THE UNIVERSITY OF CHICAGO

STUDIES OF THE STRATEGIC SYNTHESES OF NATURAL PRODUCTS WITH CONTIGUOUS ALL-CARBON QUATERNARY STEREOCENTERS

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE DIVISION OF THE PHYSICAL SCIENCES
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DOCTOR OF PHILOSOPHY

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BY
CHENG PENG

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List of Abbreviations

Ac	Acetyl
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
BPin	pinacolboryl
Bz	Benzoyl
COSY	Correlated spectroscopy
CSA	Camphor-10-sulfonic acid
dr	Diastereomeric ratio
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
1,2-DCE	1,2-Dichloroethene
DIBAL-H	Diisobutylaluminium hydride
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl
HMPA	Hexamethylphosphoramide
i-Pr	Isopropyl
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide

LiHMDS	Lithium bis(trimethylsilyl)amide
*m*CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
Ms	Mesylate
MS	Molecular sieves
NBS	N-Bromosuccinimide
n-Bu	n-Butyl
NHC	N-heterocyclic Carbenes
nOe	Nuclear Overhauser effect
Ph	Phenyl
*p*TSA	*p*-Toluenesulfonic acid monohydrate
TBAF	Tetrabutylammonium fluoride
TBS	tert-Butyldimethylsilyl
t-Bu	tert-Butyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid or trifluoroacetyl
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl

Acknowledgments

The past 5 years have been a unique, unforgettable, and fantastic journey for me in many aspects.

To begin with, I would like to dedicate this dissertation to Prof. Han-Chu Peng (彭汉初), my dearest grandfather. Prof. Hanchu Peng was born in 1930 and strived to complete his medical education through the most tragic and chaotic time of China, at Zhongnan University Xiangya Medical College. He dedicated his whole life as an ENT doctor and educator. He was one of the pioneers in China to open hearing clinics, and an activist in helping deaf children. He was awarded the Lifetime Achievement Award in ENT by the Shanxi Medical University. As a passionate educator, he had a significant influence on my early life and education. He and my grandmother Jun-Hua Liu, used to take me to every museum in Beijing when I was young. I still remember, as an 8-year-old kid, reading his books in autopsy, which, in my early life, bonded me closely to physical and medical science. Under his influence, many of my family members choose to become doctors or scientists. And he would have been the first person I share my excitement of receiving a Ph.D. degree if he hadn't passed in March 2021. It is my forever regret not being able to share this important moment of my life with him. May the spirits of this dissertation find him well.

Then I would like to share my greatest gratitude to my parents. They always share understanding and love no matter where we are each located. They raised me to be considerate to people, but critical to work. Their generous support through my years of education removed any concerns in my life, allowing me to be fully devoted to research. I sincerely regret not being able to spend more time with them in the past years, which I really hope to change in the time to come.

A Picture of me with my grandparents in 2016.

Next, my life partner, wife-to-be, Xi Yang, has always been helpful in the past years. We met in Chicago and started our relationship in 2019. During the time she spent working in China, the pandemic hit, and we could not see each other for 2 years. But our relationship was somehow made stronger. I am always grateful for her willingness to listen and understand me. We have had a great time together and will have an incredible future to come.

Special thanks to Prof. Scott Snyder and everyone in the Snyder lab. My conversations with Scott have always been insightful and educational. And through my time working here, I found a lot of things I have in common with him: we engage with (and get annoyed by) the broadest picture and the smallest details, we always try to make our works educationally impactful, and of course, we both love to cook. Having a role model to mentor me through the past years is my greatest fortune. Zhiyao Zhou, my graduate-student mentor, also played an important role in my early research. Being the smartest person in chemistry I have worked with, Zhiyao also shares all the best personalities to be a great mentor. My other collaborators, Piyush, Alex, Seth, and Bryan are all very productive and inspiring at the projects. Best wishes to my undergraduate fellows: Claire, Zach, and Guanchen, you all have the brightest future to come. I couldn't have completed so much without the help from you all. The Snyder group is a big family: we share a great working environment because we are all great friends in our personal lives. We play badminton or go to concerts, or simply get drunk together all the time. In addition, I would like to thank NIH (R01-GM132570) and the University of Chicago for funding our research.

I would like to thank Prof. Guangbin Dong and Prof. Viresh Rawal for serving on my dissertation committee and discussing chemistry with me throughout my time here. In addition, all other faculties and staff at the University of Chicago helped create this great environment for research. I am very much appreciative of your kindness and hard work.

I am also very fortunate to have met so many great friends here. A lot of great memories were shared with Fangjie, Heng, Minxing, Pei, Yu’an, and Zhiyao before the pandemic. And Taokun, Tong, Xiaomin, Ziwan, and Zhao consist of my closest circle of friends in the past two years. It is always surprising to me that I can share so many common hobbies with them. We could do any activity together: badminton, ping-pong, curling, hiking, pool, grilling, classical concerts, board games, you name it. Also, my best friend Yitian and his partner Huiting, although over in Michigan, would never mind the 4-hour drive to spend weekends with me. Thank y’all for the power you share to help me keep thriving.

Moreover, I am truly appreciative to the folks at BMS for securing my position one year before my projected graduation. This was the whole reason I could focus on the challenging synthesis of bipolarolides in my last year. Their generous support to international students is also incredibly precious. Especially, my friend Vlad, a former member of the Snyder group, and also my go-to for chemistry-related discussions, offered lots of help in my interviewing process. I really look forward to my new life and career at BMS.

Finally, it was an incredibly tough decision for me to make to leave the city of Chicago. Being the second city after Beijing where I can easily navigate without map apps, Chicago has become my second hometown. This is the place where my career and life start to unfold. Here, I screened out my first key reaction (which actually happened in 2017 during my undergrad internship), completed my first total synthesis (with no oxygen atom), found my first job (BMS is the best!), learned to cook (go search Laofangu on YouTube, you'll never regret it), had my first taste of whiskey (Scotch any day over Bourbon), found my favorite orchestra (the Chicago Symphony Orchestra, of course), got into so many new sports and hobbies (saving a page here), (almost) became married, owned my first car and home (a ton more thanks to my parents), fixed 3 water leaks in my house (someone needs a plumber?), dealt with a total loss of my electronics in a car break-in (surprisingly didn't happen in Chicago), and so much more (better stop here, I'm bout to cry). I learned to become a chemist and to live a life here. I will always be so grateful for this magical time I spent in Chicago.

Abstracts

Chapter 1 Exploring the Value and Impact of the Total Synthesis of Natural Products

The value and impact of the total synthesis of natural products are thoroughly discussed, including the primitive goal of fulfilling the supply of natural products for application purposes or for biological studies; testing and help developing methods and strategies; enabling access to a broader chemical space; and inspiring other research areas and educating chemists of the next generation. A summary of how these ideas are practiced during the research described in this dissertation is also included.

Chapter 2 A Concise Total Synthesis of (+)-Waihoensene Guided by Quaternary Center Analysis

The development of a concise synthetic route of (+)-waihoensene, a unique natural product containing 4 contiguous all-carbon quaternary centers is described. The contiguous all-carbon quaternary centers are considered as key structural elements in the synthesis and guided the stereochemical outcome of multiple steps of the synthesis.

Chapter 3 Studies Toward the Strategic Syntheses of Bipolarolides A and B

The studies toward the syntheses of bipolarolides A and B are described. A retrosynthesis based on a Prins-type cationic cyclization was explored and later evolved into the current route based on a key gold-catalyzed cyclization reaction and SmI_2-mediated radical cyclization reaction. The full

core framework of bipolarolides A and B is obtained. An asymmetric synthetic strategy has been developed. The final assembly of the natural products is underway.

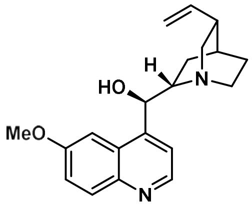
Chapter 4 The Application of Gold(I) Catalysis in the Formation of Polycyclic Systems with Contiguous All-carbon Quaternary Stereocenters

During studies toward the synthesis of bipolarolides A and B, we discovered a gold(I)-catalyzed tandem cyclization reaction that can lead to angular tricyclic systems with 3 contiguous all-carbon quaternary centers. The method was investigated in detail. Progress of the studies of applying the method in the syntheses of waihoensene and bipolarolides C and D are described. A thorough literature review of the applications of gold(I)-catalysis in the formation of all-carbon quaternary centers is also included, with our novel insight into the importance of the linear nature of gold(I)-complexes in such transformations.

Chapter 1 Exploring the Value and Impact of the Total Synthesis of Natural Products

Total synthesis is the process of constructing complex products from simpler, smaller, and more accessible molecules as starting materials. The targets of total syntheses can be diverse, while the most traditional class of targets – natural products – are arguably the most challenging, partly because they exist in nature as a defined structure, meaning chemists cannot bypass any hurdles by engineering the structure of the target molecule. At the same time, synthetic chemists often choose to challenge themselves by not only developing a successful route, but also a more elegant route compared to nature, which posts a test to science and technology, and challenges the chemists in their logic and creativity. With the advancement of handy tools such as X-ray crystallography, NMR, column chromatography, and information technologies, we are now confident that most natural products can be synthesized. However, the development of an efficient and selective synthetic route is still guided by the ingenuity and experience of the chemists.

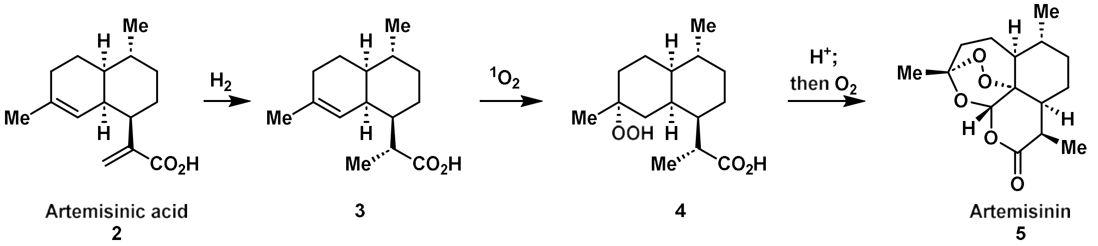
1.1 Fulfilling the Supply



Quinine
1

Figure 1.1. The chemical structure of quinine (**1**).

The primitive goal of total synthesis is simple and straightforward: fulfilling the supply of useful molecules that are scarce in nature by chemical processes. Historically, total synthesis is directly linked to the advancement of modern society. A classic story to tell is the explorations towards quinine synthesis[1]. As early as the 17th century, quinine came to the attention of Europeans seeking treatment for malaria. Bark extracts of a cinchona tree native to Peru, now believed to contain quinine (**1**), have been used to save thousands of lives. Since then, quinine has been in high demand, while its natural source, being far away from the Western world, had no way to fulfill the supply. Encouraged by the early success of the chemical syntheses of organic molecules, such as urea in 1828[2], people came up with the idea of supplying quinine by chemical synthesis. However, the atomic connectivity of **1** was not elucidated until 1908[3]; and all the stereochemical issues were only unambiguously clarified 36 years later. Now we look at the chemical structure of quinine, it is clear that the structure of the 20-carbon alkaloid with 4 stereocenters was way beyond the wildest imagination of the chemists in the 19th century. The world had to wait until 1944 to witness the first total synthesis of **1**. Woodward and Doering reported in their one-page communication the 17-step chemical synthesis of quinotoxine[4], which had been reported to be converted to quinine by Rabe in 1918[5]. Since then, more syntheses were achieved, including the first asymmetric synthesis by Stork in 2001[6]. The Stork synthesis took only 14 steps in the longest linear sequence, producing quinine in an astonishing total yield of 15%, without the involvement of any modern transition metal chemistry. More modern methods such as C-H activation[7] chemistry have been utilized in synthesizing the classic molecule[8]. The nearly 2-centuries history of quinine synthesis witnesses the advancement of people's understandings of organic chemistry and other technologies through their unceasing attempts and optimizations. Regardless of all these efforts, the original goal of finding a more efficient way to produce quinine than isolating it from nature is never achieved. The biosynthesis simply outperforms the total chemical syntheses in this case and most other scenarios when a useful natural product is needed in large quantities.

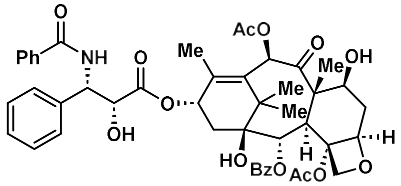


Scheme 1.1. The partial chemical synthesis of artemisinin (**5**).

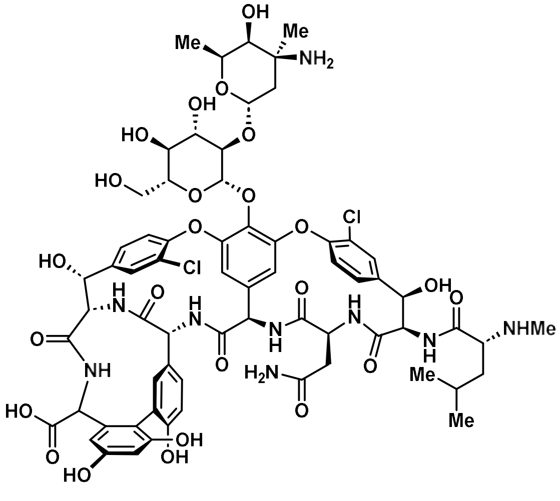
Nevertheless, partial chemical syntheses are more commonly used to help the production of such natural products. The Nobel-Prize-winning natural product, artemisinin (Qinghaosu, **5**)[9], being used as the most important component of the first-line treatments of malaria in almost any country[10], is traditionally extracted from *Artemisia annua*, which contains artemisinin up to 0.45% of its total dry weight[11]. Harvesting the natural product from the plant caused the price of artemisinin to fluctuate depending on the climate and geopolitical events. In 2011, the Keasling lab at the University of California, Berkeley; and the Amyris Biotechnologies Inc. reported a fermentation process to produce artemisinic acid (**2**) in a strain of engineered yeast[12]. A photochemical process (Scheme 1) was then developed by Sanofi-Aventis to convert **2** into artemisinin[13]. The process went into production in 2017.

More commonly, chemically synthesized natural products are being provided as precious materials for biological experiments in drug discoveries. One of our group's long-lasting collaboration programs allows us to submit all the natural products we synthesized for screenings of biological activities. This is especially valuable for the natural products that are scarce in nature. As an example, only 3.5 mg of bipolarolide A, an important synthetic target to be discussed in this dissertation, was obtained by the isolation team[14]. This greatly limited their ability to further evaluate the possible biological activities of the natural product. In fact, an *in silico* screening was conducted to identify the potential target before the isolated natural product was used in an *in virto* experiment.

1.2 The Ultimate Test to Strategies and Methodologies

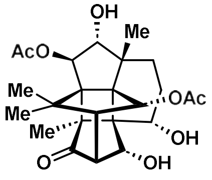


Taxol
6

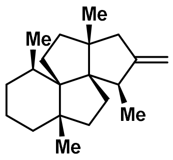


Vancomycin
7

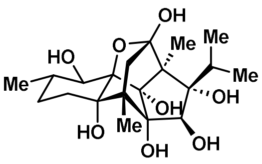
Figure 1.2. The chemical structures of taxol (**6**) and vancomycin (**7**).



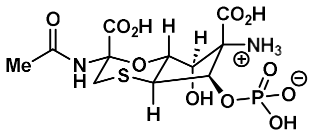
Canataxpropellane
8



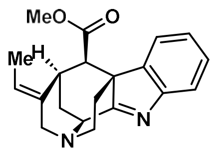
Waihoensene
9



Ryanodol
10



Tagetitoxin
11



Strictamine
12

Figure 1.3. The chemical structures of canataxpropellane (**8**), waihoensene (**9**), ryanodol (**10**), tagetitoxin (**11**), and strictamine (**12**).

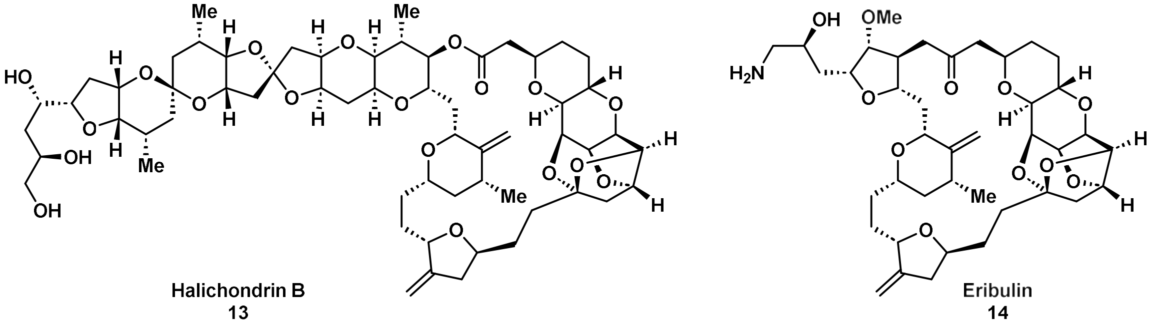
Compared to quinine, the natural products we pick as synthetic targets nowadays often have larger sizes and more complex structures. Molecules such as taxol (**6**)[15]and vancomycin (**7**)[16], remain to be the special trophies for synthetic chemists. At the same time, the diverse structures of other natural products also present a much broader range of challenges.

