Integrating Diverse Methodologies and Strategies for the Total Synthesis of Certain Alkaloids and Terpenoids

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

By

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October, 2018

Declaration

I declare that the material presented in this thesis represents the result of original work carried out, unless otherwise stated, by myself during the period 2014-2018. It has not been presented for examination for any other degree. This thesis by publication is comprised of five journal articles. Wherever possible, established methodologies have been acknowledged by citation of the relevant original publications.

Fei Tang

October, 2018

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor Prof. Martin Banwell for giving me such a precious opportunity to study in his group. The patient guidance, encouragement and advice both on research and career he has provided during the past four years played very important roles in helping me to finish my PhD studies. Under his supervision, the past four years have become an unforgettable memory for me. Thanks again to Martin, you are a tremendous mentor. I wish you the very best for the future.

A special thanks goes to Dr. Xinghua Ma, the group leader of Lab 3.27 (previously Lab 3.28). He gave me lots of help, not only in lab work but also in my daily life. He is a good mentor, also a helpful and kind friend.

Of course, I would like to thank all the members of Banwell group, especially the former and current members in both my previous lab (Lab 3.28) and my current one (Lab 3.27), namely Xinghua, Yiwen, Bora, Shen, Prue and Madushani for their helpful advice (whether it be on lab work or on daily life), the stimulating discussions and all the fun we had during the past few years. It was my honor to work with all of you.

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A very big thanks must go to my family and my girlfriend Jiwen Li - without their unbelievable love and support, I would not be able to make it.

And finally, I would like to thank China Scholarship Council and the Education Office of Chinese Embassy in Australia for their financial support.

Publications and Presentations

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

Publications:

1. Fei Tang and Martin G. Banwell. Raney Cobalt. *Encyclopedia of Reagents for Organic Synthesis* [Online (eEROS)], eds. P. L. Fuchs, A. B. Charette, T. Rovis and J. W. Bode, John Wiley & Sons Ltd. In press, **2018**.

2. Fei Tang, Martin G. Banwell and Anthony C. Willis. A Palladium-Catalyzed Ullmann Cross-Coupling/Tandem Reductive Cyclization Route to Key Members of the Uleine Alkaloid Family. *J. Org. Chem*. **2016**, 81, 2950.

3. Fei Tang, Martin G, Banwell and Anthony C. Willis. A Raney-Cobalt-Mediated Reductive Cyclization Route to the Uleine Alkaloid Gilbertine. *J. Org. Chem.* **2016**, 81, 10551.

4. Fei Tang, Benoit Bolte, Ping Lan, Martin G. Banwell, Jas Ward and Anthony C. Willis. Total Synthesis of (+)-Viridianol, a Marine-derived Sesquiterpene Embodying the Decahydrocyclobuta[*d*]indene Framework. *J. Org. Chem*. **2018**, 83, 14049.

Publications (contd):

5. Benoit Bolte, Fei Tang, Ping Lan, Anthony C. Willis and Martin G. Banwell. Synthetic Studies on the Marine-derived Sesquiterpene (+)-Viridianol: Divergent Behavior of the Two Structurally Related-fused Cyclopropanes Under the Same Hydrogenolytic Conditions. *Aust. J. Chem*. (CH18532, Accepted for publication on 11 December 2018).

Presentations:

Oral Presentation: Fei Tang, Martin G. Banwell and Anthony C. Willis. A Palladium-catalysed Ullman Cross-coupling/Reductive Cyclisation Route to the Uleine Alkaloids. *2016 RACI One Day Symposium*, Sydney, Australia, November 30th 2016.

Commentary on the Contributions of Mr Fei Tang to the Five Papers Included in this Thesis by Publication

Publication 1

This is a review article written by Professor Banwell. It incorporates descriptions of research conducted by co-author Mr Tang. Mr Tang carried out relevant literature surveys as part of his contributions to the preparation of this article.

Publication 2

This is a full paper detailing the author's extensive work directed towards establishing syntheses of key members of uleine alkaloid family. He carried out the entirety of the experimental work reported in the article save for the X-ray crystallographic studies that were conducted by Dr Anthony Willis. In addition, the author collated and formatted all the spectral data presented in the Supporting Information document. He also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Banwell wrote the body of the paper.

Publication 3

This is a full paper detailing extensive experimental work directed towards the synthesis of uleine alkaloid gilbertine. The author carried out the entirety of the experimental work reported in this article save for the X-ray crystallographic studies that were conducted by Dr Anthony Willis. In addition, the author collated and formatted all the spectral data presented in the Supporting Information document. He 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 communication detailing extensive experimental work directed towards the syntheses of a marine-derived sesquiterpene (+)-viridianol. The author carried out the most of the experimental work reported in this article save for the X-ray crystallographic studies that were conducted by Drs Anthony Willis and Jas Ward. Some exploratory studies were conducted by co-authors Drs Ping Lan and Benoit Bolte. The author collated and formatted all the spectral data presented in the Supporting Information document. He also wrote the majority 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 concerned with a model study relevant to the total synthesis of (+)-viridianol. The author acquired, collated and formatted all the spectral data presented in the Supporting Information document. Professor Banwell wrote the body of the paper.

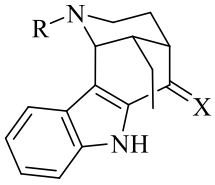
Table of Contents

Abstract

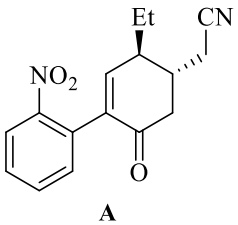
The body of this thesis is comprised of five scientific articles and is preceded by an overview that contextualizes all of this published, submitted or to-be-submitted work.

The first major part of this thesis is comprised of **publication 1**. This is a review concerned with the application of Raney-cobalt in organic synthesis. The author's work described in publications 2 and 3 featured Raney-cobalt mediated reductive cyclization reactions as key steps in the construction of the framework of various uleine alkaloids and certain of these are highlighted in this review.

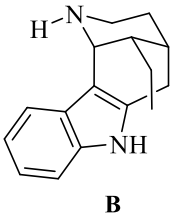
Publication 2 comprises the second major part of this thesis. This full paper details the total syntheses of key members of uleine alkaloid family (specifically uleine, noruleine, dasycarpidone, nordasycarpidone) by using a palladium-catalysed Ullmann cross-coupling reaction to generate compound **A** and the reductive cyclization of this so as to assemble the uleine alkaloid framework **B**.



R=Me, X=CH_2 (uleine)
R=H, X=CH_2 (noruleine)
R=Me, X=O (dasycarpidone)
R=H, X=O (nordasycarpidone)



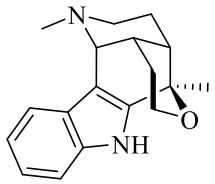
A



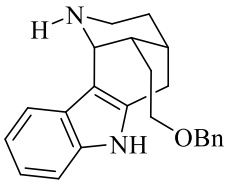
B

The third major part of this thesis is comprised of **publication 3**. This full paper describes the total synthesis of uleine alkaloid gilbertine. The key intermediate

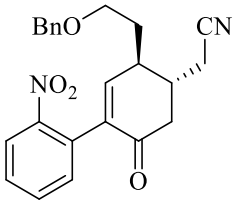
C embodying the framework of uleine-type alkaloids was assembled by the Raney-cobalt mediated reductive cyclization of intermediate **D** which was itself constructed *via* a reaction sequence including a palladium-catalysed Ullmann cross-coupling process. The end-game involved a cationic (and possibly biomimetic) cyclisation reaction that established the final, tetrahydropyran ring of gilbertine.



gilbertine

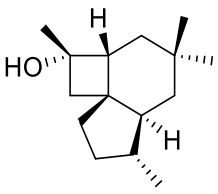


C

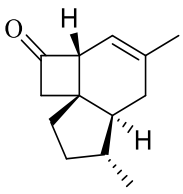


D

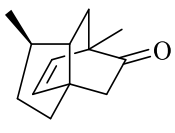
The fourth major part of this thesis is comprised of **publication 4**. This communication details the total synthesis of a marine-derived sesquiterpene (+)-viridianol. The target molecule was derived from intermediate **E** through various functional group manipulations. Compound **E** was prepared through a photochemically-promoted 1,3-acyl migration reaction involving the cyclopentannulated bicyclo[2.2.2]octenone **F**, itself constructed from the homochiral compound **G** using Negishi cross-coupling and intramolecular Diels-Alder (IMDA) cycloaddition reactions as key steps. The starting material **G**, a *cis*-1,2-dihydrocatechol, was obtained through the whole-cell biotransformation of *p*-iodotoluene using a genetically engineered micro-organism over-expressing the enzyme toluene dioxygenase.



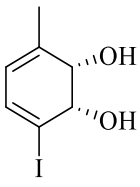
viridianol



E

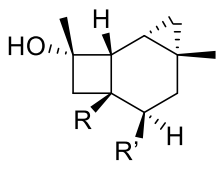


F

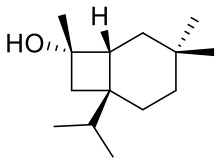


G

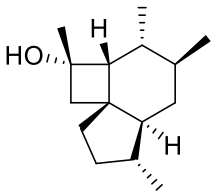
The fifth major part of this thesis is comprised of **publication 5**. This full paper details a model study relevant to the total synthesis of the marine-derived sesquiterpene (+)-viridianol. Specifically, two structurally related ring-fused cyclopropanes **H** (prepared from α-terpiene using [2+2] cycloaddition reaction and Simmons-Smith cyclopropanation as key steps) and **I** [prepared during the course of the successful total synthesis of (+)-viridianol as delineated in publication 4] were subjected to the same hydrogenolytic conditions. However, they showed dramatically divergent behavior. Specifically, hydrogenolysis of cyclopropane **H** generated the hoped-for *gem*-dimethylated cyclopropane **J**, but analogous treatment of congener **I** afforded only trace amounts of the target molecule (+)-viridianol, the major products derived from this more complex cyclopropane being the *vic*-dimethylated compound **K** and the two-fold ring-cleavage product **L**.



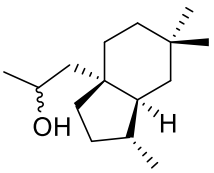
H (R = *i*-Pr, R' = H)
I ([R,R' = $(CH_2)_2CH(Me)$]



J



K

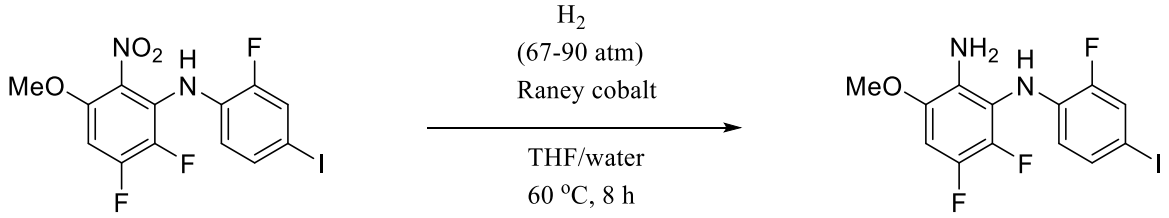


L

Thesis Overview

Publication 1: Raney Cobalt

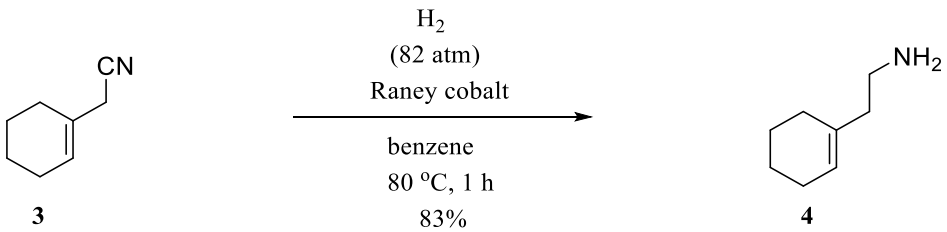
Raney cobalt, which was first prepared in the 1930s, is known to function effectively as a catalyst in certain chemoselective reductions. However, its utility in chemical synthesis does not seem to have been fully appreciated.[1] **Publication 1** reviews published work on the application of Raney cobalt in organic synthesis. For example, as shown in Scheme 1, the halogenated nitroaromatic **1** can be reduced to the corresponding aniline **2** using this catalyst and without any accompanying hydrogenolysis of associated aryl-halogen bonds.[2]



1 **2**

Scheme 1: The Chemoselective Reduction of a Poly-functional Nitro Aromatic with Raney Cobalt

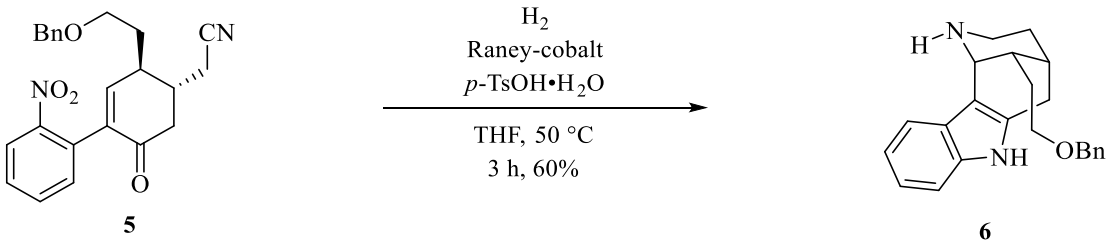
Similarly, and as shown in Scheme 2, the unsaturated nitrile **3** can be reduced to the corresponding unsaturated primary amine **4** by using Raney cobalt in the presence of hydrogen.[3]



3 **4**

Scheme 2: Nitrile Reduction with Raney Cobalt

As featured in the author's total synthesis of the alkaloid gilbertine (see Scheme 3 and the commentary on Publication 3 presented below), the polyfunctionalized cyclohexenone **5** was subjected to reductive cyclization under an atmosphere of hydrogen in the presence of 200 wt% Raney cobalt and *p*-toluenesulfonic acid and so providing the tetracyclic compound **6** in 60% yield[4] (Scheme 3). This conversion highlights the extraordinary chemoselectivties that can be achieved using the title catalyst. In particular, nitro and nitrile groups can be reduced in the presence of ketones, alkenes and benzyl ethers (*viz*. these last three functional groups remain unaffected under the reducing conditions used).



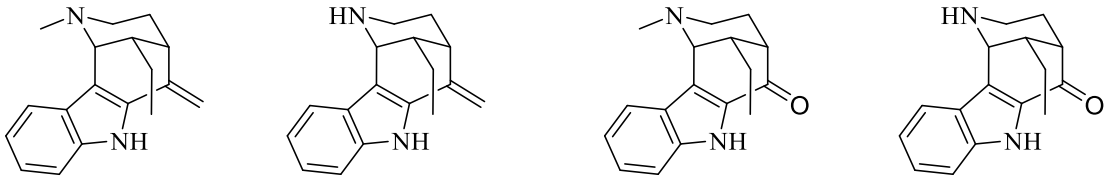
Scheme 3: A Tandem Reductive Cyclisation Mediated by Raney Cobalt

A method for the preparation of reproducibly effective Raney cobalt is also provided in this short review.

Publication 2: A Palladium-Catalyzed Ullmann Cross-coupling/Tandem Reductive Cyclization Route to Key Members of the Uleine Alkaloid Family

The tetracyclic alkaloids uleine (**7**),[5,6] noruleine (**8**),[6] dasycarpidone (**9**)[6] and nordasycarpidone (**10**)[6] (Figure 1), all of which have been isolated from a range of plant sources, including the bark of the South American shrub *Aspidosperma dasycarpon* A. DC., are considered the "original" and representative members

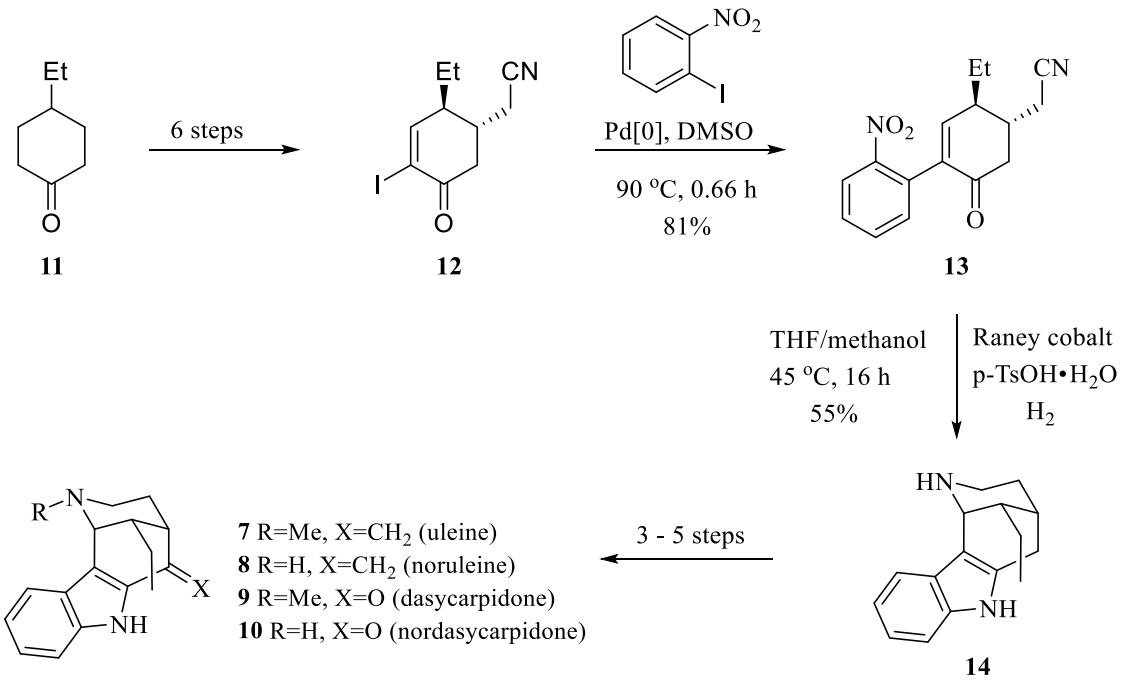
of a structurally distinct family of natural products. These are known as the uleine alkaloids. A range of interesting biological properties has been attributed to them, including analgesic, anti-inflammatory, bactericidal, anti-malarial and acetylcholinesterase (AChE)-inhibiting activities.[7] In addition, the capacity of uleine to promote the synthesis of nitric oxide has prompted investigations of the use of the source plants as an adjuvant in the treatment of patients with compromised immune systems.[8]



7 uleine | **8** noruleine | **9** dasycarpidone | **10** nordasycarpidone

Figure 1: Structures of Uleines (**7**-**10**)

Publication 2 details successful total syntheses of uleine alkaloids **7**-**10** by using palladium-catalyzed Ullmann cross-coupling and Raney cobalt mediated reductive cyclization reactions as key steps. The syntheses commenced (as shown in Scheme 4) from commercially available 4-ethylcyclohexanone (**11**), which was converted into iodide **12** in six steps. Compound **12** was subjected to a palladium-catalyzed Ullmann cross-coupling reaction with *o*-iodonitrobenzene generating product **13**. Treatment of this last compound with 200 wt % of freshly prepared Raney cobalt[1] in the presence of hydrogen and *p*-toluenesulfonic acid then afforded the reductive cyclization product **14** from which all of the target compounds **7**-**10** were then derived by relatively standard methods.

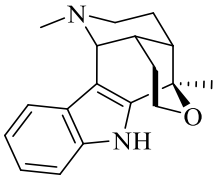


Scheme 4: Key Steps in the Syntheses of Uleine Alkaloids (**7**-**10**)

All the data obtained on the synthetically-derived alkaloids matched those reported for the corresponding natural products.[9]

Publication 3: A Raney Cobalt Mediated Reductive Cyclization Route to the Uleine Alkaloid Gilbertine

Gilbertine (**15**) (Figure 2) was isolated in 1982 by Miranda and Blechert from the Brazilian tree *Aspidosperma gilbertii* (A. P. Darte).[10] It differs from other better known members of the class[4a] such as the "parent" compound uleine (**7**), noruleine (**8**), dasycarpidone (**9**) and nordasycarpidone (**10**) by virtue of the presence of an additional tetrahydropyran-based ring system and a fourth stereogenic center. The unusual pentacyclic framework of gilbertine has been the target of various synthetic studies,[11] but only one successful total synthesis had been reported prior to the author's study.[11] An adaptation of the routes used to prepare alkaloids **7**–**10**, as reported in publication 2, was deployed in achieving a synthesis of gilbertine.

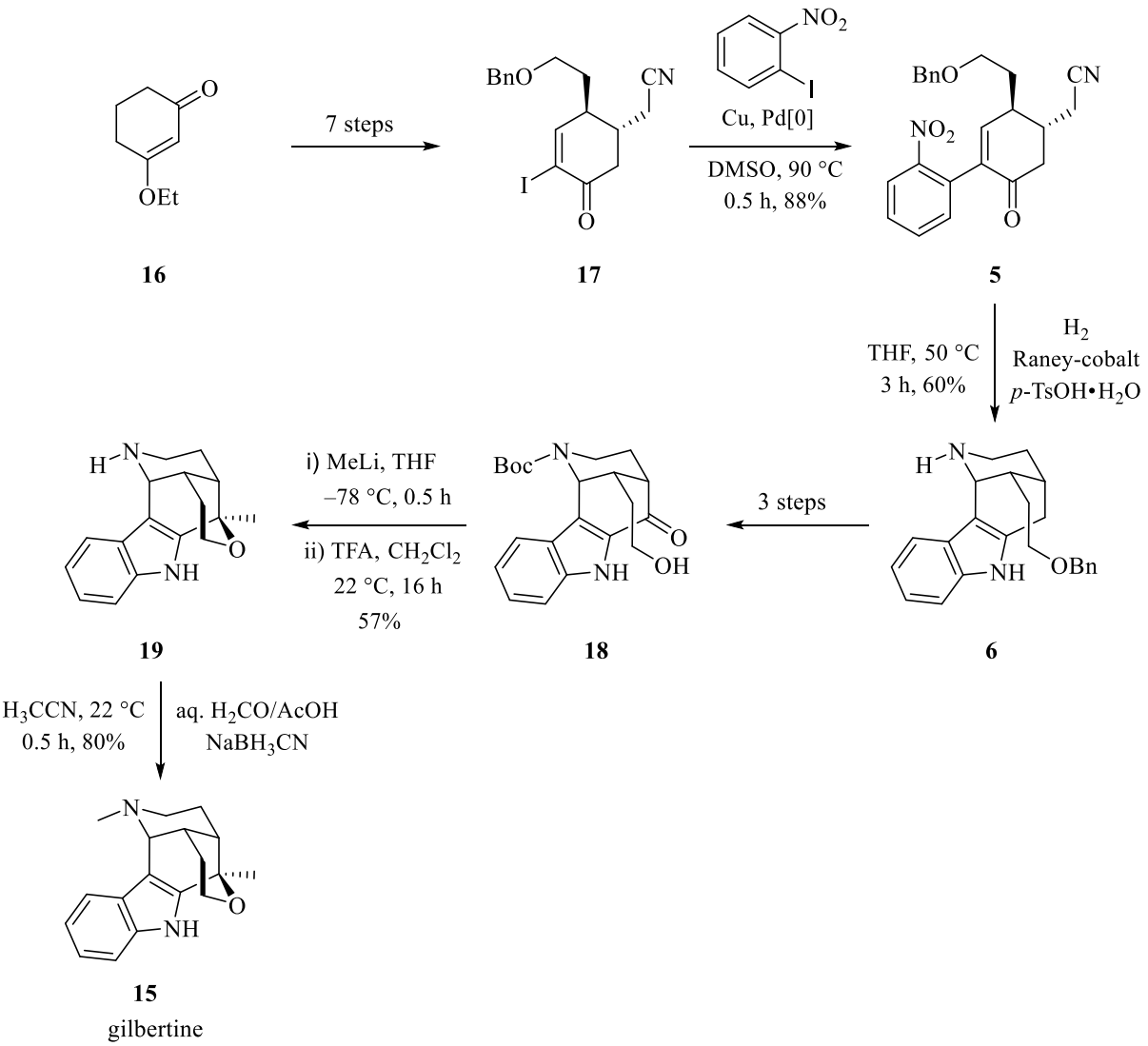


15

gilbertine

Figure 2: The Structure of Gilbertine (**15**)

So, the author's synthesis of gilbertine started (Scheme 5) from commercially available 3-ethoxy-2-cyclohexen-1-one (**16**) that was converted into iodide **17** over seven steps. Compound **17** was then subjected to the palladium-catalyzed Ullmann cross-coupling reaction with *o*-iodonitrobenzene and thus affording product **5** that upon treatment with Raney cobalt[1,4a] in the presence of hydrogen provided, via a reductive cyclization cascade, key intermediate **6**. Compound **6** was converted into ketone **18** over three steps including a PCC-mediated allylic oxidation.[4a] Intermediate **18** was elaborated to compound **19** over two steps including a TFA-mediated cationic cyclization to form the tetrahydropyran ring associated with gilbertine. Reductive methylation of the secondary amine **19** then afforded the crystalline gilbertine. All the spectral data obtained on this synthetic material matched those reported for the natural product,[10,12] and the structure of this (*viz*. the synthetic material) was confirmed by a single-crystal X-ray analysis.



Scheme 5: Key Steps Involved in the Author's Total Synthesis of Gilbertine (**15**)

Publication 4: Total Synthesis of (+)-Viridianol, A Marine-derived Sesquiterpene Embodying the Decahydrocyclobuta[d]indene Framework

There are three possible modes of annulation of a four- and a five-membered carbocycle to a common cyclohexane ring (Figure 3). The first of these, involving a linear arrangement of the constituent rings, is encountered in the sterpurene (**20**) class of sesquiterpenoid[13] while the second, **21**, represents the key structural element associated with the even more common protoilludane group of natural products.[14,15] In contrast, natural products embodying the third

such framework, namely **22**, are rare, with (+)-viridianol (**23**)[16] and (+)-trefolane A (**24**)[17] being the only two examples incorporating such a structure. Compound **23** was isolated from the red seaweed *Laurencia viridis*[18] while congener **24** was isolated more recently from cultures of the basidiomycete *Tremella foliacea*, an edible fungus.

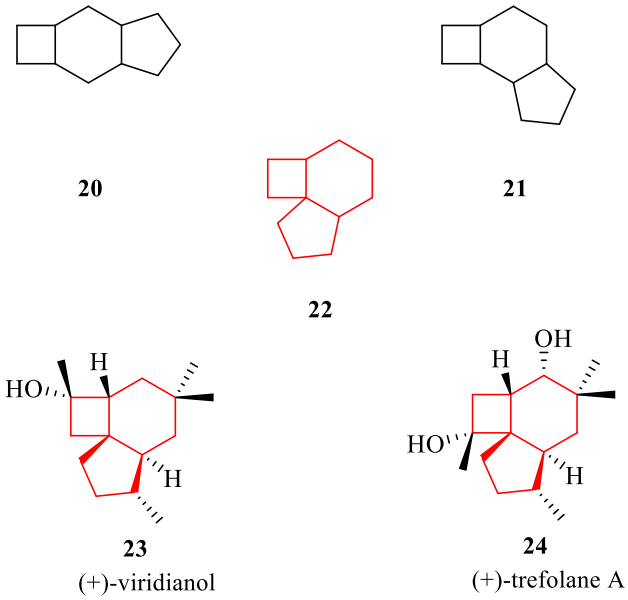
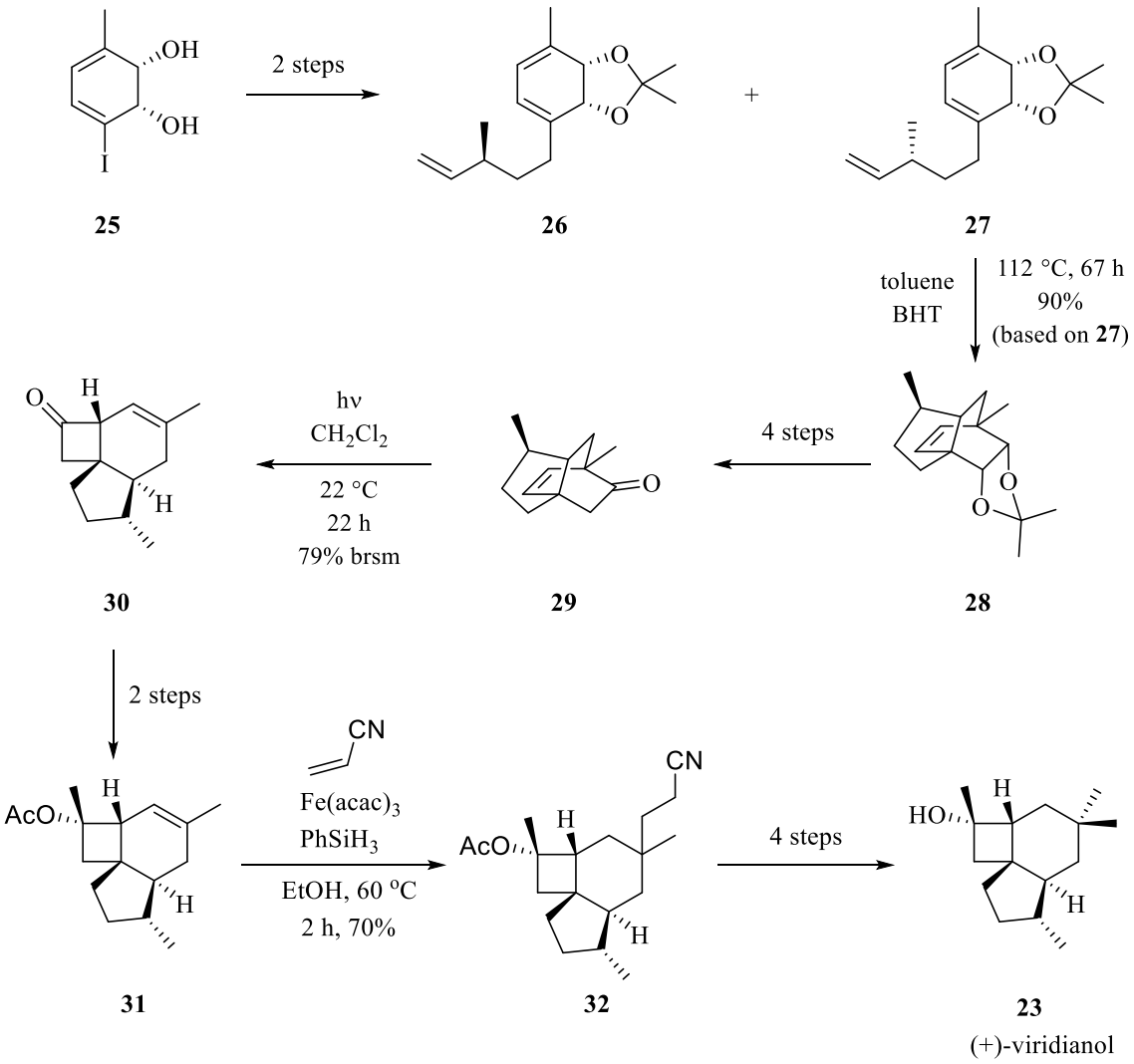


Figure 3: The Sterpurene (**20**), Protoilludane (**21**) and Decahydrocyclobuta[*d*]indene (**22**) Frameworks and the Structures of (+)-Viridianol (**23**) and (+)-Trefolane A (**24**)

The interesting biological profiles and the intriguing structures of sesquiterpenoids embodying frameworks **20**-**22** have prompted numerous efforts to develop the synthesis of them.[13-15] P**ublication 4** details the author's successful total synthesis of (+)-viridianol. This was based on the previous research[15] within the Banwell group on total syntheses of sterpurene and protoilludane-type systems.

The synthesis (Scheme 6) started from the chiral, non-racemic *cis*-1,2-dihydrocatechol **25**, a known[19] metabolite of the whole-cell biotransformation of *p*-iodotoluene.[20] A chromatographically inseparable mixture of the stereoisomeric trienes **26** and **27** was obtained from diol **25** through a two-step reaction sequence, the key one being a Negishi cross-coupling process to install

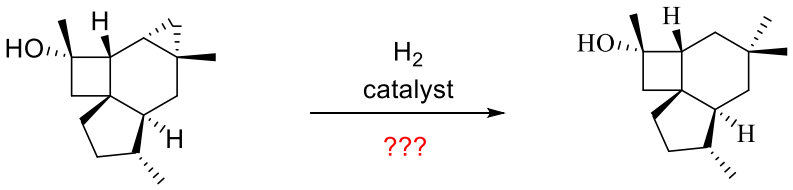
the unsaturated side-chain. Upon heating the mixture of these two trienes in refluxing toluene, only one (**27**) engaged in an intramolecular Diels-Alder cycloaddition reaction and thereby generating the desired adduct **28**. This adduct was then elaborated to the cyclopentannulated bicyclo[2.2.2]octenone **29** over four steps including ones involving deprotection, 4-acetamido-TEMPO-mediated oxidation[21] and samarium iodide-mediated reductive deoxygenation processes. Intermediate **29** was then converted into the isomeric cyclobutanone **30** via the photochemically promoted 1,3-acyl migration process (Given's rearrangement)[22] and after a further two, conventional steps, ester **31** was obtained. Subjection of compound **31** to Baran's olefin cross-coupling reaction[23] then afforded nitrile **32** as a mixture of diastereoisomers. Four more steps, including a UHP-mediated Baeyer-Villiger oxidation,[24] a Dess-Martin oxidation and a Tsuji-Wilkinson decarbonylation,[25] then gave the target molecule (+)-viridianol. The NMR spectral data acquired on this final product compared very favorably with those reported[16] by Norte and co-workers for the natural product.



Scheme 6: Key Steps in the Total Synthesis of (+)-Viridianol (**23**)

Publication 5: Synthetic Studies on the Marine-Derived Sesquiterpene (+)-Viridianol: Divergent Behaviour of Two Structurally Related Ring-Fused Cyclopropanes Under the Same Hydrogenolytic Conditions

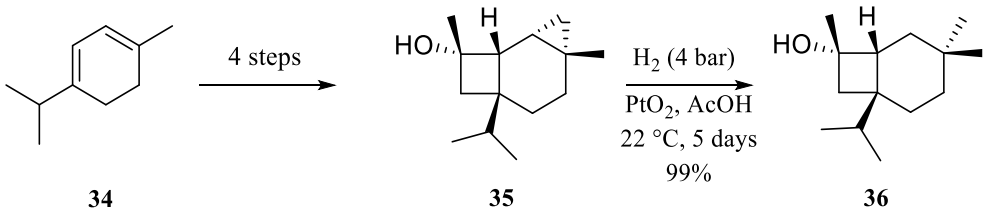
As reported in publication 4, a successful total synthesis[26] of (+)-viridianol (**23**) has been realized. During this process, a model study was conducted to investigate whether or not it might be possible to effect the hydrogenolytic ring cleavage of cyclopropane **33** (Scheme 7) and thereby establish the *gem*-dimethyl-subunit associated with the target sesquiterpene **23**.



33 **23**
(+)-viridianol

Scheme 7: A Possible Hydrogenolytic Pathway to the *gem*-Dimethyl-subunit of (+)-Viridianol (**23**)

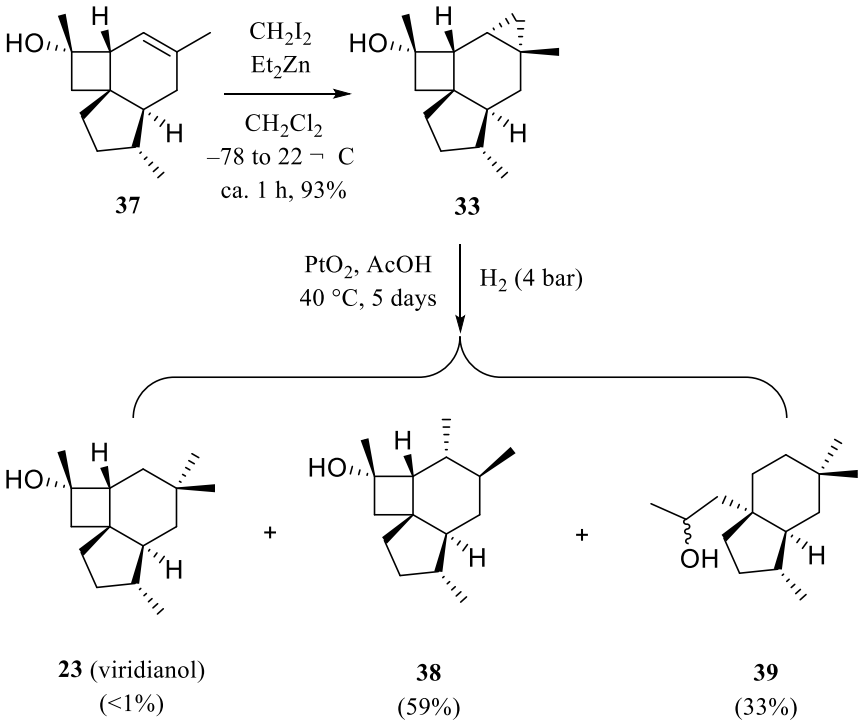
Publication 5 details the result of that model study, and the application of it to cyclopropane **33**. The model study commenced with abundant α-terpene (**34**) (Scheme 8) that was converted into cyclopropane **35** over four steps including [2+2] cycloaddition[27] and Simmons-Smith cyclopropanation reactions. Subjection of compound **35** to standard hydrogenolytic conditions[28] afforded the hoped-for *gem*-dimethylated compound **36** in exceptionally high yield.



34 **35** **36**

Scheme 8: Model Study Relevant to the Synthesis of (+)-Viridianol (**23**)

Encouraged by such a result, the same protocol was applied to compound **33** which was readily prepared (Scheme 9), by applying a Simmons-Smith-type cyclopropanation reaction to alkene **37**, itself a late-stage intermediate on the successful route[26] to (+)-viridianol. Unfortunately, the pivotal hydrogenolysis reaction afforded only traces of the targeted *gem*-dimethylated sesquiterpene (+)-viridianol (**23**), the major products being its *vic*-dimethylated isomer **38** and the two-fold ring-cleavage product **39**.



Scheme 9: Result of the Hydrogenolytic Cleavage of Cyclopropane **33**

Given the divergent behaviors of substrates **35** and **33** under the same hydrogenolytic reaction conditions it is evident that the cyclopentannulated nature the latter substrate impacts significantly on its reactivity, but the precise origins of this effect remain unclear.

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Publication One

Raney Cobalt

Fei Tang and Martin G. Banwell

Encyclopedia of Reagents for Organic Synthesis, **2018**, in press

Raney Cobalt[1]

[7440-48-4] Co (AW 58.93)
InChI = 1S/Co
InChIKey = GUTLYIVDDKVIGB-UHFFFAOYSA-N

(reagent/catalyst for the chemoselective reductive cleavage/reduction of C–X and N–O single and multiple bonds, including ones where X = halogen, N, O, and S)

Solubility: insoluble in all organic solvents and water.

Form Supplied in: gray solid suspended in water/alcohol. Freshly prepared material will contain adsorbed hydrogen that can be/is lost on prolonged standing.

Preparative Methods: normally through digestion of cobalt/aluminum alloy with aqueous sodium hydroxide at a range of temperatures. The presence of additives, including other metals and amines, can have a significant impact on the reactivity of Raney cobalt.[1]

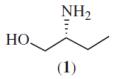
Handling, Storage, and Precautions: this sponge-metal "catalyst" is pyrophoric and should be stored under, for example, deoxygenated 1:1 v/v water/methanol in a sealed container until required for use. The container should be kept in a cool place, ideally between 3 and 30 °C. It has been reported[2] that storing the catalyst under glycols can preserve its activity. Due to risk of fire, Raney cobalt should not be stored near oils or flammable liquids or allowed to come into contact with mixtures of combustible vapors and air/oxygen. Exposure to cobalt, especially as a finely divided powder, can cause coughing, dyspnea, decreased pulmonary function, dermatitis, respiratory hypersensitivity, and/or diffuse nodular fibrosis.

Preparative Methods. A range of methods has been described for the preparation of Raney cobalt.[1] In broad terms, the earlier preparations[3] involved treating cobalt/aluminium alloy (40–46/60–54%) with sodium hydroxide in water or ethanol at 15–100 °C for about 1 h (more active material is formed at the lower temperatures) and this is followed by (often extensive) washings with water and alcohol. Some preparations recommend that the Raney cobalt so formed be used immediately. A more recent and detailed procedure[1] stresses the need to employ nickel-free cobalt–aluminum alloy in order to avoid co-production of the significantly more active Raney nickel.

Chromatographic Procedures Employing Raney Cobalt. The recognition[3d] that Raney cobalt can chemisorb organosulfur compounds without necessarily effecting desulfurization has resulted in the development of a chromatographic procedure for separating such species from other organic compounds. So, for example, a 1:1 w/w mixture of isoeugenol and 2,5-dimethylthiophene could be separated by applying it to the top of a column of freshly prepared Raney cobalt and sand followed by elution of the former compound (95% recovery of sulfur-free material) from the column with small amounts of methanol. The thiophene was then recovered by Soxhlet extraction of the Raney cobalt with methanol.

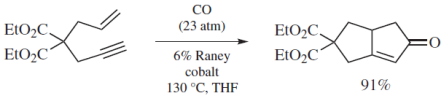
[1] See footnote 17 of reference 1.

Racemization Reactions. *R*-2-Amino-1-butanol (**1**), a by-product associated with the production of ethambutol hydrochloride, can be racemized in 76% yield over a fixed bed Raney cobalt catalyst under 2–6 atmospheres of hydrogen.[4] The racemization of *S*-quinuclidin-3-ol through its treatment with Raney cobalt and hydrogen in xylene has been reported to take place in 97% yield.[5] The selective racemization of certain 1°-amines (e.g. *S*-1-phenylethylamine) by similar means has also been described.[6]

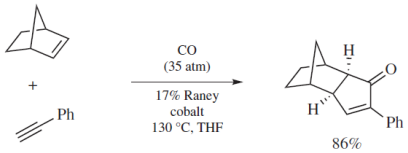


(**1**)

Catalysis of the Pauson–Khand Reaction. Raney cobalt has been shown to effect both inter- and intra-molecular Pauson–Khand reactions. Highly efficient reactions are observed at about 130 °C and 23–35 atmospheres of carbon monoxide (eqs 1 and 2) with higher catalyst loadings and pressures of CO being required for the intermolecular processes.[7]



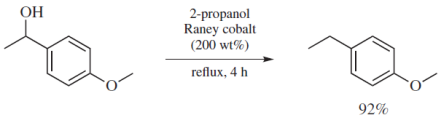
(1)



(2)

The reaction of certain unsaturated amides with carbon monoxide at high pressure and in the presence of Raney cobalt can produce cyclic imides.[8]

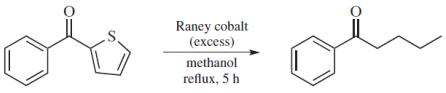
Hydrogenolyses (Including those Involving Deoxygenation and Desulfurization). Raney cobalt has been shown to effect hydrogen transfer from 2-propanol and thus allowing for the reductive deoxygenation of various benzylic alcohols. The conversion of 1-(4-methyoxyphenyl)ethanol into 4-ethylanisole is illustrative (eq 3). This same transformation is achieved more rapidly with Raney nickel but accompanying demethoxylation (to give ethylbenzene) is also observed.[9]



(3)

Biomass-derived and oxygenated hydrocarbons of various forms can be reduced with hydrogen in the presence of a range of catalysts, including Raney cobalt, and thereby providing alternatives to petroleum-based feedstocks required in the chemical manufacturing or aviation industries.[10]

The reductive desulfurization of a range of compounds can be effected using Raney cobalt.[11] So, for example, reaction of 2-benzoylthiophene with this catalyst in refluxing methanol for 5 h resulted in the formation of *n*-valerophenone as the major product of reaction (eq 4).[11]

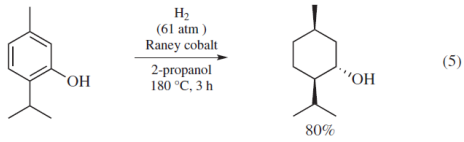


(4)

43% @17% conversion

Raney cobalt has been used to catalyze the hydrogenolytic cleavage of C–Cl bonds in a ring-fused *gem*-dichlorocyclopropane but such a process appears to offer few advantages over other reagents developed for this purpose.[12] A benzylic hydroperoxide has been reduced to the corresponding benzylic alcohol in 76% yield using hydrogen (4 atmospheres) in the presence of Raney cobalt at 25 °C.[13] On treatment with Raney cobalt at 70 °C for 4 h a *vic*-dichlorocyclobutane has been converted into the corresponding cyclobutene.[14]

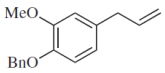
C–C Multiple Bond Reduction. Raney cobalt is not commonly used for effecting the hydrogenation of olefins or aromatic compounds because its preferred use (see below) is for the chemoselective reduction of carbonyl, nitro, and nitrile groups that are often incorporated within compounds also containing C–C multiple bonds. Nevertheless, under higher pressures of hydrogen Raney cobalt does catalyze the exhaustive reduction of benzenoid compounds to the corresponding cyclohexane. Such reactions (eq 5) can proceed in a stereoselective manner.[15]



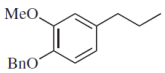
(5)

80%

Carbon–carbon double bond reduction can be achieved without accompanying hydrogenolysis of benzyl ethers as evidenced by the high-yielding conversion of the allylbenzene **2** into its saturated counterpart **3** on reaction of the former compound under hydrogen (1 atmosphere) in the presence of Raney cobalt at 25 °C.[1]



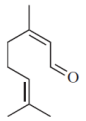
(**2**)



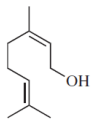
(**3**)

A molybdenum-modified Raney cobalt catalyst has been reported to effect the exhaustive hydrogenation of squalene.[16]

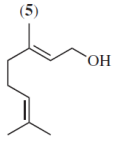
Reduction of α,β-Unsaturated Aldehydes. Raney cobalt is able to selectively catalyze the addition of the elements of hydrogen to the C=O bond of certain α,β-unsaturated aldehydes and thus producing, at least preferentially, the corresponding allylic alcohols.[17] So, for example, Raney cobalt modified in various ways allows for the highly selective addition of hydrogen to cinnamaldehyde such that cinnamyl alcohol is formed[17b] while under similar conditions a heteropolyacid-modified form of the catalyst lead to the formation of crotyl alcohol from crotonaldehyde.[17c] Using a reaction temperature of 100 °C and a hydrogen pressure of about 9 atmospheres, citral (**4**) can be selectively reduced to nerol (**5**) and geraniol (**6**) in the presence of Raney cobalt.[17d]



(**4**)

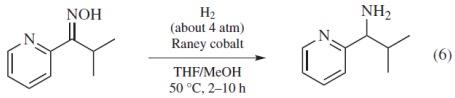


(**5**)



(**6**)

Reduction of Oximes. An early study[18] comparing the capacities of Raney cobalt and Raney nickel to reduce oximes to the corresponding 1°-amines revealed, based on a study of six substrates, that the former catalyst was very effective in this regard and allowed for the reactions to be carried out in ethanol. When Raney nickel was employed for the same purpose, an ammoniacal solvent was required to achieve comparable results. A more recent study[19] involving ketoximes derived from heteroaromatic systems afforded the corresponding aminomethylated aromatic in variable yields (eq 6). Dimeric secondary amines are observed in some instances. Hydrogenolytic cleavage of the N–O bond in an oxime, so as to generate the corresponding imine, has also been reported.[18,20]



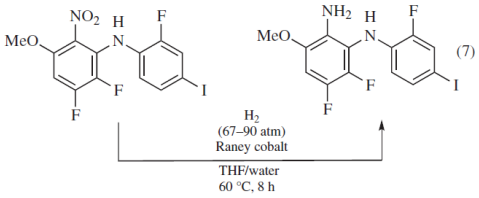
(6)

86%

Oxime *O*-methyl ethers can also be reduced to the corresponding 1°-amine under related conditions.[21]

Reduction of Nitro Compounds. Nitroaromatics are readily reduced using hydrogen in the presence of Raney cobalt. So, for example, various halogenated nitroaromatics can be reduced to the corresponding aniline (eq 7) by such means and without

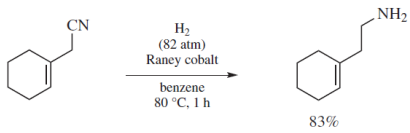
accompanying hydrogenolysis of aryl–halogen bonds.[22] The illustrated transformation can be achieved in either batch or flow mode (in the latter case at kg/day scale).[22b]



(7)

Examples of the reductive cyclization of nitroaromatic compounds using hydrogen in the presence of Raney cobalt are given below.

Reduction of Nitriles. The twofold addition of hydrogen to nitriles in the presence of Raney cobalt (so as to form the corresponding 1°-amine) probably represents the most widely exploited use of this catalyst. Reductions of unsaturated nitriles to the corresponding unsaturated 1°-amine (eq 8) are known[23] although such processes do not seem possible under transfer hydrogenation conditions employing 2-propanol.[24]

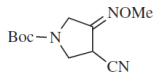


(8)

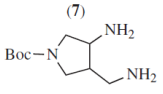
83%

Polynitrile-containing compounds can be reduced to polyamines using hydrogen in the presence of Raney cobalt although it is sometimes difficult to effect complete reduction under such conditions. The Urushibara cobalt catalyst can be more effective for such purposes.[25] Raney cobalt is reportedly superior to its nickel counterpart in terms of catalyzing the addition of hydrogen (at 200 atmospheres) to 3,4-methylenedioxybenzyl cyanide and thereby producing homopiperonylamine. This is obtained in 88% yield when ethanolic ammonia is used as solvent and a reaction temperature between 125 and 150 °C is employed.[26]

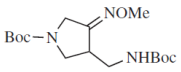
In connection with the development of a synthesis of the antibacterial agent gemifloxin (Factive®) it was shown that treatment of a 2-propanol/water solution of α-cyanooxime *O*-methyl ether **7** with hydrogen (34 atmospheres) in the presence of Raney cobalt gave diamine **8** (yield and stereochemistry not defined) while reaction of the same substrate under the same conditions save for the introduction of $(t\text{-Boc})_2O$ (to effect in situ Boc-protection) gave product **9** selectively.[27]



(**7**)



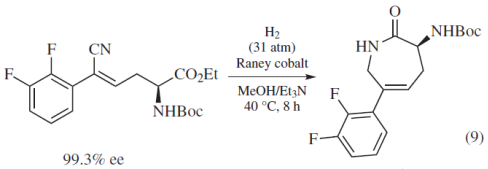
(**8**)



(**9**)

The species produced on reduction of CD_3CN by hydrogen on the surface of Raney cobalt have been examined using inelastic neutron scattering[28] and it appears that a nitrene-type species is an intermediate en route to the formation of $CD_3CH_2NH_2$.

Tandem Reductions (Including Reductive Cyclization Reactions). Reaction sequences triggered by the chemoselective Raney cobalt-catalyzed reduction (with hydrogen) of substrates containing nitrile and/or nitro groups in the presence of other potentially reducible groups have provided an effective means for assembling certain heterocyclic ring systems. So, for example, as shown in eq 9, a lactam required for the synthesis of a drug candidate was prepared through reductive lactamization of a nitrile-ester.[29] Related conversions have been reported.[30]

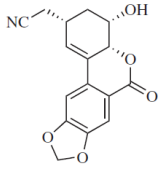


(9)

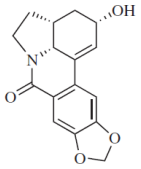
99.3% ee

50%
(80–90% ee)

In a slightly more elaborate example of a reductive cyclization process, exposure of a methanolic solution of nitrile-lactone **10** containing ammonia to 30 atmospheres of hydrogen in the presence of Raney cobalt afforded the lactam **11** in 65% yield.[31] Presumably, the first step in the reaction sequence is the conversion of the nitrile into the corresponding 1°-amine that participates in a S'_N reaction with accompanying cleavage of the lactone ring and with the product amino acid then cyclizing to give the observed lactam.



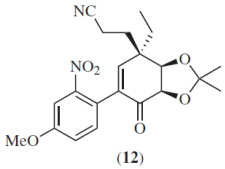
(**10**)



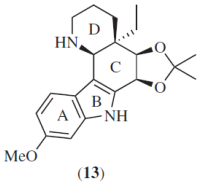
(**11**)

In a related vein, the enantiomerically pure and polyfunctionalized cyclohexenone **12** is converted into the ring-fused indole **13** (85%) on exposure to hydrogen (1 atmosphere) in the presence

of excess Raney cobalt and *p*-toluenesulfonic acid at 40 °C in methanol.[32] The reaction sequence necessarily involves selective reduction of the nitrile and nitro groups while the enone residue is retained and participates in intramolecular hetero-Michael addition and Schiff-base condensation reactions. A *cis*-ring-fused perhydroquinoline (CD rings in **13**) is inevitably formed under these reductive cyclization conditions but a protocol for their conversion into the corresponding *trans*-isomer has been reported.[33]



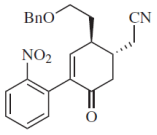
(**12**)



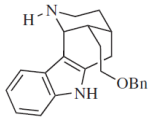
(**13**)

In a related process leading to the alkaloids limaspermidine and 1-acetylaspidoalbidine, it was shown that an *N*-hydroxyindole is initially formed during the reductive cyclization process but that on sustained exposure of this to hydrogen and Raney cobalt a clean conversion into the corresponding indole is observed.[34]

As a pivotal step in a total synthesis of the uleine alkaloid gilbertine, the polyfunctionalized cyclohexenone **14** was subjected to reductive cyclization under an atmosphere of hydrogen in the presence of 200 wt% Raney cobalt and *p*-toluenesulfonic acid.[35] This provided the tetracyclic compound **15** in 60% yield. Once again, this conversion involves CN and aromatic NO_2-group reductions (no particular order implied) with the resulting 1°-amine and aniline (or perhaps *N*-hydroxyaniline) residues undergoing intramolecular hetero-Michael and Schiff-base condensation reactions, respectively. Notably, the benzyl ether, olefinic, and ketone carbonyl residues associated with the substrate are not reduced under these conditions and thus emphasizing the chemoselectivities available when reducing polyfunctionalized compounds using hydrogen in combination with Raney cobalt. When Raney nickel is employed for the reduction of such substrates then the olefinic residue is reduced with the result that a piperidine ring is not formed.[36] Another important feature of this conversion is that the reaction can be conducted at atmospheric pressure (with hydrogen) by using an excess of Raney cobalt.[1]

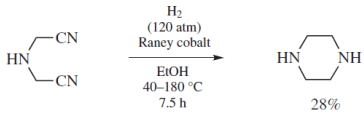


(**14**)



(**15**)

The reaction of di(cyanomethyl)amine with hydrogen in the presence of Raney cobalt provides a simple but modest yielding route to piperazine (eq 10).[37]



(10)

Related Reagents. See R-2, R-3, R-7, R-9, R-10, R-19, R-20, R-21, R-23, R-24, R-27, R-28 and R-30.

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Publication Two

A Palladium-Catalyzed Ullmann Cross-Coupling/Tandem Reductive Cyclization Route to Key Members of the Uleine Alkaloid Family

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Palladium-Catalyzed Ullmann Cross-Coupling/Tandem Reductive Cyclization Route to Key Members of the Uleine Alkaloid Family

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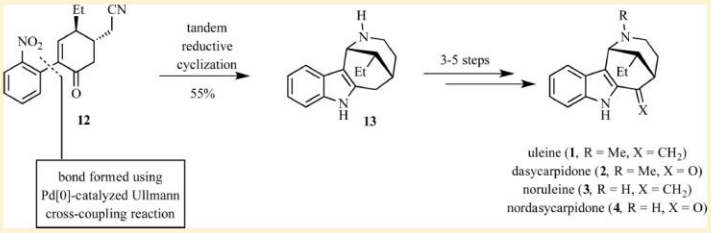
Supporting Information



ABSTRACT: The trisubstituted cyclohexenone **12**, generated through a palladium-catalyzed Ullmann cross-coupling reaction between *o*-iodonitrobenzene and a 4,5-*trans*-disubstituted 2-iodo-2-cyclohexen-1-one, engaged in a tandem reductive cyclization process upon exposure to hydrogen gas in the presence of Raney cobalt. As a result, the 1,5-methanoazocino[4,3-*b*]indole **13** was obtained and this could be readily elaborated to the racemic modifications of the alkaloids uleine, dasycarpidone, noruleine, and nordasycarpidone (**1**−**4**, respectively).

INTRODUCTION

Like the more well-known *Strychnos* alkaloids, the uleine-type natural products embody the tetracyclic 1,5-methanoazocino-[4,3-*b*]indole framework.[1] Uleine (**1**),[2,3] dasycarpidone (**2**),[3] noruleine (**3**),[3] and nordasycarpidone (**4**)[3] (Figure 1), all of which have been isolated from a range of plant sources, including the bark of the South American shrub *Aspidosperma dasycarpon* A. DC., are the "original" and representative members of the family, but others have since been identified, including, for example, C20-epimers[4] and more highly oxygenated variants.[5]

A range of interesting biological properties has been attributed to uleine and its congeners. These include analgesic, anti-inflammatory, bactericidal, antimalarial, and acetylcholinesterase (AChE)-inhibiting activities.[6] In addition, the capacity of compound **1** to promote the synthesis of nitric oxide has prompted investigations on the use of the source plants as adjuvants in the treatment of patients with compromised immune systems.[7]

Since the completion of the key studies[2,4,8] on the elucidation of the structures of the uleines, there have been numerous reports on the development of often ingenious total syntheses of compounds **1**−**4**.[9,10] These have delivered both racemic and enantiomerically enriched forms of the target compounds. The presence of the 1,5-methanoazocino[4,3-*b*]indole framework within other alkaloids has also prompted the more general development of approaches to this scaffold.[11] As part of our own efforts in the area, in 2012 we described[10f] a Raney cobalt mediated tandem reductive cyclization route to this framework and the elaboration of it to the ABCDE-ring system of the *Strychnos* alkaloids. This work was an extension of slightly earlier studies on the application of related processes to the assembly of the *Aspidosperma* alkaloids limaspermidine and 1-acetylaspidoalbidine[12] that also exploited the capacity of the palladium-catalyzed Ullmann cross-coupling reaction[13] to generate the relevant substrates for the reductive cyclization events.

Herein, we report the extension of both these earlier studies[10f] to stereocontrolled total syntheses of the racemic forms of uleine, dasycarpidone, noruleine, and nordasycarpidone. We also identify seemingly straightforward means by which this work could be extended to the enantioselective assembly of these same alkaloids.

RESULTS AND DISCUSSION

The reaction sequence leading to the substrate required for the pivotal tandem reductive cyclization event is shown in Scheme 1. Thus, 4-ethylcyclohexanone (**5**) was converted into the corresponding (and racemic) unsaturated analogue **6** (60%)[14] by treating the former compound with iodoxybenzoic acid (IBX) in DMSO under conditions defined by Nicoloau and coworkers.[15] Nucleophilic cyclopropanation of the latter compound could be achieved using the Corey−Chaykovsky ylide that had been generated in situ by well-established methods.[16] As a result, the diastereoselective formation of the

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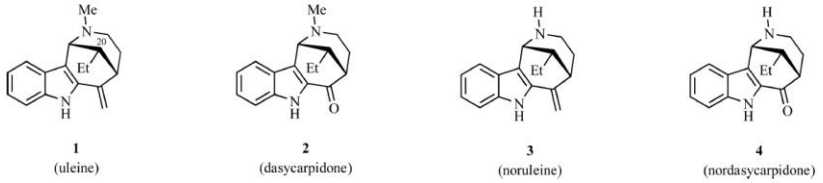
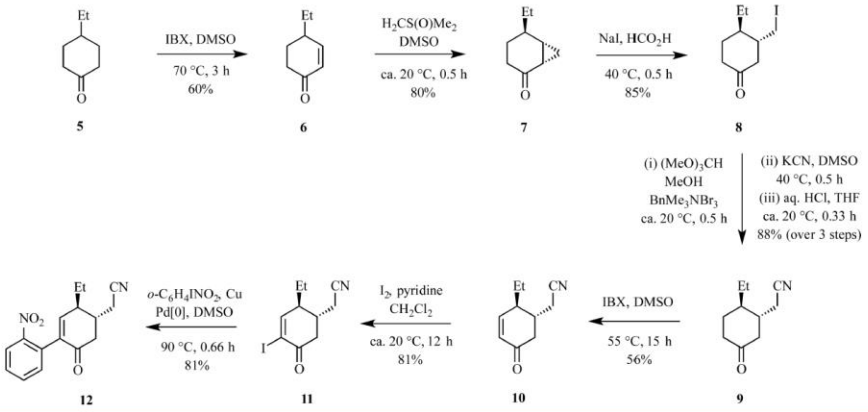


Figure 1. Structures of uleines **1**−**4**.

Scheme 1. Synthesis of Substrate 12 Required for the Tandem Reductive Cyclization Reaction



bicyclo[4.1.0]heptanone **7** (80%) was achieved, although the presence of a ca. 10% of an isomeric material (presumably the corresponding *cis*-compound) was evident in the ^{13}C NMR spectrum of this material. Treament of compound **7** with sodium iodide in formic acid resulted in a homoconjugate addition reaction[17] and formation of ca. 10:1 mixture of the desired iodomethylated product **8** (85%) and a chromatographically inseparable isomer. The substitution of the iodine within compound **8** by a nitrile residue could not be achieved directly by, for example, treating it with sodium cyanide. Rather, a 3-(enol-*exo*)-*exo*-*tet* cyclization reaction[18] took place under all conditions employed, thus regenerating the precursor cyclopropane **7**. Accordingly, and in a telescoped-type reaction sequence, compound **8** was converted into the corresponding dimethyl ketal that could now be engaged in the desired nucleophilic substitution reaction with sodium cyanide. The ensuing dimethyl ketal of the required nitrile was immediately treated with aqueous hydrochloric acid, thereby affording the targeted compound **9** in 88% yield over the three steps involved. Various attempts to effect the direct conversion of enone **6** into nitrile **9**, including through addition of the acetonitrile anion to the former compound, all failed.

Dehydrogenation of cyclohexanone **9** could be achieved with some levels of regiocontrol using IBX in DMSO[15] and the 4,5-disubstituted-2-cyclohexen-1-one **10** was thus obtained in 56% yield. Even after chromatographic purification, this material contained IBX-derived impurities. There was also some evidence for the coproduction of minor amounts of the regioisomeric enone. The (albeit modest) regioselectivity observed in this conversion is presumably the result of the steric effects exerted by the cyanomethyl group in substrate **9**.

In anticipation of perfoming a palladium-catalyzed Ullmann cross-coupling reaction,[13] cyclohexenone **10** was subjected to a Johnson-type α-iodination reaction,[19] thus affording the iodo derivative **11** (81%) that was readily obtained in spectroscopically pure form after flash chromatography. The pivotal cross-coupling of compound **11** with *o*-iodonitrobenzene proceeded smoothly when a DMSO solution of the two reaction partners was treated with copper powder and $Pd_2(dba)_3$ (ca. 8 mol % wrt **11**) and the ensuing mixture heated at 90 °C for 0.66 h. As a result, and after chromatographic purification, the crystalline product **12** was obtained in 81% yield.

All of the conventional spectroscopic data acquired on compound **12** were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis, some details of which are provided in the Experimental Section and the Supporting Information. Most importantly, this analysis confirmed the *trans* relationship between the ethyl and cyanomethyl residues within the compound. Such a relationship was essential for establishing the correct relative stereochemistry of the ethyl group at C-20 in target **1** (a vexing issue encountered in a number of earlier synthetic studies[9c]).

With compound **12** in hand, its capacity to engage in the pivotal tandem reductive cyclization reaction could be explored. When a THF/methanol solution of compound **12** containing *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, introduced to suppress intermolecular reductive alkylation reactions) was treated with 200 wt % of freshly prepared Raney cobalt[20] and exposed to an atmosphere of hydrogen gas then the desired transformation took place such that after chromatographic purification the anticipated 1,5-methanoazocino[4,3-*b*]indole

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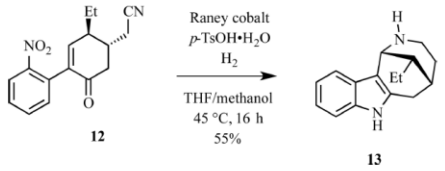
13 was obtained in 55% yield (Scheme 2). The modest yields observed during this conversion are attributed to the rather unstable nature of the product and, for example, the apparent ready propensity of it to oxidize on standing. All of the spectral data acquired on compound **13** were in accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis of a Boc derivative (see below).

