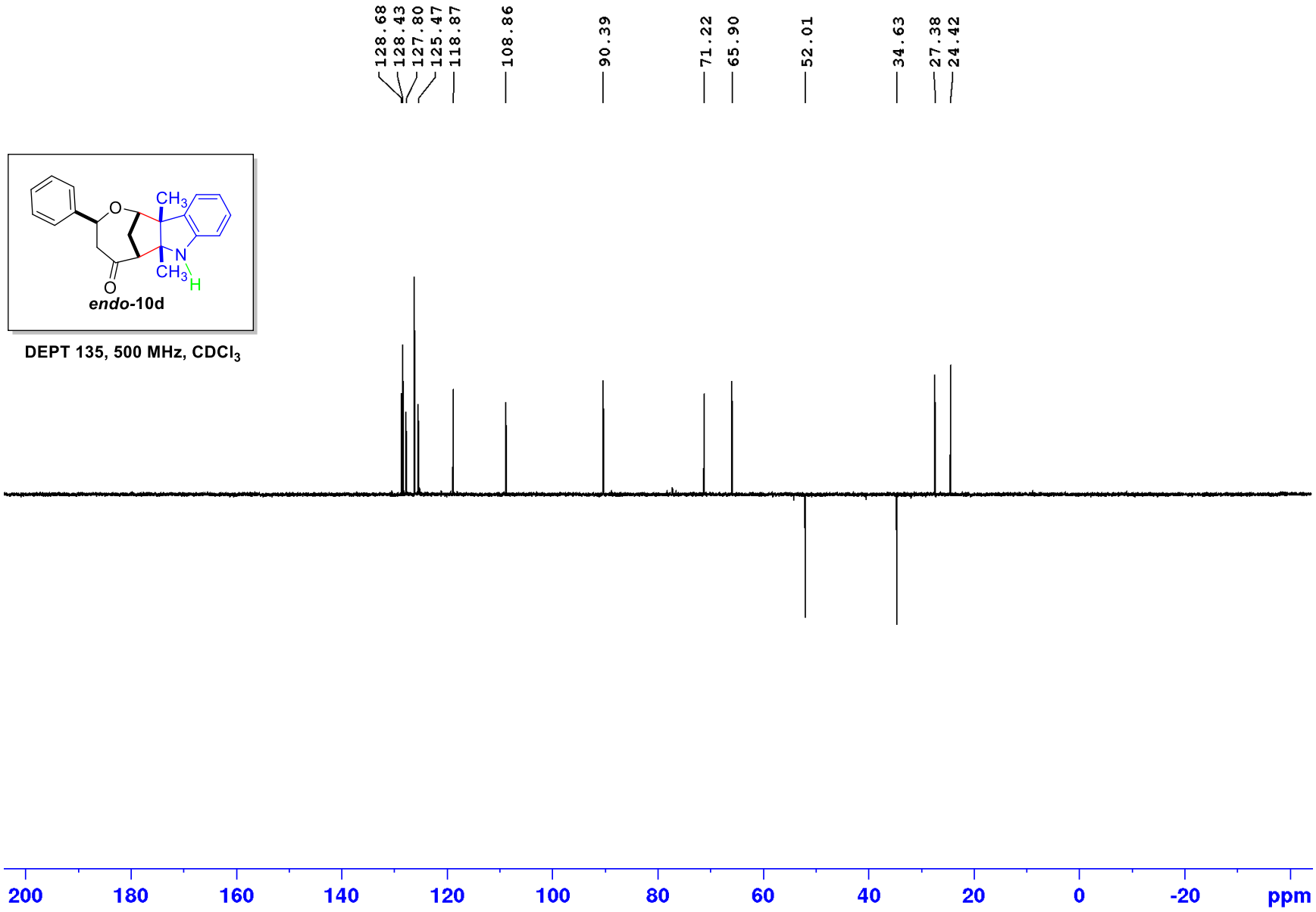


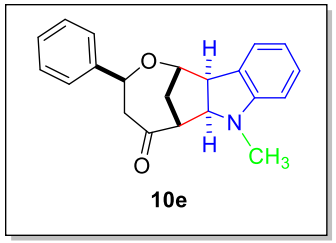


^{1}H NMR, 500 MHz, $CDCl_3$



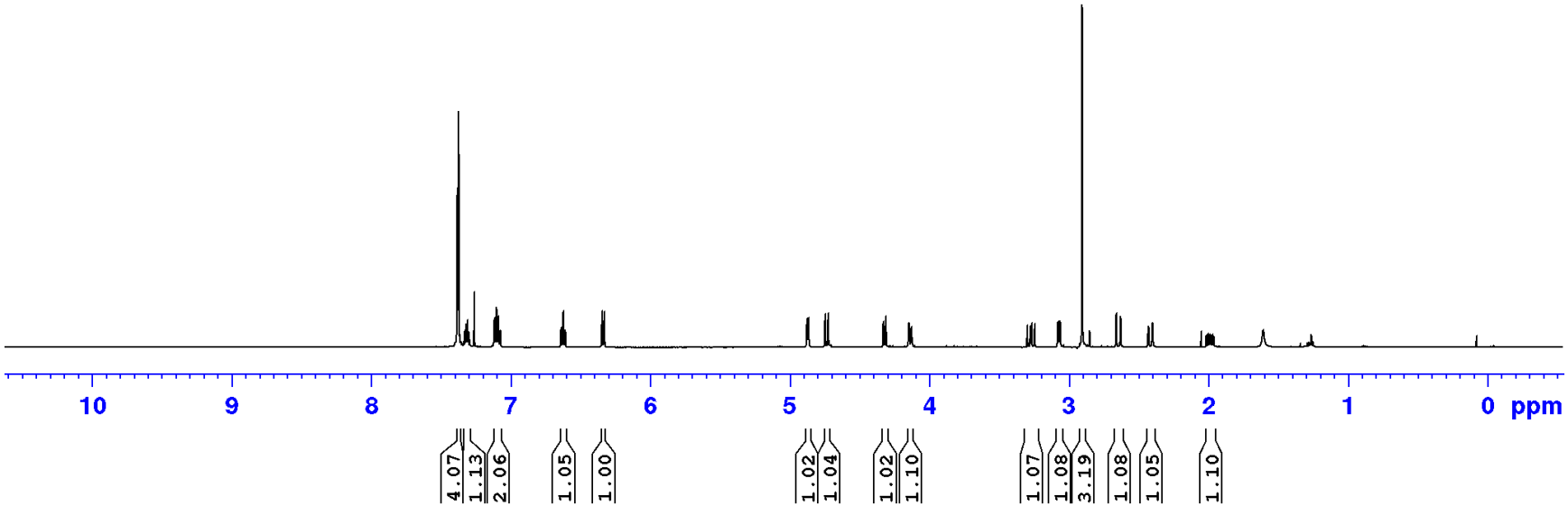
$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

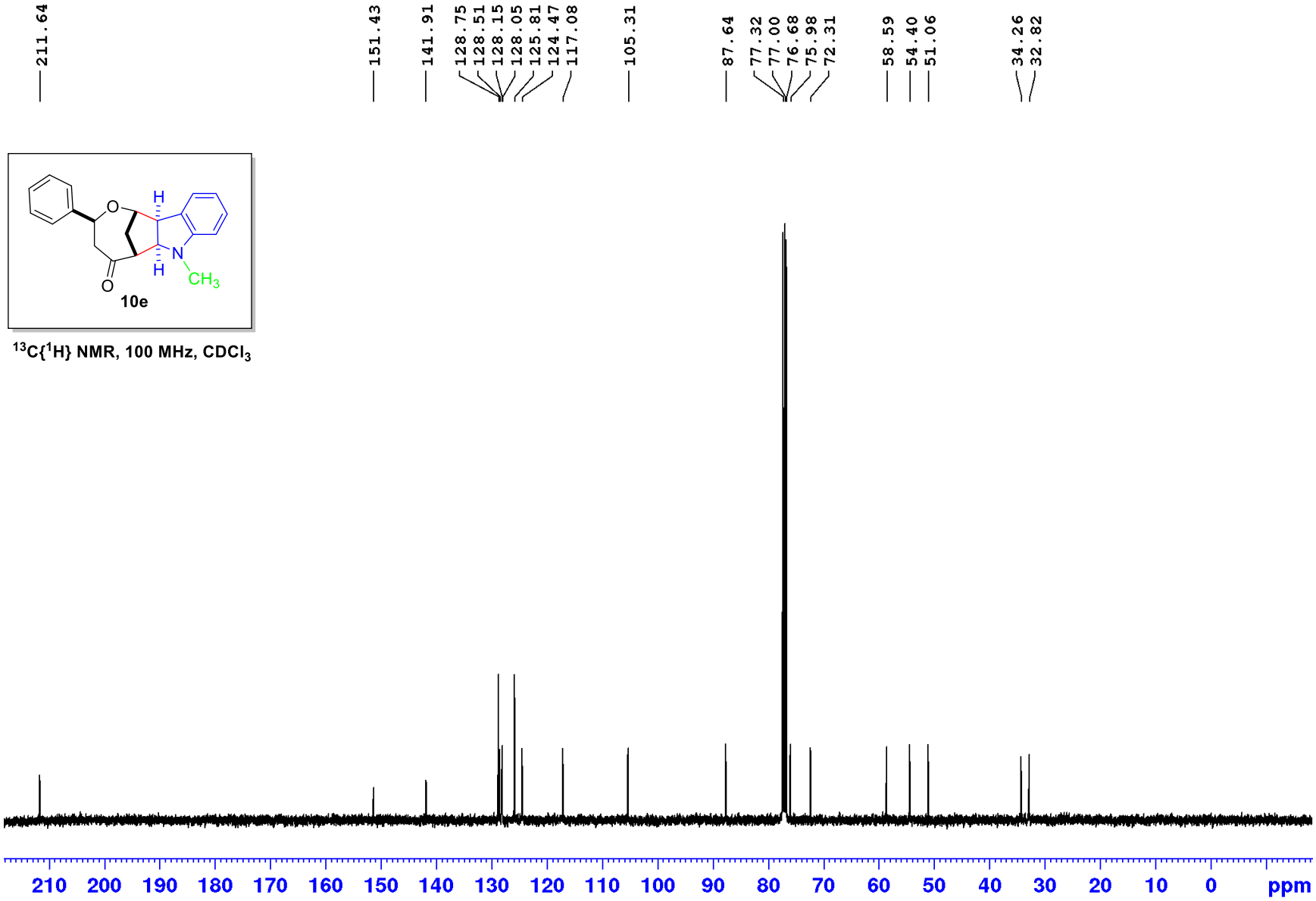

128.68
128.43
127.80
125.47
118.87
108.86
90.39
71.22
65.90
52.01
34.63
27.38
24.42
CH3
O
N
CH3
H
O
endo-10d
DEPT 135, 500 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



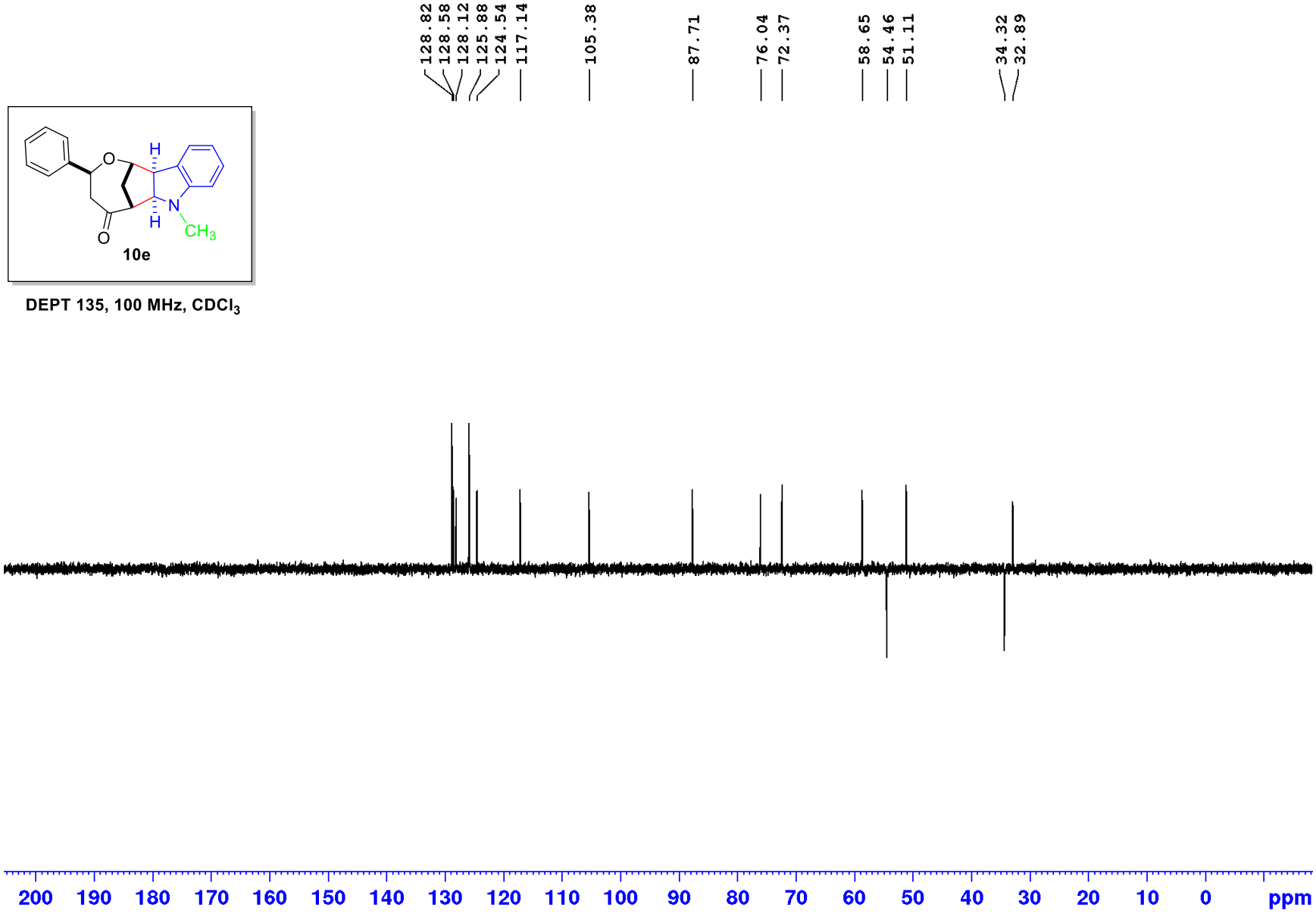
10e

^{1}H NMR, 500 MHz, $CDCl_3$



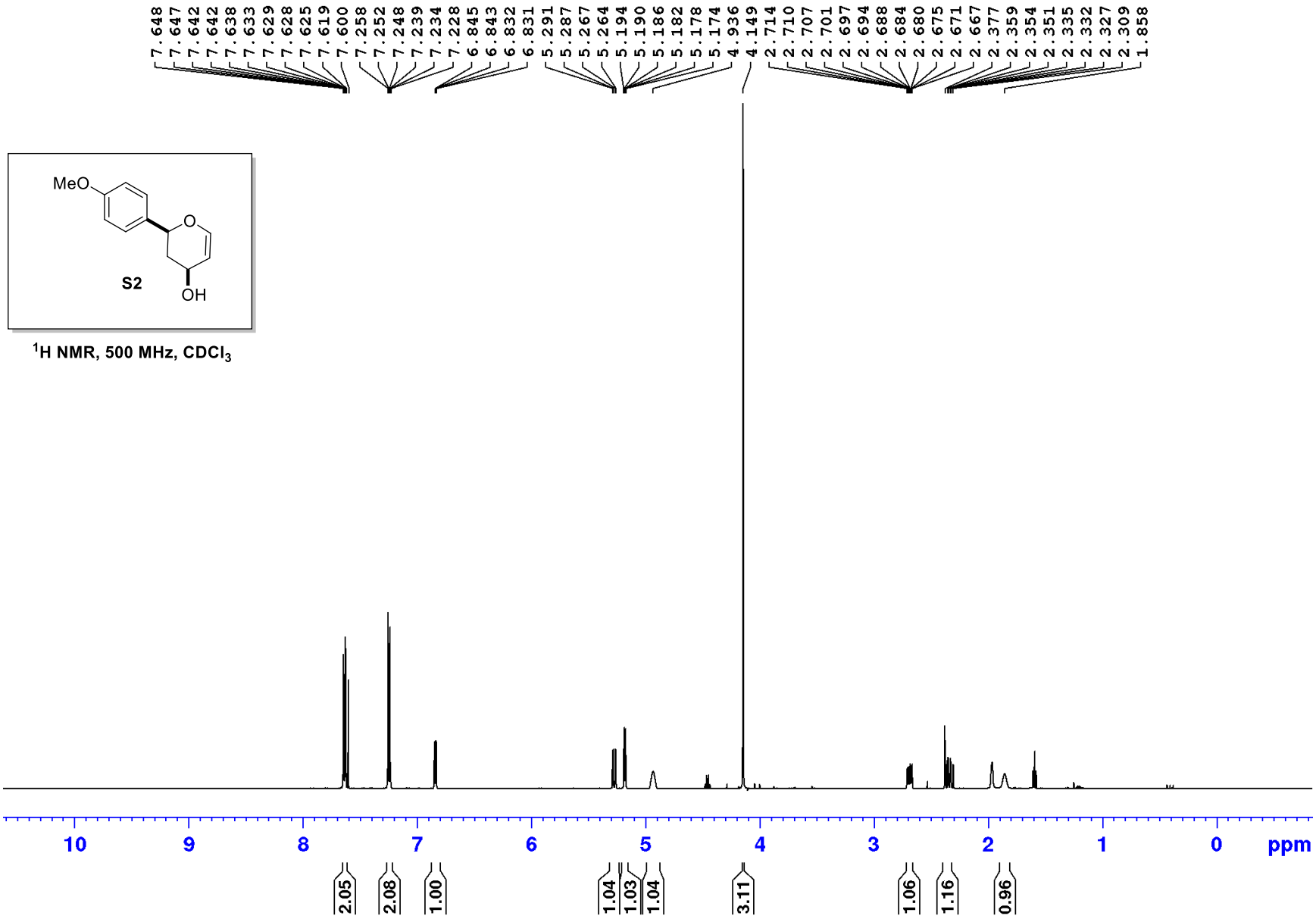


$^{13}C\{^{1}H\}$ NMR, 100 MHz, $CDCl_3$

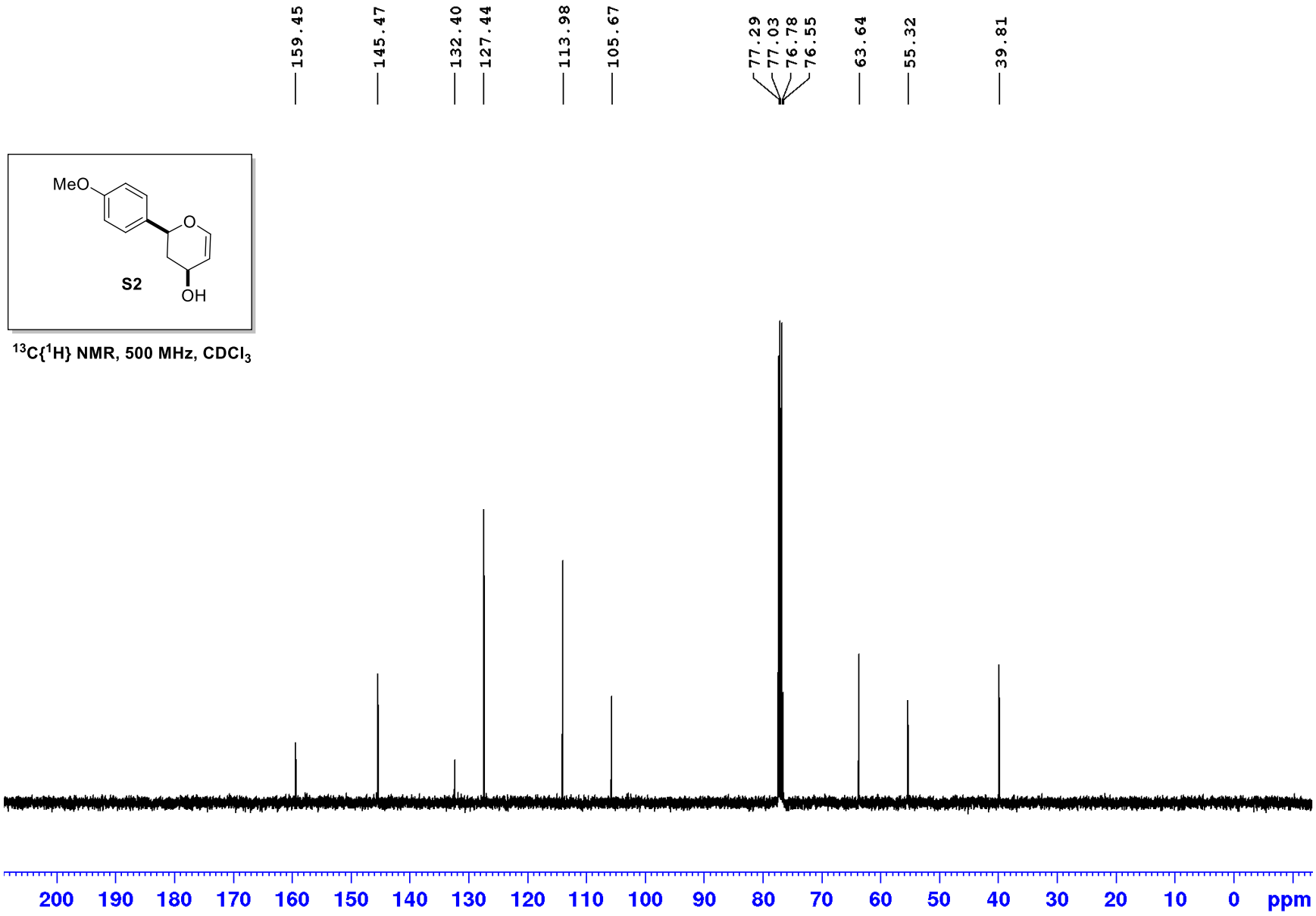


10e

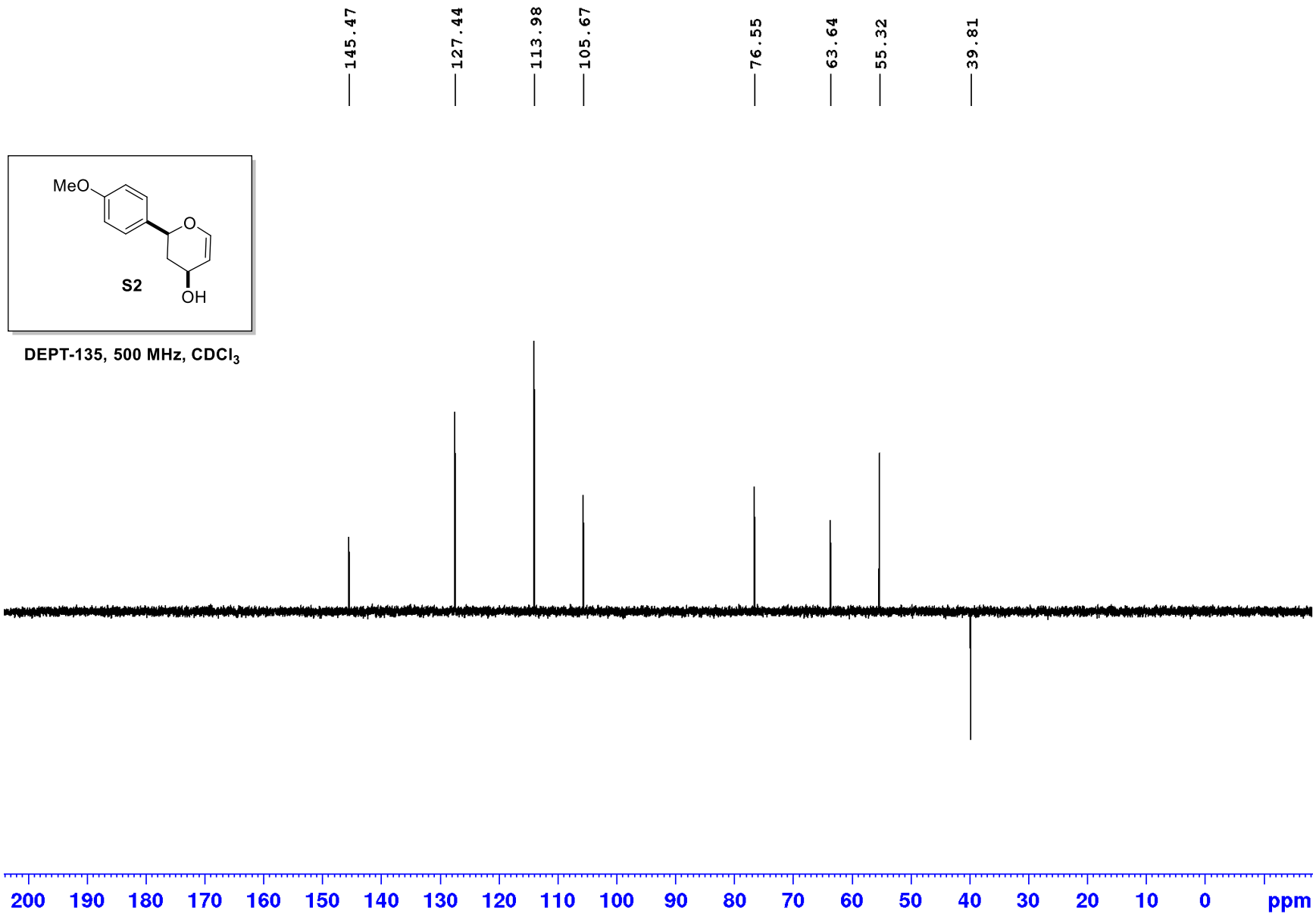
DEPT 135, 100 MHz, $CDCl_3$

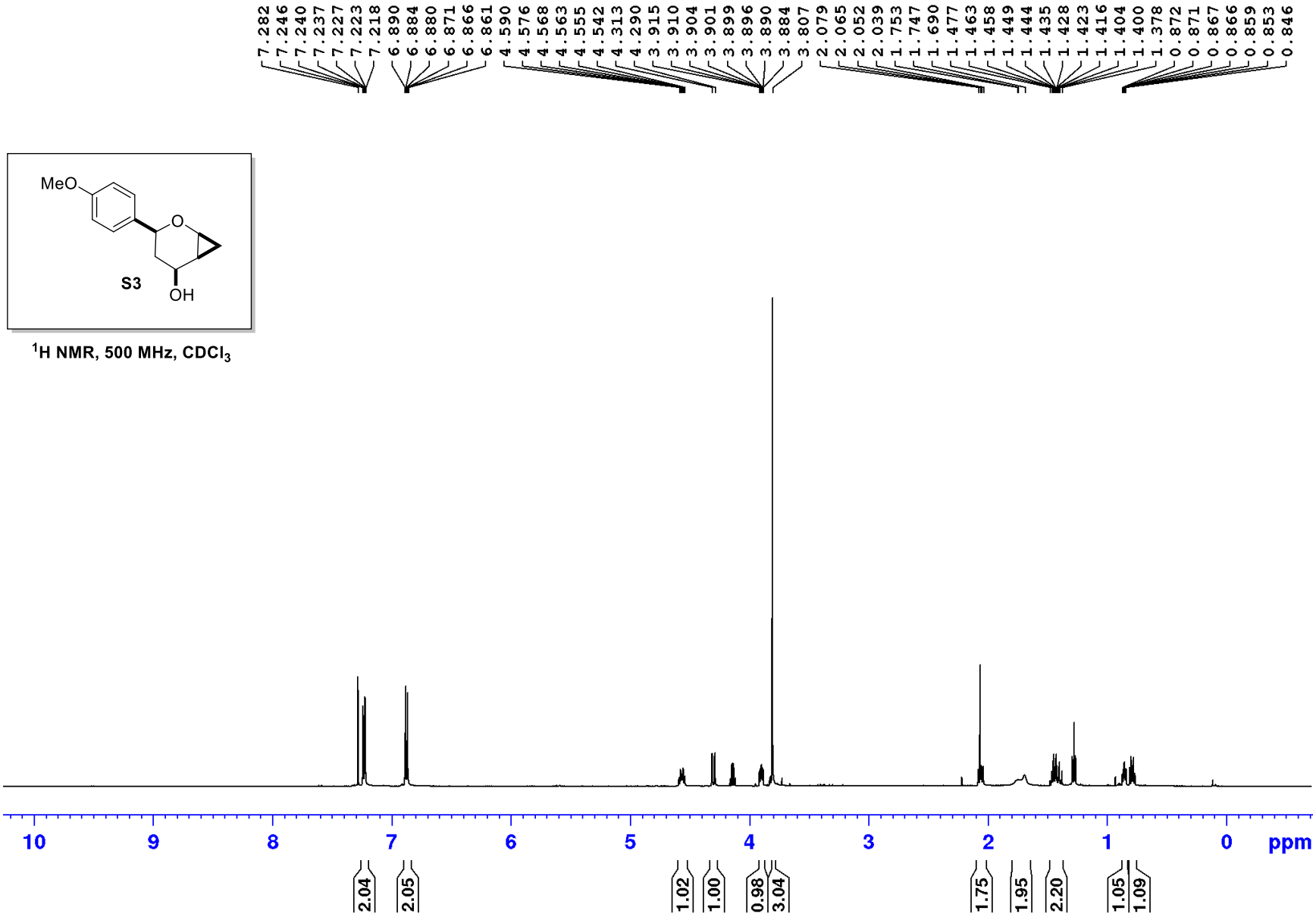


^{1}H NMR, 500 MHz, $CDCl_3$

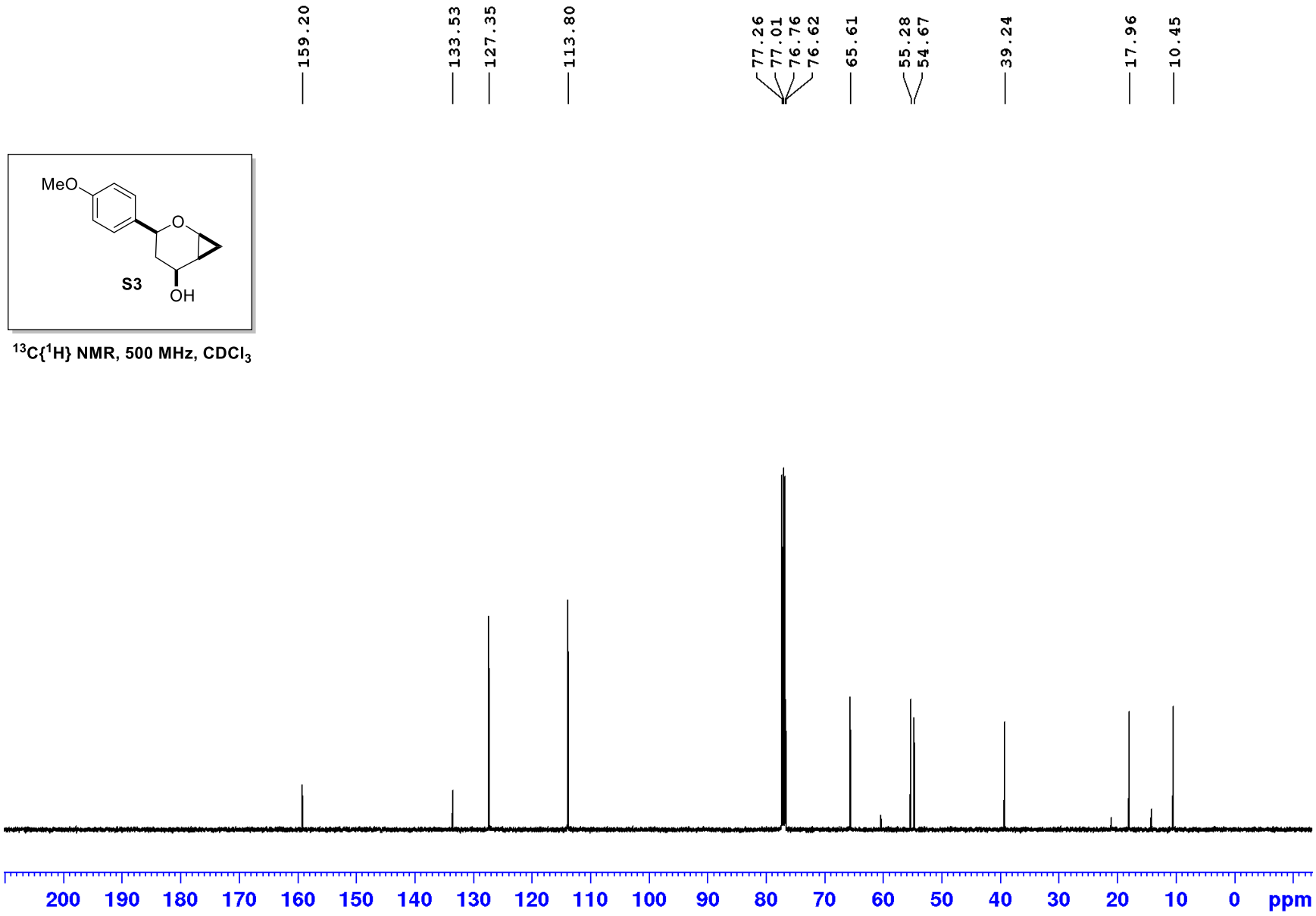


$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

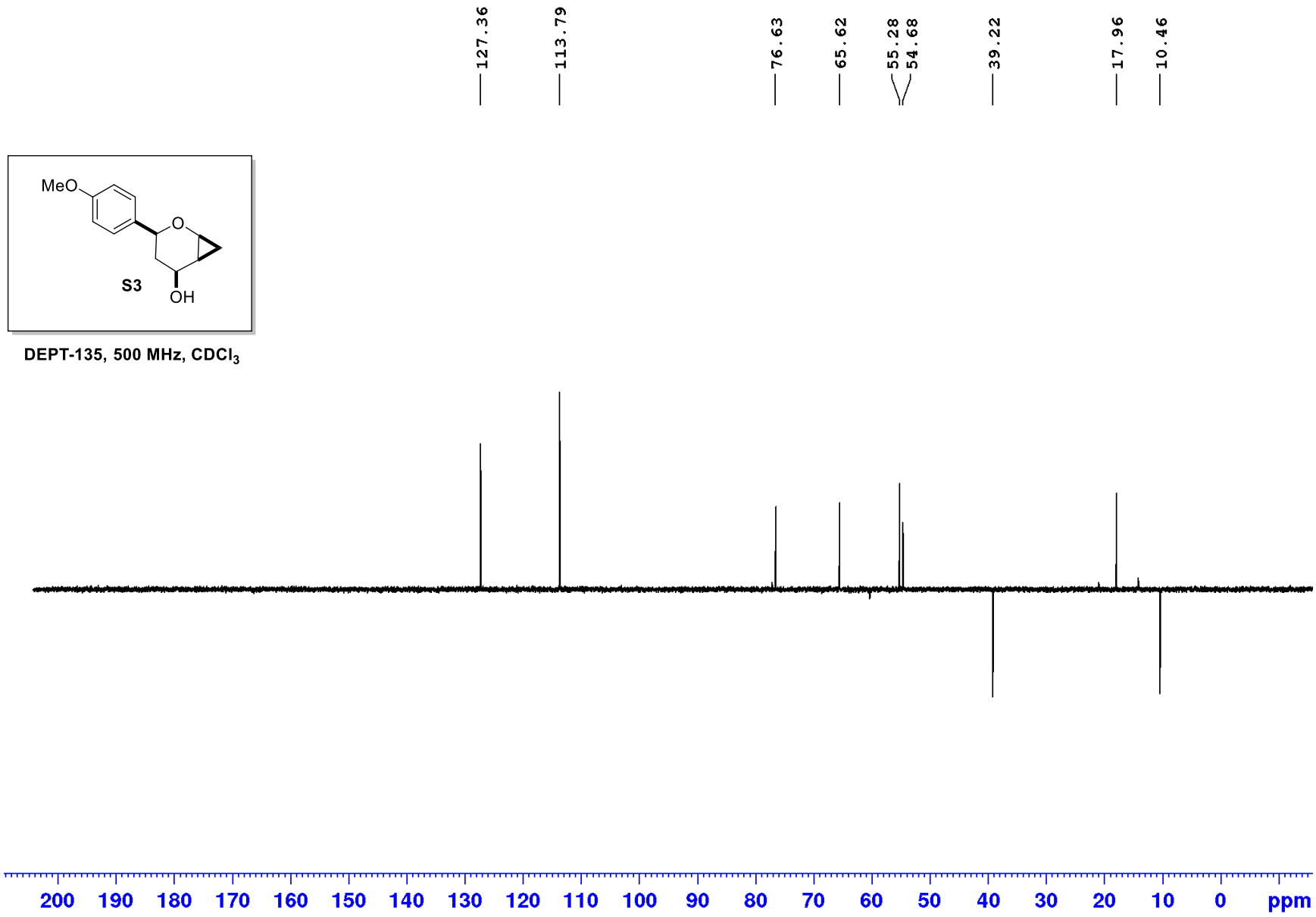

145.47
127.44
113.98
105.67
76.55
63.64
55.32
39.81
MeO
O
OH
S2
DEPT-135, 500 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



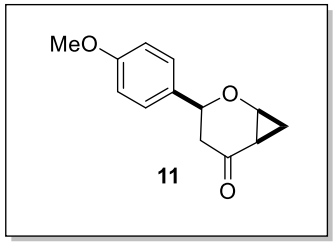
^{1}H NMR, 500 MHz, $CDCl_3$



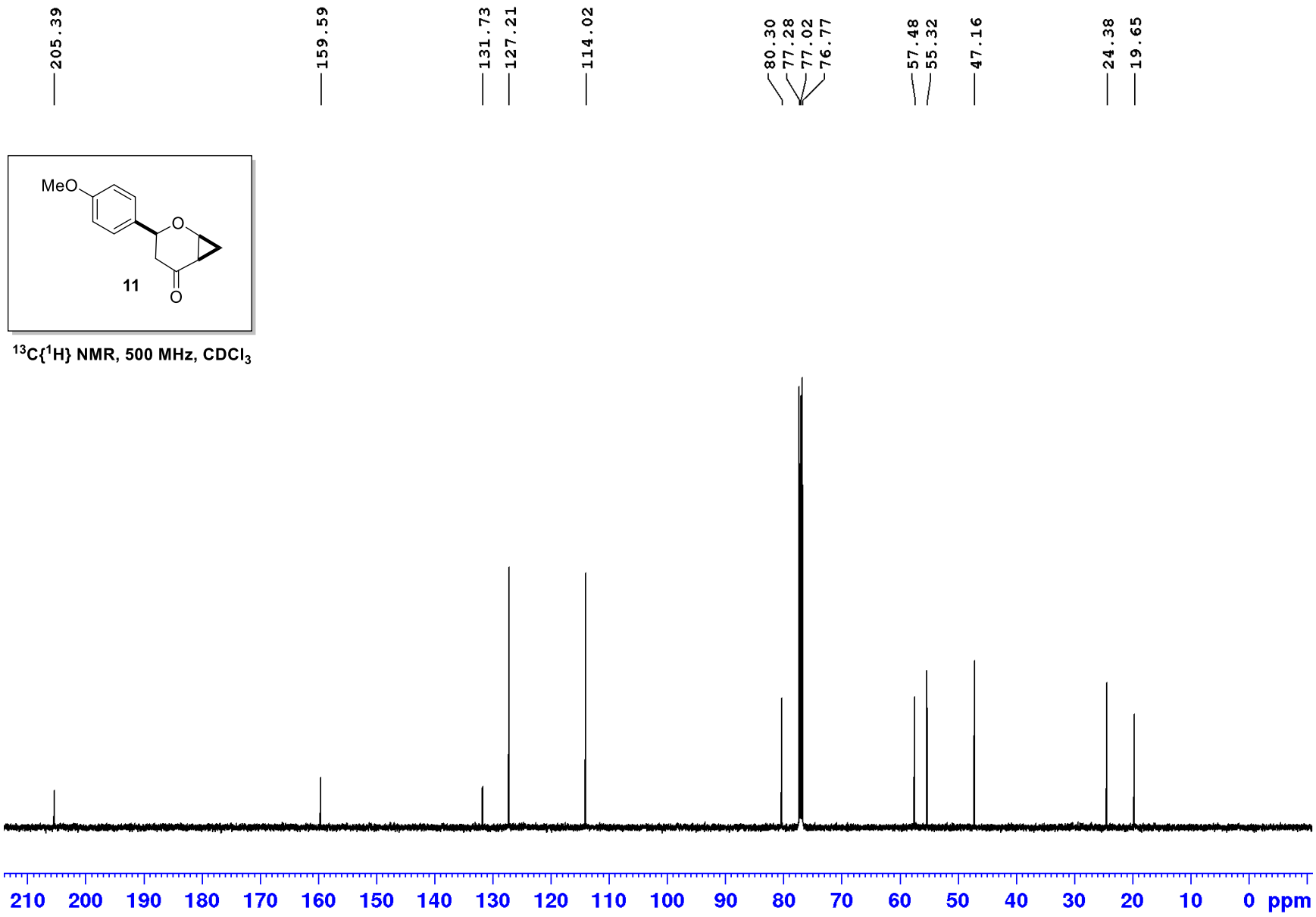
$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$



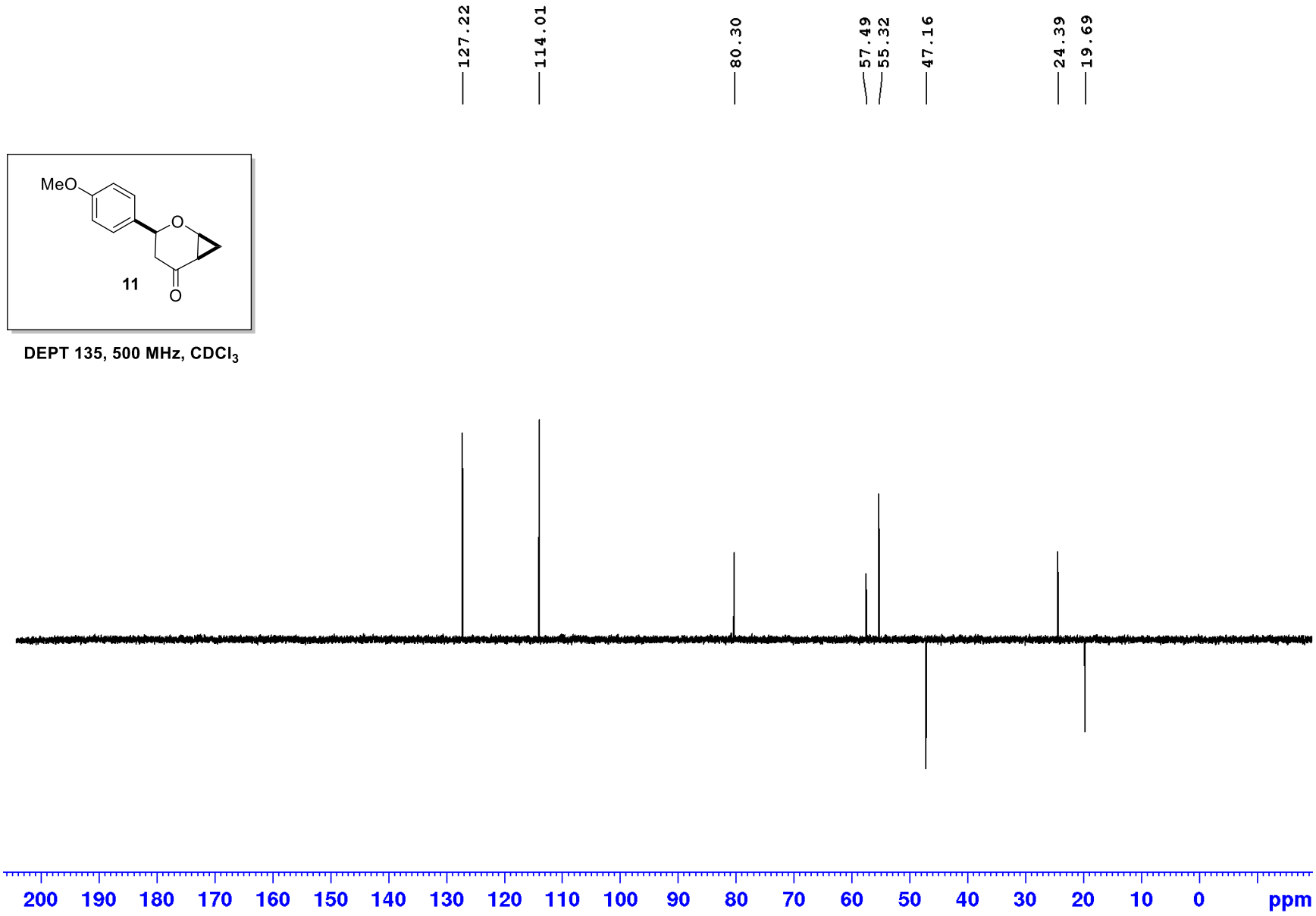
DEPT-135, 500 MHz, $CDCl_3$



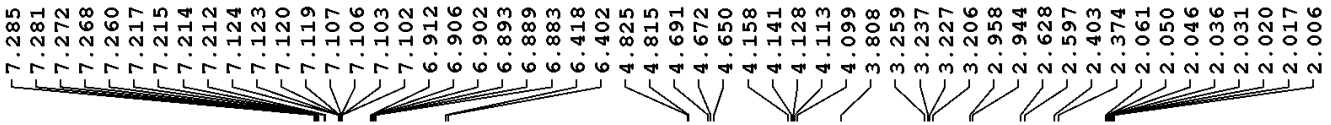
^{1}H NMR, 500 MHz, $CDCl_3$

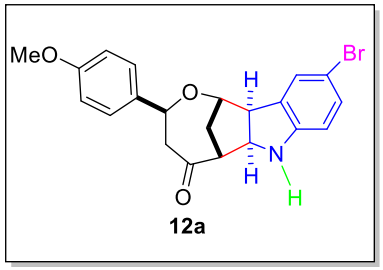


$^{13}C\{^{1}H\}$ NMR, 500 MHz, $CDCl_3$

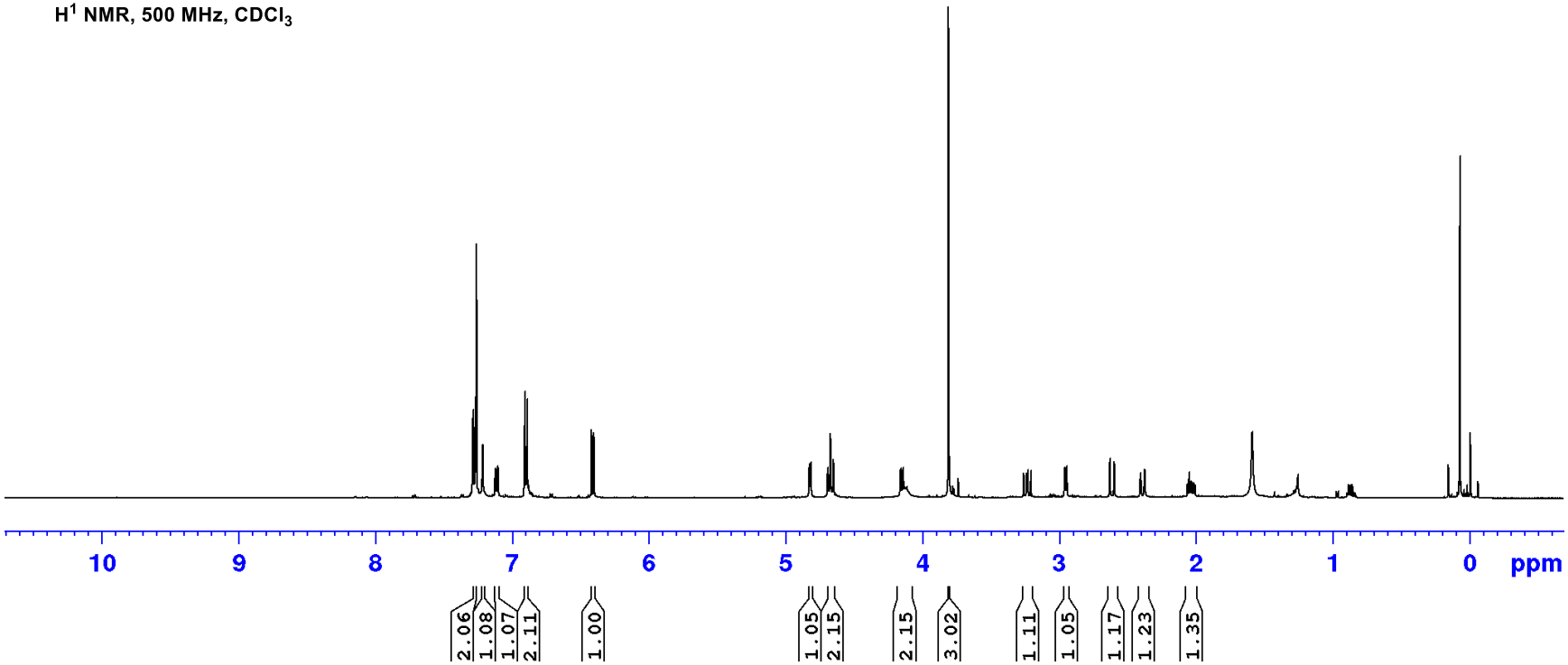


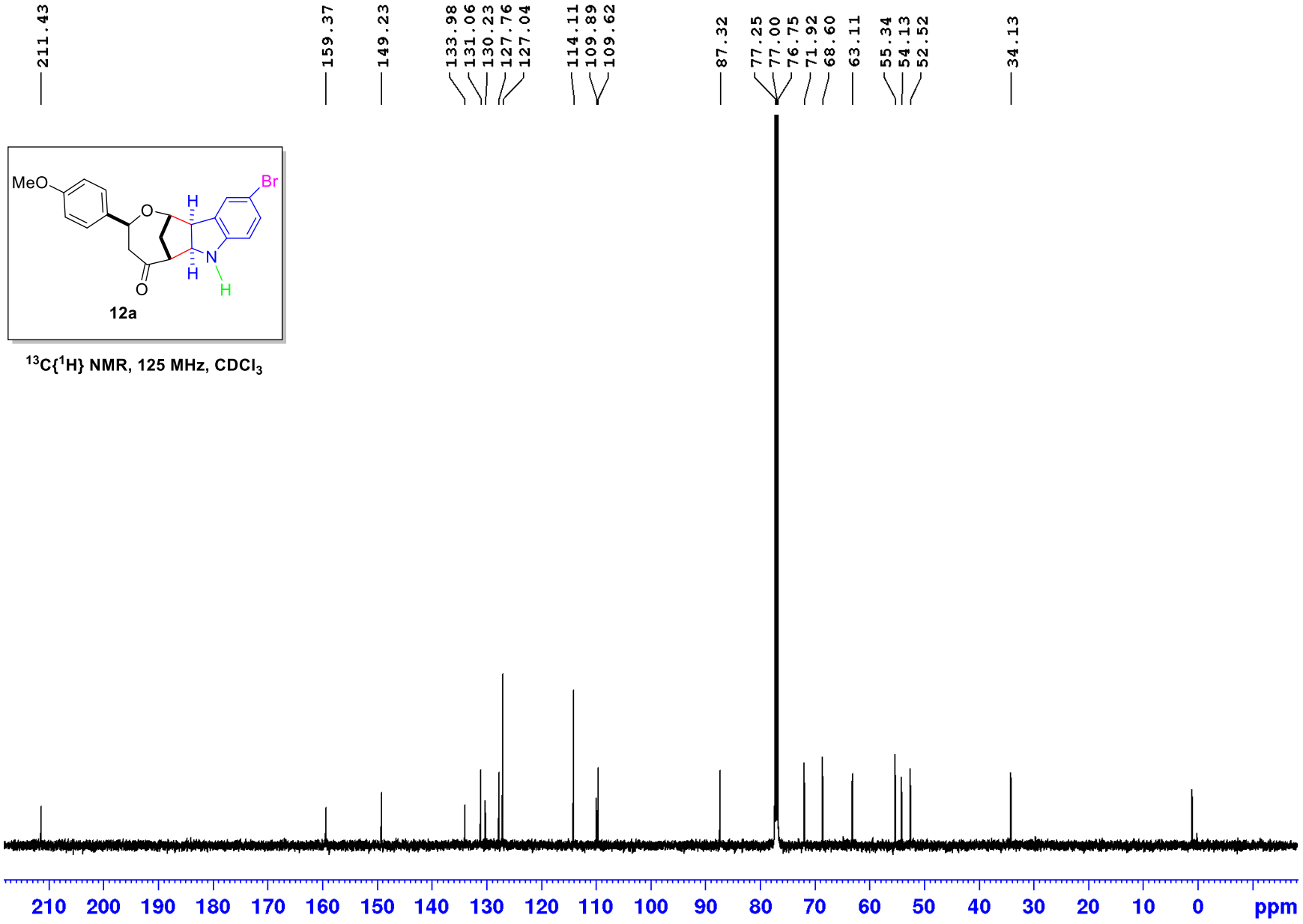
DEPT 135, 500 MHz, $CDCl_3$



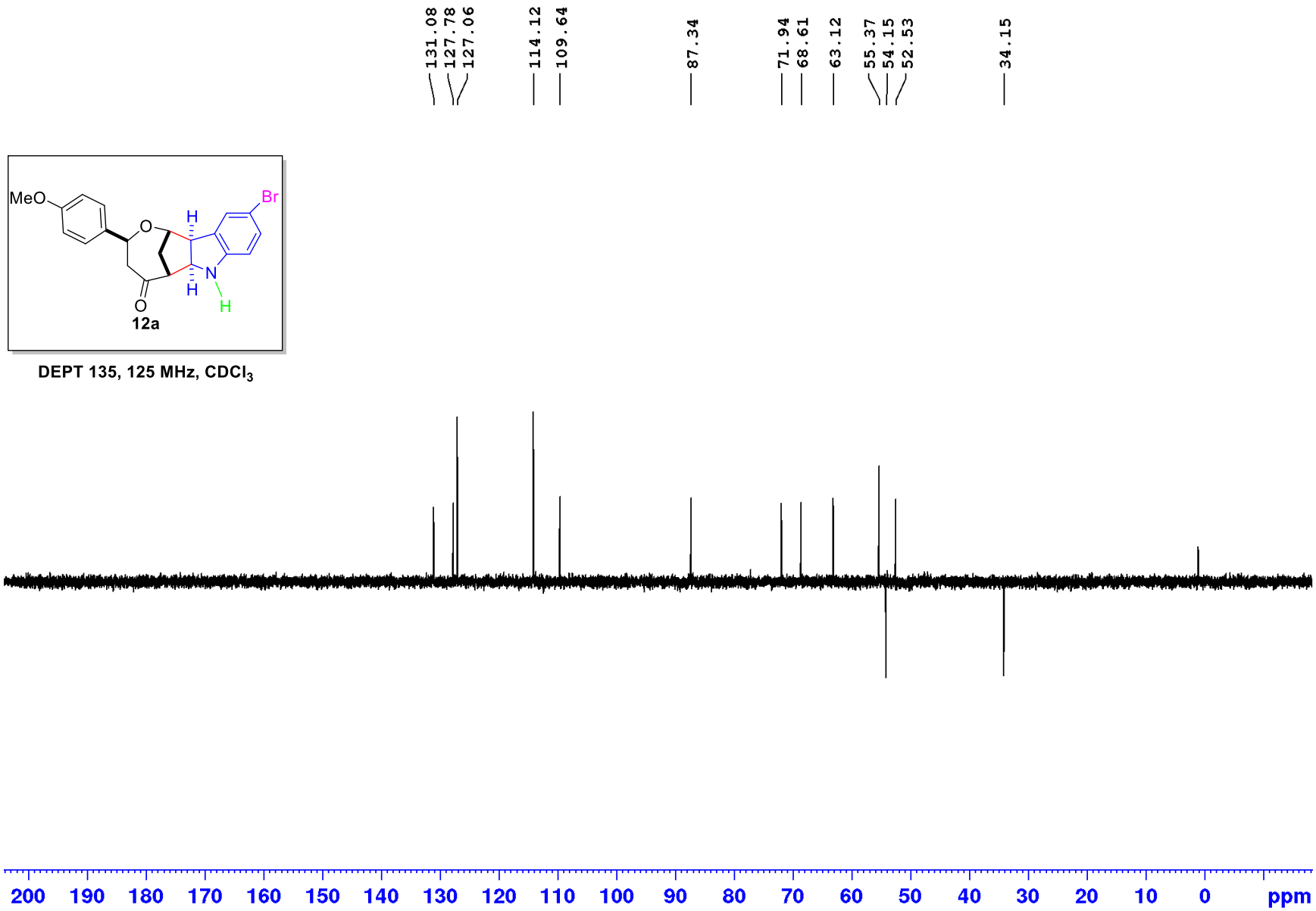


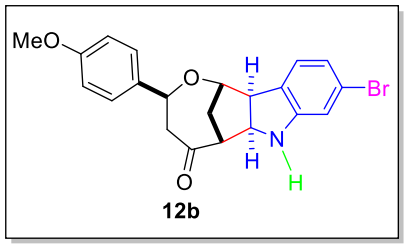
H^1 NMR, 500 MHz, $CDCl_3$





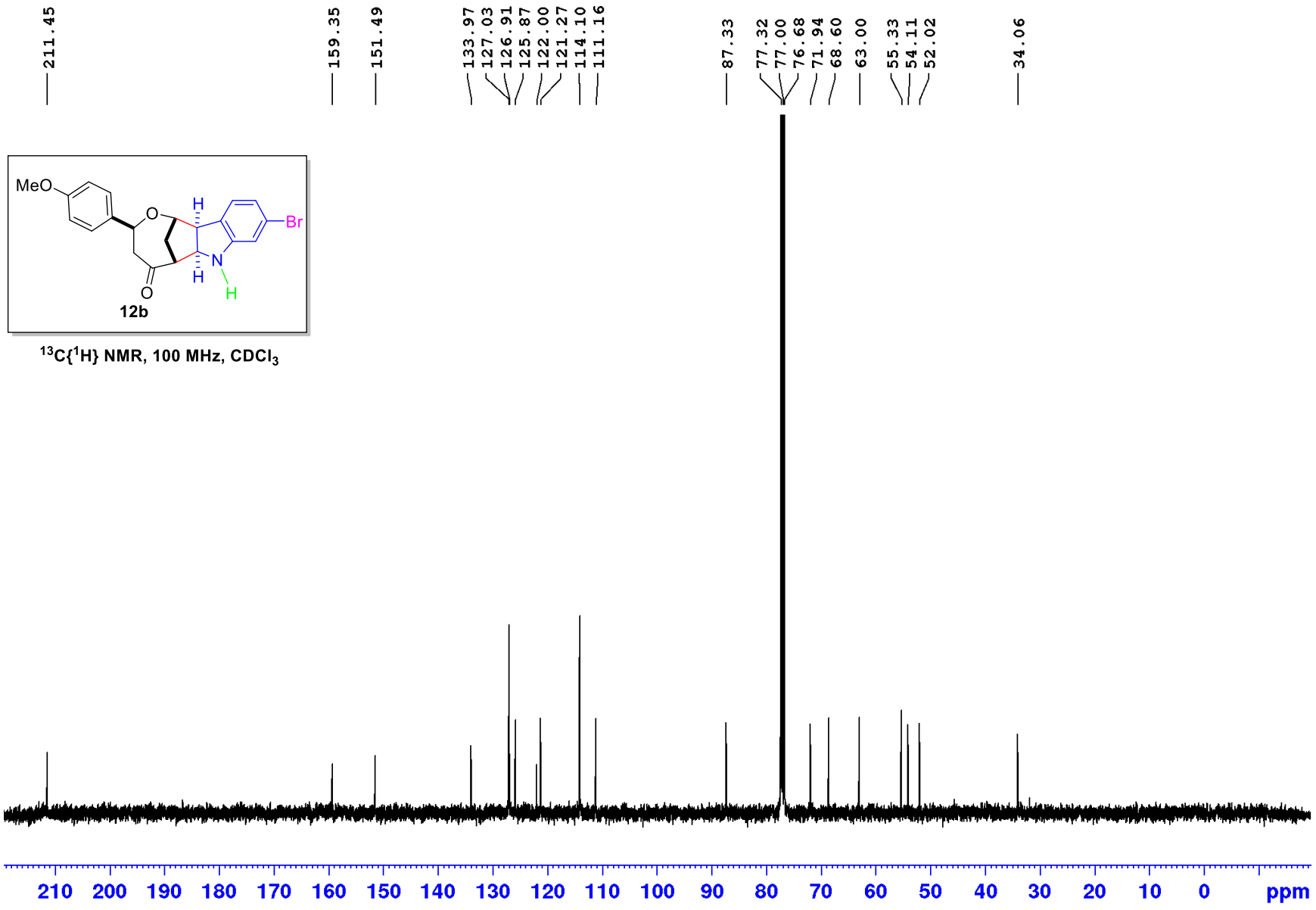
$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$


131.08
127.78
127.06
114.12
109.64
87.34
71.94
68.61
63.12
55.37
54.15
52.53
34.15
MeO
Br
O
H
N
H
H
O
12a
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

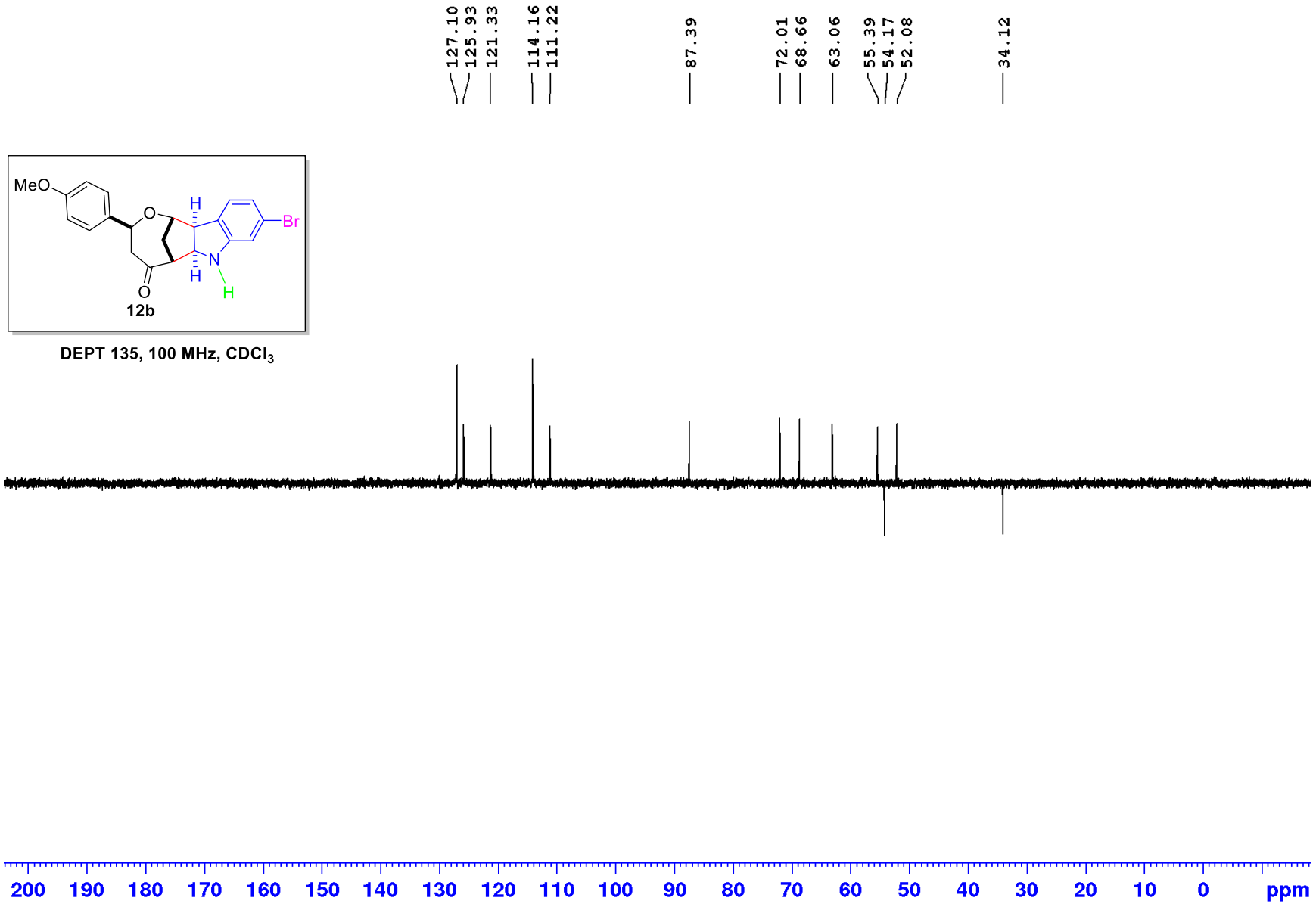


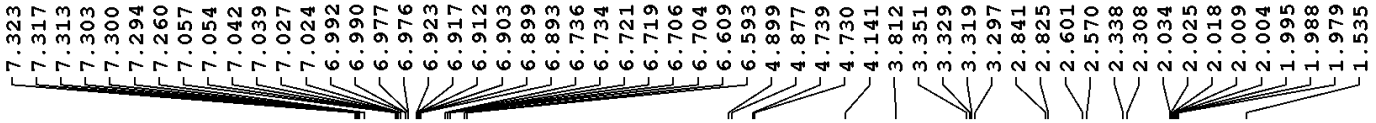
12b

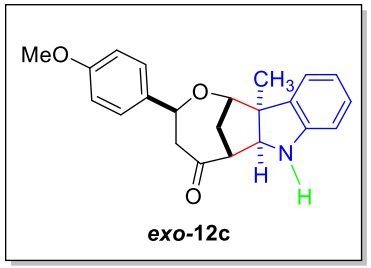
^{1}H NMR, 500 MHz, $CDCl_3$



$^{13}C\{^{1}H\}$ NMR, 100 MHz, $CDCl_3$

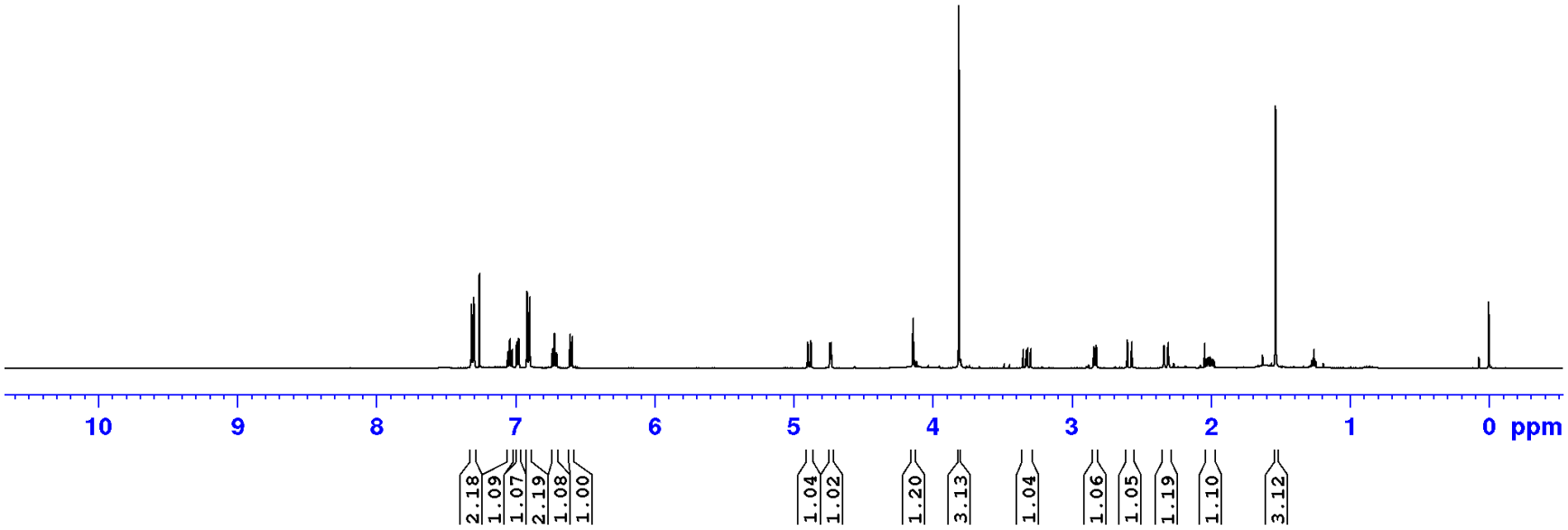

127.10
125.93
121.33
114.16
111.22
87.39
72.01
68.66
63.06
55.39
54.17
52.08
34.12
MeO
O
H
Br
N
H
H
O
12b
DEPT 135, 100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

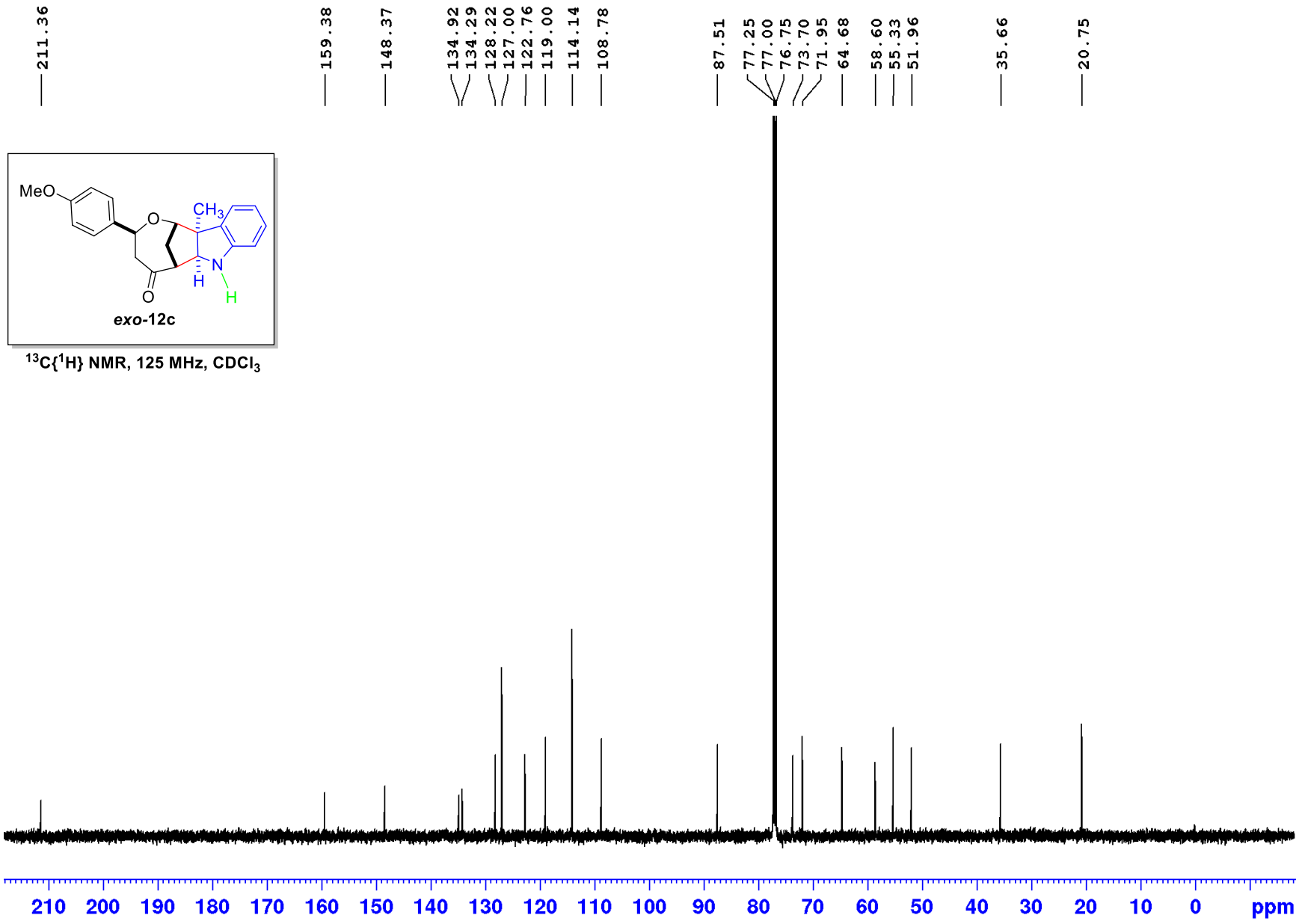


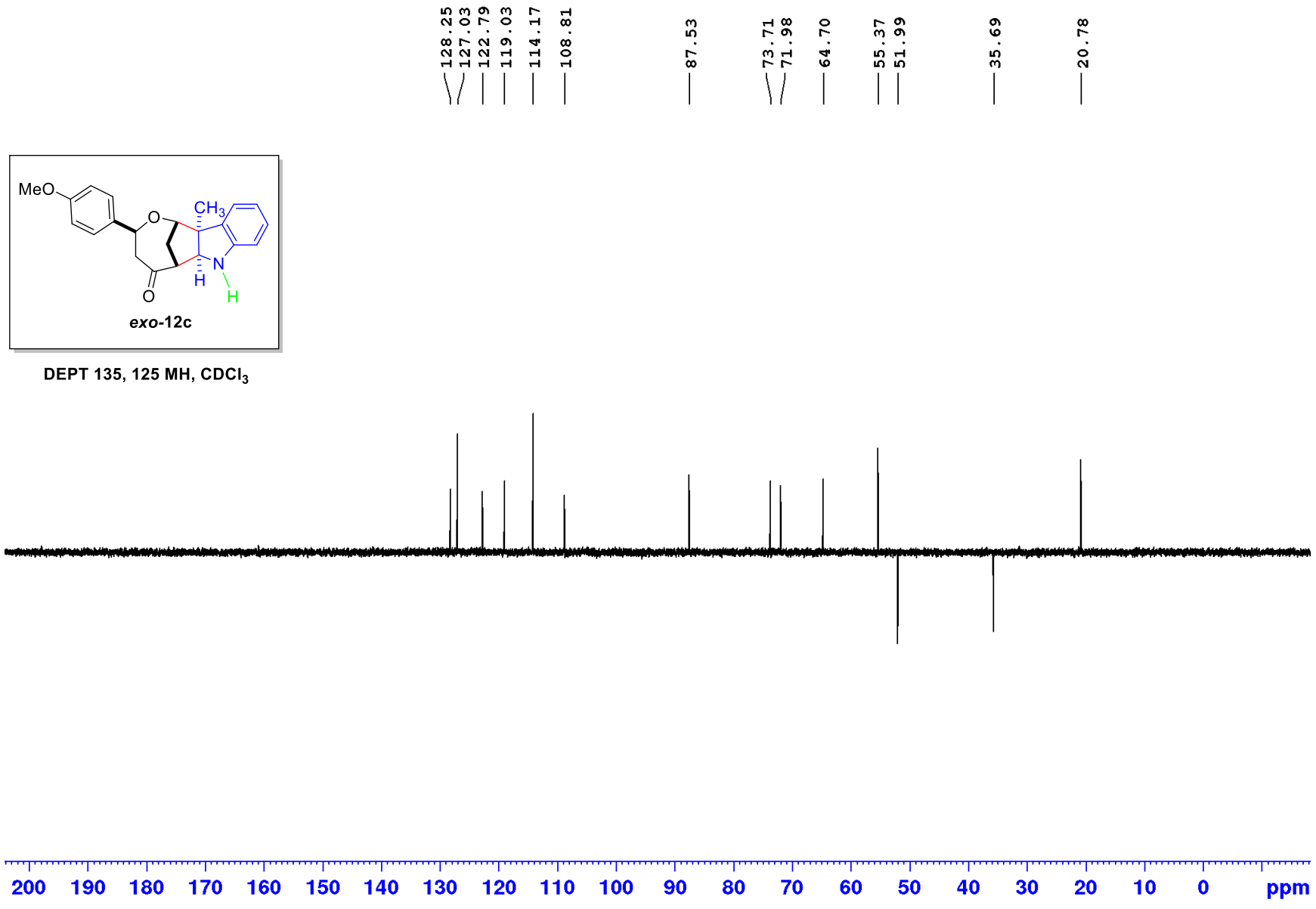


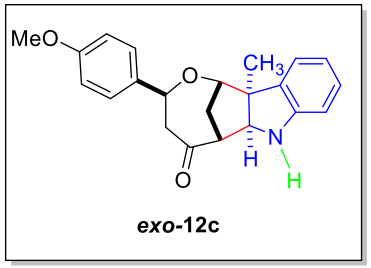
***exo*-12c**

^{1}H NMR, 500 MHz, $CDCl_3$



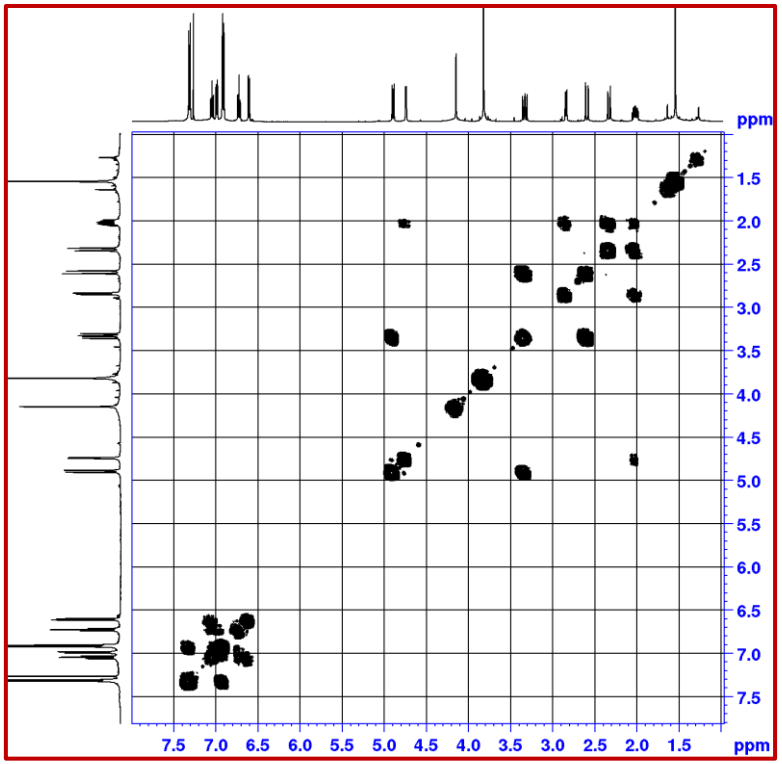

211.36
159.38
148.37
134.92
134.29
128.22
127.00
122.76
119.00
114.14
108.78
87.51
77.25
77.00
76.75
73.70
71.95
64.68
58.60
55.33
51.96
35.66
20.75
MeO
O
CH3
N
H
H
O
exo-12c
13C{1H} NMR, 125 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