Strategies have been developed targeting these challenging structural features, such as strained ring systems (represented by **8**[17]), contiguous quaternary centers (represented by **9**[18]), high oxidative states (represented by **10**[19]), richness of unconventional functional groups (represented by **11**[20]), caged frameworks (represented by **12**[21]), and more. The knowledge learned from these total syntheses is a priceless asset to be applied in the synthesis of more useful targets such as small molecule drugs.

Methods have been established to quickly access certain frameworks and functionalities. The development of organic chemistry methodologies is directly driven by natural product synthesis. In the late 20th century, the palladium catalysis cross-coupling methods, which later won the Nobel Prize in 2010, were quickly proven to be extremely valuable by being demonstrated in natural product syntheses[22]. Emerging methodologies in the early 21st century, such as C-H functionalization[23], photoredox catalysis[24], electrocatalysis[25], etc., are also being tested ultimately in total syntheses, which can offer systems with high levels of complexity similar to chemical process environments that are otherwise hard to be mimicked.

1.3 Accessing a Broader Chemical Space

One of the biggest limitations people meet when trying to understand the structure-activity relationship (SAR) of natural products, is the number and variety of derivatives that can be synthesized from the natural product. For natural products with multiple reactive functional groups, the “top-down” strategy of selectively functionalizing at a certain position can be very challenging. However, the development of total syntheses turns the process to be “bottom-up”, providing opportunities to synthesize a wide variety of derivatives at different stages of the synthesis. This strategy, commonly referred to as diversity-oriented synthesis[26], allows us to access a much broader collection of compounds that can potentially be used for high-throughput screenings in drug discovery.


Halichondrin B
13

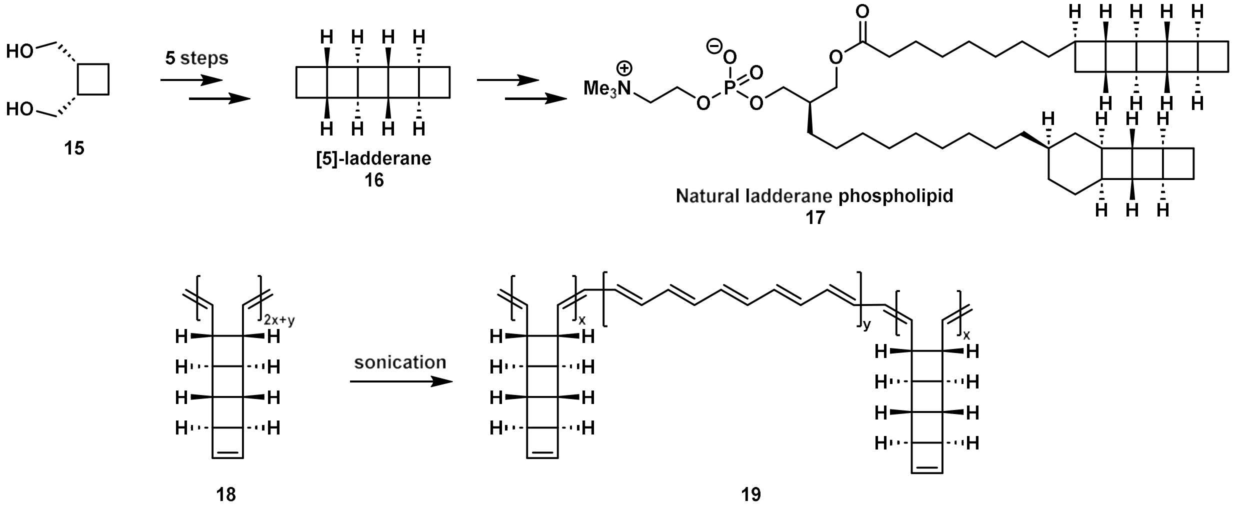
Eribulin
14

Figure 1.4. The chemical structures of halichondrin B (**13**) and eribulin (**14**).

One unique story is the discovery of eribulin (**14**). Uemura and co-workers reported the isolation of halichondrin B (**13**) from a marine sponge in 1986 and described the polyether natural product's remarkable antitumor activity *in vivo*[27]. The Kishi group first completed the total synthesis of **13** in 1991[28]. The synthetic route features a late-stage Nozaki-Hiyama-Kishi Coupling reaction to merge the polyether moiety (referred to by the authors as the left half) and the macrocycle lactone moiety (referred to by the authors as the right half). This strategy enabled the opportunity of testing the biological activities of each half of the natural product, which would be hardly possible otherwise. It was soon clear that only the right half of the natural product contributed to its anticancer activity. Under the close collaboration of Eisai, SAR studies then afforded **14** as the optimal drug molecule[29]. The most noticeable structural optimization was that macrocycle lactone was advanced into a macrocycle ketone, which was purposed for avoiding the hydrolysis of the later functionality *in vivo*. **14** can only be accessed by a lengthy chemical synthesis[30], and its mesylate salt was first approved by FDA in 2010.

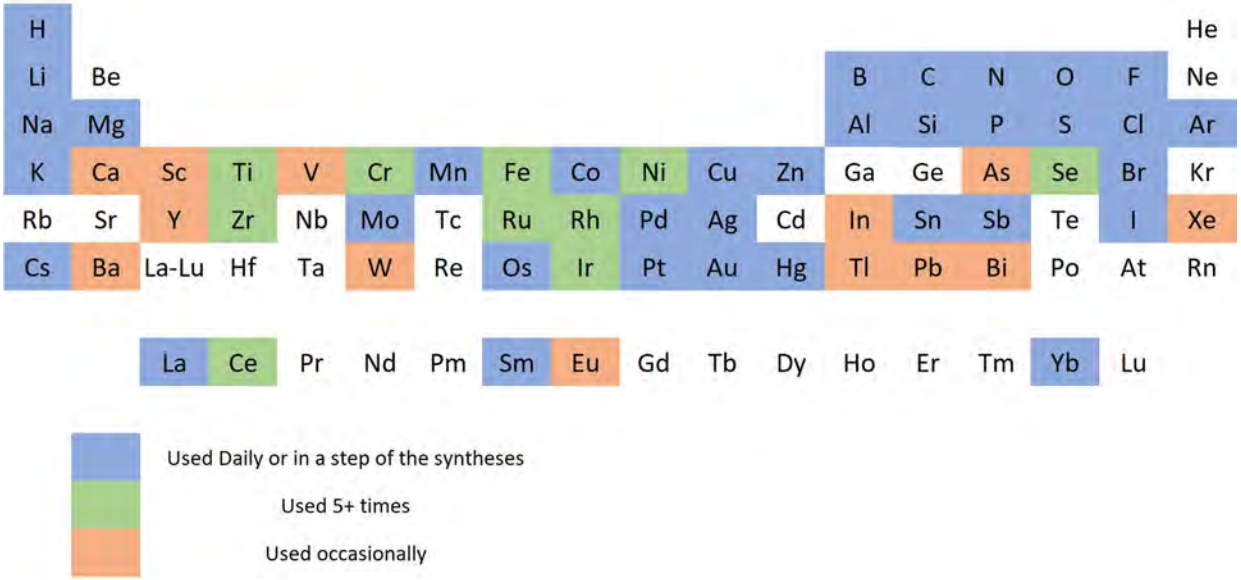
1.4 Inspiring and Educating

The total synthesis of natural products also influences other areas of research, such as material science, chemical biology, and supramolecular chemistry. Chemical synthesis is the basic tool to provide material for these studies. At the same time, synthetic chemists introduce their experiences and deeper fundamental understandings of organic chemistry to create more interdisciplinary areas.



Scheme 1.2. The total synthesis of natural ladderane phospholipid (**17**), and the so inspired preparation of polyacetylene copolymer (**19**) from polyladderane (**18**).

One notable collaboration at Stanford University well represents the incredible inspirational power of total synthesis. The Burns group lead the publication of a total synthesis of a ladderane phospholipid natural product **17** in 2016[31]. Their novel method for constructing the ladderane moiety enabled the synthesis of [5]-ladderane (**16**) on a decagram scale. In 2017, this work unexpectedly found its application in material science after being seen by the Xia group, who synthesized polyladderane **18** and found the polymer could unzip upon sonication to generate a semiconducting polyacetylene copolymer (**19**)[32]. The first author of the later publication, Zhixing Chen, now a professor at Peking University, claimed that his short experience working on natural product total synthesis is the main reason why he was interested in the work by the Burns group, which gave rise to this collaboration.



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🟦 Li	Be											🟦 B	🟦 C	🟦 N	🟦 O	🟦 F	Ne
🟦 Na	🟦 Mg											🟦 Al	🟦 Si	🟦 P	🟦 S	🟦 Cl	🟦 Ar
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Rb	Sr	🟧 Y	🟩 Zr	Nb	🟦 Mo	Tc	🟩 Ru	🟩 Rh	🟦 Pd	🟦 Ag	Cd	🟧 In	🟦 Sn	🟦 Sb	Te	🟦 I	🟧 Xe
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🟦 Used Daily or in a step of the syntheses
🟩 Used 5+ times
🟧 Used occasionally

Figure 1.5. Chemical elements applied in the research related to this dissertation.

Total synthesis of natural products also offers great educational experiences to students at different levels. Undergraduate students may learn basic organic chemistry principles and techniques to prepare them for graduate school, medical school, or other career choices. Graduate students receive the opportunity to design, conduct, and thoroughly consider all aspects of a project. Summarized in Figure 5 are the chemical elements applied during the studies described in this dissertation. Each time of practice provides an incomparable opportunity to learn about the history, properties, and potential applications of these chemical elements. Despite that an increasing number of students choose to work in pharmaceutical companies after graduate school, job candidates with backgrounds in total synthesis of natural products are still highly desirable, as “they are never scared off by the synthesis of a difficult compound with good potential”.

1.5 Practice of the Values

When conducting our new synthetic and methodologic studies, we always try to keep these ideas in mind. What made us intrigued in the synthesis of waihoensene (**9**) is the unique structure with 4 contiguous all-carbon quaternary centers. We hope that a broader chemical space can be accessed through the efforts of our synthesis. While **9** as a hydrocarbon molecule, is hardly possible to have any interesting biological activity, synthetic intermediates such as the tetracyclic enone may offer novel activities. Such structures may be hard to access conventionally. The same idea transfers to bipolarolides A and B (chapter 3). The difference in the biological activities between the two molecules suggests that the substitutional pattern on the side chain may be crucial for the activities. In our coming route, we propose to build the core structure first, and divergently synthesize both natural products by late-stage diversifications. This way, more interesting derivatives can be accessed. All of the synthetic intermediates are submitted to have their biological activities tested through a collaboration program in our group.

It should also be noted that both the tetracyclic framework of **9** and the pentacyclic core of bipolarolides A and B are highly unique. Very few if any universal strategies have been proposed. In our synthetic studies, we hope to show some generalizable conclusions that can help guide the future synthesis of such systems. For example, the detailed study of the hydrogenation step in our waihoensene synthesis (section 2.4.3) provides some novel insights into the facial selectivities in *cis*-bicyclic systems with vicinal all-carbon quaternary centers at the angular positions. In the retro-synthetic analysis of waihoensene, we innovatively consider the all-carbon quaternary centers in the molecule as key structural elements and use them to guide the stereoselectivities through the synthesis (section 2.3). During the studies toward bipolarolides A and B, we came up with a highly applicable method, the tandem gold-catalyzed cyclizations reaction, to construct angular tricyclic systems with 3 contiguous all-carbon quaternary centers (chapter 4).

Finally, aside from the projects to be described in this dissertation, many collaboration programs are conducted simultaneously. Applying our expertise in organic synthesis, we provided materials and consulting to other groups in the department in areas such as chemical biology, medicinal chemistry, and material sciences. Multiple collaborative publications are underway.

Some personal perspectives are shared as a concluding paragraph to this chapter, as well as the 8-year experience in natural product total synthesis of the author. Total synthesis is, obviously, a theme of science, driving the development of new methods and techniques. At the same time, it shares a lot of common features with engineering. Synthetic chemists, more often than not, apply tools that are readily available to solve real problems with high dimensions of complexities. And total synthesis can sometimes be great art to showcase the ingenuity of synthetic chemists, and more importantly, inspire the better syntheses to come.

References

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[1] This paragraph was inspired by: (a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods.* pp 443-463. (b) Kaufman, T. S.; Rúveda, E. A. The Quest for Quinine: Those Who Won the Battles and Those Who Won the War. *Angew. Chem., Int. Ed.* **2005**, *44*, 854–885.

[2] Wöhler, F. Ueber Künstliche Bildung Des Harnstoffs. *Ann. Phys. Chem.* **1828**, *88*, 253–256.

[3] (a) Rabe, P.; Ackerman, E.; Schneider, W. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 3655. (b) Rabe, P. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 62.

[4] Woodward, R. B.; Doering, W. E. THE TOTAL SYNTHESIS of QUININE1. *J.Am. Chem. Soc.* **1944**, *66*, 849–849.

[5] (a) Rabe, P.; Kindler, K. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 466. (b) Smith, Aaron C.; Williams, Robert M. Rabe Rest in Peace: Confirmation of the Rabe–Kindler Conversion Ofd-Quinotoxine into Quinine: Experimental Affirmation of the Woodward–Doering Formal Total Synthesis of Quinine. *Angew. Chem., Int. Ed.* **2008**, *47*, 1736–1740.

[6] Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. The First Stereoselective Total Synthesis of Quinine. *J. Am. Chem. Soc.* **2001**, *123*, 3239–3242.

[7] O' Donovan, D. H.; Aillard, P.; Berger, M.; de la Torre, A.; Petkova, D.; Knittl-Frank, C.; Geerdink, D.; Kaiser, M.; Maulide, N. C−H Activation Enables a Concise Total Synthesis of Quinine and Analogues with Enhanced Antimalarial Activity. *Ange. Chem., Int. Ed.* **2018**, *57* (33), 10737–10741.

[8] For other syntheses of quinine, see: (a) Uskokovic, M. R.; Gutzwiller, J.; Henderson, T. Total Synthesis of Quinine and Quinidine. I. *J. Am. Chem. Soc.* **1970**, *92*, 203–204. (b) Gutzwiller, J.; Uskokovic, M. Total Synthesis of Quinine and Quinidine. II. *J. Am. Chem. Soc.* **1970**, *92*, 204–205. (c) Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. Total Synthesis of Cinchona Alkaloids. 1. Synthesis of Meroquinene. *J. Am. Chem. Soc.* **1978**, *100*, 571–576. (d) Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. Total Synthesis of Cinchona Alkaloids. 1. Synthesis of Meroquinene. *J. Am. Chem. Soc.* **1978**, *100*, 571–576. (e) Gutzwiller, J.; Uskokovic, M. R. Total Synthesis of Cinchona Alkaloids. 2. Stereoselective Total Syntheses of Quinine and Quinidine. *J. Am. Chem. Soc.* **1978**, *100*, 576–581. (f) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. Catalytic Asymmetric Total Syntheses of Quinine and Quinidine. *J. Am. Chem. Soc.* **2003**, *126*, 706–707. (g) Igarashi, J.; Katsukawa, M.; Wang, Y.-G.; Acharya, H. P.; Kobayashi, Y. Stereocontrolled Synthesis of Quinine and Quinidine. *Tetrahedron Lett.* **2004**, *45*, 3783–3786. (h) Shiomi, S.; Misaka, R.; Kaneko, M.; Ishikawa, H. Enantioselective Total Synthesis of the Unnatural Enantiomer of Quinine. *Chem. Sci.* **2019**, *10*, 9433–9437.

[9] Wang, J.; Xu, C.; Wong, Y. K.; Li, Y.; Liao, F.; Jiang, T.; Tu, Y. Artemisinin, the Magic Drug Discovered from Traditional Chinese Medicine. *Engineering* **2019**, *5*, 32–39.

[10] World malaria report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

[11] Numonov, S.; Sharopov, F.; Salimov, A.; Sukhrobov, P.; Atolikshoeva, S.; Safarzoda, R.; Habasi, M.; Aisa, H. Assessment of Artemisinin Contents in Selected Artemisia Species from Tajikistan (Central Asia). *Medicines* **2019**, *6*, 23.

