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Silacycle-Templated Intramolecular Diels–Alder Cyclizations; Efforts Towards the Total Synthesis of Artatrovirenols A and B

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Paul Russell Carlson

Dissertation Committee:
Professor Scott Rychnovsky, Chair
Professor Larry Overman
Professor Elizabeth Jarvo

2023

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DEDICATION

To my parents

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ACKNOWLEDGEMENTS

I would like to give my sincere thanks to a multitude of people that have had an impact on my time here at UCI. First and foremost, I would like to thank my advisor, Professor Scott Rychnovsky. The amount of creative freedom that I have had working in your lab has allowed me to grow as a scientist in ways that would not have been possible otherwise. Failures are often an inevitability in this field, but the understanding and encouragement that you show your students has given me the confidence to pursue my own ideas and allowed me to learn from my failures rather than fear them. I have come to respect you not only as a chemist, but as a person and a leader as well.

Chuck, I want to thank you for all the mentorship that you gave me all throughout our time together. Your saintly patience and your willingness to help solve any issue were instrumental for picking up many of the skills that I learned in graduate school. On top of that, it was so much fun to work in Baller Bay with you over the years. I already miss crack o'clock, the Dud Christmas Album, clapping obnoxiously, and all the general nonsense we got up to. Thanks for the memories, man.

Sunshine, you are an incredibly talented synthetic chemist, and I am lucky to have had the opportunity to work with you. I took plenty of inspiration from your approach to synthesis and have gone on to incorporate it into my own work. Furthermore, I am greatly indebted to you in that my first successful project spawned directly from your own work. Your help in getting that project off the ground was instrumental, and I'm glad that it all came together into an interesting story in the end.

To all of the past Rychnovsky group members, I feel incredibly fortunate to have worked with such a legendary cast of characters over the years. I can't thank you all enough for the memorable times that I have had here. In particular, I would like to thank Leah Salituro, Alex Burtea, and Alex Valdez for their support and friendship. The lab can never quite be the same without you and you have all been greatly missed.

Bryant, we've shared all of the highs and the lows of grad school together. You've been a steadfast friend through it all and I'm incredibly grateful for that. You are truly deserving of the title of "stone cold;" I feel like there is nothing that can truly phase you, and I've always admired the level of perseverance that that grants you. Keep holding down the lab without me and try your best not to drown in undergrads this summer. I'm looking forward to celebrating your next big achievements very soon.

Emily, I want to thank you for the computational support that you brought to both of my projects in my time here. You added a level of theoretical understanding to my work that allowed me to tell my story with confidence, and the time and effort that you put in to achieve that is not lost on me. I will miss the joy that you spread around lab, often in the form of simply repeating the word "joy" several times without any further elaboration. Strangely enough, I think that works.

Jess, you've been a very supportive friend to me and I'm grateful for that. You've brightened many a dull day in lab by stopping by my desk and shooting the breeze about whatever is on our minds. As a chemist, I've come to admire your attention to detail and desire for perfection in everything that you do, and I think it'll take you far. Best of luck in job interviews, I know you'll do great.

Matt, I respect that you've never run out of drive to learn more and dig deeper into chemical theory. It's served you well and made you into a valuable member of the lab, and certainly the most knowledgeable graduate student that I know. I also want to thank you for keeping the NMR facility alive these past months. You're a legend for that.

Jordan, I thought that when Chuck left, I would end up living out the remainder of my graduate student days in a sad, lonely bay. Thankfully, you saw to it that that didn't come to pass. It's been an absolute pleasure to work with you in Spud Bay over this last year. I've enjoyed seeing you grow as a chemist, and I hope that I was able to contribute to that in some small way. I'm excited to see what you do next, and I wish you the best of luck.

To my colleagues, past and present, in the Vanderwal and Pronin labs, as well as the small sliver of the Overman lab that I had the good fortune of overlapping with, you have my sincere thanks. We all make up a vibrant community of synthetic organic chemistry that I've been happy to be a part of and that I feel bittersweet to leave. Thank you all for enriching my time here.

To my undergraduate advisor, Professor Paul Vadola, none of this would have happened without you. When I first joined your lab, I had no intention of pursuing a Ph.D., nor had I even considered it. However, the mentorship and encouragement that I received while working for you helped me to realize that I might just have the potential to make it happen. In addition, it was your passion for teaching and for organic chemistry that sparked my interest in this field in the first place. I am greatly in your debt, and I cannot thank you enough.

To my undergraduate mentees: Niko, Jace, and Eric (a.k.a. The Loremaster). Mentoring the three of you has been the most meaningful thing that I've done in my time in graduate

school. I know it may be difficult to think of yourself as a true scientist at this stage, but that is what you have all become, and you have my respect. It has been incredibly rewarding for me to see you all grow to that point through your own curiosity and willingness to ask questions. If you feel as though you've learned anything from me, know that I only helped you find it within yourselves.

To the boys back home: Cris, Jav, Coyne, Manny, Ed, and Miko. It's crazy to think how much all of our lives have changed since we all first met. In spite of all that change, though, our friendship has always been a constant to me. Whenever I make it back home, you all make me feel as though I never left and that nothing ever changed. Thank you for sticking with me although I'm many states away and far too often busy with other things. You are all very dear to me.

To my friends from UC Irvine: James, Shannon, Bryant, Alissa, Scott, and Barry. You have all changed my life for the better. You have brought so much joy into times that would have otherwise been grueling and lonely for me. On top of that, each and every one of you has, at times, challenged me to rethink how I see the world and the people around me, and I've become a better man as a result. I'll miss Magic nights, D&D nights, Adventure Time, hiking together, and, strangely enough, finding the word "dud" scrawled onto my fume hood when I least expect it. Although, maybe I have more of that last one coming.

Finally, I'd like to thank my family. I'd like to thank my uncle Russ for being a supportive figure throughout my life and making me feel like I belong in the Carlson family. I'd like to thank Doris and Carlos for accepting me into their family and always looking out for myself and Kaylie. I'd like to thank my cat Stella for being a constant source of joy and

emotional support, even if she doesn't know she's doing so. And, of course, I'd like to thank my parents. You have both supported me through absolutely everything in my life. Even when chasing my dreams meant having your only child move to the other side of the country, you never faltered in your encouragement. At times in my life when I've been happy to accept mediocrity, you've pushed me to expect more of myself. At times in my life when I've expected too much of myself, you've reminded me how proud you are of me and how much I've accomplished. I love you both and I look forward to being a lot closer together very soon.

Finally, I'd like to thank my fiancée, Kaylie. Your love and support have absolutely made the difference, not only in finishing this degree, but also in becoming the man that I am today. Thank you for all of the sacrifices that you've made to be with me. Thank you for putting up with the insanity of graduate school. Thank you for reminding me to take a step back and be something other than just a chemist. Thank you for picking me up off the floor when I was going through orals. At times like that when I didn't believe in myself, I instead believed in the you that believed in me, and that is the reason I was able to get this far. I am so excited to begin our next chapter together and many more after that. I love you.

VITA

Paul R. Carlson

Education

Ph.D. University of California, Irvine **Irvine, CA**
Organic Chemistry 2018 - present
Advisor: Prof. Scott D. Rychnovsky

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Chemistry (*magna cum laude*) 2014 - 2018
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Research Experience

Rychnovsky Group, UCI

- Led a team of graduate and undergraduate students in the development of a chemical methodology.
- Designed and executed synthetic routes up to 14 steps towards complex targets.
- Devised isotopic labelling experiments for mechanistic elucidation.
- Prepared a full manuscript and supporting information for publication.

Publications

1. Vacala, T. L.; **Carlson, P. R**.; Arreola-Hester, A.; Williams, C. G.; Makhoul, E. W.; Vadola, P. A. Gold-Catalyzed Dearomative Spirocyclization of N-Aryl Alkynamides for the Synthesis of Spirolactams. *J. Org. Chem.* **2018**, *83*, 1493–1501.
2. Burns, A. S.; Dooley, C.; **Carlson, P. R**.; Ziller, J. W.; Rychnovsky, S. D. Relative and Absolute Structure Assignments of Alkenes Using Crystalline Osmate Derivatives for X-Ray Analysis. *Org. Lett.* **2019**, *212*, 10125–10129.
3. **Carlson, P. R.**; Burns, A. S.; Shimizu, E. A.; Wang, S.; Rychnovsky, S. D. Silacycle-Templated Intramolecular Diels-Alder Cyclizations for the Diastereoselective Construction of Complex Carbon Skeletons. *Org. Lett.* **2021**, *23*, 2183–2188.

Skills

- Experienced in working collaboratively with a team of fellow researchers.
- Can effectively formulate and execute synthetic routes to complex organic targets.
- Experienced in acquiring and interpreting 1-D and 2-D nuclear magnetic resonance (NMR) experiments of complex organic molecules.
- Can effectively communicate research through the preparation of a publication-quality manuscript.

Presentations

1. **Carlson, P. R.**; Rychnovsky, S. D. "Silacycle-templated intramolecular Diels–Alder cyclizations for the diastereoselective construction of complex carbon skeletons." American Chemical Society National meeting and exposition, San Diego, CA. March 20-24, 2022.
2. **Carlson, P. R.**; Rychnovsky, S. D. "Efforts Towards a Total Synthesis of Artatrovirenols A and B." ACS Division of Organic Chemistry Graduate Research Symposium, Santa Barbara, CA. July 9-12, 2022.

Honors and Awards

- DePaul Presidential Scholarship **2014-2018**
- Franklin Pilchard Scholarship **2014-2018**
- Dhar Research Scholarship **2016-2017**

ABSTRACT OF THE DISSERTATION

Silacycle-Templated Intramolecular Diels–Alder Cyclizations;

Efforts Towards the Total Synthesis of Artatrovirenols A and B

by

Paul Russell Carlson

Doctor of Philosophy in Chemistry

University of California, Irvine, 2023

Professor Scott D. Rychnovsky, Chair

The first chapter of this thesis details our development of a methodology to control π-facial selectivity in intramolecular Diels–Alder cyclizations using a silacycle directing group. The genesis of this project, stemming from a recent total synthesis project in our lab, is discussed. A panel of substrates is synthesized and tested, providing insight into the capabilities and, more importantly, the limits of the methodology. Deeper mechanistic insight is gained through a deuterium-labelling study, the details of which are discussed. Finally, a selection of products delivered using this methodology are shown to be apt for further synthetic derivatization.

The second chapter of the thesis presents our ongoing synthetic approach to a pair of *Artemisia* sesquiterpenoids, artatrovirenols A and B. The isolation and characterization of these natural products is discussed as well as the isolation chemists' proposed biosynthetic pathway. We discuss the logic of our synthetic approach, which incorporates an intramolecular Diels–Alder cyclization proposed by the isolation chemists as the key step. An initial synthetic route is investigated and discussed, but ultimately abandoned as a key Nazarov cyclization proved to be

impractical. A revised synthetic route is devised and discussed, using α-santonin as the starting material. Some preliminary experiments to probe the viability of the key Diels–Alder connection are reported, without success thus far.

Chapter 1. Silacycle-Templated Intramolecular Diels–Alder Cyclizations for the Diastereoselective Construction of Complex Carbon Skeletons

1.1. Introduction

1.1.1. Background on π-Facial Selectivity in the Intramolecular Diels–Alder Reaction

The intramolecular Diels–Alder (IMDA) reaction has proven to be one of the most powerful tools in the synthetic chemist's arsenal for the expedient synthesis of complex molecules. One of the primary strengths of the IMDA as a synthetic tool is its high degree of diastereo- and regioselectivity, which has earned it the title of "key step" in a number of notable total syntheses.[1] Diastereoselectivity in the Diels–Alder reaction is canonically broken down into

three elements, which have been highlighted in the case of a prototypical IMDA reaction (Figure 1.1). Firstly, the original olefin geometry present in the diene moiety of the starting material dictates the ultimate relative stereochemistry between substituents on the ends of the diene (R^1 and a hydrogen in this example). Secondly, the original olefin geometry present in the dieneophile moiety of the starting material will dictate the ultimate relative stereochemistry between the substituents of the dienophile (R^2 and R^3 in this case). Finally, the relative stereochemistry between substituents on the diene and substituents on the dienophile (R^1 and R^2, respectively) will be dictated by the conformation of the Diels–Alder transition state, which can be either endo or exo.[2]

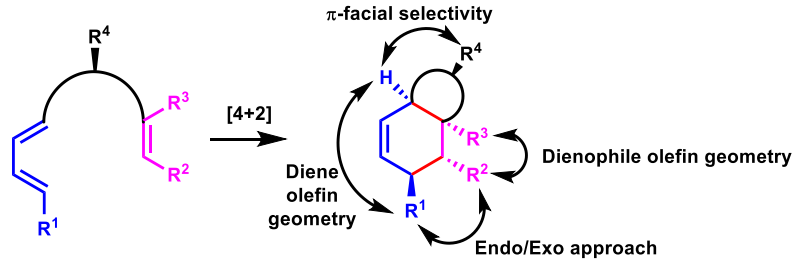
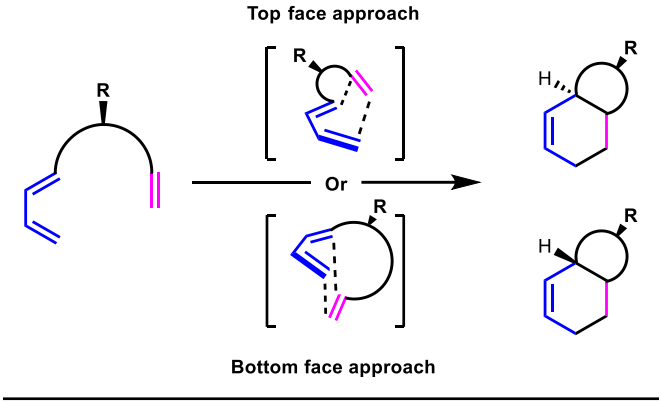


Figure 1.1. Breakdown of Diastereoselectivity in the IMDA Reaction

In addition to the three forms of diastereoselectivity discussed above, there is a fourth, often overlooked aspect of IMDA selectivity depicted in Scheme 1.1. This is π-facial selectivity, which governs the relative stereochemistry between the stereocenters on the newly formed cyclohexene ring in an IMDA reaction and those elsewhere in the molecule, hereafter referred to as spectator stereocenters (represented as R^4 in Figure 1.1). If one were to attempt an IMDA cyclization on a molecule containing spectator stereocenters, then one of two possible diastereomers could arise, depending on the preferred π-facial approach. Without control over π-facial selectivity, one might observe a mixture of the desired and undesired diastereomers or, worse yet, a preference for the undesired diastereomer. As such, the control of π-facial

selectivity is of crucial importance in IMDA reactions, particularly in complex synthetic intermediates that are likely to contain spectator stereocenters.



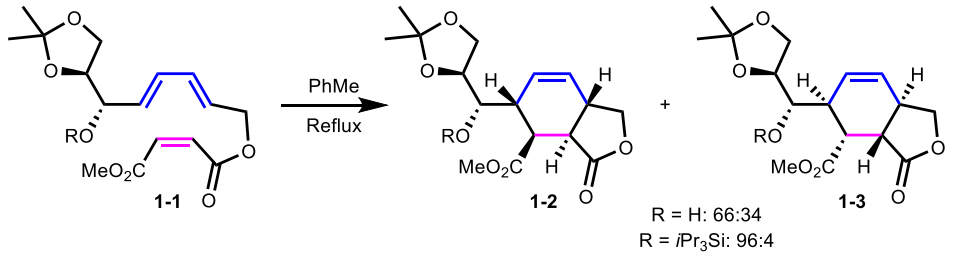
Scheme 1.1. Different Stereochemical Outcomes Arising from **π**-Facial Control

Of the four forms of diastereoselectivity discussed above, the stereocontrol imparted from the olefin geometries of the diene and dienophile are highly reliable. Endo / exo selectivity is fairly predictable in intermolecular Diels–Alder cyclizations but shows some degree of variability in the intramolecular domain.[3] One of the more challenging forms of stereoselectivity to predict out of those discussed here is that of π-facial selectivity. This fact, along with the fact that π-facial selectivity is most important in complex scaffolds that contain pre-existing stereocenters, means that the issue of understanding and controlling π-facial selectivity has seen much attention from the synthetic community.[4] Even so, the issue of controlling π-facial selectivity is still one that requires specialized solutions on a case-by-case basis. The next section will discuss some of these specialized solutions that have been previously reported in the literature.

1.1.2. Prior Approaches to the Issue of Controlling π-Facial Selectivity

As the π-facial outcome of an IMDA reaction is often difficult to predict, some strategies for π-facial control arise not by design but through serendipity. For example, Sherburn and

coworkers wondered how π-facial selectivity might be affected in their ester-tethered IMDA scaffold (**1-1**, Scheme 1.2) by the presence of a spectator stereocenter at the terminus of the diene moiety.[5] While there was no obvious rationale for why a stereocenter at this remote position would affect the facial selectivity of the IMDA cyclization, they reasoned that, at least in theory, it could impart a conformational preference. With a secondary alcohol at the allylic position of **1-1**, they found only modest facial selectivity was achieved, returning a mixture of Diels–Alder adducts **1-2** and **1-3**, with a slight preference for the former. However, when the alcohol was instead replaced with a much bulkier TIPS ether, a high degree of π-facial selectivity was observed, showing a strong selectivity for **1-2**.

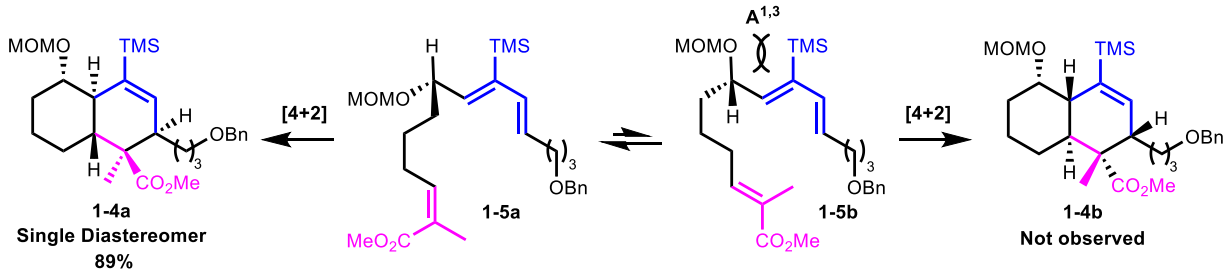


Scheme 1.2. Sherburn's Discovery of **π**-Facial Selectivity with a Remote Stereocenter

To rationalize the observed outcome, Sherburn's laboratory undertook a separate computational study on the same system.[6] After modeling 18 possible IMDA transition states, they developed an explanation incorporating subtle steric and electronic arguments that is outside the scope of this discussion. While Sherburn's strategy represents an effective means for the control of π-facial selectivity, it only necessarily holds true for this particular system. This fact, combined with the strategy's discovery through serendipity rather than by design, highlights some of the challenges with designing generalizable strategies for π-facial control.

Another common strategy to affect control of π-facial selectivity in the IMDA reaction is to install a directing group to bias the approach of the dienophile to the desired face. A

prototypical example of this approach comes from Boeckman and coworkers, who were interested in constructing hydrindene and octalin scaffolds such as **1-4** from an IMDA precursor such as **1-5** (Scheme 1.3).[7] However, because of the presence of a spectator stereocenter in the form of a secondary MOM ether, it was crucial for them to control π-facial selectivity in order to obtain the desired diastereomer of the Diels–Alder adduct (**1-4a)** and to avoid formation of the undesired diastereomer (**1-4b**) When considering this issue, one can imagine two major conformers of the starting material, **1-5a** and **1-5b**, which would lead to the two possible Diels–Alder adducts, **1-4a** and **1-4b**, respectively. The Boeckman lab showed that a trimethylsilane installed on the interior of the diene as a directing group was able to discriminate between these two crucial conformers, making the undesired conformer **1-5b** much higher in energy as a result of a prohibitive $A_{1,3}$ strain with the MOM ether. Using this strategy, they were able to deliver **1-4a** as a single diastereomer.



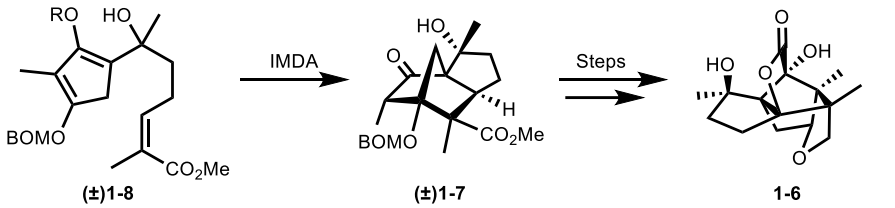
Scheme 1.3. Boeckman and Coworkers' Approach to **π**-Facial Control Using $A_{1,3}$ Strain

The Boeckman strategy described above serves as an example of a designed approach to π-facial control with a foundation in intuitive conformational analysis. Furthermore, this strategy is applicable beyond just this system and, indeed, has seen use by other groups.[8] One downside that this directing-group strategy brings is that it requires at least two additional synthetic transformations for the installation and the removal of an undesired functional group. Modern π-facial selectivity strategies should seek to improve upon the field by either forgoing the use of

directing groups or by using traceless directing groups that can be installed and/or removed without adding additional synthetic steps.

1.1.3. Controlling π-Facial Selectivity in the Synthesis of Illisimonin A

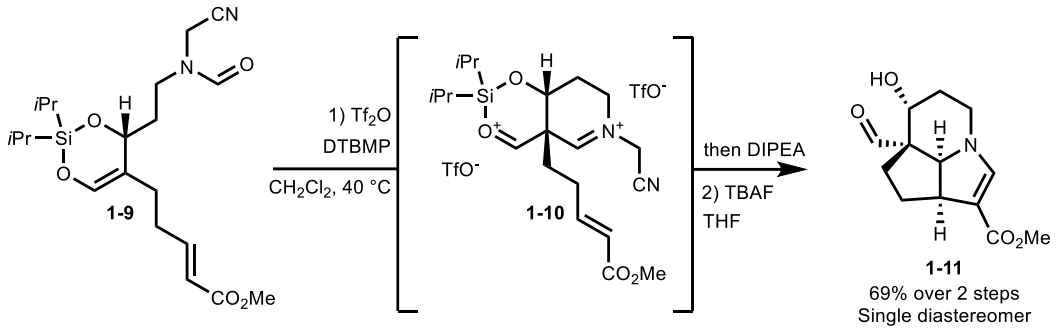
Recently in our own lab, the problem of π-facial selectivity came to the forefront in Dr. Alex Burns' total synthesis of the illicium sesquiterpenoid illisimonin A (**1-6**).[9] The proposed synthetic route to this natural product required that the tricyclic core (**1-7**) be established via an IMDA reaction from intermediate **1-8**, as laid out in Scheme 1.4. This approach seemed plausible, as IMDA reactions are well-precedented for the construction of similar norbornane scaffolds.[10] However, due to the presence of a spectator stereocenter in the form of a tertiary alcohol, it was crucial that the IMDA be π-facially selective in order to deliver the desired diastereomer of **1-7**.



Scheme 1.4. Planned IMDA cyclization en route to **1-6**

It was at this point that our lab took inspiration from the Bélanger group's work on the synthesis of the tricyclic core of calyciphylline B-type alkaloids.[11] They construct this core through an elegant cascade that is initiated by a Vilsmeier–Haack-type reaction between an enolate equivalent and an iminium moiety (Scheme 1.5). In order to render this cyclization diastereoselective, the Bélanger lab created the necessary enolate equivalent in the form of a silyl enol ether. Furthermore, they made use of the adjacent oxidation to lock this silyl enol ether as part of a dioxasiline ring (**1-9**). The rigidity of this silacycle imparted absolute facial selectivity

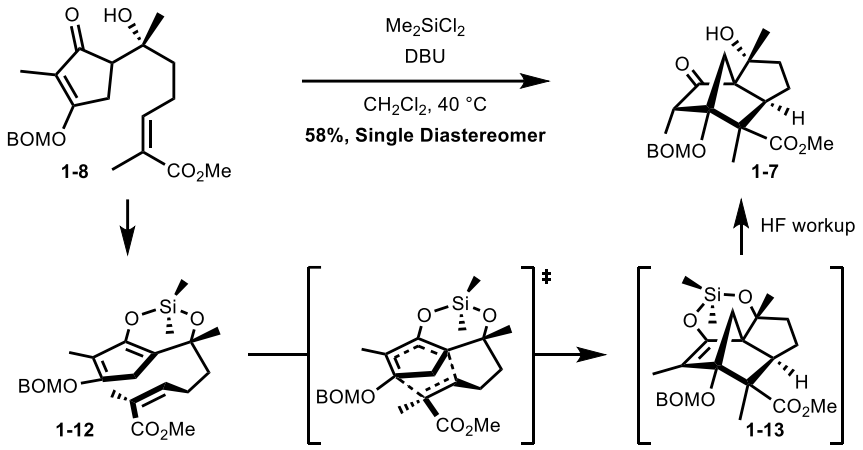
in the subsequent Vilsmeier-type cyclization to afford intermediate **1-10**. Following this initial silacycle-directed cyclization, a subsequent azomethine ylide 1,3 dipolar cycloaddition followed by cleavage of the silyl group afforded the desired tricyclic core **1-11** as a single diastereomer.



Scheme 1.5. Bélanger's Silacycle Strategy for Diastereocontrol in a Vilsmeier Cyclization

Our lab drew upon the strategy described above to impart π-facial control in the illisimonin system. This was accomplished using Me_2SiCl_2, which tethered together the ketone and alcohol oxygens of **1-8** to form a dioxasiline ring (Scheme 1.6). In coupling these two oxygens to form intermediate **1-12**, not only was the Danishefsky-type diene for the desired IMDA formed,[12] but also the added rigidity of the newly formed silacycle dictated the π-facial selectivity of the resulting IMDA, affording silacyclic adduct **1-13**. This adduct was then subjected to workup with HF, yielding **1-7** as a single diastereomer in 58% yield. While individual examples of a silacycle initiating[13] and directing[14] IMDA cyclizations exist, we were not aware of any other reactions in which they did both simultaneously. Given this fact, as well

as the level of complexity that this reaction was able to deliver, we sought to determine if this strategy held enough promise to be elaborated into a broader methodology.



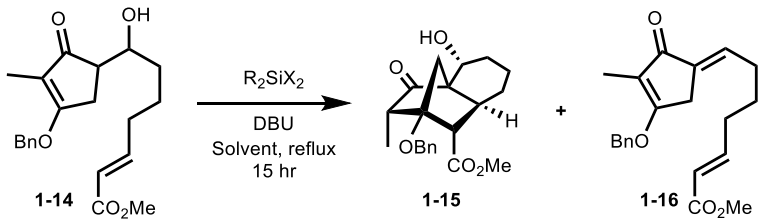
Scheme 1.6. Strategy for **π**-Facial Control in the Synthesis of Illisimonin A

We reasoned that a methodology based upon the silacycle strategy described above would have the following advantages: it would allow for complete control of up to six stereocenters, as highlighted by the formation of **1-7**. Furthermore, starting materials analogous to **1-8** would bear a β-hydroxy carbonyl functional group, allowing for their straightforward preparation through an aldol addition. Such an aldol addition would not need to be syn / anti selective, as the stereochemistry at the α carbon is ablated over the course of the reaction, allowing for diastereomeric mixtures to be employed without separation. The silacycle directing group is installed in situ and can be removed with a simple HF workup, adding no additional steps to the synthetic sequence. Finally, should a milder workup be chosen in order to preserve the silacycle and yield a product analogous to **1-13**, the resulting silyl enol ether would be a highly versatile synthon that would allow for further derivatization of the Diels–Alder adducts.[15]

1.2. Results

1.2.1. Initial Optimization Studies

We began developing the initial success with illisimonin A into a broader method with an optimization study. The model substrate chosen for optimization was **1-14** (Table 1), mainly for its greater synthetic accessibility as compared to the original illisimonin substrate **1-8**. The major differences in this new substrate are in the olefin geometry at the enoate, the substitution of the alcohol, and the presence of a benzyloxy substituent where previously there was a benzyloxymethyl acetal substituent. As an initial control experiment to ensure that none of these minor changes had an impact on the yield of the IMDA reaction, we tested **1-14** under the original conditions from the illisimonin A project (Table 1.1, entry 1) and found that it gave a comparably low yield of **1-15**.



Entry	R	X	Solvent	Temp. (°C)	Yield **1-15**	Yield **1-16**[a]
1	Me	Cl	CH_2Cl_2	40	40	-
2	*t*Bu	Cl	CH_2Cl_2	40	-	-
3	*t*Bu	OTf	CH_2Cl_2	40	30	9
4	Ph	Cl	CH_2Cl_2	40	65	9
5	Ph	Cl	$ClCH_2CH_2Cl$	80	60	-
6	***i*Pr**	**Cl**	**CH_2Cl_2**	**40**	**92**	**-**
7	*i*Pr	Cl	$ClCH_2CH_2Cl$	80	78	-
8	*i*Pr	OTf	CH_2Cl_2	40	82	-
9	*i*Pr	OTf	$ClCH_2CH_2Cl$	80	76	10

Table 1.1. Optimization Studies for the Silacycle-Templated IMDA Cyclization

Seeing as **1-14** reacted in a comparable manner with the original illisimonin substrate **1-8**, it was deemed a fit model substrate for the optimization process. Optimization focused on tweaking the identity of the bis-electrophilic silane and the reaction solvent/temperature. DBU was kept as the base, as previous studies as part of the illisimonin A synthesis found it to be

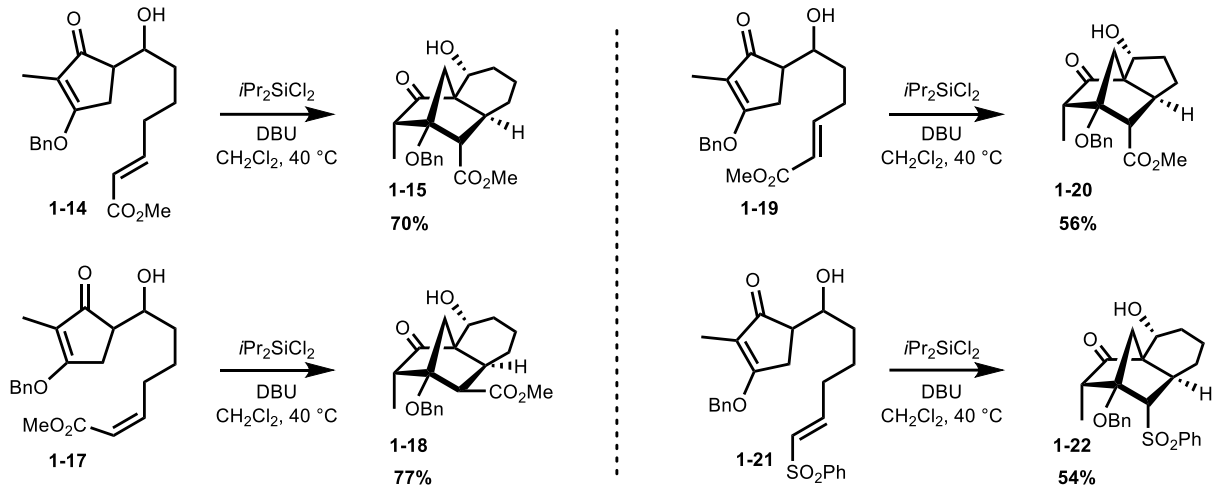
crucial for the reaction to proceed. Given that the original conditions employing the sterically unencumbered dimethyldichlorosilane returned a poor yield, we wondered if the more sterically bulky tBu$_2$SiCl$_2$ or tBu$_2$SiOTf$_2$ would yield different results (entries 2 and 3). However, neither of these *tert*-butylsilanes showed improvement over entry 1, with the first returning starting material and the second giving an unimpressive NMR yield along with competing elimination to form **1-16**.

Next, we turned to Ph$_2$SiCl$_2$, a silane with a more intermediate steric bulk (entries 4 and 5). This silane showed a promising boost in yield, although a heightened reaction temperature failed to improve upon it any further. Finally, staying within the realm of silanes with moderate steric bulk, we discovered that iPr$_2$SiCl$_2$ gave a much improved 92% NMR yield (entry 6). Neither elevated reaction temperature (entry 7) nor the corresponding silyl ditriflate (entries 8 and 9) improved any further upon the results of entry 6. Thus, the conditions described in entry 6 were taken forward as the optimal conditions for this reaction.

1.2.2. Simple Modifications

Our investigation of the substrate scope of our silacycle-templated IMDA strategy began with some simple modifications to the original system (Scheme 1.7). Scheme 1.7 summarizes the results of our model substrate **1-14** from the optimization study. The desired IMDA proceeded with a good recovered yield of **1-15**, albeit less than our measured NMR yield from Table 1.1. Nonetheless, this example demonstrates that we can deliver a cyclohexyl-fused norbornane skeleton in contrast to the cyclopentyl-fused norbornane from the synthesis of illisimonin A Additionally, we synthesized **1-17**, an analogue of **1-14** bearing a cis-olefin at the enoate. As expected, this substrate reacted smoothly to afford **1-18** with exclusive exo selectivity. With substrate **1-19**, we demonstrated an endo-selective IMDA to afford **1-20**, with a cyclopentene-

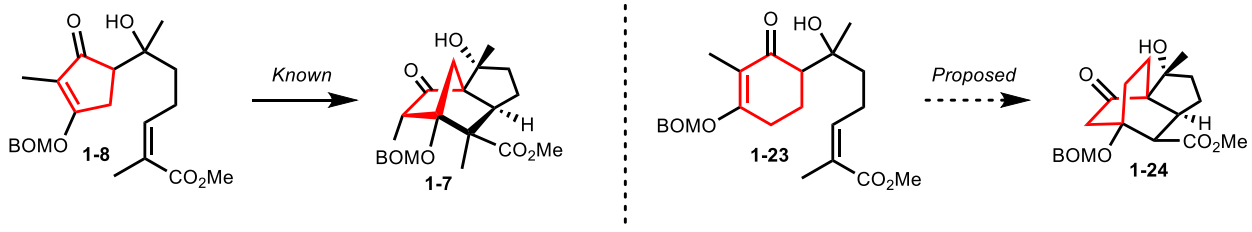
fused norbornane scaffold. This contrasts with the original illisimonin system, which showed exclusive exo selectivity. Finally, with substrate **1-21**, a vinyl sulfone proved to be a competent dienophile for this reaction, furnishing the corresponding norbornane **1-22** in moderate yield.



Scheme 1.7. Substrate Scope Bearing Simple Modifications

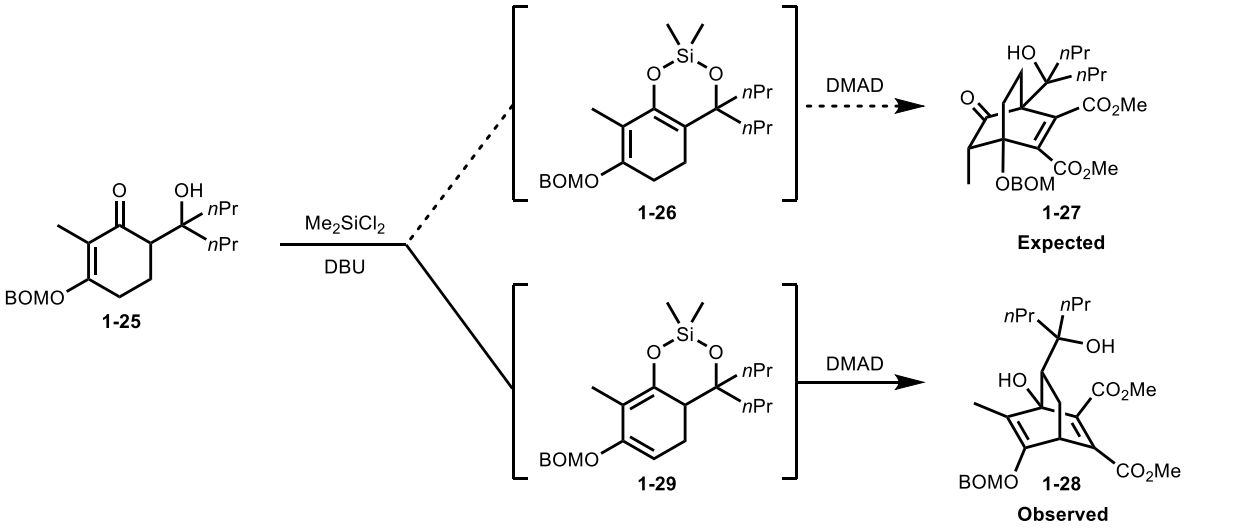
1.2.3. Six-Membered Ring Diene Studies

We next sought to test the limits of our methodology further by targeting different carbon skeletons. To this end, we wondered if we could expand the cyclopentenone ring of **1-8** to a cyclohexanone analogous to **1-23** (Scheme 1.8). This would allow us to access a 2.2.2 bicyclic scaffold such as **1-24**. Seeing as there has been much synthetic attention around 2.2.2 bicyclic scaffolds, we reasoned that this would be a useful application of our method.[16]



Scheme 1.8. Proposed Expansion of the Dienophile Ring Allowing Access to a 2.2.2 Bicyclic Skeleton

Despite the apparent simplicity of this proposed modification, we were surprised to find that when **1-23** was subjected to our standard conditions, no reaction was observed. In order to investigate the source of the problem, we first wanted to investigate if the desired diene was being formed under our standard conditions. To this end, we prepared model system **1-25** (Scheme 1.9), which lacked the dienophile moiety, and subjected it to a diene- trapping experiment in which dimethyl acetylenedicarboxylate (DMAD) was added to a mixture of **1-25** and Me_2SiCl_2. Our expectation was that **1-25** would undergo deprotonation at the α position to yield diene **1-26**, which would then go on to be captured by DMAD to yield Diels–Alder adduct **1-27**. However, the adduct that we actually observed was instead **1-28**, which was the result of a Diels–Alder addition between DMAD and **1-29**, which was itself the result of an unexpected deprotonation at the γ-position of **1-25**.



Scheme 1.9. Diene capture study

From the outcome of the mechanistic experiment described in Scheme 1.9, we reasoned that the incompatibility of substrate **1-23** with our silacycle-templated IMDA conditions was a result of the same unexpected deprotonation at the γ-position, which would produce diene **1-30**

(Figure 1.2). This particular diene would make for a challenging Diels–Alder reaction as a result of the electronic mismatch between the diene and dienophile moieties. Although it was unexpected, we wondered if the diene resulting from γ-deprotonation could still prove useful if this electronic mismatch could be remedied. To this end, we proposed the formation of diene **1-31** (Figure 1.2**)**, for which the electronics of the dienophile have been inverted relative to **1-30**.

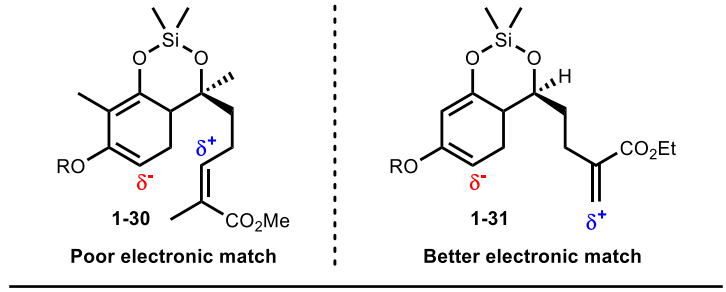
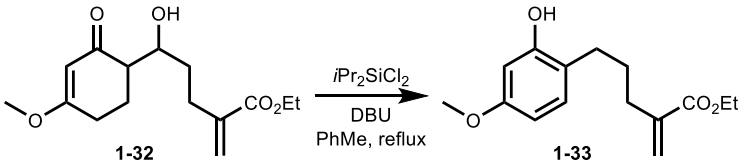


Figure 1.2. Electronic Match/Mismatch Analysis for the **γ**-Deprotonation Diene

Unfortunately, when **1-32**(Scheme 1.10), the precursor to **1-31**, was subjected to our standard conditions, no reaction was observed at lower temperatures, while at elevated temperatures arene **1-33** was the major product. This product is presumably the result of elimination of the alcohol to yield an alkene followed by isomerization of that alkene to generate

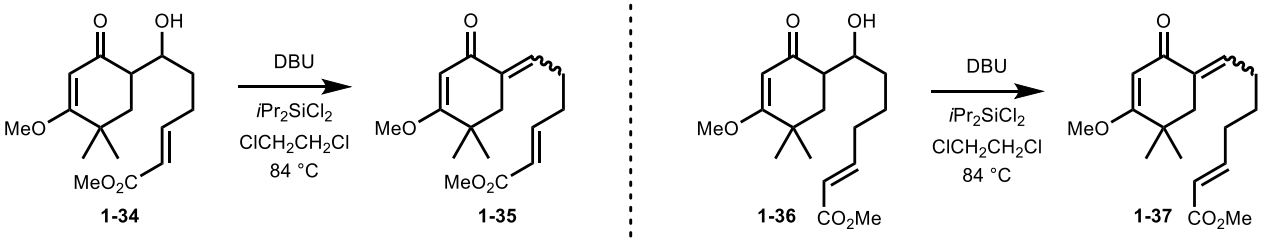


Scheme 1.10. Unexpected Aromatization of **1-32**

an aromatic ring. The fact that arene **1-33** was the major product would thus suggest that the rate of alcohol elimination is greater than the rate of the desired Diels–Alder reaction. We thus decided to work with a diene that more closely mirrored the dienes that had given us positive results thus far. To this end, we sought to create a diene analogous to **1-26** (Scheme 1.9), with the

hope that a Diels–Alder reaction with this type of diene would have a sufficient rate to compete with alcohol elimination.

In order to render γ-deprotonation impossible, we prepared **1-34**, bearing a gem-dimethyl moiety at the γ position (Scheme 1.11). Unfortunately, the major product observed was **1-35**, which was again the result of elimination of the alcohol, meaning that even the diene resulting from α deprotonation did not react quickly enough to out-compete elimination. Finally, we hypothesized that the rate of the desired Diels–Alder cycloaddition could be accelerated by extending the dienophile-bearing chain by one carbon atom and thus relieving ring strain in the Diels–Alder transition state. To this end, we prepared substrate **1-36**, which, to our disappointment, showed an identical outcome to the previous substrates, returning **1-37** as the major product. At this point, it became clear that the rate of elimination was consistently out-competing any desired Diels–Alder cyclization in the context of six-membered dienes. Thus, the decision was made to abandon this line of inquiry for the time being.

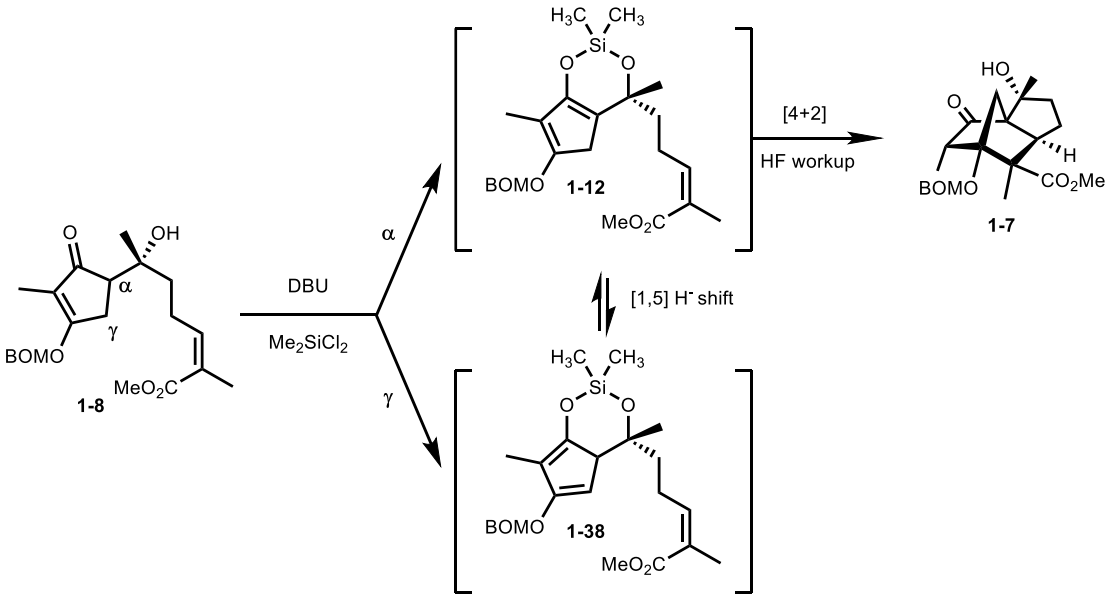


Scheme 1.11. Gem-Dimethyl Blocking of the **γ** Position

1.2.4. Mechanistic Studies of the Silacycle-Templated IMDA Reaction

We then turned our attention to elucidating the mechanism of our silacycle-templated IMDA reaction. Using the illisimonin A system as an example, our preliminary assumption was that the reaction proceeded through initial deprotonation of **1-8** (Scheme 1.12) at the α-position of our substrate to form intermediate silacycle **1-12**, which would then go on to form **1-7** directly

via a Diels–Alder cycloaddition. However, our observations of selective γ-deprotonation in the course of our studies with the six-membered dienes threw this posited mechanism into uncertainty. We reasoned that if the six-membered diene system underwent selective γ-deprotonation, then it was likely that the five-membered diene system did as well. In this scenario, deprotonation of **1-8** at the γ position would lead to intermediate **1-38**, which could then converge to **1-12** through a facile [1,5] hydride shift,[17] thus intercepting the previously described mechanistic pathway. This left us with two completely plausible mechanistic pathways that we sought to discern experimentally.

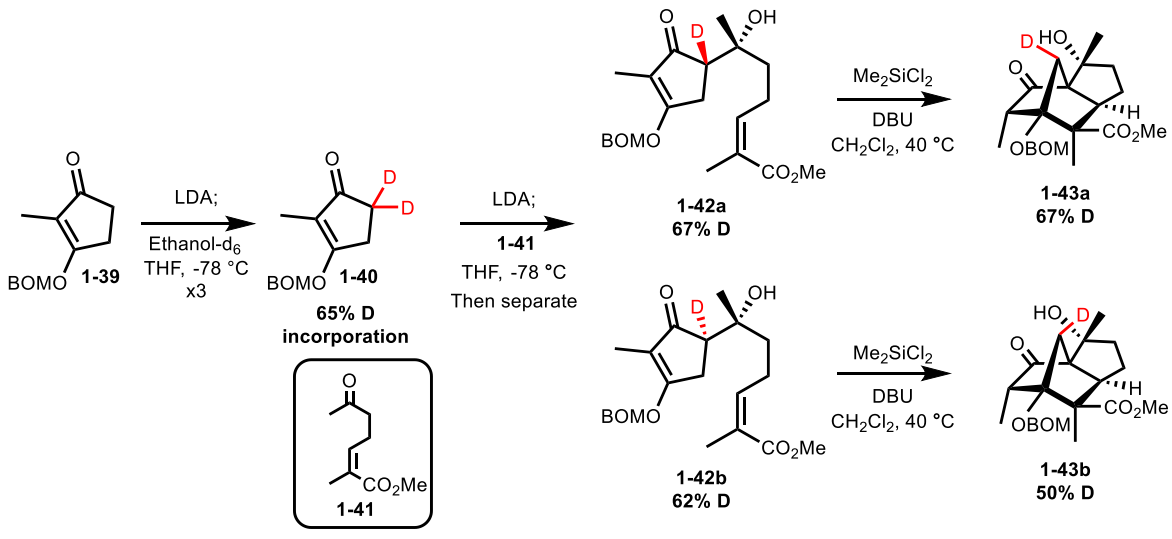


Scheme 1.12. Two Possible Mechanistic Pathways for the IMDA Reaction

To solve this mechanistic ambiguity, we proposed a substitution of the α-hydrogen of **1-8** with a deuterium atom. We reasoned that, when subjected to our standard conditions, this deuterated analogue, unlike **1-8**, would give different outcomes depending on whether it underwent α- or γ-deprotonation. If α-deprotonation were the first step, the deuterium atom would be removed, yielding a non-deuterated product. Alternatively, if γ-deprotonation were the

first step, the deuterium atom would be retained, after which it would perform a [1,5] deuteride shift, placing it on the γ position in the final Diels–Alder adduct. Finally, should both α- and γ-deprotonation compete in some ratio, we reasoned that the approximate ratio could be deduced from the extent of deuterium enrichment lost.

We found that our envisioned deuterated substrate could be synthesized first by three successive cycles of LDA deprotonation of precursor **1-39** (Scheme 1.13) followed by quenching with deuterated ethanol to yield deuterated precursor **1-40** with 65% deuterium incorporation. Next, **1-40** was coupled with ketone **1-41** to yield two diastereomers of our desired deuterated analogue, **1-42a** and **1-42b** with 67% and 62% deuterium incorporation, respectively. Finally, subjecting these two diastereomers to our original IMDA conditions returned Diels–Alder adducts **1-43a** and **1-43b** with nearly quantitative deuterium migration to the γ position (50% and 67% incorporation, respectively). Furthermore, deuterium migration was diastereospecific, with each aldol diastereomer yielding a unique epimer at the deuterated carbon.

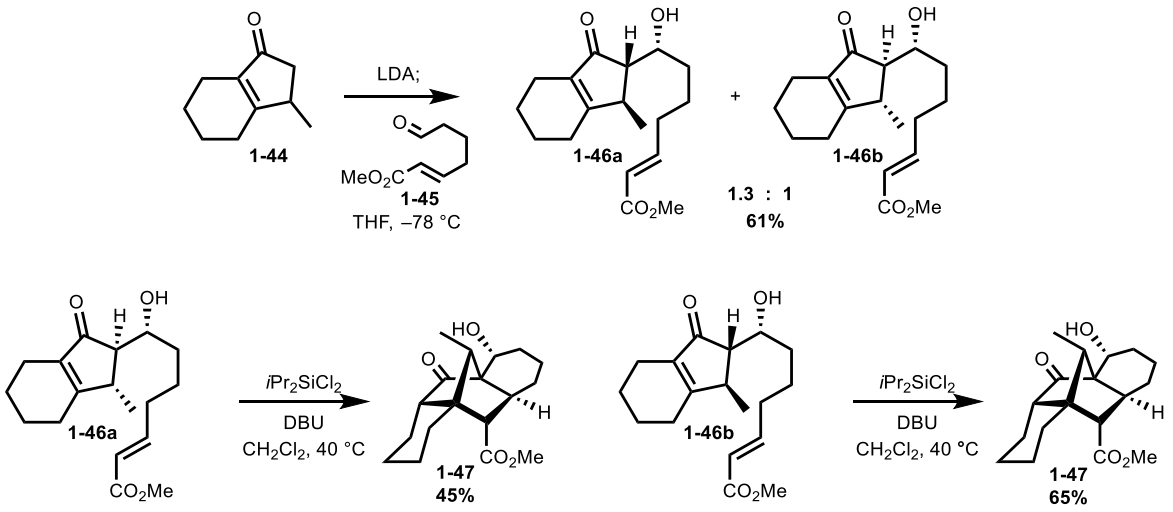


Scheme 1.13. Mechanistic Experiment Demonstrating Transfer of Deuterium

The high degree of deuterium retention in this experiment provided compelling evidence that the mechanism of formation for the reactive diene proceeds primarily through γ deprotonation. Based on the small deuterium loss from **1-42a** to **1-43a**, we can reason that less than 20% of this material undergoes an α deprotonation mechanism. For the conversion of **1-43b** to **1-43b**, quantitative deuterium retention suggests that γ deprotonation is the sole mechanism involved. Furthermore, the diastereospecific nature of deuterium migration between the two diastereomers strongly suggests that the migration occurs via a suprafacial [1,5] sigmatropic shift, leaving the γ-deprotonation route as the most plausible mechanism.

1.2.5. Stereochemical Relay Experiment

It was not lost on us that in the deuterium experiment described above, we inadvertently demonstrated the ability to transfer stereochemistry from the α-position of our starting material to the one-carbon bridge in the norbornyl skeleton of our Diels–Alder adduct. Consequently, we were inspired to design a substrate that would allow us to establish an analogous stereocenter



Scheme 1.14. Stereochemistry Relay Experiment

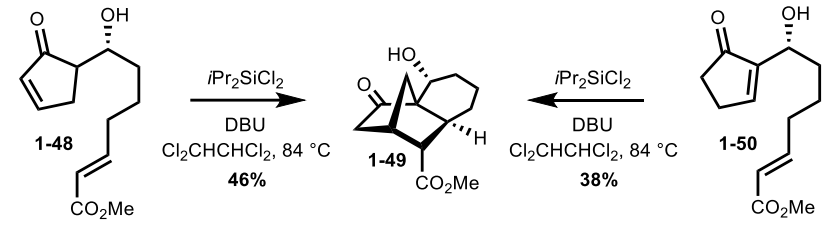
with an organic substituent as opposed to a deuterium atom. To that end, we coupled enone **1-44** (Scheme 1.14) with aldehyde **1-45**, which generated two aldol diastereomers **1-46a** and **1-46b**.Seeing as these two diastereomers differed in the stereochemistry at the α position, we anticipated that we would isolate two different epimers after subjecting each to our IMDA conditions. However, to our surprise, both diastereomers, when individually subjected to our IMDA conditions, yielded Diels–Alder adduct **1-47**.

While we are still lacking concrete experimental evidence to rationalize the above result, one possible scenario that would explain the observed results is that **1-46a** undergoes selective α-deprotonation, while **1-46b** undergoes selective γ-deprotonation. This difference in deprotonation preference may, in turn, be the result of conformational differences between the two diastereomers. Indeed, computational studies suggest that the lowest energy conformation of **1-46b** has the side-chain blocking the face of the hydrogen at the γ position, while this is not the case for **1-46a** (see page 95). Regardless, we view the formation of **1-47**, with control over seven stereocenters, to be a success.

1.2.6. Electronically Challenging Modifications

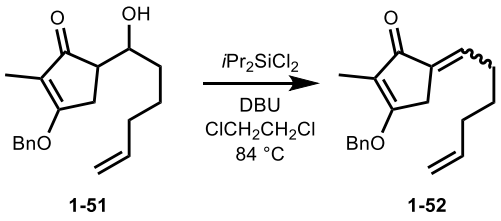
We next looked towards probing modifications to our system that would make the electronics of the Diels–Alder more challenging. To that end, we first prepared **1-48** (Scheme 1.15), which exchanged the vinylogous ester moiety of previous substrates for a simplified enone. Whereas previous substrates bearing a vinylogous ester functional group led to a highly activated Danishefsky-type diene[18] with two oxygen substituents, **1-48**, with only a single oxygen, should have less favorable electronics. It was no surprise then, when we discovered that this substrate required a higher temperature than previously observed in order to proceed. Gratifyingly though, we did observe the formation of the desired Diels–Alder adduct **1-49** in

46% yield. Interestingly, we also found that **1-50**, a constitutional isomer of **1-48**, also afforded **1-49** under our standard conditions in 38% yield. This convergence is further evidence for the role of [1,5] hydride shifts in the mechanism of our reaction, as it would be impossible to form the reactive diene directly from **1-50** without them.



Scheme 1.15. Substrates Lacking a Vinylogous Ester Moiety

In an effort to further challenge the electronics of our system ,we prepared substrate **1-51**, which lacked additional activating functional groups (Scheme 1.16). Unfortunately, when subjected to our standard conditions, this substrate demonstrated that elimination of the alcohol was the dominant pathway, yielding enone **1-52** with unknown olefin geometry. Thus, we began to establish the minimum level of electronic activation that is necessary in order for the desired Diels–Alder cycloaddition to dominate over competing alcohol elimination.

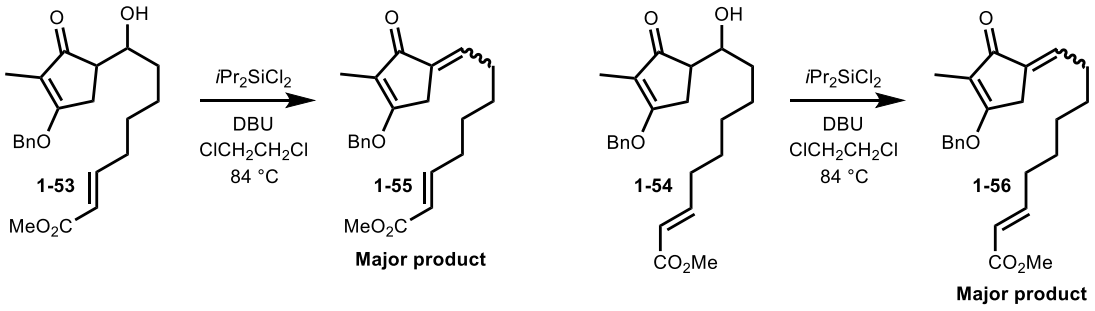


Scheme 1.16. Highly Electronically Deactivated Substrate

1.2.7. Miscellaneous Modifications

At this stage, we had proven the viability of our method for the formation of norbornanes with fused 5- and 6-membered rings, but we next wondered if we could deliver larger ring sizes. To this end, we prepared substrates **1-53** and **1-54**, both of which featured extended side chains

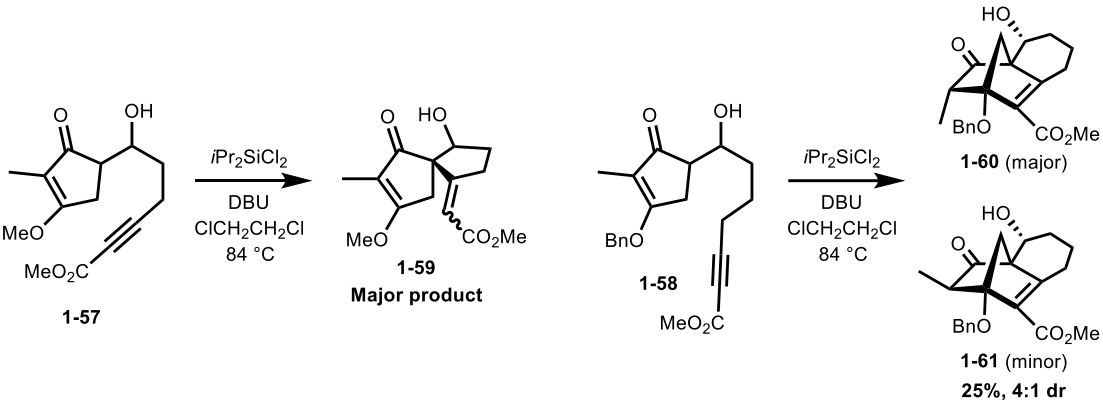
which, in theory, would give 7- and 8-fused norbornane skeletons upon IMDA cycloaddition. To our disappointment, both of these substrates led exclusively to **1-55** and **1-56** (olefin geometry unknown), which once again suggests that alcohol elimination is the dominant pathway over the desired Diels–Alder pathway. In this particular case, we ascribe the slow rate of the Diels–Alder not to electronic factors as in previous examples, but to an excessive entropy of transition state ($\Delta S^{\ddagger}$), owing to the additional rotational degrees of freedom afforded by a longer tether length.



Scheme 1.17. Failed Attempts to Engage Longer Tether Lengths

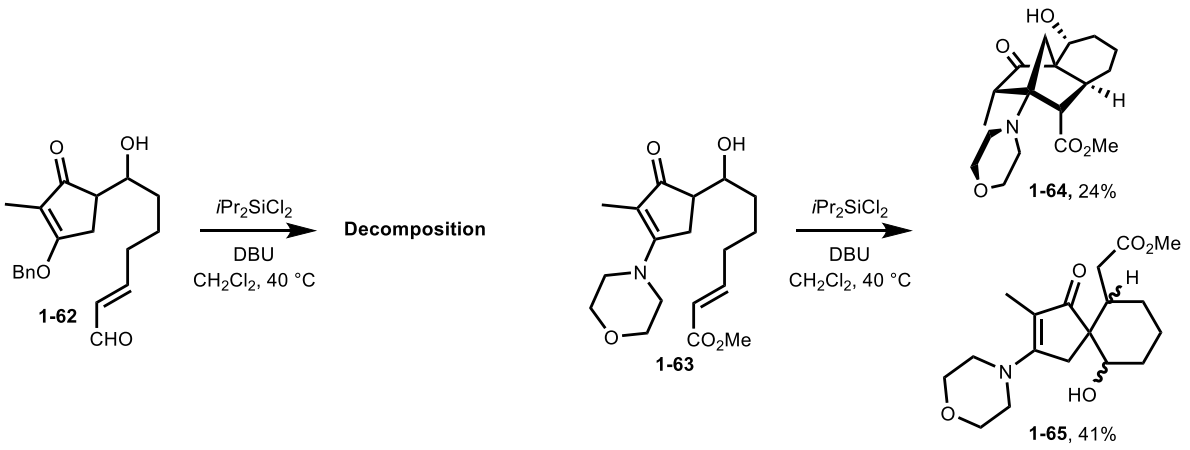
Seeing as most of our attempts to modify the carbon skeleton of our starting materials were unsuccessful thus far, we decided to stay within the carbon frameworks that had given positive results and investigate further functional group modifications. We first experimented with swapping the dienophile with an alkyne using substrates **1-57** and **1-58** (Scheme 1.18), which differed only in their tether lengths. Interestingly, **1-57**, which bore the shorter tether chain, returned mainly **1-59**, which was the result of only a single Michael addition between the cyclopentenone ring and the ynoate moiety. We hypothesize that the preference for this outcome over the desired Diels–Alder cycloaddition could stem from excessive ring strain in the Diels–Alder transition state owing to the linear nature of the alkyne. In support of this hypothesis, **1-58**, which should experience less ring strain in the Diels–Alder transition state owing to its longer tether length, returned the desired Diels–Alder adduct **1-60**, albeit in low yield. Interestingly, we

also observed the formation of an additional diastereomer, **1-61**. While all previous substrates thus far showed absolute selectivity for the formation of this methyl stereocenter, that selectivity was diminished in this system. This outcome likely stems from the added planarity of the bicycle in the kinetic protonation step. This outcome is in line with previous studies of norbornene and norbornadiene selectivity.[19]



Scheme 1.18. Alkyne Dienophiles

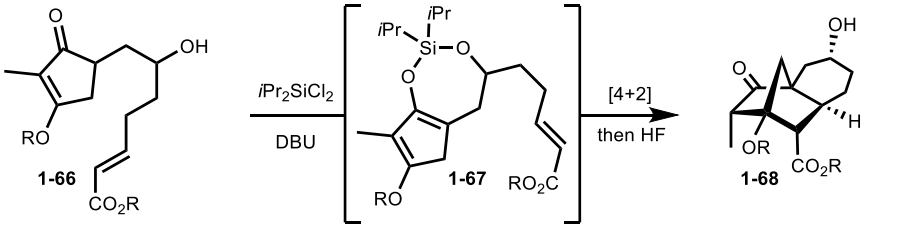
In addition to the dienophile itself, we also investigated changing the identity of the activating groups on both the dienophile and on the diene. To this end, we prepared substrates **1-62** (Scheme 1.19), which had an aldehyde as the dienophile activating group, and **1-63**, which had a morpholine as the diene activating group. Subjecting these to our standard IMDA conditions, we found, firstly, that the reaction of aldehyde **1-62** led only to a complex mixture. Seeing as this was the only substrate thus far to lead to that outcome, we concluded that an aldehyde moiety is simply not tolerated by our conditions. Secondly, we found that the reaction of morpholine **1-63** led partially to the desired Diels–Alder adduct **1-64** in low yield, but we also observed about twice as much of by-product **1-65**. We believe that this by-product may be the result of a retro-Michael addition from **1-64**, which would be particularly favorable in this system owing to the establishment of a vinylogous amide.



Scheme 1.19. Exploring Substitution of Activating Groups

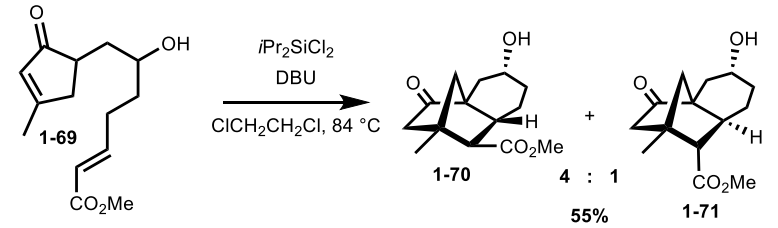
1.2.8. Seven-Membered Silacycle

Given the outcomes of a number of the previously described substrates, it was evident that a β alcohol in our system was a problematic functionality. The competing elimination of this β alcohol was severely limiting the range of modifications that we could make to our system and, thus, the range of possible unique products that we could deliver with our method. While the alcohol could not simply be removed as it served as a crucial anchor point for our silacycle, we wondered if it could be relocated elsewhere on the molecule without sacrificing the efficacy of our method. The simplest version of this idea would be to build a substrate such as **1-66** (Scheme 1.20), in which the alcohol has simply been moved to the γ position. While alcohol elimination is certainly still possible in this scenario, we reasoned that the rate of elimination should be much slower without an acidic α proton immediately adjacent to the alcohol. This proposed modification, while simple in theory, would require the formation of a seven-membered silacycle intermediate analogous to **1-67**. Should this intermediate be able to engage in a Diels–Alder cycloaddition, we would then anticipate the formation of **1-68**.



Scheme 1.20. Hypothetical Seven-Membered Silacycle System

While accessing a molecule analogous to **1-66** proved to be synthetically challenging, we found success in preparing **1-69** (Scheme 1.21), which simply lacked an activating group on the cyclopentenone moiety. Subjecting **1-69** to our standard conditions at elevated temperature afforded two IMDA adducts, **1-70** and **1-71**, which were the result of an exo and endo Diels–Alder, respectively. Much to our surprise, the exo adduct was the major product in this reaction, whereas all of the previous substrates thus far that bore a trans alkene afforded the endo Diels–Alder adduct exclusively.

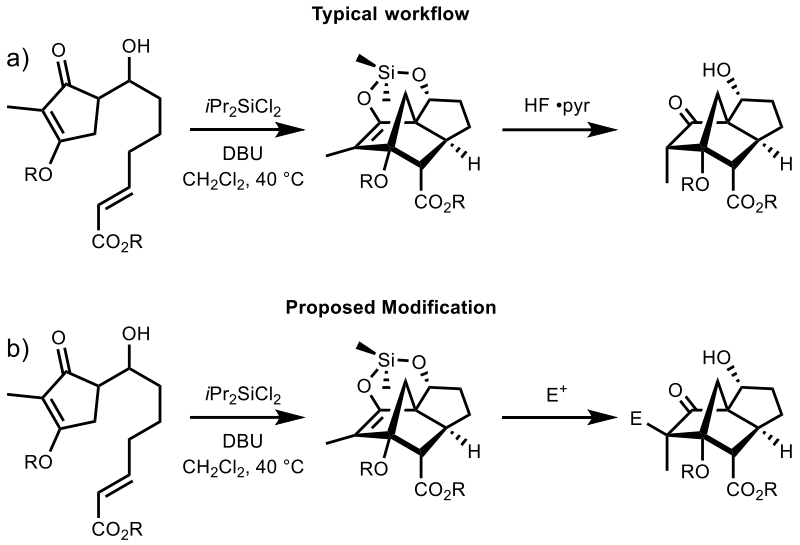


Scheme 1.21. Seven-Membered Silacycle Experiment

1.2.9. Product Derivatizations

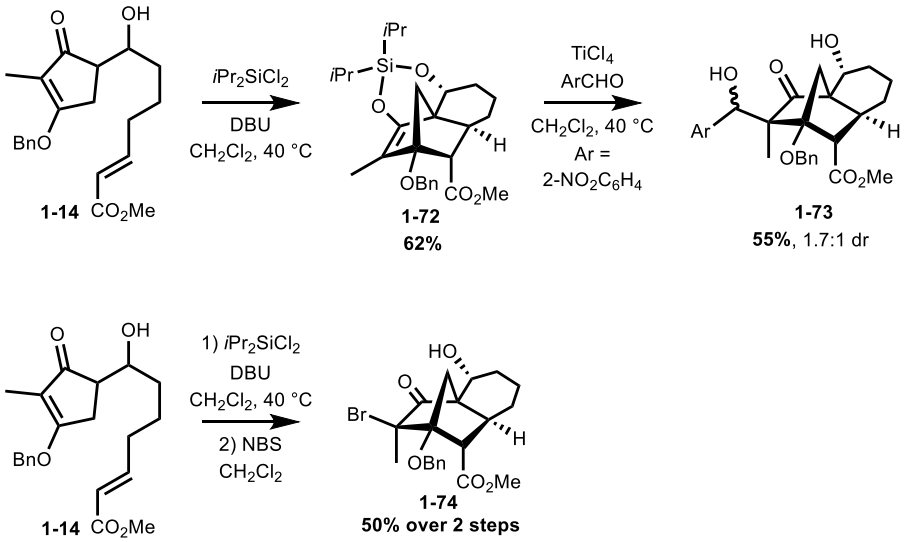
Thus far, the workflow of our method involved the use of HF•pyridine to destroy the silacycle that was the immediate result of IMDA cyclization, returning a norbornone product (Scheme 1.22a). While this procedure was reliable, we also recognized that the silacycle intermediate held a synthetic potential that we had thus far not explored. For example, it should be able to engage in silyl enol ether-type chemistry such as the capture of electrophiles to return an α-functionalized ketone (Scheme 1.22b). We reasoned that if we could affect such an

electrophile capture in our system, it would demonstrate appealing synthetic applications for our methodology.



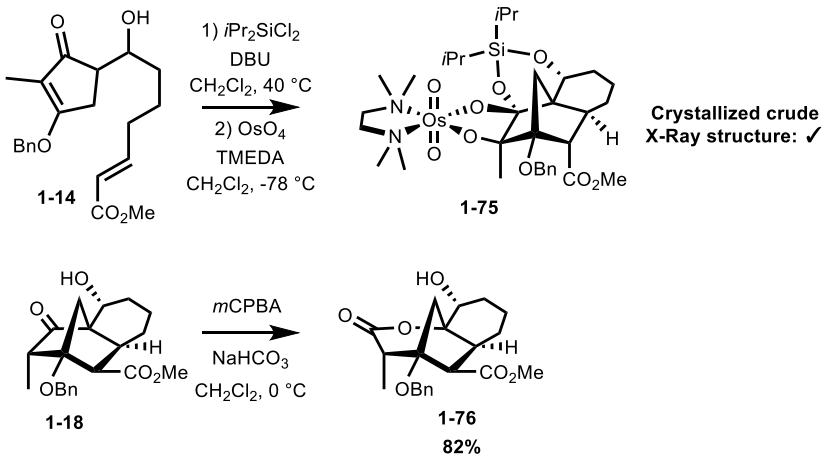
Scheme 1.22. Proposed Strategy for the Capture of Electrophiles with the Silacycle Intermediate

We quickly found that the silacycle intermediate itself (**1-72**, Scheme 1.23) could be isolated in moderate yield when the HF workup was omitted. Subjecting this silacycle to prototypical Mukaiyama Aldol conditions led to the formation of aldol adduct **1-73**, bearing a



Scheme 1.23. Demonstrations of Electrophile Capture Using the Intermediate Silacycle

newly formed quaternary center, in moderate yield.[17b] We also found that less sensitive reaction conditions allowed us to omit the purification of the silacycle intermediate and react directly with the crude reaction mixture. For example, the crude reaction mixture could be reacted with NBS to yield α bromide **1-74**. We were pleased that these examples revealed the silacycle to be not only an effective directing group, but also a useful functional handle as well.



Scheme 1.24. Miscellaneous Product Derivatization

Two more miscellaneous product derivatizations that we were able to affect are described in Scheme 1.24. Taking crude **1-72** without further purification and subjecting it to standard osmylation conditions afforded osmate ester **1-75**, which was crystallized directly without prior purification.[20] The structure of **1-75** was confirmed through x-ray diffraction, cementing our confidence in our stereochemical assignments. Finally, we demonstrated that Diels–Alder adduct **1-18** could be further derivatized via Bayer-Villiger oxidation to afford lactone **1-76** in good yield.

1.3. Conclusion

We have demonstrated that a dioxasiline ring serves as an effective directing group for the control of π-facial selectivity in IMDA cyclizations while serving the dual function of forming the reactive diene. Using this highly diastereoselective strategy we have successfully set up to seven stereocenters in a single reaction. We found that this directing group is easily installed in situ and may be removed with an HF workup or otherwise preserved as a silyl enol ether. This silyl enol ether serves as a useful functional handle for further manipulations. Importantly, we also discovered a number of substrates that fail to engage in the desired IMDA cyclization, allowing us to define the limits of our method. Finally, we have elucidated an interesting mechanism involving γ deprotonation followed by a [1,5] hydride shift to form the reactive diene.

1.4. Acknowledgements

We would like to acknowledge the contribution of Dr. Alexander Burns, who ran some of the preliminary experiments for this project and aided in the design of the deuterium labelling study. Furthermore, this work was supported in part by a grant from the National Science Foundation (NSF CHE 210674). We are grateful for their support.

1.5. Supporting Information

1.5.1. General Experimental

All chemicals were purchased from Sigma–Aldrich, Alfa Aesar, TCI, or Fisher Scientific and used without further purification. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. Solvents were purchased as ACS grade or better and passed through activated alumina columns prior to use. Unless otherwise stated, reactions were performed in flame dried glassware under an atmosphere of argon. Reaction progress was

monitored by thin layer chromatography (TLC) using glass plates coated with a 250 μm layer of 60 Å silica gel (SiO_2). TLC plates were visualized using either a UV lamp at 254 nm, potassium permanganate or cerium molybdate (Hanessian's stain). Column chromatography was performed using forced flow on silica gel columns or with an automated purification system on prepacked silica gel columns.

^{1}H NMR spectra were recorded at 500 MHz or 600 MHz using either a Bruker DRX500 (cryoprobe) or Bruker AVANCE600 (cryoprobe) at 298.0 K. ^{13}C NMR spectra were recorded at 125 MHz or 150 MHz on a Bruker DRX500 (cryoprobe) or Bruker AVANCE600 (cryoprobe) at 298.0 K. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent peak or to a tetramethylsilane (TMS) standard. NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublets of doublets, dt = doublet of triplets, dtd = doublet of triplets of doublets, bs = broad singlet), coupling constants (*J*) in hertz (Hz), and integration. For partially deuterated compounds, the percentage deuterium incorporation is calculated based on the proton integration value at the deuterated position. In ^{13}C NMR spectra of partially deuterated compounds, carbons within 2-4 sigma bonds of the deuterium atom occasionally exhibit a measurably different chemical shift from their fully protiated counterparts, leaving these spectra with more carbon signals than expected. High-resolution mass spectrometry was performed using ESI-TOF.

1.5.2. General Procedure A: Formation of Aldol Adducts

To a round bottom flask equipped with a magnetic stir bar was added a solution of freshly distilled diisopropylamine *i*Pr$_2$NH in dry THF (1.2 equiv, 1.4 M). The solution was cooled to –78 °C and *n*Butyl lithium (2.5 M in hexanes, 1.1 equiv) was added dropwise. The solution was

warmed to 0 °C for 5 min, after which it was cooled to –78 °C and a solution of enone in THF (1.0 equiv, 1.2 M) was added dropwise. The reaction was stirred at –78 °C for 1 h, at which time a solution of aldehyde or ketone in THF (1.2 equiv, 1.4 M) was added quickly. The reaction was stirred for another 5 min before being quenched with a saturated solution of aqueous NH_4Cl (0.50 reaction volumes) and warmed to rt. The reaction mixture was transferred to a separatory funnel, the organic phase collected, and the aqueous phase extracted with CH_2Cl_2 (3 x 1.0 reaction volume). The combined organic layers were washed once with brine, dried over Na_2SO_4, and concentrated in vacuo. Product mixtures were then purified by flash column chromatography.

1.5.3. General Procedure B: Silacycle Formation and Diels–Alder Cyclization

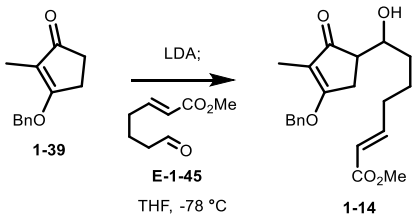
Unless otherwise indicated, aldol adducts are taken as a mixture of syn and anti diastereomers in the same diastereomeric ratio as they were isolated from the previous aldol reaction. Hydroxyketone (1.0 equiv) was dissolved in CH_2Cl_2 (0.20 M) in a scintillation vial equipped with a septum. This solution was cooled to 0 °C and a solution of diisopropyldichlorosilane in CH_2Cl_2 (2.0 equiv, 0.40 M) was added slowly. Immediately afterwards, a solution of DBU in CH_2Cl_2 (6.0 equiv, 0.40 M) was added slowly. The reaction was stirred at 0 °C for 10 min and then at rt for 10 min. The reaction vessel was opened to air momentarily and the septum was exchanged with a Teflon-lined cap. The sealed vessel was stirred at 40 °C for 13 h. Subsequently, the mixture was cooled to rt, at which point it was diluted with pyridine (0.10 reaction volumes). A 70% solution of HF•pyr (0.010 reaction volumes) was added slowly and the reaction stirred for 30 min, after which a saturated aqueous solution of $NaHCO_3$ was added slowly until bubbling had ceased. The resulting biphasic solution was transferred to a separatory funnel and the organic layer collected. The aqueous layer was

extracted with CH_2Cl_2 (3 x 1.0 reaction volume), and the combined organic layers were washed with a saturated solution of cupric sulfate (2 x 1.0 reaction volume). The combined cupric sulfate layers were back-extracted with one reaction volume of CH_2Cl_2, after which the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. All Diels–Alder adducts were obtained as a single diastereomer as determined by ^{13}C NMR of the crude reaction mixture. The product mixtures were purified by flash column chromatography.

1.5.4. General Procedure C: DMP Oxidation of Primary Alcohols

No precaution was taken to exclude air or water from the reaction. To a round bottom flask was added CH_2Cl_2 (0.10 M), DMP (1.5 equiv), primary alcohol (1.0 equiv), and $NaHCO_3$(10 equiv). The reaction was stirred for one h open to air, after which time it was transferred to a separatory funnel and diluted with water until all the $NaHCO_3$ was solvated. One reaction volume of a saturated aqueous solution of $Na_2S_2O_3$ was added and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (3 x 1.0 reaction volume). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The product mixtures were purified by flash column chromatography.

1.5.5. Experimental Procedures and Compound Characterization



Methyl (E)-7-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-7-hydroxyhept-2-enoate (1-14):

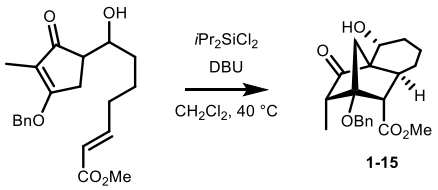
Following general procedure A, **1-39** (0.89 g, 4.4 mmol, 1.0 equiv) was deprotonated with LDA (0.51 g, 4.8 mmol, 1.1 equiv) and reacted with **E-1-45** (0.75g, 5.3 mmol, 1.2 equiv) in THF (10 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford **1-14 major** and **1-14 minor** (0.49 g, 30% combined yield, 1.2:1 dr):

Major diastereomer:

Yellow oil; $\mathbf{R_f}$ = 0.39 (3:2 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 5H), 6.96 (dt, *J* = 15.6, 6.6 Hz, 1H), 5.83 (d, *J* = 15.7 Hz, 1H), 5.25 (s, 2H), 4.80 (s, 1H), 3.72 (s, 3H), 3.61 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.79 (dd, *J* = 17.3, 6.9 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.29 (d, *J* = 17.3 Hz, 1H), 2.26 – 2.18 (m, 2H), 1.78 – 1.69 (m, 1H), 1.67 (s, 3H), 1.61 – 1.53 (m, 1H), 1.51 – 1.42 (m, 2H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.4, 183.7, 167.2, 149.4, 135.6, 129.0, 128.8, 127.2, 121.3, 116.3, 72.4, 71.4, 51.5, 48.9, 35.1, 32.2, 29.1, 23.5, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.1673, found 381.1672.

Minor Diastereomer:

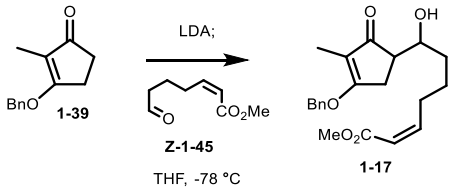
Yellow oil; $\mathbf{R_f}$ = 0.40 (3:2 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 10.3, 4.3 Hz, 2H), 7.38 – 7.34 (m, 3H), 6.95 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.82 (d, *J* = 15.7 Hz, 1H), 5.28 – 5.23 (m, 2H), 4.13 (s, 1H), 3.72 (s, 3H), 2.71 – 2.61 (m, 2H), 2.60 – 2.55 (m, 1H), 2.42 (bs, 1H), 2.27 – 2.19 (m, 2H), 1.73 – 1.68 (m, 1H), 1.65 (s, 3H), 1.53 – 1.45 (m, 2H), 1.42 – 1.36 (m, 1H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 206.6, 184.6, 167.2, 149.2, 135.9, 129.0, 128.7, 127.2, 121.4, 117.2, 71.2, 69.8, 51.6, 50.6, 34.0, 32.1, 26.6, 24.7, 6.2; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.1673, found 381.1666.



Methyl-2-(benzyloxy)-5-hydroxy-3-methyl-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-15):

Following general procedure B, **1-14** (0.20 g, 0.56 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (0.20 mL, 1.1 mmol, 2.0 equiv) and DBU (0.50 mL, 3.4 mmol, 6.0 equiv) in CH_2Cl_2 (6.0 mL) from 0 to 40 °C. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-15** as a clear oil (0.14 g, 70% yield, single diastereomer): $\mathbf{R_f}$ = 0.39 (3:7 EtOAc:Hex); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.1 Hz, 1H), 5.03 (d, *J* = 1.9 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.26 (s, 1H), 3.71 (s, 3H), 2.88 (d, *J* = 3.7 Hz, 1H), 2.72 (q, *J* = 6.9 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.41 (d, *J* = 9.8 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.91 – 1.83 (m, 1H), 1.81 (d, *J* = 15.6 Hz, 1H), 1.52 (dd, *J* = 9.7, 1.5 Hz, 1H), 1.42 (d, *J* = 13.5 Hz, 1H), 1.37 – 1.29 (m, 1H), 1.29 – 1.21 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H);

$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 219.9, 172.5, 138.1, 128.6, 128.0, 127.6, 86.6, 66.8, 66.4, 56.4, 53.7, 52.1, 50.7, 40.8, 34.8, 31.9, 29.5, 18.2, 7.8; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_5$ $[M+Na]^+$: 358.1673, found 358.1674. Relative stereochemistry was assigned by ^1H NOESY (see page 186) and by analogy to **1-75**.



Methyl (Z)-7-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-7-hydroxyhept-2-enoate (1-17):

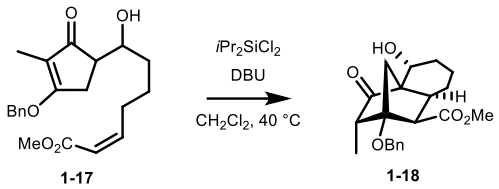
Following general procedure A, **1-39** (0.33 g, 1.7 mmol, 1.0 equiv) was deprotonated with LDA (0.19 g, 1.8 mmol, 1.1 equiv) and reacted with **Z-1-45** (0.31 mL, 2.0 mmol, 1.2 equiv) in THF (4.0 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford **1-17** as a yellow oil (0.25 g, 43% yield, 1.6:1 dr):

Major Diastereomer:

R_f = 0.46 (3:2 EtOAc:Hex, UV); **^1H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.40 – 7.34 (m, 3H), 6.24 (dt, *J* = 11.5, 7.6 Hz, 1H), 5.79 (d, *J* = 11.4 Hz, 1H), 5.25 (s, 2H), 4.80 (s, 1H), 3.70 (s, 3H), 3.65 (td, *J* = 9.3, 2.7 Hz, 1H), 2.79 (dd, *J* = 17.3, 6.5 Hz, 1H), 2.72 – 2.64 (m, 2H), 2.46 (t, *J* = 7.1 Hz, 1H), 2.32 (d, *J* = 17.9 Hz, 1H), 1.75 – 1.69 (m, 1H), 1.68 (s, 3H), 1.65 – 1.59 (m, 1H), 1.53 – 1.45 (m, 2H); **$^{13}C\{^1H\}$ NMR** (150 MHz, $CDCl_3$) δ 208.5, 183.8, 167.1, 150.8, 135.7, 129.1, 128.8, 127.2, 119.6, 116.4, 72.4, 71.4, 51.2, 48.9, 35.4, 29.1, 28.9, 24.5, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.1673, found 381.1672.

Minor Diastereomer:

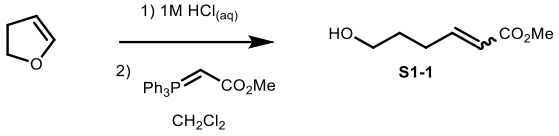
R_f = 0.43 (3:2 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.38 – 7.34 (m, 3H), 6.23 (dt, *J* = 11.6, 7.6 Hz, 1H), 5.79 (d, *J* = 11.5 Hz, 1H), 5.27 (d, *J* = 12.4 Hz, 1H), 5.24 (d, *J* = 12.4 Hz, 1H), 4.17 (d, *J* = 3.5 Hz, 1H), 3.70 (s, 3H), 2.75 – 2.64 (m, 3H), 2.64 – 2.58 (m, 2H), 2.29 (d, *J* = 5.5 Hz, 1H), 1.67 (s, 3H), 1.53 – 1.38 (m, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 206.6, 184.4, 167.0, 150.4, 135.9, 129.0, 128.7, 127.2, 119.8, 117.2, 71.2, 70.0, 51.2, 50.5, 34.1, 28.8, 26.7, 25.6, 6.2; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.1673, found 381.1668.



Methyl-2-(benzyloxy)-5-hydroxy-3-methyl-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-18):

Following general procedure B, **1-17** (0.25 g, 0.71 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (0.25 mL, 1.4 mmol, 2.0 equiv) and DBU (0.63 mL, 4.2 mmol, 6.0 equiv) in CH_2Cl_2 (10 mL) from 0 to 40 °C. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-18** as a clear oil (0.20 g 77% yield, single diastereomer): **R_f** = 0.48 (3:7 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 5H), 4.99 (s, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.21 (s, 1H), 3.61 (s, 3H), 3.07 (d, *J* = 9.2 Hz, 1H), 2.77 (d, *J* = 10.0 Hz, 1H), 2.60 (q, *J* = 6.9 Hz, 1H), 2.19 – 2.06 (m, 1H), 1.76 – 1.61 (m, 4H), 1.48 – 1.40 (m, 1H), 1.40 – 1.34 (m, 1H), 1.32 – 1.24 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ

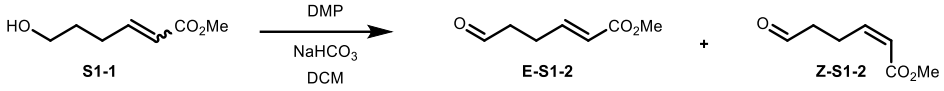
220.9, 171.0, 138.3, 128.5, 127.8, 127.4, 85.6, 68.0, 67.0, 57.7, 51.5, 51.4, 47.4, 37.2, 35.8, 29.6, 25.2, 18.0, 7.8; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_5$ $[M+Na]^+$: 381.1673, found 381.1669. The ~10 Hz coupling constant between the adjacent methine protons established the relative stereochemistry of the ester. Remaining stereochemistry was established in analogy with **1-15**.



Methyl 6-hydroxyhex-2-enoate (S1-1):

No precaution was taken to exclude air or water from the reaction. A round bottom flask charged with 2,3-dihydro-2H-furan (1.9 mL, 25 mmol, 1.0 equiv) was cooled to 0 °C and an aqueous solution of HCl (5.0 mL, 0.20 M) was added slowly. This mixture was stirred at 0 °C for 15 min and then 1 h at rt. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layers were washed with brine (5.0 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was then dissolved in THF (60 mL) and transferred to a round bottom flask charged with a magnetic stir bar and reflux condenser. Methyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (10 g, 30 mmol, 1.2 equiv) was added and the reaction was refluxed for 13 h. After this time, the crude reaction was concentrated in vacuo and diluted with a 7:3 Et_2O: pentanes solution. This mixture was stirred for 45 min, during which time triphenylphosphine oxide precipitated as a white solid. The mixture was filtered to remove the phosphine oxide and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford clear oil **S1-1** as an inseparable mixture of olefin isomers (1.2 g, 34% yield, 20:1 E:Z); all

spectral data are consistent with those reported.[21] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 3.68 (d, *J* = 16.3 Hz, 3H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.34 – 2.22 (m, 2H), 1.89 (bs, 1H), 1.76 – 1.63 (m, 2H). Only E isomer peaks are reported



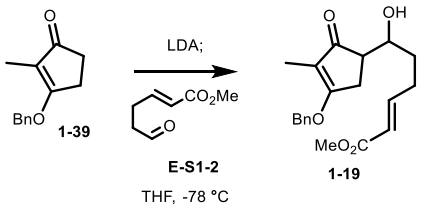
Methyl (E)-6-hydroxyhex-2-enoate (S1-2)

Following general procedure C, **S1-1** (1.2 g, 8.5 mmol, 1.0) was reacted with DMP (5.4 g, 13 mmol, 1.5 equiv) and $NaHCO_3$ (7.1g, 85 mmol, 10 equiv) in CH_2Cl_2 (85 mL). The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **E-S1-2** as a pale-yellow oil (0.70 g) 58% yield).

E-S1-2

All spectral data are consistent with those reported;[22] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 6.93 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.84 (d, *J* = 15.7 Hz, 1H), 3.71 (s, 3H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.52 (q, *J* = 6.9 Hz, 2H).

Z-S1-2 was not isolated.

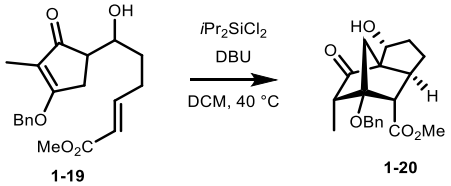


Methyl (E)-6-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-6-hydroxyhex-2-enoate (1-19):

Following general procedure A, **1-39** (0.83 g, 4.1 mmol, 1.0 equiv) was deprotonated with LDA (0.48 g, 4.5 mmol, 1.1 equiv) and reacted with **E-S1-2** (0.70 g, 4.9 mmol, 1.2 equiv) in THF (10 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford the major diastereomer of **1-19** as a yellow oil (0.25 g, 18% yield). The minor diastereomer was unable to be isolated in acceptable purity:

Major diastereomer

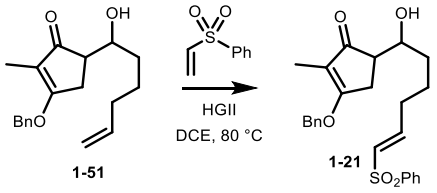
R_f = 0.41 (3:2 EtOAc:Hex, UV); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 5H), 6.96 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.24 (s, 2H), 4.82 (s, 1H), 3.70 (s, 3H), 3.62 (s, 1H), 2.78 (dd, *J* = 17.1, 6.3 Hz, 1H), 2.51 – 2.39 (m, 2H), 2.37 – 2.25 (m, 2H), 1.66 (s, 3H), 1.62 – 1.54 (m, 2H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 208.1, 183.7, 167.2, 149.0, 135.6, 129.0, 128.8, 127.2, 121.4, 116.3, 71.8, 71.4, 51.5, 48.9, 34.0, 28.9, 27.8, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.1516, found 367.1532.



Methyl-6-(benzyloxy)-3-hydroxy-5-methyl-4-oxooctahydro-3a,6-methanoindene-7-carboxylate (1-20):

This reaction was performed with diastereopure **1-19**, consisting only of the major diastereomer of the previous reaction. Following general procedure B, **1-19** (0.25 g, 0.72 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (0.26 mL, 1.5 mmol, 2.0 equiv) and DBU (0.65 mL, 4.3 mmol, 6.0 equiv) in CH_2Cl_2 (10 mL) from 0 to 40 °C. The product mixture was purified by

flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford to afford **1-20** as a yellow oil (0.14 g 56% yield, single diastereomer): $\mathbf{R_f}$ = 0.53 (2:3 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.58 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 4.2 Hz, 1H), 4.17 (s, 1H), 3.74 (s, 3H), 3.15 (d, *J* = 6.1 Hz, 1H), 3.09 – 3.01 (m, 1H), 2.67 (q, *J* = 7.3 Hz, 1H), 2.53 – 2.39 (m, 1H), 2.13 – 2.03 (m, 1H), 2.02 (d, *J* = 9.7 Hz, 1H), 1.92 (ddd, *J* = 13.8, 9.0, 4.4 Hz, 1H), 1.67 (dd, *J* = 9.7, 1.4 Hz, 1H), 1.54 – 1.44 (m, 1H), 1.07 (d, *J* = 7.4 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 216.1, 172.2, 138.1, 128.6, 127.9, 127.6, 87.6, 73.8, 66.3, 65.1, 54.2, 52.1, 50.8, 43.7, 42.0, 35.5, 29.8, 8.4; **HRMS (ESI-TOF)** m / z calcd for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.1516, found 367.1518. Relative stereochemistry was established in analogy with **1-15**.



(E)-3-(benzyloxy)-5-(1-hydroxy-6-(phenylsulfonyl)hex-5-en-1-yl)-2-methylcyclopent-2-en-1-one (1-21):

To a scintillation vial equipped with a stir bar and charged with $ClCH_2CH_2Cl$ (10 mL, 0.18 M) was added **1-51** (0.55 g, 1.8 mmol, 1.0 equiv), phenyl vinyl sulfone (1.0 g, 6.0 mmol, 3.3 equiv), and Hoveyda-Grubbs 2nd Generation catalyst (0.10 g, 0.18 mmol, 10% loading). The vial was sealed and the mixture was heated to 80 °C for 13 h. The reaction mixture was transferred to a separatory funnel and washed with an aqueous solution of tris(hydroxymethyl)phosphine (10 mL, 0.25 M).[23] The aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL), after which the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue

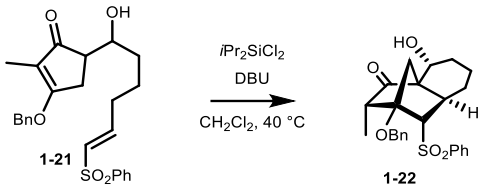
was purified by flash column chromatography using 0 – 70% EtOAc in hexanes as the eluting solvent to afford **1-21** as a yellow oil (0.39 g, 49% yield, 1.2:1 dr):

Major Diastereomer:

R_f = 0.54 (7:3 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.37 (t, *J* = 8.2 Hz, 3H), 6.99 (dt, *J* = 15.0, 6.6 Hz, 1H), 6.34 (d, *J* = 15.1 Hz, 1H), 5.29 – 5.23 (m, 2H), 4.86 (bs, 1H), 3.60 (td, *J* = 8.4, 2.4 Hz, 1H), 2.78 (dd, *J* = 17.1, 7.0 Hz, 1H), 2.42 (ddd, *J* = 10.2, 7.2, 2.4 Hz, 1H), 2.32 – 2.23 (m, 3H), 1.77 – 1.70 (m, 1H), 1.67 (s, 3H), 1.63 – 1.56 (m, 2H), 1.52 – 1.40 (m, 2H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.4, 183.8, 146.8, 140.7, 135.7, 133.4, 130.9, 129.4, 129.1, 128.8, 127.7, 127.2, 116.3, 72.3, 71.5, 48.8, 34.9, 31.3, 29.1, 23.1, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{25}H_{28}O_5S$ $[M+Na]^+$: 463.1550, found 463.1552.

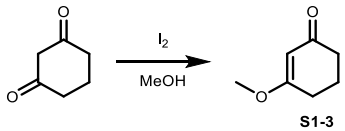
Minor Diastereomer:

R_f = 0.45 (7:3 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.33 (m, 5H), 6.97 (dt, *J* = 15.0, 6.6 Hz, 1H), 6.33 (d, *J* = 15.1 Hz, 1H), 5.28 – 5.22 (m, 2H), 4.11 (d, *J* = 8.1 Hz, 1H), 2.64 (s, 2H), 2.58 – 2.54 (m, 1H), 2.31 – 2.22 (m, 2H), 1.81 – 1.67 (m, 2H), 1.64 (s, 3H), 1.55 – 1.33 (m, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 206.5, 184.7, 146.7, 140.7, 135.9, 133.4, 130.9, 129.4, 129.0, 128.7, 127.7, 127.2, 117.2, 71.3, 69.7, 50.5, 33.7, 31.3, 26.7, 24.3, 6.2; **HRMS (ESI-TOF)** m / z calcd for $C_{25}H_{28}O_5S$ $[M+Na]^+$: 463.1550, found 463.1572.



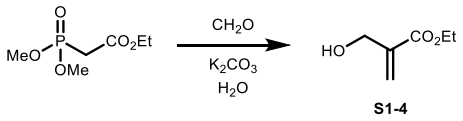
2-(benzyloxy)-5-hydroxy-3-methyl-1-(phenylsulfonyl)octahydro-4H-2,4a-methanonaphthalen-4-one (1-22):

Following general procedure B, **1-21** (0.39 g, 0.89 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (0.32 mL, 1.8 mmol, 2.0 equiv) and DBU (0.80 mL, 5.4 mmol, 6.0 equiv) in CH_2Cl_2 (10 mL) from 0 to 40 °C. The product mixture was purified by flash column chromatography using 0 – 35% EtOAc in hexanes as the eluting solvent to afford **1-22** as a foamy white solid (0.21 g 54% yield, single diastereomer): $\mathbf{R_f}$ = 0.53 (2:3 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.30 (m, 5H), 5.02 (d, *J* = 2.0 Hz, 1H), 4.71 – 4.61 (m, 2H), 4.23 (s, 1H), 3.52 (d, *J* = 4.8 Hz, 1H), 2.97 (q, *J* = 7.0 Hz, 1H), 2.53 (dt, *J* = 10.9, 4.2 Hz, 1H), 2.26 (d, *J* = 10.0 Hz, 1H), 1.75 – 1.66 (m, 3H), 1.58 (d, *J* = 7.1 Hz, 3H), 1.29 – 1.16 (m, 3H), 1.01 (qd, *J* = 12.0, 2.5 Hz, 1H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 218.2, 141.3, 137.5, 133.9, 129.5, 128.7, 128.2, 128.1, 127.6, 89.1, 72.6, 67.2, 66.7, 56.5, 53.7, 42.0, 36.3, 31.2, 28.9, 17.9, 9.1; **HRMS (ESI-TOF)** m / z calcd for $C_{25}H_{28}O_5S$ $[M+Na]^+$: 463.1550, found 463.1560. Relative stereochemistry was established in analogy with **1-15**.



3-methoxycyclohex-2-en-1-one--cyclohexane-1,3-dione (**S1-3**):

To a 25 mL round-bottom flask equipped with a stir bar was added 1,3-cyclohexanedione (0.34 g, 3.0 mmol, 1.0 equiv) and MeOH (7.0 mL, 0.43 M), with no effort made to exclude air or moisture. To this stirred solution was added iodine (23 mg, 90 μmol, 3.0 mol%). The reaction mixture was stirred for 2 h, after which time it was concentrated in vacuo and redissolved in CH_2Cl_2 (10 mL). This solution was transferred to a 30 mL separatory funnel and washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic phases were dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography using 0 – 40% EtOAc in hexanes as the eluting solvent to afford **S1-3** as an orange oil (0.26 g 70% yield). All spectral data are consistent with those reported;[24] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 3.53 (s, 2H), 2.25 (t, J = 6.1 Hz, 1H), 2.16 (t, J = 6.5 Hz, 1H), 1.91 – 1.74 (m, 1H).

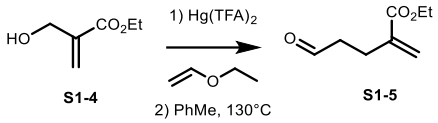


S1-4

Ethyl 2-(hydroxymethyl)acrylate (S1-4):

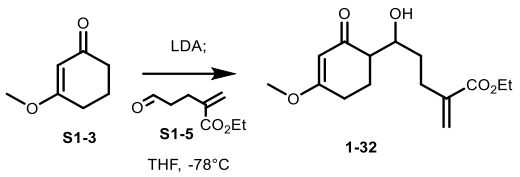
To a round bottom flask charged with a magnetic stir bar was added ethyl 2-(dimethoxyphosphoryl) acetate (2.0 mL, 10 mmol, 1.0 equiv) and a 37% w/v solution of formaldehyde in water (10 mL, 1.0 M), with no precautions taken to exclude air or water. A solution of K_2CO_3 (2.8 g, 20 mmol, 2.0 equiv) in water (10 mL, 1.0 M) was added dropwise to the reaction mixture, which was then stirred for 30 min. The reaction was diluted with a saturated aqueous solution of NH_4Cl (10 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The

residue was purified by flash column chromatography using 20% EtOAc in hexanes as the eluting solvent to afford **S1-4** as a clear oil (0.88 g 63% yield of **S1-4**); all spectral data are consistent with those reported;[25] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.81 (s, 1H), 4.30 (s, 2H), 4.21 (q, *J* = 7.1, 2H), 2.59 (bs, 1H), 1.29 (t, *J* = 7.2, 3H).



Ethyl 2-methylene-4-oxobutanoate (S1-5):

To a round bottom flask equipped with a stir bar and ethyl vinyl ether (6.3 mL, 1.0 M) was added **S1-4** (0.81 g, 6.3 mmol, 1.0 equiv) and mercury (II) trifluoroacetate (0.13 g, 0.31 mmol, 5.0 mol%). The reaction was stirred at rt for 10 h, after which it was diluted with a saturated aqueous solution of $NaHCO_3$ (6.0 mL) and transferred to a separatory funnel. The organic phase was collected, and the aqueous phase extracted with Et_2O (3 x 6.0 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator, taking care to avoid the use of excessive vacuum, as the product was volatile. The product mixture was then dissolved in toluene (12 mL, 0.53 M), transferred to a sealed tube, and heated to 130 °C for 6 h, after which it was concentrated on a rotary evaporator, again taking care to avoid excessive vacuum, and purified by flash column chromatography, using 10% EtOAc in hexanes as the eluting solvent to afford **S1-5** as a clear oil (0.43 g 40% yield of **S1-5**); all spectral data are consistent with those reported;[25] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 6.18 (s, 1H), 5.57 (d, *J* = 0.9, 1H), 4.20 (q, *J* = 7.1, 2H), 2.63 (s, 4H), 1.28 (t, *J* = 7.1, 3H).



Ethyl 5-hydroxy-5-(4-methoxy-2-oxocyclohex-3-en-1-yl)-2-methylenepentanoate (1-32)

Following general procedure A, **S1-3** (0.11 g, 0.83 mmol, 1.0 equiv) was deprotonated with LDA (93 mg, 0.87 mmol, 1.1 equiv) and reacted with **S1-5** (0.16 g, 1.0 mmol, 1.2 equiv) in THF (2.0 mL) at –78 °C. The product mixture was purified by flash column chromatography using 40% EtOAc in hexanes as the eluting solvent to afford **1-32** as a yellow oil (0.15 g 52% yield of **1-32**, 5:1 dr, relative configurations unassigned):

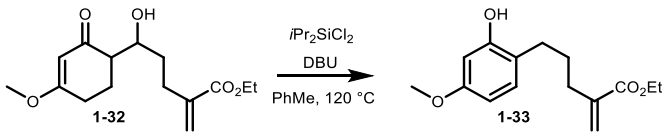
Major Diastereomer:

R_f = 0.28 (1:1 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.58 (s, 1H), 5.34 (s, 1H), 4.79 (d, *J* = 1.3, 1H), 4.18 (q, *J* = 7.1, 2H), 3.83 (tt, *J* = 8.2, 2.5, 1H), 3.69 (s, 3H), 2.55 – 2.45 (m, 2H), 2.44 – 2.36 (m, 2H), 2.22 (ddd, *J* = 13.0, 8.1, 4.8, 1H), 2.06 (dq, *J* = 12.9, 4.8, 1H), 1.76 – 1.69 (m, 1H), 1.68 – 1.56 (m, 2H), 1.28 (t, *J* = 7.1, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 203.4, 179.1, 167.4, 140.7, 125.2, 102.3, 71.4, 60.7, 56.0, 49.6, 32.9, 28.6, 27.3, 23.8, 14.3; **FT-IR** (cm^{-1}) 3414, 2939, 1711, 1621; **HRMS (ESI-TOF)** *m / z* calcd for $C_{15}H_{22}O_5$ $[M+Na]^+$: 305.1365, found 305.1352.

Minor Diastereomer:

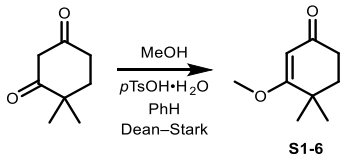
R_f = 0.19 (1:1 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.58 (s, 1H), 5.38 (s, 1H), 4.20 (q, *J* = 7.1, 2H), 4.14 (d, *J* = 4.3, 1H), 3.69 (s, 3H), 2.89 (s, 1H), 2.54 (ddd, *J* = 14.4, 9.6, 4.8, 1H), 2.49 (dd, *J* = 10.9, 6.2, 1H), 2.46 (dt, *J* = 17.4, 4.2, 1H), 2.41 – 2.34 (m, 2H), 2.00 – 1.93 (m, 2H), 1.73 – 1.66 (m, 1H), 1.66 – 1.57 (m, 1H), 1.30 (t, *J* = 7.1, 3H); **^{13}C{^{1}H} NMR**

(150 MHz, $CDCl_3$) δ 201.4, 179.0, 167.4, 140.6, 125.3, 102.9, 69.9, 60.8, 56.0, 50.3, 32.1, 29.0, 28.8, 21.7, 14.4; **FT-IR** (cm^{-1}) 3451, 2933, 1711, 1645; **HRMS (ESI-TOF)** *m / z* calcd for $C_{15}H_{22}O_5$ $[M+Na]^+$: 305.1365, found 305.1375.



ethyl 5-(2-hydroxy-4-methoxyphenyl)-2-methylenepentanoate (1-33):

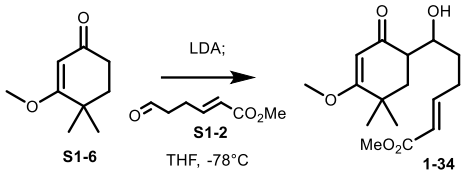
Following a modified general procedure B, **1-32** (30 mg, 0.11 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (39 μL, 0.21 mmol, 2.0 equiv) and DBU (95 µL, 0.64 mmol, 6.0 equiv) in toluene (1.0 mL) from 0 °C to 120 °C. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-33**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.00 (d, J = 8.3 Hz, 1H), 6.43 (dd, J = 8.3, 1.5 Hz, 1H), 6.38 (s, J = 1.7 Hz, 1H), 6.15 (s, 1H), 5.55 (s, 1H), 5.13 (d, J = 19.9 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 2.57 (t, J = 7.7 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.82 – 1.72 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 167.7, 159.1, 154.5, 140.9, 130.7, 124.8, 120.4, 106.0, 102.0, 60.9, 55.4, 31.7, 29.0, 28.9, 14.3.



3-methoxy-4,4-dimethylcyclohex-2-en-1-one (S1-6)

To a 25 mL round-bottom flask equipped with a stir bar was added dimethylcyclohexane-1,3-dione (2.0 g, 14 mmol, 1.0 equiv), MeOH (2.0 mL, 7.0 M), benzene (10 mL, 1.4 M), and *p*TsOH•H_2O (27 mg, 0.14 mmol, 1.0 mol%), with no precautions taken to exclude air or

moisture. The flask was fitted with a Dean–Stark trap and the reaction mixture heated to reflux for 20 h, after which it was concentrated in vacuo. The product mixture was purified by flash column chromatography using 30% EtOAc in hexanes as the eluting solvent to afford **S1-6** as a yellow oil (0.38 g) containing 3 wt% solvent (17% yield of **S1-6**); all spectral data are consistent with those reported;[26] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (s, 1H), 3.67 (s, 3H), 2.40 (t, *J* = 6.7, 2H), 1.82 (t, *J* = 6.7, 2H), 1.20 (s, 6H).



Methyl (E)-6-hydroxy-6-(4-methoxy-5,5-dimethyl-2-oxocyclohex-3-en-1-yl)hex-2-enoate (1-34):

Following general procedure A, **S1-6** (0.15 g, 0.97 mmol, 1.0 mmol) was deprotonated with LDA (0.10 g, 0.93 mmol, 1.0 equiv) and reacted with **S1-2** (0.17 g, 1.2 mmol, 1.2 equiv) in THF (2.5 mL) at –78 °C. The product mixture was purified by flash column chromatography using 40 – 50% EtOAc in hexanes as the eluting solvent to afford **1-34** (0.11 g 37% yield, 3:1 dr, relative configurations unassigned):

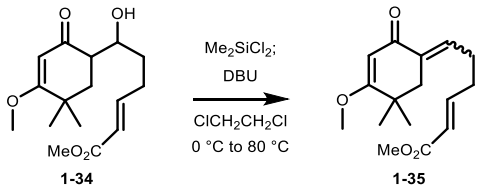
Major Diastereomer:

R_f = 0.48 (1:1 EtOAc:Hex, UV); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.5, 7.0 Hz, 1H), 5.79 (d, J = 15.7 Hz, 1H), 5.17 (s, 1H), 5.01 (s, 1H), 3.76 (t, J = 8.1 Hz, 1H), 3.64 (s, 3H), 3.63 (s, 3H), 3.60 (d, J = 8.0 Hz, 1H), 2.42 – 2.21 (m, 3H), 1.60 (m, 2H), 1.54 – 1.45 (m, 1H), 1.18 (s, 3H), 1.11 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 203.3, 184.4, 167.3, 149.5, 121.3, 100.7,

71.5, 56.4, 51.5, 46.8, 39.3, 36.3, 32.3, 27.7, 27.0, 25.1; **FT-IR** (cm^{-1}) 3421, 2949, 1720, 1645; **HRMS (ESI-TOF)** *m / z* calcd for $C_{16}H_{24}O_5$ $[M+Na]^+$: 319.1521, found 319.1525.

Minor Diastereomer:

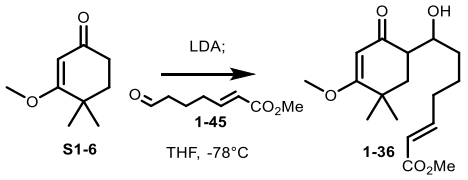
R_f = 0.27 (1:1 EtOAc, UV); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.98 (dt, J = 15.4, 6.9 Hz, 1H), 5.85 (d, J = 15.6 Hz, 1H), 5.25 (s, 1H), 4.18 – 4.05 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.06 (d, J = 6.3 Hz, 1H), 2.61 – 2.44 (m, 2H), 2.32 – 2.21 (m, 1H), 1.77 – 1.55 (m, 3H), 1.52 – 1.43 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H); **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 201.3, 184.3, 167.2, 149.2, 121.3, 101.2, 70.1, 56.3, 51.5, 47.0, 37.0, 36.3, 31.3, 29.2, 27.0, 25.1; **FT-IR** (cm^{-1}) 3435, 2948, 1721, 1651; **HRMS (ESI-TOF)** *m / z* calcd for $C_{16}H_{24}O_5$ $[M+Na]^+$: 319.1521, found 319.1528.



Methyl (2E)-6-(4-methoxy-5,5-dimethyl-2-oxocyclohex-3-en-1-ylidene)hex-2-enoate (1-35):

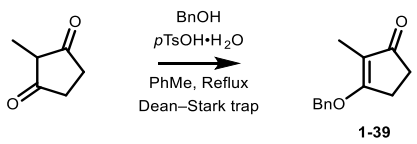
Using general procedure B, **1-34** (25 mg 84 μmol, 1.0 equiv) was reacted with dimethyldichlorosilane (20 μL, 0.17 mmol, 2.0 equiv), and DBU (76 μL, 0.51 mmol, 6.0 equiv) in $ClCH_2CH_2Cl$ (1.0 mL) from 0 to 84 °C for 16 hr. The product mixture was purified by flash column chromatography using 0 – 40% EtOAc in hexanes as the eluting solvent to afford **1-35** as a yellow oil (6.0 mg 25% yield of **1-35**, single olefin isomer, E/Z unassigned): **R_f =** 0.41 (1:1 EtOAc:Hex, UV); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 15.3, 6.3, 1H), 6.65 (t, *J* = 7.0, 1H), 5.85 (d, *J* = 15.6, 1H), 5.36 (s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.48 (s, 2H), 2.35 (t, *J* = 10.0, 4H), 1.17 (s, 6H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 188.9, 183.5, 167.0, 148.0, 135.0, 133.9,

121.9, 101.0, 56.2, 51.6, 40.2, 37.5, 31.5, 26.5, 26.3; **FT-IR** (cm^{-1}) 2926, 1722, 1663; **HRMS (ESI-TOF)** *m / z* calcd for $C_{16}H_{22}O_4$ $[M+Na]^+$: 301.1416, found 301.1421.



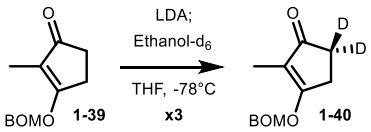
methyl (E)-7-hydroxy-7-(4-methoxy-5,5-dimethyl-2-oxocyclohex-3-en-1-yl)hept-2-enoate (1-36):

Following general procedure A, **S1-6** (0.15 g, 0.97 mmol, 1.0 mmol) was deprotonated with LDA (0.11 g, 1.0 mmol, 1.1 equiv) and reacted with **1-45** (0.19 g, 1.2 mmol, 1.2 equiv) in THF (10 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford the more polar diastereomer of **1-36** (53 mg 18% yield): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.97 (dt, J = 15.6, 7.0 Hz, 1H), 5.83 (dt, J = 15.6, 1.5 Hz, 1H), 5.26 (s, J = 9.5 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 2.87 (d, J = 6.5 Hz, 1H), 2.57 (ddd, J = 14.0, 4.5, 3.1 Hz, 1H), 2.25 (qd, J = 7.1, 1.3 Hz, 2H), 1.80 – 1.70 (m, 1H), 1.65 – 1.46 (m, 4H), 1.42 – 1.34 (m, 1H), 1.24 (s, J = 11.9 Hz, 3H), 1.19 (s, J = 8.0 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 201.4, 184.2, 167.3, 149.4, 121.3, 101.3, 70.5, 56.3, 51.5, 47.1, 36.9, 36.3, 32.2, 27.1, 25.2, 25.0.; **HRMS (ESI-TOF)** m / z calcd for $C_{17}H_{26}O_5$ $[M+Na]^+$: 333.1678, found 333.1684. The less polar diastereomer was inseparable from residual starting material.



3-(benzyloxy)-2-methylcyclopent-2-en-1-one (1-39):

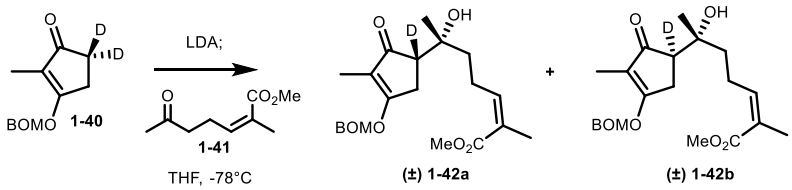
To a round bottom flask equipped with a stir bar and charged with toluene (50 mL, 0.50 M) was added 2-methylcyclopentane-1,3-dione (2.8 g, 25 mmol, 1.0 equiv), tosic acid monohydrate (0.48 g, 2.5 mmol, 0.10 equiv), and benzyl alcohol (7.8 mL, 75 mmol, 3.0 equiv). The flask was equipped with a Dean–Stark trap and the reaction mixture was refluxed for 2 h. Once the starting material had been fully consumed as indicated by TLC analysis, the reaction mixture was allowed to cool to ambient temperature and diluted with a saturated aqueous solution of $NaHCO_3$ (25 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was purified by flash column chromatography using 0 – 70% EtOAc in hexanes as the eluting solvent to afford **1-39** as a yellow oil (4.2 g, 84% yield): $\mathbf{R_f}$ = 0.40 (3:2, EtOAc:Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 5.21 (s, 2H), 2.64 (s, 2H), 2.44 – 2.36 (m, 2H), 1.66 (s, 3H). **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 205.4, 183.7, 136.1, 129.0, 128.6, 127.1, 117.1, 70.9, 33.7, 25.4, 6.3; **HRMS (ESI-TOF)** m / z calcd for $C_{13}H_{14}O_2$ $[M+Na]^+$: 225.0887, found 225.0889.



3-((Benzyloxy)methoxy)-2-methylcyclopent-2-en-1-one-5,5-d$_2$ (1-40):

To a round bottom flask charged with a stir bar and THF (3.0 mL, 0.47 M) was added diisopropylamine (1.0 mL, 7.2 mmol, 5.0 equiv). The solution was cooled to –78 °C and *n*BuLi(2.5 M in hexanes, 2.6 mL, 6.5 mmol 4.5 equiv) was added dropwise. The solution was warmed to 0 °C for 10 min, after which it was cooled to –78 °C and 3-((benzyloxy)methoxy)-2-methylcyclopent-2-en-1-one[9] (0.34 g, 1.4 mmol, 1.0 equiv) as a solution in THF (2.0 mL, 0.70

M) was added dropwise. The reaction was stirred for 1 h, after which ethanol-d_6 (0.50 mL) was added rapidly. The reaction was allowed to warm to rt and was then diluted with a saturated aqueous solution of NH_4Cl (5.0 mL). The mixture was transferred to a separatory funnel and the organic layer collected. The aqueous layer was extracted with CH_2Cl_2 (3 x 2.0 mL). The combined organic layers were washed with brine (5.0 mL), dried with Na_2SO4, and concentrated in vacuo. The residue was subjected to this same procedure twice more, after which it was purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford **1-40** as a yellow oil (0.27 g, 80% yield, 65% deuterium incorporation); $\mathbf{R_f}$ **=** 0.11 (1:1 EtOAc, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 5.32 (s, 2H), 4.72 (s, 2H), 2.76 – 2.67 (m, 2H), 2.48 – 2.39 (m, 0.71H, partially deuterated), 1.65 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 205.9, 205.8(8), 205.8(5), 182.3, 182.2(3), 182.1(8), 136.6, 128.7, 128.4, 128.1, 118.3(7), 118.3(5), 91.8, 71.2, 33.7, 33.5, 33.4, 33.3, 24.8(7), 24.7(9), 24.7, 6.1 (See general procedure for explanation of excess carbon peaks); **^{2}H NMR** (77 MHz, benzene) δ 1.50 (s, 1D). **HRMS (ESI-TOF)** *m / z* calcd for $C_{14}H_{16}O_3$ [undeuterated M + Na]$^+$: 255.0992, found 255.0995, *m / z* calcd for $C_{14}H_{15}DO_3$ [monodeuterated M + Na]$^+$: 256.1055, found 256.1054, *m / z* calcd for $C_{14}H_{14}D_2O_3$ (bis-deuterated M + Na)$^+$: 257.1118, found 257.1107.



Methyl (Z)-6-(4-((benzyloxy)methoxy)-3-methyl-2-oxocyclopent-3-en-1-yl-1-d)-6-hydroxy-2-methylhept-2-enoate (1-42):

Following general procedure A, **1-40** (89 mg, 0.38 mmol, 1.0 equiv) was deprotonated with LDA (42 mg, 0.40 mmol, 1.1 equiv) and reacted with **1-41**[9] (77 mg, 0.45 mmol, 1.2 equiv) in THF

(1.0 mL) at –78 °C. The crude residue was purified by flash column chromatography using 0 – 40% EtOAc in hexanes as the eluting solvent to afford **1-42a** and **1-42b** (0.10 g) containing 1.0 wt% CH_2Cl_2 (60% combined yield of **1-42a** and **1-42b**, with 62% and 67% deuterium incorporation, respectively, 1.7:1 dr):

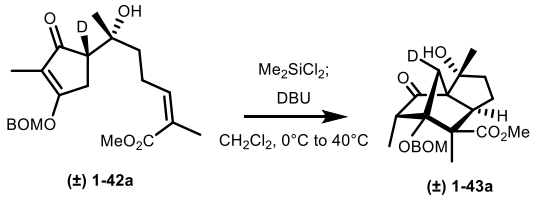
1-42a:

Clear oil; $\mathbf{R_f}$ **=** 0.42 (1:1 EtOAc:Hex, UV); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.93 (t, *J* = 7.6, 1H), 5.33 (s, 2H), 4.73 (d, *J* = 11.8, 1H), 4.70 (d, *J* = 12.0, 1H), 4.37 (s, 1H), 3.70 (s, 3H), 2.84 (d, *J* = 17.8, 1H), 2.66 (dd, *J* = 7.0, 2.6, 0.33H, partially deuterated), 2.62 – 2.45 (m, 3H), 1.86 (s, 3H), 1.61 (s, 3H), 1.46 – 1.36 (m, 2H), 1.15 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 208.2(2), 208.2(0), 182.6(3), 182.5(7), 168.5, 143.5, 136.5, 128.7, 128.4, 128.1, 127.0, 118.7(1), 118.6(9), 92.2, 73.9, 73.8, 71.5, 54.3, 51.3, 36.1, 28.6, 28.5, 25.1(3), 25.1(0), 23.9, 20.7, 5.9 (See general procedure for explanation of excess carbon peaks); **HRMS (ESI-TOF)** *m / z* calcd for $C_{23}H_{30}O_6$ [undeuterated M + Na]$^+$: 425.1935, found 425.1937, *m / z* calcd for $C_{23}H_{29}DO_6$ [deuterated M + Na]$^+$: 426.1998, found 426.1996; Relative stereochemistry was retrospectively deduced from the structure of **1-43a** under the assumption that deuterium migration took place via a suprafacial [1,5] sigmatropic rearrangement.

1-42b:

Clear oil; $\mathbf{R_f}$ **=** 0.57 (1:1 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 5.98 (t, *J* = 7.6 Hz, 1H), 5.35 (d, *J* = 6.9 Hz, 1H), 5.32 (d, *J* = 6.9 Hz, 1H), 3.70 (s, 3H), 2.88 (d, *J* = 17.8 Hz, 1H), 2.69 (dd, *J* = 7.0, 2.5 Hz, 0.38H, partially deuterated), 2.67 – 2.52 (m, 2H), 2.35 (d, *J* = 17.8 Hz, 1H), 1.88 (s, 3H), 1.63 (s, 3H), 1.60 – 1.45 (m, 2H), 1.00 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 209.2(7), 209.2(5), 182.8(5), 182.7(9), 168.5, 143.5, 136.5,

128.8, 128.5, 128.2, 127.1, 118.7(1), 118.6(9), 92.2, 73.7(4), 73.6(9) (See general procedure for explanation of excess carbon peaks), 71.6, 51.5, 51.4, 40.4(4), 40.4(3), 28.7, 28.6, 23.8, 22.7, 20.8, 5.9; **HRMS (ESI-TOF)** *m / z* calcd for $C_{23}H_{30}O_6$ [undeuterated M + Na]$^+$: 425.1935, found 425.1915, *m / z* calcd for $C_{23}H_{29}DO_6$ [deuterated M + Na]$^+$: 426.1998, found 426.2004; Relative stereochemistry was retrospectively deduced from the structure of **1-43b** under the assumption that deuterium migration took place via a suprafacial [1,5] sigmatropic rearrangement.

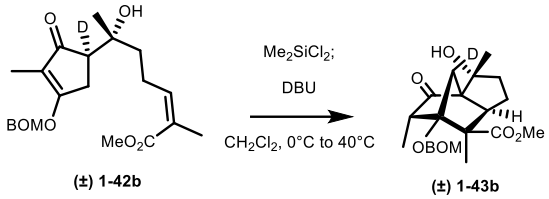


(±) 1-42a (±) 1-43a

Epi-methyl 6-((benzyloxy)methoxy)-3-hydroxy-3,5,7-trimethyl-4-oxooctahydro-3a,6-methanoindene-7-carboxylate-8-d (1-43a):

Following a modified general procedure 2, **1-42a** (35 mg, 90 μmol, 1.0 equiv) was reacted with dimethyldichlorosilane (22 μL, 0.18 mmol, 2.0 equiv) and DBU (80 μL, 0.54 mmol, 6.0 equiv) in CH_2Cl_2 (1.0 mL) from 0 °C to 40 °C. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-43a** as a clear oil (3.2 mg 9.0% yield, 67% deuterium incorporation, single diastereomer). Note: significant mass balance was lost through cleavage of the BOM group during HF workup: $\mathbf{R_f}$ **=** 0.27 (1:1 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 5.06 (d, *J* = 7.7, 1H), 4.83 (d, *J* = 7.6, 1H), 4.68 (d, *J* = 11.7, 1H), 4.61 (d, *J* = 11.7, 1H), 4.27 (s, 1H), 3.71 (s, 3H), 3.06 – 3.01 (m, 1H), 2.96 (q, *J* = 7.1, 1H), 2.34 (dd, *J* = 10.9, 6.0, 1H), 2.15 – 2.04 (m, 1H), 1.95 (dd, *J* = 9.9, 2.2, 0.33H, partially deuterated), 1.86 – 1.81 (m, 2H), 1.52 – 1.45

(m, 1H), 1.43 (s, 3H), 1.30 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 217.9, 174.1, 137.5, 128.7, 128.1(1), 128.0(9), 92.5, 89.0(4), 88.9(8), 79.8, 70.2, 68.2, 68.1, 58.2(6), 58.2(5), 57.1(5), 57.1(3), 56.1(5), 56.1(4), 51.9, 40.5, 40.3, 25.1, 24.6, 21.8, 10.3 (See general procedure for explanation of excess carbon peaks); **HRMS (ESI-TOF)** *m / z* calcd for $C_{23}H_{30}O_6$ [undeuterated M + Na]$^+$: 425.1935, found 425.1929, *m / z* calcd for $C_{23}H_{29}DO_6$ [deuterated M + Na]$^+$: 426.1998, found 426.1991; stereochemistry of the deuterium atom was established in reference to the protiated analogue of **1-43a**, for which full 2D NMR characterization has been performed.[9]

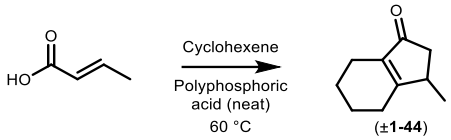


(±) 1-42b (±) 1-43b

Methyl 6-((benzyloxy)methoxy)-3-hydroxy-3,5,7-trimethyl-4-oxooctahydro-3a,6-methanoindene-7-carboxylate-8-d (1-43b):

Following a modified general procedure 2, **1-42b** (68 mg, 0.17 mmol, 1.0 equiv) was reacted with dimethyldichlorosilane (42 μL, 0.35 mmol, 2.0 equiv) and DBU (0.15 mL, 1.0 mmol, 6.0 equiv) in CH_2Cl_2 (2.0 mL) from 0 °C to 40 °C. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-43b** as a clear oil (5.0 mg, 7.0% yield, 50% deuterium incorporation, single diastereomer). Note: significant mass balance was lost through cleavage of the BOM group during HF workup: **R_f =** 0.27 (1:4 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.06 (d, *J* = 7.5, 1H), 4.83 (d, *J* = 7.5, 1H), 4.68 (d, *J* = 11.6, 1H), 4.61 (d, *J* = 11.6, 1H), 4.27 (s, 1H), 3.71 (s, 3H), 3.04 (d, *J* = 9.9, 0.50H, partially deuterated), 2.96 (q, *J* = 6.5, 1H), 2.34 (dd, *J* = 9.6, 6.0, 1H), 2.16 – 2.02 (m, 1H), 1.99 – 1.92 (m, 1H), 1.88 – 1.77 (m, 2H), 1.53 – 1.45 (m,

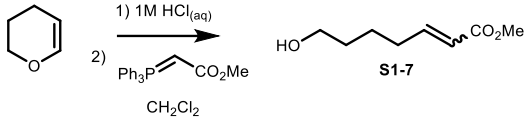
1H), 1.42 (s, 3H), 1.30 (s, 6H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 217.9, 174.1, 137.5, 128.7, 128.1(1), 128.0(8), 92.5, 89.0(4), 88.9(7), 79.7(6), 79.7(5), 70.2, 68.2, 68.1, 58.3, 57.1(5), 57.1(2), 56.2, 51.9, 40.6, 40.3, 25.1, 24.6, 21.8, 10.3 (See general procedure for explanation of excess carbon peaks); **HRMS (ESI-TOF)** *m / z* calcd for $C_{23}H_{30}O_6$ [undeuterated M + Na]$^+$: 425.1935, found 425.1951, *m / z* calcd for $C_{23}H_{29}DO_6$ [deuterated M + Na]$^+$: 426.1998, found 426.1990; stereochemistry of the deuterium atom was established in reference to the protiated analogue of **1-43b**, for which full 2D NMR characterization has been performed.[9]



3-Methyl-2,3,4,5,6,7-hexahydro-1H-inden-1-one (1-44)

No precaution was made to exclude air or water from the reaction. Following the literature procedure,[27] crotonic acid (2.6 g, 30 mmol, 1.0 equiv) and polyphosphoric acid (20 mL, 1.5 M) were slurried together in a round bottom flask under mechanical stirring due to the viscosity of polyphosphoric acid. This slurry was heated to 60 °C and cyclohexene (3.0 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was mechanically stirred for two h, after which 10% aqueous NaOH (20 mL) was added and the mixture was stirred for 16 h. The crude reaction was transferred to a separatory funnel and diluted with water (20 mL). This caused a significant exotherm and ice would be recommended instead for dilution. The aqueous mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 20% EtOAc in hexanes as the eluting solvent to afford **1-44** as a clear oil (0.47 g, 12% yield): All spectral data are consistent with those reported;[27] **^{1}H NMR**

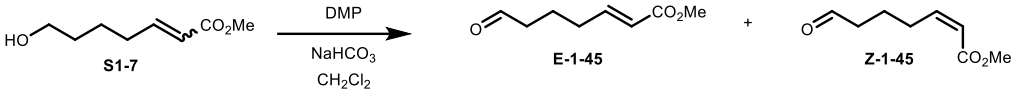
(500 MHz, $CDCl_3$) δ 2.77 – 2.68 (m, 1H), 2.61 (dd, *J* = 18.5, 6.4 Hz, 1H), 2.40 (dt, *J* = 19.7, 6.7 Hz, 1H), 2.21 – 2.08 (m, 3H), 1.95 (dd, *J* = 18.5, 1.9 Hz, 1H), 1.79 – 1.63 (m, 3H), 1.63 – 1.54 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 3H).



Methyl-7-hydroxyhept-2-enoate (S1-7):

No precaution was taken to exclude air or water from the reaction. A round bottom flask charged with dihydropyran (6.4 mL, 75 mmol, 1.0 equiv) was cooled to 0 °C and an aqueous solution of HCl (15 mL, 0.20 M) was added slowly. This mixture was stirred at 0 °C for 15 min and then 1 h at rt. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was then dissolved in THF (0.20 L) and transferred to a round bottom flask equipped with a magnetic stir bar and a reflux condenser. Methyl-2-(triphenyl-λ^5-phosphaneylidene) acetate (30 g, 90 mmol, 1.2 equiv) was added and the solution was refluxed for 13 h. After this time, the crude reaction mixture was concentrated in vacuo and diluted with a 7:3 Et_2O : pentanes solution. This mixture was stirred for 45 min, during which time triphenylphosphine oxide precipitated as a white solid. The mixture was filtered to remove the phosphine oxide and the filtrate was purified by flash column chromatography using 70% Et_2O in pentanes as the eluting solvent to afford pale yellow oil **S1-7** as an inseparable mixture of olefin isomers (6.5g, 54% yield of **S1-7,** 10:1 E:Z); all spectral data are consistent with those reported;[29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 15.6, 6.9, 1H, E isomer), 6.24 (dt, *J* = 11.5, 7.6, 1H, Z isomer), 5.82 (dt, *J* = 15.6, 1.5, 1H, E isomer), 5.78 (dt, *J* = 11.5, 1.6, 1H, Z

isomer), 3.71 (s, 3H, E isomer), 3.69 (s, 3H, Z isomer), 3.64 (t, *J* = 6.2, 2H, E and Z isomers), 2.66 (qd, *J* = 7.6, 1.6, 1H, Z isomer), 2.23 (qd, *J* = 7.2, 1.4, 2H, E isomer), 1.68 (bs, 1H, E and Z isomers), 1.62 – 1.48 (m, 4H, E and Z isomers).



Methyl-7-oxohept-2-enoate (1-45):

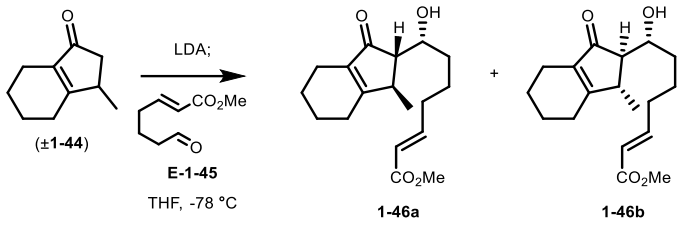
Following general procedure C, **S1-7** (6.5 g, 41 mmol, 1.0 equiv) was reacted with DMP (26 g, 0.61 mmol, 1.5 equiv) and $NaHCO_3$ (34 g, 0.41 mol, 20 equiv) in CH_2Cl_2 (0.40 L). The product mixture was purified by flash column chromatography using 0 – 20% EtOAc in hexanes as the eluting solvent to afford **E-1-45** (5.0 g) and **Z-1-45** (0.31 g) as pale yellow oils (83% combined yield of **1-45**).

E-1-45

All spectral data are consistent with those reported;[28] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.88 (dt, *J* = 16.0, 7.0, 1H), 5.81 (d, *J* = 15.6, 1H), 3.69 (s, 3H), 2.45 (t, *J* = 7.1, 2H), 2.22 (q, *J* = 7.1, 2H), 1.77 (p, *J* = 7.0, 2H).

Z-1-45

All spectral data are consistent with those reported;[29] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.18 (dt, *J* = 11.4, 7.6 Hz, 1H), 5.81 (d, *J* = 11.5 Hz, 1H), 3.69 (s, 3H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 1.83 – 1.72 (m, 2H).



Methyl (E)-7-hydroxy-7-(1-methyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-inden-2-yl)hept-2-enoate (1-46):

Following general procedure A, **1-44** (0.37 g, 2.7 mmol, 1.0 equiv) was deprotonated with LDA (0.32 g, 3.0 mmol, 1.1 equiv) and reacted with **E-1-45** (0.51 g, 3.3 mmol, 1.2 equiv) in THF (7.0 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 45% EtOAc in hexanes as the eluting solvent to afford **1-46a** as a crystalline white solid and **1-46b** as a clear oil (0.51 g, 61% combined yield of **1-46**, 1.3:1 dr):

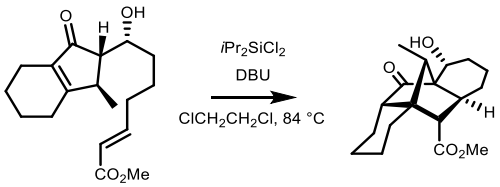
1-46a (Major diastereomer):

$\mathbf{R_f}$ = 0.53 (3:2 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.83 (d, *J* = 15.7 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.72 (s, 3H), 2.68 (d, *J* = 4.9 Hz, 1H), 2.40 (dt, *J* = 19.0, 6.3 Hz, 1H), 2.30 – 2.15 (m, 3H), 2.14 – 2.09 (m, 2H), 2.07 (t, *J* = 2.8 Hz, 1H), 1.84 – 1.64 (m, 5H), 1.63 – 1.55 (m, 1H), 1.55 – 1.47 (m, 3H), 1.18 (d, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 209.2, 178.1, 167.2, 149.2, 138.1, 121.4, 70.6, 59.6, 51.6, 38.0, 34.0, 32.1, 26.1, 24.9, 22.3, 21.7, 20.0, 18.4; **HRMS (ESI-TOF)** m / z calcd for $C_{18}H_{26}O_4$ $[M+Na]^+$: 329.1724, found 329.1717.

1-46b (Minor diastereomer):

$\mathbf{R_f}$ = 0.63 (3:2 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.5, 6.9 Hz, 1H), 5.83 (d, *J* = 15.7 Hz, 1H), 4.56 (bs, 1H), 3.71 (s, 3H), 3.62 (td, *J* = 9.2, 2.4 Hz, 1H), 2.40 (dt, *J* =

19.3, 6.3 Hz, 1H), 2.34 (qd, *J* = 6.6, 2.1 Hz, 1H), 2.30 – 2.20 (m, 2H), 2.19 – 2.08 (m, 3H), 1.90 (dd, *J* = 9.5, 2.2 Hz, 1H), 1.80 – 1.72 (m, 2H), 1.72 – 1.64 (m, 2H), 1.63 – 1.49 (m, 4H), 1.18 (d, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 211.1, 178.0, 167.2, 149.4, 137.4, 121.2, 72.2, 58.2, 51.5, 40.3, 35.2, 32.2, 26.1, 23.7, 22.2, 21.5, 19.9, 18.1; **HRMS (ESI-TOF)** m / z calcd for $C_{18}H_{26}O_4$ $[M+Na]^+$: 329.1724, found 329.1713. For both **1-46a** and **1-46b**, the relative stereochemistry of the methyl center and the adjacent methine center was determined by ^{1}H NOESY analysis (see page 243 and 247). The stereochemistry at the alcohol stereocenter was assigned based on analysis of coupling constants (see page 94 for details).

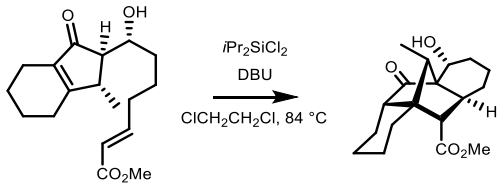


1-46a **1-47**

Methyl-4-hydroxy-11-methyl-10-oxododecahydro-4a,8a-methanoanthracene-9-carboxylate (1-47):

Following a modified general procedure B, **1-46a** (57 mg, 0.19 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (52 µL, 0.29 mmol, 1.5 equiv, single diastereomer) and DBU (85 µL) in $ClCH_2CH_2Cl$ (2.0 mL) from 0 to 84 °C for 16 hr. The product mixture was purified by flash column chromatography using 0 – 25% EtOAc in hexanes as the eluting solvent to afford **1-47** as a white crystalline solid (37 mg, 65% yield): $\mathbf{R_f}$ = 0.41 (3:7 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.19 (s, 1H), 3.67 (s, 3H), 2.42 (dt, *J* = 11.4, 5.7 Hz, 1H), 2.31 (q, *J* = 6.9 Hz, 1H), 2.27 (d, *J* = 5.0 Hz, 1H), 2.12 (dd, *J* = 11.7, 3.9 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.86 – 1.80 (m, 3H), 1.77 (dd, *J* = 13.9, 2.1 Hz, 1H), 1.74 – 1.68 (m, 1H), 1.67 – 1.60 (m, 2H), 1.48 – 1.35 (m, 3H), 1.31-1.25 (m, 1H), 1.25 – 1.17 (m, 1H), 1.06 (qt, *J* =

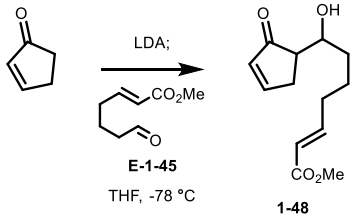
13.2, 3.6 Hz, 1H), 0.84 (d, *J* = 6.9 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 221. 8, 175.6, 66.0, 61.0, 57.8, 52.6, 52.0(4), 52.0(0), 46.7, 38.5, 31.7, 29.7, 29.0, 25.2, 21.6, 19.8, 18.1, 8.2; **HRMS (ESI-TOF)** m / z calcd for $C_{18}H_{26}O_4$ $[M+Na]^+$: 329.1724, found 329.1719. Relative stereochemistry was established by ^1H NOESY (see page 253).



1-46b **1-47**

Methyl-4-hydroxy-11-methyl-10-oxododecahydro-4a,8a-methanoanthracene-9-carboxylate (1-47):

Following a modified general procedure B, **1-46b** (0.12 g) was reacted with diisopropyldichlorosilane (0.10 mL) and DBU (0.16 mL) in $Cl_2CH_2CH_2Cl_2$ (4.0 mL) from 0 to 84 °C for 16 hr. The product mixture was purified by flash column chromatography using 0 – 20% EtOAc in hexanes as the eluting solvent to afford **1-47**. All spectral data were identical to the Diels–Alder adduct of **1-46a**.



1-48

Methyl (E)-7-hydroxy-7-(2-oxocyclopent-3-en-1-yl)hept-2-enoate (1-48):

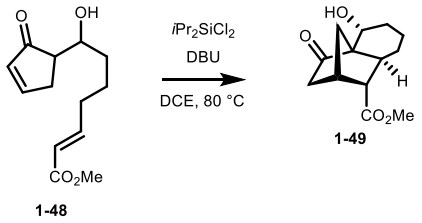
Following general procedure A, 2-cyclopenten-1-one (0.14 mL, 1.7 mmol, 1.0 equiv) was deprotonated with LDA (0.20 g, 1.9 mmol, 1.1 equiv) and reacted with **E-1-45** (0.29 g, 2.0 mmol, 1.2 equiv) in THF (4.0 mL) at –78 °C. The product mixture was purified by flash column

chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford the major diastereomer of **1-48** as a clear oil (0.13 g 34% yield).

Major diastereomer:

R_f = 0.33 (3:2 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.1 Hz, 1H), 7.01 – 6.91 (m, 1H), 6.21 (s, 1H), 5.83 (d, *J* = 15.7 Hz, 1H), 4.25 (s, 1H), 3.72 (s, 3H), 3.68 (t, *J* = 8.5 Hz, 1H), 2.83 (d, *J* = 17.2 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.29 – 2.19 (m, 2H), 1.73 (s, 1H), 1.62 – 1.47 (m, 3H); **^{13}C{^{1}H} NMR** (150 MHz, CDCl3) δ 213.5, 167.2, 164.8, 149.3, 134.0, 121.3, 72.0, 51.5, 49.5, 35.0, 32.7, 32.1, 23.6; **HRMS (ESI-TOF)** m / z calcd for $C_{13}H_{18}O_4$ $[M+Na]^+$: 261.1098, found 261.1097.

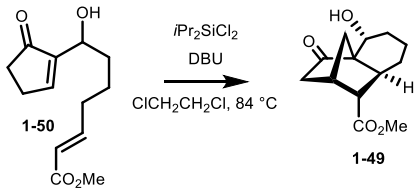
Minor diastereomer was unable to be isolated in acceptable purity



Methyl-5-hydroxy-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-49):

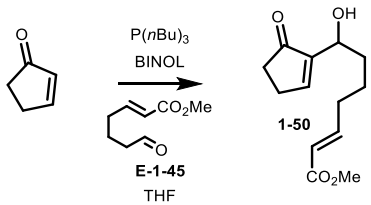
Following a modified general procedure B, **1-48** (0.11 g, 0.45 mmol, 1.0 equiv, single diastereomer) was reacted with diisopropyldichlorosilane (0.16 mL, 0.91 mmol, 2.0 equiv) and DBU (0.41 mL, 2.7 mmol, 6.0 equiv) in $ClCH_2CH_2Cl$ (3.0 mL) from 0 to 84 °C for 16 hr. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-49** as a white solid (49 mg 46% yield): **R_f** = 0.29 (3:7 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.03 (d, *J* = 2.3 Hz, 1H), 4.26 (t, *J* = 2.5 Hz, 1H), 3.68 (s, 3H), 2.90 (s, 1H), 2.63 (t, *J* = 4.3 Hz, 1H), 2.39 (dt, *J* = 12.0, 4.2 Hz,

1H), 2.16 (s, 2H), 2.11 (d, *J* = 10.4 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.85 – 1.77 (m, 2H), 1.57 (d, *J* = 10.5 Hz, 1H), 1.41 (dp, *J* = 13.8, 3.6 Hz, 1H), 1.34 (tq, *J* = 14.2, 2.7 Hz, 1H), 1.20 (qd, *J* = 12.9, 3.8 Hz, 1H), **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 221.5, 173.6, 67.0, 59.1, 53.4, 52.2, 42.3, 38.3, 37.0, 35.3, 31.5, 29.8, 18.6; **HRMS (ESI-TOF)** m / z calcd for $C_{13}H_{18}O_4$ $[M+Na]^+$: 261.1098, found 261.1099. The relative stereochemistry of the methine proton at the 6-5 ring junction was established based on its ~4 Hz coupling constant with the methine proton adjacent to the ester. The remaining relative stereochemistry was established by ^{1}H NOESY (see page 260).



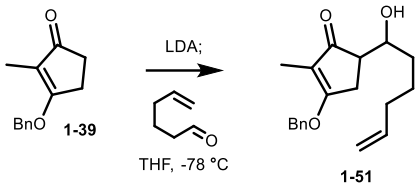
Methyl-5-hydroxy-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-49):

Following a modified general procedure B, **1-50** (0.35 g, 1.5 mmol, 1.0 equiv, single diastereomer) was reacted with diisopropyldichlorosilane (0.53 mL, 2.9 mmol, 2.0 equiv) and DBU (1.3 mL, 8.8 mmol, 6.0 equiv) in $Cl_2CH_2CH_2Cl$ (15 mL) from 0 to 84 °C for 16 hr. The product mixture was purified by flash column chromatography using 0 – 25% EtOAc in hexanes as the eluting solvent to afford **1-49** as a white solid (0.13 g 38% yield). All spectral data match the Diels–Alder adduct of **1-48**.



Methyl (E)-7-hydroxy-7-(5-oxocyclopent-1-en-1-yl)hept-2-enoate (1-50):

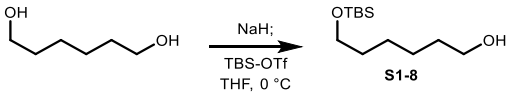
To a round bottom flask charged with THF (2.0 mL, 0.50 M) equipped with a stir bar was added racemic 1,1′-bi-2-naphthol (71 mg, 0.25 mmol, 0.25 equiv), 2-cyclopenten-1-one (0.25 mL, 3.0 mmol, 3.0 equiv), and **E-1-45** (0.15 g, 1.0 mmol, 1.0 equiv). The reaction mixture was sparged with argon over 10 min, after which tributylphosphine (0.12 mL, 0.50 mmol, 0.50 equiv) was added dropwise. The reaction mixture was stirred for 1 h, after which it was cooled to 0 °C and the reaction was quenched with HCl (1.5 mL). The mixture was transferred to a separatory funnel and the organic layer collected. The aqueous layer was extracted with EtOAc (3 x 2.0 mL) The crude residue was purified by flash column chromatography using 0 – 65% EtOAc in hexanes as the eluting solvent to afford **1-50** as a clear oil (0.15 g, 68% yield): $\mathbf{R_f}$ = 0.42 (7:3 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.93 (dt, *J* = 16.0, 6.5 Hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 4.44 (s, 1H), 3.70 (s, 3H), 2.92 (bs, 1H), 2.61 (s, 2H), 2.49 – 2.39 (m, 2H), 2.23 (q, *J* = 6.8 Hz, 2H), 1.74 – 1.59 (m, 3H), 1.58 – 1.46 (m, 1H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 210.1, 167.2, 158.1, 149.2, 147.7, 121.4, 67.6, 51.5, 35.4, 35.3, 32.0, 26.7, 24.0; **HRMS (ESI-TOF)** m / z calcd for $C_{13}H_{18}O_4$ $[M+Na]^+$: 261.1098, found 261.1094.



3-(benzyloxy)-5-(1-hydroxyhex-5-en-1-yl)-2-methylcyclopent-2-en-1-one (1-51)

Following general procedure A, **1-39** (1.0 g, 5.0 mmol, 1.0 equiv) was deprotonated with LDA (0.58 g, 5.4 mmol, 1.1 equiv) and reacted with hex-5-en-1-al (0.58 g, 5.9 mmol, 1.2 equiv) in THF (12 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 35% EtOAc in hexanes as the eluting solvent to afford yellow oil **1-51** as an

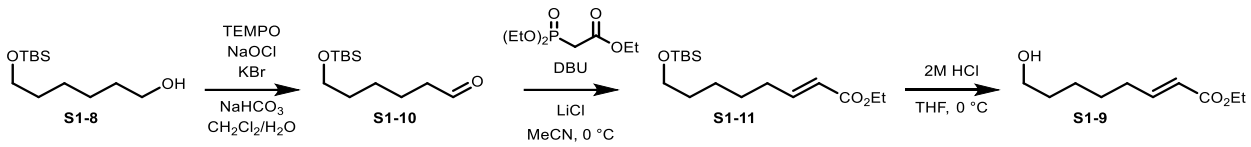
inseparable mixture of diastereomers (0.64 mg, 38% yield, 1:1.2 dr): $\mathbf{R_f}$ = 0.32 (2:3 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 5H), 5.84 – 5.74 (m, 1H), 5.28 – 5.21 (m, 2H), 5.03 – 4.97 (m, 1H), 4.97 – 4.93 (m, 1H), 4.19 – 4.14 (m, 0.46H), 3.66 – 3.59 (m, 0.55H), 2.79 (dd, *J* = 17.0, 6.6 Hz, 0.57H), 2.72 – 2.62 (m, 1H), 2.59 (dt, *J* = 6.2, 2.9 Hz, 0.48H), 2.46 (ddd, *J* = 9.6, 7.1, 2.8 Hz, 0.57H), 2.30 (d, *J* = 17.4 Hz, 0.58H), 2.14 – 2.05 (m, 2H), 1.69 – 1.65 (m, 3H), 1.65 – 1.57 (m, 1H), 1.54 – 1.36 (m, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.5, 206.7, 184.4, 183.7, 138.8, 138.7, 135.9, 135.7, 129.0(2), 129.0(0), 128.8, 128.7, 127.2(1), 127.1(6), 117.2, 116.3, 114.9, 114.7, 72.6, 71.4, 71.2, 70.1, 50.5, 49.0, 35.1, 34.1, 33.7, 33.7, 29.1, 26.6, 25.4, 24.3, 6.2, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{19}H_{24}O_3$ $[M+Na]^+$: 323.1618, found 323.1610.



6-((tert-butyldimethylsilyl)oxy)hexan-1-ol (S1-8):

To a 500 mL round bottom flask equipped with a stir bar was added hexane-1,6-diol (5.0 g, 42 mmol, 1.0 equiv) and THF (0.20 L, 0.21 M). This stirred solution was cooled to 0 °C and NaH (60% dispersion in mineral oil, 1.7 g, 42 mmol, 1.0 equiv) was added portion-wise. The resulting mixture was warmed to rt and stirred for an additional 3 h. After this time, TBSOTf (9.6 mL, 42 mmol, 1.0 equiv) was added dropwise and the solution was stirred for an additional 16 h, after which it was diluted with water (0.10 L) and transferred to a 500 mL separatory funnel. The crude reaction mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography using 0 – 25% EtOAc in hexanes as the eluting solvent to afford **S1-8** (2.1 g 22% yield). All spectral data are consistent with those reported;[30] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.64 (t, J = 6.7

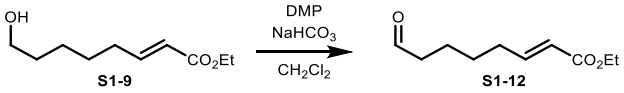
Hz, 1H), 3.60 (t, J = 6.6 Hz, 1H), 1.57 (p, J = 6.7 Hz, 1H), 1.52 (p, J = 6.7 Hz, 1H), 1.43 – 1.33 (m, 1H), 1.32 (bs, 1H), 0.89 (s, 2H), 0.04 (s, 1H); **$^{13}C\{^{1}H\}$ NMR** (125 MHz, $CDCl_3$) δ 63.3, 63.1, 32.9, 32.9, 26.1, 25.8, 25.7, 18.5, -5.1.



ethyl (E)-8-hydroxyoct-2-enoate (S1-9):

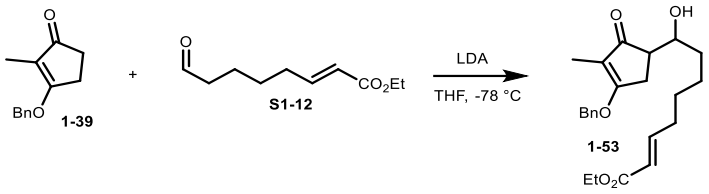
To a 200 mL round bottom flask equipped with a stir bar was added **S1-8** (2.1 g, 9.1 mmol, 1.0 equiv) and CH_2Cl_2 (23 mL, 0.40 M), with no efforts taken to exclude air or moisture. This solution was cooled to 0 °C and TEMPO (0.14 g, 0.90 mmol, 10 mol%) was added, followed by a solution of KBr (1.2 g, 10 mmol, 1.1 equiv) and $NaHCO_3$ (0.84 g, 10 mmol, 1.1 equiv) in water (46 mL, 0.20 M). To this vigorously stirred biphasic mixture was added NaOCl (8.25% w/v solution in H_2O, 7.5 mL, 10 mmol, 1.1 equiv) dropwise. After 15 min, the reaction mixture was transferred to a 250 mL separatory funnel and the organic phase was collected. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (0.10 L), dried over Na_2SO_4, and concentrated in vacuo to afford crude **S1-10**, which was taken to the next step without further purification. To a 250 mL round-bottom flask equipped with a stir bar was added triethylphosphonoacetate (2.6 mL, 13 mmol, 1.5 equiv), MeCN (0.10 L, 0.087 M), and LiCl (0.55 g, 13 mmol, 1.5 equiv). Next, DBU (1.9 mL, 13 mmol, 1.5 equiv) was added and the reaction mixture was cooled to 0 °C. A solution of crude **S1-10** in MeCN (10 mL, 0.91 M) was cannulated into the first solution dropwise, after which the reaction mixture was stirred for an additional 30 min. Cold water (50 mL) was added, and the resulting mixture was transferred to a 200 mL separatory funnel, where it was extracted with Et_2O (3 x 20 mL).

The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford crude **S1-11**, which was taken to the next step without further purification. It was transferred to a 250 mL round-bottom flask equipped with a stir bar and dissolved in THF (0.10 L, 0.091 M). This solution was cooled to 0 °C and HCl (2.0 M in H_2O, 44 mL, 0.21 M) was added. The resulting mixture was stirred for 5 h, after which it was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography using 30 % EtOAc in hexanes as the eluting solvent to afford **S1-9** (0.80 g 47% yield): All spectral data are consistent with those reported;[31] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (dt, J = 15.5, 7.0 Hz, 1H), 5.81 (d, J = 15.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 2.21 (qd, J = 7.5, 1.5 Hz, 2H), 1.57 (p, J = 6.5 Hz, 2H), 1.49 (p, J = 7.5 Hz, 2H), 1.44 – 1.34 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H).



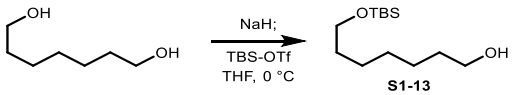
ethyl (E)-8-oxooct-2-enoate (S1-12):

Following general procedure C, **S1-9** (0.40 g, 2.2 mmol, 1.0 equiv) was reacted with DMP (1.4 g, 3.2 mmol, 1.5 equiv) and $NaHCO_3$ (3.6 g, 43 mmol, 20 equiv) in CH_2Cl_2 (20 mL). The product mixture was purified by flash column chromatography using 0 – 20 % EtOAc in hexanes as the eluting solvent to afford **S1-12** as a clear oil (0.18 g 46% yield): $\mathbf{R_f}$ = 0.57 (2:3 EtOAc:Hex, $KMnO_4$);[32] All spectral data are consistent with those reported; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.79 – 9.71 (m, 1H), 6.97 – 6.87 (m, 1H), 5.88 – 5.73 (m, 1H), 4.23 – 4.11 (m, 2H), 2.49 – 2.40 (m, 2H), 2.27 – 2.16 (m, 2H), 1.74 – 1.57 (m, 2H), 1.57 – 1.43 (m, 2H), 1.31 – 1.22 (m, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 202.3, 166.7, 148.4, 121.9, 60.3, 53.6, 43.7, 32.0, 27.6, 21.6, 14.4.



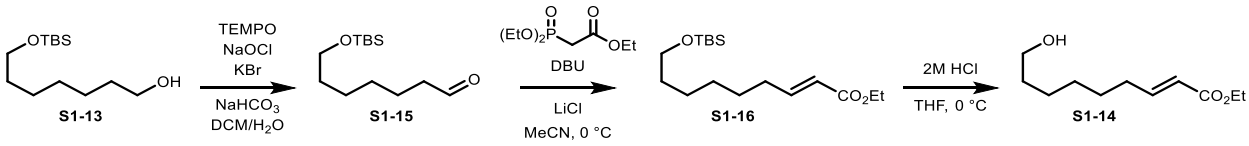
ethyl (E)-8-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-8-hydroxyoct-2-enoate (1-53):

Following general procedure A, **1-39** (0.17 g, 0.82 mmol, 1.0 equiv) was deprotonated with LDA (0.12 g, 1.2 mmol, 1.1 equiv) and reacted with **S1-12** (0.18 g, 0.99 mmol, 1.2 equiv) in THF (10 mL, 0.10 M) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 50% EtOAc in hexanes to afford **1-53** as a clear oil (30 mg 9.0% yield, 2:1 dr, inseparable): $\mathbf{R_f}$ = 0.23 (2:3 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 5H), 6.94 (dt, J = 11.5, 6.3 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 5.25 (s, 2H), 4.17 (q, J = 6.9 Hz, 2H), 4.14 – 4.10 (m, 0.39H), 3.62 (s, 0.67H), 2.79 (dd, J = 17.3, 6.9 Hz, 0.75H), 2.66 (s, 0.68H), 2.59 (s, 0.40H), 2.45 (t, J = 7.1 Hz, 0.76H), 2.30 (d, J = 17.4 Hz, 1H), 2.25 – 2.15 (m, 2H), 1.65 (m, 3H), 1.57 – 1.36 (m, 6H), 1.27 (m, 5H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.4, 206.6, 184.5, 183.7, 166.9, 166.8, 149.2, 149.1, 135.9, 135.7, 129.0(1), 128.9(5), 128.8, 128.7, 127.1(9), 127.1(5), 121.6, 121.5, 117.2, 116.3, 72.6, 71.4, 71.2, 70.1, 60.3, 50.5, 48.9, 35.5, 34.3, 32.3, 32.2, 29.0, 28.2, 28.0, 26.6, 25.7, 24.7, 14.4, 6.2, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{23}H_{30}O_5$ $[M+Na]^+$: 409.1991, found 409.1985.



7-((tert-butyldimethylsilyl)oxy)heptan-1-ol (S1-13):

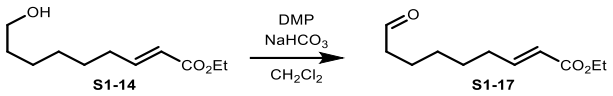
To a 500 mL round bottom flask equipped with a stir bar was added heptane-1,7-diol (6.0 g, 45 mmol, 1.0 equiv) and THF (0.20 L, 0.23 M). This stirred solution was cooled to 0 °C and NaH (1.1 g, 45 mmol, 1.0 equiv) was added portionwise. The resulting mixture was warmed to rt and stirred for an additional 3 h. After this time, TBSOTf (10 mL, 45 mmol, 1.0 equiv) was added dropwise and the solution was stirred for an additional 16 h, after which it was diluted with water (0.10 L) and transferred to a 500 mL separatory funnel. The crude reaction mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography using 0 – 25% EtOAc in hexanes as the eluting solvent to afford **S1-13** (1.7 g 16% yield): All spectral data are consistent with those reported;[33] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.63 (t, J = 6.6 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 1.62 – 1.44 (m, 4H), 1.42 – 1.23 (m, 7H), 0.89 (s, 9H), 0.04 (s, 6H).



ethyl (E)-9-hydroxynon-2-enoate (S1-14):

To a 200 mL round bottom flask equipped with a stir bar was added **S1-13** (1.7 g, 7.0 mmol, 1.0 equiv) and CH_2Cl_2 (18 mL, 0.39 M), with no efforts taken to exclude air or moisture. This solution was cooled to 0 °C and TEMPO (11 mg, 70 μmol, 1.0 mol%) was added, followed by a solution of KBr (0.92 g, 7.7 mmol, 1.1 equiv) and $NaHCO_3$ (0.65 g, 7.7 mmol, 1.1 equiv) in water (35 mL, 0.20 M). To this vigorously stirred biphasic mixture was added NaOCl (8.25% w/v solution in H_2O, 5.7 mL, 7.7 mmol, 1.1 equiv) dropwise. After 15 min, the reaction mixture was transferred to a 250 mL separatory funnel and the organic phase was collected. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with

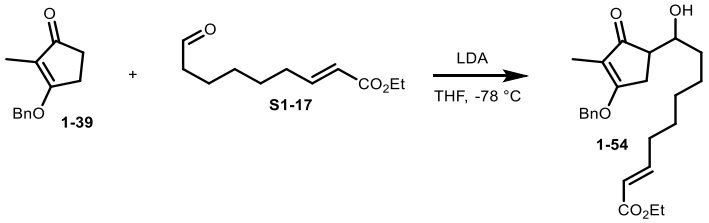
brine (0.10 L), dried over Na_2SO_4, and concentrated in vacuo to afford crude **S1-15**, which was taken to the next step without further purification. To a 250 mL round-bottom flask equipped with a stir bar was added triethylphosphonoacetate (2.0 mL, 9.7 mmol, 1.4 equiv), MeCN (65 mL, 0.11 M), and LiCl (0.41 g, 9.7 mmol, 1.4 equiv). Next, DBU (1.5 mL, 9.7 mmol, 1.4 equiv) was added and the reaction mixture was cooled to 0 °C. A solution of crude **S1-15** in MeCN (8.0 mL, 0.88 M) was cannulated into the first solution dropwise, after which the reaction mixture was stirred for an additional 30 min. Cold water (50 mL) was added, and the resulting mixture was transferred to a 200 mL separatory funnel, where it was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford crude **S1-16**, which was taken to the next step without further purification. It was transferred to a 250 mL round-bottom flask equipped with a stir bar and dissolved in THF (0.10 L, 0.070 M). This solution was cooled to 0 °C and HCl (2.0 M in H_2O, 35 mL, 0.20 M) was added. The resulting mixture was stirred for 5 h, after which it was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography using 30% EtOAc in hexanes as the eluting solvent to afford **S1-14** (0.50 g 36% yield over 3 steps): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (dt, J = 15.6, 6.9 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.63 (t, J = 6.6 Hz, 2H), 2.19 (q, J = 7.2 Hz, 2H), 1.64 (bs, 1H), 1.60 – 1.51 (m, 2H), 1.51 – 1.41 (m, 2H), 1.41 – 1.31 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H).



S1-14 S1-17

ethyl (E)-9-oxonon-2-enoate (S1-17):

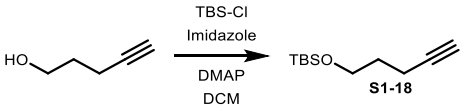
Following general procedure C, **S1-14** (0.50 g, 2.5 mmol, 1.0 equiv) was reacted with DMP (1.6 g, 3.8 mmol, 1.5 equiv) and $NaHCO_3$ (4.2 g, 50 mmol, 20 equiv) in CH_2Cl_2 (25 mL). The product mixture was purified by flash column chromatography using 0 – 20 % EtOAc in hexanes as the eluting solvent to afford **S1-17** as a clear oil (0.22 g 44% yield): $\mathbf{R_f}$ = 0.62 (2:3 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 6.93 (dt, J = 15.6, 4.8 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.20 (q, J = 7.2 Hz, 2H), 1.63 (s, 2H), 1.52 – 1.43 (m, 2H), 1.39 – 1.31 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 202.6, 166.8, 148.9, 121.7, 60.3, 43.9, 32.0, 28.7, 27.9, 21.9, 14.4.



ethyl (E)-9-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-9-hydroxynon-2-enoate (1-54):

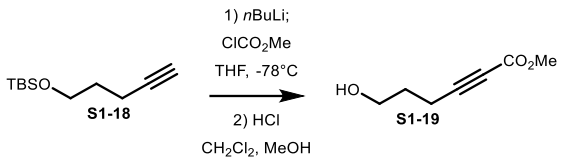
Following general procedure A, **1-39** (0.19 g, 0.93 mmol, 1.0 equiv) was deprotonated with LDA (0.14 g, 1.3 mmol, 1.4 equiv) and reacted with **S1-17** (0.22 g, 1.3 mmol, 1.4 equiv) in THF (10 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 50% EtOAc in hexanes to afford **1-54s** as a clear oil (24 mg 6.0% yield, 1.1:1 dr, inseparable): $\mathbf{R_f}$ = 0.53 (3:2 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 5H), 6.99 – 6.91 (m, 1H), 5.80 (d, J = 15.6 Hz, 1H), 5.25 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.15 – 4.09 (m, 1H), 3.65 – 3.59 (m, 1H), 2.79 (dd, J = 17.2, 6.8 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.59 (s, 1H), 2.45 (t, J = 7.1 Hz, 1H), 2.31 (d, J = 17.4 Hz, 1H), 2.19 (q, J = 7.1 Hz, 2H), 1.67 (s, 3H), 1.54 –

1.30 (m, 9H), 1.28 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 208.5, 206.7, 184.5, 183.7, 166.9(2), 166.8(9), 149.4, 149.3, 135.9, 135.7, 129.0(2), 128.9(6), 128.8, 128.7, 127.2,(0) 127.1(7), 121.4(9), 121.4(6), 72.7, 71.4, 71.2, 70.2, 60.3, 53.6, 50.5, 49.0, 35.6, 34.5, 32.2, 29.2, 29.1(3), 29.0(6), 28.0(8), 28.0(5), 26.6, 26.0, 24.9, 14.4, 6.2, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{24}H_{32}O_5$ $[M+Na]^+$: 423.2148, found 423.2152.



Tert-butyldimethyl(pent-4-yn-1-yloxy)silane (S1-18):

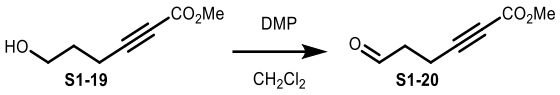
To a round bottom flask charged with a stir bar and CH_2Cl_2 (25 mL, 0.20 M) was added pent-4-yn-1-ol (0.48 mL, 5.0 mmol, 1.0 equiv), TBSCl (2.0 g, 13 mmol, 2.5 equiv), DMAP (61 mg, 0.50 mmol, 0.10 equiv), and imidazole (1.0 g, 15 mmol, 3.0 equiv) at 0 °C. The reaction was allowed to warm to rt and stirred for 2 h, after which time it was diluted with a saturated aqueous solution of NH_4Cl (20 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **S1-18** as a clear oil (0.67 g 67% yield of **S1-18**); all spectral data are consistent with those reported;[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.70 (t, *J* = 6.1, 2H), 2.27 (td, *J* = 7.1, 2.5, 2H), 1.92 (t, *J* = 2.5, 1H), 1.72 (p, *J* = 6.5, 2H), 0.90 (s, 9H), 0.05 (s, 6H).



Methyl 6-((tert-butyldimethylsilyl)oxy)hex-2-ynoate (S1-19):

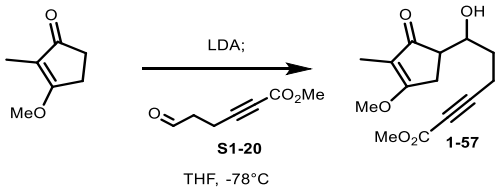
To a 50 mL round bottom flask equipped with a stir bar and THF (15 mL, 0.27 M) was added **S1-18** (0.67 g, 4.1 mmol, 1.0 equiv). The solution was cooled to –78 °C and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol, 1.2 equiv) was added dropwise. The reaction was warmed to 0 °C for 40 min, after which it was cooled to –78 °C and methyl chloroformate (0.41 mL, 5.3 mmol, 1.3 equiv) was added dropwise. The reaction was diluted with a saturated aqueous solution of NH_4Cl (10 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product mixture was then transferred to a 20 mL round bottom flask equipped with a magnetic stir bar, CH_2Cl_2 (1.3 mL, 0.25 M), and MeOH (5.5 mL, 0.60 M). Without taking any precautions to exclude air or water from the solution, it was cooled to 0 °C and HCl (1.0 M in H_2O, 5.0 mL, 0.66 M) was added slowly. The reaction was allowed to warm to rt and was stirred for 6 h, after which it was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was purified by flash column chromatography using 5 – 55% EtOAc in hexanes as the eluting solvent to afford **S1-19** as a yellow oil (0.25 g 51% yield of **S1-19**); all spectral data are consistent with those reported;[34] **^{1}H NMR** (500 MHz,

$CDCl_3$) δ 3.74 (s, 1H), 3.69 – 3.61 (m, 2H), 2.37 (t, *J* = 6.5, 2H), 1.71 – 1.65 (m, 4H), 1.63 (s, 1H).



Methyl 6-oxohex-2-ynoate (S1-20):

To a round bottom flask (used without flame-drying) charged with a magnetic stir bar and CH_2Cl_2 (3.0 mL, 0.33 M) was added **S1-19** (0.14 g, 1.0 mmol, 1.0 equiv) and DMP (0.46 g, 1.1 mmol, 1.1 equiv). The reaction was stirred for 45 min, after which it was poured into a biphasic solution of Et_2O(3.0 mL), saturated aqueous $Na_2S_2O_3$ (1.5 mL), and saturated aqueous $NaHCO_3$ (1.5 mL). This biphasic mixture was stirred vigorously for 45 min, after which it was added to a separatory funnel and the organic phase was collected. The aqueous phase was extracted with Et_2O (3 x 4.0 mL). The combined organic layers were washed with brine (4.0 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was purified by flash column chromatography using 5 – 30% EtOAc in hexanes as the eluting solvent to afford **S1-20** as a pale yellow oil (0.21 g 73% yield of **S10**); all spectral data are consistent with those reported;[34] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 3.74 (s, 1H), 2.61 (t, *J* = 7.1, 2H), 2.41 (t, *J* = 6.9, 2H), 1.89 (p, *J* = 7.0, 2H).



Methyl 6-hydroxy-6-(4-methoxy-3-methyl-2-oxocyclopent-3-en-1-yl) hex-2-ynoate (1-57)

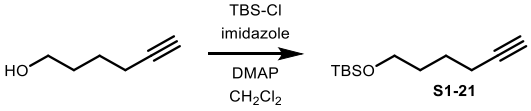
Following general procedure A, 3-methoxy-2-methylcyclopent-2-en-1-one (76 mg, 0.60 mmol, 1.0 equiv), was deprotonated with LDA (67 mg, 0.63 mmol, 1.1 equiv) and reacted with **S1-20** (0.10 g, 0.72 mmol, 1.2 equiv) in THF (1.5 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford **1-57** as a clear oil (63 mg 39% yield, 3:2 dr, relative configurations unassigned):

Major Diastereomer:

R_f = 0.55 (4:1 EtOAc, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.98 (s, 1H), 3.98 (s, 3H), 3.74 (s, 3H), 3.71 (td, *J* = 8.4, 2.4, 1H), 2.81 (dd, *J* = 17.4, 1.2, 1H), 2.58 (dtd, *J* = 17.4, 6.0, 1.2, 1H), 2.54 (dt, *J* = 17.4, 7.6, 1H), 2.46 (ddd, *J* = 9.8, 7.1, 2.8, 1H), 2.27 (d, *J* = 17.8, 1H), 1.85 – 1.77 (m, 1H), 1.77 – 1.69 (m, 1H), 1.62 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.1, 184.6, 154.3, 115.6, 89.7, 73.2, 71.3, 57.1, 52.7, 48.2, 33.7, 28.5, 14.4, 5.9; **FT-IR** (cm^{-1}) 3402, 2923, 2236, 1710, 1614; **HRMS (ESI-TOF)** *m / z* calcd for $C_{14}H_{18}O_5$ $[M+Na]^+$: 289.1052, found 289.1059.