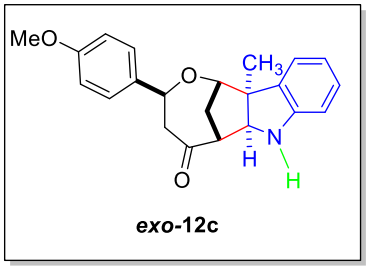

128.25
127.03
122.79
119.03
114.17
108.81
87.53
73.71
71.98
64.70
55.37
51.99
35.69
20.78
MeO
O
CH3
N
H
H
O
exo-12c
DEPT 135, 125 MH, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



***exo*-12c**

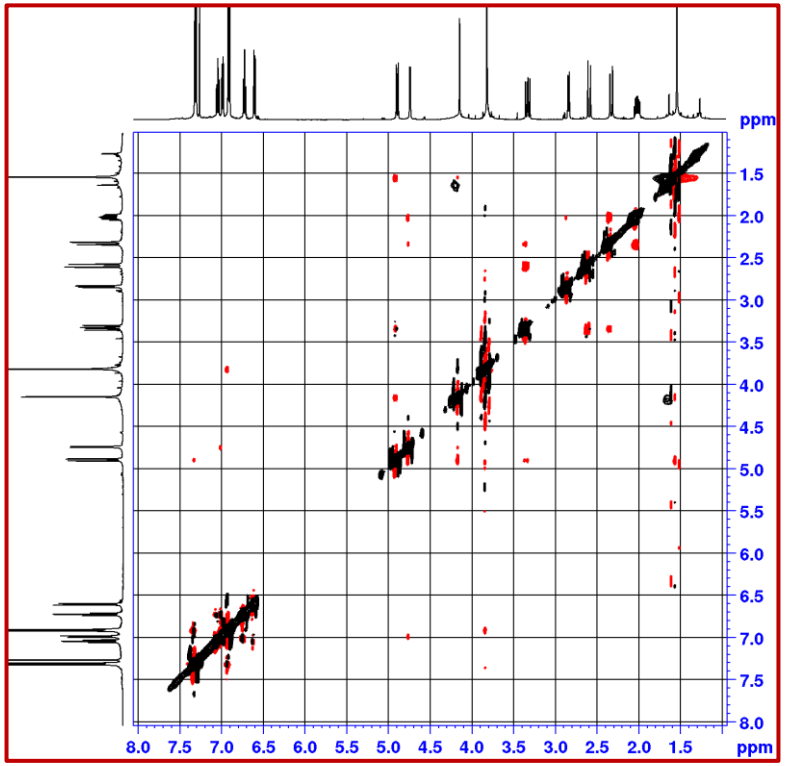
(COSY, 500 MHz)

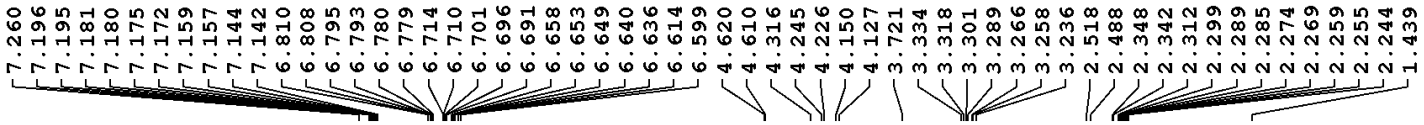


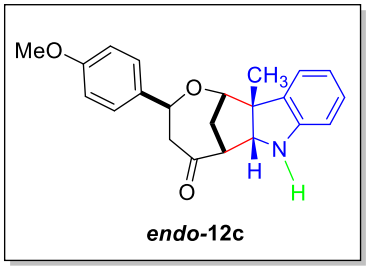


***exo*-12c**

(NOESY, 500 MHz)

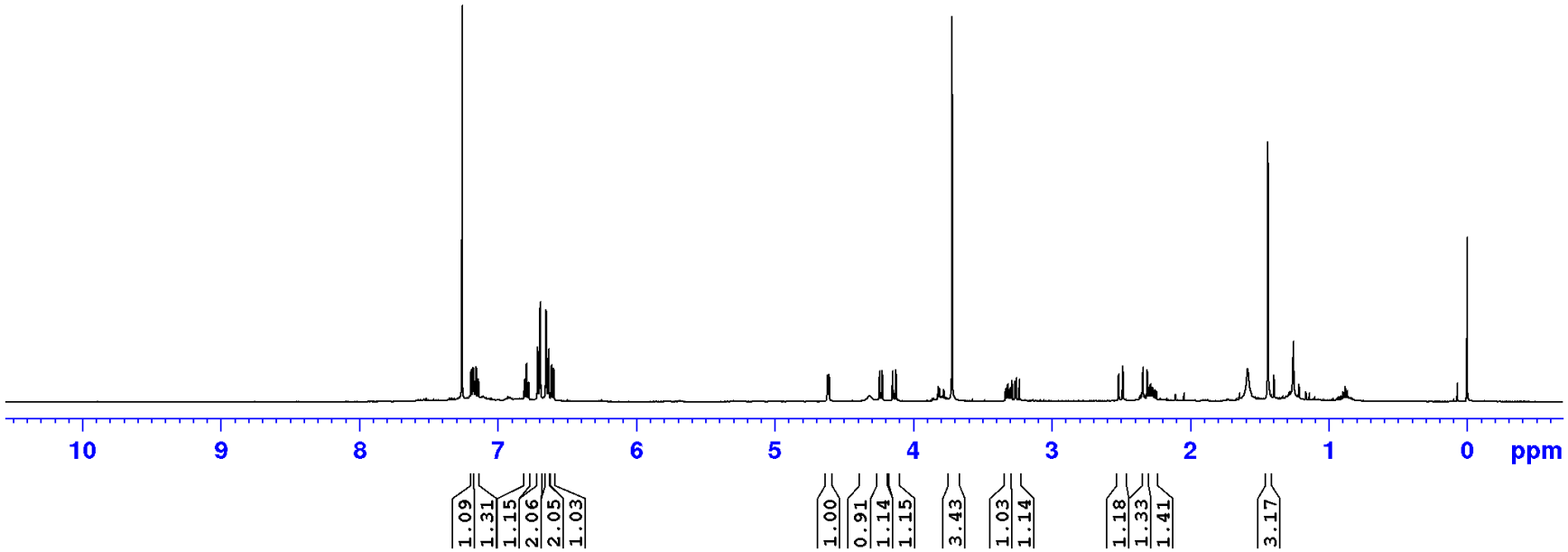


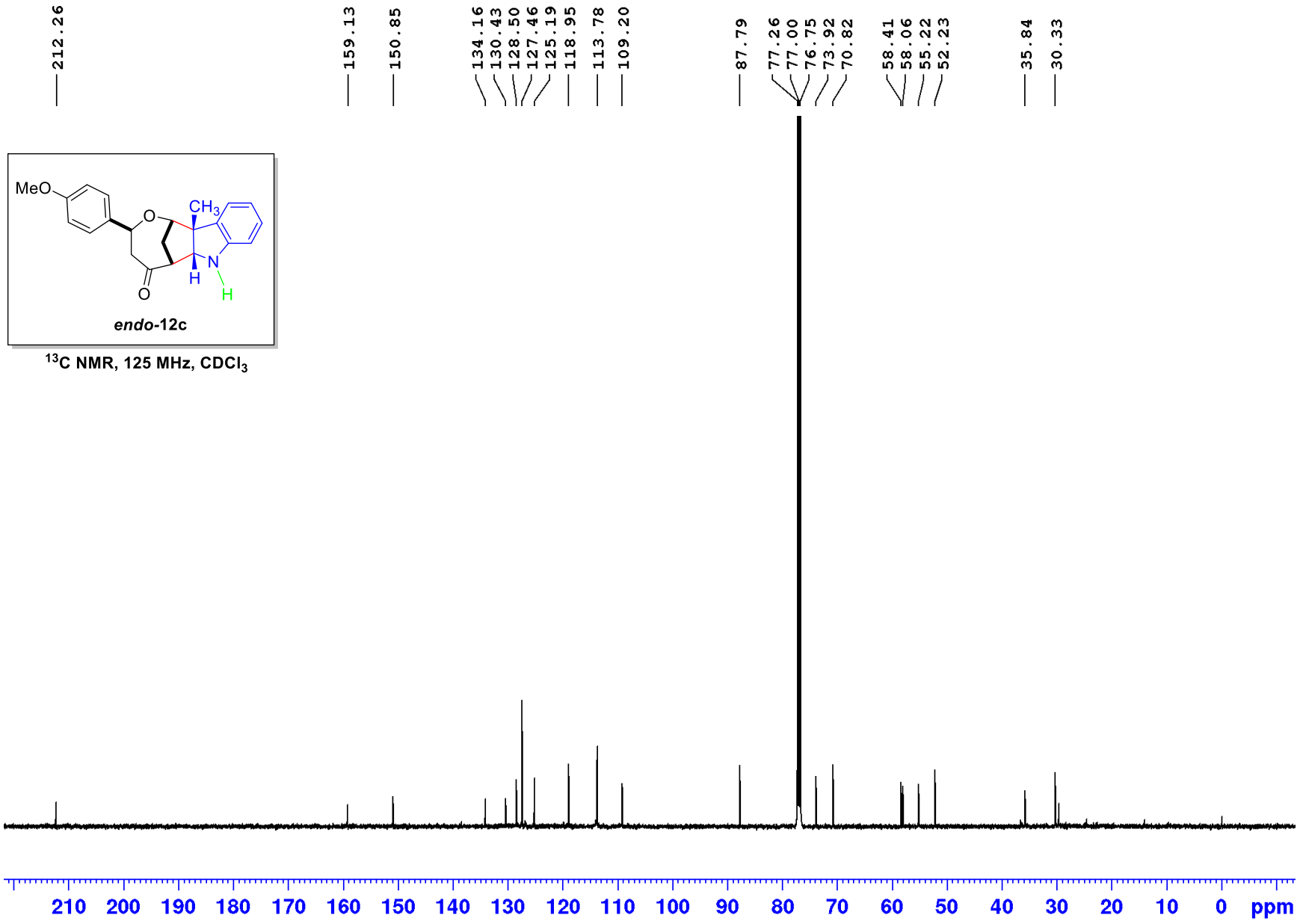




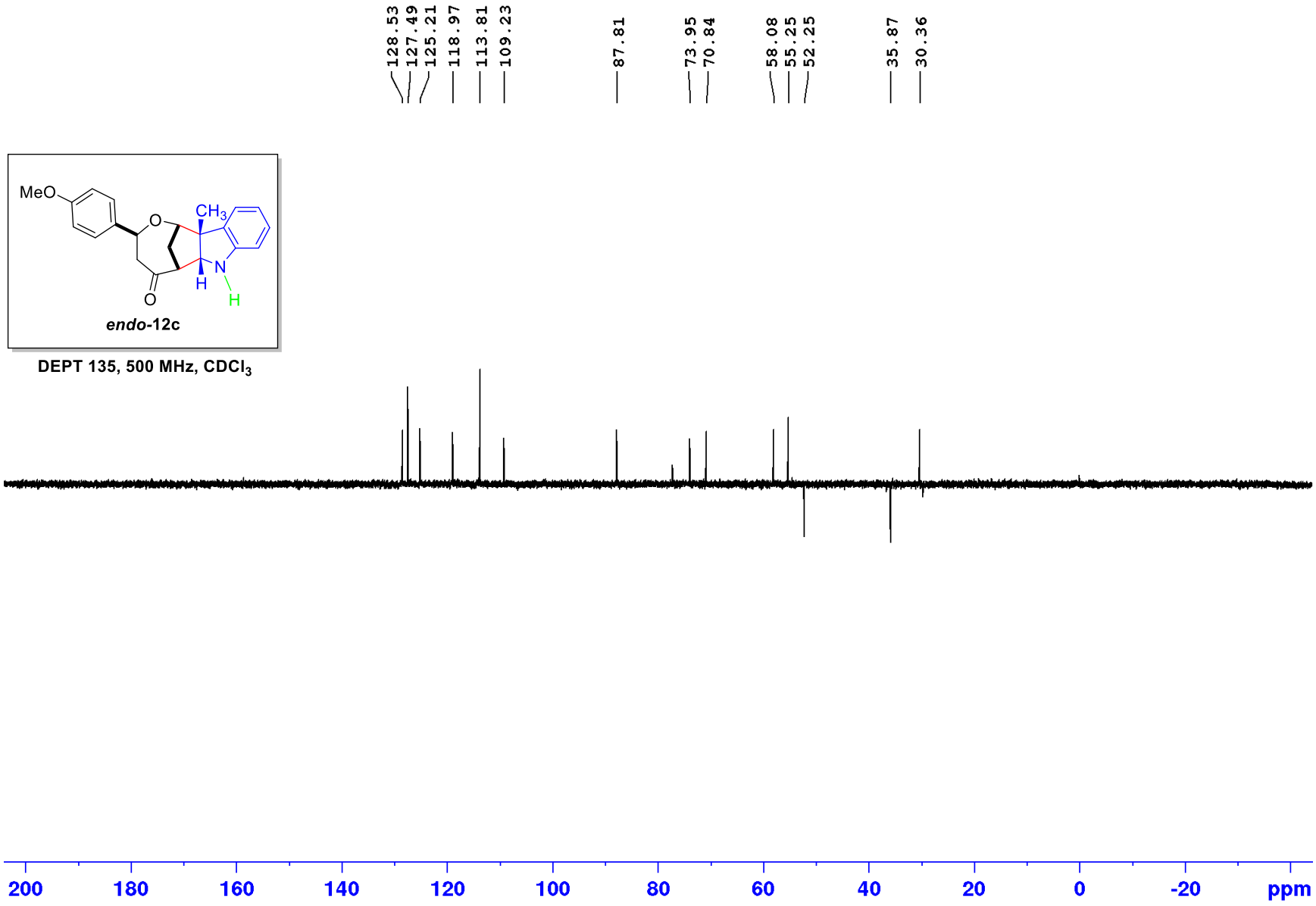
***endo*-12c**

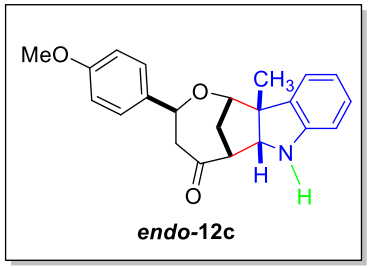
^{1}H NMR, 500 MHz, $CDCl_3$





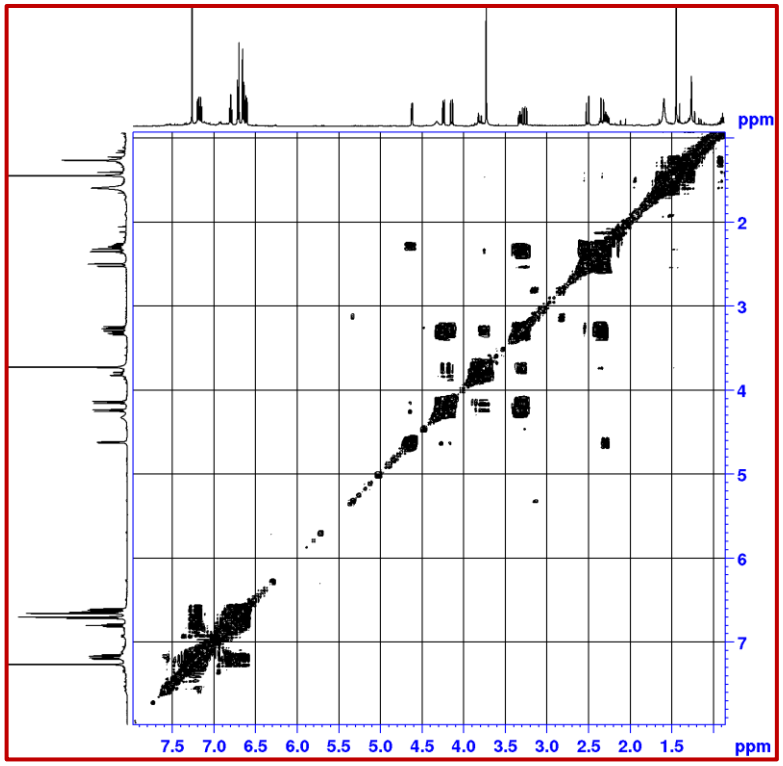
^{13}C NMR, 125 MHz, $CDCl_3$

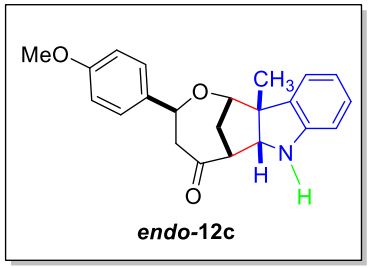

128.53
127.49
125.21
118.97
113.81
109.23
87.81
73.95
70.84
58.08
55.25
52.25
35.87
30.36
MeO
O
CH3
H
N
H
O
endo-12c
DEPT 135, 500 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



endo-12c

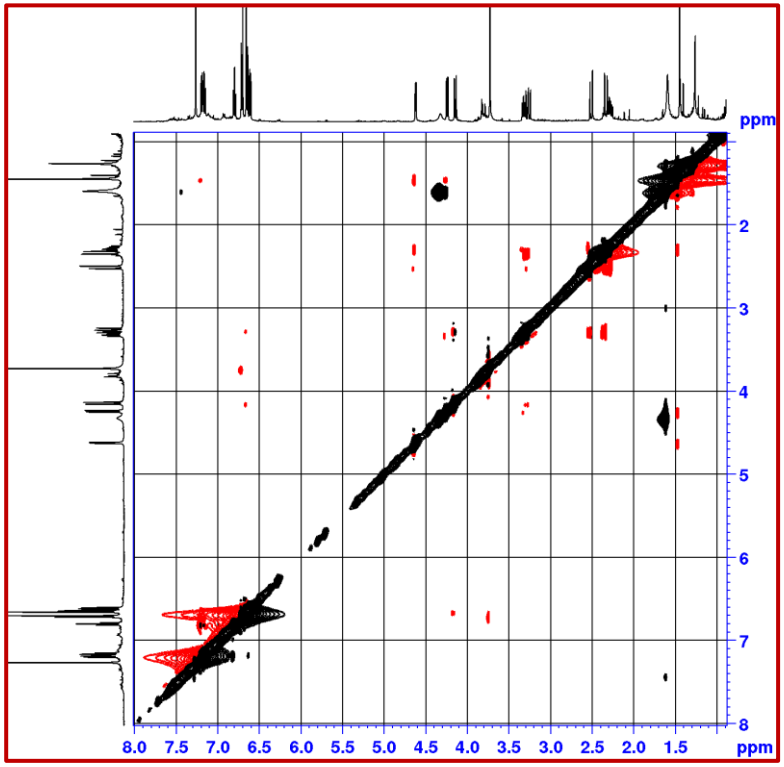
(COSY, 500 MHz)

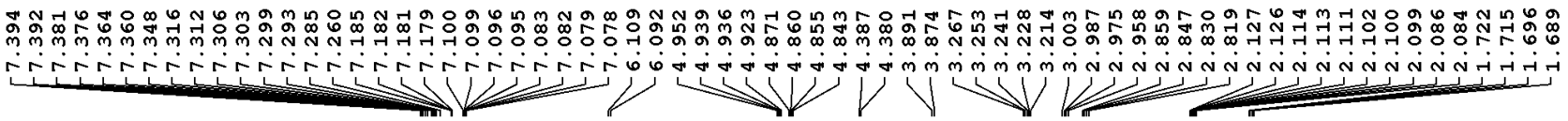


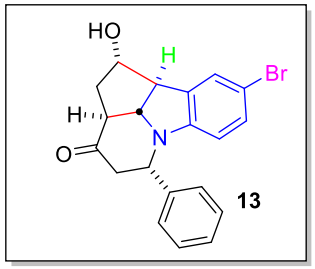


endo-12c

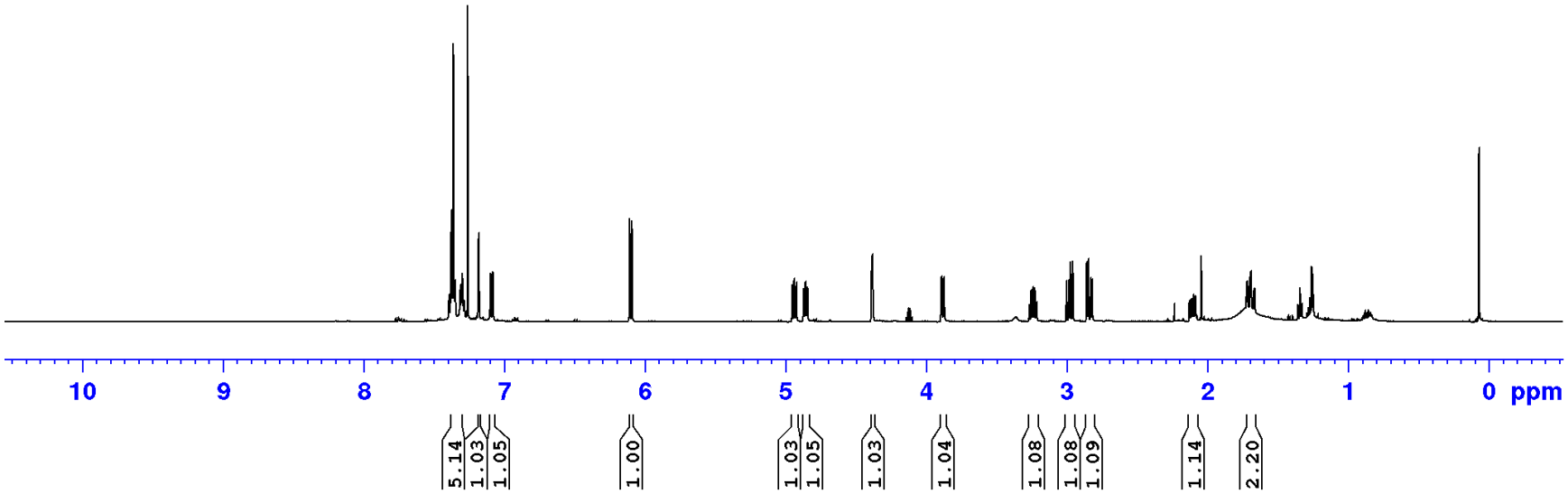
(NOESY, 500 MHz)

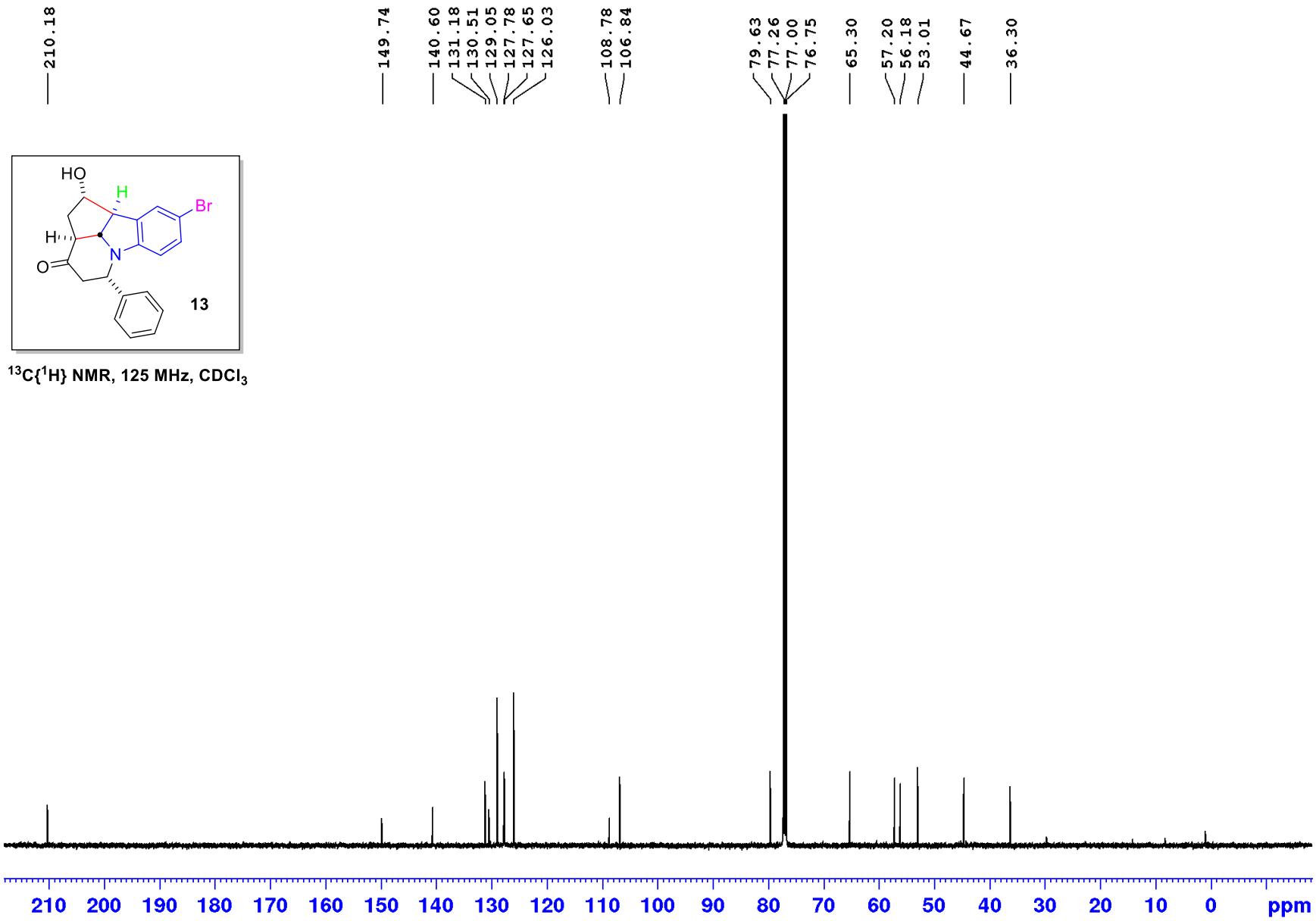




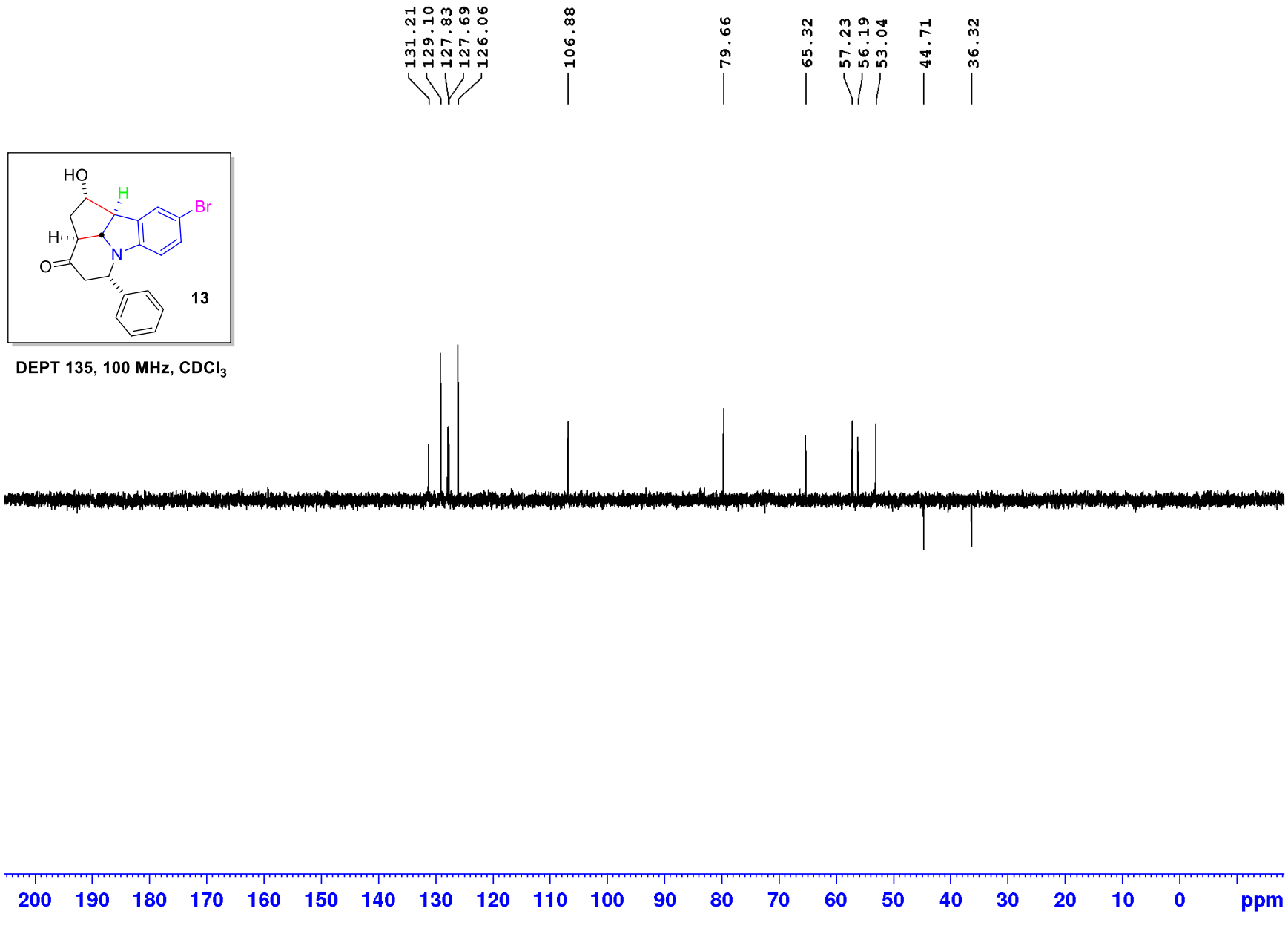


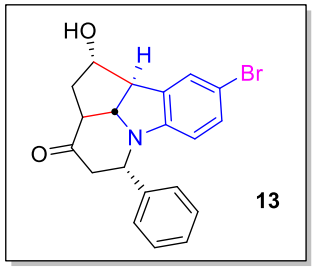
^{1}H NMR, 500 MHz, $CDCl_3$

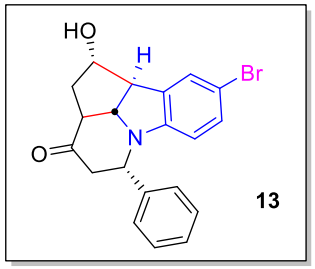




$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$

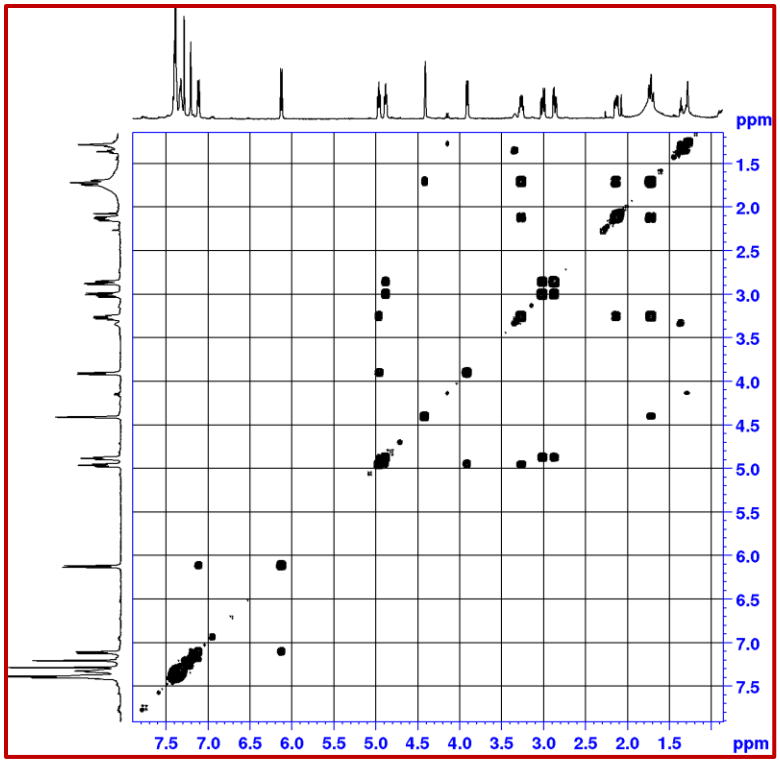

131.21
129.10
127.83
127.69
126.06
106.88
79.66
65.32
57.23
56.19
53.04
44.71
36.32
HO
H
Br
H
N
O
13
DEPT 135, 100 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

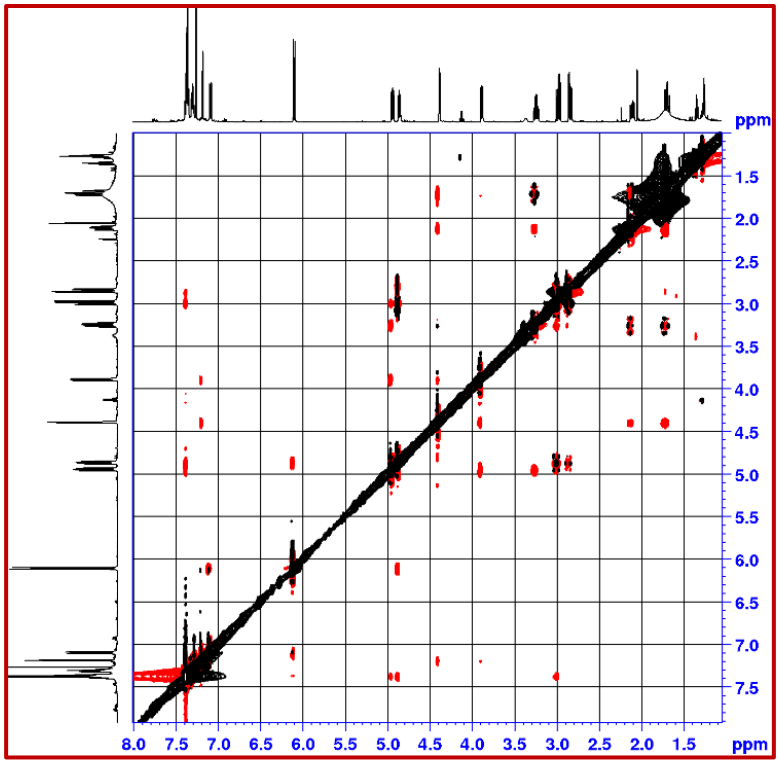


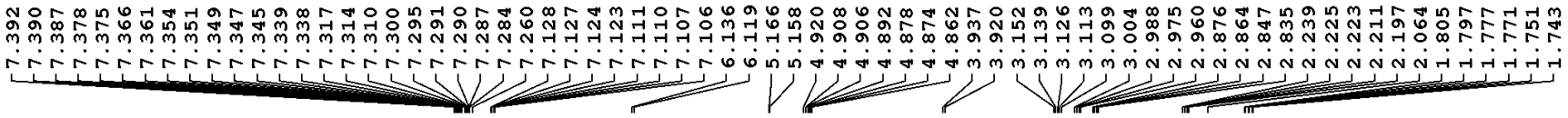


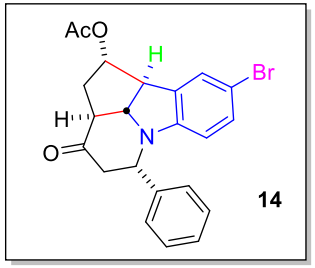
(COSY, 500 MHz)

(NOESY, 500 MHz)

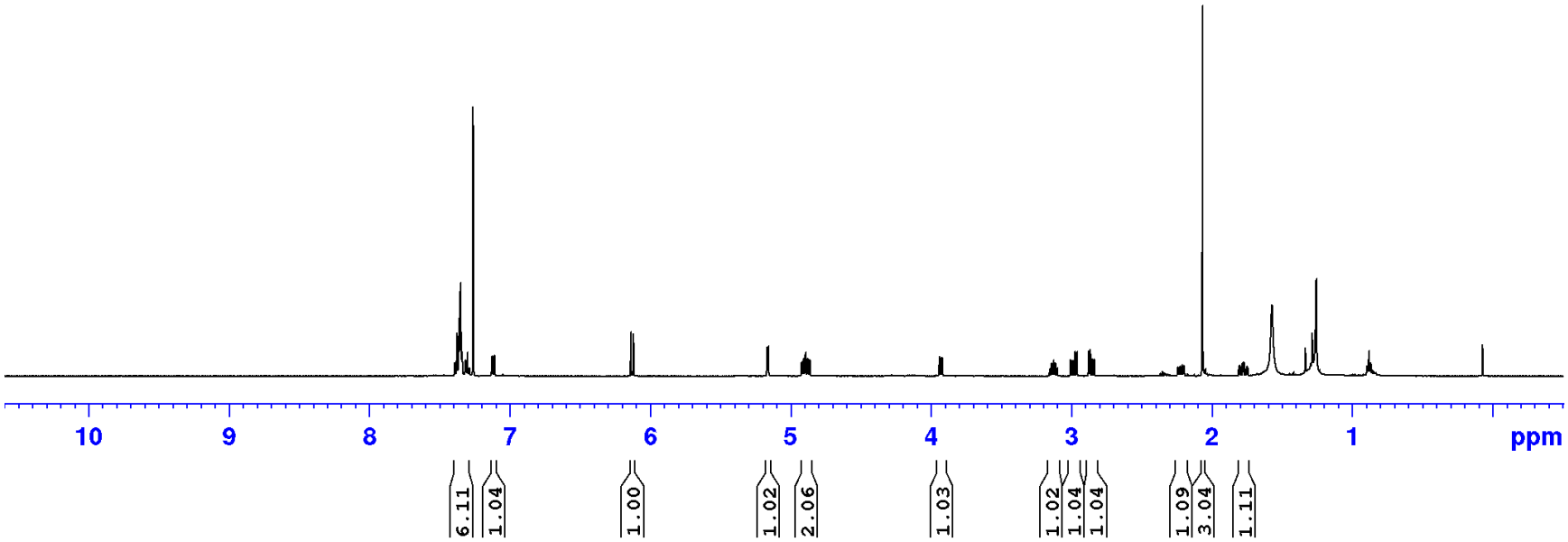


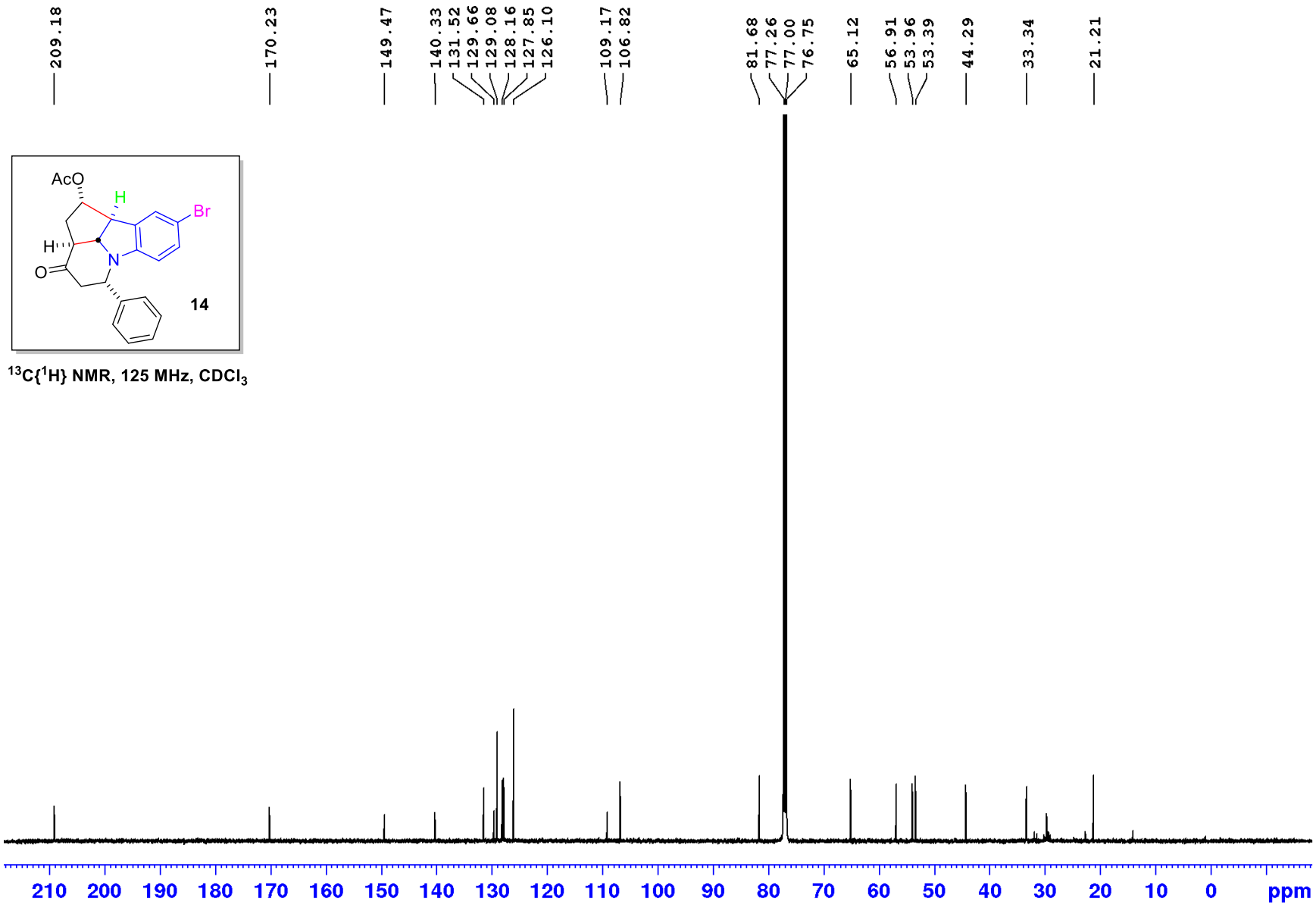




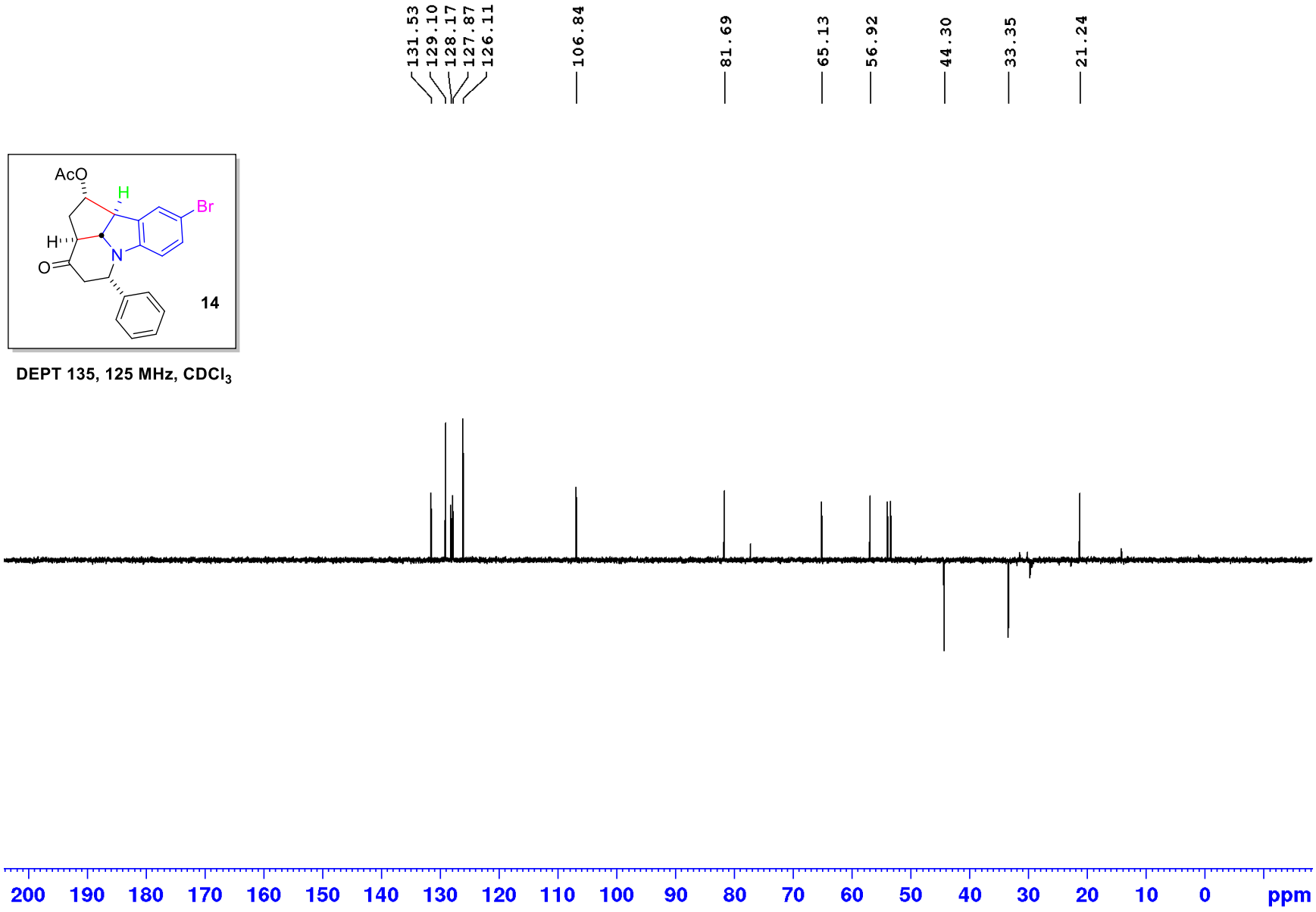


^{1}H NMR, 500 MHz, $CDCl_3$





$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$



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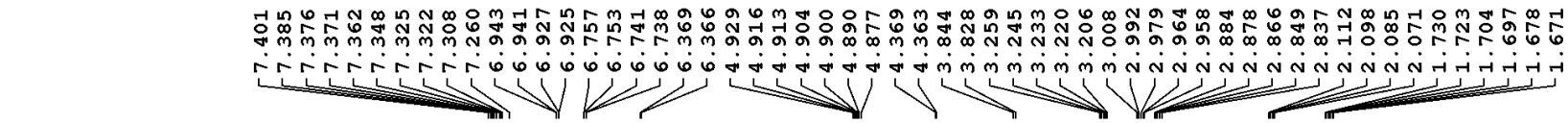

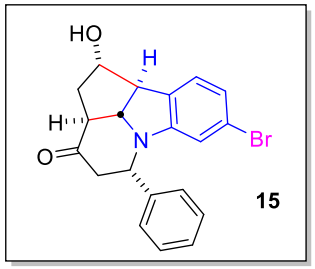

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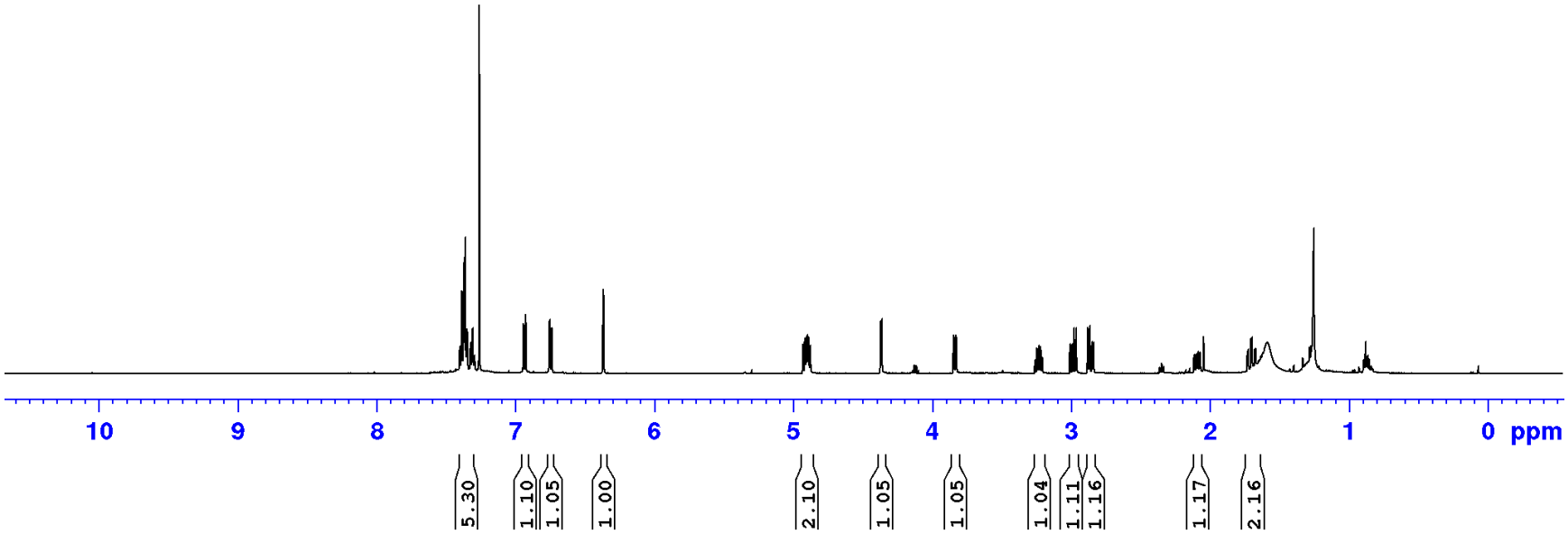

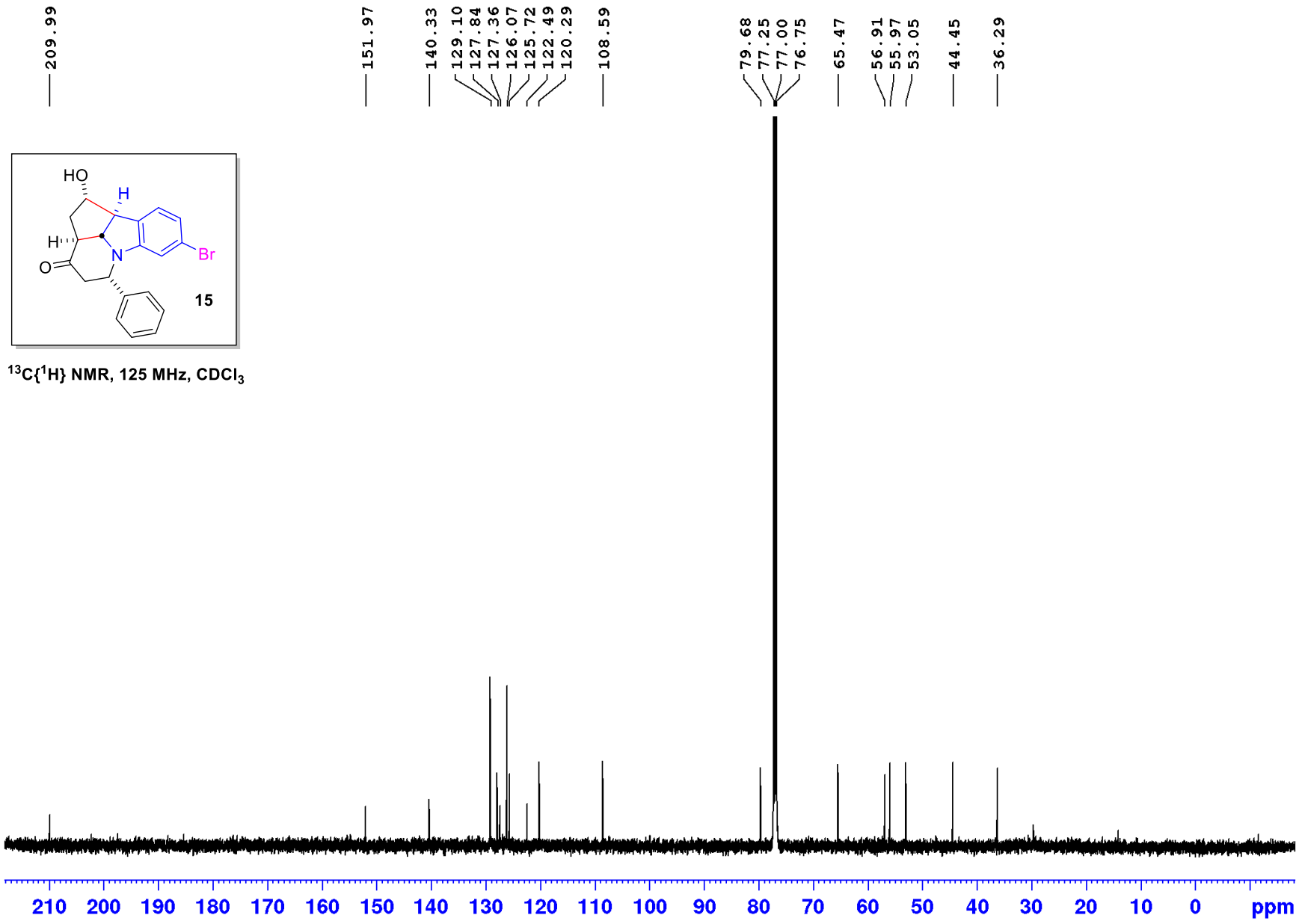

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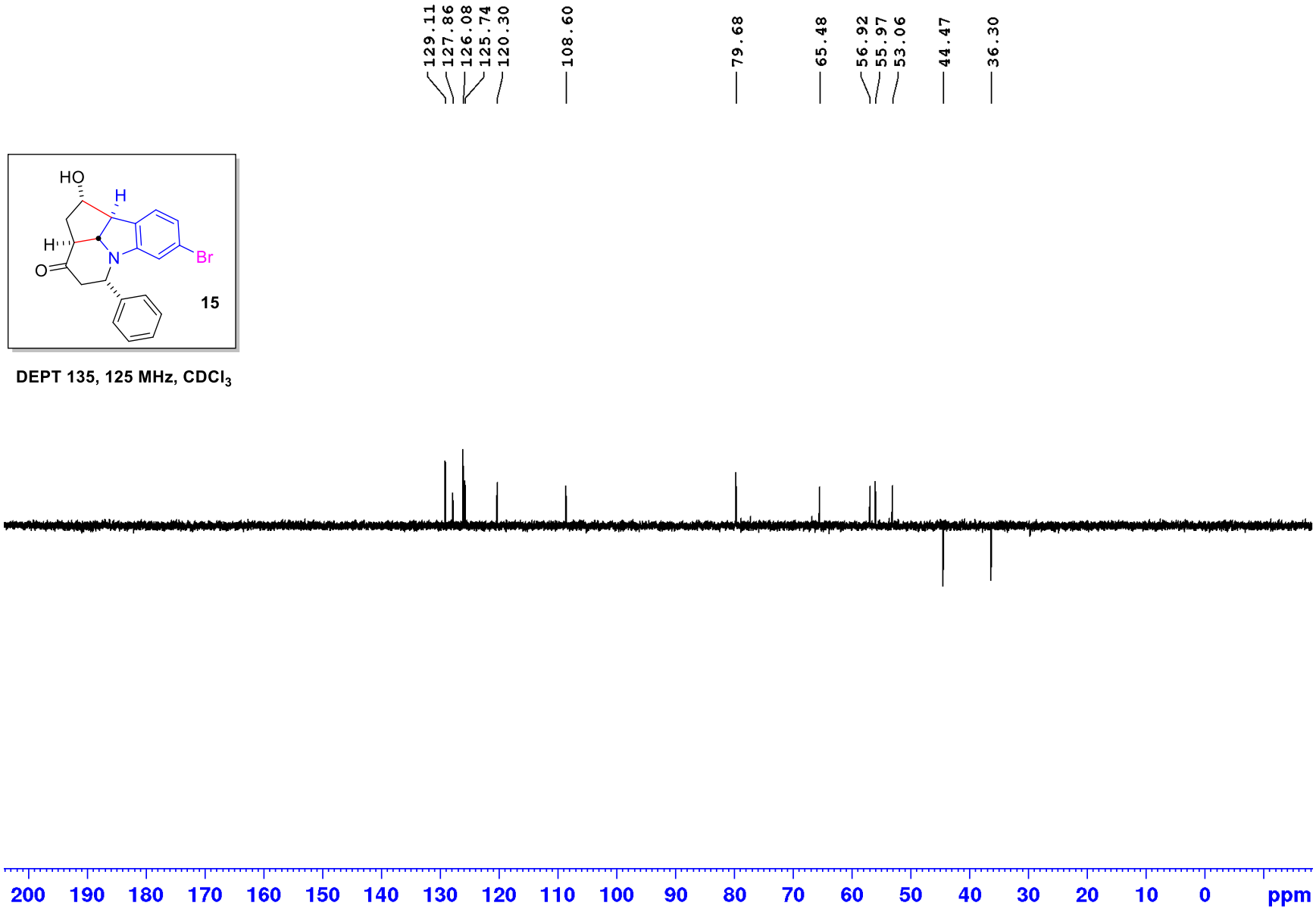

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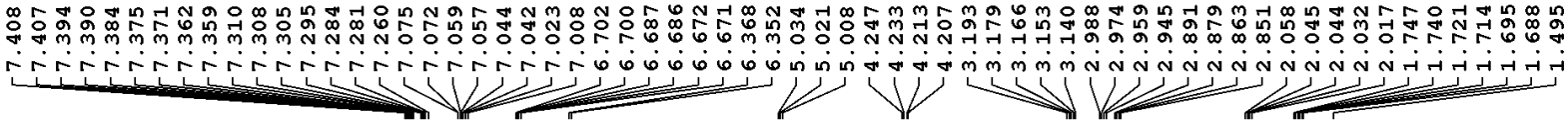

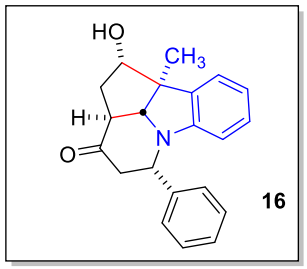

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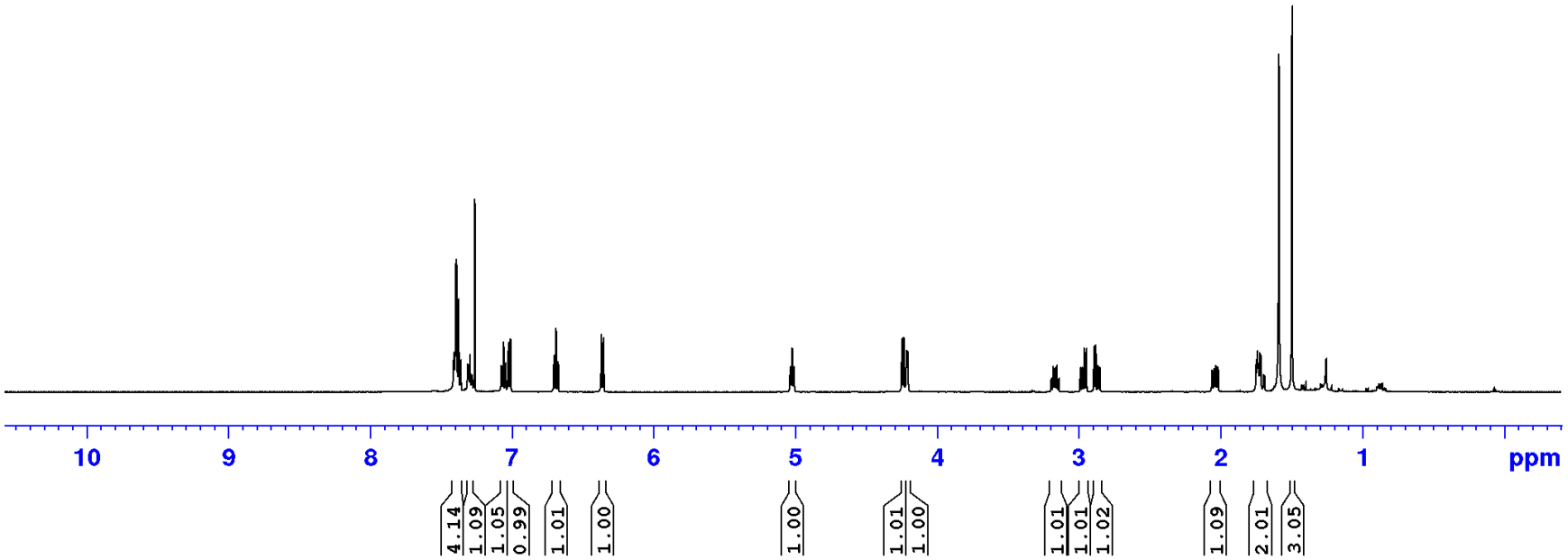

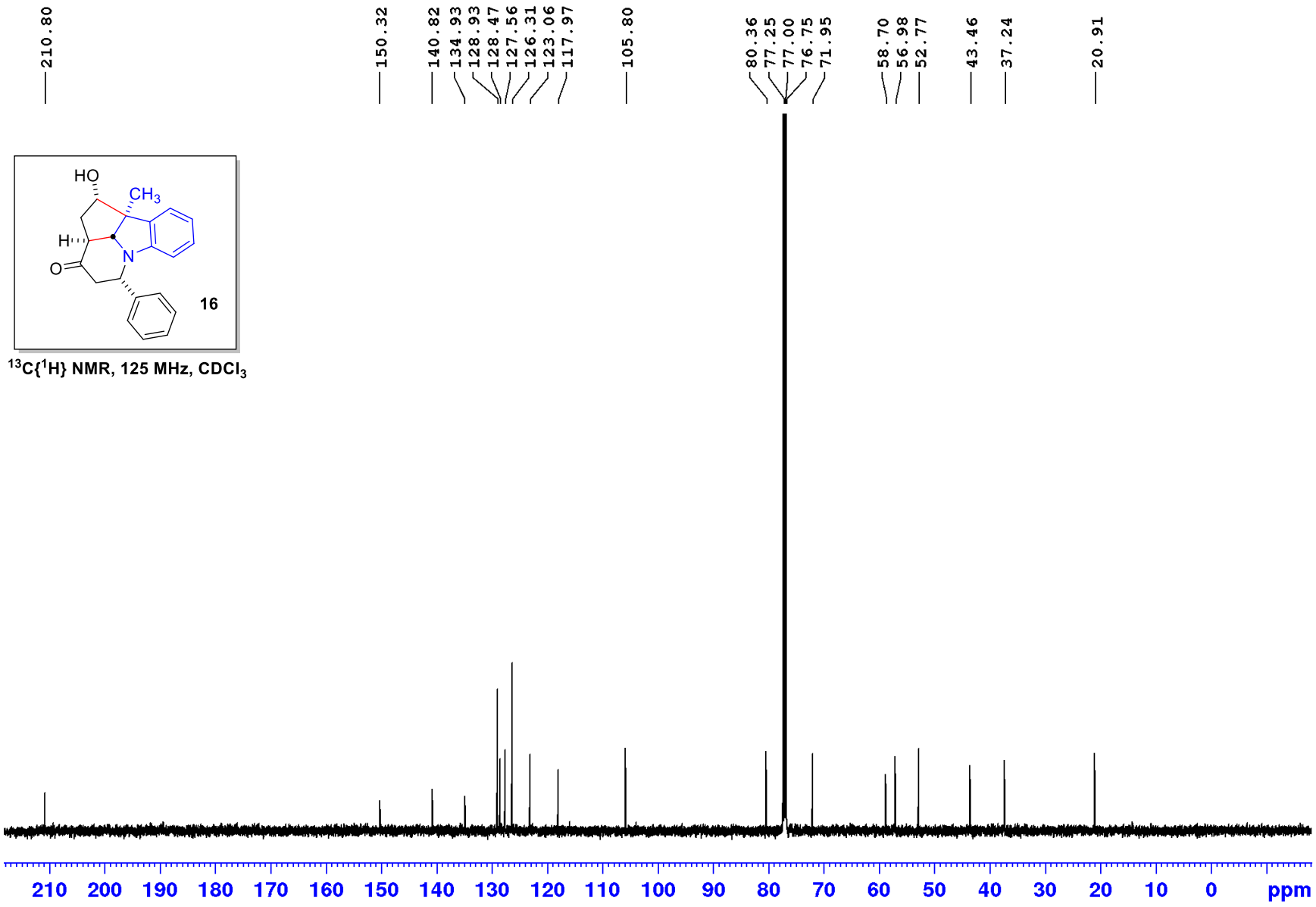

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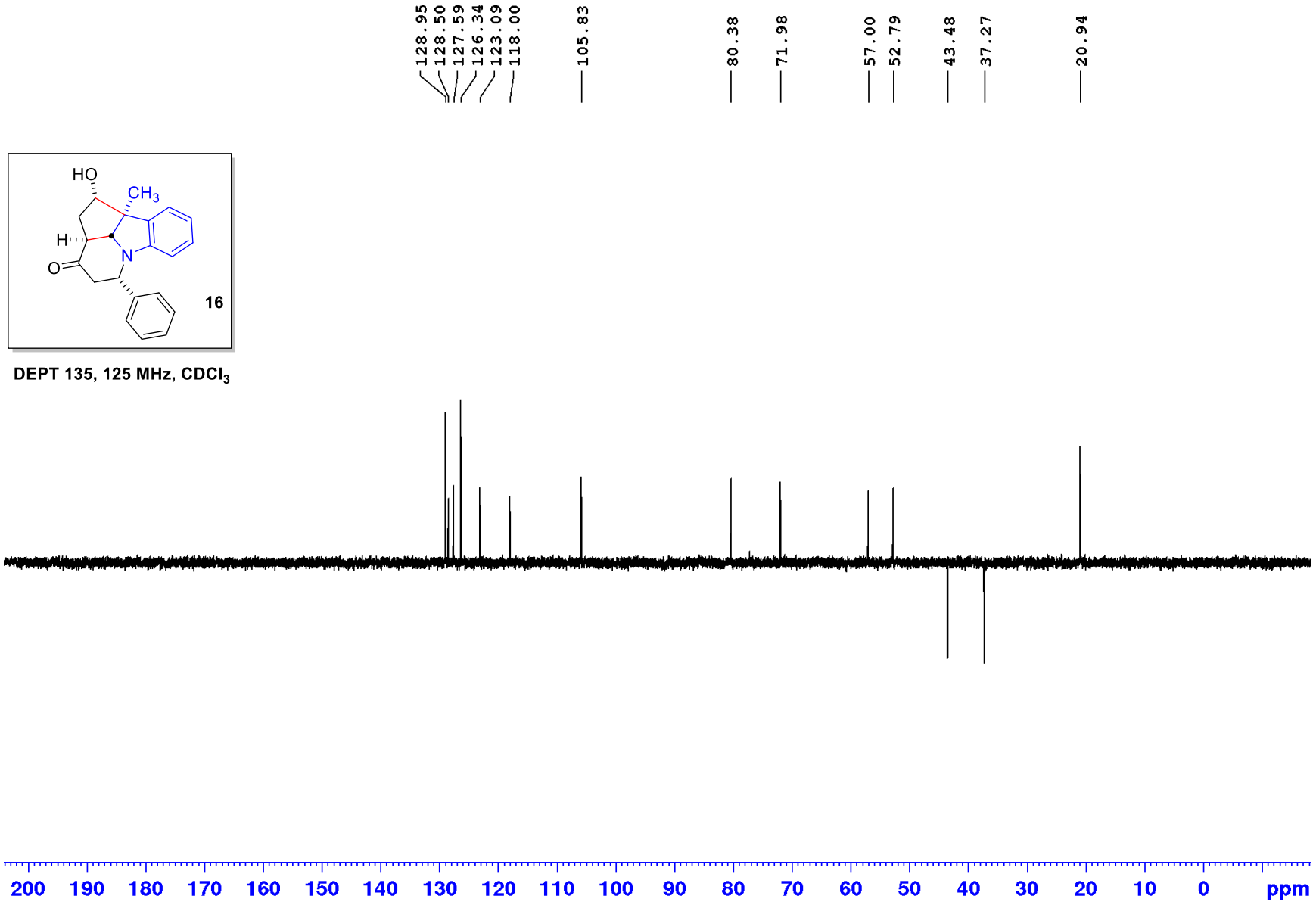
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H
N
O
16
DEPT 135, 125 MHz, CDCl3
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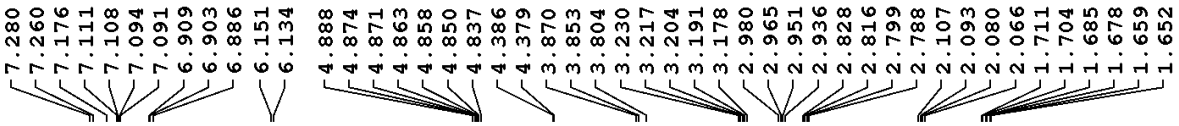

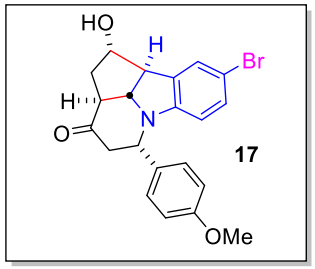

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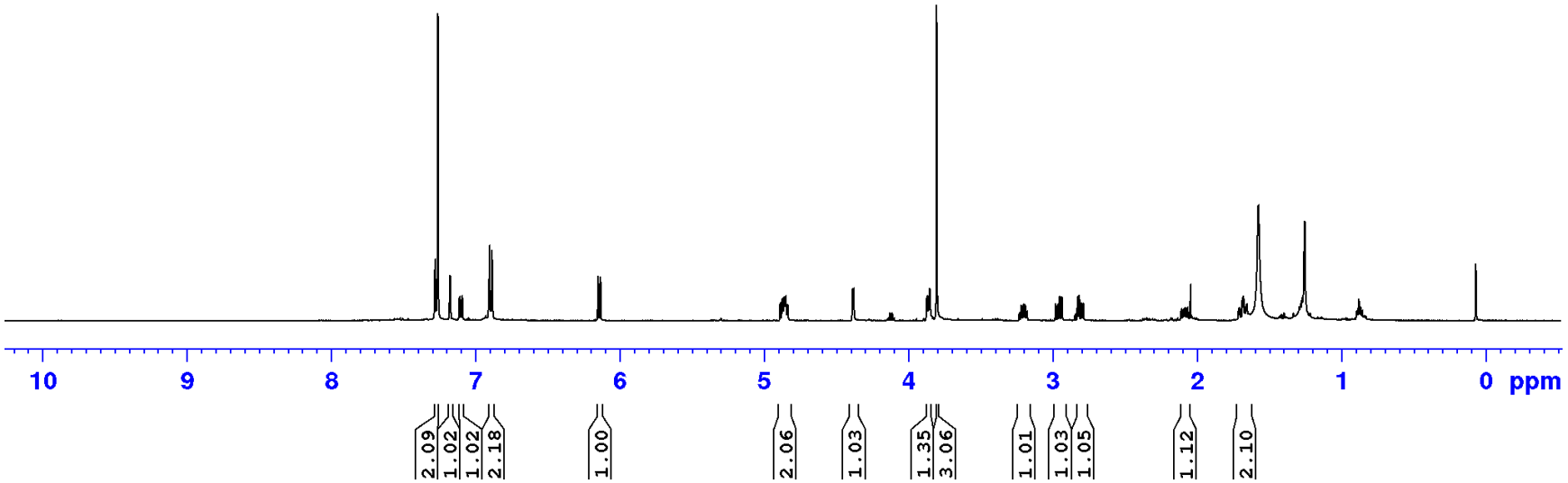
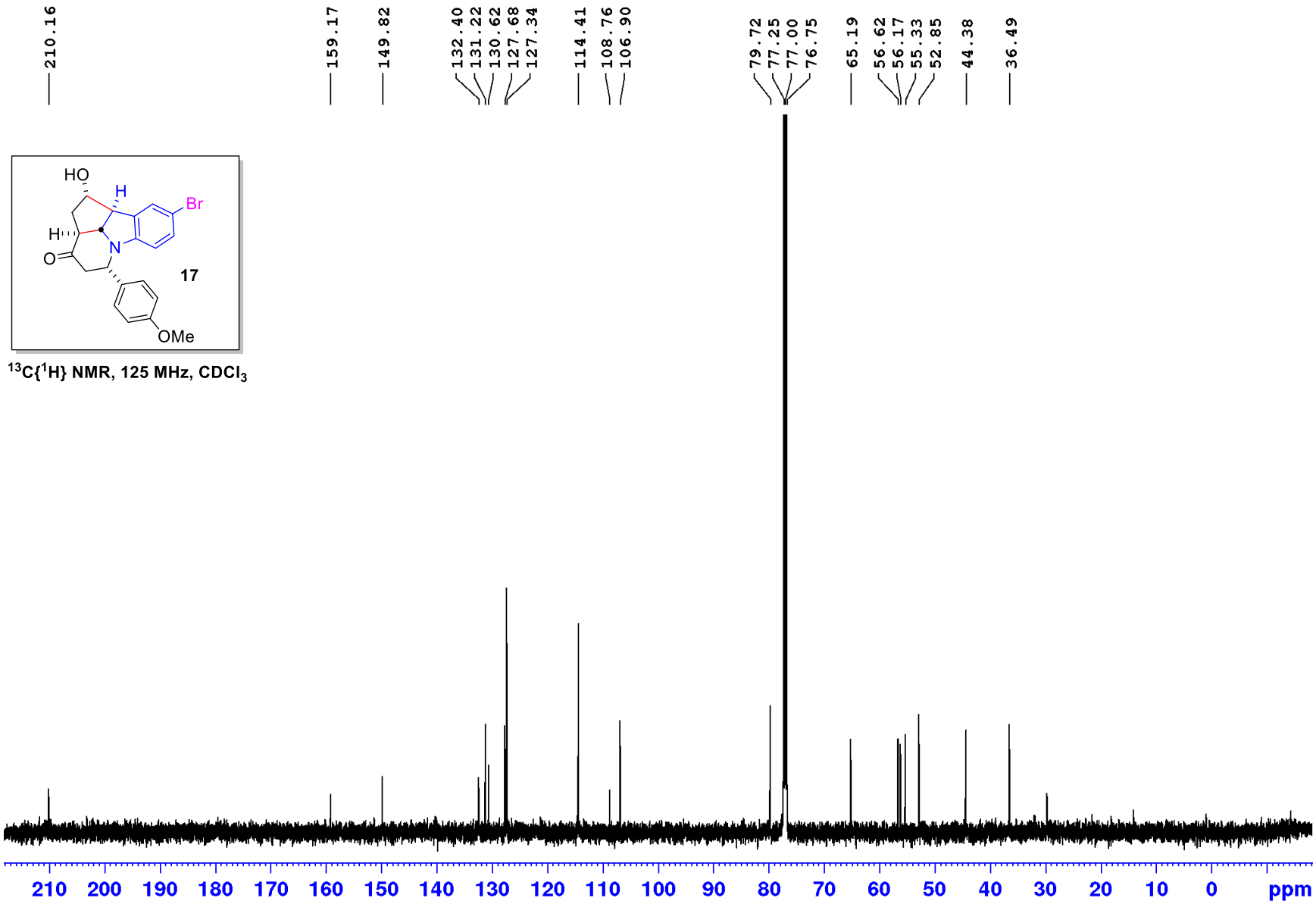
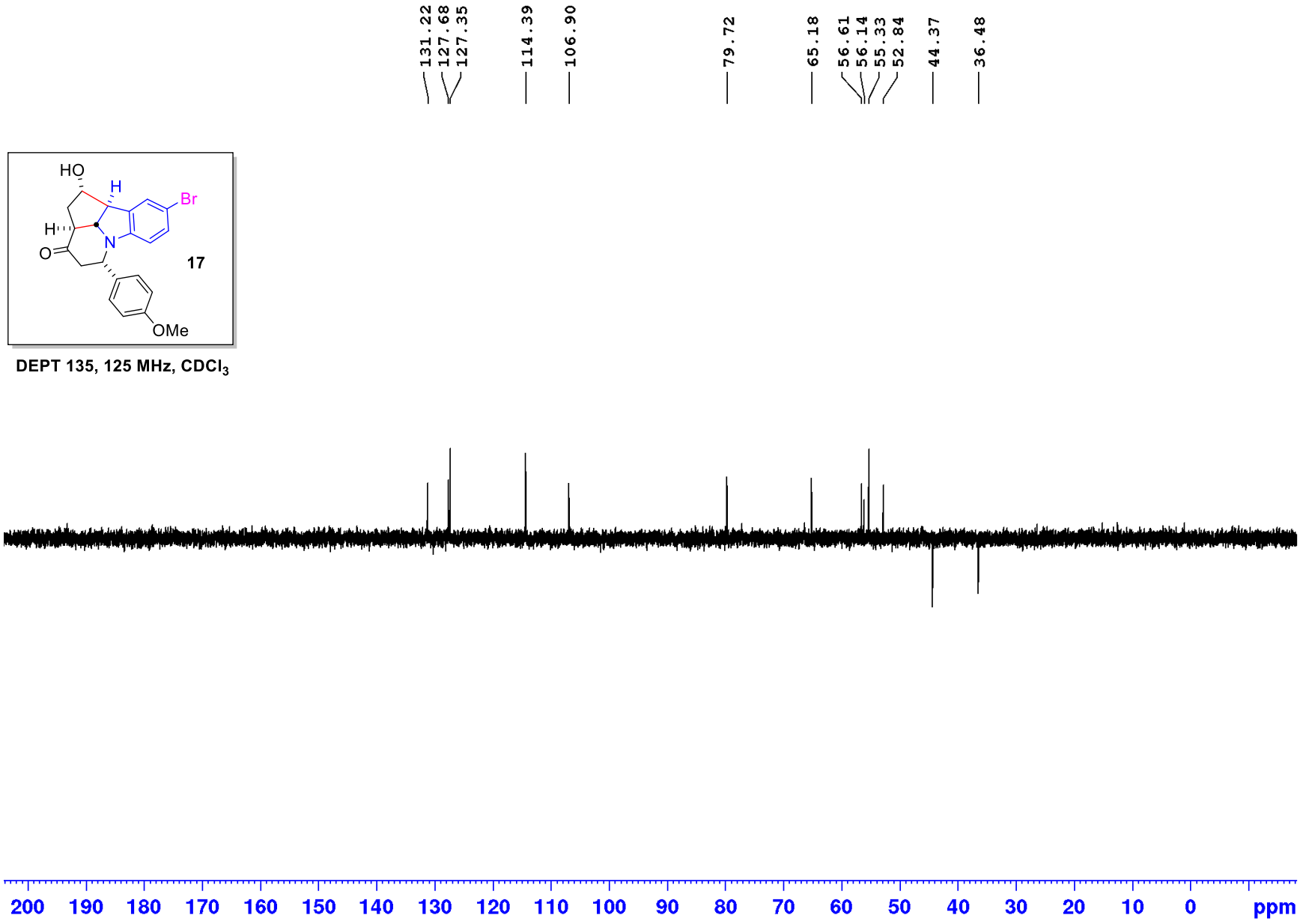