[12] Ro, D.-K.; Paradise, E. M.; Ouellet, M.; Fisher, K. J.; Newman, K. L.; Ndungu, J. M.; Ho, K. A.; Eachus, R. A.; Ham, T. S.; Kirby, J.; Chang, M. C. Y.; Withers, S. T.; Shiba, Y.; Sarpong, R.;

Keasling, J. D. Production of the Antimalarial Drug Precursor Artemisinic Acid in Engineered Yeast. *Nature* **2006**, *440*, 940–943.

[13] Dhainaut, J.; Dlubala, A.; Guevel, R.; Medard, A.; Oddon, G.; Raymond, N.; Turconi, J. Photochemical process for producing artemisinin. U.S. Pat. Appl. 2011/0065933, 2011.

[14] Liu, M.; Sun, W.; Shen, L.; He, Y.; Liu, J.; Wang, J.-P.; Hu, Z.; Zhang, Y. Bipolarolides A–G: Ophiobolin-Derived Sesterterpenes with Three New Carbon Skeletons from *Bipolaris* Sp. TJ403-B1. *Angew. Chem., Int. Ed.* **2019**, *58*, 12091–12095.

[15] For a recent review on the total syntheses of taxol, see: Min, L.; Han, J.-C.; Zhang, W.; Gu, C.-C.; Zou, Y.-P.; Li, C.-C. Strategies and Lessons Learned from Total Synthesis of Taxol. *Chem. Rev.* **2023**, *123*, 4934–4971.

[16] For a review on the total syntheses of vancomycin, see: (a) Okano, A.; Isley, N. A.; Boger, D. L. Total Syntheses of Vancomycin-Related Glycopeptide Antibiotics and Key Analogues. *Chem. Rev.* **2017**, *117*, 11952–11993. For a recent synthesis of vancomycin, see: (b) Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. Next-Generation Total Synthesis of Vancomycin. *J. Am. Chem. Soc.* **2020**, *142*, 16039–16050.

[17] Schneider, F.; Samarin, K.; Zanella, S.; Gaich, T. Total Synthesis of the Complex Taxane Diterpene Canataxpropellane. *Science* **2020**, *367*, 676–681.

[18] The total syntheses of waihoensene will be discussed in detail in chapter 2.

[19] For selected syntheses of ryanodol, see: (a) Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Saint-Laurent, L.; Saintonge, R.; Soucy, P.; Ruest, L.; Deslongchamps, P. Total Synthesis of Ryanodol. *Can. J. Chem.* **1979**, *57*, 3348–3354. (b) Nagatomo, M.; Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. Total Synthesis of Ryanodol. *J. Am. Chem. Soc.* **2014**, *136*, 5916–5919. (c) Chuang, K. V.; Xu, C.; Reisman, S. E. A 15-Step Synthesis of (+)-Ryanodol. *Science* **2016**, *353*, 912–915.

[20] He, C.; Chu, H.; Stratton, T. P.; Kossler, D.; Eberle, K. J.; Flood, D. T.; Baran, P. S. Total Synthesis of Tagetitoxin. *J. Am. Chem. Soc.* **2020**, *142*, 13683–13688.

[21] For selected syntheses of strictamine, see: (a) Ren, W.; Wang, Q.; Zhu, J. Total Synthesis of (±)-Strictamine. *Angew. Chem., Int. Ed.* **2016**, *55*, 3500–3503. (b) Nishiyama, D.; Ohara, A.; Chiba, H.; Kumagai, H.; Oishi, S.; Fujii, N.; Ohno, H. Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization. *Org. Lett.* **2016**, *18*, 1670–1673. (c) Eckermann, R.; Breunig, M.; Gaich, T. Formal Total Synthesis of (±)-Strictamine – the [2,3]-Stevens Rearrangement for Construction of Octahydro-2H-2,8-Methanoquinolizines. *Chem. Commun.* **2016**, *52*, 11363–11365. (d) Smith, M. W.; Zhou, Z.; Gao, A. X.; Shimbayashi, T.; Snyder, S. A. A 7-Step Formal Asymmetric Total Synthesis of Strictamine via an Asymmetric Propargylation and Metal-Mediated Cyclization. *Org. Lett.* **2017**, *19*, 1004–1007. (e) Picazo, E.; Morrill, L. A.; Susick, R. B.; Moreno, J.; Smith, J. M.; Garg, N. K. Enantioselective Total Syntheses of Methanoquinolizidine-Containing Akuammiline Alkaloids and Related Studies *J. Am. Chem. Soc.* **2018**, *140*, 6483–6492. (f) Takayama, H.; Sato, K.; Takanashi, N.; Kogure, N.; Kitajima, M. Formal Total Synthesis of (±)-Strictamine. *Heterocycles* **2018**, *97*, 365. (g) Li, W.; Chen, Z.; Yu, D.; Peng, X.; Wen, G.; Wang, S.; Xue, F.; Liu, X.; Qin, Y. Asymmetric Total Syntheses of the Akuammiline Alkaloids (−)-Strictamine and (−)-Rhazinoline. *Angew. Chem., Int. Ed.* **2019**, *58*, 6059–6063. (h) Gao, B.; Yao, F.; Zhang, Z.; Ding, H. Total Synthesis of (+)-Alsmaphorazine c and Formal Synthesis of (+)-Strictamine: A Photo-Fries Approach. *Angew. Chem., Int. Ed.* **2021**, *60*, 10603–10607.

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[22] For a review on the history of palladium-catalyzed cross-coupling reaction, see: Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.

[23] For a critical discussion of C-H functionalization logic from the view of total synthesis, see: (a) Gutekunst, W. R.; Baran, P. S. C-H Functionalization Logic in Total Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976. For a recent review of the application of C-H functionalization in total synthesis, see: (b) Abrams, D. J.; Provencher, P. A.; Sorensen, E. J. Recent Applications of C–H Functionalization in Complex Natural Product Synthesis *Chem. Soc. Rev.* **2018**, *47*, 8925–8967.

[24] For a review of the application of photoredox catalysis in total synthesis, see: Pitre, S. P.; Overman, L. E. Strategic Use of Visible-Light Photoredox Catalysis in Natural Product Synthesis. *Chem. Rev.* **2021**, *122*, 1717–1751.

[25] For a review of the application of electrocatalysis in total synthesis, see: Munda, M.; Niyogi, S.; Shaw, K.; Kundu, S.; Nandi, R.; Bisai, A. Electrocatalysis as a Key Strategy for the Total Synthesis of Natural Products. *Org. Biomol. Chem.* **2022**, *20*, 727–748.

[26] Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **2000**, *287*, 1964–1969.

[27] Hirata, Y.; Uemura, D. Halichondrins - Antitumor Polyether Macrolides from a Marine Sponge. *Pure&Appl. Chem.* **1986**, *58*, 701–710.

[28] Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. Total Synthesis of Halichondrin B and Norhalichondrin B. *J. Am. Chem. Soc.* **1992**, *114* (8), 3162–3164.

[29] (a) Seletsky, B. M.; Wang, Y.; Hawkins, L. D.; Palme, M. H.; Habgood, G. J.; DiPietro, L. V.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. Structurally Simplified Macrolactone Analogues of Halichondrin B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5547–5550. (b) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. J. Macrocyclic Ketone Analogues of Halichondrin B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551–5554.

[30] Austad, B. C.; Calkins, T. L.; Chase, C. L.; Fang, F. G.; Horstmann, T.; Hu, Y.; Lewis, B.; Niu, X.; Noland, T. L.; Orr, J.; Schnaderbeck, M. J.; Zhang, H.; Asakawa, N.; Asai, N.; Chiba, H.; Hasebe, T.; Hoshino, Y.; Ishizuka, H.; Takashi Kajima; Akio Kayano. Commercial Manufacture of Halaven®: Chemoselective Transformations En Route to Structurally Complex Macrocyclic Ketones. *Synlett* **2013**, *24*, 333–337.

[31] Mercer, J. A. M.; Cohen, C. M.; Shuken, S. R.; Wagner, A. M.; Smith, M. W.; Moss, F. R.; Smith, M. D.; Vahala, R.; Gonzalez-Martinez, A.; Boxer, S. G.; Burns, N. Z. Chemical Synthesis and Self-Assembly of a Ladderane Phospholipid. *J. Am. Chem. Soc.* **2016**, *138*, 15845–15848.

[32] Chen, Z.; Jaron; Zhu, X.; Joseph; Pfattner, R.; Cegelski, L.; Martínez, T. J.; Burns, N. Z.; Xia, Y. Mechanochemical Unzipping of Insulating Polyladderene to Semiconducting Polyacetylene. *Science* **2017**, *357*, 475–479.

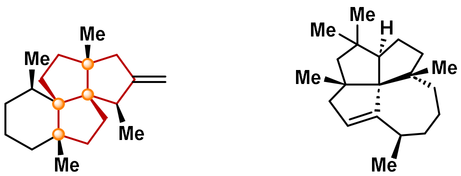
Chapter 2 A Concise Total Synthesis of (+)-Waihoensene Guided by Quaternary Center Analysis

2.1 Introduction

2.1.1 Natural Products with Contiguous All-carbon Quaternary Stereocenters

All-carbon quaternary stereocenters are carbon-centered stereocenters in organic molecules that have four carbon substitutions. While they are not traditionally viewed as functional groups, they have a great impact on a molecule's conformation, properties, and reactivities[1]. One of the most dramatic effects is that a quaternary center brings strong steric hindrance to itself and the carbons next to it. For example, an S_N2 reaction is hardly possible on a quaternary carbon for forming an all-carbon quaternary center. And they are extremely hard on carbons with quaternary centers next to them. Because of this, when attempting to synthesize systems with contiguous quaternary centers, many reactions in our chemistry toolbox are incapacitated. It is made even more challenging when controlling the stereochemistry of such centers. At the same time, the high degree of substitution in such systems brings more complexity to the structures. Despite the challenges, synthetic chemists have been trying to synthesize such molecules with their creativities for decades.

2.1.2 Waihoensene



1
Waihoensene

2
Laurenene

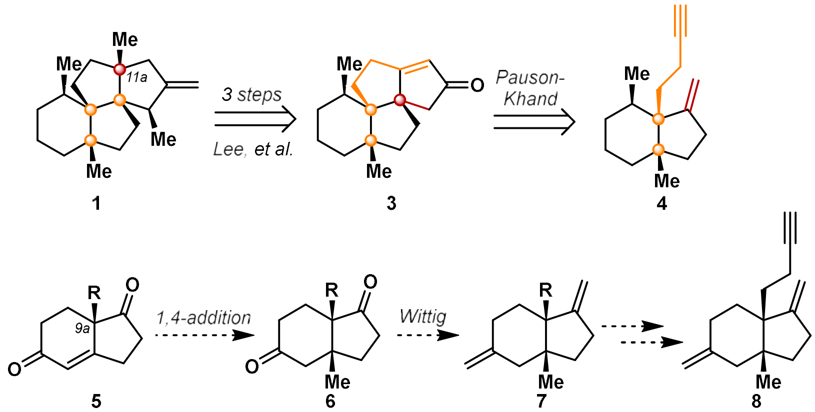
Figure 2.1. The structures of waihoensene and laurenene.

As one of the very few examples of natural products with 4 or more contiguous all-carbon quaternary stereocenters, the tetracyclic diterpene waihoensene (**1**) has been viewed by synthetic chemists as a unique challenge. In addition to the contiguous quaternary centers, the angular tetracyclic framework also adds strain and congestion to the molecule[2]. The absence of any traditional reactive functional groups other than an alkene also makes the synthesis of the molecule even more challenging. Biologically, it was isolated from *Podocarpus totara var. waihoensis*[3], which contains a high level of laurenene and was hypothesized to be an acid-mediated rearrangement product from Laurenene (**2**)[4]. From the isolation of waihoensene in 1997 by the Weavers group to early 2020 when we completed the synthetic studies, only one racemic total synthesis and two model studies had been reported. The Moore group first synthesized the framework of waihoensene utilizing an intramolecular aldol reaction in 1999, with no further attempts reported towards the natural product[5]. The first total synthesis was reported by the Lee group in 2017, in which a tandem cycloaddition strategy developed previously by their group was applied to give **(±)-1** in 23 steps[6]. In 2020, a model study was reported by the Tu group[7]. By designing a tandem Castro–Stephens coupling/acyloxy shift/cyclization/semipinacol rearrangement sequence, they accessed the tetracyclic framework of **1**.

As one of our group's long-lasting interests, we synthesized various terpene natural products with multiple quaternary centers[8]. We are determined to take the challenge of developing a concise and enantioselective route toward this unique natural product. In our early studies, we focused on forming the tetracyclic framework in a concise and elegant fashion. Two approaches were attempted based on the symmetry of the tetracyclic framework[9]. However, it was later proven that the formation of contiguous quaternary centers in the molecule was very challenging at a late stage.

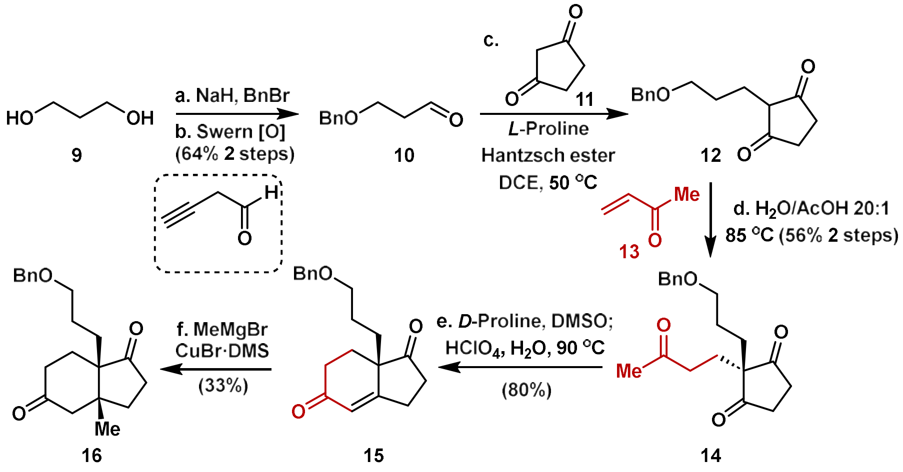
2.2 A Key Disconnection Based on Pauson-Khand Reaction

2.2.1 Retro-Synthetic Analysis and A Quick Model Study



Scheme 2.1. Retro-Synthetic Analysis of waihoensene (**1**), and a proposed model study from Hajos-Parrish-ketone-like structure **5**.

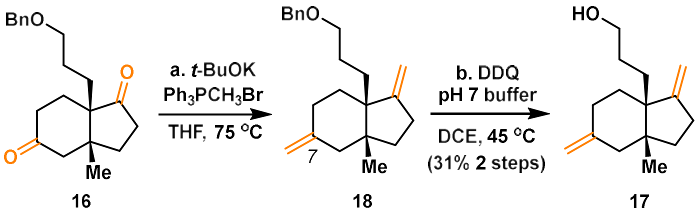
Given the challenges discussed above, we decided to reconsider the synthetic strategy by treating the contiguous quaternary centers as key structural elements. We were hoping to: 1) use a reliable disconnection for each step of forming one of the quaternary centers; 2) start from forming one quaternary center asymmetrically, and use that quaternary center to guide the stereochemistry of the rest of the molecule. Retrosynthetically, we realized the Lee group's approach for forming the C-11a quaternary center was a good starting point, leading back to **3** with a cyclopentenone structure. We immediately identified that the unique framework of **3** could come from a Pauson-Khand reaction[10], which is a powerful reaction for forming quaternary centers. We then identified that bicyclic **4** could derive from a Hajos-Parrish-ketone[11]-like structure **5**. Overall, in this disconnection, we start by constructing the C-9a quaternary center asymmetrically, and all the reactions forming the rest of the quaternary centers should have good stereochemistry control.



