New Methods for the Synthesis of Biologically Active Natural Products

A thesis submitted for the Degree of Doctor of Philosophy of The Australian National University

by

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September, 2016

Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2013-2016 and has not been submitted for examination for any other degree. This thesis by publication is comprised of seven journal articles. Wherever possible, established methodologies have been acknowledged by citation of the original publications.

Jeremy Nugent

September, 2016.

Acknowledgements

I would first like to thank my supervisor Professor Martin Banwell. Throughout my studies I have benefited profoundly from his encouragement, assistance and knowledge. The positivity which stems from his kindness and generosity has made the last five years a very enjoyable experience.

I am indebted to Brett for training me in the lab all those years ago and for being an excellent mentor.

I would like to thank the members of the Banwell Group, especially the members of lab 3.27, past and present. Eliška, Josh, Xiang and Qiao, you have all made my journey through this PhD a very pleasant one.

I thank the technical staff of the Research School of Chemistry, most notably the Mass Spectrometry unit and the NMR team, for the fantastic support they have provided during my candidature.

To both my parents and Ellen, thank you for love and support over the past three and a half years. Without you this would not be possible.

Publications and Presentations

This thesis is submitted in publication format.

The following list details the publications and presentations that have resulted from the author's research work carried out during the course of his candidature for the Degree of Doctor of Philosophy.

PUBLICATIONS

1. Antony L. Crisp, Jiwen Li, Ping Lan, Jeremy Nugent, Eliška Matoušová, and Martin G. Banwell. The Palladium-Catalysed Intramolecular Alder-ene (IMAE) Reactions of Certain Heteroatom-Linked 1,6-Enynes: The Formation of Hexahydro-Indoles and -Benzofurans. *Aust. J. Chem.* **2015**, *68*, 1183.

2. Martin G. Banwell, Joshua Buckler, Colin J. Jackson, Ping Lan, Xinghua Ma, Eliška Matoušová and Jeremy Nugent. Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase in ***Strategies and Tactics in Organic Synthesis***, 11: pp. 29-50 (2015).

3. Jeremy Nugent, Eliška Matoušová, and Martin G. Banwell. A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring. *Eur. J. Org. Chem.* **2015**, 3771. (Featured in *Organic Chemistry Highlights* **2016**, June 20).

4. Jeremy Nugent, Martin G. Banwell and Brett D. Schwartz. Total Synthesis of the *Illicium*-derived Sesquineolignan Simonsol C. *Org. Lett.* **2016**, *18*, 3798.

5. Jeremy Nugent and Martin G. Banwell. An Eleven-step Synthesis of Galanthamine from Commercially Available Materials. *Submitted to Eur. J. Org. Chem. (Manuscript ID: ejoc.20160108).* **2016**.

6. Jeremy Nugent and Brett D. Schwartz. *N*-Methoxy-*N*-methylcyanoformamide, a Highly Reactive Reagent for the Formation of *β*-Keto Weinreb Amides and Unsymmetrical Ketones. *Org. Lett.* **2016**, *18*, 3834.

7. Jeremy Nugent and Brett D. Schwartz. Preparation of *N*-Methoxy-*N*-methylcyanoformamide. *Submitted to Org. Synth. (Manuscript ID: gv0sjhiqlszscbhsbmafin2m).* **2016**.

Conference Presentations

1. **RACI National Congress | *Poster Presentation***
   Jeremy Nugent, Eliška Matoušová and Martin G. Banwell, *Total Synthesis of (±)-Galanthamine via an Intramolecular Alder-ene (IMAE) Cyclisation and a One-Pot Diels-Alder/Aromatisation Protocol*, Adelaide, Australia, 7-14 December 2014.

Commentary on the Contributions of Mr Jeremy Nugent to the Seven Papers Included in this Thesis by Publication

Publication 1

This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Nugent. Mr Nugent carried out relevant literature surveys as part of his additional contributions to the preparation of this article.

Publication 2

This is an invited book chapter that was written by Professor Banwell. It incorporates descriptions of research conducted by the co-authors including Mr Nugent. Mr Nugent carried out relevant literature surveys as part of his additional contributions to the preparation of this document.

Publication 3

This is a full paper detailing extensive experimental work directed towards the synthesis of the complex alkaloid galanthamine. Mr Nugent carried out the entirety of the laboratory work reported in this article. In addition he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Nugent also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 4

This is a full paper detailing extensive experimental work directed towards the synthesis of the *Illicium*-derived sesquineolignan simonsol C. Mr Nugent carried out the entirety of the laboratory work reported in this article save for the X-ray crystallographic studies that were conducted by Dr Brett Schwartz. In addition, Mr Nugent collated and formatted all of the reported spectral data presented in

the Supporting Information document. Mr Nugent also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 5

This is a full paper detailing extensive experimental work directed towards a second-generation synthesis of the complex alkaloid galanthamine. Mr Nugent carried out the entirety of the laboratory work reported in this article. In addition he collated and formatted all of the reported spectral data presented in the Supporting Information document. Mr Nugent also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 6

The initial idea for this work came from Dr Brett Schwartz. Mr Nugent carried out approximately half of the experimental work reported in the paper. Mr Nugent wrote approximately half of the first draft of the paper and prepared approximately half of the associated Supporting Information.

Publication 7

The initial idea for this work came from Dr Brett Schwartz. Mr Nugent carried out approximately half of the experimental work reported in the paper. Mr Nugent wrote the first draft of the paper and composed approximately half of the associated Supporting Information.

Table of Contents

Abstract

This thesis consists of seven scientific articles and is preceded by an overview that contextualises all of this submitted/published work.

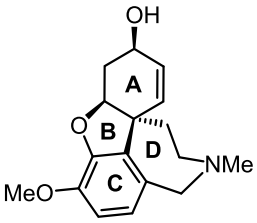
The first part of this thesis is comprised of **Publication 1**. It is concerned with the cyclisation of 1,6-enynes of the general form **A** to bicyclic isomer **B**.

A **B**

Specifically, **Publication 1** describes an extensive literature review on the chemistry of the palladium-catalysed intramolecular Alder-ene (IMAE) reaction, a powerful method for the construction of carbon-carbon bonds. This review focusses only on the cyclisation reactions of hetero-atom linked 1,6-enynes to form *cis*-fused hexahydro-indoles and -benzofurans. It serves to contextualise some of the author's other published research in the area.

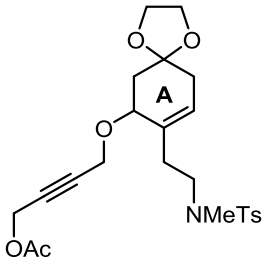
The second part of the thesis is comprised of **Publications 2** and **3** that focus on a novel synthesis of the potent and reversible acetylcholine esterase inhibitor galanthamine.

Specifically, **Publication 2** consists of an invited book chapter that details the Banwell Group's efforts to synthesis the *Amaryllidaceae* alkaloid galanthamine, as well as analogues thereof, in order to further investigate the biological properties of these compounds.

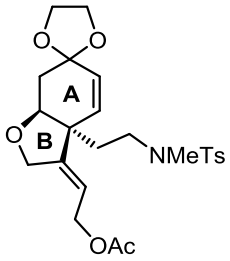


(–)-galanthamine

Similarly, **Publication 3** reports a seventeen-step reaction sequence that was used to synthesise (±)-galanthamine. This route featured an intramolecular Alder-ene cyclisation of propargyl acetate **C** to form allylic acetate **D**, an intermediate embodying the AB ring system of the natural product.

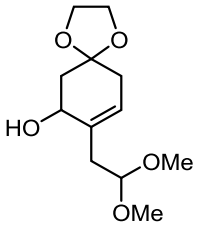


C



D

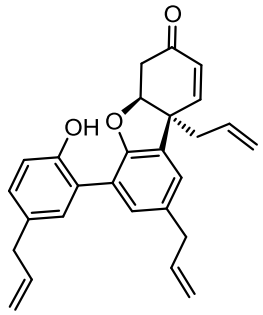
The third part of this thesis consists of **Publications 4** and **5**. These detail the application of allylic alcohol **E** in the synthesis of the sesquineolignan simonsol C and in a second-generation synthesis of (±)-galanthamine.



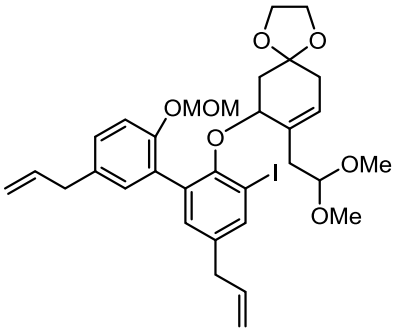
E

Specifically, then, **Publication 4** highlights the first total synthesis of the *Illicium*-derived sesquineolignan simonsol C, a natural product that displays structural similarities to galanthamine. This twelve-step synthesis of simonsol C featured an intramolecular Heck reaction of aryl iodide **F**, itself the product of a

Mitsunobu reaction using allylic alcohol **E**, to establish the tetracyclic framework of simonsol C.

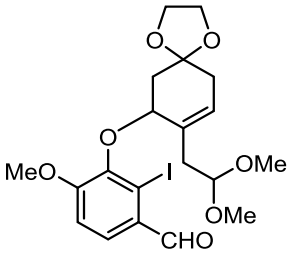


simonsol C



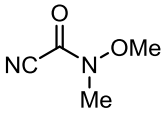
F

A second-generation synthesis of (±)-galanthamine is reported in **Publication 5**. This investigation, which used methodology developed in the aforementioned synthesis of simonsol C, involved, as a key step, an intramolecular Heck reaction of aryl iodide **G**, an intermediate derived from precursor **E**, to install the tricyclic framework of (±)-galanthamine.



G

The final section of this thesis is comprised of **Publications 6** and **7**. These focus on the formation and application of *N*-methoxy-*N*-methylcyanoformamide (**H**) in organic synthesis.



H

Publication 6 describes investigations concerned with establishing the reactivity profile of *N*-methoxy-*N*-methylcyanoformamide and its capacity to introduce the Weinreb amide functionality into organic frameworks. Specifically, it describes the reaction of this cyanoformamide with various enolates and organometallic species. **Publication 7** details the synthesis of *N*-methoxy-*N*-methylcyanoformamide (a previously unreported compound) *via* a two-step procedure.

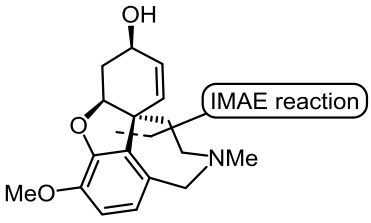
The Appendix to the thesis is comprised of a report arising from single-crystal X-ray analysis of a key compound synthesized by the author. This analysis and the derived reports are the result of studies carried out by Dr Brett Schwartz.

Thesis Overview

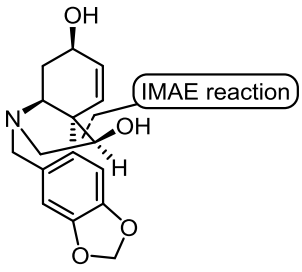
Publication 1: The Palladium-Catalysed Intramolecular Alder-ene (IMAE) Reactions of Certain Heteroatom-Linked 1,6-Enynes: The Formation of Hexahydro-Indoles and -Benzofurans

The intramolecular Alder-ene reaction is a powerful and often underutilised method for the formation of carbon-carbon bonds in organic synthesis. This publication reviews the applications of this reaction in organic synthesis with a particular emphasis on the research conducted within the author's research group.

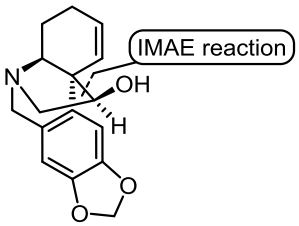
Cycloisomerizations of carbon- and heteroatom-linked 1,6-enynes have been employed within the Banwell research group for the total synthesis of various natural products. This review describes, *inter alia*, studies directed towards the syntheses of galanthamine[1], hamayne[2] as well as haemultine[3] and wherein the quaternary carbon centre of these alkaloids was formed *via* a palladium-catalysed IMAE reaction.



galanthamine



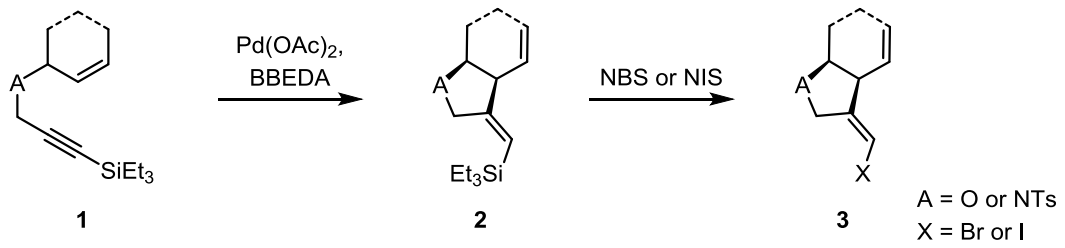
hamayne



haemultine

This review also presents some recent investigations within the Banwell research group where it was discovered that certain heteroatom-linked 1,6-enynes bearing alkynyl silanes (**1**) efficiently engaged in the intramolecular Alder-ene reaction to afford the expected heterocycles (**2**). These products could then be transformed

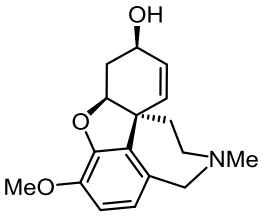
into the related and more synthetically useful alkenyl halides (**3**) on treatment with either NBS or NIS (**Scheme 1**).



Scheme 1: The IMAE reaction of 1,6-enynes of the general form **1** and the manipulation of the product alkenylsilanes **2** to give halides **3**.

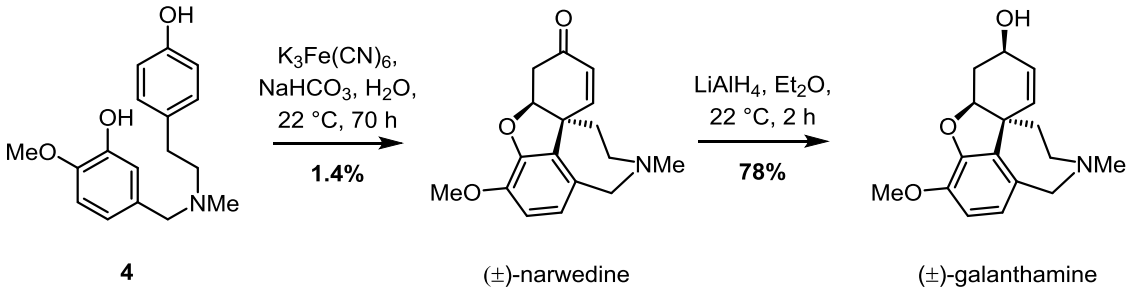
Publication 2: Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

The *Amaryllidaceae* alkaloid (–)-galanthamine,[4, 5] which has been isolated from, *inter alia*, the bulbs and flowers of the Caucasian snowdrop (*Galanthus woronowii*), is a potent, competitive and reversible inhibitor of acetylcholine esterase (AChE).[6] As a result, this alkaloid is now used for the clinical treatment of mild to moderate forms of Alzheimer's disease in Europe, Japan and the United States.[7] Synthetic chemists and pharmacologists alike have been attracted to this alkaloid for these reasons with efforts aimed at developing more potent analogues for the treatment of Alzheimer's disease. In addition, the significant costs associated with the isolation and purification of (–)-galanthamine from plant sources means that there is a high demand for the development of practical and efficient total syntheses of this alkaloid.[7]



(–)-galanthamine

Publication 2 is an invited book chapter that highlights a number of syntheses of galanthamine that have been reported in the literature.[8-10] The first of these was by Barton and co-workers[8] in 1962 who established a biomimetic approach to galanthamine through an intramolecular oxidative phenolic coupling of *N*-methylnorbelladine. Specifically, when *N*-methylnorbelladine (**4**) was treated with potassium ferricyanide in aqueous $NaHCO_3$ solution it afforded (±)-narwedine, albeit in just 1.4% yield. The latter was then reduced to a mixture of (±)-galanthamine and its epimer through exposure to $LiAlH_4$. This publication also outlines the investigations conducted by the Banwell research group into new syntheses of galanthamine[1, 11] as well as various analogues[12] of this alkaloid.



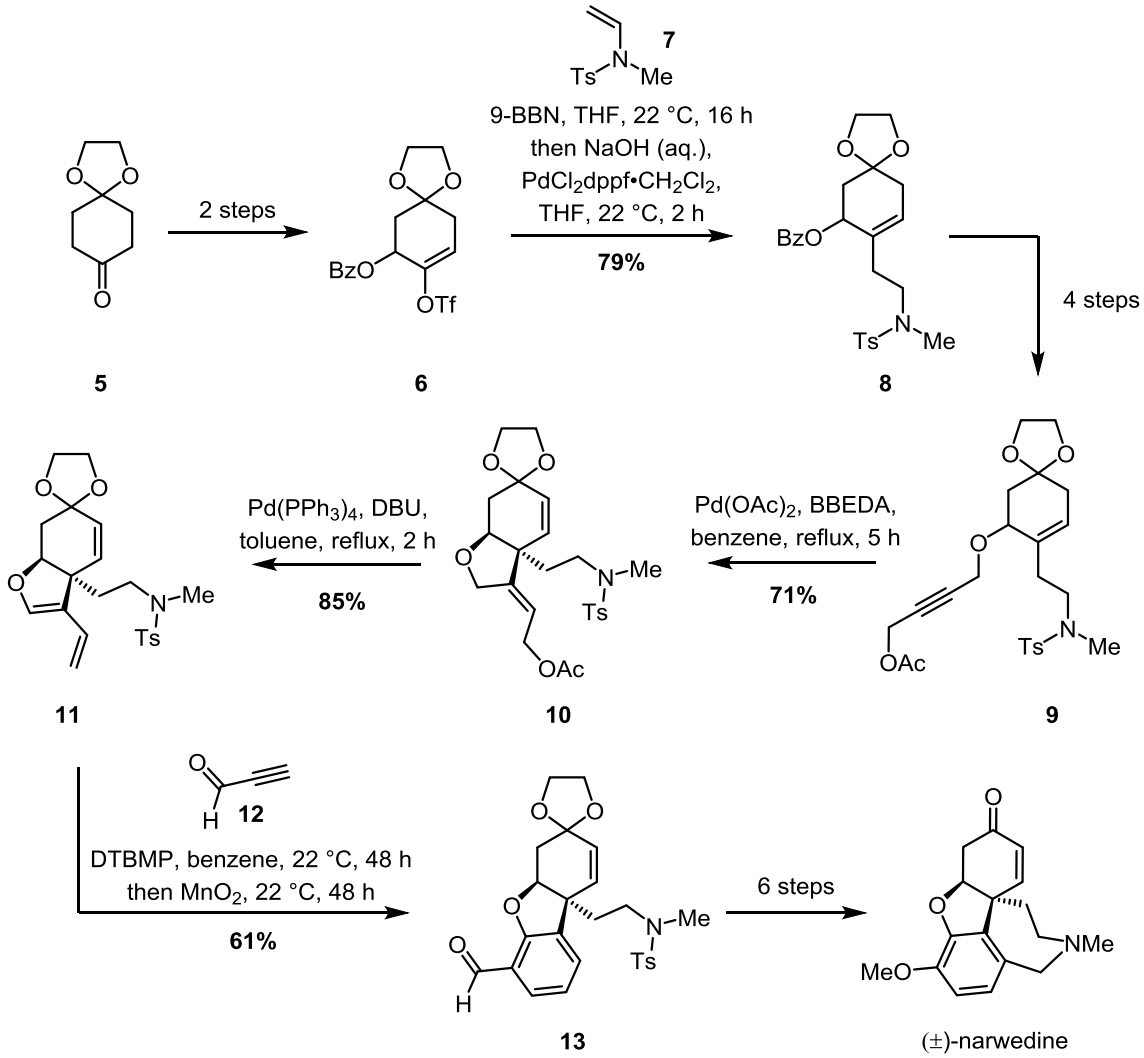
4 (±)-narwedine (±)-galanthamine

Scheme 2: The original and biomimetic synthesis of (±)-galanthamine.

Publication 3: A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring.

This publication details the author's investigations into the total synthesis of (±)-galanthamine using the intramolecular Alder-ene-mediated conversion of propargyl acetate **9** to allylic acetate **10** as a key step for installing the quaternary carbon centre of the target. Overall, a seventeen-step reaction sequence was employed starting from ketone **5** that was transformed into enol triflate **6** through two functional group interconversions. A hydroboration-Suzuki-Miyaura cross-coupling sequence involving enamine **7** was used to install the aminoethyl sidechain that would later be used for the formation of the seven-membered heterocyclic D-ring present in the title compound. Other key steps in the synthesis included applying a Tsuji-Trost-type elimination reaction within compound **10** so as to form diene **11** and a one-pot Diels-Alder

cycloaddition/aromatisation reaction of the latter compound to give benzaldehyde **13**. Six subsequent steps delivered (±)-narwedine, an established precursor to both (+)- and (–)-galanthamine.

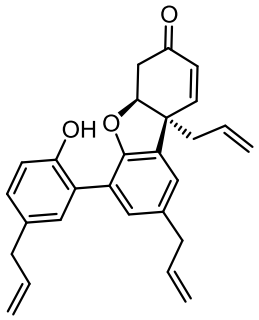


Scheme 3: Key steps involved in the synthesis of galanthamine from ketone **5**.

Publication 4: Total Synthesis of the *Illicium*-derived Sesquineolignan Simonsol C.

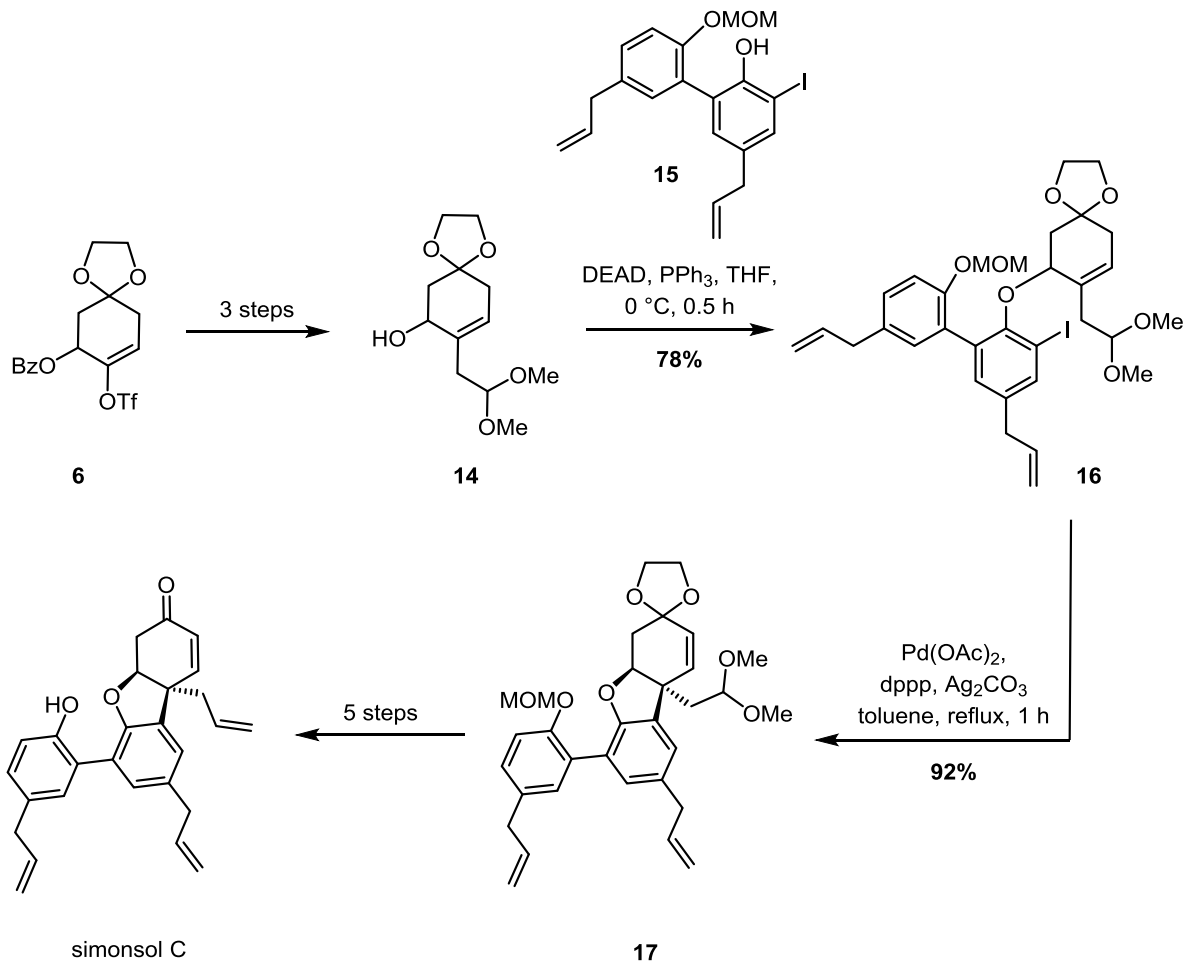
The *Illicium* genus of flowering plant is found throughout Southwest China and is known to produce a diverse range of natural products. Amongst these are various compounds which are known to display useful neurological effects including neurite-outgrowth-promoting activity and acetylcholine-esterase-inhibiting properties.[13-15] In 2012, Wang and co-workers[16] isolated the sesquineolignan

simonsol C from the toxic shrub *Illicium simonsii*. The strong structural resemblance of this natural product to (–)-galanthamine led us to speculate that simonsol C may demonstrate similar biological properties and so prompting the author's investigations into the synthesis of simonsol C.



simonsol C

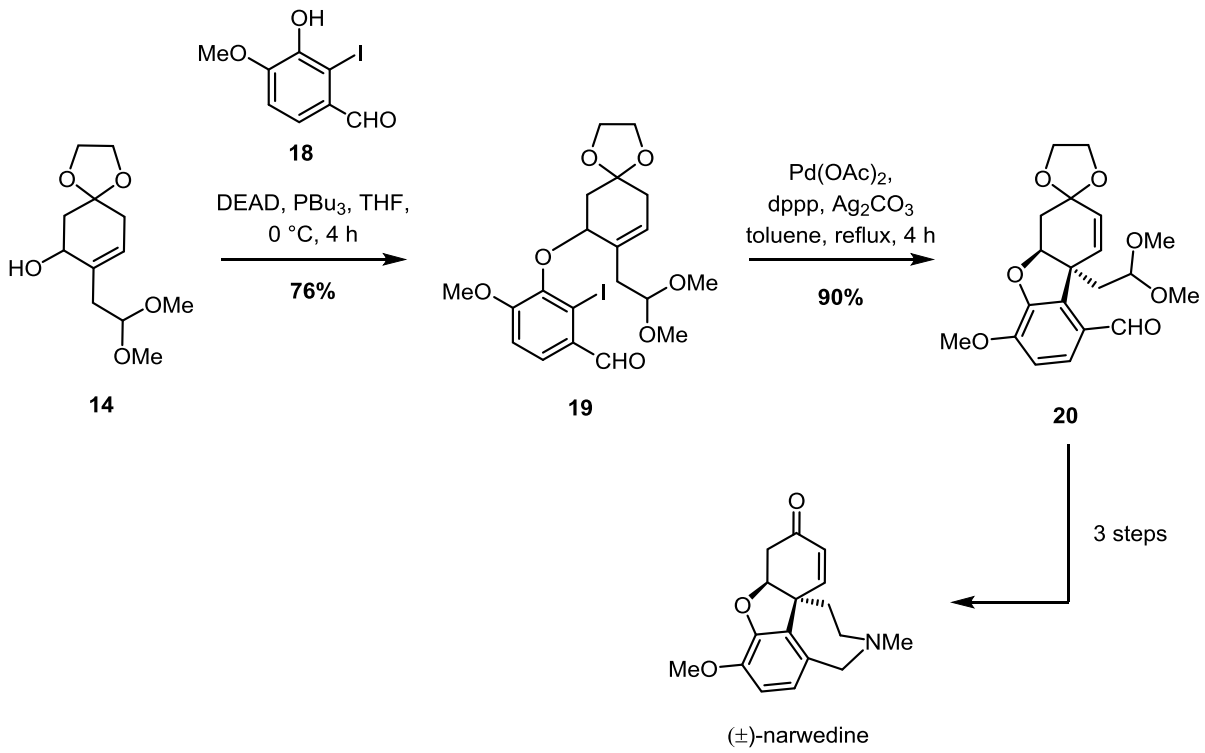
A twelve-step total synthesis of simonsol C is reported in **Publication 4**. This started with the elaboration of previously reported enol triflate **6**, over three steps, to allylic alcohol **14**. A Mitsunobu reaction using this allylic alcohol and iodophenol **15** efficiently afforded the expected product, aryl iodide **16**. This last compound was exposed to $Pd(OAc)_2$ and dppp and by such means engaged in the crucial intramolecular Heck cyclisation to afford acetal 1**7**, a compound that embodies the tetracyclic framework of simonsol C. The total synthesis of the title compound was completed in a further five steps from this intermediate.



Scheme 4: Key steps involved in the synthesis of simonsol C from enol triflate **6**.

Publication 5: An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

The aforementioned investigations into the synthesis of simonsol C suggested that (±)-galanthamine could be prepared by similar means. To this end the author explored the possibility of using the previously reported allylic alcohol **14** in a second-generation synthesis of (±)-galanthamine. Specifically, allylic alcohol **14** was engaged in a Mitsunobu reaction with iodophenol **18**, itself formed through the iodination of isovanillin, to afford the expected aryl iodide **19**. On exposure of this product to the previously defined intramolecular Heck reaction conditions acetal **20** was formed. Compound **20** embodies the tricyclic framework of the natural product and could be transformed into (±)-narwedine over a further three steps.

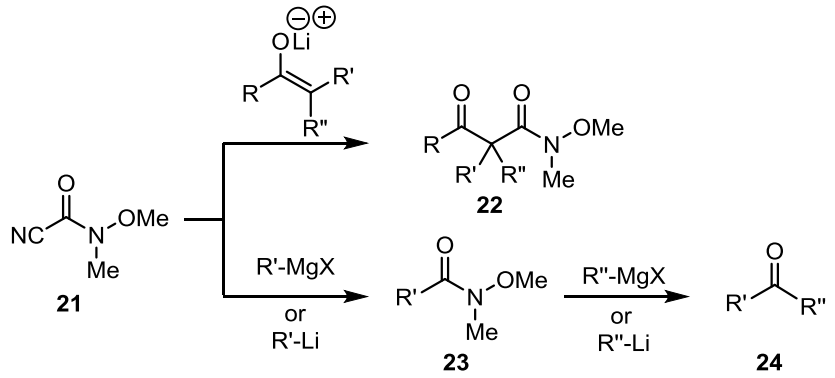


Scheme 5: Key steps involved in the second-generation synthesis of (±)-galanthamine.

Publication 6: *N*-Methoxy-*N*-methylcyanoformamide, a Highly Reactive Reagent for the Formation of *β*-Keto Weinreb Amides and Unsymmetrical Ketones.

Since the initial report by Mander,[18] methyl cyanoformate (Mander's reagent) has been used extensively in organic synthesis, especially for the formation of *β*-ketoesters from the corresponding ketone enolates. Indeed, it is the preferred reagent for this transformation since other methods give varying amounts of corresponding *O*-acylation products.[19, 20] More recently, ethyl[21], benzyl[22] and allyl[23] cyanoformates have all been successfully exploited for the synthesis of their corresponding *β*-ketoesters. Despite the popularity and widespread use of cyanoformates in this regard, it is surprising that the analogous cyanoformamides have not been exploited in the synthesis of *β*-ketoamides from the corresponding ketone enolates.

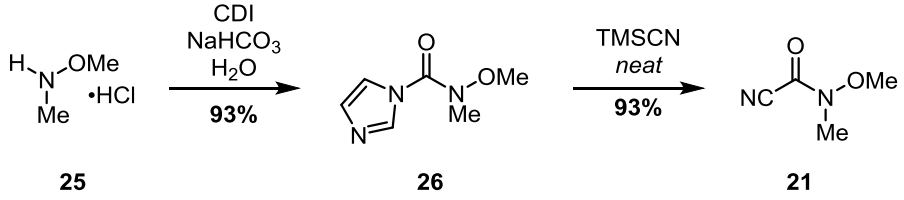
The work described in **Publication 6** is concerned with exploring the reactivity profile of *N*-methoxy-*N*-methylcyanoformamide (**21**). It details the various synthetic applications of this compound. Specifically, this report highlights the use of *N*-methoxy-*N*-methylcyanoformamide in the efficient synthesis of *β*-keto Weinreb amides (**22**) from the corresponding ketone enolates in a manner analogous to that used in the preparation of the related *β*-ketoesters. In addition, it was established that when treated with the relevant organometallic species, cyanoformamide **21** could provide either the one-carbon homologated Weinreb amide **23** or the unsymmetrical ketone **24**.



Scheme 6: Applications of *N*-methoxy-*N*-methylcyanoformamide in synthesis.

Publication 7: Preparation of *N*-Methoxy-*N*-methylcyanoformamide.

Publication 7 describes, in detail, a two-step synthesis of *N*-methoxy-*N*-methylcyanoformamide. The sequence starts with the 'in-water' reaction[17] of *N*-methoxy-*N*-methylamine hydrochloride (**25**) with CDI to form *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (**26**). Treating the latter compound with a neat solution of 1.05 equivalents of trimethylsilyl cyanide efficiently afforded the desired cyanoformamide **21** in excellent yield.



Scheme 7: Synthesis of *N*-methoxy-*N*-methylcyanoformamide.

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Publication One

The Palladium-Catalysed Intramolecular Alder-ene (IMAE) Reactions of Certain Heteroatom-Linked 1,6-Enynes: The Formation of Hexahydro-Indoles and –Benzofurans

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Account

The Palladium-Catalysed Intramolecular Alder-ene (IMAE) Reactions of Certain Heteroatom-Linked 1,6-Enynes: The Formation of Hexahydro-Indoles and -Benzofurans*

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A short review of the literature on palladium-catalysed intramolecular Alder-ene reactions of *C*-, *N*-, and *O*-linked 1,6-enynes is provided with a particular focus on the use of the latter two processes in the authors' laboratories for the purposes of constructing various alkaloids.

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Introduction

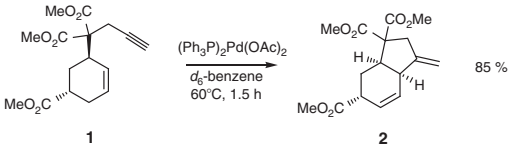
Palladium-catalysed processes are amongst the most important reactions in organic chemistry today.[1] Particularly notable examples include the Tsuji–Trost and Mizoroki–Heck reactions as well as the suite of related cross-coupling processes bearing names such as Sonogashira, Stille, Kumada, Suzuki–Miyaura, and Negishi.[2,3] Of course, the range of palladium-catalysed processes extends well beyond these, with this metal being used (often 'suspended' on an inert solid support such as charcoal) to effect the addition of dihydrogen to unsaturated organic compounds.[4] Indeed, these venerable and completely atom-economical processes,[5] in which all of the constituent atoms of the reacting partners end up in the product(s), represent some of the most important industrial processes known and the commercial value of them can be measured in the billions of dollars.[6] A perhaps less well-known type of process that can be catalysed by various palladium-based species are cycloisomerisations wherein polyunsaturated, open-chain or semi-cyclic species are converted, through intramolecular sigma-bond-forming processes, into cyclic or even polycyclic products.[7] These processes are not only completely atom-economical ones but they often also proceed with exquisite levels of regio- and/or stereo-chemical control. Furthermore, and as is often the case with other palladium-catalysed reactions, changing the nature of the ligands co-ordinating to the metal can have a profound influence not only on the type of product formed but also on the enantioselectivities that might be observed when potentially desymmetrising transformations are involved.[7] The primary focus of this short review is on one such cycloisomerisation process, namely the palladium-catalysed intramolecular Alder-ene (IMAE) reaction[8] of 1,6-enynes.

This has been described as the archetypal cycloisomerisation reaction.[7d] Two distinct variants are possible depending upon whether the atom-chain linking the reacting centres of unsaturation is an all-carbon unit or one incorporating heteroatoms such as nitrogen or oxygen. In the latter cases the products of reaction are substituted pyrrolidines and tetrahydrofurans, respectively.

The Alder-ene-Based Cycloisomerisation Reactions of 'All Carbon' 1,6-Enynes and Related Systems

While thermally-promoted variants of the title process have been known for well over half a century,[7d,8] a metal-catalysed form that proceeded efficiently and under mild conditions was only discovered in 1985 by Trost and Lautens and co-workers.[9] So, for example, these researchers established (Scheme 1) that treatment of the 1,6-enyne **1** (itself prepared via a Tsuji–Trost reaction) with 5 mol-% of the Pd^{II} species $(Ph_3P)_2Pd(OAc)_2$ in hot d_6-benzene affords the bicyclic diene **2** in 85 % yield.[9a]

Many useful variants of this type of process, including asymmetric ones, followed thereafter,[10] as did the discovery and application of homologous processes employing 1,7-enynes as substrates.[11] Interestingly, in those substrates lacking a

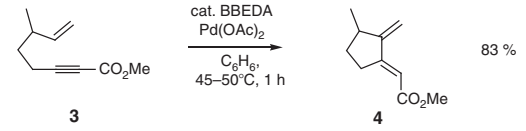


1 **2**

Scheme 1.

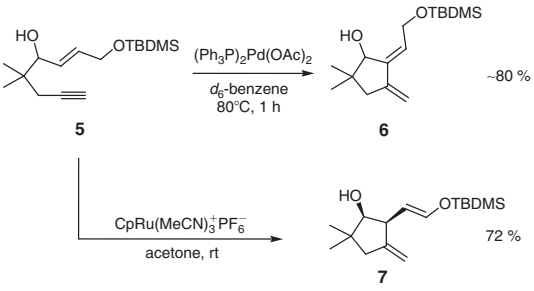
*The corresponding author, Martin G. Banwell, is the winner of the 2014 RACI H. G. Smith Memorial Medal.

hydrogen-bearing substituent at the 'outer' allylic position or where there is branching at C3, the isomerisation reaction often yields 1,3-dienes. This is exemplified by the conversion of the 1,6-enyne **3** into the isomer **4** (Scheme 2) when *N*,*N*-bis-(benzylidene)ethylenediamine (BBEDA) is used as ligand.[9d] Elegant applications of such processes in natural products synthesis abound.[7,10–13]



Scheme 2.

Since the original discovery of Trost and Lautens,[9] a range of other metal catalysts has been shown to effect the cycloisomerisations of 1,6- and 1,7-enynes and often in ways that are complementary to the processes observed using palladium. So, for example, when 1,6-enyne **5** (Scheme 3) is treated under 'conventional' conditions with $(Ph_3P)_2Pd(OAc)_2$ then the 1,3-diene **6** is formed[12] while reaction of the same substrate with the cationic ruthenium catalyst $CpRu(MeCN)_3^+PF_6^-$ affords the isomeric 1,4-diene **7** in a completely regio- and stereo-selective manner.[14] The latter conversion is notable for the efficient and selective formation of a silylenol ether in the presence a free hydroxyl group and stands as testimony to the mild nature of the reactions involved.



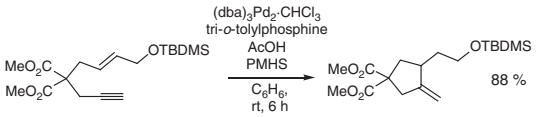
Scheme 3.

A new reaction pathway is observed when a quaternary carbon centre is introduced at the propargylic (C5) position of the substrate. For example, compound **8** is transformed into isomer **9** (40 %) (Chart 1) upon treatment under the same reaction conditions as employed for the conversion **5** → **7**. A complete change in the mechanism of the cycloisomerisation is occurring in such instances with a C–H insertion pathway now being followed.[14b]

Chart 1.

Stereochemically divergent outcomes have been observed in the ruthenium- and palladium-catalysed cycloisomerisations of cyclohexene-derived 1,7-enynes leading to decalin-containing products.[15] Extensions of such Ru-catalysed processes to the synthesis of certain alkaloid frameworks have been reported recently.[16]

Reductive cycloisomerisations of 1,6-enynes catalysed by either palladium or rhodium have been reported by Trost and Rise[17] and Jang and Kirsche,[18] respectively. In the first case (involving palladium) either triethylsilane or polymethylhydrosiloxane (PMHS) serves as the reducing agent, while dihydrogen is employed for the same purpose in the second (i.e. when rhodium is the catalyst). The conversion **10** → **11** (Scheme 4) is illustrative of the types of transformations that can be achieved by such means. Recently, the 'Trost variant' of this process has been used to construct the A-ring of various daphnane congeners.[19]

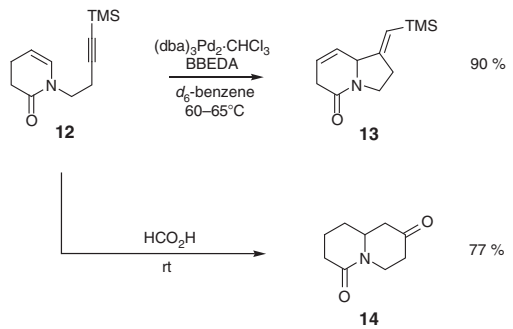


Scheme 4.

$Cp_2Ti(CO)_2$[20] and certain iron(0)-ate complexes[21] have also been shown to effect the cycloisomerisation of a range of 1,6-enynes to the corresponding cyclic 1,4-dienes in toluene at temperatures between 80 and 105°C. A novel nickel-chromium catalyst system supported on an insoluble phosphinylated polymer has also been described.[22]

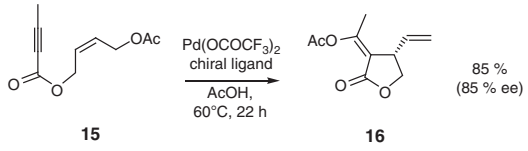
The Alder-ene-Based Cycloisomerisation Reactions of Heteroatom-Linked 1,6-Enynes and Related Systems

Substrates in which heteroatom linkers connect the reacting olefinic and acetylenic residues of 1,6-enynes can also be engaged in palladium-catalysed cycloisomerisation reactions[7] and, as illustrated below, the products of such processes have served as precursors to a range of natural products. One of the earliest examples of the title process was reported in 1992 by Trost and Pedregal[23] who demonstrated that the alkynyl *N*-acyl enamine **12** (Scheme 5) is converted into the isomeric indolizidine **13** (90 %) on exposure to 2.5 mol-% $(dba)_3Pd_2·CHCl_3$ and 10 % BBEDA in d_6-benzene at temperatures between 60 and 65°C. In stark contrast, when the same substrate is exposed to formic acid at room temperature (rt) it undergoes cationic cyclisation to generate the quinolizidine **14** in 77 % yield.



Scheme 5.

Naturally enough, reports detailing attempts to effect these types of conversions in an enantioselective manner soon followed with enantiomeric excesses of >99 % being observed in certain cases.[24,25] Related palladium(II)-catalysed IMAE reactions have been described in which accompanying acetoxy group transfer is observed as highlighted by the enantioselective conversion **15** → **16** (Scheme 6).[26,27]

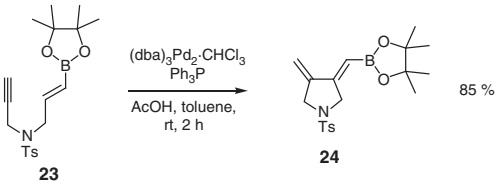


Scheme 6.

Tandem IMAE cross-coupling reactions involving *N*- and *O*-linked 1,6-enynes and aryl halides have been reported[28,29] as have oxidative variants wherein diarylation of the cyclisation product is achieved.[29] An example of the former process is shown in Scheme 7. Thus, the *N*-linked system **17** is engaged in an IMAE reaction and the palladated product of this process is intercepted in a cross-coupling reaction with bromoarene **18** such that the (presumably *cis*-ring fused) polycyclic product **19** can be obtained in 66 % yield.[28]

When the olefinic component of the substrate is part of a terminal allylic alcohol then the enolic residue in the product tautomerises to the corresponding aldehyde that can be engaged, in situ, in reductive amination reactions. So, for example, treatment of sulfonamide **20** under the conditions shown in Scheme 8 leads to the pyrrolidine aldehyde **21** (96 %) that on exposure, in the same reaction vessel, to a range of secondary-amines in the presence of dihydrogen affords the expected tertiary-amines such as **22**.[30]

As was the case with the corresponding all carbon-linked 1,6-enynes detailed above, when the heteroatom-linked systems lack allylic hydrogens at the 'outer' position then 1,3-dienes (rather than 1,4-dienes) are formed in the cycloisomerisation process. The conversion **23** → **24** (Scheme 9) exemplifies matters and the products of such processes (e.g. **24**) can participate in successive Diels–Alder cycloaddition and allylboration reactions with dienophiles and aldehydes, respectively.[31]



Scheme 9.

Anderson and co-workers have recently shown[32] that in certain heteroatom linked 1,6-enynes where a sulfonamide nitrogen is attached to the internal carbon of the alkyne residue (i.e. the substrate contains an ynamide residue) then 1,3-dienes incorporating an enamine unit are formed exclusively when a combination of $Pd(OAc)_2$ and BBEDA is used to effect the cycloisomerisation process. In some instances, ruthenium-based catalysts can be used to effect the same conversions.[32]

Rhodium(I)-based catalysts can also effect the IMAE reactions of heteroatom linked 1,6-enynes.[33–38] These can proceed in a highly enantioselective manner when appropriate chiral ligands are deployed. Zhang and co-workers have used such protocols in developing an elegant synthesis[34] of the butyrolactone-containing natural product (+)-pilocarpine (**25**) (Chart 2).

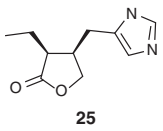
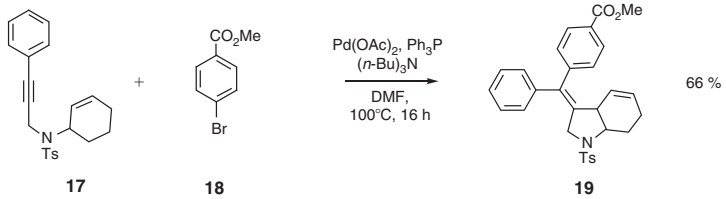
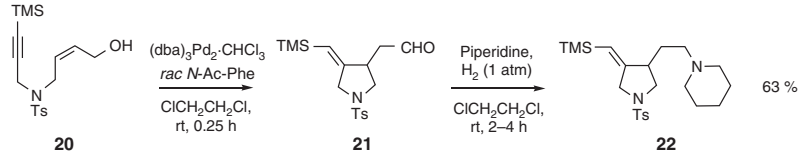


Chart 2.

In 2010 we reported[39] the outcomes of our initial studies on the palladium-catalysed IMAE reactions of *N*-linked 1,6-enynes as a means for constructing the C3a-arylhexahydroindole substructure associated with the *Amaryllidaceae* alkaloid tazettine (**26**). While we rapidly established a method for preparing an enyne, **27**, that seemed suitable for participation in the desired cycloisomerisation reaction, this process was overwhelmed by a



Scheme 7.



Scheme 8.

competing coupling of the terminal alkyne residues of two separate substrate molecules to afford a 1,3-enyne-containing heterodimer (Chart 3).

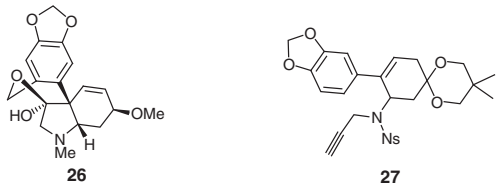


Chart 3.

In order to avoid such an event, a substrate incorporating a 'capping' methyl group was prepared by the pathway shown in Scheme 10. Thus, commercially available diallyl ketone (**28**) was converted into the ketal **29** under standard conditions and this was, in turn, subjected to a ring-closing metathesis (RCM) using Grubbs' second-generation catalyst to afford cyclopentene **30**. Addition of dibromocarbene, generated under phase-transfer conditions using triethylbenzylammonium chloride (TEBAC) as catalyst, to compound **30** then afforded adduct **31** that could be engaged in a silver cyanate promoted electrocyclic ring-opening reaction. The π-allyl cation so-formed was trapped as the corresponding isocyanate that was itself treated, in situ, with *t*-butanol and thereby affording the Boc-protected amino-cyclohexene **32**. This was converted into the corresponding nosyl-based sulfonamide, **33**, in a straightforward manner. Compound **33** participated in a Suzuki–Miyaura cross-coupling reaction with the relevant arylboronic acid to afford the arylated cyclohexene **34** that was *N*-propargylated using 1-bromobut-2-yne in the presence of sodium hydride to give the 'capped' substrate **35** required for the IMAE reaction. In the event, when compound **35** was treated with $Pd(OAc)_2$ and BBEDA an essentially quantitative yield of the desired C3a-arylhexahydroindole **36** was obtained. Interestingly, and in keeping with the observations made by Trost and Jebaratnam,[40] this particular ligand/palladium(II) catalyst combination has proven to be the most effective one we have encountered so far.

Using protocols related to those detailed immediately above we have been able to complete a total synthesis of the racemic modifications of the crinine alkaloid hamayne (**37**)[41] and the structure assigned to the related natural product haemultine (**38**) (Chart 4).[42] In each instance the exocyclic olefin associated with the product of the relevant IMAE reaction was manipulated in order to introduce the C-ring hydroxyl group with the B-ring

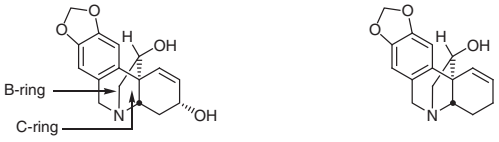
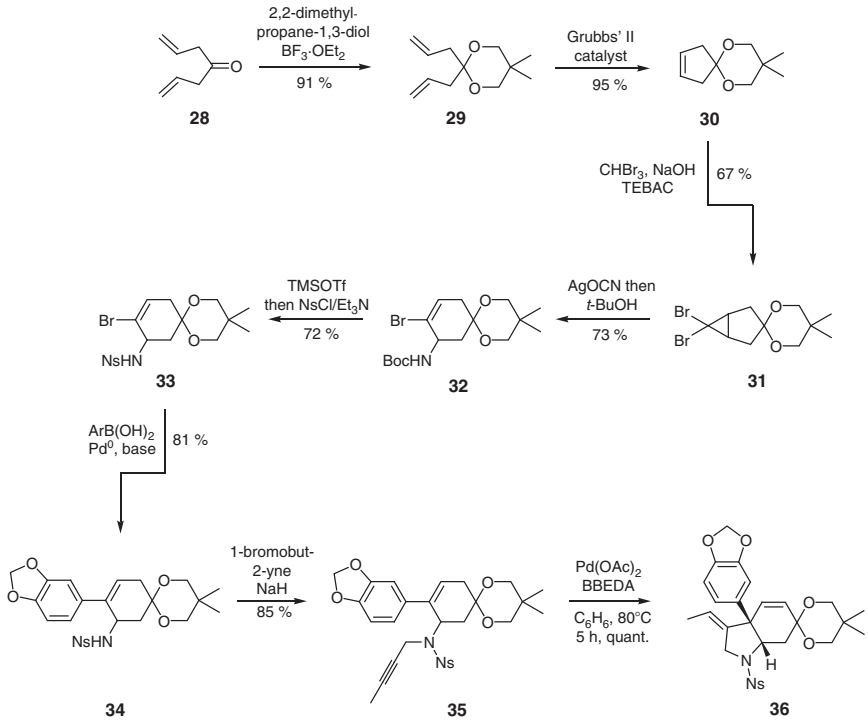


Chart 4.

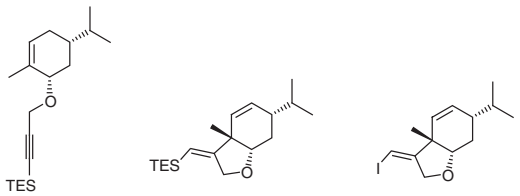


Scheme 10.

being established by subjecting a late-stage derivative of the product of the IMAE process to a Pictet–Spengler reaction.

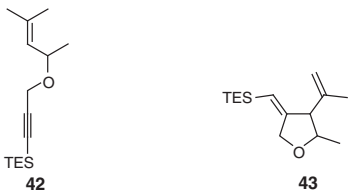
Very recently we have completed total syntheses of both the (+)- and (−)- forms of tazettine [viz. (+)- and (−)-**26**] using the same types of protocols as shown in Scheme 10 and utilising commercially available chiral amines for resolving the products of the desymmetrising electrocyclic ring opening of 6,6-dibromobicyclo[3.1.0]hexane (viz. the non-oxygenated congener of compound **31**) (M. G. Banwell, P. Lan, A. C. Willis, unpubl. data).

Encouraged by our successes in constructing hexahydroindoles using the palladium-catalysed IMAE reactions of *N*-linked 1,6-enynes, we sought to establish if the analogous oxygen heterocycles (viz. hexahydrobenzofurans) could be assembled by analogous means. In an extensive and just completed survey (J. Nugent, E. Matoušová, J. Li, M. G. Banwell, A. C. Willis, unpubl. data) that included an exploration of alternative and synthetically more useful alkyne capping groups, we prepared, inter alia, triethylsilyl (TES)-containing substrates such as **39** (Chart 5) and established that on exposure to $Pd(OAc)_2$ and BBEDA in benzene under microwave irradiation conditions this affords the expected heterocycle, **40**, in 80 % yield (the analogous conversion of the substrate lacking the TES group proceeds in just 16 % yield under the same conditions) (Chart 5). Furthermore, on treatment with *N*-iodosuccinimide in acetonitrile at 60°C alkenylsilane **40** undergoes an *ipso*-substitution reaction to give, in 82 % yield, the corresponding iodide **41** that is itself capable of engaging in a range of metal catalysed cross-coupling processes. Acyclic substrates also participate in the IMAE reaction under analogous conditions giving highly substituted furans as exemplified by the conversion **42** → **43** (the illustrated product was obtained in 74 % yield as a single diastereoisomer of yet-to-be determined configuration) (Chart 6). Spirocyclic furans are available by related means. Interestingly, various attempts to effect the same conversions using a range of seemingly relevant ruthenium and rhodium based systems were unsuccessful.



39 **40** **41**

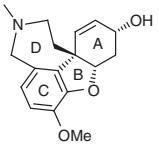
Chart 5.



42 **43**

Chart 6.

Our continuing interest in the natural product galanthamine (**44**) (Chart 7), a hexahydrobenzofuran-containing alkaloid used clinically in the treatment of the early stages of Alzheimer's disease,[43] prompted us to consider its assembly using the title protocols.



44

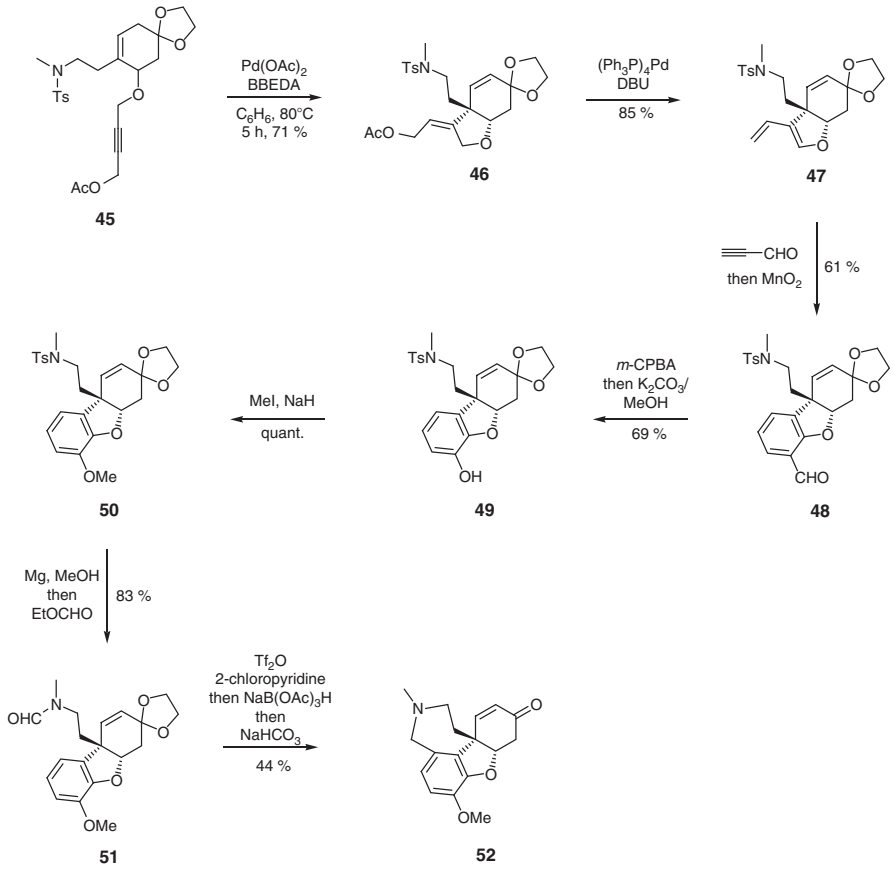
Chart 7.

In the event,[44] we were able to effect the IMAE reaction of the readily accessible *O*-linked 1,6-enyne **45** (Scheme 11) under our now standard conditions and thereby generate the bicyclic compound **46** in 71 % yield. On treatment with $(Ph_3P)_4Pd$ and the non-nucleophilic base DBU, the elements of acetic acid were lost from compound **46** and the semi-cyclic and electron-rich diene **47** thereby obtained in 85 % yield. Compound **47** readily participated in a completely regioselective Diels–Alder reaction with propynal and the initially formed adduct was aromatised by treatment with manganese oxide and thus forming the benzaldehyde **48** in 61 % yield. On exposure to *m*-chloroperbenzoic acid (*m*-CPBA) compound **48** participated in a Dakin oxidation reaction and the product formate ester was immediately hydrolysed with potassium carbonate in methanol to give phenol **49** in 69 % yield over the two steps involved. *O*-Methylation of compound **49** under standard conditions then afforded the anisole **50** in quantitative yield. The construction of the seven-membered D-ring of galanthamine was straightforward and involved the two step conversion of sulfonamide **50** into formamide **51** (83 %) that was engaged in a modified Bischler–Napieralski type cyclodehydration reaction to give, after a reductive 'workup' using sodium triacetoxy(hydrido)borate and subsequent treatment with aqueous sodium bicarbonate, (±)-narwedine **52** (44 %), an established precursor to both (+)- and (−)-galanthamine.

While this synthesis of galanthamine is not the shortest one reported it is nevertheless notable for several reasons. It is the first synthesis in which the aromatic C-ring has been constructed *de novo*. Perhaps more significantly, especially in terms of the general theme of this article, the $Pd(OAc)_2$-catalysed IMAE reaction that results in the formation of compound **46** proceeds effectively within a multi-functional substrate **45**. It also allows for the construction of the quaternary carbon centre of galanthamine and establishes an allylic acetate moiety that only engages in Tsuji–Trost type chemistry on exposure to a palladium(0)-species. In other words, the IMAE and Tsuji–Trost reactions involved here are effectively 'orthogonal' processes.

Conclusions and Future Prospects

The palladium(II)-catalysed IMAE reactions of *N*- and *O*-linked 1,6-enynes offer extraordinary capacities for the construction, under relatively mild and highly chemoselective conditions, of complex hexahydro-indoles and -benzofurans, respectively. The opportunities for the application of such processes to the synthesis of natural products and various analogues seem almost boundless. An important area of future endeavour will be the identification of enantioselective variants of broad scope and that can be conducted in operationally simple ways.



Scheme 11.

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Publication Two

Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

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Devising New Syntheses of the Alkaloid Galanthamine,

a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase

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Chapter Outline

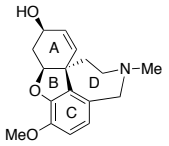
Abstract: The alkaloid (–)-galanthamine (**1**), a potent inhibitor of acetylcholine esterase (AChE), is used clinically for the symptomatic treatment of mild to moderate forms of Alzheimer's disease. The clinical demand for (–)-galanthamine together with the erosion of habitat of at least some of the source plants has created supply issues that have prompted numerous synthetic studies. Four distinct approaches for the assembly of the tetracyclic framework of compound **1** developed in the authors' laboratories are described here. Two of these exploit an enantiomerically pure metabolite produced through the whole-cell dihydroxylation of bromobenzene as a precursor to the A-ring of natural product **1**. The second of these rapidly provides enantiomerically pure compounds that molecular docking studies suggest should be strong inhibitors of AChE. A third synthesis of (–)-galanthamine involving the *de novo* assembly of the aromatic C-ring is also described, as is a failed radical cyclization-based approach.

Keywords: Alkaloid synthesis, Benzannulation, Bischler–Napieralski reaction, Bromoetherification, *cis*-1,2-dihydrocatechol, Eschenmoser–Claisen rearrangement, Galanthamine, Intramolecular Alder-ene reaction, Mitsunobu reaction, Pictet–Spengler reaction, Radical cyclization, Ribisins, Smiles rearrangement, Suzuki–Miyaura cross-coupling reaction

1. Introduction

The alkaloid (–)-galanthamine (a.k.a. galantamine, **1**) has been obtained from a variety of plant sources including Caucasian snowdrops (*Galanthus woronowii*), the summer snowflake (*Leucojum aestivum*), the wild daffodil *Narcissus pseudonarcissus* and the Red Spider Lily (*Lycoris radia*).[1] Various mythologies suggest that crude extracts of such plants have been used for millennia to treat a range of ailments but it was only in 1950 that a rather more specific report seems to have emerged on the utility of these materials. In particular, at this time a Bulgarian pharmacologist was supposed to have noted that rural populations in certain parts of Eastern Europe would rub snowdrops on their foreheads to alleviate headaches.[1a,d] Within a few years, and perhaps prompted in part by these observations, Russian researchers extracted (–)-galanthamine from *Galanthus woronowii* and were using it as a treatment for poliomyelitis, and seemingly to considerable effect.[1a,d,2] At about the same time it was also being employed in anaesthesiology as a curare reversal agent, as a treatment for myasthenia (an autoimmune or congenital neuromuscular disease) and myopathy (a muscular disease resulting in weakness) as well as for sensory and motor dysfunctions associated with CNS disorders.[1,3] However, it was the recognition that this alkaloid is a selective, competitive and reversible inhibitor of the enzyme acetylcholinesterase (AChE)[1] that can cross the blood-brain barrier that propelled it into the limelight and thence into the clinic (in the US, Europe and Japan) as an agent for the symptomatic treatment of mild to moderate vascular dementia and Alzheimer's disease.[1,4] It has also been shown to act at the nicotinic acetylcholine receptor as an allosteric potentiation ligand with the result that it triggers increased release of dopamine, serotonin, γ-aminobutyric acid, norepinephrine and related neurotransmitters.[1,5] The HBr salt of compound **1** (marketed as, *inter alia*, Nivalin, Razadyne and Reminyl) is now considered a frontline drug in helping combat the

emerging dementia pandemic. Various recent clinical case studies stand as testimony to its utility in this regard.[6]



1
[(–)-galanthamine]

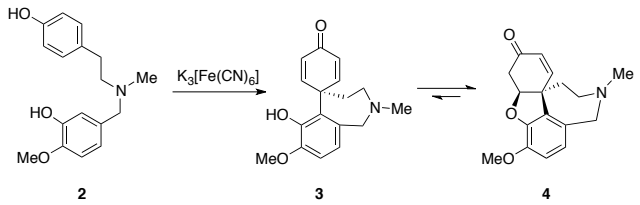
The clinical demand for (–)-galanthamine together with the erosion of habitat of at least some of the source plants has created supply issues.[1b,7] As a result new means of production of the alkaloid are being sought with *in vitro* cultivation and pathway optimization techniques[7] (in which the biosynthetic pathway[8] is "tweaked") being prominent amongst these. To date no industrially applicable (cost-effective) chemical synthesis of compound **1** has emerged[9] that addresses this supply problem although a pilot scale and biomimetic production process has been reported.[10]

As is almost invariably the case with natural-product based drug development programs, significant effort has been directed towards the identification of analogues of (–)-galanthamine with improved efficacy and/or reduced side effects (compound **1** causes, *inter alia*, gastrointestinal problems). Such studies, which are now assisted by high-resolution X-ray structures of AChE/**1** and related complexes,[11] have involved traditional medicinal chemistry,[1b,12] sophisticated QSAR analyses,[13] "biomimetic diversity-oriented synthesis"[14] and related techniques exploiting various multicomponent reactions.[15] In parallel, natural products chemists continue to screen extracts from various biological sources for new metabolites (notably alkaloids) that display AChE inhibitory properties.[16]

The circumstances described in the preceding paragraphs when considered together with the intriguing molecular architecture of (–)-galanthamine have, unsurprisingly, prompted a significant number of research groups to undertake total synthesis studies. In order to put our own group's contributions to this area into an appropriate context, some commentary on other studies of the synthesis of galanthamine is warranted. This is provided in the following section.

2. Studies on the Synthesis of Galanthamine – A Potted History

In 1960 Barton and Kirby reported[17] the first synthesis of (±)-galanthamine and thereby confirming its structure. This involved a biomimetic but low yielding (1.4%) intramolecular phenolic oxidative coupling of compound **2** (Scheme 1) to generate the spiro-fused dienone **3** that engages in a reversible intramolecular hetero-Michael addition reaction to give narwedine (**4**) that was itself converted into (±)-galanthamine on exposure to $LiAlH_4$.[17]

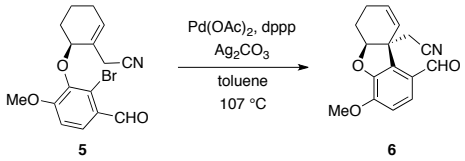


SCHEME 1: The Barton–Kirby Biomimetic Synthesis of Narwedine (**4**).

Various improvements to this process have been achieved by using, *inter alia*, slightly different substrates and/or other oxidants (notably hypervalent iodine compounds) in the pivotal coupling step.[18] An asymmetric variant of this process has been introduced[19] although this is not essential because racemic narwedine is resolved, through crystallization, into its (–)-form in the presence 1% (+)-galanthamine (*viz*. *ent*-**1**).[20,21] Reduction of (–)-narwedine with L-Selectride

then affords (–)-galanthamine in 99% yield.[20,22] In 2009 Magnus and co-workers reported[23] a somewhat related synthesis of compound **1** in which an intramolecular phenol alkylation was applied to a biphenyl-containing substrate and thus affording a spiro-dienone that could be converted, over three simple and efficient steps, into (±)-narwedine (**4**).

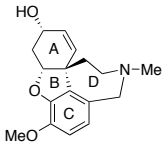
The ABC-ring system of (–)-galanthamine has also been constructed using intramolecular Heck reactions with a particularly notable and early example being described by Trost and Toste.[24] Specifically, they showed (Scheme 2) that on exposure to 15 mol % $Pd(OAc)_2$, 15 mol % of the ligand diphenylphosphinopropane (dppp) and 3 mole equiavlents of Ag_2CO_3 the allylic ether **5**, itself the product of an asymmetric allylic alkylation (AAA) reaction, was converted into compound **6** (91%). This was then carried forward over a further four steps into (–)-galanthamine.



SCHEME 2: The Pivotal Intramolecular Heck Reaction Associated with the Trost/Toste Synthesis of (–)-Galanthamine (**1**).

Several variations on this type of approach have been reported[25] as have other ingenious schemes[26,27] leading to compound **1**, the corresponding racemate or its optical antipode (*viz*. *ent*-**1**). Of particular relevance to the present discussion is Chida's synthesis of (+)-galanthamine from *D*-glucose using a combination of type-II Ferrier and Claisen rearrangement protocols. Details of this elegant work have recently been described in a personal account[27b] and are not,

therefore, presented here. It is, however, appropriate to note that, like Chida's, a significant fraction of our research effort has been devoted to devising means by which certain chiral-pool derived starting materials can be elaborated to a range of biologically active natural products. The chirons we have chosen to investigate for this purpose, including in developing certain of the various approaches to galanthamine reported here, are the *cis*-dihydrocatechols of the general form **7**.[28] Many of these compounds are available in kilogram quantities and essentially enantiomerically pure form through the whole-cell biotransformation of the corresponding aromatic, e.g. bromobenzene.



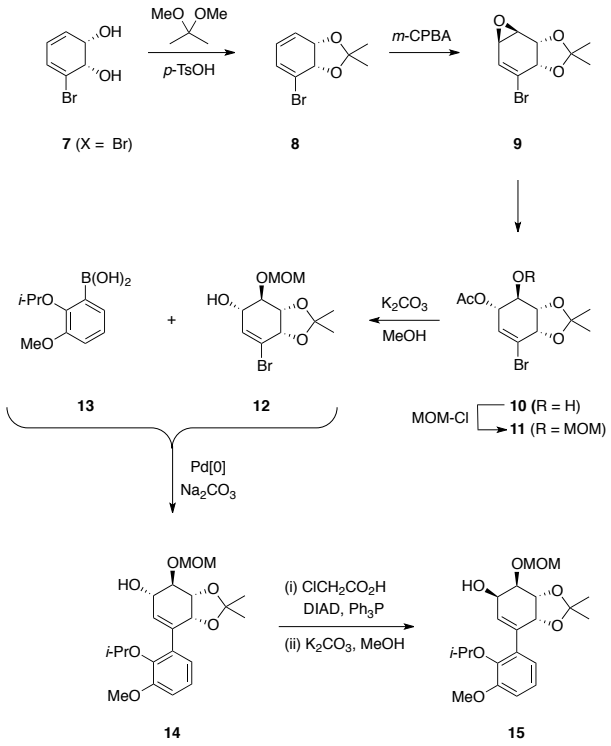
ent-**1**
[(+)-galanthamine]

7
(X = Me, Cl, Br, I...)

3. A First-Generation Chemoenzymatic Synthesis of (+)-Galanthamine

Our initial foray into the area of galanthamine synthesis was motivated a desire to see if we could parlay our knowledge[28e] of the chemistry of *cis*-1,2-dihydrocatechols into a reaction sequence that would allow for the elaboration of compound **7** (X = Br) into the A-ring of (+)-galanthamine (*ent*-**1**). This non-natural form of the alkaloid was targeted in the first instance simply because this seemed to "map" more appropriately onto the chirality of the proposed starting material. That having been said, the compound *ent*-**7** (X = Br) is also available[28e] (although it is not quite as accessible as its enantiomer) and so any success achieved in gaining access to (+)-galanthamine from *cis*-1,2-dihydrocatechol **7** (X = Br) automatically "translates" into a means for obtaining the natural product, *viz*. compound **1**.

The opening steps of our ultimately successful synthesis of (+)-galanthamine (*ent*-**1**)[29] from metabolite **7** (X = Br) are shown in Scheme 3 and involved the initial conversion of the latter into the corresponding and well known acetonide **8**.

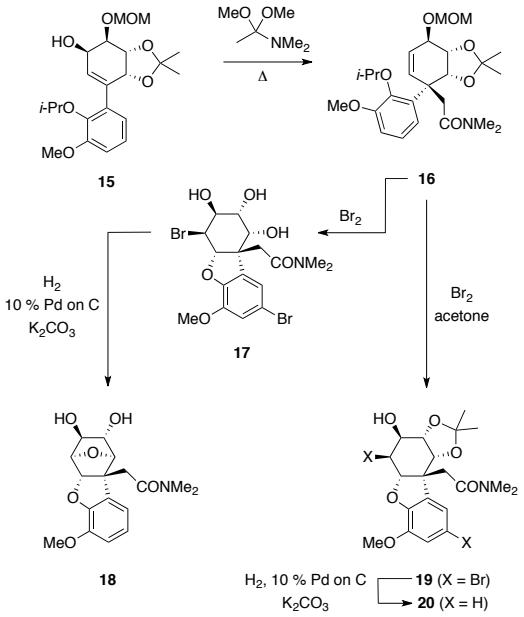


SCHEME 3: Opening Stages of a First-Generation Chemoenzymatic Synthesis of (+)-Galanthamine (*ent*-**1**).

This step provides a trap for young players in that if not carried out carefully an almost explosive acid-catalyzed dehydration and re-aromatization reaction of the substrate and/or product occurs. Regio- and stereo-controlled epoxidation at the β-face of the non-halogenated double bond within compound **8** is readily effected using *m*-chloroperbenzoic acid (*m*-CPBA)

and the epoxide **9** (90% over two steps) so-formed is then engaged in a completely selective and mineral acid catalyzed ring opening reaction with acetic acid serving as the nucleophile so as to generate alcohol **10** (81%). This is immediately protected as the corresponding MOM-ether **11** (91%) (forcing conditions required) and the associated acetate group hydrolyzed to the corresponding alcohol **12** (95%). This cyclohexenyl bromide participated in a Suzuki–Miyaura cross-coupling reaction with the readily obtained boronic acid **13** to afford the arylated cyclohexene **14** (98%). The single free hydroxyl group embedded within this last compound was engaged in a Mitsunobu reaction using α-chloroacetic acid as the nucleophile and the product ester immediately hydrolyzed using potassium carbonate in methanol to give the epimeric compound **15** (93% over two steps).

The next and particularly crucial phase of the synthesis was the construction of the quaternary carbon center associated with galanthamine as well as the formation of the furan or B ring. While it took sometime to establish the right sequence of reactions to realize such an outcome, this was eventually achieved in just three steps (Scheme 4), the first being the engagement of the allylic alcohol moiety within compound **15** in an Eschenmoser–Claisen (EC) rearrangement by treating it with the dimethyl acetal of *N*,*N*-dimethylacetamide in refluxing toluene for seven days. The amide **16** (89%) so-formed now embodies the requisite quaternary carbon center with the illustrated configuration and thus dictating that it is the (+)-form of galanthamine that will ultimately be obtained by this route.

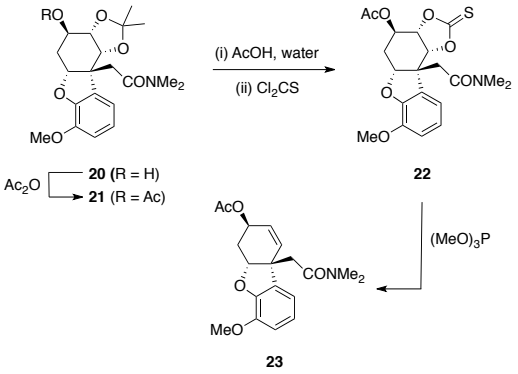


SCHEME 4: Establishing the Quaternary Carbon Center and B-ring of (+)-Galanthamine

Notably, the epimer of and precursor to allylic alcohol **15**, namely compound **14**, also engages in an analogous but even more sluggish EC rearrangement and thereby delivering the epimer of compound **16**. In principle, this epimer could serve as a precursor to (–)-galanthamine. Treatment of compound **16** with molecular bromine in toluene resulted in three distinct events: (i) cleavage of both the isopropyl aryl ether and acetonide residues; (ii) a bromo-etherification reaction (to form the desired B-ring) and, (iii), a S_EAr reaction at the electron-rich arene moiety. As a result compound **17** (69%) was obtained but on attempting to reductively debrominate it through exposure to dihydrogen in the presence of 10% Pd on C and potassium carbonate then, *inter alia*, a transannular etherification reaction took place and so producing the undesired 7-oxabicyclo[2.2.1]heptane **18** (67%). However, through the simple expedient of treating substrate **15** with molecular bromine in the presence of a mixture of toluene and acetone

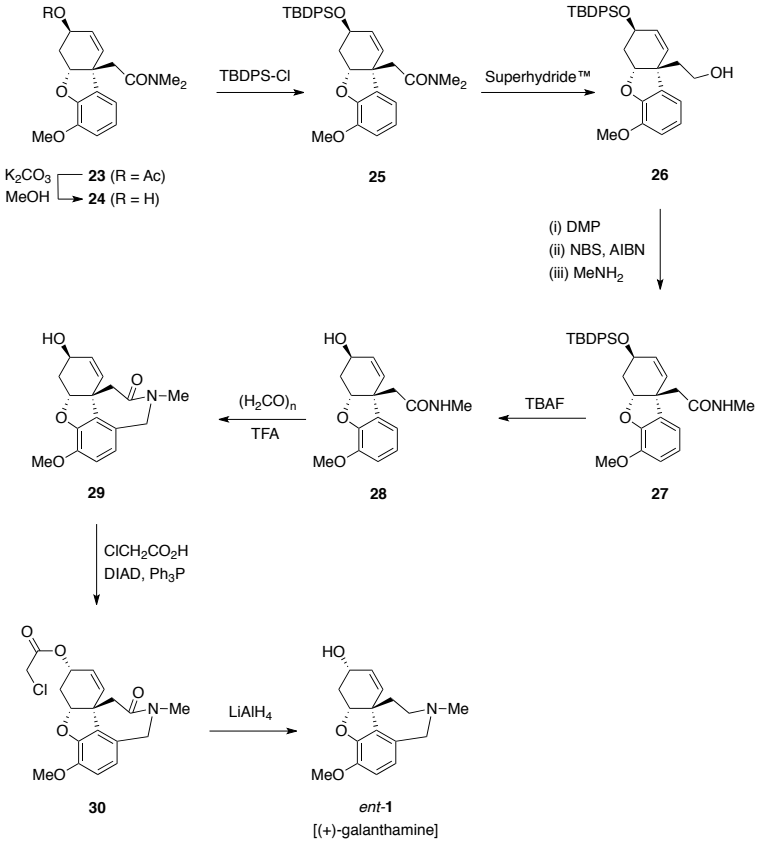
then the acetonide residue could be retained while the isopropyl aryl ether was still cleaved and with the product phenol participating, once again, in a bromoetherification reaction involving the pendant double bond of the A-ring and so affording the dibromide **19** (93%). Reductive debromination of this last compound now proceeded as desired to afford compound **20** (68%) that embodies the desired ABC-ring substructure of target *ent*-**1**.

The next phase of what was rapidly becoming a distinctly lengthy synthesis was the replacement of the now "longstanding" acetonide residue within the developing A-ring by a double bond residue. As is almost inevitable, a Corey–Winter olefination protocol was employed for this purpose. Thus, the free hydroxyl group within the A-ring of compound **20** was protected (Scheme 5) as the corresponding acetate **21** (90%) and the acetonide residue within the latter was cleaved and the diol so-formed immediately converted into the corresponding cyclic thiocarbonate, **22** (99%), by treating it with thiophosgene in the presence of 4-(*N*,*N*-diemthylamino)pyridine (DMAP). Exposure of compound **22** to a large excess of trimethylphosphite in toluene then gave the desired olefin **23** (72%).



SCHEME 5: Installing the A-Ring Double Bond

The heroic end-game "played" by Dr Xinghua Ma in completing our first generation chemoenzymatic synthesis of (+)-galanthamine is outlined in Scheme 6 and involved, as the first steps, subjecting compound **23** to an initial cleavage of the A-ring acetate group and reprotection of the resulting alcohol **24** (95%) as the corresponding *tert*-butyldiphenylsilyl (TBDPS) ether **25** (95%). This was a necessary prelude to using Superhydride™ to reduce the associated amide residue to the corresponding 2°-alcohol and thus forming compound **26** (95%). A two-pot reaction sequence followed wherein the alcohol **26** was oxidized to the corresponding aldehyde (using the Dess–Martin periodinane – DMP) that was itself subjected to a free-radical bromination with the product acyl bromide then being trapped *in situ* by added methylamine. This afforded the mono-*N*-methylated amide analogue **27** (76%) of precursor **25**. Desilylation of compound **27** using tetra-*n*-butylammonium fluoride (TBAF) and engagement of the product **28** (85%) in a Pictet–Spengler reaction using paraformaldehyde in trifluoroacetic acid (TFA) resulted in closure of the D-ring and, thereby, formation of the lactam **29** (88%). The final two steps were devoted to establishing the correct stereochemistry of the A-ring hydroxyl group and this required engagement of compound **29** in a Mitsunobu reaction using α-chloroacetic acid as the nucleophile and then subjecting the product ester/lactam **30** (93%) to a "global" reduction using $LiAlH_4$ and so providing (+)-galanthamine (*ent*-**1**) (85%), the high-field NMR spectral data for which matched those recorded on an authentic sample of its enantiomer.



SCHEME 6: The End-Game Associated with the First-Generation Chemoenzymatic Synthesis of Galanthamine (*ent*-**1**).

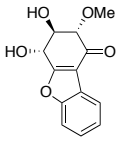
Clearly there are many deficiencies associated with this synthesis. While it could be certainly be tweaked in various ways (perhaps most notably by "fiddling" with protecting group regimes), the more important aspects of this work were the lessons learnt *en route*. In particular, the EC rearrangement reaction "shone through" as an almost uniquely effective means for establishing the quaternary carbon center of (+)-galanthamine from a precursor 2-cyclohexen-1-ol. This lesson came to the fore in our next and almost accidentally discovered second-

generation chemoenzymatic approach to galanthamine. How all this unfolded is described in the following section.

4. Total Syntheses of Members of the Ribisin Class of Neurologically Active Natural Product Inspire a Second-Generation Chemoenzymatic Approach to (+)-Galanthamine

4.1 The Ribisins

In 2012 Fukuyama and co-workers reported[30] the isolation of four new and structurally novel natural products from the fungus *Phellinus ribis,* the fruiting bodies of which are employed in traditional Chinese medicine for enhancing immunity and treating gastrointestinal cancer. On the basis of various spectroscopic analyses the benzofuran structures **31**, **32**, **33** and **34** were assigned to these compounds that were named ribisins A–D, respectively.



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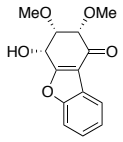

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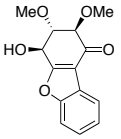

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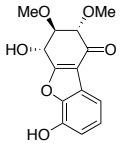
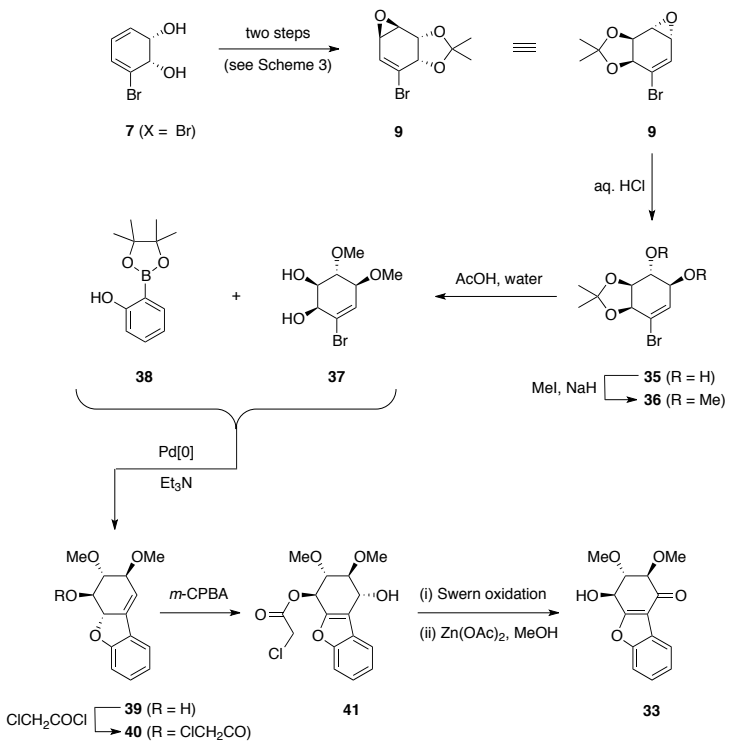


34

It was also noted that at 1 to 30 μM concentrations these natural products promote neurite outgrowth in NGF-mediated PC12 cells and could thus represent new leads for developing drugs to treat various neurodegenerative diseases.

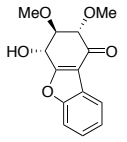
The resemblance of the polyoxygenated rings of the ribisins to the *cis*-1,2-dihydrocatechols of the general form **7** immediately struck us and prompted consideration of methods by which we could effect the necessary conversion. Our initial efforts[31] were focused on synthesizing the structure, **33**, assigned to ribisin C since this was the most active of the four compounds in the PC12-based assay. The reaction sequence used to obtain this compound is shown in Scheme 7.



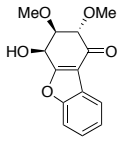
SCHEME 7: A Chemoenzymatic Synthesis of the Structure **33**, Assigned to Ribisin C

As with our first-generation synthesis of (+)-galanthamine, the reaction sequence leading to compound **33** started with the same *cis*-1,2-dihydrocatechol and this was first converted into the previously described epoxide **9**. Opening of this with aqueous HCl then provided the expected *trans*-diol **35** (63%) that was subjected to a two-fold methylation reaction and so generating compound **36** (90%) embodying the two *trans*-related methoxy residues associated with target compound **33**. Hydrolysis of the acetonide residue within bis-*O*-methyl ether **36** then afforded the *cis*-diol **37** (90%) that participated in a Suzuki–Miyaura cross-coupling reaction with the commercially available *o*-hydroxyphenyl boronic acid ester **38**. As a result the cyclohexannulated benzofuran-type system **39** (24%) was obtained and this presumably arises from the spontaneous cycloetherification of the initially formed cross-coupling product. In anticipation of introducing a hydroxyl group as a precursor to the required ketone carbonyl, alcohol **39** was protected as the corresponding α-chloroacetate **40** that we knew, from previous experience, could be removed under exceptionally mild conditions. Treatment of cyclohexene **40** with *m*-CPBA afforded the benzofuran **41** (49% from **39**) that presumably arises through rearrangement of the initially formed epoxide, a process driven by rupture of the strained three-membered ring and accompanying formation of the aromatic heterocycle associated with the observed product. Swern of oxidation of the alcohol residue within compound **41** and cleavage of the α-chloroacetate moiety within the product ketone using zinc acetate in methanol then gave target **33** (47% from **41**), the structure and relative stereochemistry of which were established by single-crystal X-ray analysis. While the ^{1}H and ^{13}C NMR data acquired on compound **33** matched those reported for ribisin C, the similar magnitudes but opposite signs associated with the specific rotations of these two materials clearly indicated that the absolute stereochemistry of the natural product had been assigned incorrectly.

As a result of the outcome just described, and because of a desire to acquire biologically active materials for testing for their neurite outgrowth promoting properties, we rapidly established[31] a reaction sequence that enabled the synthesis of compound *ent*-**33** and thus determining that this is the true structure of ribisin C. Once again, the staring material used for this purpose was the *cis*-1,2-dihydrocatechol **7** (X = Br). Using related chemistries we also prepared compounds **31**, **32** and **34** and thereby establishing[32] that the first and third of these do indeed represent the structures of ribisins A and D. Such work also enabled us to identify the true constitution of ribisin B as being represented by structure **42** and not **32**. The substantial collection of compounds produced during the course of our work on the synthesis of the ribisins has been submitted for testing in a range of relevant assays.



ent-**33**



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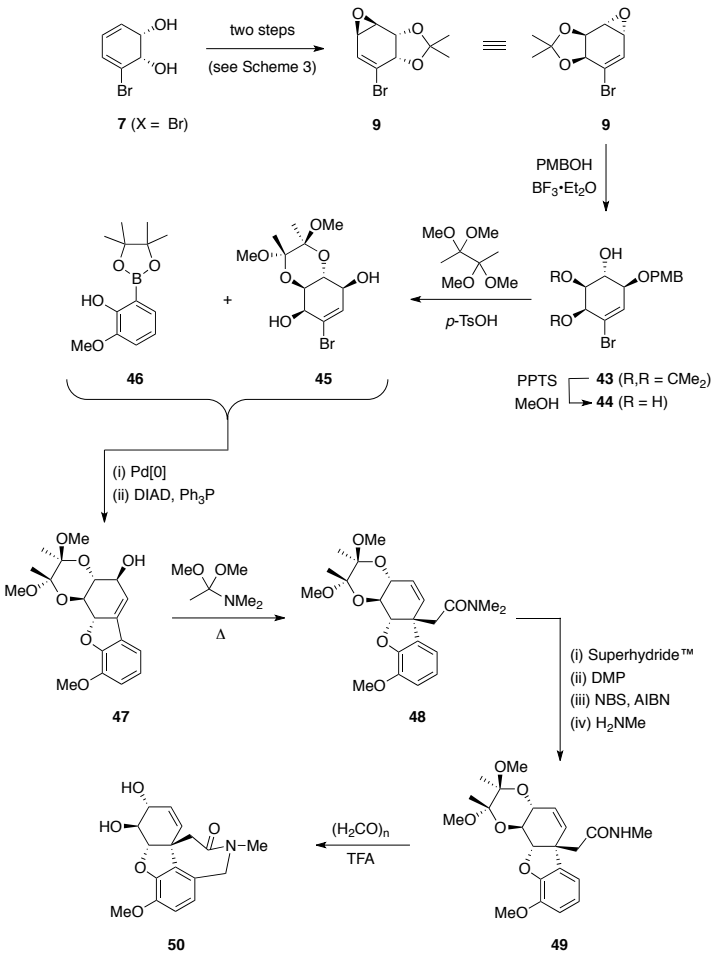
4.2 A Second-Generation Chemoenzymatic Approach to the Synthesis of (+)-Galanthamine

Rather belatedly, it occurred to us that our synthetic work on the ribisins might provide a means of readily assembling the ABC-ring system associated with galanthamine and perhaps even the alkaloid itself. There certainly appears to be some validity to this proposition as evidenced by the completion of the reaction sequence shown in Scheme 8.[33]



SCHEME 8: A Second-Generation Chemoenzymatic Approach to (+)-Galanthamine (*ent*-**1**).

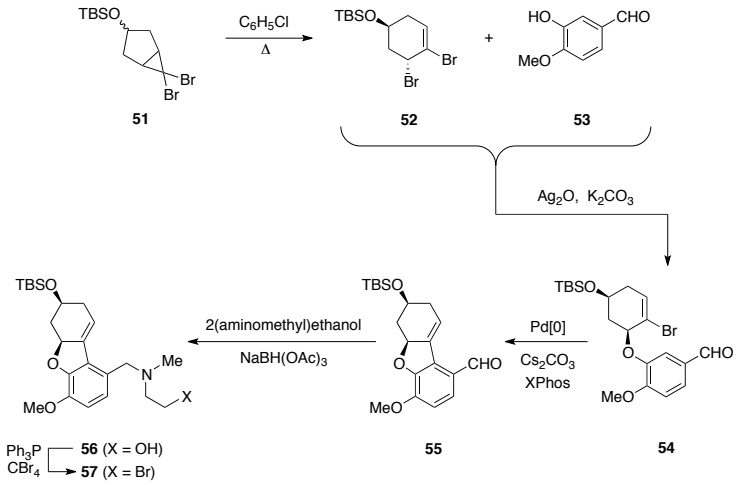
Once again, the reaction sequence starts with the *cis*-1,2-dihydrocatechol derived from the whole-cell biotransformation of bromobenzene, *viz*. compound **7** (X = Br), but the derived epoxide **9** is now opened with *p*-methoxybenzyl alcohol (PMBOH) in the presence of BF_3•Et_2O to give the tri-protected bromoconduritol **43** that upon exposure to pyridinium *p*-toluenesulfonate (PPTS) in methanol affords its mono-protected counterpart **44** (70% from **9**). Reaction of this last compound with 2,2,3,3-tetramethoxybutane in the presence of catalytic quantities of *p*-TsOH then provided the Ley-type[34] bis-ketal **45** (86%) in which, by virtue of the

operation of the anomeric effect, completely selective protection of the vicinally-related and *trans*-oriented hydroxyl groups within substrate **44** had occurred together with cleavage of the PMB ether moiety. Suzuki–Miyaura cross coupling of compound **45** with the arylboronic acid ester **46**, a compound that is readily obtained in a one-pot process from *o*-methoxyphenol using a protocol described by Hartwig,[35] afforded the anticipated product (60%) that readily engaged in an intramolecular Mitsunobu reaction to give the targeted ABC-ring containing product **47** (96%). This last compound might have been expected to be vulnerable to double-bond migration and thereby forming the isomeric and fully aromatic benzofuran. Nevertheless, and gratifyingly, it engaged in a very efficient and remarkably facile EC rearrangement reaction on being heated with dimethyl acetal of *N*,*N*-dimethylacetamide and so affording compound **48** in 86% yield. A distinctly cumbersome four-step sequence closely related to that deployed in the end-game associated with our first generation galanthamine synthesis (Scheme 6) was then used to convert this *N*,*N*-dimethylacetamide derivative into its mono-methylated counterpart **49** (73% over four steps). This last compound participated in a Pictet–Spengler reaction on treatment with paraformaldehyde in TFA, a process that was accompanied by cleavage of the associated bis-ketal moiety, and so forming the galanthamine analogue **50** (47%).

Efforts are now underway to effect the conversion of lactam **50** into (+)-galanthamine (*ent*-**1**). Interestingly, molecular docking studies similar to those reported previously[36] suggest this compound (*viz*. **50**) should bind at the active site of AChE with similar affinity to (–)-galanthamine itself. This is because the cyclohexene C-ring (of **50**) is oriented almost identically to its counterpart in (–)-galanthamine and so maintaining an architecture complementary to that of the active site of AChE and whereby it stacks against the indole ring of Trp84. Whether or not this rather tantalizing prediction is indeed correct remains to be tested experimentally.

5. An Abortive, Radical-Based Approach to (±)-Galanthamine

During the course of studies focused on the synthesis of certain crinine alkaloids we conceived of another and now exceptionally concise route to the ABC-ring substructure of galanthamine and hoped that the product so-formed would be capable of elaboration in such a way that the nitrogen-containing D-ring of the alkaloid could be annulated to it. The steps associated with the first stage of this study[36] are shown in Scheme 9 and involved a thermally-induced electrocyclic ring-opening of the readily available C3-oxygenated 6,6-dibromocyclopropane **51** and engagement of the product dibromocyclohexene **52** in an S_N2 reaction with phenol **53** to give the allyl aryl ether **54** (*ca*. 80% from **51**). This last compound

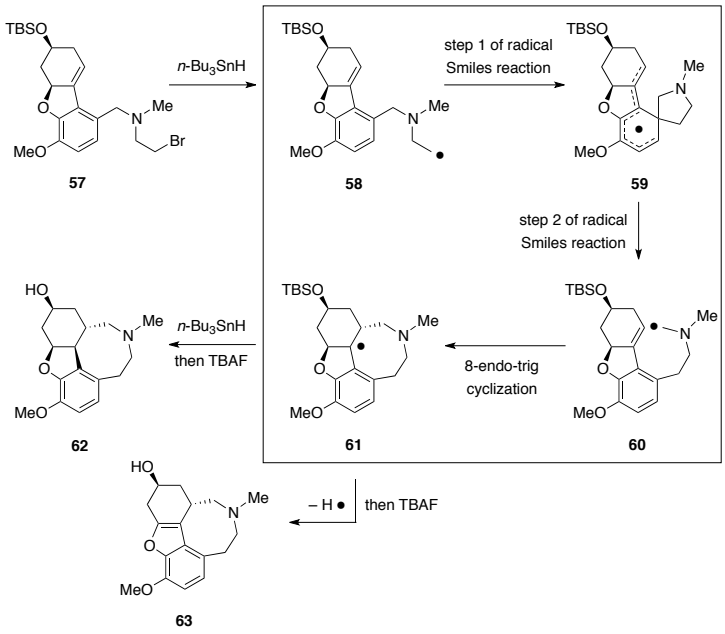


SCHEME 9: A Concise, Cyclopropane-Based Route to the ABC-Ring Substructure of Galanthamine

then participated in a Pd-catalyzed and intramolecular arylation reaction under conditions developed by Willis *et al.*[37] to give the tetrahydrodibenzo[*b*,*d*]furan **55** (ca. 65%). Reductive amination of compound **55** with *N*-methyl-2-aminoethanol in the presence of sodium

borohydride gave the desired 3°-amine **56**, the hydroxyl group within which was subjected to an Appel reaction using Ph_3P/CBr_4 and so affording bromide **57** (61% over two steps).

With compound **57** to hand we hoped that on treating it with tri-*n*-butyltin hydride this would form, through homolysis of the associated C–Br bond, the corresponding 1°-radical that would, in turn, engage in a 7-exo-trig cyclization reaction and so generating the D-ring of galanthamine. Alas, this was not to be. So, when bromide **57** was subjected to the relevant conditions two unexpected events took place (Scheme 10). First of all, the initially formed radical **58** participated in a spirocyclization onto the pendant and electron-rich arene residue and the resulting and extensively delocalized radical **59** then fragmented to give the nitrogen-stabilized congener **60** (overall a radical-based Smiles rearrangement) that now engaged in an 8-endo-trig radical cyclization to give isomer **61**.

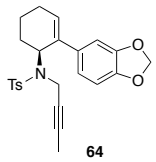


SCHEME 10: The Unexpected Radical-Based Reactions of the Tricyclic Iodide **57** – Formation of the D-Ring Galanthamine Isomer **63**.

This latter mode of cyclization is presumably driven by the formation of a benzylic radical rather than a homobenzylic one (that would have arisen from the hoped for but unobserved 7-exo-trig cyclization process). Reduction of radical **61** would then deliver, after desilylation with TBAF, the observed dihydrobenzofuran **62** (<1%) while loss of a hydrogen atom from the former species would afford, again after a TBAF treatment, benzofuran **63** (12%). The structures of products **62** and **63** were established by single-crystal analyses. Given the latter is a D-ring isomer of galanthamine we wondered if it would act as an inhibitor of AChE. Molecular docking studies predicted it wouldn't because of the distinctly different molecular shapes of the two compounds and in the event this prediction was borne out – tetracycle **63** is not an effective inhibitor of the enzyme.[36]

6. Doing Things the Hard Way – *De Novo* Construction of the Aromatic C-Ring as a Focal Point

In 2010 we reported[38] that various nitrogen-linked 1,6-enynes including compound **64** engage in rather efficient palladium-catalyzed intramolecular Alder-ene (IMAE) reactions so as to generate angularly substituted polyhydroindoles such as **65**. Subsequently, we exploited this kind of transformation as a key step in the synthesis of the racemic modification of the crinine alkaloid hamayne.[39] A notable feature of these processes is the need to "cap" the alkyne residue of the substrate with, for example, a methyl group (as seen in **64**) so as to prevent competing hetero-dimerization reactions.



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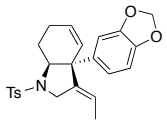

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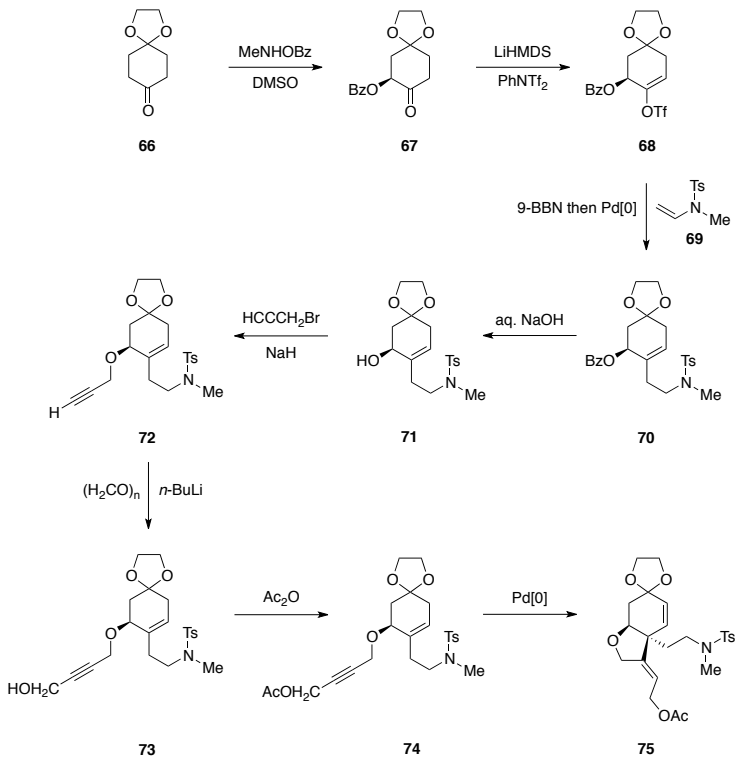
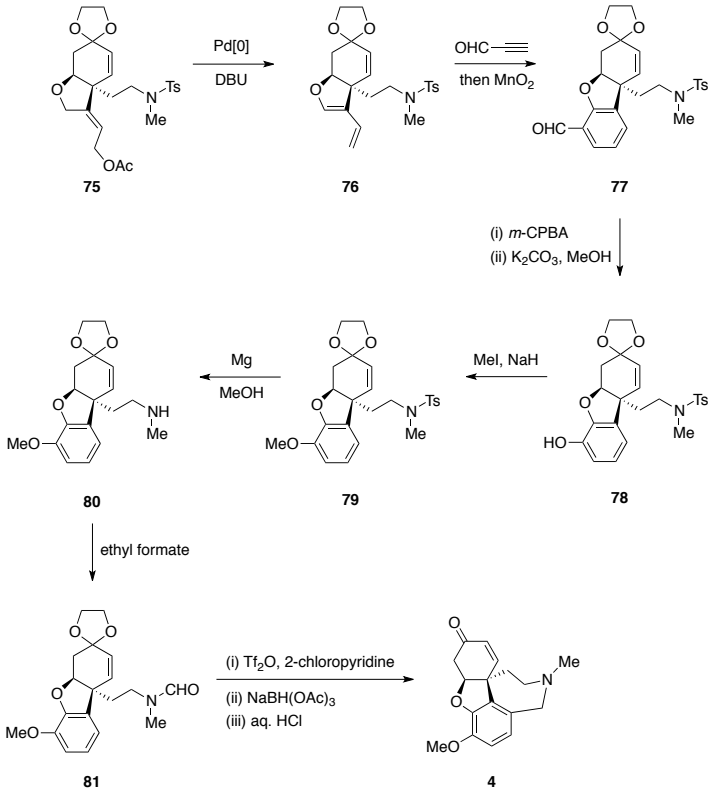
In seeking to understand the scope and limitations of such IMAE-based processes we wondered whether or not the corresponding oxygen-linked systems would undergo an analogous isomerization and thus affording angularly substituted perhydrobenzofurans related to the AB-ring system associated with galanthamine. It quickly became apparent that this was so as illustrated by the successful execution of the reaction sequence shown in Scheme 11.[40] Thus, the commercially available monoketal, **66**, of cyclohexane-1,4-dione was subjected to an α-oxidation protocol developed by Tomkinson and co-workers[41] and thus affording, in racemic form, the acyloin derivative **67** that was converted into the corresponding enol triflate **68** (73% over two steps) under standard conditions. Using a very effective procedure developed by Kamatani and Overman,[42] this last compound could then be cross-coupled with an organoborane derived from enamine **69** and so affording the β-aminoethyl-substituted compound **70** (79%). Saponification of the benzoate residue within the last compound proceeded uneventfully to give the corresponding alcohol **71** (71%) that was immediately reacted with propargyl bromide in the presence of sodium hydride to give the anticipated ether **72** (89%), the terminal alkyne moiety of which was "capped" by successive treatment with *n*-BuLi then paraformaldehyde and so giving the 1°-alcohol **73** (ca. 85%). This was then acetylated to give ester **74** (93%). Gratifyingly, on subjection to the types of conditions we have used previously for effecting IMAE reactions of related but somewhat simpler substrates, compound **74** could be efficiently isomerized to the benzofuran derivative **75** (71%).



SCHEME 11: The IMAE Route to the AB-Ring System of Galanthamine.

Compound **75** embodies the A and B rings of galanthamine as well as an angular substituent that could serve as a precursor to the D-ring. Of course, a significant challenge associated with seeking to exploit the results shown in Scheme 11 concerns the matter of incorporating the aromatic C-ring, a structural element that has been present from the outset in all previous syntheses of this alkaloid. As such, we became intrigued by the possibility that we could benzannulate compound **75** in some way and so assemble the requisite ABC-ring substructure by such means. Provided relevant protocols could be identified then novel C-ring variants of galanthamine might become accessible using this type of approach. In the event, and

as shown in Scheme 12, a suitable benzanulation protocol was identified and a synthesis of (–)-galanthamine thereby established. Thus, treatment of allylic acetate **75** with a Pd[0] catalyst in the presence of the base DBU resulted in elimination of the elements of acetic acid and, thereby, formation of the electron-rich and semi-cyclic 1,3-diene **76** (85%). This was readily engaged in a regio-selective Diels–Alder reaction with propynal and the rather unstable primary adduct so-formed treated, *in situ*, with manganese dioxide to effect its aromatization and thereby generating benzaldehyde **77** (61%). Dakin oxidation of this last compound using *m*-CPBA and cleavage of the resulting formate using potassium carbonate in methanol then gave phenol **78** (69%) that upon *O*-methylation afforded ether **79** (quantitative) that now embodies the essential "elements" of the ABC-ring substructure of galanthamine. As such it proved to be a relatively simple matter to elaborate compound **79** to (±)-narwedine, an established precursor (+)- or (–)-galanthamine.[20] Specifically, then, treatment of this last compound with magnesium turnings in methanol resulted in cleavage of the sulfonamide residue and the ensuing 2°-amine **80** (83%) was then reacted with ethyl formate to give the expected amide **81** (quantitative). Finally, subjection of compound **81** to a modified Bischler–Napieralski reaction using triflic anhydride and 2-chloropyridine,[43] reduction of the resulting acyliminium ion with $NaBH(OAc)_3$ and a mild acidic work-up (to cleave the ethylene ketal moiety) gave (±)-narwedine (**4**) albeit in an as yet unoptimized yield of 24%.



SCHEME 12: Assembling the Aromatic C-Ring of Galanthamine Using Diels–Alder Cycloaddition Chemistry and Completion of a Synthesis of (±)-Narwedine (**4**)

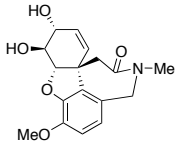
7. Conclusions

Only one of the synthetic sequences reported above has any reasonable prospect of providing an especially useful route to (–)-galanthamine and that is the so-called second-generation chemoenzymatic approach shown in Scheme 8. This was inspired by our work on the ribisins. Of course, and almost by definition, this chemistry was informed by the lessons learnt during the course of developing its first-generation counterpart. Currently the IMAE approach to the title alkaloid, as outlined in Schemes 11 and 12, is too long to be a useful means for obtaining significant quantities of galanthamine. However, and regardless of whether

refinements of it give any cause to change this assessment, it offers the capacity to construct novel aromatic C-ring analogues that might act as even more effective AChE inhibitors than (−)-galanthamine. As such it provides a quite distinct, if not a unique approach to the galanthamine framework.

In each of the instances discussed above, the successful construction of the D-ring associated galanthamine has relied on engaging an angular β-aminoethyl moiety (located at the junction between the A and B rings) in a Pictet–Spengler or Bischler–Napierlaski reaction. In two instances, the precursor to this moiety is obtained through an EC rearrangement reaction and several steps were necessary to convert the initially formed *N*,*N*-dimethylamide moiety into its mono-methyl counterpart. Clearly, then, there would be great merit in identifying a replacement for the dimethyl acetal of *N*,*N*-dimethylacetamide used in the EC rearrangement reaction with a species that generates the required mono-methylated amide directly. An even more attractive possibility would be to identify one that generates an acyl imminium ion immediately after the EC rearrangement and that thus engages in an *in situ* cyclization reaction to produce the D-ring directly. Such possibilities are under active investigation in our laboratories.

Another focus of efforts to extend our work in this area will be generating compounds such as **50** and the diol, **82**, derived from hydrolysis of bis-acetal **48**. These readily accessible systems could be regarded as hybrids of the ribisin and galanthamine structures[44] and might be expected to act as effective inhibitors of AChE. Certainly, as noted above, molecular docking studies suggest compound **50** should be active in this regard.



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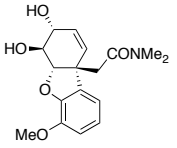

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Regardless of the outcomes of the studies foreshadowed immediately above, it is clear that the intriguing molecular architecture of galanthamine has prompted a significant number of research groups to develop new strategies and tactics for its synthesis. Not all of these have been successful but in essentially every instance important lessons have been learnt along the way and these may well provide solutions to other, yet to be recognized challenges.

Acknowledgements

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. P.L. is the grateful recipient of a CSC PhD Scholarship provided by the Government of the People's Republic of China.

References and Footnotes

1. For useful points-of-entry into the literature on the history, chemistry and pharmacology of galanthamine see: (a) Heinrich, M.; Teoh, H. L. *J. Ethnopharmacol*. **2004**, *92*, 147. (b) Marco-Contelles, J.; do Carmo Carreiras, M.; Rodríguez, C.; Villarroya, M.; García, A. G. *Chem. Rev*. **2006**, *106*, 116. (c) Marco, L.; do Carmo Carreiras, M. *Recent Pat. CNS Drug Discovery* **2006**, *1*, 105. (d) Heinrich, M. *The Alkaloids* **2010**, *68*, 157.
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3. Chandrasekhar, S.; Basu, D.; Sailu, M.; Kotamraju, S. *Tetrahedron Lett*. **2009**, *50*, 4882 and references cited therein.

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Publication Three

A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring

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A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring

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Keywords: Natural products / Total synthesis / Alkaloids / Alder-ene reactions / Diels–Alder reactions / Cycloaddition

The tetracyclic alkaloid galanthamine is used clinically in a number of countries for the symptomatic treatment of mild to moderate forms of Alzheimer's disease, and this feature coupled with its novel molecular architecture has prompted an extensive focus on its synthesis. The present study reports a new and distinct synthesis of galanthamine wherein the AB-ring substructure and associated quaternary carbon centre are constructed by using a palladium-catalyzed intramolecular Alder-ene reaction. The product of this process is engaged in a Tsuji–Trost-type reaction to generate a semicyclic diene that participates in a normal-electron-demand Diels–Alder reaction to generate, after oxidation of the initially formed adduct, the aromatic C-ring of the target alkaloid. Modified Bischler–Napieralski chemistry is then deployed to construct the seven-membered D-ring and thereby furnishing narwedine, an established precursor to both (+)- and (–)-galanthamine.

Introduction

The tetracyclic Amaryllidaceae alkaloid (–)-galanthamine (**1**) (Figure 1) has been isolated from a range of plant sources including the Caucasian snowdrop (*Galanthus woronowii*) and the Red Spider Lily (*Lycoris radia*).[1] Since the early 1950s it has been used in various clinical settings and is currently marketed in many countries for the symptomatic treatment of the early stages of Alzheimer's disease.[1,2] Galanthamine's effectiveness in this regard derives, at least in part, from its capacity to cross the blood-brain barrier and inhibit acetylcholine esterase in a selective, competitive and reversible manner.[1] The compound has also been shown to act at the nicotinic acetylcholine receptor.[3]

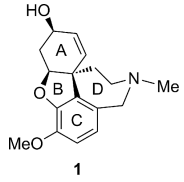

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Figure 1. Structure of (–)-galanthamine (**1**).