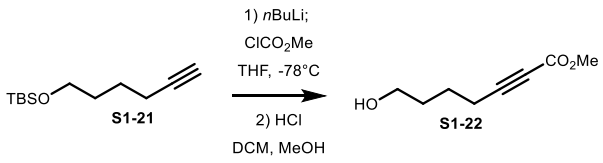
Minor Diastereomer:

R_f = 0.50 (4:1 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.21 (d, *J* = 4.5, 1H), 3.98 (s, 3H), 3.75 (s, 3H), 2.71 – 2.53 (m, 5H), 2.47 (dt, *J* = 17.4, 7.8, 1H), 1.71 (dd, *J* = 14.1, 7.2, 2H), 1.61 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.1, 184.6, 154.3, 115.6, 89.7, 73.2, 71.3, 57.1, 52.7, 48.2, 33.7, 28.5, 14.4, 6.0; **FT-IR** (cm^{-1}) 3390, 2922, 2236, 1710, 1614; **HRMS (ESI-TOF)** *m / z* calcd for $C_{14}H_{18}O_5$ $[M+Na]^+$: 289.1052, found 289.1064.



tert-butyl(hex-5-yn-1-yloxy)dimethylsilane (S1-21):

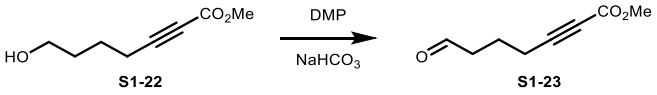
To a 50 mL round bottom flask charged with a stir bar and CH_2Cl_2 (25 mL, 0.20 M) was added hex-5-yn-1-ol (0.55 mL, 5.0 mmol, 1.0 equiv), TBSCl;(2.0 g, 13 mmol, 2.5 equiv), DMAP (61 mg, 0.50 mmol, 0.10 equiv), and imidazole (1.0 g, 15 mmol, 3.0 equiv) at 0 °C. The reaction was allowed to warm to rt and stirred for 2 h, after which time it was diluted with a saturated aqueous solution of NH_4Cl (20 mL) and transferred to a 100 mL separatory funnel. The organic layer was collected, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **S1-21** as a clear oil (0.87 g 82% yield of **S1-21**); All spectral data are consistent with those reported;[35] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.63 (t, J = 5.9 Hz, 2H), 2.21 (td, J = 6.5, 2.3 Hz, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.70 – 1.51 (m, 4H), 0.89 (s, J = 10.4 Hz, 9H), 0.05 (s, 3H).



methyl 7-hydroxyhept-2-ynoate (S1-22):

To a 50 mL round bottom flask equipped with a stir bar and THF (15 mL, 0.27 M) was added **S1-21** (0.87 g, 4.1 mmol, 1.0 equiv). The solution was cooled to –78 °C and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol, 1.2 equiv) was added dropwise. The reaction was warmed to 0 °C for 40 min, after which it was cooled to –78 °C and methyl chloroformate (0.41 mL, 5.3 mmol, 1.3 equiv) was added dropwise. The reaction was diluted with a saturated aqueous solution of NH_4Cl (10 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed

with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product mixture was then transferred to a 20 mL round bottom flask equipped with a magnetic stir bar, CH_2Cl_2 (1.6 mL, 2.6 M), and MeOH (5.5 mL, 0.74 M). Without taking any precautions to exclude air or water from the solution, it was cooled to 0 °C and HCl (1.0 M in H_2O, 6.0 mL, 0.68 M) was added slowly. The reaction was allowed to warm to rt and was stirred for 6 h, after which it was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The product mixture was purified by flash column chromatography using 5 – 55% EtOAc in hexanes as the eluting solvent to afford **S1-22** as a yellow oil (0.46 g 73% yield over 2 steps); All spectral data are consistent with those reported;[36] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.69 – 3.61 (m, 2H), 2.37 (t, J = 6.5 Hz, 2H), 1.71 – 1.65 (m, 4H), 1.63 (s, 1H).

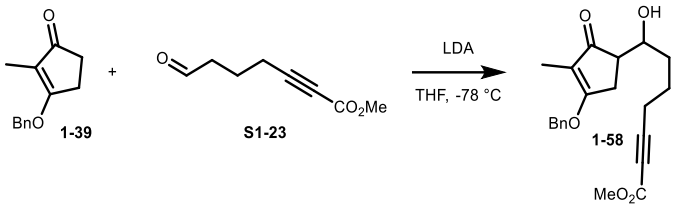


S1-22 **S1-23**

methyl 7-oxohept-2-ynoate (S1-23):

To a scintillation vial charged with a magnetic stir bar and CH_2Cl_2 (2.0 mL, 0.35 M) was added **S1-22** (0.11 g, 0.70 mmol, 1.0 equiv) and DMP (0.33 g, 0.77 mmol, 1.1 equiv). The reaction was stirred for 45 min, after which it was poured into a biphasic solution of Et_2O (3.0 mL), saturated aqueous $Na_2S_2O_3$ (1.5 mL), and saturated aqueous $NaHCO_3$ (1.5 mL). This biphasic mixture was stirred vigorously for 45 min, after which it was added to a separatory funnel and the organic phase was collected. The aqueous phase was extracted with Et_2O (3 x 4.0 mL). The combined organic layers were washed with brine (4.0 mL), dried over Na_2SO_4, and concentrated in vacuo.

The product mixture was purified by flash column chromatography using 5 – 30% EtOAc in hexanes as the eluting solvent to afford **S1-23** as a clear oil (60 mg 61% yield); all spectral data are consistent with those reported:[36] $\mathbf{R_f}$ = 0.47 (3:7 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 3.75 (s, 2H), 2.61 (t, J = 7.1 Hz, 1H), 2.41 (t, J = 7.0 Hz, 1H), 1.89 (p, J = 7.0 Hz, 2H).



methyl 7-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-7-hydroxyhept-2-ynoate (1-58):

Following general procedure A, **1-39** (0.14 g, 0.68 mmol, 1.0 equiv) was deprotonated with LDA (79 mg, 0.74 mmol, 1.1 equiv) and reacted with **S1-23** (0.13 g, 0.74 mmol, 1.2 equiv) in THF (2.0 mL) at –78 °C. The product mixture was purified by flash column chromatography using 55% EtOAc in hexanes as the eluting solvent to afford **1-58** as a yellow oil (52 mg 21% yield, 2:1 dr, relative configurations not assigned):

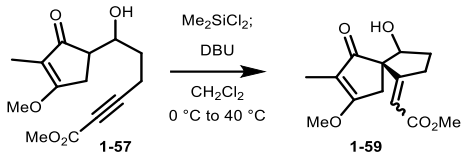
Major Diastereomer

$\mathbf{R_f}$ = 0.31 (3:2 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.38 – 7.34 (m, 3H), 5.25 (s, 2H), 3.73 (s, 3H), 3.62 (td, J = 9.2, 1.7 Hz, 1H), 2.82 (dd, J = 17.3, 6.9 Hz, 1H), 2.43 (ddd, J = 10.0, 7.5, 2.4 Hz, 1H), 2.39 (t, J = 6.9 Hz, 2H), 2.34 (d, J = 17.4 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.75 – 1.69 (m, 1H), 1.66 (s, 3H), 1.65 – 1.60 (m, 1H), 1.57 – 1.49 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 208.4, 183.9, 154.3, 135.6, 129.0, 128.8, 127.3, 116.2, 89.6,

73.4, 72.0, 71.5, 52.7, 48.7, 34.4, 29.0, 22.9, 18.4, 6.1; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{24}O_5$ $[M+Na]^+$: 379.1521, found 379.1523.

Minor Diastereomer

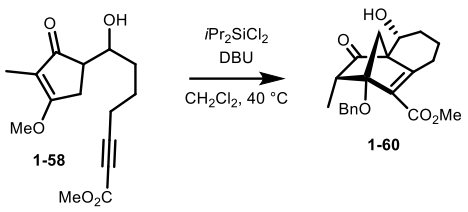
R_f = 0.23 (3:2 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 5H), 5.27 (d, J = 12.7 Hz, 1H), 5.25 (d, J = 12.5 Hz, 1H), 4.16 (d, J = 4.0 Hz, 1H), 3.75 (s, 3H), 2.68 (s, 2H), 2.61 (d, J = 2.6 Hz, 1H), 2.45 – 2.30 (m, 3H), 1.82 (tt, J = 14.3, 7.2 Hz, 1H), 1.71 – 1.59 (m, 5H), 1.53 (dd, J = 14.5, 7.3 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.5, 184.6, 154.3, 135.9, 129.0, 128.7, 127.3, 117.3, 89.5, 73.4, 71.3, 69.6, 52.7, 50.5, 33.4, 26.7, 24.2, 18.6, 6.2; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{24}O_5$ $[M+Na]^+$: 379.1521, found 379.1528.



Methyl 2-(4-hydroxy-8-methoxy-7-methyl-6-oxospiro[4.4]non-7-en-1-ylidene)acetate (1-59):

Following general procedure B, **1-57** (30 mg, 0.11 mmol, 1.0 equiv) was reacted with dimethyldichlorosilane (27 μL, 0.23 mmol, 2.0 equiv) and DBU (0.10 mL, 0.68 mmol, 6.0 equiv) in CH_2Cl_2 (1.2 mL) from 0 °C to 40 °C. The product mixture was purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford clear oil **1-59** as a 2.5:1 inseparable mixture of olefin isomers (4.5 mg, 15% yield, 2.5:1 dr, olefin geometries unassigned): **R_f =** Major isomer: 0.32 (4:1 EtOAc:Hex, UV), minor isomer: 0.25 (4:1 EtOAc:Hex); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.88 (s, 1H, maj.), 5.77 (s, 1H, min.), 4.60 (t, *J* = 6.9, 1H, min.), 4.35 (m, 1H, maj.), 3.99 (s, 3H, min.), 3.97 (s, 3H, maj.), 3.64 (s, 3H, maj.), 3.64 (s, 3H, min.), 3.34 (d, *J* = 12.3, 1H, min.), 3.27 (d, *J* = 8.4, 1H, maj.), 3.02 (m, 1H, maj. + min.),

2.84 (d, *J* = 17.8, 1H, maj.), 2.78 (d, *J* = 15.9, 1H, maj. + min.), 2.53 (dd, *J* = 16.7, 2.0, 1H, maj.), 2.45 (d, *J* = 17.7, 1H, min.), 2.29 (ddd, *J* = 16.1, 7.2, 1.8, 1H, min.), 2.15 – 2.08 (m, 1H, min.), 1.64 (s, 3H, maj.), 1.63 (s, 3H, min.); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 206.4 (min.), 205.7 (maj.), 185.4 (min.), 184.9 (maj.), 171.6 (maj. + min.), 136.7 (min.), 136.1 (maj.), 131.1 (maj.), 129.2 (min.), 116.6 (maj.), 116.2 (min.), 81.1 (maj.), 76.7 (min.), 65.3 (min.), 64.6 (maj.), 57.1 (maj.), 57.0 (min.), 52.1 (maj.), 52.0 (min.), 41.0 (maj.), 38.9 (min.), 35.7 (maj.), 34.2 (min.), 34.0 (maj.), 29.0 (min.), 6.2 (min.), 6.1 (maj.); **FT-IR** (cm^{-1}) 3405, 2972, 1735, 1688; **HRMS (ESI-TOF)** *m / z* calcd for $C_{14}H_{18}O_5$ $[M+Na]^+$: 289.1052, found 289.1046.



methyl-2-(benzyloxy)-5-hydroxy-3-methyl-4-oxo-3,4,5,6,7,8-hexahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-60):

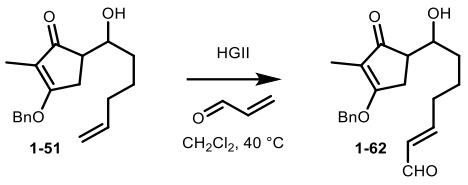
Following general procedure B, **1-58** (85 mg, 0.24 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (86 μL, 0.48 mmol, 2.0 equiv) and DBU (0.21 mL, 1.4 mmol, 6.0 equiv) in CH_2Cl_2 (6.0 mL) from 0 to 40 °C. The product mixture was purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford **1-60** (20 mg 25% yield, 4:1 dr):

Major Diastereomer

R_f = 0.36 (3:2 EtOAc, Hex); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 5.89 (s, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 10.8 Hz, 1H), 3.93 (s, 1H), 3.74 (s, 3H), 3.69 – 3.63 (m, 1H), 2.69 (q, J = 7.3 Hz, 1H), 2.42 – 2.32 (m,

1H), 2.25 – 2.16 (m, 3H), 2.05 – 1.99 (m, 1H), 1.96 (d, J = 9.3 Hz, 1H), 1.05 (d, J = 7.3 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 210.4, 171.2, 138.1, 129.2, 128.6, 128.0, 127.9, 127.7, 85.4, 69.8, 66.3, 63.4, 53.7, 52.0, 46.7, 44.7, 28.5, 25.8, 8.6; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{24}O_5$ $[M+Na]^+$: 379.1521, found 379.1534.

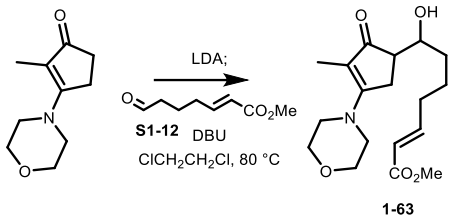
Minor diastereomer was unable to be isolated in acceptable purity.



(E)-7-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-7-hydroxyhept-2-enal (1-62):

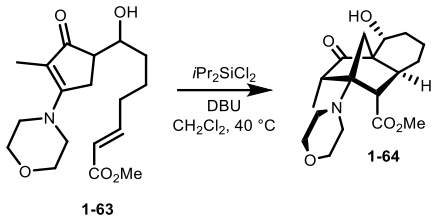
To a scintillation vial equipped with a stir bar and charged with CH_2Cl_2 (2.0 mL, 0.25 M) was added **1-51** (0.12 g, 0.40 mmol, 1.0 equiv), acrolein (0.13 mL, 2.0 mmol, 5.0 equiv), and Hoveyda-Grubbs 2nd Generation catalyst (13 mg, 0.020 mmol, 5.0 mol%). The vial was sealed and the mixture was heated to 40 °C for 13 h. The reaction mixture was transferred to a separatory funnel and washed with an aqueous solution of tris(hydroxymethyl)phosphine (10 mL, 0.25 M).[23] The aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL), after which the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 65% EtOAc in hexanes as the eluting solvent to afford the more polar diastereomer of **1-62** (32 mg 24% yield): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.51 (d, J = 7.9 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.39 – 7.34 (m, 4H), 6.84 (dt, J = 15.6, 7.2 Hz, 1H), 6.12 (dd, J = 15.6, 7.8 Hz, 1H), 5.25 (s, 2H), 4.82 (bs, 1H), 3.67 – 3.60 (m, 1H), 2.79 (dt, J = 15.0, 7.6 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.42 – 2.32 (m, 2H), 2.28 (d, J = 17.4 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.68 (s, 3H), 1.66 – 1.58 (m, 2H), 1.53 – 1.44 (m, 2H); **$^{13}C\{^{1}H\}$ NMR**

(150 MHz, $CDCl_3$) δ 208.3, 194.2, 183.7, 158.6, 135.6, 133.3, 129.1, 128.9, 127.2, 116.4, 72.4, 71.5, 48.9, 35.1, 32.7, 29.1, 23.5, 6.2; **HRMS (ESI-TOF)** m / z calcd for $C_{20}H_{24}O_4$ $[M+Na]^+$: 351.1572, found 351.1577. The less polar diastereomer of **1-62** was unable to be isolated in acceptable purity.



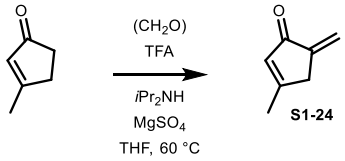
methyl (E)-7-hydroxy-7-(3-methyl-4-morpholino-2-oxocyclopent-3-en-1-yl)hept-2-enoate (1-63):

Following general procedure A, 2-methyl-3-morpholinocyclopent-2-en-1-one (0.70 g, 3.9 mmol, 1.0 equiv) was deprotonated with LDA (0.45 g, 4.3 mmol, 1.1 equiv) and reacted with **S1-12** (0.72g, 4.6 mmol, 1.2 equiv) in THF (10 mL) at –78 °C. The product mixture was purified by flash column chromatography using 0 – 10 % MeOH in CH_2Cl_2 as the eluting solvent. The resulting crude product was further purified by tritration with THF to afford the more polar diastereomer of **1-63** as a white solid (0.11 g 8.1% yield): $\mathbf{R_f}$ = 0.48 (1:19 MeOH:CH_2Cl_2, UV); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.5, 7.0 Hz, 1H), 5.81 (d, J = 15.7 Hz, 1H), 4.11 (s, 1H), 3.77 – 3.72 (m, 4H), 3.70 (s, 3H), 3.65 – 3.56 (m, 4H), 2.64 (d, J = 4.8 Hz, 1H), 2.49 (s, 1H), 2.48 – 2.42 (m, 2H), 2.23 (dd, J = 14.0, 7.1 Hz, 2H), 1.84 (s, J = 11.6 Hz, 3H), 1.76 – 1.64 (m, 1H), 1.55 – 1.35 (m, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 204.8, 171.3, 167.2, 149.4, 121.3, 108.8, 70.0, 66.9, 51.5, 49.0, 48.5, 33.8, 32.1, 28.5, 24.7, 10.5; **HRMS (ESI-TOF)** m / z calcd for $C_{18}H_{27}NO_5$ $[M+Na]^+$: 360.1787, found 360.1770. The less polar diastereomer of **1-63** was unable to be isolated in acceptable purity.



methyl-5-hydroxy-3-methyl-2-morpholino-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-64):

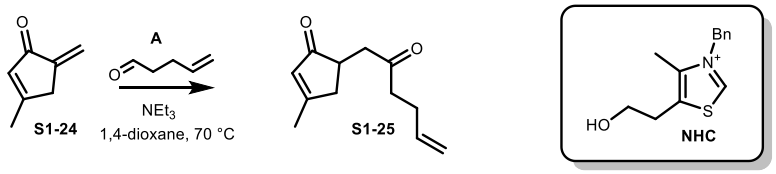
Following general procedure B, **1-63** (98 mg, 0.29 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (0.11 mL, 0.58 mmol, 2.0 equiv) and DBU (0.26 mL, 1.7 mmol, 6.0 equiv) in CH_2Cl_2 (3.0 mL) from 0 to 40 °C. The product mixture was purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **1-64** (41 mg 41% yield): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.24 (s, 1H), 3.75 (s, 4H), 3.66 (s, 3H), 2.86 – 2.78 (m, 2H), 2.77 (s, 1H), 2.69 – 2.62 (m, 2H), 2.62 – 2.51 (m, 2H), 2.12 (d, J = 10.1 Hz, 1H), 1.97 (d, J = 10.9 Hz, 1H), 1.90 – 1.74 (m, 2H), 1.46 – 1.28 (m, 3H), 1.16 (dd, J = 25.5, 12.7 Hz, 1H), 0.97 (d, J = 7.0 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 221.3, 172.7, 74.2, 67.5, 67.1, 56.3, 52.0, 50.5, 50.2, 47.6, 35.8, 35.2, 31.8, 29.5, 18.3, 8.0.



3-methyl-5-methylenecyclopent-2-en-1-one (S1-24):

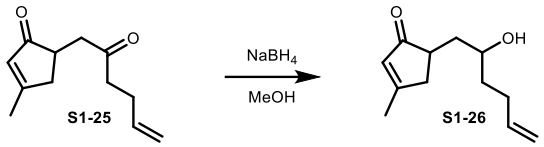
According to literature precedent,[37] 3-methylcyclopent-2-en-1-one (1.0 mL, 10 mmol, 1.0 equiv) was reacted with para-formaldehyde (2.4 g, 80 mmol, 8.0 equiv), TFA (3.0 mL, 40 mmol, 4.0 equiv), *i*Pr_2NH (2.8 mL, 20 mmol, 2.0 equiv), and anhydrous $MgSO_4$ (1.2 g, 10 mmol, 1.0 equiv) in THF (50 ml, 0.20 M). The crude product was purified by flash column chromatography using

0 – 15% EtOAc in hexanes as the eluting solvent to afford **S1-24** as a yellow oil (0.10 g 10% yield): $\mathbf{R_f}$ = 0.35 (3:7 EtOAc:Hex, UV); All spectral data are consistent with those reported;[38] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.12 (s, 1H), 6.01 (s, 1H), 5.34 (s, 1H), 3.15 (s, 2H), 2.16 (s, 3H).



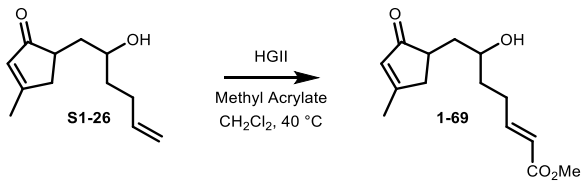
3-methyl-5-(2-oxohex-5-en-1-yl)cyclopent-2-en-1-one (S1-25):

To a dry scintillation vial equipped with a stir bar was added **S1-24** (0.10 g, 1.0 mmol, 1.0 equiv), pent-4-enal (0.30 mL, 3.0 mmol, 3.0 equiv), NEt_3 (71 μL, 0.50 mmol, 0.50 equiv), and 1,4-dioxane (2.0 mL, 0.50 M). To this stirred solution was added **NHC** (80 mg, 0.30 mmol, 30 mol%) and the reaction mixture was heated to 70 °C for 16 h. After this time, the mixture was diluted with water (1.0 mL) and transferred to a 30 mL separatory funnel, where it was extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **S1-25** as a yellow oil (68 mg 35% yield): $\mathbf{R_f}$ = 0.27 (3:7 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.93 – 5.88 (m, 1H), 5.76 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 4.99 (ddd, J = 17.1, 3.3, 1.6 Hz, 1H), 4.95 (ddd, J = 10.2, 2.8, 1.3 Hz, 1H), 2.95 (dd, J = 17.9, 3.5 Hz, 1H), 2.85 (dddd, J = 18.5, 6.8, 1.6, 0.9 Hz, 1H), 2.73 (ddt, J = 9.9, 6.5, 3.1 Hz, 1H), 2.56 – 2.42 (m, 3H), 2.33 – 2.26 (m, 2H), 2.22 – 2.15 (m, 1H), 2.09 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 210.7, 208.4, 177.6, 137.0, 129.7, 115.4, 43.7, 42.3, 41.8, 40.4, 27.8, 19.5; **HRMS (ESI-TOF)** m / z calcd for $C_{14}H_{20}O_4$ $[M+Na]^+$: 215.1048, found 215.1057.



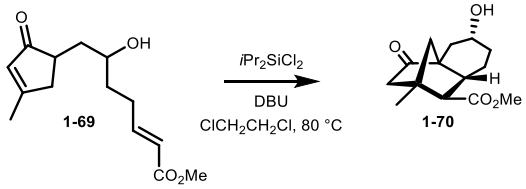
5-(2-hydroxyhex-5-en-1-yl)-3-methylcyclopent-2-en-1-one (S1-26):

To a scintillation vial equipped with a stir bar was added **S1-25** (68 mg, 0.35 mmol, 1.0 equiv) and MeOH (4.0 mL, 0.088 M). To this solution was added $NaBH_4$ (7.0 mg, 0.18 mmol, 0.50 equiv). After 30 min, incomplete conversion was observed by TLC analysis. Additional equivalents of $NaBH_4$ were added until complete conversion was observed by TLC, after which the reaction mixture was diluted with water (3.0 mL) and transferred to a 30 mL separatory funnel, where it was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo to afford **S1-26** as a yellow oil (56 mg 82% yield, 1.7:1 dr, inseparable): $\mathbf{R_f}$ = 0.17 (2:3 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.95 – 5.86 (m, 1H), 5.87 – 5.74 (m, 1H), 5.02 (d, J = 17.1 Hz, 1H), 4.94 (d, J = 10.1 Hz, 1H), 3.93 – 3.67 (m, 1H), 3.62 (br s, 1H), 2.89 – 2.55 (m, 2H), 2.40 – 1.93 (m, 6H), 1.88 – 1.67 (m, 1H), 1.65 – 1.41 (m, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 213.5, 212.9, 178.4, 178.3, 138.6(4), 138.5(9), 129.8, 129.6, 114.8(3), 114.7(5), 70.6, 70.0, 45.4, 43.9, 41.2, 41.0, 39.0(5), 39.0(2), 37.4, 36.6, 30.2, 30.1, 19.5; **HRMS (ESI-TOF)** m / z calcd for $C_{12}H_{18}O_2$ $[M+Na]^+$: 217.1205, found 217.1211.



methyl (E)-6-hydroxy-7-(4-methyl-2-oxocyclopent-3-en-1-yl)hept-2-enoate (1-69):

To a dry scintillation vial equipped with a stir bar and charged with CH_2Cl_2 (1.0 mL, 0.20 M) was added **S1-26** (56 mg, 0.29 mmol, 1.0 equiv), methyl acrylate (0.13 mL, 1.5 mmol, 5.0 equiv), and Hoveyda-Grubbs 2nd Generation catalyst (5.0 mg, 8.7 μmol, 5.0%). The vial was sealed and the mixture was heated to 40 °C for 13 h. The reaction mixture was transferred to a separatory funnel and washed with an aqueous solution of tris(hydroxymethyl)phosphine (10 mL, 0.25 M).[23] The aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL), after which the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford **1-69** (27 mg 37% yield, 1.7:1 dr, inseparable): $\mathbf{R_f}$ = 0.15 (1:1 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.02 – 6.91 (m, 1H), 5.90 (d, J = 9.8 Hz, 1H), 5.83 (dd, J = 15.8, 5.0 Hz, 1H), 4.04 (s, J = 51.6 Hz, 1H), 3.90 – 3.81 (m, 1H), 3.76 – 3.66 (m, 4H), 2.84 (td, J = 18.9, 6.7 Hz, 1H), 2.69 – 2.59 (m, 1H), 2.45 – 2.21 (m, 3H), 2.11 (s, 3H), 1.86 – 1.41 (m, 5H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.6, 212.8, 178.7, 178.5, 167.2, 167.2, 149.4, 149.2, 129.7, 129.6, 121.2(1), 121.2(0), 70.5, 69.1, 51.5, 45.7, 43.6, 41.1(2), 41.1(1), 39.0, 39.1, 36.4, 35.6, 28.8, 28.5, 19.5.



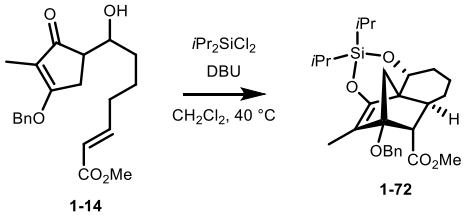
methyl (2R,8aR)-6-hydroxy-2-methyl-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-70):

Following a modified general procedure B, **1-69** (27 mg, 0.11 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (29 μL, 0.16 mmol, 1.5 equiv) and DBU (48 μL, 0.32 mmol, 3.0

equiv) in $ClCH_2CH_2Cl$ (1.0 mL) from 0 to 84 °C for 16 hr. The product mixture was purified by flash column chromatography using 0 – 50% to afford **1-70** as a white crystalline solid (12 mg 45% yield, 4:1 dr):

Major Diastereomer

R_f = 0.41 (1:1 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.44 (d, J = 9.6 Hz, 1H), 3.98 (d, J = 6.3 Hz, 1H), 3.73 (s, 3H), 2.31 (ddd, J = 12.9, 7.4, 2.7 Hz, 1H), 2.18 (d, J = 14.7 Hz, 1H), 2.14 (d, J = 7.5 Hz, 1H), 2.12 – 2.05 (m, 2H), 1.96 – 1.88 (m, 2H), 1.78 (dd, J = 14.7, 4.4 Hz, 1H), 1.63 – 1.56 (m, 2H), 1.46 (tt, J = 13.9, 3.8 Hz, 1H), 1.19 (s, 4H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 221.3, 175.0, 64.9, 60.0, 54.1, 53.9, 52.0, 49.3, 48.7, 46.3, 35.0, 33.6, 22.4, 18.4; **HRMS (ESI-TOF)** m / z calcd for $C_{14}H_{20}O_4$ $[M+Na]^+$: 275.1259, found 275.1266. Minor diastereomer was unable to be isolated in acceptable purity, **M.P.** 100 – 102 °C. Relative stereochemistry was established by X-ray diffraction (see page 90).

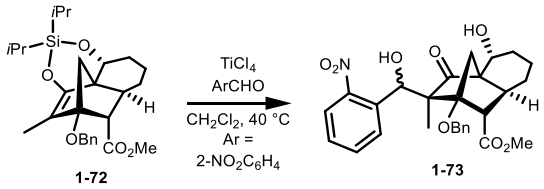


1-14 1-72

Methyl-5-(benzyloxy)-2,2-diisopropyl-4-methyl-6,6a,7,8,9,9a-hexahydro-5H-3a1,5-methanonaphtho[1,8-de][1,3,2]dioxasiline-6-carboxylate (1-72):

Following a modified general procedure B, **1-14** (0.17 g, 0.52 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (0.19 mL, 1.0 mmol, 2.0 equiv) and DBU (0.46 mL, 3.1 mmol, 6.0 equiv) in CH_2Cl_2 (5.0 mL) from 0 to 40 °C. In place of the HF • pyr workup described in general procedure B, the reaction mixture was instead cooled to 0 °C and a saturated aqueous solution of

$NaHCO_3$ (2.0 mL) was added slowly. The biphasic mixture was transferred to a separatory funnel and the organic layer collected. The aqueous layer was extracted with CH_2Cl_2 (3 x 3.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. A neutralized silica gel column was prepared by first passing three column volumes of 5% Et_3N in hexanes through the packed column. The crude residue was then loaded onto the column as a solution in a minimal amount of toluene and eluted using 0 – 5% EtOAc:Hex as the eluting solvent to afford **1-72** as a yellow oil (0.15 g, 62% yield, single diastereomer): $\mathbf{R_f}$ = 0.25 (1:19 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.24 (m, 1H), 4.61 (s, 2H), 4.38 (s, 1H), 3.67 (s, 3H), 2.79 (d, *J* = 4.0 Hz, 1H), 2.51 – 2.44 (m, 1H), 2.13 – 2.06 (m, 1H), 1.91 (d, *J* = 7.3 Hz, 1H), 1.84 (d, *J* = 12.7 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.58 (s, 1H), 1.51 (s, 3H), 1.47 – 1.41 (m, 3H), 1.24 – 1.18 (m, 1H), 1.12 – 1.07 (m, 13H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 173.8, 154.1, 139.3, 128.4, 127.3, 127.0, 109.9, 92.6, 70.0, 67.7, 56.1, 51.7, 49.8, 48.0, 41.2, 32.1, 31.0, 19.0, 17.2, 16.9(3), 16.9(0), 16.8, 13.6, 12.5, 7.6; **HRMS (ESI-TOF)** m / z calcd for $C_{27}H_{38}O_5Si$ $[M+Na]^+$: 493.2381, found 493.2377. Relative stereochemistry was established in analogy to **1-15** as well as **1-75**.

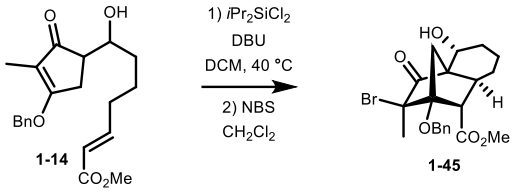


Methyl-2-(benzyloxy)-5-hydroxy-3-(hydroxy(2-nitrophenyl)methyl)-3-methyl-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-73):

To a round bottom flask equipped with a stir bar was added **1-72** (0.12 g, 0.25 mmol, 1.0 equiv), 2-nitro-benzaldehyde (75 mg, 0.50 mmol, 2.0 equiv), and CH_2Cl_2 (5.0 mL, 0.050 M). $TiCl_4$ (68

μL, 0.62 mmol, 2.5 mmol) was added dropwise and the reaction mixture was heated to 40 °C for one h, after which it was cooled and diluted with CH_2Cl_2 (5.0 mL). The mixture was transferred to a separatory funnel and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford **1-73** as a foamy white solid. Despite a sizeable R_f difference, the two diastereomers failed to separate by either automated or manual flash column chromatography on silica gel. Thus, the product was isolated as a mixture of diastereomers (71 mg, 55% yield of **1-73,** 1.7:1 dr): $\mathbf{R_f}$ = 0.34 (more polar diastereomer) and 0.58 (less polar diastereomer) (3:2 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 0.35H), 7.70 (d, *J* = 8.1 Hz, 0.59H), 7.62 – 7.56 (m, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.40 – 7.32 (m, 3H), 5.62 (bs, 0.36H), 5.35 – 5.27 (m, 1H), 5.27 – 5.22 (m, 1H), 4.57 (bs, 0.36H), 4.47 (bs, 0.58H), 3.79 (bs, 0.55H), 3.54 (s, 0.60H), 3.44 (s, 0.59H), 3.30 (s, 1.1H), 3.28 (s, 1.68H), 3.13 (dt, *J* = 12.7, 2.6 Hz, 0.64H), 3.02 – 2.95 (m, 0.76H), 2.91 (d, *J* = 18.1 Hz, 0.61H), 2.71 (dd, *J* = 10.2, 4.3 Hz, 0.61H), 2.53 (dd, *J* = 9.5, 1.5 Hz, 0.36H), 2.40 (dq, *J* = 12.9, 2.7 Hz, 0.37H), 2.32 (d, *J* = 17.9 Hz, 0.39H), 2.12 (d, *J* = 19.2 Hz, 0.68H), 2.02 – 1.91 (m, 1H), 1.91 – 1.85 (m, 1H), 1.83 (s, 2H), 1.76 (d, *J* = 11.6 Hz, 1H), 1.63 (d, *J* = 13.1 Hz, 0.55H), 1.51 (s, 1H), 1.45 (qd, *J* = 13.2, 3.1 Hz, 1H), 1.33 (t, *J* = 13.1 Hz, 0.73H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 212.2, 209.9, 185.9, 183.5, 175.9, 173.1, 149.2, 147.1, 139.0, 136.2, 135.5, 135.4, 133.9, 132.9, 129.1, 129.0, 128.9(2), 128.8(6), 128.8, 128.6(4), 128.5(6), 128.1, 127.6, 127.4, 125.3, 124.1, 117.2, 116.0, 73.1, 72.1, 71.8, 71.6, 67.7, 66.5, 56.7, 54.3, 53.7, 52.1, 51.7, 49.7, 36.1, 34.8, 33.7, 33.3, 29.4(4), 29.3(6), 28.8, 25.2, 19.9, 19.5, 6.3, 5.9; **HRMS (ESI-TOF)**

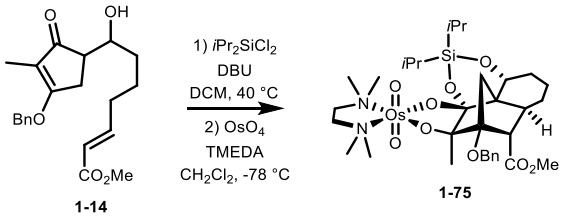
m / z calcd for $C_{28}H_{31}NO_8$ $[M+Na]^+$: 532.1943, found 532.1925. Relative stereochemistry was established in analogy to **1-15**.



Methyl-2-(benzyloxy)-3-bromo-5-hydroxy-3-methyl-4-oxooctahydro-2H-2,4a-methanonaphthalene-1-carboxylate (1-74):

Following a modified general procedure B, **1-14** (60 mg, 0.17 mmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (63 μL, 0.34 mmol, 2.0 equiv) and DBU (0.15 mL, 1.0 mmol, 6.0 equiv) in CH_2Cl_2 (2.0 mL) from 0 to 40 °C. In place of the HF • pyr workup described in general procedure B, the reaction mixture was instead cooled to 0 °C and a saturated aqueous solution of $NaHCO_3$ (2.0 mL) was added slowly. The biphasic mixture was transferred to a separatory funnel and the organic layer collected. The aqueous layer was extracted with CH_2Cl_2 (3 x 3.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Without further purification, the crude residue was added to a dram vial equipped with a stir bar and dissolved in CH_2Cl_2 (2.0 mL). *N*-Bromo-succinimide (61 mg, 0.34 mmol, 2.0 equiv) was added and the solution was stirred for one h. After this time, the mixture was transferred to a separatory funnel and washed with a saturated aqueous solution of $NaHCO_3$ (2.0 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 1.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 25% EtOAc in hexanes as the eluting solvent to afford **1-74** as a clear oil (38 mg 50% yield over two steps, single diastereomer): $\mathbf{R_f}$ = 0.25

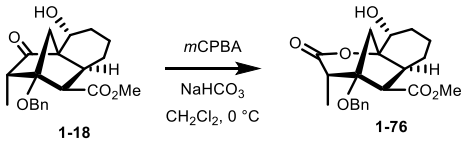
(1:4 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 4.89 (d, *J* = 11.1 Hz, 1H), 4.75 (s, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 4.33 (s, 1H), 3.71 (s, 3H), 3.05 (d, *J* = 5.3 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.40 (d, *J* = 10.2 Hz, 1H), 2.26 (d, *J* = 10.1 Hz, 1H), 2.14 (d, *J* = 9.8 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.73 (s, 3H), 1.43 (d, *J* = 13.6 Hz, 1H), 1.31 (t, *J* = 13.1 Hz, 1H), 1.19 (qd, *J* = 13.5, 4.0 Hz, 1H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 213.3, 172.1, 137.9, 128.6, 128.0, 127.4, 89.0, 68.8, 67.0, 66.8, 56.0, 52.4, 50.6, 39.8, 33.7, 32.5, 29.3, 20.5, 17.9; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{25}BrO_5$ $[M+Na]^+$: 459.0778 (^{79}Br) and 461.0761 (^{81}Br), found 459.0774 and 461.0768, respectively. Relative stereochemistry was established in analogy to **1-15**.



Methyl-5-(benzyloxy)-2,2-diisopropyl-4-methyl-6,6a,7,8,9,9a-hexahydro-5H-3a1,5-methanonaphtho[1,8-de][1,3,2]dioxasiline-6-carboxylate osmate ester (1-75):

Following a modified general procedure B, **1-14** (30 mg, 84 μmol, 1.0 equiv) was reacted with diisopropyldichlorosilane (30 μL, 0.17 mmol, 2.0 equiv) and DBU (75 μL, 0.50 mmol, 6.0 equiv) in CH_2Cl_2 (1.0 mL) from 0 to 40 °C. In place of the HF • pyr workup described in general procedure B, the reaction mixture was instead cooled to 0 °C and a saturated aqueous solution of $NaHCO_3$ (1.0 mL) was added slowly. The biphasic mixture was transferred to a separatory funnel and the organic layer collected. The aqueous layer was extracted with CH_2Cl_2 (3 x 3.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Without further purification, the crude residue was added to a dram vial equipped with a stir bar along

with TMEDA (13 μL, 92 μmol, 1.1 equiv) and the mixture was dissolved in 3:1 Et_2O:CH_2Cl_2 (0.40 mL). The reaction vessel was cooled to –78 °C and a solution of OsO_4 in 3:1 Et_2O:CH_2Cl_2 (0.20 mL, 0.42 M) was added dropwise. The reaction mixture was stirred for 30 min, after which it was warmed to rt. The crude mixture was passed through a 0.45μm nylon filter and collected in a clean, dry dram vial. A vapor-diffusion crystallization was performed by placing this dram vial, without its cap, into a scintillation vial filled with 5.0 mL of *n*-pentane and sealing the scintillation vial. After 24 h, this afforded **1-75** as dark brown crystals (No yield, single diastereomer): $\mathbf{R_f}$ = 0.27 (1:20 MeOH/ CH_2Cl_2, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 4.93 (d, *J* = 12.8 Hz, 1H), 4.76 – 4.72 (m, 2H), 3.73 (s, 3H), 3.21 (pd, *J* = 12.1, 1.1 Hz, 2H), 2.93 (s, 3H), 2.92 – 2.88 (m, 2H), 2.87 – 2.83 (m, 1H), 2.78 (s, 3H), 2.73 (s, 3H), 2.56 (dd, *J* = 9.6, 1.9 Hz, 1H), 2.54 (s, 3H), 2.50 (d, *J* = 5.9 Hz, 1H), 2.13 – 2.07 (m, 1H), 1.89 (qt, *J* = 13.2, 3.0 Hz, 1H), 1.81 (d, *J* = 12.0 Hz, 1H), 1.73 (d, *J* = 9.5 Hz, 1H), 1.39 – 1.27 (m, 3H), 1.22 (s, 3H), 1.17 – 1.15 (m, 6H), 1.12 – 1.09 (m, 1H), 1.05 (t, *J* = 7.1 Hz, 7H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 174.2, 141.2, 128.0, 126.7, 126.6, 120.0, 98.0, 91.3, 77.4, 77.0, 70.3, 69.0, 64.5, 64.0, 57.9, 52.8, 52.7, 51.7(4), 51.7(2), 50.7, 49.5, 36.6, 34.9, 33.4, 31.3, 19.2, 18.1, 18.0(0), 17.9(5), 17.8, 16.6, 16.5, 13.6; **HRMS (ESI-TOF)** m / z calcd for $C_{33}H_{54}N_2O_9OsSi$ $[M+Na]^+$: 859.3030 (^{186}Os), found 859.3005 **M.P.** 210 °C (decomp.). Relative stereochemistry was established by X-ray crystallography (see page 92).

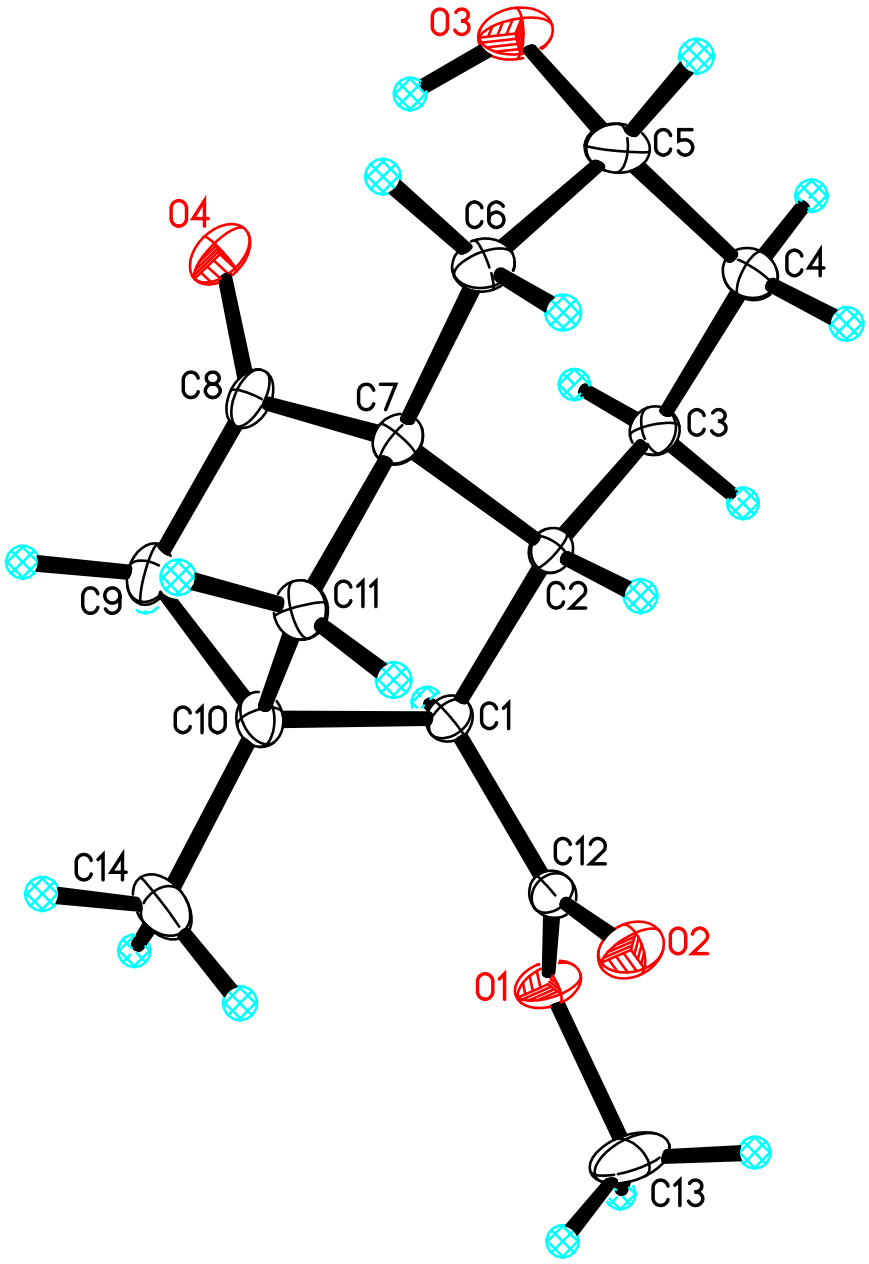


Methyl-4-(benzyloxy)-9-hydroxy-3-methyl-2-oxooctahydro-2H-4,9a methanobenzo[b]oxepine-5-carboxylate (1-76):

No precaution was made to exclude air or water from the reaction. To a round bottom flask equipped with a stir bar and charged with CH_2Cl_2 (10 mL, 0.055 M) was added **1-18** (0.20 g, 0.55 mmol, 1.0 equiv) and $NaHCO_3$ (0.18 g, 2.2 mmol, 4.0 equiv). The mixture was cooled to 0 °C and *meta*-chloroperbenzoic acid (0.19 g, 1.1 mmol, 2.0 equiv) was added. The solution was stirred at 0 °C for 13 h, after which a saturated solution of $Na_2S_2O_3$ (10 mL) was added and the mixture was warmed to ambient temperature. The mixture was transferred to a separatory funnel, the organic layer collected, and the aqueous layer extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 45% EtOAc in hexanes as the eluting solvent to afford **1-76** as a foamy white solid (0.17 g) containing 2.7 wt% CH_2Cl_2 (82% yield, single regioisomer): $\mathbf{R_f}$ = 0.32 (1:1 EtOAc:Hex, Hanessian's stain); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.01 (dd, *J* = 6.1, 2.3 Hz, 1H), 3.62 (s, 3H), 3.32 (d, *J* = 8.9 Hz, 1H), 3.10 (q, *J* = 7.0 Hz, 1H), 2.90 (d, *J* = 12.1 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.05 (d, *J* = 12.3 Hz, 1H), 1.95 – 1.79 (m, 2H), 1.76 – 1.66 (m, 1H), 1.63 – 1.55 (m, 2H), 1.53 – 1.47 (m, 1H), 1.37 (d, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 172.6, 169.7, 137.9, 128.5, 127.7, 127.0, 89.5, 82.6, 69.1, 66.7, 51.6, 49.8, 47.0, 44.5, 39.1, 27.6, 25.5, 18.1, 9.7; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{26}O_6$ $[M+Na]^+$: 397.1622, found 397.1615.

1.5.6. X-ray Crystallography Data

X-ray crystal data for 1-70 The thermal ellipsoid plot is shown at the 50% probability level.

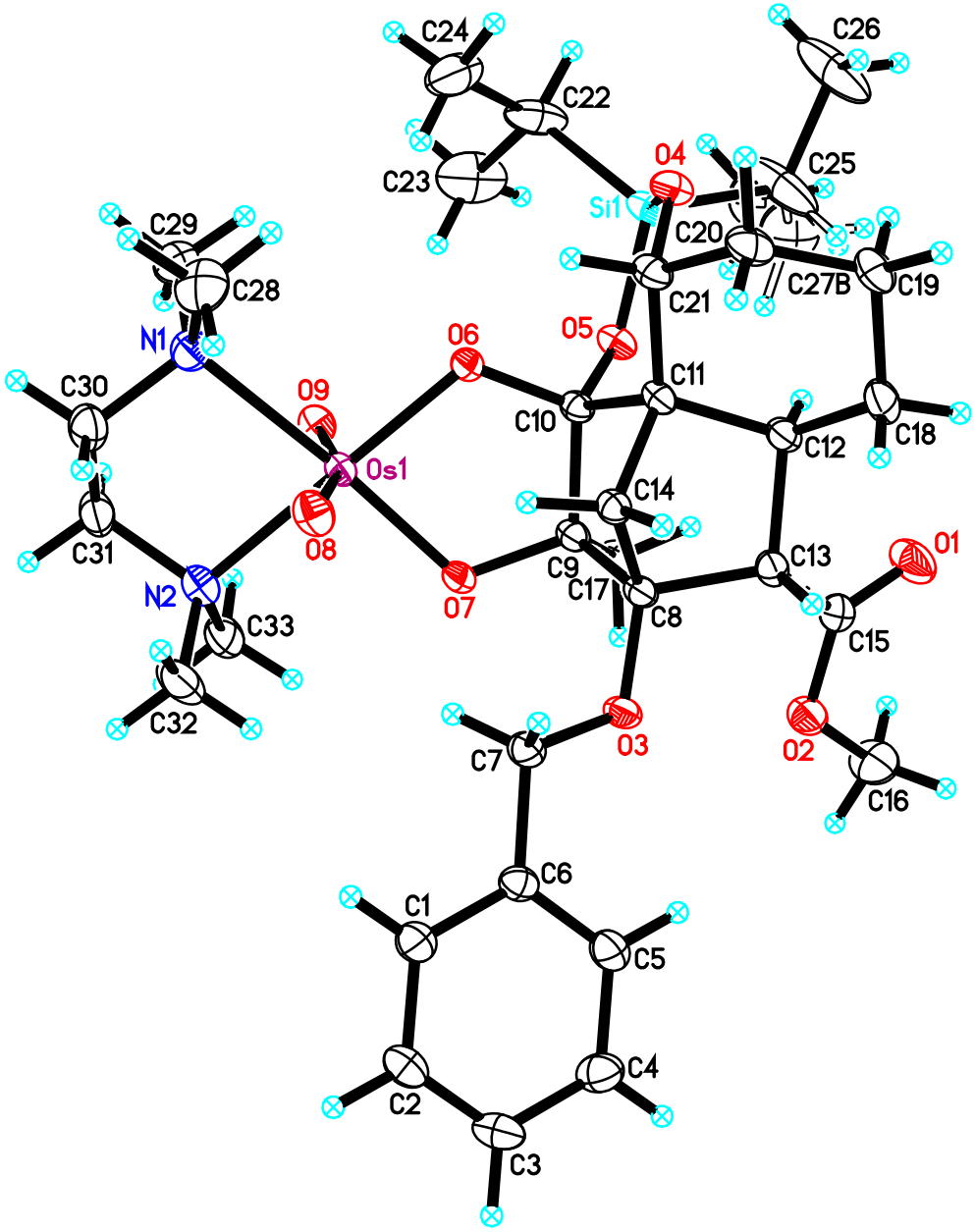


Identification code	sdr55 (Paul Carlson)	
Empirical formula	$C_{14}\ H_{20}\ O_4$	
Formula weight	252.30	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 6.5040(4) Å	a = 101.2007(10)°.
	b = 9.9615(7) Å	b = 98.9009(11)°.
	c = 10.2416(7) Å	g = 97.3800(11)°.
Volume	634.41(7) $Å^3$	
Z	2	
Density (calculated)	1.321 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	272	
Crystal color	colorless	
Crystal size	0.286 x 0.242 x 0.102 mm^3	
Theta range for data collection	2.063 to 31.043°	
Index ranges	$-9 \le h \le 9$, $-13 \le k \le 14$, $-14 \le l \le 14$	
Reflections collected	15819	
Independent reflections	3753 [R(int) = 0.0419]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.8622 and 0.7929	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3753 / 0 / 243	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I) = 3215 data]	R1 = 0.0374, wR2 = 0.0996	
R indices (all data, 0.69 Å)	R1 = 0.0449, wR2 = 0.1055	
Largest diff. peak and hole	0.421 and -0.194 $e.Å^{-3}$	

Table 1.2 Crystal Data and Structure Refinement for **1-70**.

X-ray crystal data for 1-75

The thermal ellipsoid plot is shown at the 50% probability level.



Identification code	sdr51(Paul Carlson)	
Empirical formula	C_{33} H_{54} N_2 O_9 Os Si	
Formula weight	841.07	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C*2/*c*	
Unit cell dimensions	a = 36.7754(18) Å	□ = 90°.
	b = 12.2628(6) Å	□ = 93.6849(8)°.
	c = 15.6604(8) Å	□ = 90°.
Volume	7047.8(6) Å^3	
Z	8	
Density (calculated)	1.585 Mg/m^3	
Absorption coefficient	3.707 mm^{-1}	
F(000)	3424	
Crystal color	brown	
Crystal size	0.277 x 0.251 x 0.188 mm^3	
Theta range for data collection	1.751 to 28.697°	
Index ranges	$-49 \leq h \leq 49$, $-16 \leq k \leq 16$, $-21 \leq l \leq 21$	
Reflections collected	49765	
Independent reflections	9110 [R(int) = 0.0249]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4335 and 0.3599	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9110 / 0 / 424	
Goodness-of-fit on F^2	1.077	
Final R indices [I>2sigma(I) = 8147 data]	R1 = 0.0237, wR2 = 0.0578	
R indices (all data, 0.74 Å)	R1 = 0.0286, wR2 = 0.0598	
Largest diff. peak and hole	1.921 and -0.740 e.Å^{-3}	

Table 1.3. Crystal Data and Structure Refinement for **1-75.**

*1.5.7. Stereochemical Assignment of **1-46a** and **1-46b***

For compounds **1-46a** and **1-46b**, the relative stereochemistry of the two stereocenters within the cyclopentenone ring were established by ^{1}H NOSEY. However, these NOESY experiments did not conclusively assign the relative configuration of the alcohol stereocenter. Using a similar line of reasoning to that established by Dogan and Erol,[39] we hypothesized that this stereocenter could be assigned through an analysis of coupling constants based on a rigidifying hydrogen bonding interaction between the alcohol and the ketone (Figure 1.3). Such an interaction would lead to a dihedral angle of approximately 60° between H_a and H_b for the syn aldol adduct and 180° for the anti aldol adduct. Based on the Karplus equation, these angles would yield $^{3}J_{Ha\text{-}Hb}$ coupling constants of 5 Hz and 15Hz for the syn and anti aldol adducts, respectively.

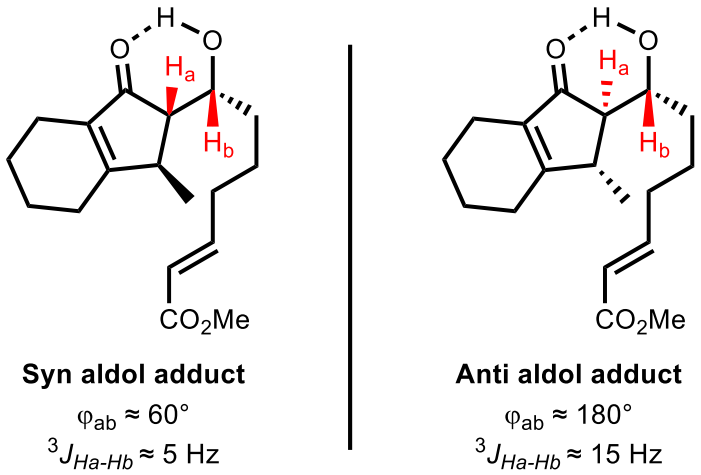
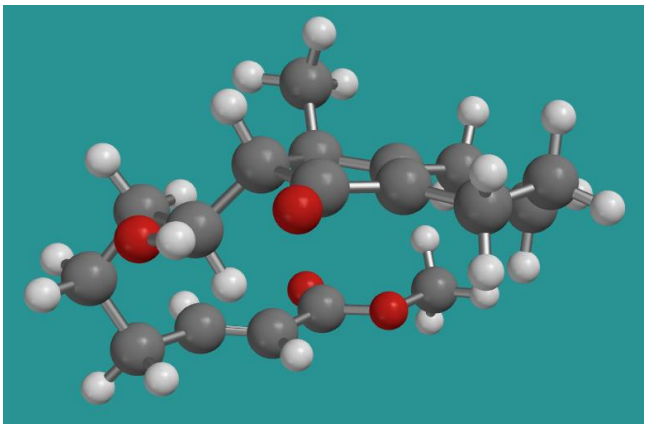


Figure 1.3. Predicted Dihedral Angles Between Ha and Hb for Compounds **1-46a** and **1-46b** based on a Rigidifying Hydrogen Bonding Interaction Between the Alcohol and Ketone.

In order to test the legitimacy of our hypothetical hydrogen bonding interaction in Figure 1.3, we calculated the lowest energy conformers for both the syn and anti aldol adducts. A conformer search was carried out in Spartan using the MMFF force field. A sample of 8-12 structures were carried into DFT calculations, and the lowest energy conformer for each isomer

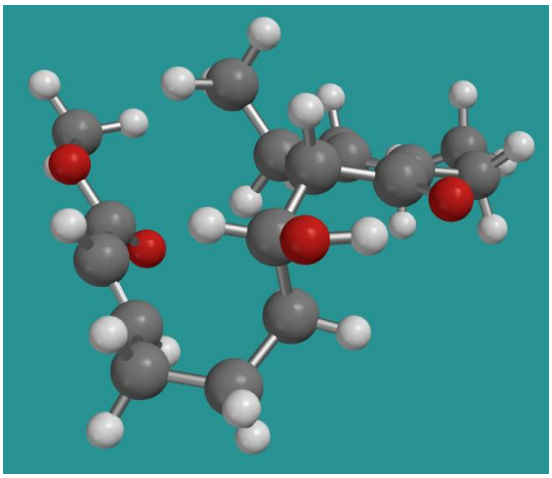
is shown in Figure 1.4. The DFT calculations used ωB97X-D/6-31G* method and basis set. The calculated dihedral angles between H_a and H_b are in good agreement with our hypothesis in Figure 1.3.



anti aldol

φ_{ab} = -176.6°

E: -1002.187660 hartrees



syn aldol

φ_{ab} = 66.1°

E: -1002.186720 hartrees

Figure 1.4. Calculated Lowest Energy Conformations for the Syn and Anti Aldol Adducts of **1-46**. Calculated Dihedral Angles Between Ha and Hb are Reported.

As the calculated lowest energy conformers for both the syn and anti aldol adducts agreed with our hypothesis in Figure 1, we assigned **1-46a** as the syn aldol adduct based on an observed $^3J_{Ha\text{-}Hb}$ of ~2.5 Hz. Similarly, **1-46b** was assigned as the anti aldol adduct based on an observed $^3J_{Ha\text{-}Hb}$ of 9.5 Hz.

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Chapter 2. Efforts Towards the Total Synthesis of Artatrovirenols A and B

2.1. Introduction

2.1.1. Artemisia Sesquiterpenoids Background

The *Artemisia* genus of plants has been a font of inspiration in natural product total synthesis for nearly half a century. The members of this genus have yielded a number of unique sesquiterpenoid natural products that have captured attention not only for their challenging complexity, but also for their useful bioactivities. Figure 2.1 presents a selection of sesquiterpenoids isolated from various *artemisia* plants: absinthin (technically a sesquiterpenoid dimer),[1] arglabin,[2] yomogin,[3] and artemisinin.[4] This set of natural products showcases the range

of bioactivities that *artemisia* natural products are capable of, with arglabin and artemisinin isolated at industrial scales for the treatment of cancer and malaria, respectively. As for the remaining two, absinthin has been used as a stomachic tonic and anthelminthic,[5] while yomogin has shown anti-proliferative activity against tumor cells.[6] In addition to their range of bioactivities, these sesquiterpenoids show an equally broad and intriguing range of molecular structure that has drawn much interest from the synthetic community.[7]

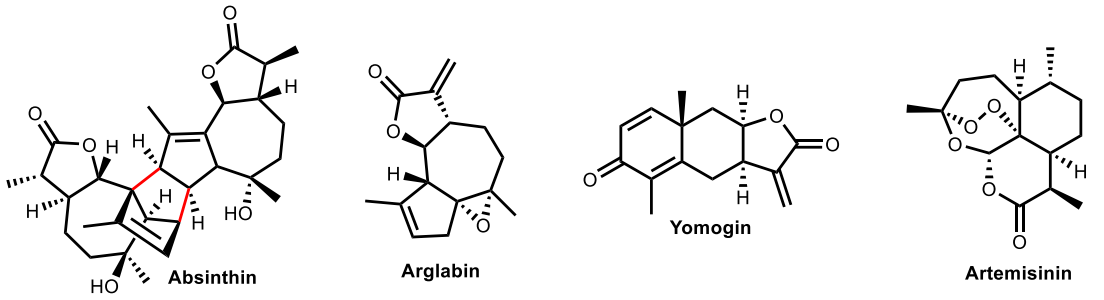


Figure 2.1. Selected *Artemisia* Terpenoids

2.1.2. Isolation of Artatrovirenols A and B

Recently, a novel pair of *artemisia* sesquiterpenoids were isolated from the plant *artemisia atrovirens* by the Chen lab, who gave them the names artatrovirenol A and artatrovirenol B (Figure 2.2).[8] Their structure and relative stereochemistry were determined by extensive 2D-NMR analysis and, in the case of artatrovirenol A, by X-ray crystallography. Additionally, their absolute configurations were determined by comparing their experimental ECD spectra with calculation. These sesquiterpenoids caught our attention as potential synthetic targets for three primary reasons. Firstly, they possess an unprecedented [$5.3.1.1^{4,11}0^{1,5}$] dodecane carbon skeleton, which presents an appealing synthetic challenge that would likely necessitate innovation and creative solutions. Secondly, the Chen lab showed that, much akin to other *artemisia* sesquiterpenes, artatrovirenol A displays an intriguing bioactivity: in cytotoxicity assays against human hepatoma cell lines (SMMC-7721), they found an IC_{50} value of 44.0 μM

for artatrovirenol A, which is similar to that of Sorafenib (10.0 μM), a small-molecule drug used to treat liver cancer in the clinic. However, despite this promising bioactivity, only 6.0 mg of artatrovirenol A were isolated from 60 kg of dried plant matter, making total synthesis a competitive option for obtaining larger amounts of this material for study. Finally, the Chen group proposed a biosynthetic pathway for artatrovirenols A and B involving a key IMDA cyclization that, while plausible, lacked any concrete evidence to support it. We reasoned that a biomimetic total synthesis of these natural products would lend credibility to the proposed biosynthetic pathway. With these considerations in mind, we decided to pursue a total synthesis of artatrovirenols A and B, using the proposed biosynthetic IMDA cyclization as the key step.

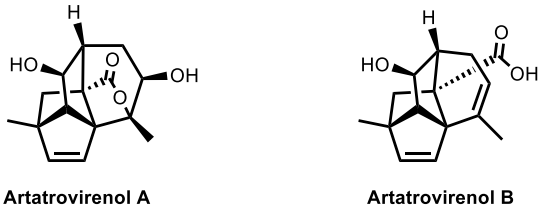
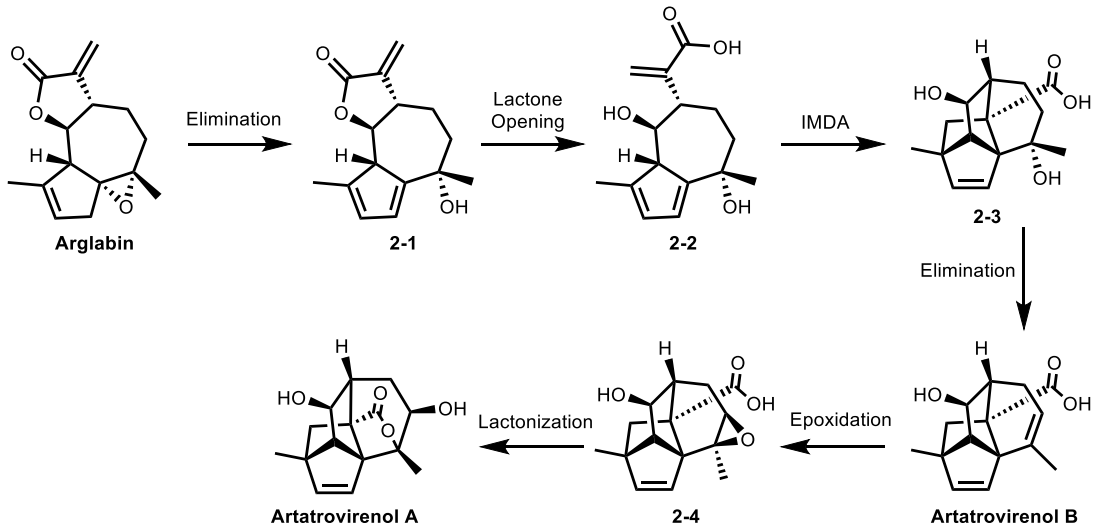


Figure 2.2 Artatrovirenols A and B, Sesquiterpenoids from *Artemisia Atrovirens*

2.1.3. Proposed Biosynthesis

The biosynthetic pathway to artatrovirenols A and B proposed by the Chen lab is outlined in Scheme 2.1. It begins from arglabin, which, as discussed previously, is a known natural product from the *artemisia* genus. They propose an opening of the epoxide in arglabin to yield diene intermediate **2-1**, followed by lactone opening to yield acrylic acid **2-2**. They then propose an IMDA cyclization between the newly formed diene and acrylic acid moieties to yield intermediate **2-3**, which, after elimination of the tertiary alcohol, would yield artatrovirenol B. Artatrovirenol B could then convert to artatrovirenol A via an epoxidation to intermediate **2-4** followed by lactonization.

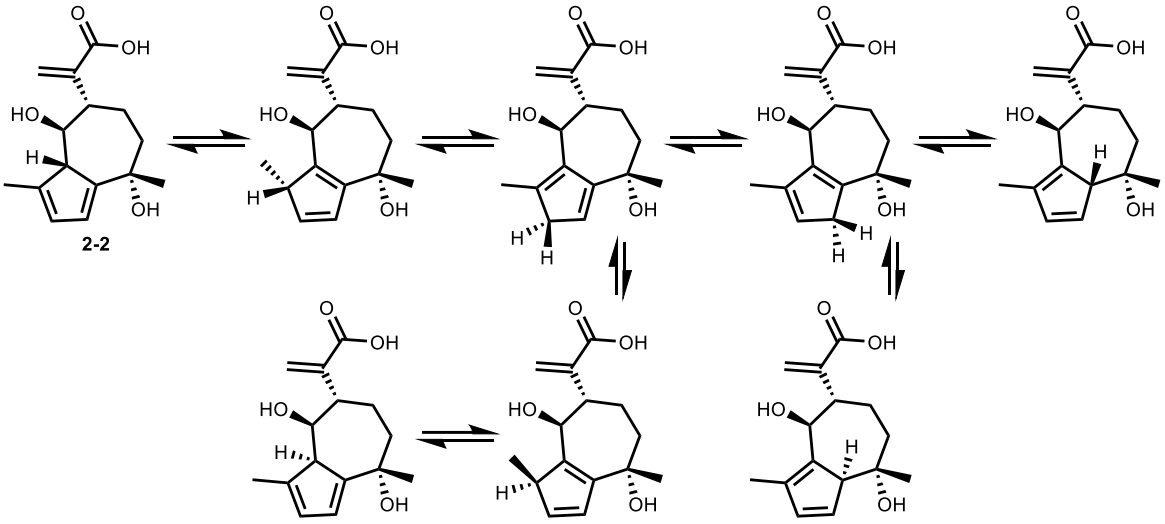


Scheme 2.1. The Chen Lab's Proposed Biosynthesis of Artatrovrienols A and B

2.1.4. Proposed Biosynthetic IMDA

Seeing as our aim was to construct a synthetic route towards artatrovirenols A and B that employed the proposed biosynthetic IMDA cyclization as the key, we began by first scrutinizing the plausibility of this IMDA cyclization. From our experience studying the mechanism of our silacycle-templated IMDA reaction described in chapter 1, we were quick to identify the possibility for facile [1,5] hydride shifts in the proposed cyclopentadiene **2-2** (Scheme 2.2). Through these [1,5] shifts, **2-2** could be in equilibrium with seven other unique dienes, which gave us pause when considering the plausibility of the IMDA cyclization. Even assuming that the Diels–Alder would show exquisite endo/exo selectivity, with eight possible dienes, there were still eight possible Diels–Alder adducts that could arise from the proposed diene **2-2**. However, considering the structures of the Diels–Alder adducts that would arise from the seven undesired dienes, we came to realize that most would lead to the formation of a four-membered ring, an anti-Bredt olefin, an inverted bridgehead position, or some combination of those three. Therefore, we hypothesized that, while all members of the equilibrium described in Scheme 2.2 would be populated upon forming the desired IMDA precursor, only **2-2** would undergo IMDA

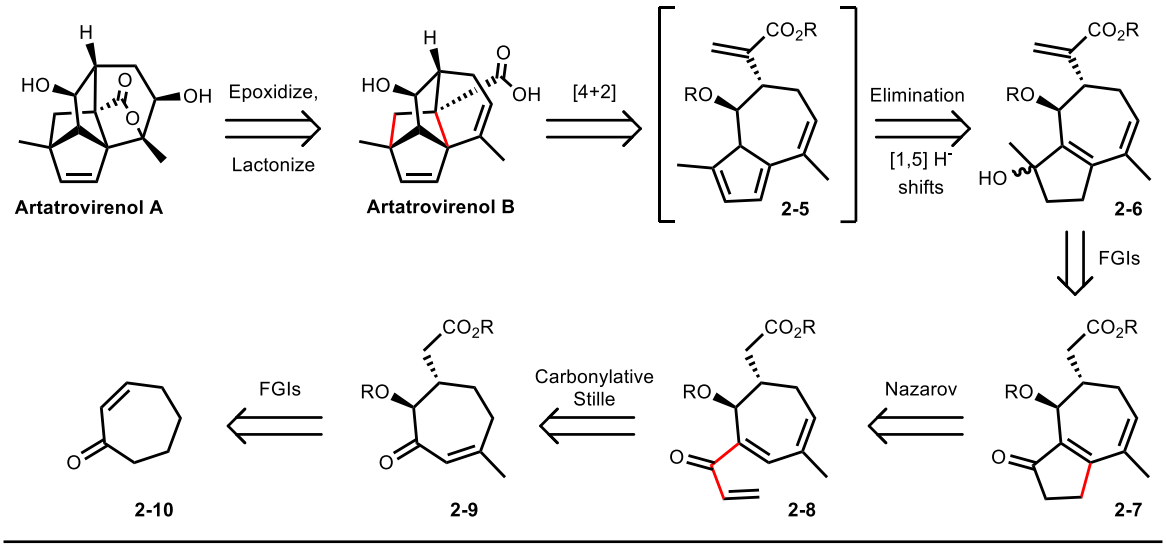
cyclization at a reasonable rate, and thus the equilibrium would funnel to **2-2** by Le Chatelier's principle.



Scheme 2.2. All Possible Cyclopentadiene Isomers of the Diels–Alder Precursor

2.1.5. Initial Retrosynthetic Analysis

Reassured with the plausibility of the proposed biosynthetic IMDA cyclization, we formulated a full retrosynthesis of artatrovirenols A and B (Scheme 2.3). In accordance with the proposal of Chen and coworkers, our retrosynthetic analysis began with deriving artatrovirenol A from artatrovirenol B via an oxidative lactonization. The skeleton of artatrovirenol B, in turn, would be constructed from an IMDA reaction of **2-5**, which would itself be derived from precursor **2-6**. In order to generate **2-5**, the alcohol of **2-6** would be eliminated to generate a cyclopentadiene intermediate, which would then convert to **2-5** via [1,5] hydride shifts. Through a number of functional group interconversions, **2-6** could be derived from extended enone **2-7**, the 7,5-ring system of which could be forged through a Nazarov cyclization from precursor **2-8**. Finally, Nazarov precursor **2-8** could be built from **2-9** via a carbonylative Stille reaction and **2-9**, in turn, could be prepared from cycloheptenone (**2-10**).

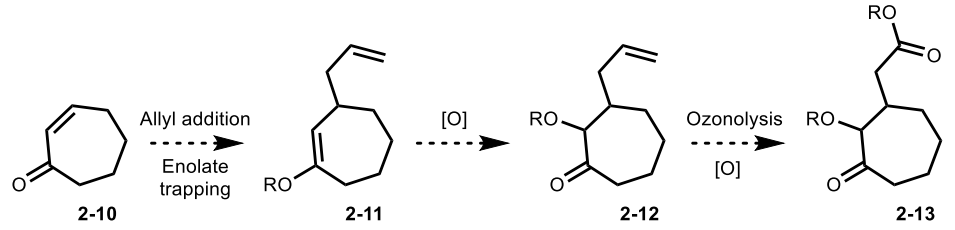


Scheme 2.3. Initial Retrosynthetic Analysis of Artatrovirenols A and B

2.2. Results

2.2.1. Functionalization of Cycloheptenone

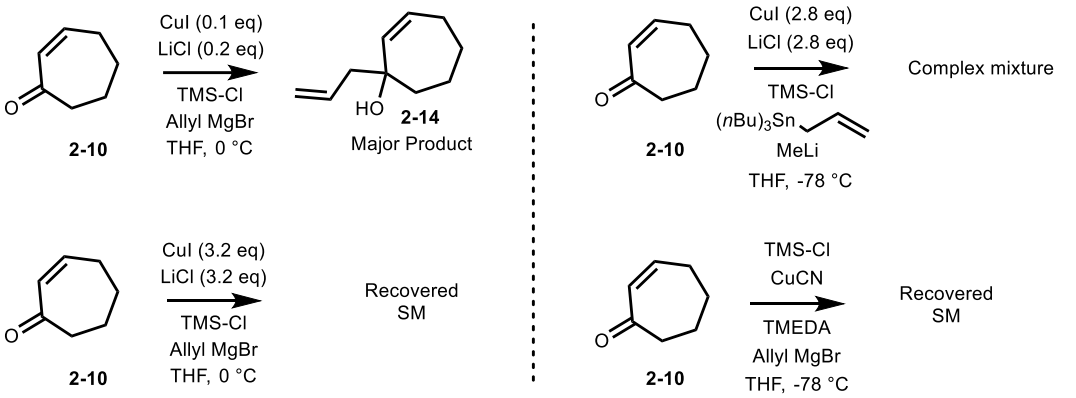
Our initial study focused on derivatizing cycloheptenone in order to install the alcohol and carboxylic acid moieties of **2-9** (Scheme 2.4). We envisioned introducing the carboxylic acid moiety masked as an allyl group, which would be added to the β-position of **2-10** via conjugate



Scheme 2.4. Envisioned Strategy for the Derivatization of Cycloheptenone

addition. After trapping the enolate resulting from this conjugate addition as an enol ether derivative analogous to **2-11**, we would then perform a Rubottom-type oxidation, yielding α-ketol **2-12**. Finally, we would unmask the carboxylic acid functional group via ozonolysis of the allyl group and further oxidation to afford **2-13**.

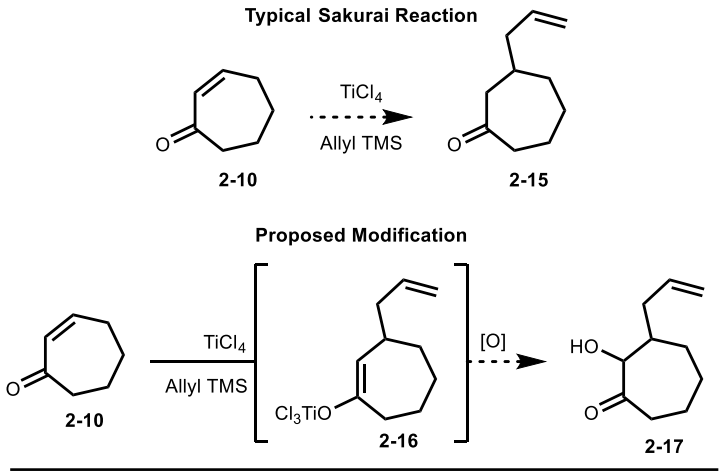
To begin the approach described above, we first attempted an allyl cuprate addition onto cycloheptenone using a number of different literature-reported conditions. Unfortunately, we were met with little success (Scheme 2.5). Attempting to form the desired allyl cuprate using catalytic copper and allyl Grignard led only to the formation of 1,2 adduct **2-14**. We interpreted this result as a sign that addition of the Grignard reagent to **2-10** was out-competing transmetallation onto the copper center. In response, we attempted the same addition with the use of stoichiometric copper so as to form the cuprate prior to addition of cycloheptenone. This approach, however, yielded only recovered starting material. Different methods of delivering allyl cuprate using allyl lithium or copper cyanide[9] were similarly unsuccessful.



Scheme 2.5. Unsuccessful Allyl Cuprate Additions

Finding no success with cuprate additions, we searched for alternative methods to perform a conjugate addition of an allyl group to an enone. One well-established method for accomplishing this is the Hosomi–Sakurai allylation, which allows for the conjugate addition of an allyl silane into an enone when activated by a strong Lewis acid to deliver a ketone analogous to **2-15** (Scheme 2.6).[10] While this method is highly effective for the conjugate addition of allyl groups, it would still leave us with an unsolved problem. If we were to synthesize intermediate **2-15**, we would then need to selectively introduce an alcohol at one of the two α positions of the

ketone. Given that the two α positions of **2-15** were highly similar in terms of sterics, we found this to be an implausible approach.

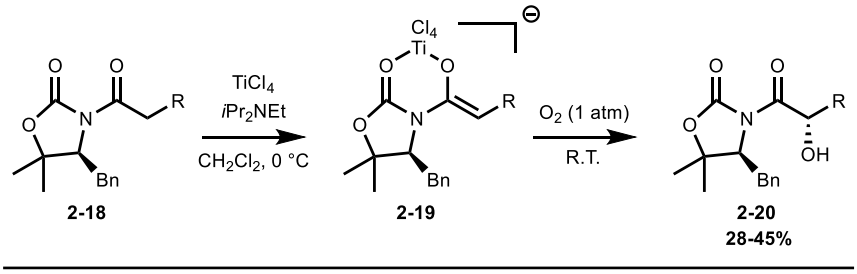


Scheme 2.6. Our Proposed Oxidative Modification to the Sakurai Allylation

Although we believed that a standard Sakurai allylation to deliver **2-15** would be problematic in our synthetic route, we envisioned a modified Sakurai allylation that we believed could deliver the regioselective oxidation that we required. As laid out in Scheme 2.6, we reasoned if we were to subject **2-10** to standard Sakurai allylation conditions, we would generate titanium enolate **2-16** in situ. While under a normal Sakurai allylation procedure, this titanium enolate would then be protonated to return the corresponding ketone **2-15**, we wondered if it would be possible to capture this intermediate oxidatively and return α-ketol **2-17** with full regiocontrol.

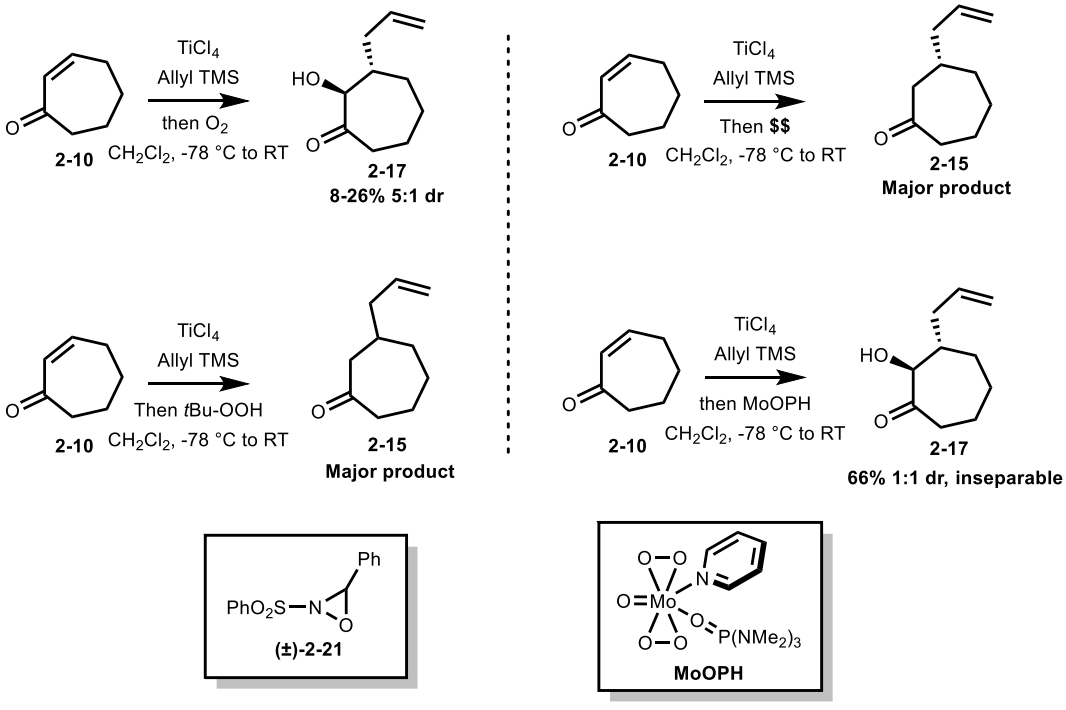
Although we did not find literature precedent for oxidatively trapping Sakurai intermediates directly, we were encouraged to find a report from Gómez-Palomino and coworkers that described a related transformation (Scheme 2.7).[11] In their approach, ketones such as **2-18** were treated with titanium (IV) chloride and Hünig's base to generate titanium enolates such as **2-19**, which were then reacted with molecular oxygen to return α-ketols such as

2-20. We wondered if we could use a similar strategy by bubbling molecular oxygen through a Sakurai reaction and achieve similar results.



Scheme 2.7. Gómez-Palomino and Coworkers' Approach to the Oxidation of Titanium Enolates

Drawing inspiration from the work of Gómez-Palomino and coworkers, we subjected **2-10** to standard Sakurai allylation conditions, with the exception being that molecular oxygen was bubbled through the reaction mixture prior to quenching with a protic source (Scheme 2.8). We were encouraged to observe formation of the desired α-ketol **2-17**, albeit in low and inconsistent

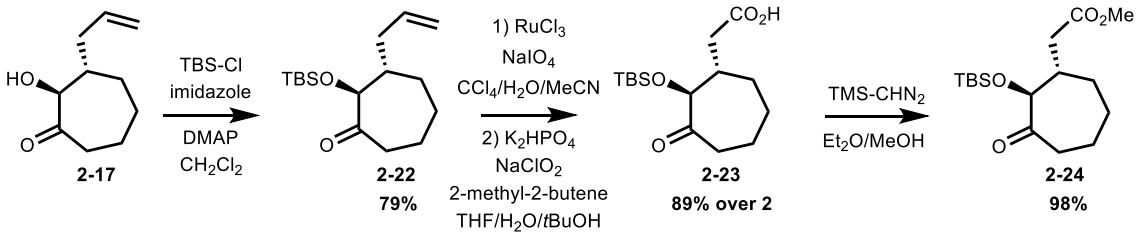


Scheme 2.8. Our Approach to Oxidatively Trapping Sakurai Intermediates

yields. We next questioned if a different oxidizing agent would more efficiently trap the titanium enolate intermediate. We found that both *t*Bu-OOH and Davis oxaziridine **2-21** were ineffective at oxidizing the titanium enolate intermediate, returning only ketone **2-15**. However, we found greater success with the use of the oxidant MoOPH, which returned the desired product in a greatly improved 66% yield as compared to molecular oxygen, albeit with diminished diastereoselectivity. Despite returning an inseparable mixture of diastereomers, we decided to move forward with the synthesis using the MoOPH conditions described in Scheme 2.8, as it provided plentiful material to study the viability of further steps in our synthetic route.

2.2.2. Synthesis of Nazarov Cyclization Precursor

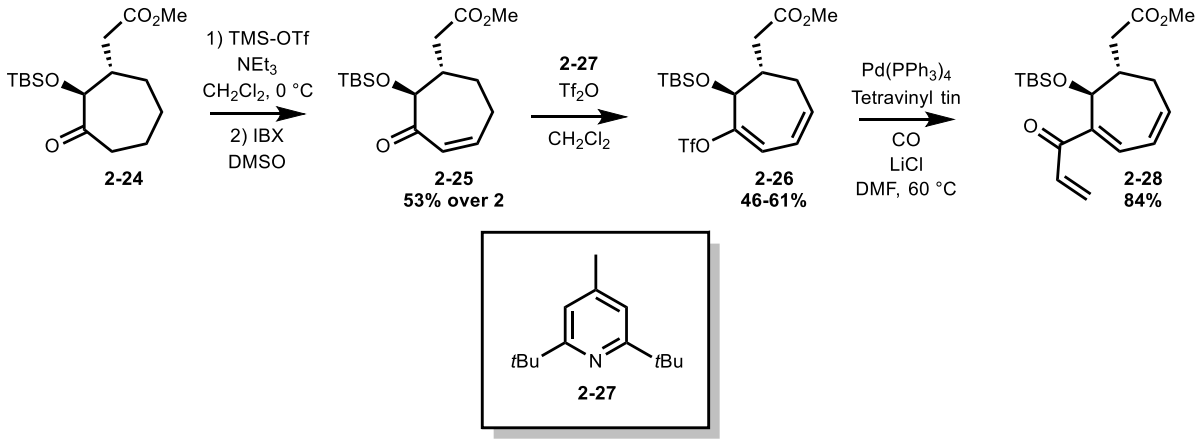
The next steps of our synthesis are laid out in Scheme 2.9. Firstly, we protected the alcohol of **2-17** to afford TBS ether **2-22**. Next, we found that a two-step sequence of oxidative cleavage followed by a Pinnick oxidation was the most effective way to unveil the masked carboxylic acid functionality of **2-23**. Finally, the carboxylic acid functionality was protected as a methyl ester to deliver **2-24**. With this intermediate, we now needed to further functionalize the ketone in preparation for the envisioned carbonylative Stille reaction.



Scheme 2.9. Early-Stage Synthetic Route

Our synthetic route towards the precursor for our envisioned Nazarov cyclization is described in Scheme 2.10. Ketone **2-24** was subjected to a two-step sequence of regioselective silyl enol ether formation followed by oxidation with IBX to return enone **2-25**. With the newly

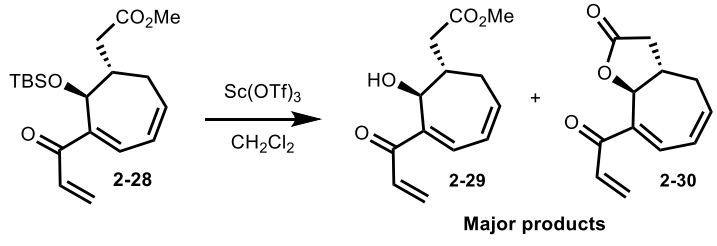
established unsaturation in **2-25**, we now had the necessary functional handle to further elaborate to extended enol triflate **2-26** by selective γ-deprotonation with hindered base **2-27**. Finally, our desired Nazarov precursor was generated via a carbonylative Stille reaction between **2-26** and tetravinyl tin to afford extended enone **2-28**.



Scheme 2.10. Synthetic Route to the Nazarov Precursor

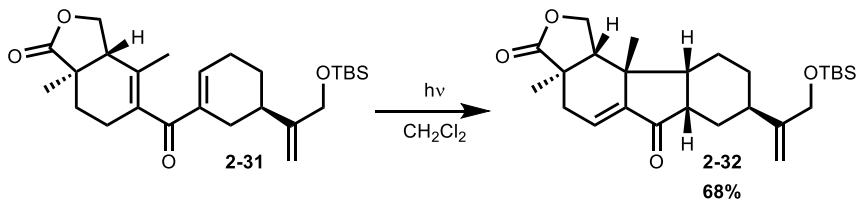
2.2.3. Nazarov Cyclization Experiments

With Nazarov cyclization precursor **2-28** in hand, we next sought to execute a Lewis-acid catalyzed Nazarov cyclization to forge the desired 7,5-ring fusion. However, exposing **2-28** to scandium triflate yielded disappointing results. Even after extended reaction times, the sole products observed were **2-29** and **2-30**, which were the result of loss of the TBS group and lactonization of the resulting alcohol, respectively.



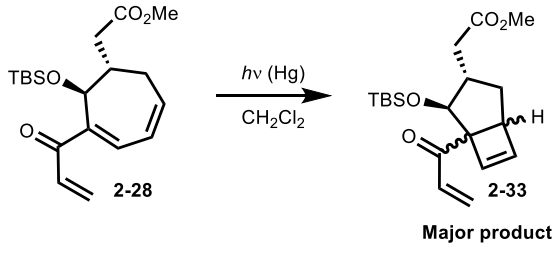
Scheme 2.11. Lewis-Acid Catalyzed Nazarov Cyclization Attempt

Finding little success with a Lewis acid catalyzed Nazarov cyclization, we turned our attention towards photochemical means of accomplishing this transformation. This approach was inspired in part by a recent report from the Gao lab, in which they demonstrated the viability of a photochemical Nazarov cyclization in the context of natural product total synthesis with their approach to the synthesis of farnesin (Scheme 2.12).[12] Specifically, they observed efficient photochemical conversion of intermediate **2-31** to complex tetracycle **2-32**.



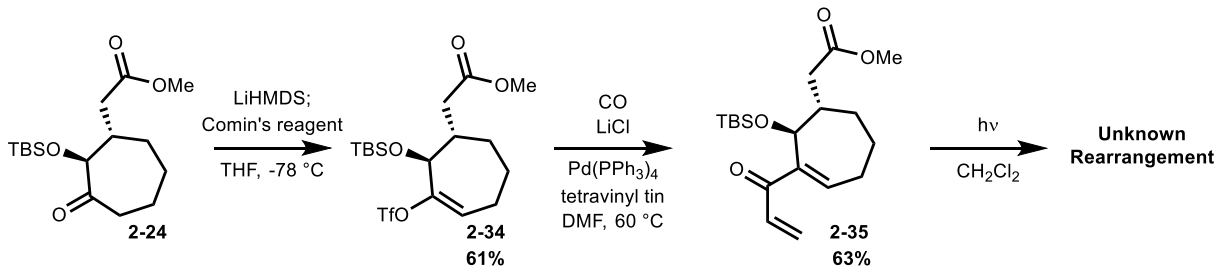
Scheme 2.12. Gao and Coworkers' Photochemical Nazarov Cyclization en Route to Farnesin

Encouraged by the above precedent, we sought to apply similar conditions to our own Nazarov precursor. However, when **2-28** was subjected to photochemical irradiation, the primary product observed was 4,5 bicycle **2-33** (Scheme 2.13), resulting from an unintended 4π electrocyclization of our starting material. Seeing as the presence of the cycloheptadiene moiety in **2-28** was to blame for this undesired reactivity, we next sought to remove the alkene distal to the ketone so as to preclude any possibility of electrocyclization.



Scheme 2.13. Unintended Photochemical 4**π** Electrocyclization

With this goal in mind, we retraced our steps and returned to intermediate **2-24**.From this intermediate, we created enol triflate **2-34** (Scheme 2.14), which was then subjected to carbonylative Stille coupling conditions to yield enone **2-35**. With this enone in hand, we now had a means to probe the viability of our desired photochemical Nazarov cyclization without the potential for interference from competing electrocyclizations. Interestingly, when **2-35** was subjected to photochemical irradiation, we observed a rearrangement to an unknown product. The fact that the rearranged species was a mixture of diastereomers made confident assignment of its structure challenging. However, it was clear that the product isolated was not the desired 7,5-bicycle.



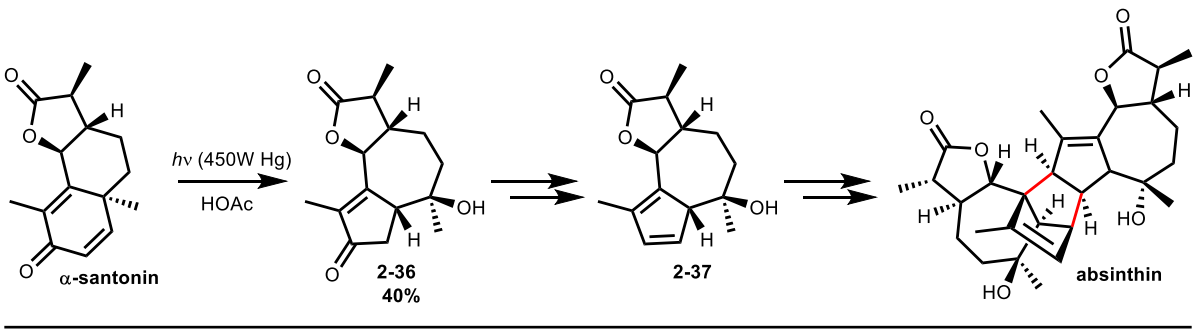
Scheme 2.14. Synthetic Route towards Simplified Nazarov Precursor and its Unexpected Rearrangement

Our inability to affect the Nazarov cyclizations described above was discouraging, especially as this particular transformation was crucial to the synthetic route being pursued. With this issue in mind, we decided that the current route was ineffective and in need of revision. Specifically, we would need a more reliable way of establishing the 7,5-bicyclic core.

2.2.4. The Photo-Santonin Rearrangement

As we searched for more effective means of establishing the 7,5-bicyclic core of our target, we came across a total synthesis report from the Zhai lab detailing their approach to the natural product absinthin (Scheme 2.15).[5] In the course of this work, they made use of a the photo-santonin rearrangement, a powerful skeletal rearrangement of α-santonin that has been

known and used synthetically since the 1950s.[13] The Zhai lab used this rearrangement to deliver intermediate **2-36**, which possessed a 7,5-bicyclic core much like the one that we had been targeting in our own total synthesis. Furthermore, the oxidation pattern of **2-36** provided useful handles to install the functionality needed for artatrovirenols A and B. Even more relevant for our project, the Zhai lab was able to derivatize **2-36** to diene **2-37**, which bore many similarities to the diene that we were targeting for our own envisioned IMDA cyclization.



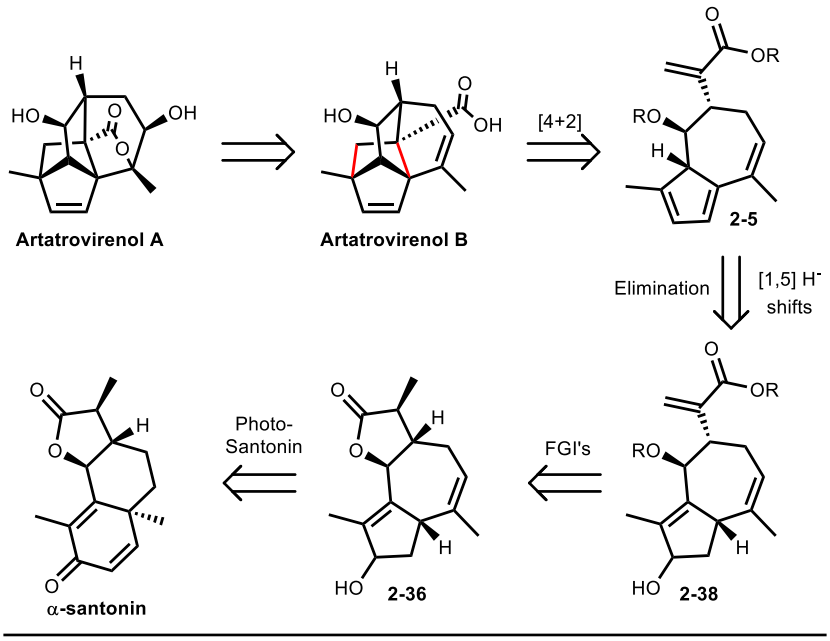
Scheme 2.15. The Zhai Lab's Approach to Absinthin

With this new information in mind, we began revising our retrosynthetic analysis with the photo-santonin rearrangement as the first step. We then planned on elaborating intermediate **2-36** to the desired diene for our IMDA.

2.2.5. Revision of our Retrosynthetic Analysis

Our revised retrosynthetic analysis is described in Scheme 2.16. The early disconnections remain the same as compared to our initial route: artatrovirenol A would be derived from artatrovirenol B via an oxidative lactonization and artatrovirenol B would be derived from diene **2-5** via an IMDA reaction. However, we now planned to derived diene **2-5** from elimination of alcohol **2-38**. This particular alcohol was chosen as a target because it could be derived, in theory, from functional group interconversions of known compound **2-36**, which is the immediate product of the photo-santonin rearrangement. We considered this route to be

particularly effective because it established the challenging 7,5-core of the natural product through known chemistry and, furthermore, allowed for the introduction of all 15 carbons of the natural product from step one.

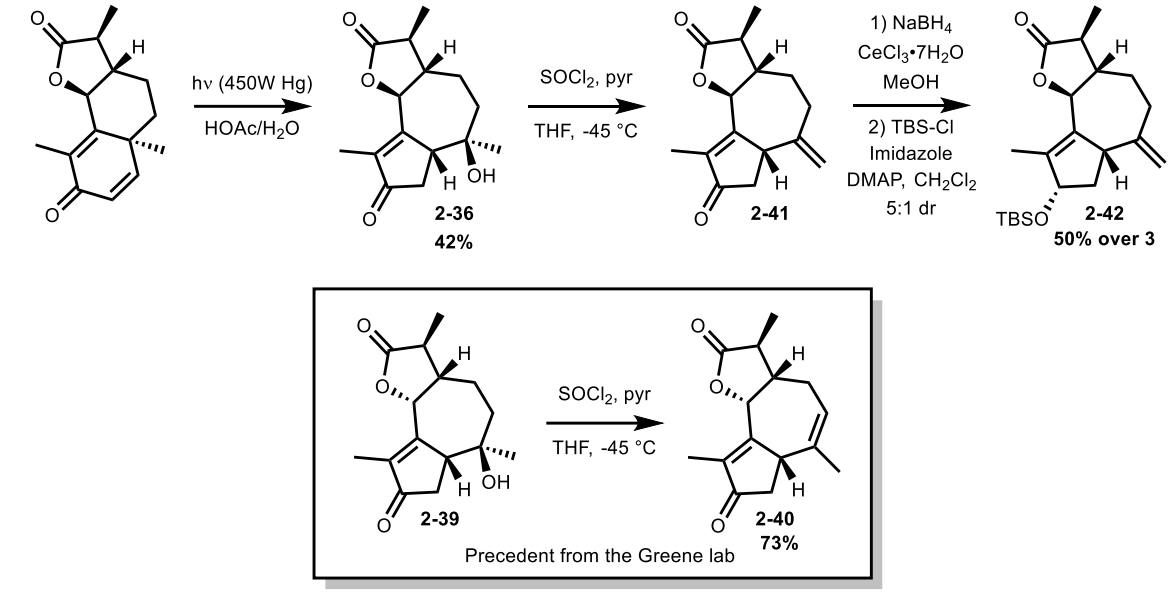


Scheme 2.16. Revised Retrosynthetic Route towards Artatrovirenols A and B

2.2.6. Revised Forward Synthesis

Our initial steps towards the revised synthetic route are laid out in Scheme 2.17. Following literature precedent,[14] we subjected α-santonin to photochemical irradiation from a mercury vapor bulb, observing the reported rearrangement to afford **2-36** in comparable yield to the literature. With this intermediate in hand, our next focus was to eliminate the tertiary alcohol to create the trisubstituted olefin present in artatrovirenol B. We were encouraged by a report from the Greene lab in which the tertiary alcohol of **2-39**, a molecule which differed from **2-36** only in a single stereocenter, was eliminated with thionyl chloride to deliver the trisubstituted olefin **2-40** exclusively.[15] Disappointingly, however, when we subjected **2-36** to the same conditions reported by Greene, we instead observed exclusive selectivity for the exocyclic 1,1

disubstituted olefin **2-41**. It would appear that the conformational difference imparted to **2-36** by the presence of a trans-lactone is sufficient to reverse the selectivity of elimination as compared to cis-lactone **2-39**.

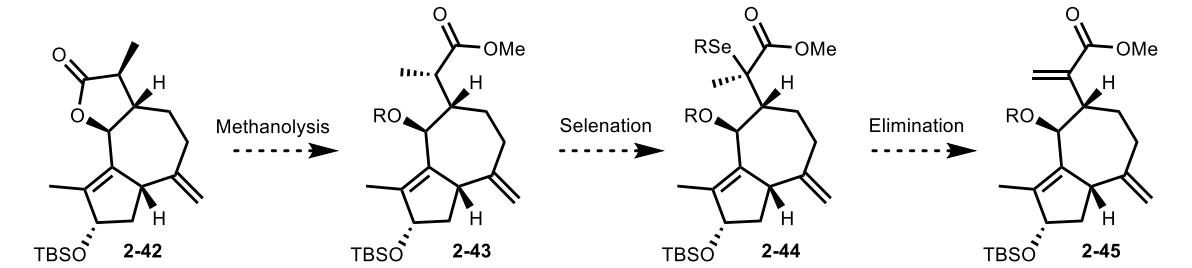


Scheme 2.17. Revised Synthesis, Early Steps

Despite the incorrect selectivity observed above, the conversion of **2-36** to **2-41** proved to be an efficient reaction capable of supplying ample material for further studies. Furthermore, we reasoned that the undesired exocyclic olefin of **2-41** could be isomerized to the desired trisubstituted olefin at a later stage. Therefore, the decision was made to carry **2-41** forward to study later steps in our route. To that end, we converted the ketone of **2-41** to a TBS ether through a two-step sequence consisting of a Luche reduction followed by a TBS protection to afford TBS ether **2-42**. With this intermediate in hand, we were poised to begin manipulating the lactone moiety to generate our desired dienophile.

2.2.7. Investigations towards Lactone Opening

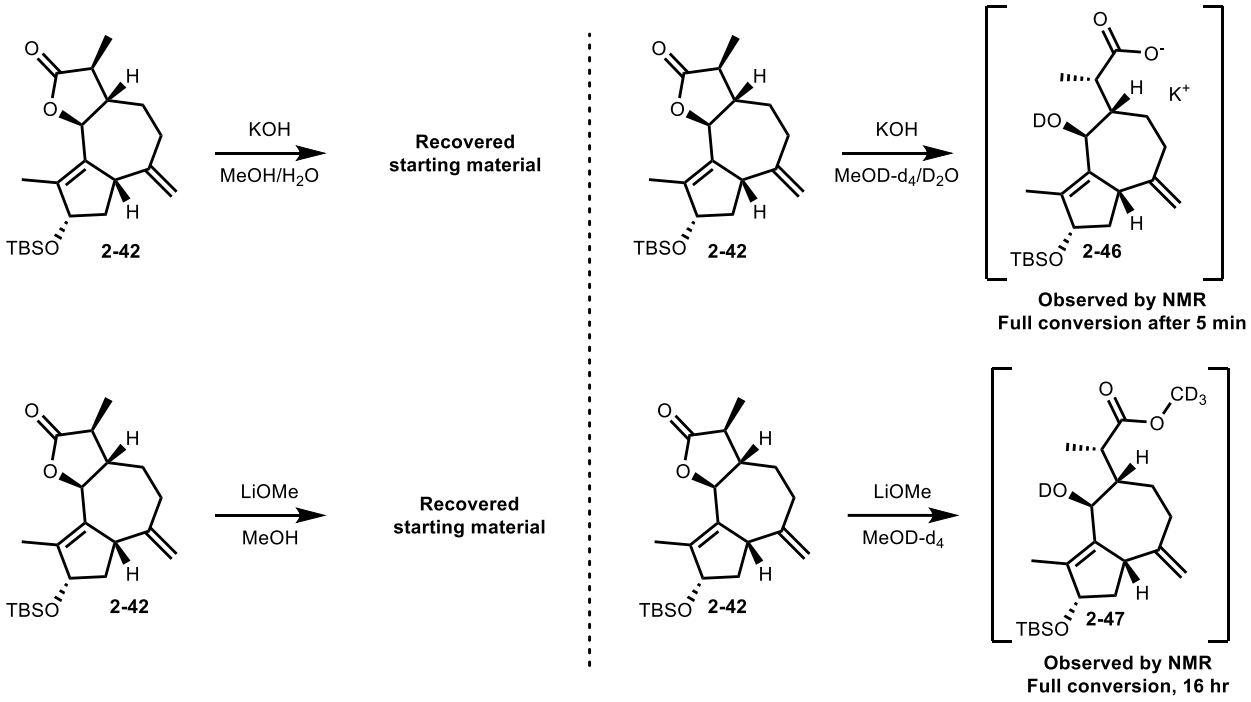
From this point in the synthesis, our envisioned route to generate the necessary dienophile for our key IMDA began with opening of the lactone ring in **2-42** by hydrolysis or methanolysis to afford an intermediate such as **2-43** (Scheme 2.18). From that point, we would only need to introduce an α-β unsaturation at the ester moiety. We envisioned this being accomplished by a two-step sequence starting with selenation of the ester to afford α-selenide **2-44** followed by elimination of that selenide to afford acrylate **2-45**.



Scheme 2.18. Initial Synthetic Approach to the Acrylate Dienophile

Our initial efforts to execute the strategy described above are laid out in Scheme 2.19. We began by subjecting **2-42** to standard conditions for the hydrolysis or methanolysis of lactones (Scheme 2.19, left), but observed only recovered starting material. We reasoned that this result could suggest one of two problems. Firstly, the lactone could have been sterically hindered enough that the rate of hydrolysis and methanolysis were negligibly slow. Alternatively, it was possible that hydrolysis and methanolysis went to completion within a reasonable time frame but that complete re-lactonization occurred upon acidic workup. In order to probe which of these two scenarios was at play, we once again subjected **2-42** to hydrolysis and methanolysis conditions, but using deuterated solvents. We then tracked the progress of the reaction by NMR, we observed complete conversion to **2-46** under hydrolysis conditions and **2-47** under methanolysis conditions (Scheme 2.19, right). This led us to the conclusion that, while the hydrolysis and

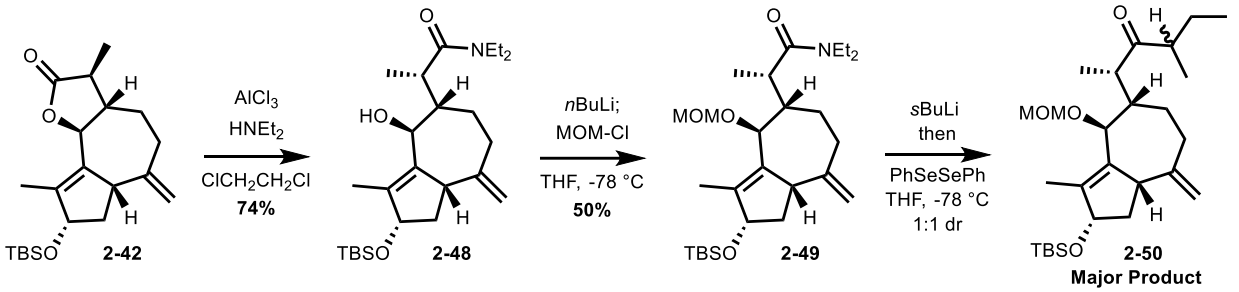
methanolysis reactions were proceeding as expected, they were undergoing complete re-lactonization upon workup, returning only starting material.



Scheme 2.19. NMR Studies of Lactone Opening under Basic Conditions

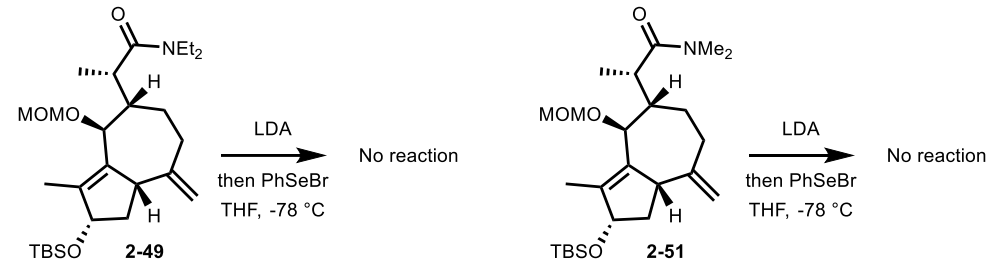
Seeing as the products of hydrolysis and methanolysis were unstable to workup conditions and thus difficult to isolate, we opted to open the lactone as a more stable functional group that would be resilient to isolation and purification. To this end, we chose to open **2-42** as diethylamide **2-48** (Scheme 2.20), which, as desired, proved to be sufficiently stable to purify and isolate. We then protected the alcohol on **2-48** as MOM ether **2-49**, precluding the possibility of re-closure of the lactone. With the lactone successfully opened, we now needed to install the necessary α-β unsaturation at the amide. In order to accomplish this, we attempted to selenate the amide at the α position and eliminate the resulting selenide. However, when we attempted to deprotonate **2-49** with *sec*-butyllithium and treat the resulting anion with diphenyldiselenide, the

only product we observed was ketone **2-50**, which resulted from direct addition of *sec*-butyllithium to the amide moiety.



Scheme 2.20. Lactone Opening as the Amide

Further attempts to deprotonate and selenate **2-49** with LDA returned only starting material (Scheme 2.21). Thinking that the steric bulk imparted by ethyl substituents on the amide was slowing the rate of deprotonation, we synthesized the dimethyl analogue **2-51**. Unfortunately, this substrate also returned only starting material. Importantly, it appeared that in both of these cases it was the initial deprotonation step that was not proceeding, as deprotonation

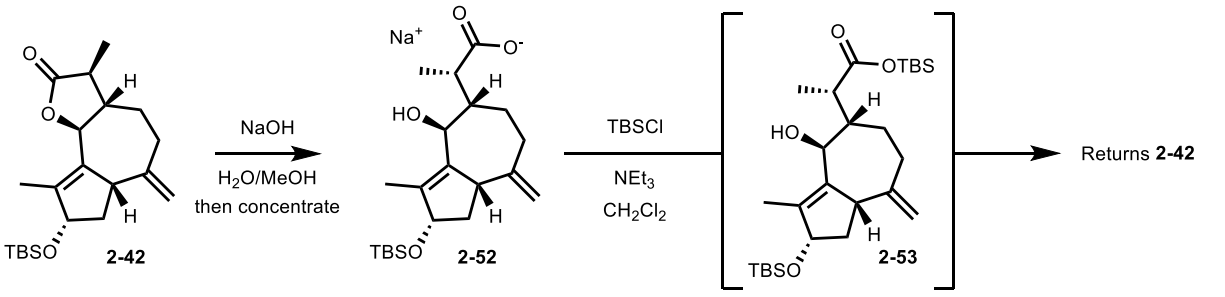


Scheme 2.21. Amides Prove Unreactive towards Selenation Conditions

of **2-49** at the α-position of the amide should at the very least lead to a mixture of diastereomers at the α-position. Seeing that we were recovering starting material as a single diastereomer instead, we concluded that the amide functional group, while stable enough to prevent re-lactonization, was also not acidic enough to undergo the desired selenation reaction. Given this

information, we wondered if a more acidic functional group such as an ester would be better suited for the envisioned selenation / elimination sequence.

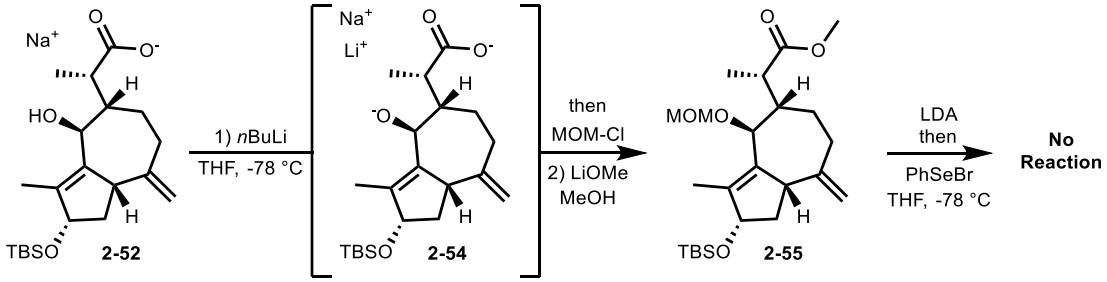
Now that we had decided to open our lactone as an ester, we returned once again to the issue of hydrolyzing the lactone. While workup and purification of the hydrolyzed product of lactone **2-42** had previously proved impractical, we found that we could omit both the workup and purification steps and simply isolate carboxylate **2-52** (Scheme 2.22). With this intermediate in hand, we reasoned that protecting the alcohol on it would preclude the possibility of re-lactonization and thus allow us to manipulate this scaffold further without the need for an amide functionality. However, when we attempted a TBS or TMS protection of the alcohol of **2-52**, we found that we recovered only re-lactonized **2-42**. We hypothesized that this undesired re-lactonization arose from the formation of TBS ester **2-53**, which underwent re-lactonization at a rate that out-competed that of TBS protection of the alcohol.



Scheme 2.22. Unsuccessful Attempt to Open the Lactone as an Ester

In order to circumvent the re-lactonization issue described in Scheme 2.22, we needed the alcohol to undergo protection at a faster rate than the carboxylate group to avoid the formation of an intermediate such as **2-53**. Our solution to this conundrum was to treat carboxylate **2-52** with *n*BuLi, creating dianion **2-54** in situ (Scheme 2.23). This dianion was then treated with MOM-Cl, which led to MOM substitution at both the alcohol and the carboxylate. Finally, treatment of this

bis-MOM protected intermediate with lithium methoxide returned methyl ester **2-55**. To our disappointment, this ester did not show improved reactivity towards selenation as compared to the amide substrate described previously, returning only starting material.



Scheme 2.23. An Ester Moiety Shows No Reactivity towards Selenation

Given the lack of reactivity of both amide **2-49** and ester **2-55**, we hypothesized that deprotonation of these substrates was the result of a prohibitive $A_{1,3}$ strain in the desired enolate (Figure 2.3). As a result, we believe that neither intermediate underwent deprotonation with LDA, explaining our full recovery of starting material without epimerization at the α position of the carbonyl. With this model in mind, we reasoned that we would need to introduce the desired selenium atom prior to opening of the lactone in order to obviate the need for deprotonation after lactone opening and thus avoid this prohibitive strain.

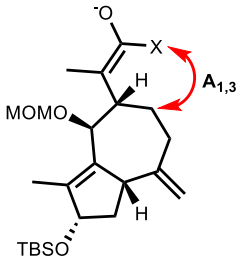
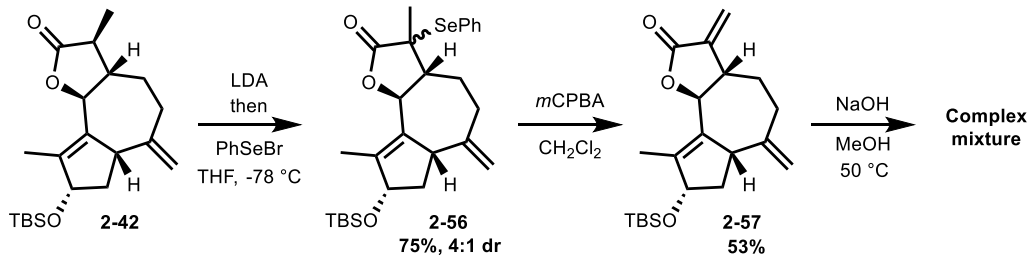


Figure 2.3. Hypothesized $A_{1,3}$ Strain Precluding Deprotonation

2.2.8. Investigations towards Unsaturated Lactone Opening

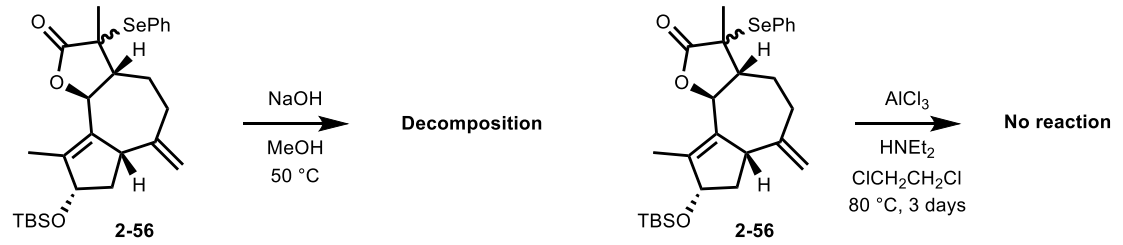
Fortunately, selenation of lactone **2-42** prior to opening proceeded smoothly to afford selenide **2-56** (Scheme 2.24). We were also pleased to observe that elimination of this selenide afforded α-methylene lactone **2-57** with almost exclusive selectivity for the desired exocyclic olefin. With the desired α-β unsaturation now installed, we looked to open the lactone of **2-57** to generate our dienophile moiety. To this end, we envisioned treating **2-57** with the same set of conditions that were used to generate **2-55** (Scheme 2.23). However, unlike its saturated counterpart, we found that exposing **2-57** to standard methanolysis conditions led to a complex mixture of products.



Scheme 2.24. Selenation / Elimination of the Lactone Renders it Base-Sensitive

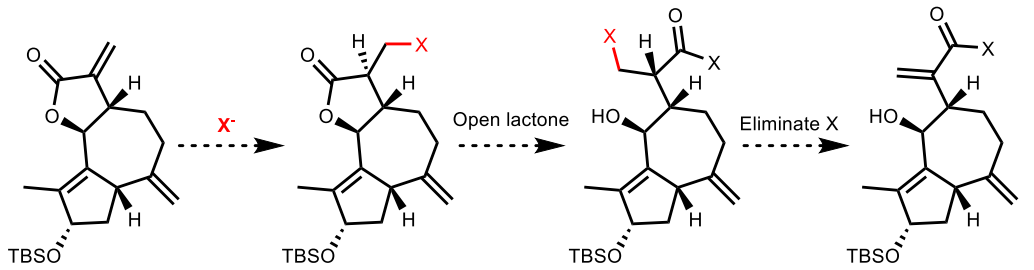
Assuming that the inclusion of a reactive α-methylene moiety on **2-57** had rendered it unstable to basic conditions, we instead wondered if it would be more viable to open the lactone at intermediate **2-56** and then eliminate the selenide afterwards. To answer that question, we subjected **2-56** to standard methanolysis conditions but found that, similarly to **2-57**, this led purely to decomposition of the starting material (Scheme 2.25). Alternatively, we considered opening the α-seleno lactone under Lewis acidic conditions that we had previously used to open the lactone of **2-42** as an amide. However, despite differing from **2-42** only in the substitution of a hydrogen for a SePh group, **2-56** showed starkly different behavior under these conditions. Even after extended reaction times of up to three days and elevated reaction temperatures, no

reaction was observed. We hypothesized that this lack of reactivity was due to steric crowding around the lactone carbonyl caused by the presence of a fully substituted α-center.



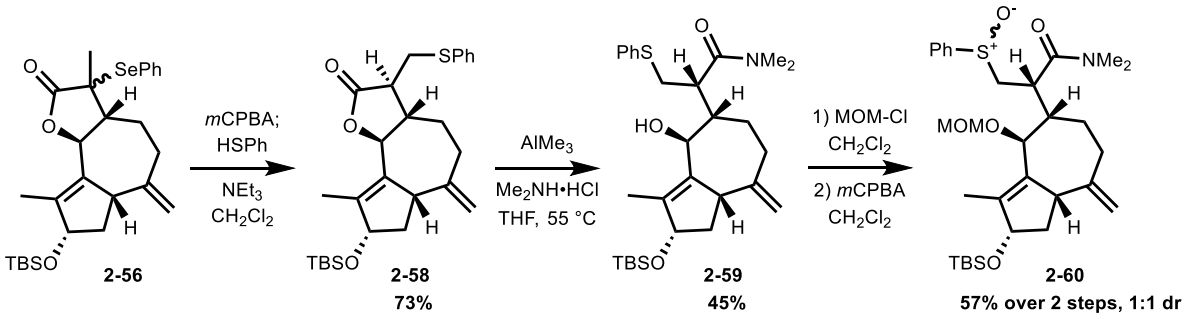
Scheme 2.25. The **α**-Selenide Proves Unstable to Base and Unreactive to Lewis Acid

It was at this point that we back-tracked to α-methylene lactone **2-57**. While this molecule represented the only success that we had had thus far in introducing the unsaturation necessary for our envisioned IMDA cyclization, the high degree of electrophilicity imparted by that unsaturation seemed to be working against us, making this intermediate unstable. Given this conundrum, masking the α-methylene lactone moiety as a more stable functional group seemed to be a prudent approach. Attempting to open the lactone of selenide **2-56** was one attempt at this type of solution, but proved unproductive, possibly as a result of steric crowding of the α-position. Our next attempt to this end would be to introduce a mask at the β position of the lactone (Scheme 2.26), which we hoped would contribute less to steric crowding of the lactone carbonyl. After lactone opening, that masking functional group could then be eliminated to return the desired acrylate.



Scheme 2.26. Hypothetical Path to the Desired Acrylate Employing Masking at the **β**-posiiton

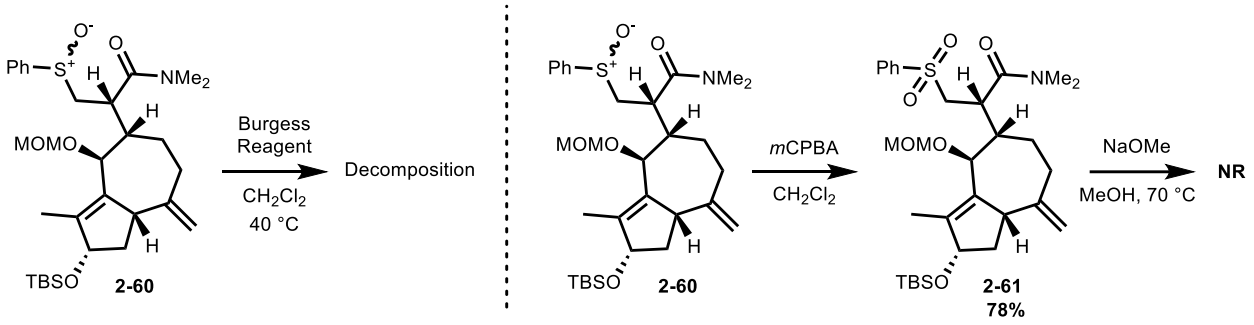
We found that we could introduce a sulfide as a β-position mask in a one-pot sequence by elimination of selenide **2-56** followed by a hetero-Michael addition with thiophenol to afford sulfide **2-58** (Scheme 2.27). In contrast to α-selenide **2-56**, we were pleased to find that the lactone of this sulfide opened relatively easily to afford dimethyl amide **2-59**. Protection of the secondary alcohol of this intermediate followed by oxidation of the sulfide afforded sulfoxide **2-60** as an inconsequential mixture of diastereomers. With this intermediate in hand, we were poised to attempt a sulfoxide elimination to afford an acrylamide that could behave as the dienophile in our envisioned IMDA.



Scheme 2.27. A Thiophenol Masking Group Tolerates Lactone Opening

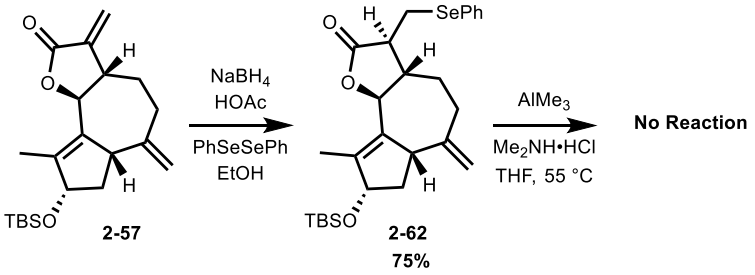
Unfortunately, we found that sulfoxide **2-60** did not easily eliminate under microwave conditions, which instead resulted in decomposition of the starting material. Furthermore, under thermal heating at lower temperatures, no reaction was observed. As a potential workaround, we oxidized sulfoxide **2-60** further to sulfone **2-61**, which we reasoned could also behave as a leaving group for elimination. However, this too yielded disappointing results, with no elimination observed even at elevated temperatures.

Although a β-sulfide as a masking group was easy to install and did not interfere with the desired lactone opening, it was ultimately unsuccessful because it was not easily removed. On the other hand, we had shown that an α-selenide as a masking group had the opposite problem: it was



Scheme 2.28. Neither Sulfoxide nor Sulfone is an Easily Removable Masking Group

easily removed via oxidation, but it interfered with the desired lactone opening. We wondered if it was possible to combine the advantages of both of these groups to create a masking group that would both tolerate the lactone opening and be easily removed. To this end, we synthesized β-selenide **2-62** by conjugate addition of phenyl selenide into **2-57** (Scheme 2.29). While the analogous α-selenide did not tolerate our lactone opening conditions, we suspected that the β-selenide would not be as sterically crowded and thus lead to a more favorable outcome. To our disappointment, we were proven wrong on this point, as subjecting **2-62** to our standard lactone opening conditions returned only starting material.



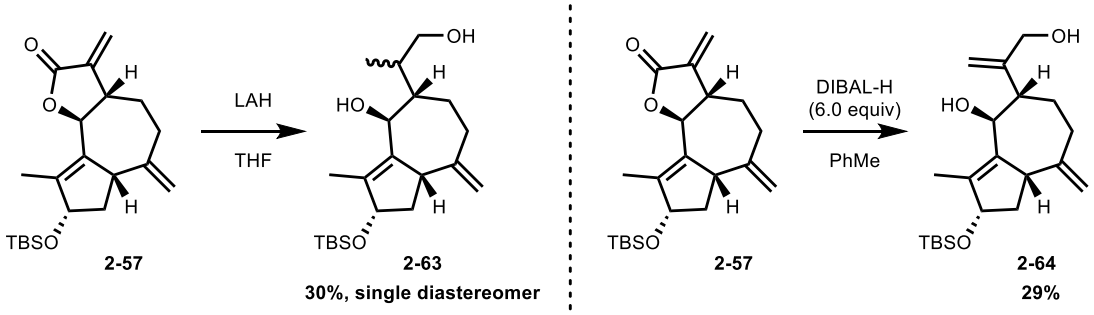
Scheme 2.29. A **β**-Selenide Masking Group Does Not Tolerate Lactone Opening

Given this new information, we were forced to revise our previous hypothesis as to why the selenide substrates were unreactive to our lactone opening conditions. Previously, we had posited that steric crowding was to blame, but when comparing β-sulfide **2-58** and β-selenide **2-62**, it is difficult to argue that the steric situation of the carbonyl carbon is significantly different

between the two. Yet, **2-58** proved to be a competent substrate for our lactone opening, while **2-62** did not. Our revised hypothesis is that the lactone opening of selenides fails to proceed not because of steric crowding, but because the selenium atom likely sequesters the active Lewis acid in solution.[16]

2.2.9. Late-Stage Synthetic Route

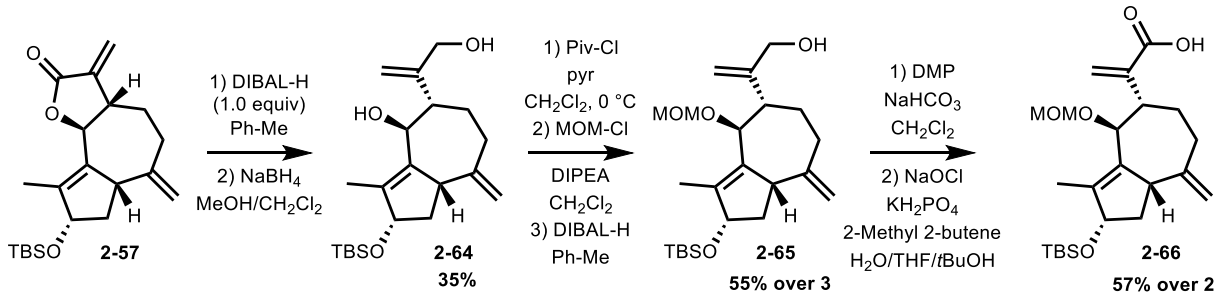
Given that our attempts at masking the conjugate acceptor of **2-57** had failed thus far, we looked to other methods of opening the lactone directly. Although it would inevitably lead to an inelegant sequence of redox manipulations, we reasoned that a reductive opening of the lactone moiety of **2-57** would be a straightforward way to push our synthesis forward. Once again, the Michael acceptor ability of the lactone proved to be problematic, as reduction attempts with LAH led exclusively to the formation of **2-63**, which presumably is the result of conjugate reduction followed by reductive lactone opening (Scheme 2.30). Fortunately, we found that it was possible to avoid conjugate reduction at least partly by using DIBAL-H as the reducing agent, yielding **2-64**. From this point, we would now need to oxidize the primary alcohol of **2-64** in order to generate our desired dienophile.



Scheme 2.30. Reductive Opening of Unsaturated Lactone **2-57** Suffers from Undesired Conjugate Reduction

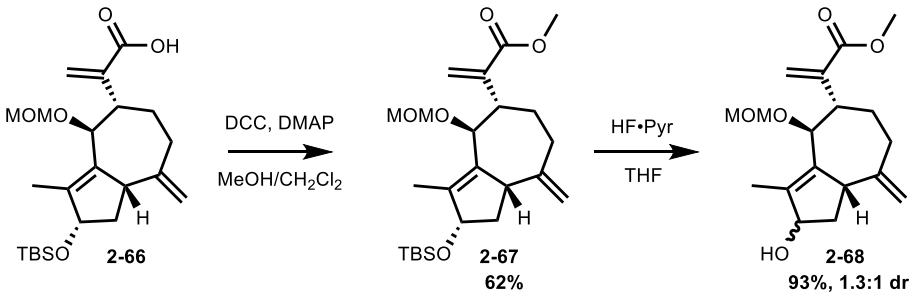
We found that **2-64** could be synthesized with slightly better efficiency and consistency via the two-step reduction sequence described in Scheme 2.31. We next needed to protect the

secondary alcohol so that we could oxidize the primary alcohol selectively. We accomplished this by first selectively protecting the primary alcohol as a pivaloyl ester, then protecting the secondary alcohol as a MOM ether, and finally unveiling the primary alcohol by reduction of the pivaloyl group to afford **2-65**. Next, this primary allylic alcohol was oxidized to an acrylate via a two-step sequence consisting of a Dess–Martin oxidation followed by a Pinnick oxidation to afford **2-66**.



Scheme 2.31. Towards the Key Diels–Alder Substrate

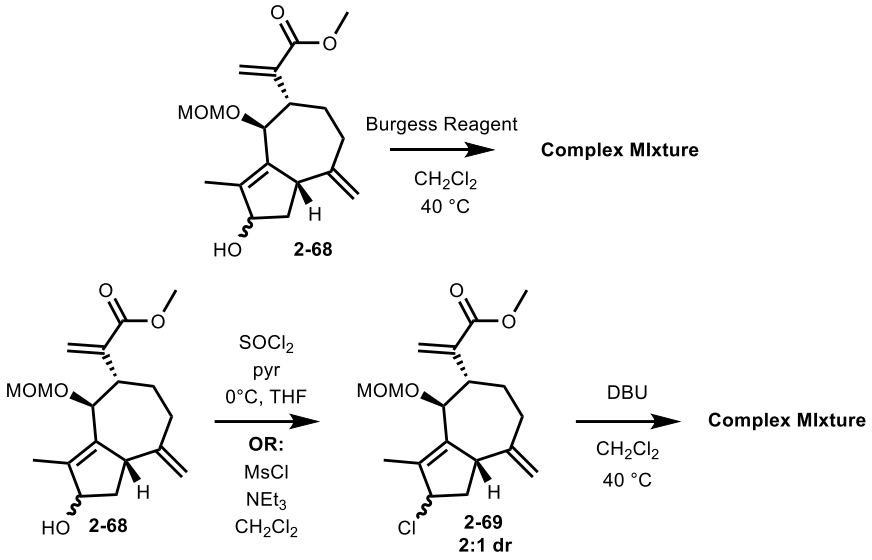
The final steps towards the synthesis of the key Diels–Alder substrate are described in Scheme 2.32. Acrylic acid **2-66** was masked as a methyl ester via a DCC coupling with methanol to afford acrylate **2-67**. The secondary TBS ether was then unveiled to secondary alcohol **2-68** by treatment with HF•pyridine. Interestingly, while **2-67** was mostly one diastereomer, **2-68** was isolated as a mixture of diastereomers, possibly suggesting that ionization of the allylic alcohol takes place under acidic conditions.



Scheme 2.32. Synthesis of the Key Diels–Alder Substrate

2.2.10. Diels–Alder Experiments

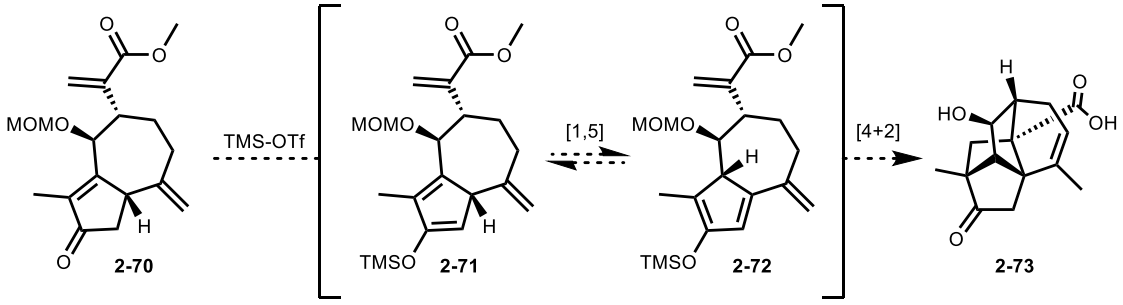
With substrate **2-68** in hand, we were now poised to attempt the key Diels–Alder cyclization. We planned to generate the necessary cyclopentadiene for this reaction by elimination of the secondary allylic alcohol. For this purpose, we attempted an elimination with Burgess reagent (Scheme 2.33), which disappointingly led only to a complex mixture of products that was difficult to interpret on the small scale that we were working on. Alternatively, we



Scheme 2.33. Unsuccessful Approaches to the Key Diels–Alder Cyclization

imagined performing this elimination with thionyl chloride, which had been effective in a previous step for the elimination of an alcohol. We found that, instead of the desired elimination, subjecting **2-68** to thionyl chloride returned the secondary chloride **2-69**. Identical results were also observed when attempting this elimination with mesyl chloride. While this chloride was not the desired product, we reasoned that it was potentially useful for the desired elimination. However, we observed no success when subjecting **2-69** to heating with DBU, which resulted only in a complex mixture of products.

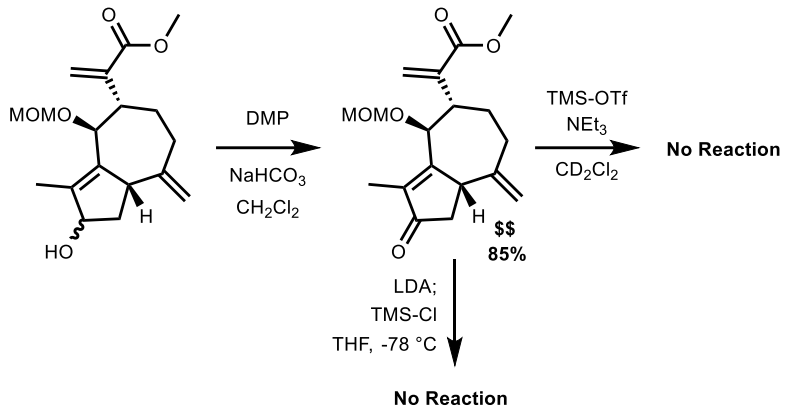
With elimination of the allylic alcohol of **2-68** was proving ineffective, we envisioned an alternate approach to affecting the desired IMDA cyclization, depicted in Scheme 2.34. In this approach, we would oxidize the alcohol of **2-68** to return ketone **2-70**, which could then be transformed to a silyl enol ether such as **2-71**. After engaging in [1,5]-hydride shifts, **2-71** would then convert to the reactive diene **2-72**, which could then engage in an IMDA to return ketone **2-73**. We reasoned that the conversion of ketone **2-70** to silyl enol ether **2-71** might be more facile than the alcohol elimination that we had been attempting previously. Furthermore, the additional oxygen on the diene as compared to our previous approach would make for a more activated alkene and potentially a more facile IMDA cyclization. While this approach would leave us with unnecessary oxidation in the form of the ketone of **2-73**, we believed that a reduction to the desired norbornene was possible.



Scheme 2.34. Alternate Approach to the Key Diels–Alder Cyclization

In order to execute the strategy described above, we performed a Dess–Martin oxidation on **2-68** to return ketone **2-70**. We then attempted to generate the desired silyl enol ether using TMSOTf and triethylamine, but observed no consumption of starting material when monitoring this reaction by NMR, even with extended reaction times and large excess of reagents. Thinking that more forcing conditions were necessary, we instead attempted to deprotonate **2-70** with

LDA and trap the resulting enolate with TMSCl. Sadly, this approach also led to complete recovery of starting material.



Scheme 2.35. The Enone Analogue of the Key Diels–Alder Substrate Proves Unreactive

2.3. Conclusion

In conclusion, we have reported efforts towards two separate synthetic approaches towards artatrovirenols A and B. While our first approach was able to install most of the desired functionality onto cycloheptenone, we ultimately found that forging the necessary 7,5-ring fusion was difficult through the Nazarov approach that we had envisioned. Learning this, we pivoted to an approach based around the photo-Nazarov cyclization and demonstrated that it was a highly effective means of establishing the necessary functionality around the core 7,5-ring system. We identified an unexpected problem step in the transformation of the lactone moiety of α-santonin to the necessary acrylate for the IMDA cyclization. Testing several methods, we finally identified a functional approach via a reductive opening of the lactone. Finally, we have performed preliminary studies on the key IMDA cyclization and identified multiple challenges in the formation of the desired diene.

2.4. Acknowledgements

This work was supported in part by a grant from the National Science Foundation (NSF CHE 210674). We are grateful for their support.

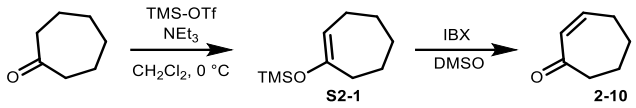
2.5. Supporting Information

2.5.1. General Experimental

All chemicals were purchased from Sigma–Aldrich, Alfa Aesar, TCI, or Fisher Scientific and used without further purification. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories. Solvents were purchased as ACS grade or better and passed through activated alumina columns prior to use. Unless otherwise stated, reactions were performed in flame dried glassware under an atmosphere of argon. Reaction progress was monitored by thin layer chromatography (TLC) using glass plates coated with a 250 μm layer of 60 Å silica gel (SiO_2). TLC plates were visualized using either a UV lamp at 254 nm, potassium permanganate or cerium molybdate (Hanessian's stain). Column chromatography was performed using forced flow on silica gel columns or with an automated purification system on prepacked silica gel columns.

^{1}H NMR spectra were recorded at 500 MHz or 600 MHz using either a Bruker DRX500 (cryoprobe) or Bruker AVANCE600 (cryoprobe) at 298.0 K. ^{13}C NMR spectra were recorded at 125 MHz or 150 MHz on a Bruker DRX500 (cryoprobe) or Bruker AVANCE600 (cryoprobe) at 298.0 K. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to the residual solvent peak or to a tetramethylsilane (TMS) standard. NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublets of doublets, dt = doublet of triplets, dtd = doublet of triplets of doublets, bs = broad singlet), coupling constants (*J*) in hertz (Hz), and integration. High-resolution mass spectrometry was performed using ESI-TOF.

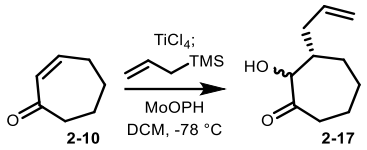
2.5.2. Experimental Procedures and Compound Characterization



cyclohept-2-en-1-one (2-10):

To a dry 500 mL round-bottom flask equipped with a stir bar was added cycloheptanone (0.13 L, 0.11 mol, 1.0 equiv), CH_2Cl_2 (0.20 L, 0.55 M), and NEt_3 (0.30 L, 0.21 mol, 2.0 equiv). This solution was cooled to 0 °C and TMSOTf (0.29 L, 0.16 mol, 1.5 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hr, after which time the reaction was quenched by the addition of saturated sodium bicarbonate (0.10 L). The resulting biphasic mixture was transferred to a 500 mL separatory funnel, where the organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo, which yielded a biphasic mixture of crude **S2-1** and NEt_3. The layers were separated and the crude **S2-1** was taken to the next step without any further purification. It was transferred to a 1 L round-bottom flask equipped with a stir bar and dissolved in DMSO (0.35 L, 0.31 M), with no effort made to exclude air or moisture. This solution was stirred vigorously and 2-iodoxybenzoic acid (45 g, 0.16 mol, 1.5 equiv) was added. The reaction mixture was stirred for 16 hr, after which time it was diluted with Et_2O (0.15 L) and saturated aqueous sodium bicarbonate (0.15 L). The resulting biphasic mixture was filtered through a glass-fritted funnel. The filtrate was transferred to a 1 L separatory funnel, the organic phase collected, and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford **2-10** as a yellow oil (8.3 g, 72% yield of **2-10**), All spectral data are consistent with

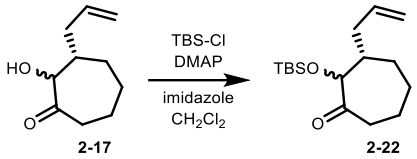
those reported;[17] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.56 (dt, J = 11.5, 5.5 Hz, 1H), 5.99 (d, J = 12.2 Hz, 1H), 2.59 (dd, J = 6.6, 5.5 Hz, 2H), 2.44 (q, J = 5.6 Hz, 2H), 1.88 – 1.73 (m, 4H).



(2S,3S)-3-allyl-2-hydroxycycloheptan-1-one (2-17):

To a dry 100 mL round-bottom flask equipped with a stir bar was added **2-10** (5.1 g, 46 mmol, 1.0 equiv) and CH_2Cl_2 (100 mL, 0.46 M). This solution was cooled to –78 °C and $TiCl_4$ (6.1 mL, 55 mmol 1.2 equiv) was added dropwise. After 5 minutes, allyltrimethylsilane (11 mL, 69 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred for 1 hr, after which a solution of MoOPH (10 g, 23 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL, 0.92 M) was cannulated rapidly into the reaction mixture. After 15 minutes, the reaction was quenched by the addition of a saturated solution of $Na_2S_2O_3$ (50 mL), after which the mixture was allowed to warm to room temperature. The resulting biphasic mixture was then poured into a saturated aqueous solution of NH_4F (100 mL) and stirred vigorously for 10 minutes. The mixture was transferred to a 500 mL separatory funnel, the organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 15% EtOAc in hexanes as the eluting solvent to afford **2-17** as a yellow oil (3.2 g, 42% yield of **2-17**, 1.1:1 dr): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.81 (dddd, J = 16.8, 10.3, 7.8, 6.6 Hz, 0.63H), 5.76 – 5.63 (m, 0.37H), 5.16 – 4.91 (m, 2H), 4.41 (d, J = 3.3 Hz, 0.28H), 4.07 (d, J = 9.2 Hz, 0.58H), 3.86 (bs, 0.28H), 3.71 (bs, 0.52H), 2.74 – 2.33 (m, 3H), 2.28 – 2.07 (m, 1H), 2.00 – 1.76 (m, 3H), 1.75 – 1.56 (m, 2H), 1.46 – 1.13 (m, 2H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 214.1, 213.9, 136.9, 136.4, 117.1, 116.6,

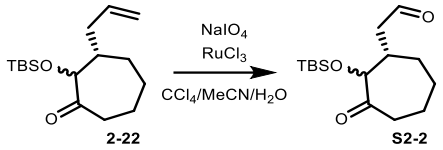
79.4, 79.4, 43.2, 41.8, 40.4, 40.0, 37.4, 32.4, 32.07, 29.9, 27.0, 25.4, 24.2, 22.6. **HRMS (ESI-TOF)** m / z calcd for $C_{10}H_{16}O_2$ $(M + Na)^+$: 191.1048, found 191.1046. This mixture of diastereomers was not separated and carried through further steps.



(2S,3S)-3-allyl-2-((tert-butyldimethylsilyl)oxy)cycloheptan-1-one (2-22):

To a 50 mL round-bottom flask equipped with a stir bar was added **2-17** (0.93 g, 5.5 mmol, 1.0 equiv, mixture of diastereomers), CH_2Cl_2 (20 mL, 0.28 M), DMAP (67 mg, 0.55 mmol, 10 mol%), and imidazole (2.3 g, 33 mmol, 6.0 equiv) with no efforts taken to exclude air or moisture. To this stirred solution was added TBS-Cl (3.3 g, 22 mmol, 4.0 equiv), after which it was stirred for 16 hr. After this time, the reaction was quenched by the addition of a saturated solution of aqueous NH_4Cl (20 mL). The resulting biphasic mixture was transferred to a 100 mL separatory funnel, the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 5% EtOAc in hexanes as the eluting solvent to afford **2-22** as a mixture of diastereomers (1.2 g 75% yield of **2-22**): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.82 – 5.67 (m, 1H), 5.08 – 4.98 (m, 2H), 4.10 (s, 0.40H), 3.94 (d, J = 6.7 Hz, 0.56H), 2.86 – 2.68 (m, 1H), 2.39 – 2.08 (m, 2H), 2.07 – 1.79 (m, 3H), 1.78 – 1.45 (m, 4H), 1.26 (dtd, J = 16.2, 7.8, 2.5 Hz, 0.67H), 1.18 – 1.08 (m, 0.46H), 0.93 (s, 4H), 0.89 (s, 5H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 215.5, 213.2, 137.1, 136.7, 116.9, 116.6, 82.6, 82.2, 43.1, 42.4, 41.1, 39.7, 38.1, 36.0, 30.7, 29.4, 26.8, 25.9, 25.9, 25.5, 24.7, 22.2, 18.2, -4.7, -

4.8, -4.9(5), -4.9(8); **HRMS (ESI-TOF)** m / z calcd for $C_{16}H_{28}O_2Si$ $(M + Na)^+$: 303.1756, found 303.1751.



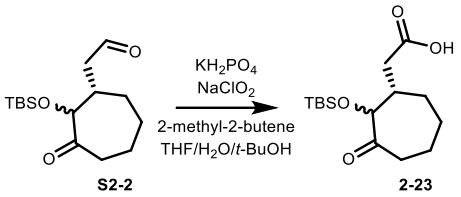
2-((1S,2S)-2-((tert-butyldimethylsilyl)oxy)-3-oxocycloheptyl)acetaldehyde (S2-2):

To a 50 mL round-bottom flask equipped with a stir bar was added **2-22** (1.2 g, 4.1 mmol, 1.0 equiv), CCl_4 (8.0 mL, 0.51 M), MeCN (5.0 mL, 0.82 M), H_2O (5.0 mL, 0.82 M), $RuCl_3$ (43 mg, 0.21 mmol, 5.0 mol%), and sodium periodate (3.5 g, 16 mmol, 4.0 equiv). This mixture was stirred vigorously for 16 hr, after which time it was diluted with Et_2O (10 mL) and a saturated solution of NH_4Cl (5.0 mL) was added. The resulting biphasic mixture was transferred to a 100 mL separatory funnel, the organic phase was collected, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to afford a mixture of **S2-2** and the desired carboxylic acid **2-23**, both a mixture of diastereomers. These two products could be separated by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent, but were typically taken forward to the next step as a mixture without any further purification.

S2-2:

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.81 – 9.58 (m, 1H), 4.14 (m, 0.37H), 4.02 (m, 0.63H), 2.76 – 2.64 (m, 1H), 2.59 (dd, J = 18.6, 7.2 Hz, 0.57H), 2.49 (d, J = 14.9 Hz, 0.43H), 2.42 – 2.14 (m, 3H), 1.93 (m, 2H), 1.70 – 1.46 (m, 3H), 1.36 (m, 1H), 0.97 – 0.79 (m, 9H), 0.11 – -0.05 (m, 6H);

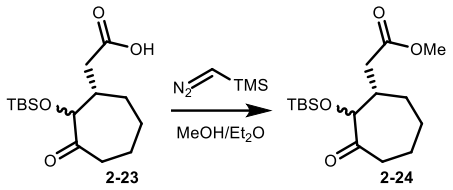
$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 213.9, 212.9, 201.3, 201.3, 82.2, 81.4, 47.5, 46.0, 40.7, 40.2, 37.5, 36.8, 31.2, 26.3, 25.8, 25.3, 23.6, 22.2, 18.2, 18.2, -4.8, -4.9, -5.1, -5.2.



S2-2 **2-23**

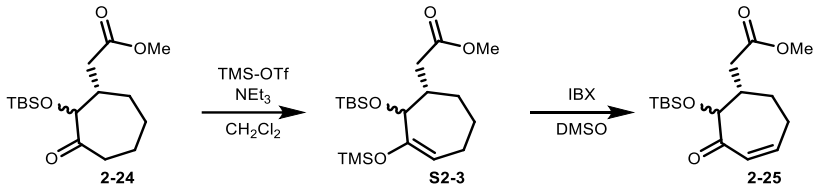
2-((1S,2S)-2-((tert-butyldimethylsilyl)oxy)-3-oxocycloheptyl)acetic acid (2-23):

To a 1 L round-bottom flask equipped with a stir bar was added a mixture of **S2-2** and **2-23** (4.1 mmol, 1.0 equiv), THF (0.16 L, 0.026 M), *tert*-butanol (40 mL, 0.10 M), and 2-methyl-2-butene (40 mL, 0.10 M), with no efforts taken to exclude air or moisture. To this stirred solution was added a chilled solution of KH_2PO_4 (12 g, 90 mmol, 22 equiv) and sodium chlorite (4.1 g, 45 mmol, 11 equiv) in water (40 mL, 0.10 M) dropwise. The reaction mixture was stirred over the course of 16 hr, after which it was diluted with a saturated solution of NH_4Cl (50 mL) and transferred to a 500 mL separatory funnel. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 40% EtOAc in hexanes as the eluting solvent to afford **2-23** as a mixture of diastereomers (1.1 g 89% yield): **^1H NMR** (500 MHz, $CDCl_3$) δ 4.19 (s, 0.43H), 4.05 (d, J = 6.0 Hz, 0.66H), 2.74 (dt, J = 14.0, 6.8 Hz, 1H), 2.55 (d, J = 11.7 Hz, 0.63H), 2.45 (dd, J = 15.8, 6.5 Hz, 0.38H), 2.41 – 2.06 (m, 3H), 2.04 – 1.33 (m, 6H), 0.99 – 0.85 (m, 9H), 0.10 – -0.04 (m, 6H); **$^{13}C\{^1H\}$ NMR** (125 MHz, $CDCl_3$) δ 214.3, 213.1, 178.2, 178.1, 82.0, 81.4, 53.6, 40.8, 40.1, 39.6, 38.8, 38.0, 36.2, 31.0, 30.6, 26.4, 25.9, 25.8, 25.4, 24.0, 22.3, 18.2, -4.7(9), -4.8(4), -5.0, -5.3.



methyl 2-((1S,2S)-2-((tert-butyldimethylsilyl)oxy)-3-oxocycloheptyl)acetate (2-24):

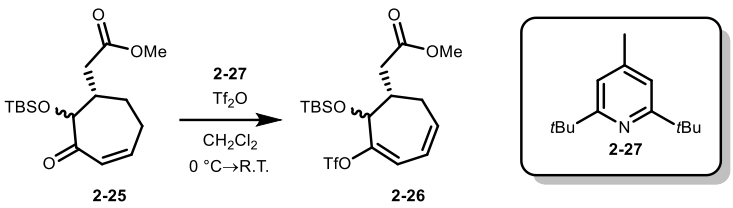
To a dry 100 mL round-bottom flask equipped with a stir bar was added **2-23** (1.1 g, 3.7 mmol, 1.0 equiv), MeOH (8.0 mL, 0.46 M), and Et_2O (28 mL, 0.13 M). This solution was chilled to 0 °C and trimethylsilyldiazomethane (2.0 M in hexanes, 2.8 mL, 5.5 mmol, 1.5 equiv) was added dropwise. The reaction mixture was allowed to stir for 1 hr at room temperature, after which it quenched by the addition of acetic acid (2.0 mL), which was added dropwise in order to avoid excessive bubbling. The reaction mixture was transferred to a 60 mL separatory funnel and washed with a saturated aqueous solution of sodium bicarbonate (20 mL). The organic phase was collected and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **2-24** as a mixture of diastereomers (0.62 g 54% yield): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.14 (d, J = 1.6 Hz, 0.33H), 4.03 (d, J = 6.8 Hz, 0.73H), 3.68 – 3.62 (m, 3H), 2.79 – 2.66 (m, 1H), 2.50 – 2.09 (m, 4H), 2.02 – 1.76 (m, 2H), 1.73 – 1.47 (m, 3H), 1.46 – 1.30 (m, 1H), 0.95 – 0.86 (m, 9H), 0.09 – 0.00 (m, 6H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 214.2, 213.0, 173.0, 172.9, 82.2, 81.5, 51.7, 40.8, 40.0, 39.7, 38.8, 38.2, 36.0, 31.0, 30.5, 26.5, 25.9, 25.8, 25.2, 24.0, 22.3, 18.2, -4.8, -4.9, -5.0, -5.3.



methyl 2-((1S,2S)-2-((tert-butyldimethylsilyl)oxy)-3-oxocyclohept-4-en-1-yl)acetate (2-25):

To a dry 25 mL round-bottom flask equipped with a stir bar was added **2-24** (0.49 g, 1.6 mmol, 1.0 equiv), CH_2Cl_2 (10 mL, 0.16 M), and NEt_3 (1.1 mL, 7.8 mmol, 5.0 equiv). This solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (1.1 mL, 6.2 mmol, 4.0 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hr, after which time the reaction was quenched by the addition of saturated sodium bicarbonate (5.0 mL). The resulting biphasic mixture was transferred to a 30 mL separatory funnel, where the organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo to yield crude **S2-3**, which was taken to the next step without any further purification. It was transferred to a scintillation vial equipped with a stir bar and dissolved in DMSO (8.0 mL, 0.19 M), with no effort made to exclude air or moisture. This solution was stirred vigorously and 2-iodoxybenzoic acid (0.63 g, 2.3 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 16 hr, after which time it was diluted with Et_2O (5.0 mL) and saturated aqueous sodium bicarbonate (5.0 mL). The resulting biphasic mixture was filtered through a glass-fritted funnel. The filtrate was transferred to a 60 mL separatory funnel, the organic phase collected, and the aqueous phase extracted with Et_2O (3 x 10 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **2-25** as a mixture of diastereomers (0.26 g 53% yield over two steps): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.78 – 6.62 (m, 1H), 5.98 (d, J = 12.1 Hz,

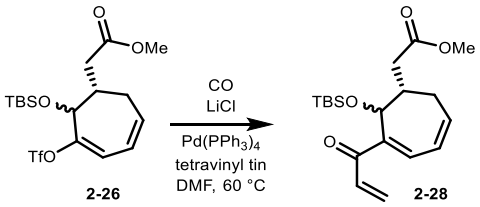
0.43H), 5.94 (d, J = 11.8 Hz, 0.60H), 4.40 (d, J = 5.1 Hz, 0.36H), 4.11 (d, J = 5.8 Hz, 0.66H), 3.72 – 3.63 (m, 3H), 2.74 – 2.51 (m, 2H), 2.51 – 2.29 (m, 2H), 2.26 (dd, J = 15.6, 8.4 Hz, 0.67H), 2.08 (dd, J = 15.8, 9.0 Hz, 0.42H), 2.04 – 1.89 (m, 1H), 1.62 – 1.50 (m, 1H), 0.92 – 0.85 (m, 9H), 0.07 – -0.02 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (125 MHz, $CDCl_3$) δ 202.8, 201.7, 173.5, 172.8, 148.0, 147.2, 130.5, 129.6, 82.4, 80.2, 51.8, 51.7, 39.1, 37.6, 36.8, 35.4, 30.1, 29.3, 27.9, 27.5, 25.9, 25.9, 25.9, 18.5, 18.3, -4.7, -5.2, -5.4.



methyl 2-((1S,2S)-2-((tert-butyldimethylsilyl)oxy)-3-(((trifluoromethyl)sulfonyl)oxy)cyclohepta-3,5-dien-1-yl)acetate (2-26):

To a dry scintillation vial equipped with a stir bar was added **2-25** (0.19 g, 0.62 mmol, 1.0 equiv), CH_2Cl_2 (6.0 mL, 0.11 M), and **2-27** (0.15 g, 0.74 mmol, 1.2 equiv). This solution was chilled to 0 °C and Tf_2O (0.11 mL, 0.68 mmol, 1.1 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for an additional 16 hr. It was then quenched by the addition of saturated aqueous sodium bicarbonate (3.0 mL) and the resulting biphasic mixture was transferred to a 30 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **2-26** as a mixture of diastereomers (0.13 g 46% yield): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.13 – 5.96 (m, 2H), 5.81 (ddd, J = 11.6, 8.4, 3.3 Hz, 0.62H), 5.70 (dddd, J = 11.8, 8.3, 2.8, 0.8 Hz, 0.38H), 4.47

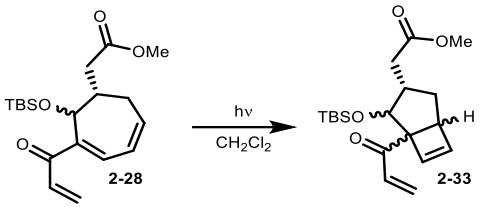
– 4.36 (m, 1H), 3.77 – 3.59 (m, 3H), 2.78 (ddd, J = 18.0, 6.2, 3.0 Hz, 0.62H), 2.58 (ddt, J = 17.9, 11.3, 3.1 Hz, 0.38H), 2.51 – 2.16 (m, 4H), 0.94 – 0.86 (m, 9H), 0.23 – 0.09 (m, 6H); **$^{13}C\{^{1}H\}$ NMR** (125 MHz, $CDCl_3$) δ 172.7, 172.6, 151.9, 151.8, 137.3, 136.9, 120.3, 120.0, 119.4, 118.5, 74.2, 73.7, 51.9, 37.7, 35.5, 34.4, 33.0, 30.4, 27.5, 25.9, 25.8, 18.4, 18.1, -4.6, -4.7(7), -4.7(9), -5.3.



methyl 2-((1S,2S)-3-acryloyl-2-((tert-butyldimethylsilyl)oxy)cyclohepta-3,5-dien-1-yl)acetate (2-28):

To a scintillation vial was added **2-26** (0.13 g, 0.28 mmol, 1.0 equiv), LiCl (36 mg, 0.85 mmol, 3.0 equiv), $Pd(PPh_3)_4$ (16 mg, 14 μmol, 5.0 mol%), and DMF (3.0 mL, 0.095 M). Through this solution was bubbled carbon monoxide gas over the course of 15 minutes, after which tetravinyl tin (77 μL, 0.43 mmol, 1.5 equiv) was added. The carbon monoxide bubbling was resumed and the reaction was heated to 60 °C for 1.5 hr, after which it was diluted with EtOAc (3.0 mL) and transferred to a 30 mL separatory funnel. The crude reaction mixture was washed with saturated aqueous sodium bicarbonate (10 mL), the organic phase was collected, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, redissolved in Et_2O, and passed through a plug of SiO_2 in order to remove residual DMF. The crude product was once again concentrated in vacuo and purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **2-28** as a mixture of diastereomers (83 mg 84% yield): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.97 –

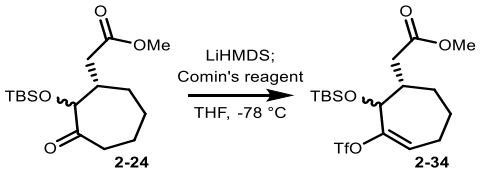
6.80 (m, 2H), 6.30 – 6.14 (m, 2H), 6.02 (ddd, J = 11.0, 7.7, 2.8 Hz, 0.75H), 5.95 (t, J = 8.6 Hz, 0.27H), 5.80 – 5.69 (m, 1H), 5.12 – 5.00 (m, 1H), 3.67 (s, 0.86H), 3.62 (s, 2.15H), 2.91 (d, J = 19.3 Hz, 0.77H), 2.67 – 2.58 (m, 0.32H), 2.55 (s, 0.77H), 2.47 (dd, J = 15.4, 6.2 Hz, 0.42H), 2.44 – 2.15 (m, 1.65H), 2.03 – 1.93 (m, 1.52H), 1.75 – 1.62 (m, 0.61H), 0.81 (s, 9H), 0.16 – 0.06 (m, 3H), -0.08 (s, 2.19H), -0.16 (s, 0.80H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 193.0, 191.4, 173.1(4), 173.0(6), 143.9, 142.6, 142.2, 142.0, 136.9, 136.1, 133.0, 132.4, 128.8, 128.5, 123.2, 122.0, 67.8, 67.5, 51.7(4), 51.7(3), 39.9, 36.8, 34.9, 33.8, 32.9, 30.2, 26.0, 25.9, 18.1, -4.3, -4.5, -5.0, -5.3; **HRMS (ESI-TOF)** m / z calcd for $C_{19}H_{30}O_4Si$ $(M + Na)^+$: 373.1811, found 373.1819.



methyl 2-(-1-acryloyl-2-((tert-butyldimethylsilyl)oxy)bicyclo[3.2.0]hept-6-en-3-yl)acetate (2-33):

To a quartz test tube was added **2-28** (15 mg, 43 μmol, 1.0 equiv) and CH_2Cl_2. Through the solution was bubbled argon gas over the course of 15 minutes, after which the tube was placed approximately 15 cm from a 450 W medium pressure Hg vapor lamp and irradiated under constant argon pressure for 1 hr. The crude rection mixture was concentrated in vacuo and purified by flash column chromatography using 0 – 5% EtOAc as the eluting solvent to afford **2-33** as a mixture of diastereomers: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.75 (dd, J = 17.1, 10.3 Hz, 1H), 6.46 (s, 0.11H), 6.39 – 6.34 (m, 1.37H), 6.33 (s, 0.46H), 6.31 (d, J = 2.1 Hz, 0.13H), 6.27 (d, J = 2.4 Hz, 0.85H), 5.72 – 5.60 (d, J = 10.3 Hz, 1H), 4.75 (d, J = 6.5 Hz, 0.12H), 4.23 (d, J = 9.2 Hz, 0.87H), 3.67 (s, 2.66H), 3.65 (s, 0.44H), 3.21 (d, J = 6.8 Hz, 0.12H), 3.11 (d, J = 6.9 Hz,

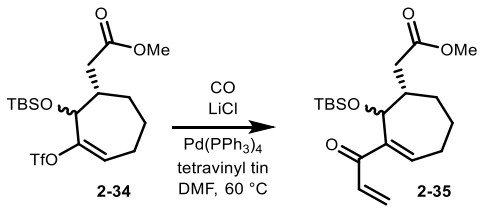
0.86H), 2.84 – 2.75 (m, 0.24H), 2.69 (dd, J = 15.2, 3.3 Hz, 0.86H), 2.60 – 2.47 (m, 1H), 2.23 (dd, J = 15.2, 10.5 Hz, 0.88H), 1.90 (dt, J = 14.5, 7.4 Hz, 0.12H), 1.79 (dd, J = 13.3, 6.1 Hz, 0.87H), 1.62 (d, J = 13.8 Hz, 0.16H), 1.28 – 1.19 (m, 1H), 0.86 (s, 1H), 0.83 (s, 8H), 0.07 (s, 2.63H), 0.04 (s, 0.43H), -0.03 (s, 0.43H), -0.09 (s, 2.63H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 199.6, 173.6, 141.3, 135.8, 132.4, 128.7, 75.5, 69.2, 51.7, 51.4, 40.9, 36.4, 28.3, 26.0, 18.1, -4.3, -4.7.



methyl 2-(-2-((tert-butyldimethylsilyl)oxy)-3-(((trifluoromethyl)sulfonyl)oxy)cyclohept-3-en-1-yl)acetate (2-34):

To a dry scintillation vial equipped with a stir bar was added hexamethyldisilazane (0.25 mL, 1.2 mmol, 1.2 equiv) and THF (1.0 mL, 1.0 M). This solution was cooled to –78 °C and *n*-butyllithium (0.44 mL, 1.1 mmol, 1.1 equiv) was added dropwise. This solution was warmed to room temperature for 5 minutes, after which it was cooled back to –78 °C and **2-24** (0.31 g, 1.0 mmol, 1.0 equiv) was added as a solution in THF (1.0 mL, 1.0 M). After stirring for 30 minutes at this same temperature, Comin's reagent (0.39 g, 1.0 mmol, 1.0 equiv) was added as a solution in THF (1.0 mL, 1.0 M). The resulting mixture was stirred for 30 minutes at –78 °C and then another 30 minutes at 0 °C, after which it was poured into a 3:1 mixture of Et_2O : pentanes (3.0 mL) and transferred to a 30 mL separatory funnel. The crude mixture was washed with aqueous sodium hydroxide (2.5 M, 3.0 mL), the organic layer was collected, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 10%

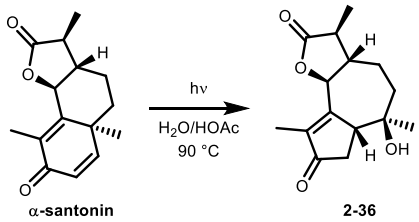
EtOAc in hexanes as the eluting solvent to afford **2-34** as a mixture of diastereomers (0.27 g 61% yield): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.01 (ddd, J = 7.6, 5.6, 2.0 Hz, -0.51H), 5.96 (ddd, J = 8.7, 4.3, 1.8 Hz, 0.48H), 4.29 (dd, J = 4.9, 1.6 Hz, 0.48H), 4.21 (s, 0.52H), 3.67 (app. d, J = 2.7 Hz, 3H), 2.43 – 2.27 (m, 3H), 2.27 – 2.16 (m, 1H), 2.16 – 2.07 (m, 1H), 1.92 – 1.77 (m, 1H), 1.71 – 1.53 (m, 3H), 0.90 (app. d, J = 3.1 Hz, 9H), 0.13 – 0.07 (m, 5H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 173.0, 172.7, 153.1, 151.9, 126.8, 125.5, 118.61 (app. qd, J = 320.3, 16.6 Hz), 75.5, 74.8, 51.8, 51.7, 39.3, 38.5, 37.3, 35.2, 30.4, 28.3, 26.0, 25.9, 25.8, 24.6, 24.1, 21.5, 18.3, 18.2, -4.8, -5.0, -5.1, -5.5.



methyl 2-(-3-acryloyl-2-((tert-butyldimethylsilyl)oxy)cyclohept-3-en-1-yl)acetate (2-35):

To a scintillation vial was added **2-34** (0.27 g, 0.61 mmol, 1.0 equiv), LiCl (77 mg, 1.8 mmol, 3.0 equiv), $Pd(PPh_3)_4$ (35 mg, 31 μmol, 5.0 mol%), and DMF (6.0 mL, 0.10 M). Through this solution was bubbled carbon monoxide gas over the course of 15 minutes, after which tetravinyl tin (0.17 mL, 0.92 mmol, 1.5 equiv) was added. The carbon monoxide bubbling was resumed and the reaction was heated to 60 °C for 1.5 hr, after which it was diluted with EtOAc (6.0 mL) and transferred to a 60 mL separatory funnel. The crude reaction mixture was washed with saturated aqueous sodium bicarbonate (20 mL), the organic phase was collected, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, redissolved in Et_2O, and passed through a plug of SiO_2 in order to remove residual DMF. The crude product was once again concentrated in vacuo and

purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **2-35** as a mixture of diastereomers (0.14 g 63% yield): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.12 (app. dddd, J = 18.2, 9.1, 4.8, 1.2 Hz, 1H), 6.84 (app. dt, J = 17.1, 10.4 Hz, 1H), 6.20 (app. ddd, J = 17.1, 12.7, 1.8 Hz, 1H), 5.72 (app. ddd, J = 10.6, 3.3, 1.8 Hz, 1H), 4.94 (dd, J = 5.4, 1.1 Hz, 0.45H), 4.90 (s, 0.53H), 3.67 (s 1.51H), 3.64 (s, 1.51H), 2.82 – 2.69 (m, 1H), 2.48 – 2.38 (m, 1H), 2.28 – 2.18 (m, 2H), 2.15 (dd, J = 15.6, 9.2 Hz, 0.61H), 2.07 – 1.96 (m, 1H), 1.88 – 1.80 (m, 0.55H), 1.69 – 1.42 (m, 3H), 0.87 (app. d, J = 4.6 Hz, 9H), 0.06 (app. d, J = 3.5 Hz, 3H), -0.09 (s 1.4H), -0.15 (s 1.44H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 191.8, 191.2, 173.5, 173.3, 148.9, 148.5, 146.6, 145.0, 132.2, 128.5(3), 128.4(7), 69.5, 69.0, 51.7, 51.6, 40.8, 39.4, 37.0, 34.3, 31.2, 28.5, 27.8, 27.5, 26.5, 26.0, 25.9, 20.7, 18.3, 18.2, -4.5, -4.8, -5.2, -5.4.

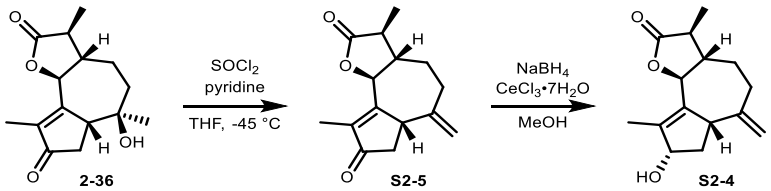


α-santonin 2-36

Isophotosantonic Lactone (2-36):

Two 100 mL quartz round-bottom flasks equipped with stir bars were charged with α-santonin (2.5 g to each flask, 5.0 g total, 20 mmol, 1.0 equiv), which was then suspended in acetic acid (20 mL to each flask, 40 mL total, 0.50 M) and water (30 mL to each flask, 60 mL total, 0.33 M). Argon was bubbled through each suspension for 15 minutes to remove any residual oxygen. The flasks were placed on opposite sides of a 450 W medium pressure Hg vapor lamp, as close to the lamp as possible, and irradiated under constant argon pressure at 90 °C for 18 hr. The crude reaction mixtures were combined, concentrated in vacuo, and purified by flash column chromatography using 50 – 90% EtOAc in hexanes as the eluting solvent to afford **2-36** as a

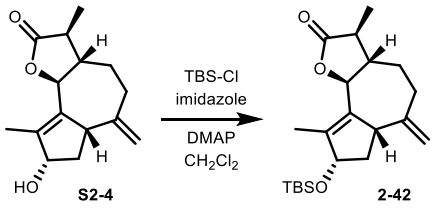
white crystalline solid (0.90 g, 42% yield): $\mathbf{R_f}$ = 0.30 (9:1 EtOAc:Hex, $KMnO_4$); All spectral data are consistent with those reported;[18] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.81 (d, J = 11.0 Hz, 1H), 3.28 – 3.15 (m, 1H), 2.60 (ddd, J = 19.7, 2.9, 0.7 Hz, 1H), 2.54 (dd, J = 19.7, 6.2 Hz, 1H), 2.32 (dq, J = 12.2, 6.9 Hz, 1H), 2.13 (qd, J = 11.3, 1.4 Hz, 1H), 2.10 – 2.05 (m, 2H), 1.89 (dd, J = 2.1, 1.6 Hz, 3H), 1.84 – 1.76 (m, 1H), 1.69 (bs, 1H), 1.49 – 1.40 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H), 0.96 (s, 3H).



(3S,3aS,6aS,8S,9bS)-8-hydroxy-3,9-dimethyl-6-methylene-3a,4,5,6,6a,7,8,9b-octahydroazuleno[4,5-b]furan-2(3H)-one (S2-4):

To a flame-dried 200 mL round-bottom flask equipped with a stir bar was added **2-36** (11 g, 42 mmol, 1.0 equiv) and THF (50 mL, 0.84 M). To a separate flame-dried 100 mL round-bottom flask was added thionyl chloride (35 mL, 1.2 M), pyridine (35 mL, 1.2 M), and THF (50 mL, 0.84 M). The solution of **2-36** was cooled to –45 °C and the thionyl chloride / pyridine solution was cannulated into it under argon pressure. The reaction mixture was warmed to room temperature over the course of ten minutes, after which it was slowly poured into a stirring ice-water mixture (0.20 L) in order to avoid an exotherm. The resulting mixture was transferred to a 1 L separatory funnel and extracted with EtOAc (3 x 0.10 L). The combined organic layers were dried with sodium sulfate and concentrated in vacuo to afford **S2-5**, for which the exocyclic olefin proved to isomerize into conjugation over the course of about a week. Thus, the crude residue was immediately carried to the next step without any further purification. The crude

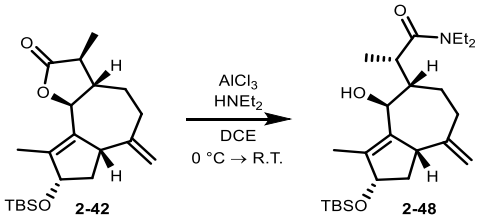
residue was transferred to a 2 L round-bottom flask equipped with a stir bar and dissolved in methanol (0.80 L, 0.053 M). To this stirred solution was added $CeCl_3 \bullet 7H_2O$ (24 g, 63 mmol, 1.5 equiv), followed by portionwise addition of $NaBH_4$ (8.0 g, 5.0 equiv, 0.21 mol). The reaction mixture was stirred for 15 minutes, at which time it was concentrated in vacuo. The crude residue was dissolved in CH_2Cl_2 (0.20 L), filtered through a plug of celite, and transferred to a 1 L separatory funnel. It was washed with saturated aqueous NH_4Cl (0.20 L), the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried with sodium sulfate and concentrated in vacuo. The crude residue was then purified by flash column chromatography using 0 – 55% EtOAc in hexanes as the eluting solvent to afford **S2-4** as an amorphous solid (7.0 g, 60% yield, 5:1 dr). Only the major diastereomer is characterized here: $\mathbf{R_f}$ = 0.40 (1:1 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.90 (app. d, J = 3.4 Hz, 2H), 4.74 (d, J = 10.7 Hz, 1H), 4.56 (t, J = 6.8 Hz, 1H), 3.30 (t, J = 6.1 Hz, 1H), 2.53 (dt, J = 13.3, 7.3 Hz, 1H), 2.41 (dt, J = 12.5, 5.4 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.16 – 2.11 (m, 1H), 2.11 – 2.04 (m, 2H), 1.88 (s, 3H), 1.83 – 1.75 (m, 1H), 1.61 (ddd, J = 13.3, 7.1, 1.0 Hz, 1H), 1.45 – 1.37 (m, 1H), 1.22 (d, J = 6.9 Hz, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 178.7, 150.3, 141.6, 134.8, 111.2, 81.2, 78.5, 49.0, 48.1, 41.8, 40.1, 36.5, 31.1, 12.8, 11.9; **HRMS (ESI-TOF)** m / z calcd for $C_{15}H_{20}O_3$ $(M + Na)^+$: 271.1310, found 271.1300.