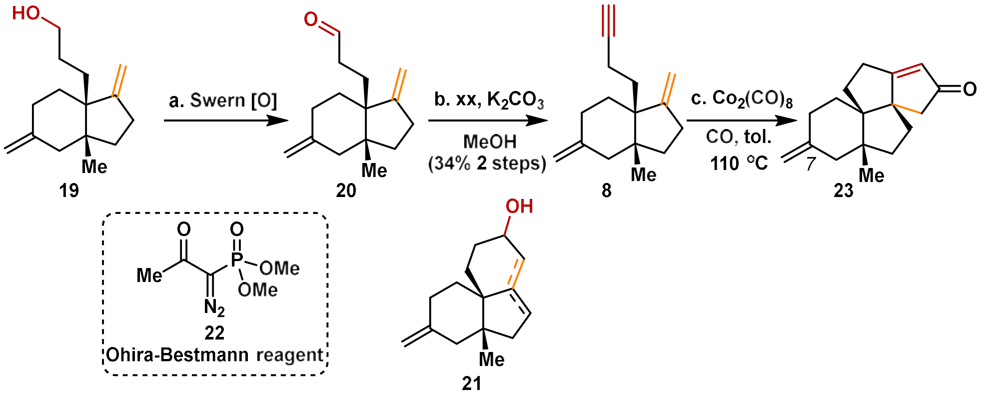
Scheme 2.2. The synthesis of diketone **16**. (a) NaH (1.02 equiv), 1,3 propanediol (1.00 equiv), THF, 0 ºC, 1 h; then TBAI (0.10 equiv), BnBr (1.03 equiv), warm to 23 ºC, 7 h, 87%. (b) Oxalyl chloride (2.0 equiv), DMSO (10 equiv), CH_2Cl_2, -78 ºC, 30 min; then reactant, 30 min; then Et_3N (10 equiv), warm to 23 ºC, 73%. (c) 1,3-cyclopenatanedione (1.0 equiv), Hantzsch ester (1.2 equiv), *L*-proline (0.5 equiv), 50 ºC, 12 h. (d) Methyl vinyl ketone (2.2 equiv), H_2O/AcOH 20/1, 85 ºC, 8 h, 56% over 2 steps. (e) *D*-proline (0.30 equiv), DMSO, 23 ºC, 12 h; then 1 M $HClO_4$ (2.0 equiv), 90 ºC, 1 h, 80%. (f) CuBr·DMS (2.5 equiv), MeMgBr (5.0 equiv), THF, -40 ºC, 30 min; then reactant, 30 min, 33%, unoptimized.

To test the reliability of the key Pauson-Khand reaction, we conducted a model study to answer this question quickly. A reductive condensation reaction[12] between 1,3-cyclopentandione (**11**) and aldehyde **10** yielded **12**. After a Robinson annulation reaction with methyl vinyl ketone (**13**), the Hajos-Parrish-ketone-like compound **15** was quickly obtained. Then a cuprate 1,4-addition was applied to give the *cis*-6/5 fused diketone **16** with vicinal quaternary centers.

We then omitted the substitutional pattern of the six-membered ring and moved on with a double methylenation reaction giving **17**. Noteworthy that a methylenation reaction on a ketone next to a quaternary center is not easy under standard conditions. Standard Wittig condition using strong lithium bases at low temperatures, Tebbe reagent at 50 ºC, and the condition shown on scheme 3 except at 40 ºC all gave methylenation only at C-7; while the Mg-$TiCl_4$ mediated methylenation condition with dichloromethane[13] lead to decomposition. Then the benzyl group was deprotected under an oxidative condition[14] to avoid hydrogenation of the alkenes. Noteworthy that our initial design chose PMB as the protecting group, but the low acid stability of the PMB group posed challenges in the Robinson annulation steps.



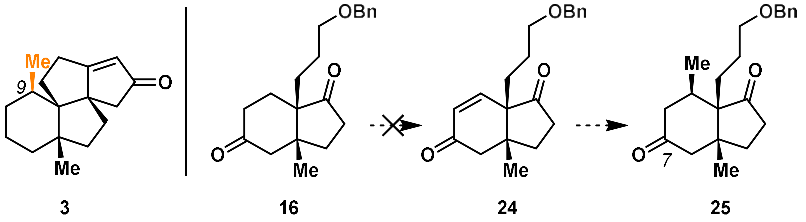
Scheme 2.3. The synthesis of alcohol **17**. (a) *t*-BuOK (11 equiv), Ph_3PCH_3Br (10 equiv), THF, 70 °C, 30 min; then **16**, 18 h. (b) DDQ (4.0 equiv), pH 7 phosphate buffer, DCE, 45 °C, 12 h, 31% over 2 steps, unoptimized.



Scheme 2.4. The completion of the model study. (a) Oxalyl chloride (1.5 equiv), DMSO (5 equiv), CH_2Cl_2, -78 °C, 30 min; then reactant, 30 min; then Et_3N (10 equiv), warm to 23 °C. (b) **22** (1.9 equiv), K_2CO_3 (3.1 equiv), MeOH, 23 °C, 12 h, 34% over 2 steps, unoptimized. (c) $Co_2(CO)_8$ (1.5 equiv), toluene, 23 °C, 30 min; then CO, 110 °C, 16 h, yield not determined, unoptimized.

Functional group manipulations were then carried out on the side chain. Swern oxidation[15] was chosen because aldehyde **20** was found to be unstable under acidic conditions, possibly through a Prins cyclization reaction to give a tentatively assigned structure **21**. A Seyferth–Gilbert homologation with the Ohira-Bestmann reagent[16] was applied to synthesize enyne **8**. We then treated **8** with a variety of Pauson-Khand conditions and found the standard condition of forming the alkyne complex with $Co_2(CO)_8$, followed by thermolysis was the most successful. Although the yield of the reaction was not determined due to scale, we were able to confirm the formation of the tetracyclic enone **23**. The addition of NMO[17] resulted in the decomposition of the alkyne-cobalt complex even at room temperature. Catalytic conditions with $[Rh(CO)Cl_2]_2$[18] also resulted in decomposition.

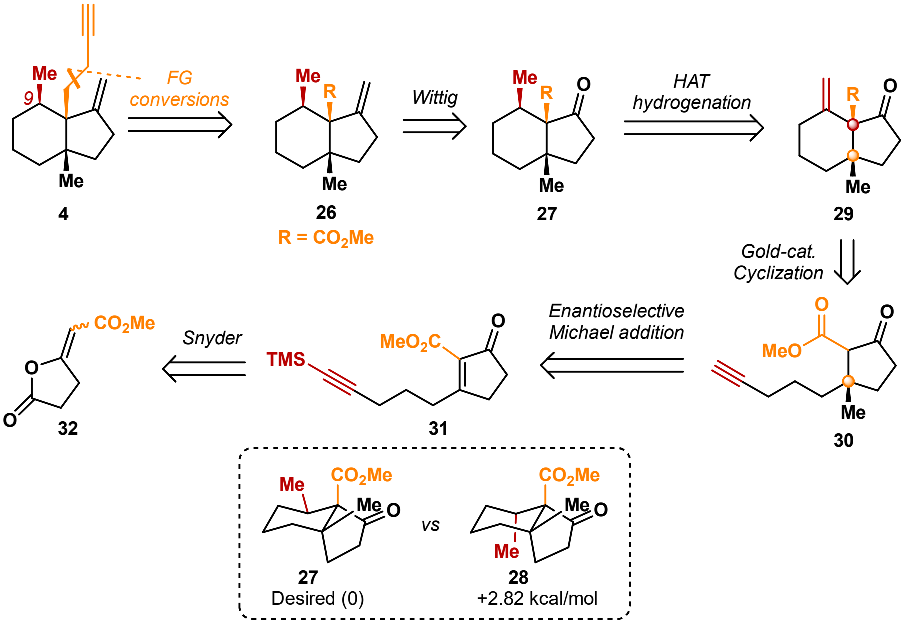
2.2.2 Challenges in Translating the Model System into the Real System



Scheme 2.5. Challenges in Translating the Model System into the Real System.

With the success of the Pauson-Khand reaction in the model system, we then moved on to translate the model system into the real system. We identified that the most suitable stage for this was on **16**, which we envisioned to oxidize to enone **24**, followed by a cuprate 1,4-addition to install the C-9 methyl group. Then the C-7 carbonyl group was envisioned to be fully reduced. However, it was found that the selective oxidation of **16** was hard to realize, partly due to the unsuccessfulness of the regioselective enolate formation on the six-membered ring. Plus, it will take at least 2 steps to fully reduce the C-7 carbonyl group to give the desired substitutional patterns in **3**. At this stage, we realized that a more elegant route was needed.

2.3 A Strategic Retrosynthetic Analysis Based on Quaternary Center Analysis

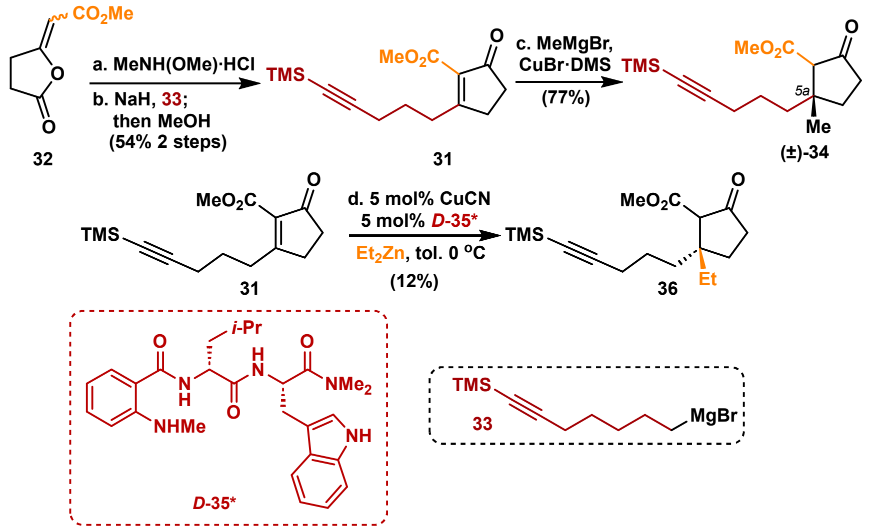


Scheme 6. A revised retrosynthetic analysis based on quaternary center analysis.

Upon reassessing the challenges and opportunities lying in the structure of **4**, we realized that the introduction of the C-9 methyl group is the most challenging part of synthesizing it. This is due to the combination of the lack of functionalities on the six-membered ring and the difficulty in controlling the stereochemistry at C-9. However, at the same time, the unfunctionalized six-membered ring was also an opportunity for introducing the ring in a more modular way, thanks to its compatibility with more reaction conditions. We revised our retrosynthetic analysis by adding these factors to our original quaternary center analysis logic. It was envisioned that the alkyne-bearing side chain could be derivatized from an ester group, through similar functional group conversions applied in the model study, tracing back to **26**. The methylene group was, again, envisioned to be synthesized from a ketone by a Wittig reaction. On **27**, we identified that the C-9 methyl group could be accessed from a methylene group by a hydrogen atom transfer (HAT) hydrogenation reaction[19], which is known to give the thermodynamically favored product. Based on the conformational analysis, in the desired isomer, **27**, the C-9 methyl group lies on the equatorial position, indicating that the desired isomer is the thermodynamically more stable isomer. To further support this discussion, we conducted a computational study, showing that **28** is 2.82 kcal/mol less stable than **27**[20]. Then, a gold-catalyzed cyclization reaction[21] was envisioned to be used for forming the second quaternary center of **29**. The reaction is known to prefer the desired cis-bicyclic product. Finally, the first quaternary center of the molecule was planned to be synthesized by an enantioselective 1,4-addition reaction[22], leading to tetrasubstituted enone **31**, which could be synthesized by a method reported by our group[23].

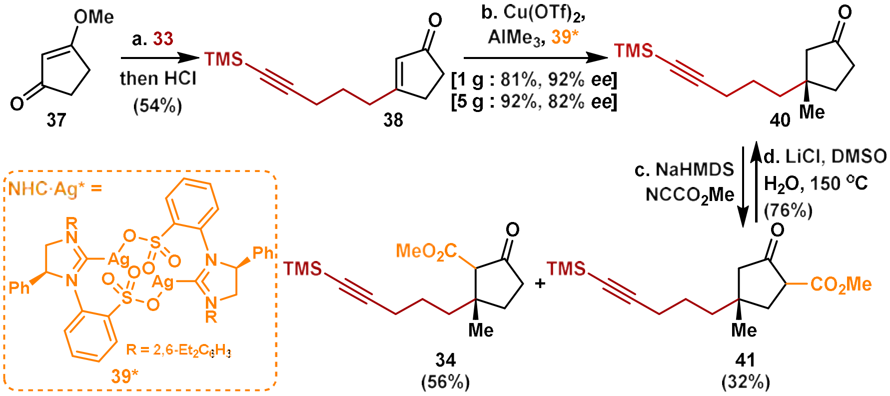
2.4 The Total Synthesis of Waihoensene

2.4.1 The Construction of the C-5a Quaternary Center by 1,4-Addition Reaction



Scheme 2.7. The synthesis of **(±)-34** and failure to convert the route asymmetric. (a) MeNHOMe·HCl (1.3 equiv), pyridine (5.0 equiv), CH_2Cl_2, 23 °C, 6 h; (b) NaH (1.3 equiv), THF, 0 °C, 30 min; then **32** (1.3 equiv), -78 to 0 °C, 1 h; then MeOH, 50 °C, 1 h, 54% over 2 steps. (c) CuBr·Me_2S (1.2 equiv), MeMgBr (2.4 equiv), THF, -40 °C, 30 min; then reactant, 2 h, 77%. (d) see ref.22.

In the forward synthesis, we started by applying our method to synthesize **32** on a 100-grams scale. Then the enol lactone ring was opened to form a Weinreb amide, which upon deprotonation, was treated by Grignard reagent **33**. After quenching the bases with methanol, a Knoevenagel condensation reaction occurred *in situ* to form cyclopentenone **31**. A racemic 1,4-addition by cuprate reagent smoothly occurred to form the C-5a quaternary center. However, significant challenges were met when trying to convert the 1,4-addition asymmetric. Although an enantioselective 1,4-addition condition on such tetrasubstituted enone has been reported by the Hoveyda group[Ref.22], we found that the condition was very sensitive and hard in operation. We successfully synthesized the required ligand ***D*-35** from unnatural amino acids. However, in all the attempts we made, only an ethyl addition product **36** was obtained in a very low yield. Any attempts with the more sensitive dimethylzinc reagent were unsuccessful. Plus, the involvement of a carbon-carbon triple bond functionality is not desirable for copper-catalyzed reactions.

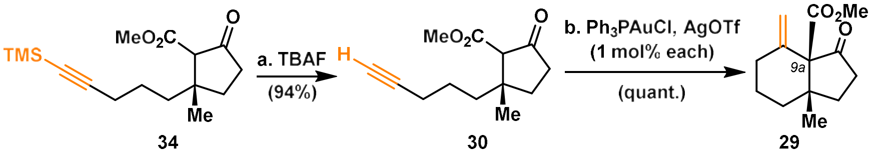


Scheme 2.8. The asymmetric synthesis of **34**. (a) (5- bromo-1-pentynyl)trimethylsilane (1.0 equiv), Mg (2.0 equiv), I_2 (trace), THF, reflux, 4 h; **37**, 0 to 23 °C, 10 h; 1 M HCl, 54%. (b) **39** (3.75 mol %), $Cu(OTf)_2$ (7.5 mol %), THF, 23 °C, 10 min, then $AlMe_3$ (3.0 equiv), 15, -78 °C, 12 h, 1 g scale: 81%, 92% *ee*; 5 g scale: 92%, 82% *ee*. (c) NaHMDS (2.3 equiv), THF, 0 °C, 2 h, then Mander's reagent (1.6 equiv), -78 °C, 3 h, 32% **41**; 56% **34** (d) LiCl (2 equiv), H_2O (5 equiv), DMSO, 150 °C, 3 h, 76%.

A different approach was then found to be successful with a little detour. Inspired by our synthesis of conidigenone[Ref.8c], an asymmetric 1,4-addition on trisubstituted enone **38** catalyzed by chiral NHC-silver ligand **39**, which method was also reported by the Hoveyda group[24], was proven to be successful. The reaction works fine on scale, slightly dropping the enantiomeric excess value.

From here, deprotonation with NaHMDS preferentially occurred on the seemingly more hindered side of the cyclopentanone. After the subsequent trapping with Mander's reagent, a 1.8:1 mixture of **34** and **41** was obtained in 88% combined yield. Extensive screenings revealed that no other conditions were superior in terms of the numerical yield of **34**, albeit LiHMDS showed a higher regioselectivity. We attribute the potential regioselectivity observed for all bases to be due to a weak directing effect from the alkyne.[25] Finally, the undesired regioisomer (**41**) could be recycled to **40** through a Krapcho decarboxylation reaction.[26]

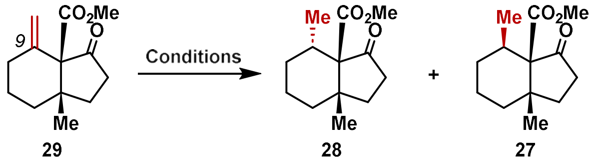
2.4.2 The Construction of the C-9a Quaternary Center by Gold-Catalyzed Cyclization



Scheme 2.9. The gold-catalyzed cyclization reaction leading to **29**. (a) TBAF (1.6 equiv), THF, 0 to 23 °C, 2 h, 94%. (b) Ph_3PAuCl (0.96 mol %), AgOTf (0.96 mol %), CH_2Cl_2, 23 °C, 4 h, quantitative.