The significant and increasing clinical demand for galanthamine together with the erosion of the habitat of certain of the producing plants is creating supply issues. Various attempts are being made to address these[4] but, thus far, no commercially viable synthesis of the alkaloid has been established.[5] Nevertheless, a range of ingenious approaches to galanthamine has been described with the first of these, reported by Barton and Kirby in 1962,[6] involving a biomimetic but low yielding intramolecular oxidative phenolic coupling reaction that established the entire ABCD-ring framework from an AC-ring precursor. Certain refinements of this basic process have been described,[7] including asymmetric variants,[8] and one has served as the basis for a pilot plant-scale production process.[9] Intramolecular Heck reactions that result in the formation of the ABC-ring substructure, including the pivotal quaternary carbon center of galanthamine, from an AC-ring precursor represents another effective approach.[10] Various others have been described[11] including ones that exploit D-glucose[12] or an enantiopure and enzymatically derived *cis*-1,2-dihydrocatechol[13] as precursors to the A-ring. Syntheses of a range of biologically active analogues of galanthamine have also been reported.[14]

Herein we report a synthesis of galanthamine that is distinct from all previous ones in that a de novo construction of the aromatic C-ring is involved and by which means a range of hitherto inaccessible analogues of this natural product should become available. The pivotal features of our approach are, (i) the use of a Pd-catalyzed intramolecu-lar Alder-ene (IMAE) reaction to construct the AB-ring substructure bearing an angular β-aminoethyl group, (ii) a Tsuji–Trost-type reaction leading to a diene that partici-pates in a completely regioselective Diels–Alder reaction with propynal and (iii) the ready elaboration of the Diels–Alder adduct to the aromatic and methoxylated C-ring of galanthamine.

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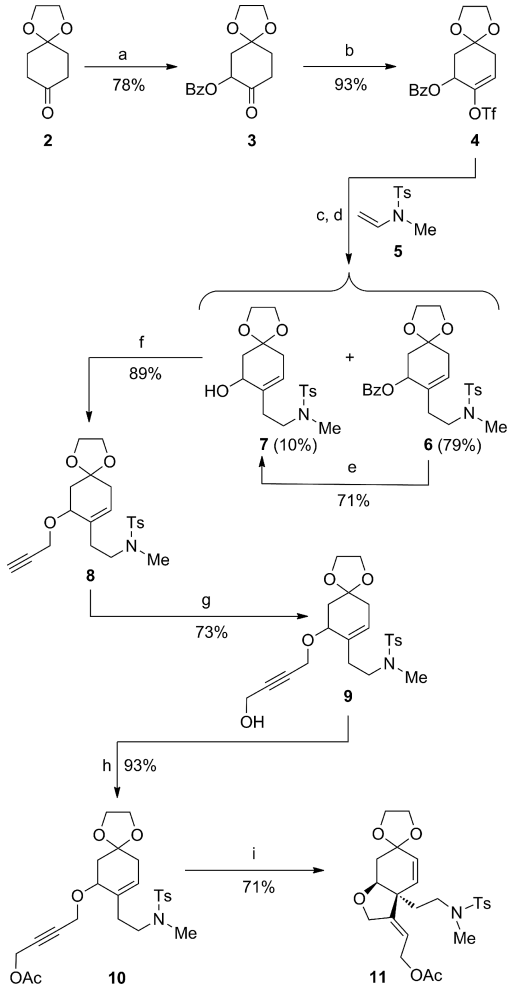
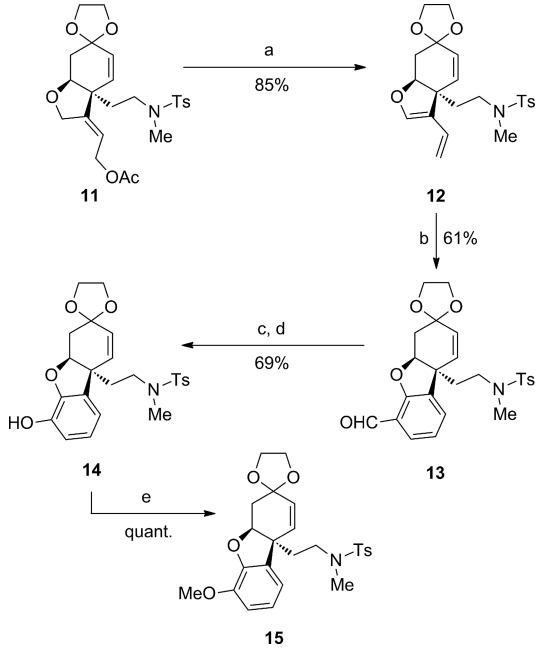
Results and Discussion

The opening stages of the synthesis, including the IMAE reaction, are shown in Scheme 1 and involve, as the first step, reaction of the commercially available monoethylene ketal **2** of cyclohexane-1,4-dione with *N*-methyl-*O*-benzoylhydroxylamine (MeNHOBz)[15] and thus affording the α-benzoyloxy derivative **3**[15] in 78% yield. This last compound was then converted, under standard conditions and in 93% yield, into the corresponding enol triflate **4** that was itself subjected to a Pd^0-catalyzed cross-coupling reaction with the in situ generated organoborane derived from 9-BBN and enamine derivative **5**[16] and thus delivering a mixture of amine derivative **6** (79%) and the corresponding alcohol **7** (10%).[17] Saponification of the benzoate residue within the former product with aqueous sodium hydroxide afforded additional quantities of alcohol **7** (71%) that was readily converted into the corresponding propargyl ether **8** (89%) upon treatment with propargyl bromide in the presence of sodium hydride. In anticipation of the above-mentioned diene-forming event and also in order to prevent dimerization of terminal alkyne **8**[18] this was "capped" with a hydroxymethyl group through its deprotonation with *n*BuLi, followed by reaction of the ensuing anion with paraformaldehyde. The resulting alcohol **9** (73%) was acetylated under standard conditions, and the ensuing ester **10** (93%) then engaged in a $Pd(OAc)_2$-mediated IMAE reaction under conditions originally defined by Trost and Pedregal in 1992[19] and exploited by us on various occasions more recently.[18,20] As a result, the hexahydrobenzofuran **11** embodying the AB-ring substructure of galanthamine was obtained in 71% yield. The use of the strong σ-donating ligand *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) in this reaction was essential to its success.



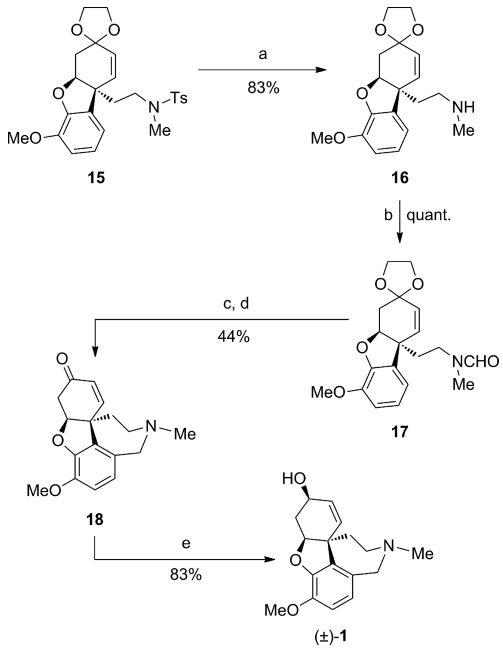
Scheme 1. Reaction sequence leading to the IMAE product **11**. Reagents and conditions: (a) MeNHOBz, DMSO, room temp., 2 h; (b) LiHMDS, then $PhNTf_2$, THF, –78 °C to room temp., ca. 4 h; (c) compound **5**, 9-BBN, THF, then NaOH (aq.), 0 °C to room temp., ca. 16 h; (d) compound **4**, $PdCl_2dppf{\cdot}CH_2Cl_2$, THF, room temp., 2 h, then H_2O_2; (e) NaOH, MeOH, 65 °C, 3 h; (f) $HCCCH_2Br$, nBu_4NI, NaH, THF, 0 °C to room temp., 48 h; (g) *n*BuLi then $(H_2CH)_n$, THF, –78 °C to room temp., 48 h; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 6 h; (i) $Pd(OAc)_2$, BBEDA, C_6H_6, 80 °C, 5 h.



Scheme 2. Construction of the aromatic C-ring: formation of compound **15**. Reagents and conditions: (a) $Pd(Ph_3P)_4$, DBU, $C_6H_5CH_3$, room temp. to 112 °C, ca. 2 h; (b) HCCCHO, DTBMP, then MnO_2, C_6H_6, room temp., 96 h; (c) *m*-CPBA, CH_2Cl_2, room temp., 46 h; (d) K_2CO_3, MeOH, room temp., 16 h; (e) MeI, NaH, THF, 0 °C to room temp., 25 h.

The next phase of the synthesis was the benzannulation of compound **11** in order to establish the aromatic C-ring of galanthamine. The means for doing so was achieved as shown in Scheme 2 and involved first treatment of this substrate with $Pd(Ph_3P)_4$ in the presence of the nitrogenous base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), thus effecting the elimination of the elements of acetic acid and so generating the diene **12** (85%). This last compound participated in a Diels–Alder cycloaddition reaction with propynal[21] at room temperature, and the so-formed adduct was immediately oxidized with manganese dioxide to afford benzaldehyde **13** (61%). The hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was added to prevent acid-catalyzed fragmentation of the initially formed adduct. On reaction with *m*-chloroperbenzoic acid, compound **13** engaged in a Dakin oxidation reaction, and the product aryl formate was cleaved with potassium carbonate in methanol. The resulting phenol **14** (69%) was then *O*-methylated with methyl iodide in the presence of sodium hydride, thus producing the methoxyarene **15** (quant.) that embodies the aromatic C-ring of galanthamine.

The completion of the synthesis of target **1** from arene **15** clearly requires introduction of the heterocyclic D-ring. The procedure for doing so is shown in Scheme 3 and involved, as the first step, treatment of compound **15** with magnesium in methanol[22] that resulted in cleavage of the associated tosyl residue and formation of the secondary amine **16** (83%). Simple heating of this last compound with neat ethyl formate provided the formamide **17** in quantitative yield, and this was subjected to a Bischler–Napieralski-type cyclodehydration reaction under conditions defined by Movassaghi and Hill.[23] Subsequent and successive treatment of the crude reaction mixture with sodium triacetoxy(hydrido)borate followed by saturated aqueous sodium hydrogen carbonate afforded (±)-narwedine (**18**) in 44% yield. The spectroscopic data acquired on this tetracyclic compound are in complete accord with those reported by Magnus and co-workers.[11c]



Scheme 3. Installation of the D-ring and completion of the synthesis. Reagents and conditions: (a) Mg, MeOH, ultrasonication, 16 h; (b) EtOCHO, 54 °C, 6 h; (c) Tf_2O, 2-chloropyridine, CH_2Cl_2, –78 °C to room temp., 20 h; (d) $NaB(OAc)_3H$, CH_2Cl_2, room temp., 2 h, then satd. aq. $NaHCO_3$; (e) L-selectride, THF, –78 °C, 3 h.

Since racemic narwedine is readily converted into either (+)- or (–)-galanthamine, the present work constitutes a formal total synthesis of both enantiomeric forms of the title alkaloid.[24] In order to further corroborate the structural assignments presented above, (±)-narwedine (**18**) was subjected to diastereoselective reduction with L-selectride,[24,25] thereby affording (±)-galanthamine [(±)-**1**] in 83% yield. The ^1H and ^{13}C NMR spectroscopic data obtained on this material also proved a good match for those recorded on the natural product.[13]

Conclusions

The work detailed here highlights the effectiveness of the palladium-catalyzed IMAE reaction for constructing hexahydrobenzofurans bearing angular substituents and, thereby, quaternary carbon centers such as those associated with galanthamine (**1**). Furthermore, the use of a Diels–Alder reaction to construct the aromatic C-ring of this alkaloid should provide the means for assembling analogues that incorporate unusual functionalities in this part of the molecular framework. Work directed towards such ends are now underway in these laboratories.

Experimental Section

General Experimental Procedures: Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ with a Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^1H NMR spectra, signals arising from the residual protio forms of the solvent were used as the internal standards. ^1H NMR spectroscopic data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of thereof. The signal due to residual $CHCl_3$ appearing at δ_H = 7.26 ppm and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C = 77.0 ppm were used to reference ^1H and ^{13}C NMR spectra, respectively. The signal due to residual CH_2Cl_2 appearing at δ_H = 5.30 ppm and the central resonance of the CD_2Cl_2 "multiplet" appearing at δ_C = 53.5 ppm were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (IR: $\tilde{\nu}_{max}$) were recorded with a Perkin–Elmer 1800 series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer, while high-

resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded with a magnetic-sector machine. Melting points were measured with an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized with a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (concd.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out according to protocols defined by Still et al.[26] with silica gel 60 (40–63 μm) as the stationary phase and with the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab chemical companies. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried by using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[27] Where necessary, reactions were performed under nitrogen.

8-{[(Trifluoromethyl)sulfonyl]oxy}-1,4-dioxaspiro[4.5]dec-8-en-7-yl Benzoate (4): A magnetically stirred solution of ketone **3**[15] (9.73 g, 35.2 mmol) in dry THF (190 mL) maintained under nitrogen was cooled to –78 °C and then treated with LiHMDS (46 mL of a 1 M solution in THF, 46 mmol). The resulting mixture was stirred at –78 °C for 0.5 h, then warmed to –40 °C and treated with *N*-phenylbis(trifluoromethanesulfonimide) (16.4 g, 46 mmol). The resulting mixture was warmed to room temperature over a period of 3 h before being quenched with NH_4Cl (150 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 4:1 v/v petroleum ether/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.5 in 3:1 v/v petroleum ether/ethyl acetate) afforded enol triflate **4** (13.37 g, 93%) as a tan solid, m.p. 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (m, 2 H), 7.59 (m, 1 H), 7.46 (m, 2 H), 6.02 (t, *J* = 4.0 Hz, 1 H), 5.88 (m, 1 H), 4.05–3.95 (complex m, 4 H), 2.66 (dt, *J* = 18.4 and 3.1 Hz, 1 H), 2.57–2.42 (complex m, 2 H), 2.14 (dd, *J* = 13.2 and 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 144.9, 133.5, 130.1, 128.6, 120.7, 118.8 (q, *J* = 320.0 Hz), 106.1, 67.8, 65.0, 64.9, 37.6, 34.8 (one signal obscured or overlapping) ppm. IR: $\tilde{\nu}_{max}$ = 2965, 2893, 1726, 1601, 1421, 1267, 1248, 1211, 1142, 1064, 877, 712 cm^{-1}. MS (EI): *m*/*z* (%) = 408 (2) [M$^{+\cdot}$], 303 (5), 287 (10), 275 (15), 153 (100), 105 (56). HRMS (EI): calcd. for $C_{16}H_{15}F_3O_7S$ [M$^{+\cdot}$] 408.0491; found 408.0485.

8-[2-(*N*,4-Dimethylphenylsulfonamido)ethyl]-1,4-dioxaspiro[4.5]dec-8-en-7-yl Benzoate (6) and *N*-[2-(9-Hydroxy-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl]-*N*,4-dimethylbenzenesulfonamide (7): A magnetically stirred solution of sulfonamide **5**[16] (15.84 g, 75 mmol) in dry THF (75 mL) maintained under nitrogen was cooled to 0 °C and then treated dropwise with 9-BBN (150 mL of a 0.5 M solution in THF, 75 mmol). After 0.17 h at 0 °C, the reaction mixture was warmed to room temperature and then stirred for 16 h before being treated dropwise with NaOH (75 mL of a 3 M aqueous solution). The resulting mixture was stirred at room temperature for 0.33 h and then treated with a solution of enol triflate **4** (21.76 g, 40 mmol) and $PdCl_2$dppf·CH_2Cl_2 (6.80 g, 6 mmol, 0.20 mol equiv.) in dry THF (120 mL). The resulting mixture was stirred at room temperature for 2 h, then cooled to 0 °C, quenched with H_2O_2 (100 mL of a 30% aqueous solution) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 7:3 v/v petroleum ether/ethyl acetate elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 7:3 v/v petroleum ether/ethyl acetate) gave benzoate **6** (14.80 g, 79%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.3 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.3 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 5.77 (t, *J* = 6.7 Hz, 1 H), 5.72 (t, *J* = 3.1 Hz, 1 H), 4.01–3.95 (complex m, 4 H), 3.14 (ddd, *J* = 13.5, 8.6 and 7.2 Hz, 1 H), 3.06 (ddd, *J* = 13.5, 8.7 and 5.8 Hz, 1 H), 2.66 (s, 3 H), 2.53–2.42 (complex m, 1 H), 2.40 (s, 3 H), 2.38–2.26 (complex m, 4 H), 1.99 (dd, *J* = 13.2 and 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 143.3, 135.0, 133.3, 132.9, 130.3, 129.7 (6), 129.8 (1), 128.6, 127.5, 126.0, 107.4, 71.2, 64.7, 64.6, 49.2, 37.2, 36.1, 35.2, 31.6, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 2969, 2926, 2887, 1713, 1599, 1451, 1339, 1268, 1160, 1108, 949, 715 cm^{-1}. MS (EI): *m*/*z* (%) = 471 (3) [M$^{+\cdot}$], 349 (10), 273 (9), 198 (100), 155 (52), 91 (47). HRMS (EI): calcd. for $C_{25}H_{29}NO_6S$ [M$^{+\cdot}$] 471.1716; found 471.1712.

Concentration of fraction B (R_f = 0.2 in 1:1 v/v petroleum ether/ethyl acetate) gave allylic alcohol **7** (1.40 g, 10%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.50 (m, 1 H), 4.13 (dt, *J* = 10.9 and 4.0 Hz, 1 H), 4.04–3.89 (complex m, 4 H), 3.27 (ddd, *J* = 13.5, 8.4 and 7.1 Hz, 1 H), 3.06 (ddd, *J* = 13.5, 8.5 and 5.4 Hz, 1 H), 3.00 (d, *J* = 10.9 Hz, 1 H), 2.72 (s, 3 H), 2.49–2.42 (complex m, 1 H), 2.41 (s, 3 H), 2.38–2.25 (complex m, 3 H), 2.07–1.96 (complex m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 136.7, 134.9, 129.7, 127.5, 123.1, 108.2, 68.5, 64.5 (3), 64.5 (0), 49.2, 39.0, 36.1, 34.8, 32.4, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 3523, 2956, 2921, 2887, 1336, 1159, 1048, 948, 721 cm^{-1}. MS (EI): *m*/*z* (%) = 367 (3) [M$^{+\cdot}$], 349 (2), 281 (18), 198 (100), 155 (70), 91 (53). HRMS (EI): calcd. for $C_{18}H_{25}NO_5S$ [M$^{+\cdot}$] 367.1453; found 367.1457.

***N*-[2-(9-Hydroxy-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl]-*N*,4-dimethylbenzenesulfonamide (7):** A magnetically stirred solution of benzoate **6** (14.8 g, 31.4 mmol) in methanol (500 mL) was treated with NaOH (100 mL of a 3 M aqueous solution) and the resulting solution heated at reflux for 3 h. The cooled reaction mixture was quenched with NH_4Cl (40 mL of a saturated aqueous solution) and then concentrated under reduced pressure. The ensuing residue was extracted with diethyl ether (3 × 50 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography (silica gel; 4:1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v petroleum ether/ethyl acetate), allylic alcohol **7** (8.18 g, 71%) as a clear, yellow oil. This material was identical, in all respects, with that obtained in the preceding step.

***N*,4-Dimethyl-*N*-{2-[9-(prop-2-yn-1-yloxy)-1,4-dioxaspiro[4.5]dec-7-en-8-yl]ethyl}benzenesulfonamide (8):** A magnetically stirred solution of allylic alcohol **7** (9.50 g, 25.9 mmol) in anhydrous THF (68 mL) was treated with tetra-*n*-butylammonium iodide (2.01 g, 4.53 mmol) and propargyl bromide (5.8 mL of a 80% solution in toluene, 51.8 mmol) before being cooled to 0 °C and treated portionwise with NaH (2.34 g of a 60% dispersion in mineral oil, 51.8 mmol). After having been stirred at 0 °C for 0.17 h, the reaction mixture was warmed to room temperature and then stirred for 48 h before being quenched with NH_4Cl (50 mL of a saturated

aqueous solution) and extracted with diethyl ether (3× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 7:3 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.4), propargyl ether **8** (9.30 g, 89%) as a clear, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 5.52 (m, 1 H), 4.31–4.25 (complex m, 1 H), 4.24 (dd, J = 16.0 and 2.4 Hz, 1 H), 4.15 (dd, J = 16.0 and 2.4 Hz, 1 H), 4.02–3.90 (complex m, 4 H), 3.20–3.05 (complex m, 2 H), 2.75 (s, 3 H), 2.50–2.43 (complex m, 1 H), 2.42 (s, 3 H), 2.38 (t, J = 2.4 Hz, 1 H), 2.35–2.14 (complex m, 4 H), 1.82 (dd, J = 12.8 and 7.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 135.1, 135.0, 129.7, 127.6, 124.0, 107.9, 80.3, 75.0, 74.6, 64.6, 64.5, 56.1, 49.5, 36.6, 35.9, 35.1, 31.6, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 3271, 2956, 2928, 2884, 2115, 1598, 1456, 1337, 1160, 1074, 1019, 948, 817, 731 cm^{-1}. MS (ESI): m/z (%) = 428 (100) [M + Na]$^+$, 406 (5) [M + H]$^+$, 351 (10). HRMS (ESI): calcd. for $C_{21}H_{27}NNaO_5S$ [M + Na]$^+$ 428.1508; found 428.1506.

***N*-(2-{9-[(4-Hydroxybut-2-yn-1-yl)oxy]-1,4-dioxaspiro[4.5]dec-7-en-8-yl}ethyl)-*N*,4-dimethylbenzenesulfonamide (9):** A magnetically stirred solution of propargyl ether **8** (9.30 g, 22.9 mmol) in anhydrous THF (100 mL) was cooled to –78 °C and then treated with *n*BuLi (16.7 mL of a 1.5 M solution in hexanes, 25.2 mmol). The ensuing solution was stirred at this temperature for 1 h before being treated with paraformaldehyde (2.06 g, 68.7 mmol). The resulting suspension was warmed to room temperature and, after 48 h, quenched with NH_4Cl (50 mL of a saturated aqueous solution), then extracted with diethyl ether (3× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 1:2 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.3), propargyl alcohol **9** (7.28 g, 73%) as a clear, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.50 (t, J = 3.8 Hz, 1 H), 4.39–4.28 (complex m, 4 H), 4.18 (dt, J = 15.9 and 1.7 Hz, 1 H), 3.95 (m, 4 H), 3.25 (m, 1 H), 3.12 (m, 1 H), 2.73 (s, 3 H), 2.51 (m, 2 H), 2.42 (s, 3 H), 2.36–2.12 (complex m, 4 H), 1.82 (dd, J = 12.8 and 7.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 135.1, 134.8, 129.8, 127.6, 124.3, 107.8, 85.5, 81.5, 73.6, 64.6, 64.5, 55.9, 51.1, 49.4, 36.1, 35.9, 34.8, 31.8, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 3468, 2926, 2883, 2250, 1956, 1597, 1335, 1160, 1069, 947, 817, 730 cm^{-1}. MS (ESI): m/z (%) = 458 (100) [M + Na]$^+$, 350 (85). HRMS (ESI): calcd. for $C_{22}H_{29}NNaO_6S$ [M + Na]$^+$ 458.1613; found 458.1614.

4-({8-[2-(*N*,4-Dimethylphenylsulfonamido)ethyl]-1,4-dioxaspiro[4.5]dec-8-en-7-yl}oxy)but-2-yn-1-yl Acetate (10): A magnetically stirred solution of propargyl alcohol **9** (7.82 g, 18.0 mmol) in anhydrous dichloromethane (100 mL) was cooled to 0 °C and then treated with triethylamine (3.00 mL, 21.6 mmol), DMAP (220 mg, 1.8 mmol) and acetic anhydride (2.1 mL, 21.6 mmol). The resulting solution was stirred at 0 °C for 6 h before being quenched with NH_4Cl (50 mL of a saturated aqueous solution) and extracted with dichloromethane (3× 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 1:1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.7 in 1:2 v/v petroleum ether/ethyl acetate), propargyl acetate **10** (7.99 g, 93%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.01 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 5.51 (m, 1 H), 4.68 (t, J = 1.9 Hz, 2 H), 4.27 (dt, J = 16.1 and 1.9 Hz, 1 H), 4.23 (m, 1 H), 4.19 (dt, J = 16.1 and 1.9 Hz, 1 H), 4.10–3.90 (complex m, 4 H), 3.19 (ddd, J = 13.2, 9.3 and 6.6 Hz, 1 H), 3.10 (ddd, J = 13.2, 9.3 and 5.3 Hz, 1 H), 2.74 (s, 3 H), 2.42 (s, 3 H), 2.37–2.13 (complex m, 5 H), 2.07 (s, 3 H), 1.82 (dd, J = 12.8 and 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 143.2, 135.1, 135.0, 129.7, 127.5, 124.0, 107.9, 83.3, 80.4, 75.1, 64.6, 64.5, 56.3, 52.4, 49.4, 36.5, 35.9, 35.0, 31.6, 21.6, 20.8 ppm. IR: $\tilde{\nu}_{max}$ = 2958, 2928, 2879, 1956, 1747, 1594, 1338, 1224, 1160, 1071, 1071, 1027, 947, 730 cm^{-1}. MS (ESI): m/z (%) = 500 (100) [M + Na]$^+$, 350 (90). HRMS (ESI): calcd. for $C_{24}H_{31}NNaO_7S$ [M + Na]$^+$ 500.1719; found 500.1714.

(*Z*)-2-{(3a*S*,7a*S*)-*rel*-3a-[2-(*N*,4-Dimethylphenylsulfonamido)ethyl]-7,7a-dihydro-2*H*-spiro(benzofuran-6,2′-[1,3]dioxolan)-3(3a*H*)-ylidene}ethyl Acetate (11): A magnetically stirred solution of propargyl acetate **10** (1.06 g, 2.1 mmol) in anhydrous benzene (30 mL) was treated with $Pd(OAc)_2$ (71 mg, 0.32 mmol) and *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) (75 mg, 0.32 mmol). The resulting solution was heated at reflux for 5 h and then concentrated under reduced pressure to give a brown oil that was subjected to flash chromatography (silica gel; 1:1 v/v petroleum ether/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.5 in 1:2 v/v petroleum ether/ethyl acetate) then gave allylic acetate **11** (754 mg, 71%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.9 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 5.65 (d, J = 10.4 Hz, 1 H), 5.64 (d, J = 10.4 Hz, 1 H), 5.39 (m, 1 H), 4.58 (d, J = 14.2 Hz, 1 H), 4.53–4.41 (complex m, 3 H), 4.15 (dd, J = 8.2 and 4.5 Hz, 1 H), 4.01–3.90 (complex m, 4 H), 3.01 (t, J = 8.2 Hz, 2 H), 2.69 (s, 3 H), 2.43 (s, 3 H), 2.06 (s, 3 H), 2.03–1.73 (complex m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 149.1, 143.5, 134.7, 133.2, 129.8, 127.7, 127.6, 115.9, 104.5, 79.8, 68.1, 65.1, 64.6, 61.7, 48.4, 46.7, 36.4, 35.3, 35.2, 21.7, 21.0 ppm. IR: $\tilde{\nu}_{max}$ = 2953, 2926, 2874, 1737, 1339, 1230, 1160, 1064, 1027, 738 cm^{-1}. MS (ESI): m/z (%) = 500 (100) [M + Na]$^+$, 478 (30) [M + H]$^+$. HRMS (ESI): calcd. for $C_{24}H_{31}NNaO_7S$ [M + Na]$^+$ 500.1719; found 500.1719.

***N*,4-Dimethyl-*N*-{2-[(3a*S*,7a*S*)-*rel*-3-vinyl-7,7a-dihydro-3a*H*-spiro(benzofuran-6,2′-[1,3]dioxolan)-3a-yl]ethyl}benzenesulfonamide (12):** A magnetically stirred solution of allylic acetate **11** (1.40 g, 2.93 mmol) in anhydrous toluene was treated with $Pd(PPh_3)_4$ (339 mg, 0.29 mmol) and the resulting solution stirred at room temperature for 0.17 h before being treated with DBU (1.32 mL, 8.79 mmol) and then heated at reflux for 2 h. The cooled reaction mixture was subjected without concentration to flash chromatography (neutral alumina; 3:1 → 1:1 petroleum ether/ethyl acetate gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.8 in 1:2 v/v petroleum ether/ethyl acetate), diene **12** (1.03 g, 85%) as a viscous, clear and colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 6.42 (s, 1 H), 6.17 (dd, J = 17.9 and 11.5 Hz, 1 H), 5.98 (d, J = 10.3 Hz, 1 H), 5.72 (d, J = 10.3 Hz, 1 H), 5.11 (d, J = 17.9 Hz, 1 H), 4.87 (d, J = 11.5 Hz, 1 H), 4.64 (dd, J = 6.6 and 5.1 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.14 (ddd, J = 13.7, 11.6 and 5.0 Hz, 1 H), 2.96 (ddd, J = 13.7, 11.6 and 5.0 Hz, 1 H), 2.72 (s, 3 H), 2.43 (s, 3 H), 2.21 (dd, J = 14.0 and 6.6 Hz, 1 H), 2.12–1.96 (complex m, 2 H), 1.82 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 143.4, 134.9, 132.4, 129.8, 127.7, 127.5 (4), 127.5 (1), 119.7, 110.0, 103.5, 83.8, 65.1, 64.6, 48.6, 46.6, 35.4, 35.3, 35.0, 21.7 ppm. IR: ῡmax = 2958, 2921, 2883, 2848, 1732, 1633, 1437, 1339, 1160, 1119, 721, 696, 542 cm^{-1}. MS (EI): m/z (%) = 417 (5) [M$^{+\cdot}$], 278 (53), 277 (100), 262 (90), 205 (70), 155 (22), 91 (47). HRMS (EI): calcd. for $C_{22}H_{27}NO_5S$ [M$^{+\cdot}$] 417.1610; found 417.1611.

***N*-{2-[(4a*S*,9b*S*)-*rel*-6-Formyl-4,4a-dihydro-9b*H*-spiro(dibenzo[*b*,*d*]-furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*,4-dimethylbenzenesulfon-**

amide (13): A magnetically stirred solution of diene **12** (530 mg, 1.27 mmol) in anhydrous benzene (30 mL) was treated with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (261 mg, 1.27 mmol) and propynal (140 μL, 2.54 mmol), the ensuing mixture maintained at room temperature for 48 h and then treated with MnO_2 (1.10 g, 12.7 mmol). The resulting mixture was stirred at room temperature for a further 48 h, then filtered through a pad of Celite and the filtrate concentrated under reduced pressure. The ensuing orange oil was subjected to flash chromatography (silica gel; 1:1 v/v petroleum ether/ethyl acetate elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1:2 v/v petroleum ether/ethyl acetate), benzaldehyde **13** (363 mg, 61%) as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (s, 1 H), 7.64 (dd, J = 7.6 and 1.4 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 2 H), 7.36 (dd, J = 7.6 and 1.4 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.00 (t, J = 7.6 Hz, 1 H), 5.95 (d, J = 10.1 Hz, 1 H), 5.81 (d, J = 10.1 Hz, 1 H), 4.98 (dd, J = 8.8 and 5.5 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.04 (ddd, J = 13.7, 10.1 and 5.8 Hz, 1 H), 2.93 (ddd, J = 13.7, 10.1 and 5.8 Hz, 1 H), 2.68 (s, 3 H), 2.41 (s, 3 H), 2.26 (dd, J = 13.4 and 5.3 Hz, 1 H), 2.07 (dd, J = 13.4 and 8.8 Hz, 1 H), 1.97 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 160.3, 143.6, 134.4, 134.0, 131.6, 129.8, 129.5, 129.2, 128.1, 127.5, 121.5, 120.6, 103.9, 86.0, 65.1, 64.8, 47.2, 46.4, 38.2, 36.3, 35.4, 21.6 ppm. IR: $\tilde{\nu}_{max}$ = 2958, 2925, 2887, 1685, 1610, 1450, 1338, 1160, 1016, 945, 732 cm^{-1}. MS (ESI): *m*/*z* (%) = 492 (100) [M + Na]$^+$, 470 (4) [M + H]$^+$. HRMS (ESI): calcd. for $C_{25}H_{27}NNaO_6S$ [M + Na]$^+$ 492.1457; found 492.1457.

***N*-{2-[(4a*S*,9b*S*)-6-Hydroxy-4,4a-dihydro-9b*H*-spiro(dibenzo[*b*,*d*]-furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*,4-dimethylbenzenesulfonamide (14):** A magnetically stirred solution of benzaldehyde **13** (300 mg, 0.64 mmol) in anhydrous dichloromethane (42 mL) was treated with *m*-CPBA (237 mg of 70% purity, 0.96 mmol). The resulting mixture was maintained at room temperature for 46 h, then quenched with NaS_2O_3 (10 mL of a 50% aqueous solution) and extracted with dichloromethane (3× 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, the ensuing brown oil dissolved in MeOH (56 mL) and the solution thus obtained treated with K_2CO_3 (884 mg, 6.4 mmol). The ensuing reaction mixture was kept at room temperature for 16 h, then concentrated under reduced pressure and the residue thus obtained treated with distilled water (30 mL) and extracted with dichloromethane (3× 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica gel; 1:4 v/v diethyl ether/dichloromethane elution). Concentration of the relevant fractions (R_f = 0.5) then gave phenol **14** (200 mg, 69%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.3 Hz, 2 H), 6.85–6.73 (complex m, 2 H), 6.68 (dd, J = 7.0 and 1.7 Hz, 1 H), 5.86 (d, J = 10.1 Hz, 1 H), 5.75 (d, J = 10.1 Hz, 1 H), 4.85 (dd, J = 7.7 and 5.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.06 (m, 1 H), 2.94 (m, 1 H), 2.68 (s, 3 H), 2.42 (s, 3 H), 2.17 (m, 2 H), 1.96 (m, 2 H) (signal due to phenolic group hydrogen obscured or overlapping) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 143.5, 141.4, 134.6, 132.4, 132.3, 129.8, 127.8, 127.5, 122.2, 116.0, 114.7, 103.9, 84.7, 65.0, 64.6, 48.6, 46.5, 37.3, 36.0, 35.3, 21.7 ppm. IR: $\tilde{\nu}_{max}$ = 3400, 2962, 2926, 2883, 1681, 1618, 1597, 1470, 1337, 1159, 1089, 1017, 946, 731, 549 cm^{-1}. MS (EI): *m*/*z* (%) = 457 (70) [M$^{+\cdot}$], 302 (62), 259 (51), 245 (80), 198 (100), 155 (87), 91 (97). HRMS (EI): calcd. for $C_{24}H_{27}NO_6S$ [M$^{+\cdot}$] 457.1559; found 457.1560.

***N*-{2-[(4a*S*,9b*S*)-*rel*-6-Methoxy-4,4a-dihydro-9b*H*-spiro(dibenzo-[*b*,*d*]furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*,4-dimethylbenzene-sulfonamide (15):** A magnetically stirred solution of phenol **14** (220 mg, 0.48 mmol) in anhydrous THF (12 mL) was cooled to 0 °C, treated with NaH (38 mg of a 60% dispersion in mineral oil, 0.96 mmol), kept at this temperature for 1 h and then treated with MeI (0.18 mL, 2.88 mmol) before being warmed to room temperature and stirred for 24 h. The ensuing mixture was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3× 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting brown oil was subjected to flash chromatography (silica gel; 1:2 v/v petroleum ether/ethyl acetate) to give, after concentration of the appropriate fractions (R_f = 0.6), methyl ether **15** (226 mg, quant.) as a colorless, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 6.87 (m, 1 H), 6.75 (m, 2 H), 5.91 (d, J = 10.1 Hz, 1 H), 5.76 (d, J = 10.1 Hz, 1 H), 4.83 (dd, J = 8.5 and 5.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.86 (s, 3 H), 3.08 (ddd, J = 13.7, 10.8 and 5.6 Hz, 1 H), 2.90 (ddd, J = 13.7, 10.8 and 5.6 Hz, 1 H), 2.67 (s, 3 H), 2.42 (s, 3 H), 2.20 (dd, J = 13.5 and 5.3 Hz, 1 H), 2.13 (dd, J = 13.5 and 8.5 Hz, 1 H), 1.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 145.3, 143.4, 134.7, 132.4 (4), 132.3 (6), 129.8, 128.4, 127.6, 121.9, 115.3, 111.9, 104.2, 84.6, 65.0, 64.7, 56.0, 48.4, 46.5, 38.0, 36.3, 35.3, 21.7 ppm. IR: $\tilde{\nu}_{max}$ = 2953, 2926, 1618, 1593, 1491, 1458, 1339, 1279, 1160, 1015, 951, 732 cm^{-1}. MS (EI): *m*/*z* (%) = 471 (80) [M$^{+\cdot}$], 316 (60), 259 (100), 216 (35), 198 (40), 155 (40), 91 (63). HRMS (EI): calcd. for $C_{25}H_{29}NO_6S$ [M$^{+\cdot}$] 471.1716; found 471.1717.

2-[(4a*S*,9b*S*)-*rel*-6-Methoxy-4,4a-dihydro-9b*H*-spiro(dibenzo[*b*,*d*]-furan-3,2′-[1,3]dioxolane)-9b-yl]-*N*-methylethan-1-amine (16): A magnetically stirred solution of methyl ether **15** (237 mg, 0.50 mmol) in anhydrous methanol (30 mL) was treated with magnesium turnings (425 mg, 17.5 mmol) and sonicated for 2 h. Further magnesium turnings (100 mg, 4.38 mmol) were added, and the resulting mixture was sonicated for an additional 2 h. This second addition/ultrasonication process was repeated a further six times. Then the reaction mixture was quenched with NH_4Cl (15 mL of a saturated aqueous solution) and extracted with ethyl acetate (3× 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil was subjected to flash chromatography (silica gel; 90:12:2 v/v/v dichloromethane/methanol/triethylamine elution) to give, after concentration of the appropriate fractions (R_f = 0.4), amine **16** (131 mg, 83%) as colorless, amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (m, 1 H), 6.79–6.70 (complex m, 2 H), 5.89 (d, J = 10.0 Hz, 1 H), 5.72 (d, J = 10.0 Hz, 1 H), 4.93 (t, J = 6.3 Hz, 1 H), 4.05–3.95 (complex m, 4 H), 3.86 (s, 3 H), 2.65–2.45 (complex m, 2 H), 2.38 (s, 3 H), 2.23 (d, J = 6.3 Hz, 2 H), 1.89 (t, J = 7.9 Hz, 2 H) (signal due to NH group proton not observed) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 145.2, 133.2 (6), 133.3 (1), 127.7, 121.7, 115.3, 111.7, 104.1, 84.8, 65.1, 64.7, 56.0, 48.5, 47.5, 39.4, 36.3, 36.1 ppm. IR: ῡmax = 2951, 2922, 2849, 2849, 1617, 1590, 1491, 1458, 1281, 1205, 1120 cm^{-1}. MS (EI): *m*/*z* (%) = 317 (47) [M$^{+\cdot}$], 272 (100), 59 (81). HRMS (EI): calcd. for $C_{18}H_{23}NO_4$ 317.1627 [M$^{+\cdot}$]; found 317.1628.

***N*-{2-[(4a*S*,9b*S*)-*rel*-6-Methoxy-4,4a-dihydro-9b*H*-spiro(dibenzo-[*b*,*d*]furan-3,2′-[1,3]dioxolane)-9b-yl]ethyl}-*N*-methylformamide (17):** A magnetically stirred solution of amine **16** (100 mg, 0.32 mmol) in ethyl formate (5 mL) was heated at reflux for 6 h. Then the cooled reaction mixture was concentrated under reduced pressure to afford formamide **17** (109 mg, quant.) as a yellow, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$; mixture of rotamers): δ = 7.96 (s, 1 H), 6.87–6.60 (complex m, 3 H), 5.93 (m, 1 H), 5.80 (m, 1 H), 4.94 (m, 1 H), 4.05–3.95 (complex m, 4 H), 3.88 (s, 1.68 H), 3.86 (s, 1.32 H),

3.45–3.30 (complex m, 1 H), 3.13 (m, 1 H), 2.87 (s, 1.32 H), 2.80 (s, 1.68 H) 2.26 (m, 1 H), 2.16–2.08 (complex m, 1 H), 1.99–1.80 (complex m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; mixture of rotamers): δ = 162.7, 162.4, 146.4, 146.3, 145.5, 145.3, 132.7, 132.4, 132.1, 132.0, 129.1, 128.5, 122.2, 121.9, 115.3, 114.9, 112.0, 111.9, 104.3, 104.2, 84.6, 84.5, 65.1, 65.0, 64.8, 64.7, 56.0 (8), 56.0 (5), 48.6, 48.4, 45.6, 40.7, 39.0, 36.5, 36.4, 36.3, 34.7, 29.7 ppm. IR: $\tilde{\nu}_{max}$ = 2956, 2927, 2883, 1671, 1617, 1589, 1491, 1458, 1397, 1281, 1207, 1118, 1013 952, 732 cm^{-1}. MS (EI): *m*/*z* (%) = 345 (90) [M$^{+\cdot}$], 286 (93), 259 (100), 241 (50), 215 (63). HRMS (EI): calcd. for $C_{19}H_{23}NO_5$ [M$^{+\cdot}$] 345.1576; found 345.1578.

(4a*S*,8a*S*)-*rel*-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-one (18) [(±)-Narwedine]: A magnetically stirred solution of formamide **17** (31.0 mg, 0.09 mmol) and 2-chloropyridine (26 μL, 0.27 mmol) in anhydrous dichloromethane (3 mL) was cooled to –78 °C and then treated dropwise with a solution of Tf_2O (37 μL, 0.23 mmol) in anhydrous dichloromethane (0.7 mL). The resulting solution was warmed to 0 °C, stirred at this temperature for 0.5 h, then warmed to room temperature and stirred for a further 20 h. The resulting mixture was then cooled to 0 °C and treated, portionwise, with $NaBH(OAc)_3$. After 0.17 h at 0 °C the reaction mixture was warmed to room temperature and maintained at this temperature for 2 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-narwedine (**18**) (11.2 mg, 44%) as a light-brown solid m.p. 185–187 °C (ref.[6] m.p. 187–190 °C). ^{1}H NMR (800 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 10.4 Hz, 1 H), 6.70 (d, *J* = 8.1 Hz, 1 H), 6.66 (d, *J* = 8.1 Hz, 1 H), 6.04 (dd, *J* = 10.4 and 1.0 Hz, 1 H), 4.73 (m, 1 H), 4.11 (d, *J* = 15.5 Hz, 1 H), 3.84 (s, 3 H), 3.75 (d, *J* = 15.5 Hz, 1 H), 3.25 (t, *J* = 13.7 Hz, 1 H), 3.16 (m, 2 H), 2.75 (dd, *J* = 17.9 and 3.5 Hz, 1 H), 2.44 (s, 3 H), 2.28 (td, *J* = 13.7 and 3.5 Hz, 1 H), 1.86 (d, *J* = 13.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 147.2, 144.5, 144.2, 130.7, 129.5, 127.3, 122.2, 112.1, 88.1, 60.8, 56.2, 54.3, 49.1, 42.5, 37.5, 33.4 ppm. IR: ṽmax = 2926, 2848, 1683, 1622, 1507, 1437, 1280, 1223, 1166, 1145, 1050, 1031, 1008, 802, 771 cm^{-1}. MS (EI): *m*/*z* (%) = 285 (100) [M$^{+\cdot}$], 284 (98), 242 (47), 174 (42), 84 (68), 58 (82). HRMS (EI): calcd. for $C_{17}H_{19}NO_3$ [M$^{+\cdot}$] 285.1365; found 285.1363.

(4a*S*,6*R*,8a*S*)-*rel*-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-6-ol [(±)-1] [(±)-Galanthamine]: A magnetically stirred solution of (±)-narwedine [(±)-**18**] (12.0 mg, 0.042 mmol) in anhydrous THF (2 mL) was cooled to –78 °C and then treated with L-selectride (0.13 mL of a 1 M solution in THF, 0.13 mmol). The resulting mixture was maintained at –78 °C for 3 h and then treated with water (1 mL) and NaOH (1 mL of a 3 M aqueous solution) before being extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil subjected to flash chromatography (silica gel, 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-galanthamine [(±)-**1**] (10 mg, 83%) as a light-brown, waxy solid. ^{1}H NMR (800 MHz, $CDCl_3$): δ = 6.66 (d, *J* = 8.1 Hz, 1 H), 6.63 (d, *J* = 8.1 Hz, 1 H), 6.06 (ddd, *J* = 10.3, 1.4 and 0.7 Hz, 1 H), 6.01 (ddd, *J* = 10.3, 5.1 and 1.4 Hz, 1 H), 4.61 (m, 1 H), 4.14 (m, 1 H), 4.10 (d, *J* = 15.4 Hz, 1 H), 3.83 (s, 3 H), 3.70 (dd, *J* = 15.4 and 0.7 Hz, 1 H), 3.28 (t, *J* = 13.5 Hz, 1 H), 3.06 (d, *J* = 14.3 Hz, 1 H), 2.69 (ddt, *J* = 15.7, 3.3 and 1.4 Hz, 1 H), 2.41 (s, 3 H), 2.09 (td, *J* = 13.5 and 3.3 Hz, 1 H), 2.01 (ddd, *J* = 15.7, 5.1 and 2.5 Hz, 1 H), 1.59 (dd, *J* = 13.5 and 2.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0, 144.3, 133.2, 129.2, 127.8, 126.9, 122.3, 111.4, 88.9, 62.2, 60.7, 56.1, 54.0, 48.4, 42.2, 33.9, 30.1 ppm. IR: $\tilde{\nu}_{max}$ = 3339, 2917, 2835, 1958, 1623, 1590, 1506, 1438, 1281, 1230, 1202, 1166, 1046 cm^{-1}. MS (EI): *m*/*z* (%) = 287 (90) [M$^{+\cdot}$], 286 (100), 270 (22), 244 (41), 216 (50), 174 (47). HRMS (EI): calcd. for $C_{17}H_{21}NO_3$ [M$^{+\cdot}$] 287.1521; found 287.1521.

Supporting Information (see footnote on the first page of this article): Tabular comparisons of the ^{13}C NMR spectroscopic data acquired on compounds **18** and (±)-**1** with those reported in the literature. ^{1}H and ^{13}C NMR spectra of compounds **4**, **6**–**18** and (±)-**1** and a comparison of the ^{1}H NMR spectrum of synthetically derived (±)-galanthamine with that recorded on an authentic sample of (–)-galanthamine.

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SUPPORTING INFORMATION

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Title: A Total Synthesis of Galanthamine Involving De Novo Construction of the Aromatic C-Ring
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Table S1: *Comparison of the ^{13}C NMR data recorded for (±)-narwedine [(±)-**18**] obtained by the route reported here with those reported in the literature.*

^{13}C NMR data for (±)-narwedine (δ_C)[a]	^{13}C NMR data reported in the literature (δ_C)[b]	$\Delta\delta_C$
194.5	194.4	+0.1
147.2	146.9	+0.3
144.5	144.3	+0.2
144.2	143.9	+0.3
130.7	130.5	+0.2
129.5	129.3	+0.2
127.3	127.0	+0.3
122.2	122.0	+0.2
112.1	111.8	+0.3
88.1	87.9	+0.2
60.8	60.6	+0.2
56.2	55.9	+0.3
54.3	54.0	+0.3
49.1	48.9	+0.2
42.6	42.4	+0.2
37.5	37.3	+0.2
33.4	33.2	+0.2

[a] Data recorded in $CDCl_3$ at 100 MHz.
[b] Data obtained from reference 1 and recorded in $CDCl_3$ at 100 MHz.

Table S2: *Comparison of the ^{13}C NMR data recorded for (±)-galanthamine [(±)-**1** obtained by the route reported here with those reported in the literature for the (+)-enantiomer.*

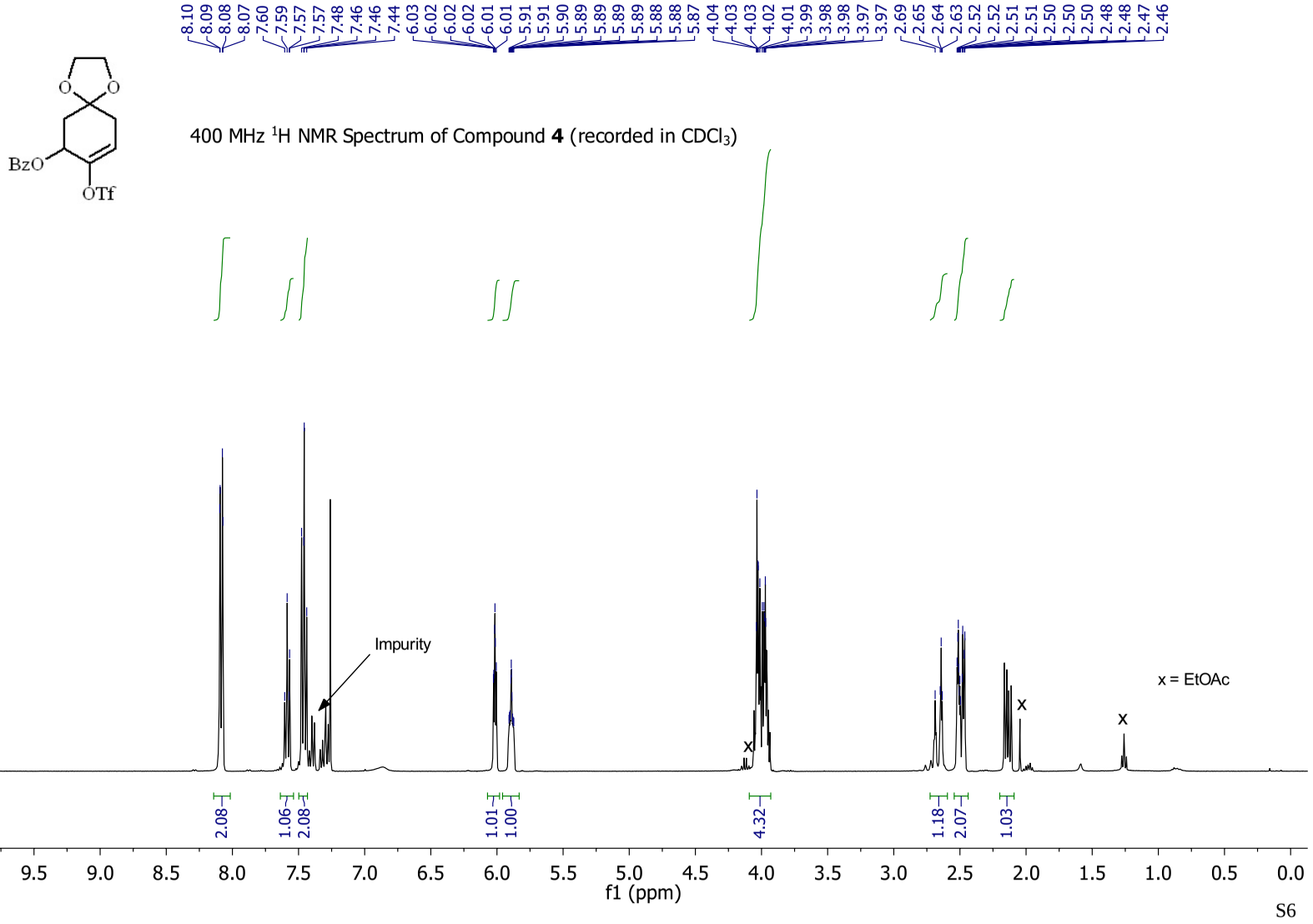
^{13}C NMR data for (±)-galanthamine (δ_C)[a]	^{13}C NMR data reported in the literature (δ_C)[b]	$\Delta\delta_C$
146.0	145.9	+0.1
144.3	144.3	+0.0
133.2	133.1	+0.1
129.2	129.3	–0.1
127.8	127.7	+0.1
126.9	126.9	+0.0
122.3	122.2	+0.1
111.4	111.2	+0.2
88.9	88.8	+0.1
62.2	62.2	+0.0
60.7	60.7	+0.0
56.1	56.0	+0.1
54.0	53.9	+0.1
48.4	48.3	+0.1
42.2	42.2	+0.0
33.9	33.9	+0.0
30.1	30.0	+0.1

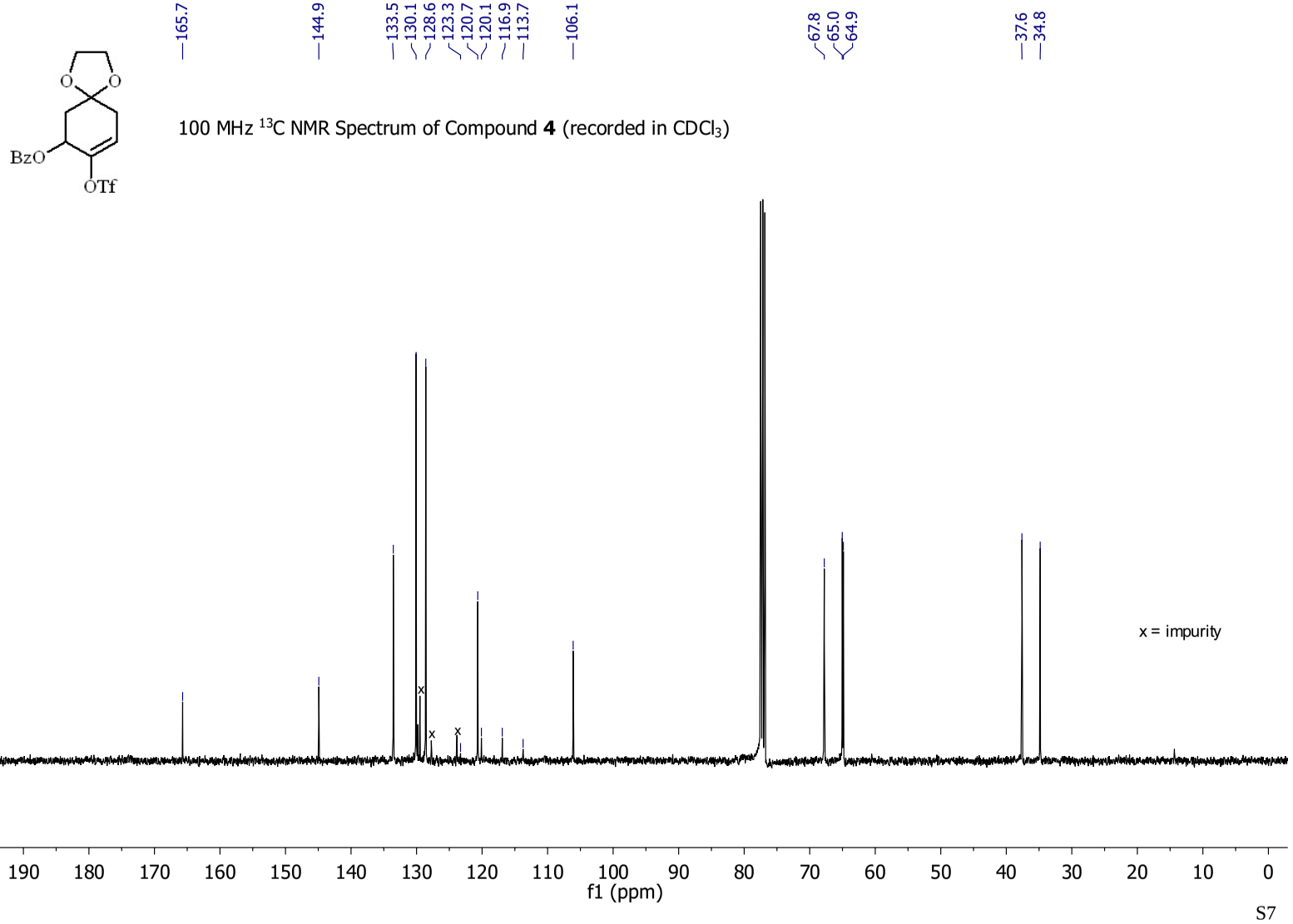
[a] Data recorded in $CDCl_3$ at 100 MHz.
[b] Data obtained from reference 2 and recorded in $CDCl_3$ at 75 MHz.

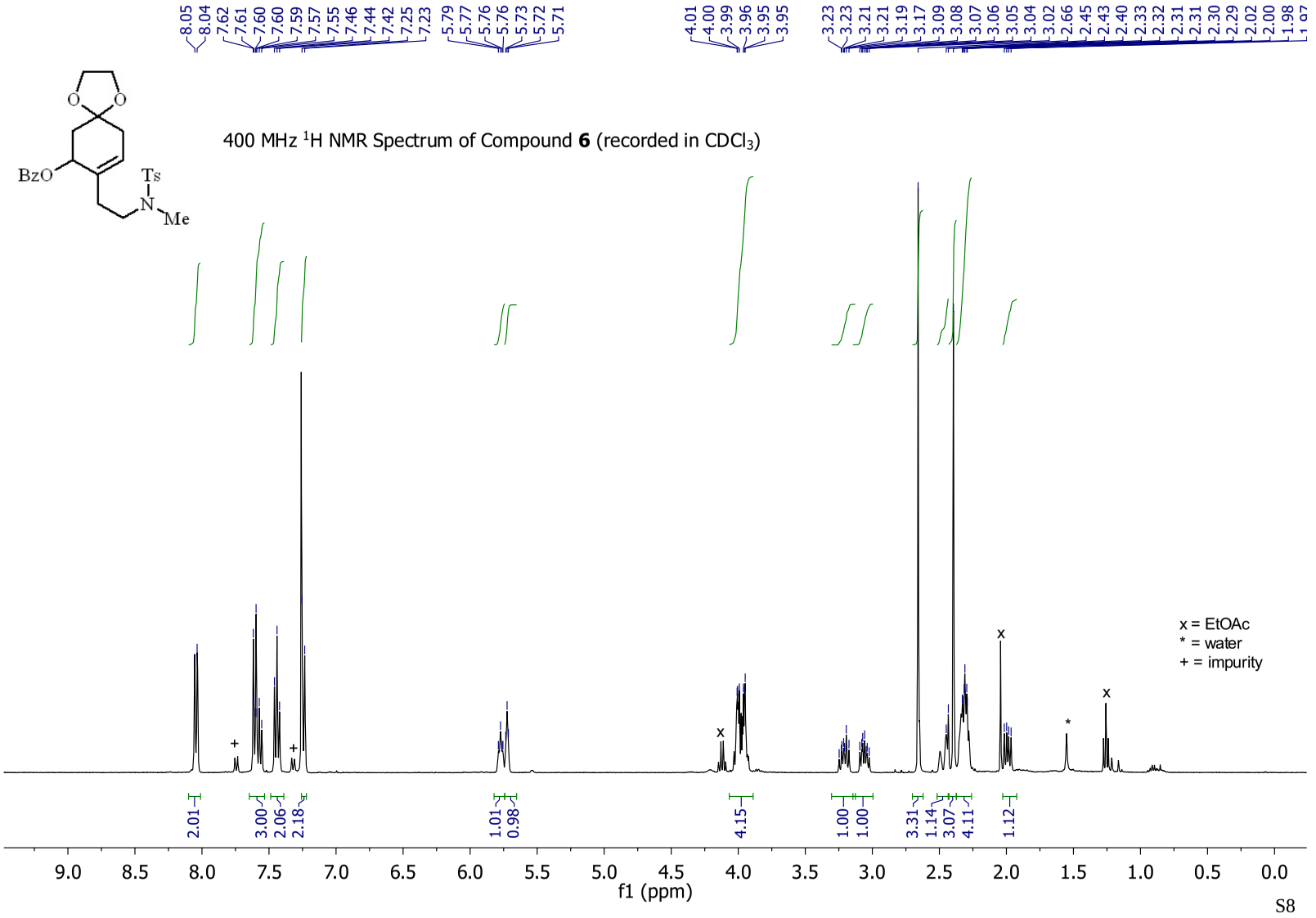
References

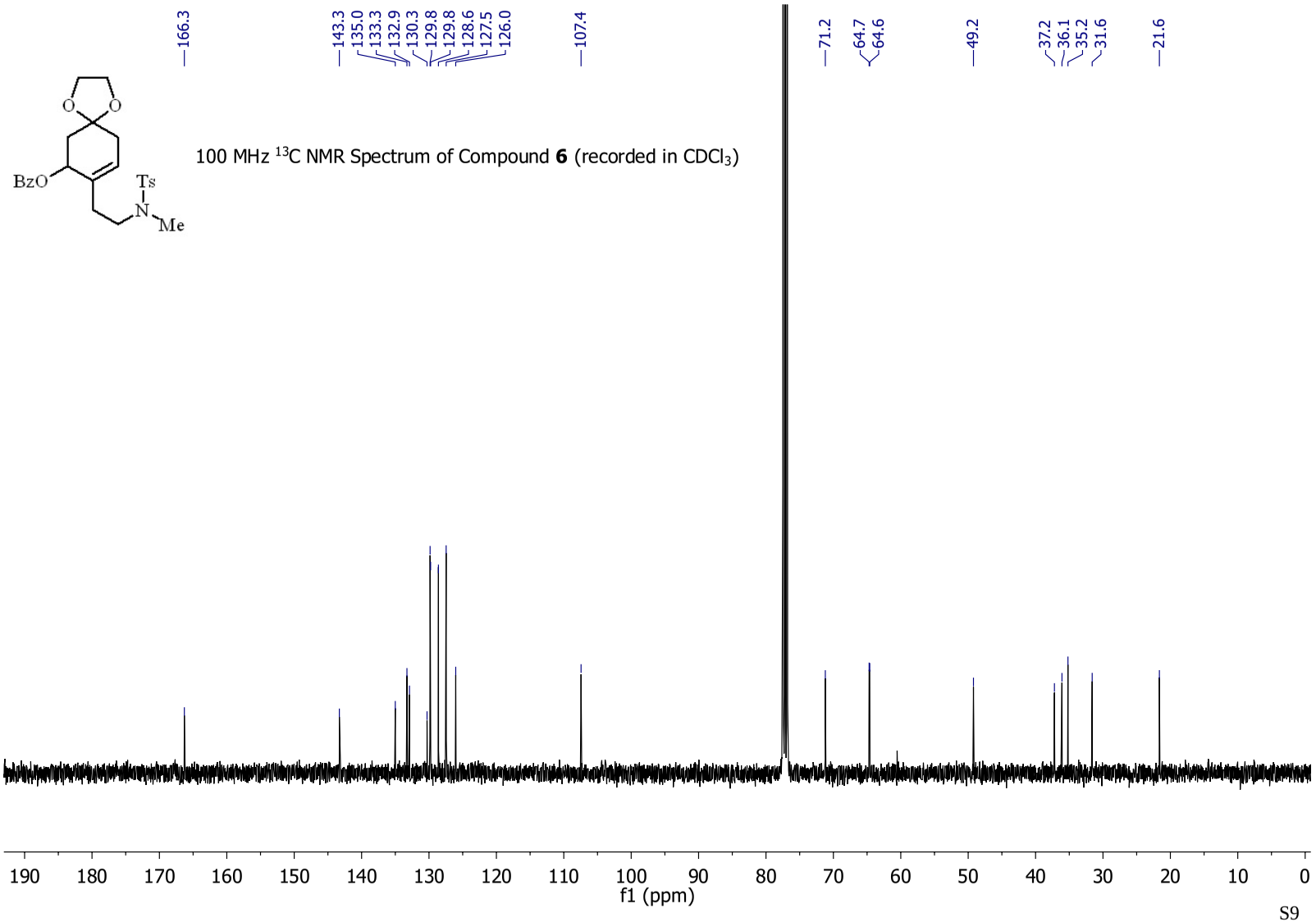
1. Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc*. **2009**, *131*, 16045.

2. Banwell, M. G.; Ma, X.; Karunaratne, O.; Willis, A. C. *Aust. J. Chem*. **2010**, *63*, 1437.


8.10 8.09 8.08 8.07 7.60 7.59 7.57 7.57 7.48 7.46 7.46 7.44 6.03 6.02 6.02 6.02 6.01 6.01 5.91 5.91 5.90 5.89 5.89 5.89 5.89 5.88 5.88 5.87 4.04 4.03 4.03 4.02 4.01 3.99 3.98 3.98 3.97 3.97 2.69 2.65 2.64 2.63 2.52 2.52 2.51 2.51 2.50 2.50 2.50 2.48 2.48 2.47 2.46
BzO
OTf
400 MHz ^{1}H NMR Spectrum of Compound **4** (recorded in $CDCl_3$)
Impurity
x = EtOAc
x
x
x
2.08
1.06
2.08
1.01
1.00
4.32
1.18
2.07
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

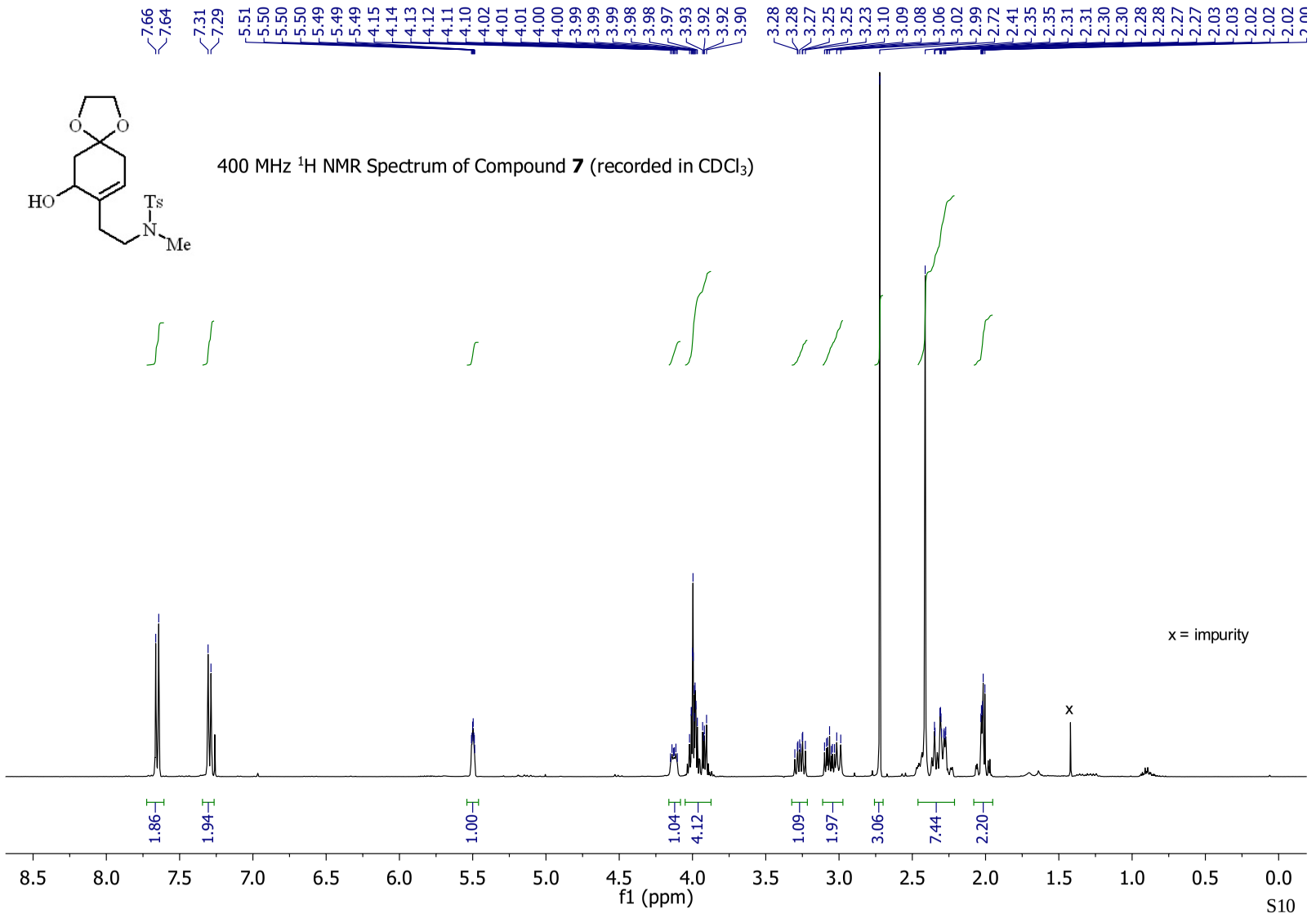

165.7
144.9
133.5
130.1
128.6
123.3
120.7
120.1
116.9
113.7
106.1
67.8
65.0
64.9
37.6
34.8
BzO
OTf
O
O
100 MHz ^{13}C NMR Spectrum of Compound **4** (recorded in $CDCl_3$)
x = impurity
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

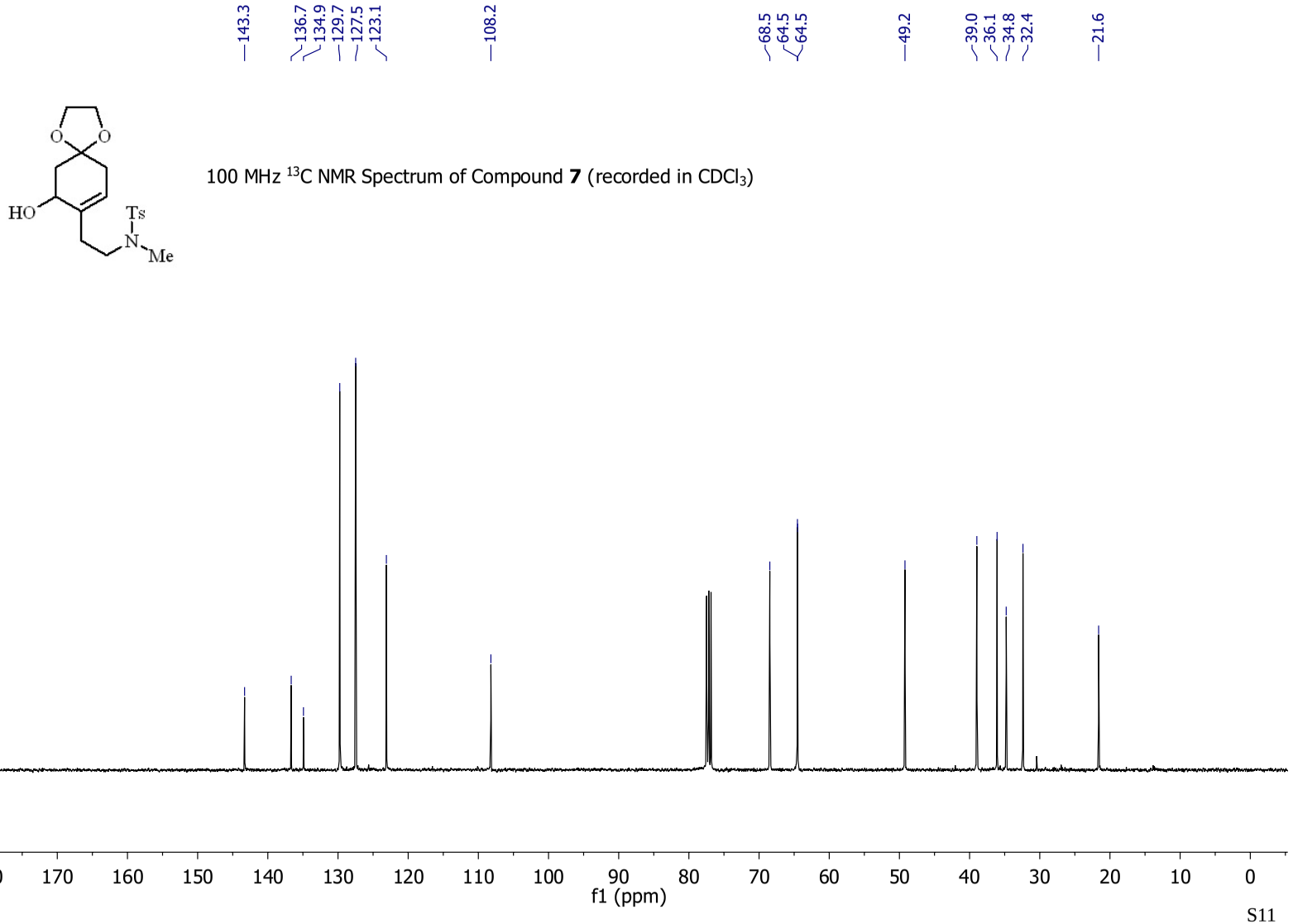

8.05
8.04
7.62
7.61
7.60
7.60
7.59
7.57
7.55
7.46
7.44
7.42
7.25
7.23
5.79
5.77
5.76
5.76
5.73
5.72
5.71
4.01
4.00
3.99
3.96
3.95
3.95
3.23
3.23
3.21
3.21
3.19
3.17
3.09
3.08
3.07
3.06
3.05
3.04
3.02
2.66
2.45
2.43
2.40
2.33
2.32
2.31
2.31
2.30
2.29
2.02
2.00
1.98
BzO
Ts
N
Me
400 MHz ^{1}H NMR Spectrum of Compound **6** (recorded in $CDCl_3$)
x = EtOAc
* = water
+ = impurity
2.01
3.00
2.06
2.18
1.01
0.98
4.15
1.00
1.00
3.31
1.14
3.07
4.11
1.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



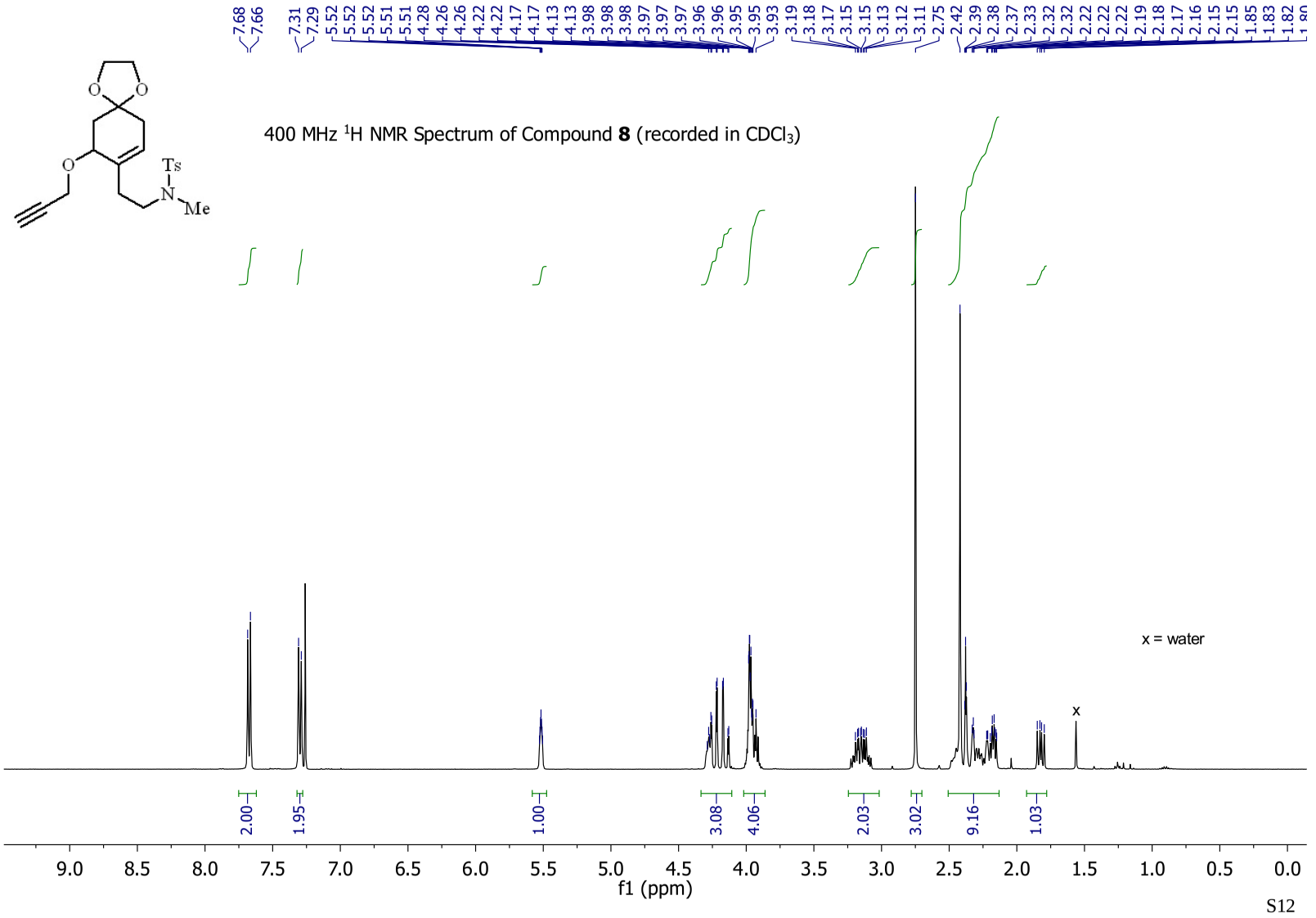
100 MHz ^{13}C NMR Spectrum of Compound **6** (recorded in $CDCl_3$)

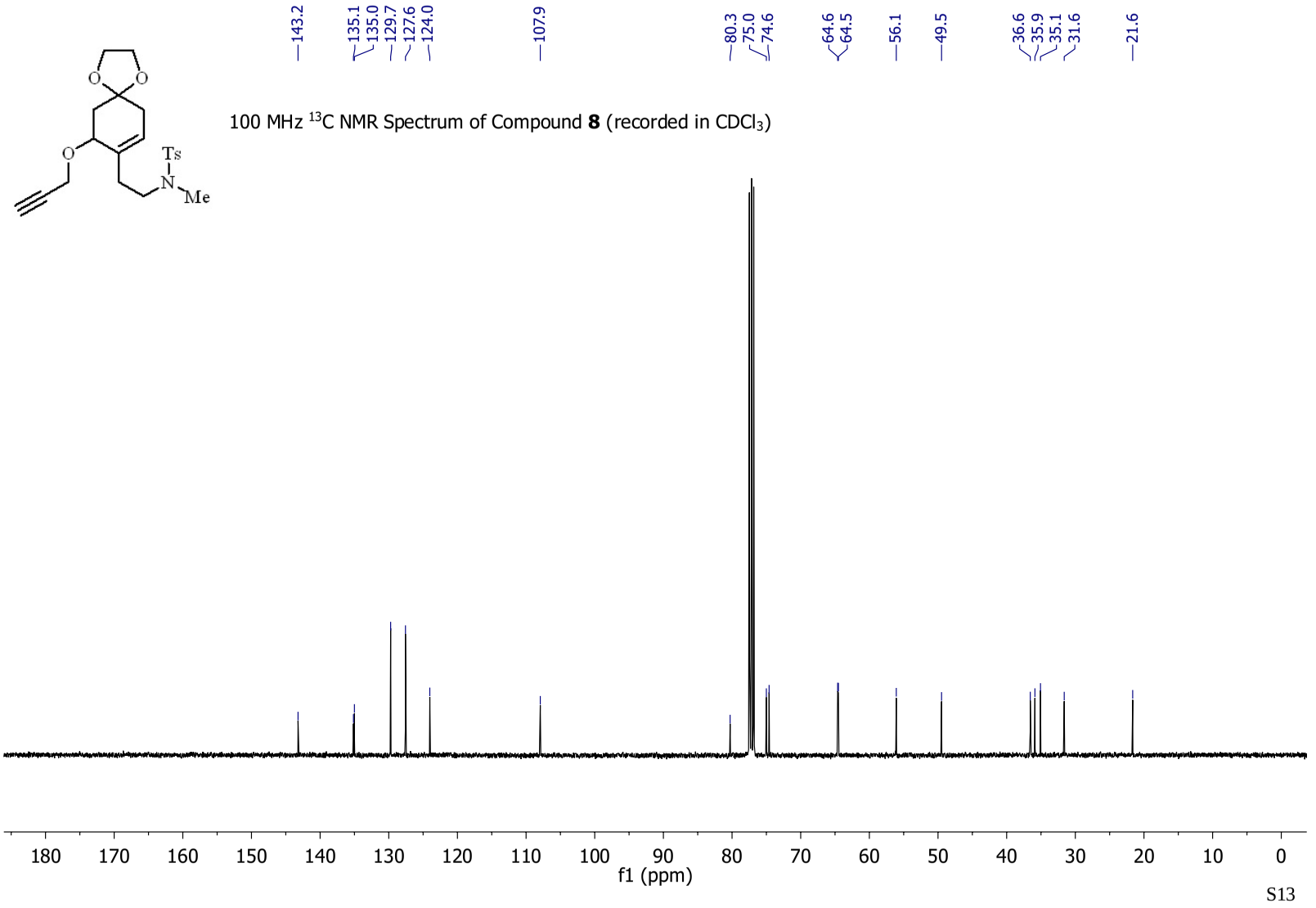
77


400 MHz ^{1}H NMR Spectrum of Compound **7** (recorded in $CDCl_3$)
HO
O
O
Ts
N
Me
x = impurity
x
1.86
1.94
1.00
1.04
4.12
1.09
1.97
3.06
7.44
2.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

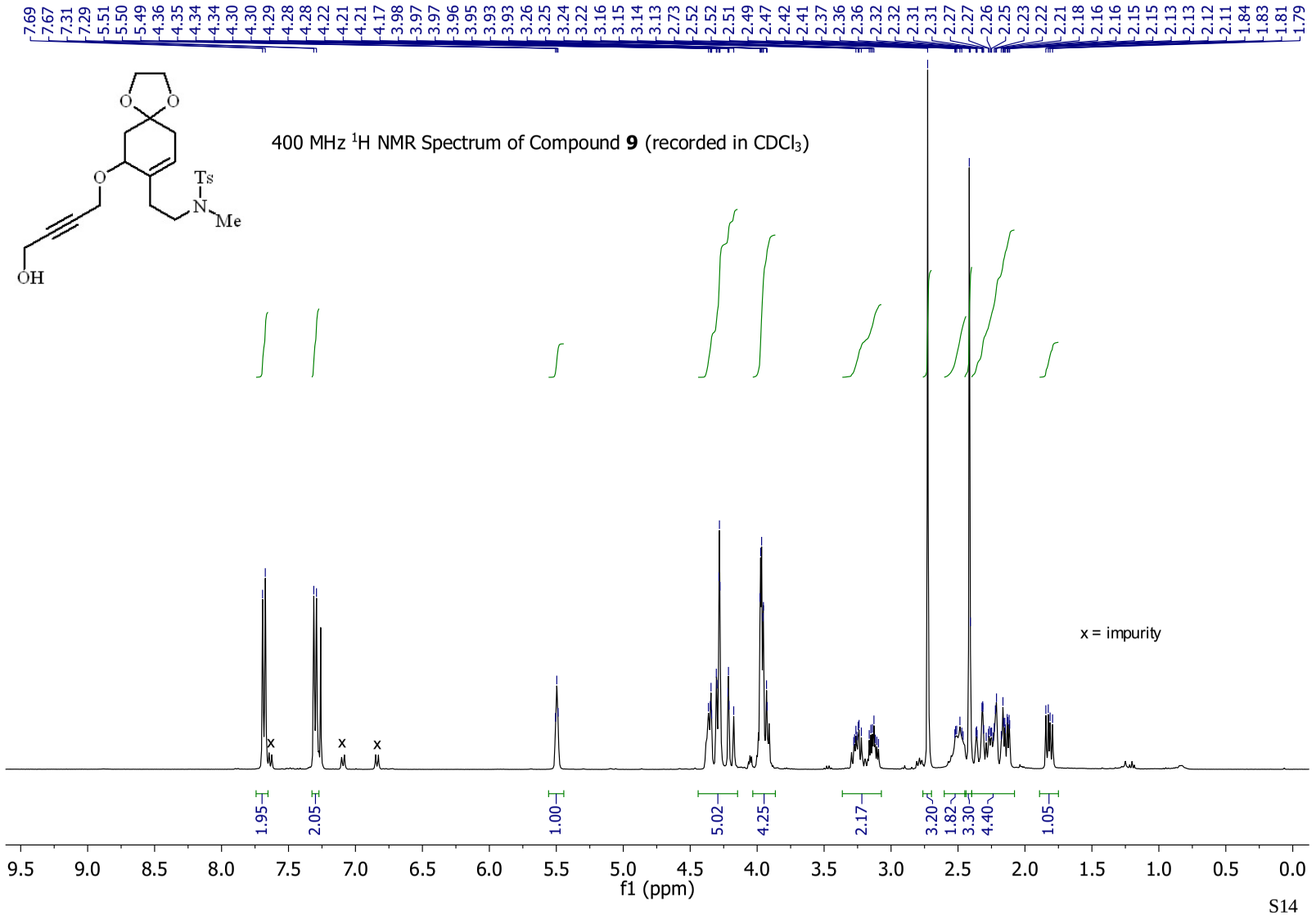


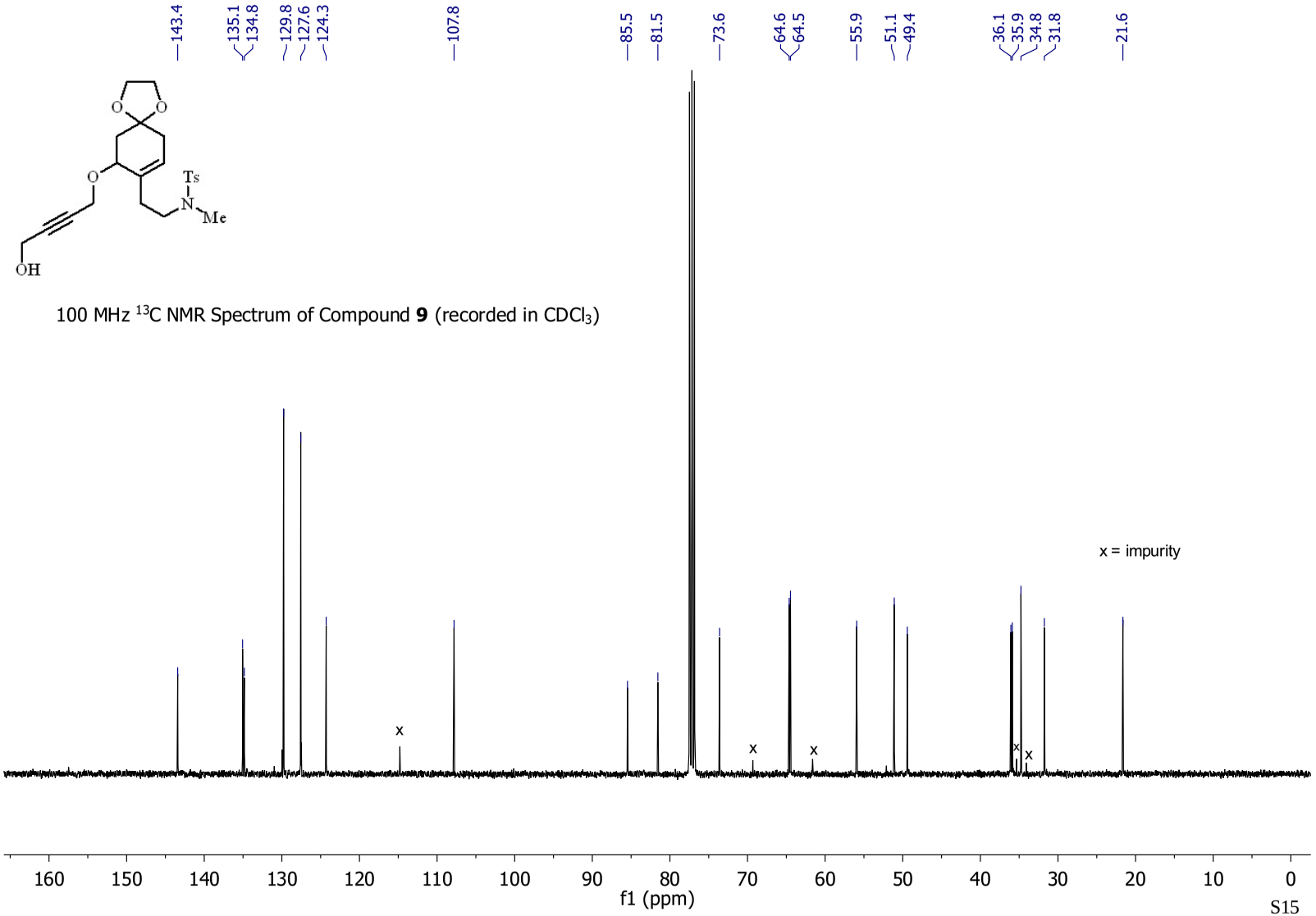
100 MHz ^{13}C NMR Spectrum of Compound **7** (recorded in $CDCl_3$)


7.68
7.66
7.31
7.29
5.52
5.52
5.51
5.51
4.28
4.26
4.26
4.22
4.22
4.17
4.17
4.13
4.13
3.98
3.98
3.98
3.97
3.97
3.97
3.96
3.96
3.95
3.95
3.93
3.19
3.18
3.17
3.15
3.15
3.13
3.12
3.11
2.75
2.42
2.39
2.38
2.37
2.33
2.32
2.32
2.22
2.22
2.22
2.19
2.18
2.17
2.16
2.15
2.15
1.85
1.83
1.82
O
O
O
Ts
N
Me
400 MHz ¹H NMR Spectrum of Compound 8 (recorded in CDCl3)
x = water
x
2.00
1.95
1.00
3.08
4.06
2.03
3.02
9.16
1.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

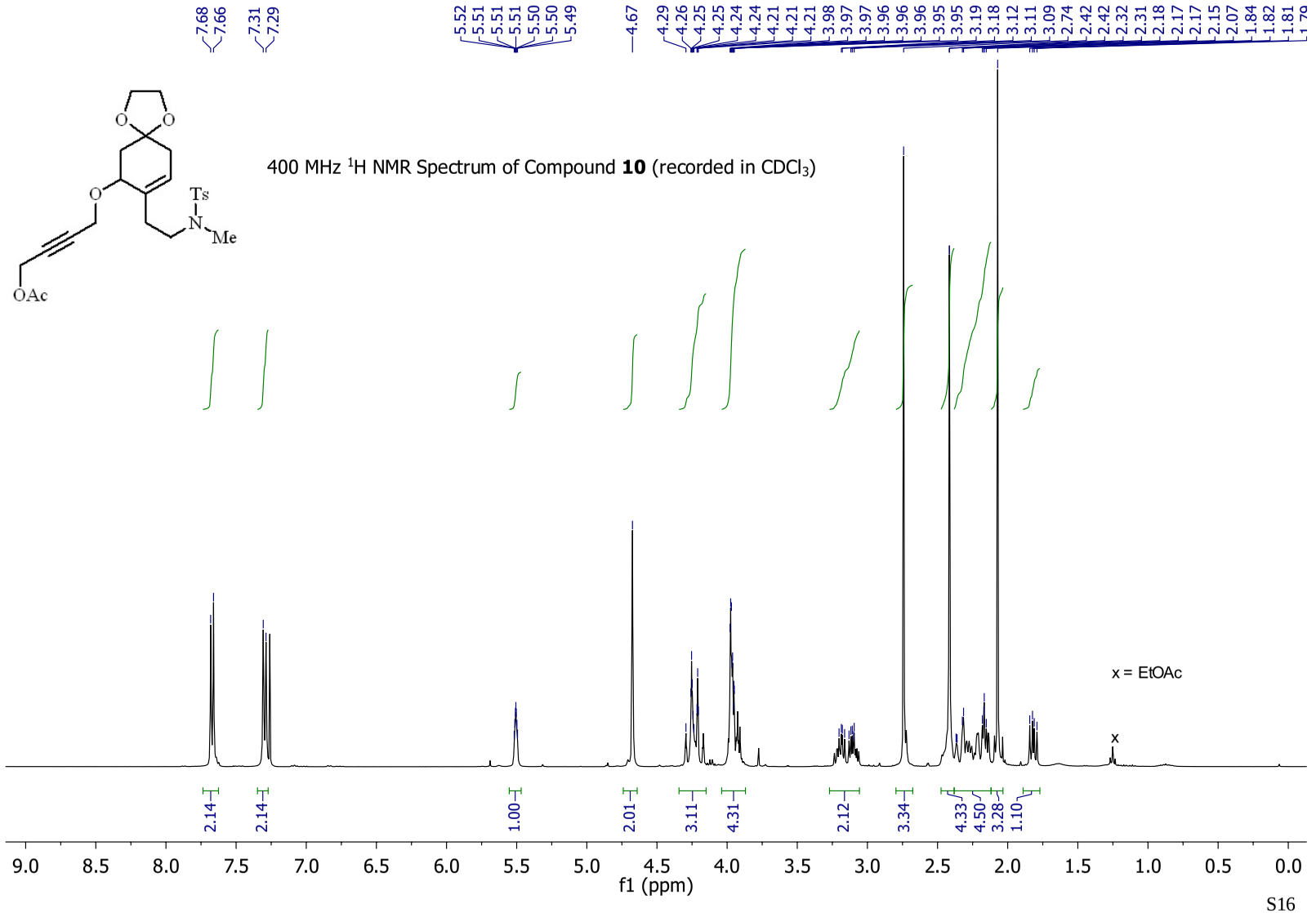


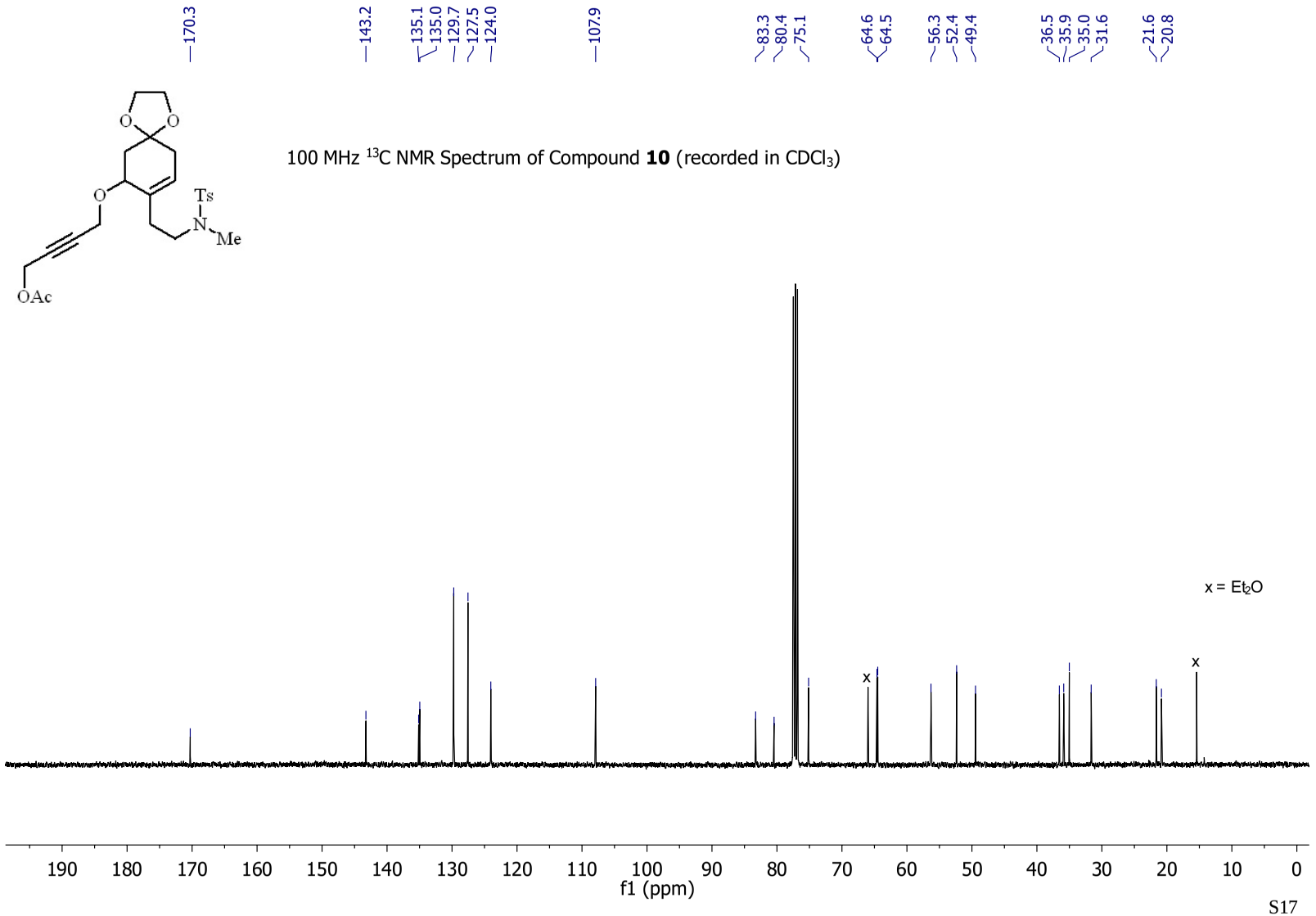
100 MHz ^{13}C NMR Spectrum of Compound **8** (recorded in $CDCl_3$)


400 MHz ^{1}H NMR Spectrum of Compound **9** (recorded in $CDCl_3$)
Ts
N
Me
O
OH
x = impurity
1.95
2.05
1.00
5.02
4.25
2.17
3.20
1.82
3.30
4.40
1.05
f1 (ppm)

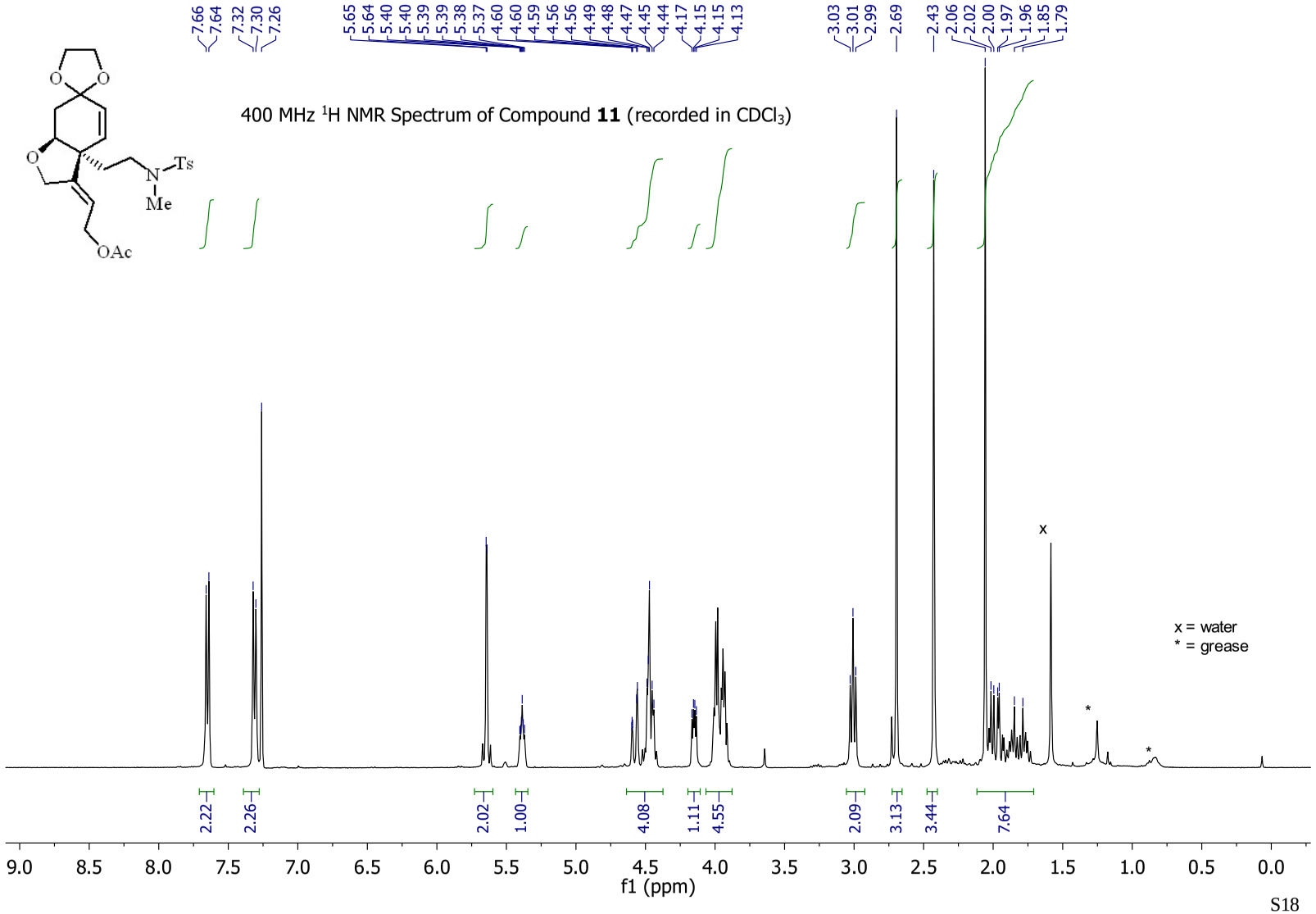


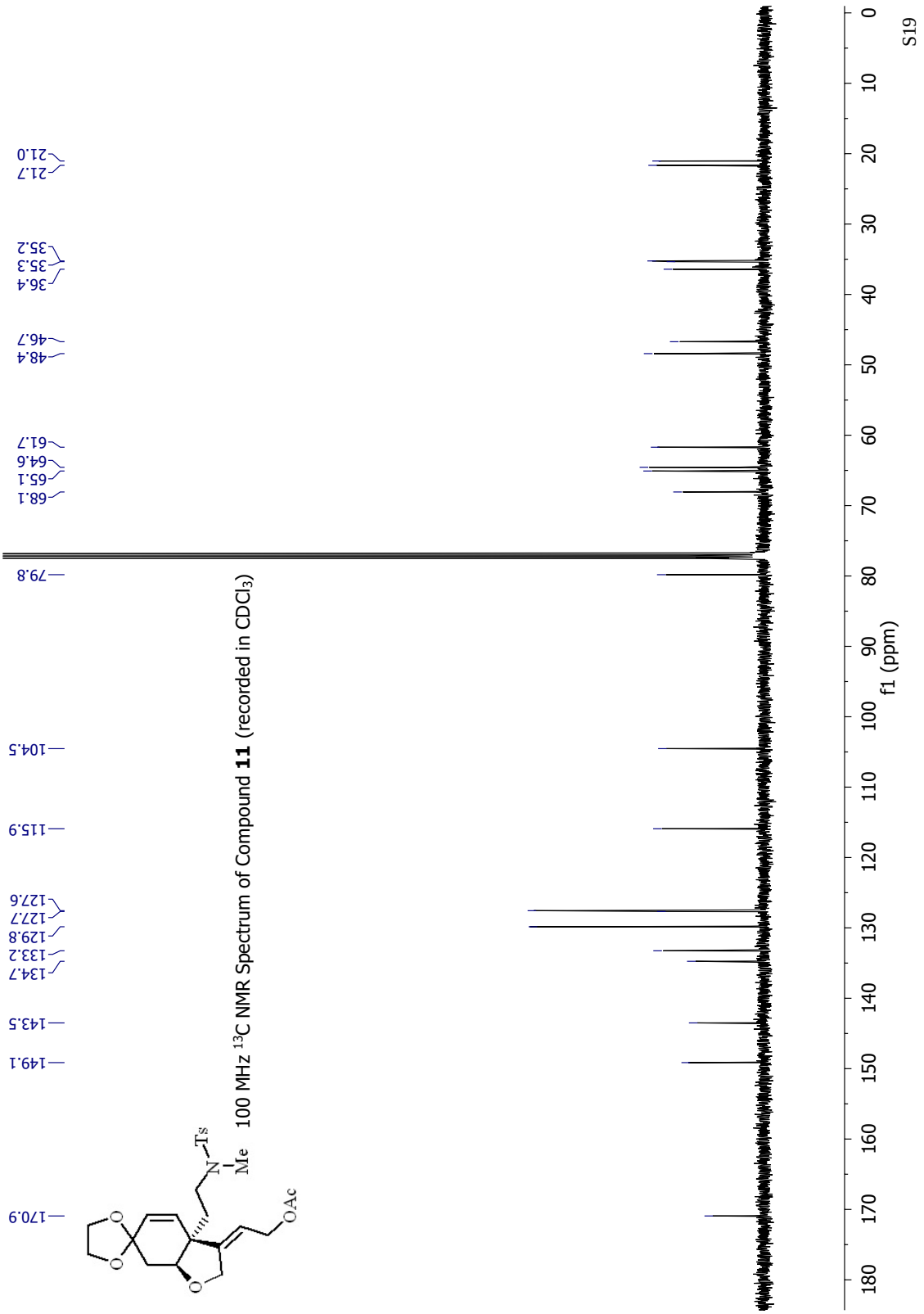
100 MHz ^{13}C NMR Spectrum of Compound **9** (recorded in $CDCl_3$)

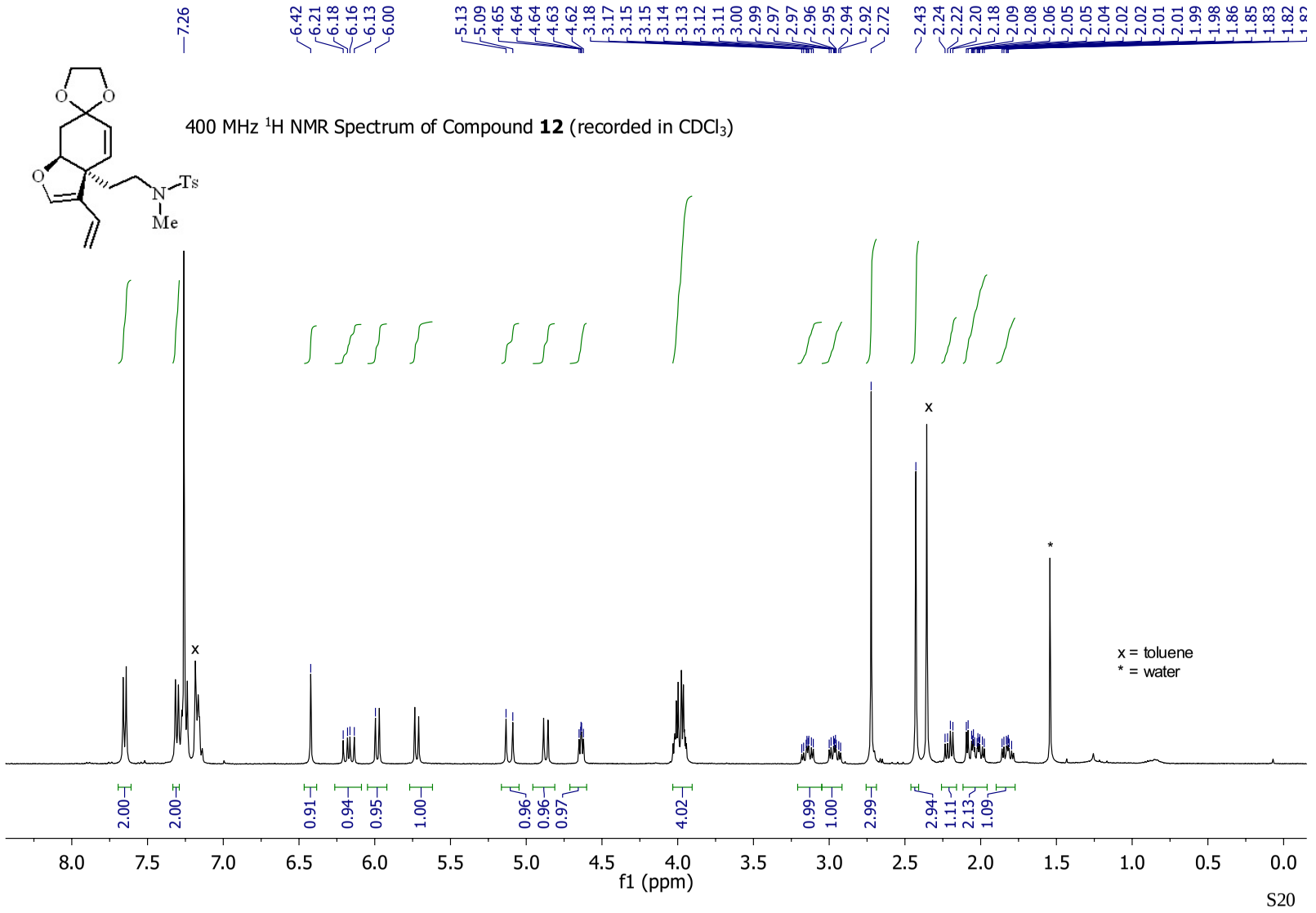

400 MHz ^{1}H NMR Spectrum of Compound **10** (recorded in $CDCl_3$)
Ts
N
Me
O
OAc
x = EtOAc
x
f1 (ppm)

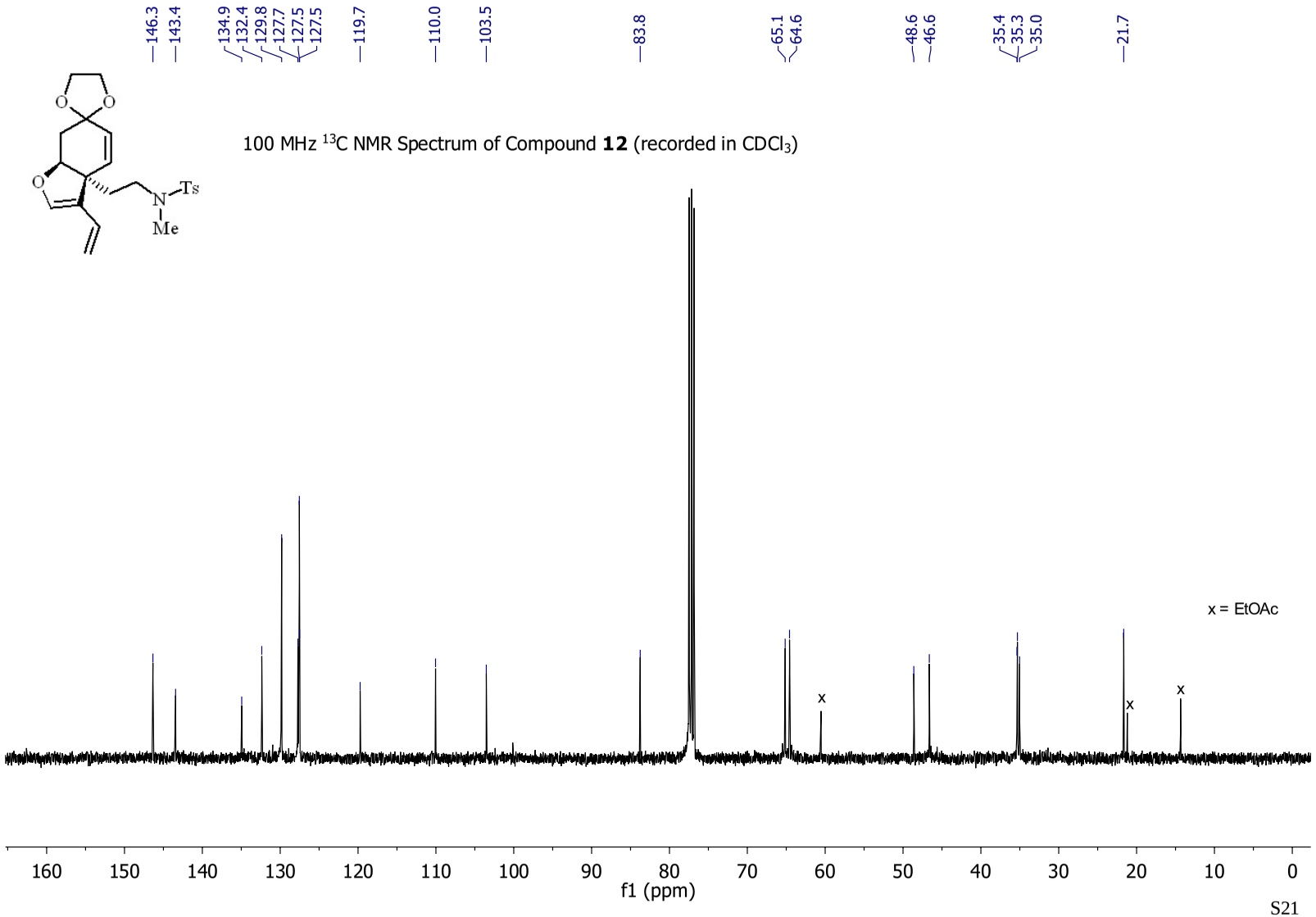


100 MHz ^{13}C NMR Spectrum of Compound **10** (recorded in $CDCl_3$)

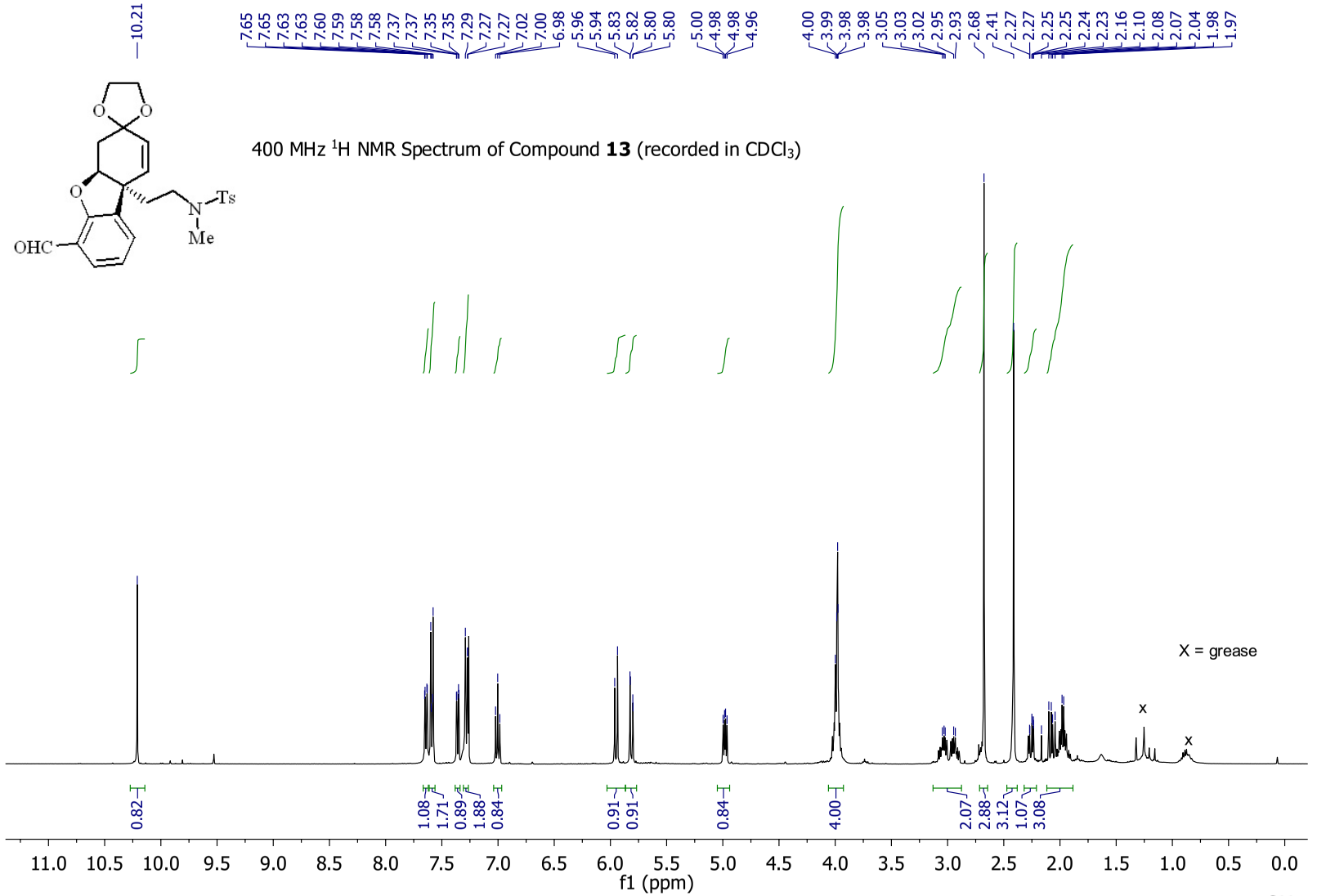

400 MHz ^{1}H NMR Spectrum of Compound **11** (recorded in $CDCl_3$)
7.66
7.64
7.32
7.30
7.26
5.65
5.64
5.40
5.40
5.39
5.39
5.38
5.37
4.60
4.60
4.59
4.56
4.56
4.49
4.48
4.47
4.45
4.44
4.17
4.15
4.15
4.13
3.03
3.01
2.99
2.69
2.43
2.06
2.02
2.00
1.97
1.96
1.85
1.79
Ts
N
Me
OAc
x
x = water
* = grease
2.22
2.26
2.02
1.00
4.08
1.11
4.55
2.09
3.13
3.44
7.64
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