S2-4 2-42

(3S,3aS,6aS,8S,9bS)-8-((tert-butyldimethylsilyl)oxy)-3,9-dimethyl-6-methylene-3a,4,5,6,6a,7,8,9b-octahydroazuleno[4,5-b]furan-2(3H)-one (2-42):

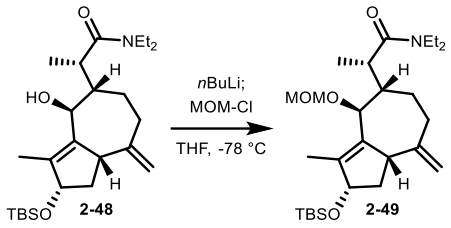
To a 500 mL round-bottom flask equipped with a stir bar was added **S2-4** (7.0 g, 28 mmol, 1.0 equiv), imidazole (12 g, 0.17 mmol, 6.0 equiv), DMAP (0.34 g, 2.8 mmol, 10 mol%), and CH_2Cl_2 (0.25 L, 0.11 M). To this stirred solution was added TBS-Cl (17 g, 0.11 mol, 4.0 equiv). The reaction mixture was stirred for 16 hr, after which it was quenched by the addition of MeOH (50 mL), followed by saturated aqueous NH_4Cl (0.10 L) and transferred to a 500 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried with sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography using 0 – 10% EtOAc in hexanes as the eluting solvent to afford **2-42** as a yellow oil (6.0 g, 59% yield): $\mathbf{R_f}$ = 0.30 (1:9 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.89 (d, J = 14.2 Hz, 2H), 4.75 (d, J = 10.7 Hz, 1H), 4.55 (td, J = 7.0, 1.1 Hz, 1H), 3.28 (t, J = 6.6 Hz, 1H), 2.45 – 2.35 (m, 2H), 2.27 – 2.17 (m, 1H), 2.17 – 1.97 (m, 3H), 1.81 (s, 3H), 1.65 – 1.55 (m, 1H), 1.47 – 1.36 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 178.8, 150.4, 143.0, 133.3, 111.2, 81.2, 78.4, 48.9, 47.9, 41.8, 41.2, 35.9, 31.1, 26.0, 18.4, 12.9, 12.2, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{34}O_3Si$ $(M + Na)^+$: 385.2175, found 385.2190.



(S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-hydroxy-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-diethylpropanamide (2-48):

To a dry 1-dram vial equipped with a stir bar was added $AlCl_3$ (0.19 g, 1.4 mmol, 1.3 equiv) and $ClCH_2CH_2Cl$ (1.0 mL, 1.1 M). This suspension was cooled to 0 °C and $HNEt_2$ (0.29 mL, 2.8

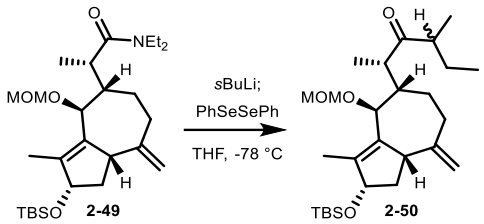
mmol, 2.5 equiv) was added to it dropwise. This mixture was allowed to stir for 15 minutes, after which it was warmed to room temperature and **2-42** (0.41 g, 1.1 mmol, 1.0 equiv) as a solution in $ClCH_2CH_2Cl$ (1.0 mL, 1.1 M) was added dropwise. The reaction mixture was stirred for 16 hr at room temperature, after which it was quenched by the addition of aqueous 1M NaOH (2.0 mL). After stirring for 30 minutes, the biphasic mixture was transferred to a 30 mL separatory funnel. The organic phase was collected, and the aqueous phase was washed with CH_2Cl_2 (3 x 5.0 mL). The combined organic phases were dried with sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford **2-48** as a white crystalline solid (0.35 g, 69% yield): $\mathbf{R_f}$ = 0.30 (3:2 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.87 (d, J = 1.8 Hz, 1H), 4.72 (s, 1H), 4.49 (t, J = 6.6 Hz, 1H), 4.41 (d, J = 6.3 Hz, 1H), 3.48 – 3.37 (m, 3H), 3.36 – 3.29 (m, 1H), 3.24 – 3.17 (m, 1H), 2.71 (p, J = 6.9 Hz, 1H), 2.34 (dt, J = 12.8, 7.3 Hz, 1H), 2.31 – 2.25 (m, 1H), 2.23 – 2.12 (m, 3H), 1.81 (dtd, J = 9.7, 7.3, 2.4 Hz, 1H), 1.62 (s, 3H), 1.59 – 1.51 (m, 1H), 1.45 (ddd, J = 12.9, 7.7, 6.4 Hz, 1H), 1.16 (t, J = 7.1 Hz, 3H), 1.13 – 1.08 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 176.0, 152.2, 140.5, 139.2, 111.0, 79.1, 70.2, 48.5, 45.1, 42.1, 41.4, 40.5, 36.8, 30.5, 26.0, 23.7, 18.3, 16.0, 14.7, 13.1, 11.7, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{25}H_{45}NO_3Si$ $(M + Na)^+$: 458.3066, found 458.3067, $[\alpha]_D^{21.4}$ = -9.51 (c = 1.08 in $CHCl_3$)



(S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-diethylpropanamide (2-49):

To a dry scintillation vial equipped with a stir bar was added **2-48** (0.35 g, 0.95 mmol, 1.0 equiv) and THF (5.0 mL, 0.19 M). The solution was cooled to –78 °C and *n*-butyl-lithium (2.5 M in hexanes, 0.42 mL, 1.1 mmol, 1.1 equiv) was added dropwise. The reaction mixture was warmed to 0 °C and stirred for 1 hr, after which chloromethyl methyl ether (0.45 mL, 3.8 mmol, 4.0 equiv) was added. After stirring at room temperature 1 hr, the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL) and transferred to a 30 mL separatory funnel, where it was extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified using flash column chromatography with 0 – 30% EtOAc in hexanes as the eluting solvent to afford **2-49** as a yellow oil (0.24 g, 69% yield): $\mathbf{R_f}$ = 0.35 (3:7 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.83 (d, J = 1.2 Hz, 1H), 4.66 (s, 1H), 4.50 (t, J = 6.3 Hz, 1H), 4.46 – 4.40 (m, 3H), 3.55 – 3.39 (m, 2H), 3.32 (s, 3H), 3.29 (t, J = 7.8 Hz, 1H), 3.26 – 3.18 (m, 1H), 3.12 (dq, J = 14.3, 7.0 Hz, 1H), 2.80 (p, J = 6.8 Hz, 1H), 2.38 – 2.20 (m, 3H), 2.18 – 2.06 (m, 1H), 1.89 (dtd, J = 14.6, 7.4, 1.7 Hz, 1H), 1.61 (s, 3H), 1.58 – 1.49 (m, 1H), 1.45 (ddd, J = 13.0, 7.0, 6.3 Hz, 1H), 1.13 – 1.04 (m, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 175.2, 152.7, 143.2, 136.0, 110.7, 93.4, 79.0, 72.6, 55.4, 48.7, 42.4, 41.8, 41.3, 40.3, 35.1, 30.1, 25.9, 21.7, 18.2, 14.6, 14.3, 13.1, 11.7, -4.3, -

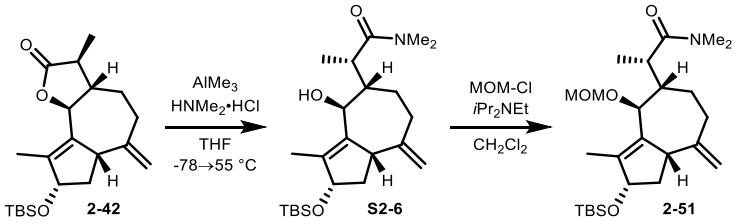
4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{27}H_{49}NO_4Si$ $(M + Na)^+$: 502.3329, found 502.3317, $[\alpha]_D^{20.8}$ **= 17.6** (c = 1.15 in $CHCl_3$).



(2S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-4-methylhexan-3-one (2-50):

To a dry 1-dram vial was added **2-49** (55 mg, 0.12 mmol, 1.0 equiv) and THF (1.0 mL, 0.12 M). The solution was cooled to –78 °C and *sec*-butyllithium (1.4 M solution in cyclohexane, 90 µL, 0.13 mmol, 1.1 equiv) was added dropwise, after which the reaction mixture was stirred for 45 minutes at –78 °C. Next, PhSeSePh (43 mg, 0.14 mmol, 1.2 equiv) was added as a solution in THF (0.50 mL) and the reaction mixture was stirred for 30 minutes at –78 °C at which time the reaction was quenched by the addition of saturated aqueous NH_4Cl (0.50 mL). The mixture was transferred to a 30 mL separatory funnel and extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified via flash column chromatography with hexanes as the eluting solvent to afford **2-50**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.84 (dd, J = 7.4, 1.9 Hz, 1H), 4.62 (d, J = 15.9 Hz, 1H), 4.55 (t, J = 6.6 Hz, 1H), 4.49 (dd, J = 6.8, 2.3 Hz, 1H), 4.42 (d, J = 6.8 Hz, 1H), 4.36 (dd, J = 8.5, 3.2 Hz, 1H), 3.37 (s, 4H), 3.07 – 2.92 (m, 1H), 2.79 – 2.66 (m, 1H), 2.47 – 2.26 (m, 3H), 2.07 – 1.94 (m, 1H), 1.74 – 1.69 (m, 3H), 1.69 – 1.58 (m, 1H), 1.44 – 1.20 (m, 4H), 1.05 – 0.95 (m, 6H), 0.90 (d, J = 11.3 Hz, 9H), 0.83 (dt, J = 18.1, 7.4 Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 217.8, 217.1, 151.8, 151.6, 144.7, 144.7, 134.9, 134.9, 112.1, 112.0, 93.2, 93.2, 79.1, 73.4,

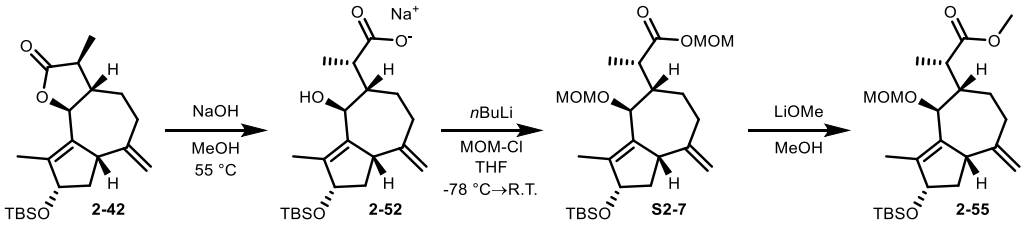
73.2, 55.6, 55.6, 49.2, 49.2, 47.6, 45.8, 45.7, 45.5, 41.5, 41.4, 39.5, 39.3, 29.3, 29.1, 27.5, 26.0, 25.7, 20.8, 20.7, 18.3, 17.9, 16.5, 12.3, 12.0, 11.5, 11.5, 9.6, 9.4, -4.3, -4.7.



(S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-dimethylpropanamide (2-51):

To a dry 1-dram vial equipped with a stir bar was added $HNMe_2$•HCl (45 mg, 0.55 mmol, 2.0 equiv) and THF (1.0 mL, 0.28 M). This suspension was cooled to –78 °C and $AlMe_3$ (2.0 M in toluene, 0.28 mL, 0.55 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 30 minutes at –78 °C, after which time **2-42** (0.10 g, 0.28 mmol, 1.0 equiv) was added as a solution in THF (1.0 mL, 0.28 M). The vial was sealed and the reaction mixture was heated to 55 °C for 5 hr, after which time 1.0 M HCl (1.0 mL) was added very slowly, as vigorous bubbling occurred. The crude reaction mixture was transferred to a 30 mL separatory funnel, diluted with a saturated aqueous solution of Rochelle's salt (10 mL), and extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried with sodium sulfate and concentrated in vacuo to afford crude **S2-6**. This intermediate proved to re-lactonize to **2-42** over the course of 24 hr, so it was used immediately in the next step without further purification. The crude residue was transferred to a scintillation vial and dissolved in CH_2Cl_2. (5.0 mL, 0.056 M). *i*Pr_2NEt (0.58 mL, 2.2 mmol, 12 equiv) was added to the solution, followed by chloromethyl methyl ether (0.17 mL, 2.2 mmol, 8.0 equiv). The reaction mixture was stirred for 16 hr with no precautions made to exclude air or moisture, after which time saturated aqueous NH_4Cl (5.0 mL) was added and the

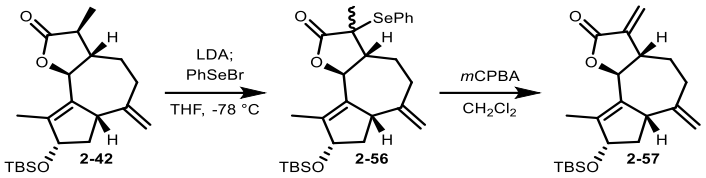
biphasic mixture transferred to a 60 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 55% EtOAc in hexanes as the eluting solvent to afford **2-51** as a yellow oil (45 mg 70% yield): $\mathbf{R_f}$ = 0.37 (1:1 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.76 (s, 1H), 4.69 (s, 1H), 4.52 – 4.46 (m, 2H), 4.45 (app. s, 2H), 3.32 (s, 3H), 3.25 (t, J = 7.4 Hz, 1H), 2.96 (s, 3H), 2.91 (s, 3H), 2.77 (p, J = 7.1 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.30 (dt, J = 12.3, 7.2 Hz, 1H), 2.15 – 2.07 (m, 2H), 1.90 – 1.80 (m, 1H), 1.73 – 1.63 (m, 1H), 1.55 (s, 3H), 1.39 (ddd, J = 12.5, 8.3, 7.2 Hz, 1H), 1.04 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 175.9, 152.9, 142.9, 136.1, 110.4, 93.9, 78.8, 72.8, 55.5, 48.9, 42.2, 42.0, 37.1, 35.9, 34.6, 29.5, 25.9, 23.4, 18.2, 14.7, 11.4, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{25}H_{45}NO_4Si$ $(M + Na)^+$: 474.3015, found 474.3028, $[\alpha]_D^{21.8}$ = -3.81 (c = 4.0 in $CHCl_3$).



methyl (S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)propanoate (2-55):

To a scintillation vial equipped with a stir bar was added **2-42** (0.10 g, 0.28 mmol, 1.0 equiv), followed by NaOH (0.11 M, 3.0 mL, 0.33 mmol, 1.2 equiv), with no precautions to exclude air or moisture from the mixture. The mixture was stirred for 1 hr, after which time it was concentrated in vacuo to afford crude **2-52**. The crude residue was dissolved in toluene (1.0 mL) and concentrated in vacuo 3 times in order to remove residual water. It was then transferred to a

dry scintillation vial and dissolved in THF (3.0 mL, 0.093 M). The solution was cooled to –78 °C and *n*BuLi (2.5 M in hexanes, 0.13 mL, 0.33 mmol, 1.2 equiv) was added dropwise. After continuing to stir for 5 minutes at –78 °C, chloromethyl methyl ether (63 µL, 0.83 mmol, 3.0 equiv) was added dropwise. The reaction mixture was stirred for an additional 16 hr, after which it was quenched by the addition of saturated aqueous NH_4Cl (1.0 mL). The resulting biphasic mixture was transferred to a 30 mL separatory funnel. The organic phase was collected and the aqueous phase extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate and concentrated in vacuo to afford crude **S2-7**. It was then transferred to a dry 1-dram vial equipped with a stir bar and dissolved in MeOH (1.5 mL, 0.092 M). To this stirred solution was added LiOMe (31 mg, 0.83, 6.0 equiv) and the resulting mixture was stirred for 2 hr, after which time the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL). The resulting solution was transferred to a 30 mL separatory funnel and extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 5% EtOAc in hexanes as the eluting solvent to afford **2-55** as a clear oil (6.0 mg 10% yield): $\mathbf{R_f}$ = 0.34 (1:9 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.76 (d, J = 2.0 Hz, 1H), 4.70 (s, 1H), 4.53 (t, J = 7.0 Hz, 1H), 4.49 – 4.41 (m, 3H), 3.68 (s, 3H), 3.34 (s, 3H), 2.69 (p, J = 7.4 Hz, 1H), 2.43 (qd, J = 6.7, 4.2 Hz, 1H), 2.35 (dt, J = 12.5, 7.2 Hz, 1H), 2.17 (dt, J = 13.3, 6.5 Hz, 1H), 2.11 – 2.04 (m, 1H), 1.66 – 1.60 (m, 4H), 1.36 (ddd, J = 12.4, 8.8, 7.3 Hz, 1H), 1.13 (d, J = 7.2 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 177.1, 152.6, 144.7, 134.6, 111.0, 93.5, 79.0, 72.8, 55.6, 51.7, 48.9, 42.3, 41.8, 39.5, 29.0, 26.0, 24.1, 18.4, 13.6, 11.8, -4.2, -4.6; **HRMS (ESI-TOF)** m / z calcd for $C_{24}H_{42}O_5Si$ $(M + Na)^+$: 461.2699, found 461.2709.

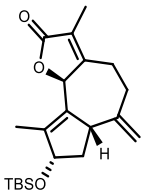


(3aS,6aS,8S,9bS)-8-((tert-butyldimethylsilyl)oxy)-9-methyl-3,6-dimethylene-3a,4,5,6,6a,7,8,9b-octahydroazuleno[4,5-b]furan-2(3H)-one (2-57):

To a dry 250 mL round bottom flask was added *i*Pr_2NH (3.3 mL, 23 mmol, 1.4 equiv) and THF (0.10 L, 0.17 M). This solution was cooled to –78 °C and *n*BuLi (2.5 M in hexanes, 8.6 mL, 22 mmol, 1.3 equiv) was added dropwise. The reaction mixture was allowed to warm to 0 °C for 5 minutes, after which it was once again cooled to –78 °C and **2-42** (6.0 g, 17 mmol, 1.0 equiv), was added dropwise as a solution in THF (50 mL, 0.34 M). The reaction mixture was stirred at –78 °C for one hr, at which time PhSeBr (5.1 g, 22 mmol, 1.3 equiv) was added rapidly as a solution in THF (50 mL, 0.34 M). The reaction mixture was warmed to room temperature for 15 minutes, after which it was quenched with saturated aqueous NH_4Cl (20 mL), transferred to a 500 mL separatory funnel, and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 5% EtOAc in hexanes as the eluting solvent to afford **2-56** (6.8 g, 78%) as a mixture of multiple diastereomers. To a 500 mL round-bottom flask equipped with a stir bar was added **2-56** (9.9 g, 19 mmol, 1.0 equiv) and CH_2Cl_2 (0.20 L, 0.095 M). This solution was stirred open to air and *meta*-chloroperbenzoic acid (5.3 g, 23 mmol, 1.2 equiv) was added, after which the reaction mixture was stirred for 1 hr. The reaction was quenched with saturated aqueous sodium bicarbonate (0.10 L) and the resulting biphasic mixture was transferred to a 500 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over sodium sulfate,

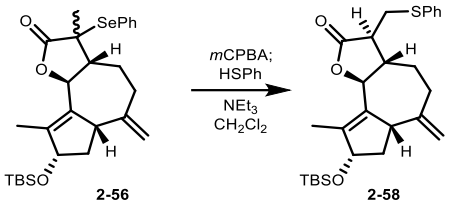
concentrated in vacuo, and purified by flash column chromatography using 0 –15% EtOAc in hexanes as the eluting solvent to afford **2-57** as a clear oil (3.7 g, 53% yield): $\mathbf{R_f}$ = 0.56 (1:4 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.22 (d, J = 3.4 Hz, 1H), 5.49 (d, J = 3.1 Hz, 1H), 4.93 (d, J = 4.7 Hz, 2H), 4.76 (dq, J = 10.4, 1.8 Hz, 1H), 4.57 (t, J = 6.6 Hz, 1H), 3.30 (t, J = 7.5 Hz, 1H), 2.98 (tq, J = 10.8, 3.2 Hz, 1H), 2.50 – 2.36 (m, 2H), 2.29 – 2.15 (m, 2H), 1.86 (s, 3H), 1.64 (ddd, J = 12.3, 9.2, 7.8 Hz, 1H), 1.54 – 1.46 (m, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 170.4, 149.7, 142.4, 139.4, 133.0, 119.8, 111.7, 81.9, 78.5, 48.8, 44.2, 41.1, 36.0, 30.3, 26.0, 18.4, 12.1, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{32}O_3Si$ $(M - tBu)^+$: 303.1417 found 303.1406.

Minor side product:



(6aS,8S,9bS)-8-((tert-butyldimethylsilyl)oxy)-3,9-dimethyl-6-methylene-5,6,6a,7,8,9b-hexahydroazuleno[4,5-b]furan-2(4H)-one (S2-8):

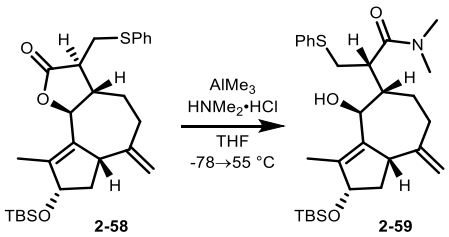
Yellow oil (450 mg 6.5% yield): $\mathbf{R_f}$ = 0.51 (1:4 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.77 (s, 1H), 4.76 (s, 1H), 4.50 (t, J = 6.6 Hz, 1H), 3.13 (t, J = 6.8 Hz, 1H), 2.77 (ddd, J = 16.6, 9.1, 7.7 Hz, 1H), 2.49 (ddd, J = 16.8, 9.4, 7.6 Hz, 1H), 2.43 – 2.35 (m, 2H), 2.21 (ddd, J = 11.9, 7.4, 3.9 Hz, 1H), 1.86 (d, J = 1.2 Hz, 3H), 1.76 (s, 3H), 1.44 (dt, J = 13.3, 6.8 Hz, 1H), 0.90 (s, 10H), 0.09 (s, 3H), 0.07 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 174.8, 160.5, 150.2, 148.1, 131.9, 124.9, 111.3, 78.6, 78.3, 48.5, 41.8, 30.4, 27.3, 26.0, 18.3, 12.0, 8.5, -4.4, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{32}O_3Si$ $(M + Na)^+$: 383.2018, found 383.2010.



(3R,3aS,6aS,8S,9bS)-8-((tert-butyldimethylsilyl)oxy)-9-methyl-6-methylene-3-((phenylthio)methyl)-3a,4,5,6,6a,7,8,9b-octahydroazuleno[4,5-b]furan-2(3H)-one (2-58)

In a scintillation vial equipped with a stir bar, **2-56** (0.50 g, 0.87 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL, 0.087 M), with no precautions taken to exclude air or water. To this stirred solution was added *meta*-chloroperbenzoic acid (0.22 g, 0.95 mmol, 1.1 equiv) and the reaction mixture was stirred for an additional hr. At that time, NEt_3 (0.36 mL, 2.6 mmol, 3.0 equiv) was added followed by thiophenol (0.18 mL, 1.7 mmol, 2.0 equiv). After an additional hr, saturated aqueous NH_4Cl (3.0 mL) was added and the resulting biphasic mixture was transferred to a 60 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 10% EtOAc in hexanes as the eluting solvent to afford **2-58** as a yellow oil (0.30 g, 73% yield, single diastereomer): $\mathbf{R_f}$ = 0.48 (1:4 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 4.86 (s, 1H), 4.82 (s, 1H), 4.74 (d, J = 11.0 Hz, 1H), 4.54 (t, J = 6.4 Hz, 1H), 3.49 (dd, J = 14.0, 3.8 Hz, 1H), 3.24 (s, 1H), 3.12 (dd, J = 14.0, 6.8 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.48 – 2.36 (m, 2H), 2.29 – 2.21 (m, 1H), 2.19 – 2.09 (m, 1H), 1.95 (dt, J = 12.9, 6.5 Hz, 1H), 1.79 (d, J = 9.3 Hz, 3H), 1.55 (dt, J = 12.5, 8.4 Hz, 1H), 1.44 – 1.34 (m, 1H), 0.91 (s, 9H), 0.10 (d, J = 5.9 Hz, 3H), 0.08 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 176.5, 150.1, 143.6, 135.9, 132.9, 129.9, 129.3, 126.8, 111.3, 81.0, 78.4, 48.7, 46.8, 45.1, 41.4, 35.2, 33.0, 31.4, 26.0, 18.4, 12.2, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for

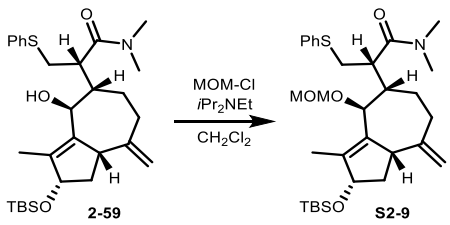
$C_{27}H_{38}O_3SSi$ $(M + Na)^+$: 493.2209, found 493.2195. Relative stereochemistry was assigned by a lack of coupling between the two adjacent methine protons in the ^1H NOESY spectrum (see page 385).



(R)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-hydroxy-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-dimethyl-3-(phenylthio)propanamide (2-59):

To a dry scintillation vial equipped with a stir bar was added $HNMe_2$•HCl (0.10 g, 1.3 mmol, 2.0 equiv) and THF (5.0 mL, 0.13 M). This suspension was cooled to –78 °C and $AlMe_3$ (2.0 M in toluene, 0.64 mL, 1.3 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 30 minutes at –78 °C, after which time **2-58** (0.30 g, 0.64 mmol, 1.0 equiv) was added as a solution in THF (5.0 mL, 0.13 M). The vial was sealed and the reaction mixture was heated to 55 °C for 5 hr, after which time 1.0 M HCl (1.0 mL) was added very slowly, as vigorous bubbling occurred. The crude reaction mixture was transferred to a 60 mL separatory funnel, diluted with a saturated aqueous solution of Rochelle's salt (20 mL), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried with sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 60% EtOAc in hexanes as the eluting solvent to afford **2-59** as an orange oil (0.16 g 45% yield): $\mathbf{R}_f$ = 0.44 (3:2 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (d, J = 7.3 Hz, 2H), 7.30 – 7.26 (m, 2H), 7.17 (t, J = 7.4 Hz, 1H), 4.89 (s, 1H), 4.63 (s, 1H), 4.47 (t, J = 6.1 Hz, 1H), 4.41 (d, J = 7.0 Hz, 1H), 3.44 (t, J = 6.7 Hz, 1H), 3.31 (dd, J = 13.5, 10.8 Hz, 1H), 3.20 – 3.13 (m, 2H), 2.92 (s, 3H), 2.90 (s, 3H), 2.34

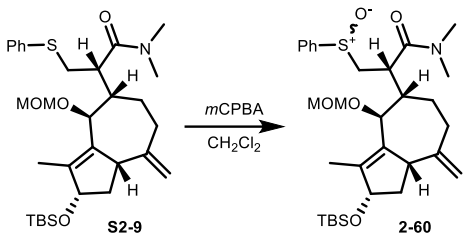
(dt, J = 13.2, 7.6 Hz, 1H), 2.29 – 2.22 (m, 2H), 2.22 – 2.16 (m, 1H), 1.94 (dtd, J = 14.6, 8.2, 2.2 Hz, 1H), 1.63 (d, J = 1.3 Hz, 3H), 1.58 – 1.51 (m, 1H), 1.49 (dt, J = 12.8, 5.9 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 174.0, 151.6, 140.7, 139.2, 136.6, 129.6, 129.0, 126.3, 111.0, 79.1, 69.1, 48.2, 44.6, 42.3, 40.9, 37.8, 36.1, 35.1, 30.7, 26.0, 23.2, 11.6, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{29}H_{45}NO_3SSi$ $(M + Na)^+$: 538.2787, found 538.2784.



(S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-dimethyl-3-(phenylthio)propanamide (S2-9):

In a scintillation vial, **2-59** (0.16 g, 0.29 mmol, 1.0 equiv) was dissolved in CH_2Cl_2. (5.0 mL, 0.058 M). *i*Pr_2NEt (0.20 mL, 1.1 mmol, 4.0 equiv) was added to the solution, followed by chloromethyl methyl ether (65 μL, 0.86 mmol, 3.0 equiv). The reaction mixture was stirred for 16 hr with no precautions made to exclude air or moisture, after which time saturated aqueous NH_4Cl (5.0 mL) was added and the biphasic mixture transferred to a 60 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 40% EtOAc in hexanes as the eluting solvent to afford **S2-9** as an orange oil (0.12 g 77% yield): $\mathbf{R_f}$ = 0.52 (2:3 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H),

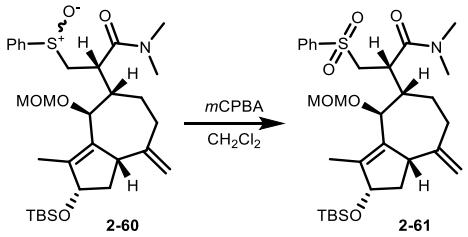
4.89 (s, 1H), 4.62 (s, 1H), 4.52 (t, J = 6.0 Hz, 1H), 4.40 (d, J = 6.5 Hz, 1H), 4.36 (t, J = 6.9 Hz, 2H), 3.36 – 3.27 (m, 2H), 3.21 (s, 3H), 3.16 (ddd, J = 9.0, 5.9, 2.7 Hz, 1H), 3.08 (dd, J = 12.8, 2.7 Hz, 1H), 2.94 (s, 3H), 2.91 (s, 3H), 2.38 – 2.25 (m, 3H), 2.20 (ddd, J = 14.0, 8.0, 5.6 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.64 (s, 3H), 1.57 – 1.45 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 173.5, 151.5, 143.2, 136.7, 135.8, 129.8, 129.0, 126.4, 111.6, 93.5, 79.1, 72.8, 55.6, 48.7, 42.6, 41.9, 40.5, 37.5, 36.1, 34.1, 30.5, 26.0, 20.9, 18.3, 11.6, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{31}H_{49}NO_4SSi$ $(M + Na)^+$: 582.3049, found 582.3052.



(2S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-dimethyl-3-(phenylsulfinyl)propanamide (2-60):

To a half-dram vial equipped with a stir flea was added **S2-9** (4.5 mg, 8.0 μmol, 1.0 equiv) and CH_2Cl_2 (0.50 mL, 0.016 M). This solution was stirred open to air and *meta*-chloroperbenzoic acid (1.4 mg, 8.0 μmol, 1.0 equiv) was added, after which the reaction mixture was stirred for 1 hr. The reaction was quenched with saturated aqueous sodium bicarbonate (0.50 mL) and the resulting biphasic mixture was transferred to a 30 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 –60% EtOAc in hexanes as the eluting solvent to afford a 1.2:1 mixture

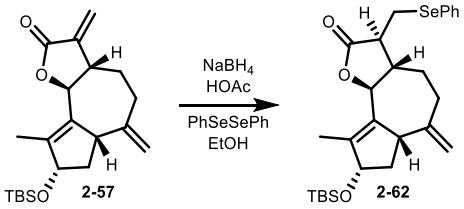
of diastereomers of **2-60** as a clear oil (4.0 mg 86% yield): $\mathbf{R_f}$ = 0.33 (3:7 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.0 Hz, 1H), 7.59 – 7.41 (m, 4H), 4.90 (d, J = 1.7 Hz, 0.53H), 4.84 (d, J = 1.9 Hz, 0.42H), 4.70 (s, 0.52H), 4.65 (s, 0.42H), 4.52 (app. q, J = 7.3 Hz, 1H), 4.48 – 4.46 (m, 1H), 4.45 (d, J = 6.4 Hz, 0.48H), 4.41 (d, J = 6.6 Hz, 0.56H), 4.35 – 4.29 (m, 1H), 3.70 (ddd, J = 11.9, 3.6, 2.1 Hz, 0.49H), 3.54 (dd, J = 13.8, 8.3 Hz, 0.42H), 3.42 (s, 1.5H), 3.41 – 3.28 (m, 3.7H), 3.18 (s, 1.5H), 3.02 (s, 1.5H), 2.95 – 2.89 (m, 1.9H), 2.67 (dd, J = 12.4, 2.1 Hz, 0.52H), 2.63 (s, 1.3H), 2.45 – 2.31 (m, 2H), 2.21 – 2.07 (m, 1H), 1.69 – 1.63 (m, 3H), 1.42 (dt, J = 13.1, 6.3 Hz, 1H), 0.91 – 0.85 (m, 9H), 0.10 – 0.02 (m, 6H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 172.6, 172.2, 151.4, 151.1, 144.5, 144.4, 134.9, 134.8, 130.9, 130.9, 129.4, 129.0, 124.6, 123.9, 112.4, 112.1, 94.0, 93.3, 79.1, 73.9, 72.6, 58.7, 56.1, 56.0, 54.1, 49.2, 48.9, 42.2, 41.7, 41.1, 40.9, 37.6, 37.5, 37.1, 36.2, 35.9, 34.8, 29.9, 29.7, 29.6, 26.0, 26.0, 21.2, 20.8, 11.6, 11.6, -4.3, -4.3, -4.6, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{31}H_{49}NO_5SSi$ $(M + Na)^+$: 598.2999, 598.3011.



(S)-2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)-N,N-dimethyl-3-(phenylsulfonyl)propanamide (2-61):

To a half-dram vial equipped with a stir flea was added **2-60** (5.0 mg, 8.7 μmol, 1.0 equiv) and CH_2Cl_2 (0.50 mL, 0.017 M). This solution was stirred open to air and *meta*-chloroperbenzoic acid (2.0 mg, 8.7 μmol, 1.0 equiv) was added, after which the reaction mixture was stirred for 1

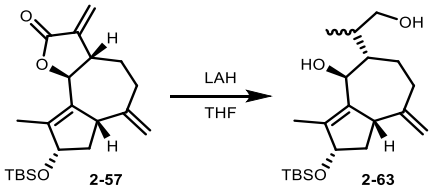
hr. The reaction was quenched with saturated aqueous sodium bicarbonate (0.50 mL) and the resulting biphasic mixture was transferred to a 30 mL separatory funnel. The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 –50% EtOAc in hexanes as the eluting solvent to afford **2-61** as a clear oil (4.0 mg 78% yield): $\mathbf{R_f}$ = 0.36 (1:1 EtOAc:Hex, KMnO4); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.7 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 4.90 (s 1H), 4.68 (s, 1H), 4.53 (t, J = 6.2 Hz, 1H), 4.48 (d, J = 6.6 Hz, 1H), 4.43 (d, J = 6.6 Hz, 1H), 4.31 (d, J = 7.7 Hz, 1H), 4.01 (dd, J = 13.9, 10.5 Hz, 1H), 3.62 (dd, J = 10.2, 3.3 Hz, 1H), 3.41 (s, 3H), 3.33 (s, 1H), 3.06 (s, 3H), 3.01 (d, J = 14.1 Hz, 1H), 2.74 (s, 3H), 2.44 – 2.31 (m, 2H), 2.22 – 2.15 (m, 1H), 2.11 (ddd, J = 15.0, 9.9, 5.6 Hz, 1H), 1.81 – 1.76 (m, 1H), 1.70 (s, 3H), 1.50 – 1.42 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 171.5, 150.9, 144.6, 139.7, 134.6, 133.8, 129.1, 128.2, 112.5, 93.5, 79.1, 73.0, 56.1, 55.1, 48.9, 42.1, 40.7, 37.3, 36.9, 36.2, 29.9, 29.7, 26.0, 20.3, 11.6, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for 614.2947 $(M + Na)^+$: 614.2947, found 614.2960.



(3S,3aS,6aS,8S,9bS)-8-((tert-butyldimethylsilyl)oxy)-9-methyl-6-methylene-3-((phenylselanyl)methyl)-3a,4,5,6,6a,7,8,9b-octahydroazuleno[4,5-b]furan-2(3H)-one (2-62):

To a dry 1-dram vial was added $NaBH_4$ (25 mg, 0.65 mmol, 3.2 equiv) and PhSeSePh (66 mg, 0.31 mmol, 1.5 equiv), which were then dissolved in ethanol (1.0 mL, 0.20 M). This solution was

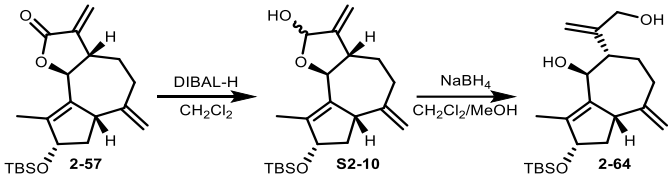
stirred for 30 minutes, after which time acetic acid (52 µL, 0.91 mmol, 4.5 equiv) was added followed by **2-57** (73 mg, 0.20 mmol, 1.0 equiv) as a solution in EtOH (1.0 mL, 0.20 M). After stirring for 1 hr, the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL) and the resulting mixture was transferred to a 30 mL separatory funnel. The reaction mixture was extracted with EtOAc (3 x 5.0 mL) and the combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 15% EtOAc in hexanes as the eluting solvent to afford **2-62** as a yellow oil (78 mg 75% yield): $\mathbf{R_f}$ = 0.30 (3:17 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 2H), 7.31 – 7.22 (m, 3H), 4.86 (s, 1H), 4.80 (s 1H), 4.74 (d, J = 11.1 Hz, 1H), 4.55 (t, J = 6.0 Hz, 1H), 3.29 (dd, J = 13.2, 4.4 Hz, 1H), 3.26 – 3.13 (m, 2H), 2.63 (dt, J = 11.5, 4.9 Hz, 1H), 2.47 – 2.37 (m, 2H), 2.27 – 2.19 (m, 1H), 2.01 – 1.93 (m, 1H), 1.88 – 1.76 (m, 4H), 1.61 – 1.54 (m, 1H), 1.40 – 1.31 (m, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 176.7, 150.1, 143.4, 133.1, 133.0, 130.4, 129.4, 127.5, 111.3, 81.0, 78.4, 48.8, 47.7, 45.2, 41.2, 35.4, 31.2, 26.0, 25.7, 18.4, 12.2, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{27}H_{38}O_3SeSi$ $(M + Na)^+$: 541.1655, found 541.1648. Relative stereochemistry was established in analogy to **2-58**.



(2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-5-((R)-1-hydroxypropan-2-yl)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-4-ol (2-63):

To a dry 1-dram vial containing $LiAlH_4$ (4.2 mg, 0.11 mmol, 2.0 equiv) was added **2-57** (20 mg, 55 µmol, 1.0 equiv) as a solution in THF (0.50 mL, 0.11 M). The reaction mixture was stirred for

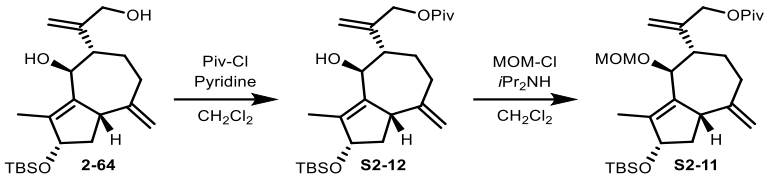
1 hr, after which time the reaction was quenched by the slow addition of a saturated aqueous solution of Rochelle's salt (0.50 mL). The reaction mixture was then transferred to a 30 mL separatory funnel and extracted with EtOAc (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 40% EtOAc in hexanes as the eluting solvent to afford **2-63** as a clear oil (6.0 mg, 30% yield, single diastereomer): $\mathbf{R_f}$ = 0.42 (1:1EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.72 (s, 1H), 4.53 (t, J = 6.7 Hz, 1H), 4.48 (d, J = 7.5 Hz, 1H), 3.66 (dd, J = 10.9, 5.3 Hz, 1H), 3.56 (dd, J = 10.9, 5.4 Hz, 1H), 3.46 (t, J = 7.1 Hz, 1H), 2.45 – 2.28 (m, 2H), 2.14 – 2.06 (m, 1H), 1.89 – 1.83 (m, 1H), 1.80 – 1.74 (m, 2H), 1.70 (s, 3H), 1.55 – 1.47 (m, 1H), 1.46 – 1.35 (m, 2H), 0.94 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.08 (app. d, 6H); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ 152.1, 141.3, 138.8, 111.6, 79.1, 70.9, 66.7, 48.7, 42.7, 41.9, 37.3, 30.1, 26.0, 24.3, 18.4, 14.1, 11.6, -4.3, -4.6; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{38}O_3Si$ $(M + Na)^+$: 389.2488, found 389.2490.



(2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-5-(3-hydroxyprop-1-en-2-yl)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-4-ol (2-64):

To a dry 500 mL round-bottom flask was added **2-57** (3.7 g, 10 mmol, 1.0 equiv) and CH_2Cl_2 (0.20 L, 0.050 M). The solution was cooled to 0 °C and DIBAL-H (2.0 mL, 11 mmol, 1.1 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 40 minutes, after which it was quenched by the addition of a saturated aqueous solution of

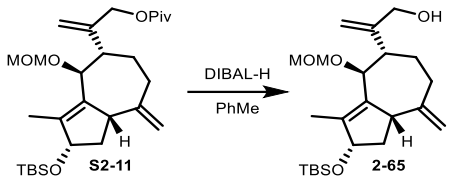
Rochelle's salt (0.10 L). The crude mixture was transferred to a 500 mL separatory funnel, the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were combined and concentrated in vacuo to afford crude **S2-10**. The crude residue was taken to the next step without further purification. The crude **S2-10** (10 mmol, 1.0 equiv) was transferred to a 500 mL round-bottom flask equipped with a stir bar and dissolved in CH_2Cl_2 (0.20 L, 0.050 M) and MeOH (50 mL, 0.20 M), with no precautions taken to exclude air or moisture. To this solution was added $NaBH_4$ (1.9 g, 50 mmol, 5.0 equiv). The reaction mixture was stirred for 1 hr after which it was quenched by the addition of saturated aqueous NH_4Cl (50 mL). The resulting biphasic mixture was transferred to a 500 mL separatory funnel, where the organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 50% EtOAc in hexanes as the eluting solvent to afford **2-64** as a clear oil (1.3 g 34% yield over 2 steps): $\mathbf{R_f}$ = 0.40 (1:1 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.18 (s, 1H), 5.04 (s, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 4.51 (t, J = 6.7 Hz, 1H), 4.42 (d, J = 9.5 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.50 (t, J = 7.3 Hz, 1H), 2.59 – 2.54 (m, 1H), 2.44 (dt, J = 13.0, 7.5 Hz, 1H), 2.34 (dt, J = 13.5, 8.1 Hz, 1H), 2.10 (ddd, J = 13.2, 9.2, 4.0 Hz, 1H), 1.74 (s, 3H), 1.68 – 1.55 (m, 2H), 1.37 (dt, J = 12.9, 7.0 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 152.2, 151.9, 143.0, 138.4, 112.7, 110.6, 78.8, 71.9, 66.3, 48.4, 45.3, 42.2, 29.8, 29.5, 26.0, 18.3, 11.6, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{21}H_{36}O_3Si$ $(M + Na)^+$: 387.2332, found 387.2334.



2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)allyl pivalate (S2-11):

To a dry 50 mL round-bottom flask was added **2-64** (1.3 g, 3.4 mmol, 1.0 equiv), CH_2Cl_2 (17 mL, 0.20 M), and pyridine (1.1 mL, 14 mmol, 4.0 equiv). This solution was cooled to 0 °C and pivaloyl chloride (0.54 mL, 4.5 mmol, 1.3 equiv) was added. The reaction mixture was stirred at 0 °C for 7 hr, after which it was quenched by the addition of saturated aqueous sodium bicarbonate (5.0 mL). The resulting biphasic mixture was transferred to a 60 mL separatory funnel, where the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, passed through a short plug of SiO_2, and concentrated in vacuo to afford crude **S2-12**, which was taken to the next step without any further purification. The crude **S2-12** (0.48 g, 1.1 mmol, 1.0 equiv) was transferred to a 50 mL round-bottom flask equipped with a stir bar, to which CH_2Cl_2 (10 mL, 0.11 M) and *i*Pr_2NEt (0.74 mL, 4.3 mmol, 4.0 equiv) were added. To this stirred solution was added chloromethyl methyl ether (0.25 mL, 3.2 mmol, 3.0 equiv), after which the reaction mixture was stirred for 16 hr. After this time, saturated aqueous NH_4Cl (3.0 mL) was added and the resulting biphasic mixture was transferred to a 60 mL separatory funnel. The organic phase was collected, while the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic phases were combined, dried over sodium sulfate, and purified by flash column chromatography using 5% EtOAc in hexanes as the eluting solvent to afford **S2-11** as a yellow oil (0.32 g, 62% yield over two steps of **S2-11**): $\mathbf{R_f}$ = 0.42 (1:9 EtOAc:Hex, $KMnO_4$); **^{1}H NMR**

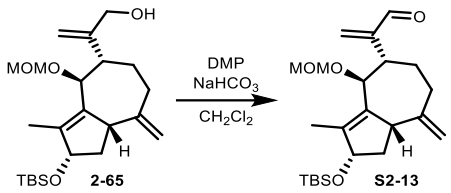
(500 MHz, $CDCl_3$) δ 5.11 (s, 1H), 5.07 (s, 1H), 4.84 (d, J = 2.0 Hz, 1H), 4.69 (s, 1H), 4.64 – 4.56 (m, 2H), 4.54 (t, J = 6.7 Hz, 1H), 4.49 (d, J = 8.4 Hz, 1H), 4.44 (d, J = 6.8 Hz, 1H), 4.35 (d, J = 6.8 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.26 (s, 3H), 2.63 (td, J = 8.9, 4.2 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.12 (ddd, J = 14.4, 8.4, 6.5 Hz, 1H), 1.72 (d, J = 1.2 Hz, 3H), 1.66 – 1.58 (m, 2H), 1.38 (ddd, J = 13.2, 7.2, 6.5 Hz, 1H), 1.22 (s, 9H), 0.89 (d, J = 2.7 Hz, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **$^{13}C\{^1H\}$ NMR** (125 MHz, $CDCl_3$) δ 178.3, 152.0, 148.2, 144.5, 135.0, 112.0, 111.6, 92.9, 79.1, 75.0, 67.1, 55.5, 49.0, 43.2, 41.8, 29.4, 27.8, 27.4, 26.0, 18.3, 16.3, 11.7, -4.3, -4.7; **HRMS (GCMS CI$^+$)** m / z calcd for $C_{28}H_{48}O_5Si$ $(M)^+$: 492.3271, found 492.3265



2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)prop-2-en-1-ol (2-65):

To a dry 50 mL round-bottom flask equipped with a stir bar was added **S2-11** (0.42 g, 0.85 mmol, 1.0 equiv) and toluene (20 mL, 0.043 M). To this stirred solution DIBAL-H (0.46 mL, 2.6 mmol, 3.0 mmol) was added dropwise. The reaction mixture was stirred for 40 minutes, after which it was quenched by the addition of a saturated aqueous solution of Rochelle's salt (10 mL). The resulting biphasic mixture was transferred to a 60 mL separatory funnel, the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were combined, concentrated in vacuo, and purified by flash column chromatography using 0 – 35% EtOAc in hexanes as the eluting solvent to afford **2-65** as a clear oil (0.21 g 79% yield): $\mathbf{R}_f$ = 0.40 (3:7 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.84 (d, J = 2.0 Hz, 1H), 4.70 (s, 1H), 4.54 (t, J = 6.6 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.36

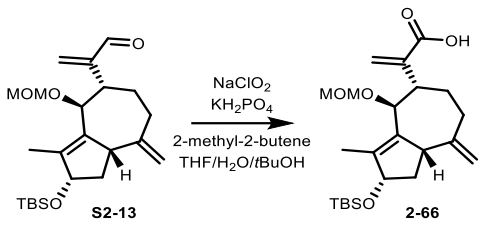
(d, J = 6.8 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.43 – 3.35 (m, 1H), 3.29 (s, 3H), 2.64 (ddd, J = 11.5, 8.8, 2.7 Hz, 1H), 2.50 – 2.27 (m, 3H), 2.17 – 2.08 (m, 1H), 1.74 (d, J = 1.2 Hz, 3H), 1.71 – 1.63 (m, 1H), 1.61 – 1.53 (m, 1H), 1.39 (ddd, J = 13.1, 7.1, 6.3 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 153.4, 151.9, 145.0, 134.8, 111.6, 110.9, 92.8, 79.1, 76.1, 66.7, 55.8, 49.0, 42.7, 41.8, 29.4, 28.1, 26.0, 18.3, 11.7, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{23}H_{40}O_4Si$ $(M + Na)^+$: 431.2594, found 431.2591.



2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylaldehyde (S2-13):

To a scintillation vial equipped with a stir bar was added **2-65** (0.27 g, 0.60 mmol, 1.0 equiv), CH_2Cl_2 (6.0 mL, 0.10 M), and $NaHCO_3$ (1.0 g, 12 mmol, 20 equiv), with no precautions taken to exclude air or moisture from the mixture. To this stirred solution was added Dess–Martin periodinane (0.38 g, 0.91 mmol, 1.5 equiv). After 1 hr, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (3.0 mL) and the resulting biphasic mixture was transferred to a 30 mL separatory funnel. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 20% EtOAc in hexanes as the eluting solvent to afford **S2-13** as a clear oil (0.21 g 85% yield): $\mathbf{R_f}$ = 0.29 (1:9 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.44 (s, 1H), 6.04 (s, 1H), 4.84 (s, 1H), 4.75 (s, 1H), 4.61 (d, J = 7.0 Hz, 1H), 4.54 (t, J = 6.8 Hz, 1H), 4.44 (d, J = 6.7 Hz,

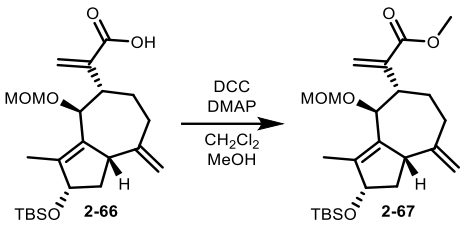
1H), 4.37 (d, J = 6.7 Hz, 1H), 3.38 (t, J = 7.6 Hz, 1H), 3.25 (s, 3H), 3.20 (td, J = 7.9, 3.6 Hz, 1H), 2.46 – 2.32 (m, 2H), 2.16 (dt, J = 13.3, 6.6 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.68 – 1.58 (m, 4H), 1.38 (dt, J = 13.2, 7.8 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (125 MHz, $CDCl_3$) δ 194.6, 152.7, 152.1, 144.4, 135.3, 134.9, 111.5, 93.2, 79.0, 73.3, 55.5, 49.1, 42.1, 39.0, 29.6, 28.1, 26.0, 18.3, 12.0, -4.3, -4.7; **HRMS (ESI-TOF)** m / z calcd for $C_{23}H_{38}O_4Si$ $(M + Na)^+$: 429.2437, found 429.2438.



2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylic acid (2-66):

To a 50 mL round-bottom flask equipped with a stir bar was added **S2-13** (61 mg, 0.15 mmol, 1.0 equiv), 2-methyl-2-butene (1.5 mL, 0.10 M), *t*BuOH (1.5 mL, 0.10 M), and THF (6.0 mL, 0.025 M) with no precautions taken to exclude air or water. To this stirred solution was added a chilled solution of $NaClO_2$ (0.15 g, 1.7 mmol, 11 equiv) and KH_2PO_4 (0.45 g, 3.3 mmol, 22 equiv) in H_2O (6.0 mL, 0.025 M) dropwise. The reaction mixture was stirred for 16 hr, after which time it was diluted with saturated aqueous sodium chloride (5.0 mL) and transferred to a 60 mL separatory funnel, where it was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 20% EtOAc in hexanes as the eluting solvent to afford **2-66** as a clear oil (51 mg, 80% yield): $\mathbf{R_f}$ = 0.21 (1:4 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.81 (s, 1H), 4.87 (d, J = 1.7 Hz, 1H), 4.74 (s, 1H), 4.65 (d, J = 7.8 Hz, 1H), 4.55 (t,

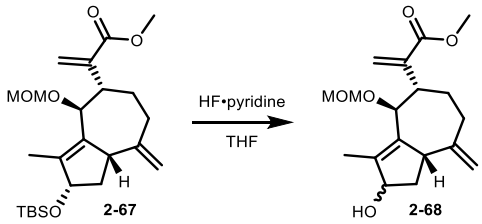
J = 6.7 Hz, 1H), 4.46 (d, J = 6.8 Hz, 1H), 4.38 (d, J = 6.8 Hz, 1H), 3.40 (t, J = 7.7 Hz, 1H), 3.27 (s, 3H), 3.17 – 3.11 (m, 1H), 2.52 – 2.32 (m, 2H), 2.24 – 2.09 (m, 1H), 1.88 – 1.74 (m, 1H), 1.71 (s, 3H), 1.66 – 1.57 (m, 1H), 1.44 – 1.35 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 172.4, 151.8, 144.7, 143.4, 134.6, 127.6, 111.8, 93.0, 79.1, 74.3, 55.5, 49.1, 42.0, 41.9, 29.5, 28.1, 26.0, 18.3, 11.8, -4.3, -4.6; **HRMS (ESI-TOF)** m / z calcd for $C_{23}H_{38}O_5Si$ $(M + Na)^+$: 445.2386, found 445.2381, $[\alpha]_D^{20.6}$ = -23.73 (c = 5.1 in $CHCl_3$)



methyl 2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (2-67):

To a dry scintillation vial was added **2-66** (0.14 g, 0.33 mmol, 1.0 equiv), CH_2Cl_2 (1.7 mL, 0.19 M), and DMAP (40 mg, 0.33 mmol, 1.0 equiv). To this stirred solution was added a solution of DCC (82 mg, 0.40 mmol, 1.2 equiv) in CH_2Cl_2 (1.7 mL, 0.19 M). The reaction mixture was stirred for 1 hr, after which time MeOH (0.82 mL, 0.40 M) was added. After stirring for 16 more hr, the reaction was quenched by the addition of saturated aqueous NH_4Cl (2.0 mL). The resulting biphasic mixture was transferred to a 60 mL separatory funnel, the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 10% EtOAc in hexanes as the eluting solvent to afford **2-67** as a clear oil (90 mg 62% yield): $\mathbf{R}_f$ = 0.42 (1:9 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.22 (d, J = 0.8 Hz, 1H), 5.70 (s, 1H), 4.86 (d, J = 2.0 Hz, 1H), 4.74 (s, 1H), 4.66 (d, J = 7.7 Hz, 1H), 4.55

(t, J = 6.8 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 4.37 (t, J = 7.5 Hz, 1H), 3.76 (s, 3H), 3.39 (t, J = 7.7 Hz, 1H), 3.25 (s, 3H), 3.16 – 3.11 (m, 1H), 2.47 – 2.36 (m, 2H), 2.20 – 2.11 (m, 1H), 1.85 – 1.75 (m, 1H), 1.69 (d, J = 1.2 Hz, 3H), 1.64 – 1.55 (m, 1H), 1.39 (ddd, J = 12.9, 7.6, 6.7 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (150 MHz, $CDCl_3$) δ 167.9, 152.1, 144.4, 143.6, 134.8, 125.5, 111.6, 93.1, 79.1, 73.9, 55.4, 52.0, 49.1, 42.6, 41.9, 29.6, 28.2, 26.0, 18.3, 11.7, -4.3, -4.6; **HRMS (ESI-TOF)** m / z calcd for $C_{24}H_{40}O_5Si$ $(M + Na)^+$: 436.2645, found 436.2662, $[\alpha]_D^{temp}$ = -8.87 (c = 1.40 in CH_2Cl_2)



methyl 2-((2S,4S,5S,8aS)-2-((tert-butyldimethylsilyl)oxy)-4-(methoxymethoxy)-3-methyl-8-methylene-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (2-68):

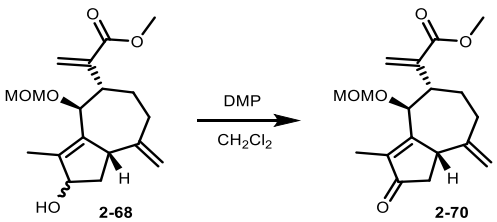
To a dry 1-dram vial was added **2-67** (90 mg, 0.21 mmol, 1.0 equiv) and THF (2.0 mL, 1.1 M). To this stirred solution was added 70% HF•pyridine (0.56 mL, 0.37 M) dropwise. The reaction mixture was stirred for hr, after which it was quenched by slow addition of saturated aqueous sodium bicarbonate (1.0 mL), which produced vigorous bubbling. The resulting biphasic mixture was transferred to a 30 mL separatory funnel, the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by column chromatography using 40% EtOAc in hexanes as the eluting solvent to afford two diastereomers **2-68a** and **2-68**b as clear oils (35 mg of **2-68a** and 27 mg of **2-68b**, 93% combined yield):

2-68a

R_f = 0.37 (1:1 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.23 (d, J = 0.8 Hz, 1H), 5.69 (s, 1H), 4.88 (d, J = 1.7 Hz, 1H), 4.77 (s, 1H), 4.70 (d, J = 7.3 Hz, 1H), 4.57 (t, J = 6.7 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 4.39 (d, J = 6.8 Hz, 1H), 3.76 (s, 3H), 3.43 (t, J = 7.4 Hz, 1H), 3.26 (s, 3H), 3.17 – 3.10 (m, 1H), 2.55 (dt, J = 13.4, 7.7 Hz, 1H), 2.37 (dt, J = 13.7, 6.8 Hz, 1H), 2.20 (dt, J = 13.9, 7.1 Hz, 1H), 1.84 – 1.77 (m, 1H), 1.84 – 1.77 (m, 1H), 1.76 (d, J = 1.3 Hz, 3H), 1.69 – 1.62 (m, 1H), 1.41 (dt, J = 13.3, 6.7 Hz, 1H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 167.8, 151.6, 143.3, 143.1, 136.8, 125.6, 111.9, 93.3, 79.2, 73.6, 55.5, 52.0, 49.1, 43.0, 41.2, 30.2, 28.3, 11.6.

2-68b

R_f = 0.23 (1:1 EtOAc:Hex, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.21 (d, J = 0.8 Hz, 1H), 5.65 (s, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 4.66 (d, J = 7.8 Hz, 1H), 4.62 (t, J = 5.1 Hz, 1H), 4.56 (d, J = 6.9 Hz, 1H), 4.41 (d, J = 6.9 Hz, 1H), 3.75 (s, 3H), 3.72 (t, J = 5.9 Hz, 1H), 3.27 (s, 3H), 3.10 (ddd, J = 10.5, 8.2, 3.3 Hz, 1H), 2.16 (t, J = 7.0 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.78 (d, J = 1.6 Hz, 3H), 1.72 – 1.58 (m, 2H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 167.7, 151.5, 143.3, 142.6, 138.1, 125.5, 111.3, 93.4, 80.0, 73.5, 55.5, 52.0, 48.8, 43.6, 41.2, 31.4, 28.4, 11.7.



methyl 2-((4S,5S,8aS)-4-(methoxymethoxy)-3-methyl-8-methylene-2-oxo-1,2,4,5,6,7,8,8a-octahydroazulen-5-yl)acrylate (2-70):

To a 1-dram vial equipped with a stir bar was added **2-68** (5.0 mg, 16 μmol, 1.0 equiv), CH_2Cl_2 (1.0 mL, 0.016 M), and $NaHCO_3$ (26 mg, 0.31 mmol, 20 equiv), with no precautions taken to exclude air or moisture from the mixture. To this stirred solution was added Dess–Martin periodinane (10 mg, 23 μmol, 1.5 equiv). After 1 hr, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (1.0 mL) and the resulting biphasic mixture was transferred to a 30 mL separatory funnel. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo, and purified by flash column chromatography using 0 – 30% EtOAc in hexanes as the eluting solvent to afford **2-70** as a clear oil (4.2 mg 85% yield): $\mathbf{R_f}$ = 0.45 (2:3 EtOAc:Hex, UV); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.69 (s, 1H), 5.02 (d, J = 7.1 Hz, 1H), 5.01 (s, 1H), 4.90 (s, 1H), 4.52 (d, J = 6.9 Hz, 1H), 4.49 (d, J = 6.9 Hz, 1H), 3.83 – 3.74 (m, 4H), 3.29 (s, 3H), 3.28 – 3.23 (m, 1H), 2.77 (dd, J = 18.9, 7.1 Hz, 1H), 2.27 (ddd, J = 13.7, 7.3, 6.2 Hz, 1H), 2.17 – 2.09 (m, 2H), 1.82 – 1.71 (m, 5H); **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ 208.9, 168.5, 167.4, 148.7, 142.1, 141.1, 126.5, 113.9, 94.5, 74.5, 55.7, 52.1, 44.9, 43.0, 42.6, 29.9, 28.0, 8.7; **HRMS (ESI-TOF)** m / z calcd for $C_{18}H_{24}O_5$ $(M + Na)^+$: 343.1521, found 343.1507.

2.6. References

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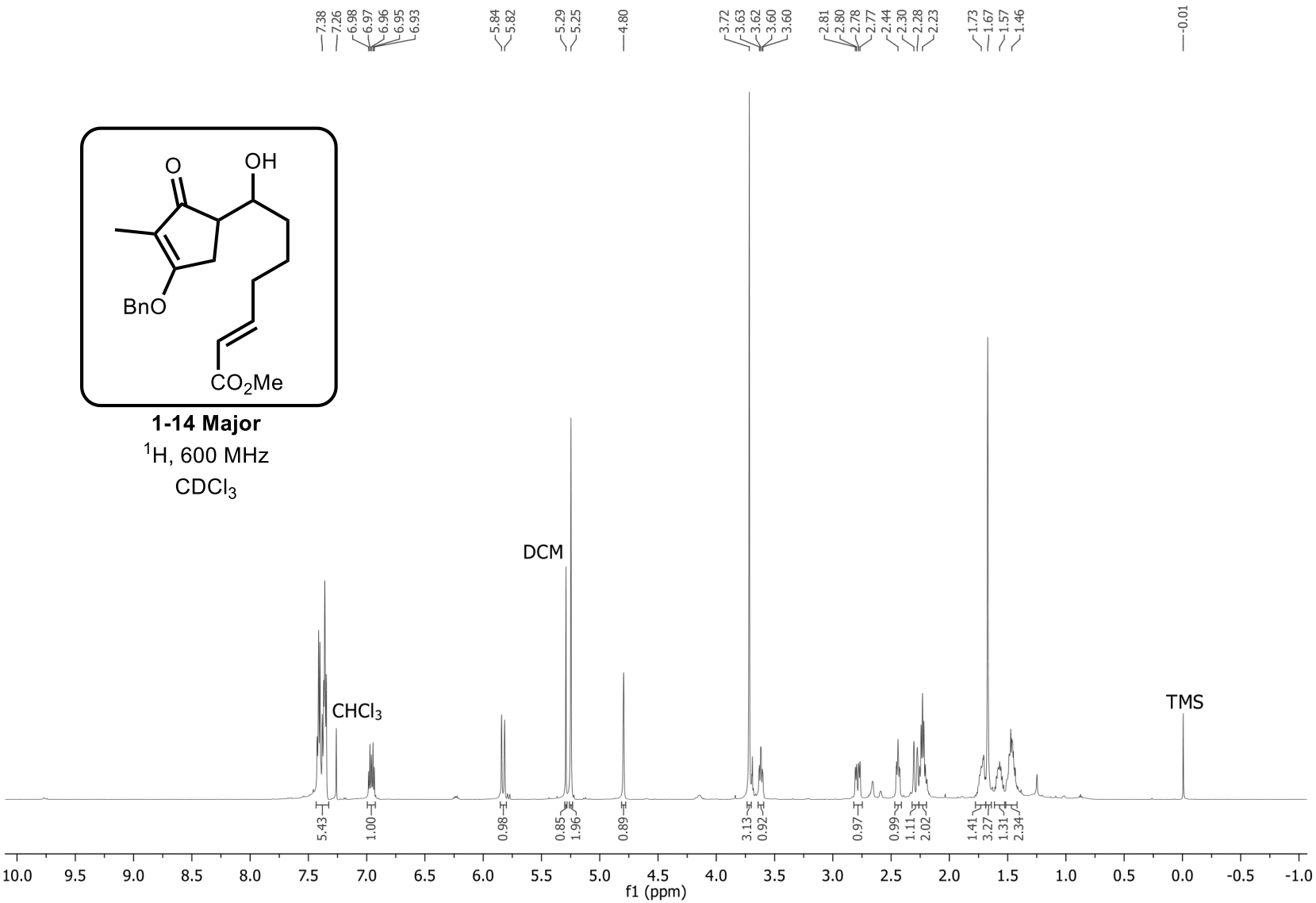
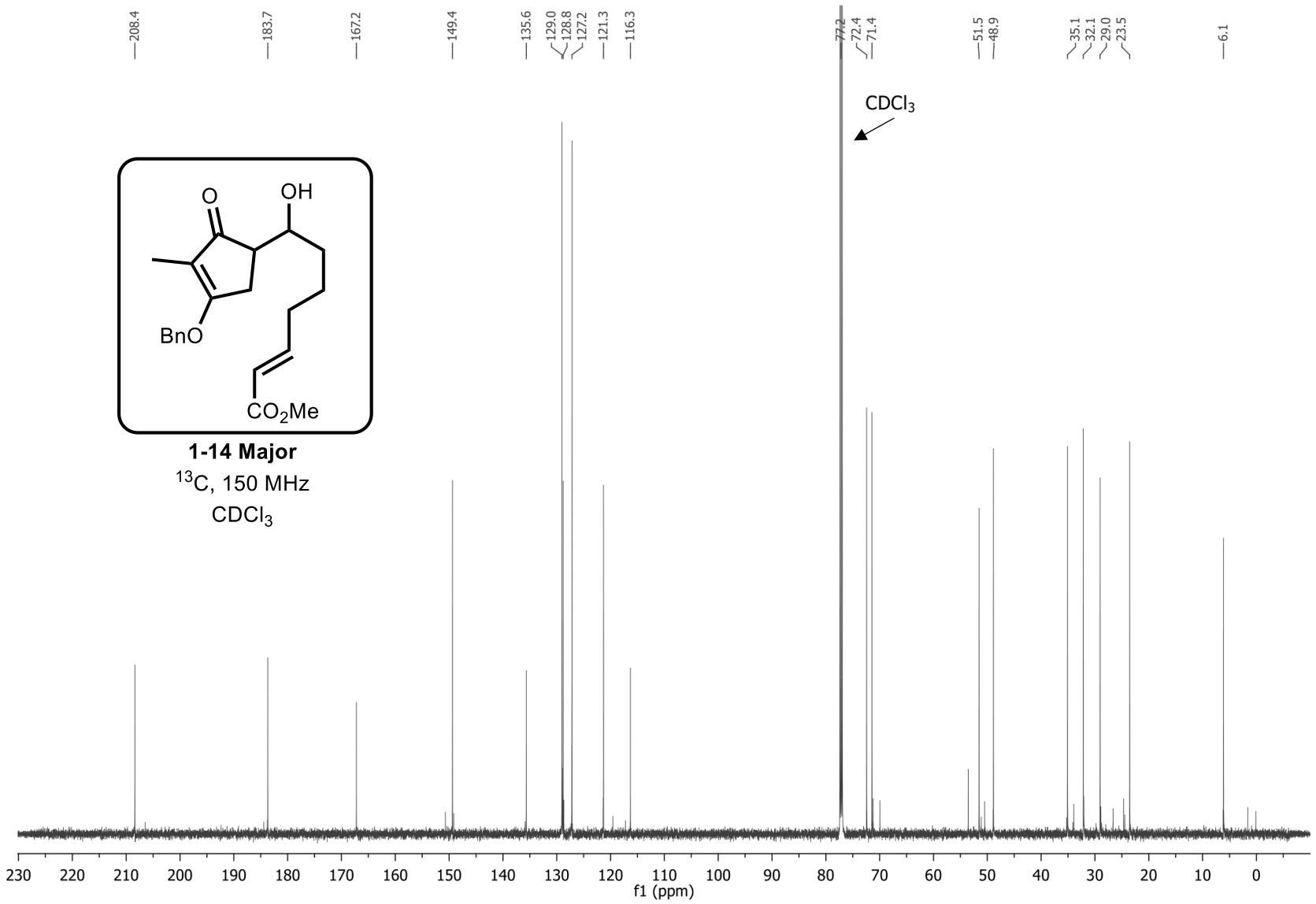
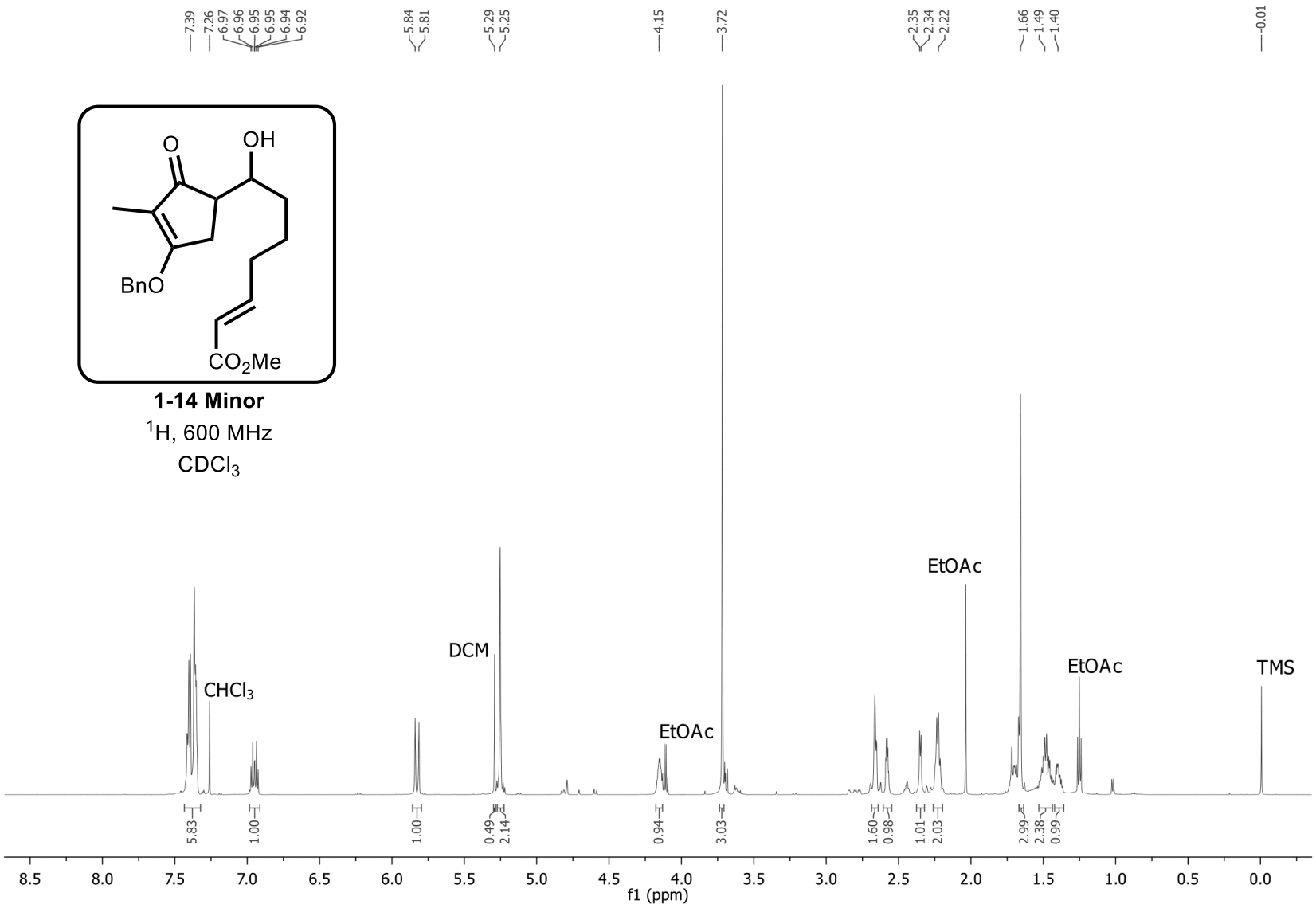
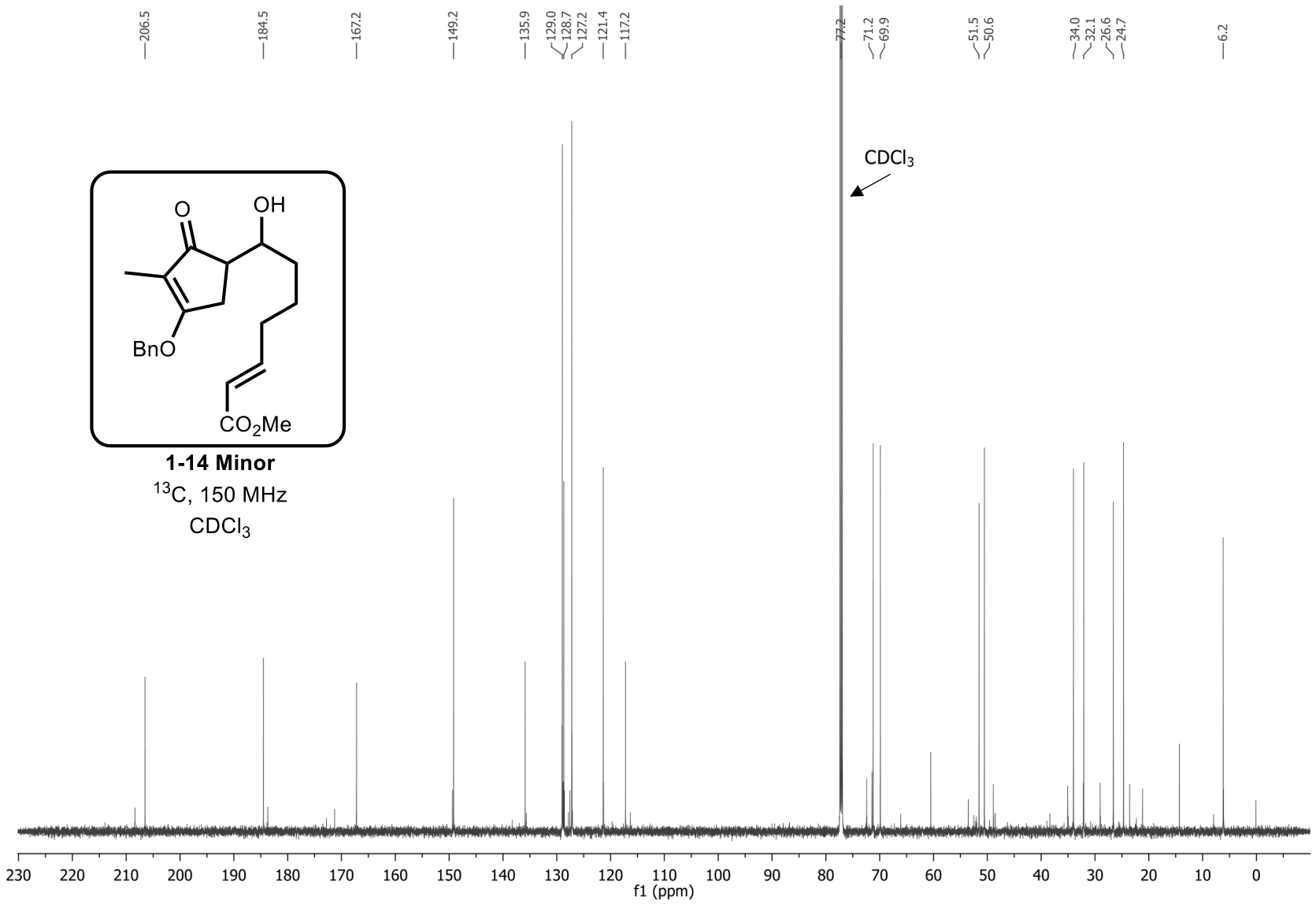
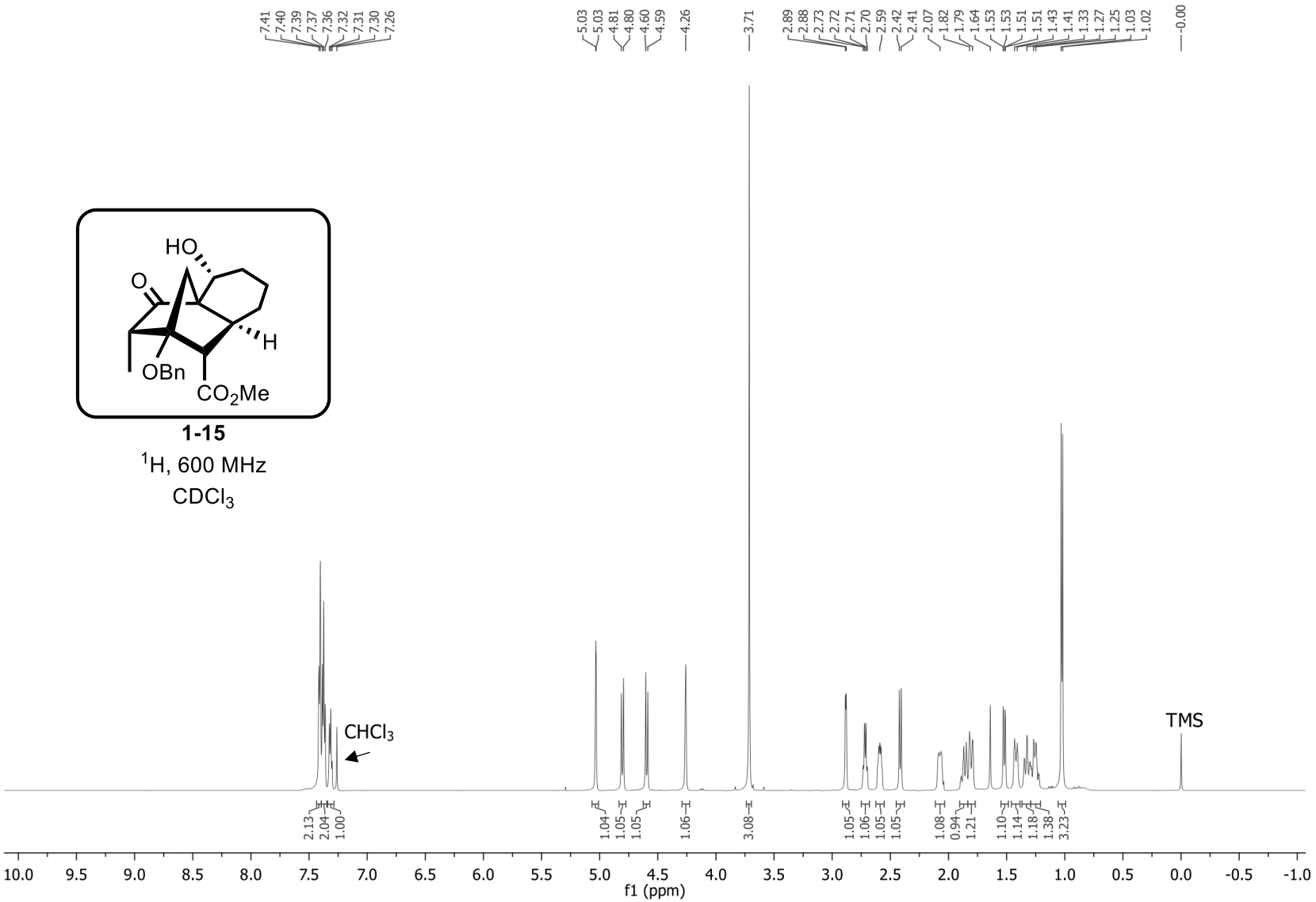
Appendix A: Spectral Data for Compounds in Chapter 1


7.38
7.26
6.98
6.97
6.96
6.95
6.93
5.84
5.82
5.29
5.25
4.80
3.72
3.63
3.62
3.60
3.60
2.81
2.80
2.78
2.77
2.44
2.30
2.28
2.23
1.73
1.67
1.57
1.46
-0.01
O
OH
BnO
CO2Me
1-14 Major
1H, 600 MHz
CDCl3
DCM
CHCl3
TMS
5.43
1.00
0.98
0.85
1.96
0.89
3.13
0.92
0.97
0.99
1.11
2.02
1.41
3.27
1.31
2.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


208.4
183.7
167.2
149.4
135.6
129.0
128.8
127.2
121.3
116.3
77.2
72.4
71.4
51.5
48.9
35.1
32.1
29.0
23.5
6.1
CDCl3
O
OH
BnO
CO2Me
1-14 Major
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.39
7.26
6.97
6.96
6.95
6.95
6.94
6.92
5.84
5.81
5.29
5.25
4.15
3.72
2.35
2.34
2.22
1.66
1.49
1.40
-0.01
O
OH
BnO
CO2Me
1-14 Minor
1H, 600 MHz
CDCl3
CHCl3
DCM
EtOAc
EtOAc
EtOAc
TMS
5.83
1.00
1.00
0.49
2.14
0.94
3.03
1.60
0.98
1.01
2.03
2.99
2.38
0.99
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


206.5
184.5
167.2
149.2
135.9
129.0
128.7
127.2
121.4
117.2
77.2
71.2
69.9
51.5
50.6
34.0
32.1
26.6
24.7
6.2
CDCl3
O
OH
BnO
CO2Me
1-14 Minor
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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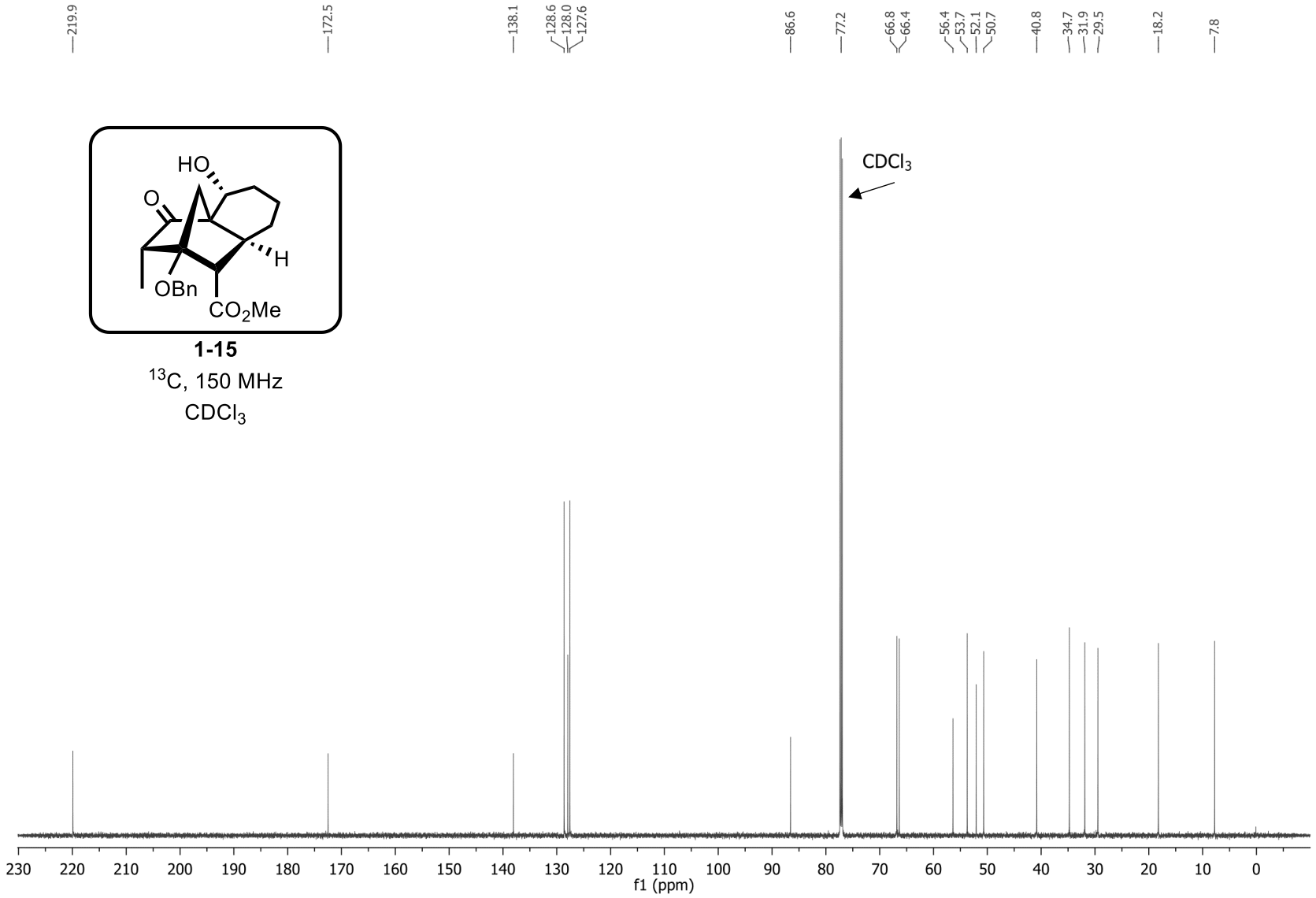
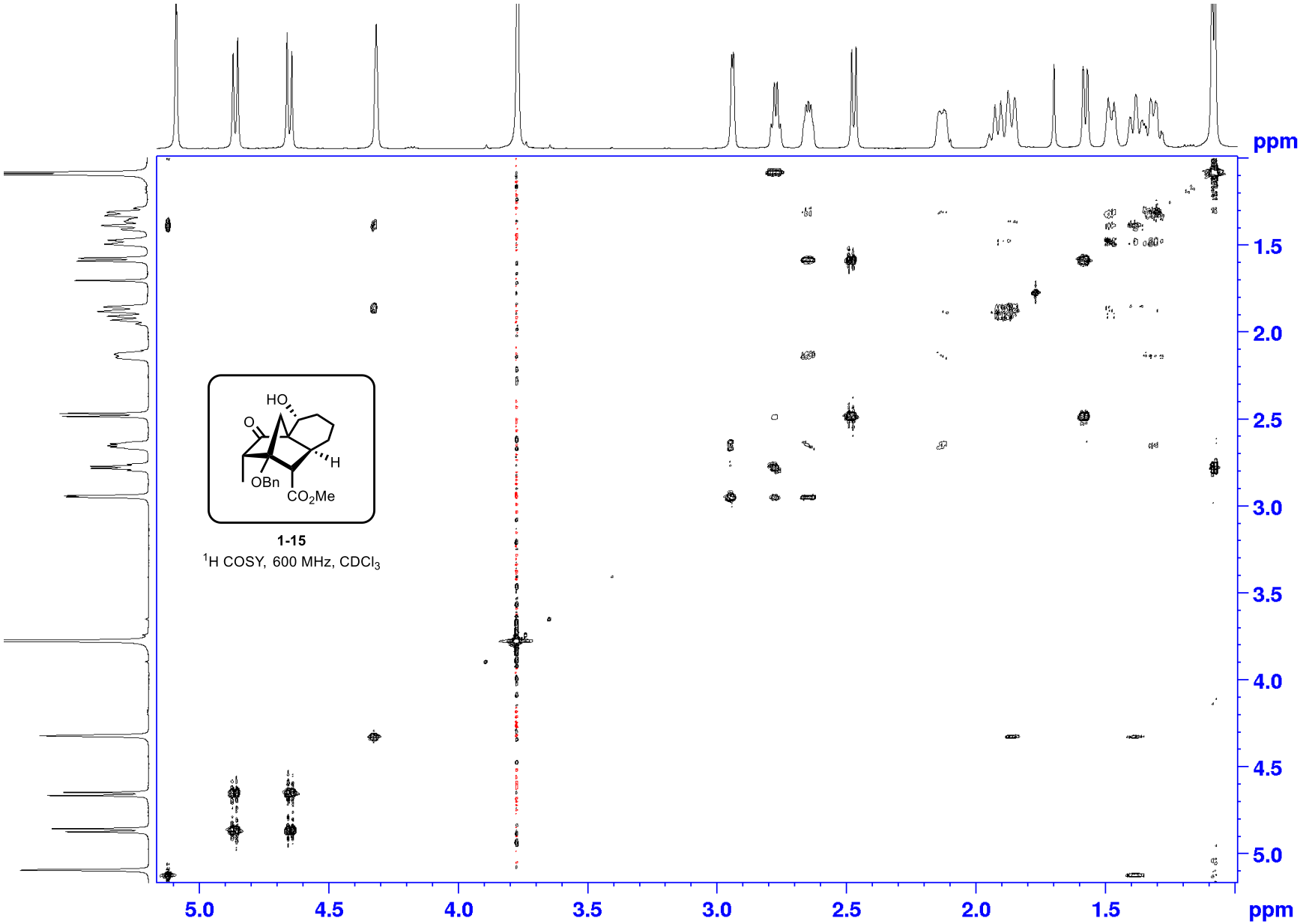
O
H
OBn
CO2Me
1-15
1H, 600 MHz
CDCl3
CHCl3
TMS
f1 (ppm)

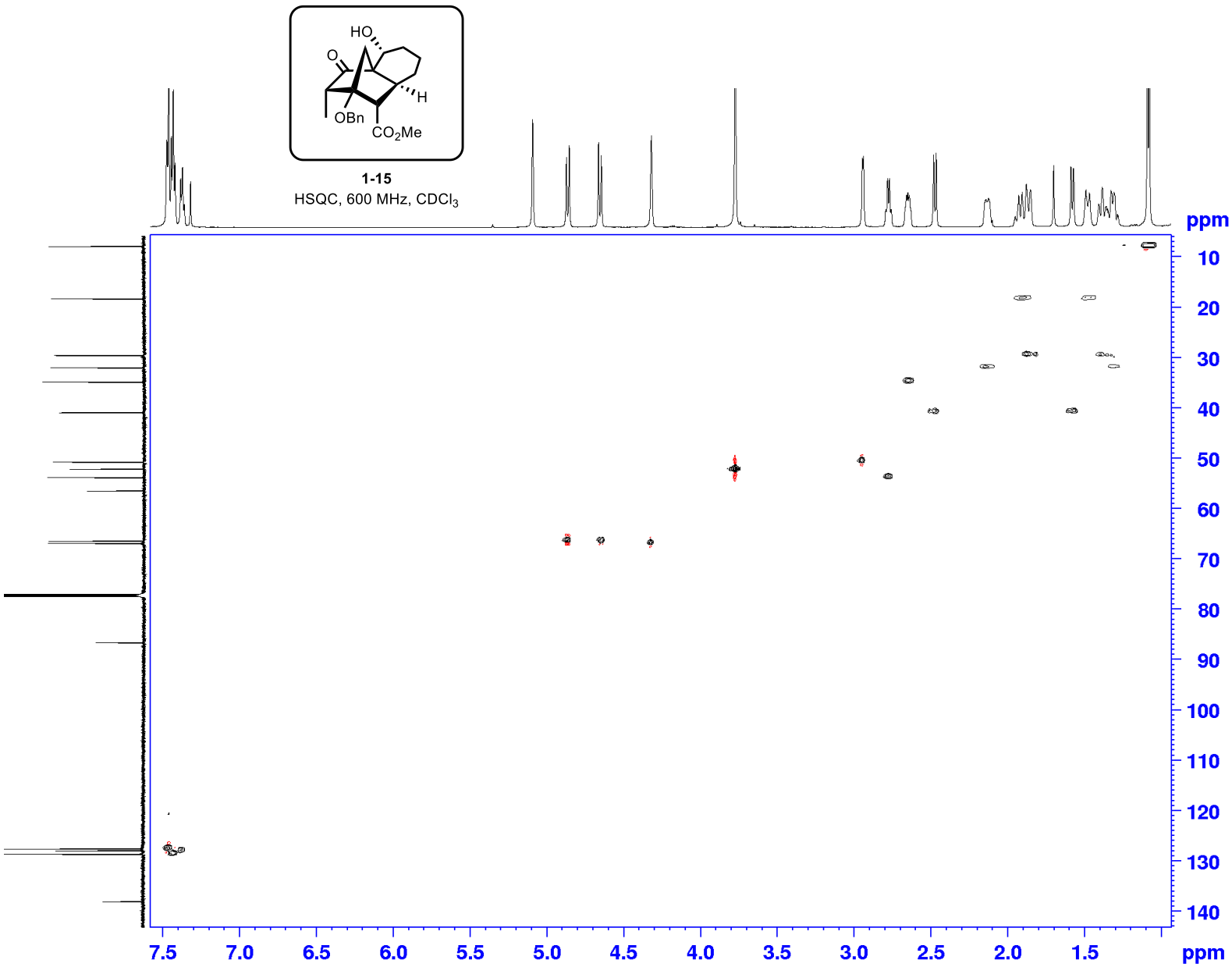


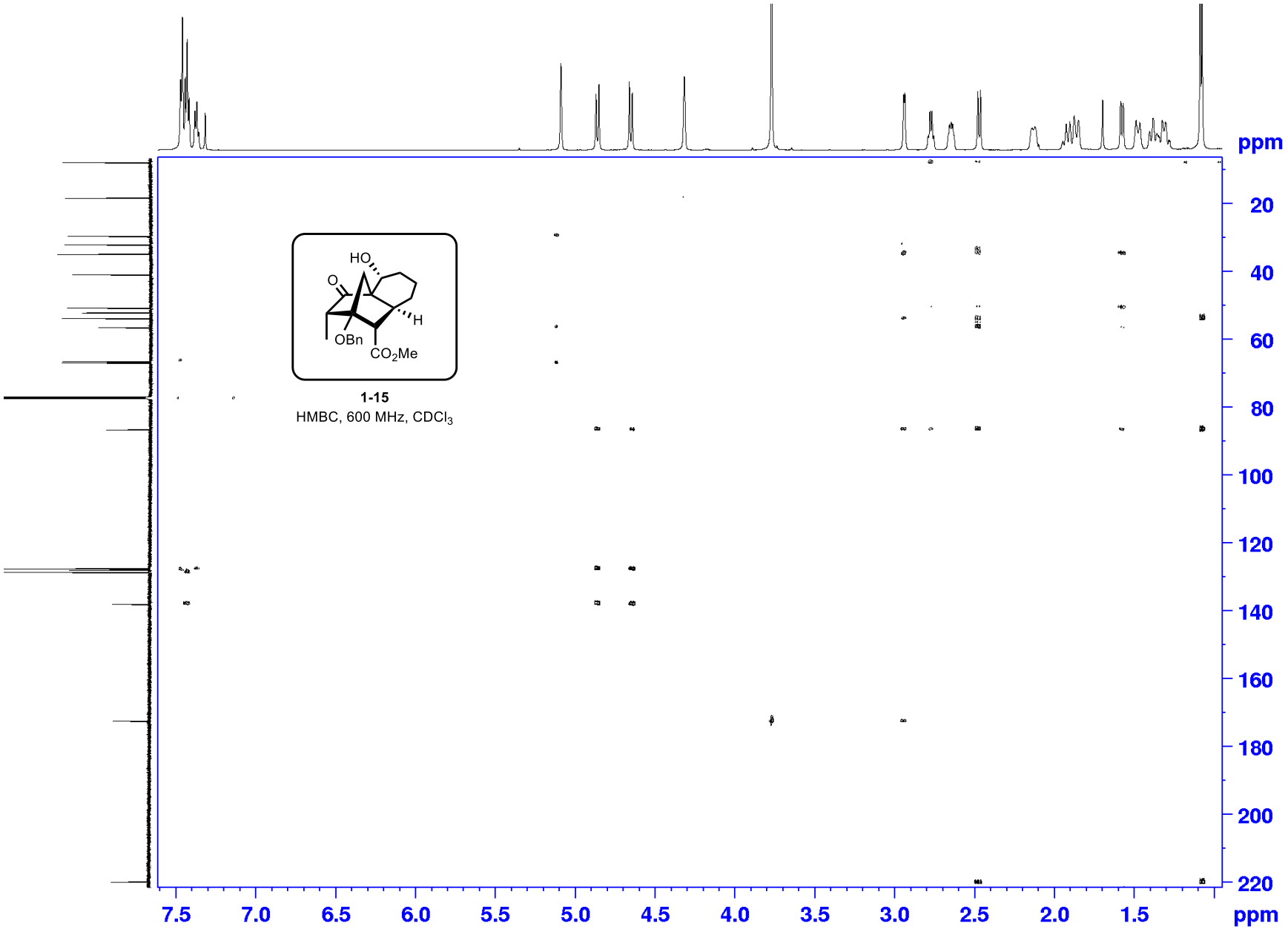
1-15

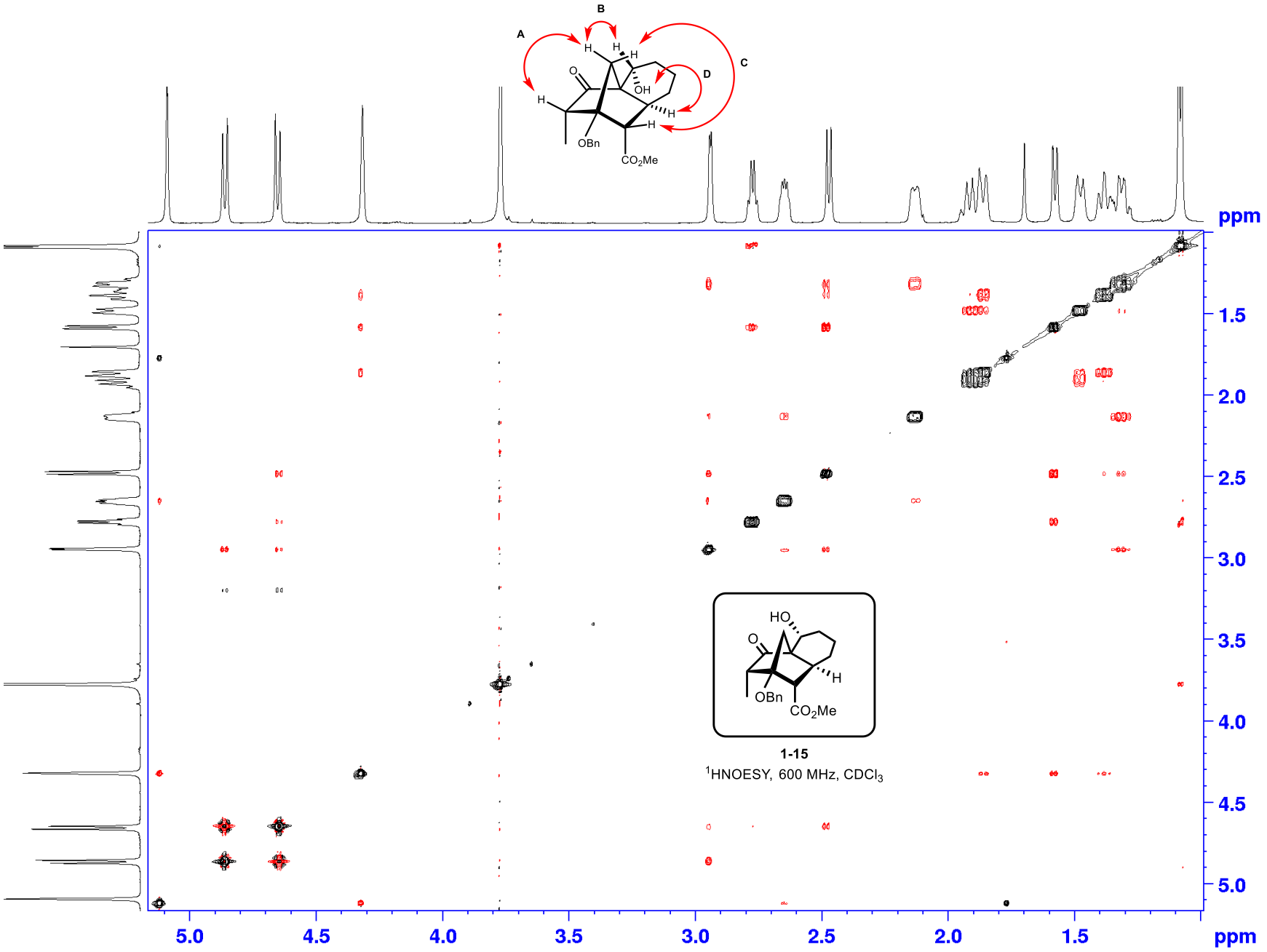
^{13}C, 150 MHz

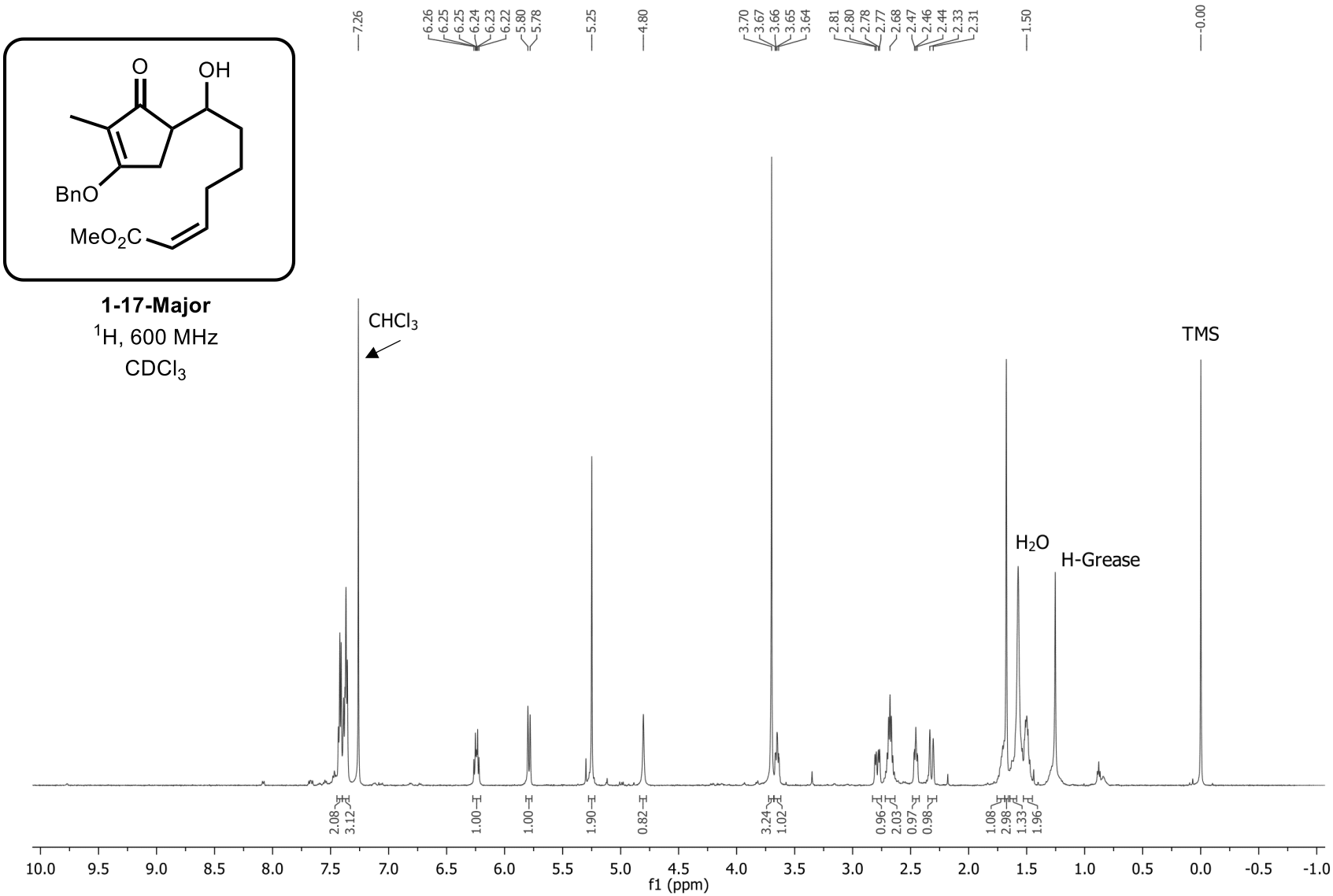
$CDCl_3$

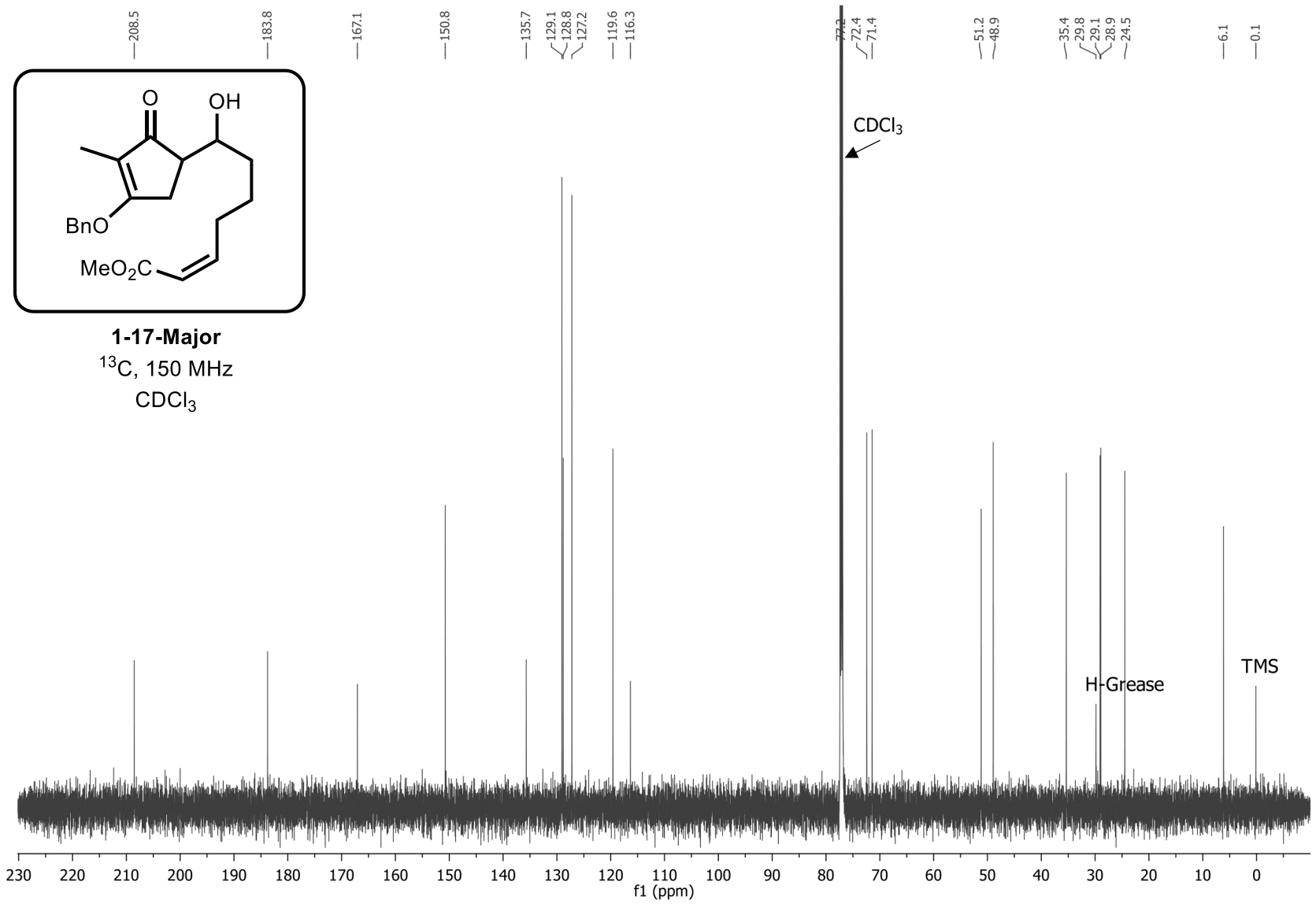

HO
O
OBn
CO2Me
H
1-15
1H COSY, 600 MHz, CDCl3
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


HO
O
H
OBn
CO2Me
1-15
HSQC, 600 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


HO
O
H
OBn
CO2Me
1-15
HMBC, 600 MHz, CDCl3
ppm
20
40
60
80
100
120
140
160
180
200
220
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


A
B
C
D
OBn
CO2Me
OH
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
HO
OBn
CO2Me
1-15
1HNOESY, 600 MHz, CDCl3

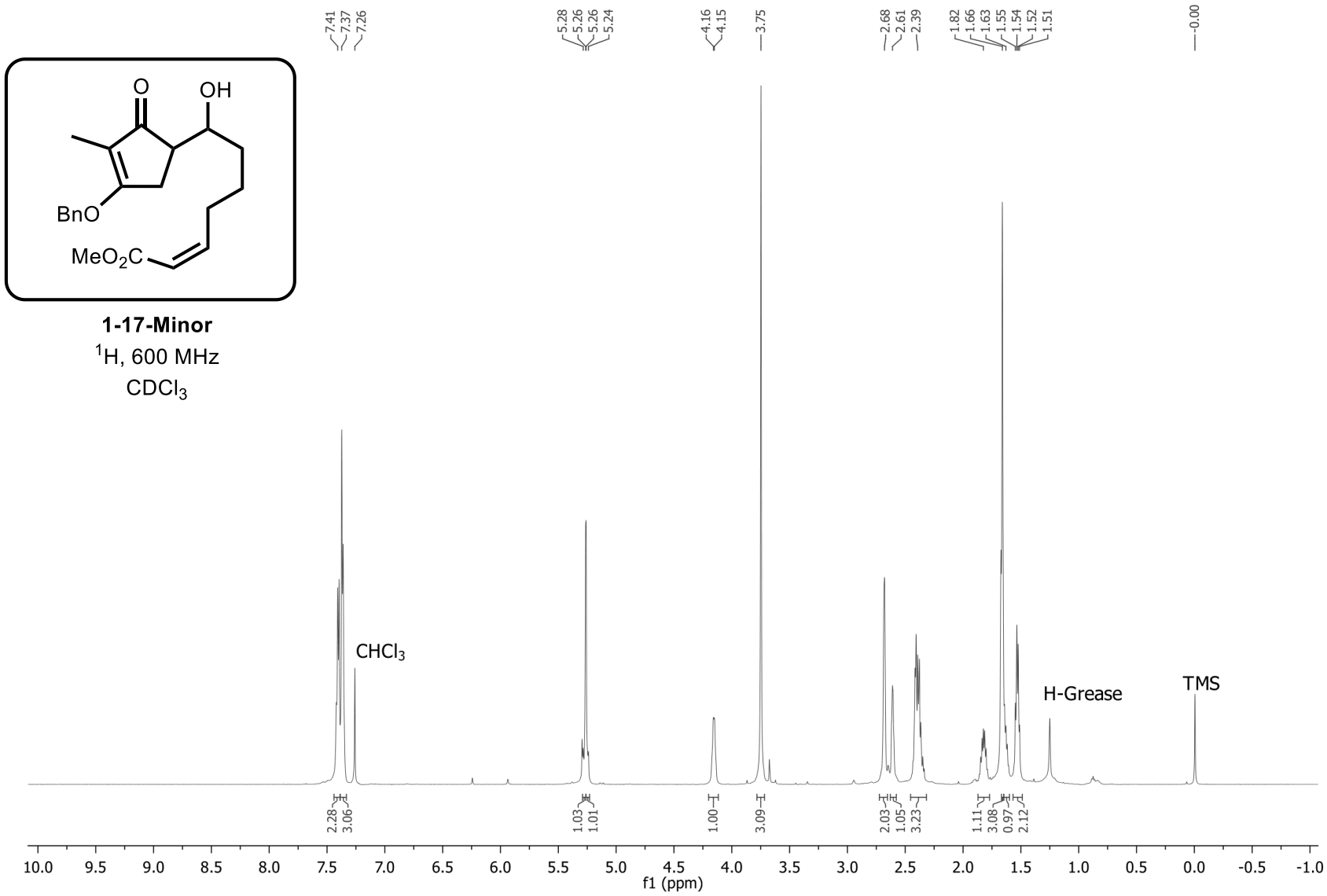

O
OH
BnO
MeO2C
1-17-Major
1H, 600 MHz
CDCl3
CHCl3
TMS
H2O
H-Grease
f1 (ppm)

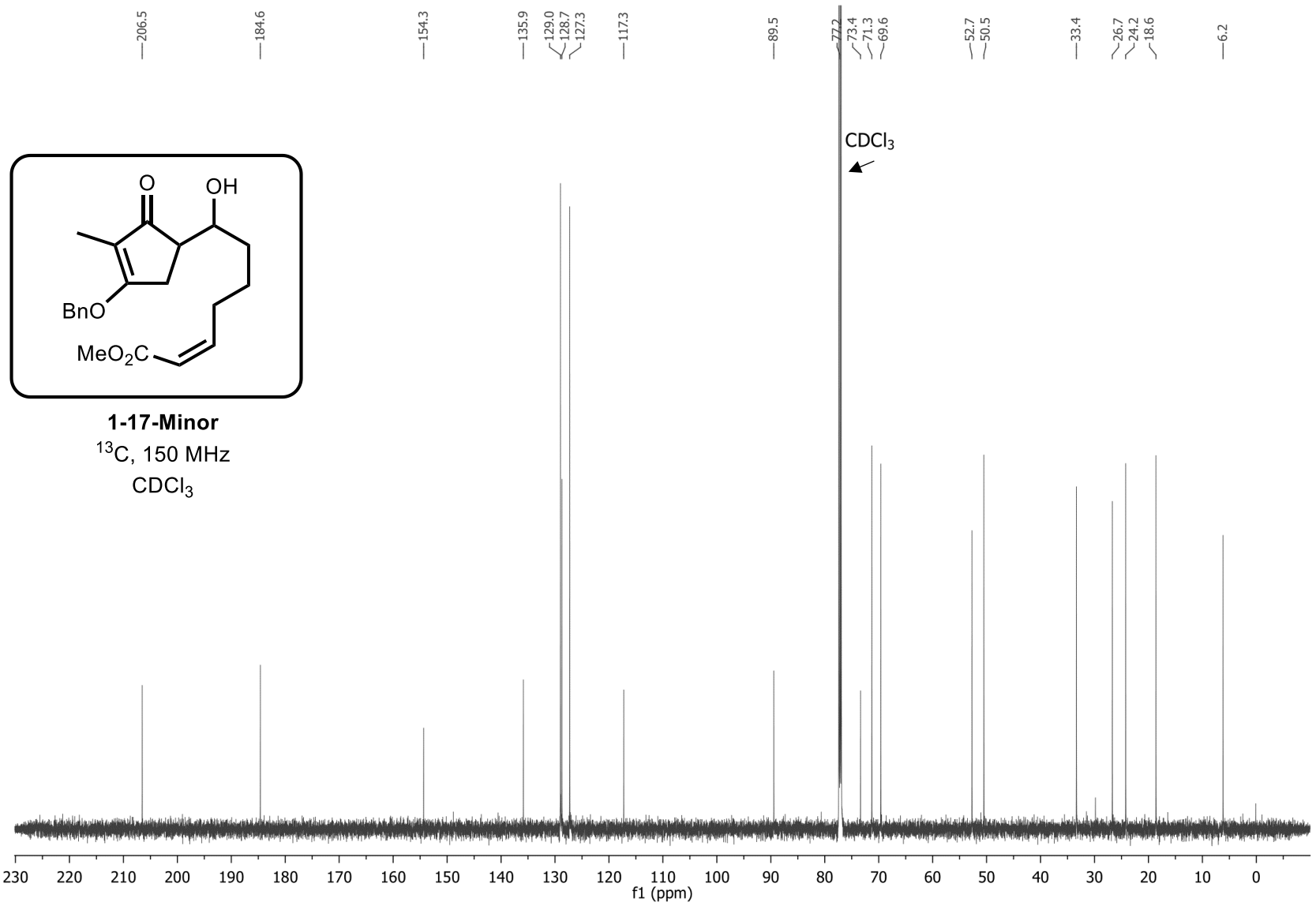


1-17-Major

^{13}C, 150 MHz

$CDCl_3$


O
OH
BnO
MeO2C
1-17-Minor
1H, 600 MHz
CDCl3
7.41
7.37
7.26
5.28
5.26
5.26
5.24
4.16
4.15
3.75
2.68
2.61
2.39
1.82
1.66
1.63
1.55
1.54
1.52
1.51
-0.00
CHCl3
H-Grease
TMS
2.28
3.06
1.03
1.01
1.00
3.09
2.03
1.05
3.23
1.11
3.08
0.97
2.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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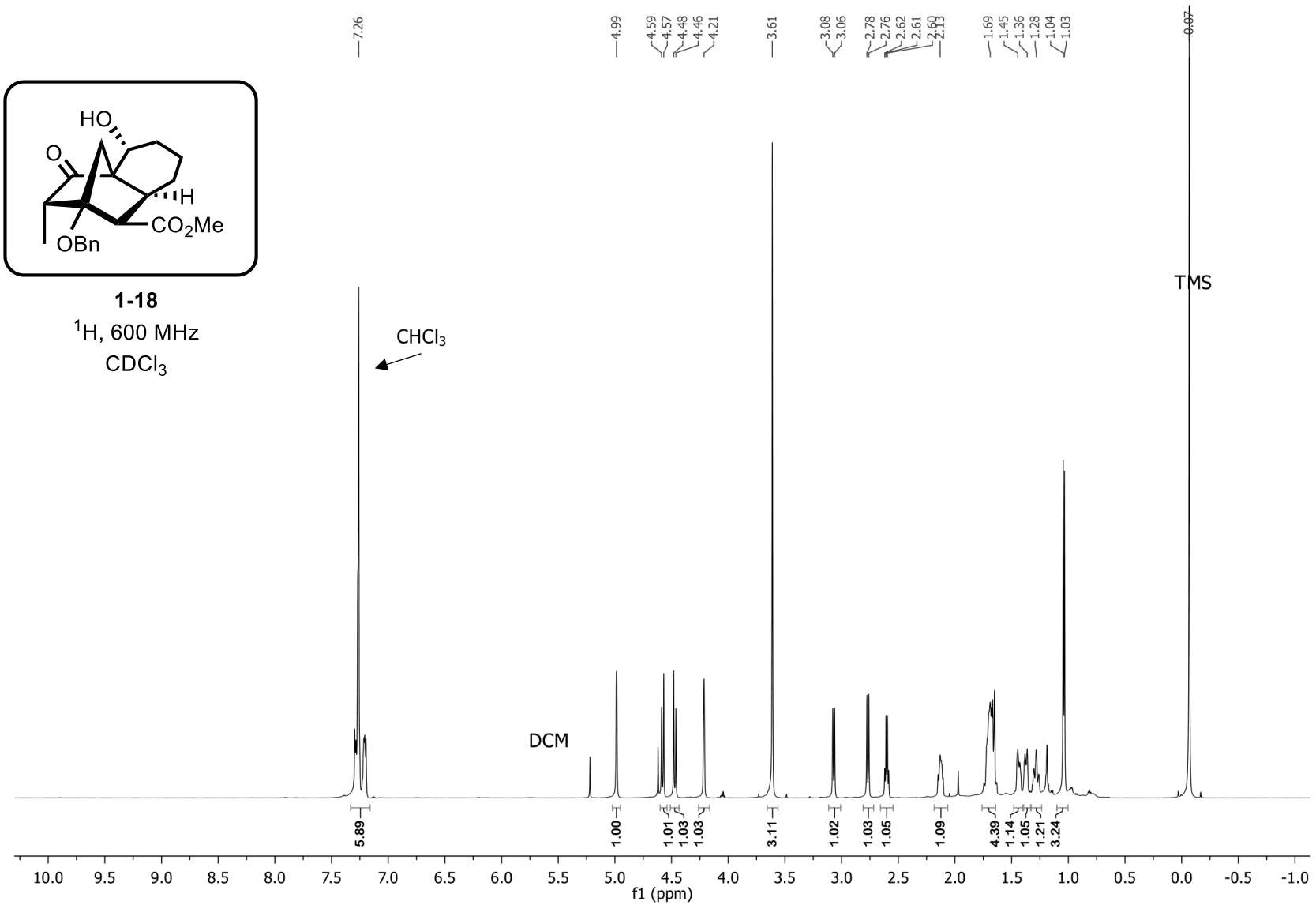
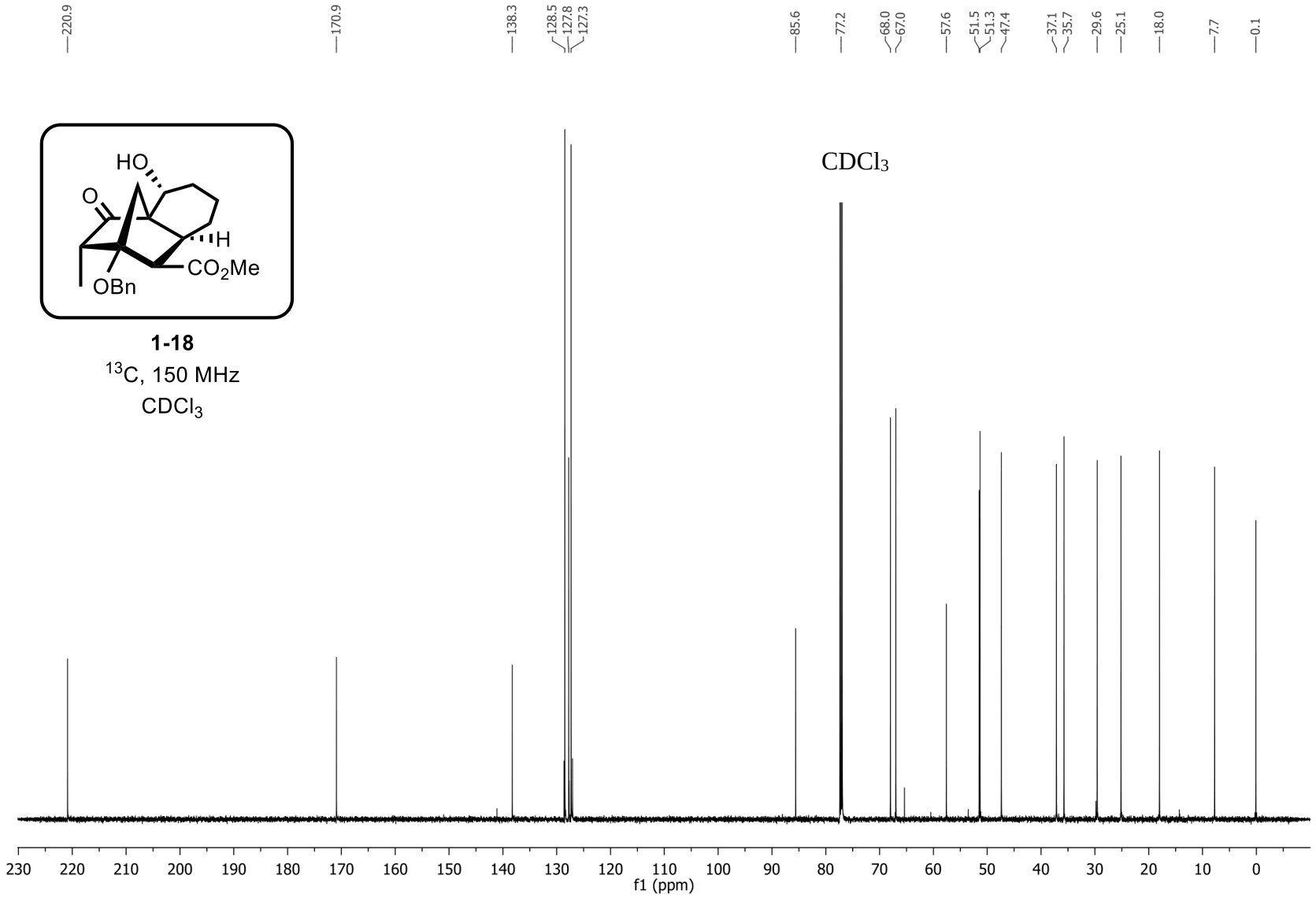
184.6
154.3
135.9
129.0
128.7
127.3
117.3
89.5
77.2
73.4
71.3
69.6
52.7
50.5
33.4
26.7
24.2
18.6
6.2
CDCl3
O
OH
BnO
MeO2C
1-17-Minor
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
O
H
CO2Me
OBn
1-18
1H, 600 MHz
CDCl3
CHCl3
DCM
TMS
7.26
4.99
4.59
4.57
4.48
4.46
4.21
3.61
3.08
3.06
2.78
2.76
2.62
2.61
2.60
2.13
1.69
1.45
1.36
1.28
1.04
1.03
0.07
5.89
1.00
1.01
1.03
1.03
3.11
1.02
1.03
1.05
1.09
4.39
1.14
1.05
1.21
3.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


220.9
170.9
138.3
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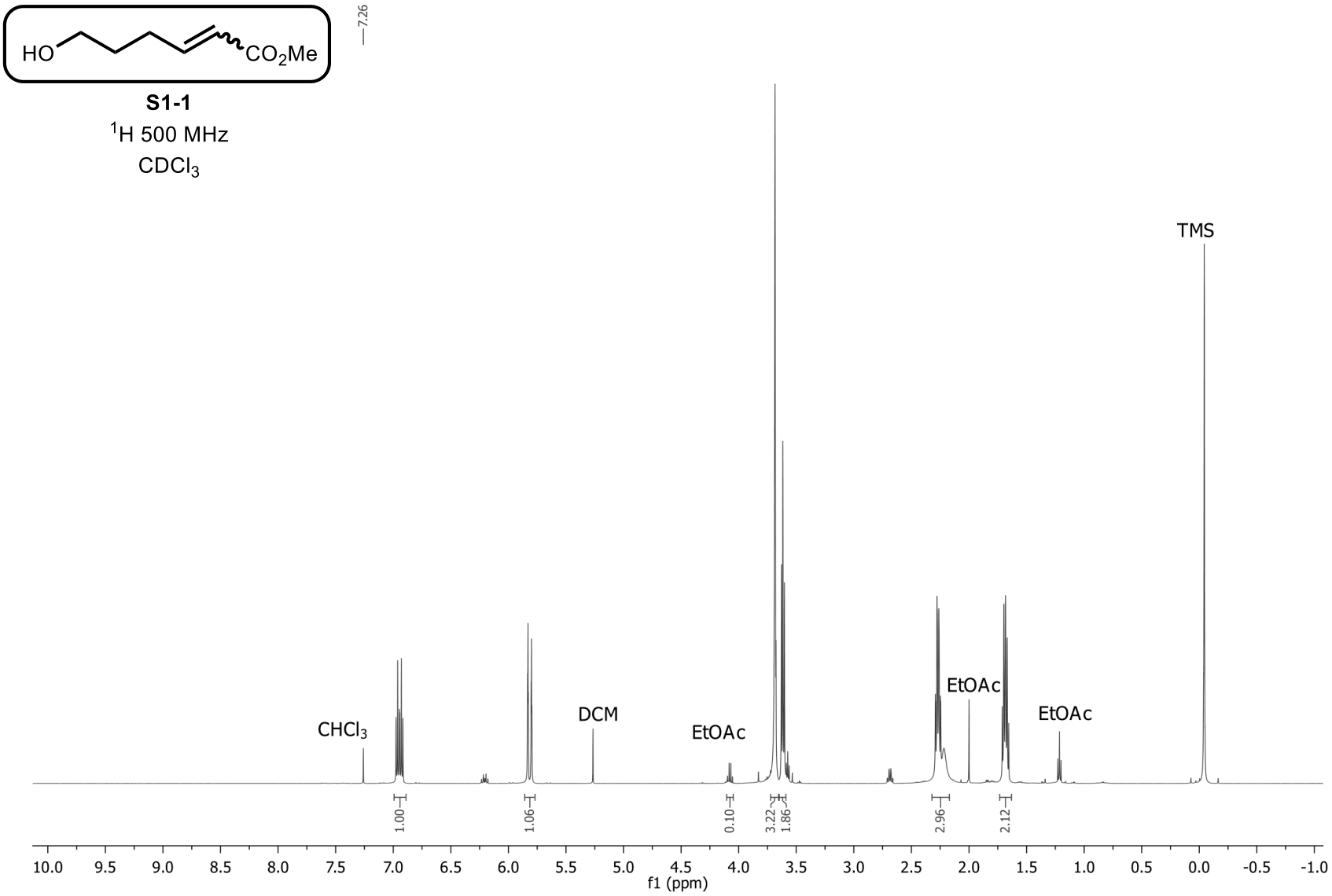
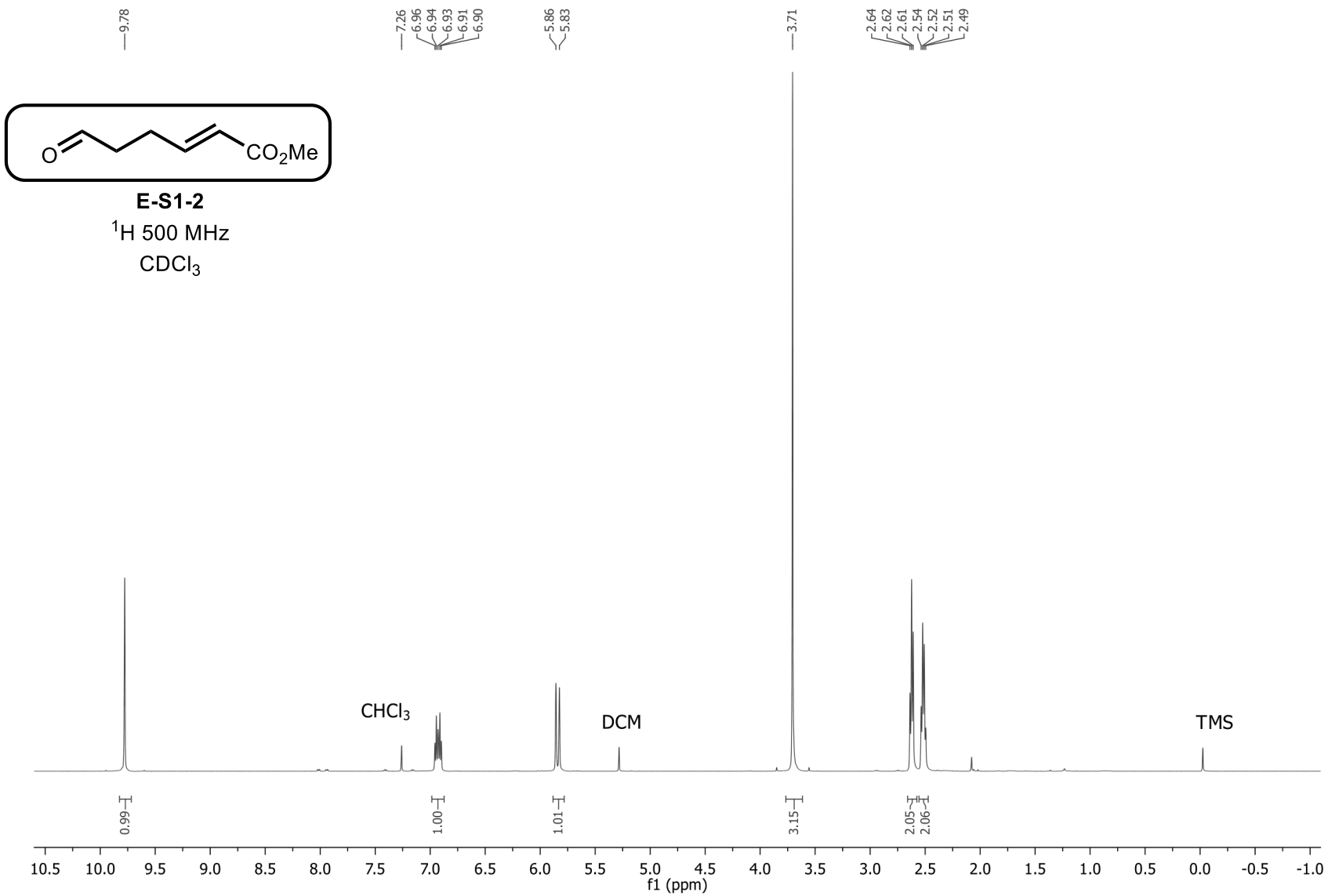
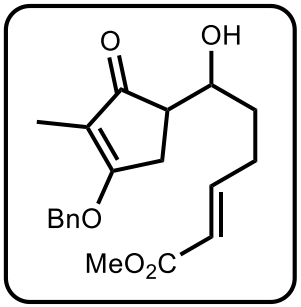
127.8
127.3
85.6
77.2
68.0
67.0
57.6
51.5
51.3
47.4
37.1
35.7
29.6
25.1
18.0
7.7
0.1
HO
O
H
CO2Me
OBn
CDCl3
1-18
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
CO2Me
7.26
S1-1
1H 500 MHz
CDCl3
TMS
CHCl3
DCM
EtOAc
EtOAc
EtOAc
1.00
1.06
0.10
3.22
1.86
2.96
2.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

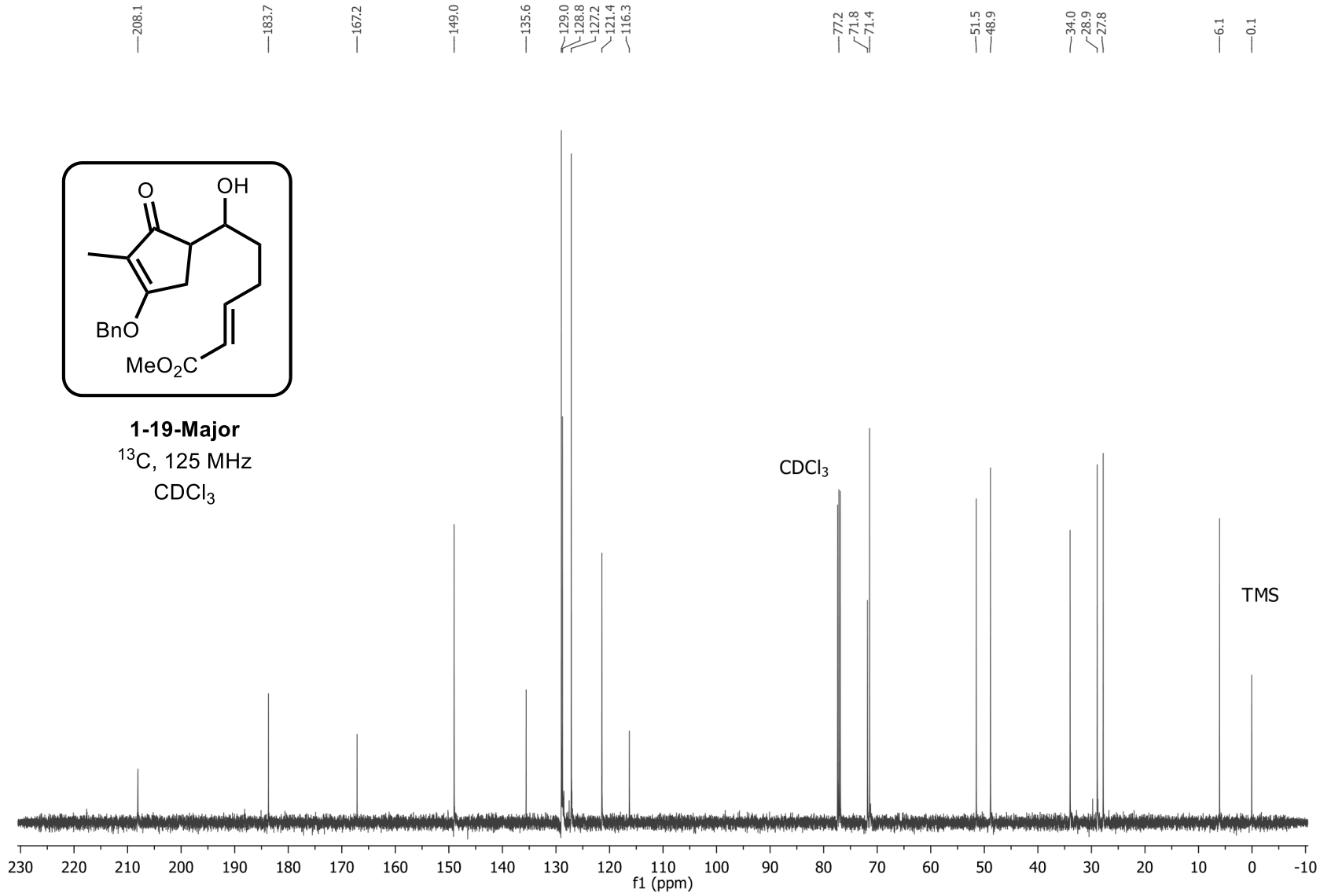

9.78
7.26
6.96
6.94
6.93
6.91
6.90
5.86
5.83
3.71
2.64
2.62
2.61
2.54
2.52
2.51
2.49
O
CO2Me
E-S1-2
1H 500 MHz
CDCl3
CHCl3
DCM
TMS
0.99
1.00
1.01
3.15
2.05
2.06
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

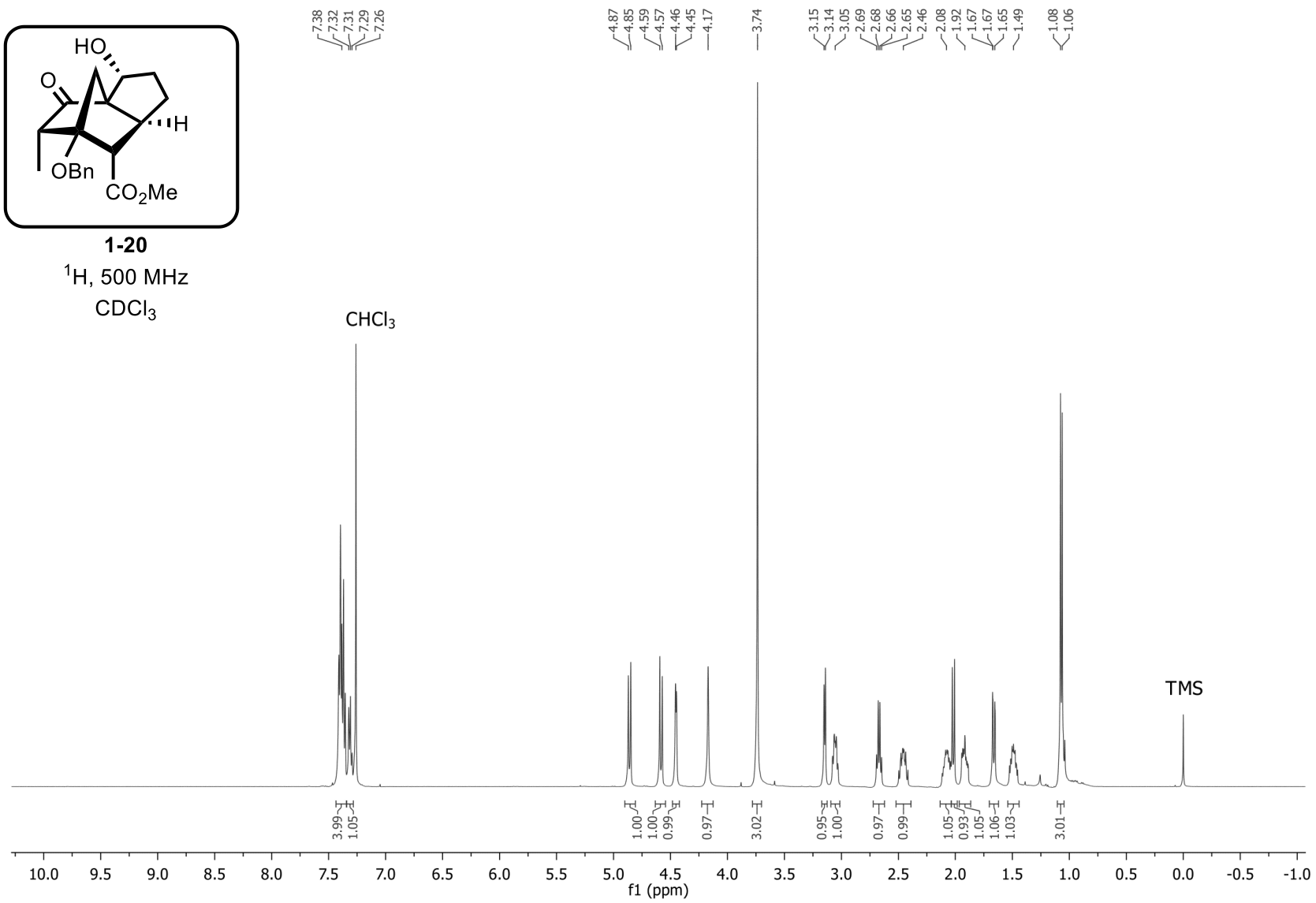


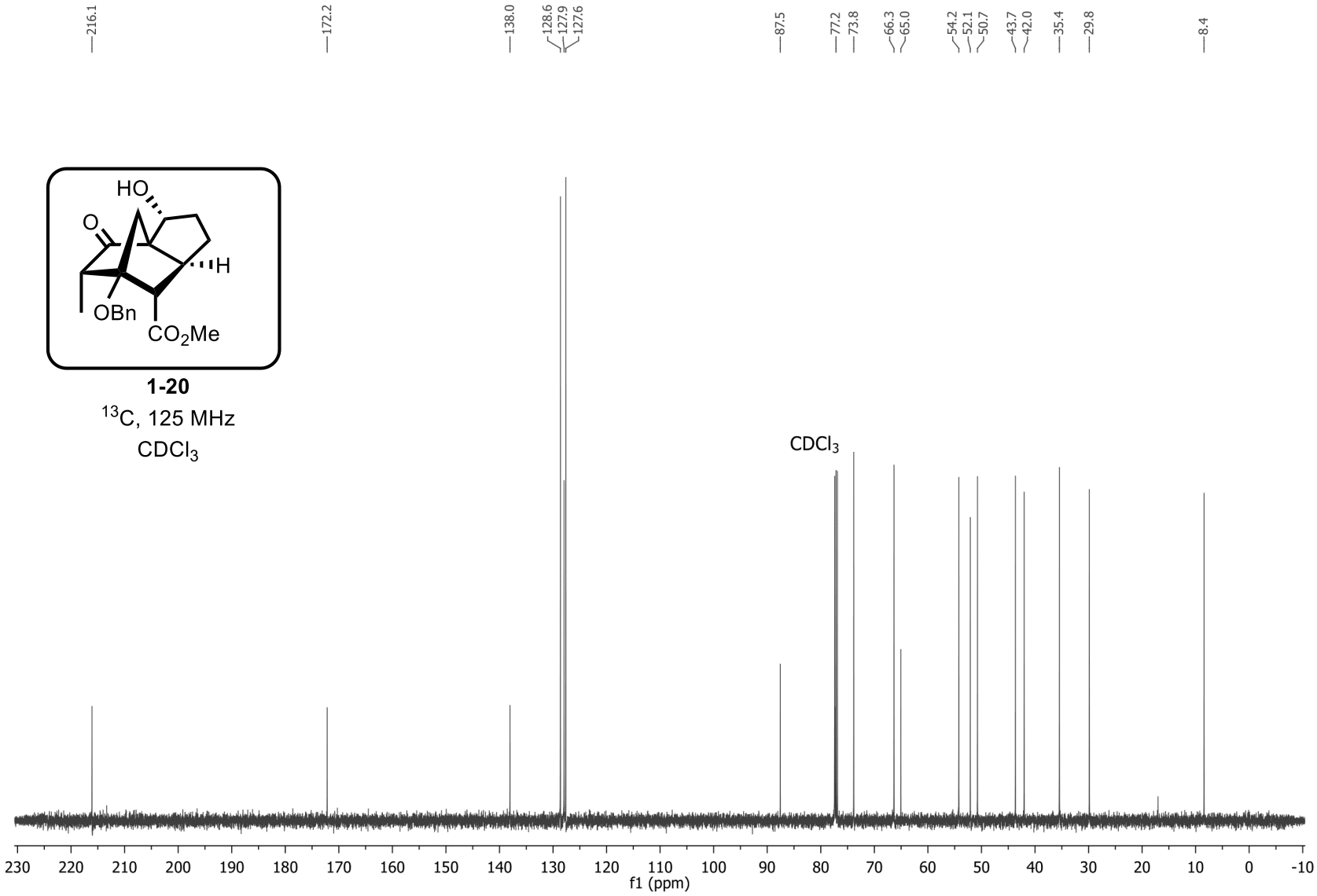
1-19-Major

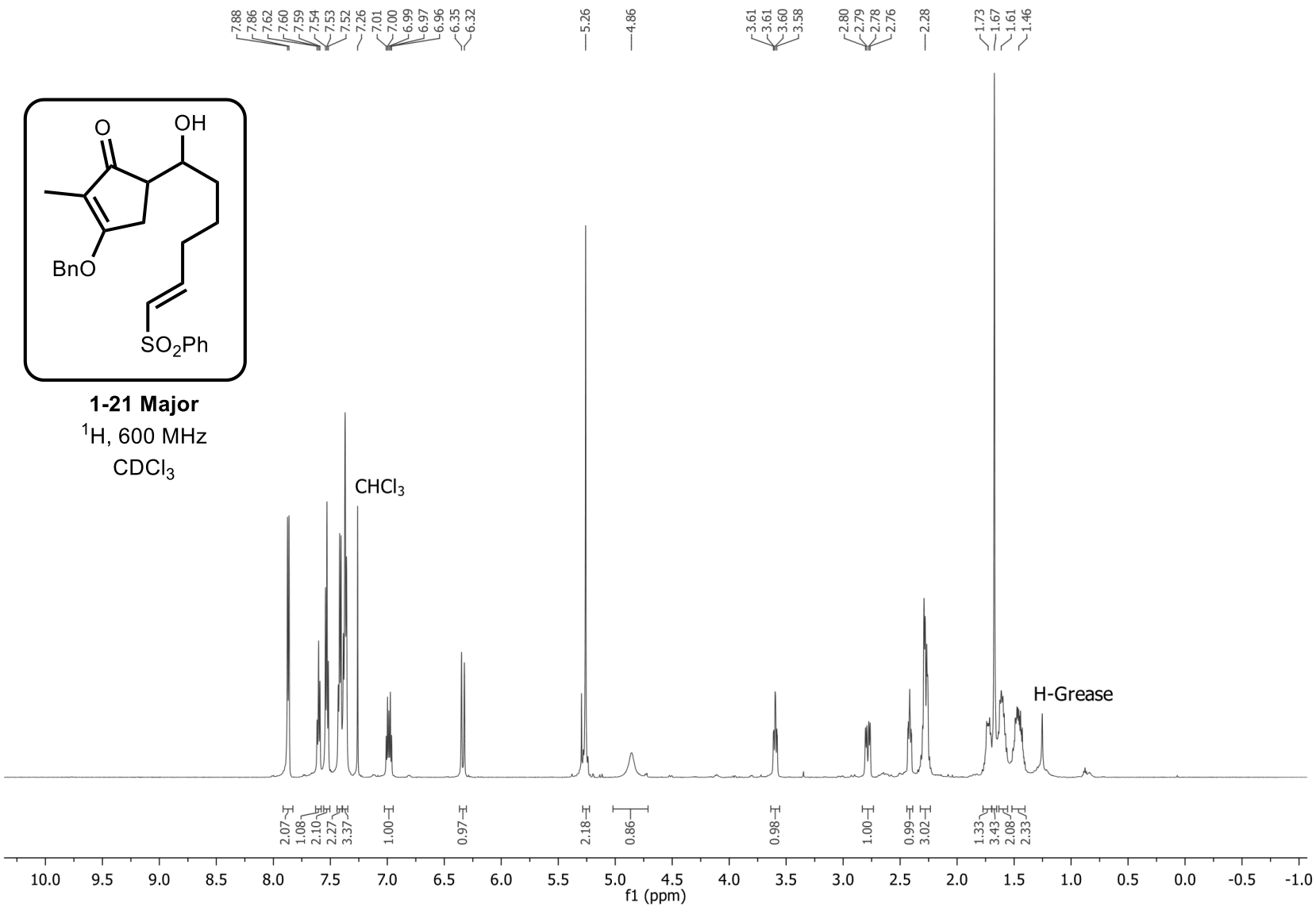
^{1}H, 500 MHz

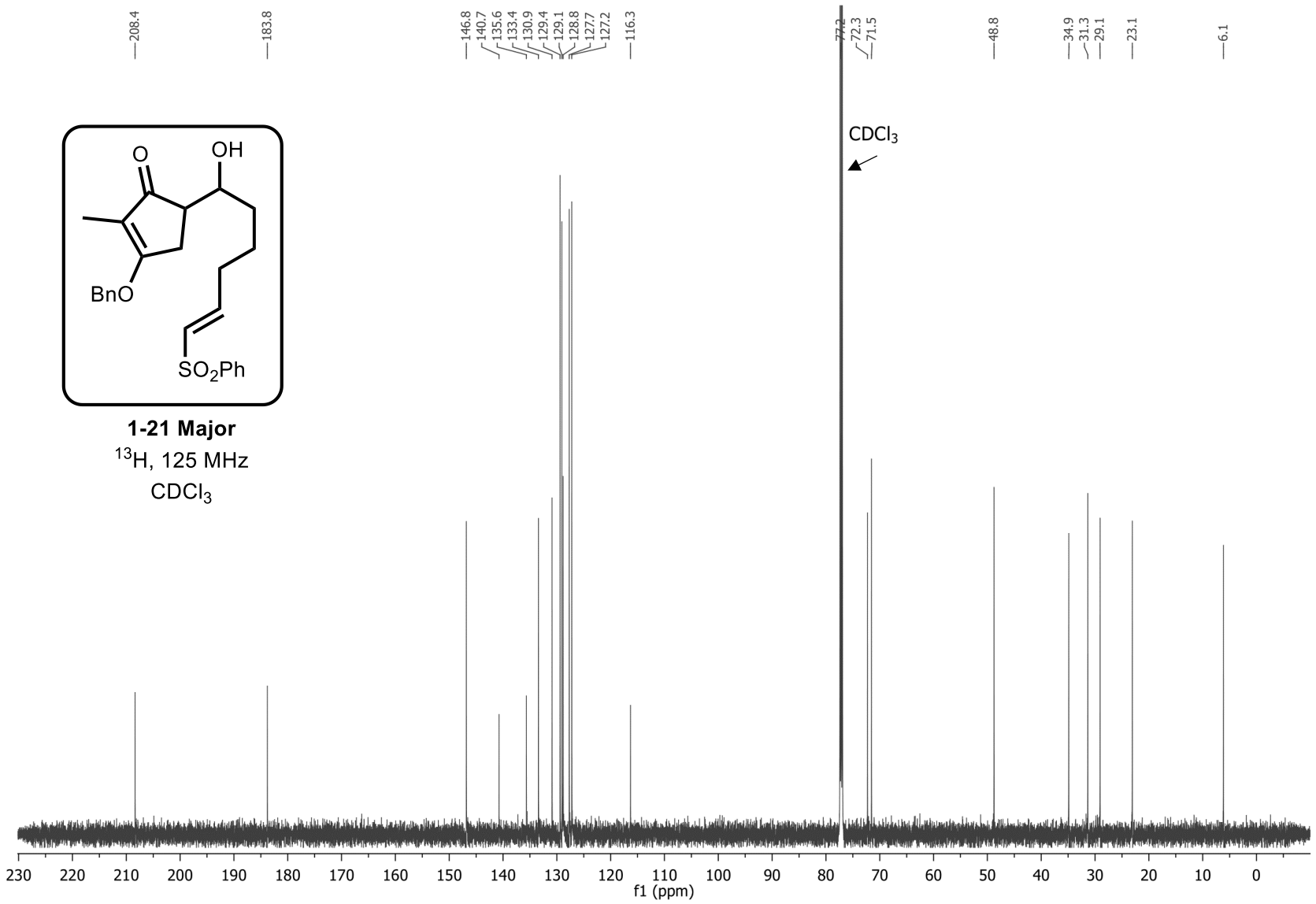
$CDCl_3$

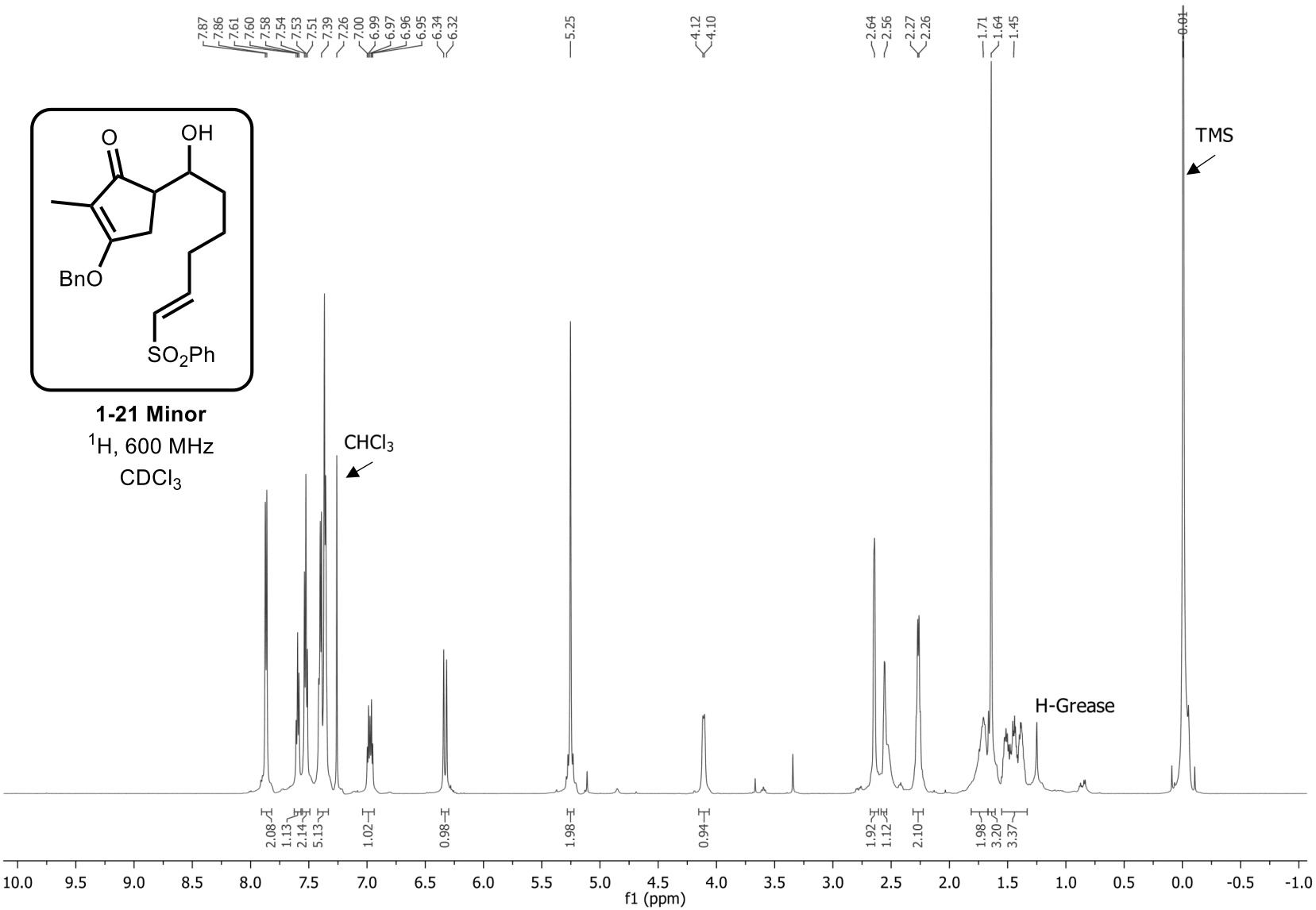

208.1
183.7
167.2
149.0
135.6
129.0
128.8
127.2
121.4
116.3
77.2
71.8
71.4
51.5
48.9
34.0
28.9
27.8
6.1
0.1
O
OH
BnO
MeO2C
1-19-Major
13C, 125 MHz
CDCl3
CDCl3
TMS
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

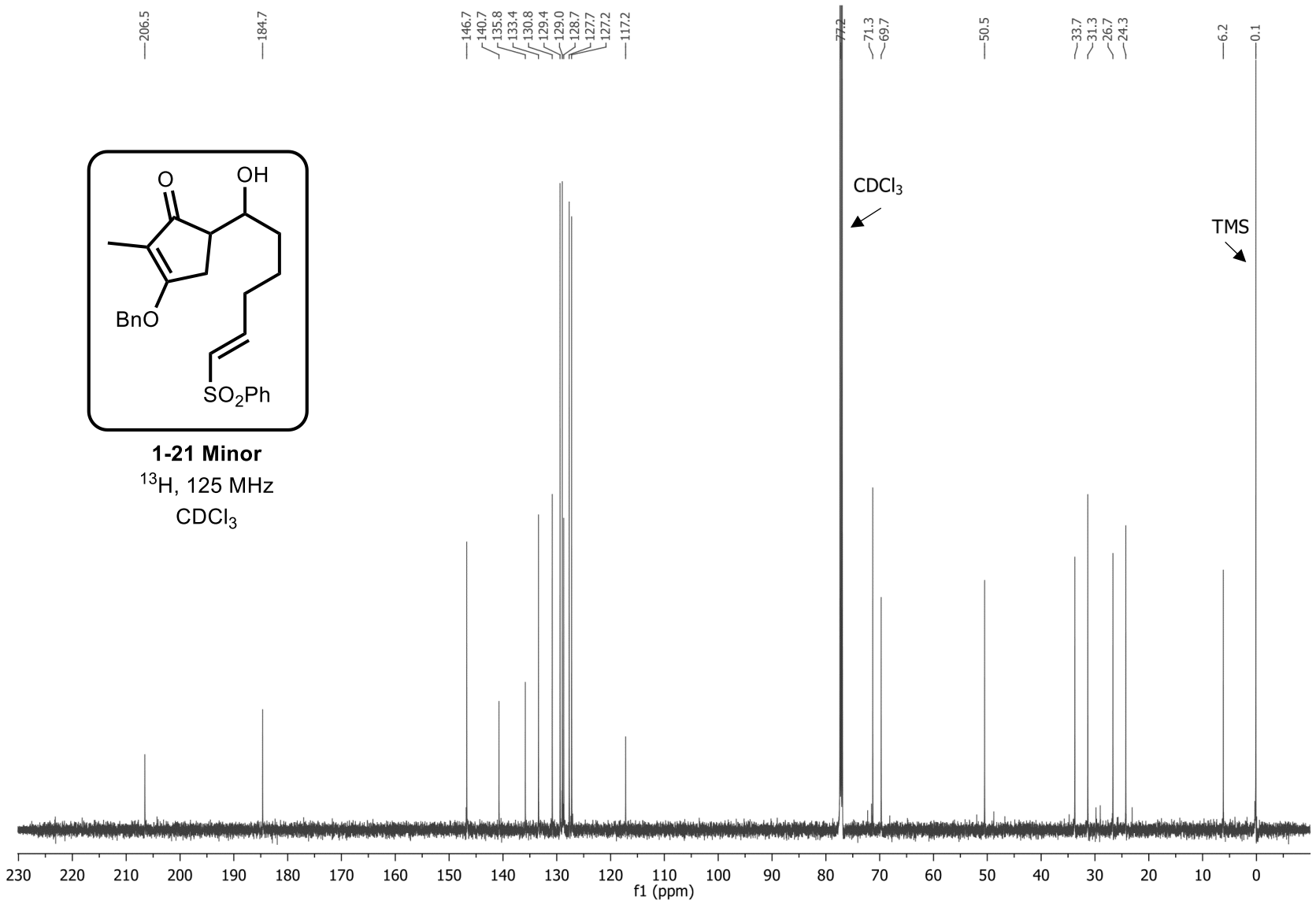

HO
O
H
OBn
CO2Me
1-20
1H, 500 MHz
CDCl3
CHCl3
TMS
f1 (ppm)

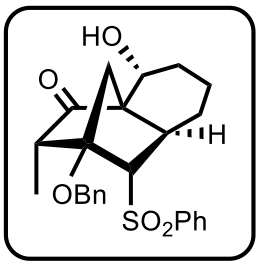

216.1
172.2
138.0
128.6
127.9
127.6
87.5
77.2
73.8
66.3
65.0
54.2
52.1
50.7
43.7
42.0
35.4
29.8
8.4
HO
O
H
OBn
CO2Me
1-20
13C, 125 MHz
CDCl3
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.88
7.86
7.62
7.60
7.59
7.54
7.53
7.52
7.26
7.01
7.00
6.99
6.97
6.96
6.35
6.32
5.26
4.86
3.61
3.61
3.60
3.58
2.80
2.79
2.78
2.76
2.28
1.73
1.67
1.61
1.46
O
OH
BnO
SO2Ph
1-21 Major
1H, 600 MHz
CDCl3
CHCl3
H-Grease
2.07
1.08
2.10
2.27
3.37
1.00
0.97
2.18
0.86
0.98
1.00
0.99
3.02
1.33
3.43
2.08
2.33
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


208.4
183.8
146.8
140.7
135.6
133.4
130.9
129.4
129.1
128.8
127.7
127.2
116.3
77.2
72.3
71.5
48.8
34.9
31.3
29.1
23.1
6.1
CDCl3
O
OH
BnO
SO2Ph
1-21 Major
13H, 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.87
7.86
7.61
7.60
7.58
7.54
7.53
7.51
7.39
7.26
7.00
6.99
6.97
6.96
6.95
6.34
6.32
5.25
4.12
4.10
2.64
2.56
2.27
2.26
1.71
1.64
1.45
0.01
TMS
O
OH
BnO
SO2Ph
1-21 Minor
1H, 600 MHz
CDCl3
CHCl3
H-Grease
2.08
1.13
2.14
5.13
1.02
0.98
1.98
0.94
1.92
1.12
2.10
1.98
3.20
3.37
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

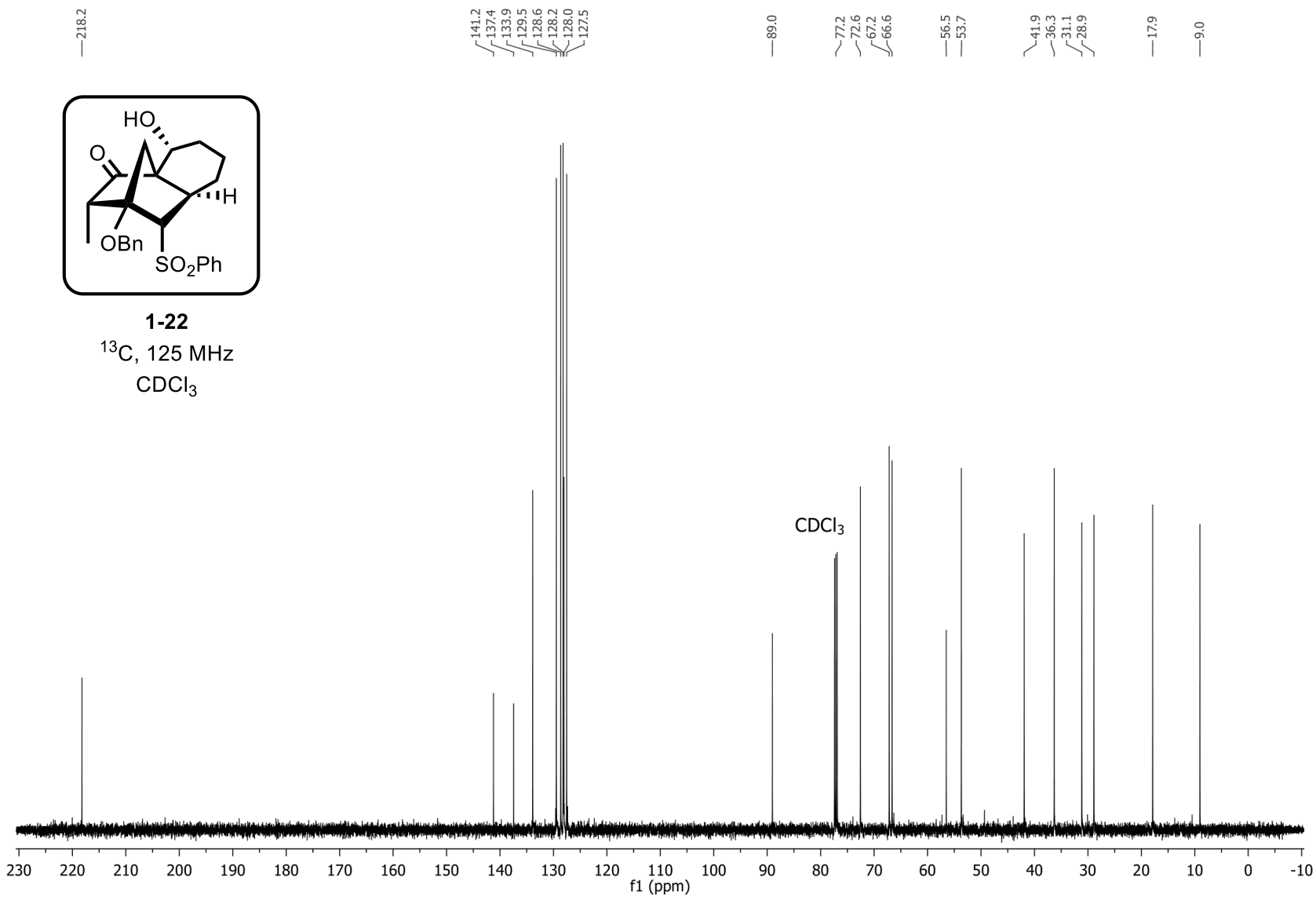

206.5
184.7
146.7
140.7
135.8
133.4
130.8
129.4
129.0
128.7
127.7
127.2
117.2
77.2
71.3
69.7
50.5
33.7
31.3
26.7
24.3
6.2
0.1
O
OH
BnO
SO2Ph
CDCl3
TMS
1-21 Minor
13H, 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