The TMS protecting group on **34** was smoothly removed by TBAF. Then the cyclization reaction from the alkyne **30** proceeded quantitatively with only 1 mol% each of Ph_3PAuCl and AgOTf to afford the desired bicyclic ketone **29**. Critically, this reaction proved to be highly reliable even on gram scalable. To our knowledge, this gold-catalyzed cyclization reaction was the first leading to the formation of a six-membered ring containing two vicinal quaternary carbons starting from a five-membered ring precursor, which made us realize that the gold-catalyzed cyclization reaction was an extremely powerful, yet underestimated tool for the formation of quaternary centers, especially for contiguous ones.

2.4.3 The Synthesis of Enyne 4



Entry	Condition	**28***	**27***	**28 : 27**
1	Mn(dpm)$_3$, TBHP, PhSiH$_3$, *i*-PrOH	19%	47% [a]	1 : 2.5
2	Mn(dpm)$_3$, TBHP, Ph(i-PrO)SiH$_2$, *i*-PrOH	trace	56% [a]	-
3	Mn(dpm)$_3$, TBHP, Ph(i-PrO)SiH$_2$, hexanes	10%	39% [a]	1 : 3.9
4	H$_2$, Pd/C, EtOH	8%	20%	1 : 2.5
5	H$_2$, PtO$_2$, DCM	24%	76%	1 : 3.2
6	H$_2$, Wilkinson's catalyst, benzene	15%	48% [b]	1 : 3.2
7	H$_2$, Crabtree's catalyst, DCM	65%	11%	5.9 : 1

Table 2.1. Screening of conditions for the facial selective reduction of **29**.

* Isolated yields, reaction ran at 20-50 mg scales

[a] Unidentified by-product is observed and hard to separate from the product

[b] As an inseparable mixture with starting material

With the success of the gold-catalyzed cyclization reaction, we then moved on to the facial selective hydrogenation reaction to set the C-9 stereochemistry. As we have discussed before, we were hoping to use the HAT hydrogenation conditions to make the thermodynamically more stable product. Indeed, under these conditions (entry 1-3), one of the isomers is preferentially formed. However, the reaction overall gave quite a complex mixture, and we were not able to purify the main product in the reaction to confirm its structure. To obtain a cleaner sample of the product, we attempted some traditional heterogeneous catalyzed hydrogenation conditions (entries 4-5). Surprisingly, under these conditions, the same isomer was preferred. Fortunately, we were able to purify the major product and obtained a single crystal structure from it, which turned out to be the desired isomer **27**. We attribute the unexpected selectivity to two factors: 1) the ester group is blocking the alkene from the *convex* face; 2) the closest carbon on the five-membered ring to the alkene is sp^2 hybridized, meaning that it is planar and have no atoms to block the alkene from the *concave* face. Finally, we also attempted two homogeneous hydrogenation conditions (entries 6-7) and found that with the catalysis of Crabtree's catalyst, the selectivity was reversed, possibly due to the directing effect from the ester group[27]. As such, these results could provide guidance on stereo-divergent applications of such intermediates for the synthesis of other molecules.

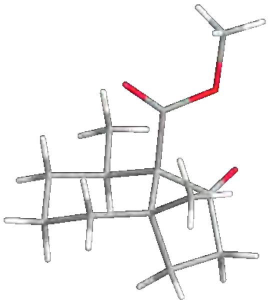
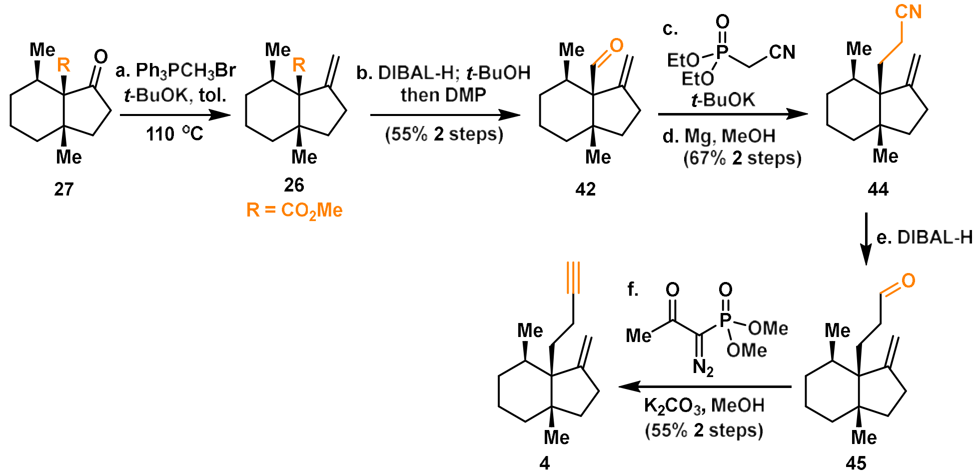


Figure 2.2. The X-Ray structure of **27**.

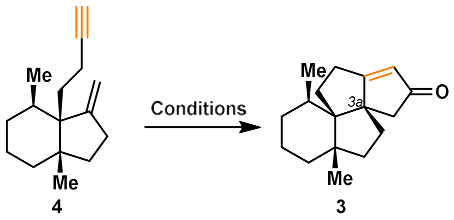
Following the hydrogenation reaction, we made multiple attempts to construct the enyne functionalities required for the Pauson-Khand reaction. While more results will be discussed in a later section (2.4.6), herein is the successful approach. First off, a Wittig reaction with a similar condition that we used for the model system gave the alkene moieties in **18**. Then the ester was reduced to the primary alcohol by DIBAL-H, the reaction was quenched with *t*-BuOH and DMP was added in situ to oxidize the product to aldehyde **42**. A Horner-Wadsworth-Emmons reaction[28] was then applied to extend the side chain, giving a 1.7:1 *cis*:*trans* mixture of unsaturated nitriles, which was both reduced under a single electron transfer (SET) based condition to give saturated nitrile **44**[29]. Then the nitrile was reduced by DIBAL-H to aldehyde **45**, which was not stable on silica, but without purification was converted to **4**.



Scheme 2.10. Functional group manipulations leading to enyne **4**. (a) *t*-BuOK (9.0 equiv), Ph_3PCH_3Br (10.0 equiv), toluene, reflux, 1 h, then **27**, 12 h. (b) DIBAL-H (2.0 equiv), CH_2Cl_2, -78 °C, 1 h, then *t*-BuOH (30 equiv), $NaHCO_3$ (10.0 equiv), Dess-Martin periodinane (8.0 equiv), 23 °C, 1 h, 55% over 2 steps. (c) diethyl cyanomethylphosphonate (4.6 equiv), *t*-BuOK (5.0 equiv), THF, 23 °C, 1 h, then **42**, reflux, 18 h, 93%, *cis* : *trans* = 1.7 : 1. (d) Mg (30 equiv), MeOH (0.02 M), 0 to 23 °C, 3 h, 72%. (e) DIBAL-H (1.8 equiv), CH_2Cl_2, 0 °C, 1 h. (f) **22** (1.5 equiv), K_2CO_3 (2.5 equiv), MeOH, 30 °C, 12 h, 55% over 2 steps.

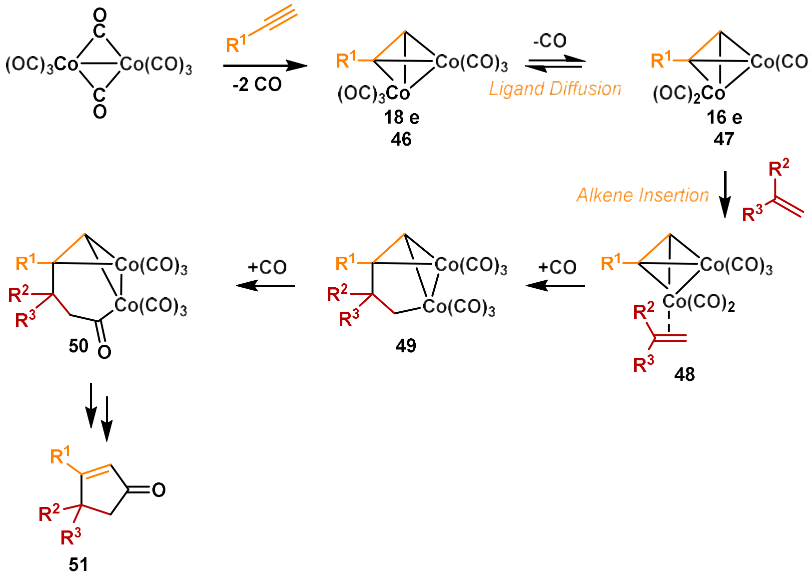
2.4.4 The Construction of the C-3a Quaternary Center by Pauson-Khand Reaction

Despite the similarity between **4** and model compound **8**, the compounds behave differently under Pauson-Khand reactions. This is possibly due to the additional hindrance brought by the C-9 methyl group to the reaction centers. Given the success of the standard condition that involves the formation of a cobalt-alkyne complex followed by its thermolysis, we started our screenings accordingly. With the thermolysis step at 110 °C, we did observe the formation of product **3**, which we matched the NMR to the same intermediate from the Lee group's synthesis. However, the yield was very inconsistent and dropped drastically at scale. We hypothesized that this is due to the slow heating at a large scale, so we increased the thermolysis temperature to 170 °C and switched the solvent to mesitylene. The yield was still somewhat inconsistent, but the lowest yield was increased to 50%, which made the reaction more reliable in terms of material throughput. Some other conditions involving the addition of additives did not prove fruitful. We hypothesized that given the extreme hindrance near the reaction center, the alkene insertion step of the transformation was likely to be the rate-determining step. While most of the additives serve to accelerate the ligand-diffusion step in the mechanism[30] (see scheme 11), which is traditionally believed to be the rate-determining step of the transformation, they are not able to help the formation of the C-3a quaternary center.



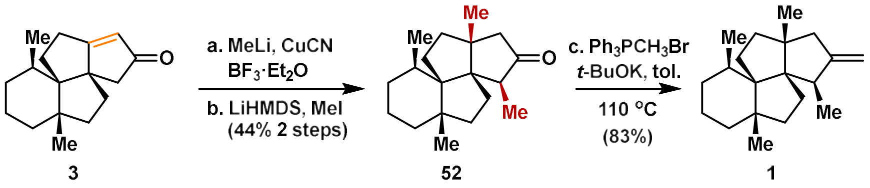
Entry	Condition	Result
1	$Co_2(CO)_8$, toluene, CO, 110 °C	20-50% + unknown complex
2	$Co_2(CO)_8$, mesitylene; CO, 170 °C	50-84%
3	$Co_2(CO)_8$, DCE; $CyNH_2$, 80 °C, 1 h	Decomposed
4	$Co_2(CO)_8$, DCM; NMO, 40 °C, 12 h	N.R. (Co complex)
5	$Co_2(CO)_8$, DCE; NMO, 40-75 °C in 1 h	Decomposed

Table 2.2. Screening of conditions for the Pauson-Khand reaction of **4**.



Scheme 2.11. The mechanism of the Pauson-Khand reaction.

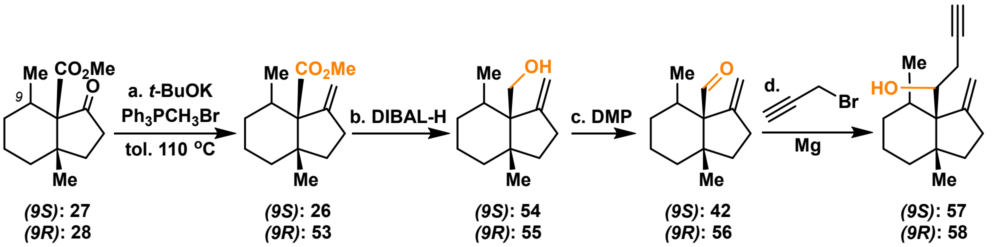
2.4.5 End Game



Scheme 2.12. The completion of the synthesis of **1**. (a) CuCN (3.0 equiv), MeLi (6.0 equiv), THF, -78 to 23 ºC, 10 min, then BF3·Et2O (2.4 equiv), then **3**, -78 to -55 ºC, 2 h, 54%. (b) LiHMDS (2.0 equiv), THF, 0 °C, 2 h, then MeI (5.0 equiv), 0 to 23 ºC, 12 h, 81%. (o) *t*-BuOK (9.0 equiv), Ph_3PCH_3Br (10.0 equiv), toluene, reflux, 1 h, then **52**, 1 h, 83%.

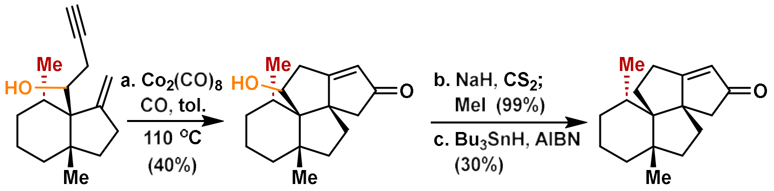
Finally, the last 3 steps from Lee's synthesis were replicated and optimized to yield **1**. The sequence started from a 1,4-addition reaction involving higher-order cuprate[31], followed by regio-selective deprotonation and methylation, giving **52**. While the Lee group chose to use the Petasis reagent[32] for the challenging methylenation reaction to complete the synthesis, we found that the Wittig condition we applied earlier in the synthesis could give a better yield of **1**. After silica column chromatography, the natural product was obtained with a decent yield. For better analytical results, we further purified the sample with C18 reverse phase preparative thin layer chromatography (PTLC).

2.4.6 Other Attempts Failed to Yield the Natural Products



Scheme 2.13. The synthesis of enyne **57** and **58** by 1,2-addition with allenylmagnesium bromide. (a) *t*-BuOK (9.0 equiv), Ph_3PCH_3Br (10.0 equiv), toluene, reflux, 1 h, then reactant, 1 h. (b) DIBAL-H (2.0 equiv), CH_2Cl_2, -78 ºC, 1 h, **54**: 67% over 2 steps; **55**: 64% over 2 steps. (c) $NaHCO_3$ (10 equiv), Dess-Martin periodinane (2 equiv), CH_2Cl_2, 0 to 23 °C, 2 h, **42** and **56**: 94%. (d) Allenylmagnesium bromide (1.5 equiv), THF, 0 ºC, 10 min, **57**: 98%; **58**: quantitative.

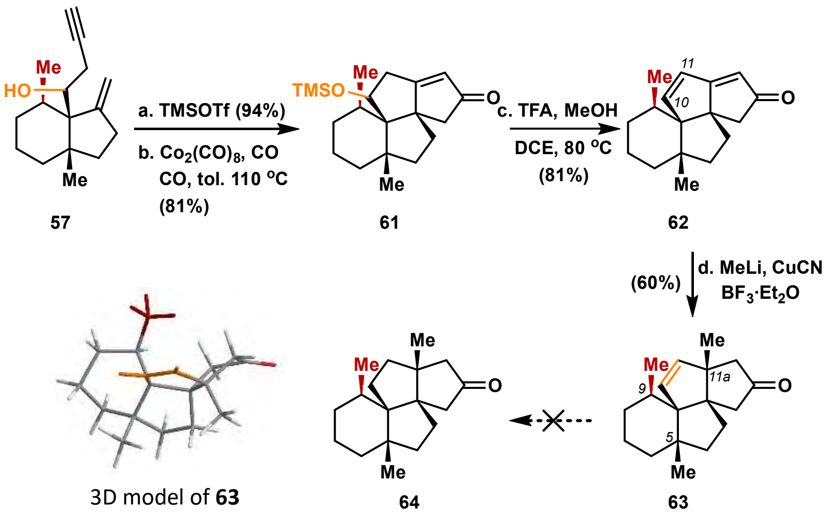
Before we succeeded with the route described in 2.4.3, we attempted several other ways to synthesize the enyne functionalities required for the Pauson-Khand reaction. One of the most intuitive ways was to functionalize aldehyde **42** directly with allenylmegnesium bromide. Notable, by the time we attempted this approach, we have not confirmed the structures of the hydrogenation products, thus we subjected each **27** and **28** to the same sequence, and synthesized both **57** and **58**, each as a single diastereomer with the stereochemistry of the secondary alcohol unconfirmed. Surprisingly, these isomers behave very differently in the following steps.