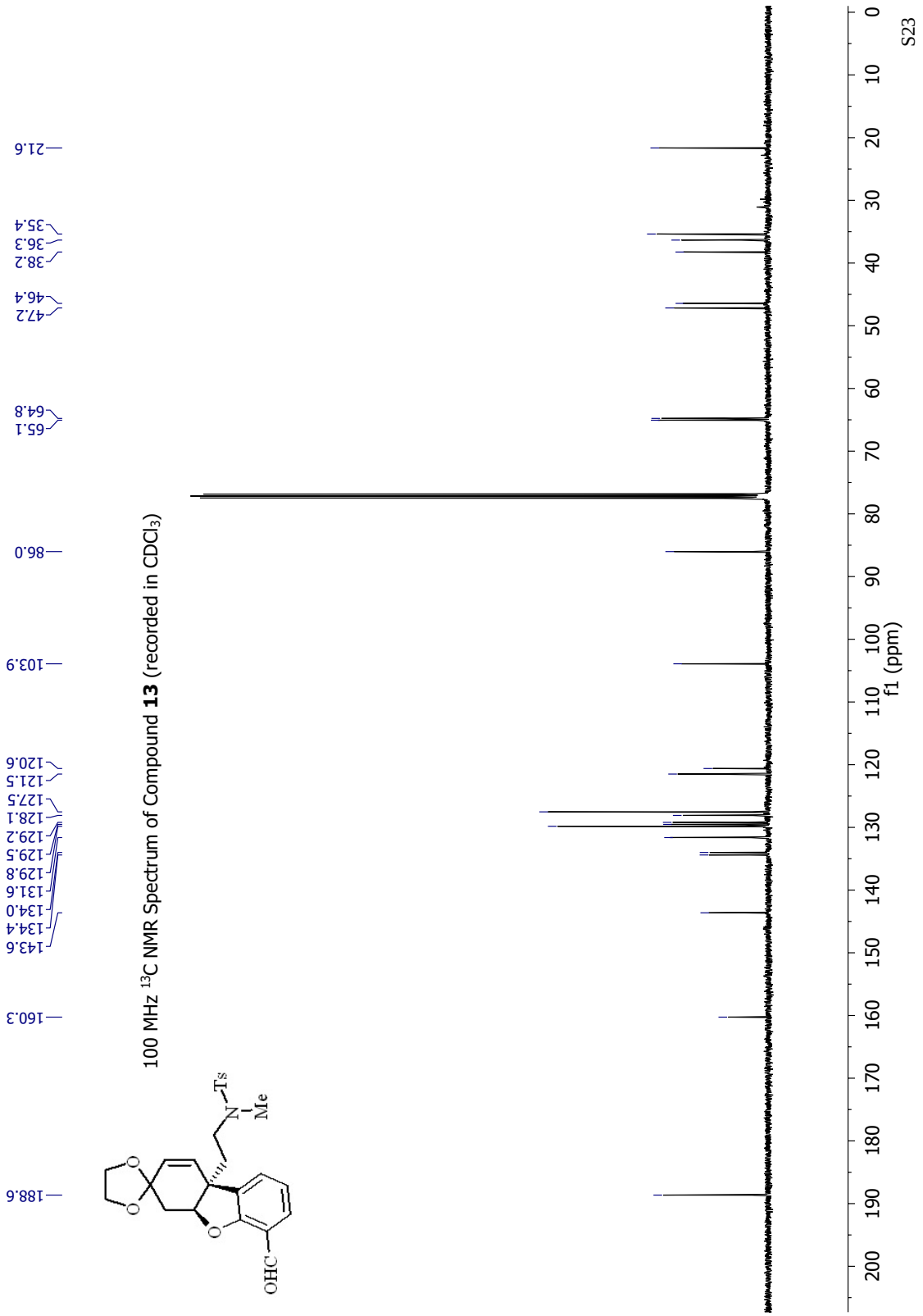

100 MHz ^{13}C NMR Spectrum of Compound **11** (recorded in CDCl$_3$)
170.9
149.1
143.5
134.7
133.2
129.8
127.7
127.6
115.9
104.5
79.8
68.1
65.1
64.6
61.7
48.4
46.7
36.4
35.3
35.2
21.7
21.0
Ts
N
Me
OAc
f1 (ppm)

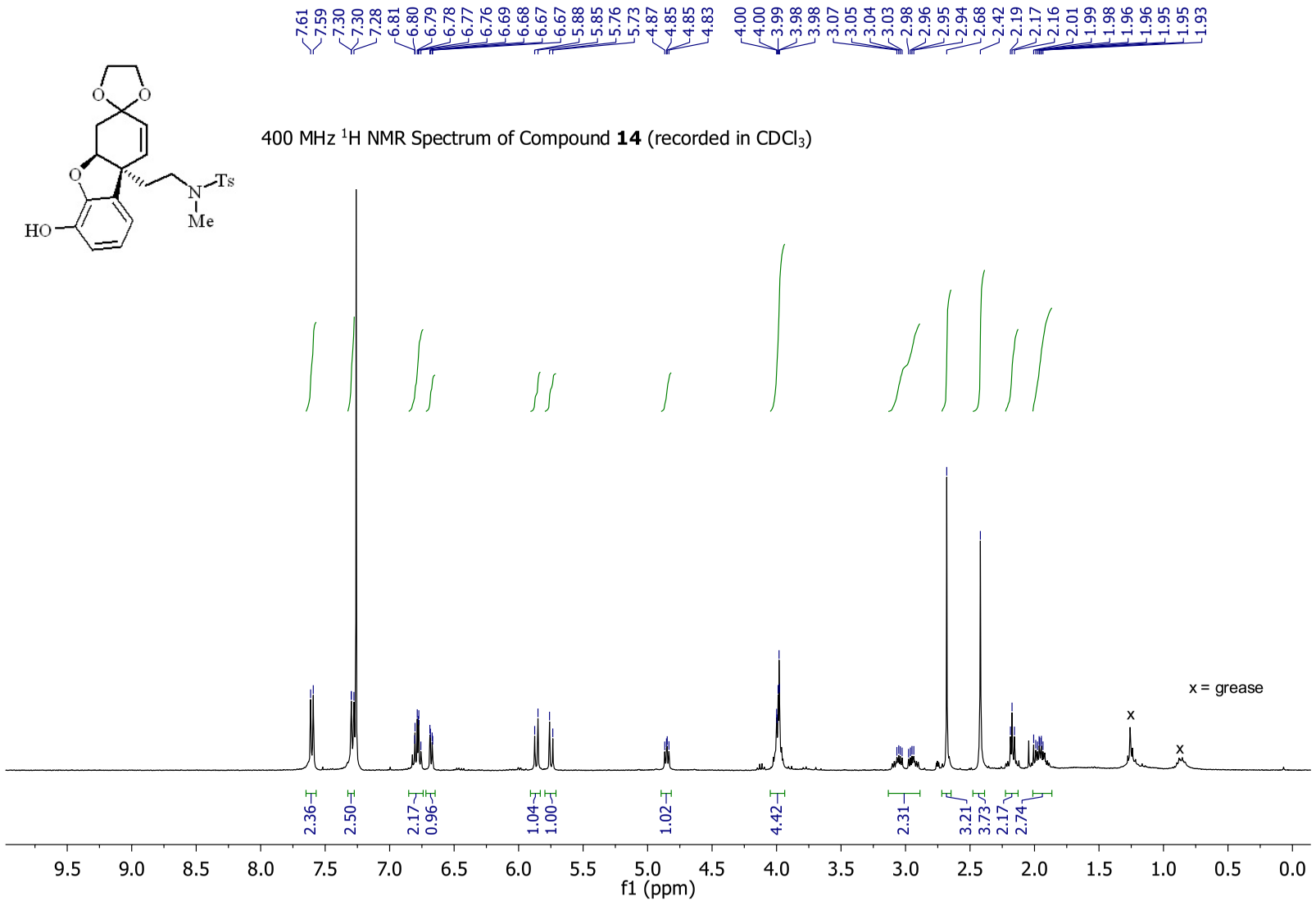

7.26
6.42
6.21
6.18
6.16
6.13
6.00
5.13
5.09
4.65
4.64
4.64
4.63
4.62
3.18
3.17
3.15
3.15
3.14
3.13
3.12
3.11
3.00
2.99
2.97
2.97
2.96
2.95
2.94
2.92
2.72
2.43
2.24
2.22
2.20
2.18
2.09
2.08
2.06
2.05
2.05
2.04
2.02
2.02
2.01
2.01
1.99
1.98
1.86
1.85
1.83
1.82
400 MHz ¹H NMR Spectrum of Compound 12 (recorded in CDCl3)
O
O
O
N
Ts
Me
x
x
*
x = toluene
* = water
2.00
2.00
0.91
0.94
0.95
1.00
0.96
0.96
0.97
4.02
0.99
1.00
2.99
2.94
1.11
2.13
1.09
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

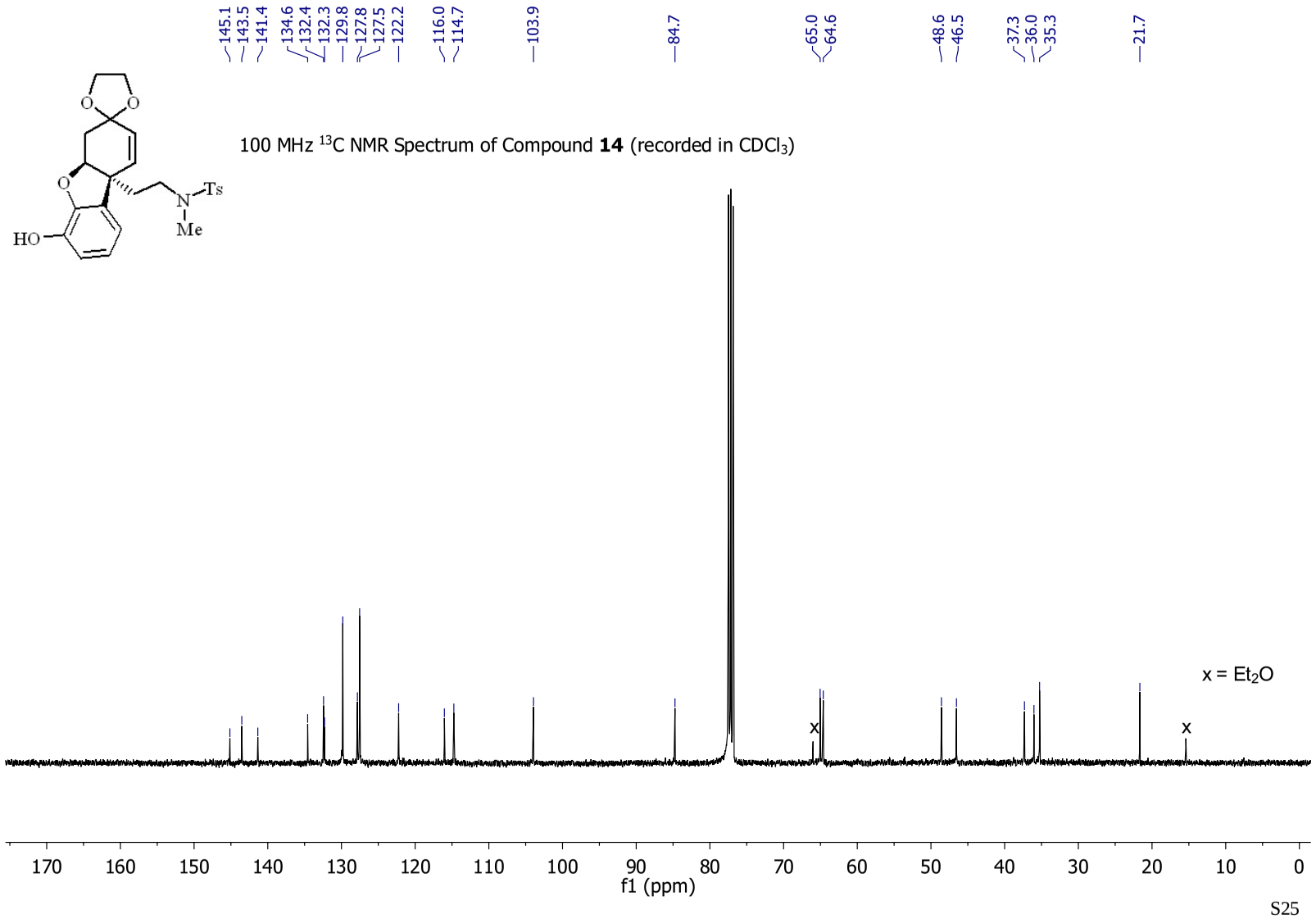


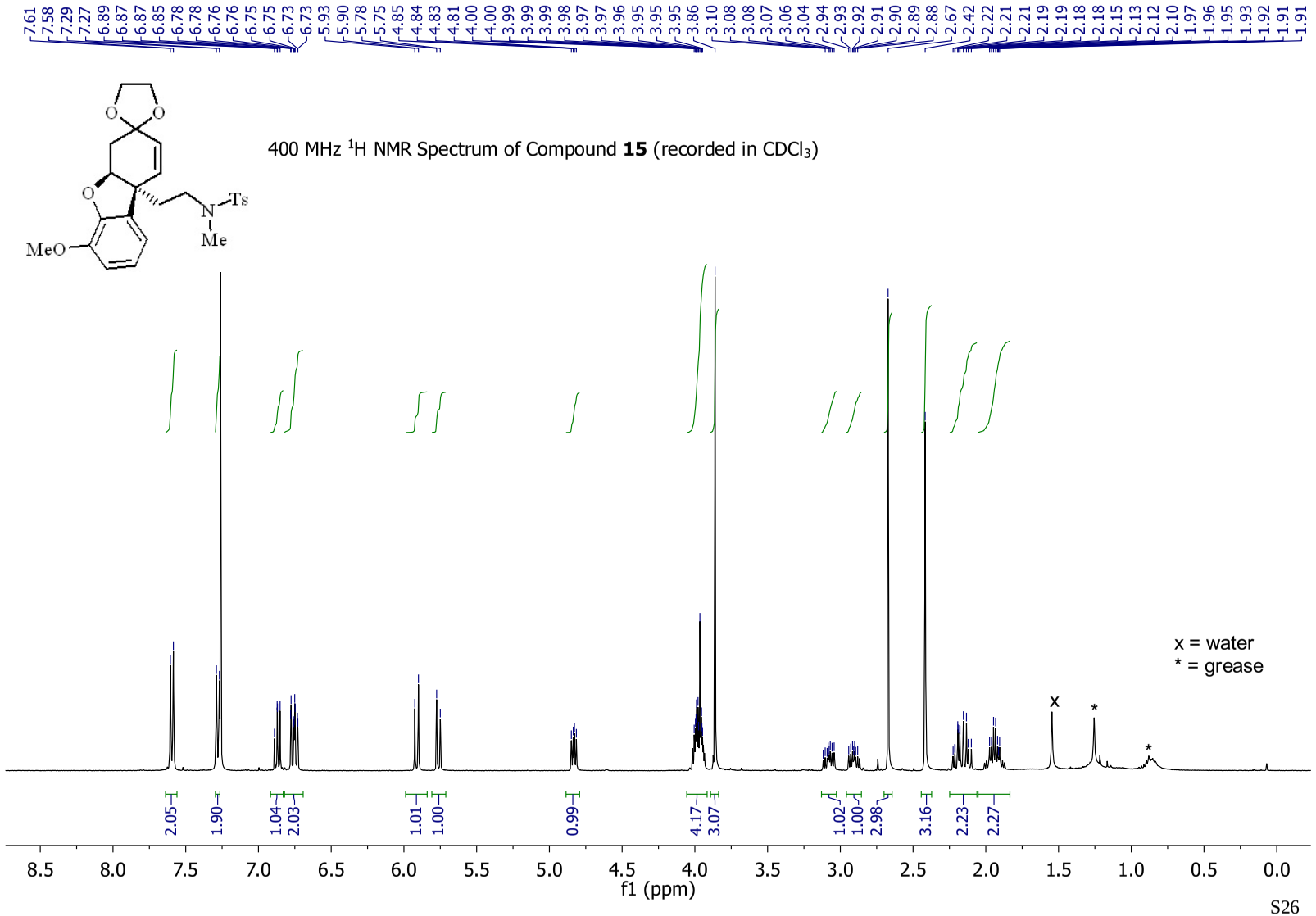
100 MHz ^{13}C NMR Spectrum of Compound **12** (recorded in $CDCl_3$)

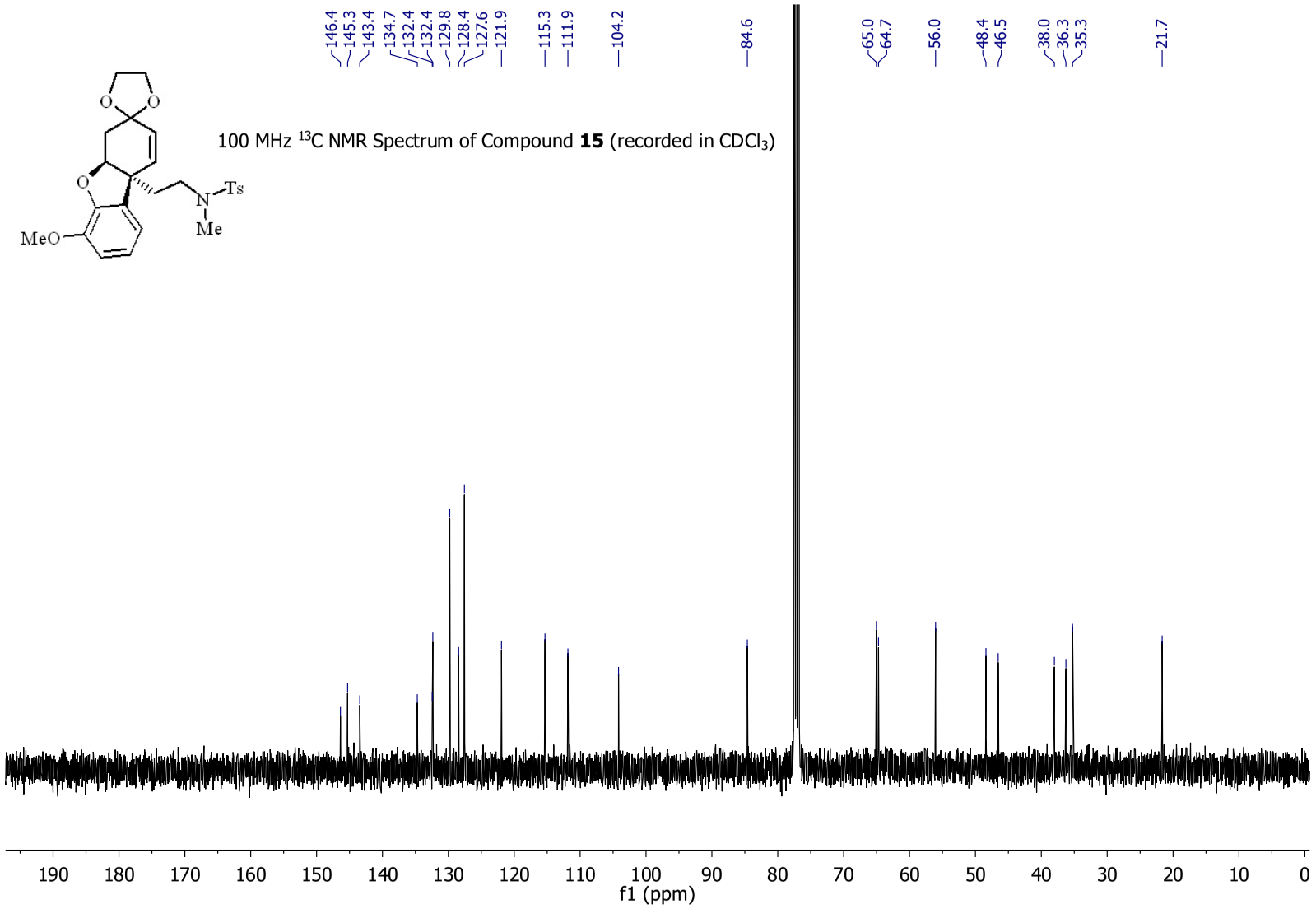

400 MHz ^{1}H NMR Spectrum of Compound **13** (recorded in $CDCl_3$)
OHC
N
Ts
Me
X = grease
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound **13** (recorded in CDCl$_3$)
188.6
160.3
143.6
134.4
134.0
131.6
129.8
129.5
129.2
128.1
127.5
121.5
120.6
103.9
86.0
65.1
64.8
47.2
46.4
38.2
36.3
35.4
21.6
Ts
N
Me
OHC
O
O
O
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

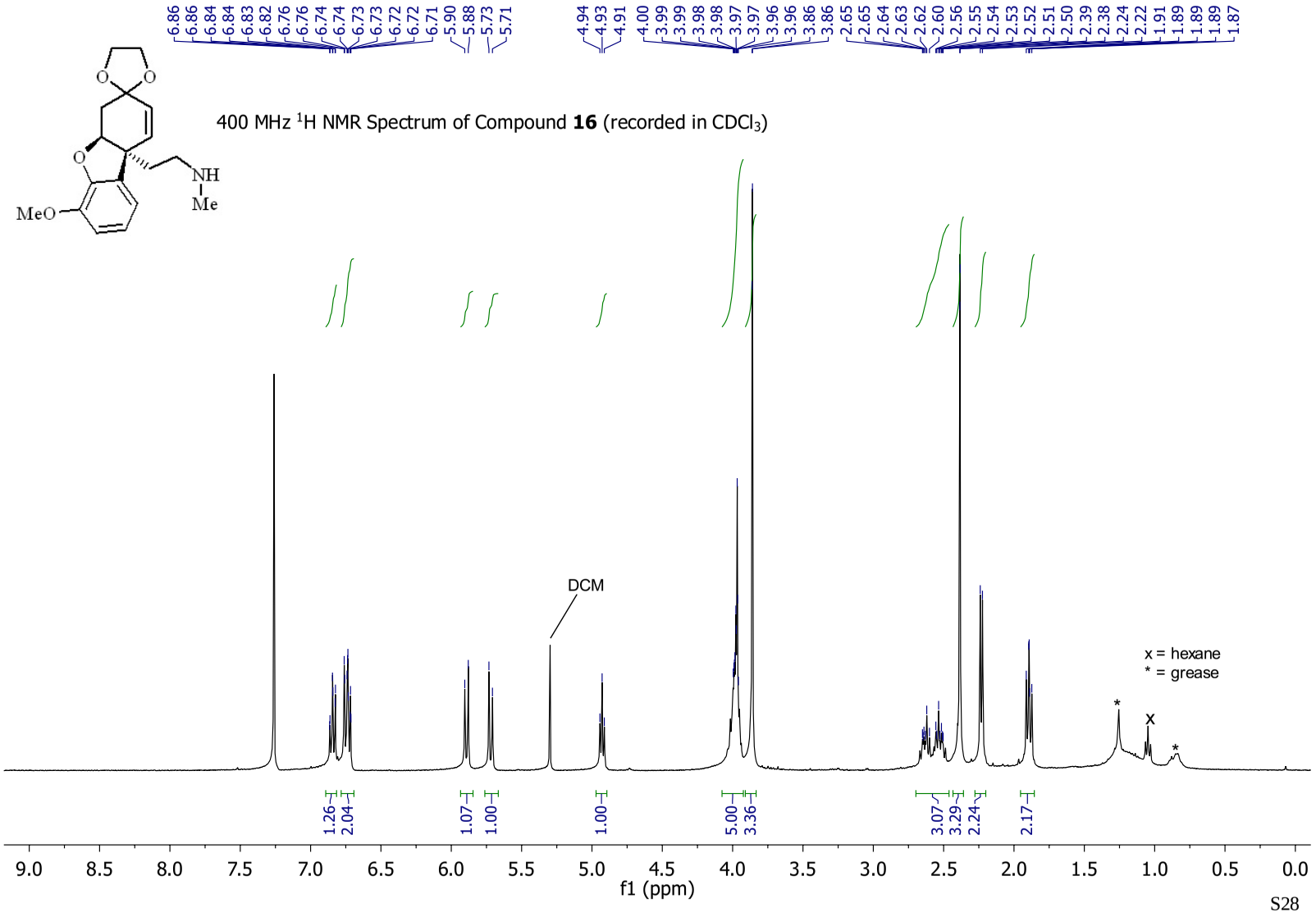

7.61 7.59 7.30 7.30 7.28 6.81 6.80 6.79 6.78 6.77 6.76 6.69 6.68 6.67 6.67 5.88 5.85 5.76 5.73 4.87 4.85 4.85 4.83 4.00 4.00 3.99 3.98 3.98 3.07 3.05 3.04 3.03 2.98 2.96 2.95 2.94 2.68 2.42 2.19 2.17 2.16 2.01 1.99 1.98 1.96 1.96 1.95 1.95 1.93
O
O
O
N
Ts
Me
HO
400 MHz ^{1}H NMR Spectrum of Compound **14** (recorded in $CDCl_3$)
x = grease
x
x
2.36 2.50 2.17 0.96 1.04 1.00 1.02 4.42 2.31 3.21 3.73 2.17 2.74
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

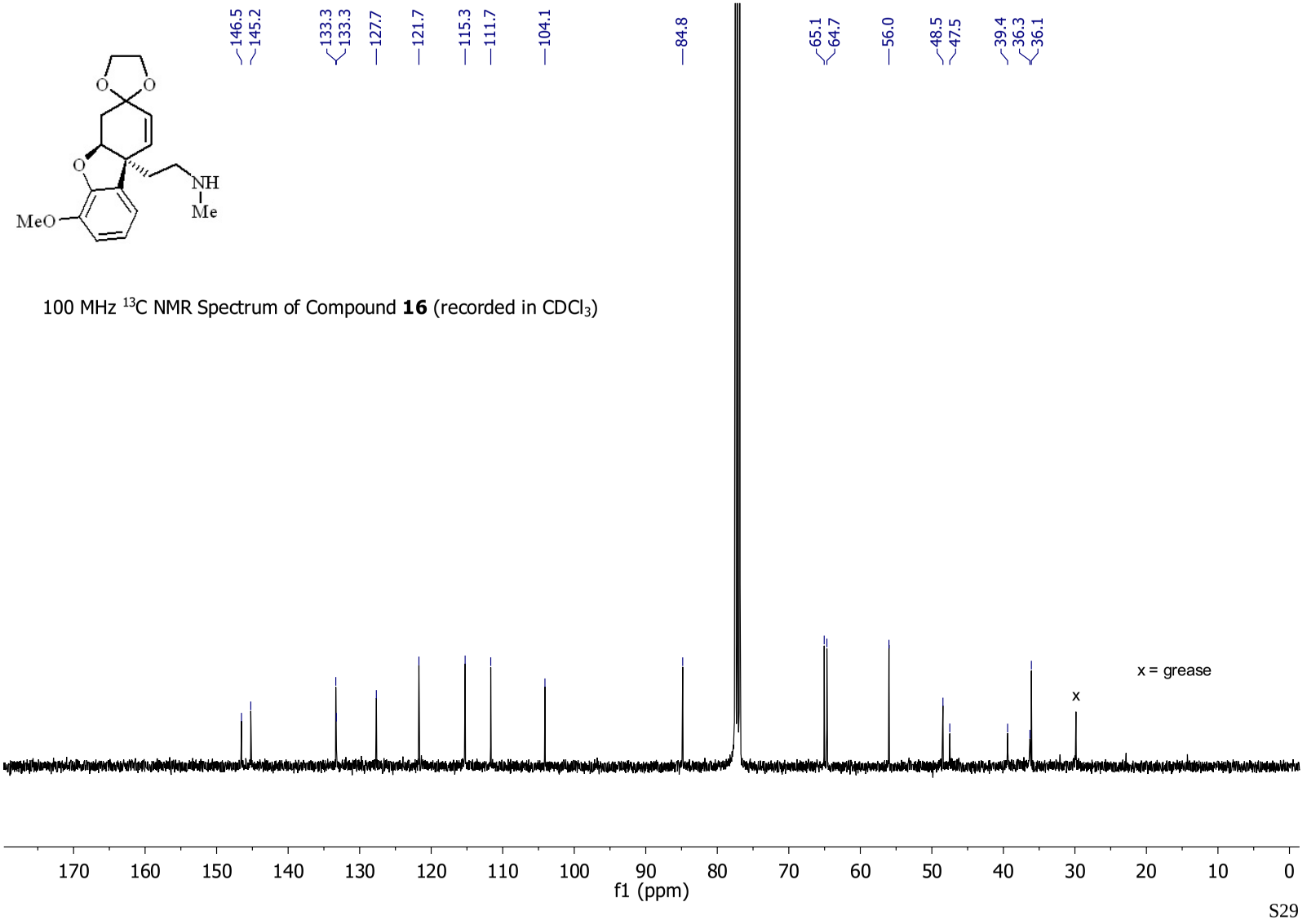

145.1
143.5
141.4
134.6
132.4
132.3
129.8
127.8
127.5
122.2
116.0
114.7
103.9
84.7
65.0
64.6
48.6
46.5
37.3
36.0
35.3
21.7
100 MHz ^{13}C NMR Spectrum of Compound **14** (recorded in $CDCl_3$)
O
O
O
HO
N
Ts
Me
x = Et_2O
x
x
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.61 7.58 7.29 7.27 6.89 6.87 6.87 6.85 6.78 6.78 6.76 6.76 6.75 6.75 6.73 6.73 5.93 5.90 5.78 5.75 5.85 4.84 4.83 4.81 4.00 4.00 3.99 3.99 3.99 3.98 3.97 3.97 3.96 3.95 3.95 3.95 3.86 3.10 3.08 3.08 3.07 3.06 3.04 2.94 2.93 2.92 2.91 2.90 2.89 2.88 2.67 2.42 2.22 2.21 2.21 2.19 2.19 2.18 2.18 2.15 2.13 2.12 2.10 1.97 1.96 1.95 1.93 1.92 1.91 1.91
O
O
O
N
Ts
Me
MeO
400 MHz ^{1}H NMR Spectrum of Compound **15** (recorded in $CDCl_3$)
x = water
* = grease
x
*
*
2.05 1.90 1.04 2.03 1.01 1.00 0.99 4.17 3.07 1.02 1.00 2.98 3.16 2.23 2.27
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

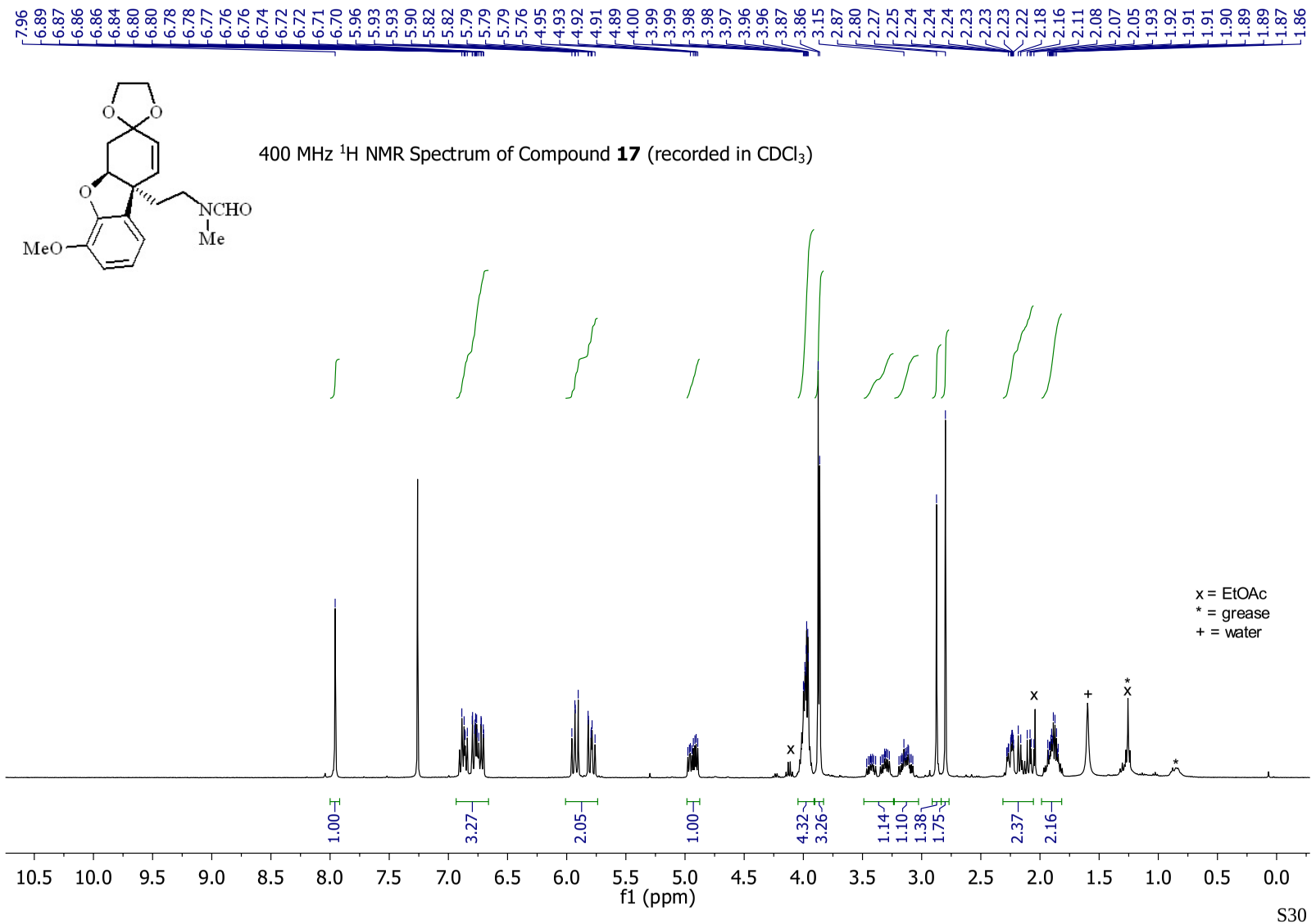


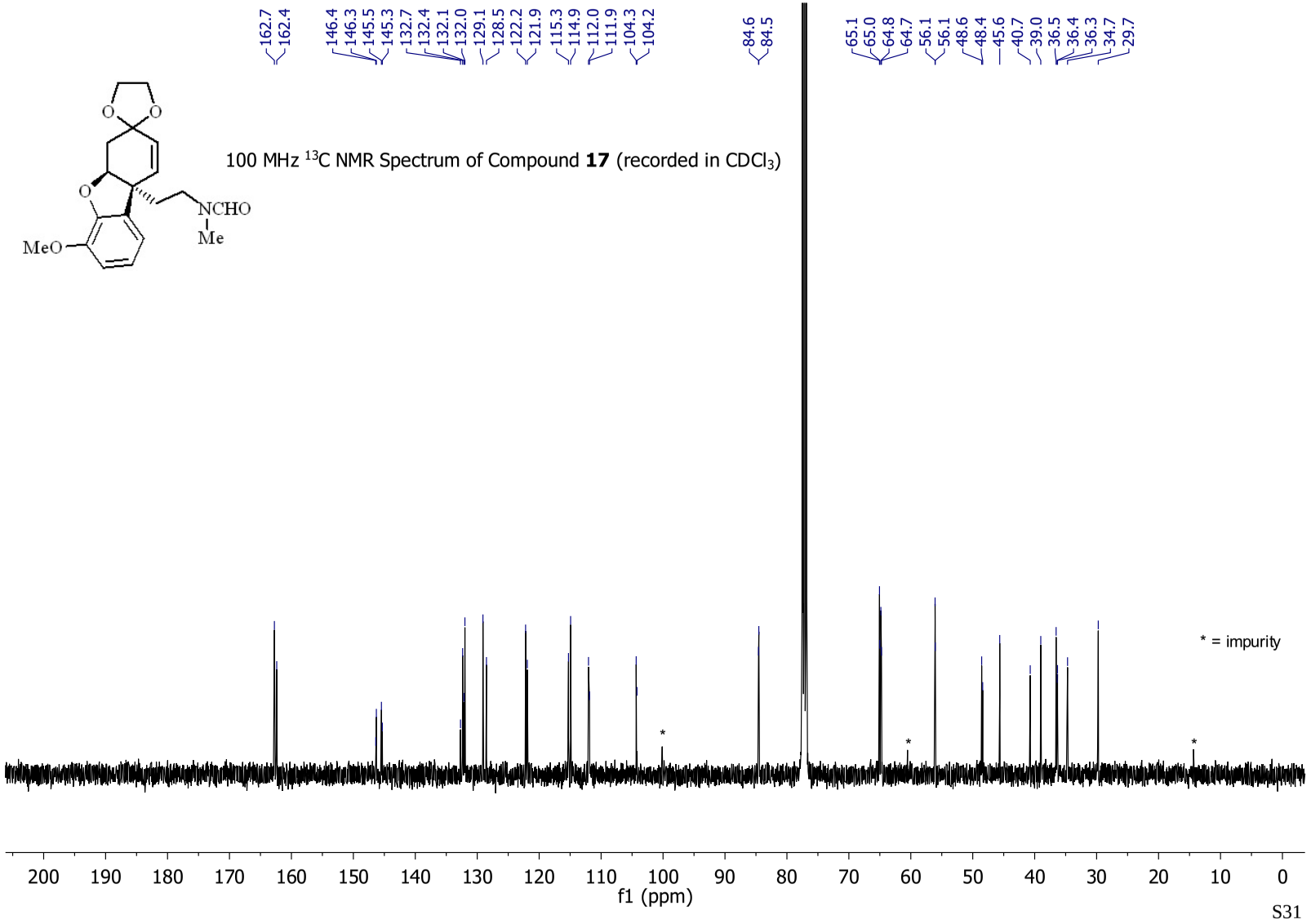
100 MHz ^{13}C NMR Spectrum of Compound **15** (recorded in $CDCl_3$)

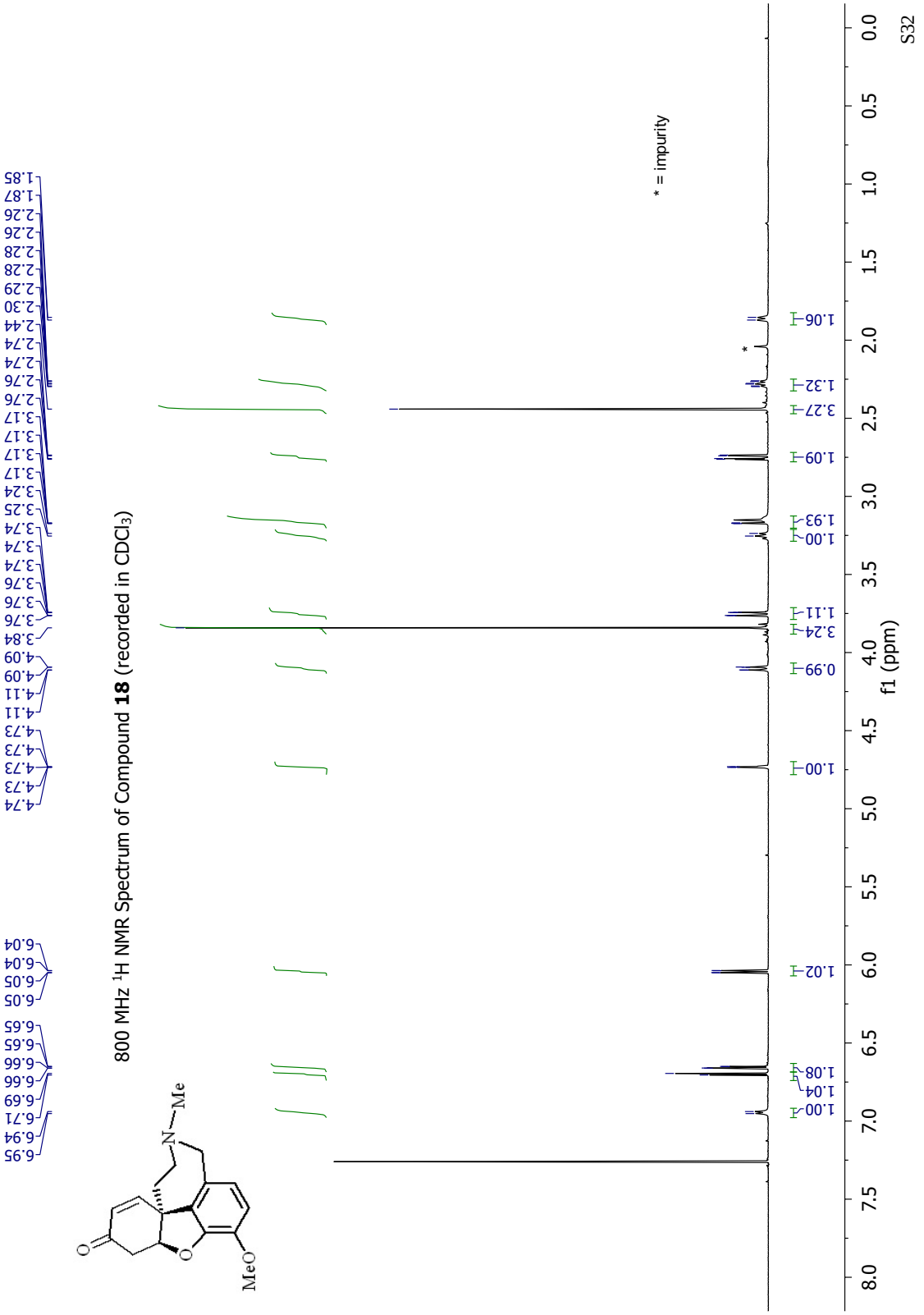

6.86 6.86 6.84 6.84 6.83 6.82 6.76 6.76 6.74 6.74 6.73 6.73 6.72 6.72 6.71 5.90 5.88 5.73 5.71
4.94 4.93 4.91 4.00 3.99 3.99 3.98 3.98 3.97 3.97 3.96 3.96 3.86 3.86 2.65 2.65 2.64 2.63 2.62 2.60 2.56 2.55 2.54 2.53 2.52 2.51 2.50 2.39 2.38 2.24 2.22 1.91 1.89 1.89 1.89 1.87
O
O
O
NH
Me
MeO
400 MHz ^{1}H NMR Spectrum of Compound **16** (recorded in $CDCl_3$)
DCM
x = hexane
* = grease
1.26
2.04
1.07
1.00
1.00
5.00
3.36
3.07
3.29
2.24
2.17
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

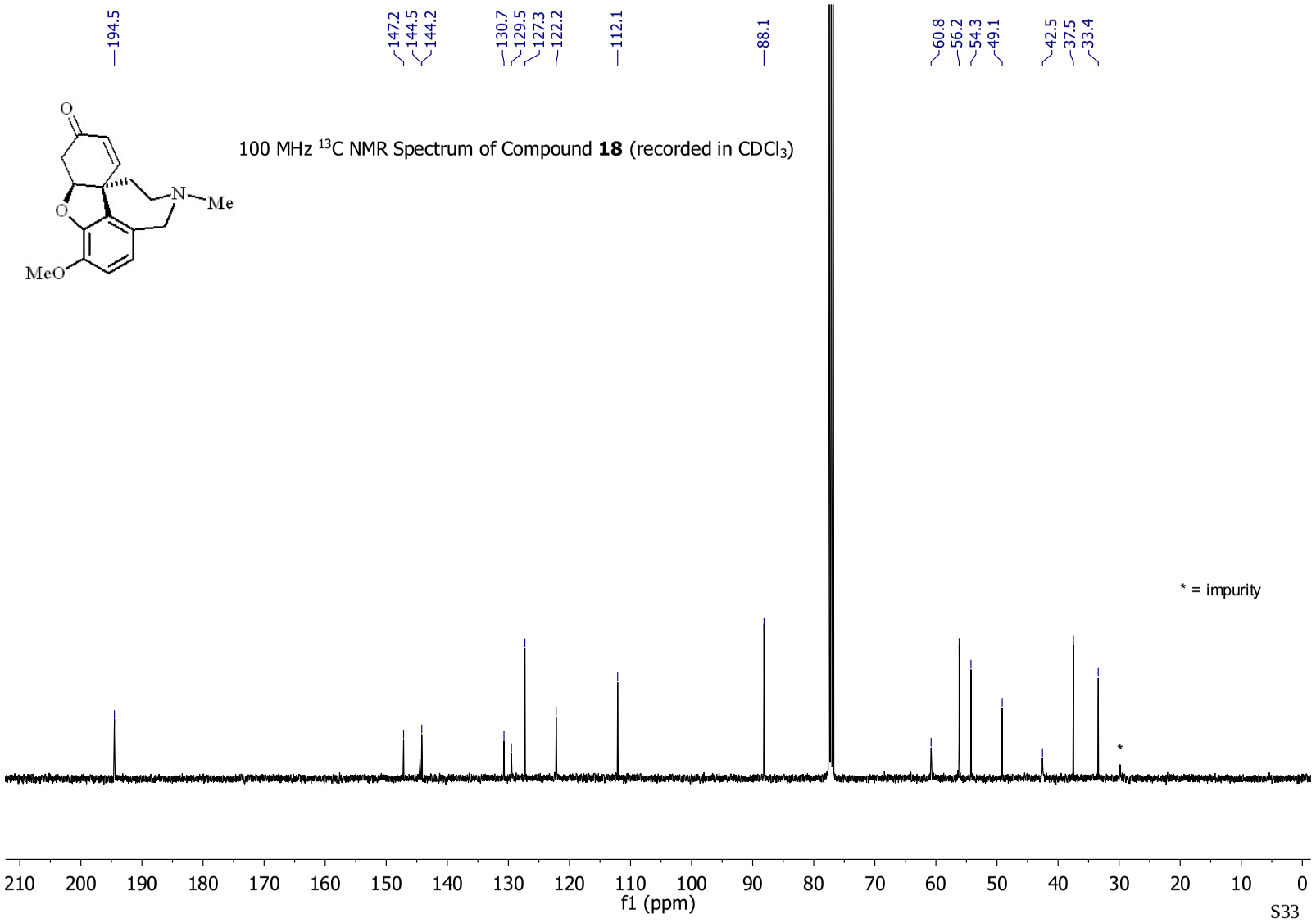


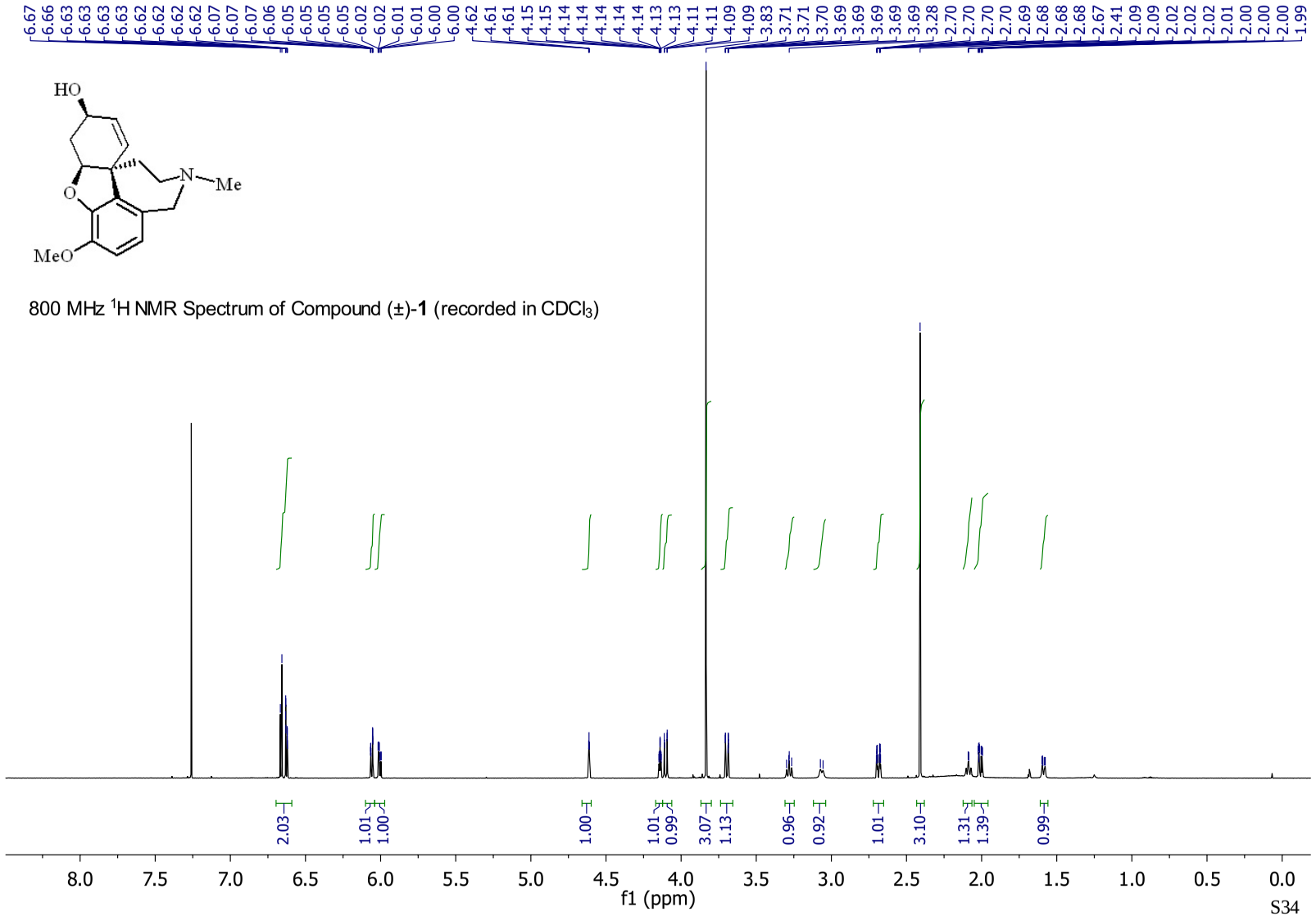
100 MHz ^{13}C NMR Spectrum of Compound **16** (recorded in $CDCl_3$)


7.96 6.89 6.87 6.86 6.86 6.84 6.80 6.80 6.78 6.78 6.77 6.76 6.76 6.74 6.72 6.72 6.71 6.70 5.96 5.93 5.93 5.90 5.82 5.82 5.79 5.79 5.79 5.76 4.95 4.93 4.92 4.91 4.89 4.00 3.99 3.99 3.98 3.98 3.97 3.96 3.96 3.87 3.86 3.15 2.87 2.80 2.27 2.25 2.24 2.24 2.24 2.23 2.23 2.23 2.22 2.18 2.16 2.11 2.08 2.07 2.05 1.93 1.92 1.91 1.91 1.90 1.89 1.87 1.86
O
O
O
NCHO
Me
MeO
400 MHz ^{1}H NMR Spectrum of Compound **17** (recorded in $CDCl_3$)
x = EtOAc
* = grease
+ = water
1.00
3.27
2.05
1.00
4.32
3.26
1.14
1.10
1.38
1.75
2.37
2.16
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

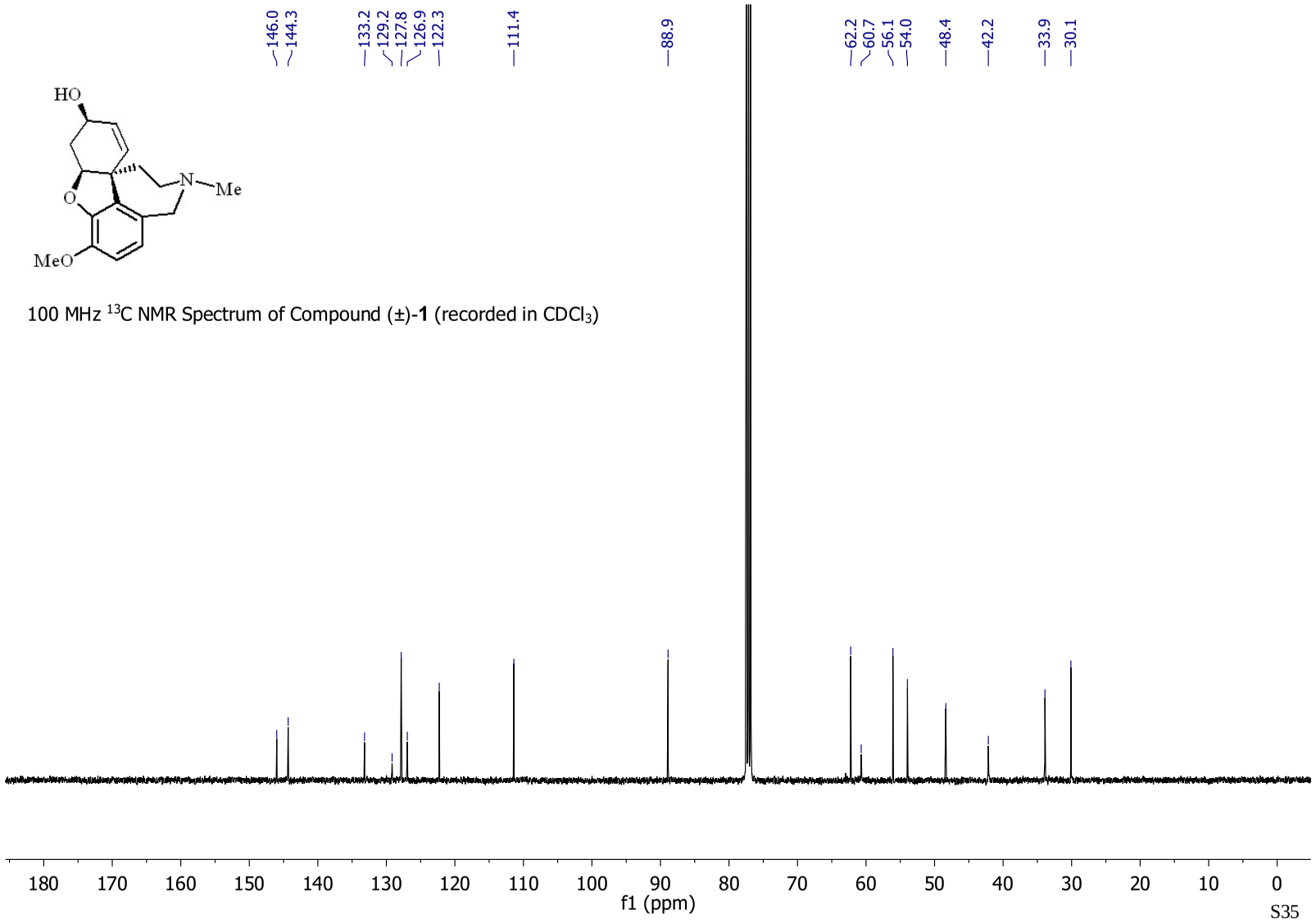

162.7
162.4
146.4
146.3
145.5
145.3
132.7
132.4
132.1
132.0
129.1
128.5
122.2
121.9
115.3
114.9
112.0
111.9
104.3
104.2
84.6
84.5
65.1
65.0
64.8
64.7
56.1
56.1
48.6
48.4
45.6
40.7
39.0
36.5
36.4
36.3
34.7
29.7
O
O
O
NCHO
Me
MeO
100 MHz ^{13}C NMR Spectrum of Compound **17** (recorded in $CDCl_3$)
* = impurity
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


800 MHz ^{1}H NMR Spectrum of Compound **18** (recorded in $CDCl_3$)
* = impurity
f1 (ppm)
S32
MeO
N
Me
O
O


194.5
147.2
144.5
144.2
130.7
129.5
127.3
122.2
112.1
88.1
60.8
56.2
54.3
49.1
42.5
37.5
33.4
O
O
N
Me
MeO
100 MHz ^{13}C NMR Spectrum of Compound **18** (recorded in $CDCl_3$)
* = impurity
*
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

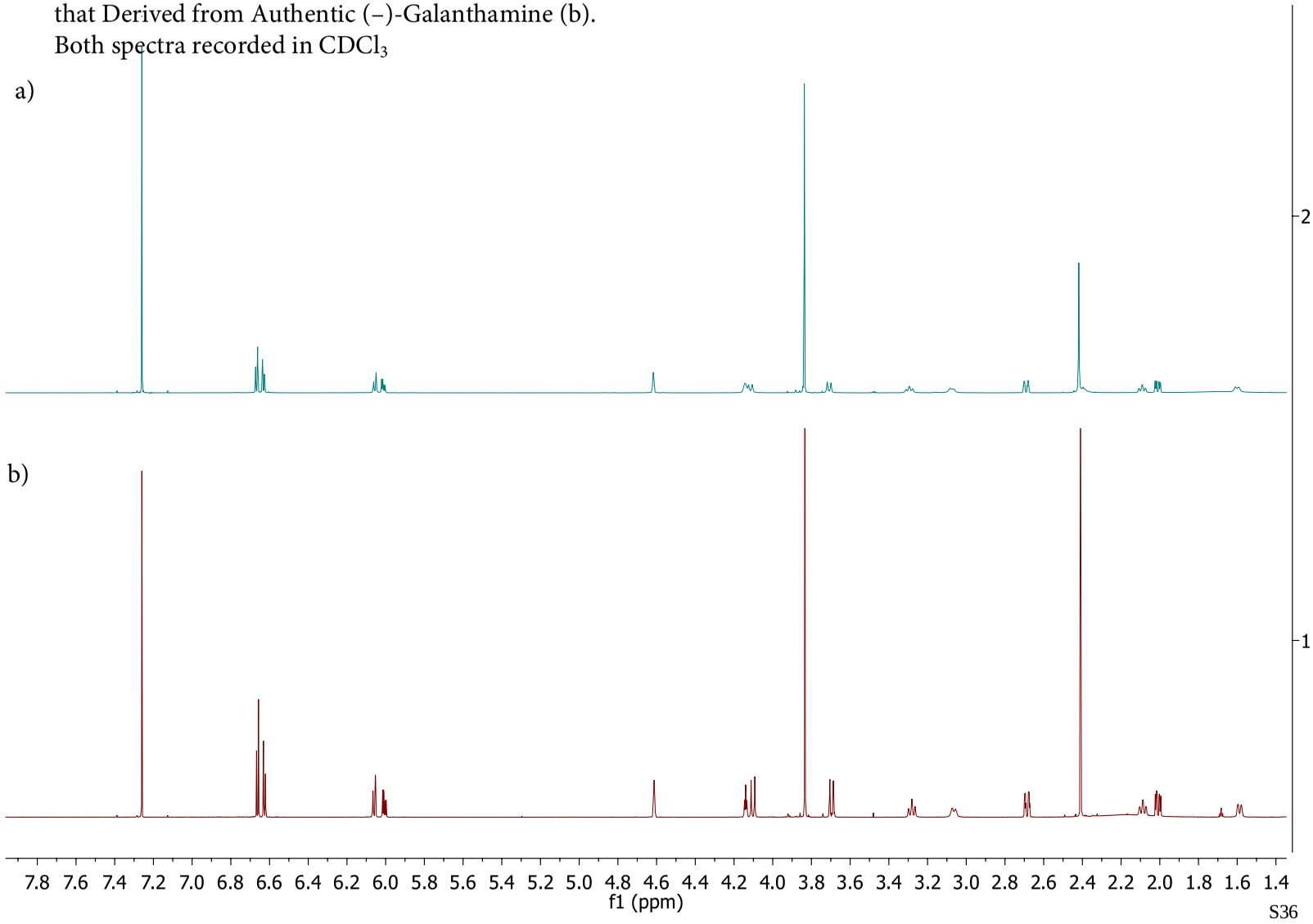


800 MHz ^{1}H NMR Spectrum of Compound (±)-**1** (recorded in $CDCl_3$)



100 MHz ^{13}C NMR Spectrum of Compound (±)-**1** (recorded in $CDCl_3$)

Figure S1: Comparison of the 800 MHz ^{1}H NMR Spectrum of Synthetically-Derived (±)-Galanthamine (a) with that Derived from Authentic (–)-Galanthamine (b).
Both spectra recorded in $CDCl_3$



S36

Publication Four

Total Synthesis of the *Illicium*-derived Sesquineolignan Simonsol C.

Jeremy Nugent, Martin G. Banwell and Brett D. Schwartz

Org. Lett. ***2016****, 18,* 3798.

Organic LETTERS

Letter

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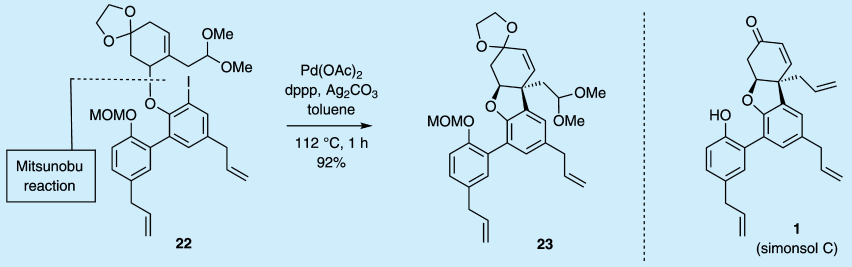
Total Synthesis of the *Illicium*-Derived Sesquineolignan Simonsol C

Jeremy Nugent, Martin G. Banwell,* and Brett D. Schwartz

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

Supporting Information



ABSTRACT: The racemic form of the title natural product **1** has been synthesized by engaging, as a key step, the iodoarene-tethered cyclohexene **22** in an intramolecular Heck reaction to give compound **23**. This angularly substituted tetrahydrodibenzo[*b*,*d*]furan was elaborated over a further five steps into target (±)-**1**.

The *Illicium* genus of flowering plants is commonly encountered in various parts of Asia, and a range of secondary metabolites produced by them, including certain sesquineolignans,[1] display potentially useful neurological effects.[2−5] These include, *inter alia*, neurite-outgrowth-promoting and acetylcholine-esterase-inhibiting properties.[4−7] Recently, Wang and co-workers reported[5] the isolation of a series of such compounds, including simonsol C (**1**) (Figure 1),[8]

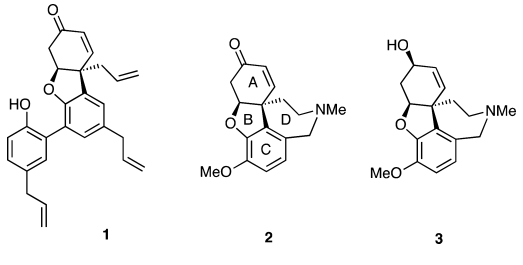


Figure 1. Structures of simsonsol C (**1**), narwedine (**2**), and galanthamine (**3**).

from the aerial parts of the toxic shrub *Illicium simonsii* collected in the Yunnan Province of southwest China. The tetrahydrodibenzo[*b*,*d*]furan substructure associated with compound **1**[9] bears a strong resemblance to the ABC-ring system of narwedine (**2**), an important precursor to the alkaloid galanthamine (**3**) that is now used clinically in the symptomatic treatment of Alzheimer's disease.[10]

Our continuing interest in the chemistry of galanthamine[11] and certain neurotrophically active metabolites derived from *Illicium* species[12] together with the absence of any reported synthetic approaches to the structurally distinct framework of simonsol C or its congeners prompted us to begin investigations in this area.[13,14] Herein we report the successful total synthesis of the racemic modification of compound **1** via a 12-step sequence that should permit access to other members of this interesting class of natural products.

The presence of three allyl residues, including an angular one, within the framework of the title compound presents various challenges including maintaining the positional integrity of the associated double bonds and achieving the required chemoselectivity in the reactions to be used. The retrosynthetic analysis employed in the present study is shown in Figure 2. It was envisaged that the central furan ring would be accessible through an intramolecular Heck reaction involving a substrate of the general form **4**, and this could itself be assembled using an intermolecular Mitsunobu reaction between the 2-allylcyclohex-2-en-1-ol **5** and a halogenated phenol of the general form **6**.

The synthetic sequence used to generate a seemingly suitable halogenated phenol is shown in Scheme 1 and involved initial monoprotection, under standard conditions, of commercially available magnolol (**7**) as the corresponding and previously unreported *tert*-butyldimethylsilyl (TBS) ether **8** (98%). Regioselective electrophilic bromination of the phenolate derived from compound **8** using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)[15] then afforded compound **9** (89%), the spectral data for which were in complete accord with the assigned structure.

The synthesis of the A-ring precursor **5** started (Scheme 2) with the α-benzoyloxylation of commercially available cyclohexane-1,2-dione monoethylene ketal (**10**).[16] The resulting and previously reported[11b,16] oxidation product **11** (78%) was then

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Org. Lett. 2016, 18, 3798−3801

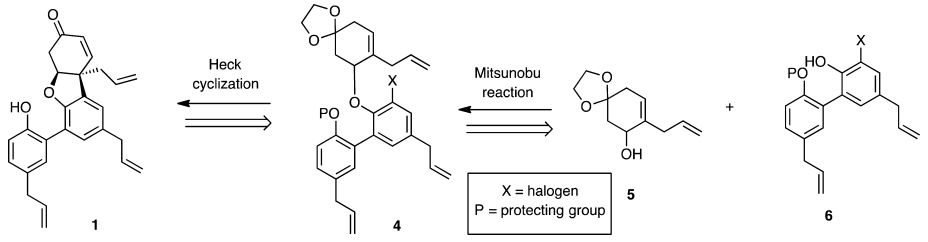
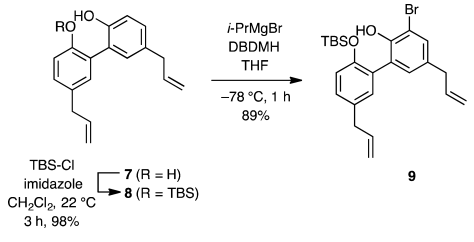
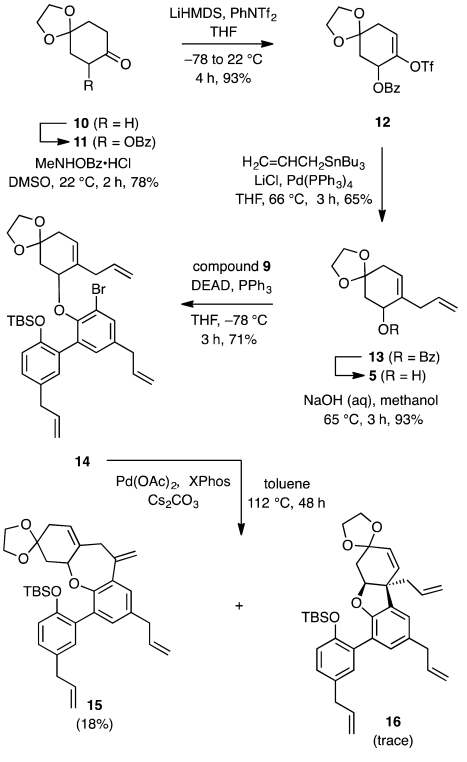


Figure 2. Retrosynthetic analysis of simonsol C used in the present study.

Scheme 1. Synthesis of Magnolol Derivative 9



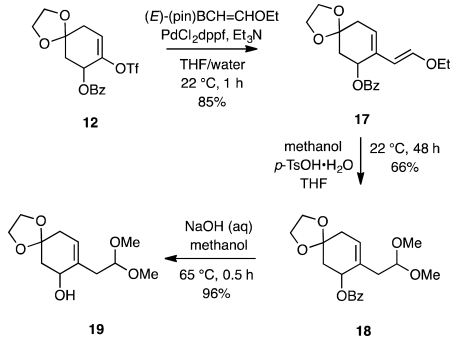
Scheme 2. Intervention of a 7-*exo*-trig Heck Cyclization Reaction



converted, by standard methods, into the corresponding enol triflate **12**[11b] (93%) that was itself engaged in a Stille cross-coupling reaction with allyltri-*n*-butylstannane in the presence of $Pd(PPh_3)_4$ and lithium chloride to give the nonconjugated diene **13** in 65% yield. Cleavage of the ester residue within this last compound was readily achieved using sodium hydroxide in methanol, and the resulting and targeted alcohol **5** (93%) participated, at −78 °C,[17] in a Mitsunobu reaction with the halogenated magnolol derivative **9** to give the desired coupling product **14** in 71% yield when diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) were used as the activating agents. Disappointingly, when compound **14** was exposed to $Pd(OAc)_2$, XPhos, and cesium carbonate in refluxing toluene,[18] a reagent combination shown to be effective for promoting Heck-type cyclization reactions,[19] the oxepin derivative **15** (18%) proved to be the one isolable and fully characterizable product of reaction. Only trace amounts of the coproduced and desired isomer **16** were detected. Examination of various other reaction conditions led to essentially the same outcome. Compound **15** is clearly the product of a 7-*exo*-trig cyclization process involving the allyl residue appended to the cyclohexene ring of substrate **14**. On this basis, masking of the offending allyl group was undertaken in order to ensure that the desired 5-*exo*-trig Heck cyclization reaction would take place.

The reaction pathway leading to a congener of compound **5** that lacks an interfering allyl group is shown in Scheme 3. Thus,

Scheme 3. Synthesis of Acetal 19



Suzuki−Miyaura cross-coupling of the enol triflate **12** described earlier with (*E*)-(pin)BCH═CHOEt[20] afforded the enol ether **17** (85%) that was itself treated with methanol and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) to produce acetal **18** (66%). The benzoate residue within this last compound was cleaved under standard conditions to give the targeted A-ring precursor **19** (96%).

Various aspects of the foregoing study resulted in the conclusion that the magnolol derivative of the general form **6** (see Figure 2) required for Mitsunobu coupling with compound **19** should incorporate a MOM protecting group[21] and iodine (rather than bromine). Accordingly, magnolol (**7**) was first treated (Scheme 4) with triethylamine and chloromethyl methyl ether (MOM-Cl, prepared under

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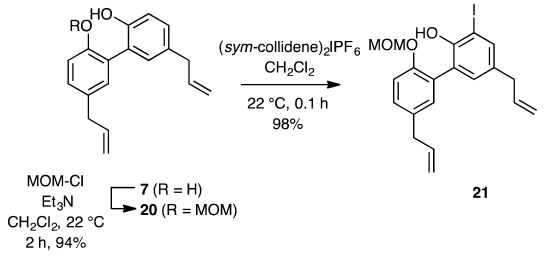
Org. Lett. 2016, 18, 3798−3801

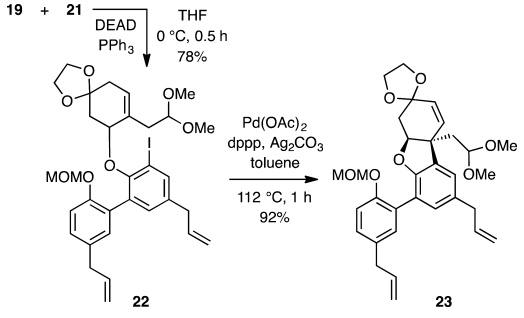
Scheme 4. Synthesis of Magnolol Derivative 21



conditions defined by Berliner and Belecki[22]), thus producing the targeted ether **20** (94%) that was immediately treated with bis(*sym*-collidine)iodine(I) hexafluorophosphate,[23,24] thereby effecting a regioselective iodination reaction to generate the desired compound **21** in 98% yield.

With compounds **19** and **21** to hand their coupling under standard Mitsunobu conditions was investigated (Scheme 5).

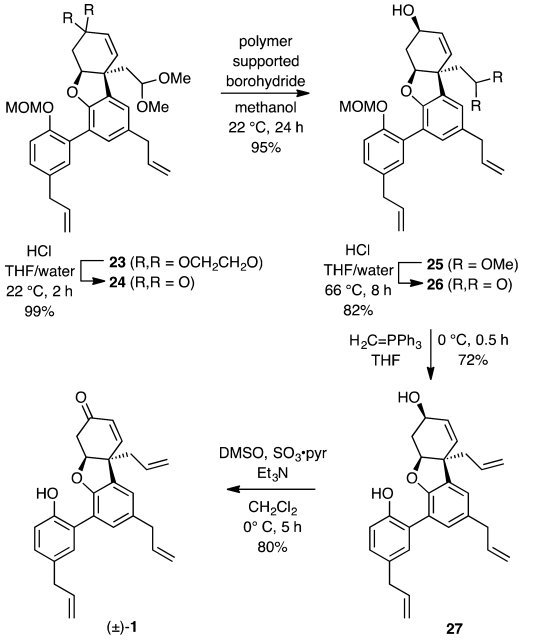
Scheme 5. Synthesis and Heck Cyclization of Compound 22



By such means the substrate, **22**, required for the pivotal Heck reaction was obtained in 78% yield. Treatment of aryl iodide **22** with $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (dppe), and silver carbonate in refluxing toluene[25] for 1 h allowed the desired 5-*exo*-trig Heck cyclization reaction to take place and so producing the tetrahydrodibenzofuran **23** in 92% yield. All the spectral data recorded on this material were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis (see below).

The elaboration of Heck cyclization product **23** to racemic simonsol C [(±)-**1**] followed the route shown in Scheme 6. This involved the initial and selective hydrolysis of the associated ethylene ketal moiety within the former compound using aqueous HCl in THF at 22 °C, affording enone **24** in 99% yield. Reduction of compound **24** with polymer-supported borohydride proceeded in a highly diasteroselective manner to give the allylic alcohol **25** in 95% yield,[26,27] and this was then treated, under reflux, with aqueous HCl in THF to provide aldehyde **26** (82%).[28] Wittig olefination of this last compound gave the triallyl-containing compound **27** (72%), the structure of which was confirmed by single-crystal X-ray analysis [see Supporting Information (SI) for details]. Finally, oxidation of allylic alcohol **27** under the Parikh–Doering conditions[29] afforded racemic simonsol C [(±)-**1**] in 80% yield. All the spectral data obtained on this material were in complete accord with the assigned structure and matched those reported for the natural product by Wang and co-workers (see the SI for relevant comparisons of the ^{13}C NMR spectral data).[5]

Scheme 6. Completion of the Synthesis of (±)-Simonsol C



The synthetic sequence reported here serves to further highlight the utility of the intramolecular Heck reaction as a means for effecting the assembly of heterocyclic ring systems embodying angular substituents[25,30] and the capacity of the Mitsunobu reaction to engage phenolic residues in C–O bond formation for the purposes of constructing tetrahydrodibenzo-[*b*,*d*]-furans.[31,32]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01799.

Experimental procedures, spectroscopic and analytical data, NMR spectra of new compounds, and X-ray data for compound **27** (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(6) For representative recent examples of biologically active sesquineolignans isolated from other sources, see: (a) Song, C.-W.; Wang, S.-M.; Zhou, L.-L.; Hou, F.-F.; Wang, K.-J.; Han, Q.-B.; Li, N.; Cheng, Y.-X. *J. Agric. Food Chem.* **2011**, *59*, 1199. (b) Cui, H.; Xu, B.; Wu, T.; Xu, J.; Yuan, Y.; Gu, Q. *J. Nat. Prod.* **2014**, *77*, 100. (c) Shi, Y.; Liu, Y.; Li, Y.; Li, L.; Qu, J.; Ma, S.; Yu, S. *Org. Lett.* **2014**, *16*, 5406. (d) Zhu, J.-Y.; Cheng, B.; Zheng, Y.-J.; Dong, Z.; Lin, S.-L.; Tang, G.-H.; Gu, Q.; Yin, S. *RSC Adv.* **2015**, *5*, 12202.
(7) For examples of other neolignans displaying neurite-outgrowth-promoting properties, see: Cheng, X.; Harzdorf, N. L.; Shaw, T.; Siegel, D. *Org. Lett.* **2010**, *12*, 1304 and references therein.
(8) Simonsol C is an optically active compound {$[\alpha]^{18}_{D}$ −10.5 (*c* 0.3, $CHCl_3$)}, but its absolute configuration has not yet been defined. We have chosen to represent it in the illustrated manner so as to emphasize its structural resemblance to the natural or (−)-enantiomeric form of galanthamine.
(9) For an example of a structurally related sesquilignan isolated from *Illicium dunnianum*, see: Sy, L.-K.; Brown, G. D. *Phytochemistry* **1996**, *43*, 1417.
(10) For useful points-of-entry into the literature on the history, chemistry, and pharmacology of galanthamine, see: (a) Henrich, M.; Teojh, H. L. *J. Ethnopharmacol.* **2004**, *92*, 147. (b) Marco-Contelles, J.; do Carmo-Carreiras, M.; Rodríguez, C.; Villarroya, M.; García, A. G. *Chem. Rev.* **2006**, *106*, 116. (c) Marco, L.; do Carmo Carreiras, M. *Recent Pat. CNS Drug Discovery* **2006**, *1*, 105. (d) Heinrich, M. *Alkaloids* **2010**, *68*, 157.
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(24) Attempts to effect this iodination reaction using *N*-iodosuccinimide resulted in competing reaction at one or both of the allyl groups within substrate **20**.
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(27) A small amount of the epimeric allylic alcohol was formed during this reduction.
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Org. Lett. 2016, 18, 3798−3801

SUPPORTING INFORMATION FOR:

Total Synthesis of the *Illicium*-Derived Sesquineolignan Simonsol C

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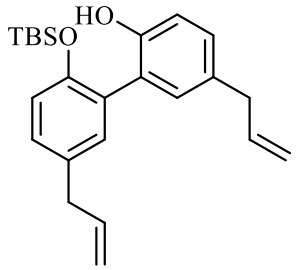
General Experimental Protocols

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (n_{max}) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*[1] with silica gel 60 (40–63 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al.*[2] Where necessary, reactions were performed under an nitrogen atmosphere.

Specific Chemical Transformations
Compound 8

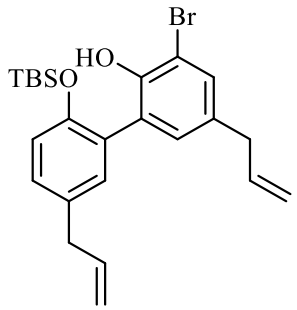


8

A magnetically stirred solution of magnolol (**7**) (1.00 g, 3.76 mmol) and imidazole (272 mg, 4.00 mmol) in dry dichloromethane (40 mL) maintained at 22 °C under a nitrogen atmosphere was treated with TBS-Cl (301 mg, 5.00 mmol). The ensuing light-yellow mixture was stirred at this temperature for 1 h then treated with NH_4Cl (30 mL of a saturated aqueous solution) before being extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 95:5 v/v hexane/ethyl acetate), compound **8** (1.40 g, 98%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 2.3 Hz, 1H), 7.09 (m, 2H), 7.05 (d, J = 2.3 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.41 (s, 1H), 5.98 (m, 2H), 5.15–5.05 (complex m, 4H), 3.37 (m, 4H), 0.83 (s, 9H), –0.05 (broad s, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 150.0, 138.2, 137.6, 134.8, 132.4, 132.3, 131.2, 130.2, 129.5, 129.1, 127.1, 120.7, 117.9, 116.0, 115.4, 39.6, 39.5, 25.6, 18.1, –4.6
IR (KBr) ν_{max} 3397, 2955, 2931, 2858, 1639, 1494, 1257, 1231, 912, 877, 840 cm^{-1}
MS (ESI, –ve) *m/z* 379 [$(M - H)^-$, 90%], 265 (100)
HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{24}H_{32}O_2Si$ 380.2172, found 380.2177.

Compound 9

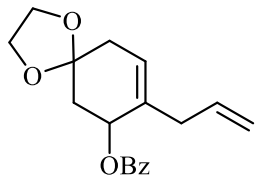


9

A magnetically stirred solution of compound **8** (1.30 g, 3.42 mmol) in dry THF (13 mL) maintained at −78 °C was treated with *i*-PrMgBr (1.6 mL of a 2.3 M solution in 2-methyltetrahydrofuran, 3.70 mmol). The ensuing mixture was maintained at this temperature for 0.5 h before being treated with DBDMH (772 mg, 2.70 mmol). The resulting yellow mixture was maintained at −78 °C for 1 h before being treated with NH_4Cl (30 mL of a saturated aqueous solution) and then extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 95:5 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 95:5 v/v hexane/ethyl acetate), compound **9** (1.40 g, 89%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2.2 Hz, 1H), 7.11 (m, 2H), 7.00 (d, J = 2.2 Hz, 1H), 6.87 (m, 1H), 6.60 (s, 1H), 5.89 (m, 2H), 5.15–5.05 (complex m, 4H), 3.38 (d, J = 6.8 Hz, 1H), 3.33 (d, J = 6.8 Hz, 2H), 0.82 (s, 9H), –0.03 (broadened s, 6H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 148.7, 137.5, 137.3, 134.5, 133.5, 132.4, 132.0, 130.8, 129.6, 129.5, 128.3, 120.6, 116.2, 116.1, 112.0, 39.6, 39.1, 25.5, 18.1, –4.6
IR (KBr) ν_{max} 3521, 3342, 2955, 2930, 2858, 1641, 1494, 1471, 1248, 916, 841, 783 cm^{-1}
MS (ESI, –ve) *m/z* 459 and 457 [$(M - H)^-$, 50 and 45%], 345 and 343 (both 30), 81 and 79 (95 and 100)
HRMS (ESI, –ve) *m/z* [$(M - H)^-$ calcd for $C_{24}H_{30}{}^{79}BrO_2Si$ 457.1198, found 457.1180.

Compound 13

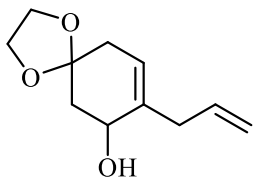


13

A magnetically stirred solution of compound **12**[3] (7.91 g, 19.4 mmol) and LiCl (2.48 g, 58.5 mmol) in dry THF (130 mL) was treated, sequentially, with allyltributylstannane (7.25 mL, 23.4 mmol) and $Pd(PPh_3)_4$ (2.25 g, 10 mol%). The resulting yellow mixture was heated at reflux for 3 h then cooled and treated with NH_4Cl (30 mL of a saturated aqueous solution) before being extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8.5:1:0.5 v/v hexane/ethyl acetate/triethylamine elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 7:3 v/v hexane/ethyl acetate), compound **13** (3.79 g, 65%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.88–5.71 (complex m, 2H), 5.66 (m, 1H), 5.08–4.95 (complex m, 2H), 4.00 (m, 4H), 2.86 (m, 2H), 2.48 (m, 1H), 2.40–2.27 (complex m, 2H), 2.00 (dd, J = 12.8 and 7.2 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 135.5, 135.0, 133.1, 130.5, 129.8, 128.5, 124.1, 117.0, 107.6, 71.5, 64.7, 64.6, 37.4, 37.2, 36.1
IR (KBr) ν_{max} 2971, 2920, 2879, 1715, 1265, 1108, 1069, 1052, 1026, 948, 712 cm^{-1}
MS (ESI, +ve) *m/z* 323 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{18}H_{20}NaO_4$ 323.1259, found 323.1259.

Compound 5

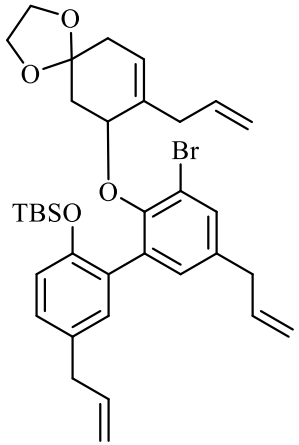


5

A magnetically stirred solution of compound **13** (1.00 g, 3.33 mmol) in methanol (50 mL) was treated with NaOH (10 mL of a 3 M aqueous solution, 30 mmol) then heated at reflux for 2 h. The resulting solution was cooled then treated with water (300 mL) and extracted with diethyl ether (5 x 60 mL). The combined organic phases were washed with brine (1 x 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give compound **5** (607 mg, 93%) as a clear, colorless oil. This material was used without further purification in the next step of the reaction sequence.

R_f = 0.4 (in 7:3 v/v hexane/ethyl acetate)
^{1}H NMR (400 MHz, $CDCl_3$) 5.84 (m, 1H), 5.45 (broad s, 1H), 5.13–5.00 (complex m, 2H), 4.11 (m, 1H), 4.05–3.90 (complex m, 4H), 3.11–2.86 (complex m, 3H), 2.30 (m, 2H), 2.08 (dt, J = 13.8 and 2.3 Hz, 1H), 1.98 (dd, J = 13.8 and 4.9 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 136.4, 121.3, 116.5, 108.4, 68.3, 64.6, 64.5, 39.0, 38.3, 36.1
IR (KBr) ν_{max} 3428, 2957, 2890, 1638, 1413, 1361, 1249, 1122, 1047, 1011, 947, 914 cm^{-1}
MS (ESI, +ve) *m/z* 219 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{11}H_{16}NaO_3$ 219.0997, found 219.0995.

Compound 14



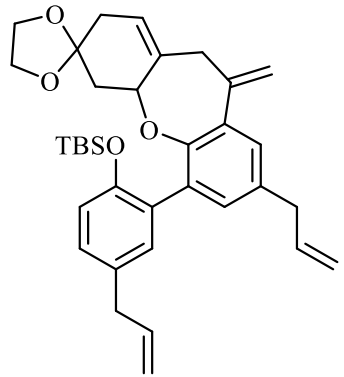
14

A magnetically stirred solution of compound **5** (393 mg, 2.00 mmol), compound **9** (1.10 g, 2.36 mmol) and PPh_3 (621 mg, 2.36 mmol) in dry THF (45 mL) maintained at −78 °C was treated, dropwise, with DEAD (380 μl, 2.36 mmol). The resulting orange mixture was maintained at −78 °C for 3 h then warmed to room temperature before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and after concentration of the appropriate fractions (R_f = 0.6 in 6:1 v/v hexane/ethyl acetate) compound **14** (904 mg, 71%) was obtained as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.05–6.97 (complex m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 5.96 (m, 2H), 5.79 (m, 1H), 5.27 (m, 1H), 5.14–4.92 (complex m, 6H), 4.48 (m, 1H), 3.85 (m, 1H), 3.75 (m, 3H), 3.32 (m, 4H), 3.00 (dm, J = 16.7 Hz, 1H), 2.55 (dm, J = 16.7 Hz, 1H), 2.29 (dm, J = 17.3 Hz, 1H), 2.05 (dm, J = 17.3 Hz, 1H), 1.90–1.70 (complex m, 2H), 0.78 (s, 9H), 0.11 (m, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 150.4, 137.7, 137.6, 136.9, 136.7, 135.7, 134.1, 132.3(1), 132.2(9), 132.1, 131.6, 129.8, 129.1, 120.5, 118.9, 118.5, 116.4, 116.0, 115.8, 108.6, 79.0, 64.4, 64.2, 39.5, 39.3, 37.4, 36.1, 36.0, 25.5, 18.0, –4.2, –4.4
IR (KBr) ν_{max} 3079, 2955, 2930, 2893, 2861, 1639, 1497, 1251, 1125, 1055, 1017, 913, 839, 780 cm^{-1}
MS (ESI, +ve) *m/z* 661 and 659 [$(M+Na)^+$, 100 and 95%]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{35}H_{45}{}^{79}BrNaO_4Si$ 659.2168, found 659.2169.

Compound 15

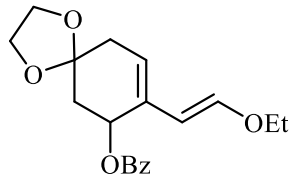


15

A magnetically stirred and degassed solution of compound **14** (20 mg, 0.032 mmol), Xphos (6.2 mg, 0.013 mmol), $Pd(OAc)_2$ (1.7 mg, 0.007 mmol) and Cs_2CO_3 (31 mg, 0.096 mmol) in toluene (2 mL) was heated at reflux for 48 h. The ensuing black mixture was cooled then subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 6:1 v/v hexane/ethyl acetate), compound **15** (3 mg, 18%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 2.4 Hz, 1H), 7.08 (m, 1H), 7.00 (m, 2H), 6.78 (d, J = 8.1 Hz, 1H), 5.96 (m, 2H), 5.40 (broad s, 1H), 5.30 (s, 1H), 5.13–5.02 (complex m, 5H), 4.75 (m, 1H), 3.98–3.80 (complex m, 4H), 3.45 (d, J = 14.0 Hz, 1H), 3.34 (m, 4H), 3.14 (d, J = 14.0 Hz, 1H), 2.35–2.06 (complex m, 3H), 1.76 (dd, J = 12.3 and 10.4 Hz, 1H), 0.74 (s, 9H), 0.00 (s, 3H), –0.17 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 151.4, 144.8, 139.6, 138.1, 137.8, 133.2, 131.6, 131.5, 131.4, 131.2(1), 131.1(9), 130.8, 128.2, 127.7, 119.7, 117.8, 115.7, 115.6, 113.4, 108.7, 79.5, 64.7, 64.5, 42.4, 39.7(2), 39.7(1), 37.8, 35.9, 25.6, 18.1, –4.3, –4.7
IR (KBr) ν_{max} 2957, 2930, 2893, 2856, 1639, 1494, 1240, 1440, 1240, 1126, 1034, 909, 839, 780 cm^{-1}
MS (ESI, +ve) *m/z* 579 [$(M+Na)^+$, 95%], 574 (100), 557 (60).
HRMS (ESI, +ve) $(M+Na)^+$ calcd for $C_{35}H_{44}NaO_4Si$ 579.2907, found 579.2914.

Compound 17



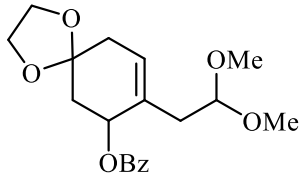
17

A magnetically stirred and degassed solution of compound **12** (5.20 g, 12.7 mmol) and triethylamine (13 mL) in THF/water (50 mL of a 9:1 mixture) was treated, sequentially, with (*E*)-(pin)BCH=CHOEt[4] (3.27 g, 16.5 mmol) and $PdCl_2dppf•CH_2Cl_2$ (727 mg, 7 mol%). The resulting dark-red mixture was maintained at 22 °C for 1 h then cooled to 0 °C and treated with H_2O_2 (20 mL of a 30% aqueous solution) and NH_4Cl (20 mL of a saturated aqueous solution). After 0.5 h at 0 °C the reaction mixture was warmed to 22 °C then extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (1 x 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate), compound **17** (3.57 g, 85%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 6.47 (d, J = 12.9 Hz, 1H), 5.90 (m, 1H), 5.72 (m, 1H), 5.48 (d, J = 12.9 Hz, 1H), 4.05–3.80 (complex m, 4H), 3.68 (m, 2H), 2.52 (dd, J = 18.4 and 4.3 Hz, 1H), 2.41 (dd, J = 18.4 and 4.3 Hz, 1H), 2.28 (m, 1H), 2.09 (m, 1H), 1.17 (t, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 147.2, 133.1, 131.7, 130.5, 129.9, 128.4, 123.6, 107.1, 105.7, 69.2, 65.5, 64.7, 64.4, 36.9, 36.2, 14.8
IR (KBr) ν_{max} 2976, 2880, 1707, 1657, 1265, 1107, 946, 713 cm^{-1}
MS (ESI, +ve) *m/z* 401 (100%), 353 [$(M+Na)^+$, 60%]
HRMS (ESI, +ve) $(M+Na)^+$ calcd for $C_{19}H_{22}NaO_5$ 353.1365, found 353.1362.

Compound 18



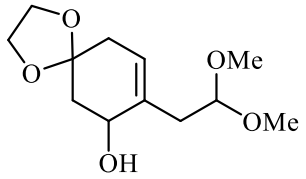
18

A magnetically stirred solution of compound **17** (500 mg, 1.53 mmol) in dry THF/methanol (11 mL of a 10:1 v/v mixture) was treated with *p*-TsOH•H_2O (30 mg, 0.15 mmol). The resulting mixture was maintained at 22 °C for 48 h then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 2:1 v/v hexane/ethyl acetate), compound **18** (352 mg, 66%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.56 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.78 (m, 2H), 4.50 (t, *J* = 5.6 Hz, 1H), 3.97 (m, 4H), 3.28 (s, 6H), 2.48 (m, 2H), 2.41–2.28 (complex m, 3H), 1.99 (dd, *J* = 13.2 and 7.0 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 133.1, 131.9, 130.6, 129.8, 128.5, 126.3, 107.4, 103.7, 71.7, 64.7, 64.6, 53.5, 53.1, 37.2, 36.4, 36.1
IR (KBr) ν_{max} 2940, 2889, 2833, 1712, 1269, 1111, 1065, 1047, 713 cm^{-1}
MS (ESI, +ve) *m/z* 371 [$(M+Na)^+$, 100%]

HRMS (ESI, +ve) $(M+Na)^+$ calcd for $C_{19}H_{24}NaO_6$ 371.1471, found 371.1479.

Compound 19

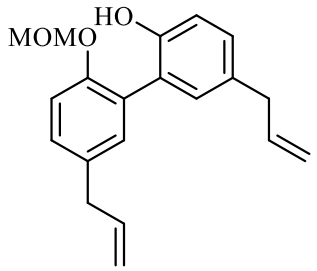


19

A magnetically stirred solution of compound **18** (1.40 g, 4.02 mmol) in methanol (50 mL) was treated with NaOH (20 mL of a 3 M aqueous solution, 60 mmol) and then heated at reflux for 0.5 h. The resulting solution was cooled then treated with water (300 mL) and extracted with ethyl acetate (5 x 60 mL). The combined organic phases were washed with brine (1 x 50 mL) before dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give compound **19** (943 mg, 96%) as a light-yellow oil. This material was used without further purification in the next step of the reaction sequence.

R_f = 0.3 (in 1:2 v/v hexane/ethyl acetate)
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (t, J = 3.9 Hz, 1H), 4.55 (m, 1H), 4.20 (m, 1H), 4.05–3.90 (complex m, 4H), 3.36 (s, 3H), 3.34 (s, 3H), 3.24 (d, J = 9.5 Hz, 1H), 2.60 (m, 1H), 2.39 (dd, J = 14.6 and 4.7 Hz, 1H), 2.31 (m, 2H), 2.05 (dd, J = 13.5 and 4.7 Hz, 1H), 1.99 (dd, J = 13.5 and 4.7 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 123.4, 108.2, 104.1, 68.6, 64.5(3), 64.5(2), 53.6, 52.8, 39.2, 37.3, 36.2
IR (KBr) ν_{max} 3452, 2954, 2931, 2893, 2832, 1362, 1119, 1042 cm^{-1}
MS (ESI, +ve) *m/z* 267 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) $(M+Na)^+$ calcd for $C_{12}H_{20}NaO_5$ 267.1208, found 267.1205

Compound 20

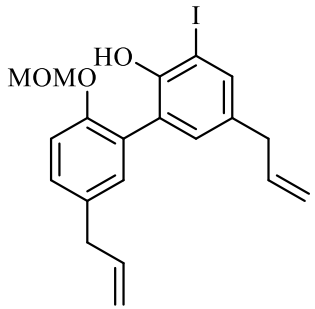


20

A magnetically stirred solution of magnolol (1.00 g, 3.76 mmol) and triethylamine (0.74 mL, 5.30 mmol) in dry dichloromethane (5 mL) was treated with a freshly prepared solution of MOMCl[5] (10 mL of a 1 M solution in dichloromethane, 10.0 mmol). The resulting light-yellow solution was maintained at 22 °C for 2 h then treated with NH_4Cl (10 mL of a saturated aqueous solution). After a further 0.25 h the reaction mixture was extracted with diethyl ether (3 x 10 mL) and the combined organic phases washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give compound **20** (1.10 g, 94%) as a light-yellow oil. This material was used without further purification in the next step of the reaction sequence.

R_f = 0.8 (in 7:3 v/v hexane/ethyl acetate)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.06 (complex m, 5H), 6.96 (d, J = 8.2 Hz, 1H), 6.05 (s, 1H), 5.98 (m, 2H), 5.12 (s, 2H), 5.10–5.04 (complex m, 4H), 3.41–3.39 (complex m, 4H), 3.37 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0(4), 152.0(2), 138.0, 137.4, 135.5, 132.6, 132.5, 131.3, 129.5(3), 129.5(0), 128.5, 126.2, 117.3, 116.8, 116.1, 115.7, 96.2, 56.6, 39.6(4), 39.6(0)
IR (KBr) ν_{max} 3405, 2979, 2902, 1636, 1498, 1229, 1150, 986, 907, 820 cm^{-1}
MS (ESI, +ve) *m/z* 333 [(M+Na)$^+$, 100%]
HRMS (ESI, +ve) (M+Na)$^+$ calcd for $C_{20}H_{22}NaO_3$ 333.1467, found 333.1463.

Compound 21

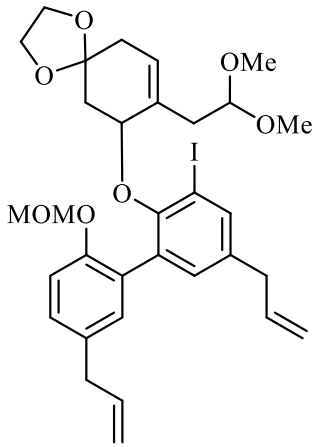


21

A magnetically stirred solution of compound **20** (1.10 g, 3.50 mmol) in dichloromethane (100 mL) was treated with $(collidene)_2IPF_6$[6] (2.00 g, 4.00 mmol). The ensuing green mixture was maintained at 22 °C for 0.1 h then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.8 in 2:1 v/v hexane/ethyl acetate), compound **21** (1.50 g, 98%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 2.1 Hz, 1H), 7.18 (m, 2H), 7.09 (d, J = 1.8 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H), 6.33 (s, 1H), 5.95 (m, 2H), 5.15 (s, 2H), 5.12–5.05 (complex m, 4H), 3.38 (d, J = 6.7 Hz, 2H), 3.36 (s, 3H), 3.33 (d, J = 6.7 Hz, 2H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 150.9, 138.6, 137.3, 137.2, 135.1, 134.2, 132.2, 132.0, 129.9, 128.0, 126.2, 116.5, 116.3, 116.2, 96.0, 86.1, 56.6, 39.5, 39.0
IR (KBr) ν_{max} 3365, 3077, 2919, 2853, 1639, 1496, 1458, 1229, 1155, 1078, 997, 912 cm^{-1}
MS (ESI, +ve) *m/z* 459 $[(M+Na]^+$, 100%]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{20}H_{21}INaO_3$ 459.0433, found 459.0432.

Compound 22



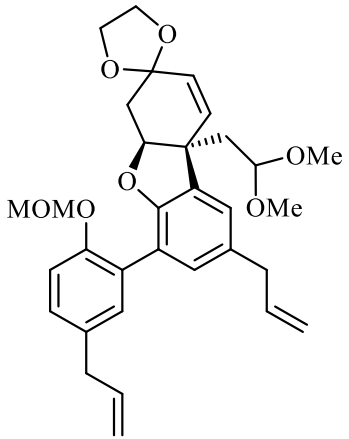
22

A magnetically stirred solution of compound **19** (940 mg, 3.85 mmol), compound **21** (2.00 g, 4.62 mmol) and PPh_3 (1.20 g, 4.62 mmol) in dry THF (90 mL) maintained at 0 °C was treated, dropwise, with DEAD (740 μL, 4.62 mmol). The resulting orange mixture was maintained at 0 °C for 0.5 h then warmed to room temperature before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 2:1 v/v hexane/ethyl acetate), compound **22** (1.99 g, 78%) as a clear, light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 2.2 Hz, 1H), 7.11 (m, 2H), 7.08 (m, 1H), 7.03 (d, J = 2.2 Hz, 1H), 5.94 (m, 2H), 5.43 (d, J = 5.1 Hz, 1H), 5.13–5.03 (complex m, 6H), 4.61 (t, J = 5.6 Hz, 1H), 4.42 (m, 1H), 3.90–3.75 (complex m, 4H), 3.41–3.29 (complex m, 13H), 2.36–2.32 (complex m, 3H), 2.06 (m, 1H), 1.80 (m, 2H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 152.3, 138.5, 137.5, 136.9, 136.6, 133.5, 132.9, 132.1, 131.4, 129.5, 128.3, 123.2, 116.5, 116.0, 115.4, 108.5(3), 108.5(2), 103.9, 95.1, 94.6, 78.7, 64.3(4), 64.3(0), 56.1, 53.9, 53.1, 39.5, 39.0, 37.2, 36.3, 36.0 (one signal obscured or overlapping)

IR (KBr) ν_{max} 2969, 2921, 2898, 2830, 1642, 1497, 1438, 1225, 113, 1042, 999 cm^{-1}
MS (ESI, +ve) *m/z* 685 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{32}H_{39}INaO_7$ 685.1638, found 685.1636.

Compound 23

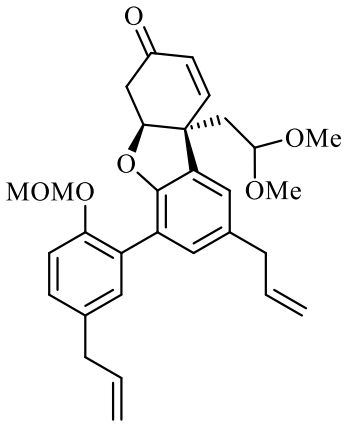


23

A magnetically stirred and thoroughly degassed solution of compound **22** (2.00 g, 3.02 mmol) in dry toluene (111 mL) maintained under a nitrogen atmosphere was treated, sequentially, with $Pd(OAc)_2$ (69 mg, 10 mol%), dppp (255 mg, 20 mol%) and Ag_2CO_3 (2.60 g, 9.30 mmol). The resulting heterogeneous mixture was heated at reflux for 1 h then cooled, filtered through a pad of diatomaceous earth and the filtrate evaporated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 1:1 v/v hexane/ethyl acetate), compound **23** (1.49 g, 92%) as a light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.15 (m, 1H), 7.02 (m, 1H), 7.09 (m, 1H), 6.88 (d, J = 1.9 Hz, 1H), 6.03–5.91 (complex m, 3H), 5.76 (d, J = 10.1 Hz, 1H), 5.11–4.99 (complex m, 7H), 4.44 (m, 1H), 3.97 (m, 4H), 3.39 (s, 3H), 3.37–3.34 (complex m, 4H), 3.28 (s, 3H), 3.27 (s, 3H), 2.22–1.96 (complex m, 4H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.2, 138.0, 137.8, 133.5(3), 133.5(0), 132.5, 132.1, 131.8, 130.6, 128.8, 127.5(1), 127.5(0), 122.3, 121.6, 116.0, 115.7, 115.6, 104.4, 102.1, 95.6, 84.3, 64.8, 64.6, 56.0, 52.9, 52.6, 47.3, 42.9, 39.9, 39.6, 35.8
IR (KBr) ν_{max} 2977, 2957, 2896, 2832, 1720, 1642, 1502, 1461, 1121, 1012, 920 cm^{-1}
MS (ESI, +ve) *m/z* 557 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) $(M+H)^+$ calcd for $C_{32}H_{39}O_7$ 535.2696, found 535.2698.

Compound 24



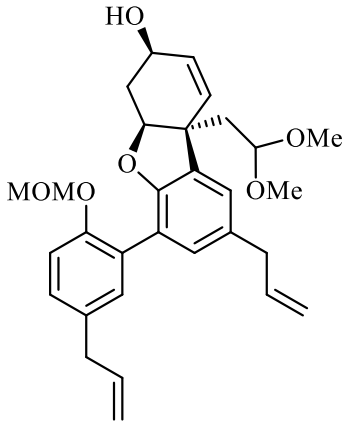
24

A magnetically stirred solution of compound **23** (1.48 g, 2.77 mmol) in THF (80 mL) was treated with HCl (20 mL of a 1 M aqueous solution, 20 mmol). The resulting mixture was maintained at 22 °C for 2 h then treated with $NaHCO_3$ (30 mL of a saturated aqueous solution) and

extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give compound **24** (1.35 g, 99%) as a light-yellow oil. This material was used without purification in the next step of the reaction sequence.

R_f = 0.6 (in 1:1 v/v hexane/ethyl acetate)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.05 (complex m, 4H), 6.99 (d, J = 1.9 Hz, 1H), 6.53 (dd, J = 10.2 and 1.8 Hz, 1H), 6.03 (d, J = 10.2 Hz, 1H), 5.98 (m, 2H), 5.16–4.97 (complex m, 6H), 4.94 (m, 1H), 4.55 (m, 1H), 3.44–3.30 (complex m, 13H), 2.94 (broad s, 2H), 2.40 (dd, J = 14.6 and 4.1 Hz, 1H), 2.28 (dd, J = 14.6 and 6.8 Hz, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 154.8, 153.6, 148.4, 137.6(4), 137.6(1), 137.6(0), 133.5, 133.2, 131.4, 131.2(3), 131.2(2), 129.2, 127.1, 126.9, 121.9, 116.0, 115.8, 115.6, 101.8, 95.5, 85.5, 56.0, 53.1, 52.8, 47.0, 39.9, 39.8, 39.5, 38.6
IR (KBr) ν_{max} 2901, 2830, 1682, 1499, 1468, 1122, 1073, 905, 724 cm^{-1}
MS (ESI, +ve) *m/z* 513 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) $(M+Na)^+$ calcd for $C_{30}H_{34}NaO_6$ 513.2253, found 513.2259.

Compound 25



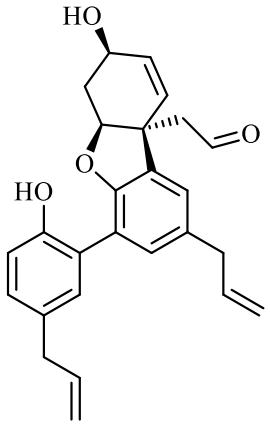
25

A magnetically stirred solution of compound **24** (1.35 g, 2.75 mmol) in methanol (100 mL) was treated, in one portion, with polymer-bound borohydride (7.0 g of Amberlyst A26, 2.5 mmol active hydride per g, 17.5 mmol). The resulting mixture was stirred at 22 °C for 24 h then filtered through a sintered glass funnel and the retained solids washed with methanol (6 x 40 mL). The combined filtrates were concentrated under reduced pressure to give compound **25** (1.29 g, 95%) as a pale yellow oil and as a 10:1 mixture of diastereoisomers. This material was used without purification in the next step of the reaction sequence.