$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$



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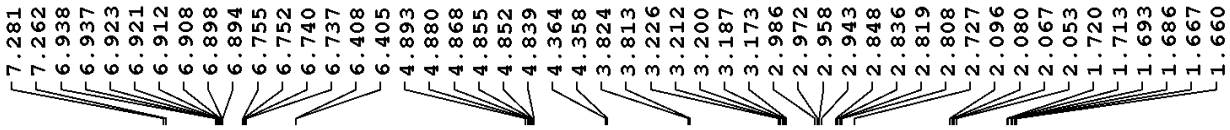

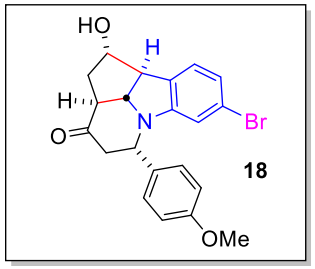

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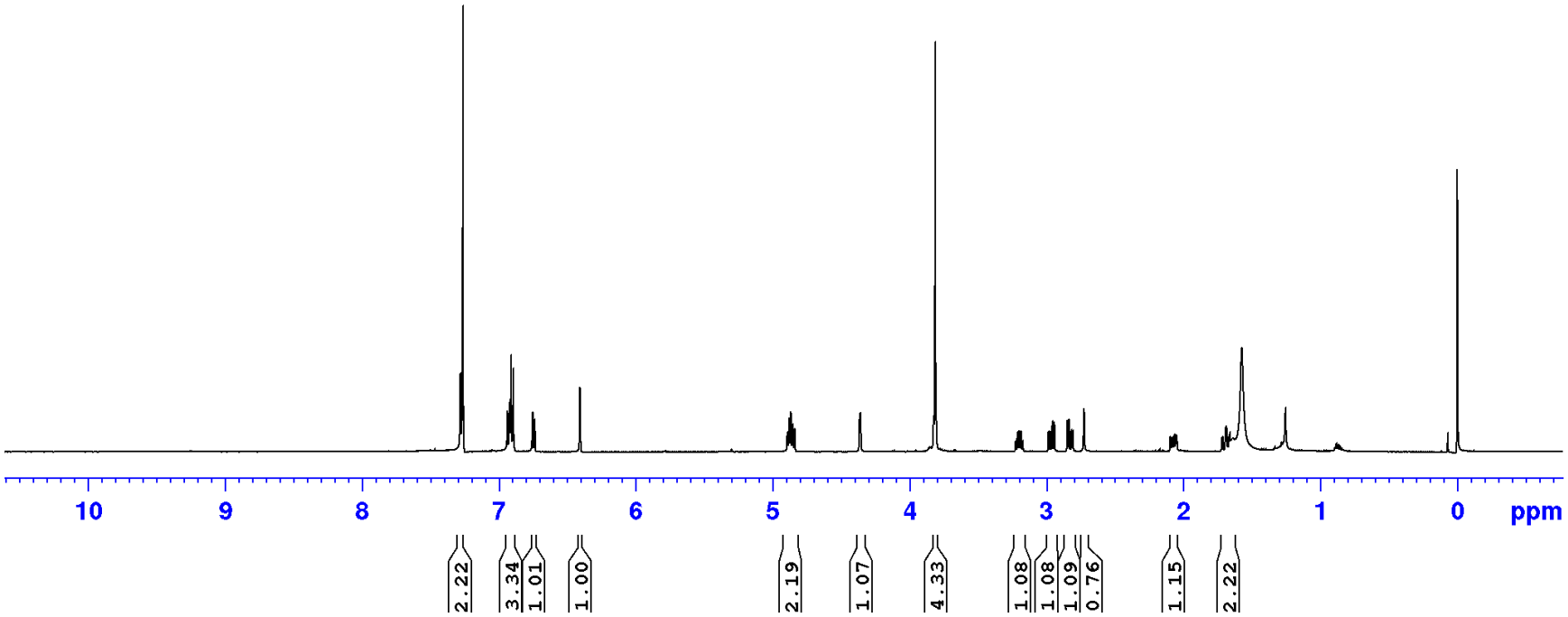

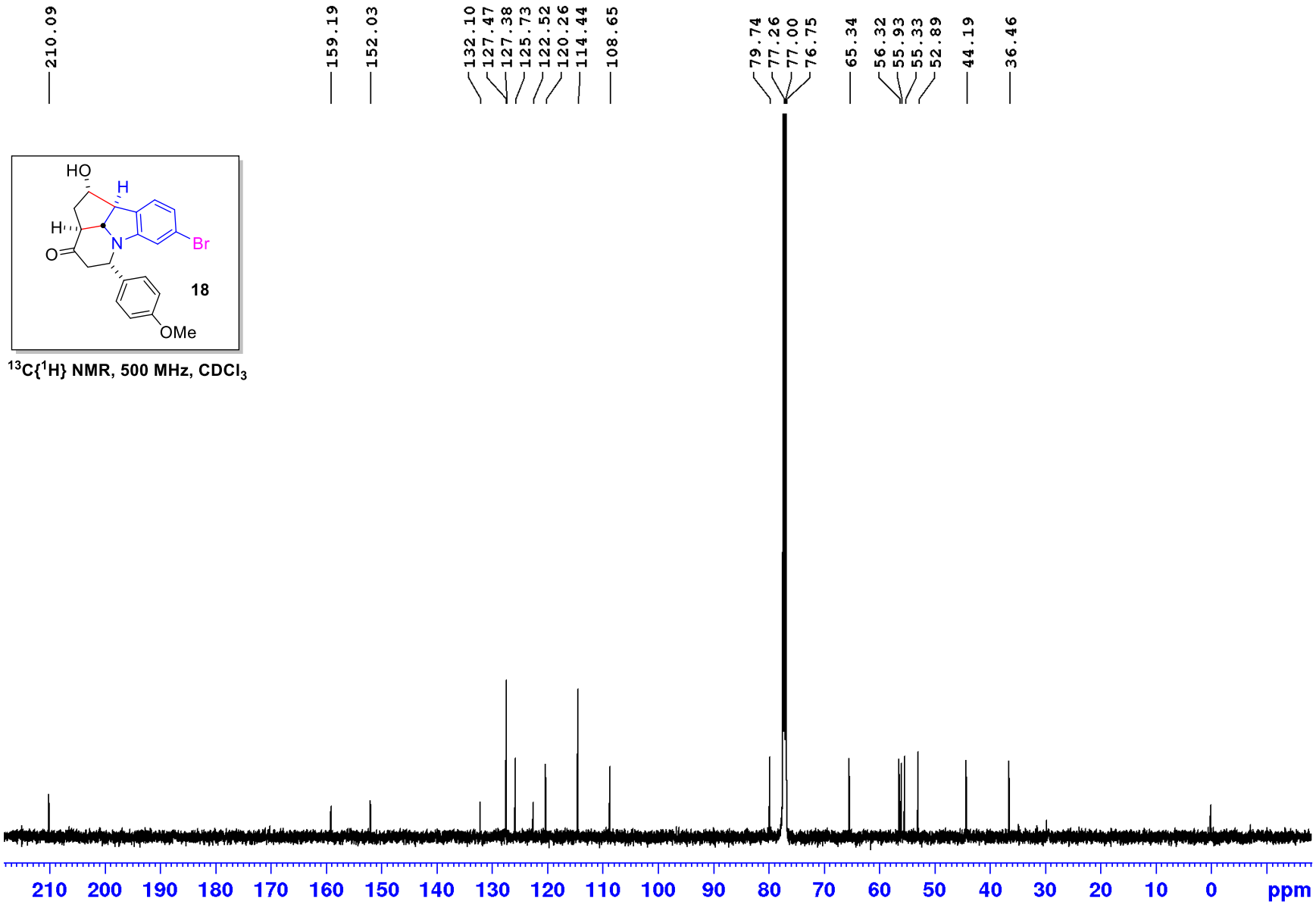

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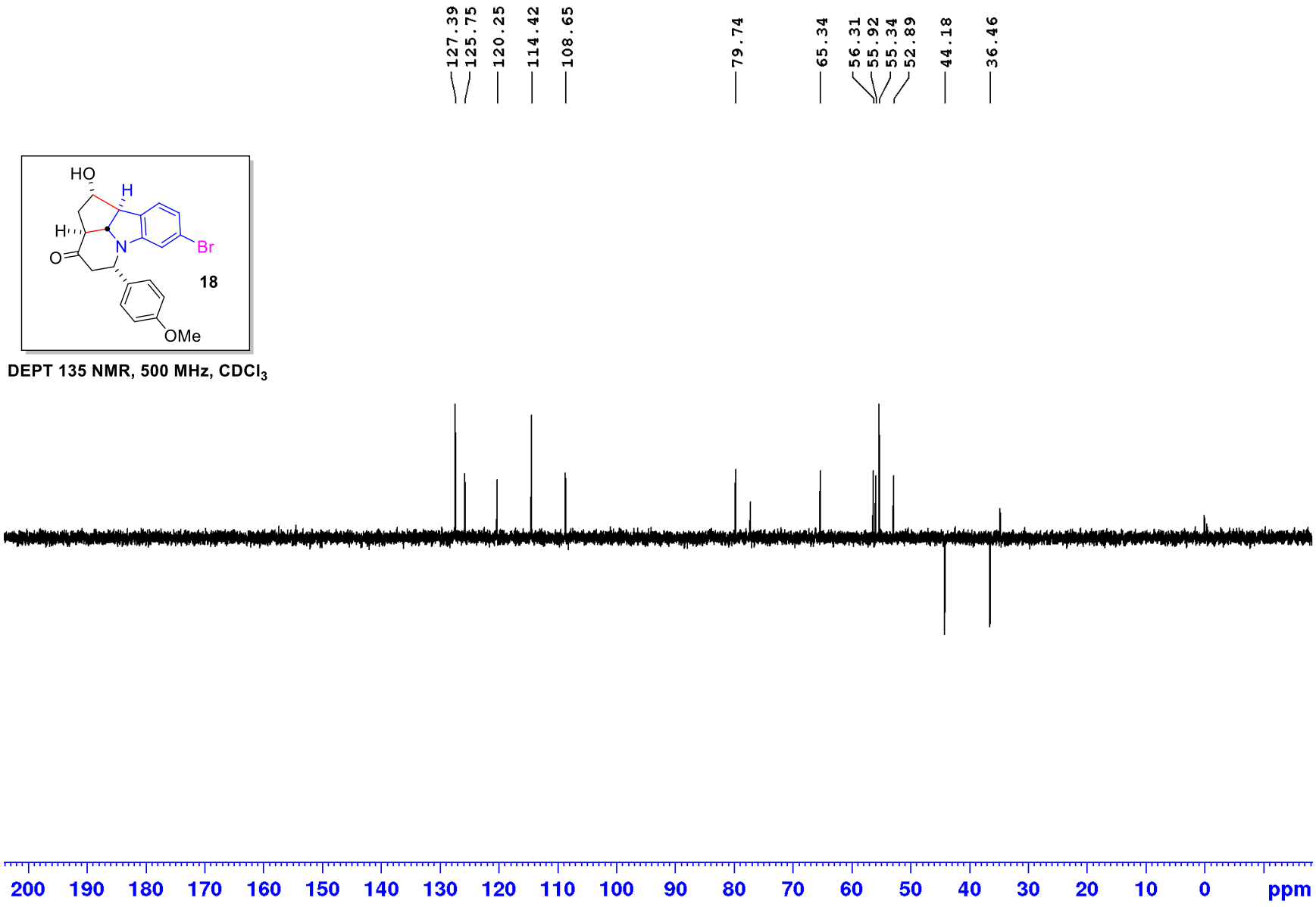

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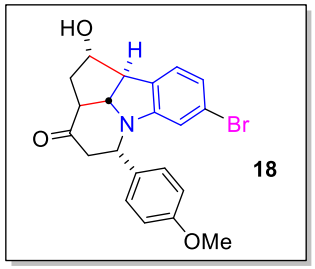

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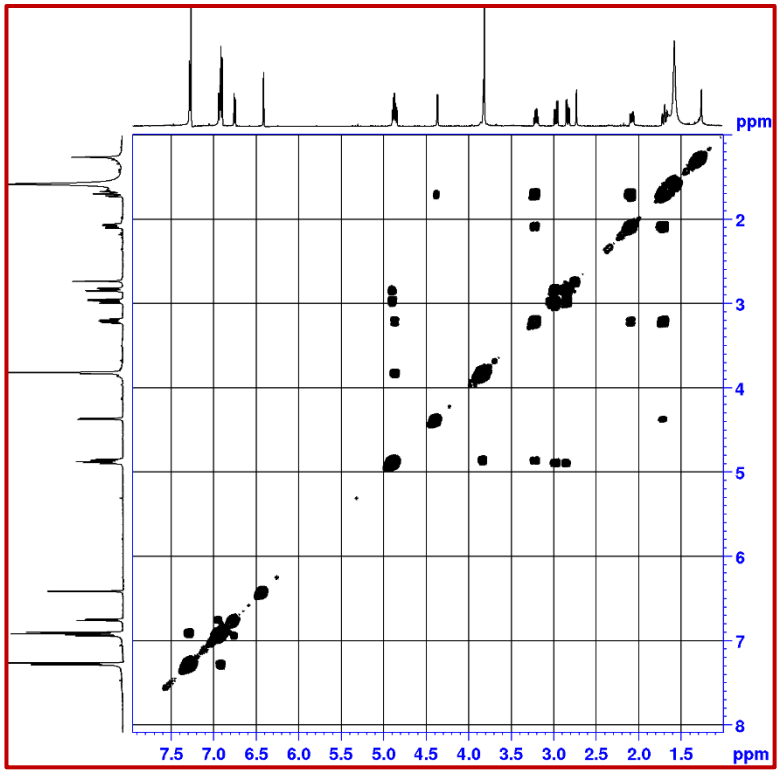

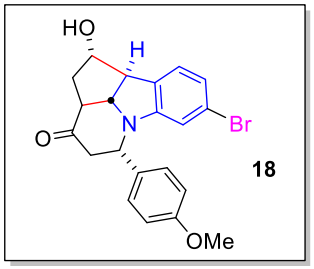

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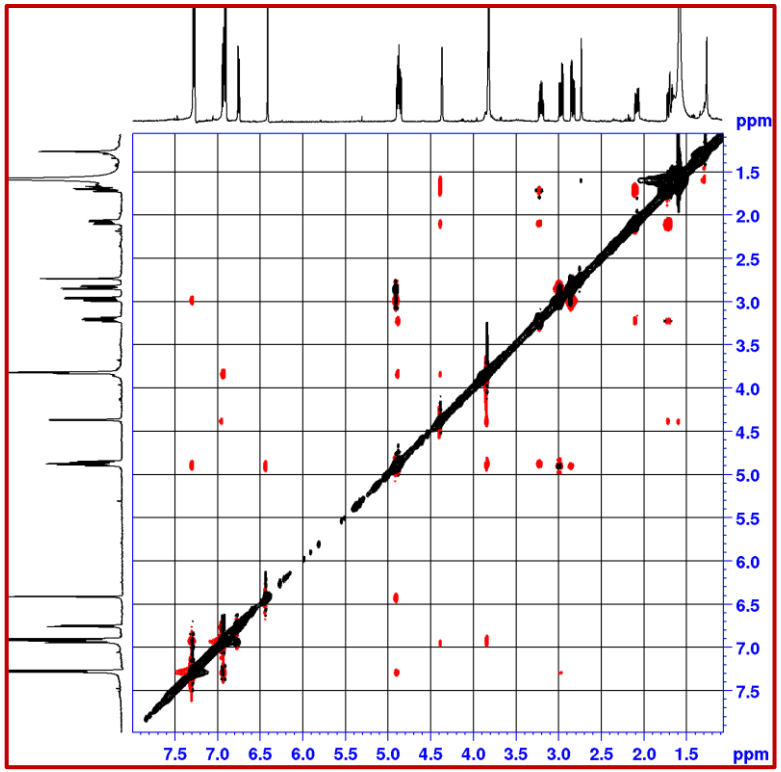

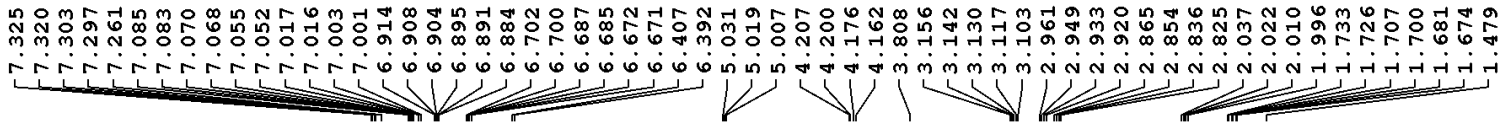

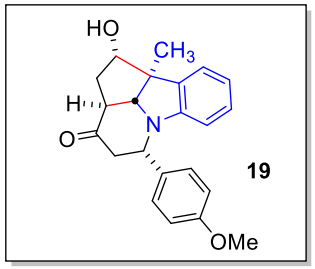

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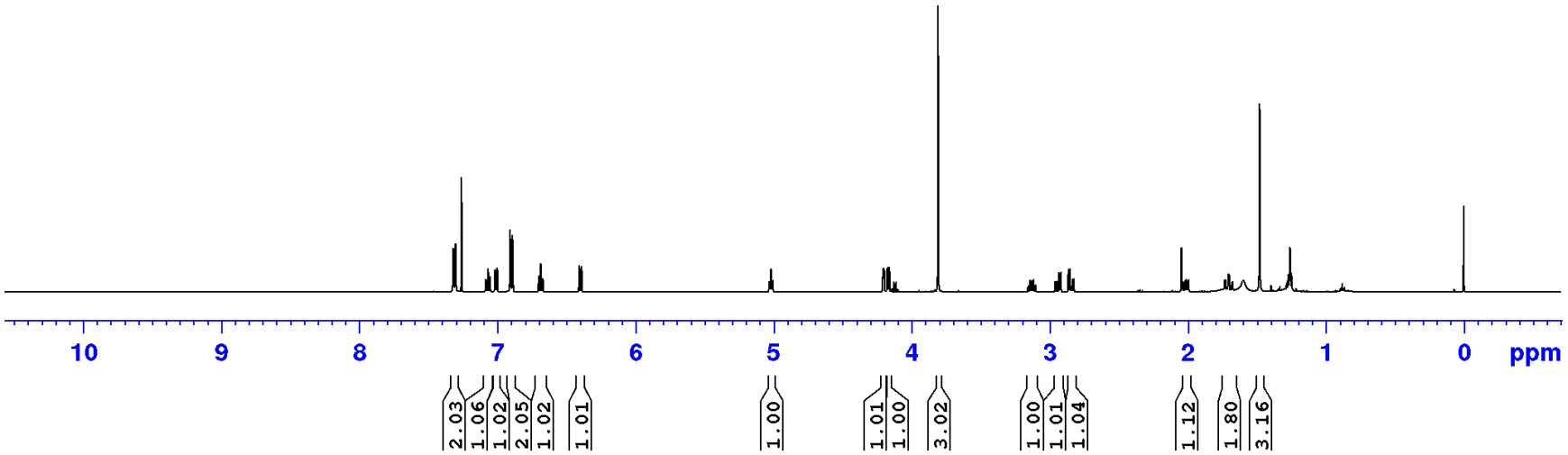

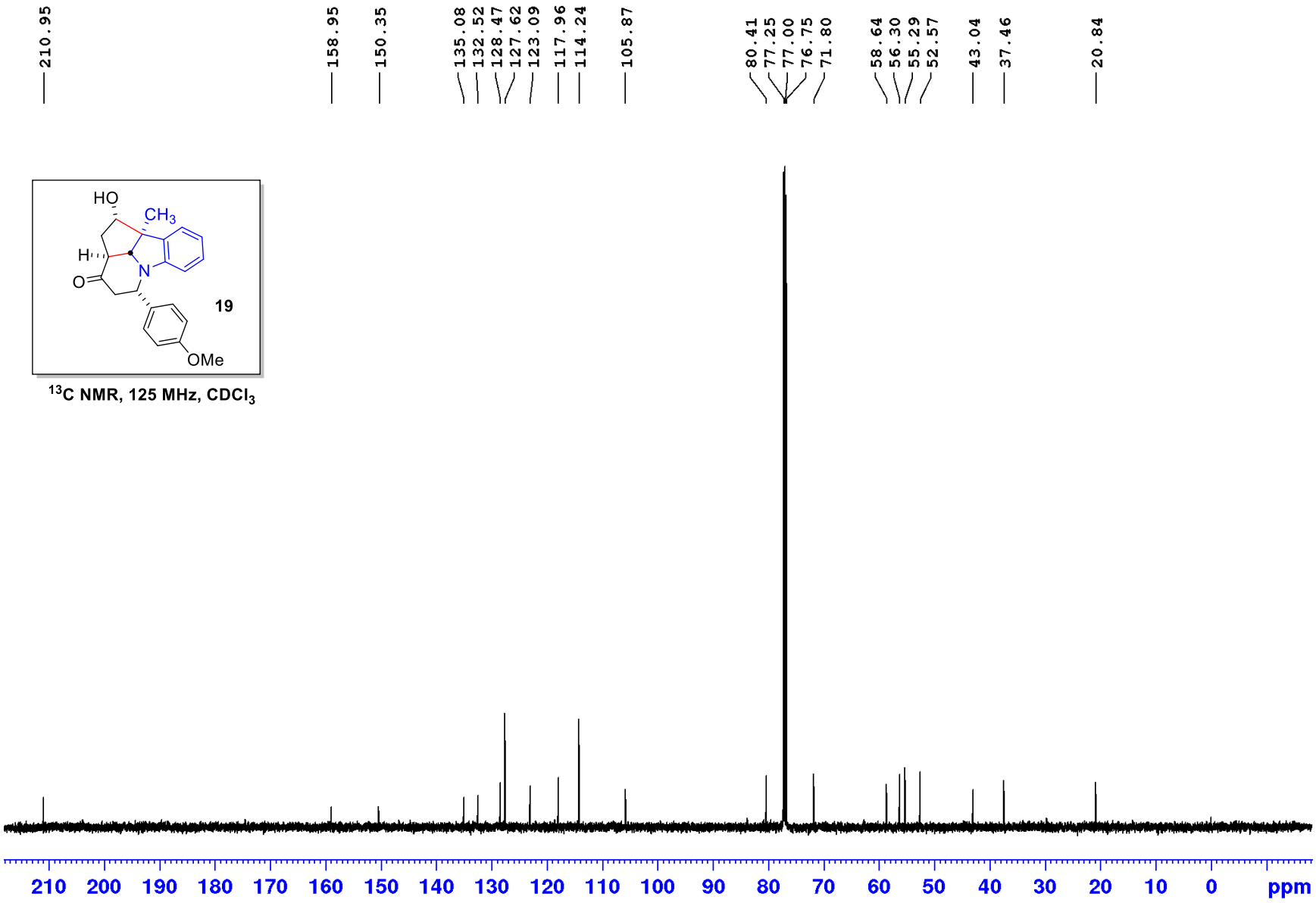

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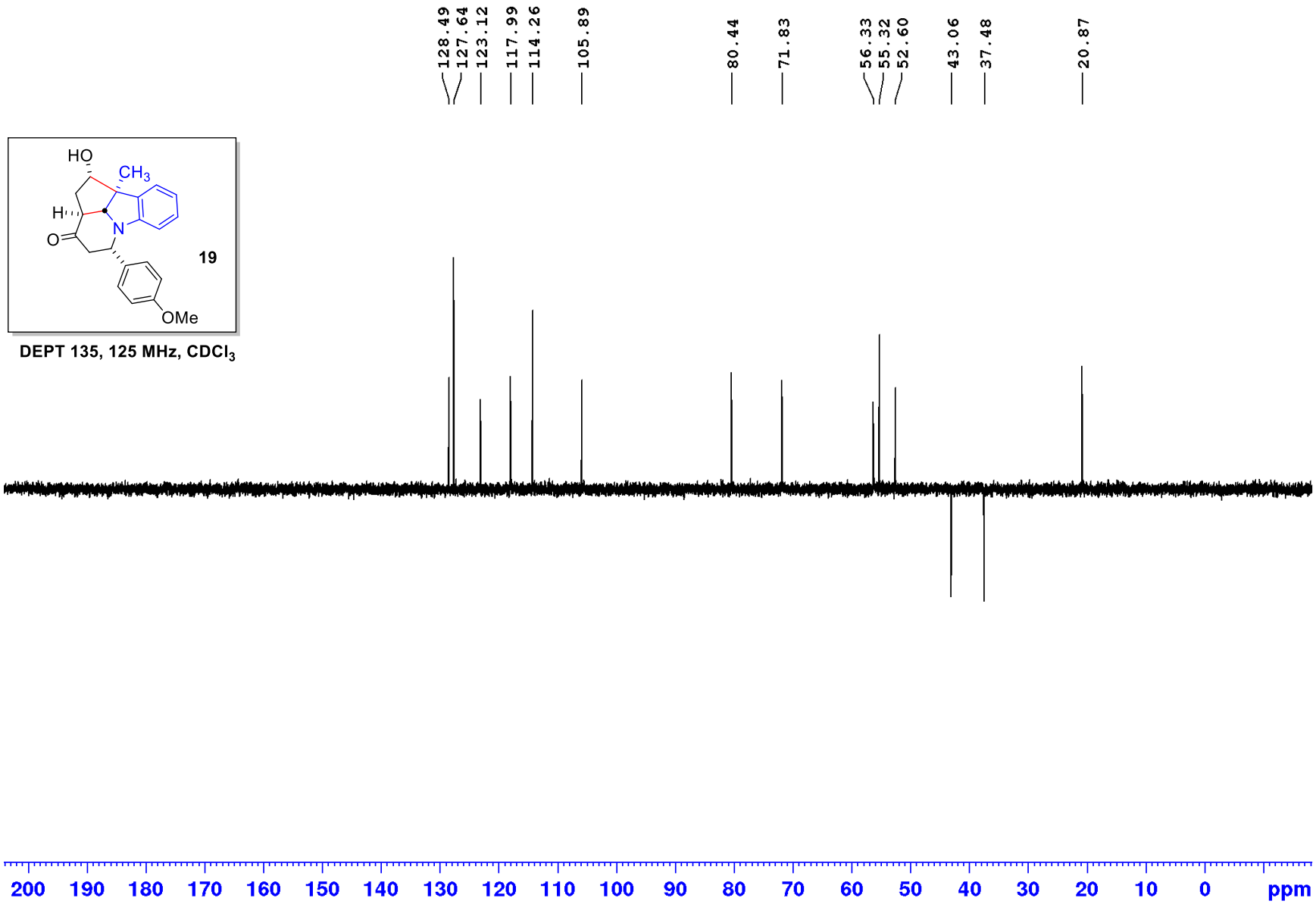
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HO
CH3
H
O
N
OMe
19
DEPT 135, 125 MHz, CDCl3
200
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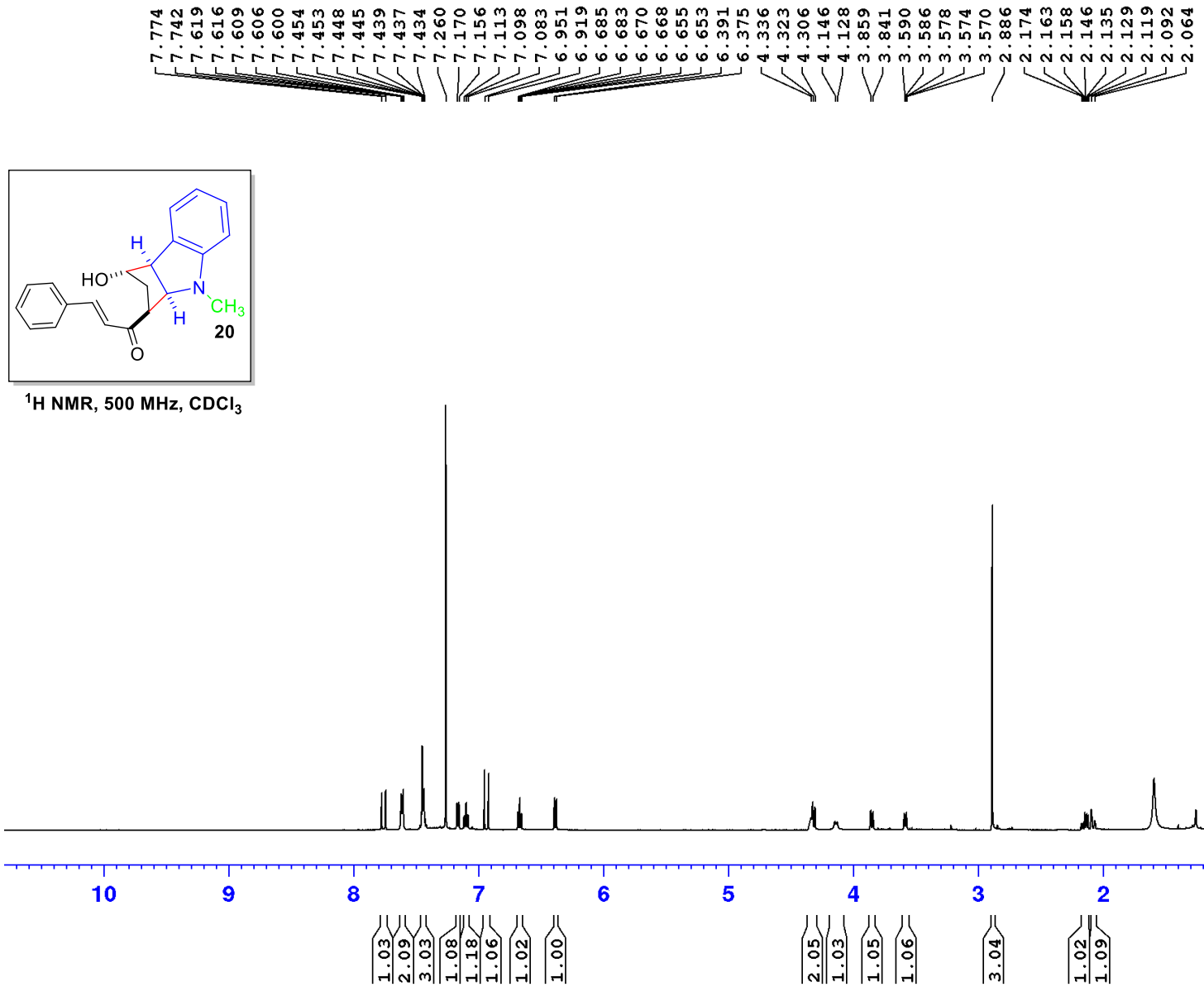
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1H NMR, 500 MHz, CDCl3
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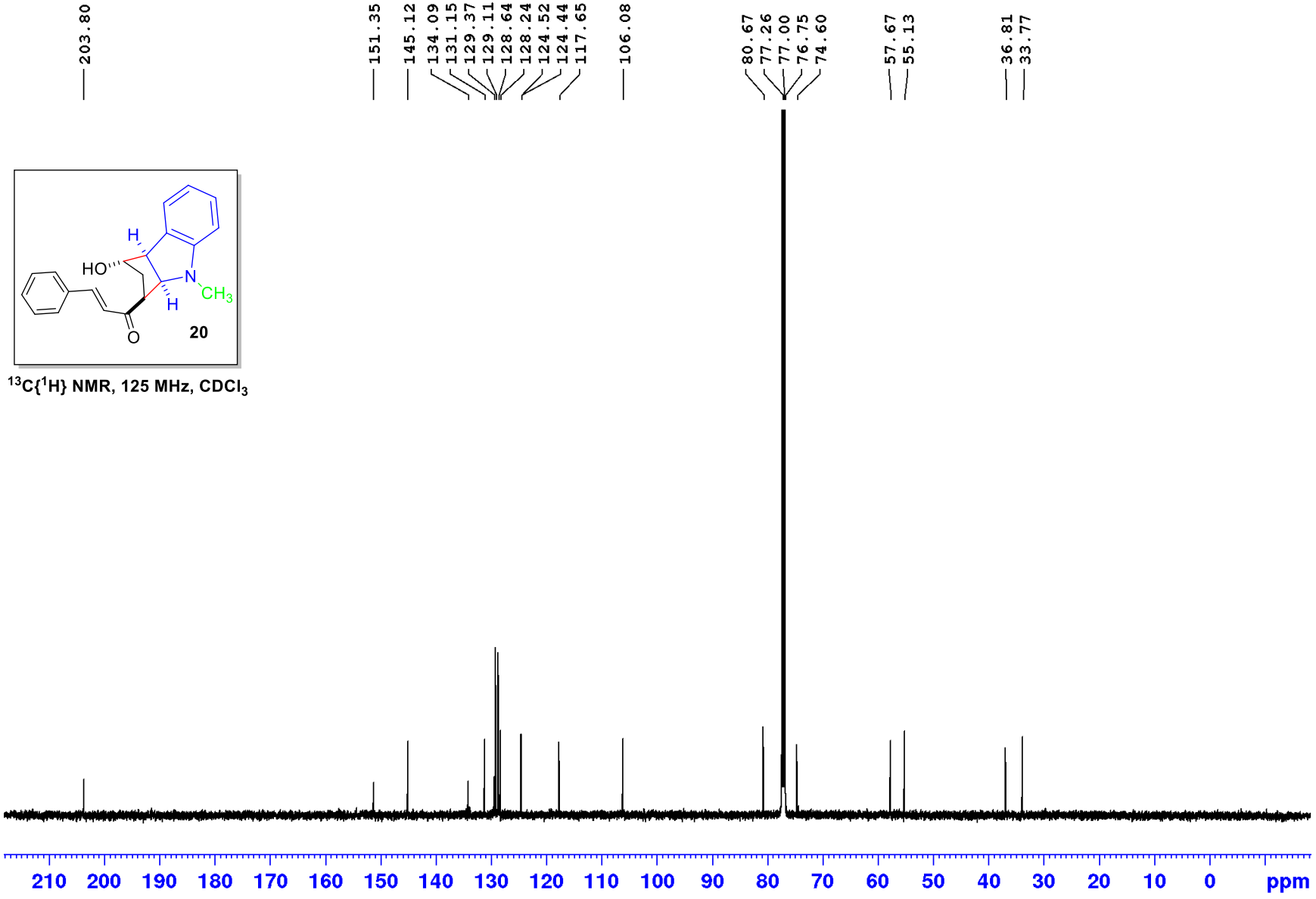
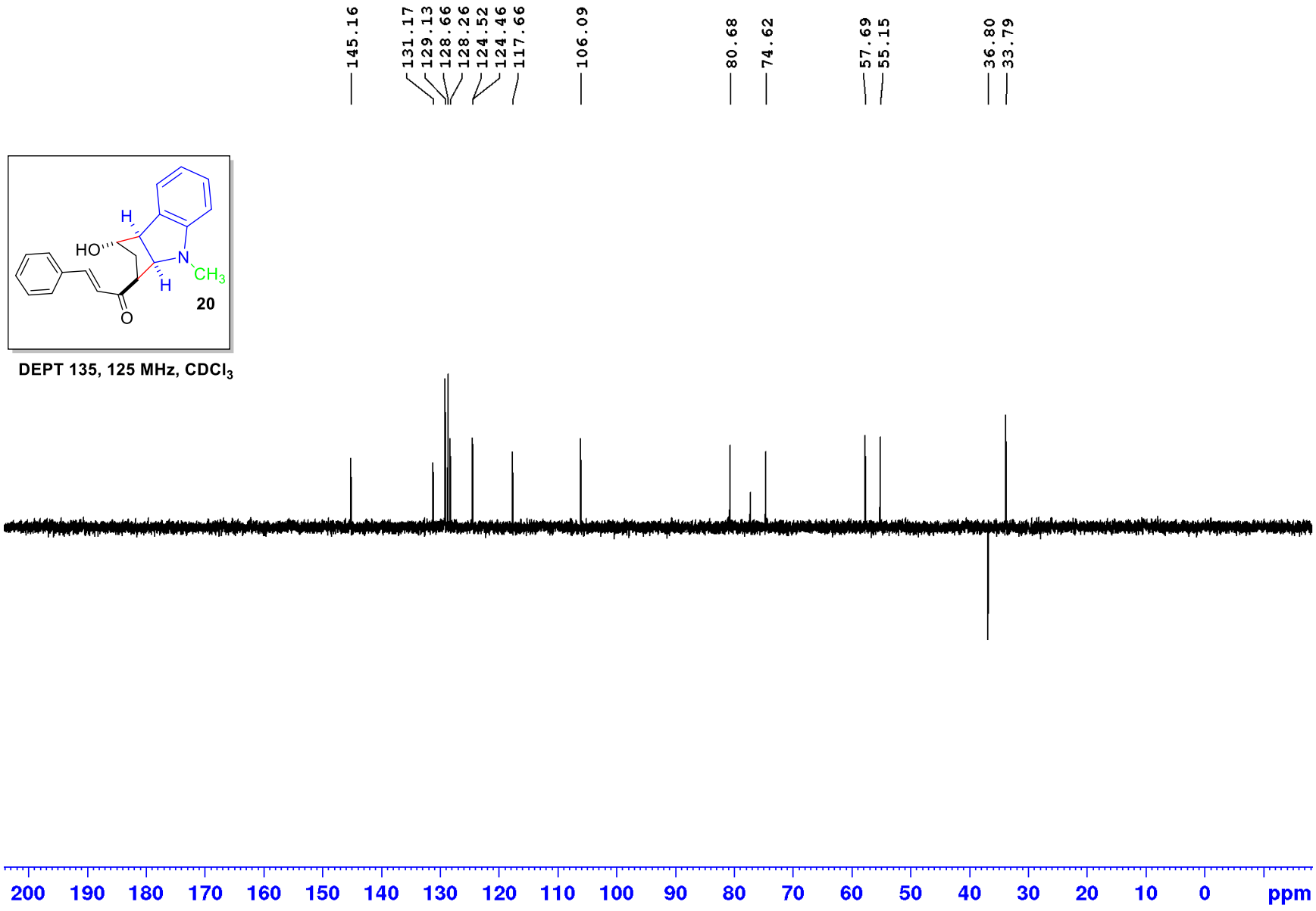


$^{13}C\{^{1}H\}$ NMR, 125 MHz, $CDCl_3$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H
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CH3
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DEPT 135, 125 MHz, CDCl3
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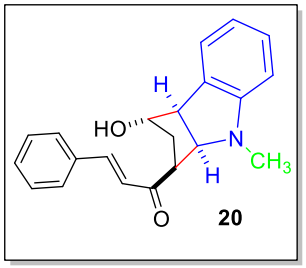

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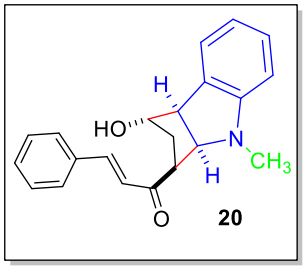

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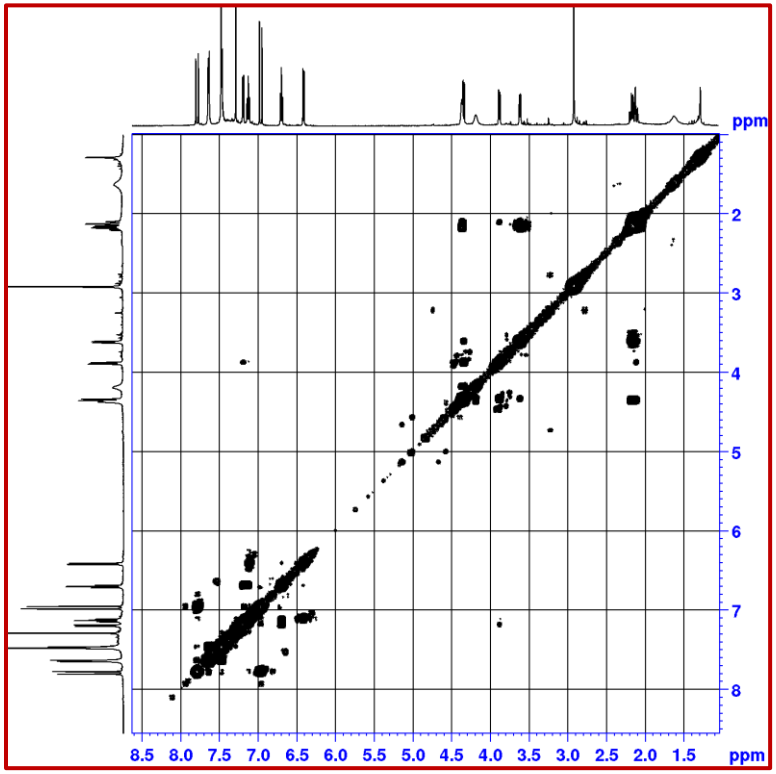
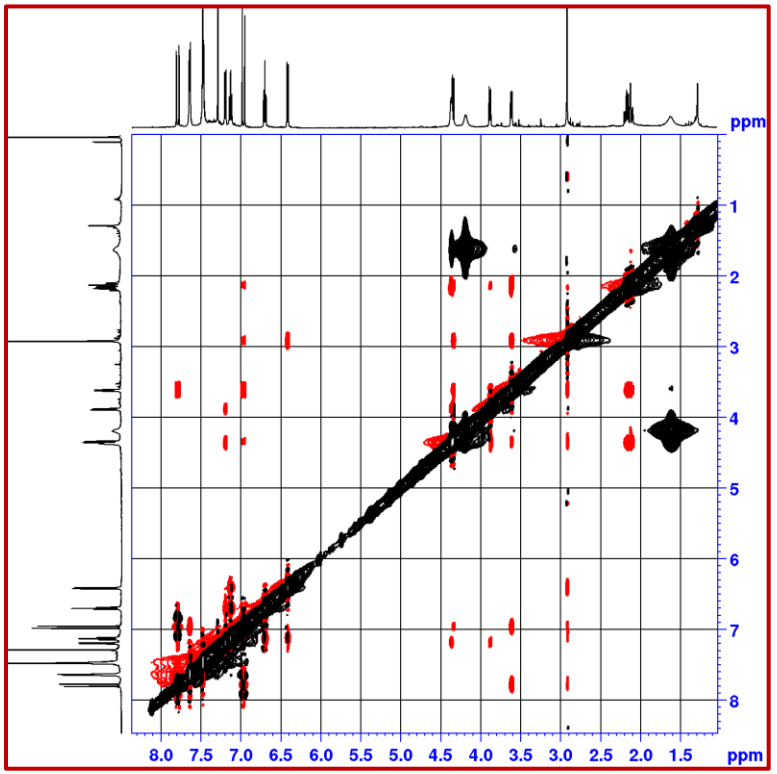
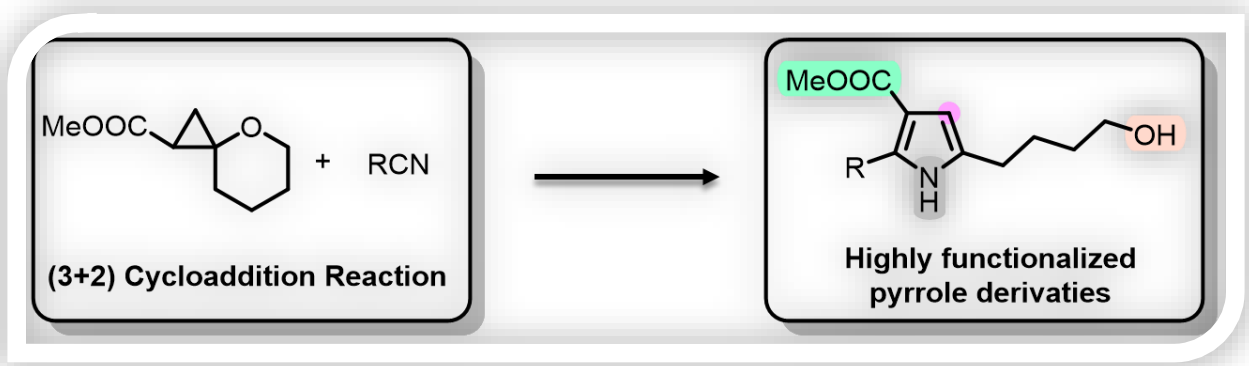




Chapter 3 – Part A

(3+2) Cycloaddition Reaction of Spiro-cyclopropane Carboxylated Sugars and Nitriles: Synthesis of Highly Functionalized Pyrrole Derivatives



Abstract:

A carbohydrate-derived spiro-cyclopropane carboxylates efficiently undergoes a Lewis acid mediated [3 + 2] dipolar cycloaddition with nitriles. A chiral, highly functionalized, 2,3,5-trisubstituted pyrrole derivative is formed as the cycloadduct with sugar fragment intact as a polyhydroxy alkyl chain. Various alkyl and aryl nitriles have been employed to show the generality. A multiple cascade bond making and breaking happens including cycloaddition, dehydration, aromatization and tautomerization occurs to afford pyrrole derivatives in good to excellent overall yield. Further, post-synthetic transformations have been done on the cycloadducts to build potential molecular scaffolds to show the application of the developed methodology.

3.1.1 Introduction

Emerging as a class of heterocycles, pyrroles are frequently seen in pharmaceuticals, natural products, and biologically active scaffolds.[1] They perform diverse functions as pharmacophore and they are featured in various commercial drugs like Fluvastatin, Atorvasatin, Aloracetam and Isamoltane etc. (Figure 1).[2]

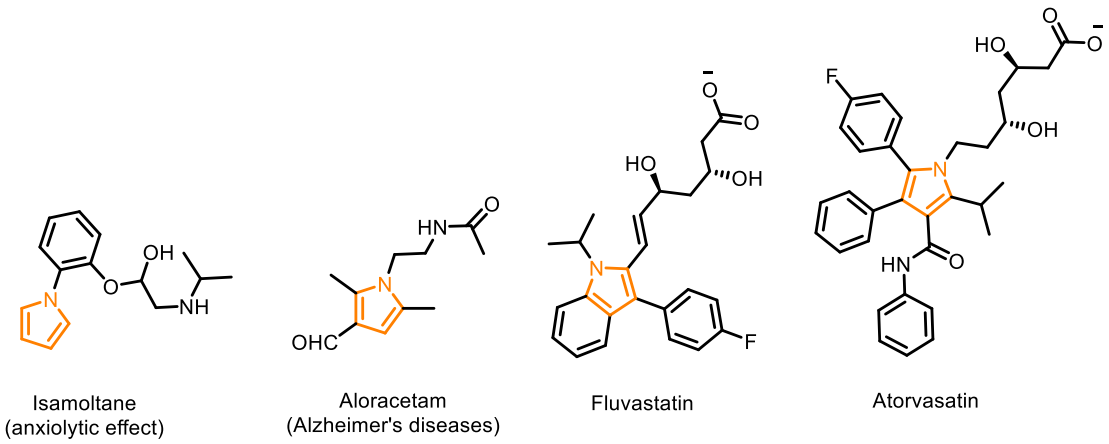
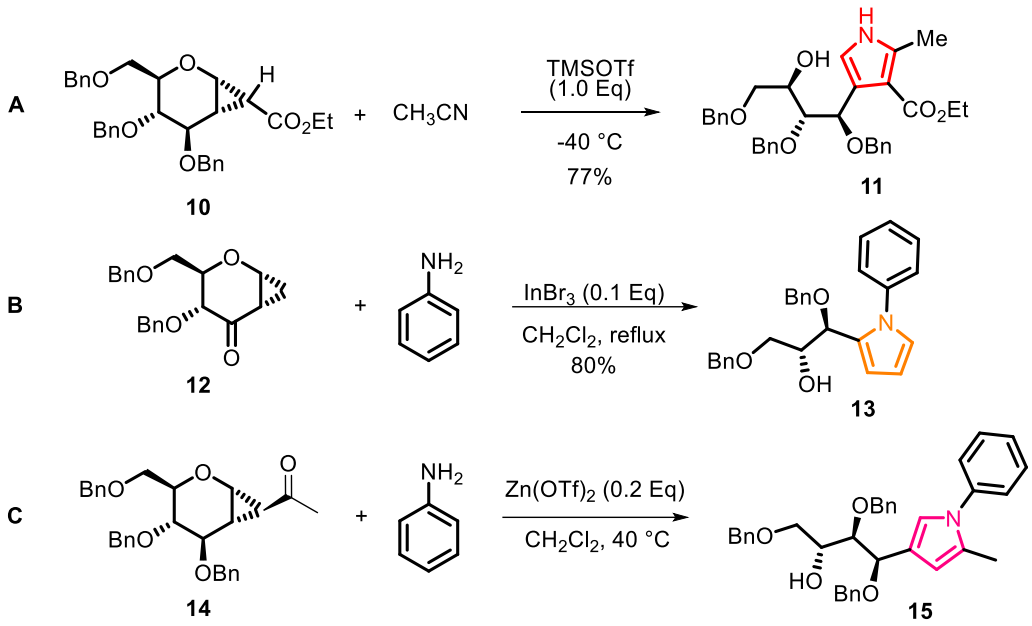


Figure 1: Pyrrole containing bioactive molecules with pharmacological relevance.

There are several classic synthetic methods for the construction of these five membered heterocyclic ring systems namely, Hantzsch reaction and the Paal-Knorr synthesis.[3] In addition, there are several approaches recently reported for the construction of multifunctionalized or the multi-substituted pyrroles. However, construction of polysustituted chiral pyrrole derivatives with varied therapeutic and biological applications has grabbed tremendous attention from past few years. And the very means of their synthesis is via carbohydrates due to their plentiful sources, low cost, amiable reaction conditions and varied chirality. Our survey through the literature gave insights regarding the significant use of both protected and unprotected sugars for the construction of multi-substituted pyrrole derivatives.[4]

Our group has been working on the carbohydrate-derived donor acceptor cyclopropanes (DACs) and demonstrated fascinating chemistry.[5] A brief study on the past reports showed us that carbohydrate-derived DACs are flourishing chiral synthons which are incorporated in synthesis of pyrrole and its derivatives with the sugar fragment being intact in the product contributing to the chirality.

Pagenkopf and coworker in 2003,[6] reported cycloaddition reactions with glycal-derived 1,2-cyclopropane carboxylate and nitrile to form the highly functionalized pyrrole derivative with intact sugar fragment (Scheme 1, A; Chapter 1, table 2). The representative example is depicted in scheme 1 where glucose-derived 1,2-cyclopropane carboxylate **10** and acetonitrile undergoes a TMSOTf mediated (3+2) cycloaddition to give 2-methyl pyrrole derivative **11** in 77% yield. The methodology accomplished various sugar derivatives and nitrile substrates.



Scheme 1: Previous work for synthesis of substituted pyrroles using carbohydrate-derived DACs.

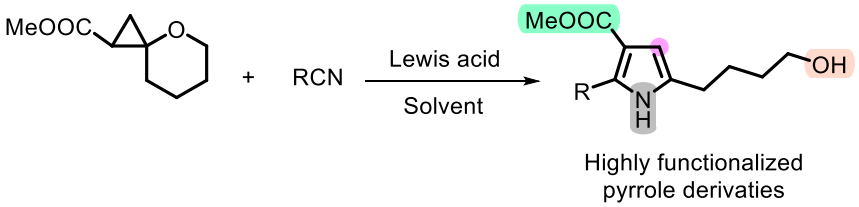
Recently, Zhang *et al.,* reported[7] a protocol for the synthesis of a 2-polyhydroxyalkyl pyrrole **13** by using 3-oxo-1,2-cyclopropanated sugar **12** and primary amines in the presence of indium bromide. (Scheme 1, B). The reaction proceeded through a sequence of steps involving ring expansion, intramolecular nucleophilic attack, ring cleavage and dehydration to give the substituted pyrrole derivative. The scope of the methodology was showcased by incorporating various 3-oxo-1,2-cyclopropanated sugars and primary amines to synthesize different *N*-substituted 2-alkylated pyrroles.

Very recently, Huawu Shao et al. reported[8] a $Zn(OTf)_2$ mediated 3-polyhydroxyalkyl pyrrole **15** synthesis from sugar-derived 1,2-cyclopropanated ketone **14** and primary amines (Scheme 1, C).

The methodology was amenable to various sugar cyclopropanes and alkyl and aryl amines. This allowed to access various *N*-substituted 3-polyhydroxyalkylated pyrrole derivatives.

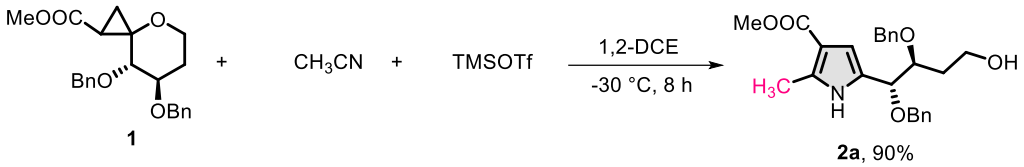
3.1.2 Results and Discussion

Envisaging a similar chemistry, we intended to explore pyrrole synthesis via a Lewis acid mediated (3+2) cycloaddition of a unique carbohydrate-derived DAC substrate and nitriles. Herein we report the (3+2) cycloaddition reaction of spiro-cyclopropane carboxylated sugars and nitriles for the efficient synthesis of Highly Functionalized Pyrrole Derivatives (Scheme 2).



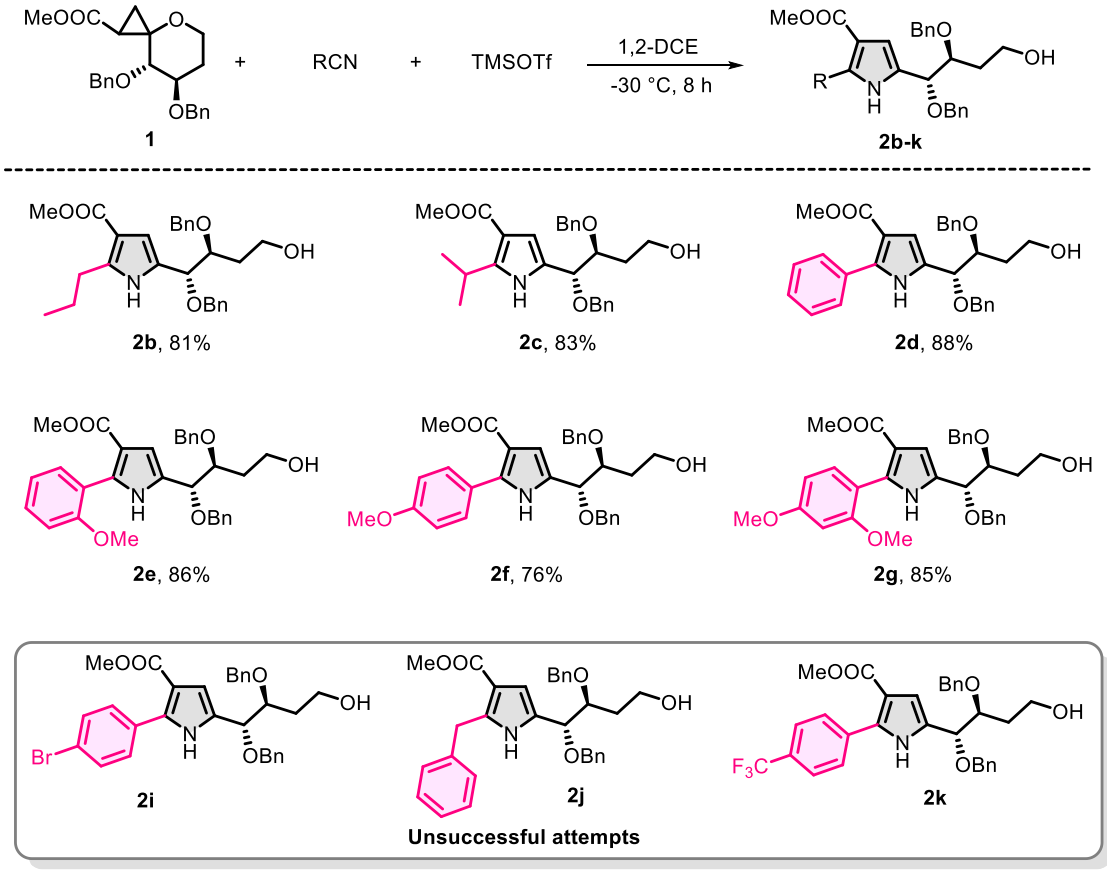
Scheme 2: Our work

Our investigation began with the model substrate **1**[9] and acetonitrile. At -78 °C, the reactats in DCM as the solvent was treated with 0.5 equivalent of TMSOTf. Prolong continuation of stirring at this temperature did not form any expected product. Even when the temperature was raised to -60 °C and 2 equivalents of nitrile substrate was used, unfortunately there was no product formation. However, when the reaction temperature further raised to -40 °C and 3 equivalents of acetonitrile was used, a new spot was identified along with unreacted starting material in the reaction medium, during the TLC analysis. This was isolated and characterized, after which it was found that the required cycloadduct product **2a** was formed in 30% yield. Further, the solvent was replaced with 1,2-dichloroethane and the temperature was still raised to -30 °C, with treatment of 0.5 equivalent of TMSOTf, the reaction afforded the required cycloadduct **2a** in 60% yield. Ultimately, at -30 °C temperature, 3 equivalents of nitrile substrate in 1,2-dichloroethane solvent, reacted with cyclopropane substrate **1** in the presence of equimolar ratio of TMSOTf, provided the 2,3,5-substituted pyrrole derivative **2a** in 90% isolated yield.



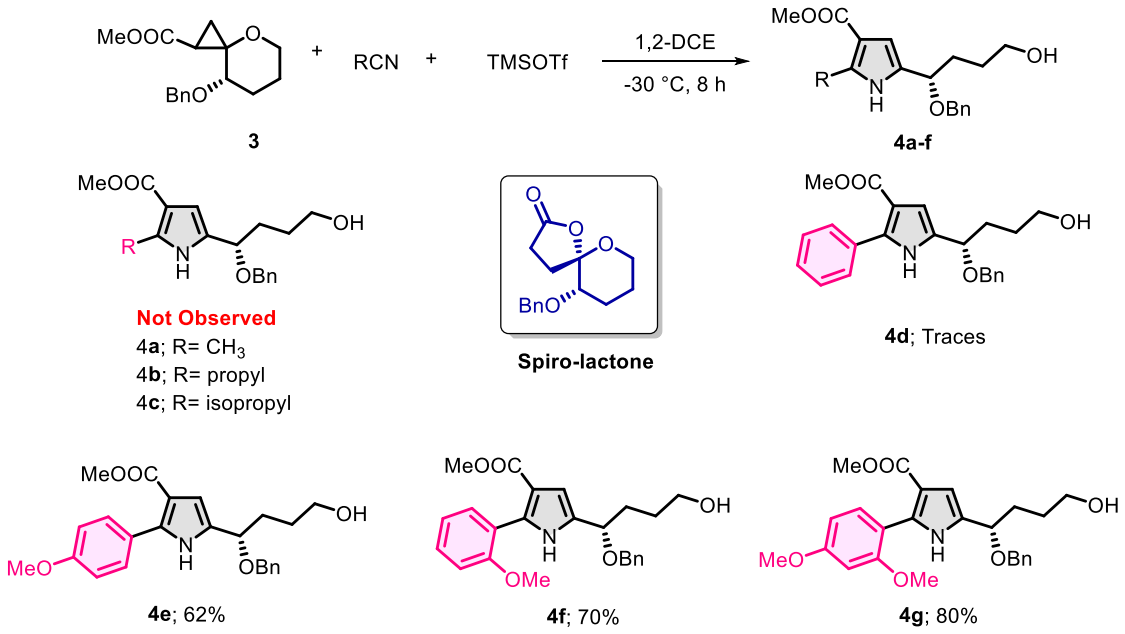
Scheme 3: (3+2) cycloaddition of DAC 1 and acetonitrile.

With this optimized condition in hand, scope of nitrile substrates was investigated. Firstly, when alkyl nitriles like butyronitrile and isobutyronitrile were employed for the (3+2) cycloaddition reaction with spiro-cyclopropane carboxylated sugar **1**, the pyrrole cycloadducts **2b** and **2c** were formed in 81% and 83% yield respectively.



Scheme 4: (3+2) cycloaddition reactions of spiro-cyclopropane carboxylate 1 and various nitriles.

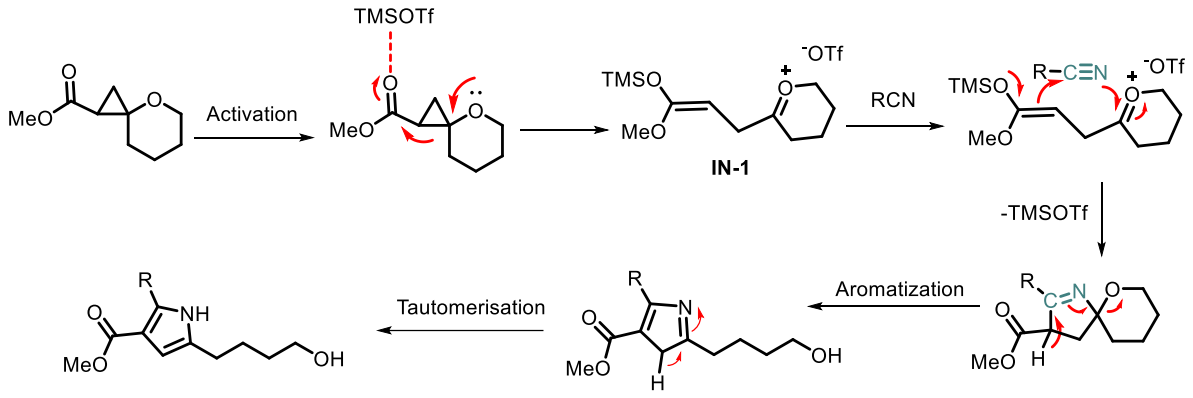
Further we screened for aryl nitriles. In this regard, when benzonitrile was reacted with cyclopropane **1**, we obtained the cycloadduct **2d** in 88% yield. In a similar way, when phenyl acetonitrile was used, there was no product formation possibly due to lack of appropriate charge formation on the nitrile substrate. We took forward the screening procedure by incorporating the substituted aryl nitriles. Initially, with a mild electron donating group substituent like 5-bromo benzonitrile was subjected to (3+2) cycloaddition reaction with cyclopropane **1**. Regrettably, there was no formation of the cycloadducts. A quick shift to stronger electron donating substitutions over the benzene ring, gave a fruitful result very smoothly. When ortho-methoxy benzonitrile and para-methoxy benzonitrile was employed in the (3+2) cycloaddition reaction with cyclopropane **1** under standard reaction condition, the cycloadducts **2e** and **2f** were efficiently formed in 86% and 76% yield respectively. Similarly, when cyclopropane **1** and 2,4-dimethoxy benzonitrile was subjected to TMSOTf mediated (3+2) cycloaddition reaction, the 2,3,5-substitute pyrrole derivative **2g** was obtained in 85% yield. However, it was found that electron withdrawing substituent like trifluoromethyl group on the benzene ring was unsuitable for the reaction and did not provide desired cycloadduct.



Scheme 5: (3+2) cycloaddition reactions of spiro-cyclopropane carboxylate 3 and various nitriles.

Next, the generality was further explored with respect to spiro-cyclopropane carboxylated sugar. In this regard, glucose-derived cyclopropane **3**[10] was subjected to (3+2) cycloaddition reaction with various alkyl nitriles (Scheme 5). We anticipated to obtain the alkyl substituted pyrrole cycloadducts (**4a-4c**). But it failed to provide any cycloadduct products, instead, it provided a **spiro-lactone** as the only product. When benzonitrile was used as the reacting 1,2-dipolar synthon, the reaction with cyclopropane **3**, offered the cycloadduct **4d** only in trace amounts. To our delight, when electron rich nitriles such as 2-methoxy, 4-methoxy and 2,4-dimethoxy benzonitrile incorporated in (3+2) cycloaddition with spiro-cyclopropane carboxylated sugar **3**, provided the polysubstituted pyrrole derivatives (**4e-4g**) as the cycloadducts in excellent yield.

Based on the type of cycloadducts that formed during the reaction, a possible reaction mechanism is proposed. TMSOTf mediated activation of spiro-cyclopropane carboxylated sugar forms the ring opened oxocarbenium ion intermediate **IN-I.** This is attacked by the nitrile functionality and forms a five membered intermediate that rapidly undergoes tautomerization followed by aromatization to give the 2,3,5-trisubstituted pyrrole cycloadduct.



Scheme 5: Plausible mechanism for the formation of tri-substituted pyrrole.

3.1.3 Conclusion

In conclusion, a highly functionalized pyrrole derivatives have been constructed efficiently by (3+2) cycloaddition of nitriles and spiro-cyclopropane carboxylated sugars. This powerful strategy is amenable to various nitriles and spiro-cyclopropanes. This foresees a great application as it can

be utilized for diverse post-synthetic transformations to construct unique scaffolds. The synthetic modifications have been carried out and described in the upcoming parts of this chapter.

3.1.4 References

1. (a) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem.* **1995**, *38*, 3895–3901.
   (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313–2316.
   (c) Lee, H.; Lee, J.; Lee, S.; Shin, Y.; Jung, W.; Kim, J.-H.; Park, K.; Kim, K.; Cho, H. S.; Ro, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3069–3072.
   (d) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhimana, S.; Sharma, P. *RSC Adv.* **2015**, *5*, 15233-15266.
2. (a) Manzoni, M.; Rollini, M. *Appl. Microbiol. Biotechnol.* **2002**, *58*, 555–564.
   (b) Murphy, C.; Deplazes, E.; Cranfield, C. G.; Garcia, A. *Int. J. Mol. Sci.* **2020**, *21*, 8745-8774.
3. (a) Hantzsch, A. Ber. **1890**, *23*, 1474-1483.
   (b) Paal, C. Ber. **1885**, *18*, 367-371.
   (c) Knorr, L. Ber. **1885**, *18,* 299- 311.
   (d) Elming, N.; Clauson-Kaas, N. *Acta Chem. Scand.* **1952**, *5*, 867- 874.
   (e) Patterson, J. M. *Synthesis.* **1976**, 281-304.
   (f) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1*. **1999**, 2849-2866.
4. (a) Gónzalez, F. G.; Sánchez, A. G. *Adv. Carbohydr. Chem. Biochem*. **1965**, *20*, 303-355.
   (b) Perez, J. A. G.; Albarran, J. C. P.; Requejo, J. L. J.; Gonzalez, M. A. *Carbohydr. Res.* **1984**, *132*, 153-161.
   (c) Chiara, J.-L.; Gómez-Sánchez, A.; Hidalgo, F.-J.; Yruela, I. *Carbohydr. Res.* **1989**, *188*, 55-62.
   (d) Gómez-Sánchez, A.; Mancera, M.; Rosado, F.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 1*. **1980**, 1199-1205.
   (d) Bhattacharya, R.; Atta, A. K.; Dey, D.; Pathak, T. *J. Org. Chem.* **2009**, *74*, 669-67.

(e) Reddy, V. V.; Reddy, B. S. *Tetrahedron*, **2021**, *97*, 132389-132394.

(f) Adhikary, N. D.; Kwon, S.; Chung, W.-J.; Koo, S. *J. Org. Chem.* **2015**, *80*, 7693-7701.

(g) Yadav, J. S.; Reddy, B.; Sreenivas, M.; Satheesh, G. *Synthesis.* **2007**, *2007*, 1712-1716.

(h) Nagarapu, L.; Chary, M. V.; Satyender, A.; Supriya, B.; Bantu, R. *Synthesis.* **2009**, *2009*, 2278-2282.

(i) Rokade, S. M.; Garande, A. M.; Ahmad, N. A.; Bhate, P. M. *RSC Advances*, **2015**, *5*, 2281-2284.

(j) Xia, M.; Lambu, M. R.; Tatina, M. B.; Judeh, Z. M. A. *J. Org. Chem.* **2021**, *86*, 837–849.

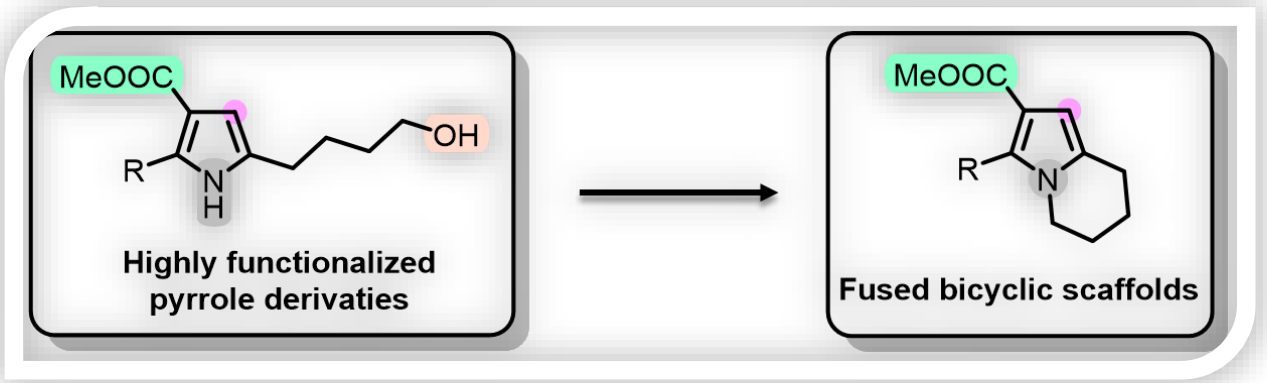
(k) Xia, M.; Lambu, M. R.; Judeh, Z. M. A. *J. Org. Chem.* **2022**, *87*, 12115–12131

(l) Xia, M.; Moussa, Z.; Judeh, Z. M. A. *Asian J. Org. Chem.* **2022**, *11*, e202200367.

5. Ganesh, V.; Sridhar, P. R.; Chandrasekaran, S. *Isr. J. Chem.* **2016**, *56*, 417-432.
6. Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099–510.
7. Wang, P.; Song, S.; Miao, Z.; Yang, G.; Zhang. A. *Org. Lett.* **2013**, *15*, 3852–3855.
8. Shen, X.; Xia, J.; Liang, P.; Ma, X.; Jiaoa, W.; Shao, H. *Org. Biomol. Chem.* **2015**, *13*, 10865–10873.
9. Ramakrishna, B.; Sridhar, P. R. *Org. Lett.* **2013**, *15*, 4474–4477.

Chapter 3 – Part B

En route to the synthesis of tetrahydroindolizines based scaffolds



Abstract:

Heterocyclic compounds such as indolizidines and tetrahydroindolizines (THIs) have played a crucial role as glycomimetic which has glycosidase inhibitory effect. The synthetic utility of the (3+2) cycloadducts, i.e., 2,3,5-trisubstituted pyrroles, is effectively showcased. Mitsunobu reaction mediated deoxygenation-cyclization between the terminal alcohol and secondary amine of the pyrrole derivative offered the fused aza-bicyclic ring derivatives which has THI core structure. A library of variable substituted THI derivatives are synthesized.

3.2.1 Introduction

Glycosidase inhibitors have played a promising role in drug-development.[1] These perform diverse biological activities and have many types of beneficial effects.[2] Several classes of secondary metabolites contribute to the inhibitory activity and azabicyclic ring skeleton is present as the core in them. Polyhydroxy alkaloids with azabicyclic ring core are emerging as a potent inhibitor of glycosidases.[3] Among them, indolizidines and tetrahydro indolizines (Figure 1) are considered as the analogs of the aromatic indolizine or as azabicyclo[4.3.0]nonanes.

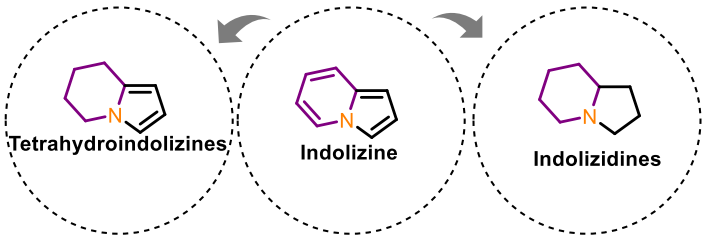


Figure 1: Aza-bicyclic ring frameworks present in alkaloids.

The natural and non-natural polyhydroxy indolizidines like castanospermine, 6-epi-castanospermine, swainsonine, lentiginosine etc., have attracted considerable attention as they structurally mimic bioactive carbohydrates and are recognized as potential antimicrobial, antitumor antidiabetic, and anti-inflammatory agents (Figure 2, A).[4]

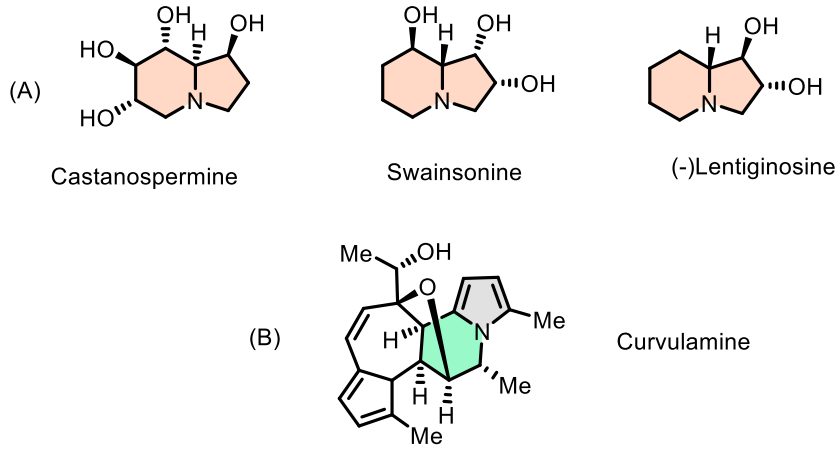


Figure 2: Examples of polyhydroxy indolizidines and tetrahydro indolizines.

In a similar way, tetrahydroindolizines (THIs) present as a core skeleton in several bioactive natural products, also exhibit potent inhibitory activities against harmful microbes. For example, curvulamine (Figure 2, B), obtained from *Curvularia sp.* IFB-Z10, exhibit excellent antimicrobial activity.[5] Polyhydroxy alkaloids and THIs, like many other families of natural compounds, have served as structural models for a significant number of synthetic counterparts. Even though they are present in many living organisms, the compounds are obtained in a very small amount which is insufficient to meet the needs of the scientific community.