1-22

^{1}H, 500 MHz

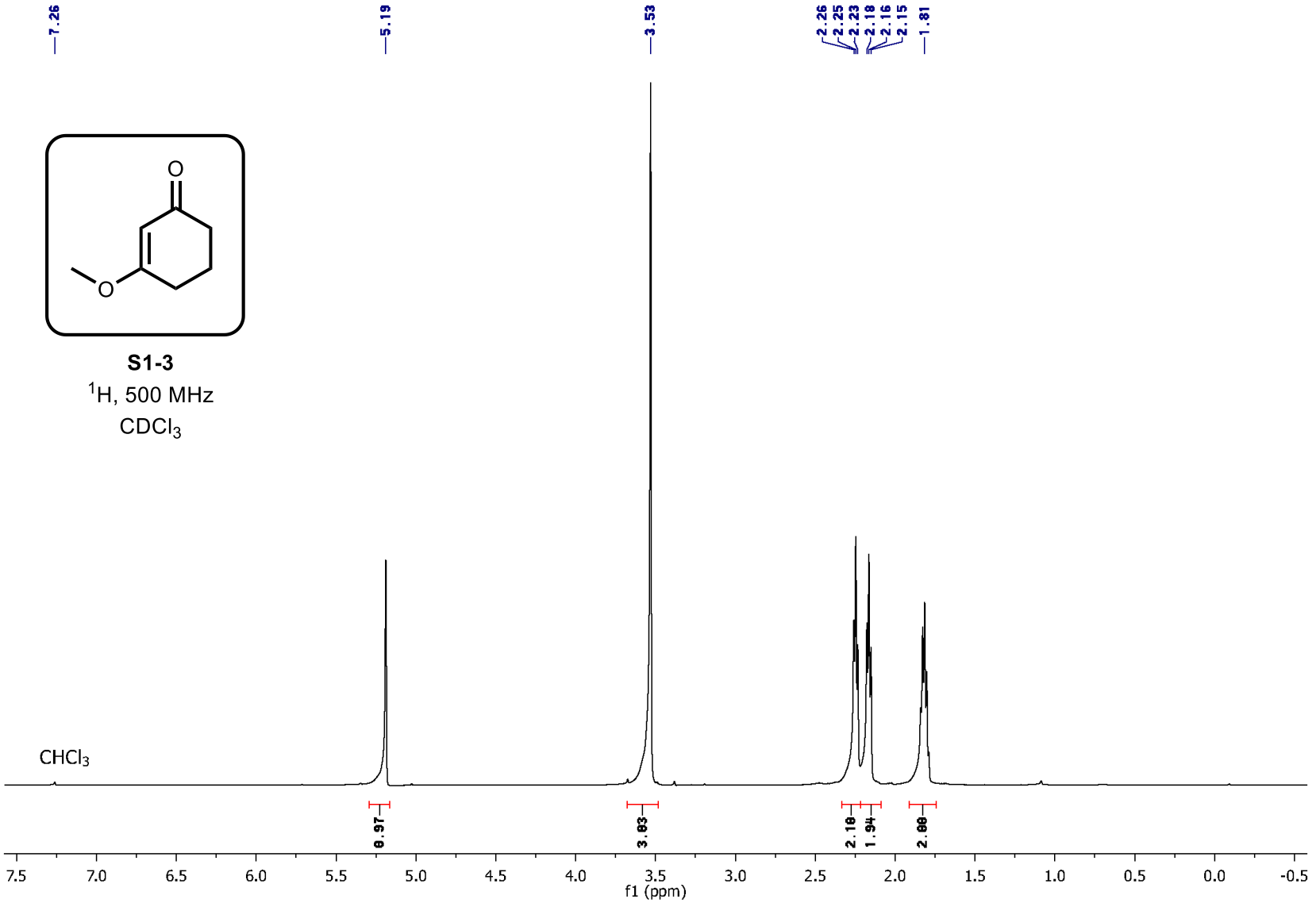
$CDCl_3$

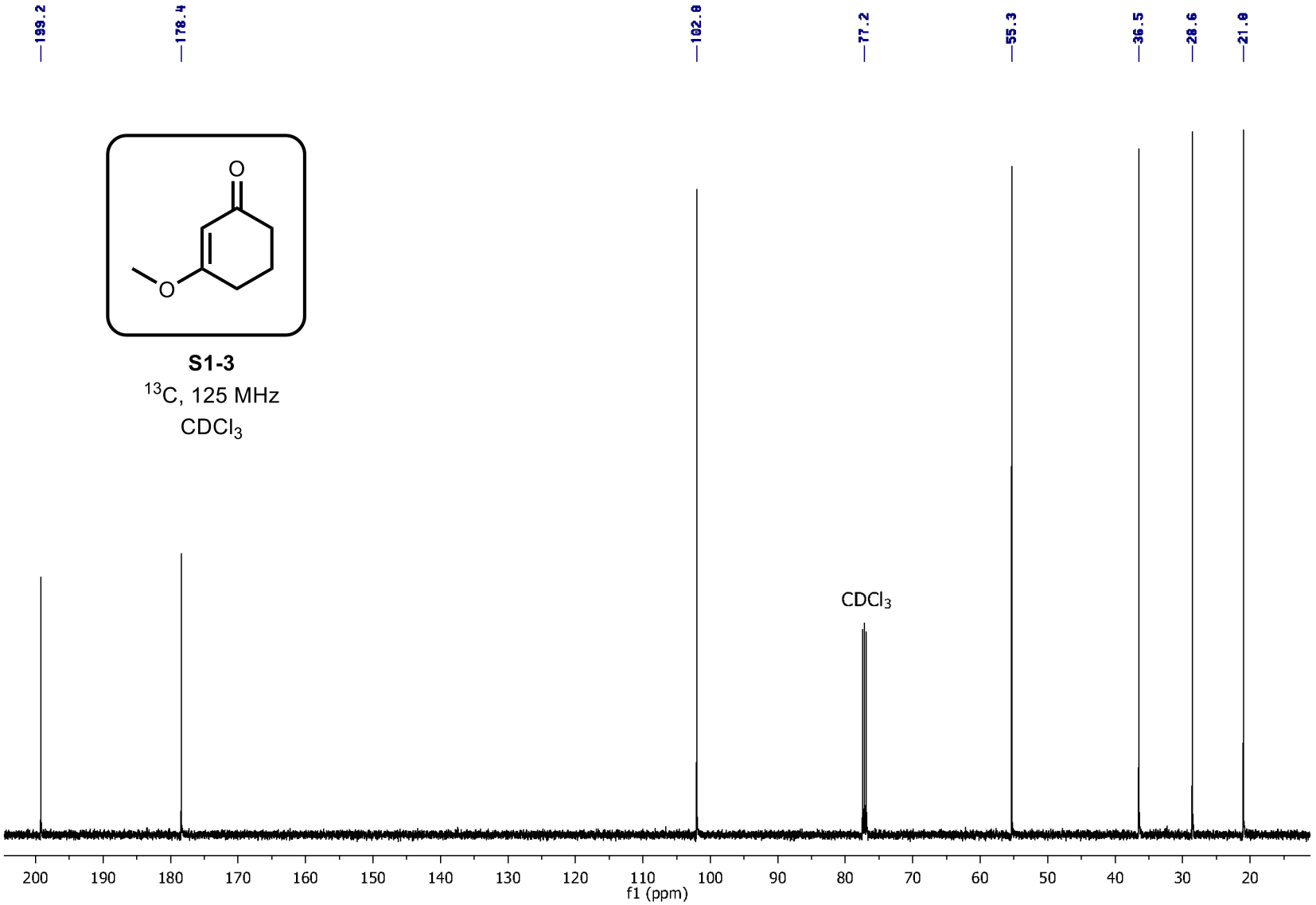


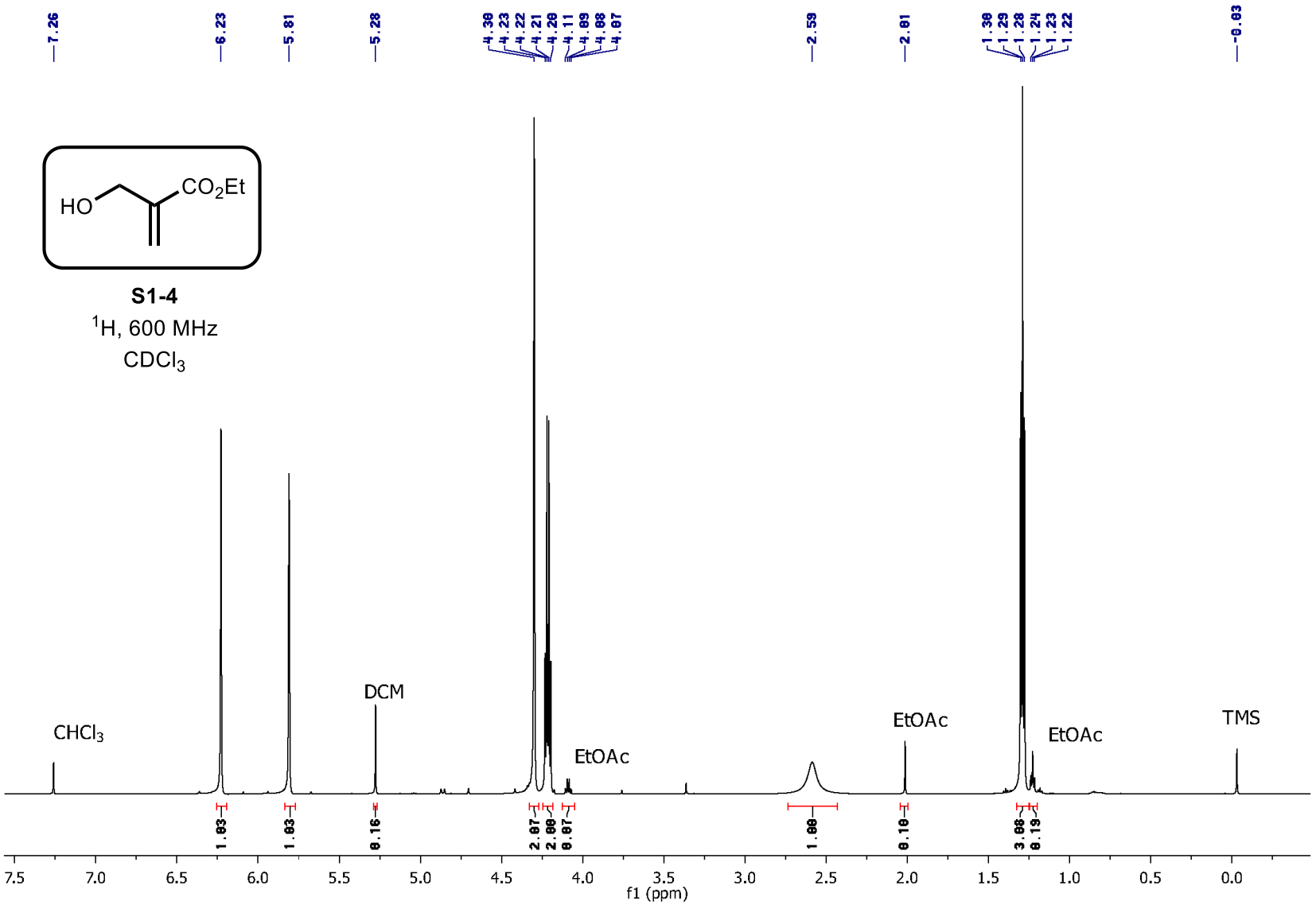
1-22

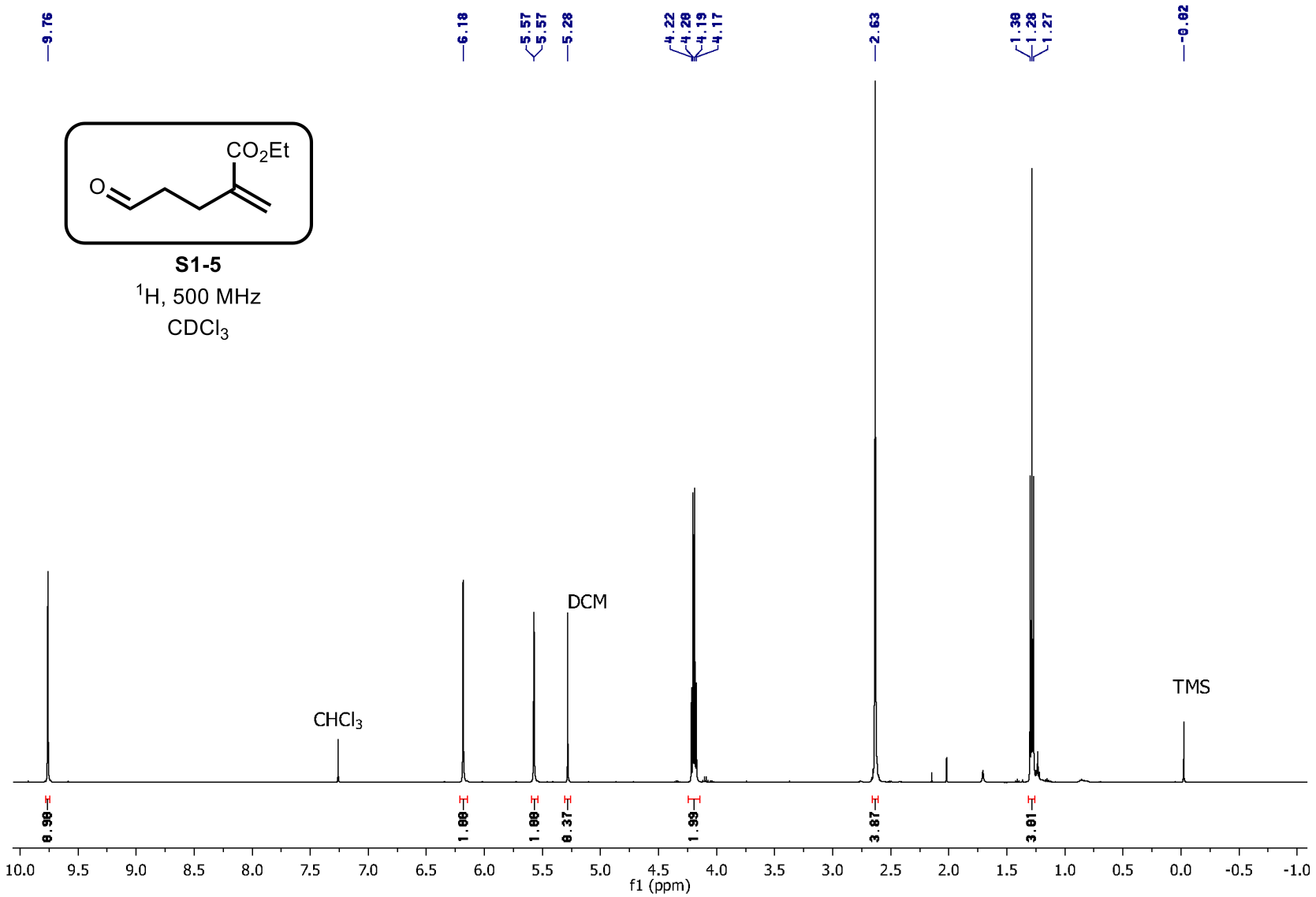
^{13}C, 125 MHz

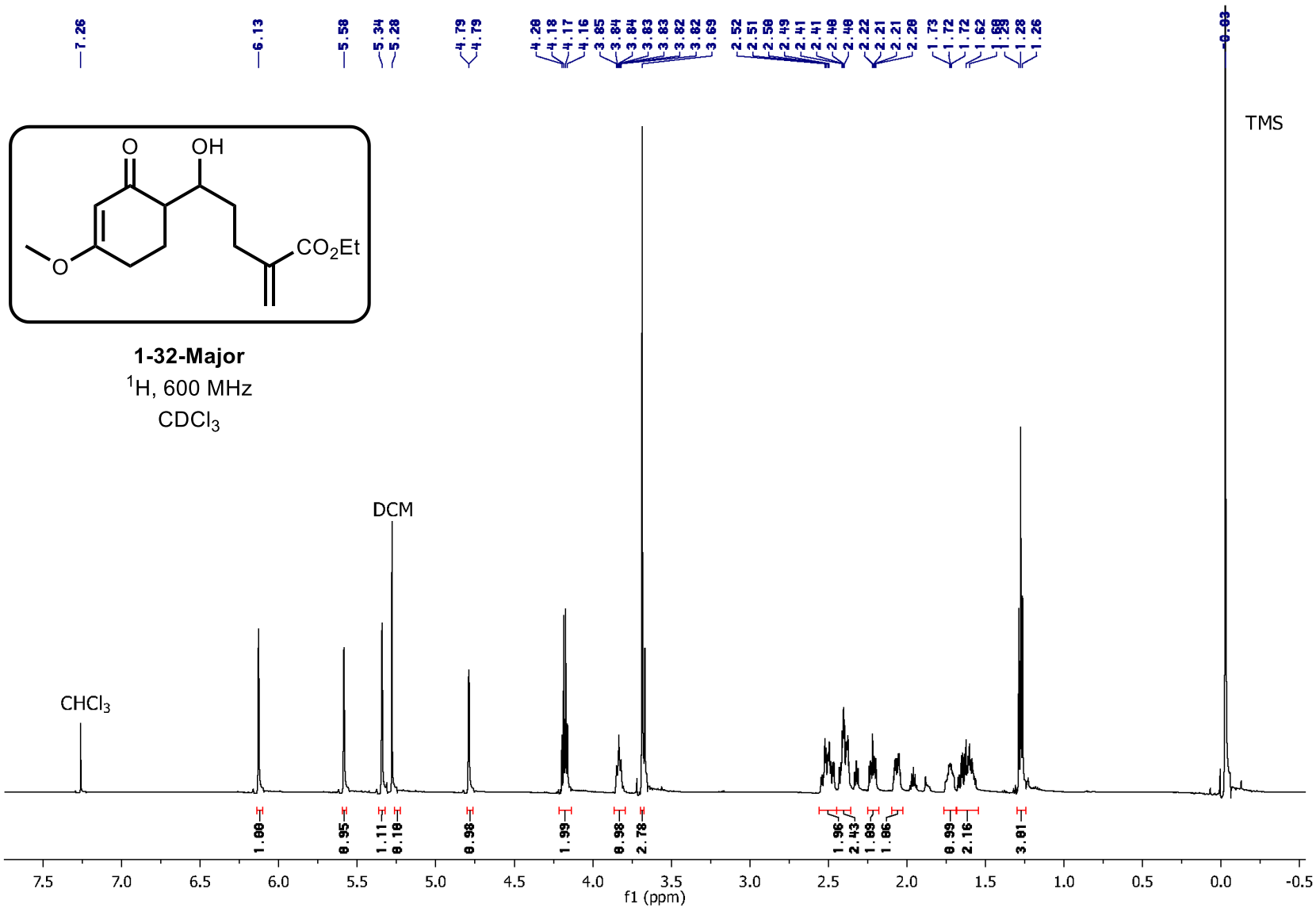
$CDCl_3$

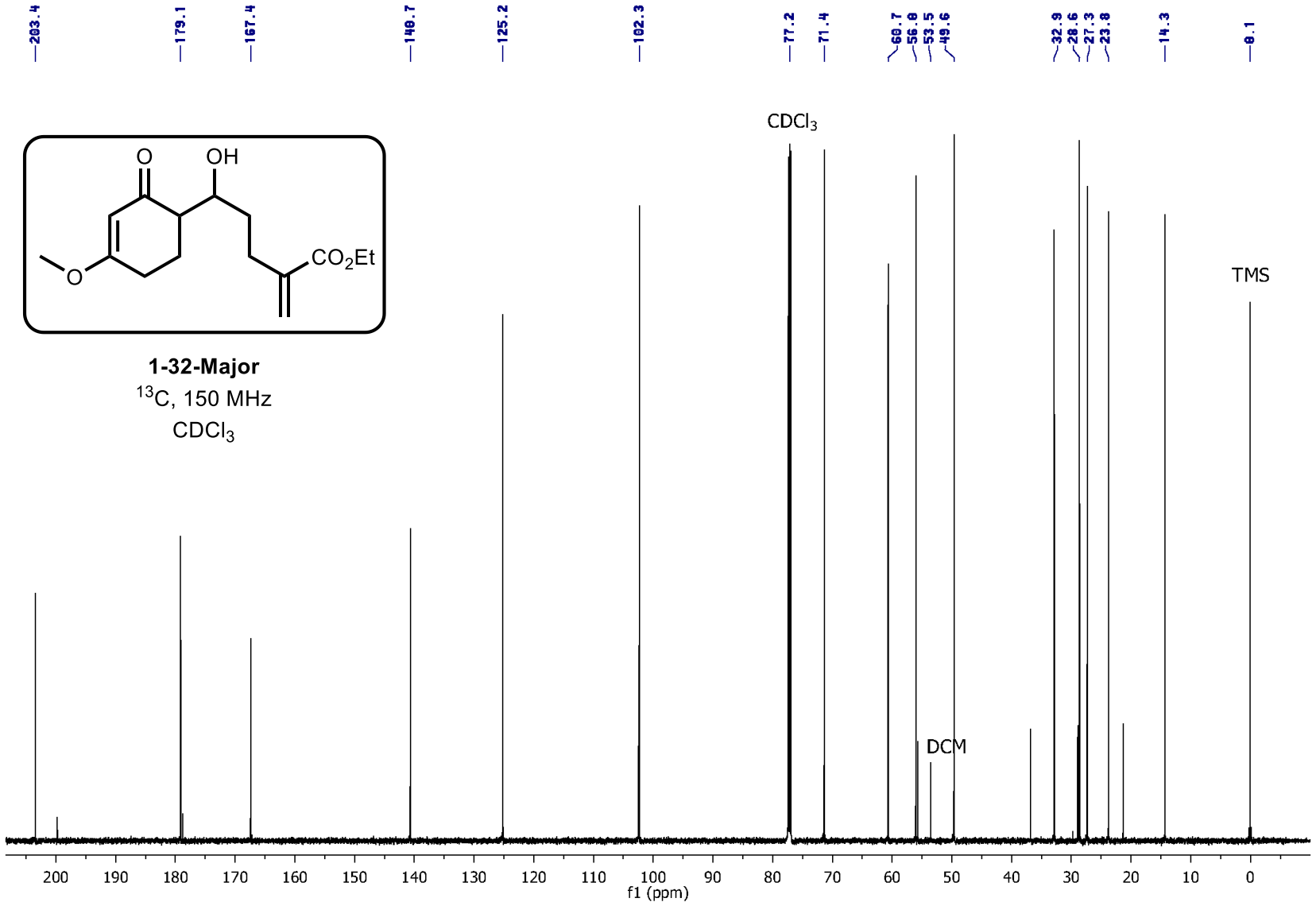

7.26
5.19
3.53
2.26
2.25
2.23
2.18
2.16
2.15
1.81
O
O
S1-3
1H, 500 MHz
CDCl3
CHCl3
0.97
3.03
2.10
1.94
2.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

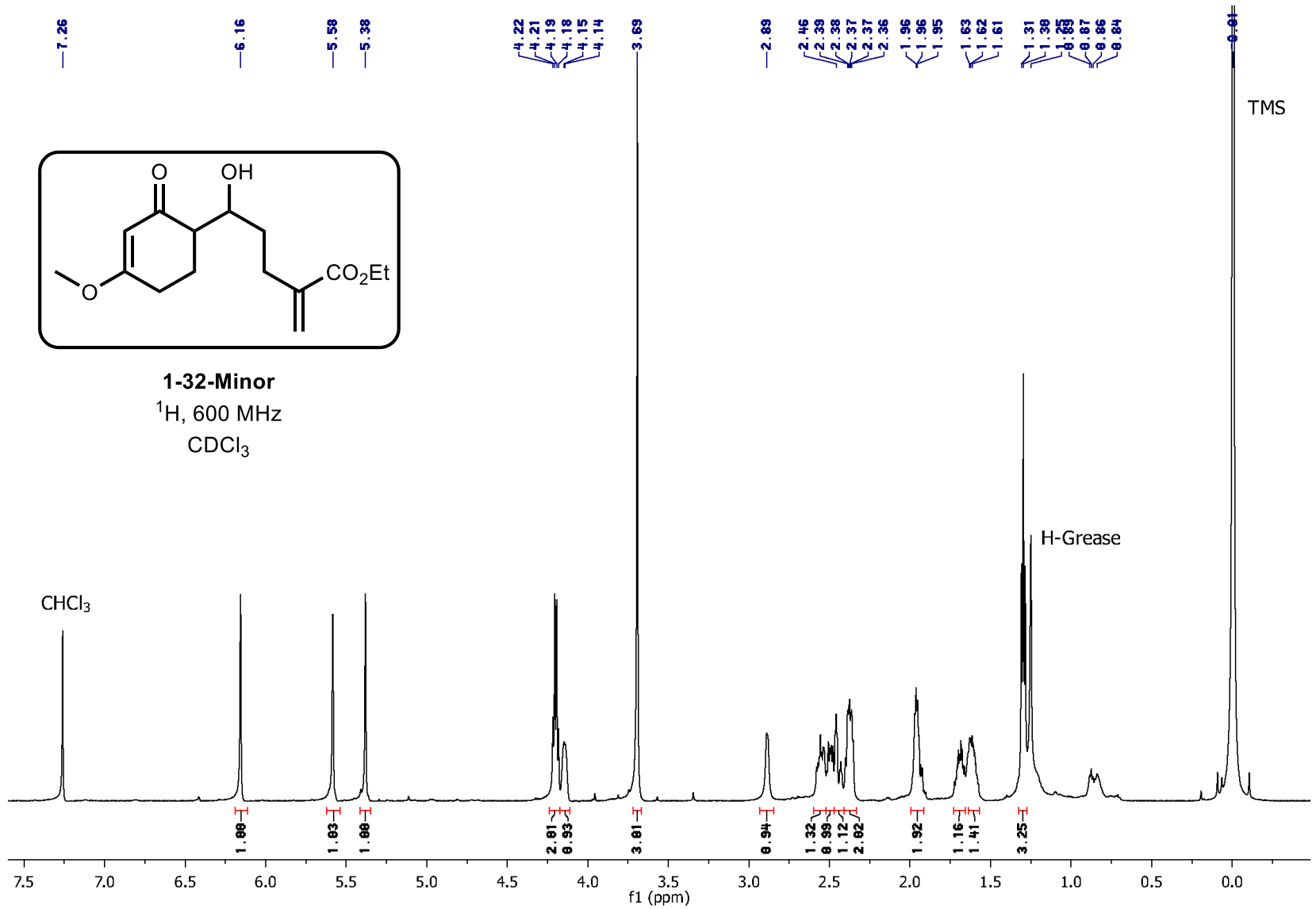

199.2
178.4
102.8
77.2
55.3
36.5
28.6
21.0
O
O
S1-3
13C, 125 MHz
CDCl3
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

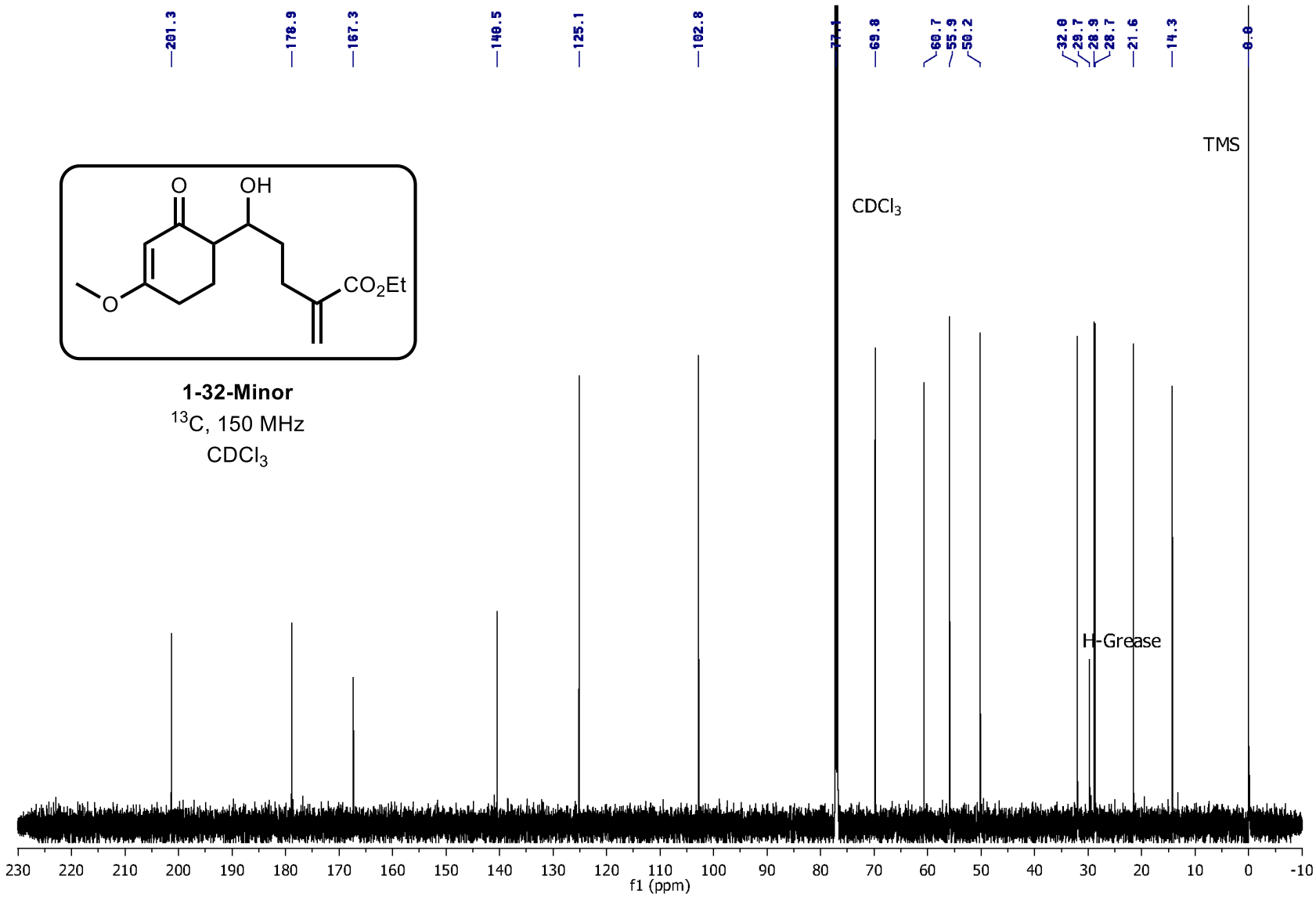

7.26
6.23
5.81
5.28
4.30
4.23
4.22
4.21
4.20
4.11
4.09
4.08
4.07
2.59
2.01
1.30
1.29
1.28
1.24
1.23
1.22
0.03
HO
CO2Et
S1-4
1H, 600 MHz
CDCl3
CHCl3
DCM
EtOAc
EtOAc
EtOAc
TMS
1.03
1.03
0.16
2.07
2.00
0.07
1.00
0.10
3.00
0.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

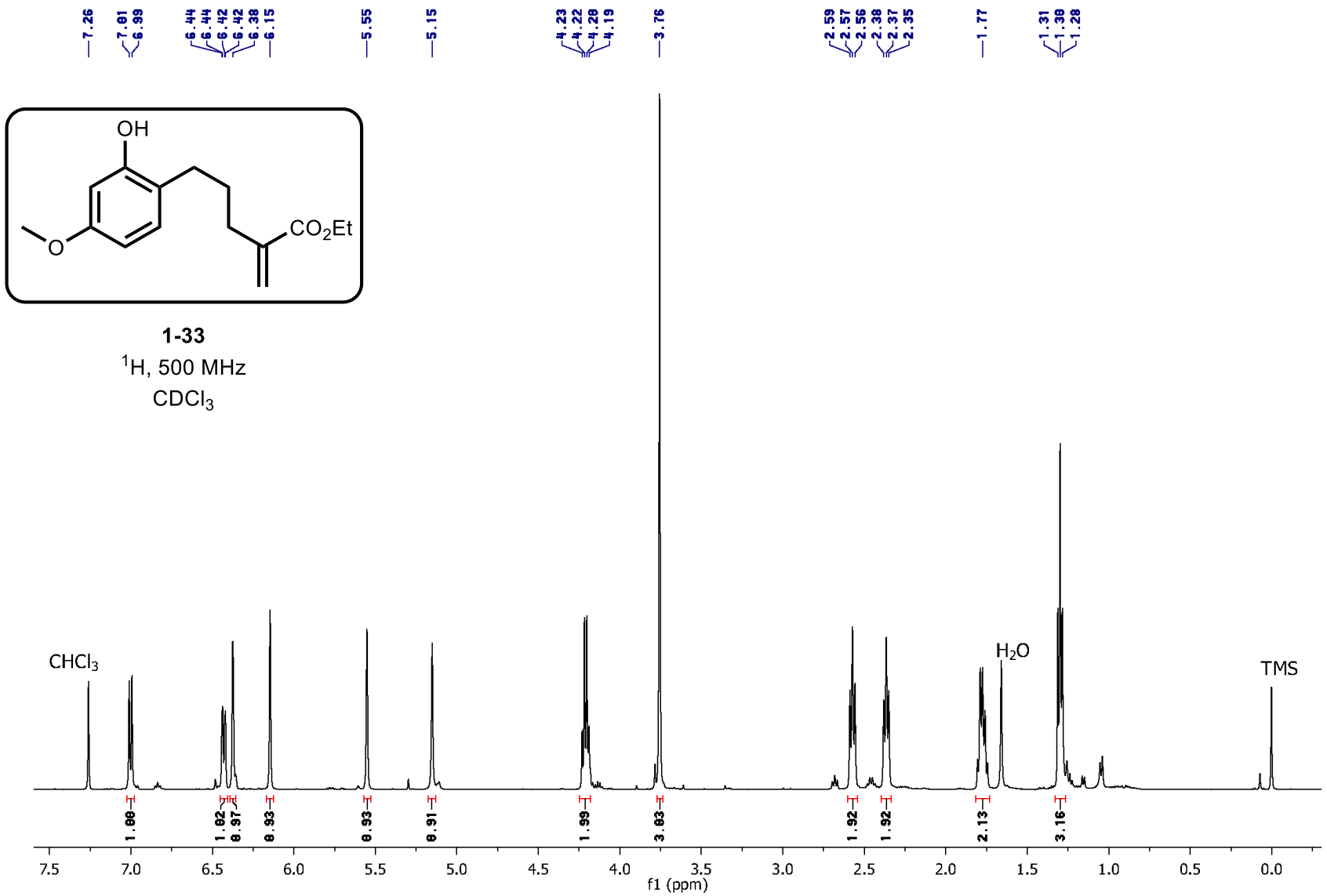

9.76
6.18
5.57
5.57
5.28
4.22
4.20
4.19
4.17
2.63
1.30
1.28
1.27
-0.02
CO2Et
O
S1-5
1H, 500 MHz
CDCl3
CHCl3
DCM
TMS
0.90
1.00
1.00
0.37
1.99
3.87
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

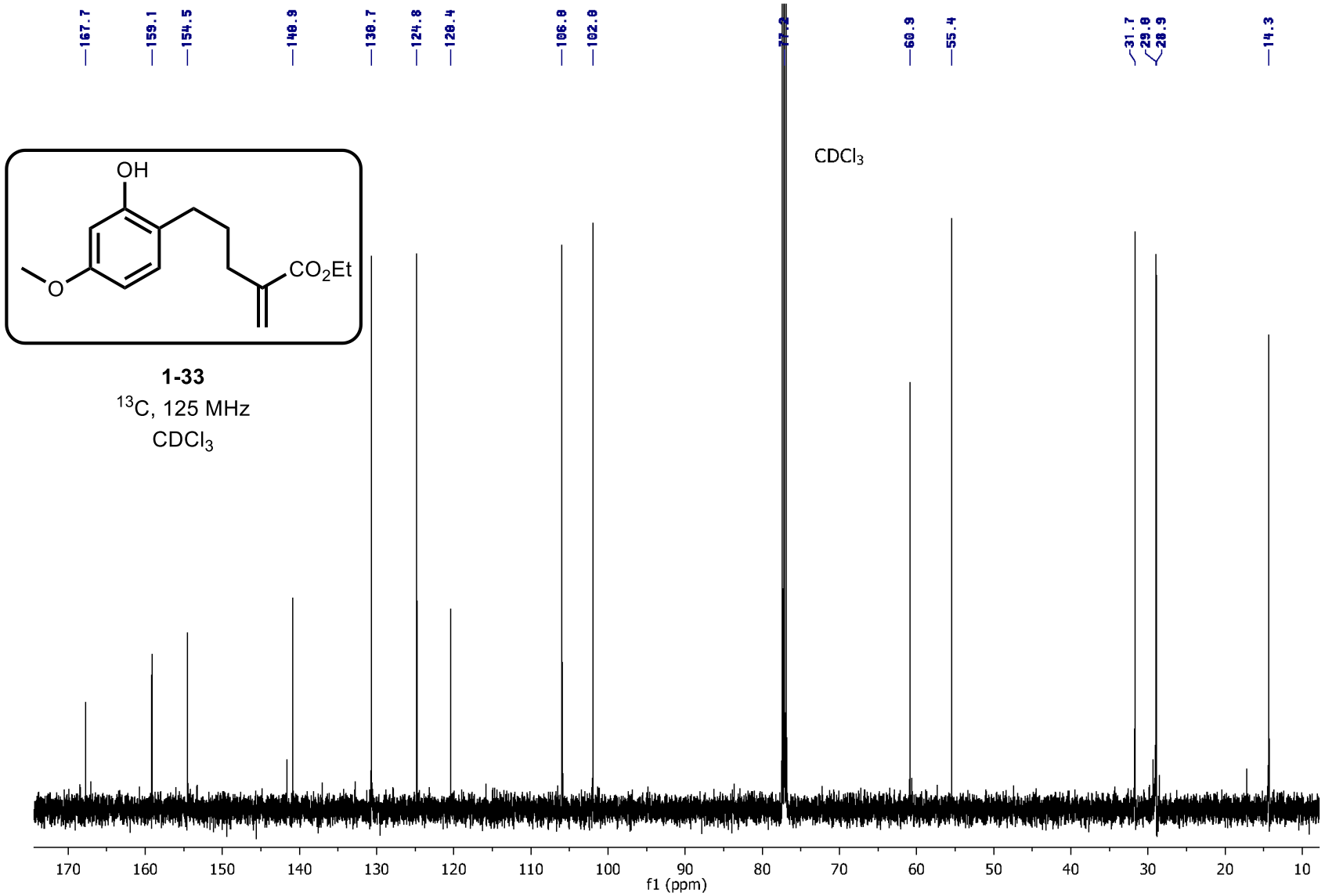

7.26
6.13
5.58
5.34
5.28
4.79
4.79
4.20
4.18
4.17
4.16
3.85
3.84
3.84
3.83
3.83
3.82
3.82
3.69
2.52
2.51
2.50
2.49
2.41
2.41
2.40
2.40
2.22
2.21
2.21
2.20
1.73
1.72
1.72
1.62
1.28
1.26
0.03
TMS
O
OH
O
CO2Et
1-32-Major
1H, 600 MHz
CDCl3
DCM
CHCl3
1.00
0.95
1.11
0.10
0.98
1.99
0.98
2.78
1.96
2.43
1.89
1.86
0.99
2.16
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

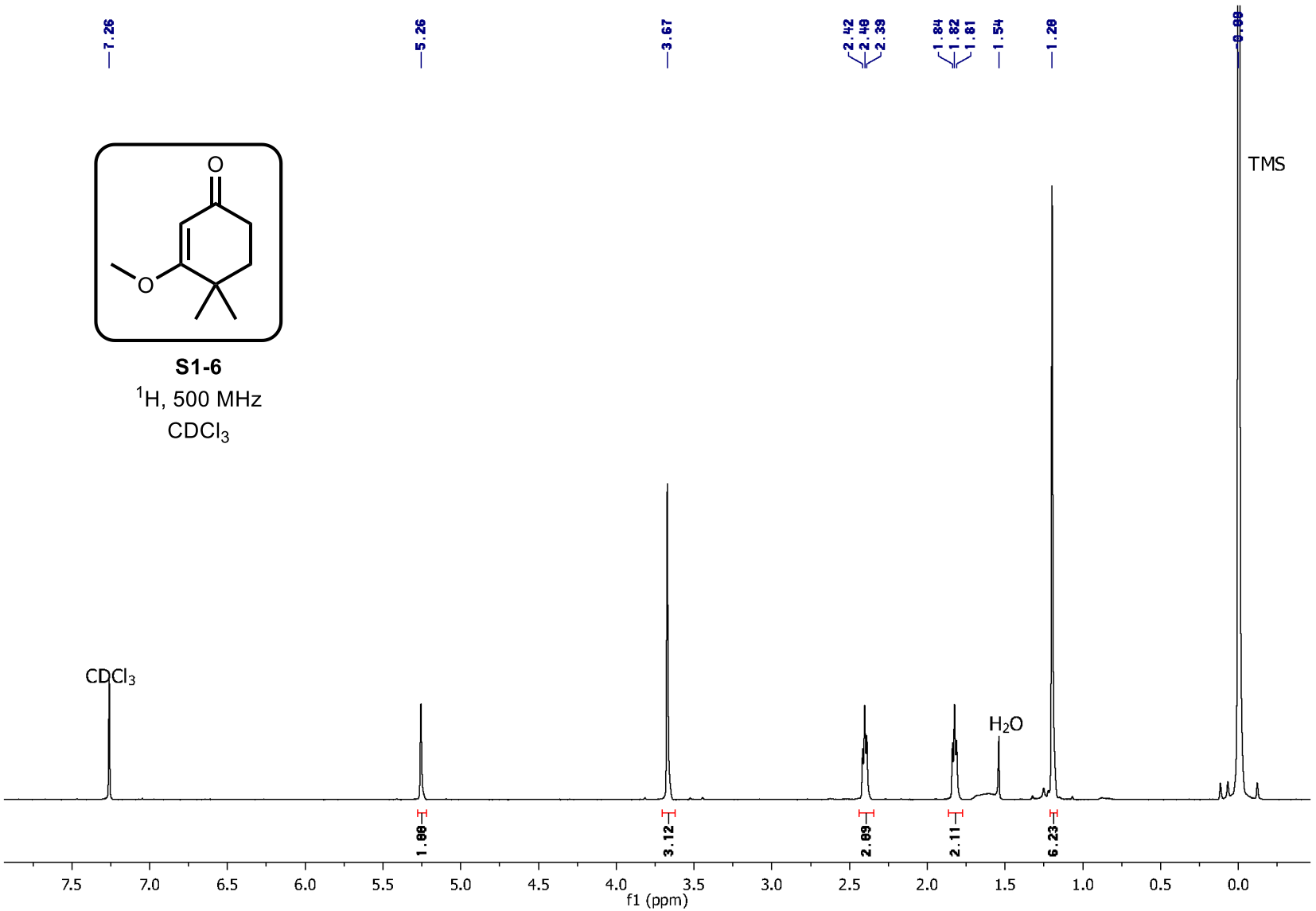

203.4
179.1
167.4
140.7
125.2
102.3
77.2
71.4
60.7
56.0
53.5
49.6
32.9
28.6
27.3
23.8
14.3
0.1
O
OH
O
CO2Et
1-32-Major
13C, 150 MHz
CDCl3
CDCl3
TMS
DCM
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

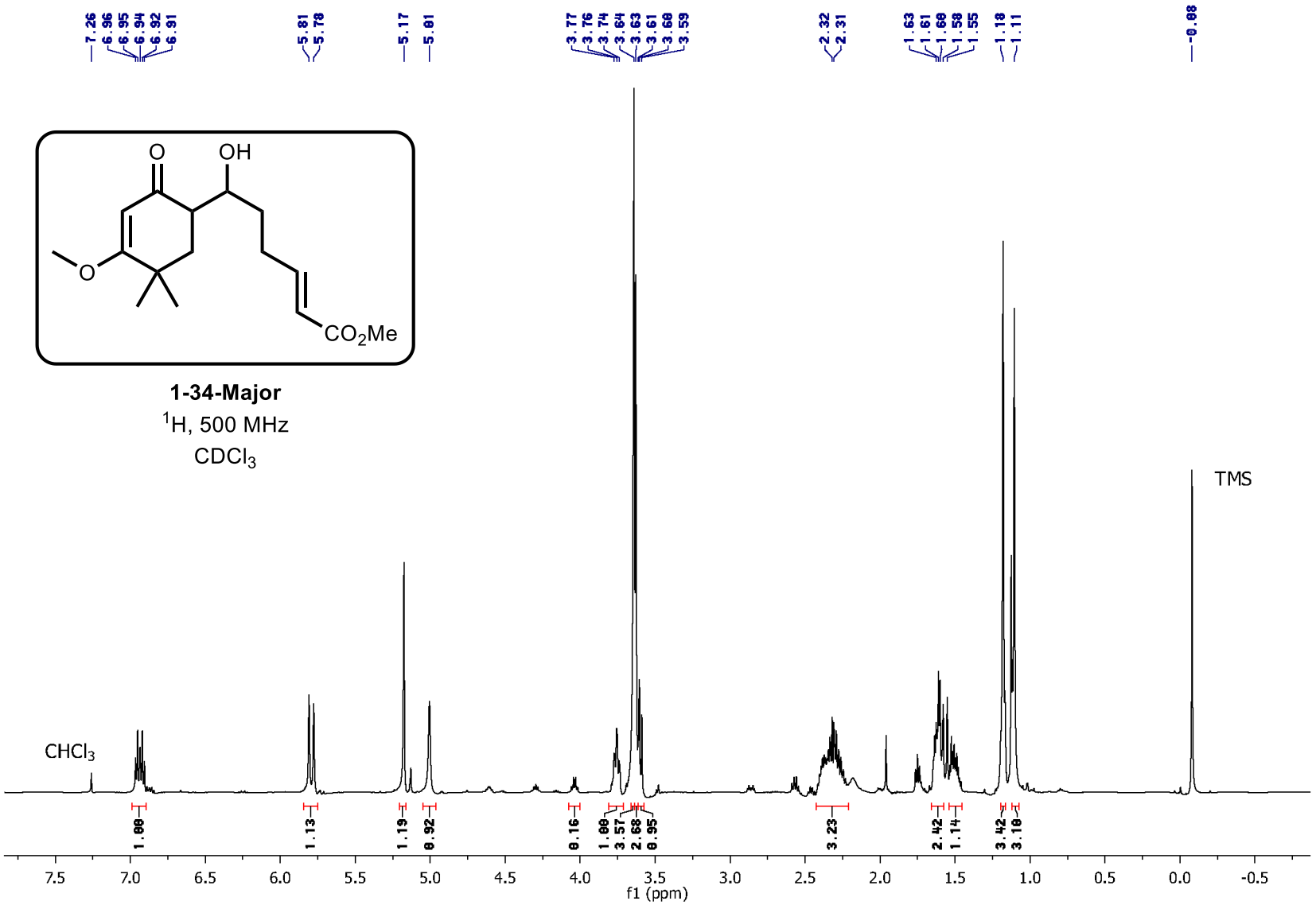

7.26
6.16
5.58
5.38
4.22
4.21
4.19
4.18
4.15
4.14
3.69
2.89
2.46
2.39
2.38
2.37
2.37
2.36
1.96
1.96
1.95
1.63
1.62
1.61
1.31
1.30
0.87
0.86
0.84
0.01
TMS
O
OH
O
CO2Et
1-32-Minor
1H, 600 MHz
CDCl3
H-Grease
CHCl3
1.00
1.03
1.00
2.01
0.93
3.01
0.94
1.32
0.99
1.12
2.02
1.92
1.16
1.41
3.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

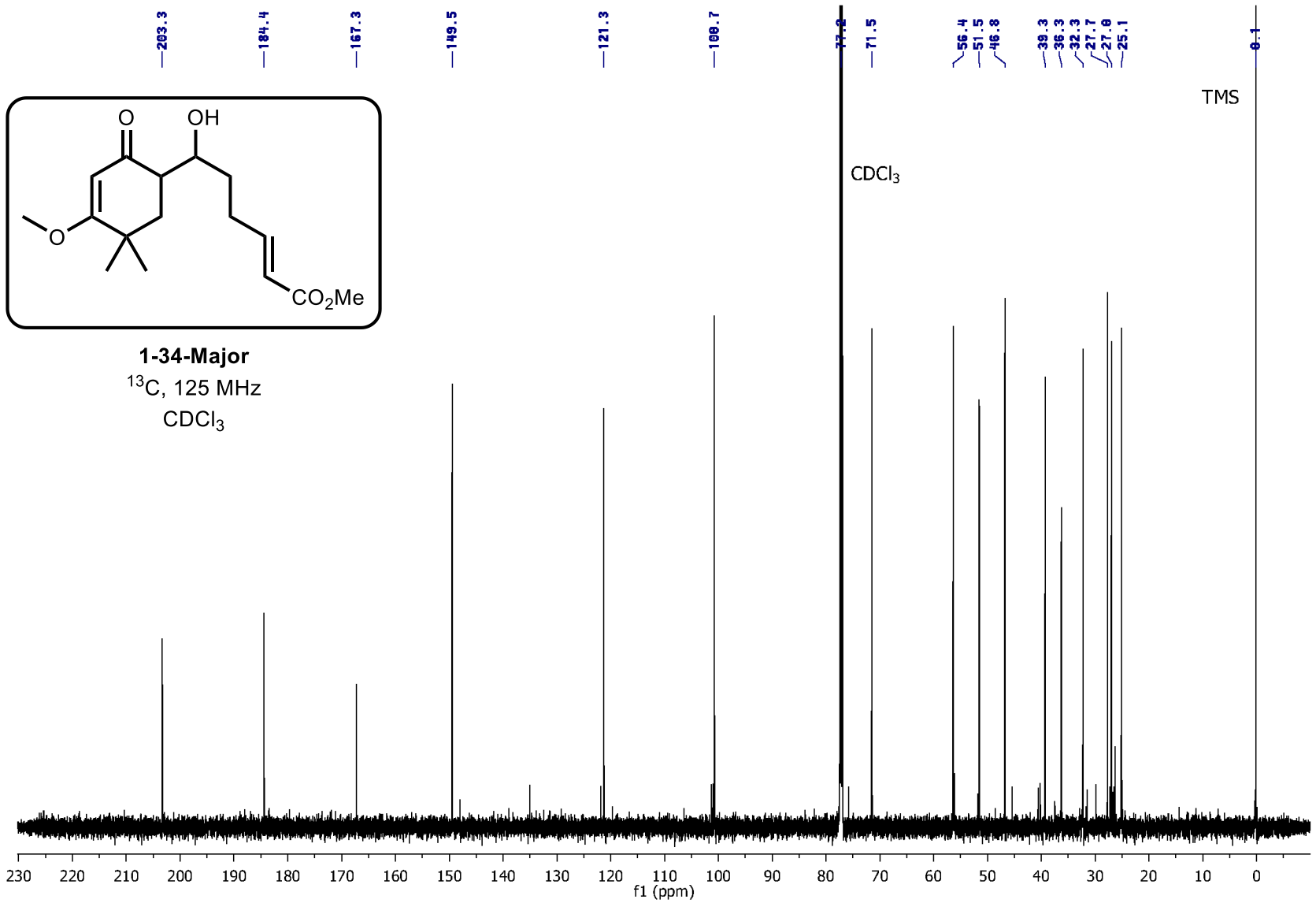

201.3
178.9
167.3
148.5
125.1
102.8
77.1
69.8
60.7
55.9
50.2
32.0
29.7
28.9
28.7
21.6
14.3
0.0
TMS
CDCl3
H-Grease
O
OH
O
CO2Et
1-32-Minor
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

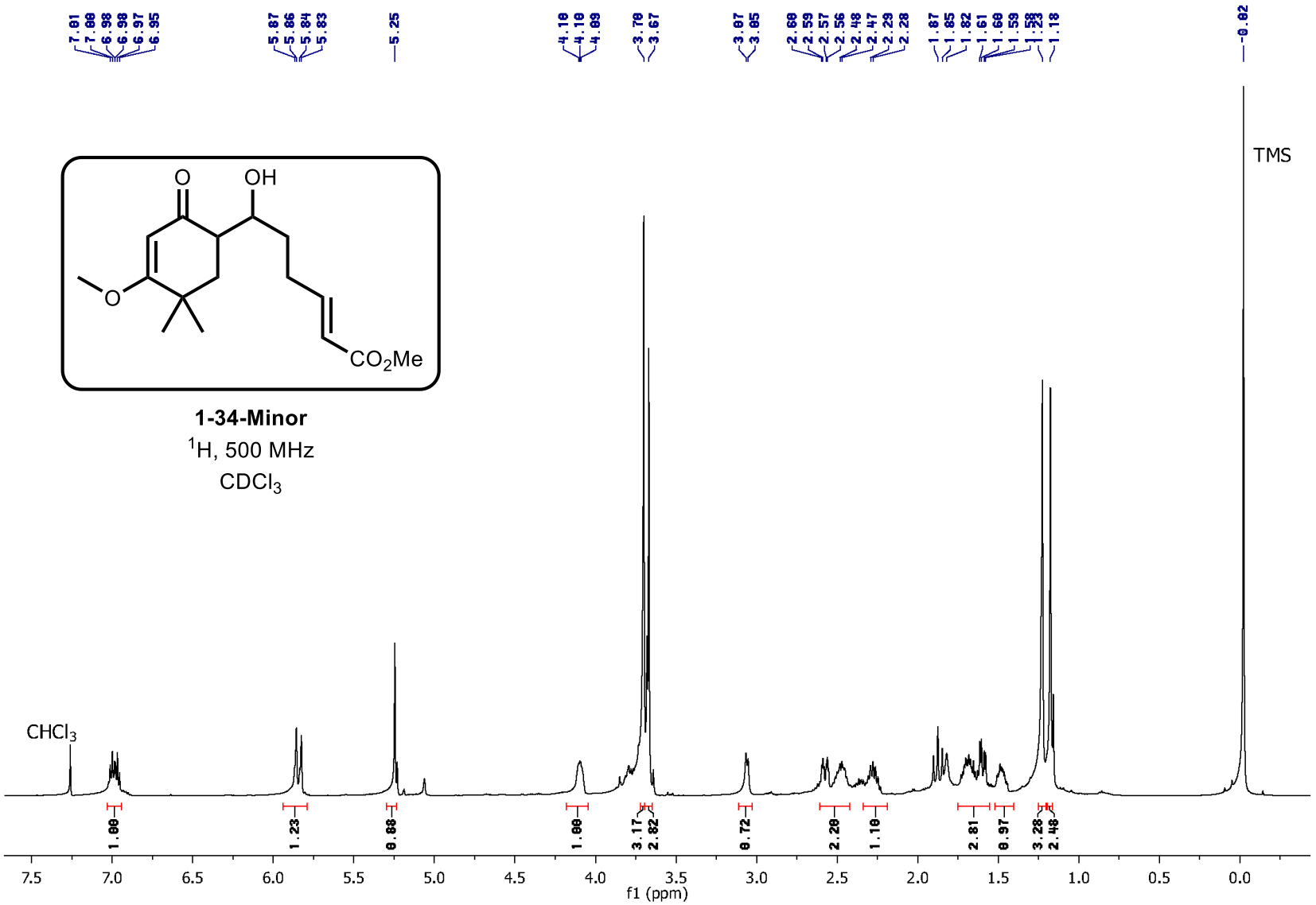

7.26
7.01
6.99
6.44
6.44
6.42
6.42
6.38
6.15
5.55
5.15
4.23
4.22
4.20
4.19
3.76
2.59
2.57
2.56
2.38
2.37
2.35
1.77
1.31
1.30
1.28
OH
O
CO2Et
1-33
1H, 500 MHz
CDCl3
CHCl3
H2O
TMS
1.00
1.02
0.97
0.93
0.93
0.91
1.99
3.03
1.92
1.92
2.13
3.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

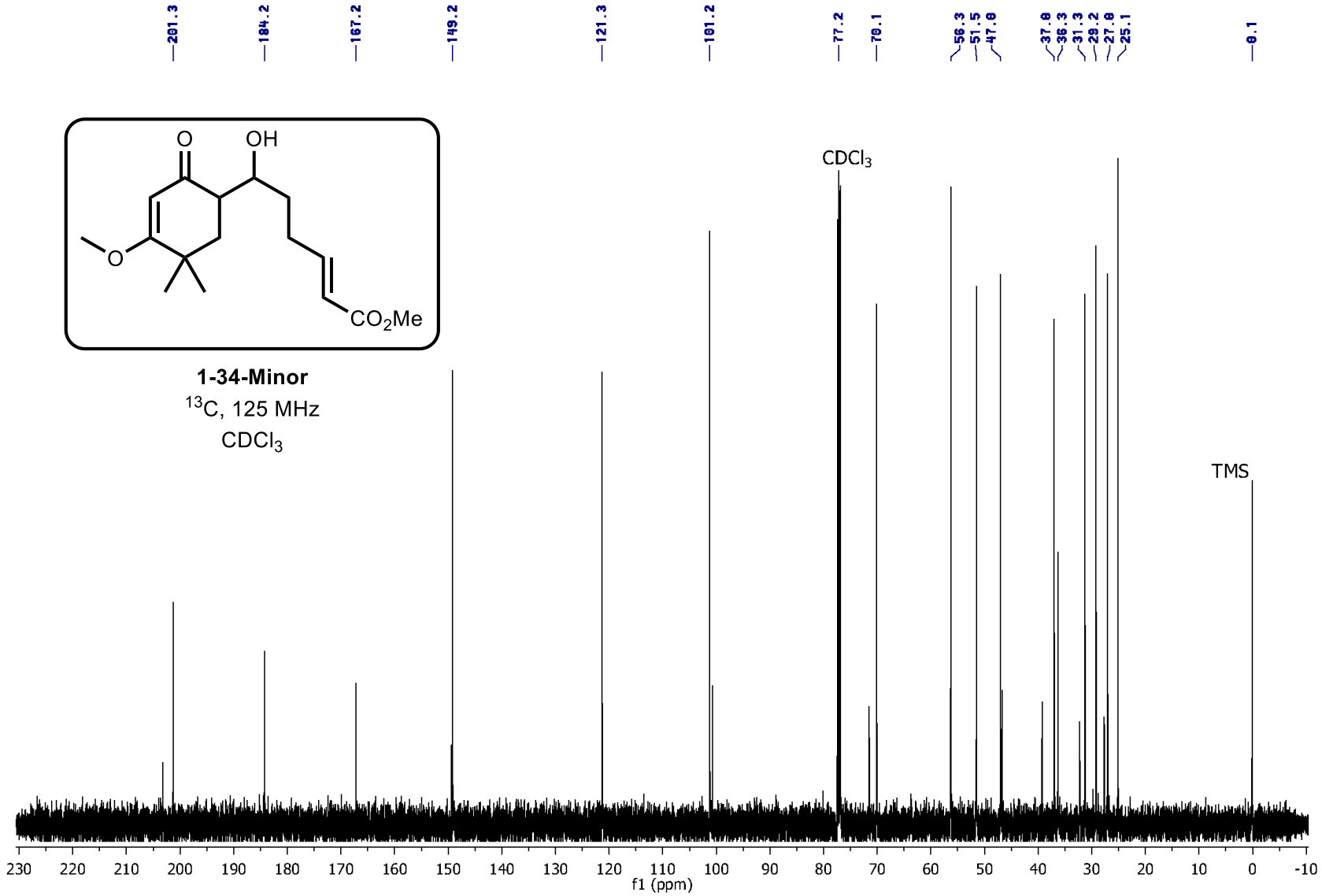

167.7
159.1
154.5
140.9
130.7
124.8
120.4
106.0
102.0
77.2
60.9
55.4
31.7
29.0
28.9
14.3
CDCl3
OH
O
CO2Et
1-33
13C, 125 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

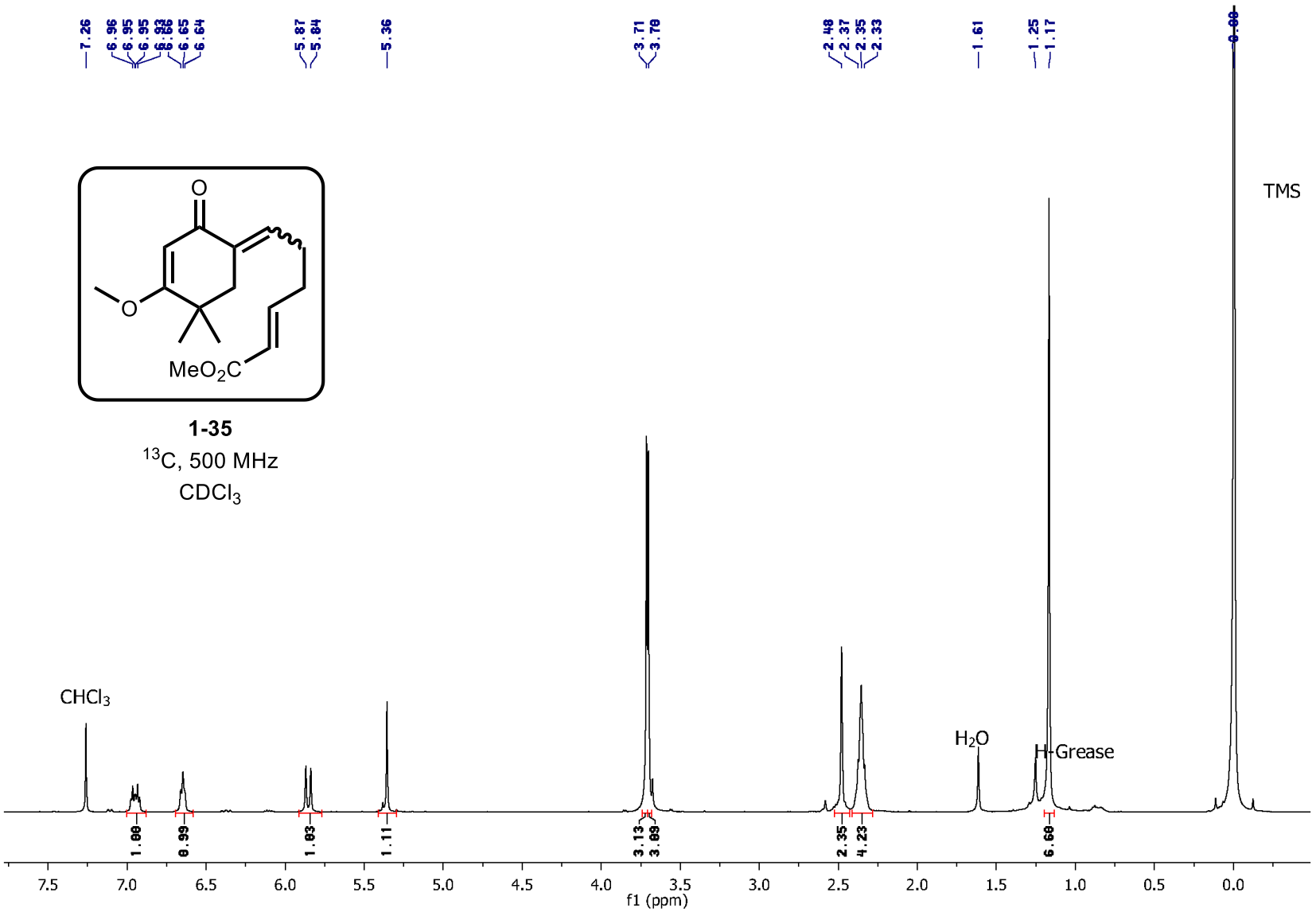

7.26
5.26
3.67
2.42
2.40
2.39
1.84
1.82
1.81
1.54
1.20
0.00
O
O
S1-6
1H, 500 MHz
CDCl3
TMS
CDCl3
H2O
1.00
3.12
2.09
2.11
6.23
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

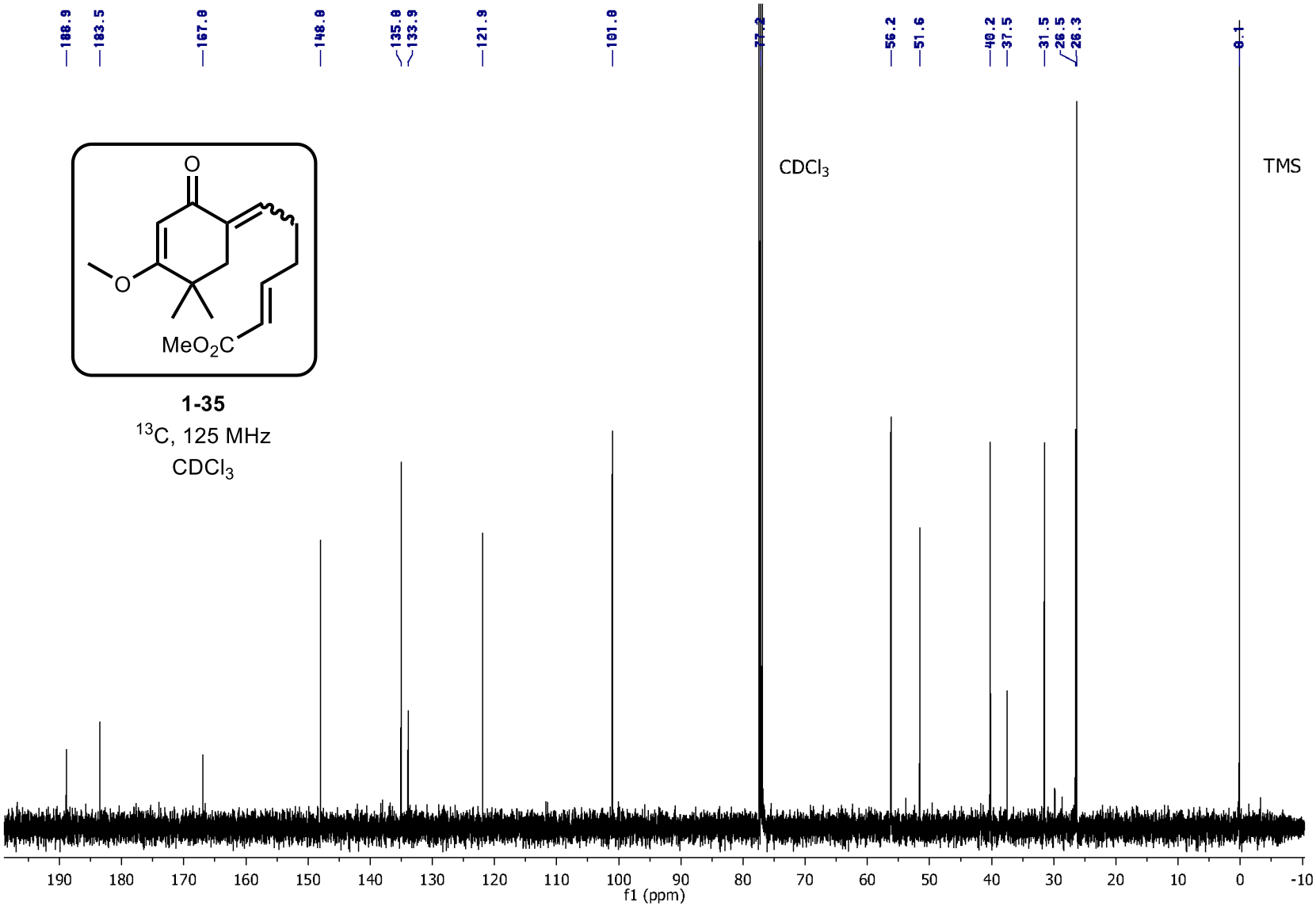

7.26
6.96
6.95
6.94
6.92
6.91
5.81
5.78
5.17
5.01
3.77
3.76
3.74
3.64
3.63
3.61
3.60
3.59
2.32
2.31
1.63
1.61
1.60
1.58
1.55
1.18
1.11
0.00
O
OH
O
CO2Me
1-34-Major
1H, 500 MHz
CDCl3
CHCl3
TMS
1.00
1.13
1.19
0.92
0.16
1.00
3.57
2.68
0.95
3.23
2.42
1.14
3.42
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

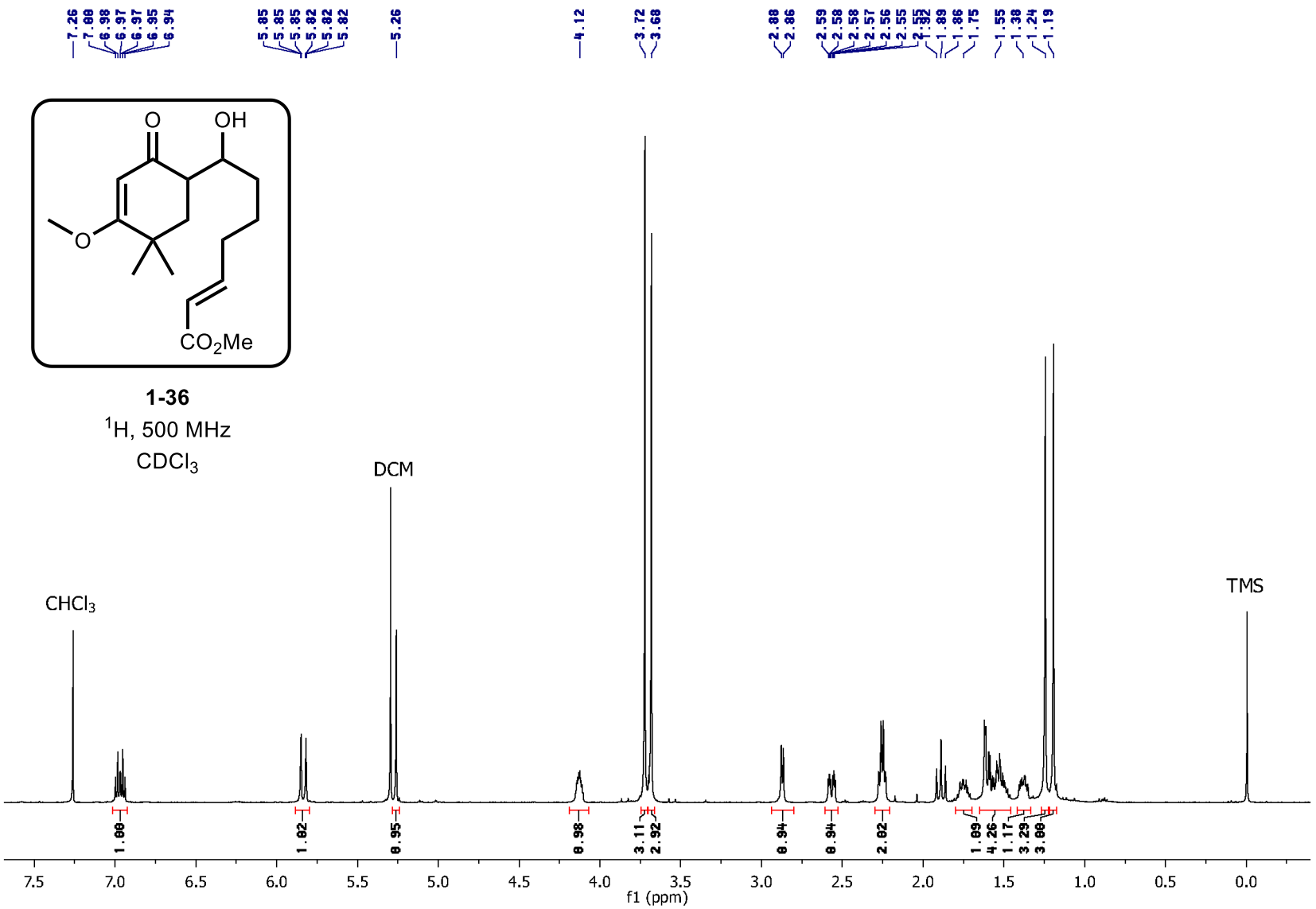

203.3
184.4
167.3
149.5
121.3
100.7
77.2
71.5
56.4
51.5
46.8
39.3
36.3
32.3
27.7
27.0
25.1
0.1
TMS
CDCl3
O
OH
O
CO2Me
1-34-Major
13C, 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

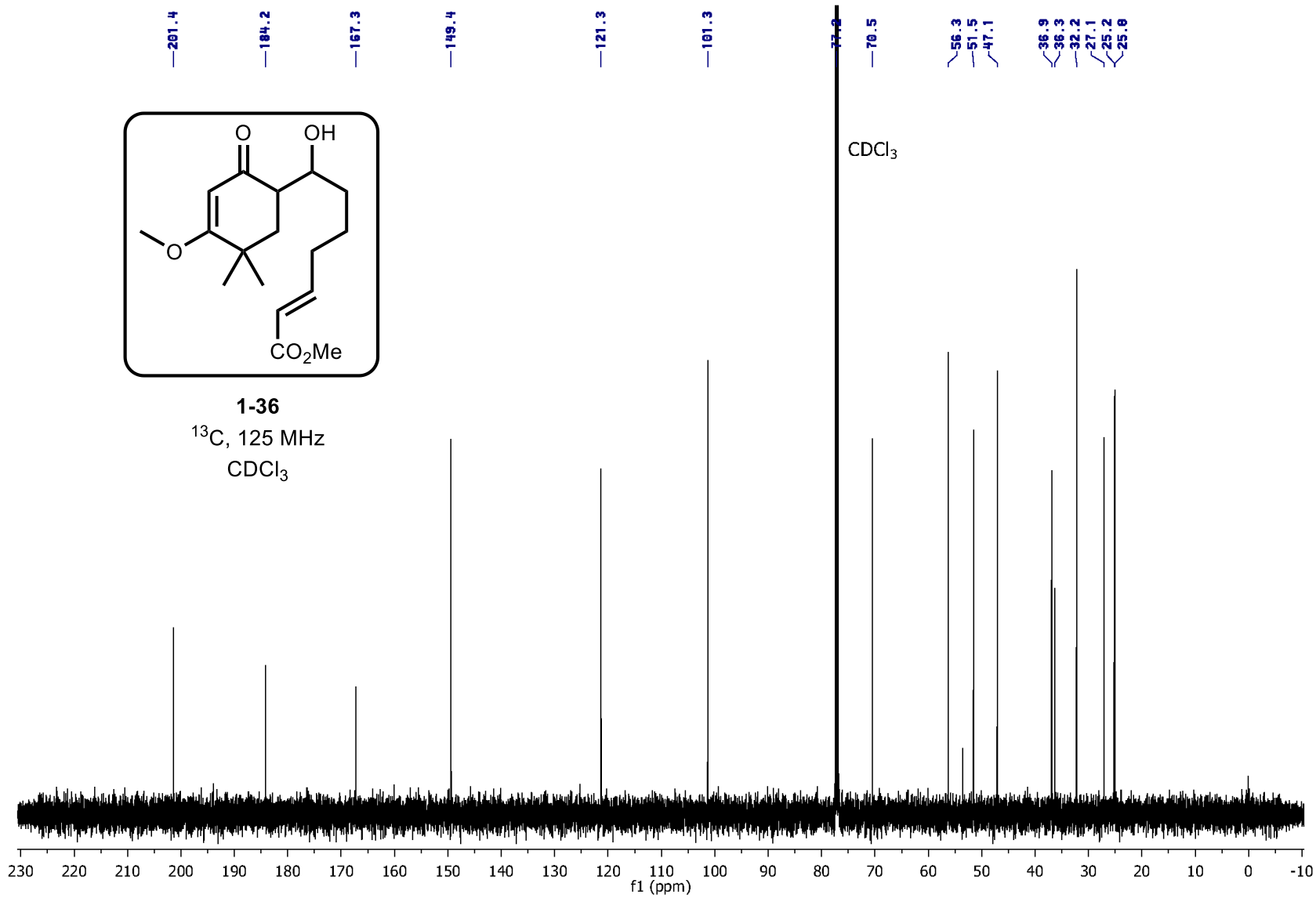

7.01
7.00
6.98
6.98
6.97
6.95
5.87
5.86
5.84
5.83
5.25
4.10
4.10
4.09
3.70
3.67
3.07
3.05
2.60
2.59
2.57
2.56
2.48
2.47
2.29
2.28
1.87
1.85
1.82
1.61
1.60
1.59
1.23
1.18
-0.02
TMS
O
OH
O
CO2Me
1-34-Minor
1H, 500 MHz
CDCl3
CHCl3
1.00
1.23
0.88
1.00
3.17
2.82
0.72
2.20
1.10
2.81
0.97
3.28
2.48
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

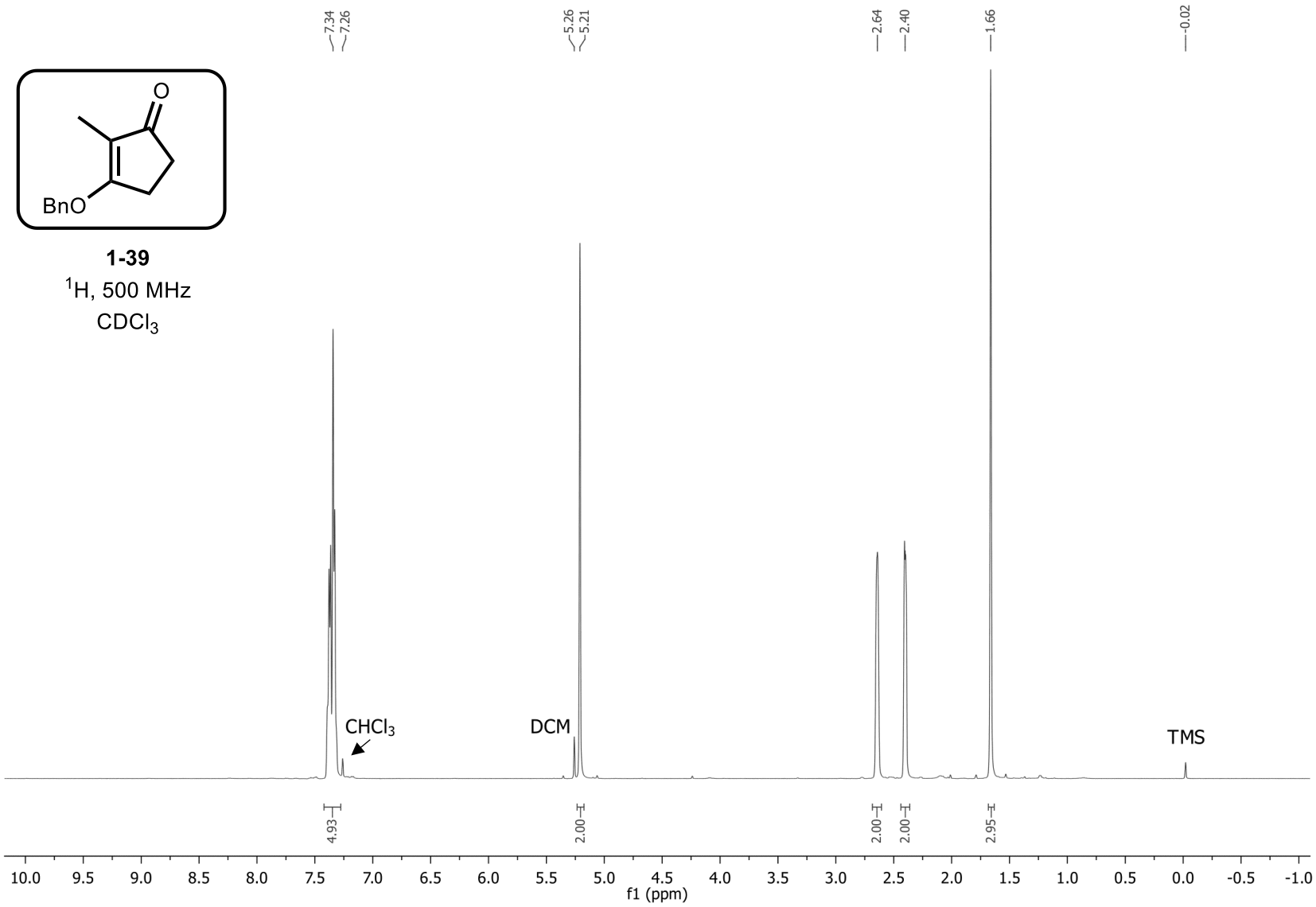

201.3
184.2
167.2
149.2
121.3
101.2
77.2
70.1
56.3
51.5
47.0
37.0
36.3
31.3
29.2
27.0
25.1
0.1
O
OH
O
CO2Me
CDCl3
TMS
1-34-Minor
13C, 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

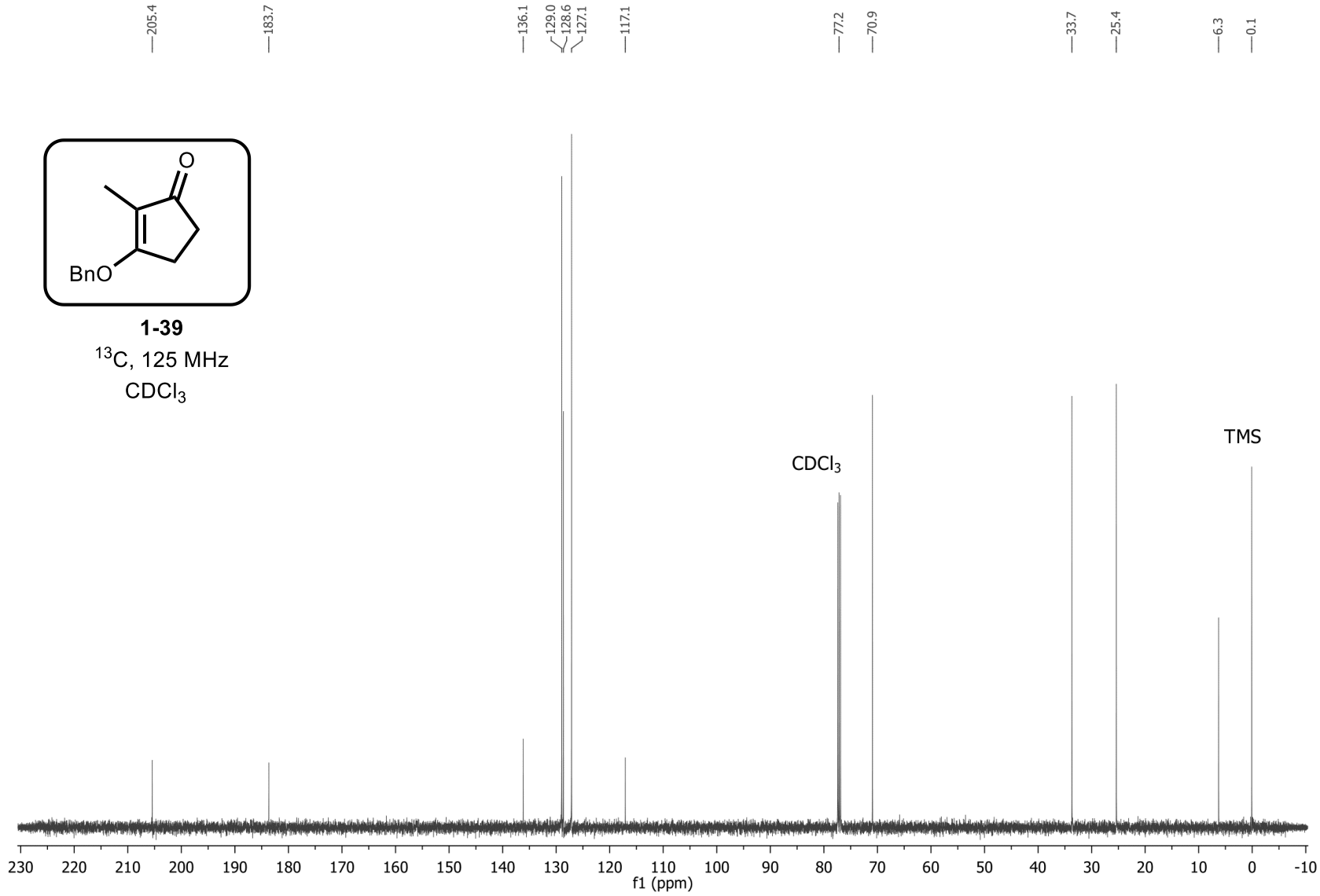

7.26
6.96
6.95
6.95
6.65
6.64
5.87
5.84
5.36
3.71
3.70
2.48
2.37
2.35
2.33
1.61
1.25
1.17
0.00
TMS
O
O
MeO2C
1-35
13C, 500 MHz
CDCl3
CHCl3
H2O
H-Grease
1.00
0.99
1.03
1.11
3.13
3.09
2.35
4.23
6.60
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

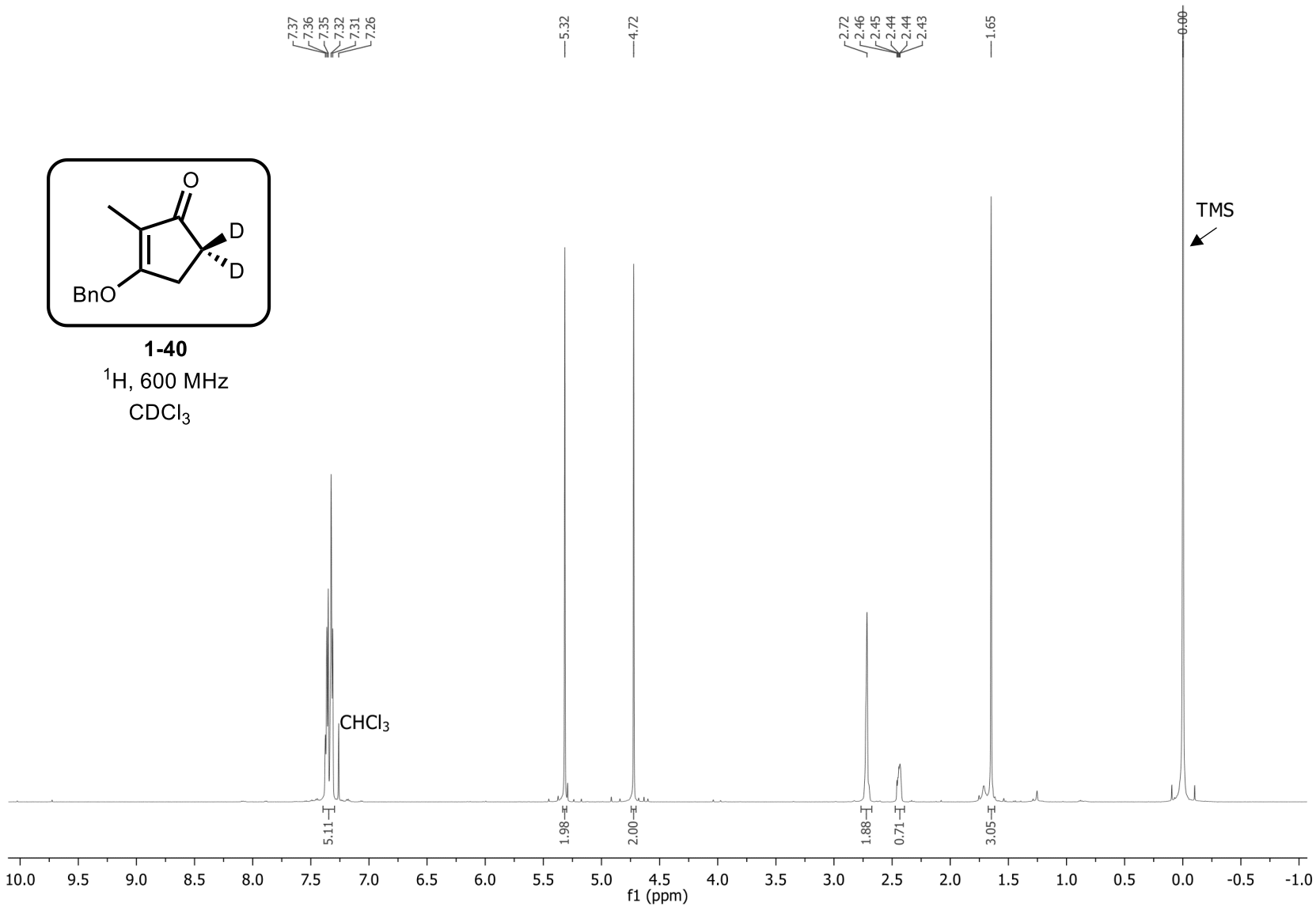

188.9
183.5
167.0
148.0
135.0
133.9
121.9
101.0
77.2
56.2
51.6
40.2
37.5
31.5
26.5
26.3
0.1
CDCl3
TMS
O
O
MeO2C
1-35
13C, 125 MHz
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

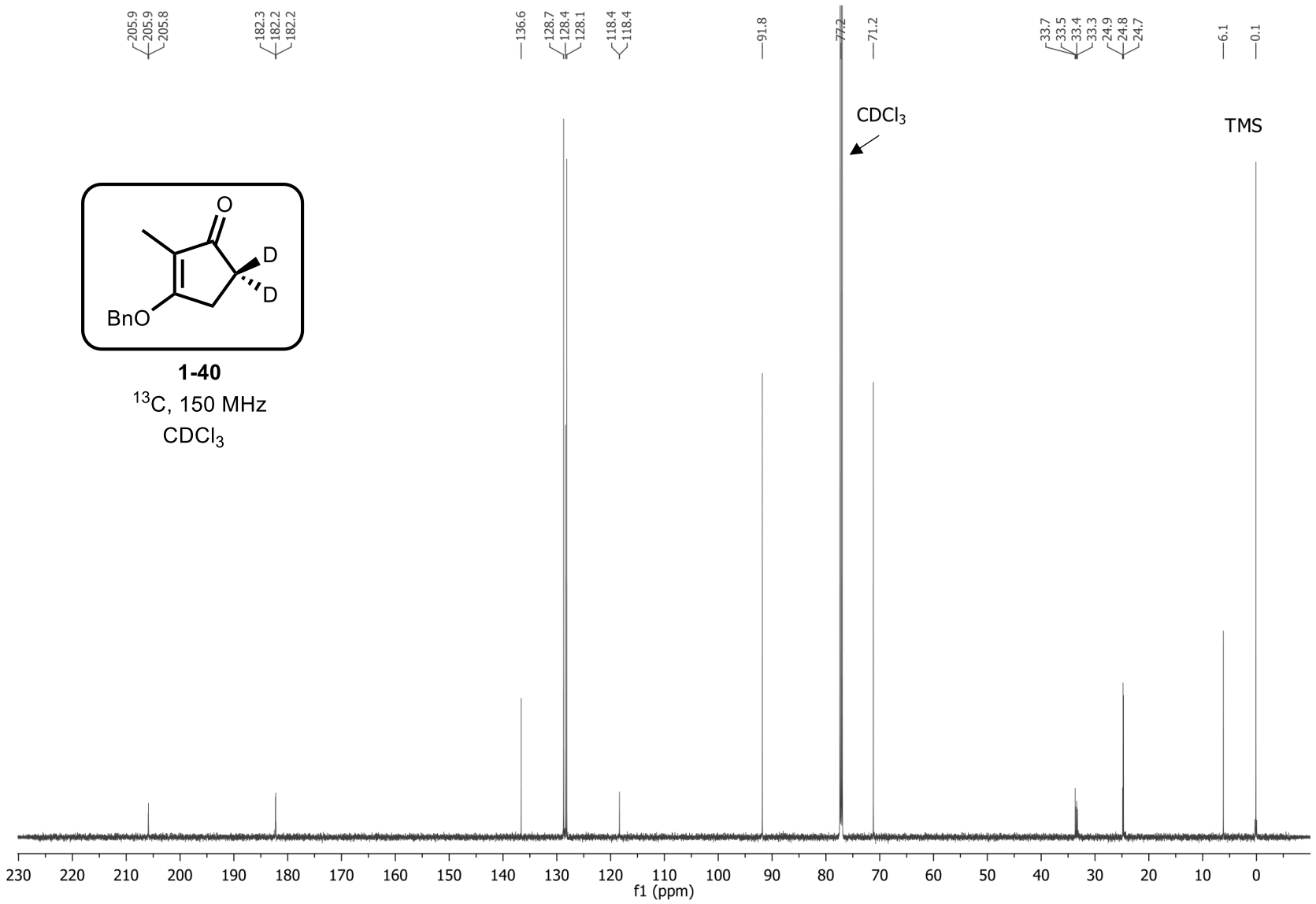

7.26
7.08
6.98
6.97
6.97
6.95
6.94
5.85
5.85
5.85
5.82
5.82
5.82
5.26
4.12
3.72
3.68
2.88
2.86
2.59
2.58
2.58
2.57
2.56
2.55
1.89
1.86
1.75
1.55
1.38
1.24
1.19
O
OH
O
CO2Me
1-36
1H, 500 MHz
CDCl3
DCM
CHCl3
TMS
1.00
1.02
0.95
0.98
3.11
2.92
0.94
0.94
2.02
1.09
4.26
1.17
3.29
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


201.4
184.2
167.3
149.4
121.3
101.3
77.0
70.5
56.3
51.5
47.1
36.9
36.3
32.2
27.1
25.2
25.0
O
OH
O
CO2Me
CDCl3
1-36
13C, 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.34
7.26
5.26
5.21
2.64
2.40
1.66
-0.02
O
BnO
1-39
1H, 500 MHz
CDCl3
CHCl3
DCM
TMS
4.93
2.00
2.00
2.00
2.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


205.4
183.7
136.1
129.0
128.6
127.1
117.1
77.2
70.9
33.7
25.4
6.3
0.1
O
BnO
1-39
13C, 125 MHz
CDCl3
CDCl3
TMS
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

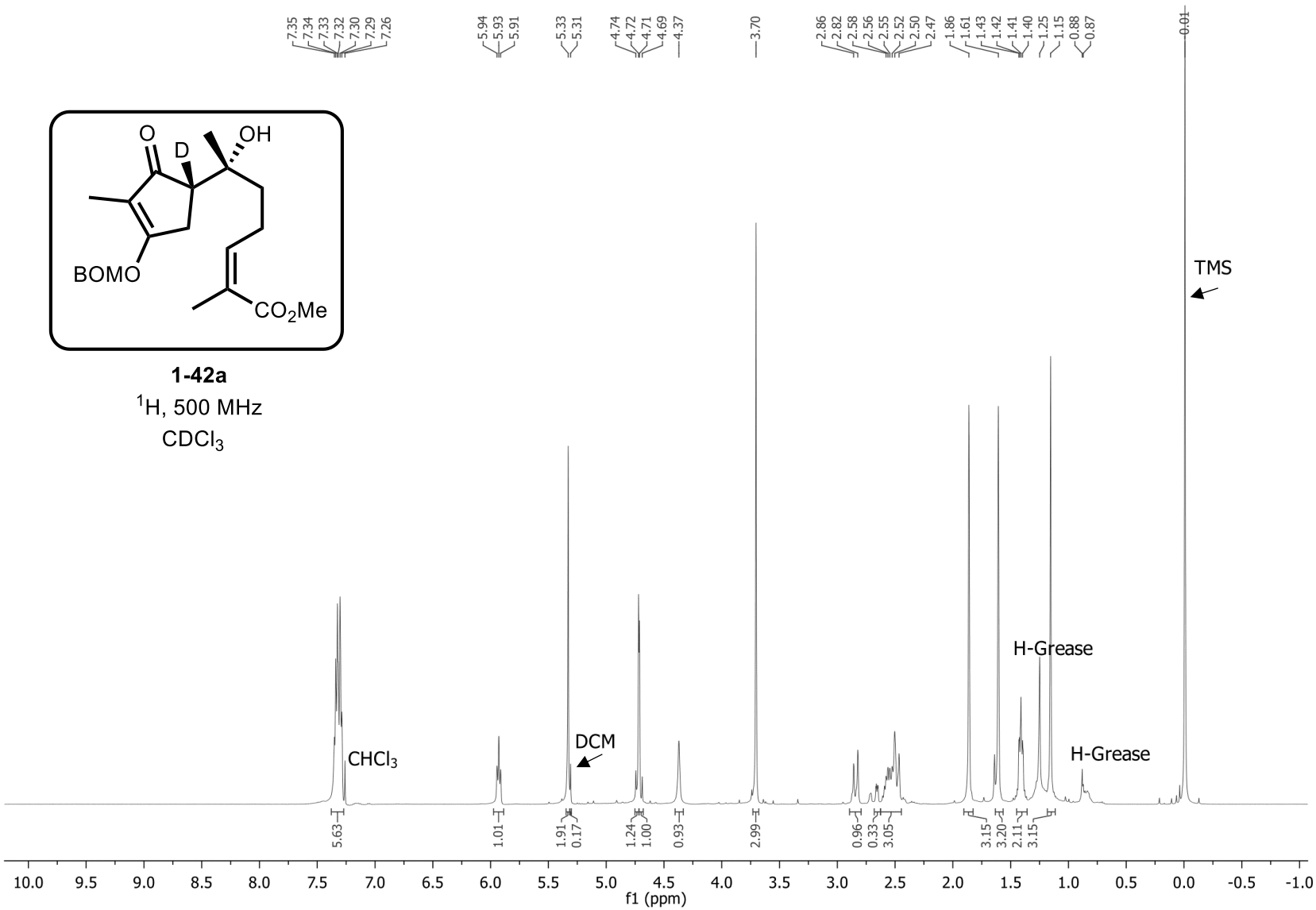

7.37
7.36
7.35
7.32
7.31
7.26
5.32
4.72
2.72
2.46
2.45
2.44
2.44
2.43
1.65
0.00
TMS
O
D
D
BnO
1-40
1H, 600 MHz
CDCl3
CHCl3
5.11
1.98
2.00
1.88
0.71
3.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

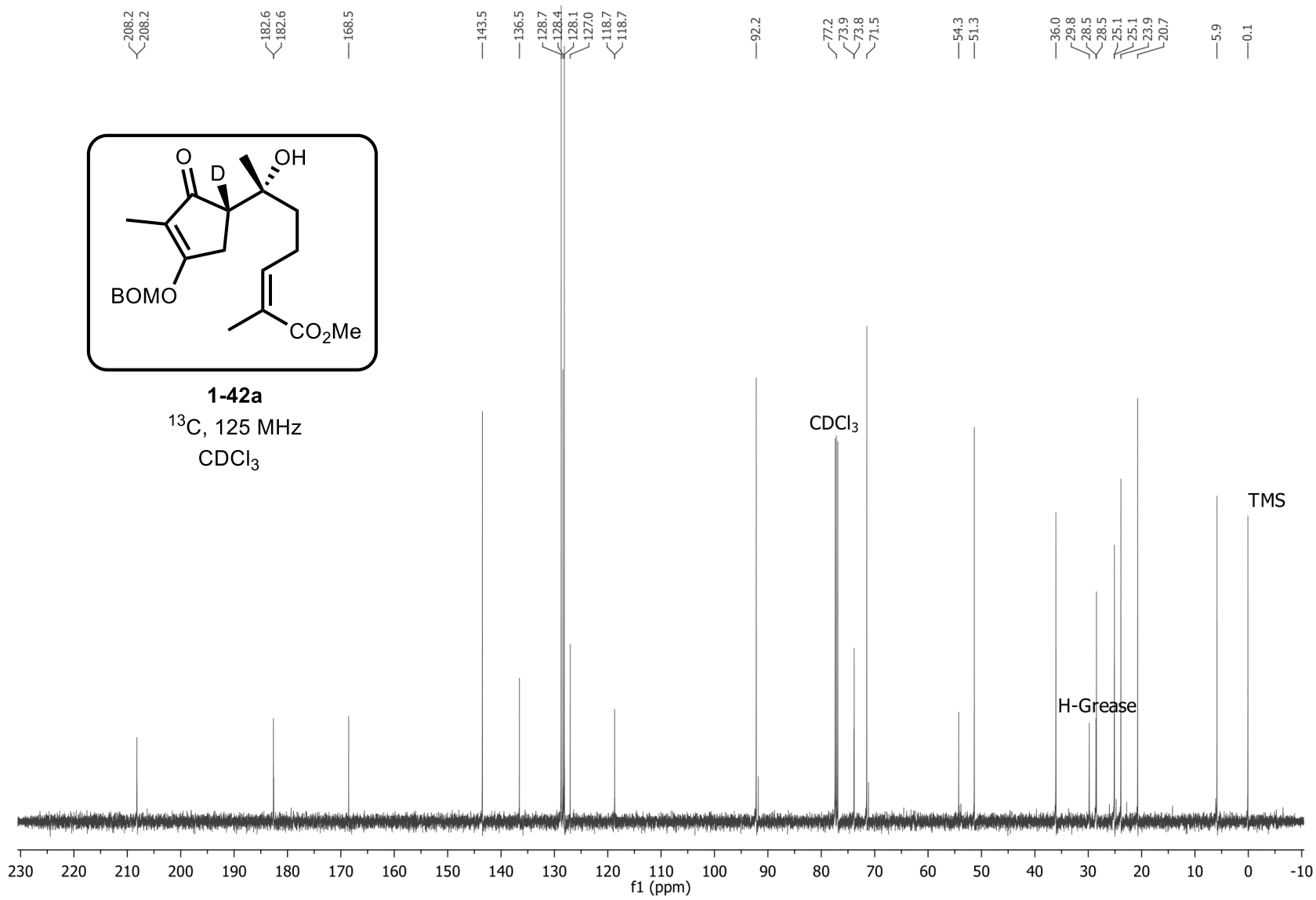


1-40

^{13}C, 150 MHz

$CDCl_3$

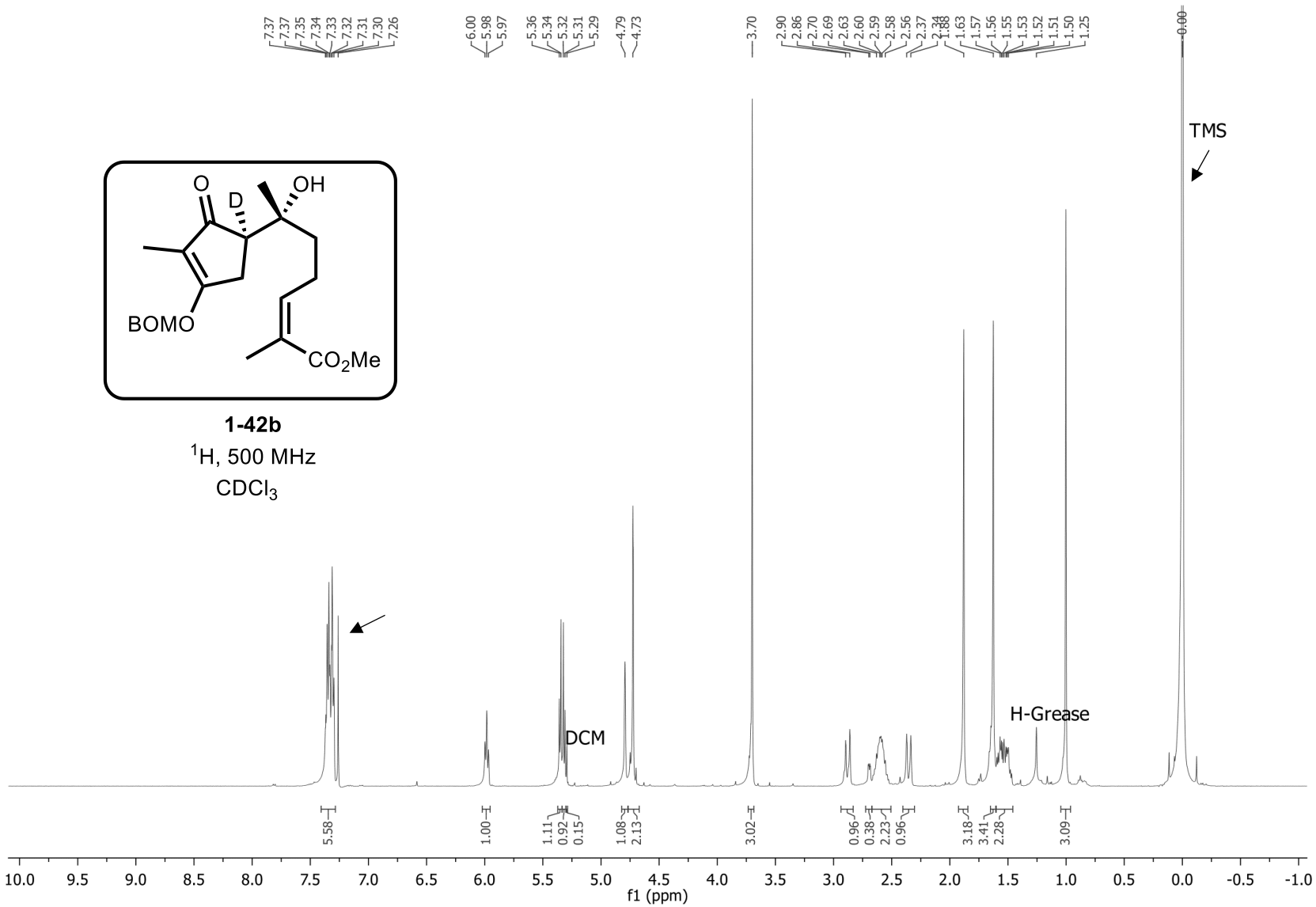

O
D
OH
BOMO
CO2Me
1-42a
1H, 500 MHz
CDCl3
TMS
H-Grease
H-Grease
DCM
CHCl3
f1 (ppm)

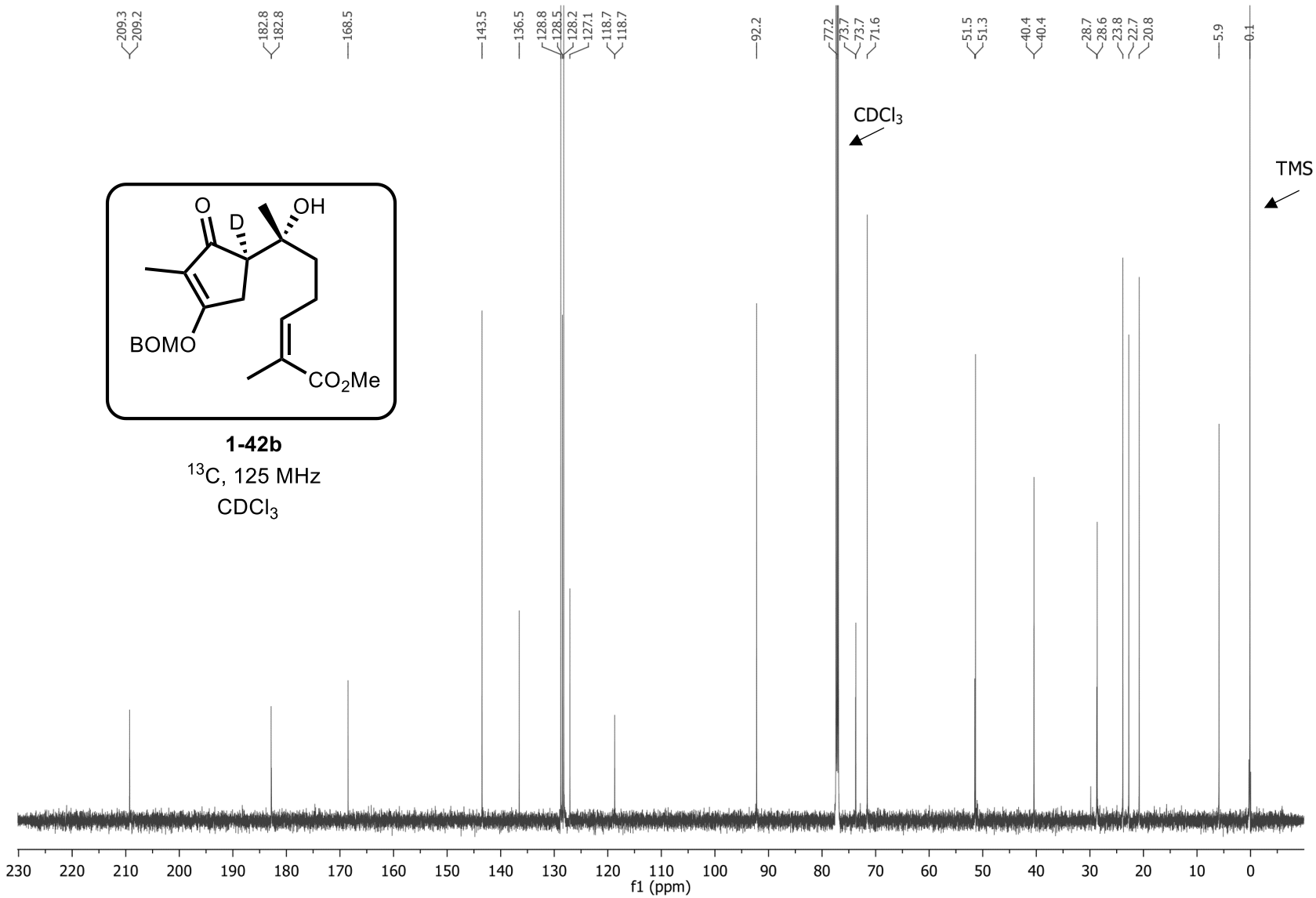


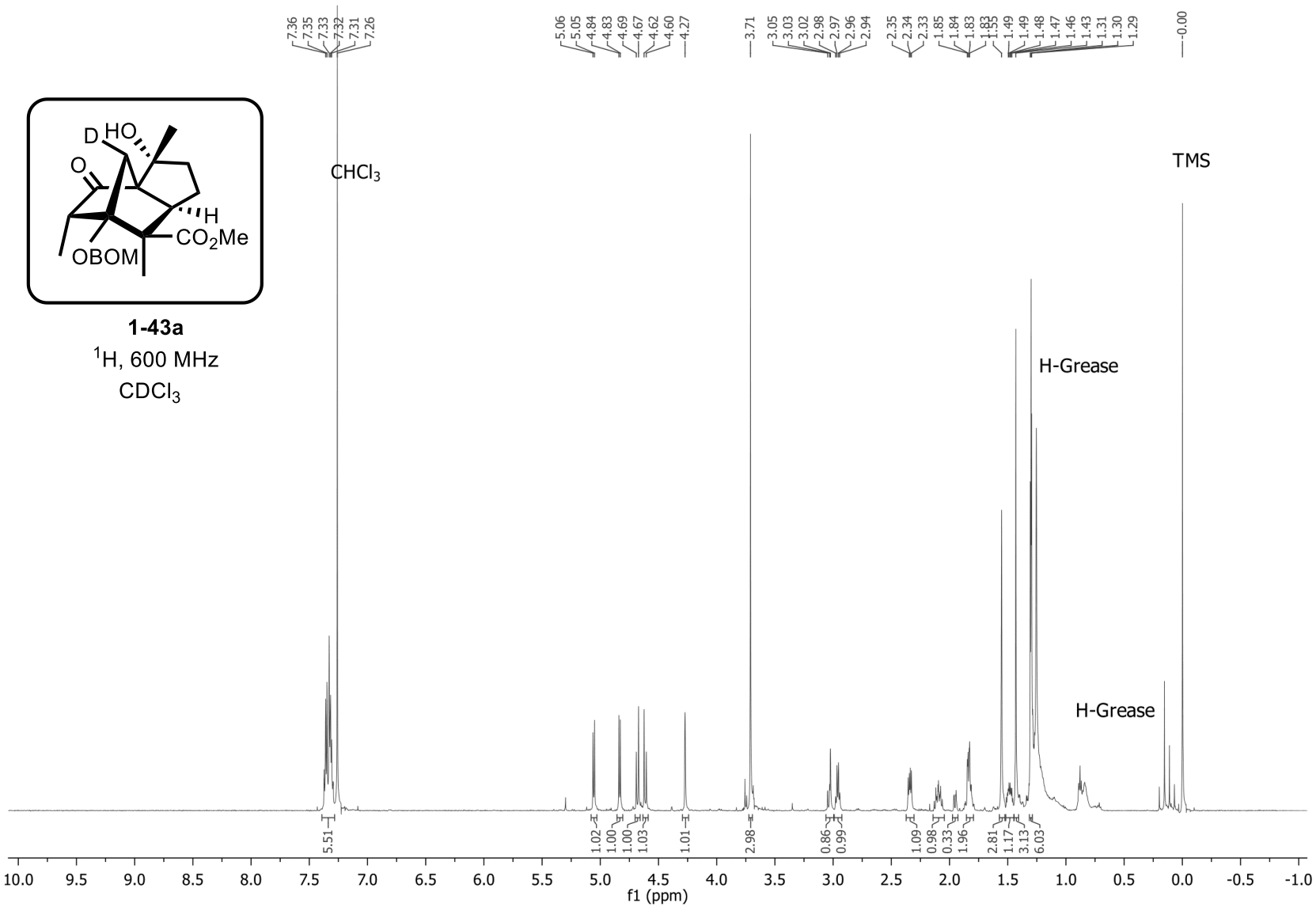
1-42a

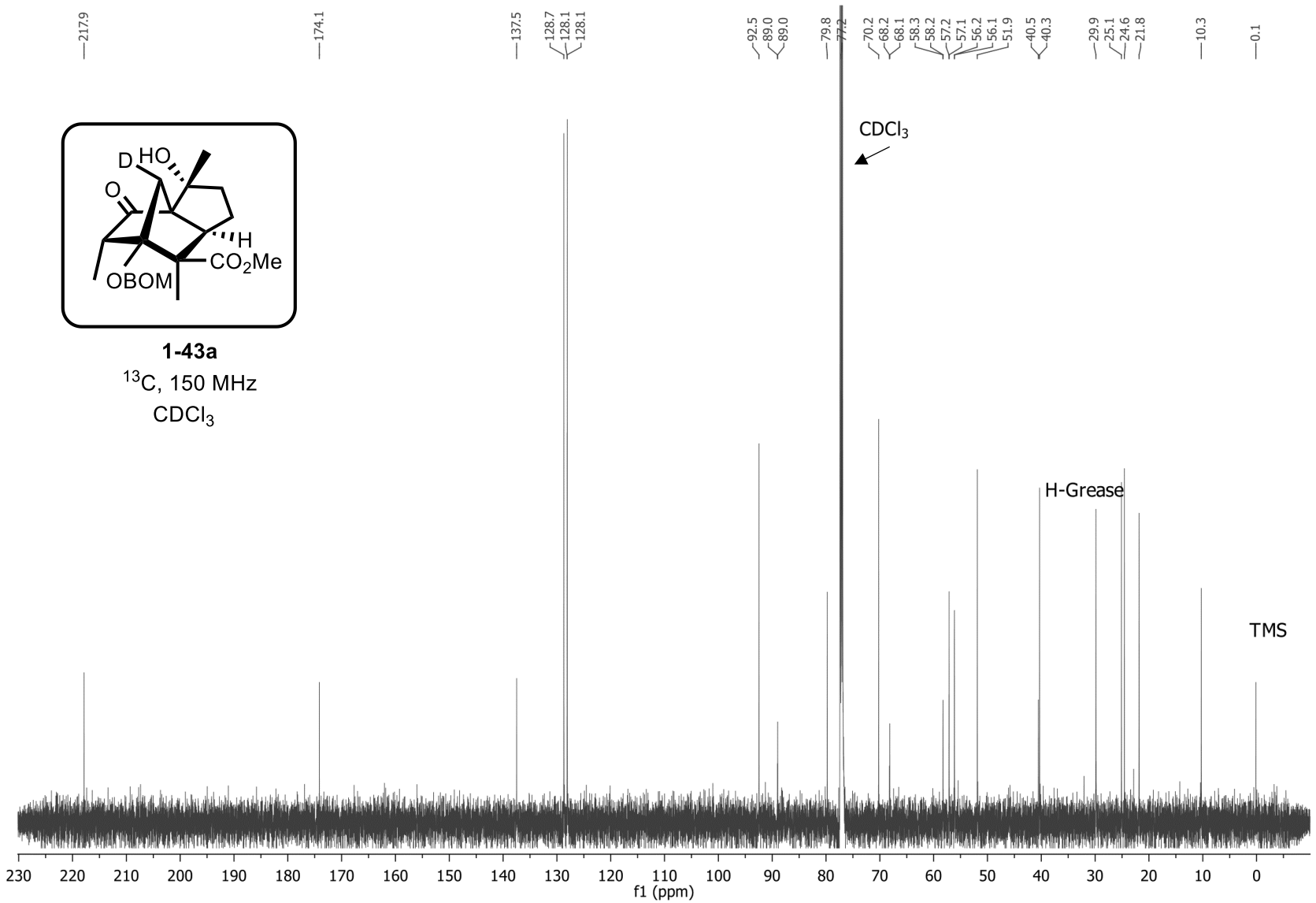
^{13}C, 125 MHz

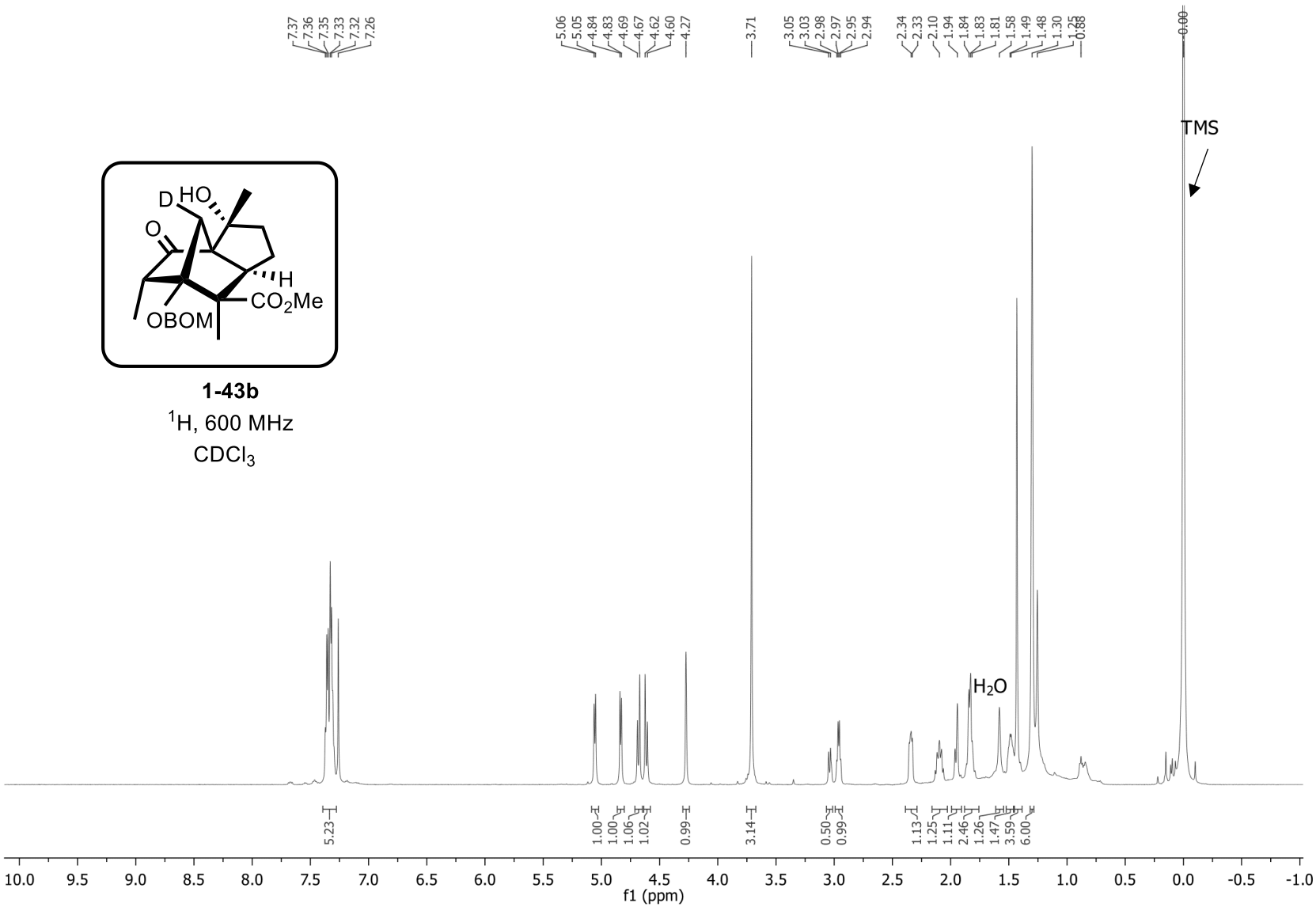
$CDCl_3$

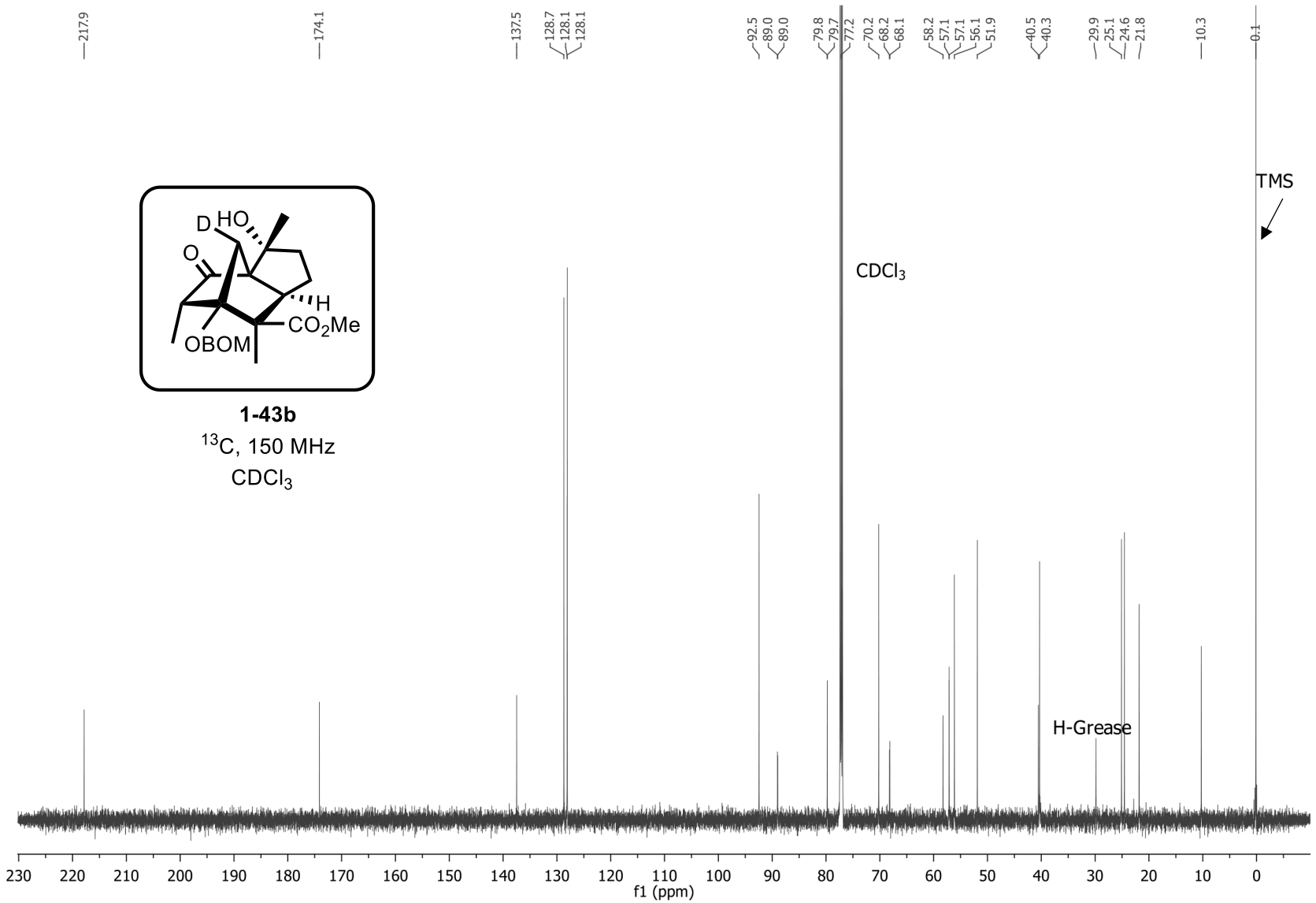

O
D
OH
BOMO
CO2Me
1-42b
1H, 500 MHz
CDCl3
TMS
DCM
H-Grease
f1 (ppm)

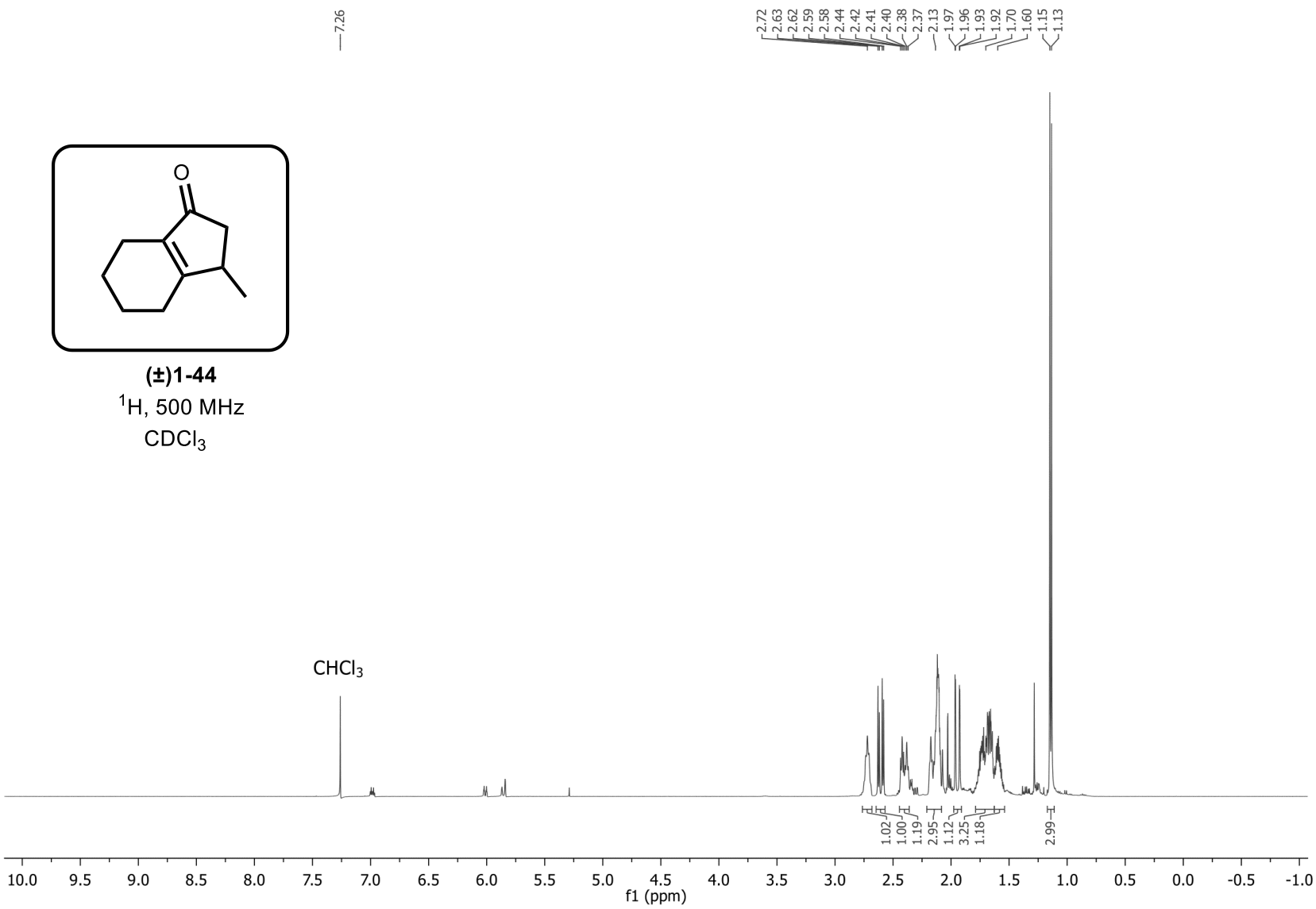

209.3
209.2
182.8
182.8
168.5
143.5
136.5
128.8
128.5
128.2
127.1
118.7
118.7
92.2
77.2
73.7
73.7
71.6
51.5
51.3
40.4
40.4
28.7
28.6
23.8
22.7
20.8
5.9
0.1
CDCl3
TMS
O
D
OH
BOMO
CO2Me
1-42b
13C, 125 MHz
CDCl3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


D
HO
O
H
CO2Me
OBOM
1-43a
1H, 600 MHz
CDCl3
CHCl3
TMS
H-Grease
H-Grease
f1 (ppm)


217.9
174.1
137.5
128.7
128.1
128.1
92.5
89.0
89.0
79.8
77.2
70.2
68.2
68.1
58.3
58.2
57.2
57.1
56.2
56.1
51.9
40.5
40.3
29.9
25.1
24.6
21.8
10.3
0.1
CDCl3
H-Grease
TMS
D
HO
O
H
CO2Me
OBOM
1-43a
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


D
HO
O
H
CO2Me
OBOM
1-43b
1H, 600 MHz
CDCl3
TMS
H2O
f1 (ppm)

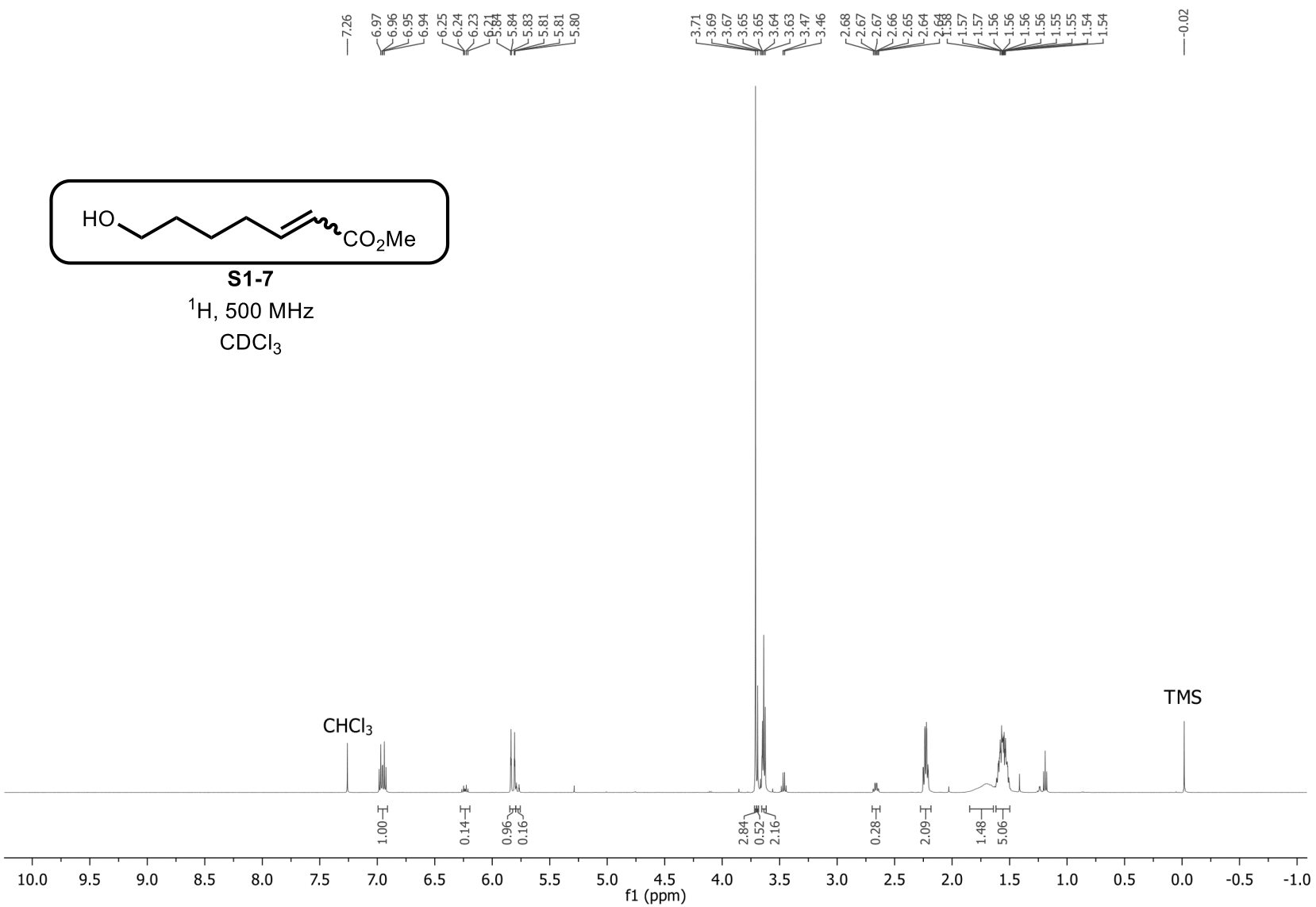

217.9
174.1
137.5
128.7
128.1
128.1
92.5
89.0
89.0
79.8
79.7
77.2
70.2
68.2
68.1
58.2
57.1
57.1
56.1
51.9
40.5
40.3
29.9
25.1
24.6
21.8
10.3
0.1
TMS
CDCl3
H-Grease
D
HO
O
H
CO2Me
OBOM
1-43b
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

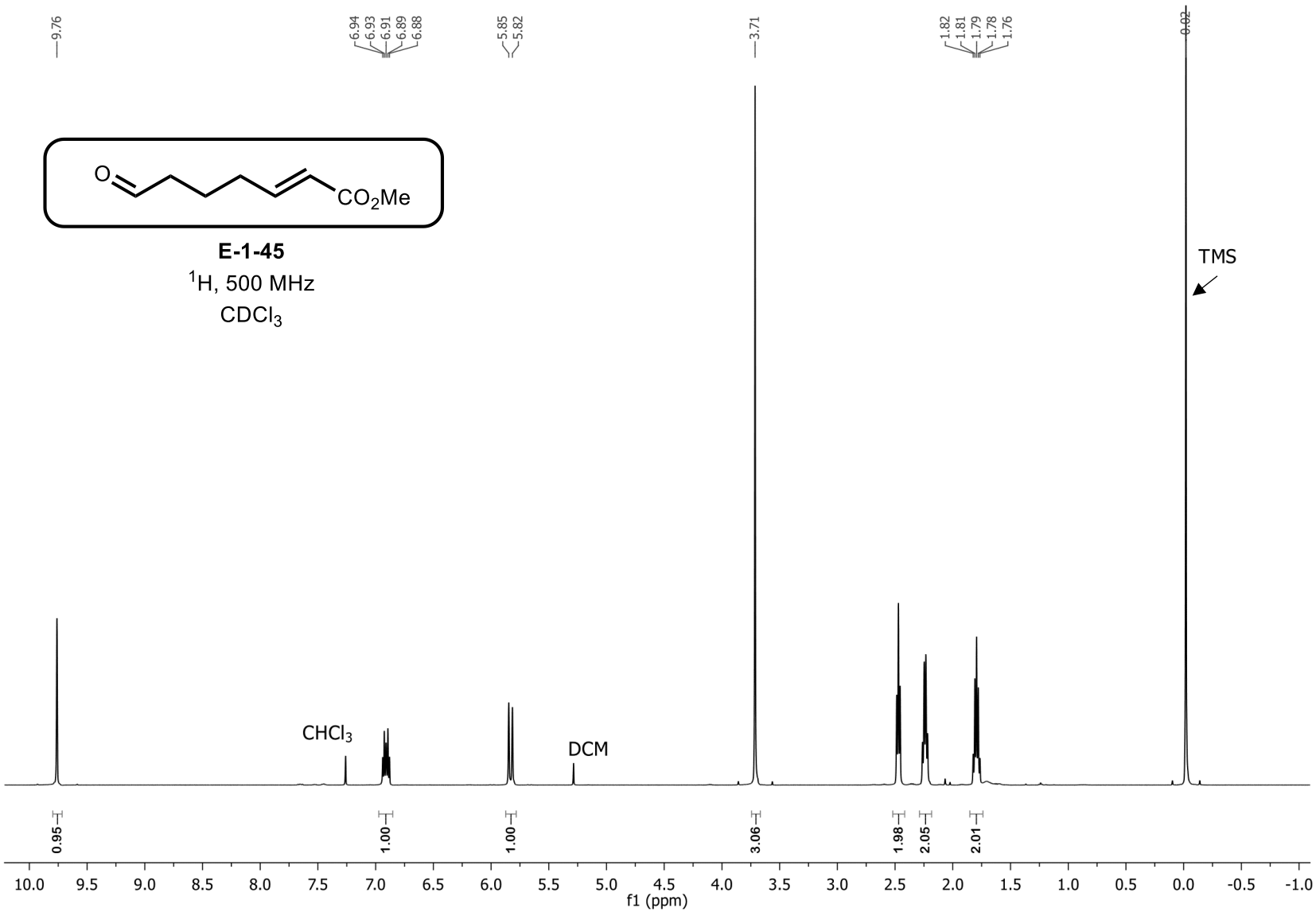


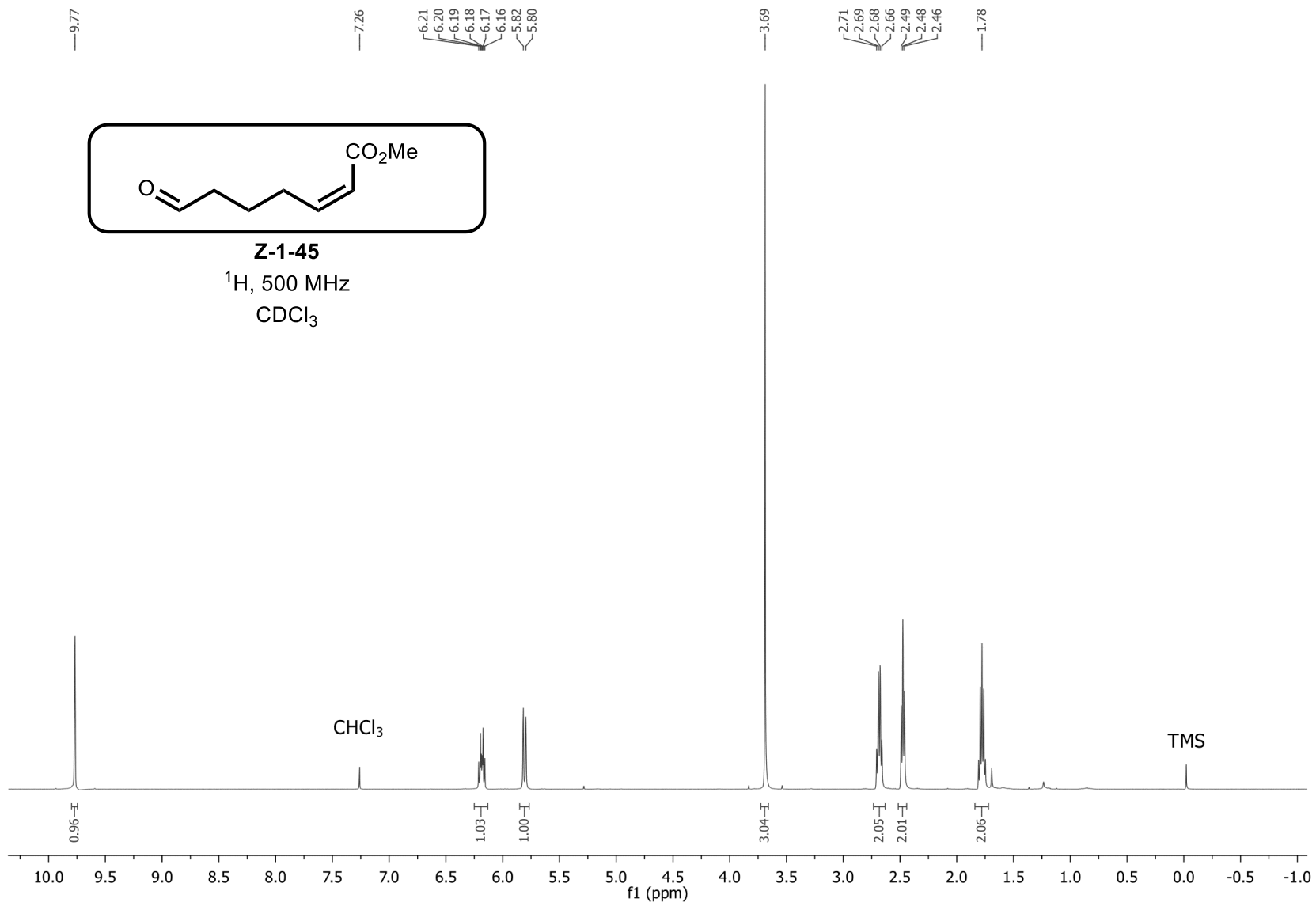
(±)1-44

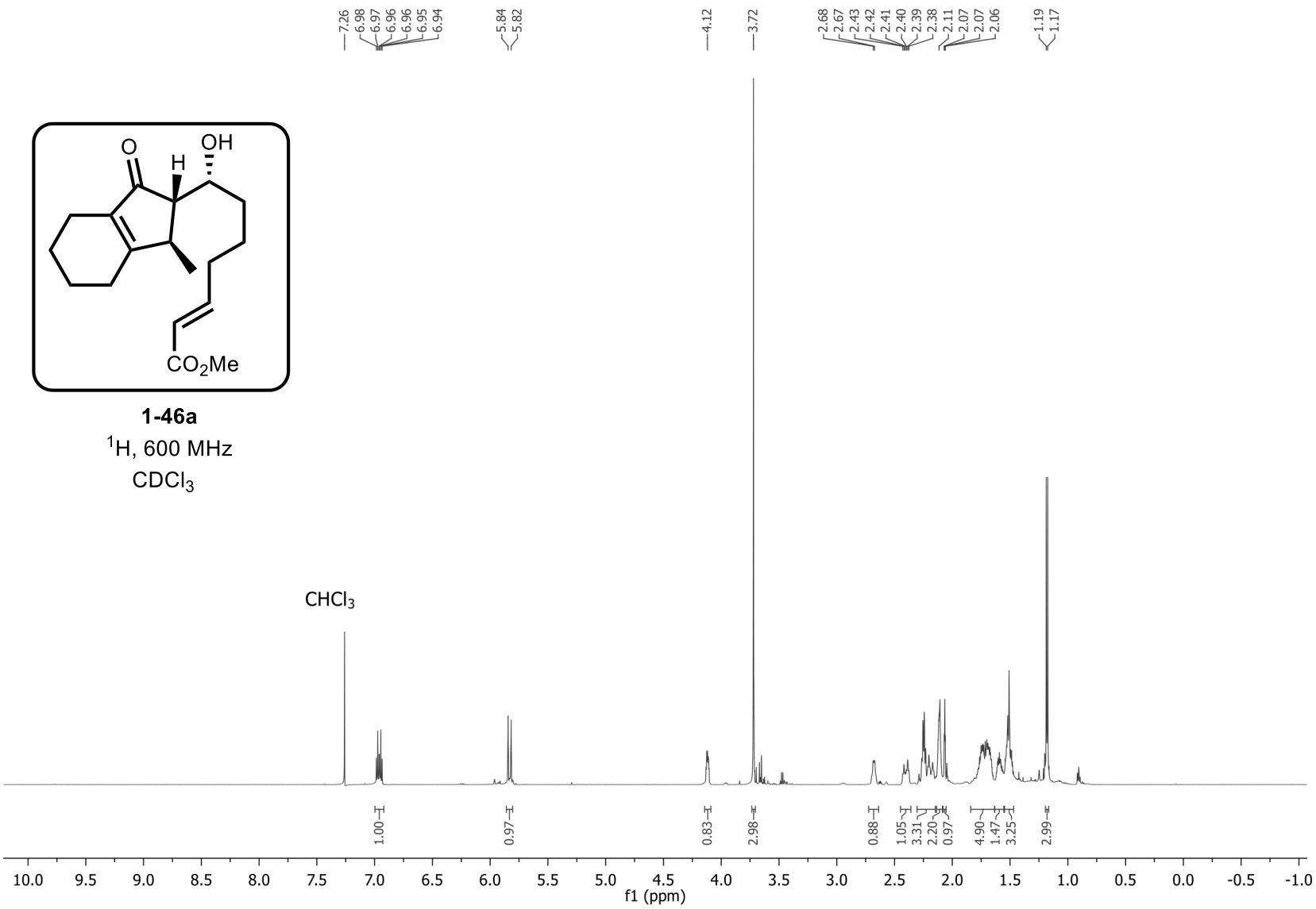
^{1}H, 500 MHz

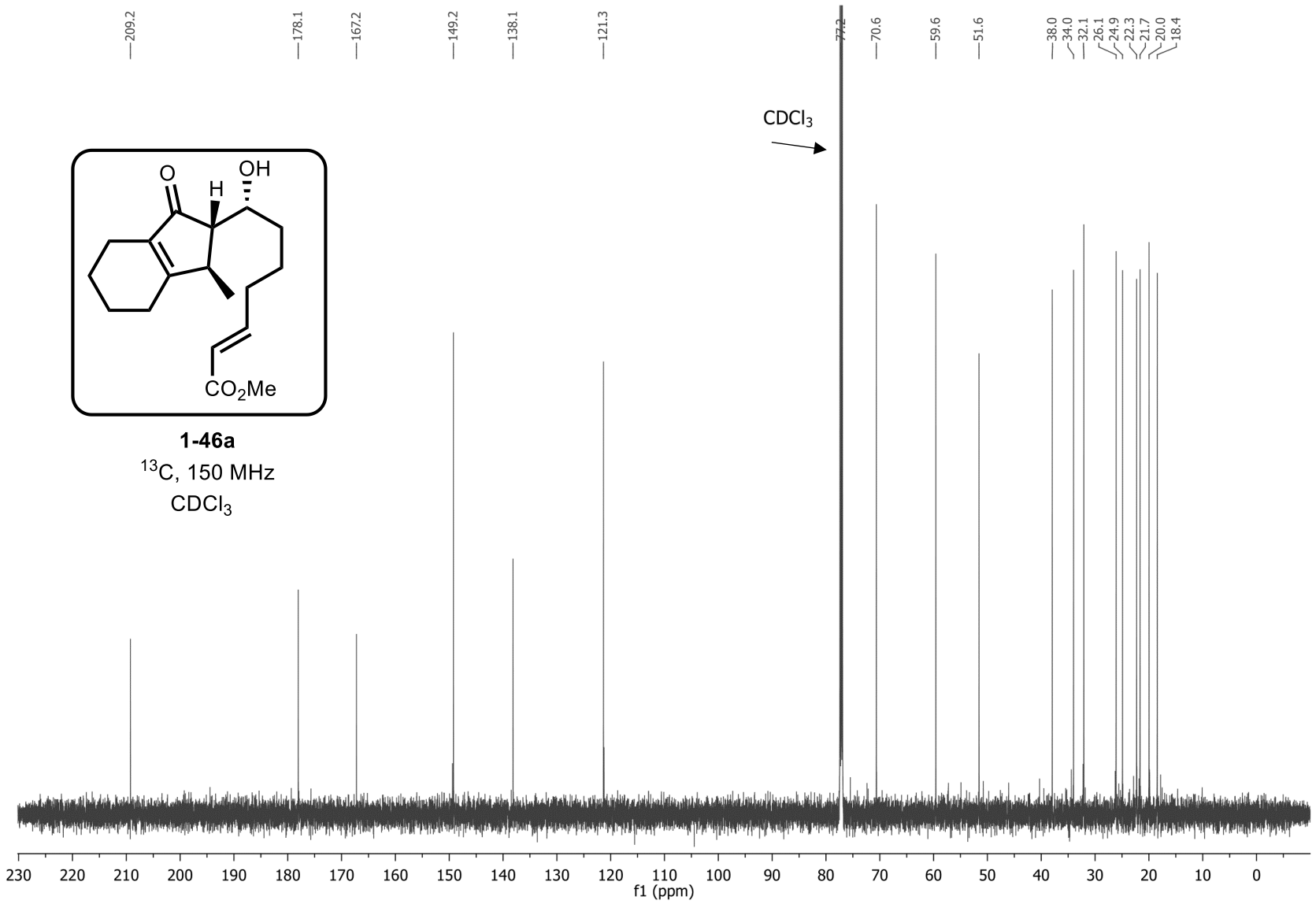
$CDCl_3$

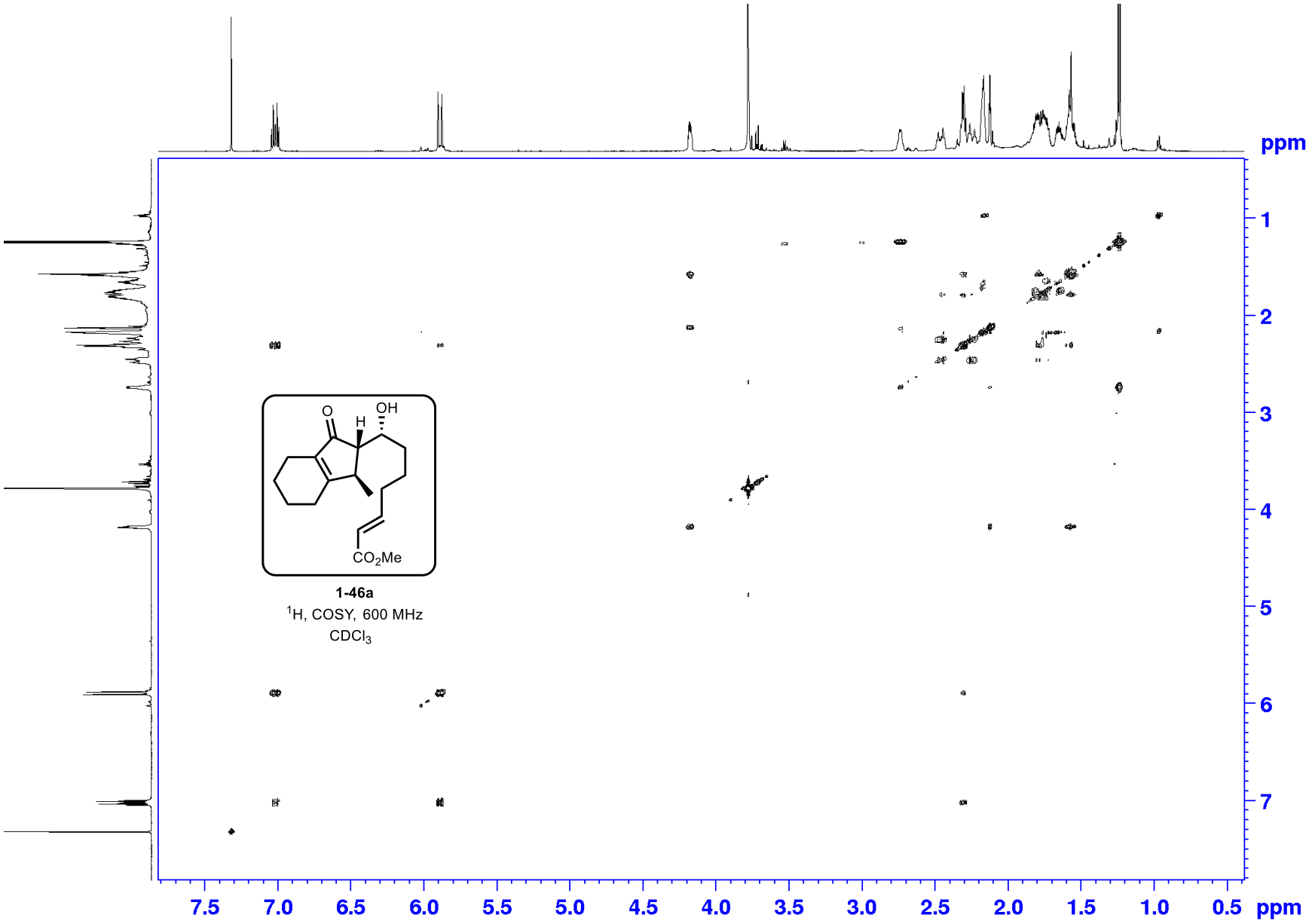

HO
CO2Me
S1-7
1H, 500 MHz
CDCl3
CHCl3
TMS
f1 (ppm)

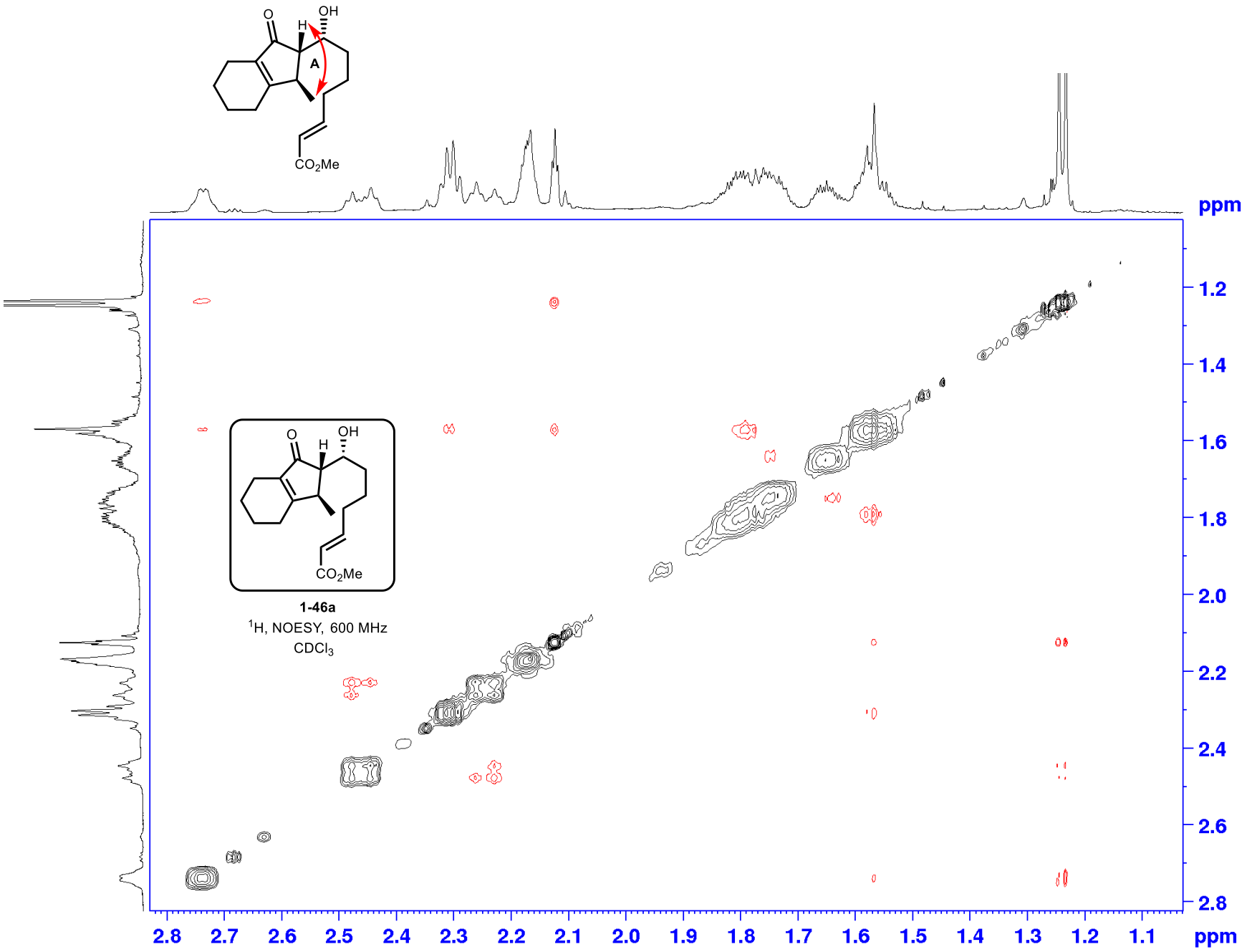

9.76
6.94
6.93
6.91
6.89
6.88
5.85
5.82
3.71
1.82
1.81
1.79
1.78
1.76
0.02
O
CO2Me
E-1-45
1H, 500 MHz
CDCl3
TMS
CHCl3
DCM
0.95
1.00
1.00
3.06
1.98
2.05
2.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

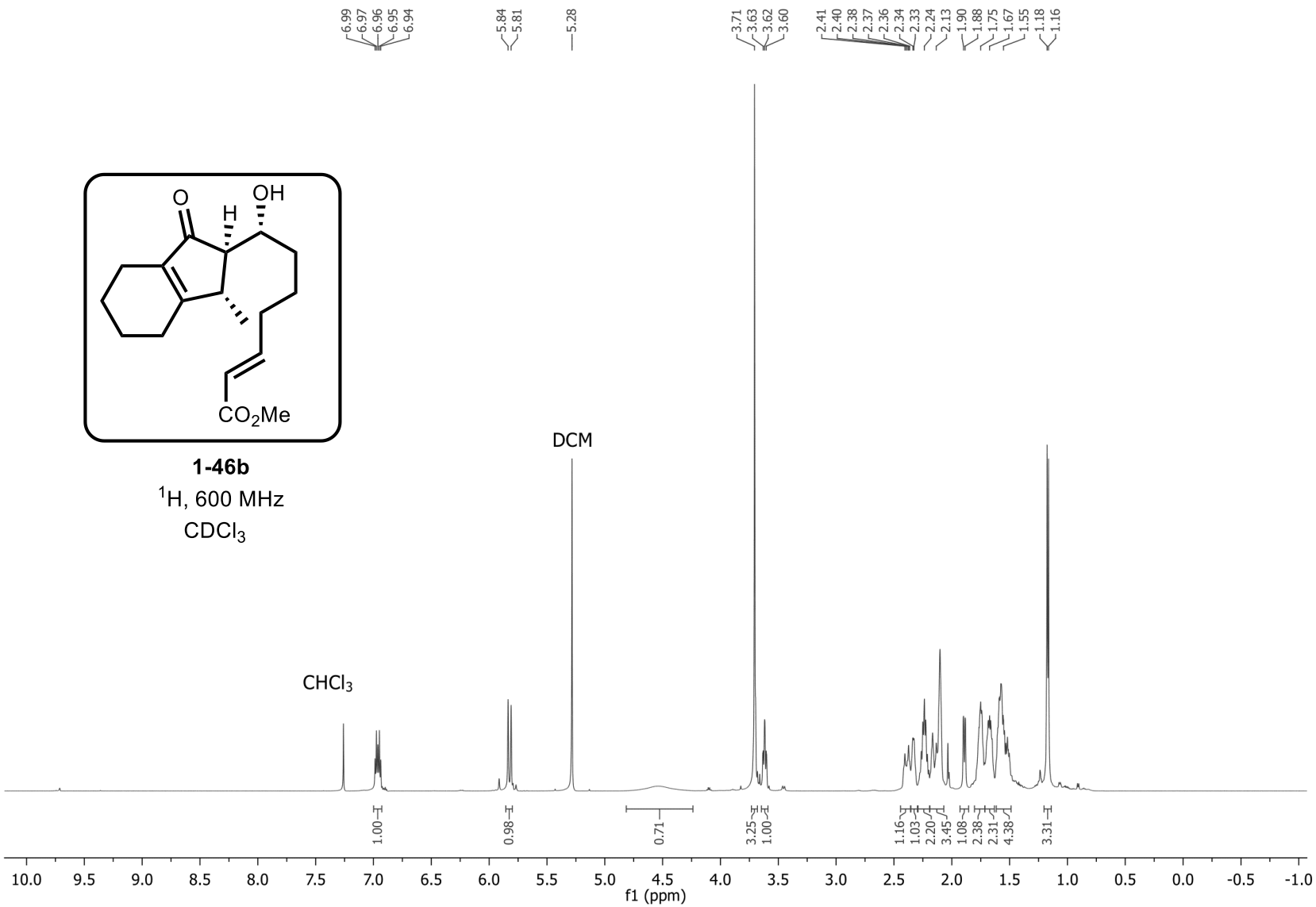

9.77
7.26
6.21
6.20
6.19
6.18
6.17
6.16
5.82
5.80
3.69
2.71
2.69
2.68
2.66
2.49
2.48
2.46
1.78
CO2Me
O
Z-1-45
1H, 500 MHz
CDCl3
CHCl3
TMS
0.96
1.03
1.00
3.04
2.05
2.01
2.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


7.26
6.98
6.97
6.96
6.96
6.95
6.94
5.84
5.82
4.12
3.72
2.68
2.67
2.43
2.42
2.41
2.40
2.39
2.38
2.11
2.07
2.07
2.06
1.19
1.17
O
H
OH
CO2Me
1-46a
1H, 600 MHz
CDCl3
CHCl3
1.00
0.97
0.83
2.98
0.88
1.05
3.31
2.20
0.97
4.90
1.47
3.25
2.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


209.2
178.1
167.2
149.2
138.1
121.3
77.2
70.6
59.6
51.6
38.0
34.0
32.1
26.1
24.9
22.3
21.7
20.0
18.4
CDCl3
O
H
OH
CO2Me
1-46a
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


ppm
1
2
3
4
5
6
7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
O
H
OH
CO2Me
1-46a
1H, COSY, 600 MHz
CDCl3

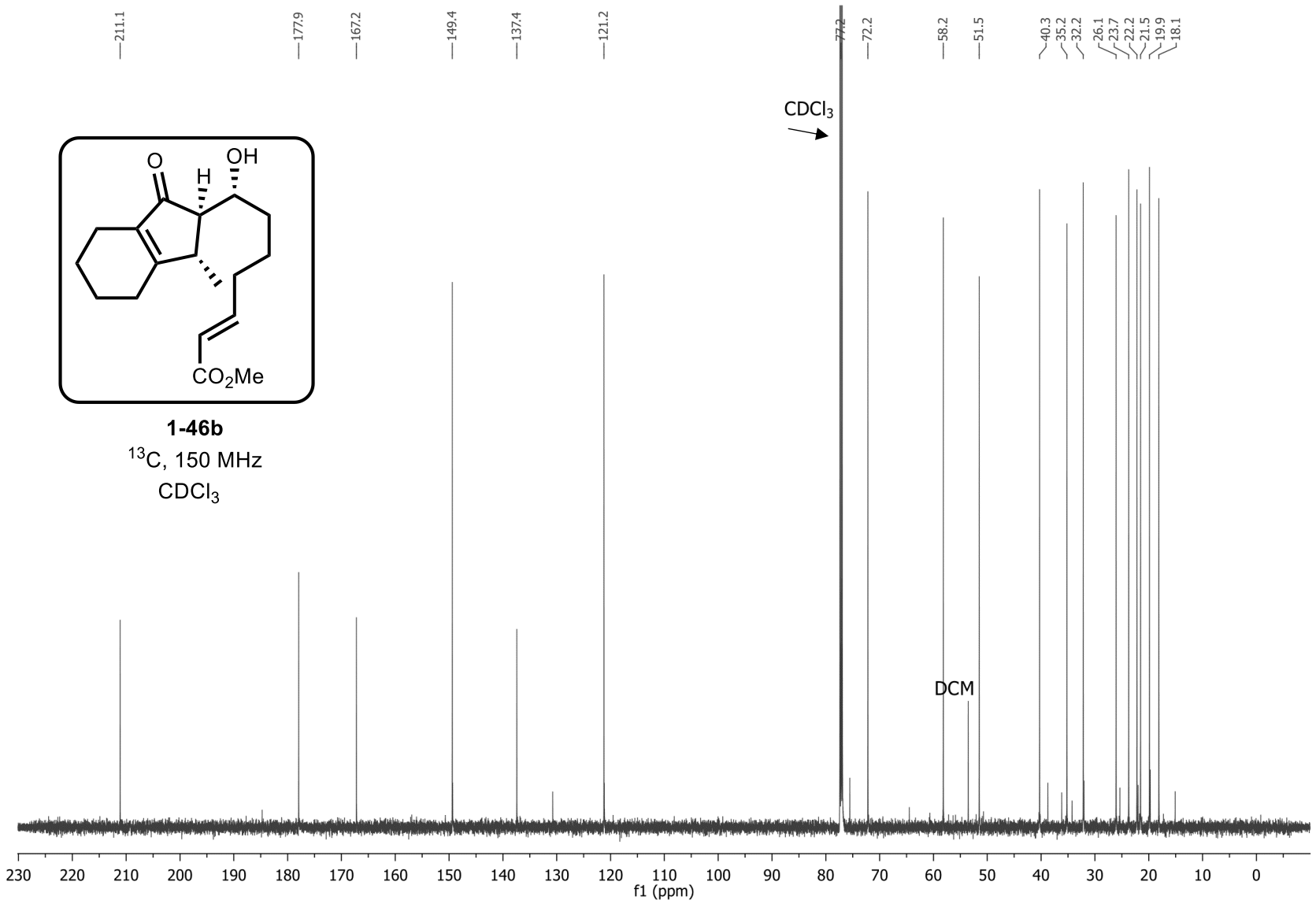

O
H
OH
A
CO2Me
ppm
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 ppm
1-46a
1H, NOESY, 600 MHz
CDCl3

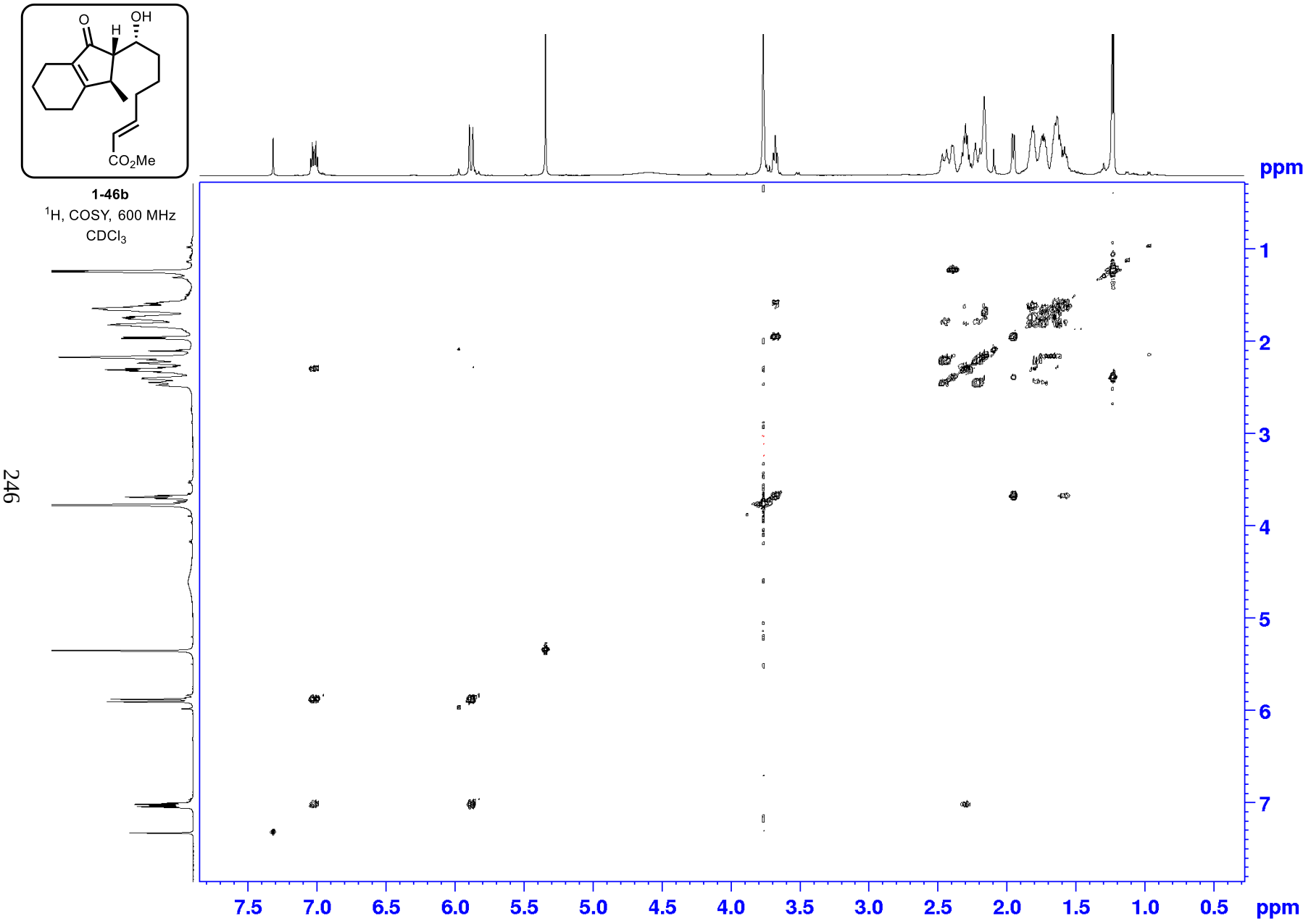


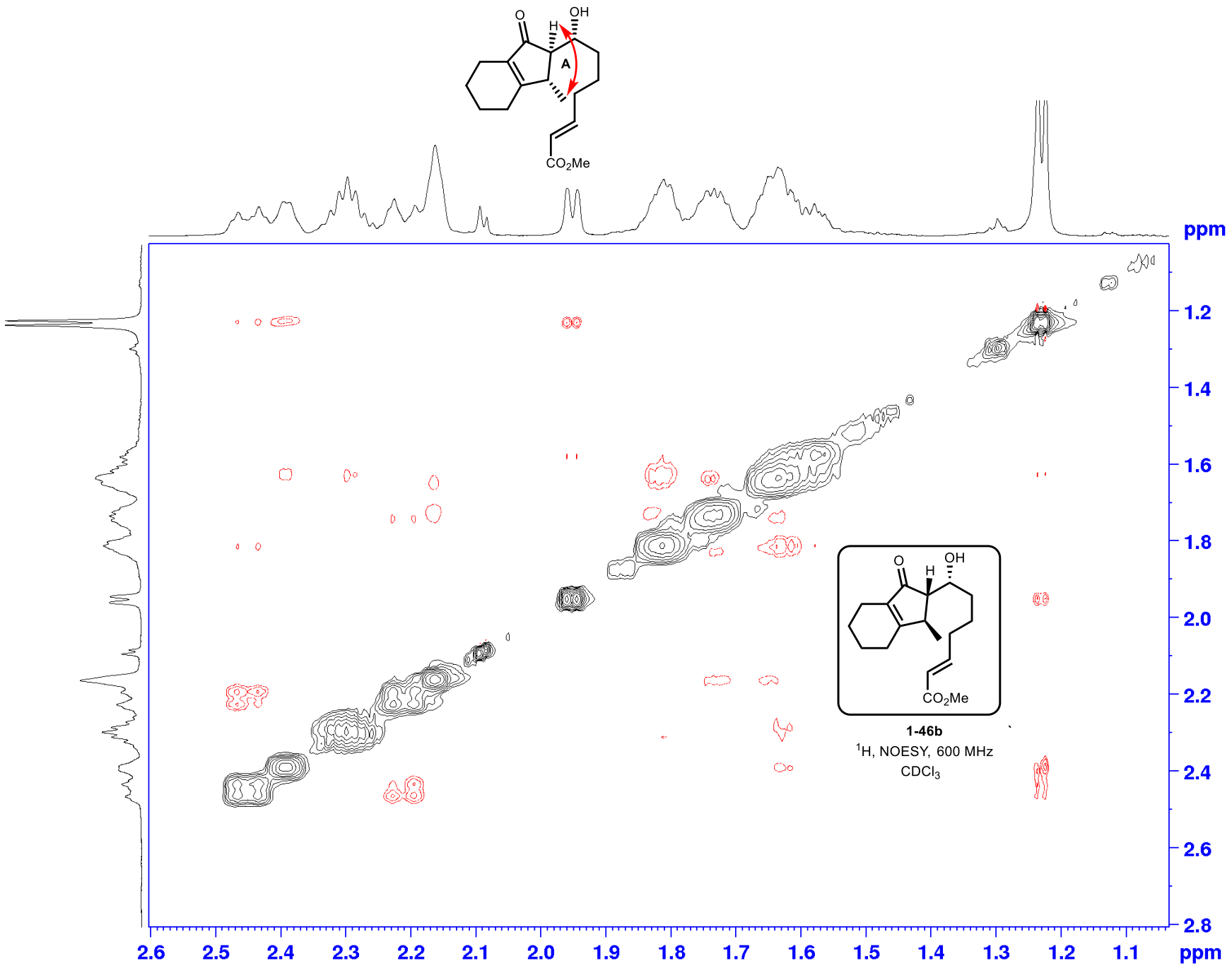
1-46b

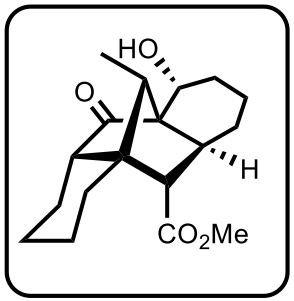
^{1}H, 600 MHz

$CDCl_3$


211.1
177.9
167.2
149.4
137.4
121.2
77.2
72.2
58.2
51.5
40.3
35.2
32.2
26.1
23.7
22.2
21.5
19.9
18.1
CDCl3
DCM
O
H
OH
CO2Me
1-46b
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
H
OH
CO2Me
1-46b
1H, COSY, 600 MHz
CDCl3
ppm
1
2
3
4
5
6
7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

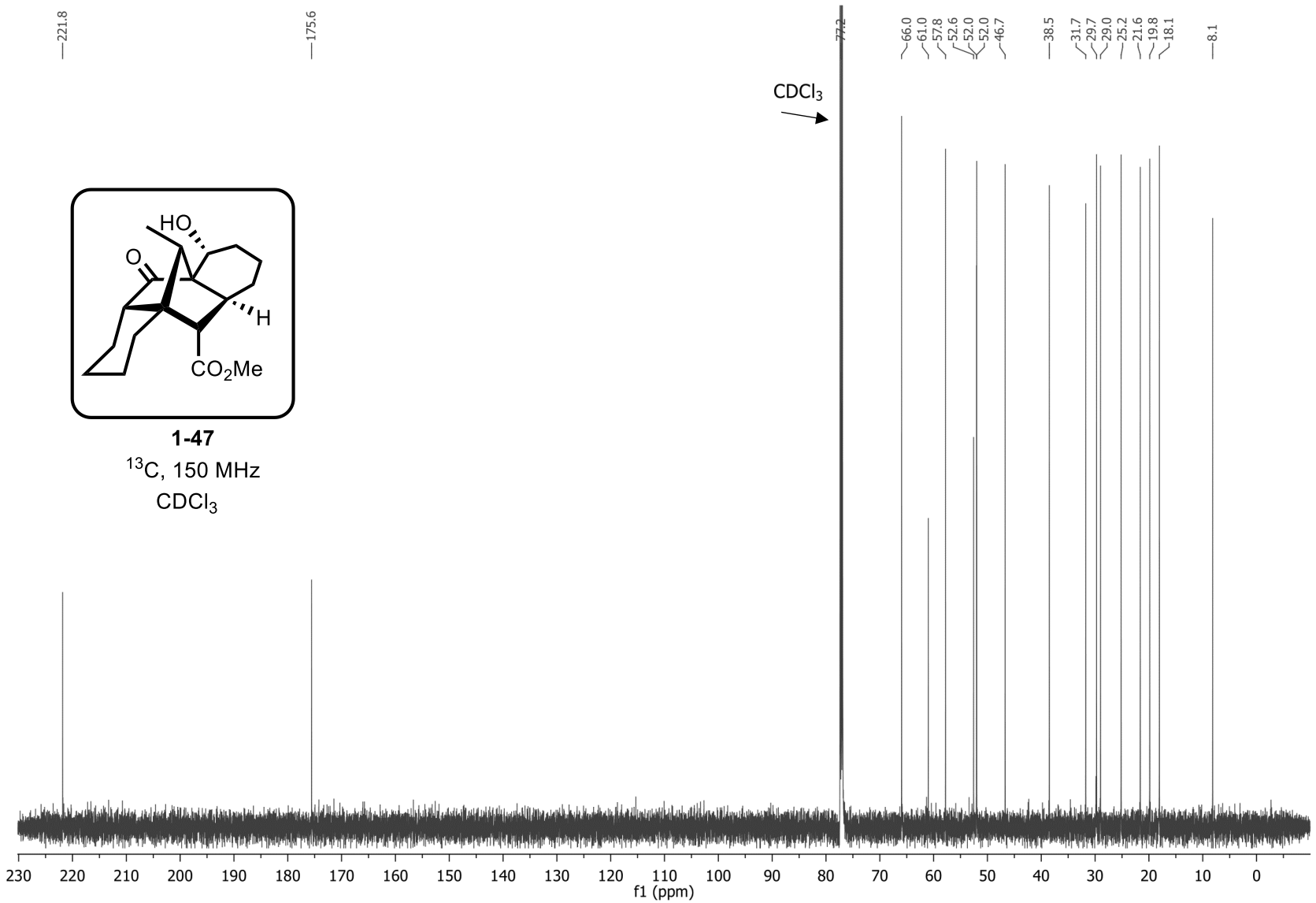

O
OH
H
A
CO2Me
ppm
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
ppm
1-46b
1H, NOESY, 600 MHz
CDCl3