R_f = 0.2 (minor diasteroisomer) and 0.4 (in 2:1 v/v hexane/ethyl acetate)
^{1}H NMR (400 MHz, $CDCl_3$) δ (major diastereoisomer) 7.14–7.08 (complex m, 3H), 6.96 (m, 2H), 6.09–5.91 (complex m, 3H), 5.54 (d, J = 10.0 Hz, 1H), 5.12 (m, 1H), 5.09–5.00 (complex m, 4H), 4.86 (m, 1H), 4.81 (d, J = 6.7 Hz, 1H), 4.46 (m, 1H), 4.13 (m, 1H), 3.49 (d, J = 11.4 Hz, 1H), 3.38 (m, 4H), 3.29 (s, 3H), 3.28 (s, 3H), 3.09 (s, 3H), 2.52 (m, 1H), 2.26–2.01 (complex m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (major diastereoisomer) 153.9, 153.2, 137.8, 137.4, 134.9, 133.7, 133.0, 131.2, 131.0, 130.0, 129.2(3), 129.2(1), 128.2, 122.2, 121.7, 118.4, 115.9, 115.7, 101.8, 96.9, 85.9, 61.6, 56.0, 52.5(3), 52.4(8), 46.5, 39.8, 39.6, 39.5, 30.6
IR (KBr) ν_{max} 3493, 2916, 2827, 1639, 1499, 1468, 1119, 1043, 992, 905, 798 cm^{-1}
MS (ESI, +ve) *m/z* 515 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{30}H_{36}NaO_6$ 515.2410, found 515.2408.

Compound 26

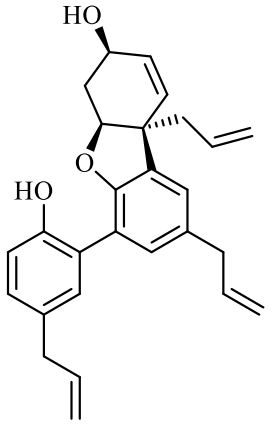


26

A magnetically stirred solution of compound **25** (1.28 g, 2.60 mmol) in THF (66 mL) was treated with HCl (33 mL of a 1 M aqueous solution, 33 mmol) then heated at reflux for 8 h. The resulting mixture was cooled then treated with $NaHCO_3$ (40 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 x 40 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl

acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v hexane/ethyl acetate), compound **26** (858 mg, 82%) as a pale-yellow solid, mp = 70–72 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 2.6 Hz, 1H), 8.20 (broad s, 1H), 7.15–6.95 (complex m, 4H), 6.85 (d, J = 8.2 Hz, 1H), 5.99 (m, 3H), 5.74 (dd, J = 10.0 and 1.4 Hz, 1H), 5.17–5.06 (complex m, 4H), 4.81 (broad s, 1H), 4.26 (broad s, 2H), 3.40 (d, J = 6.6 Hz, 2H), 3.37 (d, J = 6.6 Hz, 2H), 2.94 (dd, J = 16.0 and 2.6 Hz, 1H), 2.83 (dd, J = 16.0 and 2.6 Hz, 1H), 2.63 (dd, J = 15.2 and 3.7 Hz, 1H), 2.06 (m, 1H)
^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 153.4, 152.4, 137.9, 137.6, 134.0, 132.0, 131.6, 130.8, 130.7, 130.5, 129.4, 127.8, 124.5, 122.2(3), 122.1(9), 116.2, 116.1, 115.7, 85.0, 61.3, 49.4, 46.6, 39.9, 39.5, 30.3
IR (KBr) ν_{max} 3436, 3187, 3019, 2903, 2829, 1721, 1640, 1467, 1407, 1213, 1053, 756 cm^{-1}
MS (ESI, −ve) *m/z* 401 [$(M–H)^-$, 100%]
HRMS (ESI , –ve) $(M–H)^-$ calcd for $C_{26}H_{25}O_4$ 401.1753, found 401.1763.

Compound 27

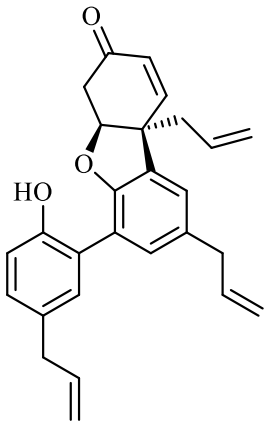


27

A magnetically stirred solution of methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol) in dry THF (70 mL) was cooled to 0 °C then treated with *n*-BuLi (6.25 mL of a 1.6 M solution in hexanes, 10.0 mmol). The resulting orange-colored mixture was maintained at this temperature for 0.5 h then treated with a solution of aldehyde **26** (700 mg, 1.74 mmol) in dry THF (30 mL). The resulting yellow mixture was maintained at 0 °C for 0.5 h then treated with HCl (30 mL of a 1 M aqueous solution) and extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v hexane/ethyl acetate), compound **27** (502 mg, 72%) as a white, crystalline solid, mp = 110-112 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–6.96 (complex m, 4H), 6.88 (d, J = 8.2 Hz, 1H), 6.05–5.92 (complex m, 3H), 5.79–5.62 (complex m, 2H), 5.18–5.01 (complex m, 6H), 4.77 (broad s, 1H), 4.21 (m, 1H), 3.40 (d, J = 6.9 Hz, 2H), 3.36 (d, J = 6.9 Hz, 2H), 2.63 (dd, J = 14.2 and 7.0 Hz, 1H), 2.53 (m, 2H), 1.97 (m, 1H) (signals due to the hydroxyl group protons not observed)
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.5, 138.0, 137.9, 133.6, 133.4, 133.1, 132.5, 131.8, 130.8, 129.9, 129.2, 127.2, 124.8, 122.2, 121.8, 118.7, 116.3, 115.8, 115.6, 85.0, 61.6, 48.1, 41.1, 40.0, 39.6, 31.0
IR (KBr) ν_{max} 3436, 3181, 3076, 2918, 1637, 1507, 1469, 1416, 1222, 1043, 987, 910, 732 cm^{-1}
MS (ESI, +ve) *m/z* 439 (80%), 423 [$(M+Na)^+$, 100]
HRMS (ESI, +ve) *m/z* $(M+Na)^+$ calcd for $C_{27}H_{28}NaO_3$ 423.1936, found 423.1934.

Compound (±)-1



1

A magnetically stirred solution of compound **27** (50 mg, 0.125 mmol) in dry dichloromethane (3.5 mL) and dry DMSO (1.5 mL) was treated with triethylamine (75 µl, 0.50 mmol) and cooled to 0 °C. The resulting mixture was treated with SO_3•pyr (60 mg, 0.375 mmol), maintained at 0 °C for 3 h then treated with further portions of triethylamine (75 µl, 0.500 mmol) and SO_3•pyr (60 mg, 0.375 mmol). After a further 0.5 h the reaction mixture was treated with HCl (5 mL of a 1 M aqueous solution) and extracted with dichloromethane (2 x 5 mL). The combined organic phases were washed with brine (1 x 5 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 2:1 v/v hexane/ethyl acetate), compound (±)-**1** (40 mg, 80%) as a white, amorphous solid.

^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.67 (s, 1H), 7.23 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 7.01 (dd, J = 8.2 and 2.3 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.71 (dd, J = 10.2 and 1.9 Hz, 1H), 6.07–5.87 (complex m, 4H), 5.28 (dd, J = 17.1 and 1.7 Hz, 1H), 5.18

(dd, J = 10.2 and 2.1 Hz, 1H), 5.14–4.97 (complex m, 5H), 3.40 (d, J = 6.8 Hz, 2H), 3.31 (d, J = 7.1 Hz, 2H), 2.97 (dd, J = 14.1 and 7.1 Hz, 1H), 2.92–2.77 (complex m, 3H)
^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ see **Table S1**
IR (KBr) ν_{max} 3386, 3081, 2974, 2913, 1682, 1642, 1499, 1415, 1220, 997, 915 cm^{-1}
MS (ESI, +ve) *m/z* 421 [$(M+Na)^+$, 100%]
HRMS (ESI, +ve) $(M+Na)^+$ calcd for $C_{27}H_{26}NaO_3$ 421.1780, found 421.1781.

Table S1: *Comparison of the ^{13}C NMR Data Recorded for Compound (±)-**1** Obtained by the Present Route with Those Reported by Wang*[6]

^{13}C NMR Data for Compound (±)-**1** (δ_C)[a]	^{13}C NMR Data from Wang (δ_C)[b]	Δδ
195.1	195.1	+0.1
155.3	155.2	+0.1
153.6	153.5	0
149.5	149.5	+0.1
139.1	139.0	+0.1
139.0	138.9	+0.1
134.3	134.2	+0.1
133.9	133.8	+0.1
132.8	132.7	+0.1
132.0	131.9	+0.1
131.9	131.8	+0.1
131.7	131.6	+0.1
129.7	129.7	0
127.6	127.5	+0.1
125.0	124.9	+0.1
123.3	123.3	0
122.3	122.2	+0.1
119.7	119.6	+0.1
117.3	117.2	+0.1
115.8	115.7	+0.1
115.5	115.5	0
85.8	85.7	+0.1
49.6	49.5	+0.1
40.8	40.7	+0.1
40.4	40.3	+0.1
39.9	39.9	0
39.4	39.3	+0.1

[a]spectrum recorded in $CDCl_3$ at 200 MHz; [b]data obtained from reference 4, spectrum recorded in $CDCl_3$ at 125 MHz.

Crystallographic Study

Crystallographic Data for Compound 27

$C_{27}H_{28}O_3$, $M = 400.47$, $T = 150$ K, triclinic, space group $P\bar{1}$, $Z = 4$, $a = 9.9759(2)$ Å, $b = 13.6806(3)$ Å, $c = 17.6508(4)$ Å; $\alpha = 109.1900(19)°$, $\beta = 96.4682(17)°$, $\gamma = 98.2575(16)°$; $V = 2218.30(5)$ Å^3, $D_x = 1.199$ g cm^{-3}, 8471 unique data ($2\Theta_{max} = 144.0°$), $R = 0.052$ [for 7181 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.143$ (all data), $S = 0.99$.

Structure Determination

Images were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and data extracted using the CrysAlis package.[7] Structure solution was by direct methods (SIR92).[8] The structure of compound **27** was refined using the CRYSTALS program package.[9] Atomic coordinates, bond lengths and angles, and displacement parameters for compound **27** have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1482403). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

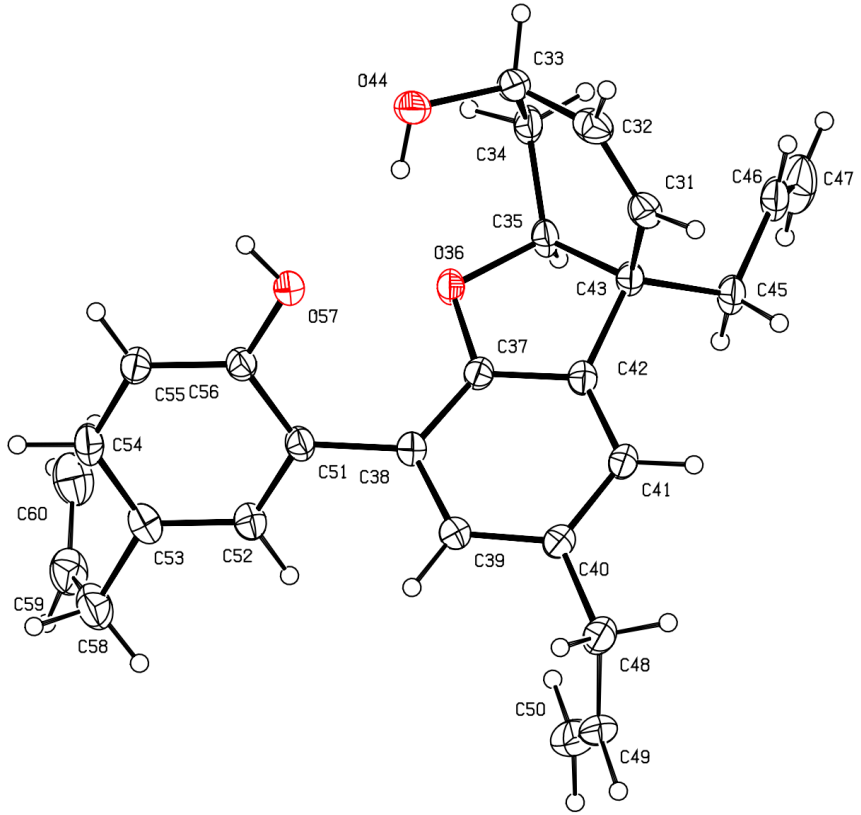


Figure S1: Structure of one selected molecule of compound **27** (CCDC 1482403) in the asymmetric unit with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

References

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*., **1978**, *43*, 2923.
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7. CrysAlis PRO Version 1.171.37.35h (release 09-02-2015 CrysAlis171.NET) (compiled Feb 9 2015,16:26:32) Agilent Technologies: Oxfordshire, UK.
8. SIR92. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.,* **1994**, *27*, 435.
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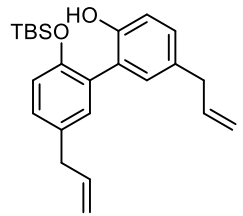
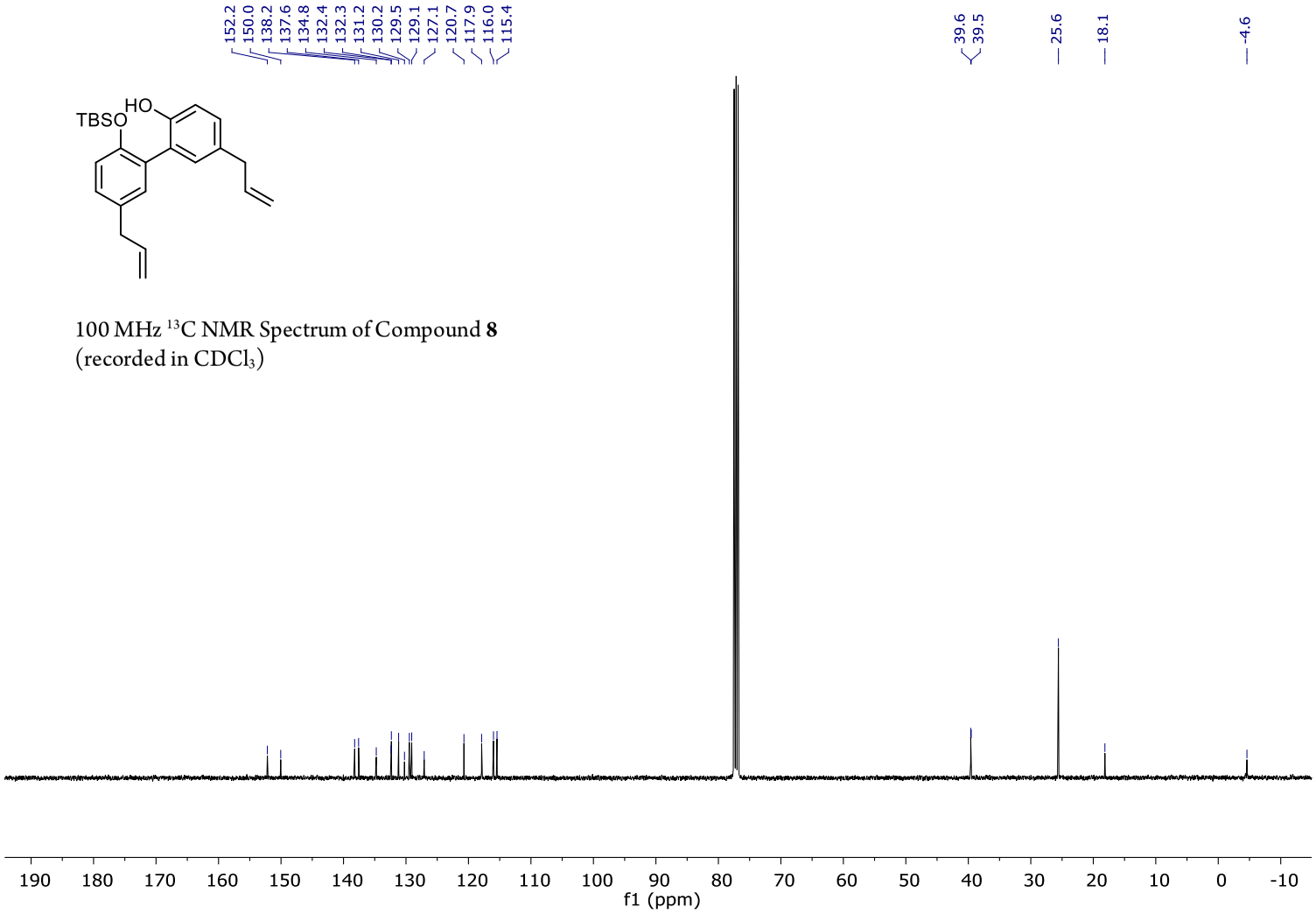
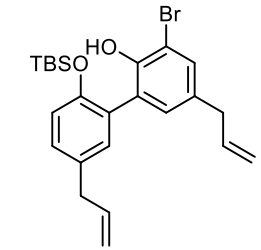


400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



100 MHz ^{13}C NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



400 MHz ^{1}H NMR Spectrum of Compound **9**
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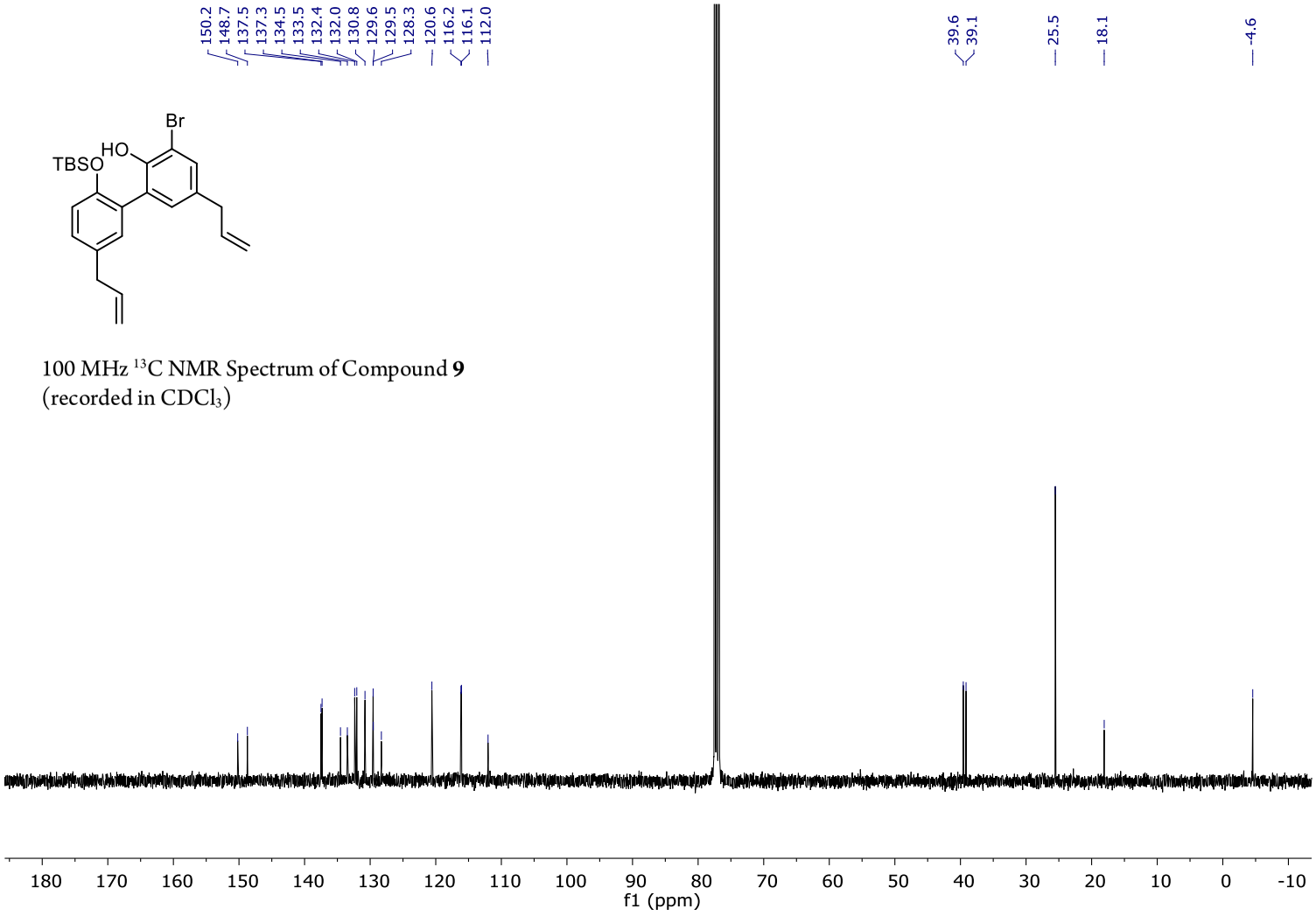
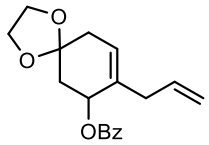
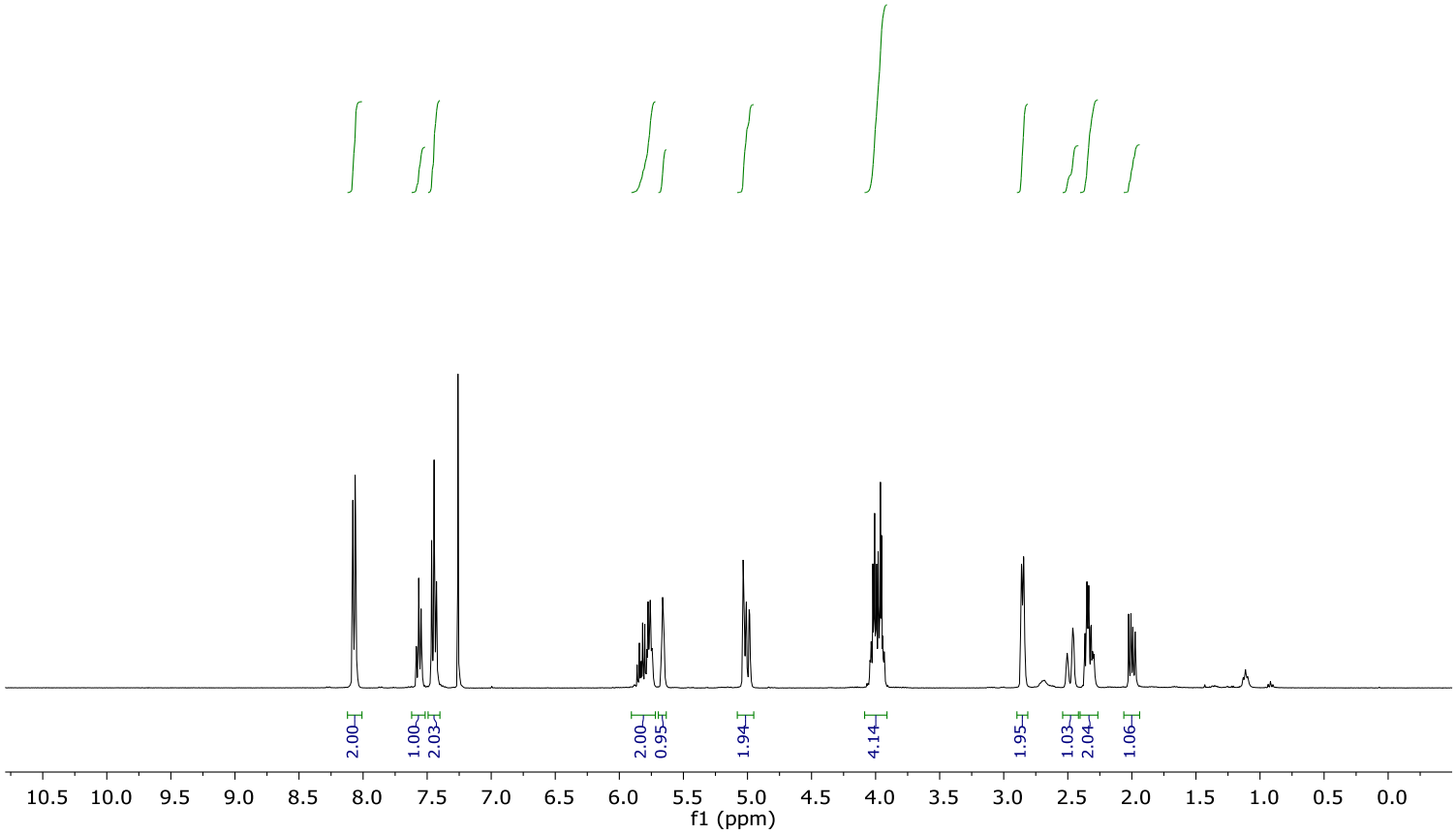
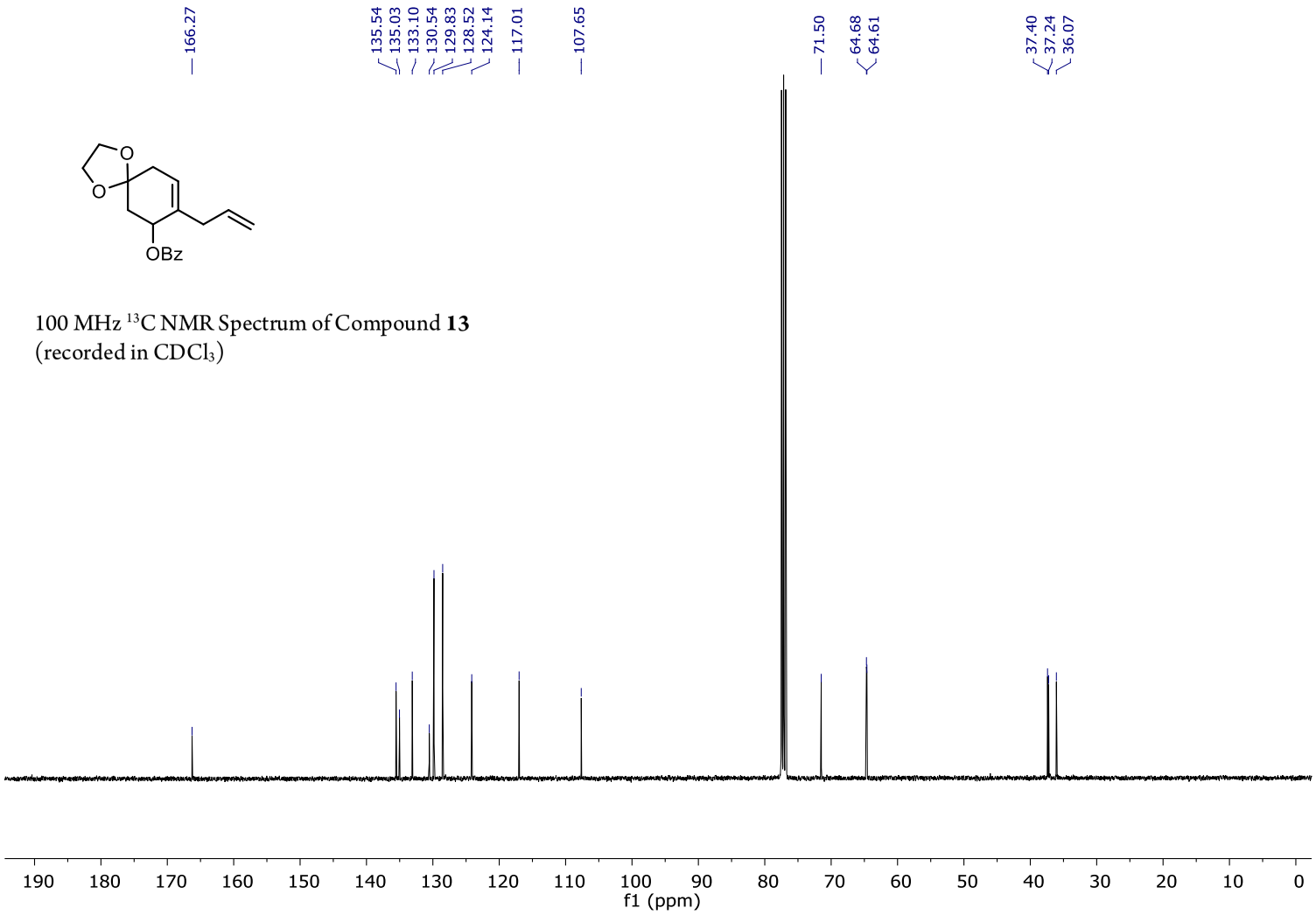


100 MHz ^{13}C NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



400 MHz ^{1}H NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)





100 MHz ^{13}C NMR Spectrum of Compound **13**
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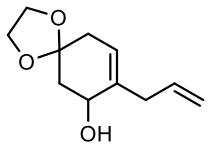
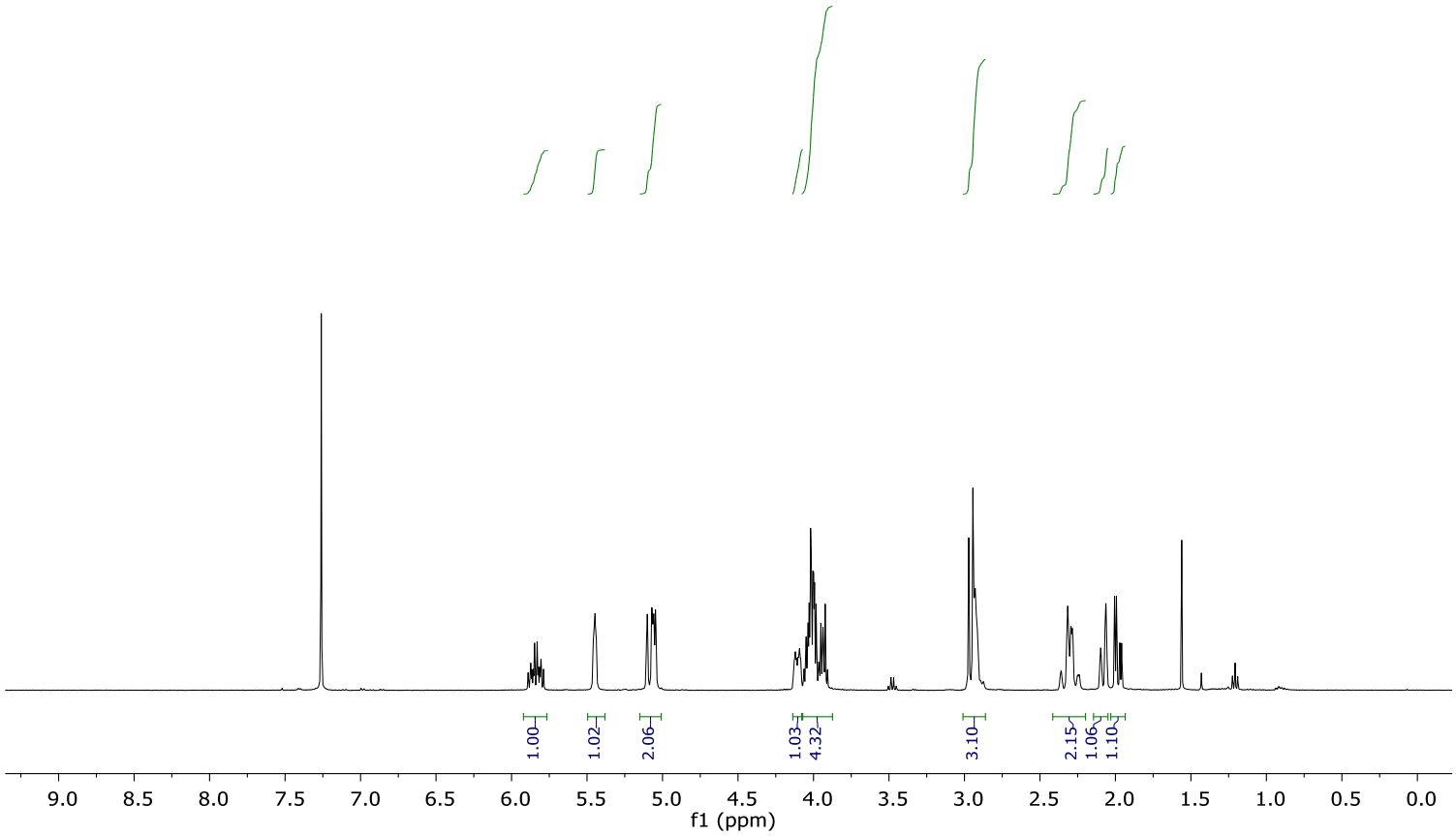
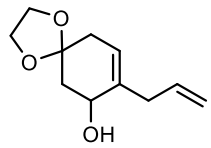


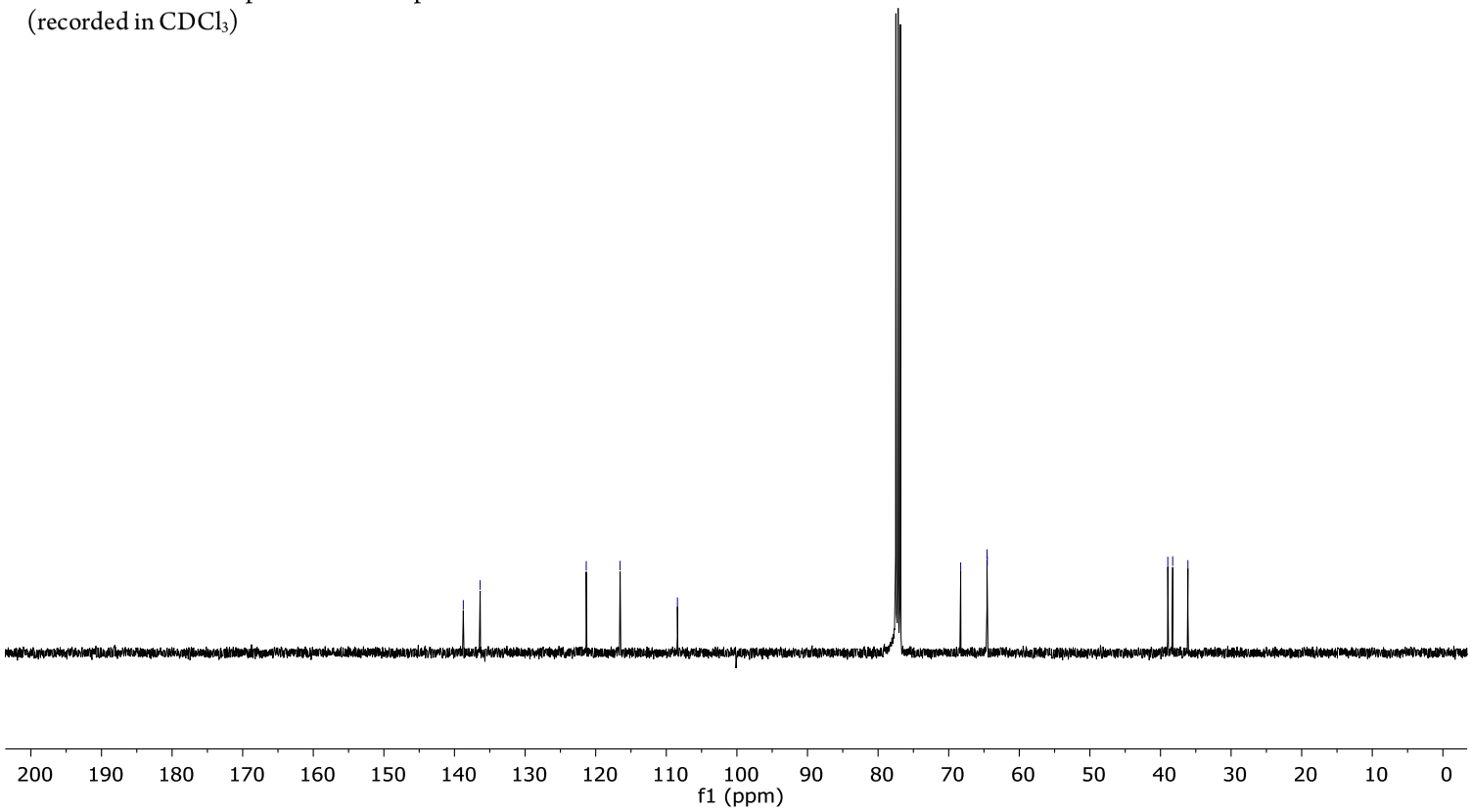
400 MHz ^{1}H NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)

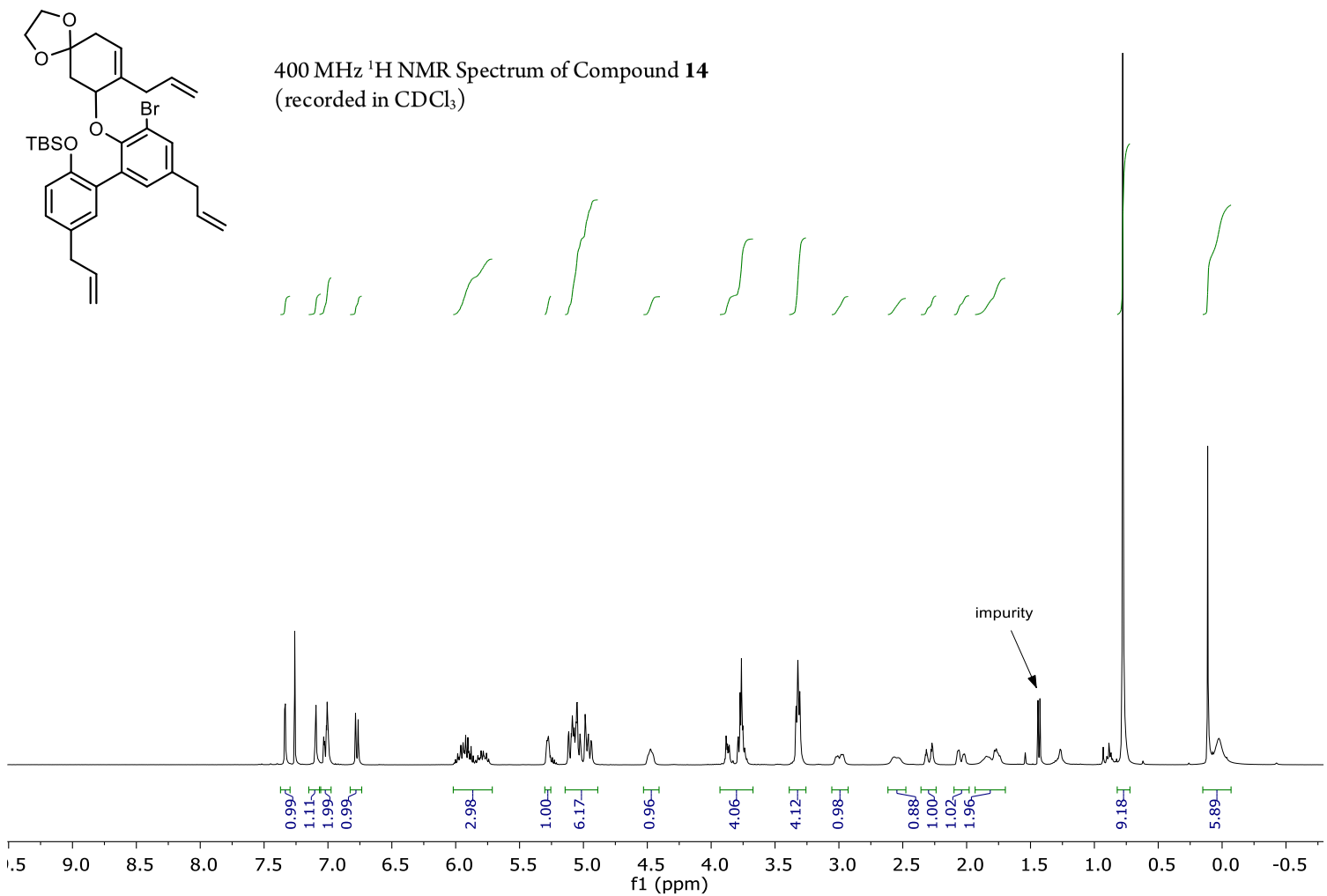


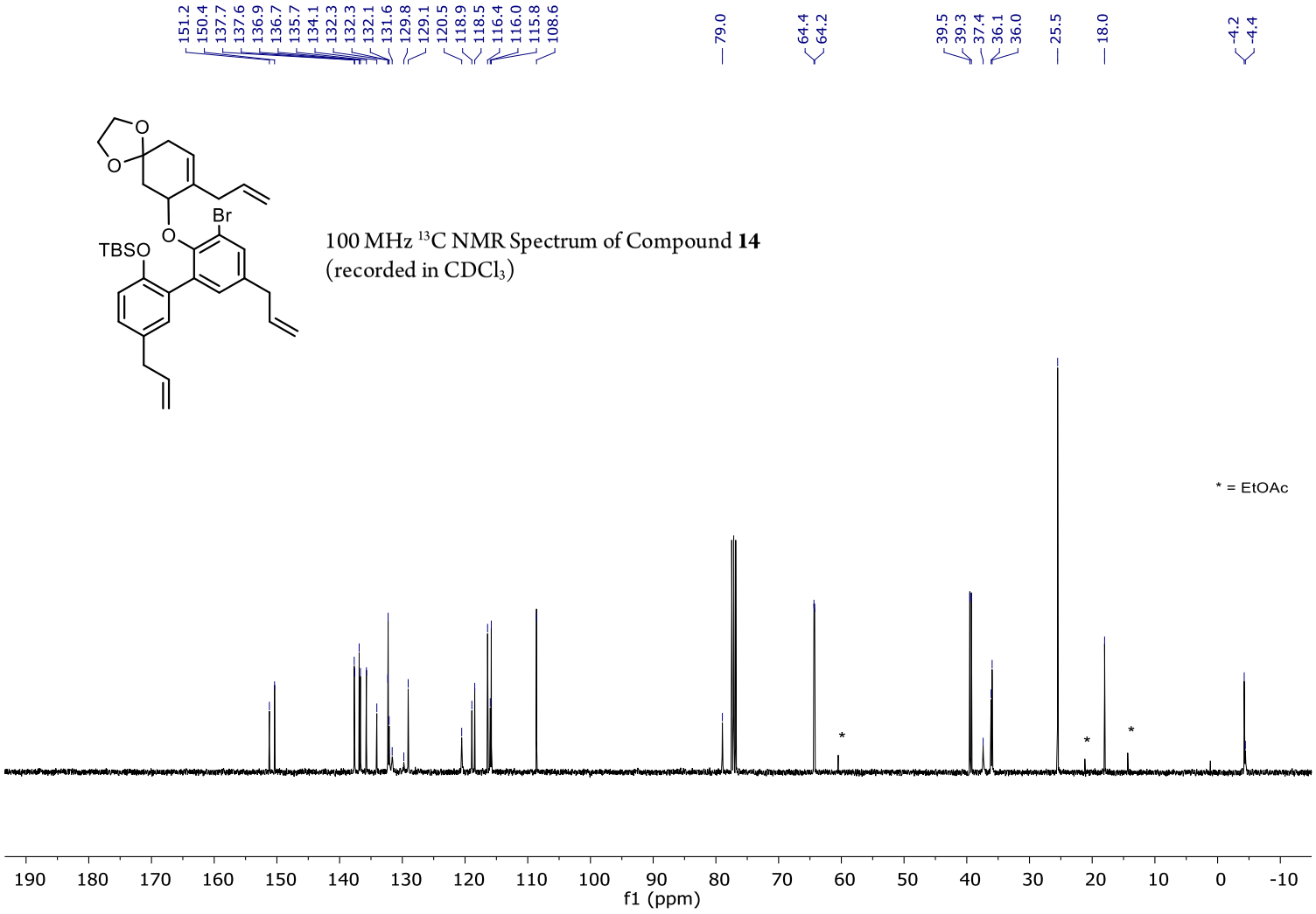


138.75
136.37
121.34
116.54
108.42
68.30
64.58
64.53
38.97
38.27
36.12

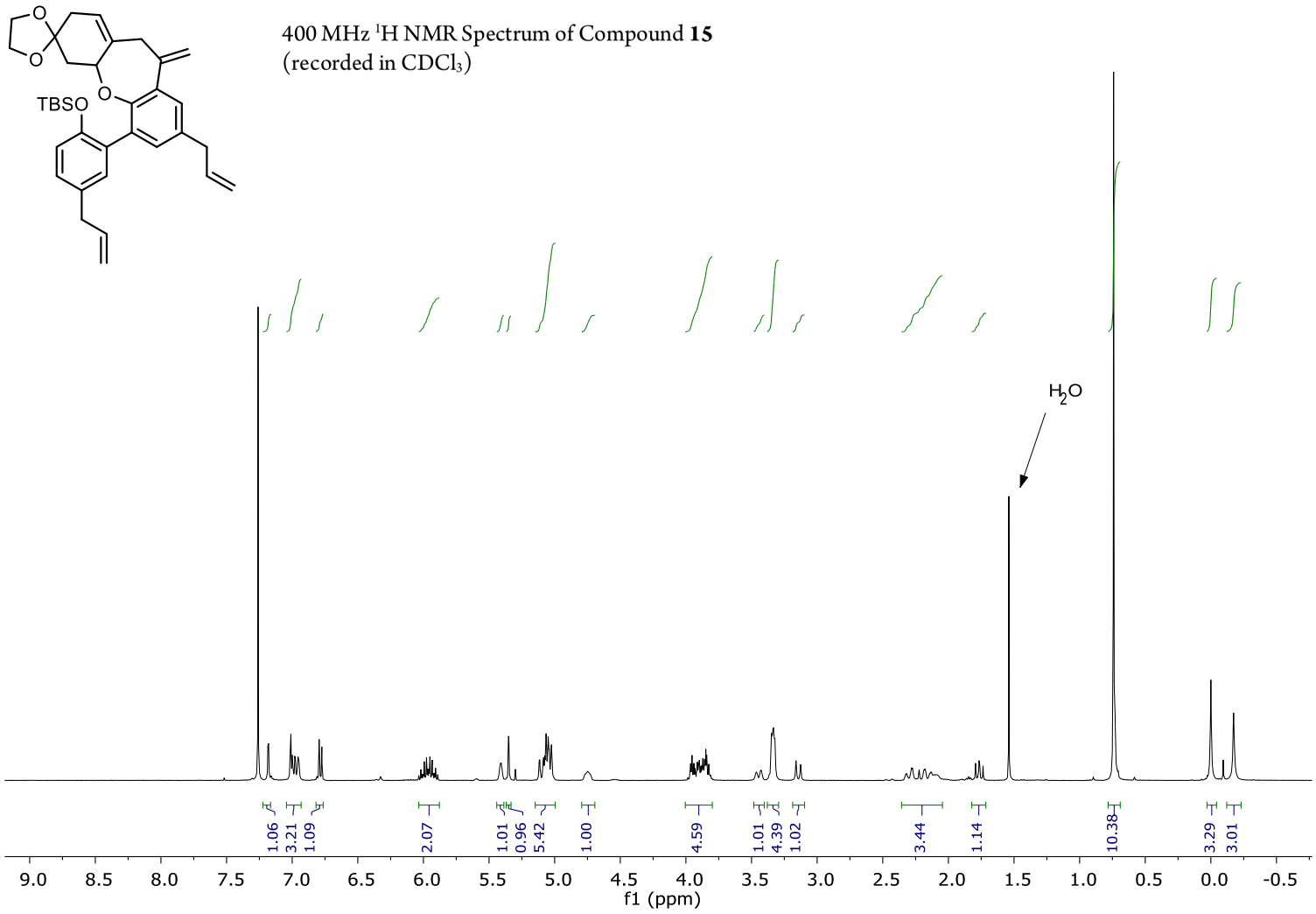
100 MHz ^{13}C NMR Spectrum of Compound **5**
(recorded in $CDCl_3$)



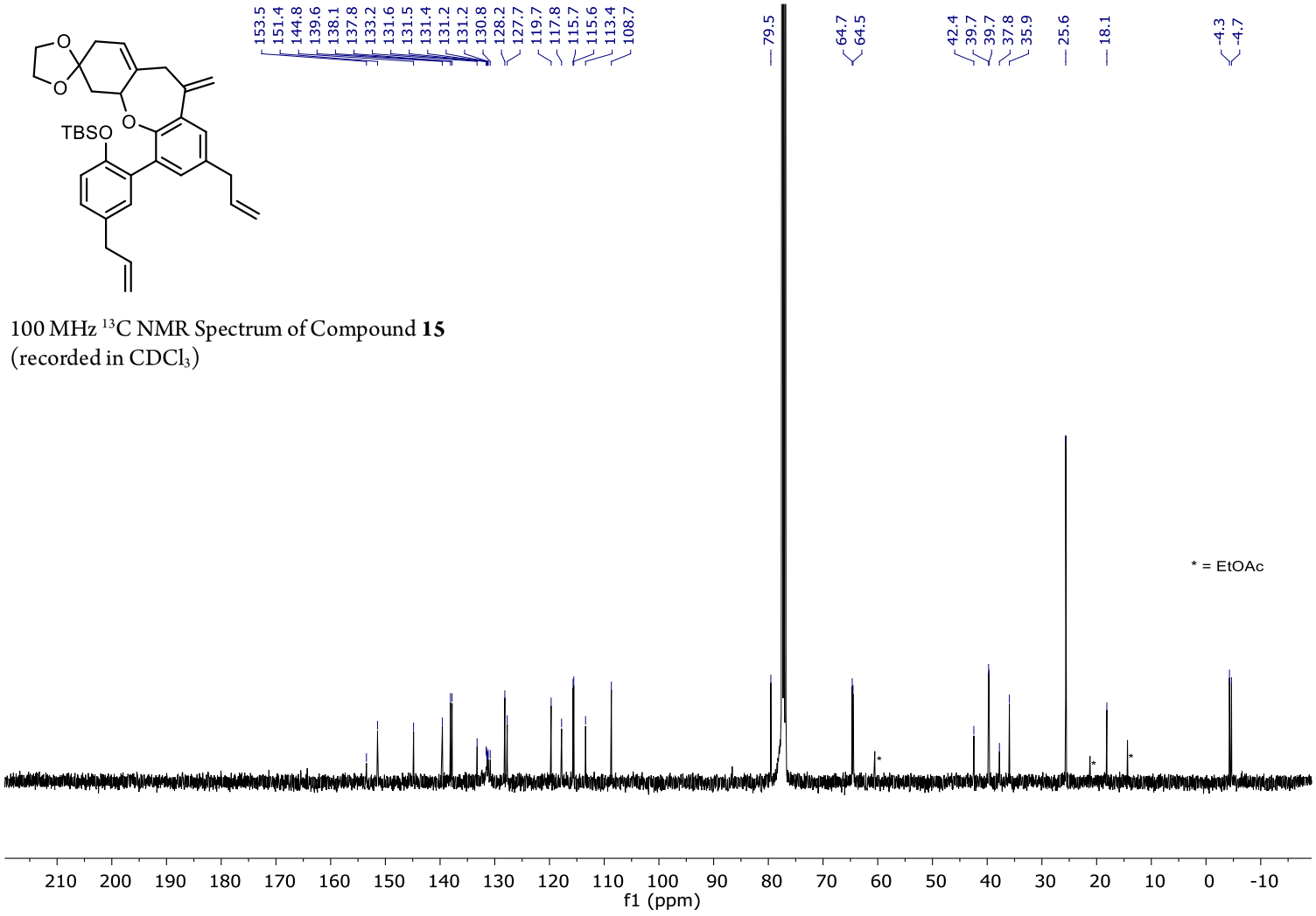

400 MHz ¹H NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)
TBSO
Br
O
O
O
impurity
0.99
1.11
1.99
0.99
2.98
1.00
6.17
0.96
4.06
4.12
0.98
0.88
1.00
1.02
1.96
9.18
5.89
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



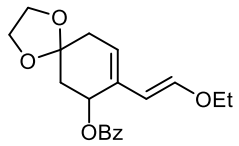
100 MHz ^{13}C NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)



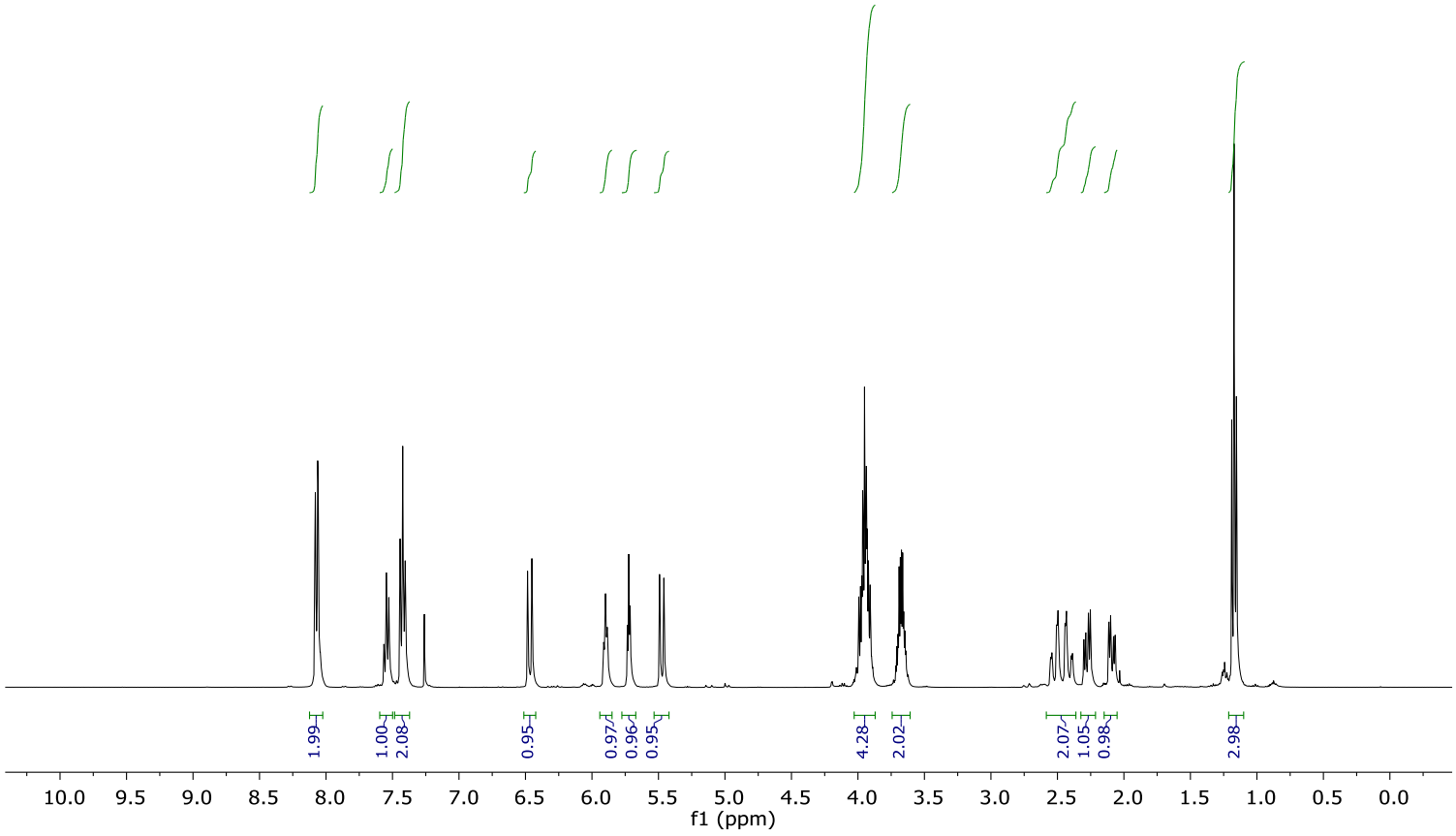
400 MHz ^{1}H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

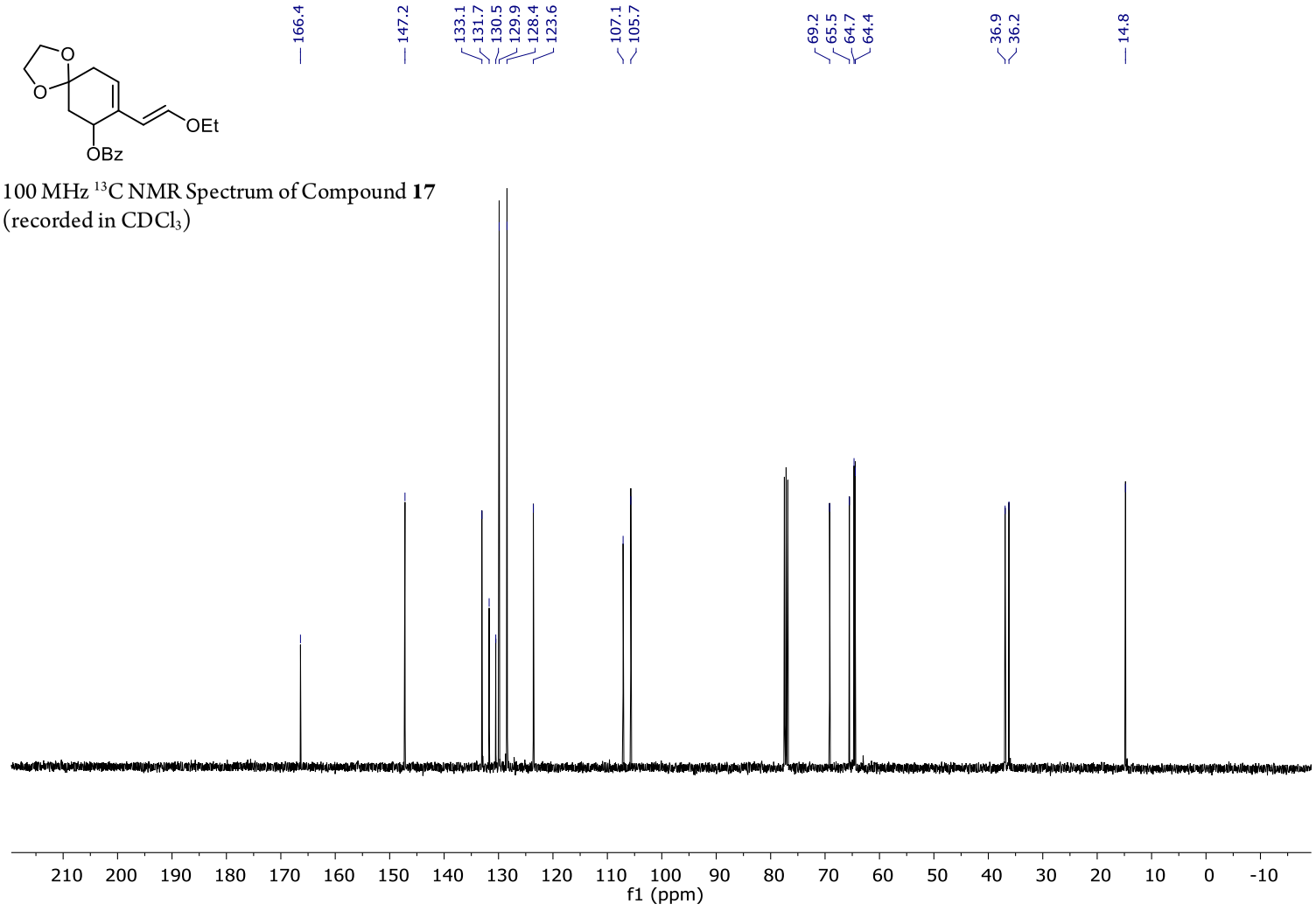


100 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

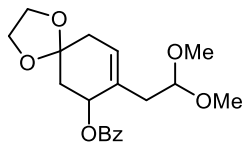


400 MHz ^{1}H NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

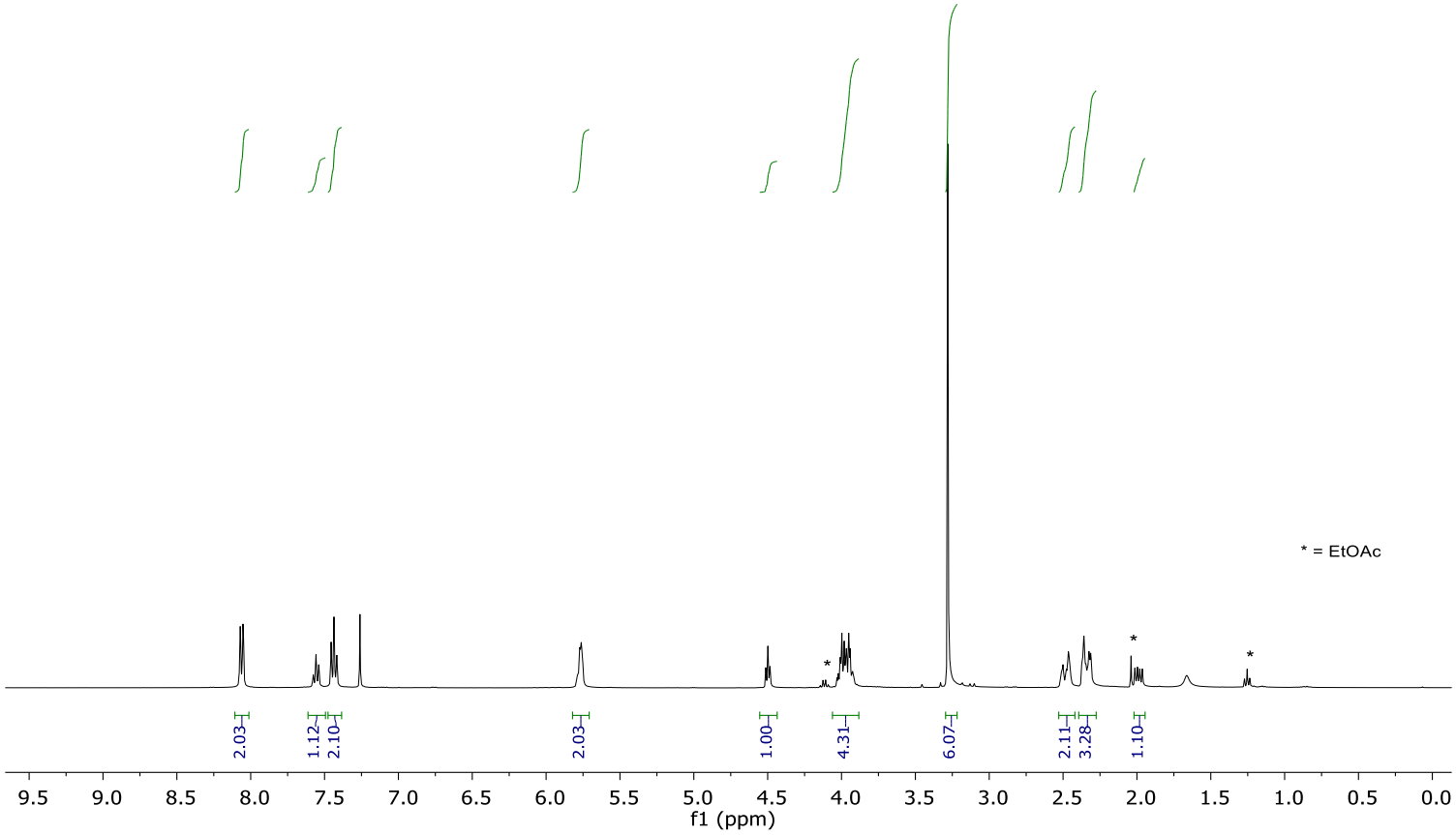


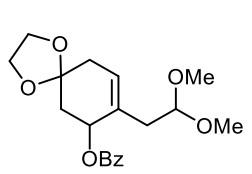


100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)

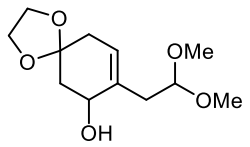


400 MHz ^{1}H NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)

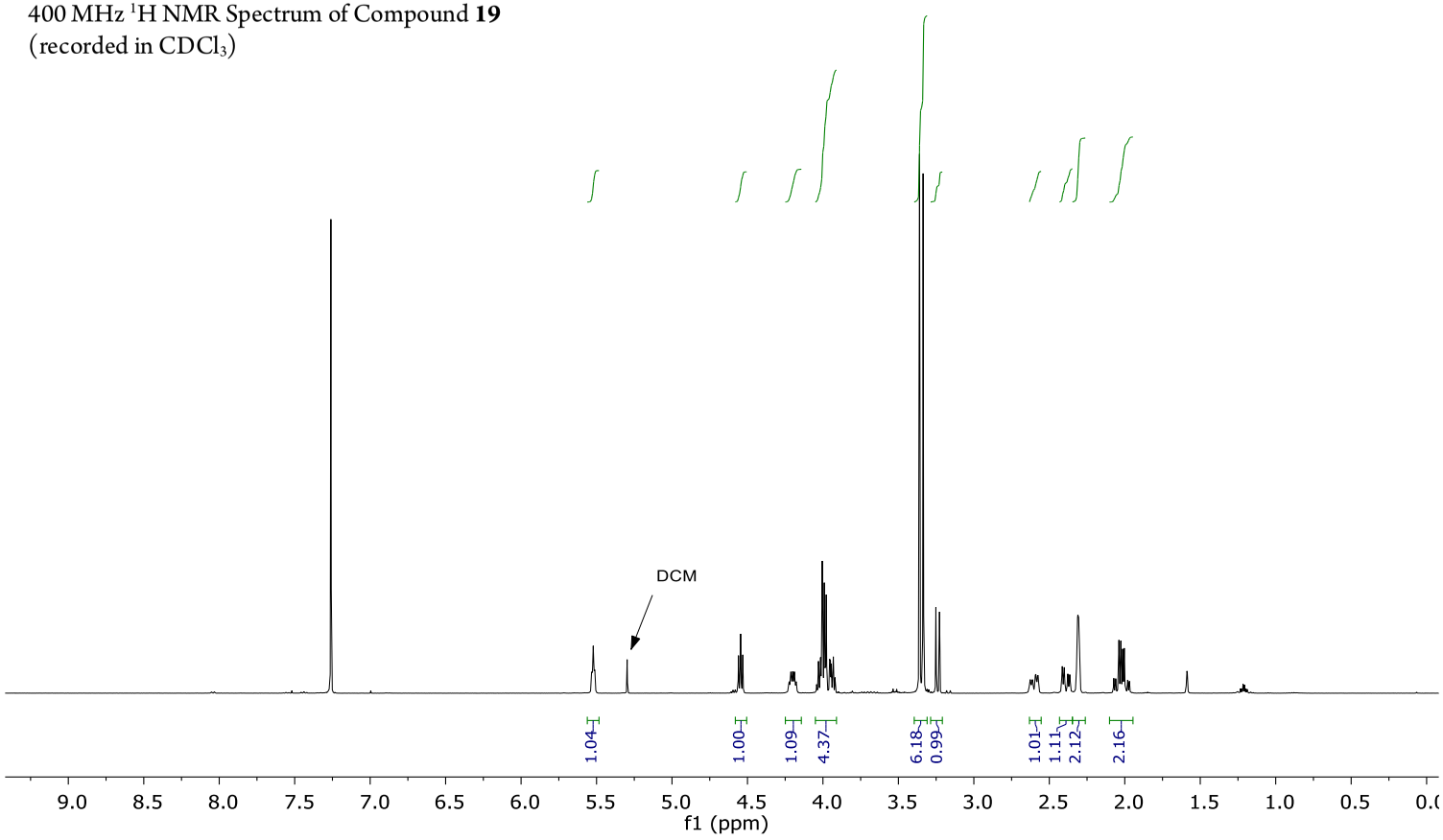


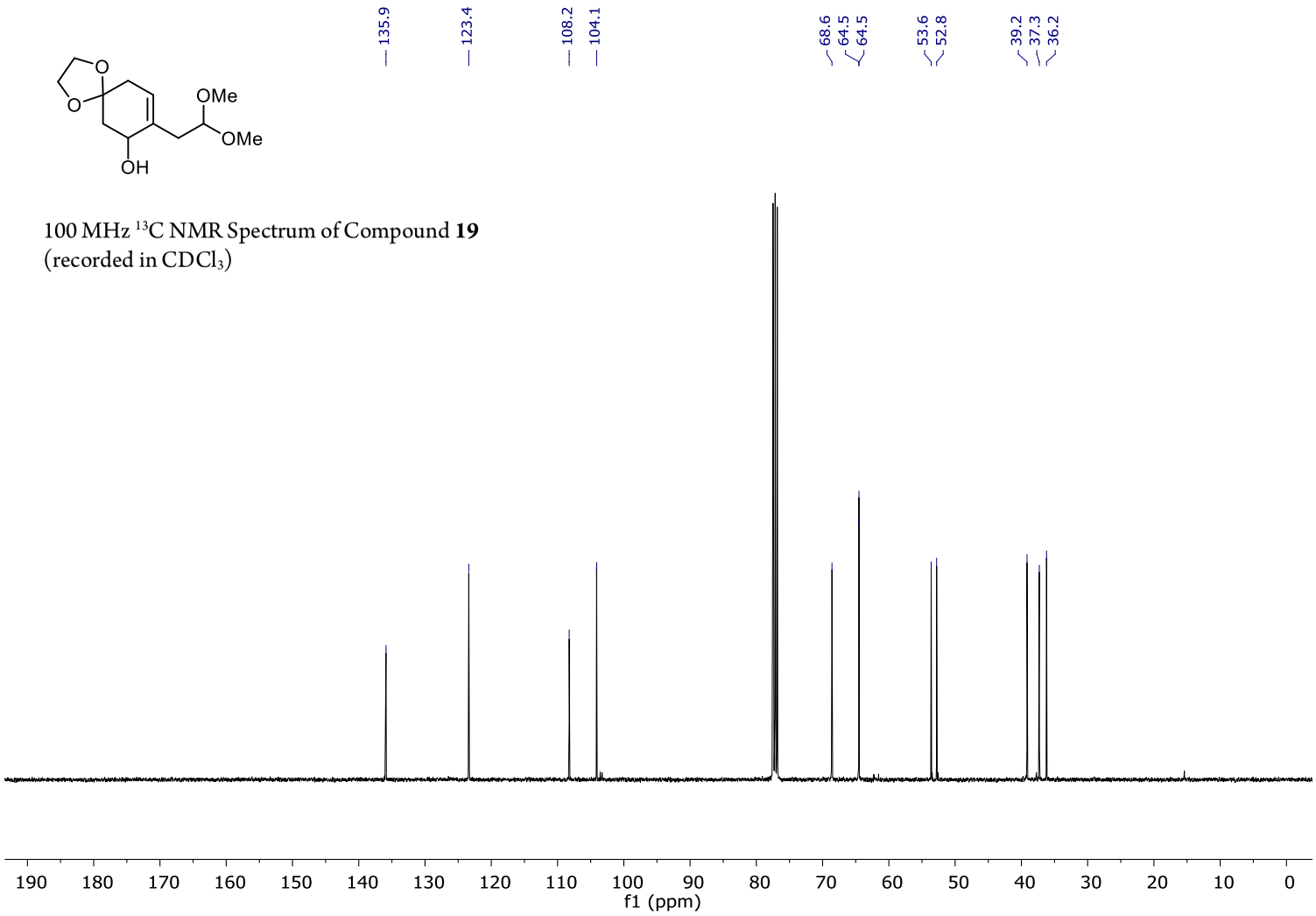


100 MHz ^{13}C NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)

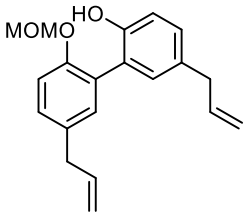


400 MHz ^{1}H NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)

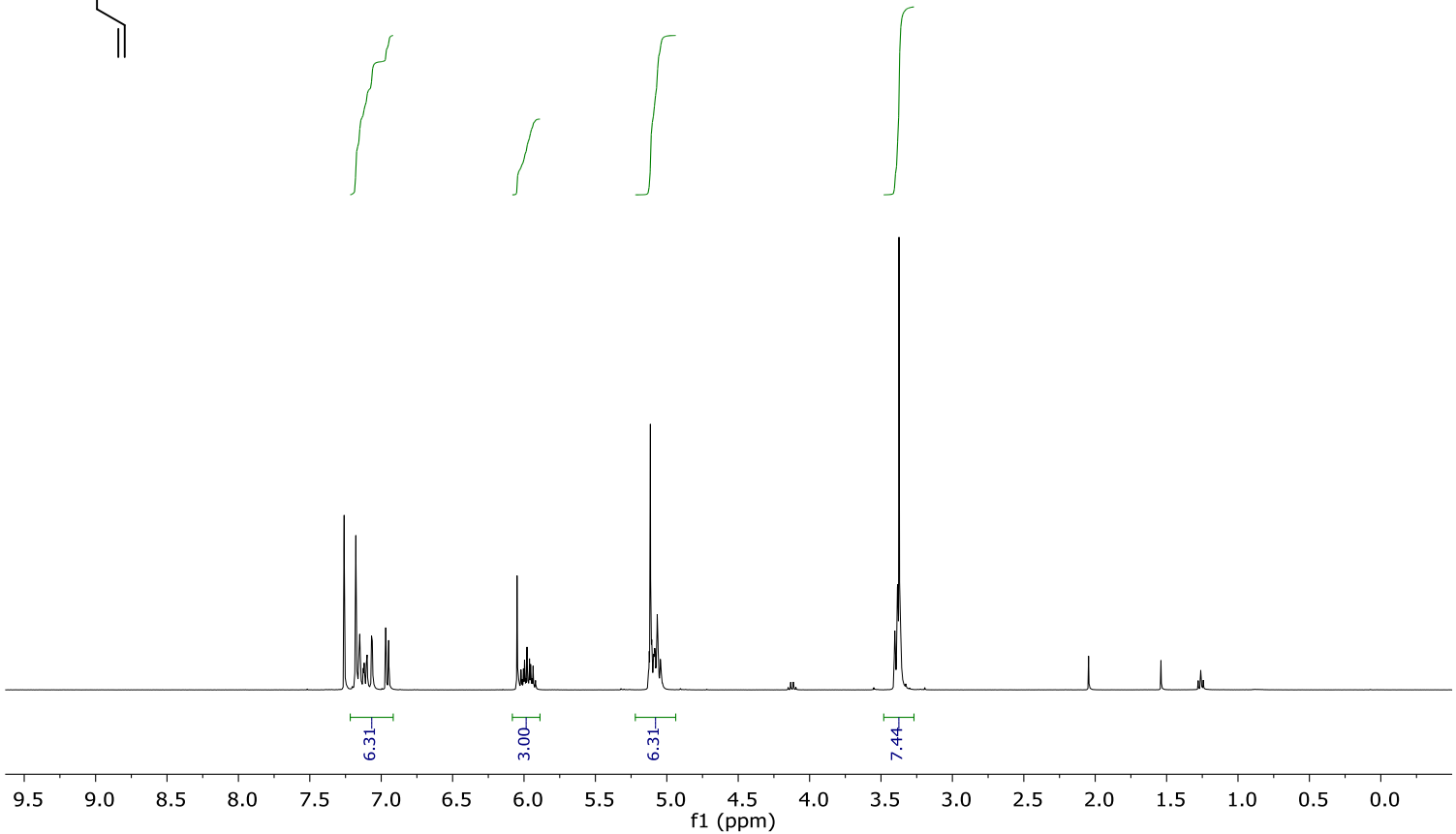


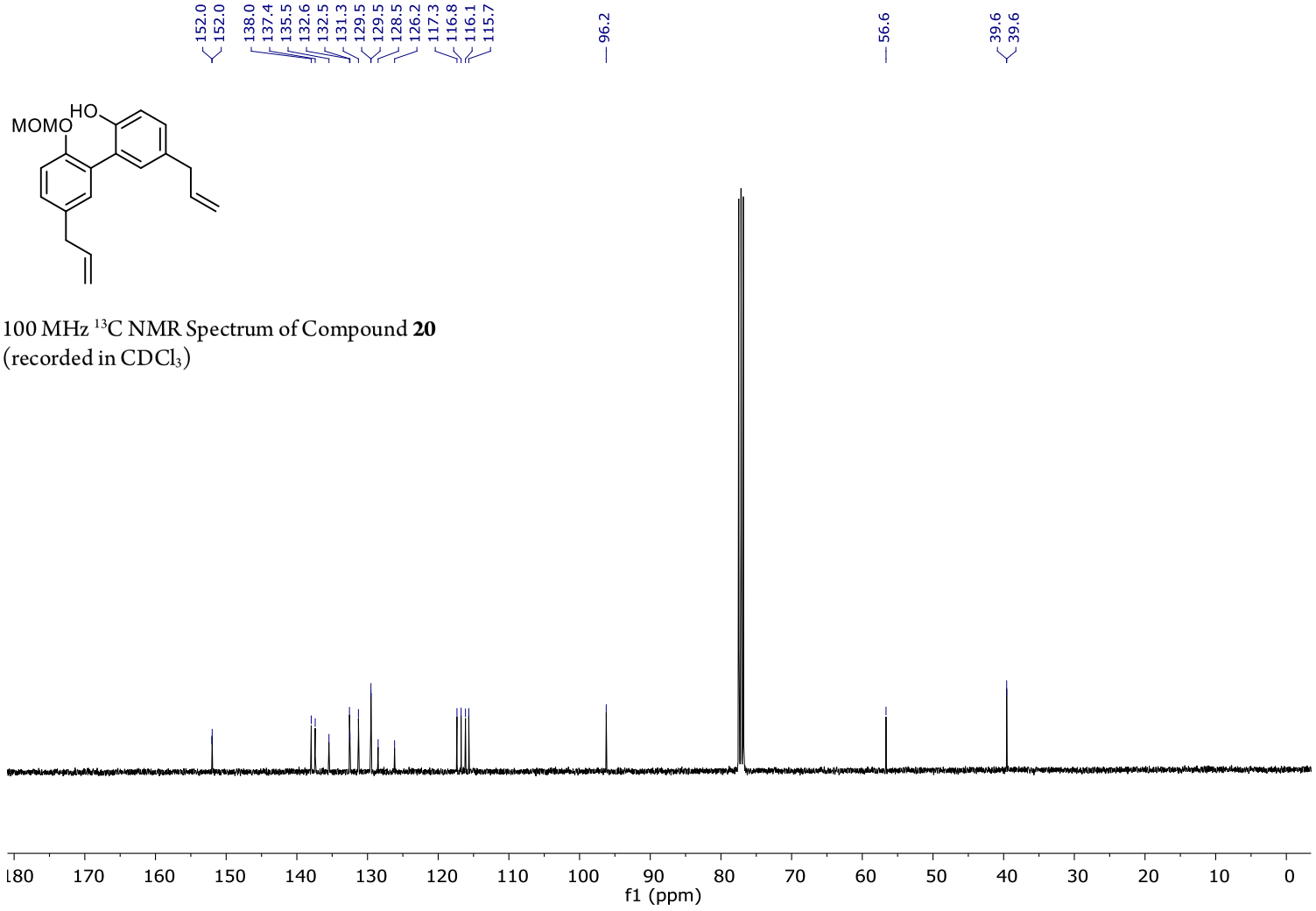


100 MHz ^{13}C NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)

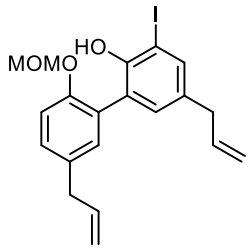


400 MHz ^{1}H NMR Spectrum of Compound **20**
(recorded in $CDCl_3$)

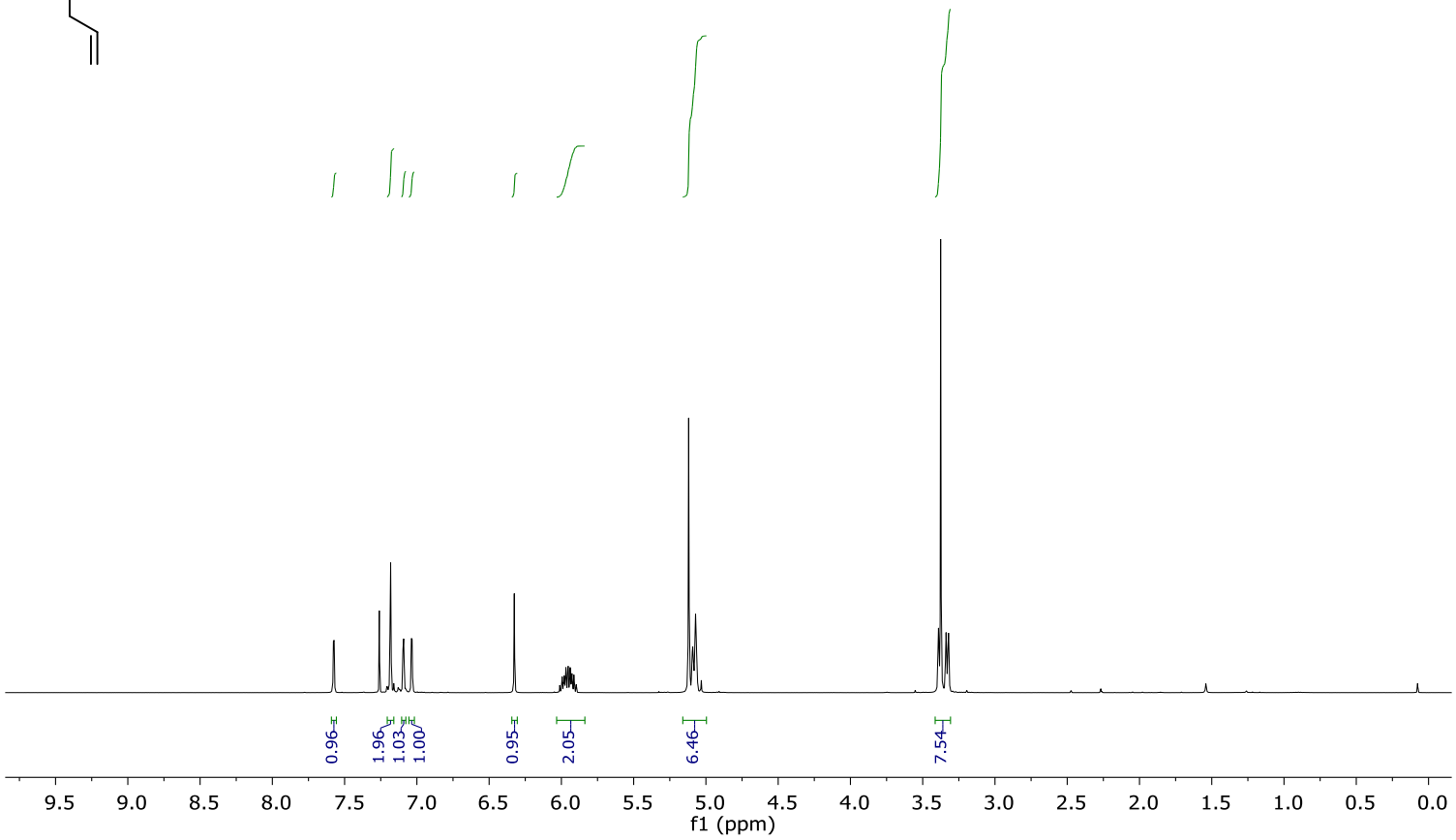


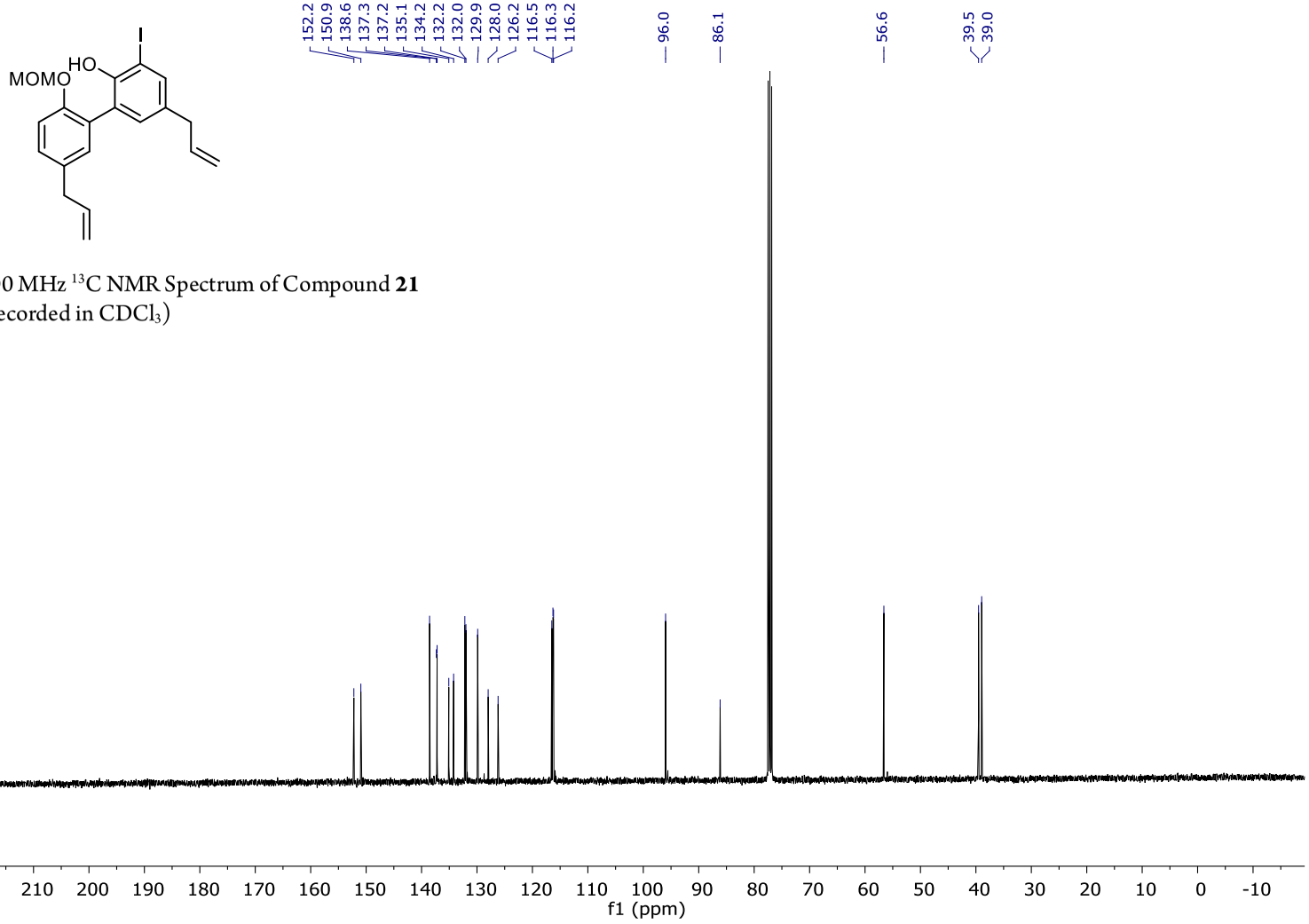


100 MHz ^{13}C NMR Spectrum of Compound **20**
(recorded in $CDCl_3$)

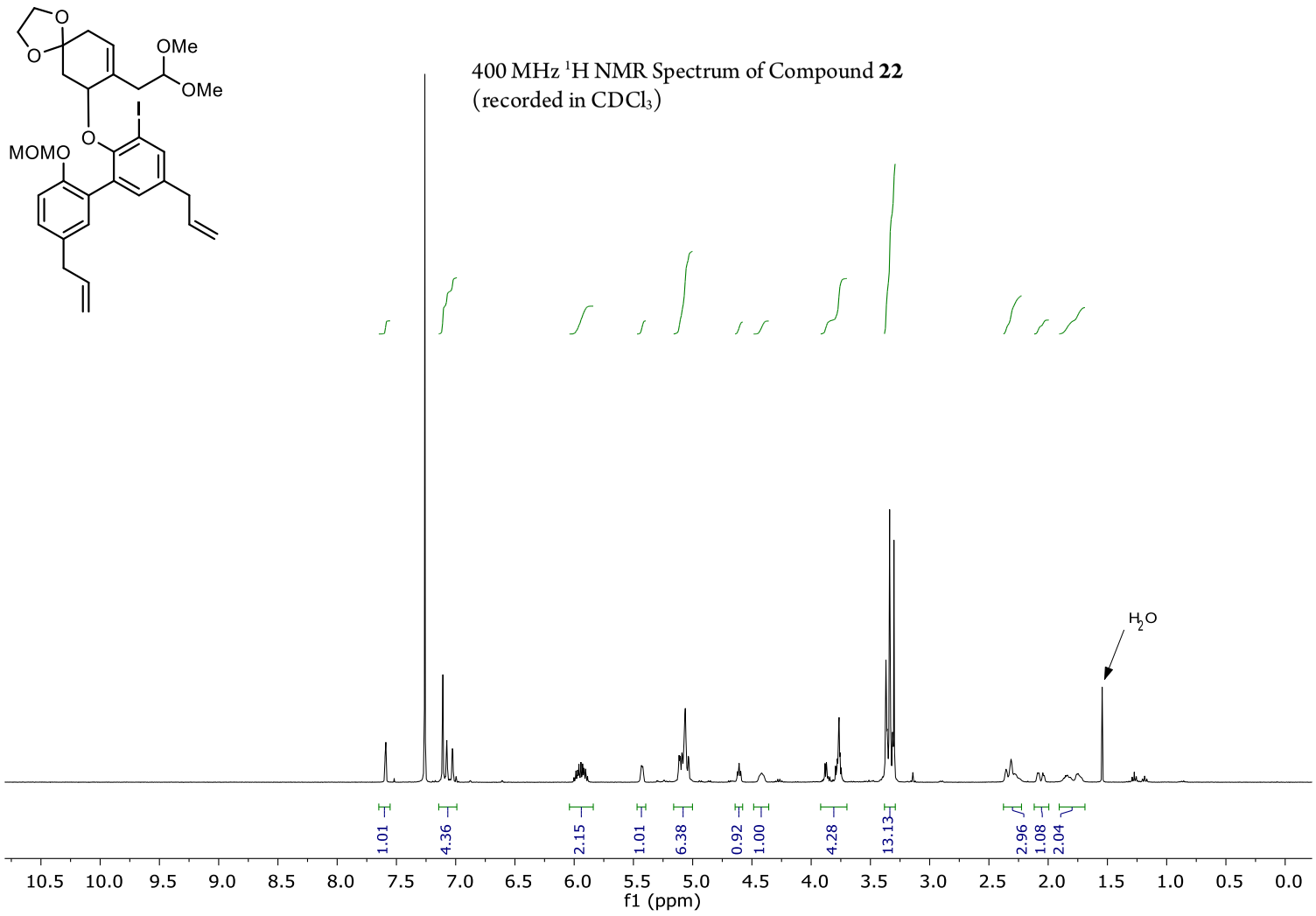


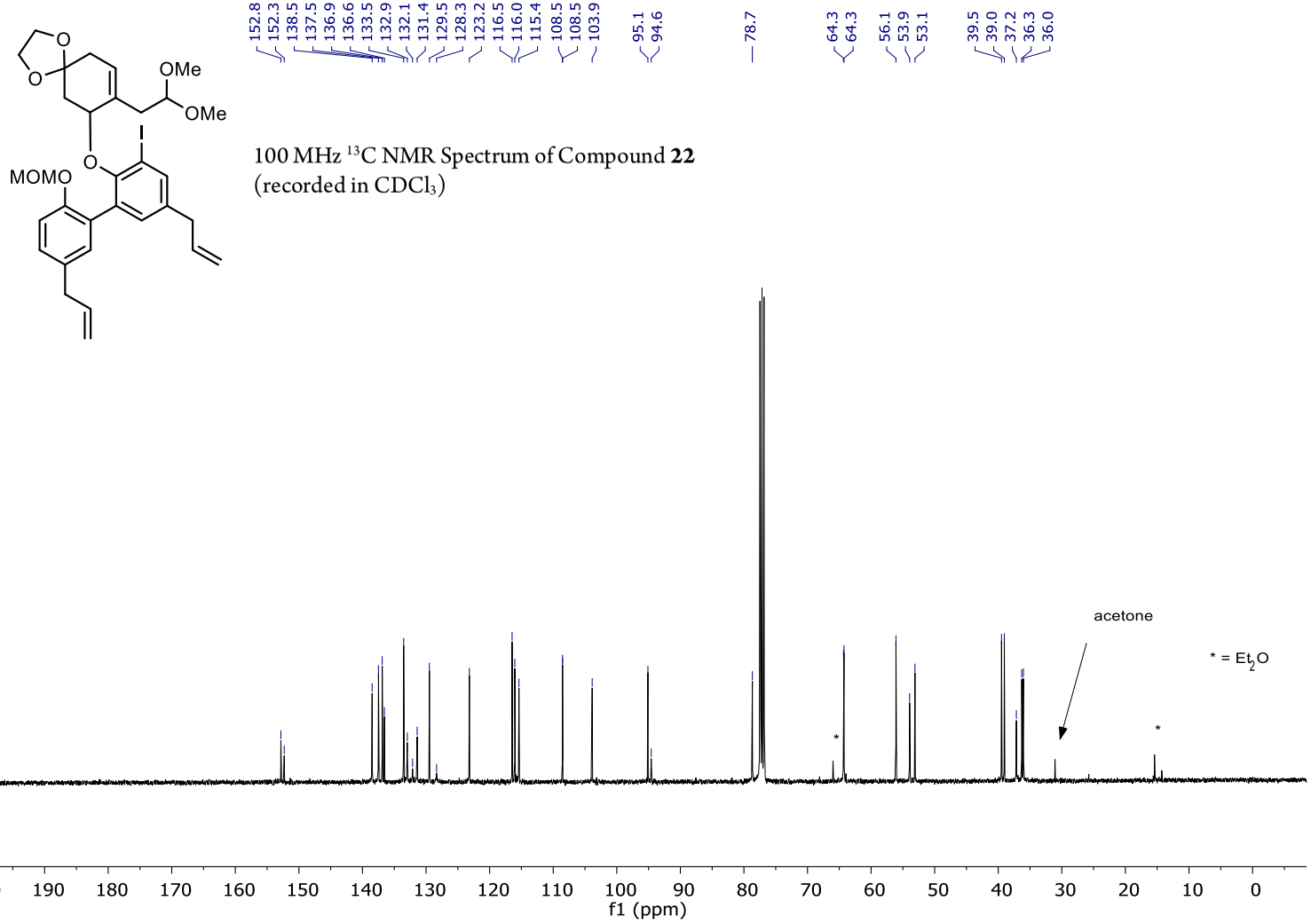
400 MHz ^{1}H NMR Spectrum of Compound **21**
(recorded in $CDCl_3$)



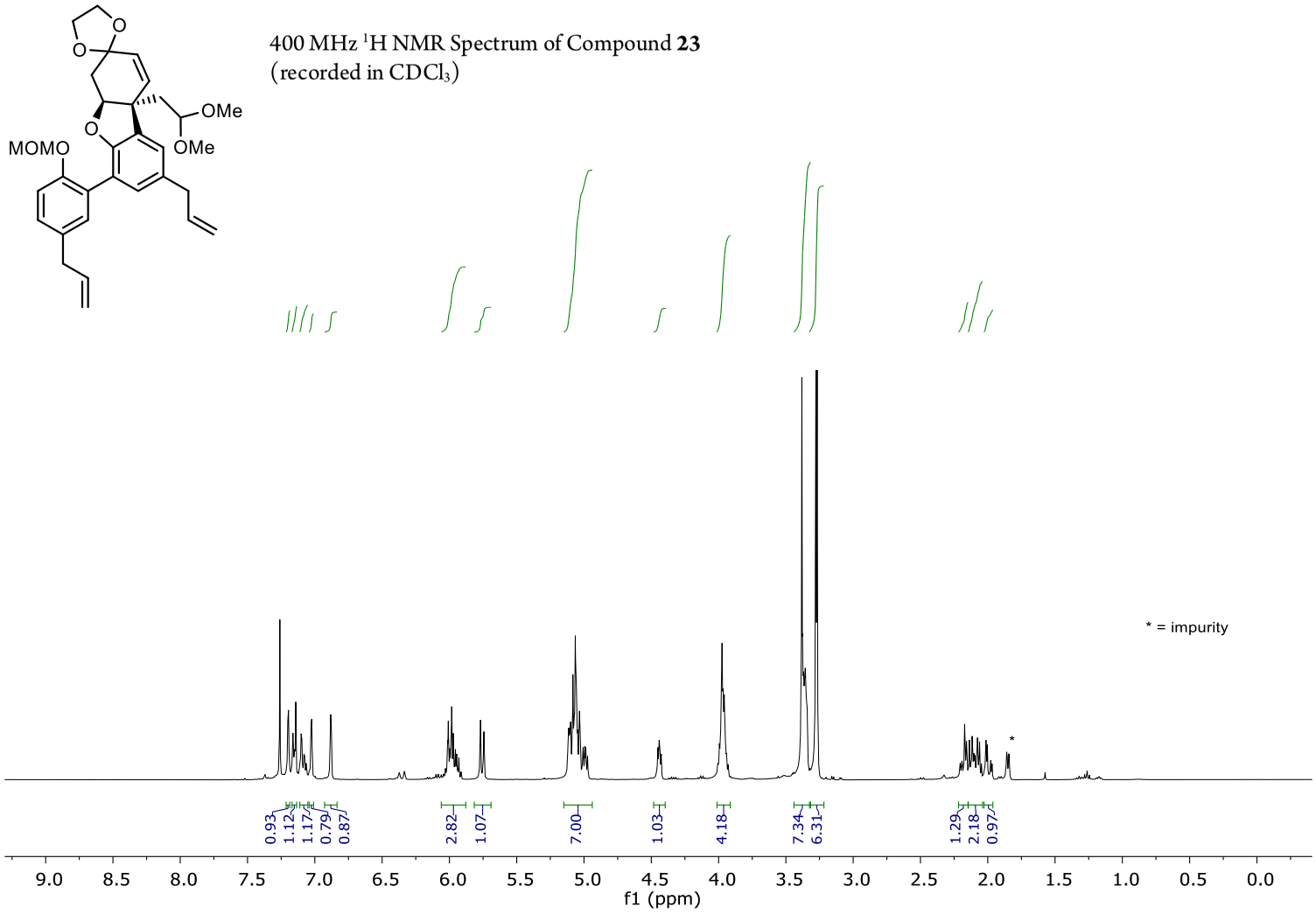


100 MHz ^{13}C NMR Spectrum of Compound **21**
(recorded in $CDCl_3$)

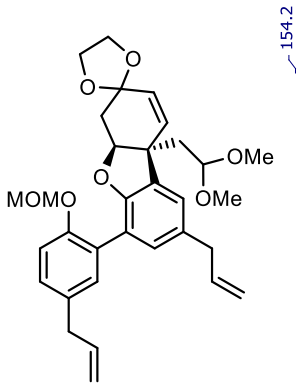

OMe
OMe
I
O
MOMO
400 MHz ^{1}H NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)
H_2O
1.01
4.36
2.15
1.01
6.38
0.92
1.00
4.28
13.13
2.96
1.08
2.04
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



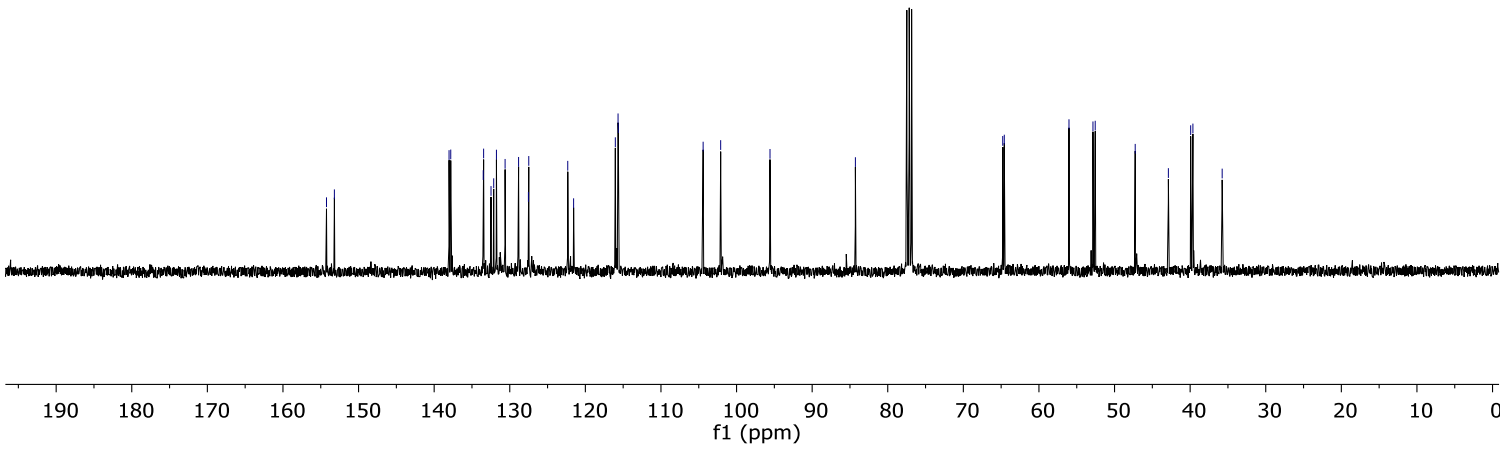
100 MHz ^{13}C NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)

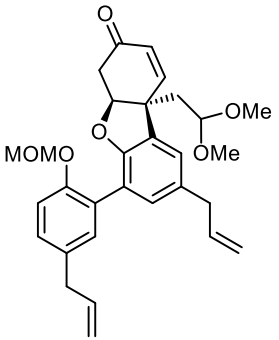


400 MHz ^{1}H NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)

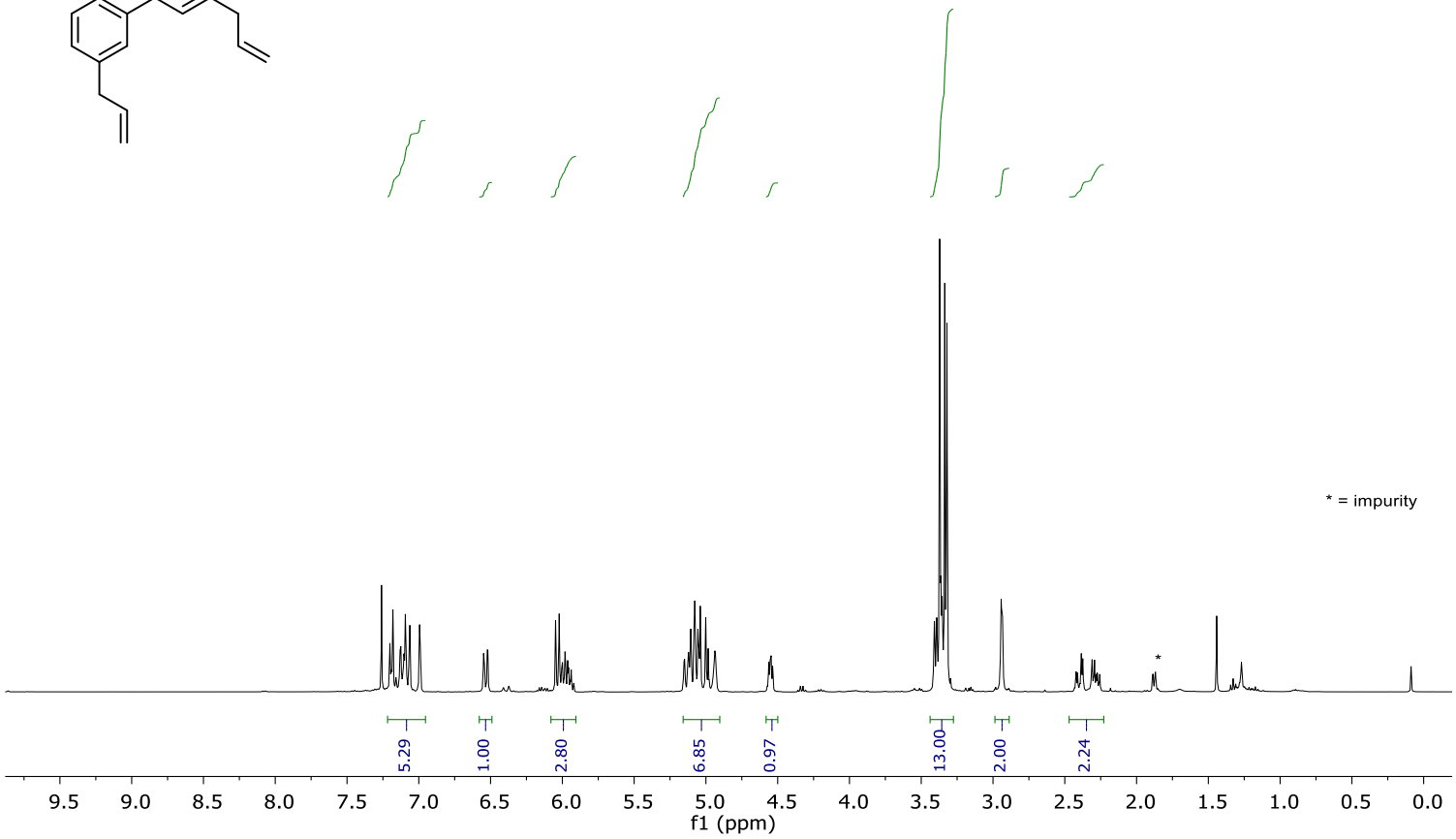


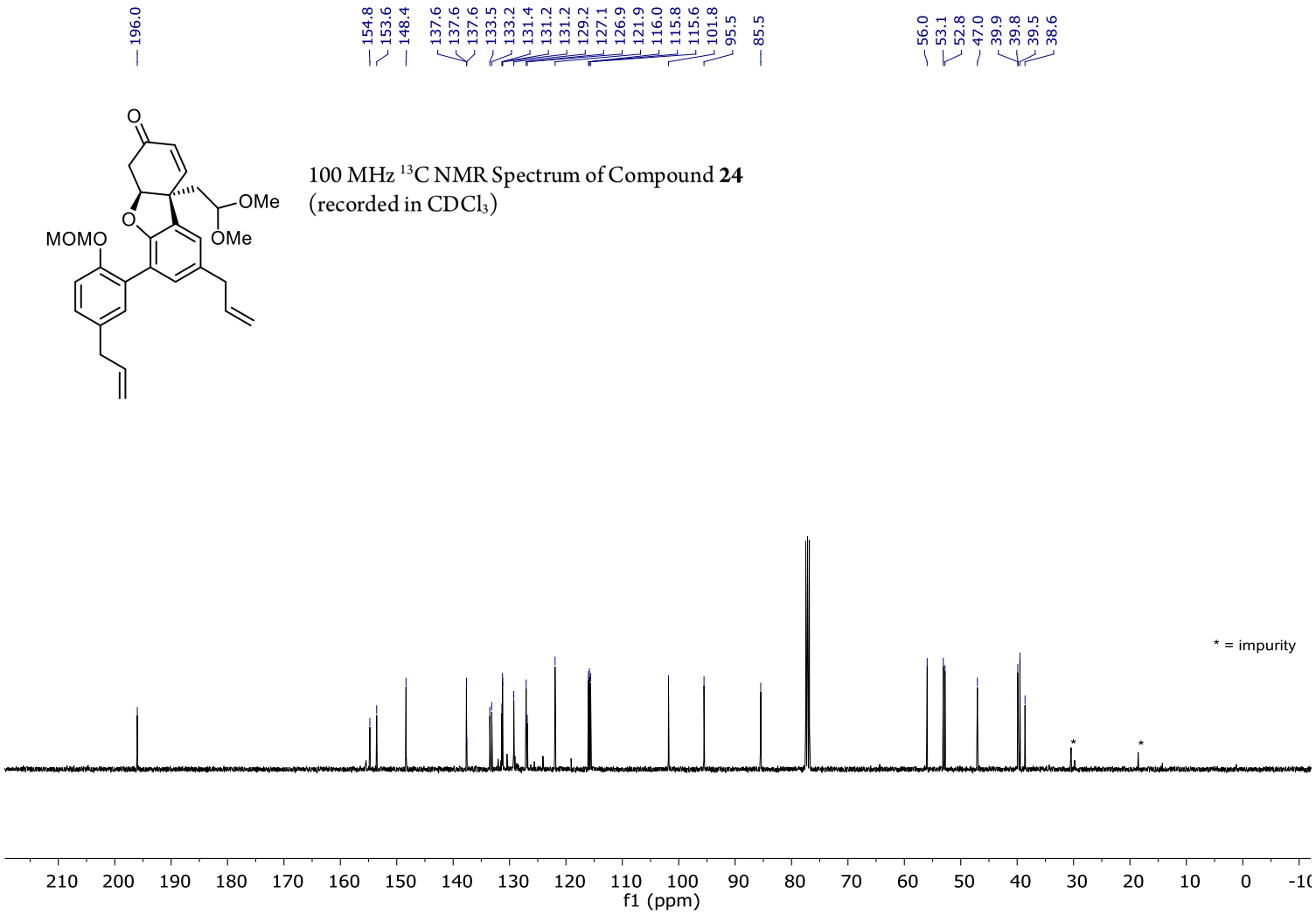
100 MHz ^{13}C NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)