Scheme 2. Pivotal Tandem Reductive Cyclization Reaction



Interestingly, compound **13** has served as an advanced intermediate in a total synthesis of the *Strychnos* alkaloid tubotaiwine reported by Bosch and co-workers.[11a]

The route used in elaborating compound **13** to noruleine (**3**) and then, through *N*-methylation, to uleine (**1**) is shown in Scheme 3. Thus, the 2°-amine **13** was first converted into the corresponding Boc derivative **14** (80%), the structure of which was confirmed through a single-crystal X-ray analysis (see the Experimental Section and the Supporting Information for details). In $CDCl_3$ solutions at room temperature, this material existed as a ca. 1:1 mixture of rotamers. Upon treating a dichloromethane solution of carbamate **14** with pyridinium chlorochromate (PCC), a relatively smooth oxidation reaction took place to deliver ketone **15** (75%), and on reacting this with methyllithium at −78 °C, the 3°-alcohol **16** was produced. This last compound was not isolated but simply treated with a ca. 4-fold excess of trifluoroacetic acid at ambient temperature. As a result, both dehydration and cleavage of the Boc group took place (no specific order of events implied). After workup and chromatographic purification, noruleine (**3**) was obtained in 75% yield.

A comparison of the ^1H and ^{13}C NMR spectral data acquired on this material with those recorded by Patir and Ertürk[9e] on their (synthetically derived) material revealed an excellent match (see Table 1 for a comparison of the ^{13}C NMR data sets).

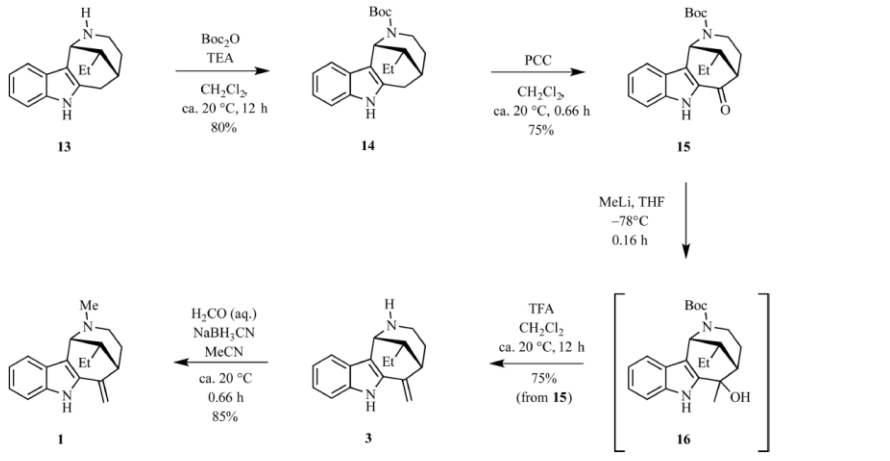
Table 1. Comparison of the ^{13}C NMR Data Recorded for Synthetically Derived Compounds 3 and 1 with Those Reported for Noruleine (3) and Uleine (1)

^{13}C NMR data for compd **3** (δ_C)[a]	^{13}C NMR data for noruleine (δ_C)[b]	^{13}C NMR data for compd **1** (δ_C)[a]	^{13}C NMR data for uleine (δ_C)[b]
138.7	138.6	138.7	138.7
137.1	137.1	136.6	136.6
134.9	135.0	135.2	135.2
126.8	126.8	129.4	129.4
123.0	122.9	122.8	122.7
119.8	119.7	119.9	119.9
118.6	118.5	119.6	119.5
111.5	111.2	110.8	110.7
110.9	110.9	107.7	107.7
106.7	106.9	106.9	106.8
49.3	49.3	56.6[c]	55.6[c]
45.8	45.6	46.3	46.1
40.6	40.5	46.1	46.3
37.4	37.3	44.3	44.3
35.0	34.8	39.5	39.5
24.6	24.6	34.7	34.7
11.8	11.7	24.4	24.4
		11.8	11.8

[a]Spectrum recorded in $CDCl_3$ at 100 MHz. [b]Data obtained from ref 9e; spectrum recorded in $CDCl_3$ at 125 or 150 MHz. [c]The difference in these δ_C values could arise from variations in the pH of the medium in which each spectrum was acquired.

The conversion of noruleine (**3**) into uleine (**1**) proved a straightforward matter and simply involved (Scheme 3) subjecting the former compound to a reductive methylation reaction using a combination of formaldehyde and sodium

Scheme 3. Elaboration of the Tandem Reductive Cyclization Product 13 to Noruleine (3) and Uleine (1)



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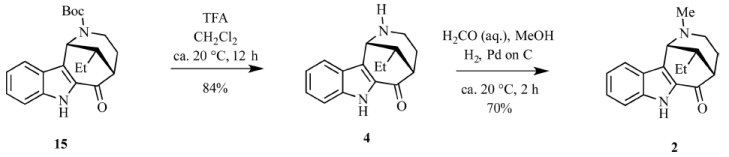
Scheme 4. Completion of Syntheses of Nordasycarpidon (4) and Dasycarpidone (2)



cyanoborohydride. By such means, parent compound **1** was obtained in 85% yield and all the derived spectral data were, once again, a good match with those reported by others (see Table 1, for example).

Completion of syntheses of nordasycarpidone (**4**) and dasycarpidone (**2**) proved equally straightforward and involved, as shown in Scheme 4, TFA-induced cleavage of compound **15** to give, in 84% yield, the former natural product. Reductive methylation of this product (viz. **4**) using formaldehyde and hydrogen gas in the presence of palladium on carbon then gave dasycarpidone (**2**) in 70% yield.

As before, all of the spectroscopic data obtained on compounds **2** and **4** were in accord with the assigned structures and, with one minor discrepancy (see Table 2), matched those reported by Bosch and co-workers.[9a]

Table 2. Comparison of the ^{13}C NMR Data Recorded for Synthetically Derived Compounds 4 and 2 with Those Reported for Nordasycarpidone (4) and Dasycarpidone (2)

^{13}C NMR data for compd 4 (δ_C)[a]	^{13}C NMR data for nordasycarpidone (δ_C)[b]	^{13}C NMR data for compd 2 (δ_C)[a]	^{13}C NMR data for dasycarpidone (δ_C)[b]
193.2[c]	193.9[c]	193.2	193.5
138.7	139.0	138.0	138.1
132.8	132.9	132.8	132.9
127.1	127.0	127.7	127.8
125.1	125.1	126.8	126.9
122.8[c]	123.8[c]	121.9	122.0
121.0	121.0	121.1	121.1
121.0	120.8	119.7	119.9
112.9	113.0	112.6	112.7
49.0	49.0	56.4	56.2
48.7	49.0	49.7	49.6
47.2	47.4	46.4	46.3
37.2	37.2	46.1	46.0
29.8	30.2	44.1	44.0
25.2	25.0	30.2	30.1
11.7	11.5	25.0	24.8
		11.8	11.8

[a]Spectrum recorded in $CDCl_3$ at 100 MHz. [b]Data obtained from ref 9a; spectrum recorded in $CDCl_3$ at 125 MHz. [c]The difference in these δ_C values could arise from variations in the pH of the medium in which each spectrum was acquired.

CONCLUSION

The work reported here, when considered in conjunction with our previous studies,[10f,12,21] serves to emphasize the considerable utility of both the palladium-catalyzed Ullmann cross-coupling reaction and certain tandem reductive cyclization processes, especially when these are applied together within a given synthetic sequence. The capacity to exploit such processes in the assembly of other biologically relevant heterocyclic frameworks is the subject of ongoing studies in our laboratories.

It should also be noted that rather efficient methods for the synthesis of optically active 4-substituted 2-cyclohexenones, including the *S*-enantiomer of **6**, have been reported.[22] Accordingly, there is every prospect that the work reported here could be applied in a straightforward manner to the enantioselective synthesis of the uleines and, perhaps even, the *Strychnos* alkaloids.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^1H) 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. 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 ^1H and ^{13}C NMR spectra, respectively. ^1H 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. Infrared spectra (ν_{max}) were recorded on an 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 (concd)/water (37.5 g/7.5 g/37.5 g/720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL), *p*-anisaldehyde or vanillin/sulfuric acid (concd)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[23] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[24] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *4-Ethylcyclohex-2-en-1-one (6).* A magnetically stirred solution of 4-ethylcyclohexanone (2.00 g, 15.9 mmol) in DMSO (50 mL) was treated with IBX (9.10 g, 32.5 mmol) and the resulting mixture heated at 70 °C for 3 h and then cooled to room temperature and quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The ensuing mixture was filtered through diatomaceous earth, and the solids thus retained washed with diethyl ether (3 × 20 mL). The aqueous phase was extracted with diethyl ether (3 × 40 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuring black oil was subjected to flash chromatography (silica, 1:50 → 1:20 v/v ethyl acetate/hexane gradient elution), and concentration of relevant

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fractions (R_f = 0.4 in 1:7 v/v ethyl acetate/hexane elution) afforded the title compound **6**[14] (1.18 g, 60%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (ddd, J = 10.2, 2.6, and 1.4 Hz, 1H), 5.98 (dd, J = 10.2 and 2.2 Hz, 1H), 2.50 (dt, J = 16.7 and 4.7 Hz, 1H), 2.42−2.27 (complex m, 2H), 2.16−2.08 (complex m, 1H), 1.76−1.62 (complex m, 1H), 1.62−1.39 (complex m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.0, 155.0, 129.0, 37.7, 37.0, 28.2, 27.5, 11.4; IR ν_{max} 2963, 1683, 1461, 1390, 1148, 942, 854, 742 cm^{-1}; MS (ESI, + ve) m/z 125 [(M + H)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_8H_{12}NaO$ 147.0786, found 147.0787.

*rac-(1S,5R,6S)-5-Ethylbicyclo[4.1.0]heptan-2-one (**7**).* A magnetically stirred suspension of NaH (82 mg, 3.4 mmol) in dry DMSO (10 mL) was treated with Me_3SOI (441 mg, 2.0 mmol), and after being maintained at room temperature for 0.17 h, the reaction mixture was warmed to 50 °C and stirred for a further 0.34 h. The cooled mixture was treated with enone **6** (224 mg, 1.8 mmol) and then stirred at room temperature for 0.5 h before being quenched with H_2O (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:15 → 1:10 v/v ethyl acetate/hexane gradient elution) and concentration of relevant fractions (R_f = 0.3 in 1:7 v/v ethyl acetate/hexane) afforded a ca. 10:1 mixture of the title compound **7** and the diastereoisomeric cyclopropane (224 mg, 90%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17−2.05 (complex m, 2H), 1.93−1.83 (complex m, 1H), 1.82−1.65 (complex m, 2H), 1.66−1.32 (complex m, 4H), 1.27−1.09 (complex m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.8, 33.5, 33.1, 27.4, 25.5, 24.2, 23.8, 12.8, 12.0; IR ν_{max} 2960, 1686, 1462, 1345, 1246, 1197, 939, 883, 824 cm^{-1}; MS (ESI, + ve) m/z 161 [(M + Na)$^+$, 3%], 139 [(M + H)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_9H_{14}NaO$ 161.0942, found 161.0939.

*rac-(3R,4R)-4-Ethyl-3-(iodomethyl)cyclohexan-1-one (**8**).* A magnetically stirred solution of ketone **7** (510 mg, 4.0 mmol) and NaI (2.20 g, 14.7 mmol) in HCOOH (10 mL) was heated at 40 °C for 0.5 h and then cooled to room temperature and quenched with H_2O (15 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) and brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:18 v/v ethyl acetate/hexane elution), and concentration of relevant fractions (R_f = 0.5 in 1:7 v/v ethyl acetate/hexane) afforded a ca. 10:1 mixture of the title compound **8** and a diastereoisomer (930 mg, 95%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (dd, J = 10.3 and 4.9 Hz, 1H), 3.24 (dd, J = 10.3 and 2.9 Hz, 1H), 2.46−2.25 (complex m, 4H), 2.16−2.04 (complex m, 1H), 1.73−1.40 (complex m, 3H), 1.36−1.14 (complex m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.7, 47.1, 41.6, 40.9, 40.7, 28.8, 24.2, 15.2, 10.4; IR ν_{max} 2960, 2873, 1716, 1461, 1427, 1318, 1218, 1177 cm^{-1}; MS (ESI, + ve) m/z 289 [(M + Na)$^+$, 100], 267 [(M + H)$^+$, 23]; HRMS (M + Na)$^+$ calcd for $C_9H_{15}INaO$ 289.0065, found 289.0067.

*rac-2-[(1R,2R)-2-Ethyl-5-oxocyclohexyl]acetonitrile (**9**). Step i.* A magnetically stirred solution of iodide **8** (1.08 g, 4.1 mmol) in anhydrous MeOH (10 mL) was treated with trimethyl orthoformate (480 μL, 4.5 mmol) and benzyltrimethylammonium tribromide (30 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 0.5 h, quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil, presumed to contain the dimethyl ketal of compound **8**, was immediately subjected to the reaction conditions defined in step ii.

Step ii. A magnetically stirred solution of crude material obtained from step i in DMSO (6 mL) was treated with KCN (480 mg, 7.4 mmol). The resulting solution was stirred at 40 °C for 0.5 h and then quenched with H_2O (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were concentrated under reduced pressure, and the yellow oil thus obtained, and presumed to contain the dimethyl ketal of compound **9**, was immediately subjected to the reaction conditions defined in step iii.

Step iii. A magnetically stirred solution of the oil obtained from step ii in THF (10 mL) was treated with HCl (5 mL of a 1 M aqueous solution) (CAUTION: possibility of HCN generation) and the resulting mixture stirred at room temperature for 0.33 h before being quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution) and then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution), and concentration of relevant fractions (R_f = 0.2 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **9** (590 mg, 88%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (dd, J = 17.1 and 6.3 Hz, 1H), 2.45−2.25 (complex m, 5H), 2.13−2.03 (complex m, 1H), 1.93−1.85 (complex m, 1H), 1.66−1.59 (complex m, 2H), 1.49−1.32 (complex m, 1H), 1.31−1.15 (complex m, 1H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.2, 117.5, 45.6, 40.4, 39.9, 38.3, 29.1, 24.5, 21.9, 10.5; IR ν_{max} 2964, 2877, 2245, 1715, 1464, 1426, 1328, 1250, 1193, 954, 853 cm^{-1}; MS (ESI, + ve) m/z 188 [(M + Na)$^+$, 45], 166 [(M + H)$^+$, 30], 122 (100); HRMS (M + Na)$^+$ calcd for $C_{10}H_{15}NNaO$ 188.1051, found 188.1052.

*rac-2-[(1R,2S)-2-Ethyl-5-oxocyclohex-3-en-1-yl]acetonitrile (**10**).* A magnetically stirred solution of ketone **9** (280 mg, 1.7 mmol) in DMSO (10 mL) was treated with *p*-TsOH·H_2O (90 mg, 0.5 mmol) and IBX (960 mg, 3.4 mmol) and then heated at 55 °C for 15 h. The cooled reaction mixture was quenched with $NaHCO_3$ (15 mL of a saturated aqueous solution) and then filtered through a pad of diatomaceous earth. The solids thus retained were washed with ethyl acetate (3 × 20 mL), and the separated aqueous phase associated with the filtrate was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.3 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **10** (150 mg, 56%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81 (dd, J = 10.2 and 2.9 Hz, 1H), 6.00 (dd, J = 10.2 and 2.1 Hz, 1H), 2.58 (dd, J = 16.2 and 4.0 Hz, 1H), 2.46 (t, J = 6.0 Hz, 2H), 2.42−2.21 (complex m, 3H), 1.73−1.63 (complex m, 1H), 1.59−1.43 (complex m, 1H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 152.4, 129.3, 117.5, 41.5, 40.9, 34.9, 24.4, 21.6, 10.4; IR ν_{max} 2966, 2257, 1679, 1389, 1249, 868, 504 cm^{-1}; MS (ESI, + ve) m/z 186 [(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{10}H_{13}NNaO$ 186.0895, found 186.0897.

*rac-2-[(1R,2S)-2-Ethyl-4-iodo-5-oxocyclohex-3-en-1-yl]-acetonitrile (**11**).* A magnetically stirred solution of enone **10** (140 mg, 0.48 mmol) in CH_2Cl_2/pyridine (4 mL of a 1:1 v/v mixture) maintained at room temperature was treated dropwise with a solution of molecular iodine (330 mg, 1.20 mmol) in CH_2Cl_2/pyridine (4 mL of a 1:1 v/v mixture). The ensuing solution was stirred at room temperature for 12 h and then treated with H_2O (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed, sequentially, with HCl (1 × 20 mL of a 1 M aqueous solution), $Na_2S_2O_3$ (1 × 20 mL of a 10% w/w aqueous solution), and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:6 → 1:3 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **11** (190 mg, 81%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 3.2 Hz, 1H), 2.90 (dd, J = 16.3 and 4.1 Hz, 1H), 2.72−2.49 (complex m, 4H), 2.46−2.33 (complex m, 1H), 1.81−1.71 (complex m, 1H), 1.68−1.53 (complex m, 1H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.0, 160.8, 117.0, 103.0, 45.3, 40.5, 35.1, 24.3, 21.4, 10.6; IR ν_{max} 2964, 2245, 1686, 1589, 1461, 1421, 1329, 1191, 1116, 948, 899,

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772 cm^{-1}; MS (ESI, + ve) m/z 312 [$(M + Na)^+$, 100], 290 [$(M + H)^+$, 14]; HRMS (M + Na)$^+$ calcd for $C_{10}H_{12}INNaO$ 311.9861, found 311.9862.

Compound ***12***. A magnetically stirred solution of iodide **11** (240 mg, 0.86 mmol) and *o*-iodonitrobenzene (420 mg, 1.7 mmol) in DMSO (4 mL) was treated with $Pd_2(dba)_3$ (60 mg, 0.07 mmol) and Cu powder (260 mg, 4.1 g.atom). The resulting mixture was heated at 90 °C for 0.66 h before being cooled to room temperature and then diluted with ethyl acetate (10 mL). The mixture thus obtained was filtered through diatomaceous earth, and the solids thus retained were washed with ethyl acetate (3 × 10 mL). The combined filtrates were washed with water (2 × 30 mL) and the combined aqueous phases extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/hexane gradient elution) and concentration of relevant fractions (R_f = 0.2 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **12** (190 mg, 81%) as a yellow, crystalline solid: mp = 109−113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, J = 8.2 and 1.2 Hz, 1H), 7.65 (td, J = 7.9 and 1.3 Hz, 1H), 7.53 (td, J = 7.9 and 1.5 Hz, 1H), 7.36−7.18 (complex m, 1H), 6.89 (d, J = 3.5 Hz, 1H), 2.81 (dd, J = 16.1 and 4.0 Hz, 1H), 2.76−2.43 (complex m, 5H), 1.95−1.78 (complex m, 1H), 1.76−1.67 (complex m, 1H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.9, 148.5, 148.0, 139.3, 133.6, 131.6, 131.3, 129.3, 124.5, 117.6, 41.3, 41.2, 34.8, 24.9, 21.6, 10.8; IR ν_{max} 2971, 2245, 1683, 1524, 1353, 1184, 854, 788 cm^{-1}; MS (ESI, + ve) m/z 307 [$(M + Na)^+$, 100], 285 [$(M + H)^+$, 22]; HRMS (M + Na)$^+$ calcd for $C_{16}H_{16}N_2NaO_3$ 307.1059, found 307.1059.

Compound ***13***. A magnetically stirred solution of nitrile **12** (200 mg, 0.70 mmol), *p*-TsOH·H_2O (700 mg, 3.7 mmol), and Raney cobalt (430 mg, 200% w/w) in THF/methanol (15 mL of a 1:1 v/v mixture) was heated at 45 °C for 16 h while being maintained under an atmosphere of hydrogen. The resulting mixture was cooled to room temperature then filtered through diatomaceous earth, and the solids thus retained were washed with methanol (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 1:20 → 1:5 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.4 in 1:4 v/v methanol/dichloromethane) afforded the title compound **13**[9a,11a] (93 mg, 55%) as a clear, unstable yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.03 (m, 2H), 2.91 (dd, J = 17.4 and 6.6 Hz, 1H), 2.67−2.35 (complex m, 3H), 2.20 (broad s, 1H), 2.01−1.75 (complex m, 2H), 1.54 (d, J = 13.4 Hz, 2H), 1.31−1.01 (complex m, 3H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.3, 136.0, 126.8, 121.1, 119.4, 117.4, 110.6, 107.2, 48.8, 43.4, 37.1, 34.0, 29.9, 25.6, 24.0, 11.8; IR ν_{max} 2958, 2925, 2873, 1617, 1456, 1304, 1238, 1010, 906, 727 cm^{-1}; MS (ESI, + ve) m/z 241 [$(M + H)^+$, 100], 224 (45), 198 (30); HRMS (M + H)$^+$ calcd for $C_{16}H_{21}N_2$ 241.1705, found 241.1702.

Compound ***14***. A magnetically stirred solution of amine **13** (87 mg, 0.36 mmol) in dichloromethane (5 mL) was treated with Boc_2O (157 mg, 0.72 mmol) and triethylamine (300 μL, 2.2 mmol). The ensuing mixture was stirred at room temperature for 12 h, quenched with H_2O (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **14** (98 mg, 80%) as a white, crystalline solid and a ca. 1:1 mixture of rotamers: mp = 216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (mixture of rotamers) 10.91 (s, 0.5H), 10.85 (s, 0.5H), 7.41 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 10.7 and 7.8 Hz, 1H), 7.02−6.89 (complex m, 2H), 5.36 (s, 0.5H), 5.27 (s, 0.5H), 3.62 (dd, J = 13.2 and 5.5 Hz, 0.5H), 3.52 (dd, J = 13.3 and 5.7 Hz, 0.5H), 2.96 (dd, J = 17.8 and 6.7 Hz, 1H), 2.60 (dd, J = 17.7 and 13.1 Hz, 1H), 2.46−2.35 (complex m, 1H), 2.25 (broad s, 1H), 1.85−1.59 (complex m, 3H), 1.52 (s, 4.5H), 1.35 (s, 4.5H), 1.25−1.10 (complex m, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (mixture of rotamers) 154.6, 154.1, 136.8, 136.7, 126.9, 126.8, 120.7(1), 120.6(5), 118.8, 118.2, 117.6, 111.3, 111.1, 105.9, 105.5, 78.9, 78.6, 48.1, 46.9, 43.6, 43.2, 37.2, 36.0, 33.4, 33.2, 29.3, 28.7, 28.5, 25.0, 23.7, 23.6, 12.2, 12.1; IR ν_{max} 3402, 3301, 2961, 2929, 2874, 1662, 1462, 1416, 1365, 1308, 1169, 1127, 864, 742 cm^{-1}; MS (ESI, + ve) m/z 363 [$(M + Na)^+$, 100%], 341 [$(M + H)^+$, 33]; HRMS (M + Na)$^+$ calcd for $C_{21}H_{28}N_2NaO_2$ 363.2048, found 363. 2047.

Compound ***15***. A magnetically stirred solution of compound **14** (45 mg, 0.13 mmol) in dichloromethane (5 mL) was treated with PCC (57 mg, 0.27 mmol), and the ensuing mixture stirred at room temperature for 0.66 h then quenched with isopropyl alcohol (3 mL). The resulting mixture was treated with water (15 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **15** (35 mg, 75%) as a clear, yellow oil and a ca. 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (mixture of rotamers) 9.89 (s, 0.5H), 9.81 (s, 0.5H), 7.95 (d, J = 8.2 Hz, 0.5H), 7.80 (d, J = 8.1 Hz, 0.5H), 7.53 (t, J = 9.3 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.21 (m, 1H), 5.85 (s, 0.5H), 5.67 (s, 0.5H), 3.99 (dd, J = 14.0 and 5.5 Hz, 0.5H), 3.79 (dd, J = 14.3 and 5.7 Hz, 0.5H), 2.86 (s, 1H), 2.79−2.60 (complex m, 1H), 2.22 (t, J = 7.3 Hz, 1H), 2.15−1.87 (complex m, 2H), 1.65 (s, 4.5H), 1.45 (s, 4.5H), 1.43−1.34 (complex m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (mixture of rotamers) 193.0, 155.0, 154.3, 138.6, 132.4, 127.3, 125.4, 125.3, 123.0, 122.7, 122.3, 121.6, 121.1, 112.9, 112.5, 80.3, 79.9, 48.3, 48.1, 47.8, 47.0, 46.7, 36.9, 35.7, 31.6, 30.2, 28.7, 28.4, 24.9, 24.8, 22.7, 11.8; IR ν_{max} 3268, 2964, 2932, 2876, 1649, 1470, 1407, 1366, 1277, 1254, 1154, 1127, 1019, 867, 747 cm^{-1}; MS (ESI, + ve) m/z 731 [(2 M + Na)$^+$, 100], 377 [$(M + Na)^+$, 50]; HRMS (M + Na)$^+$ calcd for $C_{21}H_{26}N_2NaO_3$ 377.1841, found 377.1843.

*Noruleine (****3****). Step i*. A magnetically stirred solution of ketone **15** (14 mg, 0.04 mmol) in THF (4 mL) was cooled to −78 °C and then treated with methyllithium (40.0 μL of a 3.0 M solution in diethoxymethane). The resulting mixture was stirred at −78 °C for 0.16 h and then quenched with water (15 mL). After the resulting mixture was warmed to room temperature, the aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil, presumed to contain the anticipated *tert*-alcohol, was subjected to step ii of the reaction sequence as described immediately below.

Step ii. A magnetically stirred solution of the yellow oil obtained from step i in dichloromethane (4 mL) was treated with trifluoroacetic acid (15 μL, 0.19 mmol). The resulting mixture was stirred at room temperature for 12 h and then concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.5 in 1:4 v/v methanol/dichloromethane) afforded the title compound **3**[9e] (7.5 mg, 75%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 5.20 (s, 1H), 4.93 (s, 1H), 4.32 (s, 1H), 2.89−2.36 (complex m, 3H), 2.26−1.88 (complex m, 3H), 1.60 (d, J = 12.6 Hz, 1H), 1.18−0.98 (complex m, 2H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 1; IR ν_{max} 3230, 2960, 2930, 1672, 1613, 1454, 1325, 1201, 1179, 1134, 906, 798, 740 cm^{-1}; MS (ESI, + ve) m/z 253 [$(M + H)^+$, 40], 236 (100); HRMS (M + H)$^+$ calcd for $C_{17}H_{21}N_2$ 253.1705, found 253.1701.

*Uleine (****1****)*. A magnetically stirred solution of amine **3** (15 mg, 0.06 mmol) in acetonitrile (4 mL) was treated, sequentially, with formaldehyde (100 μL of a 35% w/w aqueous solution, 1.2 mmol) and $NaCNBH_3$ (8 mg, 0.13 mmol). The resulting mixture was stirred at room temperature for 0.66 h and then quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was

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extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution), and concentration of relevant fractions (R_f = 0.6 in 1:4 v/v methanol/dichloromethane) afforded the title compound **1**[9e] (13 mg, 85%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 5.29 (s, 1H), 5.02 (s, 1H), 4.12 (d, J = 2.0 Hz, 1H), 2.72 (d, J = 2.0 Hz, 1H), 2.58−2.42 (complex m, 1H), 2.32 (s, 3H), 2.25−1.96 (complex m, 3H), 1.72 (d, J = 7.6 Hz, 1H), 1.22−1.04 (complex m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 1; IR ν_{max} 3231, 2957, 2926, 1668, 1456, 1320, 1050, 880, 738 cm^{-1}; MS (ESI, + ve) m/z 267 [(M + H)$^+$, 85], 236 (100); HRMS (M + H)$^+$ calcd for $C_{18}H_{23}N_2$ 267.1861, found 267.1860.

*Nordasycarpidone (**4**).* A magnetically stirred solution of ketone **15** (17 mg, 0.05 mmol) in dichloromethane (4 mL) was treated with trifluoroacetic acid (15 μL, 0.19 mmol) and the ensuing mixture stirred at room temperature for 12 h before being concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution) and concentration of relevant fractions (R_f = 0.6 in 1:4 v/v methanol/dichloromethane) afforded the title compound **4**[9a] (10 mg, 84%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.89 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.14 (broad s, 1H), 4.83 (s, 1H), 2.97 (broad s, 1H), 2.75 (s, 2H), 2.49 (s, 1H), 2.17 (m, 1H), 1.86 (d, J = 12.7 Hz, 1H), 1.31−1.23 (complex m, 2H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 2; IR ν_{max} 3255, 2960, 1654, 1541, 1474, 1328, 1199, 1132, 908, 800, 746 cm^{-1}; MS (ESI, + ve) m/z 255 [(M + H)$^+$, 55], 238 (100); HRMS (M + H)$^+$ calcd for $C_{16}H_{19}N_2O$ 255.1497, found 255.1499.

*Dasycarpidone (**2**).* A magnetically stirred solution of compound **4** (15 mg, 0.06 mmol) in methanol (5 mL) was treated with 10% Pd on carbon (3 mg) and formaldehyde (200 μL of a 35% w/v aqueous solution, 2.3 mmol). The resulting mixture was stirred at room temperature for 2 h while being maintained under an atmosphere of hydrogen. The mixture thus obtained was filtered through diatomaceous earth, and the solids thus retained were washed with methanol (3 × 10 mL). The combined filtrates were diluted with water (30 mL) and dichloromethane (30 mL), and the separated aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution), and concentration of relevant fractions (R_f = 0.7 in 1:4 v/v methanol/dichloromethane) afforded the title compound **2**[9a] (11 mg, 70%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.31 (m, 1H), 7.12 (m, 1H), 4.24 (s, 1H), 2.63 (broad s, 1H), 2.55 (d, J = 7.0 Hz, 1H), 2.32 (s, 1H), 2.27 (s, 3H), 2.15−1.94 (complex m, 2H), 1.85 (d, J = 9.7 Hz, 1H), 1.34−1.04 (complex m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 2; IR ν_{max} 3262, 2929, 1650, 1531, 1467, 1325, 1151, 1021, 744, 489 cm^{-1}; MS (ESI, + ve) m/z 269 [(M + H)$^+$, 73], 238 (100); HRMS (M + H)$^+$ calcd for $C_{17}H_{21}N_2O$ 269.1654, found 269.1655.

Crystallographic Studies. *Crystallographic Data for Compound **12**:* $C_{16}H_{16}N_2O_2$, M = 284.31, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.56836(10) Å, b = 12.02612 (14) Å, c = 14.15115(14) Å; V = 1458.19(3) Å^3, D_x = 1.295 g cm^{-3}, 2890 unique data ($2\theta_{max}$ = 144.8°), R = 0.027 [for 2828 reflections with $I > 2.0\sigma(I)$]; R_w = 0.069 (all data), S = 1.0.

*Crystallographic Data for Compound **14**:* $C_{21}H_{28}N_2O_2$, M = 340.47, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 10.1738(2) Å, b = 10.6826(1) Å, c = 17.3464(3) Å; β = 103.2796(16)°; V = 1834.84(5) Å^3, D_x = 1.232 g cm^{-3}, 3623 unique data ($2\theta_{max}$ = 144.6°), R = 0.031 [for 3271 reflections with $I > 2.0\sigma(I)$]; R_w = 0.075 (all data), S = 0.99.

Structure Determinations. 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.[25] The structure solutions were solved by direct methods (SIR92).[26] The structures of compounds **12** and **14** were refined using the CRYSTALS program package.[27] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds **12** and **14** have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1450903 and 1450904). 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00240.

X-ray crystallographic data for compound **12** (CIF)
X-ray crystallographic data for compound **14** (CIF)
Anisotropic displacement ellipsoid plot derived from the single-crystal analyses of compounds **12** and **14**; ^{1}H and ^{13}C NMR spectra for compounds **1**−**4** and **6**−**15** (PDF)

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Notes

The authors declare no competing financial interest.

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SUPPORTING INFORMATION FOR:

A Palladium-catalyzed Ullmann Cross-coupling/Tandem Reductive Cyclisation Route to Key Members of the Uleine Alkaloid Family

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

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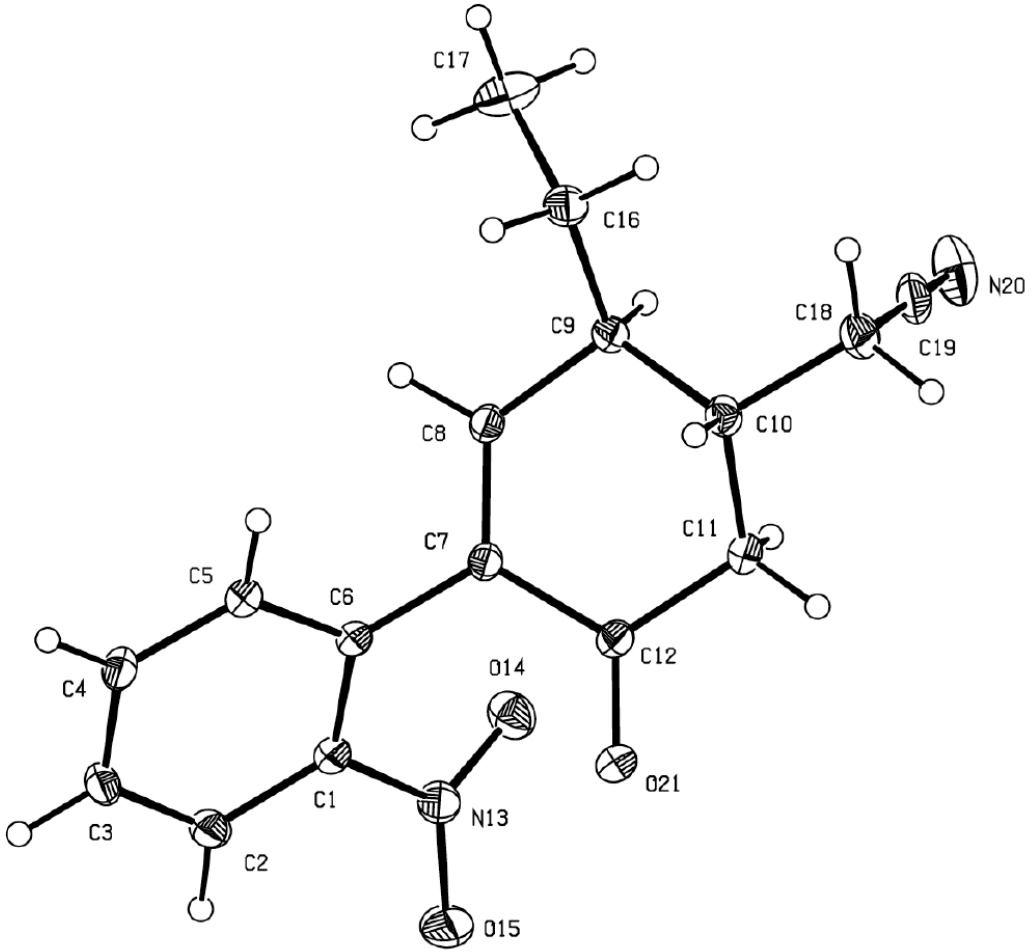


Figure S1: Structure of compound **12** (CCDC 1450903) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

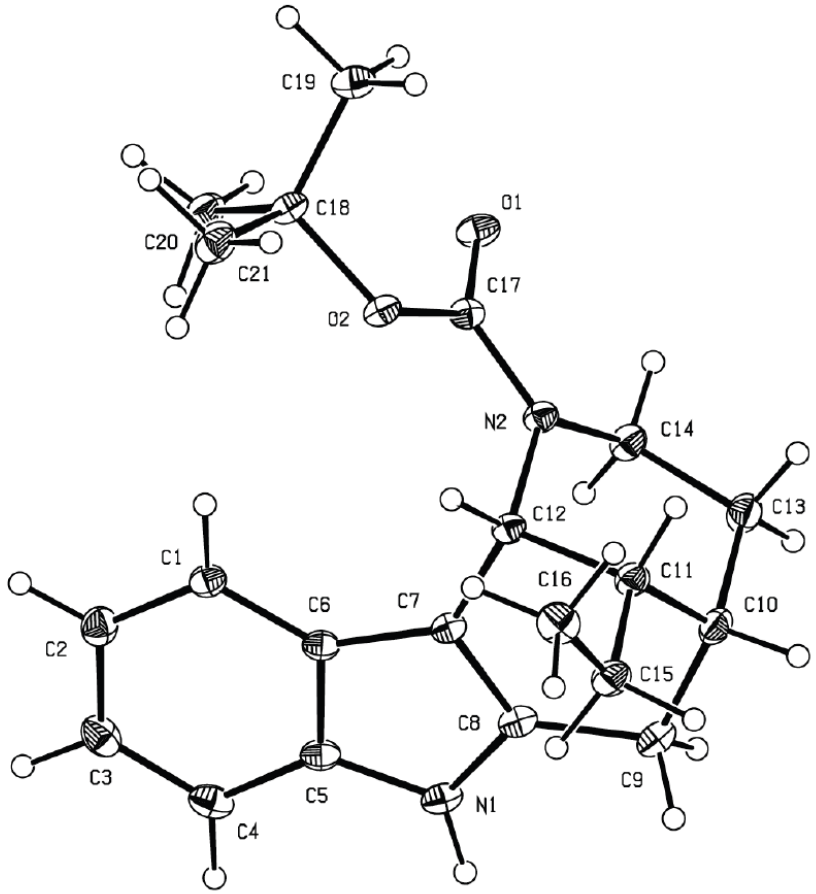
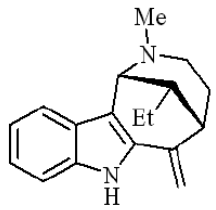


Figure S2: Structure of compound **14** (CCDC 1450904) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

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



100 MHz ^{13}C NMR Spectrum of Compound **1**
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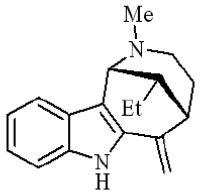

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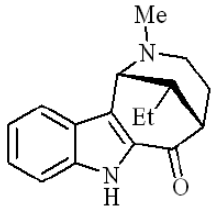

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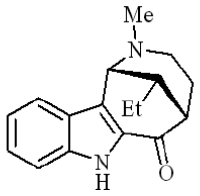

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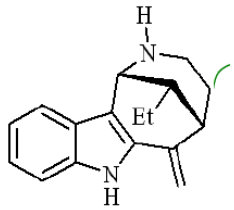

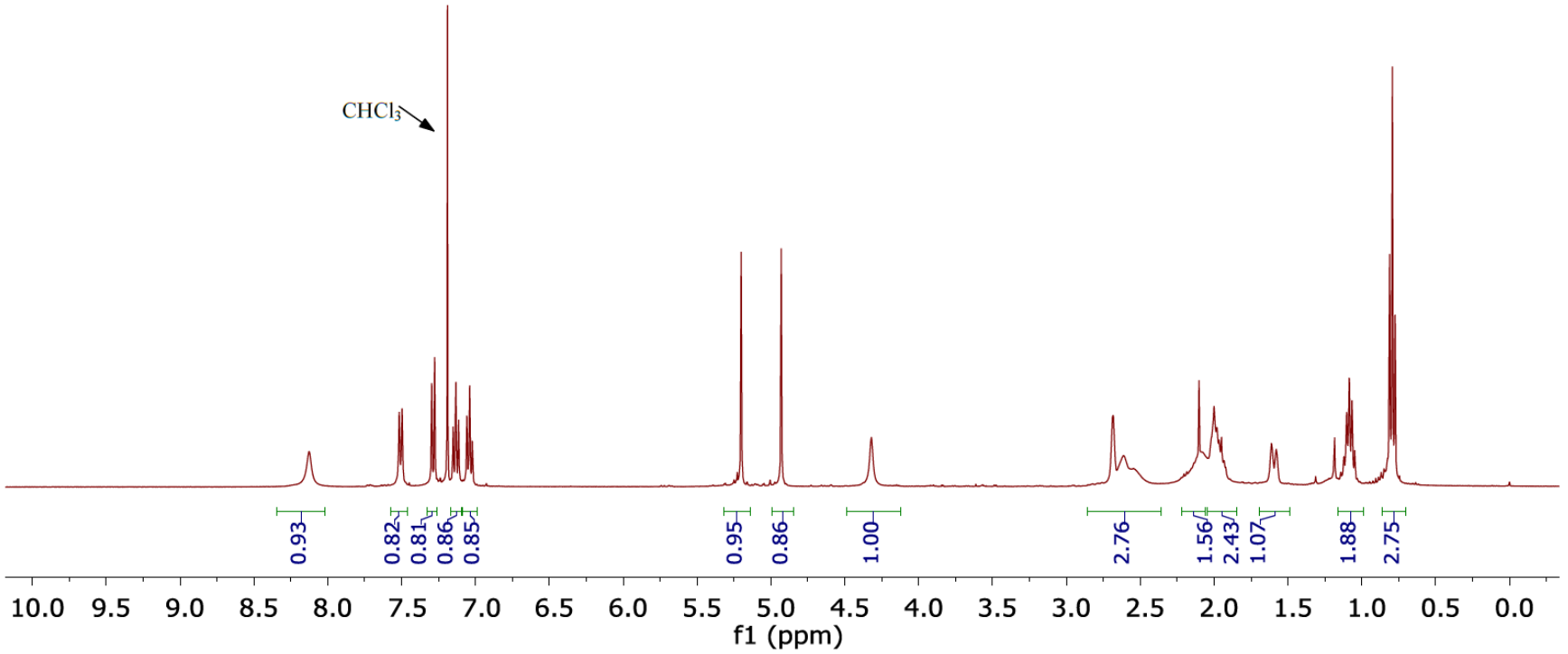

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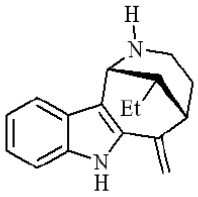

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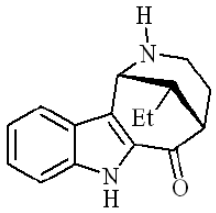

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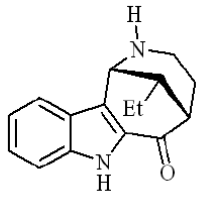
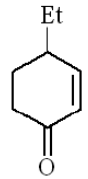
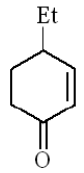


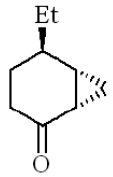
400 MHz ^{1}H NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)



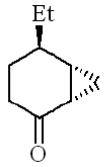
100 MHz ^{13}C NMR Spectrum of Compound **6**
(recorded in $CDCl_3$)



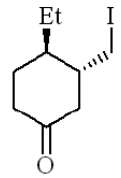
400 MHz ^{1}H NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)



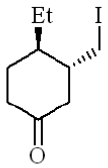
100 MHz ^{13}C NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)



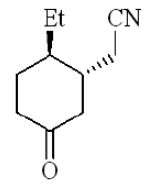
400 MHz ^{1}H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



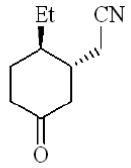
100 MHz ^{13}C NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



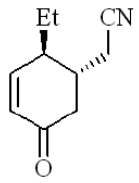
400 MHz ^{1}H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



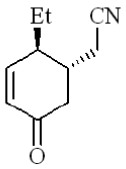
100 MHz ^{13}C NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



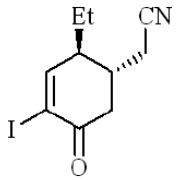
400 MHz ^{1}H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)



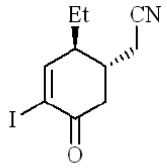
100 MHz ^{13}C NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)



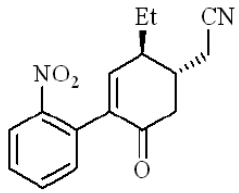
400 MHz ^{1}H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)

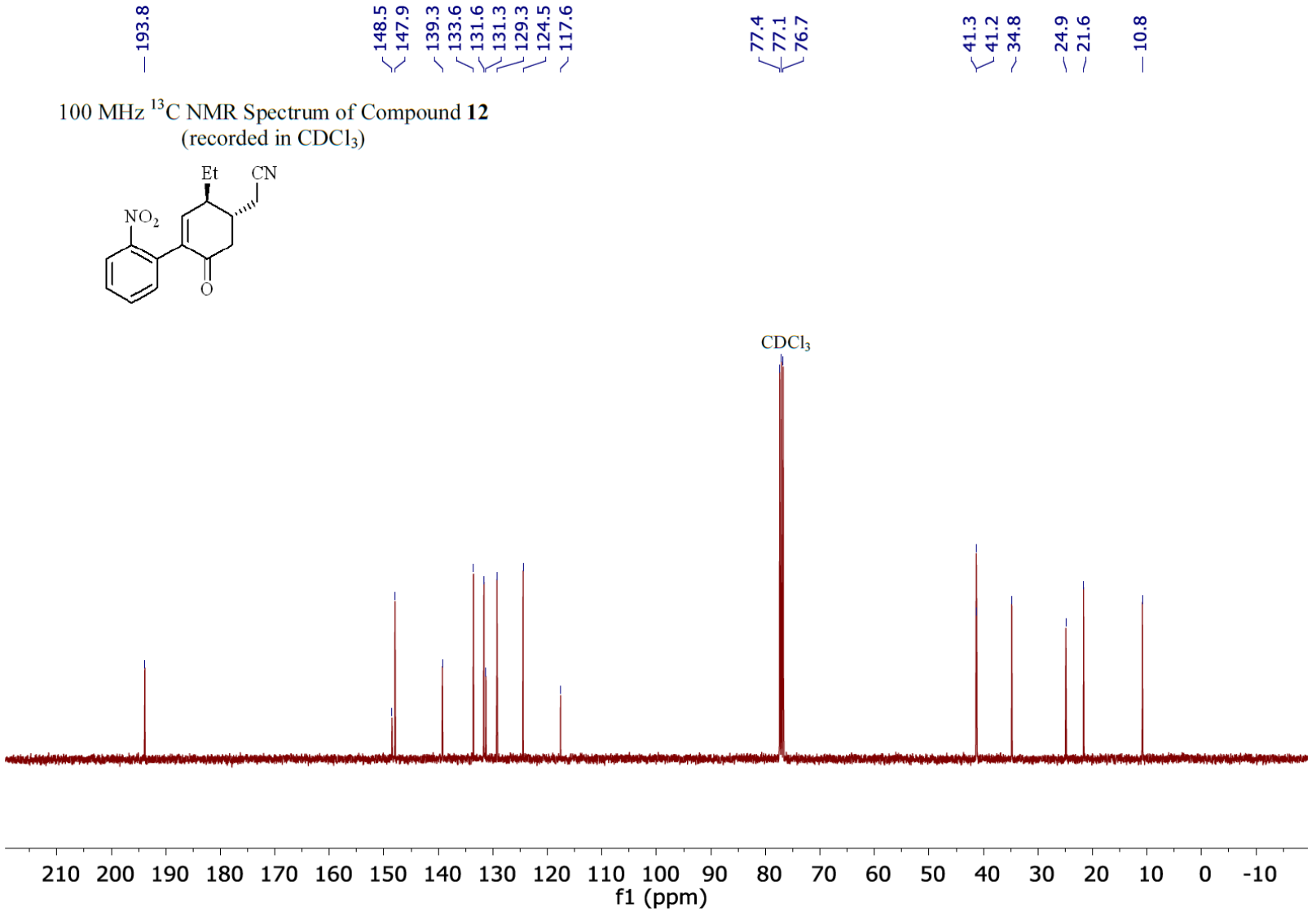


100 MHz ^{13}C NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)



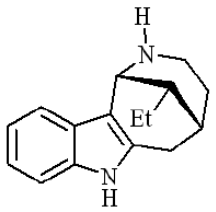
400 MHz ^{1}H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)



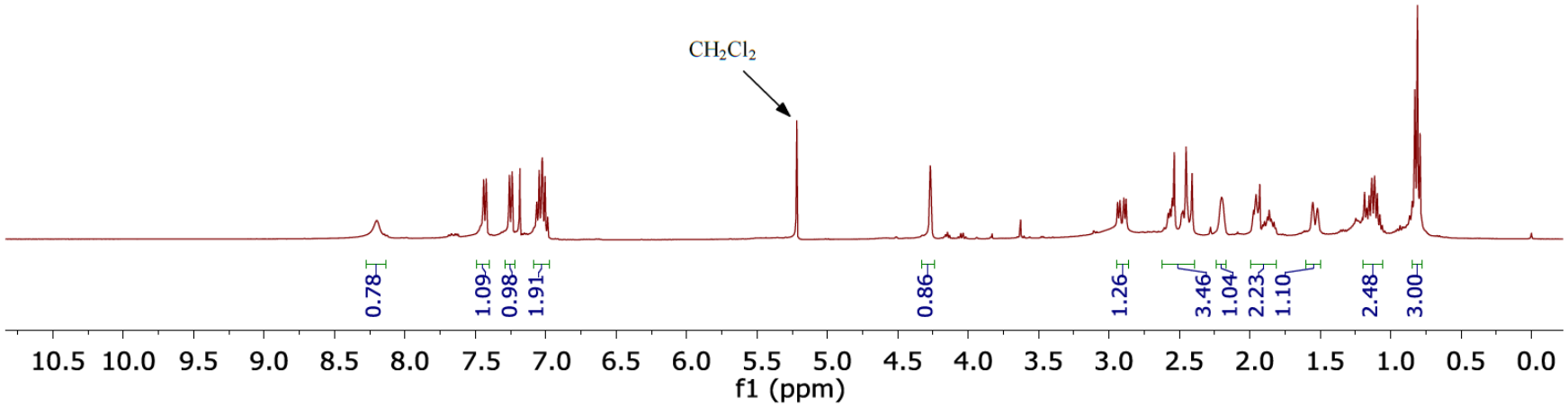


100 MHz ^{13}C NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)

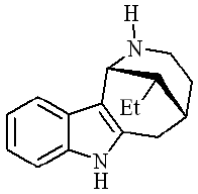
400 MHz ^{1}H NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)



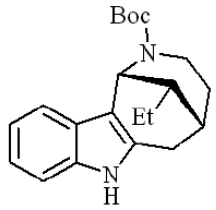
58



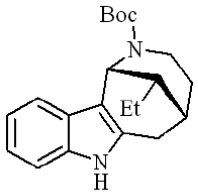
100 MHz ^{13}C NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)



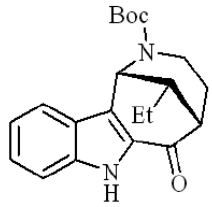
400 MHz ^{1}H NMR Spectrum of Compound **14**
(recorded in DMSO-d_6)

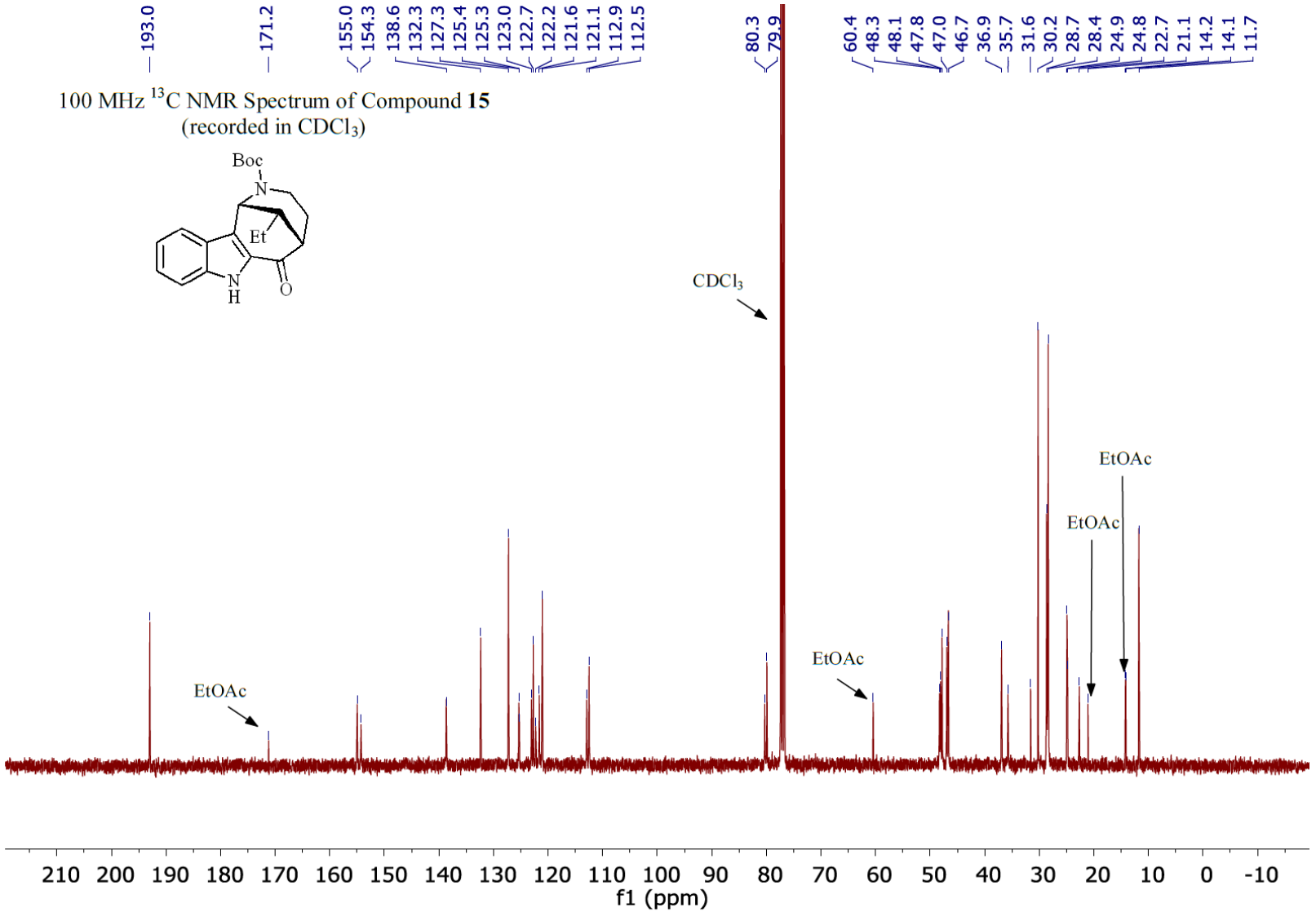


100 MHz ^{13}C NMR Spectrum of Compound **14**
(recorded in DMSO-d_6)



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




193.0
171.2
155.0
154.3
138.6
132.3
127.3
125.4
125.3
123.0
122.7
122.2
121.6
121.1
112.9
112.5
80.3
79.9
60.4
48.3
48.1
47.8
47.0
46.7
36.9
35.7
31.6
30.2
28.7
28.4
24.9
24.8
22.7
21.1
14.2
14.1
11.7
100 MHz ^{13}C NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)
Boc
N
Et
N
H
O
$CDCl_3$
EtOAc
EtOAc
EtOAc
EtOAc
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)

Publication Three

A Raney-Cobalt-Mediated Reductive Cyclization Route to the Uleine Alkaloid Gilbertine

Fei Tang, Martin G. Banwell and Anthony C. Willis

J. Org. Chem., **2016**, *81*, 10551-10557

JOC The Journal of Organic Chemistry

Note

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A Raney Cobalt Mediated Reductive Cyclization Route to the Uleine Alkaloid Gilbertine

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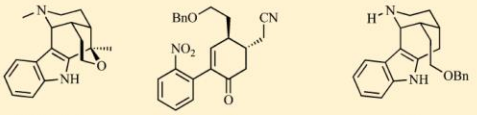
Supporting Information

ABSTRACT: Reductive cyclization of the 2,4,5-trisubstituted cyclohexenone **16** using dihydrogen in the presence of Raney cobalt afforded compound **17** (60%) that could be elaborated over a further five steps, including one involving a cationic cyclization process, into the racemic modification of the unusual uleine alkaloid gilbertine. Single-crystal X-ray analyses of compounds (±)-**1**, **16**, and a derivative of **17** are reported.

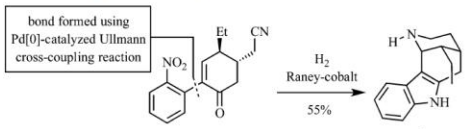


The uleine alkaloid (−)-gilbertine (**1**) was isolated in 1982 by Miranda and Blechert from the Brazilian tree *Aspidosperma gilbertii* (A. P. Duarte).[1] It differs from other, better known members of the class[2] such as the parent compound uleine (**2**), noruleine (**3**), dasycarpidone (**4**), and nordasycarpidone (**5**) by virtue of the presence of an additional, tetrahydropyran-based ring system and a fourth stereogenic center at C16.[3] The unusual pentacyclic framework associated with gilbertine has been the target of various synthetic studies,[4,5] but only one successful (and enantioselective) total synthesis has been reported to date. Thus, in 2004, Jiricek and Blechert reported[4] a cationic cascade cyclization of a tetrahydrocarbazole that successively established the piperidine and tetrahydropyran rings of (−)-gilbertine (Figure 1).

Figure 1. Structures of gilbertine (**1**) and certain simpler uleine alkaloids.

Recently, we reported[2] that when the α-arylated cyclohexeneone **6**, itself prepared through a palladium-catalyzed Ullmann cross-coupling reaction, was treated with dihydrogen in the presence of Raney cobalt[6] then a tandem reductive cyclization process took place (Scheme 1) to afford the tetracyclic indole **7** (55%) that embodies the uleine framework.[7] Through relatively straightforward manipulations, compound **7** was converted into the racemic modifications of alkaloids **2**−**5**. Herein, we describe the extension of these protocols to the synthesis of (±)-gilbertine and report the first single-crystal X-ray analysis of this molecular framework.

Scheme 1. Pivotal Tandem Reductive Cyclization Reaction Used To Prepare the Simpler Uleine Alkaloids 2−5



Inspired by the closing stages of the Jiricek−Blechert synthesis,[4] we envisaged that the tetrahydropyran ring of gilbertine could be formed through intramolecular nucleophilic attack of a C23 hydroxyl group onto a tertiary carbocation formed at C16 (see Figure 1 for the numbering scheme) within the uleine framework. Accordingly, the key subtarget associated with the present study was a protected form of the β-hydroxyethyl analogue of compound **6**. The synthesis of such a system is shown in Scheme 2 and involved initial alkylation of the ketone enolate derived from commercially available 3-ethyoxy-2-cyclohexen-1-one (**8**) with the benzyl ether of 2-iodoethanol.[8] Product **9** (50%) was reduced with lithium aluminum hydride, and the resulting allylic alcohol was subjected to acidic workup, thus providing the γ-substituted cyclohexenone **10** (75%). Nucleophilic cyclopropanation of this last compound using the Corey−Chaykovsky ylide[9] then afforded, in a highly diastereoselective manner,[10] the bicyclo[4.1.0]heptanone **11** (81%) that on treatment with sodium iodide in formic acid engaged in a homoconjugate addition reaction[2] to afford the *trans*-3,4-disubstituted cyclohexanone **12** in 82% yield. As with our earlier study,[2] a three-stage but operationally simple conversion of iodide **12** into nitrile **13** was required in order to prevent the former

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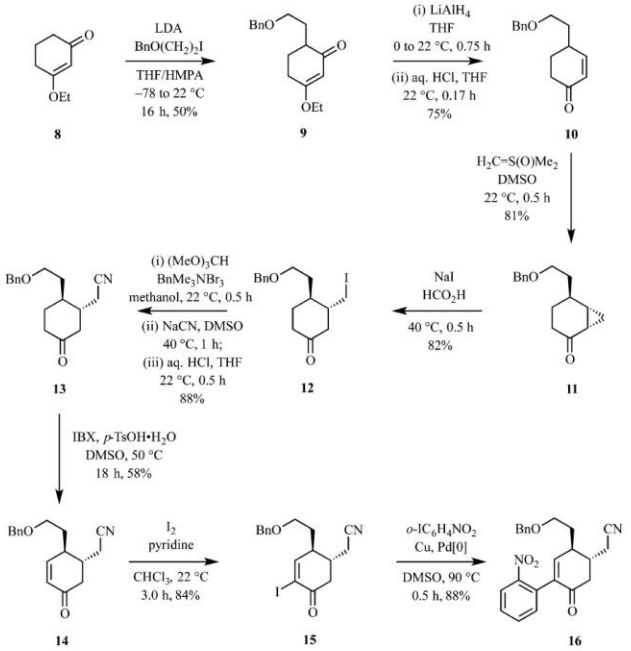
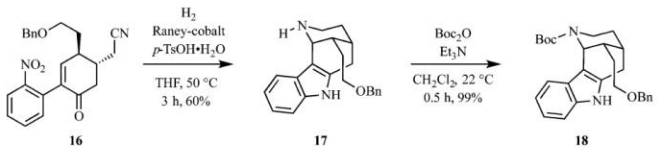
Scheme 2. Synthesis of the Substrate Required for the Tandem Reductive Cyclization Reaction



Scheme 3. Tandem Reductive Cyclization Reaction



compound from engaging in a 3-(enol-*exo*)-*exo*-*tet* cyclization reaction, thereby re-forming cyclopropane **11**. Specifically, then, cyclohexanone **12** was treated with trimethyl orthoformate and benzyltrimethylammonium tribromide, thus generating the dimethyl ketal that was immediately reacted with sodium cyanide in DMSO. The ketal residue associated with the product nitrile was cleaved using aqueous HCl in THF and the cyclohexanone **13** thereby obtained in 88% over the three steps involved. A modestly regioselective dehydrogenation of this last compound was achieved using 2-iodoxybenzoic acid (IBX) in the presence of *p*-TsOH·H_2O,[11] and the product cyclohexenone **14** (58%) was subjected to a Johnson-type α-iodination reaction[12] using molecular iodine in the presence of pyridine. Compound **15** (84%) thus formed was engaged in a palladium(0)-catalyzed Ullmann cross-coupling reaction[13] with *o*-iodonitrobenzene, and the targeted substrate, **16**, required for the pivotal reductive cyclization reaction, was obtained in 88% yield. All of the spectral data acquired on compound **16** were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis, details of which are provided in the Experimental Section and the Supporting Information.

When compound **16** was exposed to dihydrogen in the presence of Raney cobalt[6] and *p*-TsOH·H_2O (Scheme 3), the anticipated reductive cyclization reaction took place, delivering tetracycle **17** in 60% yield. No hydrogenolytic cleavage of the associated benzyl ether moiety was observed, thus further emphasizing the chemoselectivity of reductions involving this catalyst system. Given the nature of the closing steps of the planned synthesis, the piperidine nitrogen within product **17** was protected, under standard conditions, as the corresponding *tert*-butyl carbamate **18** (99%). While the interpretation of the NMR spectral data recorded on compound **18** was complicated by the presence of carbamate rotamers,[14] its structure was confirmed through a single-crystal X-ray analysis.

The completion of the synthesis of (±)-gilbertine proved straightforward and involved (Scheme 4) the pyridinium chlorochromate (PCC) mediated oxidation of compound **18** to the corresponding ketone **19** (57%),[2] the benzyl ether moiety of which was cleaved using dihydrogen in the presence of 10% palladium on carbon and thus affording alcohol **20**

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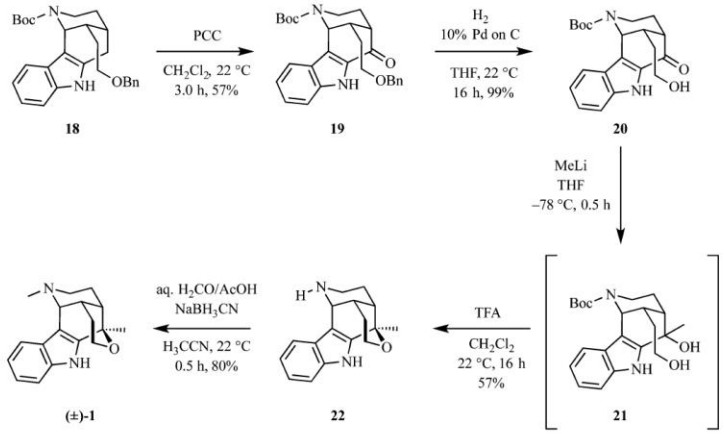
Scheme 4. Completion of the Synthesis of (±)-Gilbertine



(99%). Treatment of this last compound with an excess of methyllithium presumably resulted in the formation of the required C16-centered tertiary alcohol **21** (or an anionic form thereof), but this was not isolated. Rather, the reaction mixture was quenched with trifluoroacetic acid (TFA), and this resulted not only in the desired cationic cyclization process to form the required tetrahydropyran ring but also in cleavage of the Boc group, thereby producing (±)-norgilbertine (**22**) (57%). Reductive methylation of this last compound using formaldehyde in the presence of sodium cyanoborohydride then gave (±)-gilbertine [(±)-**1**] as a crystalline solid. All of the derived spectral data matched those reported[1,3] for both the natural product and previously synthesized material (see the Supporting Information for relevant comparisons of the ^{13}C NMR data sets). A single-crystal X-ray analysis of this last compound could also be obtained, details of which are provided in the Experimental Section and the SI.

The work detailed above serves to emphasize the utility of the Raney cobalt-mediated reductive cyclization protocol as a means for assembling the uleine framework. Given that an enantiomerically enriched form of enone **10** can be obtained through desymmetrization of the corresponding and prochiral cyclohexanone using Koga–Simpkins bases,[15] the present work is also likely to provide access to either enantiomeric form of gilbertine.

■ EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^1H) 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. 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 ^1H and ^{13}C NMR spectra, respectively. ^1H NMR data are presented 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. Infrared spectra (ν_{max}) were recorded on an 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 (concd)/water (37.5 g:7.5 g:37.5 g:720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL)), *p*-anisaldehyde or vanillin/sulfuric acid (concd)/ethanol (15 g:2.5 mL:250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[16] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[17] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations: *(±)-6-(2-(Benzyloxy)-ethyl)-3-ethoxycyclohex-2-en-1-one (**9**).* A magnetically stirred solution of diisopropylamine (4.2 mL, 0.03 mol) in THF (15 mL) maintained under an atmosphere of nitrogen was cooled to −78 °C before being treated with *n*-BuLi (16.0 mL, 1.6 M in hexanes, 0.025 mol). The resulting solution was stirred at −78 °C for 0.17 h, warmed to 22 °C, and stirred at this temperature for 0.33 h. The ensuing mixture was treated with enone **8** (3.0 g, 0.02 mol), and stirring continued for 0.5 h before a solution of 1-(benzyloxy)-2-iodoethane[8] (6.8 g, 0.03 mol) in HMPA (6 mL) was added dropwise. The solution thus formed was stirred at room temperature for 16 h and then quenched with water (15 mL), and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil so formed was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/petroleum ether) afforded the title compound **9** (2.9 g, 50%) as a clear, light-yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.21 (complex m, 5H), 5.33 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.90 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 2.51–2.34 (complex m, 3H), 2.32–2.24 (complex m, 1H), 2.14–2.06 (complex m, 1H), 1.79–1.69 (complex m, 1H), 1.65–1.57 (complex m, 1H), 1.37 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3, 176.8, 138.6, 128.3, 127.6, 127.5, 102.2, 72.8, 68.4, 64.2, 42.5, 29.7, 28.4, 26.9, 14.2; IR ν_{max} 2938, 2863, 1650, 1604, 1378,

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1358, 1187, 1097, 736, 697 cm^{-1}; MS (ESI, +ve) m/z 297 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{22}NaO_3$ 297.1467, found 297.1469.

*(±)-4-(2-(Benzyloxy)ethyl)cyclohex-2-en-1-one (**10**).* A magnetically stirred solution of compound **9** (360 mg, 1.31 mmol) in THF (10 mL) maintained under a nitrogen atmosphere was cooled to 0 °C and then treated with $LiAlH_4$ (1.30 mL of a 1.0 M solution in THF, 1.30 mmol). The resulting mixture was stirred at 0 °C for 0.17 h and then warmed to room temperature, and stirring was continued at this temperature for another 0.5 h. After this time, the reaction mixture was quenched with water (4 mL), and then sufficient HCl (1 M aqueous solution) was added to attain a pH of 1−2. The solution thus obtained was stirred vigorously at room temperature for 0.17 h and then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/petroleum ether) afforded the title compound **10** (230 mg, 75%) as a clear, colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.29 (complex m, 5H), 6.90 (dm, J = 10.2 Hz, 1H), 6.00 (dm, J = 10.2 Hz, 1H), 4.55 (s, 2H), 3.73−3.46 (complex m, 2H), 2.71−2.63 (complex m, 1H), 2.51 (dt, J = 16.8 and 4.9 Hz, 1H), 2.38 (m, 1H), 2.17−2.09 (complex m, 1H), 1.91−1.83 (complex m, 1H), 1.79−1.63 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 154.9, 138.2, 129.0, 128.5, 127.7(3), 127.6(6), 73.1, 67.4, 36.9, 34.5, 33.3, 28.6; IR ν_{max} 3320, 3030, 2927, 2862, 1674, 1453, 1390, 1254, 1210, 1097, 739, 658 cm^{-1}; MS (ESI, +ve) m/z 253 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{15}H_{18}NaO_2$ 253.1204, found 253.1208.

*rac-(1S,5S,6S)-5-(2-(Benzyloxy)ethyl)bicyclo[4.1.0]heptan-2-one (**11**).* A magnetically stirred suspension of NaH (41 mg, 1.7 mmol) in dry DMSO (10 mL) was treated with Me_3SOI (224 mg, 1.0 mmol) and after being maintained at room temperature for 0.17 h the reaction mixture was warmed to 50 °C and stirred at this temperature for a further 0.34 h. The cooled reaction mixture was treated with enone **10** (213 mg, 0.9 mmol) and then stirred at room temperature for 0.5 h before being quenched with water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.4 in 1:7 v/v ethyl acetate/petroleum ether) afforded the title compound **11** (183 mg, 81%) as a clear, colorless oil containing ca. 15% of an impurity assumed to be the diastereoisomeric cyclopropane: ^1H NMR ($CDCl_3$, 400 MHz) δ (major product) 7.33−7.17 (complex m, 5H), 4.45 (s, 2H), 3.52 (broadened t, J = 6.3 Hz, 2H), 2.22−2.13 (complex m, 1H), 2.09 (dd, J = 8.3 and 5.8 Hz, 2H), 1.81−1.41 (complex m, 6H), 1.19−1.05 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major product) 209.5, 138.4, 128.4, 127.6(2), 127.6(0), 73.0, 68.1, 34.4, 33.1, 28.6, 25.5, 24.1, 24.0, 12.7; IR ν_{max} 3029, 2928, 2861, 1687, 1453, 1353, 1248, 1102, 738, 698 cm^{-1}; MS (ESI, +ve) m/z 267 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{16}H_{20}NaO_2$ 267.1361, found 267.1359.

*rac-(3R,4S)-4-(2-(Benzyloxy)ethyl)-3-(iodomethyl)cyclohexan-1-one (**12**).* A magnetically stirred solution of ketone **11** (1.10 g, 4.5 mmol) and NaI (1.70 g, 11.3 mmol) in formic acid (10 mL) was heated at 40 °C for 0.5 h, cooled to room temperature, and quenched with water (15 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with $NaHCO_3$ (50 mL of a saturated aqueous solution) then brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:15 → 1:5 v/v ethyl acetate/petroleum ether gradient elution) and concentration of relevant fractions (R_f = 0.6 in 1:3 v/v ethyl acetate/petroleum ether) afforded the title compound **12** (1.40 g, 82%) as a clear, yellow oil containing ca. 15% of an impurity assumed to be the *cis*-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ (major product) 7.43−7.27 (complex m, 5H), 4.54 (ABq, J = 10.5 Hz, 2H), 3.60 (t, J = 6.5 Hz, 2H), 3.46 (dd, J = 10.4 and 5.0 Hz, 1H), 3.27 (dd, J = 10.4 and 2.9 Hz, 1H), 2.47−2.24 (complex m, 4H), 2.14−2.07 (complex m, 1H), 2.00−1.92 (complex m, 1H), 1.89−1.77 (complex m, 1H), 1.60−1.45 (complex m, 2H), 1.44−1.34 (complex m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major product) 210.5, 138.3, 128.4, 127.7, 127.6, 73.1, 67.6, 47.2, 42.3, 40.6, 37.5, 31.6, 29.3, 15.0; IR ν_{max} 3029, 2935, 2862, 1713, 1453, 1425, 1359, 1317, 1265, 1218, 1177, 1099, 738, 698 cm^{-1}; MS (ESI, +ve) m/z 395 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{16}H_{21}INaO_2$ 395.0484, found 395.0486.

*rac-2-((1R,2S)-2-(2-(Benzyloxy)ethyl)-5-oxocyclohexyl)acetonitrile (**13**). Step i.* A magnetically stirred solution of iodide **12** (1.40 g, 3.8 mmol) in anhydrous MeOH (10 mL) was treated with trimethyl orthoformate (1.80 mL, 5.7 mmol) and benzyltrimethylammonium tribromide (32 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 0.5 h, quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil, presumed to contain the dimethyl ketal of compound **12**, was immediately subjected to the reaction conditions defined in step ii.

Step ii. A magnetically stirred solution of crude material obtained from step i in DMSO (6 mL) was treated with KCN (366 mg, 5.6 mmol). The resulting solution was stirred at 40 °C for 1 h, quenched with water (15 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were concentrated under reduced pressure, and the yellow oil thus obtained, and presumed to contain the dimethyl ketal of compound **12**, was immediately subjected to the reaction conditions defined in step iii.

Step iii. A magnetically stirred solution of the oil obtained from step ii in THF (10 mL) was treated with HCl (5 mL of a 1 M aqueous solution) and the resulting mixture stirred at room temperature for 0.5 h before being quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution) and then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.3 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **13** (880 mg, 88%) as a white solid: mp = 60−63 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.29 (complex m, 5H), 4.53 (ABq, J = 10.0 Hz, 2H), 3.65−3.49 (complex m, 2H), 2.63 (dd, J = 17.1 and 6.2 Hz, 1H), 2.53 (m, 1H), 2.49−2.32 (complex m, 4H), 2.15−2.08 (complex m, 1H), 2.06−1.87 (complex m, 3H), 1.66−1.46 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.0, 138.1, 128.5, 127.8, 127.7, 117.4, 73.2, 67.3, 45.7, 40.3, 39.0, 36.7, 32.0, 29.8, 22.2; IR ν_{max} 2855, 2245, 1713, 1454, 1424, 1361, 1200, 1098, 739, 699 cm^{-1}; MS (ESI, +ve) m/z 294 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{21}NNaO_2$ 294.1470, found 294.1464

*rac-2-((1R,2S)-2-(2-(Benzyloxy)ethyl)-5-oxocyclohex-3-en-1-yl)-acetonitrile (**14**).* A magnetically stirred solution of ketone **13** (680 mg, 2.5 mmol) in DMSO (10 mL) was treated with *p*-TsOH·H_2O (143 mg, 0.8 mmol) and IBX (1.02 g, 3.6 mmol) and then heated at 55 °C for 18 h. The cooled reaction mixture was quenched with $NaHCO_3$ (15 mL of a saturated aqueous solution) and then filtered through a pad of diatomaceous earth. The solids thus retained were washed with ethyl acetate (3 × 20 mL), and the separated aqueous phase associated with the filtrate was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine (1 × 50 mL) and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:3 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.2 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **14** (389 mg, 58%) as a clear, colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.20 (complex m, 5H), 6.78 (dd, J = 10.2 and 3.3 Hz, 1H), 5.97 (dd, J = 10.2 and 2.3 Hz, 1H), 4.43 (broadened s, 2H), 3.52 (m, 2H), 2.66−2.24 (complex m, 6H), 1.96−1.69 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 152.2, 137.8, 129.1, 128.5, 127.9, 127.7,

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117.5, 73.3, 67.1, 41.4, 37.7, 35.8, 31.9, 21.7; IR ν_{max} 3032, 2863, 2246, 1676, 1454, 1421, 1391, 1355, 1251, 1095, 740, 699 cm^{-1}; MS (ESI, +ve) m/z 292 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{19}NNaO_2$ 292.1313, found 292.1310.

*rac-2-((1R,2S)-2-(2-(Benzyloxy)ethyl)-4-iodo-5-oxocyclohex-3-en-1-yl)acetonitrile (**15**).* A magnetically stirred solution of enone **14** (300 mg, 1.1 mmol) in $CHCl_3$/pyridine (4 mL of a 1:1 v/v mixture) maintained at room temperature was treated, dropwise, with a solution of molecular iodine (1.0 g, 3.6 mmol) in $CHCl_3$/pyridine (15 mL of a 1:1 v/v mixture). The solution thus obtained was stirred at room temperature for 3 h and then treated with water (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed, sequentially, with HCl (1 × 20 mL of a 1 M aqueous solution), $Na_2S_2O_3$ (1 × 20 mL of a 10% w/v aqueous solution), and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:6 → 1:3 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.3 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **15** (370 mg, 84%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 3.3 Hz, 1H), 7.48−7.30 (complex m, 5H), 4.53 (ABq, J = 10.1 Hz, 2H), 3.62 (m, 2H), 2.90 (dd, J = 16.3 and 4.0 Hz, 1H), 2.80−2.74 (complex m, 1H), 2.68−2.40 (complex m, 4H), 2.06−1.81 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.0, 160.8, 137.7, 128.6, 128.0, 127.8, 117.1, 102.6, 73.4, 66.8, 42.2, 40.4, 35.9, 31.5, 21.5; IR ν_{max} 3030, 2922, 2861, 2245, 1682, 1588, 1453, 1418, 1362, 1329, 1098, 738, 698 cm^{-1}; MS (ESI, +ve) m/z 418 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{18}INNaO_2$ 418.0280, found 418.0279.

*rac-2-((4R,5S)-5-(2-(Benzyloxy)ethyl)-2′-nitro-2-oxo-2,3,4,5-tetrahydro[1,1′-biphenyl]-4-yl)acetonitrile (**16**).* A magnetically stirred solution of iodide **15** (300 mg, 0.76 mmol) and *o*-iodonitrobenzene (378 mg, 1.5 mmol) in DMSO (5 mL) was treated with $Pd_2(dba)_3$ (55 mg, 0.06 mmol) and Cu powder (195 mg, 3.1 g.atom). The resulting mixture was heated at 90 °C for 0.5 h before being cooled to room temperature and then diluted with ethyl acetate (10 mL). The ensuing mixture was filtered through diatomaceous earth and the solids thus retained washed with ethyl acetate (3 × 10 mL). The combined filtrates were washed with water (2 × 30 mL) and the combined aqueous phases extracted with ethyl acetate (3 × 30 mL). The combined organic phases were themselves washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:4 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.2 in 1:2 v/v ethyl acetate/petroleum ether) gave the title compound **16** (261 mg, 88%) as a yellow, crystalline solid: mp = 74−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, J = 7.9 and 1.5 Hz, 1H), 7.61−7.47 (complex m, 2H), 7.41−7.29 (complex m, 5H), 7.13 (dd, J = 7.3 and 1.7 Hz, 1H), 6.91 (d, J = 3.9 Hz, 1H), 4.55 (ABq, J = 10.5 Hz, 2H), 3.69 (t, J = 5.7 Hz, 2H), 2.92 (broad s, 1H), 2.87−2.77 (complex m, 1H), 2.72−2.54 (complex m, 4H), 2.15−1.94 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7, 148.5, 148.1, 138.6, 137.8, 133.5, 131.6, 131.2, 129.1, 128.5, 127.9, 124.4, 117.7, 73.4, 67.4, 41.1, 38.3, 35.6, 32.4, 21.7 (one signal obscured or overlapping); IR ν_{max} 3031, 2923, 2862, 2245, 1679, 1523, 1351, 1100, 854, 739, 699 cm^{-1}; MS (ESI, +ve) m/z 413 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{23}H_{22}N_2NaO_4$ 413.1477, found 413.1481.

*rac-(1R,5R,12S)-12-(2-(Benzyloxy)ethyl)-2,3,4,5,6,7-hexahydro-1H-1,5-methanoazocino[4,3-b]indole (**17**).* A magnetically stirred mixture of nitrile **16** (310 mg, 0.79 mmol), *p*-TsOH·H_2O (747 mg, 4.0 mmol), and Raney cobalt (620 mg, 200% w/w) in THF (15 mL) and maintained under dihydrogen was heated at 50 °C for 3 h. The resulting mixture was cooled to room temperature and filtered through diatomaceous earth, and the solids thus retained washed with methanol (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a pale-yellow oil that was subjected to flash chromatography (silica, 1:20 → 1:10 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.4 in 1:7 v/v methanol/dichloromethane) afforded the title compound **17** (165 mg, 60%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.29−7.19 (complex m, 6H), 7.11−6.95 (complex m, 2H), 4.39 (s, 2H), 4.23 (s, 1H), 3.43 (m, 2H), 2.93 (dd, J = 17.5 and 6.6 Hz, 1H), 2.66−2.36 (complex m, 3H), 2.31−2.14 (complex m, 3H), 1.99−1.79 (complex m, 1H), 1.62−1.48 (complex m, 1H), 1.46−1.38 (complex m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 136.3, 135.8, 128.3, 127.7, 127.5, 126.8, 121.1, 119.4, 117.4, 110.6, 107.4, 72.9, 68.6, 49.0, 39.0, 37.0, 34.1, 31.3, 30.4, 25.7; IR ν_{max} 3190, 3054, 2916, 2854, 1618, 1453, 1362, 1236, 1094, 1073, 735, 697 cm^{-1}; MS (ESI, +ve) m/z 347 [$(M + H)^+$, 100]; HRMS $(M + H)^+$ calcd for $C_{23}H_{27}N_2O$ 347.2123, found 347.2122.

*tert-Butyl rac-(1R,5R,12S)-12-(2-(Benzyloxy)ethyl)-1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b]indole-2-carboxylate (**18**).* A magnetically stirred solution of secondary amine **17** (100 mg, 0.29 mmol) in dichloromethane (5 mL) was treated with Boc_2O (76 mg, 0.35 mmol) and triethylamine (121 μL, 0.87 mmol). The ensuing mixture was stirred at room temperature for 0.5 h, quenched with water (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:3 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.6 in 1:1 v/v ethyl acetate/petroleum ether) afforded the title compound **18** (129 mg, 99%) as a white, crystalline solid and a ca. 1:1 mixture of rotamers: mp = 148−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (broad s, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.41−7.27 (complex m, 6H), 7.13 (m, 2H), 5.50 (s, 1H), 4.51 (q, J = 11.9 Hz, 2H), 3.77 (m, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.06 (dd, J = 17.5 and 6.6 Hz, 1H), 2.62 (m, 2H), 2.32 (broad s, 1H), 2.24 (m, 1H), 1.94 (m, 1H), 1.74−1.58 (complex m, 3H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1, 154.7, 138.5, 136.4, 136.2(4), 136.2(1), 135.4, 128.5, 128.4, 127.7, 127.6(3), 127.6(0), 127.5(5), 127.0, 126.2, 121.3, 119.5, 119.4, 118.1, 110.6, 110.4, 107.2, 79.4, 79.3, 73.1(0), 73.0(6), 68.5, 68.2, 46.3, 38.6, 36.6, 35.7, 33.3, 30.8, 30.7, 30.4, 29.8, 28.7, 28.6, 28.6, 28.5, 26.7, 25.2; IR ν_{max} 3300, 2975, 2928, 2868, 1659, 1454, 1415, 1355, 1168, 1115, 740, 698 cm^{-1}; MS (ESI, +ve) m/z 469 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{28}H_{34}N_2NaO_3$ 469.2467, found 469.2470.

*tert-Butyl rac-(1R,5S,12S)-12-(2-(Benzyloxy)ethyl)-6-oxo-1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b]indole-2-carboxylate (**19**).* A magnetically stirred solution of compound **18** (80 mg, 0.18 mmol) in dichloromethane (5 mL) was treated with pyridinium chlorochromate (96 mg, 0.45 mmol) and the ensuing mixture stirred at room temperature for 3 h and then quenched with 2-propanol (3 mL). The resulting mixture was treated with water (15 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate/petroleum ether gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:2 v/v ethyl acetate/petroleum ether) afforded the title compound **19** (47 mg, 57%) as a clear, yellow oil and a ca. 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.03 (m, 1H), 7.84 (d, J = 8.2 Hz, 0.5H), 7.69 (d, J = 8.1 Hz, 0.5H), 7.43−7.18 (complex m, 7H), 7.11 (m, 1H), 5.75 (s, 0.5H), 5.62 (s, 0.5H), 4.54−4.28 (complex m, 2H), 3.88 (m, 0.5H), 3.69 (m, 0.5H), 3.44 (t, J = 6.2 Hz, 2H), 2.70 (broad s, 1H), 2.63−2.53 (complex m, 1H), 2.44 (broad s, 1H), 2.06−1.75 (complex m, 2H), 1.60 (m, 2H), 1.51 (s, 4.5H), 1.35 (s, 4.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.4, 154.9, 154.2, 138.3, 132.3, 128.4, 127.6, 127.4, 125.4, 125.3, 122.8, 121.8, 121.1, 112.7, 112.3, 80.4, 79.9, 73.1, 67.8, 48.3, 47.1, 46.6, 43.6, 43.1, 36.8, 35.6, 32.0, 30.1, 28.6, 28.4; IR ν_{max} 3257, 2975, 2930, 2862, 1655, 1470, 1407, 1356, 1276, 1253, 1152, 1117, 746, 734 cm^{-1}; MS (ESI, +ve) m/z 483 [$(M + Na)^+$, 100]; HRMS $(M + Na)^+$ calcd for $C_{28}H_{32}N_2NaO_4$ 483.2260, found 483.2257.

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*tert-Butyl (1R,5S,12S)-12-(2-Hydroxyethyl)-6-oxo-1,3,4,5,6,7-hexahydro-2H-1,5-methanoazocino[4,3-b]indole-2-carboxylate (**20**).* A magnetically stirred solution of compound **19** (35 mg, 0.08 mmol) in THF (8 mL) was treated with Pd/C (3.5 mg of 10% w/w material). The resulting mixture was stirred at room temperature for 16 h under an atmosphere of dihydrogen and then filtered through diatomaceous earth, and the solids thus retained were washed with ethyl acetate (3 × 15 mL). The combined filtrates were concentrated under reduced pressure to afford a light yellow oil that was subjected to flash chromatography (silica, 1:4 → 1:2 v/v ethyl acetate/petroleum ether gradient elution). Concentration of the relevant fractions (R_f = 0.1 in 1:1 v/v ethyl acetate/petroleum ether) afforded the title compound **20** (28 mg, 99%) as a clear, yellow oil and a ca. 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (broad s, 1H), 7.83 (broad s, 0.5H), 7.71 (broad s, 0.5H), 7.46−7.26 (complex m, 2H), 7.12 (m, 1H), 5.74 (broad s, 0.5H), 5.58 (broad s, 0.5H), 3.87 (broad s, 0.5H), 3.72−3.60 (complex m, 2.5H), 2.74 (broad s, 1H), 2.59 (broad s, 1H), 2.44 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.60 (m, 2H), 1.53 (m, 4.5H), 1.35 (s, 4.5H) (signal due to hydroxyl group proton not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.7, 155.0, 154.2, 138.6, 132.3, 127.4, 125.3, 122.9, 122.6, 121.7, 121.2, 112.8, 112.5, 80.2, 60.3, 48.5, 46.8, 43.2, 42.7, 36.8, 35.5, 34.8, 30.1, 28.5, 28.4; IR ν_{max} 3274, 2923, 2853, 1653, 1409, 1366, 1277, 1252, 1150, 1013, 746 cm^{-1}; MS (ESI, +ve) *m*/*z* 393 [(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{21}H_{26}N_2NaO_4$ 393.1790, found 393.1790.

*rac-(1R,5S,6R,15S)-1-Methyl-1,3,4,5,6,11-hexahydro-6,1,5-(epiminopropane[1,3,3]triyl)oxocino[3,4-b]indole (**22**). Step i.* A magnetically stirred solution of ketone **20** (25 mg, 0.07 mmol) in THF (4 mL) was cooled to −78 °C and then treated with methyllithium (135 μL of a 3.0 M solution in diethoxymethane). The resulting mixture was stirred at −78 °C for 0.5 h and then quenched with water (15 mL). After the resulting mixture was warmed to room temperature, the aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil, presumed to contain the anticipated *tert*-alcohol, was subjected to the step ii of the reaction sequence as described immediately below.

Step ii. A magnetically stirred solution of the yellow oil obtained from step i in dichloromethane (4 mL) was treated with trifluoroacetic acid (26 μL, 0.35 mmol). The resulting mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 1:20 → 1:10 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.4 in 1:3 v/v methanol/dichloromethane) afforded the title compound **22** (10.3 mg, 57%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 800 MHz) δ 8.15 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.23 (m, 1H), 7.17 (m, 1H), 4.43 (broad s, 1H), 3.47 (m, 1H), 2.91 (m, 1H), 2.60 (broad s, 1H), 2.50 (broad s, 1H), 2.44 (broad s, 1H), 2.12 (broad s, 1H), 2.03 (m, 1H), 1.91−1.79 (complex m, 2H), 1.70−1.67 (complex m, 1H), 1.67 (s, 3H), 1.54 (dd, *J* = 13.9 and 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 136.6, 134.8, 124.8, 122.8, 120.2, 119.1, 111.4, 70.7, 60.3, 50.0, 41.5, 36.5, 36.4, 29.5, 26.4, 22.3 (signal due to one carbon obscured or overlapping); IR ν_{max} 3259, 2930, 1454, 1382, 1323, 1306, 1037, 1070, 912, 876, 830, 731 cm^{-1}; MS (ESI, +ve) *m*/*z* 269 [(M + H)$^+$, 65], 252 (100); HRMS (M + H)$^+$ calcd for $C_{17}H_{21}N_2O$ 269.1654, found 269.1656.

*rac-(1R,5S,6R,15S)-1,12-Dimethyl-1,3,4,5,6,11-hexahydro-6,1,5-(epiminopropane[1,3,3]triyl)oxocino[3,4-b]indole [(±)-**1**].* A magnetically stirred solution of the secondary amine **22** (10 mg, 0.04 mmol) in acetonitrile (4 mL) was treated, sequentially, with formaldehyde (67 μL of a 35% w/v aqueous solution, 0.8 mmol), acetic acid (40 μL of a 30% w/v aqueous solution, 0.2 mmol), and $NaCNBH_3$ (5 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 0.5 h and then quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:25 → 1:10 v/v methanol/dichloromethane gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v methanol/dichloromethane) afforded the title compound **1** (8.4 mg, 80%) as a light-yellow, crystalline solid: mp = 122−125 °C. ^{1}H NMR ($CDCl_3$, 800 MHz) δ 8.31 (s, 1H), 7.60 (dd, *J* = 7.9 and 1.0 Hz, 1H), 7.40 (dt, *J* = 8.1 and 0.9 Hz, 1H), 7.21 (m, 1H), 7.15 (m, 1H), 4.08 (s, 1H), 3.43 (dd, *J* = 11.7 and 7.6 Hz, 1H), 2.62 (m, 1H), 2.51 (broad s, 1H), 2.40 (broad s, 1H), 2.38 (s, 3H), 2.09−1.88 (complex m, 4H), 1.85 (m, 1H), 1.65 (s, 3H), 1.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 136.3, 135.2, 127.2, 122.4, 120.0, 119.9, 111.3, 108.4, 71.1, 60.6, 57.4, 45.6, 44.3, 40.5, 37.5, 29.5, 26.8, 22.2; IR ν_{max} 3230, 3054, 2930, 1457, 1380, 1324, 1305, 1194, 1083, 1029, 740, 625, 615 cm^{-1}; MS (ESI, +ve) *m*/*z* 283 [(M + H)$^+$, 100]; HRMS (M + H)$^+$ calcd for $C_{18}H_{23}N_2O$ 283.1810, found 283.1807.

Crystallographic Studies. *Crystallographic Data. Compound (±)-**1**:* $C_{18}H_{22}N_2O$, *M* = 282.39, *T* = 150 K, monoclinic, space group $P2_1$, *Z* = 4, *a* = 8.2370(2) Å, *b* = 21.2108(4) Å, *c* = 8.4707(2) Å; β = 98.7489(19)°; *V* = 1462.72(6) Å^3, D_x = 1.282 g cm^{-3}, 5741 unique data ($2\theta_{max}$ = 144.6°), *R* = 0.052 [for 5497 reflections with $I > 2.0\sigma(I)$]; w*R* = 0.137 (all data), *S* = 1.00.

*Compound **16**:* $C_{23}H_{22}N_2O_4$, *M* = 390.44, *T* = 150 K, triclinic, space group $P\bar{1}$, *Z* = 2, *a* = 5.8560(2) Å, *b* = 11.9176(4) Å, *c* = 15.3239(4) Å; α = 109.830(4)°, β = 97.254(3)°, γ = 99.900(3); *V* = 971.19(7) Å^3, D_x = 1.335 g cm^{-3}, 3819 unique data ($2\theta_{max}$ = 144.6°), *R* = 0.041 [for 3382 reflections with $I > 2.0\sigma(I)$]; w*R* = 0.105 (all data), *S* = 0.99.

*Compound **18**:* $C_{28}H_{34}N_2O_3$, *M* = 446.59, *T* = 150 K, monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 10.2934(2) Å, *b* = 10.7138(2) Å, *c* = 22.2707(3) Å; β = 90.0949(14)°; *V* = 2456.04(7) Å^3, D_x = 1.208 g cm^{-3}, 4848 unique data ($2\theta_{max}$ = 144.6°), *R* = 0.038 [for 4609 reflections with $I > 2.0\sigma(I)$]; w*R* = 0.097 (all data), *S* = 1.00.

Structure Determination. Images were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[18] The structure solutions were solved by direct methods (SIR92).[19] The structures of compounds (±)-**1**, **16**, and **18** were refined using the CRYSTALS program package.[20] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1482400, 1482401, and 1482402). 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01424.

Anisotropic displacement ellipsoid plots derived from the single-crystal X-ray analyses of compounds (±)-**1**, **16**, and **18** and ^{1}H and ^{13}C NMR spectra of compounds **9**−**20**, **22**, and (±)-**1** (PDF)

X-ray crystallographic data for (±)-**1** (CIF)

X-ray crystallographic data for **16** (CIF)

X-ray crystallographic data for **18** (CIF)

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Notes

The authors declare no competing financial interest.

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J. Org. Chem. 2016, 81, 10551−10557

SUPPORTING INFORMATION FOR:

A Raney-Cobalt-Mediated Reductive Cyclization Route to the Uleine Alkaloid Gilbertine

Fei Tang, Martin G. Banwell* and Anthony C. Willis

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

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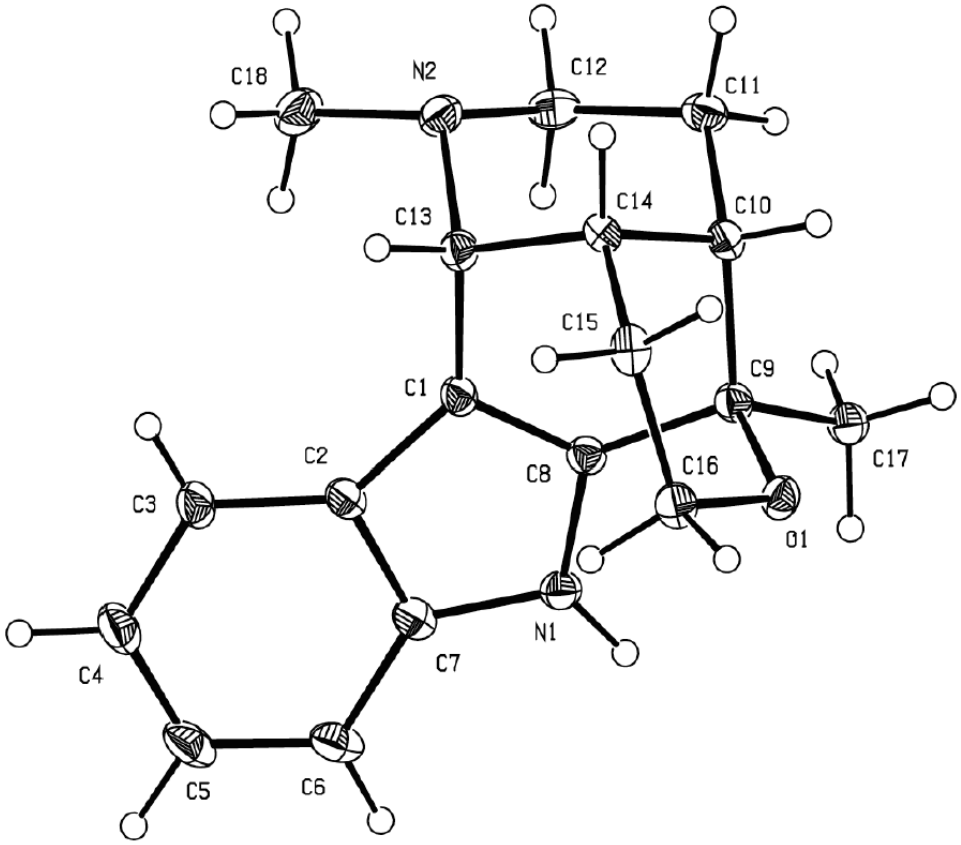


Figure S1: Structure of compound (±)-**1** (CCDC 1482400) with labeling of selected atoms. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

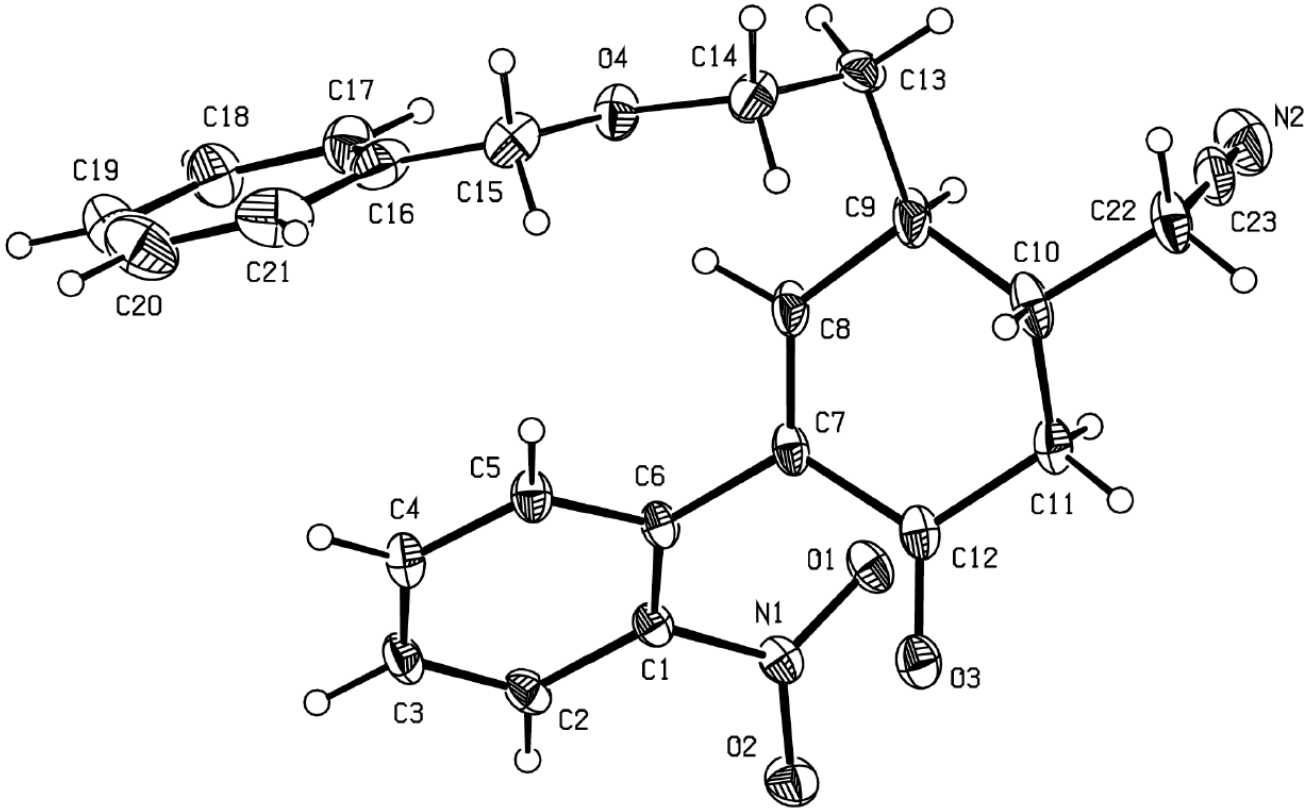


Figure S2: Structure of compound **16** (CCDC 1482401) with labeling of selected atoms showing only the major sites of disordered atoms (C13, C14, O4, C15: occupancy 0.55). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

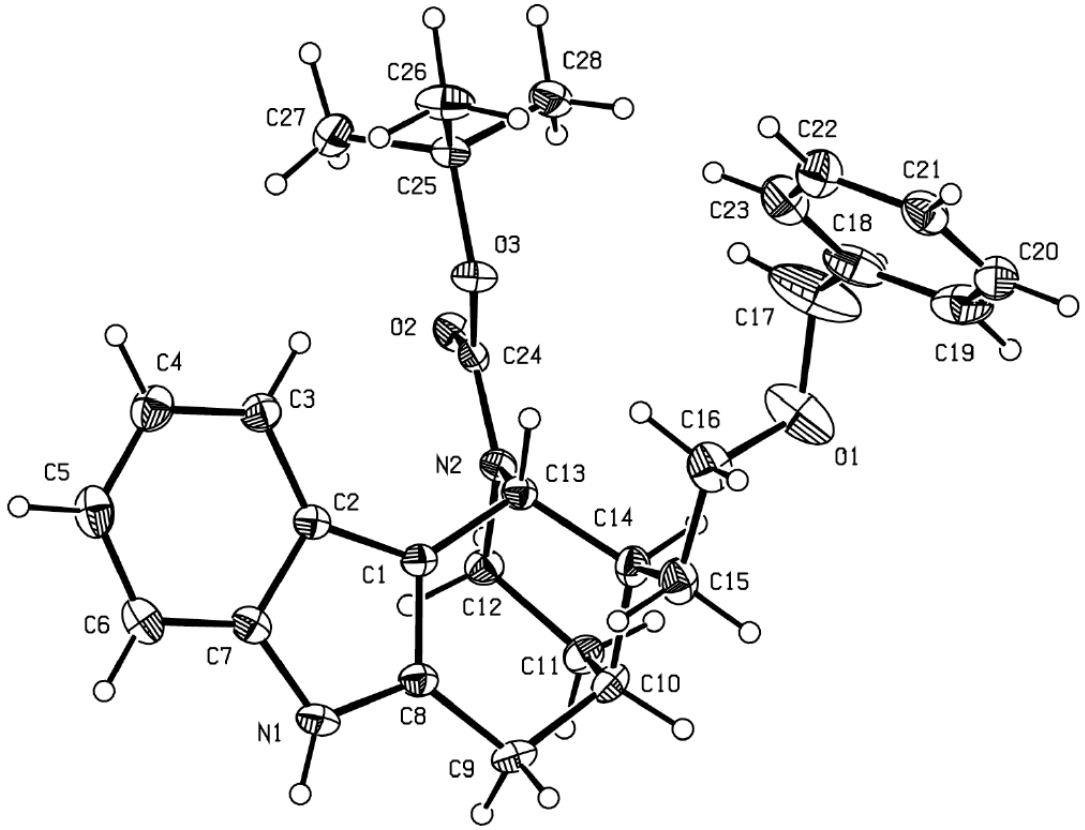
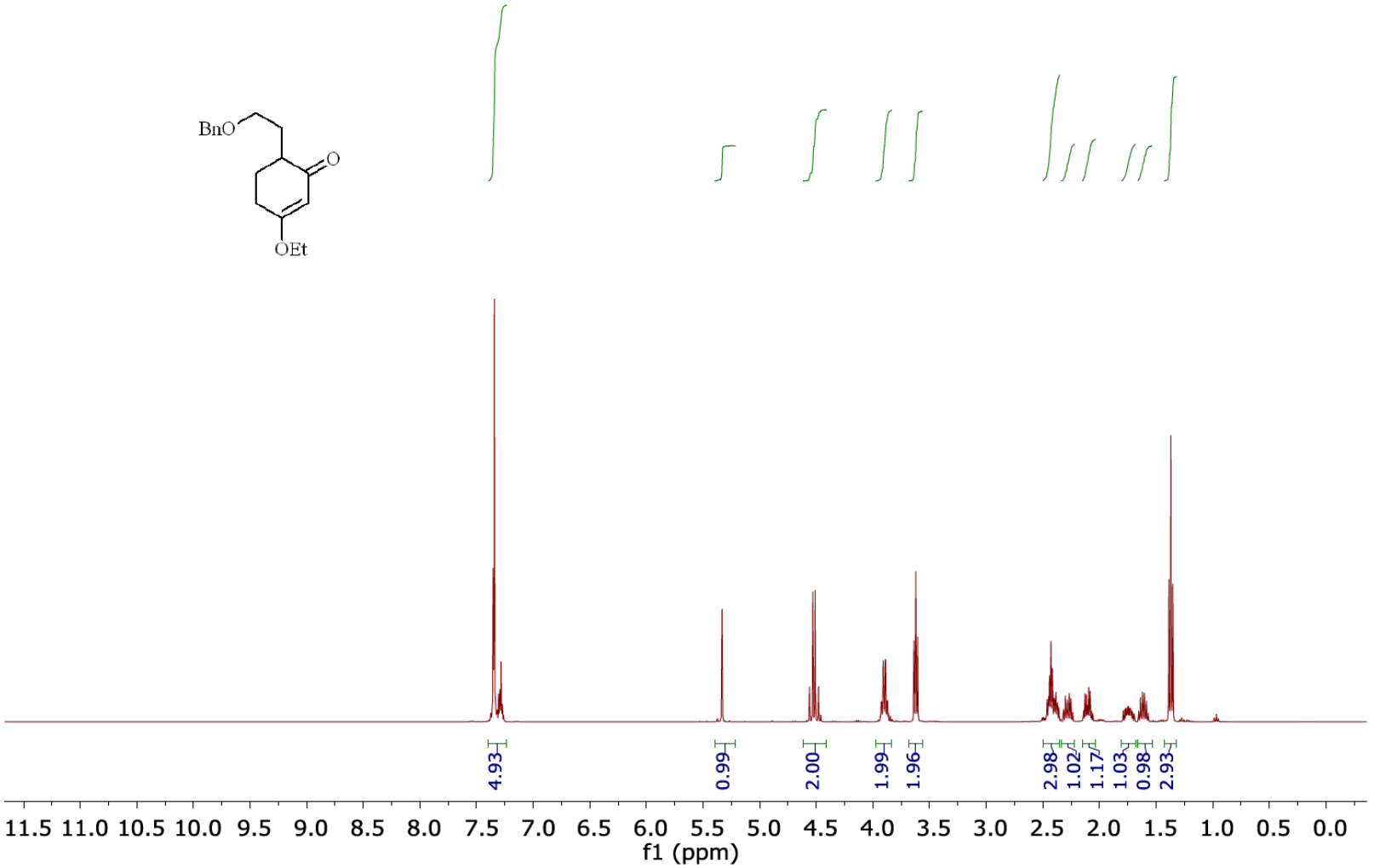


Figure S3: Structure of compound **18** (CCDC 1482402) with labeling of selected atoms Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

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

(recorded in $CDCl_3$)



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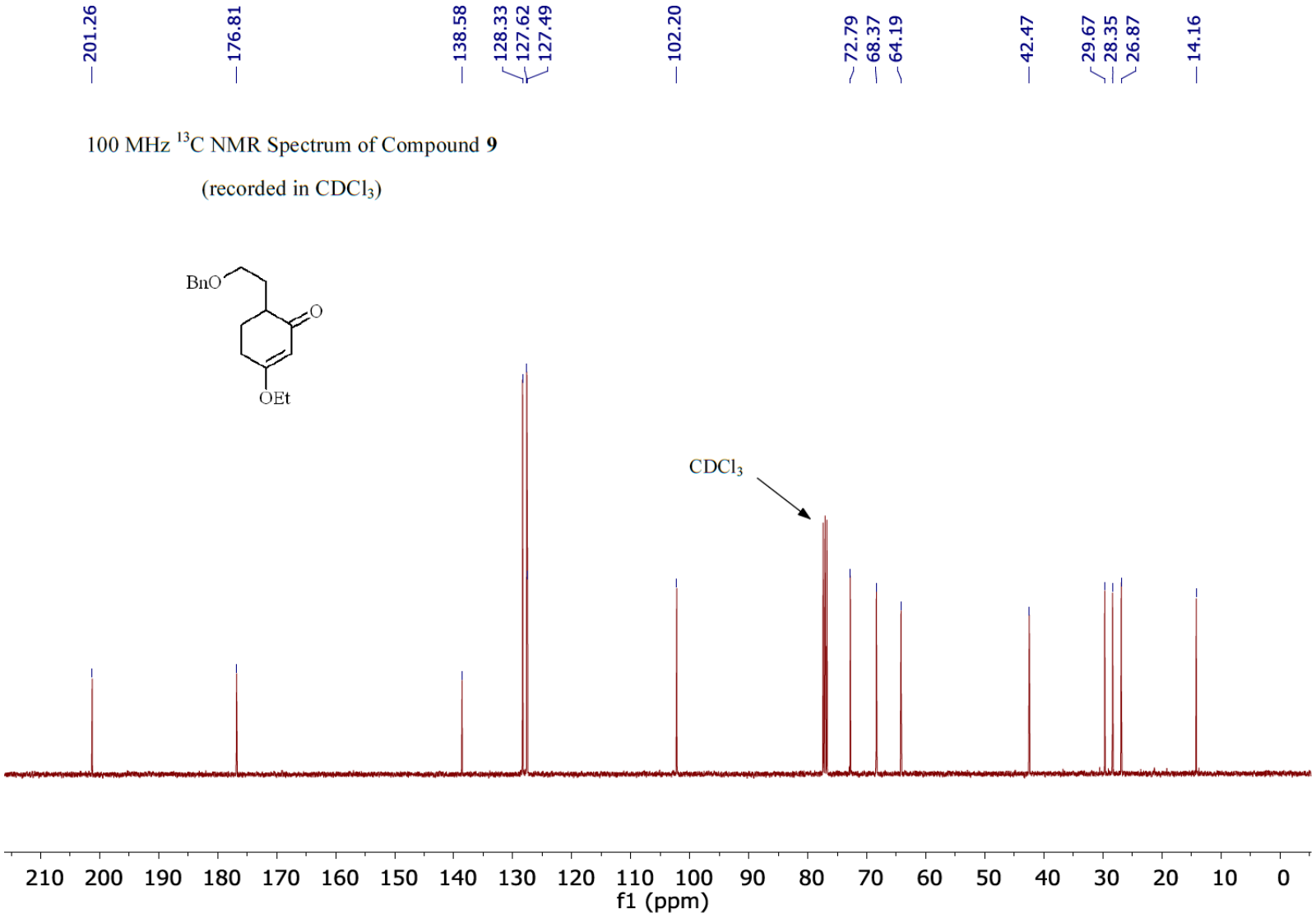


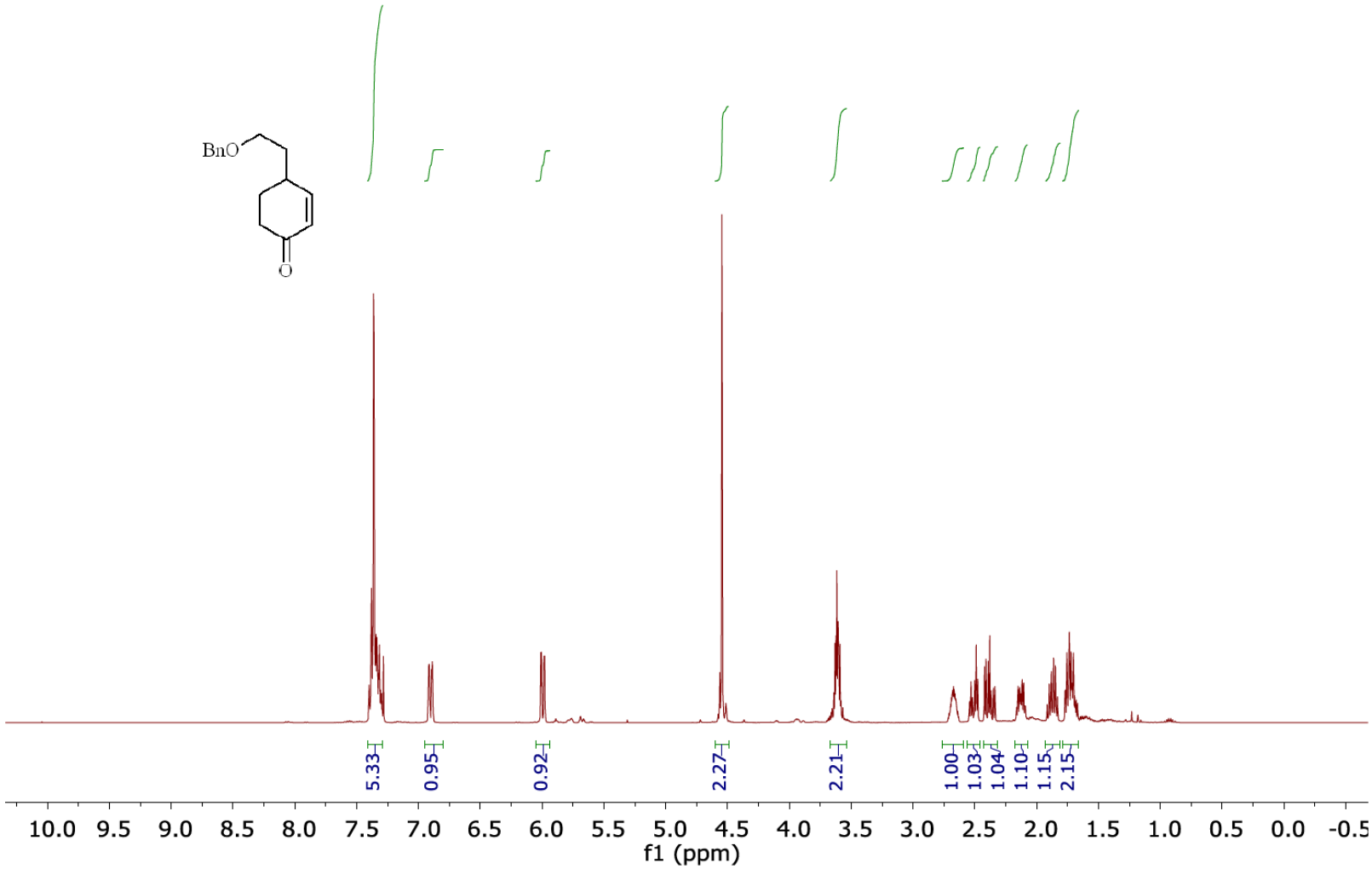
100 MHz ^{13}C NMR Spectrum of Compound **9**

(recorded in $CDCl_3$)

77

400 MHz ^{1}H NMR Spectrum of Compound **10**

(recorded in $CDCl_3$)



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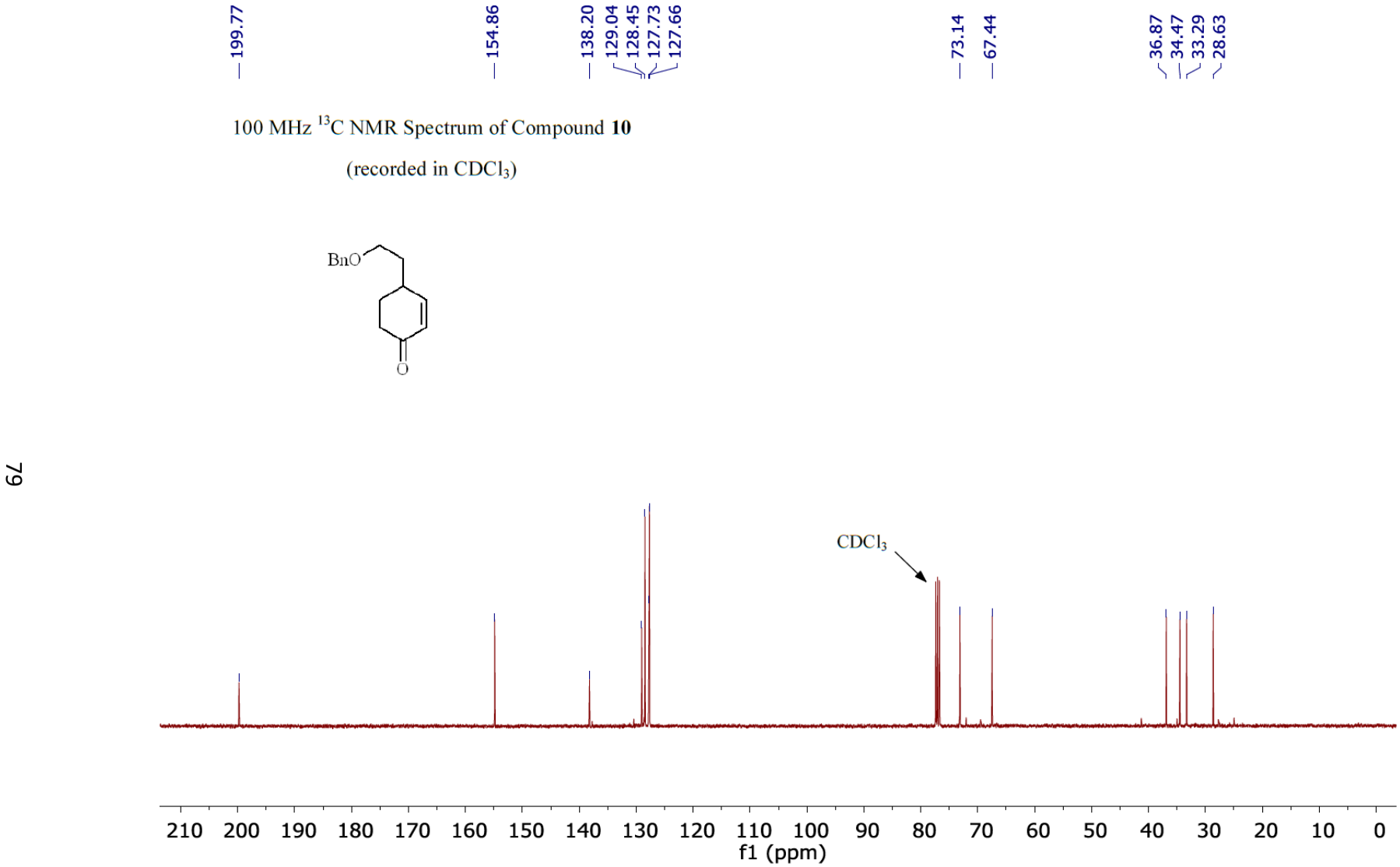


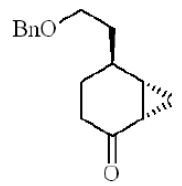
100 MHz ^{13}C NMR Spectrum of Compound **10**

(recorded in $CDCl_3$)

79

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

(recorded in $CDCl_3$)



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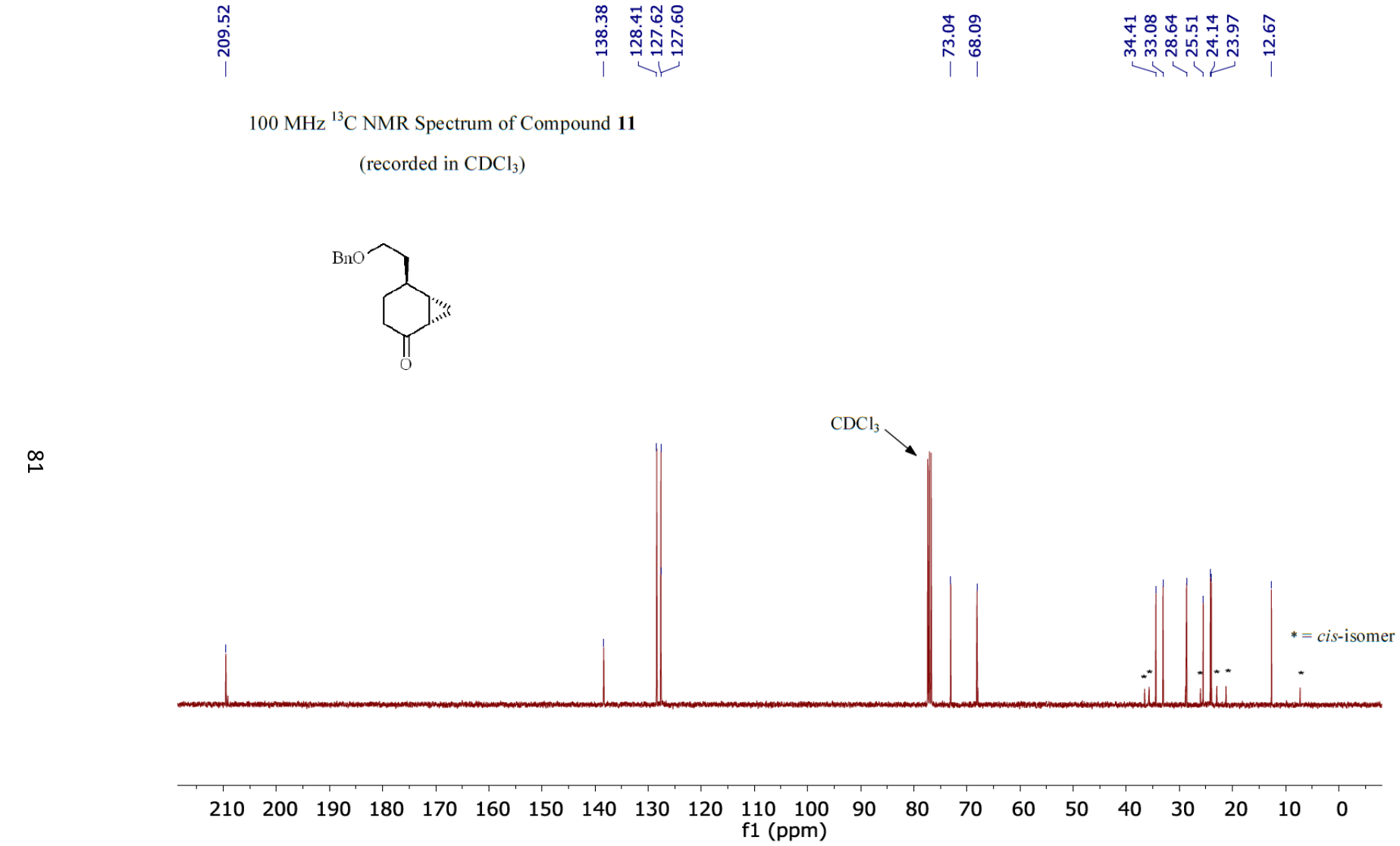


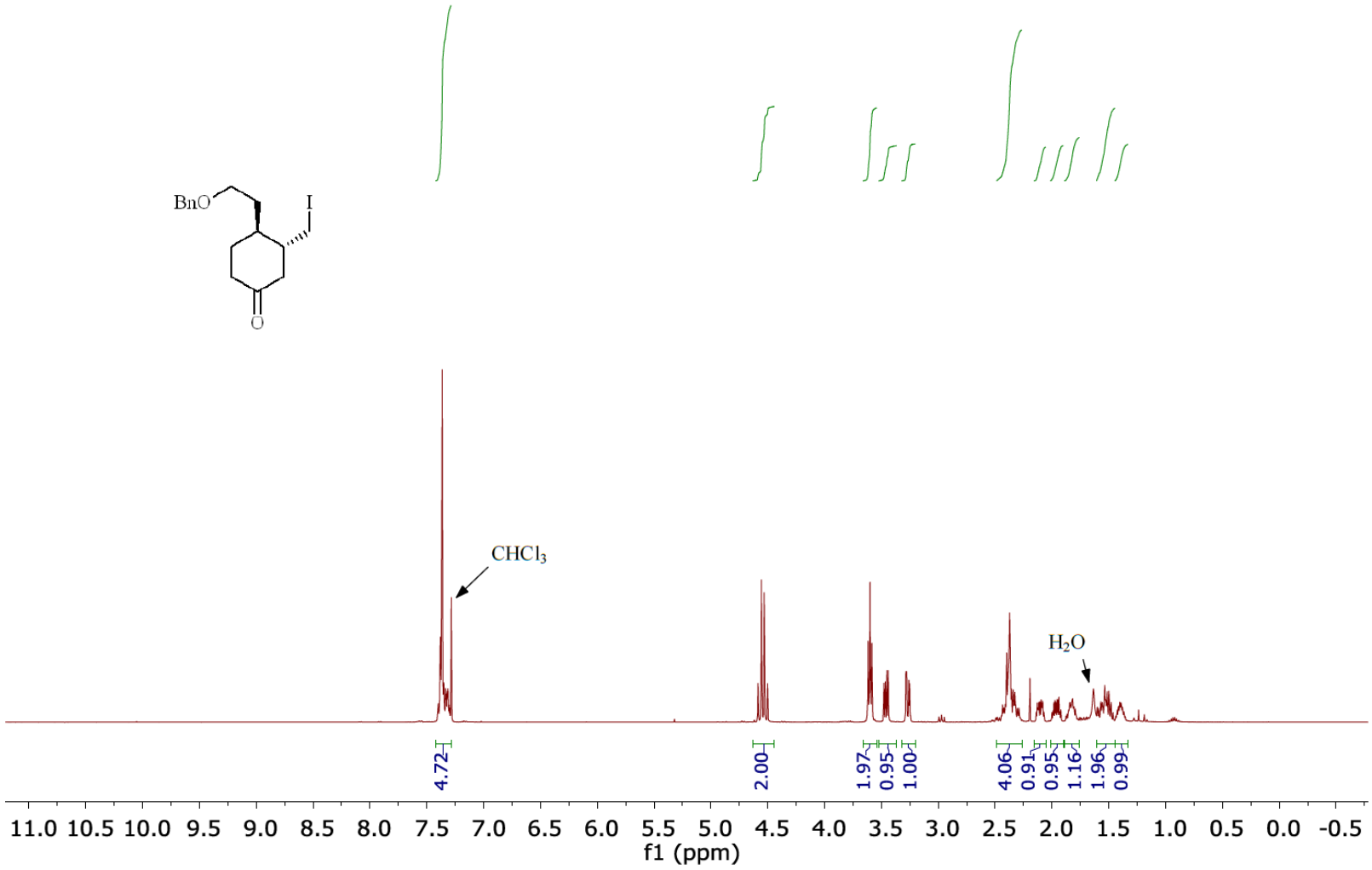
100 MHz ^{13}C NMR Spectrum of Compound **11**

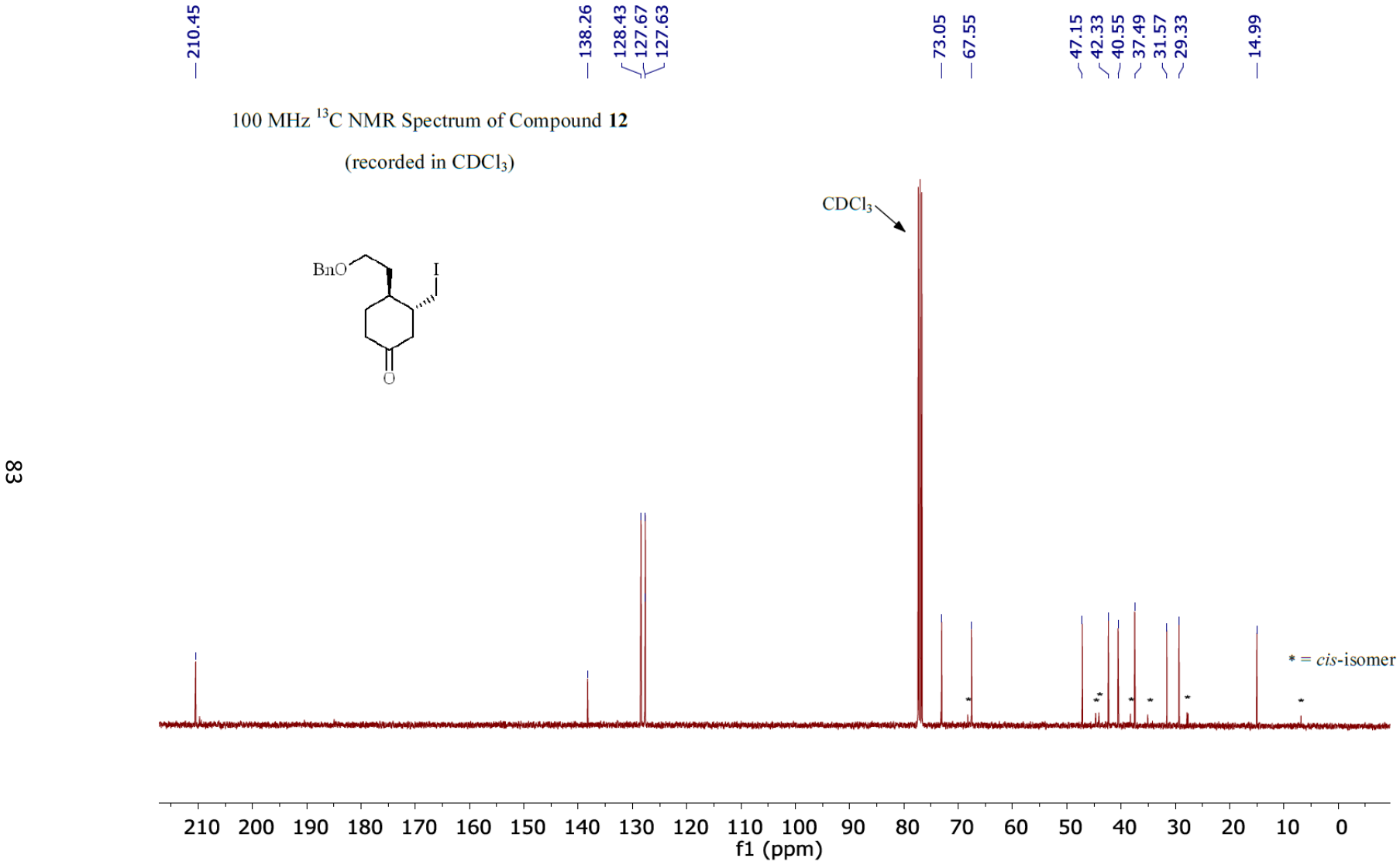
(recorded in $CDCl_3$)