In this regard, several synthetic routes are developed majorly based on very efficient precursors like carbohydrates and proline derivatives (Figure 3).[6]

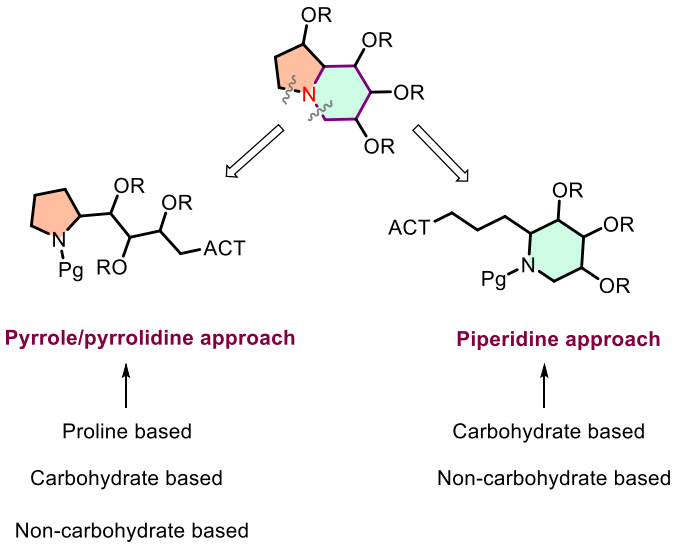
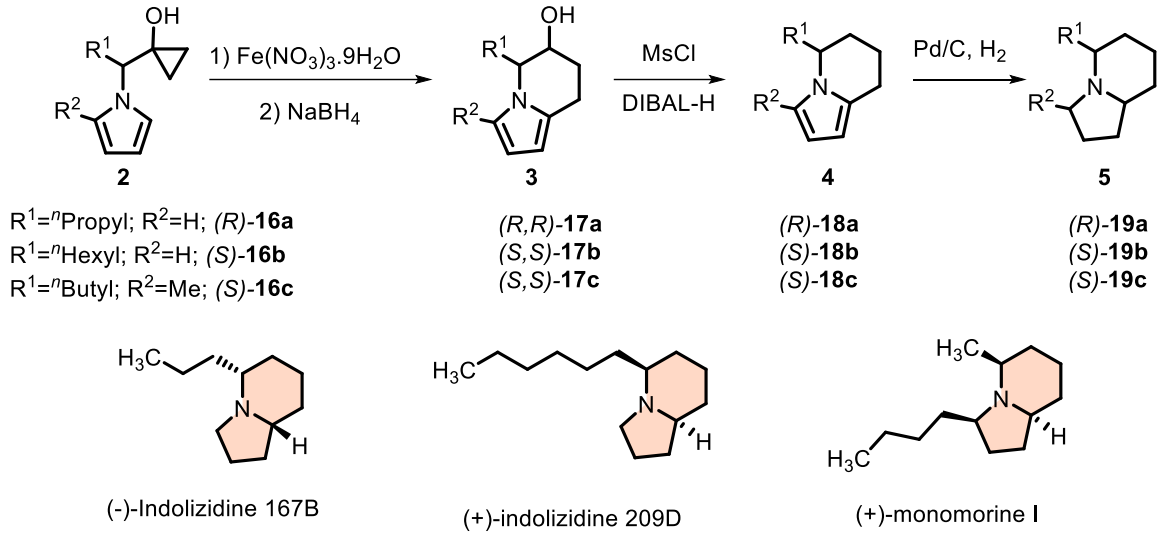


Figure 3: Methods to construct indolizine and THI skeletons.

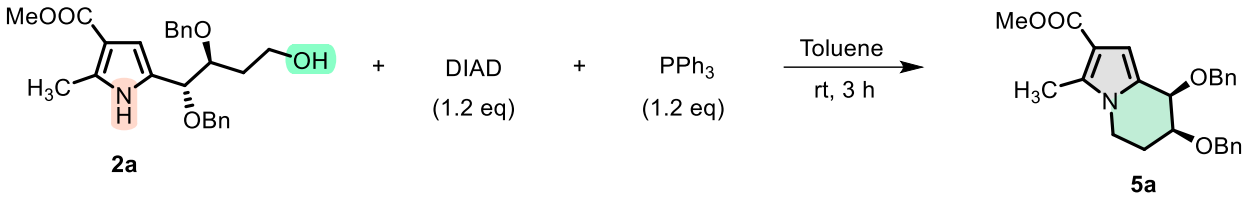
Very recently, Zhang and coworkers, reported the ring-opening followed by ring closing arylation of chiral pyrrolylcyclopropanols **16** substrates in the presence of $Fe(NO_3)_3$ to synthesize novel THI derivative (Scheme 1).[7] Further, reduction of the pyrrole moiety of few of the THI derivatives provided the indolizine alkaloids namely indolizidine 209D, indolizidine 167B, and monomorine (Scheme 1).



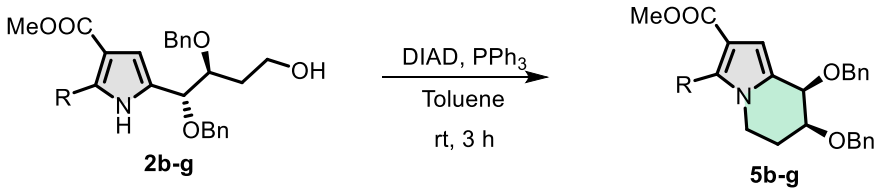
Scheme 1: Synthesis of indolizine natural products from pyrrolylcyclopropanols.

3.2.2 Results and Discussion:

Post-synthetic transformations and applications has always benefited for the synthetic organic chemistry fraternity. Knowing the importance of polyhydroxy alkaloids like indolizines and tetrahydroindolizines, we envisaged a unique post-synthetic transformation of pyrrole cycloadducts obtained in the part A to construct the THI core skeleton. Our work presented in this chapter, is the new protocol to access novel chiral tetrahydroindolizines (THIs) from the 2,3,5-trisubstituted pyrrole derivatives. Our investigation began with the methyl substituted pyrrole cycloadduct **2a**. Mitsunobu reaction condition was employed where the alcohol functionality was activated and cyclized while undergoing deoxygenation. Cycloadduct **2a** in the presence of diisopropylazadicarboxylate (DIAD) and triphenylphosphine (Ph_3P) in toluene solvent at room temperature offered the THI derivative **5a** in 90% yield within 3 hours (Scheme 2).



Scheme 2: Synthesis of methyl substituted THI derivative from cycloadduct *via* Mitsunobu reaction condition.



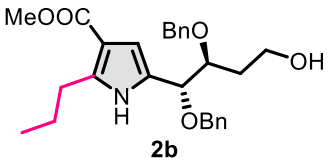
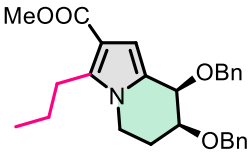
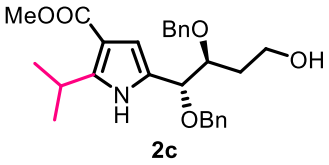
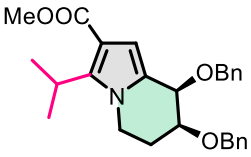
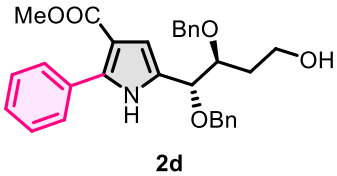
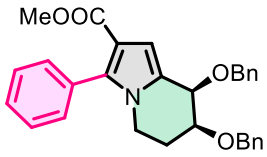
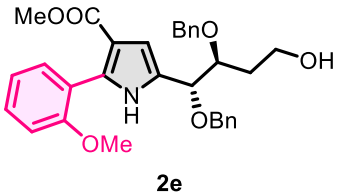
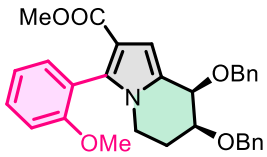
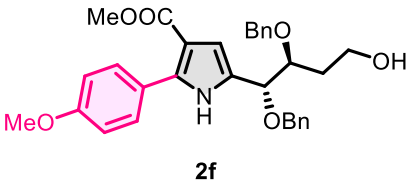
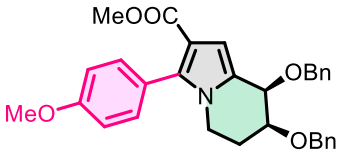
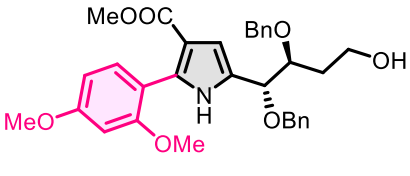
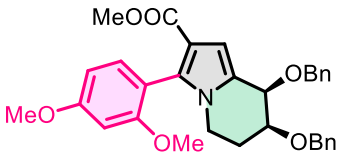
Entry	Cycloadduct	THI derivatives	Yield
1	 **2b**		**5b**; 92%
2	 **2c**		**5c**; 90%
3	 **2d**		**5d**; 95%
4	 **2e**		**5e**; 85%
5	 **2f**		**5f**; 87%
6	 **2g**		**5g**; 83%

Table 1: Synthesis of THI derivatives from cycloadducts.

After the initial success, we subjected the 2-alkyl substituted pyrrole derivatives **2b** and **2c** for the cyclization. We obtained the THI derivative **5b** and **5c** in 92% and 90% yield respectively. Further, the phenyl substituted pyrrole derivative **2d** gave the THI derivative **5d** in 95% yield when treated with DIAD and Ph_3P in toluene solvent. Similarly, aryl substituted pyrrole cycloadducts **2e-g** offered the THI derivatives in excellent yields.

Further we subjected the cycloadducts **4e-g** derived from cyclopropane **3** for the Mitsunobu cyclization (Table 2). We observed an anomality in the results. The cycloadduct **4e** when treated with DIAD and Ph_3P, probably after formation of product **6e**, underwent elimination rapidly to give compound **7e** in 90% yield. The benzyl functionality was knocked off by lone pair delocalization to form conjugated double bond system **7e** which is more favored. Further, cycloadduct **4g** also provided the eliminated product **7g** in 93% yield. However, we observed that cycloadduct **4f** under Mitsunobu reaction condition gave the THI derivative **6f** in 70% yield.

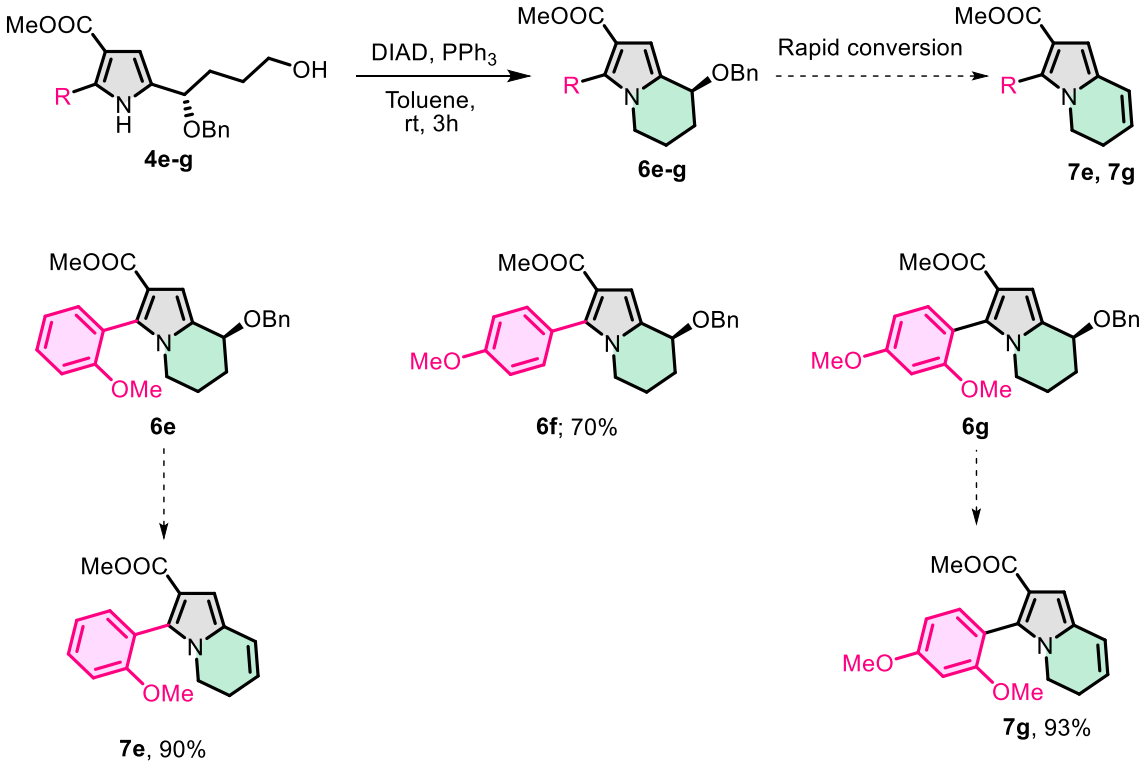


Table 2: Synthesis of fused aza-bicycles and THI derivative from pyrrole derivatives.

3.2.3 Conclusion

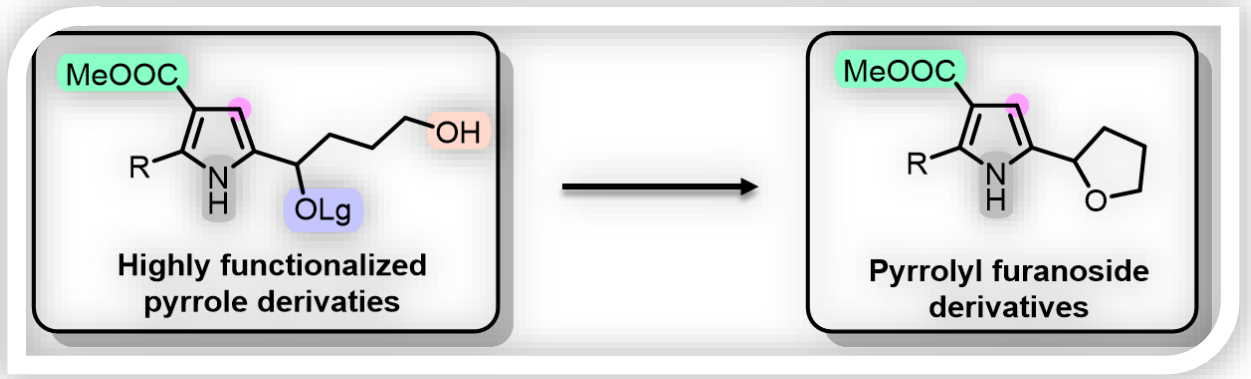
In conclusion, we have performed an efficient post-synthetic transformation using Mitsunobu reaction conditions. The tetrahydroindolizine (THI) derivatives were obtained by 2,3,5-substitued pyrrole derivative in good to excellent yield. Further scope and transformation of the formed THI derivatives to construct indolizine derivatives and other potential bioactive molecule is in progress.

3.2.4 References

1) (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515−553.
(b) Asano, N. *Glycobiology*. **2003**, *13*, 93R−104R.
2) Inouye, S.; Tsuruoka, T.; Nida, T. J. *Antibiot.* **1966**, *19*, 288−292.
3) Elbein, A. D.; Molyneux, R. J. *Comprehensive Natural Products Chemistry*. **1999**, 129–60.
4) (a) Asano, N. Wiley-VCH: Weinheim, **2008**; pp 111−138.
(b) Asano, N. In Glycoscience: Chemistry and Chemical Biology; Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, **2008**; pp 1887−1911.
5) Han, W. B.; Lu, Y. H.; Zhang, A. H.; Zhang, G. F.; Mei, Y. N.; Jiang, N.; Lei, X.; Song, Y. C.; Ng, S. W.; Tan, R. X. *Org. Lett.* **2014**, *16*, 5366−5369.
6) Koskinen, A. M. P.; Kallatsa, O. A. Tetrahedron. **2003,** *59*, 6947–6954.
7) Liu, S.; Su, X.; Jiang, D.; Xiong, H.; Miao, D.; Fu, L.; Qiu, H.; He, L.; Zhang, M. *Org. Lett.* **2023**, *25*, 2058−2062.

Chapter 3 – Part C

En route to the synthesis of C-pyrrolyl furanoside derivatives



Abstract:

C-furanosides have been employed as building blocks in the synthesis of several naturally occurring compounds and molecules with biological activity. Their importance has found place as nucleoside inhibitors. Various C-pyrrolyl furanosides were synthesized by transforming the (3+2) cycloadducts i.e., 2,3,5-substituted pyrroles. The suitably positioned benzyl group on the polyhydroxy alkyl chain of pyrrole derivative is efficiently subjected for post-synthetic transformation. In the presence of catalytic amount of Lewis acid, a carbocation mediated S_N1 substitution reaction occurs to offer various pyrrole attached furanoside derivatives.

3.3.1 Introduction

C-glycosides from natural as well as non-natural origin, plays a significant role in therapeutics.[1] Following a brief survey, we found that molecular hybridization technique has found a strong base in scientific community in drug development technology.[2] In this view, the synthesis of glycoconjugates or glyco-hybrids which contains carbohydrates as biopotential scaffold and heterocyclic molecules as pharmacophores has attained an immense interest among the scientific community.

Heterocyclic molecules are unique class of organic molecules that contain a hetero atom in the cyclic ring. They are present in the core structures of major classes of natural products.[3] Pyrrole is one among them which is known for being a biologically potent scaffold with a wide range of functions. Pyrrole along with combination of other heterocycles form various pharmacophore and are often incorporated in the drugs such as antibiotics, atrorvastatin, anti-inflammants, antitumor agents and immunosuppressants etc.[4]

Owing to the significance of variety of pyrrole and other heterocyclic scaffolds in therapeutics, several studies have been attempted to construct glycoconjugates. The furanosyl glyco-conjugates containing nitrogen heterocycles form important class of nucleoside inhibitors which displays various biological activities (Figure 1).

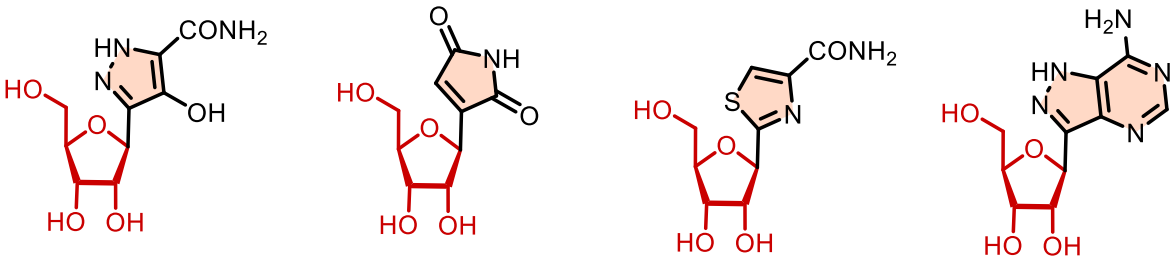


Figure 1: Examples of biologically active *C*-nucleosides.

In this view we found that pyrrole substituted sugars especially the *C*-pyrrolyl glycosides can be a promising library of molecules with potential biological applications. A very few approaches have

been reported for the synthesis of *C*-pyrrolyl glycosides.[5] Contributing to this, we report the synthesis of *C*-pyrrolyl- furanoside derivatives. This work has been carried out as a part of post-synthetic modifications of the cycloadducts introduced in part A of chapter 3.

3.3.2 Results and discussion

We envisioned that the pyrrole cycloadducts obtained in part A of this chapter, with suitably positioned alcohol and the benzyl functionality will undergo cyclization *via* a S_N1 type of substitution reaction. To begin with, we chose methyl substituted pyrrole cycloadduct **2a** obtained from spirocyclopropane **1** as our substrate. Compound **2a** was treated with catalytic amount of Lewis acid $BF_3{\cdot}OEt_2$ in dichloromethane solvent at 0 °C. The reaction offered the furanoside product **8aβ:8aα** as a mixture of anomers (1:0.6) in 95% yield. The ratios of the formed anomers were found out by the proton NMR and the coupling constant. To see the stereochemical control and anomeric selectivity, we decreased the reaction temperature to -78 °C. However, there was no improvement in the anomeric selectivity. When $BF_3{\cdot}OEt_2$ was replaced with TMSOTf, the yield was decreased with retention in anomeric selectivity. Hence, reaction was standardized to catalytic $BF_3{\cdot}OEt_2$ as Lewis acid and 0 °C as the reaction temperature.

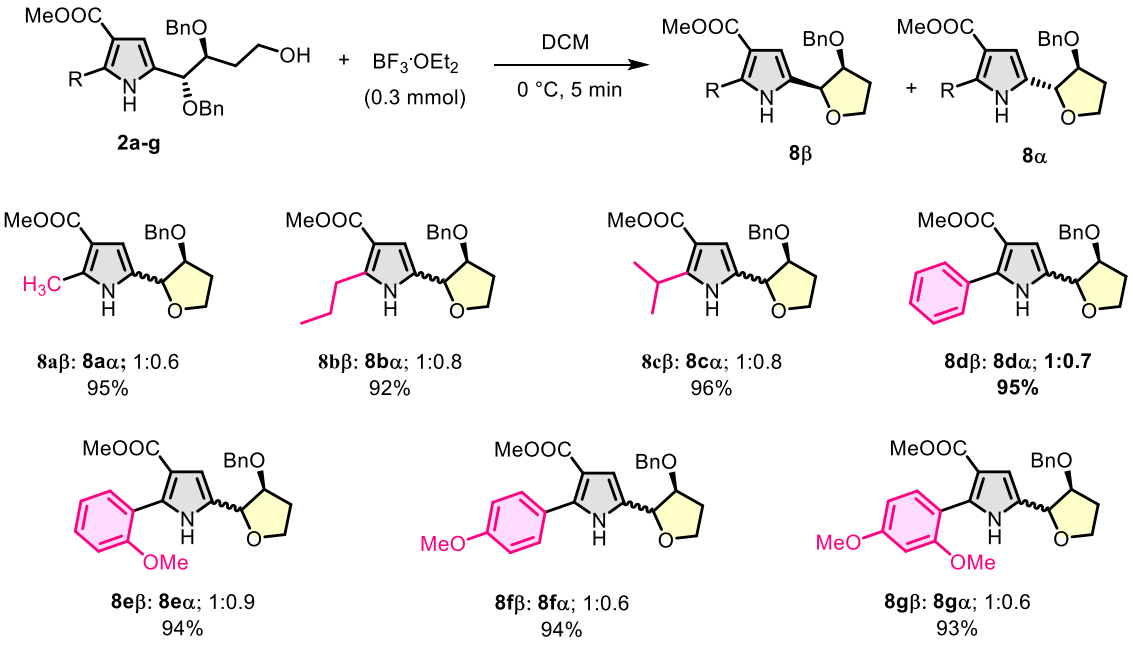
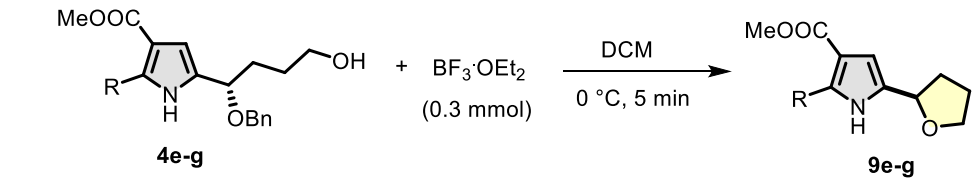
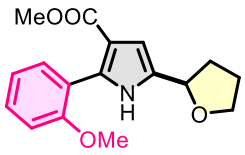


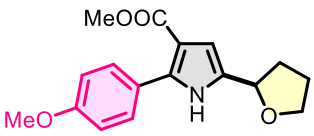
Table 1: Synthesis of *C*-pyrrolyl furanoside derivatives.

Further, the 2-alkyl substituted pyrrole cycloadducts **2b** and **2c** was subjected to Lewis acid mediated cyclization. The *C*-pyrrolyl furanoside **8bβ:8bα** and **8cβ:8cα** was formed in the ratio of 1:0.8 anomeric mixtures. At this stage, we were able to separate a portion of the major isomer **8bβ** and we thoroughly characterized the compound *via* NMR and HRMS studies. In the similar way, the aryl substituted pyrrole cycloadducts **2d-2g** was subjected to Lewis acid mediated substitution-cyclization reaction to obtain the *C*-pyrrolyl furanoside derivatives as the anomeric mixtures (Table 1). The phenyl substituted pyrrole cycloadduct provided the furanoside derivative **8dβ:8dα** in 1:0.7 ratio of anomers in 95% yield. However, ortho methoxy-aryl substituted pyrrole cycloadduct offered the cyclized furanoside product **8eβ:8eα** in 1:0.9 ratio of anomers. To our delight, we were able to separate the minor isomer **8eα** which was characterized by NMR studies. Further we found the results of the cycloadducts **2f** and **2g.** In the first case, we obtained the *C*-pyrrolyl furanoside derivative **8fβ-8fα** in 1:0.6 anomeric ratio and 94% overall yield. Ultimately, when 2,4-dimethoxy-aryl substituted pyrrole cycloadduct was subjected to Lewis acid mediated substitution reaction, we obtained the furanoside derivative **8gβ-8gα** as a mixture of 1:0.6 ratio of anomers in 93% yield. Furthermore, the cycloadducts obtained from spiro-cyclopropane **3** were also subjected to substitution reaction. The aryl substituted pyrrole cycloadducts **4e-g** were treated with $BF_3{\cdot}OEt_2$ at 0 °C and we obtained the 5-tetrahydrofuryl substituted pyrrole derivatives (**9e-9g**) as an enantiomeric mixture in excellent yield (Table 2).

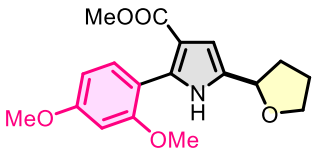




9e; 94%



9f; 95%

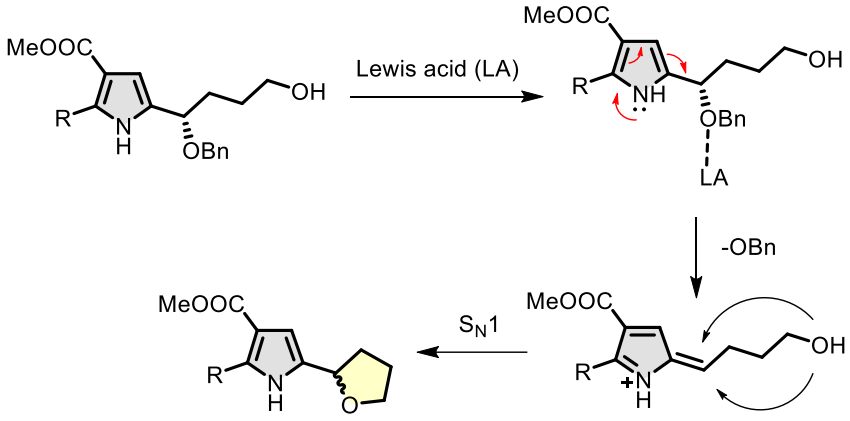


9g; 93%

Table 2: Synthesis of THF-substituted pyrrole derivatives.

Possible mechanism

We propose a possible mechanism for the formation of *C*-pyrrolyl furanosides. The Lewis acid catalyst coordinates with the benzyl group present on the vinylic position of the pyrrole ring. As a result of electron delocalization, the benzyl group easily eliminates leaving a stable carbocation.



Scheme 2: Possible mechanism for *C*-pyrrolyl furanoside formation.

This electrophilic center is attacked by the terminal alcohol from both faces *via* a S_N1 type of reaction giving rise to both *cis*- and *trans*-glycosides in variable ratios. Since there are no bulky groups present in the vicinity, carbocation mediated substitution occurs to give rise to anomeric mixture.

3.3.3 Conclusion

In conclusion, we efficiently performed a post-synthetic transformation to synthesize pyrrolyl-C-glycosides from pyrrole cycloadducts. We have opened a new platform for designing potential nucleoside inhibitors.

3.3.4 References

1. (a) Y, Yang.; Yu, B. *Chem. Rev.* **2017**, *117*, 12281–12356.

(b) Parida, S. P.; Das, T.; Ahemad, M. A.; Pati, T.; Mohapatra, S.; Nayak, S. *Carbohydr. Res.* **2023**, *530*, 108856 -108883.

2. Bérubé G. Expert Opin *Drug Discov.* **2016**, *11*, 281-305.
3. Joule, J. A. *Adv Heterocycl Chem*. **2016**, *119*, 81-106.
4. Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem.*, **1995**, *38*, 3895–3901.

   (b) Wurz, R. P.; Charette, A. B. *Org. Lett.*, **2005**, *7*, 2313–2316.

   (c) Lee, H.; Lee, J.; Lee, S.; Shin, Y.; Jung, W.; Kim, J.-H.; Park, K.; Kim, K.; Cho, H. S.; Ro, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3069–3072.
5. (a) Sánchez, A. G.; Toledano, E.; Guillén, M. G. *J. Chem. Soc., Perkin Trans. 1.* **1974**, 1237-1243.

   (b) Casiraghi, G.; Cornia, M.; Rassu, G.; Sante, C. D.; Spanu, P. Tetrahedron, **1992**, *48*, 5619-5628.

   (c) (d) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Divyavani, C.; Basha, S. J.; Sarma, A. V. S. J. Org. Chem. 2008, 73, 3252.

   (d) Reddy, B. V. S.; Jain, R.; Bhargavi, K. O.; Swain, M.; Yadav, J. S. *Synthesis*. **2011**, *2*, 337–341.

Experimental Details

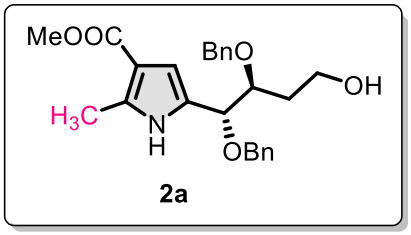
Chapter 3 – Part A: (3+2) Cycloaddition Reaction of Spiro-cyclopropane Carboxylated Sugars and Nitriles: Synthesis of Highly Functionalized Pyrrole Derivatives

General procedure A for Lewis acid catalyzed (3+2) cycloaddition

To a solution of spiro-cyclopropane carboxylated sugar derivative (1 mmol) and respective nitrile (3 mmol) in 1,2-DCE (8 mL) was added TMSOTf (1.0 Eq) at -30 °C under argon atmosphere. The reaction was stirred at ambient temperature for 8 hours and monitored by TLC until the completion. The reaction mixture was quenched by adding saturated solution of $NaHCO_3$ and extracted with DCM, dried with Na_2SO_4 and concentrated in vaco. The crude product was purified using silica gel column chromatography to obtain the desired product.

Compound characterization

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-methyl-1*H*-pyrrole-3-carboxylate (2a):



2a

Compound **2a** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and acetonitrile (64.0 mg, 1.56 mmol) by following **general procedure A.** Yield: 203.2 mg (0.46 mmol), 90%; *Rf*: 0.5 (30% EtOAc/hexane); colorless oil.

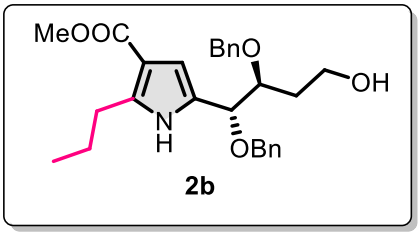
IR (neat): 3318, 3065, 3028, 2946, 1675 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.77 (s, 1H), 7.23-7.32 (m, 10H), 6.45 (d, 1H, *J* = 2.5 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 4.49 (dd, 2H, *J* = 5.5 Hz, 12.0 Hz), 4.36 (d, 1H, *J* = 4.5 Hz), 4.27 (d, 1H, *J* = 12.0 Hz), 3.76-3.79 (m, 4H), 3.59-3.62 (m, 2H), 2.40 (s, 3H), 1.84 (s, 1H), 1.73 (dd, 2H, *J* = 6.0 Hz, 11.5 Hz).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 166.0, 138.0, 137.6, 136.0, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 126.9, 111.0, 110.3, 80.1, 76.1, 73.5, 70.6, 59.5, 50.7, 33.6, 13.2 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{30}NO_5$ $[M+H]^+$: 424.2124, found: 424.2125.

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-propyl-1*H*-pyrrole-3-carboxylate (2b):



2b

Compound **2b** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and butyronitrile (107.8 mg, 1.56 mmol) by following **general procedure A.** Yield: 190.0 mg (0.42 mmol), 81%; *Rf*: 0.4 (30% EtOAc/hexane); colorless oil.

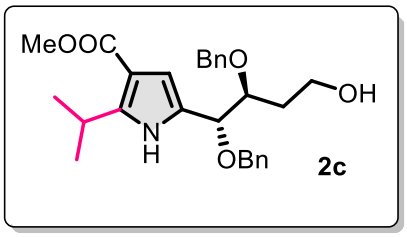
IR (neat): 3320, 3035, 2946, 2863, 1680 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.72 (s, 1H), 7.26-7.35 (m, 10H), 6.49 (d, 1H, *J* = 3.0 Hz), 4.58 (d, 1H, *J* = 11.5 hz), 4.52 (dd, 2H, *J* = 3.0 Hz, 11.5 Hz), 4.41 (d, 1H, *J* = 4.5 Hz), 4.31 (d, 1H, 11.5 Hz), 3.78-3.81 (m, 4H), 3.64 (t, 2H, *J* = 6.0 Hz), 2.85-2.91 (m, 1H), 2.75-2.81 (m, 1H), 1.76-1.81 (m, 2H), 1.65 (s,1H), 1.51 (m, 2H), 0.90 (t, 3H, *J* = 7.5 Hz).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 165.8, 140.6, 138.0, 137.6, 128.5, 128.5, 128.2, 128.1, 127.9, 127.9, 126.8, 110.6, 110.4, 80.1, 76.0, 73.3, 70.7, 59.6, 50.7, 33.6, 29.2, 22.4, 13.8 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{27}H_{34}NO_5$ $[M+H]^+$: 452.2437, found: 452.2430.

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-isopropyl-1*H*-pyrrole-3-carboxylate (2c):



2c

Compound **2c** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and isobutyronitrile (107.8 mg, 1.56 mmol) by following **general procedure A.** Yield: 194.7 mg (0.43 mmol), 83%; *Rf*: 0.4 (30% EtOAc/hexane); colorless oil.

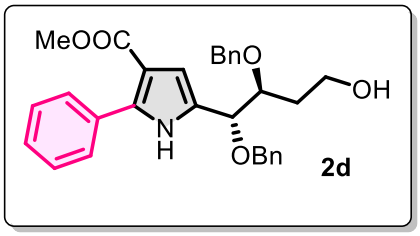
IR (neat): 3318, 3065, 2968, 2946, 1675 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.85 (bs, 1H), 7.26-7.35 (m, 10H), 6.49 (d, 1H, *J* = 2.5 Hz), 4.51-4.56 (m, 3H), 4.43 (d, 1H, *J* = 4.5 Hz), 4.32 (d, 1H, *J* = 12.0 Hz), 3.77-3.81 (m, 4H), 3.72-3.76 (m, 1H), 3.61-3.65 (m, 2H), 1.77-1.82 (m, 2H), 1.67 (s, 1H), 1.16 (d, 3H *J* = 7.0 Hz), 1.14 (d, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.7, 146.0, 138.0, 137.6, 128.5, 128.5, 128.2, 127.9, 126.7, 110.4, 109.5, 80.1, 76.0, 73.0, 70.9, 59.5, 50.7, 33.5, 26.0, 21.9, 21.7.

HRMS (ESI-TOF) *m/z*: calcd for $C_{27}H_{33}NO_5Na$ [M+Na] : 474.2256, found: 474.2260.

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-phenyl-1*H*-pyrrole-3-carboxylate (2d):



Compound **2d** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and benzonitrile (160.8 mg, 1.56 mmol) by following **general procedure A.** Yield: 222.0 mg (0.46 mmol), 88%; *Rf*: 0.5 (30% EtOAc/hexane); yellow oil.

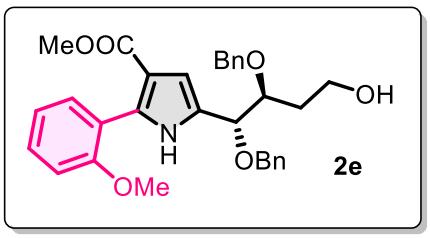
IR (neat): 3439, 3065, 3036, 2945, 2883, 1690 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.06 (bs, 1H), 7.47-7.50 (m, 2H), 7.28-7.38 (m, 8H), 7.20-7.25 (m, 5H), 6.67 (d, 1H, *J* = 3.0 Hz), 4.60 (d, 1H, *J* = 4.0 Hz), 4.58 (d, 1H, *J* = 3.0 Hz), 4.49 (d, 1H, *J* = 3.5 Hz), 4.48 (d, 1H, *J* = 3.5 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 3.82-3.85 (m, 1H), 3.76 (s, 3H), 3.65 (t, 2H, *J* = 5.0 Hz), 1.78-1.86 (m, 2H), 1.72 (bs, 1H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.4, 137.7, 137.5, 137.4, 131.7, 129.0, 128.7, 128.5, 128.5, 128.2, 128.1, 128.1, 127.9, 127.9, 111.9, 111.2, 75.7, 73.3, 71.0, 59.4, 51.0, 33.4 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{32}NO_5$ $[M+H]^+$: 486.2280, found: 486.2282.

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-(2-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (2e):



Compound **2e** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and 2-methoxybenzonitrile (207.7 mg, 1.56 mmol) by following **general procedure A.** Yield: 230.3 mg (0.44 mmol), 86%; *Rf*: 0.3 (30% EtOAc/hexane); yellow oil.

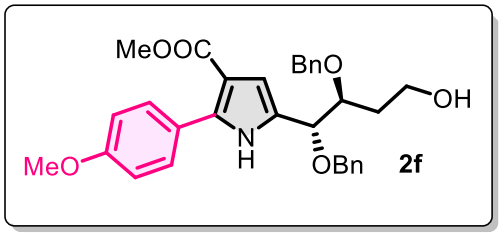
IR (neat): 3345, 3026, 2946, 1701 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.38 (s, 1H), 7.65 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 7.30-7.36 (m, 6H), 7.25 (d, 5H, *J* = 7.5 Hz), 7.02 (td, 1H, *J* = 1.0 Hz, 8.0 Hz, 15.5 Hz), 6.93 (d, 1H, *J* = 8.0 Hz), 6.67 (d, 1H, *J* = 3.0Hz), 4.62 (dd, 2H, *J* = 9.0 Hz, 11.5), 4.53-4.56 (m, 2H), 4.40 (d, 1H, *J* = 12.0 Hz), 3.82-3.85 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.65 (t, 2H, *J* = 5.5 Hz), 1.75-1.83 (m, 2H), 1.61 (s, 1H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ =165.4, 156.4, 137.8, 132.8, 132.2, 130.3, 129.6, 128.5, 128.4, 127.8, 127.7, 127.5, 120.4, 120.2, 113.0, 111.0, 107.3, 84.0, 79.4, 71.6, 67.4, 55.7, 50.9, 32.3.

HRMS (ESI-TOF) *m/z*: calcd for $C_{31}H_{34}NO_6$ $[M+H]^+$: 516.2386, found: 516.2385.

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (2f):



Compound **2f** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and 4-methoxybenzonitrile (207.7 mg, 1.56 mmol) by following **general procedure A.** Yield: 203.6 mg (0.39 mmol), 76%; *Rf*: 0.3 (30% EtOAc/hexane); yellow oil.

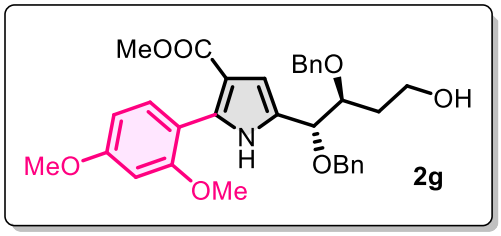
IR (neat): 3301, 2946, 1700 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 7.41-7.44 (m, 2H), 7.29-7.36 (m, 5H), 7.22-7.26 (m, 5H), 6.88-6.91 (m, 2H), 6.64 (d, 1H, J = 2.5 Hz), 4.59-4.61 (m, 2H), 4.48-4.51 (m, 2H), 4.37 (d, 1H *J* = 12.0 Hz), 3.82-3.85 (m, 4H), 3.76 (s, 3H), 3.67 (t, 2H, *J* = 5.5 Hz), 1.99 (s, 1H), 1.79-1.88 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 165.4, 159.6, 137.8, 137.7, 137.5, 130.0, 128.5, 128.5, 128.2, 128.1, 127.9, 124.3, 113.6, 111.8, 110.7, 80.0, 75.8, 73.3, 71.0, 59.5, 55.3, 50.9, 33.5.

HRMS (ESI-TOF) *m/z*: calcd for $C_{31}H_{34}NO_6$ $[M+H]^+$: 516.2386, found: 516.2389.

methyl 5-((1*R*,2*S*)-1,2-bis(benzyloxy)-4-hydroxybutyl)-2-(2,4-dimethoxyphenyl)-1*H*-pyrrole-3-carboxylate (2g):



Compound **2g** was synthesized from spiro-cyclopropane carboxylated sugar **1** (200 mg, 0.52 mmol) and 2,4-dimethoxybenzonitrile (247.85 mg, 1.56mmol) by following **general procedure A.** Yield: 240.9 mg (0.44 mmol), 85%; *Rf*: 0.3 (40% EtOAc/hexane); yellow oil.

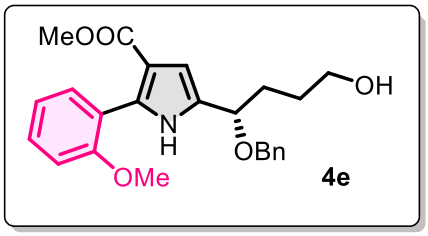
IR (neat): 3389, 3004, 2947, 2358, 1730 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.31 (s, 1H), 7.62 (d, 1H, *J* = 8.5 Hz), 7.29-7.35 (m, 5H), 7.25-7.27 (m, 5H), 6.64 (d, 1H, *J* = 3.0 Hz), 6.56 (dd, 1H, *J* = 2.5 Hz, 8.5 Hz), 6.48 (d, 1H, *J* = 2.0 Hz), 4.62 (d, 2H, *J* = 11.5 Hz), 4.54 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 4.5 Hz), 4.39 (d, 1H, *J* = 11.5 Hz), 3.81-3.85 (m, 4H), 3.75 (s, 3H), 3.64-3.65 (m, 5H), 1.99 (s, 1H), 1.76-1.8 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.5, 161.0, 157.5, 138.0, 137.7, 134.0, 133.2, 128.4, 128.2, 128.1, 127.9, 127.8, 112.8, 111.6, 111.1, 104.3, 98.7, 80.0, 76.4, 73.4, 70.9, 59.8, 55.5, 55.4, 50.9, 33.6 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{32}H_{36}NO_7$ $[M+H]^+$: 546.2492, found: 546.2490.

methyl (*S*)-5-(1-(benzyloxy)-4-hydroxybutyl)-2-(2-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (4e):



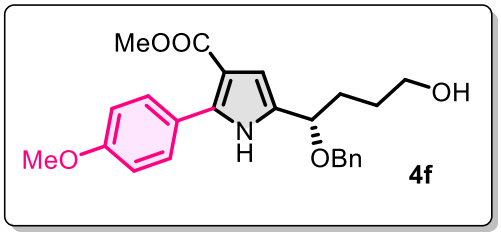
Compound **4e** was synthesized from spiro-cyclopropane carboxylated sugar **3** (200 mg, 0.72 mmol) and 2-methoxybenzonitrile (289.3 mg, 2.17 mmol) by following **general procedure A.** Yield: 206.2 mg (0.50 mmol), 70%; *Rf*: 0.4 (40% EtOAc/hexane); yellow oil.

IR (neat): 3301, 2946, 2938, 1689 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.30 (s, 1H), 7.67 (dd, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.27-7.35 (m, 6H), 7.01-7.04 (m, 1H), 6.96 (d, 1H, *J* = 8.0 Hz), 6.61 (d, 1H, *J* = 3.0 Hz), 4.51 (d, 1H, *J* = 11.5 Hz), 4.48 (dd, 1H, *J* = 6.0 Hz, *J* = 7.0 Hz), 4.37 (d, 1H, *J* = 12.0 Hz), 3.78 (s, 3H), 3.73 (s, 3H), 3.62 (t, 2H, *J* = 6.5 Hz), 1.94-2.01 (m, 1H), 1.84-1.91 (m, 1H), 1.64-1.72 (m, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.5, 156.3, 137.8, 133.5, 132.4, 130.6, 129.6, 128.4, 127.9, 127.8, 120.4, 120.0, 112.2, 111.0, 110.4, 74.4, 70.3, 62.6, 55.6, 50.9, 33.0, 28.7 ppm.

methyl (*S*)-5-(1-(benzyloxy)-4-hydroxybutyl)-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (4f):



Compound **4f** was synthesized from spiro-cyclopropane carboxylated sugar **3** (200 mg, 0.72 mmol) and 4-methoxybenzonitrile (289.3 mg, 2.17 mmol) by following **general procedure A.** Yield: 182.6 mg (0.44 mmol), 62%; *Rf*: 0.4 (40% EtOAc/hexane); yellow oil.

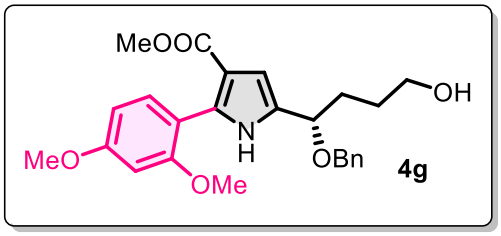
IR (neat): 3281, 2941, 2938, 1673 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.91 (s, 1H), 7.51-7.53 (m, 2H), 7.26-7.35 (m, 5H), 6.92-6.95 (m, 2H), 6.58 (d, 1H, *J* = 2.5 Hz), 4.49 (d, 1H, *J* = 11.5 Hz), 4.43 (dd, 1H, *J* = 5.5 Hz, *J* = 7.0 Hz), 4.37 (d, 1H, *J* = 11.5 Hz), 3.83 (s, 3H), 3.75 (s, 3H), 3.62 (t, 2H, *J* = 6.0 Hz), 1.94-2.01 (m, 1H), 1.82-1.89 (m, 1H), 1.74 (bs, 1H), 1.60-1.71 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.4, 159.6, 137.8, 137.6, 130.9, 130.1, 128.5, 128.0, 127.9, 124.4, 113.6, 110.9, 110.8, 74.4, 70.4, 62.5, 55.3, 50.9, 32.8, 28.8 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{24}H_{28}NO_5$ $[M+H]^+$: 410.1967, found: 410.1964.

methyl (S)-5-(1-(benzyloxy)-4-hydroxybutyl)-2-(2,4-dimethoxyphenyl)-1H-pyrrole-3-carboxylate (4g):



Compound **4g** was synthesized from spiro-cyclopropane carboxylated sugar **3** (200 mg, 0.72 mmol) and 2,4-dimethoxybenzonitrile (353.8 mg, 2.17 mmol) by following **general procedure A.** Yield: 252.9 mg (0.57 mmol), 80%; *Rf*: 0.3 (40% EtOAc/hexane); yellow oil.

IR (neat): 3301, 2946, 2944, 1689 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.20 (s, 1H), 7.63 (d, 1H, *J* = 8.5 Hz), 7.26-7.35 (m, 5H), 6.59 (d, 1H, *J* = 3.0 Hz), 6.58 (dd, 1H, *J* = 2.0 Hz, *J* = 8.5 Hz), 6.51 (d, 1H, *J* = 2.0 Hz), 4.50 (d, 1H, *J* = 11.5 Hz), 4.46 (dd, 1H, *J* = 5.5 Hz, *J* = 7.0 Hz), 4.36 (d, 1H, *J* = 11.5 Hz), 3.84 (s, 3H), 3.75-3.74 (m, 6H), 3.62 (t, 2H, *J* = 6.5 Hz), 1.94-2.01 (m, 1H), 1.84-1.91 (m, 1H), 1.64-1.72 (m, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 165.5, 161.0, 157.5, 137.9, 133.9, 133.2, 130.2, 128.4, 127.9, 127.8, 112.8, 111.5, 110.3, 104.4, 98.7, 74.5, 70.3, 62.6, 55.6, 55.4, 50.8, 33.0, 28.8 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{30}NO_6$ $[M+H]^+$: 440.2073, found 44.2068.

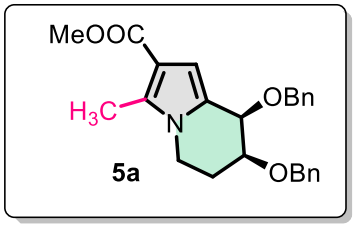
Chapter 3 – Part B: *En* Route to the Synthesis of Tetrahydroindolizines Based Scaffolds

General procedure B for Mitsunobu reaction

A solution of substituted pyrrole cycloadduct (1 mmol) in toluene (15 mL) was degassed for 15 min. To this solution, diisopropyl azadicarboxylate (DIAD) and triphenylphosphine (Ph_3P) was added at room temperature. The reaction was monitored by TLC until completion after which the solvent was evaporated under *vaco* to obtain the crude. Further the crude was purified by silica-gel column chromatography and characterized.

Compound characterization

methyl (7*S*,8*R*)-7,8-bis(benzyloxy)-3-methyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (5a):



Compound **5a** was synthesized from cycloadduct **2a** (50 mg, 0.12 mmol) by following **general procedure B.** Yield: 43.0 mg (0.11 mmol), 90%; *Rf*: 0.5 (10% EtOAc/hexane); yellow oil.

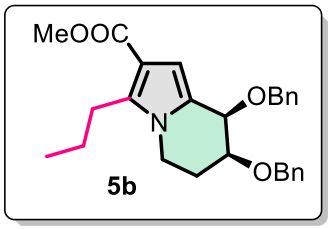
IR (neat): 3030, 2873, 2873, 1691 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.25-7.35 (m, 10 H), 6.59 (s, 1H), 4.64 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 4.49-4.54 (m, 2H), 3.97-3.99 (m, 1H), 3.81-3.87 (m, 2H), 3.80 (s, 3H), 2.49 (s, 3H), 2.40-2.46 (m, 1H), 2.09-2.14 (m, 1H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 166.0, 138.3, 138.0, 135.8, 128.4, 128.4, 127.7, 127.7, 127.6, 127.5, 125.3, 111.3, 110.8, 72.8, 71.0, 69.9, 69.9, 50.7, 38.7, 23.2, 10.8.

HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{28}NO_4$ $[M+H]^+$: 406.2018, found: 406.3533.

methyl (7S,8R)-7,8-bis(benzyloxy)-3-propyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (5b):



Compound **5b** was synthesized from cycloadduct **2b** (50 mg, 0.11 mmol) by following **general procedure B.** Yield: 44.1 mg (0.1 mmol), 92%; *Rf*: 0.5 (10% EtOAc/hexane); yellow oil.

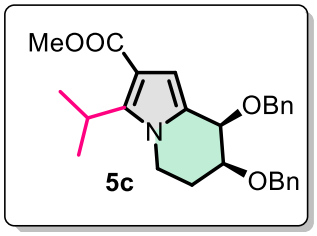
IR (neat): 3033, 2928, 2869, 1695 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.24-7.34 (m, 10H), 6.58 (s, 1H), 4.64 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.5 Hz), 4.50-4.52 (m, 2H), 3.96-3.99 (m, 1H), 388-3.90 (m, 2H), 3.79 (s, 3H), 2.85 (m, 2H), 2.38-2.45 (m, 1H), 2.06-2.11 (m, 1H), 1.55-1.60 (m, 2H), 0.98 (t, 3H, *J* = 7.5 Hz).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.8, 140.4, 138.3, 138.1, 128.4, 128.4, 127.7, 127.7, 127.5, 125.4, 111.1, 110.9, 73.1, 71.0, 70.3, 70.1, 50.6, 38.6, 26.9, 23.6, 22.5, 14.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{27}H_{32}NO_4$ $[M+H]^+$: 434.2334, found: 434.2331.

methyl (7*S*,8*R*)-7,8-bis(benzyloxy)-3-isopropyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (5c):



Compound **5c** was synthesized from cycloadduct **2c** (50 mg, 0.11 mmol) by following **general procedure B.** Yield: 43.2 mg (0.09 mmol), 95%; *Rf*: 0.5 (10% EtOAc/hexane); colorless oil.

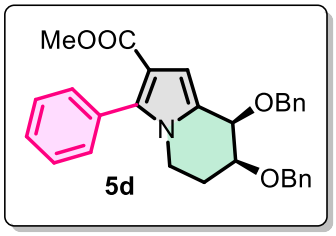
IR (neat): 2959,2927, 2876, 1694 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.25-7.35 (m, 10H), 6.58 (s, 1H), 4.64 (d, 1H, *J* = 12.0 Hz), 4.58 (d, 1H, *J* = 12.5 Hz), 4.55 (d, 1H, *J* = 12.5 Hz), 4.50-4.53 (m, 2H), 3.94-3.99 (m, 3H), 3.78-3.84 (m, 4H), 2.38-2.45 (m, 1H), 2.04-2.09 (m, 1H), 1.34-1.37 (m, 6H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.7, 144.6, 138.3, 138.1, 128.4, 128.4, 127.7, 127.7, 127.6, 125.4, 111.9, 110.5, 73.0, 70.9, 70.8, 70.2, 50.7, 40.1, 25.1, 24.1, 20.2, 20.1.

HRMS (ESI-TOF) *m/z*: calcd for $C_{27}H_{32}NO_4$ $[M+H]^+$: 434.2331, found: 434.2323.

methyl (7*S*,8*R*)-7,8-bis(benzyloxy)-3-phenyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (5d):



Compound **5d** was synthesized from cycloadduct **2d** (50 mg, 0.10 mmol) by following **general procedure B.** Yield: 44.3 mg (0.09 mmol), 95%; *Rf*: 0.5 (10% EtOAc/hexane); yellow oil.

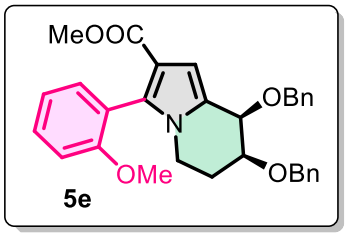
IR (neat): 3030, 2945, 2860, 1698 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.44 (m, 15H), 6.74 (s, 1H), 4.71 (d, 1H, *J* = 11.5 Hz), 4.58-4.60 (m, 4H), 3.98-4.01 (m, 1H), 3.74-3.80 (m, 1H), 3.66-3.70 (m, 1H), 3.65 (s, 3H), 2.31-2.38 (m, 1H), 1.97-2.02 (m, 1H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 165.2, 138.2, 138.1, 138.0, 131.6, 130.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.6, 126.9, 112.8, 111.4, 73.3, 71.0, 70.8, 70.4, 50.7, 40.0, 24.0.

HRMS (ESI-TOF) *m/z*: calcd for $C_{30}H_{30}NO_4$ $[M+H]^+$: 468.2175, found: 468.2176.

methyl (7*S*,8*R*)-7,8-bis(benzyloxy)-3-(2-methoxyphenyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate (5e):



Compound **5e** was synthesized from cycloadduct **2e** (50 mg, 0.09 mmol) by following **general procedure B.** Yield: 41.0 mg, 85%; *Rf:* 0.5 (10% EtOAc/hexane); colorless oil.

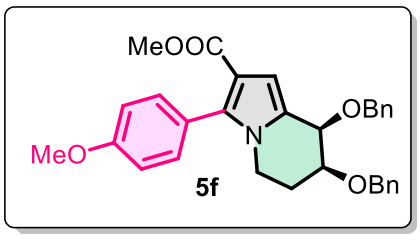
IR (neat): 3062, 3033, 2944, 1693 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.28-7.43 (m, 12H), 7.04 (td, 1H, *J* = 6.0 Hz, *J* = 10.0 Hz), 6.99 (t, 1H, *J* = 8.0 Hz) 6.77 (d, 1H, *J* = 5.0 Hz) 4.77 (d, 1H, *J* = 11.5 Hz), 4.60-4.66 (m, 4H), 4.01-4.04 (m, 1H), 3.86-3.92 (m, 1/2H), 3.75-3.79 (m, 3H), 3.68-3.71 (m, 1H), 3.66-3.68 (m, 3H), 3.55-3.60 (m, 1/2H), 2.31-2.41 (m, 1H), 1.96-2.07 (m, 1H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ= 165.2, 159.5, 138.2, 138.0, 131.7, 128.4, 127.8, 127.7, 127.6, 127.6, 126.7, 123.6, 113.4, 112.7, 111.3, 73.4, 71.0, 70.9, 70.4, 55.2, 50.7, 39.9, 24.0.

HRMS (ESI-TOF) *m/z*: calcd for $C_{31}H_{32}NO_5$ $[M+H]^+$: 498.2280, found: 498.2283.

methyl (7*S*,8*R*)-7,8-bis(benzyloxy)-3-(4-methoxyphenyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate (5f):



Compound **5f** was synthesized from cycloadduct **2f** (50 mg, 0.09 mmol) by following **general procedure B.** Yield: 47.9 mg, 87%; *Rf*: 0.5 (10% EtOAc/hexane); colorless oil.

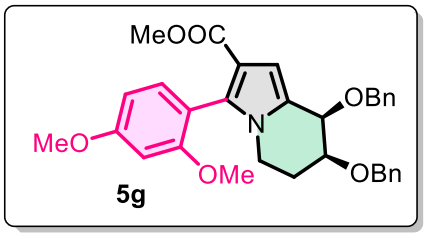
IR (neat): 3033, 2943, 2853, 1698 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.27-7.38 (m, 12H), 6.95-6..98 (m, 2H), 6.73 (s, 1H), 4.71 (d, 1H, *J* = 12.0 Hz), 4.58-4.60 (m, 4H) 3.98-4.01 (m, 1H), 3.85 (s, 3H), 3.75-3.80 (m, 1H), 3.68-3.72 (m, 1H), 3.67 (s, 3H), 32.32-2.38 (m, 1H), 1.97-2.03 (m, 1H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.2, 159.5, 138.2, 138.0, 131.7, 128.4, 127.8, 127.7, 127.6, 127.6, 126.7, 123.6, 113.4, 112.7, 111.3, 73.4, 71.0, 70.9, 70.4, 55.2, 50.7, 39.9, 24.0.

HRMS (ESI-TOF) *m/z*: calcd for $C_{31}H_{32}NO_5$ $[M+H]^+$: 498.2280, found: 498.2285.

methyl (7*S*,8*R*)-7,8-bis(benzyloxy)-3-(2,4-dimethoxyphenyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate (5g):



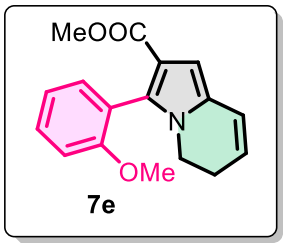
Compound **5g** was synthesized from cycloadduct **2g** (50 mg, 0.09 mmol) following **general procedure B.** Yield: 40.1 mg (0.07 mmol), 83%; *Rf:* 0.4 (10% EtOAc/hexane); yellow oil.

IR (neat): 3455, 3025, 2968, 2944, 1732 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.35 (m, 10H), 7.18 (dd, 1H, *J* = 6.0 Hz, *J* = 8.5 Hz), 6.72 (d, 1H, *J* = 5.0 Hz), 6.55 (dt, *J* = 2.5 Hz, *J* = 5.5 Hz), 6.52 (dd, 1H, *J* = 2.0 Hz, *J* = 7.0 Hz), 4.73 (d, 1H, *J* = 12.0 Hz), 4.59-4.62 (m, 4H), 3.98-4.01 (m, 1H), 3.84 (s, 3H), 3.70-3.74 (m, 3H), 3.53-3.68 (m, 5H), 2.29-2.36 (m, 1H), 1.93-2.02 (m, 1H).

HRMS (ESI-TOF) *m/z*: calcd for $C_{32}H_{34}NO_6$ $[M+H]^+$: 528.2386, found: 528.2382.

methyl 3-(2-methoxyphenyl)-5,6-dihydroindolizine-2-carboxylate (7e):



Compound **6a** was synthesized from cycloadduct **4a** (50 mg, 0.12 mmol) by following **general procedure B.** Yield: 31.0 mg (0.10 mmol), 90%; *Rf*: 0.6 (10% EtOAc/hexane); colorless oil.

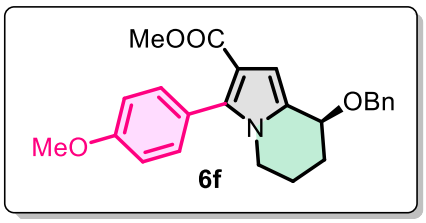
IR (neat): 2921, 2850, 1701 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.40 (t, 1H, *J* = 0.5 Hz), 7.30 (d, 1H, *J* = 6.5 Hz), 7.03 (t, 1H, *J* = 7.5 Hz), 6.97 (d, 1H, *J* = 8.0 Hz), 6.52 (s, 1H), 6.44 (d, 1H, *J* = 10 Hz), 5.78-5.82 (m, 1H), 3.71-3.77 (m, 4H), 3.59-3.63 (m, 4H), 2.38-2.41 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ= **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ= 165.1, 157.6, 135.1, 132.9, 130.2, 128.9, 120.7, 120.2, 120.1, 120.0, 113.0, 110.9, 107.3, 55.5, 50.7, 41.4, 23.9.

HRMS (ESI-TOF) *m/z*: calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287, found: 284.1283.

methyl (*S*)-8-(benzyloxy)-3-(4-methoxyphenyl)-5,6,7,8-tetrahydroindolizine-2-carboxylate (6f):



Compound **6a** was synthesized from cycloadduct **4b** (50 mg, 0.12 mmol) by following **general procedure B.** Yield: 33.4 mg, 70%; *Rf*: 0.6 (10% EtOAc/hexane); yellow oil.

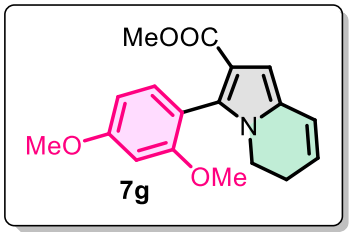
IR (neat): 2948, 2920, 1699 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.26-7.39 (m, 7H), 6.95-6.96 (m, 2H), 6.67 (s, 1H), 4.67 (d, 1H, *J* = 12 Hz), 4.56-4.59 (m, 2H), 3.84 (s, 3H), 3.77-3.81 (m, 1H), 3.66 (s, 3H), 3.49-3.55 (m, 1H), 2.23-2.2 (m, 1H), 2.16-2.21 (m, 1H), 1.84-1.91 (m, 1H), 1.77-1.81 (m, 1H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.4, 159.5, 138.6, 137.9, 131.7, 128.4, 128.4, 127.7, 127.5, 123.7, 113.5, 112.4, 109.9, 69.8, 68.7, 55.3, 50.8, 44.3, 27.4, 18.8.

HRMS (ESI-TOF) *m/z*: calcd for $C_{24}H_{26}NO_4$ $[M+H]^+$: 392.1864, found: 392.1862.

methyl 3-(2,4-dimethoxyphenyl)-5,6-dihydroindolizine-2-carboxylate (7g):



Compound **6c** was synthesized from cycloadduct **4c** (50 mg, 0.59 mmol) by following **general procedure B.** Yield: 33.1 mg (0.10 mmol), 93%; *Rf*: 0.5 (10% EtOAc/hexane); Colorless oil.

IR (neat): 2923, 2864, 1700 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, 1H, *J* = 8.8 Hz), 6.57 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.53 (d, 1H, *J* = 2.0 Hz), 6.50 (s, 1H), 6.43 (d, 1H, *J* = 10.0 Hz), 5.77-5.81 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.70-3.73 (m, 1H), 3.59-3.66 (m, 4H), 3.37-2.41 (m, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.2, 161.5, 158.7, 135.2, 133.5, 128.7, 120.6, 120.2, 112.9, 112.5, 107.2, 104.3, 98.6, 55.5, 55.4, 50.6, 41.3, 24.0 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1392, found: 313.1392.

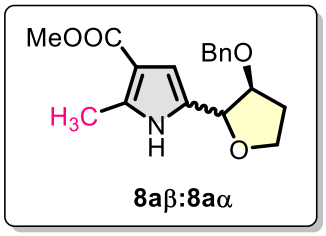
Chapter 3 – Part C: *En* route to the synthesis of C-pyrrolyl furanoside derivatives

General procedure C

The cycloadducts (1 mmol) was dissolved in 10 ml of dry dichloromethane and cooled to 0 °C. To this solution, $BF_3.OEt_2$ (0.3 mmol) was added dropwise. Further progress in the reaction was monitored by TLC and after completion, reaction was quenched with saturated bicarbonate solution. The compound was extracted using dichloromethane, it was dried over sodium sulphate, concentrate in vaco to obtain the crude. The crude is purified over silica gel chromatography to get the product.

Compound characterization

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (8aβ:8aα):



8aβ:8aα

Compound **8aβ:8aα** was synthezised from cycloadduct **2a** (50 mg, 0.12 mmol) by following **general procedure C.** Combined yield of anomers: 35.92 mg (0.11 mmol), 95%; *Rf*: 0.6 (30% EtOAc/hexane); yellow oil.

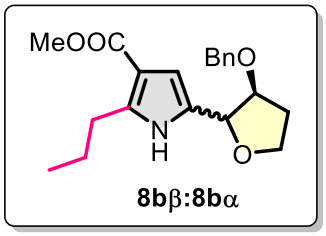
IR (neat): 3290, 2968, 2879, 1676 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.84 (s, 0.6H), 8.44 (s, 1H), 7.26-7.37 (m, 7H), 7.1-7.17 (m, 1H), 6.52 (d, 1/2H, *J* = 1.0 Hz, 3.0 Hz), 6.32 (dd, 2H, J = 0.5 Hz, 2.5 Hz), 4.93 (d, 1H, *J* = 2.5 Hz), 4.68 (d, 0.6H, J = 3.5 Hz), 4.57 (s, 2H), 4.45 (d, 1/2H, *J* = 11.5 Hz), 4.21-4.23 (m, 1H), 4.17- (d, 0.6H, *J* = 11.0 Hz), 4.10-4.15 (m, 1H), 4.01-4.06 (m, 1H), 3.96-34.00 (m, 1H), 3.87-3.91 (m, 0.6H), 3.78-3.79 (m, 5H), 2.47 (s, 3H), 2.40 (m, 1.78H), 2.21-2.26 (m, 1H), 2.07-2.12 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 166.1, 165.9, 137.8, 137.7, 136.2, 135.2, 128.8, 128.5, 127.9, 127.8, 127.7, 127.6, 125.3, 111.7, 110.8, 110.4, 106.4, 83.7, 81.1, 79.4, 77.6, 71.8, 71.6, 67.3, 66.0, 50.7, 50.7, 32.8, 32.4, 13.1(2) ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1549, found: 316.1555.

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-propyl-1*H*-pyrrole-3-carboxylate (8bβ:8bα):



8bβ:8bα

Compound **8bβ:8bα** was synthesized from cycloadduct **2a** (50 mg, 0.11 mmol) by following **general procedure C.** Combined yield of anomers: 34.98 mg (0.10 mmol), 92%; *Rf*: 0.6 (30% EtOAc/hexane); yellow oil.

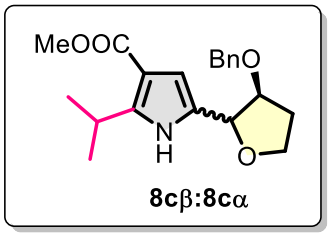
IR (neat): 3297, 2955, 2870, 1677 cm^{-1}.

***NMR data for major isomer:* ^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 8.43 (bs, 1H), 7.28-7.37 (m, 5H), 6.32 (dd, 1H, *J* = 1.0 Hz, *J* = 3.0 Hz), 4.93 (d, 1H, *J* = 2.5 Hz), 4.57 (s, 2 H), 4.22-4.24 (m, 1H), 4.02-4.07 (m, 1H), 3.95-3.99 (m, 1H), 3.78 (s, 3H), 2.81-2.92 (m, 2H), 2.07-2.12 (m, 2H), 1.59-1.66 (m, 2H), 0.94 (t, 3H, *J* = 7.0 Hz).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.7, 139.8, 137.8, 128.7, 128.5, 127.8, 127.7, 111.3, 106.4, 83.6, 79.4, 71.6, 67.2, 50.7, 32.4, 29.1, 22.6, 13.9 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{26}NO_4$ $[M+H]^+$: 344.1862, found: 344.1865.

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-isopropyl-1*H*-pyrrole-3-carboxylate (8cβ:8cα):



8cβ:8cα

Compound **8cβ:8cα** was synthesized from cycloadduct **2c** (50 mg, 0.11 mmol) by following **general procedure C.** Combined yield of anomer: 36.49 mg (0.10 mmol), 96%; *Rf*: 0.6 (30% EtOAc/hexane); yellow oil.

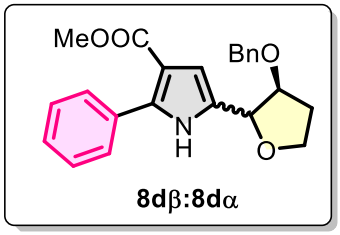
IR (neat): 3307, 3011, 2959, 1678 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.92 (s, 0.8H), 8.41 (s, 1H), 7.26-7.37 (m, 9H), 7.20-7.21 (m, 1.8H), 6.52 (d, 0.8H, *J* = 2.5 Hz), 6.32 (dd, 1H, J = 0.5 Hz, 2.5 Hz), 4.93 (d, 1H, *J* = 2.0 Hz), 4.66-4.70 (m, 1H), 4.50 (s, 2H), 4.48 (d, 0.8H, *J* = 11.5 Hz), 4.22-4.25 (m, 2H), 4.14-4.25 (m, 2H), 4.05 (dd, 1H, *J* = 8.5 Hz, 15.5 Hz), 3.95-4.00 (m, 1H), 3.88-3.92 (m, 0.9H), 3.736-3.78 (m, 6.9H), 3.65-3.71 (m, 0.9H), 2.28-2.33 (m, 0.9H), 2.18-2.25 (m, 1H), 2.0-2.1 (m, 2.5H), 1.22-1.25 (m, 8.8H), 1.11 (d, 2.9H, J = 7.0 Hz), 1.01 (d, 2.9H, J = 7.0 Hz).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.8, 165.6, 137.8, 137.7, 128.5, 128.5, 127.9, 127.8, 127.7, 127.6, 110.9, 110.1, 109.1, 106.5, 83.5, 81.0, 79.4, 77.6, 71.6, 71.4, 67.3, 65.9, 50.7, 50.6, 32.5, 32.4, 26.0, 26.0, 22.0, 21.8, 21.7, 21.5 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{26}NO_4$ $[M+H]^+$: 344.1862, found: 344.1868

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-phenyl-1*H*-pyrrole-3-carboxylate (8dβ:8dα):



8dβ:8dα

Compound **8dβ:8dα** was synthesized from cycloadduct **2d** (50 mg, 0.10 mmol) by following **general procedure C.** Combined yield of anomers: 35.83 mg (0.095 mmol), 95%; *Rf*: 0.6 (30% EtOAc/hexane); yellow oil.

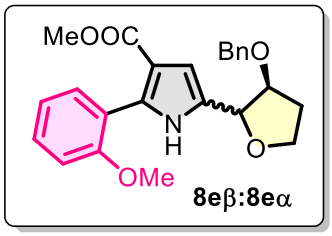
IR (neat): 3271, 3027, 2946, 1700cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.02 (s, 1H), 8.60 (s, 1H), 7.14-7.58 (m, 21H), 6.71 (d, 1H, *J* = 3.0 Hz), 6.54-6.51 (m, 1H), 5.00 (d, 1H, *J* = 2.0 Hz), 4.76 (d, 1H, *J* = 3.5 Hz), 4.61 (s, 2H), 4.32 (m, 1H), 4.25-4.28 (m, 2H), 4.18-4.23 (m, 1H), 4.13-4.18 (m, 1H), 3.99-3.40 (m, 2H), 3.91-3.95 (m, 1H), 3.74 (d, 6H, *J* = 2.5 Hz), 2.20-2.33 (m, 2H), 2.09-2.13 (m, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.4, 165.2, 137.8, 137.8, 137.5, 136.7, 132.0, 131.9, 130.9, 128.8, 128.7, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.7, 112.2, 112.1, 110.9, 108.0, 83.9, 81.1, 79.4, 77.5, 71.8, 71.6, 67.5, 66.1, 50.9, 50.9, 32.5, 32.4 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{23}H_{24}NO_4$ $[M+H]^+$: 378.1705, found: 378.1726.

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-(2-methoxyphenyl)-1H-pyrrole-3-carboxylate (8eβ:8eα):



Compound **8eβ:8eα** was synthesized from cycloadduct **2e** (50 mg, 0.091 mmol) by following **general procedure C.** Combined yield of anomers: 37.12 mg (0.091 mmol), 94%; *Rf*: 0.4 (30% EtOAc/hexane); yellow oil.

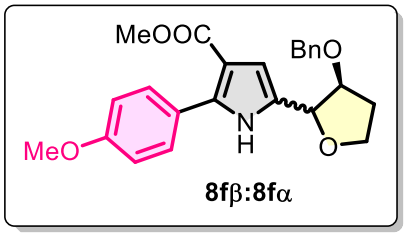
IR (neat): 3288, 2924, 2914, 1693 cm^{-1}.

NMR data for minor isomer: **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 9.45 (bs, 1H), 7.54 (dd, 1H, *J* = 2.0 Hz, *J* = 7.5 Hz), 7.30-7.34 (m, 1H), 7.21-7.24 (m, 3H), 7.16-7.17 (m, 2H), 6.99 (td, 1H, *J* = 1.0 Hz, *J* = 7.5 Hz), 6.91-6.93 (m, 1H), 6.72 (d, 1H, *J* = 2.5 Hz), 4.79 (d, 1H, *J* = 3.5 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.34 (d, 1H, *J* = 12.0 Hz), 4.15-4.19 (m, 2H), 391-3.96 (m, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 2.23-2.27 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.6, 156.6, 137.9, 132.1, 129.5, 128.4, 127.6, 127.5, 120.2, 111.3, 110.8, 80.7, 77.7, 71.6, 66.1, 55.4, 50.8, 32.8 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{24}H_{26}NO_5$ $[M+H]^+$: 408.1811, found: 408.1815.

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (8fβ:8fα)



Compound **8fβ:8fα** was synthesized from cycloadduct **2f** (50 mg, 0.097 mmol) by following **general procedure C.** Combined yield of anomers: 37.12 mg (0.091 mmol), 94%; *Rf*: 0.4 (30% EtOAc/hexane); yellow oil.

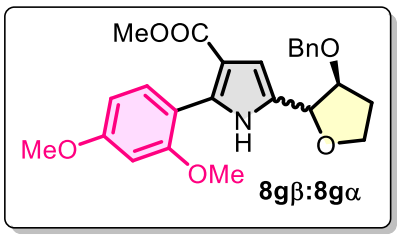
IR (neat): 3290, 3005, 2946, 1699 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.07 (bs, 0.6H), 8.72 (bs, 1H), 7.76-7.78 (m, 0.6H), 7.51-7.52 (m, 2H), 7.32-7.38 (m, 8.6H), 7.17-7.19 (m, 1.5H), 6.92-6.96 (m, 2.36H) 6.83-6.86 (m, 1.5H), 6.71 (d, 0.6H, *J* = 3.0 Hz), 6.51 (dd, 1H, *J* = 0.5 Hz, *J* = 2.5 Hz), 5.01 (d, 1H, *J* = 2.0 Hz), 4.77 (d, 0.6H, *J* = 3.5 Hz), 4.46 (d, 0.6H, *J* = 5.5 Hz), 4.62 (s, 2H), 4.52 (d, 0.7H, *J* = 11.0 Hz), 4.29-4.31 (m, 1H), 4.26 (m, 0.7H), 4.15-4.18 (m, 1H), 4.04-4.09 (m, 1H), 3.99-4.03 (m, 1H), 3.92-3.96 (m, 0.7), 3.84-3.85 (m, 5.8H), 3.76-3.77 (m, 4.9H), 2.22-2.34 (m, 1.6H), 2.09-2.19 (m, 2.5H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.5, 165.3, 159.6, 159.4, 137.9, 137.7, 137.5, 137.0, 130.3, 130.1, 130.0, 128.7, 128.5, 127.9, 127.8, 127.7, 127.7, 127.5, 126.9, 124.5, 124.3, 113.7, 113.5, 113.4, 112.0, 111.3, 110.2, 107.8, 83.7, 81.1, 79.3, 77.5, 71.7, 71.6, 67.3, 66.1, 55.3, 50.9, 50.8, 32.5, 32.3 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{24}H_{26}NO_5$ $[M+H]^+$: 408.1811, found: 408.1813.

methyl (S)-5-(3-(benzyloxy)tetrahydrofuran-2-yl)-2-(2,4-dimethoxyphenyl)-1*H*-pyrrole-3-carboxylate (8gβ:8gα):



8gβ:8gα

Compound **8gβ:8gα** was synthesized from cycloadduct **2g** (50 mg, 0.091 mmol) by following **general procedure C.** Combined yield of anomers: 36.99 mg (0.084 mmol), 93%; *Rf*: 0.5 (40% EtOAc/hexane); yellow oil.

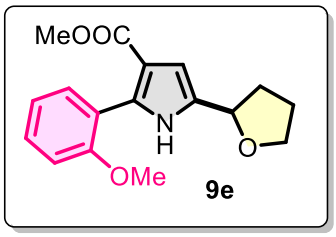
IR (neat): 3317, 3010, 2945, 1737 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.41 (s, 1/2H), 8.98 (s, 1H), 7.55 (d, 1H, *J* = 8.5 Hz), 7.49 (d, 0.67H, J = 8.5 Hz), 7.26-7.36 (m, 5H), 7.21-7.22 (m, 2H), 7.15-7.15 (m, 1H), 6.68 (d, 1/2H, *J* = 3.0Hz), 6.45-6.56 (m, 4H), 5.02 (d, 1H, J = 1.0 Hz), 4.74 (d, 1/2H, *J* = 3.5 Hz), 4.62 (d, 1H, *J* = 12.0 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1/2H, *J* = 12.0 Hz), 4.30 (d, 1/2H, *J* = 12.0 Hz), 4.28-4.31 (m, 1H), 4.11-4.17 (m, 1.6H), 4.04-4.09 (m, 1H), 3.97-4.01 (m, 1H), 3.88-3.92 (m, 1H), 3.88 (d, 5H, J = 2.0 Hz), 3.78 (s, 3H), 3.72 (d, 5H, J = 2.0 Hz),

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.6, 165.4, 161.0, 160.8, 157.8, 157.6, 137.9, 137.8, 134.3, 133.2, 133.0, 132.9, 129.8, 128.5, 128.3, 127.8, 127.7, 127.6, 127.4, 126.4, 113.4, 112.9, 112.3, 111.5, 111.2, 107.1, 104.3, 104.1, 98.7, 98.5, 83.9, 80.7, 79.4, 77.7, 71.6, 71.6, 67.3, 66.1, 55.6, 55.4, 55.4, 55.3, 50.8, 50.7, 32.8, 32.4 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{25}H_{28}NO_6$ $[M+H]^+$: 438.1917, found: 438.1915.

methyl 2-(2-methoxyphenyl)-5-(tetrahydrofuran-2-yl)-1*H*-pyrrole-3-carboxylate (9e):



9e

Compound **9e** was synthesized from cycloadduct **4e** (50 mg, 0.12 mmol) by following **general procedure C.** Yield of enantiomeric mixture: 34.53 mg (0.11 mmol) 94%; *Rf*: 0.5 (30% EtOAc/hexane); yellow oil.