1-47

^{1}H, 600 MHz

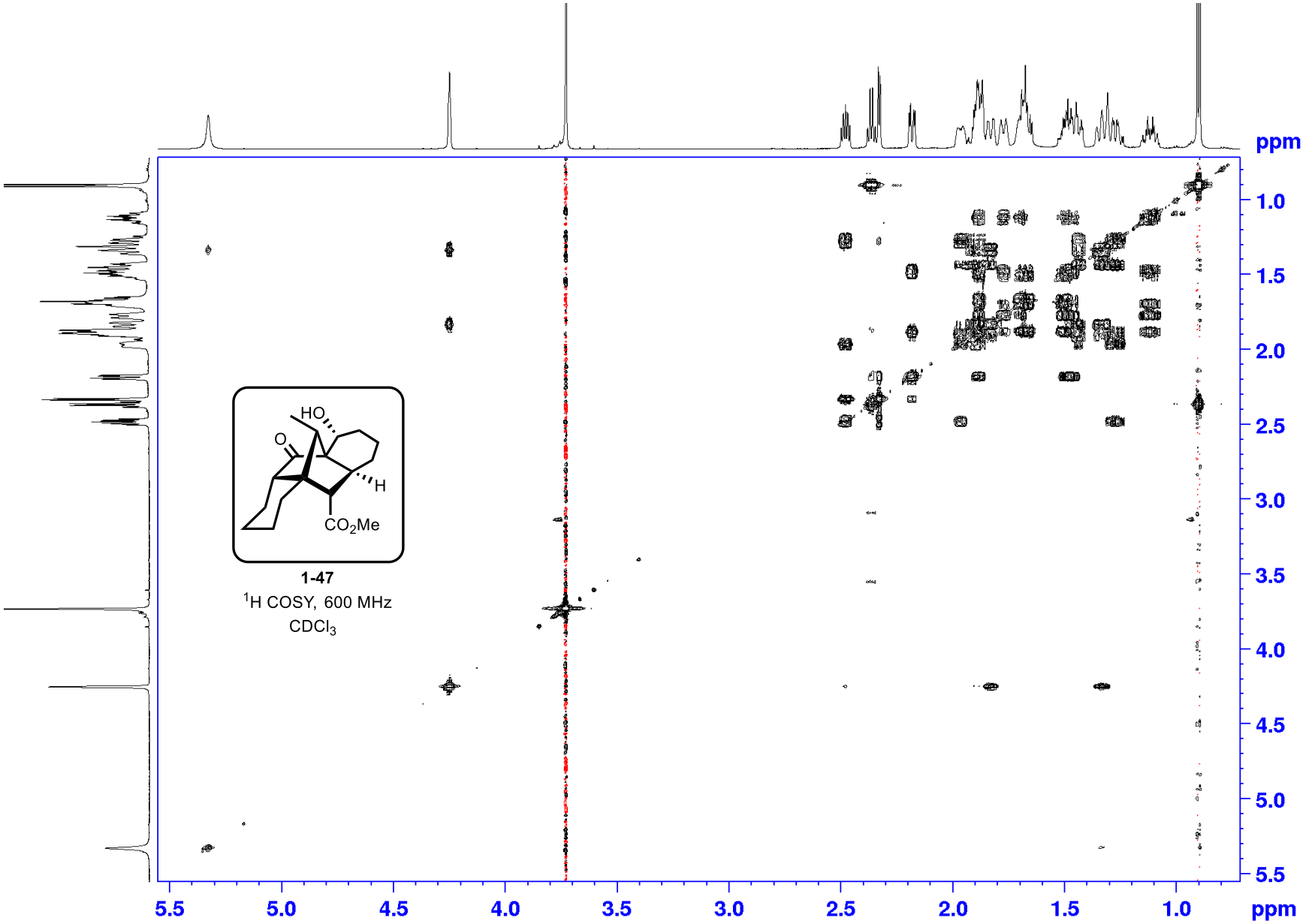
$CDCl_3$

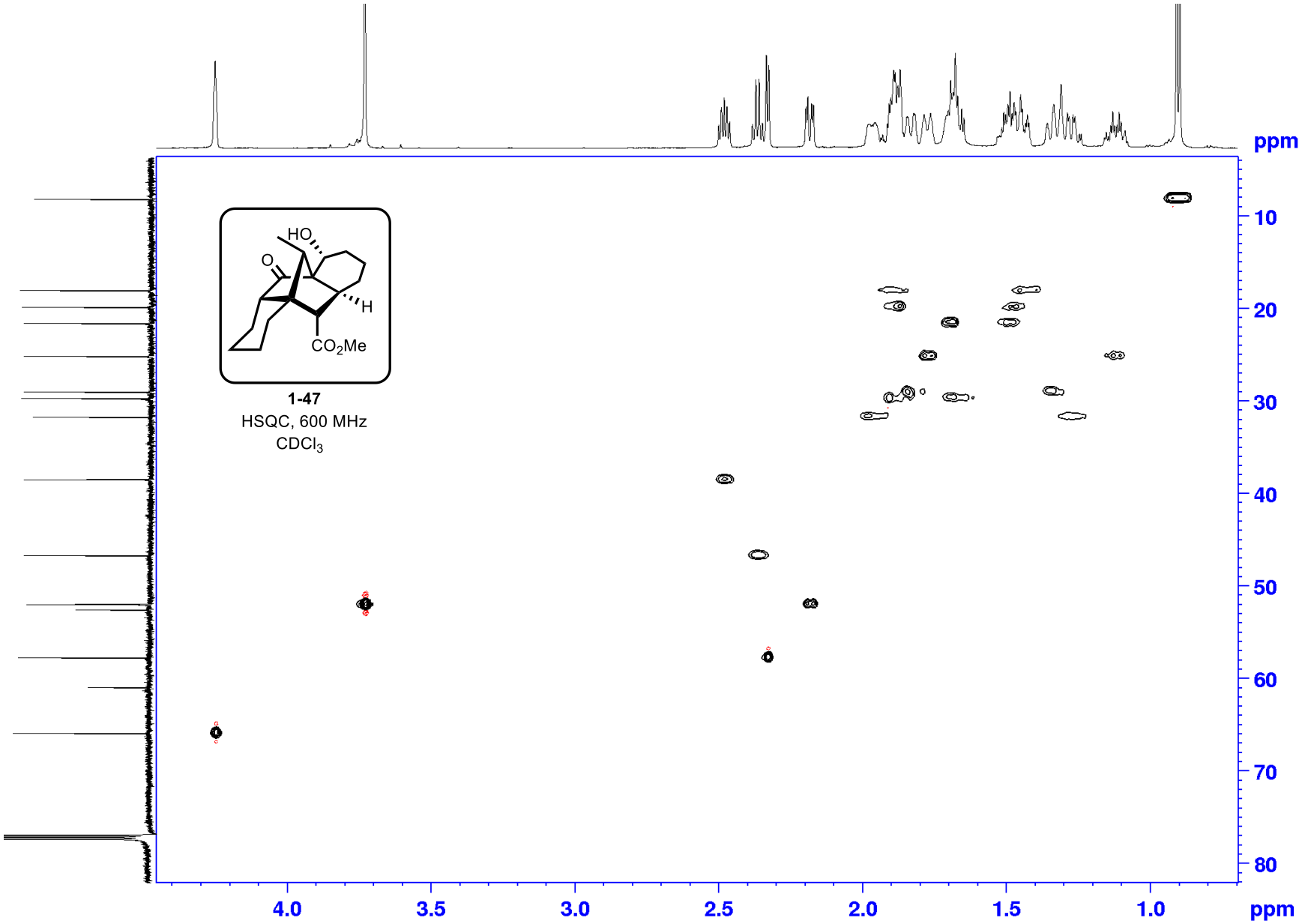


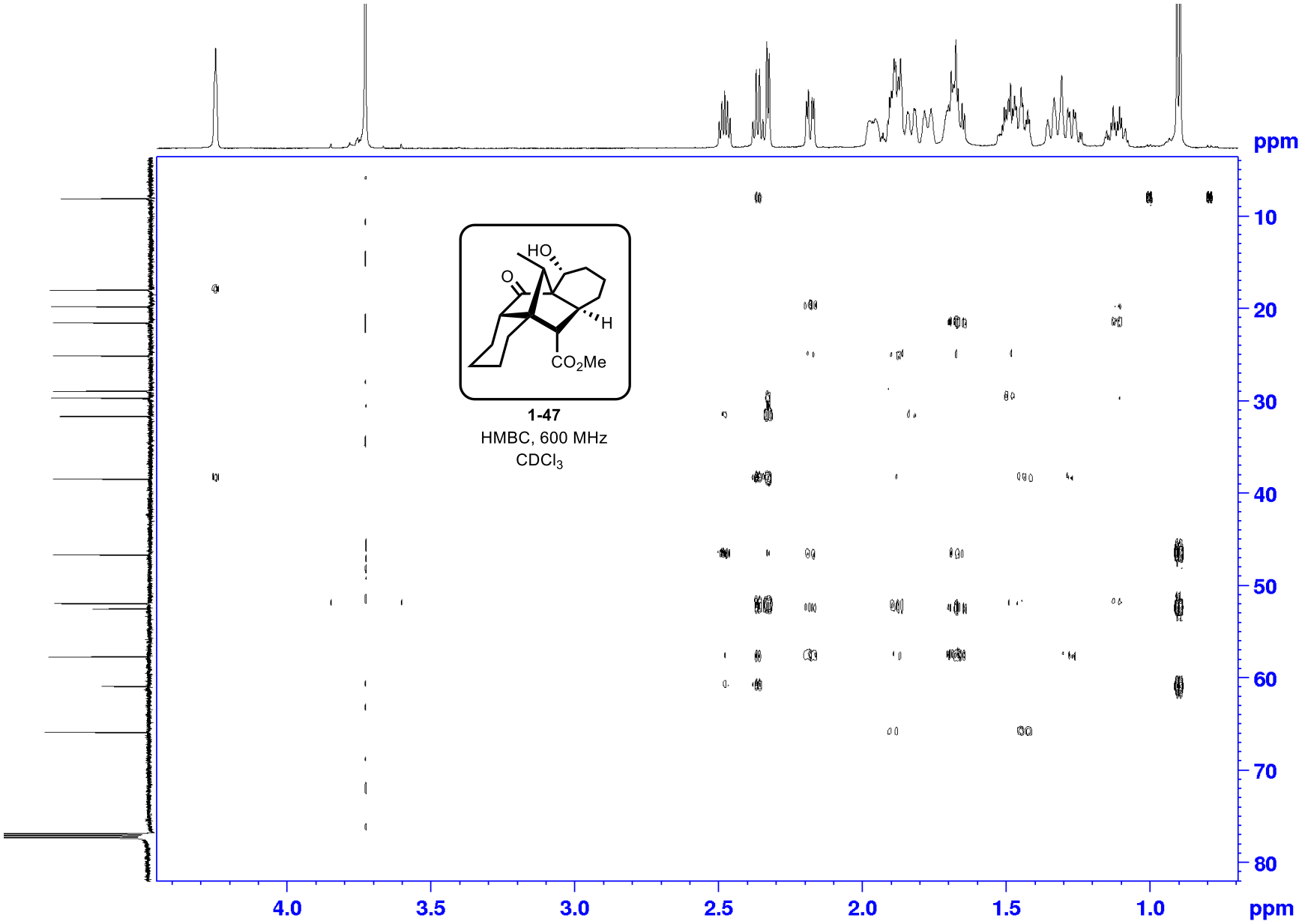
1-47

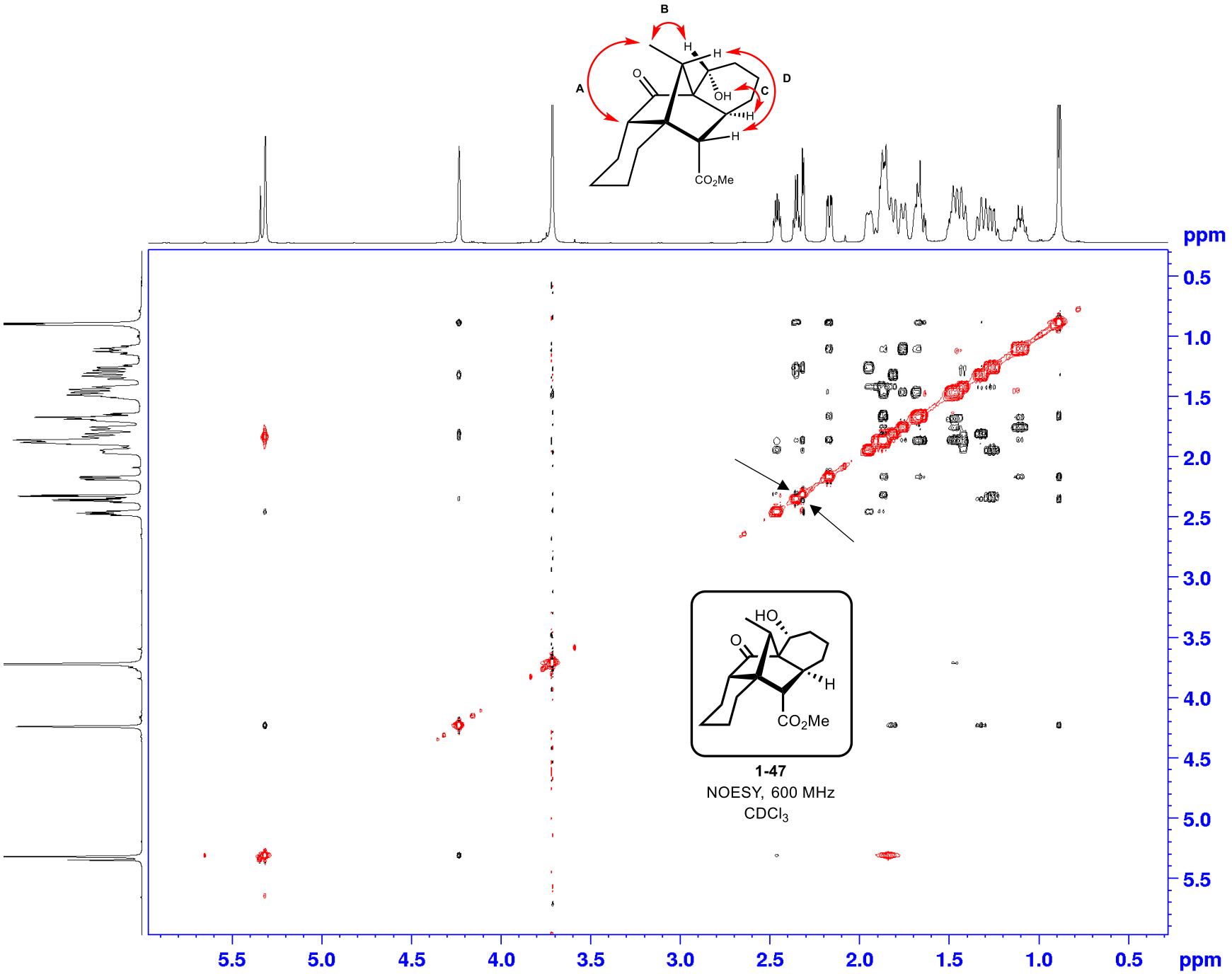
^{13}C, 150 MHz

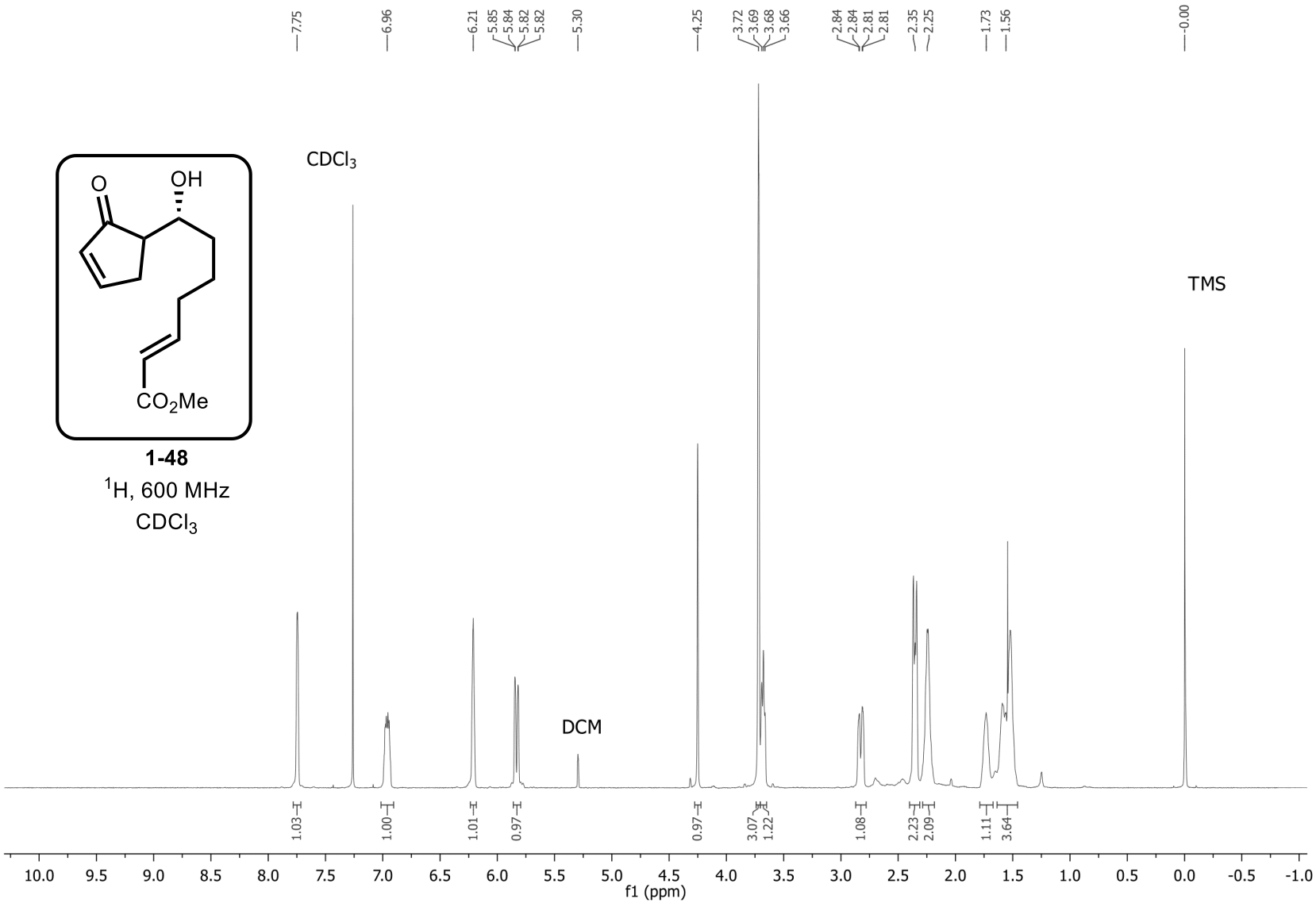
$CDCl_3$


HO
O
H
CO2Me
1-47
1H COSY, 600 MHz
CDCl3
ppm
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


HO
O
H
CO2Me
1-47
HSQC, 600 MHz
CDCl3
ppm
10
20
30
40
50
60
70
80
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


HO
O
H
CO2Me
1-47
HMBC, 600 MHz
CDCl3
ppm
10
20
30
40
50
60
70
80
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

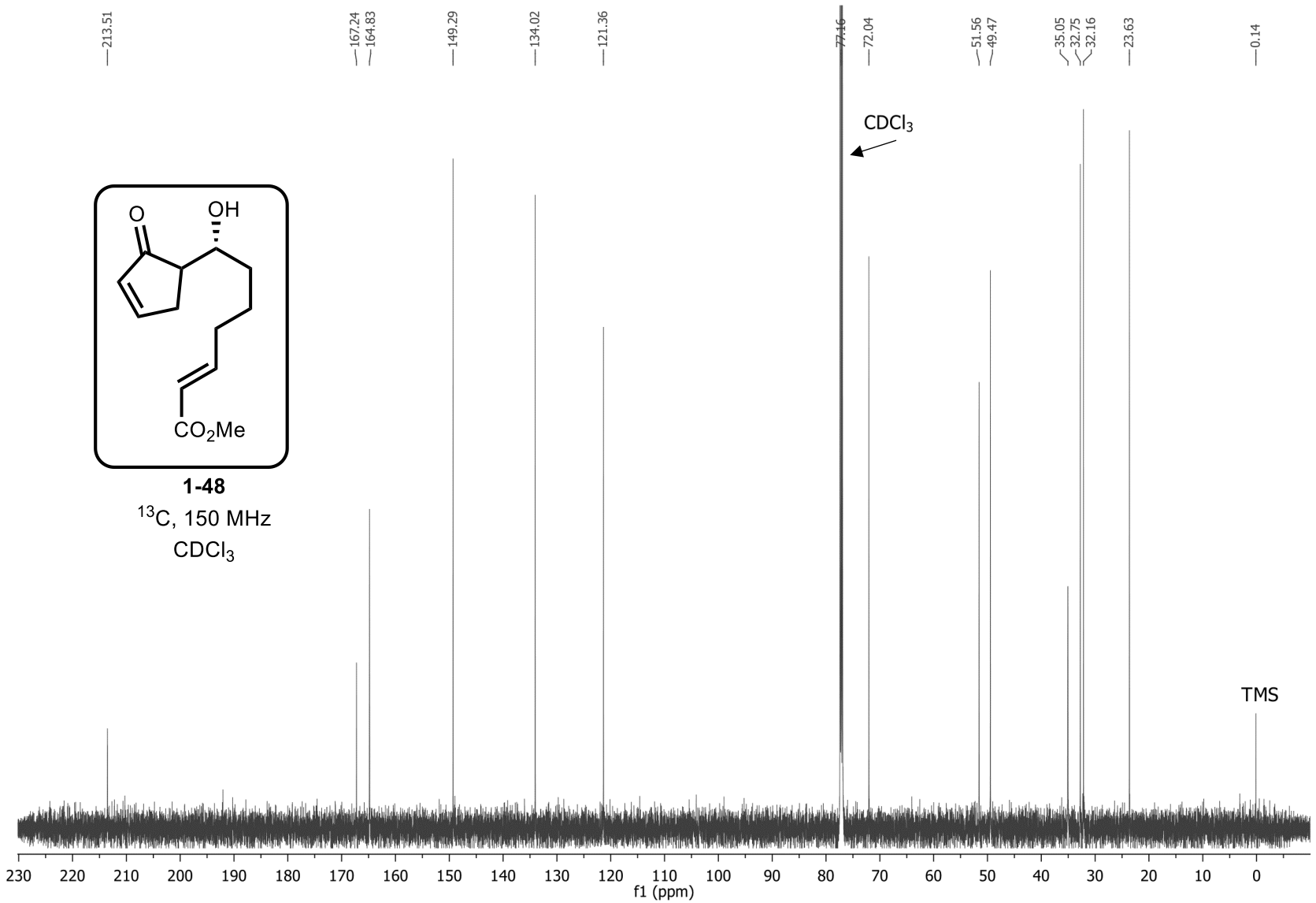

B
A
D
C
H
H
O
OH
H
H
CO2Me
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
HO
O
H
CO2Me
1-47
NOESY, 600 MHz
CDCl3

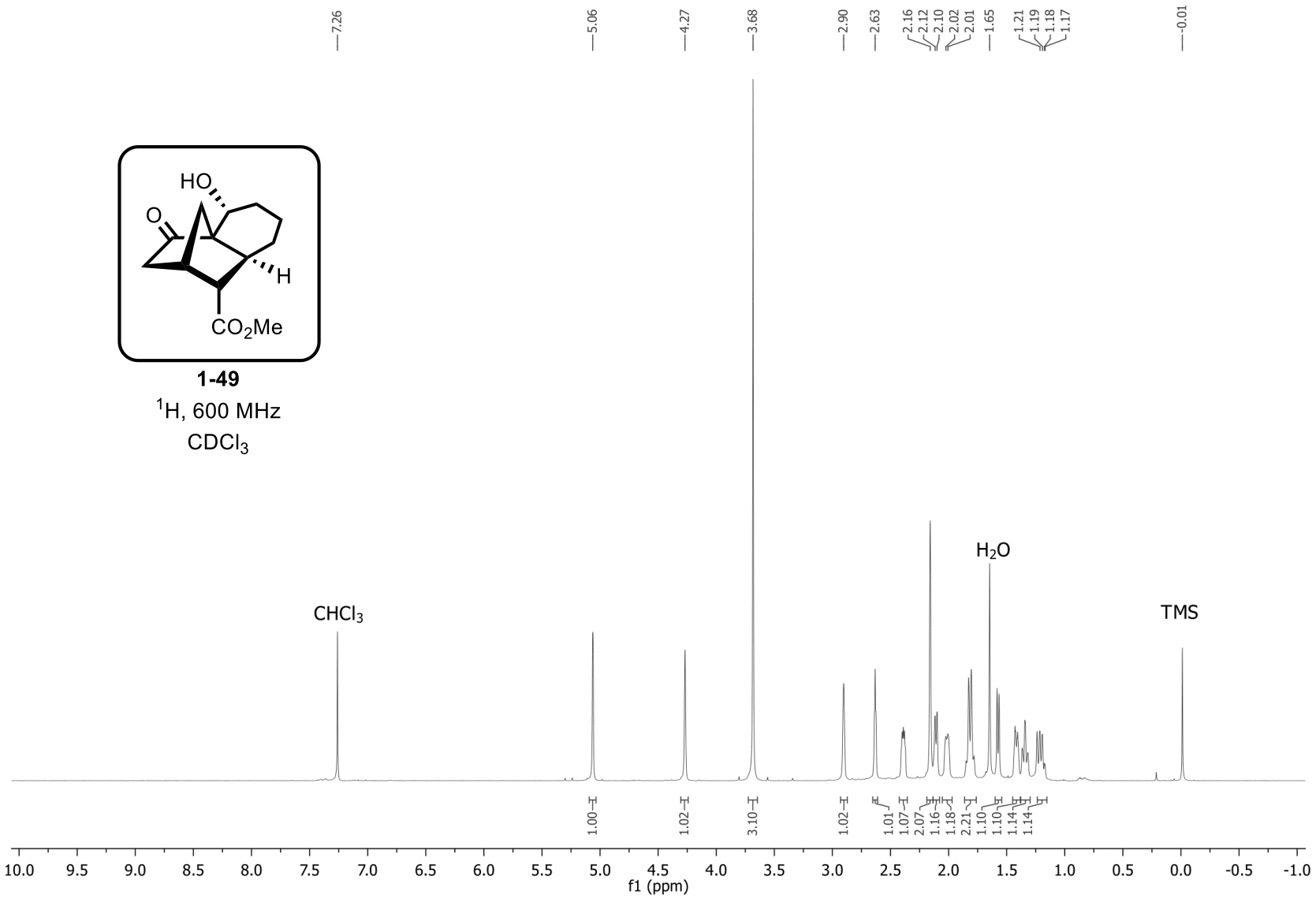


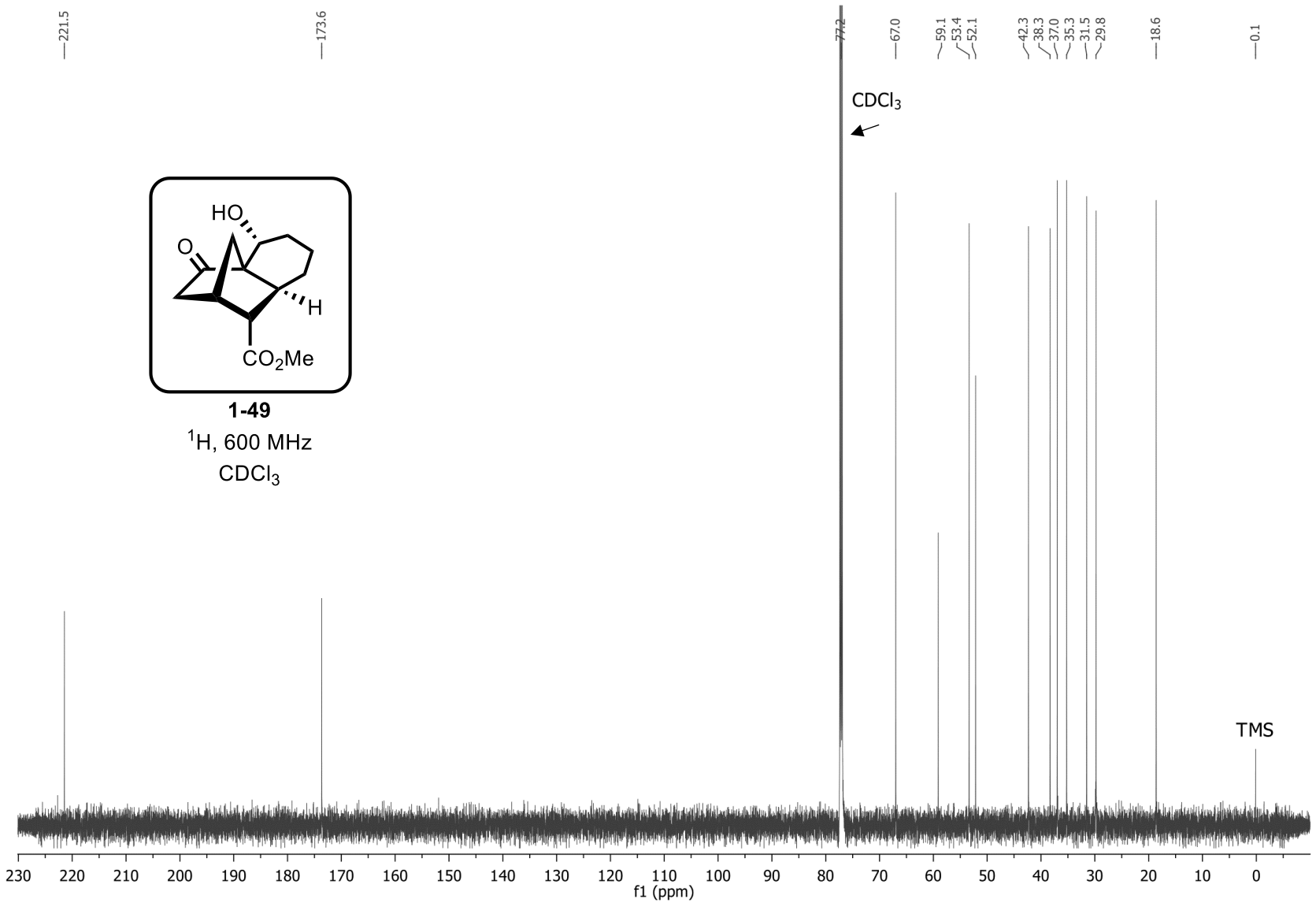
1-48

^{1}H, 600 MHz

$CDCl_3$


213.51
167.24
164.83
149.29
134.02
121.36
77.16
72.04
51.56
49.47
35.05
32.75
32.16
23.63
0.14
CDCl3
TMS
O
OH
CO2Me
1-48
13C, 150 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

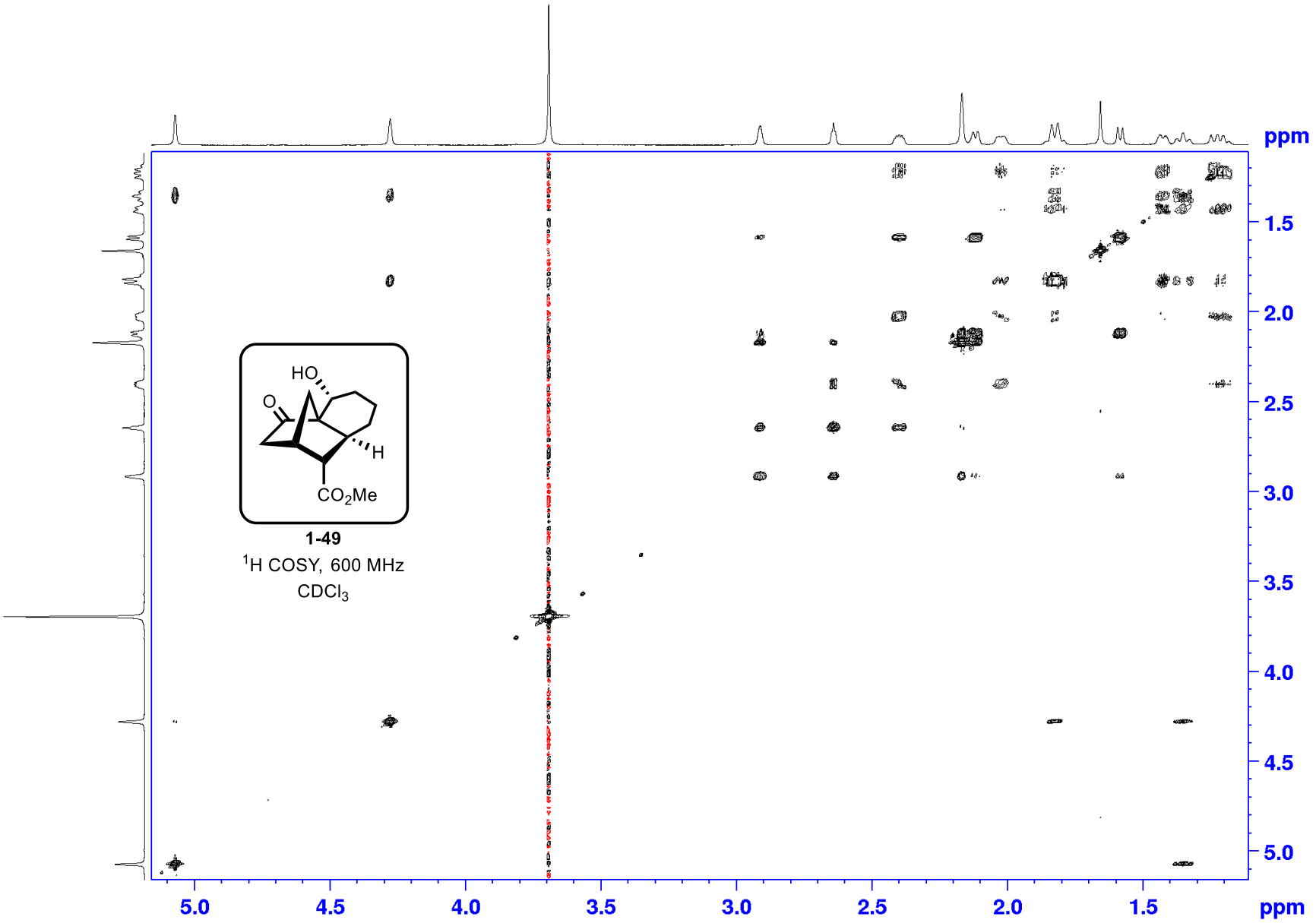

7.26
5.06
4.27
3.68
2.90
2.63
2.16
2.12
2.10
2.02
2.01
1.65
1.21
1.19
1.18
1.17
-0.01
HO
O
H
CO2Me
1-49
1H, 600 MHz
CDCl3
CHCl3
H2O
TMS
1.00
1.02
3.10
1.02
1.01
1.07
2.07
1.16
1.18
2.21
1.10
1.10
1.14
1.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

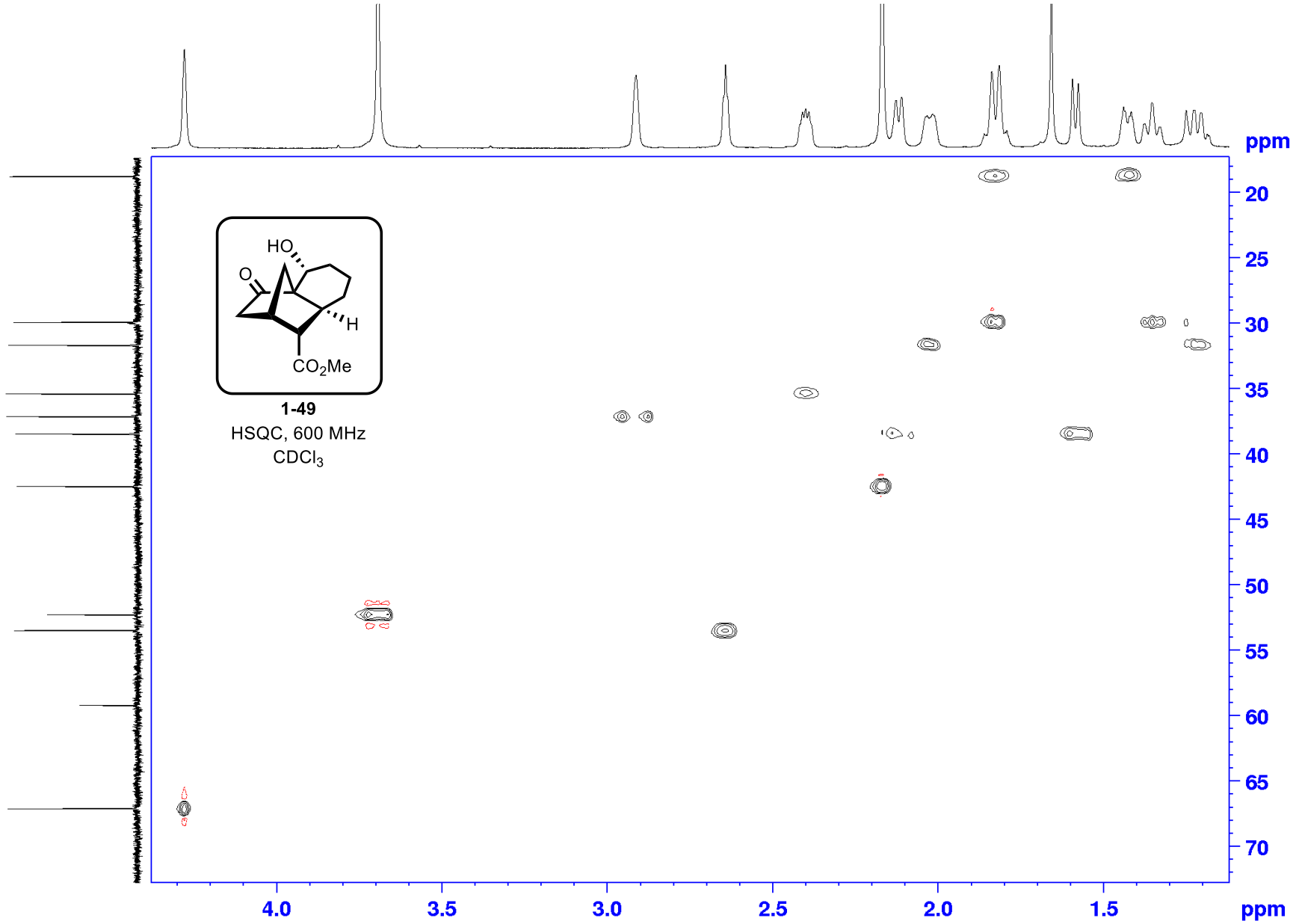


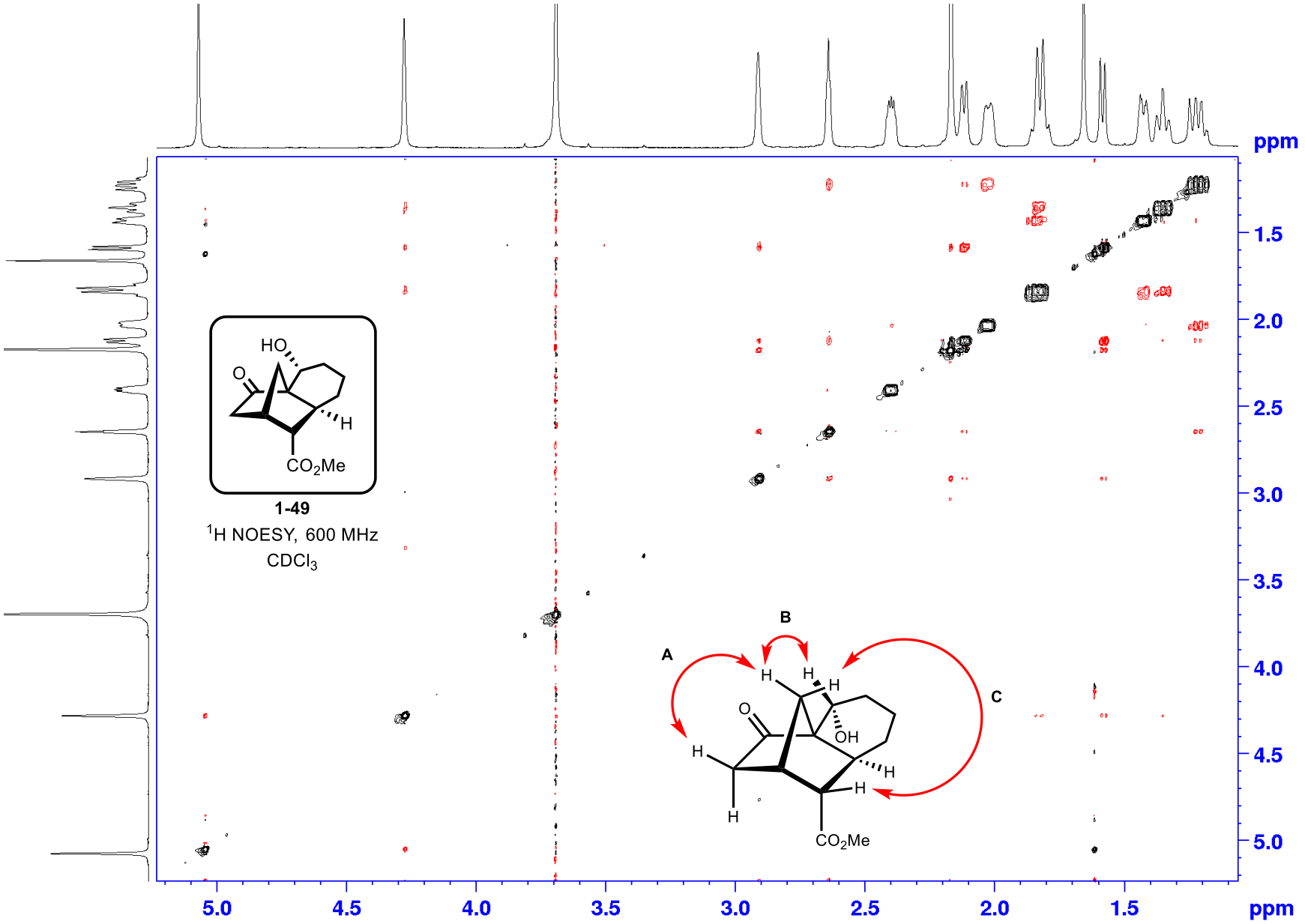
1-49

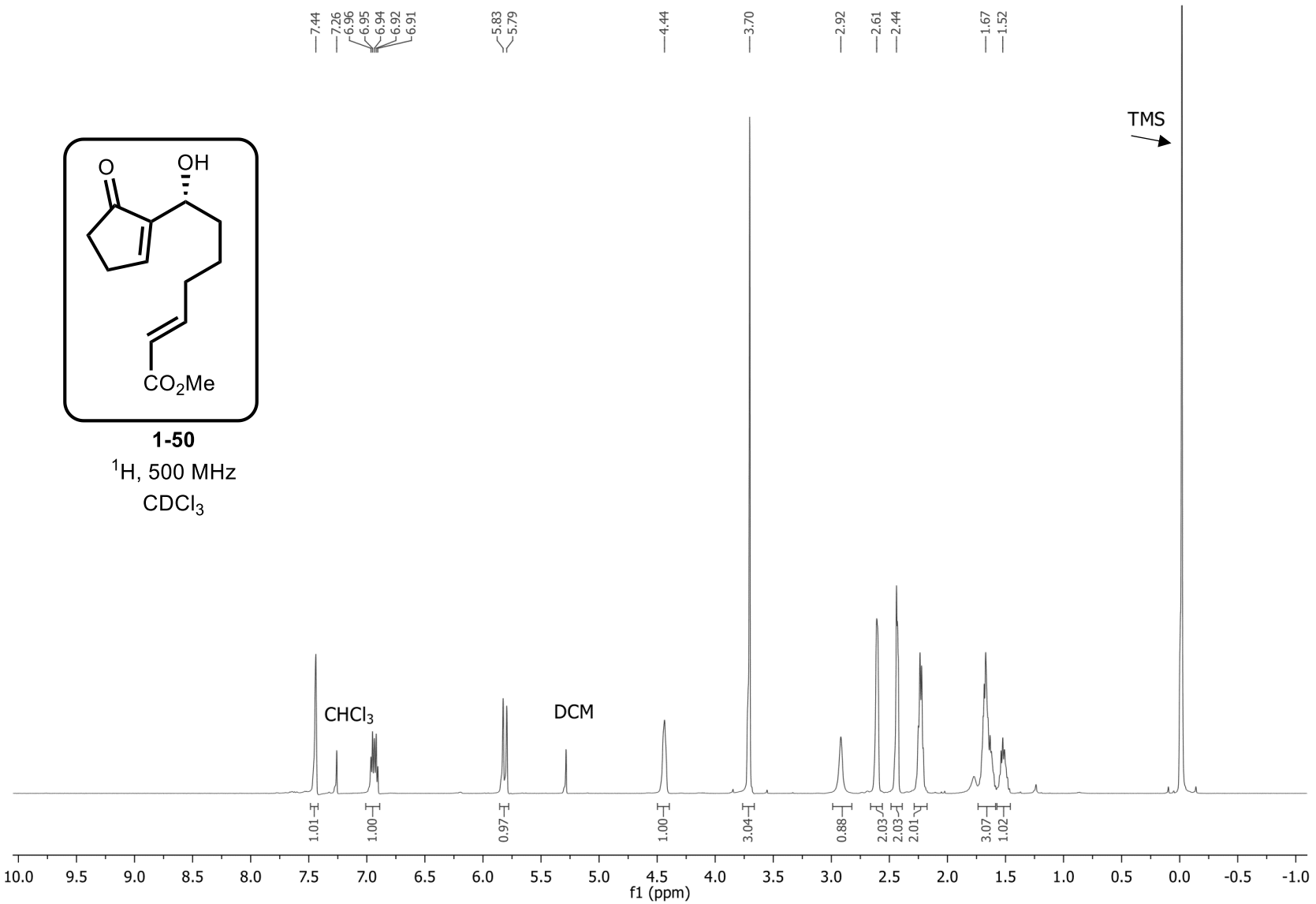
^{1}H, 600 MHz

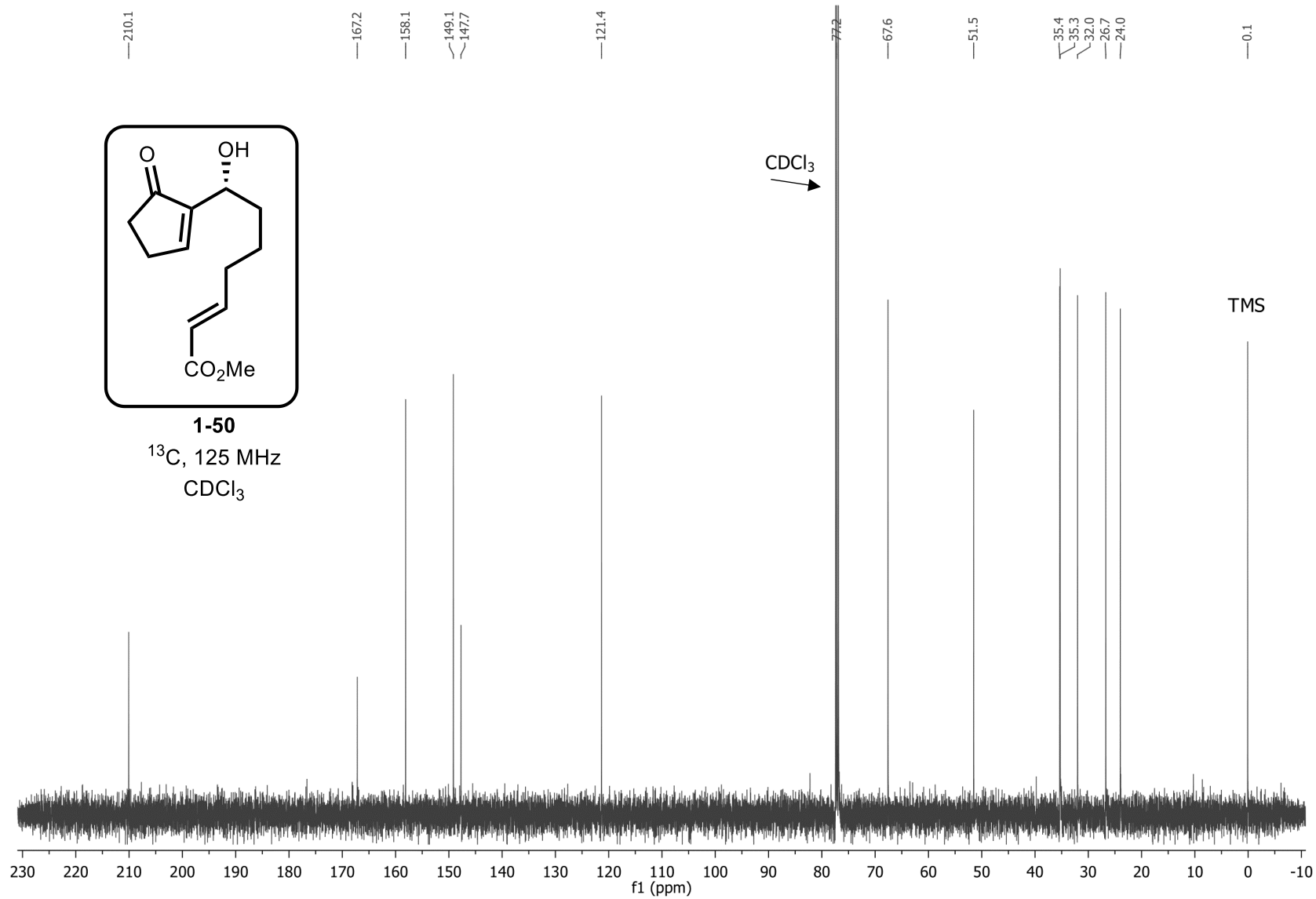
$CDCl_3$

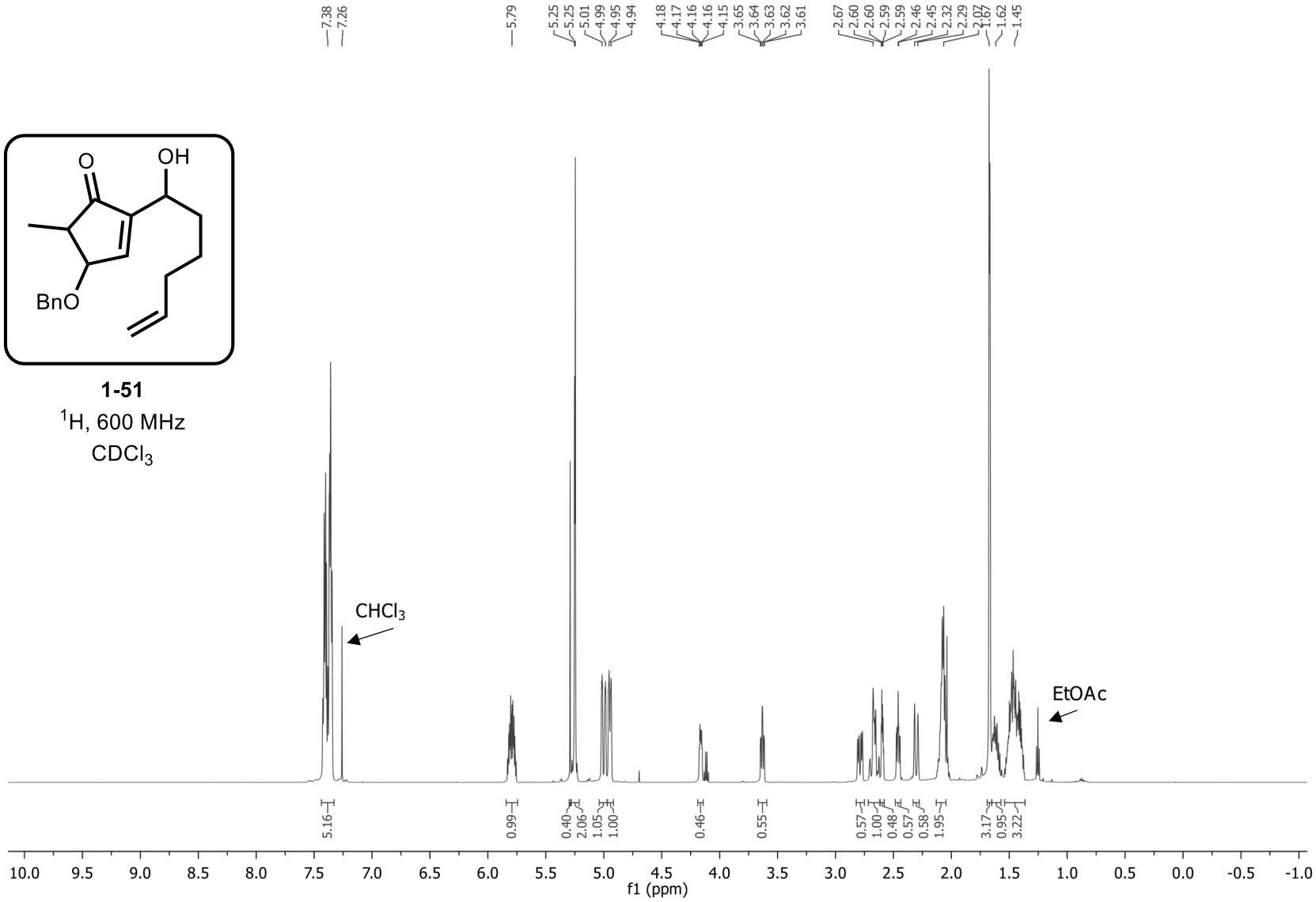

HO
O
H
CO2Me
1-49
1H COSY, 600 MHz
CDCl3
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

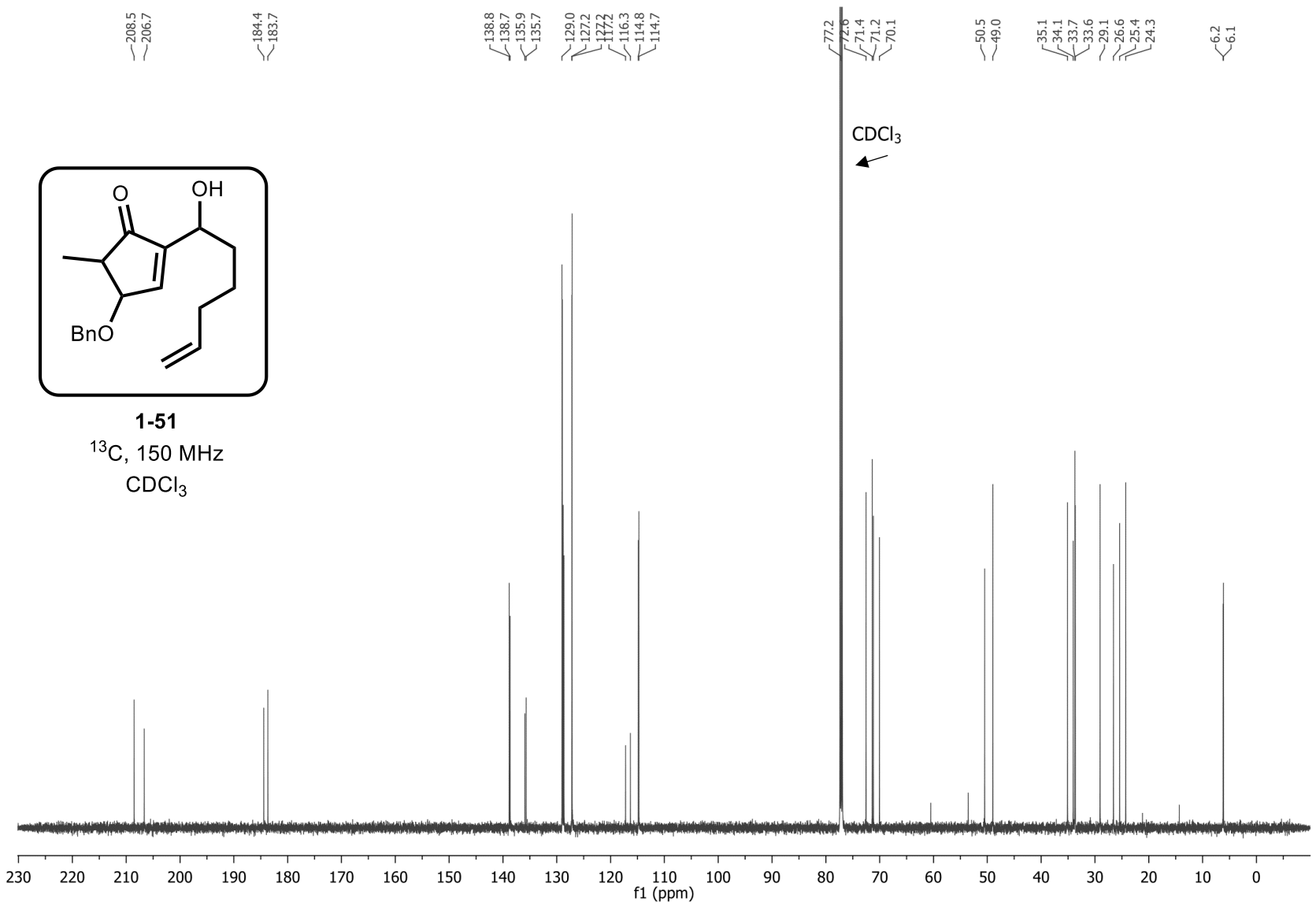

HO
O
H
CO2Me
1-49
HSQC, 600 MHz
CDCl3
ppm
20
25
30
35
40
45
50
55
60
65
70
4.0
3.5
3.0
2.5
2.0
1.5
ppm


HO
O
H
CO2Me
1-49
1H NOESY, 600 MHz
CDCl3
A
B
C
H
H
H
O
OH
H
H
H
H
CO2Me
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


7.44
7.26
6.96
6.95
6.94
6.92
6.91
5.83
5.79
4.44
3.70
2.92
2.61
2.44
1.67
1.52
TMS
O
OH
CO2Me
1-50
1H, 500 MHz
CDCl3
CHCl3
DCM
1.01
1.00
0.97
1.00
3.04
0.88
2.03
2.03
2.01
3.07
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


210.1
167.2
158.1
149.1
147.7
121.4
77.2
67.6
51.5
35.4
35.3
32.0
26.7
24.0
0.1
O
OH
CO2Me
CDCl3
TMS
1-50
13C, 125 MHz
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

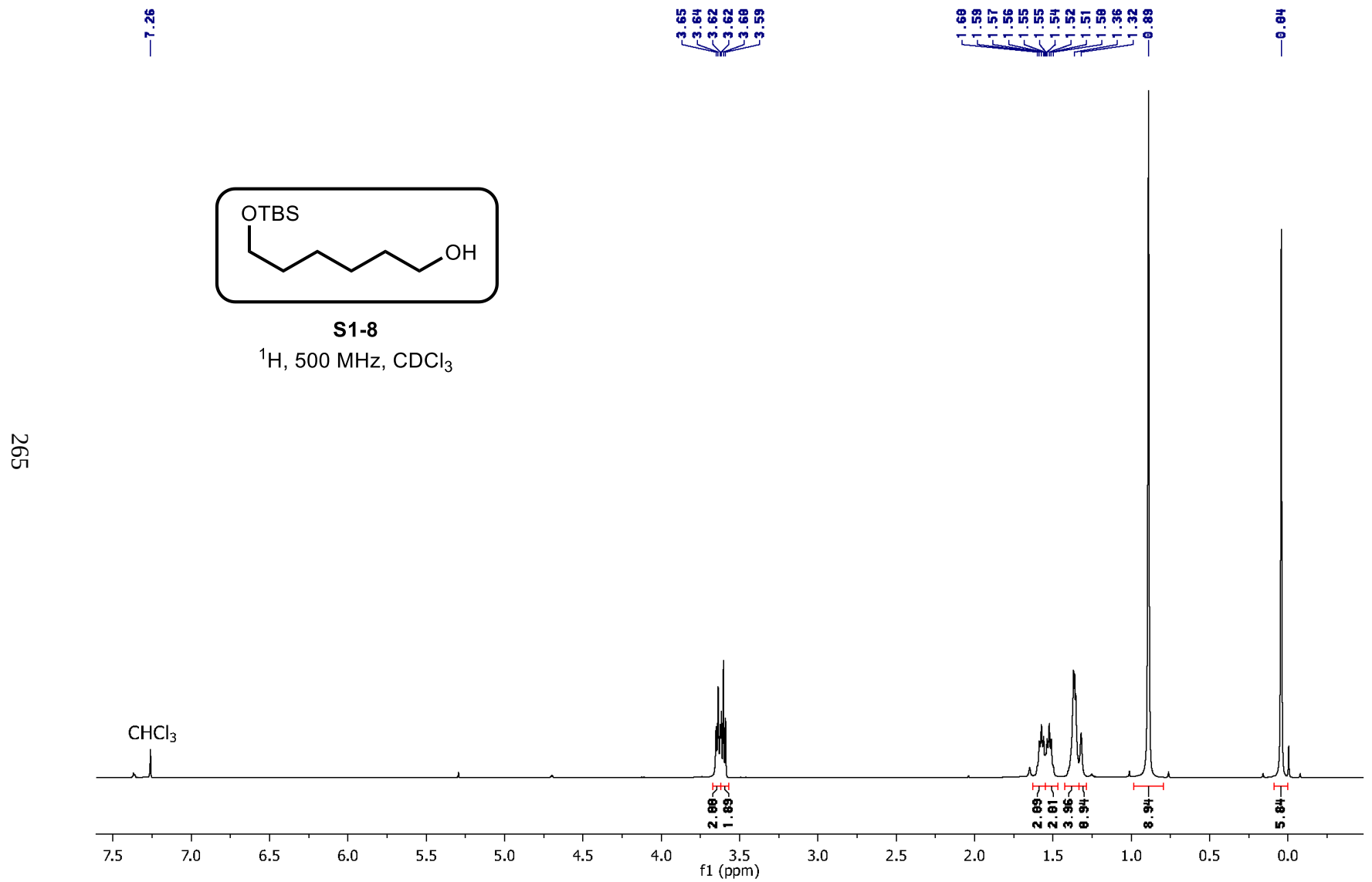

O
OH
BnO
1-51
1H, 600 MHz
CDCl3
7.38
7.26
5.79
5.25
5.25
5.01
4.99
4.95
4.94
4.18
4.17
4.16
4.16
4.15
3.65
3.64
3.63
3.62
3.61
2.67
2.60
2.60
2.59
2.59
2.46
2.45
2.32
2.29
2.07
1.67
1.62
1.45
CHCl3
EtOAc
5.16
0.99
0.40
2.06
1.05
1.00
0.46
0.55
0.57
1.00
0.48
0.57
0.58
1.95
3.17
0.95
3.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

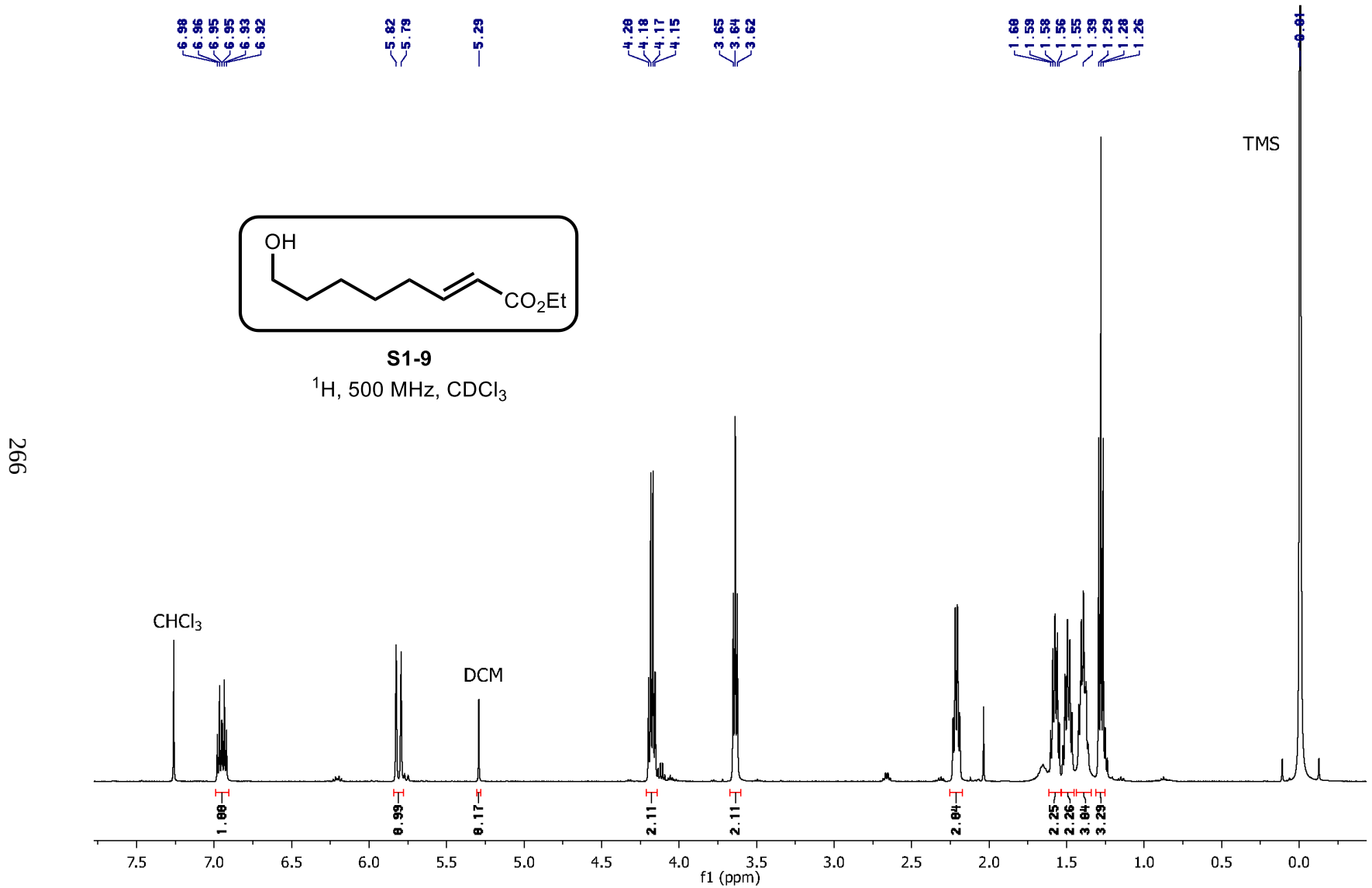


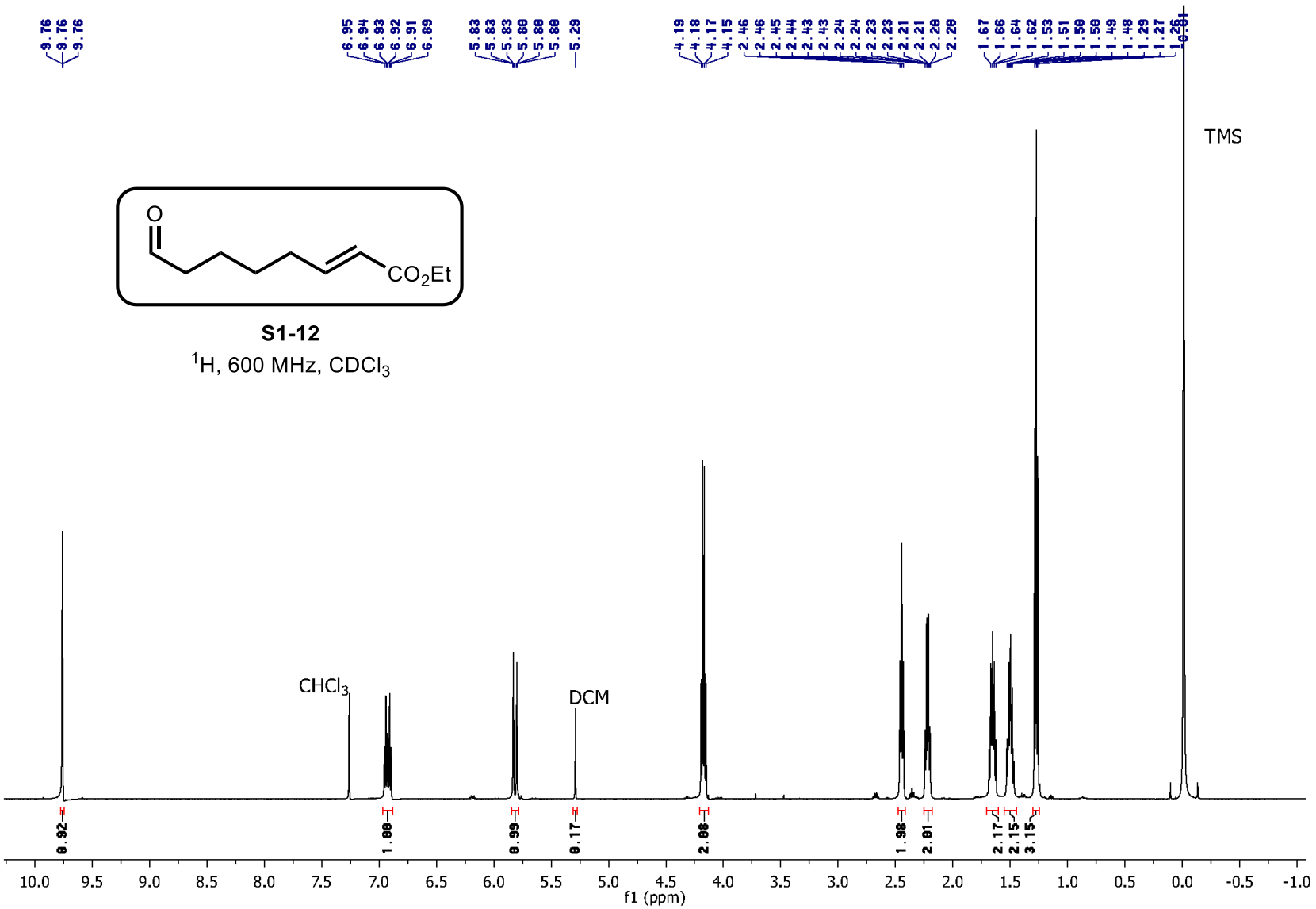
1-51

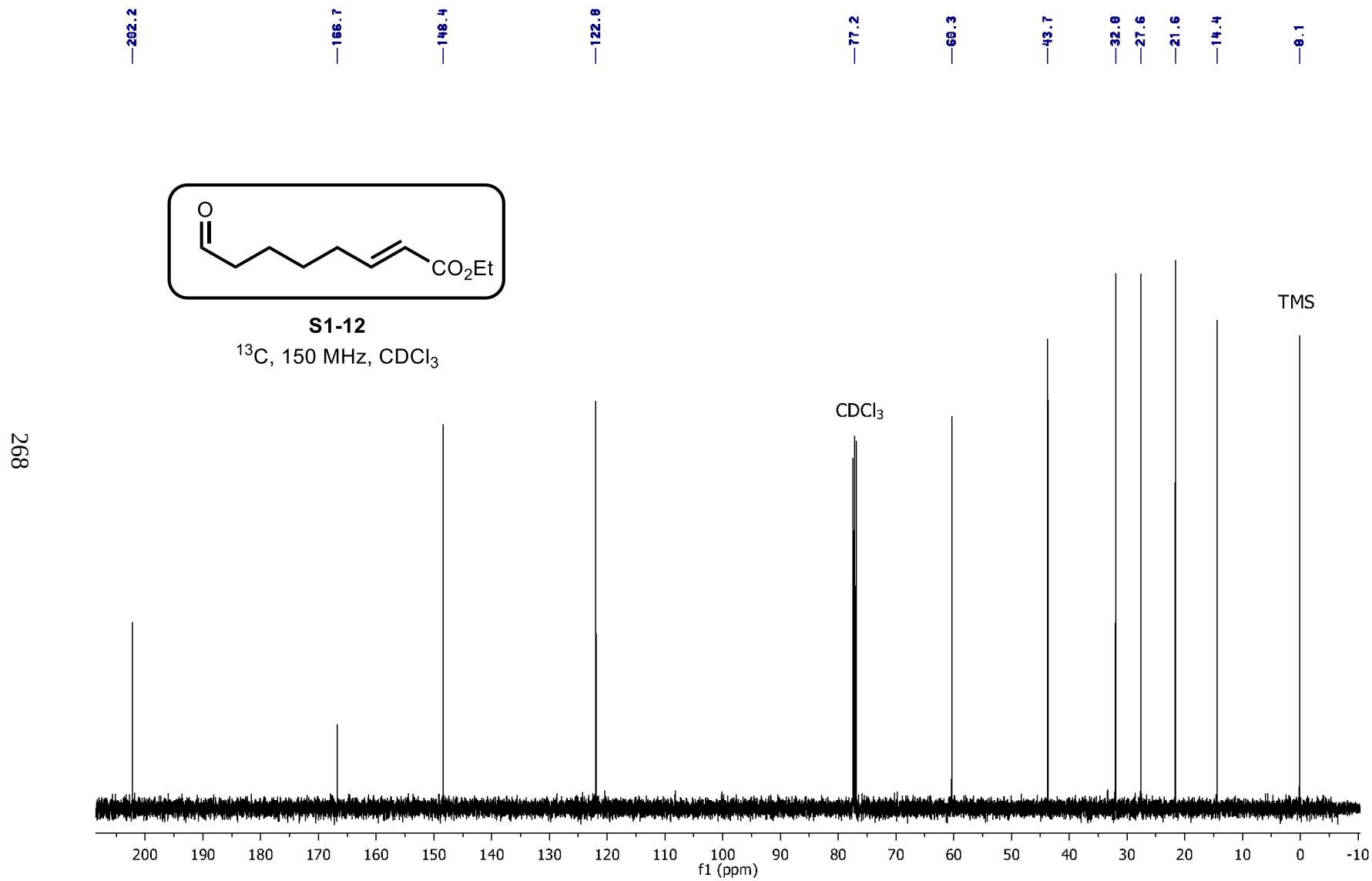
^{13}C, 150 MHz

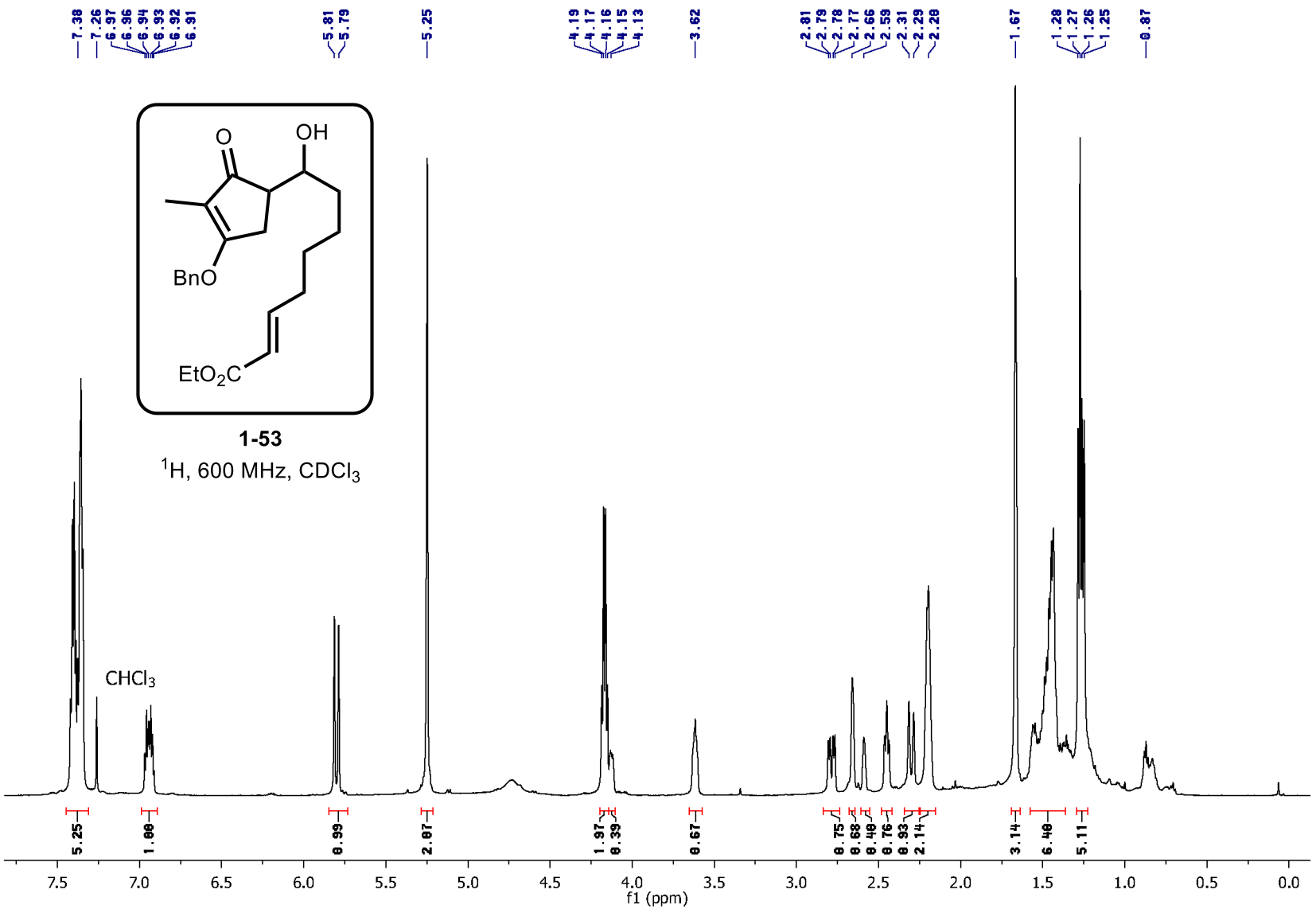
$CDCl_3$

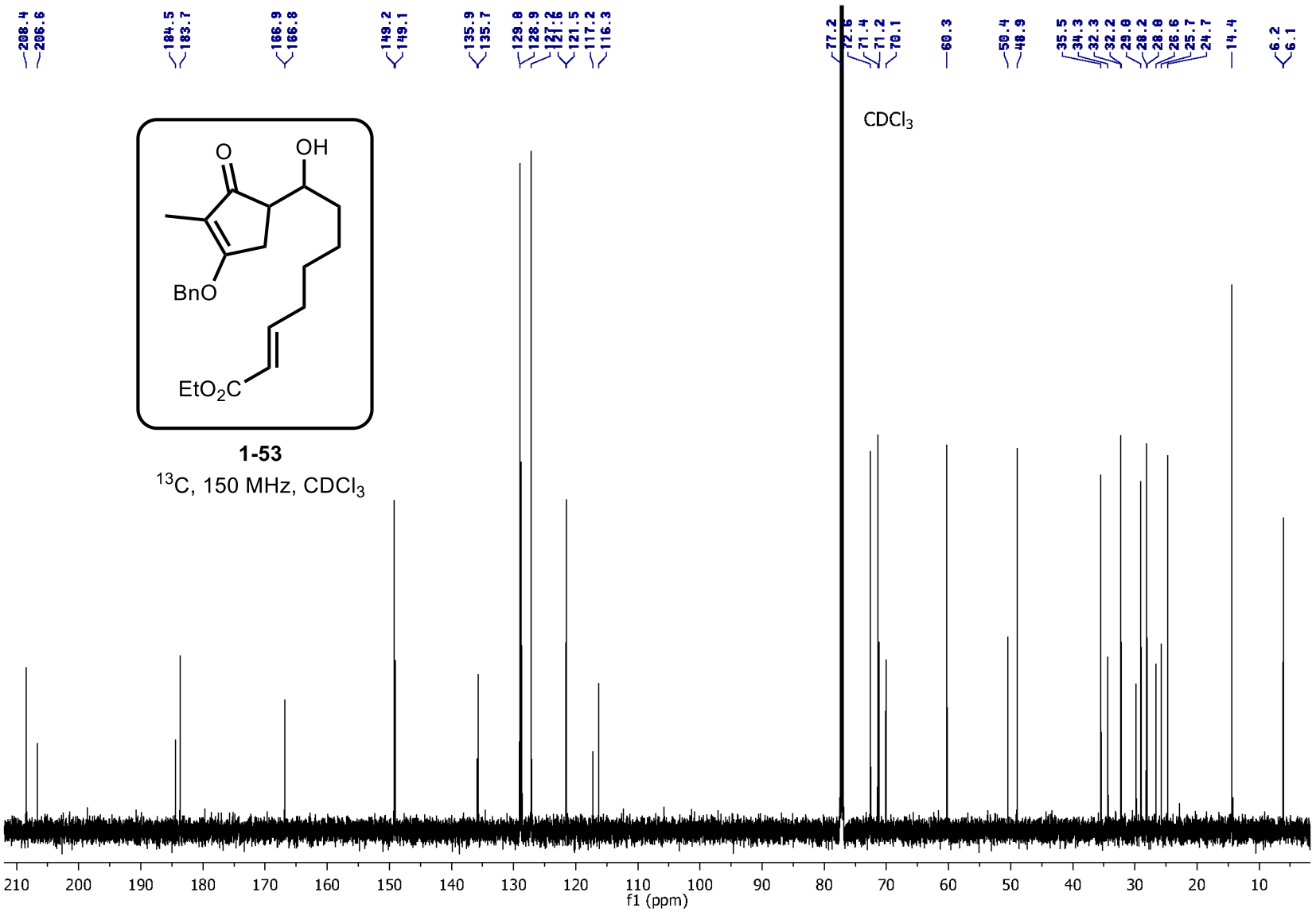

7.26
3.65
3.64
3.62
3.62
3.60
3.59
1.60
1.59
1.57
1.56
1.55
1.55
1.54
1.52
1.51
1.50
1.36
1.32
0.89
0.04
OTBS
OH
S1-8
1H, 500 MHz, CDCl3
CHCl3
2.00
1.89
2.09
2.01
3.96
0.94
8.94
5.84
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

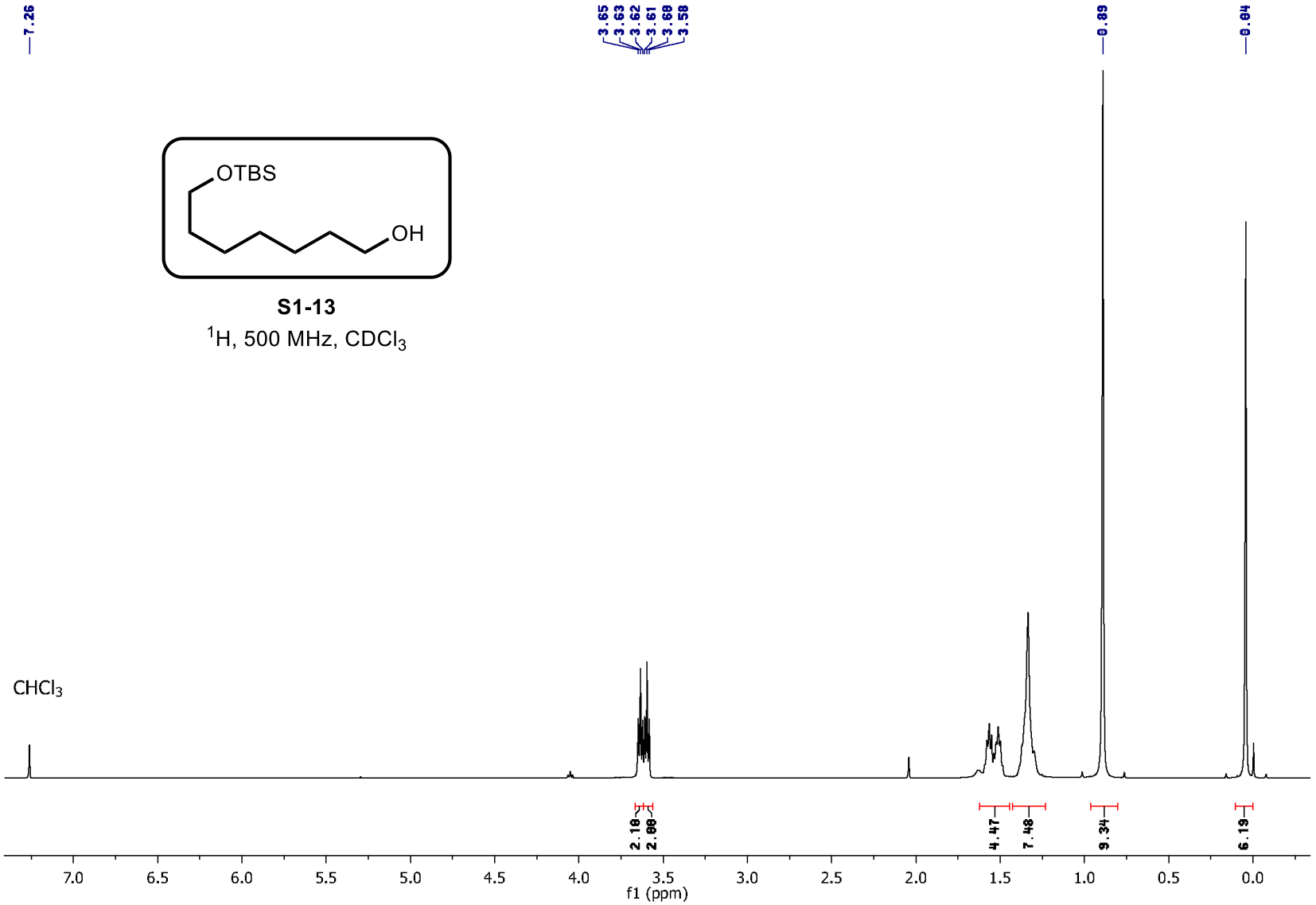

6.98
6.96
6.95
6.95
6.93
6.92
5.82
5.79
5.29
4.20
4.18
4.17
4.15
3.65
3.64
3.62
1.60
1.59
1.58
1.56
1.55
1.39
1.29
1.28
1.26
0.01
TMS
OH
CO2Et
S1-9
1H, 500 MHz, CDCl3
CHCl3
DCM
1.00
0.99
0.17
2.11
2.11
2.04
2.25
2.26
3.04
3.29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

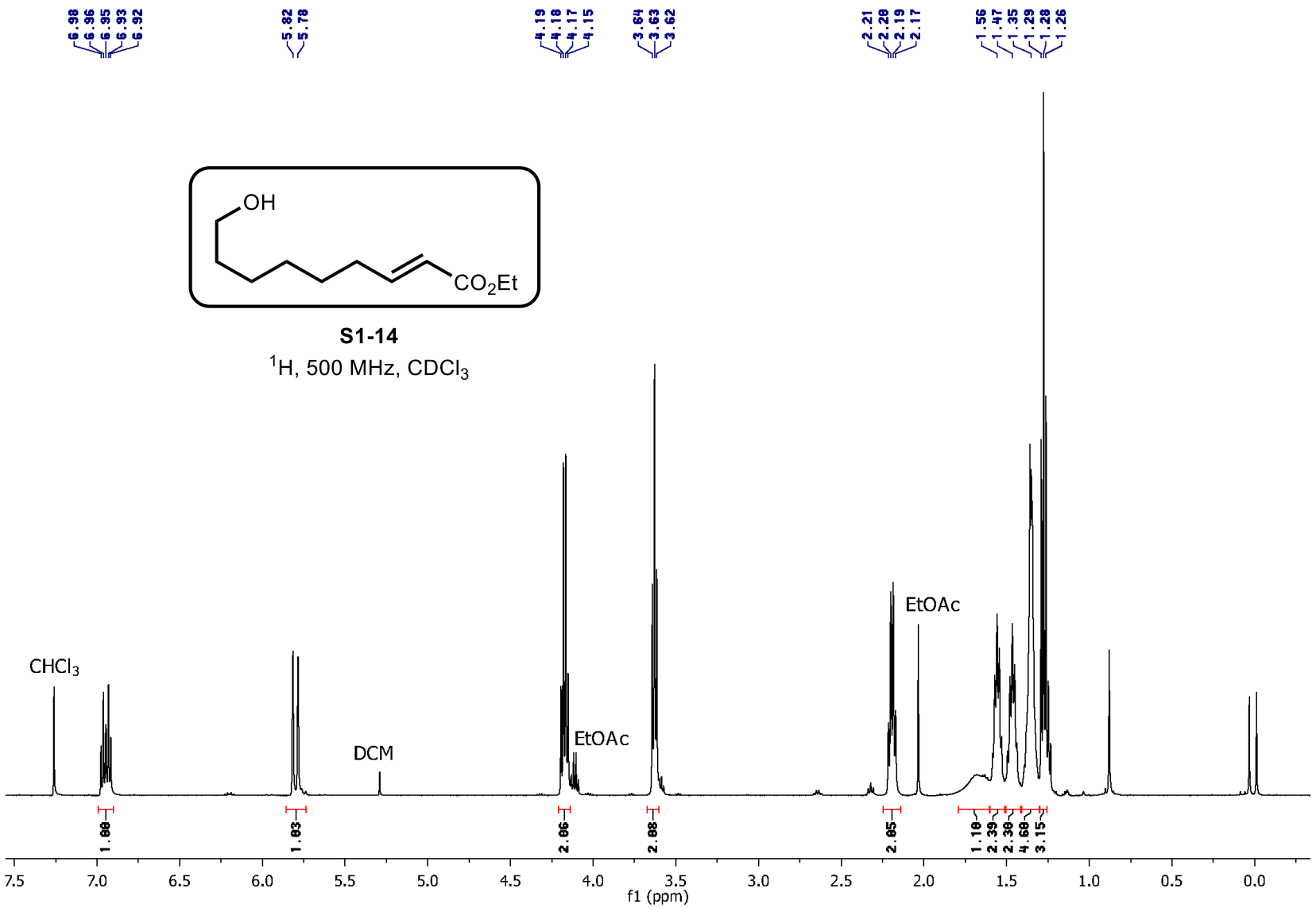

9.76
9.76
9.76
6.95
6.94
6.93
6.92
6.91
6.89
5.83
5.83
5.83
5.80
5.80
5.80
5.29
4.19
4.18
4.17
4.15
2.46
2.46
2.45
2.44
2.43
2.43
2.24
2.24
2.23
2.23
2.21
2.21
2.20
2.20
1.67
1.66
1.64
1.62
1.53
1.51
1.50
1.50
1.49
1.48
1.29
1.27
1.26
0.00
TMS
O
CO2Et
S1-12
1H, 600 MHz, CDCl3
CHCl3
DCM
0.92
1.00
0.99
0.17
2.08
1.98
2.01
2.17
2.15
3.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

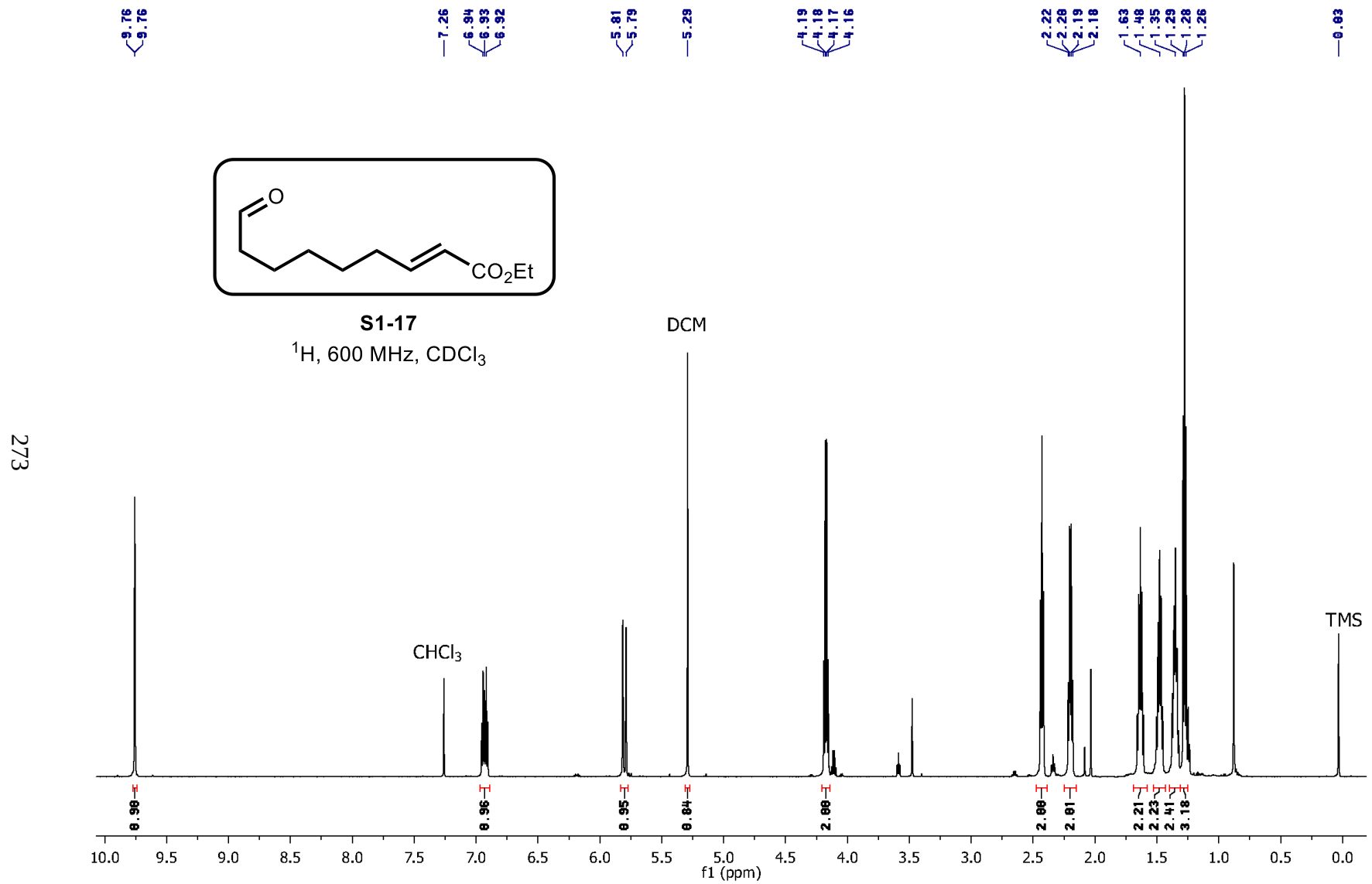

202.2
166.7
148.4
122.8
77.2
60.3
43.7
32.0
27.6
21.6
14.4
0.1
O
CO2Et
S1-12
13C, 150 MHz, CDCl3
CDCl3
TMS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

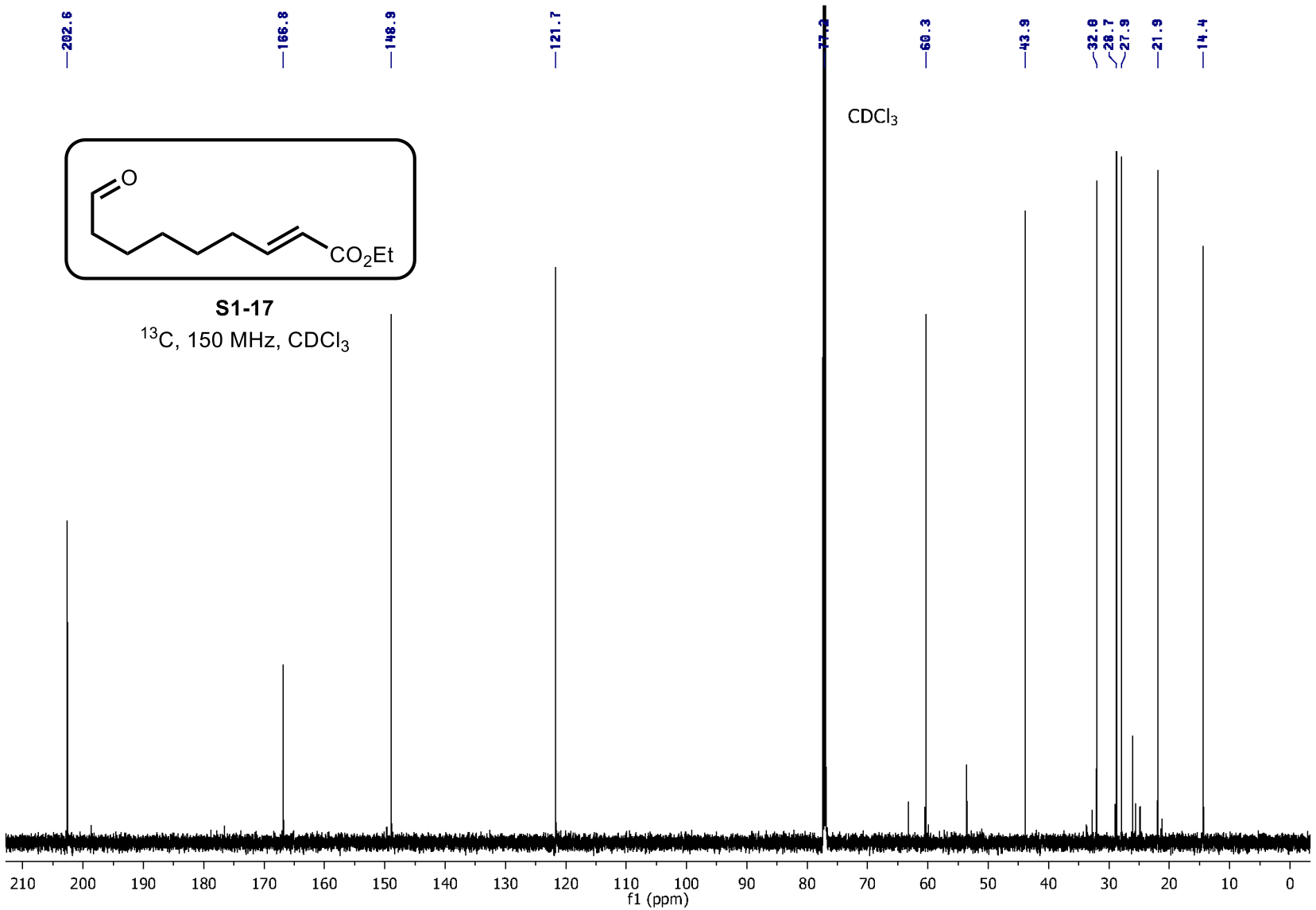

7.38
7.26
6.97
6.96
6.94
6.93
6.92
6.91
5.81
5.79
5.25
4.19
4.17
4.16
4.15
4.13
3.62
2.81
2.79
2.78
2.77
2.66
2.59
2.31
2.29
2.28
1.67
1.28
1.27
1.26
1.25
0.87
O
OH
BnO
EtO2C
1-53
1H, 600 MHz, CDCl3
CHCl3
5.25
1.00
0.99
2.07
1.97
0.39
0.67
0.75
0.68
0.40
0.76
0.93
2.14
3.14
6.40
5.11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

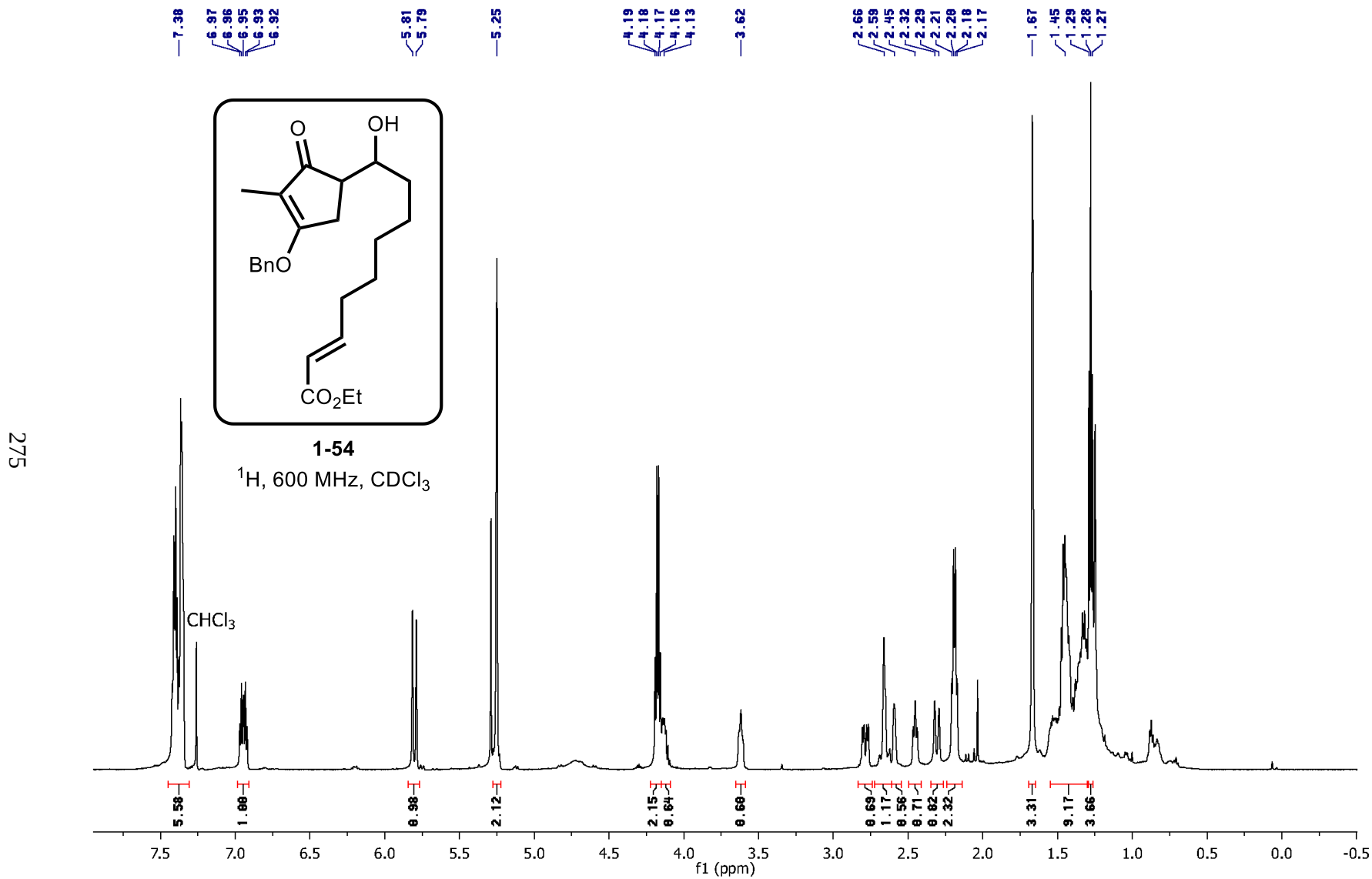

208.4
206.6
184.5
183.7
166.9
166.8
149.2
149.1
135.9
135.7
129.0
128.9
127.2
121.5
117.2
116.3
77.2
72.6
71.4
71.2
70.1
60.3
50.4
48.9
35.5
34.3
32.3
32.2
29.0
28.2
28.0
26.6
25.7
24.7
14.4
6.2
6.1
CDCl3
O
OH
BnO
EtO2C
1-53
13C, 150 MHz, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

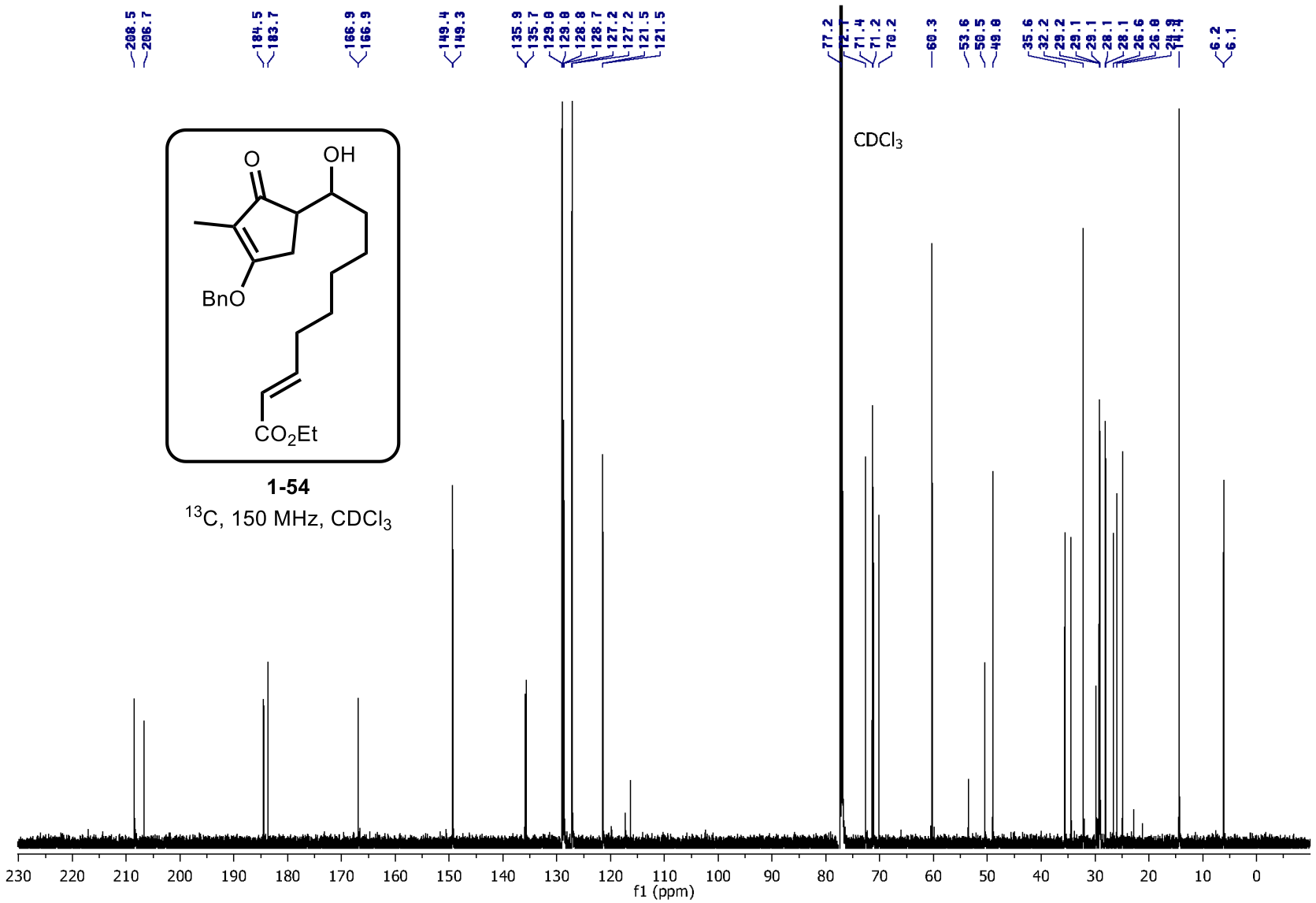

7.26
3.65
3.63
3.62
3.61
3.60
3.58
0.89
0.04
OTBS
OH
S1-13
1H, 500 MHz, CDCl3
CHCl3
2.18
2.00
4.47
7.48
9.34
6.19
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


6.98
6.96
6.95
6.93
6.92
5.82
5.78
4.19
4.18
4.17
4.15
3.64
3.63
3.62
2.21
2.20
2.19
2.17
1.56
1.47
1.35
1.29
1.28
1.26
OH
CO2Et
S1-14
1H, 500 MHz, CDCl3
CHCl3
DCM
EtOAc
EtOAc
1.00
1.03
2.06
2.08
2.85
1.18
2.39
2.30
4.68
3.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


9.76
9.76
7.26
6.94
6.93
6.92
5.81
5.79
5.29
4.19
4.18
4.17
4.16
2.22
2.20
2.19
2.18
1.63
1.48
1.35
1.29
1.28
1.26
0.03
O
CO2Et
S1-17
1H, 600 MHz, CDCl3
DCM
CHCl3
TMS
0.90
0.96
0.95
0.84
2.00
2.00
2.01
2.21
2.23
2.41
3.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

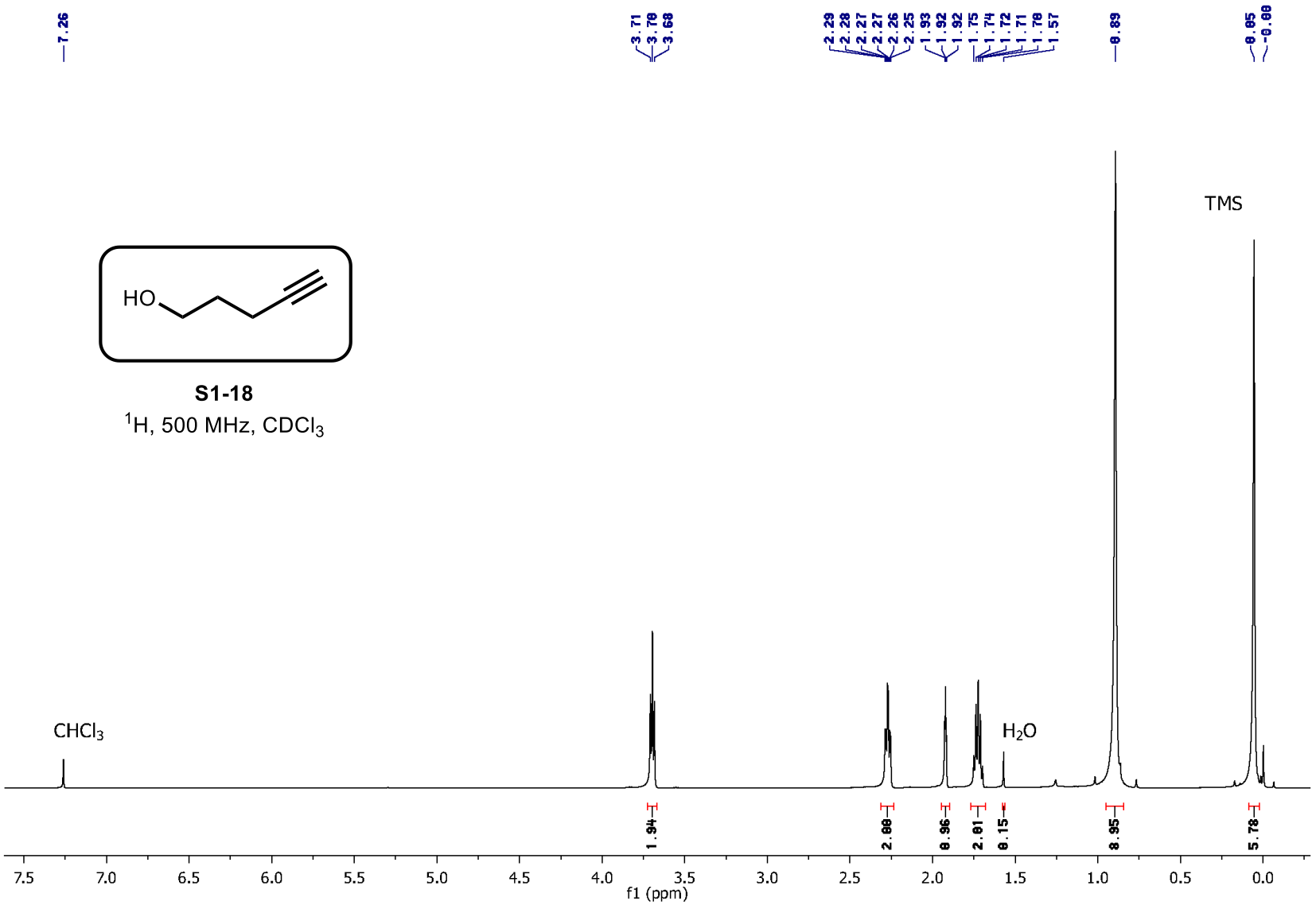

202.6
166.8
148.9
121.7
77.4
60.3
43.9
32.0
28.7
27.9
21.9
14.4
CDCl3
O
CO2Et
S1-17
13C, 150 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.38
6.97
6.96
6.95
6.93
6.92
5.81
5.79
5.25
4.19
4.18
4.17
4.16
4.13
3.62
2.66
2.59
2.45
2.32
2.29
2.21
2.20
2.18
2.17
1.67
1.45
1.29
1.28
1.27
O
OH
BnO
CO2Et
1-54
1H, 600 MHz, CDCl3
CHCl3
5.58
1.00
0.98
2.12
2.15
0.84
0.60
0.69
1.17
0.56
0.71
0.82
2.32
3.31
9.17
3.66
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



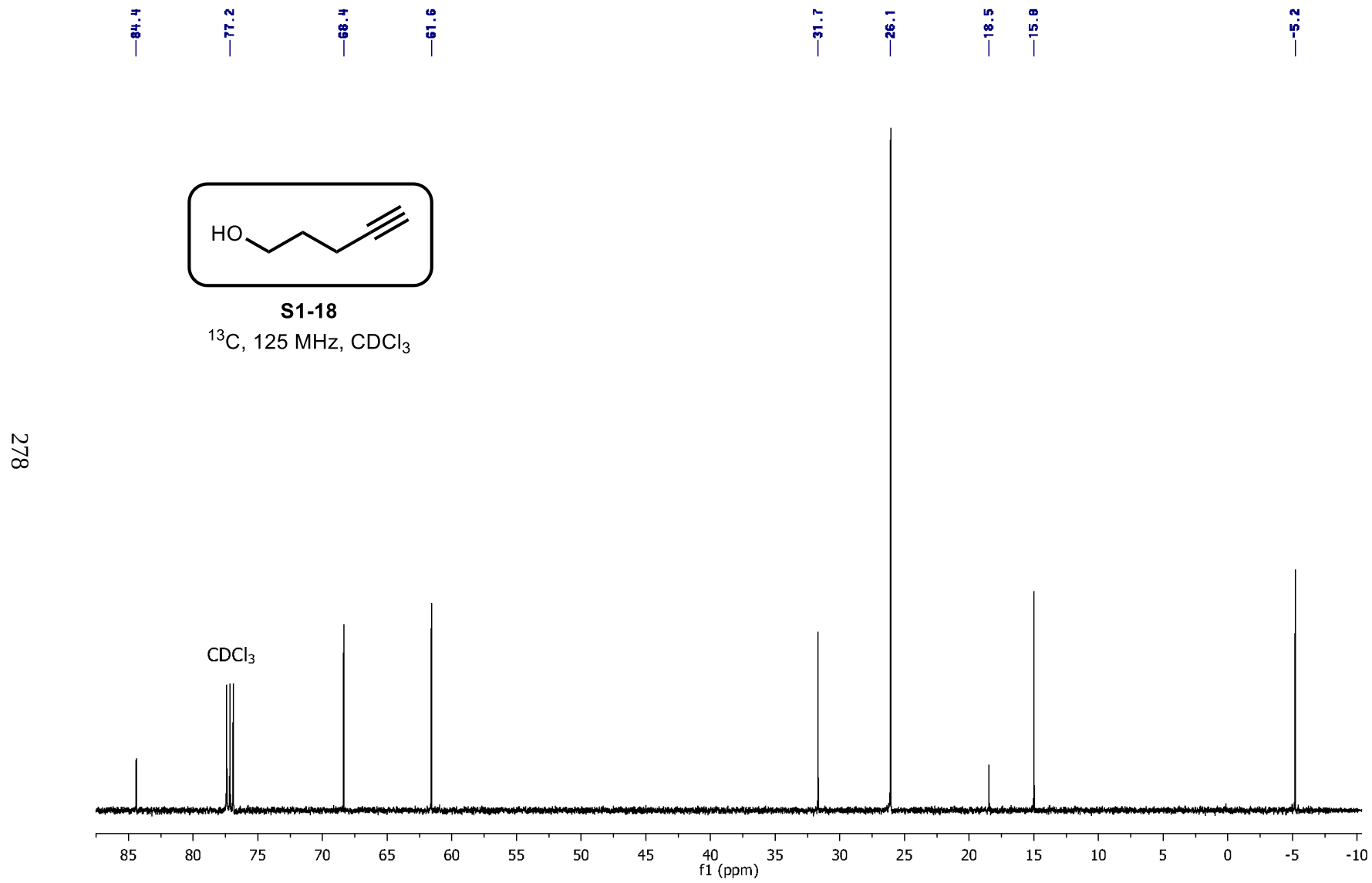
1-54

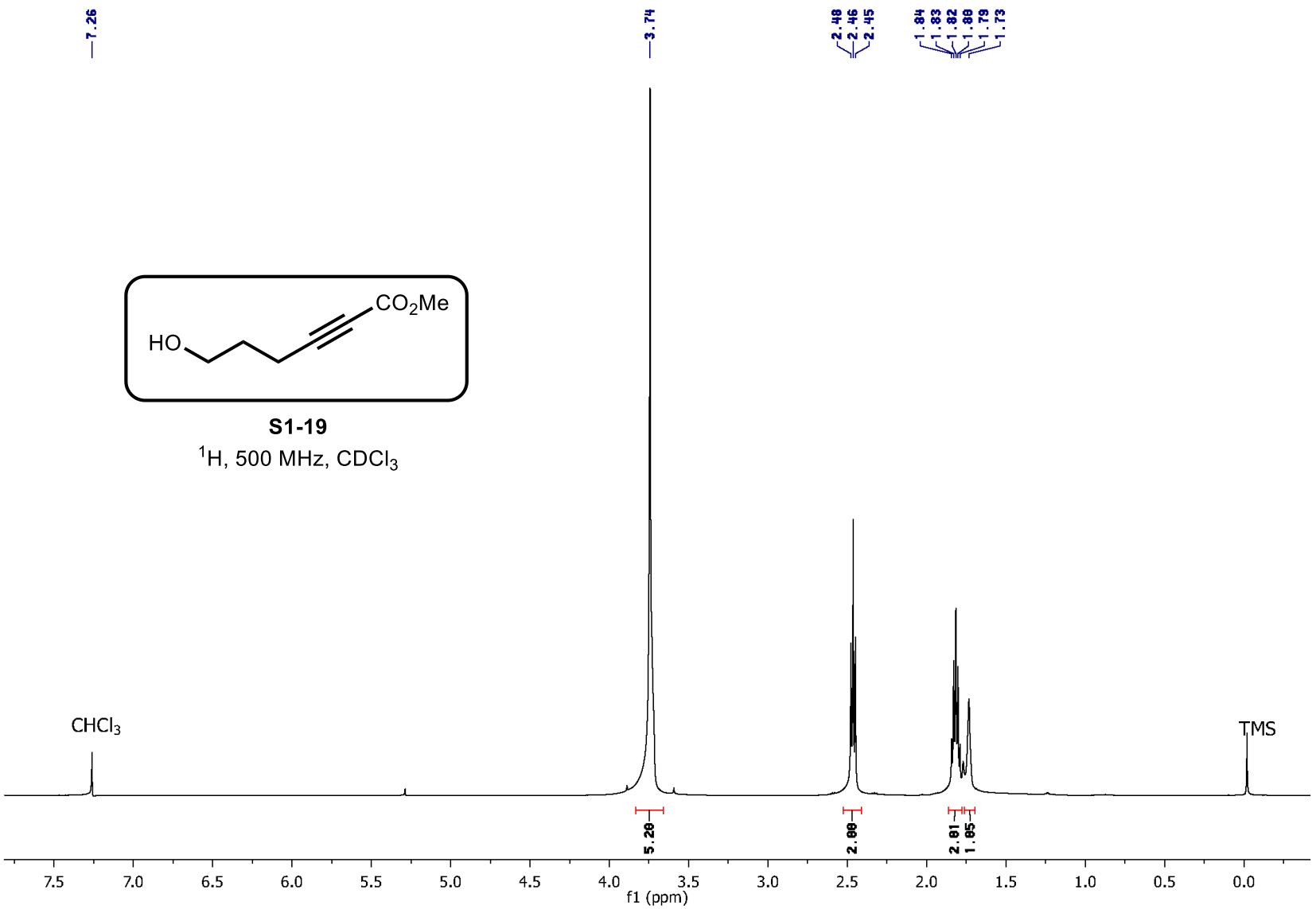
^{13}C, 150 MHz, $CDCl_3$

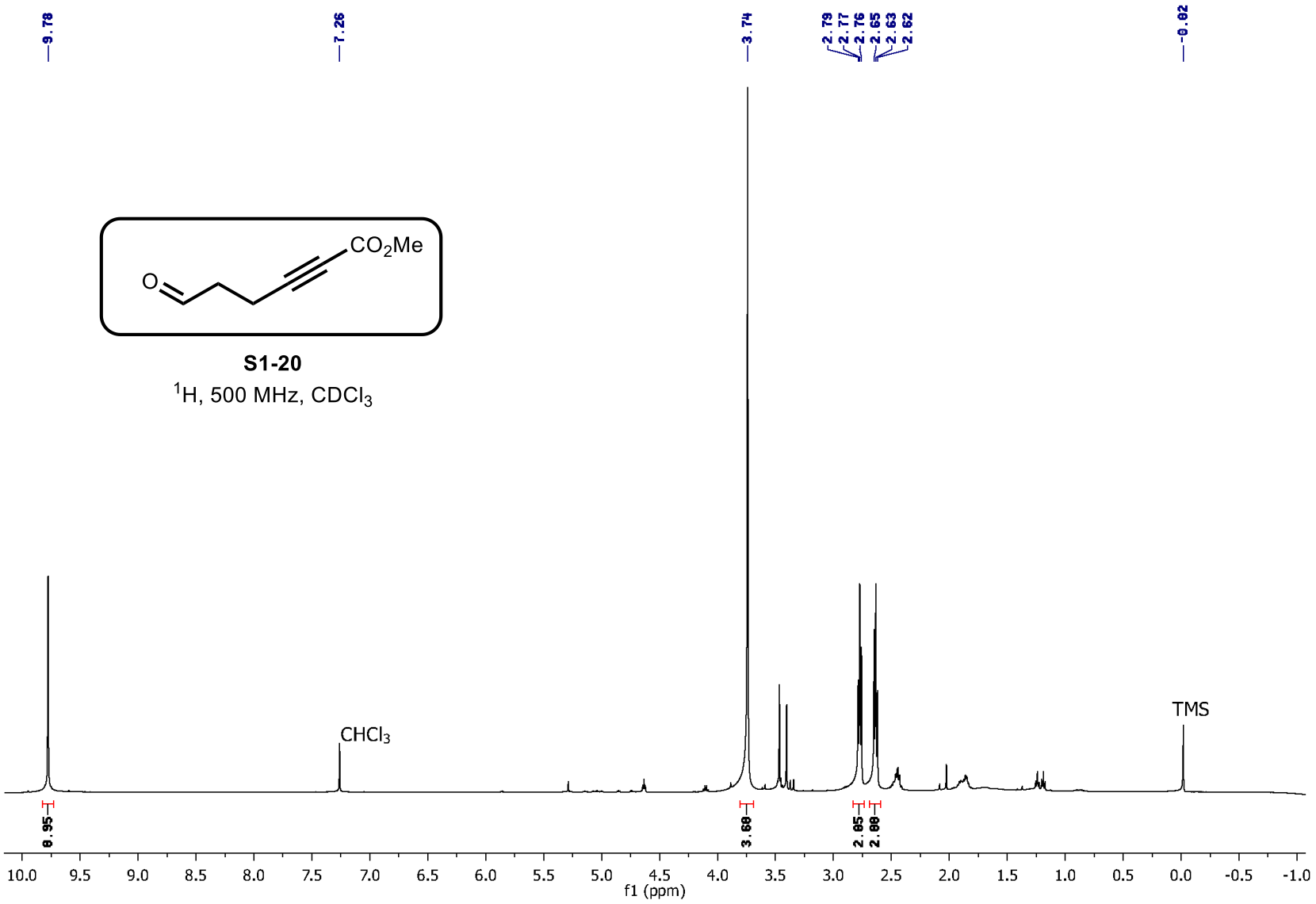


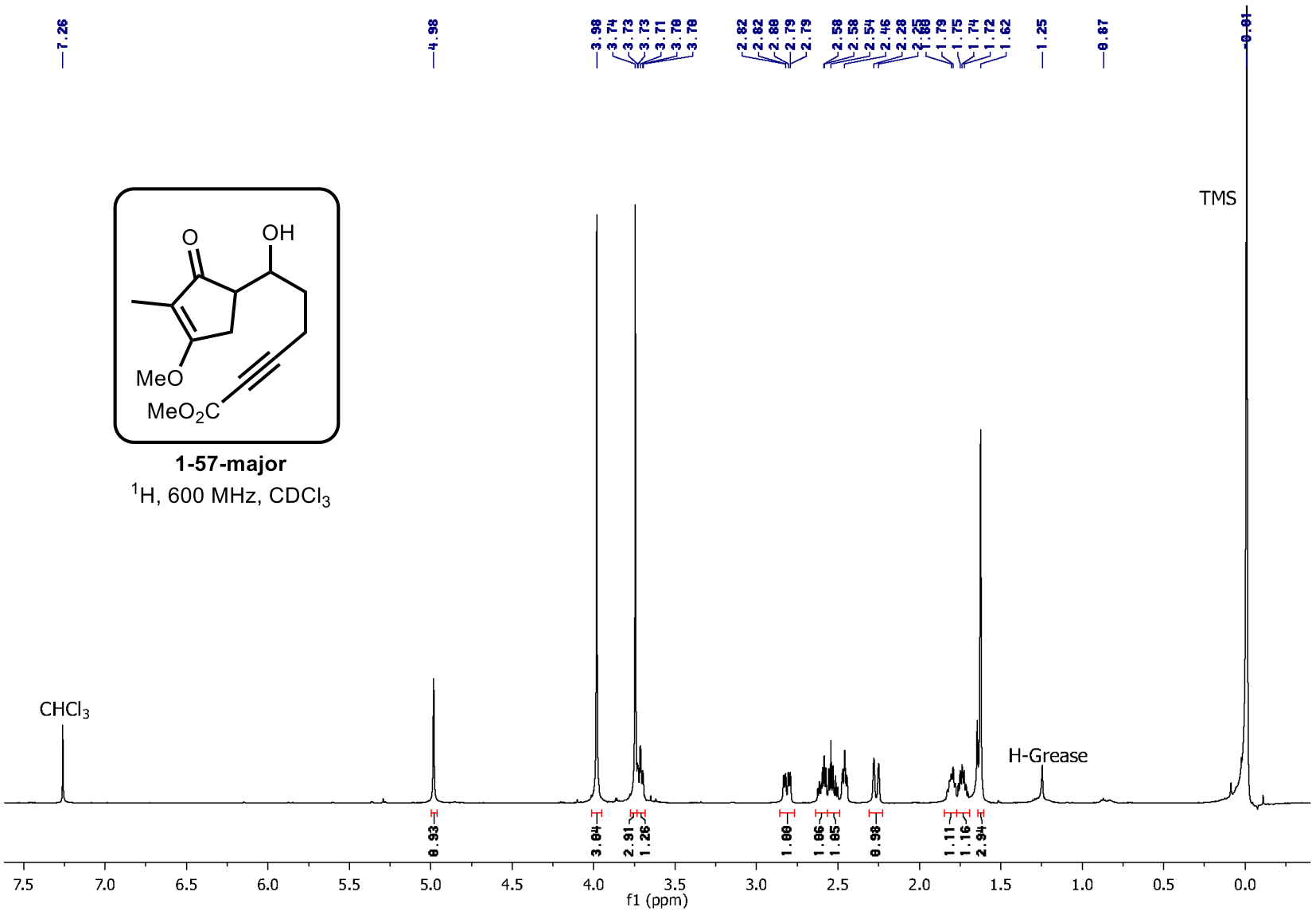
S1-18

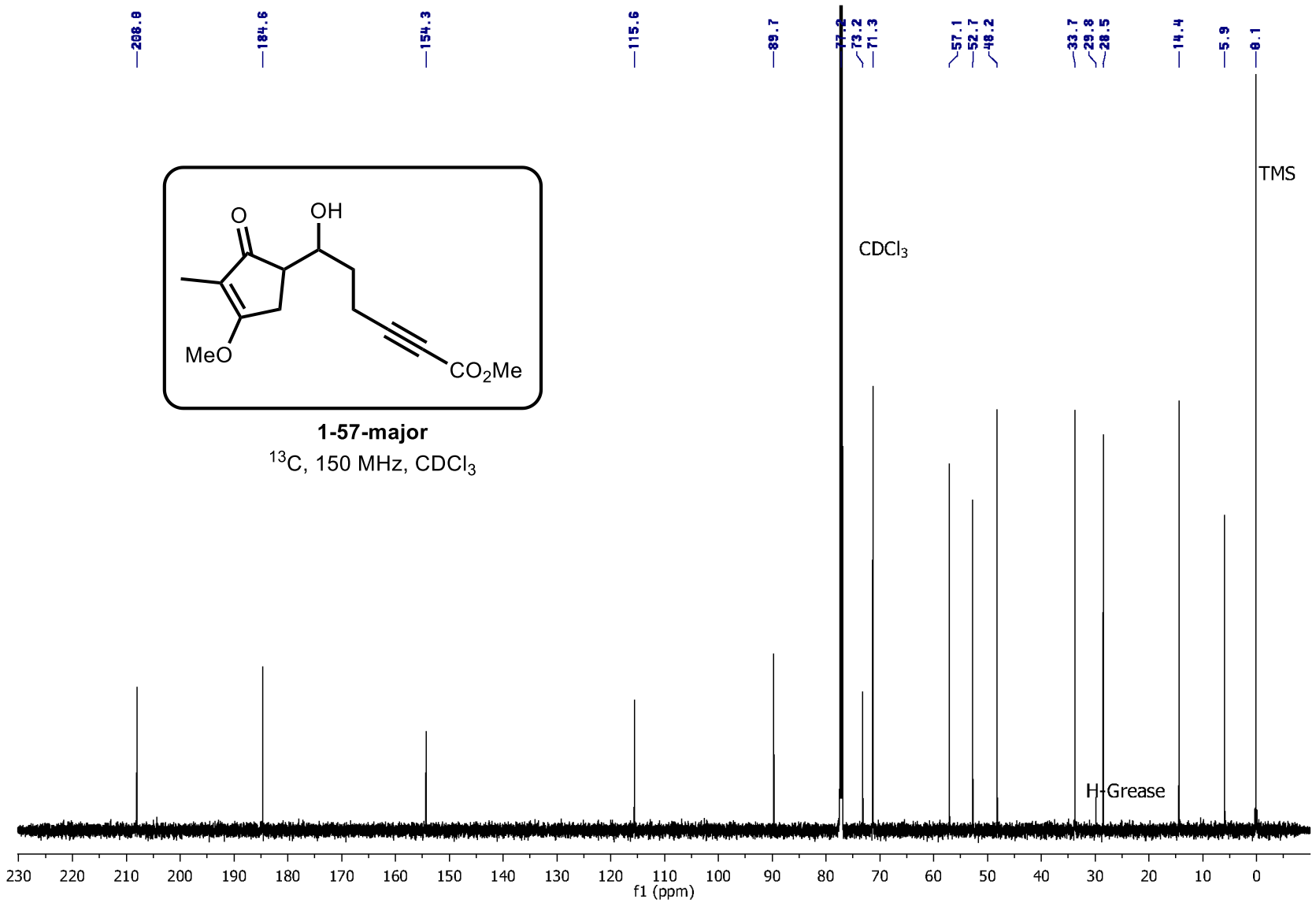
^{1}H, 500 MHz, $CDCl_3$


84.4
77.2
68.4
61.6
31.7
26.1
18.5
15.0
-5.2
HO
S1-18
13C, 125 MHz, CDCl3
CDCl3
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
f1 (ppm)


7.26
3.74
2.48
2.46
2.45
1.84
1.83
1.82
1.80
1.79
1.73
HO
CO2Me
S1-19
1H, 500 MHz, CDCl3
CHCl3
TMS
5.20
2.00
2.01
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

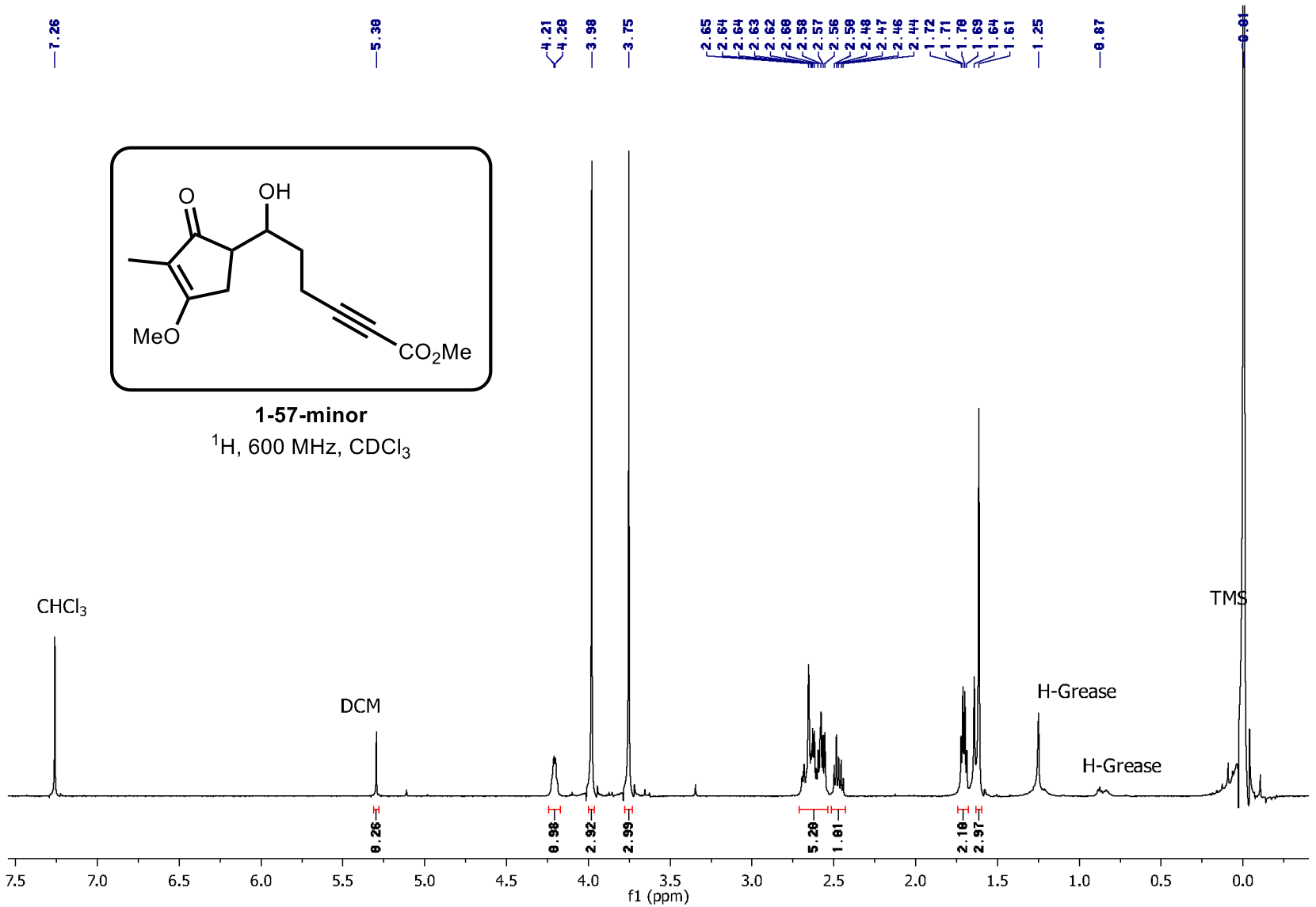

9.78
7.26
3.74
2.79
2.77
2.76
2.65
2.63
2.62
-0.02
CO2Me
O
S1-20
1H, 500 MHz, CDCl3
CHCl3
TMS
0.95
3.00
2.05
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

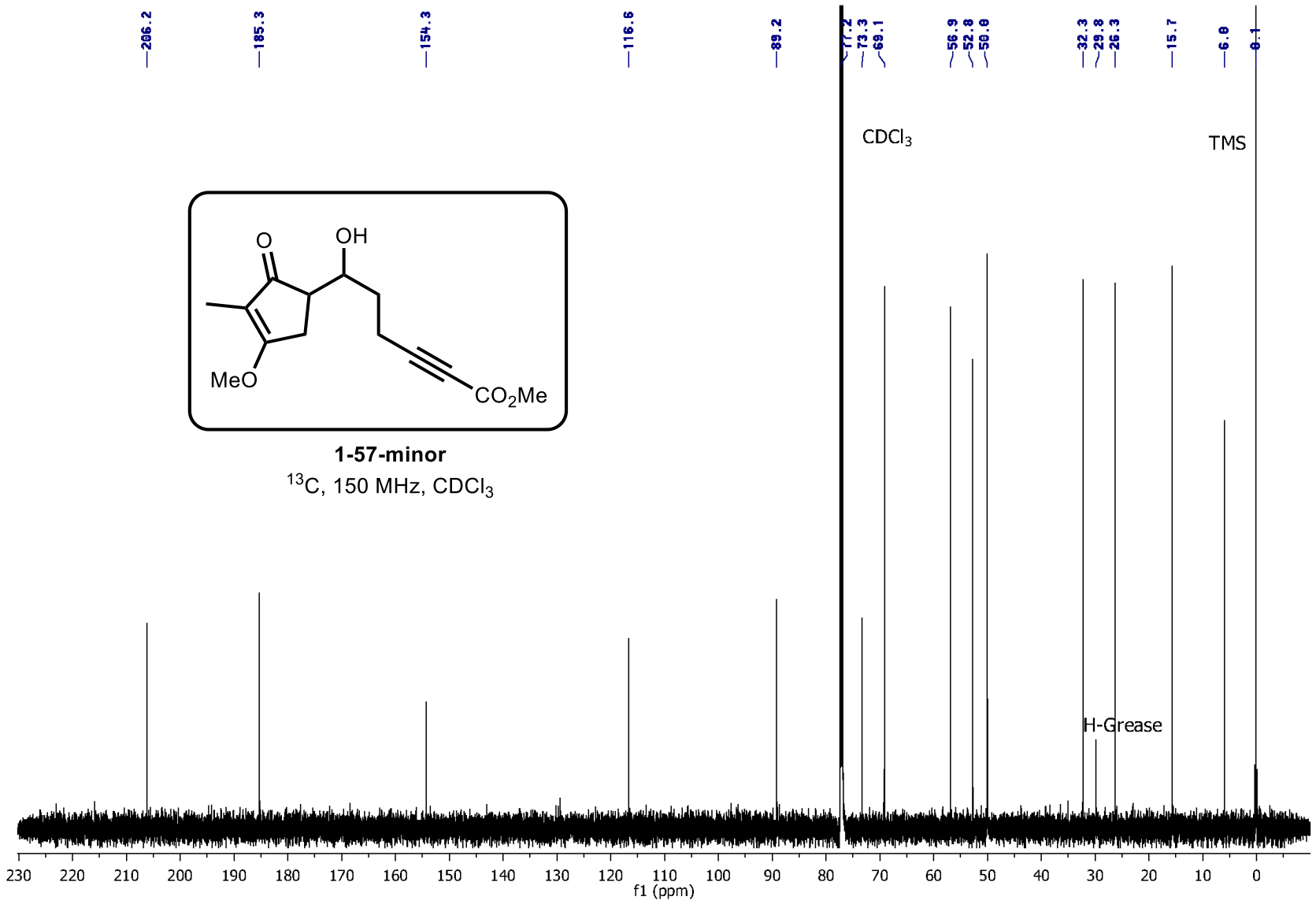

7.26
4.98
3.98
3.74
3.73
3.73
3.71
3.70
3.70
2.82
2.82
2.80
2.79
2.79
2.58
2.58
2.54
2.46
2.28
2.25
2.08
1.79
1.75
1.74
1.72
1.62
1.25
0.87
0.01
TMS
O
OH
MeO
MeO2C
1-57-major
1H, 600 MHz, CDCl3
CHCl3
H-Grease
0.93
3.04
2.91
1.26
1.00
1.06
1.05
0.98
1.11
1.16
2.94
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



1-57-major

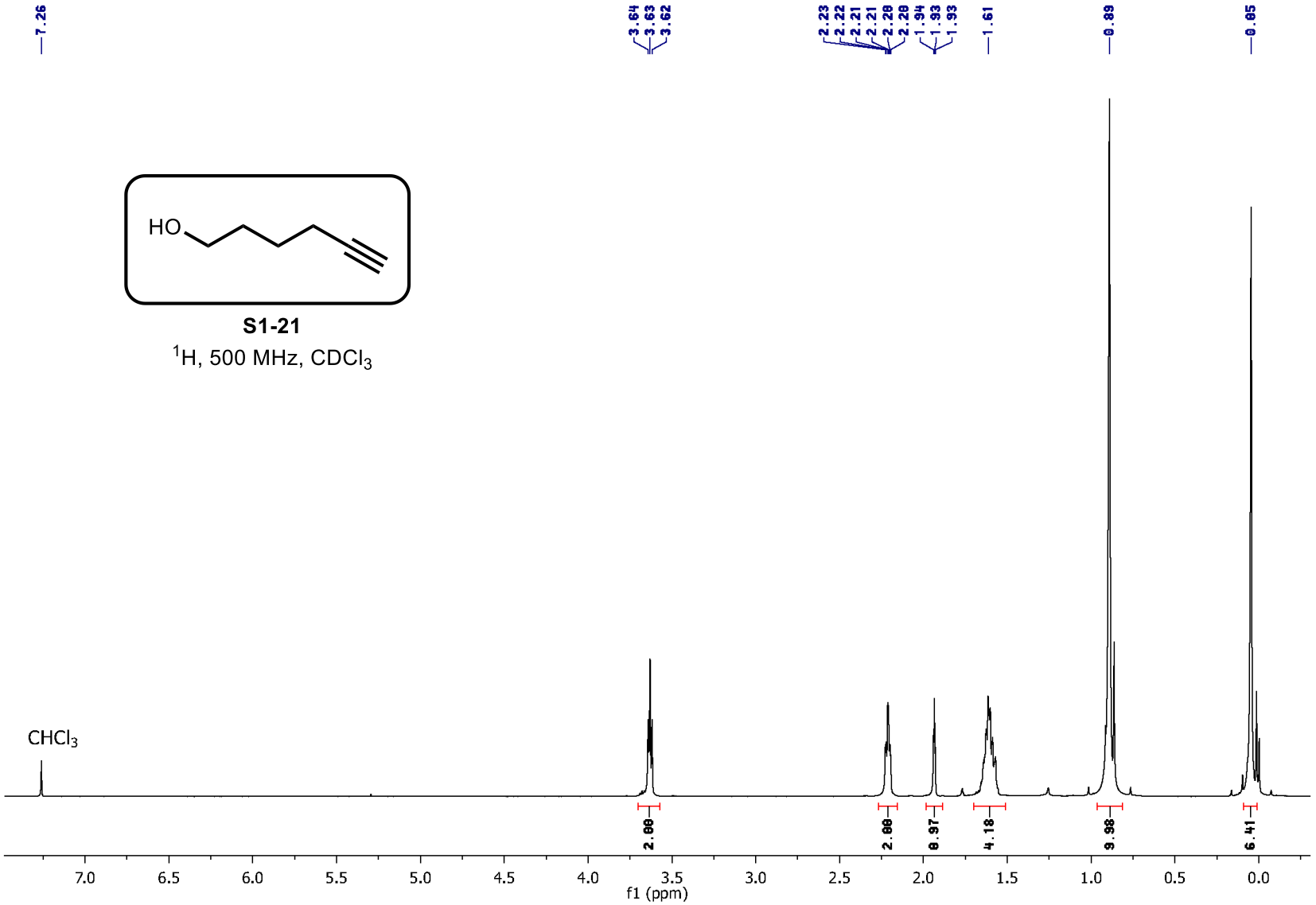
^{13}C, 150 MHz, $CDCl_3$

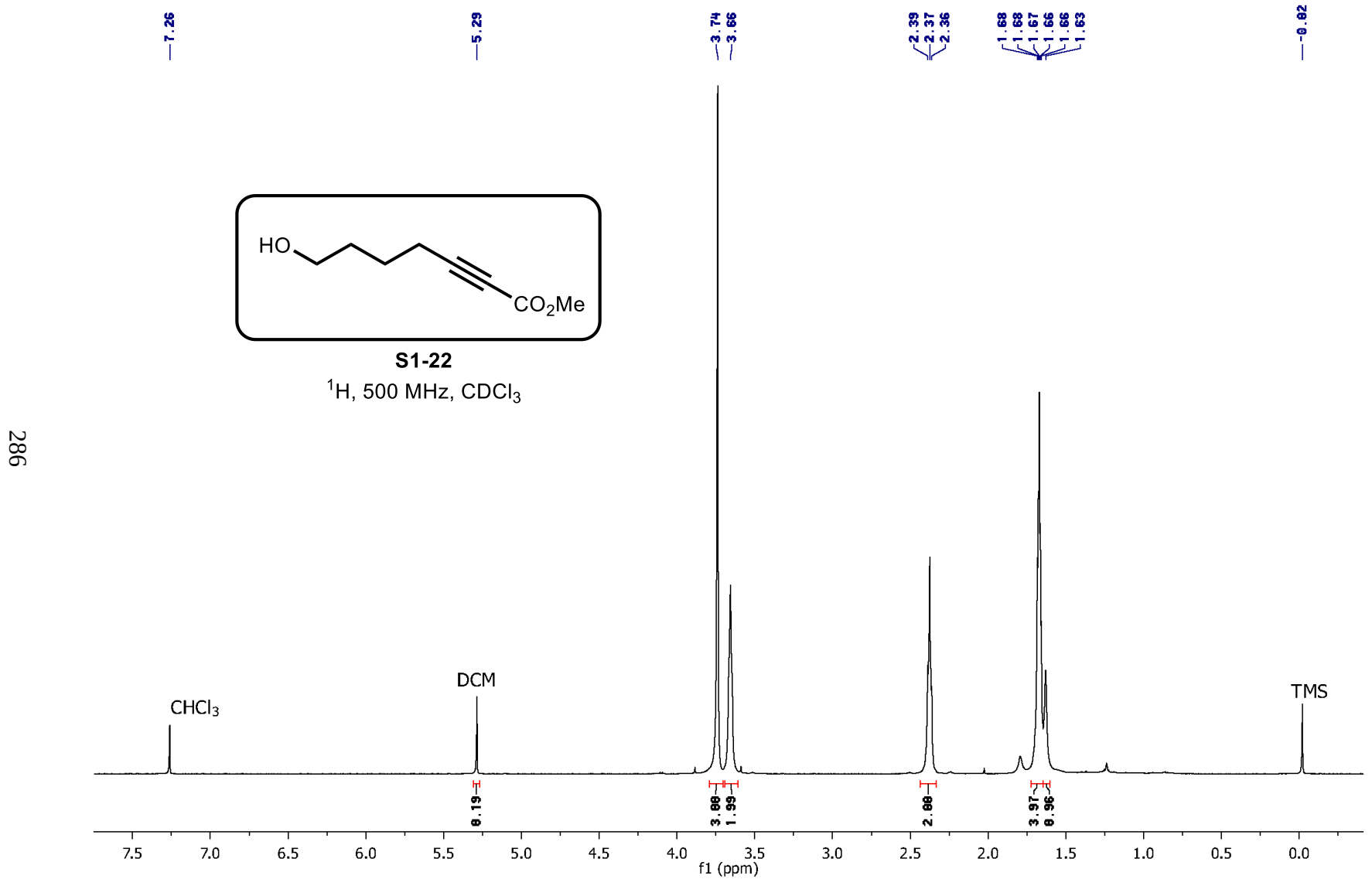

7.26
5.30
4.21
4.20
3.98
3.75
2.65
2.64
2.64
2.63
2.62
2.60
2.58
2.57
2.56
2.50
2.48
2.47
2.46
2.44
1.72
1.71
1.70
1.69
1.64
1.61
1.25
0.87
0.01
O
OH
MeO
CO2Me
1-57-minor
1H, 600 MHz, CDCl3
CHCl3
DCM
H-Grease
H-Grease
TMS
0.26
0.98
2.92
2.99
5.20
1.81
2.10
2.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

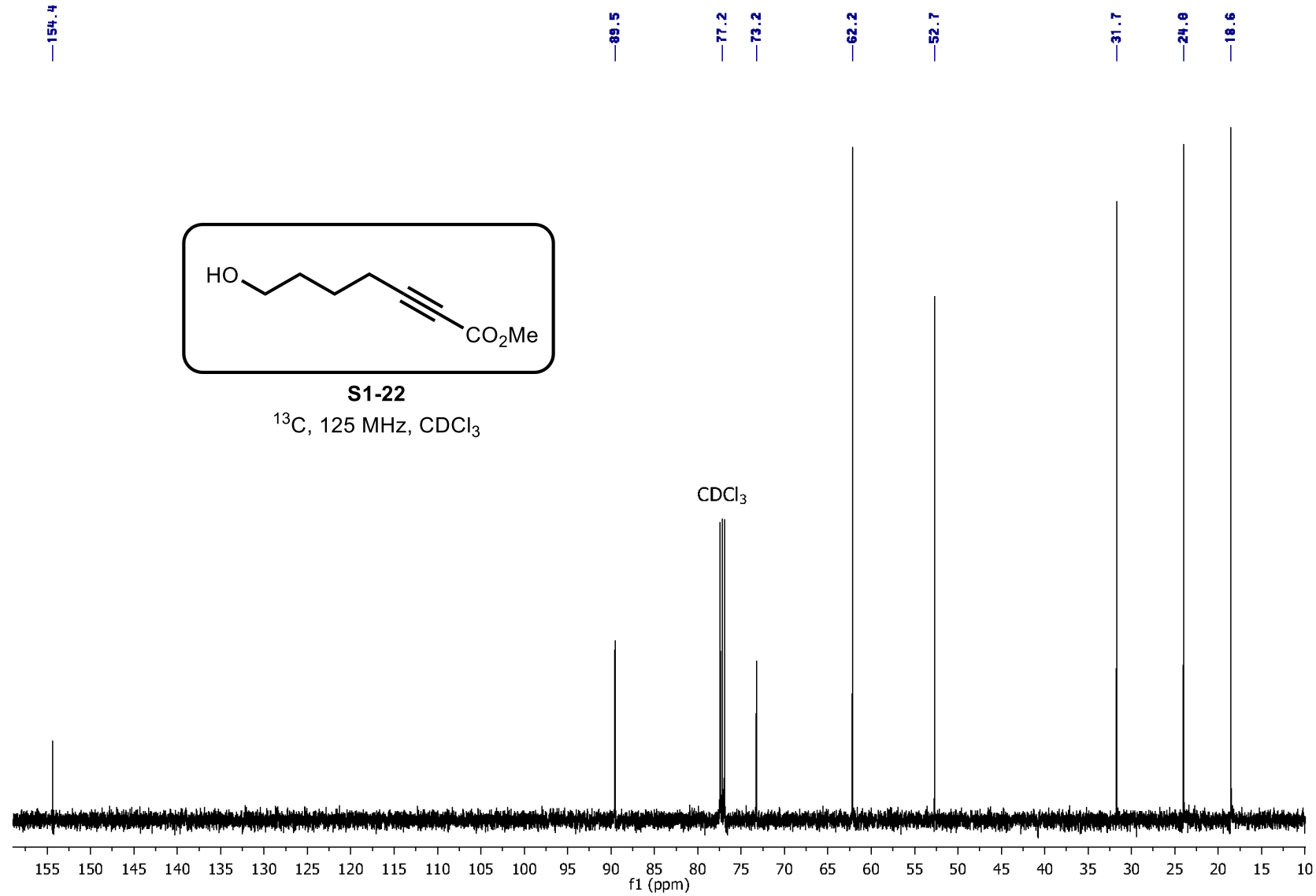


1-57-minor

^{13}C, 150 MHz, $CDCl_3$

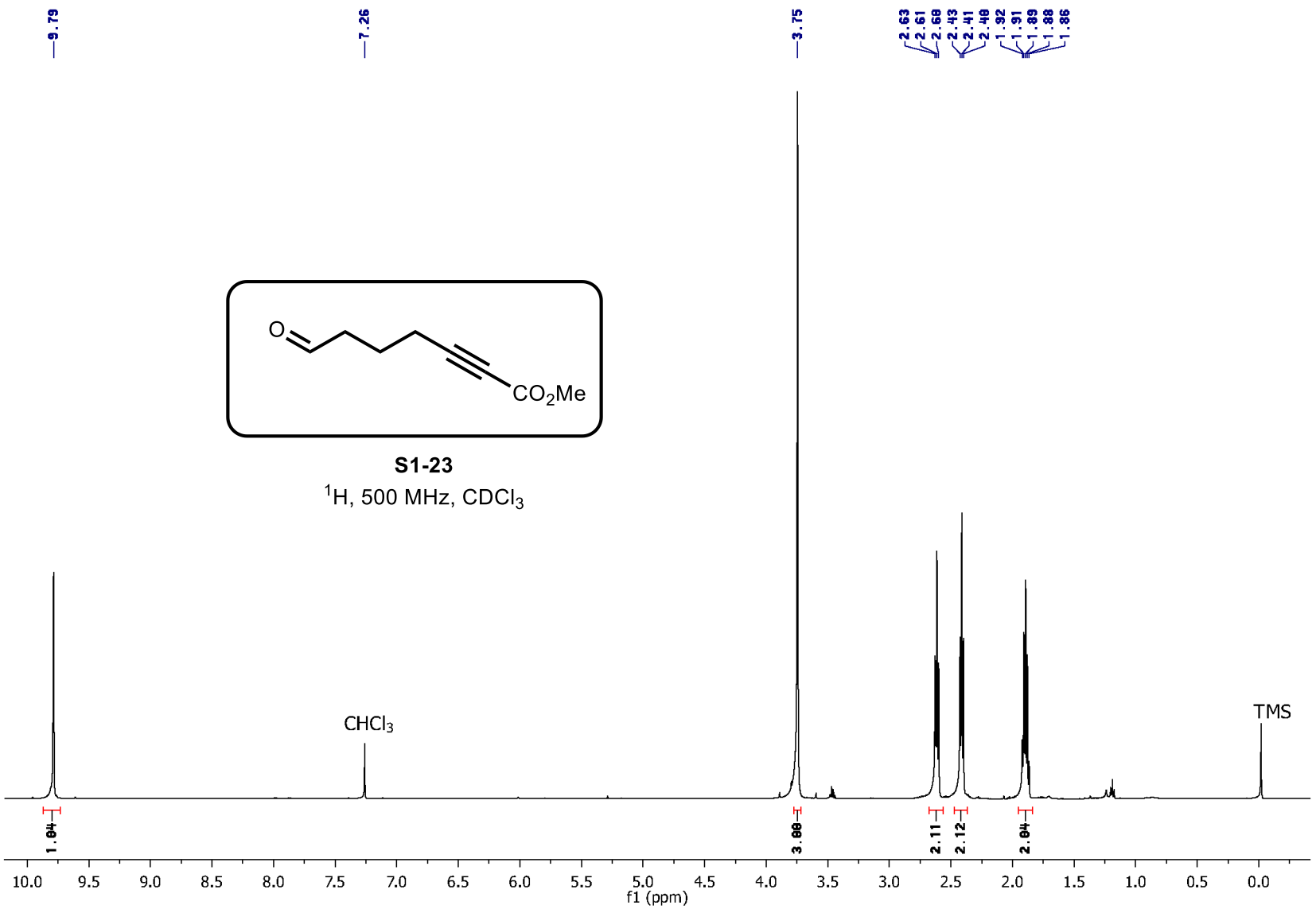

7.26
3.64
3.63
3.62
2.23
2.22
2.21
2.21
2.20
2.20
1.94
1.93
1.93
1.61
0.89
0.05
HO
S1-21
1H, 500 MHz, CDCl3
CHCl3
2.00
2.00
0.97
4.18
9.98
6.41
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

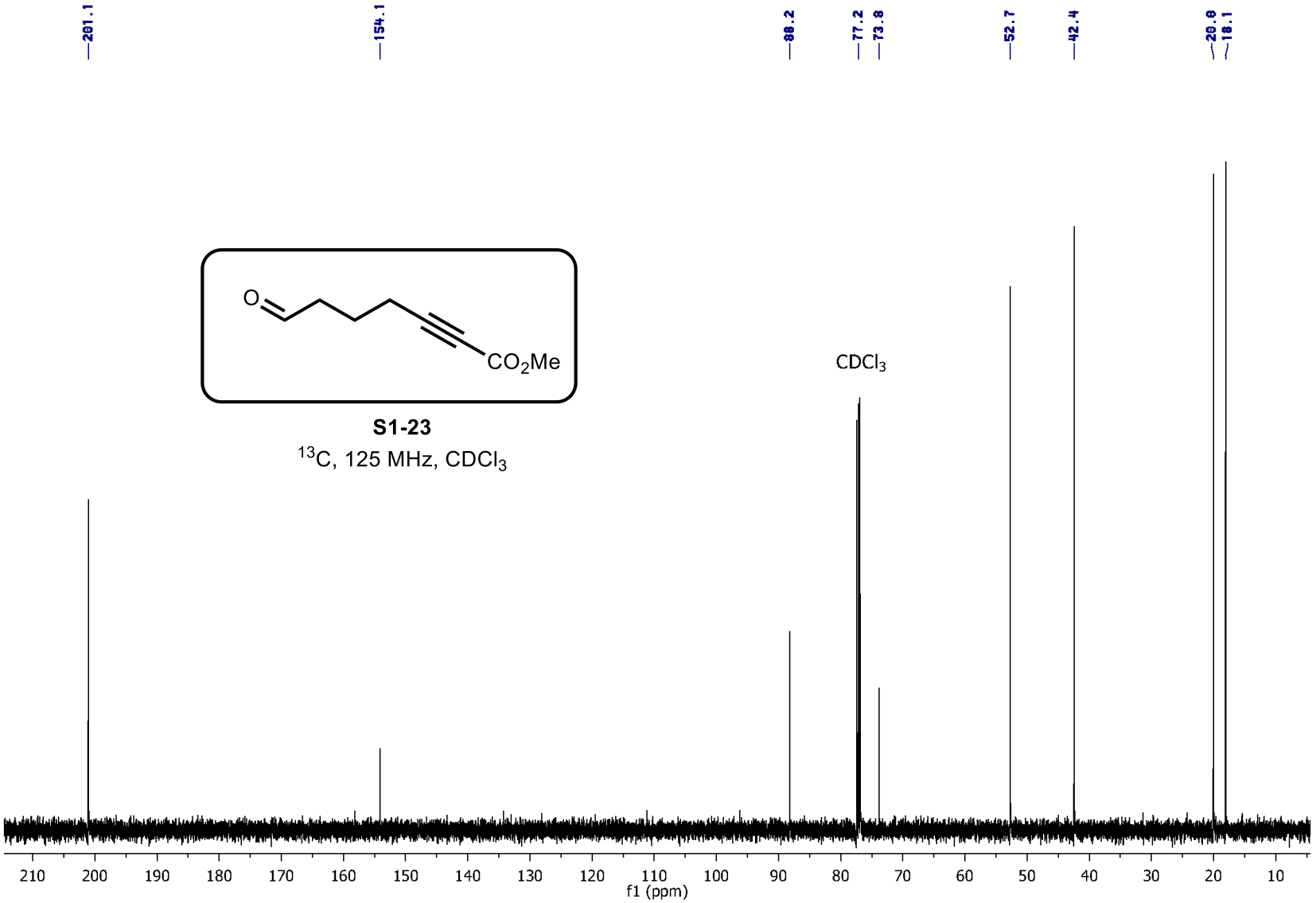

7.26
5.29
3.74
3.66
2.39
2.37
2.36
1.68
1.68
1.67
1.66
1.66
1.63
0.02
HO
CO2Me
S1-22
1H, 500 MHz, CDCl3
CHCl3
DCM
TMS
0.19
3.00
1.99
2.00
3.97
0.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



S1-22

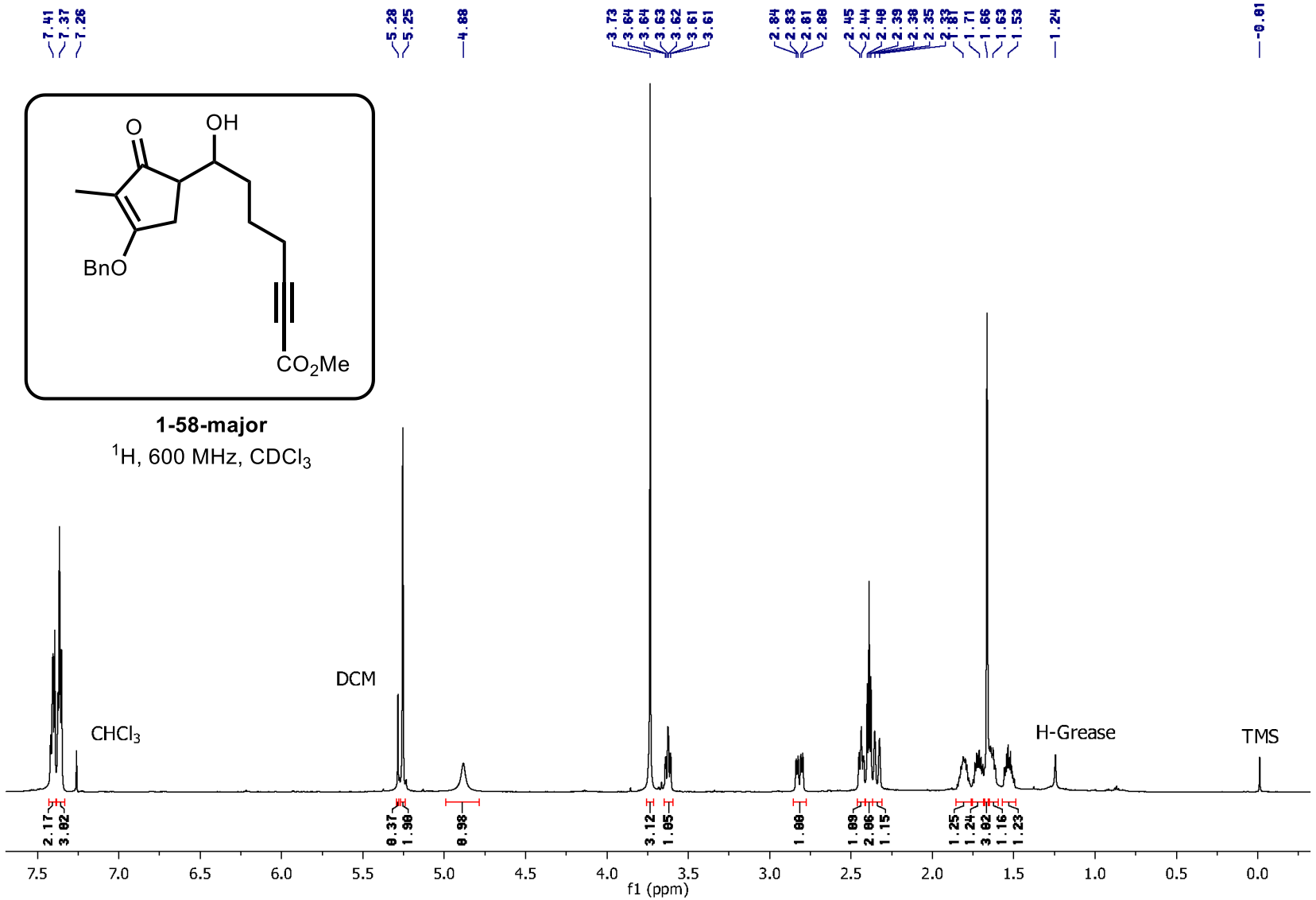
^{13}C, 125 MHz, $CDCl_3$

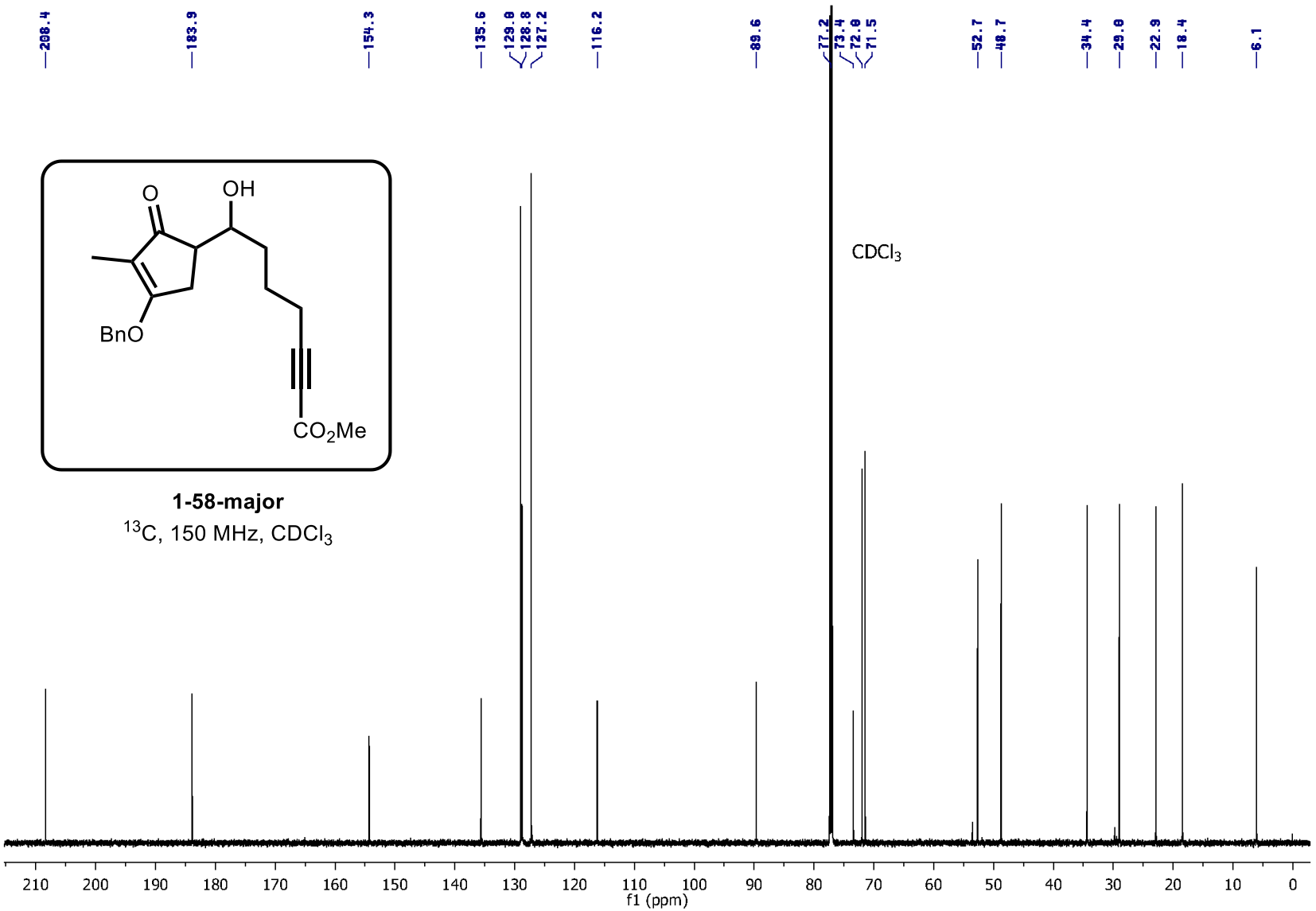

9.79
7.26
3.75
2.63
2.61
2.60
2.43
2.41
2.40
1.92
1.91
1.89
1.88
1.86
O
CO2Me
S1-23
1H, 500 MHz, CDCl3
CHCl3
TMS
1.04
3.00
2.11
2.12
2.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



S1-23

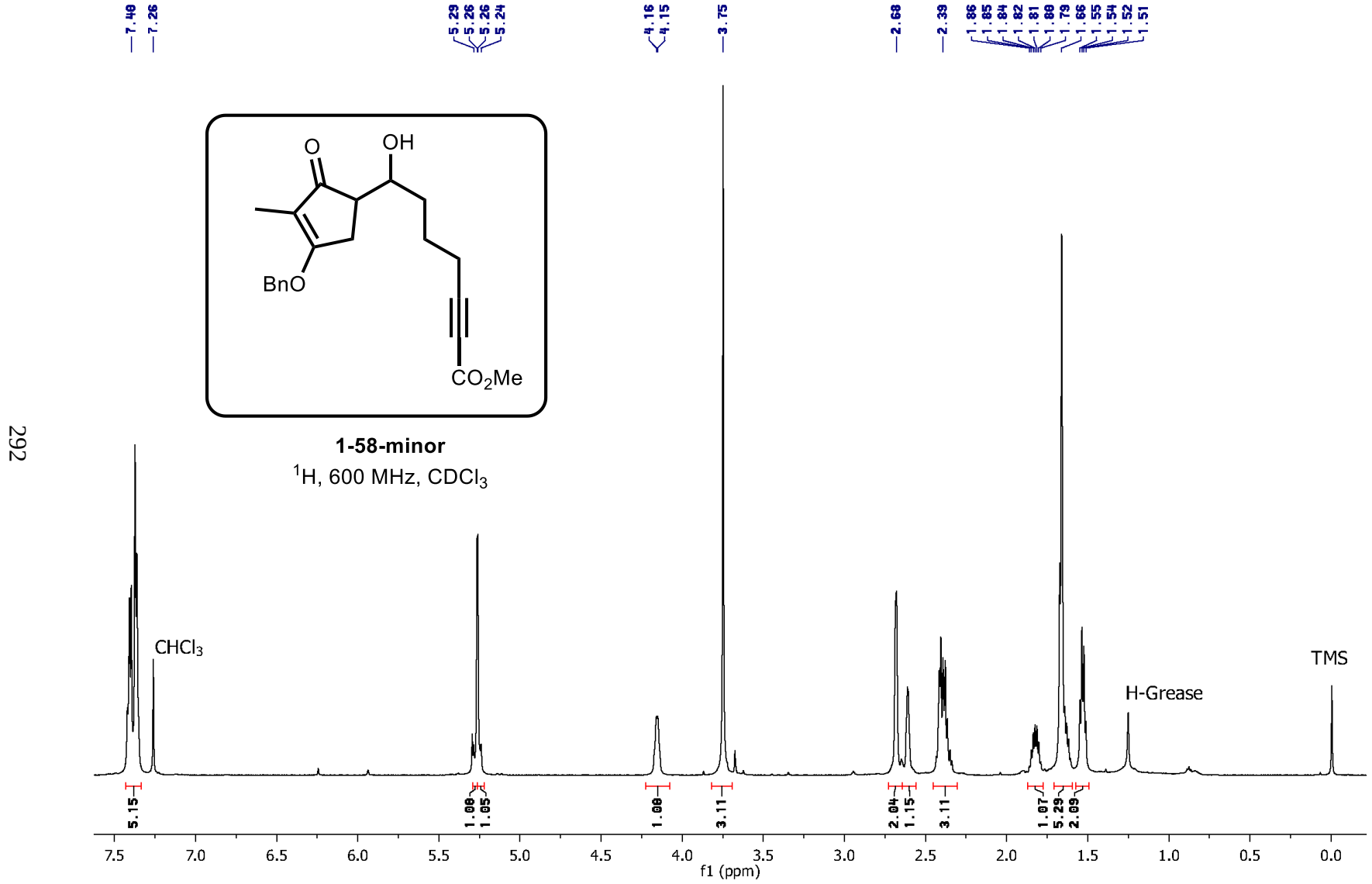
^{13}C, 125 MHz, $CDCl_3$

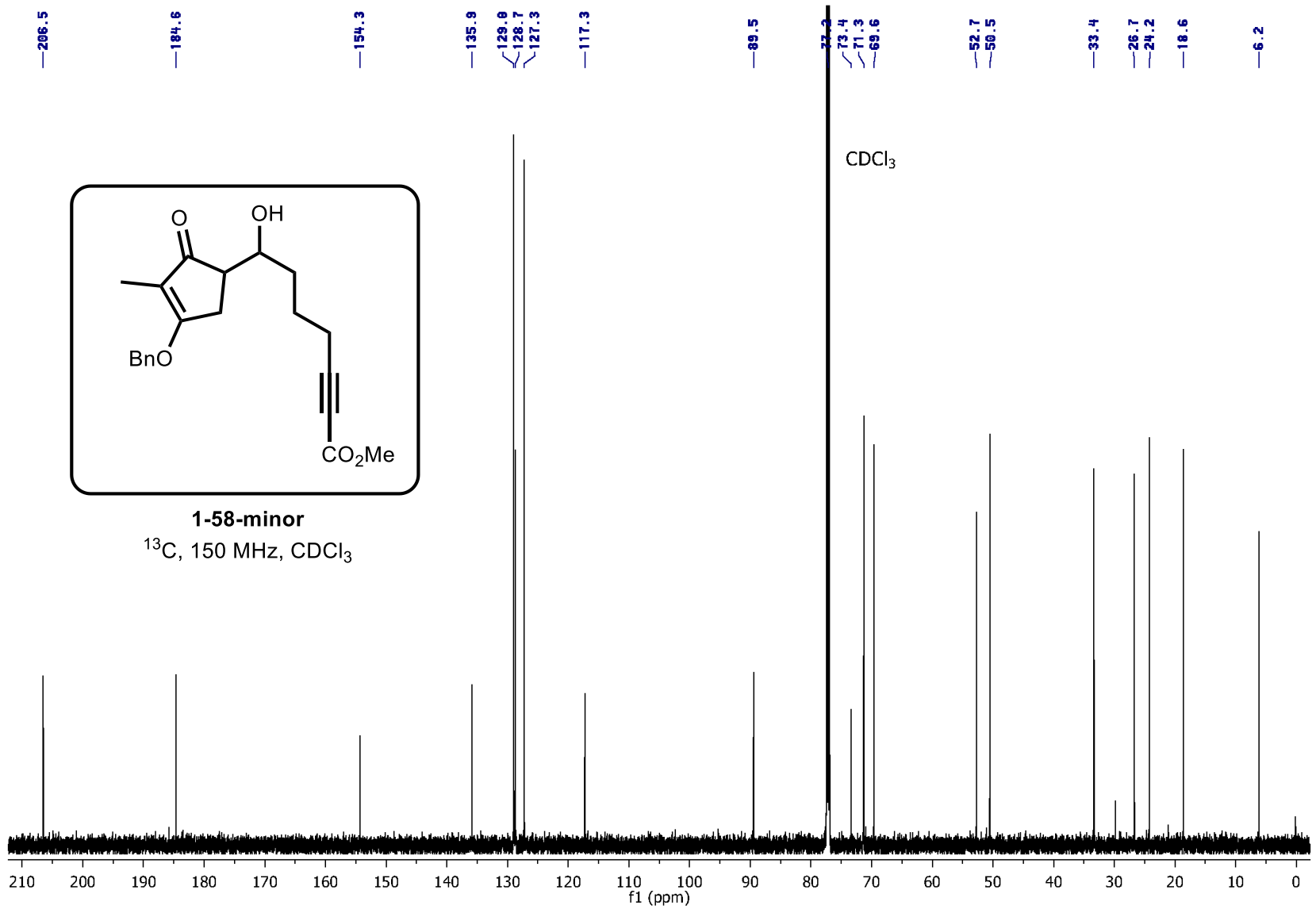

7.41
7.37
7.26
5.28
5.25
4.88
3.73
3.64
3.64
3.63
3.62
3.61
3.61
2.84
2.83
2.81
2.80
2.45
2.44
2.40
2.39
2.38
2.35
1.81
1.71
1.66
1.63
1.53
1.24
-0.01
O
OH
BnO
CO2Me
1-58-major
1H, 600 MHz, CDCl3
CHCl3
DCM
H-Grease
TMS
2.17
3.02
0.37
1.90
0.98
3.12
1.85
1.00
1.89
2.06
1.15
1.25
1.24
3.02
1.16
1.23
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