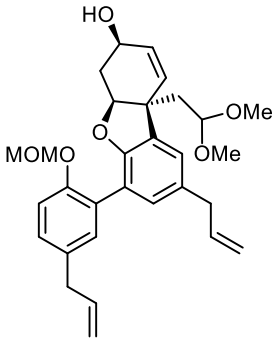


400 MHz ^{1}H NMR Spectrum of Compound **24**
(recorded in $CDCl_3$)

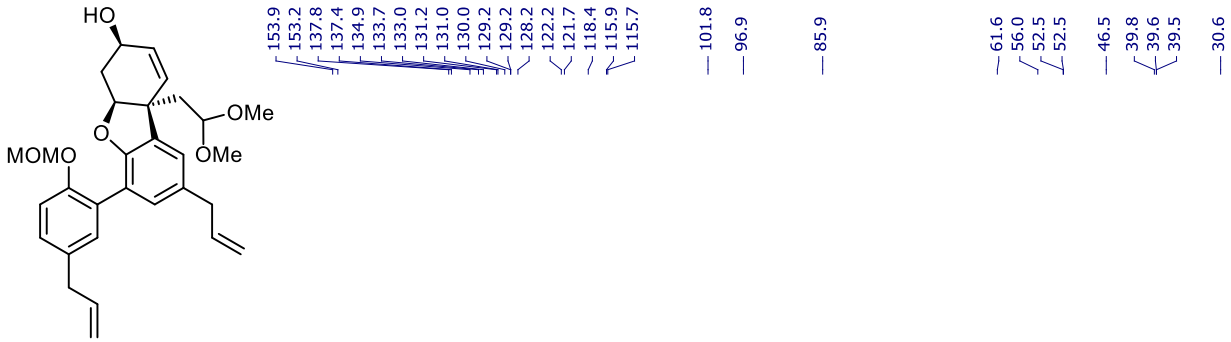




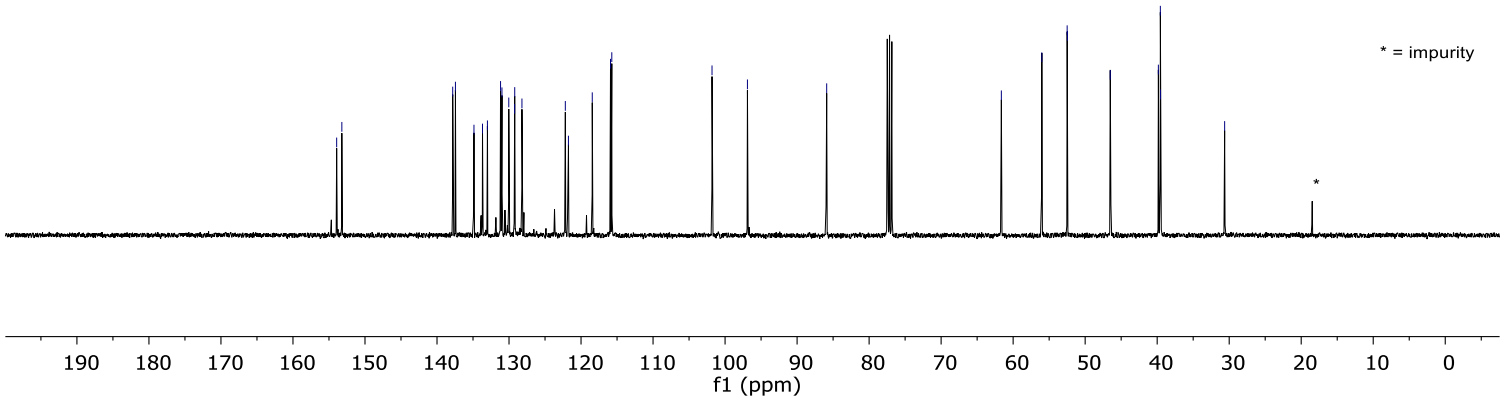
100 MHz ^{13}C NMR Spectrum of Compound **24**
(recorded in $CDCl_3$)

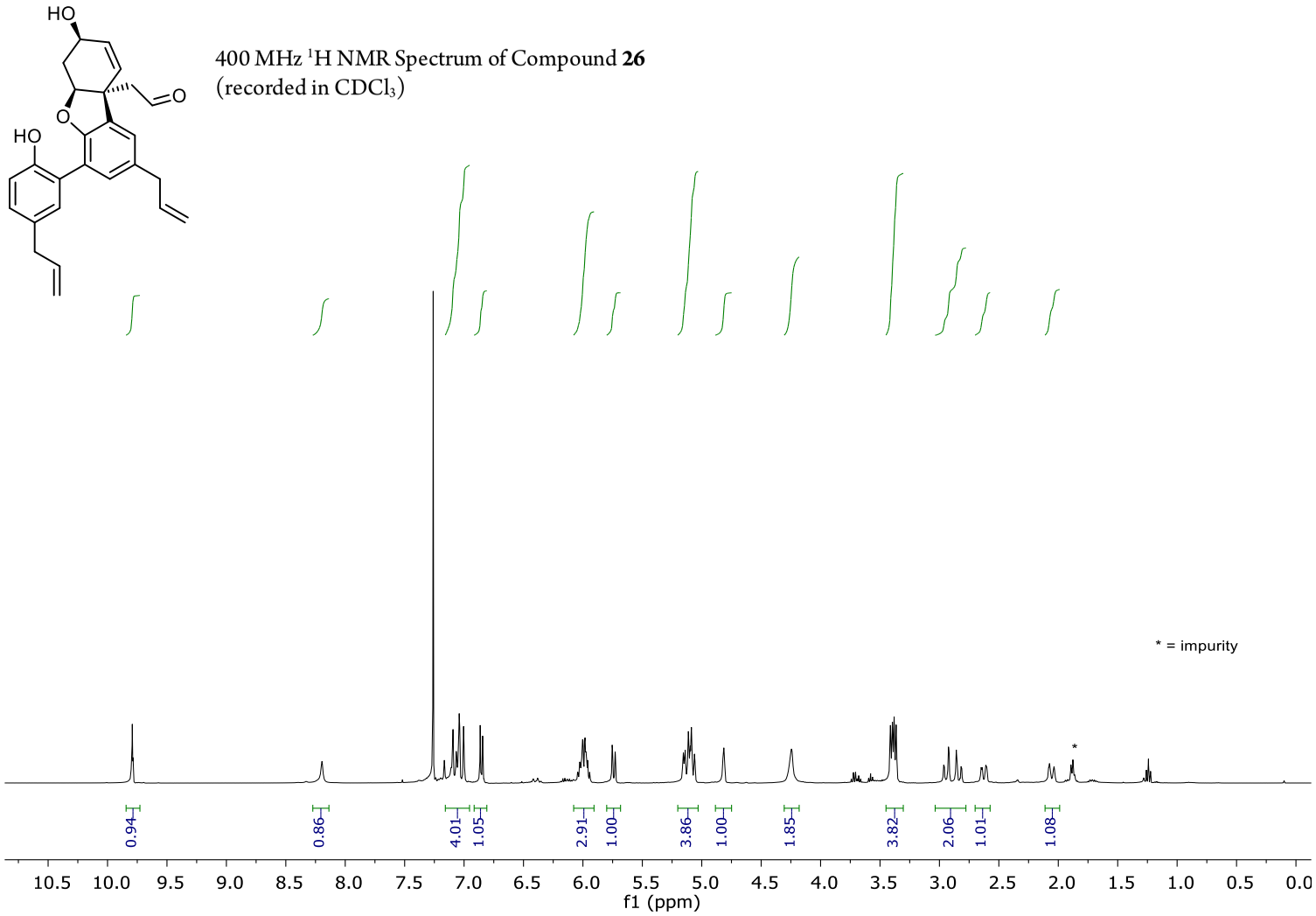


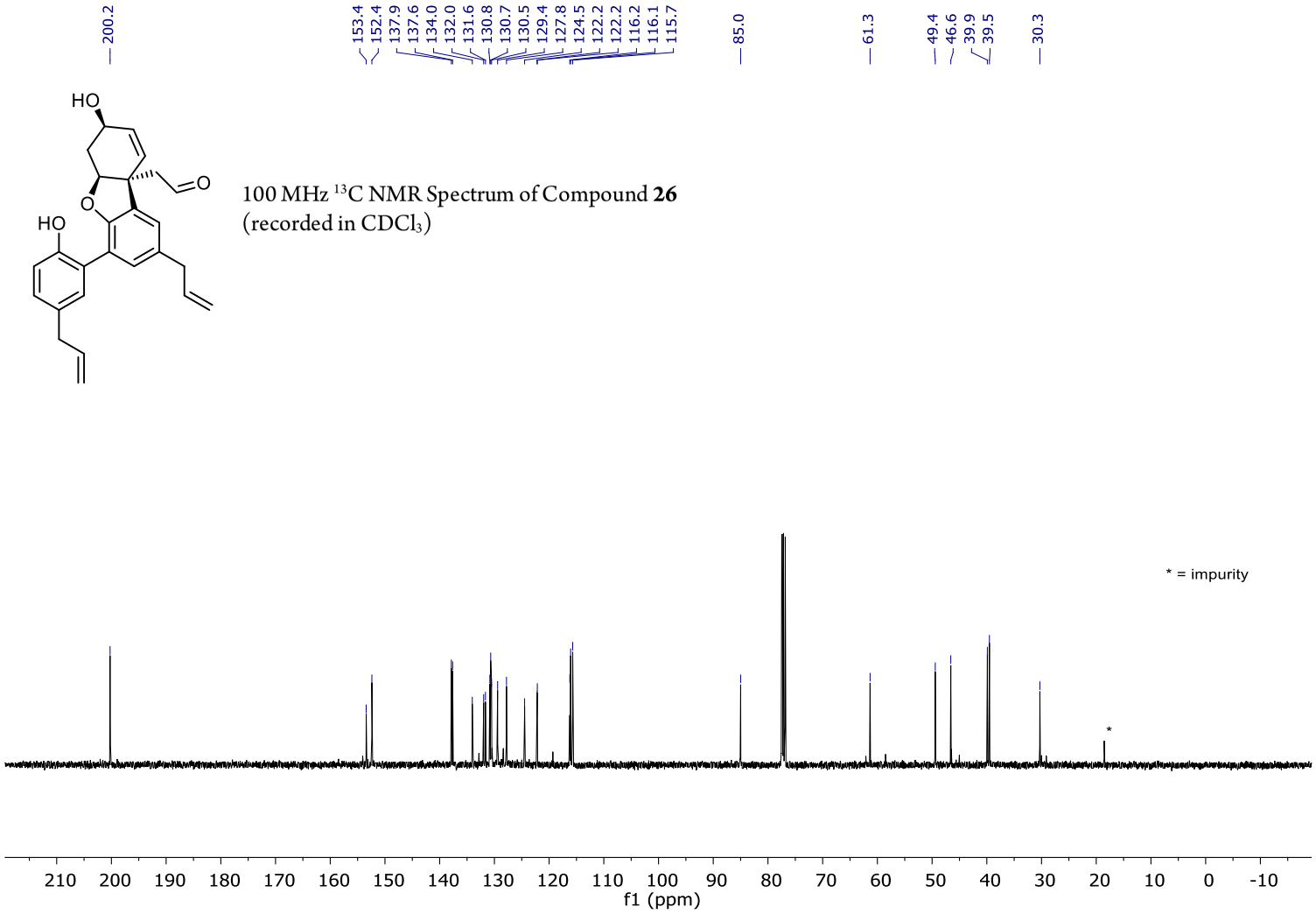
400 MHz ^{1}H NMR Spectrum of Compound **25**
(recorded in $CDCl_3$)



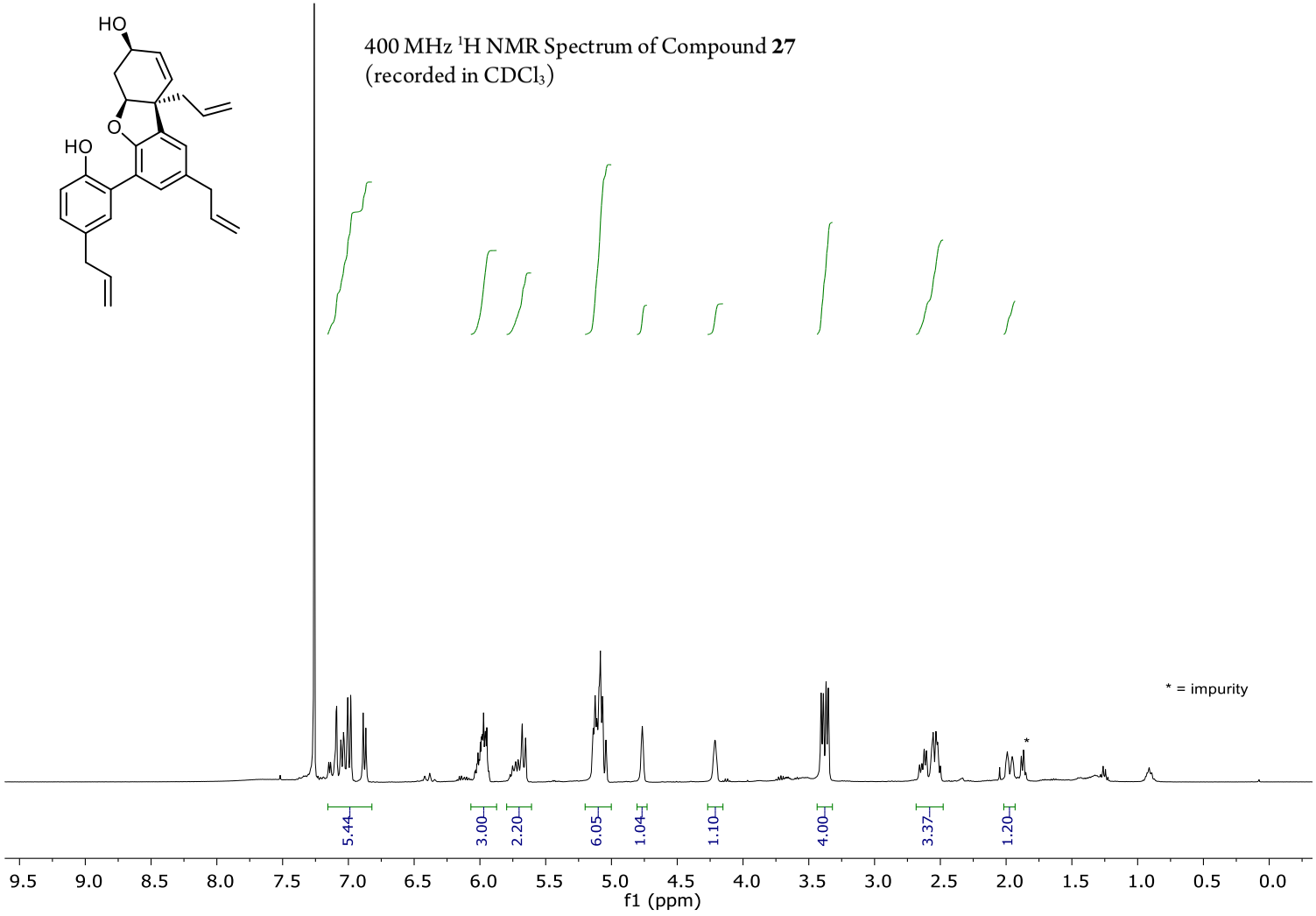
100 MHz ^{13}C NMR Spectrum of Compound **25**
(recorded in $CDCl_3$)

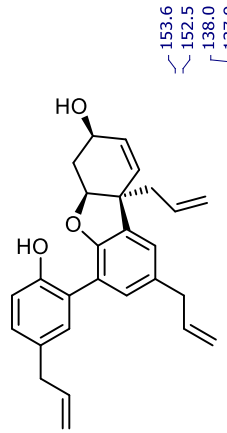



HO
O
HO
400 MHz ¹H NMR Spectrum of Compound 26
(recorded in CDCl₃)
* = impurity
0.94
0.86
4.01
1.05
2.91
1.00
3.86
1.00
1.85
3.82
2.06
1.01
1.08
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

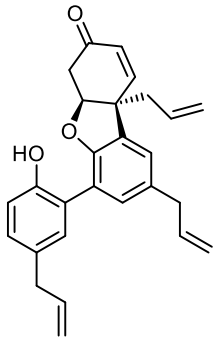


100 MHz ^{13}C NMR Spectrum of Compound **26**
(recorded in $CDCl_3$)

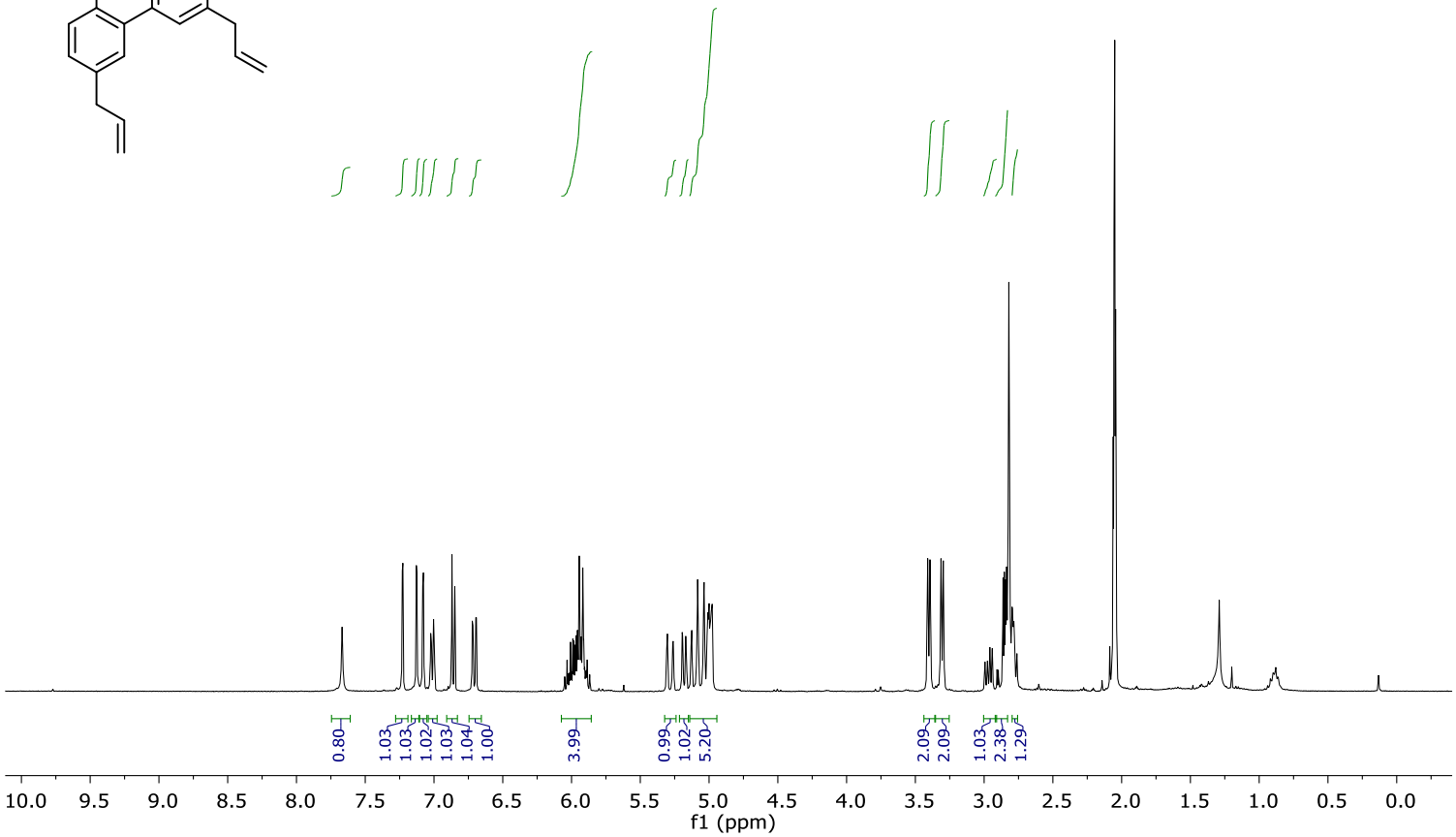

HO
HO
O
400 MHz ^{1}H NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)
* = impurity
5.44
3.00
2.20
6.05
1.04
1.10
4.00
3.37
1.20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

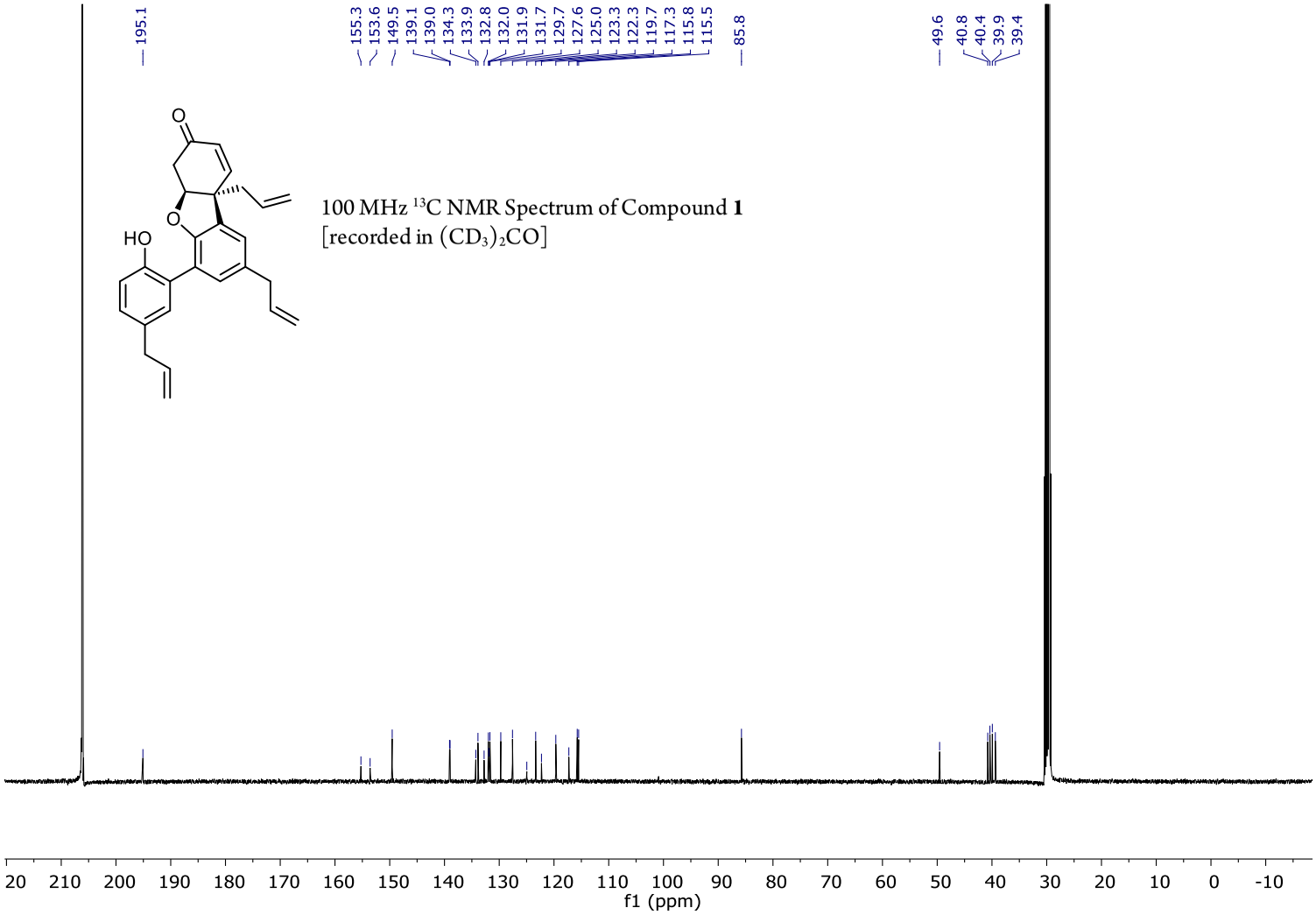


100 MHz ^{13}C NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)



400 MHz ^{1}H NMR Spectrum of Compound **1**
[recorded in $(CD_3)_2CO$]





100 MHz ^{13}C NMR Spectrum of Compound **1**
[recorded in $(CD_3)_2CO$]

Publication Five

An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

Jeremy Nugent and Martin G. Banwell

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An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

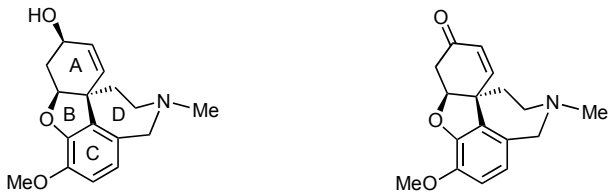
Jeremy Nugent[a] and Martin G. Banwell[a]*

Keywords: galanthamine, Heck cyclisation, Mitsunobu reaction, narwedine, reductive amination

Narwedine, an immediate precursor to the therapeutically valuable alkaloid (–)-galanthamine, has been synthesised by engaging an iodinated isovanillin derivative in an intermolecular Mitsunobu reaction with a 2-cyclohexen-1-ol derivative. The resulting aryl ether participated in a very efficient intramolecular Heck reaction to give, after hydrolysis of the primary cyclisation product, a tetracyclic lactol. This last compound is an advanced intermediate associated with the Magnus synthesis of narwedine and could be elaborated to narwedine itself under reductive amination conditions. As a result, an eleven-step synthesis of galanthamine has been established.

Introduction

(–)-Galanthamine (**1**, a.k.a. galantamine) is a key alkaloid produced by a number of plants including the common snowdrop *(Galanthus nivalis*), the related species *Galanthus woronowii* and the red spider lily (*Lycoris radiate*).[1] In some instances it co-occurs with normally trace amounts of (–)-narwedine (**2**), the *N*-demethyl analogue of which is the likely biogenetic precursor (to **1**).[2] Originally galanthamine was used as a treatment for certain paralytic and neuropathic conditions.[1] However, the discovery that it is an orally available and reversible inhibitor of acetylcholine esterase (AChE) capable of crossing the blood/brain barrier has led to its use in the symptomatic treatment of mild to moderate forms of Alzheimer's Disease (AD),[1,3] the leading cause of dementia.[4] Given the projections for the increase in the incidence of AD among ageing populations in more developed countries, the demand for reliable supplies of galanthamine is almost certain to increase.[5] At the present time it appears that the required quantities of compound **1** are obtained from a combination of cultivation (and extraction) of the producing plants[6] and by total synthesis.[7] While the precise contributions that each of these make to the total supply chain remains unclear, the continuing focus on developing more productive cultivars and more effective growing methods[6] suggest the synthetic approach is the less significant one.



1 **2**

Figure 1: The structures of (–)-galanthamine (**1**) and (–)-narwedine (**2**).

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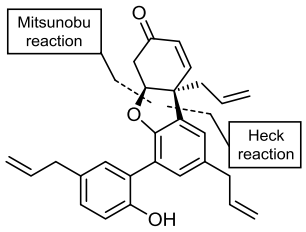
Supporting information for this article is available on the WWW under http://dx.doi.org…

This situation is a reflection, to some extent at least, of the challenges that remain in assembling the tetracyclic framework of galanthamine, especially its associated quaternary carbon center. The original synthesis of the alkaloid, reported by Barton and Kirby in 1962,[8] was a biomimetic one involving a low-yielding, intramolecular oxidative phenolic coupling leading to racemic narwedine [(±)-(**2**)] that can be diastereoselectively reduced to the congener **1** under a variety of conditions. A significant development in the area was the discovery that racemic narwedine can, through a fractional crystallisation process coupled with reversible E1cB/hetero-Michael addition reactions, be converted, in its entirety, into either of its constituent enantiomers using "seeding" quantities of either (+)- or (–)-galanthamine.[9] A modified version of the Barton/Kirby process, when linked with the capacity for the dynamic kinetic resolution process just mentioned, allowed Fröhlich and Jordis to develop a pilot-plant scale synthesis of (–)-narwedine that now seems to be part of the galanthamine supply chain.[7] In 2009 Magnus and co-workers reported[10] using an intramolecular alkylation of a phenol derivative as the basis for establishing a seven-step synthesis of racemic narwedine and seemingly representing the shortest/most efficient route to galanthamine described thus far. In 2000 Trost and Toste exploited an intramolecular Heck reaction for assembling the ABC-ring system and the associated quaternary carbon centre of galanthamine.[11] This work inspired a number of related approaches.[12] Other ingenious ones have also emerged in the intervening period.[13,14]

As part of our ongoing interest in developing new routes to galanthamine[13b] we have described two total syntheses to date, one involving a Pd-catalysed intramolecular Alder-ene reaction followed by a Diels-Alder cycloaddition (the second step serving to effect the *de novo* assembly of the aromatic A-ring)[13a] and the other being a chemoenzymatic approach.[15] Recently, and as part of a continuing program to identify new AChE inhibitors,[16] we reported[17] the first synthesis of the sesquineolignan simonsol C (**3**), a compound that bears a strong structural resemblance to narwedine. Accordingly, we sought to apply the key steps used in the assembly of the former compound, namely an intermolecular Mitsunobu reaction followed by an intramolecular Heck reaction, to a synthesis of the racemic modification of narwedine (**2**).[18] The successful outcome of such work is detailed below.



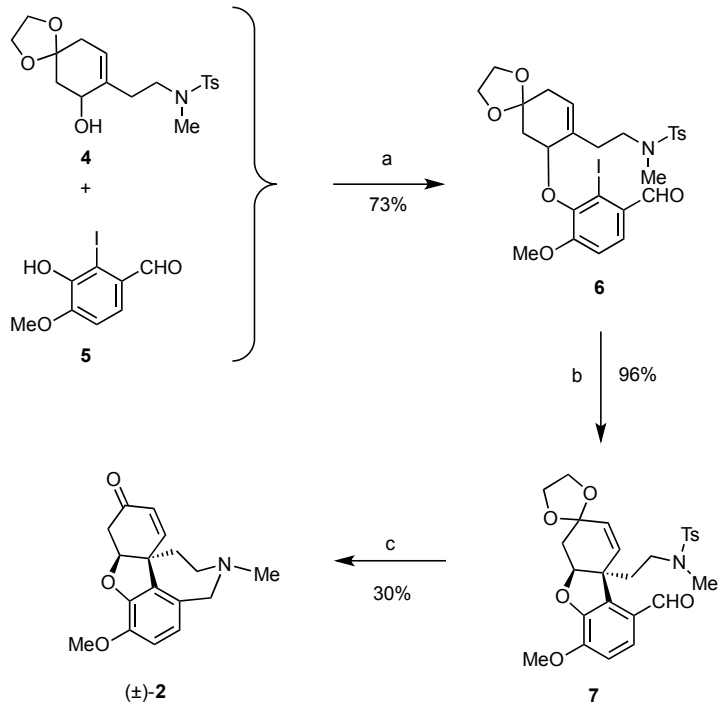
3

Figure 2: The structure of simonsol C (**3**) and the two key bond-forming events used in its synthesis.

Results and Discussion

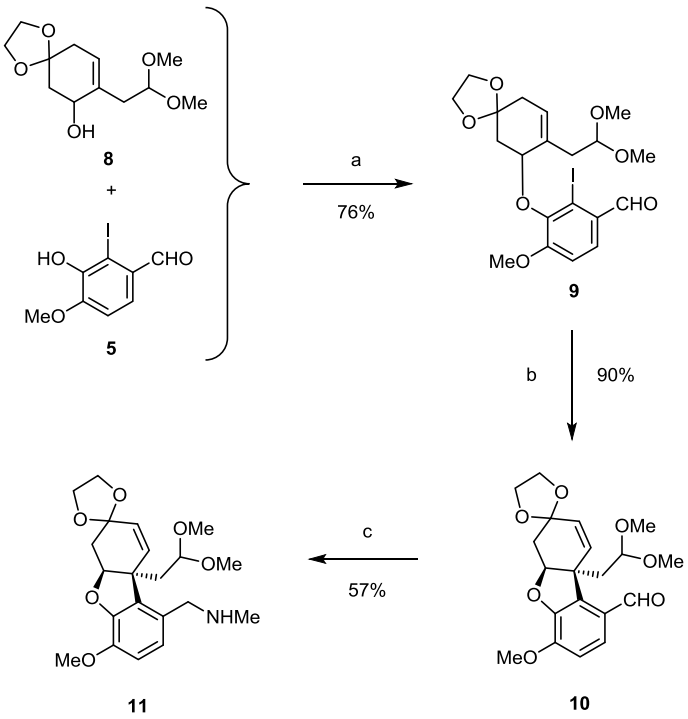
In our first route to racemic narwedine (Scheme 1), the previously reported[17] allylic alcohol **4** (available in four steps from commercially available cyclohexane-1,4-dione mono-ethylene ketal) was engaged in an intramolecular Mitsunobu reaction[19] with the readily available iodinated derivative, **5**,[20] of isovanillin where the latter coupling partner served as the nucleophile.[21] The ether **6** (73%) thus formed was subjected to an

intramolecular Heck reaction under the indicated conditions[22] and thus affording the tricyclic sulfonamide **7** in 96% yield. Finally, successive treatment of the last compound with sodium naphthalenide (to cleave the tosyl group) then a solution of sodium triacetoxyborohydride in moist acetic acid (to reduce the imine resulting from the intramolecular Schiff base condensation reaction and to hydrolyse the ketal residue) gave a rather complex mixture from which (±)-narwedine [(±)-**2**] could be isolated 30% yield. This material was identical, in all respects, with an authentic sample of compound **2** prepared by our earlier route.[13a]



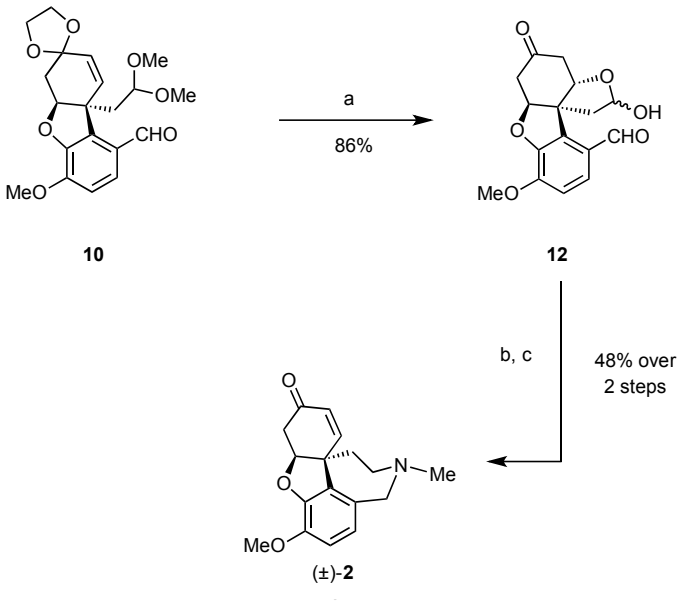
Scheme 1. A new route to (±)-narwedine [(±)-**2**]. Reagents and conditions (a) Bu_3P, TMAD, THF, 0 to 22 °C, 16 h; (b) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene, 112 °C, 3 h; (c) $NaC_{10}H_8$, THF, –78°C, 0.2 h then AcOH, $NaBH(OAc)_3$, 18 °C, 4 h. TMAD = *N*,*N*,*N*,*N*'-tetramethylazodicarboxamide; dppp = 1,3-bis(diphenylphosphino)propane.

In an effort to establish an improved procedure for closing the D-ring of narwedine the reaction sequence shown in Scheme 2 was pursued. Specifically, the previously reported[17] congener **8** of compound **4** was reacted with phenol **5** under Mitsunobu conditions and the ether **9** (76%) so formed engaged in an intramolecular Heck reaction to afford the benzofuran **10** in 90% yield. Subjection of this last compound to reductive amination conditions using methylamine and sodium triacetoxyborohydride in acetic acid/dichloromethane then gave the 2°-amine **11** in 57% yield. This modest yield, the rather complex mixture of products arising from the various attempts to carry compound **11** forward to narwedine, and the outcomes of the studies presented immediately below prompted the abandonment of this approach. Part of the difficulty associated with finishing this approach most likely arises from orchestrating the required sequence of acetal and ketal cleavage reactions. Thus, the latter functionality reacts faster than the former[17] and so introducing the unwanted possibilities of both intra- and inter-molecular reactions between a 2-cyclohexen-1-one residue and a pendant 2°-amine.



Scheme 2. Attempts to establish an improved synthesis of the D-ring. Reagents and conditions (a) Bu_3P, DEAD, THF, 0 to 22 °C, 4 h; (b) $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene, 112 °C, 4 h; (c) H_2NMe, AcOH, $NaBH(OAc)_3$, DCM, 22 °C, 16 h. DEAD = diethyl azodicarboxylate.

The ultimately more effective route to racemic narwedine found during the course of the present study is shown in Scheme 3. This involved the one-pot and acid-catalysed hydrolysis of both the acetal and ketal residues within the Heck cyclisation product **10** using 1 M aqueous HCl in refluxing THF and thereby affording lactol **12** in 86% yield and that was found to exist largely in one anomeric form. This compound almost certainly arises through the initially produced hemiacetal adding in an intramolecular hetero-Michael addition reaction to the 2-cyclohexen-1-one revealed by hydrolysis of the ketal moiety. It is the key intermediate associated with the Magnus group's synthesis of (±)-narwedine.[10] In seeking to effect the conversion **12** → **2** we chose to build upon the somewhat limited amount of experimental detail provided by this group[10] and ultimately found that on sequential treatment of the former compound with the hydrochloride salt of methylamine in the presence of sodium cyanoborohyride and acetic acid gave a boron complex of narwedine that could be cleaved using methanesulfonic acid in refluxing 1,4-dioxane. By such means compound **2** was obtained in 48% yield over the two operations involved. Once again, the spectral data acquired on this product matched those derived from an authentic sample. In addition, the material produced by the route described here was reduced with L-selectride[9,23] and thus providing (±)-galanthamine [(±)-**1**] in 83% yield. This material was identical, in all respects, with an authentic sample.[15]



10 **12** (±)-**2**

Scheme 3. A synthesis of (±)-narwedine [(±)-**2**] *via* the Magnus lactol **12**. Reagents and conditions (a) 1 M aq. HCl, THF, 60 °C, 2 h; (b) H_3NMeCl, Et_3N, AcOH, $NaBH(OAc)_3$, 1,4-dioxane, 22 °C, 30 h; (c) 20% v/v aq. $MeSO_3H$, 1,4-dioxane, 101 °C, 5 h.

Conclusion

When the five steps required to obtained compound **8** from commercially available cyclohexane-1,4-dione mono-ethylene ketal are taken into account,[17] the reaction sequence described here and leading to (±)-narwedine is ten steps in length. This compares with the seven involved in the Magnus synthesis[10] that continues to set the benchmark for efficiency in this challenging area. That said, the capacities for refinement of our approach as well as the opportunities for the generation of novel and biologically active analogues of galanthamine are areas of research that continue in our laboratories. Establishing a shorter synthesis of compound **8** is clear a priority. The present work also serves to emphasize the utility of combining the products of the intermolecular Mitsunobu reaction of 2-halogenophenols and allylic alcohols with the Heck cyclization reaction for the rapid assembly of benzofurans.[24] Efforts to extend such processes in various ways represent an ongoing focus and the results of such studies will be reported in due course.

Experimental Section

General Experimental Procedures: Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a FTIR Spectrometer. Samples were analysed as thin films on KBr plates. Low-resolution ESI mass spectra

were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[25] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al*.[26] Where necessary, reactions were performed under an nitrogen atmosphere.

(±)-*N*-(2-(9-(3-Formyl-2-iodo-6-methoxyphenoxy)-1,4-dioxaspiro[4.5]dec-7-en-8-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide (6): A magnetically stirred solution of alcohol **4**[17] (515 mg, 1.40 mmol), phenol **5**[20] (545 mg, 1.96 mmol) and tri-*n*-butylphosphine (0.50 mL, 1.96 mmol) in dry THF (25 mL) was cooled to 0 °C then treated with TMAD[19] (341 mg, 1.96 mmol). The resulting yellow solution was maintained at this temperature for 0.5 h then warmed to and maintained at room temperature for 18 h. The resulting suspension was treated with silica and the mixture thus obtained concentrated under reduced pressure. The free-flowing powder thus obtained was subjected to flash chromatography (silica, 2:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate), compound **6** (641 mg, 73%) as a cream-coloured foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.73-7.63 (complex m, 3H), 7.26 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.8 Hz, 1H), 5.57 (m, 1H), 5.31 (m, 1H), 3.99-3.77 (complex m, 7H), 3.32 (m, 2H), 2.77 (s, 3H), 2.59 (m, 2H), 2.43 (m, 1H), 2.40 (s, 3H), 2.20 (m, 2H), 1.86 (ddd, J = 12.0, 5.9 and 2.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 157.1, 145.6, 143.0, 134.9(4), 134.8(9), 129.5, 129.2, 127.3, 126.7, 123.3, 111.8, 108.1, 101.5, 78.7, 64.3, 64.2, 56.1, 49.5, 37.8, 35.9, 34.9, 31.0, 21.4 ppm. IR: ν_{max} = 2978, 2937, 2880, 1682, 1573, 1476, 1336, 1273, 1246, 1159, 1019, 941, 729 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 650 (100) [$(M+Na)^+$]. HRMS (ESI, +ve): calcd for $C_{26}H_{30}INNaO_7S$ [$(M+Na)^+$] 650.0685; found 650.0685.

***rac*-*N*-(2-((4a*S*,9b*S*)-9-Formyl-6-methoxy-4,4a-dihydro-9b*H*spiro-[dibenzo[*b*,*d*]furan-3,2'-[1,3]dioxolane]-9b-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide (7)**: A magnetically stirred and thoroughly degassed solution of compound **6** (240 mg, 0.382 mmol) in dry toluene (5 mL) maintained under a nitrogen atmosphere was treated, sequentially, with $Pd(OAc)_2$ (8.8 mg, 10 mol%), dppp (32.5 mg, 20 mol%) and Ag_2CO_3 (317 mg, 1.15 mmol). The resulting heterogeneous mixture was heated under reflux for 3 h then cooled, filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v DCM/diethyl ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.8 in 8:2 v/v DCM/diethyl ether), compound **7** (184 mg, 96%) as a light-yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.36 (d, J =

8.4 Hz, 1H), 7.28 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 10.3 Hz, 1H), 5.70 (d, J = 10.3 Hz, 1H), 4.95 (m, 1H), 4.03-3.90 (complex m, 7H), 3.05 (m, 1H), 2.83 (m, 1H), 2.68 (s, 3H), 2.41 (s, 3H), 2.37 (m, 1H), 2.23 (m, 2H), 2.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 150.2, 148.1, 143.1, 134.7, 131.6, 131.3, 130.1, 129.5, 128.0, 127.2, 126.5, 110.6, 103.2, 84.4, 64.8, 64.4, 56.0, 49.6, 46.4, 35.3, 34.7, 34.5, 21.3. IR: ν_{max} = 2959, 2932, 2885, 1686, 1607, 1571, 1506, 1436, 1337, 1284, 1159, 1015, 912, 729 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 522 (100) [$(M+Na)^+$]. HRMS (ESI, +ve): calcd for $C_{26}H_{29}NNaO_7S$ [$(M+Na)^+$] 522.1562; found 522.1561.

***rac*-(4a*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-*b*enzo[2,3]benzofuro-[4,3-*cd*]azepin-6-one [(±)-narwedine, 2]**: A magnetically stirred solution of compound **7** (300 mg, 0.60 mmol) in dry THF (10 mL) was cooled to −78 °C then treated, dropwise, with sodium naphthalenide [prepared from napthalene (256 mg, 2.0 mmol) and sodium metal (48 mg, 2.0 mmol) in dry THF (10 mL)] until the dark-green colour of the reducing agent remained. The resulting solution was treated with acetic acid (2 mL) (CAUTION) then warmed to 0 °C and treated with sodium triacetoxyborohydride (200 mg, 0.90 mmol). The solution thus obtained was maintained at 22 °C for 4 h then treated with HCl (5 mL of a 1 M aqueous solution), maintained at 22 °C for 1 h then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with $CHCl_3$ (3 x 20 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-narwedine (**2**)[13a] (50 mg, 29%) as an off-white powder, m.p. = 185–187 °C. ^{1}H NMR (800 MHz, $CDCl_3$): δ 6.95 (d, J = 10.4 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.04 (dd, J = 10.4 and 1.0 Hz, 1H), 4.73 (m, 1H), 4.11 (d, J = 15.5 Hz, 1H), 3.84 (s, 3H), 3.75 (d, J =15.5 Hz, 1H), 3.25 (t, J = 13.7 Hz, 1H), 3.16 (m, 2H), 2.75 (dd, J = 17.9 and 3.5 Hz, 1H), 2.44 (s, 3H), 2.28 (td, J = 13.7 and 3.5 Hz, 1H), 1.86 (d, J = 13.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 147.2, 144.5, 144.2, 130.7, 129.5, 127.3, 122.2, 112.1, 88.1, 60.8, 56.2, 54.3, 49.1, 42.5, 37.5, 33.4 ppm. IR: ν_{max} = 2926, 2848, 1683, 1622, 1507, 1437, 1280, 1223, 1166, 1145, 1050, 1031, 1008, 802, 771 cm^{-1}. MS (EI): *m/z* (%) = 285 (100) [$M^{+\cdot}$], 284 (98), 242 (47), 174 (42), 84 (68), 58 (82). HRMS (EI): calcd for $C_{17}H_{19}NO_3$ [$M^{+\cdot}$] 285.1365; found 285.1363.

(±)3-((8-(2,2-Dimethoxyethyl)-1,4-dioxaspiro[4.5]dec-8-en-7-yl)oxy)-2-iodo-4-methoxy-benzaldehyde (9): A magnetically stirred solution of compound **8**[17] (530 mg, 2.16 mmol), compound **5** (840 mg, 3.05 mmol) and tri-*n*-butylphosphine (0.88 mL, 3.05 mmol) in dry THF (40 mL) was cooled to 0 °C then treated with DEAD (0.48 mL, 3.05 mmol). The resulting yellow solution was maintained at 0 °C for 0.25 h then warmed and maintained at room temperature for 4 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate elution) and after concentration of the appropriate fractions (R_f = 0.3 in 1:1 v/v hexane/ethyl acetate) compound **9** (830 mg, 76%) was obtained as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 5.64 (m, 1H), 5.33 (m, 1H), 4.78 (t, J = 5.8 Hz, 1H), 4.05–3.76 (complex m, 4H), 3.94 (s, 3H), 3.38 (s, 3H), 3.35 (s, 3H), 2.69 (m, 2H), 2.48 (m, 1H), 2.26 (m, 2H), 1.89 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 157.1, 146.0, 133.5, 129.3, 126.6, 123.8, 111.8, 108.3, 103.6, 101.8, 79.2, 64.4, 64.2, 56.1, 53.5, 52.8, 38.0, 36.0(4), 36.0(1) ppm. IR: ν_{max} = 2937, 2887, 2829, 1682, 1573, 1475, 1439, 1272, 1245, 1017, 811, 729 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 527 (100)

[(M+Na)$^+$]. HRMS (ESI, +ve): calcd for $C_{20}H_{25}INaO_7$ [(M+Na)$^+$] 527.0543; found 527.0554.

***rac*-(4a*S*,9b*S*)-9b-(2,2-Dimethoxyethyl)-6-methoxy-4a,9b-dihydro-4*H*-spiro[dibenzo[*b*,*d*]furan-3,2'-[1,3]dioxolane]-9-carbaldehyde (10)**: A magnetically stirred and thoroughly degassed solution of compound **9** (1.50 g, 2.97 mmol) in dry toluene (60 mL) maintained under a nitrogen atmosphere was treated, sequentially, with $Pd(OAc)_2$ (68 mg, 10 mol%), dppp (251 mg, 20 mol%) and Ag_2CO_3 (2.40 g, 8.9 mmol). The resulting heterogeneous mixture was heated at reflux for 4 h then cooled, filtered through a pad of diatomaceous earth and the filtrate evaporated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v DCM/diethyl ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 9:1 v/v DCM/diethyl ether), compound **10** (1.00 g, 90%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 10.3 Hz, 1H), 5.72 (d, J = 10.3 Hz, 1H), 5.23 (m, 1H), 4.32 (t, J = 5.2 Hz, 1H), 3.95 (m, 7H), 3.23 (s, 3H), 3.22 (s, 3H), 2.37–2.16 (complex m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 150.2, 148.3, 132.1, 131.5, 130.6, 127.7, 126.7, 110.4, 103.4, 102.7, 85.0, 64.9, 64.4, 56.0, 53.1, 53.0, 48.9, 39.8, 35.0 ppm. IR: ν_{max} = 2934, 2888, 2836, 2730, 1686, 1607, 1570, 1283, 1117, 1045, 1013 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 399 (100) [(M+Na)$^+$]. HRMS (ESI, +ve): calcd for $C_{20}H_{24}NaO_7$ [(M+Na)$^+$] 399.1420; found 399.1422.

***rac*-1-((4a*S*,9b*S*)-9b-(2,2-Dimethoxyethyl)-6-methoxy-4a,9b-dihydro-4*H*spiro[dibenzo[*b*,*d*]furan-3,2'-[1,3]dioxolan]-9-yl)-*N*-methylmethanamine (11)**: A magnetically stirred solution of compound **10** (100 mg, 0.265 mmol), methylamine (0.2 mL of a 2 M solution in THF, 0.4 mmol) and AcOH (0.1 mL) in dry DCM (2 mL) was treated with sodium triacetoxyborohydride (85 mg, 0.4 mmol). The resulting mixture was maintained at room temperature for 16 h then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica gel; 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.2), compound **11** (60 mg, 57%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.19 (d, J = 10.2 Hz, 1H), 5.75 (d, J = 10.2 Hz, 1H), 5.07 (m, 1H), 4.37 (t, J = 5.0 Hz, 1H), 4.31 (broad s, 1H), 3.96 (m, 4H), 3.84 (s, 3H), 3.77 (s, 2H), 3.24 (s, 3H), 3.21 (s, 3H), 2.46 (s, 3H), 2.24–2.03 (complex m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 144.7, 132.2, 130.3, 128.2, 126.8, 122.5, 111.5, 104.1, 102.0, 83.8, 64.7, 64.5, 55.8, 52.7, 52.6, 51.6, 49.3, 41.3, 35.3, 35.1 ppm. IR: ν_{max} = 2954, 2934, 2891, 2835, 2789, 1621, 1581, 1506, 1428, 1277, 1203, 1116, 1046, 1014, 966, 948 cm^{-1} MS (ESI, +ve): *m/z* (%) = 392 (100) [(M+H)$^+$]. HRMS (ESI, +ve): calcd for $C_{21}H_{30}NO_6$ [(M+H)$^+$] 392.2073; found 392.2075.

Compound 12: A magnetically stirred solution of compound **10** (360 mg, 0.96 mmol) in THF (20 mL) was treated with HCl (5 mL of a 1 M aqueous solution) then heated at reflux for 2 h. The resulting mixture was cooled to room temperature then treated with $NaHCO_3$ (20 mL of a saturated aqueous solution) and extracted with EtOAc (4 x 15 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing off-white powder was subjected to flash chromatography (silica gel; 2:1 v/v hexane/EtOAc) to give, after concentration of the appropriate fractions (R_f = 0.3), compound **12**[10] (250 mg, 86%) as a white powder, m.p. = 188−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ

(major anomer) 9.81 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.17 (d, J = 11.4 Hz, 1H), 5.64 (m, 1H), 4.79 (t, J = 3.1 Hz, 1H), 4.57 (t, J = 2.9 Hz, 1H), 3.99 (s, 3H), 3.08–2.98 (complex m, 2H), 2.84 (dd, J = 18.2 and 2.9 Hz, 1H), 2.75 (dd, J = 18.2 and 3.5 Hz, 1H), 2.34–2.20 (complex m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major anomer) 204.6, 192.4, 150.5, 149.6, 133.5, 129.7, 125.9, 111.3, 98.3, 90.1, 77.5, 56.3, 53.9, 46.9, 39.1, 38.2 ppm. IR: ν_{max} = 3444, 2945, 2916, 2846, 1720, 1681, 1608, 1572, 1437, 1292, 1240, 1203, 1049 cm^{-1}. MS (ESI, +ve): *m/z* (%) = 327 (100) [(M+Na)$^+$]. HRMS (ESI, +ve): calcd for $C_{16}H_{16}NaO_6$ [(M+Na)$^+$] 327.0845; found 327.0844.

***rac*-(4a*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro-[4,3-*cd*]azepin-6-one [(±)-narwedine, (±)-2]**: A magnetically stirred solution of compound **12** (110 mg, 0.36 mmol) and freshly recrystallised methylamine hydrochloride (35 mg, 0.51 mmol) in dry 1,4-dioxane (6 mL) was treated with and triethylamine (0.1 mL, 0.7 mmol) then the vessel was sealed and maintained at room temperature for 30 h. The resulting suspension was then treated with acetic acid (0.5 mL, 8.7 mmol) and sodium cyanoborohydride (42 mg, 0.67 mmol) and maintained at room temperature for a further 24 h. The resulting suspension was then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with $CHCl_3$ (4 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing residue was immediately suspended in 1,4-dioxane (5 mL) then treated with $MeSO_3H$ (0.5 mL of a 20% aqueous solution) and the resulting mixture heated at reflux for 4 h then cooled to room temperature and treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and extracted with $CHCl_3$ (4 x 15 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica gel; 9:1 v/v DCM:MeOH) to give, after concentration of the appropriate fractions (R_f = 0.3), compound (±)-**2** (49 mg, 48%) as an off-white powder. This material was identical, in all respects, with that obtained by the route detailed above.

***rac*-(4a*S*,6*R*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzo-furo[4,3-*cd*]azepin-6-ol [(±)-galanthamine, (±)-1]**:A magnetically stirred solution of (±)-narwedine [(±)-**2**] (12.0 mg, 0.042 mmol) in anhydrous THF (2 mL) was cooled to –78 °C and then treated with L-selectride (0.13 mL of a 1 M solution in THF, 0.13 mmol). The resulting mixture was maintained at –78 °C for 3 h and then treated with water (1 mL) and NaOH (1 mL of a 3 M aqueous solution) before being extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure, and the ensuing brown oil subjected to flash chromatography (silica gel, 9:1 v/v dichloromethane/methanol) to give, after concentration of the appropriate fractions (R_f = 0.3), (±)-galanthamine [(±)-**1**][15] (10 mg, 83%) as a light-brown, waxy solid. ^{1}H NMR (800 MHz, $CDCl_3$): δ 6.66 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.06 (ddd, J = 10.3, 1.4 and 0.7 Hz, 1H), 6.01 (ddd, J = 10.3, 5.1 and 1.4 Hz, 1H), 4.61 (m, 1H), 4.14 (m, 1H), 4.10 (d, J = 15.4 Hz, 1H), 3.83 (s, 3H), 3.70 (dd, J = 15.4 and 0.7 Hz, 1H), 3.28 (t, J = 13.5 Hz, 1H), 3.06 (d, J = 14.3 Hz, 1H), 2.69 (ddt, J = 15.7, 3.3 and 1.4 Hz, 1H), 2.41 (s, 3H), 2.09 (td, J = 13.5 and 3.3 Hz, 1H), 2.01 (ddd, J = 15.7, 5.1 and 2.5 Hz, 1H), 1.59 (dd, J = 13.5 and 2.1 Hz, 1H) (signal due to hydroxyl group proton not observed) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 144.3, 133.2, 129.2, 127.8, 126.9, 122.3, 111.4, 88.9, 62.2, 60.7, 56.1, 54.0, 48.4, 42.2, 33.9, 30.1 ppm. IR: ν_{max} = 3339, 2917, 2835, 1958, 1623, 1590, 1506, 1438, 1281, 1230, 1202, 1166, 1046 cm^{-1}. MS (EI): *m/z* (%) = 287 (90) [M$^{+\cdot}$],

286 (100), 270 (22), 244 (41), 216 (50), 174 (47). HRMS (EI): calcd for $C_{17}H_{21}NO_3$ [$M^{+\cdot}$] 287.1521; found 287.1521.

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24. For a useful point-of-entry into the literature on the synthesis of such systems see: N. Takeda, M. Ueda, S. Kagehira, H. Komei, N. Tohnai, M. Miyata, T. Naito, O. Miyata, *Org. Lett*., **2013**, *15*, 4382.
25. W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923.
26. A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics*, **1996**, *15*, 1518.

SUPPORTING INFORMATION FOR:

An Eleven-step Synthesis of Galanthamine from Commercially Available Materials

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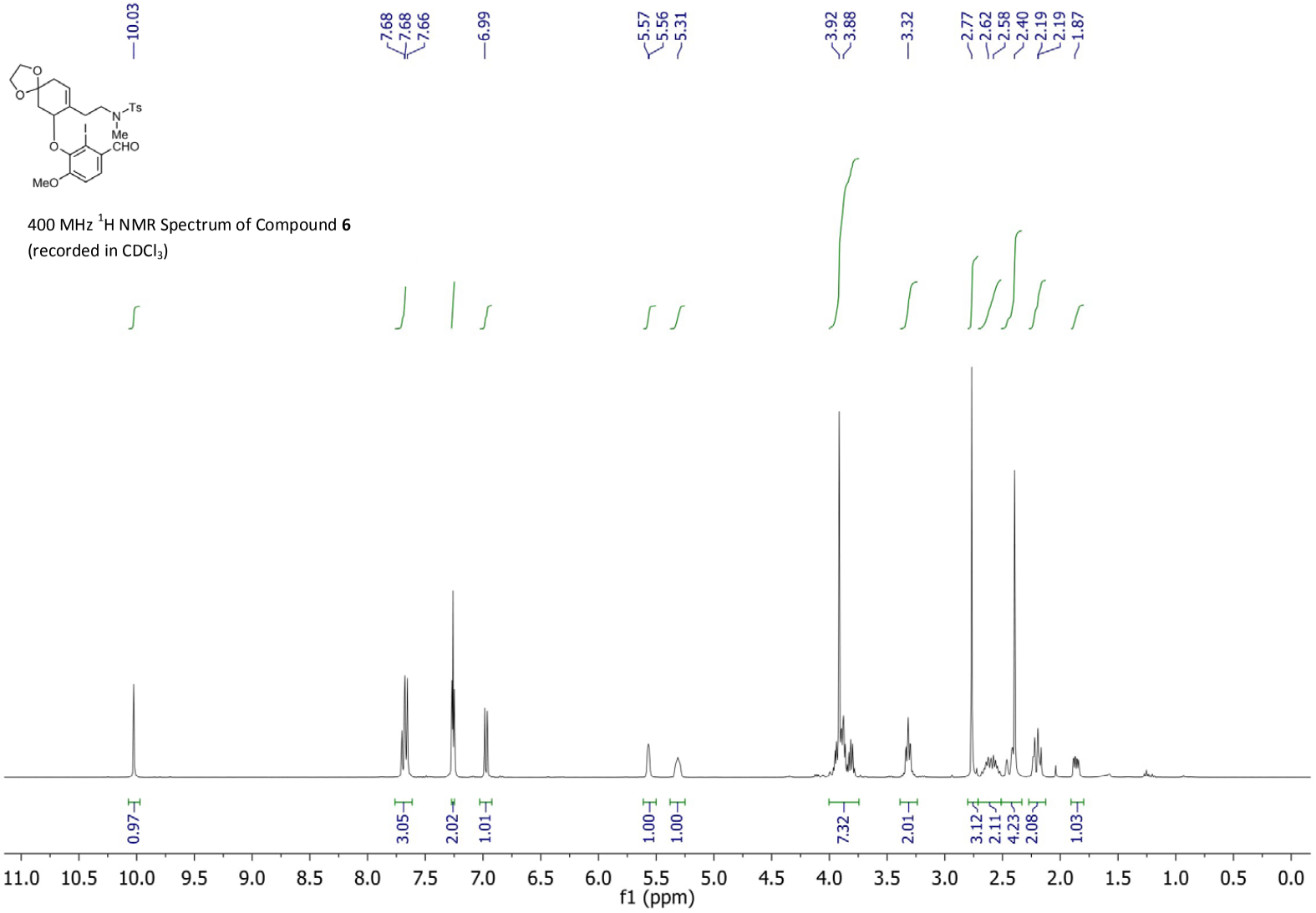
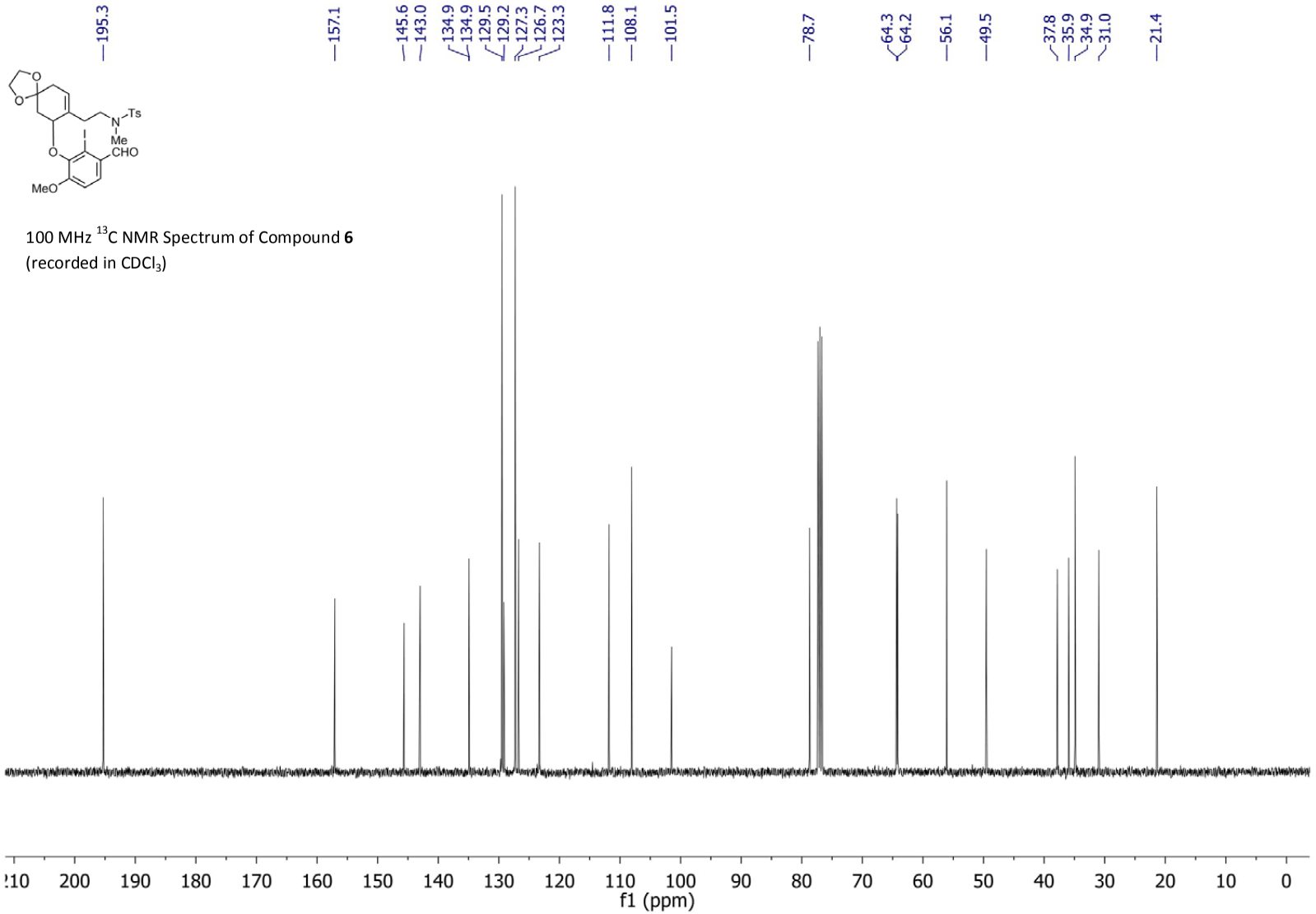
CONTENTS:



400 MHz ^{1}H NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)



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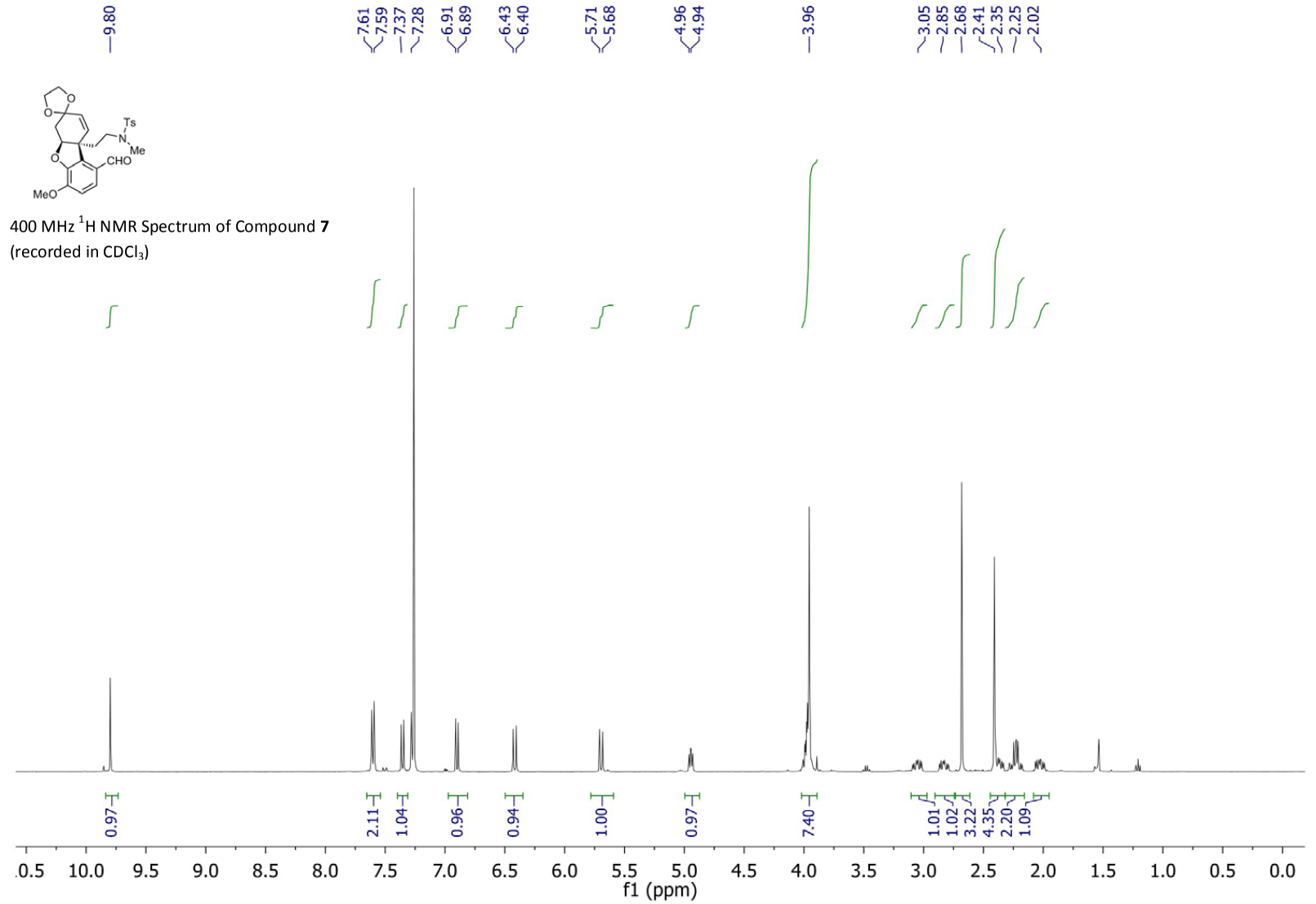

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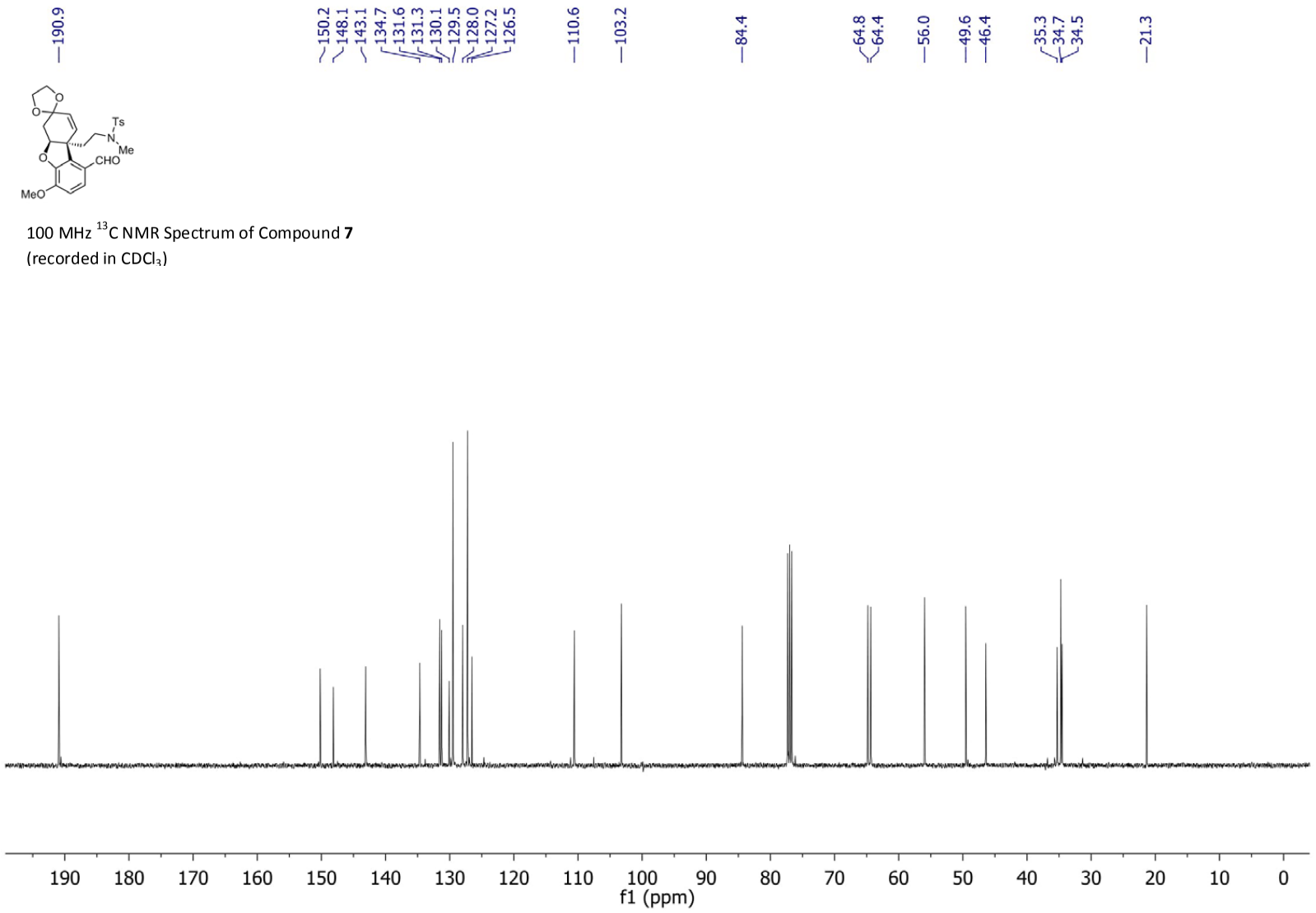

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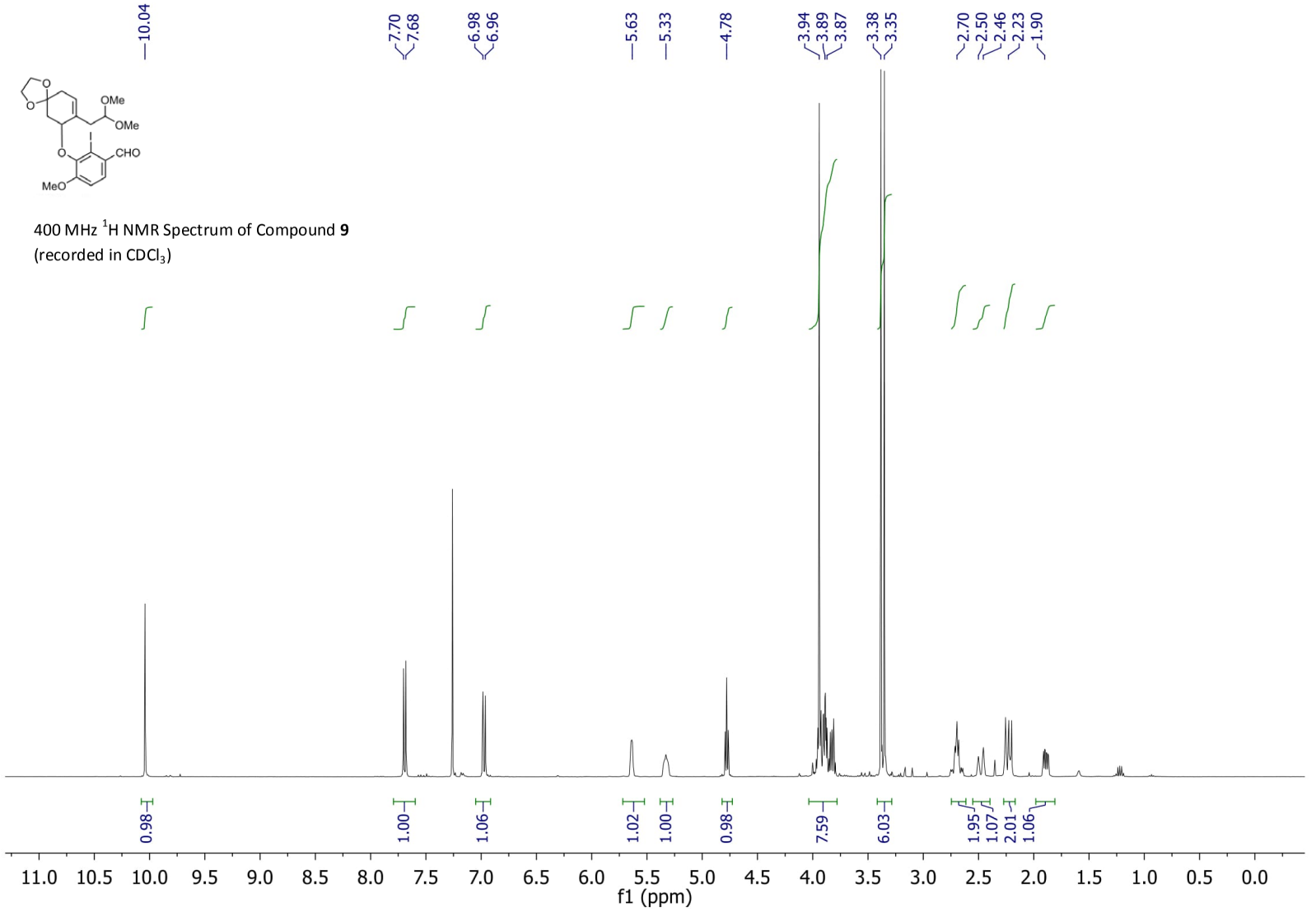

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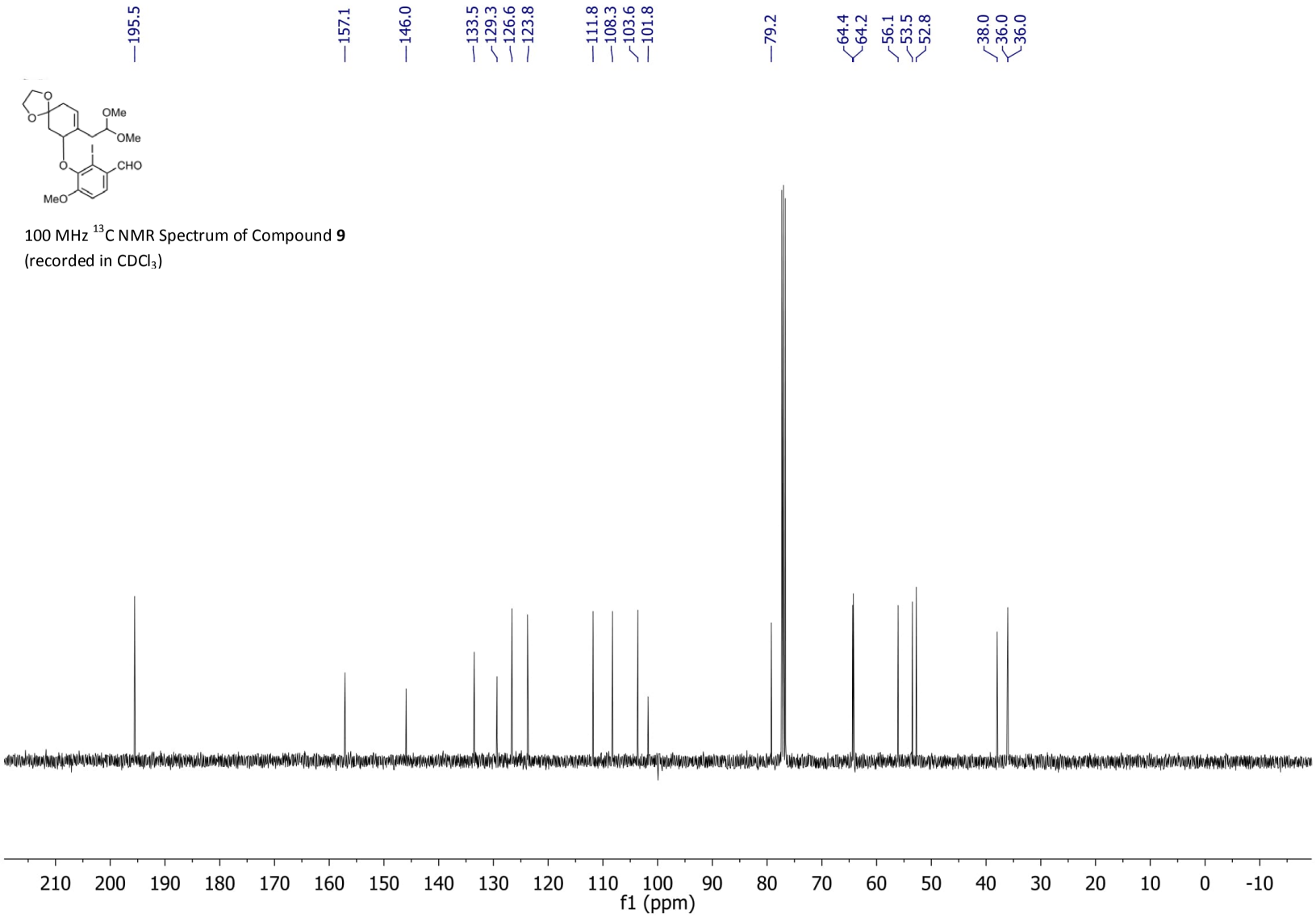

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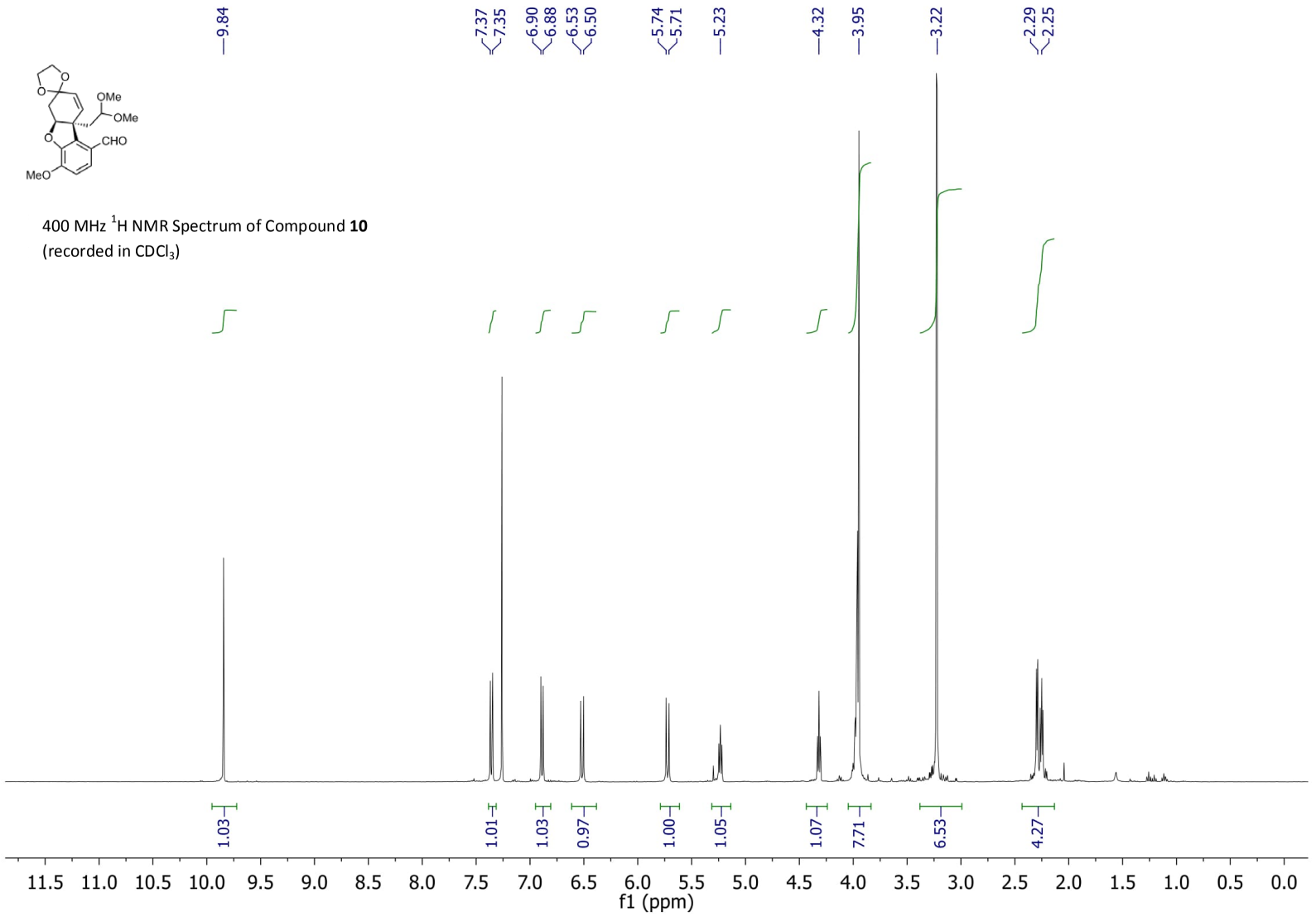
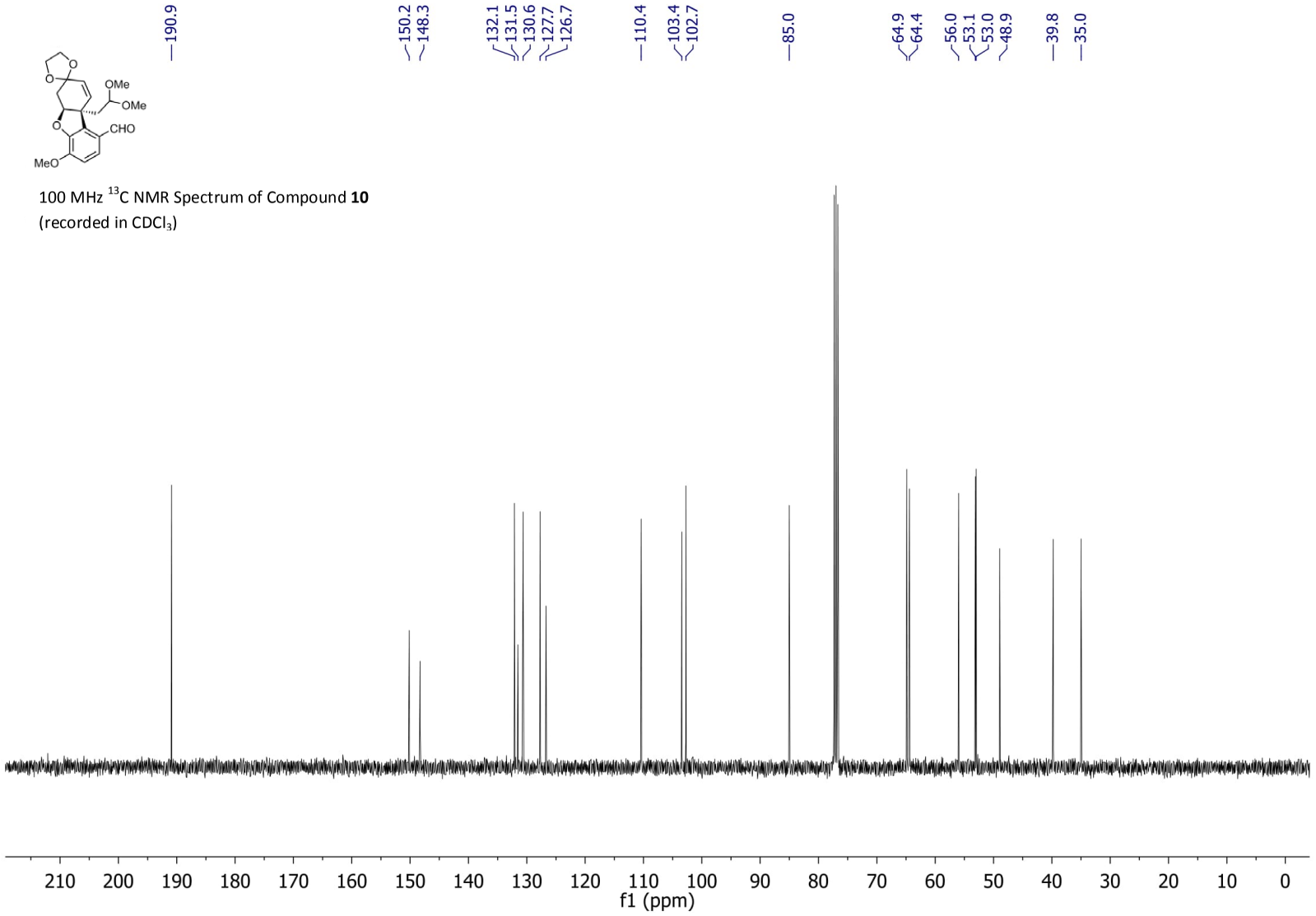

9.84
7.37
7.35
6.90
6.88
6.53
6.50
5.74
5.71
5.23
4.32
3.95
3.22
2.29
2.25
OMe
OMe
CHO
MeO
400 MHz ^{1}H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)
1.03
1.01
1.03
0.97
1.00
1.05
1.07
7.71
6.53
4.27
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



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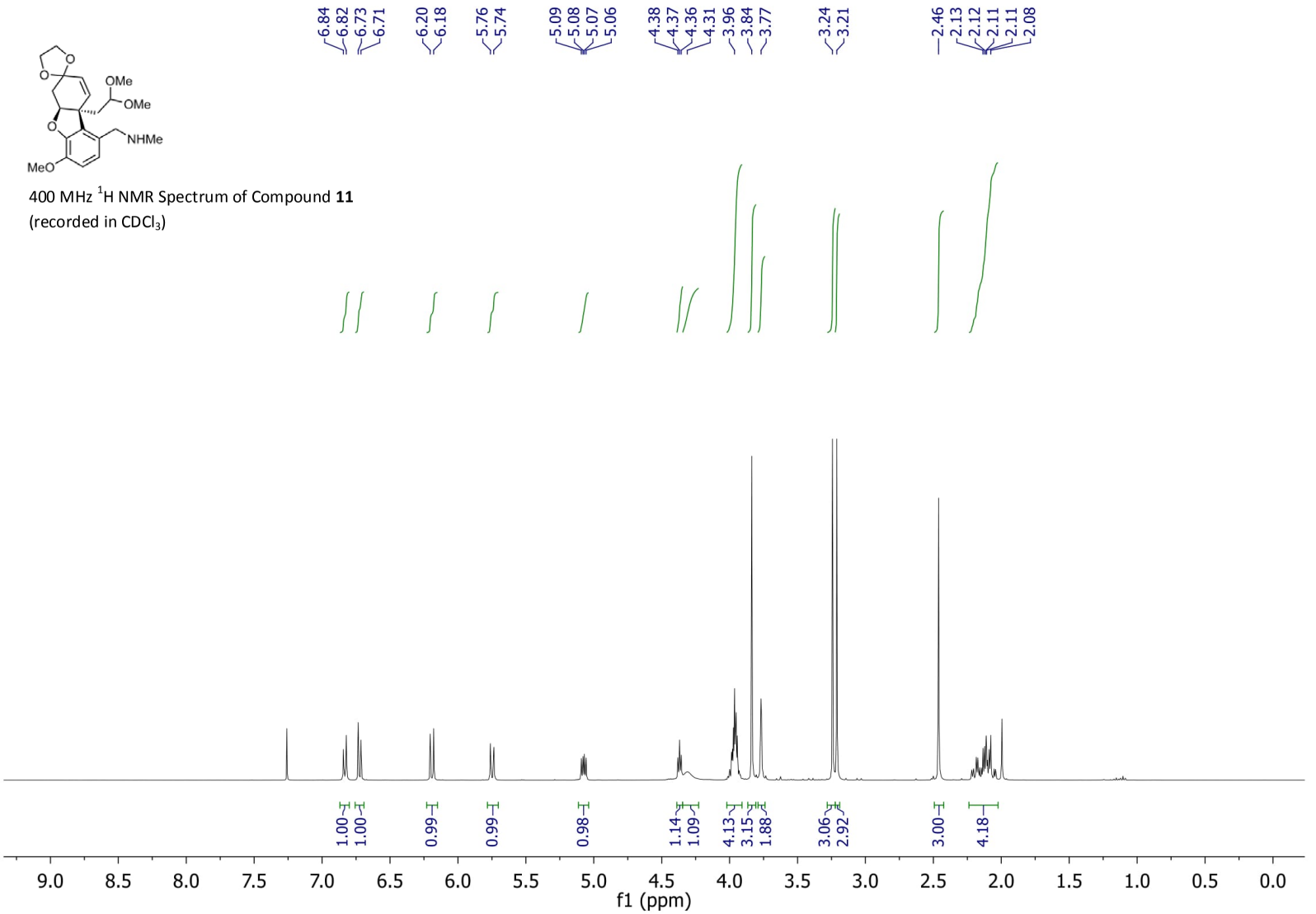

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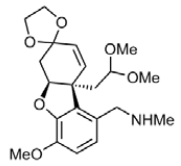

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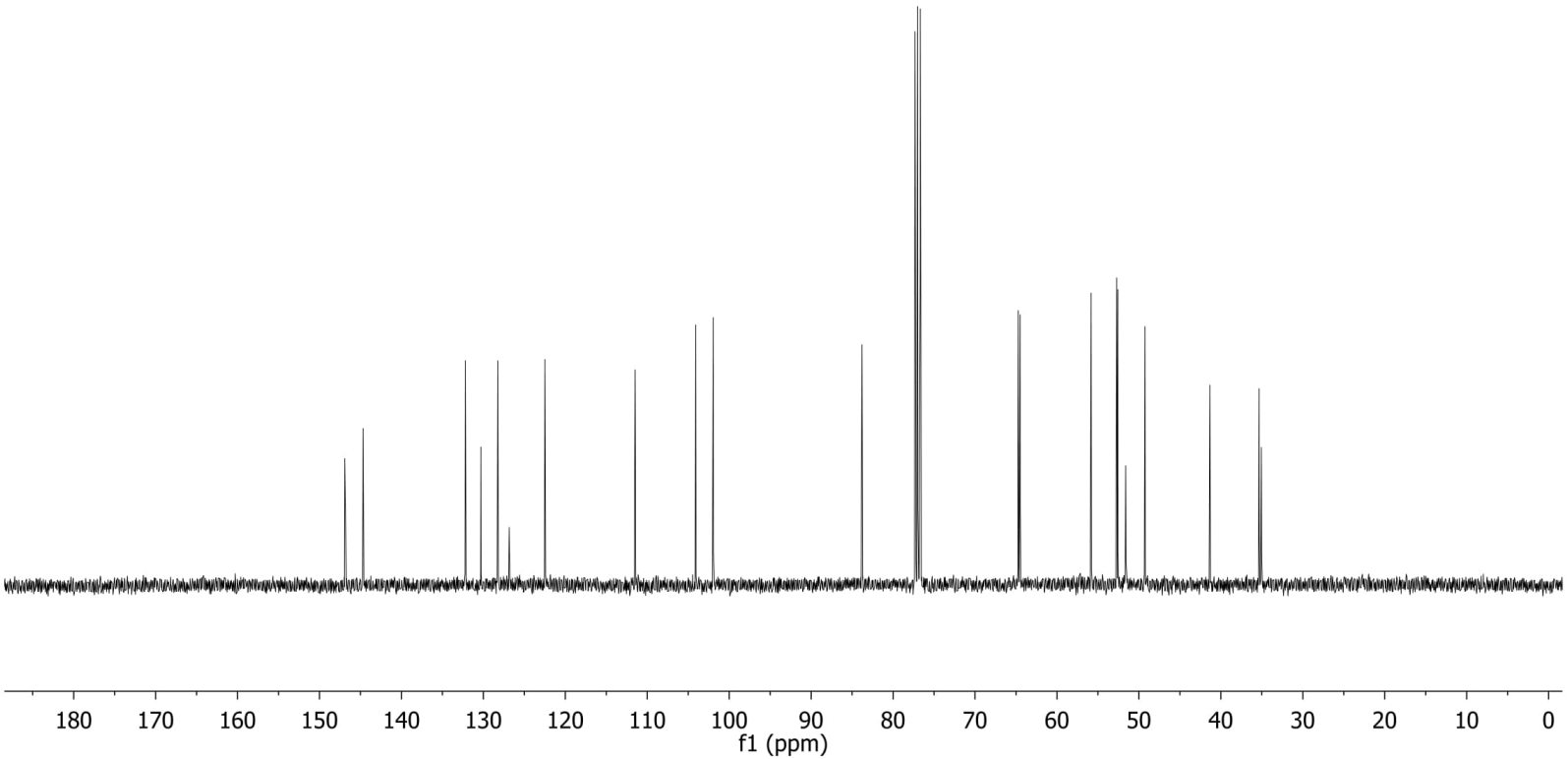
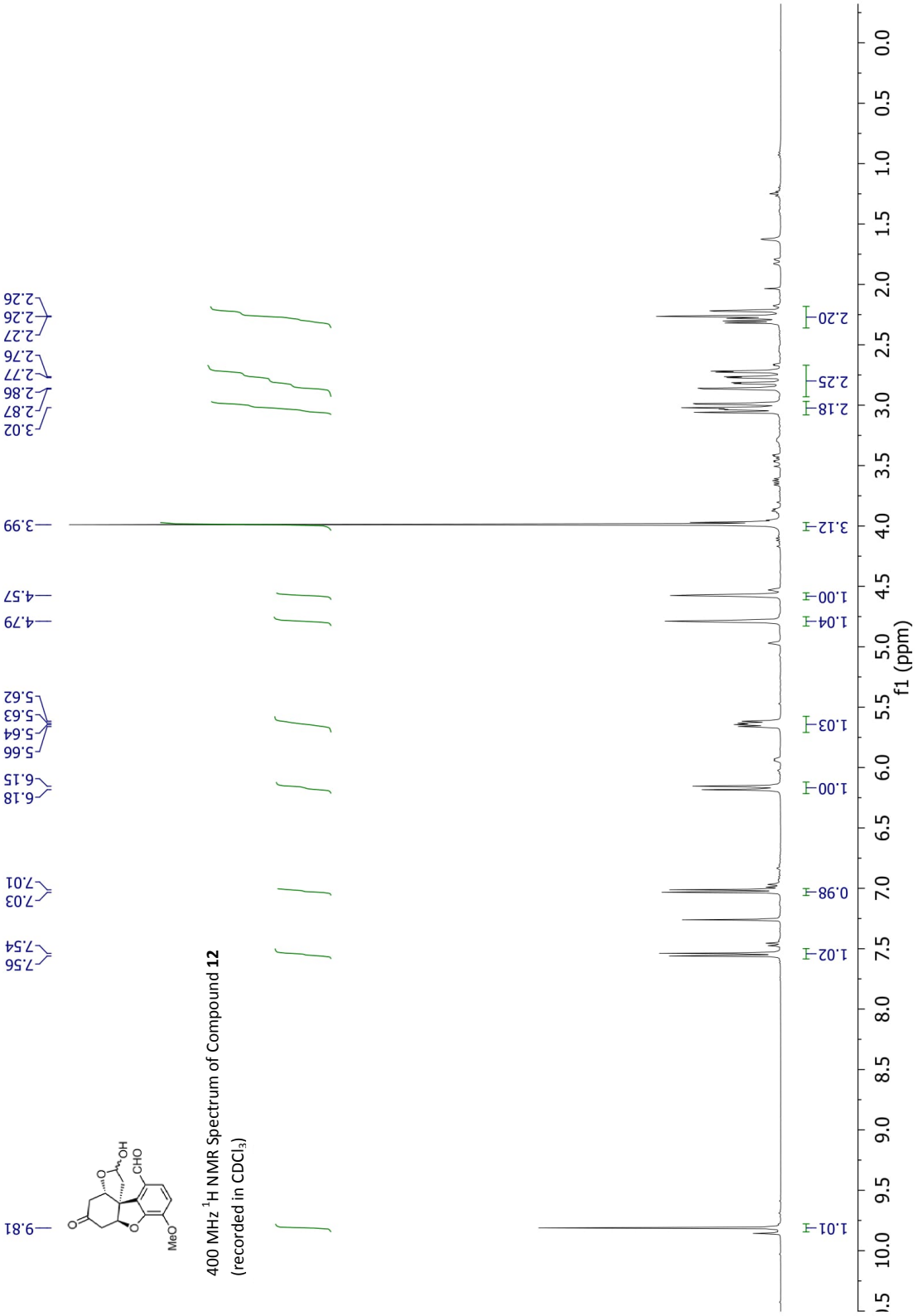
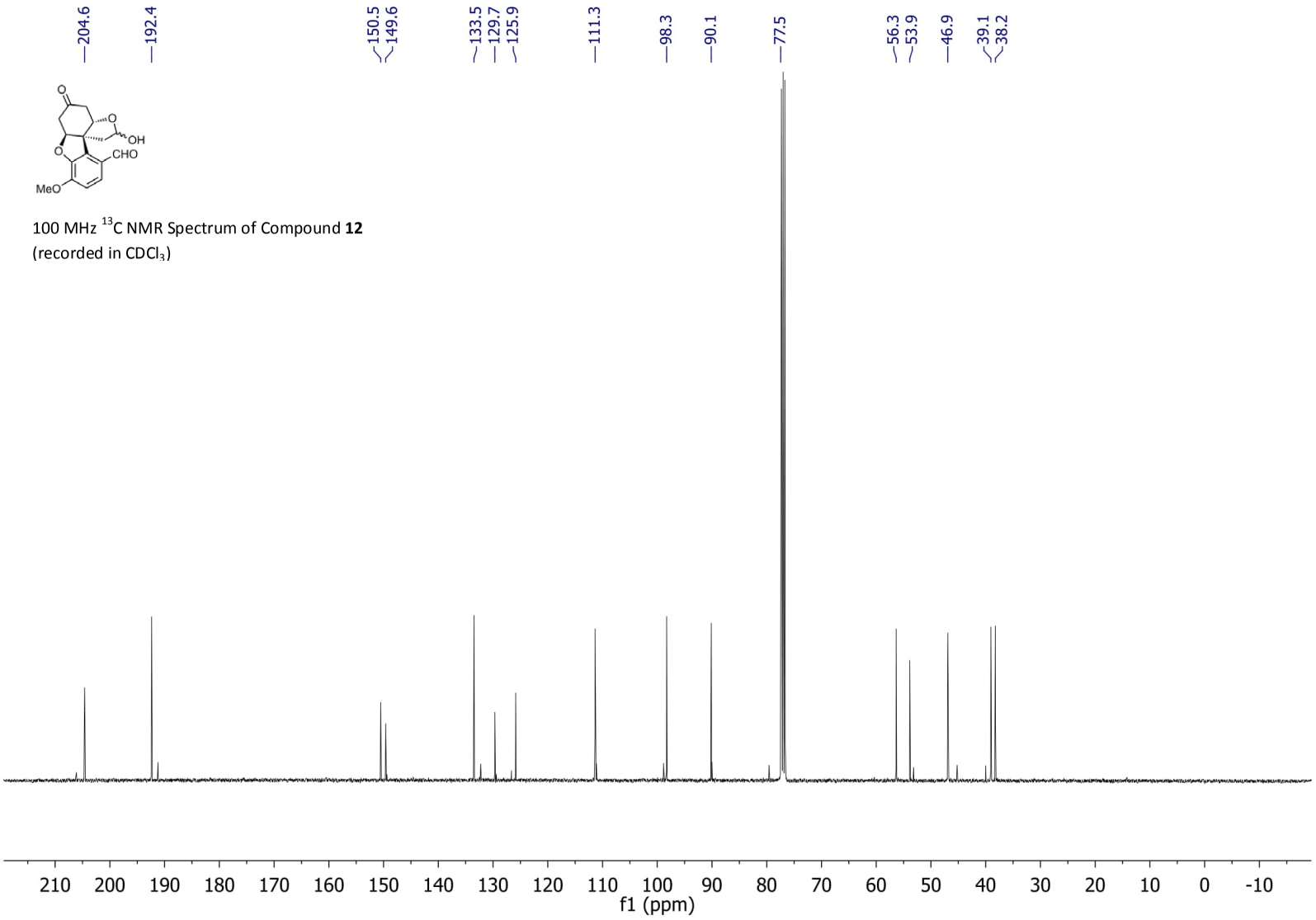



400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)
f1 (ppm)
9.81
7.56
7.54
7.03
7.01
6.18
6.15
5.66
5.64
5.63
5.62
4.79
4.57
3.99
3.02
2.87
2.86
2.77
2.76
2.27
2.26
2.26
1.01
0.98
1.02
1.00
1.03
1.04
1.00
3.12
2.18
2.25
2.20
CHO
OH
MeO



100 MHz ^{13}C NMR Spectrum of Compound **12**
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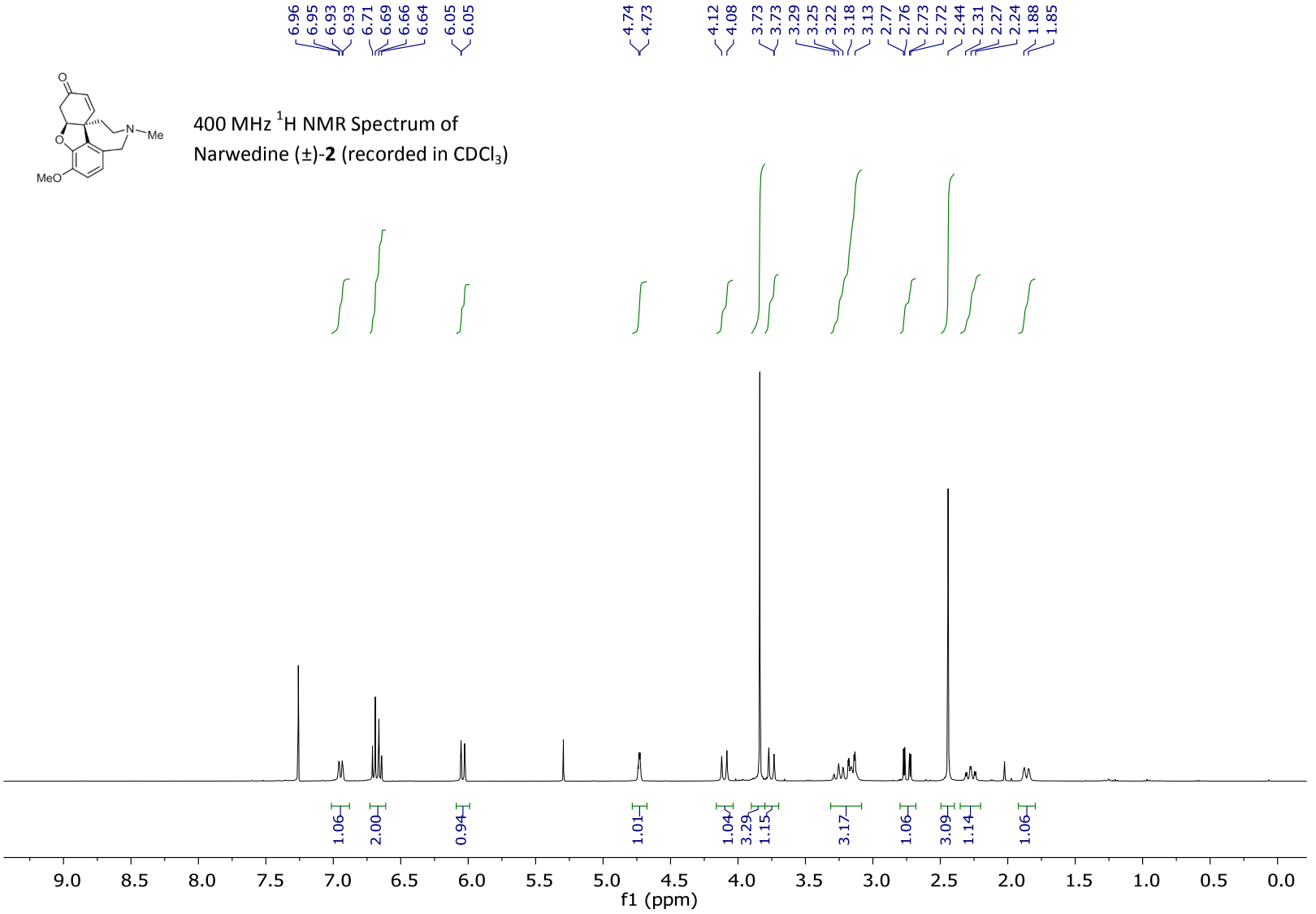
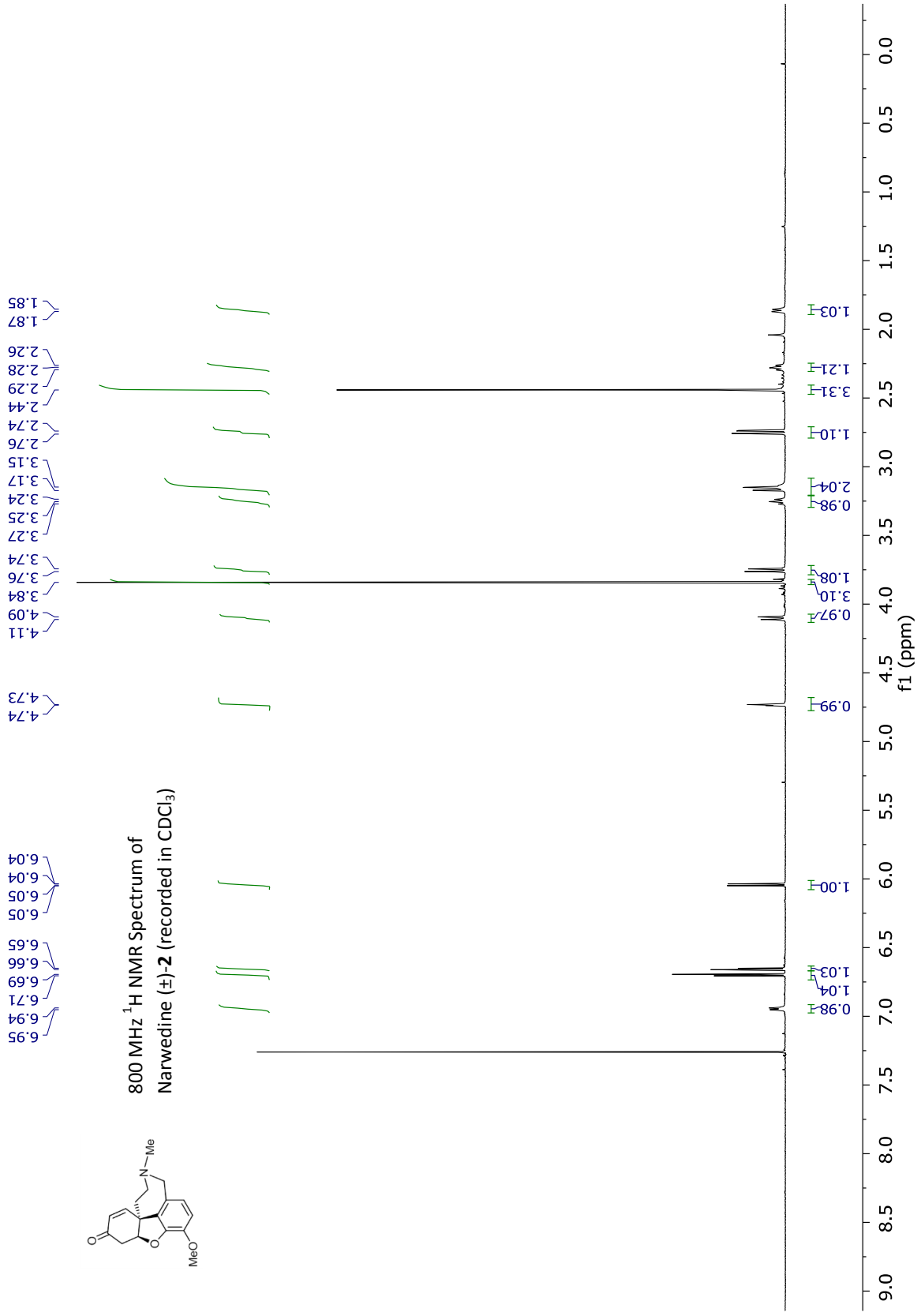

6.96
6.95
6.93
6.93
6.71
6.69
6.66
6.64
6.05
6.05
4.74
4.73
4.12
4.08
3.73
3.73
3.29
3.25
3.22
3.18
3.13
2.77
2.76
2.73
2.72
2.44
2.31
2.27
2.24
1.88
1.85
O
O
N
Me
MeO
400 MHz ^{1}H NMR Spectrum of
Narwedine (±)-**2** (recorded in $CDCl_3$)
1.06
2.00
0.94
1.01
1.04
3.29
1.15
3.17
1.06
3.09
1.14
1.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


800 MHz ^{1}H NMR Spectrum of
Narwedine (±)-**2** (recorded in $CDCl_3$)
N
Me
O
MeO
6.95
6.94
6.71
6.69
6.66
6.65
6.05
6.05
6.04
6.04
4.74
4.73
4.11
4.09
3.84
3.76
3.74
3.27
3.25
3.24
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3.15
2.76
2.74
2.44
2.29
2.28
2.26
1.87
1.85
1.03
1.21
3.31
1.10
2.04
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1.08
3.10
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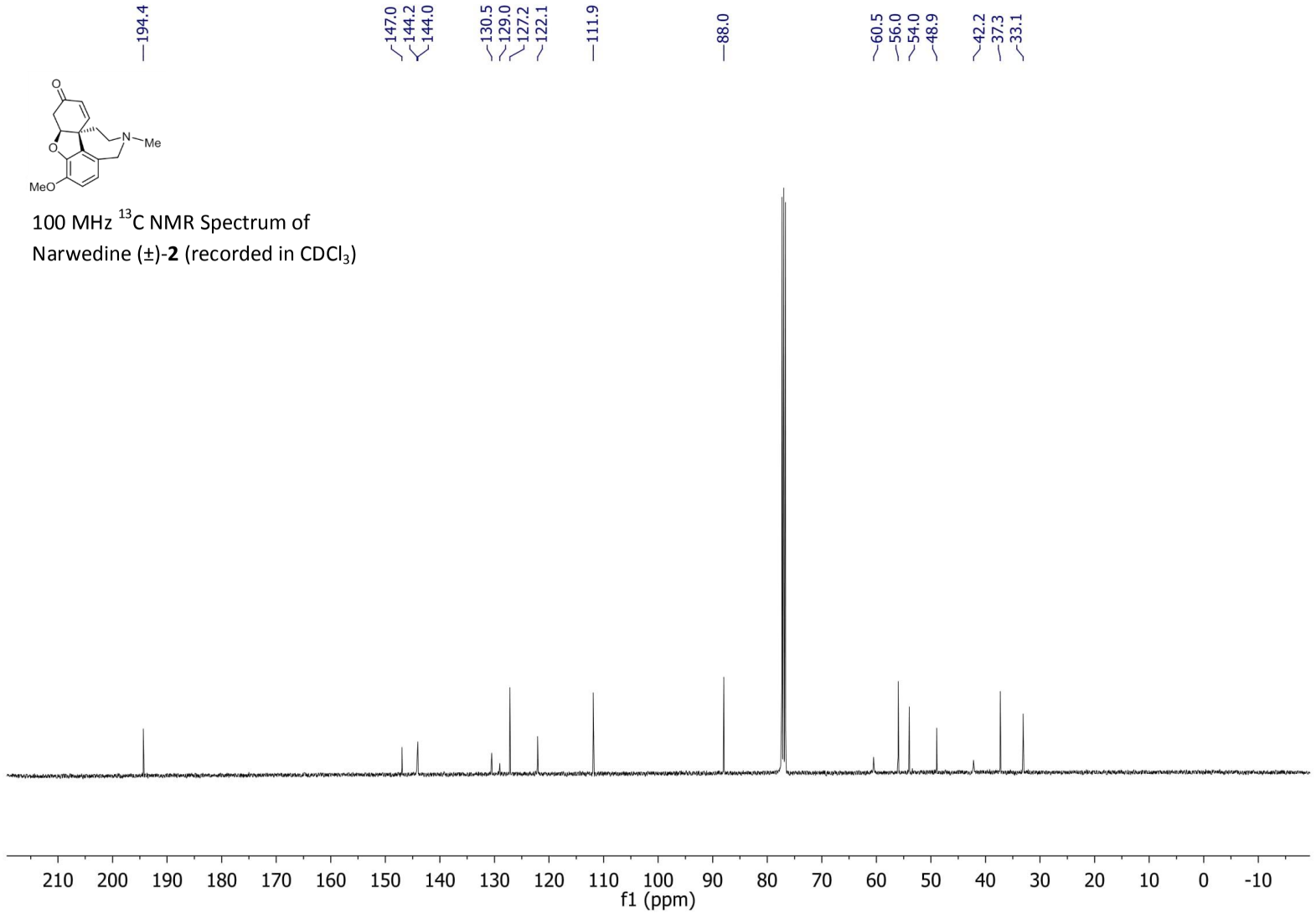
0.99
1.00
1.03
1.04
0.98
f1 (ppm)



100 MHz ^{13}C NMR Spectrum of
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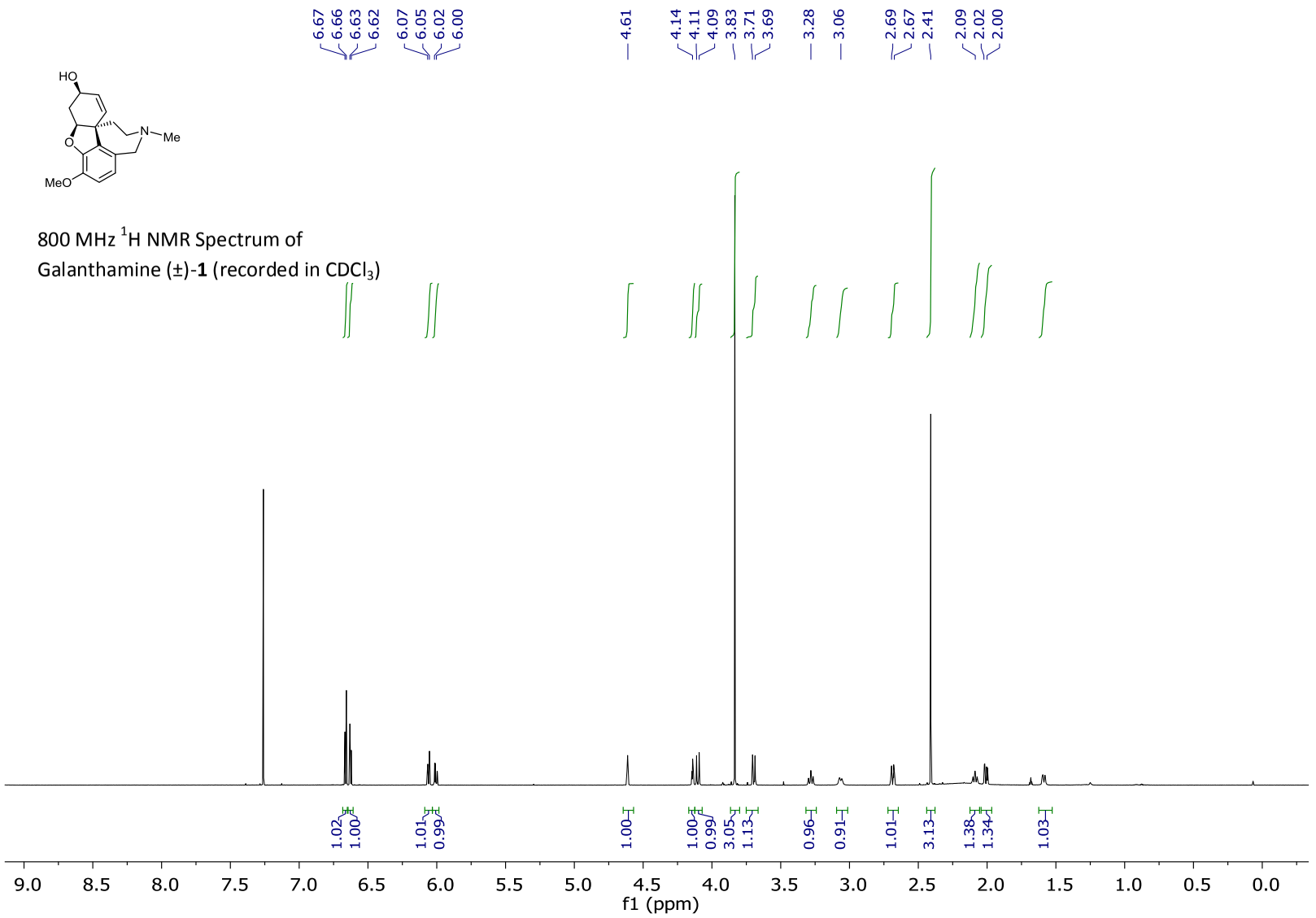

800 MHz ^{1}H NMR Spectrum of
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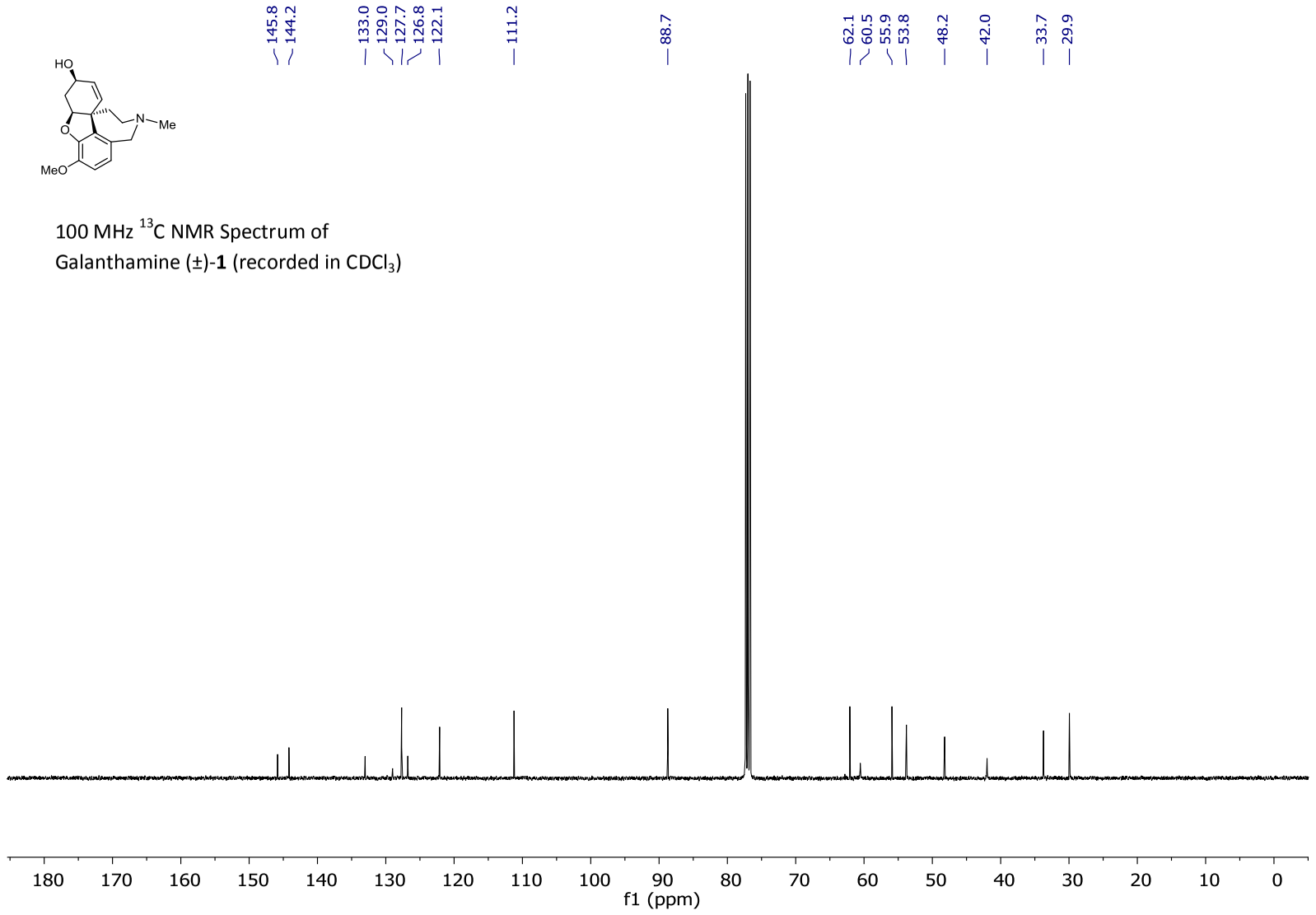

100 MHz ^{13}C NMR Spectrum of
Galanthamine (±)-**1** (recorded in $CDCl_3$)

Publication Six

N-Methoxy-*N*-methylcyanoformamide, a Highly Reactive Reagent for the Formation of *β*-Keto Weinreb Amides and Unsymmetrical Ketones

Jeremy Nugent and Brett. D. Schwartz

Org. Lett. **2016**. *18*, 3834.