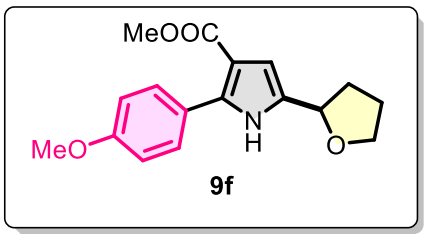
IR (neat): 3263, 2947, 2944, 1691 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 7.58 (dd, 1H, *J* = 1.5Hz, 7.5 Hz), 7.29-7.33 (m, 1H), 6.99 (td, 1H, *J*= 1.0 Hz, 7.5 Hz), 6.95 (d, 1H, *J* = 8.0 Hz), 6.51 (dd, 1H, *J* = 0.5 Hz. 3.0 Hz), 4.99 (t, 1H, *J* = 6.5), 3.88-3.91 (m, 1H), 3.82-3.87 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 2.22-2.29 (m, 1H), 2.02-2.09 (m, 1H), 1.96-2.03 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.5, 156.5, 132.9, 132.3, 132.2, 129.5, 120.4, 120.3, 112.6, 111.0, 107.4, 74.2, 68.0, 55.6, 50.8, 31.6, 25.7 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$: 302.1392, found: 302.1396.

methyl 2-(4-methoxyphenyl)-5-(tetrahydrofuran-2-yl)-1*H*-pyrrole-3-carboxylate (9f):



9f

Compound **9f** was synthesized from cycloadduct **4f** (50 mg, 0.12 mmol) by following **general procedure C.** Yield of enantiomeric mixture: 34.89 mg (0.11 mmol), 95%; *Rf*: 0.5 (30% EtOAc/hexane); yellow oil.

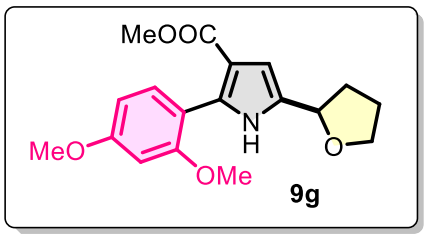
IR (neat): 3273, 2948, 2944, 1690 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.60 (s, 1H), 7.51-7.53(m, 2H), 6.92-6.94 (m, 2H), 6.50 (dd, 1H, *J*= 1.0 Hz, 3.0 Hz), 4.95 (t, 1H, J = 6.0 Hz), 3.89-3.93 (m, 1H), 3.85-3.88 (m, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 2.24-2.30 (m, 1H), 2.04-2.08 (m, 1H), 1.97-2.03 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 209.6, 151.7, 138.4, 137.6, 128.6, 128.4, 128.3, 128.1, 127.7, 127.5, 127.3, 125.9, 124.5, 118.7, 109.3, 83.9, 80.1, 73.9, 73.0, 72.3, 70.8, 66.4, 54.2, 52.5, 37.1 ppm.

HRMS (ESI-TOF) *m/z*: calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$: 302.1392, found: 302.1396.

methyl 2-(2,4-dimethoxyphenyl)-5-(tetrahydrofuran-2-yl)-1*H*-pyrrole-3-carboxylate (9g):



9g

Compound **9g** was synthesized from cycloadduct **4g** (50 mg, 0.11 mmol) by following **general procedure A.** Yield of enantiomeric mixture: 34.79 mg (0.10 mmol), 93%; *Rf*: 0.4 (30% EtOAc/hexane); yellow oil.

IR (neat): 3271, 2947, 2944, 1698 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 9.00 (bs, 1H), 7.55 (d, 1H, *J* = 8.5 Hz), 6.54 (dd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz), 6.51 (d, 1H, *J* = 2.0 Hz), 6.49 (dd, 1H, *J* = 1.0 Hz, *J* = 3.0 Hz), 4.96 (t, 1H, *J* = 6.0 Hz), 3.84-3.92 (m, 2H), 3.83 (s, 3H), 3.79 (m, 3H), 3.71 (m, 3H), 2.23-2.28 (m, 1H), 2.03-2.09 (m, 1H), 1.94-2.02 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 165.5, 160.9, 157.7, 133.2, 133.0, 131.9, 113.1, 112.0, 107.3, 104.3, 98.7, 74.2, 68.0, 55.6, 55.4, 50.8, 31.5, 25.7 ppm.

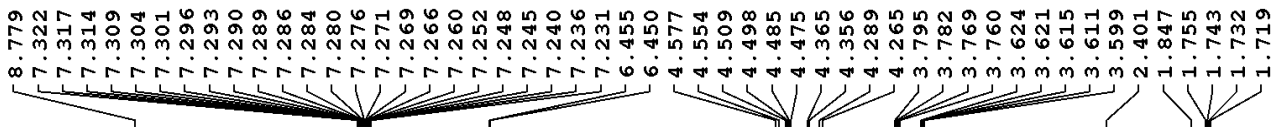
HRMS (ESI-TOF) *m/z*: calcd for $C_{18}H_{22}NO_5$ $[M+H]^+$: 332.1498, found: 332.1498.

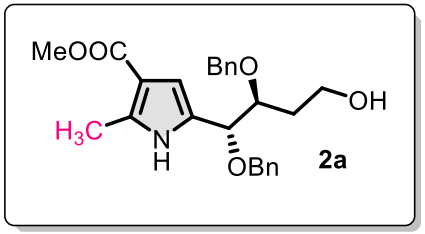
Compound Characterization: ^{1}H, ^{13}C, DEPT 135 NMR data

Chapter 3 – Part A: **(3+2) Cycloaddition Reaction of Spirocyclopropane carboxylated sugars and nitriles: Synthesis of Highly Functionalized Pyrrole Derivatives.**

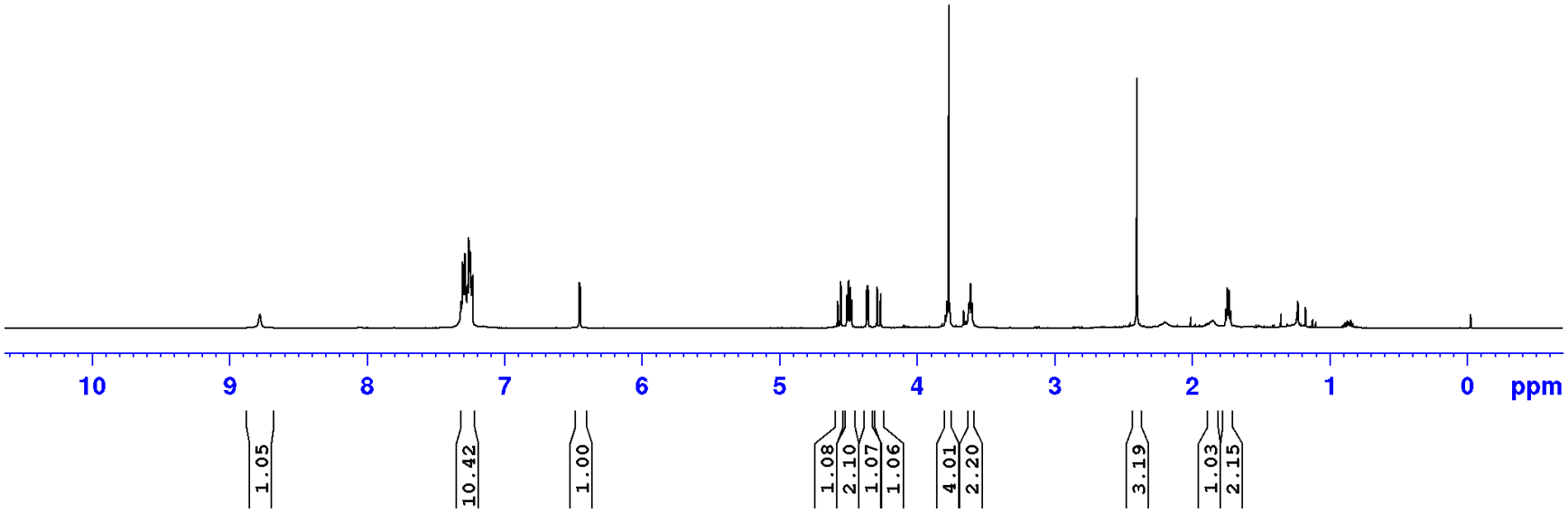
Chapter 3 – Part B: **Post-synthetic transformations: En route to the synthesis of indolizidines based scaffolds.**

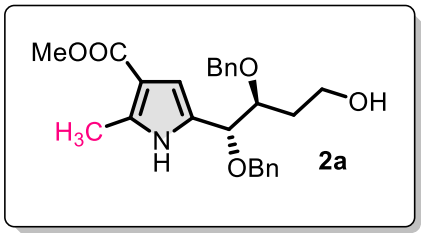
Chapter 3 – Part C: **Post-synthetic transformations: En route to the synthesis of C-pyrrolyl furanoside derivatives.**



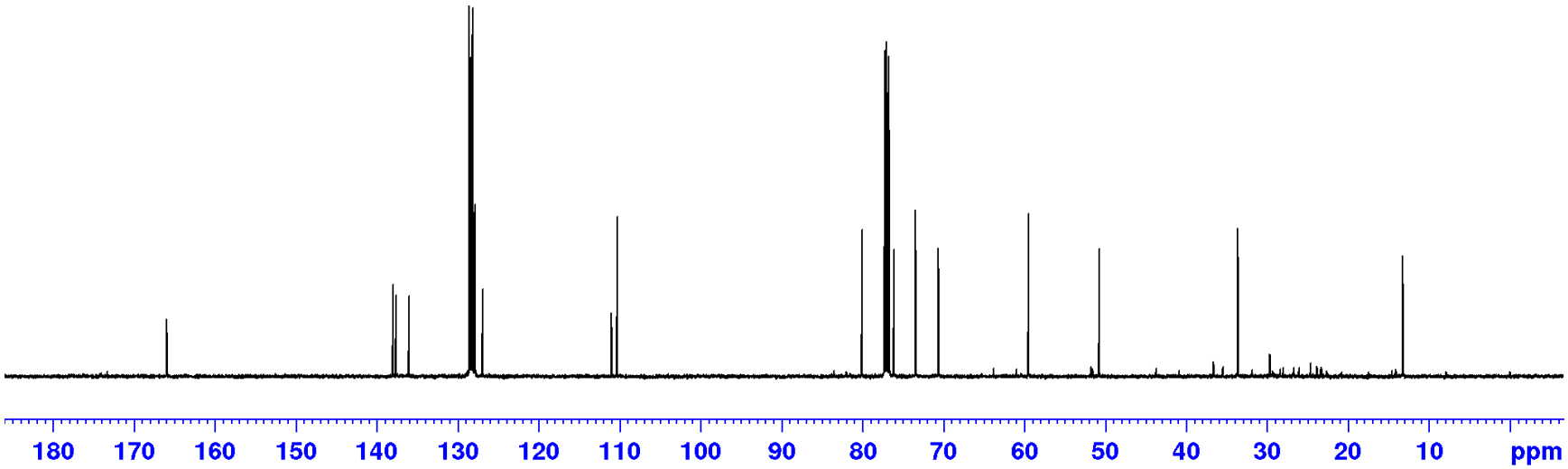


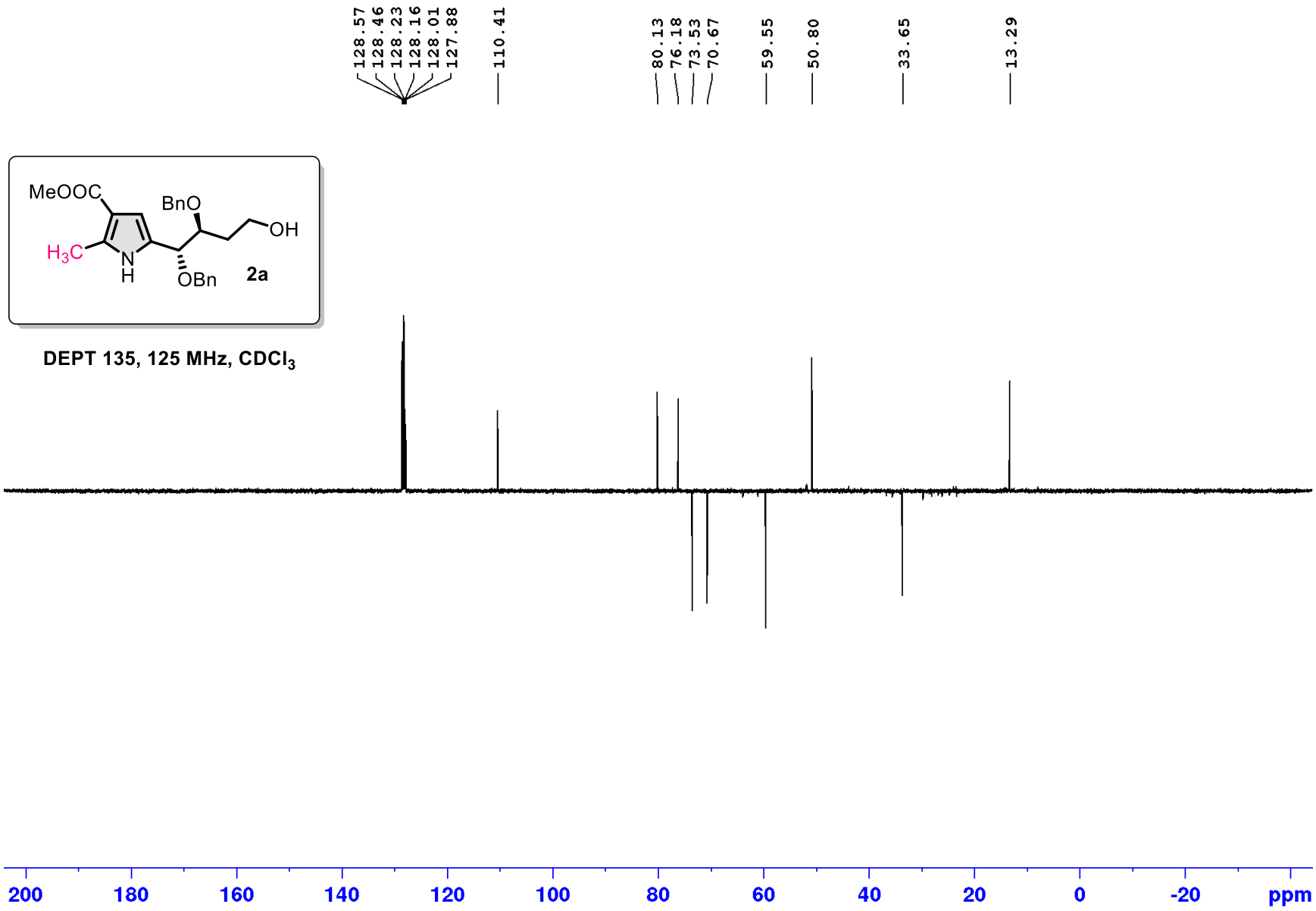
^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$

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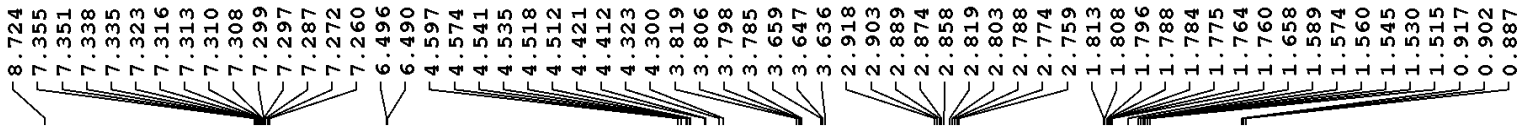
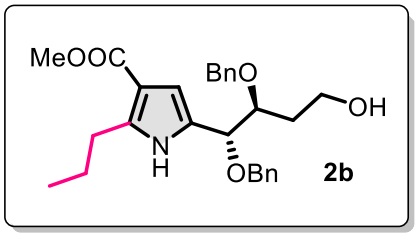
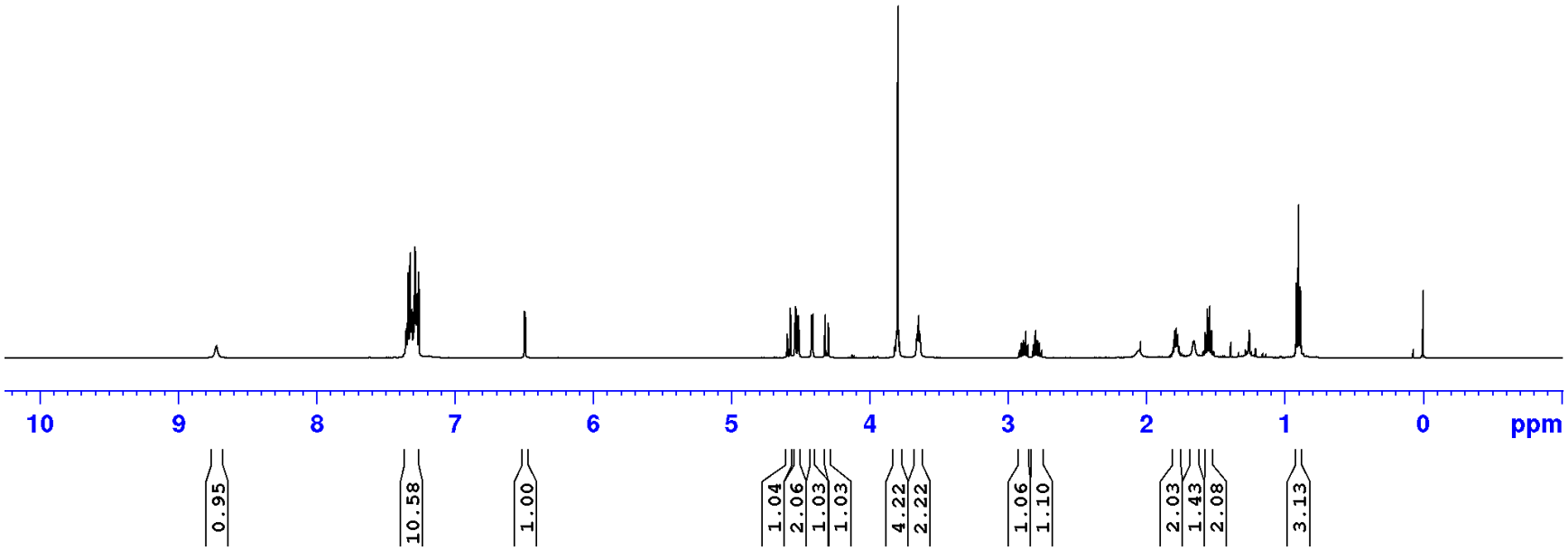
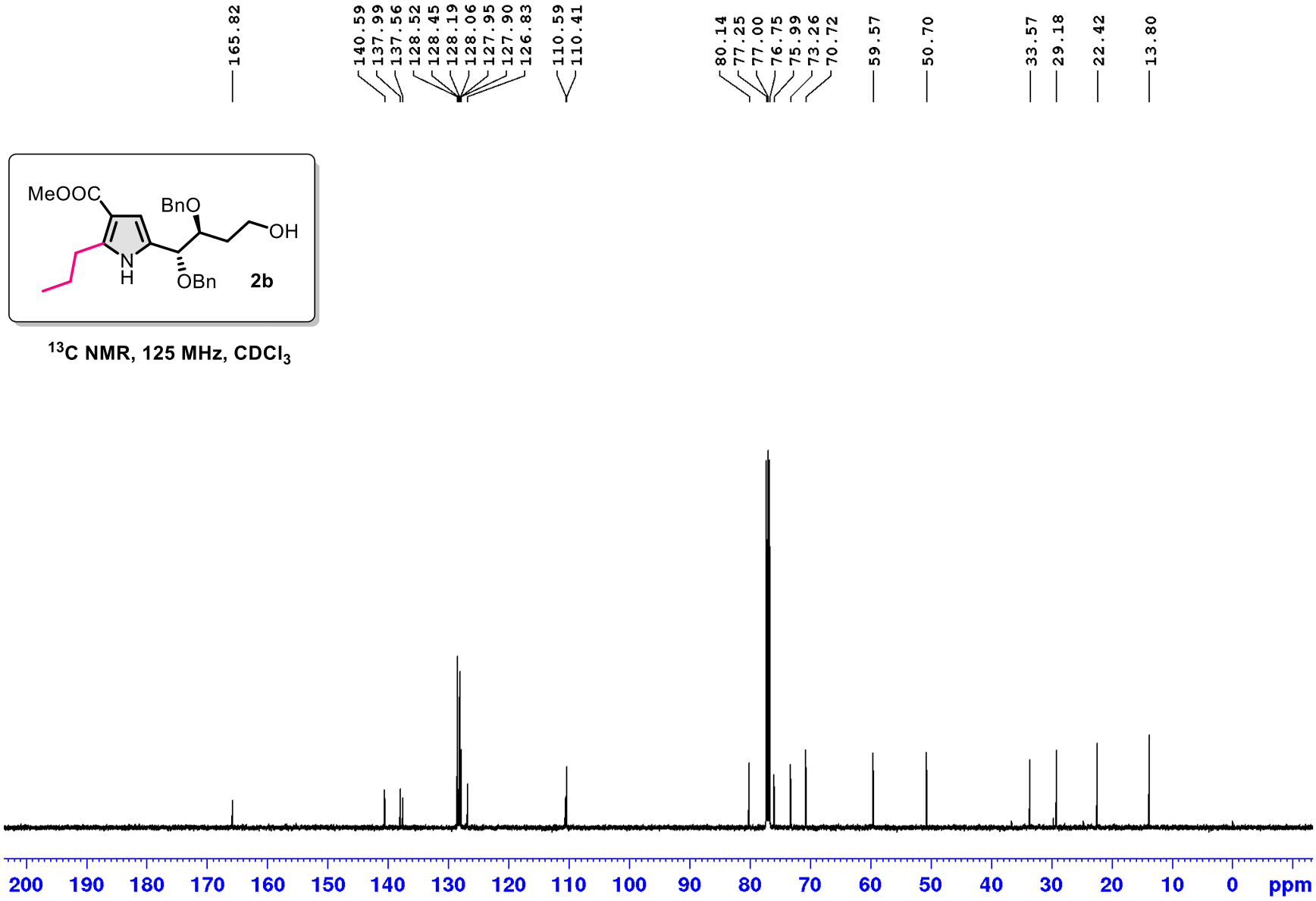
128.16
128.01
127.88
110.41
80.13
76.18
73.53
70.67
59.55
50.80
33.65
13.29
MeOOC
BnO
OH
H3C
N
H
OBn
2a
DEPT 135, 125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



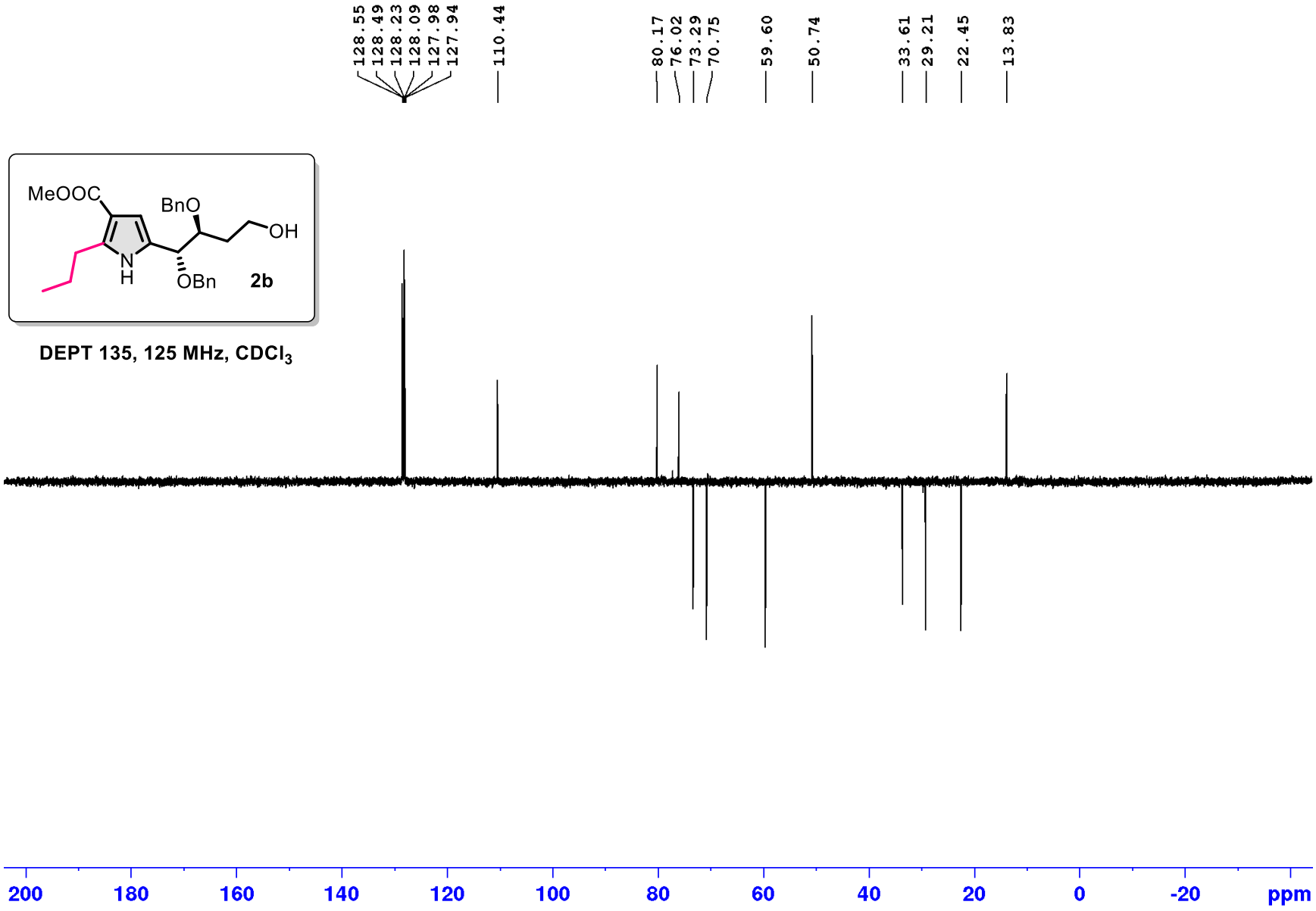


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$


128.55
128.49
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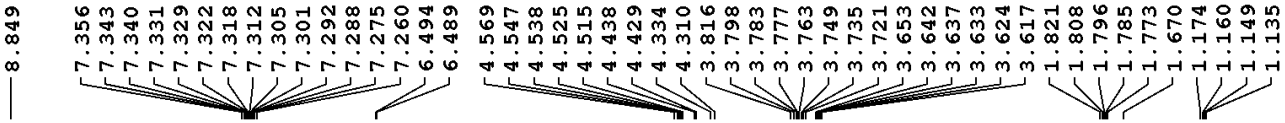
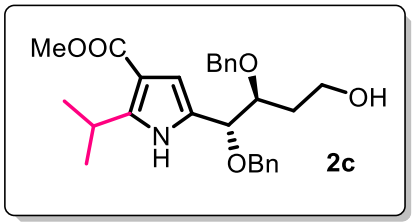
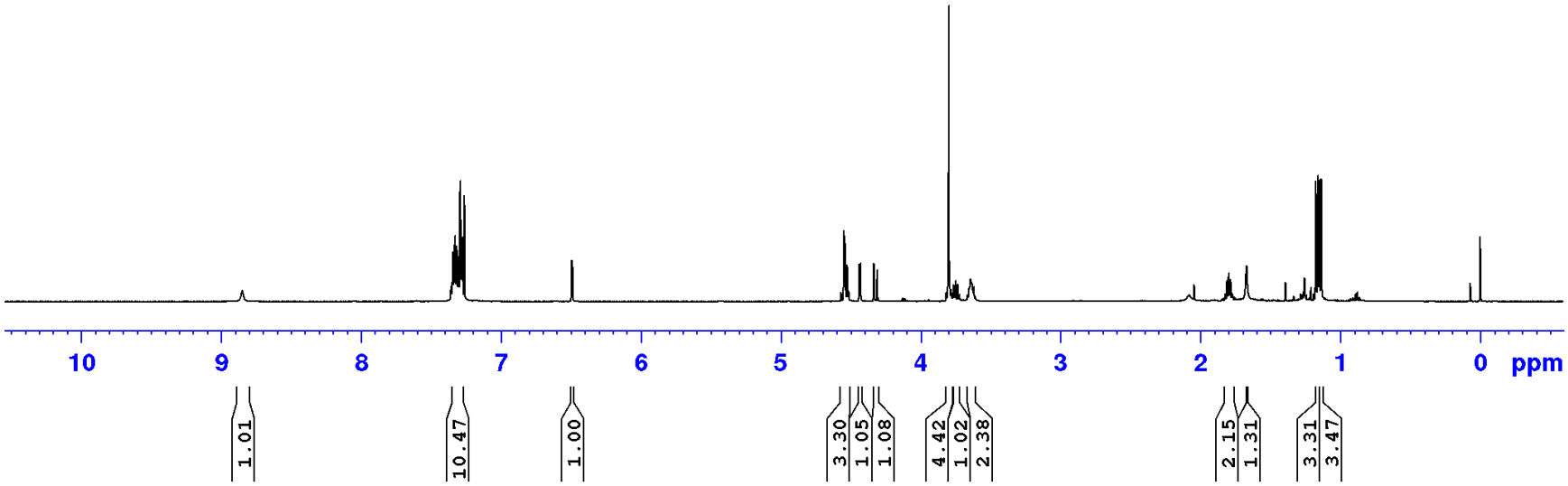
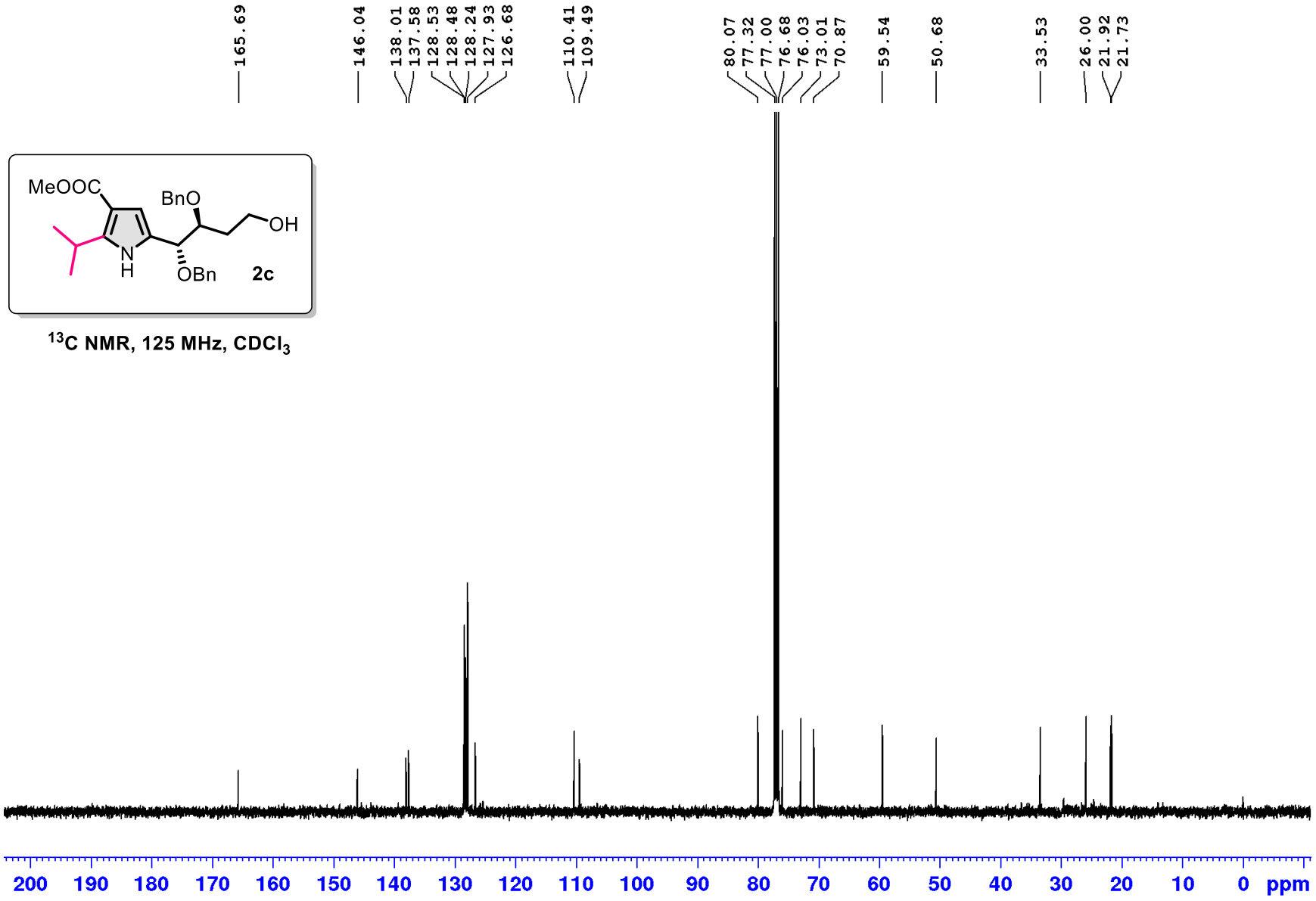
128.09
127.98
127.94
110.44
80.17
76.02
73.29
70.75
59.60
50.74
33.61
29.21
22.45
13.83
MeOOC
BnO
OH
N
H
OBn
2b
DEPT 135, 125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



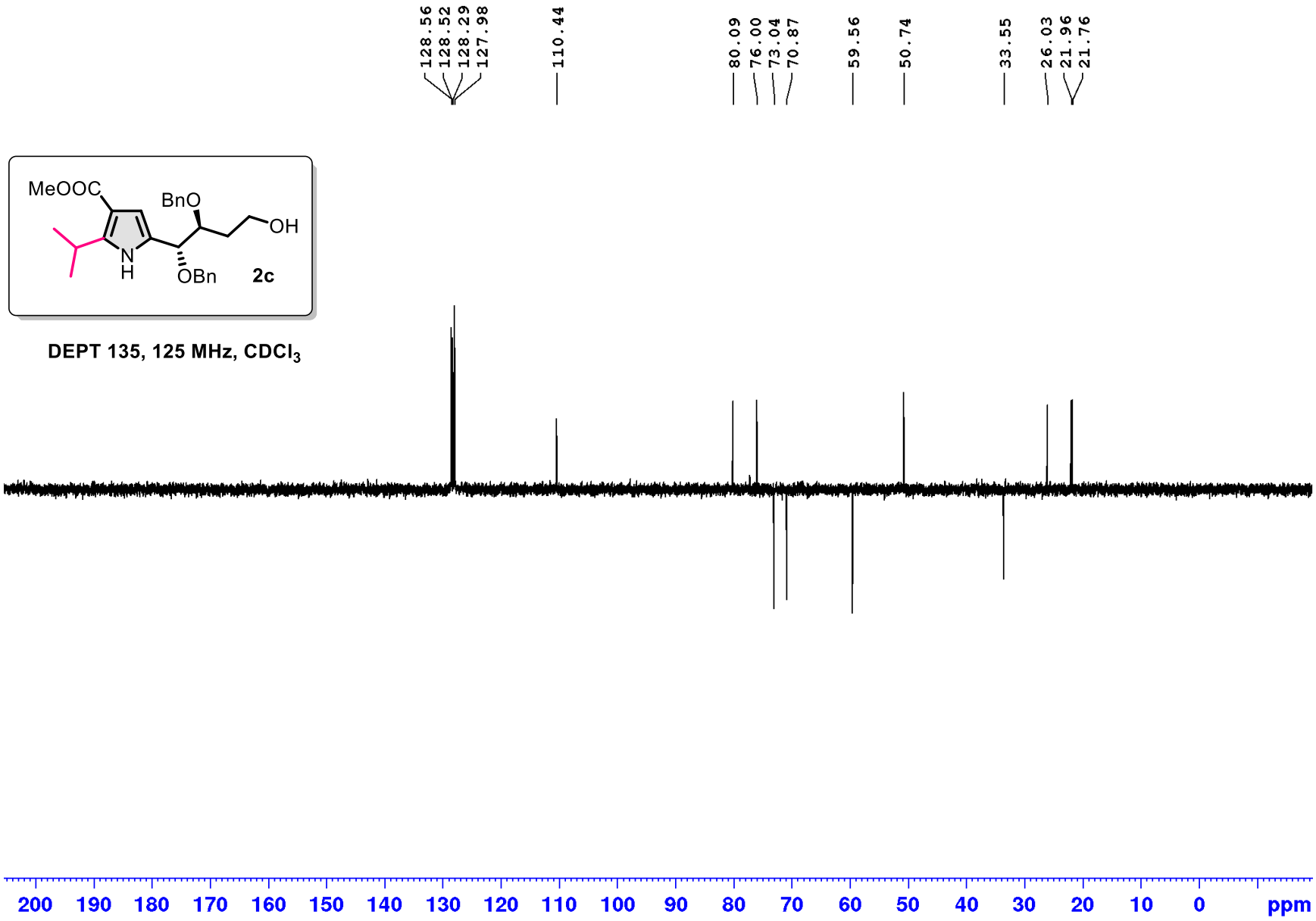


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$


128.56
128.52
128.29
127.98
110.44
80.09
76.00
73.04
70.87
59.56
50.74
33.55
26.03
21.96
21.76
MeOOC
BnO
OH
N
H
OBn
2c
DEPT 135, 125 MHz, CDCl3
200
190
180
170
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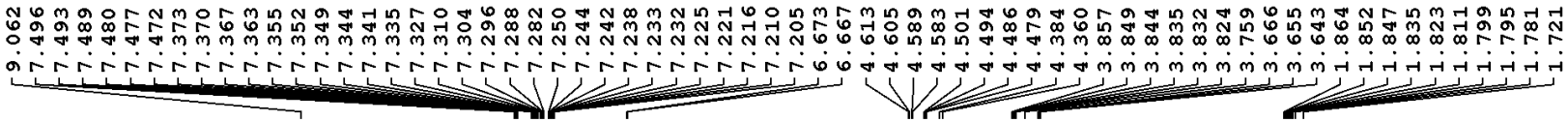
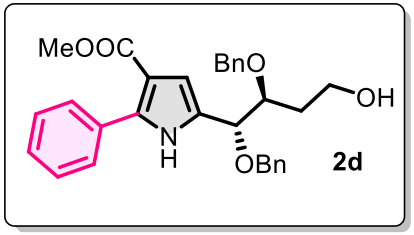
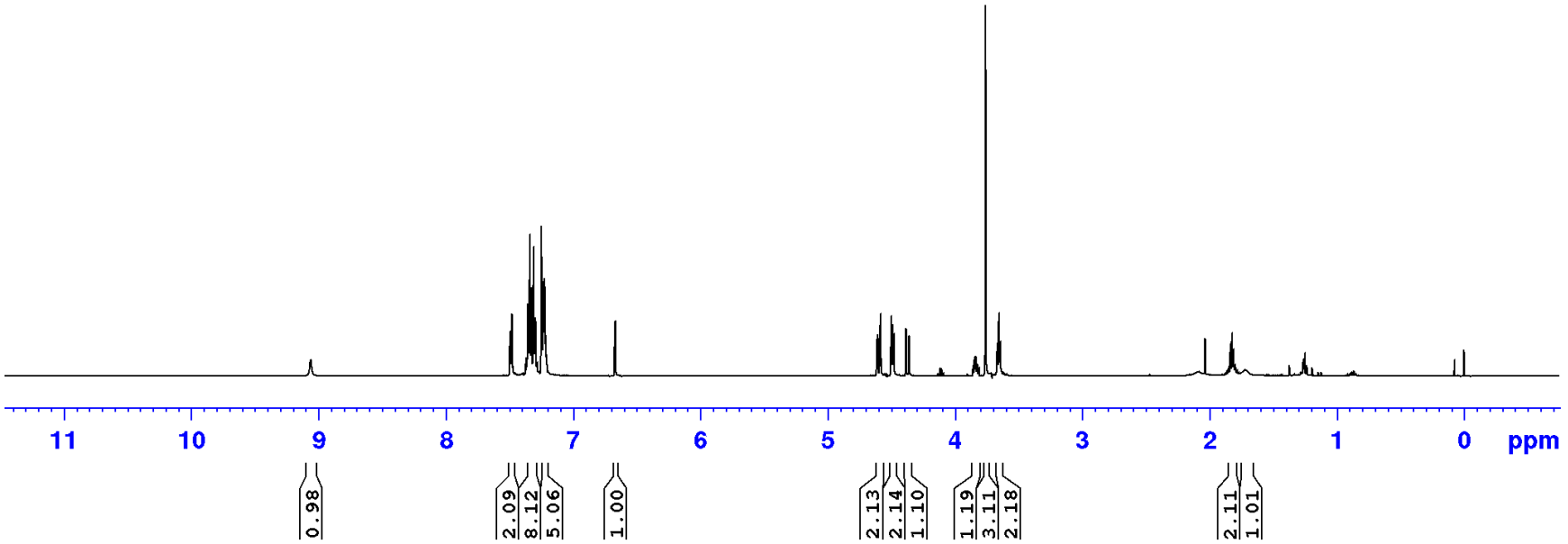
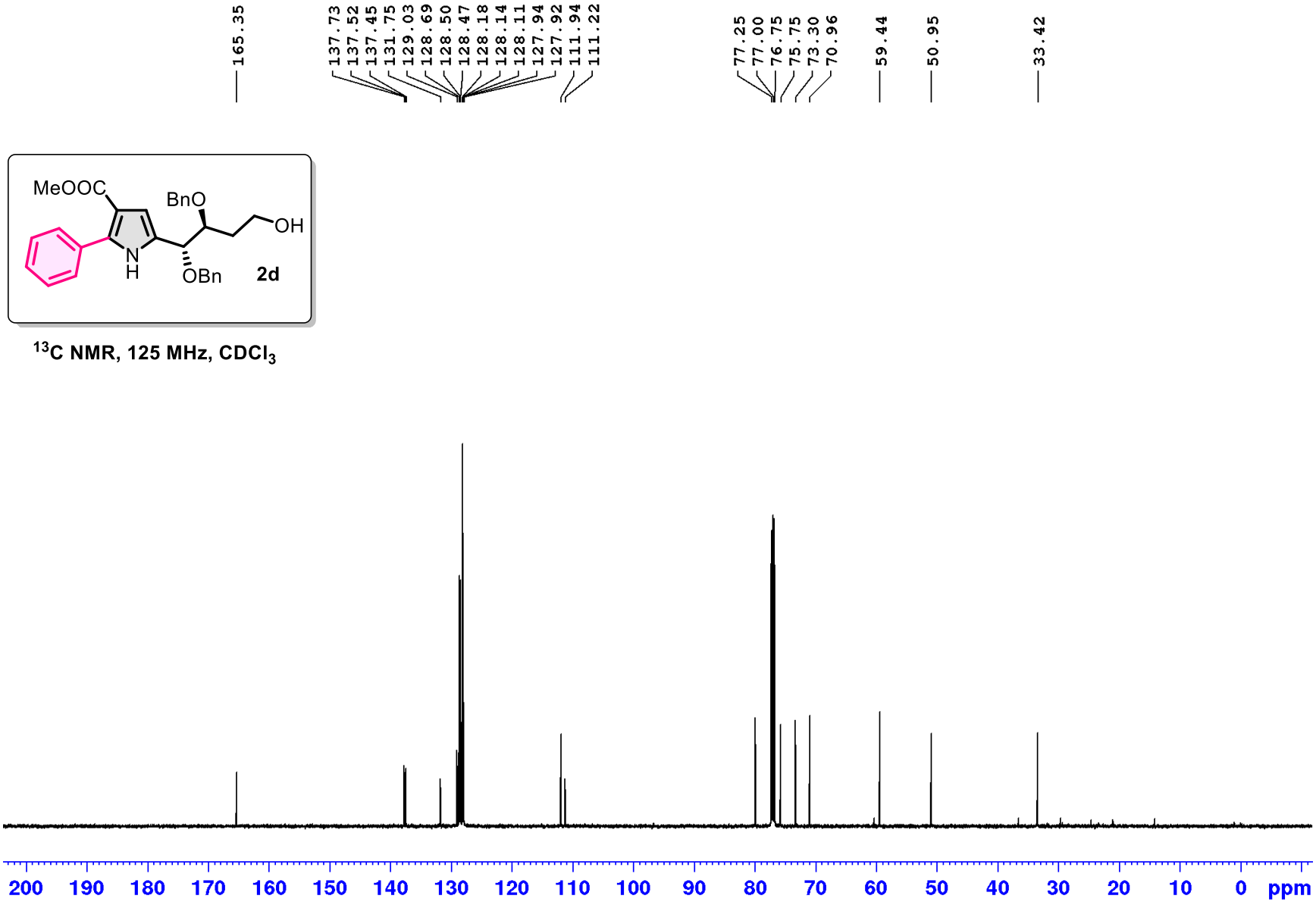
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



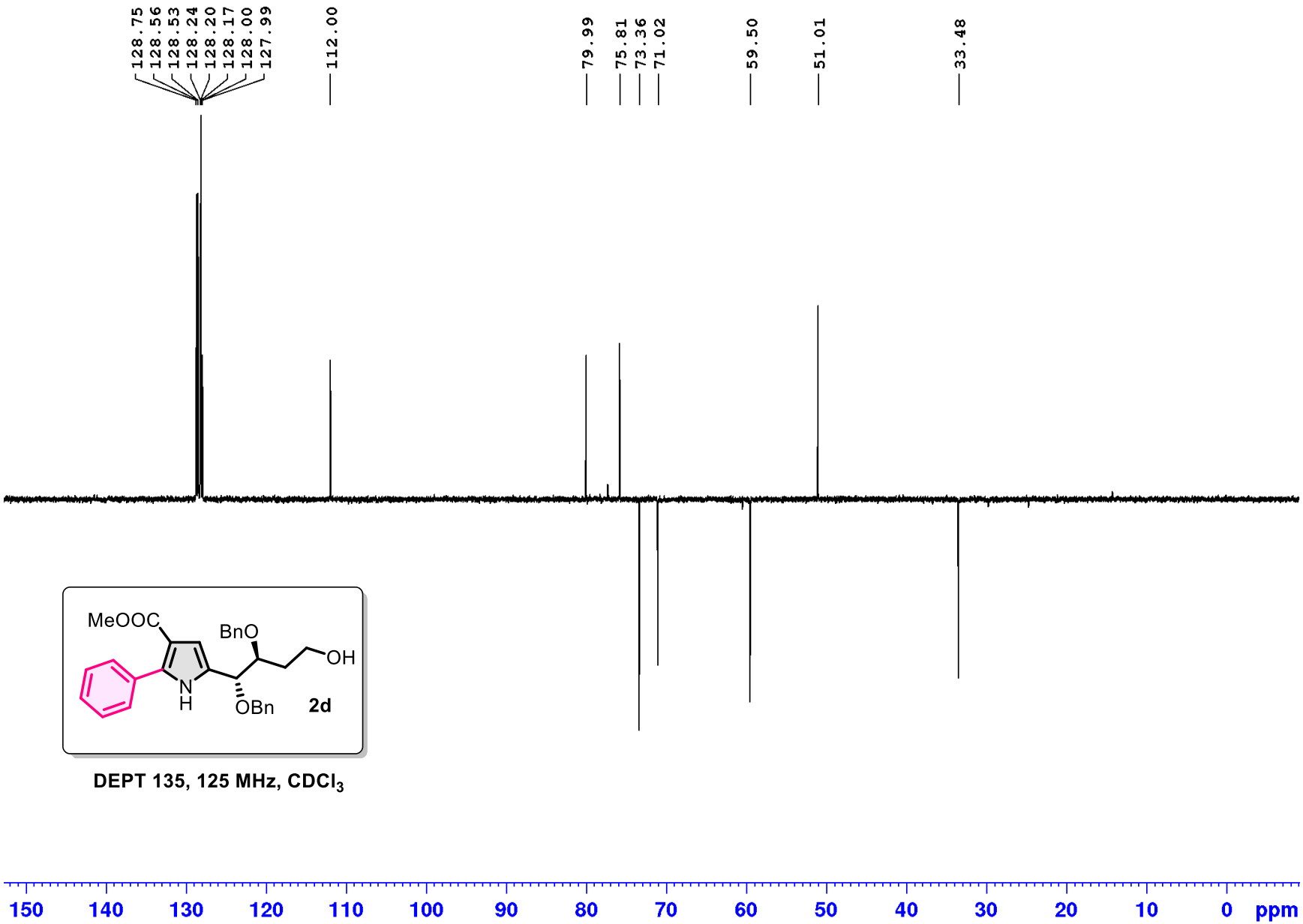


^{1}H NMR, 500 MHz, $CDCl_3$

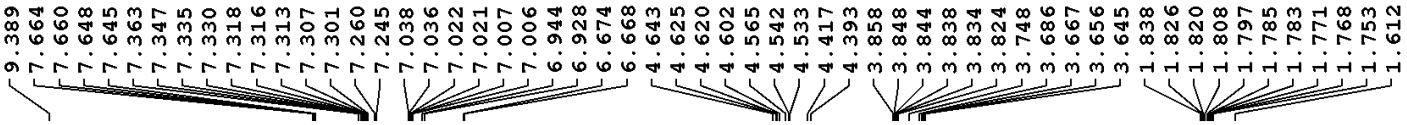


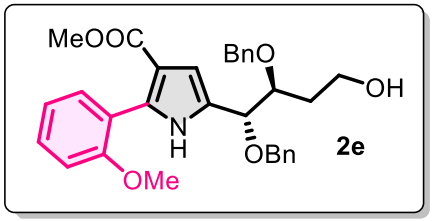


^{13}C NMR, 125 MHz, $CDCl_3$

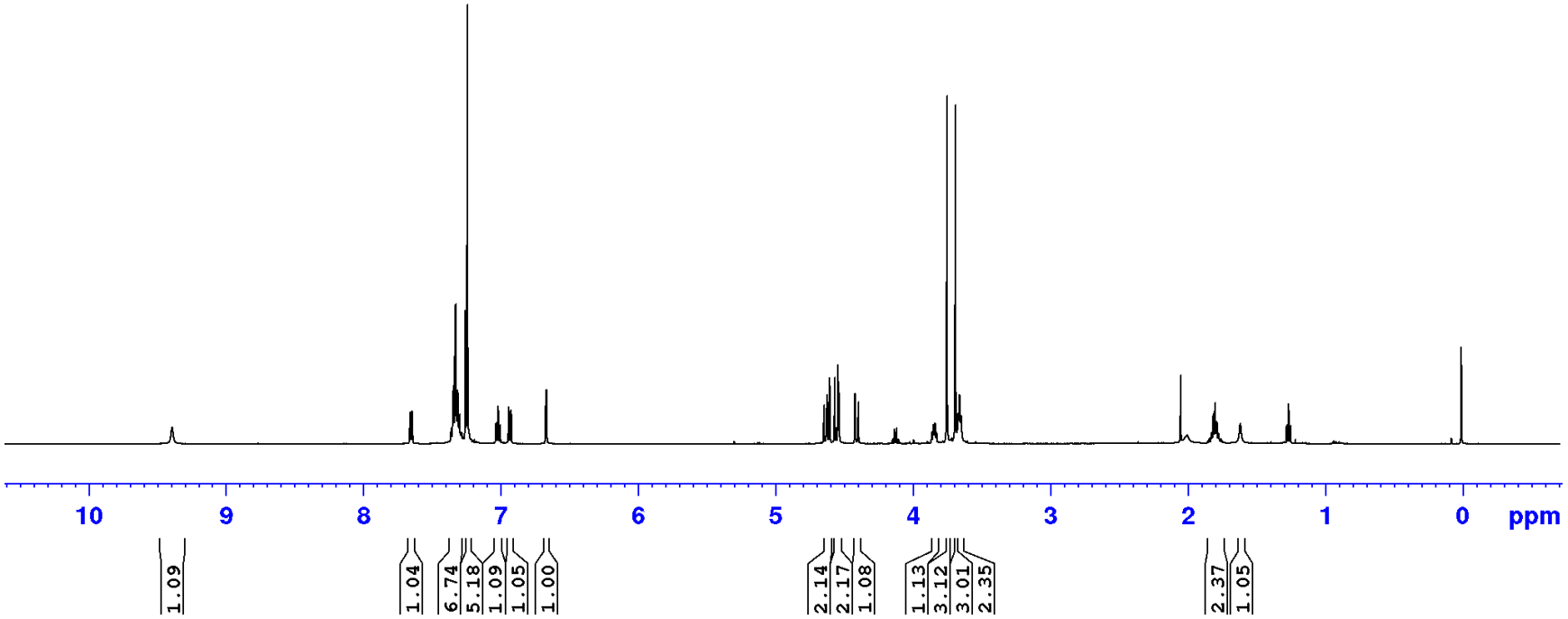


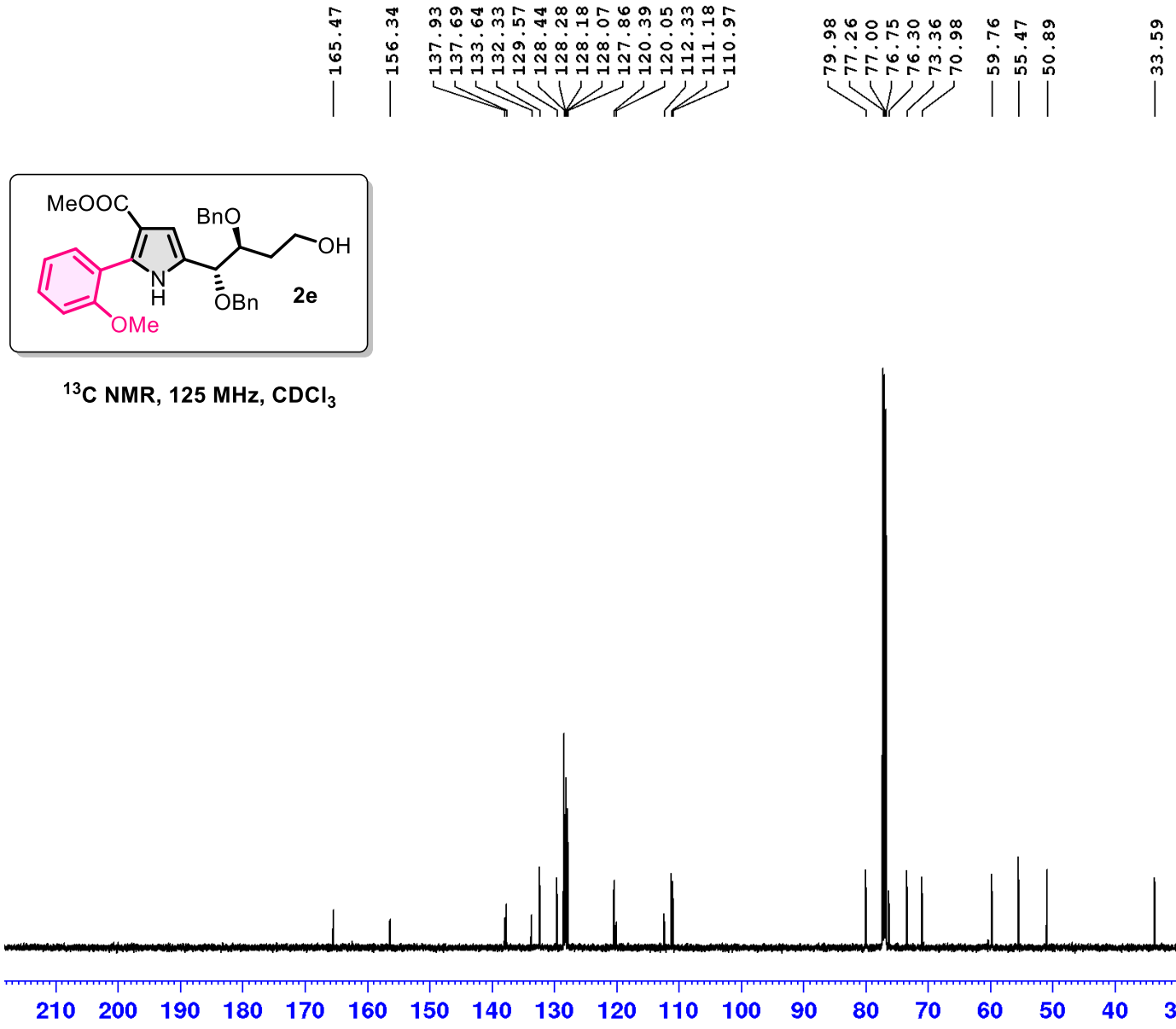
DEPT 135, 125 MHz, $CDCl_3$



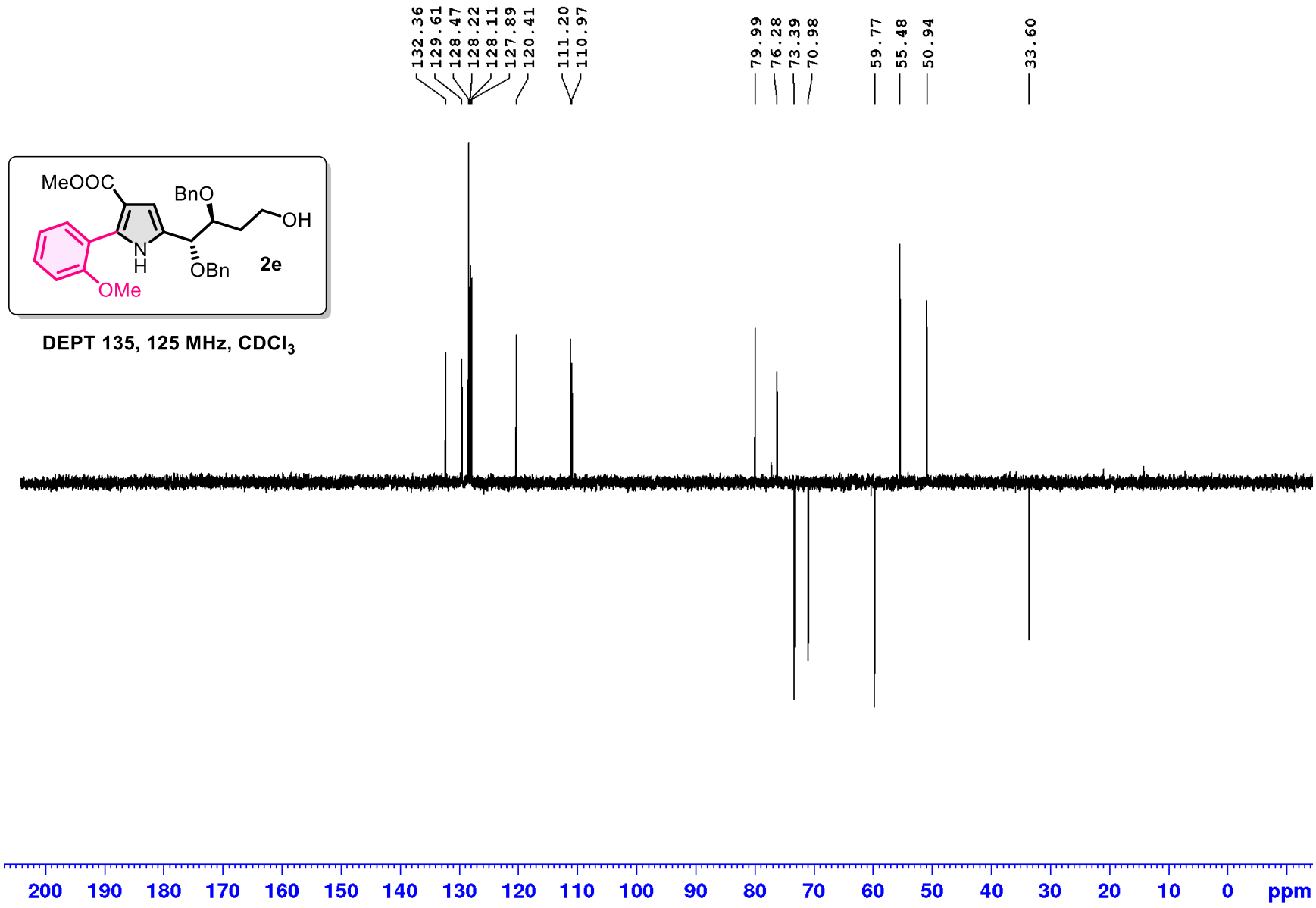


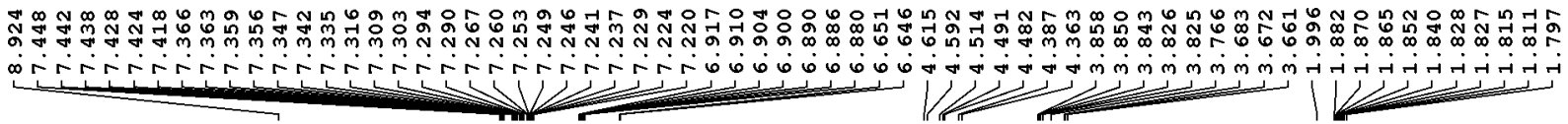
^{1}H NMR, 500 MHz, $CDCl_3$

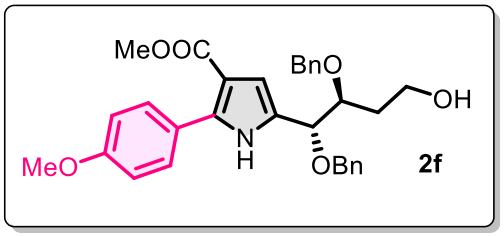




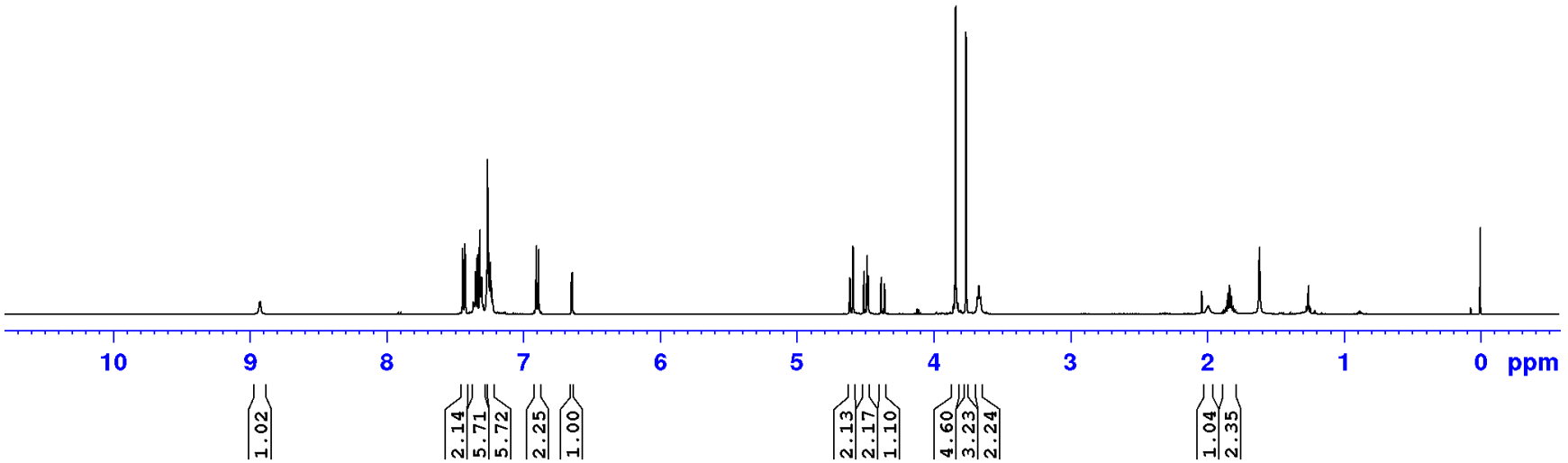
^{13}C NMR, 125 MHz, $CDCl_3$

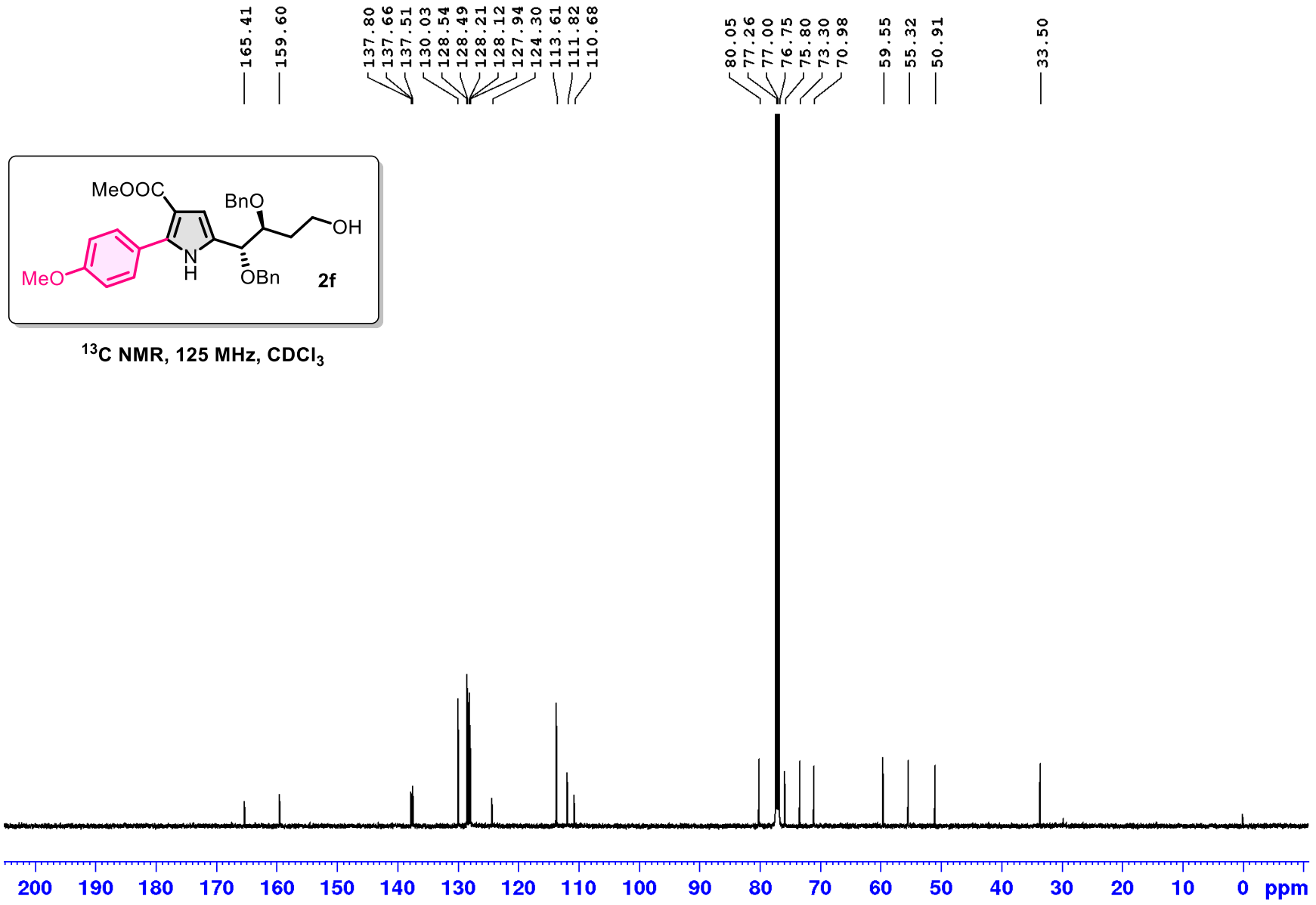

132.36
129.61
128.47
128.22
128.11
127.89
120.41
111.20
110.97
79.99
76.28
73.39
70.98
59.77
55.48
50.94
33.60
MeOOC
BnO
OH
N
H
OBn
OMe
2e
DEPT 135, 125 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



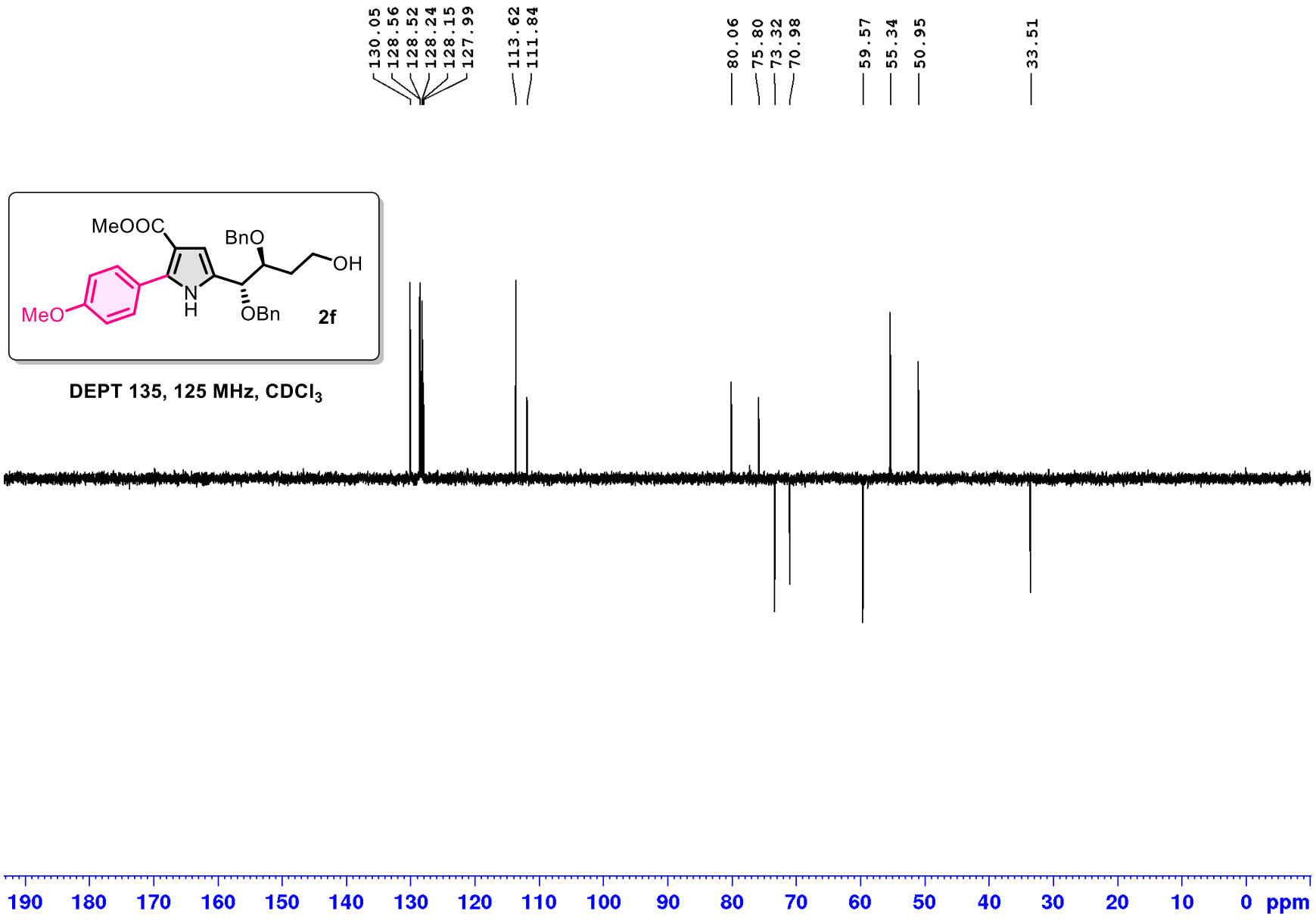


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$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128.56
128.52
128.24
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127.99
113.62
111.84
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75.80
73.32
70.98
59.57
55.34
50.95
33.51
MeOOC
BnO
OH
N
H
MeO
OBn
2f
DEPT 135, 125 MHz, CDCl3
190
180
170
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140
130
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100
90
80
70
60
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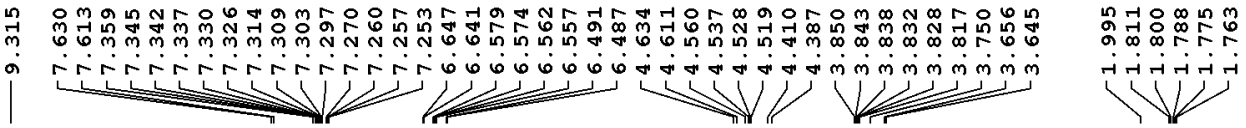
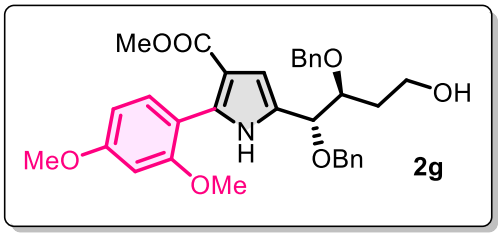
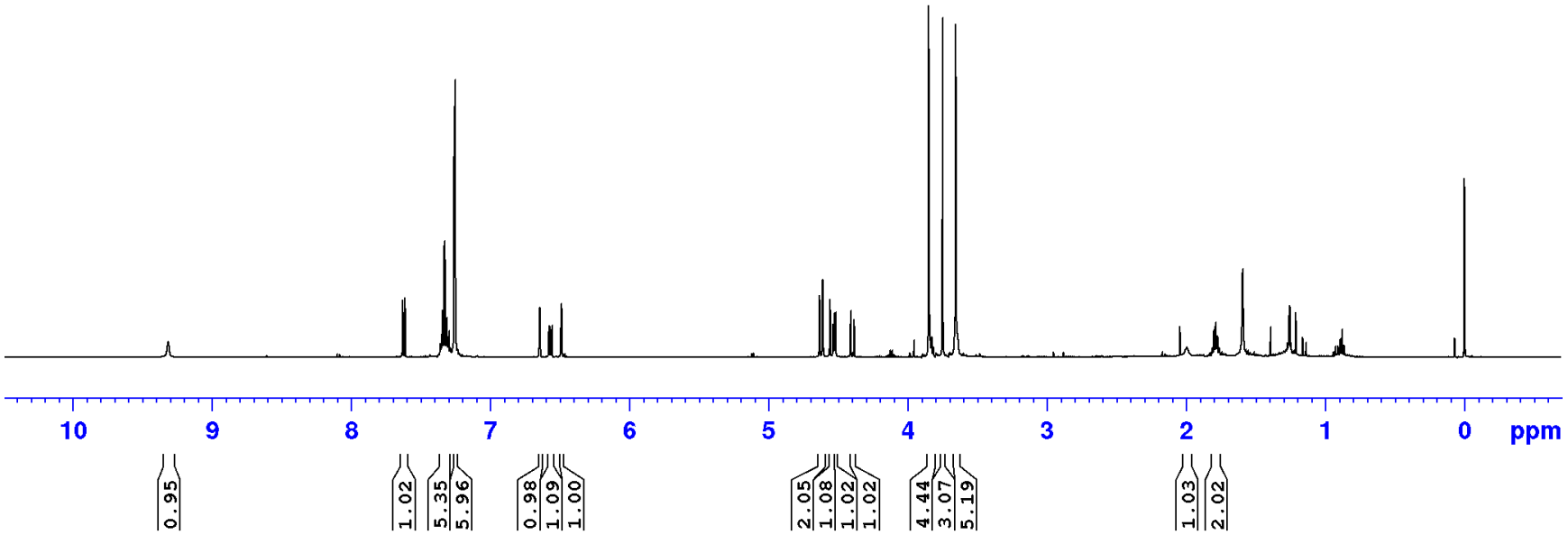
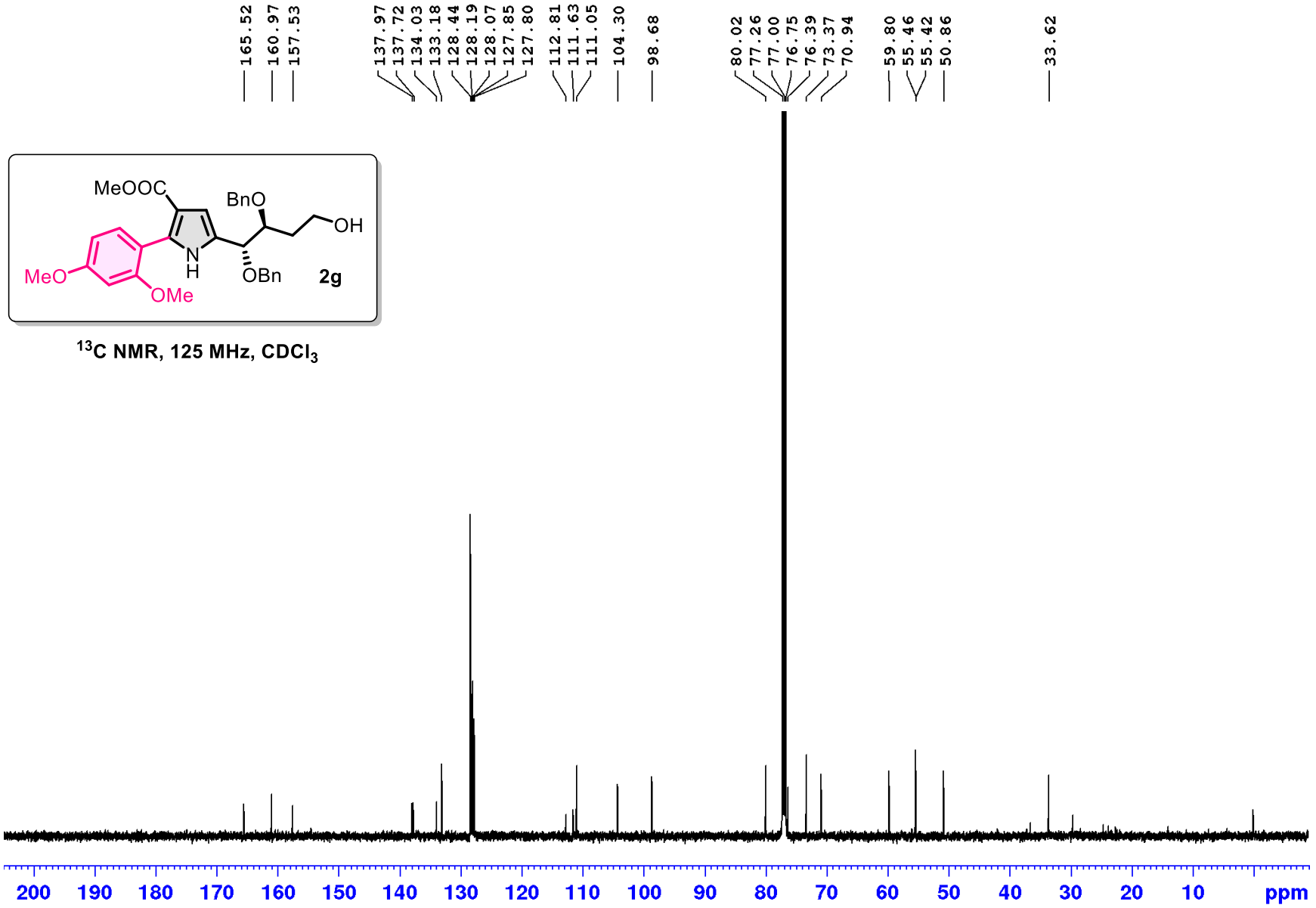
40
30
20
10
0
ppm