81

400 MHz ^{1}H NMR Spectrum of Compound **12**

(recorded in $CDCl_3$)

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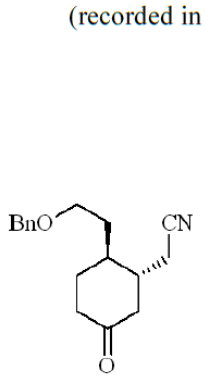
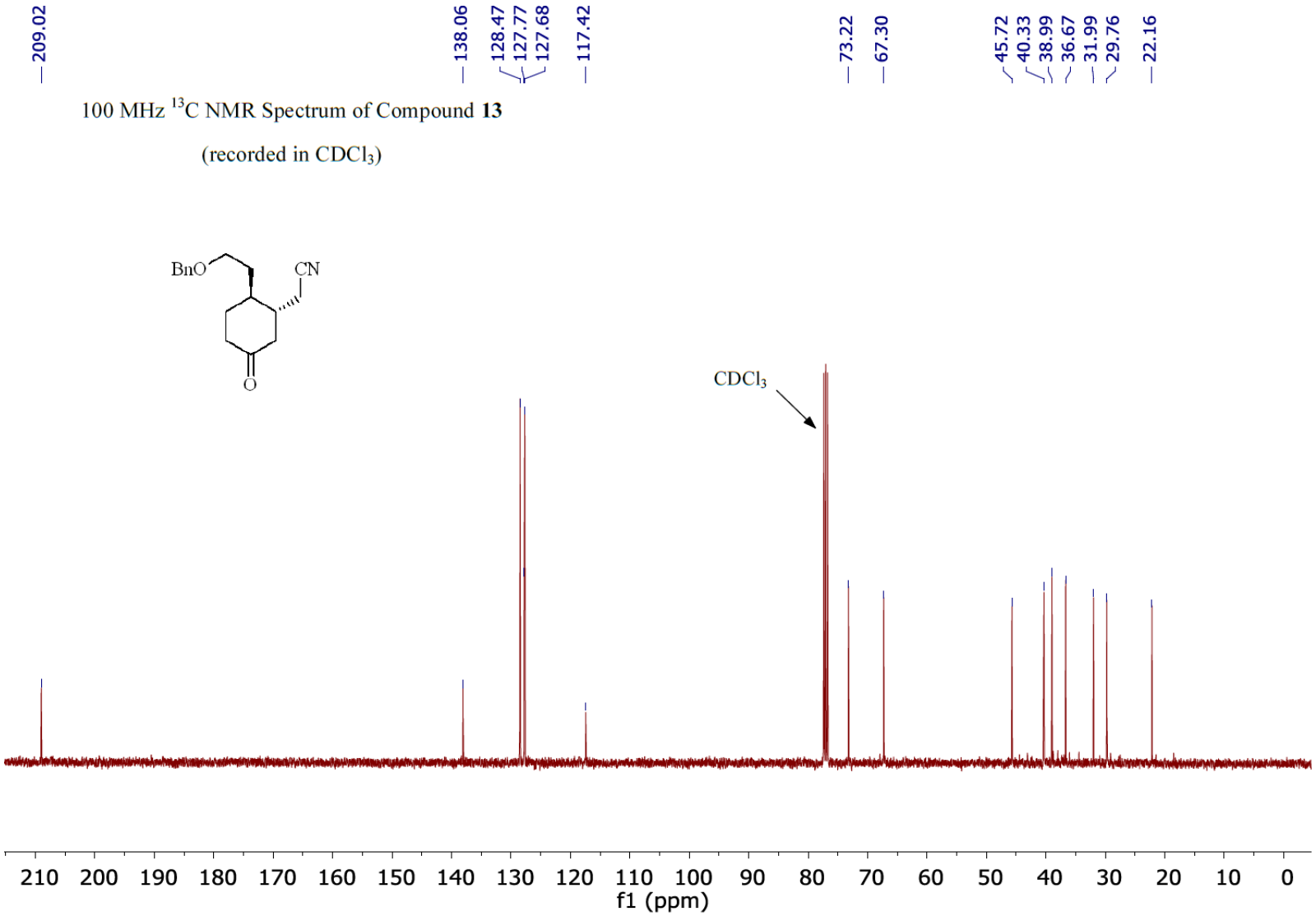
40.55
37.49
31.57
29.33
14.99
100 MHz ^{13}C NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)
$CDCl_3$
BnO
I
O
* = *cis*-isomer
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **13**

(recorded in $CDCl_3$)



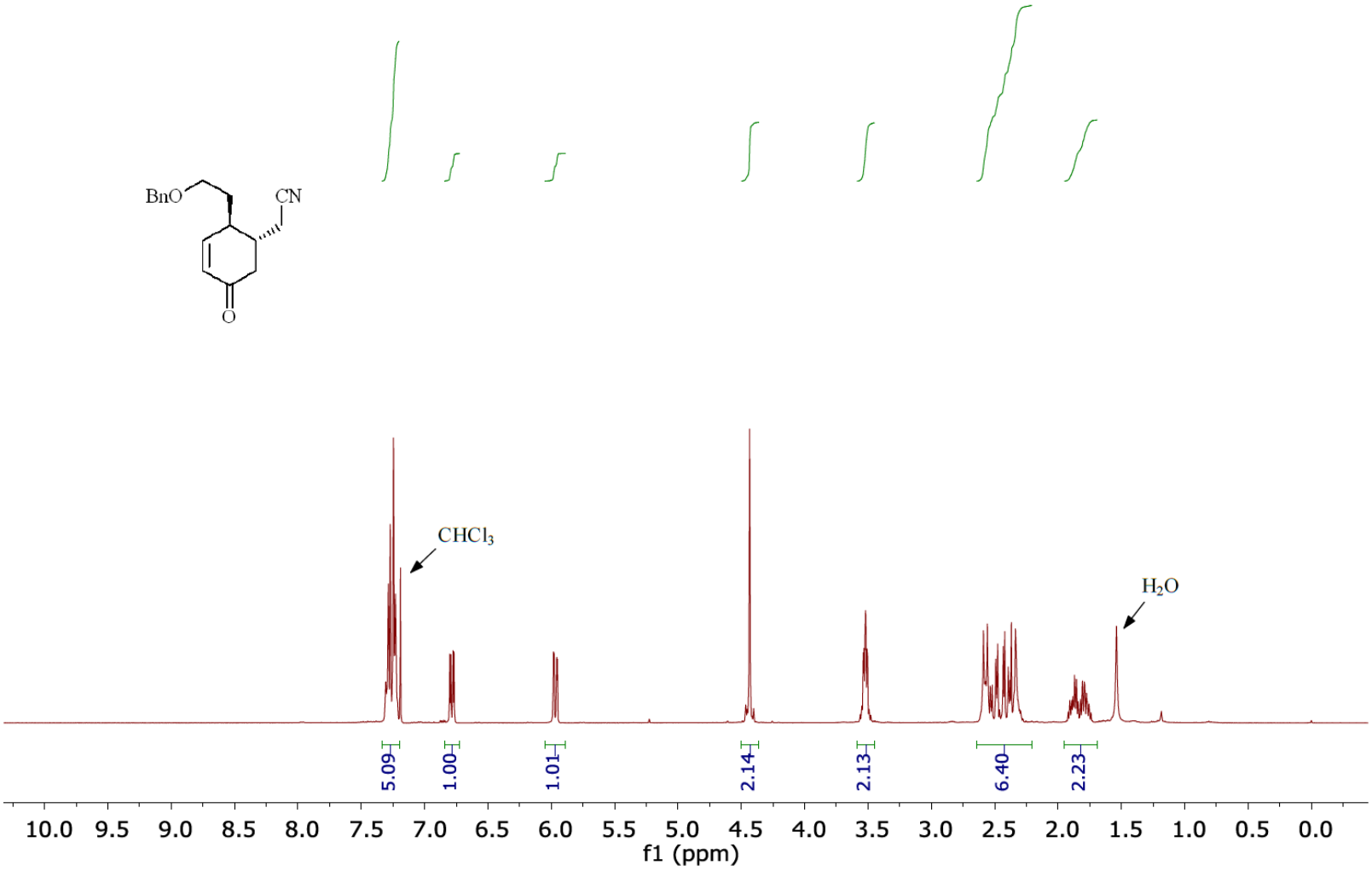


100 MHz ^{13}C NMR Spectrum of Compound **13**

(recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **14**

(recorded in $CDCl_3$)



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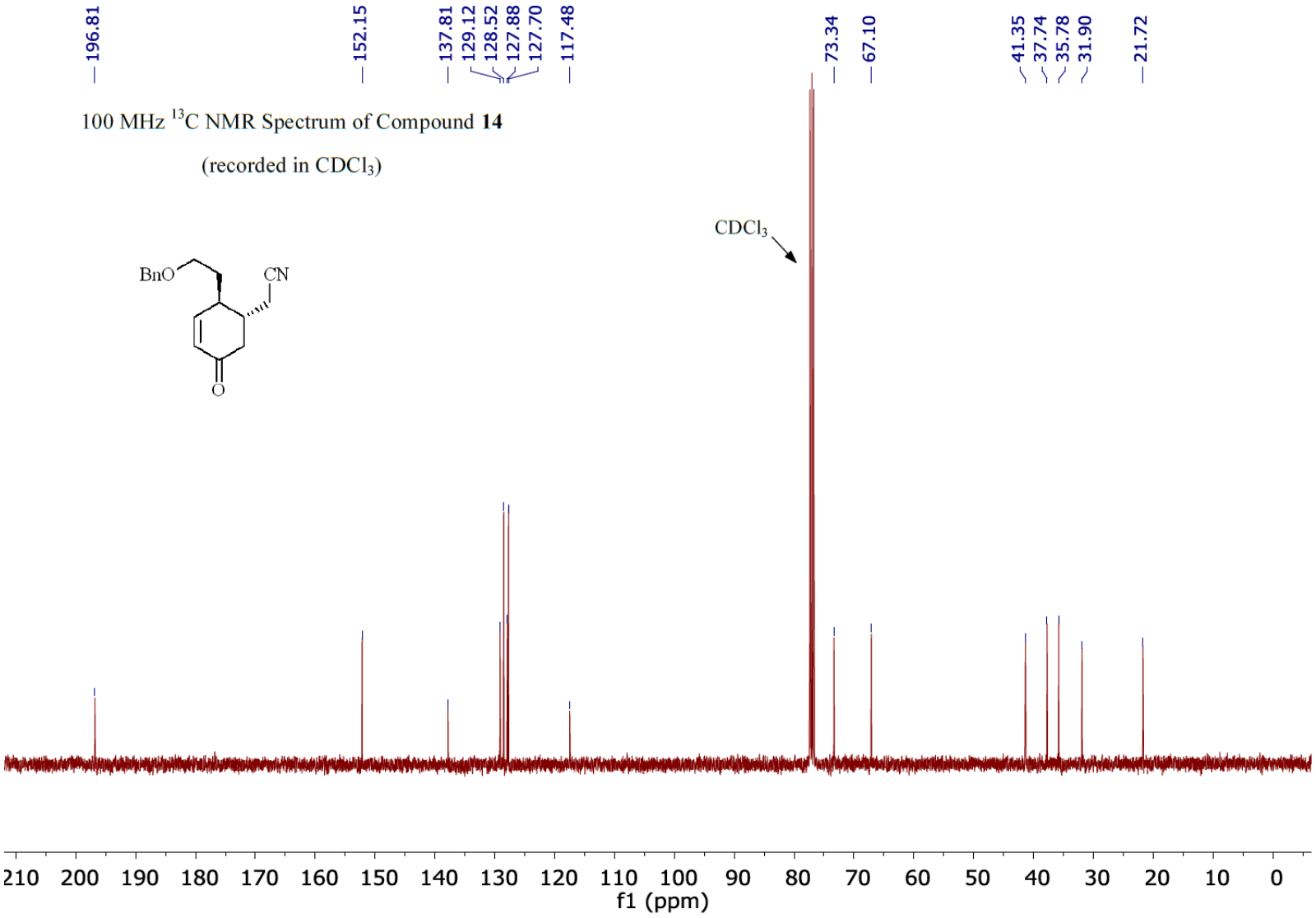
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31.90
21.72
100 MHz ^{13}C NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)
$CDCl_3$
BnO
CN
O
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f1 (ppm)

87

400 MHz ^{1}H NMR Spectrum of Compound **15**

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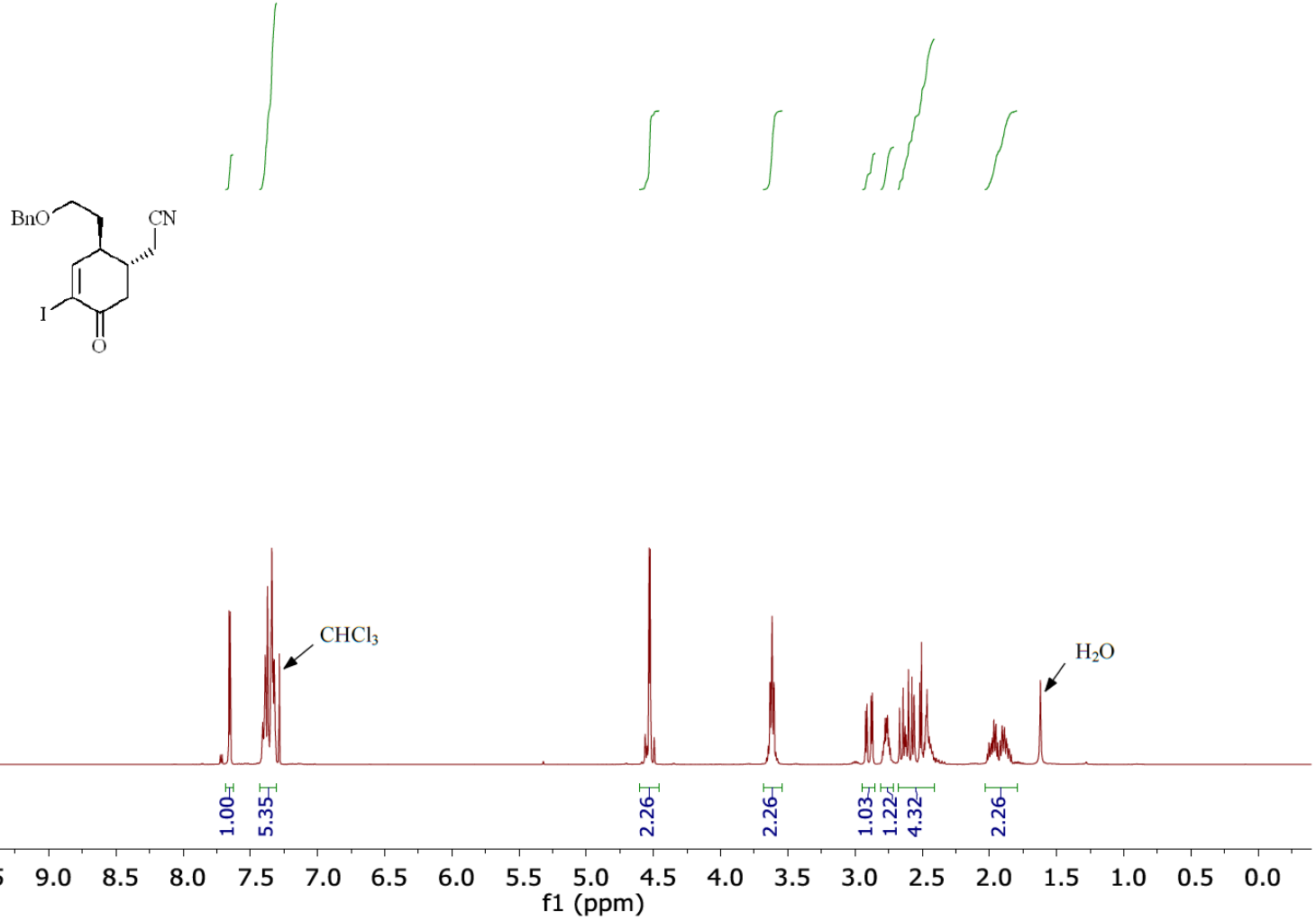

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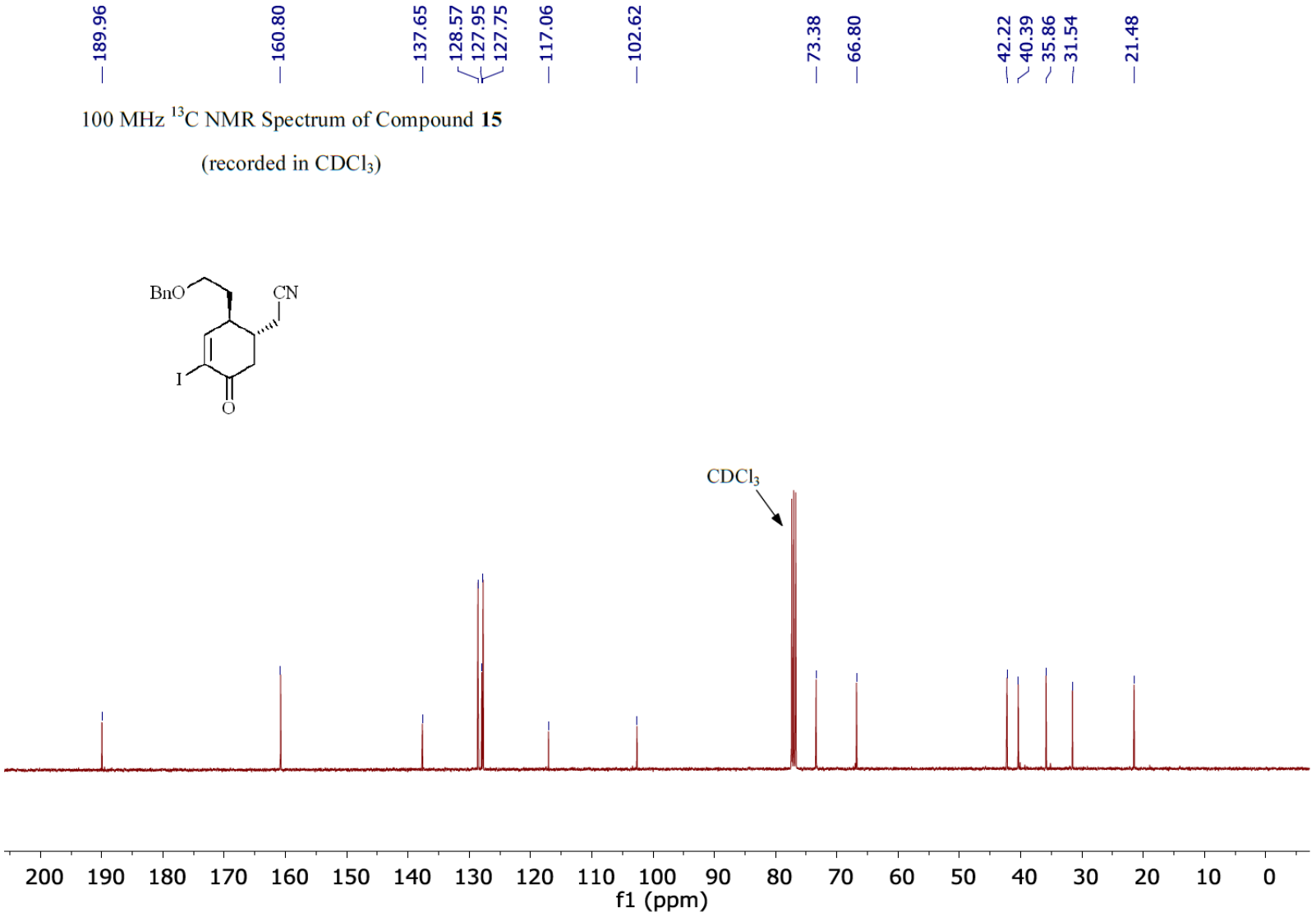
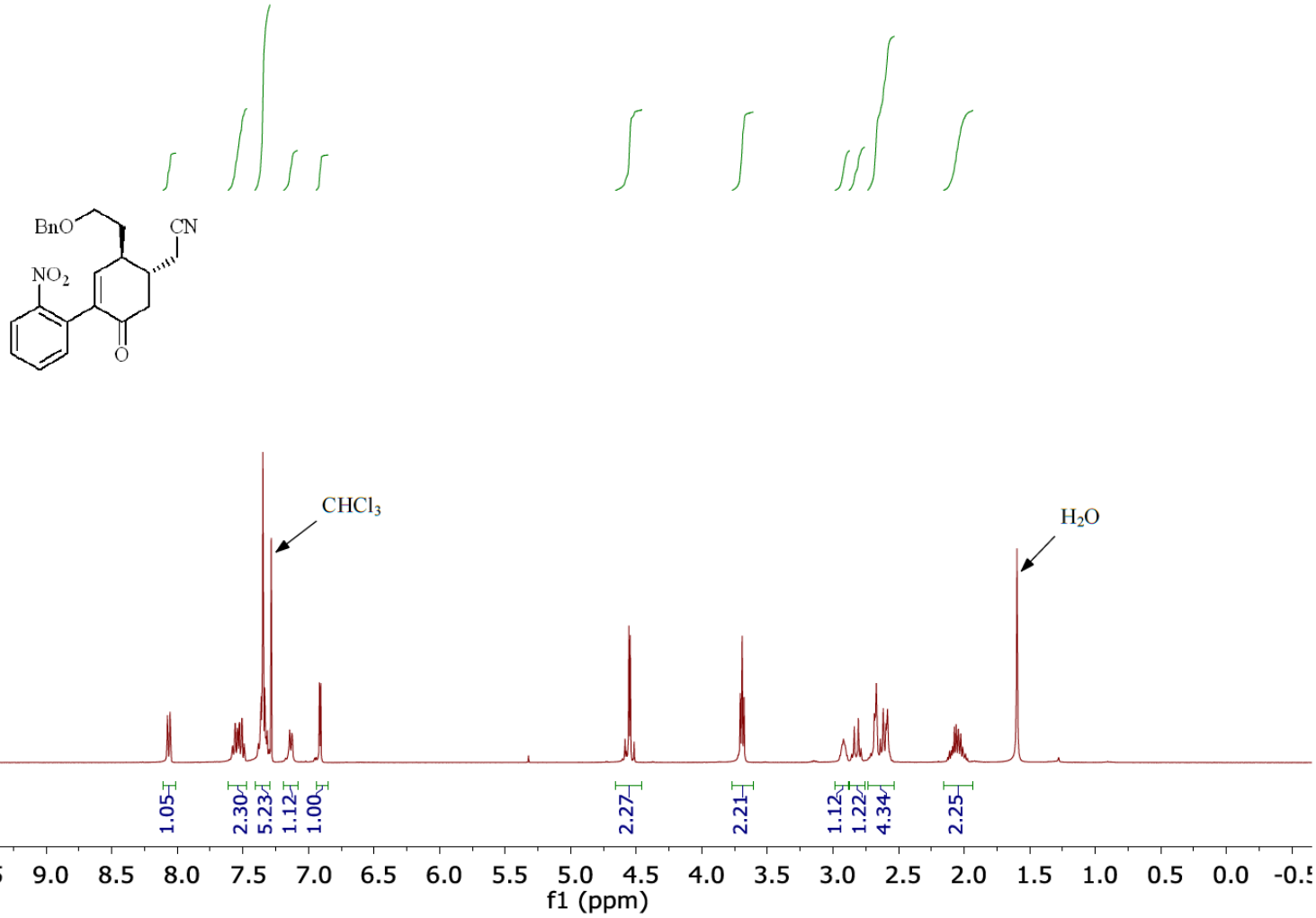


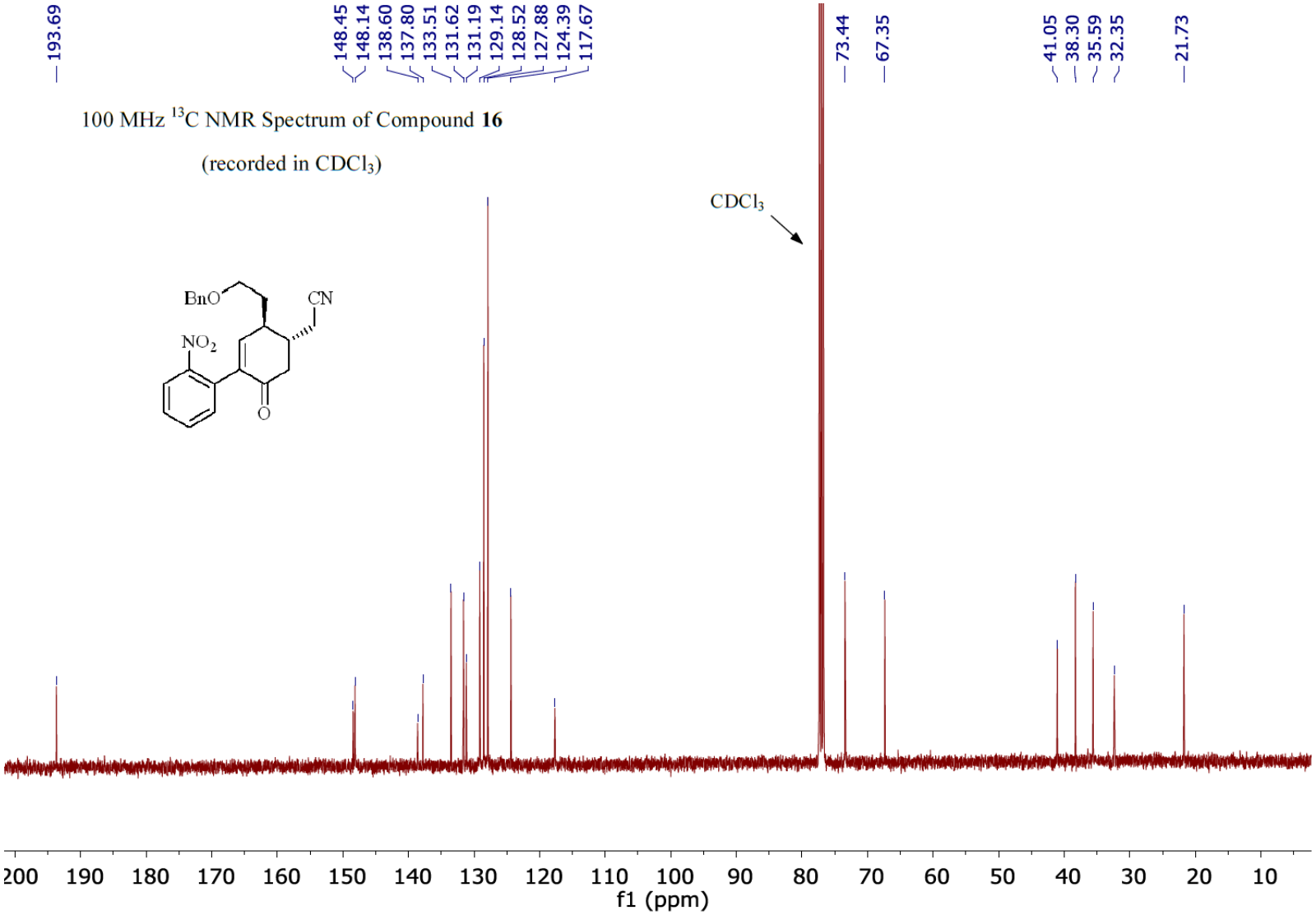
100 MHz ^{13}C NMR Spectrum of Compound **15**

(recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **16**

(recorded in $CDCl_3$)

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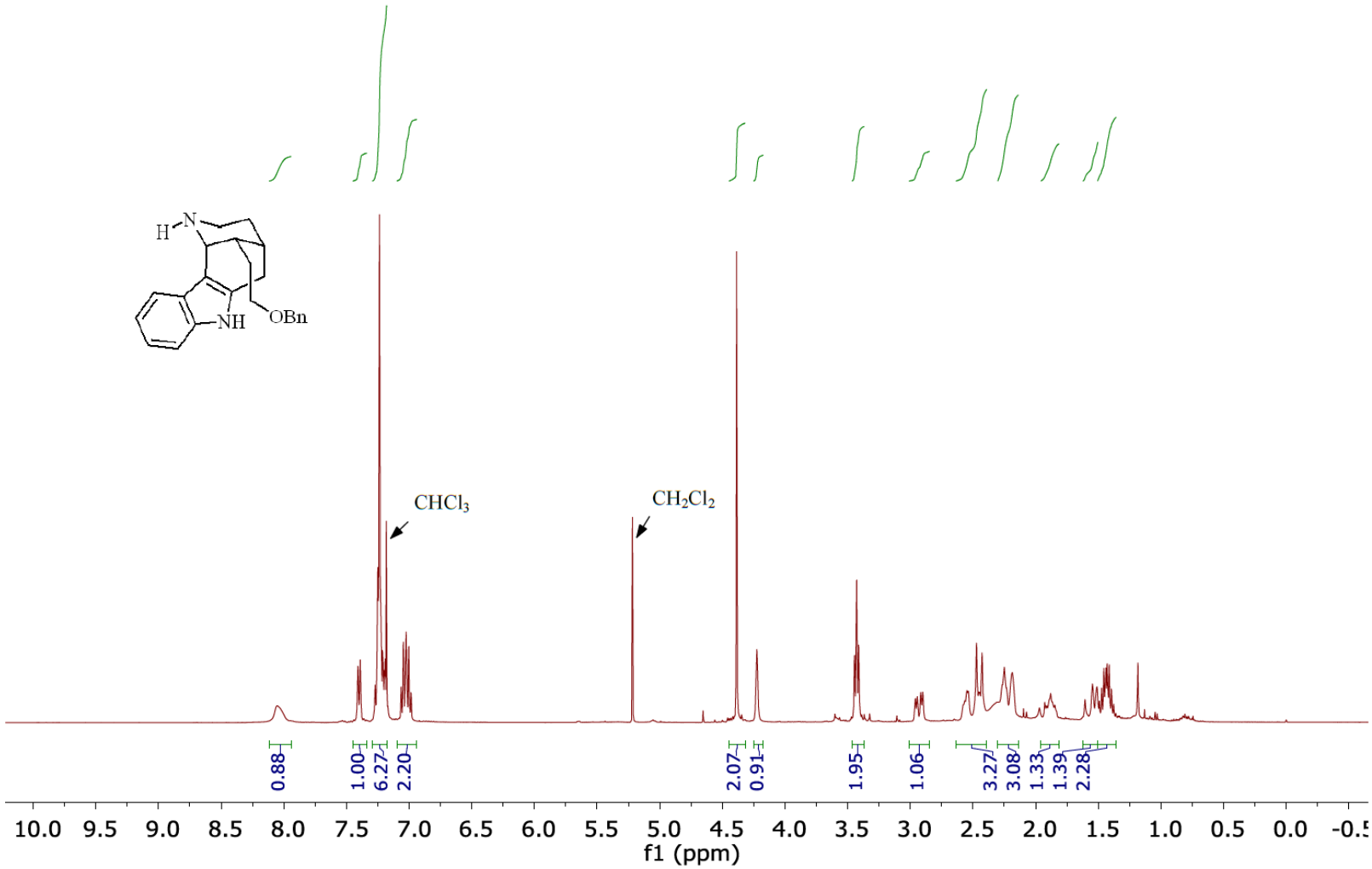
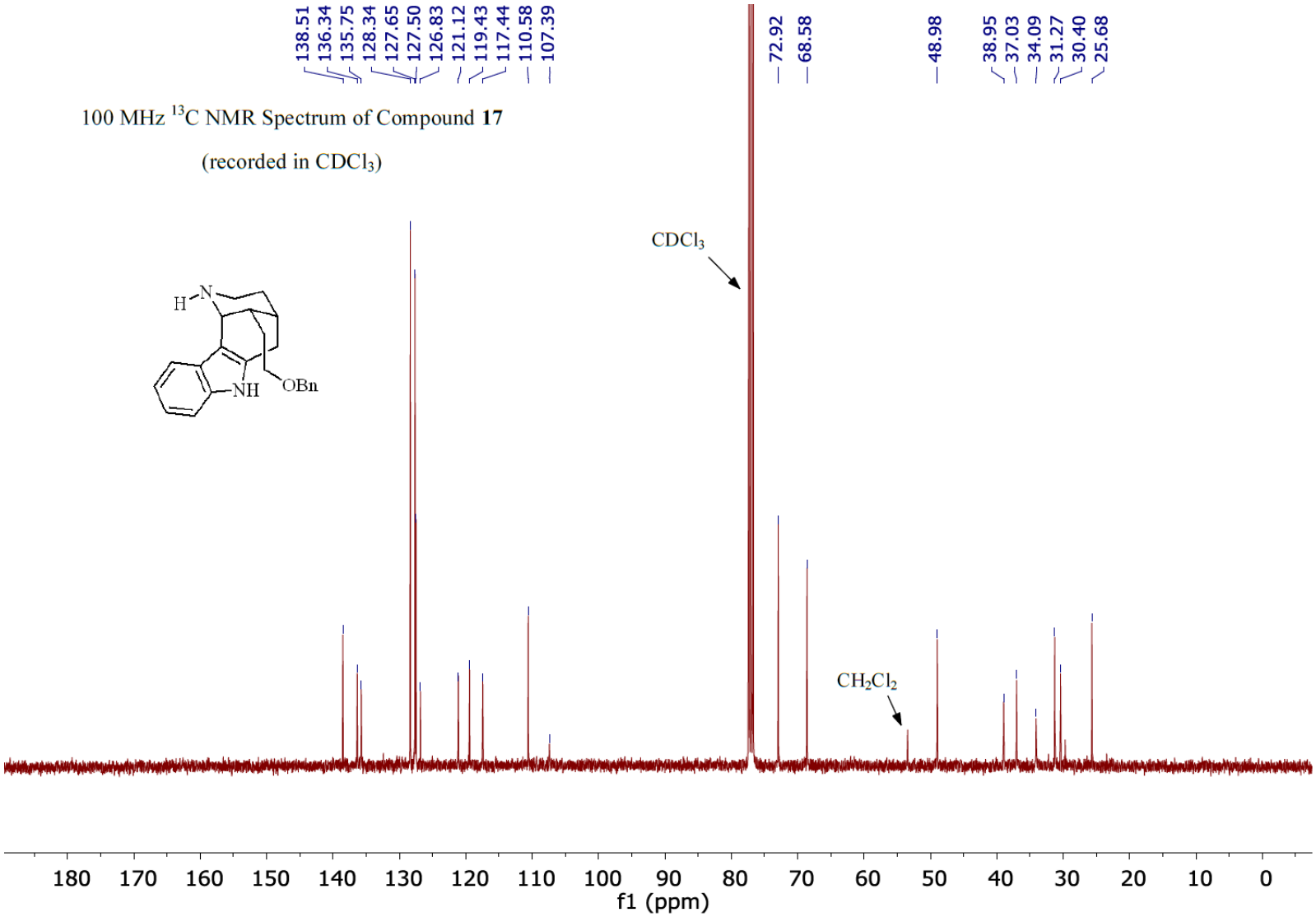
124.39
117.67
73.44
67.35
41.05
38.30
35.59
32.35
21.73
100 MHz ^{13}C NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)
$CDCl_3$
BnO
CN
NO_2
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **17**

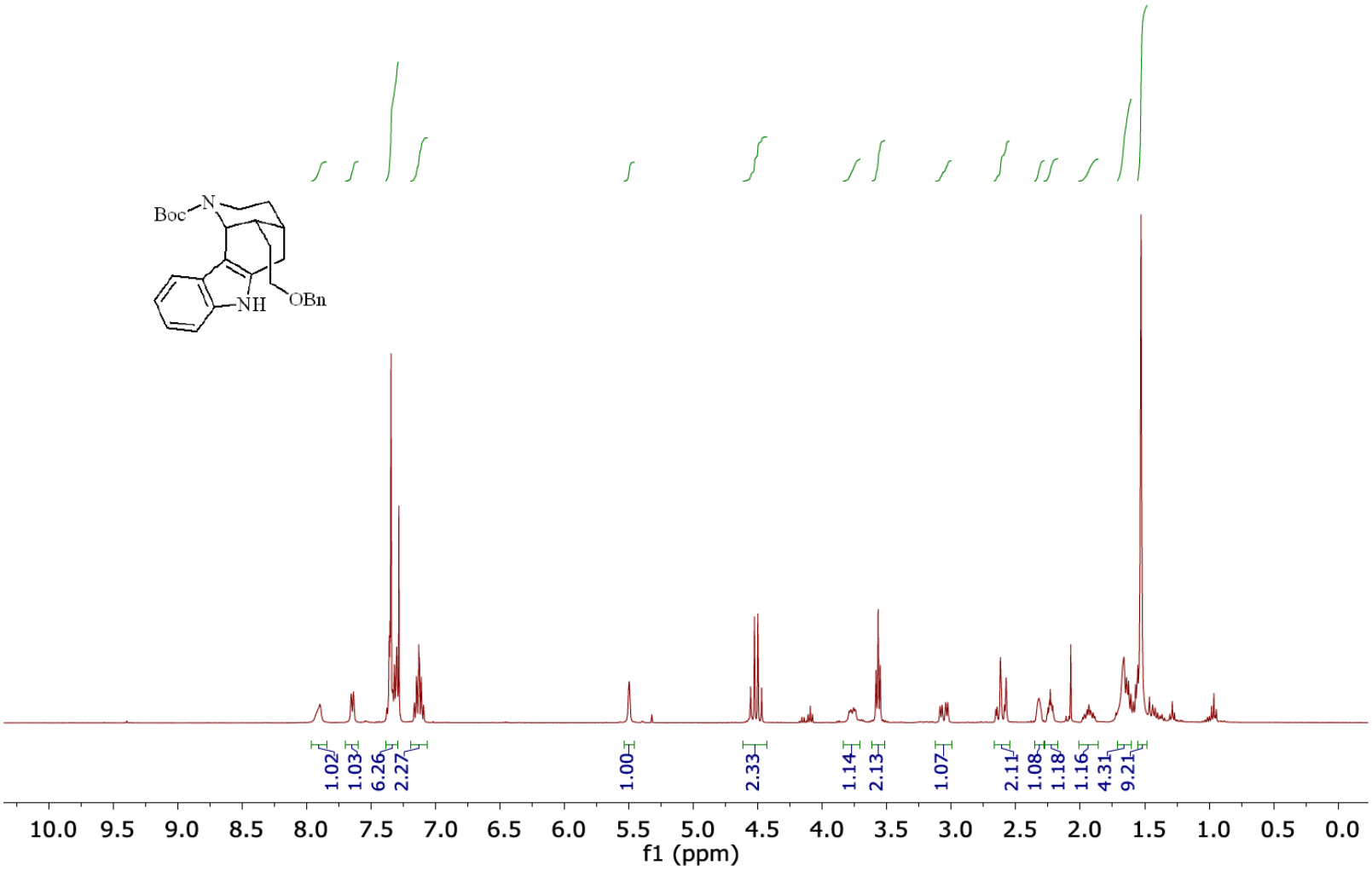
(recorded in $CDCl_3$)

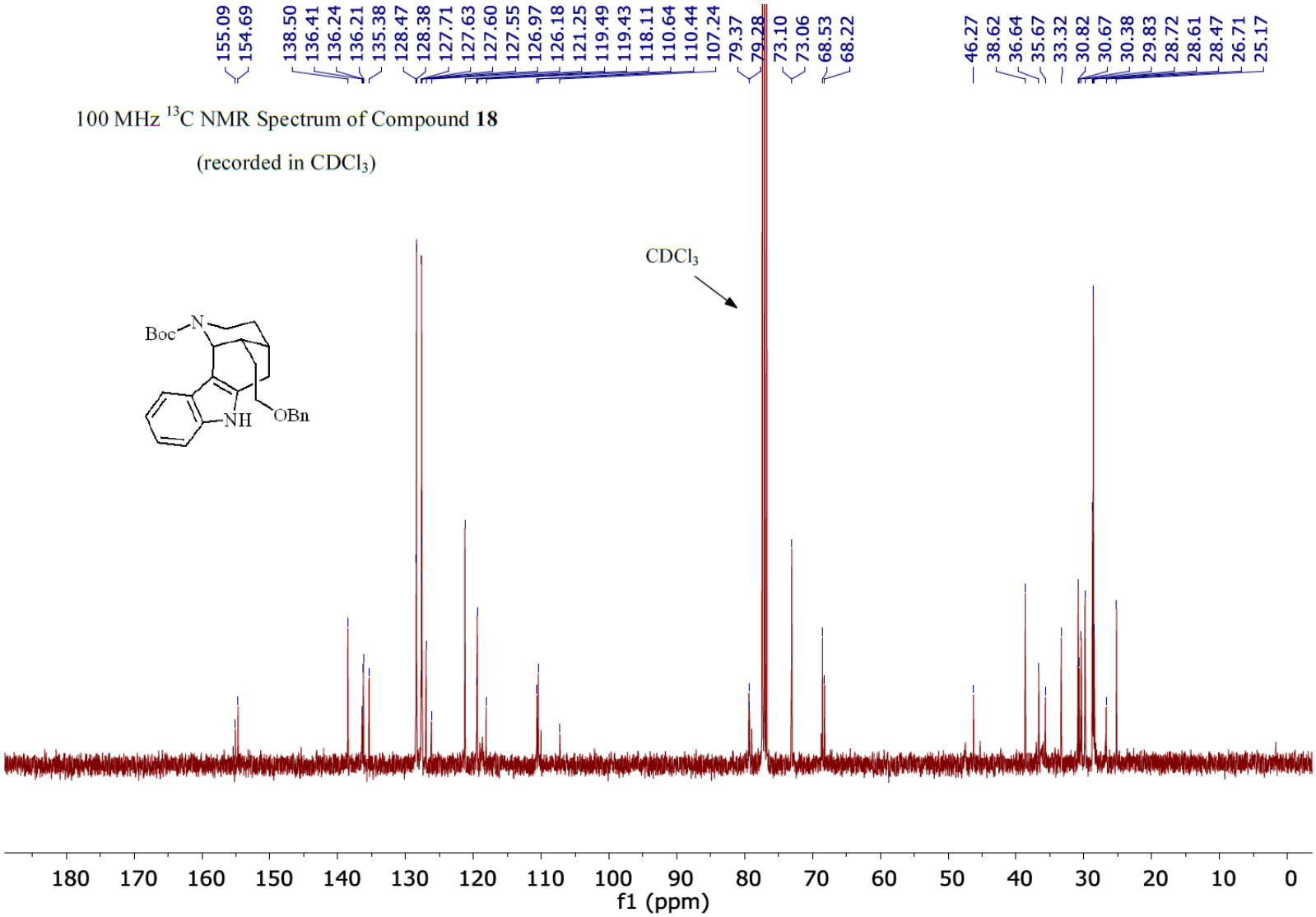



138.51
136.34
135.75
128.34
127.65
127.50
126.83
121.12
119.43
117.44
110.58
107.39
72.92
68.58
48.98
38.95
37.03
34.09
31.27
30.40
25.68
100 MHz ^{13}C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)
$CDCl_3$
CH_2Cl_2
H
N
NH
OBn
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **18**

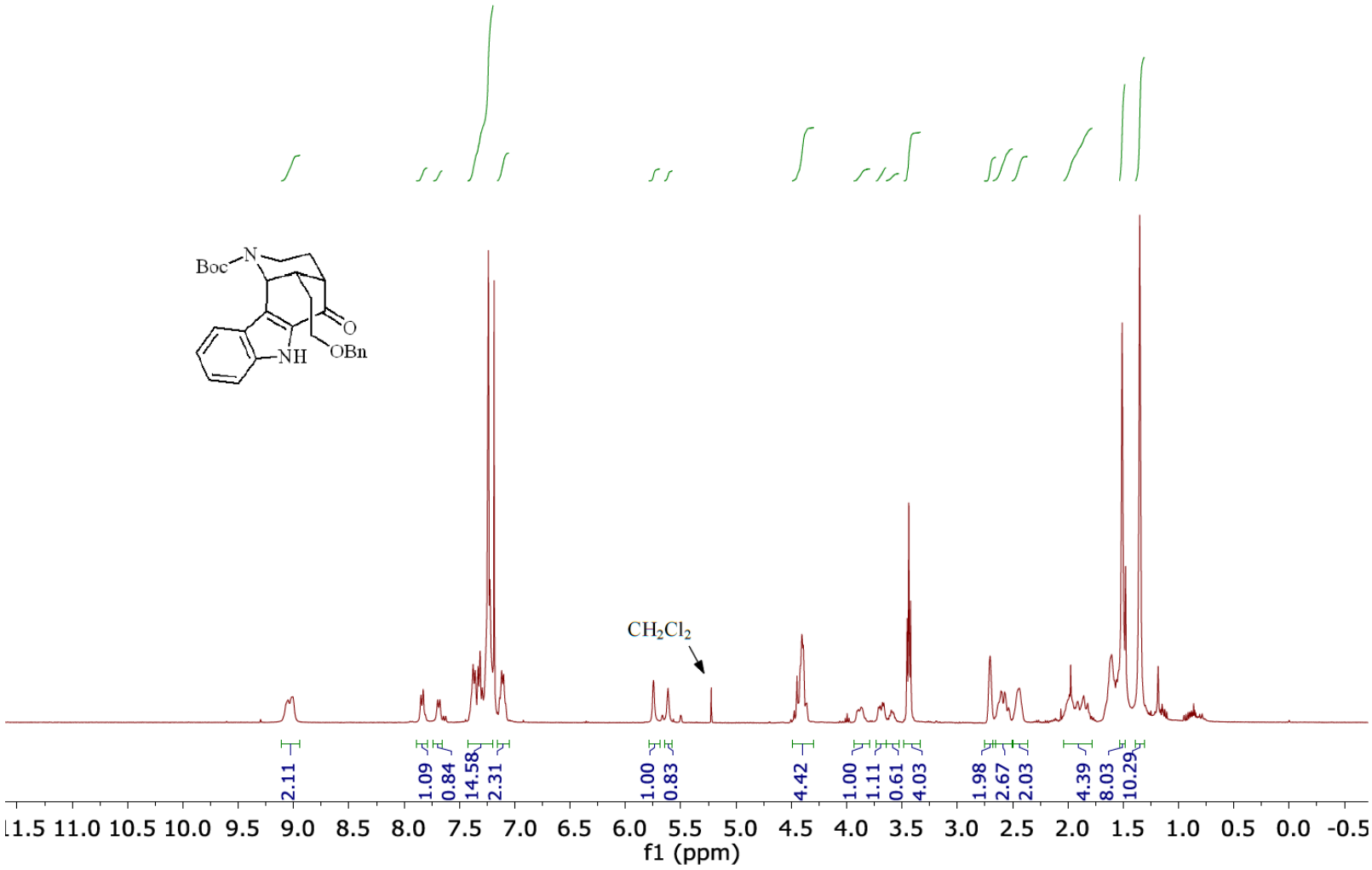
(recorded in $CDCl_3$)



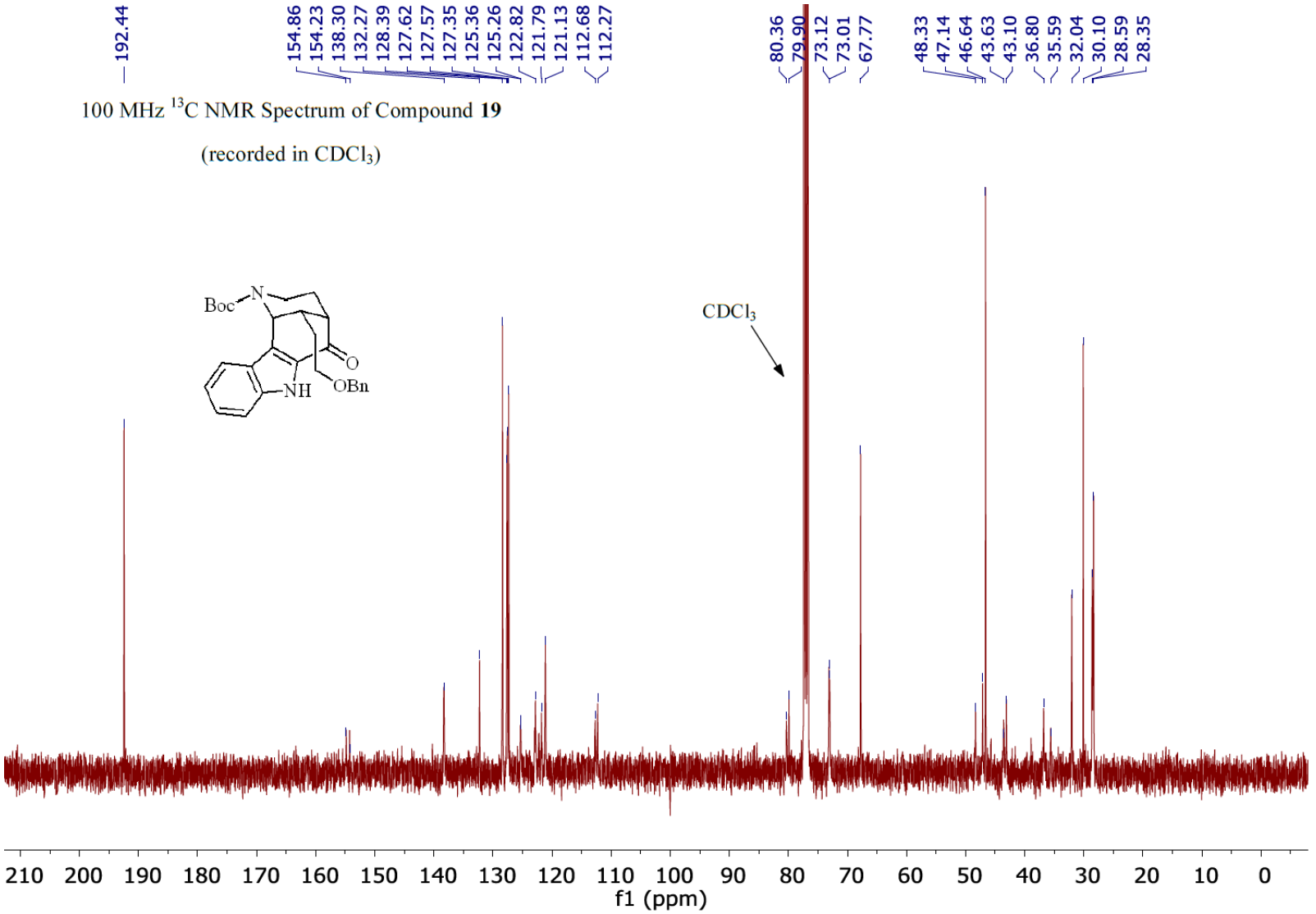

155.09
154.69
138.50
136.41
136.24
136.21
135.38
128.47
128.38
127.71
127.63
127.60
127.55
126.97
126.18
121.25
119.49
119.43
118.11
110.64
110.44
107.24
79.37
79.28
73.10
73.06
68.53
68.22
46.27
38.62
36.64
35.67
33.32
30.82
30.67
30.38
29.83
28.72
28.61
28.47
26.71
25.17
100 MHz ^{13}C NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)
$CDCl_3$
Boc
N
NH
OBn
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **19**

(recorded in $CDCl_3$)

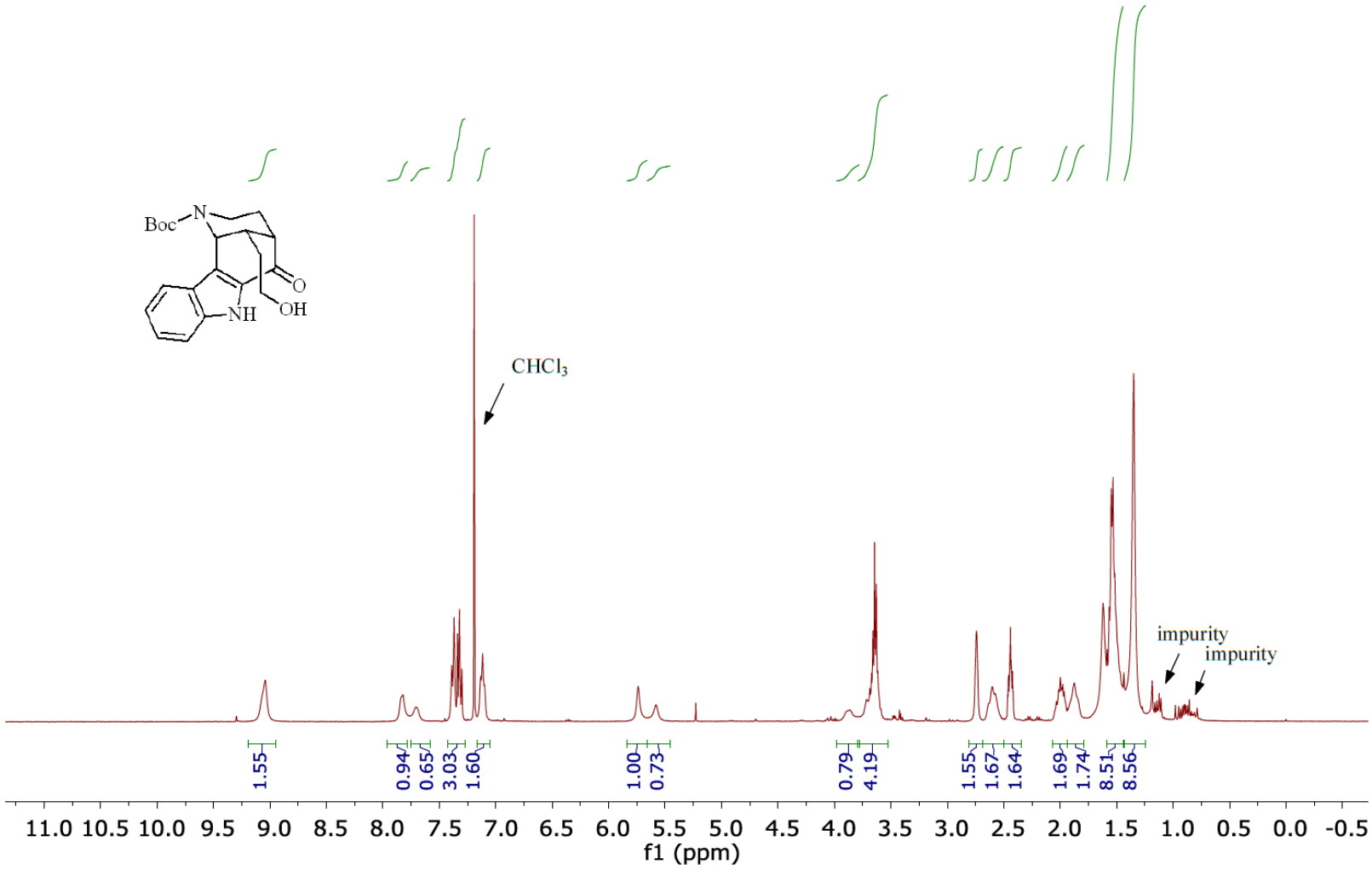


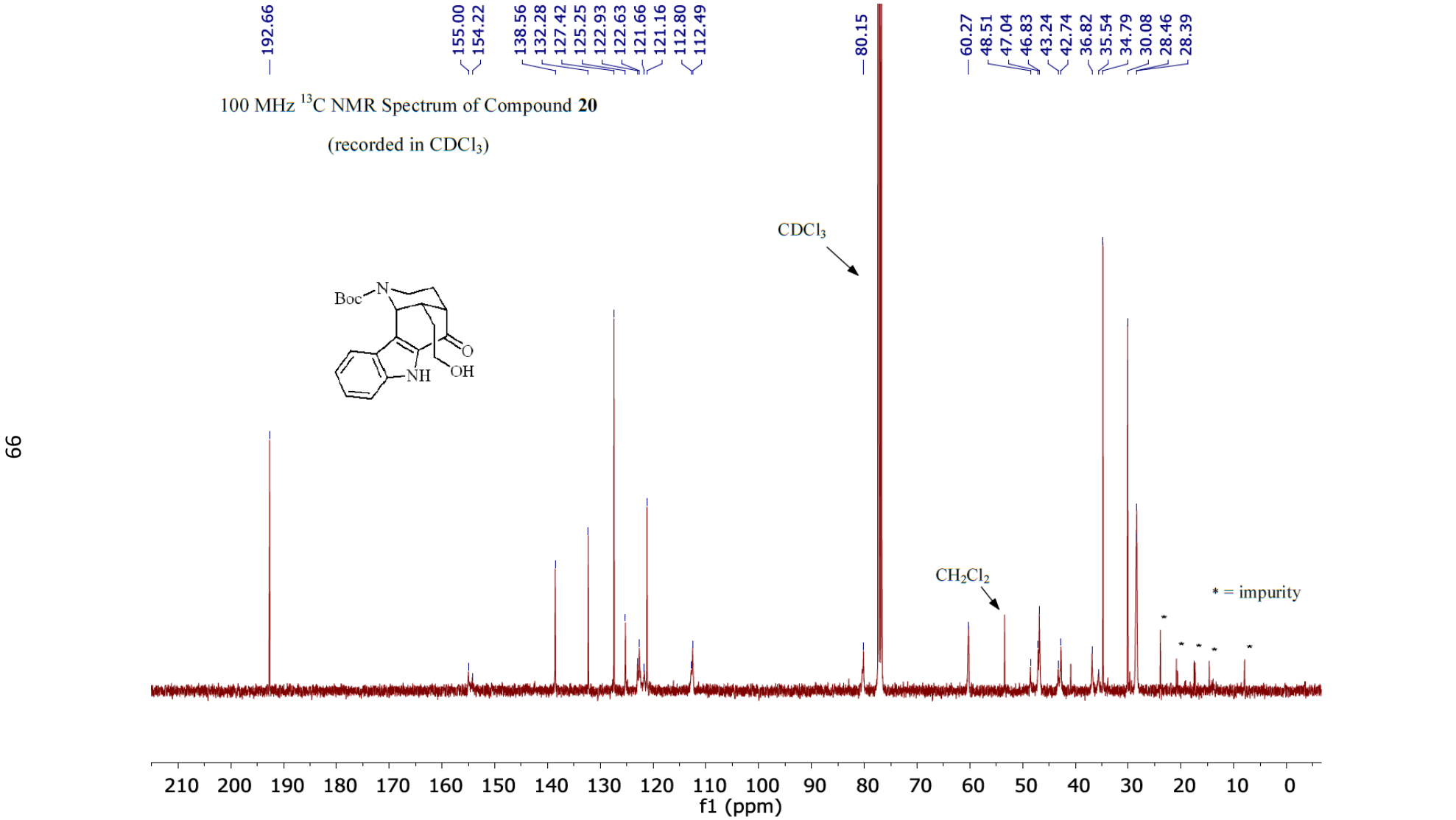
96


192.44
154.86
154.23
138.30
132.27
128.39
127.62
127.57
127.35
125.36
125.26
122.82
121.79
121.13
112.68
112.27
80.36
79.90
73.12
73.01
67.77
48.33
47.14
46.64
43.63
43.10
36.80
35.59
32.04
30.10
28.59
28.35
100 MHz ^{13}C NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)
Boc
N
O
NH
OBn
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

400 MHz ^{1}H NMR Spectrum of Compound **20**

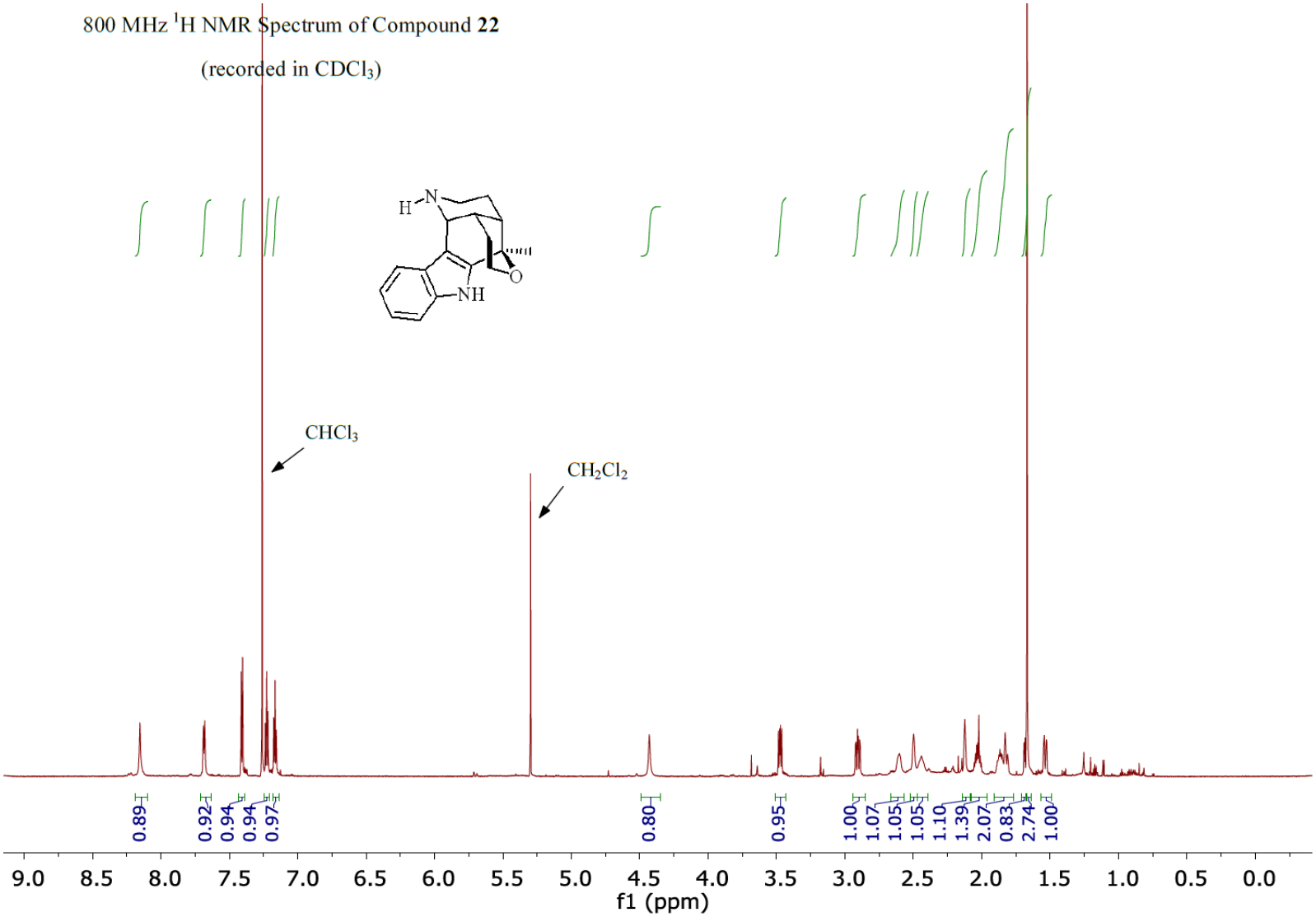
(recorded in $CDCl_3$)




192.66
155.00
154.22
138.56
132.28
127.42
125.25
122.93
122.63
121.66
121.16
112.80
112.49
80.15
60.27
48.51
47.04
46.83
43.24
42.74
36.82
35.54
34.79
30.08
28.46
28.39
100 MHz 13C NMR Spectrum of Compound 20
(recorded in CDCl3)
CDCl3
Boc
N
O
OH
NH
CH2Cl2
* = 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)