Organic LETTERS

Letter

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N-Methoxy-*N*-methylcyanoformamide, a Highly Reactive Reagent for the Formation of β-Keto Weinreb Amides and Unsymmetrical Ketones

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[†]Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

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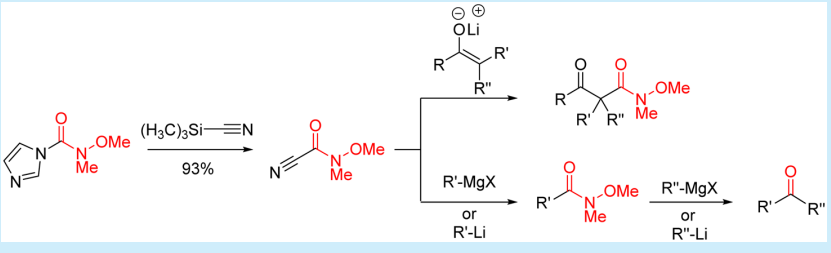
Supporting Information



ABSTRACT: A rapid and straightforward synthesis of the new and highly reactive reagent *N*-methoxy-*N*-methylcyanoformamide from trimethylsilyl cyanide and *N*-methoxy-*N*-methylcarbamoylimidazole, is reported. This reagent enables the one-pot preparation of β-carbonyl Weinreb amides from lithium enolates, one-carbon homologated Weinreb amides, and unsymmetrical ketones in one-pot procedures from various organometallic species.

The vast synthetic utility of Weinreb amides[1] has led to a significant amount of research into methods of synthesizing compounds bearing this functionality.[2] Weinreb amides are usually synthesized from the corresponding activated carboxylic acid equivalents[2] or are installed directly from an organometallic species and an *N*-methoxy-*N*-methylcarbamoyl electrophile such as **1**,[3] **2**,[4] or **3**[5] (Figure 1).

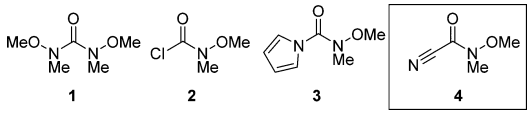
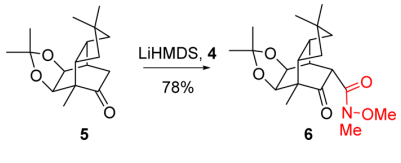


Figure 1. *N*,*O*-dimethylcarbamoylating reagents.

β-Keto Weinreb amides are commonly encountered intermediates in organic synthesis.[6] A recent synthetic study in our laboratory involved the conversion of ketone **5**[7] to the corresponding β-keto Weinreb amide **6** (Scheme 1). During our investigation, we discovered that the reaction of the lithium enolate of **1** with common *N*-methoxy-*N*-methylcarbamoylating reagents such as **1** and **2** either did not proceed or resulted in *O*-carbamoylation. Surprisingly, despite Mander's pioneering work[8] using methyl cyanoformate for the selective *C*-carbomethoxylation of enolates, a direct transformation from ketones to the β-keto Weinreb amides has not been described. Accordingly, we focused on synthesizing and using the previously unreported Mander-type cyanoformamide **4**.

Scheme 1. Direct Transformation of Ketone 5 to β-Keto Weinreb Amide 6



Initially, access to **4** was achieved using conditions reported by Weber[9] for the synthesis of isobutyl cyanoformate. Thus, exposure of *N*-methoxy-*N*-methylcarbamoyl chloride (**2**)[4c] to potassium cyanide in DCM resulted in the formation of **4** (Scheme 2, pathway a). The lithium enolate derived from **5**, formed upon exposure to LiHMDS, reacted rapidly at −78 °C with **4** to provide the desired β-keto Weinreb amide **6** in 78% yield with >99% *dr*. The moderate yields associated with the synthesis of **4** and the use of triphosgene prompted us to explore a more practical and scalable procedure. An assessment of the literature revealed few examples detailing the preparation of cyanoformamides,[10] the majority of which were unsuitable for scale-up. Sarpong's report[11] of the use of imidazole carbamoylating urea reagent **7** encouraged us to use this as a more accessible alternative to *N*-methoxy-*N*-methylcarbamoyl chloride. To access **7**, we opted to use a modification of

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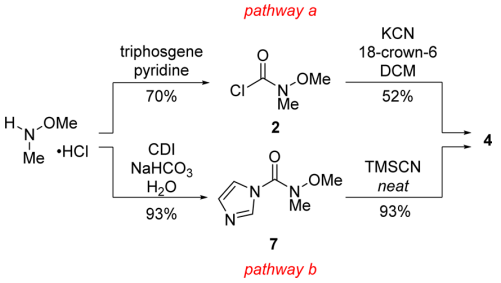
Org. Lett. 2016, 18, 3834−3837

Scheme 2. Synthesis of *N*-Methoxy-*N*-methylcyanoformamide (4)



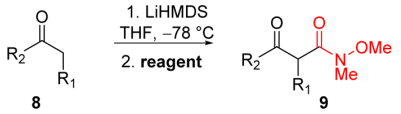
Padiya's "In Water" imidazole carbonylation procedure[12] (Scheme 2, pathway b), thus generating the required urea conveniently, rapidly, and in high yield.

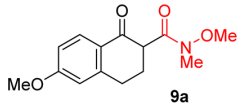
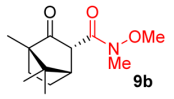
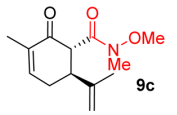
The synthesis of **4** from **7** required a cyanide source, and the restrictions imposed on access to inorganic cyanides encouraged the use of readily available trimethylsilyl cyanide (TMSCN). A number of conditions were screened for the condensation of **7** with TMSCN in various solvents, but excellent yields were only obtained using a "green", anhydrous, solvent-free mixture. This reaction is amenable to scale-up and can be performed with only 1.05 equiv of TMSCN at 18 °C for 18 h or similarly for 10 min at 100 °C in 93% yield. Efforts to isolate **4** directly from the reaction flask by fractional distillation were unfortunately hampered by contamination of 1-trimethylsilylimidazole, which shares a similar boiling point. To avoid this issue, the reaction was quenched with an aqueous workup prior to isolation.[13] *N*-Methoxy-*N*-methylcyanoformamide is a colorless oil after distillation (bp 81−84 °C, 19 mmHg) and should be stored under an inert atmosphere. While we did not notice appreciable degeneration of the reagent after storage in a Schlenk flask under inert, anhydrous conditions for 2 months at room temperature, we recommend storage below 0 °C. Care must be taken to avoid exposure to **4**, especially via inhalation and skin contact, and it should be treated as highly toxic, as the reagent decomposes slowly in water/moist air, presumably to liberate HCN, CO_2, and *N*,*O*-dimethylhydroxylamine, the last of which can react slowly with **4** to form the symmetrical urea **1**.[14]

With an efficient synthesis of **4** in hand, we initiated a comparison study of this reagent with the recently reported *N*-methoxy-*N*-methylcarbamoylpyrrole (**3**)[5] and imidazole reagent **7** in regard to their ability to react with lithium enolates to directly synthesize *β*-keto Weinreb amides (Table 1). All of the carbamoylating reagents were successful in converting 6-methoxy-1-tetralone to **9a** (entry 1), but the reactions involving reagents **3** and **7** both required extended reaction times and warming to room temperature. In contrast, reactions with **4** were complete within 15 min at −78 °C. In the case of hindered ketones (entries 2 and 3) only cyanoformamide **4** efficiently formed the product Weinreb amides (**9b** and **9c**) in high yields.[15]

We next turned to an investigation of the substrate scope of cyanoformamide **4** for the formation of *β*-carbonyl Weinreb amides. We subjected the reagent to a variety of lithium enolates (Scheme 3) and discovered that enones (**8c**−**f**), aryl ketones and lactones (**8a**, **8g**, **8h**, **8i**, and **8l**), and saturated cyclic and aliphatic ketones (**8j** and **8k**) were all suitable substrates.[16] These compounds all underwent clean and

Table 1. Screening of *N*-Methoxy-*N*-methylcarbamoyl Reagents 3, 4, and 7 with Lithium Enolates



entry	product	reagent 3[a]	reagent 7[a]	reagent 4[b]
1	 **9a**	71%	66%	**86%**
2	 **9b**	13% *dr* 95:5	20% *dr* 95:5	**87%** *dr* 95:5
3	 **9c**	24% *dr* > 99:1	23% *dr* > 99:1	**83%** *dr* > 99:1

[a]Reaction conditions: **8** (1.0 mmol), LiHMDS (1.1 mmol), THF, −78 °C, 1 h, then **3** or **7** (1.1 mmol), −78 °C → 18 °C, 20 h. [b]Reaction conditions: **8** (1.0 mmol), LiHMDS (1.1 mmol), THF, −78 °C, 1 h, then **4** (1.1 mmol), −78 °C, 0.25 h.

efficient reactions to afford the product *β*-carbonylamides in excellent yields at low temperature. Surprisingly, the major product derived from the reaction of **4** with cyclohexanone, **9j**, was initially found to be the cyanohydrin−product adduct. However, it was discovered that the cyanohydrin could be easily transformed directly into the required *β*-keto Weinreb amide simply by quenching the reaction with aqueous NaOH and stirring at room temperature for 1 h. Unfortunately, under our standard conditions the quaternary products **9l** and **9m** were not observed. In the case of **9l**, deprotonation at 0 °C and addition of **4** at −78 °C allowed efficient product formation. Under our standard conditions, **9m** was not observed, but instead, only the *O*-carbamoylated product was isolated. Extended reaction times at higher temperatures (−40 to 18 °C) resulted in complex reaction mixtures. To alleviate this problem, the reaction was conducted in diethyl ether with the addition of HMPA, which provided good yields of the quaternary product **9m**. The less toxic additive DMPU gave similar results.

We next investigated the ability of **4** to act as a general means to install the Weinreb amide functionality through reaction with various organometallic species. Lithiated species (Table 2, entries 1−3) were highly reactive toward **4** and selective for the single one-carbon-homologated Weinreb amide addition products (**10a**−**c**). No reaction of **4** with Grignard reagents was observed at −78 °C in THF; however, when the reaction was conducted at 0 °C and with 1 equiv of nucleophile, only the single-addition products (**10a**, **10d**, and **10e**) were observed (entries 4−6). Surprisingly, and in contrast with reagent **3**,[5] the reaction of sp^2-hybridized Grignard reagents with reagent **4** allowed the selective formation of the monoaddition products (**10d** and **10e**).

We predicted that **4** could act as a carbonyl dication synthon[3a,5] in the one-pot formation of unsymmetrical ketones, hence, we subjected **4** to various organometallics in a sequential

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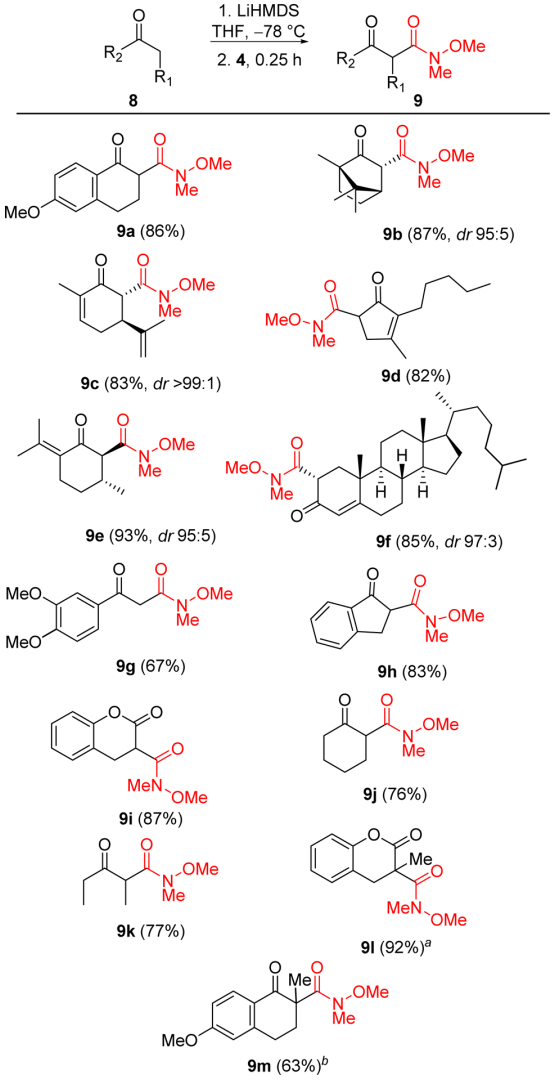
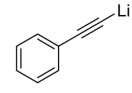
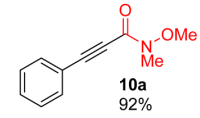
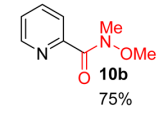
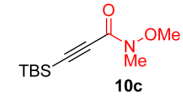
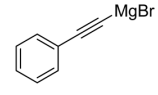
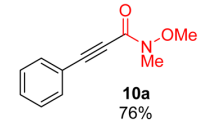
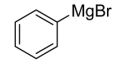
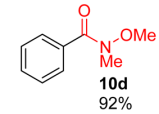
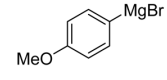
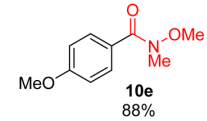
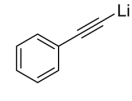
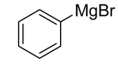
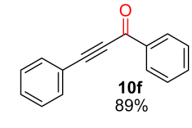
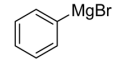
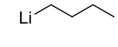
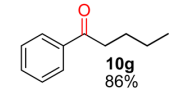
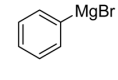
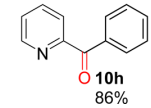
Scheme 3. Scope of Lithium Enolate Addition to Cyanoformamide 4



[a]Reaction conditions: **8l** (1.0 mmol), LiHMDS (1.1 mmol), THF, 0 °C, 0.5 h, then **4** (1.1 mmol), −78 °C → −40 °C, 0.5 h. [b]Reaction conditions: **8m** (1.0 mmol), LDA (1.1 mmol), Et_2O, −78 °C, 1 h, then 0 °C for 0.25 h, −78 °C, **4** (1.1 mmol), then HMPA (1.0 mmol), −78 °C, 0.5 h.

Table 2. Scope of *N,O*-Dimethylcarbamoylation and Unsymmetrical Ketone Synthesis

entry	first nucleophile	second nucleophile	product[a]
1		-	 **10a** 92%
2		-	 **10b** 75%
3		-	 **10c** 76%
4		-	 **10a** 76%
5		-	 **10d** 92%
6		-	 **10e** 88%
7			 **10f** 89%
8			 **10g** 86%
9			 **10h** 86%

[a]Isolated yields. For reaction conditions, refer to the Supporting Information.

manner (Table 2, entries 7–9). In all three cases we obtained excellent yields of the desired ketones (**10f–h**) regardless of the nature of the first or second nucleophile (i.e., Grignard or organolithium).[5]

In summary, we have reported a very useful reagent for the preparation of *β*-carbonyl Weinreb amides from their respective lithium enolates in excellent yields. *N*-Methoxy-*N*-methylcyanoformamide can also be exposed to reactive organometallic species to afford one-carbon-homologated Weinreb amides or used as a carbonyl dication synthon to prepare unsymmetrical ketones in a highly selective manner. Because of the versatility and reliability of this reagent, it should serve as a useful addition to the synthetic chemist's toolbox.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01844.

Experimental procedures, spectroscopic and analytical data, and NMR spectra of new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(13) ^{1}H and ^{13}C NMR spectral data obtained on the crude reaction mixture confirmed the presence of a 1:1 mixtutre of **4** and 1-trimethylsilylimidazole. See the Supporting Information for details.

(14) The half-life in D_2O at 18 °C is 39 h. If decomposition of **4** is observed, purification by flash chromatography (elution with ether) or distillation can be performed. See the Supporting Information for details.

(15) The stereochemistry was assigned on the basis of a combination of mechanistic expectations and spectral data.

(16) Preliminary results suggest that the lithium enolates derived from simple lactones and lactams react efficiently with reagent **4**.

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Supporting Information for

N-Methoxy-N-methylcyanoformamide, a Highly Reactive Reagent for the Formation of β-Keto-Weinreb Amides and Unsymmetrical Ketones.

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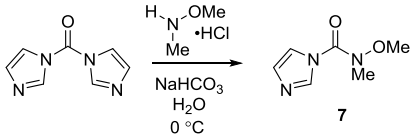
General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 or 500 MHz for proton and 100 or 125 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (d) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; b = broad or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*[1] with silica gel 60 (40-63 mm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Tetrahydrofuran (THF), methanol and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[1] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Experimental Procedures and Product Characterization

*N-Methoxy-N-methylcarbamoyl imidazole **7**.*

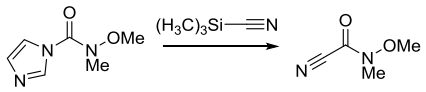


A magnetically stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (20.0 g, 205 mmol), ice (100 g) and $NaHCO_3$ (100 mL of a saturated aqueous solution) in water (100 mL) in a 1L conical flask was maintained at 0 °C (ice/water) then treated, portionwise over a period of 2 minutes, with *N*,*N*′-carbonyldiimidazole (43.2 g, 267 mmol). The resultant mixture was maintained at 0 °C for 0.33 h then extracted with DCM (4 × 50 mL). The combined organic phases were washed with brine (25 mL) then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give compound **7** (29.6 g, 93%) as a pale yellow oil which was then held under high vacuum (1 mmHg, 18 ºC) for 5 h and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.56 (t, *J* = 1.4 Hz, 1H), 7.05 (s, 1H), 3.68 (s, 3H), 3.38 (s, 3H).

Spectra were consistent with those previously reported.[2]

*N-Methoxy-N-methylcyanoformamide **4**. Preparation at 0 - 18 °C / 18 hours*



This reaction should be carried out in a well maintained and fully functioning fume-hood, wearing appropriate personal protective equipment. Magnetically stirred *N*-methoxy-*N*-methylcarbamoylimidazole **7** (15.5 g, 100 mmol) at 0 °C (ice/water bath) was treated dropwise via a pressure equalising dropping addition funnel, under an atmosphere of nitrogen, with trimethylsilyl cyanide (13.1 mL, 105 mmol **CAUTION!**). The cold bath was removed and replaced with an empty glass evaporating dish and the reaction stirred for 18 h. The solution was then poured onto a mixture of aqueous sodium bicarbonate (50 mL satd. solution) and ice (50 g), stirred for 0.10 h and then extracted with DCM (5 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated by rotary evaporation (415 mmHg, water bath at 35 °C) and then the residue was dissolved in ether (20 mL) and loaded onto a pad of silica (55 g, pre-wetted with ether), in a sintered vacuum funnel (60 mm I.D.) and washed through with ether (~400 mL, monitored by TLC analysis). The ethereal solution was then concentrated by rotary evaporation (415 mmHg, water bath at 35 °C), then held at 10 mmHg at 18 °C for 0.5 h to afford *N*-methoxy-*N*-methylcyanoformamide **4** as a pale yellow, clear, free flowing oil (10.6 g, 93%) and can be used without further purification to undertake the described transformations. A portion of the product (4.36 g) was distilled by short-path (b.p. 81-84 °C, 19 mmHg) to afford **4** (3.61 g, 83%) as a colorless oil (m.p. 8-11 °C). Distillation typically leads to approximately 5% impurity of the symmetrical urea, 1,3-dimethoxy-1,3-dimethylurea.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 3H), 3.28 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 110.0, 63.2, 32.3.
^{1}H NMR (C_6D_6, 400 MHz) δ 2.92 (s, 3H), 2.38 (s, 3H).
^{13}C NMR (C_6D_6, 100 MHz) δ 144.3, 110.9, 62.4, 31.4.
MS (EI): *m/z* (%) 114 ($M^{+\bullet}$, 47%), 99 (9), 88 (18), 84 (68), 83 (19), 71 (19), 60 (77), 57 (31), 54 (100).
HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $[C_4H_6N_2O_2]^{+\bullet}$: 114.0424; found, 114.0430.
IR (KBr) ν_{max} 2946, 2238 1687, 1460, 1395, 1199, 987, 710 cm^{-1}.

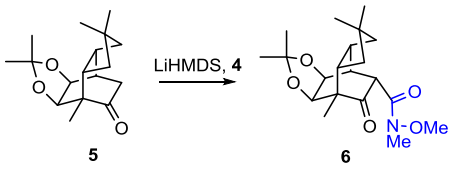
*N-Methoxy-N-methylcyanoformamide **4**. Preparation at 100 °C / 10 minutes*

This reaction should be carried out in a well maintained and fully functioning fume-hood, wearing appropriate personal protective equipment. Magnetically stirred *N*-methoxy-*N*-methyl carbamoyl imidazole **7** (15.5 g, 100 mmol) in a two necked round-bottomed flask (free from any scratches or imperfections) at 0 °C (ice/water bath) fitted with dry ice / acetone condenser, was treated dropwise via a pressure equalising dropping addition funnel, under an atmosphere of nitrogen, with trimethylsilyl cyanide (13.2 mL, 105 mmol **CAUTION!**). The cold bath was removed and replaced with an oil bath and heated to 100 °C and maintained, with stirring at this temperature for 0.2 h. The mixture was cooled to 0 °C and the reaction worked up as above for the preparation at room temperature (10.5 g, 92%).

*N-Methoxy-N-methyl cyanoformamide **4**. Preparation from N-methoxy-N-methylcarbamoyl chloride **2**.*

Following a procedure analogous to that used by Weber[3] for isobutyl cyanoformate: A magnetically stirred solution of *N*-methoxy-*N*-methylcarbamoyl chloride[4] (9.40 g, 76.1 mmol) in DCM (40 mL) at 0 °C (ice/water bath) under an atmosphere of nitrogen was treated with potassium cyanide (5.45 g, 84.0 mmol, **CAUTION!**) portion-wise over 1 minute followed by 18-crown-6 (100 mg). The reaction was warmed to 18 °C over 48 h and then the mixture was vacuum filtered through a 1 cm pad of sand and concentrated by distillation at atmospheric pressure. The crude oil was then distilled through a 10 cm vigreux (b.p. 81-84 °C, 19 mmHg) to afford **4** (4.77 g, 55%) as a colorless oil.

*β-Keto-Weinreb amide **6***



5 **6**

A magnetically stirred solution of ketone **5**[5] (200 mg, 0.72 mmol) in dry THF (5 mL) was cooled to −78 °C then treated dropwise with LiHMDS [generated from *n*-butyllithium (675 µL of a 1.6 M solution in hexanes, 1.08 mmol) and hexamethyldisilazane (233 µL, 1.11 mmol) in THF (10 mL)] . The resulting mixture was maintained at this temperature for 0.5 h then warmed to to 0 °C for 0.08 h then recooled to −78 °C and treated with **4** (106 mg, 0.94 mmol). After 0.5 h at −78 °C the mixture was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 to 1:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **6** (205 mg, 78%) as a colorless oil.

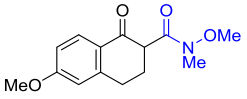
^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.81 (dd, *J* = 7.9, 3.7 Hz, 1H), 4.06 (d, *J* = 7.9 Hz, 1H), 3.84 (m, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 2.98 (dddd, *J* = 11.8, 10.2, 8.5, 2.9 Hz, 1H), 2.63 (td, *J* = 11.8, 7.9 Hz, 1H), 2.54 (ddd, *J* = 6.2, 2.2, 2.2 Hz, 1H), 1.60 (ddd, *J* = 12.6, 8.5, 2.2 Hz, 1H), 1.52 (s, 3H), 1.46 (ddd, *J* = 12.6, 7.9, 2.1 Hz, 1H), 1.35 (s, 3H), 1.27 – 1.16 (m, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.70 (dd, *J* = 12.6 Hz, 1H)
^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.3, 170.0, 109.6, 76.8, 73.3, 61.3, 53.0, 48.1, 43.6, 42.5, 38.1 (2C), 37.5, 31.7, 30.9, 28.6, 27.0, 25.5, 24.0, 15.2.
MS (EI): *m*/*z* (%) 365 ($M^{+\bullet}$, 3), 350 (22), 279 (100), 219 (60), 218 (55), 217 (45), 161 (38).
HRMS (EI) *m*/*z* $M^{+\bullet}$ calcd for $[C_{20}H_{31}NO_5]^{+\bullet}$: 365.2197; found, 365.2194;
IR (KBr) ν_{max} 2942, 1733, 1660, 1382, 1208. 1065, 1001, 886.

*General procedure for enolisation with LiHMDS and addition of **4**:*

A magnetically stirred solution of the appropriate ketone or ester (1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with LiHMDS (1.10 mL of a 1 M solution in THF, 1.10 mmol). The resultant mixture was maintained at this temperature for 1 h then treated with cyanoformamide **4** (125 mg, 1.10 mmol). After 15 minutes at −78 °C the reaction was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 5 mL). The combined organic phases were

washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica) to afford, after concentration of the appropriate fractions, the required Weinreb amide.

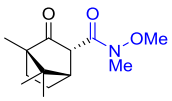
β-Keto-Weinreb amide ***9a***



Compound **9a** was prepared from 6-methoxy-1-tetralone according to the general procedure. Purified by flash chromatography (silica, 1:1 hexane/EtOAc) to afford **9a** (227 mg, 86%) as a white solid, mp. 95 – 100 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, *J* = 8.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.70 (d, *J* = 2.6 Hz, 1H), 4.06 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.29 (s, 3H), 3.06 – 2.97 (m, 2H), 2.51 (m, 1H), 2.24 (m, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.1, 171.4, 163.8, 146.4, 130.1, 125.8, 113.3, 112.5, 61.4, 55.4, 50.9, 32.0, 28.7, 26.2.
MS (+LRESI) *m/z* (%) 264 (30) $[M+H]^+$, 286 (100) $[M+Na]^+$
HRMS (+ESI) *m/z* $[M+Na]^+$ calcd for $[C_{14}H_{17}NNaO_4]^+$: 286.1050; found, 286.1048;
IR (KBr) ν_{max} 1667, 1643, 1596, 1423, 1356, 1251, 1237, 987, 814 cm^{-1}.

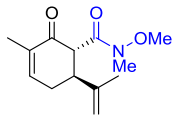
β-Keto-Weinreb amide ***9b***



Compound **9b** was prepared from (1*R*)-(+)-camphor according to the general procedure. Purified by flash chromatography (silica, 3:1 hexane/EtOAc) to afford **9b** (208 mg, 87%, *dr* 95:5) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.70 (s, 3H), 3.60 (d, *J* = 3.0 Hz, 1H), 3.18 (s, 3H), 2.38 (dd, *J* = 4.4, 4.4 Hz, 1H), 1.84 – 1.75 (complex m, 1H), 1.69 – 1.55 (complex m, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1, 170.7, 61.5, 58.4, 53.7, 47.0, 46.0, 32.0, 29.4, 22.2, 19.6, 18.9, 9.6.
MS (+LRESI) *m/z* (%) 262 (100) $[M+Na]^+$, 501 (30) $[2M+Na]^+$
HRMS (+ESI) *m/z* $[M+Na]^+$ calcd for $[C_{13}H_{21}NNaO_3]^+$: 262.1414; found, 262.1411;
IR (KBr) ν_{max} 2963m 1750, 1656, 1447, 1379, 1176, 1102, 730 cm^{-1}.
$[\alpha]_D$ = + 76.7 (*c* 0.6, $CDCl_3$)

β-Keto-Weinreb amide ***9c***



Compound **9c** was prepared from (*S*)-(+)-carvone according to the general procedure. Purified by flash chromatography (silica, 1:1 hexane/EtOAc) to afford **9c** (197 mg, 83%, *dr* >99:1) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (m, 1H), 4.81 (m, 2H), 4.10 (d, J = 12.9 Hz, 1H), 3.72 (s, 3H), 3.32-3.20 (complex m, 4H), 2.51 (dt, J = 18.6, 5.4 Hz, 1H), 2.34 (m, 1H), 1.80 (dt, J = 2.6, 1.3 Hz, 3H), 1.76 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 170.8, 145.4, 144.6, 135.1, 112.0, 61.4, 54.0, 44.9, 32.0, 31.1, 20.4, 15.8.

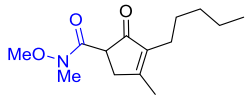
MS (EI) *m/z* (%) = 237 ($M^{+\bullet}$, 3), 177 (60), 149 (100).

HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1354.

IR (KBr) ν_{max} 2973, 2923, 1673, 1650, 1380 cm^{-1}.

[α]$_D$ = + 88.9 (*c* 1.0, $CHCl_3$).

β-Keto-Weinreb amide ***9d***



Compound **9d** was prepared from dihydrojasmone according to the general procedure. Purified by flash chromatography (silica, 1:1 hexane/EtOAc) to afford **9d** (208 mg, 82%) as a pale yellow oil.

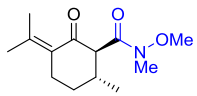
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (m, 1H), 3.75 (s, 3H), 3.12 (s, 3H), 2.75 (d, J = 18.1 Hz, 1H), 2.53 (dd, J = 18.1, 7.0 Hz, 1H), 2.05 (m, 2H), 1.98 (s, 3H), 1.26(m, 2H), 1.16 (m, 4H), 0.75 (t, J = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 170.7, 170.4, 139.0, 139.0, 61.8, 47.5, 32.1, 31.6, 27.8, 23.2, 22.4, 17.1, 13.9.

MS (EI): *m/z* (%) = 253 ($M^{+\bullet}$, 42), 193 (100), 149 (100).

HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $C_{14}H_{23}NO_3$: 253.1672. Found: 253.1671.

IR (KBr) ν_{max} 2951, 2930, 2856, 1700, 1659, 1640, 1383 cm^{-1}.

β-Keto-Weinreb amide ***9e***



Compound **9e** was prepared from (*R*)-(+)-pulegone according to double the scale of the general procedure. Purified by flash chromatography (silica, 4:1 hexane/EtOAc) to afford **9e** (42 mg, 93%, *dr* 95:5) as a colorless oil.

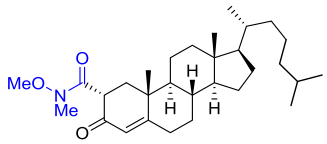
^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.70 (s, 3H), 3.52 (d, *J* = 10.5 Hz, 1H), 3.27 (s, 3H), 2.72 (dt, *J* = 15.6, 4.1 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.33 (m, 1H), 1.99 (d, *J* = 1.4 Hz, 3H), 1.94 (ddt, *J* = 13.2, 4.6, 3.5 Hz, 1H), 1.80 (s, 3H), 1.42 (qd, *J* = 12.6, 4.6 Hz, 1H), 0.99 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.6, 171.5, 144.0, 130.9, 61.5, 61.3, 33.9, 31.9, 31.7, 28.3, 23.1, 22.3, 20.8.

IR (KBr) ν_{max} 2929, 1651, 1444, 1380, 1290, 1170, 974, 765 cm^{-1}.

[α]$_D$ = − 16.38 (*c* 1.7, $CDCl_3$)

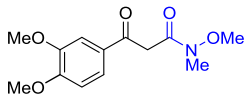
β-Keto-Weinreb amide ***9f***



Compound **9f** was prepared from (+)-4-cholesten-3-one according to the general procedure. Purified by flash chromatography (silica, 1:10 hexane/EtOAc) to afford **9f** (400 mg, 85%, *dr* 97:3) as a white solid, mp. 147 – 149 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74 (d, *J* = 1.2 Hz, 1H), 4.00 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.69 (s, 3H), 3.26 (s, 3H), 2.36 (m, 1H), 2.27 (ddd, *J* = 14.6, 4.5, 2.5 Hz, 1H), 2.16 (dd, *J* = 13.9, 13.9 Hz, 1H), 2.06 – 1.96 (complex m, 2H), 1.89 – 1.76 (complex m, 2H), 1.63 – 1.43 (complex m, 4H), 1.43 – 1.19 (complex m, 5H), 1.22 (s, 3H), 1.18 – 0.94 (m, 10H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.69 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.9, 171.4, 171.2, 123.1, 61.4, 55.9, 55.7, 53.9, 45.9, 42.3, 39.5, 39.4, 38.7, 38.5, 36.1, 35.7, 35.5, 32.7, 32.0, 31.9, 28.1, 28.0, 24.1, 23.7, 22.8, 22.5, 20.8, 18.6, 17.7, 11.9.
MS (+LRESI) *m/z* (%) 472 (100) $[M+H]^+$, 494 (50) $[M+Na]^+$.
HRMS (+ESI) *m/z* $[M+Na]^+$ calcd for $[C_{30}H_{49}NNaO_3]^+$: 494.3605; found, 494.3604.
IR (KBr) ν_{max} 2934, 2866, 1668, 1651, 1451, 1384, 1173, 966 cm^{-1}.
[α]$_D$ = + 94.5 (*c* 1.0, $CDCl_3$)

β-Keto-Weinreb amide ***9g***

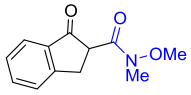


Compound **9g** was prepared from 3′,4′-dimethoxyacetophenone according to double the scale of the general procedure. Purified by flash chromatography (silica, 5:1 hexane/EtOAc) to afford **9g** (356 mg, 67%) as an 87:13 mixture of keto and enol tautomers as a cream solid, mp. 60 – 65 ºC.

^{1}H NMR ($CDCl_3$, 500 MHz) *Keto tautomer* δ 7.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.09 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.68 (s, 3H), 3.24 (s, 3H).
^{1}H NMR ($CDCl_3$, 500 MHz) *Enol tautomer* δ 7.42 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.00 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.76 (s, 3H), 3.27 (s, 3H).

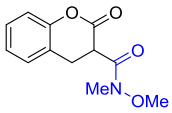
^{13}C NMR ($CDCl_3$, 125 MHz) *87:13 Mixture of keto and enol tautomers* δ 191.8, 172.8, 171.4, 168.6, 153.6, 151.3, 149.0, 148.7, 129.5, 123.3, 119.3, 110.6, 110.3, 110.0, 109.0, 83.0, 61.2, 60.2, 55.9, 55.9, 55.8, 44.0, 32.1.
MS (+LRESI) *m/z* (%) 290 (100) $[M+Na]^+$.
HRMS (+ESI) *m/z* $[M+Na]^+$ calcd for $[C_{13}H_{17}NNaO_5]^+$: 290.0933; found, 290.0999.
IR (KBr) ν_{max} 2972, 1667, 1634, 1584, 1512, 1417, 1321, 1268, 1152, 1025, 1008, 884, 796 cm^{-1}.

β-Keto-Weinreb amide ***9h***



Compound **9h** was prepared from 1-indanone according to the general procedure. Purified by flash chromatography (silica, 2:1 hexane/EtOAc) to afford **9h** (182 mg, 83%) as a pale yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 4.29 (m, 1H), 3.83 (s, 3H), 3.45 (m, 1H), 3.33 (m, 1H), 3.27 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 170.2, 154.1, 135.5, 135.0, 127.4, 126.4, 124.2, 61.6, 50.1, 32.2, 30.6.
MS (EI): *m/z* (%) = 219 ($M^{+\bullet}$, 33), 159 (100), 131 (80).
HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $C_{12}H_{13}NO_3$: 219.0890. Found: 219.0895.
IR (KBr) ν_{max} 2973, 2935, 1713, 1649 cm^{-1}.

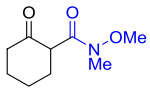
β-Carbonyl-Weinreb amide **9i**



Compound **9i** was prepared from 3,4-dihydrocoumarin according to the general procedure. Purified by flash chromatography (silica, 2:1 hexane/EtOAc) to afford **9i** (204 mg, 87%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.19 (complex m, 2H), 7.10 (m, 1H), 7.04 (m, 1H), 4.18 (dd, J = 12.9, 6.3 Hz, 1H), 3.72 (s, 3H), 3.27 (s, 3H), 3.49 (dd, J = 16.1, 12.9 Hz, 1H), 2.96 (dd, J = 16.1, 6.3 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 165.6, 151.2, 128.3, 128.0, 124.6, 121.7, 116.5, 61.5, 42.2, 32.1, 26.7.
MS (EI): *m/z* (%) = 235 ($M^{+\bullet}$, 20), 175 (39), 147 (100).
HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $C_{12}H_{13}NO_4$: 235.0839. Found: 235.0846.
IR (KBr) ν_{max} 2976, 2943, 1760, 1659, 1138 cm^{-1}.

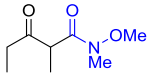
β-Keto-Weinreb amide ***9j***



Compound **9j** was prepared from cyclohexanone according to the general procedure. Purified by flash chromatography (silica, 4:1 hexane/EtOAc) to afford **9j** (140 mg, 76%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (m, 1H), 3.64 (s, 3H), 3.23 (s, 3H), 2.53 (m, 1H), 2.37 (m, 1H), 2.24-1.92 (complex m, 4H), 1.88-1.62 (complex m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 170.8, 61.2, 53.7, 41.9, 32.0, 29.7, 27.2, 23.7.
MS (EI): *m/z* (%) = 185 ($M^{+\bullet}$, 20), 125 (100).
HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $C_9H_{15}NO_3$: 185.1046. Found: 185.1055.
IR (KBr) ν_{max} 2939, 2865, 1711, 1653, 1385 cm^{-1}.

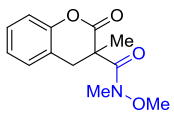
β-Keto-Weinreb amide ***9k***



Compound **9k** was prepared according to the general procedure. Purified by flash chromatography (silica, 4:1 hexane/EtOAc) to afford **9k** (130 mg, 77%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (m, 1H), 3.66 (s, 3H), 3.20 (s, 3H), 2.50 (m, 2H), 1.33 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 171.9, 61.1, 49.8, 33.6, 32.4, 13.1, 7.5.
MS (EI): *m/z* (%) = 173 ($M^{+\bullet}$, 3), 113 (42).
HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $C_8H_{15}NO_3$: 173.1046. Found: 173.1048.
IR (KBr) ν_{max} 2980, 2941, 1719, 1661, 1460, 1381 cm^{-1}.

β-Keto-Weinreb amide ***9l***



A magnetically stirred solution of 3-methylchroman-2-one (168 mg, 1.0 mmol) in dry THF (5 mL) was cooled to 0 °C then treated with LiHMDS (1.1 mL of a 1 M solution in THF, 1.1 mmol). The resulting mixture was maintained at this temperature for 0.5 h then cooled to −78 °C and treated with cyanoformamide 4 (125 mg, 1.1 mmol). After 0.1 h at −78 °C the mixture was warmed to −40 °C and maintained at this temperature for 0.5 h before being treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate)

to afford, after concentration of the appropriate fractions compound 9l (230 mg, 92%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 7.03 (m, 1H), 3.64 (s, 3H), 3.56 (d, J = 15.6 Hz, 1H), 3.12 (s, 3H), 2.78 (d, J = 15.6 Hz, 1H), 1.56 (m, 3H).

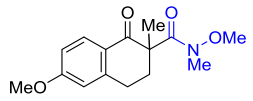
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.9, 151.1, 128.4, 128.2, 124.5, 121.4, 116.2, 60.4, 47.9, 35.0, 33.0, 21.6.

MS (EI): m/z (%) = 249 ($M^{+\bullet}$, 20), 234 (39), 161 (100).

HRMS (EI) m/z $M^{+\bullet}$ calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.1003.

IR (KBr) ν_{max} 2985, 2939, 1759, 1655, 1457, 1231 cm^{-1}.

β-Keto-Weinreb amide ***9m***



A magnetically stirred solution of 6-methoxy-2-methyl-1-tetralone (190 mg, 1.00 mmol) in dry ether (3 mL) was cooled to −78 °C then treated dropwise with lithium diisopropylamide (1.29 mL, 1.05 mmol, 0.81 M solution in ether [generated from *n*-butyllithium (7.00 mL of a 1.5 M solution in hexanes) and diisopropylamine (1.60 mL, 11.5 mmol) in ether (4.3 mL)]. The resulting mixture was maintained at this temperature for 1 h then warmed to 0 °C for 0.25 h then recooled to −78 °C and treated with **4** (125 mg, 1.10 mmol) followed by hexamethylphosphoramide (HMPA) (179 µL, 1.00 mmol) After 0.5 h at −78 °C the mixture was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with DCM (3 × 10 mL). The combined organic phases were washed with lithium chloride (10 mL, 5% w/v), brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **9m** (174 mg, 63%) as white crystals, m.p. 89 – 92 ºC. The reaction was carried out in duplicate with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (250 µL) in place of HMPA to afford **9m** (173 mg, 63%) as white crystals, m.p. 89 – 92 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, J = 8.7 Hz, 1H), 6.79 (dd, J = 8.7, 2.5 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H), 3.29 (s, 3H), 3.12 (s, 3H), 2.96 (ddd, J = 16.6, 11.6, 4.8 Hz, 1H), 2.81 (ddd, J = 16.6, 4.6, 4.6 Hz, 1H), 2.54 (ddd, J = 13.0, 11.6, 4.8 Hz, 1H), 1.81 (dt, J = 13.0, 4.6 Hz, 1H), 1.41 (s, 3H).

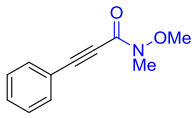
^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.3, 174.3, 163.3, 144.8, 129.8, 125.1, 113.3, 112.2, 59.0, 55.3, 52.7, 32.7, 31.9, 25.7, 20.1.

MS (EI): m/z (%) 277 ($M^{+\bullet}$, 8), 217 (9), 189 (30), 161 (100), 91 (10).

HRMS (EI) m/z $M^{+\bullet}$ calcd for $[C_{15}H_{19}NO_4]^{+\bullet}$: 277.1309; found, 277.1316;

IR (KBr) ν_{max} 1653, 1598, 1457, 1374, 1346, 1262, 1230, 1093, 999, 858 cm^{-1}.

*Weinreb amide **10a** – Prepared from lithium phenyl acetylide*

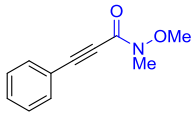


A magnetically stirred solution of phenyl acetylene (102 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with LiHMDS (1.1 mL of a 1M solution in THF, 1.1 mmol). The resulting mixture was maintained at this temperature for 20 minutes then treated with cyanoformamide 4 (125 mg, 1.1 mmol). The resulting mixture was maintained at −78 °C for 15 minutes then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10a** (174 mg, 92%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.1 Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 3.84 (s, 3H), 3.29 (br m, 3H).

All spectra were consistent with those previously reported.[6]

*Weinreb amide **10a** – Prepared from magnesium phenyl acetylide*



A magnetically stirred solution of phenyl acetylene (102 mg, 1.0 mmol) in dry THF (5 mL) was cooled to 0 °C then treated with MeMgBr (0.33 mL of a 3M solution in Et_2O, 1.1 mmol). The resulting mixture was maintained at this temperature for 1 h then treated with cyanoformamide 4 (125 mg, 1.1 mmol). After 0.25 h at 0 °C the reaction was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10a** (144 mg, 76%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.1 Hz, 2H), 7.43 (m, 1H), 7.37 (m, 2H), 3.84 (s, 3H), 3.29 (br m, 3H).

All spectra were consistent with those previously reported.[6]

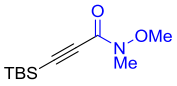
*Weinreb amide **10b***

A magnetically stirred solution of 2-bromopyridine (158 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with *n*-butyllithium (0.8 mL of a 1.45 M solution in hexanes, 1.1 mmol). The resulting solution was stirred at −78 °C for 1 hour then treated with cyanoformamide 4 (125 mg, 1.1 mmol) and warmed to 0 °C over 20 minutes. The reaction was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10b** (125 mg, 75%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.8 Hz, 1H), 7.78 (td, J = 7.7, 1.7 Hz, 1H), 7.66 (broad s, 1H), 7.35 (dd, J = 7.7, 4.8 Hz, 1H), 3.75 (s, 3H), 3.40 (s, 3H).

All spectra were consistent with those previously reported.[7]

*Weinreb amide **10c***



A magnetically stirred solution of tert-butyl(ethynyl)dimethylsilane (228 mg, 2.0 mmol) in dry THF (8 mL) was cooled to −78 °C then treated with *n*-Butyl lithium (1.0 mL of a 2.05 M solution in hexanes, 2.05 mmol). The resulting mixture was maintained at this temperature for 0.25 h then treated with cyanoformamide 4 (228 mg, 2.0 mmol). The resulting mixture was maintained at −78 °C for 0.1 h then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10c** (399 mg, 88%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 3H), 3.23 (s, 3H), 0.98 (s, 9H), 0.19 (s, 6H).

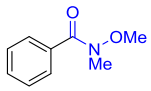
^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.7, 109.9, 95.8, 62.0, 32.2, 25.9 (3C), 16.4, -5.3 (2C).

MS (+LRESI) *m/z* (%) 228 (100) $[M+H]^+$.

HRMS (+ESI) *m/z* $[M+Na]^+$ calcd for $[C_{11}H_{21}NNaO_2Si]^+$: 250.1234; found, 250.1236.

IR (KBr) ν_{max} 2955, 2932, 1647, 1472, 1463, 1410, 1381, 1252, 1118, 1007, 940, 842, 828, 779, 724 cm^{-1}.

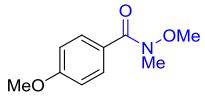
Weinreb amide ***10d***



A magnetically stirred solution of cyanoformamide 4 (125 mg, 1.1 mmol) in dry THF (5 mL) at 0 °C was treated, dropwise, with a solution of phenylmagnesium bromide (1.0 mL of a 1M solution in THF, 1.0 mmol). The resulting mixture was maintained at this temperature for 15 minutes then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10d** (152 mg, 92%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.41 (m, 3H), 3.55 (s, 3H), 3.36 (s, 3H).
All spectra were consistent with those previously reported.[8]

Weinreb amide ***10e***

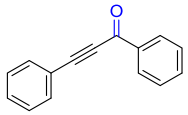


A magnetically stirred solution of 4-bromoanisole (0.126 mL, 1.0 mmol), magnesium turnings (26 mg, 1.0 mmol) and a crystal of iodine in dry THF (5 mL) was heated at 50 °C for 30 minutes. The resulting suspension was cooled to 0 °C and treated with cyanoformamide 4 (125 mg, 1.1 mmol). After 15 minutes at this temperature the mixture was treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10e** (171 mg, 88%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.56 (s, 3H), 3.35 (s, 3H).

All spectra were consistent with those previously reported.[88]

Ketone ***10f***



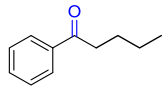
A magnetically stirred solution of phenyl acetylene (102 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with LiHMDS (1.1 mL of a 1M solution in THF, 1.1 mmol). The

resulting mixture was maintained at this temperature for 0.33 h then treated with cyanoformamide 4 (125 mg, 1.1 mmol). The resulting mixture was maintained at −78 °C for 15 minutes then warmed to 0 °C and treated with PhMgBr (1.5 mL of a 1M solution in THF, 1.5 mmol). The resulting mixture was maintained at this temperature for 30 minutes then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10f** (184 mg, 89%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 2H), 7.70 (m, 2H), 7.64 (m, 1H), 7.56 – 7.47 (complex m, 3H), 7.43 (m, 2H).

All spectra were consistent with those previously reported.[9]

*Ketone **10g***

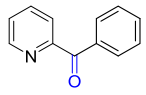


A magnetically stirred solution of cyanoformamide 4 (125 mg, 1.1 mmol) in dry THF (5 mL) at 0 °C was treated, dropwise, with a solution of phenylmagnesium bromide (1.0 mL of a 1M solution in THF, 1.0 mmol). The resulting mixture was maintained at this temperature for 0.25 h then cooled to −78 °C and treated with *n*-butyllithium (1 mL of a 1.5 M solution in hexanes, 1.5 mmol). The reaction was maintained at this temperature for 20 minutes then treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10g** (140 mg, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 7.55 (m, 1H), 7.46 (m, 2H), 2.97 (dd, J = 7.4 Hz, 2H), 1.73 (m, 2H), 1.42 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

All spectra were consistent with those previously reported.[10]

*Ketone **10h***



A magnetically stirred solution of 2-bromopyridine (158 mg, 1.0 mmol) in dry THF (5 mL) was cooled to −78 °C then treated with *n*-butyllithium (0.8 mL of a 1.45 M solution in hexanes, 1.1 mmol). The resulting solution was stirred at −78 °C for 1 h then treated with cyanoformamide 4 (125 mg, 1.1 mmol) and warmed to 0 °C over 0.33 h then treated with PhMgBr (1.5 mL of a 1M solution in THF, 1.5 mmol). The reaction was maintained at this temperature for 20 minutes then treated with $NaHCO_3$

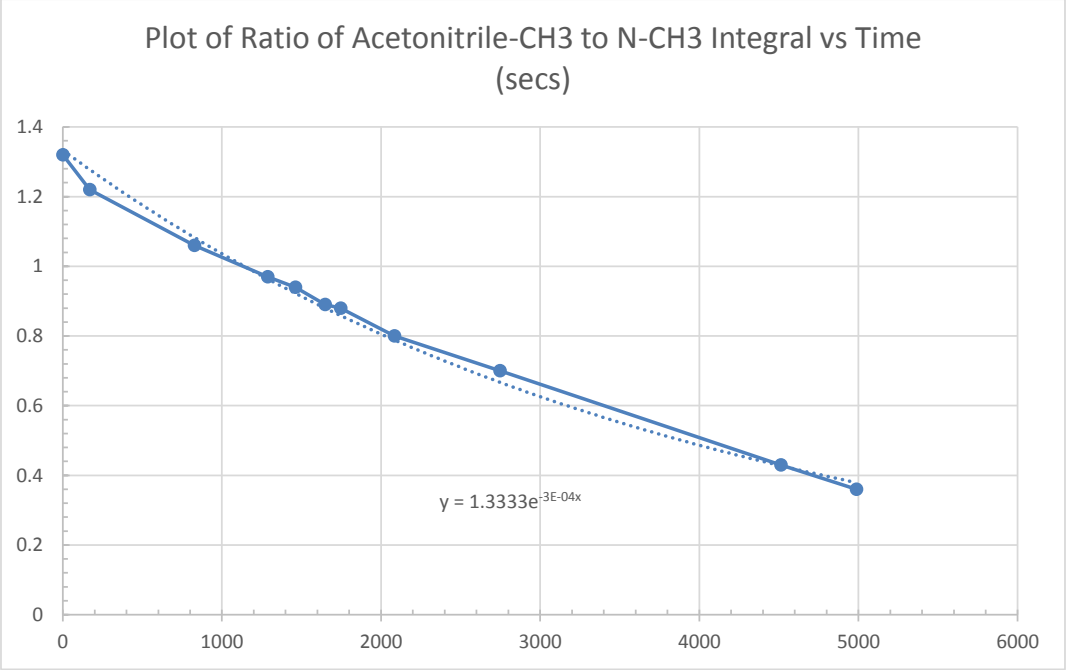
(5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 5 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the appropriate fractions compound **10h** (159 mg, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dt, J = 4.8, 1.3 Hz, 1H), 8.06 (m, 3H), 7.91 (td, J = 7.7, 1.7 Hz, 1H), 7.60 (m, 1H), 7.49 (m, 3H).

All spectra were consistent with those previously reported.[11]

Half-life determination experiment.

An NMR tube was charged with cyanoformamide **4** (5 µL), acetonitrile (2 µL) and D_2O (0.5 mL) and shaken vigorously for 30 seconds. The ^{1}H NMR spectrum was recorded at regular intervals and the ratio of the N$\underline{CH_3}$ to $\underline{CH_3}$CN integral was recorded. The $t_{1/2}$ was calculated to be 2344 minutes (39 h).



References

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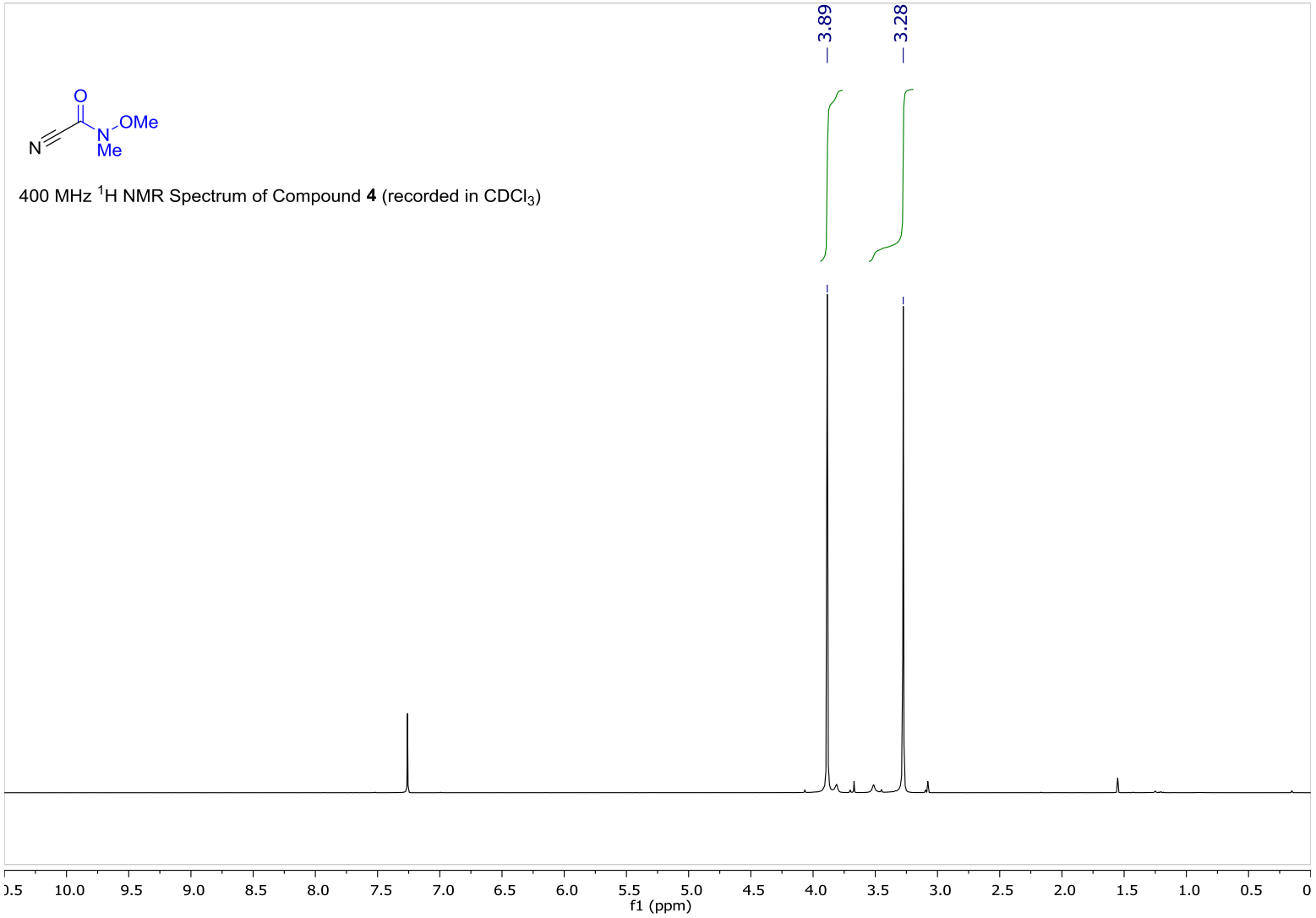
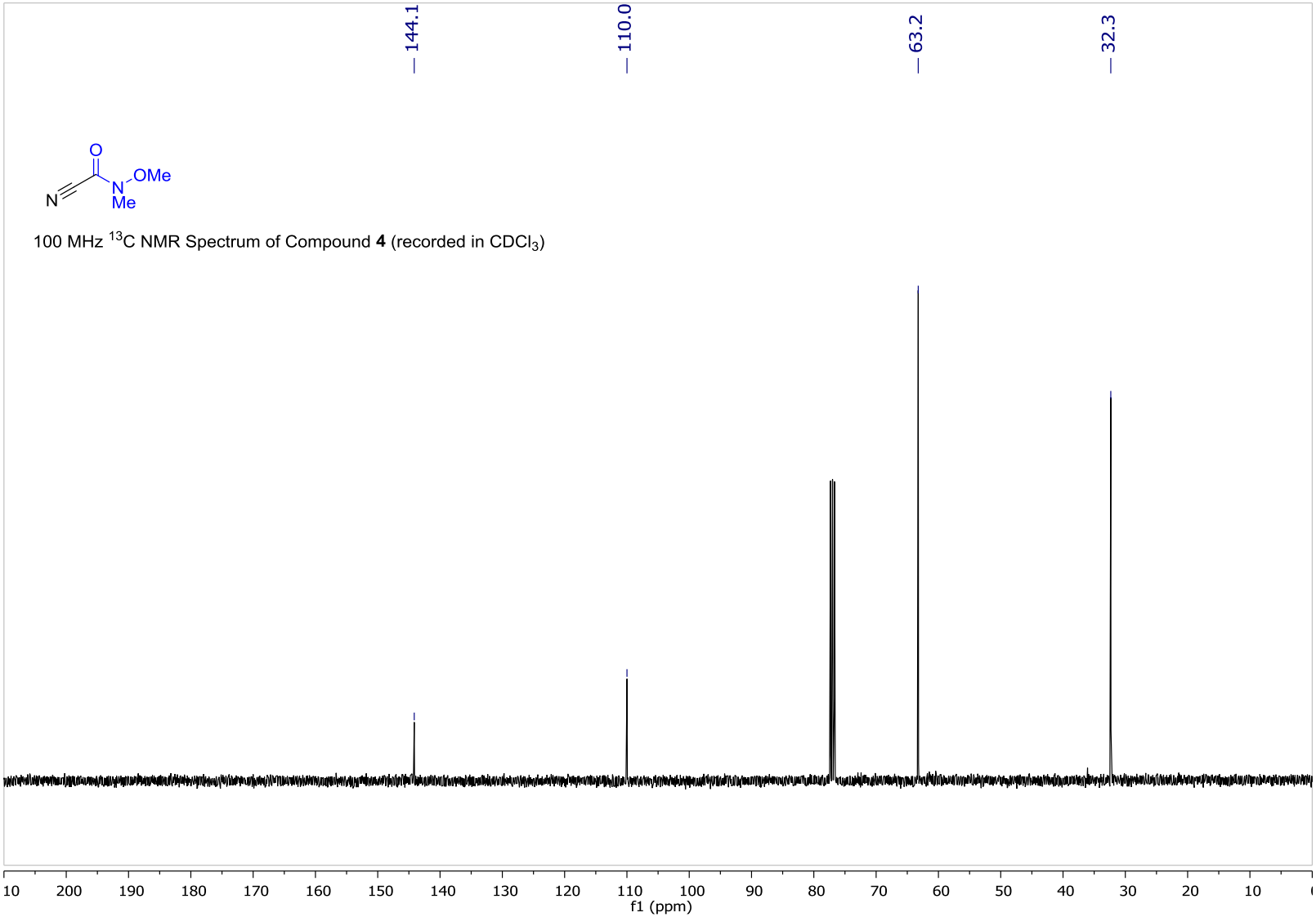
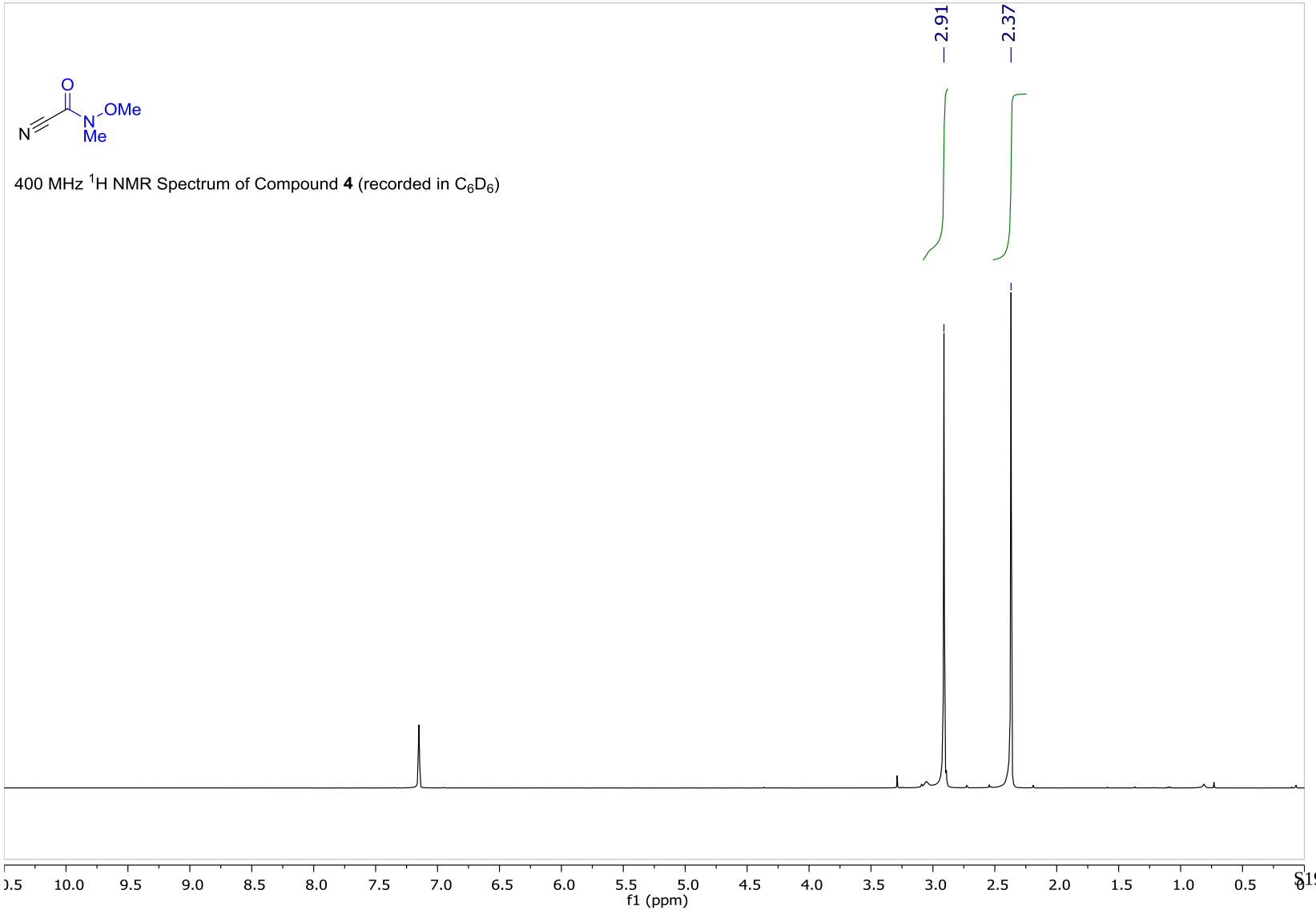
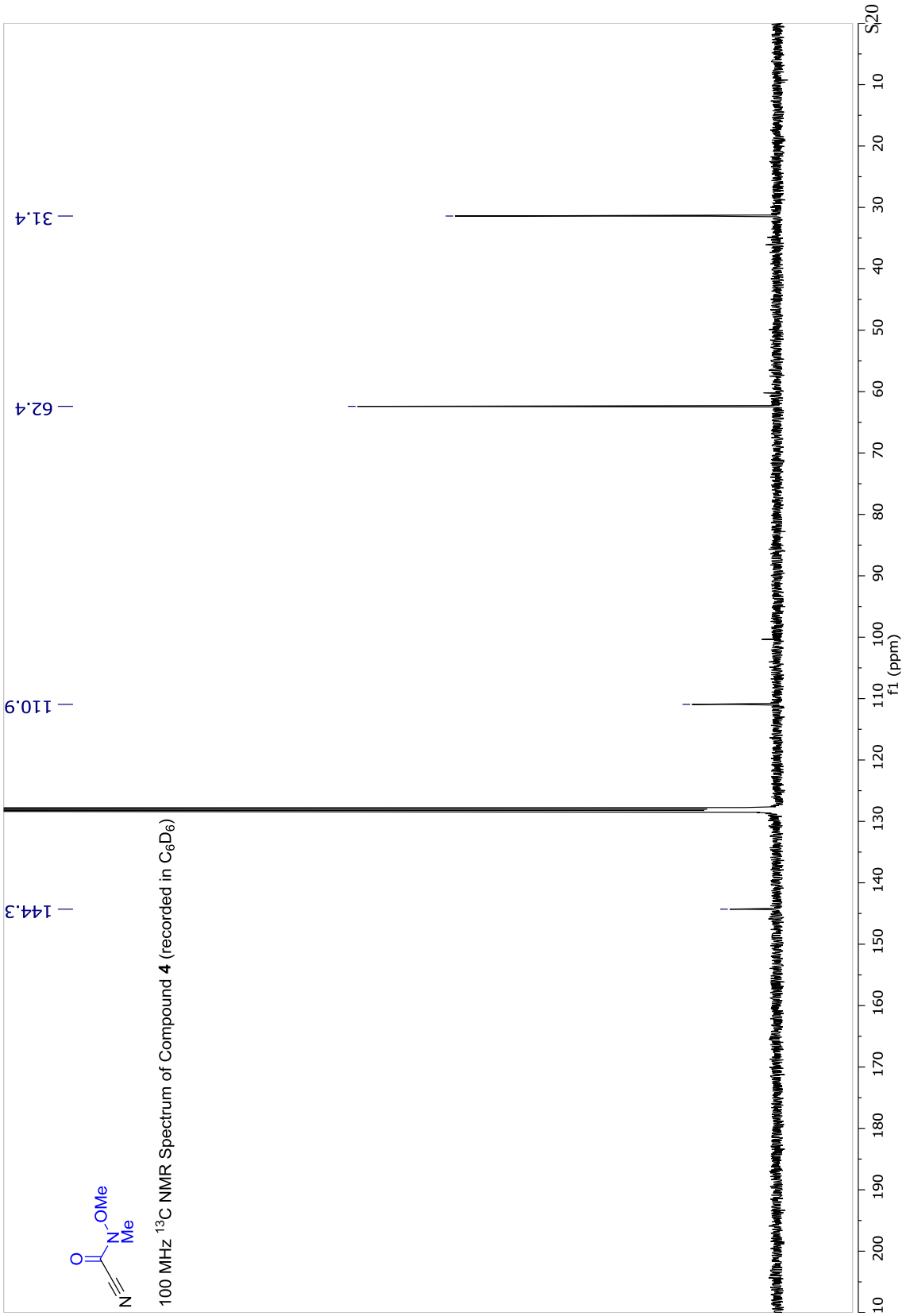
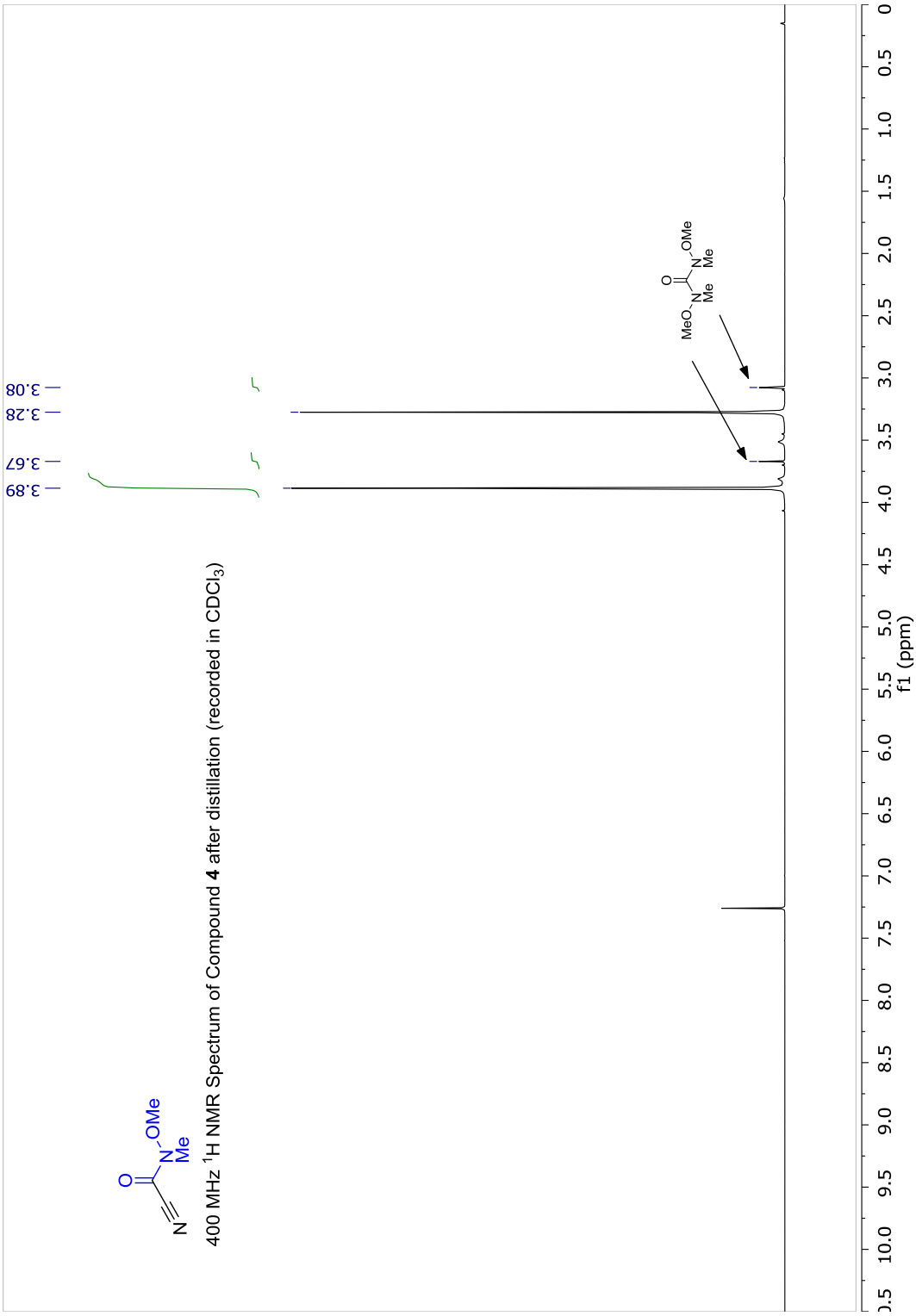
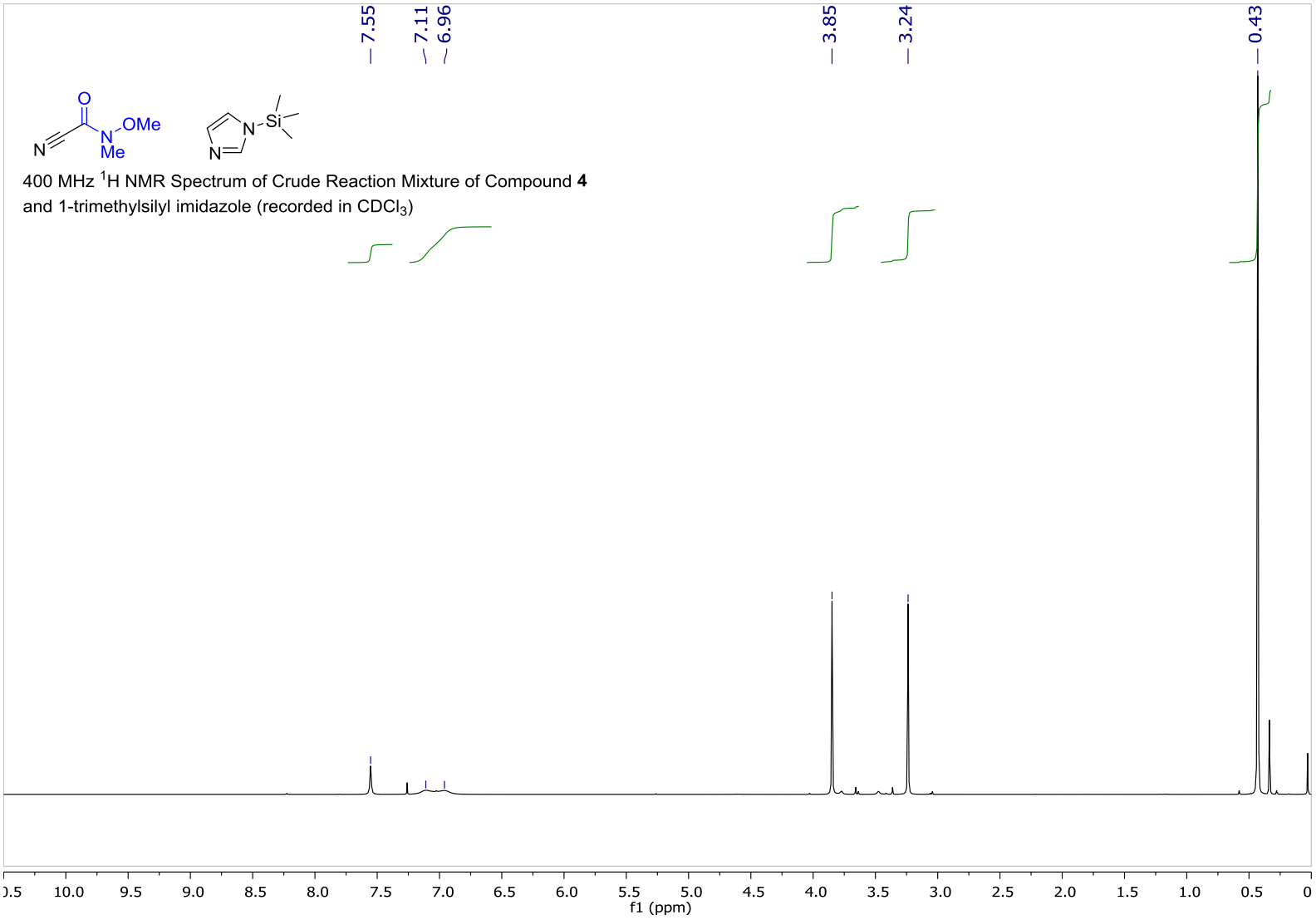

3.89
3.28
O
N
OMe
Me
N
400 MHz ^{1}H NMR Spectrum of Compound **4** (recorded in $CDCl_3$)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


144.1
110.0
63.2
32.3
O
N
OMe
Me
N
100 MHz ^{13}C NMR Spectrum of Compound **4** (recorded in $CDCl_3$)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

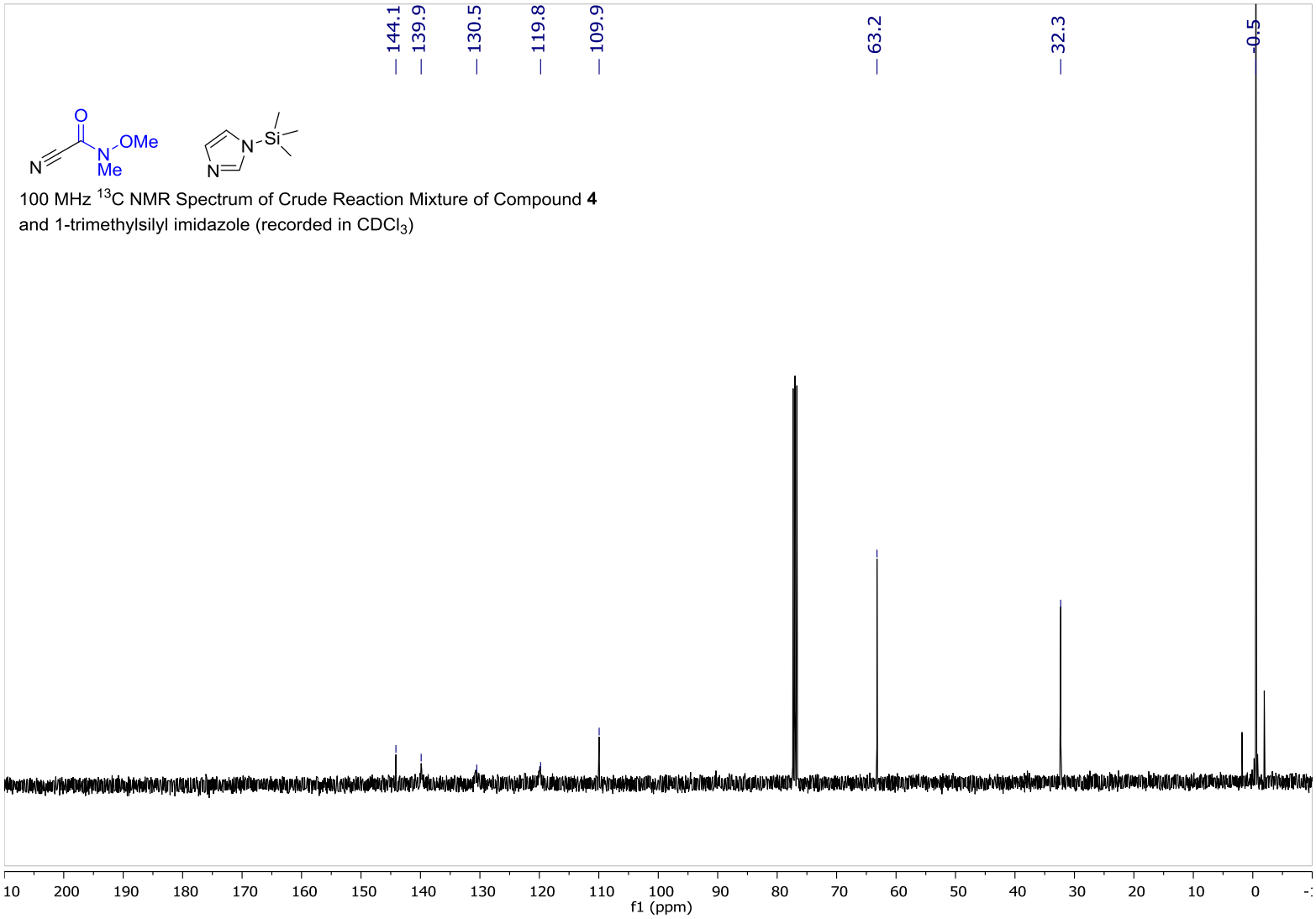

O
N
OMe
Me
N
2.91
2.37
400 MHz ^{1}H NMR Spectrum of Compound **4** (recorded in C_6D_6)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


100 MHz ^{13}C NMR Spectrum of Compound **4** (recorded in C_6D_6)
144.3
110.9
62.4
31.4
f1 (ppm)
S20

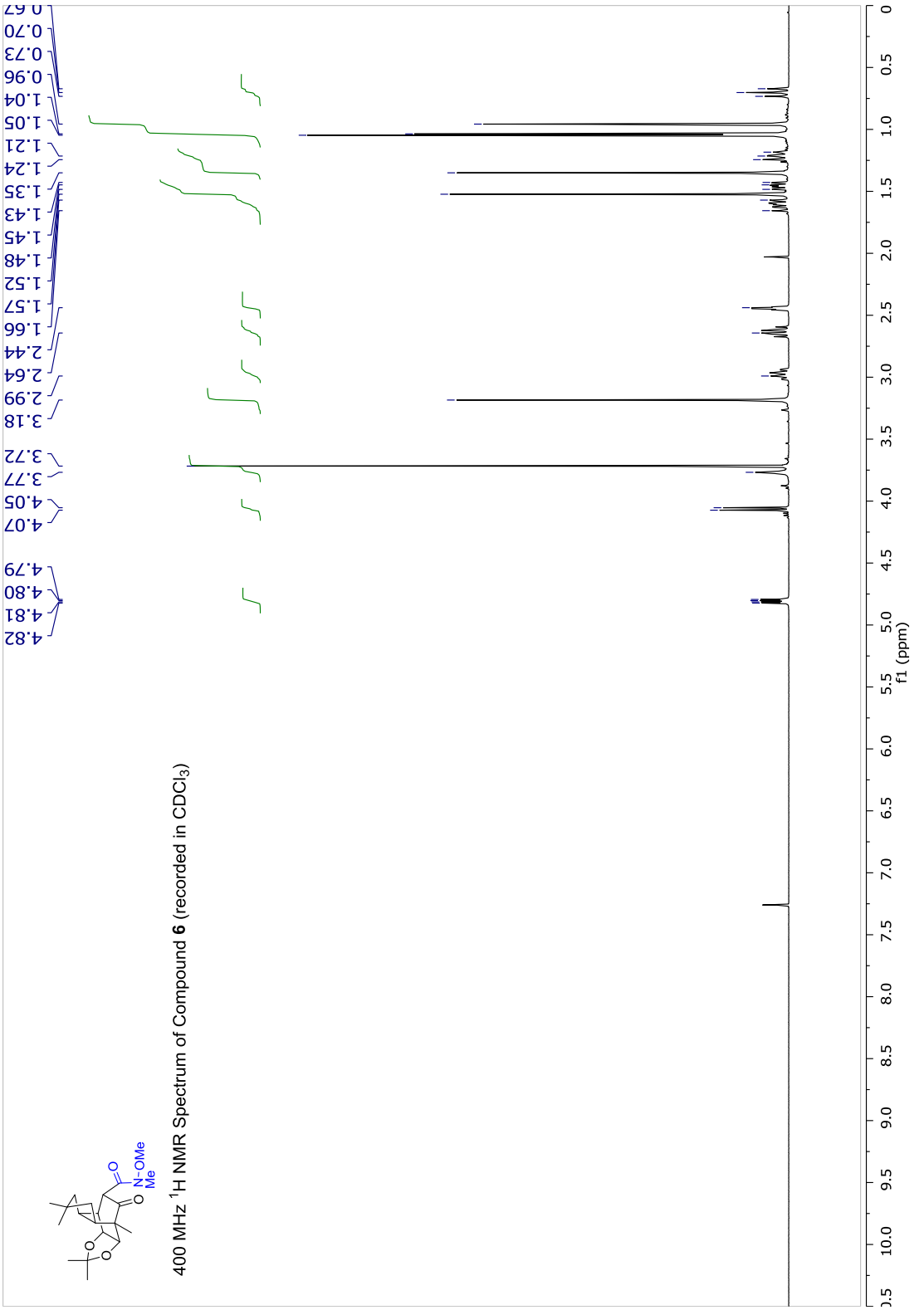

400 MHz ^{1}H NMR Spectrum of Compound **4** after distillation (recorded in $CDCl_3$)
3.89
3.67
3.28
3.08
MeO
N
Me
O
N
Me
OMe
f1 (ppm)

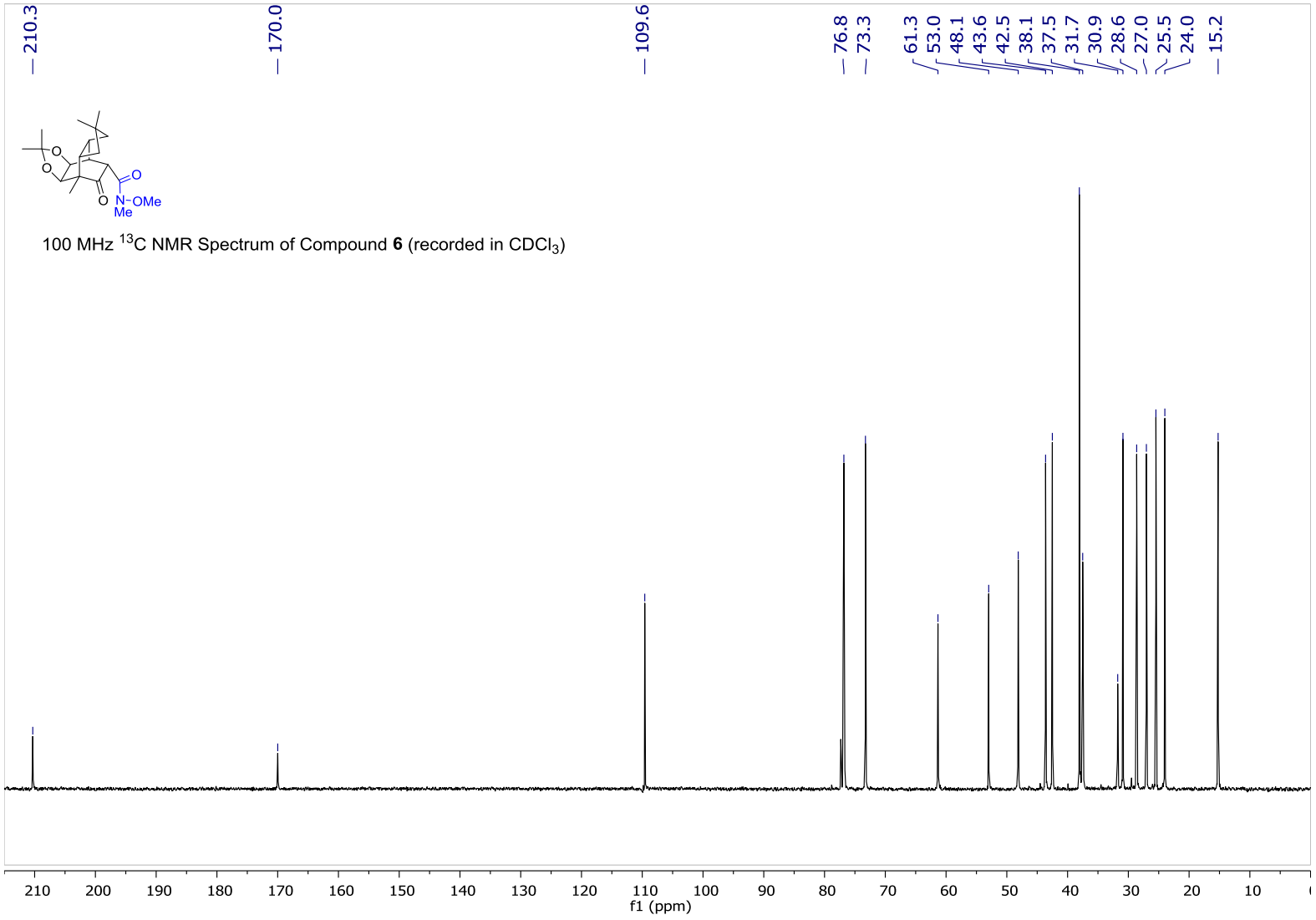


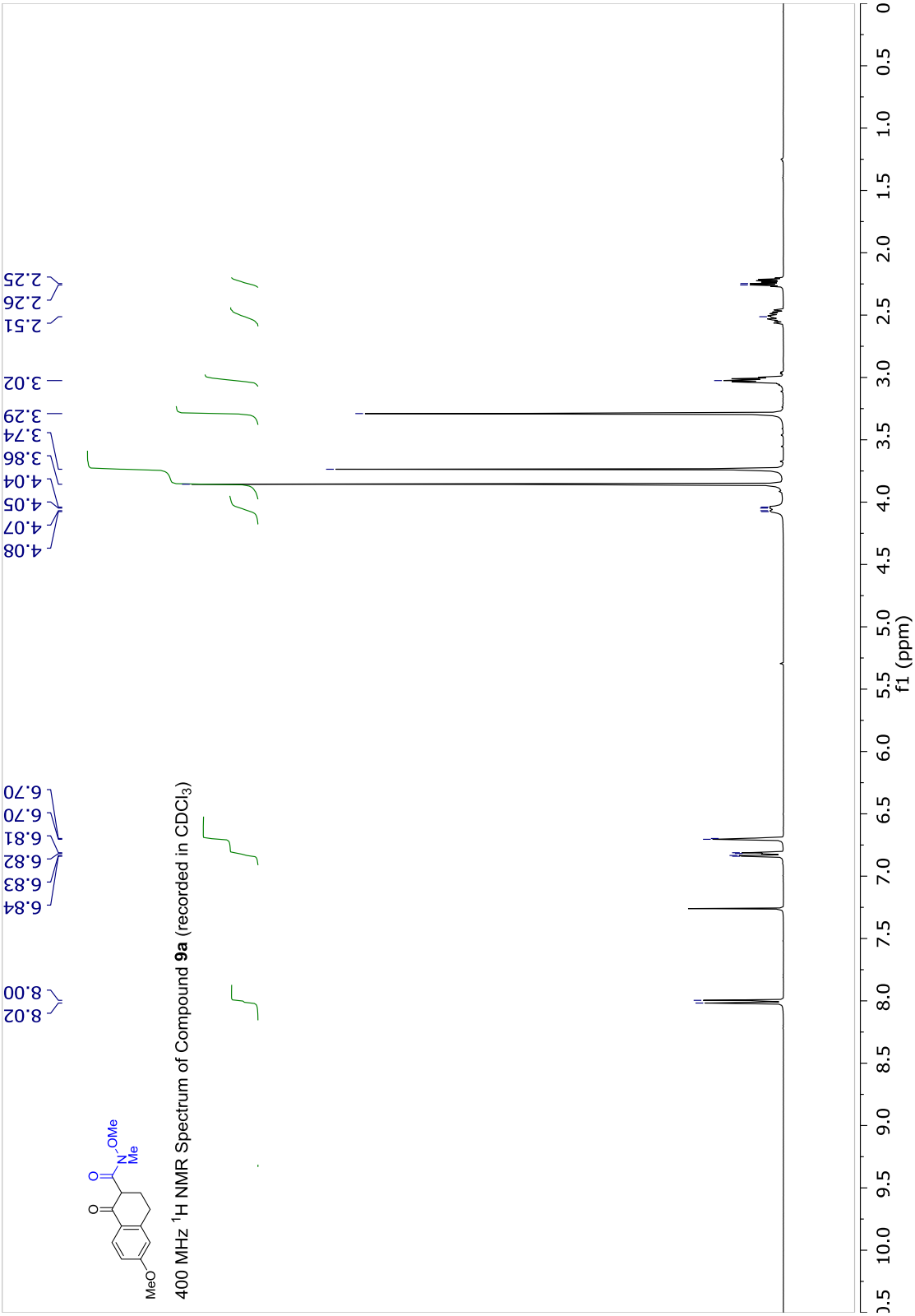
400 MHz ^{1}H NMR Spectrum of Crude Reaction Mixture of Compound **4** and 1-trimethylsilyl imidazole (recorded in $CDCl_3$)

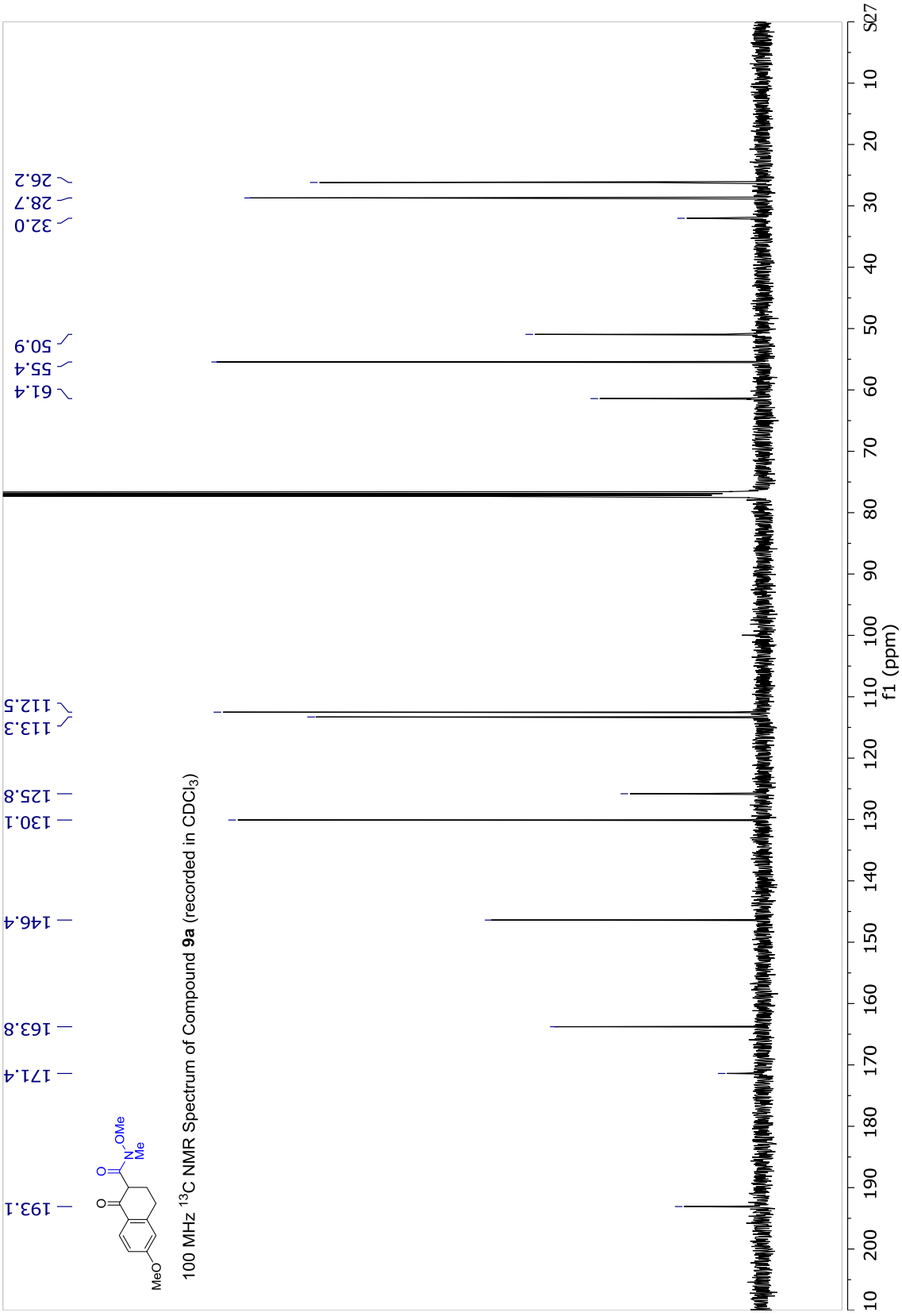


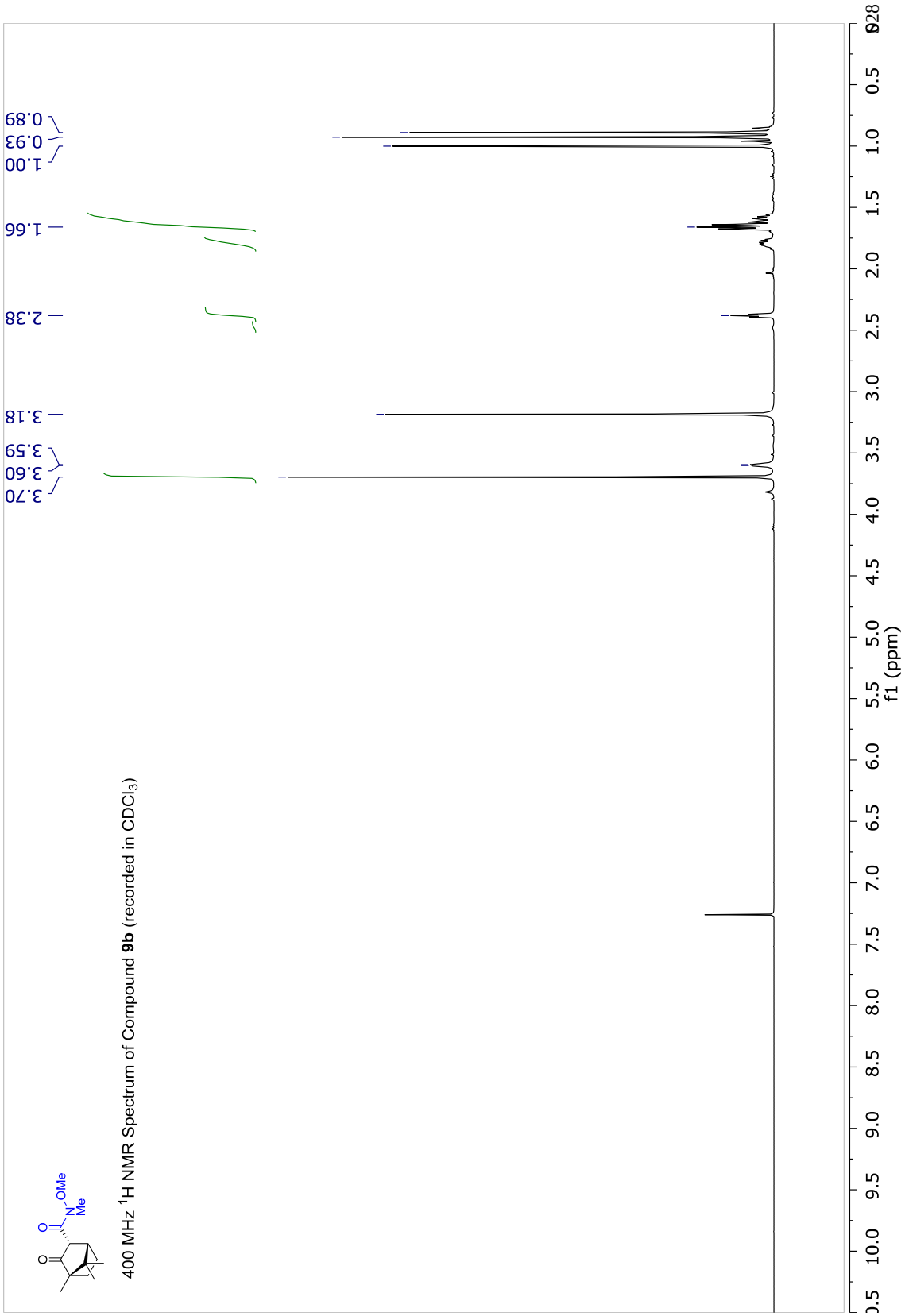
100 MHz ^{13}C NMR Spectrum of Crude Reaction Mixture of Compound **4** and 1-trimethylsilyl imidazole (recorded in $CDCl_3$)