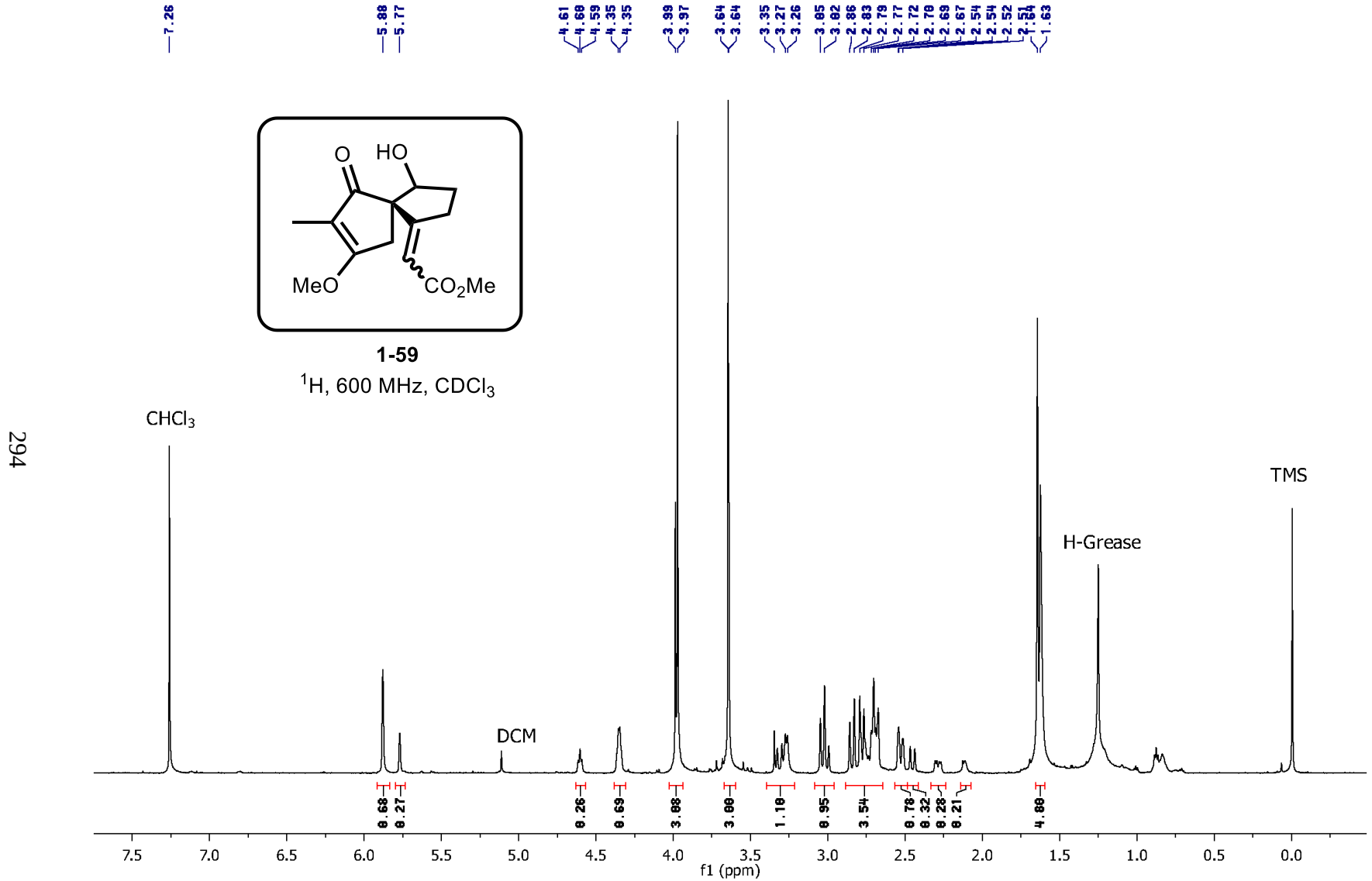


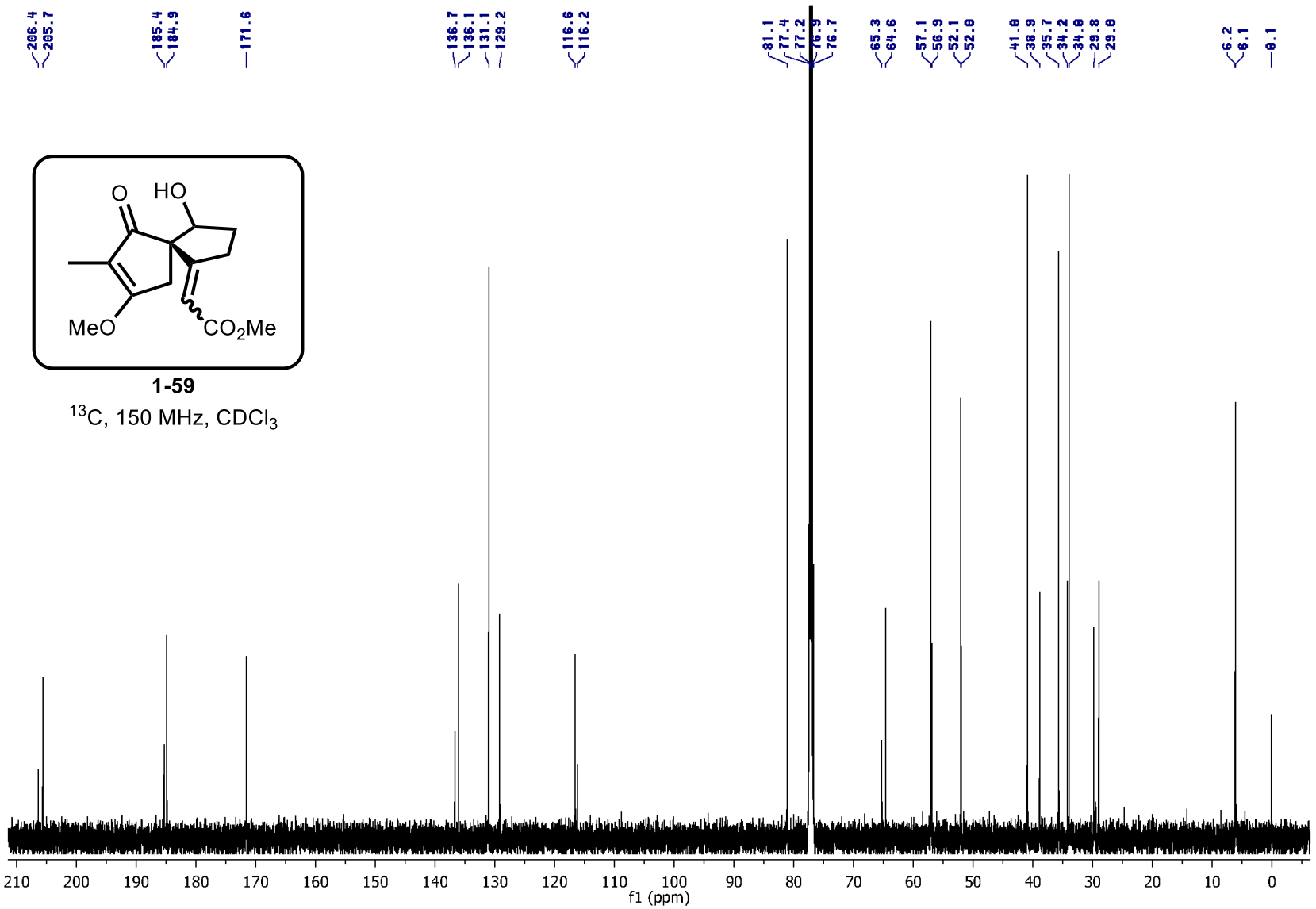
1-58-major

^{13}C, 150 MHz, $CDCl_3$


7.40
7.26
5.29
5.26
5.26
5.24
4.16
4.15
3.75
2.68
2.39
1.86
1.85
1.84
1.82
1.81
1.80
1.79
1.66
1.55
1.54
1.52
1.51
O
OH
BnO
CO2Me
1-58-minor
1H, 600 MHz, CDCl3
CHCl3
TMS
H-Grease
5.15
1.00
1.05
1.00
3.11
2.04
1.15
3.11
1.07
5.29
2.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

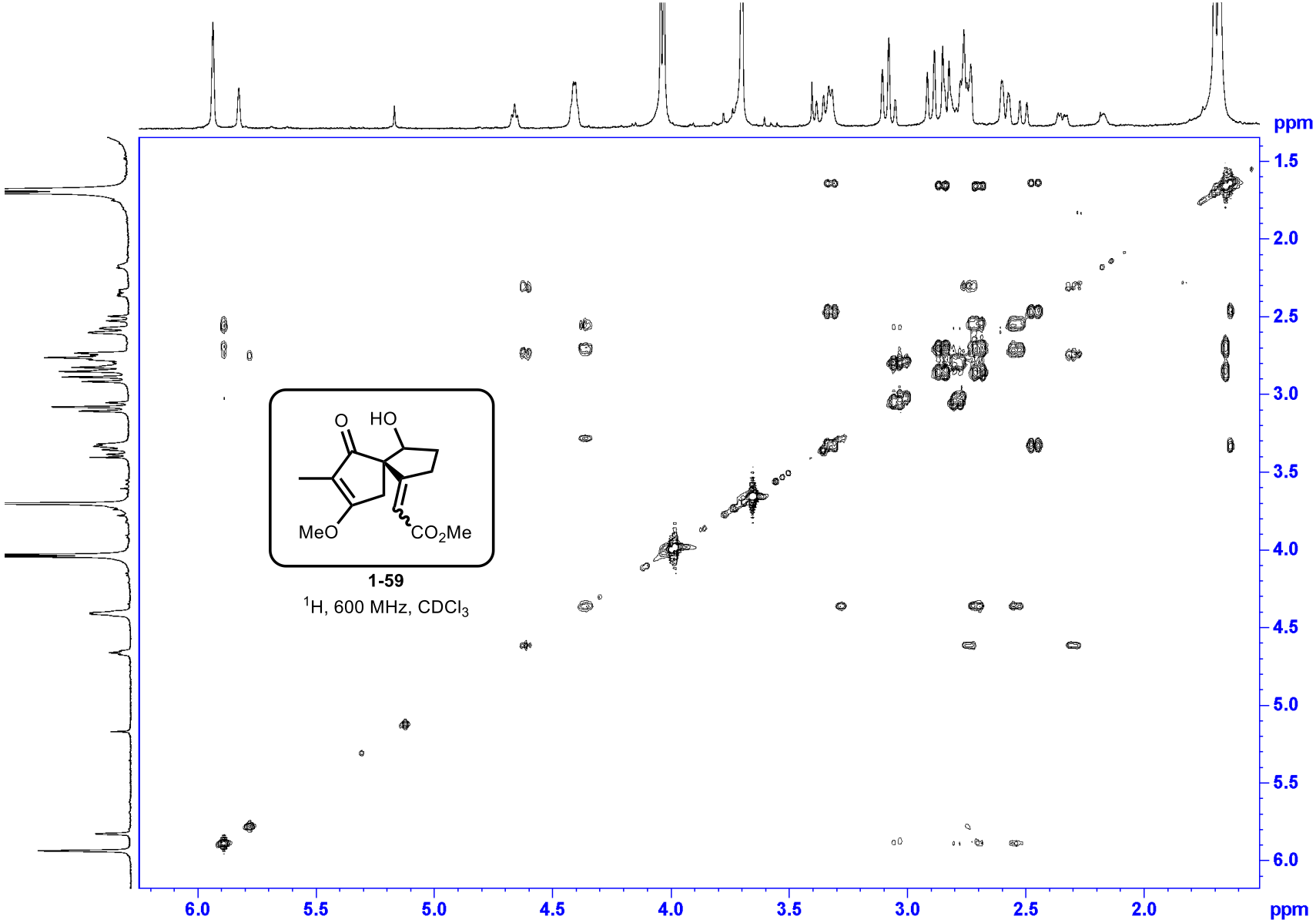

206.5
184.6
154.3
135.9
129.0
128.7
127.3
117.3
89.5
77.2
73.4
71.3
69.6
52.7
50.5
33.4
26.7
24.2
18.6
6.2
CDCl3
O
OH
BnO
CO2Me
1-58-minor
13C, 150 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

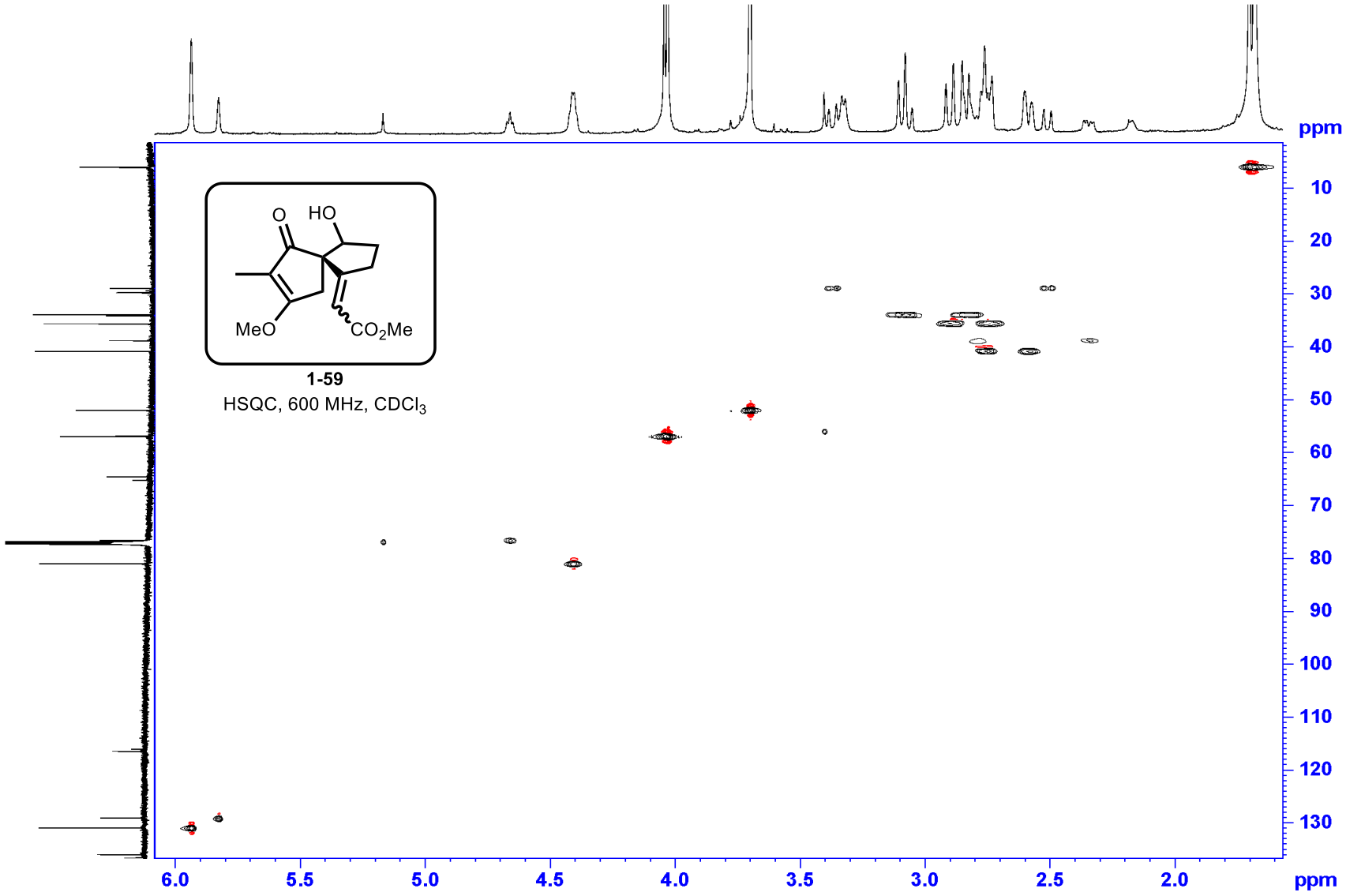

7.26
5.88
5.77
4.61
4.60
4.59
4.35
4.35
3.99
3.97
3.64
3.64
3.35
3.27
3.26
3.05
3.02
2.86
2.83
2.79
2.77
2.72
2.70
2.69
2.67
2.54
2.54
2.52
2.51
1.64
1.63
O
HO
MeO
CO2Me
1-59
1H, 600 MHz, CDCl3
CHCl3
DCM
H-Grease
TMS
0.68
0.27
0.26
0.69
3.08
3.00
1.10
0.95
3.54
0.78
0.32
0.28
0.21
4.80
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

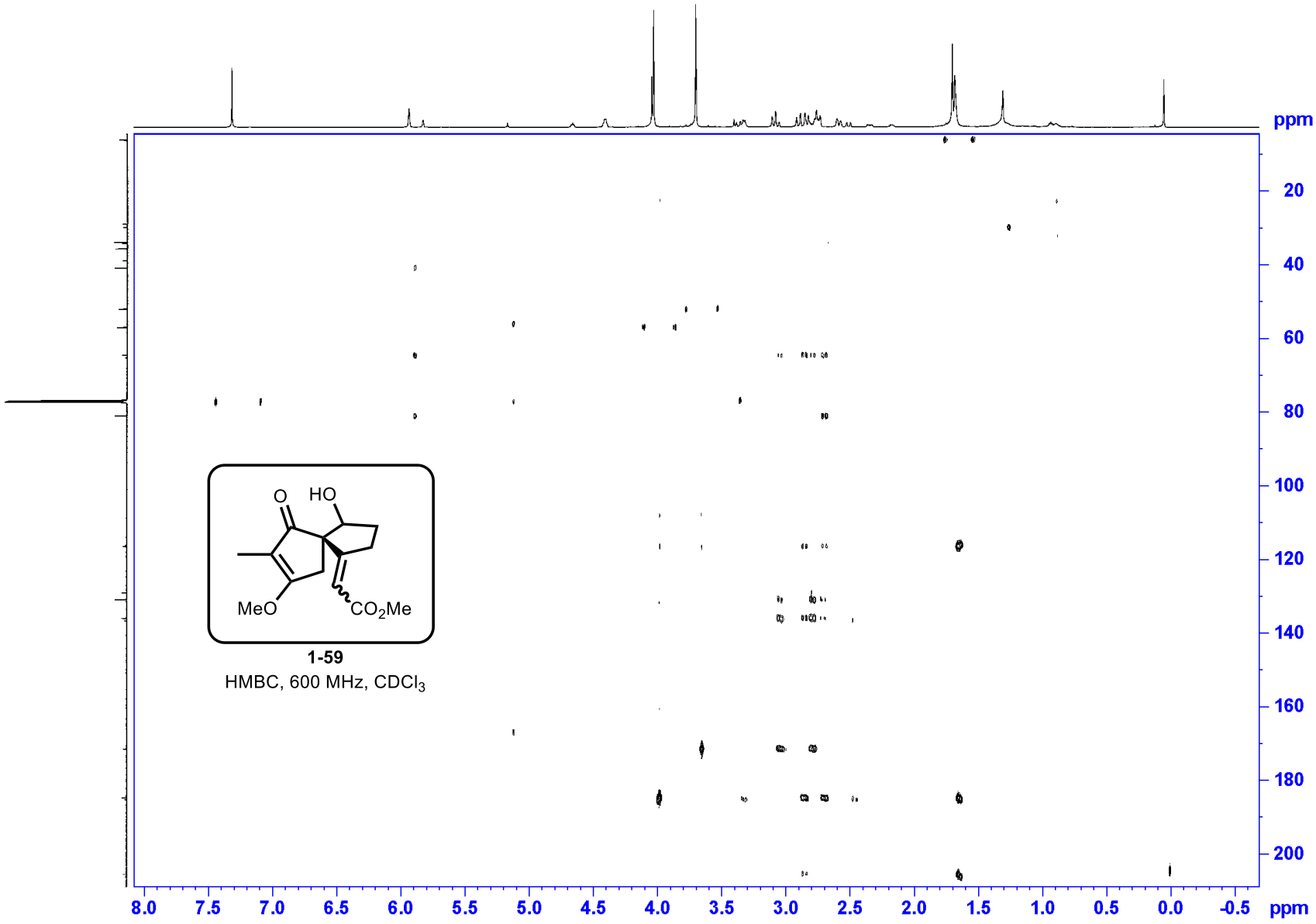


1-59

^{13}C, 150 MHz, $CDCl_3$

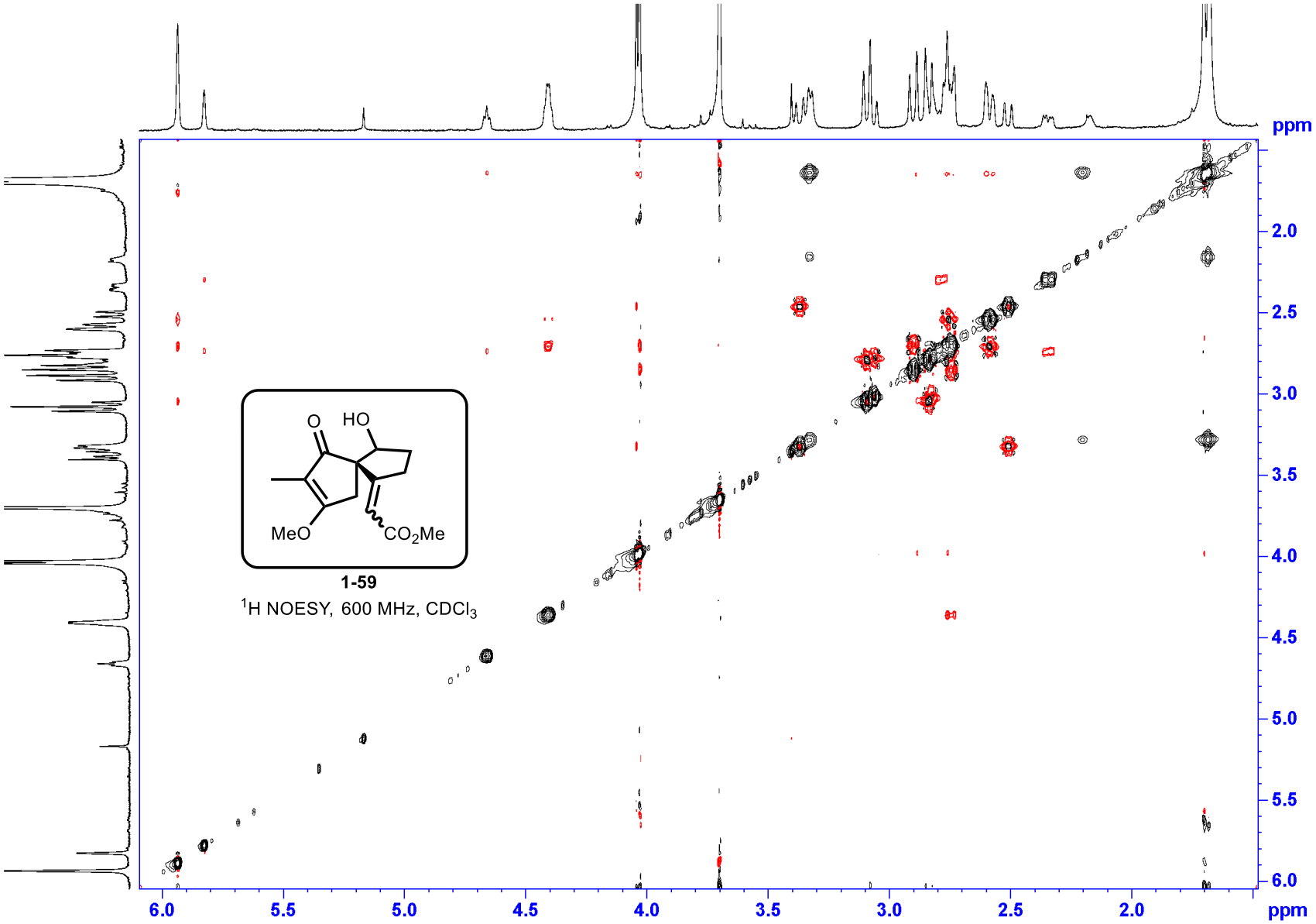

O
HO
MeO
CO2Me
1-59
1H, 600 MHz, CDCl3
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
ppm
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

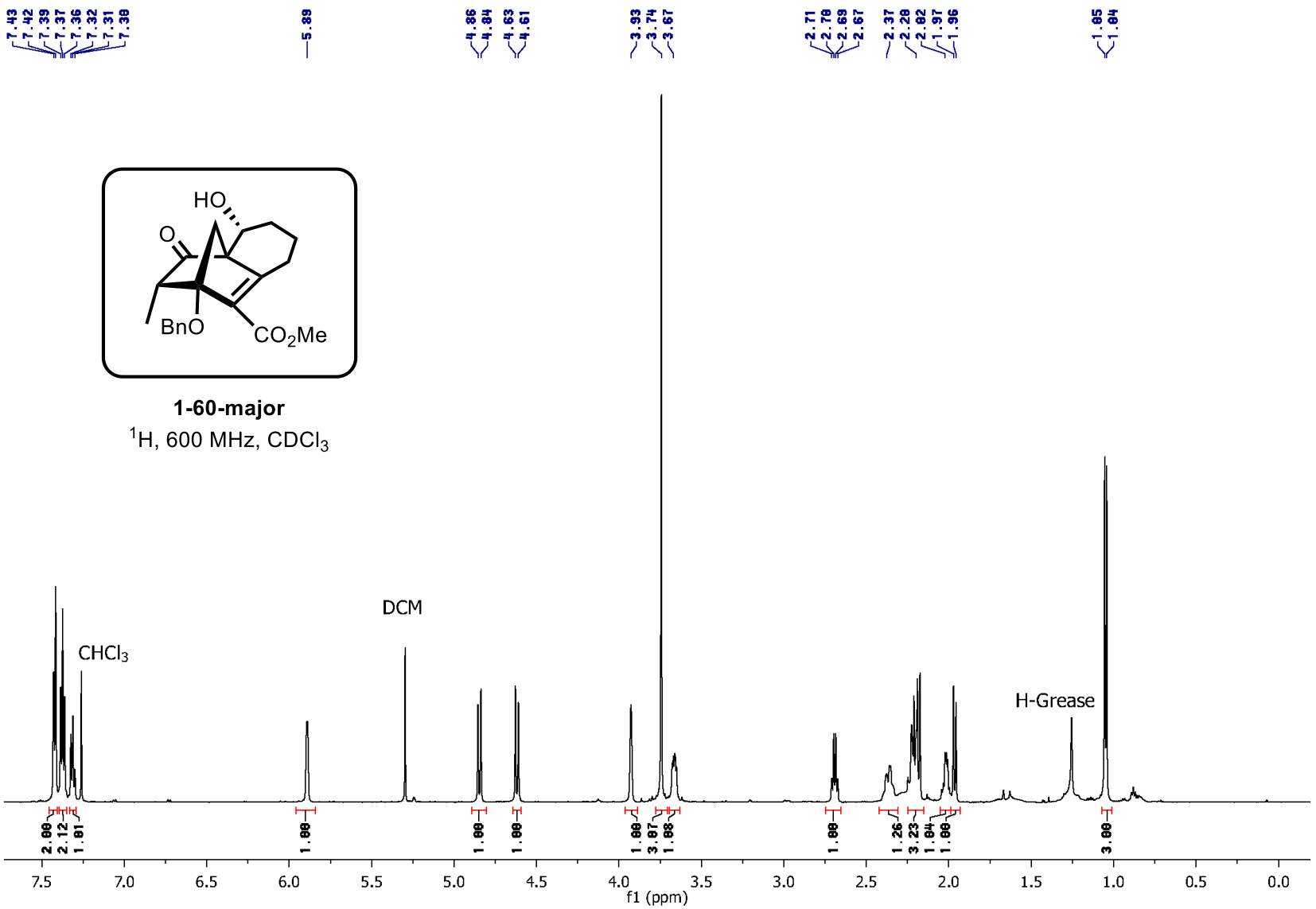

O
HO
MeO
CO2Me
1-59
HSQC, 600 MHz, CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm



1-59

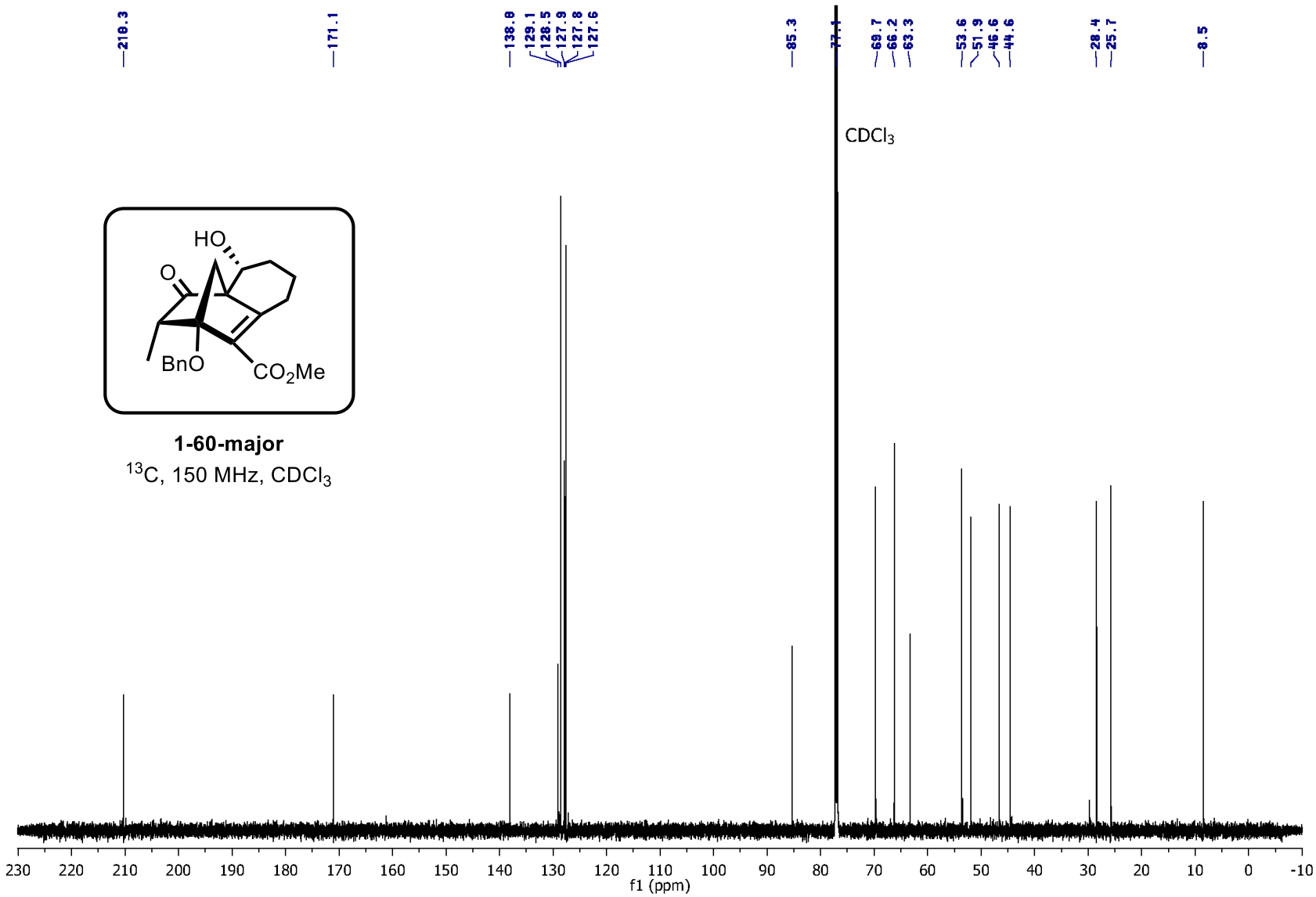
HMBC, 600 MHz, $CDCl_3$

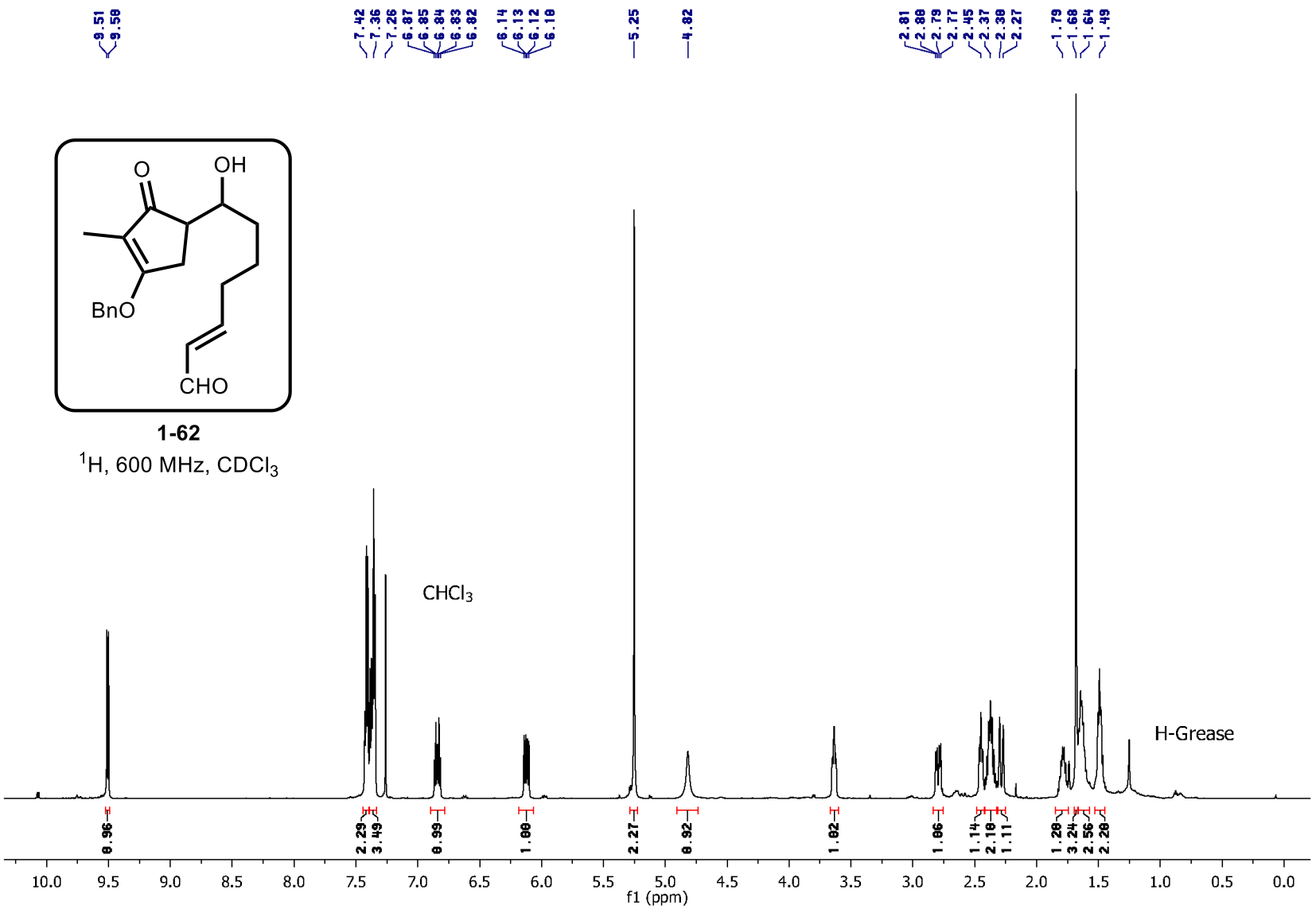

O
HO
MeO
CO2Me
1-59
1H NOESY, 600 MHz, CDCl3
ppm
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

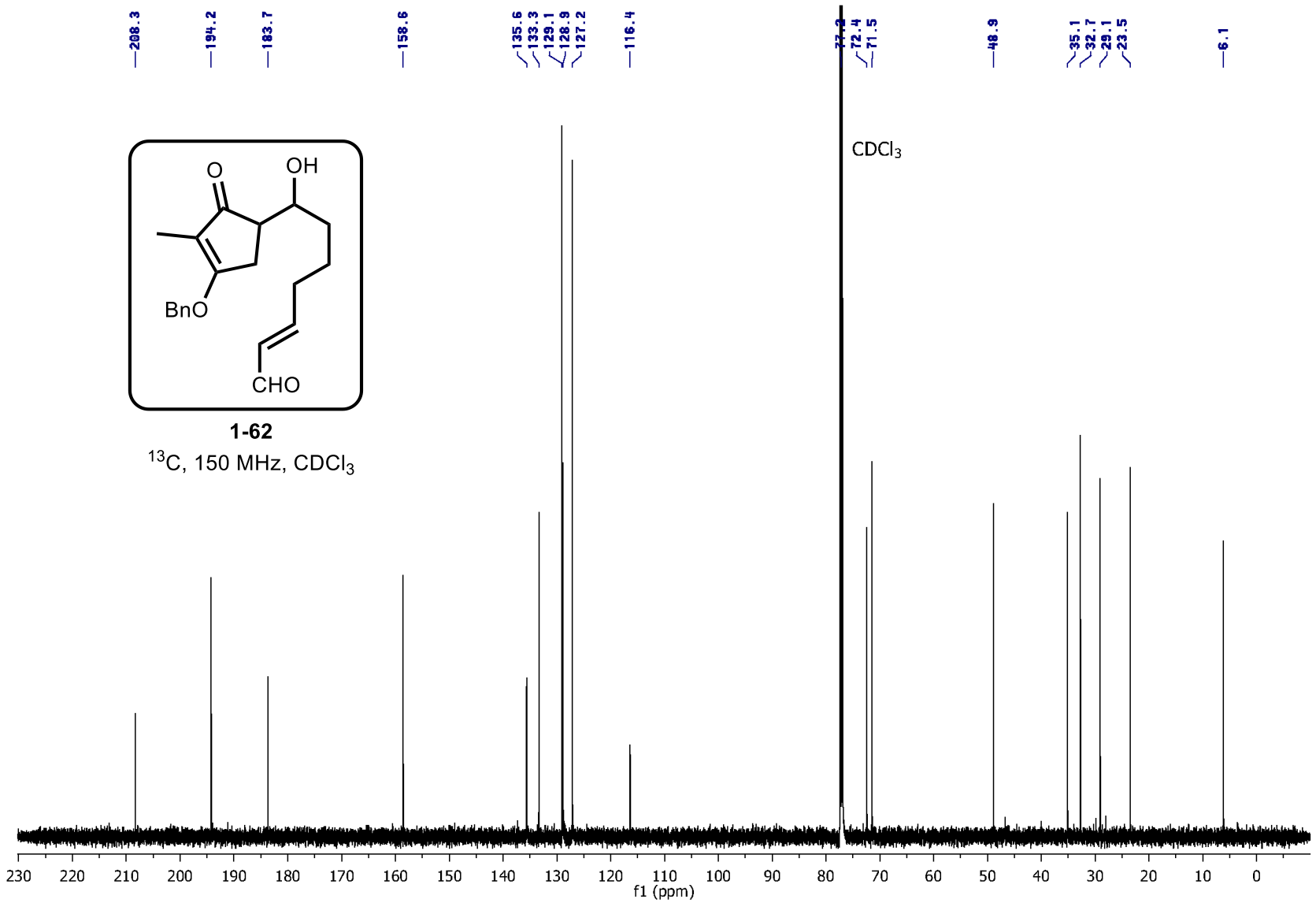


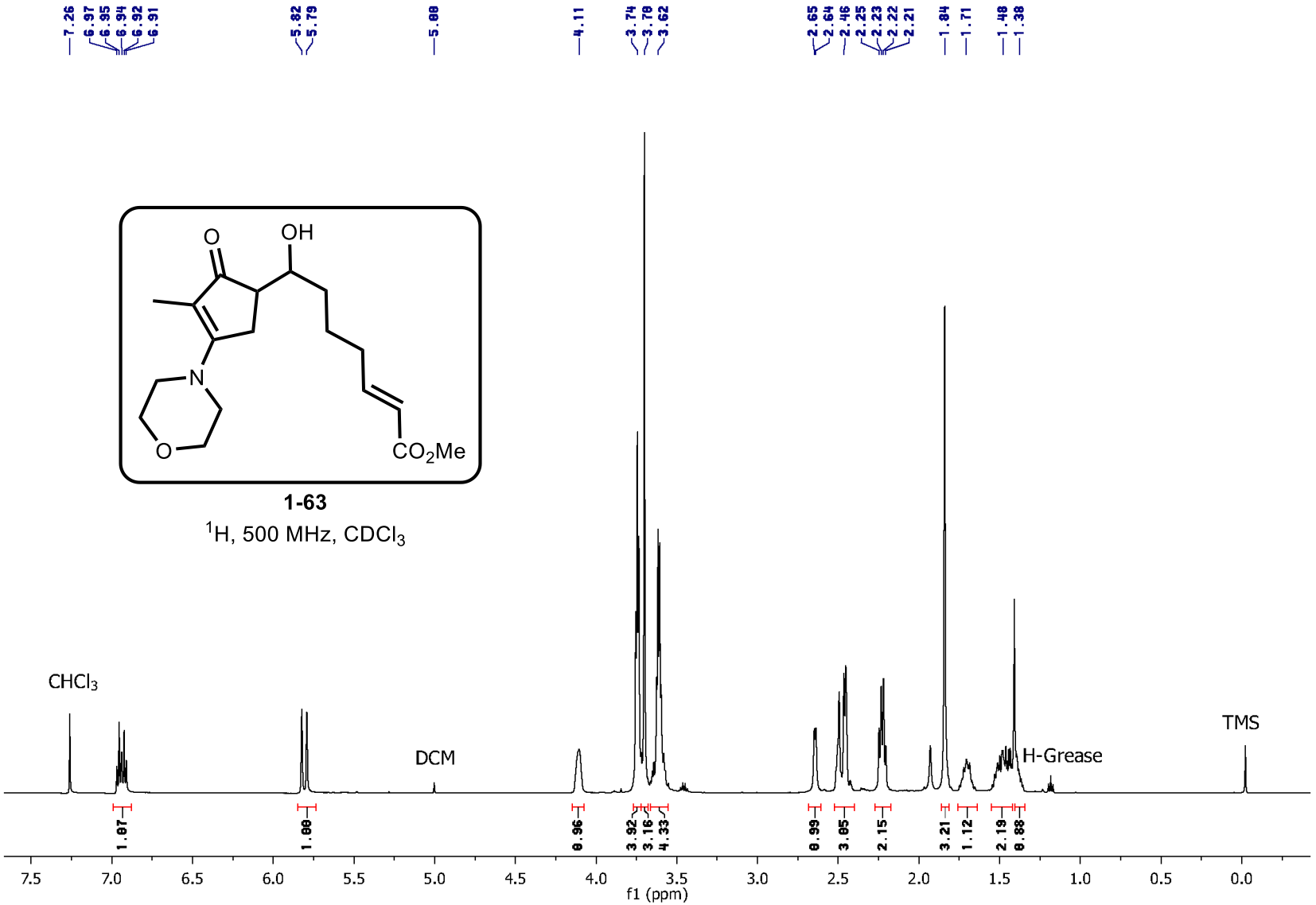
1-60-major

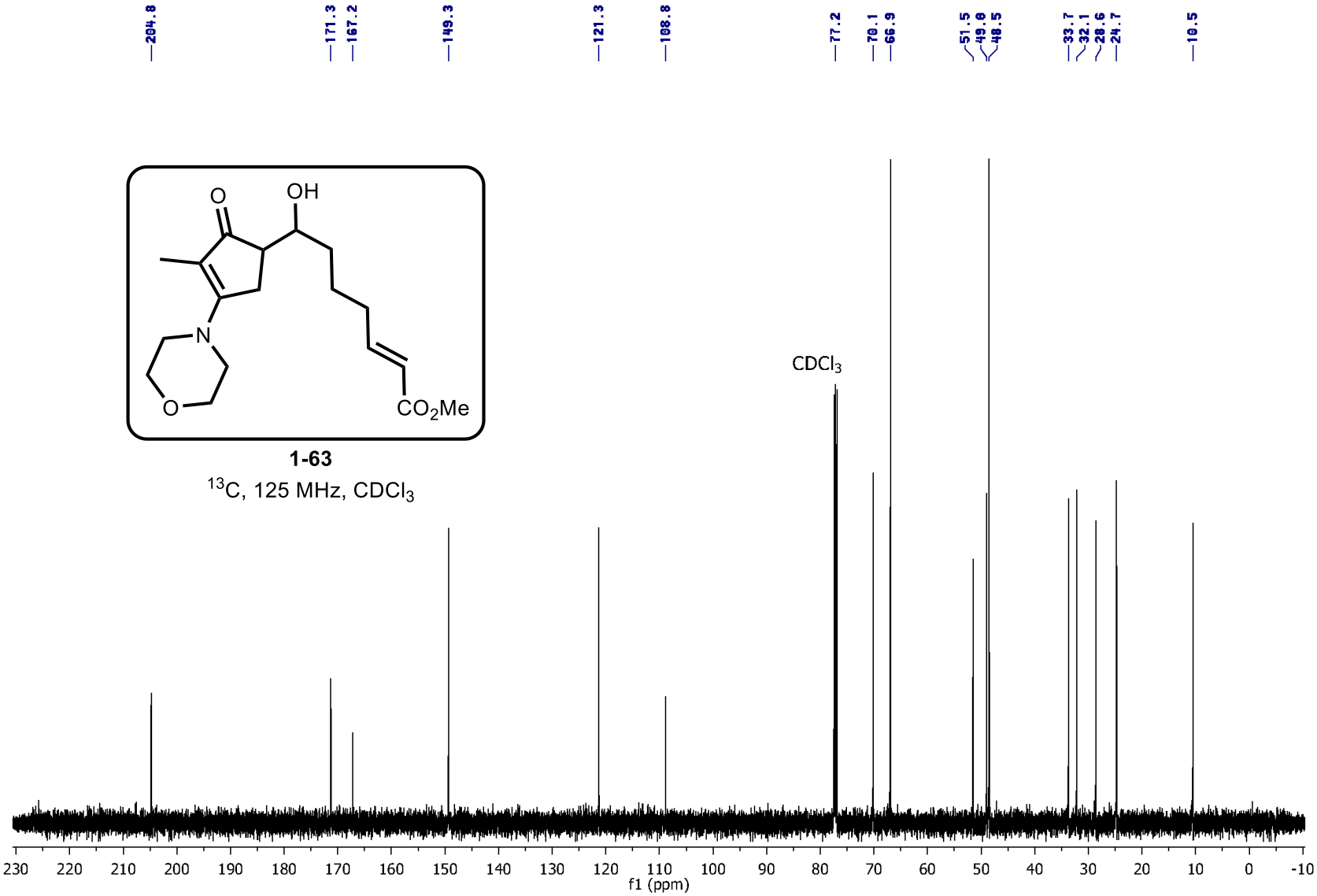
^{1}H, 600 MHz, $CDCl_3$


210.3
171.1
138.0
129.1
128.5
127.9
127.8
127.6
85.3
77.4
69.7
66.2
63.3
53.6
51.9
46.6
44.6
28.4
25.7
8.5
CDCl3
HO
O
BnO
CO2Me
1-60-major
13C, 150 MHz, CDCl3
f1 (ppm)


9.51
9.50
7.42
7.36
7.26
6.87
6.85
6.84
6.83
6.82
6.14
6.13
6.12
6.10
5.25
4.82
2.81
2.80
2.79
2.77
2.45
2.37
2.30
2.27
1.79
1.68
1.64
1.49
O
OH
BnO
CHO
1-62
1H, 600 MHz, CDCl3
CHCl3
H-Grease
0.96
2.29
3.49
0.99
1.00
2.27
0.92
1.02
1.06
1.14
2.10
1.11
1.20
3.24
2.56
2.20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

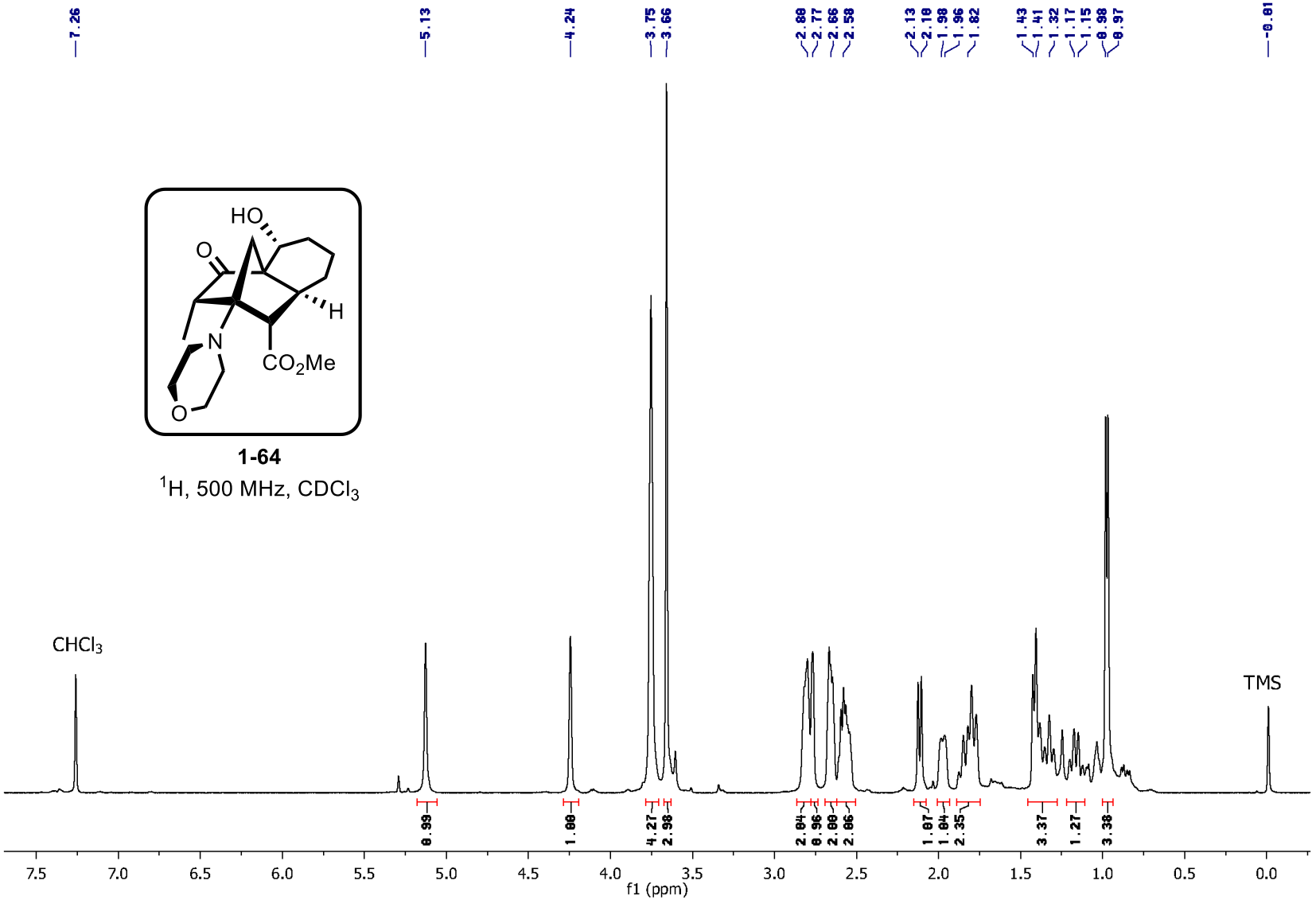

208.3
194.2
183.7
158.6
135.6
133.3
129.1
128.9
127.2
116.4
77.2
72.4
71.5
48.9
35.1
32.7
29.1
23.5
6.1
CDCl3
O
OH
BnO
CHO
1-62
13C, 150 MHz, CDCl3
f1 (ppm)


7.26
6.97
6.95
6.94
6.92
6.91
5.82
5.79
5.08
4.11
3.74
3.70
3.62
2.65
2.64
2.46
2.25
2.23
2.22
2.21
1.84
1.71
1.48
1.38
O
OH
N
O
CO2Me
1-63
1H, 500 MHz, CDCl3
CHCl3
DCM
H-Grease
TMS
1.07
1.00
0.96
3.92
3.16
4.33
0.99
3.05
2.15
3.21
1.12
2.19
0.88
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



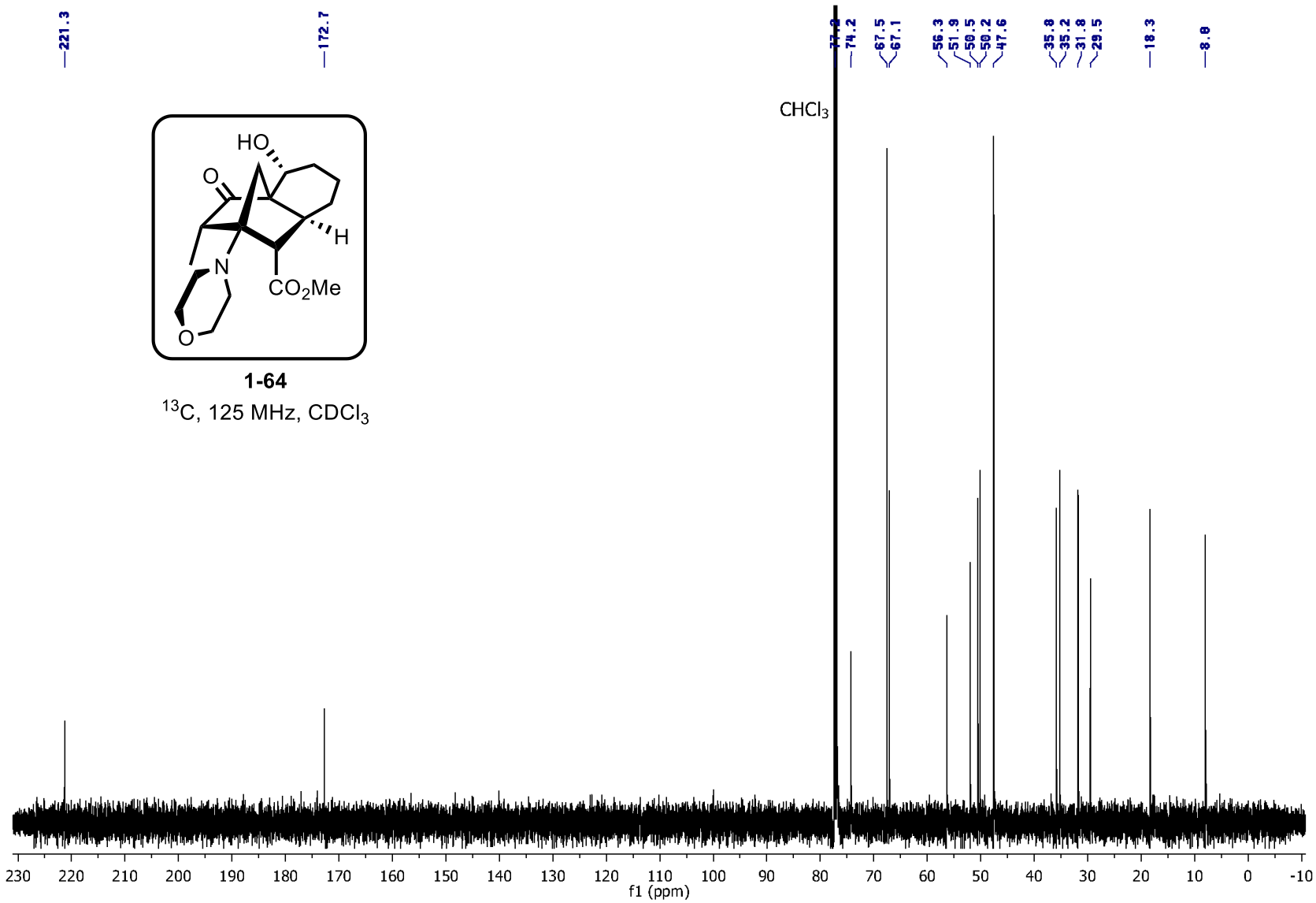
1-63

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



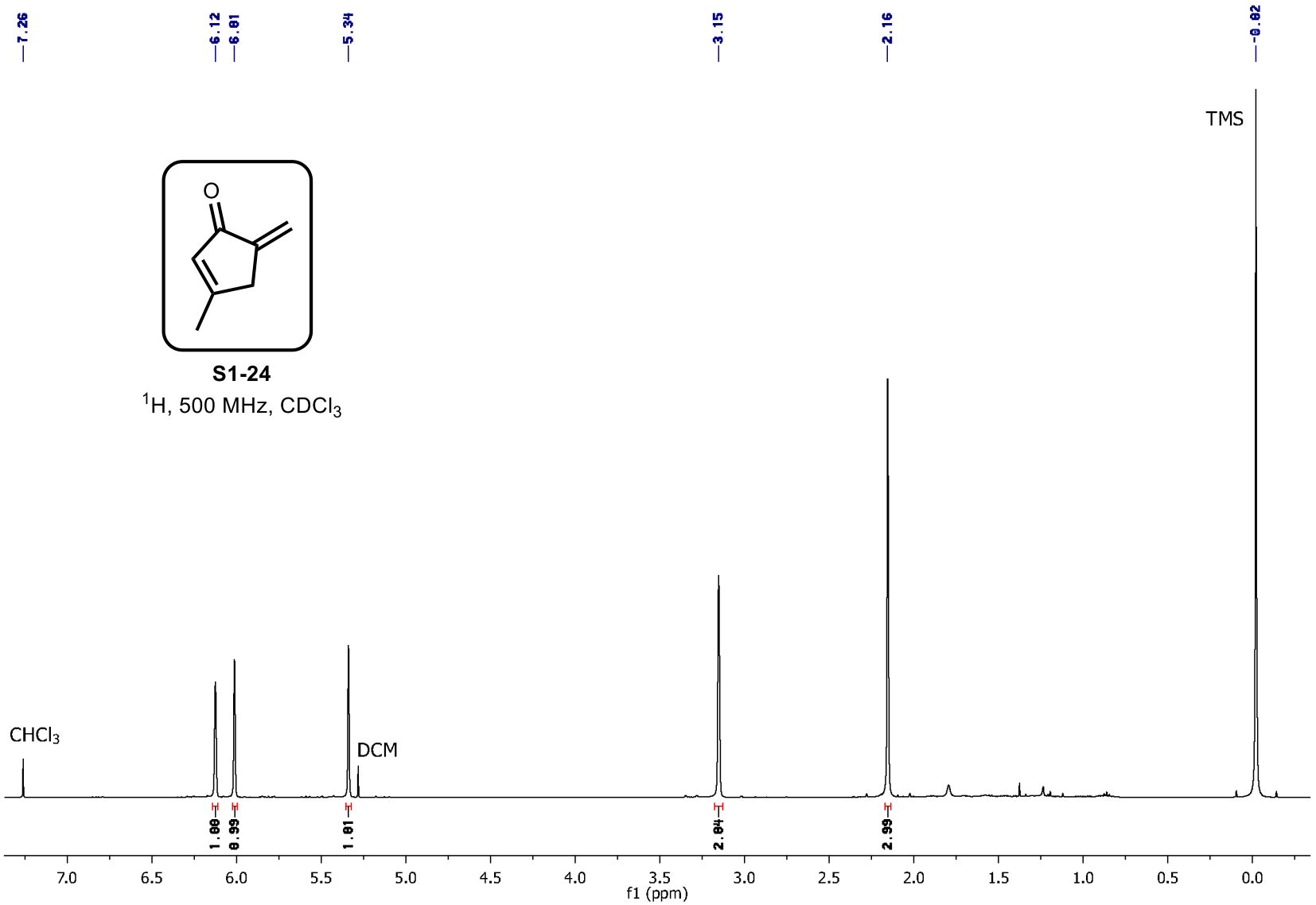
1-64

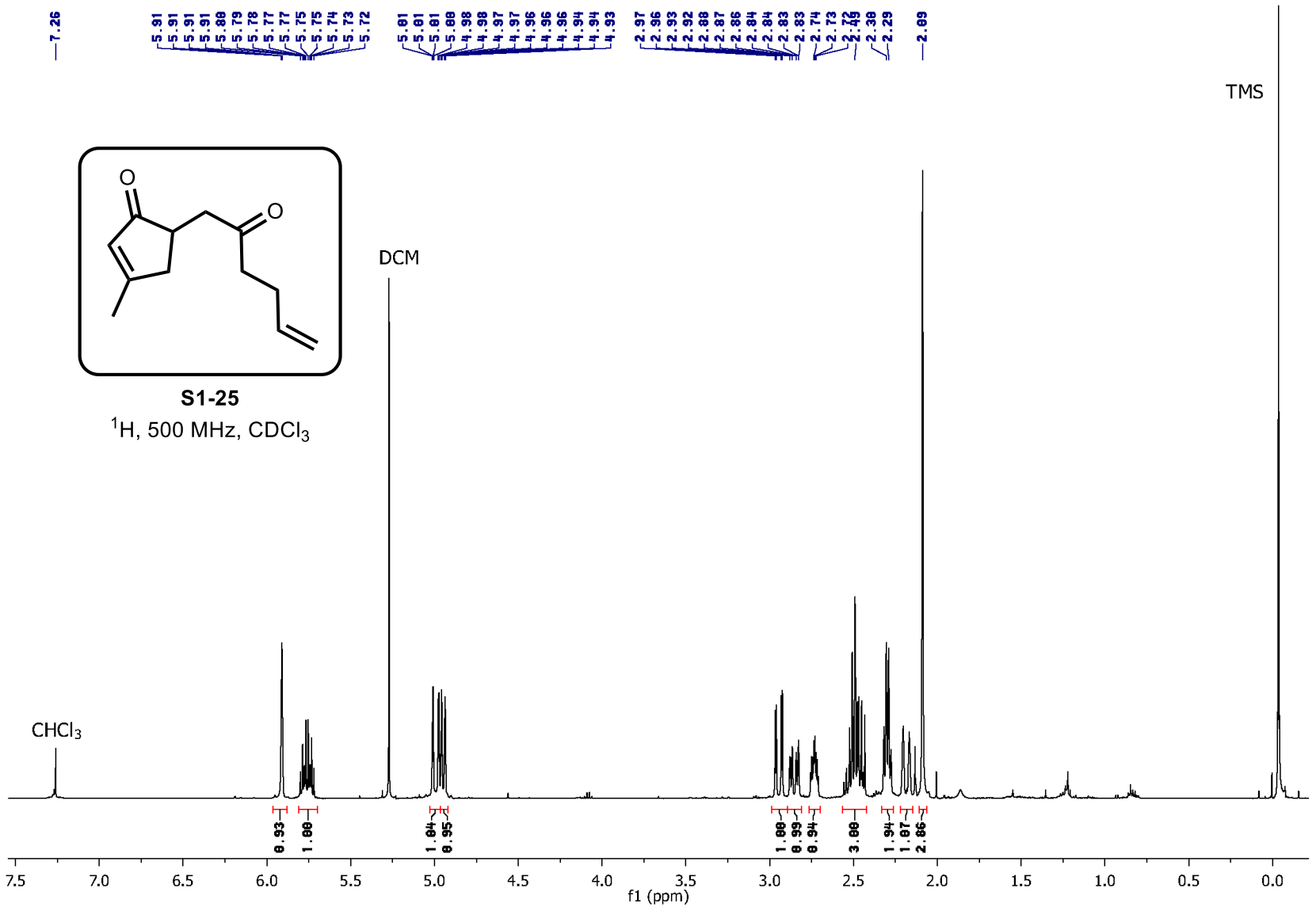
^{1}H, 500 MHz, $CDCl_3$

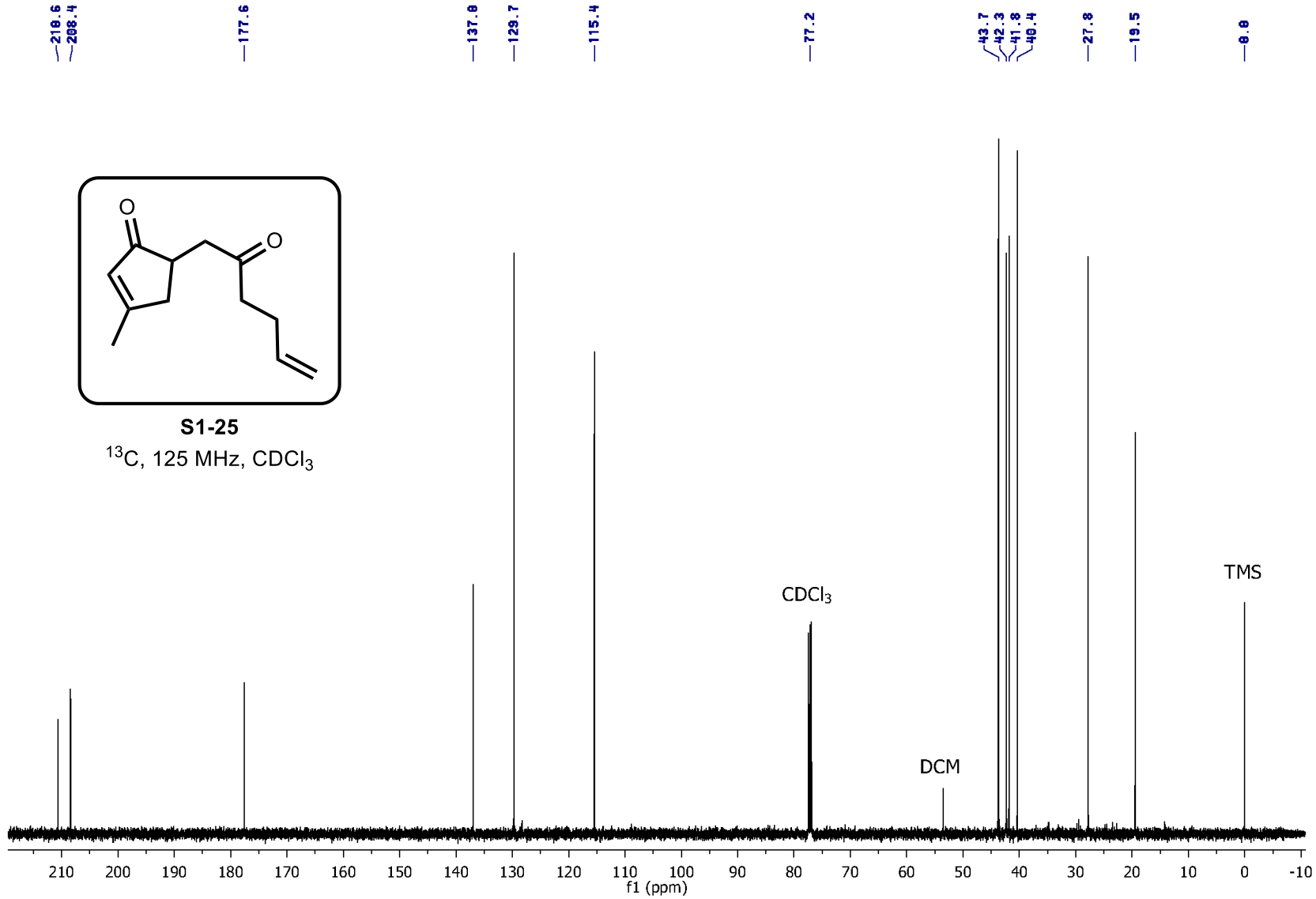


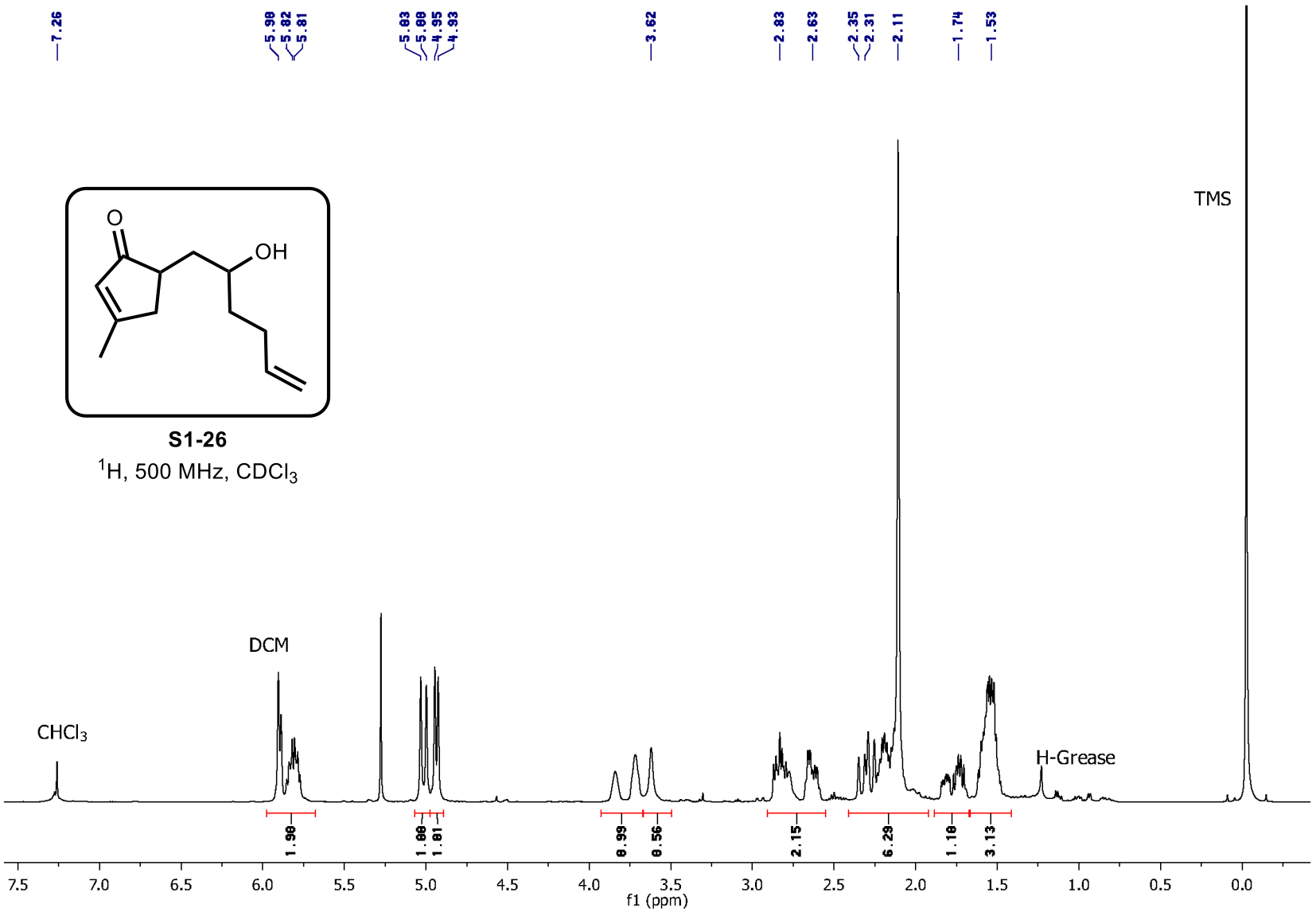
1-64

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


7.26
6.12
6.01
5.34
3.15
2.16
0.02
TMS
O
S1-24
1H, 500 MHz, CDCl3
CHCl3
DCM
1.00
0.99
1.01
2.04
2.99
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

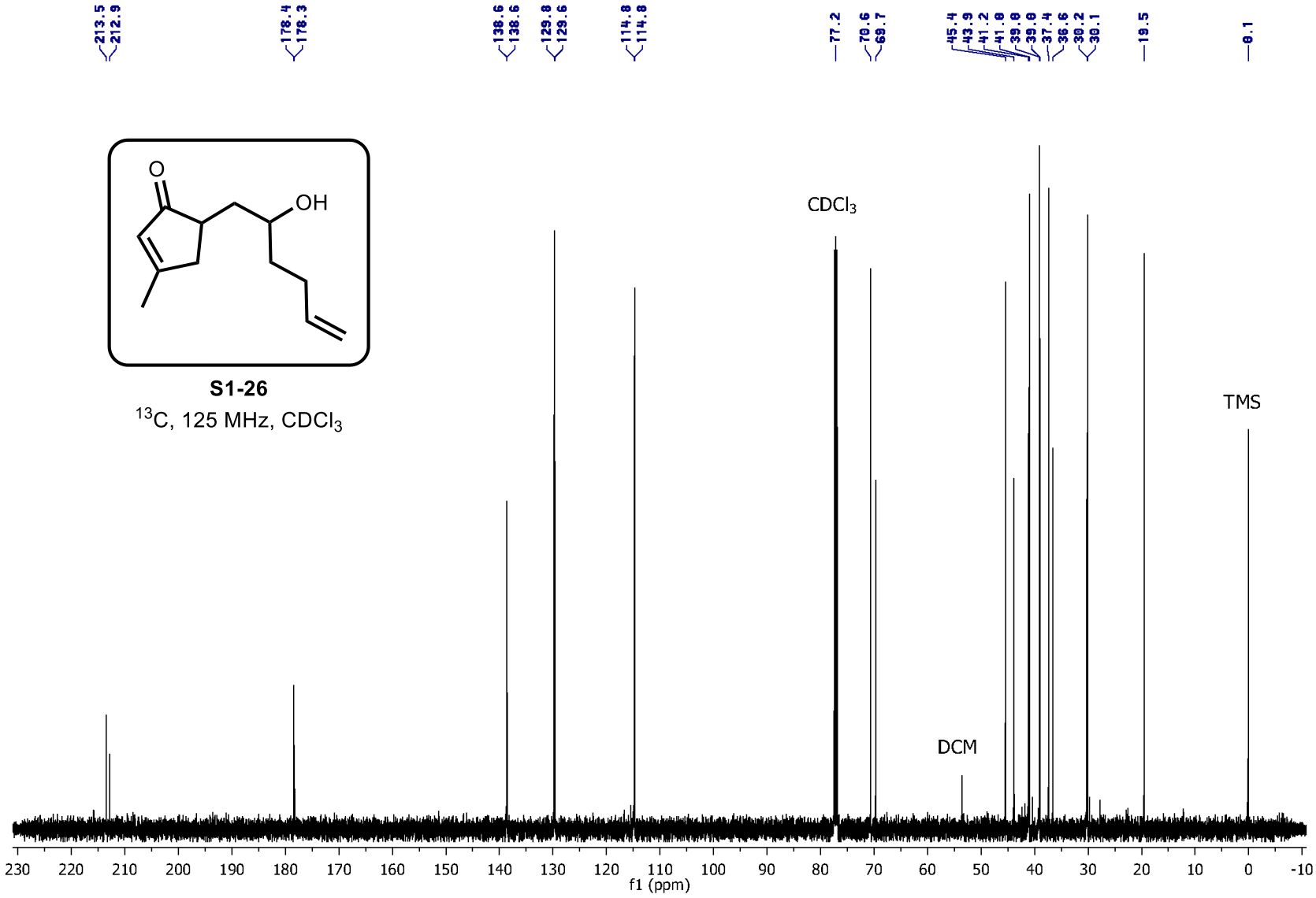

7.26
5.91
5.91
5.91
5.91
5.80
5.79
5.78
5.77
5.77
5.75
5.75
5.74
5.73
5.72
5.01
5.01
5.01
5.00
4.98
4.98
4.97
4.97
4.96
4.96
4.96
4.94
4.94
4.93
2.97
2.96
2.93
2.92
2.88
2.87
2.86
2.84
2.84
2.83
2.83
2.74
2.73
2.49
2.30
2.29
2.09
TMS
DCM
CHCl3
O
O
S1-25
1H, 500 MHz, CDCl3
0.93
1.00
1.04
0.95
1.00
0.99
0.94
3.00
1.94
1.07
2.86
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


210.6
208.4
177.6
137.0
129.7
115.4
77.2
43.7
42.3
41.8
40.4
27.8
19.5
0.0
O
O
S1-25
13C, 125 MHz, CDCl3
CDCl3
DCM
TMS
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)



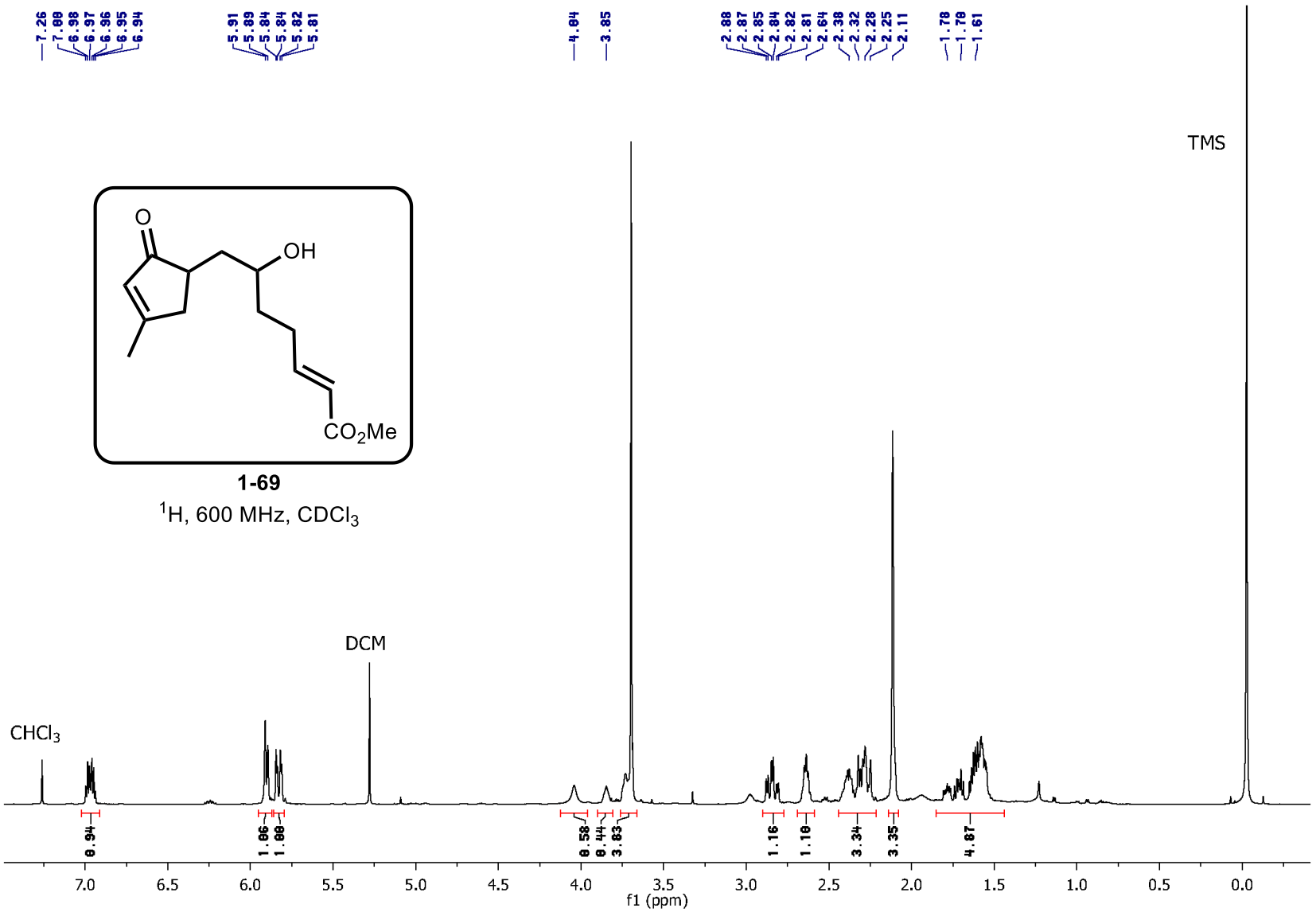
S1-26

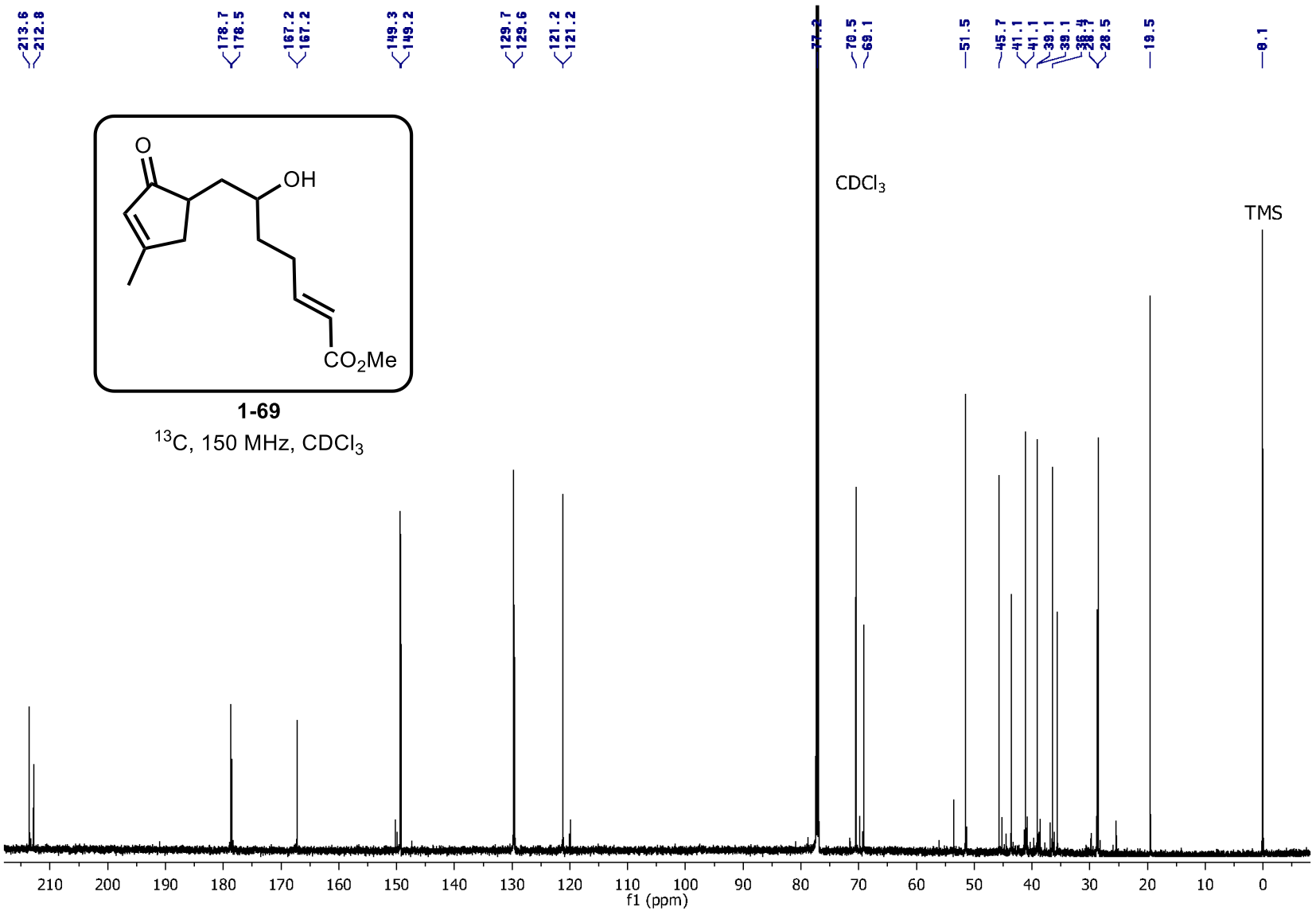
^{1}H, 500 MHz, $CDCl_3$



S1-26

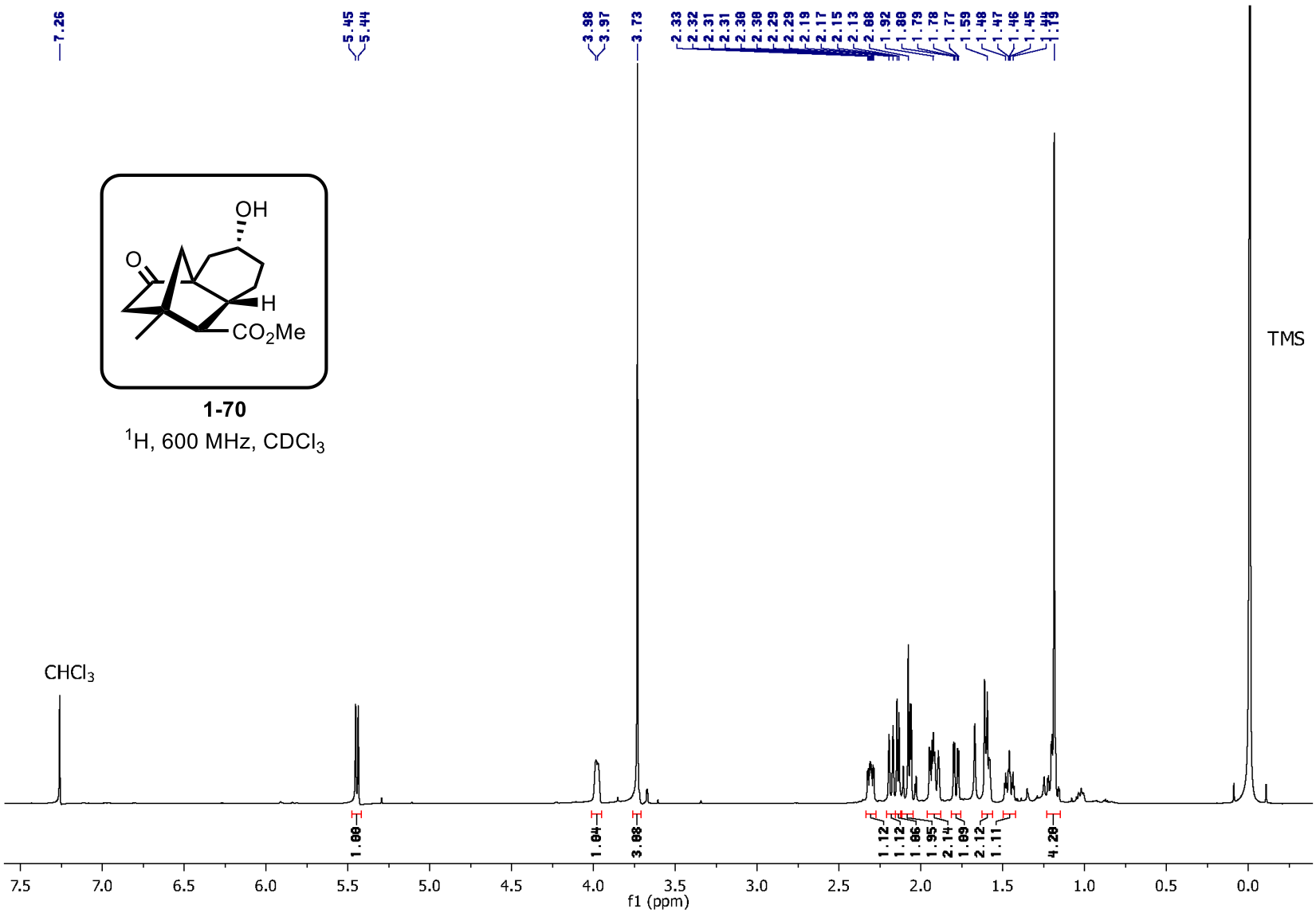
^{13}C, 125 MHz, $CDCl_3$


7.26
7.00
6.98
6.97
6.96
6.95
6.94
5.91
5.89
5.84
5.84
5.82
5.81
4.04
3.85
2.88
2.87
2.85
2.84
2.82
2.81
2.64
2.38
2.32
2.28
2.25
2.11
1.78
1.70
1.61
TMS
O
OH
CO2Me
1-69
1H, 600 MHz, CDCl3
DCM
CHCl3
0.94
1.06
1.00
0.58
0.44
3.83
1.16
1.10
3.34
3.35
4.87
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



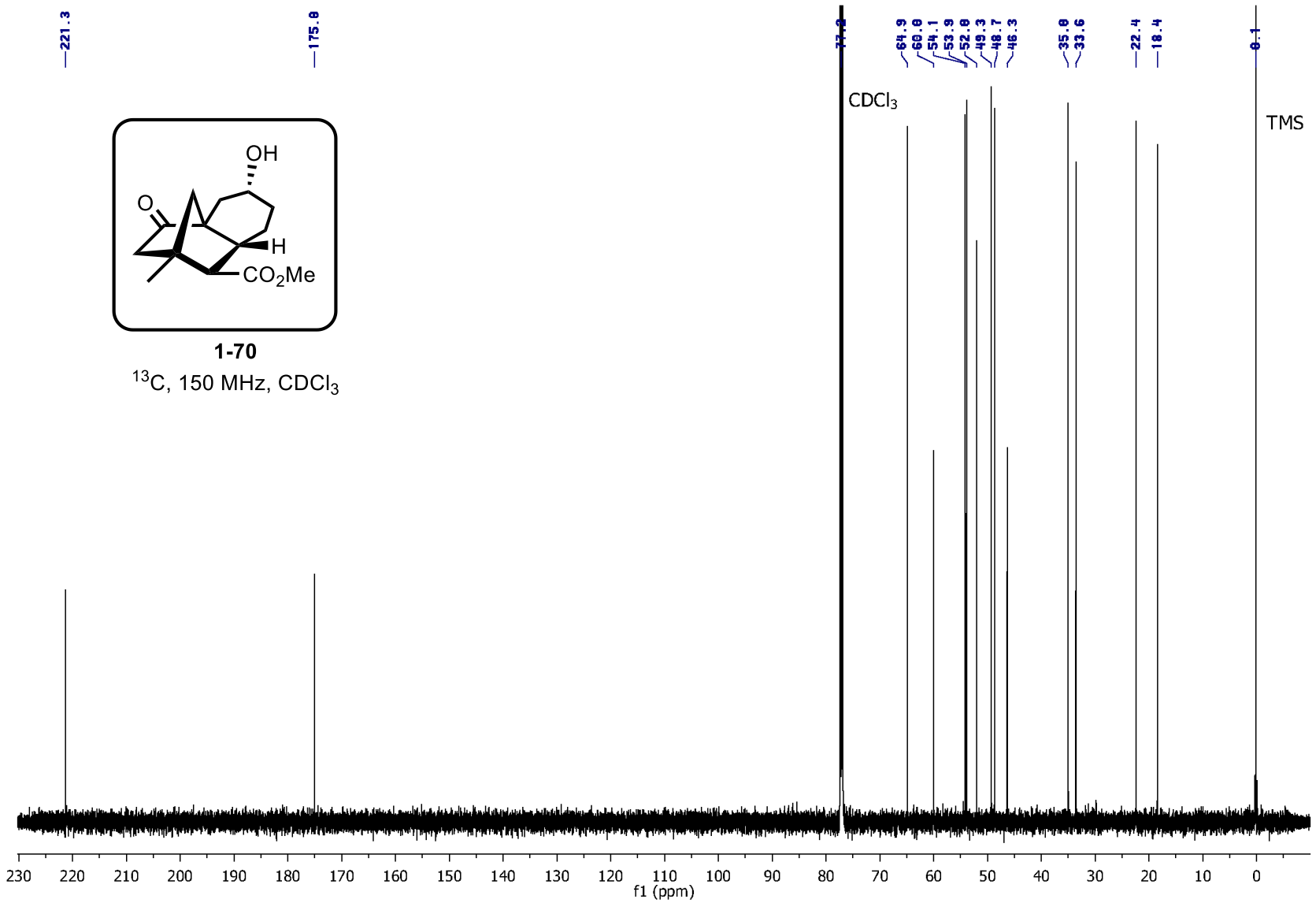
1-69

^{13}C, 150 MHz, $CDCl_3$



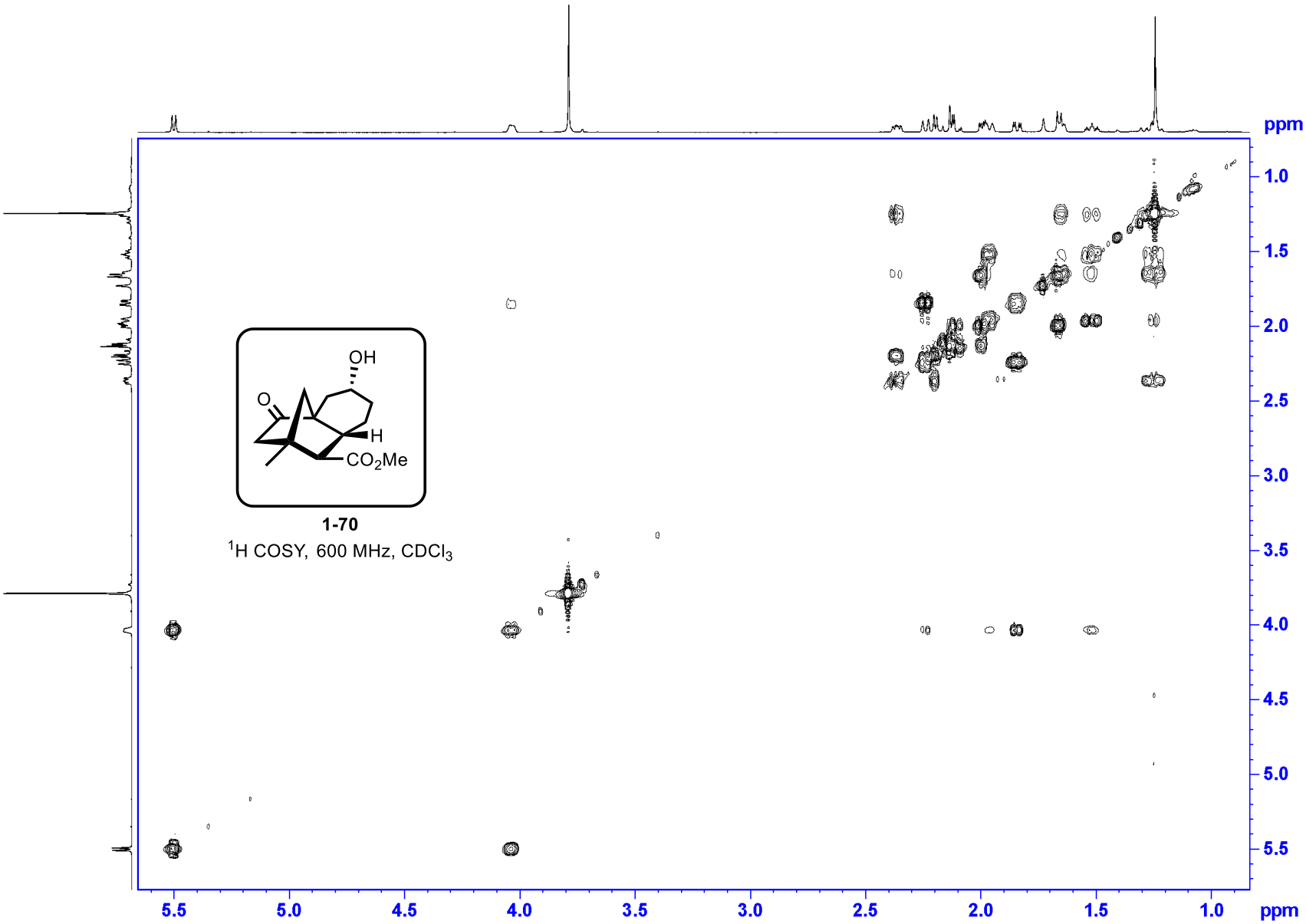
1-70

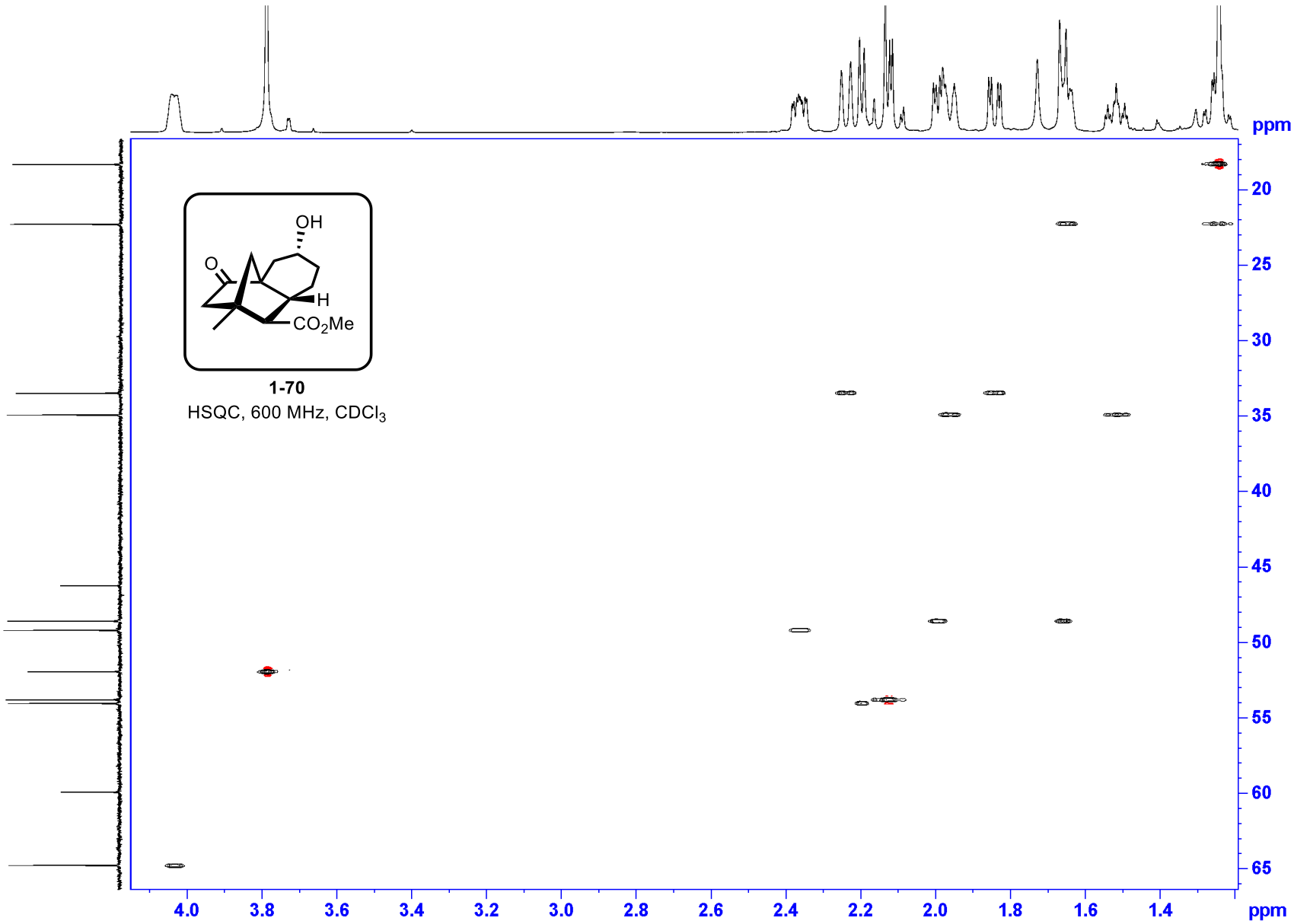
^{1}H, 600 MHz, $CDCl_3$

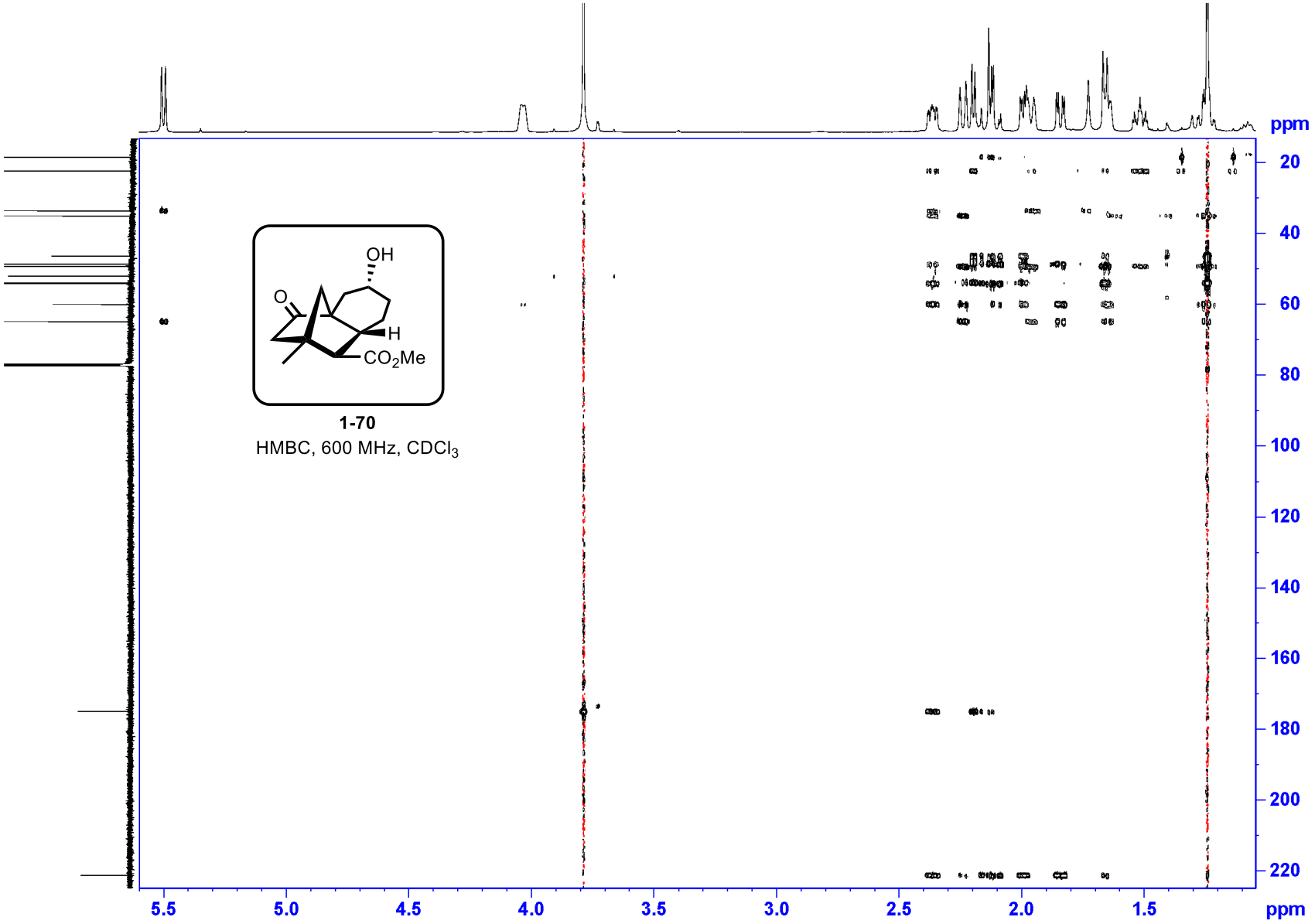


1-70

^{13}C, 150 MHz, $CDCl_3$

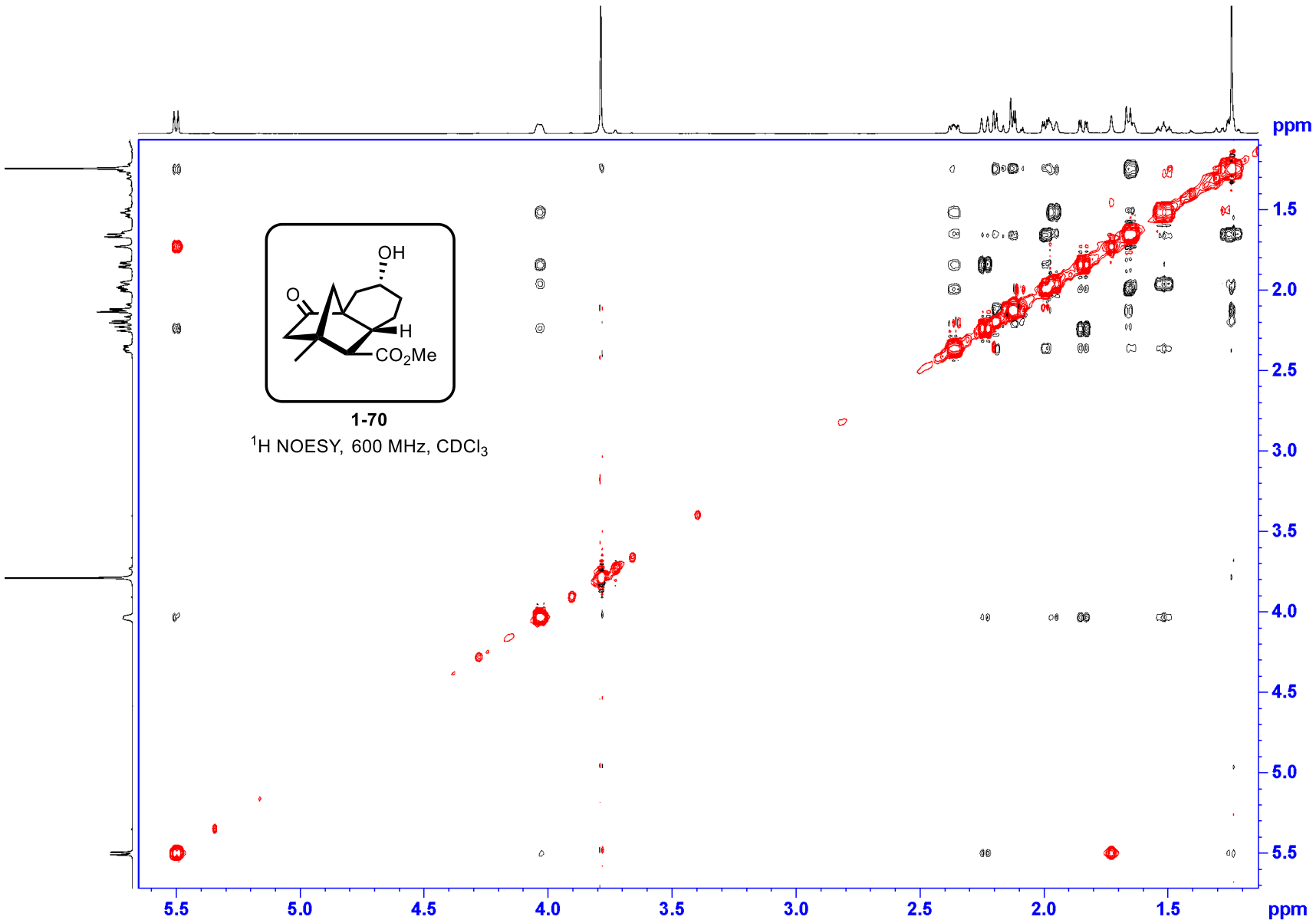

OH
O
H
CO2Me
1-70
1H COSY, 600 MHz, CDCl3
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
ppm

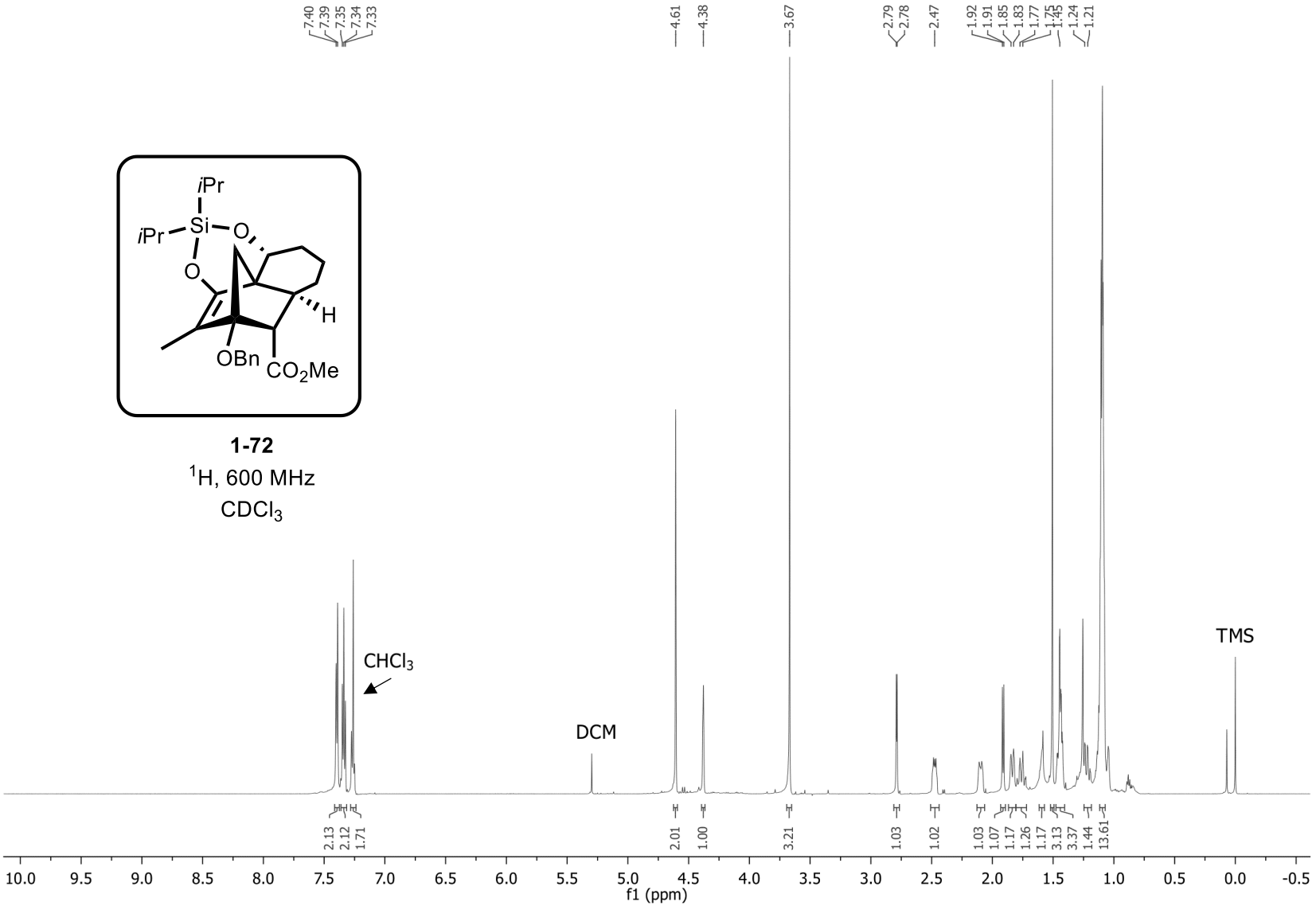

OH
O
H
CO2Me
1-70
HSQC, 600 MHz, CDCl3
ppm
20
25
30
35
40
45
50
55
60
65
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
ppm

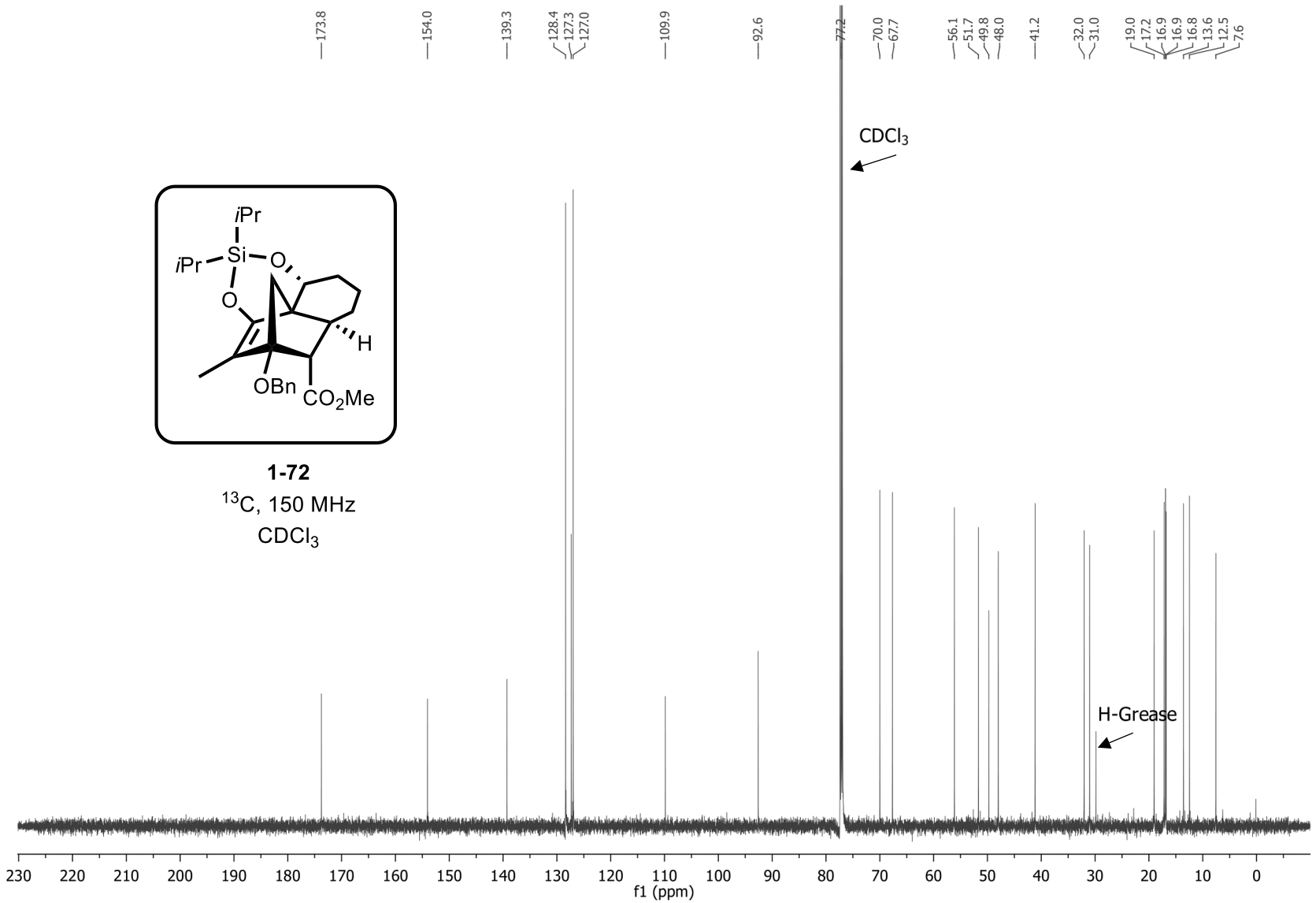


1-70

HMBC, 600 MHz, $CDCl_3$


OH
O
H
CO2Me
1-70
1H NOESY, 600 MHz, CDCl3
ppm
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

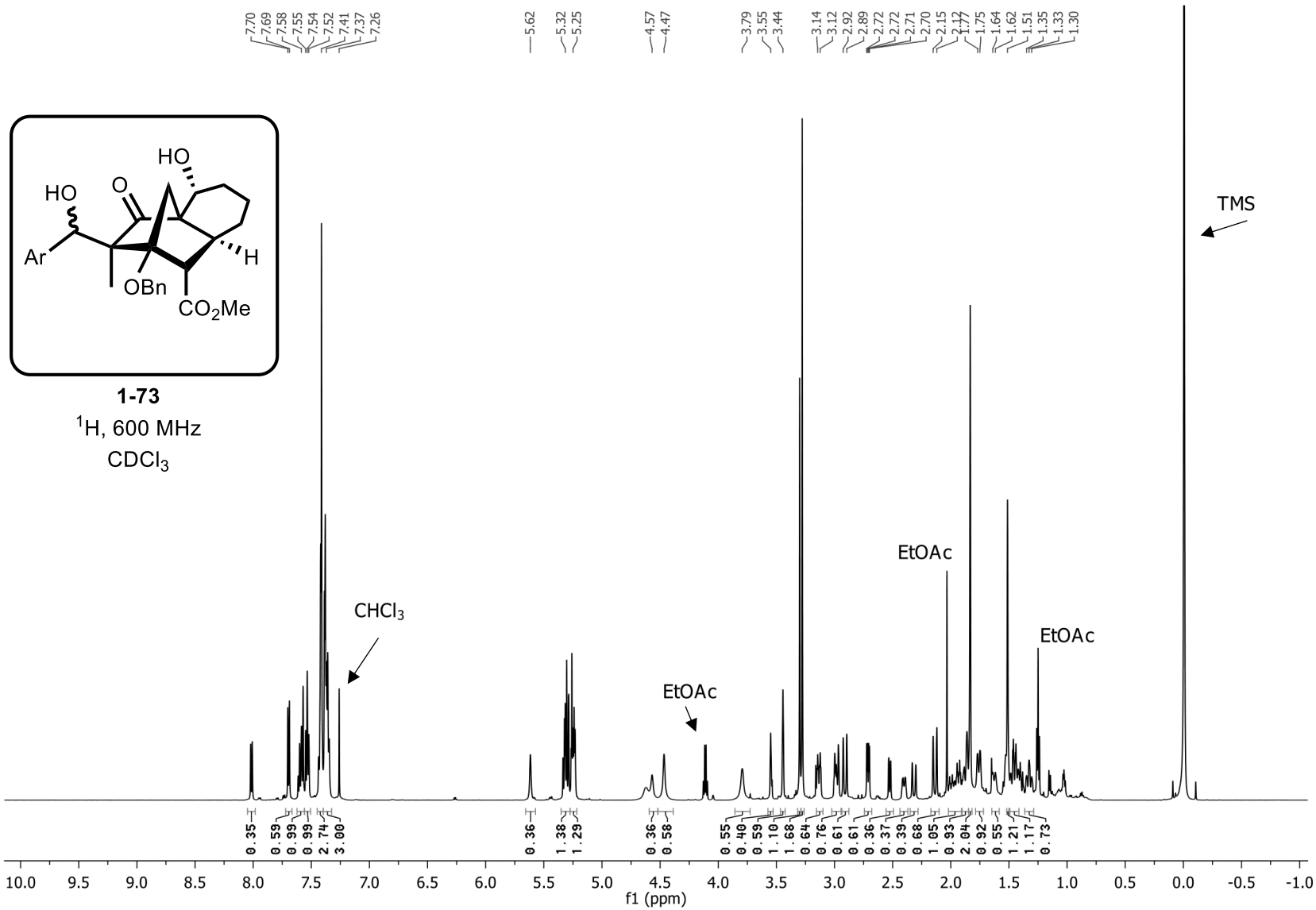

7.40
7.39
7.35
7.34
7.33
4.61
4.38
3.67
2.79
2.78
2.47
1.92
1.91
1.85
1.83
1.77
1.75
1.45
1.24
1.21
iPr
iPr
Si
O
O
H
OBn
CO2Me
1-72
1H, 600 MHz
CDCl3
CHCl3
DCM
TMS
2.13
2.12
1.71
2.01
1.00
3.21
1.03
1.02
1.03
1.07
1.17
1.26
1.17
3.13
3.37
1.44
13.61
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

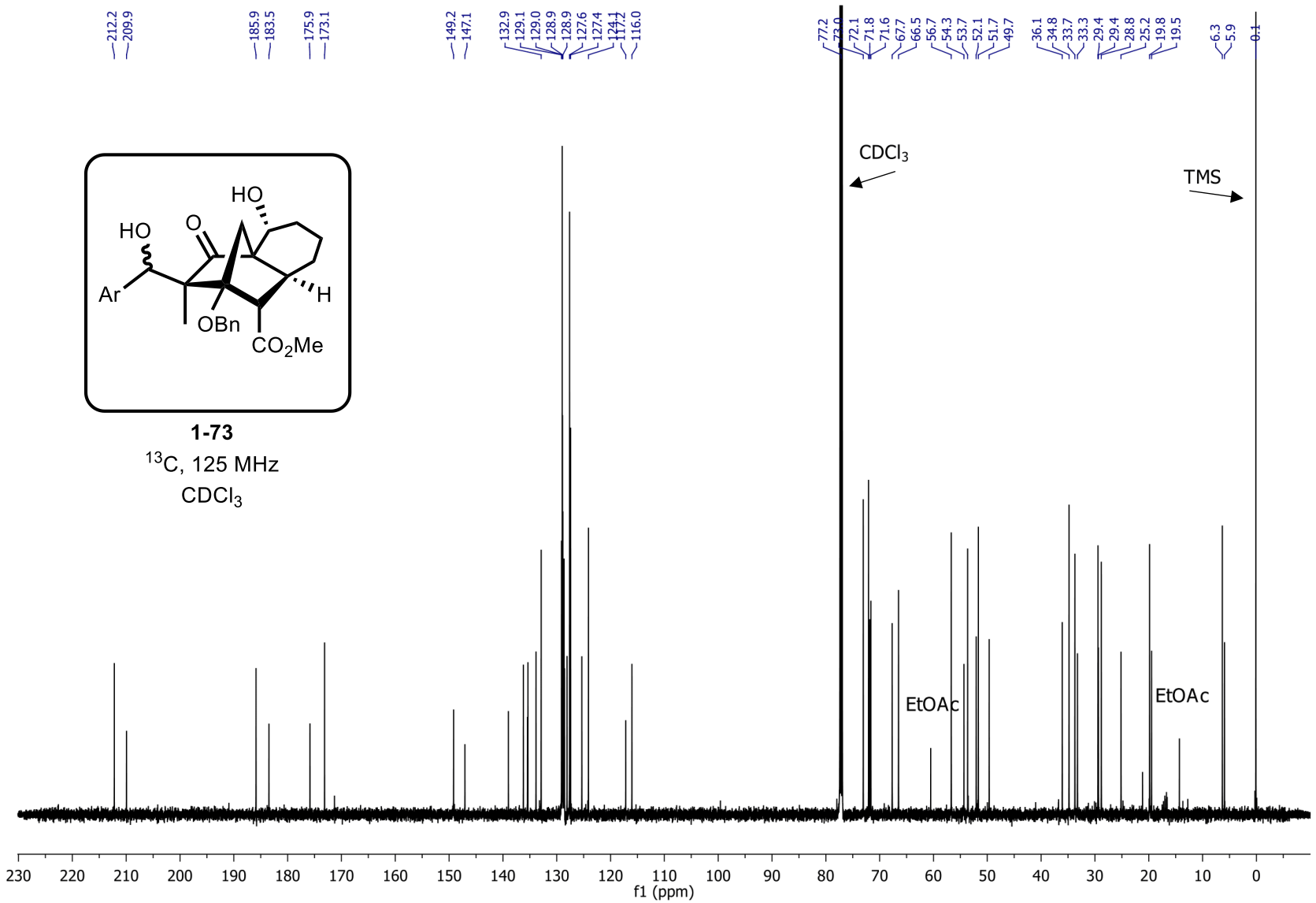


1-72

^{13}C, 150 MHz

$CDCl_3$

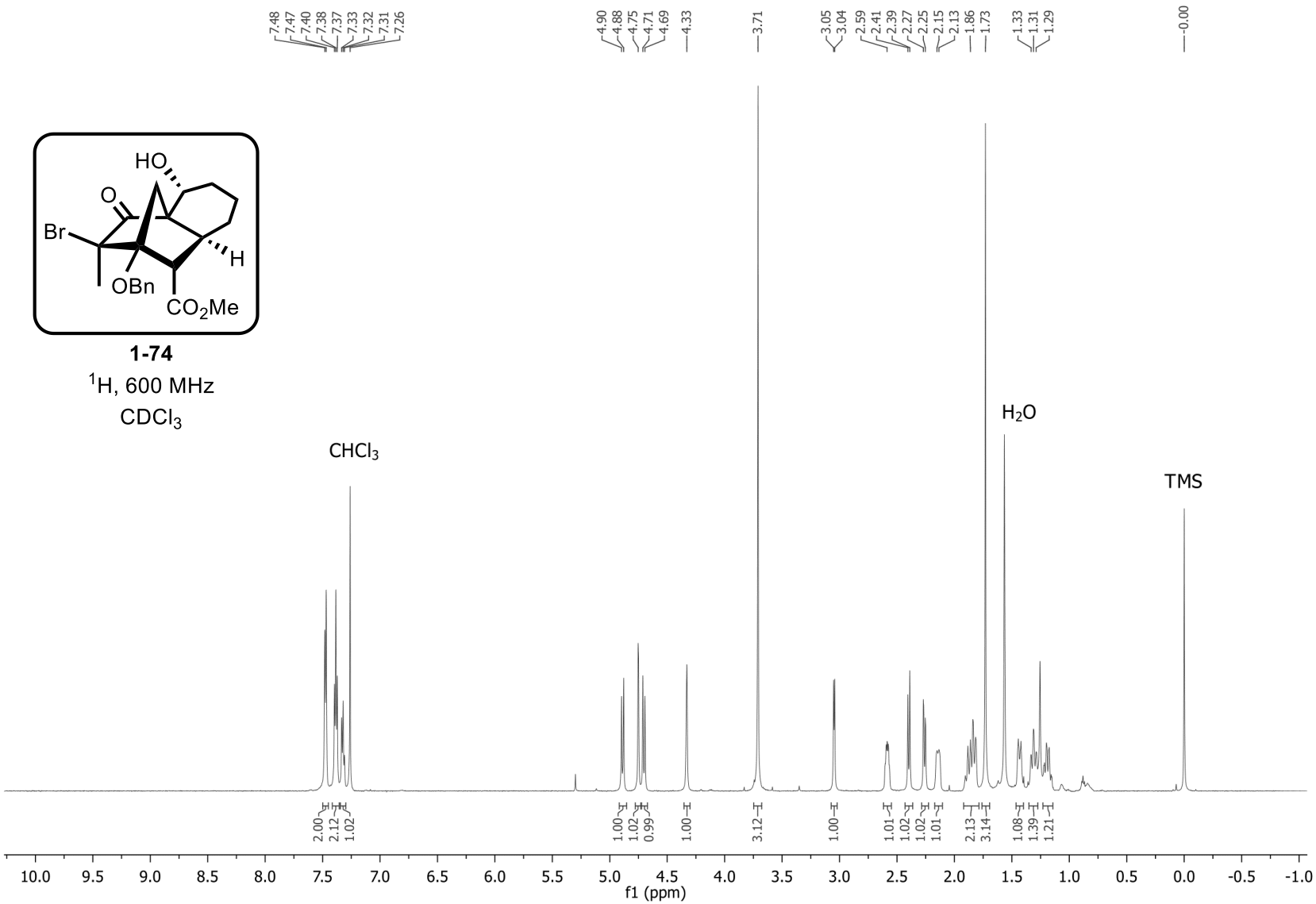

HO
O
HO
Ar
H
OBn
CO2Me
1-73
1H, 600 MHz
CDCl3
TMS
CHCl3
EtOAc
EtOAc
EtOAc
f1 (ppm)

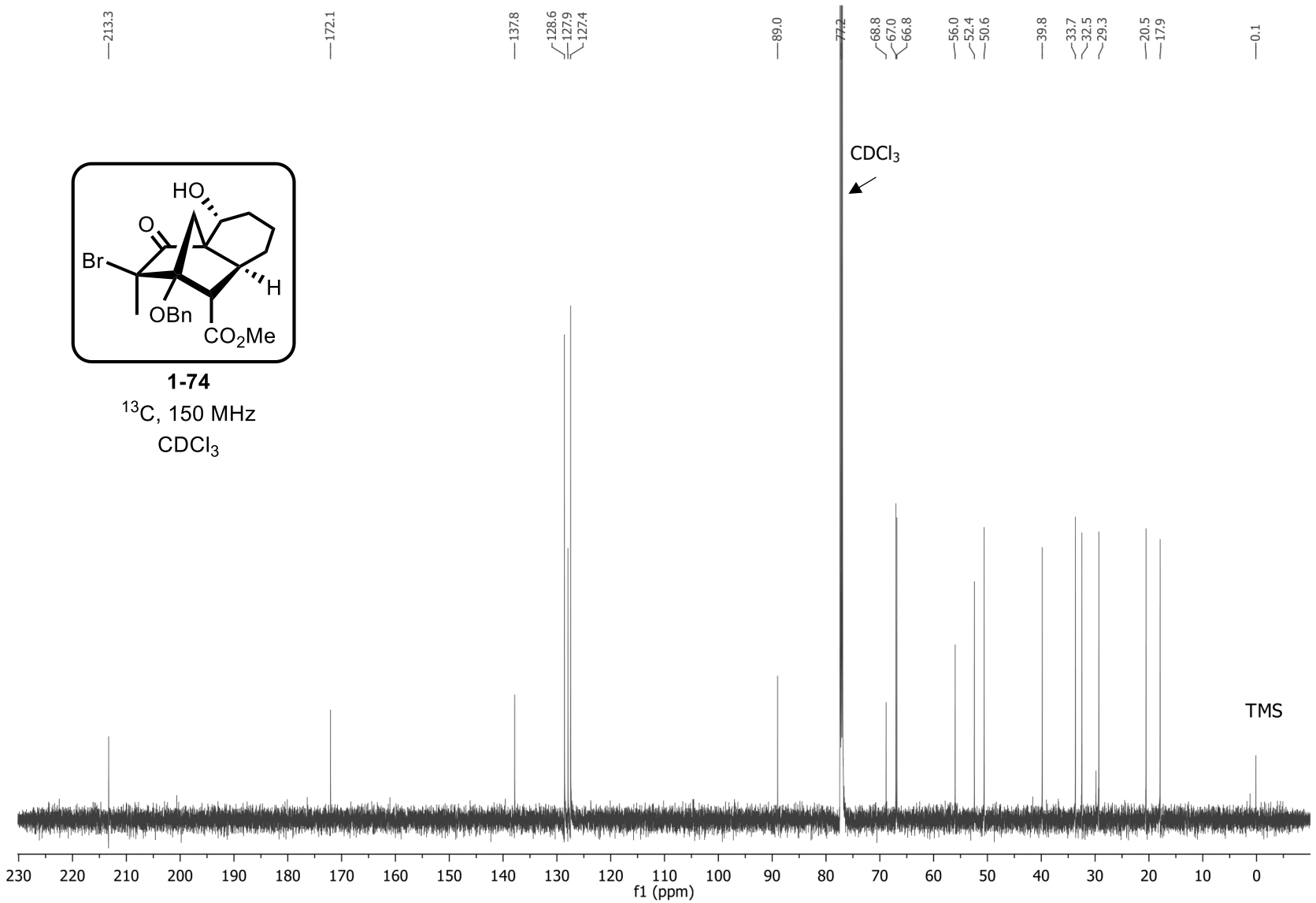


1-73

^{13}C, 125 MHz

$CDCl_3$

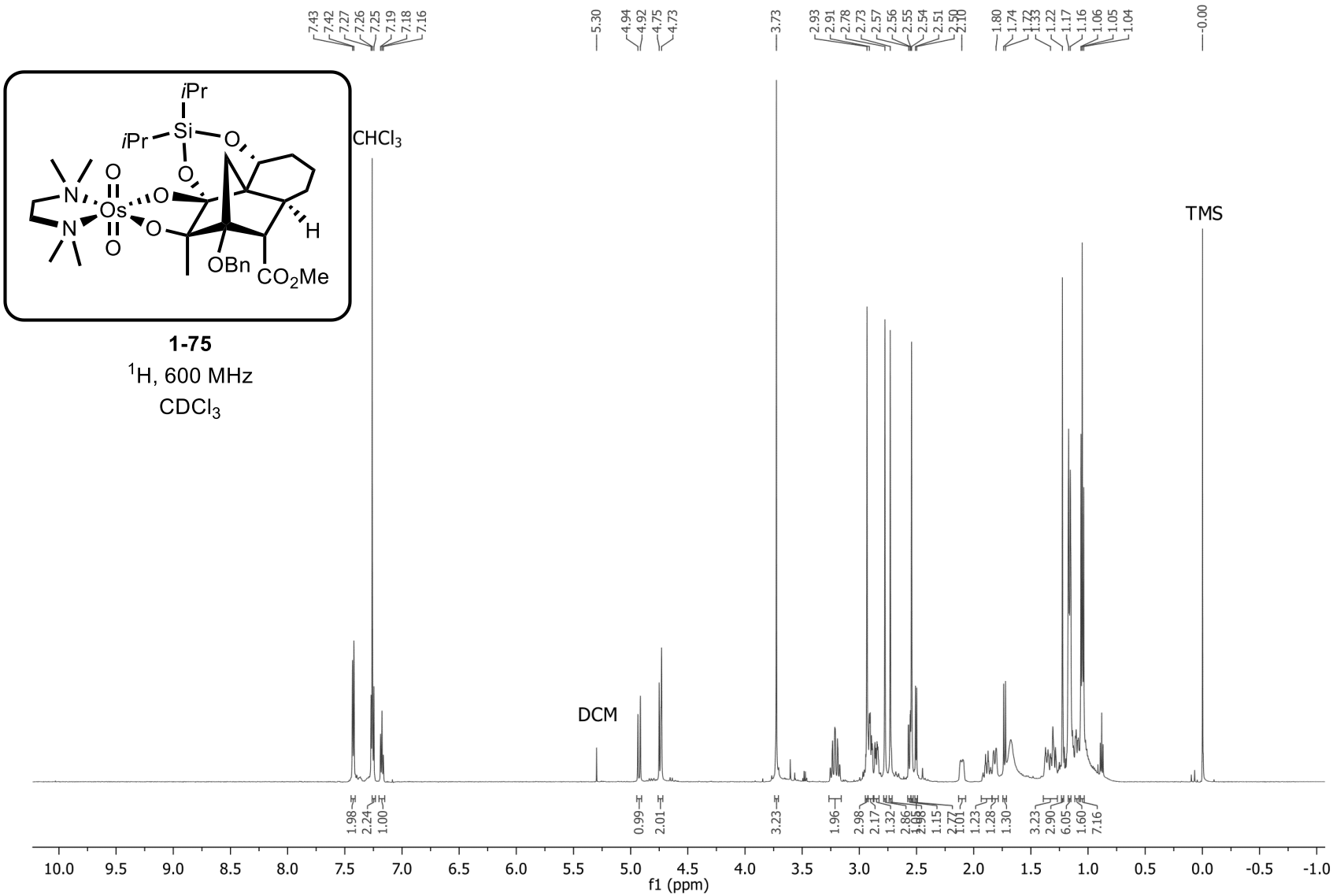

HO
O
Br
H
OBn
CO2Me
1-74
1H, 600 MHz
CDCl3
CHCl3
H2O
TMS
f1 (ppm)

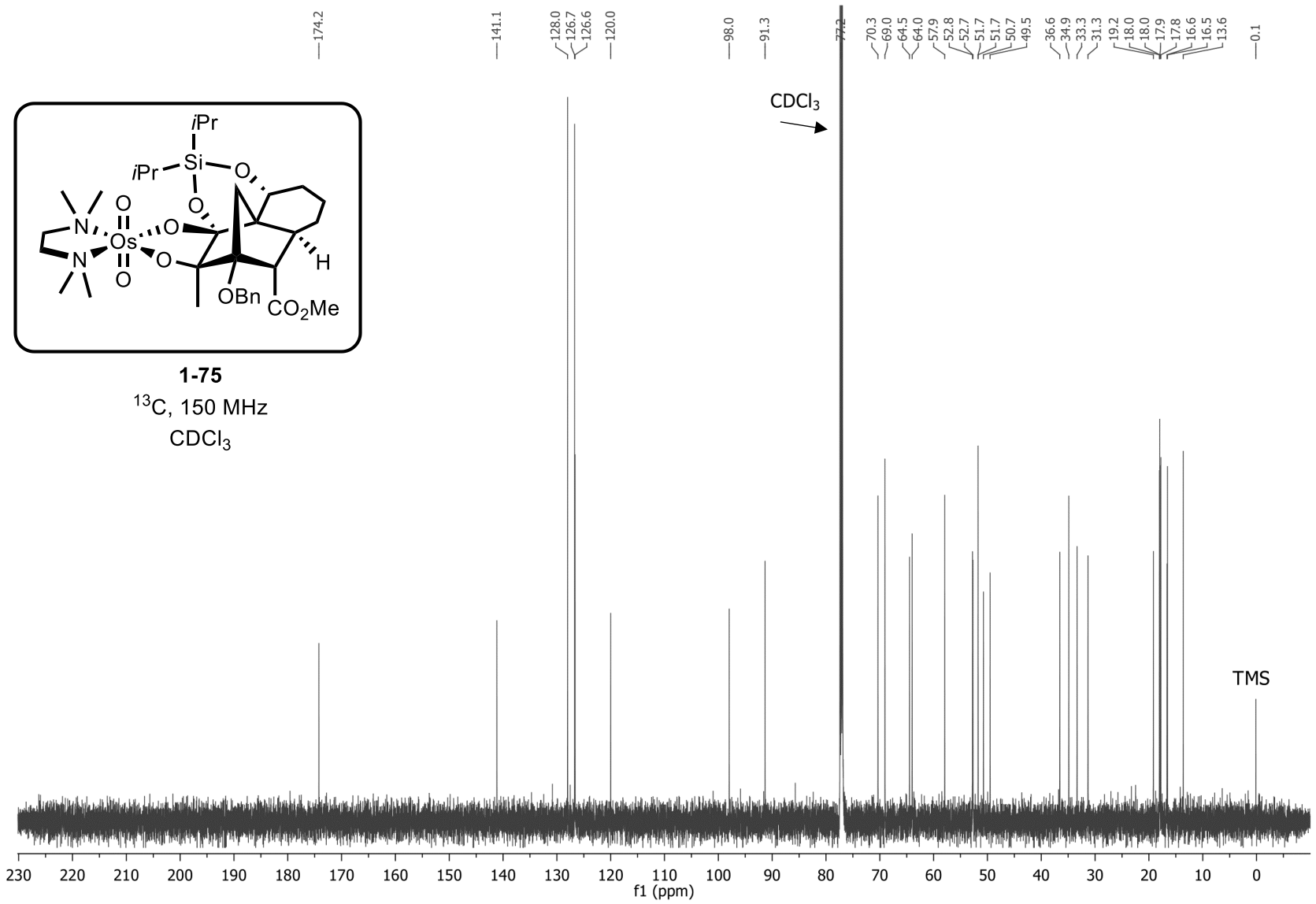


1-74

^{13}C, 150 MHz

$CDCl_3$

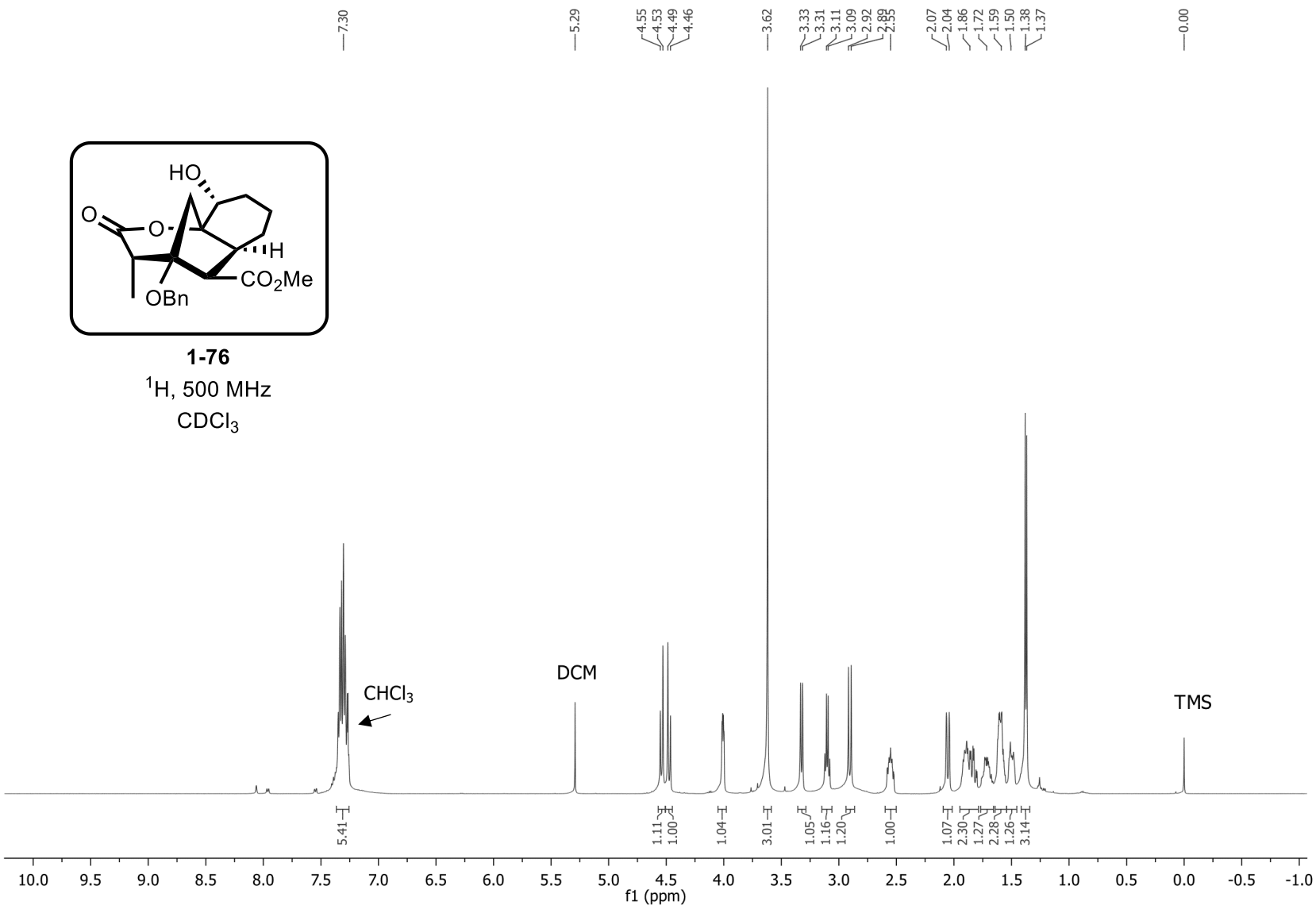

iPr
iPr
Si
O
O
O
N
Os
O
O
N
O
O
H
OBn
CO2Me
1-75
1H, 600 MHz
CDCl3
CHCl3
DCM
TMS
7.43
7.42
7.27
7.26
7.25
7.19
7.18
7.16
5.30
4.94
4.92
4.75
4.73
3.73
2.93
2.91
2.78
2.73
2.57
2.56
2.55
2.54
2.51
2.10
1.80
1.74
1.22
1.17
1.16
1.06
1.05
1.04
-0.00
1.98
2.24
1.00
0.99
2.01
3.23
1.96
2.98
2.17
1.32
1.15
1.01
1.23
1.28
1.30
3.23
2.90
6.05
1.60
7.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

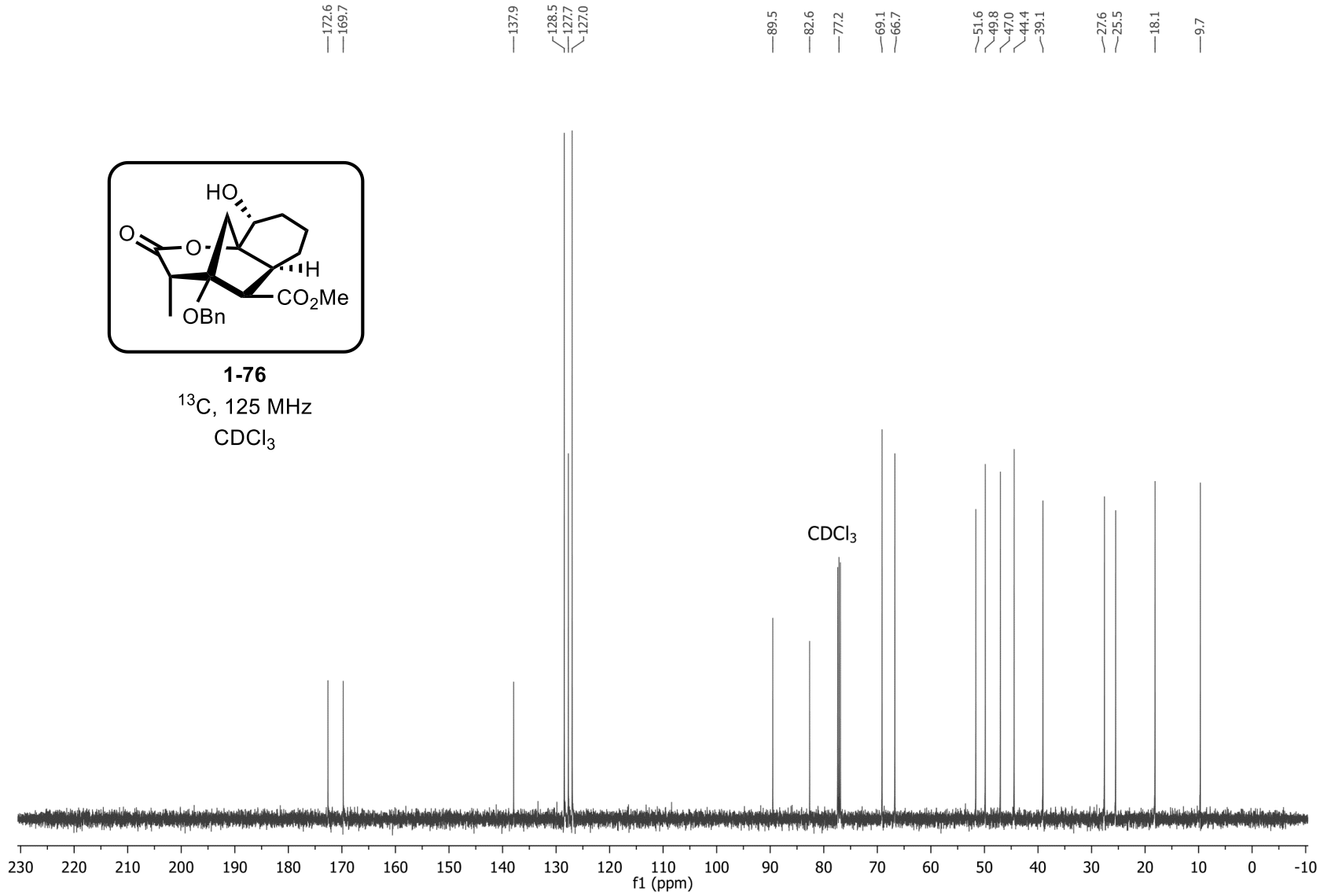


1-75

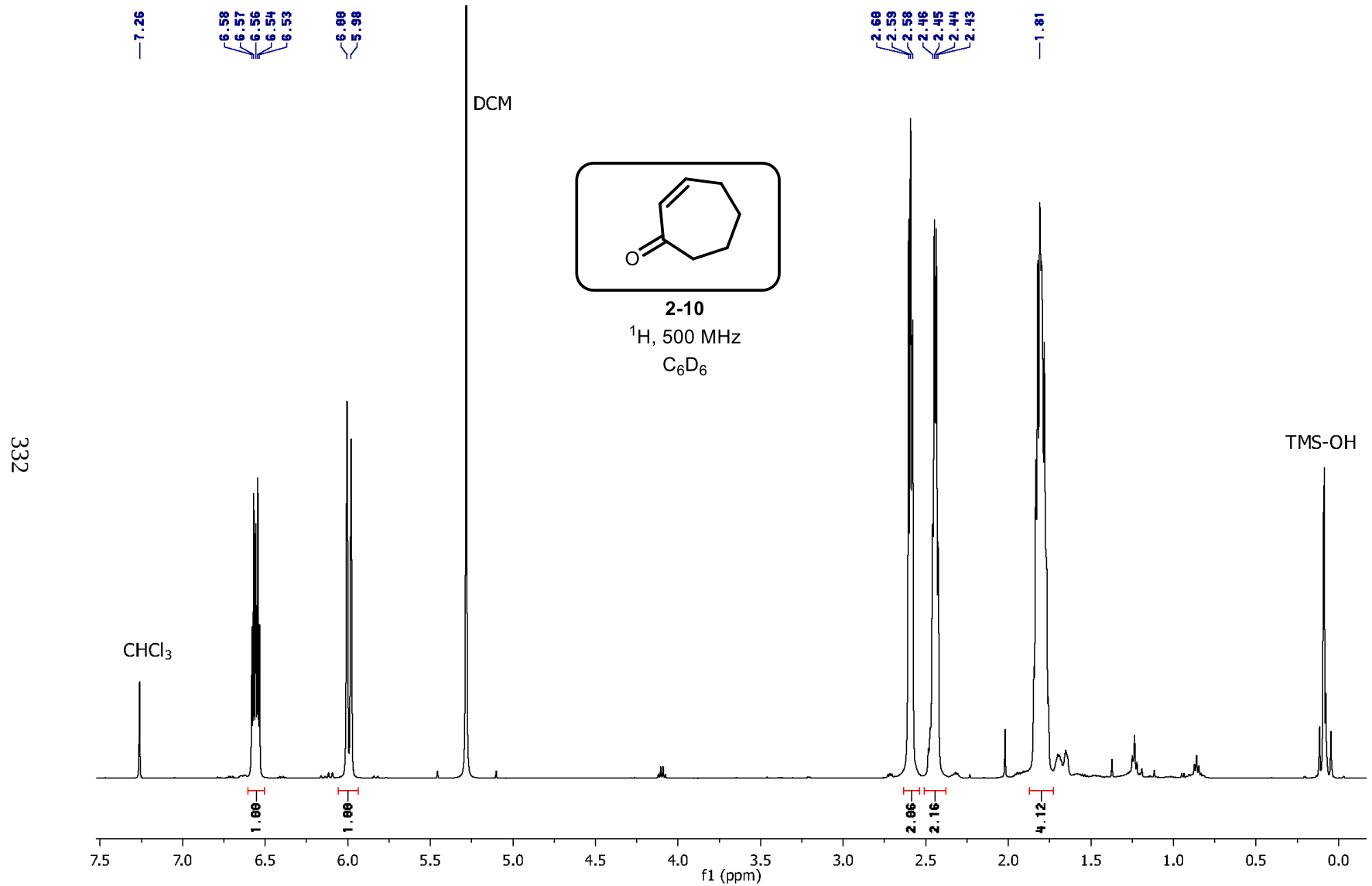
^{13}C, 150 MHz

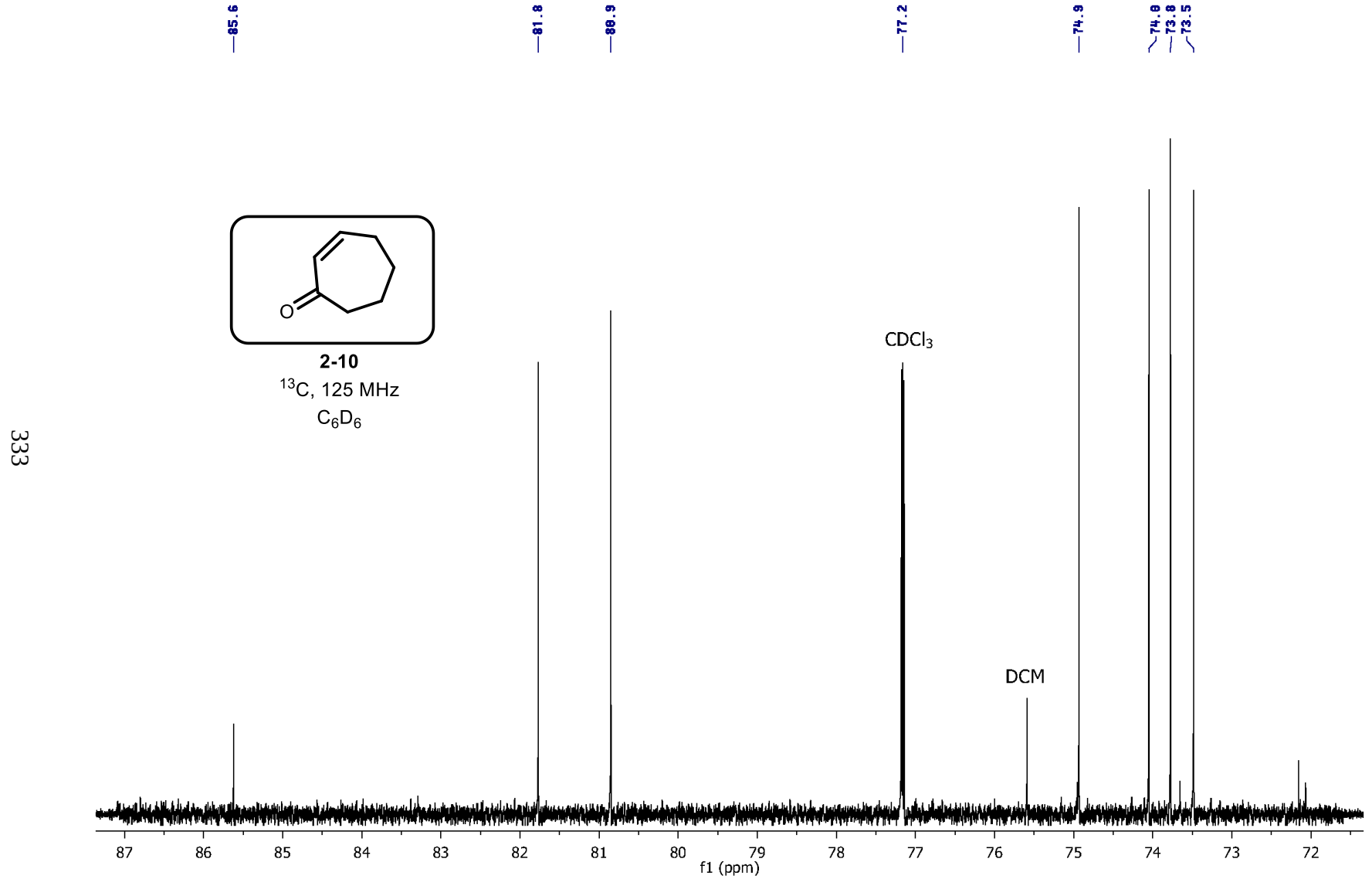
$CDCl_3$

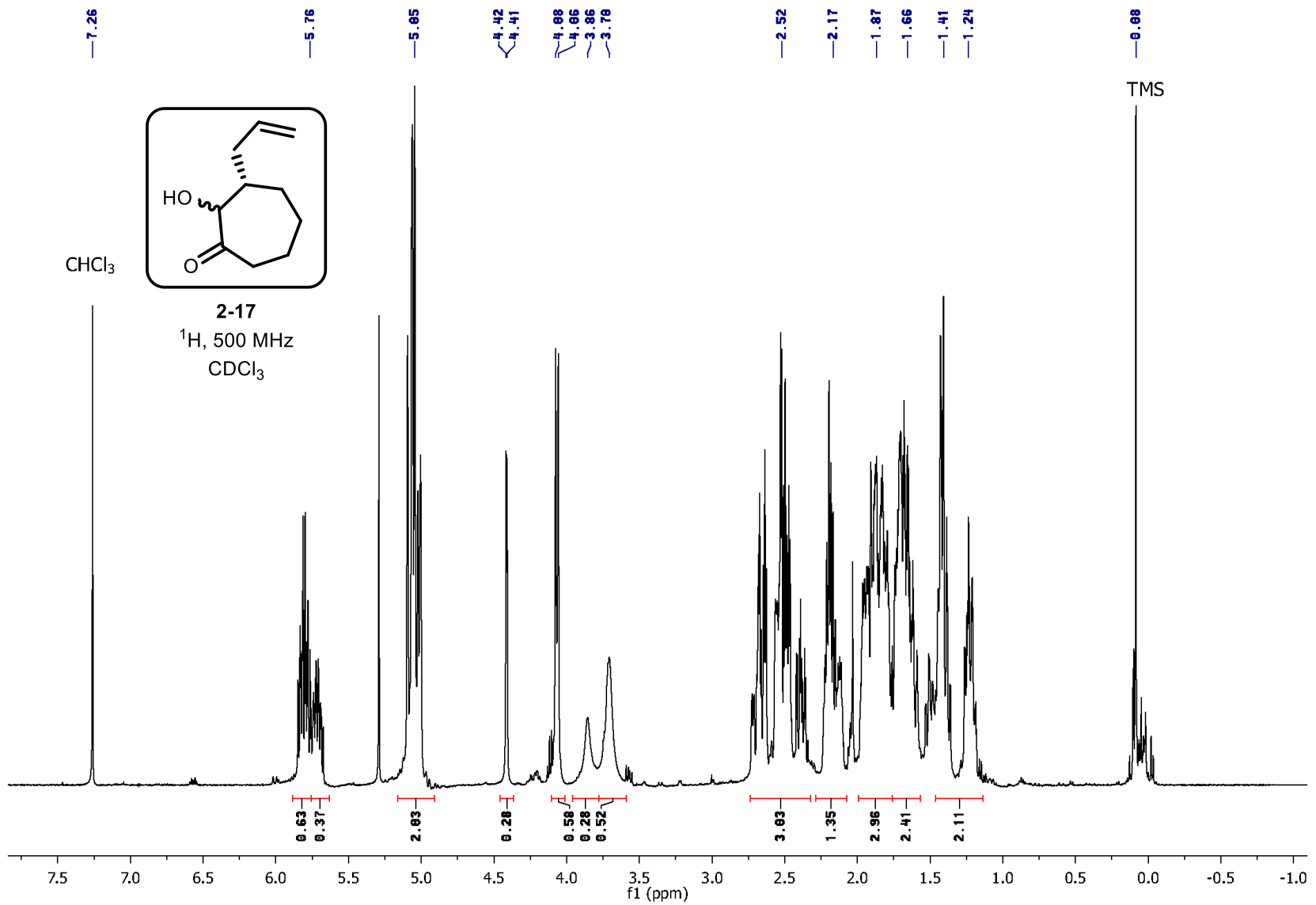

HO
O
O
H
CO2Me
OBn
1-76
1H, 500 MHz
CDCl3
7.30
5.29
4.55
4.53
4.49
4.46
3.62
3.33
3.31
3.11
3.09
2.92
2.89
2.55
2.07
2.04
1.86
1.72
1.59
1.50
1.38
1.37
0.00
CHCl3
DCM
TMS
5.41
1.11
1.00
1.04
3.01
1.05
1.16
1.20
1.00
1.07
2.30
1.27
2.28
1.26
3.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

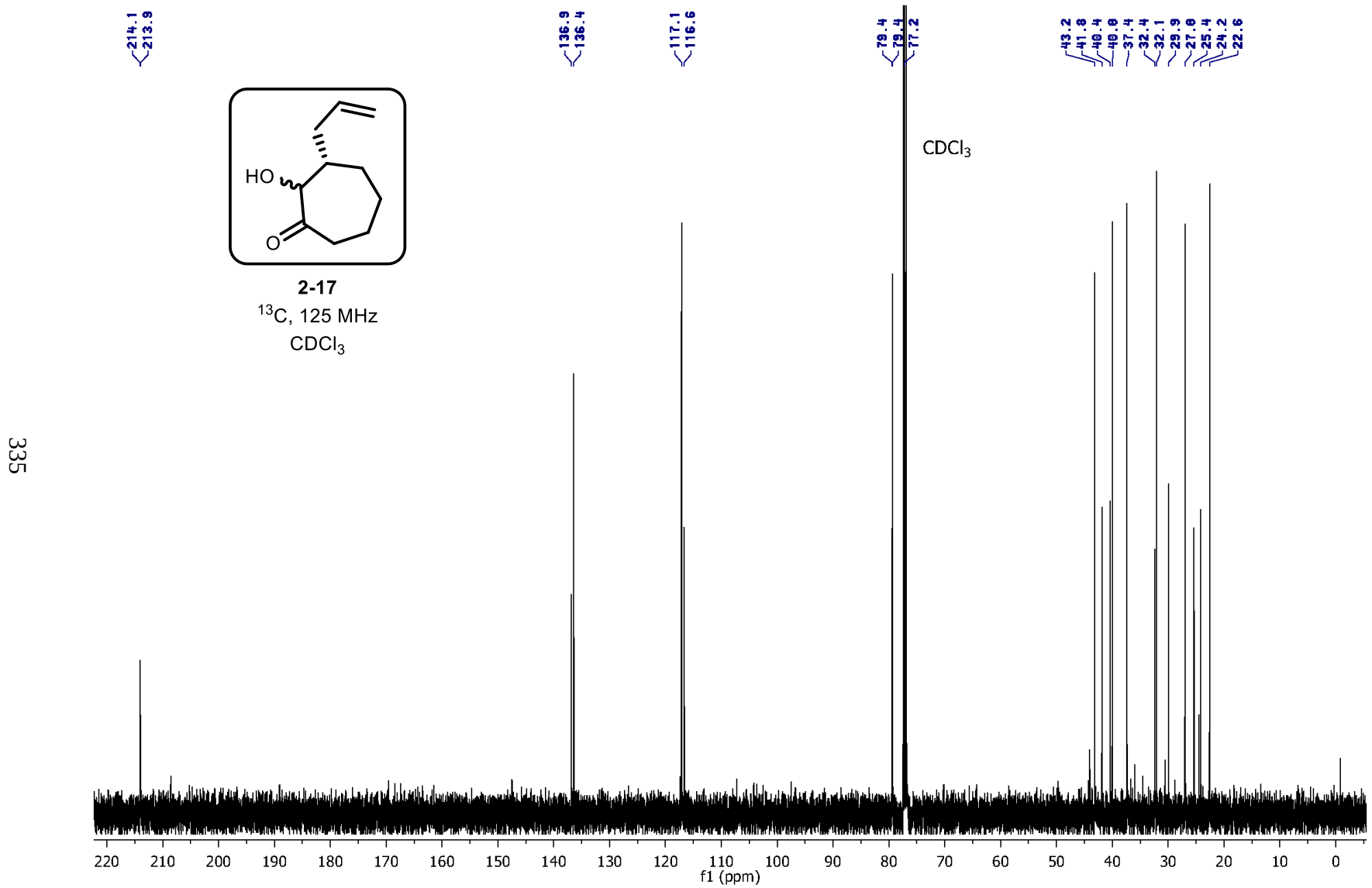

172.6
169.7
137.9
128.5
127.7
127.0
89.5
82.6
77.2
69.1
66.7
51.6
49.8
47.0
44.4
39.1
27.6
25.5
18.1
9.7
HO
O
O
H
CO2Me
OBn
1-76
13C, 125 MHz
CDCl3
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

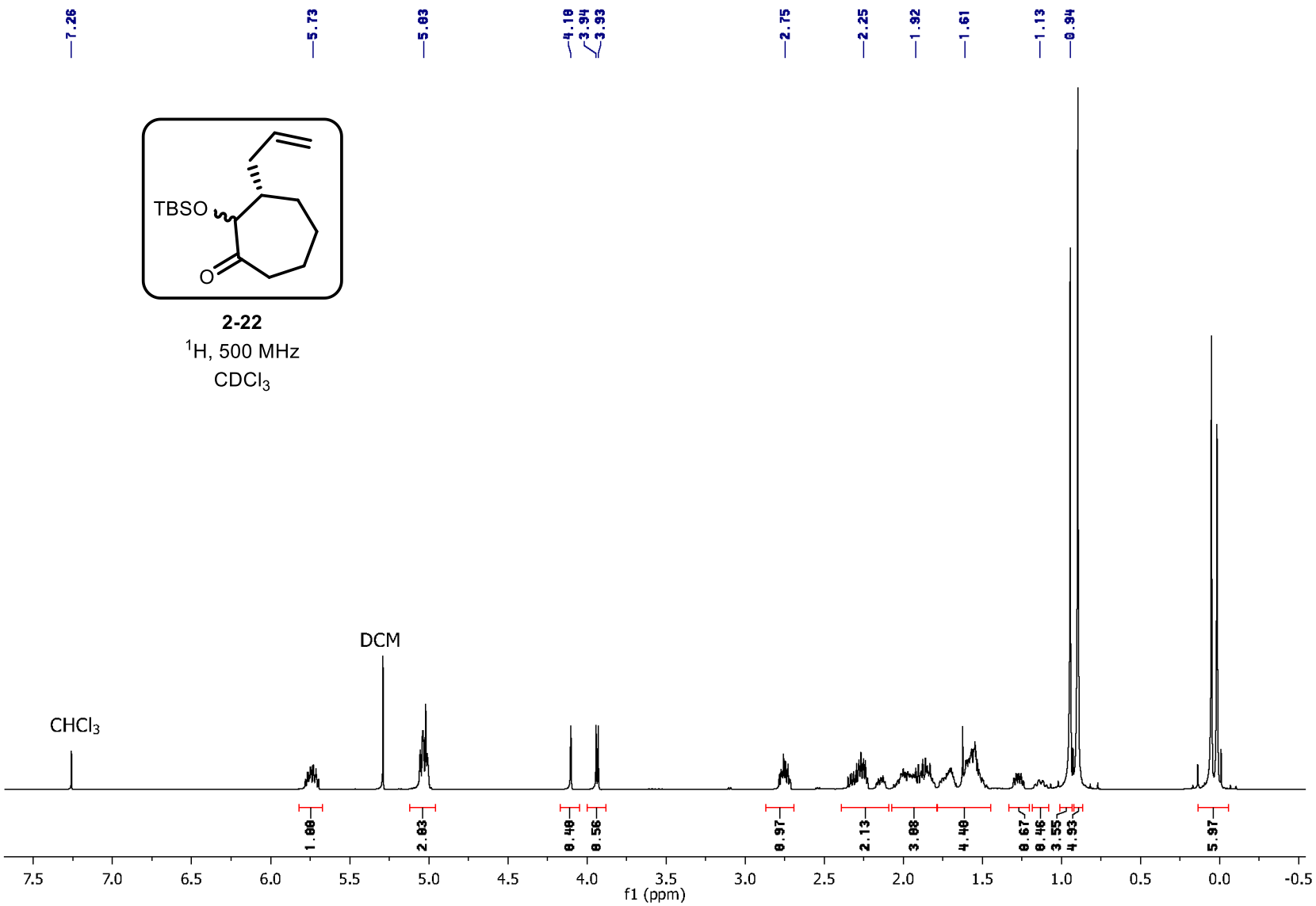
Appendix B: Spectral Data for Compounds in Chapter 2

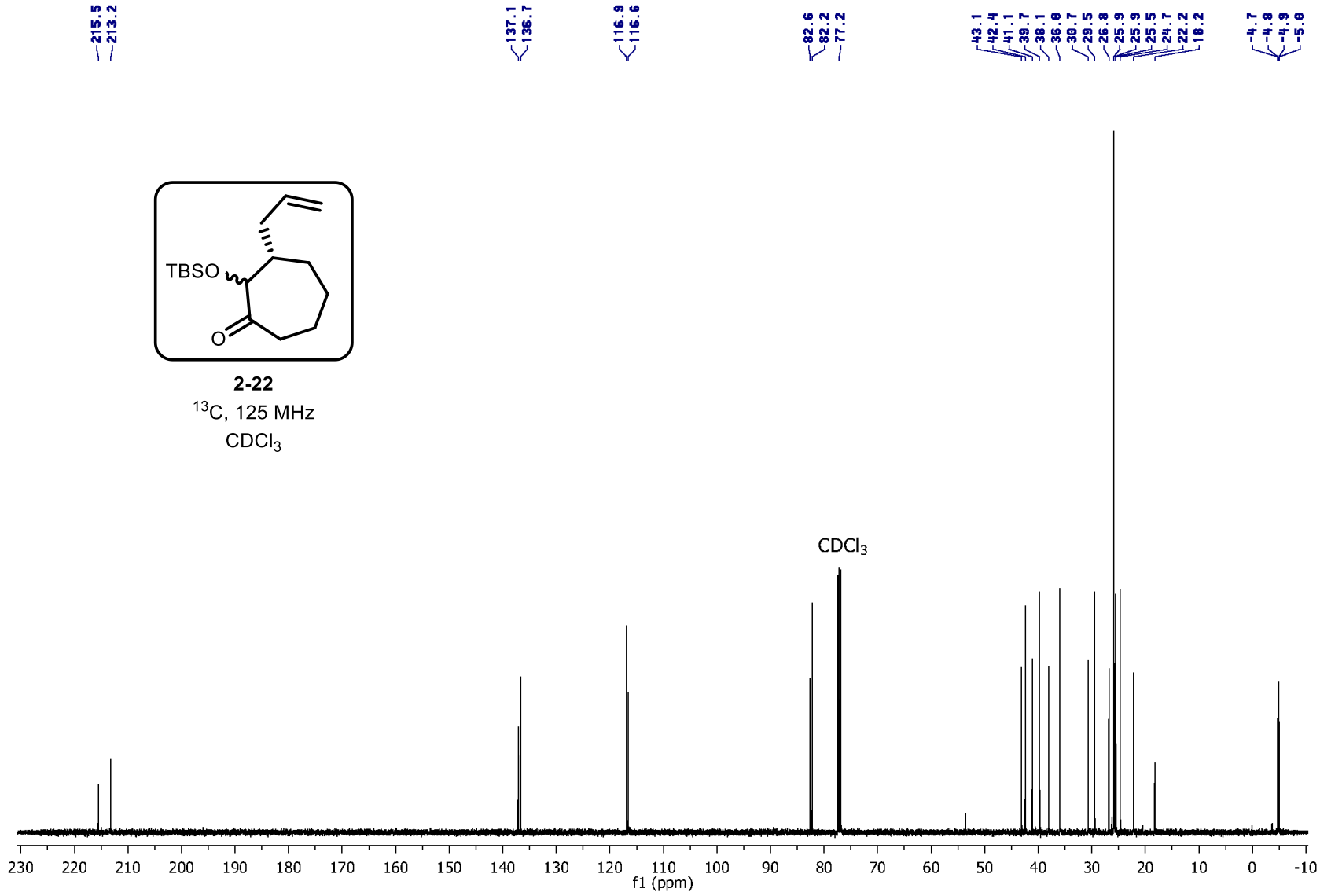

7.26
6.58
6.57
6.56
6.54
6.53
6.00
5.98
2.60
2.59
2.58
2.46
2.45
2.44
2.43
1.81
DCM
O
2-10
1H, 500 MHz
C6D6
TMS-OH
CHCl3
1.00
1.00
2.06
2.16
4.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


85.6
81.8
80.9
77.2
74.9
74.0
73.8
73.5
O
2-10
13C, 125 MHz
C6D6
CDCl3
DCM
87
86
85
84
83
82
81
80
79
78
77
76
75
74
73
72
f1 (ppm)


7.26
5.76
5.85
4.42
4.41
4.08
4.06
3.86
3.70
2.52
2.17
1.87
1.66
1.41
1.24
0.08
TMS
CHCl3
HO
O
2-17
1H, 500 MHz
CDCl3
0.63
0.37
2.03
0.28
0.58
0.28
0.52
3.03
1.35
2.96
2.41
2.11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


214.1
213.9
136.9
136.4
117.1
116.6
79.4
79.1
77.2
43.2
41.8
40.4
40.0
37.4
32.4
32.1
29.9
27.0
25.4
24.2
22.6
CDCl3
HO
O
2-17
13C, 125 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

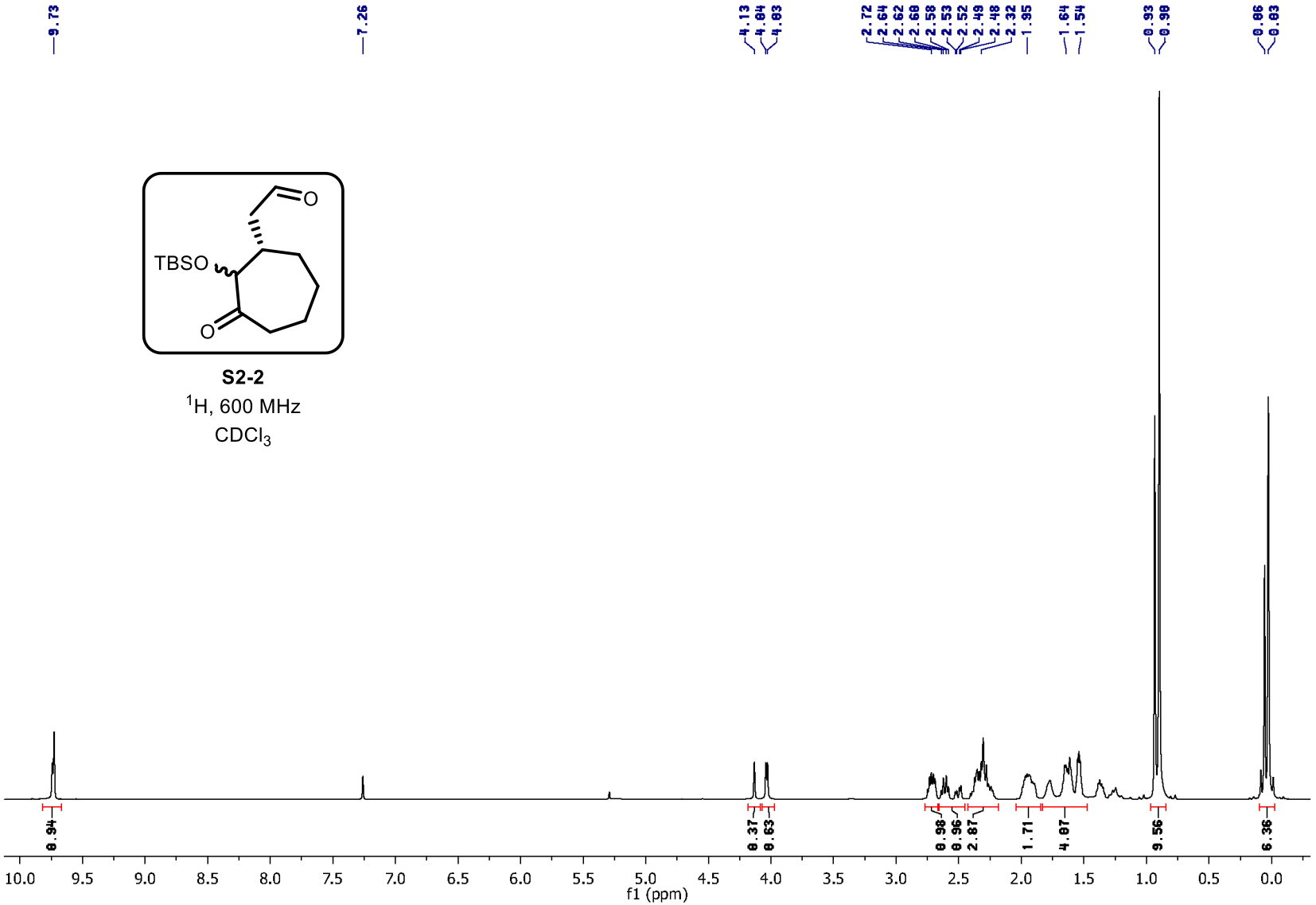

7.26
5.73
5.03
4.10
3.94
3.93
2.75
2.25
1.92
1.61
1.13
0.94
TBSO
O
2-22
1H, 500 MHz
CDCl3
DCM
CHCl3
1.00
2.03
0.40
0.56
0.97
2.13
3.08
4.40
0.67
0.46
3.55
4.93
5.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