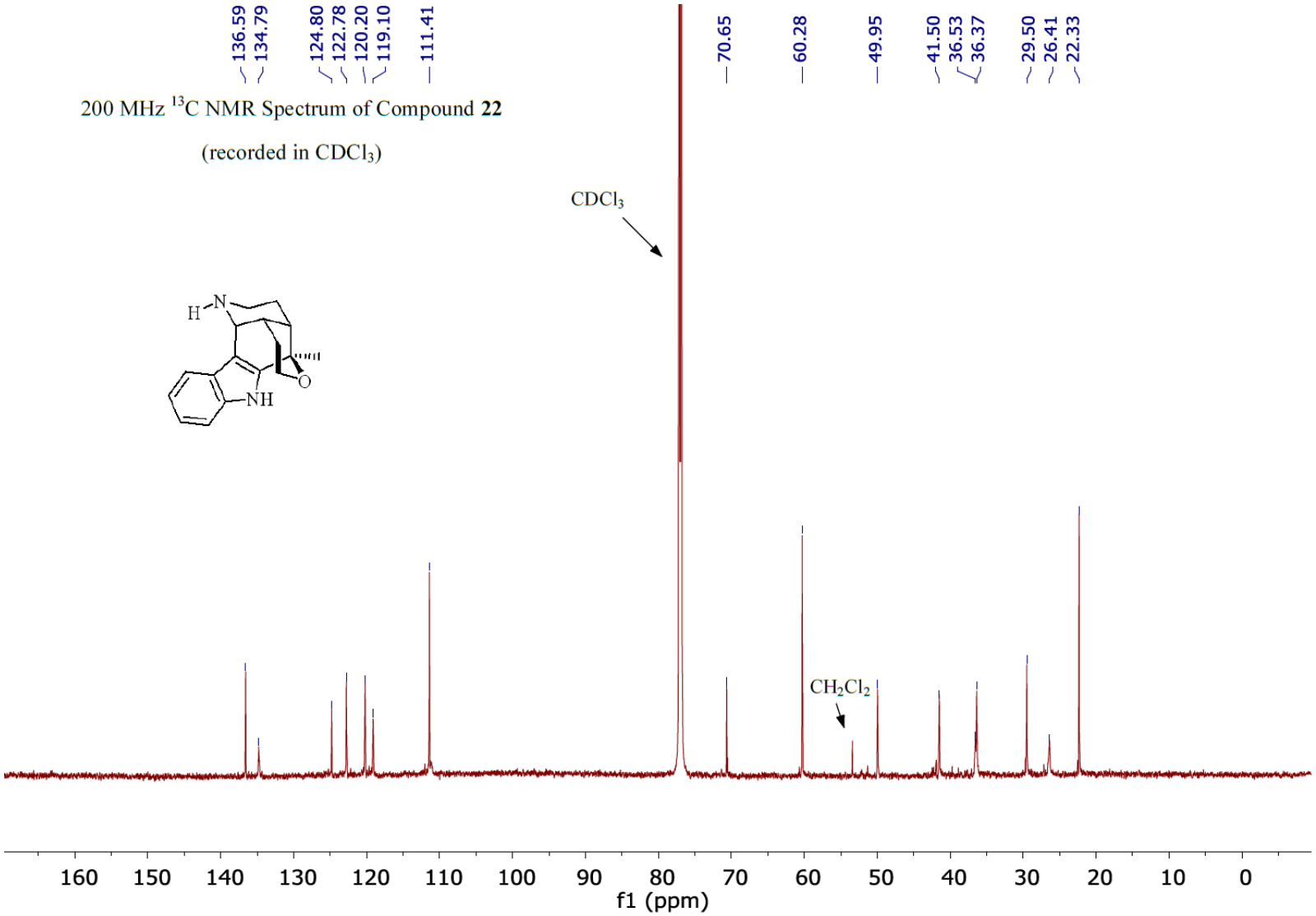
800 MHz ^{1}H NMR Spectrum of Compound **22**

(recorded in $CDCl_3$)



100

101

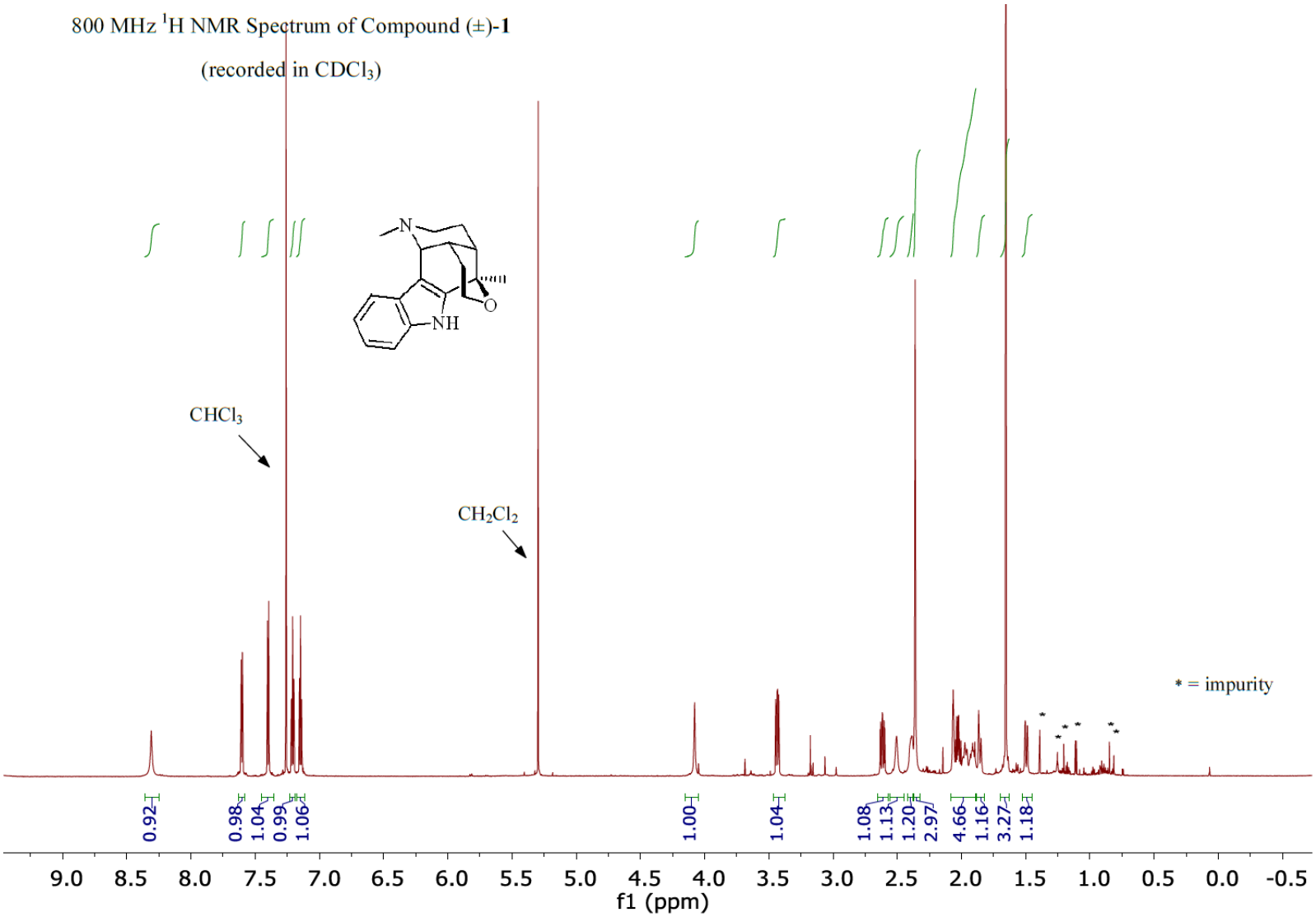


200 MHz ^{13}C NMR Spectrum of Compound **22**

(recorded in $CDCl_3$)

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

(recorded in $CDCl_3$)



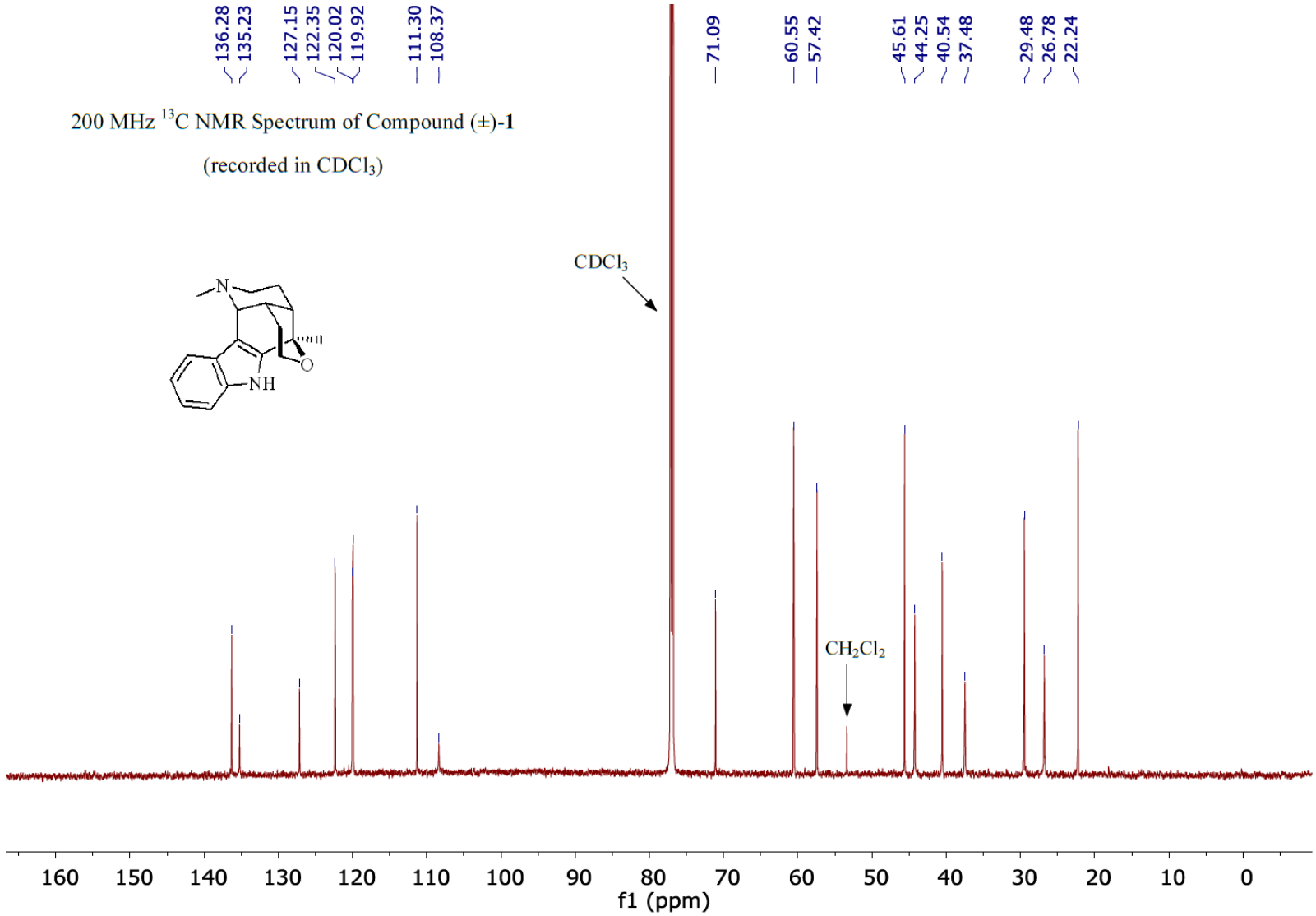

136.28
135.23
127.15
122.35
120.02
119.92
111.30
108.37
71.09
60.55
57.42
45.61
44.25
40.54
37.48
29.48
26.78
22.24
200 MHz ^{13}C NMR Spectrum of Compound (±)-1
(recorded in $CDCl_3$)
$CDCl_3$
CH_2Cl_2
N
NH
O
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

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

^{13}C NMR Data for Compound (±)-**1** (δ_C)[a]	^{13}C NMR Data from Blechert (δ_C)[b]	Δδ
136.3	136.2	+0.1
135.2	135.0	+0.2
127.2	127.3	–0.1
122.4	122.3	+0.1
120.0	120.1	–0.1
119.9	119.9	0
111.3	111.2	+0.1
108.4	108.8	–0.4
71.1	71.0	+0.1
60.6	60.6	0
57.4	57.3	+0.1
45.6	45.6	0
44.3	44.5	–0.2
40.5	40.7	–0.2
37.5	37.8	–0.3
29.5	29.6	–0.1
26.8	27.0	–0.2
22.2	22.3	–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.

Publication Four

Total synthesis of (+) – Viridianol, a Marine-derived Sesquiterpene Embodying the Decahydrocyclobuta[d]indene Framework

Fei Tang, Ping Lan, Benoit Bolte, Martin G. Banwell, Jas S. Ward and Anthony C. Willis

J. Org. Chem. **2018**, *83*, 14049-14056

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Total Synthesis of (+)-Viridianol, a Marine-Derived Sesquiterpene Embodying the Decahydrocyclobuta[*d*]indene Framework

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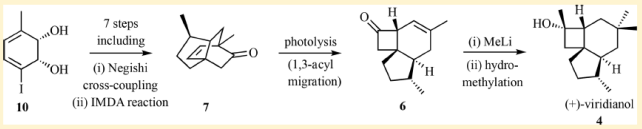
Supporting Information



ABSTRACT: A total synthesis of the title sesquiterpene **4** is described that starts with the chiral, non-racemic *cis*-1,2-dihydrocatechol **10** obtained through the whole-cell biotransformation of *p*-iodotoluene. Compound **10** is elaborated over seven steps, including Negishi cross-coupling and intramolecular Diels−Alder (IMDA) cycloaddition reactions, to ketone **7** that engages in a photochemically promoted 1,3-acyl migration and so affording cyclobutanone **6**. Compound **6** was converted over further steps into the title compound **4**.

INTRODUCTION

As shown in structures **1**−**3** (Figure 1), there are three possible modes of annulation of a four- and a five-membered carbocycle

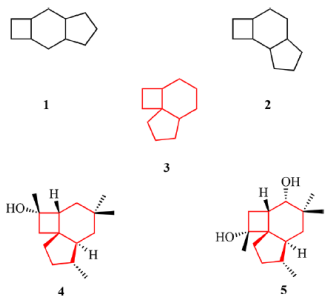


Figure 1. Sterpurene (**1**), protoilludane (**2**), and decahydrocyclobuta[*d*]indene (**3**) frameworks and the structures of sesquiterpenes (+)-viridianol (**4**) and trefolane A (**5**).

to a common cyclohexane ring. The first of these, involving a linear arrangement of the constituent rings, is encountered in the sterpurene class of sesquiterpenoid[1] while the second represents the key structural element associated with the even more common protoilludane group of natural products.[2,3] In contrast, tricarbocycle **3** (decahydrocyclobuta[*d*]indene), which incorporates a quaternary carbon center, is rare among natural products, with (+)-viridianol (**4**)[4] and (+)-trefolane A (**5**)[5] being the only two examples of sesquiterpenoids embodying this framework identified thus far. Compound **4** was isolated from the red seaweed *Laurencia viridis*[6] while congener **5** was obtained, more recently, from cultures of the basidiomycete *Tremella foliacea*, an edible fungus.

The interesting biological profiles of the sterpurenes and protoilludanes have prompted numerous efforts to develop syntheses of them.[1−3] A unified approach to the associated frameworks has been established by us and wherein intra- or intermolecular Diels−Alder reactions of enzymatically derived and homochiral *cis*-1,2-dihydrocatechols with dienophiles have provided cyclopentannulated bicyclo[2.2.2]octenones that themselves engage in photochemically promoted 1,3-acyl migration reactions, affording compounds embodying frameworks **1** and **2**, respectively. By such means we have been able to effect total syntheses of the protoilludane natural product armillarivin,[3a] *ent*-8-deoxydihydrotsugicoline,[3b] and *ent*-radudiol[3b] as well as the enantiomer[7] of the structure assigned, albeit incorrectly, to a sterpurene isolated from the culture broth of *Stereum purpureum*, a fungus that causes silver-leaf disease.[8] It is against this background that we now report related protocols that have enabled us to establish a total synthesis of (+)-viridianol (**4**), thus confirming the structure of this rare type of sesquiterpene.[5]

The retrosynthetic analysis employed in developing an approach to (+)-viridianol (**4**) is shown in Figure 2. Thus, it was envisaged this could be derived through functional group interconversions (FGIs) from the tricyclic β,γ-unsaturated ketone **6**, itself the anticipated product of a photochemically promoted 1,3-acyl migration reaction involving the cyclopentannulated bicyclo[2.2.2]octenone **7**.[9] This last compound was considered to be accessible through the application of conventional FGIs to congener **8**, the likely product of an intramolecular Diels−Alder (IMDA) reaction of triene **9**.[10]

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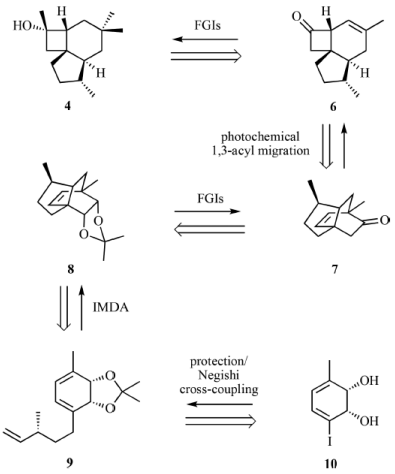


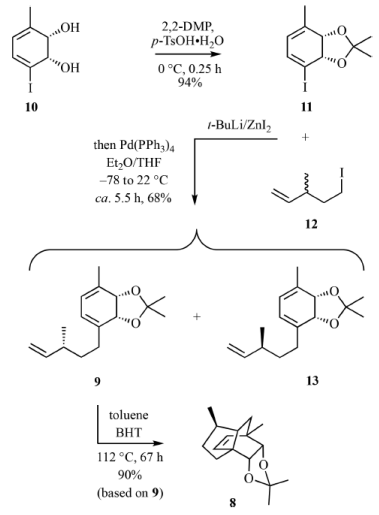
Figure 2. A retrosynthetic analysis of (+)-viridianol (**4**).

Compound **9** was expected to be available through various manipulations, most particularly a Negishi cross-coupling reaction, from the chiral, non-racemic *cis*-1,2-dihydrocatechol **10**, a known[11] metabolite of the whole-cell biotransformation of *p*-iodotoluene using micro-organisms that overexpress the enzyme toluene dioxygenase.[12] The successful implementation of this approach is detailed below.

RESULTS AND DISCUSSION

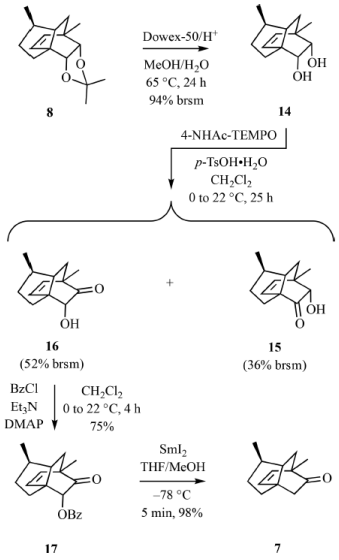
The synthesis of the IMDA adduct **8** is shown in Scheme 1 and starts with the conversion, under conventional conditions, of compound **10** into the corresponding and previously reported[13] acetonide **11** (94%). This last compound was subjected to a Negishi cross-coupling with the organozinc species obtained by treating the racemic modification of iodide **12**[14] with *tert*-butyllithium and then zinc iodide. As a result, a chromatographically inseparable mixture of the diastereoisomeric trienes **9** and **13** was obtained. When this was heated in refluxing toluene in the presence of butylated hydroxytoluene (BHT), the first of these participated in an IMDA cycloaddition reaction to give adduct **8** in 45% yield (or 90% based on the reacting substrate **9**) with the near epimerically pure triene **13** being recovered in 87% yield. The selective participation of triene **9** in the cycloaddition process is attributed to an exo-orientation of the side-chain methyl group at the transition state associated with this reaction compared with a sterically more demanding endo-orientation of the equivalent group in substrate **13** (thus preventing its IMDA reaction under the conditions employed).

Scheme 1. Synthesis of IMDA Adduct 8



The elaboration of cycloadduct **8** to cyclopentannulated bicyclo[2.2.2]octenone **7** is shown in Scheme 2. This involved

Scheme 2. Elaboration of IMDA Adduct 8 to Cyclopentannulated Bicyclo[2.2.2]octenone 7



hydrolyzing the acetonide moiety associated with the former compound using acidified DOWEX-50 in aqueous methanol at 65 °C, thus affording diol **14** in 94% yield (brsm). Oxidation of compound **14** using the sterically demanding oxaammonium salt[15] obtained through the *p*-toluenesulfonic acid-promoted disproportionation of the 4-acetamido-TEMPO afforded a chromatographically separable mixture of acyloins **15** (52%) and **16** (36%), and the structure of the first of these was confirmed by single-crystal X-ray analysis, details of which are provided in Supporting Information (SI). Esterification of compound **16** using benzoyl chloride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) gave the benzoate **17** (75%), and exposure of this to samarium iodide in THF containing methanol resulted in the anticipated

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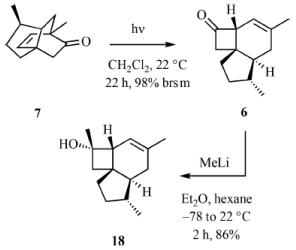
reductive deoxygenation process and, thereby, the formation of ketone **7** (98%), the substrate required for the pivotal photochemically promoted 1,3-acyl migration.

As shown in Scheme 3, when a dichloromethane solution of ketone **7** was subjected to direct irradiation using a high-

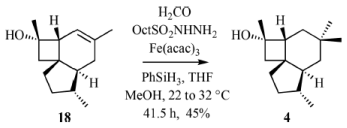
Scheme 3. Photochemical Rearrangement of Bicyclo[2.2.2]octenone 7 to Isomer 6 and the Stereoselective Elaboration of the Latter to Tertiary Alcohol 18



pressure mercury vapor lamp, then the anticipated product, namely compound **6**, resulting from a 1,3-acyl migration reaction (Givens rearrangement)[9] was obtained in 62% yield (79% brsm). All of the spectral data acquired on this material were in complete accord with the assigned structure. Most notably the infrared spectrum displayed a diagnostic cyclobutanone carbonyl absorption band at 1781 cm^{-1} while in the ^{13}C NMR spectrum the resonance due to the sp^2-hybridized carbon associated with this group appeared at δ 208.1 ppm. On treating this photoproduct with methyllithium in diethyl ether at −78 °C, a completely diastereoselective addition reaction took place wherein the nucleophilic addition to the cyclobutanone residue of the substrate took place from the exo-face, thus leading to the tertiary alcohol **18** in 86% yield.

Formally, the conversion of compound **18** into target **4** requires Markovnikov-type addition of the elements of methane to the trisubstituted double bond of the former compound. An iron-mediated method for the direct hydromethylation of unactivated alkenes has recently been reported,[16] and on applying this to alkene **18** (Scheme 4),

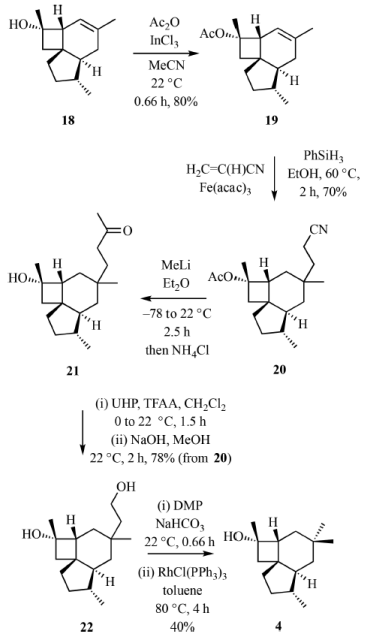
Scheme 4. Completion of a Synthesis of (+)-Viridianol (4) via Direct Hydromethylation of Alkene 18



(+)-viridianol (**4**) was obtained in 45% yield as the major product of reaction. However, this was contaminated with inseparable impurities (tentatively identified as the products of direct reduction of the olefinic residue within substrate **18**) that confounded our analysis of the derived NMR spectral data. Extensive attempts to purify the rather volatile compound **4** obtained by this pathway, including through the application of HPLC techniques, were all unsuccessful. Esterification of the hydroxyl group of compound **4** (and its contaminant) in various ways also failed to provide chromatographically separable materials. In addition, all modifications to the hydromethylation reaction itself failed to improve matters.

Given these difficulties, a less direct but related route from alkene **18** to target **4** was pursued, and this ultimately led to a completely clean product as well as crystalline intermediates that could be subjected to single-crystal X-ray analysis. So, compound **18** was acetylated (Scheme 5) under conditions

Scheme 5. Synthesis of Spectroscopically Pure (+)-Viridianol (4) from Alkene 18



defined by Chakraborti[17] and the derived ester **19** (80%) reacted with acrylonitrile in the presence of $PhSiH_3$ and $Fe(acac)_3$[16] leading, regioselectively, to adduct **20** (70%) that was obtained as a 2:1 mixture of diastereoisomers.

Treatment of this mixture of nitriles with methyl lithium gave, after an acidic workup using ammonium chloride, the corresponding mixture of keto-alcohols **21**, and on exposing these, as a mixture, to urea hydroperoxide (UHP) in the presence of trifluoroacetic anhydride[18], a Baeyer−Villiger oxidation reaction took place. The mixture of product esters was saponified, the resulting diols **22** (78% combined yield of a 2:1 mixture of epimers from **20**) could be separated chromatographically, and each proved to be crystalline, allowing for single-crystal X-ray analyses of both of them and establishing the illustrated absolute configuration of the compounds in the series (see SI for details). Oxidation of these diols with Dess−Martin periodinane (DMP) gave the corresponding aldehydes, and each of these was immediately subject to decarbonylation using Wilkinson's catalyst [$RhCl(PPh_3)_3$],[19] thus affording target **4** in 40% yield (from **22**). All of the IR, MS, ^1H, and ^{13}C NMR spectral data obtained on compound **4**, details of which are presented in Experimental

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Section, were in complete accord with the assigned structure. The NMR spectral data just mentioned compare very favorably with those reported[4] by Norte and co-workers for the natural product (see SI for tabulated comparisons). Similarly, the specific rotation of the synthetic material was close to that reported for the natural product {$[\alpha]_D$ +3.9 (*c* 0.3, $CHCl_3$) vs $[\alpha]_D$ +4.5 (*c* 0.15, $CHCl_3$)}.

■ CONCLUSIONS

The present study represents the first directed toward the synthesis of those two natural products incorporating the decahydrocyclobuta[*d*]indene framework (**3**), namely (+)-viridianol (**4**) and (+)-trefolane A (**5**). This work also emphasizes the utility of the Givens-type rearrangement of bicyclo[2.2.2]-octenones as a means for generating cyclobutannulated cyclohexenes in a range of settings, including ones where the photoproduct incorporates an all-carbon quaternary center.[20]

■ 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 Varian 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 the internal standards. ^{1}H NMR data are reported 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, and 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 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 on a magnetic-sector machine. Melting points were measured on 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 as supplied by Merck. 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 (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 following protocols defined by Still et al.[21] with silica gel 60 (40−63 μm) as the stationary phase and using AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from Sigma−Aldrich, Merck, TCI, Strem, or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX, BDH, or Unilab chemical companies. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[22] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *Compound* ***12***. A magnetically stirred solution of triphenylphosphine (22.0 g, 84 mmol) and imidazole (5.7 g, 84 mmol) in dry dichloromethane (200 mL) maintained at 0 °C was treated with iodine (21.0 g, 83 mmol) in five portions over 0.33 h. After 0.5 h, 3-methyl-4-penten-1-ol[14] (8.0 g, 80.0 mmol) was added dropwise. The resulting suspension was stirred at 22 °C for 4 h before being concentrated under reduced pressure to ca. 100 mL. The orange slurry thus obtained was diluted with hexane (500 mL) and then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure and the ensuing pale-yellow liquid subjected to flash column chromatography (silica gel, pentane elution). Concentration of the relevant fractions (R_f = 0.7) then gave compound **12** (10.0 g, 60%) as a clear, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.02 (m, 2H), 3.30−3.10 (complex m, 2H), 2.28 (m, 1H), 1.80 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 114.1, 40.0, 38.7, 19.7, 4.9; IR (KBr) ν_{max} 3077, 2958, 2920, 1640, 1452, 1418, 1373, 1238, 1179, 994, 917 cm^{-1}; MS (EI, 70 ev) *m*/*z* 210 ($M^{+\bullet}$, 21%), 209 (95), 155 (15), 127 (20), 83 (40) 81 (38), 55 (100). Satisfactory high-resolution mass spectral data could not be obtained for this compound.

Compounds ***9*** *and* ***13***. A magnetically stirred solution of iodide **12** (2.90 g, 13.7 mmol) in dry diethyl ether (70 mL) maintained at −78 °C under a nitrogen atmosphere ed, over 4 min, with *t*-BuLi (17.7 mL of 1.7 M solution in pentane, 30.1 mmol). After a further 3 min, a solution of anhydrous ZnI_2 (4.80 g, 15.1 mmol) (dried under high vacuum at 120 °C for 20 h) in dry THF (15 mL) was added to the reaction mixture that was stirred at −78 °C for a further 10 min before being allowed to warm to 22 °C over 1.0 h. A solution of acetonide **11**[13] (4.0 g, 13.7 mmol) and $Pd(PPh_3)_4$ (790 mg, 0.69 mmol) in dry THF (15 mL) was then added dropwise to give an initially yellow-colored reaction mixture. After stirring for 4 h at 22 °C, the reaction mixture was quenched with $NaHCO_3$ (40 mL of a saturated aqueous solution) and the separated aqueous phase extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with brine (1 × 100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:50 v/v diethyl ether/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.6), a ca. 1:1 mixture of compounds **9** and **13** (2.30 g, 68%) as a clear, colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72−5.63 (complex m, 6H), 4.98−4.90 (complex m, 4H), 4.51−4.46 (complex m, 4H), 2.21−2.12 (complex m, 6H), 1.86 (s, 6H), 1.51−1.46 (complex m, 4H), 1.41 (s, 6H), 1.35 (s, 6H), 1.01 (d, *J* = 1.0 Hz, 3H), 0.99 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 144.3, 135.5, 131.8(4), 131.8(2), 119.7, 119.1, 112.9, 112.7, 105.7, 75.7, 74.3(4), 74.2(9), 37.5, 37.4, 34.2, 34.1, 31.4, 31.3, 27.0, 25.4, 20.3, 20.0, 19.8 (eight signals obscured or overlapping); IR (KBr) ν_{max} 3077, 2915, 1670, 1638, 1452, 1378, 1236, 1162, 1015, 911, 872 cm^{-1}; MS (ESI, +ve) *m*/*z* 303 [(M + MeOH + Na)$^+$, 100%], 302 (55), 271 (25), 199 (20), 121 (20); HRMS (EI, 70 eV) [M − Me•]$^+$ Calcd for $C_{15}H_{21}O_2$ 233.1542; found 233.1544.

Compounds ***8*** *and* ***13***. A magnetically stirred, 1:1 mixture of compounds **9** and **13** (600 mg, 2.42 mmol) in toluene (400 mL) containing butylated hydroxytoluene (BHT) (16 mg, 0.07 mmol) was heated at 120 °C for 67 h and then cooled to 22 °C before being and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:50 v/v diethyl ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6) gave compound **13** (260 mg, 87% recovery) as a clear, colorless liquid, $[\alpha]_D^{20}$ = +27 (*c* = 2.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72−5.64 (complex m, 3H), 4.99−4.91 (complex m, 2H), 4.51−4.46 (complex m, 2H), 2.22−2.14 (complex m, 3H), 1.87 (s, 3H), 1.51−1.46 (complex m, 2H), 1.42 (s, 3H), 1.35 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 135.5, 131.8, 119.7, 119.1, 112.9, 105.7, 75.7, 74.3, 37.5, 34.1, 31.3, 27.0, 25.4, 20.4, 19.8; IR (KBr) ν_{max} 2961, 2916, 2869, 1669, 1637, 1451, 1378, 1369, 1236, 1156, 1059, 1037, 1013, 911, 871 cm^{-1}; MS (EI, 70 ev) *m*/*z* 233 [(M − Me•)$^+$, 1%], 191 (35), 190 (45), 175 (20), 161 (30), 134 (40), 122 (45), 121 (100), 108 (52), 91 (40); HRMS (EI, 70 eV) [M − Me•]$^+$ Calcd for $C_{15}H_{21}O_2$ 233.1542; found 233.1542.

Concentration of fraction B [R_f = 0.5(5)] gave compound **8** (270 mg, 90% based on **9**) as a clear, colorless liquid, $[\alpha]_D^{20}$ = +7.4 (*c* = 5.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, *J* = 8.2 Hz, 1H), 5.69 (d, *J* = 8.2 Hz, 1H), 4.01 (d, *J* = 7.1 Hz, 1H), 3.85 (d, *J* = 7.1 Hz, 1H), 1.99−1.96 (complex m, 2H), 1.73−1.65 (complex m, 1H), 1.39−1.33 (complex m, 4H), 1.30 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.14−1.06 (complex m, 1H), 0.90 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR

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(100 MHz, $CDCl_3$) δ 135.8, 134.4, 108.2, 85.3, 83.9, 51.0, 49.5, 40.1, 39.5, 35.2, 33.1, 31.7, 25.6, 24.9, 21.5, 18.8; IR (KBr) ν_{max} 3037, 2949, 2921, 1457, 1369, 1265, 1206, 1166, 1093, 1064, 1001, 877 cm^{-1}; MS (EI, 70 ev) m/z 248 ($M^{+\bullet}$, < 1%), 233 [$(M - Me\bullet)^+$, 30], 191 (28), 190 (85), 175 (30), 161 (35), 148 (100), 133 (48), 119 (33), 105 (75), 91 (40); HRMS (EI, 70 eV) [$M - Me\bullet$]$^+$ Calcd for $C_{15}H_{21}O_2$ 233.1542; found 233.1544.

Compound ***14***. A magnetically stirred suspension of acetonide **8** (180 mg, 0.72 mmol) in methanol/water (15 mL of a 2:1 v/v mixture) was treated with Dowex-50 (600 mg of acidified material) and the ensuing mixture heated at 70 °C for 24 h before being cooled and filtered. The filtrate was concentrated under reduced pressure to give a residue that was dissolved in ethyl acetate (50 mL) and the resulting solution then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (1 × 30 mL) and the combined organic phases then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:50 v/v diethyl ether/hexane elution →1:2 v/v ethyl acetate/hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 1:50 v/v diethyl ether/hexane) gave starting acetonide **8** (27 mg, 15% recovery) as a clear, colorless liquid. The spectral data acquired for this material matched those recorded for an authentic sample.

Concentration of fraction B (R_f = 0.2) gave compound **14** (120 mg, 80% or 94% brsm) as a white, crystalline solid, mp = 94−96 °C, $[\alpha]_D^{20}$ = +7.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, J = 8.1 Hz, 1H), 5.79 (d, J = 8.1 Hz, 1H), 3.68 (d, J = 7.3 Hz, 1H), 3.51 (d, J = 7.3 Hz, 1H), 2.50 (broad s, 2H), 2.03−1.93 (complex m, 2H), 1.76−1.72 (complex m, 1H), 1.47 (dd, J = 12.6 and 9.3 Hz, 1H), 1.39−1.25 (complex m, 3H), 1.21 (s, 3H), 1.18−1.14 (complex m, 1H), 0.88 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 134.9, 76.8, 75.1, 52.3, 49.0, 40.8, 39.8, 36.8, 32.6, 31.7, 21.2, 18.4; IR (KBr) ν_{max} 3347, 3034, 2944, 2920, 2865, 1384, 1094, 1061, 975, 923, 846, 720 cm^{-1}; MS (ESI, +ve) m/z 231 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) [$M + Na$]$^+$ Calcd for $C_{13}H_{20}O_2Na$ 231.1361; found 231.1359.

Compounds ***15*** *and* ***16***. A magnetically stirred solution of diol **14** (470 mg, 2.26 mmol) in dichloromethane (20 mL) maintained at 0 °C was treated, dropwise over 1 h, with a solution of *p*-TsOH·H_2O (640 mg, 3.38 mmol) and 4-acetamido-TEMPO (960 mg, 4.52 mmol) in dichloromethane (100 mL). The ensuing mixture was stirred at 22 °C for 24 h and then quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution) and the separated aqueous phase extracted with dichloromethane (1 × 30 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the resulting light-yellow oil was subjected to flash column chromatography (silica gel, 1:5 v/v ethyl acetate/hexane elution) to afford three fractions, A, B, and C.

Concentration of fraction A (R_f = 0.35) gave compound **15** (220 mg, 47% or 52% brsm) as a clear, colorless oil contaminated with an isomer tentatively assigned as its hydroxy-epimer, $[\alpha]_D^{20}$ = −146 (c = 3.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, J = 7.8 Hz, 1H), 5.66 (d, J = 7.8 Hz, 1H), 3.49 (s, 1H), 2.71 (broad s, 1H), 2.24 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.70−1.62 (complex m, 2H), 1.49 (m, 1H), 1.33 (m, 1H), 1.30 (s, 3H), 1.19 (dd, J = 12.5 and 6.7 Hz, 1H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 140.7, 130.8, 74.4, 60.5, 47.6, 43.3, 40.0, 36.8, 32.7, 25.3, 20.0, 17.8; IR (KBr) ν_{max} 3445, 3040, 2950, 2928, 2868, 1726, 1456, 1376, 1077, 1033, 714 cm^{-1}; MS (EI, 70 ev) m/z 206 ($M^{+\bullet}$, 10%), 178 (68), 163 (42), 149 (78), 135 (80), 121 (40), 105 (100), 91 (80); HRMS (EI, 70 eV) $M^{+\bullet}$ Calcd for $C_{13}H_{18}O_2$ 206.1307; found 206.1307. A small sample of this material dissolved in dichloromethane was allowed to stand in a fridge at ca. 5 °C over a sustained period, thus yielding a solid suitable for single-crystal X-ray analysis (details provided below).

Concentration of fraction B (R_f = 0.3) gave compound **16** (150 mg, 32% or 36% brsm) as a clear, colorless oil, $[\alpha]_D^{20}$ = +252 (c = 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (d, J = 7.9 Hz, 1H), 5.90 (d, J = 7.9 Hz, 1H), 3.50 (s, 1H), 2.75 (m, 1H), 2.05 (m, 2H), 1.80 (m, 2H), 1.65−1.40 (complex m, 3H), 1.30 (m, 1H), 1.20 (s, 3H), 0.93 (d, J = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0, 139.5, 133.2, 76.8, 53.5, 51.1, 49.6, 40.0, 35.1, 32.6, 30.1, 18.5, 17.4; IR (KBr) ν_{max} 3442, 3040, 2949, 2920, 2867, 1721, 1453, 1377, 1113, 1025, 1009, 817, 690 cm^{-1}; MS (ESI, +ve) m/z 229 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) [$M + Na$]$^+$ Calcd for $C_{13}H_{18}O_2Na$ 229.1204; found 229.1207.

Concentration of the fraction C (R_f = 0.1) gave starting diol **14** (84 mg, 18% recovery) as a white, crystalline solid that was identical, in all respects, to an authentic sample.

Compound ***17***. A magnetically stirred mixture of acyloin **16** (160 mg, 0.78 mmol) in dry dichloromethane (20 mL) maintained at 0 °C was treated with benzoyl chloride (180 μL, 1.60 mmol), Et_3N (300 μL, 2.16 mmol), and then DMAP (29 mg, 0.24 mmol). Once these additions were complete, the reaction mixture was warmed to and stirred at 22 °C for 4 h, poured into HCl (20 mL of a 1 M solution), and then extracted with dichloromethane (2 × 30 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica gel, 1:25 v/v diethyl ether/hexane elution). Concentration of the relevant fractions (R_f = 0.6) gave compound **17** (180 mg, 75%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +199 (c = 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 1H), 7.53 (m, 1H), 7.40 (m, 2H), 6.15 (d, J = 8.0 Hz, 1H), 5.97 (d, J = 8.0 Hz, 1H), 5.19 (s, 1H), 2.04−1.80 (complex m, 5H), 1.76 (m, 1H), 1.65 (m, 1H), 1.40 (m, 1H), 1.35 (dd, J = 12.8 and 6.1 Hz, 1H), 1.26 (s, 3H), 0.99 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 166.1, 139.1, 133.6, 133.0, 129.8, 129.7, 128.2, 75.9, 52.6, 51.0, 50.0, 40.1, 35.3, 32.4, 30.0, 18.5, 17.5; IR (KBr) ν_{max} 3038, 2948, 2867, 1735, 1601, 1451, 1378, 1314, 1268, 1176, 1111, 1068, 1025, 710 cm^{-1}; MS (ESI, +ve) m/z 643 [(2 M + Na)$^+$, 80%], 333 [$(M + Na)^+$, 100], 311 [$(M + H)^+$, 25]; HRMS (ESI, +ve) [$M + Na$]$^+$ Calcd for $C_{20}H_{22}O_3Na$ 333.1467; found 333.1468.

Compound ***7***. A magnetically stirred solution of keto-ester **17** (200 mg, 0.64 mmol) in THF/methanol (21 mL of a 2:1 v/v mixture) maintained under nitrogen was cooled to −78 °C then treated, dropwise, with SmI_2 (0.1 M solution in THF) until a bright-blue color persisted (ca. 5 min). The resulting mixture was then poured into K_2CO_3 (20 mL of a saturated aqueous solution) and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash column chromatography (silica gel, 1:50 v/v diethyl ether/hexane elution), and concentration of the relevant fractions (R_f = 0.7) afforded ketone **7** (120 mg, 98%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +207 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, J = 8.0 Hz, 1H), 5.88 (d, J = 8.0 Hz, 1H), 2.19 (d, J = 17.6 Hz, 1H), 2.06−2.01 (complex m, 1H), 1.95−1.88 (complex m, 1H), 1.91 (d, J = 17.6 Hz, 1H), 1.79 (m, 1H), 1.63 (m, 1H), 1.49−1.40 (complex m, 3H), 1.26 (dd, J = 12.6 and 5.4 Hz, 1H), 1.19 (s, 3H), 0.94 (d, J = 5.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9, 141.3, 134.3, 53.9, 50.3, 49.4, 47.0, 40.6, 37.0, 33.0, 32.1, 18.8, 17.7; IR (KBr) ν_{max} 2920, 2867, 1721, 1452, 1383, 1261, 1070, 801, 732 cm^{-1}; MS (ESI, +ve) m/z 213 [$(M + Na)^+$, 100%], 191 [$(M + H)^+$, 25], 121 (75); HRMS (ESI, +ve) [$M + Na$]$^+$ Calcd for for $C_{13}H_{18}ONa$ 213.1255; found 213.1256.

Compound ***6***. A magnetically stirred solution of ketone **7** (1.30 g, 6.84 mmol) in degassed, dry dichloromethane (130 mL) was irradiated with a high-pressure mercury lamp (Philips 125 W HPL-N lamp with water-jacketed cooling to 5 °C; CAUTION! Avoid eye contact with lamp) for 22 h at 22 °C. The ensuing mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica gel, 1:50 v/v diethyl ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.35) gave compound **6** (806 mg, 62% or 79% brsm) as a clear, colorless oil, $[\alpha]_D^{20}$ = −133 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (m, 1H), 3.26 (m, 1H), 2.94 (dd, J = 17.7 and 2.5 Hz, 1H), 2.85 (dd, J = 17.7 and 4.2 Hz, 1H), 2.13 (m, 1H), 2.02 (m, 1H), 1.93−1.83 (complex m, 3H), 1.73

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(broadened s, 3H), 1.61−1.57 (complex m, 2H), 1.26 (m, 1H), 1.01 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 135.0, 114.4, 64.4, 53.3, 47.4, 38.0, 37.6, 37.5, 31.1, 29.3, 24.4, 20.5; IR (KBr) ν_{max} 2949, 2866, 1781, 1447, 1384, 1144, 1080, 1046 cm^{-1}; MS (ESI, +ve) m/z 213 [(M + Na)$^+$, 20%], 191 [(M + H)$^+$, 75], 147 (100); HRMS (ESI, +ve) [M + Na]$^+$ Calcd for for $C_{13}H_{18}ONa$ 213.1255; found 213.1256.

Concentration of fraction B (R_f = 0.3) gave a clear, colorless liquid, tentatively identified as starting compound **7** (150 mg, 38% recovery) contaminated with ca. 15% of photoproduct **6**. This mixture was reirradiated under the same conditions as defined above to afford additional quantities of compound **6** (131 mg, 72% combined yield).

Compound ***18***. A magnetically stirred solution of compound **6** (190 mg, 1.00 mmol) in dry diethyl ether (5 mL) maintained at −78 °C under an atmosphere of nitrogen was treated with MeLi (2.50 mL of a 1.0 M solution in hexane, 2.50 mmol). The ensuing mixture was then allowed to warm to 22 °C over 2 h before being treated with NH_4Cl (10 mL of a saturated solution) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine (1 × 20 mL) and then water (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:4 v/v diethyl ether/pentane elution) to afford, after concentration of the appropriate fractions (R_f = 0.3), compound **18** (177 mg, 86%) as a clear, colorless oil, $[\alpha]_D^{20}$ = −15 (c = 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (broadened s, 1H), 2.33 (broadened s, 1H), 2.17 (dd, J = 17.5 and 6.3 Hz, 1H), 2.00−1.94 (complex m, 2H), 1.92 (d, J = 17.8 Hz, 1H), 1.86−1.62 (complex m, 4H), 1.78 (s, 3H), 1.48 (m, 1H), 1.42 (s, 3H), 1.24 (m, 1H), 1.12 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 118.1, 71.4, 51.0, 48.4, 45.7, 38.2, 37.2, 36.4, 30.9, 29.3, 28.8, 24.8, 20.4; IR (neat) ν_{max} 3560, 3459, 2947, 2865, 1448, 1375, 1349, 1233, 1171, 1146, 968, 941, 908, 873 cm^{-1}; MS (ESI, +ve) m/z 413 [(2 M + H)$^+$, 20%], 229 [(M + Na)$^+$, 95], 105 (100); HRMS (ESI, +ve) [M + Na]$^+$ Calcd for for $C_{14}H_{22}ONa$ 229.1568; found 229.1563.

Compound ***4***. A magnetically stirred solution of formaldehyde (35% solution, 55.2 mg, 0.64 mmol) in THF (3 mL) maintained at 22 °C under nitrogen was treated with *n*-octanesulfonyl hydrazide (111 mg, 0.53 mmol), and the ensuing mixture was stirred for 4 h. The resulting solution was added, along with olefin **18** (44.2 mg, 0.21 mmol), $Fe(acac)_3$ (75.7 mg, 0.21 mmol), and methanol (18.5 μL, 0.42 mmol), to THF (750 μL) maintained under a flow of nitrogen. The ensuing mixture was subjected to two freeze−pump−thaw deoxygenation cycles and then treated with $PhSiH_3$ (46.4 mg, 0.42 mmol). Two further freeze−pump−thaw deoxygenation cycles were applied to the resulting solution that was then stirred under a nitrogen atmosphere at 32 °C for 20 h. The reaction mixture was cooled to 22 °C, and then a second aliquot of the hydrazone, prepared as described above from formaldehyde and *n*-octanesulfonyl hydrazide, was added to the reaction mixture. After 4 h, $Fe(acac)_3$ (75.7 mg, 0.21 mmol), $PhSiH_3$ (46.4 mg, 0.42 mmol), and anhydrous THF (0.5 mL) were added to the reaction mixture, the resulting solution was degassed by three freeze−pump−thaw deoxygenation cycles, and the reaction mixture was heated at 32 °C for 20 h before being cooled and then concentrated under reduced pressure. The residue was diluted with methanol (6 mL) and the resulting solution heated at 60 °C for 1.5 h while being maintained under a nitrogen atmosphere. After this time, the reaction mixture was cooled to 22 °C and then diluted with brine (5 mL) then extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine (1 × 20 mL), dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:20 → 1:5 v/v diethyl ether/pentane gradient elution) to give two fractions, A and B.

Concentration of fraction A [R_f = 0.2(2) in 1:5 v/v diethyl ether/pentane elution] gave the starting compound **18** (13.1 mg, 30%,) as a clear, colorless oil. The spectral data derived from this material matched those recorded for an authentic sample.

Concentration of fraction B [R_f = 0.2(0) in 1:5 v/v diethyl ether/pentane elution] gave an impure sample of compound **4** (21 mg, ca. 45%) as a white, amorphous solid. A comparison of the ^{1}H and ^{13}C NMR spectral data derived from this material with those recorded on a sample prepared by the methods detailed below established that viridianol was the major product, but this was contaminated by inseparable byproducts including ones tentatively assigned as arising from the addition of the elements of hydrogen to the starting material.

Compound ***19***. A magnetically stirred solution of compound **18** (120 mg, 0.58 mmol) in acetonitrile (500 μL) maintained at 22 °C under nitrogen was treated with Ac_2O (71 mg, 0.7 mmol) and $InCl_3$ (6.4 mg, 0.029 mmol). After 0.66 h, the reaction mixture was treated with $NaHCO_3$ solution (5 mL of a saturated aqueous solution) and then extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine (1 × 20 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica gel, 1:10 v/v diethyl ether/hexane elution). Concentration of the appropriate fractions (R_f = 0.6) gave compound **19** (110 mg, 80%) as a clear, colorless oil, $[\alpha]_D^{22}$ = −83 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 2.42 (s, 1H), 2.15−2.04 (complex m, 2H), 1.92 (dd, J = 12.4 and 3.2 Hz, 1H), 1.86 (s, 3H), 1.85−1.75 (complex m, 2H), 1.75−1.64 (complex m, 1H), 1.64 (s, 3H), 1.61 (s, 3H), 1.47−1.35 (complex m, 1H), 1.21−1.02 (complex m, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 133.1, 118.6, 80.0, 50.4, 48.8, 42.7, 38.9, 38.2, 36.4, 31.0, 28.8, 26.3, 24.6, 21.8, 20.3; IR (neat) ν_{max} 2928, 2865, 1737, 1435, 1370, 1259, 1208, 1019 cm^{-1}; MS (ESI, +ve) m/z 271 [(M + Na)$^+$, 100%]; HRMS (ESI, +ve) [M + Na]$^+$ Calcd for for $C_{16}H_{24}O_2Na$ 271.1669; found 271.1669.

Compound ***20*** *(α- and β-epimers)*. A magnetically stirred solution of alkene **19** (100 mg, 0.4 mmol) and $Fe(acac)_3$ (213 mg, 0.6 mmol) in ethanol (600 μL) containing ethylene glycol (200 μL) and maintained at 22 °C was treated with acrylonitrile (64 mg, 1.2 mmol) and then $PhSiH_3$ (87 mg, 0.8 mmol). The ensuing mixture was heated at 60 °C for 2 h, cooled to 22 °C, and then diluted with diethyl ether (5 mL) before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:10−1:3 v/v diethyl ether/hexane elution) to afford, after concentration of the appropriate fractions (R_f = 0.4 in 1:3 v/v diethyl ether/hexane elution), an inseparable 2:1 mixture of the diastereoisomeric forms of compound **20** (85 mg, 70%) as a clear, colorless oil, $[\alpha]_D^{22}$ = −4.1 (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31−2.14 (complex m, 3H), 2.16−1.98 (complex m, 2H), 1.92 (s, 2H), 1.91 (s, 1H), 1.86 (m, 1H), 1.79−1.67 (complex m, 1H), 1.69−1.48 (complex m, 4H), 1.58 (s, 2H), 1.56 (s, 1H), 1.48−1.33 (complex m, 1H), 1.34−1.13 (complex m, 4H), 1.04 (m, 1H), 0.89−0.79 (complex m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 170.1, 120.6, 120.5, 78.4, 78.3, 50.7, 50.3, 49.0(0), 48.9(5), 48.5, 48.4, 41.0, 40.9, 40.5, 40.3, 40.2, 39.9, 39.4, 38.8, 38.7, 36.9, 34.0(3), 33.9(9), 33.4(0), 33.3(6), 31.8(8), 31.8(6), 27.4, 25.3, 25.1, 21.7, 21.2, 21.1, 12.4, 12.2 (two signals obscured or overlapping); IR (neat) ν_{max} 2932, 2228, 1732, 1458, 1371, 1251, 1219, 1151, 1019 cm^{-1}; MS (ESI, +ve) m/z 326 [(M + Na)$^+$, 100%], 304 [(M + H)$^+$, <1]; HRMS (ESI, +ve) [M + H]$^+$ Calcd for for $C_{19}H_{30}NO_2$ 304.2271; found 304.2272.

Compound ***22*** *(α- and β-epimers)*. A magnetically stirred solution of compound **20** (70 mg of a 2:1 mixture of epimers, 0.23 mmol) in dry diethyl ether (4 mL) maintained at −78 °C under an atmosphere of nitrogen was treated with MeLi (1.38 mL of a 1.0 M solution in hexane, 1.38 mmol). The ensuing mixture was stirred at −78 °C for 0.17 h, warmed to 22 °C over 0.5 h, stirred at this temperature for 2 h, and then quenched with NH_4Cl (5 mL of a saturated aqueous solution) before being diluted with water (5 mL). The ensuing mixture was extracted with diethyl ether (3 × 15 mL), and the combined organic phases were washed with brine (1 × 10 mL), dried ($MgSO_4$), filtered, and then concentrated under reduced pressure to give a light-yellow oil presumed to contain compound **21** as a mixture of α- and β-epimers. Without purification, a magnetically stirred solution of this oil in CH_2Cl_2 (4 mL) was cooled to 0 °C and then treated with UHP (261 mg, 2.7 mmol) and TFAA (291 mg, 1.39

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mmol) in CH_2Cl_2 (4 mL). The ensuing mixture was warmed to 22 °C, stirred at this temperature for 1 h, quenched with $Na_2S_2O_3$ solution (2 mL of a saturated aqueous solution), and then concentrated under reduced pressure to give a light-yellow oil presumed to contain an epimeric mixture of the anticipated acetates. A magnetically stirred solution of this oil in methanol (3 mL) maintained at 22 °C was treated with NaOH (184 mg, 4.6 mmol) in methanol (3 mL), and after 2 h the reaction mixture was diluted with water (4 mL) and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:1 v/v ethyl acetate/hexane elution), thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.1) afforded compound **22** (α-epimer) (30 mg, 52% from **20**) as a clear, colorless oil, $[\alpha]_D^{21}$ = −3.3 (c = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (t, J = 7.5 Hz, 2H), 2.01 (d, J = 11.9 Hz, 1H), 1.96−1.86 (complex m, 2H), 1.83−1.66 (complex m, 2H), 1.66−1.39 (complex m, 7H), 1.38 (s, 3H), 1.36−1.16 (complex m, 4H), 1.00 (m, 1H), 0.86 (d, J = 6.9 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.8, 59.7, 50.9, 50.7, 48.7, 46.7, 41.8, 40.6, 39.1, 39.0, 34.7, 33.5, 31.4, 29.3, 26.8, 21.3; IR (neat) ν_{max} 3351, 2948, 2924, 1457, 1374, 1228, 1152, 1056, 1017 cm^{-1}; MS (ESI, +ve) m/z 275 [(M + Na)$^+$, 100%], 253 [(M + H)$^+$, <1]; HRMS (ESI, +ve) [M + Na]$^+$ Calcd for for $C_{16}H_{28}O_2Na$ 275.1982; found 275.1980. A portion of this oil was dissolved in hexane/dichloromethane and the resulting solution allowed to evaporate slowly, providing some crystals, one of which was used for single-crystal X-ray analysis.

Concentration of fraction B [R_f = 0.1(5)] gave compound **22** (β-epimer) (15 mg, 26% from **20**) as a white, crystalline solid, mp = 130 °C, $[\alpha]_D^{21}$ = +2.4 (c = 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (m, 2H), 2.02 (d, J = 12.1 Hz, 1H), 1.95−1.86 (complex m, 2H), 1.84−1.67 (complex m, 2H), 1.59 (m, 1H), 1.49−1.40 (complex m, 5H), 1.39 (s, 3H), 1.32−1.11 (complex m, 4H), 1.07−0.95 (complex m, 2H), 0.93 (s, 3H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.8, 59.9, 50.7, 50.4, 48.9, 44.4, 41.8, 40.4, 39.1, 38.9, 35.3, 33.5, 31.3, 29.2, 28.6, 21.3; IR (neat) ν_{max} 3335, 2948, 2922, 1458, 1375, 1231, 1153, 1050, 1020 cm^{-1}; MS (ESI, +ve) m/z 275 [(M + Na)$^+$, 100%], 253 [(M + H)$^+$, <1]; HRMS (ESI, +ve) [M + Na]$^+$ Calcd for for $C_{16}H_{28}O_2Na$ 275.1982; found 275.1980.

Compound **4**. A mixture of DMP (63 mg, 0.15 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added, dropwise, to a magnetically stirred solution of compound **22** (25 mg, of a ca. 2:1 mixture of α- and β-epimers, 0.1 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at 22 °C for 0.66 h, quenched with $NaHCO_3$ (4 mL of a saturated aqueous solution), and then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil. Without purification, this material, which is presumed to contain the epimeric aldehydes derived from the starting alcohols, was treated, while being maintained under nitrogen, with a solution of Wilkinson's catalyst (185 mg, 0.2 mmol) in degassed toluene (1.5 mL). The ensuing solution was heated to 80 °C, stirred at this temperature for 4 h before being cooled to 22 °C, diluted with water (5 mL), and then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine (1 × 20 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:1 v/v CH_2Cl_2/*n*-pentane elution) to afford, after concentration of the appropriate fractions (R_f = 0.5), compound **4** (8.8 mg, 40% from **22**) as an amorphous, white solid, mp = 70−72 °C, $[\alpha]_D^{21}$ = +3.9 (c = 0.3, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.07 (d, J = 11.9 Hz, 1H), 2.03−1.94 (complex m, 2H), 1.87 (ddd, J = 12.6, 7.0, 2.4 Hz, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.48 (m, 1H), 1.45 (s, 3H), 1.40−1.23 (complex m, 5H), 1.06 (m, 1H), 0.98 (s, 3H), 0.97 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 70.7, 50.9, 50.9, 49.4, 42.6, 40.5, 39.2, 38.8, 36.4, 33.6, 31.9, 29.2, 29.1, 29.0, 21.2; ^{1}H NMR (600 MHz, C_6D_5N) δ 2.39 (d, J = 11.2 Hz, 1H), 2.11−2.01 (complex m, 2H), 1.94−1.86 (complex m, 2H), 1.76 (m, 1H), 1.66 (m, 1H), 1.64 (s, 3H), 1.55 (dd, J = 13.7 and 6.2 Hz, 1H), 1.46 (m, 1H), 1.33 (m, 1H), 1.30−1.23 (complex m, 2H), 1.12−1.02 (complex m, 1H), 0.98 (m, 1H), 0.98 (s, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, C_6D_5N) δ 69.8, 51.4, 51.4, 50.3, 42.7, 40.9, 40.0, 39.0, 37.2, 34.0, 32.2, 30.2, 29.3, 29.3, 21.3; IR (neat) ν_{max} 3361, 2949, 2923, 2863, 1460, 1363, 1217, 1102, 987, 941 cm^{-1}; MS (EI, 70 ev) m/z 222 (M$^{+\bullet}$, 2%), 204 (10), 179 (12), 165 (35), 164 (97), 149 (100), 113 (87), 108 (99), 95 (95), 93 (94); HRMS (EI, 70 eV) M$^{+\bullet}$ Calcd for $C_{15}H_{26}O$ 222.1984; found 222.1986.

X-ray Crystallographic Studies. *Crystallographic Data. Crystallographic Data for Compound* ***15***. $C_{13}H_{18}O_2$, M = 206.28, T = 150 K, triclinic, space group $P\bar{1}$, Z = 4, a = 9.5733(3) Å, b = 11.0102(5) Å, c = 12.0302(4) Å; α = 77.447(4)°, β = 67.451(3)°, γ = 85.529(3)°; V = 1143.08(8) Å^3, D_x = 1.199 mg cm^{-3}, 4496 unique data ($2\theta_{max}$ = 144.4°), R = 0.041 [for 4098 reflections with $I > 2.0\sigma(I)$]; Rw = 0.109 (all data), S = 0.99.

Crystallographic Data for Compound ***22*** *(α-epimer).* $C_{16}H_{18}O_2$, M = 252.38, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 8, a = 9.5839(1) Å, b = 12.7030(1) Å, c = 24.8305(3) Å; V = 3022.97(5) Å^3, D_x = 1.109 mg cm^{-3}, 6097 unique data ($2\theta_{max}$ = 147.8°), R = 0.040 [for 6001 reflections with $I > 2.0\sigma(I)$]; Rw = 0.109 (all data), S = 1.04.

Crystallographic Data for Compound ***22*** *(β-epimer).* $C_{16}H_{28}O_2$, M = 252.38, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.3617(2) Å, b = 8.7528(2) Å, c = 26.7339(7) Å; V = 1488.62(7) Å^3, D_x = 1.126 mg cm^{-3}, 2960 unique data ($2\theta_{max}$ = 147.6°), R = 0.045 [for 2649 reflections with $I > 2.0\sigma(I)$]; Rw = 0.113 (all data), S = 1.03.

Structure Determinations. Images for compounds **15**, **22** (α-epimer), and **22** (β-epimer) were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[23] The structures were solved with ShelXT[24] and refined using ShelXL[25] in OLEX2.[26] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1863280, 1863281, and 1863282). 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02626.

Tabular comparisons of the NMR data recorded for synthetically derived (+)-viridianol with those reported for the natural product, X-ray-derived plots for compounds **15**, **22** (α-epimer), and **22** (β-epimer), and copies of the NMR spectra of compounds **4**, **6**−**9**, and **12**−**22** (PDF)

X-ray crystallographic data for compound **15** (CIF)

X-ray crystallographic data for compound **22** (α-epimer) (CIF)

X-ray crystallographic data for compound **22** (β-epimer) (CIF)

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.joc.8b02626
J. Org. Chem. 2018, 83, 14049−14056

SUPPORTING INFORMATION FOR:

Total Synthesis of (+)-Viridianol, a Marine-derived Sesquiterpene Embodying the Decahydrocyclobuta[*d*]indene Framework

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Table S1: *Comparison of the ^{1}H NMR Spectral Data Reported[5] by Norte et al for (+)-Viridianol with the Equivalent Data Recorded for Compound **4** Prepared by the Present Route*

δ_H (*ex*. Norte)[a,b]	δ_H (*ex*. Present Route)[c]	δ_H (*ex*. Norte)[d,e]	δ_H (*ex*. Present Route)[f]
2.08, J = 12 Hz, 1H	2.07, d, J = 11.9 Hz, 1H	2.38, 1H	2.39, J = 11.2 Hz, 1H
1.98, J = 12.9, 7.1, 3.5 Hz, 1H	2.03-1.94, complex m, 2H	2.08, 1H	2.11-2.01, complex m, 2H
1.97, J = 12, 3.5 Hz, 1H	–	2.03, 1H	–
1.88, J = 12, 7, 2.5 Hz, 1H	1.87, ddd, J = 12.6, 7.0, 2.4 Hz, 1H	1.91, 1H	1.94-1.86, complex m, 2H
1.78, J = 12, 7, 7, 2.5 Hz, 1H	1.78, m, 1H	1.88, 1H	–
1.67, J = 12, 11, 7 Hz, 1H	1.66, m, 1H	1.76, 1H	1.76, m, 1H
1.48, J = 8.5, 7, 6.7, 6.7, 6.7, 5 Hz, 1H	1.48, m, 1H	1.66, 1H	1.66, m, 1H
1.46, 3H	1.45, 3H	1.64, 3H	1.64, s, 3H
1.39, J = 13.5, 12.9 Hz, 1H	1.40-1.23, complex m, 5H	1.54, 1H	1.55, dd, J = 13.7, 6.2 Hz, 1H
1.32, J = 12.9, 7.1 Hz, 1H	–	1.46, 1H	1.46, m, 1H
1.30, J = 14.8, 5.8 Hz, 1H	–	1.33, 1H	1.33, m, 1H
1.28, J = 11.6, 5.8, 5 Hz, 1H	–	1.27, 1H	1.30-1.23, complex m, 2H
1.05, J = 12, 11, 8.5, 7 Hz, 1H	1.06, m, 1H	1.07, 1H	1.12-1.02, complex m, 1H
0.99, J = 14.8, 11.6 Hz, 1H	0.97, m, 1H	0.98, 1H	0.98, m, 1H
0.98, 3H	0.98, 3H	0.98, 3H	0.98, 3H
0.92, J = 6.7 Hz, 3H	0.92, d, J = 6.8 Hz, 3H	0.91, 3H	0.91, d, J = 6.8 Hz, 3H
0.86, 3H[g]	0.86, s, 3H	0.87, 3H[g]	0.88, s, 3H

[a] Spectrum recorded in $CDCl_3$ at undefined field strength, data taken from reference 1;
[b] Multiplicity of resonance not reported;
[c] Spectrum recorded in $CDCl_3$ at 600 MHz;
[d] Spectrum recorded in C_5D_5N at undefined field strength, data taken from reference 1;
[e] Multiplicity of resonance and coupling constant data not reported;
[f] Spectrum recorded in C_5D_5N at 600 MHz;
[g] resonance due to OH group proton not recorded.

Table S2: *Comparison of the ^{13}C NMR Spectral Data Reported[5] by Norte and Co-workers for (+)-Viridianol with the Equivalent Data Recorded for Compound **4** Prepared by the Present Route*

δ_C (*ex.* Norte)[a]	δ_C (*ex.* Present Route)[b]	**Δδ**	δ_C (*ex.* Norte)[c]	δ_C (*ex.* Present Route)[d]	**Δδ**
70.7(2)	70.7(3)	+0.01	69.7(4)	69.7(6)	+0.02
50.9(1)	50.8(9)	–0.02	51.4(1)	51.4(2)	+0.01
50.9(0)	50.8(9)	–0.01	51.3(3)	51.3(5)	+0.02
49.4(4)	49.4(2)	–0.02	50.2(9)	50.3(1)	+0.02
42.5(9)	42.5(8)	–0.01	42.7(3)	42.7(4)	+0.01
40.4(9)	40.4(8)	–0.01	40.8(7)	40.8(8)	+0.01
39.2(6)	39.2(4)	–0.02	40.0(2)	40.0(4)	+0.02
38.7(5)	38.7(5)	0.00	38.9(3)	38.9(5)	+0.02
36.3(5)	36.3(5)	0.00	37.1(5)	37.2(1)	+0.06
33.5(8)	33.5(8)	0.00	33.9(5)	33.9(9)	+0.04
29.1(5)	31.8(8)	+2.73[e]	32.3(0)	32.2(3)	+0.03
29.1(1)	29.1(6)	+0.05	30.3(2)	30.1(6)	–0.06
29.0(5)	29.1(1)	+0.06	29.3(2)	29.3(3)	+0.01
21.1(7)	29.0(4)	+7.87[e]	29.2(4)	29.2(7)	+0.03
21.1(7)	21.1(8)	+0.01	21.2(8)	21.3(1)	+0.03

[a] Spectrum recorded in $CDCl_3$ at undefined field strength, data taken from reference 1;
[b] Spectrum recorded in $CDCl_3$ at 150 MHz;
[c] Spectrum recorded in C_5D_5N at undefined field strength, data taken from reference 1;
[d] Spectrum recorded in C_5D_5N at 150 MHz;
[e] We attribute these differences to transcription errors in the composition of the data presented in reference 1.