58 59 60

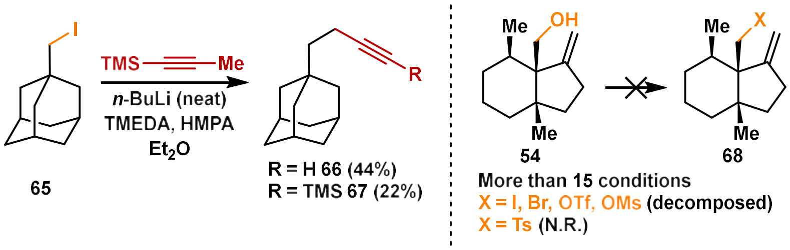
Scheme 2.14. The synthesis of tetracyclic enone **60**. (a) $Co_2(CO)_8$ (1.2 equiv), toluene, 23 °C, 30 min; then CO, 110 °C, 16 h, 40%, unoptimized. (b) CS_2 (20 equiv), NaH (5 equiv), THF, 1.5 h; then MeI (25 equiv), 10 min, 99%. (c) Bu_3SnH (2.0 equiv), AIBN (10 mol%), toluene, 80 °C, 6 h, 30%, unoptimized.

With **58**, which has the undesired configuration at C-9, the Pauson-Khand reaction successfully gave the tetracyclic product **59**. Then, the secondary hydroxyl group was removed smoothly by Barton's deoxygenation sequence[33]. We compared the NMR of **60** to that of ref.6 and found that they did not match, which gave us a clue that **28** was the desired isomer after the hydrogenation reaction.



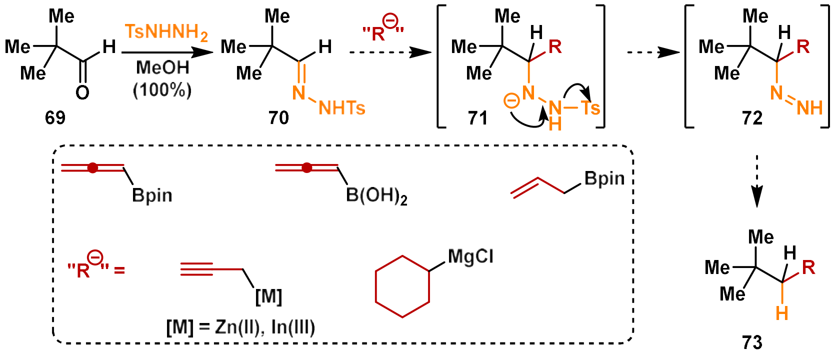
Scheme 2.15. The synthesis of alkene **63**, and the failure of its conversion to **64**. (a) 2,6-lutidine (10 equiv), TMSOTf (5.0 equiv), CH_2Cl_2, 0 °C, 1 h, 94%. (b) $Co_2(CO)_8$ (1.2 equiv), toluene, 23 °C, 30 min; then CO, 110 °C, 16 h, 81%, unoptimized. (c) DCE:MeOH:TFA = 100:5:6, 80 °C, 16 h, 81%, unoptimized. (d) CuCN (3.0 equiv), MeLi (6.0 equiv), THF, -78 to 23 °C, 10 min, then BF3·Et2O (2.4 equiv), then **62**, -78 to -55 °C, 2 h, 60%, unoptimized.

When we tried to repeat the same sequence on **57**, we found that the Pauson-Khand reaction no longer works with the free hydroxyl group. This result, in addition to the different reactivity of **4** and **8** as we described before, indicates that the C-9 methyl group may influence the conformation of the substrates, and may impact the Pauson-Khand reaction. Barton's deoxygenation sequence on **57** was unsuccessful, giving a complex mixture of products. Delightfully, we found that with the secondary alcohol protected with a TMS group, the Pauson-Khand reaction worked with high yield. A potential explanation for the success of the reaction may be the steric repulsion between the silyl group and the C-9 methyl group forced the substrate into a more favorable conformation for the Pauson-Khand reaction, although we think further experiments are needed for a better understanding of the step. We attempted to deprotect **61** and repeat Barton's deoxygenation sequence. However, any attempts to synthesize the xanthate proved unfruitful due to the steric hindrance around the secondary alcohol. Upon heating with trifluoracetic acid, the silyl ether in **61** was eliminated into diene **62**. We were unsuccessful in selectively reducing the C10-C11 double bond at this stage. However, the 1,4-addition condition with a higher-order cuprate was able to selectively attack the C-11a position, giving **63**. Surprisingly, a seemingly easy hydrogenation reaction that could lead to **64** was unsuccessful. We attempted multiple homogeneous and heterogeneous catalysts, under high temperatures and high pressures, as well as diimide reduction conditions[34], but only observed the reduction of the ketone with the alkene untouched. A 3D model of **63** may reveal the reason: the alkene is blocked from the top face by the C-9 methyl group and the cyclopentanone ring, and from the bottom face by the C-5 and C-11a methyl groups, making it hard to be approached by any reductant.



Scheme 2.16. Attempts to a direct C-C bond formation by S_N2 mechanism. Condition for the model study: *n*-BuLi (4.0 equiv, free of solvent), 1-(Trimethylsilyl)propyne (6.0 equiv), Et_2O, TMEDA, -20 ºC, 3.5 h; then **65**, HMPA, Et_2O, 15 min, 44% **66** + 22% **67**.

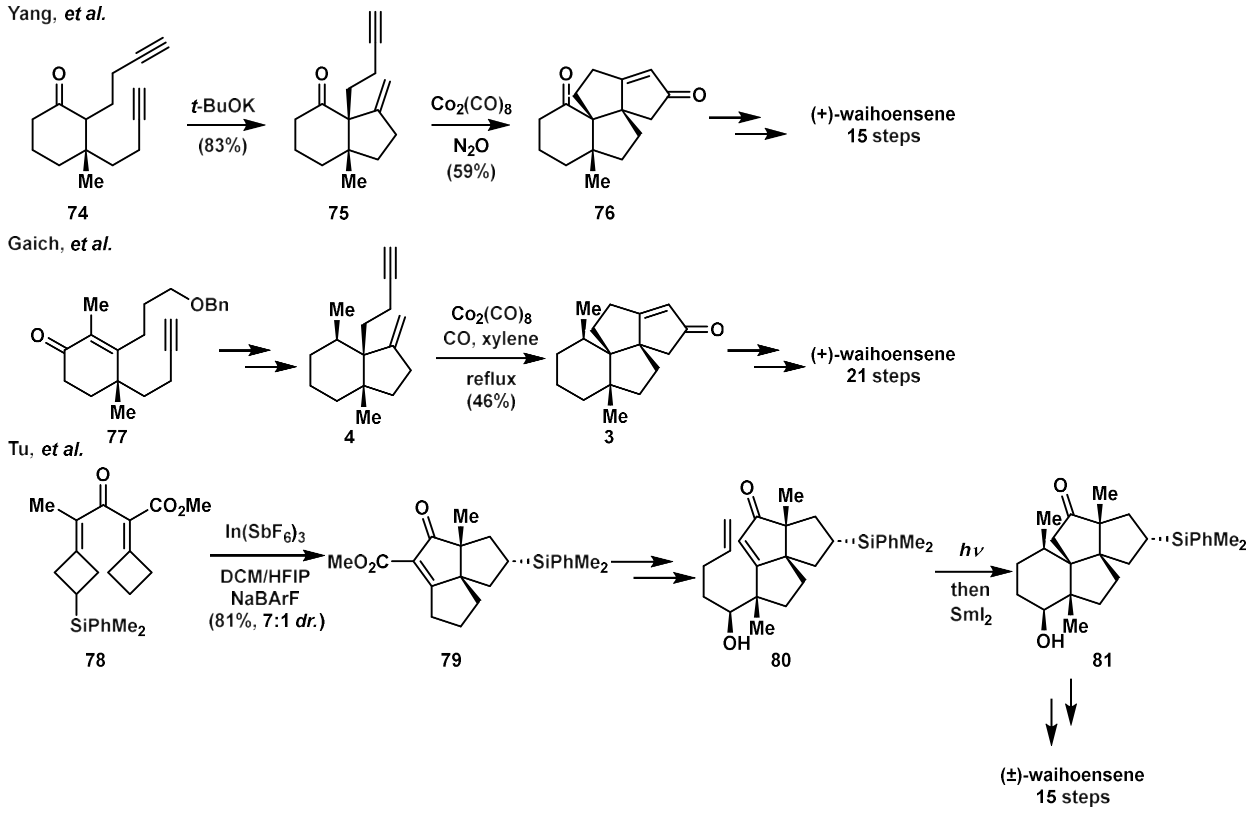
We realized that most of the challenges we met came from the unnecessary oxygen functionalities at C-10. To remove it at an earlier stage, we projected to introduce the alkyne by an S_N2 reaction or alkyl-propargyl coupling reaction. Despite the S_N2 reaction being successful with a condition reported by the Corey group[35] on model substrate **65**, which mimics the quaternary center next to the reaction center, we were never able to install a strong leaving group on C-10. This is possibly due to its proximity to the alkene, leading to rearrangements under cationic pathways.



Scheme 2.17. Attempts toward a direct sp^3-sp^3 C-C bond formation reaction mediated by hydrazone.

We also tried to design a new direct sp^3-sp^3 C-C bond formation reaction mediated by hydrazone. In this design, we projected an alkylation to tosyl hydrazone **70** by carbon-centered nucleophiles such as boronic ester derivatives and organometallic reagents. Unfortunately, all the nucleophiles we have screened proved unreactive to **70**. The unsuccessfulness might be due to multiple reasons: an organometallic reagent might prefer to deprotonate the substrate instead of a nucleophilic attach; boronic ester derivatives may not coordinate with the imine-like nitrogen with the neighboring electron-withdrawing nitrogen atom; and finally, the substrate has a quaternary center next to the electrophilic carbon atom. Further literature investigation revealed that a similar transformation has been realized by the Myers group[36], but the hydrazone had to be further protected by a TBS group to eliminate the possibility of deprotonation. This sequence is not preferable to our approach described in 2.4.3 in terms of step count, thus we did not attempt to apply it in the synthesis.

2.5 Summary



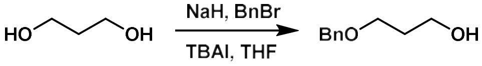
Scheme 2.18. Syntheses of **1** published by other groups since 2020.

In conclusion, we have completed an enantioselective total synthesis of (+)-waihoensene (**1**) in 17 steps from commercially available starting materials. We attribute the conciseness and reliability of our synthetic route to the design through careful analysis of the structure of the target molecule and intermediates, especially by viewing the quaternary centers as a central organizing feature. At the same time, we demonstrated the powerfulness of the gold-catalyzed cyclization reaction in the formation of contiguous quaternary centers.

As a side note, we completed the last NMR collection one day before the University of Chicago shut down because of COVID-19. Soon after the submission of our paper, we were pleasantly surprised to see the common interest in the natural product from multiple other groups around the world. The Yang group[37] and the Gaich group[38] each published a synthetic route in 2020, using the Pauson-Khand reaction as the key disconnection. The Tu group later published another formal synthesis route in 2021[39].

Supporting Information

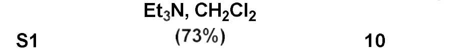
Model Study



9

S1

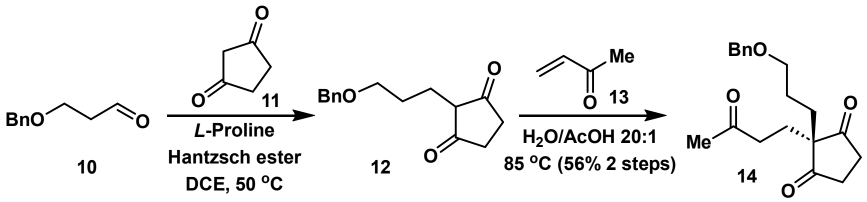
Benzyl-protected alcohol **S1**: To a 2000 mL round bottom flask equipped with a magnetic stir bar was charged sodium hydride (60% suspension in mineral oil, 12.6 g, 314 mmol, 1.02 equiv). The flask was degassed with argon, and equipped with an argon balloon, then anhydrous THF (800 mL) was added. The flask was cooled to 0 ºC, and 1,3-propanediol (**9**) (22.6 mL, 23.3 g, 306.2 mmol, 1.00 equiv) was added dropwise. *Caution: significant gas release.* The resultant suspension was stirred at 0 ºC for 1 h. Then tetrabutylammonium iodide (11.7 g, 31.7 mmol, 0.10 equiv) and benzyl bromide (37.5 mL, 54.0 g, 315.8 mmol, 1.03 equiv) were sequentially added. The reaction mixture was allowed to 23 ºC and stirred at that temperature for 7 hours. Upon completion, the reaction mixture was quenched by careful addition of water (300 mL). The contents were then transferred to a separatory funnel and diluted with Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (300 mL), dried (Na_2SO_4), filtered, and concentrated at a pressure higher than 150 torr. The residue was transferred to a 100 mL round bottom flask. Distillation under reduced pressure (approx. 80 ºC, 10 torr) gives benzyl-protected alcohol **S1** (43.9 g, 87% yield) as a colorless oil. **S1**: ^{1}H NMR (500 MHz, CDCl3) δ 7.40 – 7.27 (m, 5H), 4.53 (s, 2H), 3.79 (t, *J* = 5.6 Hz, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 1.87 (p, *J* = 5.7 Hz, 2H).



S1

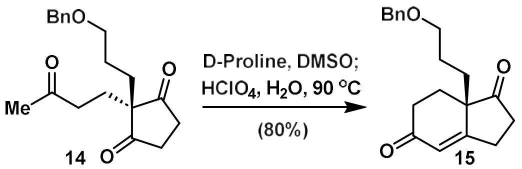
10

Aldehyde **10**: To a 2000 mL round bottom flask equipped with a magnetic stir bar was charged oxalyl chloride (31.0 mL, 35.8 g, 360 mmol, 2.0 equiv). Dichloromethane (1000 mL) was added, then the reaction flask was cooled to -78 °C. Dimethyl sulfoxide (130 mL, 140 g, 1800 mmol, 10 equiv) was added to the reaction mixture, which was then stirred for 30 minutes. A solution of benzyl-protected alcohol **S1** (30.0 g, 181 mmol, 1.0 equiv) in dichloromethane (200 mL) was cannulated into the reaction mixture. Upon the completion of addition, the reaction mixture was stirred at -78 °C for 30 minutes. Triethyl amine (260 mL, 182 g, 1800 mmol, 10 equiv) was then added, and the reaction flask was allowed to warm up slowly to 23 °C, at which time TLC analysis shows the complete consumption of **S1**. The reaction mixture was quenched by careful addition of saturated $NaHCO_3$ solution (500 mL). The contents were then transferred to a separatory funnel and diluted with water (300 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (300 mL), dried (Na_2SO_4), filtered, and concentrated at a pressure higher than 150 torr. The crude residue was purified via flash column chromatography (silica gel, pentane/Et_2O, 2/1) to give aldehyde **10** (21.7 g, 73% yield) as a colorless oil. **10**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, J = 1.7 Hz, 1H), 7.41 – 7.27 (m, 5H), 4.54 (s, 2H), 3.82 (t, J = 6.1 Hz, 2H), 2.71 (td, J = 6.1, 1.9 Hz, 2H).

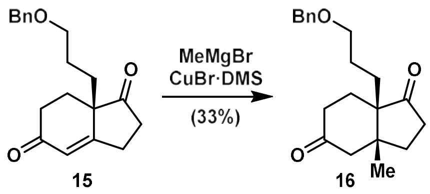


Triketone **14**: To a 250 mL round bottom flask equipped with a magnetic stir bar was charged aldehyde **10** (3.54 g, 18.2 mmol, 1.0 equiv) and 1,2-dichloroethane (70 mL). 1,3-Cyclopentanedione (**11**) (1.79 g, 28.2 mmol, 1.0 equiv), Hantzsch ester (5.53 g, 21.8 mmol, 1.2 equiv), and *L*-proline (1.05 g, 9.1 mmol, 0.50 equiv) were sequentially added to the flask, and the reaction mixture was stirred at 50 °C for 12 h. Upon completion, the stir bar was extracted, and the reaction mixture was concentrated. The crude residue was purified via flash column chromatography (silica gel, hexanes/EtOAc, 1/1 to remove Hantzsch-ester-related products, then CH_2Cl_2/MeOH 10/1 to elute diketone **12**). The resultant product was a mixture mainly consisting of diketone **12** and was used in the following step without further purification.

The previous mixture was transferred to a 20 mL vial, to which was sequentially added a magnetic stir bar, methyl vinyl ketone (**13**) (90%, 3.50 mL, 3.02 g, 40.0 mmol, 2.2 equiv), acetic acid (0.50 mL) and water (10.0 mL, 20/1 to acetic acid). The vial was sealed by a screw-on cap, and was heated at 85 °C for 8 h. Upon completion, the reaction mixture was transferred to a separatory funnel and diluted water (10 mL) and Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified via flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give triketone **14** (3.23 g, 56% yield over 2 steps) as a colorless oil. **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 4.39 (s, 2H), 3.34 (t, *J* = 5.9 Hz, 2H), 2.77 (d, *J* = 7.5 Hz, 1H), 2.73 (d, *J* = 5.6 Hz, 1H), 2.59 (d, *J* = 5.5 Hz, 1H), 2.56 (d, *J* = 7.4 Hz, 1H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 3H), 1.84 (t, *J* = 7.2 Hz, 2H), 1.71 (dd, *J* = 10.2, 6.2 Hz, 2H), 1.55 – 1.45 (m, 2H).