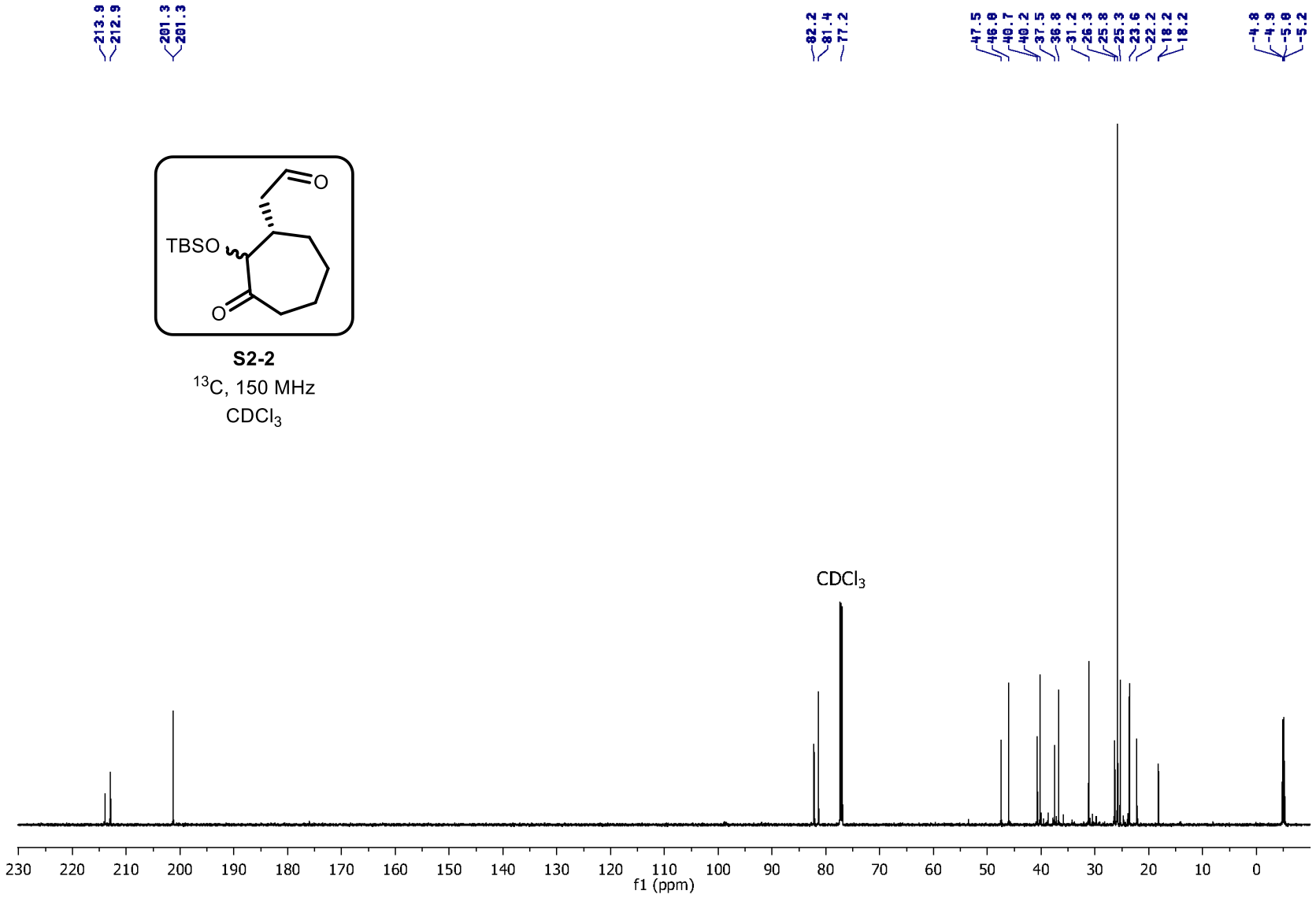


2-22

^{13}C, 125 MHz

$CDCl_3$

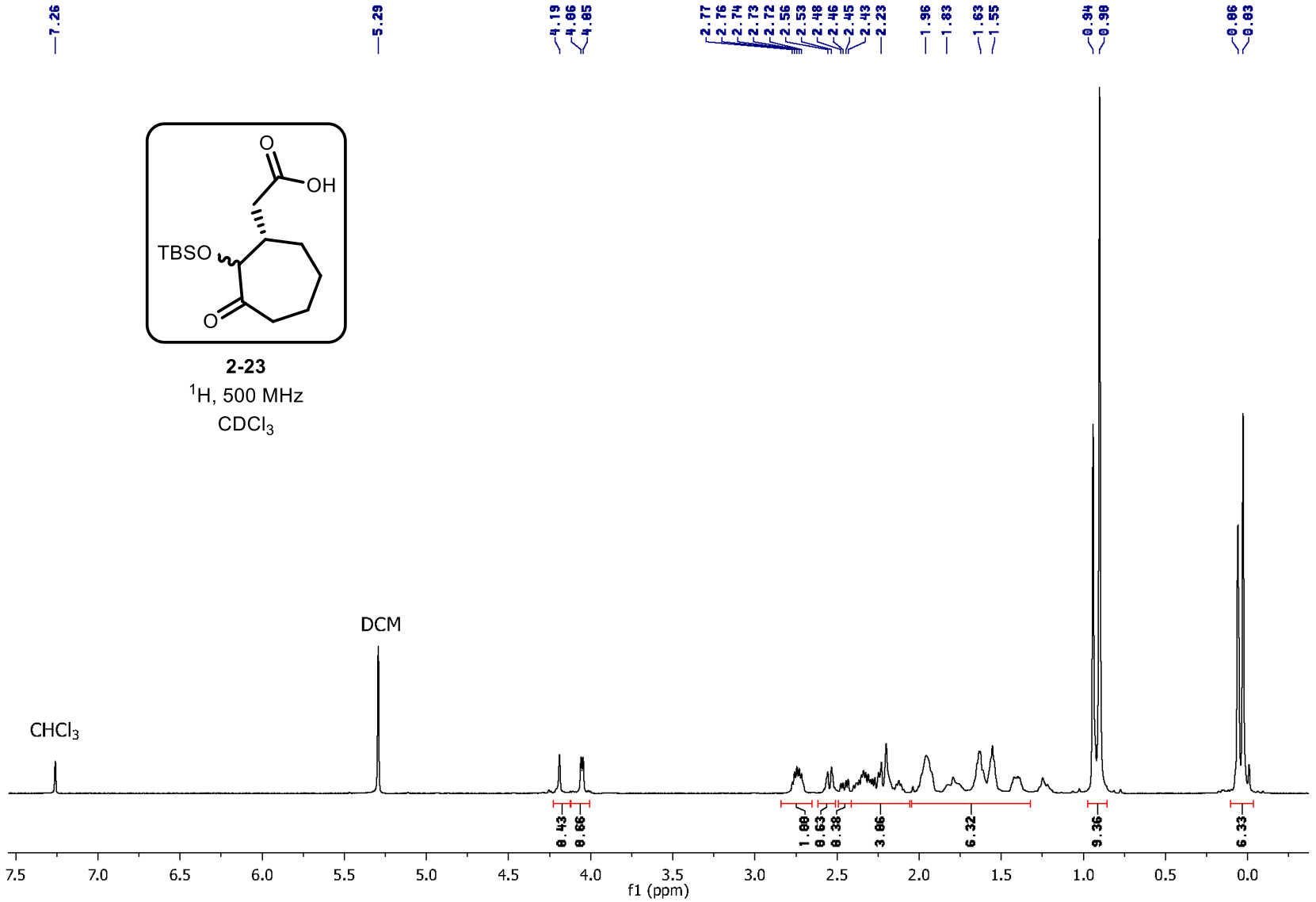

9.73
7.26
4.13
4.04
4.03
2.72
2.64
2.62
2.60
2.58
2.53
2.52
2.49
2.48
2.32
1.95
1.64
1.54
0.93
0.90
0.06
0.03
TBSO
O
O
S2-2
1H, 600 MHz
CDCl3
0.94
0.37
0.63
0.98
0.96
2.87
1.71
4.07
9.56
6.36
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

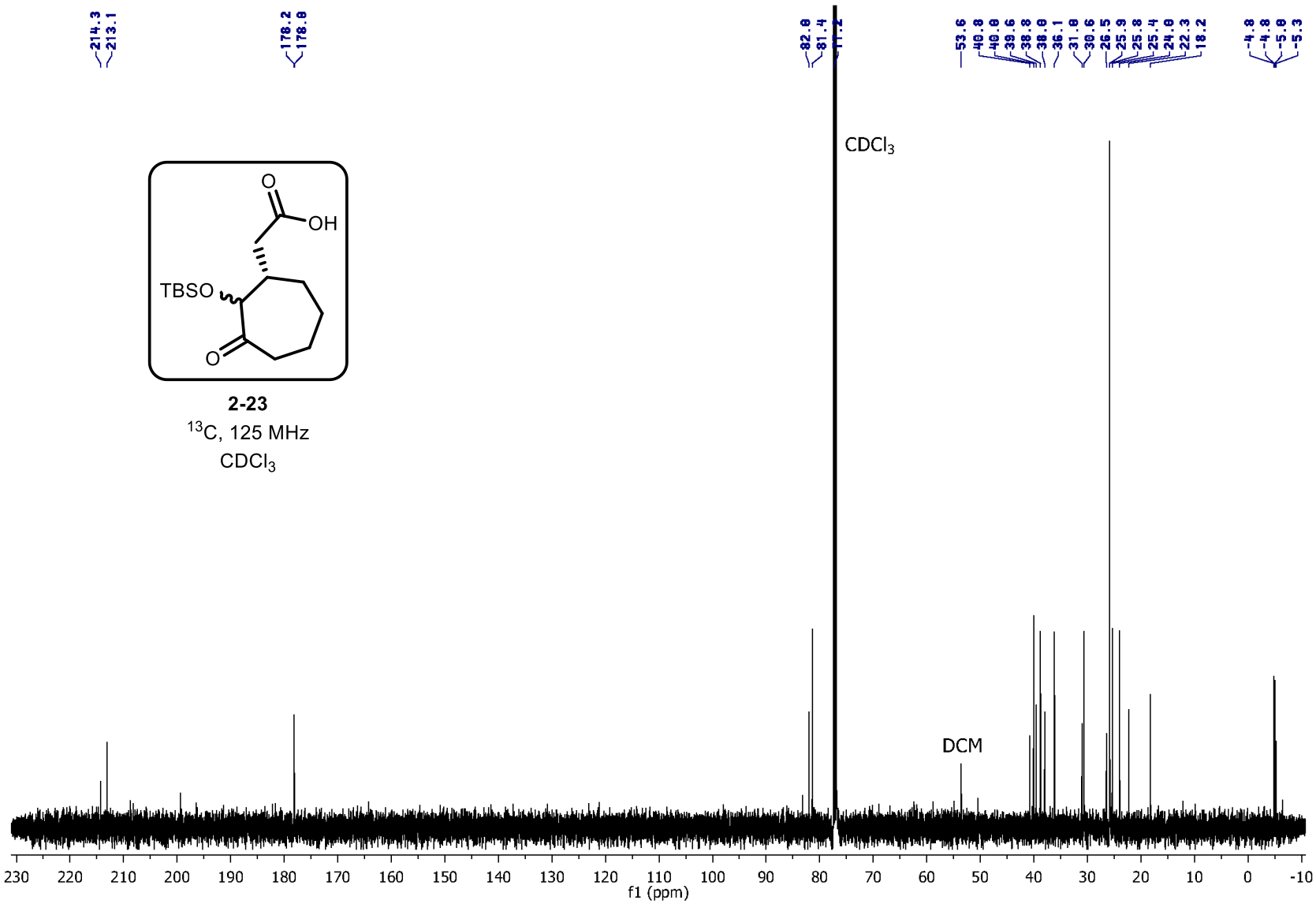


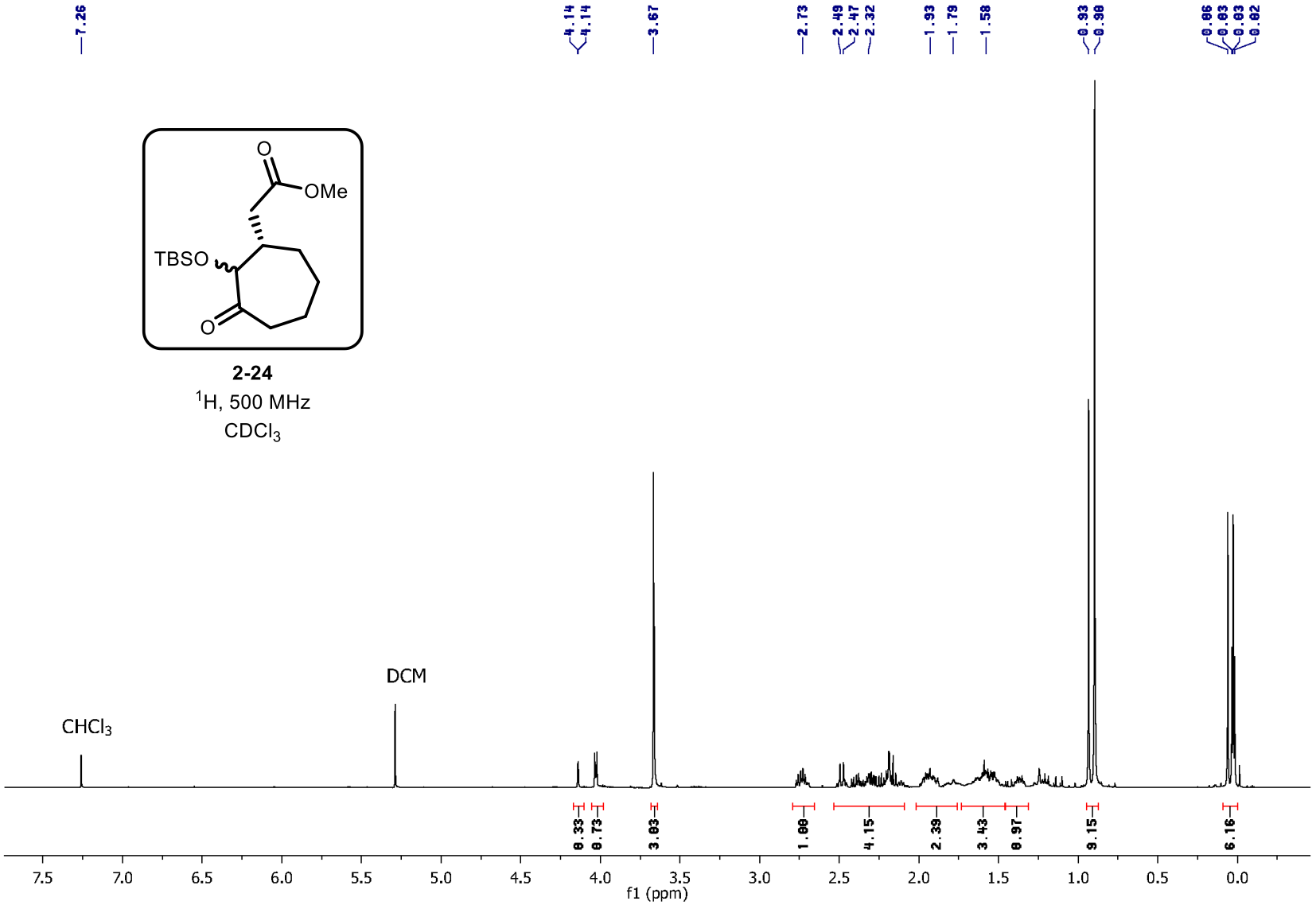
S2-2

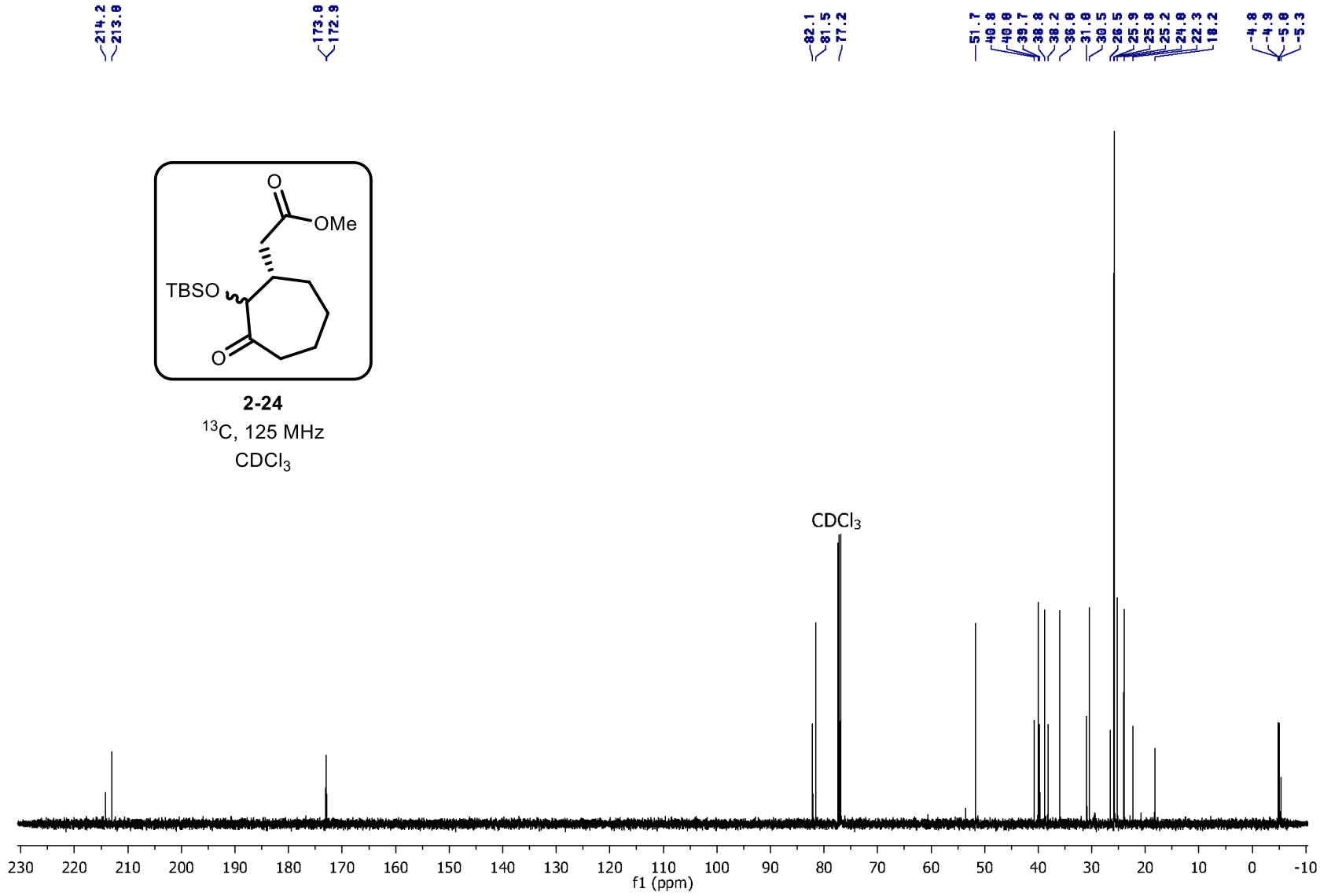
^{13}C, 150 MHz

$CDCl_3$


7.26
5.29
4.19
4.06
4.05
2.77
2.76
2.74
2.73
2.72
2.56
2.53
2.48
2.46
2.45
2.43
2.23
1.96
1.83
1.63
1.55
0.94
0.90
0.06
0.03
O
OH
TBSO
O
2-23
1H, 500 MHz
CDCl3
DCM
CHCl3
0.43
0.66
1.00
0.63
0.38
3.06
6.32
9.36
6.33
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


214.3
213.1
178.2
178.0
82.0
81.4
77.2
53.6
40.8
40.0
39.6
38.8
38.0
36.1
31.0
30.6
26.5
25.9
25.8
25.4
24.0
22.3
18.2
-4.8
-4.8
-5.0
-5.3
CDCl3
DCM
O
OH
TBSO
O
2-23
13C, 125 MHz
CDCl3
f1 (ppm)

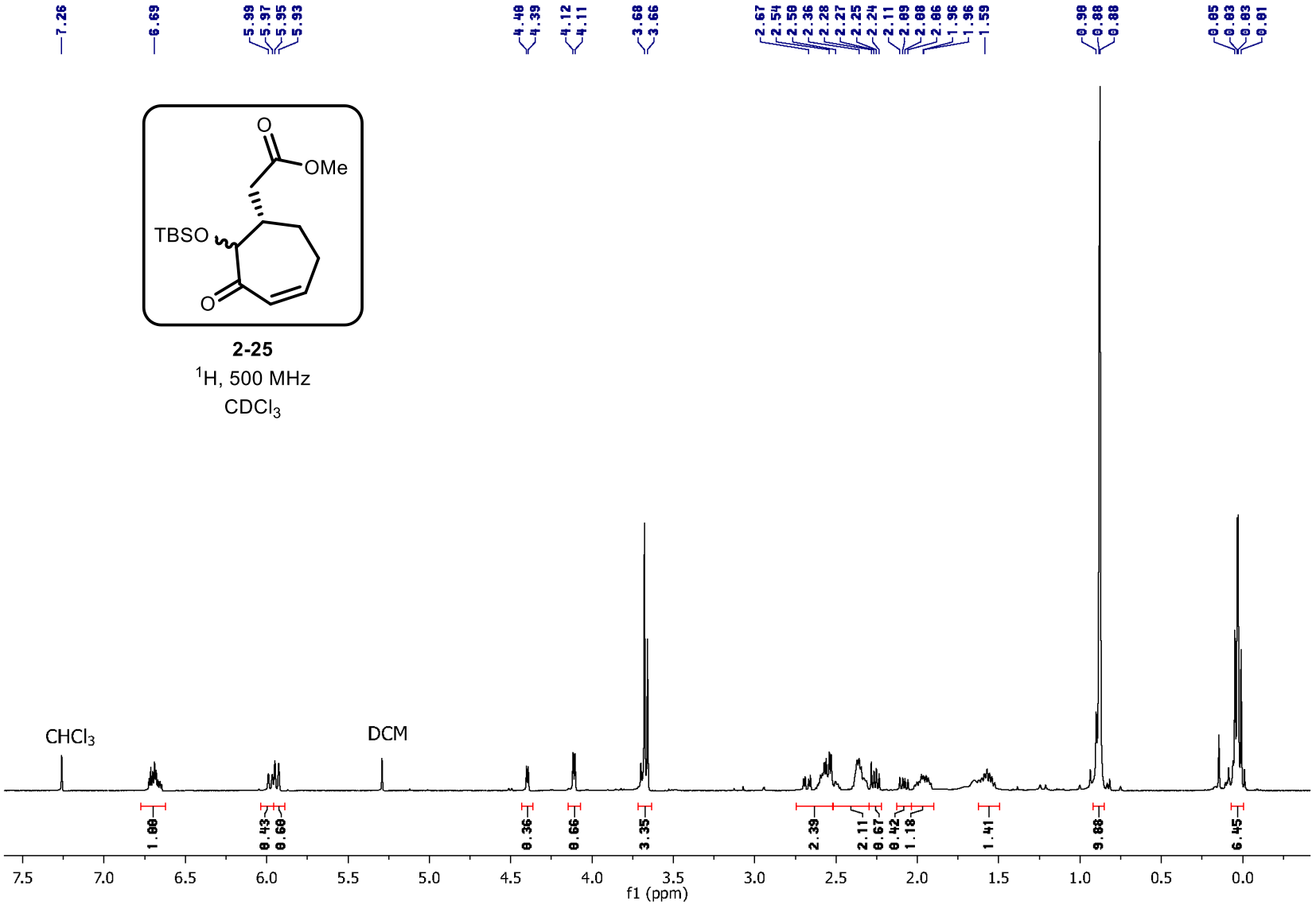

7.26
4.14
4.14
3.67
2.73
2.49
2.47
2.32
1.93
1.79
1.58
0.93
0.90
0.06
0.03
0.03
0.02
O
OMe
TBSO
O
2-24
1H, 500 MHz
CDCl3
CHCl3
DCM
0.33
0.73
3.03
1.00
4.15
2.39
3.43
0.97
9.15
6.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

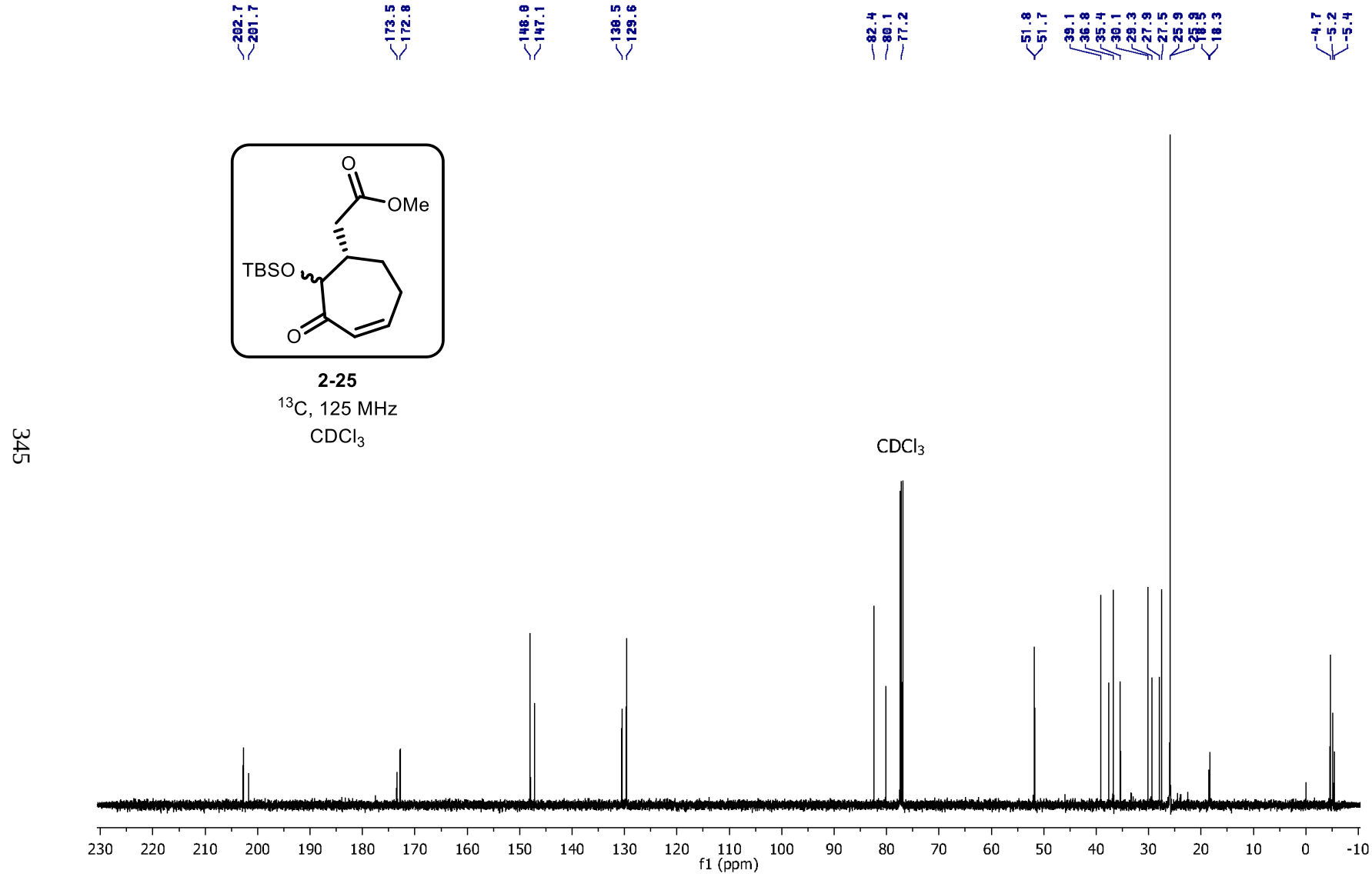


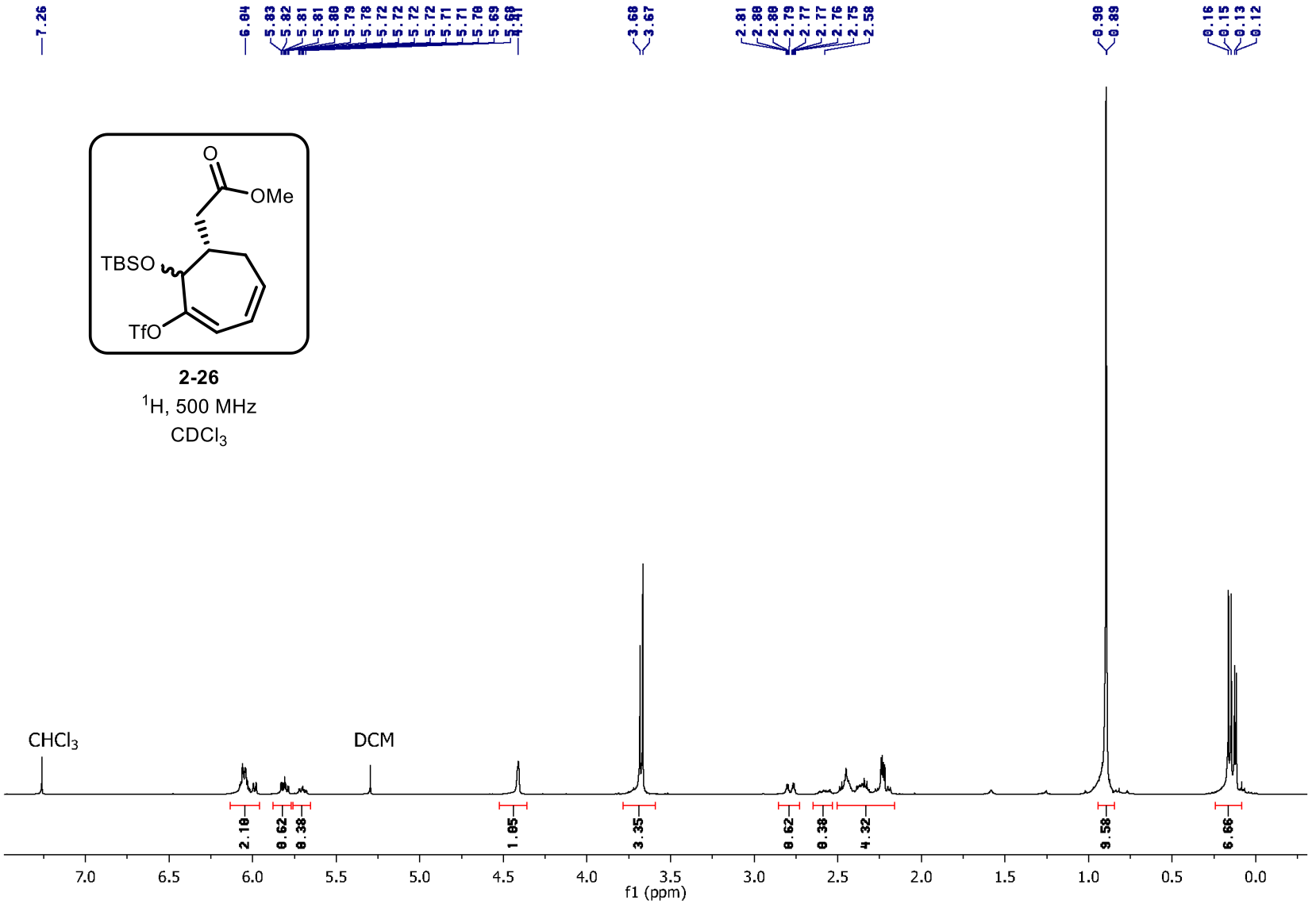
2-24

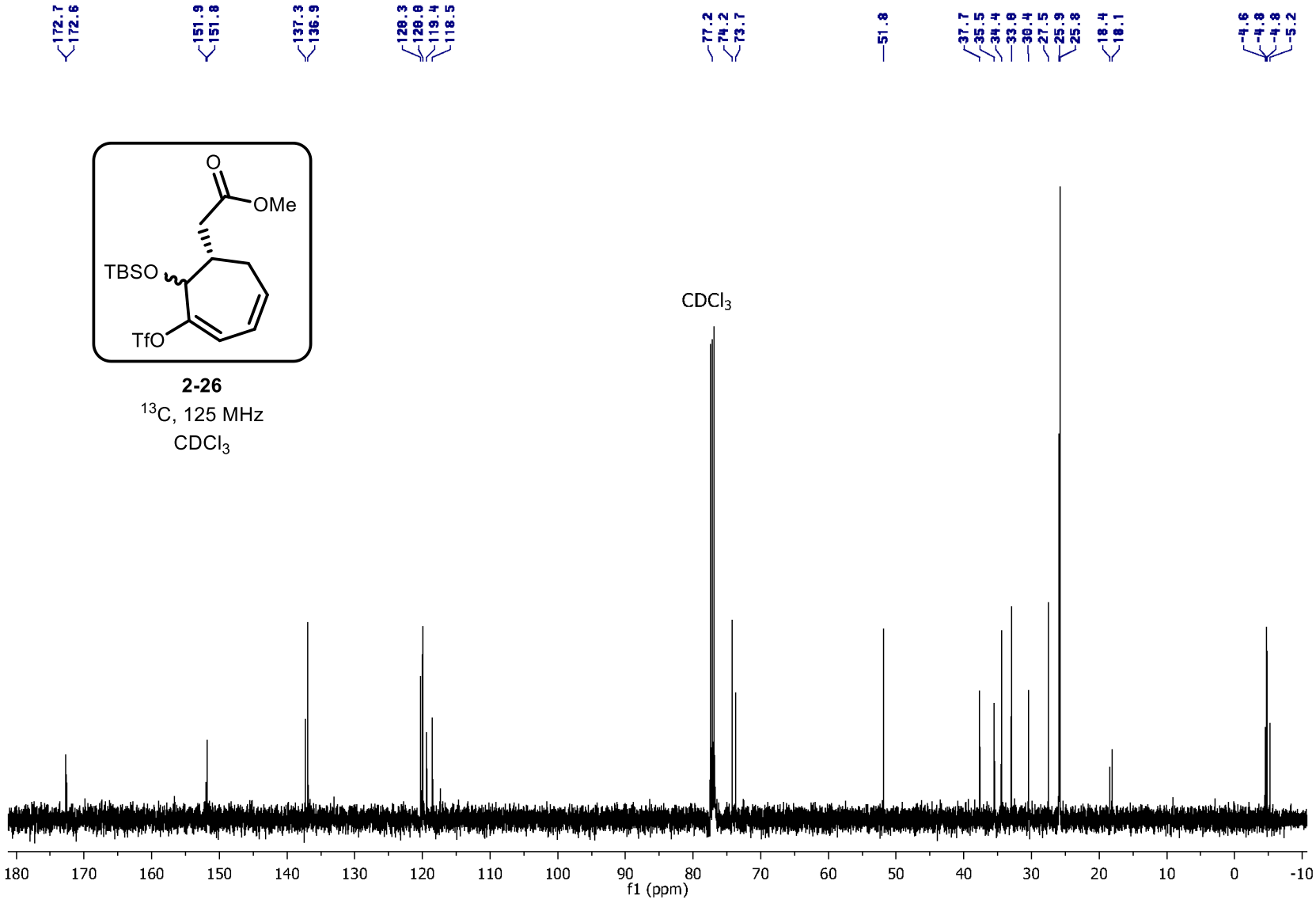
^{13}C, 125 MHz

$CDCl_3$


7.26
6.69
5.99
5.97
5.95
5.93
4.40
4.39
4.12
4.11
3.68
3.66
2.67
2.54
2.50
2.36
2.28
2.27
2.25
2.24
2.11
2.09
2.08
2.06
1.96
1.96
1.59
0.90
0.88
0.88
0.05
0.03
0.03
0.01
O
OMe
TBSO
O
2-25
1H, 500 MHz
CDCl3
CHCl3
DCM
1.00
0.43
0.60
0.36
0.66
3.35
2.39
2.11
0.67
0.42
1.18
1.41
9.88
6.45
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


202.7
201.7
173.5
172.8
148.8
147.1
130.5
129.6
82.4
80.1
77.2
51.8
51.7
39.1
36.8
35.4
30.1
29.3
27.9
27.5
25.9
25.8
18.5
18.3
-4.7
-5.2
-5.4
O
OMe
TBSO
O
2-25
13C, 125 MHz
CDCl3
CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

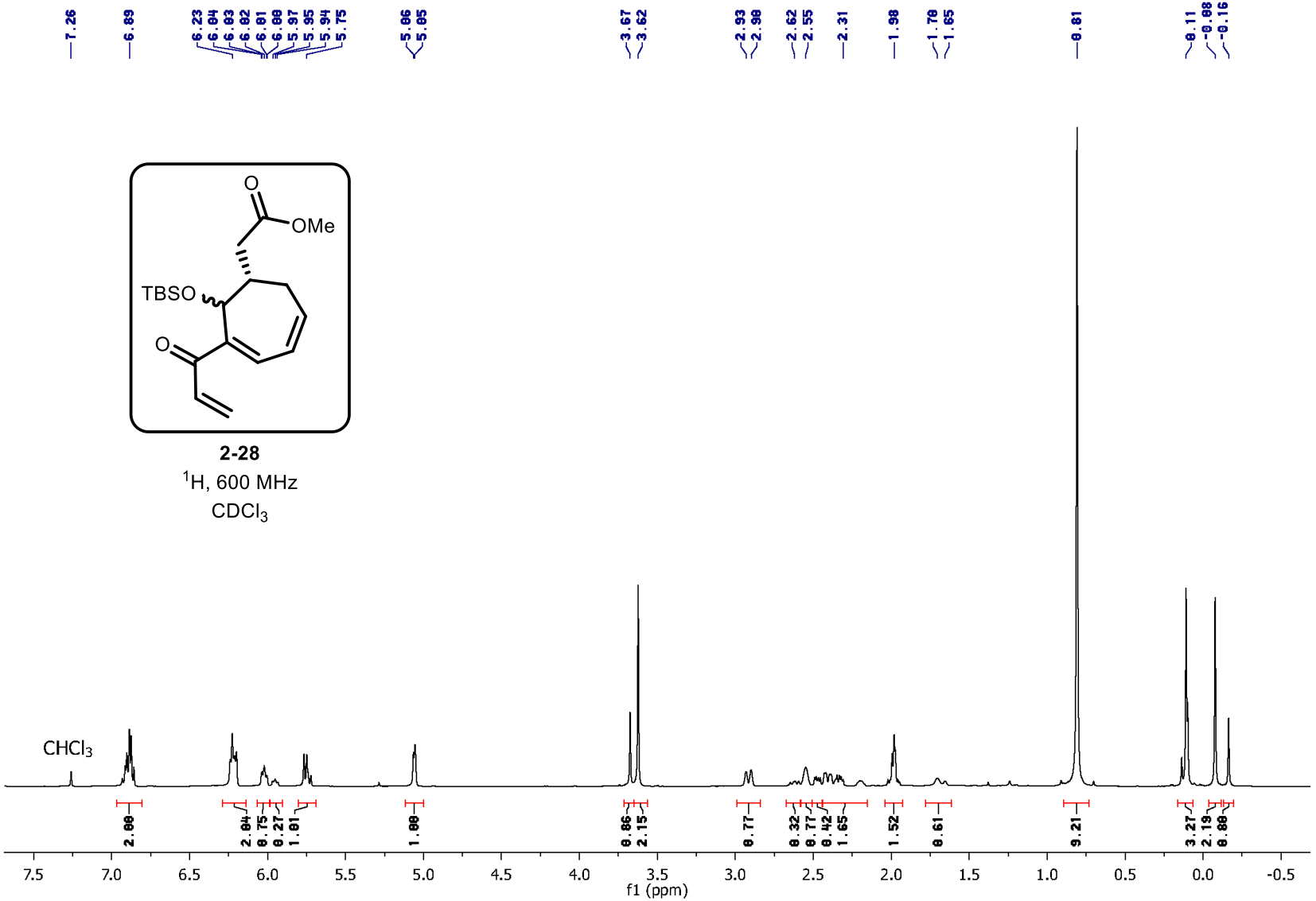

7.26
6.04
5.83
5.82
5.81
5.81
5.80
5.79
5.78
5.72
5.72
5.72
5.71
5.71
5.70
5.69
3.68
3.67
2.81
2.80
2.80
2.79
2.77
2.77
2.76
2.75
2.58
0.90
0.89
0.16
0.15
0.13
0.12
O
OMe
TBSO
TfO
2-26
1H, 500 MHz
CDCl3
CHCl3
DCM
2.10
0.62
0.38
1.05
3.35
0.62
0.38
4.32
9.58
6.66
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



2-26

^{13}C, 125 MHz

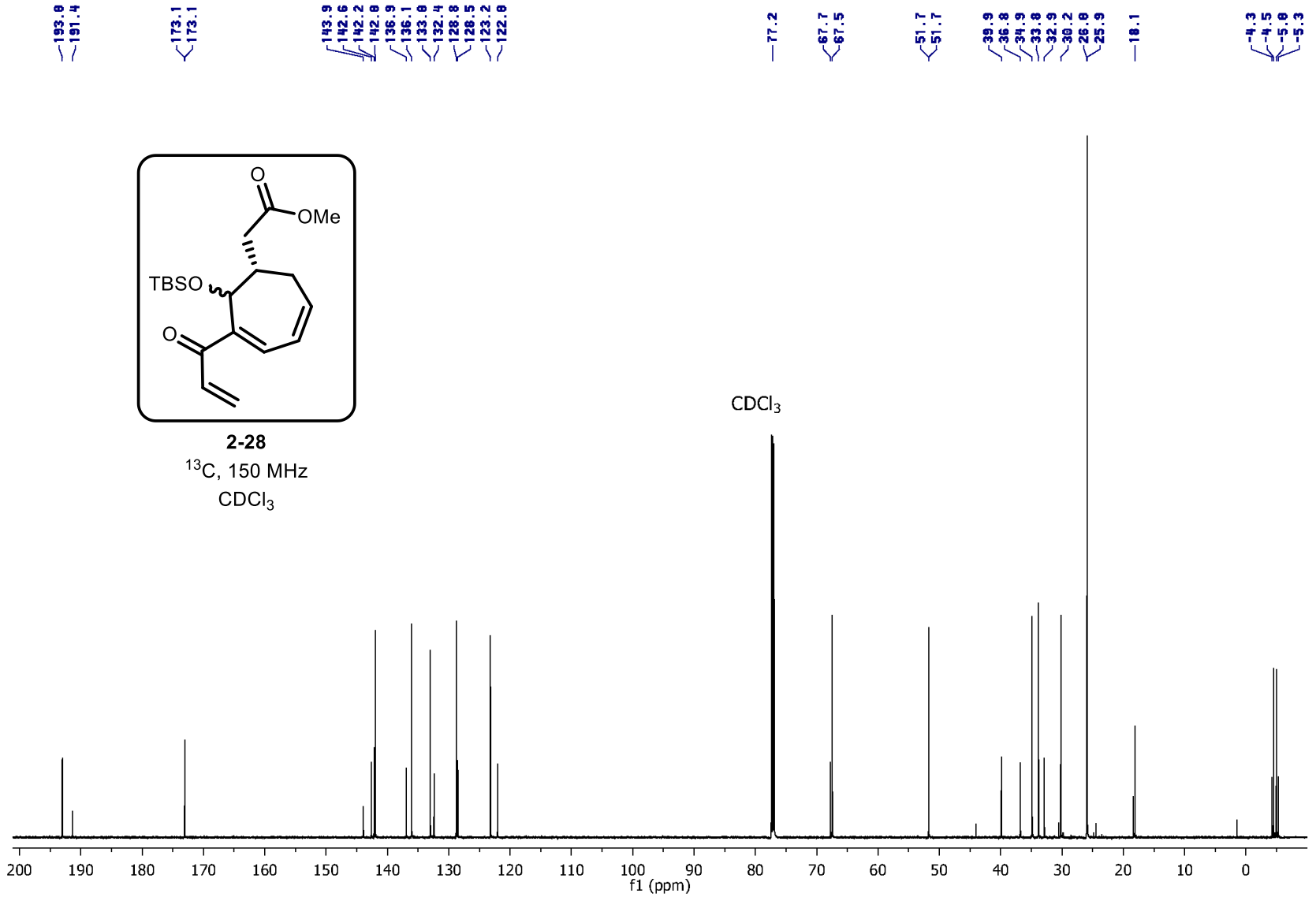
$CDCl_3$

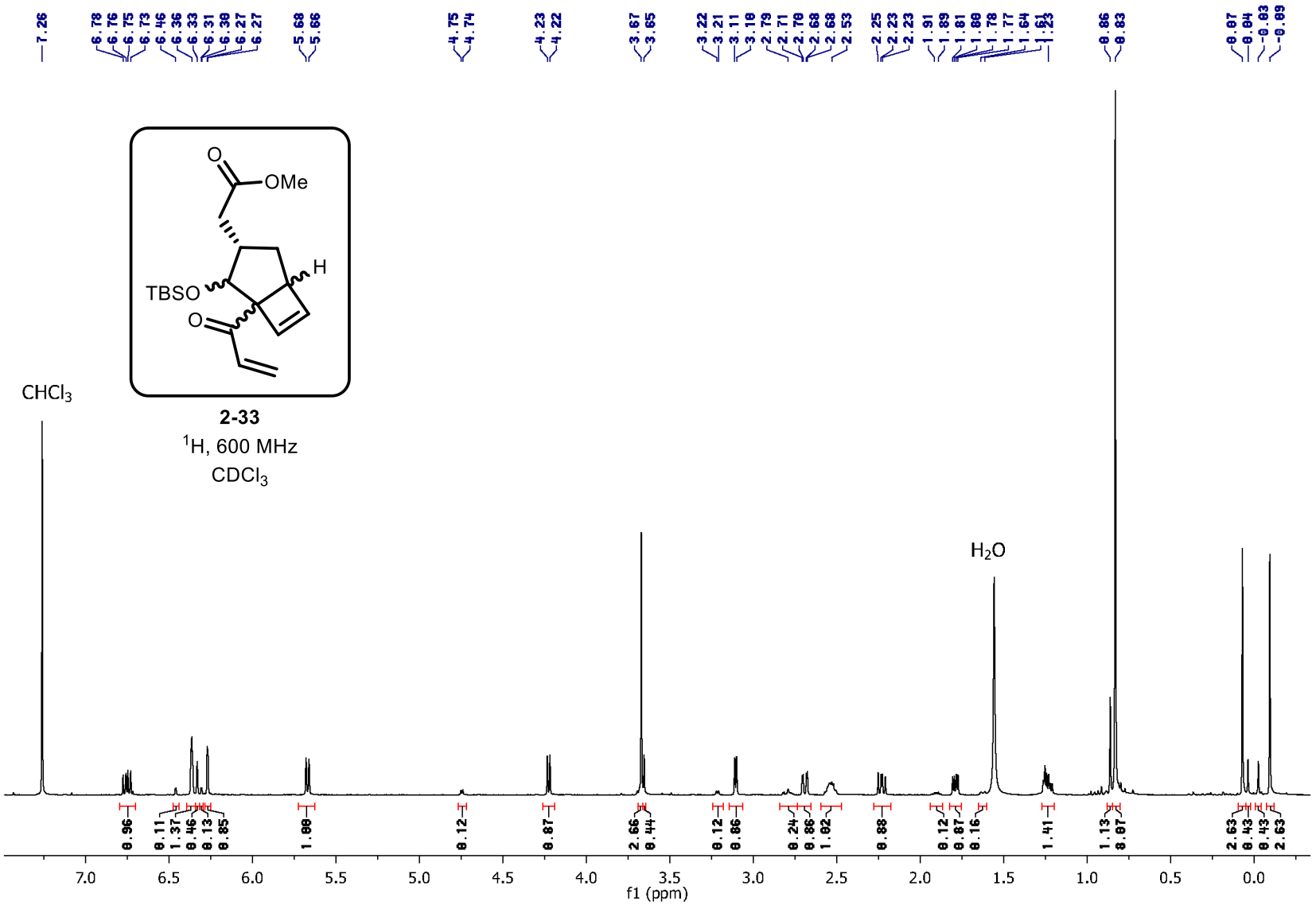


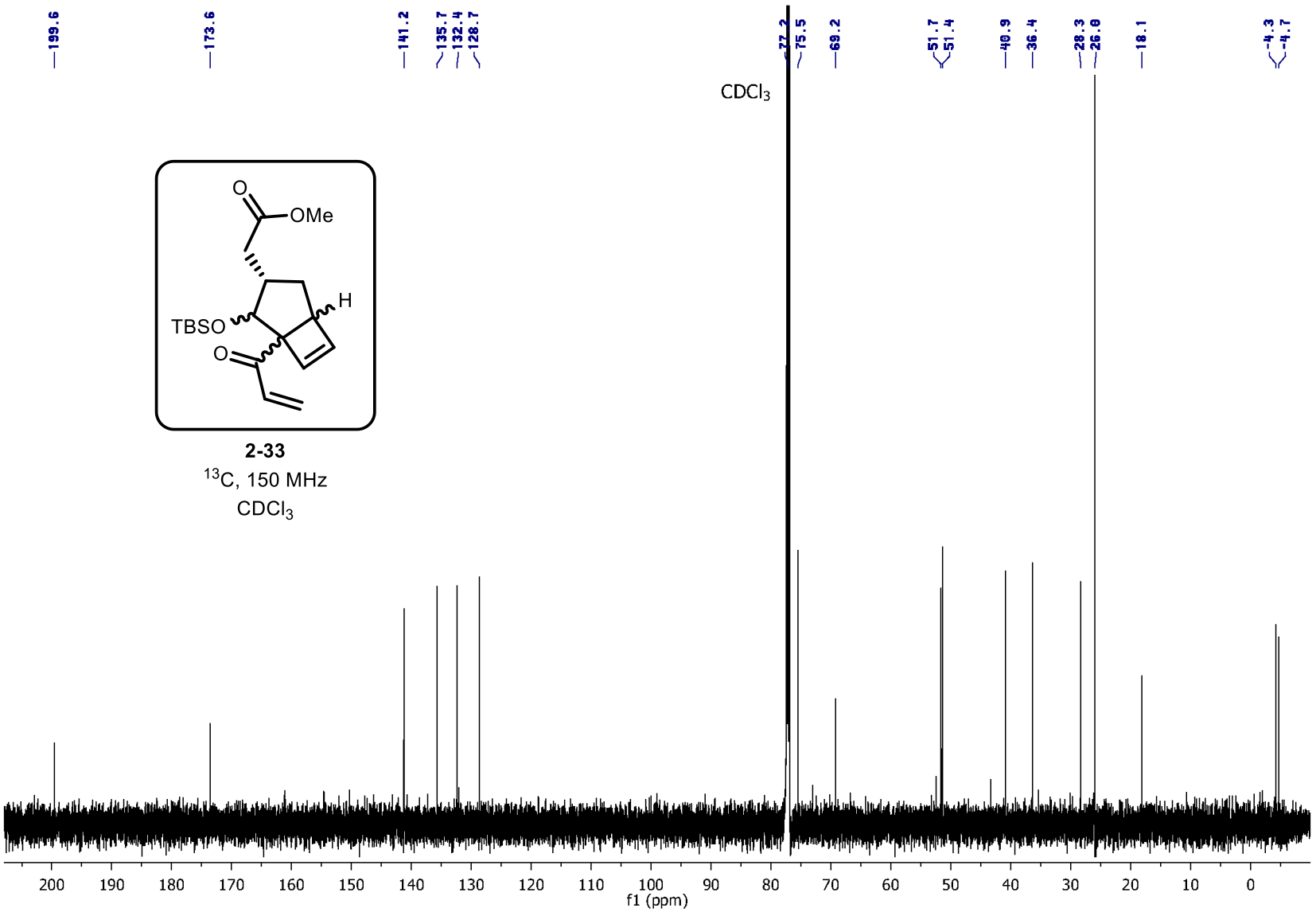
2-28

^{1}H, 600 MHz

$CDCl_3$


193.0
191.4
173.1
173.1
143.9
142.6
142.2
142.0
136.9
136.1
133.0
132.4
128.8
128.5
123.2
122.0
77.2
67.7
67.5
51.7
51.7
39.9
36.8
34.9
33.8
32.9
30.2
26.0
25.9
18.1
-4.3
-4.5
-5.0
-5.3
O
OMe
TBSO
O
CDCl3
2-28
13C, 150 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

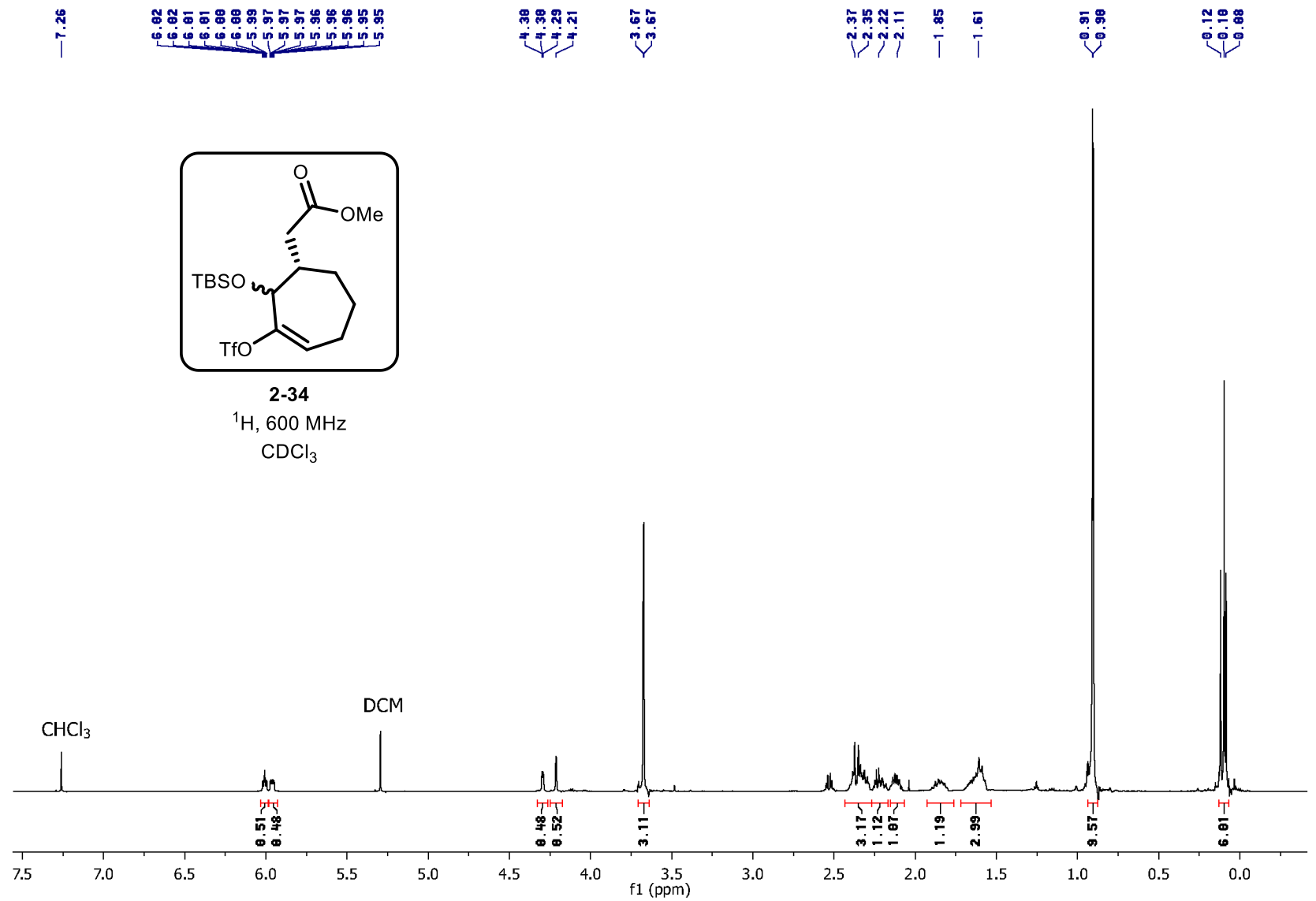

7.26
6.78
6.76
6.75
6.73
6.46
6.36
6.33
6.31
6.30
6.27
6.27
5.68
5.66
4.75
4.74
4.23
4.22
3.67
3.65
3.22
3.21
3.11
3.10
2.79
2.71
2.70
2.68
2.68
2.53
2.25
2.23
2.23
1.91
1.89
1.81
1.80
1.78
1.77
1.64
1.61
1.23
0.86
0.83
0.07
0.04
-0.03
-0.09
O
OMe
H
TBSO
O
CHCl3
2-33
1H, 600 MHz
CDCl3
H2O
0.96
0.11
1.37
0.46
0.13
0.85
1.00
0.12
0.87
2.66
0.44
0.12
0.86
0.24
0.86
1.02
0.88
0.12
0.87
0.16
1.41
1.13
0.87
2.63
0.43
0.43
2.63
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



2-33

^{13}C, 150 MHz

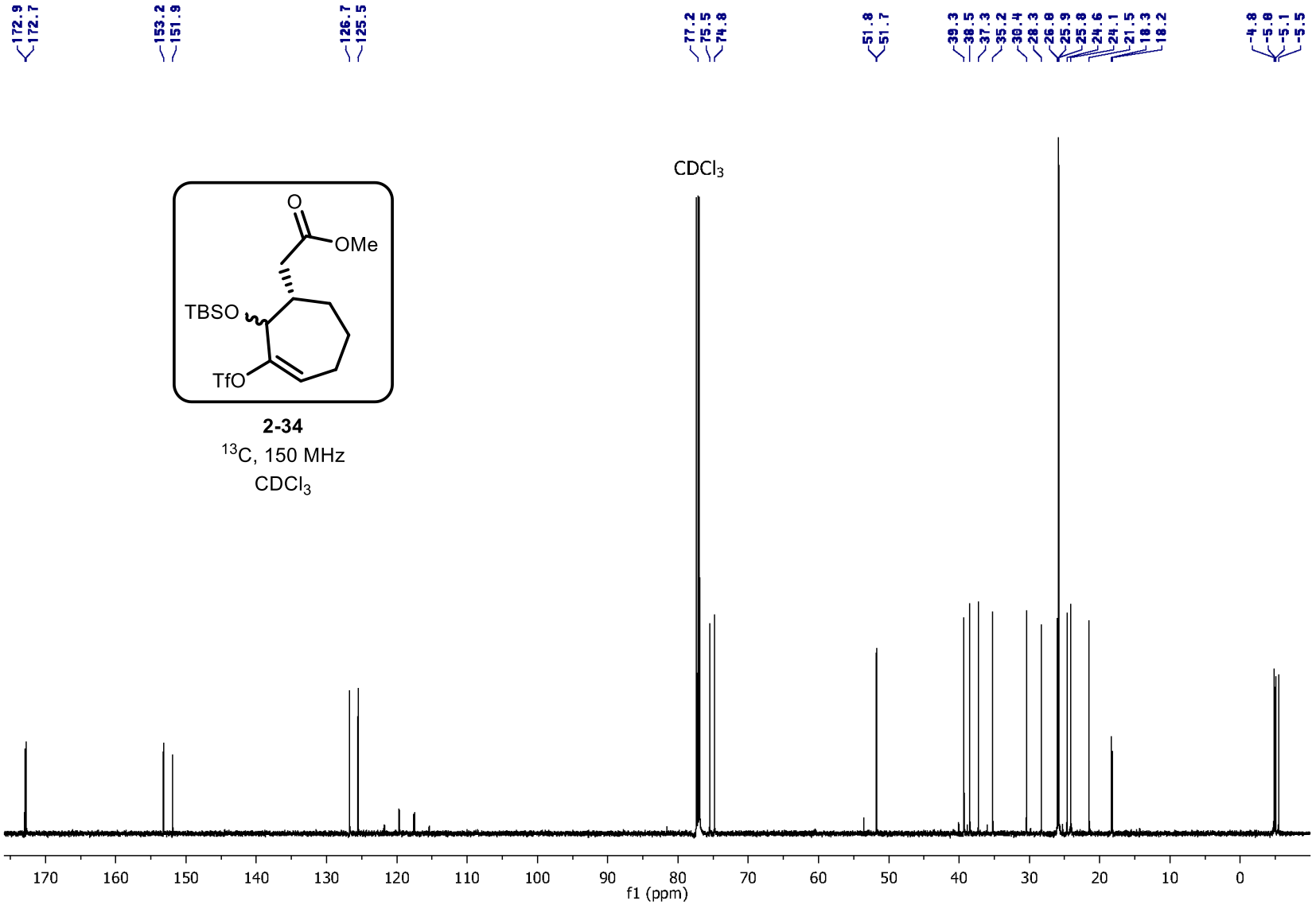
$CDCl_3$



2-34

^{1}H, 600 MHz

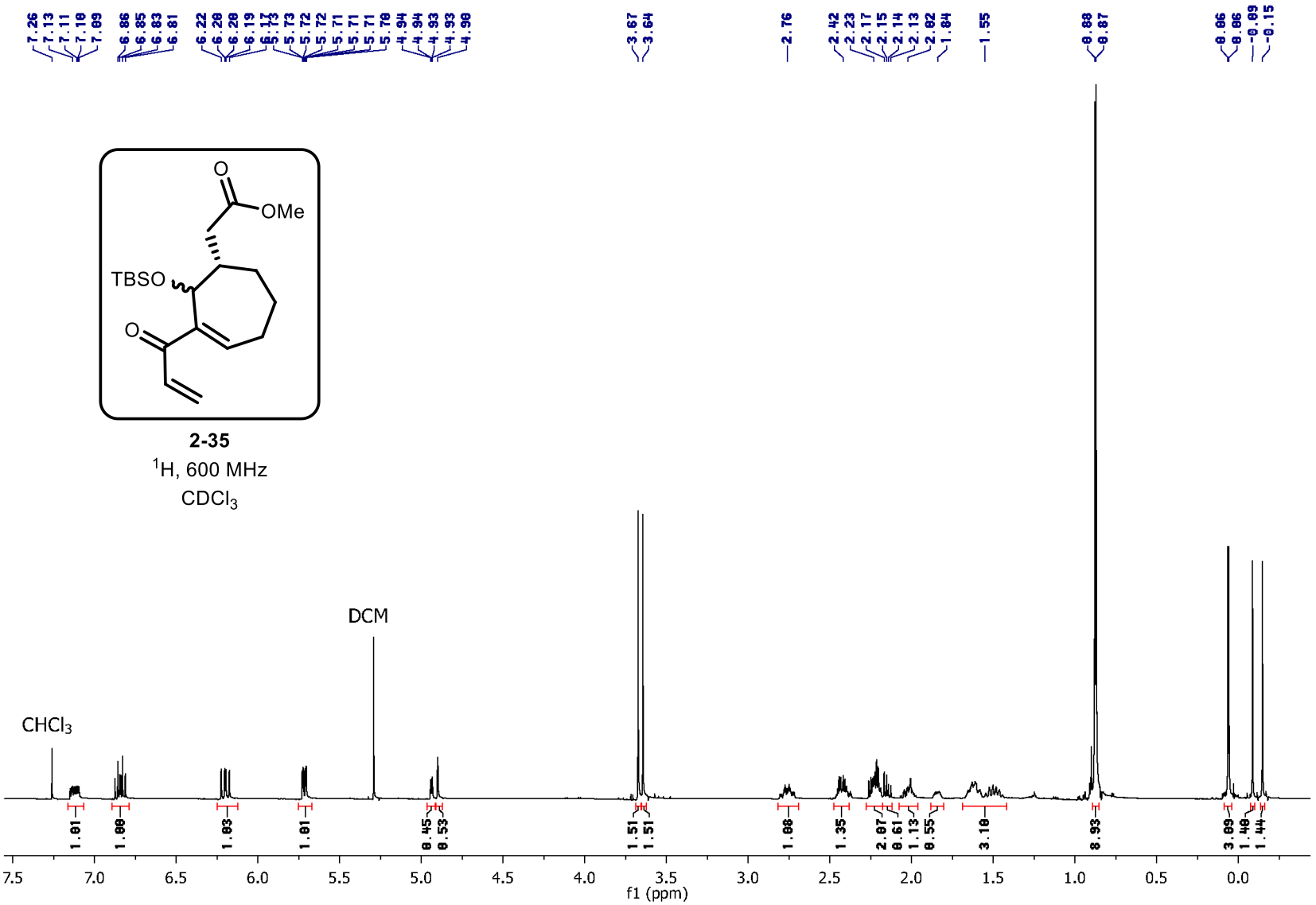
$CDCl_3$

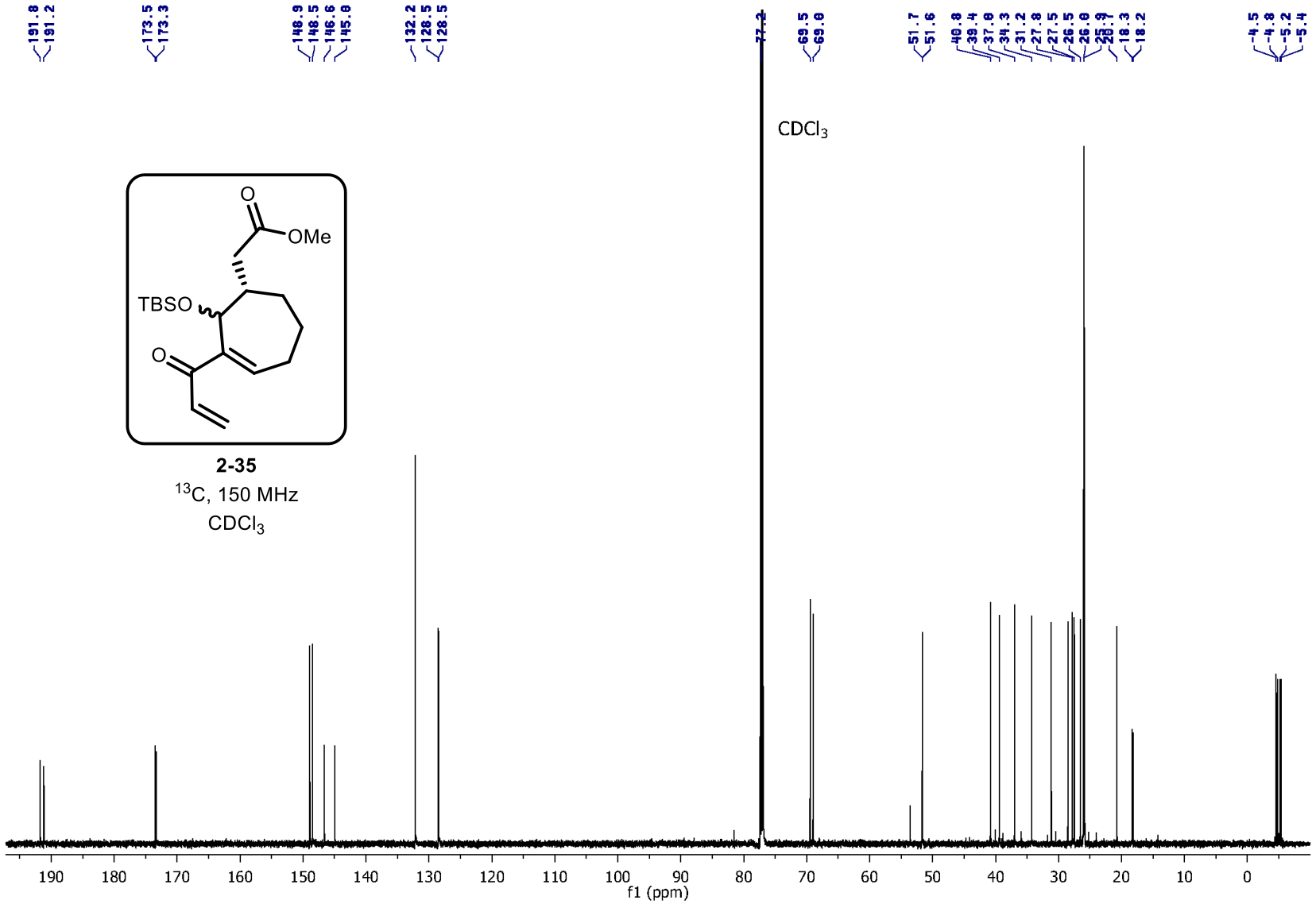


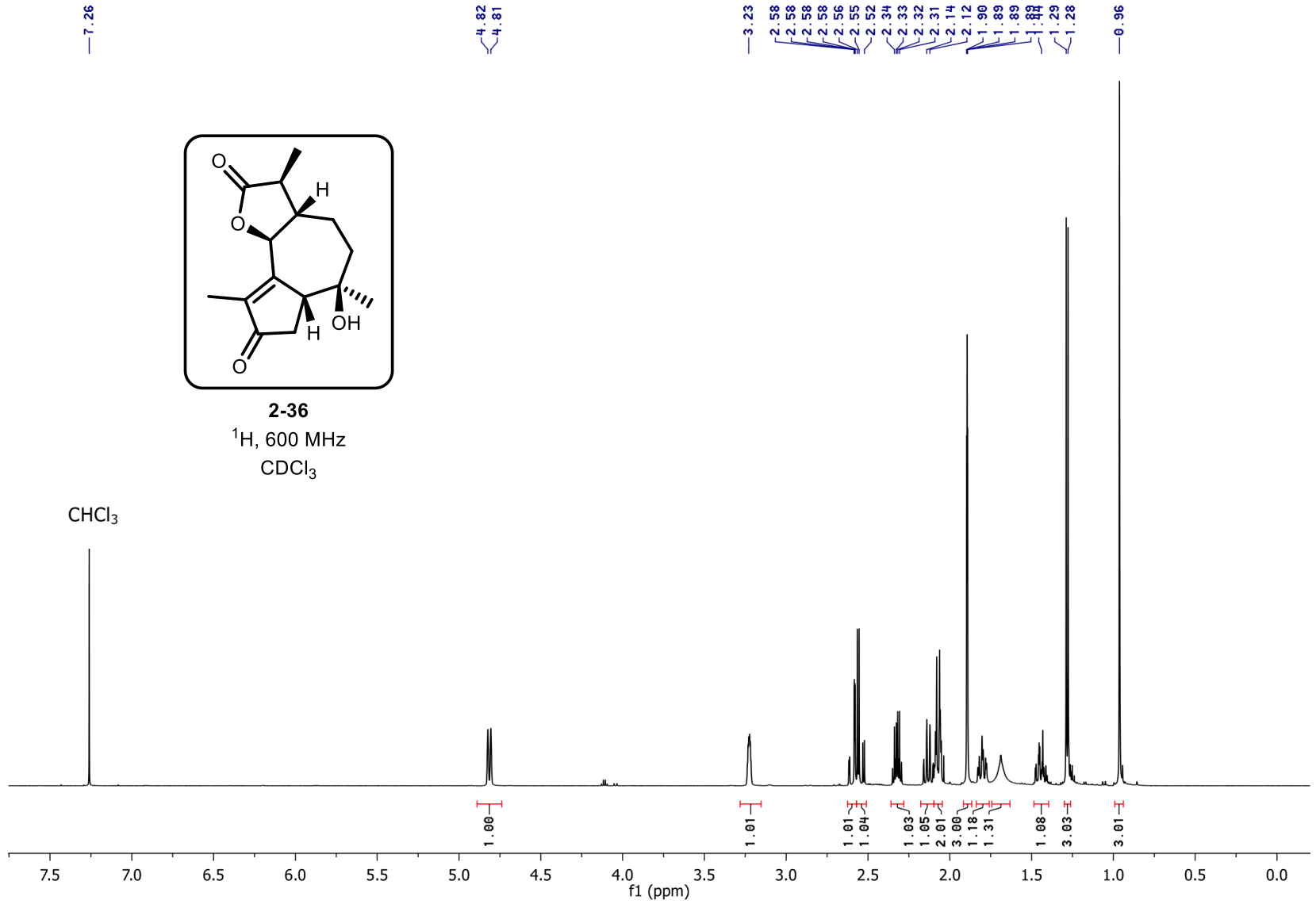
2-34

^{13}C, 150 MHz

$CDCl_3$


7.26
7.13
7.11
7.10
7.09
6.86
6.85
6.83
6.81
6.22
6.20
6.20
6.19
6.17
6.13
5.73
5.72
5.72
5.71
5.71
5.71
5.70
4.94
4.94
4.93
4.93
4.90
3.67
3.64
2.76
2.42
2.23
2.17
2.15
2.14
2.13
2.02
1.84
1.55
0.88
0.87
0.06
0.06
-0.09
-0.15
O
OMe
TBSO
O
2-35
1H, 600 MHz
CDCl3
DCM
CHCl3
1.01
1.00
1.03
1.01
0.45
0.53
1.51
1.51
1.08
1.35
2.07
0.61
1.13
0.55
3.10
8.93
3.09
1.40
1.44
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

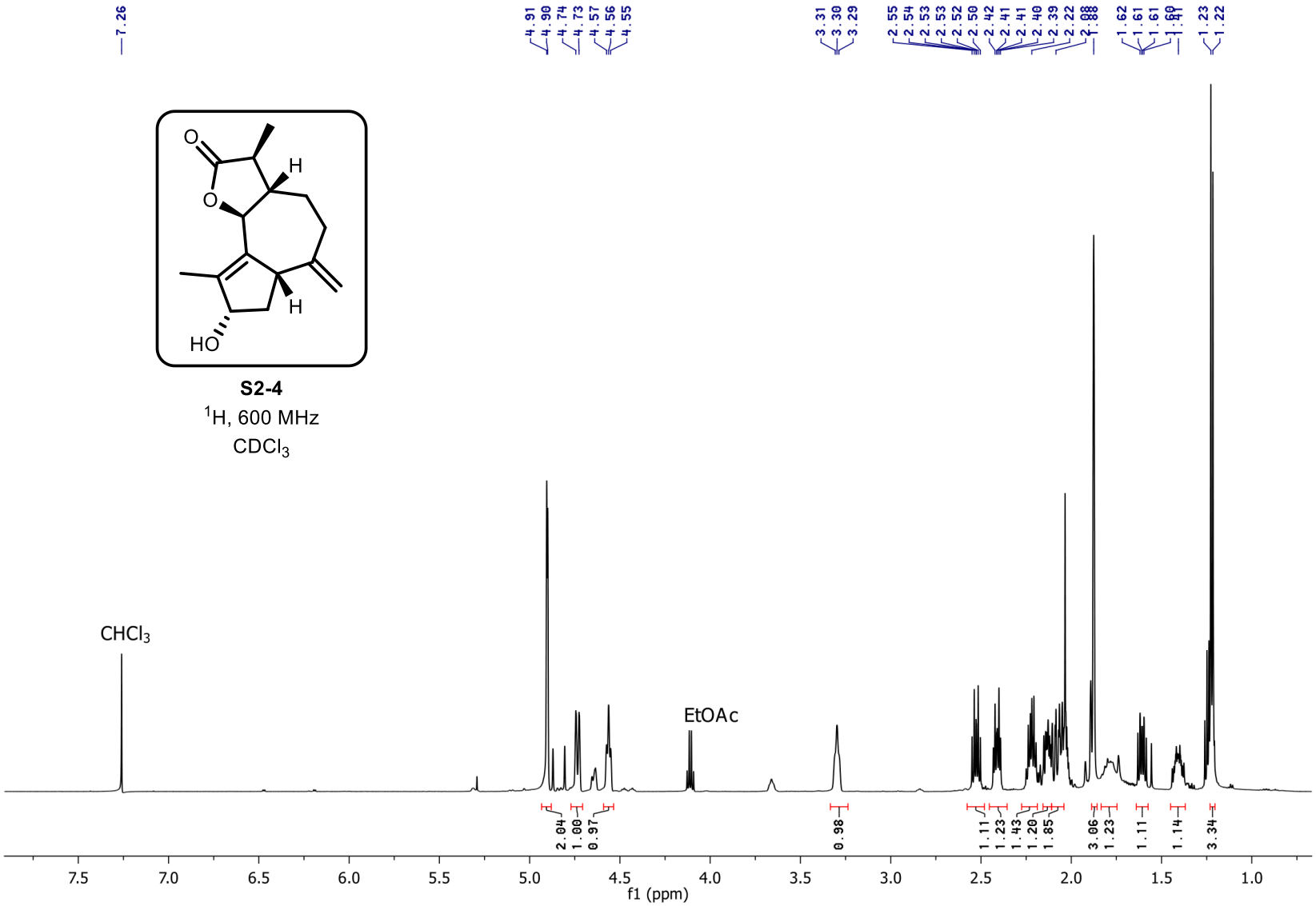

191.8
191.2
173.5
173.3
148.9
148.5
146.6
145.0
132.2
128.5
128.5
77.2
69.5
69.0
51.7
51.6
40.8
39.4
37.0
34.3
31.2
27.8
27.5
26.5
26.0
25.9
25.7
18.3
18.2
-4.5
-4.8
-5.2
-5.4
CDCl3
O
OMe
TBSO
O
2-35
13C, 150 MHz
CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

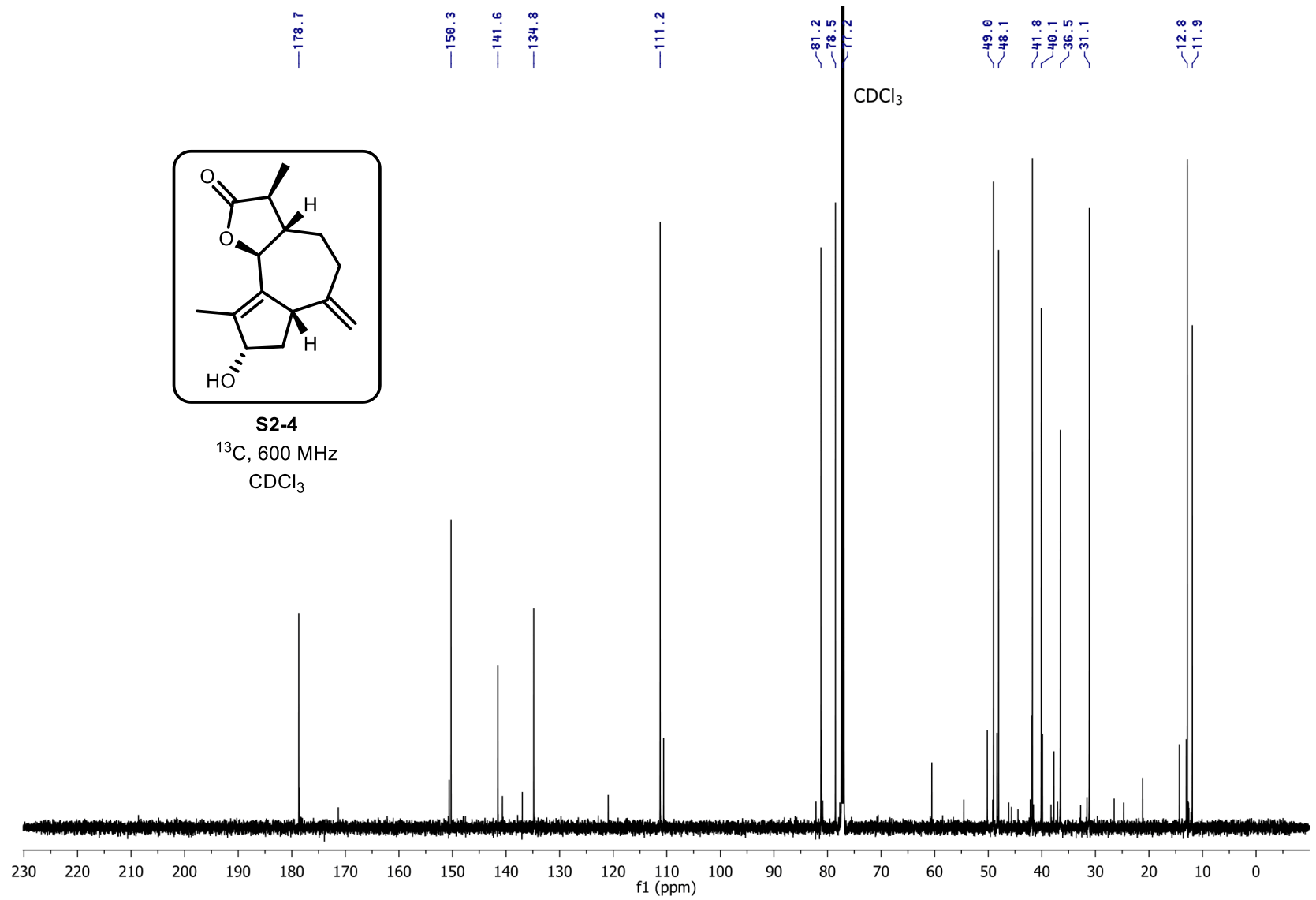


2-36

^{1}H, 600 MHz

$CDCl_3$

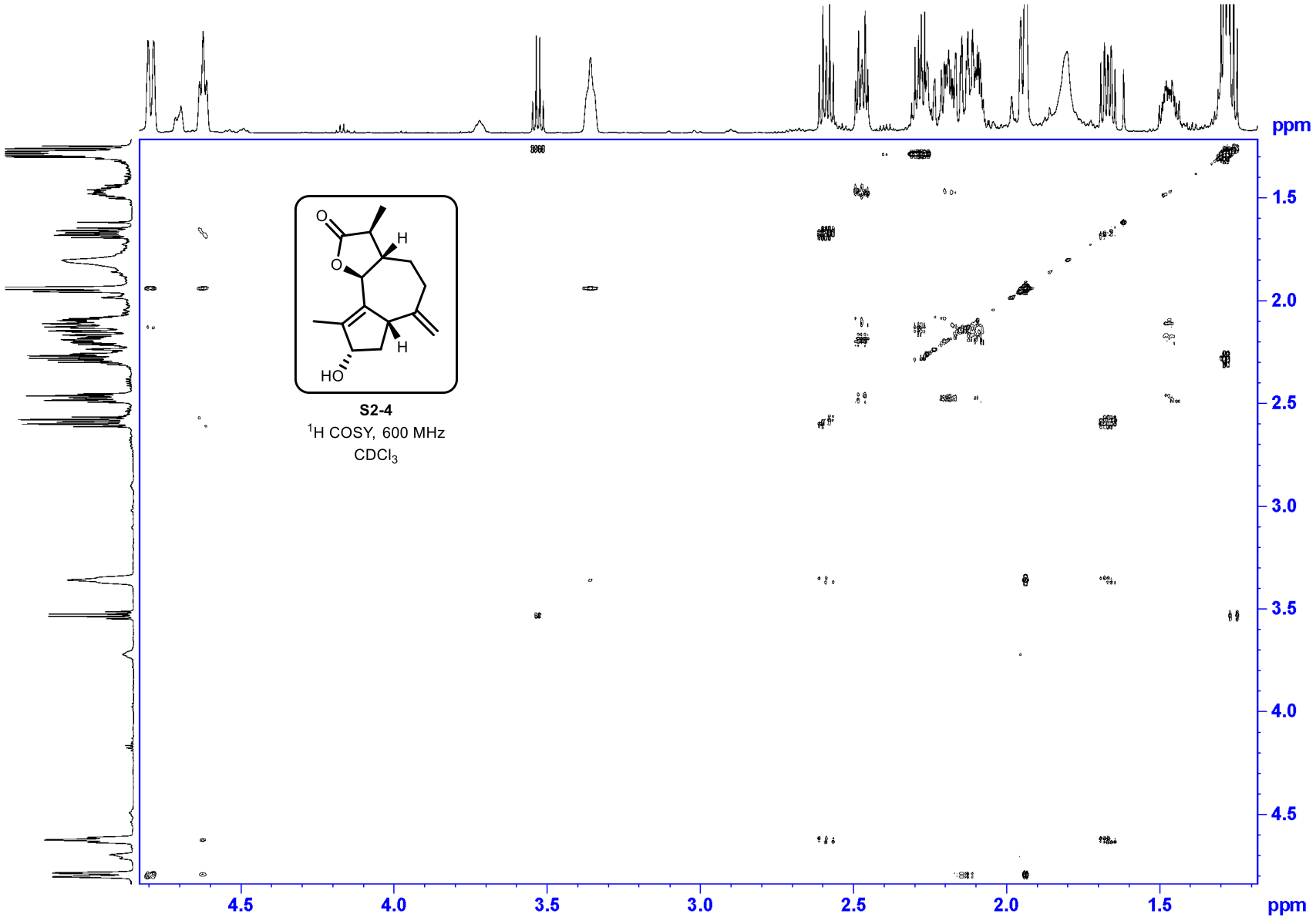

7.26
4.91
4.90
4.74
4.73
4.57
4.56
4.55
3.31
3.30
3.29
2.55
2.54
2.53
2.53
2.52
2.50
2.42
2.41
2.41
2.40
2.39
2.22
1.88
1.62
1.61
1.61
1.60
1.23
1.22
O
O
H
H
HO
S2-4
1H, 600 MHz
CDCl3
CHCl3
EtOAc
2.04
1.00
0.97
0.98
1.11
1.23
1.43
1.20
1.85
3.06
1.23
1.11
1.14
3.34
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)



S2-4

^{13}C, 600 MHz

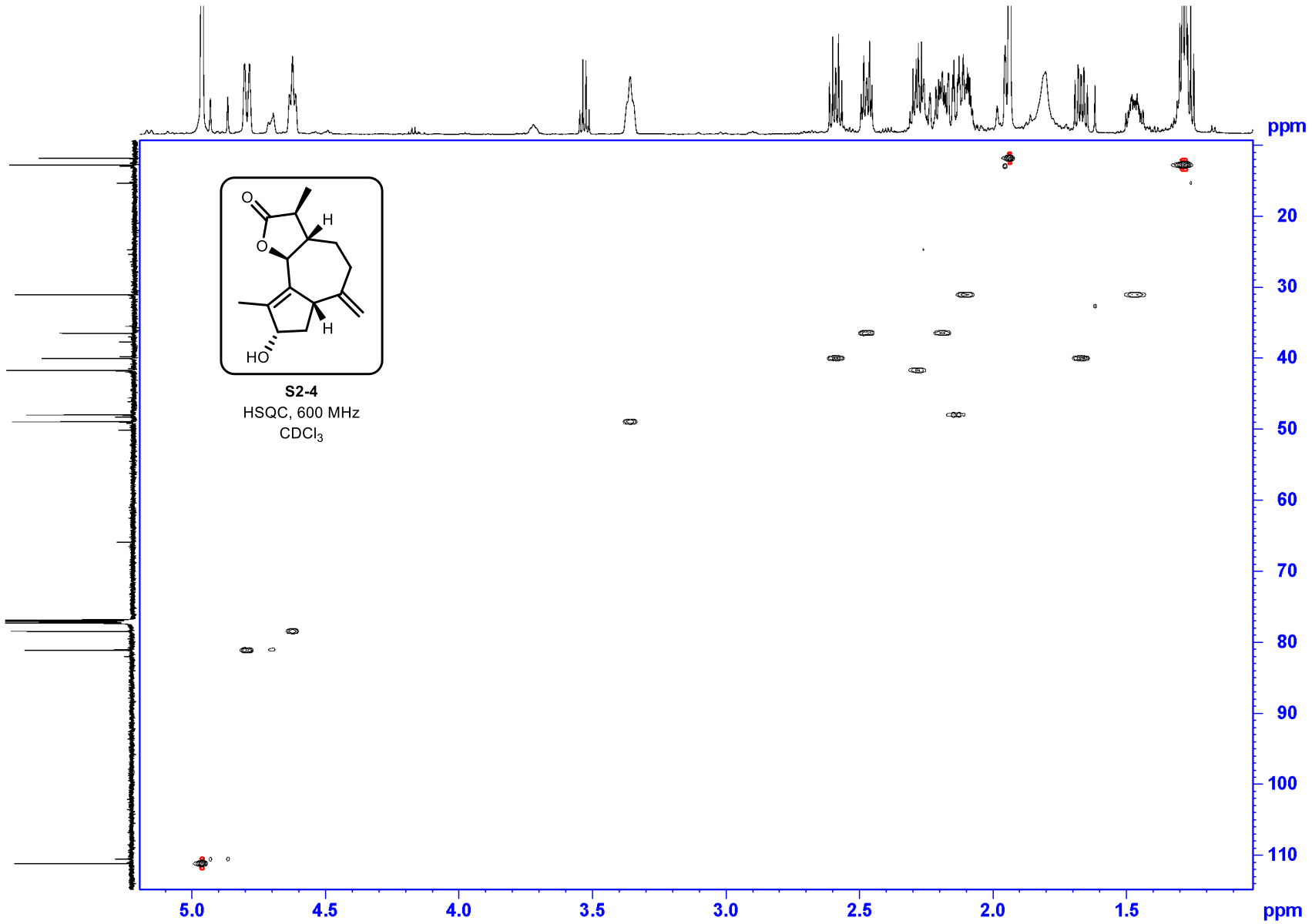
$CDCl_3$

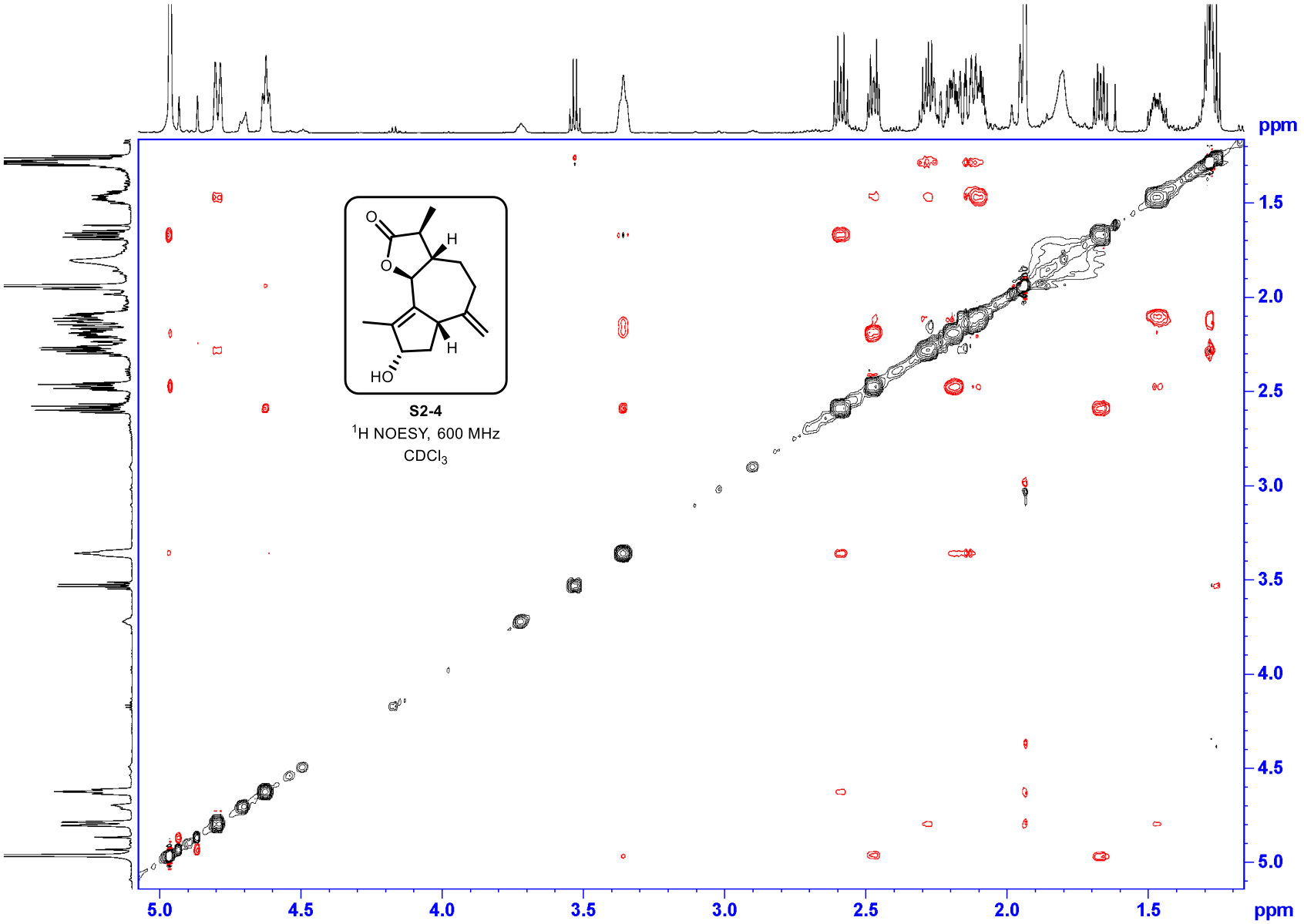


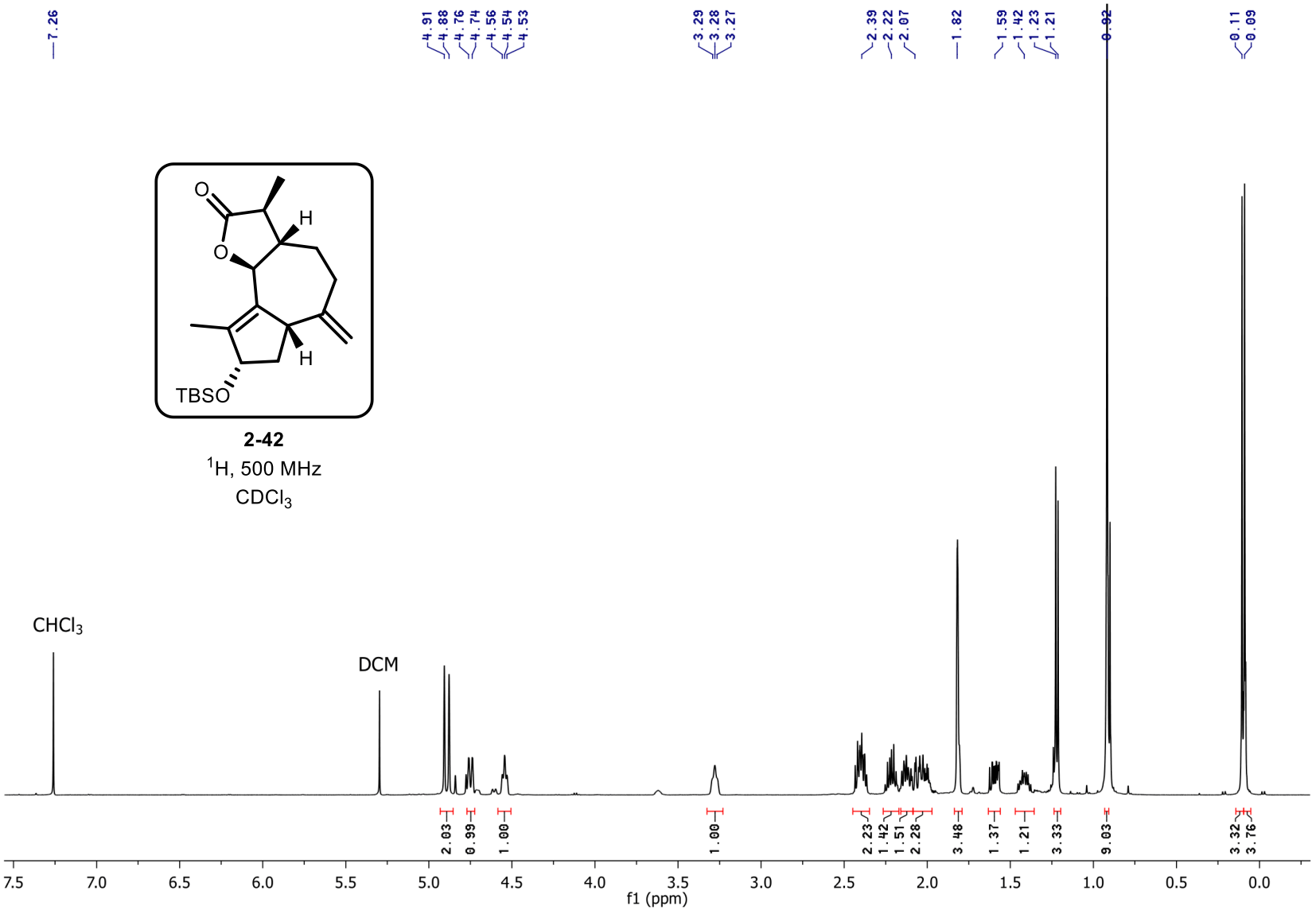
S2-4

^{1}H COSY, 600 MHz

$CDCl_3$


O
O
H
H
HO
S2-4
HSQC, 600 MHz
CDCl3
ppm
20
30
40
50
60
70
80
90
100
110
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

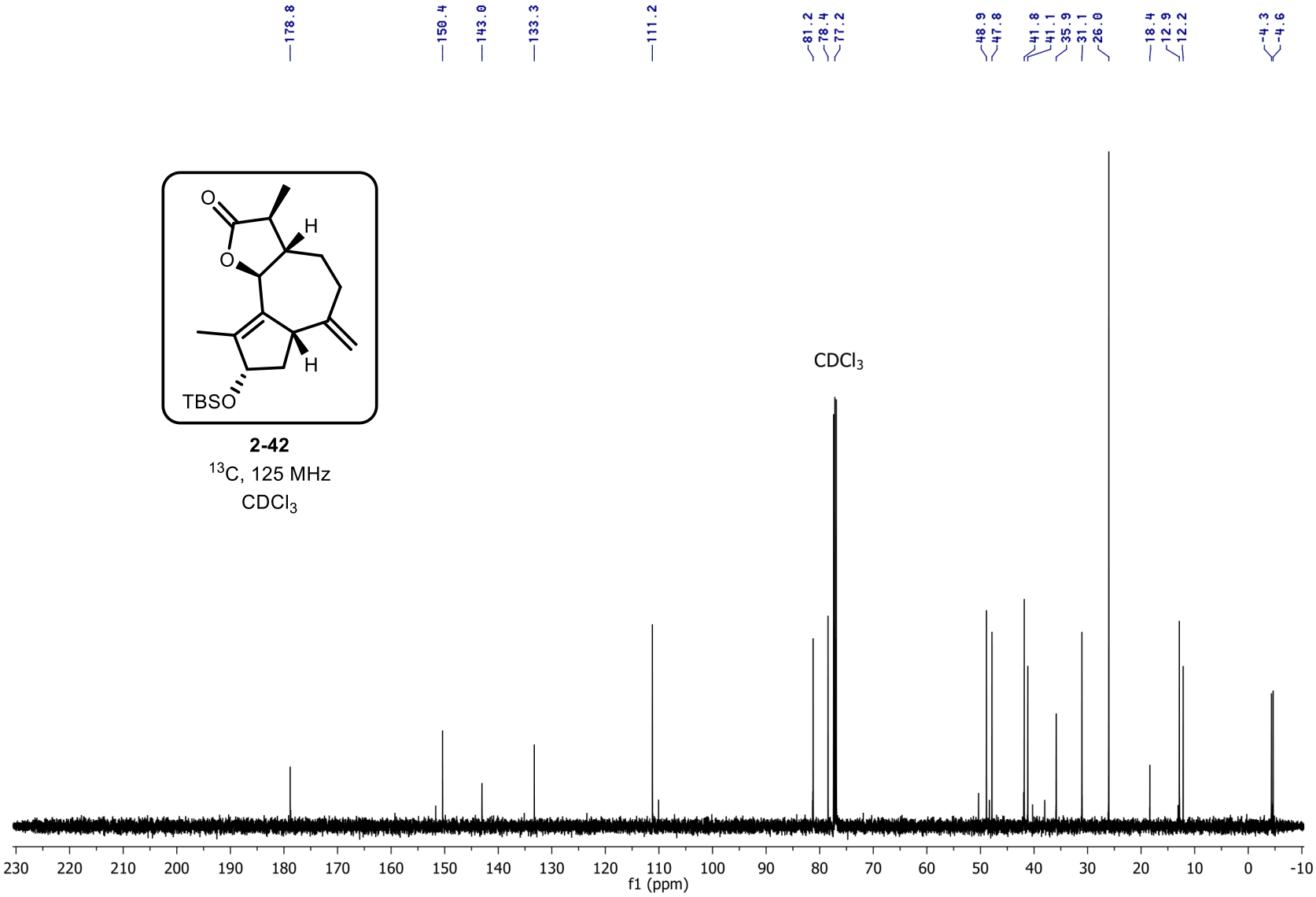

S2-4
^{1}H NOESY, 600 MHz
$CDCl_3$
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5



2-42

^{1}H, 500 MHz

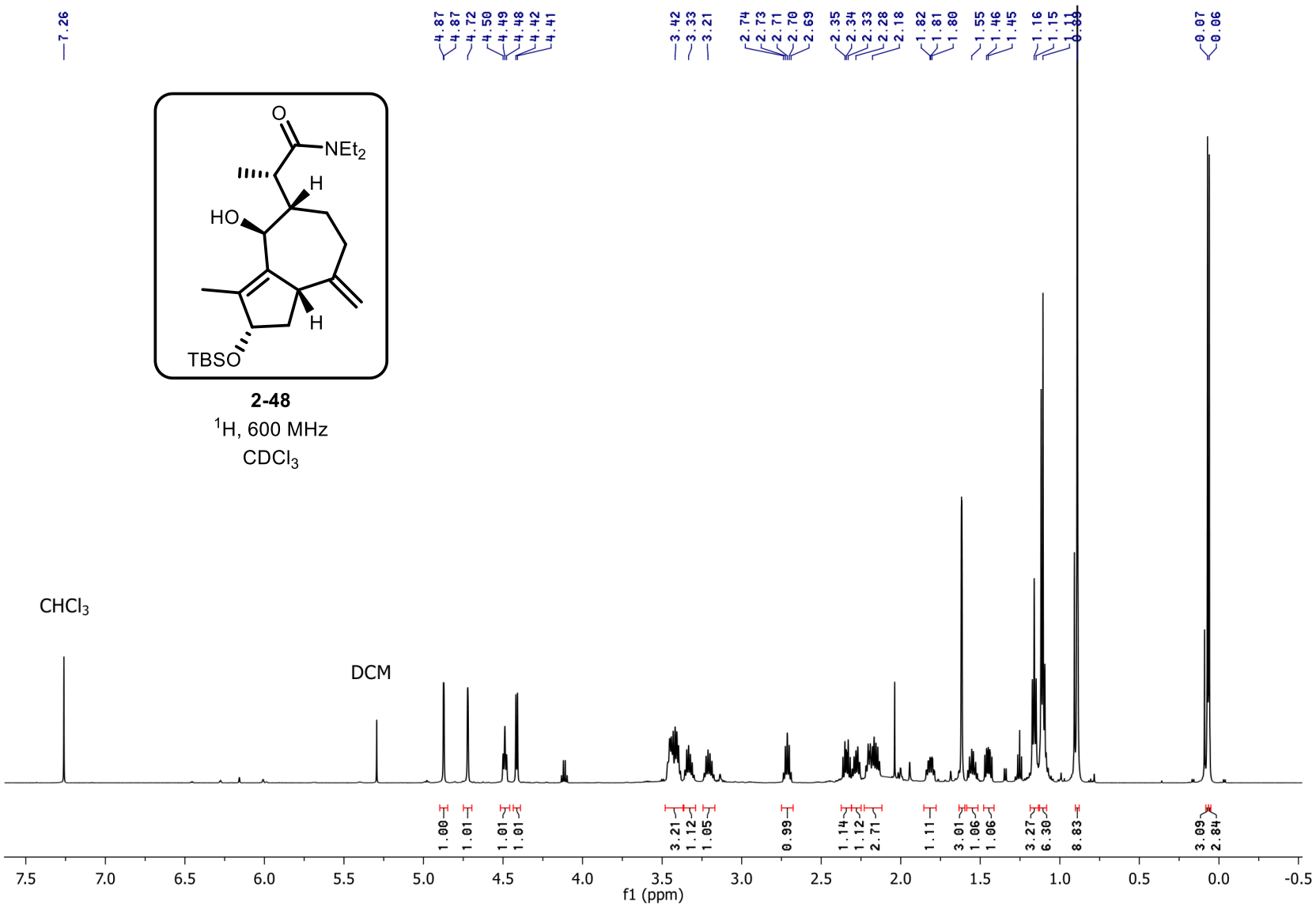
$CDCl_3$



2-42

^{13}C, 125 MHz

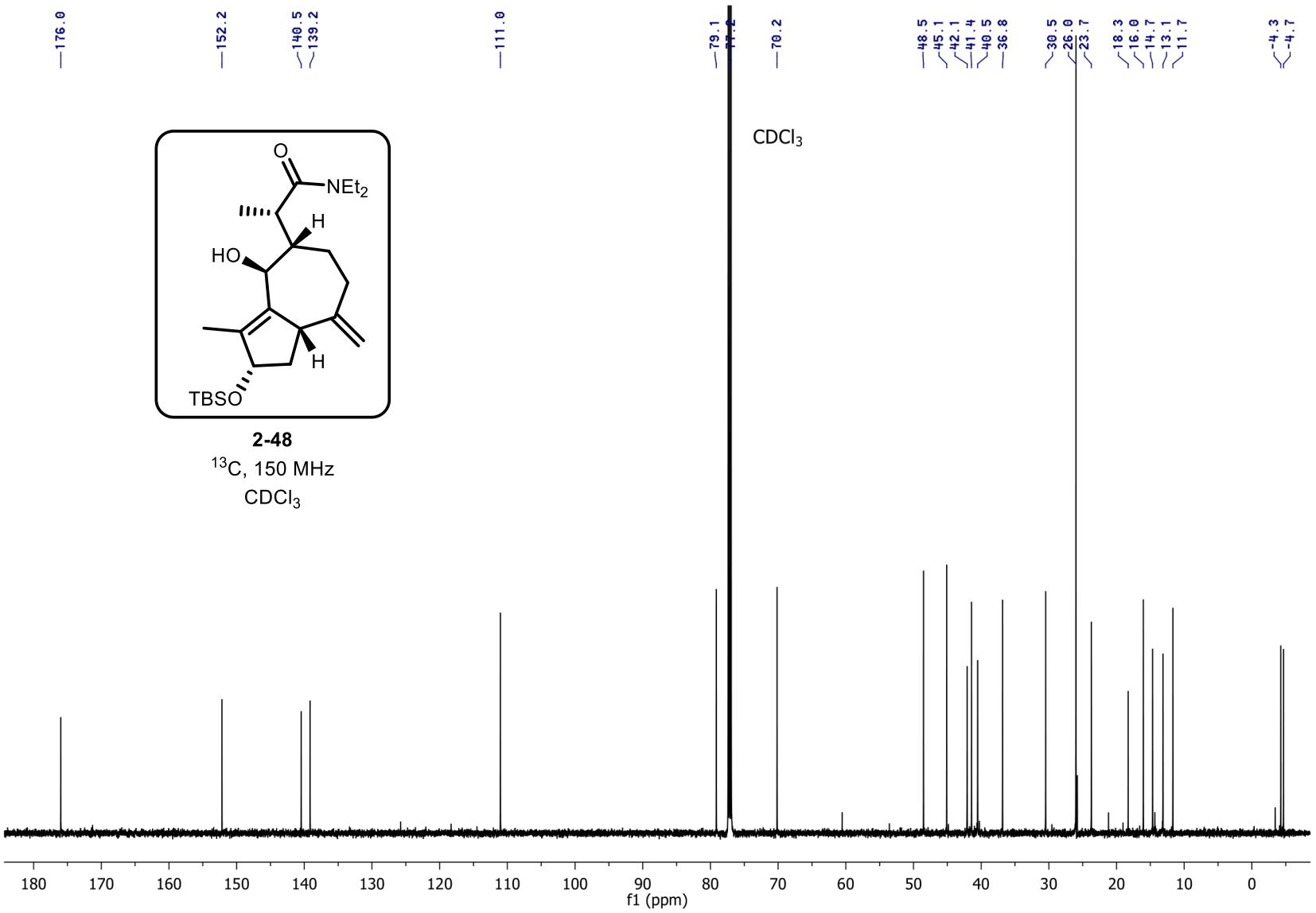
$CDCl_3$



2-48

^{1}H, 600 MHz

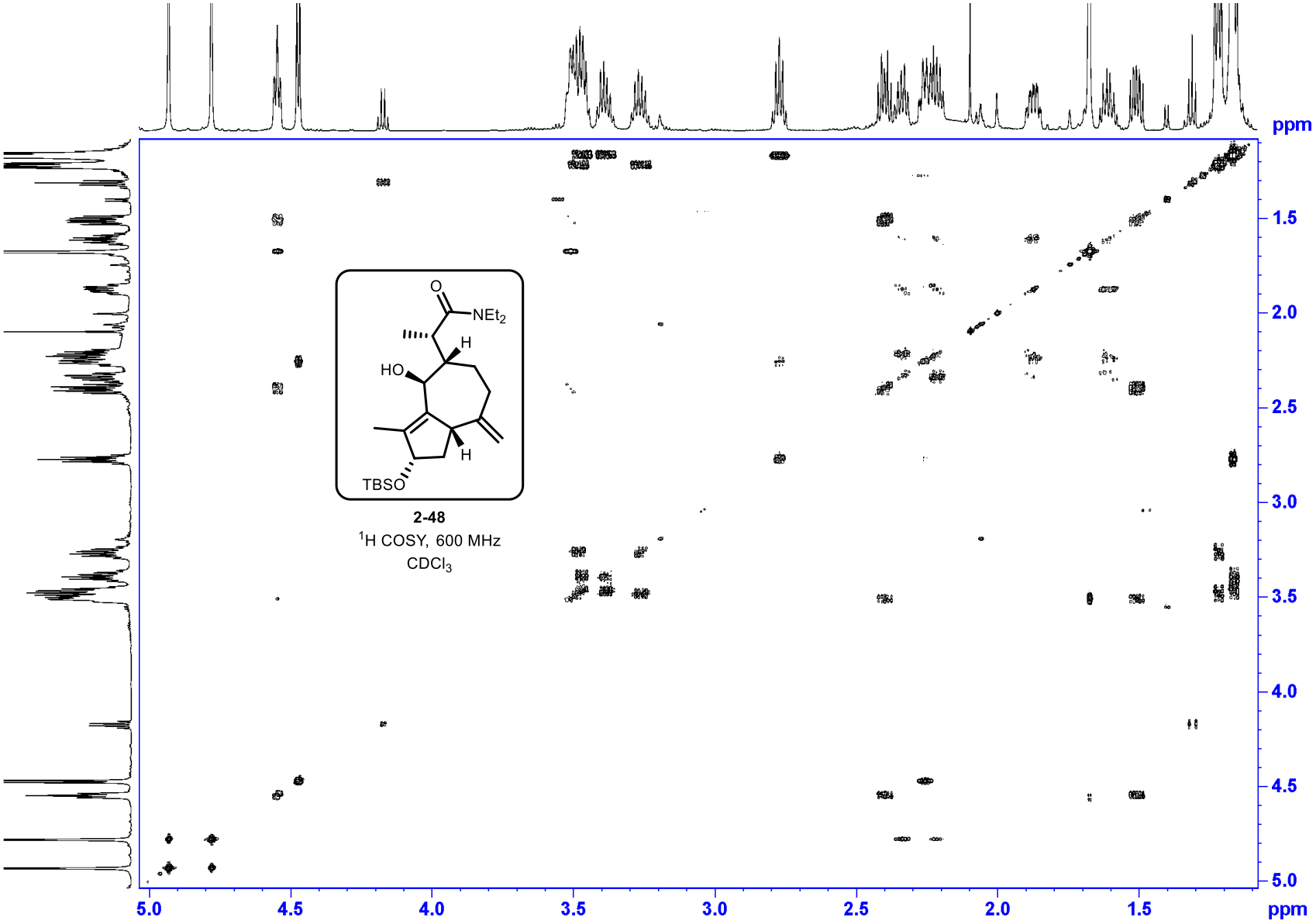
$CDCl_3$

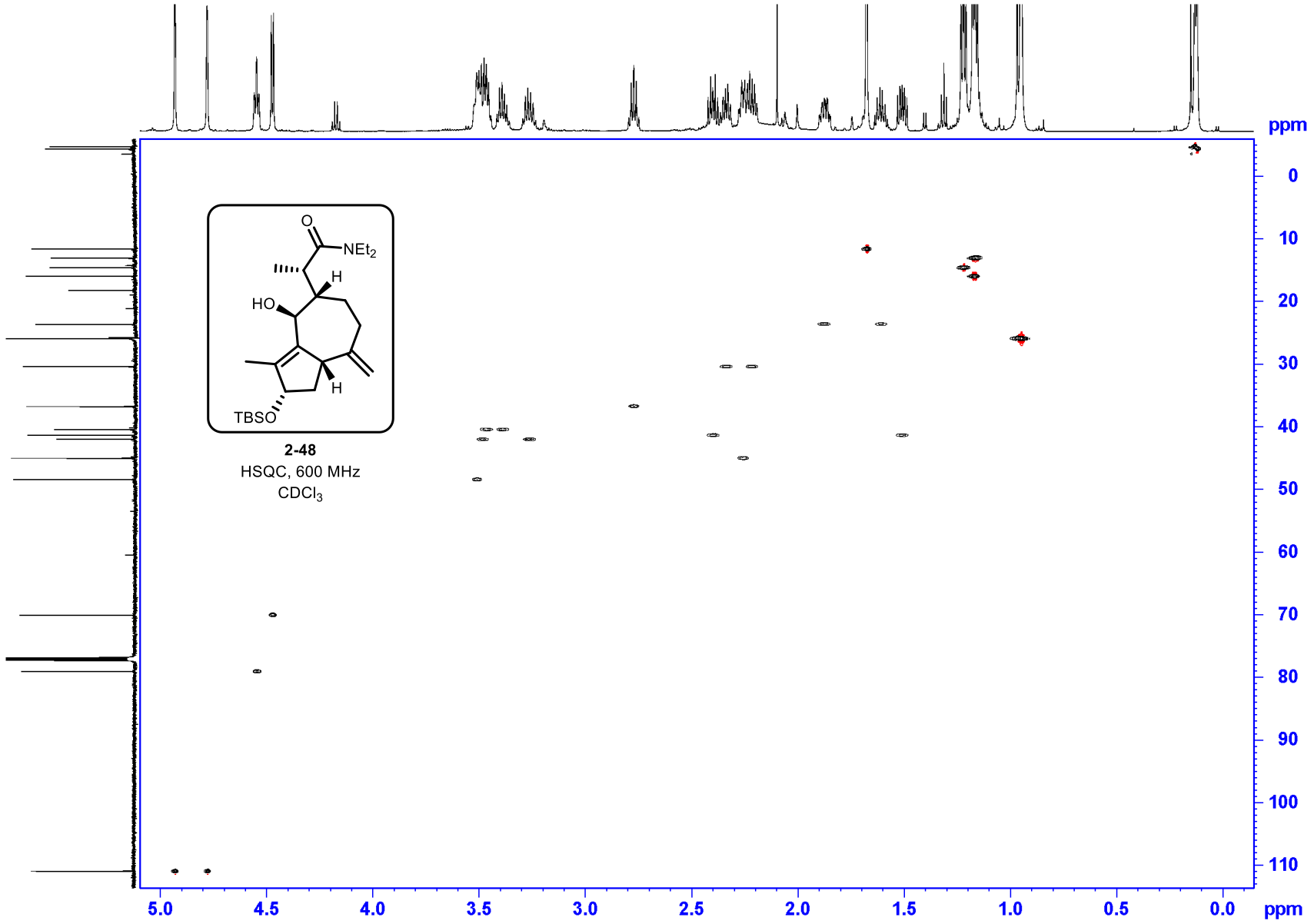


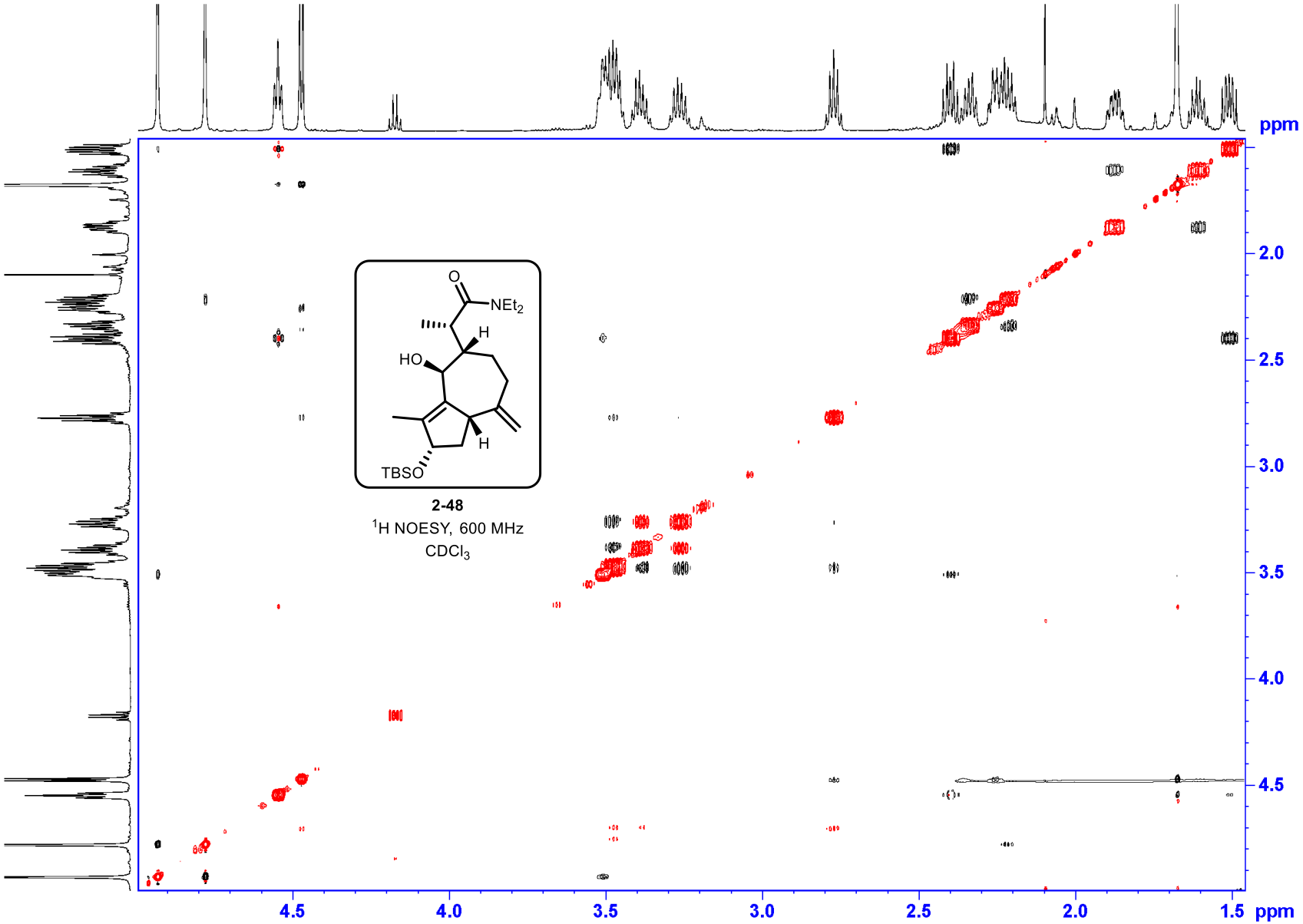
2-48

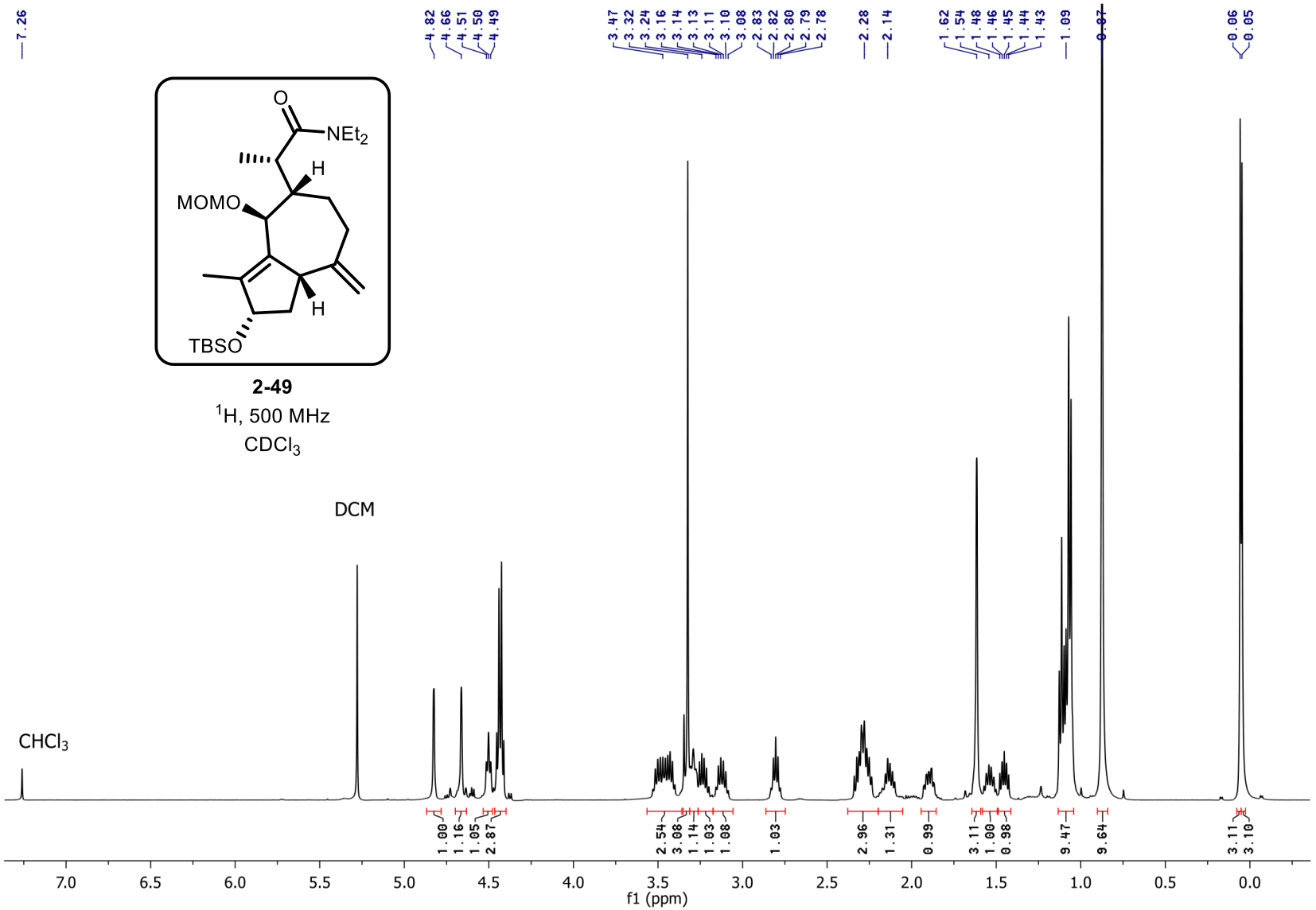
^{13}C, 150 MHz

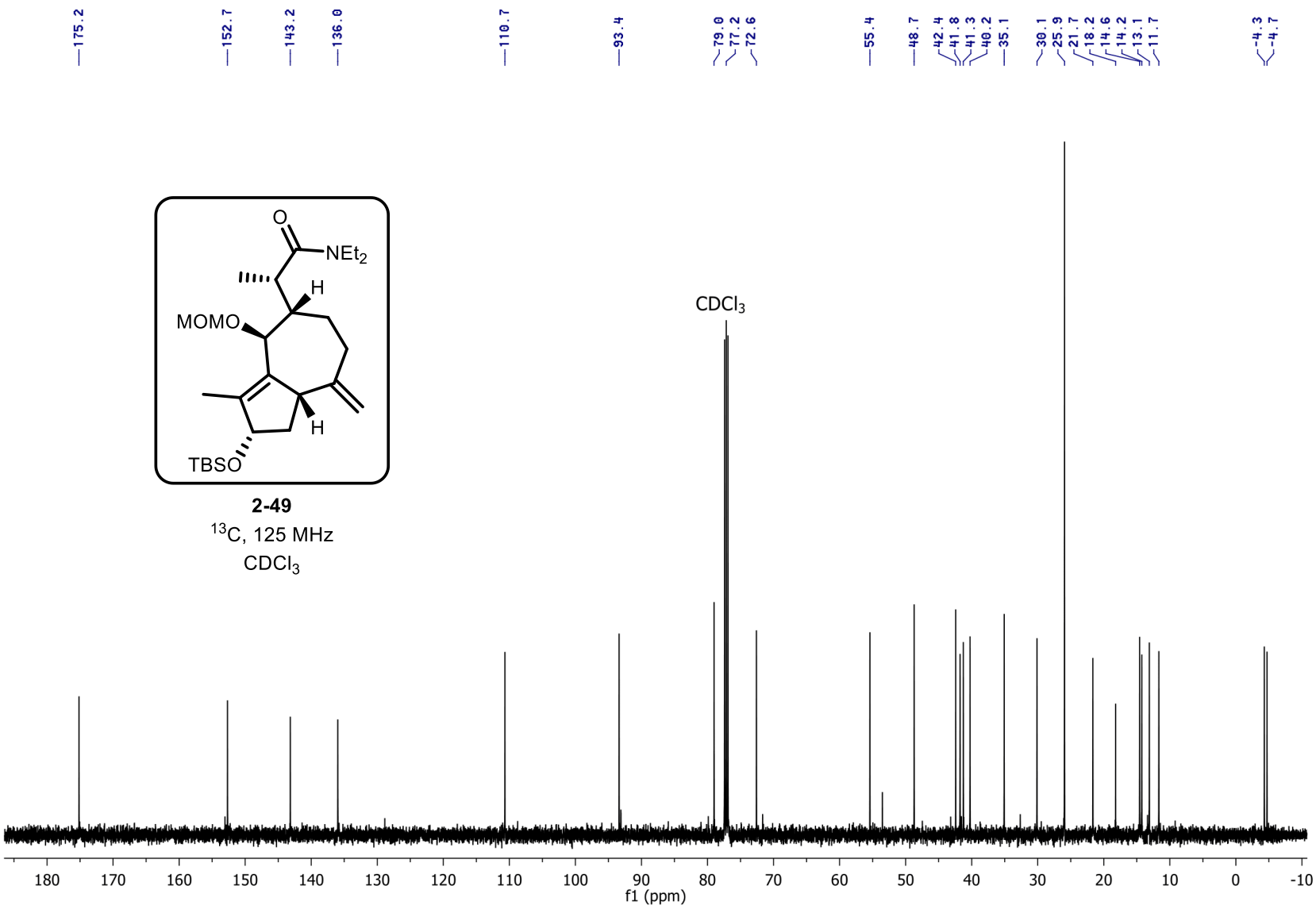
$CDCl_3$


O
NEt2
H
HO
H
TBSO
2-48
1H COSY, 600 MHz
CDCl3
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


O
NEt2
H
HO
H
TBSO
2-48
HSQC, 600 MHz
CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


O
NEt2
H
HO
H
TBSO
2-48
1H NOESY, 600 MHz
CDCl3
ppm
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

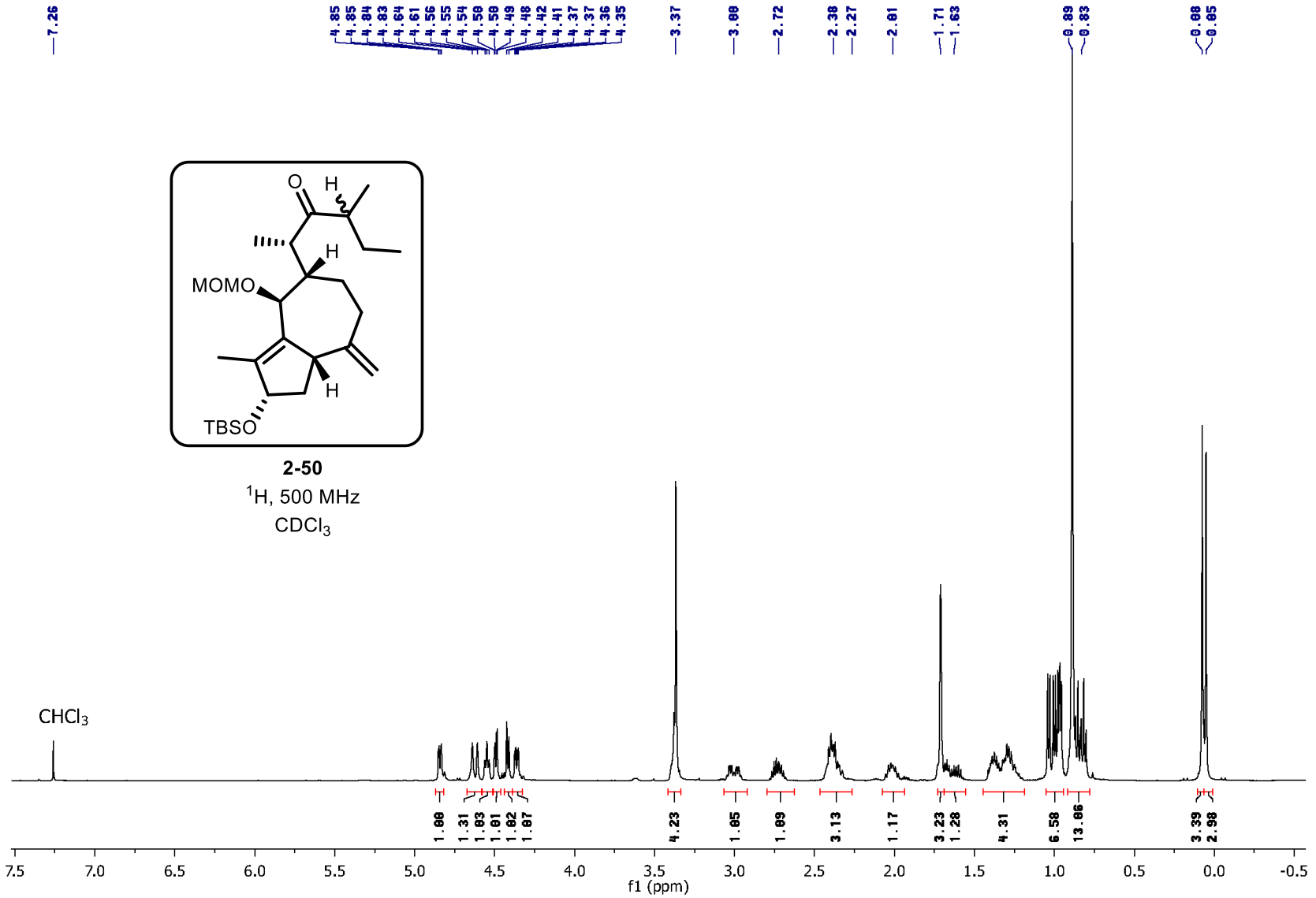

7.26
4.82
4.66
4.51
4.50
4.49
3.47
3.32
3.24
3.16
3.14
3.13
3.11
3.10
3.08
2.83
2.82
2.80
2.79
2.78
2.28
2.14
1.62
1.54
1.48
1.46
1.45
1.44
1.43
1.09
0.87
0.06
0.05
O
NEt2
H
MOMO
H
TBSO
2-49
1H, 500 MHz
CDCl3
DCM
CHCl3
1.00
1.16
1.05
2.87
2.54
3.08
1.14
1.03
1.08
1.03
2.96
1.31
0.99
3.11
1.00
0.98
9.47
9.64
3.11
3.10
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

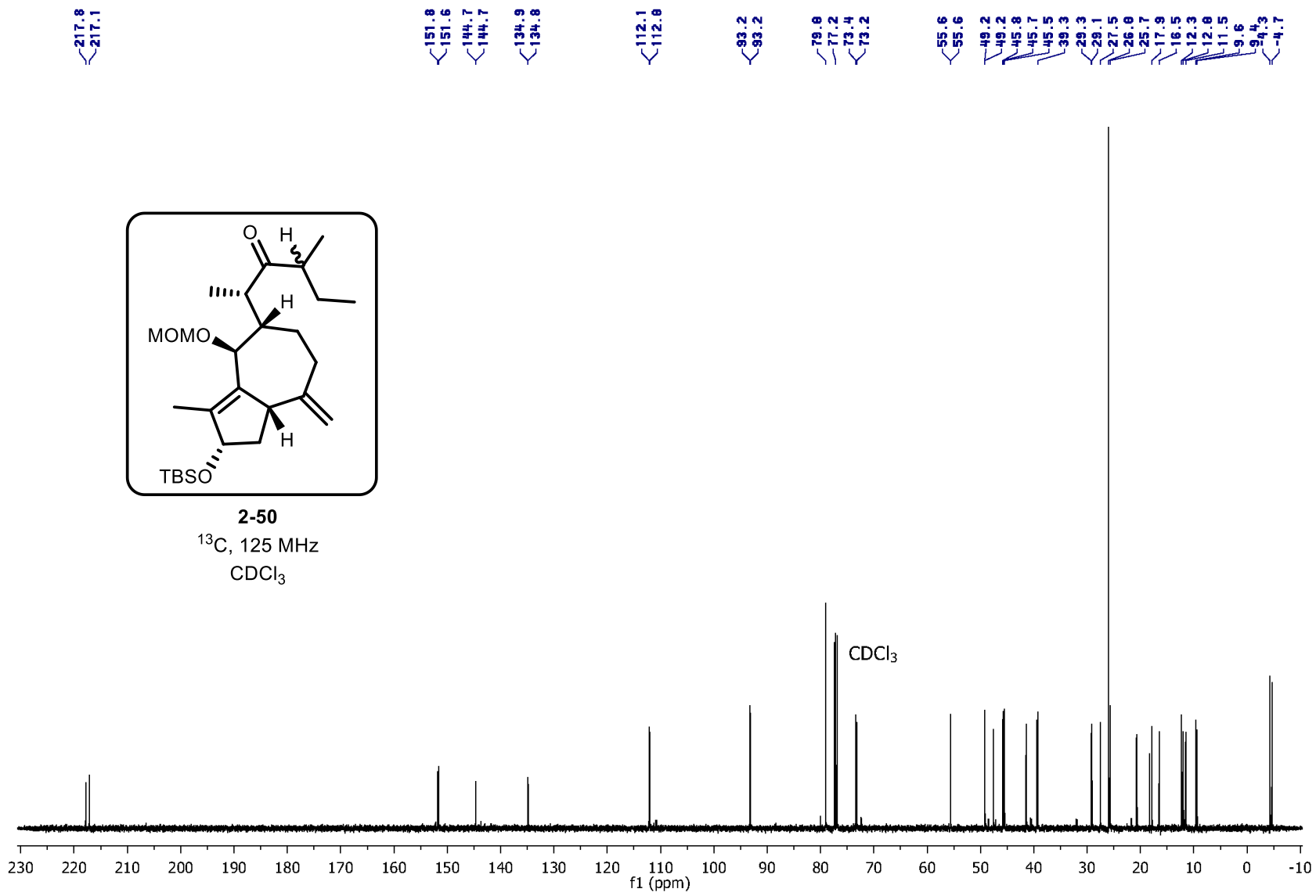


2-49

^{13}C, 125 MHz

$CDCl_3$

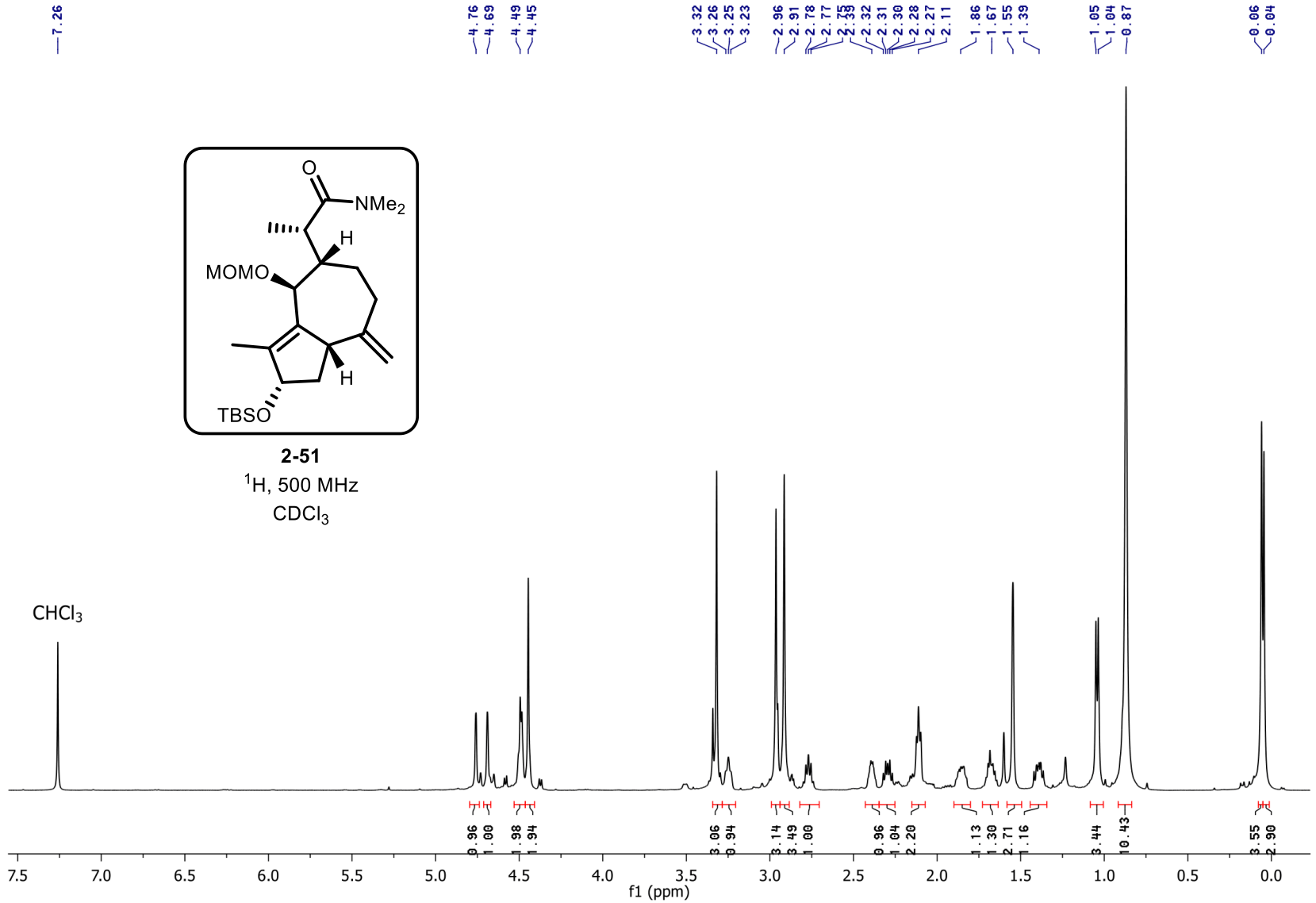

7.26
4.85
4.85
4.84
4.83
4.64
4.61
4.56
4.55
4.54
4.50
4.50
4.49
4.48
4.42
4.41
4.37
4.37
4.36
4.35
3.37
3.00
2.72
2.38
2.27
2.01
1.71
1.63
0.89
0.83
0.08
0.05
O
H
H
MOMO
H
TBSO
2-50
1H, 500 MHz
CDCl3
CHCl3
1.00
1.31
1.03
1.01
1.02
1.07
4.23
1.85
1.89
3.13
1.17
3.23
1.28
4.31
6.58
13.06
3.39
2.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

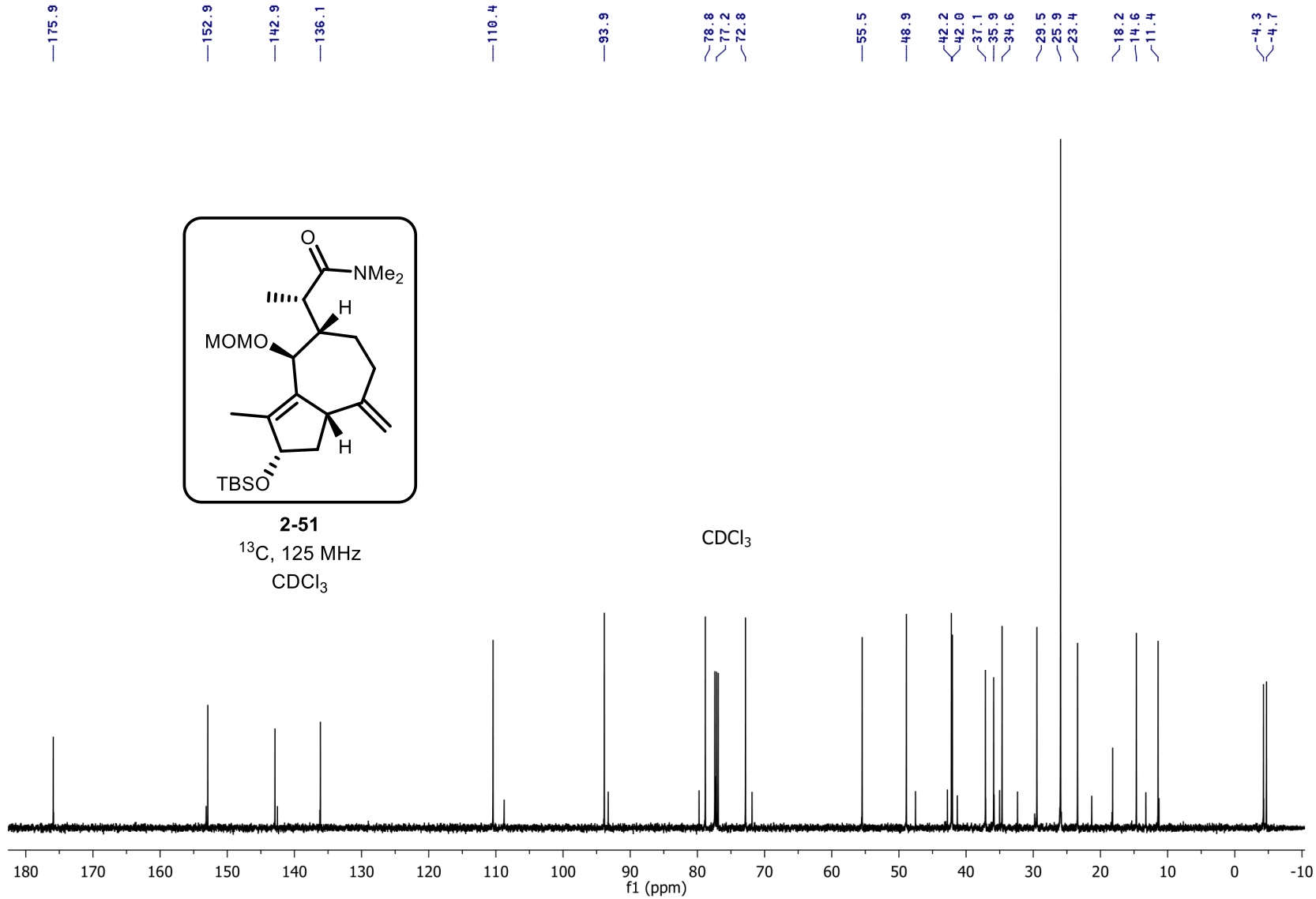


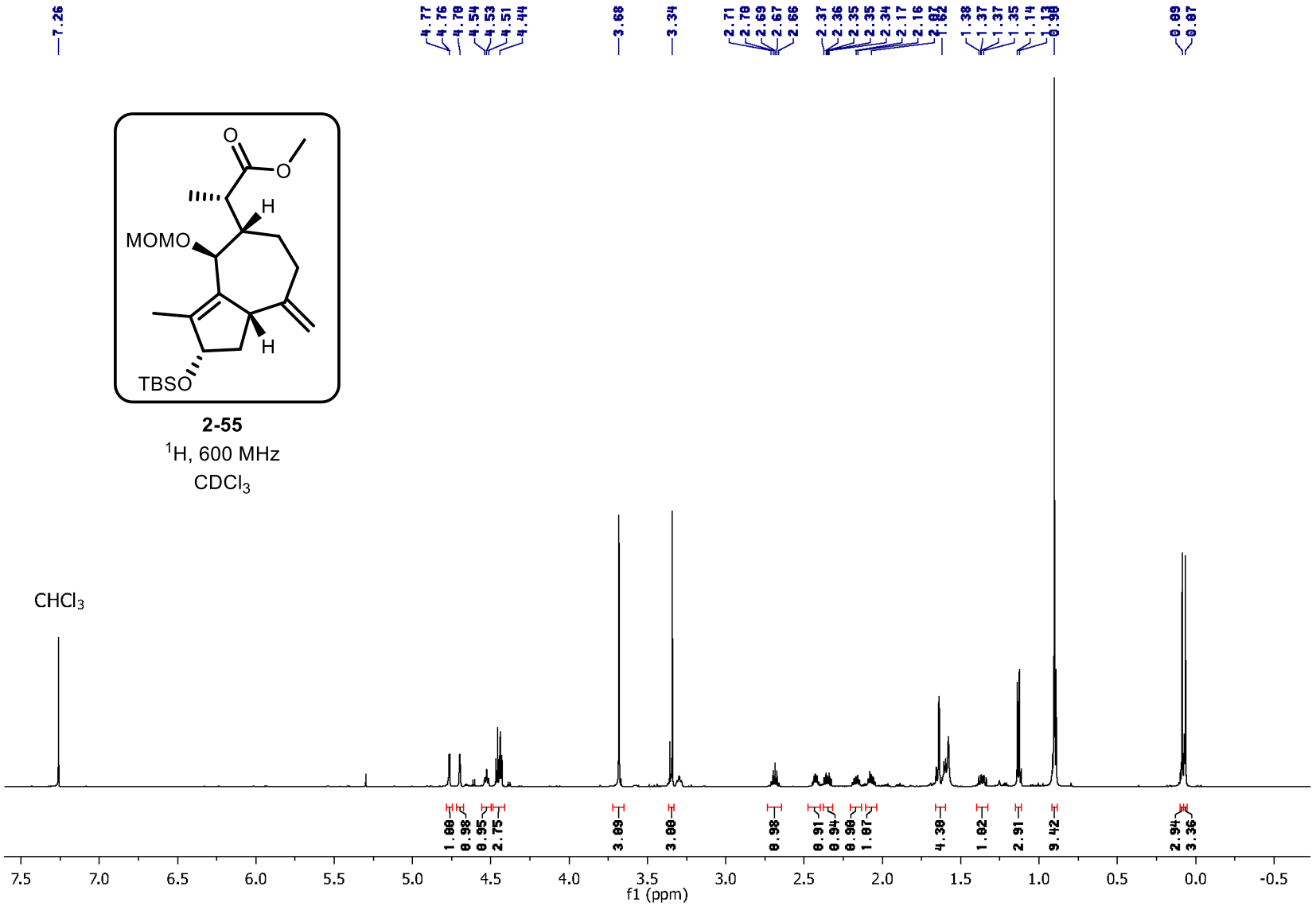
2-50

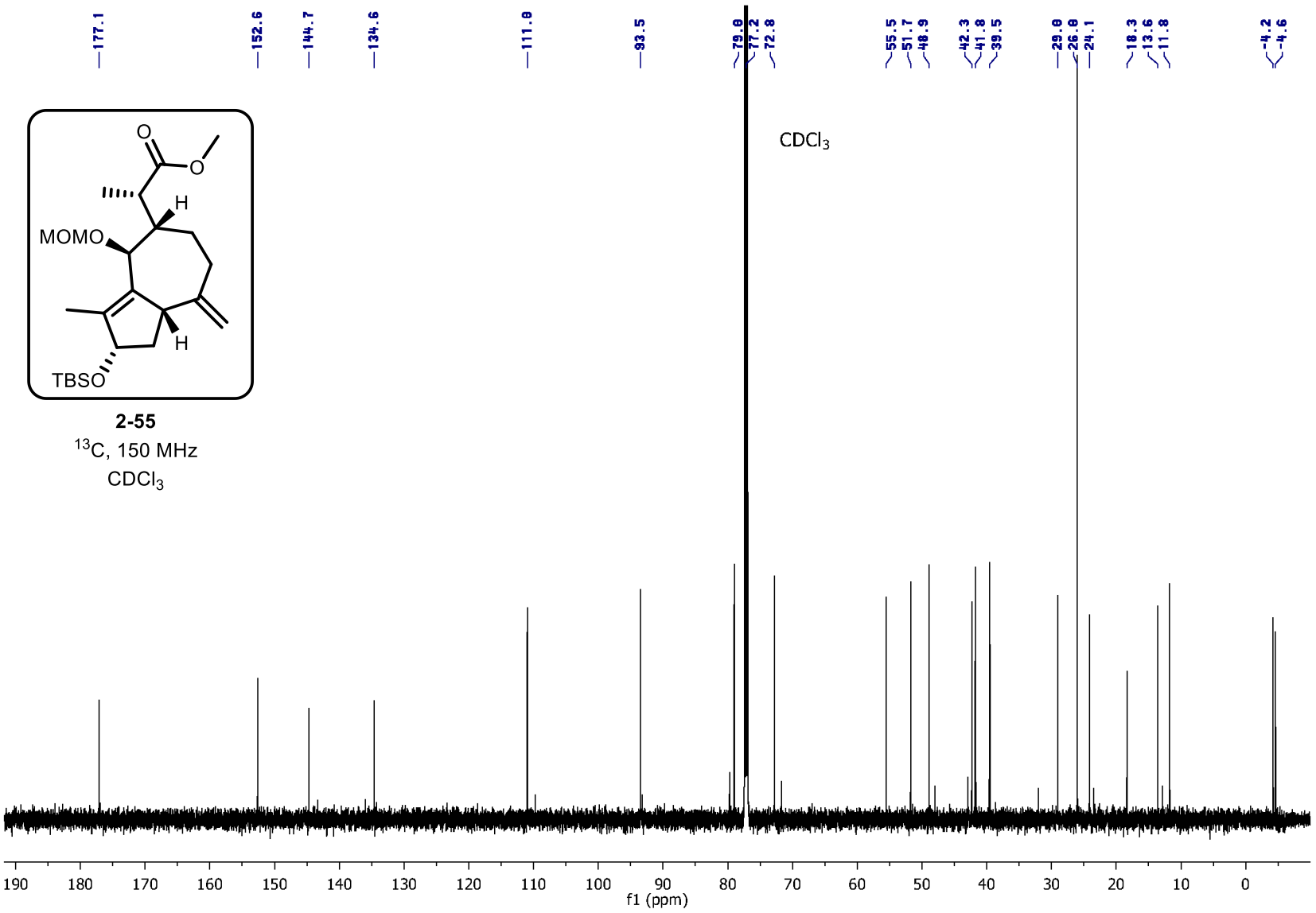
^{13}C, 125 MHz

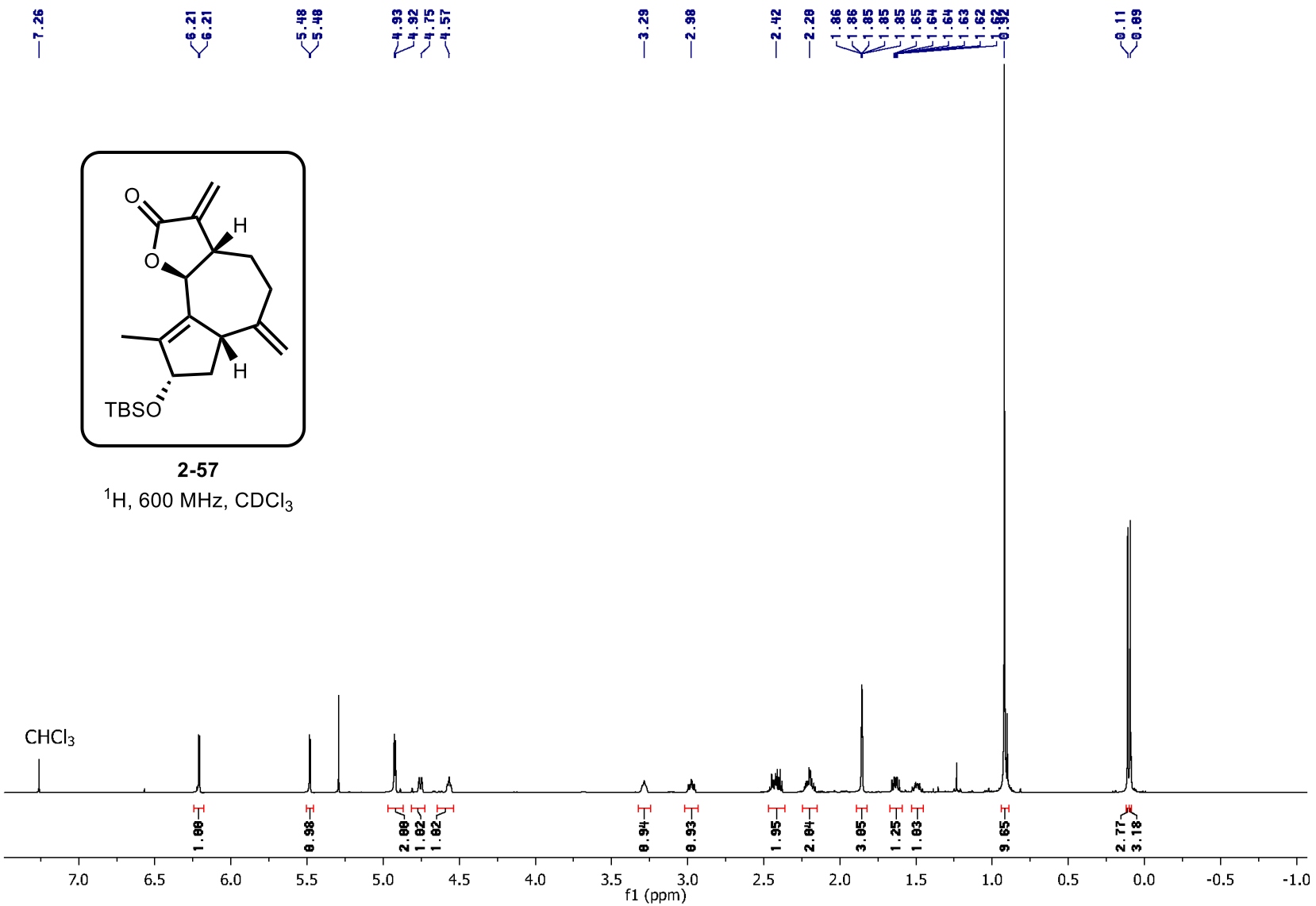
$CDCl_3$


7.26
4.76
4.69
4.49
4.45
3.32
3.26
3.25
3.23
2.96
2.91
2.78
2.77
2.75
2.33
2.32
2.31
2.30
2.28
2.27
2.11
1.86
1.67
1.55
1.39
1.05
1.04
0.87
0.06
0.04
O
NMe2
H
MOMO
H
TBSO
2-51
1H, 500 MHz
CDCl3
CHCl3
0.96
1.00
1.98
1.94
3.06
0.94
3.14
3.49
1.00
0.96
1.04
2.20
1.13
1.30
2.71
1.16
3.44
10.43
3.55
2.90
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


175.9
152.9
142.9
136.1
110.4
93.9
78.8
77.2
72.8
55.5
48.9
42.2
42.0
37.1
35.9
34.6
29.5
25.9
23.4
18.2
14.6
11.4
-4.3
-4.7
O
NMe2
H
MOMO
H
TBSO
2-51
13C, 125 MHz
CDCl3
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

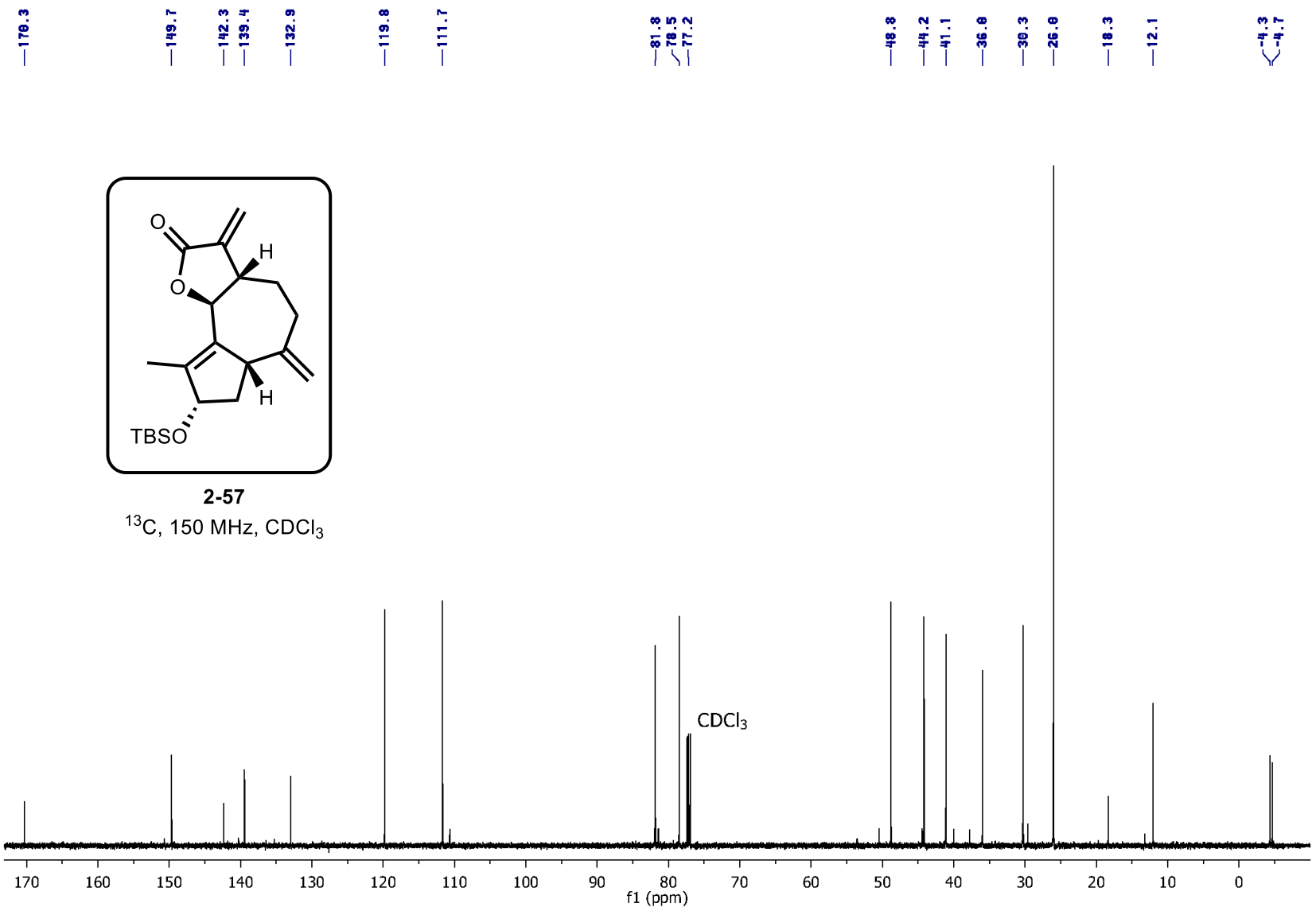

7.26
4.77
4.76
4.70
4.54
4.53
4.51
4.44
3.68
3.34
2.71
2.70
2.69
2.67
2.66
2.37
2.36
2.35
2.35
2.34
2.17
2.16
1.38
1.37
1.37
1.35
1.14
0.09
0.07
O
O
H
MOMO
H
TBSO
2-55
1H, 600 MHz
CDCl3
CHCl3
1.00
0.98
0.95
2.75
3.09
3.00
0.98
0.91
0.94
0.90
1.07
4.30
1.02
2.91
9.42
2.94
3.36
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


177.1
152.6
144.7
134.6
111.0
93.5
79.0
77.2
72.8
55.5
51.7
48.9
42.3
41.8
39.5
29.0
26.0
24.1
18.3
13.6
11.8
-4.2
-4.6
CDCl3
O
O
H
MOMO
H
TBSO
2-55
13C, 150 MHz
CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



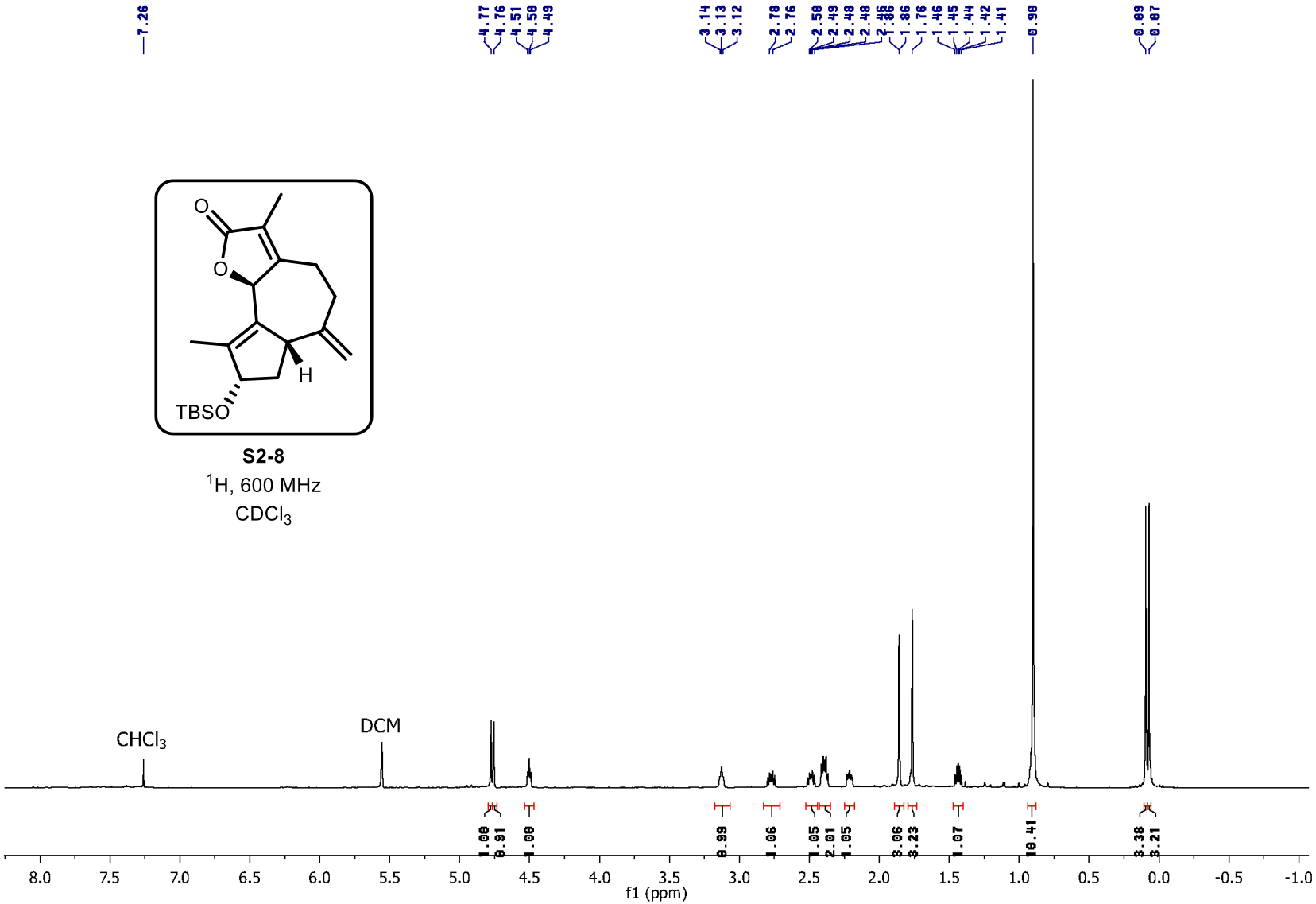
2-57

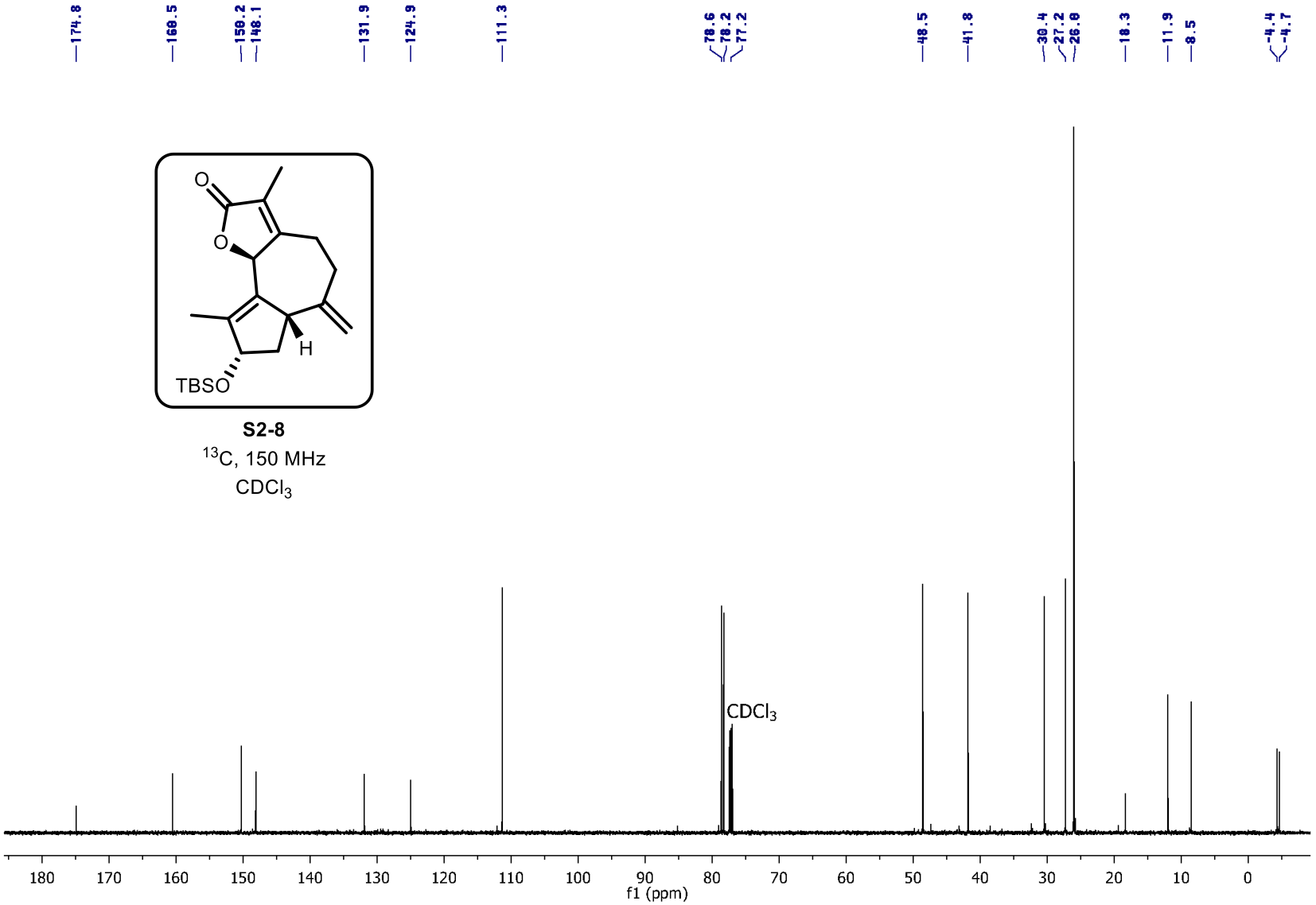
^{1}H, 600 MHz, $CDCl_3$



2-57

^{13}C, 150 MHz, $CDCl_3$

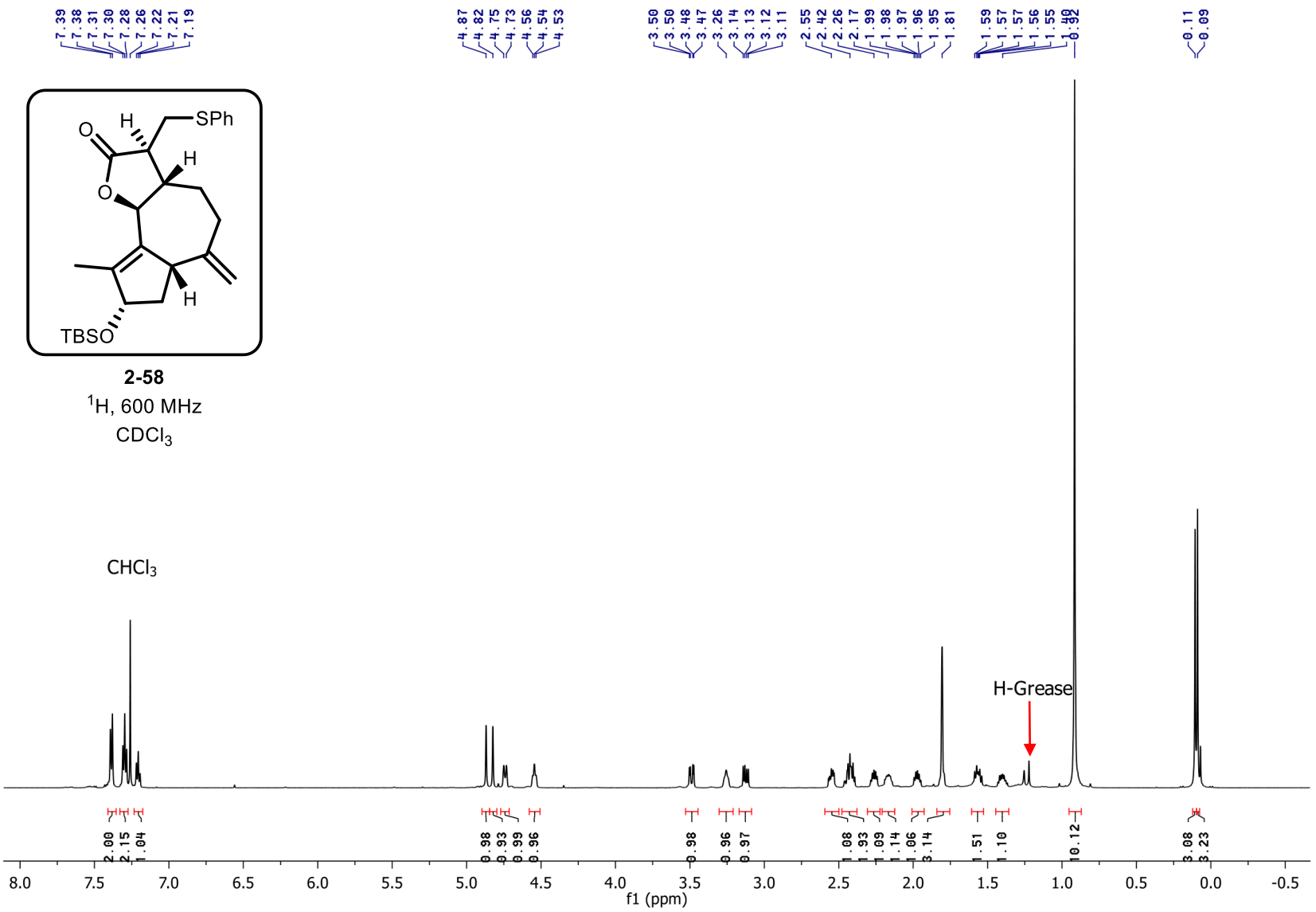

7.26
4.77
4.76
4.51
4.50
4.49
3.14
3.13
3.12
2.78
2.76
2.50
2.49
2.48
2.48
2.46
1.86
1.76
1.46
1.45
1.44
1.42
1.41
0.98
0.89
0.87
O
O
H
TBSO
S2-8
1H, 600 MHz
CDCl3
CHCl3
DCM
1.00
0.91
1.00
0.99
1.06
1.05
2.01
1.05
3.06
3.23
1.07
10.41
3.38
3.21
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