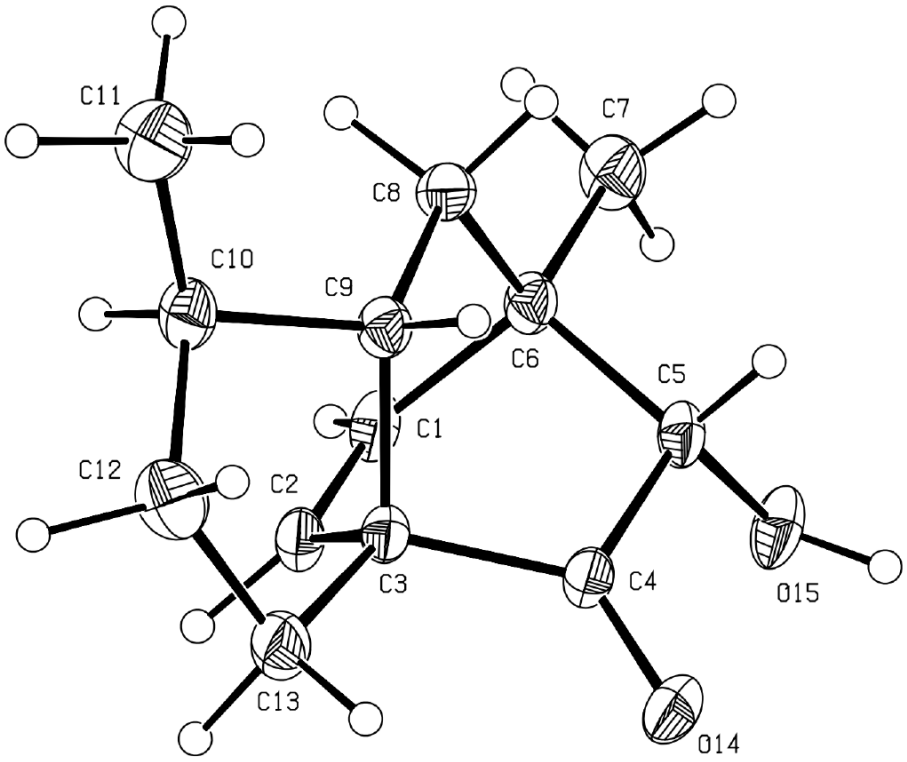


Figure S1: Structure of compound **15** (CCDC 1863280). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

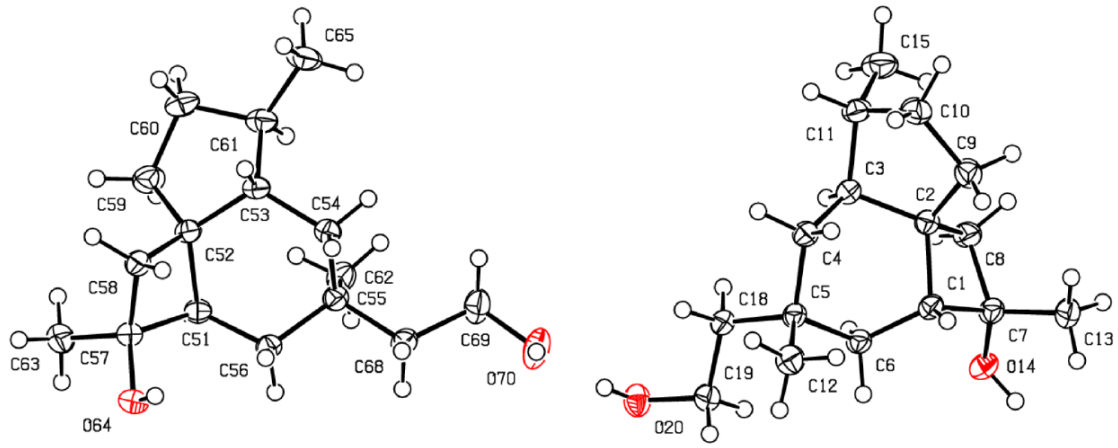


Figure S2: Structure of compound **22** (α-epimer) (CCDC 1863282) showing the two molecules in the unit cell. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

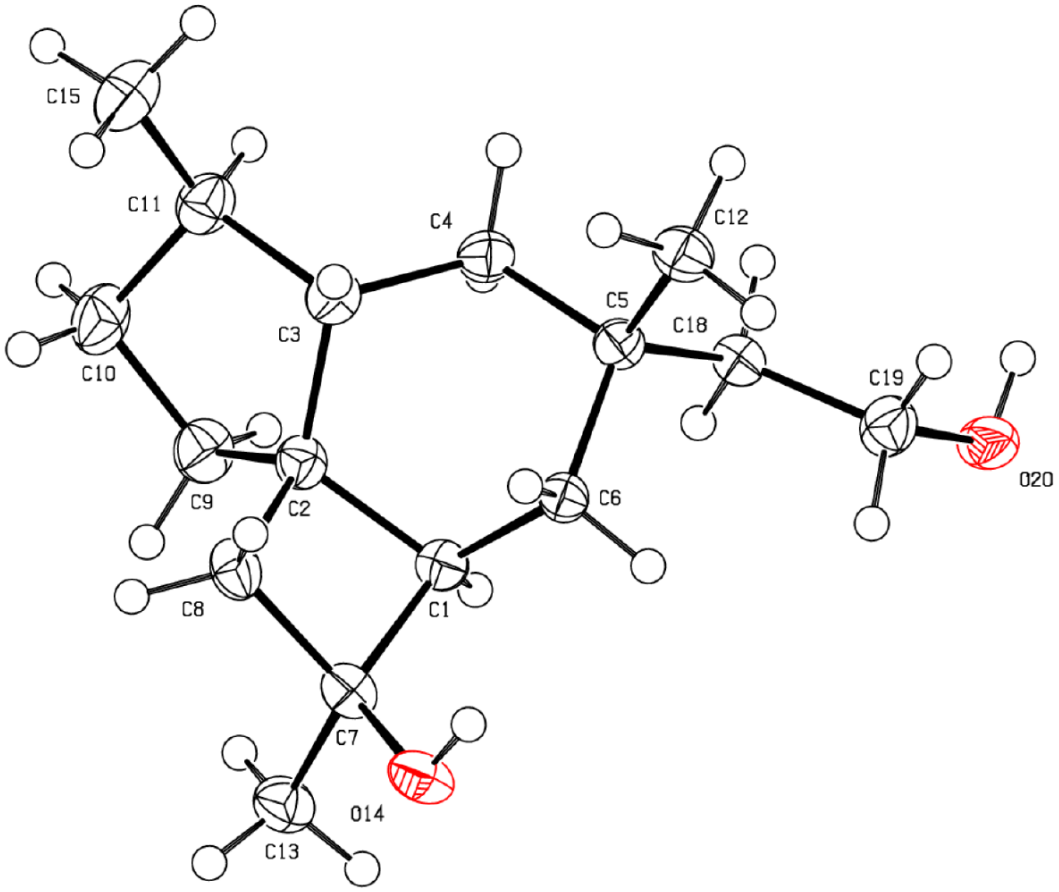
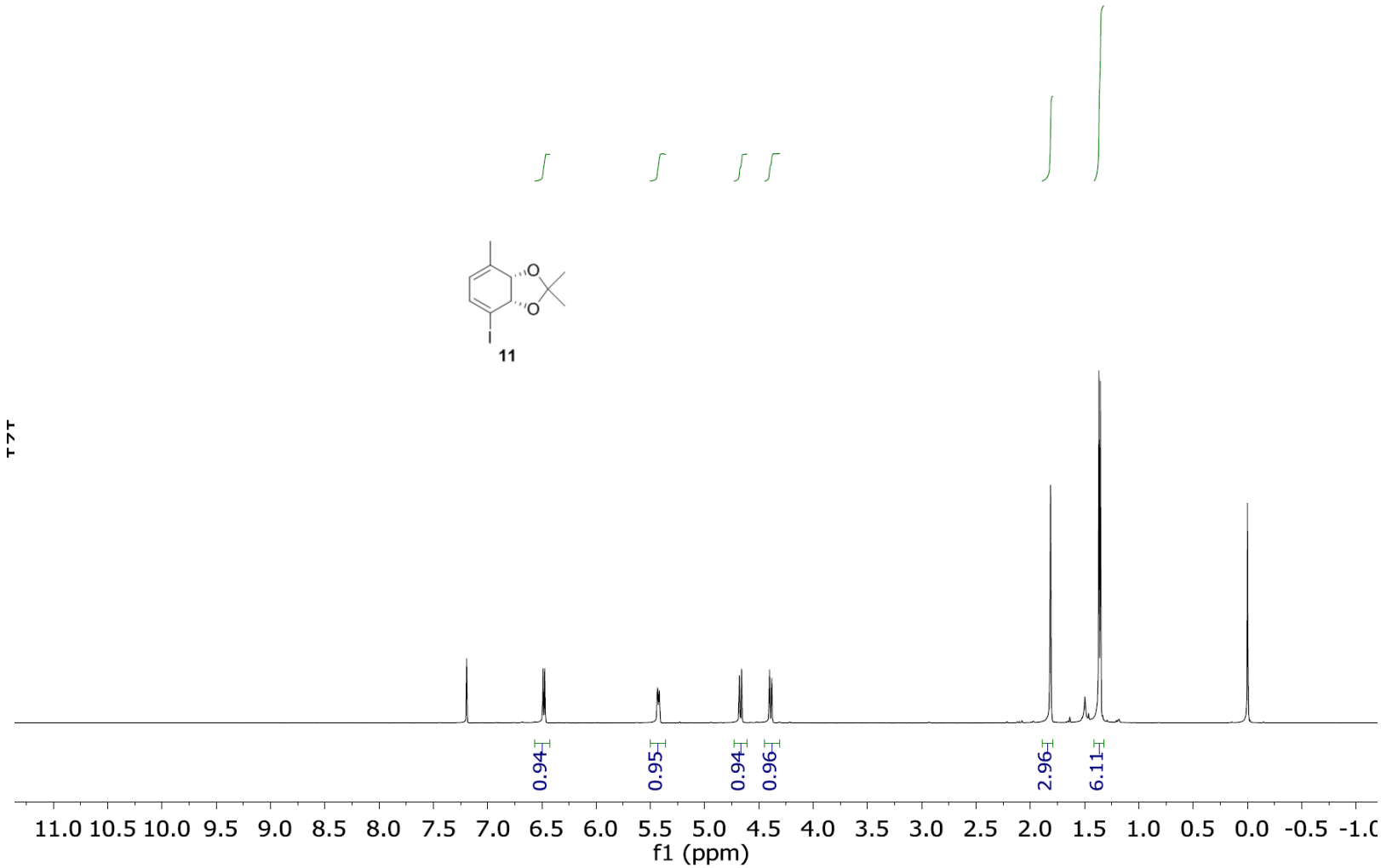


Figure S3: Structure of compound **22** (β-epimer) (CCDC 1863281). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

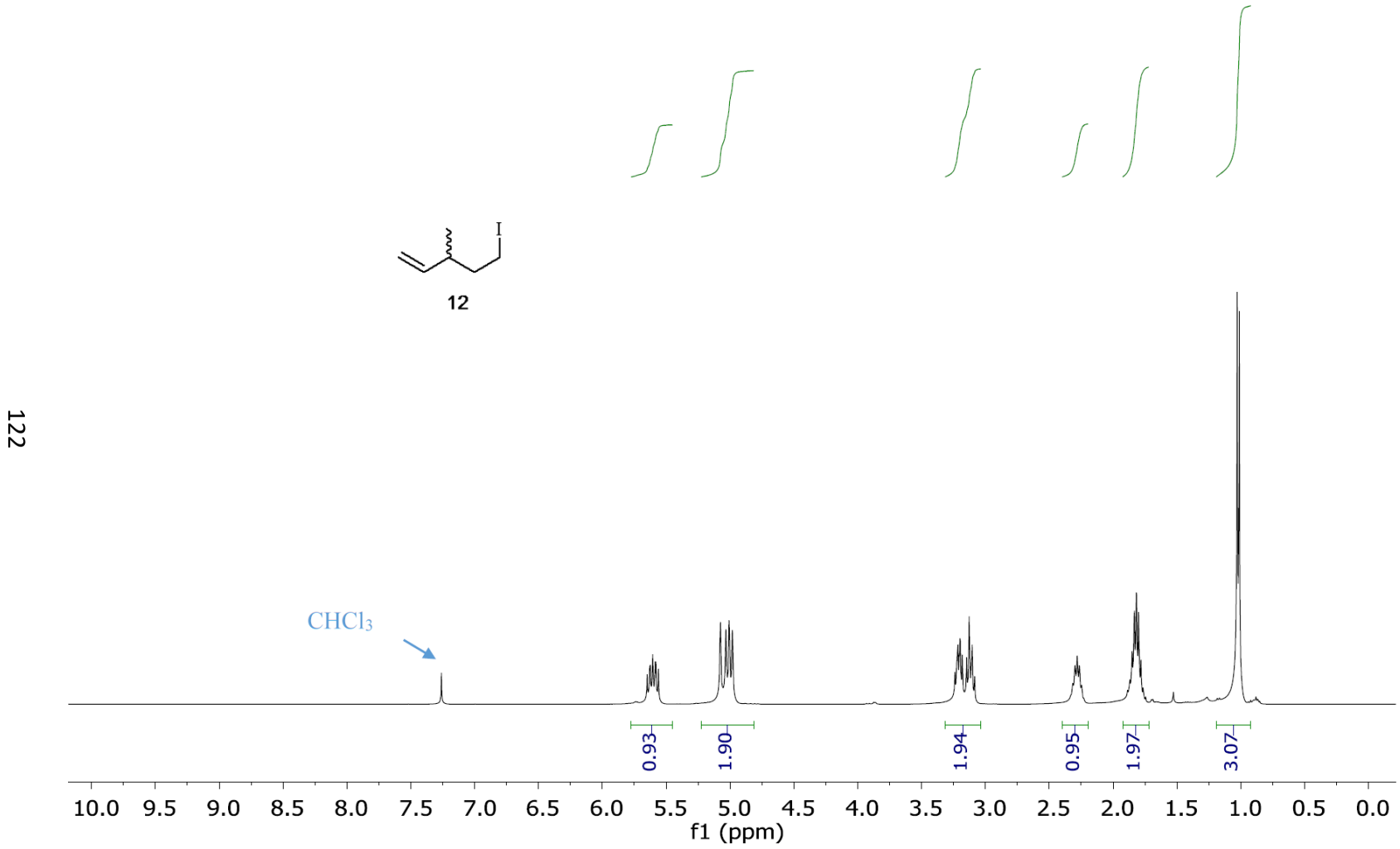
Reference

1. Norte, M.; Fernández, J. J.; Souto, M. L. Viridianol, a Rearranged Sesquiterpene with a Novel Carbon Skeleton from *Laurencia viridis*. *Tetrahedron Lett.*, **1994**, *35*, 4607-4610.

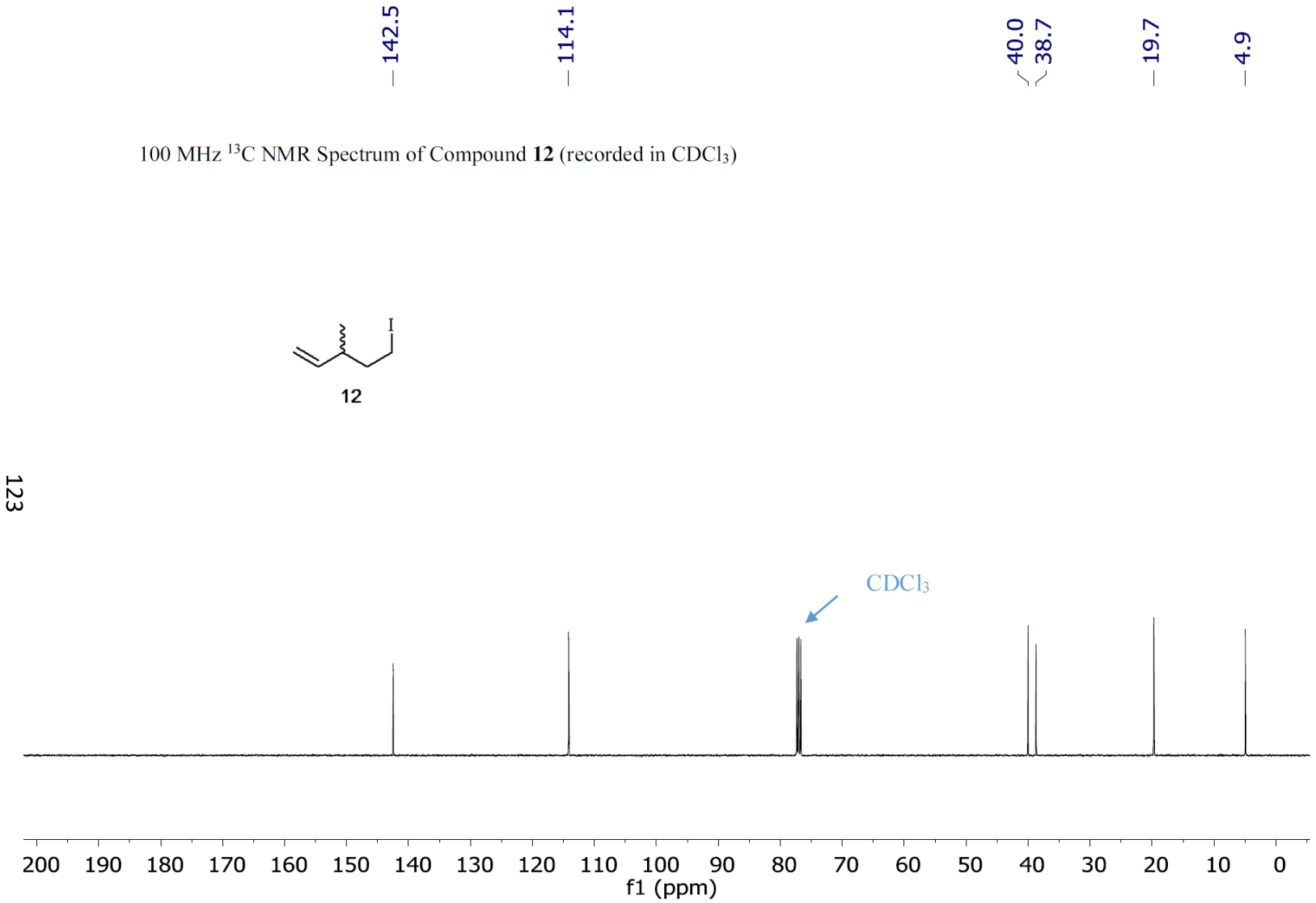
400 MHz ^{1}H NMR Spectrum of Compound **11** (recorded in $CDCl_3$)



400 MHz ^{1}H NMR Spectrum of Compound **12** (recorded in $CDCl_3$)

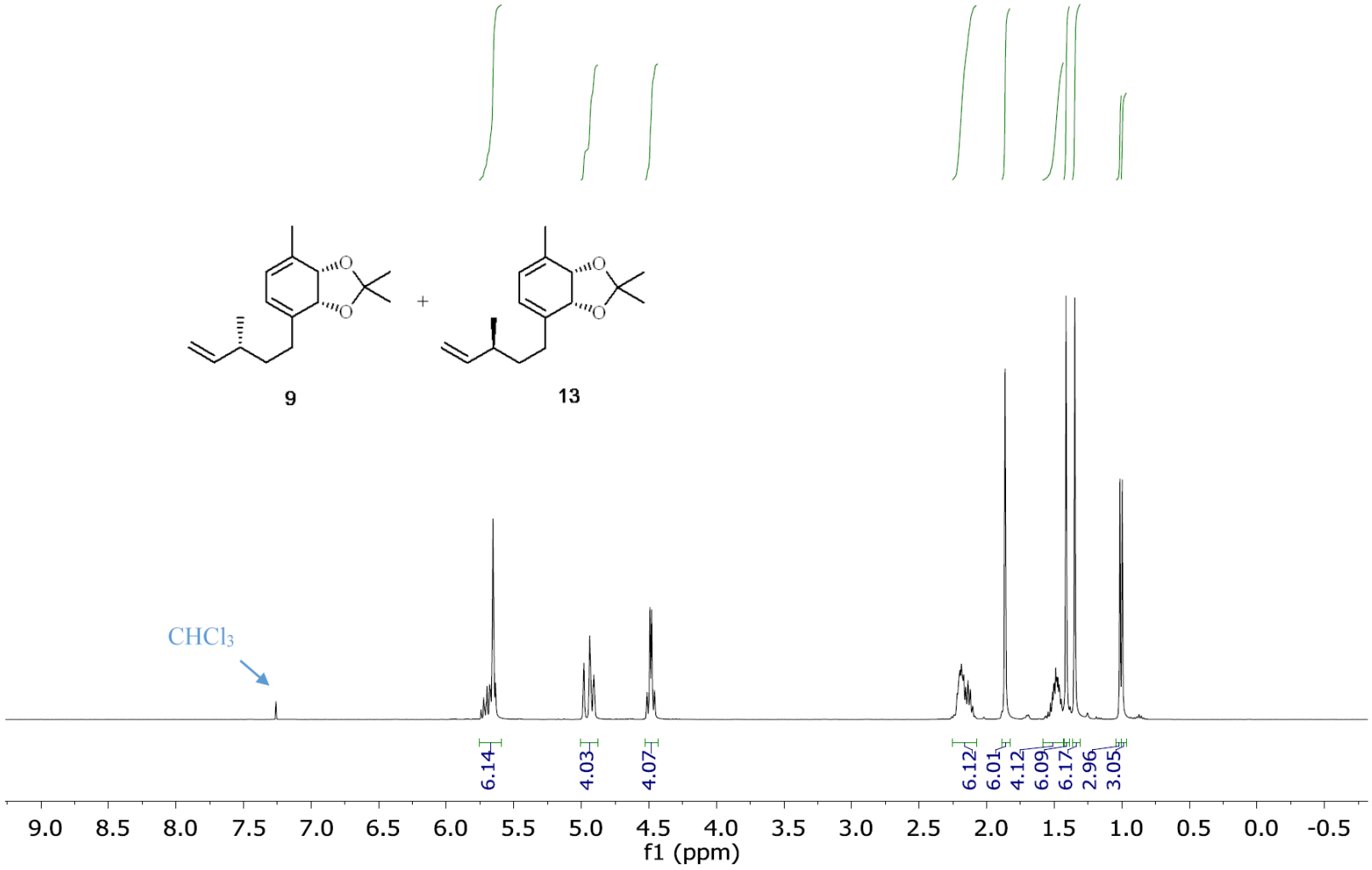


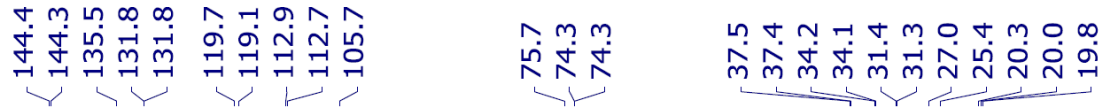
122



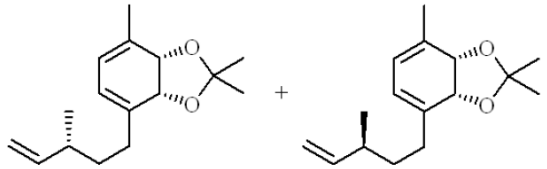
100 MHz ^{13}C NMR Spectrum of Compound **12** (recorded in $CDCl_3$)

400 MHz ^{1}H NMR Spectrum of Compound **9** and **13** (recorded in $CDCl_3$)



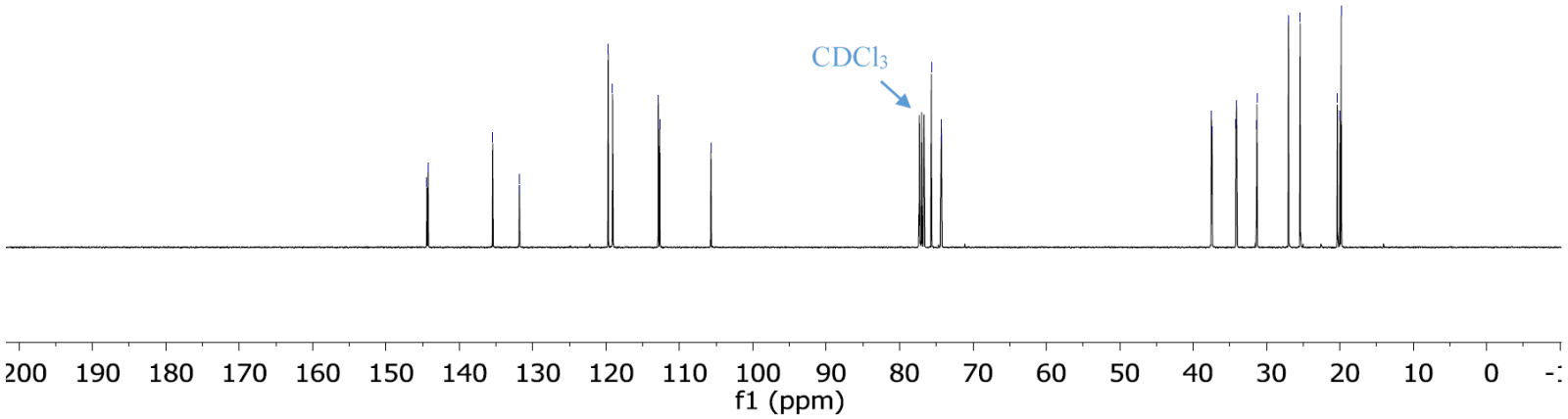


100 MHz ^{13}C NMR Spectrum of Compound **9** and **13** (recorded in $CDCl_3$)

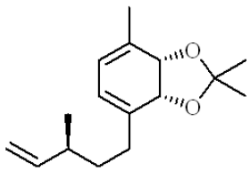


9 + **13**

125

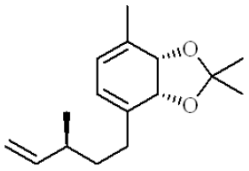


400 MHz ^{1}H NMR Spectrum of Compound **13** (recorded in $CDCl_3$)



13

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



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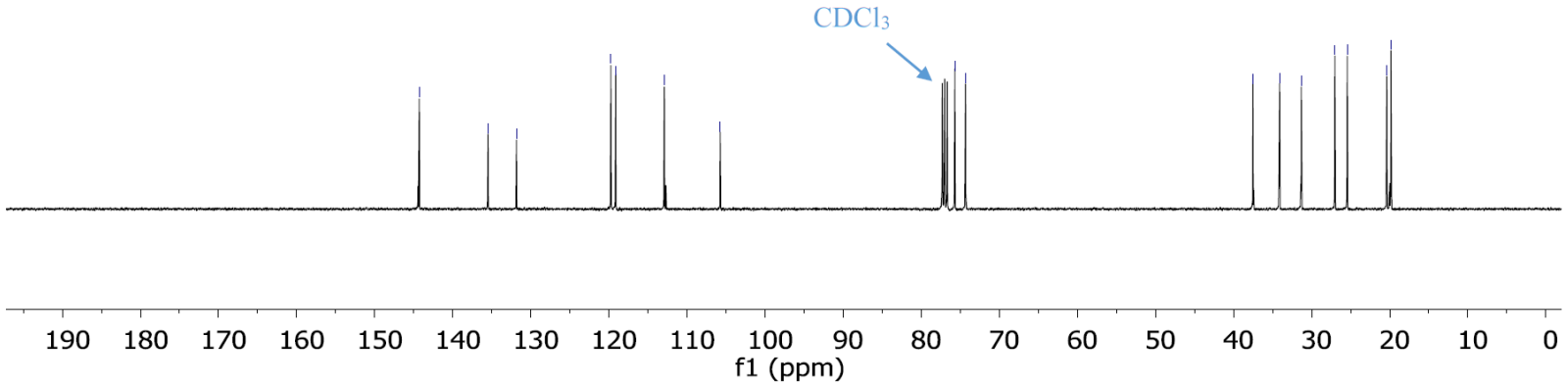
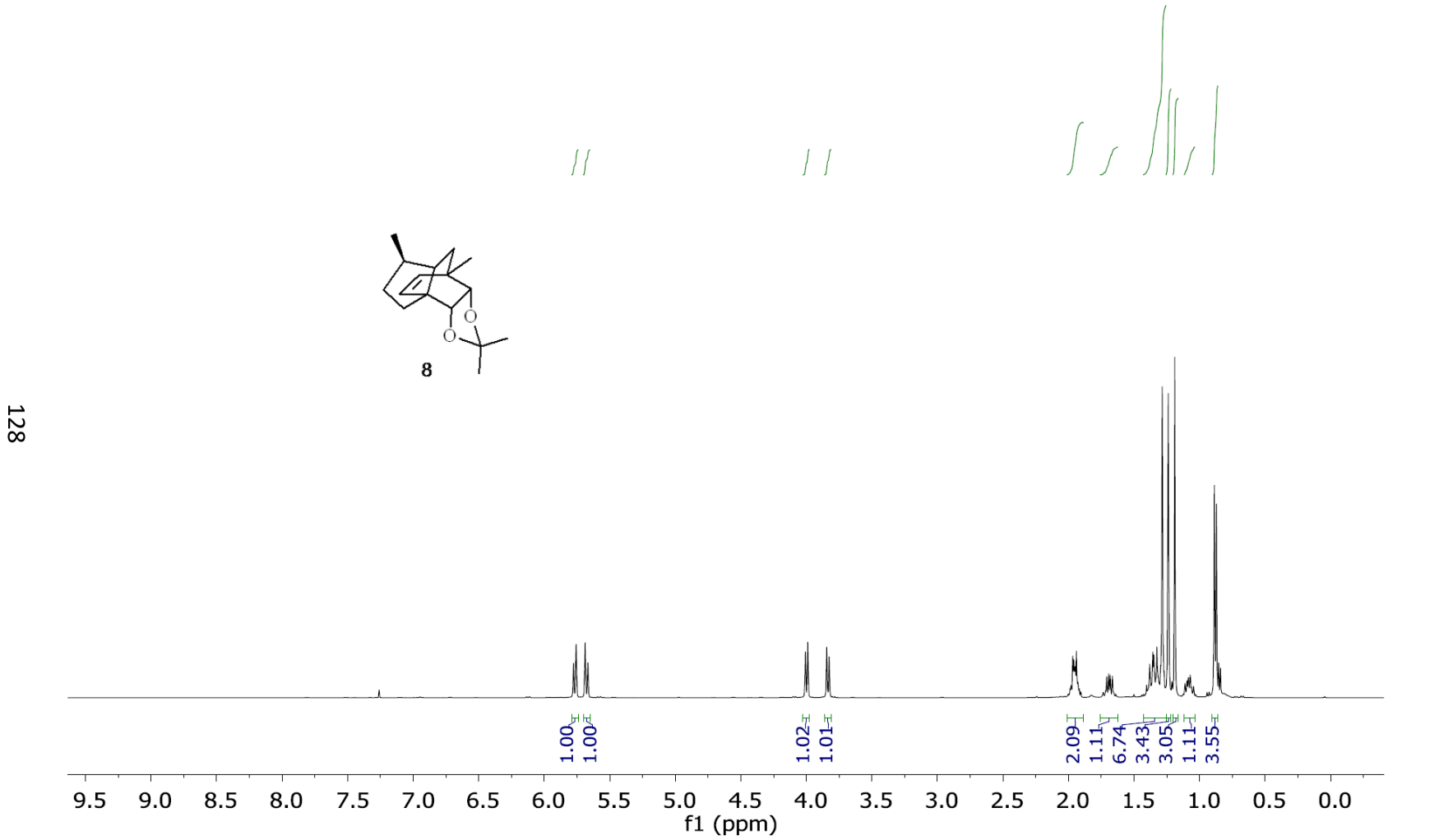
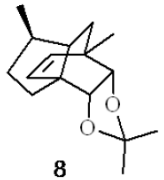


400 MHz ^{1}H NMR Spectrum of Compound **8** (recorded in $CDCl_3$)



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



8

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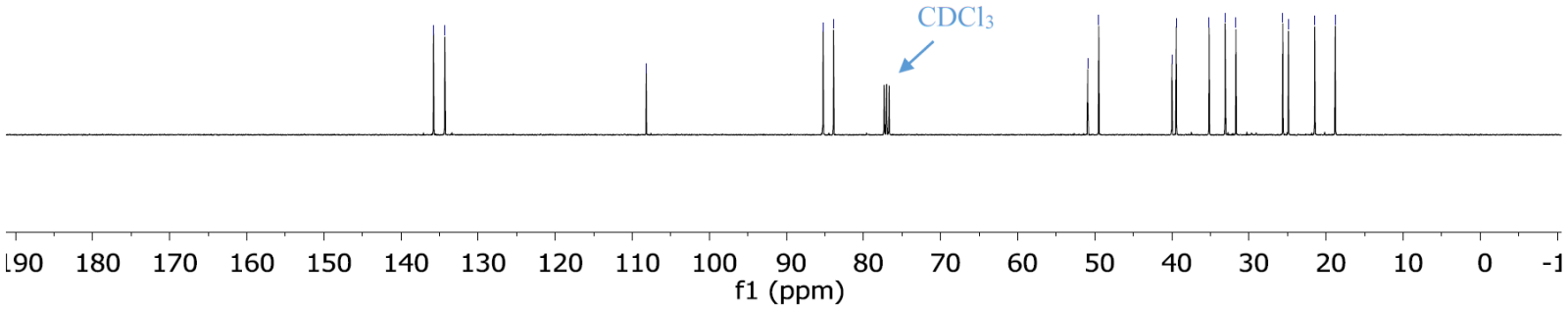
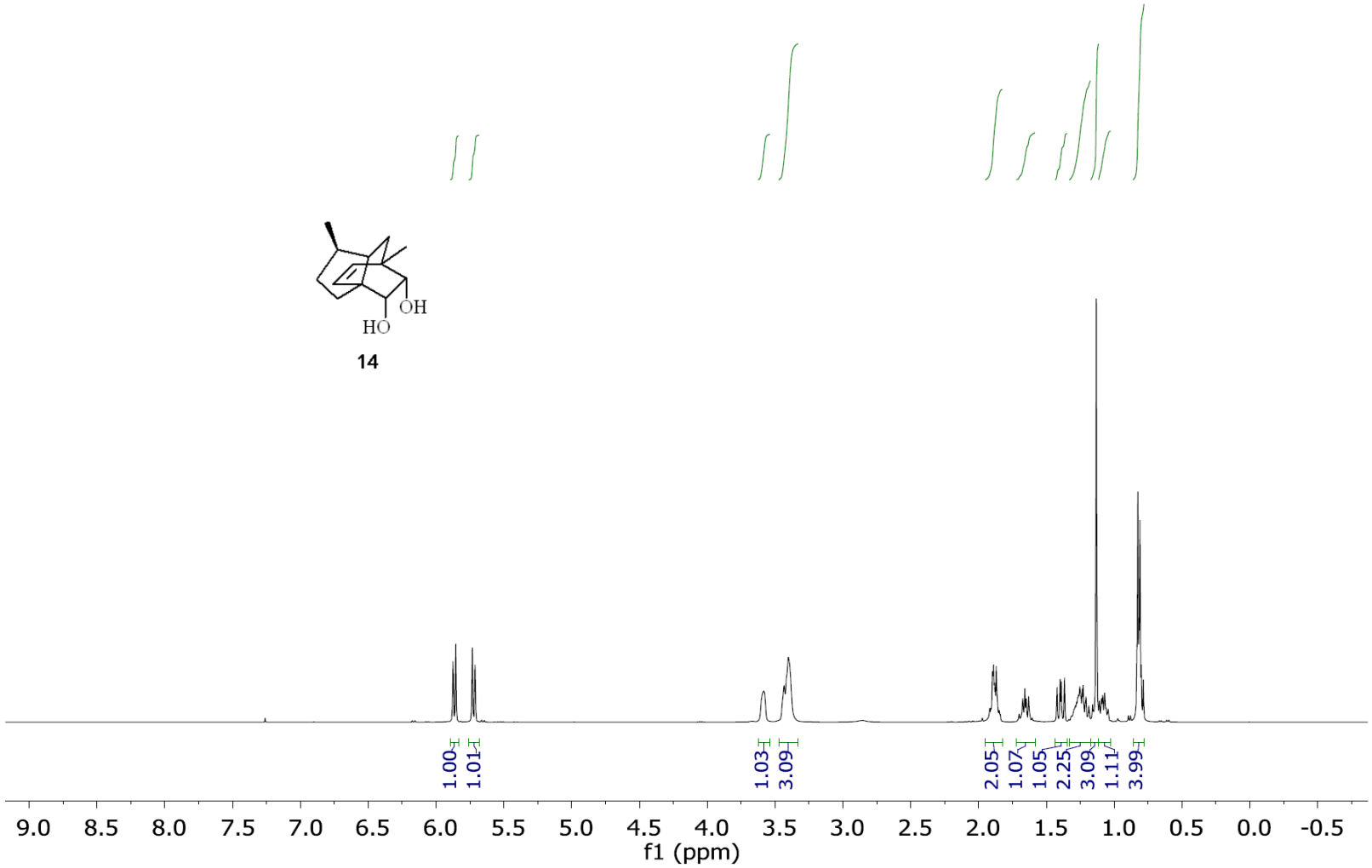


400 MHz ^{1}H NMR Spectrum of Compound **14** (recorded in $CDCl_3$)



14

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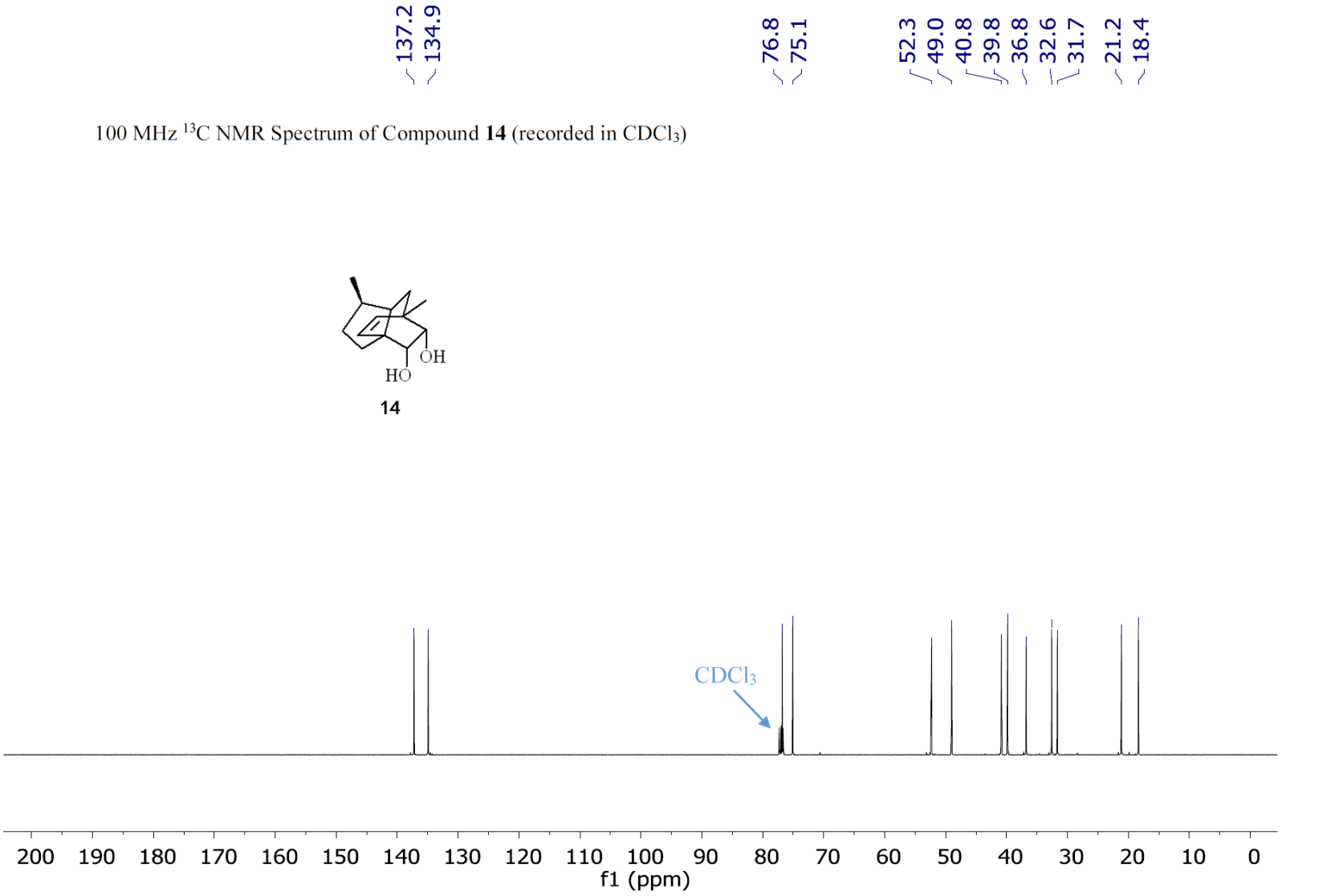
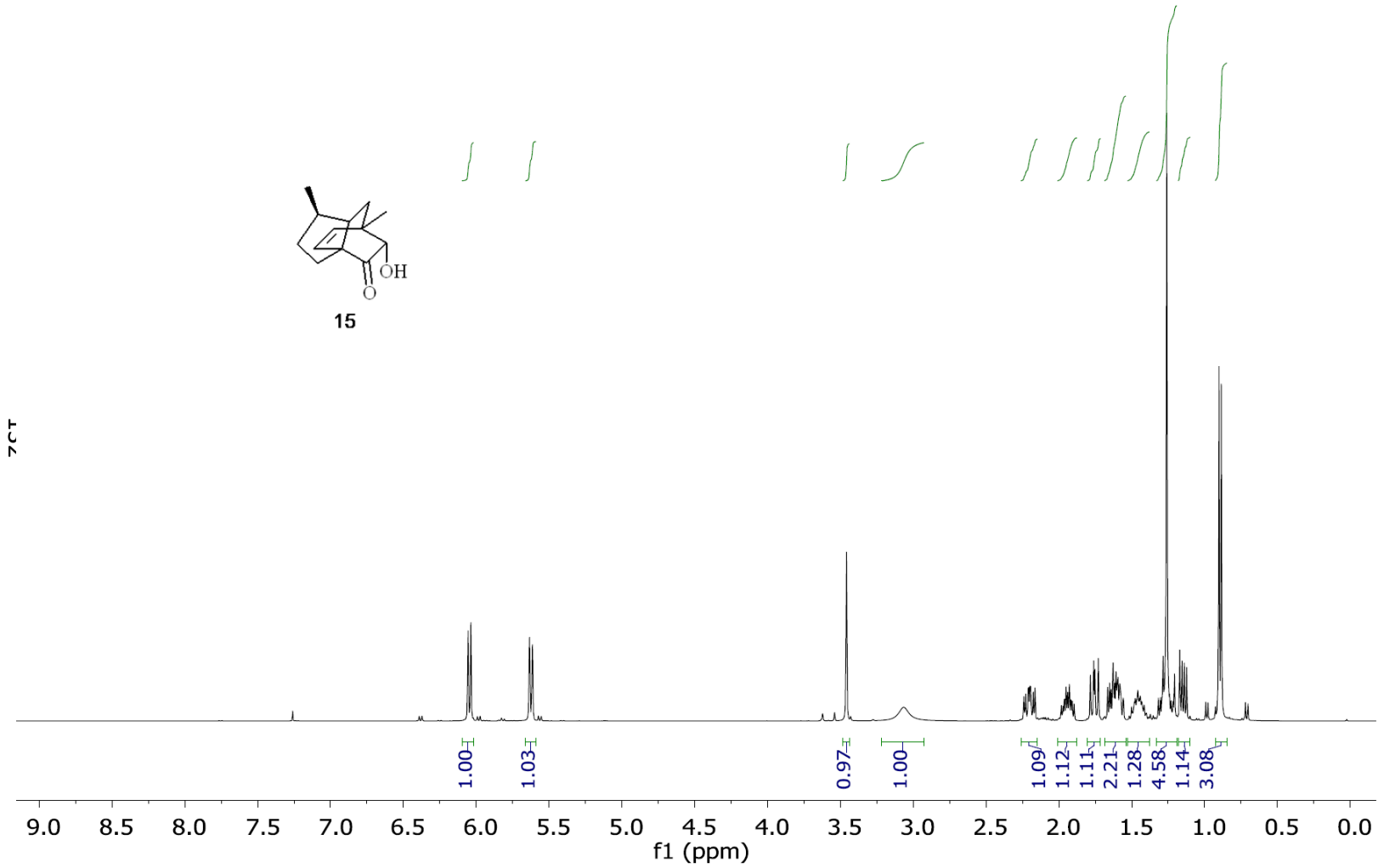
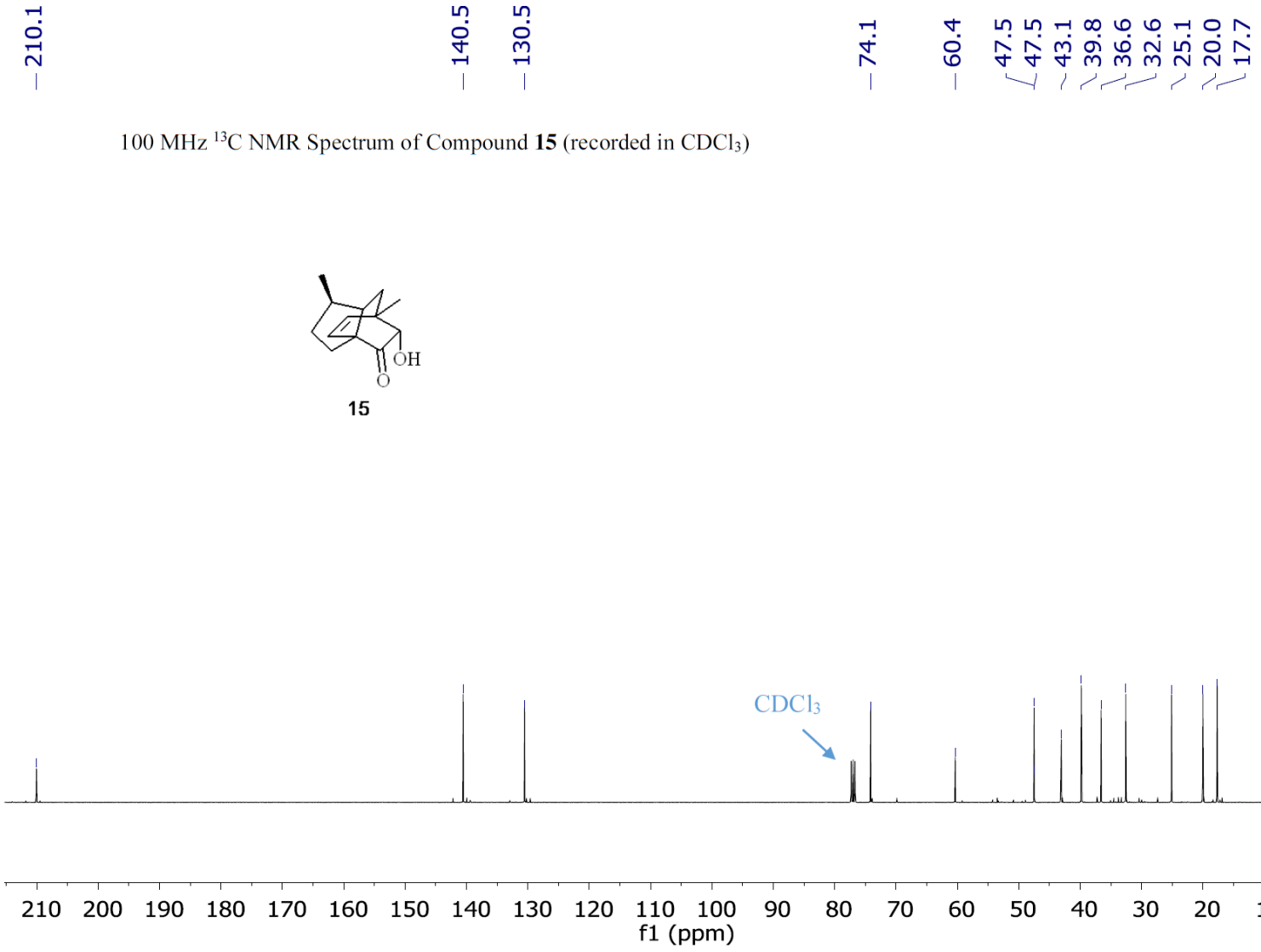


100 MHz ^{13}C NMR Spectrum of Compound **14** (recorded in $CDCl_3$)

131

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

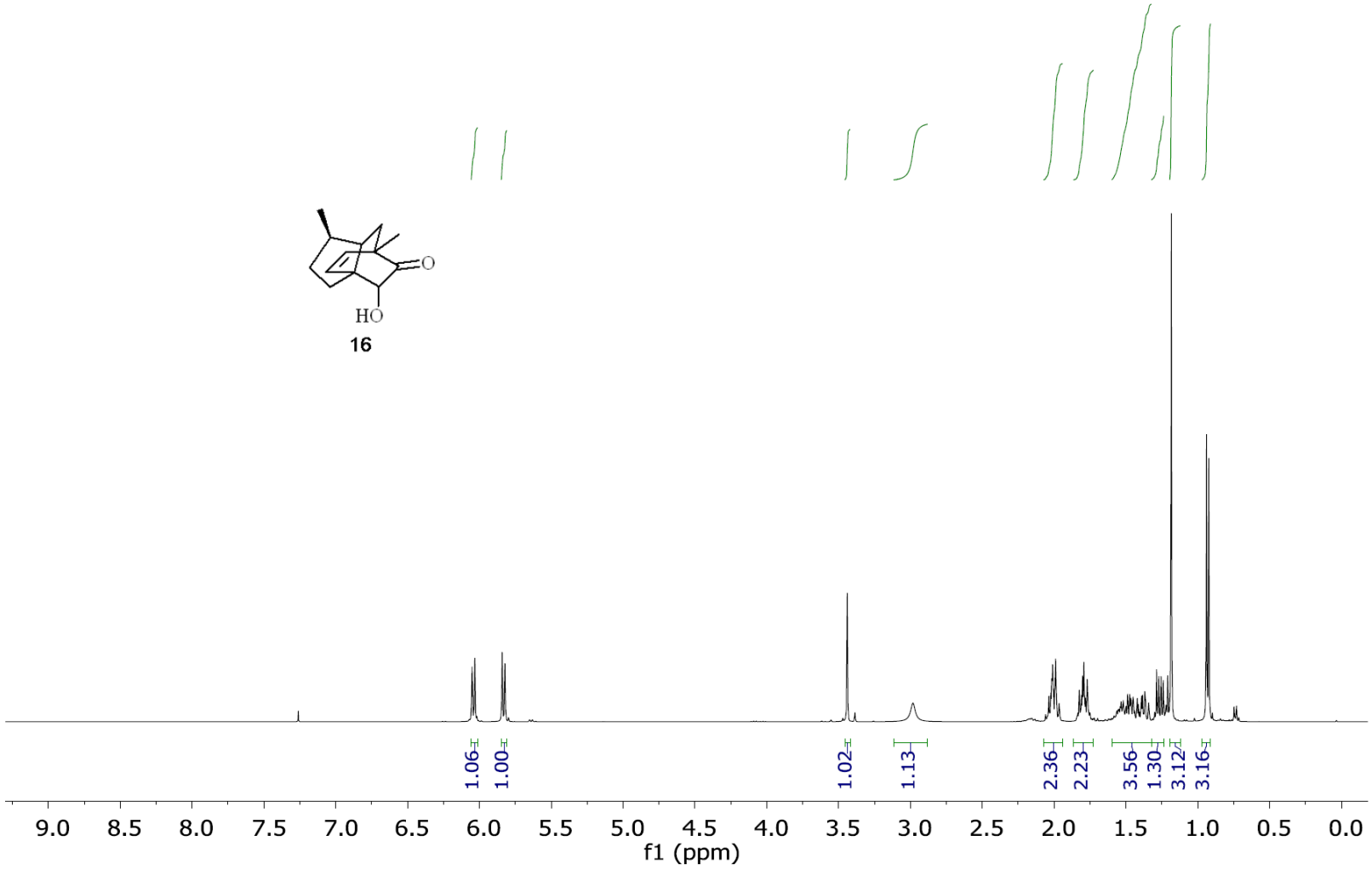




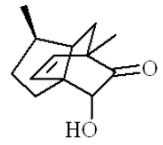
100 MHz ^{13}C NMR Spectrum of Compound **15** (recorded in $CDCl_3$)

15

400 MHz ^{1}H NMR Spectrum of Compound **16** (recorded in $CDCl_3$)

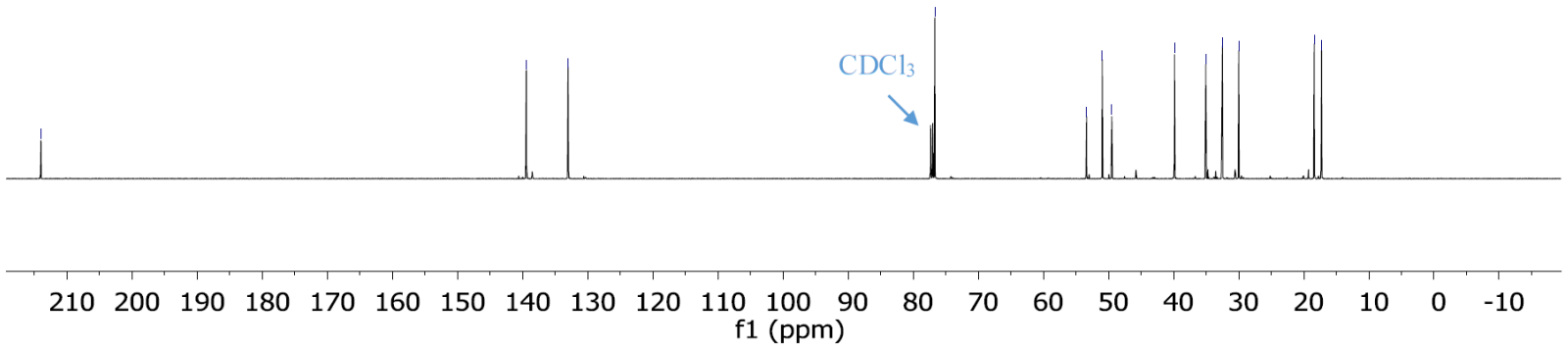


100 MHz ^{13}C NMR Spectrum of Compound **16** (recorded in $CDCl_3$)

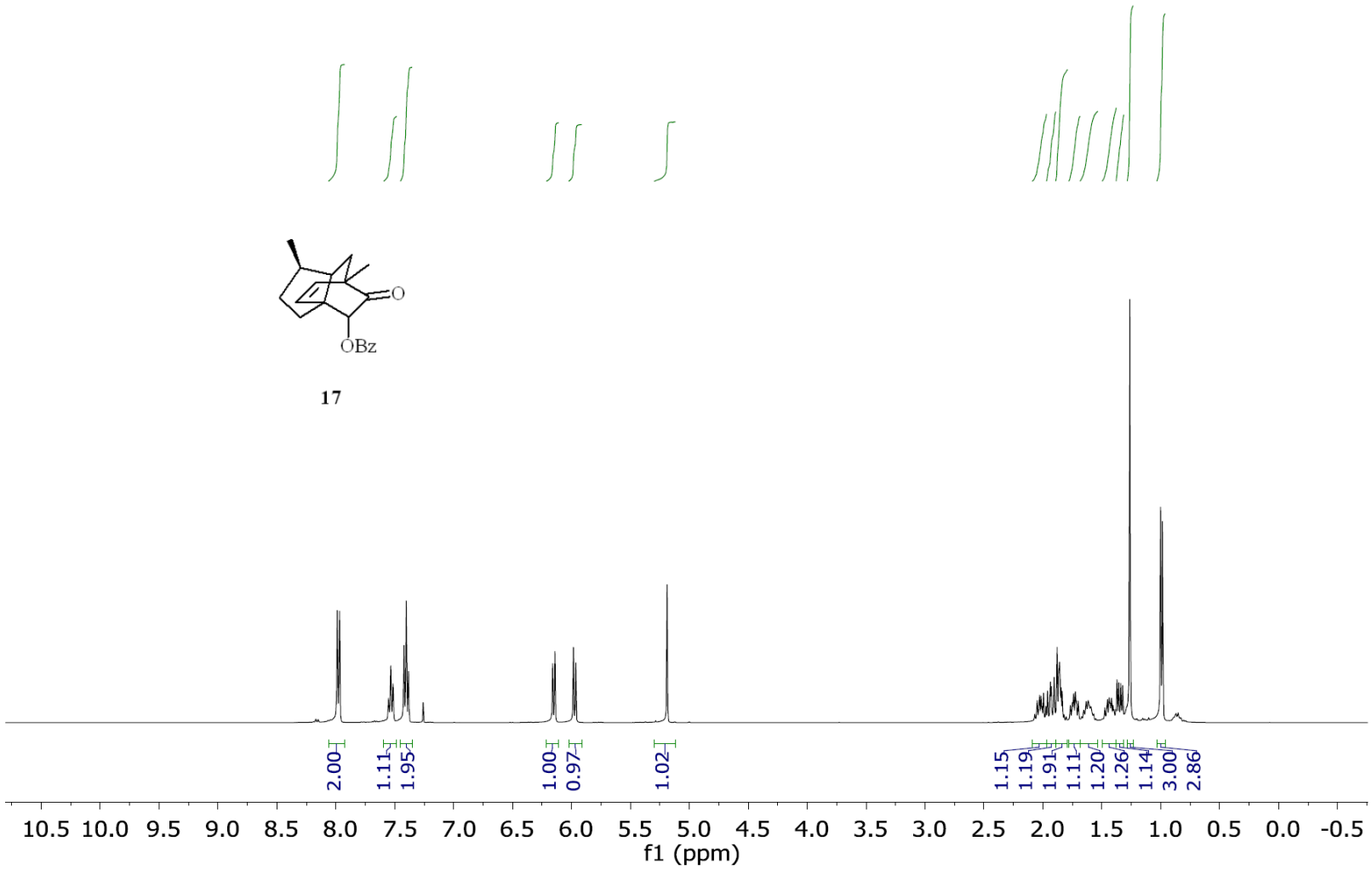


16

135



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

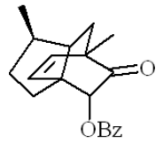


17

136

208.0
166.1
139.1
133.6
133.0
129.8
129.7
128.2
75.9
52.6
51.0
50.0
40.1
35.3
32.4
30.0
18.5
17.5

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



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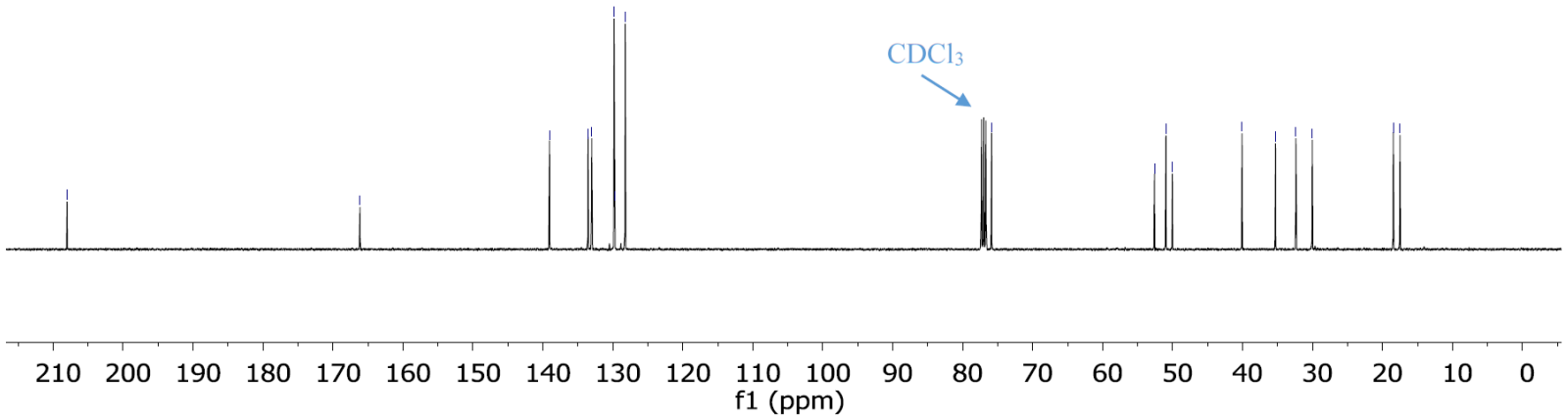
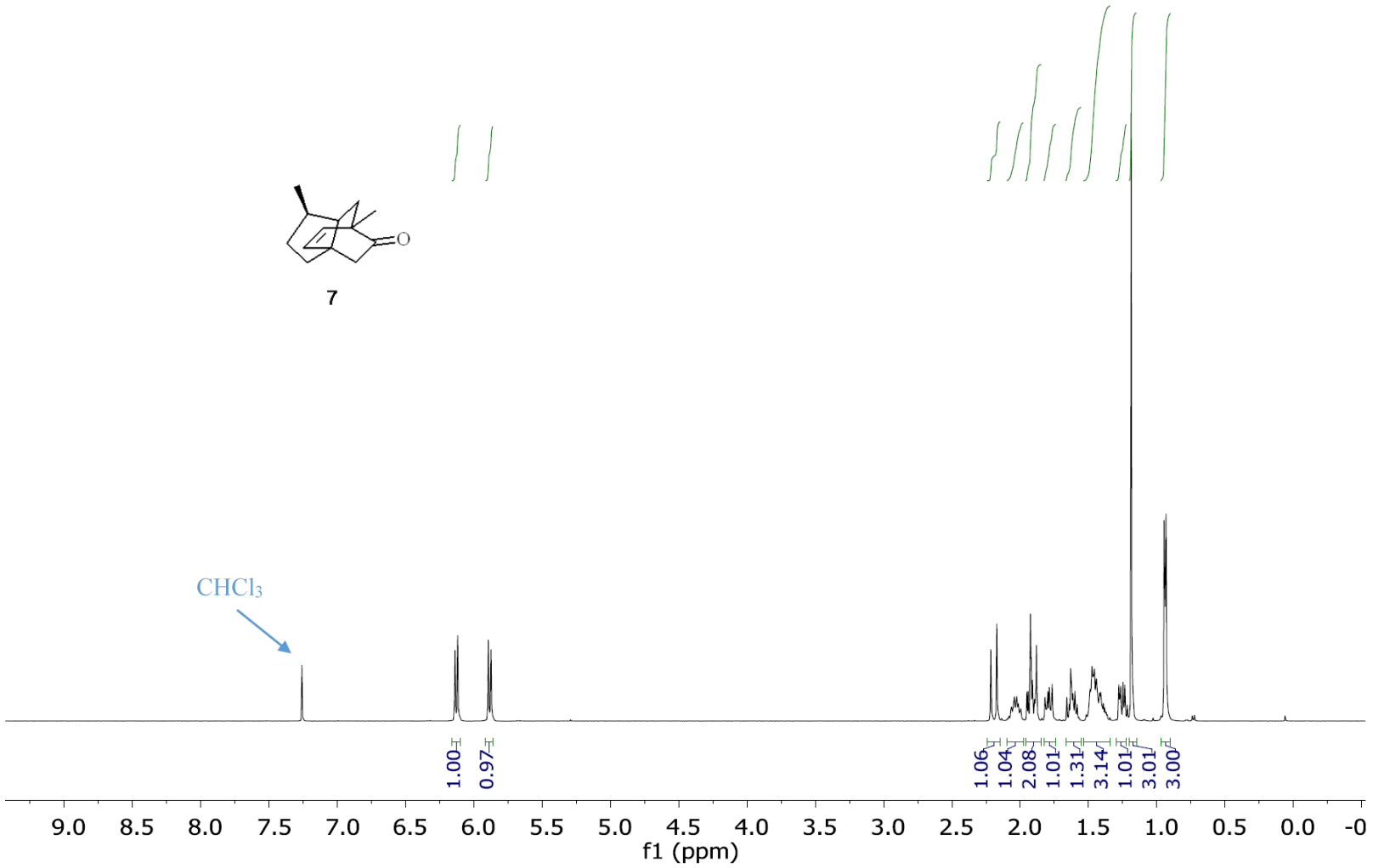
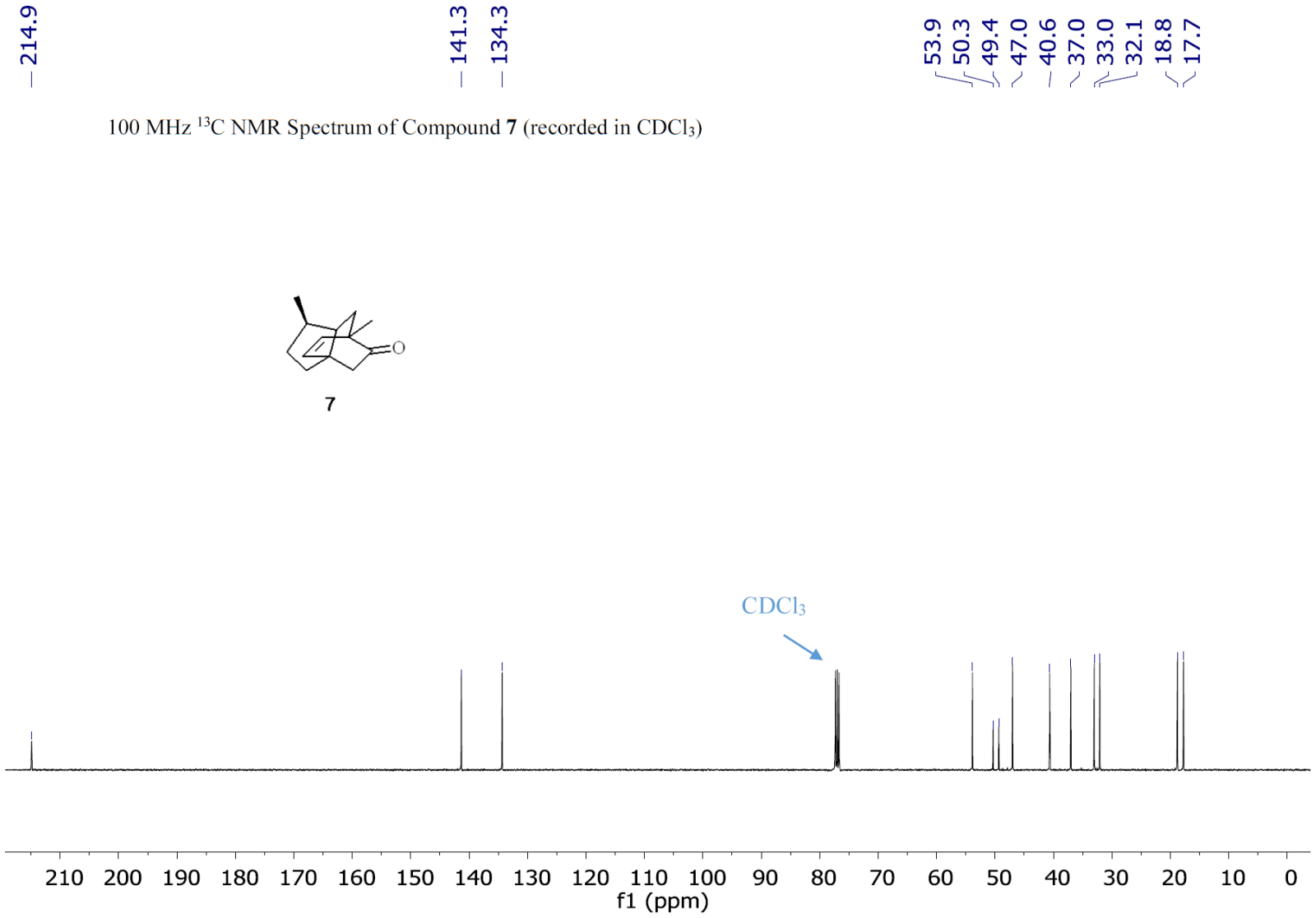