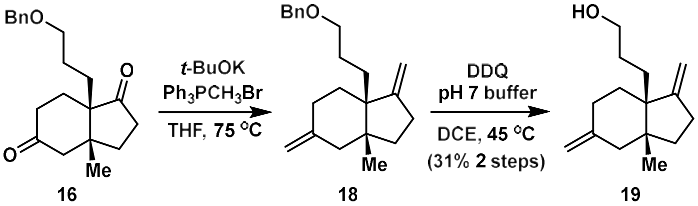


Hajos-Parrish-ketone-like diketone **15**: To a 250 mL round bottom flask equipped with a magnetic stir bar was charged triketone **14** (3.23 g, 10.0 mmol, 1.0 equiv). Dimethyl sulfoxide (30 mL) and *D*-proline (0.35 g, 3.1 mmol, 0.30 equiv) were sequentially added. The reaction mixture was stirred at 23 °C for 12 h, at which time TLC analysis showed the complete consumption of triketone **14**. Perchloric acid (1 M solution in water, 20.0 mL, 20.0 mmol, 2.0 equiv) was added to the reaction mixture, which was then heated to 90 °C and stirred at that temperature for 1 h. Upon completion, the reaction mixture was transferred to a separatory funnel and diluted water (50 mL) and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified via flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give Hajos-Parrish-ketone-like diketone **15** (2.37 g, 80% yield) as a colorless oil. **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.97 (s, 1H), 4.46 (s, 2H), 3.43 (t, J = 6.0 Hz, 2H), 2.96 (dddd, J = 17.4, 11.6, 9.3, 2.6 Hz, 1H), 2.77 (ddd, J = 17.5, 10.0, 3.0 Hz, 1H), 2.69 (ddd, J = 19.4, 11.4, 2.8 Hz, 1H), 2.51 – 2.34 (m, 3H), 2.24 (ddd, J = 13.9, 5.1, 2.2 Hz, 1H), 1.89 – 1.59 (m, 5H).



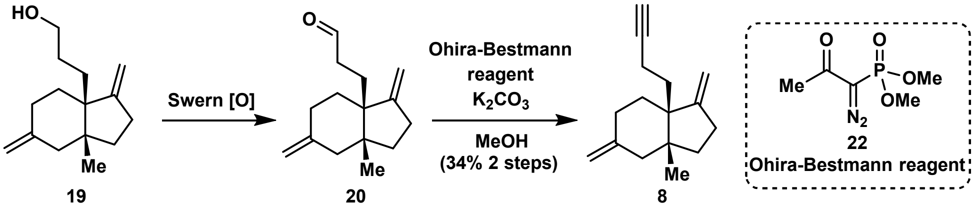
Diketone **16**: A flame dried, 250 mL round bottom flask at 23 °C was charged with CuBr·Me_2S (4.10 g, 20.0 mmol, 2.5 equiv), a magnetic stir bar, and anhydrous THF (100 mL). The resultant solution was then cooled to -40 °C. MeMgBr (3.0 M in Et_2O, 13.5 mL, 40.0 mmol, 5.0 equiv) was added dropwise and the resultant solution was stirred at -40 °C for 30 min. Hajos-Parrish-ketone-like diketone **15** (2.37 g, 7.94 mmol, 1.0 equiv) was then added dropwise as a solution in THF (30 mL) and the resultant solution was stirred at -40 °C for 2 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and warmed to 23 °C. The contents were then transferred to a separatory funnel and diluted with Et_2O (100 mL) and H_2O

(100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 2/1) of the resultant residue gave diketone **16** (825 mg, 33% yield) as a colorless oil. **16**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 4.47 (s, 2H), 3.43 (ddt, *J* = 9.5, 6.8, 3.3 Hz, 2H), 2.49 – 2.30 (m, 3H), 2.29 – 2.11 (m, 3H), 2.08 (dd, *J* = 13.7, 2.2 Hz, 1H), 1.95 (ddd, *J* = 13.4, 10.3, 7.9 Hz, 1H), 1.69 – 1.37 (m, 6H), 1.06 (s, 3H).



Alcohol **19**: To a flame dried, 500 mL round bottom flask in a glove box equipped with a magnetic stir bar was added KO*t*-Bu (700 mg, 6.23 mmol, 10.0 equiv). The flask was then taken out of the glove box, charged with anhydrous THF (15 mL), and heated to 70 °C until the solution became homogenous (typically in 10 minutes). Ph_3PCH_3Br (2.45 g, 6.85 mmol, 11.0 equiv) was then added in a single portion. The resulting bright yellow suspension was stirred at 70 °C for 1 h. Finally, a solution of diketone **16** (196 mg, 0.623 mmol, 1.0 equiv) in anhydrous THF (5 mL) was added, and stirring was continued for 18 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (20 mL). The reaction contents were then transferred to a separatory funnel, diluted with Et_2O (20 mL), and the layers were separated. The aqueous layer was then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 15/1→8/1) to give the desired product **18** contaminated with Ph_3P, which was directly taken for the next step.

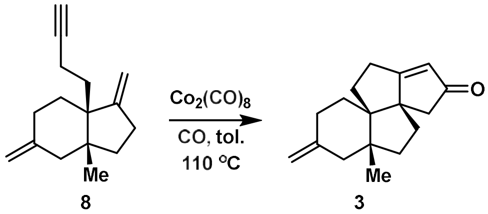
To a 50 mL round bottom flask was charged a solution of the previous mixture in 1,2-dichloroethane (30 mL). Aqueous phosphate buffer (5 mL, pH=7, 0.1 M) was added, followed by DDQ (560 mg, 2.47 mmol, 4.0 equiv). The reaction mixture was heated to 45 °C and stirred at that temperature for 12 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of aqueous NaOH solution (1M, 20 mL). The reaction contents were then transferred to a separatory funnel, diluted with water (20 mL) and CH_2Cl_2 (20 mL), and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 1/1) to give alcohol **19** as a colorless oil (42.8 mg, 31% yield over 2 steps). **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (d, *J* = 2.2 Hz, 1H), 4.70 (d, *J* = 2.5 Hz, 1H), 4.61 (q, *J* = 1.9 Hz, 1H), 4.51 (q, *J* = 2.0 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.40 (tq, *J* = 7.4, 2.3 Hz, 2H), 2.11 (td, *J* = 13.1, 5.0 Hz, 1H), 2.03 (d, *J* = 13.0 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.66 (ddd, *J* = 13.1, 5.7, 3.9 Hz, 2H), 1.45 (dq, *J* = 9.2, 6.7 Hz, 2H), 1.38 – 1.27 (m, 1H), 1.26 (d, *J* = 4.2 Hz, 2H), 1.24 – 1.10 (m, 2H), 0.90 (s, 3H).



Enyne **8**: To a 25 mL round bottom flask equipped with a magnetic stir bar was charged oxalyl chloride (21.0 μL, 31.0 mg, 0.241 mmol, 1.5 equiv). Dichloromethane (3.0 mL) was added, then the reaction flask was cooled to -78 °C. Dimethyl sulfoxide (60.0 μL, 63.3 mg, 0.81 mmol, 5.0

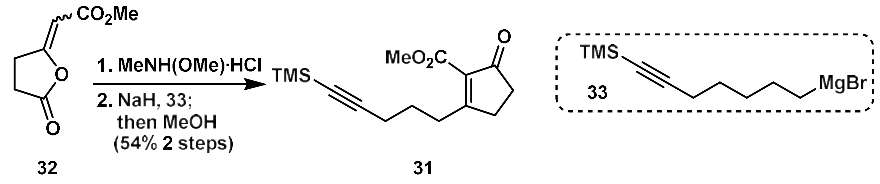
equiv) was added to the reaction mixture, which was then stirred for 30 minutes. A solution of alcohol **19** (35.4 mg, 0.161 mmol, 1.0 equiv) in dichloromethane (2.0 mL) was cannulated into the reaction mixture. Upon the completion of addition, the reaction mixture was stirred at -78 ºC for 30 minutes. Triethyl amine (0.25 mL, 170 mg, 1.61 mmol, 10 equiv) was then added, and the reaction flask was allowed to warm up slowly to 23 ºC, at which time TLC analysis shows the complete consumption of **19**. The reaction mixture was quenched by careful addition of saturated $NaHCO_3$ solution (5 mL). The contents were then transferred to a separatory funnel and diluted with water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The resultant crude mixture was taken directly to the next step.

In a 25 mL round bottom flask equipped with a magnetic stir bar was added a solution of the previous mixture in anhydrous methanol (5 mL). A solution of Ohira-Bestmann reagent (**22**) (58 mg, 0.30 mmol, 1.9 equiv) in anhydrous methanol (1 mL) was added, followed by K_2CO_3 (68 mg, 0.50 mmol, 3.1 equiv). The reaction mixture was stirred at 23 ºC for 12 h. Upon completion, the reaction contents were quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (30 mL). The mixture was then diluted with Et_2O (10 mL) and H_2O (10 mL) and the contents were transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, $1/0 \rightarrow 30/1 \rightarrow 10/1$) afforded enyne **8** (11.6 mg, 34% yield over 2 steps) as a light yellow oil. **8**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (t, $J = 2.1$ Hz, 1H), 4.68 (d, $J = 2.5$ Hz, 1H), 4.62 (d, $J = 2.3$ Hz, 1H), 4.52 (q, $J = 1.9$ Hz, 1H), 2.42 (ddd, $J = 10.6, 5.5, 2.9$ Hz, 2H), 2.14 – 1.95 (m, 4H), 1.92 – 1.85 (m, 1H), 1.66 (ddd, *J* = 13.1, 5.9, 4.0 Hz, 2H), 1.54 (s, 1H), 1.51 – 1.37 (m, 1H), 1.36 – 1.28 (m, 1H), 1.25 (m, 3H), 0.91 (s, 3H).

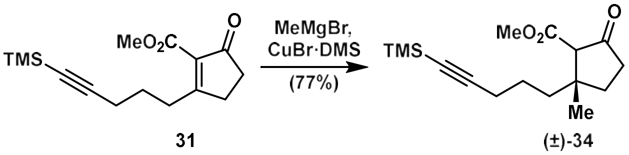


Tetracyclic enone **3**: To a flame dried, 10 mL vial at 23 °C equipped with a magnetic stir bar was added alkyne **8** (3.7 mg, 0.017 mmol, 1.0 equiv). Anhydrous toluene (0.40 mL) was then added under an argon atmosphere. $Co_2(CO)_8$ (9.0 mg, 0.026 mmol, 1.5 equiv, weighed out in a glove box and placed in a plastic microcentrifuge tube) and added to the reaction vial in a single portion at 23 °C. The resulting dark brown solution turned wine red after stirring for 30 minutes, at which point TLC analysis indicated full consumption of the starting material and the formation of a red complex. The reaction system was then degassed with CO, adapted with a balloon filled with CO, and heated to 110 °C using a pre-heated oil bath. The solution was stirred at this temperature for an additional 16 h during which time a cobalt mirror formed along the walls. Upon completion, the reaction the mixture was diluted with hexanes (1 mL) and directly loaded onto a column (silica gel), and eluted with hexanes to remove mesitylene. Subsequent flash column chromatography (silica gel, hexanes/EtOAc, 4/1) yielded tetracyclic enone **3** (yield was not determined due to scale) as a colorless oil. **3**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (d, *J* = 2.1 Hz, 1H), 4.73 (s, 1H), 4.64 (d, *J* = 2.5 Hz, 1H), 2.85 (d, *J* = 17.0 Hz, 1H), 2.58 (ddd, *J* = 12.4, 8.9, 4.6 Hz, 1H), 2.50 (dt, *J* = 17.4, 9.3 Hz, 1H), 2.35 (d, *J* = 17.0 Hz, 1H), 2.24 (ddd, *J* = 14.2, 10.6, 3.7 Hz, 1H), 2.16 – 2.08 (m, 2H), 1.97 (dt, *J* = 14.0, 9.2 Hz, 1H), 1.83 (d, *J* = 12.6 Hz, 1H), 1.81 – 1.76 (m, 1H), 1.68 (dt, *J* = 13.3, 9.9 Hz, 1H), 1.64 – 1.40 (m, 4H), 1.30 (t, *J* = 7.0 Hz, 1H), 0.99 (s, 3H).

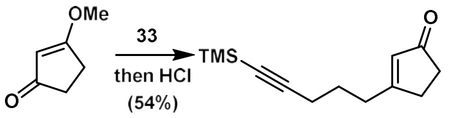
The Synthesis of Waihoensene (1)



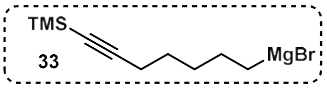
Tetra-substituted enone **31**: A flame dried, 100 mL round bottom flask equipped with a magnetic stir bar at 23 °C was charged with the enol lactone **32** (6.91 g, 40.6 mmol, 1.0 equiv), CH_2Cl_2 (120 mL), pyridine (16.4 mL, 16.06 g, 203 mmol, 5.0 equiv) and *N*, *O*-dimethyl hydroxylamine hydrochloride (5.15 g, 52.8 mmol, 1.3 equiv), and the resultant solution was stirred at 23 °C for 6 h. Upon completion, the reaction contents were concentrated directly, redissolved in toluene (300 mL), filtered through a pad of Celite, and concentrated again. The resultant residue was dissolved in anhydrous THF (160 mL), the mixture was cooled to 0 °C, and NaH (60% dispersion in mineral oil, 2.11 g, 52.8 mmol, 1.3 equiv) was added in a single portion. The resultant contents were stirred for 30 min at 0 °C before being cooled down to –78 °C. In another flame dried, 250 mL 2-necked round bottom flask equipped with a magnetic stir bar and a condenser at 23 °C were added activated Mg turnings (1.98 g, 81.2 mmol, 2.0 equiv), THF (40 mL), and a crystal of I_2 under a positive argon flow. The second flask was then heated to 80 °C followed by addition of a partial amount (~5 mL) of a solution of (5-bromopent-1-ynyl)trimethylsilane (8.33 g, 40.6 mmol, 1.0 equiv) in anhydrous THF (40 mL, 1 M); after the color of I_2 dissipated, the remaining solution of (5-bromopent-1-ynyl)trimethylsilane in anhydrous THF was slowly added to the reaction mixture via syringe while maintaining the reaction contents at reflux. After stirring for 4 h, the so-formed Grignard reagent **33** was cooled down and added to the previous reaction mixture at –78 °C. The temperature of the resultant mixture was warmed to 0 °C and stirring was continued for 1 h. Upon completion, the reaction contents were quenched by the careful addition of MeOH (60 mL), heated to 50 °C, and stirred for ~60 min with the reaction being closely monitored closely by TLC to avoid any deprotection of the TMS protecting group attached to the alkyne. Upon completion, the reaction contents were cooled down to 23 °C, and 1 M HCl (150 mL) was added. The reaction contents were transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified via flash column chromatography (silica gel, hexanes/EtOAc, 1/1) to give tetra-substituted enone **31** (6.05 g, 54% yield) as a white solid. **31**: $R_f = 0.45$ (silica gel, hexanes/EtOAc, 1/1); IR (film) ν_{max} 2956, 2174, 1746, 1716, 1624, 1436, 1361, 1295, 1250, 1229, 1166, 1024, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 2.88–2.81 (m, 2 H), 2.72–2.65 (m, 2 H), 2.51–2.45 (m, 2 H), 2.31 (t, $J = 7.0$ Hz, 2 H), 1.85–1.72 (m, 2 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.46, 187.46, 163.57, 132.67, 105.71, 86.82, 52.87, 35.90, 31.77, 30.48, 26.59, 19.94, 0.05; HRMS (ESI) calcd for $C_{15}H_{23}SiO_3^+$ [M + H^+] 279.1411, found 279.1415.