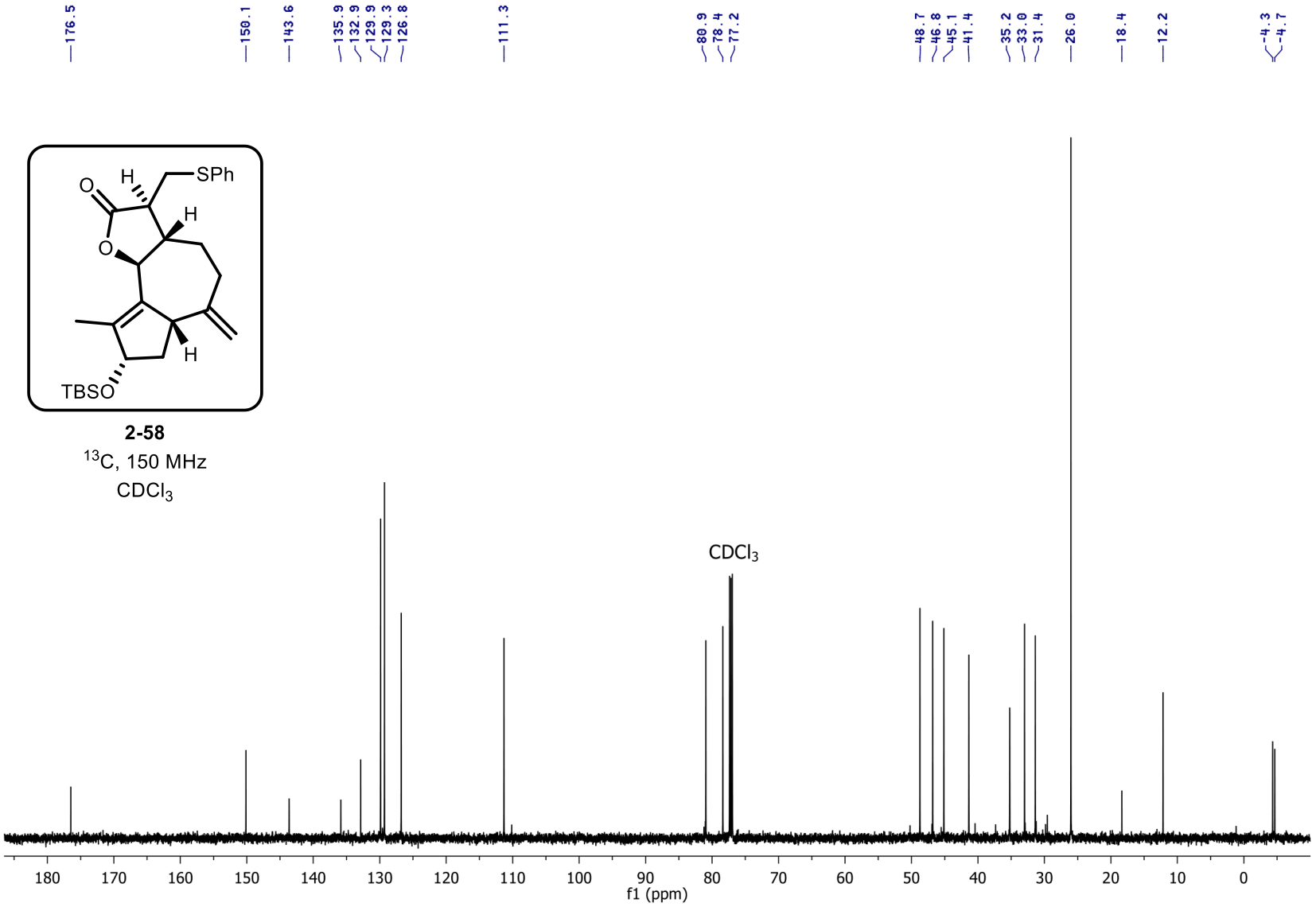


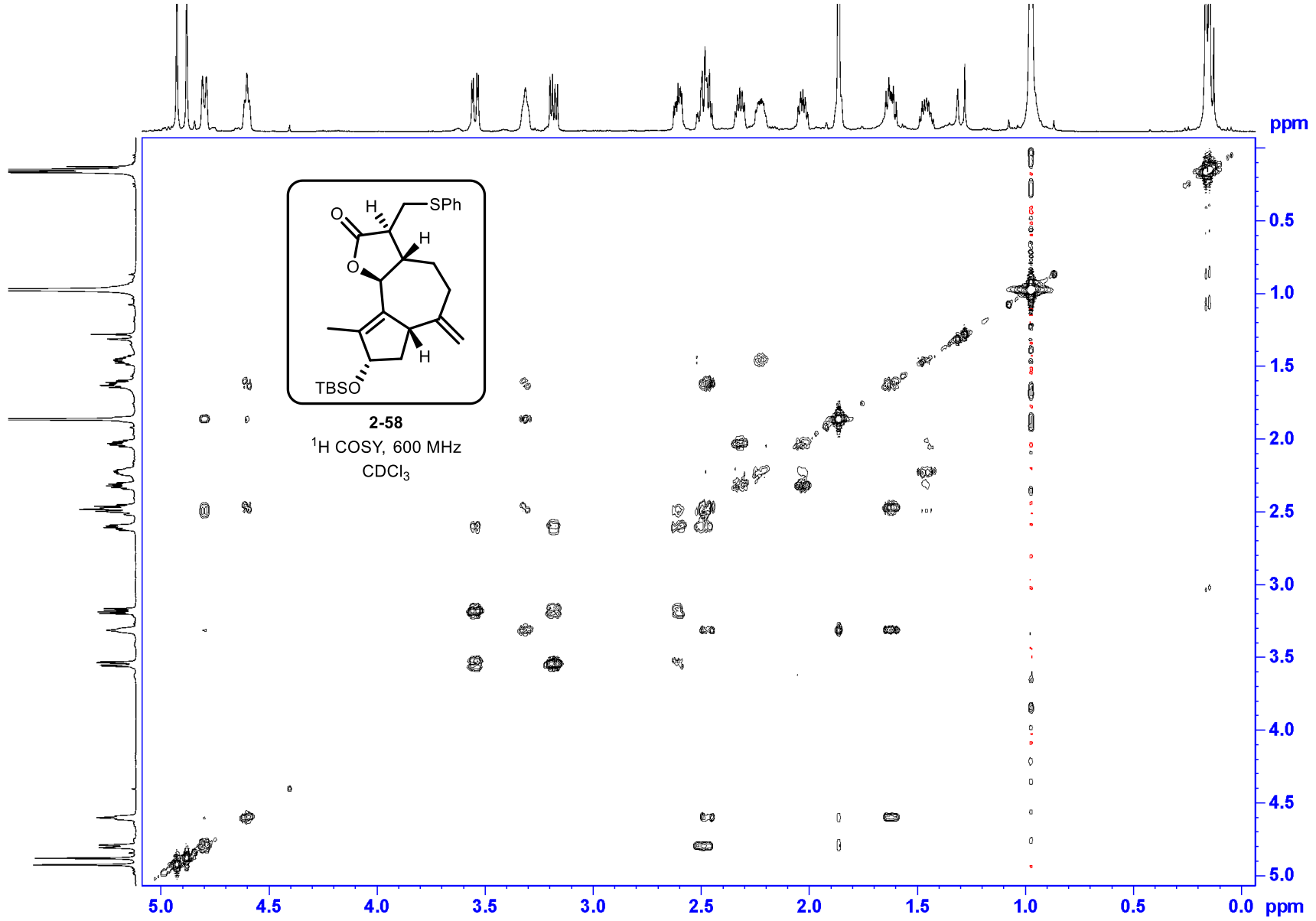
S2-8

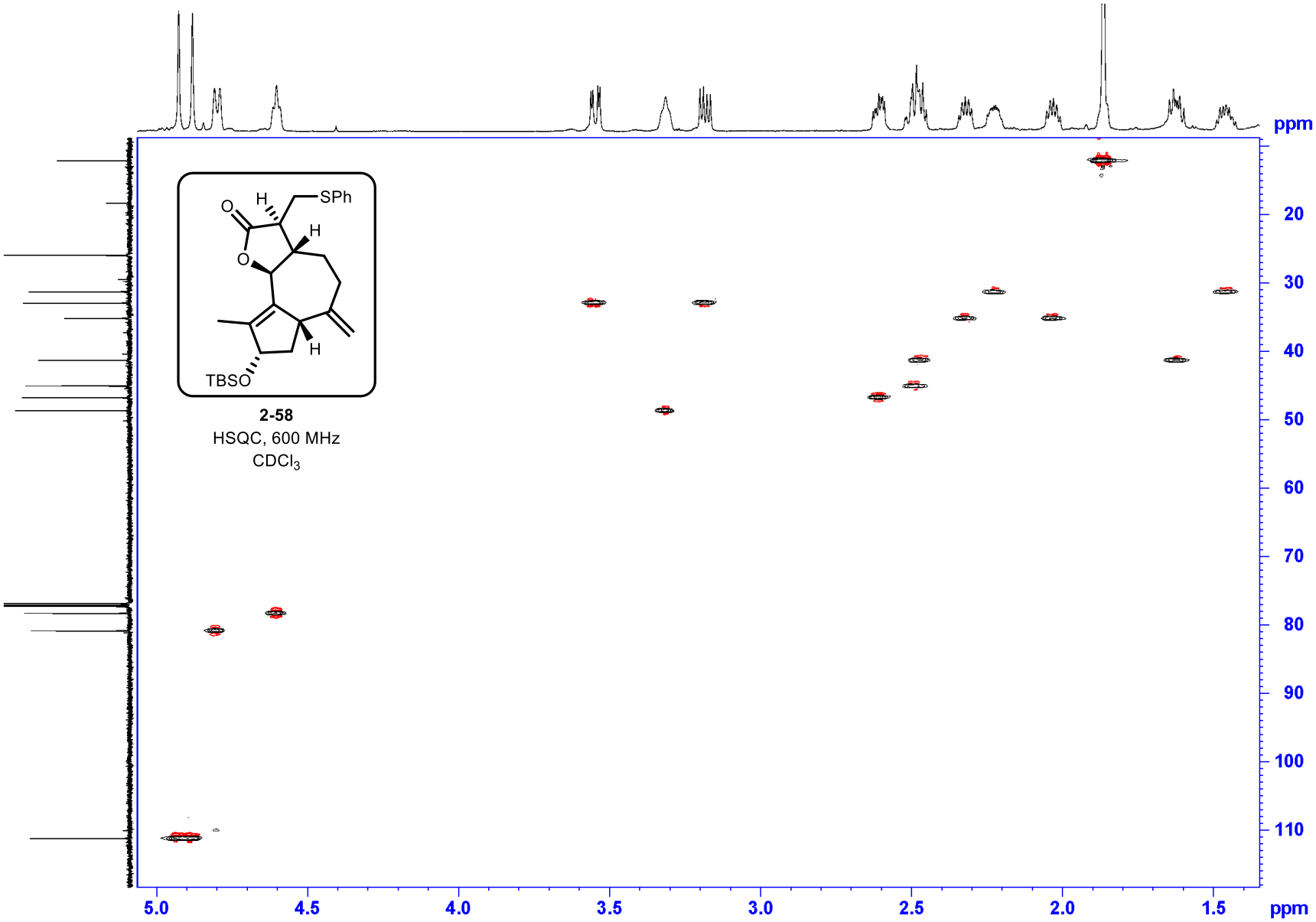
^{13}C, 150 MHz

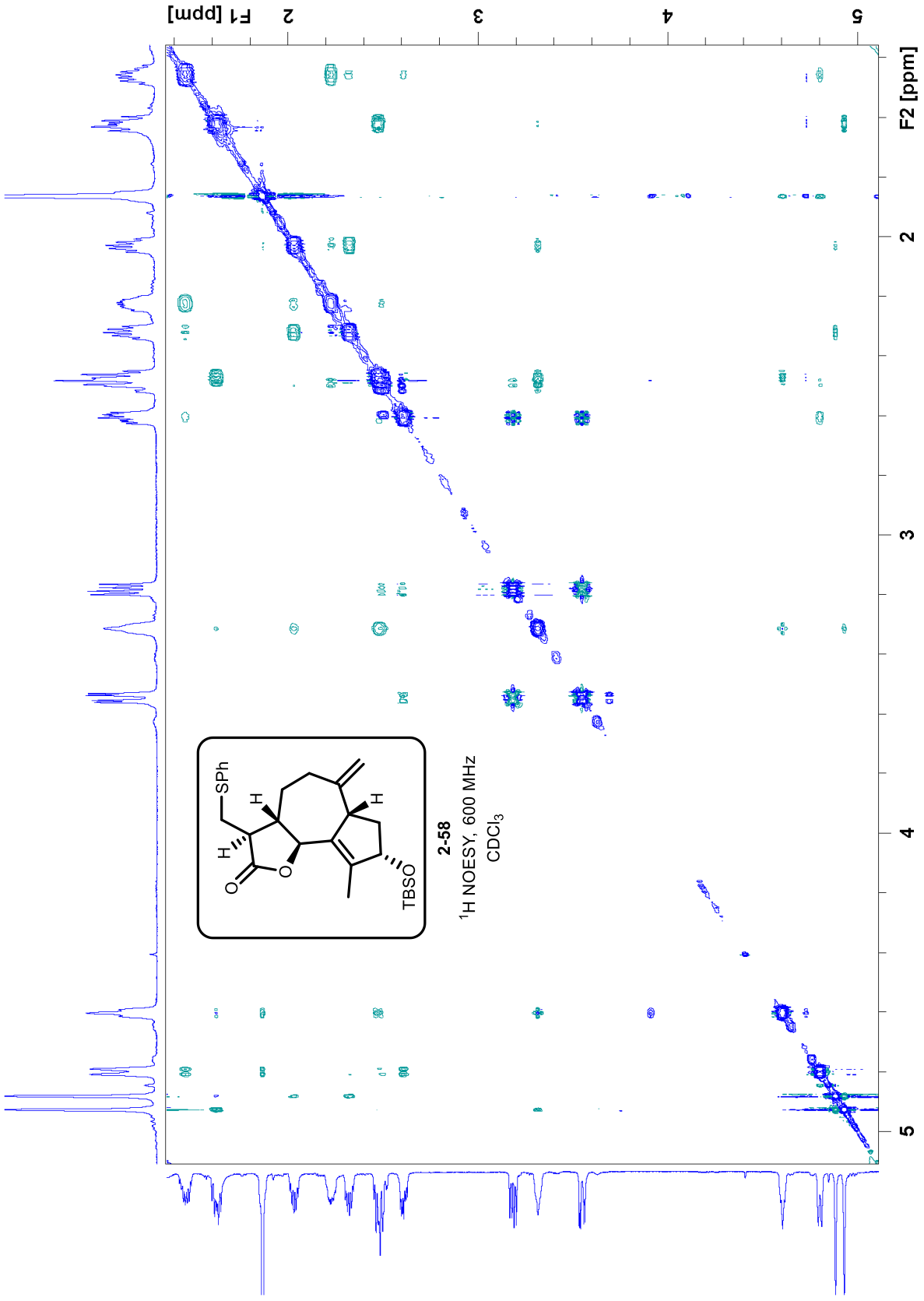
$CDCl_3$

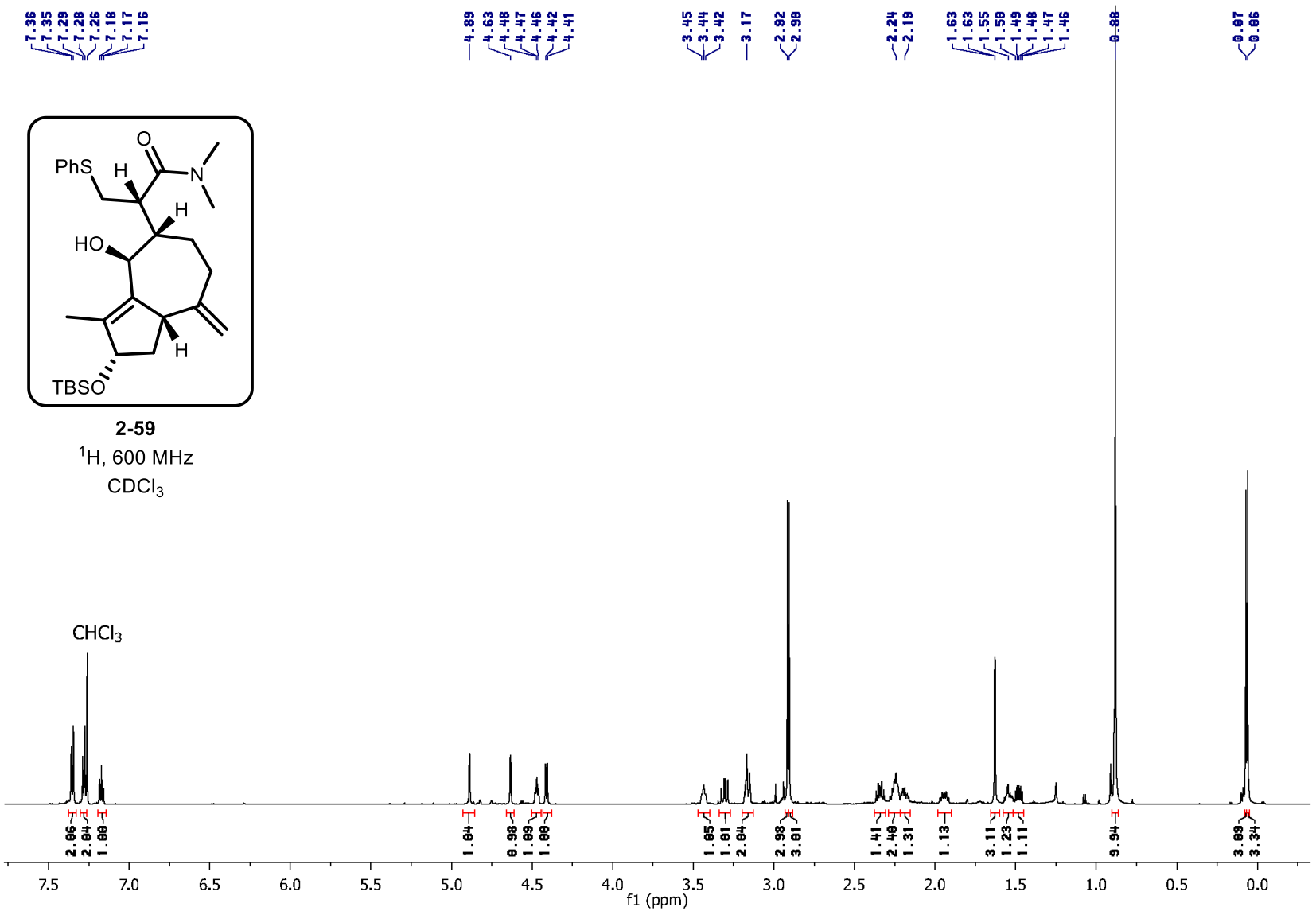

7.39
7.38
7.31
7.30
7.28
7.26
7.22
7.21
7.19
4.87
4.82
4.75
4.73
4.56
4.54
4.53
3.50
3.50
3.48
3.47
3.26
3.14
3.13
3.12
3.11
2.55
2.42
2.26
2.17
1.99
1.98
1.97
1.96
1.95
1.81
1.59
1.57
1.57
1.56
1.55
0.92
0.11
0.09
H
SPh
O
H
O
H
TBSO
2-58
1H, 600 MHz
CDCl3
CHCl3
H-Grease
2.00
2.15
1.04
0.98
0.93
0.99
0.96
0.98
0.96
0.97
1.08
1.93
1.09
1.14
1.06
3.14
1.51
1.10
10.12
3.08
3.23
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

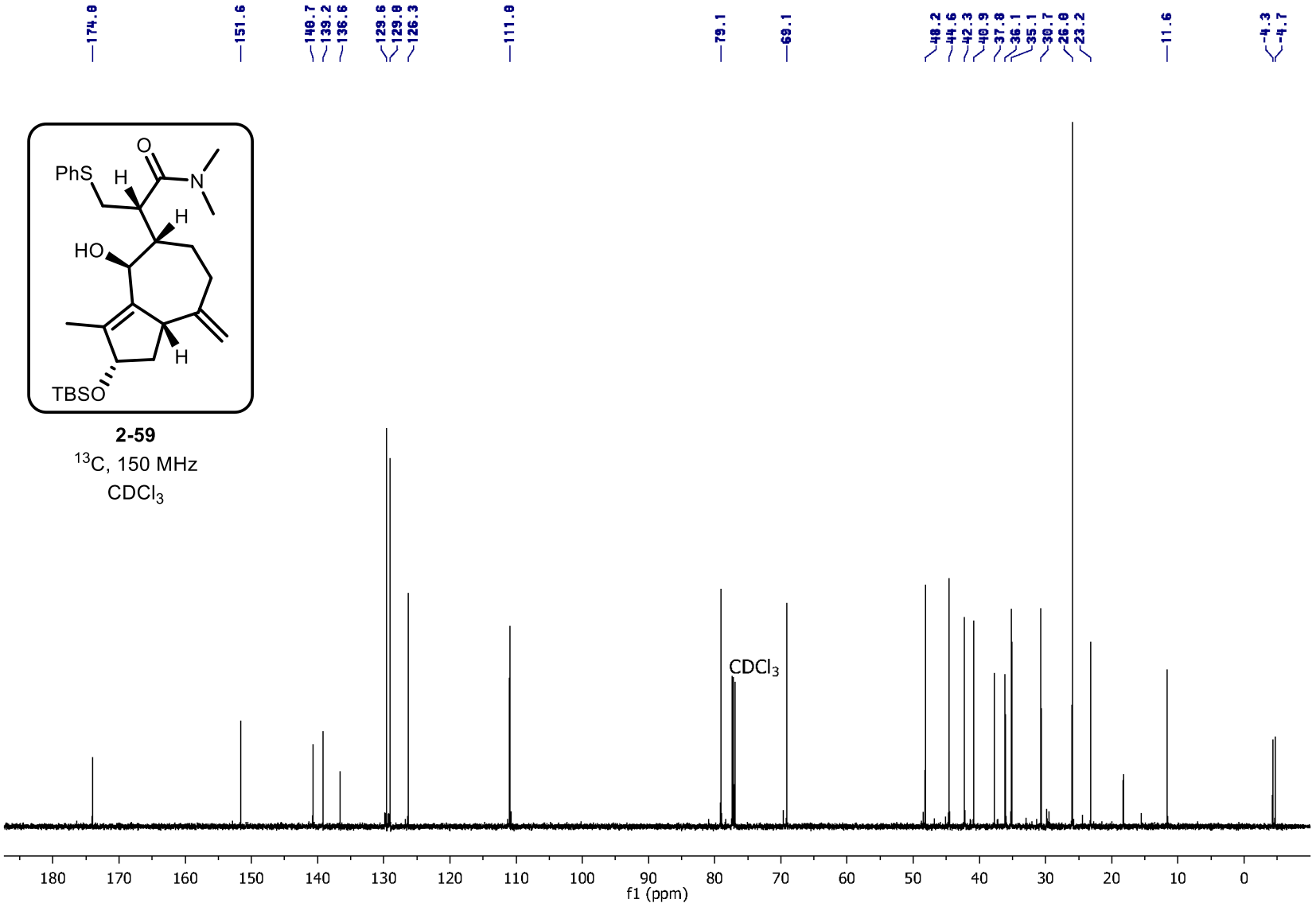

176.5
150.1
143.6
135.9
132.9
129.9
129.3
126.8
111.3
80.9
78.4
77.2
48.7
46.8
45.1
41.4
35.2
33.0
31.4
26.0
18.4
12.2
-4.3
-4.7
O
H
SPh
H
O
H
TBSO
2-58
13C, 150 MHz
CDCl3
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
SPh
O
H
O
H
TBSO
2-58
^{1}H COSY, 600 MHz
$CDCl_3$
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


O
H
SPh
H
O
H
TBSO
2-58
HSQC, 600 MHz
CDCl3
ppm
20
30
40
50
60
70
80
90
100
110
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


F1 [ppm]
2
3
4
5
F2 [ppm]
2
3
4
5
SPh
H
H
H
O
O
TBSO
2-58
^{1}H NOESY, 600 MHz
$CDCl_3$

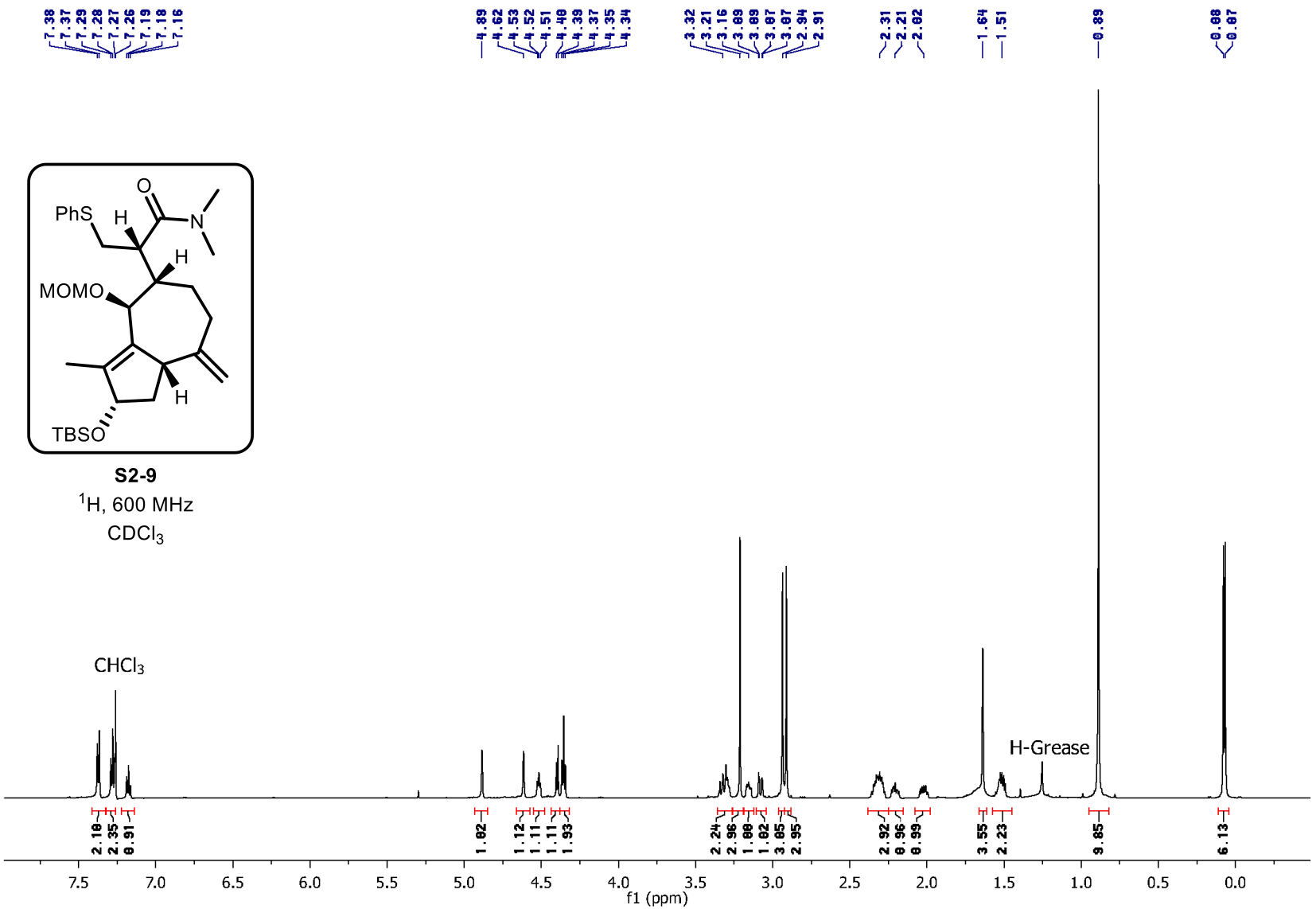

7.36
7.35
7.29
7.28
7.26
7.18
7.17
7.16
4.89
4.63
4.48
4.47
4.46
4.42
4.41
3.45
3.44
3.42
3.17
2.92
2.90
2.24
2.19
1.63
1.63
1.55
1.50
1.49
1.48
1.47
1.46
0.88
0.07
0.06
O
PhS
H
N
H
HO
H
TBSO
2-59
1H, 600 MHz
CDCl3
CHCl3
2.06
2.04
1.00
1.04
0.98
1.09
1.00
1.05
1.01
2.04
2.98
3.01
1.41
2.40
1.31
1.13
3.11
1.23
1.11
9.94
3.09
3.34
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



2-59

^{13}C, 150 MHz

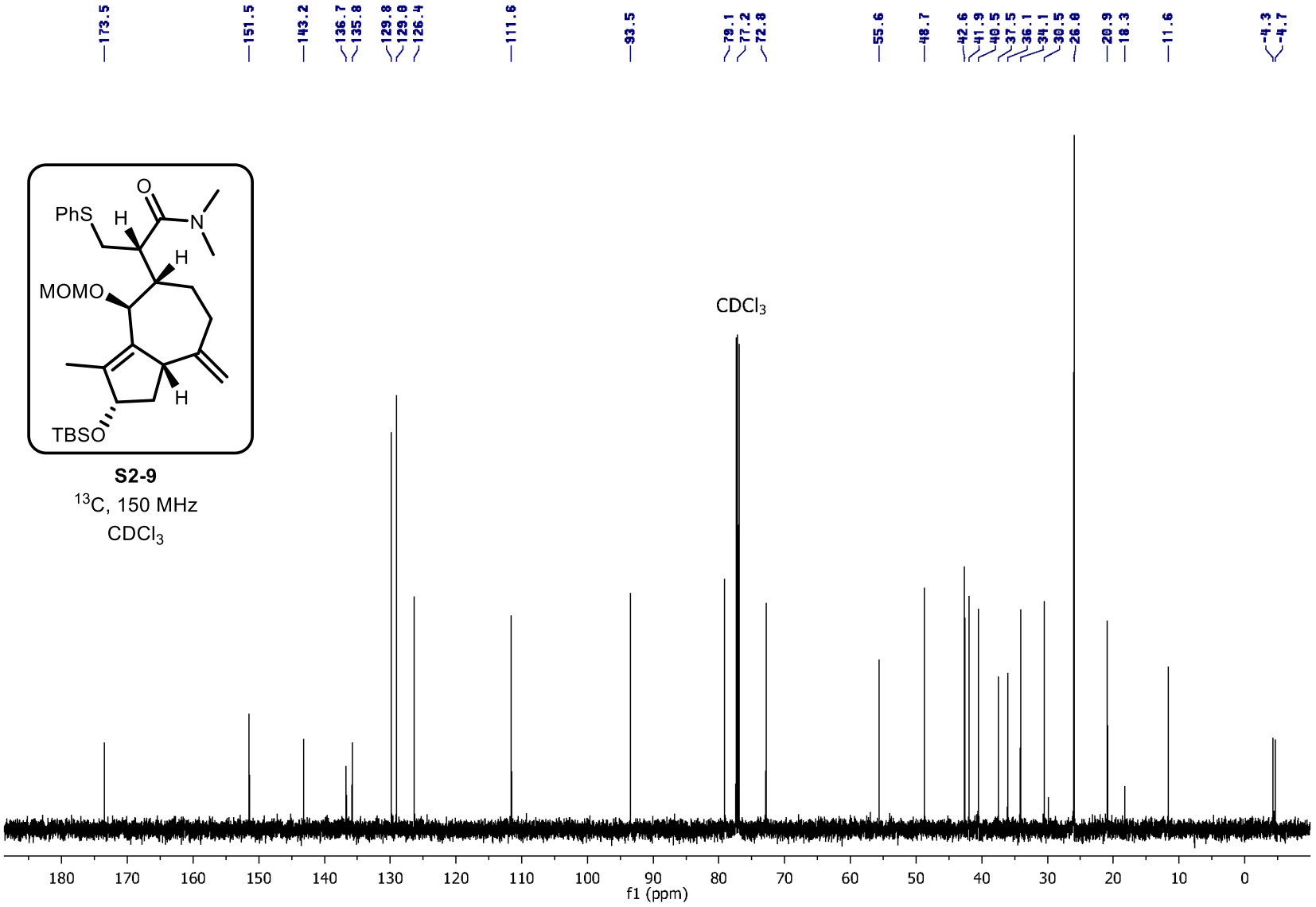
$CDCl_3$



S2-9

^{1}H, 600 MHz

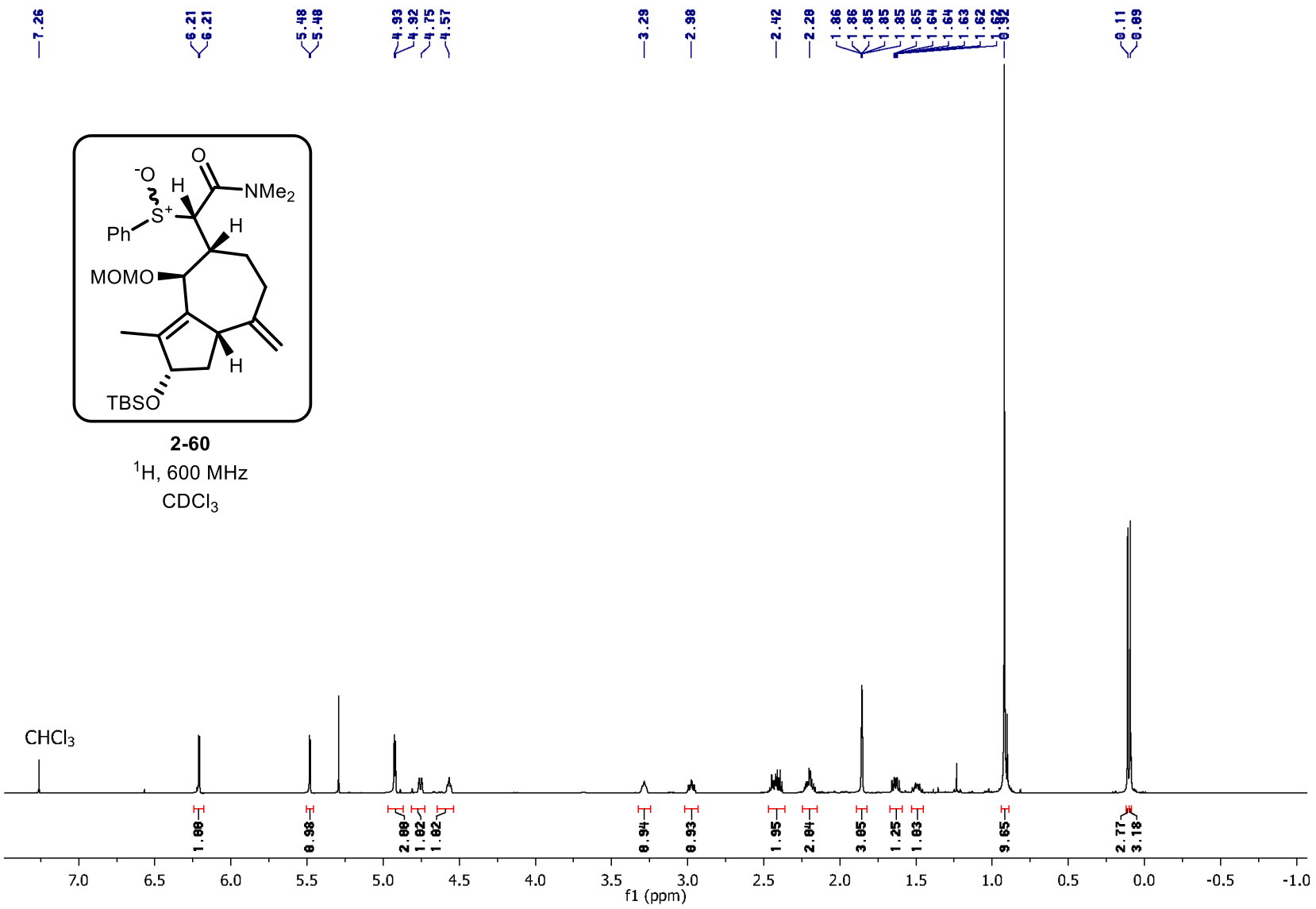
$CDCl_3$



S2-9

^{13}C, 150 MHz

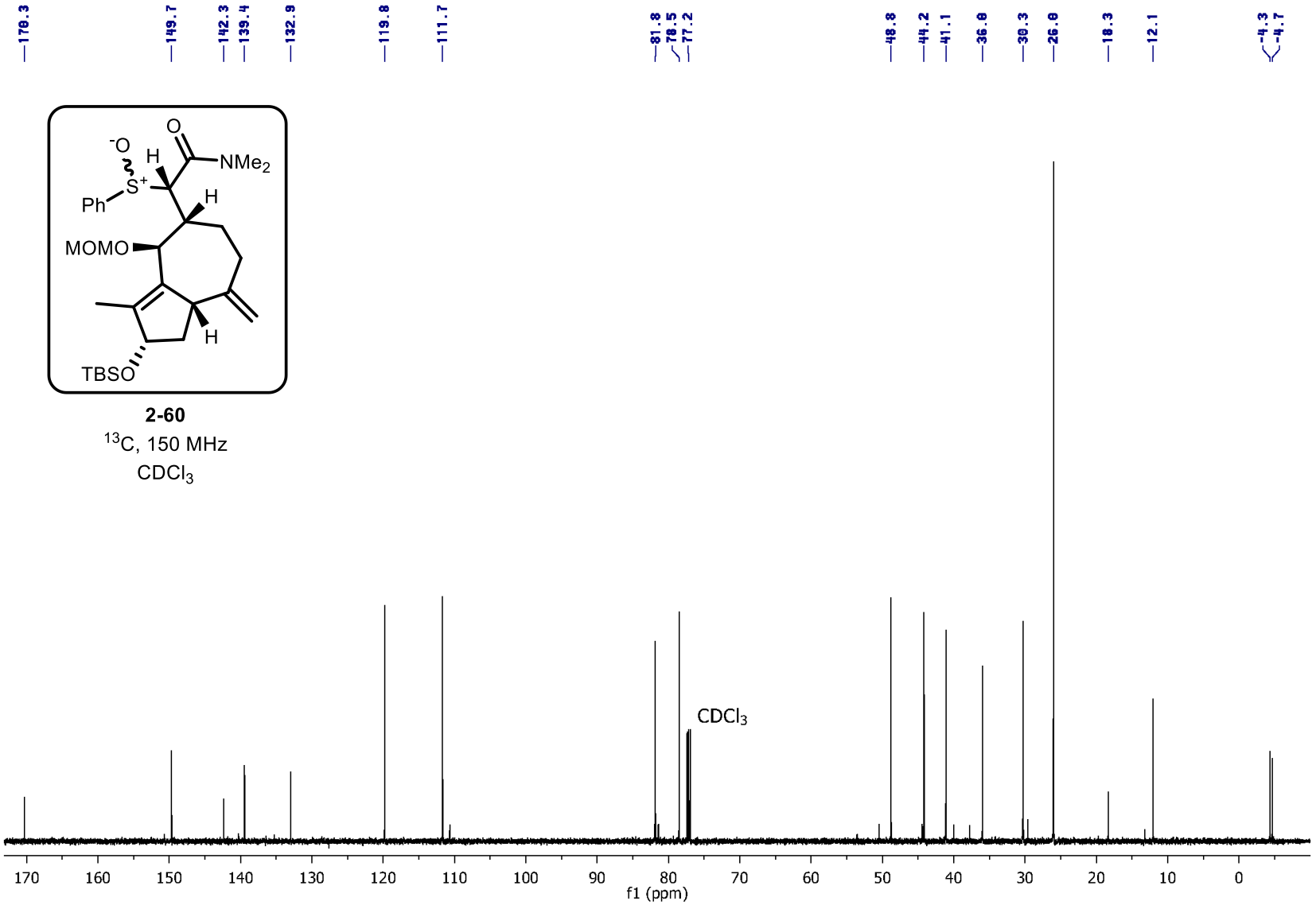
$CDCl_3$



2-60

^{1}H, 600 MHz

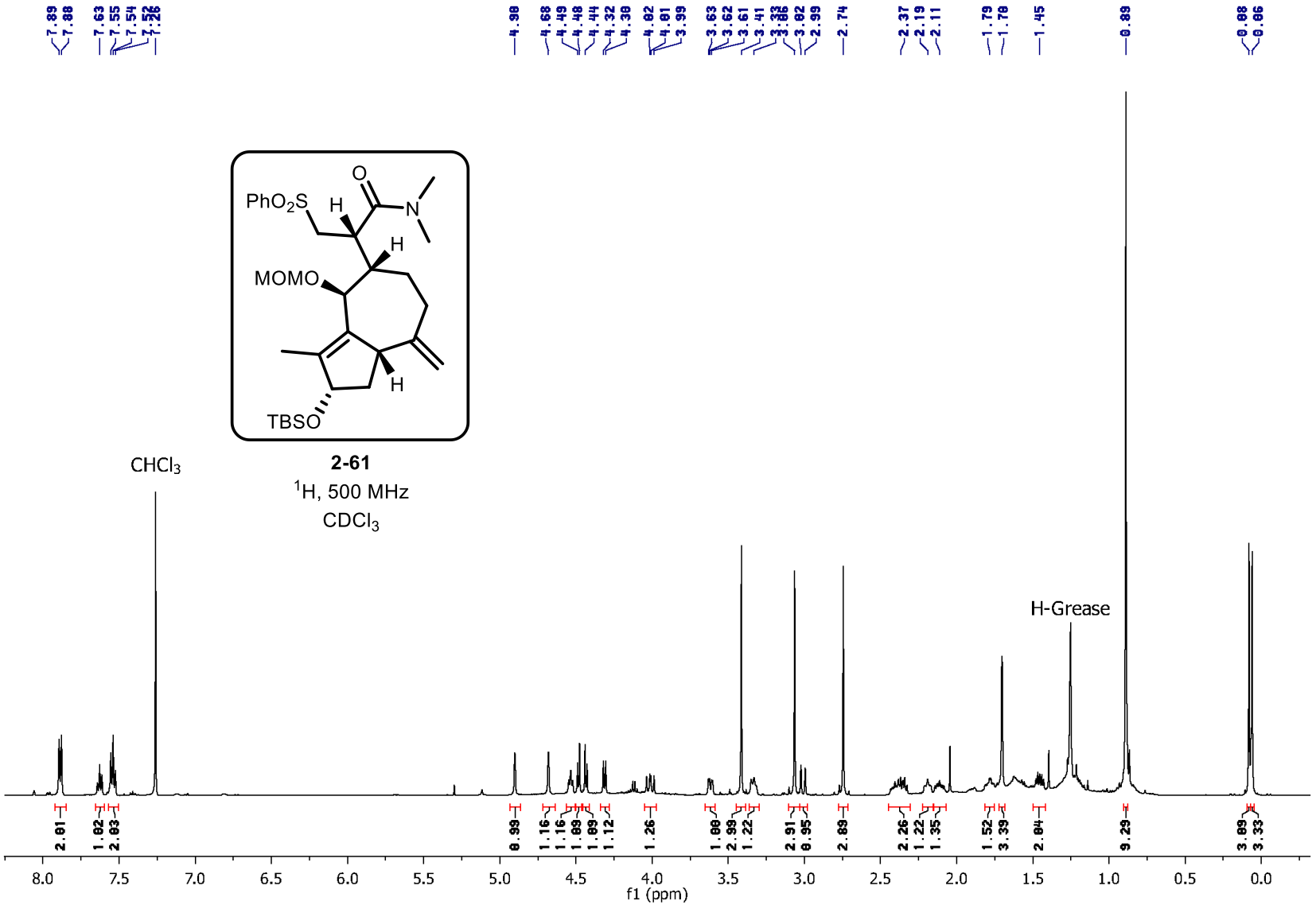
$CDCl_3$

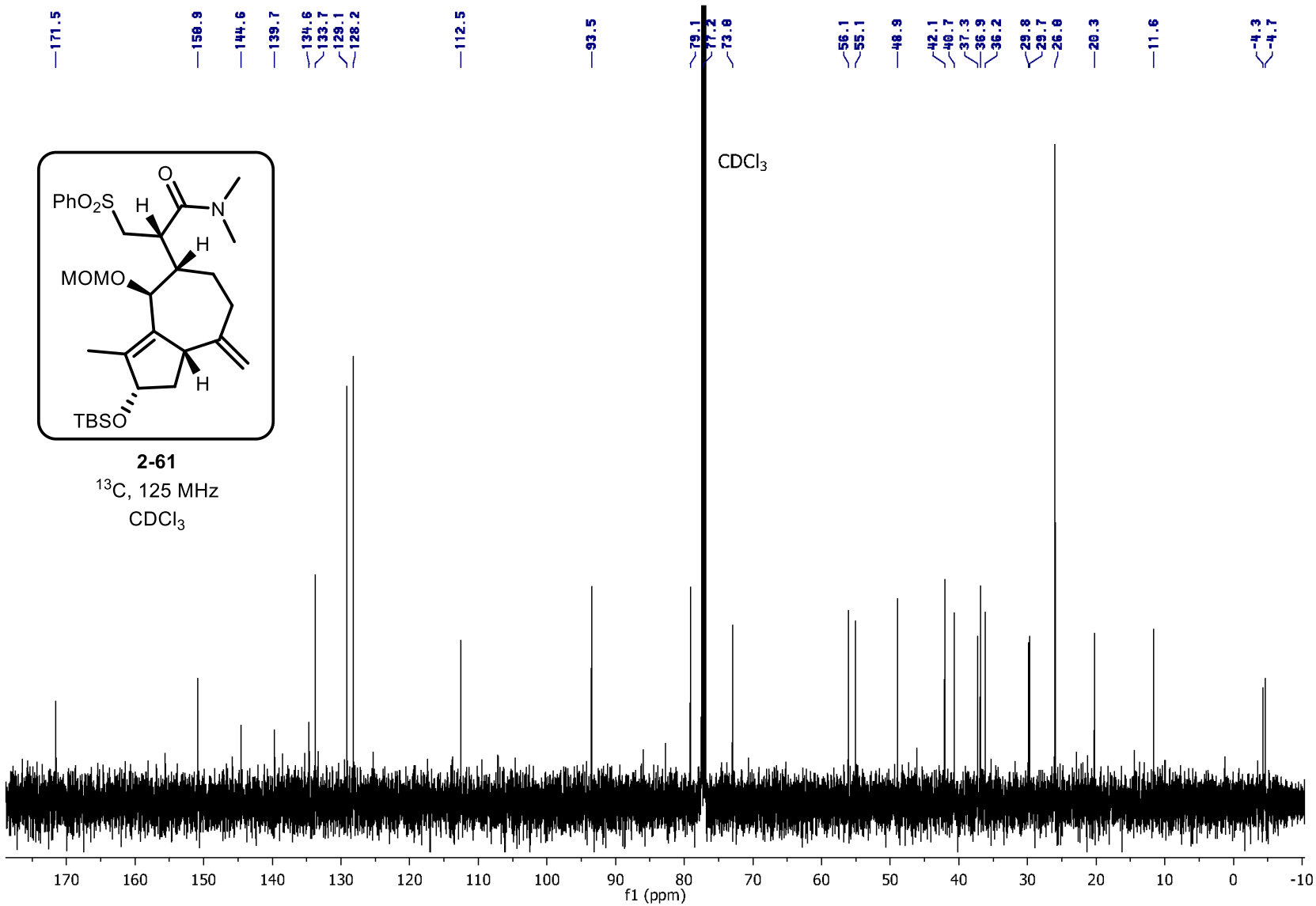


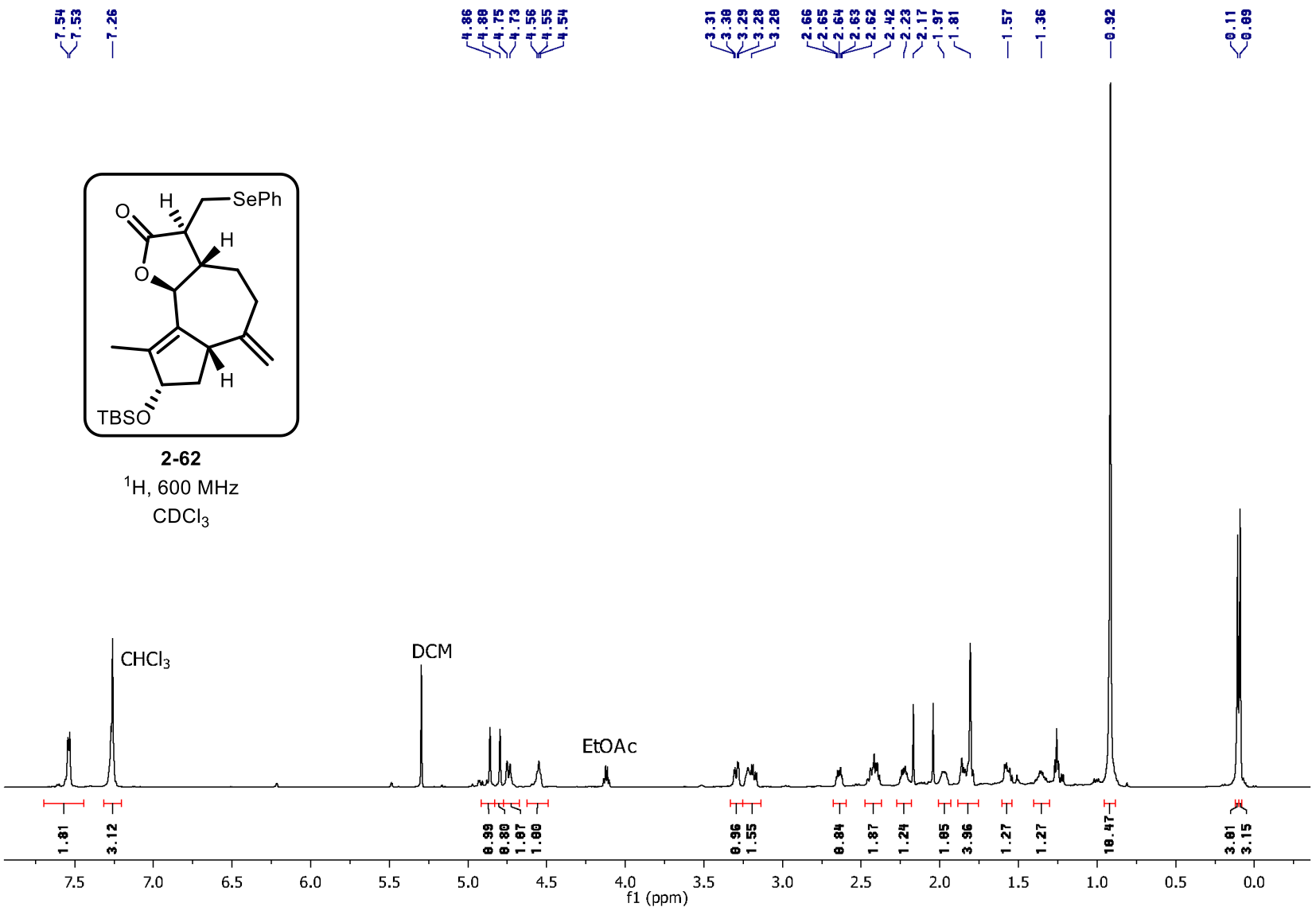
2-60

^{13}C, 150 MHz

$CDCl_3$


7.89
7.88
7.63
7.55
7.54
7.52
7.26
4.90
4.68
4.49
4.48
4.44
4.32
4.30
4.02
4.01
3.99
3.63
3.62
3.61
3.41
3.33
3.06
3.02
2.99
2.74
2.37
2.19
2.11
1.79
1.78
1.45
0.89
0.08
0.06
PhO2S
H
O
N
H
MOMO
H
TBSO
CHCl3
2-61
1H, 500 MHz
CDCl3
H-Grease
2.01
1.02
2.03
0.99
1.16
1.16
1.09
1.09
1.12
1.26
1.00
2.99
1.22
2.91
0.95
2.89
2.26
1.22
1.35
1.52
3.39
2.04
9.29
3.09
3.33
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

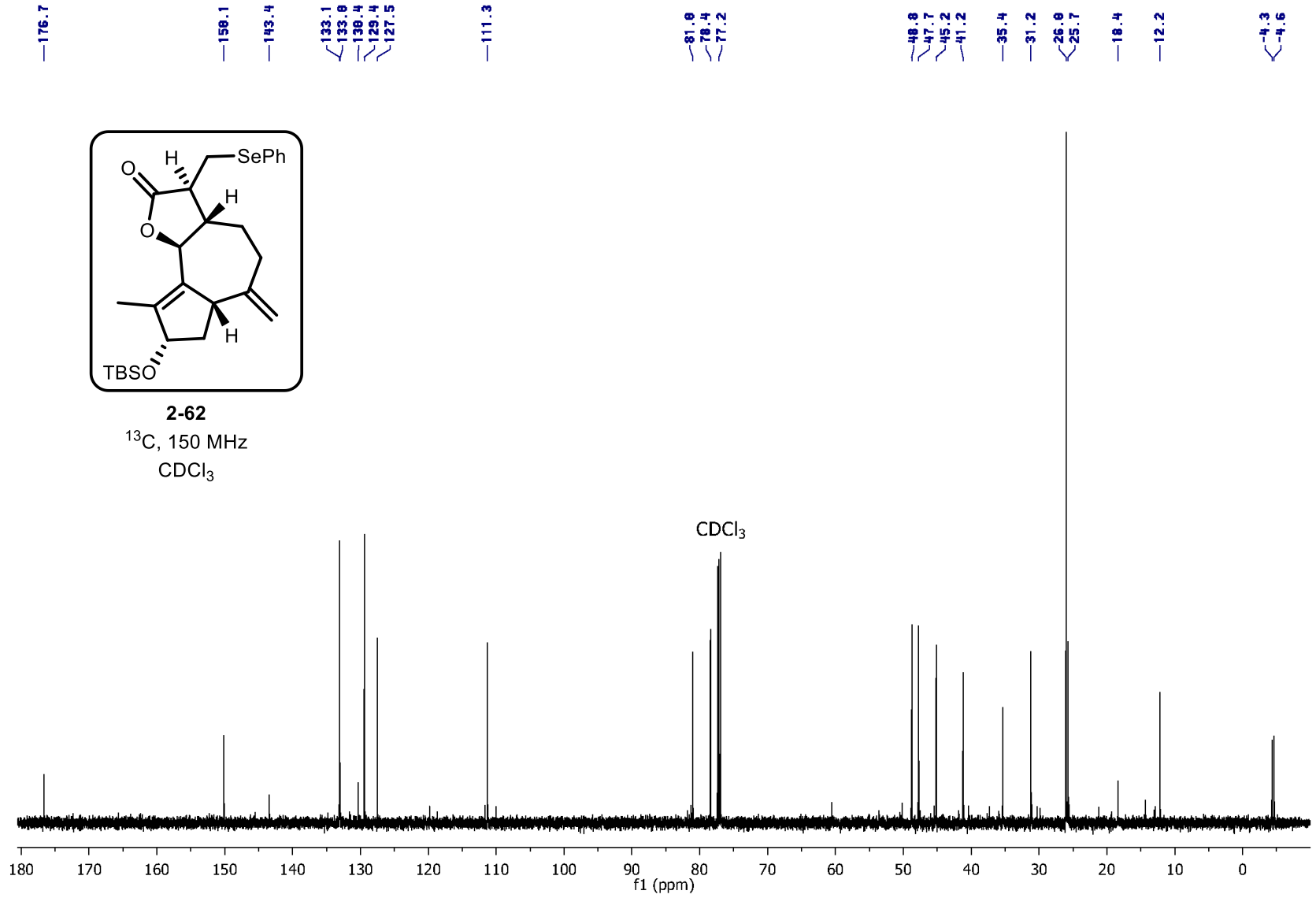

171.5
150.9
144.6
139.7
134.6
133.7
129.1
128.2
112.5
93.5
79.1
77.2
73.0
56.1
55.1
48.9
42.1
40.7
37.3
36.9
36.2
29.8
29.7
26.0
20.3
11.6
-4.3
-4.7
CDCl3
PhO2S
H
O
N
H
MOMO
H
TBSO
2-61
13C, 125 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



2-62

^{1}H, 600 MHz

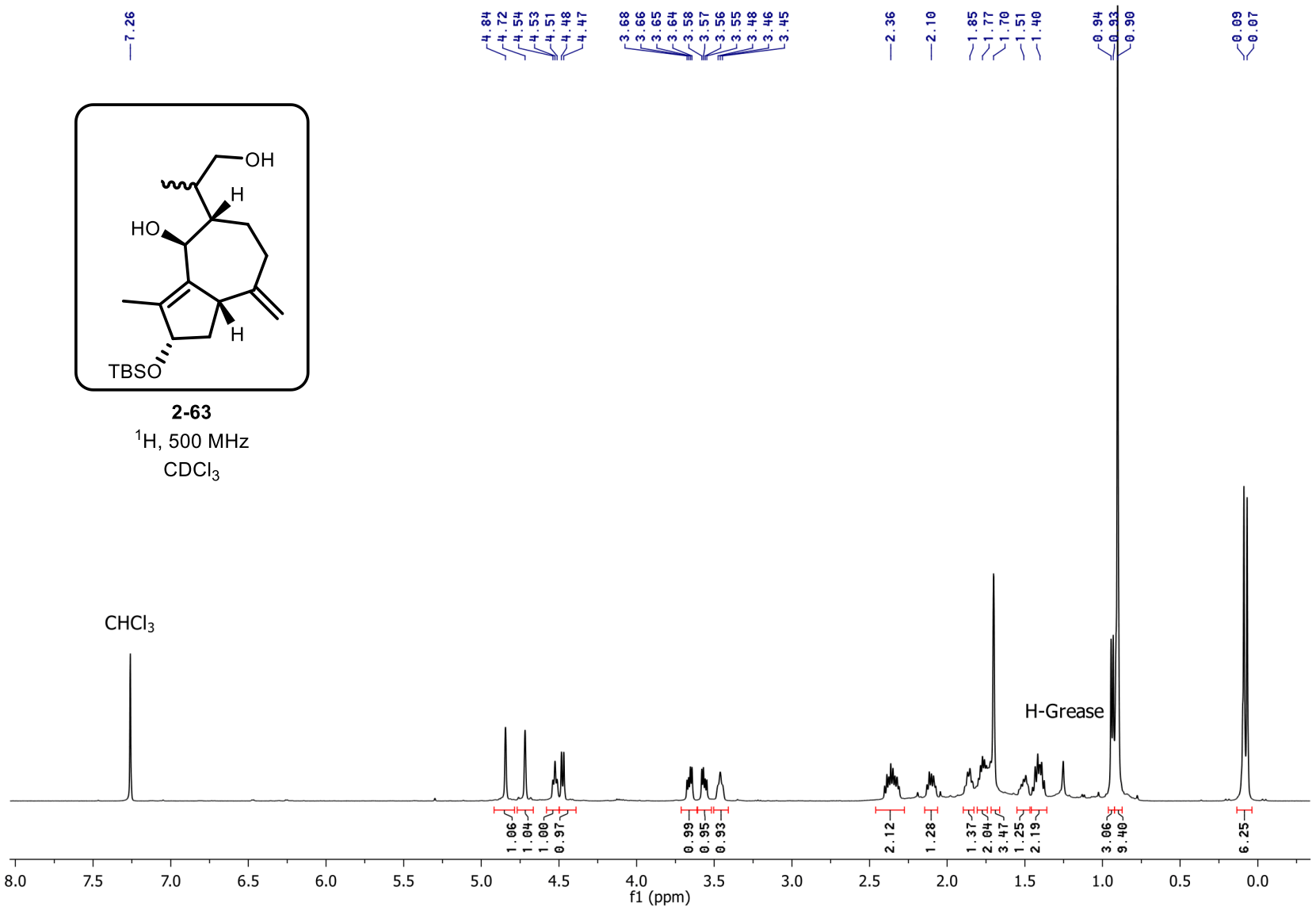
$CDCl_3$



2-62

^{13}C, 150 MHz

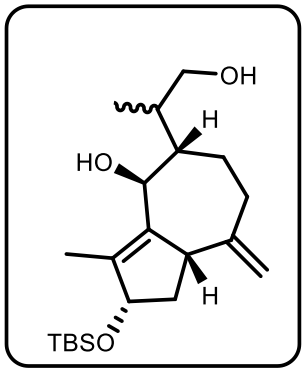
$CDCl_3$



2-63

^{1}H, 500 MHz

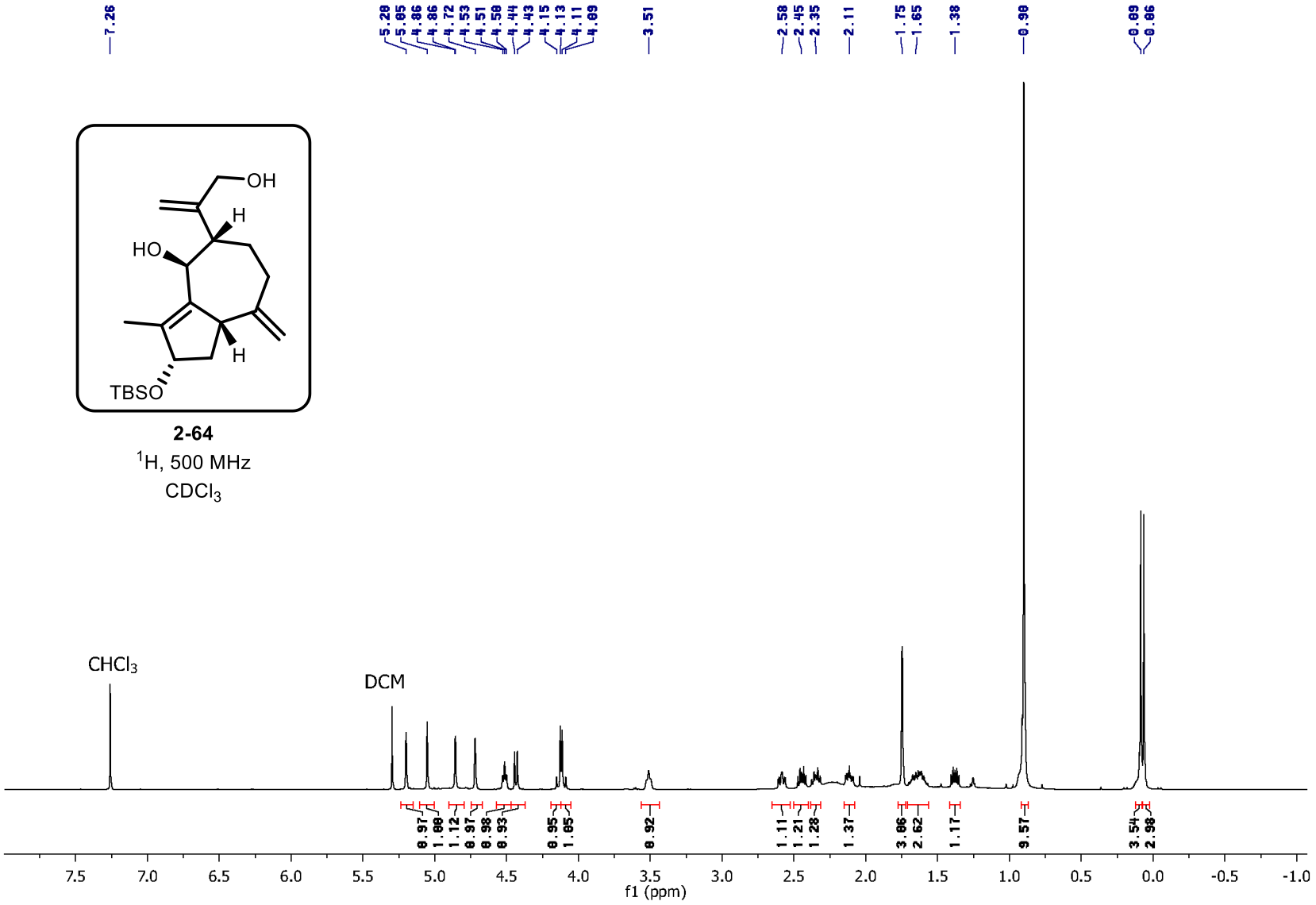
$CDCl_3$



2-63

^{13}C, 125 MHz

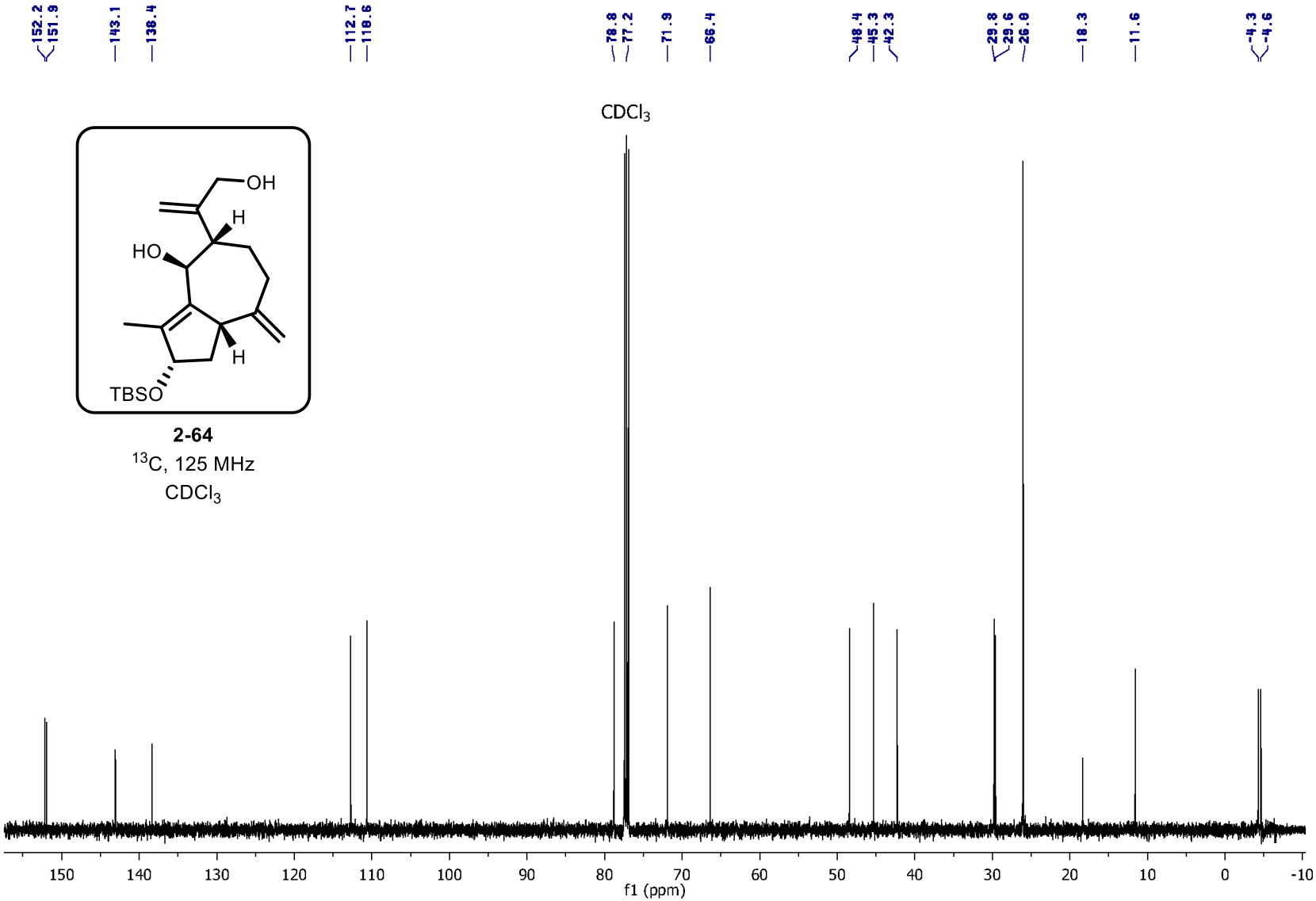
$CDCl_3$



2-64

^{1}H, 500 MHz

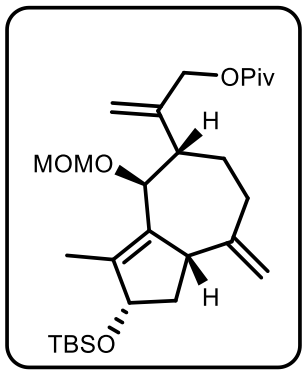
$CDCl_3$



2-64

^{13}C, 125 MHz

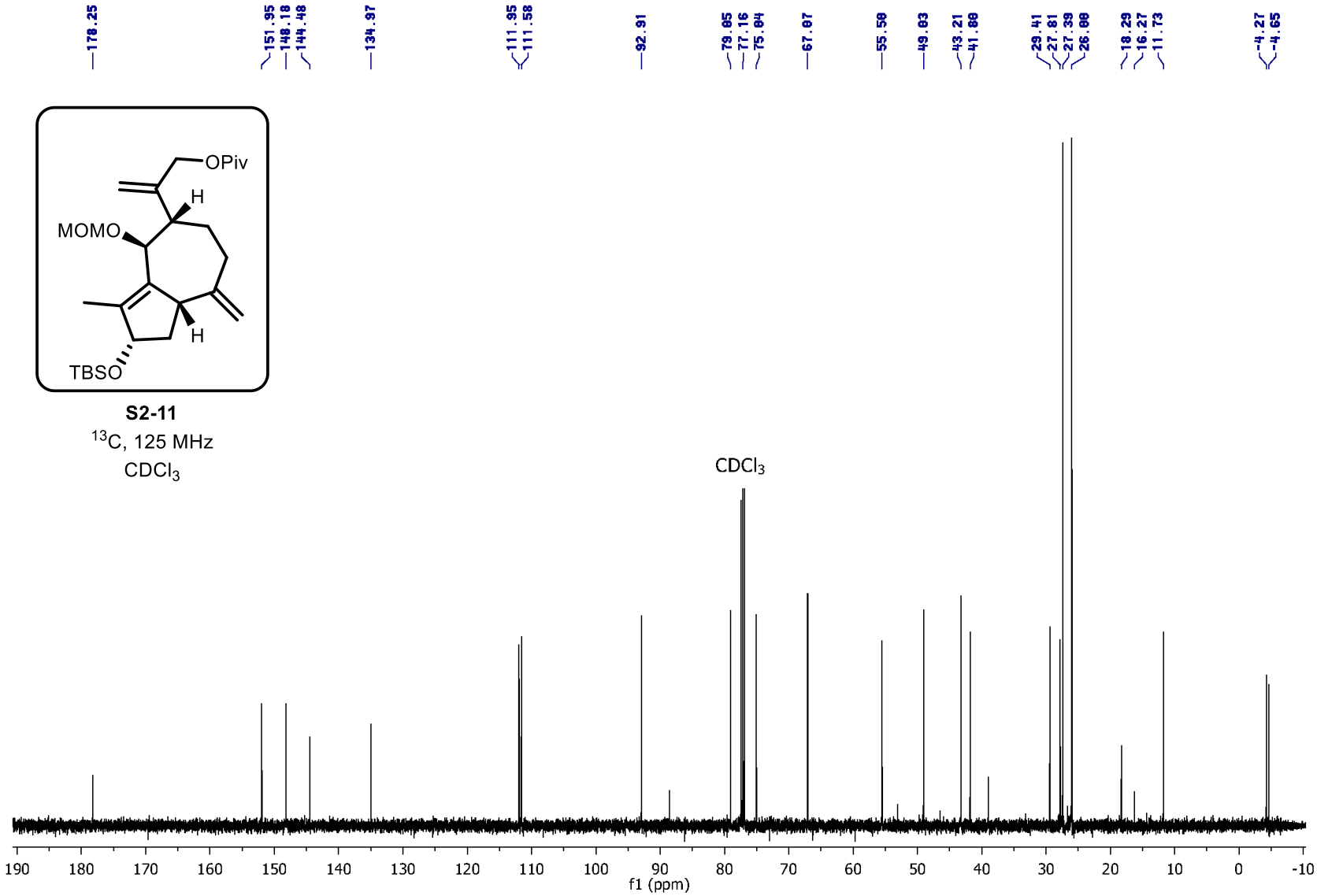
$CDCl_3$



S2-11

^{1}H, 500 MHz

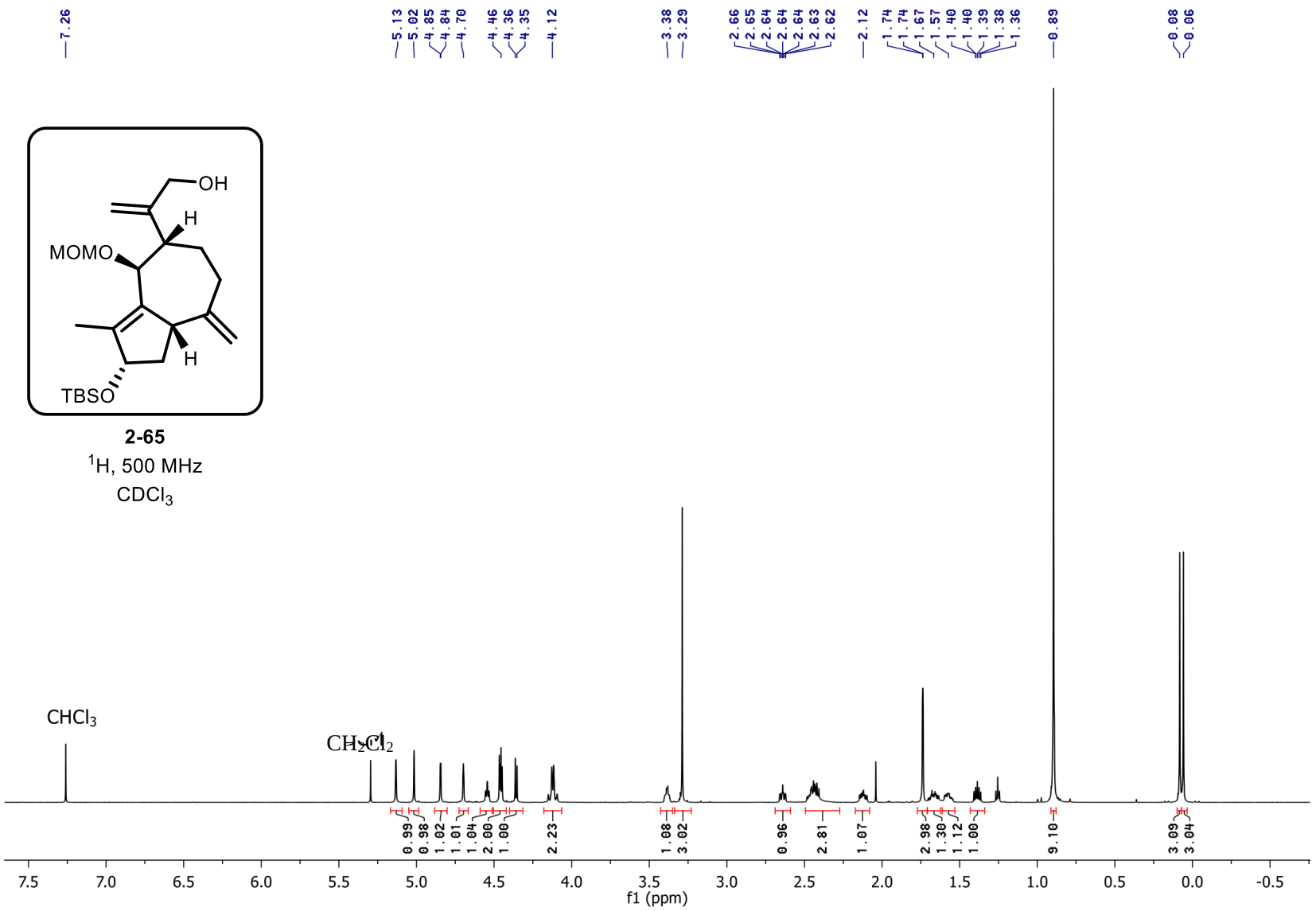
$CDCl_3$



S2-11

^{13}C, 125 MHz

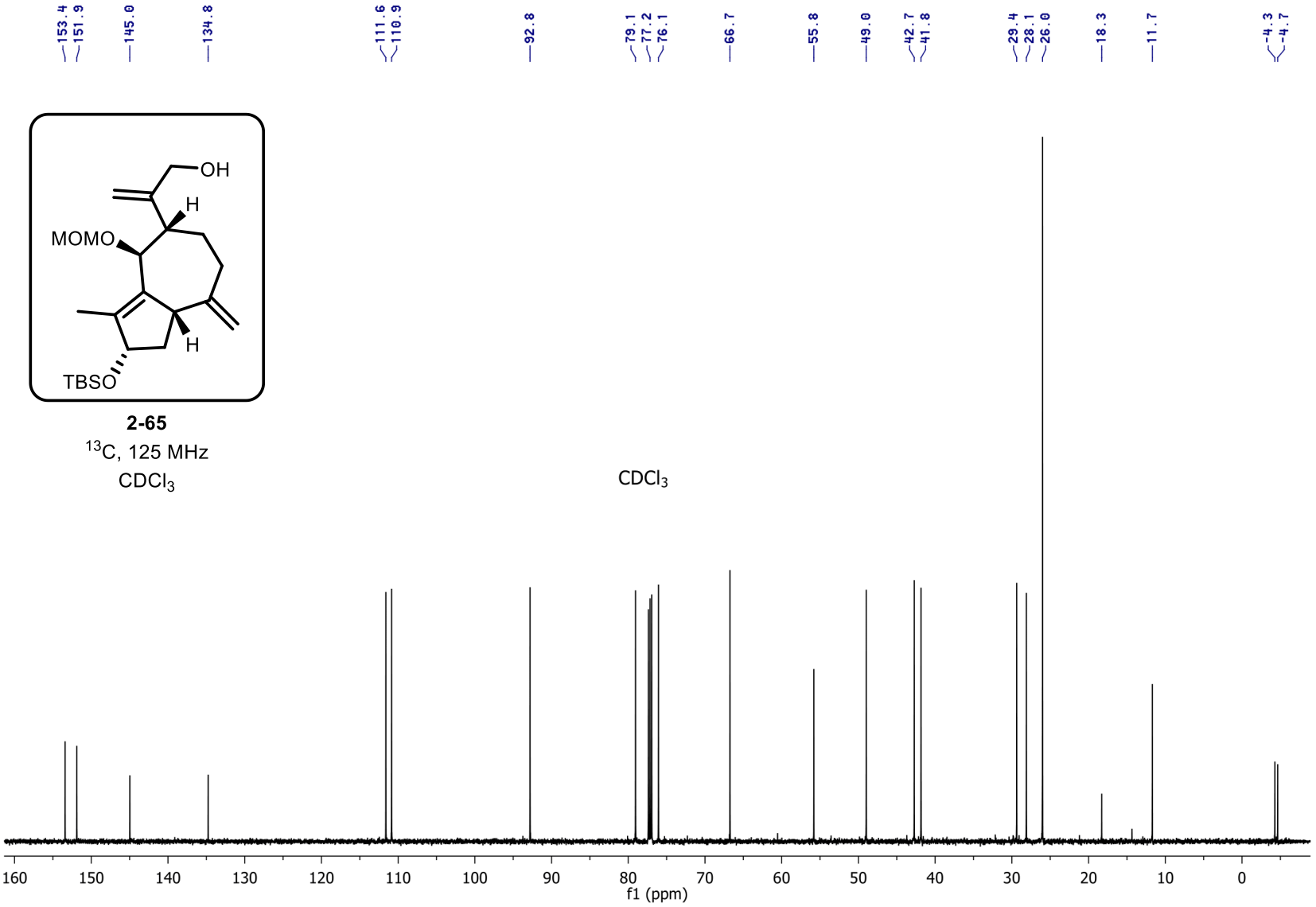
$CDCl_3$

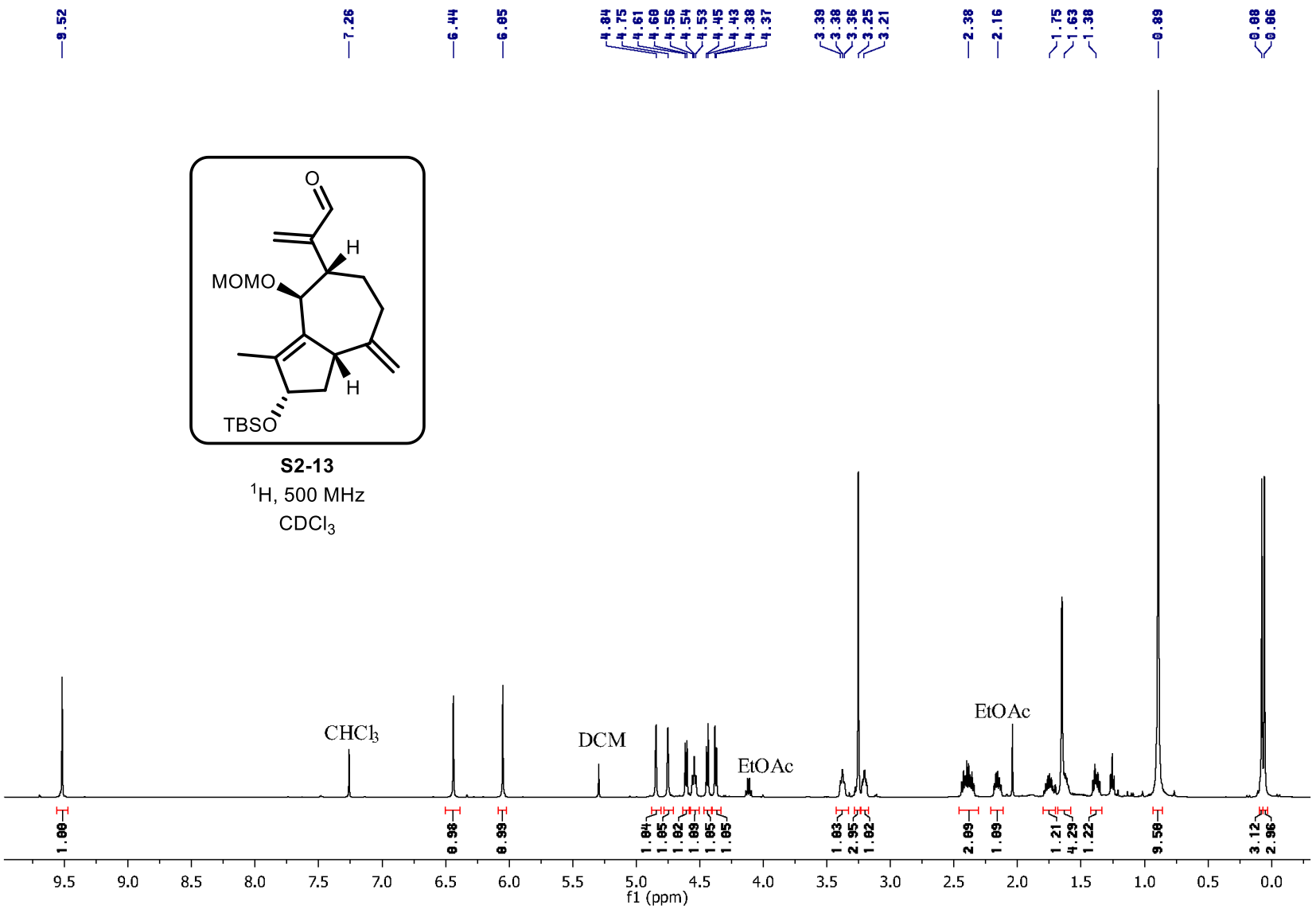


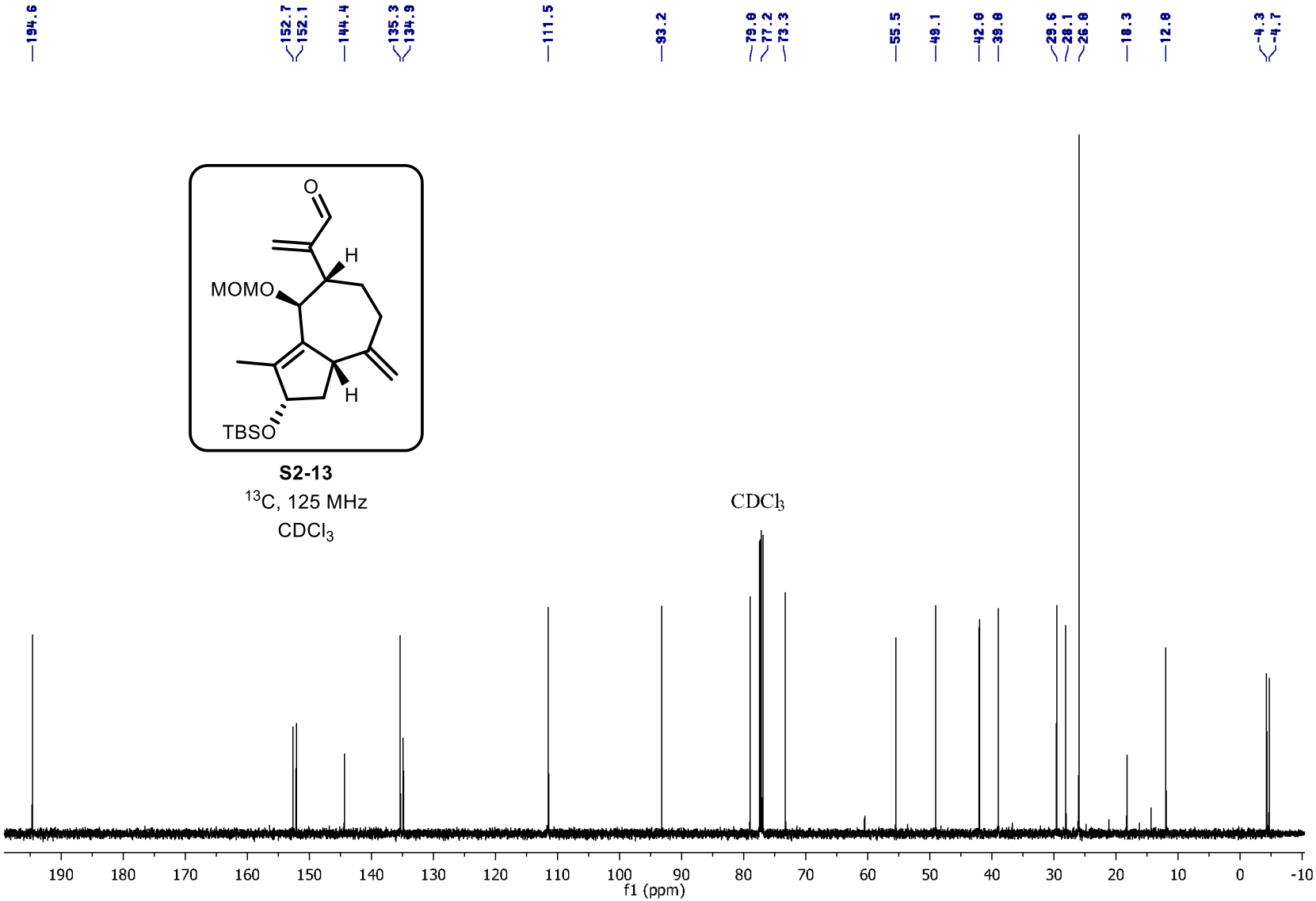
2-65

^{1}H, 500 MHz

$CDCl_3$


153.4
151.9
145.0
134.8
111.6
110.9
92.8
79.1
77.2
76.1
66.7
55.8
49.0
42.7
41.8
29.4
28.1
26.0
18.3
11.7
-4.3
-4.7
OH
H
MOMO
H
TBSO
2-65
13C, 125 MHz
CDCl3
CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

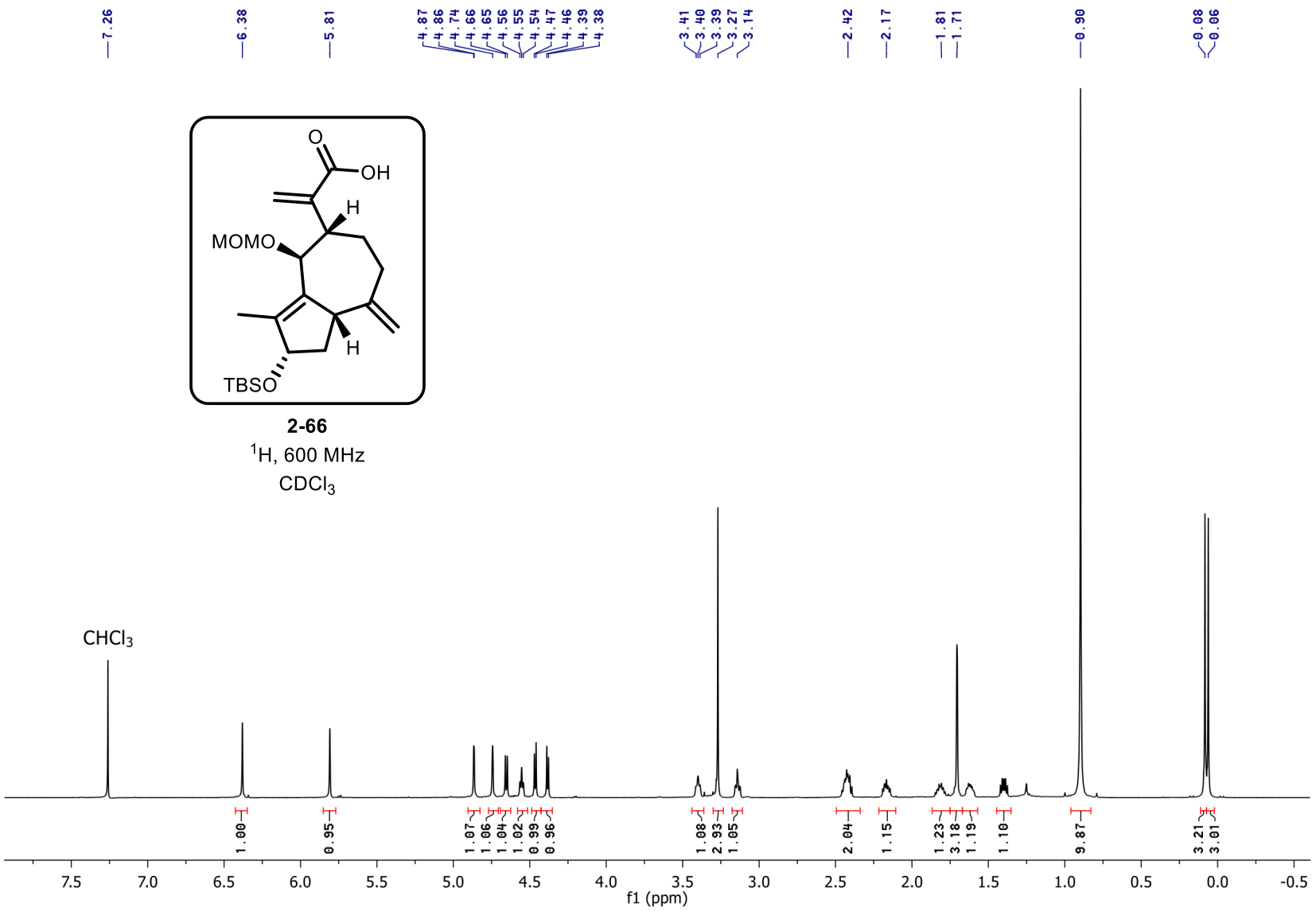

9.52
7.26
6.44
6.05
4.84
4.75
4.61
4.60
4.56
4.54
4.53
4.45
4.43
4.38
4.37
3.39
3.38
3.36
3.25
3.21
2.38
2.16
1.75
1.63
1.38
0.89
0.08
0.06
O
H
MOMO
H
TBSO
S2-13
1H, 500 MHz
CDCl3
CHCl3
DCM
EtOAc
EtOAc
1.00
0.98
0.99
1.04
1.05
1.02
1.09
1.05
1.05
1.03
2.95
1.02
2.09
1.09
1.21
4.29
1.22
9.50
3.12
2.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

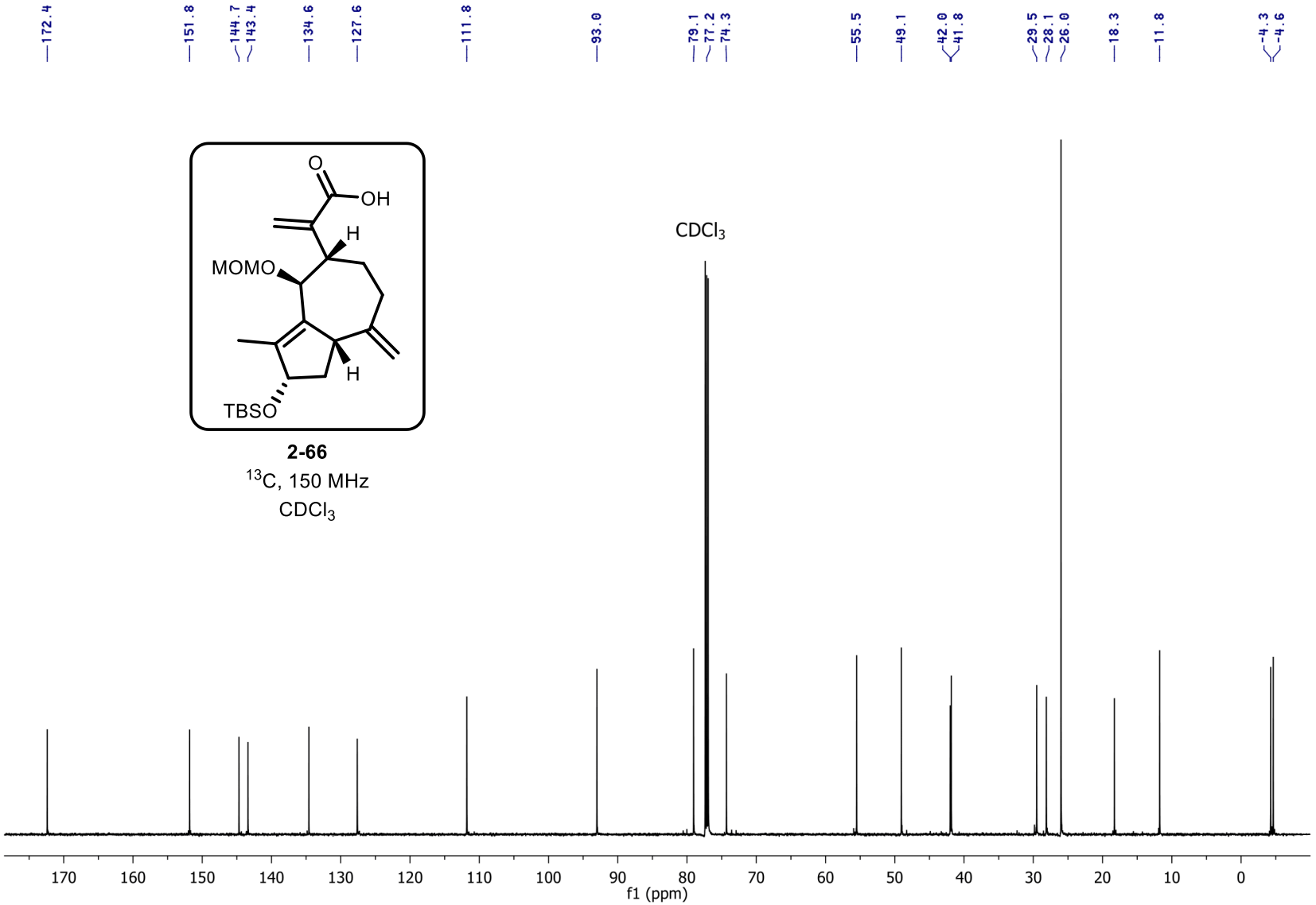


S2-13

^{13}C, 125 MHz

$CDCl_3$

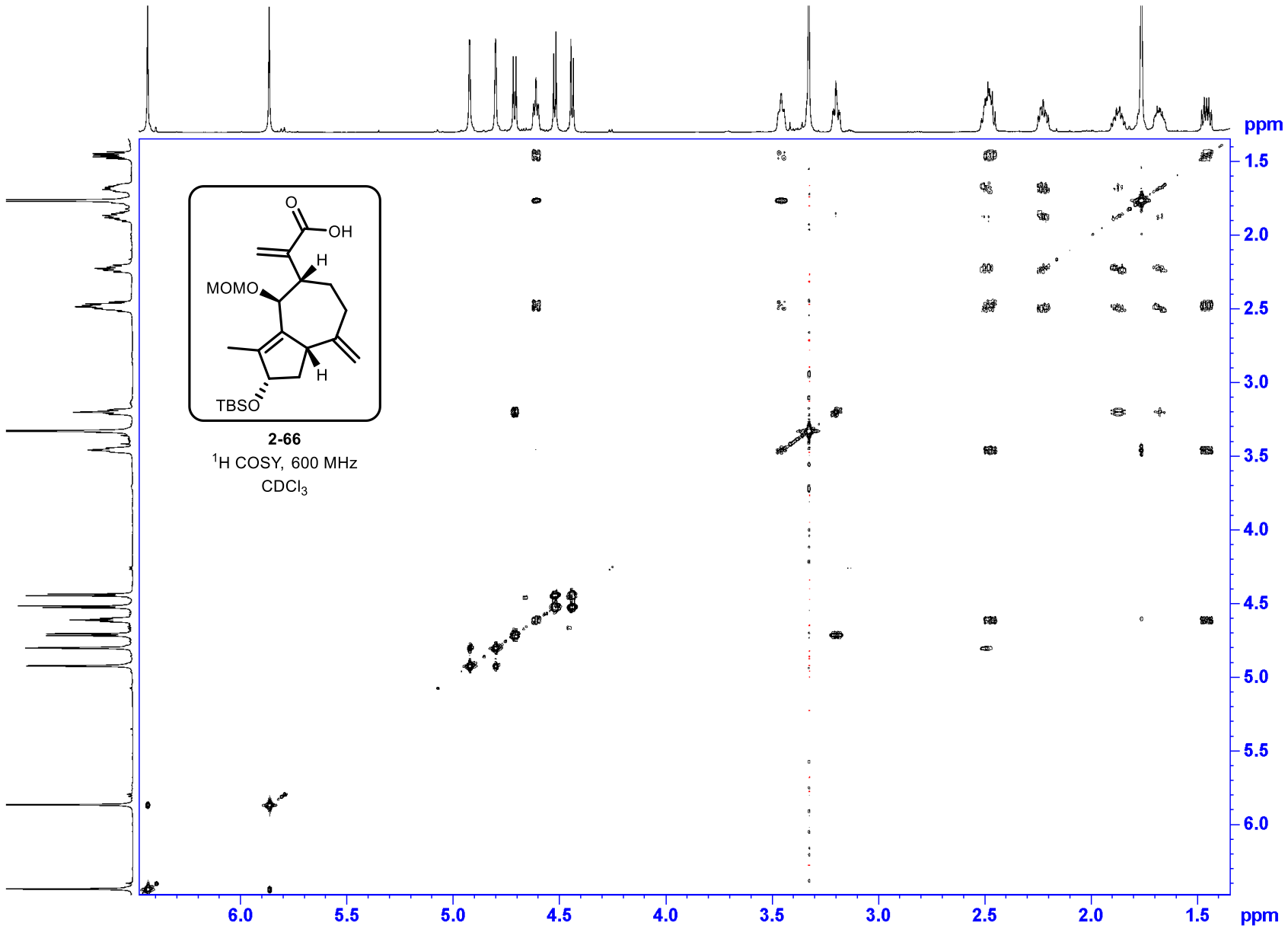

7.26
6.38
5.81
4.87
4.86
4.74
4.66
4.65
4.56
4.55
4.54
4.47
4.46
4.39
4.38
3.41
3.40
3.39
3.27
3.14
2.42
2.17
1.81
1.71
0.90
0.08
0.06
O
OH
H
MOMO
H
TBSO
2-66
1H, 600 MHz
CDCl3
CHCl3
1.00
0.95
1.07
1.06
1.04
1.02
0.99
0.96
1.08
2.93
1.05
2.04
1.15
1.23
3.18
1.19
1.10
9.87
3.21
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

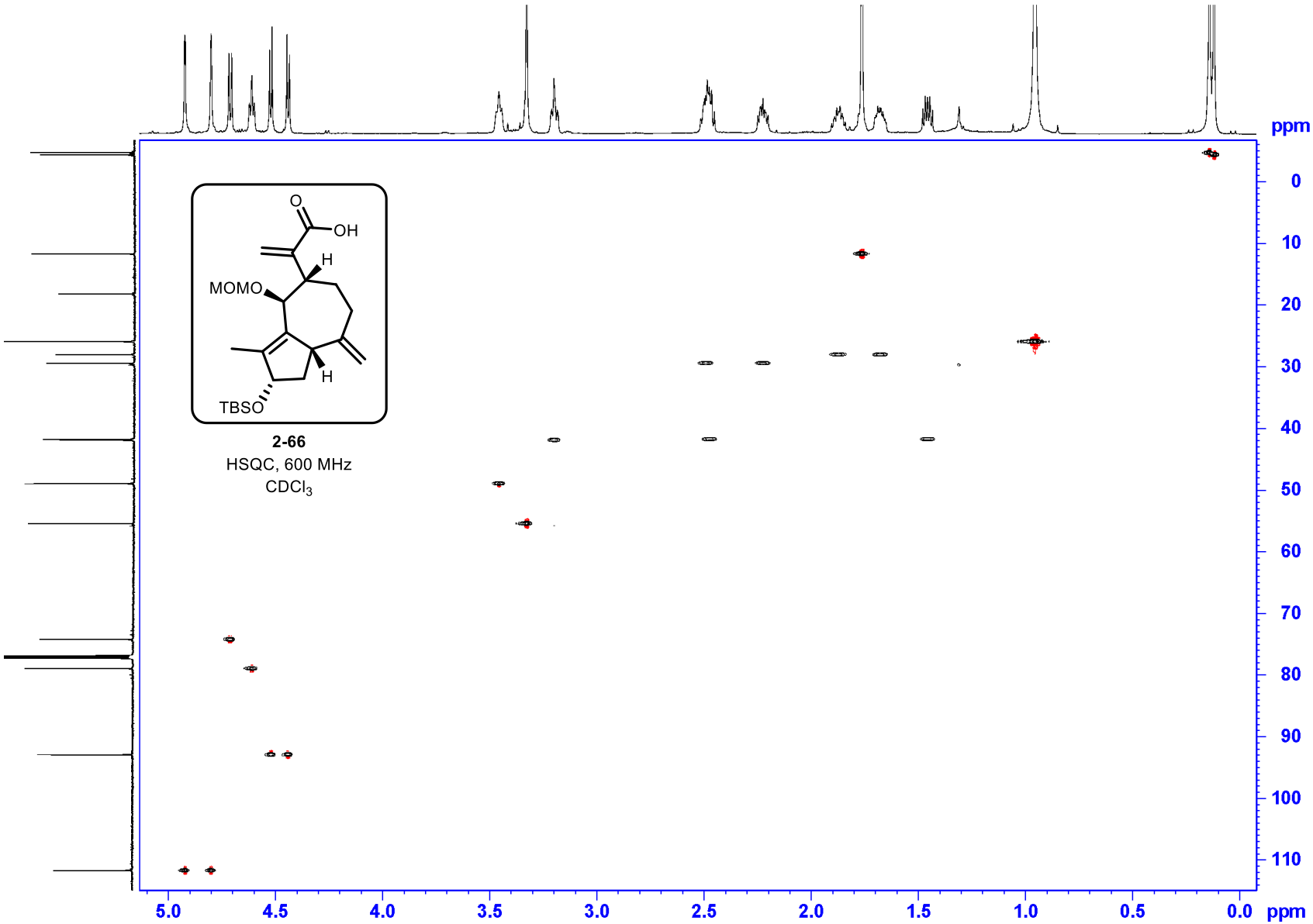


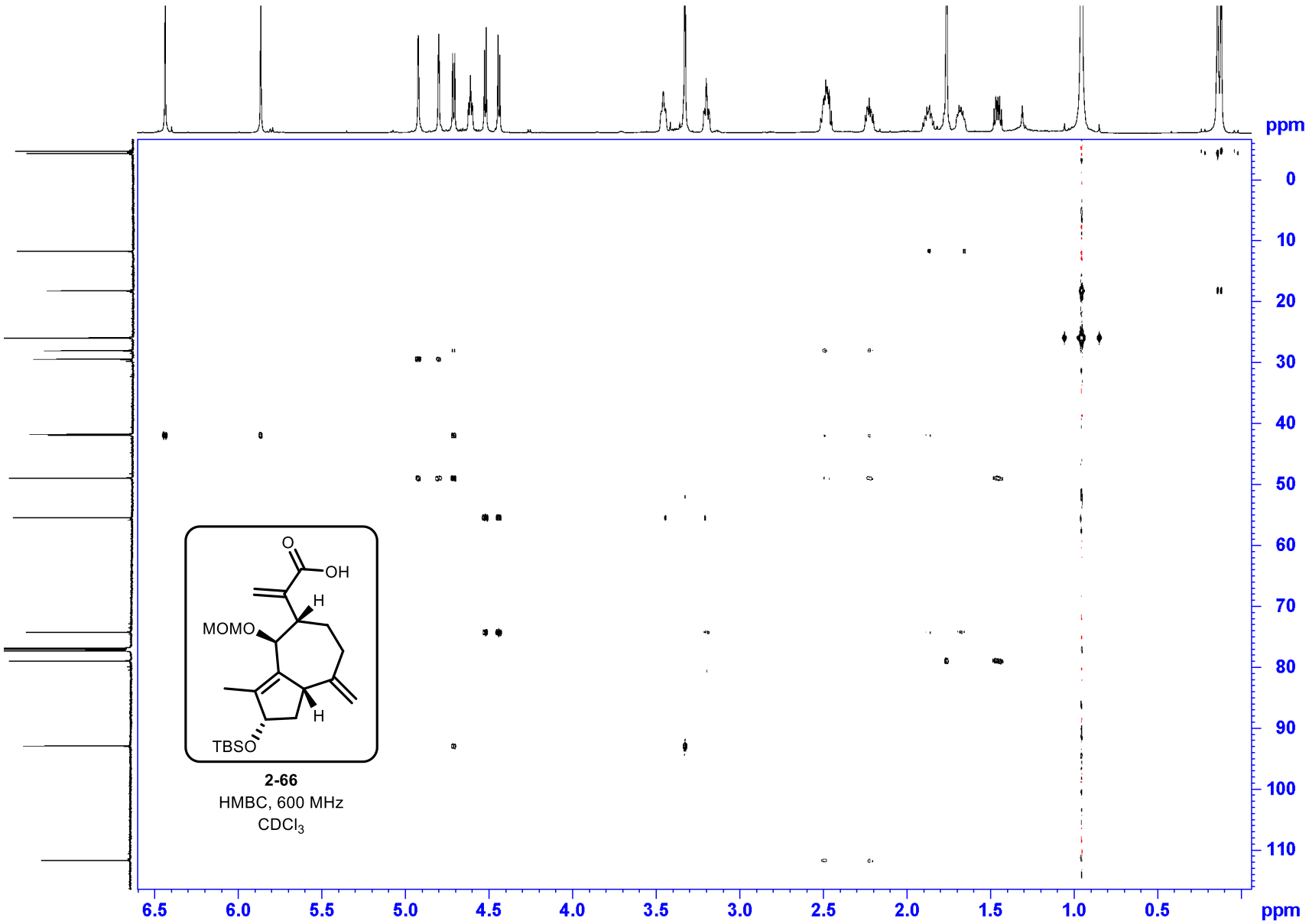
2-66

^{13}C, 150 MHz

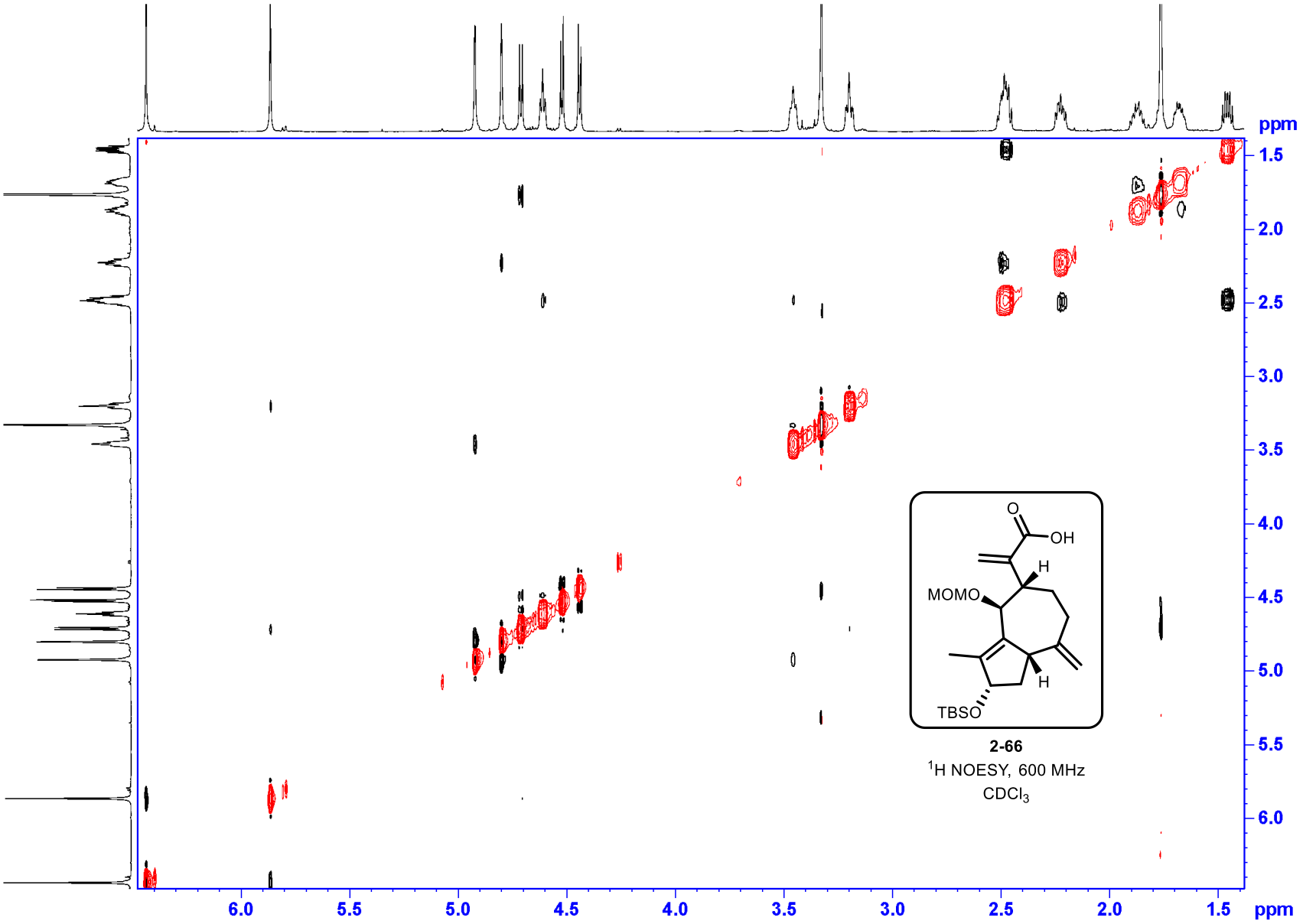
$CDCl_3$

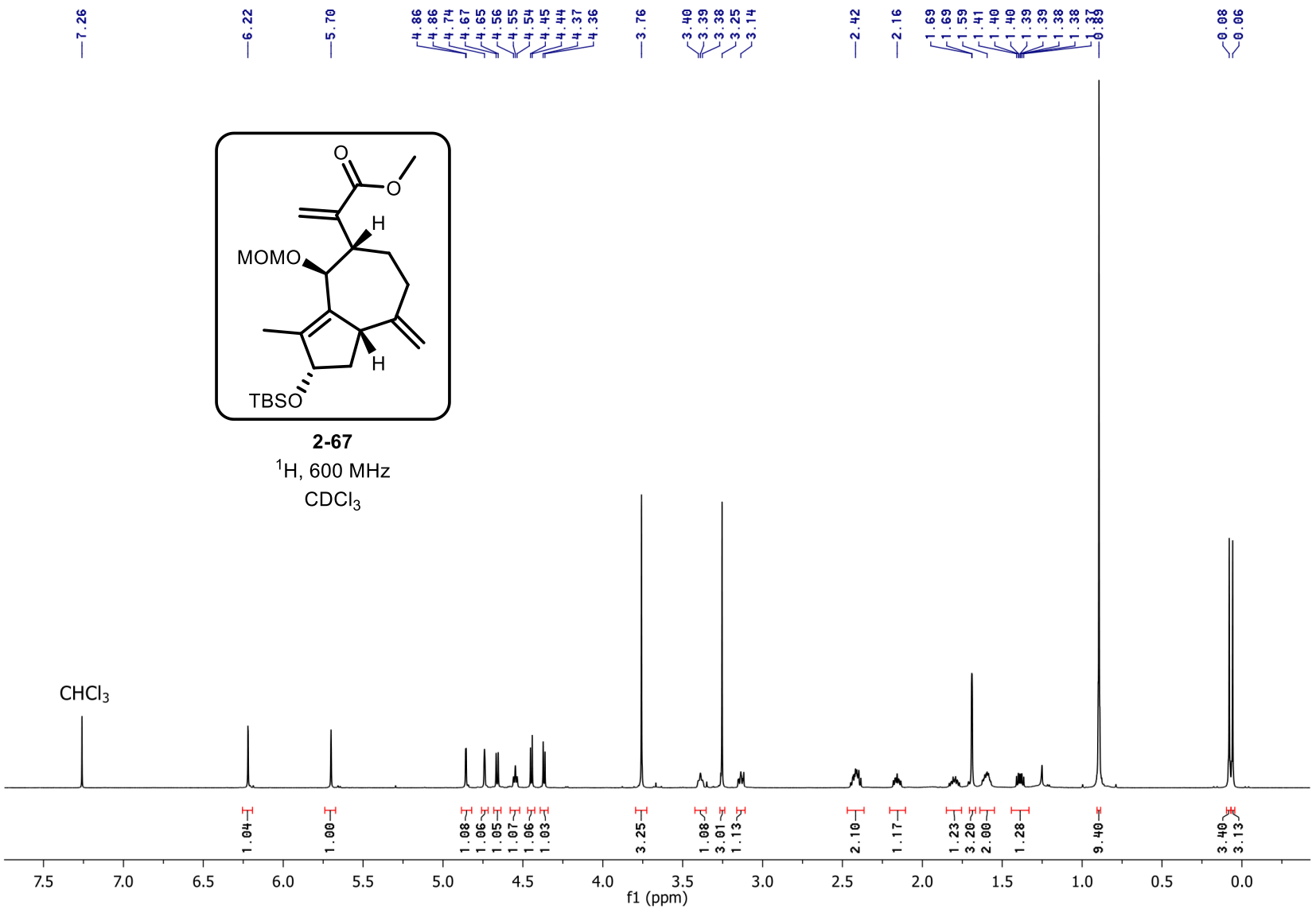

O
OH
H
MOMO
H
TBSO
2-66
1H COSY, 600 MHz
CDCl3
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

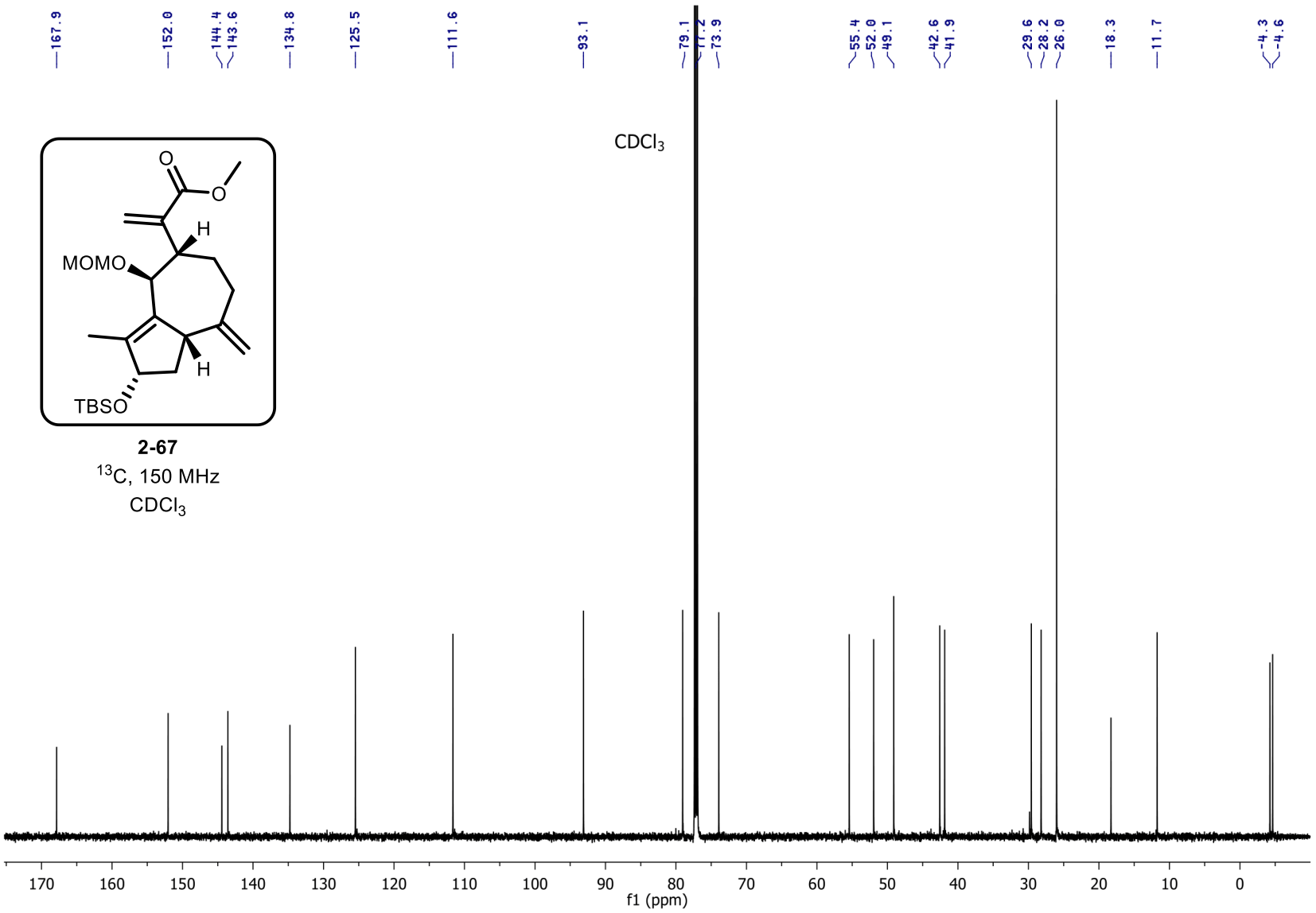

O
OH
H
MOMO
H
TBSO
2-66
HSQC, 600 MHz
CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm



2-66
HMBC, 600 MHz
$CDCl_3$


ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
O
OH
H
MOMO
H
TBSO
2-66
1H NOESY, 600 MHz
CDCl3

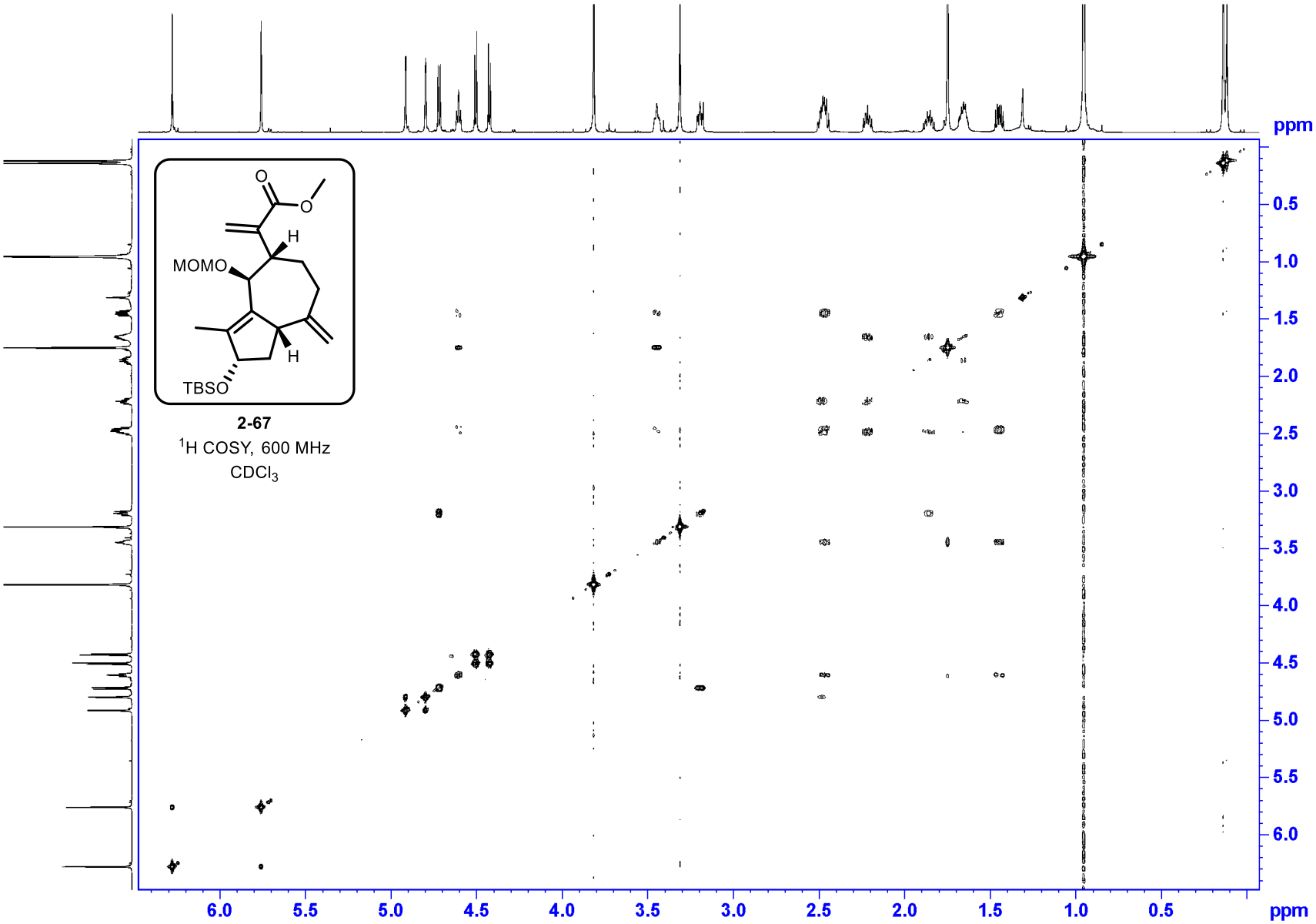

7.26
6.22
5.70
4.86
4.86
4.74
4.67
4.65
4.56
4.55
4.54
4.45
4.44
4.37
4.36
3.76
3.40
3.39
3.38
3.25
3.14
2.42
2.16
1.69
1.69
1.59
1.41
1.40
1.40
1.39
1.39
1.38
1.38
0.89
0.08
0.06
O
O
H
MOMO
H
TBSO
2-67
1H, 600 MHz
CDCl3
CHCl3
1.04
1.00
1.08
1.06
1.05
1.07
1.06
1.03
3.25
1.08
3.01
1.13
2.10
1.17
1.23
3.20
2.00
1.28
9.40
3.40
3.13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

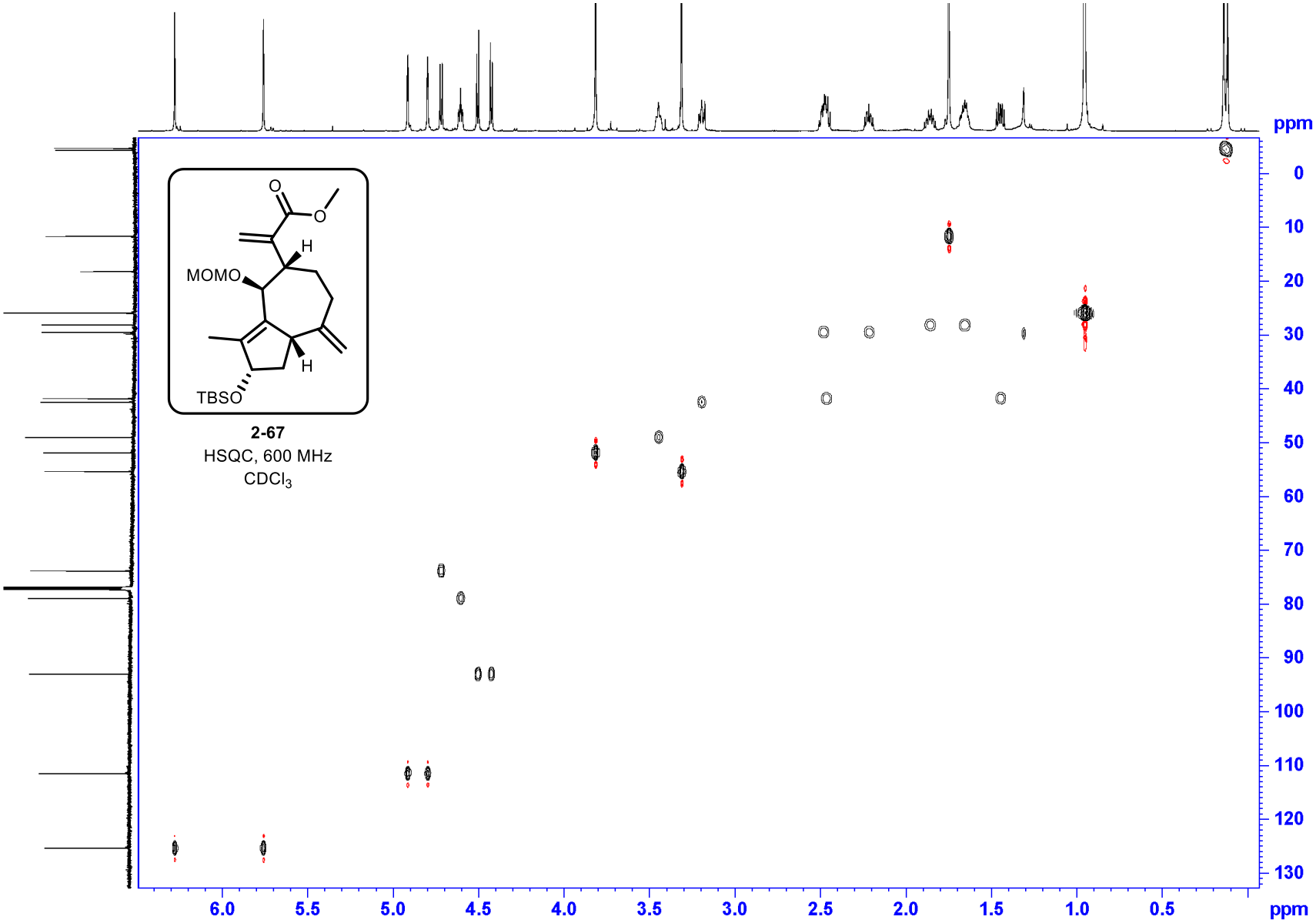


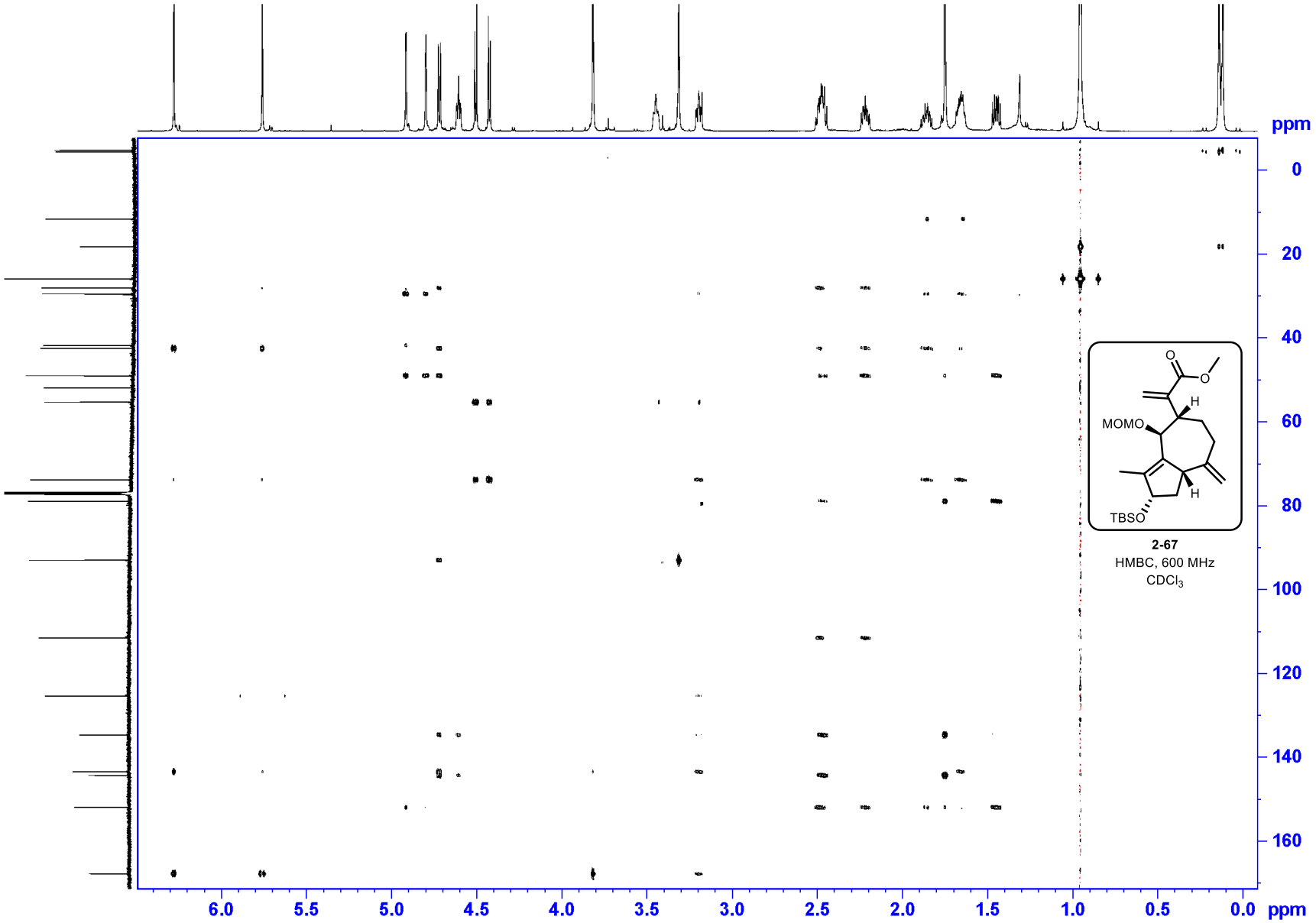
2-67

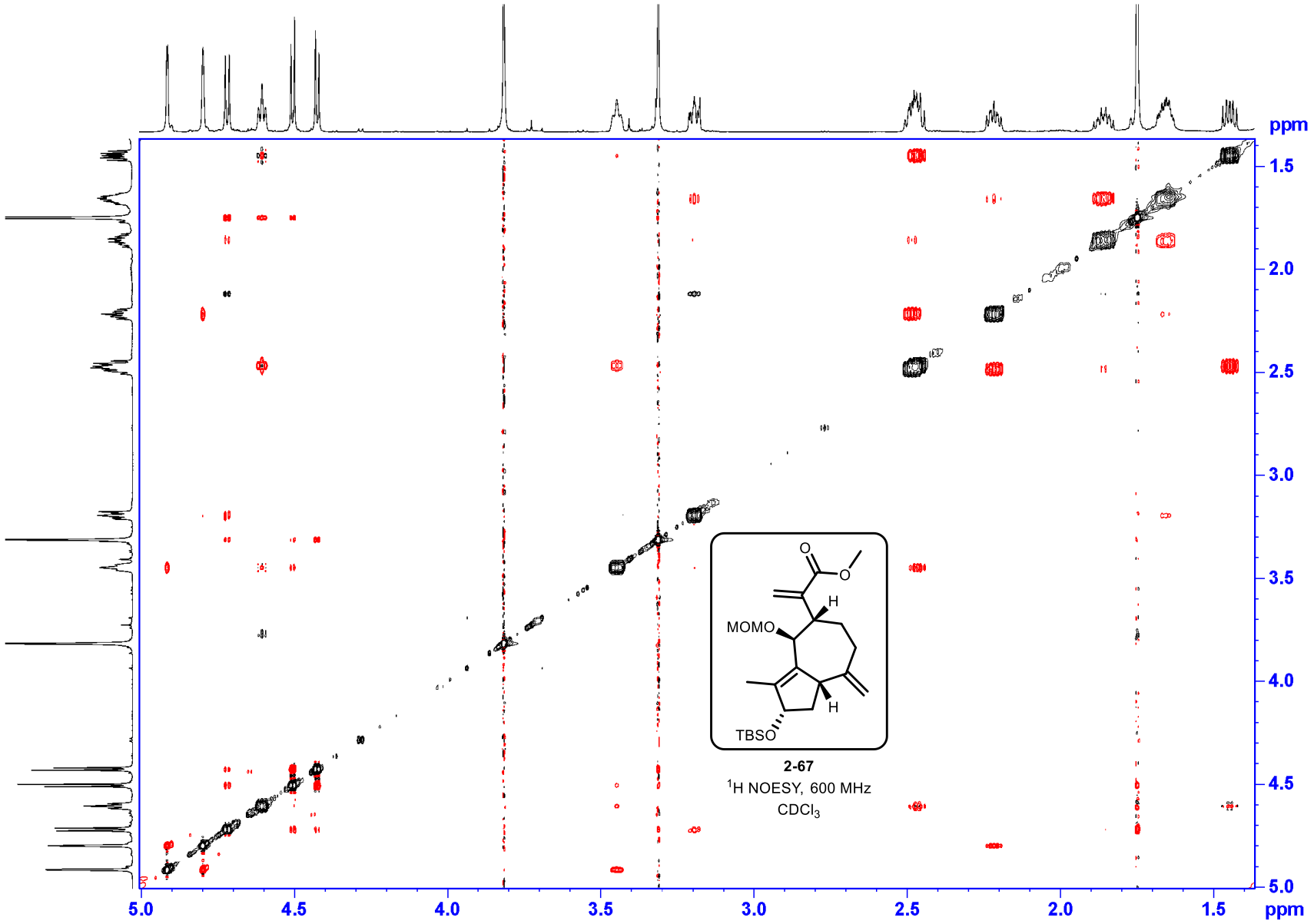
^{13}C, 150 MHz

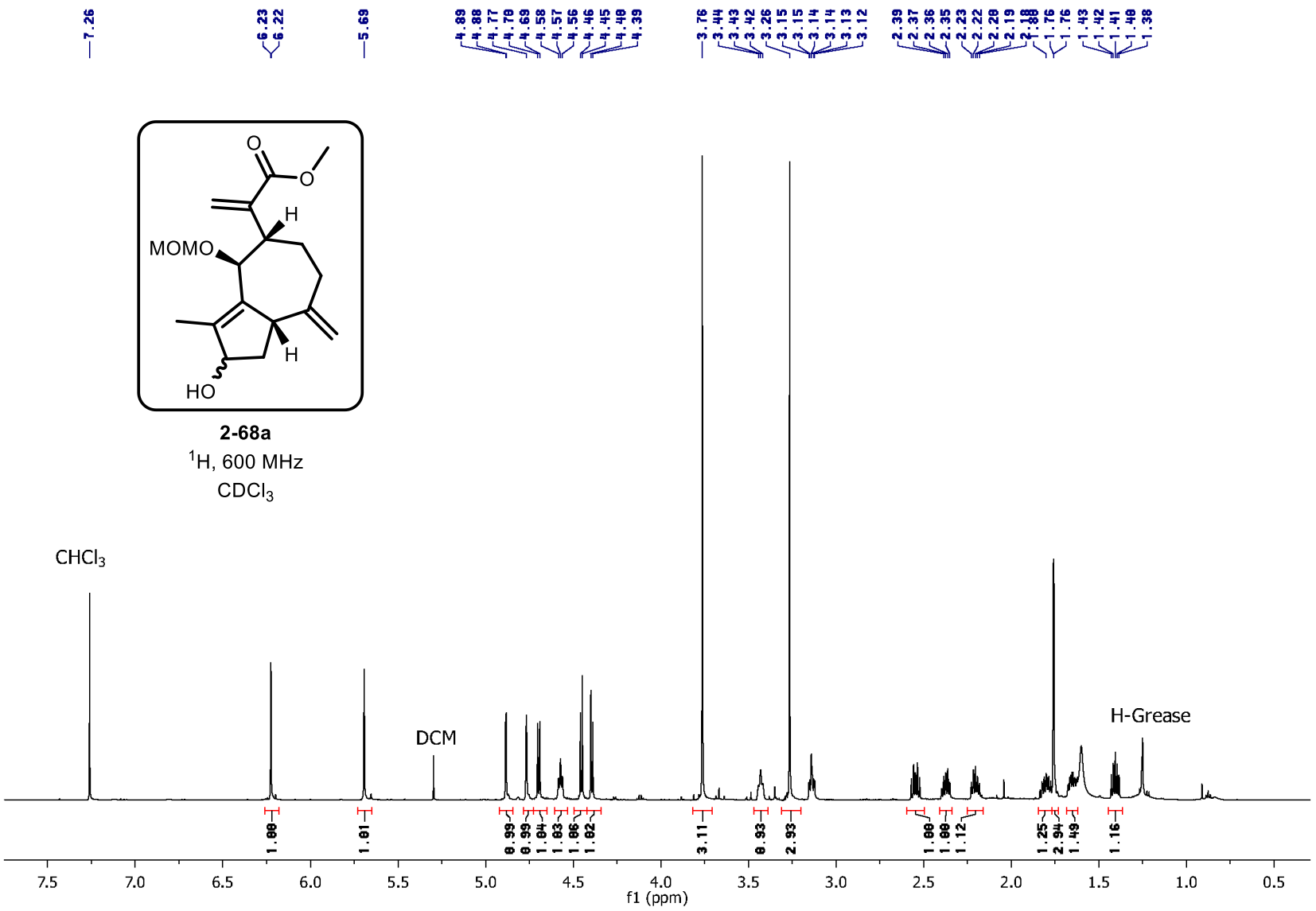
$CDCl_3$

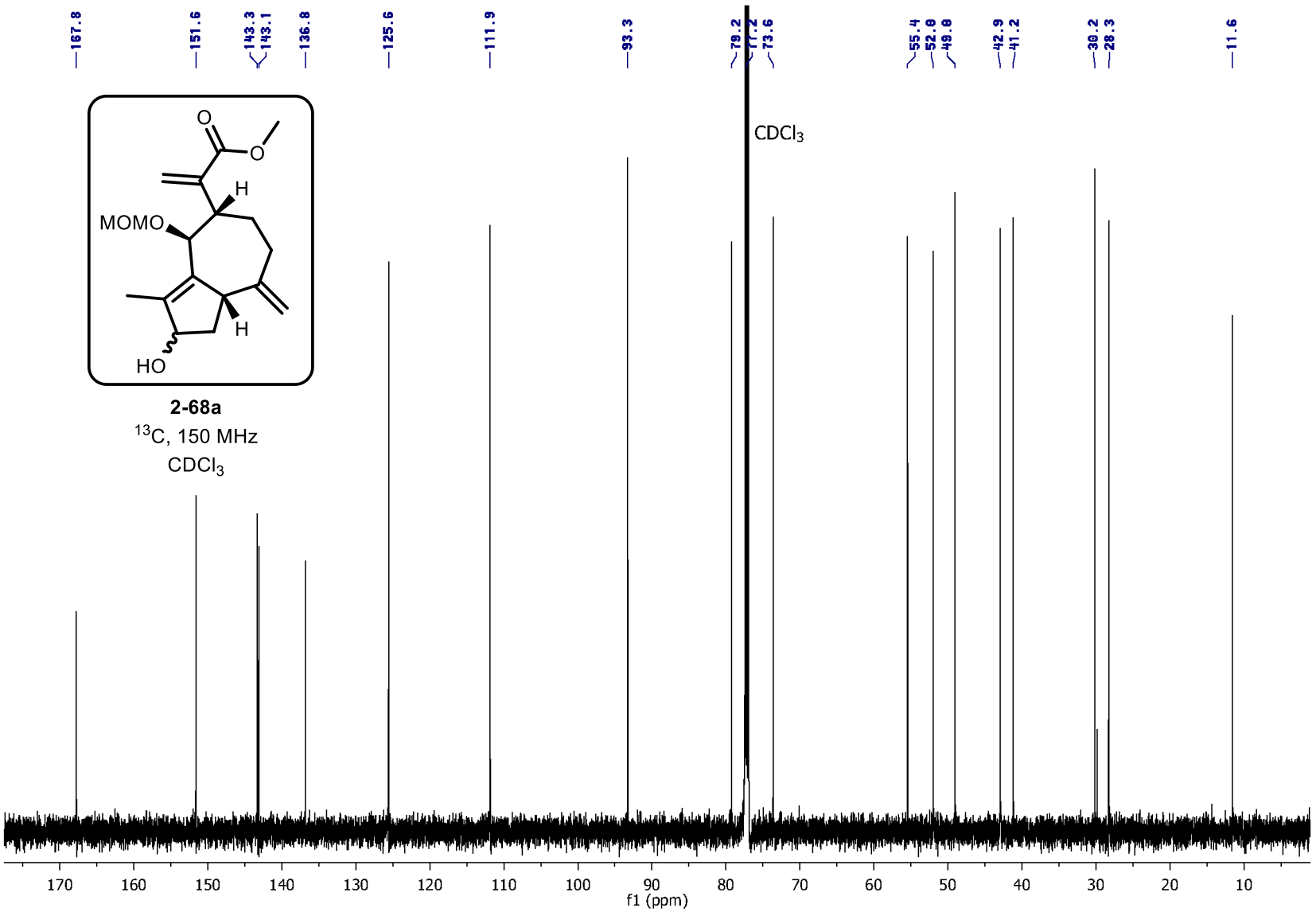

O
O
H
MOMO
H
TBSO
2-67
^{1}H COSY, 600 MHz
$CDCl_3$
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

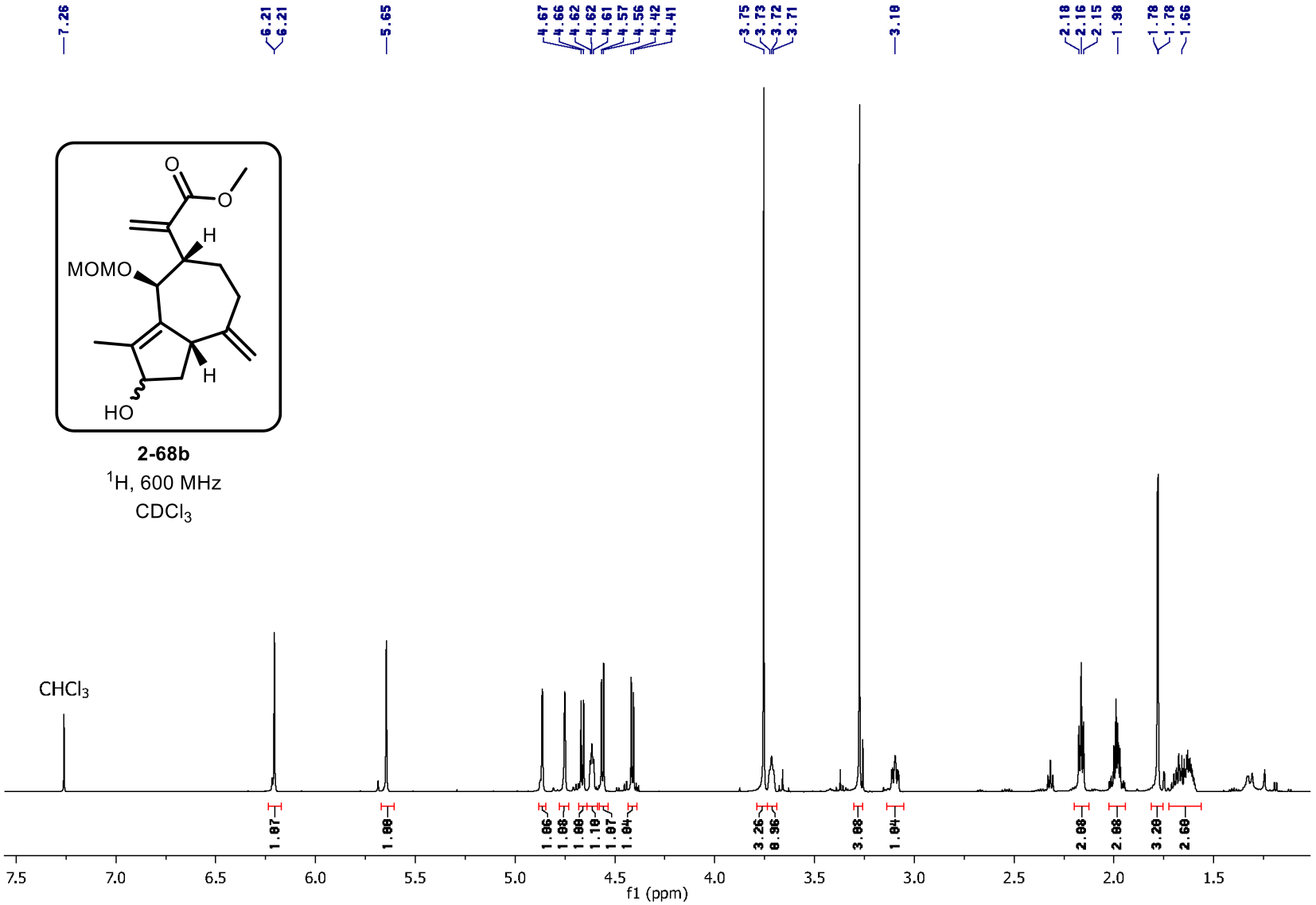

O
O
H
MOMO
H
TBSO
2-67
HSQC, 600 MHz
CDCl3
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

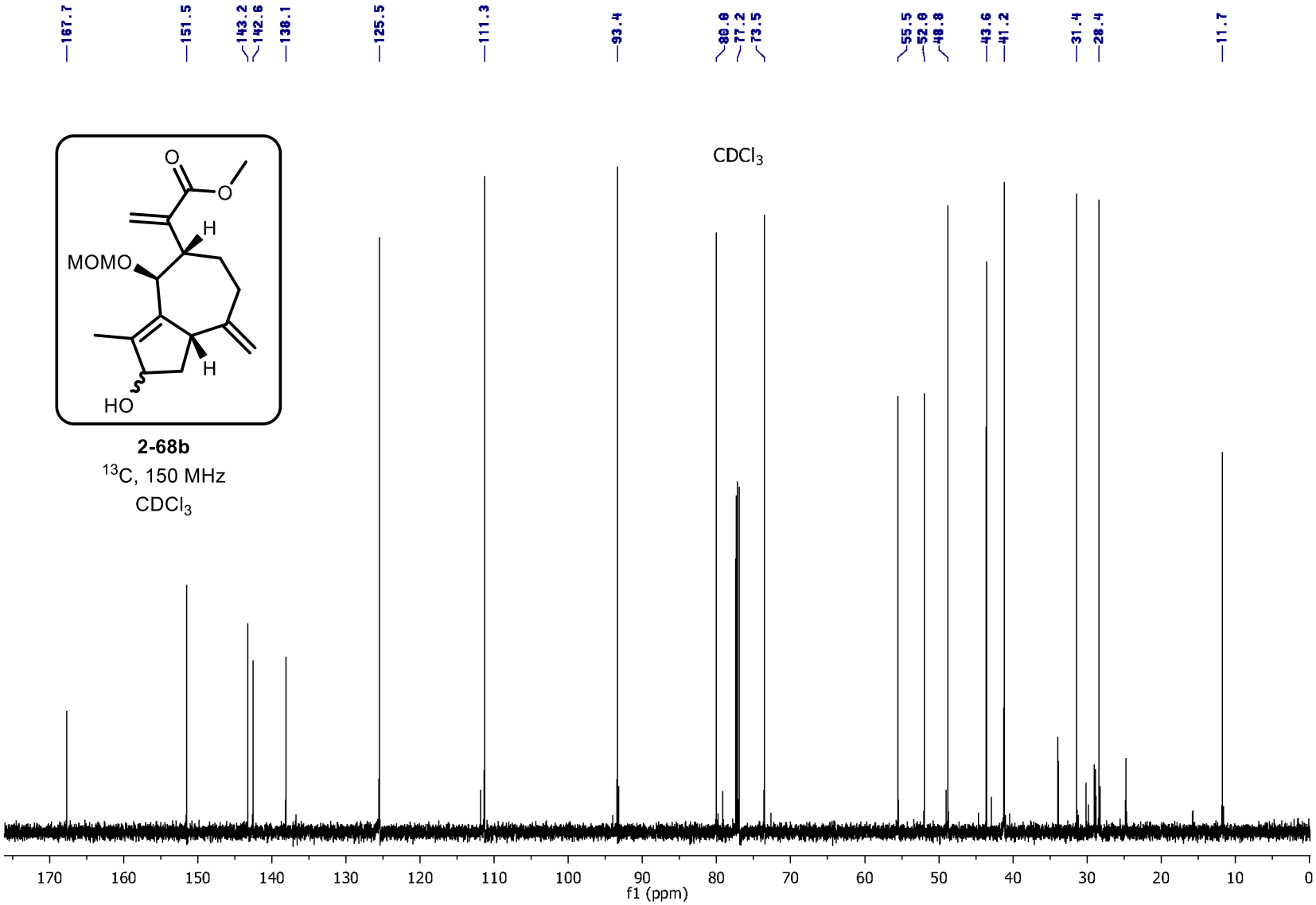

ppm
0
20
40
60
80
100
120
140
160
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
O
O
H
MOMO
H
TBSO
2-67
HMBC, 600 MHz
CDCl3

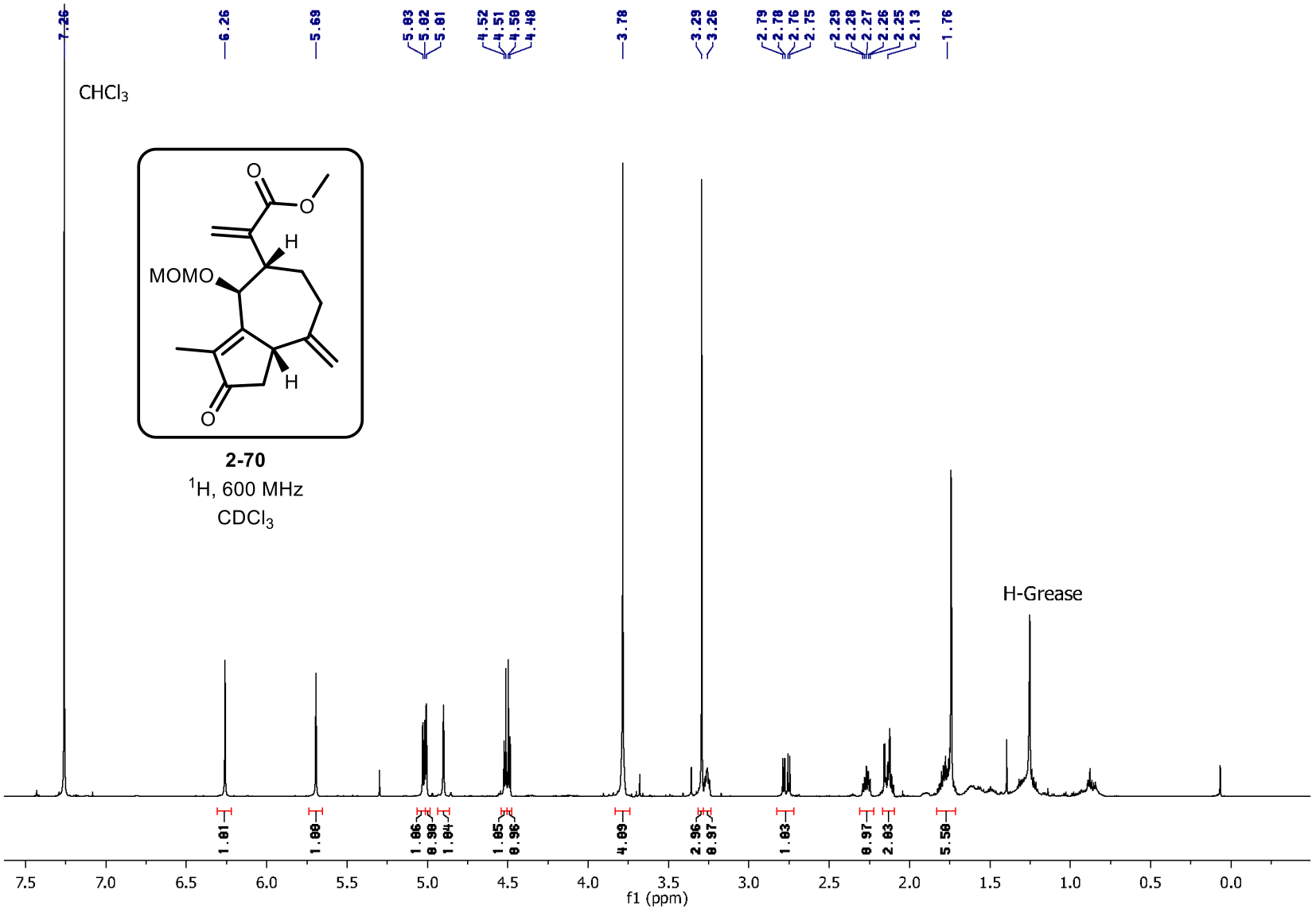

ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
O
O
H
MOMO
H
TBSO
2-67
^{1}H NOESY, 600 MHz
$CDCl_3$

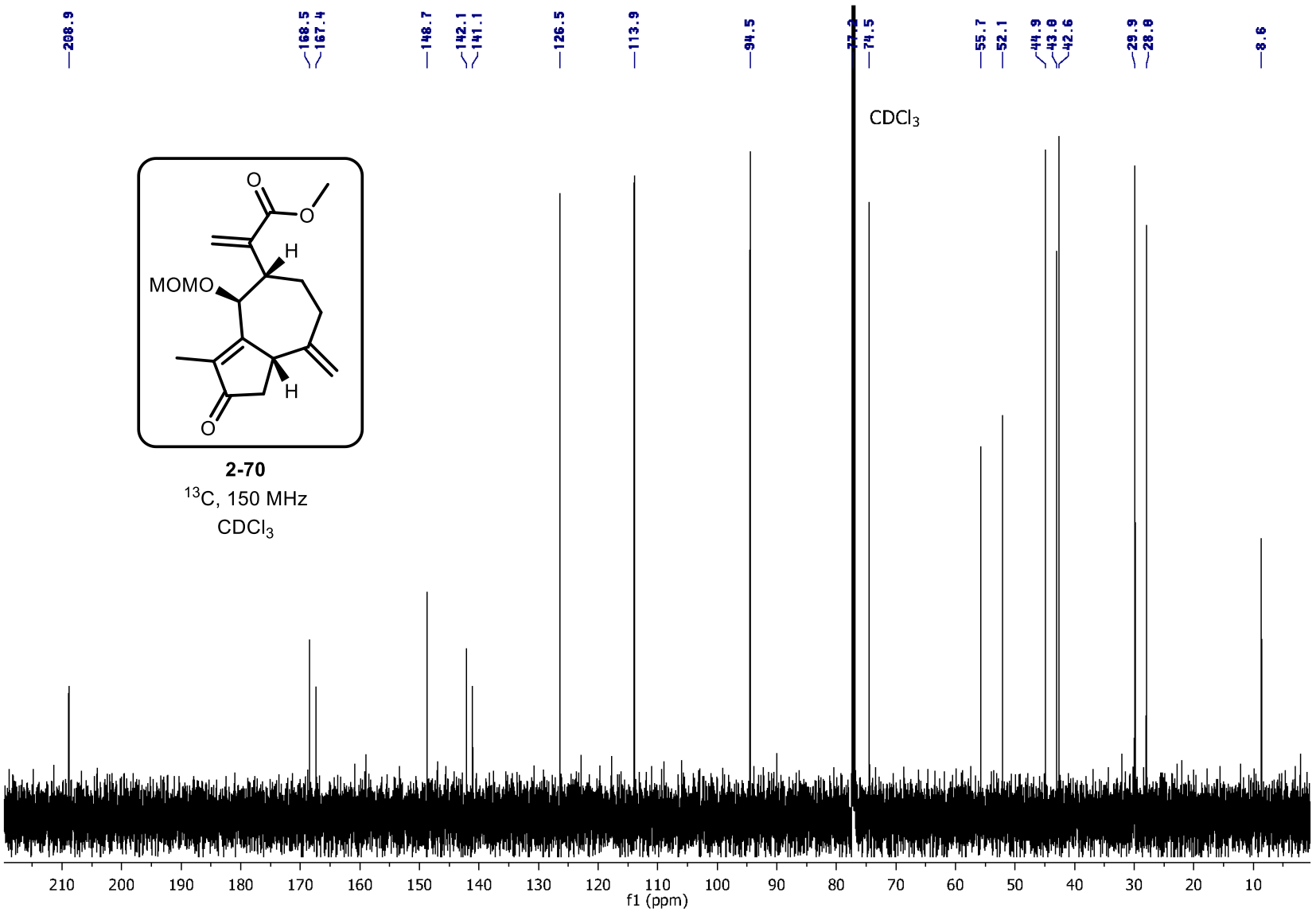

7.26
6.23
6.22
5.69
4.89
4.88
4.77
4.70
4.69
4.58
4.57
4.56
4.46
4.45
4.40
4.39
3.76
3.44
3.43
3.42
3.26
3.15
3.15
3.14
3.14
3.13
3.12
2.39
2.37
2.36
2.35
2.23
2.22
2.20
2.19
1.88
1.76
1.76
1.43
1.42
1.41
1.40
1.38
O
O
H
MOMO
H
HO
2-68a
1H, 600 MHz
CDCl3
CHCl3
DCM
H-Grease
1.00
1.01
0.99
0.99
1.04
1.03
1.06
1.02
3.11
0.93
2.93
1.00
1.00
1.12
1.25
2.94
1.49
1.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

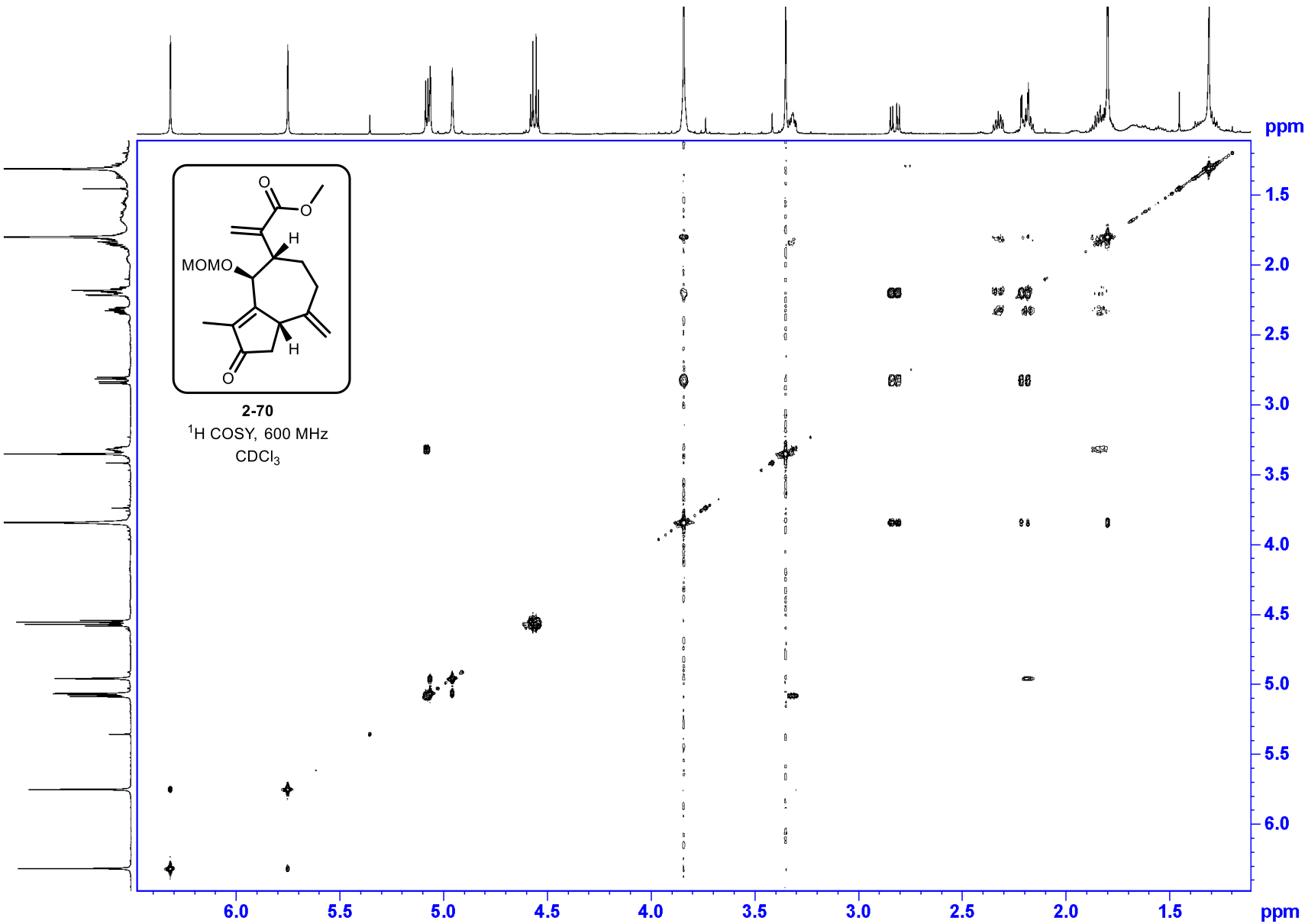

167.8
151.6
143.3
143.1
136.8
125.6
111.9
93.3
79.2
77.2
73.6
55.4
52.0
49.8
42.9
41.2
30.2
28.3
11.6
CDCl3
O
O
H
MOMO
H
HO
2-68a
13C, 150 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

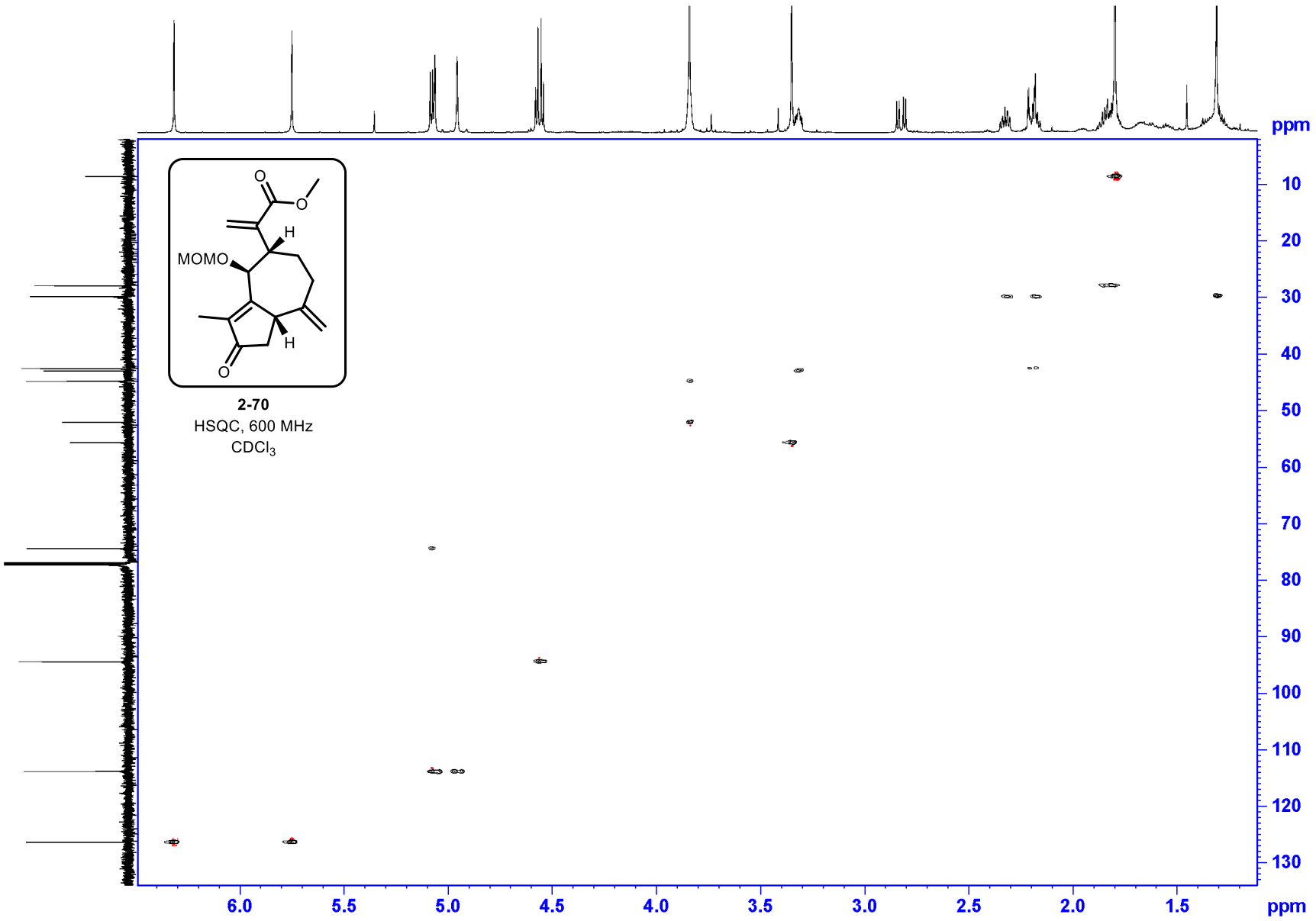

7.26
6.21
6.21
5.65
4.67
4.66
4.62
4.62
4.61
4.57
4.56
4.42
4.41
3.75
3.73
3.72
3.71
3.10
2.18
2.16
2.15
1.98
1.78
1.78
1.66
O
O
H
MOMO
H
HO
2-68b
1H, 600 MHz
CDCl3
CHCl3
1.07
1.00
1.06
1.08
1.08
1.10
1.07
1.04
3.26
8.96
3.08
1.04
2.08
2.08
3.20
2.60
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

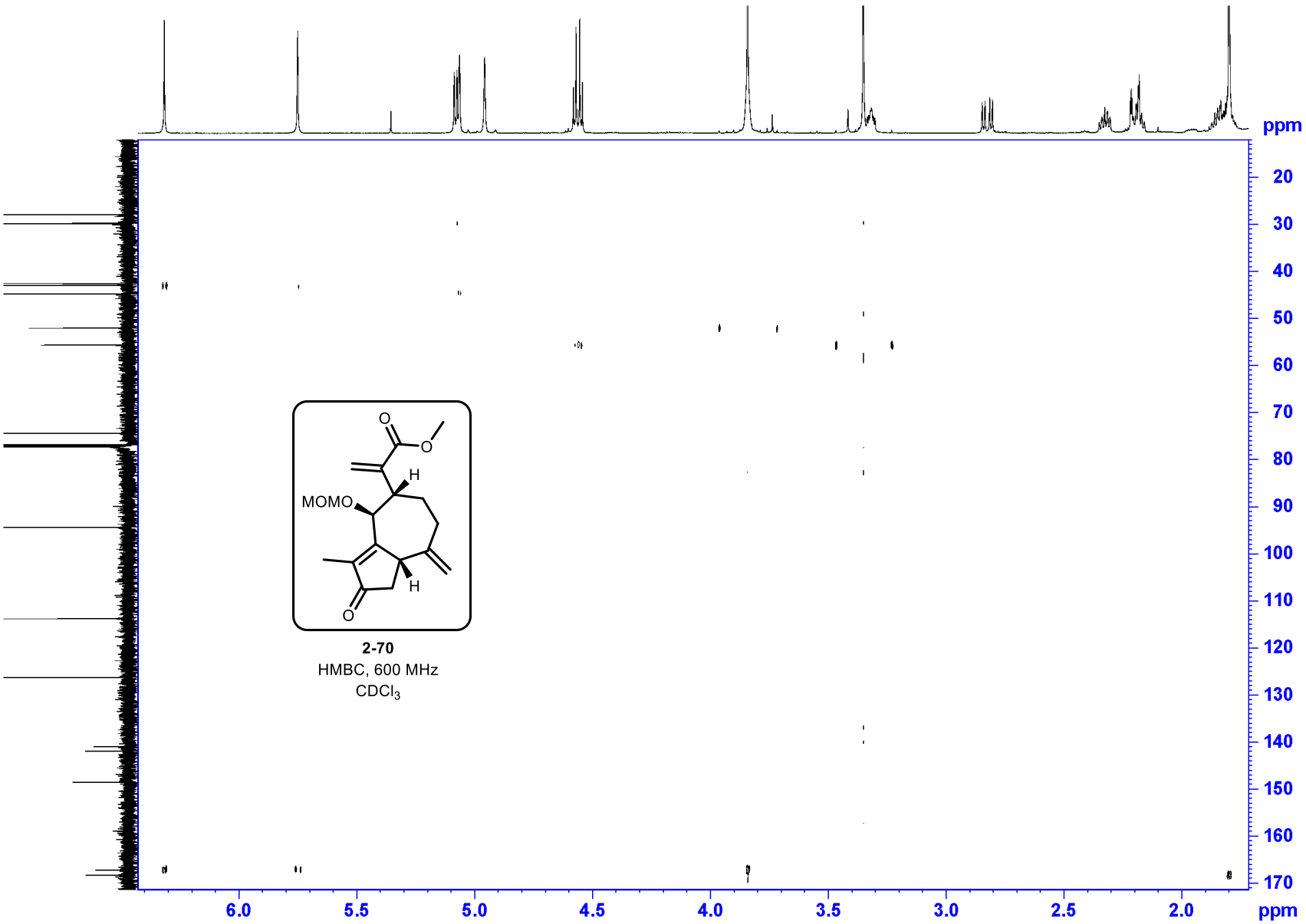

167.7
151.5
143.2
142.6
138.1
125.5
111.3
93.4
80.0
77.2
73.5
55.5
52.0
48.8
43.6
41.2
31.4
28.4
11.7
CDCl3
O
O
H
MOMO
H
HO
2-68b
13C, 150 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.26
6.26
5.69
5.03
5.02
5.01
4.52
4.51
4.50
4.48
3.78
3.29
3.26
2.79
2.78
2.76
2.75
2.29
2.28
2.27
2.26
2.25
2.13
1.76
CHCl3
MOMO
O
O
H
H
O
2-70
1H, 600 MHz
CDCl3
H-Grease
1.01
1.00
1.06
0.90
1.04
1.05
0.96
4.09
2.96
0.97
1.03
0.97
2.03
5.50
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


208.9
168.5
167.4
148.7
142.1
141.1
126.5
113.9
94.5
77.3
74.5
55.7
52.1
44.9
43.0
42.6
29.9
28.0
8.6
CDCl3
MOMO
O
O
H
H
O
2-70
13C, 150 MHz
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


MOMO
O
O
H
H
O
2-70
1H COSY, 600 MHz
CDCl3
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


O
O
H
MOMO
H
O
2-70
HSQC, 600 MHz
CDCl3
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm



2-70
HMBC, 600 MHz
$CDCl_3$