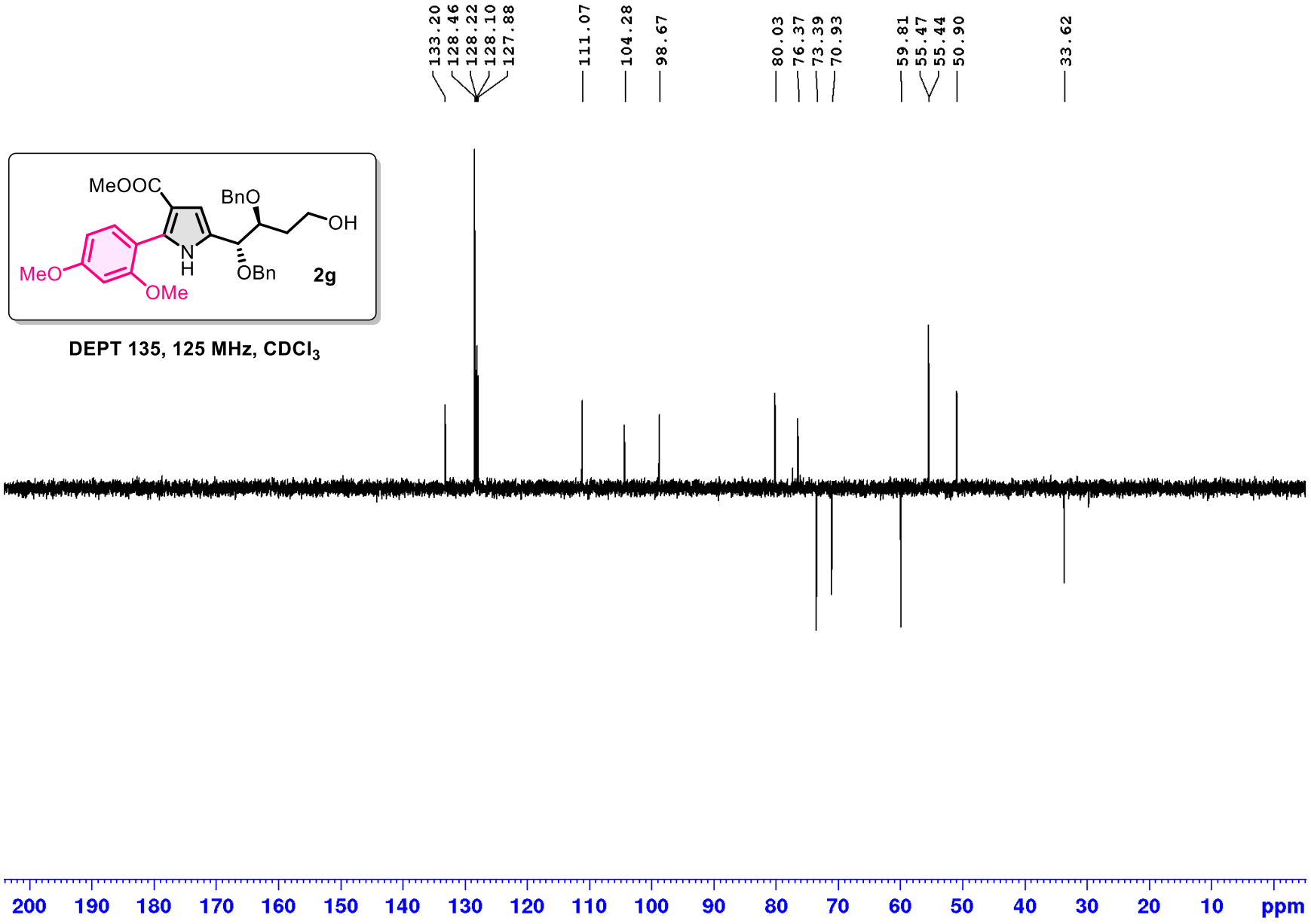


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$


133.20
128.46
128.22
128.10
127.88
111.07
104.28
98.67
80.03
76.37
73.39
70.93
59.81
55.47
55.44
50.90
33.62
MeOOC
BnO
OH
N
H
MeO
OMe
OBn
2g
DEPT 135, 125 MHz, CDCl3
200
190
180
170
160
150
140
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120
110
100
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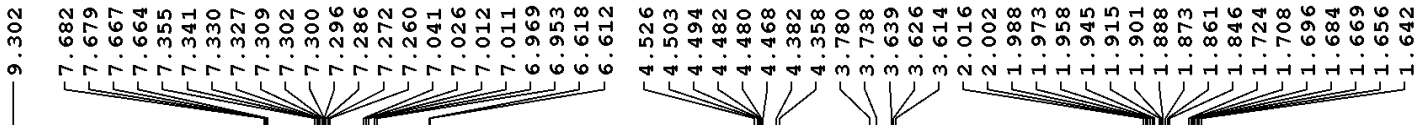
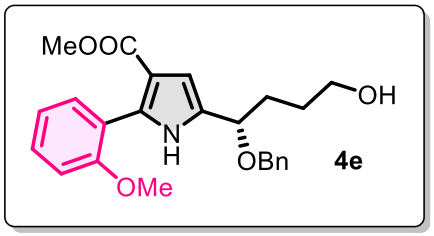
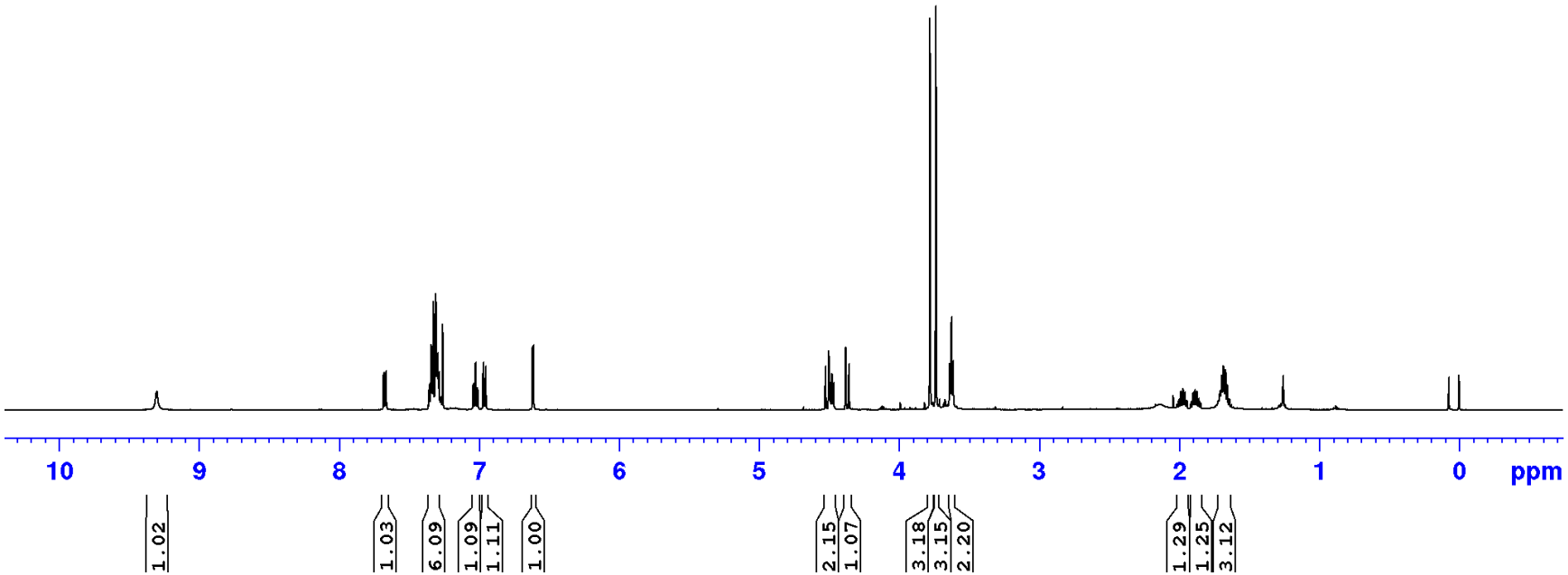
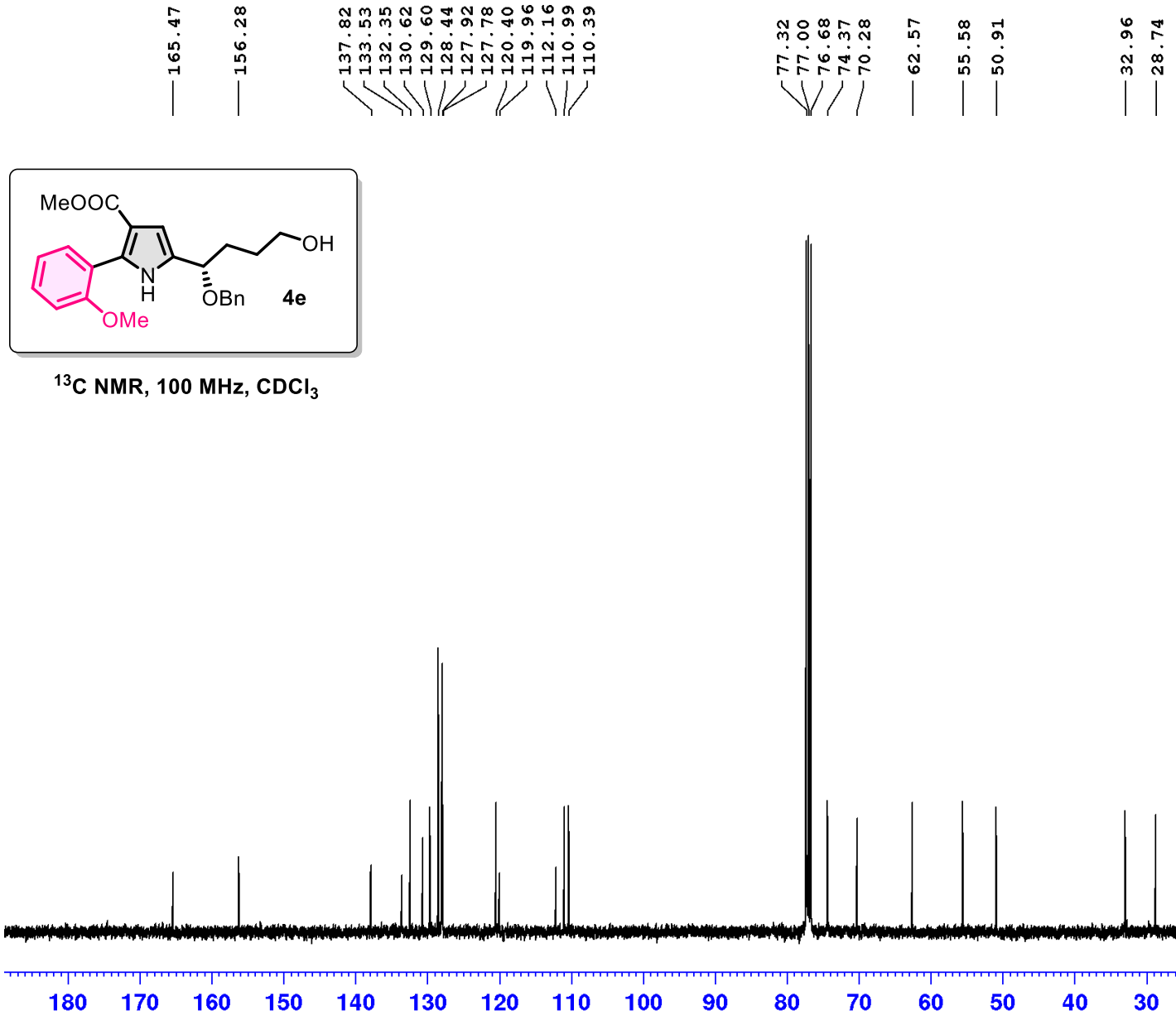
80
70
60
50
40
30
20
10
ppm



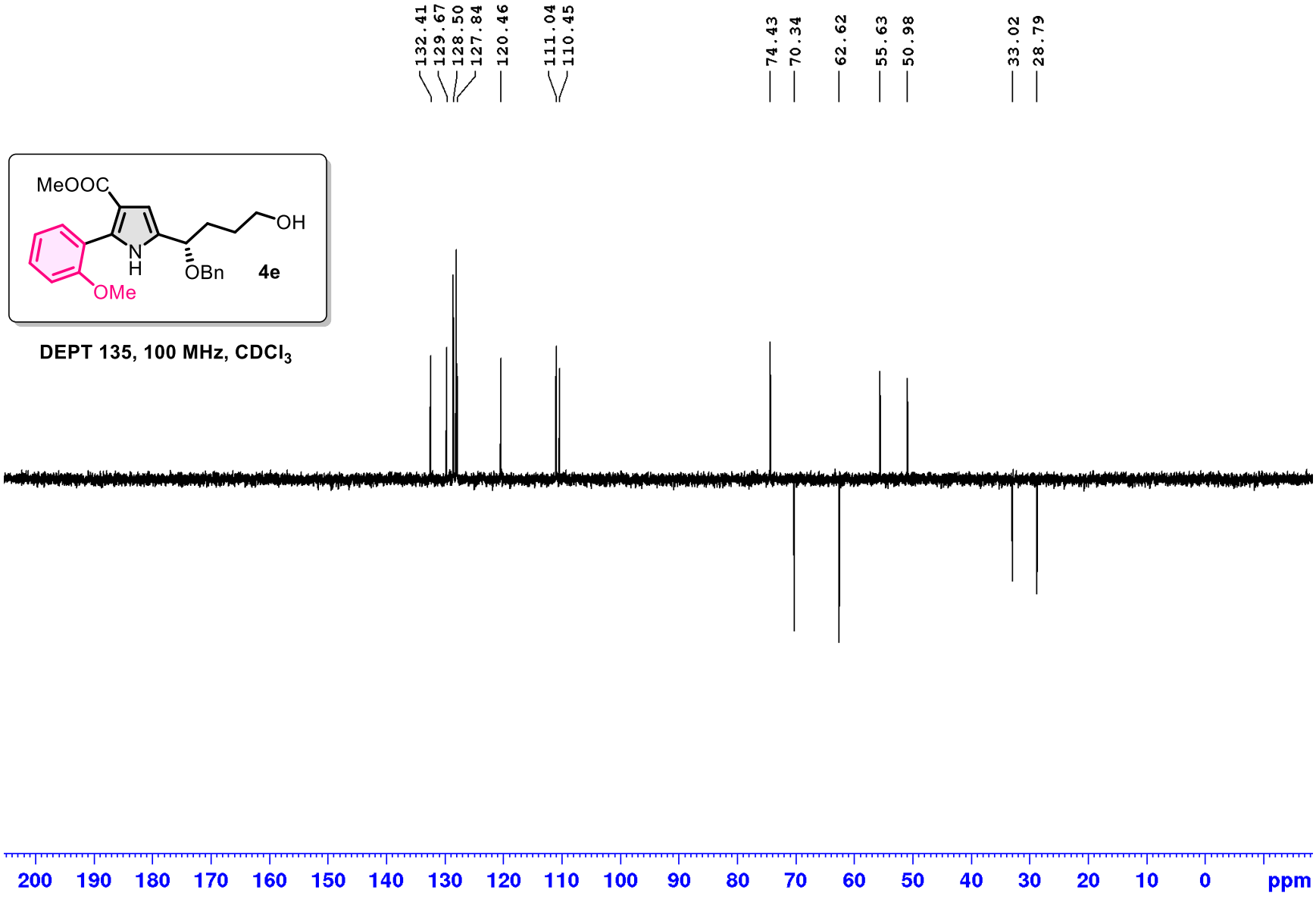


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 100 MHz, $CDCl_3$


132.41
129.67
128.50
127.84
120.46
111.04
110.45
74.43
70.34
62.62
55.63
50.98
33.02
28.79
MeOOC
OH
N
H
OBn
OMe
4e
DEPT 135, 100 MHz, CDCl3
200
190
180
170
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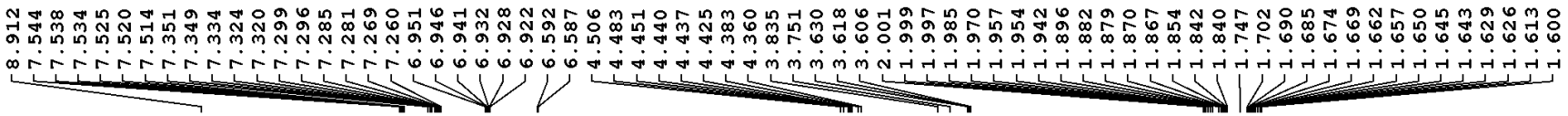
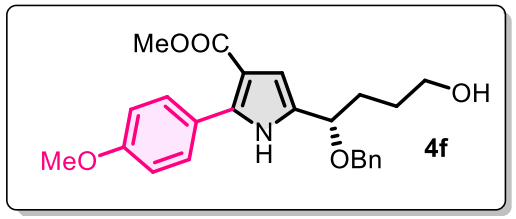
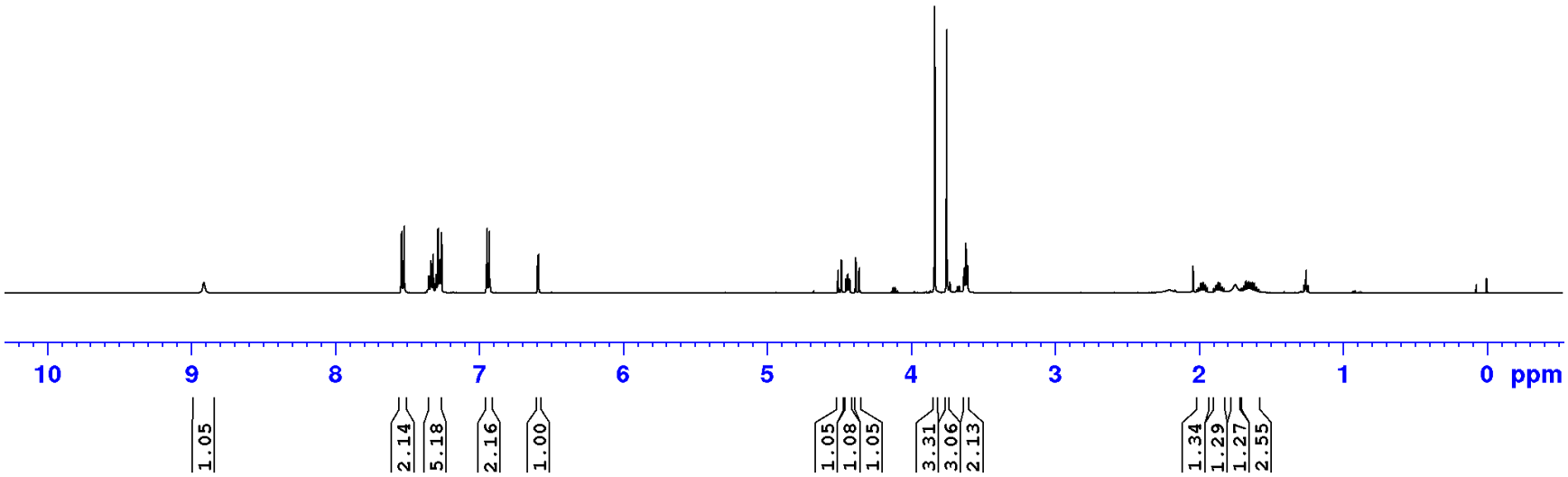
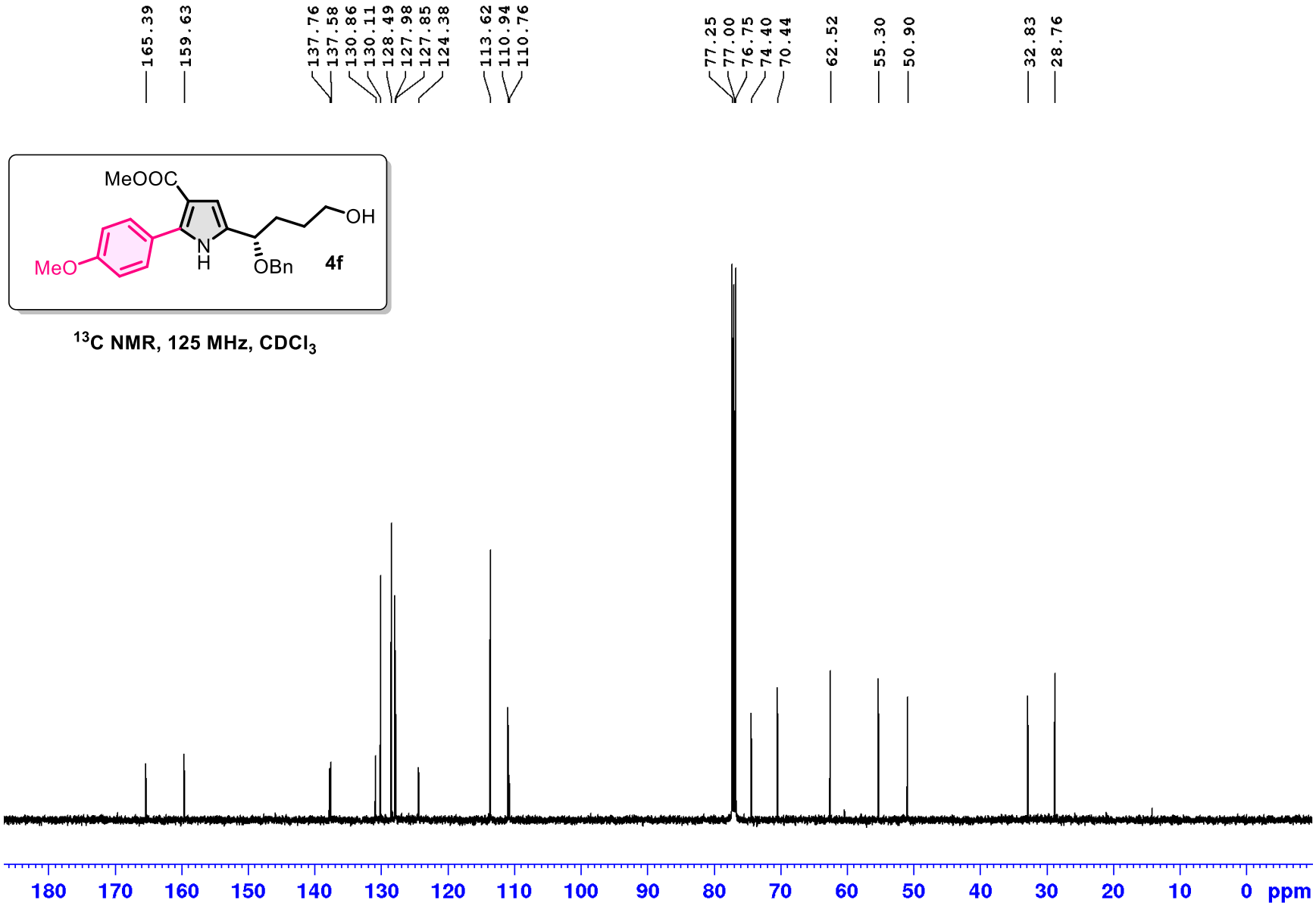
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



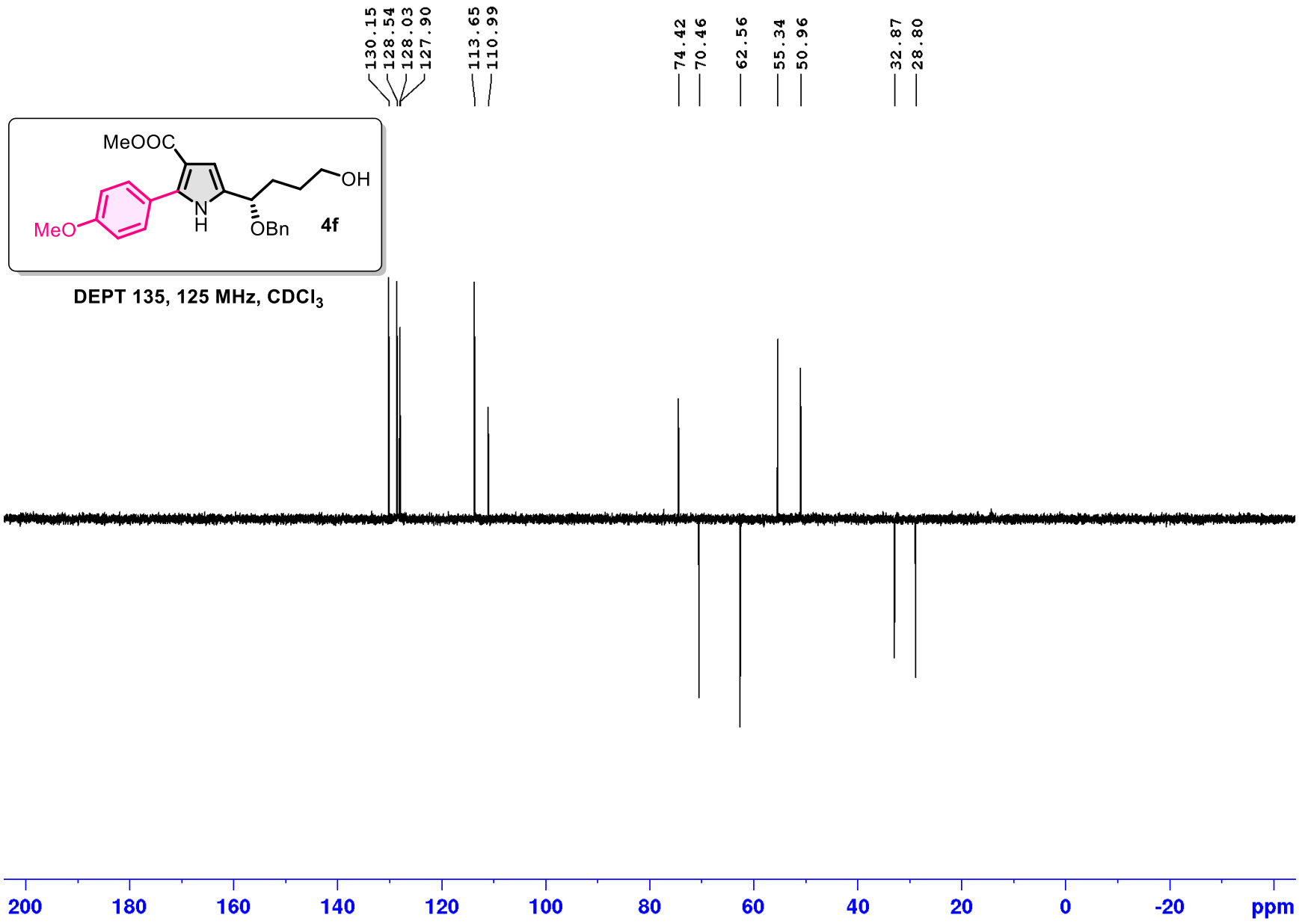


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$


130.15
128.54
128.03
127.90
113.65
110.99
74.42
70.46
62.56
55.34
50.96
32.87
28.80
MeOOC
OH
N
H
MeO
OBn
4f
DEPT 135, 125 MHz, CDCl3
200
180
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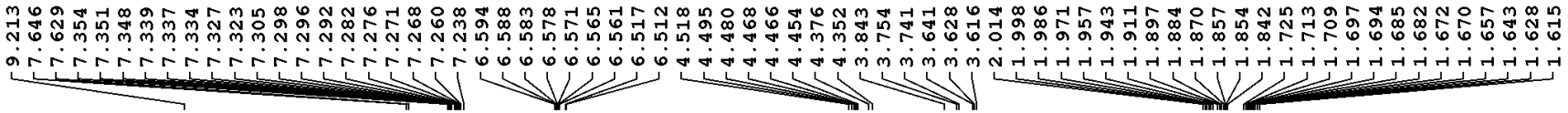
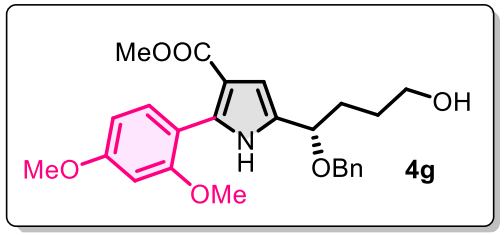
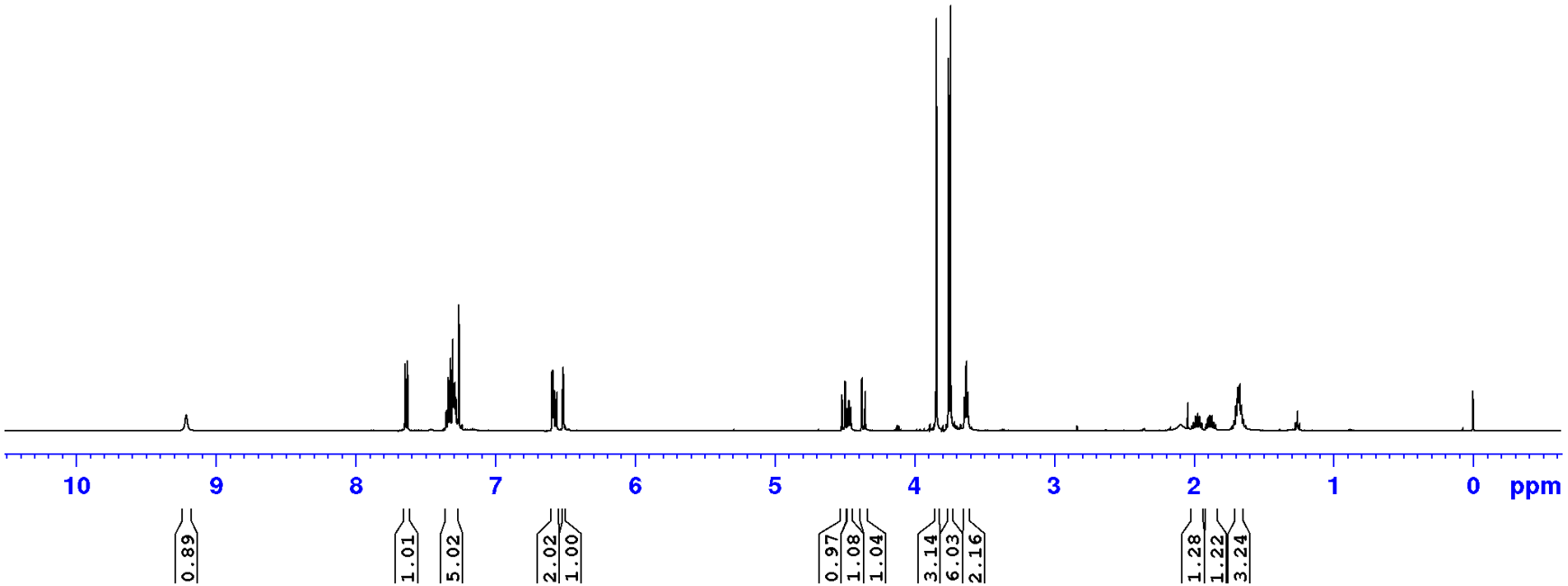
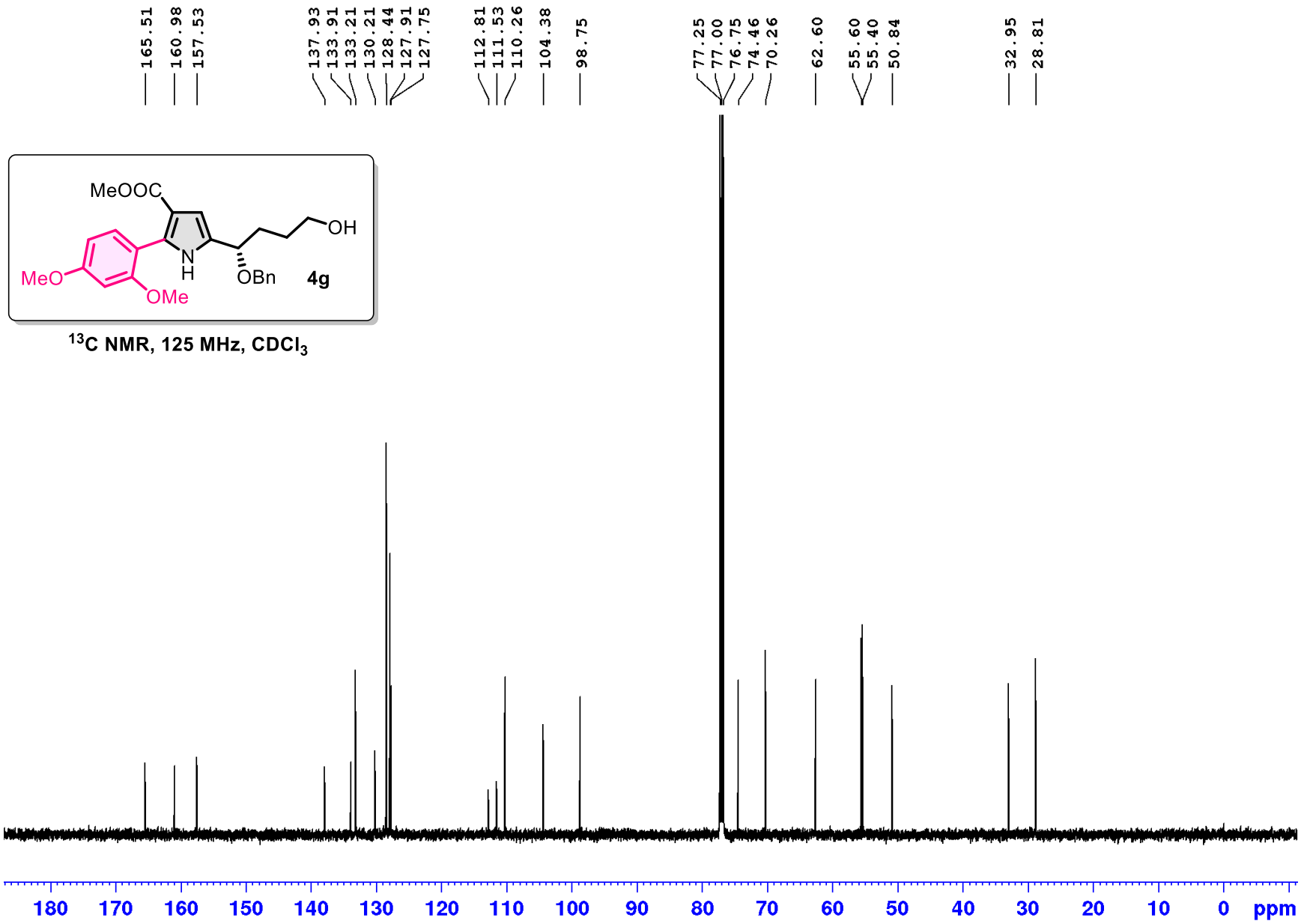
140
120
100
80
60
40
20
0
-20
ppm



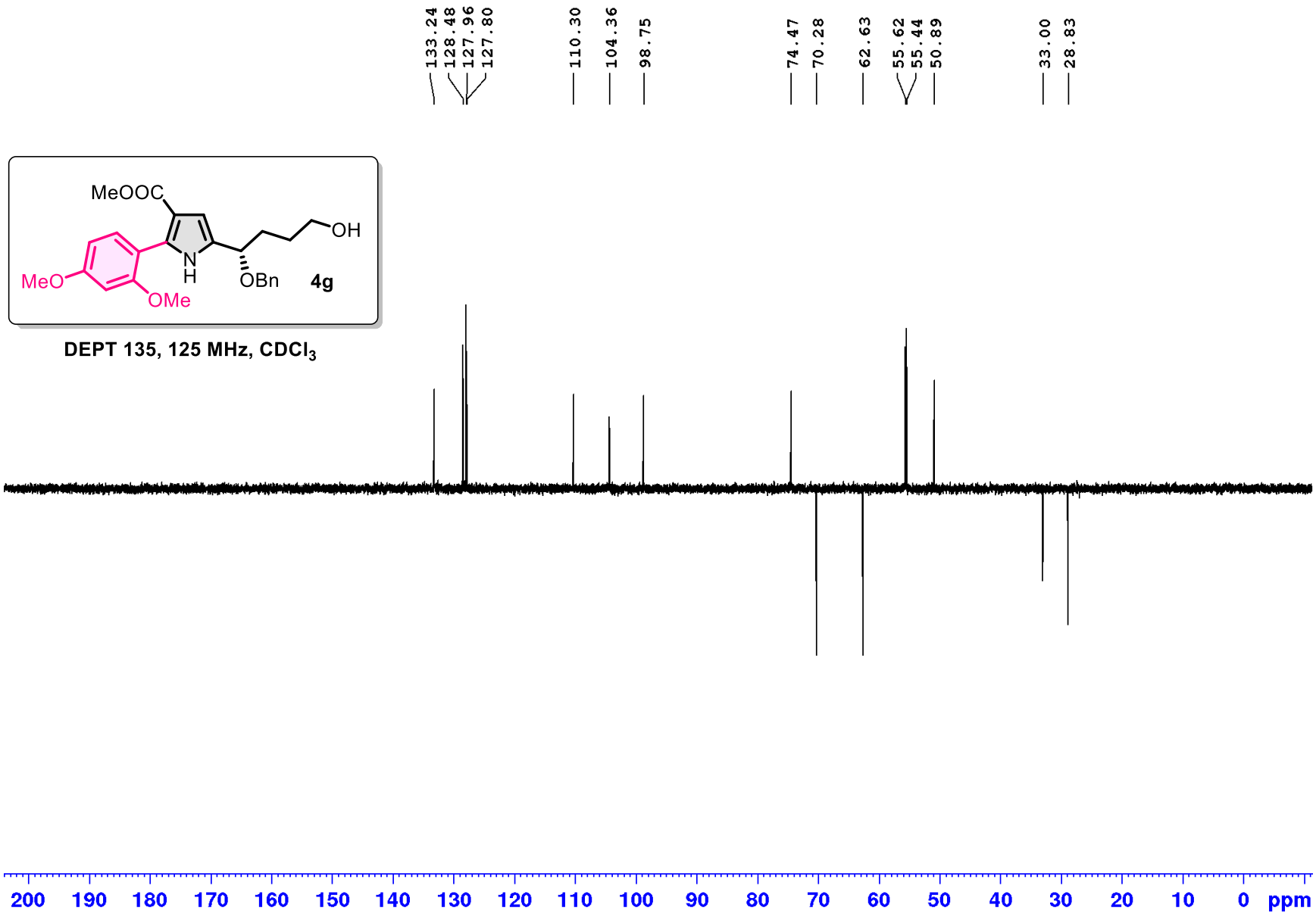


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$


133.24
128.48
127.96
127.80
110.30
104.36
98.75
74.47
70.28
62.63
55.62
55.44
50.89
33.00
28.83
MeOOC
OH
N
H
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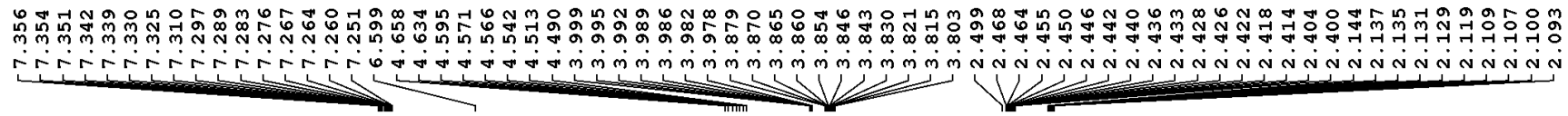
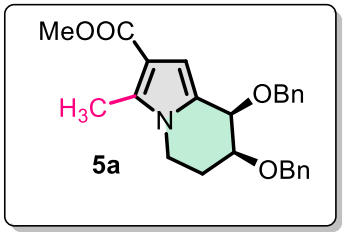
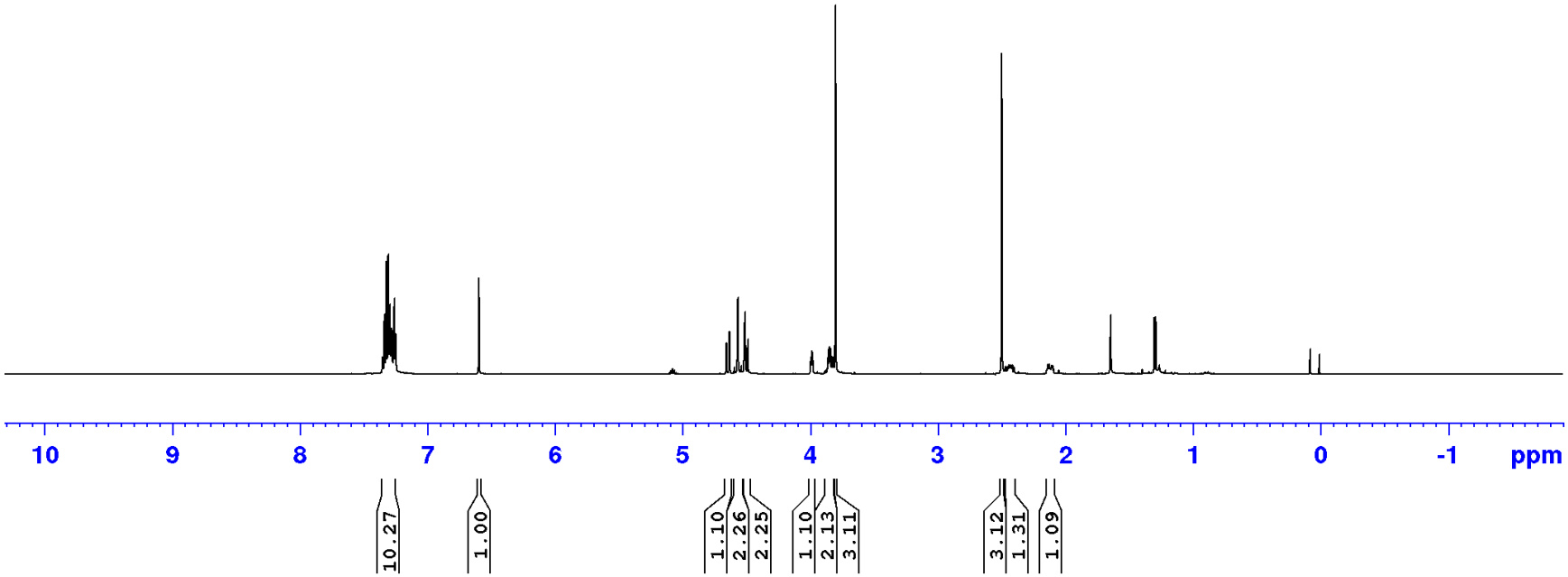
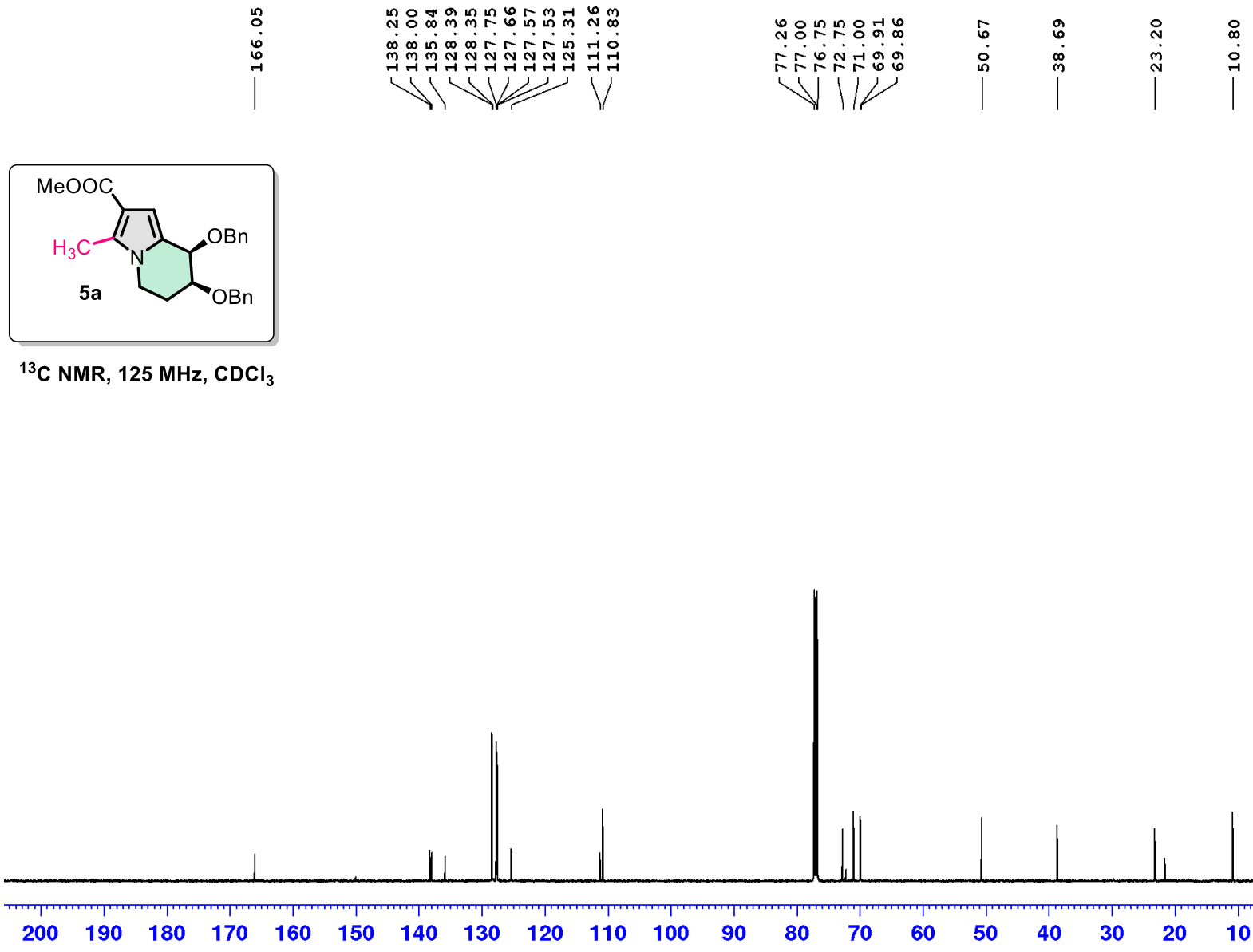
OMe
OBn
4g
DEPT 135, 125 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



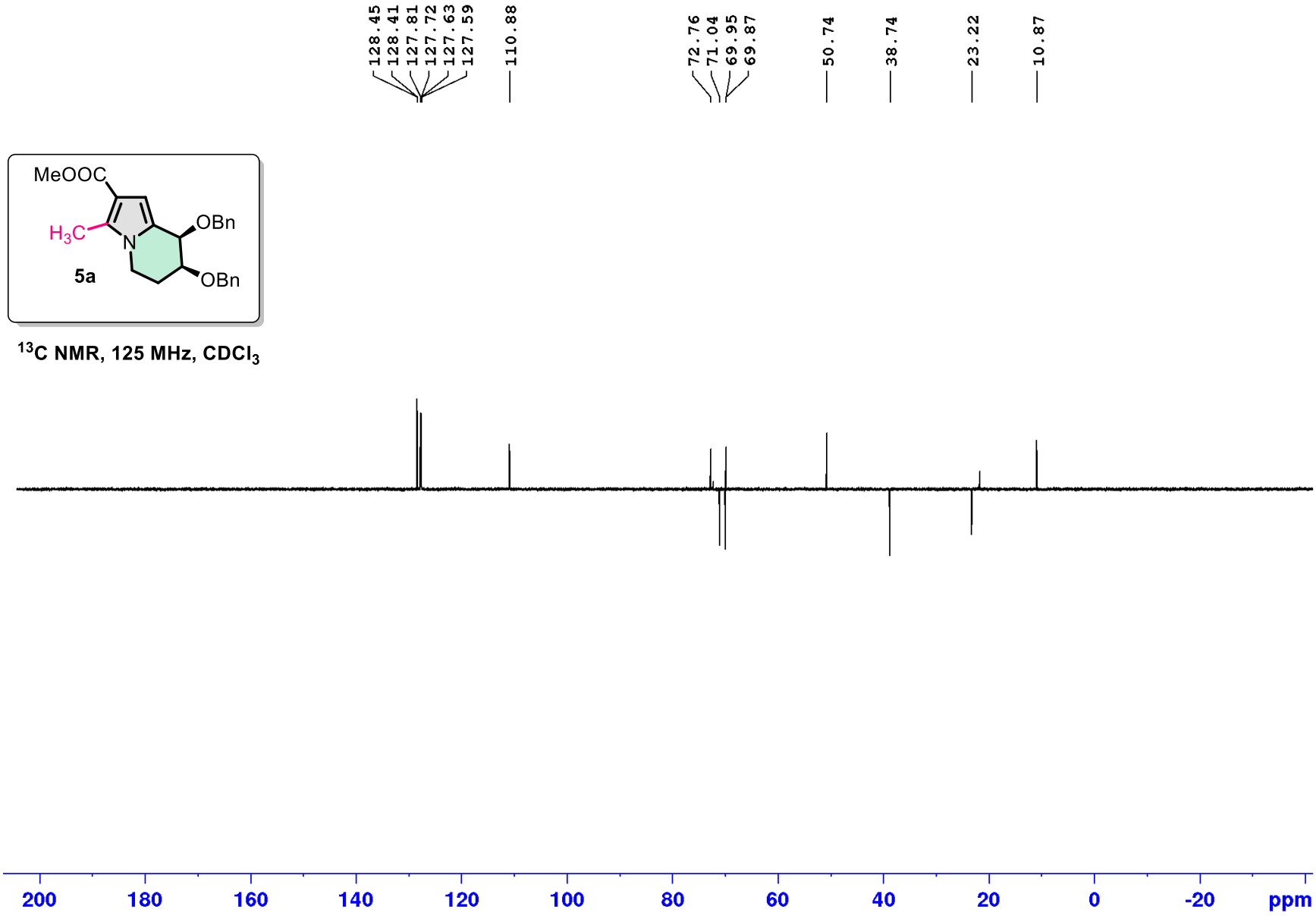


^{1}H NMR, 500 MHz, $CDCl_3$

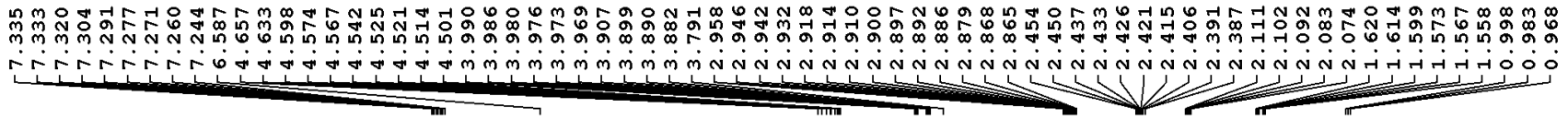


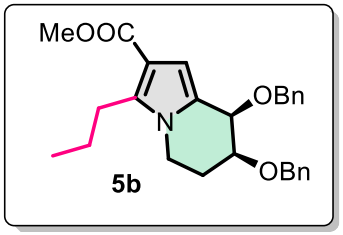


^{13}C NMR, 125 MHz, $CDCl_3$

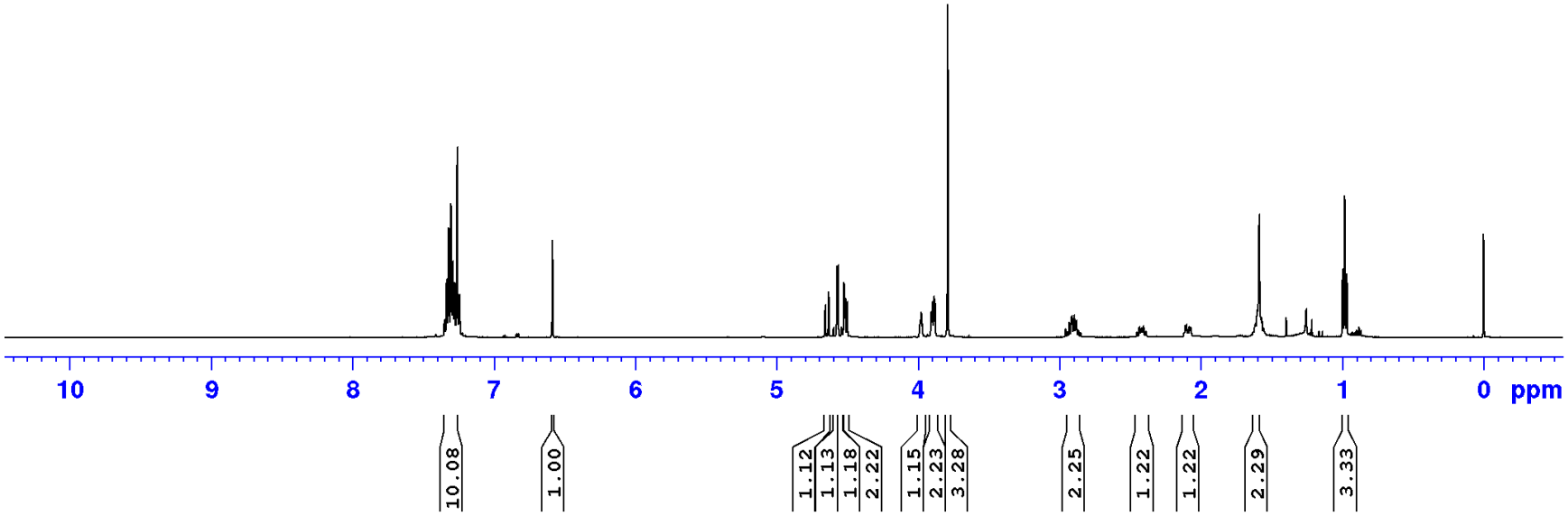


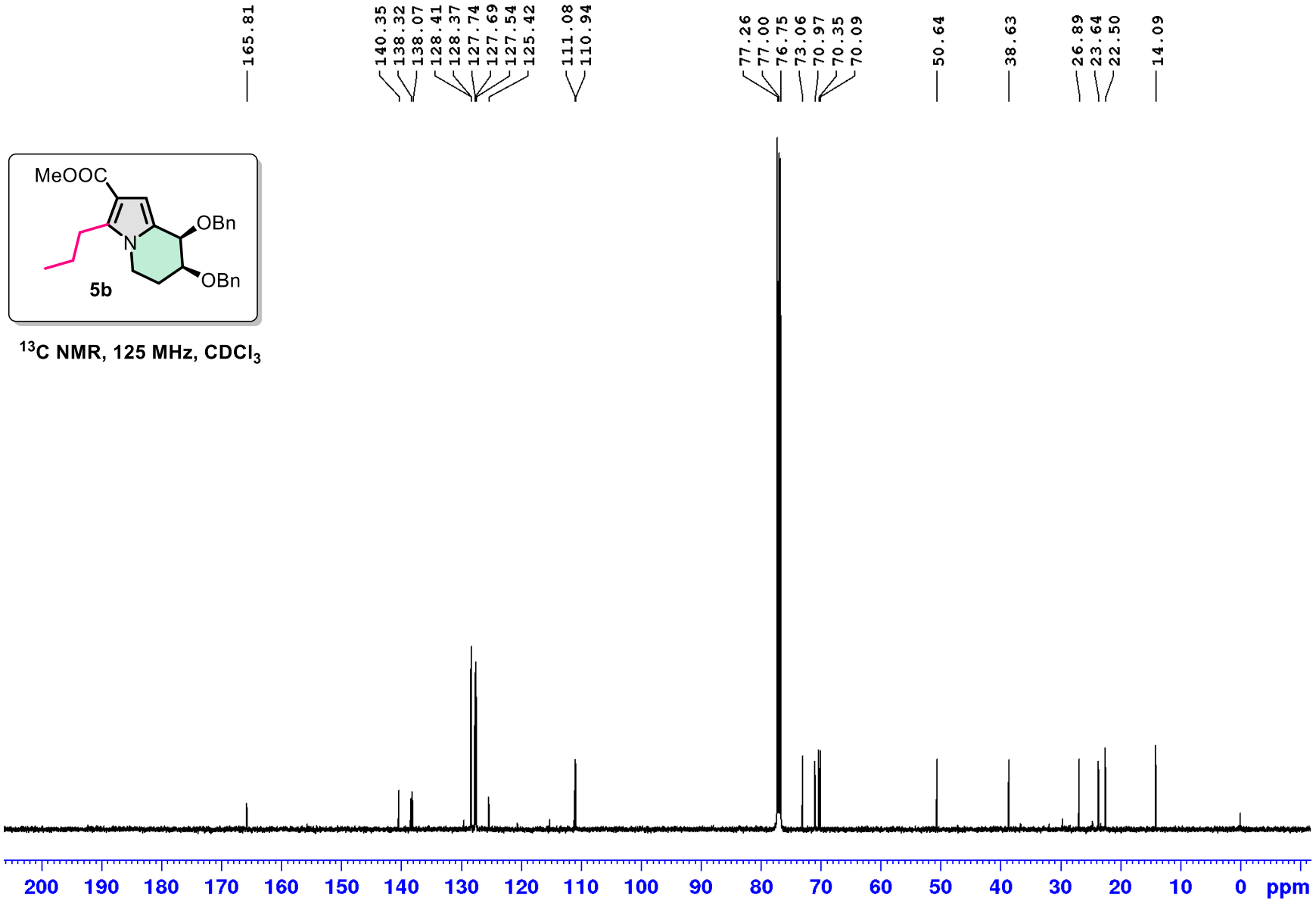
^{13}C NMR, 125 MHz, $CDCl_3$



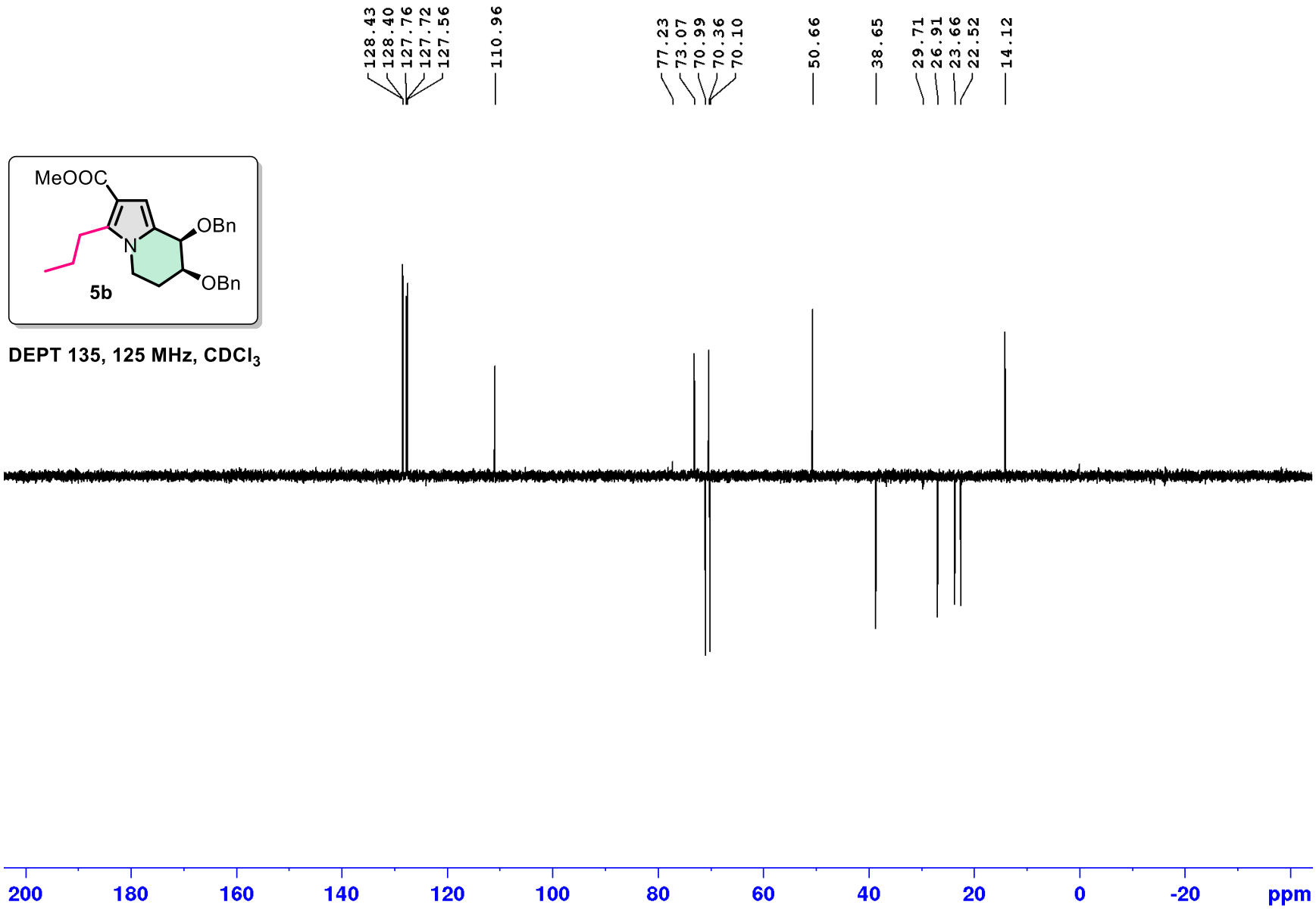


^{1}H NMR, 500 MHz, $CDCl_3$

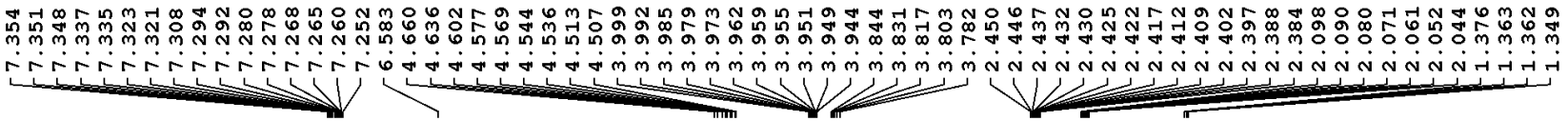


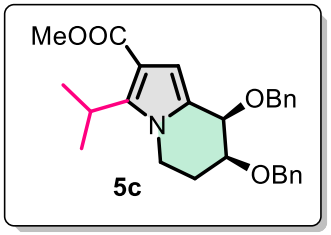


^{13}C NMR, 125 MHz, $CDCl_3$

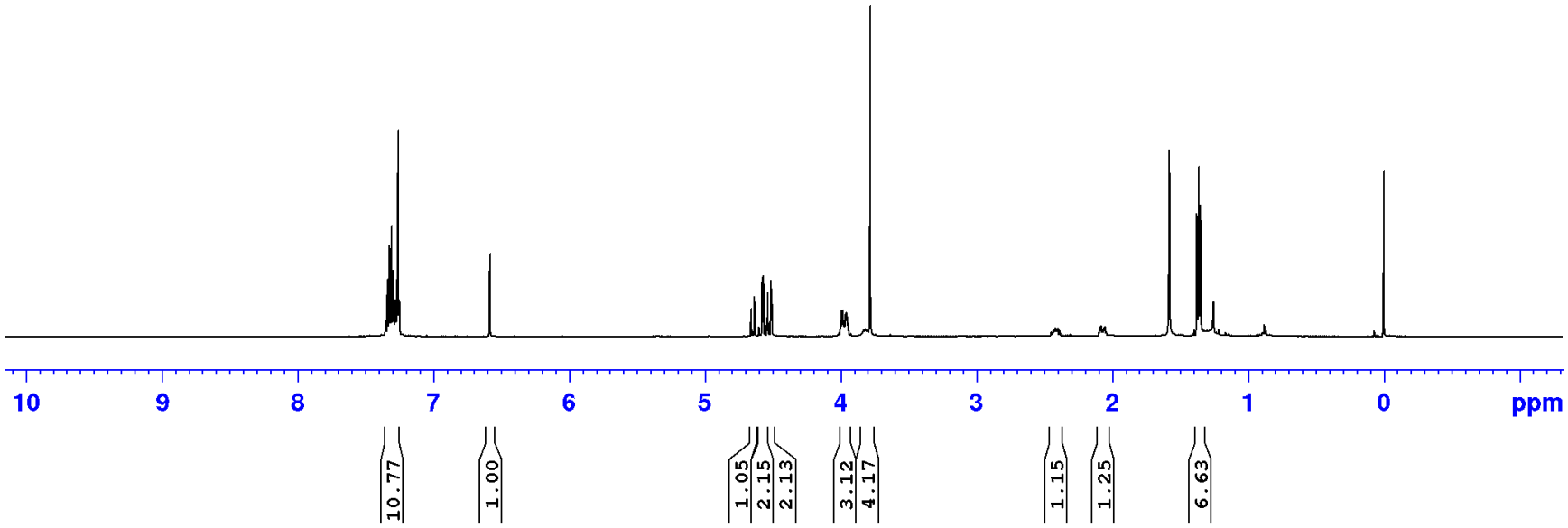


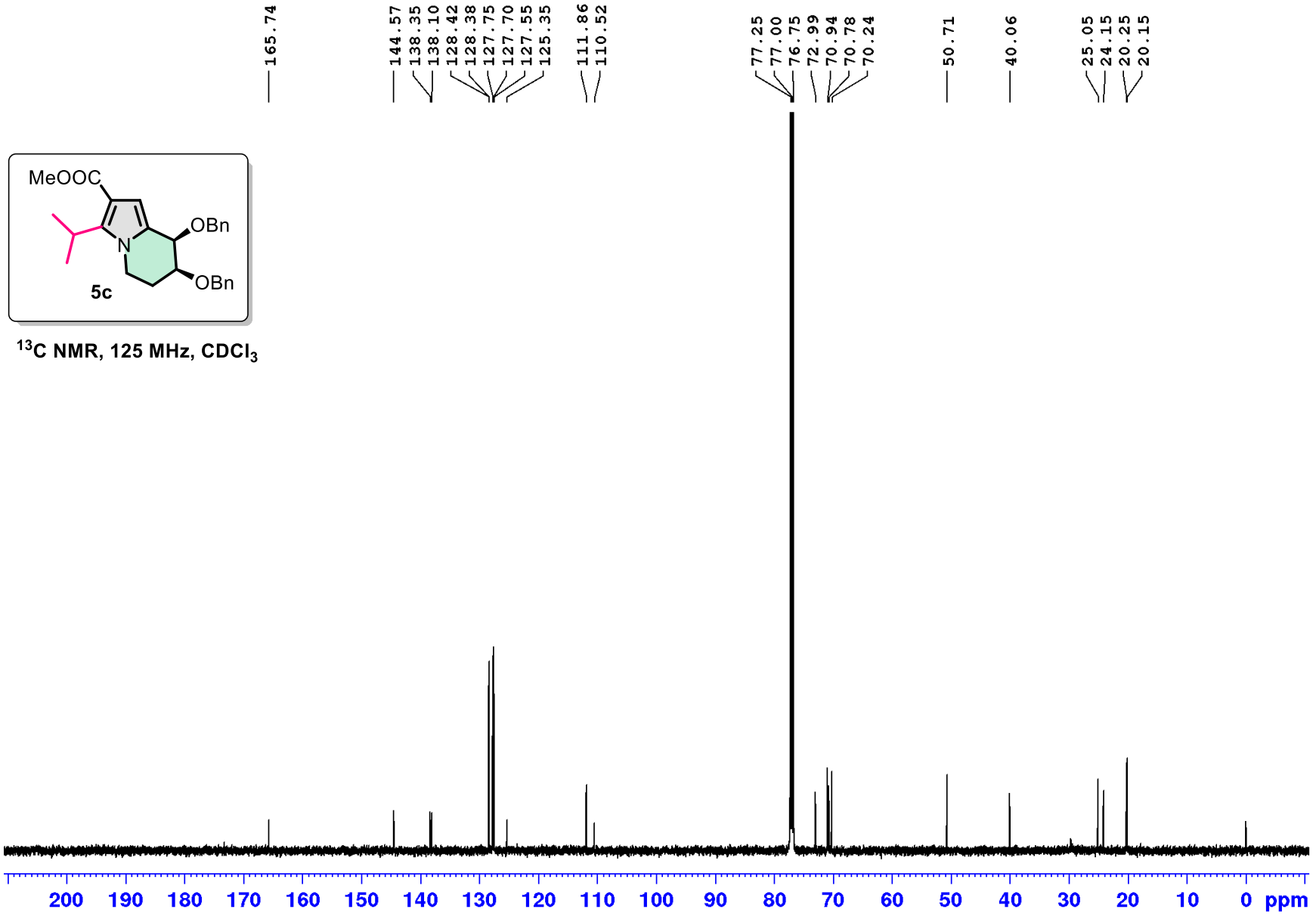
DEPT 135, 125 MHz, $CDCl_3$



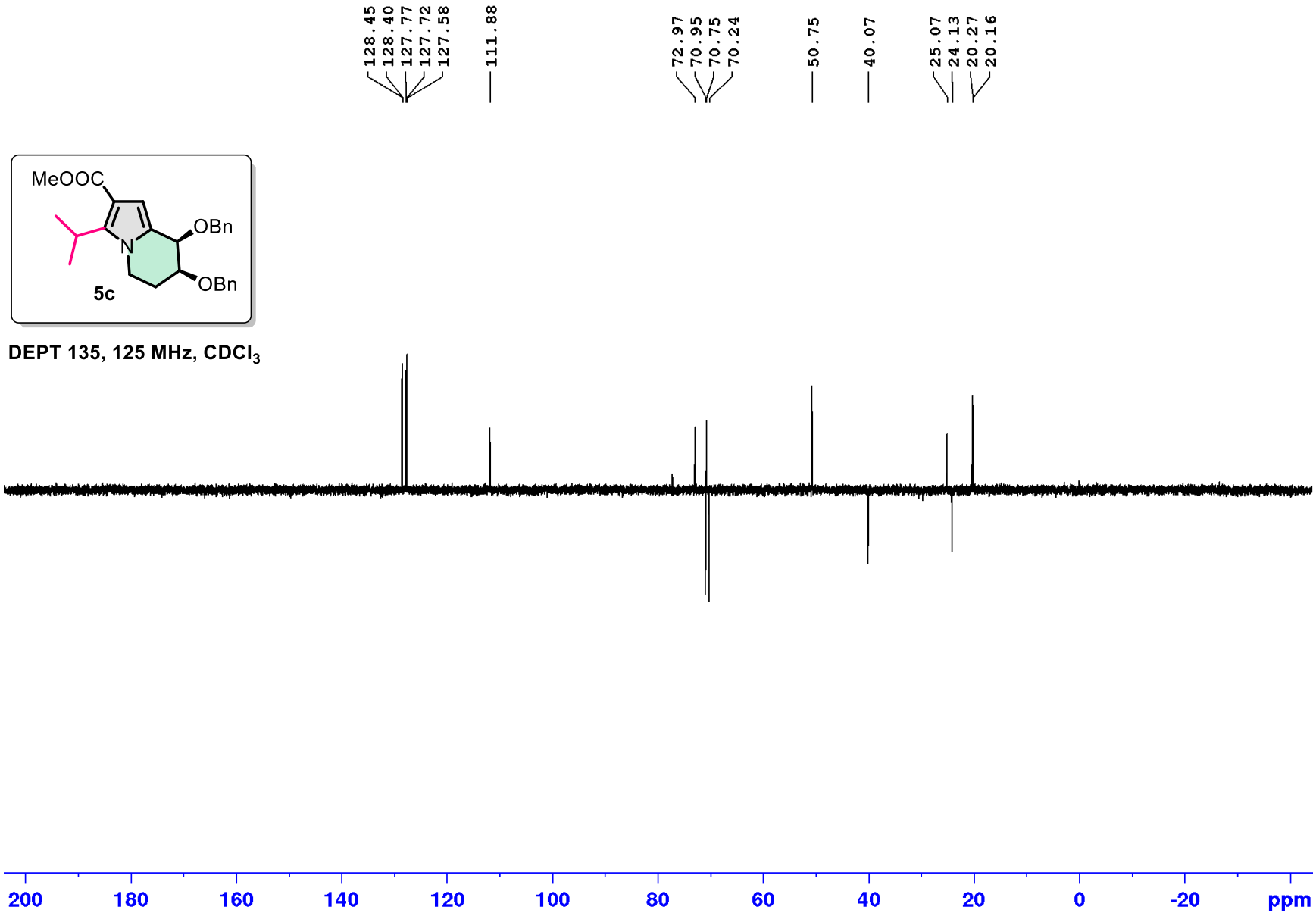


^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$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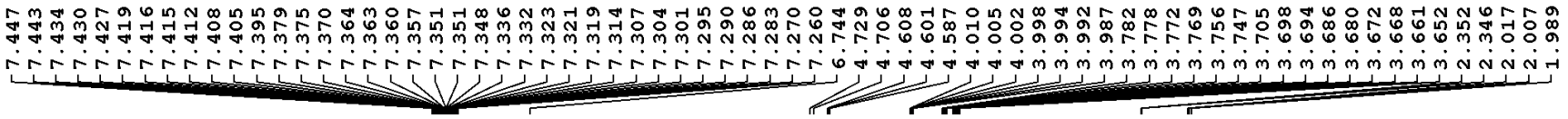
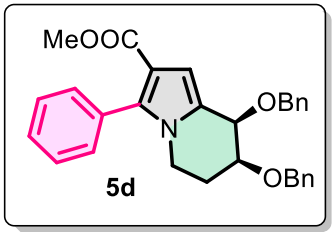
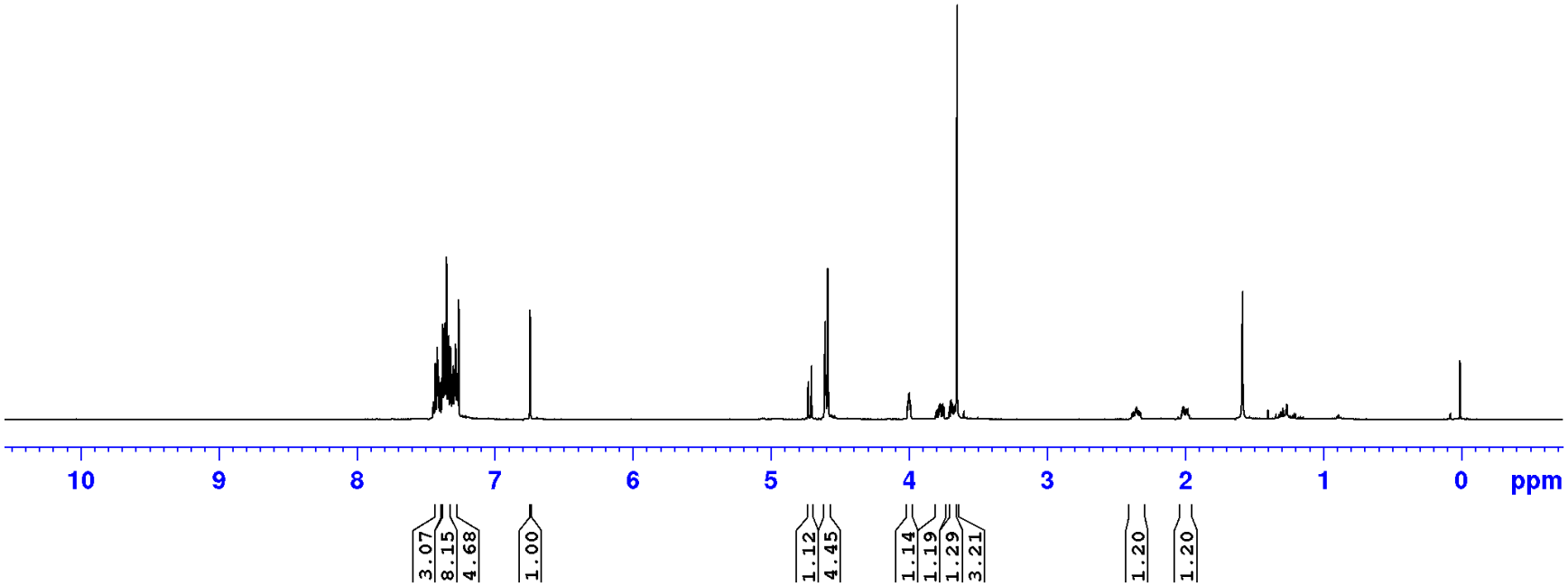
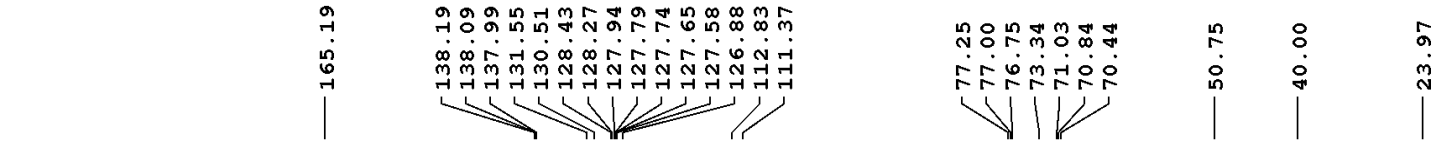
128.40
127.77
127.72
127.58
111.88
72.97
70.95
70.75
70.24
50.75
40.07
25.07
24.13
20.27
20.16
MeOOC
OBn
OBn
N
5c
DEPT 135, 125 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