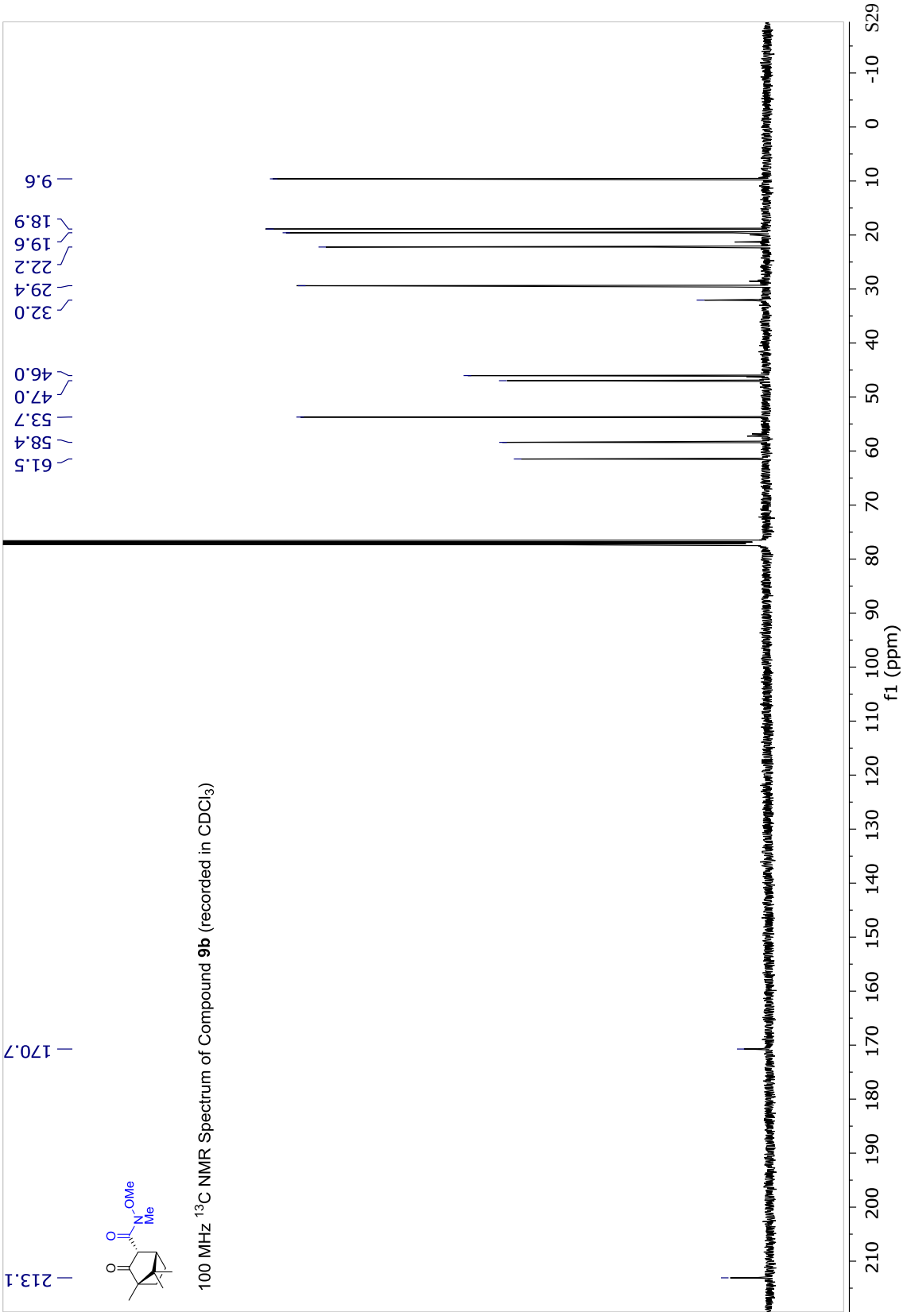

400 MHz ^{1}H NMR Spectrum of Compound **6** (recorded in $CDCl_3$)
N-OMe
Me
O
f1 (ppm)

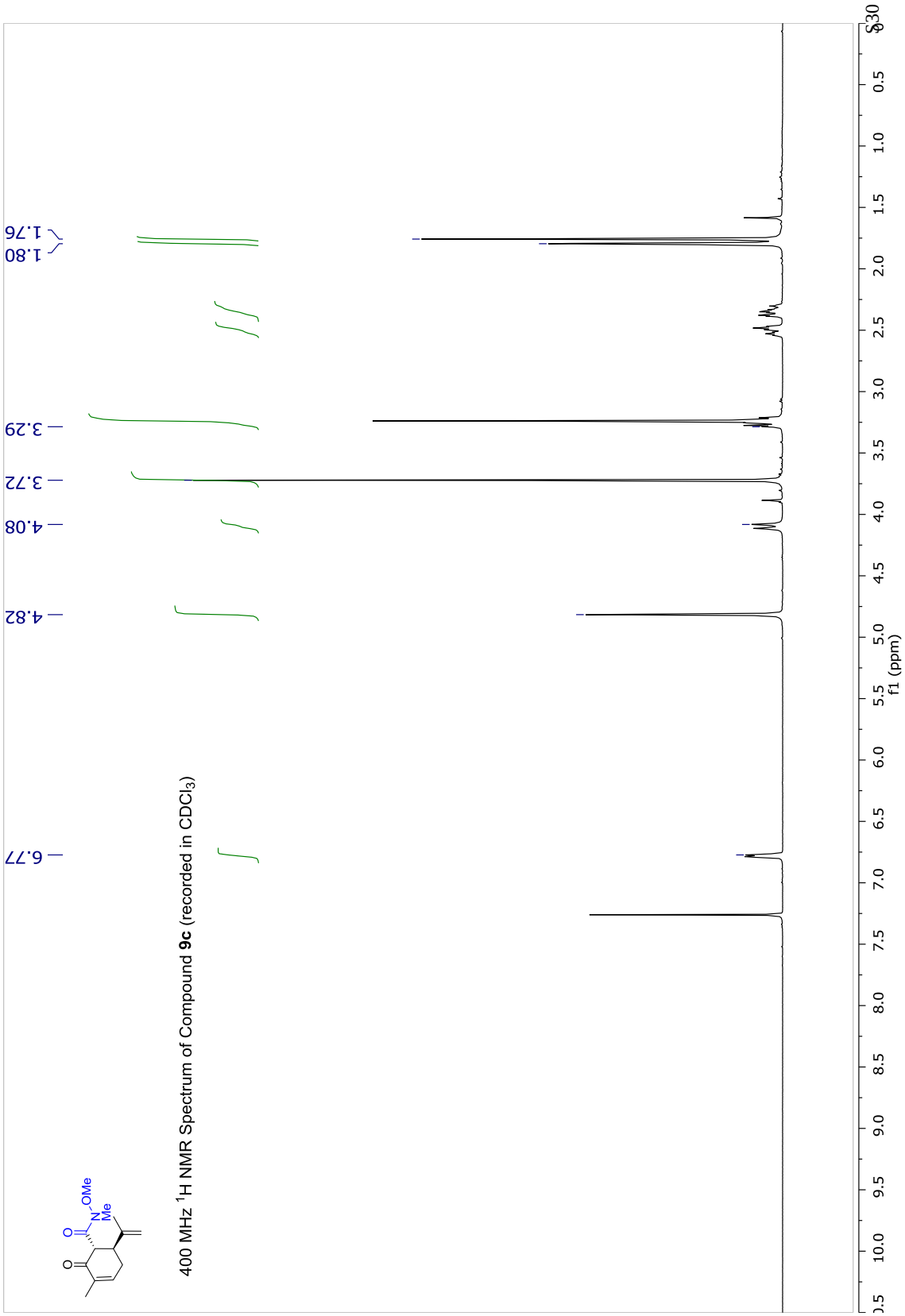

210.3
170.0
109.6
76.8
73.3
61.3
53.0
48.1
43.6
42.5
38.1
37.5
31.7
30.9
28.6
27.0
25.5
24.0
15.2
O
O
O
O
N-OMe
Me
100 MHz ^{13}C NMR Spectrum of Compound **6** (recorded in $CDCl_3$)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

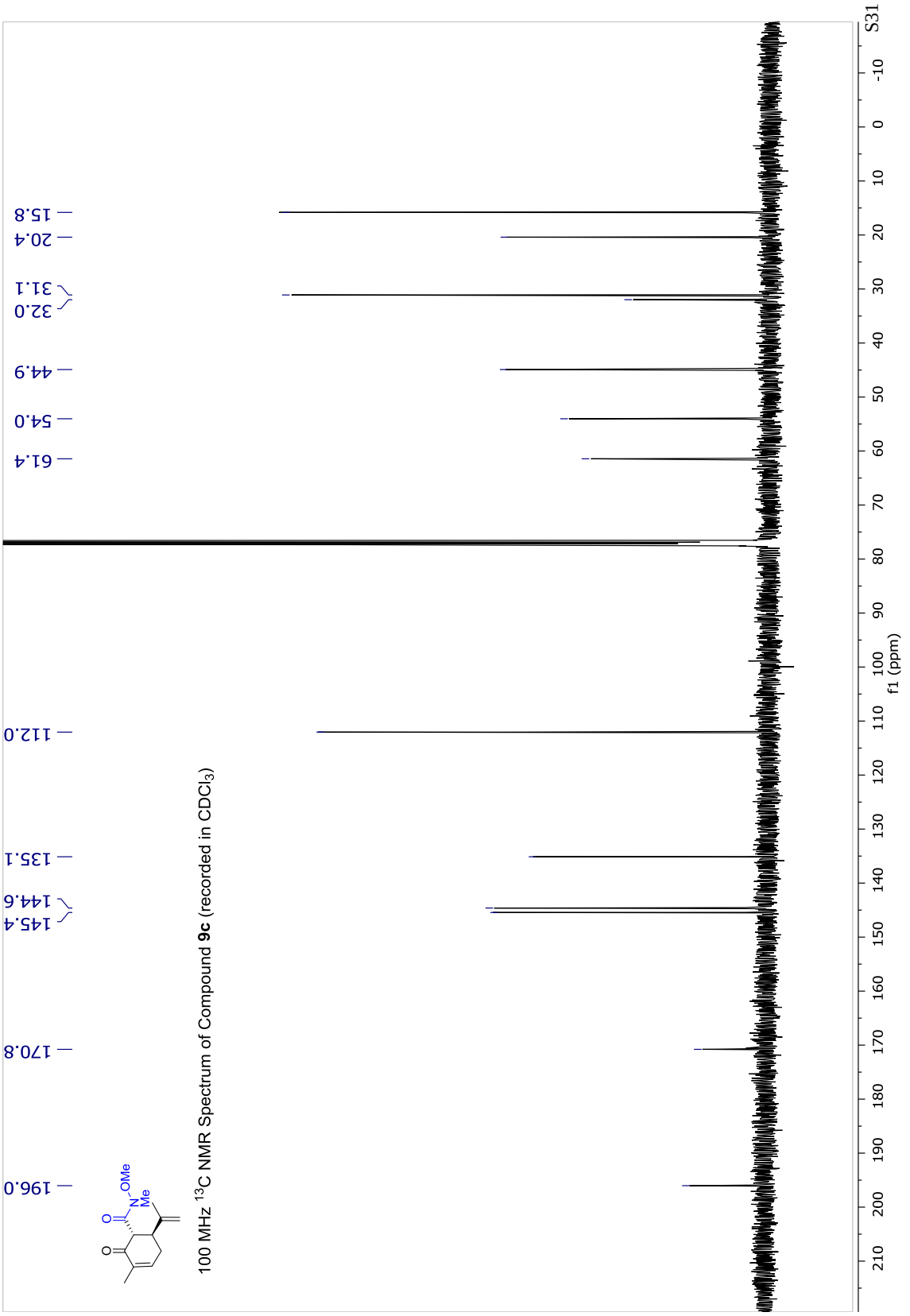

400 MHz ^{1}H NMR Spectrum of Compound **9a** (recorded in $CDCl_3$)
MeO
O
N
OMe
Me
8.02
8.00
6.84
6.83
6.82
6.81
6.70
6.70
4.08
4.07
4.05
4.04
3.86
3.74
3.29
3.02
2.51
2.26
2.25
f1 (ppm)

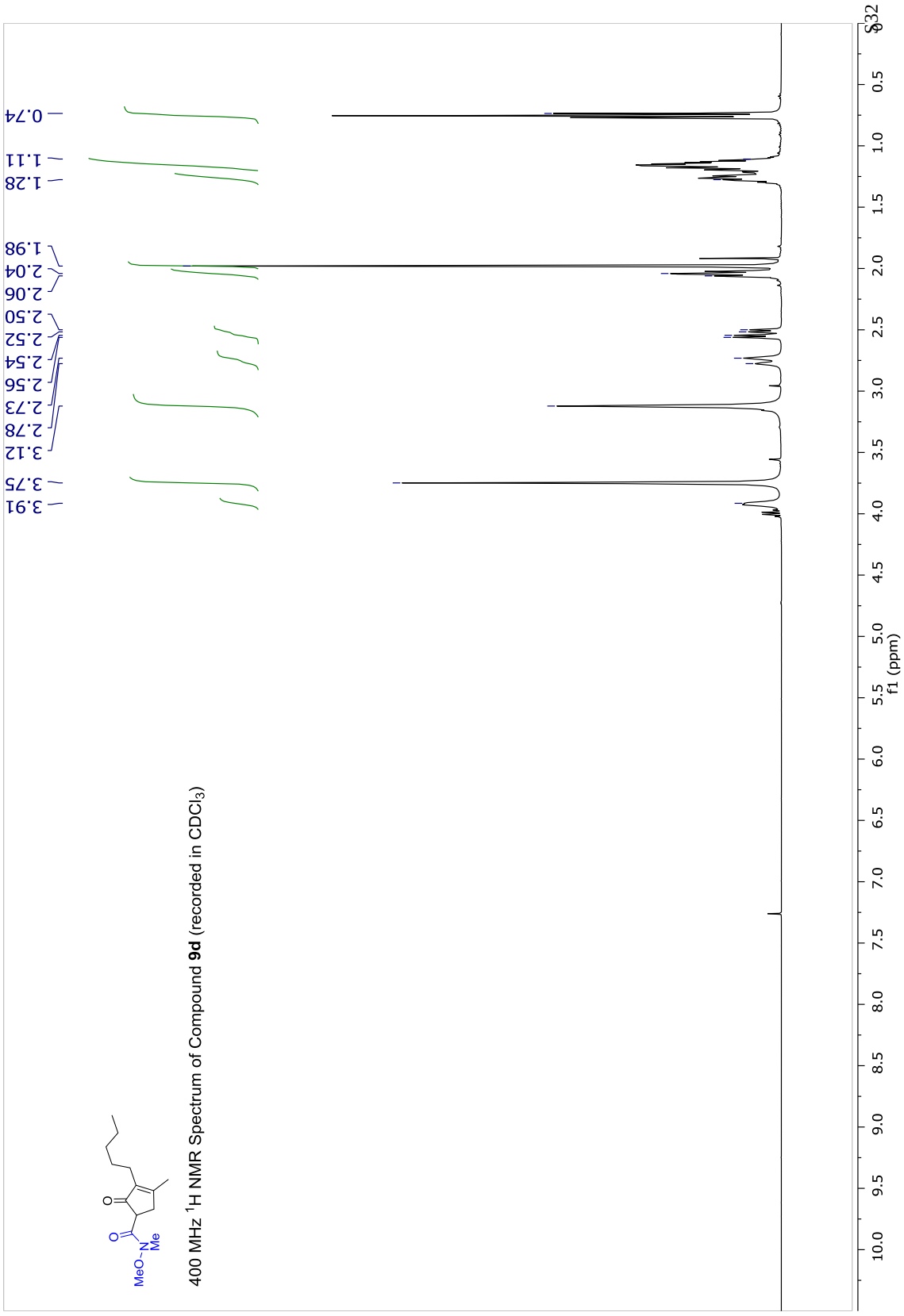

100 MHz ^{13}C NMR Spectrum of Compound **9a** (recorded in $CDCl_3$)
193.1
171.4
163.8
146.4
130.1
125.8
113.3
112.5
61.4
55.4
50.9
32.0
28.7
26.2
MeO
OMe
N
Me
O
O
f1 (ppm)
S27

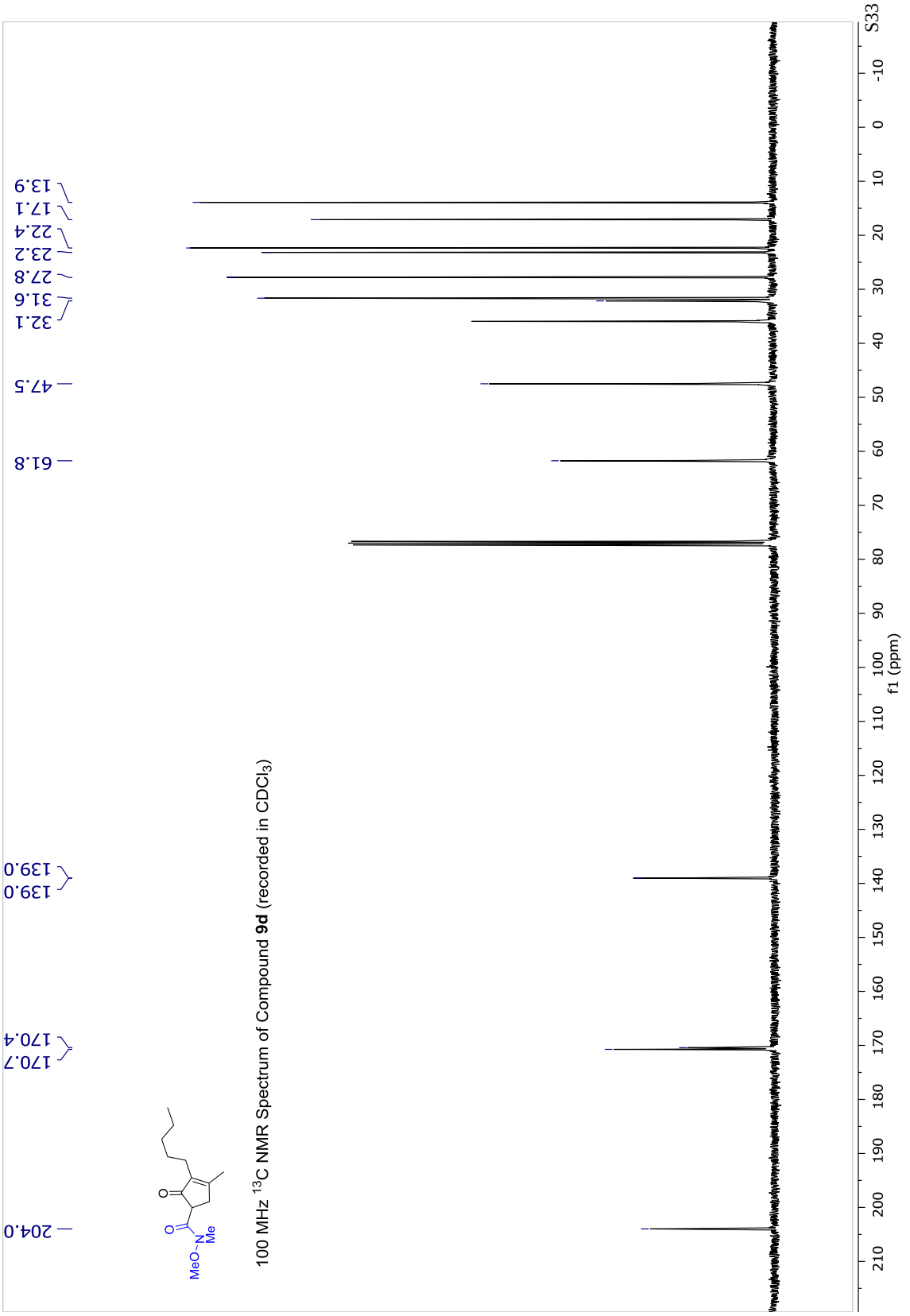

400 MHz ^{1}H NMR Spectrum of Compound **9b** (recorded in $CDCl_3$)
O
N
OMe
Me
O
3.70
3.60
3.59
3.18
2.38
1.66
1.00
0.93
0.89
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

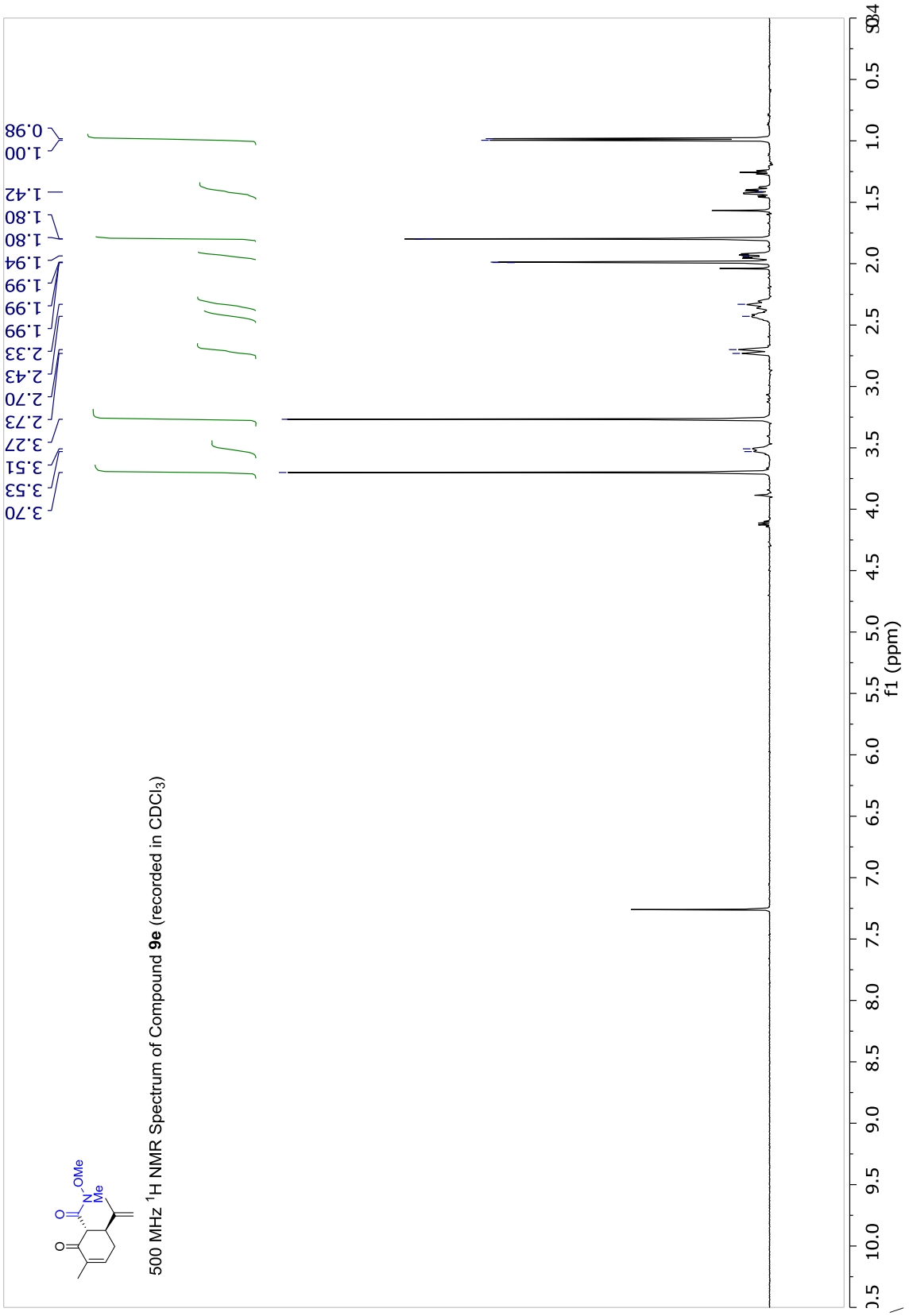

100 MHz ^{13}C NMR Spectrum of Compound **9b** (recorded in $CDCl_3$)
213.1
170.7
61.5
58.4
53.7
47.0
46.0
32.0
29.4
22.2
19.6
18.9
9.6
O
N
OMe
Me
f1 (ppm)

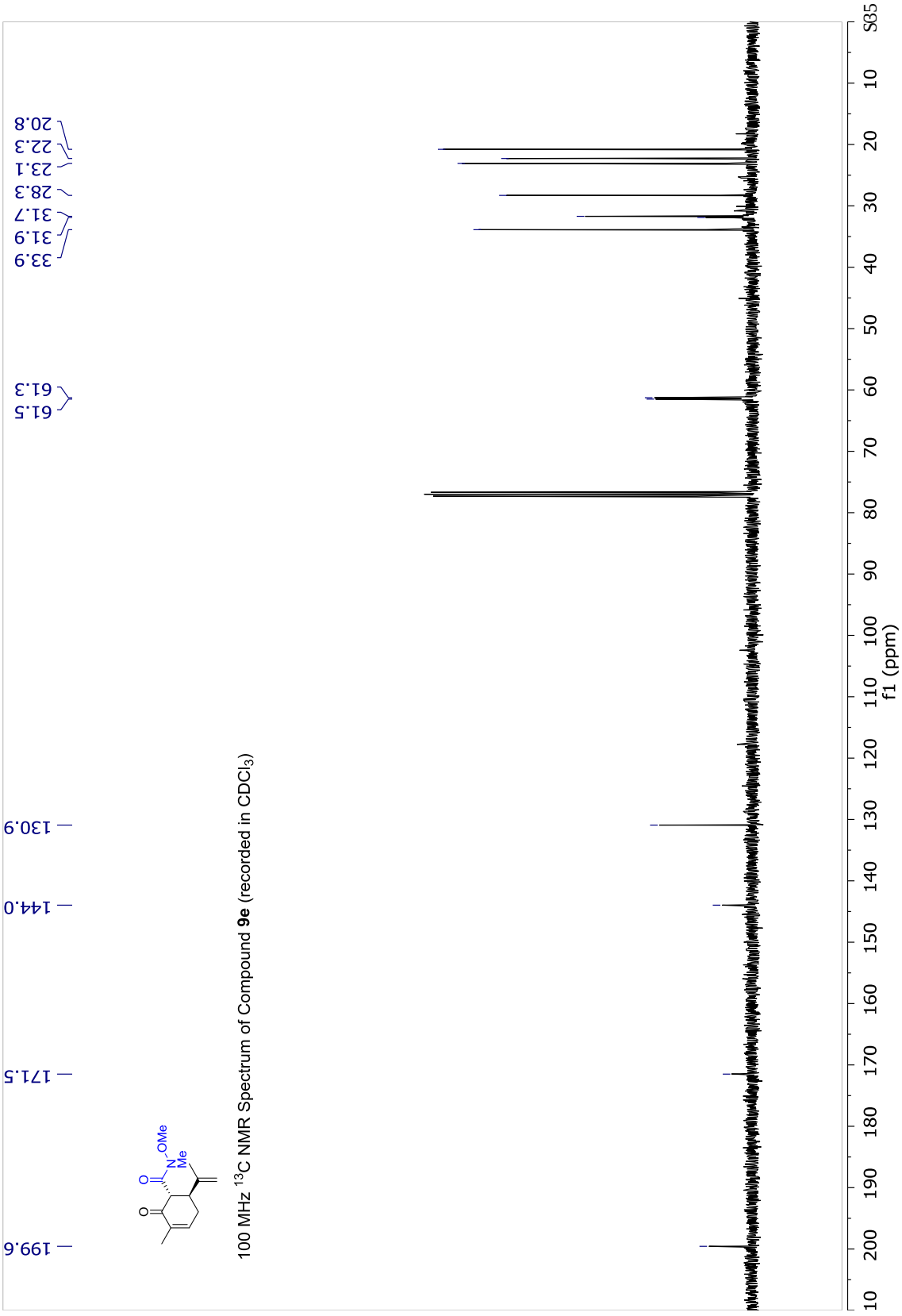

400 MHz ^{1}H NMR Spectrum of Compound **9c** (recorded in $CDCl_3$)
6.77
4.82
4.08
3.72
3.29
1.80
1.76
f1 (ppm)

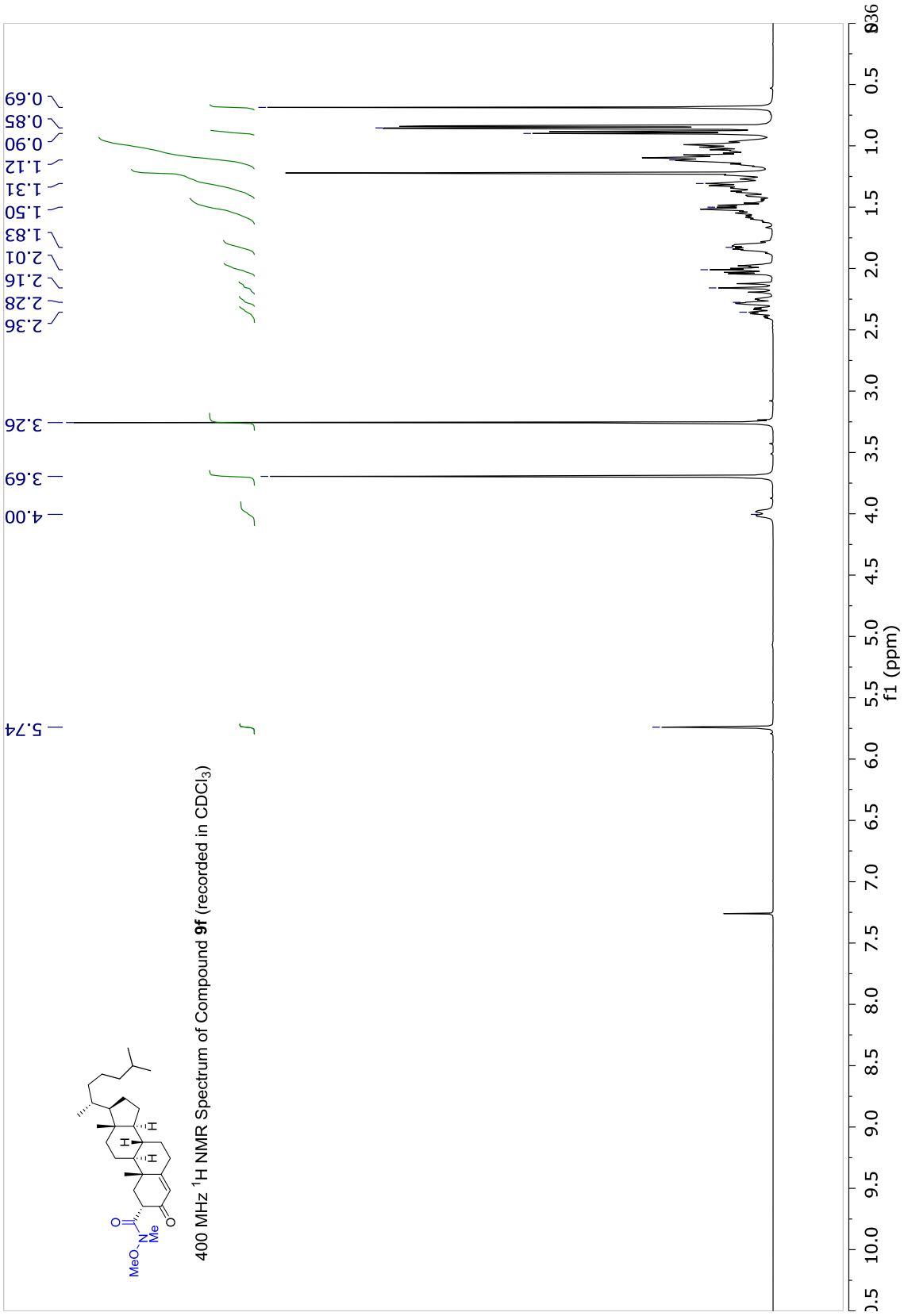

100 MHz ^{13}C NMR Spectrum of Compound **9c** (recorded in $CDCl_3$)
196.0
170.8
145.4
144.6
135.1
112.0
61.4
54.0
44.9
32.0
31.1
20.4
15.8
f1 (ppm)
S31

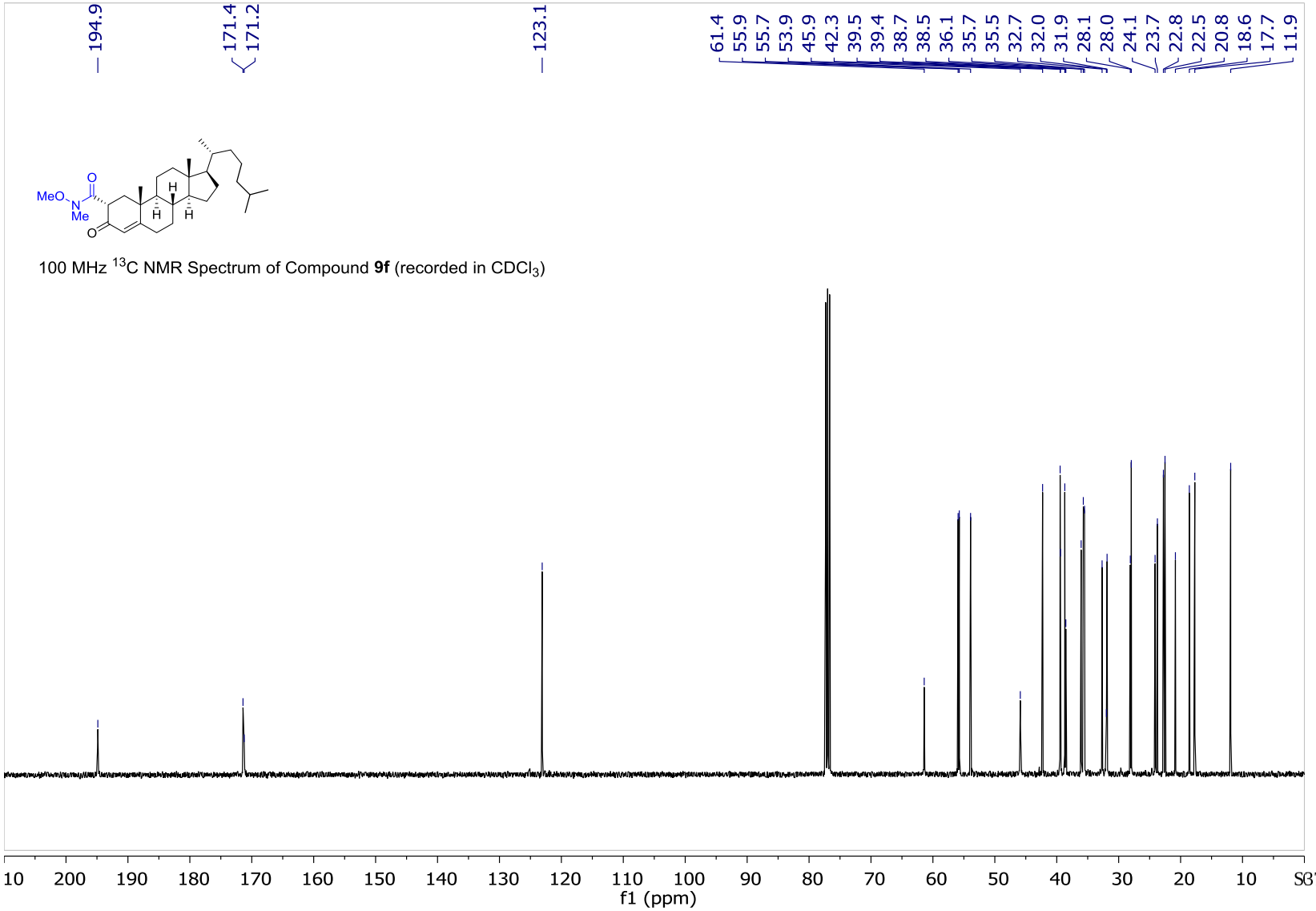

0.74
1.11
1.28
1.98
2.04
2.06
2.50
2.52
2.54
2.56
2.73
2.78
3.12
3.75
3.91
MeO
N
Me
O
O
400 MHz ^{1}H NMR Spectrum of Compound **9d** (recorded in $CDCl_3$)
f1 (ppm)

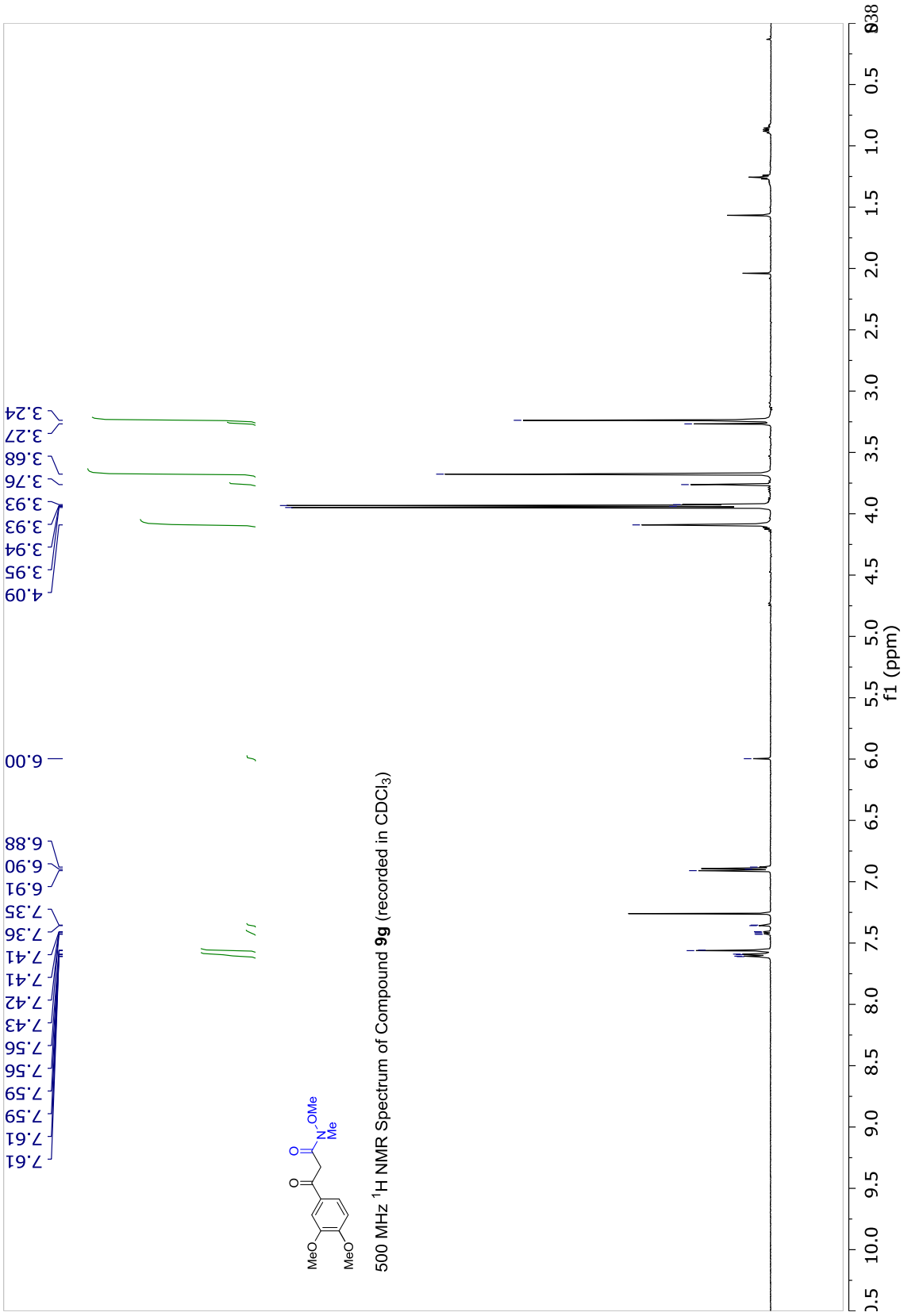

100 MHz ^{13}C NMR Spectrum of Compound **9d** (recorded in $CDCl_3$)
204.0
170.7
170.4
139.0
139.0
61.8
47.5
32.1
31.6
27.8
23.2
22.4
17.1
13.9
MeO
N
Me
O
O
f1 (ppm)
S33

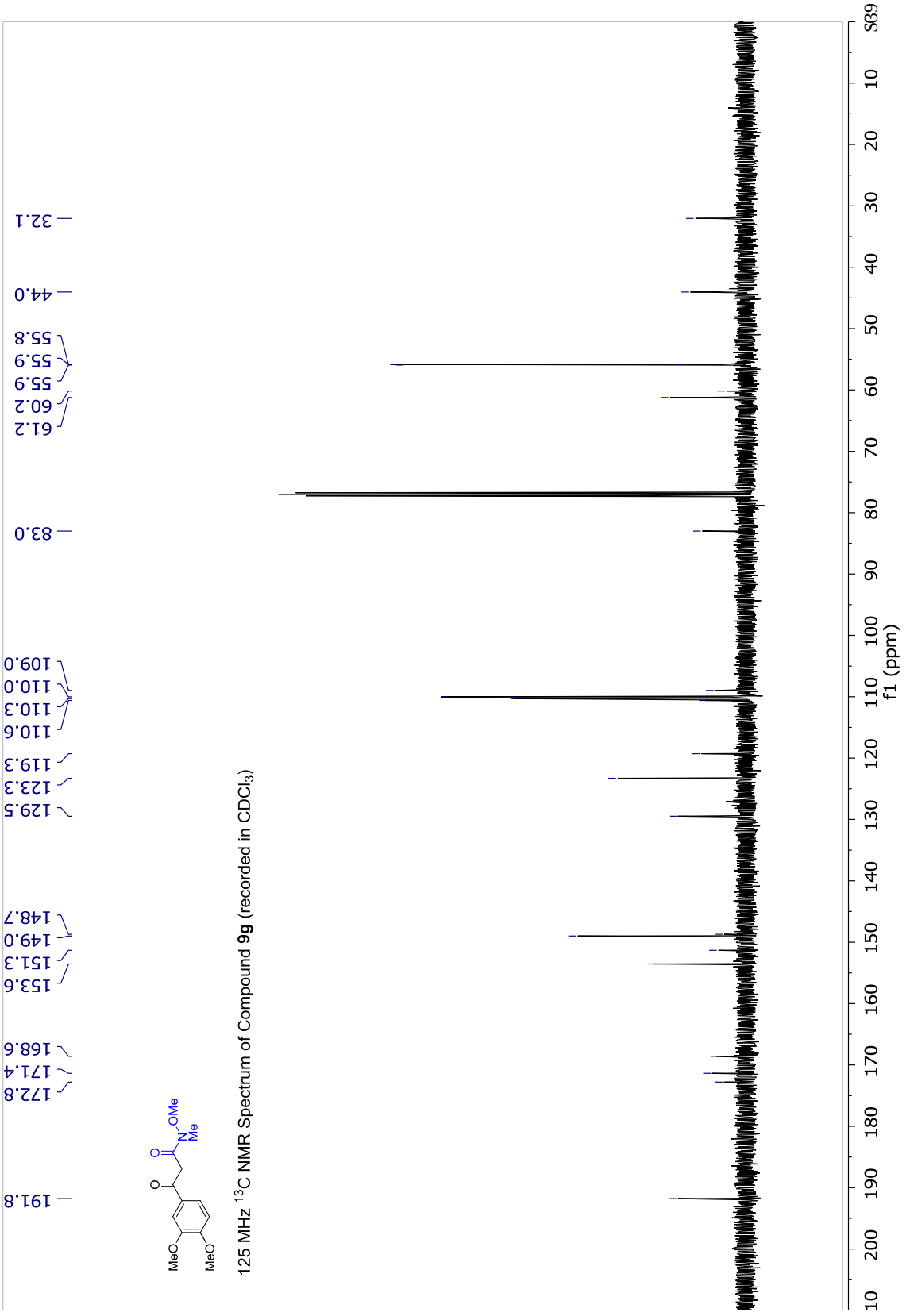

500 MHz ^{1}H NMR Spectrum of Compound **9e** (recorded in $CDCl_3$)
O
O
N
OMe
Me
3.70
3.53
3.51
3.27
2.73
2.70
2.43
2.33
1.99
1.99
1.99
1.94
1.80
1.80
1.42
1.00
0.98
f1 (ppm)

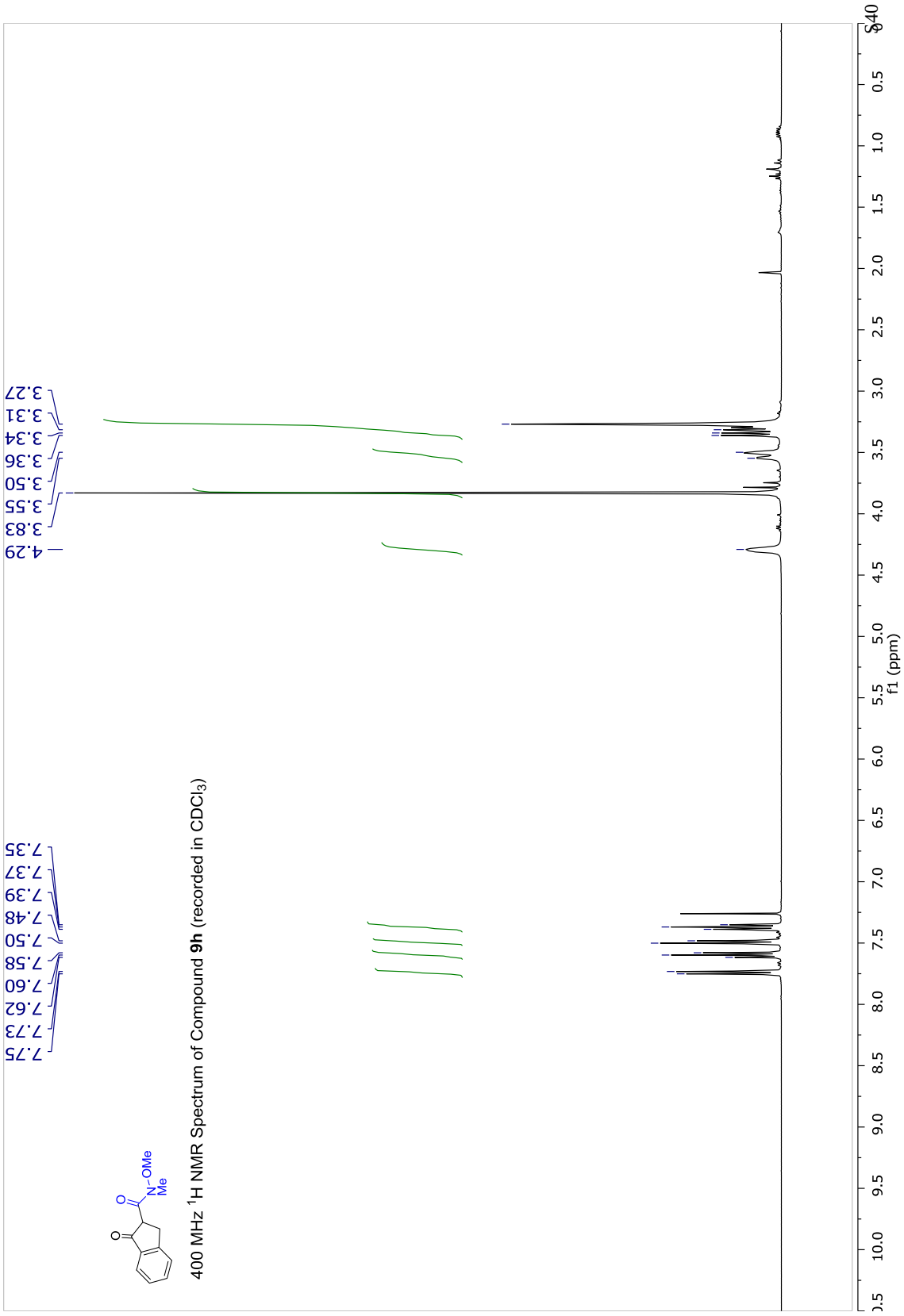

100 MHz ^{13}C NMR Spectrum of Compound **9e** (recorded in $CDCl_3$)
199.6
171.5
144.0
130.9
61.5
61.3
33.9
31.9
31.7
28.3
23.1
22.3
20.8
OMe
Me
N
O
O
f1 (ppm)

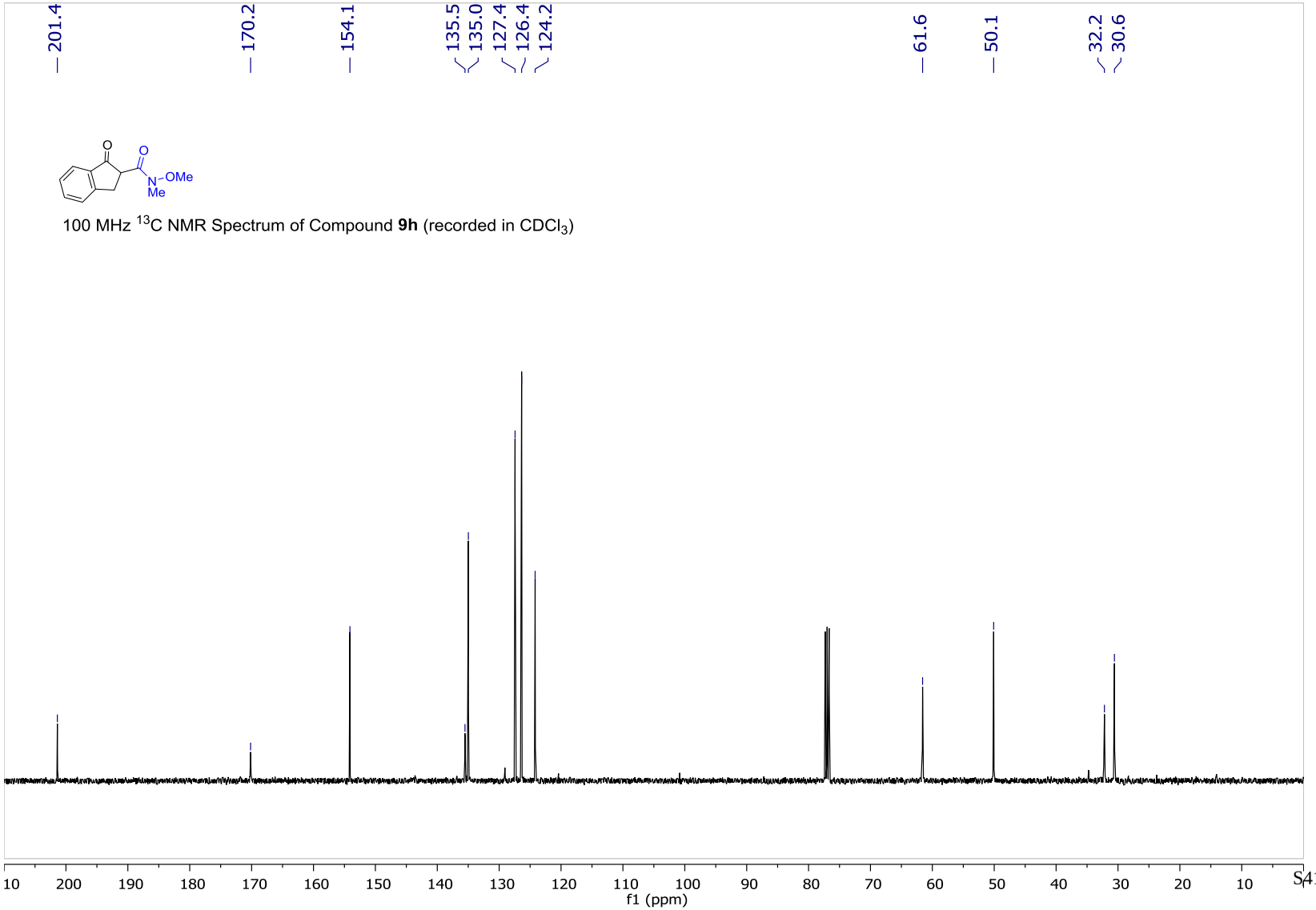

400 MHz ^{1}H NMR Spectrum of Compound **9f** (recorded in $CDCl_3$)
f1 (ppm)
5.74
4.00
3.69
3.26
2.36
2.28
2.16
2.01
1.83
1.50
1.31
1.12
0.90
0.85
0.69


194.9
171.4
171.2
123.1
61.4
55.9
55.7
53.9
45.9
42.3
39.5
39.4
38.7
38.5
36.1
35.7
35.5
32.7
32.0
31.9
28.1
28.0
24.1
23.7
22.8
22.5
20.8
18.6
17.7
11.9
MeO
N
Me
O
O
H
H
H
100 MHz ^{13}C NMR Spectrum of Compound **9f** (recorded in $CDCl_3$)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

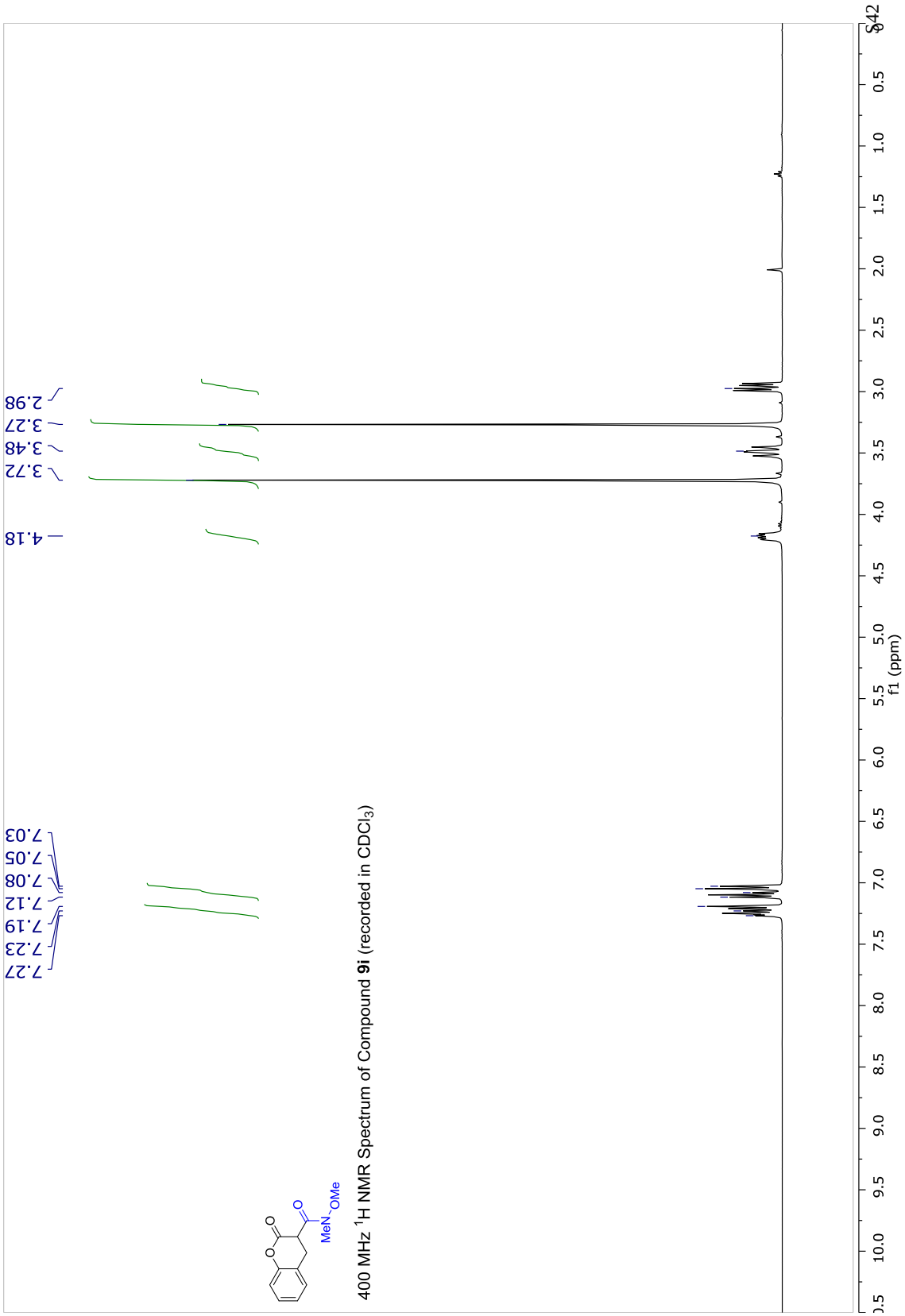

500 MHz ^{1}H NMR Spectrum of Compound **9g** (recorded in $CDCl_3$)
MeO
MeO
O
O
N
OMe
Me
7.61
7.61
7.59
7.59
7.56
7.56
7.43
7.42
7.41
7.41
7.36
7.35
6.91
6.90
6.88
6.00
4.09
3.95
3.94
3.93
3.93
3.76
3.68
3.27
3.24
f1 (ppm)

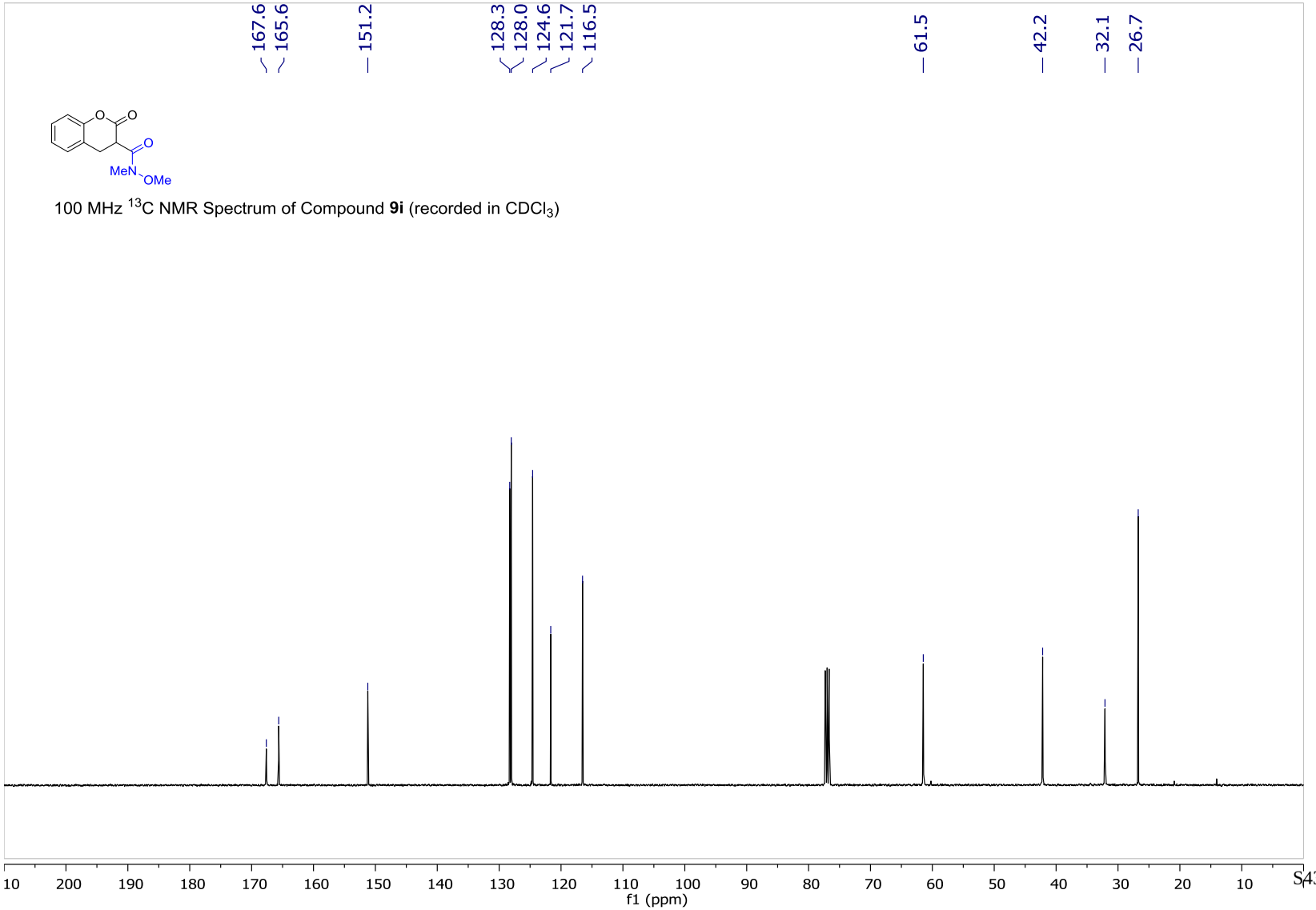

125 MHz ^{13}C NMR Spectrum of Compound **9g** (recorded in CDCl$_3$)
MeO
MeO
O
O
N
OMe
Me
191.8
172.8
171.4
168.6
153.6
151.3
149.0
148.7
129.5
123.3
119.3
110.6
110.3
110.0
109.0
83.0
61.2
60.2
55.9
55.9
55.8
44.0
32.1
f1 (ppm)

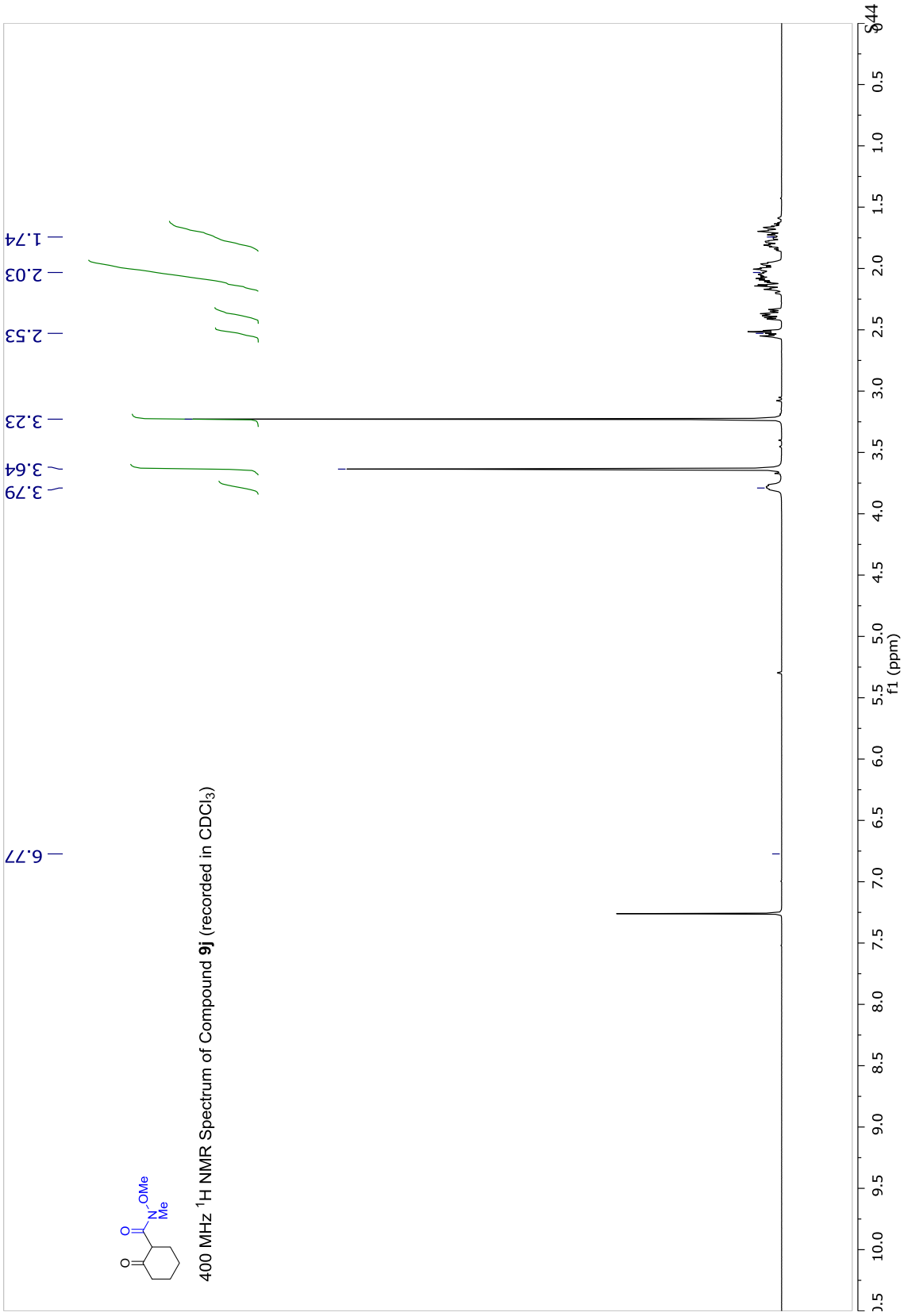

400 MHz ^{1}H NMR Spectrum of Compound **9h** (recorded in $CDCl_3$)
O
N-OMe
Me
7.75
7.73
7.62
7.60
7.58
7.50
7.48
7.39
7.37
7.35
4.29
3.83
3.55
3.50
3.36
3.34
3.31
3.27
f1 (ppm)

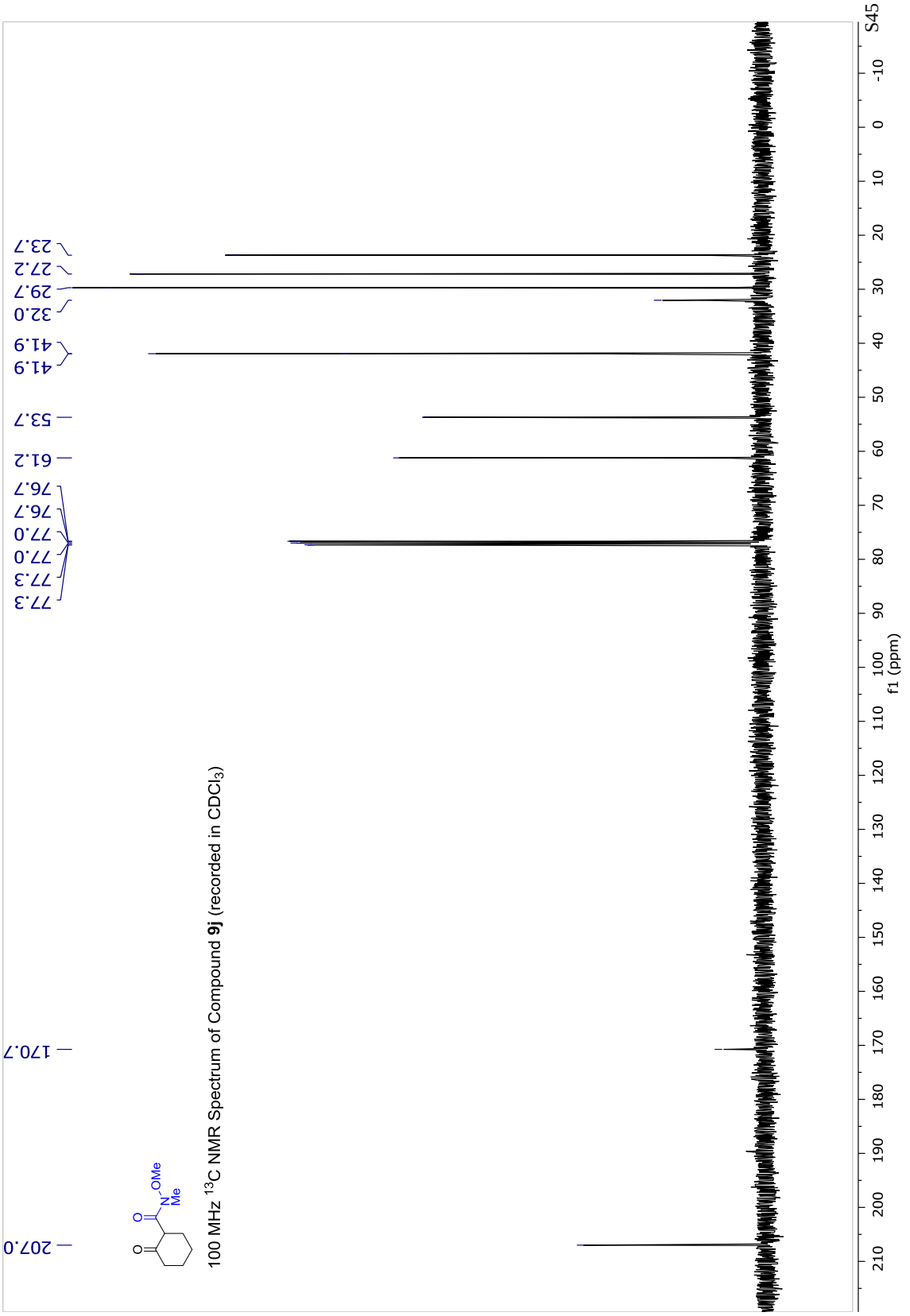


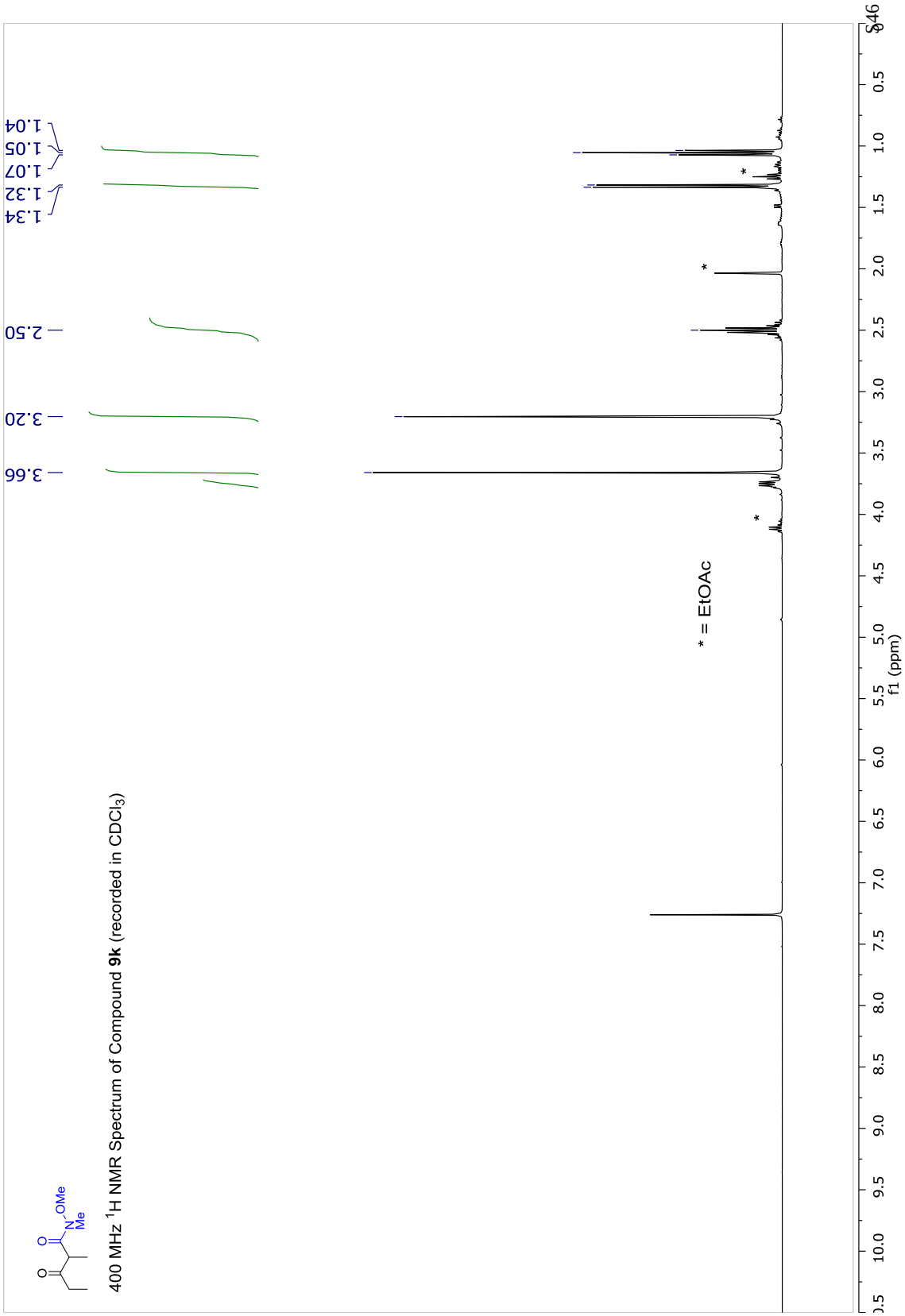
100 MHz ^{13}C NMR Spectrum of Compound **9h** (recorded in $CDCl_3$)

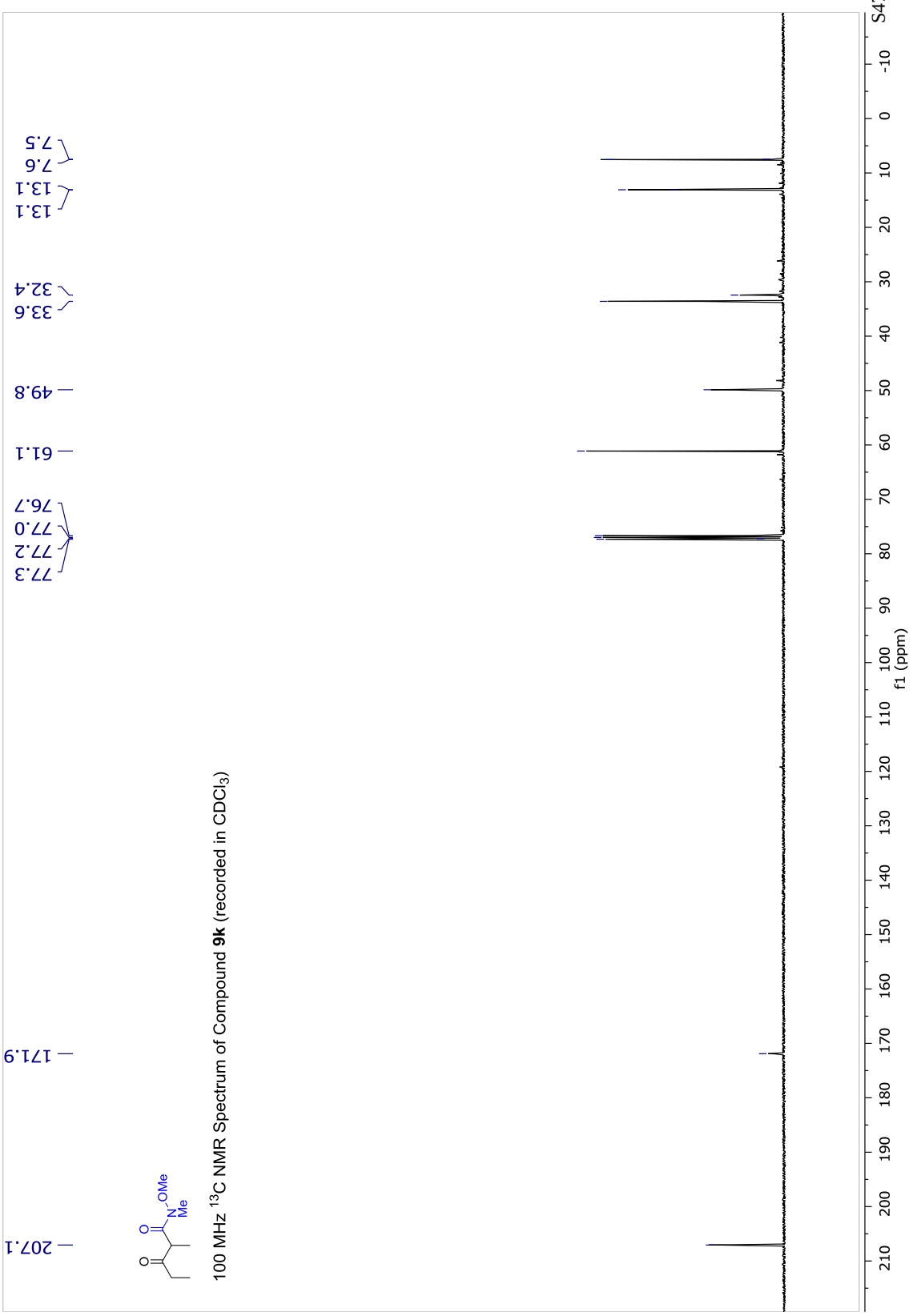

7.27
7.23
7.19
7.12
7.08
7.05
7.03
4.18
3.72
3.48
3.27
2.98
MeN
OMe
O
O
O
400 MHz ^{1}H NMR Spectrum of Compound **9i** (recorded in $CDCl_3$)
f1 (ppm)

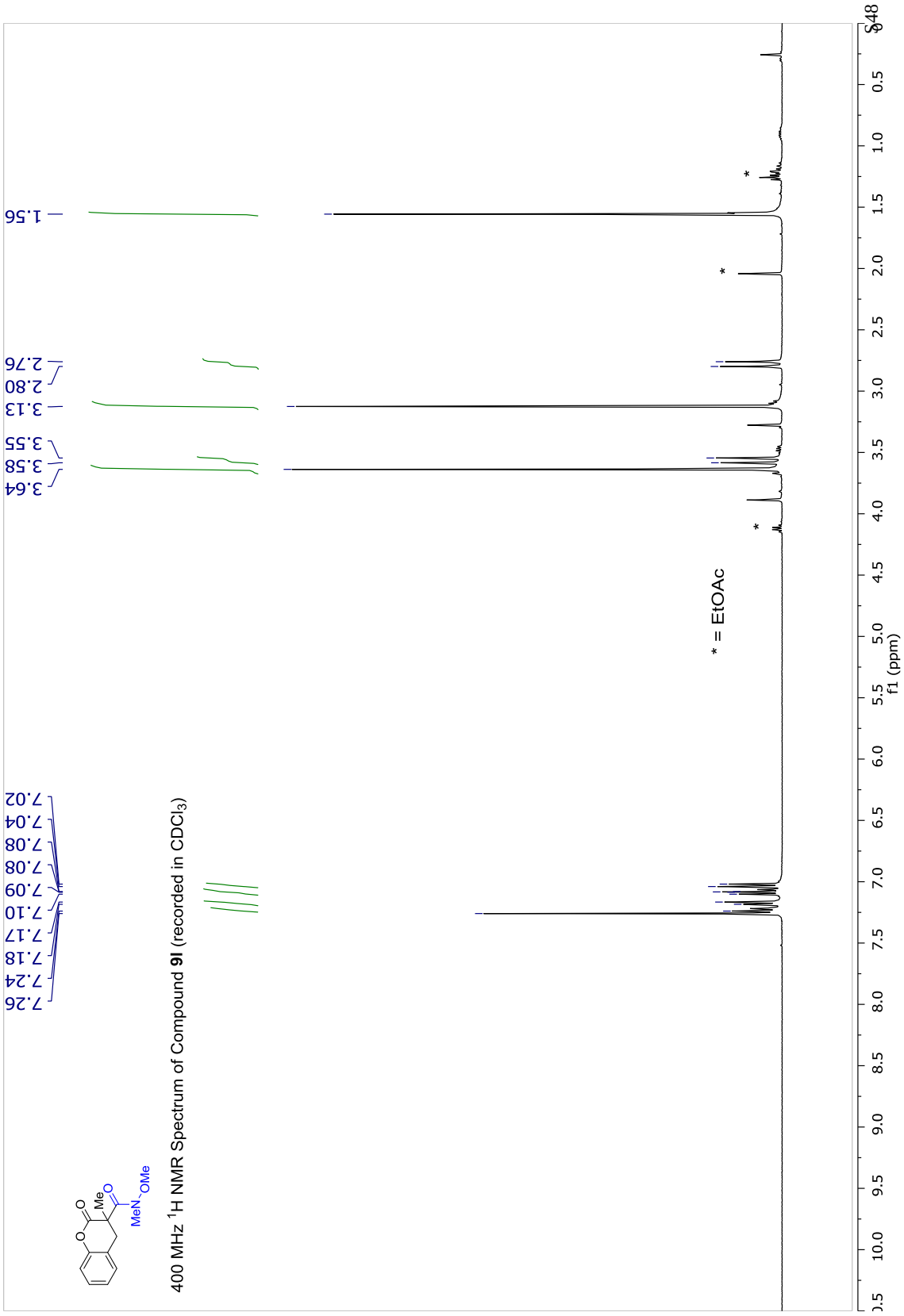

167.6
165.6
151.2
128.3
128.0
124.6
121.7
116.5
61.5
42.2
32.1
26.7
MeN
OMe
100 MHz ^{13}C NMR Spectrum of Compound **9i** (recorded in $CDCl_3$)
f1 (ppm)

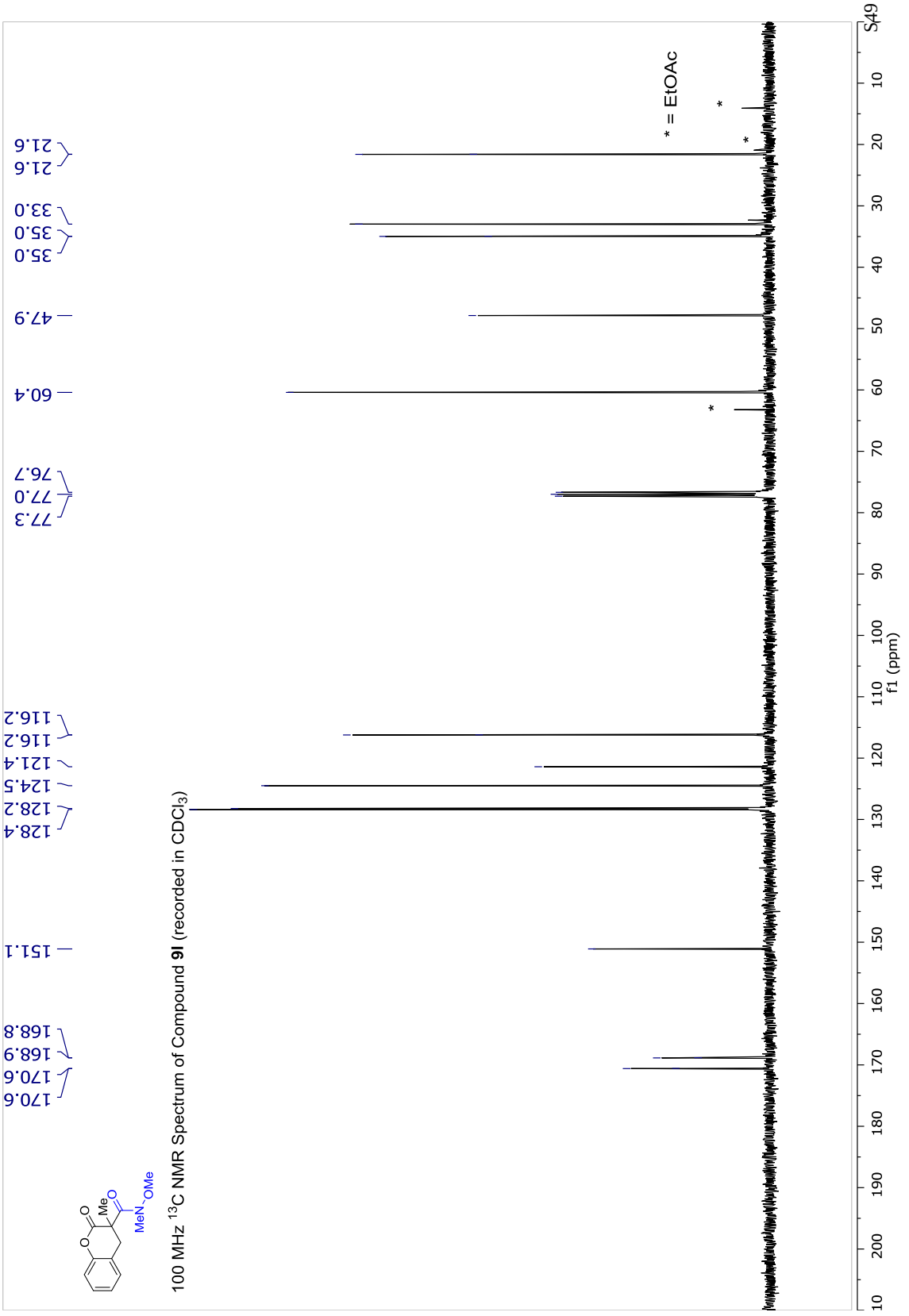

400 MHz ^{1}H NMR Spectrum of Compound **9j** (recorded in $CDCl_3$)
6.77
3.79
3.64
3.23
2.53
2.03
1.74
f1 (ppm)

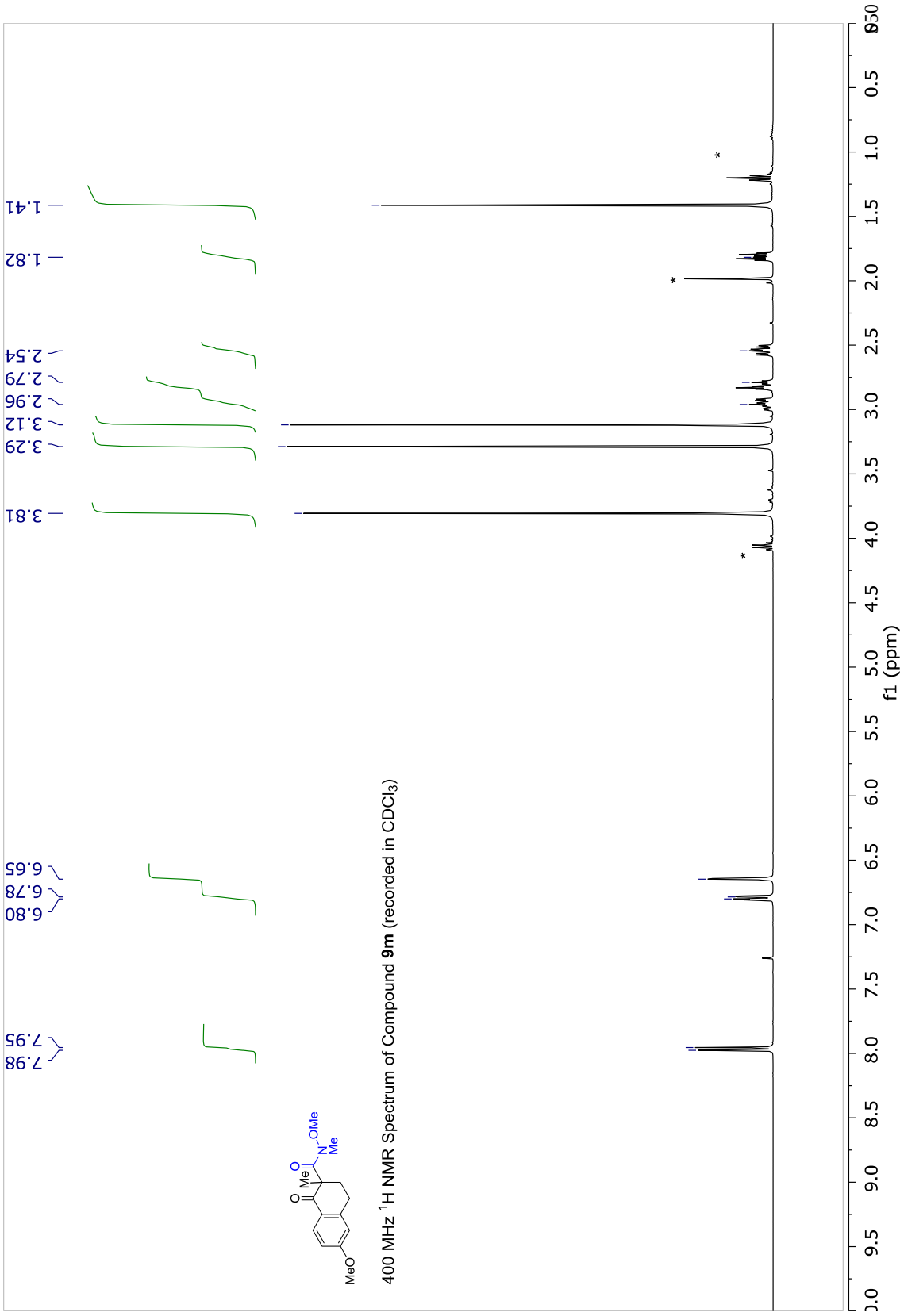

100 MHz ^{13}C NMR Spectrum of Compound **9j** (recorded in $CDCl_3$)
207.0
170.7
77.3
77.3
77.0
77.0
76.7
76.7
61.2
53.7
41.9
41.9
32.0
29.7
27.2
23.7
OMe
Me
f1 (ppm)
S45

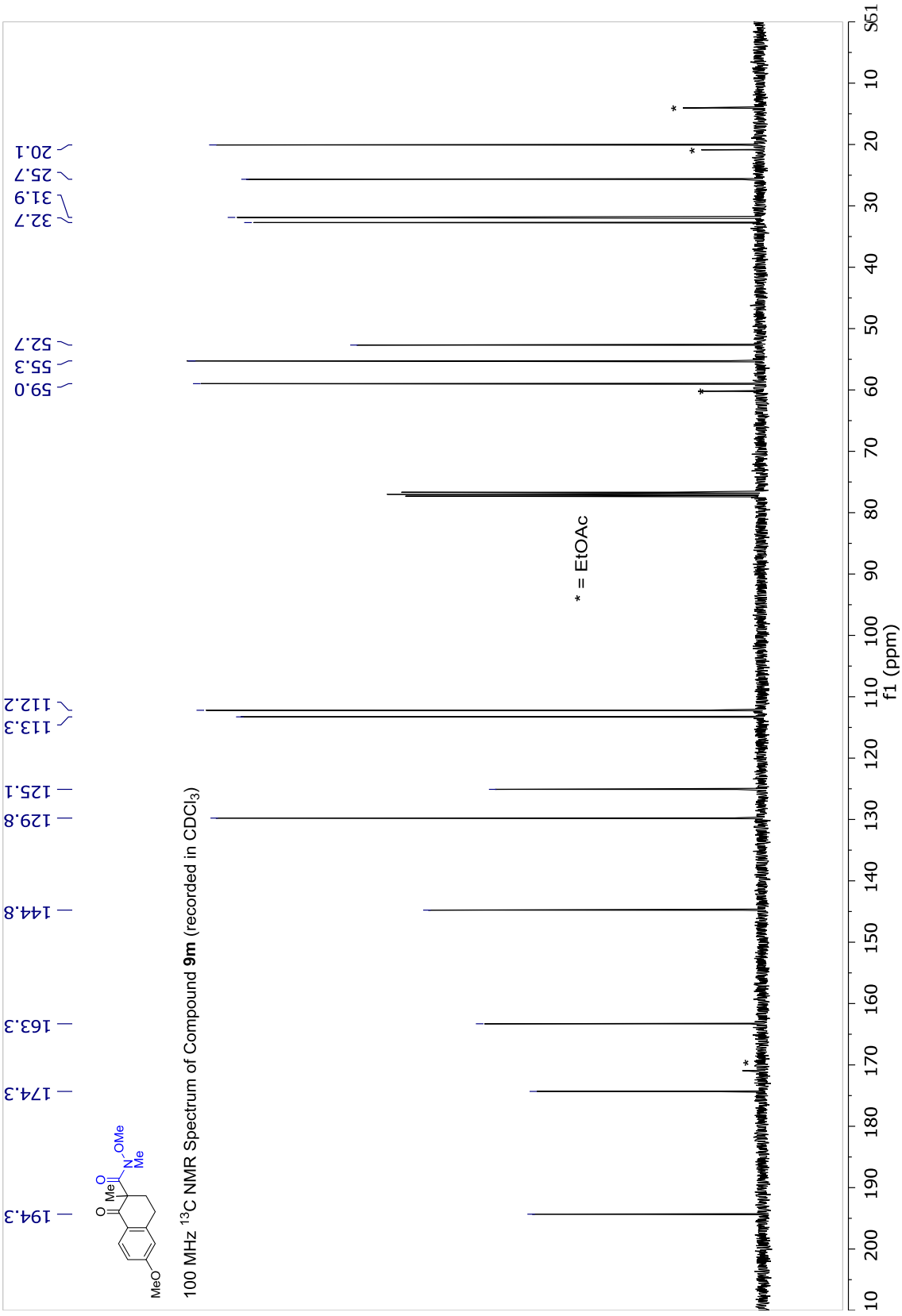

400 MHz ^{1}H NMR Spectrum of Compound **9k** (recorded in $CDCl_3$)
* = EtOAc
f1 (ppm)
3.66
3.20
2.50
1.34
1.32
1.07
1.05
1.04

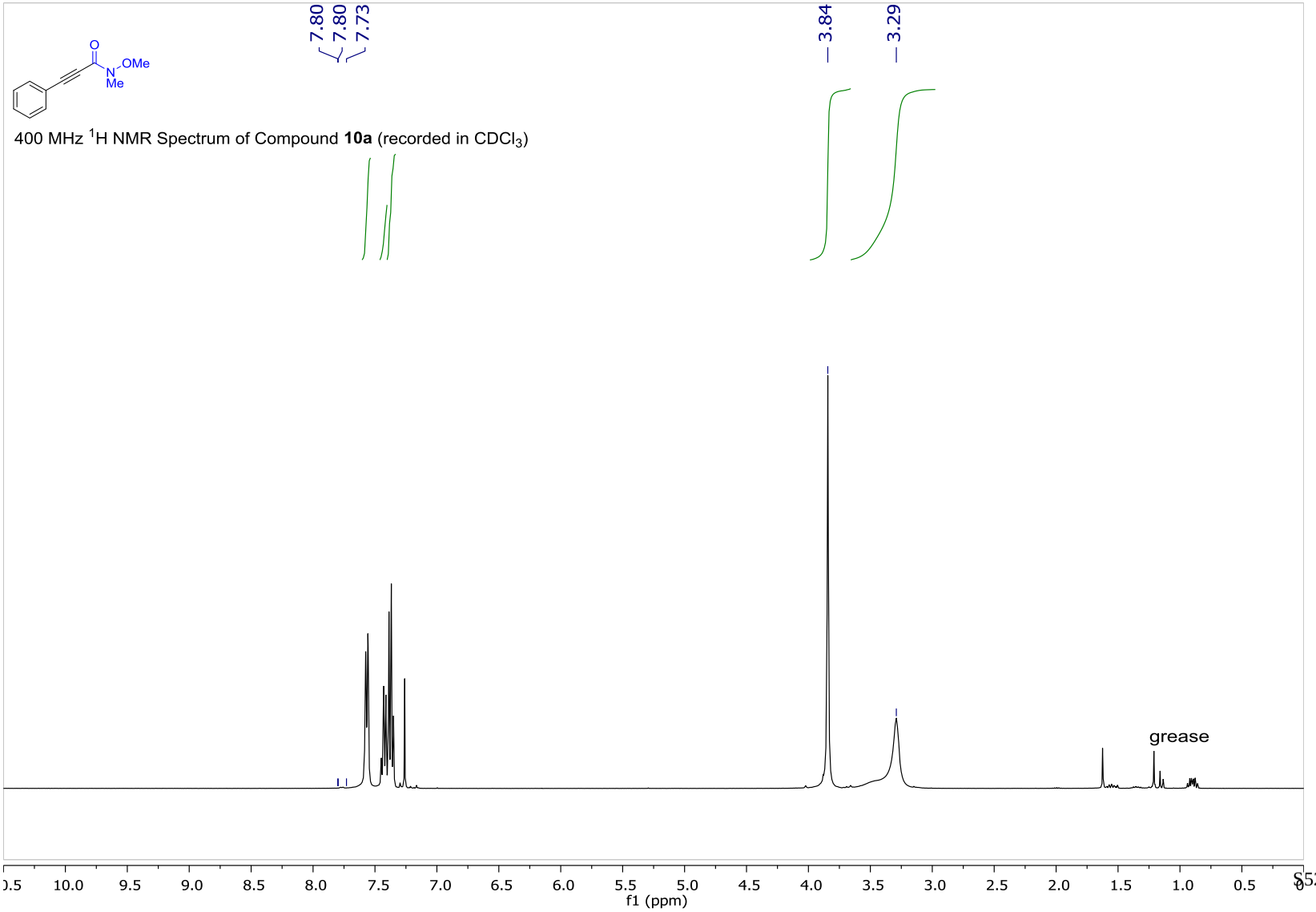

100 MHz ^{13}C NMR Spectrum of Compound **9k** (recorded in $CDCl_3$)
207.1
171.9
77.3
77.2
77.0
76.7
61.1
49.8
33.6
32.4
13.1
13.1
7.6
7.5
OMe
N
Me
O
O
f1 (ppm)
S47


400 MHz ^{1}H NMR Spectrum of Compound **9l** (recorded in $CDCl_3$)
* = EtOAc
f1 (ppm)
7.26
7.24
7.18
7.17
7.10
7.09
7.08
7.08
7.04
7.02
3.64
3.58
3.55
3.13
2.80
2.76
1.56
Me
MeN
OMe

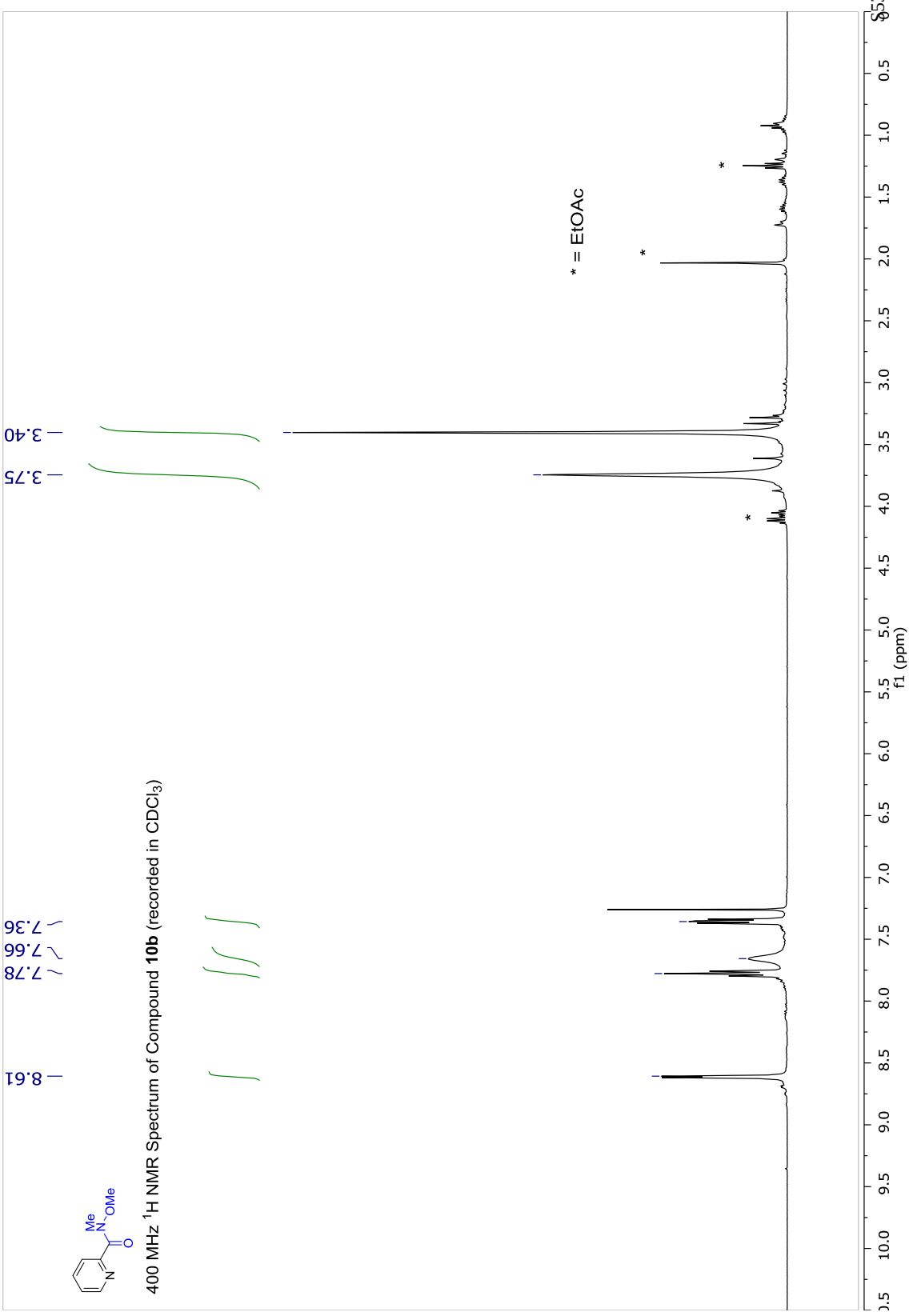

100 MHz ^{13}C NMR Spectrum of Compound **9l** (recorded in CDCl$_3$)
* = EtOAc
f1 (ppm)
170.6
170.6
168.9
168.8
151.1
128.4
128.2
124.5
121.4
116.2
116.2
77.3
77.0
76.7
60.4
47.9
35.0
35.0
33.0
21.6
21.6
MeN
OMe
Me
O
O
O

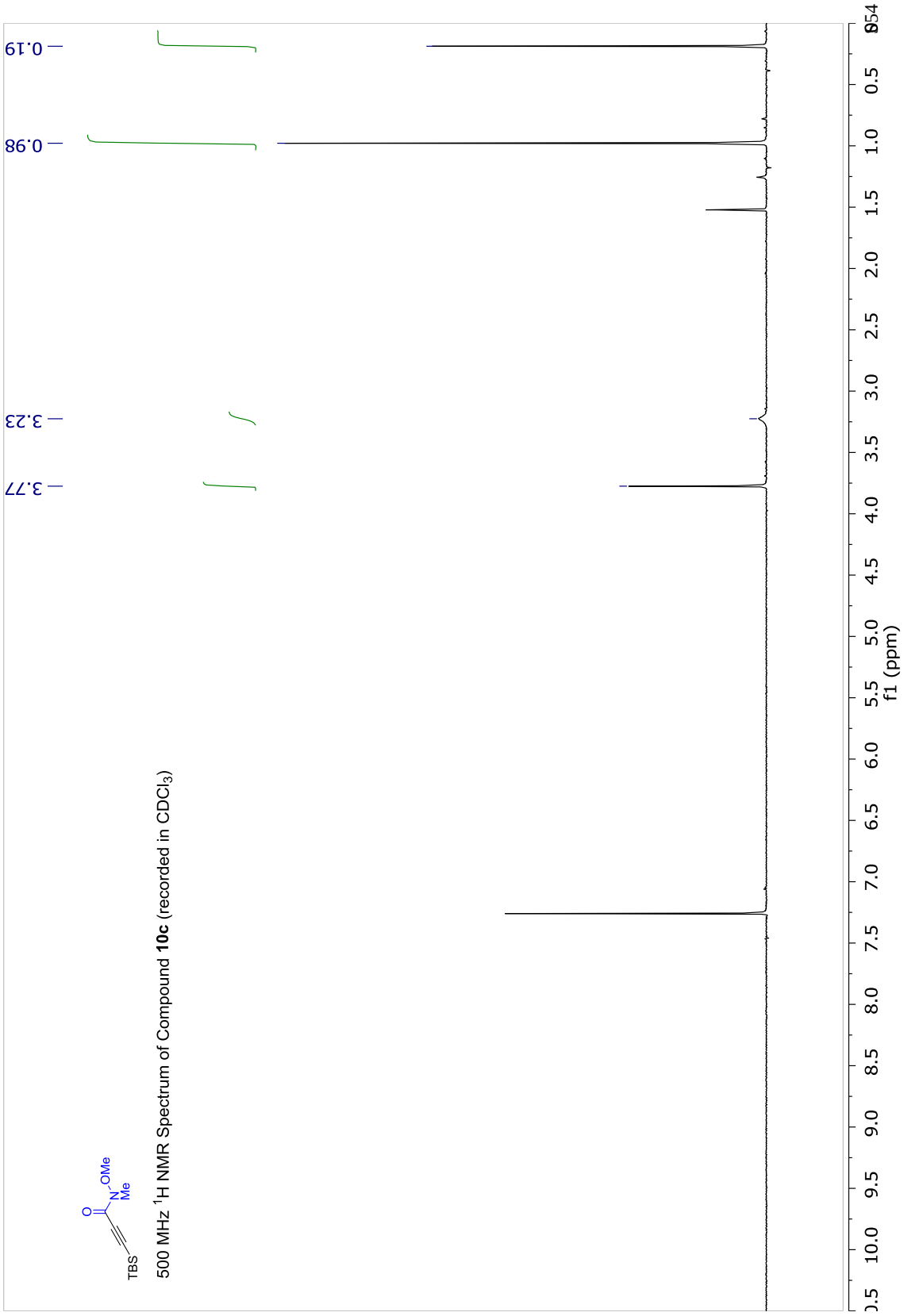

7.98
7.95
6.80
6.78
6.65
3.81
3.29
3.12
2.96
2.79
2.54
1.82
1.41
MeO
Me
O
OMe
N
Me
O
400 MHz ^{1}H NMR Spectrum of Compound **9m** (recorded in $CDCl_3$)
f1 (ppm)

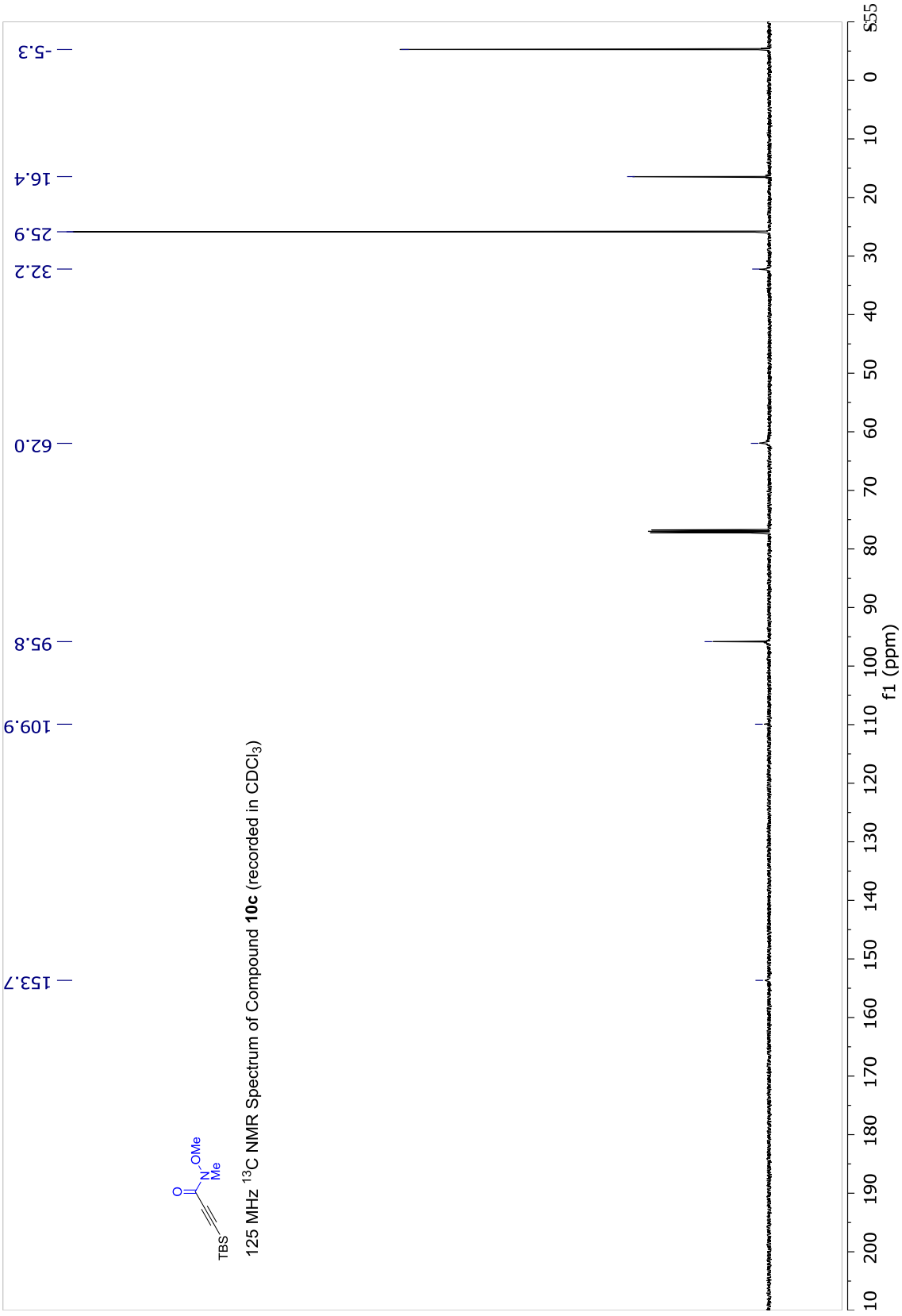

100 MHz ^{13}C NMR Spectrum of Compound **9m** (recorded in $CDCl_3$)
* = EtOAc
194.3
174.3
163.3
144.8
129.8
125.1
113.3
112.2
59.0
55.3
52.7
32.7
31.9
25.7
20.1
MeO
Me
OMe
N
Me
f1 (ppm)
S51

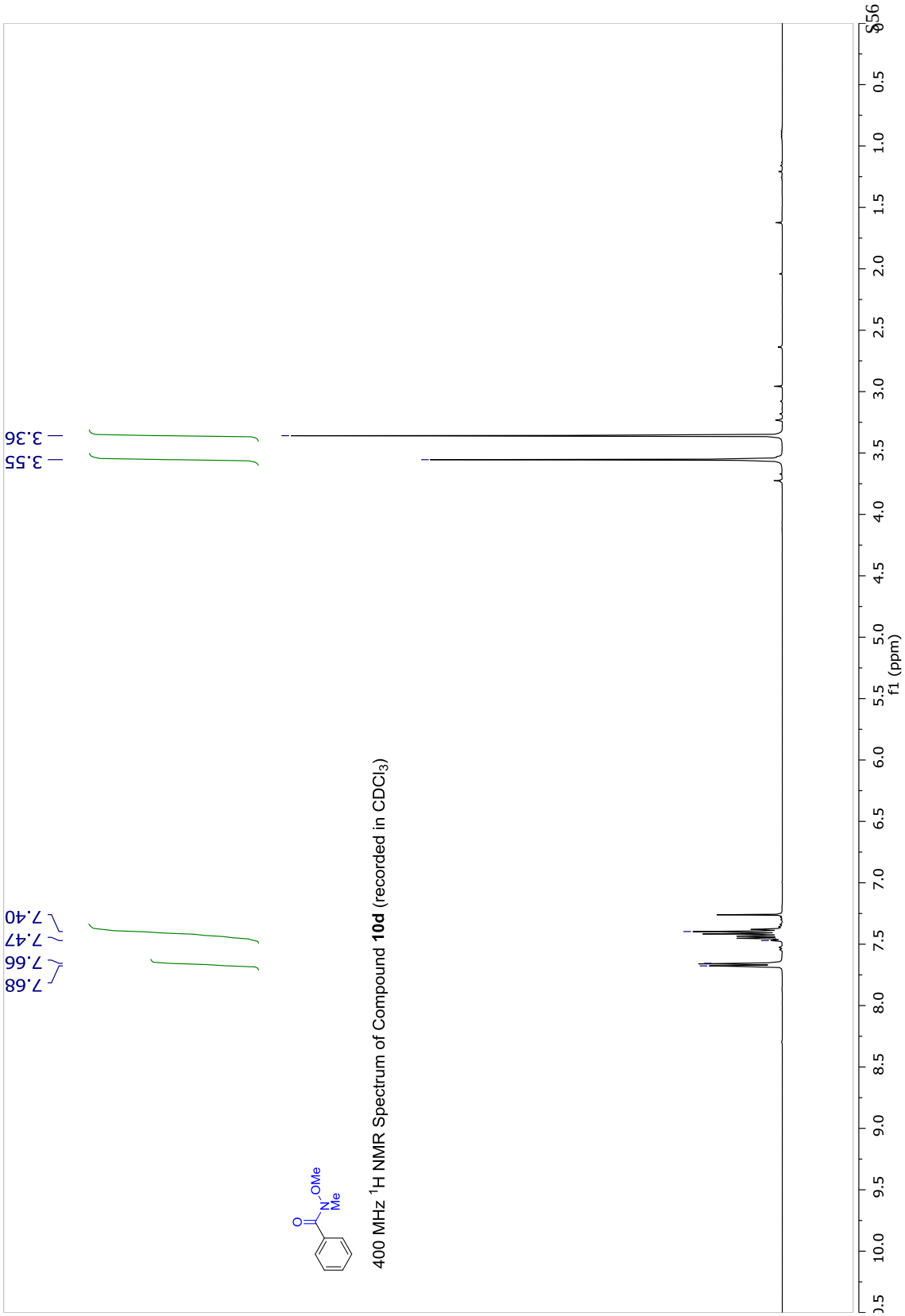


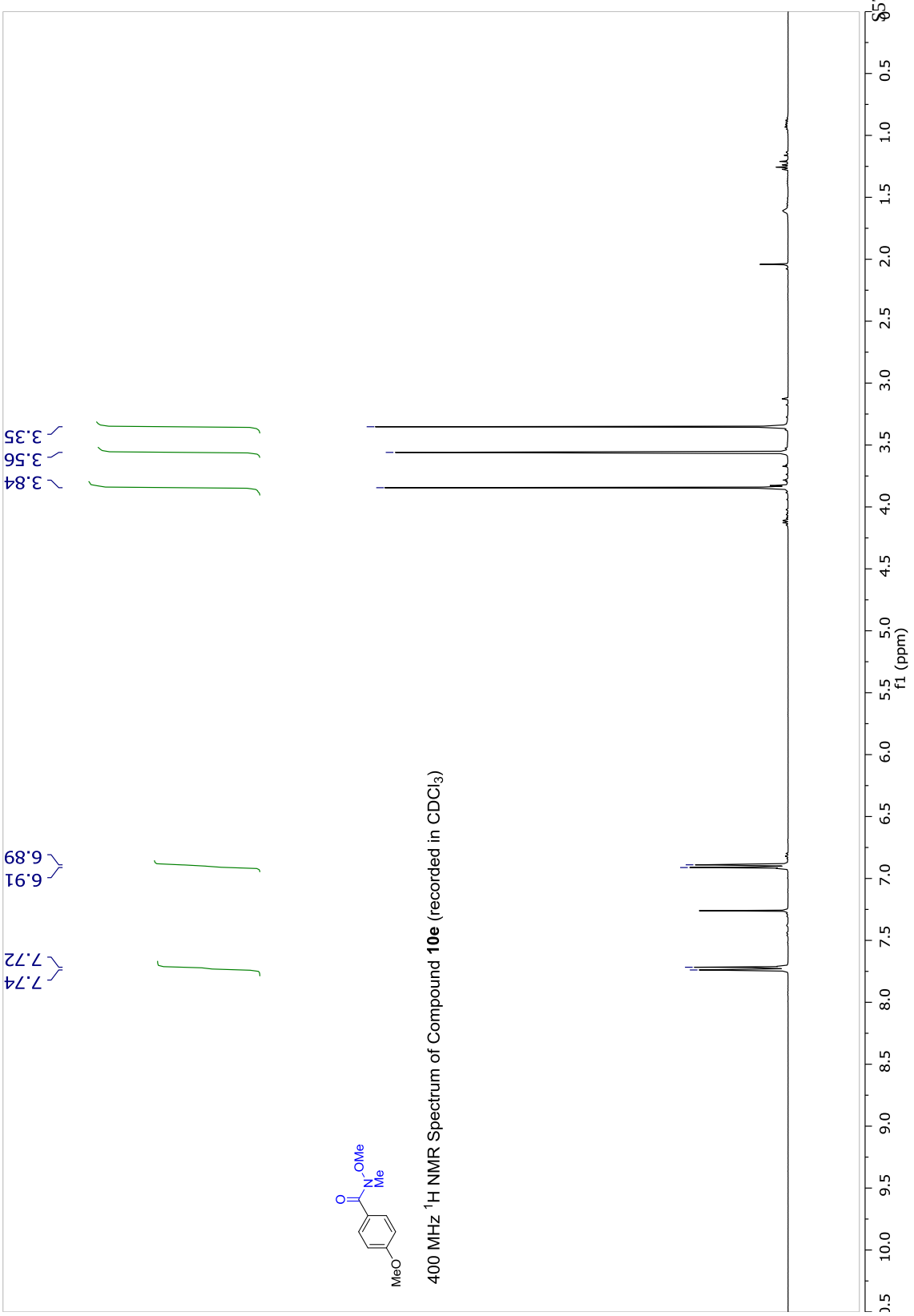
400 MHz ^{1}H NMR Spectrum of Compound **10a** (recorded in $CDCl_3$)

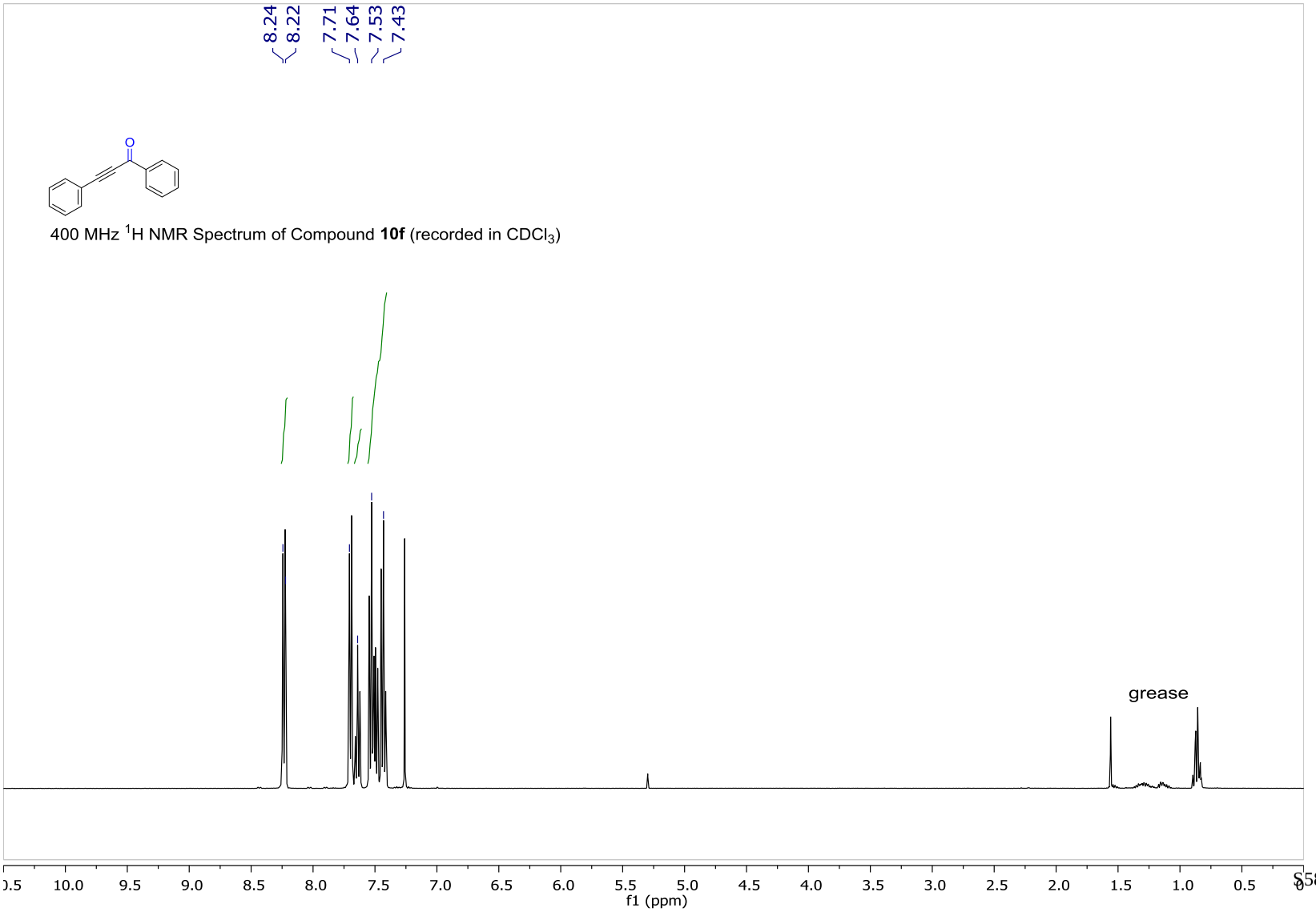

400 MHz ^{1}H NMR Spectrum of Compound **10b** (recorded in $CDCl_3$)
8.61
7.78
7.66
7.36
3.75
3.40
* = EtOAc
f1 (ppm)


500 MHz ^{1}H NMR Spectrum of Compound **10c** (recorded in $CDCl_3$)
TBS
O
N
OMe
Me
0.19
0.98
3.23
3.77
f1 (ppm)

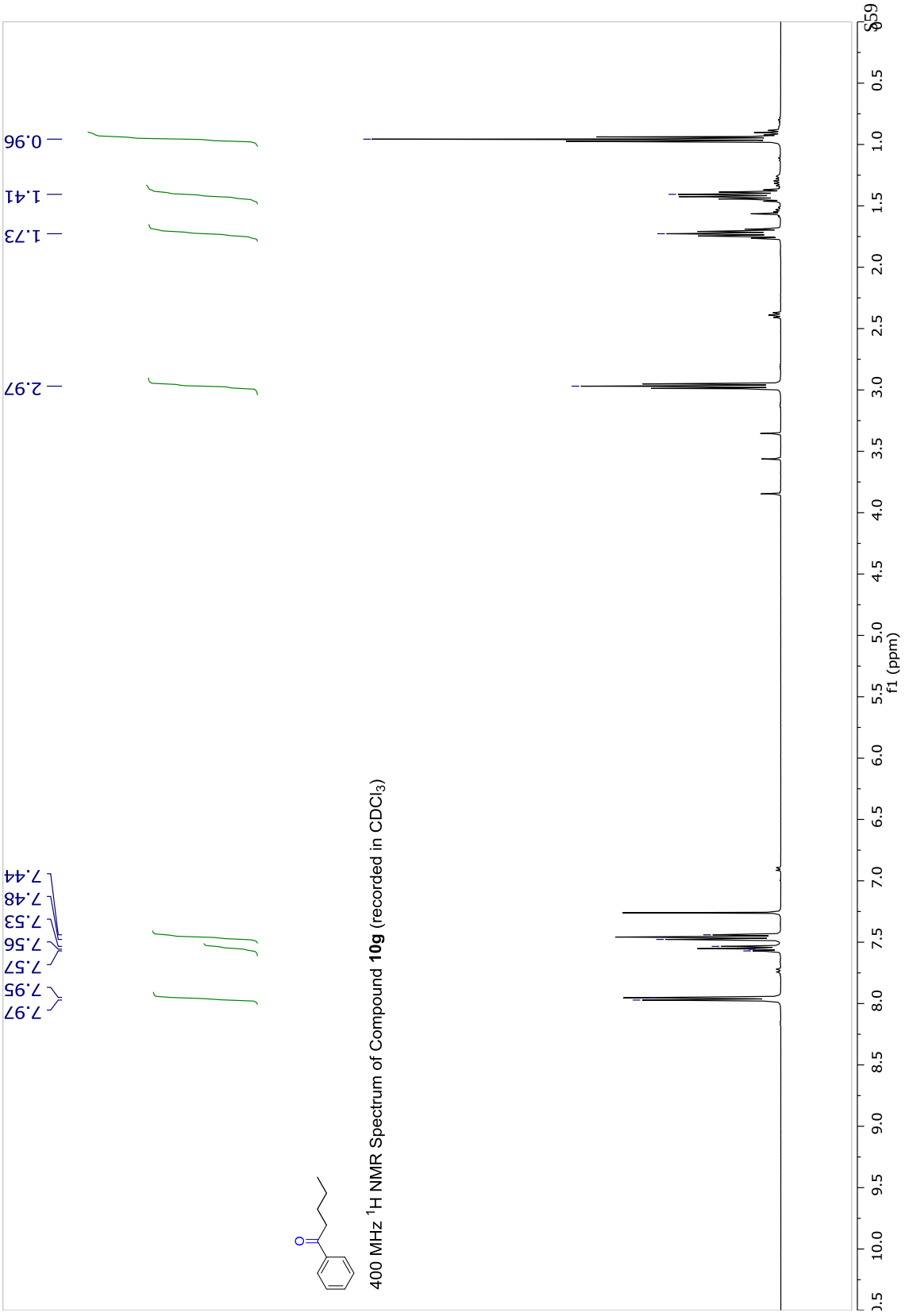

125 MHz ^{13}C NMR Spectrum of Compound **10c** (recorded in CDCl$_3$)
TBS
O
N
OMe
Me
-5.3
16.4
25.9
32.2
62.0
95.8
109.9
153.7
f1 (ppm)

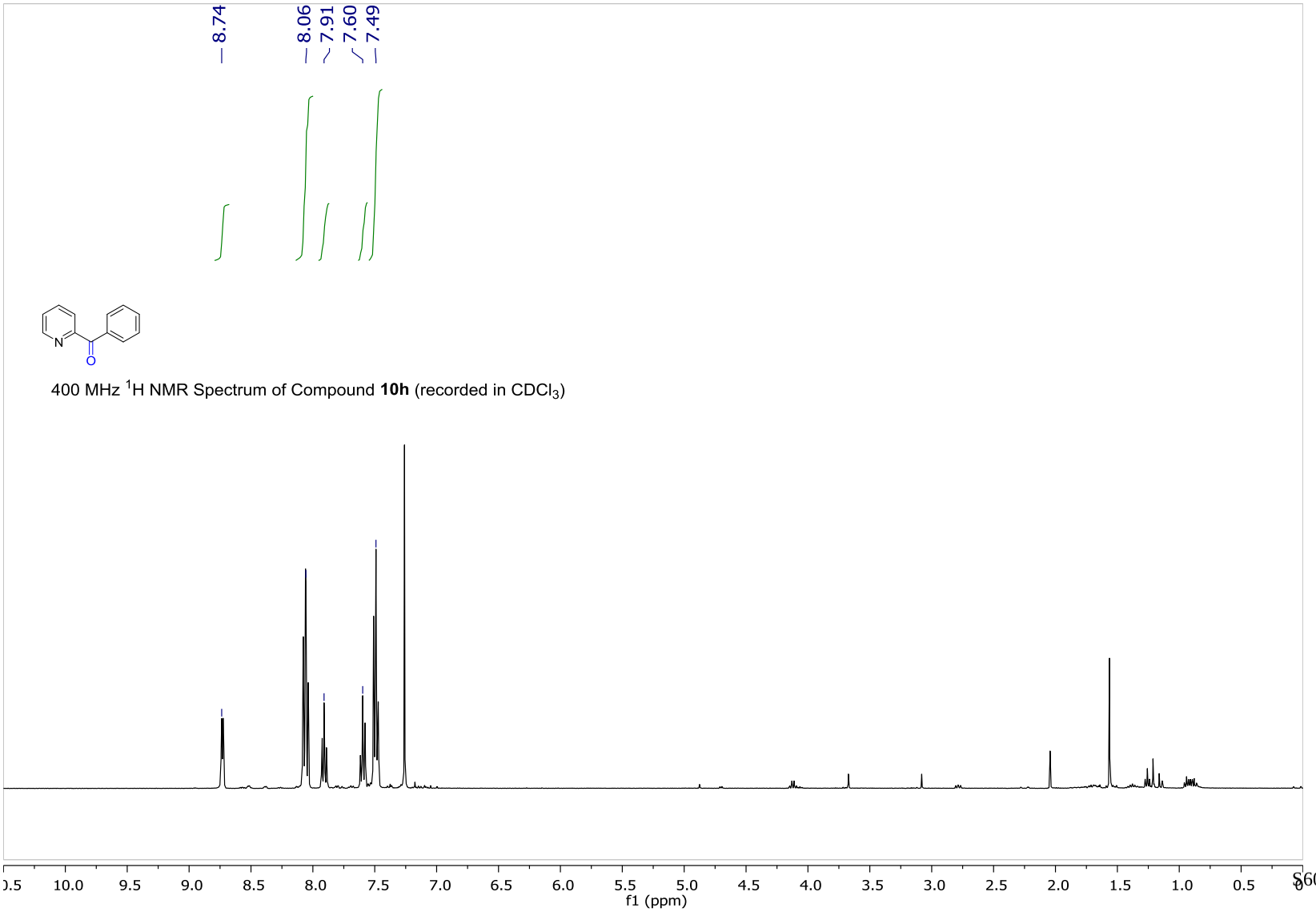

S56
400 MHz ^{1}H NMR Spectrum of Compound **10d** (recorded in CDCl$_3$)
7.68
7.66
7.47
7.40
3.55
3.36
f1 (ppm)


400 MHz ^{1}H NMR Spectrum of Compound **10e** (recorded in $CDCl_3$)
O
N
OMe
Me
MeO
7.74
7.72
6.91
6.89
3.84
3.56
3.35
f1 (ppm)


8.24
8.22
7.71
7.64
7.53
7.43
O
400 MHz ^{1}H NMR Spectrum of Compound **10f** (recorded in $CDCl_3$)
grease
f1 (ppm)

270


400 MHz ^{1}H NMR Spectrum of Compound **10g** (recorded in $CDCl_3$)
0.96
1.41
1.73
2.97
7.44
7.48
7.53
7.56
7.57
7.95
7.97
f1 (ppm)


8.74
8.06
7.91
7.60
7.49
N
O
400 MHz ^{1}H NMR Spectrum of Compound **10h** (recorded in $CDCl_3$)
f1 (ppm)

Publication Seven

Preparation of *N*-Methoxy-*N*-methylcyanoformamide

Jeremy Nugent and Brett D. Schwartz

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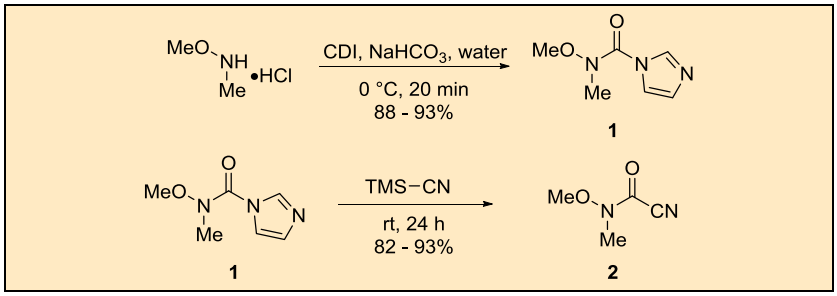
Organic Syntheses

Preparation of *N*-Methoxy-*N*-methylcyanoformamide

Jeremy Nugent and Brett D. Schwartz*

Research School of Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, ACT 2601, Australia.