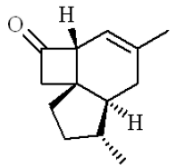
400 MHz ^{1}H NMR Spectrum of Compound **7** (recorded in $CDCl_3$)



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



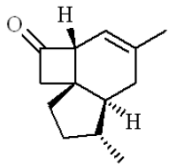
400 MHz ^{1}H NMR Spectrum of Compound **6** (recorded in $CDCl_3$)



6

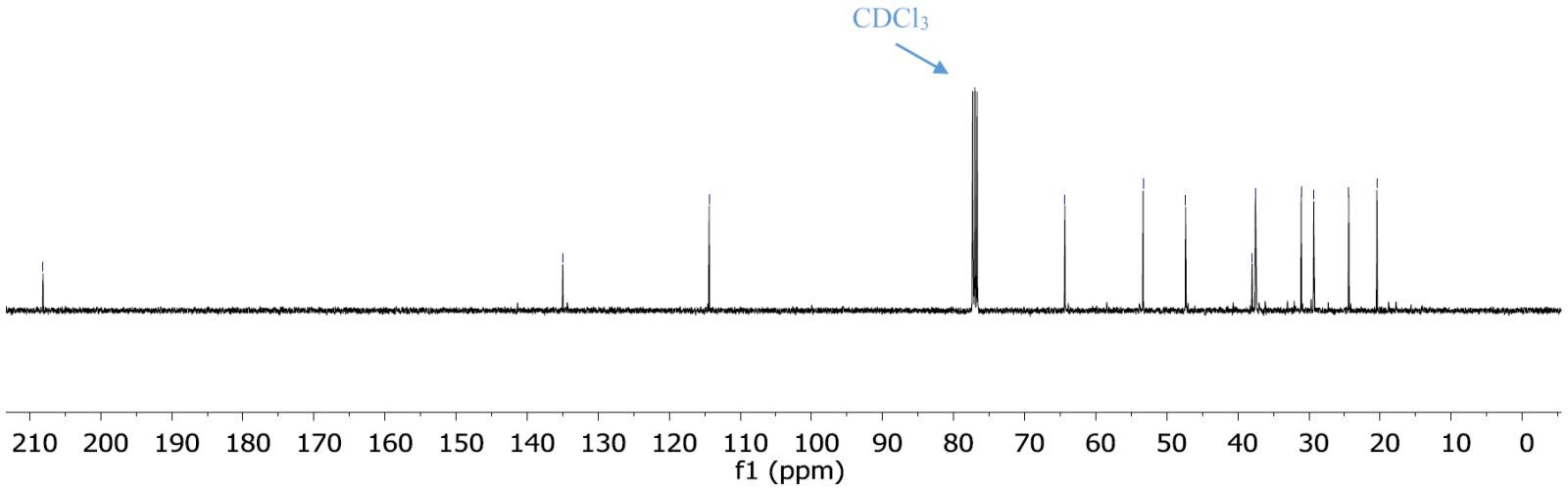
208.1
135.0
114.4
64.3
53.3
47.4
38.0
37.5
37.5
31.1
29.3
24.4
20.5

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

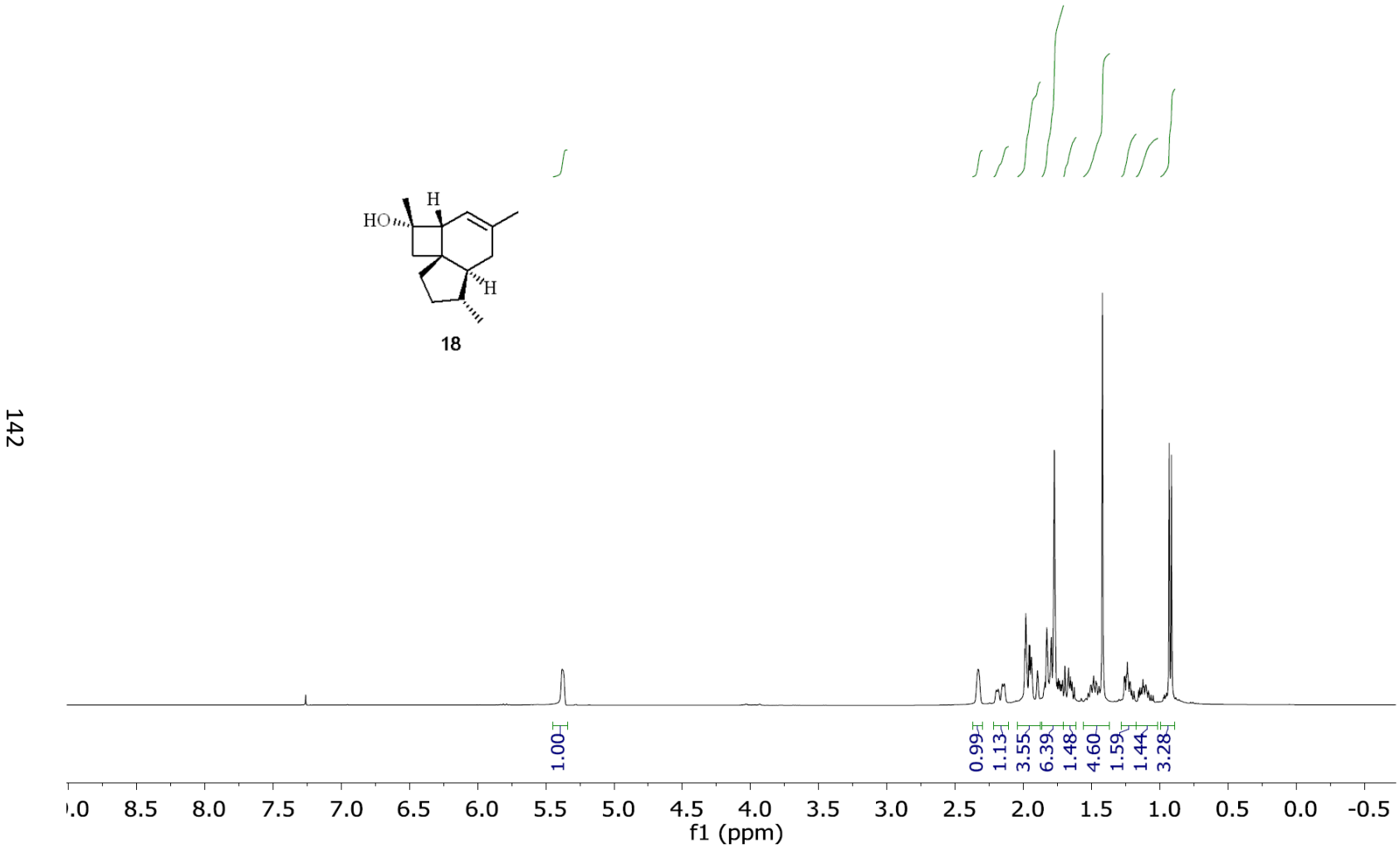


6

141

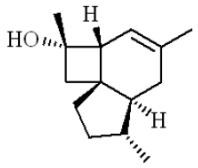


400 MHz ^{1}H NMR Spectrum of Compound **18** (recorded in $CDCl_3$)

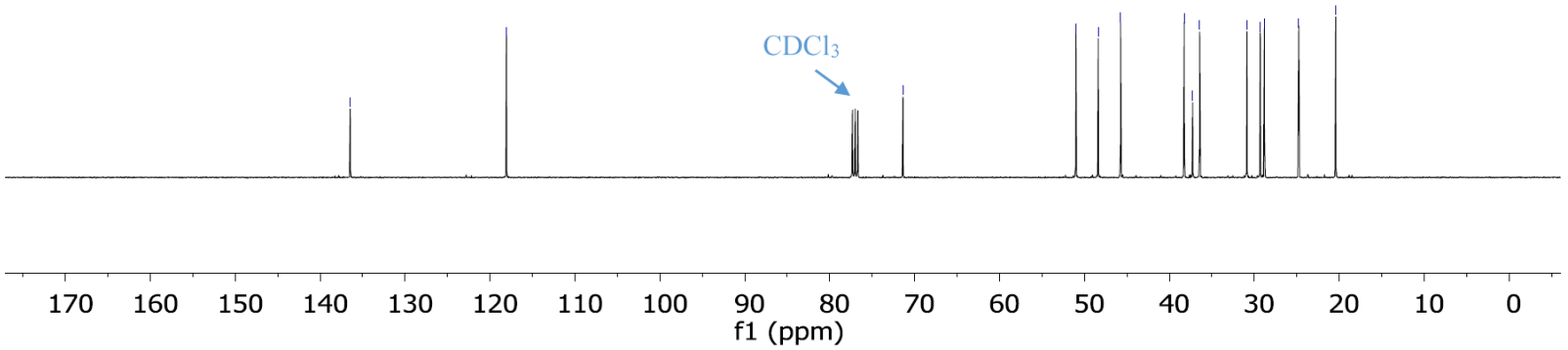


142

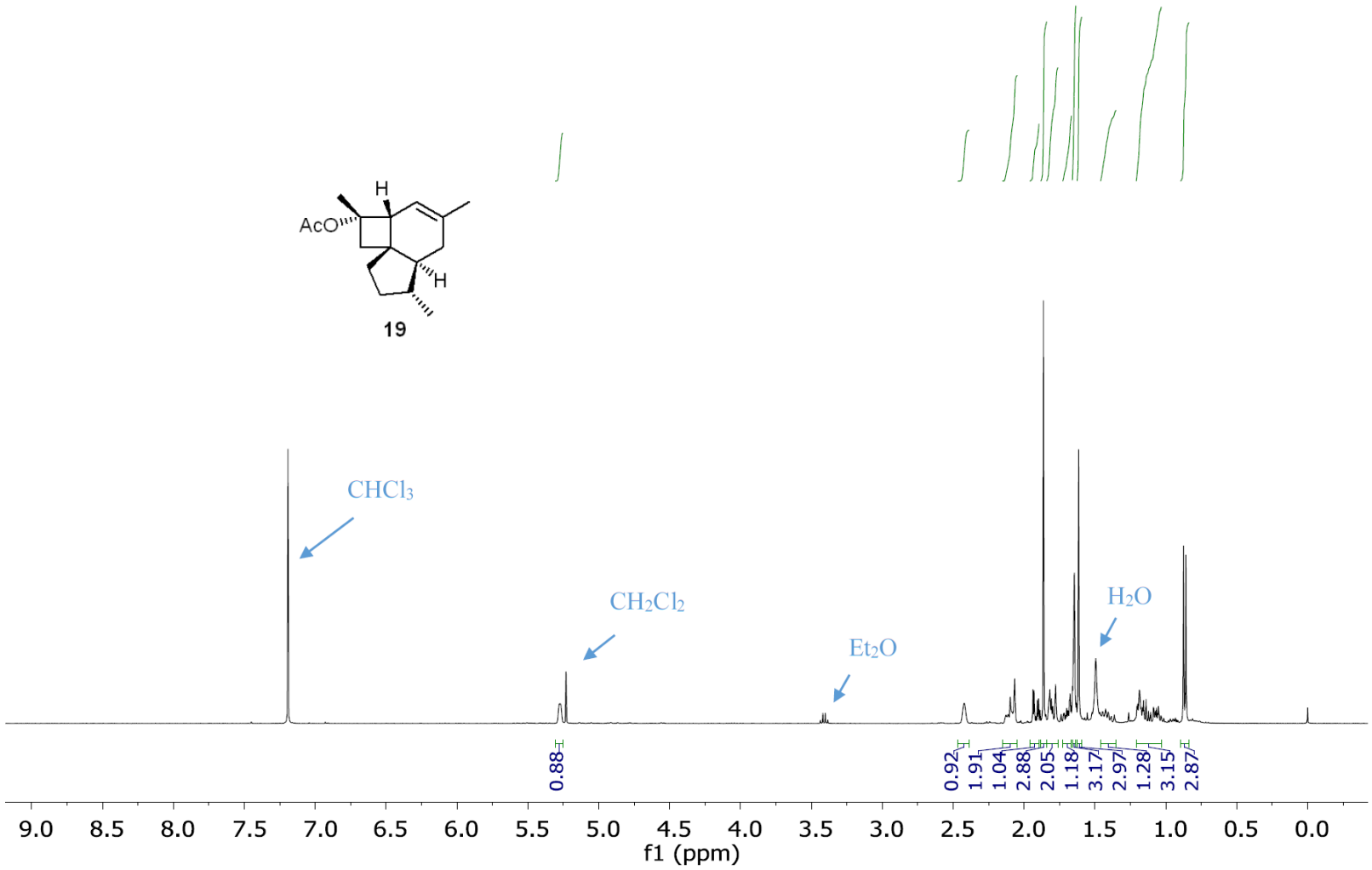
100 MHz ^{13}C NMR Spectrum of Compound **18** (recorded in $CDCl_3$)



18

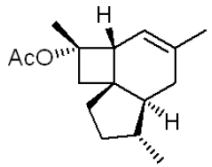


400 MHz ^{1}H NMR Spectrum of Compound **19** (recorded in $CDCl_3$)



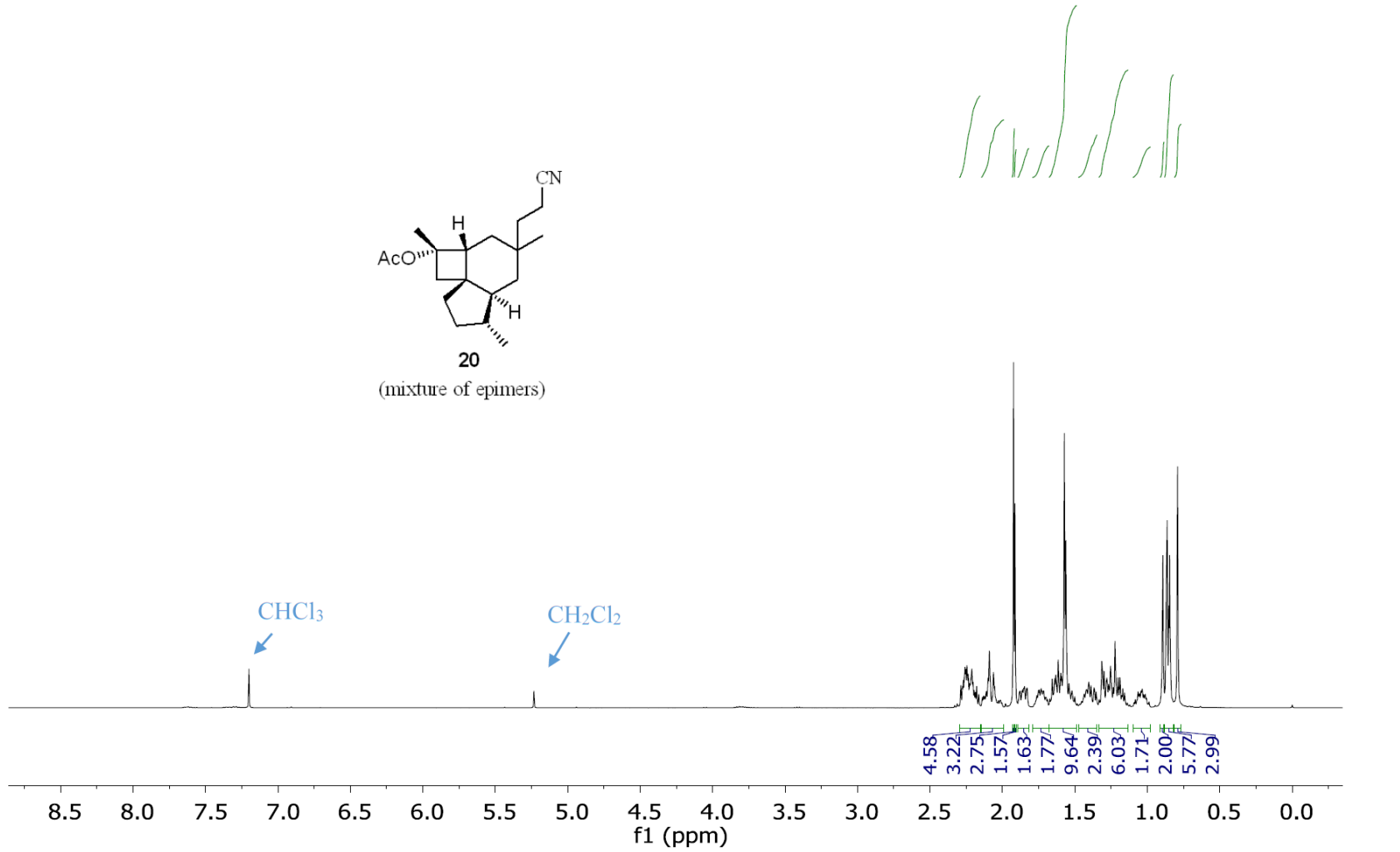
144

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

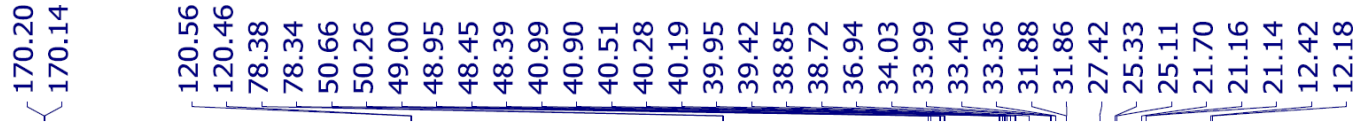


19

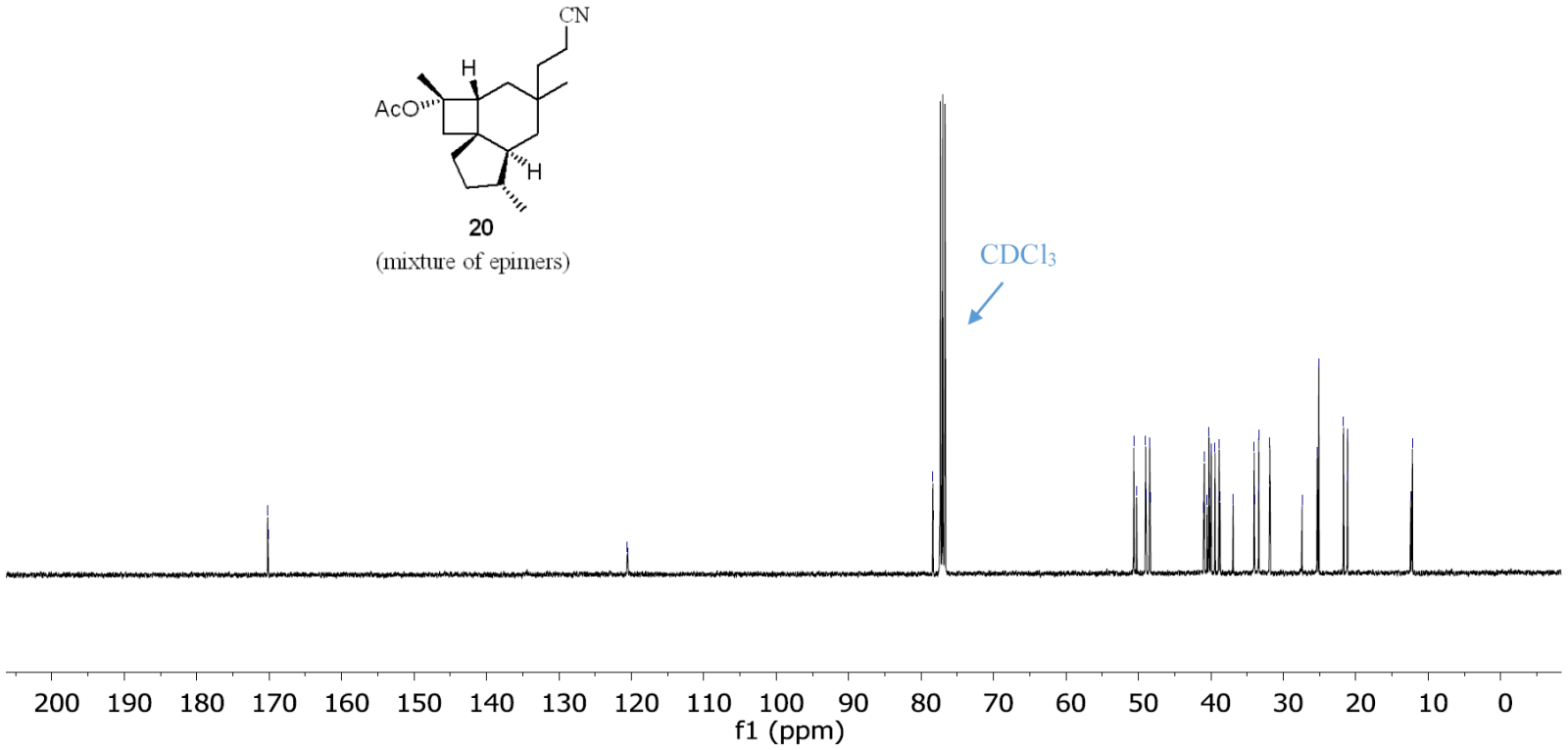
400 MHz ^{1}H NMR Spectrum of Compound **20** (mixture of epimers) (recorded in $CDCl_3$)



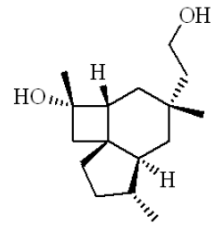
146



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



400 MHz ^{1}H NMR Spectrum of Compound **22** (α-epimer) (recorded in $CDCl_3$)

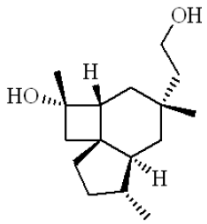


22
(α-epimer)

100 MHz ^{13}C NMR Spectrum of

Compound **22** (α-epimer)

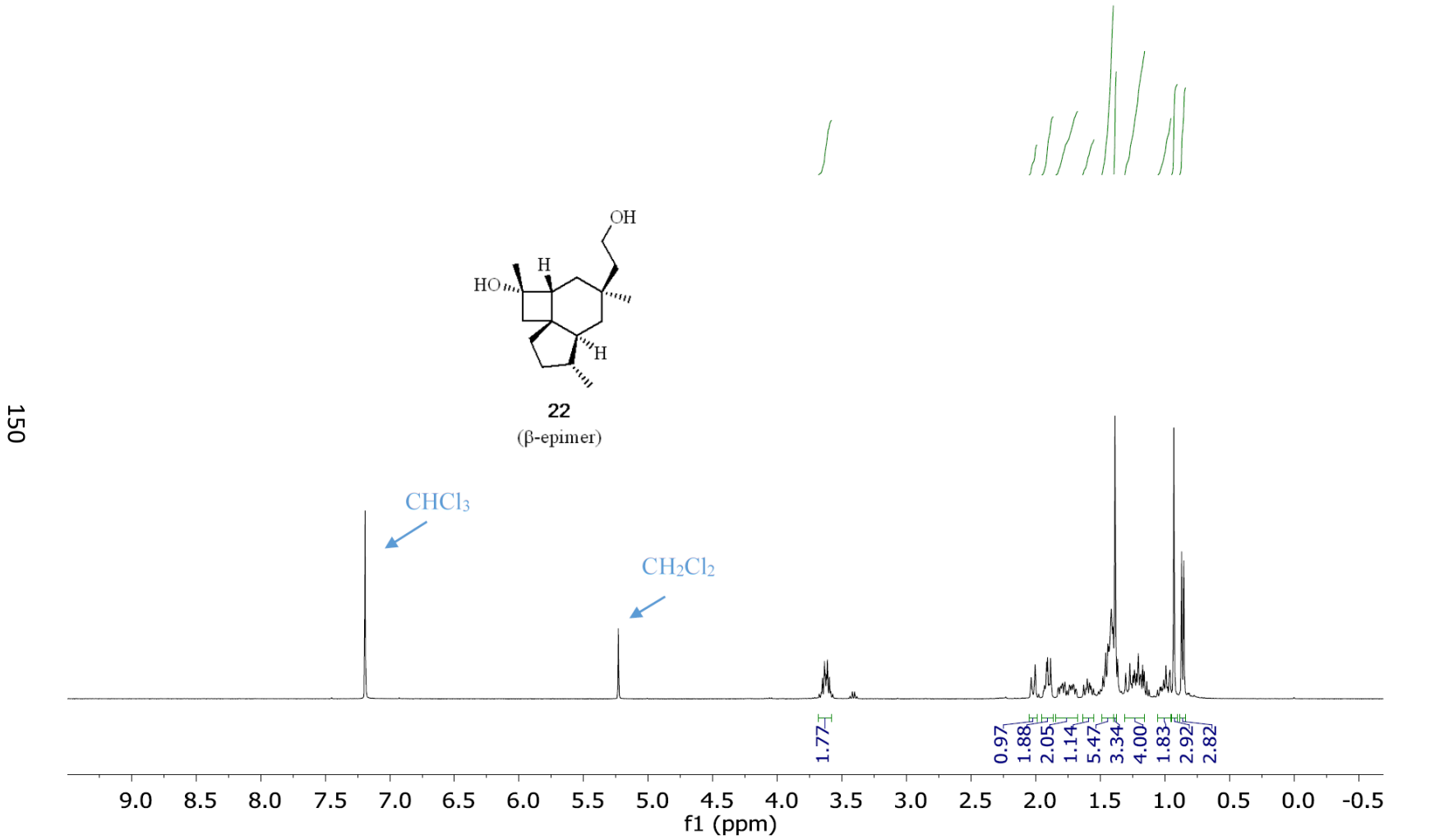
(recorded in $CDCl_3$)



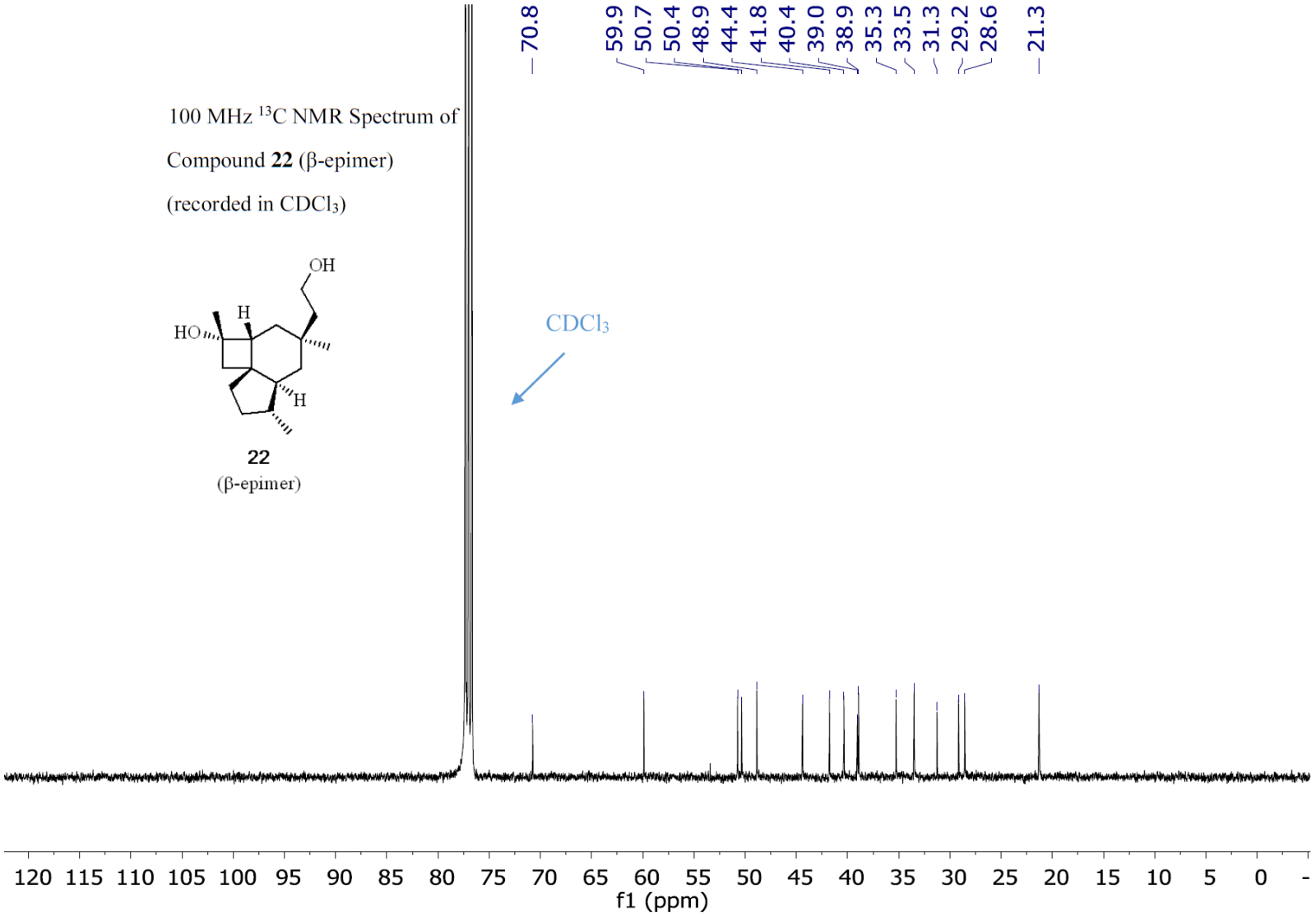
22

(α-epimer)

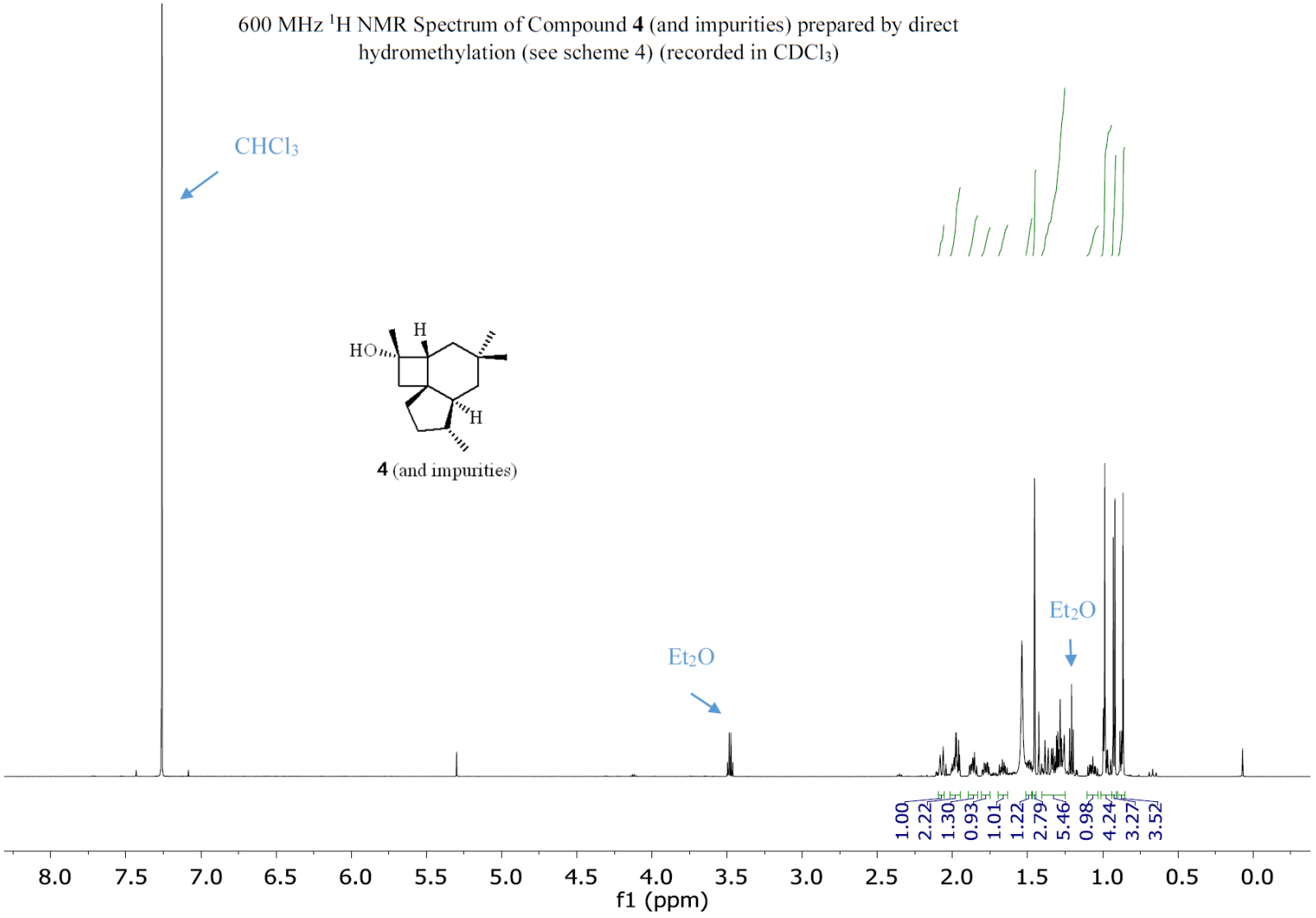
400 MHz ^{1}H NMR Spectrum of Compound **22** (β-epimer) (recorded in $CDCl_3$)

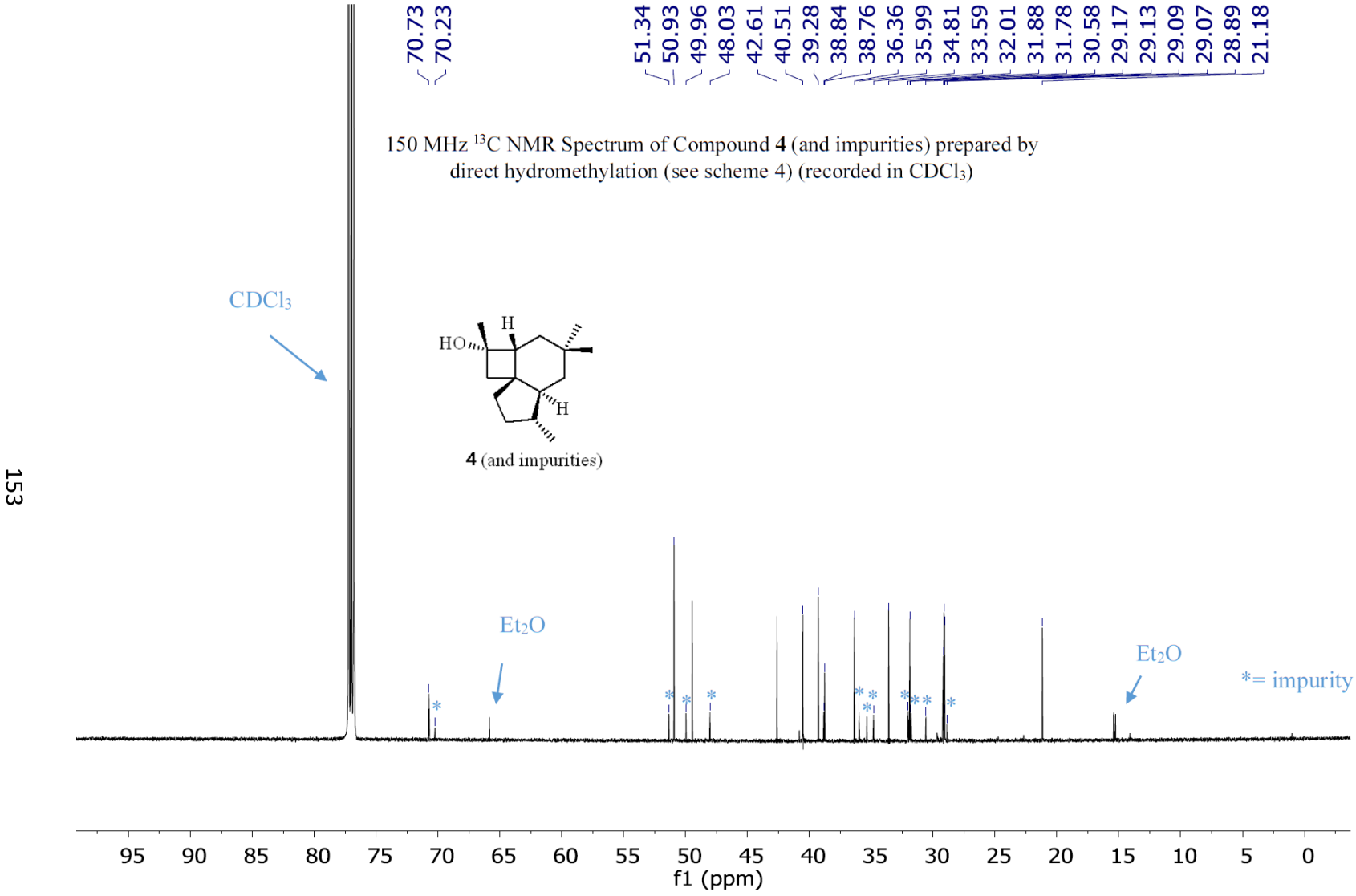


150


70.8
59.9
50.7
50.4
48.9
44.4
41.8
40.4
39.0
38.9
35.3
33.5
31.3
29.2
28.6
21.3
100 MHz ^{13}C NMR Spectrum of
Compound **22** (β-epimer)
(recorded in $CDCl_3$)
OH
H
HO
H
22
(β-epimer)
$CDCl_3$
120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -
f1 (ppm)

600 MHz ^{1}H NMR Spectrum of Compound **4** (and impurities) prepared by direct hydromethylation (see scheme 4) (recorded in $CDCl_3$)



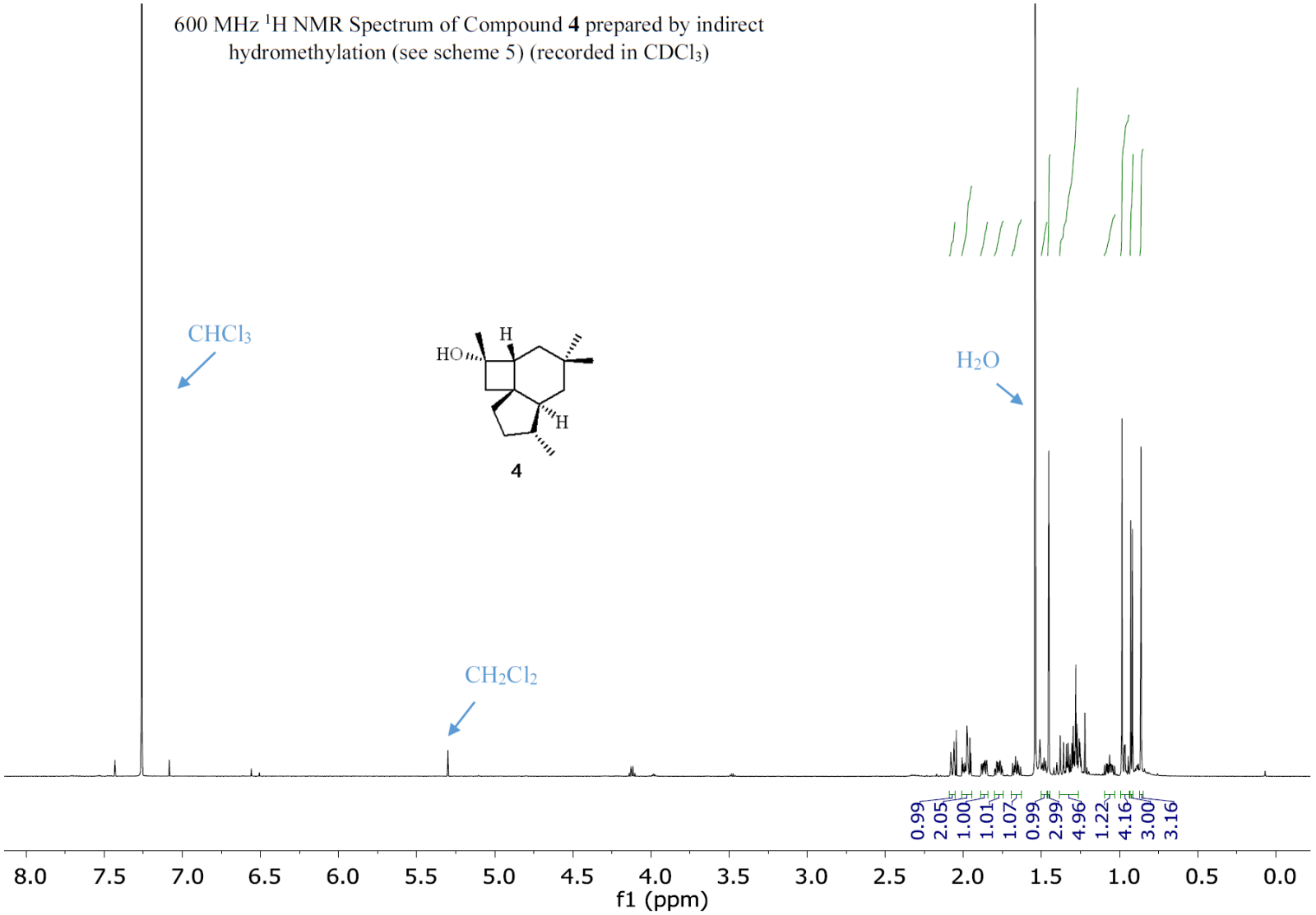


150 MHz ^{13}C NMR Spectrum of Compound **4** (and impurities) prepared by direct hydromethylation (see scheme 4) (recorded in $CDCl_3$)

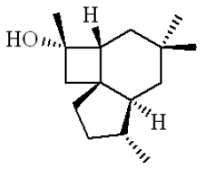
4 (and impurities)

153

600 MHz ^{1}H NMR Spectrum of Compound **4** prepared by indirect hydromethylation (see scheme 5) (recorded in $CDCl_3$)

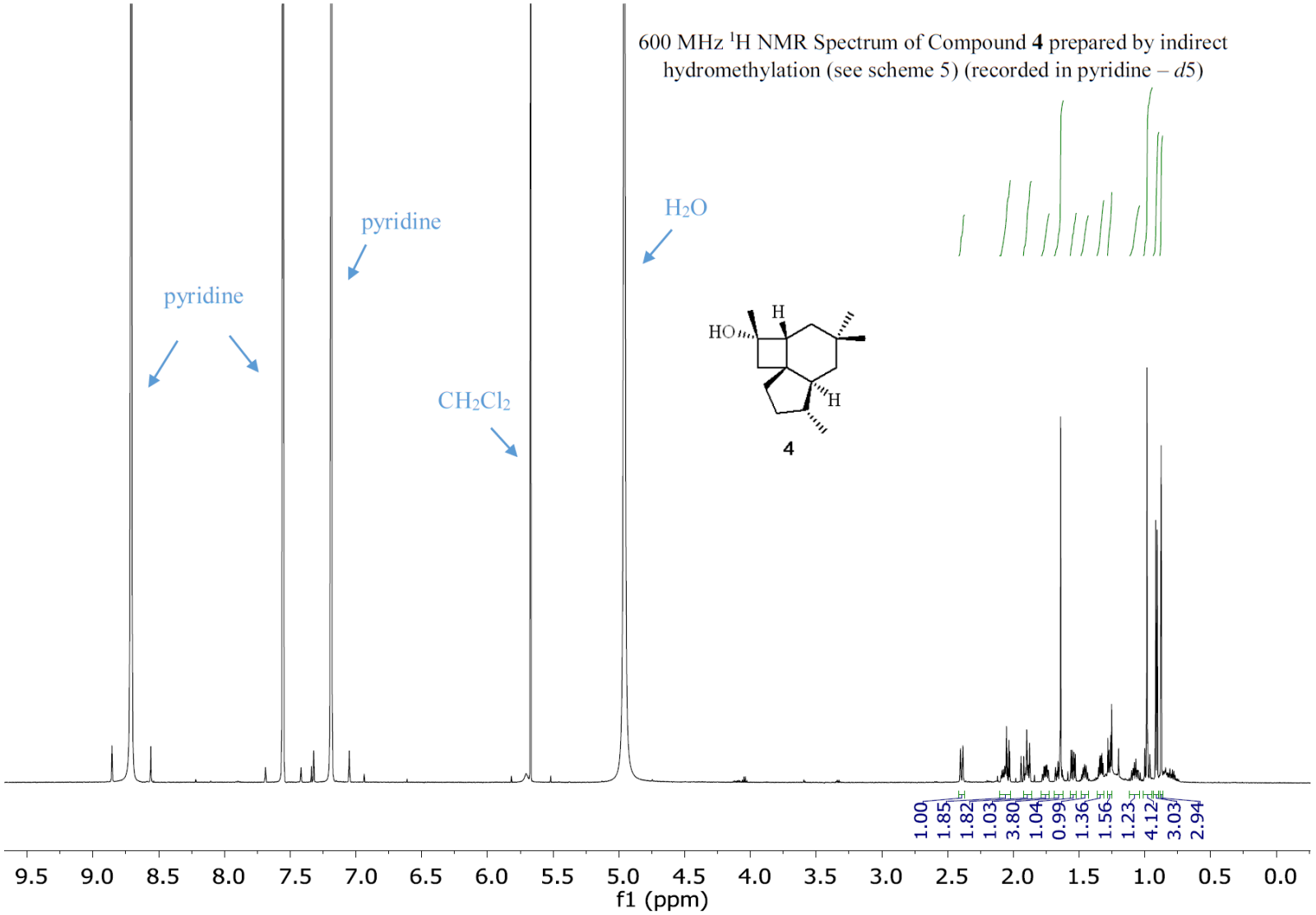


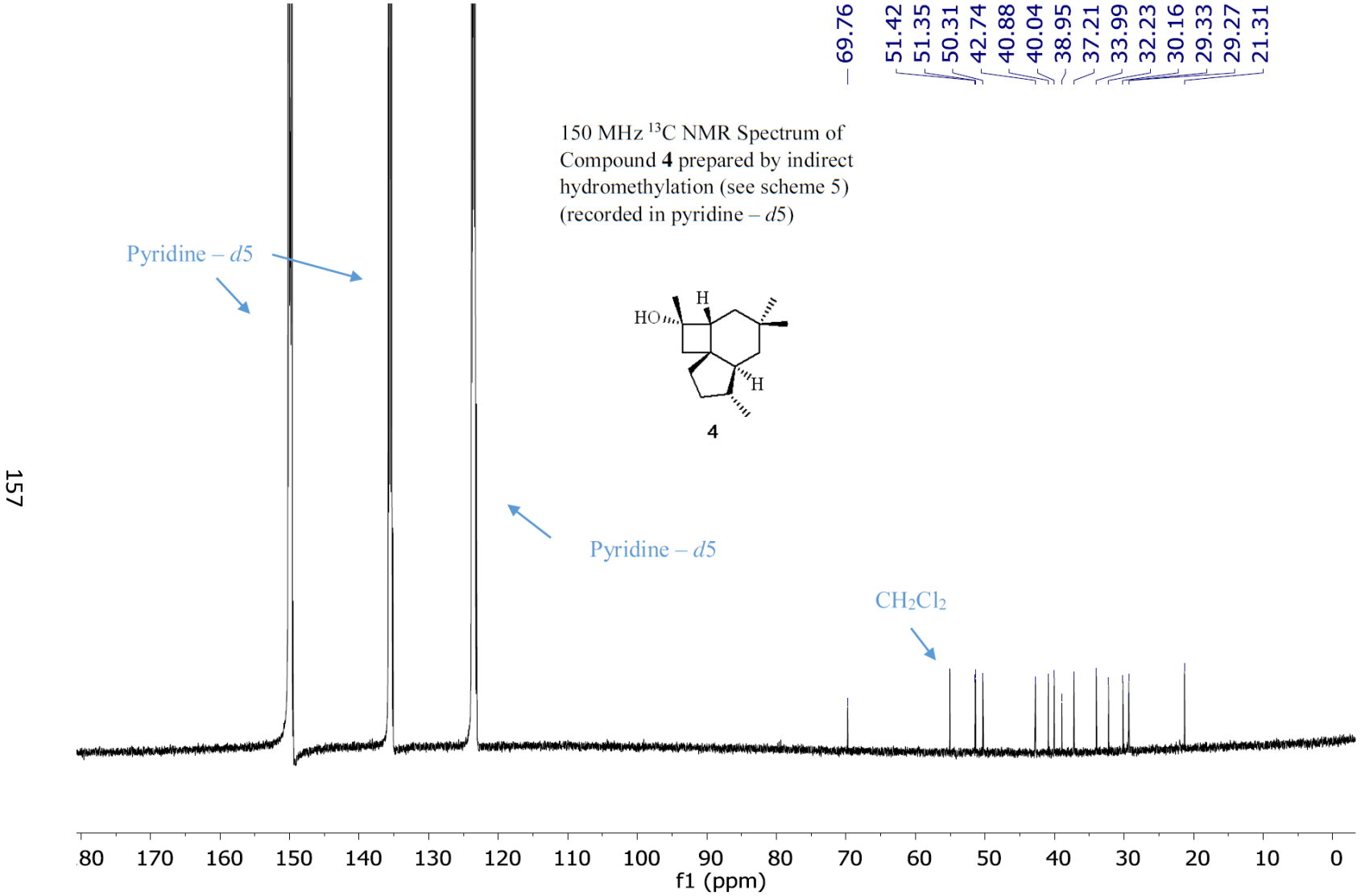
150 MHz ^{13}C NMR Spectrum of Compound **4** prepared by indirect hydromethylation (see scheme 5) (recorded in $CDCl_3$)



4

600 MHz ^{1}H NMR Spectrum of Compound **4** prepared by indirect hydromethylation (see scheme 5) (recorded in pyridine – *d*5)




69.76
51.42
51.35
50.31
42.74
40.88
40.04
38.95
37.21
33.99
32.23
30.16
29.33
29.27
21.31
150 MHz ^{13}C NMR Spectrum of Compound **4** prepared by indirect hydromethylation (see scheme 5) (recorded in pyridine – *d*5)
Pyridine – *d*5
Pyridine – *d*5
CH_2Cl_2
HO
H
H
4
f1 (ppm)

157

Publication Five

Synthetic Studies on the Marine-Derived Sesquiterpene (+)-Viridianol: Divergent Behaviour of Two Structurally Related Ring-Fused Cyclopropanes Under the Same Hydrogenolytic Conditions

Benoit Bolte, Fei Tang, Ping Lan, Anthony C. Willis and Martin G. Banwell

Aust. J. Chem. **2018 (**CH18532, accepted for publication on 11 December 2018**)**

Synthetic Studies on the Marine-Derived Sesquiterpene (+)-Viridianol: Divergent Behaviour of Two Structurally Related Ring-Fused Cyclopropanes Under the Same Hydrogenolytic Conditions.

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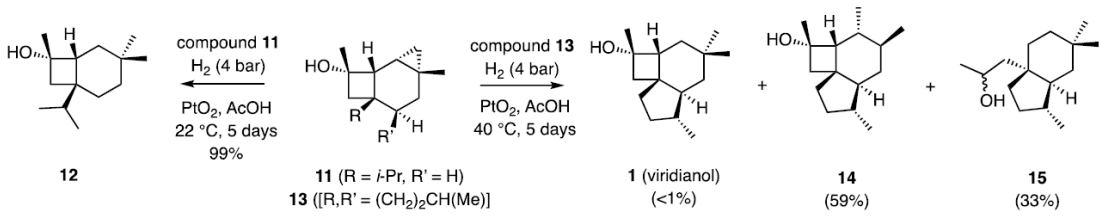
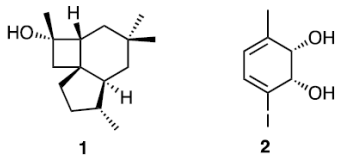


ABSTRACT: Hydrogenolytic cleavage of the ring-fused cyclopropane **11** using hydrogen in the presence of platinum oxide afforded the *gem*-dimethylated cyclohexane **12** in 99% yield. In contrast, analogous treatment of congener **13** afforded only trace amounts of the targeted and *gem*-dimethylated sesquiterpene (+)-viridianol (**1**), the major products of reaction now being the *vic*-dimethylated compound **14** and the two-fold ring-cleavage product **15**.

INTRODUCTION

One subset of the multitude of sesquiterpenoid natural products generated by terrestrial and marine organisms[1] embodies a four- and a five-membered ring fused to a common six-membered one. Among the three possible arrangements of such mutually-fused rings,[2] the one seen in the red seaweed-derived natural product (+)-viridianol (**1**)[3] is the rarest with only one other natural product, (+)-trefolane A,[4] embodying this ring system that necessarily incorporates a quaternary carbon center at the junction between the constituent rings. Recently,[5] we detailed a total synthesis of (+)-viridianol **1** that started with the enantiomerically enriched *cis*-1,2-dihydrocatechol **2**,[6] a compound that is readily obtained through the whole-cell biotransformation of *p*-iodotoluene.[7]

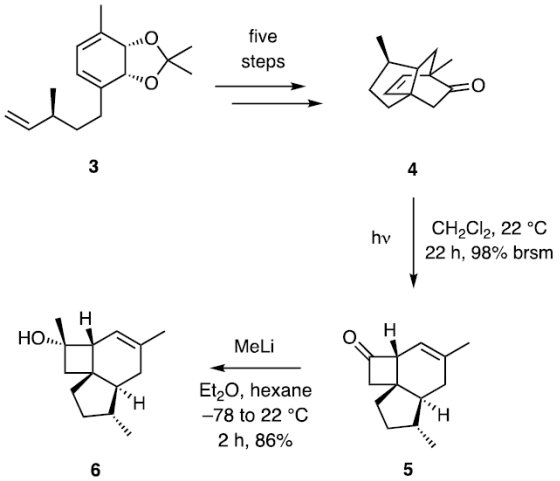


1 2

Figure 1: The structure of the sesquiterpene (+)-viridianol (**1**) and the starting material, **2**, used in its recently reported total synthesis.

Various of the key steps employed in this total synthesis[5] are shown in Scheme 1. The first of these was the formation of the triene **3** through engagement of the acetonide derivative of diol **2** in a metal-for-iodine exchange reaction with the ensuing organozinc species then participating in a Negishsi cross-coupling with an ω-unsaturated primary iodide. Triene **3** participated in a thermally-induced, type I intramolecular Diels-Alder cycloaddition reaction and thus yielding an adduct that was elaborated over a further five steps into cyclopentannulated bicyclo[2.2.2]octenone **4**. A photochemically-promoted and highly efficient 1,3-acyl migration (Givens rearrangement)[8] of compound **4** followed and thus yielding the octahydrocyclobuta[*d*]indene **5** embodying the full carbon framework of (+)-viridianol (**1**). Treatment of cyclobutanone **5** with methyllithium resulted in a stereoselective addition reaction and thereby providing the tertiary allylic alcohol **6** incorporating a further key structural element of target **1**. In a formal sense, the conversion **6** $\rightarrow$ **1** required to complete the synthesis through establishment of the *gem*-dimethyl subunit associated with the latter requires the Markovnikov-type hydromethylation of the former compound (an unactivated olefin), a process for which few direct methods have been reported.[9] As such we sought to pursue indirect methods involving olefinic cyclopropanation followed by hydrogenolysis of the resulting three-membered ring. This protocol that has been applied with considerable success in a range of settings,[10] although not to any great extent with tri- or more highly-substituted cyclopropanes. Details of our efforts to effect such a transformation are presented in the following section.

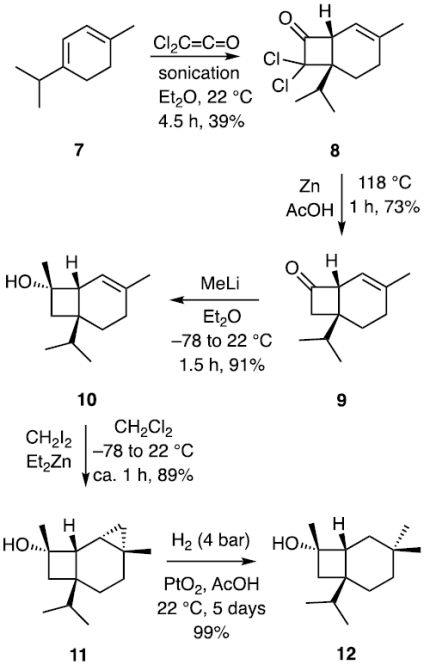
Scheme 1: Key steps associated with the formation of the octahydrocyclobuta[*d*]indene framework of (+)-viridianol and leading to tertiary-alcohol **6**.



RESULTS AND DISCUSSION

The length and complexity of the reaction sequence leading to compound **6** did not lend itself to the accumulation of this material in sufficient quantity for the purposes of conducting the extensive studies of the cyclopropanation/hydrogenolysis protocol it was thought would be necessary in defining a means for introducing the *gem*-dimethyl group associated with target **1**. As such, a model study was pursued in the first instance. Details are presented in Scheme 2.

Scheme 2: The synthesis of tertiary alcohol **10**, an analogue of compound **6**, and its two-step Markownikoff hydromethylation leading to the *gem*-dimethylated cyclohexane **12**



Following protocols established by Greene,[11] commercially available α-terpinene (**7**) was treated, under ultrasonication conditions, with *in situ* generated dichloroketene and thereby affording the required [2+2] cycloadduct **8** in 39% yield after chromatographic purification. Treatment of compound **8** with freshly activated zinc powder in acetic acid under reflux for 1 h resulted in two-fold dechlorination and the formation of cyclobutanone **9** that was obtained in 73% yield. At low temperatures, addition of methyllithium to ketone **9** proceeded in an *exo*-fashion and thereby forming the *endo*-configured alcohol **10** in 91% yield. Compound **10** represents a model for congener **6** and

so methods for its two-step hydromethylation, via a cyclopropanation/hydrogenolysis sequence, was explored.

The hydroxyl group within compound **10** served to direct a low-temperature Furukawa-type cyclopropanation reaction[12] and thus leading to the formation of the crystalline tricyclo[5.2.0.0^{2,4}]nonane **11** in 89% yield. All of the spectral data acquired on cyclopropane **11** were in accord with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis, details of which are provided in the Experimental Section and the Supporting Information.

A range of catalysts has been employed in the hydrogenolytic cleavage of ring-fused cyclopropanes[10] and among the most conspicuous of these is platinum oxide. Accordingly, and taking leads from the work of Overman[13] and Jones,[14] an acetic acid solution of cyclopropane **11** was exposed to dihydrogen at 4 bar in the presence of PtO_2 at 22 °C for 5 days and after workup the anticipated *gem*-dimethylated compound **12** was obtained in 99% yield. The spectral data derived from product **12** were in complete accord with the illustrated structure. Notably, in the high field region of the 400 MHz ^{1}H NMR spectrum, three three-proton singlets and two three-proton doublets were evident, as would be expected for structure **12**. These resonances are only consistent with the illustrated mode of cyclopropane ring cleavage and not the other two possibilities that would lead to either a seven-membered ring or a vicinally dimethylated product that would displayed two, three-proton doublets in the derived ^{1}H NMR spectrum. In the ^{13}C NMR spectrum of compound **12** the expected fourteen resonances were observed with three of these being due to quaternary carbons, a situation that is only consistent with the illustrated outcome among the three possible modes of cyclopropane ring-cleavage within substrate **11**.

Encouraged by the outcomes of the model study detailed immediately above, compound **6** was subjected to reaction with diiodomethane in the presence of Et_2Zn (Scheme 3) and thus affording the anticipated cyclopropane **13** as a single diastereoisomer in 93% yield. As was the case with the analogous conversion shown in Scheme 2, in this instance it is assumed that the hydroxyl group associated with substrate **6** directs delivery of the

methylene unit incorporated into product **13** such that the illustrated stereochemical outcome is observed. This is an entirely credible outcome given that delivery of the methylene unit to substrate **6** would not only be directed by the hydroxyl group but also take place at that face of the olefin opposite the cyclopentane ring that is annulated to opposing side of the six-membered ring.

When compound **13** was exposed to hydrogen under exactly the same conditions as employed for the conversion **11** → **12** then a rather complex product mixture was obtained. Disappointingly, only trace amounts of (+)-viridianol (**1**) were obtained with its *vic*-dimethylated isomer **14** (59%) predominating and the two-fold reductive cleavage product **15** (33% of a *ca*. 3:1 mixture of diastereoisomers) being the other major product of reaction. These three reactions products could be separated from one another by careful flash column chromatography.