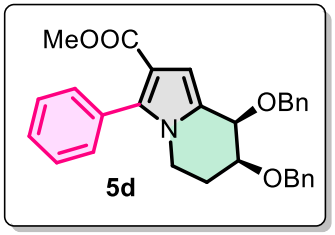




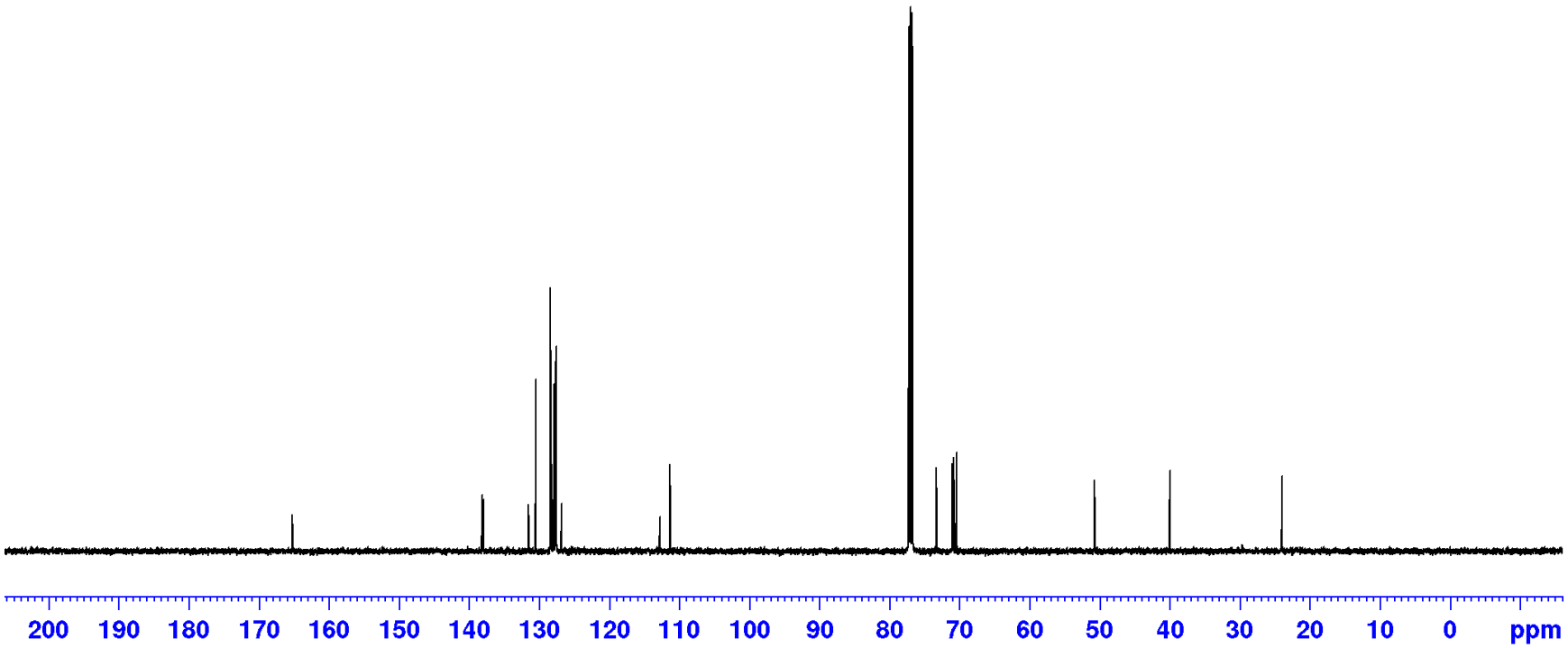
^{1}H NMR, 500 MHz, $CDCl_3$

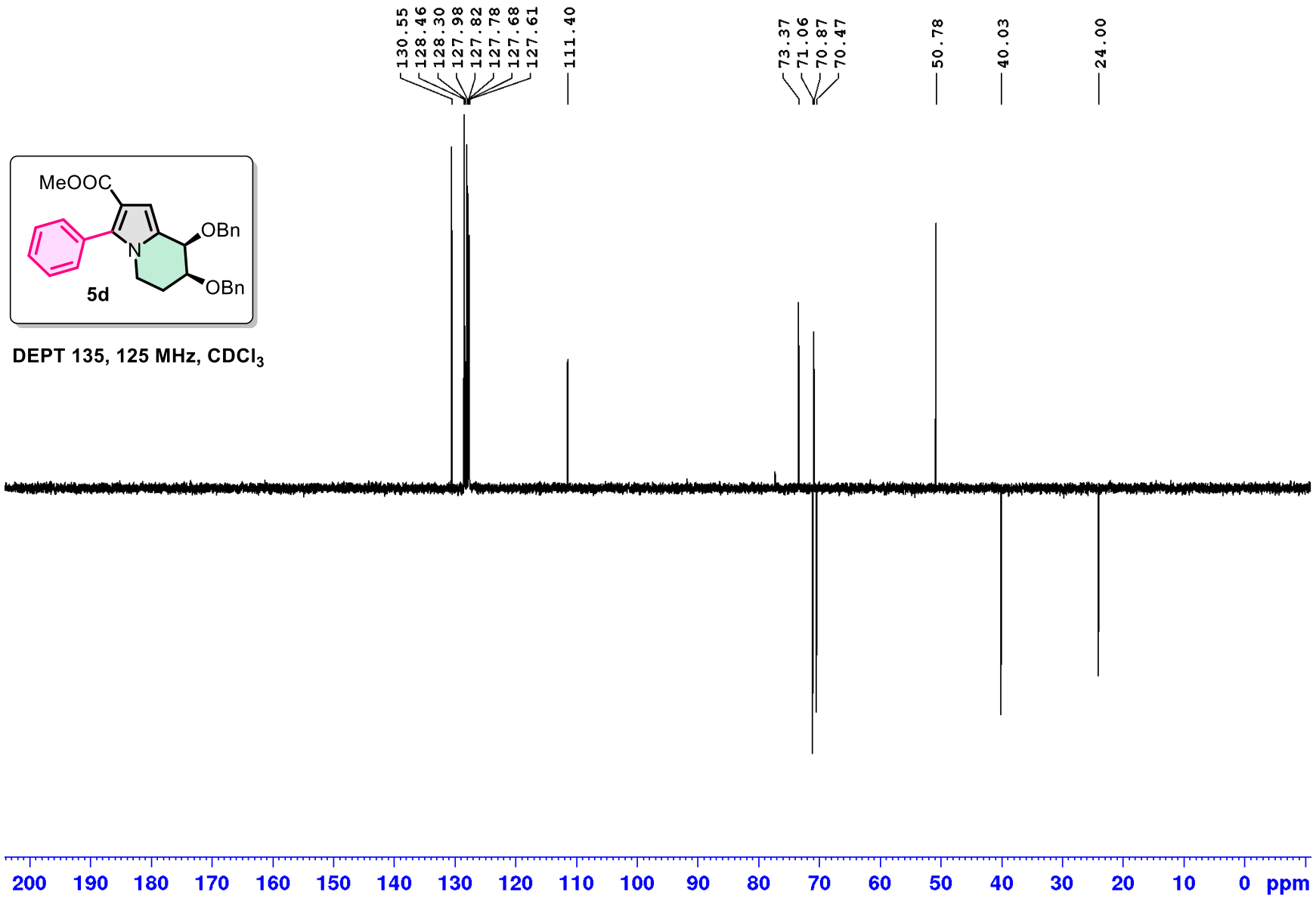


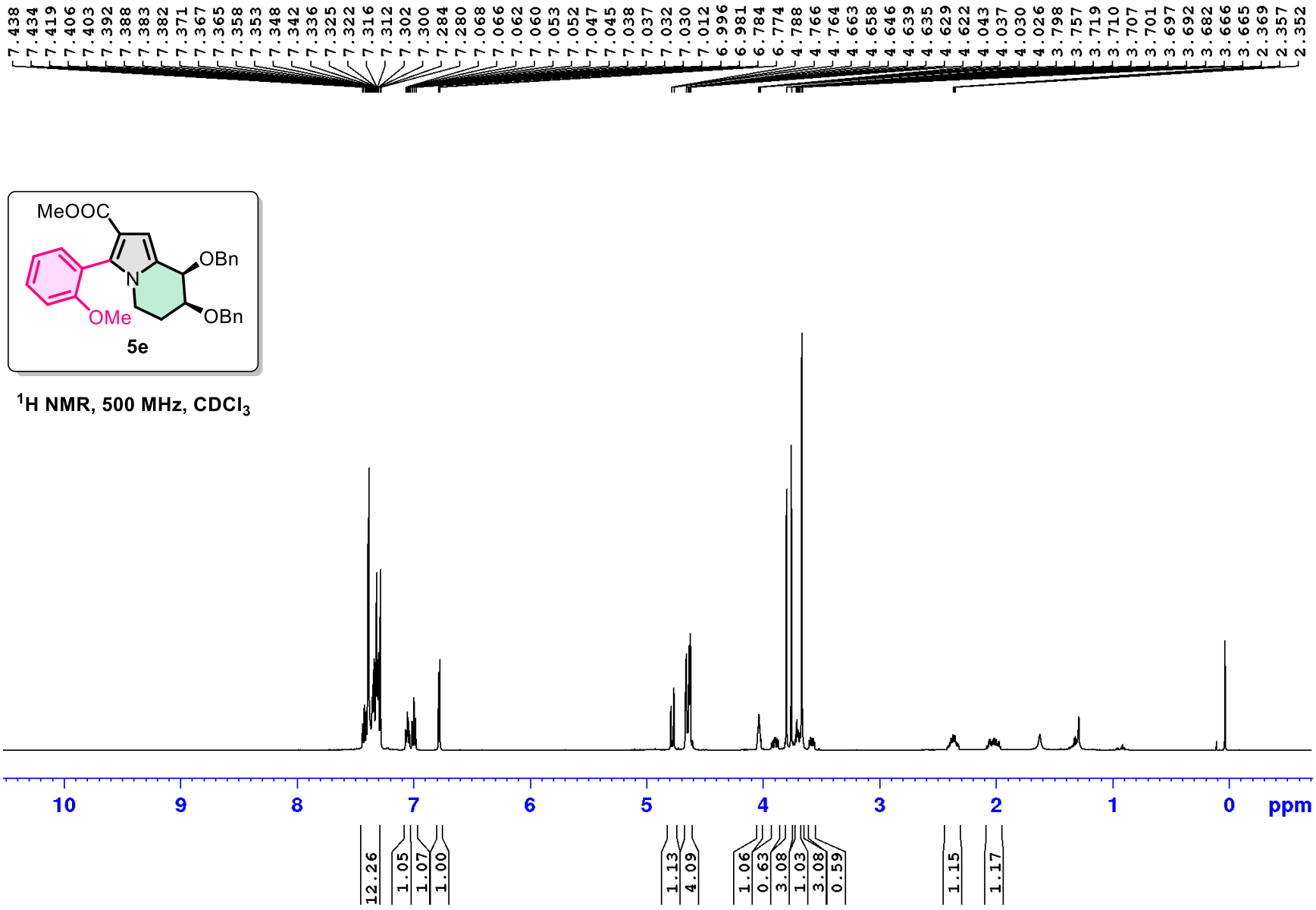




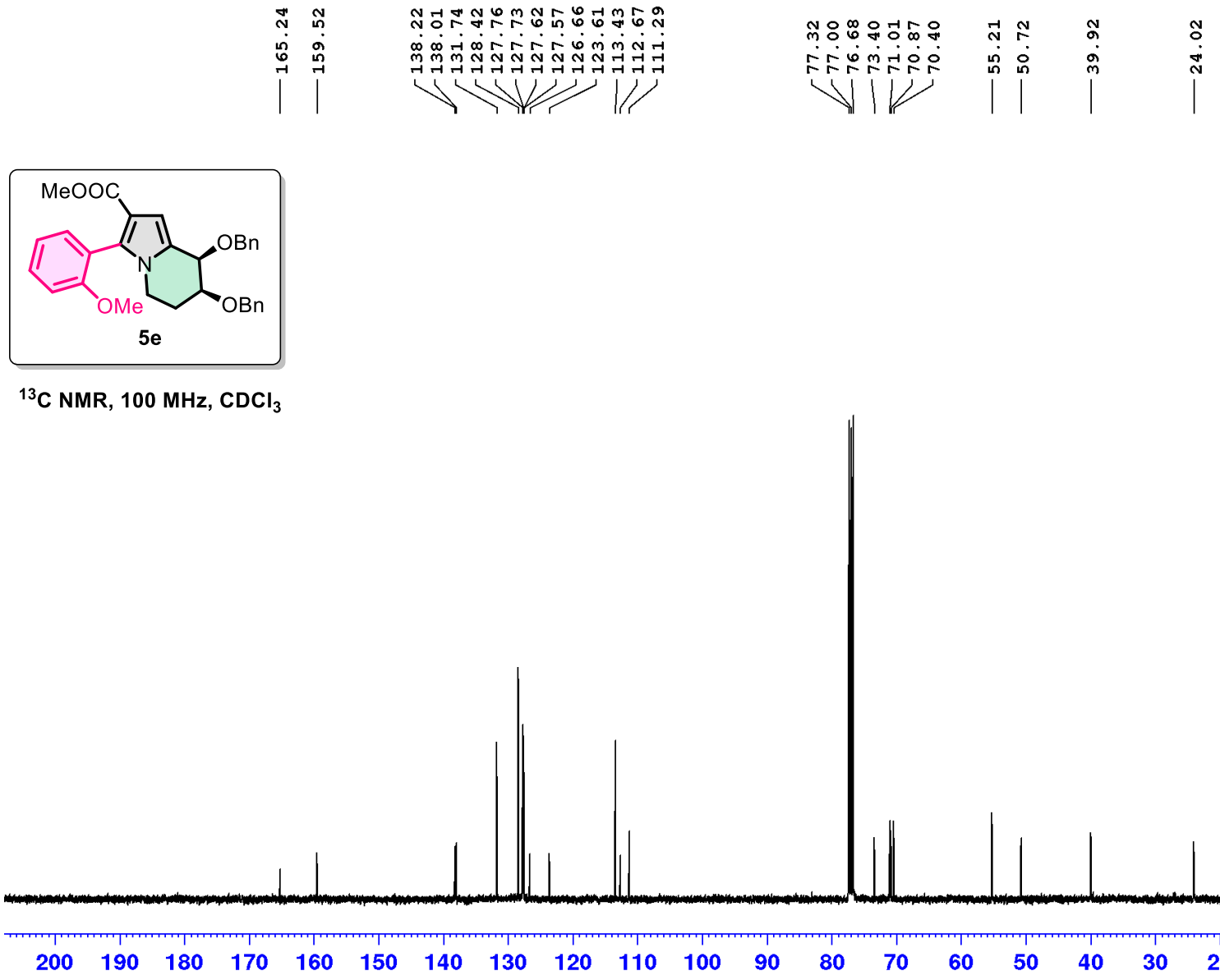
^{13}C NMR, 125 MHz, $CDCl_3$



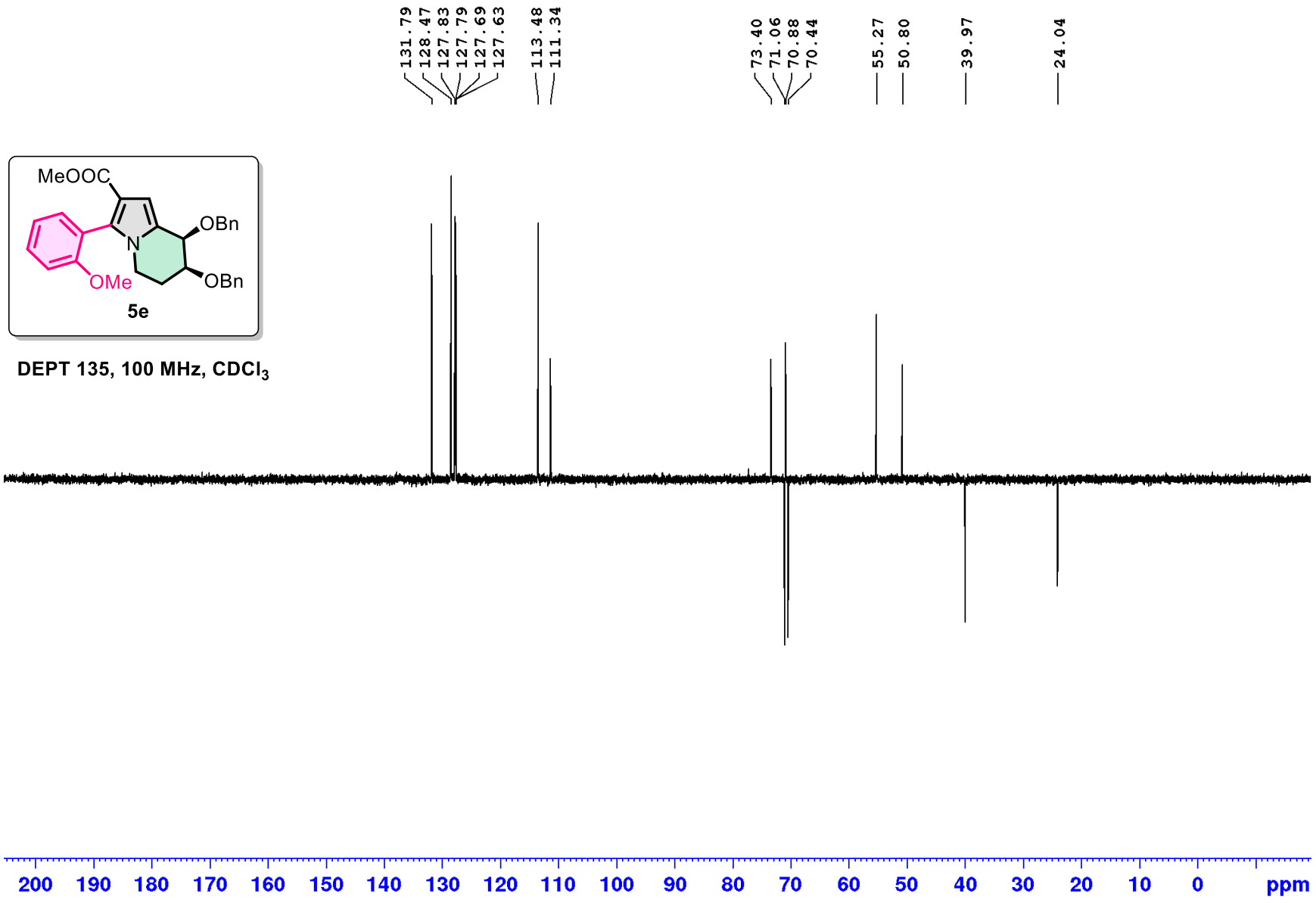

130.55
128.46
128.30
127.98
127.82
127.78
127.68
127.61
111.40
73.37
71.06
70.87
70.47
50.78
40.03
24.00
MeOOC
OBn
OBn
N
5d
DEPT 135, 125 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

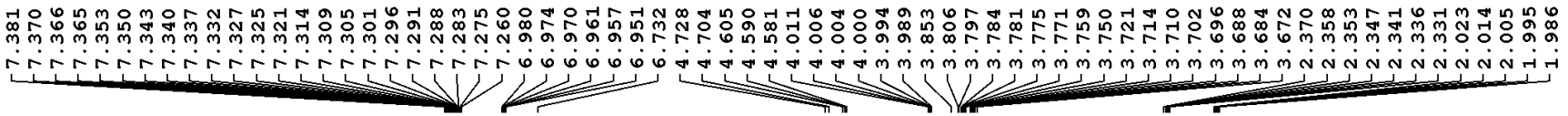


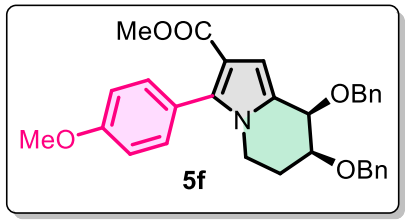
^{1}H NMR, 500 MHz, $CDCl_3$



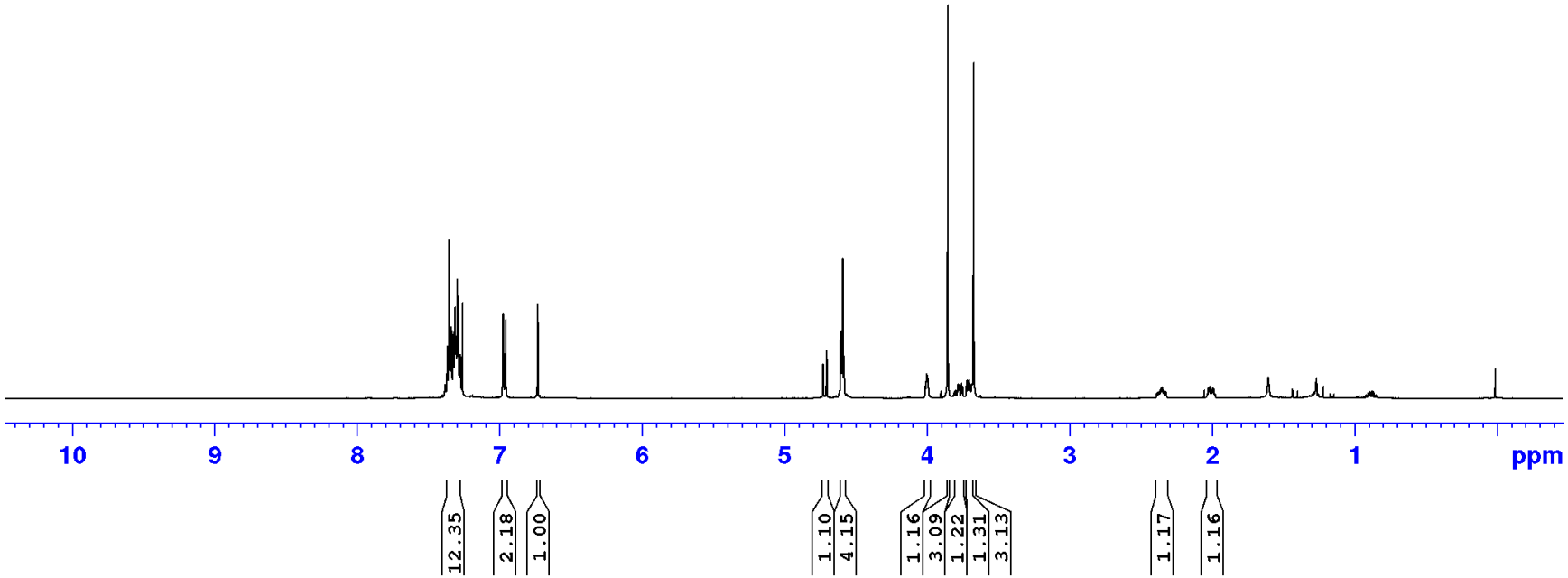
^{13}C NMR, 100 MHz, $CDCl_3$

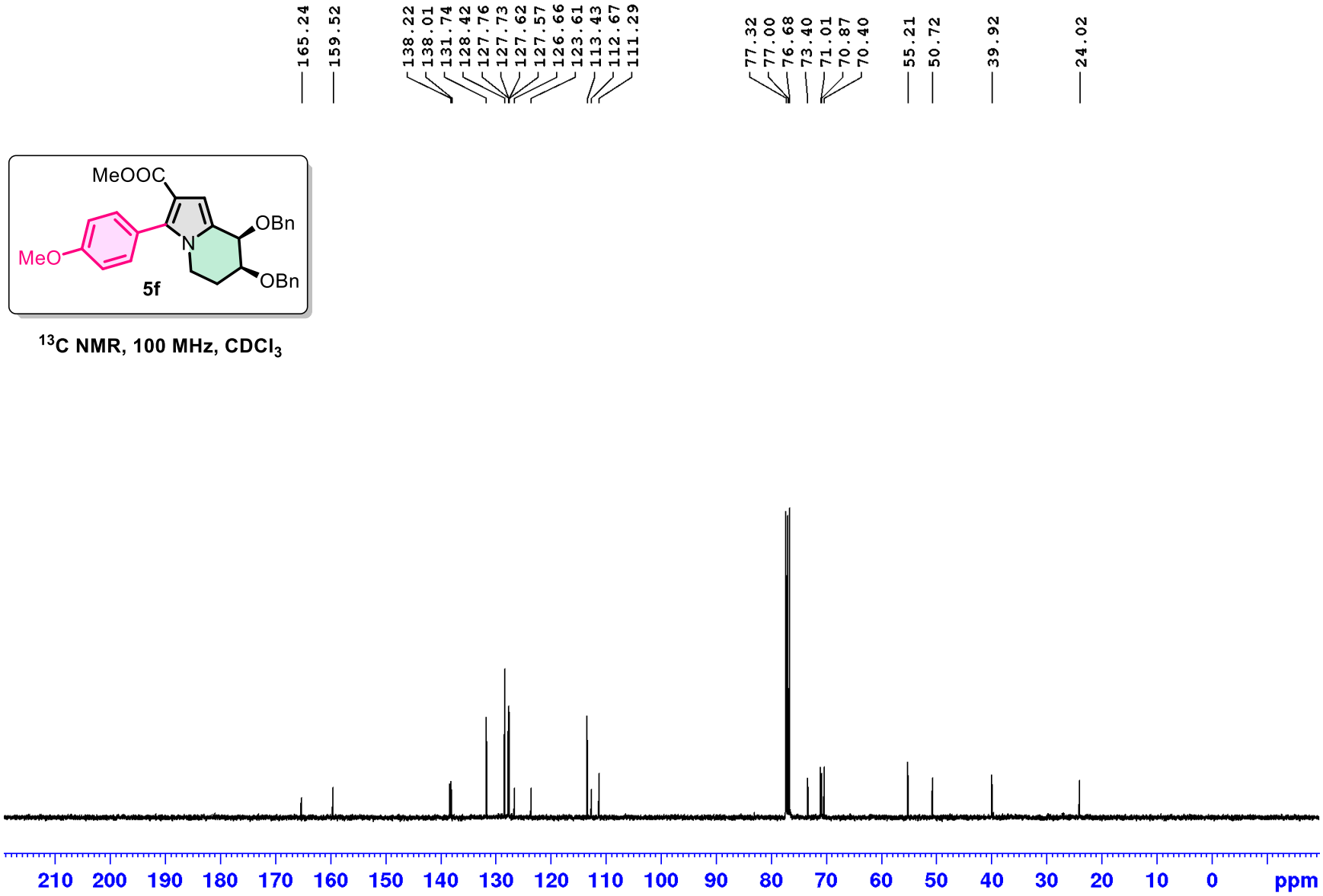

131.79
128.47
127.83
127.79
127.69
127.63
113.48
111.34
73.40
71.06
70.88
70.44
55.27
50.80
39.97
24.04
MeOOC
OBn
N
OMe
OBn
5e
DEPT 135, 100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



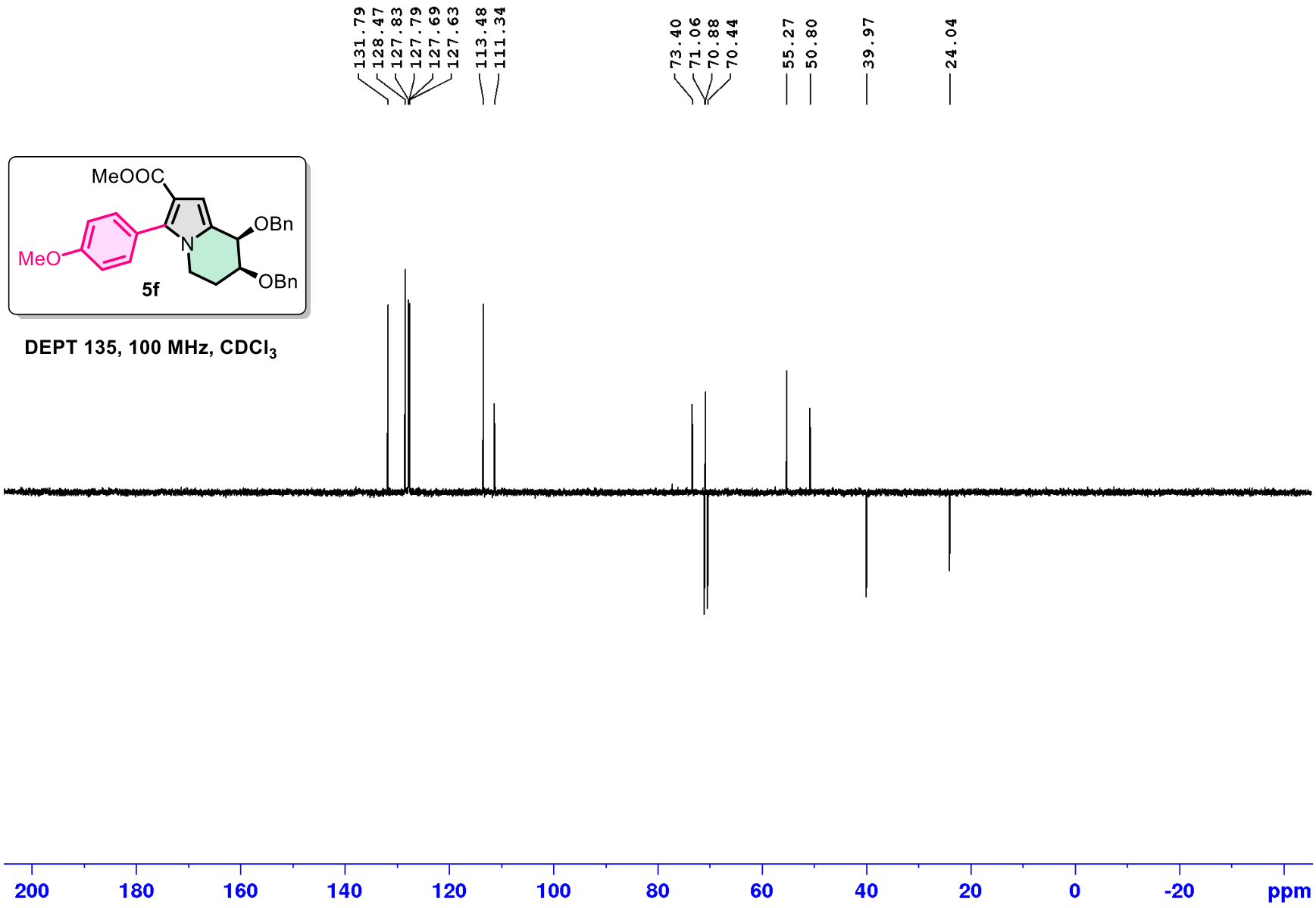


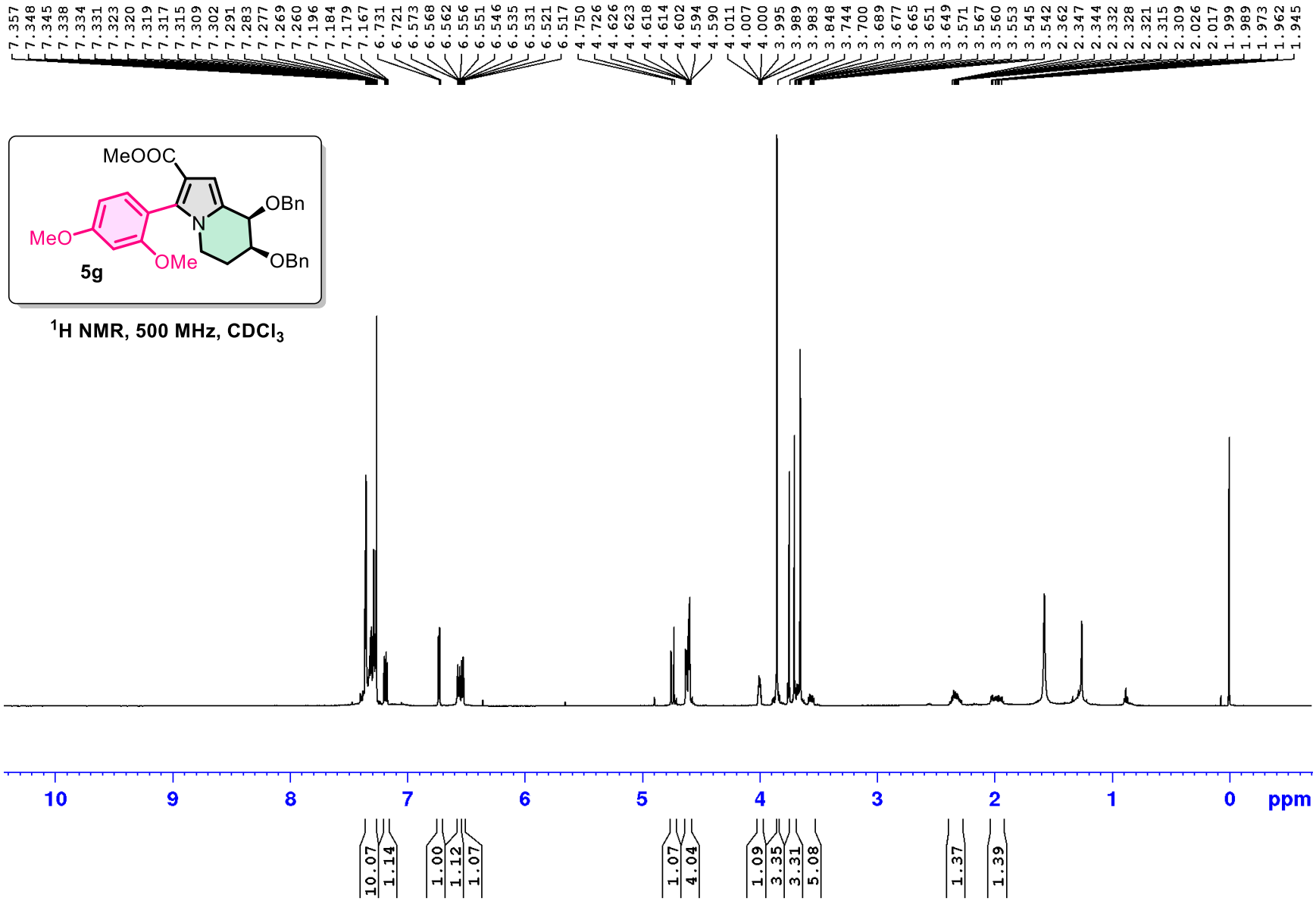
^{1}H NMR, 500 MHz, $CDCl_3$

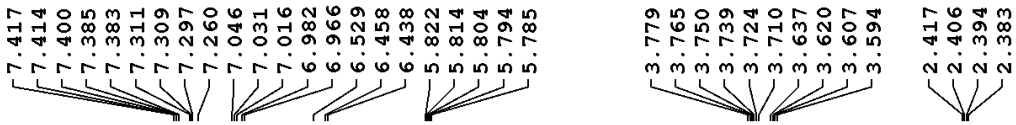


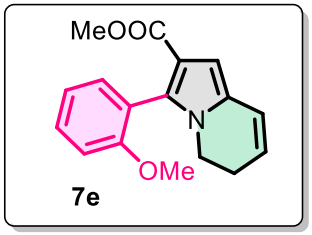


^{13}C NMR, 100 MHz, $CDCl_3$


131.79
128.47
127.83
127.79
127.69
127.63
113.48
111.34
73.40
71.06
70.88
70.44
55.27
50.80
39.97
24.04
MeOOC
OBn
MeO
N
OBn
5f
DEPT 135, 100 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

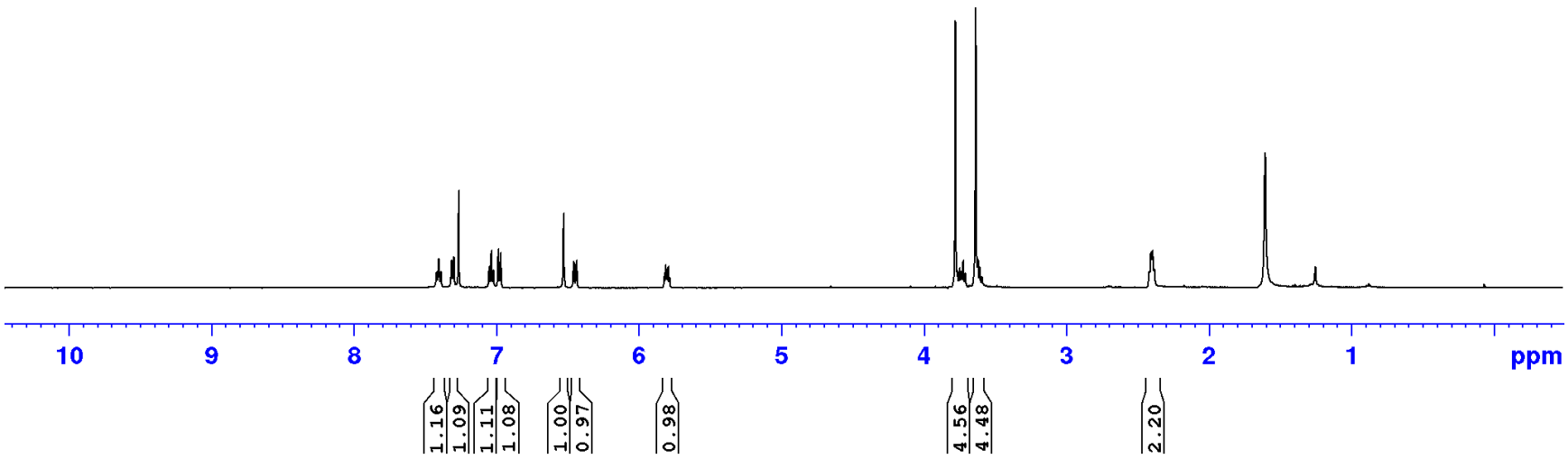

7.357
7.348
7.345
7.338
7.334
7.331
7.323
7.320
7.319
7.317
7.315
7.309
7.302
7.291
7.283
7.277
7.269
7.260
7.196
7.184
7.179
7.167
6.731
6.721
6.573
6.568
6.562
6.556
6.551
6.546
6.535
6.531
6.521
6.517
4.750
4.726
4.626
4.623
4.618
4.614
4.602
4.594
4.590
4.011
4.007
4.000
3.995
3.989
3.983
3.848
3.744
3.700
3.689
3.677
3.665
3.651
3.649
3.571
3.567
3.560
3.553
3.545
3.542
2.362
2.347
2.344
2.332
2.328
2.321
2.315
2.309
2.026
2.017
1.999
1.989
1.973
1.962
1.945
MeOOC
OBn
MeO
N
OMe
OBn
5g
1H NMR, 500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
0
ppm
10.07
1.14
1.00
1.12
1.07
1.07
4.04
1.09
3.35
3.31
5.08
1.37
1.39

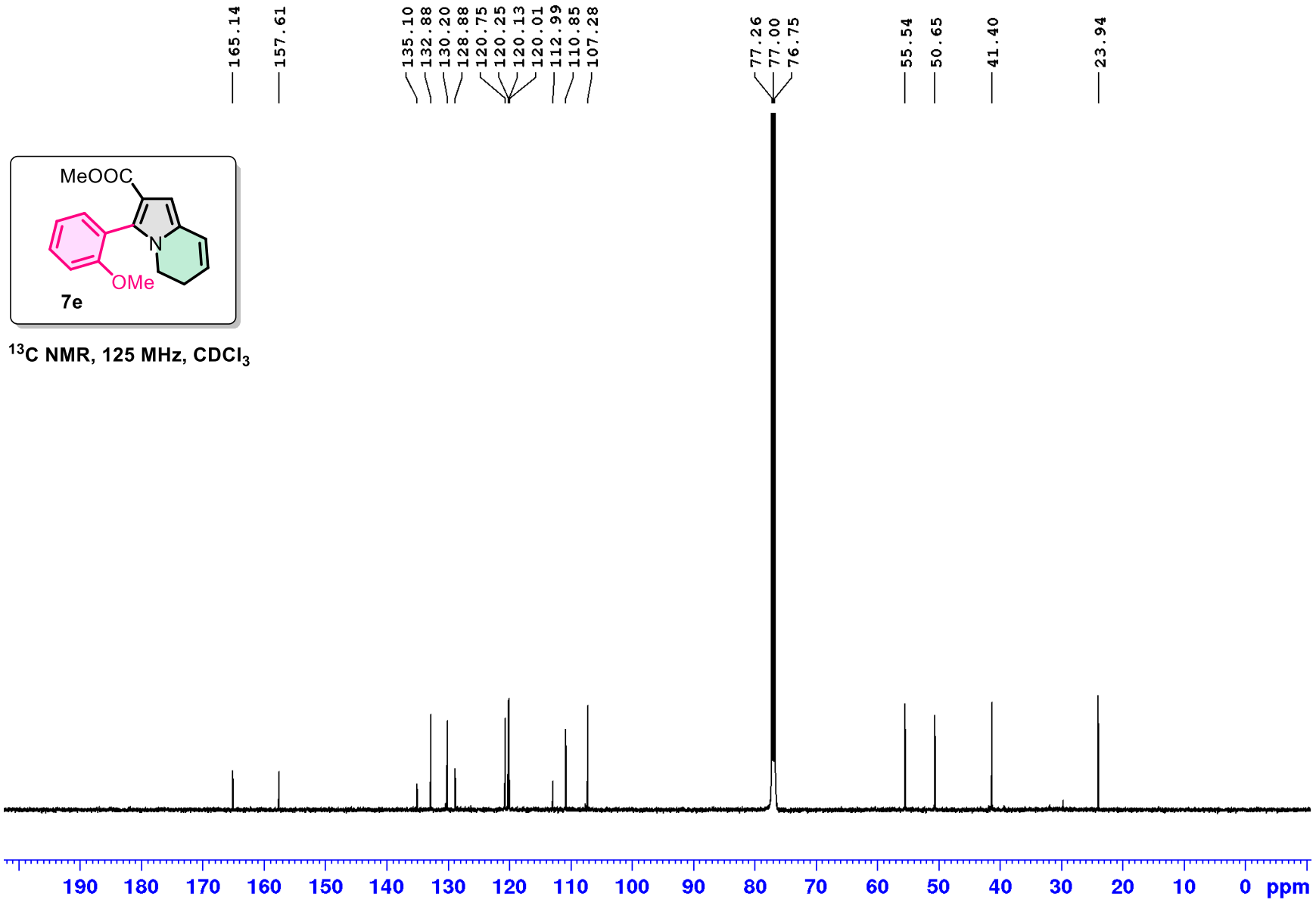




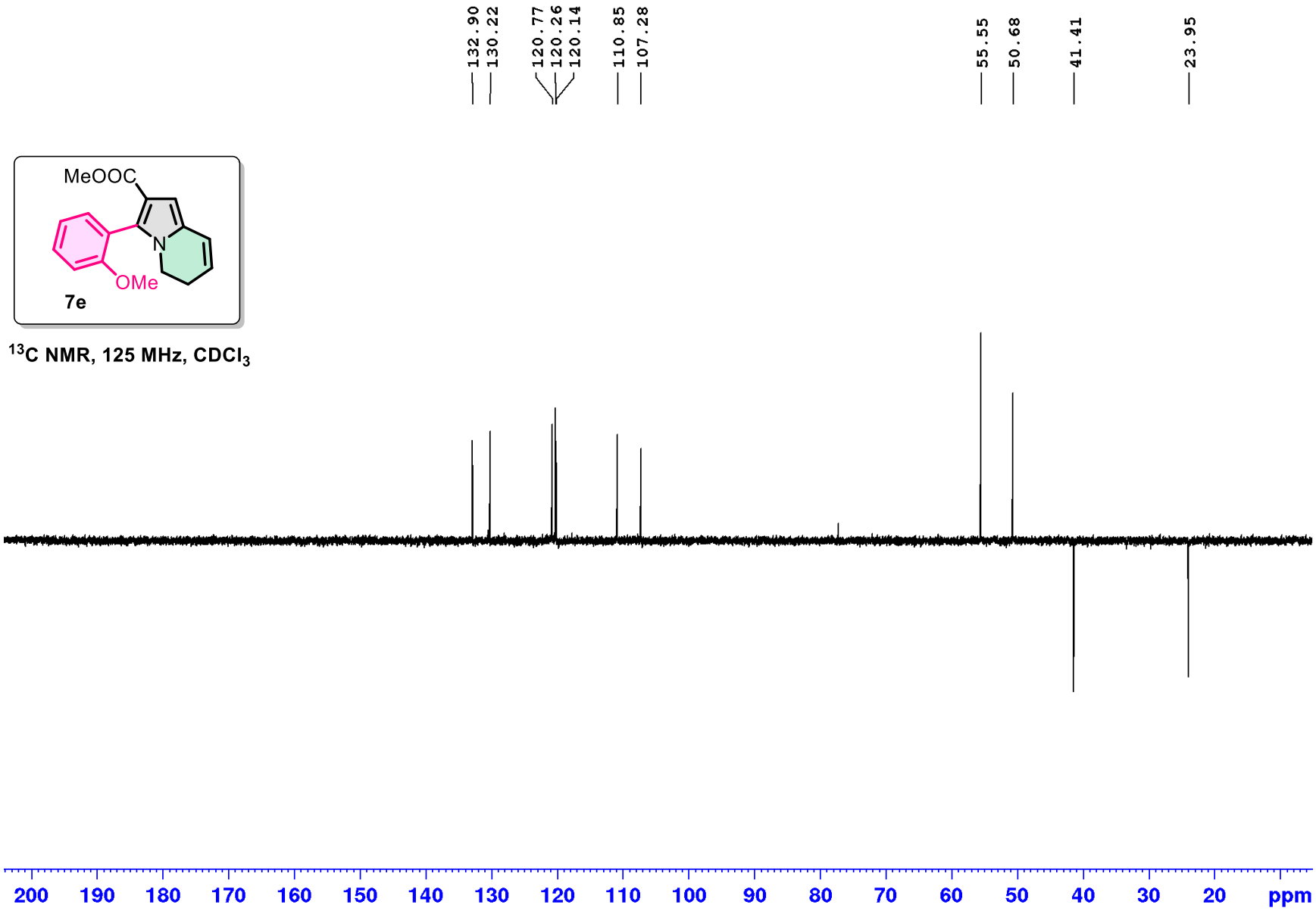
7e

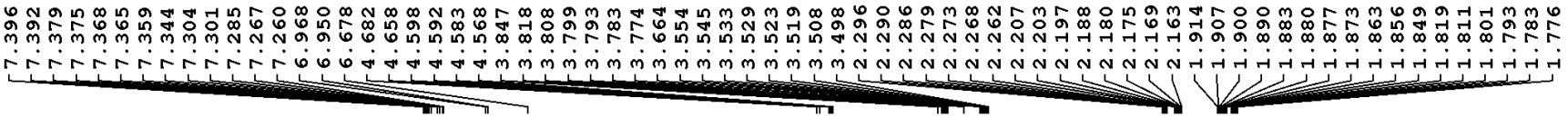
^{1}H NMR, 500 MHz, $CDCl_3$

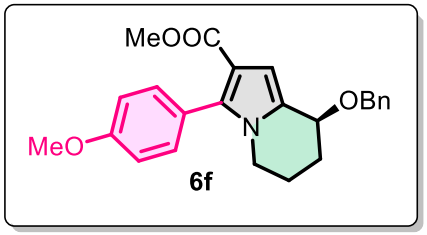




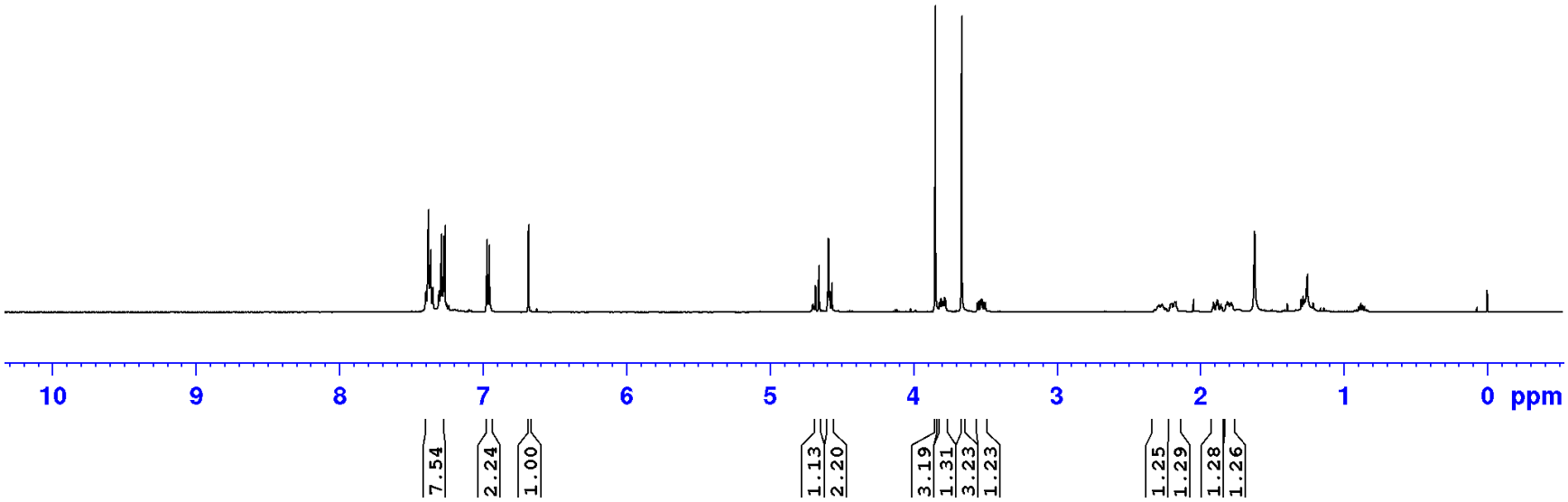
^{13}C NMR, 125 MHz, $CDCl_3$

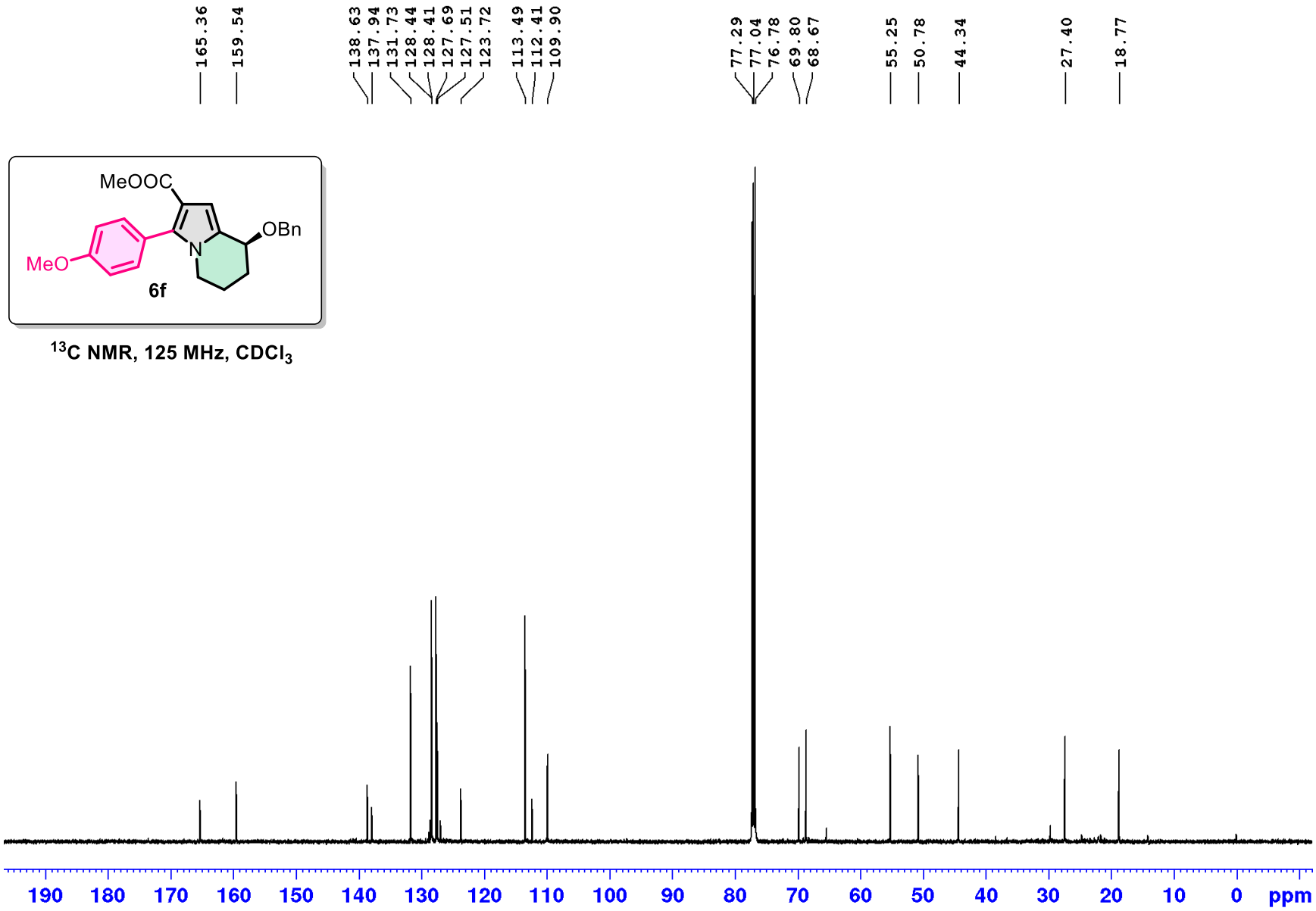

132.90
130.22
120.77
120.26
120.14
110.85
107.28
55.55
50.68
41.41
23.95
MeOOC
N
OMe
7e
^{13}C NMR, 125 MHz, CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



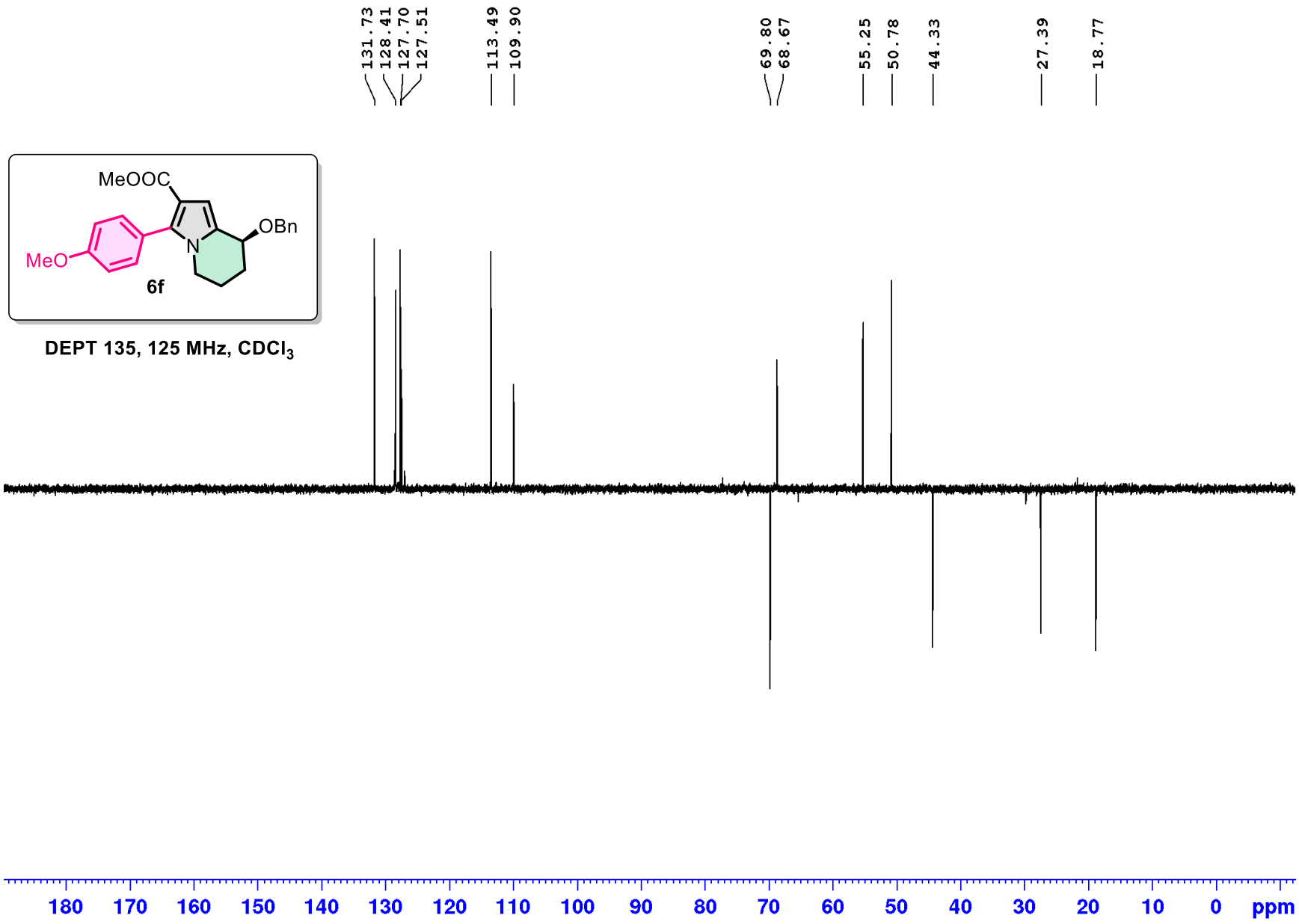


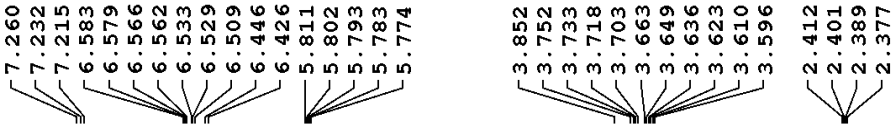
^{1}H NMR, 500 MHz, $CDCl_3$

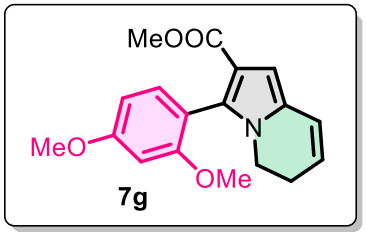




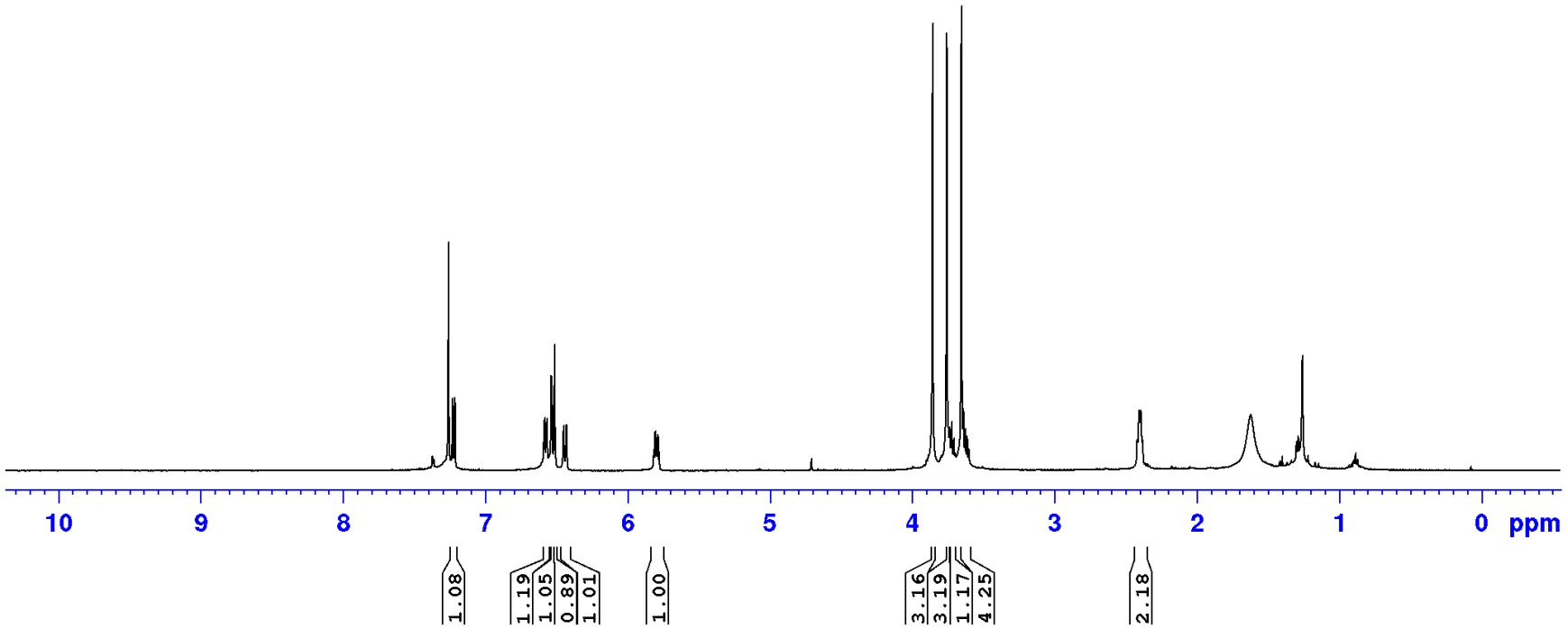
^{13}C NMR, 125 MHz, $CDCl_3$

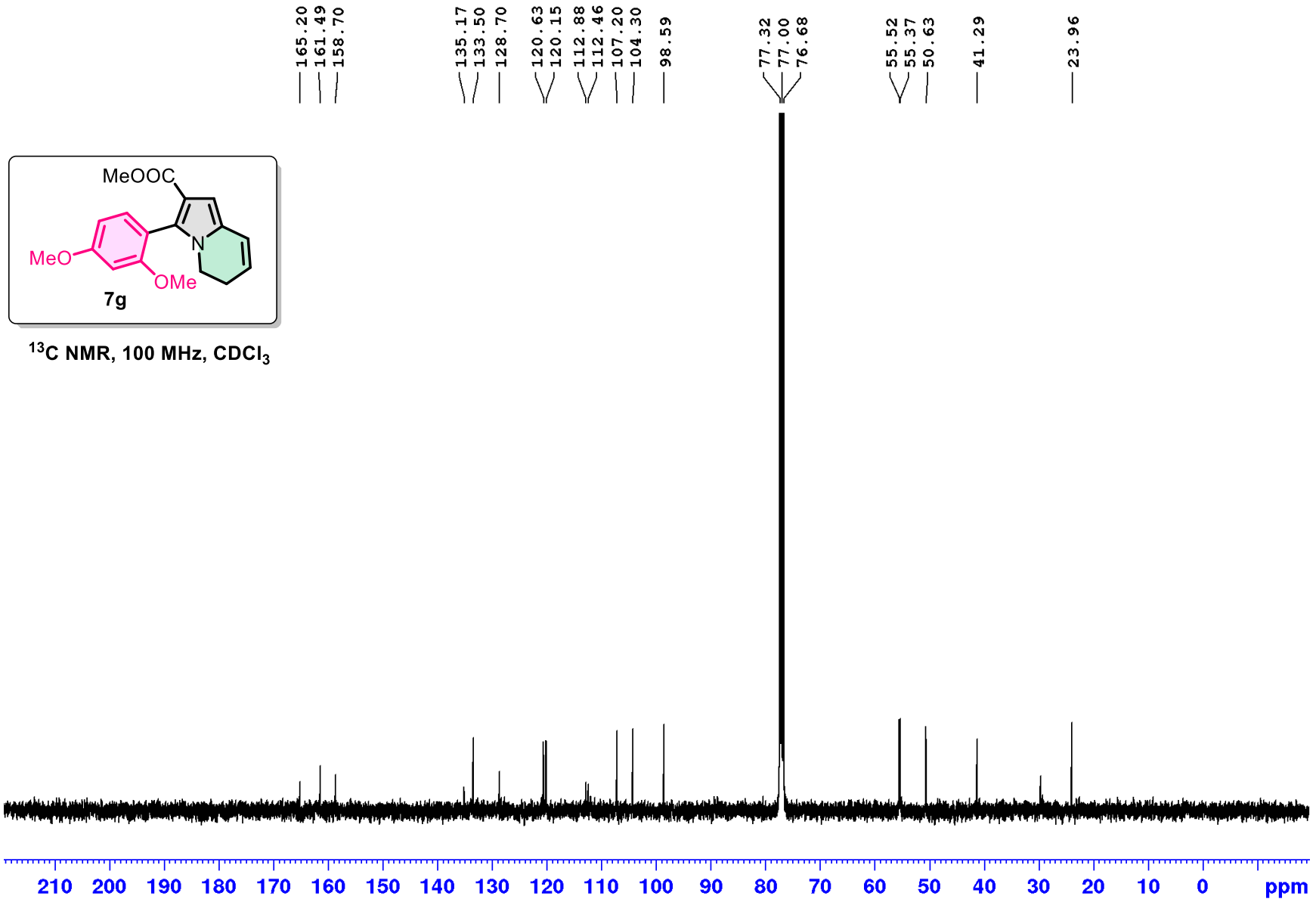

131.73
128.41
127.70
127.51
113.49
109.90
69.80
68.67
55.25
50.78
44.33
27.39
18.77
MeOOC
OBn
MeO
N
6f
DEPT 135, 125 MHz, CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



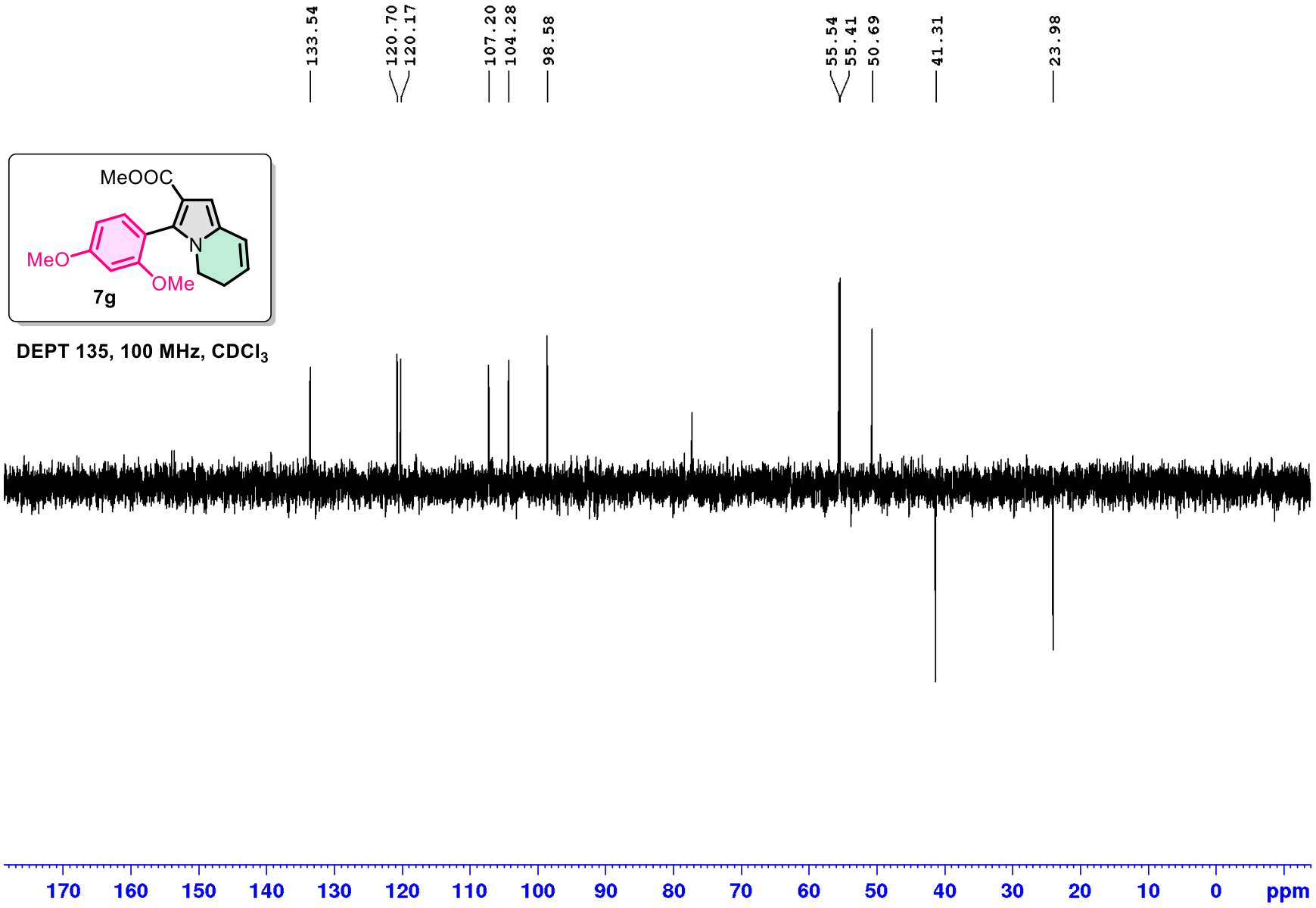


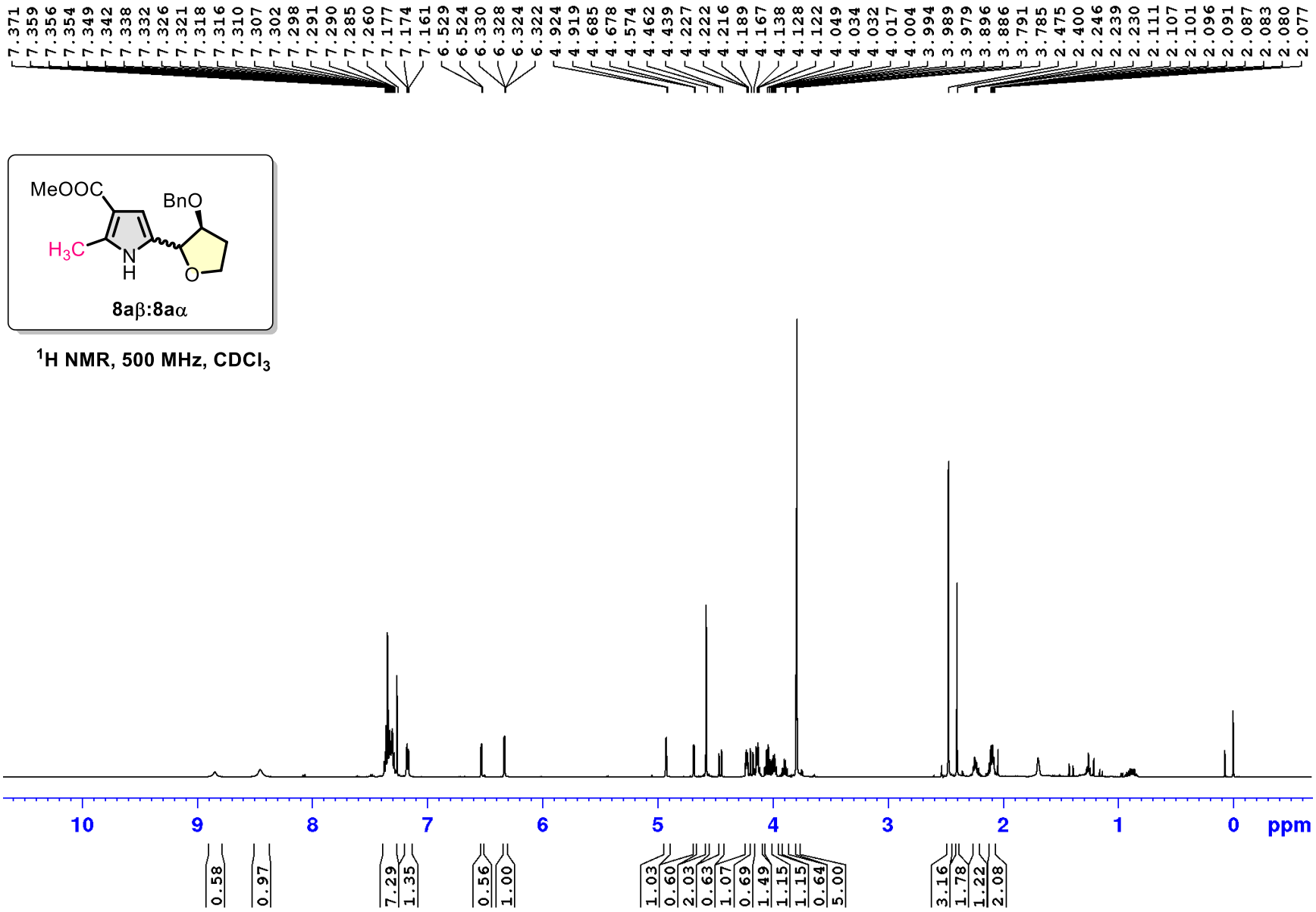
^{1}H NMR, 500 MHz, $CDCl_3$

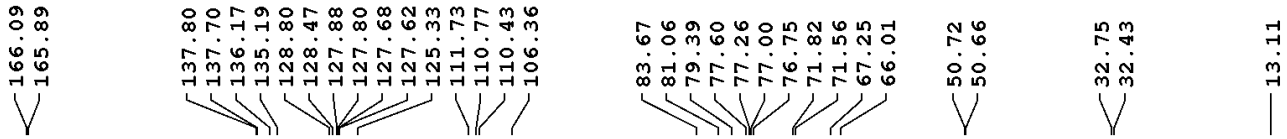


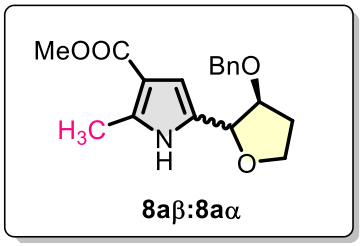


^{13}C NMR, 100 MHz, $CDCl_3$


133.54
120.70
120.17
107.20
104.28
98.58
55.54
55.41
50.69
41.31
23.98
MeOOC
MeO
OMe
N
7g
DEPT 135, 100 MHz, CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

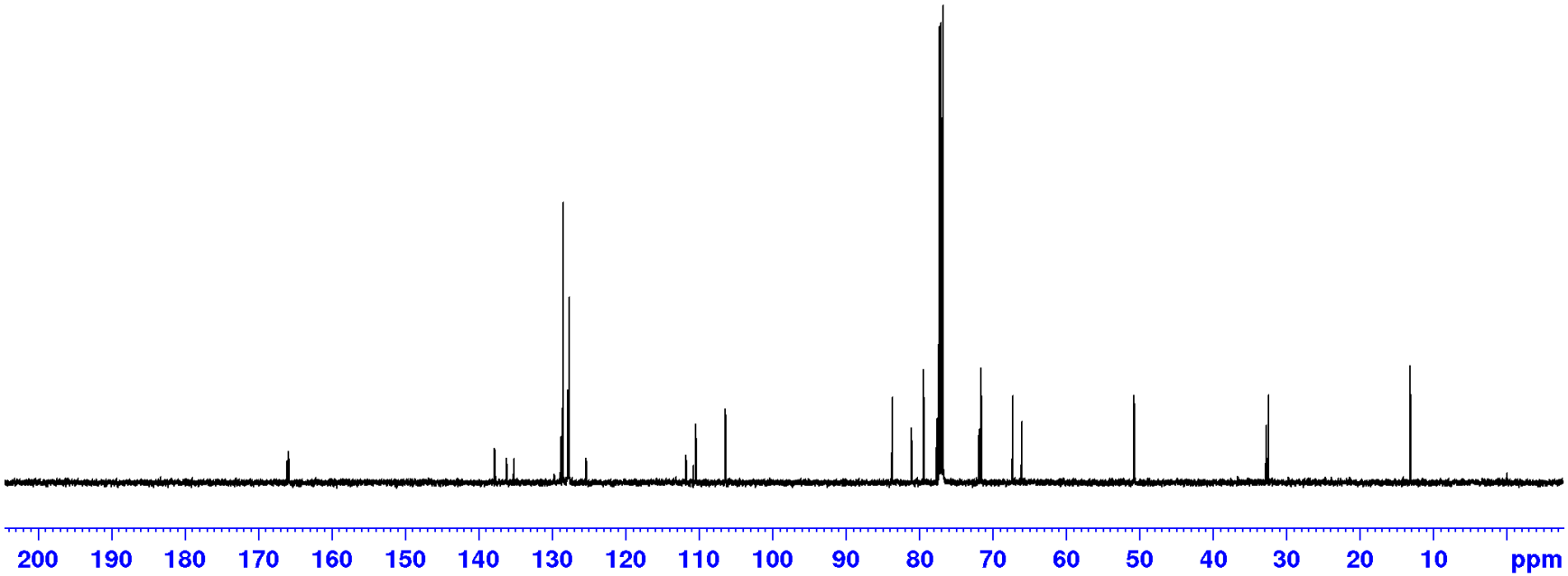

7.371 7.359 7.356 7.354 7.349 7.342 7.338 7.332 7.326 7.321 7.318 7.316 7.310 7.307 7.302 7.298 7.291 7.290 7.285 7.260 7.177 7.174 7.161 6.529 6.524 6.330 6.328 6.324 6.322 4.924 4.919 4.685 4.678 4.574 4.462 4.439 4.227 4.222 4.216 4.189 4.167 4.138 4.128 4.122 4.049 4.034 4.032 4.017 4.004 3.994 3.989 3.979 3.896 3.886 3.791 3.785 2.475 2.400 2.246 2.239 2.230 2.111 2.107 2.101 2.096 2.091 2.087 2.083 2.080 2.077
MeOOC
BnO
H3C
N
H
O
8aβ:8aα
1H NMR, 500 MHz, CDCl3
10 9 8 7 6 5 4 3 2 1 0 ppm
0.58 0.97 7.29 1.35 0.56 1.00 1.03 0.60 2.03 0.63 1.07 0.69 1.49 1.15 1.15 0.64 5.00 3.16 1.78 1.22 2.08