Checked by Names in Palatino 10 pt Italics and xxxxxxxxxxx



Procedure

Caution! Trimethylsilyl cyanide is highly toxic and flammable. Ensure that trimethylsilyl cyanide is used only in a well ventilated fumehood with appropriate protective equipment.

A. *N-methoxy-N-methyl-1H-imidazole-1-carboxamide (**1**).* A 1-L conical flask open to the atmosphere is equipped with a Teflon-coated, octagonal shaped stir bar (51 × 8 mm) then charged with *N*,*O*-dimethylhydroxylamine hydrochloride (20.0 g, 205 mmol, 1.0 equiv) (Note 1), ice (100 g), $NaHCO_3$ (100 mL of a saturated aqueous solution) and water (100 mL, at 0-4 °C) (Figure 1). The reaction vessel is maintained at 0 °C in an ice-water bath then treated, portionwise over a period of two minutes, with *N*,*N′*-carbonyldiimidazole (CDI) (43.2 g, 267 mmol) (Note 2) (Note 3). The resulting mixture is maintained at 0 °C for 0.33 h then the

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mixture is transferred to a 500-mL separatory funnel and extracted with DCM (4 × 50 mL)(Note 4). The combined organic phases are washed with brine (1 × 40 mL), transferred to a 500-mL conical flask then dried over Na_2SO_4 (22 g). Half of the solution is gravity filtered, using a cotton wool plug in a glass funnel, into a 150-mL round-bottomed flask with concentration of the filtrate under reduced pressure (40 °C, 430 mmHg, rotary evaporation). The above filtration and concentration procedure is repeated on the remaining half of the dried organic layer. The resulting pale-yellow colored oil is then held at high vacuum (0.5 mmHg, 18 ºC, 4 h) with stirring, to remove traces of DCM to yield *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (**1**) (28.0-29.6 g, 88-93% yield at 98.8% purity) as a lemon-gold colored oil that is used without further purification (Note 5).

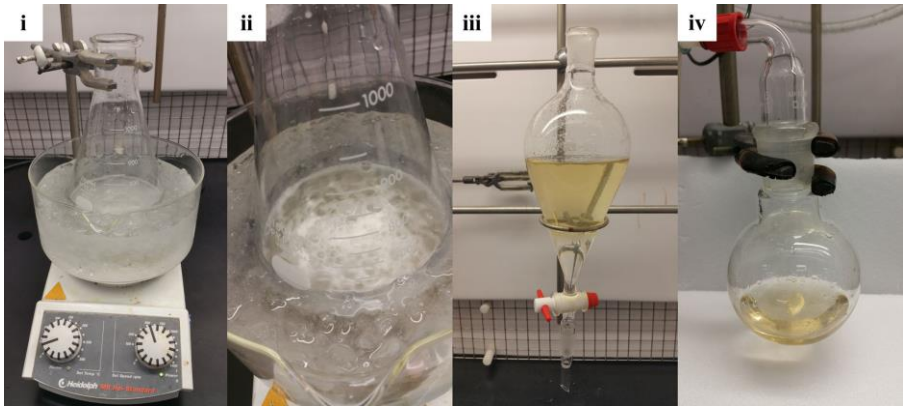


Figure 1. (i) Setup for procedure A; (ii) release of CO_2 during final stages of addition of CDI; (iii) separation of layers; (iv) product 1 after rotary evaporation.

B. *N-methoxy-N-methylcyanoformamide* (**2**). A flame-dried 50-mL single-necked, round-bottomed flask equipped with a Teflon-coated, egg-shaped stir bar (10 × 19 mm) is fitted with 25-mL pressure-equalising dropping addition funnel fitted with a glass gas inlet adapter which is connected to a nitrogen-vacuum double manifold (Figure 2). The flask is charged with a portion of *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (**1**, 15.5 g, 100 mmol) prepared as described above then placed under vacuum (1 mmHg) and backfilled with nitrogen three times. The reaction vessel is cooled to 0 °C and the pressure equalising dropping addition funnel charged with trimethylsilyl cyanide (13.1 mL, 105 mmol **CAUTION!**) (Note 6). Trimethylsilyl cyanide is then added to the flask

dropwise over 5 min. When the addition is complete the reaction vessel is warmed to room temperature (18 °C) and stirred at this temperature for 24 h. The reaction mixture is then poured into a 250-mL conical flask equipped with a Teflon-coated, octagonal shaped stir bar (51 × 8 mm) then charged with $NaHCO_3$ (50 mL satd. aqueous solution) and ice (50 g). The resulting mixture is stirred for 0.10 h then extracted with DCM (5 × 20 mL)(Note 4). The combined organic layers are washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4 (22 g), and the filtrate concentrated by rotary evaporation (415 mmHg, 35 °C).

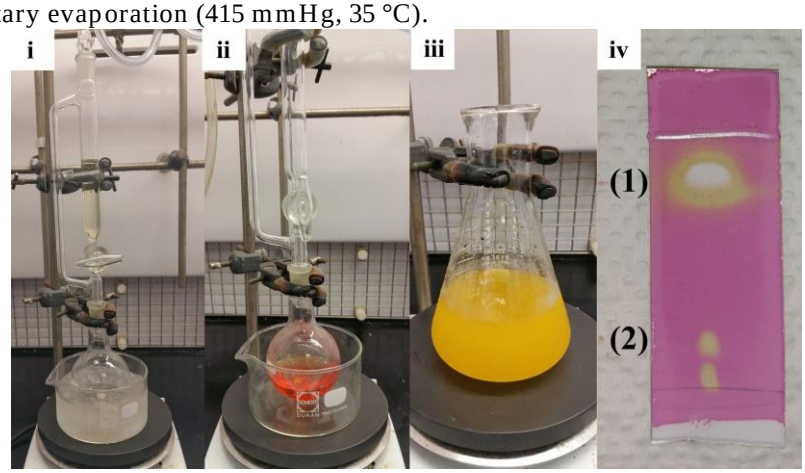


Figure 2. (i) Setup for procedure B before addition of TMSCN; (ii) 24 h after addition of TMSCN; (iii) quenching of reaction with aqueous $NaHCO_3$; (iv) TLC analysis of crude reaction mixture after 24 h (elution with diethyl ether): (1) *N*-methoxy-*N*-methylcyanoformamide (2) *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide.

The residue is dissolved in diethyl ether (20 mL) (Note 7) and the resulting solution loaded onto a pad of silica (55 g, pre-wetted with diethyl ether on top of 10 mm of sand)(Note 8) by pipette in a sintered vacuum funnel (60 mm internal diameter, 350 mL total volume, grade 1 sinter) and eluted through with diethyl ether (400 mL) into a 500-mL round bottom flask by gentle vacuum suction (~400 mmHg) and monitored by TLC analysis (Note 9) (Figure 3). The ethereal solution is then concentrated by rotary evaporation (415 mmHg, 35 °C) until approximately 25 mL of the original solution remained then transferred by funnel to a 100-mL pear shaped flask (for convenience). The solution is then concentrated further by rotary evaporation and then at the pump for 4 h (10 mmHg, 18 °C) to remove traces of diethyl ether to afford *N*-

methoxy-N-methylcyanoformamide **2** (9.4 - 10.6 g, 82 - 93% yield at 96.2 % purity) as a pale-yellow, clear, free-flowing oil that can be used without further purification (Note 10. Distillation (9.35 g) through a short-path distillation bridge (Note 11) affords compound **2** as colourless free-flowing liquid (8.60 g, 92% at 94.4% purity) (Note 12).

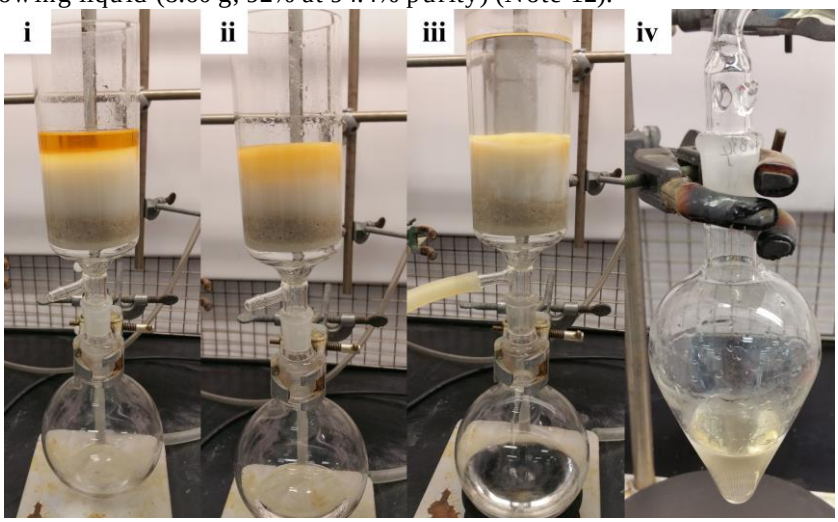


Figure 3. (i) Setup for purification of *N*-methoxy-*N*-methylcyanoformamide (2); (ii) loading ; (iii) elution with diethyl ether; (iv) product after rotary evaporation.

Notes

1. *N*,*O*-Dimethylhydroxylamine hydrochloride (99%) was purchased from AK Scientific and used as supplied.
2. *N*,*N*′-Carbonyldiimidazole (CDI) (98%) was purchased from AK Scientific and used as supplied.
3. When all *N*,*O*-dimethylhydroxylamine hydrochloride has reacted, addition of excess *N*,*N*′-carbonyldiimidazole results in carbon dioxide evolution.
4. Dichloromethane EMSURE®, ACS, 99.8% was purchased from Merck and used as supplied.
5. The reaction has been performed three times at the scale described above by the submitters. On one of these occasions trace amounts (~4%) of imidazole was observed. Spectral data for (**1**) were consistent with those reported.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.52 (t, *J* = 1.4 Hz, 1H), 7.00 (s, 1H), 3.63 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 137.7, 129.3, 118.6, 77.0, 61.2, 34.4.

6. Trimethylsilyl cyanide (98%) was purchased from Sigma-Aldrich and used as supplied.
7. Diethyl ether was purchased from Honeywell (Burdick and Jackson 99.9%, preservative free) and used after purification through activated alumina using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*[3]
8. Silica (Davisil®, 40-63 μm) was purchased from Grace and used as supplied. Sand (acid washed, LR) was purchased from UNILAB and used as supplied.
9. Only trace amounts of compound **2** were evident by TLC after elution with 400 mL of diethyl ether. Analysis using diethyl ether elution and staining with potassium permanganate solution, product **2** R_f = 0.84.
10. Product **2** after purification through silica contained approximately 1-2% 1,3-dimethoxy-1,3-dimethylurea.[4] Product **2** has the following physical and spectroscopic data: ^{1}H NMR 97:3 *mixture of rotamers* (400 MHz, $CDCl_3$) δ 3.89 (s, OCH_3, *major*) & 3.76 (s, OCH_3, *minor*), 3.47 (s, NCH_3, *minor*) 3.28 (s, NCH_3, *major*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 110.0, 63.2, 32.2; MS (EI): *m/z* (%) 114 ($M^{+\cdot}$, 47%), 99 (9), 88 (18), 84 (68), 83 (19), 71 (19), 60 (77), 57 (31), 54 (100); HRMS (EI) *m/z* $M^{+\bullet}$ calcd for $[C_4H_6N_2O_2]^{+\bullet}$: 114.0424; found, 114.0430; IR (KBr) ν_{max} 2946, 2238 1687, 1460, 1395, 1199, 987, 710 cm^{-1}.
11. The distillation is carried out using a fractional short-path distillation bridge with a 5 cm Vigreux (see Figure 4). Vigorous magnetic stirring is employed throughout the duration of the distillation and a $CO_{2(s)}$ / ethanol trap is in place between the Schlenk line and the vacuum pump. Chilled water is circulated through the condenser and the setup is evacuated to 19 mmHg and heating of the oil bath to 110 °C is initiated. The first ~300 μL of distillate is discarded and the fraction boiling at 81-84 °C, 19 mmHg (25 mbar) is collected into a 25-mL Schlenk flask.

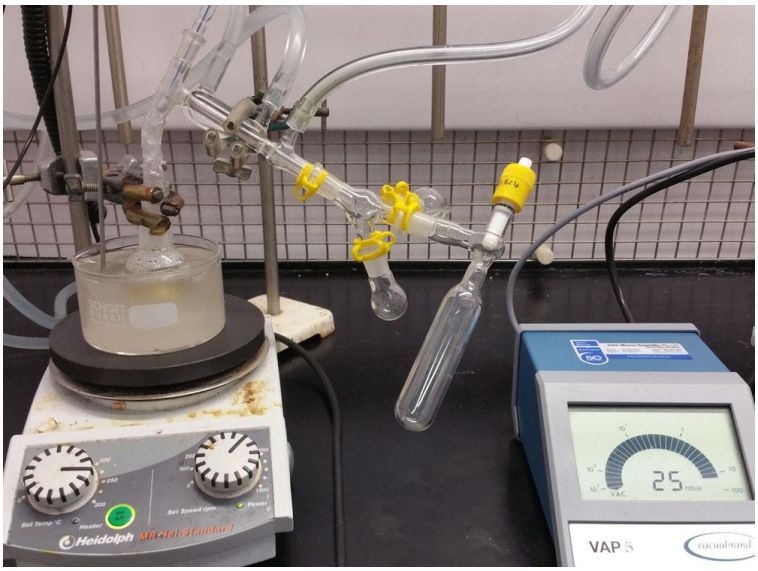


Figure 4. Setup used by submitters for the distillation of compound 2.

12. Product **2** after distillation contained approximately 2% 1,3-dimethoxy-1,3-dimethylurea.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale

that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

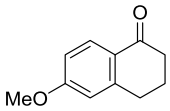
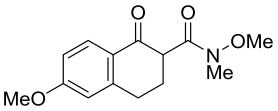
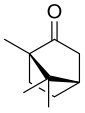
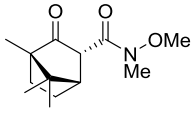
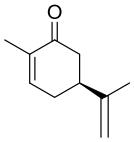
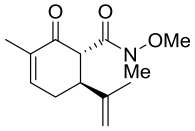
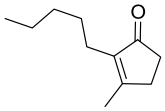
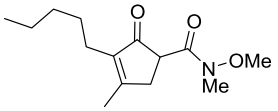
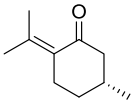
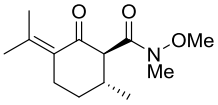
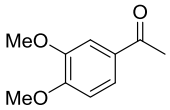
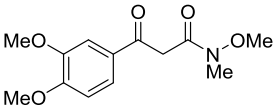
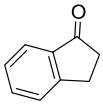
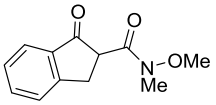
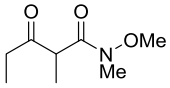
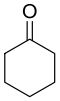
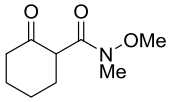
The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

In 1983 Mander and colleagues reported the use of methyl cyanoformate for the selective *C*-acylation of ketone enolates to form *β*-ketoesters.[5] Since this report cyanoformates have been the preferred reagent for this transformation, other reagents regularly give varying amounts of the unwanted *O*-acylation products.[6] In recent times the ethyl[7], benzyl[8] and allyl[9] cyanoformates have all been successfully employed for the synthesis of the corresponding *β*-ketoesters in organic synthesis. Despite the popularity and widespread use of cyanoformates the analogous cyanoformamides have never been exploited in the synthesis of *β*-ketoamides from the corresponding ketones.

Recently, our laboratory required a concise synthesis of a *β*-keto Weinreb amide from the corresponding ketone. Our investigations established that the reagents commonly used for the synthesis of Weinreb amides from organometallic reagents were unsuccessful when applied in the reaction of ketone enolates.[10] This prompted our investigation into the reactivity of *N*-methoxy-*N*-methylcyanoformamide, a compound we anticipated would exhibit similar reactivity to the related cyanoformates. We discovered that, when treated with *N*-methoxy-*N*-methylcyanoformamide, a wide range of ketone enolates efficiently underwent selective *C*-carbamoylation to form the product *β*-ketoamides in excellent yields (Table 1).

Table 1. *C*-Carbamoylation of Ketones using *N*-Methoxy-*N*-methylcyanoformamide (2)

Entry	Substrate	Product	Yield[a]
1			86%
2			87%
3			83%
4			82%
5			93%
6			67%
7			83%
8			77%
9			76%

[a] ketone (1.0 mmol), LiHMDS (1.1 mmol), THF, –78 °C, 1 h, then **2** (1.1 mmol), –78 °C, 0.25 h.

The procedure reported herein was derived from our original communication[10] and is both operationally simple and requires a minimal amount of purification. The ease of synthesis of **2** coupled with the efficiency and versatility of the reaction of compound **2** with enolates suggests that this reagent is an excellent addition to the synthetic chemist's toolbox.

References

1. Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia. Email: brett.schwartz@anu.edu.au. BDS is indebted to Prof. Martin Banwell (The Australian National University) and Dr Keats Nelms (Beta Therapeutics Pty Ltd) for financial support. JN is grateful to the Australian Government for an APA scholarship.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

N,*O*-dimethylhydroxylamine hydrochloride: Methanamine, *N*-methoxy-, hydrochloride; (6638-79-5)
N,*N'*-carbonyldiimidazole: 1*H*-Imidazole, 1,1'-carbonylbis-; (530-62-1)
trimethylsilyl cyanide: Silanecarbonitrile, trimethyl-; (7677-24-9)

Jeremy Nugent received his undergraduate degree from The Australian National University, Canberra. He is currently undertaking his postgraduate studies in the Research School of Chemistry at The Australian National University under the direction of Professor Martin Banwell. The main focus of Jeremy's current research is the development of new strategies for the synthesis of biologically active natural products.

Brett D. Schwartz received his Ph.D. in organic chemistry in 2005 under the supervision of Professor James J. De Voss at The University of Queensland. After more than a decade of post-doctoral research he now resides as a Senior Postdoctoral Fellow at The Australian National University in Canberra.

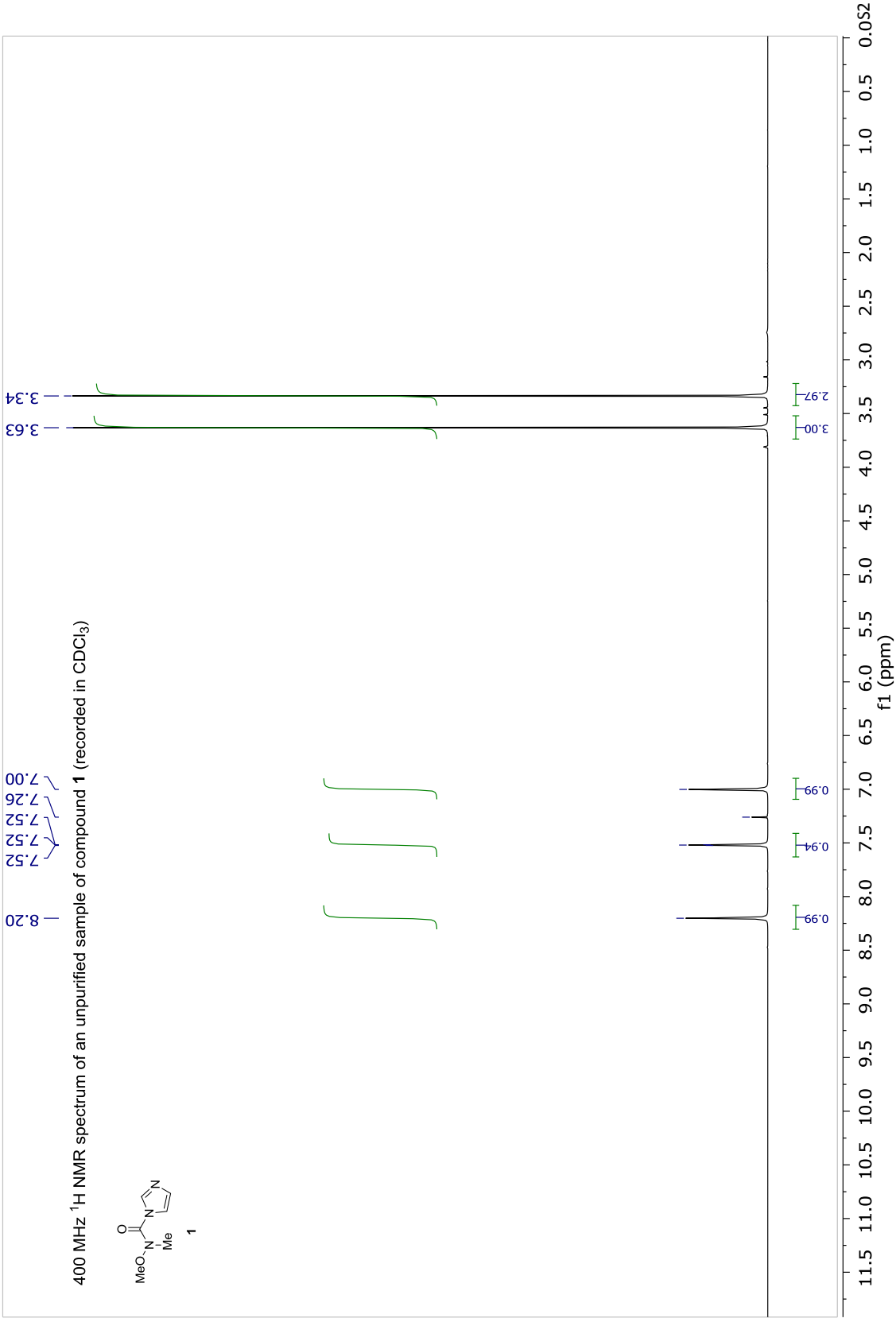
Supporting Information for

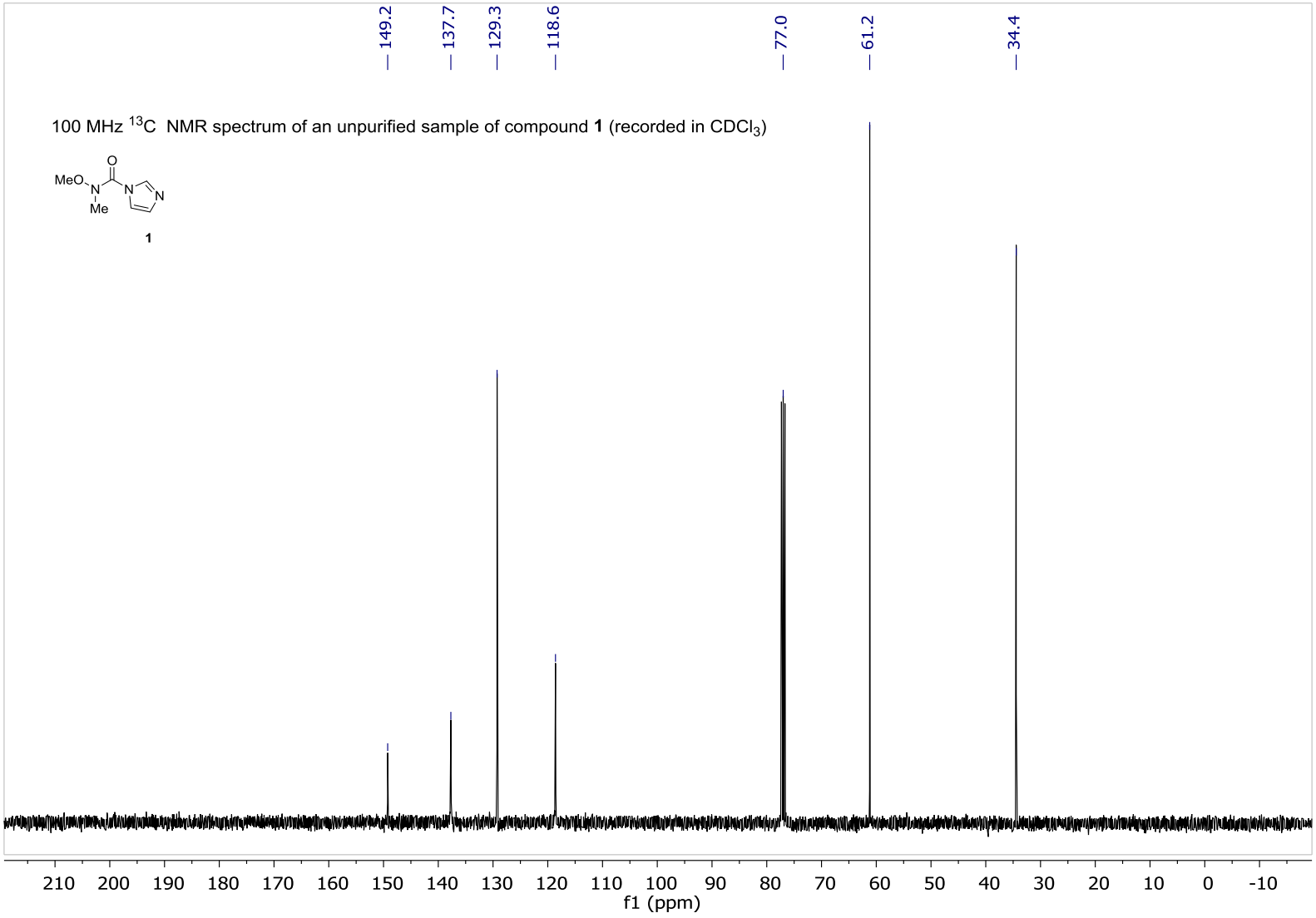
Preparation of N-Methoxy-N-methylcyanoformamide

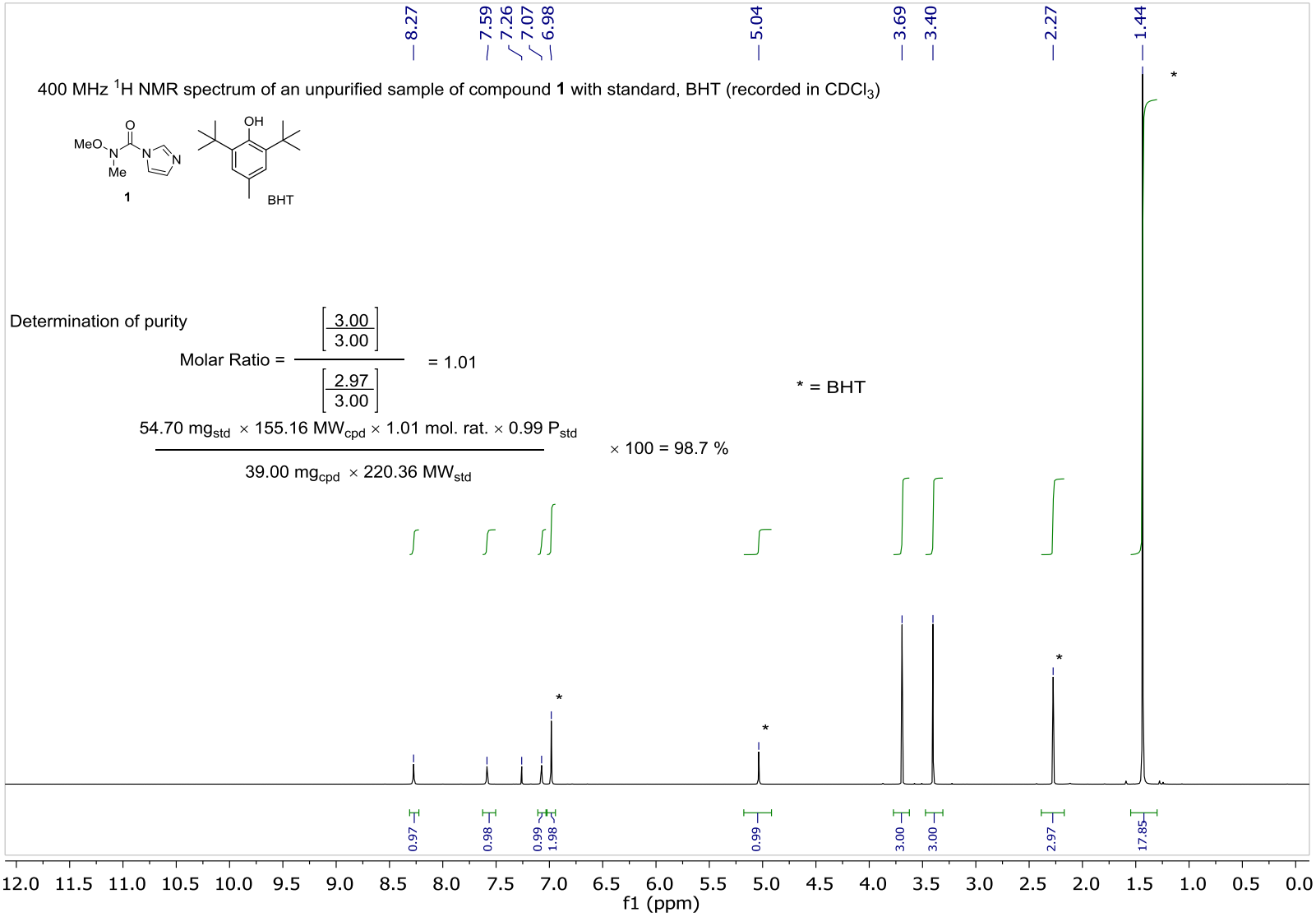
Jeremy Nugent and Brett D. Schwartz*

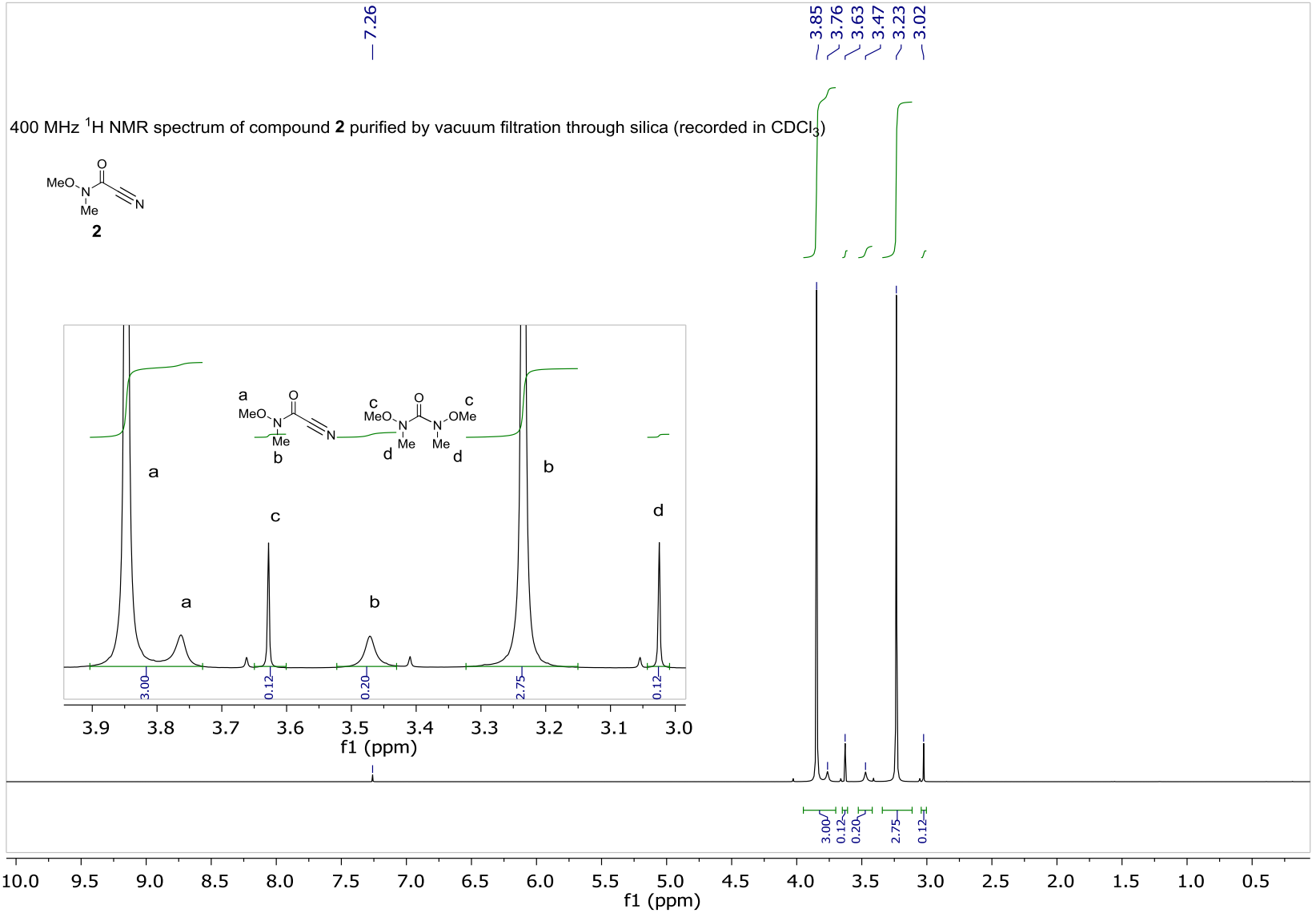
Research School of Chemistry, Institute of Advanced Studies,
The Australian National University, Canberra, ACT 2601, Australia.

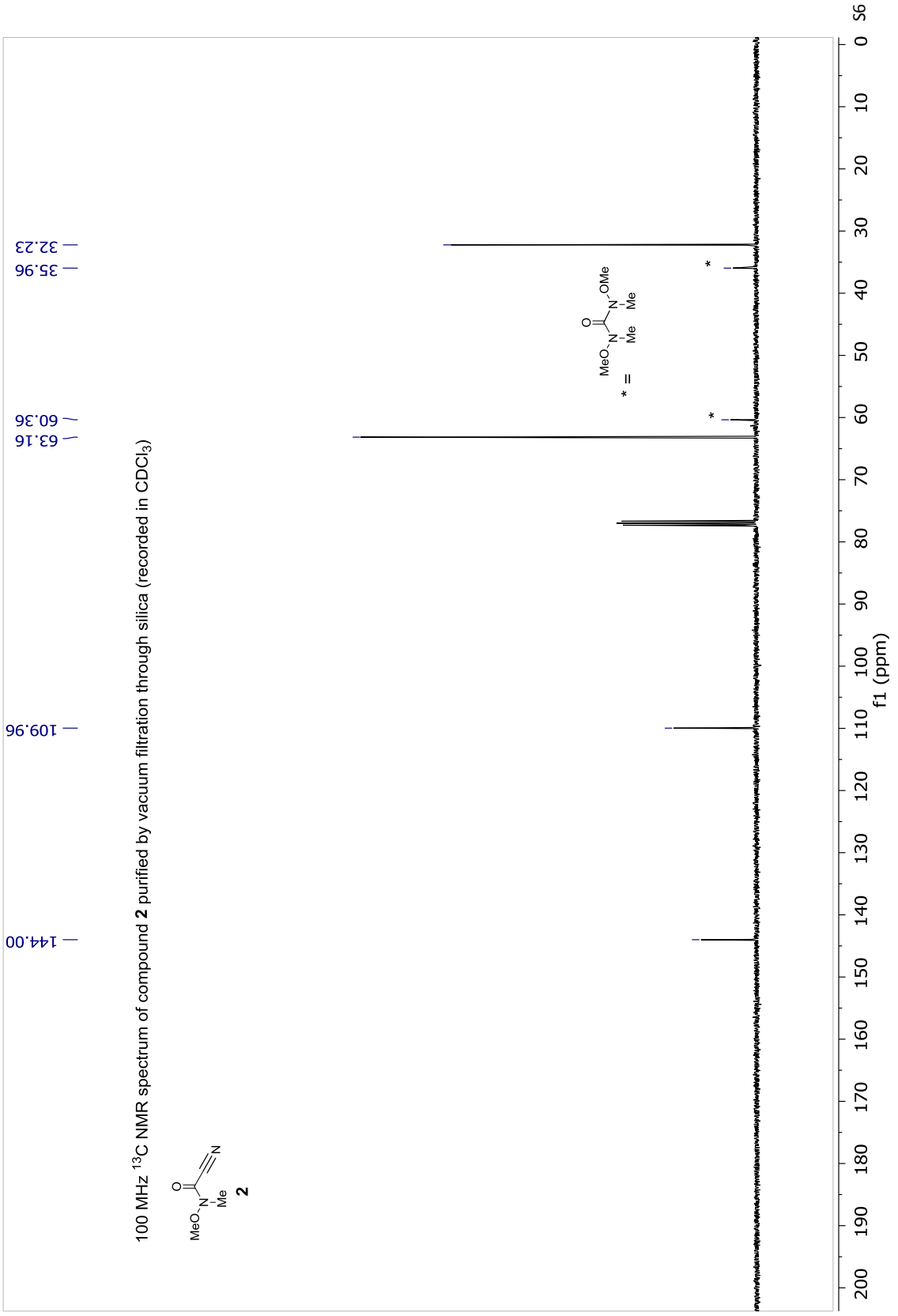
Contents **Page**

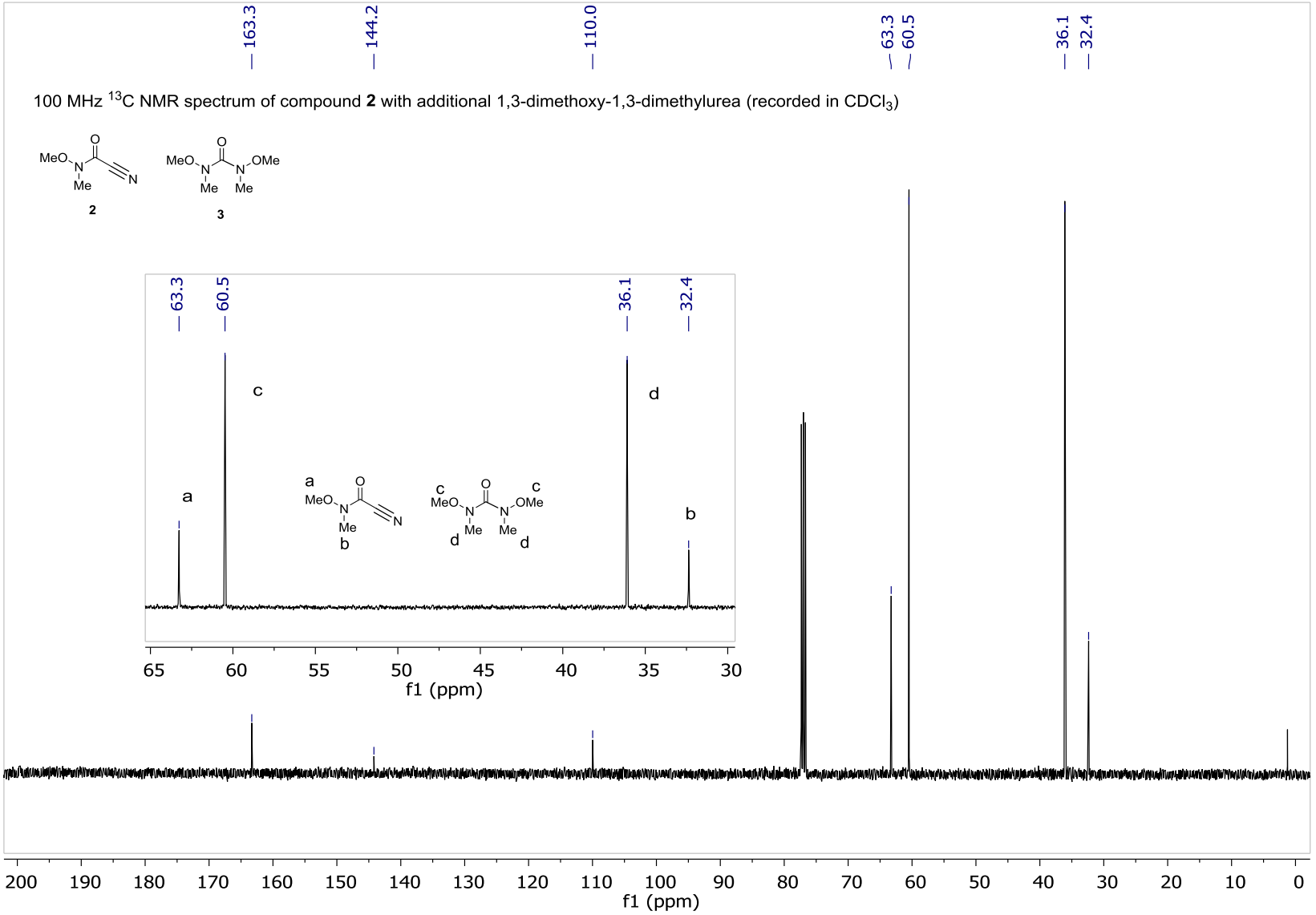

400 MHz ^{1}H NMR spectrum of an unpurified sample of compound **1** (recorded in $CDCl_3$)
1
MeO
Me
8.20
7.52
7.52
7.52
7.26
7.00
3.63
3.34
0.99
0.94
0.99
3.00
2.97
f1 (ppm)

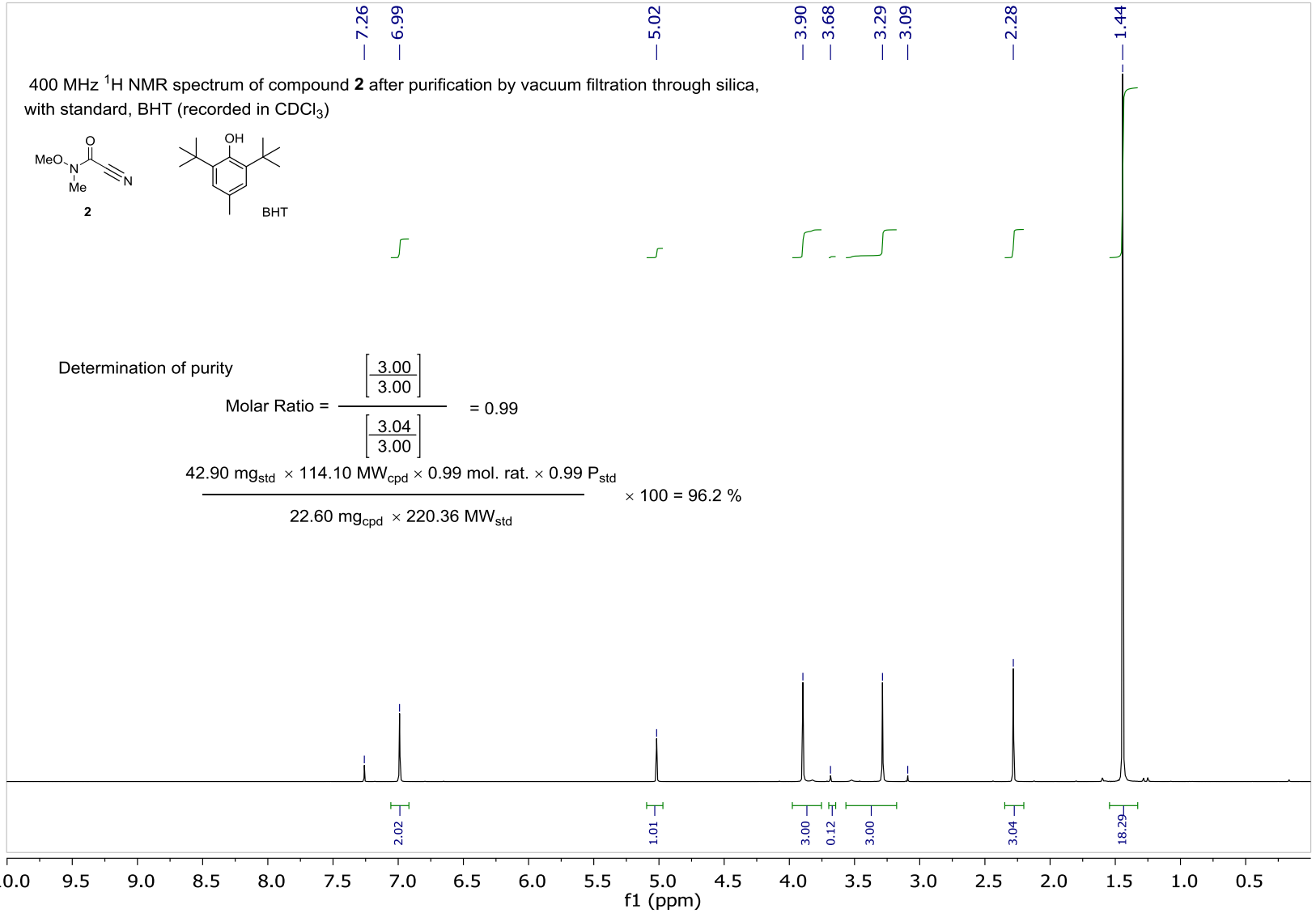

149.2
137.7
129.3
118.6
77.0
61.2
34.4
100 MHz ^{13}C NMR spectrum of an unpurified sample of compound **1** (recorded in $CDCl_3$)
MeO
N
Me
O
N
N
1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

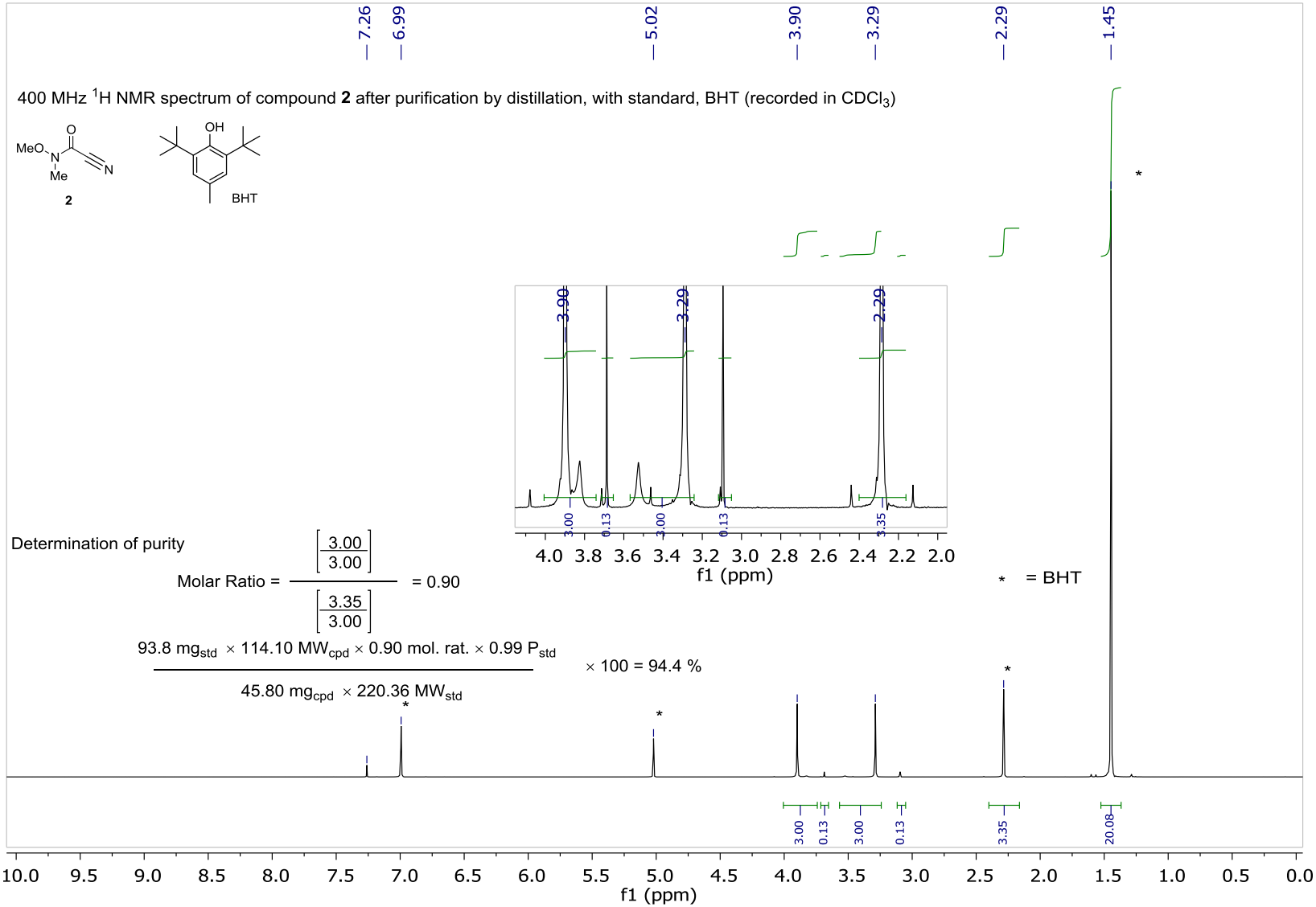

8.27
7.59
7.26
7.07
6.98
5.04
3.69
3.40
2.27
1.44
400 MHz ^{1}H NMR spectrum of an unpurified sample of compound **1** with standard, BHT (recorded in $CDCl_3$)
MeO
N
O
N
N
Me
1
OH
BHT
Determination of purity
Molar Ratio = $\frac{\left[\frac{3.00}{3.00}\right]}{\left[\frac{2.97}{3.00}\right]}$ = 1.01
$\frac{54.70\ mg_{std} \times 155.16\ MW_{cpd} \times 1.01\ mol.\ rat. \times 0.99\ P_{std}}{39.00\ mg_{cpd} \times 220.36\ MW_{std}} \times 100 = 98.7\ \%$
* = BHT
0.97
0.98
0.99
1.98
0.99
3.00
3.00
2.97
17.85
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


7.26
3.85
3.76
3.63
3.47
3.23
3.02
400 MHz ^{1}H NMR spectrum of compound **2** purified by vacuum filtration through silica (recorded in $CDCl_3$)
MeO
N
Me
O
N
2
a
b
c
d
3.00
0.12
0.20
2.75
0.12
f1 (ppm)


100 MHz ^{13}C NMR spectrum of compound **2** purified by vacuum filtration through silica (recorded in $CDCl_3$)
2
* =
144.00
109.96
63.16
60.36
35.96
32.23
f1 (ppm)

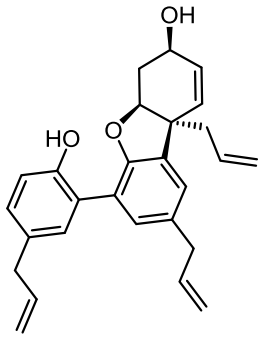

163.3
144.2
110.0
63.3
60.5
36.1
32.4
100 MHz ^{13}C NMR spectrum of compound **2** with additional 1,3-dimethoxy-1,3-dimethylurea (recorded in $CDCl_3$)
2
3
a
b
c
d
f1 (ppm)
f1 (ppm)


7.26
6.99
5.02
3.90
3.68
3.29
3.09
2.28
1.44
400 MHz ^{1}H NMR spectrum of compound **2** after purification by vacuum filtration through silica, with standard, BHT (recorded in $CDCl_3$)
MeO
N
Me
O
N
2
OH
BHT
Determination of purity
Molar Ratio = [3.00/3.00] / [3.04/3.00] = 0.99
42.90 mg_{std} × 114.10 MW_{cpd} × 0.99 mol. rat. × 0.99 P_{std} / 22.60 mg_{cpd} × 220.36 MW_{std} × 100 = 96.2 %
2.02
1.01
3.00
0.12
3.00
3.04
18.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

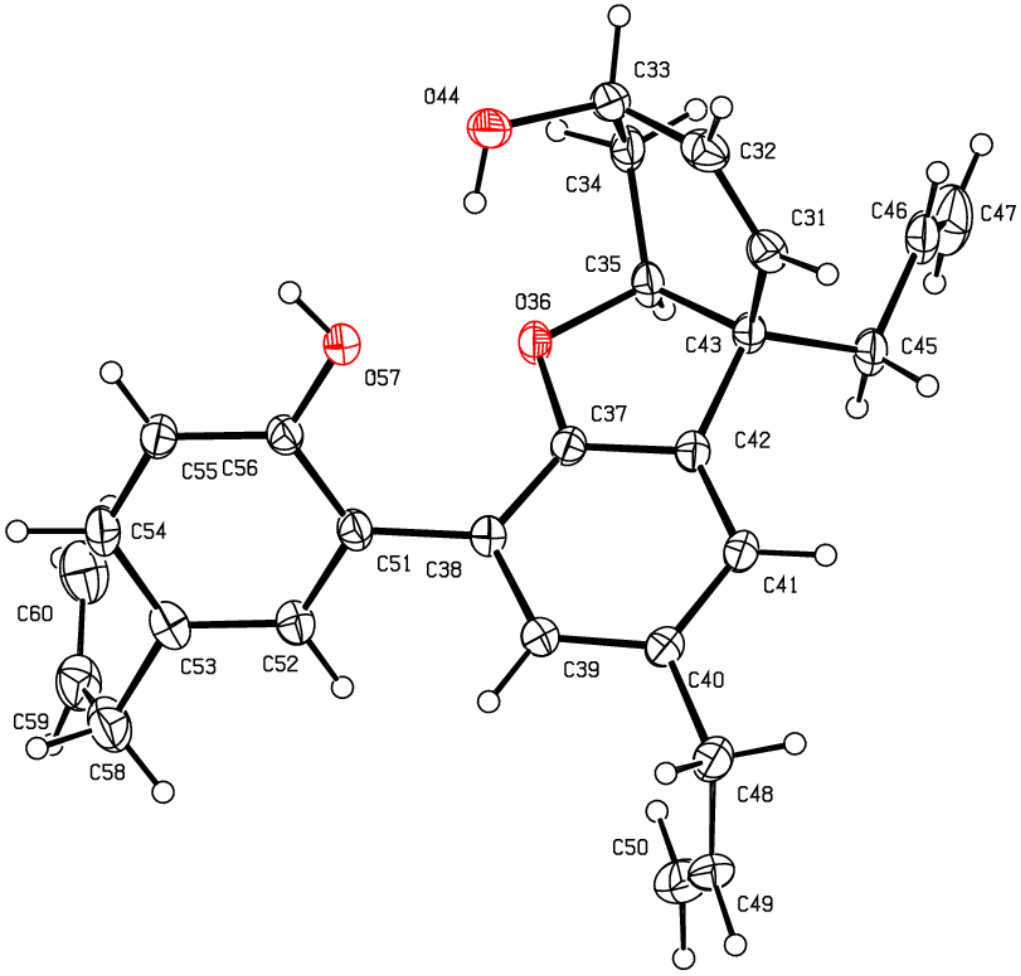

7.26
6.99
5.02
3.90
3.29
2.29
1.45
400 MHz ^{1}H NMR spectrum of compound **2** after purification by distillation, with standard, BHT (recorded in $CDCl_3$)
MeO
N
Me
O
N
2
OH
BHT
*
3.90
3.29
2.29
3.00
0.13
3.00
0.13
3.35
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0
f1 (ppm)
Determination of purity
Molar Ratio = [3.00/3.00] / [3.35/3.00] = 0.90
93.8 mg$_{std}$ × 114.10 MW$_{cpd}$ × 0.90 mol. rat. × 0.99 P$_{std}$ / 45.80 mg$_{cpd}$ × 220.36 MW$_{std}$ × 100 = 94.4 %
* = BHT
3.00
0.13
3.00
0.13
3.35
20.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

Appendix

Single-crystal X-ray report for compound **27** of **publication 4**.



27



Crystal structure of $C_{54}H_{56}O_6$ — banBDS_21

Jeremy Nugent, Martin G. Banwell and Brett D. Schwartz*

Research School of Chemistry, The Australian National University, Canberra, A. C. T. 2601, Australia

Correspondence email: u4691352@anu.edu.au

Abstract

The crystal structure of $C_{54}H_{56}O_6$. is reported.

1. Comment

The crystallographic asymmetric unit consists of two molecules of $C_{27}H_{28}O_3$.

2. Synthesis and crystallization

The compound was prepared by JN is a racemate and was recrystallized from ethanol / water The sample ID is JN-dihydrosimonsolC

Related literature

Computing details

Data collection: *CrysAlis PRO*, (Agilent, 2015); cell refinement: *CrysAlis PRO*, (Agilent, 2015); data reduction: *CrysAlis PRO*, (Agilent, 2015); program(s) used to solve structure: *SUPERFLIP* (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *PLATON* (Spek, 2008); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Acknowledgements

Dr Tony Willis is acknowledged for assitance with resolving disorder issues.

References

CrysAlis PRO, Agilent Technologies, Version 1.171.37.35h (release 09-02-2015 CrysAlis171 .NET) (compiled Feb 9 2015,16:26:32)

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Palatinus, L. & Chapuis, G. (2007). *J. Appl. Cryst.* **40**, 786–790.

Spek, A. L. (2008). *PLATON*, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

(banBDS_21)

Crystal data

$C_{27}H_{28}O_3$
M_r = 400.47
Triclinic, $P\overline{1}$
Hall symbol: -P 1
a = 9.9759 (2) Å
b = 13.6806 (3) Å
c = 17.6508 (4) Å
α = 109.1900 (19)°
β = 96.4682 (17)°
γ = 98.2575 (16)°
V = 2218.30 (5) Å^3
Z = 4
F(000) = 855.891
D_x = 1.199 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 10944 reflections
θ = 5–72°
μ = 0.61 mm^{-1}

T = 150 K
Rod, colourless

0.44 × 0.07 × 0.04 mm

Data collection

Oxford Diffraction SuperNova diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *CrysAlis PRO*, (Agilent, 2015)
T_{min} = 0.75, T_{max} = 0.98
24412 measured reflections

8471 independent reflections
7181 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.027
θ_{max} = 72.0°, θ_{min} = 3.5°
h = −11→9
k = −16→16
l = −21→21

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.052
$wR(F^2)$ = 0.143
S = 0.99
8471 reflections
604 parameters
44 restraints
Primary atom site location: Other

Hydrogen site location: difference Fourier map
H atoms treated by a mixture of independent and constrained refinement
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.07P)^2 + 1.21P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.009
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.46 e Å^{-3}

Special details

Refinement
H atoms were added at calculated positions and were rided to atoms to which they were bonded. Disorder was observed in several of the allyl side-chains. Additional atom sites were added as appropriate and restraints in distances and angles were applied during refinement. The major features of the final difference map are largely within the disorder. Some peaks suggest further disorder existed which was not modelled here as its apparent occupancy was insignificant.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}	Occ. (<1)
O6	0.27481 (13)	0.73850 (9)	0.24961 (8)	0.0351	
O14	0.27042 (15)	0.70687 (11)	0.07930 (9)	0.0424	
O27	0.27654 (15)	0.91133 (10)	0.19061 (8)	0.0386	
O36	0.67824 (12)	0.03905 (9)	0.08966 (8)	0.0341	
O44	0.7079 (2)	0.01195 (11)	−0.07272 (9)	0.0565	
O57	0.77502 (15)	0.22650 (10)	0.04834 (8)	0.0400	
C1	−0.0087 (2)	0.60270 (14)	0.14403 (11)	0.0372	
C2	0.0491 (2)	0.60634 (14)	0.08096 (11)	0.0395	
C3	0.1982 (2)	0.60642 (14)	0.07754 (12)	0.0403	
C4	0.2653 (2)	0.57227 (15)	0.14420 (13)	0.0429	
C5	0.2246 (2)	0.62475 (13)	0.22531 (12)	0.0367	
C7	0.17964 (18)	0.78667 (13)	0.29130 (10)	0.0314	
C8	0.19887 (19)	0.89428 (14)	0.33343 (10)	0.0326	
C9	0.0900 (2)	0.92876 (14)	0.37123 (11)	0.0368	
C10	−0.0327 (2)	0.86114 (16)	0.36582 (12)	0.0412	
C11	−0.0480 (2)	0.75417 (15)	0.32078 (12)	0.0395	
C12	0.05906 (19)	0.71723 (14)	0.28424 (10)	0.0335	
C13	0.06828 (19)	0.60981 (14)	0.22519 (11)	0.0356	
C15	0.0089 (2)	0.51577 (15)	0.24936 (13)	0.0455	
C16	0.0563 (3)	0.5249 (2)	0.33568 (16)	0.0445	0.779
C17	−0.0173 (4)	0.5329 (3)	0.3928 (2)	0.0642	0.779
C18	−0.1492 (3)	0.90371 (19)	0.40639 (15)	0.0574	

C19	−0.2747 (4)	0.8844 (3)	0.35158 (19)	0.0716	0.836
C20	−0.3887 (3)	0.8172 (3)	0.3439 (3)	0.1128	
C21	0.32470 (19)	0.96798 (13)	0.33498 (11)	0.0332	
C22	0.4075 (2)	1.03517 (14)	0.40828 (11)	0.0378	
C23	0.5251 (2)	1.10435 (15)	0.41068 (12)	0.0437	
C24	0.5601 (2)	1.10664 (16)	0.33685 (13)	0.0465	
C25	0.4790 (2)	1.04296 (15)	0.26307 (12)	0.0417	
C26	0.3614 (2)	0.97400 (13)	0.26192 (11)	0.0346	
C28	0.6136 (3)	1.17471 (19)	0.49080 (15)	0.0613	
C29	0.6015 (6)	1.2894 (3)	0.5145 (2)	0.0880	0.762
C30	0.5288 (9)	1.3307 (4)	0.4749 (3)	0.1438	0.762
C31	0.8933 (2)	−0.10967 (14)	0.02527 (11)	0.0362	
C32	0.8499 (2)	−0.10828 (15)	−0.04808 (12)	0.0440	
C33	0.7075 (2)	−0.09476 (14)	−0.07423 (12)	0.0461	
C34	0.6082 (2)	−0.12460 (14)	−0.02314 (12)	0.0414	
C35	0.66481 (19)	−0.07620 (13)	0.06678 (11)	0.0338	
C37	0.79111 (18)	0.08394 (13)	0.15013 (10)	0.0307	
C38	0.82412 (19)	0.19039 (13)	0.19730 (11)	0.0324	
C39	0.9405 (2)	0.22072 (14)	0.25792 (11)	0.0356	
C40	1.0211 (2)	0.14999 (14)	0.27026 (11)	0.0360	
C41	0.98607 (19)	0.04421 (14)	0.21923 (11)	0.0331	
C42	0.87025 (18)	0.01156 (13)	0.15943 (10)	0.0309	
C43	0.80946 (18)	−0.09449 (13)	0.09315 (10)	0.0304	
C45	0.8041 (2)	−0.18713 (14)	0.12498 (12)	0.0379	
C46	0.7344 (2)	−0.29089 (15)	0.06209 (14)	0.0452	
C47	0.6277 (3)	−0.3525 (2)	0.0700 (2)	0.0721	
C48	1.1441 (2)	0.18934 (16)	0.33768 (13)	0.0460	
C49	1.1137 (4)	0.2196 (3)	0.42196 (17)	0.0482	0.731
C50	0.9941 (4)	0.2080 (3)	0.44254 (19)	0.0633	0.731
C51	0.74336 (18)	0.26958 (13)	0.18621 (11)	0.0327	
C52	0.6919 (2)	0.33274 (14)	0.25131 (12)	0.0373	
C53	0.6225 (2)	0.41217 (15)	0.24587 (13)	0.0421	
C54	0.6067 (2)	0.42863 (15)	0.17196 (13)	0.0420	
C55	0.6557 (2)	0.36701 (14)	0.10572 (12)	0.0382	
C56	0.72353 (18)	0.28697 (13)	0.11212 (11)	0.0333	
C58	0.5618 (3)	0.47513 (18)	0.31656 (15)	0.0570	
C59	0.4090 (3)	0.4363 (3)	0.30621 (19)	0.0547	0.779
C60	0.3264 (3)	0.3673 (3)	0.2416 (2)	0.0593	0.779
C116	0.0659 (15)	0.4176 (11)	0.1899 (8)	0.0834*	0.221
C117	0.1634 (19)	0.3670 (15)	0.2075 (11)	0.1047*	0.221
C119	−0.2808 (13)	0.8269 (12)	0.3858 (9)	0.0616*	0.164
C129	0.713 (2)	1.2694 (13)	0.5012 (13)	0.1371	0.238
C130	0.695 (3)	1.3621 (13)	0.5069 (15)	0.1635	0.238
C149	1.1330 (16)	0.2666 (13)	0.4137 (8)	0.0913*	0.269
C150	1.243 (2)	0.3066 (16)	0.4744 (11)	0.1400*	0.269
C159	0.491 (2)	0.4240 (19)	0.3669 (15)	0.0600*	0.091
C160	0.380 (2)	0.45227 (10)	0.39296 (10)	0.0600*	0.091
C259	0.6766 (18)	0.5368 (14)	0.3944 (9)	0.0600*	0.130
C260	0.712 (2)	0.5262 (16)	0.4659 (10)	0.0600*	0.130
H1	0.270 (2)	0.753 (2)	0.1250 (16)	0.0500*	
H2	0.287 (2)	0.9369 (19)	0.1544 (15)	0.0500*	
H3	0.717 (2)	0.052 (2)	−0.0239 (16)	0.0500*	

H4	0.756 (2)	0.2446 (19)	0.0072 (15)	0.0500*	
H11	−0.1059	0.5948	0.1379	0.0452*	
H21	−0.0076	0.6091	0.0350	0.0473*	
H31	0.2035	0.5553	0.0268	0.0491*	
H41	0.3623	0.5903	0.1494	0.0519*	
H42	0.2383	0.4980	0.1291	0.0519*	
H51	0.2666	0.5997	0.2645	0.0448*	
H91	0.0999	1.0016	0.4022	0.0444*	
H111	−0.1314	0.7071	0.3151	0.0475*	
H151	−0.0884	0.5079	0.2410	0.0555*	0.779
H152	0.0340	0.4543	0.2145	0.0555*	0.779
H153	0.0427	0.5277	0.3048	0.0555*	0.221
H154	−0.0887	0.5032	0.2405	0.0555*	0.221
H161	0.1511	0.5251	0.3501	0.0514*	0.779
H171	0.0245	0.5383	0.4455	0.0769*	0.779
H172	−0.1128	0.5331	0.3821	0.0769*	0.779
H181	−0.1210	0.9779	0.4325	0.0698*	0.836
H182	−0.1657	0.8723	0.4460	0.0698*	0.836
H183	−0.1675	0.9602	0.3893	0.0698*	0.164
H184	−0.1198	0.9295	0.4637	0.0698*	0.164
H191	−0.2764	0.9244	0.3166	0.0876*	0.836
H201	−0.4661	0.8114	0.3050	0.1345*	0.836
H202	−0.3937	0.7748	0.3771	0.1345*	0.836
H203	−0.3987	0.8658	0.3167	0.1345*	0.164
H204	−0.4634	0.7621	0.3378	0.1345*	0.164
H221	0.3818	1.0334	0.4581	0.0453*	
H241	0.6412	1.1527	0.3371	0.0565*	
H251	0.5037	1.0465	0.2135	0.0503*	
H281	0.7070	1.1700	0.4872	0.0751*	0.762
H282	0.5868	1.1497	0.5321	0.0751*	0.762
H283	0.5513	1.1995	0.5263	0.0751*	0.238
H284	0.6625	1.1303	0.5098	0.0751*	0.238
H291	0.6527	1.3348	0.5659	0.1047*	0.762
H301	0.5302	1.4043	0.4968	0.1825*	0.762
H302	0.4754	1.2896	0.4231	0.1825*	0.762
H311	0.9842	−0.1209	0.0361	0.0437*	
H321	0.9118	−0.1163	−0.0858	0.0531*	
H331	0.6770	−0.1412	−0.1289	0.0557*	
H341	0.5894	−0.1992	−0.0382	0.0503*	
H342	0.5254	−0.1010	−0.0336	0.0503*	
H351	0.6022	−0.1010	0.0962	0.0409*	
H391	0.9657	0.2926	0.2924	0.0426*	
H411	1.0411	−0.0047	0.2255	0.0405*	
H451	0.8956	−0.1920	0.1429	0.0460*	
H452	0.7558	−0.1730	0.1696	0.0460*	
H461	0.7701	−0.3139	0.0129	0.0544*	
H471	0.5886	−0.4175	0.0274	0.0853*	
H472	0.5893	−0.3320	0.1184	0.0853*	
H481	1.1962	0.1350	0.3304	0.0555*	0.731
H482	1.1977	0.2495	0.3327	0.0555*	0.731
H483	1.2180	0.2190	0.3175	0.0555*	0.269
H484	1.1659	0.1298	0.3492	0.0555*	0.269

H491	1.1902	0.2500	0.4650	0.0586*	0.731
H501	0.9860	0.2301	0.4985	0.0775*	0.731
H502	0.9142	0.1780	0.4019	0.0775*	0.731
H521	0.7047	0.3211	0.3016	0.0452*	
H541	0.5615	0.4832	0.1668	0.0510*	
H551	0.6425	0.3791	0.0556	0.0461*	
H581	0.5778	0.5469	0.3205	0.0691*	0.779
H582	0.6057	0.4694	0.3652	0.0691*	0.779
H583	0.6357	0.5304	0.3491	0.0691*	0.0910
H584	0.4944	0.5037	0.2927	0.0691*	0.0910
H585	0.5165	0.5240	0.3013	0.0691*	0.13
H586	0.4976	0.4288	0.3309	0.0691*	0.13
H591	0.3677	0.4656	0.3523	0.0652*	0.779
H601	0.3611	0.3350	0.1934	0.0694*	0.779
H602	0.2315	0.3498	0.2433	0.0694*	0.779
H1161	0.0239	0.3896	0.1318	0.1000*	0.221
H1171	0.2119	0.3882	0.2605	0.1257*	0.221
H1172	0.1884	0.3097	0.1648	0.1257*	0.221
H1191	−0.2791	0.7752	0.4109	0.0739*	0.164
H1291	0.8040	1.2560	0.4986	0.1990*	0.238
H1301	0.7751	1.4121	0.5114	0.2203*	0.238
H1302	0.6089	1.3831	0.5104	0.2203*	0.238
H1491	1.0474	0.2873	0.4220	0.1096*	0.269
H1501	1.3287	0.2859	0.4661	0.1680*	0.269
H1502	1.2354	0.3579	0.5245	0.1680*	0.269
H1591	0.5239	0.3678	0.3785	0.0720*	0.091
H1601	0.3464	0.5084	0.3816	0.0720*	0.091
H1602	0.3353	0.4189	0.4253	0.0720*	0.091
H2591	0.7394	0.5908	0.3871	0.0720*	0.13
H2601	0.7884	0.5707	0.5051	0.0720*	0.13
H2602	0.6540	0.4740	0.4782	0.0720*	0.13

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O6	0.0332 (7)	0.0270 (6)	0.0418 (7)	0.0049 (5)	0.0003 (5)	0.0100 (5)
O14	0.0537 (9)	0.0344 (7)	0.0365 (7)	0.0087 (6)	0.0092 (6)	0.0085 (6)
O27	0.0506 (8)	0.0323 (6)	0.0294 (6)	0.0018 (6)	0.0020 (6)	0.0103 (5)
O36	0.0321 (6)	0.0257 (6)	0.0431 (7)	0.0082 (5)	−0.0021 (5)	0.0118 (5)
O44	0.1057 (14)	0.0271 (7)	0.0326 (7)	0.0091 (7)	−0.0029 (8)	0.0114 (6)
O57	0.0528 (8)	0.0339 (7)	0.0350 (7)	0.0171 (6)	0.0045 (6)	0.0116 (5)
C1	0.0370 (10)	0.0288 (8)	0.0392 (10)	0.0036 (7)	−0.0028 (8)	0.0075 (7)
C2	0.0451 (11)	0.0314 (9)	0.0367 (9)	0.0094 (8)	−0.0039 (8)	0.0076 (7)
C3	0.0494 (11)	0.0293 (9)	0.038 (1)	0.0091 (8)	0.0070 (8)	0.0058 (7)
C4	0.0427 (11)	0.0328 (9)	0.0519 (11)	0.0150 (8)	0.0038 (9)	0.0112 (8)
C5	0.0399 (10)	0.0250 (8)	0.0428 (10)	0.0067 (7)	−0.0035 (8)	0.0119 (7)
C7	0.0337 (9)	0.0299 (8)	0.0303 (8)	0.0073 (7)	0.0004 (7)	0.0114 (7)
C8	0.0392 (10)	0.0305 (8)	0.0269 (8)	0.0047 (7)	−0.0003 (7)	0.0111 (7)
C9	0.0480 (11)	0.0319 (9)	0.0288 (8)	0.0083 (8)	0.0056 (8)	0.0086 (7)
C10	0.0462 (11)	0.0428 (10)	0.0355 (9)	0.0085 (9)	0.0104 (8)	0.0137 (8)
C11	0.0379 (10)	0.0408 (10)	0.0392 (10)	0.0027 (8)	0.0058 (8)	0.0154 (8)
C12	0.0364 (9)	0.0304 (8)	0.0320 (8)	0.0034 (7)	−0.0009 (7)	0.0123 (7)

C13	0.0380 (10)	0.0276 (8)	0.0388 (9)	0.0038 (7)	−0.0006 (8)	0.0117 (7)
C15	0.0532 (12)	0.0316 (9)	0.0485 (11)	0.0010 (9)	0.0004 (9)	0.0156 (8)
C16	0.0463 (15)	0.0413 (13)	0.0496 (15)	0.0018 (11)	0.0030 (12)	0.0252 (12)
C17	0.079 (2)	0.065 (2)	0.0519 (17)	0.0081 (17)	0.0157 (16)	0.0257 (15)
C18	0.0581 (14)	0.0515 (13)	0.0598 (14)	0.0102 (11)	0.0252 (11)	0.0114 (11)
C19	0.067 (2)	0.091 (3)	0.0509 (17)	0.049 (2)	0.0091 (14)	0.0044 (16)
C20	0.0519 (19)	0.114 (3)	0.125 (3)	0.0247 (19)	0.0052 (19)	−0.020 (2)
C21	0.0388 (10)	0.0253 (8)	0.0340 (9)	0.0050 (7)	0.0012 (7)	0.0103 (7)
C22	0.0469 (11)	0.0300 (9)	0.0336 (9)	0.0050 (8)	0.0004 (8)	0.0107 (7)
C23	0.0484 (12)	0.0338 (9)	0.0429 (10)	−0.0004 (8)	−0.0049 (9)	0.0133 (8)
C24	0.0441 (11)	0.0379 (10)	0.0548 (12)	−0.0039 (8)	0.0022 (9)	0.0199 (9)
C25	0.0491 (12)	0.0362 (9)	0.0418 (10)	0.0053 (8)	0.0086 (9)	0.0172 (8)
C26	0.0415 (10)	0.0265 (8)	0.0334 (9)	0.0053 (7)	0.0017 (7)	0.0092 (7)
C28	0.0641 (15)	0.0528 (13)	0.0522 (13)	−0.0149 (11)	−0.0139 (11)	0.0176 (11)
C29	0.142 (5)	0.0345 (17)	0.056 (2)	−0.018 (2)	−0.034 (3)	0.0060 (15)
C30	0.276 (10)	0.047 (2)	0.078 (3)	0.017 (4)	−0.032 (4)	0.009 (2)
C31	0.0349 (9)	0.0304 (9)	0.0410 (10)	0.0051 (7)	0.0067 (8)	0.0100 (7)
C32	0.0564 (12)	0.0328 (9)	0.0388 (10)	0.0008 (8)	0.0110 (9)	0.0096 (8)
C33	0.0721 (14)	0.0251 (9)	0.0352 (9)	0.0056 (9)	−0.0072 (9)	0.0096 (7)
C34	0.0405 (10)	0.0247 (8)	0.0533 (11)	0.0052 (7)	−0.0104 (9)	0.0127 (8)
C35	0.0330 (9)	0.0245 (8)	0.0461 (10)	0.0077 (7)	0.0042 (7)	0.0150 (7)
C37	0.0305 (9)	0.0300 (8)	0.0325 (8)	0.0073 (7)	0.0024 (7)	0.0126 (7)
C38	0.0355 (9)	0.0295 (8)	0.0343 (9)	0.0092 (7)	0.0053 (7)	0.0130 (7)
C39	0.0425 (10)	0.0293 (8)	0.0331 (9)	0.0076 (7)	0.0015 (7)	0.0098 (7)
C40	0.0389 (10)	0.0362 (9)	0.0337 (9)	0.0081 (8)	0.0012 (7)	0.0145 (7)
C41	0.0346 (9)	0.0345 (9)	0.0352 (9)	0.0113 (7)	0.0048 (7)	0.0171 (7)
C42	0.0331 (9)	0.0293 (8)	0.0341 (8)	0.0093 (7)	0.0073 (7)	0.0142 (7)
C43	0.0311 (9)	0.0266 (8)	0.0359 (9)	0.0078 (7)	0.0034 (7)	0.0136 (7)
C45	0.0413 (10)	0.0312 (9)	0.0467 (10)	0.0114 (8)	0.0051 (8)	0.0201 (8)
C46	0.0425 (11)	0.0313 (9)	0.0643 (13)	0.0095 (8)	−0.0029 (9)	0.0230 (9)
C47	0.0553 (15)	0.0512 (14)	0.114 (2)	−0.0026 (11)	−0.0060 (15)	0.0461 (15)
C48	0.0508 (12)	0.0382 (10)	0.0469 (11)	0.0064 (9)	−0.0078 (9)	0.0182 (9)
C49	0.0570 (19)	0.0411 (17)	0.0343 (14)	0.0071 (14)	−0.0142 (13)	0.0053 (11)
C50	0.077 (3)	0.076 (2)	0.0369 (16)	0.0270 (19)	0.0052 (15)	0.0156 (15)
C51	0.0320 (9)	0.0247 (8)	0.0398 (9)	0.0058 (7)	0.0023 (7)	0.0101 (7)
C52	0.0405 (10)	0.0323 (9)	0.0415 (10)	0.0094 (8)	0.0087 (8)	0.0144 (8)
C53	0.0439 (11)	0.0320 (9)	0.0505 (11)	0.0115 (8)	0.0126 (9)	0.0112 (8)
C54	0.0417 (11)	0.0332 (9)	0.0551 (12)	0.0156 (8)	0.0069 (9)	0.0179 (8)
C55	0.0389 (10)	0.0343 (9)	0.0425 (10)	0.0107 (8)	0.0006 (8)	0.0155 (8)
C56	0.0323 (9)	0.0267 (8)	0.0372 (9)	0.0058 (7)	0.0000 (7)	0.0084 (7)
C58	0.0707 (16)	0.0472 (12)	0.0614 (14)	0.0285 (11)	0.0243 (12)	0.0186 (11)
C59	0.0603 (19)	0.0634 (18)	0.0568 (17)	0.0341 (15)	0.0293 (15)	0.0272 (15)
C60	0.0531 (18)	0.0553 (17)	0.081 (2)	0.0185 (14)	0.0276 (16)	0.0298 (17)
C129	0.199 (17)	0.098 (10)	0.099 (11)	0.023 (12)	−0.013 (13)	0.029 (9)
C130	0.258 (19)	0.067 (9)	0.148 (14)	−0.002 (11)	0.050 (14)	0.023 (10)

Geometric parameters (Å, º)

O6—C5	1.465 (2)	C32—C33	1.499 (3)
O6—C7	1.377 (2)	C32—H321	0.950
O14—C3	1.446 (2)	C33—C34	1.513 (3)
O14—H1	0.84 (3)	C33—H331	0.950

O27—C26	1.370 (2)	C34—C35	1.509 (3)
O27—H2	0.83 (3)	C34—H341	0.950
O36—C35	1.4750 (19)	C34—H342	0.950
O36—C37	1.372 (2)	C35—C43	1.546 (2)
O44—C33	1.451 (2)	C35—H351	0.950
O44—H3	0.84 (3)	C37—C38	1.388 (2)
O57—C56	1.362 (2)	C37—C42	1.390 (2)
O57—H4	0.85 (3)	C38—C39	1.398 (2)
C1—C2	1.322 (3)	C38—C51	1.488 (2)
C1—C13	1.513 (2)	C39—C40	1.397 (3)
C1—H11	0.950	C39—H391	0.950
C2—C3	1.495 (3)	C40—C41	1.398 (3)
C2—H21	0.950	C40—C48	1.507 (3)
C3—C4	1.525 (3)	C41—C42	1.384 (2)
C3—H31	0.950	C41—H411	0.950
C4—C5	1.506 (3)	C42—C43	1.521 (2)
C4—H41	0.950	C43—C45	1.543 (2)
C4—H42	0.950	C45—C46	1.496 (3)
C5—C13	1.543 (3)	C45—H451	0.950
C5—H51	0.950	C45—H452	0.950
C7—C8	1.387 (2)	C46—C47	1.310 (3)
C7—C12	1.387 (3)	C46—H461	0.950
C8—C9	1.397 (3)	C47—H471	0.950
C8—C21	1.485 (3)	C47—H472	0.950
C9—C10	1.398 (3)	C48—C49	1.486 (4)
C9—H91	0.950	C48—C149	1.437 (12)
C10—C11	1.393 (3)	C48—H481	0.950
C10—C18	1.520 (3)	C48—H482	0.950
C11—C12	1.382 (3)	C48—H483	0.950
C11—H111	0.950	C48—H484	0.950
C12—C13	1.519 (2)	C49—C50	1.289 (5)
C13—C15	1.545 (3)	C49—H491	0.950
C15—C16	1.502 (3)	C50—C149	1.711 (17)
C15—C116	1.629 (12)	C50—H501	0.950
C15—H151	0.950	C50—H502	0.950
C15—H152	0.950	C51—C52	1.392 (3)
C15—H153	0.950	C51—C56	1.402 (3)
C15—H154	0.950	C52—C53	1.392 (3)
C16—C17	1.298 (4)	C52—H521	0.950
C16—H153	0.562	C53—C54	1.391 (3)
C16—H161	0.950	C53—C58	1.510 (3)
C17—H171	0.950	C54—C55	1.384 (3)
C17—H172	0.950	C54—H541	0.950
C18—C19	1.427 (4)	C55—C56	1.395 (2)
C18—C119	1.485 (12)	C55—H551	0.950
C18—H181	0.950	C58—C59	1.510 (4)
C18—H182	0.950	C58—C159	1.480 (16)
C18—H183	0.950	C58—C259	1.587 (14)
C18—H184	0.950	C58—H581	0.950
C19—C20	1.319 (5)	C58—H582	0.950
C19—H191	0.950	C58—H583	0.950
C20—C119	1.199 (12)	C58—H584	0.950

C20—H201	0.950	C58—H585	0.950
C20—H202	0.950	C58—H586	0.950
C20—H203	0.950	C59—C60	1.315 (5)
C20—H204	0.950	C59—H584	1.263
C21—C22	1.400 (2)	C59—H586	0.975
C21—C26	1.404 (3)	C59—H591	0.950
C22—C23	1.385 (3)	C60—H601	0.950
C22—H221	0.950	C60—H602	0.950
C23—C24	1.396 (3)	C116—C117	1.337 (15)
C23—C28	1.512 (3)	C116—H152	0.690
C24—C25	1.387 (3)	C116—H1161	0.987
C24—H241	0.950	C117—H1171	0.934
C25—C26	1.389 (3)	C117—H1172	0.978
C25—H251	0.950	C119—H1191	0.950
C28—C29	1.511 (5)	C129—C130	1.279 (16)
C28—C129	1.461 (15)	C129—H1291	0.950
C28—H281	0.950	C130—H1301	0.950
C28—H282	0.950	C130—H1302	0.950
C28—H283	0.950	C149—C150	1.352 (15)
C28—H284	0.950	C149—H1491	0.950
C29—C30	1.265 (7)	C150—H1501	0.950
C29—C129	1.22 (2)	C150—H1502	0.950
C29—C130	1.32 (2)	C159—C160	1.305 (18)
C29—H291	0.950	C159—H1591	0.950
C30—C130	1.64 (3)	C160—H1601	0.950
C30—H301	0.950	C160—H1602	0.950
C30—H302	0.950	C259—C260	1.331 (16)
C31—C32	1.325 (3)	C259—H2591	0.950
C31—C43	1.513 (3)	C260—H2601	0.950
C31—H311	0.950	C260—H2602	0.950

C5—O6—C7	106.29 (13)	C34—C33—H331	107.6
C3—O14—H1	108.6 (17)	C33—C34—C35	112.28 (16)
C26—O27—H2	109.9 (17)	C33—C34—H341	108.8
C35—O36—C37	106.69 (12)	C35—C34—H341	108.8
C33—O44—H3	108.0 (17)	C33—C34—H342	108.7
C56—O57—H4	109.4 (16)	C35—C34—H342	108.8
C2—C1—C13	124.91 (18)	H341—C34—H342	109.5
C2—C1—H11	117.5	C34—C35—O36	107.25 (13)
C13—C1—H11	117.5	C34—C35—C43	115.72 (15)
C1—C2—C3	124.03 (17)	O36—C35—C43	105.67 (13)
C1—C2—H21	118.0	C34—C35—H351	109.4
C3—C2—H21	118.0	O36—C35—H351	109.3
C2—C3—O14	111.85 (15)	C43—C35—H351	109.3
C2—C3—C4	111.12 (17)	O36—C37—C38	124.00 (15)
O14—C3—C4	112.15 (16)	O36—C37—C42	112.98 (15)
C2—C3—H31	107.1	C38—C37—C42	123.02 (16)
O14—C3—H31	107.2	C37—C38—C39	115.67 (15)
C4—C3—H31	107.1	C37—C38—C51	123.72 (16)
C3—C4—C5	112.25 (15)	C39—C38—C51	120.61 (16)
C3—C4—H41	108.7	C38—C39—C40	122.98 (16)
C5—C4—H41	108.7	C38—C39—H391	118.5

C3—C4—H42	108.9	C40—C39—H391	118.6
C5—C4—H42	108.8	C39—C40—C41	119.07 (16)
H41—C4—H42	109.5	C39—C40—C48	119.44 (17)
C4—C5—O6	107.75 (15)	C41—C40—C48	121.49 (16)
C4—C5—C13	114.93 (16)	C40—C41—C42	119.24 (16)
O6—C5—C13	106.21 (14)	C40—C41—H411	120.4
C4—C5—H51	109.3	C42—C41—H411	120.4
O6—C5—H51	109.3	C37—C42—C41	119.96 (16)
C13—C5—H51	109.2	C37—C42—C43	108.10 (15)
O6—C7—C8	123.87 (16)	C41—C42—C43	131.85 (15)
O6—C7—C12	113.17 (15)	C35—C43—C42	100.53 (13)
C8—C7—C12	122.90 (17)	C35—C43—C31	111.51 (15)
C7—C8—C9	115.61 (17)	C42—C43—C31	108.47 (14)
C7—C8—C21	121.86 (17)	C35—C43—C45	112.53 (14)
C9—C8—C21	122.48 (16)	C42—C43—C45	112.67 (14)
C8—C9—C10	123.08 (17)	C31—C43—C45	110.69 (14)
C8—C9—H91	118.5	C43—C45—C46	113.28 (15)
C10—C9—H91	118.4	C43—C45—H451	108.5
C9—C10—C11	118.91 (18)	C46—C45—H451	108.4
C9—C10—C18	120.73 (18)	C43—C45—H452	108.5
C11—C10—C18	120.34 (19)	C46—C45—H452	108.6
C10—C11—C12	119.38 (18)	H451—C45—H452	109.5
C10—C11—H111	120.4	C45—C46—C47	124.7 (3)
C12—C11—H111	120.3	C45—C46—H461	117.7
C7—C12—C11	120.07 (16)	C47—C46—H461	117.6
C7—C12—C13	107.92 (16)	C46—C47—H471	120.1
C11—C12—C13	131.57 (17)	C46—C47—H472	119.9
C5—C13—C12	100.36 (14)	H471—C47—H472	120.0
C5—C13—C1	110.77 (16)	C40—C48—C49	116.0 (2)
C12—C13—C1	105.23 (14)	C40—C48—C149	118.4 (6)
C5—C13—C15	114.33 (15)	C40—C48—H481	107.8
C12—C13—C15	114.54 (16)	C49—C48—H481	107.8
C1—C13—C15	110.85 (15)	C40—C48—H482	108.0
C13—C15—C16	115.89 (17)	C49—C48—H482	107.8
C13—C15—C116	103.4 (6)	H481—C48—H482	109.5
C13—C15—H151	107.9	C40—C48—H483	107.3
C16—C15—H151	107.8	C149—C48—H483	107.3
C13—C15—H152	107.9	C40—C48—H484	107.1
C16—C15—H152	107.7	C149—C48—H484	107.0
H151—C15—H152	109.5	H483—C48—H484	109.5
C13—C15—H153	110.9	C48—C49—C50	126.5 (3)
C116—C15—H153	110.3	C48—C49—H491	116.7
C13—C15—H154	111.2	C50—C49—H491	116.7
C116—C15—H154	111.5	C49—C50—H501	119.8
H153—C15—H154	109.5	C149—C50—H501	119.2
C15—C16—C17	127.4 (3)	C49—C50—H502	120.2
C15—C16—H161	116.2	C149—C50—H502	115.8
C17—C16—H161	116.4	H501—C50—H502	120.0
C16—C17—H171	119.7	C38—C51—C52	120.26 (16)
C16—C17—H172	120.3	C38—C51—C56	121.47 (16)
H171—C17—H172	120.0	C52—C51—C56	118.17 (16)
C10—C18—C19	114.2 (2)	C51—C52—C53	122.83 (18)

C10—C18—C119	115.3 (6)	C51—C52—H521	118.5
C10—C18—H181	108.2	C53—C52—H521	118.7
C19—C18—H181	107.8	C52—C53—C54	117.56 (18)
C10—C18—H182	108.4	C52—C53—C58	121.15 (19)
C19—C18—H182	108.7	C54—C53—C58	121.25 (18)
H181—C18—H182	109.5	C53—C54—C55	121.29 (17)
C10—C18—H183	107.8	C53—C54—H541	119.4
C119—C18—H183	106.8	C55—C54—H541	119.3
C10—C18—H184	108.4	C54—C55—C56	120.28 (18)
C119—C18—H184	109.0	C54—C55—H551	119.8
H183—C18—H184	109.5	C56—C55—H551	119.9
C18—C19—C20	127.3 (4)	C51—C56—C55	119.85 (17)
C18—C19—H191	116.4	C51—C56—O57	118.65 (15)
C20—C19—H191	116.3	C55—C56—O57	121.47 (16)
C19—C20—H201	119.5	C53—C58—C59	111.9 (2)
C19—C20—H202	120.5	C53—C58—C159	121.2 (9)
H201—C20—H202	120.0	C53—C58—C259	111.5 (7)
C119—C20—H203	118.9	C53—C58—H581	108.8
C119—C20—H204	121.1	C59—C58—H581	108.8
H203—C20—H204	120.0	C53—C58—H582	108.9
C8—C21—C22	121.66 (16)	C59—C58—H582	108.9
C8—C21—C26	120.17 (15)	H581—C58—H582	109.5
C22—C21—C26	118.14 (17)	C53—C58—H583	104.5
C21—C22—C23	122.31 (18)	C159—C58—H583	111.1
C21—C22—H221	118.8	C53—C58—H584	104.6
C23—C22—H221	118.9	C159—C58—H584	105.5
C22—C23—C24	118.00 (18)	C53—C58—H585	109.4
C22—C23—C28	121.1 (2)	C259—C58—H585	109.4
C24—C23—C28	120.9 (2)	C53—C58—H586	109.5
C23—C24—C25	121.34 (19)	C259—C58—H586	107.6
C23—C24—H241	119.4	H583—C58—H584	109.5
C25—C24—H241	119.3	H585—C58—H586	109.5
C24—C25—C26	119.80 (18)	C58—C59—C60	128.2 (3)
C24—C25—H251	120.1	C58—C59—H591	115.7
C26—C25—H251	120.1	C60—C59—H591	116.1
C21—C26—C25	120.38 (17)	C59—C60—H601	120.5
C21—C26—O27	117.80 (16)	C59—C60—H602	119.5
C25—C26—O27	121.82 (17)	H601—C60—H602	120.0
C23—C28—C29	114.0 (2)	C15—C116—C117	129.8 (12)
C23—C28—C129	124.4 (8)	C15—C116—H1161	117.2
C23—C28—H281	108.6	C117—C116—H1161	113.0
C29—C28—H281	108.4	C116—C117—H1171	120.4
C23—C28—H282	108.0	C116—C117—H1172	120.7
C29—C28—H282	108.3	H1171—C117—H1172	118.8
H281—C28—H282	109.5	C18—C119—C20	132.7 (12)
C23—C28—H283	105.6	C18—C119—H1191	113.6
C129—C28—H283	104.3	C20—C119—H1191	113.7
C23—C28—H284	106.0	C28—C129—C130	130.2 (19)
C129—C28—H284	106.7	C28—C129—H1291	112.4
H283—C28—H284	109.5	C29—C129—H1291	172.2
C28—C29—C30	127.5 (3)	C130—C129—H1291	117.1
C30—C29—C129	124.4 (11)	C129—C130—H1301	116.5

C28—C29—C130	123.0 (11)	C129—C130—H1302	123.3
C28—C29—H291	115.8	H1301—C130—H1302	120.0
C30—C29—H291	116.7	C48—C149—C150	120.0 (13)
C28—C29—H1302	158.9	C48—C149—H1491	119.9
C129—C29—H1302	102.8	C150—C149—H1491	120.1
C29—C30—H301	119.1	C149—C150—H1501	120.2
C29—C30—H302	120.8	C149—C150—H1502	119.8
C130—C30—H302	131.8	H1501—C150—H1502	120.0
H301—C30—H302	120.0	C58—C159—C160	120.8 (15)
C32—C31—C43	125.08 (18)	C58—C159—H1591	119.6
C32—C31—H311	117.4	C160—C159—H1591	119.5
C43—C31—H311	117.5	C159—C160—H1601	119.9
C31—C32—C33	123.05 (19)	C159—C160—H1602	120.1
C31—C32—H321	118.5	H1601—C160—H1602	120.0
C33—C32—H321	118.5	C58—C259—C260	135.0 (15)
C32—C33—O44	110.86 (17)	C58—C259—H2591	113.0
C32—C33—C34	111.58 (16)	C260—C259—H2591	111.8
O44—C33—C34	111.22 (17)	C259—C260—H2601	122.7
C32—C33—H331	107.6	C259—C260—H2602	117.2
O44—C33—H331	107.8	H2601—C260—H2602	120.0

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O14—H1···O6	0.84 (3)	2.27 (3)	2.887 (2)	130 (2)
O14—H1···O27	0.84 (3)	2.08 (3)	2.828 (2)	147 (2)
O27—H2···O44^{i}	0.83 (3)	1.80 (3)	2.630 (2)	174 (2)
O44—H3···O36	0.84 (3)	2.14 (3)	2.822 (2)	138 (2)
O44—H3···O57	0.84 (3)	2.26 (3)	2.936 (2)	137 (2)
O57—H4···O14^{i}	0.85 (3)	1.86 (3)	2.711 (2)	175 (2)

Symmetry code: (i) −*x*+1, −*y*+1, −*z*.