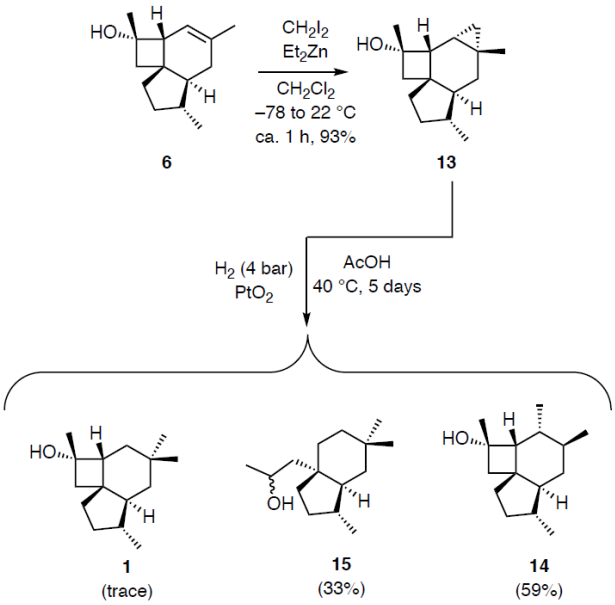
The structure of compound **1** obtained by the pathway shown in Scheme 3 was confirmed through comparison of the derived spectral data with those obtained on an authentic sample prepared by a hydromethylation route.[5]

In the ^{1}H NMR spectrum of compound **14** three, three-proton doublets were observed in the high-field region and so suggesting the presence of three methyl groups attached to tertiary rather than quaternary carbon centres. The illustrated configuration of the newly established stereogenic centres in product **14** are assigned on the basis that hydrogenolytic cleavage of the cyclopropane ring within substrate would proceed through addition of the elements of dihydrogen from the notionally more accessible *exo*-face of the bicyclo[4.1.0]heptane substrate. Such a pathway would establish the illustrated *trans*-relationship between the methyl groups attached to the six-membered ring. The ^{13}C NMR spectrum of product **14** displayed the expected fifteen resonances while the infra-red spectrum showed a strong O-H stretching band at 3342 cm^{-1}. Mass spectral data could not be acquired on this material due to its high volatility.

The most notable features in the ^{1}H NMR spectrum of compound **15** were a one-proton oxymethine resonance at δ 3.97 and, in the higher field region, two, three-proton singlets

together with two, three-proton doublets. The former pair of signals arise from the *gem*-dimethyl moiety associated with the six-membered ring while the latter derive from the methyl groups attached to methine carbons including, in one case, an oxymethine carbon and thus resonating at notably lower field than the other (δ 1.25 vs 1.00 ppm). The ^{13}C NMR spectrum of alcohol **15** displayed two sets of fifteen resonances and thus indicating it is a *ca.* 3:1 mixture of disastereoisomers due to the presence of both the *R*- and *S*-epimeric forms at the hydroxyl-bearing carbon. The IR spectrum of compound **15** displayed a prominent OH stretching band at 3363 cm^{-1} but no molecular ion could be observed in the mass spectrum due to its volatility. Clearly, compound **15** arises though successive and regio-selective hydrogenolyses of the three and the four-membered rings in substrate **13** but the ordering of these events remains unclear. In particular, due to a lack of material, (+)-viridianol could not be re-subjected to the reaction conditions so as to determine if it serves as a precursor to alcohol **15**.

Scheme 3:



The regio-selective but non-stereoselective nature of the hydrogenolytic cleavage of the cyclobutane ring necessarily involved in the conversion **13** → **15** is noteworthy and it might be argued that this process is influenced by the ability of the flanking cyclopropane

to stabilize developing positive charge at the closest of the cyclobutane ring carbons and this ring is cleaved first. If this were the case then (+)-viridianol would not be a precursor to compound **15**.

CONCLUSION

Given the divergent behaviors of substrates **11** and **13** under the same hydrogenolytic reaction conditions it is evident that the cyclopentannulated nature the latter compound impacts significantly on its reactivity. While the precise origins of this effect remain unclear, the selectivities associated the reductive ring-cleavage of three- and four-membered carbocycles would seem to be delicately balanced. As such, substrates incorporating two or more such moieties seem likely to engage in competitive processes and thus making synthetic planning involving such conversions rather challenging. The present work, when considered alongside our recently reported[5] total synthesis of (+)-viridianol (**1**), clearly demonstrate that the development of direct, broadly applicable and high-yielding means for effecting the Markovnikov hydromethylation of unsymmetric alkenes remains an important objective.

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 101 MHz for carbon nuclei. 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. ^{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. Infrared spectra (ν_{max}) were recorded on a FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Optical rotations were recorded in the indicated solvent at 20 °C. 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. 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.*[15] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al.*[16] Where necessary, reactions were performed under an atmosphere of nitrogen.

Specific Chemical Transformations

(rel-1*R*,6*R*)-8,8-Dichloro-1-isopropyl-4-methylbicyclo[4.2.0]oct-4-en-7-one (8). A mag -netically stirred suspension of α-terpinene (**7**) (8.10 mL, 50 mmol) and zinc dust (9.80 g, 150 mmol) in diethyl ether (150 mL) maintained under nitrogen at 22 °C and contained in a 500 mL round-bottomed flask equipped with a Liebig condenser was treated, dropwise over 0.5 h and under sonication, with trichloroacetyl chloride (5.60 mL, 100 mmol). Sonication was continued for a further 4 h then the reaction mixture was cooled and concentrated under reduced pressure to *ca*. 50 mL. The residue thus obtained was diluted with hexane (200 mL) and the resulting mixture filtered through a short pad of TLC-grade silica gel and the solids thus retained washed with hexane/diethyl ether (500 mL of a *ca*. 4:1 v/v mixture). The combined filtrates were concentrated under reduced pressure and the ensuing dark-brown residue subjected to flash column chromatography (silica gel, 9:1 v/v 40-60 petroleum spirits/dichloromethane) to give, after concentration of the appropriate fractions (R_f = 0.4), compound **8** (3.60 g, 39%) as a clear, light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (d, J = 6.7 Hz, 1H), 3.79 (d, J = 6.7 Hz, 1H), 2.54 (hept, J = 6.9 Hz, 1H), 2.13 (m, 1H), 1.95-1.83 (complex m, 3H), 1.75 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 140.2, 114.1, 92.5, 59.1, 49.9, 34.3, 27.7, 23.3, 18.4, 17.9 (one signal obscured or overlapping); IR (neat) ν_{max} 2965, 2935, 1803, 1463, 1445, 1389, 1370, 1232, 890, 836, 797, 716 cm^{-1}; MS (EI, 70 eV) *m/z* 250, 248 and 246 ($M^{+\bullet}$, 10, 65 and 95%), 222, 220 and 218 (10, 50

and 80), 213 and 211 (40 and 100); HRMS Calcd for $C_{12}H_{16}O^{35}Cl_2$: 246.0578. Found: 246.0576.

(rel-1*R*,6*R*)-1-Isopropyl-4-methylbicyclo[4.2.0]oct-4-en-7-one (9). A magnetically stirred mixture of compound **8** (3.60 g, 14.6 mmol) and zinc dust (5.00 g, 77 mmol) in acetic acid (50 mL) was heated under reflux for 1 h then cooled to 22 °C and the resulting suspension concentrated under reduced pressure. The residue so obtained was diluted with dichloromethane (100 mL) and the mixture thus formed filtered through a short pad of Celite™. The pad was washed with additional dichloromethane (100 mL) and the combined filtrates washed with $NaHCO_3$ (3 x 50 mL of a saturated solution), water (1 × 100 mL) and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:1 v/v 40-60 petroleum spirits/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.3), compound **9** (1.91 g, 73%) as a clear, pale-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (m, 1H), 3.33 (m, 1H), 2.70 (ABq, J = 17.3 Hz, 2H), 2.12 (m, 1H), 1.96 (m, 1H), 1.79 (hept, J = 6.8 Hz, 1H), 1.75 (s, 3H), 1.60 (m, 1H), 1.49 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.1, 137.5, 115.1, 62.1, 51.1, 35.4, 34.7, 26.4, 23.7, 22.6, 17.1, 17.0; IR (neat) ν_{max} 2962, 2931, 2876, 1778, 1464, 1446, 1387, 1369, 1130, 1107, 1073, 820 cm^{-1}; MS (ESI, +ve) *m/z* 201 [(M+ Na)$^+$, 100%]; HRMS (ESI, +ve) Calcd for $C_{12}H_{18}ONa$: 201.1255. Found: 201.1256.

(rel-1*R*,6*R*,7*S*)-1-Isopropyl-4,7-dimethylbicyclo[4.2.0]oct-4-en-7-ol (10). A magnetically stirred solution of compound **9** (1.80 g, 10.0 mmol) in diethyl ether (50 mL) maintained under a nitrogen atmosphere was cooled to –78 °C then treated with MeLi (12.5 mL of a 1.6 M solution in diethyl ether, 20 mmol). The resulting mixture was kept at –78 °C for 1 h then allowed to warm to 22 °C over 0.5 h before being treated with NH_4Cl (25 mL of a saturated aqueous solution) and water (25 mL) then extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with water (1 × 50 mL) and brine (1 × 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 9:1 v/v 40-60 petroleum spirits/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.25), compound **10** (1.87 g, 91%) as clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, J = 6.5 Hz, 1H), 2.47 (d, J = 6.5 Hz, 1H), 2.16

(broad s, 1H), 2.05-1.98 (complex m, 2H), 1.87 (dd, J = 13.0 and 2.0 Hz, 1H), 1.81 (s, 3H), 1.78 (hept, J = 7.0 Hz, 1H), 1.65 (d, J = 12.9 Hz, 1H), 1.37 (s, 3H), 1.30-1.20 (complex m, 2H), 0.81 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5, 119.2, 70.1, 49.3, 44.3, 36.6, 34.2, 30.0, 27.1, 24.1, 22.9, 16.6, 16.4; IR (neat) ν_{max} 3543, 3469, 2959, 2925, 2874, 1447, 1383, 1367, 1343, 1238, 1159, 1089, 953, 885, 860 cm^{-1}; Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

(rel-1*R*,2*S*,4*S*,7*R*,9*S*)-7-Isopropyl-4,9-dimethyltricyclo[5.2.0.02,4]nonan-9-ol (11). A magnetically stirred solution of compound **10** (333 mg, 1.70 mmol) in dry dichloromethane (5 mL) maintained under nitrogen was cooled to –78 °C then treated with CH_2I_2 (560 μL, 6.8 mmol) and Et_2Zn (3.4 mL of a 1.0 M solution in hexane, 3.4 mmol). The ensuing mixture was allowed to warm to 22 °C over 1 h then quenched with NH_4Cl (10 mL of a saturated solution) and extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) and water (1 × 10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:9 v/v diethyl ether/pentane elution) to give, after concentration of the appropriate fractions (R_f = 0.4), compound **11** (332 mg, 89%) as a clear, colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (broad s, 1H), 2.37 (dd, J = 7.0 and 2.4 Hz, 1H), 2.00 (dd, J = 12.8 and 2.4 Hz, 1H), 1.70-1.45 (complex m, 3H), 1.40-1.30 (complex m, 2H), 1.28 (s, 3H), 1.03 (s, 3H), 0.92 (m, 1H), 0.76 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 0.64 (m, 1H), 0.32 (dd, J = 8.6 and 4.2 Hz, 1H) (resonance due to one proton obscured or overlapping); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.4, 50.7, 46.2, 36.3, 31.5, 30.5, 28.6, 26.4, 26.0, 17.7, 16.6, 16.3, 13.2, 12.6; IR (neat) ν_{max} 3592, 3459, 2954, 1468, 1448, 1383, 1367, 1234, 1208, 1172, 1102, 1090, 1050, 953, 909, 890 cm^{-1}. Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

A sample of this material was subjected to sublimation (40 °C/400 mm Hg) to give compound **11** as colorless needles, m.p. = 66-69 °C, one of which proved suitable for single-crystal X-ray analysis.

(rel-1*R*,6*R*,7*S*)-1-isopropyl-4,4,7-trimethylbicyclo[4.2.0]octan-7-ol (12). A Parr hydrogenator was charged with mixture of compound **11** (250 mg, 1.20 mmol), PtO_2 (250 mg, 100% w/w) and glacial acetic acid (20 mL) and then pressurized with hydrogen gas (4

bar). The reaction vessel and its contents were shaken at 22 °C for 5 days and after this time the residual hydrogen was displaced with nitrogen and the ensuing mixture diluted with diethyl ether (50 mL) before being washed with $NaHCO_3$ (3 × 50 mL of a saturated solution), brine (1 × 50 mL) and water (3 × 50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The black residue thus obtained was subjected to flash column chromatography (silica gel, 1:4 v/v diethyl ether/pentane elution) to give, after concentration of the appropriate fractions (R_f = 0.3), compound **12** (248 mg, 99%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (m, 1H), 1.92 (dd, J = 12.6 and 2.7 Hz, 1H), 1.85-1.75 (complex m, 2H), 1.64 (dd, J = 14.3 and 7.0 Hz, 1H), 1.51-1.08 (complex m, 6H), 1.35 (s, 3H), 0.95 (s, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.81 (s, 3H), 0.79 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.1, 44.6, 44.5, 36.1, 34.5, 33.9, 33.1, 33.0, 31.4, 27.9, 27.5, 24.5, 17.1, 16.6; IR (neat) ν_{max} 3284, 2953, 2924, 2863, 1460, 1384, 1376, 1361, 1243, 1219, 1162, 1146, 1077, 961, 738, 711 cm^{-1}. Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

(1*S*,2a*S*,5*R*,5a*S*,6a*R*,7a*S*,7b*R*)-1,5,6a-trimethyldecahydro-2*H*cyclobuta[*d*]cyclopropa-[*f*]inden-1-ol (13). A magnetically stirred solution of compound **6** (150 mg, 0.73 mmol) in dry dichloromethane (7 mL) and maintained under nitrogen was cooled to –78 °C then treated with CH_2I_2 (0.23 mL, 2.91 mmol) and Et_2Zn (1.5 mL of a 1.0 M solution in hexane, 1.50 mmol). The ensuing mixture was allowed to warm to 22 °C over 1 h then quenched with NH_4Cl (10 mL of a saturated solution) before being extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 20 mL) and water (1 × 20 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 1:4 v/v diethyl ether/pentane elution) to give, after concentration of the appropriate fractions (R_f 0.3), compound **13** (139 mg, 93%) as a clear, colorless oil, $[\alpha]_D^{20}$ = –23 (c = 4.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (broad s, 1H), 2.50 (s, 1H), 1.95 (dd, J = 12.3 and 3.2 Hz, 1H), 1.85-175 (complex m, 2H), 1.68-1.59 (complex m, 2H), 1.54-1.39 (complex m, 2H), 1.38 (s, 3H), 1.20-1.00 (complex m, 2H), 1.10 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (m, 1H), 0.70-0.63 (complex m, 2H), 0.40 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.6, 55.5, 51.4, 50.8, 41.7, 40.7, 35.7, 35.5, 32.7, 28.6, 25.8, 20.9, 16.3, 16.1, 12.8; IR (neat) ν_{max} 3591, 3464, 2947, 2919, 2866, 1452, 1375, 1351, 1225, 1155, 964, 942 cm^{-1}; MS (ESI, +ve) *m/z* 463 [(2M+Na)$^+$,

6%], 275 [(M+Na+MeOH)$^+$, 40%], 243 [(M+Na)$^+$, 100], 221 [(M+H)$^+$, <1]; HRMS Calcd for (M+H)$^+$, $C_{15}H_{25}O$: 221.1905. Found: 221.1908.

Hydrogenolytic Cleavage of Cyclopropane 13. Formation of Compounds 1, 14, 15. A Parr hydrogenator containing a mixture of compound **13** (100 mg, 0.45 mmol), PtO_2 (100 mg, 100% w/w) and glacial acetic acid (10 mL) was charged with hydrogen (4 bar) then stirred magnetically at 40 °C for 5 days. The cooled reaction mixture was flushed with nitrogen then diluted with diethyl ether (50 mL) before being washed with $NaHCO_3$ (3 x 50 mL of a saturated solution), brine (1 × 50 mL) and water (1 × 50 mL) then dried (Na_2SO_4) filtered and concentrated under reduced pressure. The ensuing black residue was subjected to flash column chromatography (silica gel, 9:1 → 4:1 v/v pentane/diethyl ether gradient elution) to give four fractions, A-D.

Concentration of fraction A [R_f = 0.2(8) in 9:1 v/v pentane/diethyl ether] gave compound **13** (2 mg, 2% recovery) as a clear, colorless film. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B [R_f = 0.2(5) in 9:1 v/v pentane/diethyl ether] gave compound **14** (59 mg, 59%) as a clear, colorless oil, $[\alpha]_D^{20}$ = +42 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03-1.91 (complex m, 1H), 1.93 (dd, *J* = 12.0 and 1.6 Hz, 1H), 1.87-1.35 (complex m, 8H), 1.34 (s, 3H), 1.25 (m, 1H), 1.09-0.95 (complex m, 2H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90-0.70 (m, 1H), 0.85 (d, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.6, 56.1, 53.1, 52.3, 42.8, 42.0, 39.4, 33.5, 33.3, 31.8, 31.1, 30.2, 21.0, 18.3, 16.9; IR (neat) ν_{max} 3442, 2949, 2924, 2855, 1456, 1374, 1220 1179, 944, 809 cm^{-1}. Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

Concentration of fraction C [R_f = 0.2(3) 9:1 v/v pentane/diethyl ether] gave a clear, colorless film tentatively as compound **1** (< 1 mg, <1%). A comparison of the ^{1}H and ^{13}C NMR spectra derived from this material with these derived from an authentic sample of viridianol[5] clearly established that present fraction contained the natural product as the major component.

Concentration of fraction D (R_f = 0.3 in 7:3 v/v pentane/diethyl ether) gave a pale-yellow oil tentatively identified as a *ca.* 3:1 mixture of the diastereoisomeric forms of compound **15** (33 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (major isomer) 3.97 (m, 1H), 1.87 (m, 2H), 1.67 (complex m, 1H), 1.55-1.00 (complex m, 12H), 1.21 (d, *J* = 6.1 Hz,

3H), 0.96 (d, J = 6.4 Hz, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (major isomer) 65.8, 52.5, 47.7, 42.8, 38.0, 37.6, 37.1, 34.8, 32.2, 32.1, 29.9, 29.4, 28.9, 25.8, 20.8; IR (neat) ν_{max} 3363, 2949, 2865, 1459, 1373, 1124, 1072, 1022, 938 cm^{-1}. Due to its volatility, satisfactory MS and HRMS data could not be obtained on this material.

Crystallographic Study on Compound 11

Crystal data

Compound 11: $C_{14}H_{24}O$, M = 208.34, T = 150 K, monoclinic, space group $P2_1$, Z = 2, a = 8.7607(2), b = 5.6817(1), c = 13.1703(4) Å, β = 106.551(3)°, V = 628.40(3) Å^3, D_x = 1.101 g.cm^{-3}, 1364 unique data ($2\theta_{max}$ = 144.4°), 1332 with $I > 2.0\sigma(I)$; R = 0.033, Rw = 0.086, S = 1.00.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ = 0.71073 Å) and data extracted using the DENZO package.[17] Structure solution was by direct methods (SIR92).[18] The structure of compound **11** was refined using the CRYSTALS program package.[19] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC Deposition number 1863886). 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.

ASSOCIATED CONTENT

Supporting Information

Anisotropic displacement ellipsoid plot from the single-crystal X-ray analysis of compound **11**. ^{1}H and ^{13}C NMR spectra of compounds **8-15**. This material is available free-of-charge via the Internet at http://ajc…….

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Notes

The authors declare no competing financial interest

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Supplementary Material for:

Synthetic Studies on the Marine-Derived Sesquiterpene (+)-Viridianol:

Divergent Behaviour of Two Structurally Related, Ring-Fused Cyclopropanes Under the Same Hydrogenolytic Conditions.

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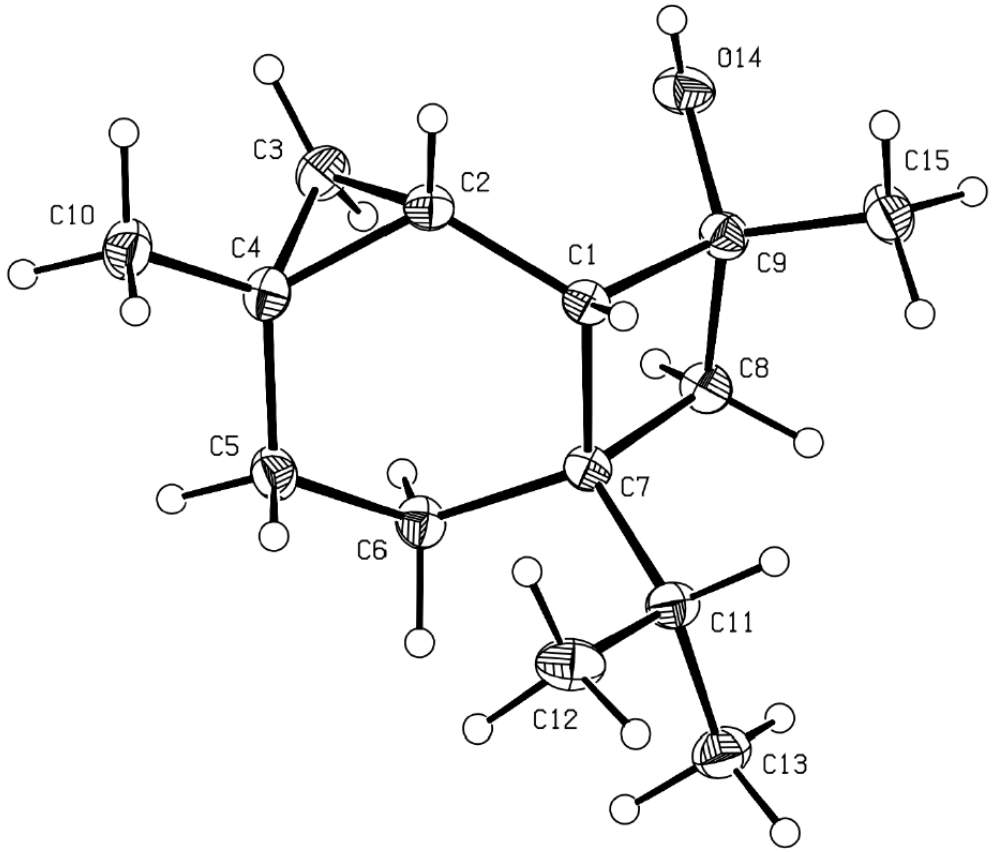
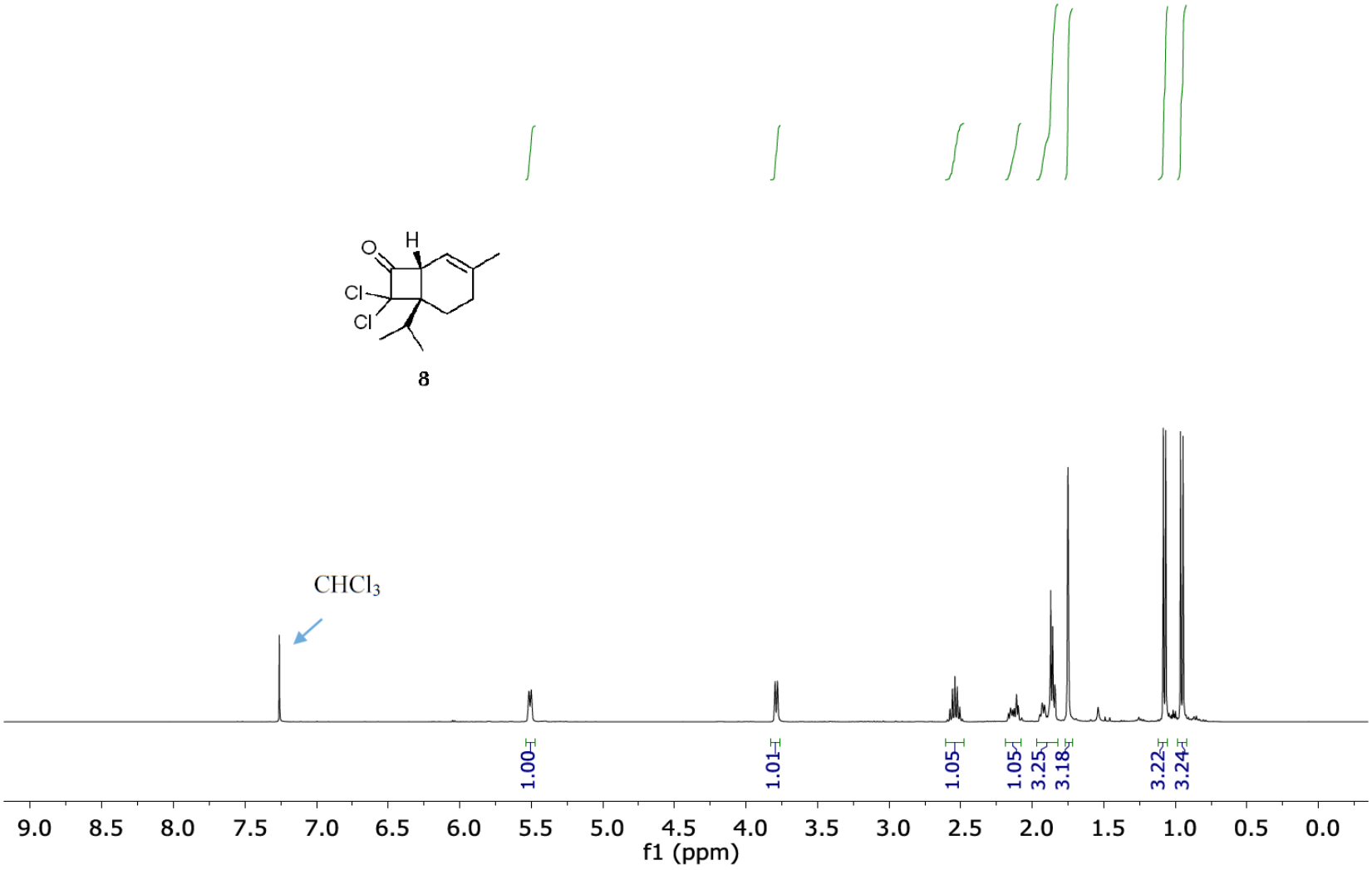


Figure S1: Structure of compound **11** (CCDC 1863886) with labelling of selected atoms.
Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

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



194.7
140.2
114.1
92.5
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27.7
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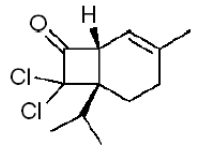
17.9

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



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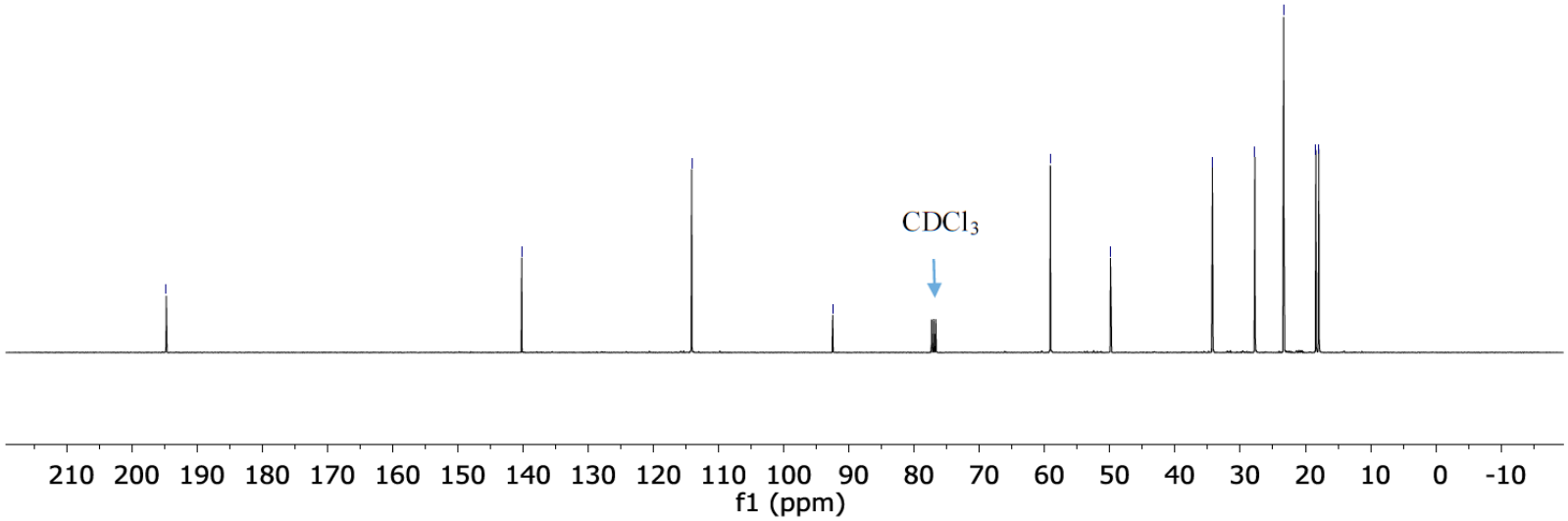

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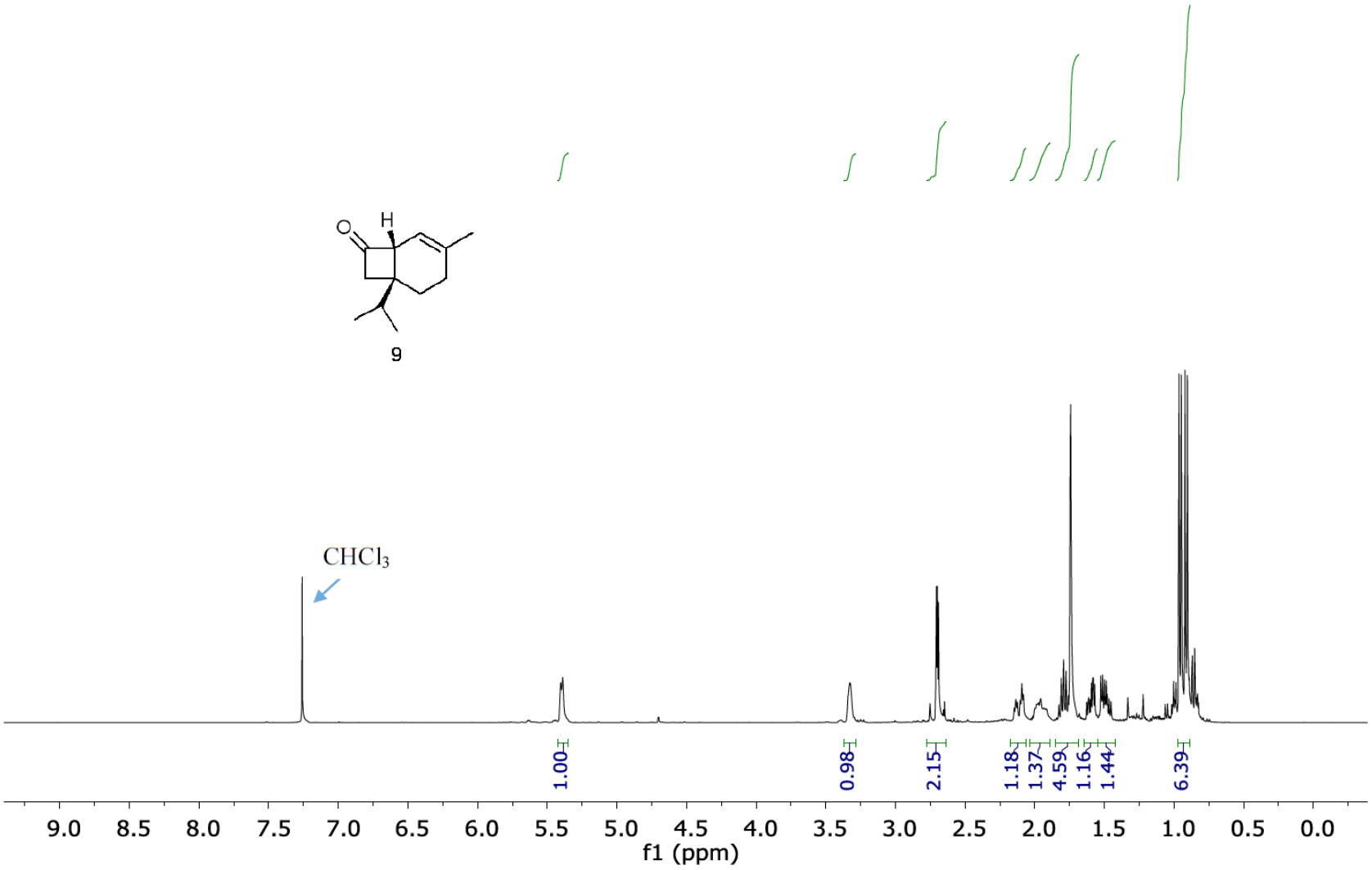

207.1
137.5
115.1
62.1
51.1
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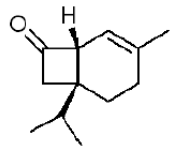
22.6
17.1
17.0

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



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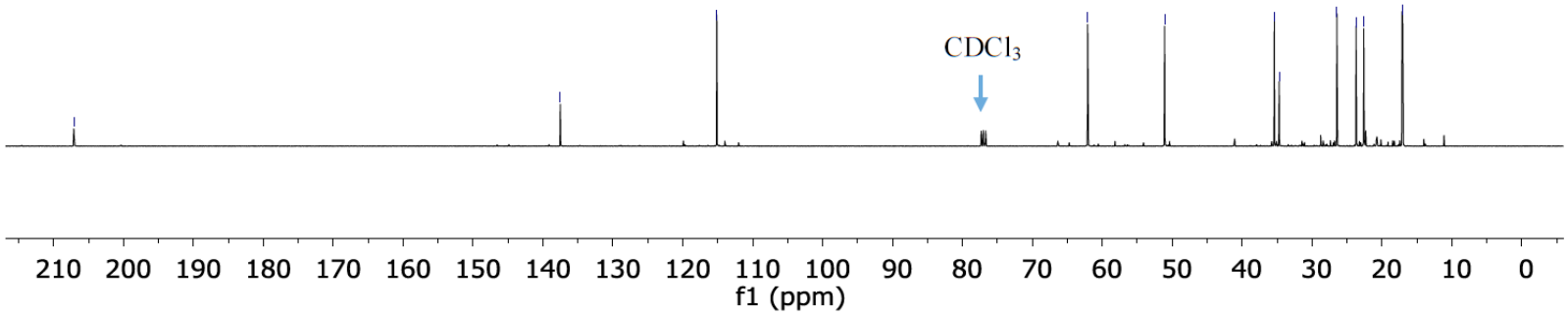

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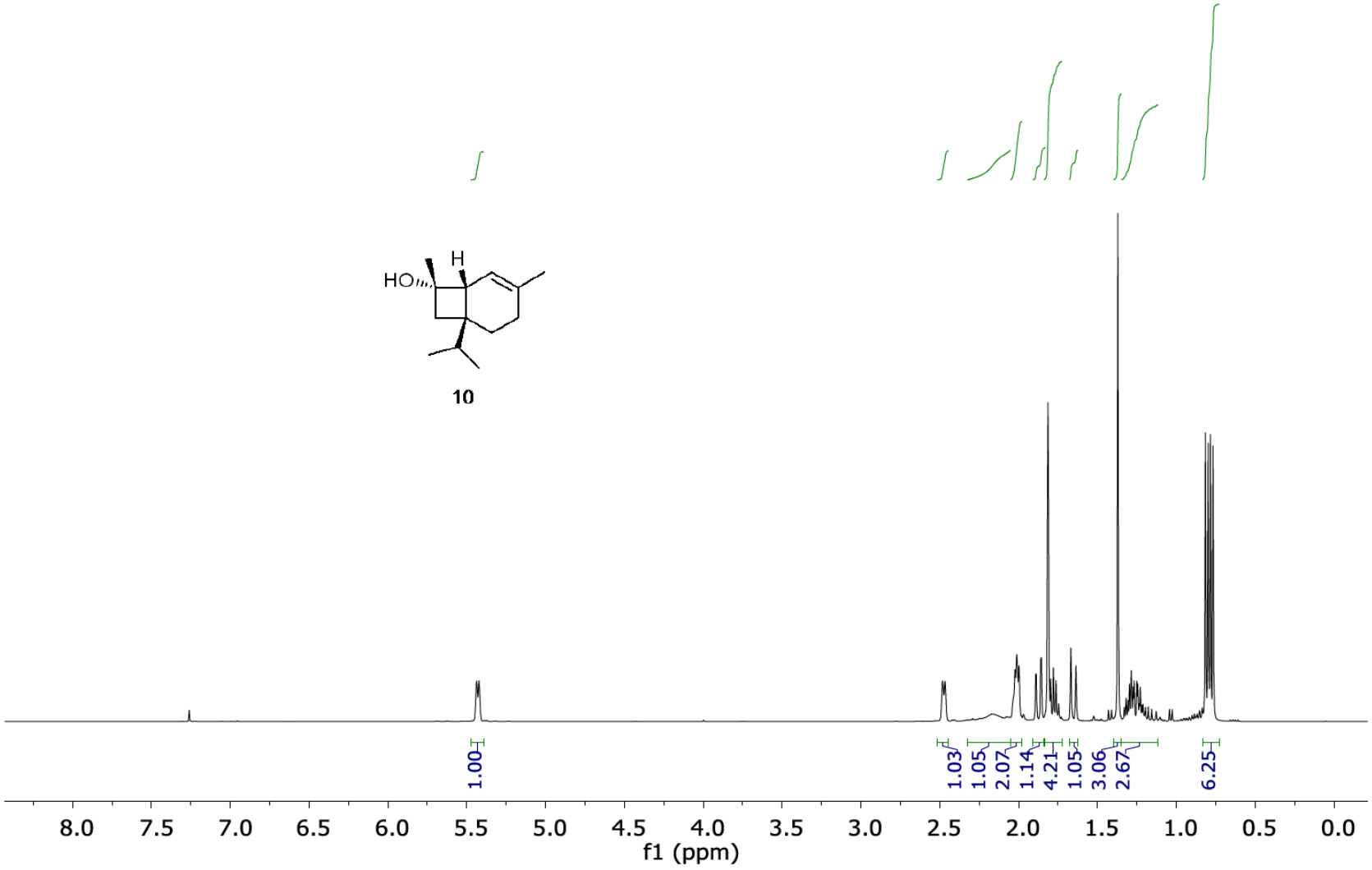

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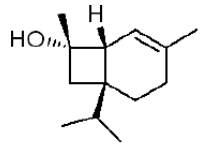

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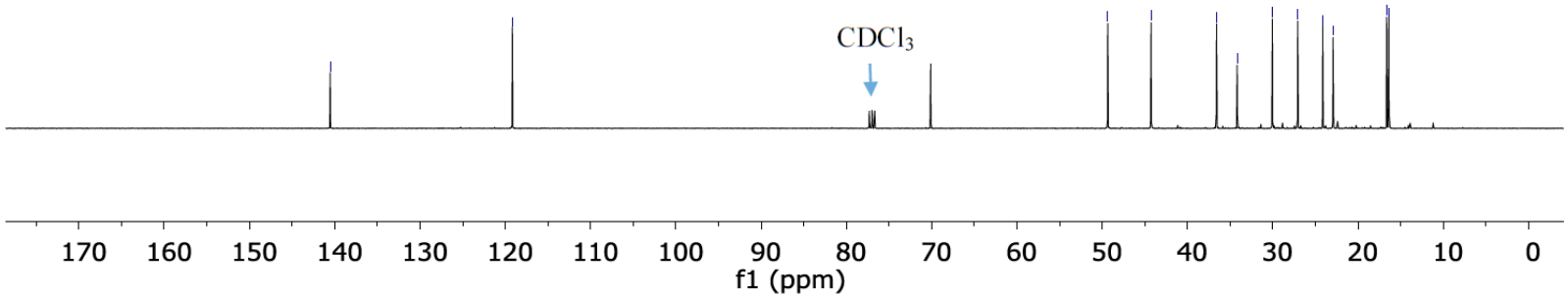

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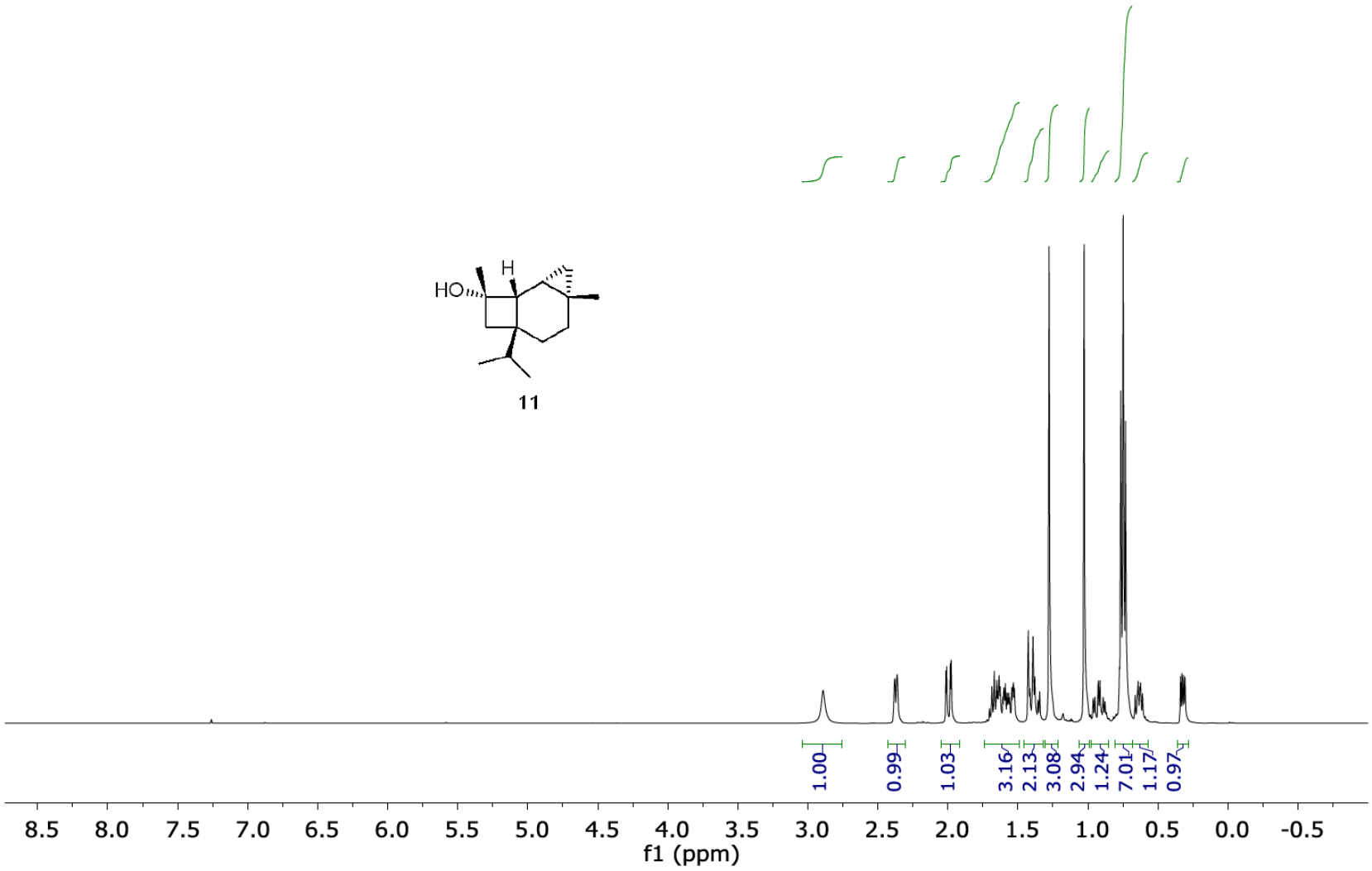
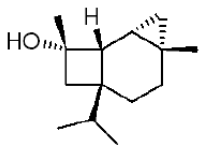


100 MHz ^{13}C NMR Spectrum of Compound **11** (recorded in $CDCl_3$)



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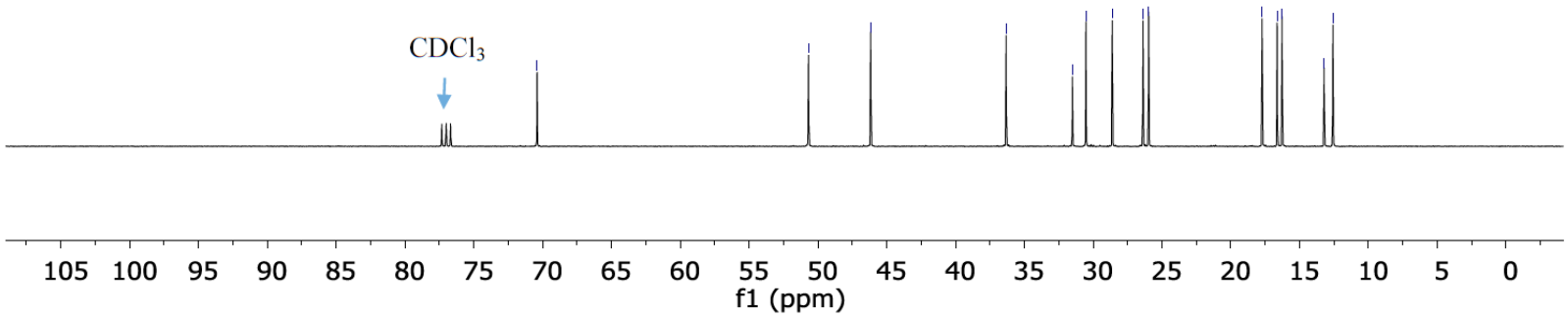
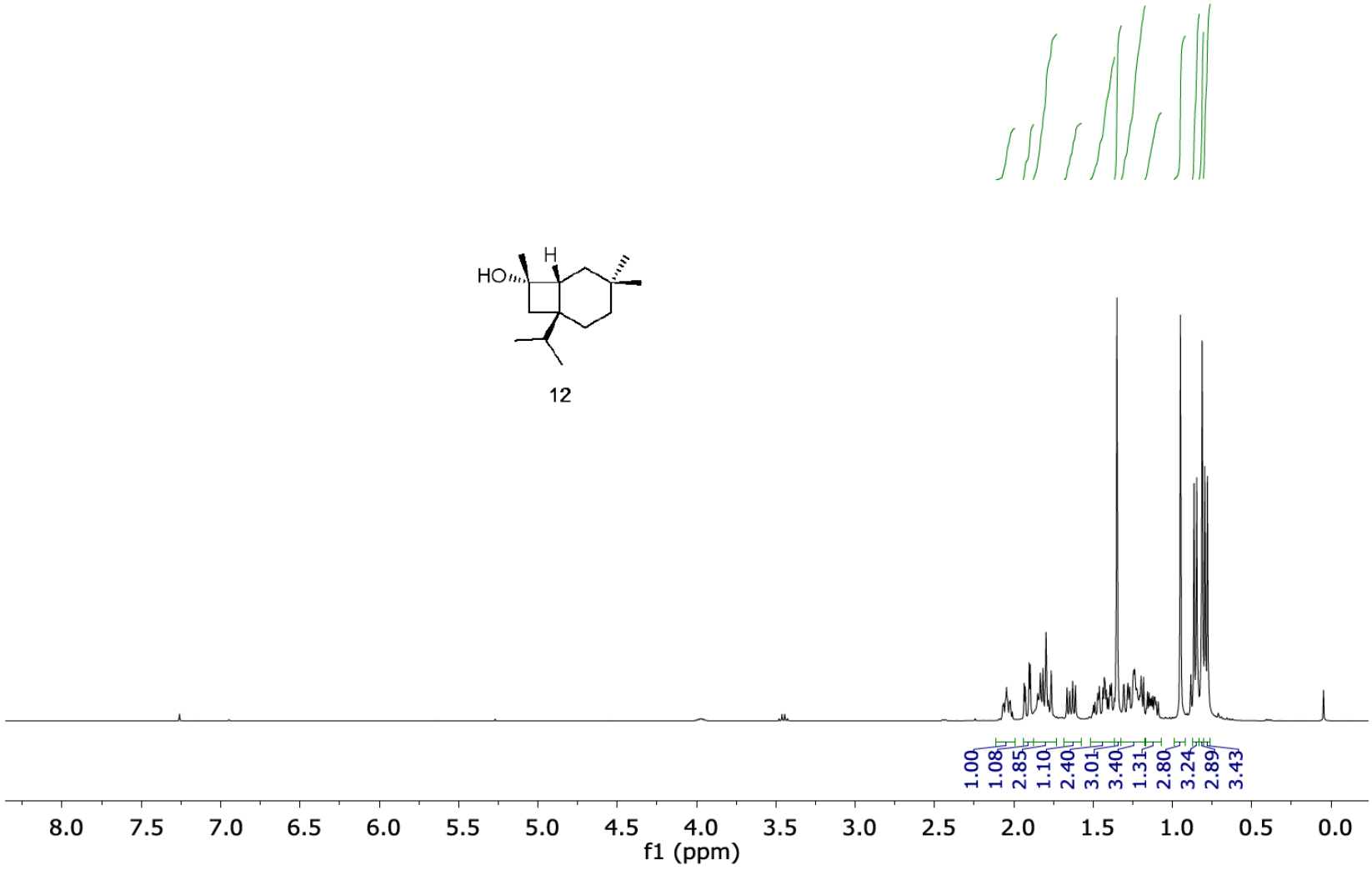
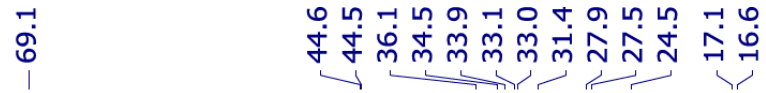
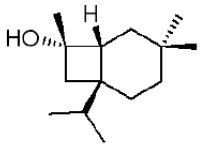


400 MHz ^{1}H NMR Spectrum of Compound **12** (recorded in $CDCl_3$)





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



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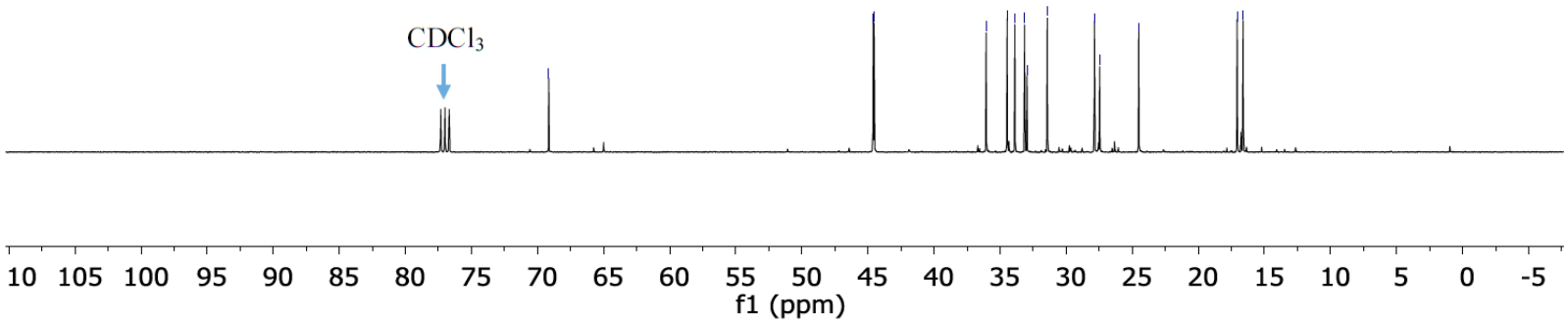
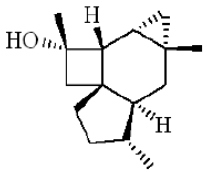


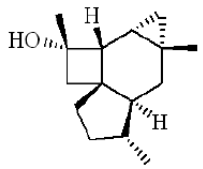
400 MHz ^{1}H NMR Spectrum of Compound **13** (recorded in $CDCl_3$)



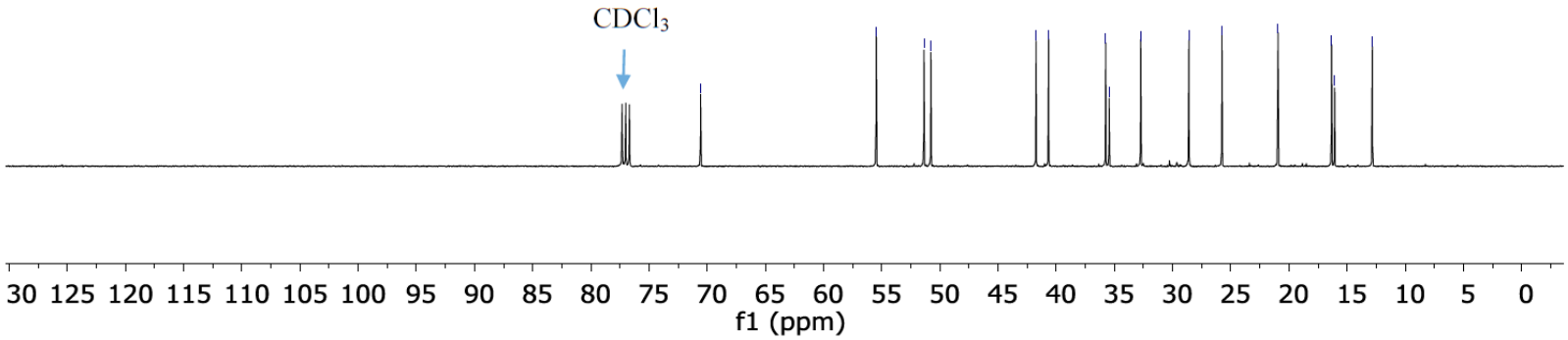
13

70.6
55.5
51.4
50.8
41.7
40.7
35.7
35.5
32.7
28.6
25.8
20.9
16.3
16.1
12.8

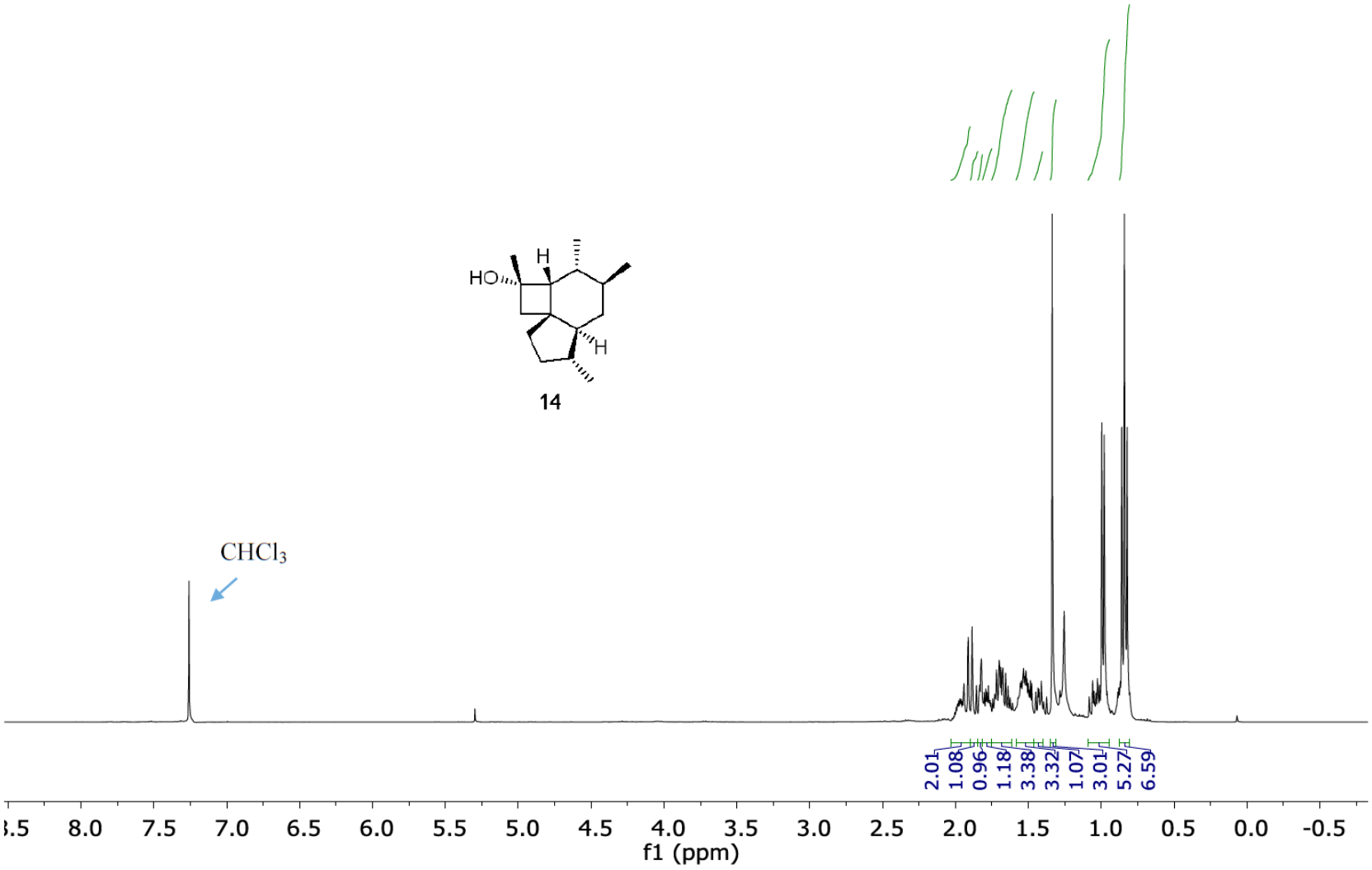
100 MHz ^{13}C NMR Spectrum of Compound **13** (recorded in $CDCl_3$)

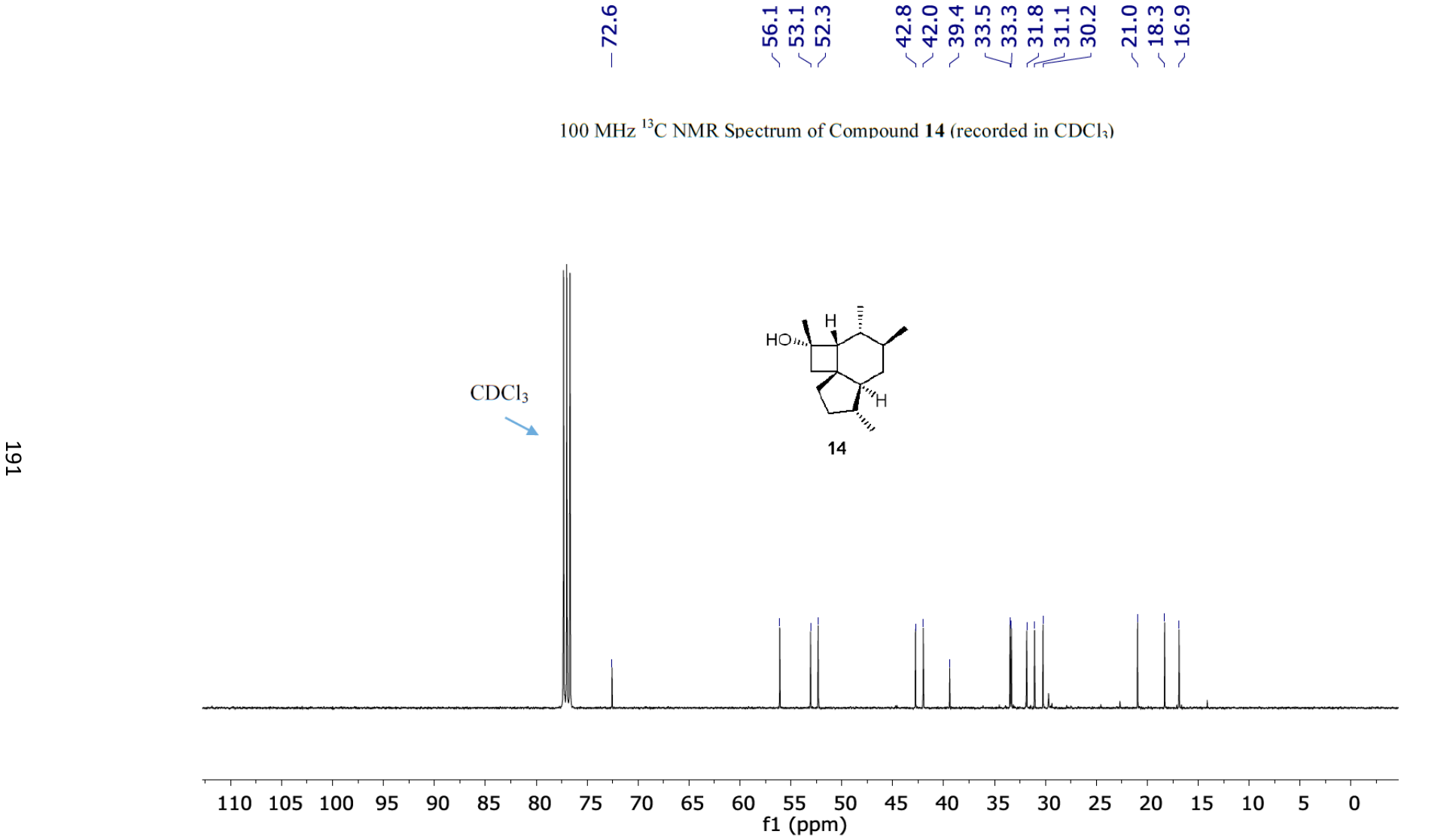


13



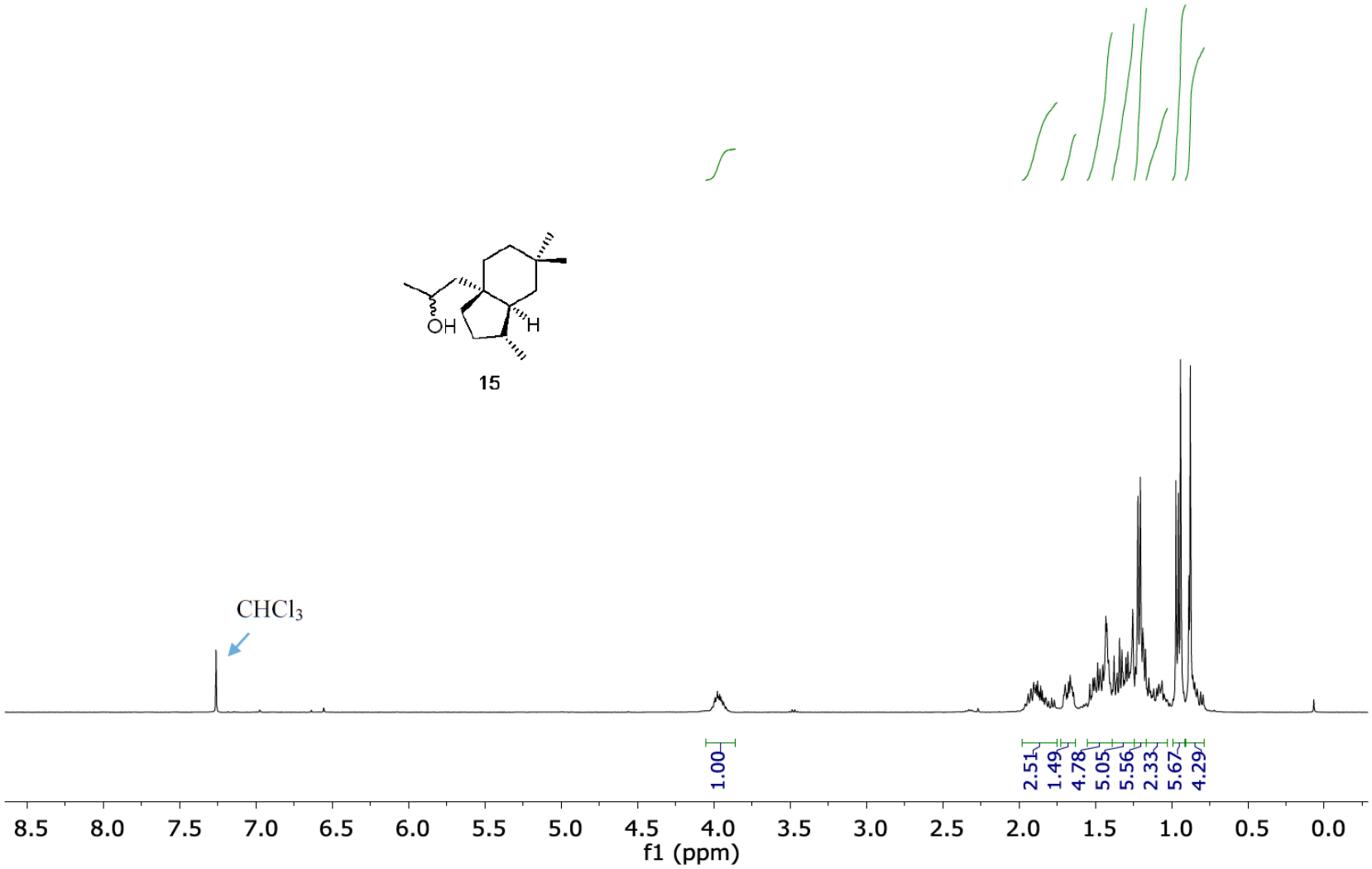
400 MHz ^{1}H NMR Spectrum of Compound **14** (recorded in $CDCl_3$)





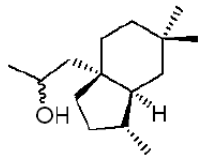
100 MHz ^{13}C NMR Spectrum of Compound **14** (recorded in $CDCl_3$)

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



66.4 65.8 52.6 52.5 47.7 42.8 38.0 38.0 37.6 37.1 36.7 34.8 32.2 32.1 32.0 29.9 29.5 29.4 29.4 28.9 25.9 25.8 20.8 20.7

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



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