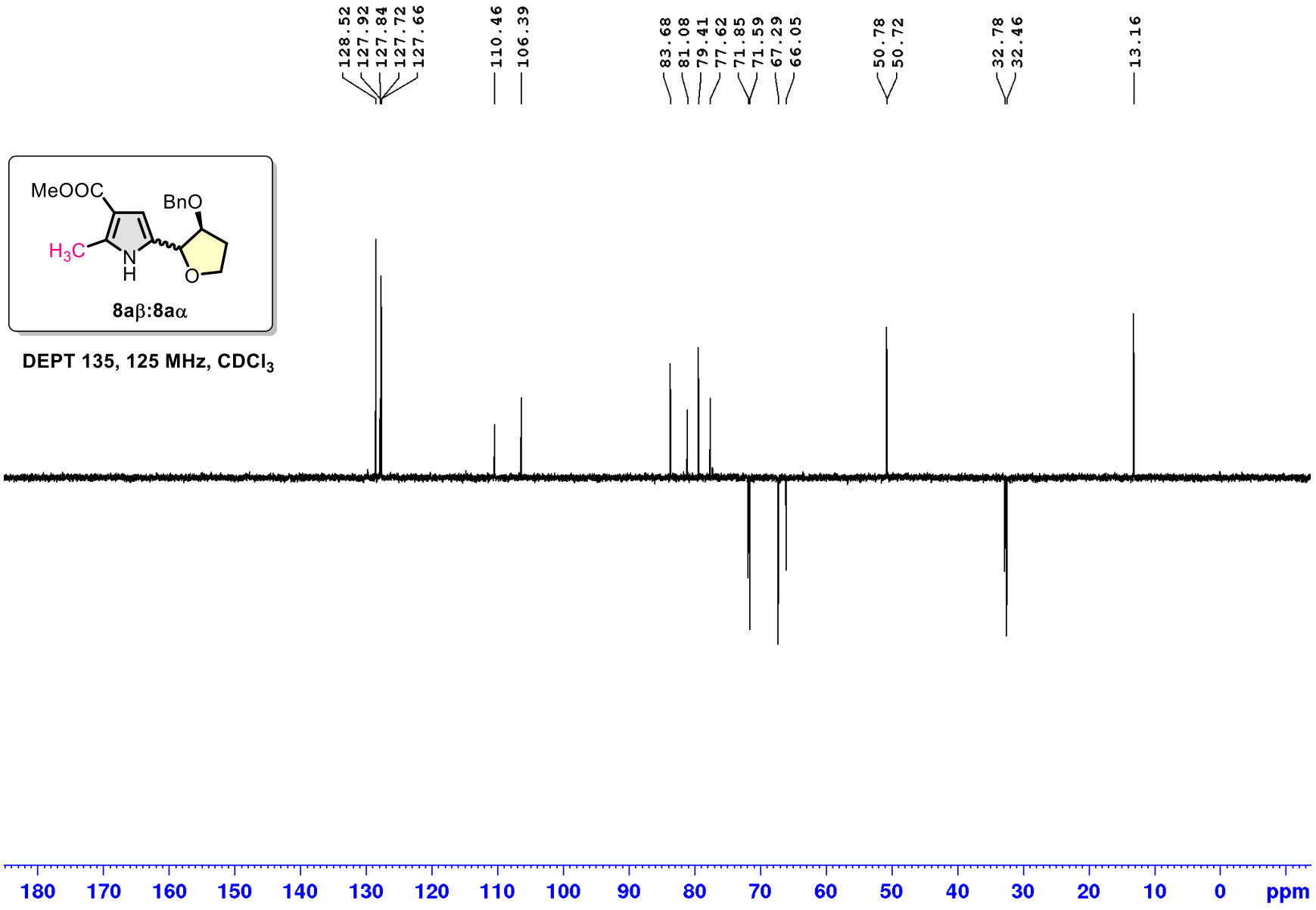


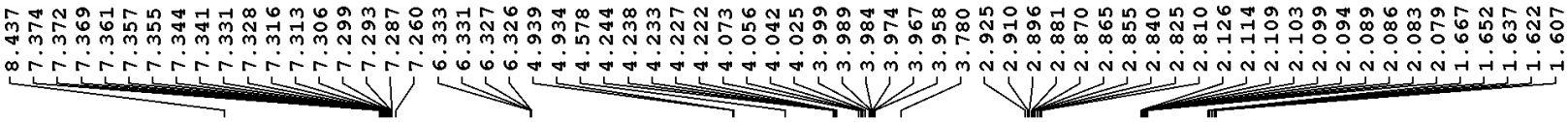


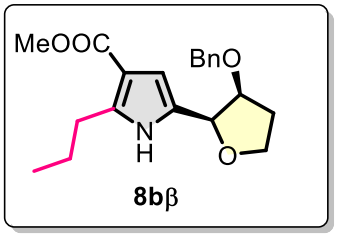
8aβ:8aα

^{13}C NMR, 125 MHz, $CDCl_3$



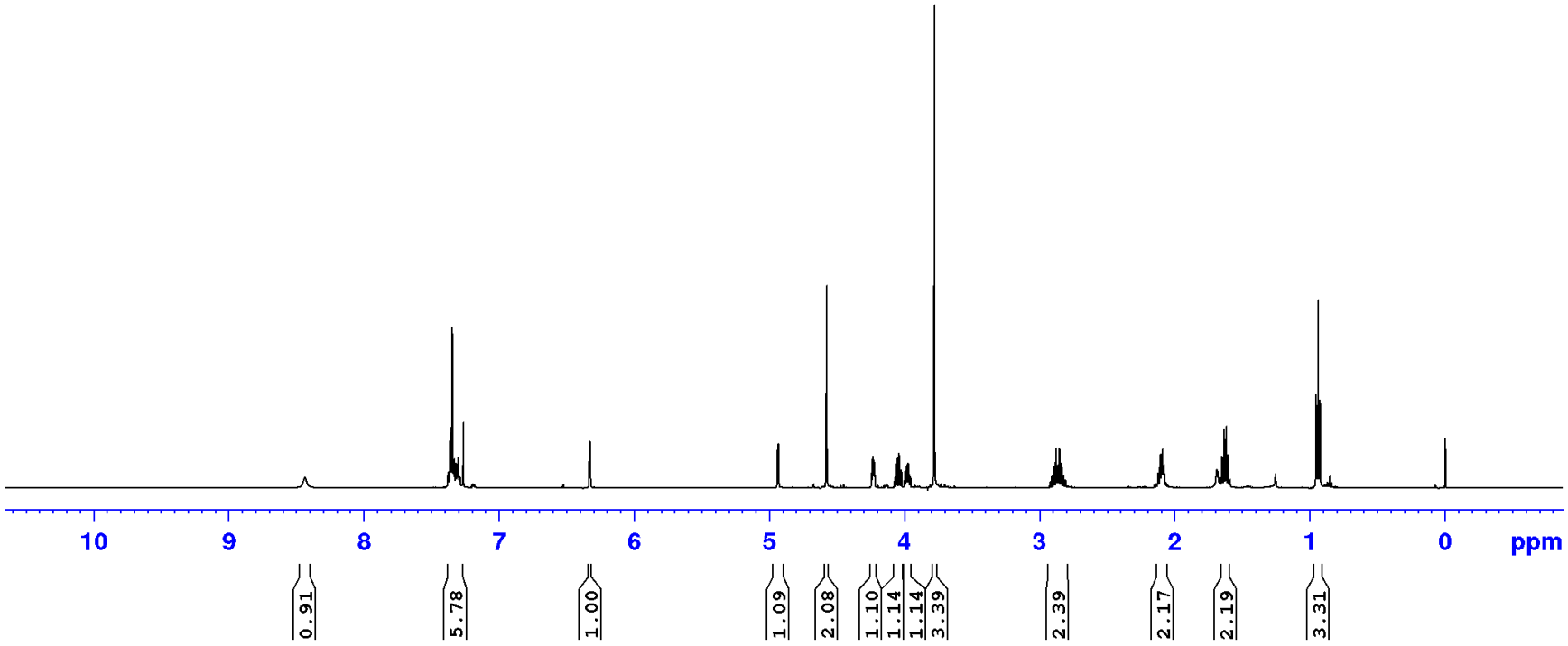

128.52
127.92
127.84
127.72
127.66
110.46
106.39
83.68
81.08
79.41
77.62
71.85
71.59
67.29
66.05
50.78
50.72
32.78
32.46
13.16
MeOOC
BnO
H3C
N
H
O
8aβ:8aα
DEPT 135, 125 MHz, CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

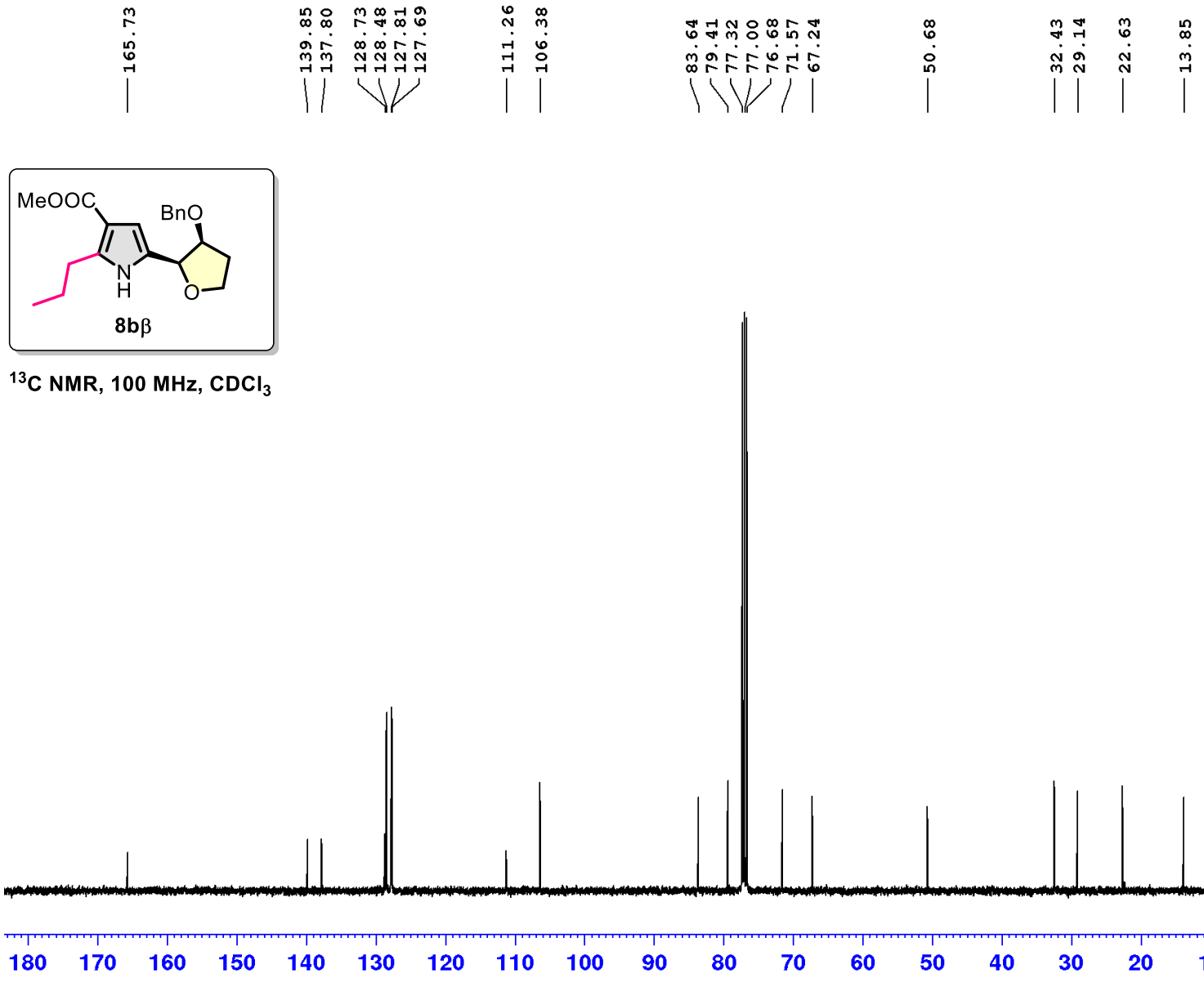




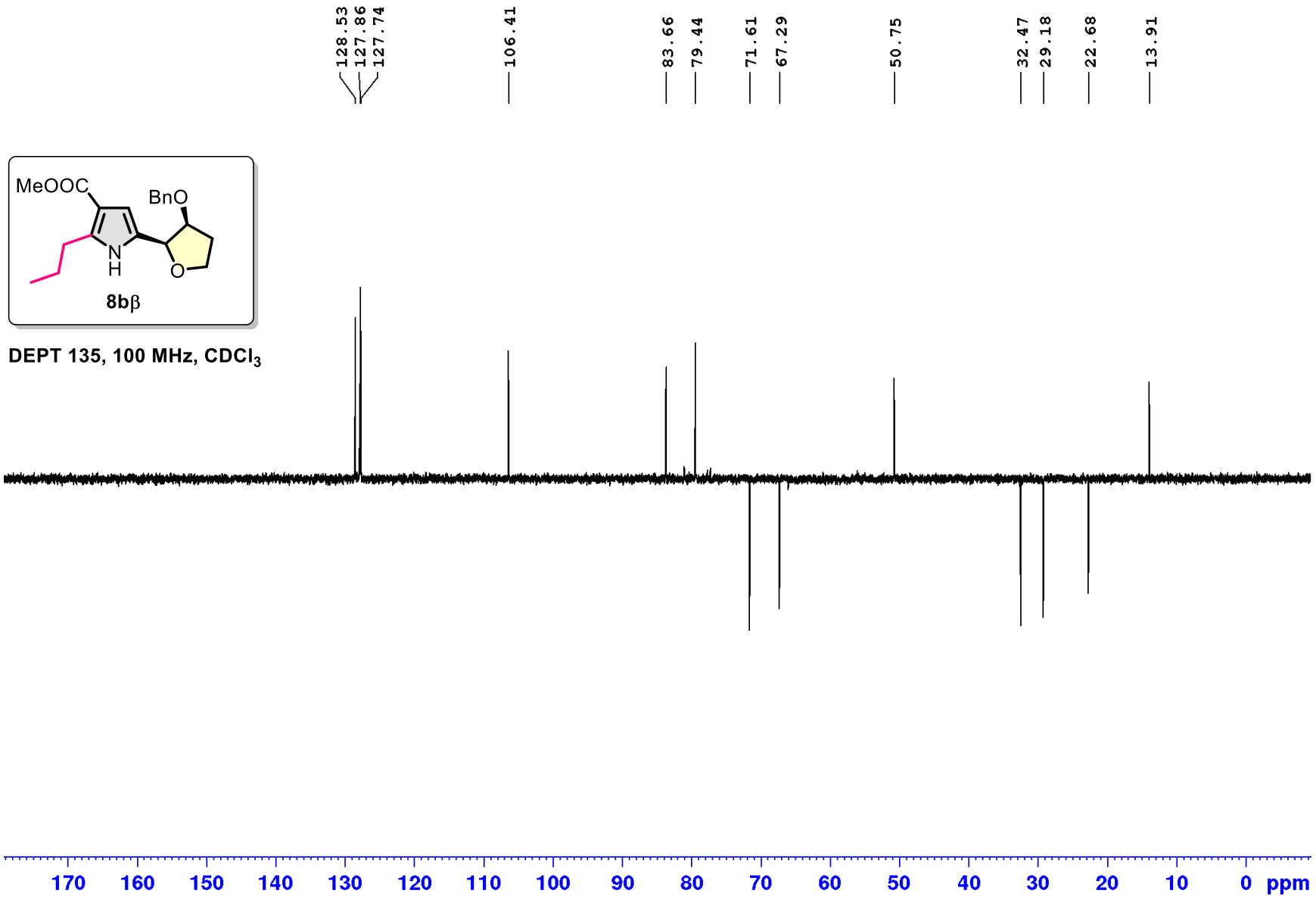
8bβ

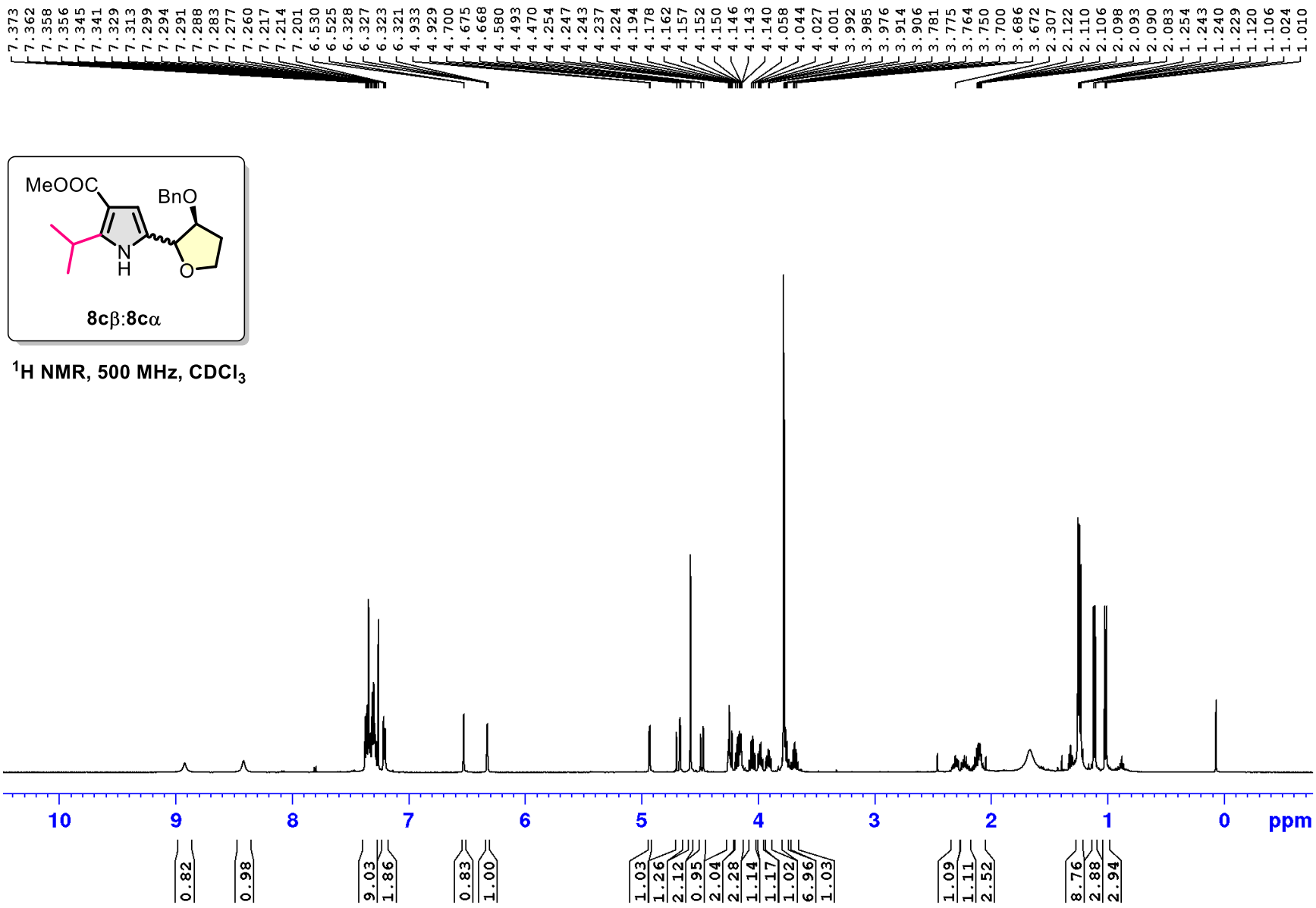
^{1}H NMR, 500 MHz, $CDCl_3$



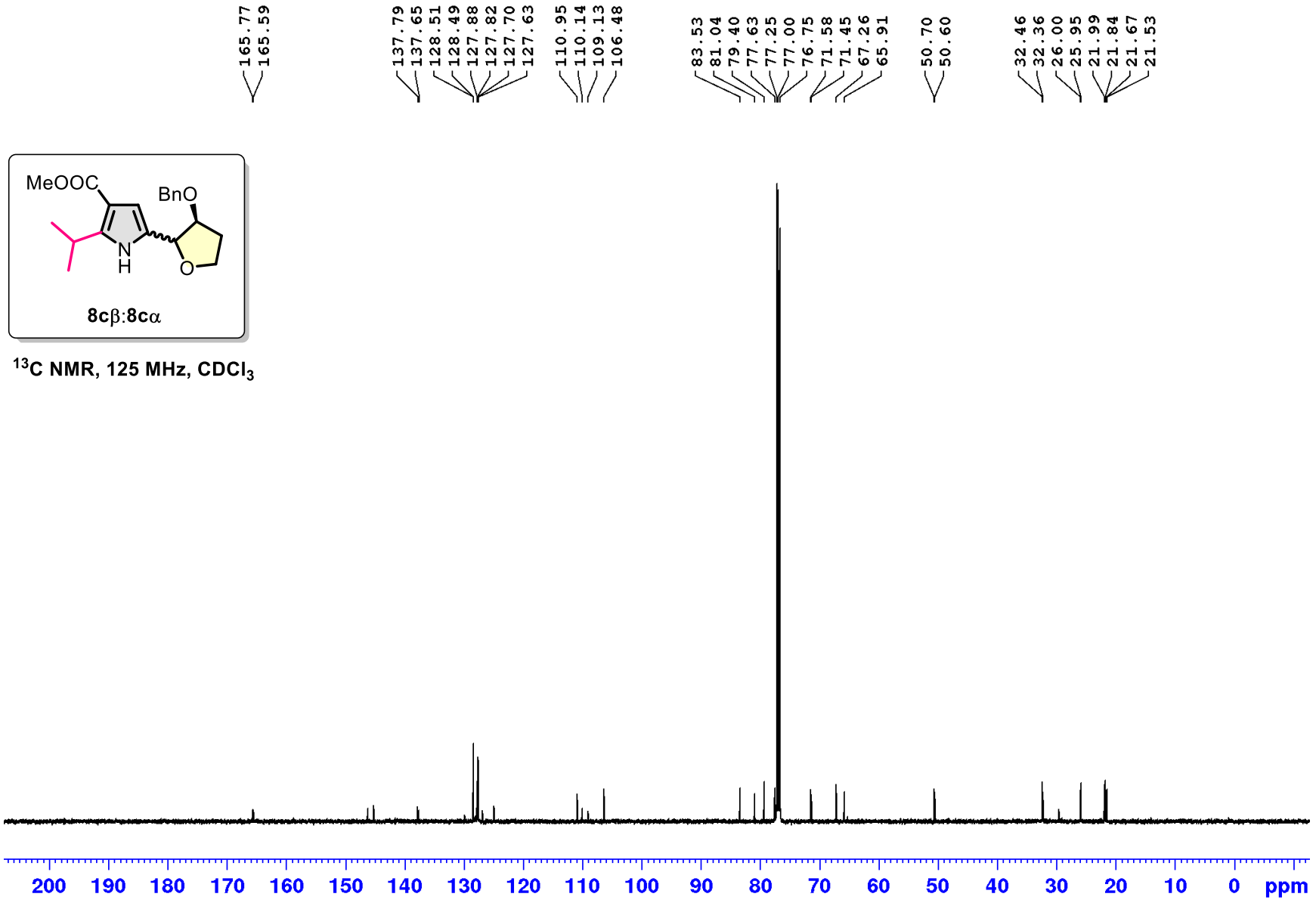


^{13}C NMR, 100 MHz, $CDCl_3$


128.53
127.86
127.74
106.41
83.66
79.44
71.61
67.29
50.75
32.47
29.18
22.68
13.91
MeOOC
BnO
N
H
O
8bβ
DEPT 135, 100 MHz, CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



^{1}H NMR, 500 MHz, $CDCl_3$



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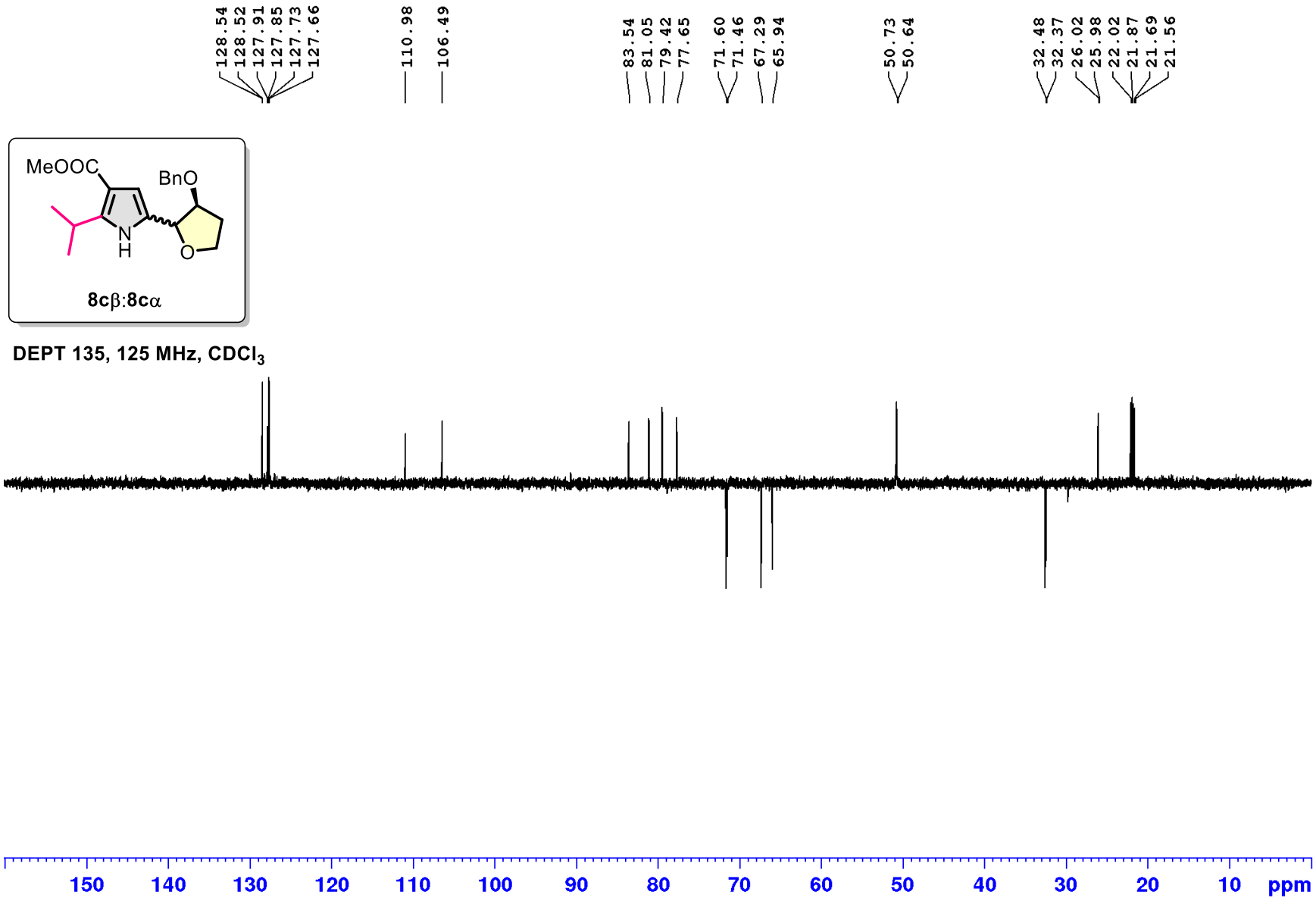
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128.52
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127.85
127.73
127.66
110.98
106.49
83.54
81.05
79.42
77.65
71.60
71.46
67.29
65.94
50.73
50.64
32.48
32.37
26.02
25.98
22.02
21.87
21.69
21.56
MeOOC
BnO
N
H
O
8cβ:8cα
DEPT 135, 125 MHz, CDCl3
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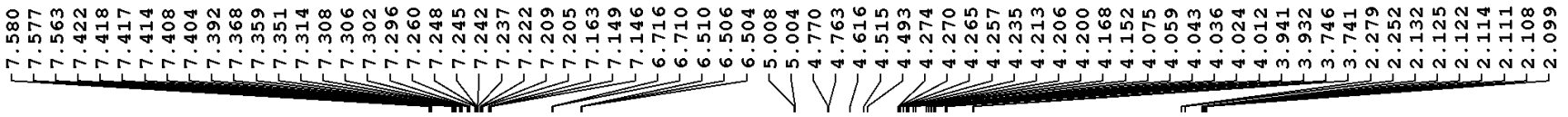
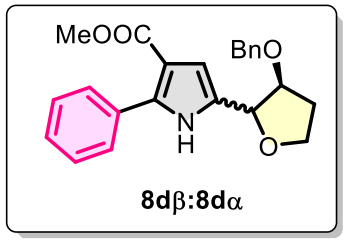
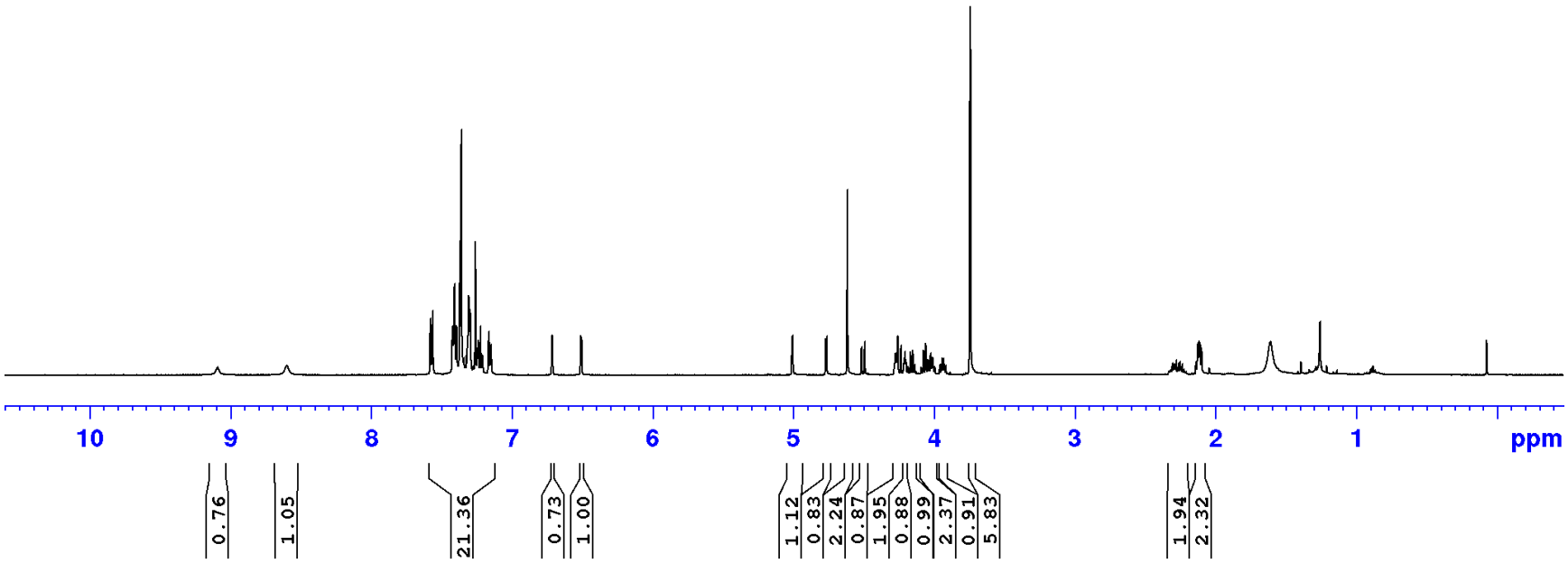
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

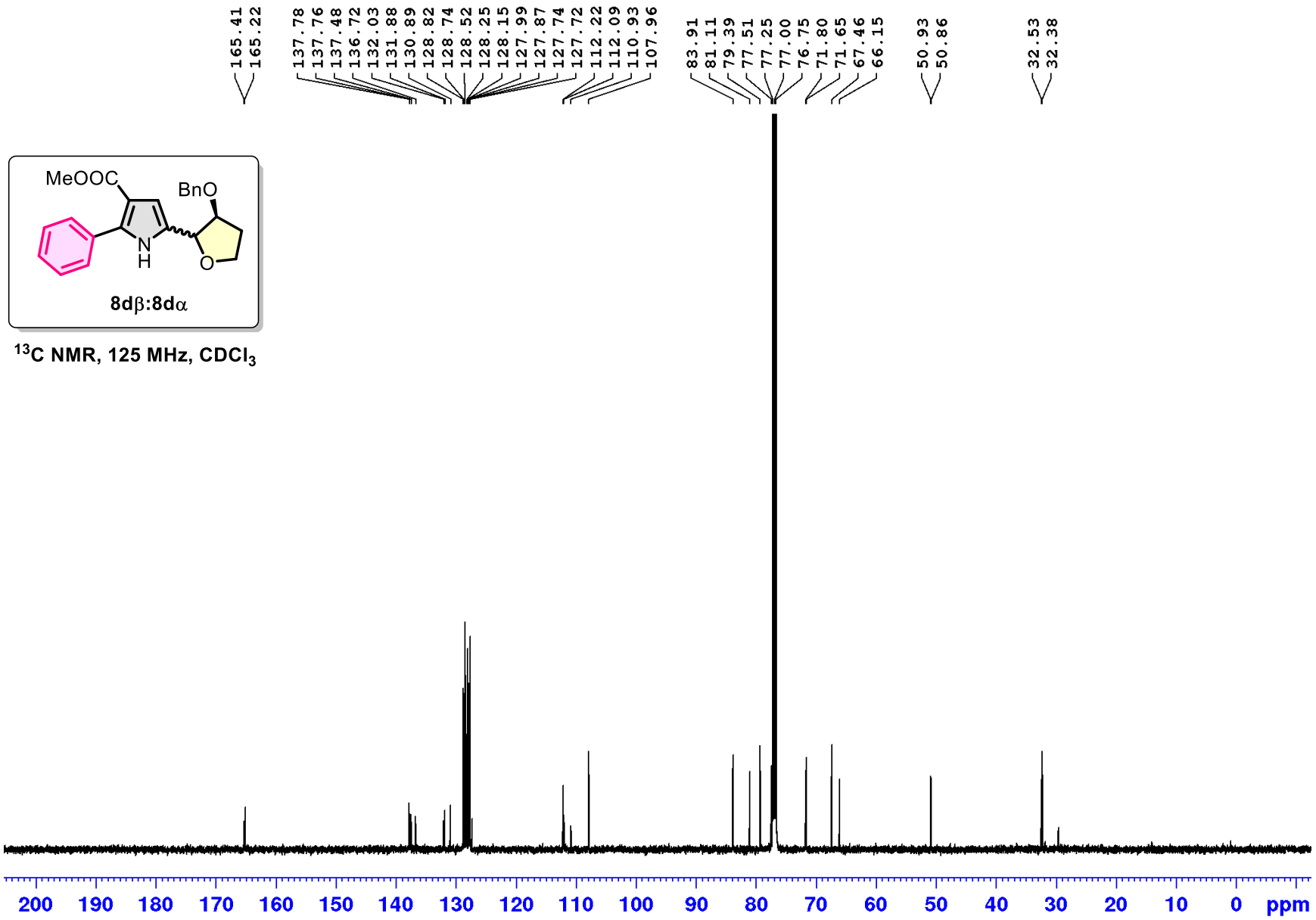




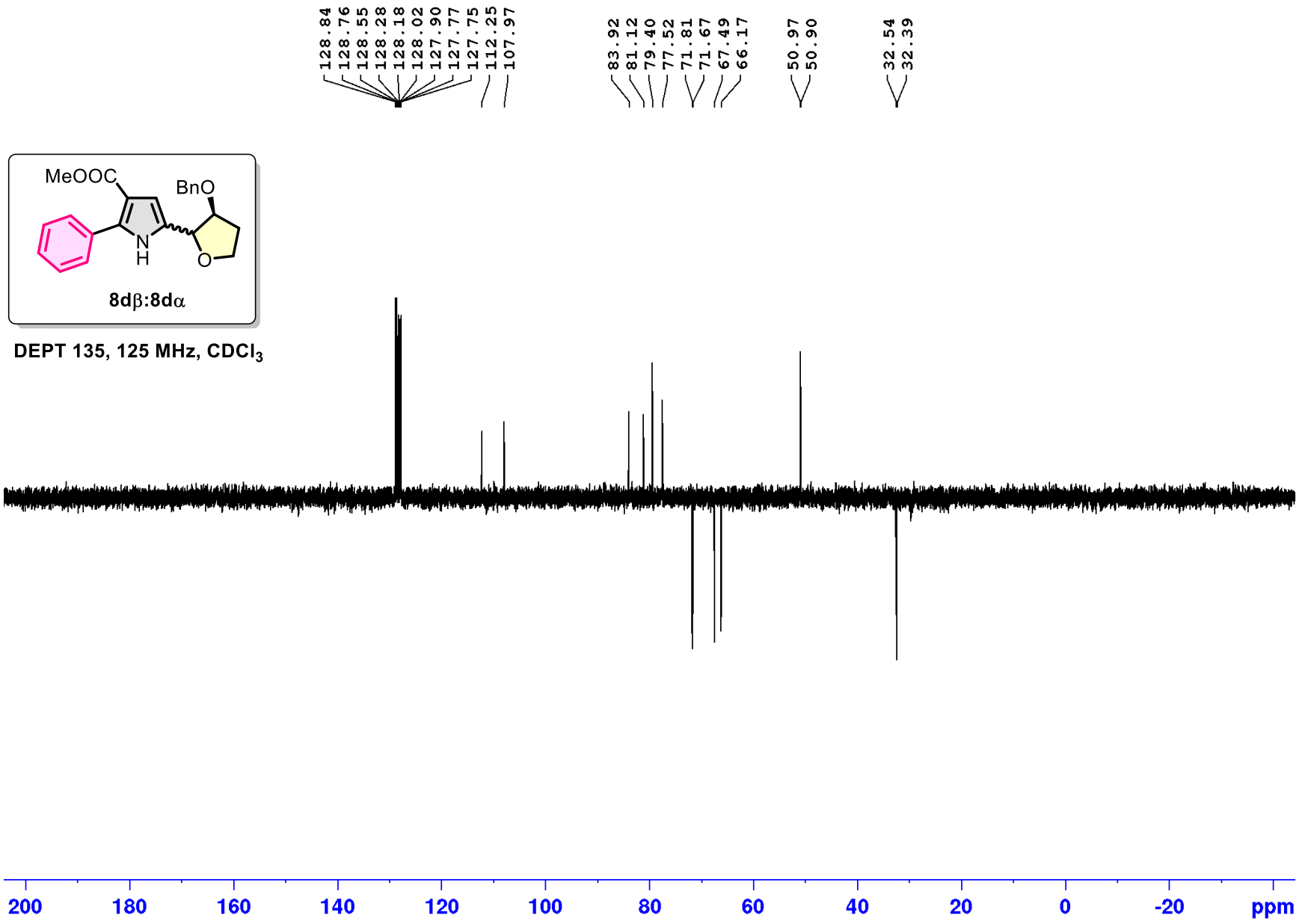
8dβ:8dα

^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 125 MHz, $CDCl_3$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128.02
127.90
127.77
127.75
112.25
107.97
83.92
81.12
79.40
77.52
71.81
71.67
67.49
66.17
50.97
50.90
32.54
32.39
MeOOC
BnO
N
H
O
8dβ:8dα
DEPT 135, 125 MHz, CDCl3
200
180
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20
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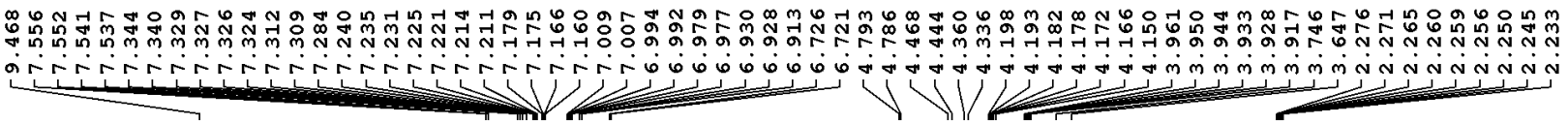
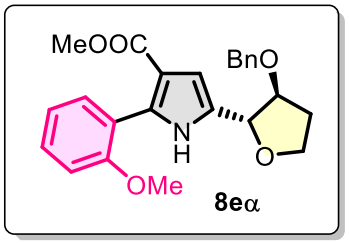
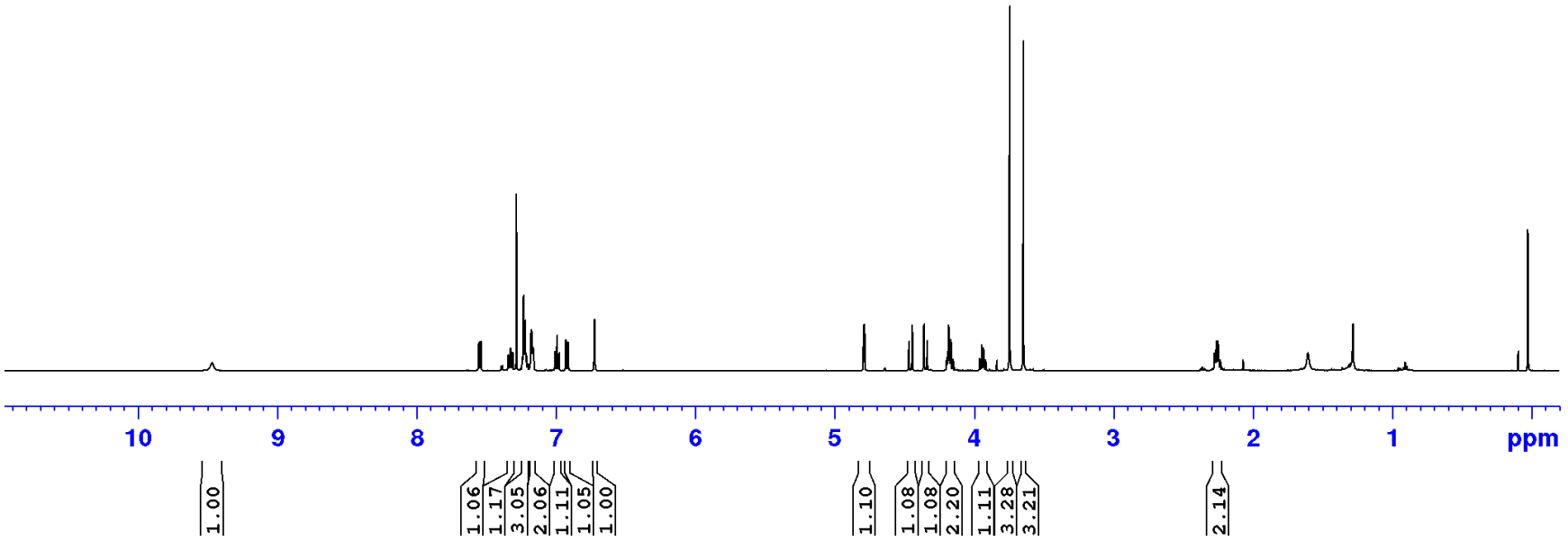
-20
ppm

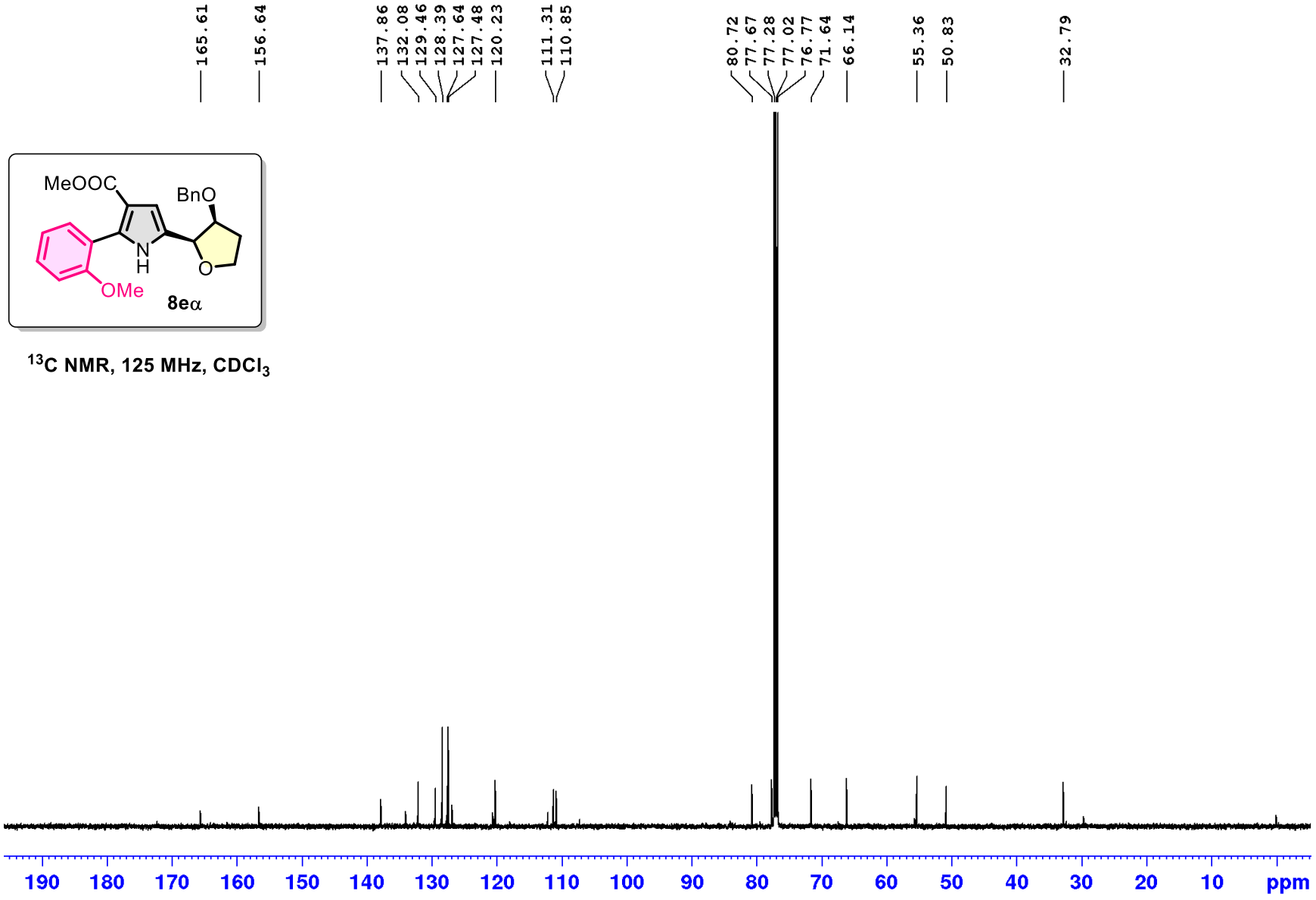




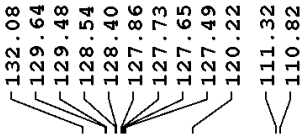
8eα

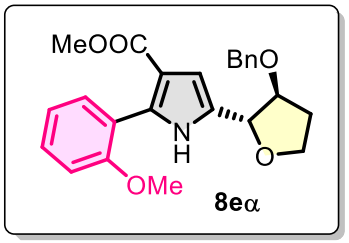
^{1}H NMR, 500 MHz, $CDCl_3$





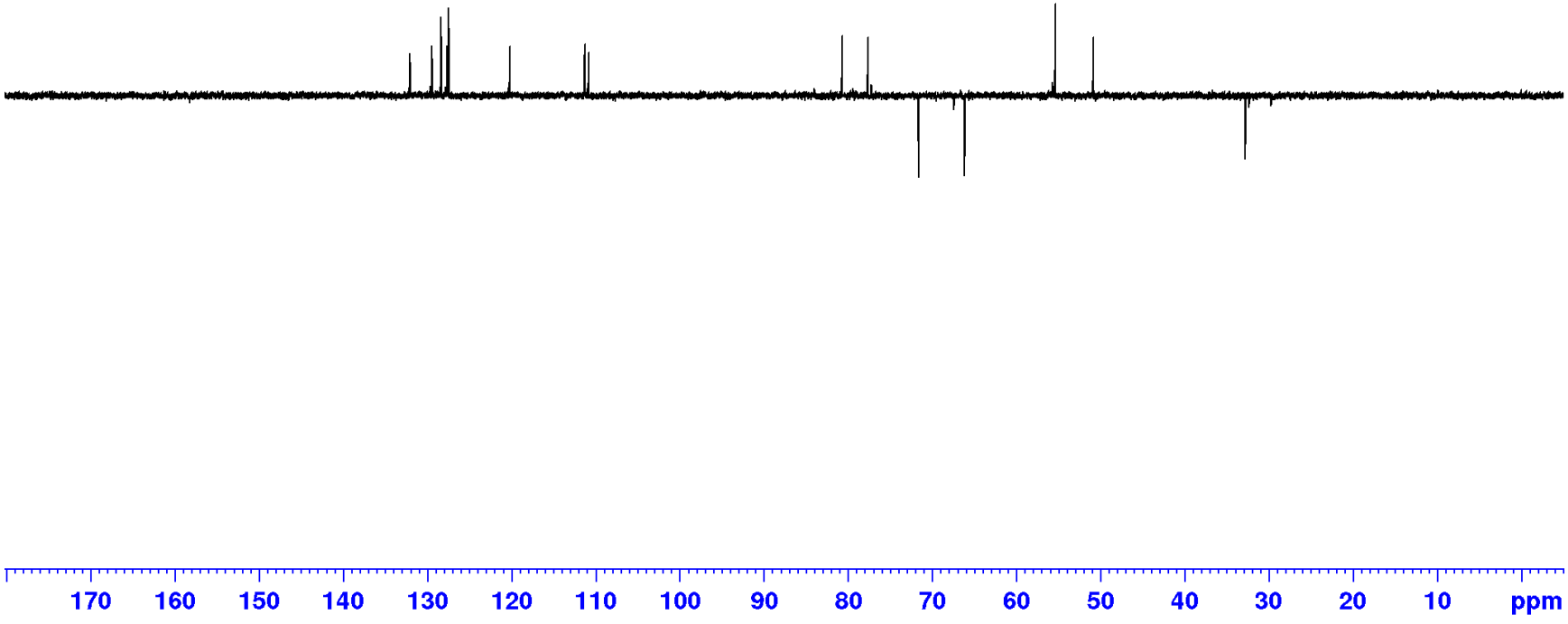
^{13}C NMR, 125 MHz, $CDCl_3$

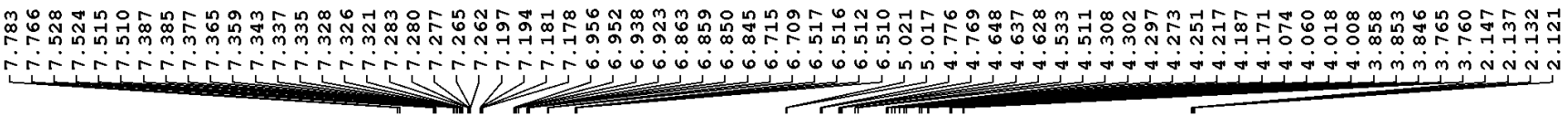


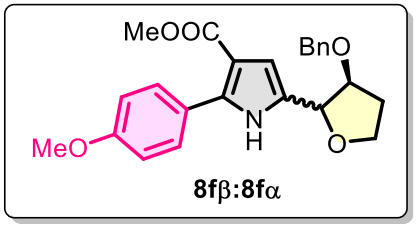


8eα

DEPT 135, 125 MHz, $CDCl_3$

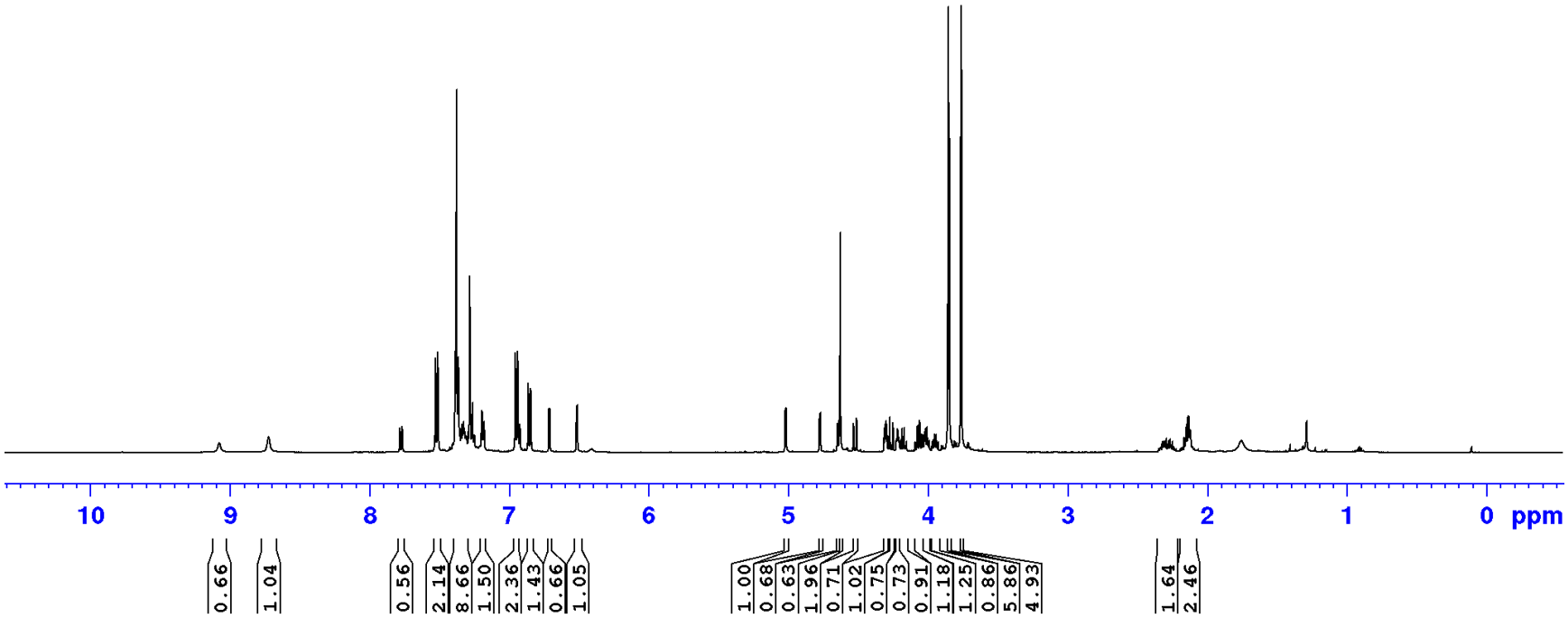


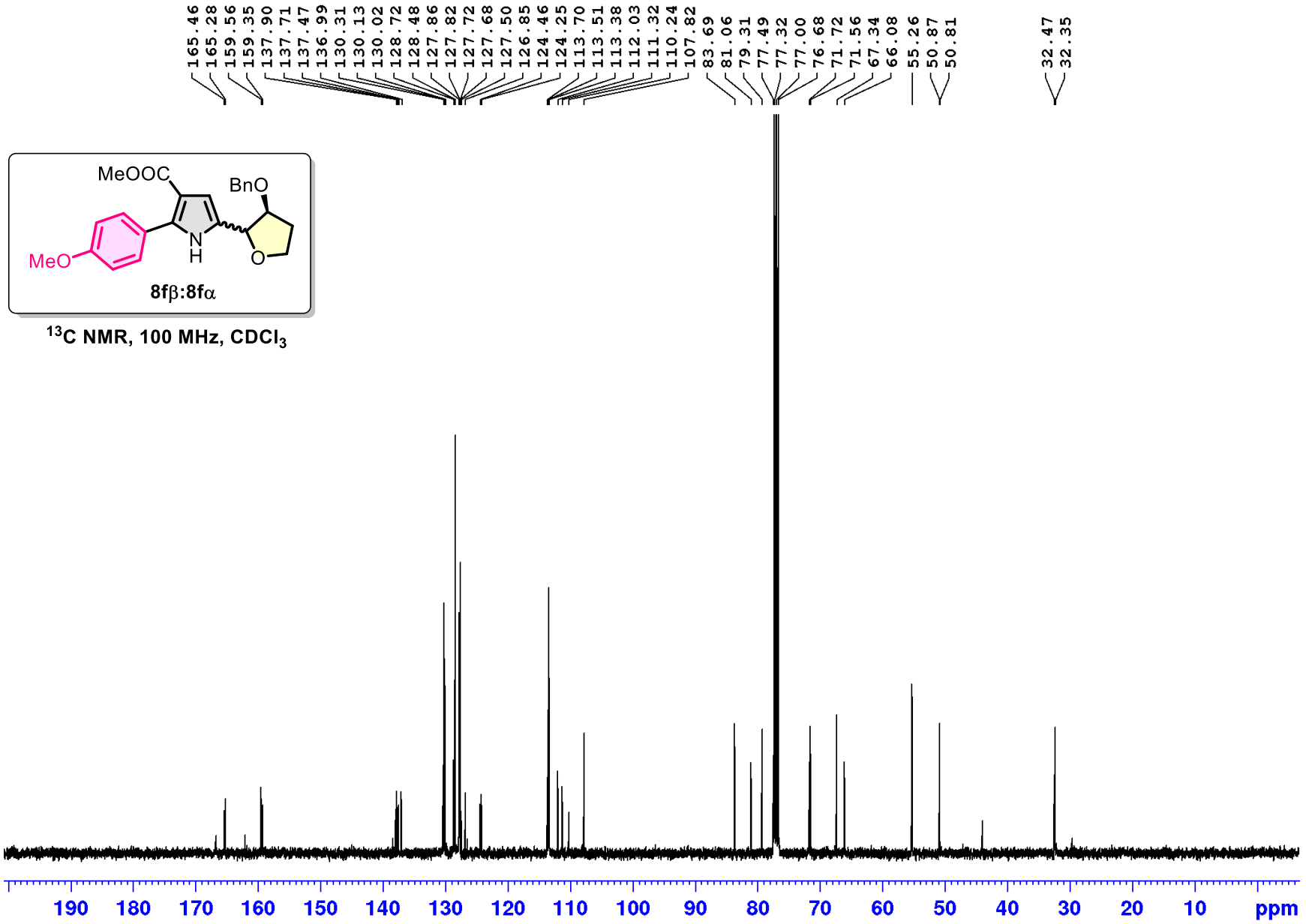




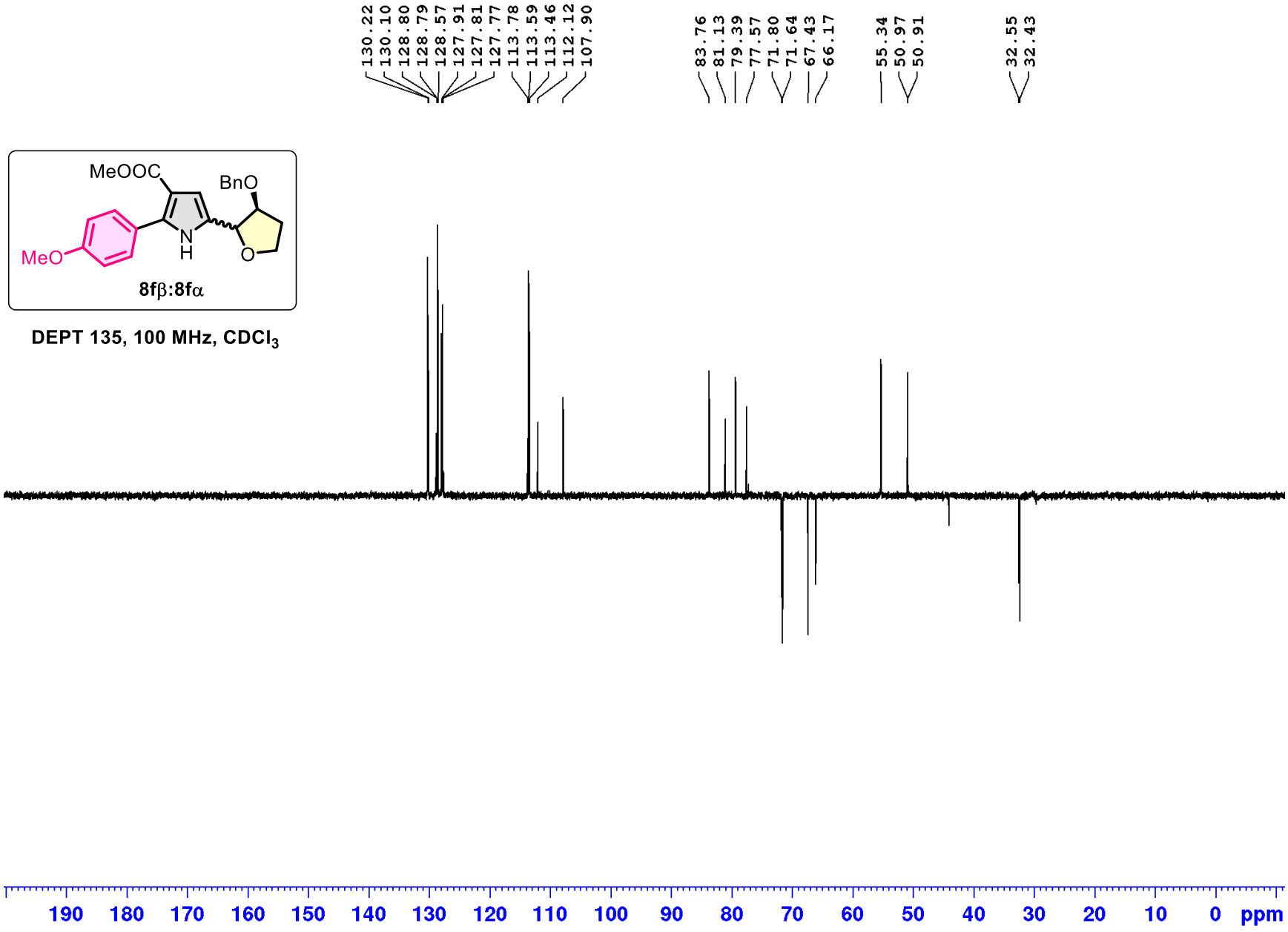
8fβ:8fα

^{1}H NMR, 500 MHz, $CDCl_3$





^{13}C NMR, 100 MHz, $CDCl_3$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83.76
81.13
79.39
77.57
71.80
71.64
67.43
66.17
55.34
50.97
50.91
32.55
32.43
MeOOC
BnO
MeO
N
H
O
8fβ:8fα
DEPT 135, 100 MHz, CDCl3
190
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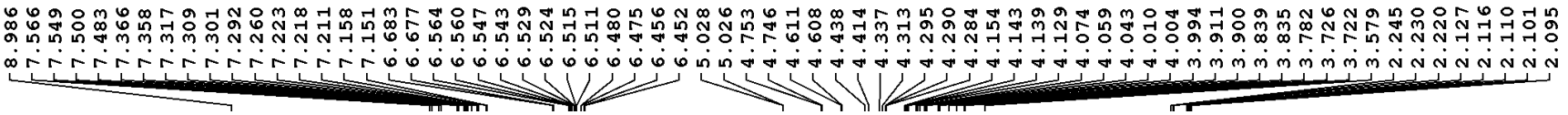
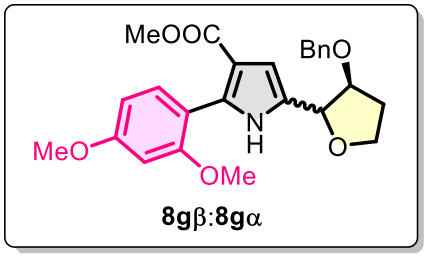
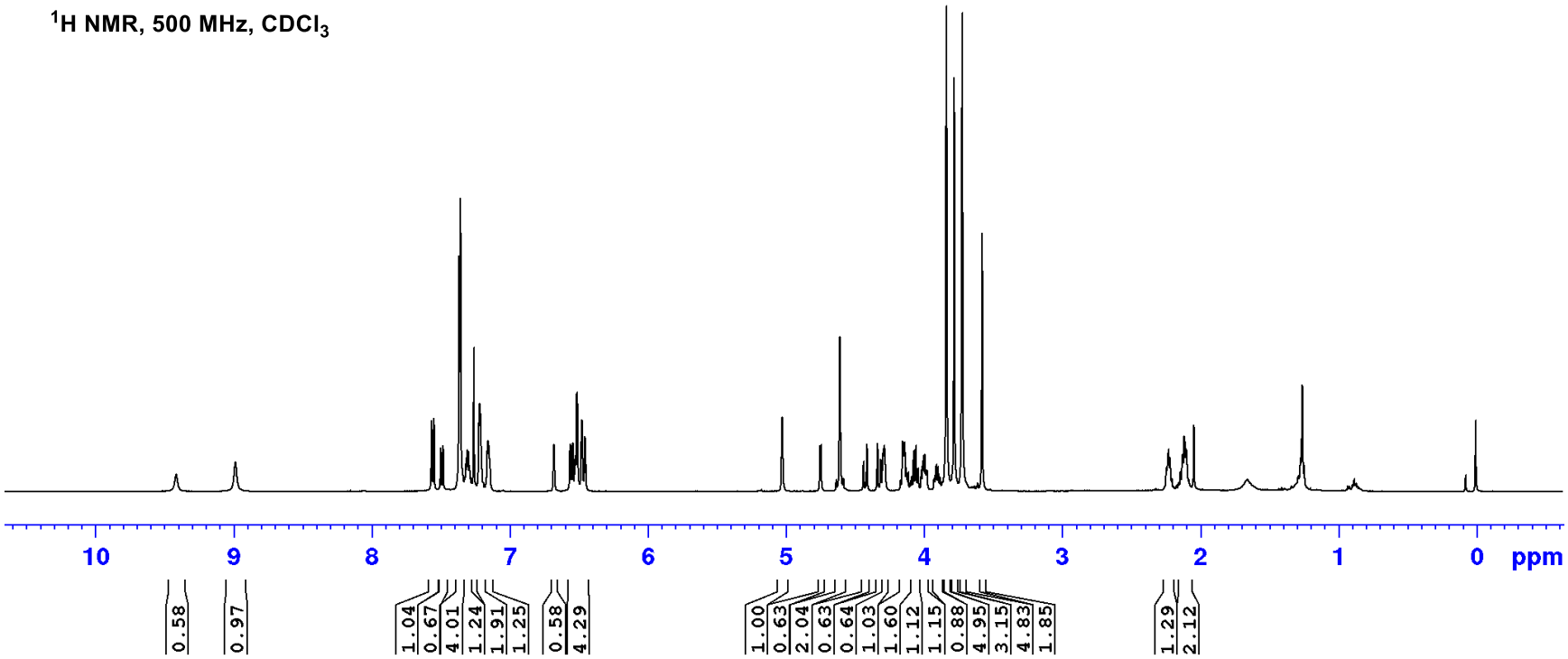
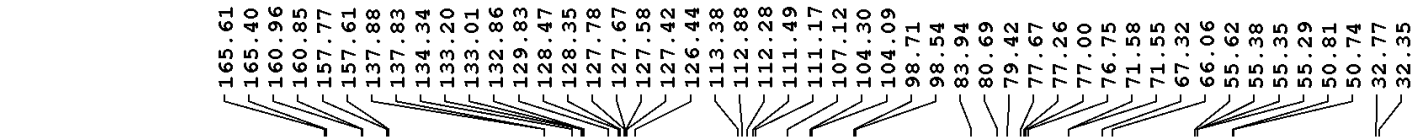


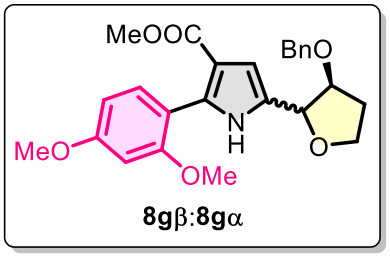


8gβ:8gα

^{1}H NMR, 500 MHz, $CDCl_3$

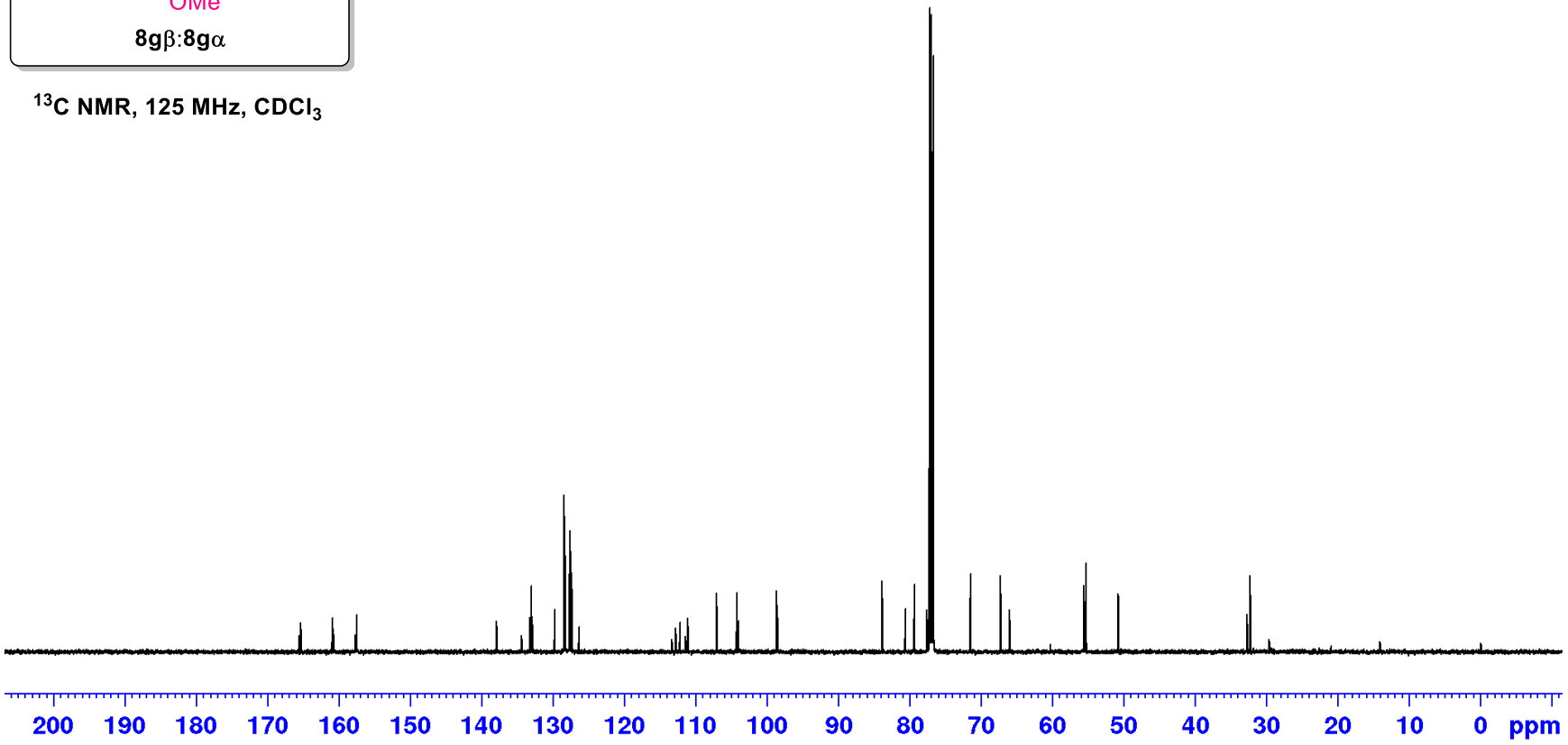


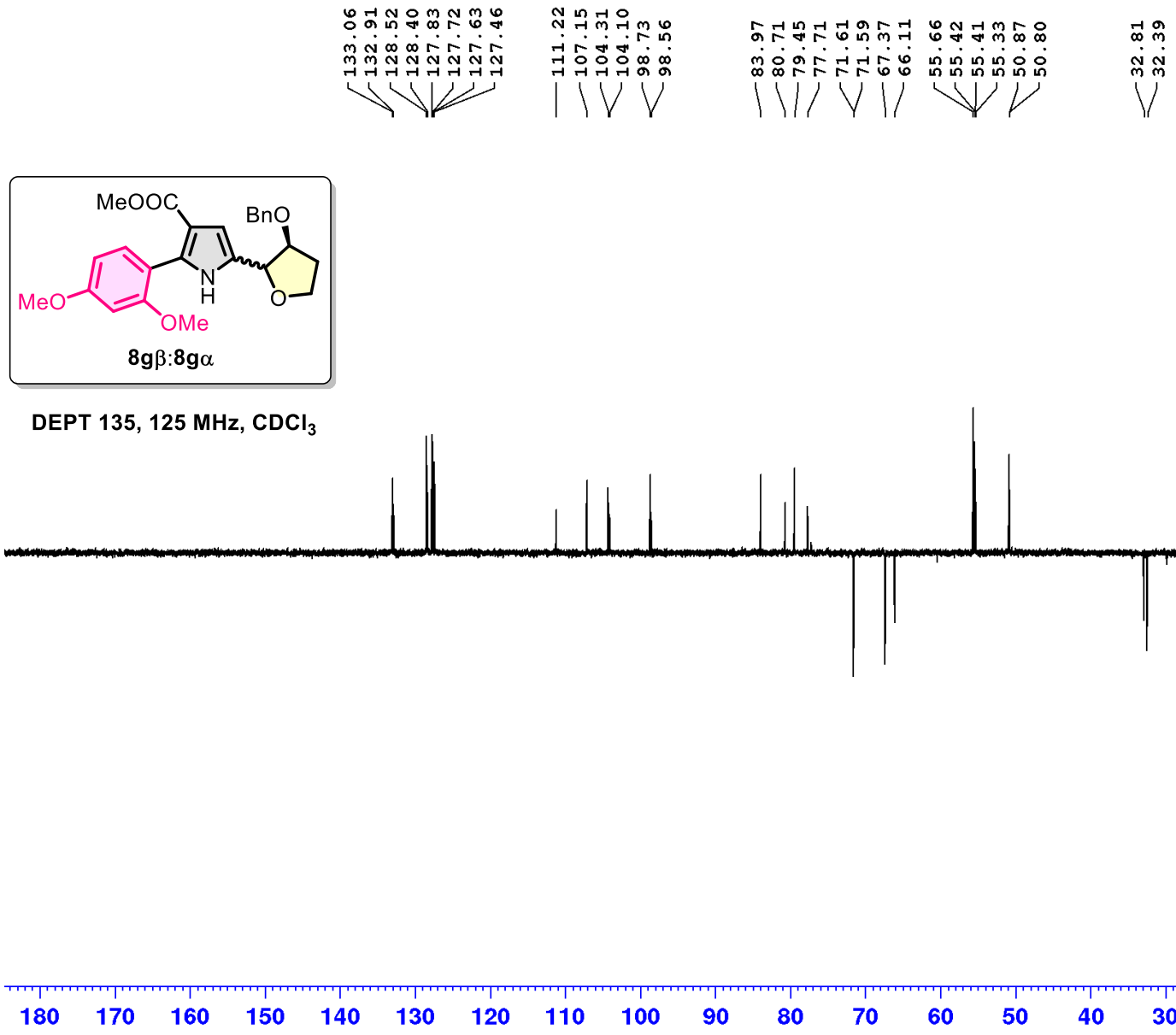




8gβ:8gα

^{13}C NMR, 125 MHz, $CDCl_3$

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71.59
67.37
66.11
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55.41
55.33
50.87
50.80
32.81
32.39
MeOOC
BnO
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DEPT 135, 125 MHz, CDCl3
180
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ppm

(3+2) Cycloaddition Reactions of Carbohydrate-Derived Donor-Acceptor Cyclopropanes

by M V Kamala Lakshmi

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