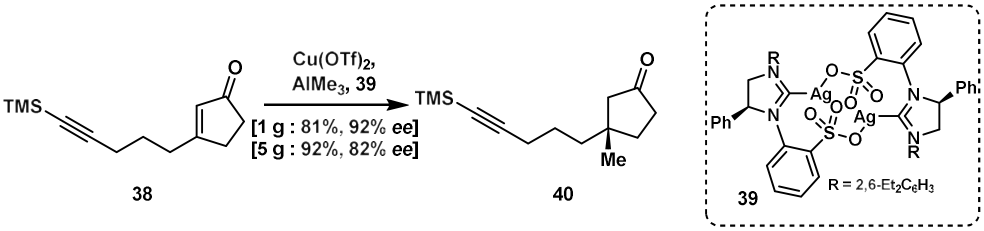
β-Keto-ester **(±)-34:** A flame dried, 250 mL round bottom flask at 23 °C was charged with $CuBr{\cdot}Me_2S$ (3.55 g, 17.2 mmol, 1.2 equiv), a magnetic stir bar, and anhydrous THF (56 mL). The resultant solution was then cooled to –40 °C. MeMgBr (3.0 M in Et_2O, 11.5 mL, 34.5 mmol, 2.4 equiv) was added dropwise and the resultant solution was stirred at –40 °C for 30 min. The tetrasubstituted enone **31** (4.00 g, 14.4 mmol, 1.0 equiv) was then added dropwise as a solution in THF (56 mL) and the resultant solution was stirred at –40 °C for 2 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and warmed to 23 °C. The contents were then transferred to a separatory funnel and diluted with Et_2O (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), H_2O, and brine, dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/EtOAc, 9/1) of the resultant residue gave β-keto-ester **(±)-34** (3.26 g, 77% yield) as a colorless oil. **(±)-34**: $R_f = 0.32$ (silica gel, hexanes/EtOAc, 9/1); IR (film) ν_{max} 2956, 2361, 2338, 2174, 1757, 1751, 1734, 1718, 1700, 1684, 1653, 1636, 1616, 1576, 1559, 1540, 1507, 1457, 1249, 843, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) reported for a 4 : 2 : 1 ratio of two keto diastereomers and the enol tautomer δ 10.82 (s, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 2.98 (s, 1 H), 2.92 (s, 1 H), 2.56–2.29 (m, 2 H), 2.29–2.09 (m, 2 H), 1.98–1.27 (m, 6 H), 1.16 (s, 3 H), 1.11 (s, 3 H), 1.07 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.05, 212.40, 176.74, 169.23, 168.97, 107.61, 106.85, 106.77, 85.07, 84.92, 84.36, 65.78, 64.81, 51.96, 51.92, 50.92, 44.3, 43.81, 43.70, 40.76, 39.68, 36.48, 36.19, 36.12, 33.86, 33.26, 33.23, 30.98, 27.28, 25.47, 24.52, 23.75, 23.61, 21.23, 20.44, 20.29, 0.22, 0.18, 0.17; HRMS (ESI) calcd for $C_{16}H_{27}SiO_3^+$ [M + H$^+$] 295.1724, found 295.1740.



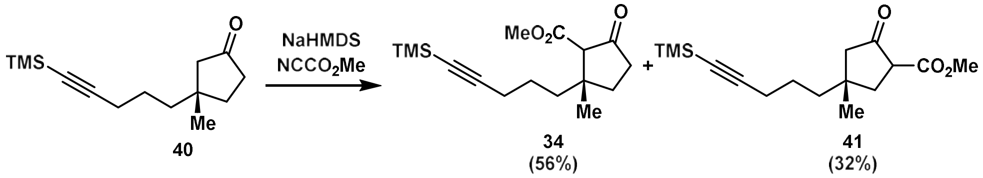
37 **38**



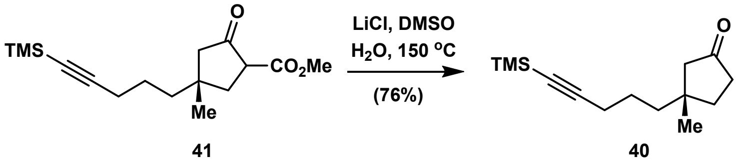
Enone **38:** To a flame-dried, 500 mL 2-necked round bottom flask at 23 °C equipped with a magnetic stir bar and a condenser were added activated Mg turnings (2.10 g, 86.0 mmol, 2.0 equiv), anhydrous THF (43 mL), and a chip of I_2 under a positive argon flow. The reaction contents were then heated at 80 °C followed by the addition of a partial amount (~5 mL) of a solution of (5-bromopent-1-ynyl)trimethylsilane (8.90 g, 43.0 mmol, 1.0 equiv) in anhydrous THF (43 mL, 1 M) via syringe; after the color of I_2 dissipated, the remaining solution of (5-bromopent-1-ynyl)trimethylsilane in anhydrous THF was added slowly via syringe while maintaining the reaction contents at 80 °C. After stirring for 4 h at 80 °C, the reaction contents were transferred to a solution of 3-methoxy-2-cyclopenten-1-one (**37**) (4.86 g, 43.0 mmol, 1.0 equiv) in anhydrous THF (86.0 mL, 0.5 M) at 0 °C via cannula over the course of ~30 min. Once the addition was complete, the mixture was gradually warmed to 23 °C and stirred at that temperature for 10 h. Upon completion, the reaction contents were quenched by the slow addition of 1 M HCl (100 mL) and stirred for 30 min before being transferred to a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic layers was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to give an orange oil. The resultant residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 3/1) to give enone **38** (5.13 g, 54% yield) as a yellow oil. **38**: $R_f = 0.50$ (silica gel, hexanes/EtOAc, 3/1); IR (film) ν_{max} 2958, 2361, 2340, 2174, 1710, 1675, 1617, 1249, 1183, 842, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1 H), 2.62 (dt, $J = 4.7, 2.5$ Hz, 2 H), 2.55 (t, $J = 7.7$ Hz, 2 H), 2.48–2.40 (m, 2 H), 2.33 (t, $J = 6.9$ Hz, 2 H), 1.84 (p, $J = 7.8$ Hz, 2 H), 0.18 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.93, 181.84, 129.78, 105.87, 85.73, 35.29, 32.35, 31.57, 25.99, 19.50, 0.11; HRMS (ESI) calcd for $C_{13}H_{21}SiO^+$ [M + H^+] 221.1356, found 221.1358.



Ketone **40:** To a flame-dried, 500 mL 3-necked round bottom flask at 23 °C in a glove box and equipped with a magnetic stir bar were added (NHC·Ag)$_2$ dimer complex **39** (synthesized following the procedure described in ref.24, 1.10 g, 1.01 mmol, 0.0375 equiv) and Cu(OTf)$_2$ (0.731 g, 2.02 mmol, 0.075 equiv). The reaction flask was then covered with aluminum foil, brought out of the glove box, and attached to an N$_2$-line via a vacuum bend. Fully degassed THF (216 mL, 3 cycles of the freeze-pump-thaw method) was then added via syringe. After stirring the resulting turquois-blue solution at 23 °C for 10 min, the contents were cooled down to −78 °C and AlMe$_3$ (2.0 M in hexanes, 40.4 mL, 80.9 mmol, 3.0 equiv) was added dropwise via syringe over the course of 30 min. After the addition was complete, a solution of enone **38** (5.80 g, 27.0 mmol, 1.0 equiv) in fully degassed THF (54 mL) was added slowly via cannula. The resulting dark solution was stirred at –78 °C for 12 h in the absence of light. Upon completion, the reaction mixture was very slowly quenched at –78 °C by the addition of saturated aqueous Rochelle's salt (100 mL). The resulting frozen black mixture was diluted with Et$_2$O (100 mL) and stirred at 23 °C for 30 min until the organic layer had cleared with black precipitates forming on the bottom of the flask. The resulting biphasic mixture was filtered through a pad of Celite and the filtrate was then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et$_2$O (3 × 200 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated to afford a yellow oil. Purification of that residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave ketone **40** (5.70 g, 92% yield, 82% *ee*) as a light yellow oil. The enantiomeric excess of the reaction was determined by analyzing the product obtained by TBAF deprotection followed by Sonogashira coupling with PhI (for details, see the HPLC section). Performing the reaction at smaller scales (~1 g of **38**) increased the *ee* up to 92% with an 81% yield. **40**: $R_f = 0.30$ (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{23} = -28.2°$ ($c = 0.1$, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2956, 2900, 2361, 2338, 2174, 1743, 1718, 1700, 1653, 1559, 1457, 1406, 1249, 1157, 843, 760, 639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.32–2.26 (m, 2 H), 2.23 (t, $J = 5.5$ Hz, 2 H), 2.11–2.00 (m, 2 H), 1.86–1.72 (m, 2 H), 1.62–1.56 (m, 1 H), 1.55–1.46 (m, 3 H), 1.05 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.72, 107.03, 84.85, 52.23, 40.87, 39.34, 36.73, 35.16, 24.96, 24.18, 20.42, 0.15; HRMS (ESI) calcd for $C_{14}H_{25}SiO^+$ [M + H^+] 237.1669, found 237.1677.

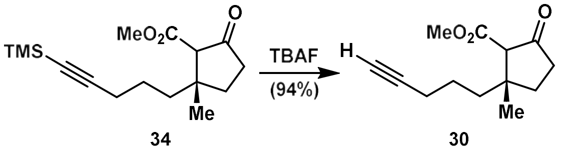


β-Keto-ester **34:** To a flame dried, 500 mL round bottom flask equipped with a magnetic stir bar at 23 °C was added NaHMDS (1.0 M in THF, 55.1 mL, 55.1 mmol, 2.3 equiv) and anhydrous THF (90 mL). The solution was cooled down to 0 °C followed by the addition of ketone **40** (5.70 g, 24.1 mmol, 1.0 equiv) as a solution in anhydrous THF (10 mL). The mixture was stirred for 2 h before being cooled down to –78 °C. Mander’s reagent (3.28 g, 3.06 mL, 38.5 mmol, 1.6 equiv) was then added and the resulting mixture was stirred at –78 °C for 3 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (100 mL) and diluted with EtOAc (100 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 19/1) gave keto-ester **34** (3.95 g, 56% yield) as a colorless oil and the regioisomer **41** (2.30 g, 32% yield) as a colorless oil. **34**: $[\alpha]_D^{23} = -23.0°$ (c = 0.1, $CHCl_3$, 92% *ee*); $R_f = 0.28$ (silica gel, hexanes/EtOAc, 9/1); $[\alpha]_D^{23} = -27.2°$ (c = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2956, 2360, 2341, 2173, 1758, 1731, 1664, 1436, 1341, 1307, 1250, 1149, 1040, 843, 760, 638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, reported for a 1.25 : 1 ratio of two keto diastereomers and a very small amount of enol tautomer) δ 3.74 (s, 3H), 3.42–3.30 (m, 1 H), 2.30–2.03 (m, 5 H), 1.66–1.32 (m, 5 H), 1.17 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 0.15 (s, 9 H), 0.14 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.26, 211.17, 169.85, 169.80, 106.82, 106.64, 85.12, 84.96, 53.63, 53.52, 52.54, 52.53, 51.96, 51.84, 50.99, 45.71, 41.66, 40.47, 39.32, 39.28, 38.59, 37.63, 37.41, 37.39, 27.57, 25.90, 24.78, 24.14, 23.94, 20.42, 20.35, 20.26, 0.12, 0.09; HRMS (ESI) calcd for $C_{16}H_{27}SiO_3^+$ [M + H^+] 295.1724, found 295.1739.

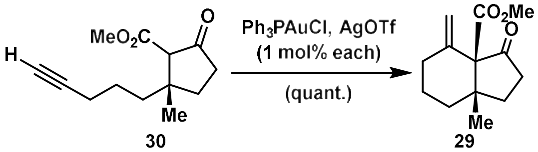


Ketone **40**: A 50 mL round bottom flask at 23 °C equipped with a magnetic stir bar was charged with β-keto-ester **41** (1.51 g, 5.13 mmol, 1.0 equiv), LiCl (0.435 g, 10.3 mmol, 2.0 equiv), H_2O (0.462 mL, 0.462 g, 25.6 mmol, 5.0 equiv) and DMSO (13 mL). The reaction contents were then warmed to 150 °C and stirred at that temperature for 3 h. Upon completion, the reaction contents were cooled to 23 °C and then diluted by the addition of Et_2O (50 mL) and H_2O (25 mL). The contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with

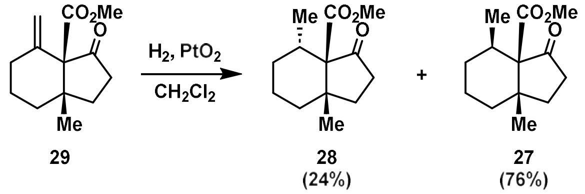
H_2O and brine, dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave ketone **40** (0.870 g, 76% yield) as a light-yellow oil.



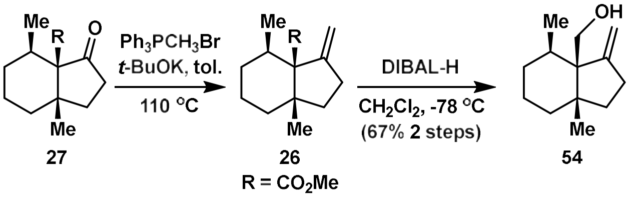
Alkyne **30**: To a flame dried, 500 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added a solution of β-keto-ester **34** (3.95 g, 13.4 mmol, 1.0 equiv) in anhydrous THF (150 mL). The resultant solution was then cooled to 0 °C and TBAF (1.0 M in THF, 22.0 mL, 22.0 mmol, 1.6 equiv) was then added slowly. The cooling bath was removed, and the solution was allowed to warm with stirring at 23 °C for 2 h. Upon completion, the reaction contents were quenched with saturated aqueous NH_4Cl (50 mL) and diluted with Et_2O (50 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water and brine, dried (MgSO4), filtered, and concentrated to afford a yellow oil. Purification of the residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→ 4/1) gave alkyne **30** (2.80 g, 94% yield) as a colorless oil. **30**: $R_f = 0.52$ (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D^{23} = -21.4°$ (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 3289, 2953, 2874, 2360, 2342, 1756, 1727, 1653, 1615, 1436, 1408, 1348, 1279, 1221, 1160, 1110, 1033, 668, 633 cm^{-11}; ^1H NMR (500 MHz, $CDCl_3$, reported for a 1.45 : 1 : 5 ratio of two keto diastereomers and the enol tautomer) δ 10.79 (s, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 2.98 (s, 1 H), 2.91 (s, 1 H), 2.55–2.28 (m, 2 H), 2.23–2.09 (m, 2 H), 1.94 (dt, *J* = 11.2, 2.8 Hz, 1 H), 1.85–1.75 (m, 1 H), 1.68 (td, *J* = 12.8, 4.4 Hz, 1 H), 1.60–1.27 (m, 4 H), 1.15 (s, 3 H), 1.09 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 213.25, 212.52, 176.80, 170. 80, 169.30, 169.09, 106.83, 84.74, 84.05, 83.96, 68.91, 68.79, 68.29, 65.73, 64.88, 52.08, 52.03, 50.98, 44.91, 43.89, 43.75, 40.83, 39.64, 36.66, 36.25, 36.17, 33.97, 33.49, 33.27, 31.04, 27.38, 25.52, 24.38, 23.68, 23.43, 21.27, 19.07, 19.06, 18.96; HRMS (ESI) calcd for $C_{13}H_{19}O_3^+$ [M + H$^+$] 223.1329, found 223.1322.



Alkene **29**: To a flame dried, 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added a solution of alkyne **30** (2.80 g, 12.6 mmol, 1.0 equiv) in anhydrous CH$_2$Cl$_2$ (100 mL) followed by Ph$_3$PAuCl (60.0 mg, 0.12 mmol, 0.96 mol %) and AgOTf (31.0 mg, 0.12 mmol, 0.96 mol %). The resultant cloudy mixture was stirred at 23 °C for 4 h. Upon completion, the reaction mixture was concentrated directly to a volume of ~20 mL and diluted with hexanes (~40 mL). The resultant mixture was loaded directly on a column for purification by flash column chromatography (silica gel, hexanes/Et$_2$O, 6/1→3/1) to afford alkene **29** (2.80 g, 100% yield) as a colorless oil. **29**: R$_f$ = 0.49 (silica gel, hexanes/Et$_2$O, 2/1); $[\alpha]_D^{23}$ = +109.4° (*c* = 0.1, CHCl$_3$, 92% *ee*); IR (film) ν_{max} 3276, 3090, 2948, 2873, 2849, 1728, 1724, 1633, 1434, 1411, 1384, 1325, 1311, 1255, 1202, 1164, 1142, 1121, 1107, 1081, 1057, 1026, 994, 913, 799, 618, 582, 400 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.04 (s, 1 H), 4.74 (s, 1 H), 3.69 (d, *J* = 1.4 Hz, 3 H), 2.48 (tdd, *J* = 12.5, 5.8, 2.8 Hz, 1 H), 2.44–2.30 (m, 2 H), 2.25 (dt, *J* = 14.1, 4.3 Hz, 1 H), 2.05 (dt, *J* = 13.4, 9.1 Hz, 1 H), 1.74–1.57 (m, 3 H), 1.56–1.48 (m, 1 H), 1.40 (ddd, *J* = 12.8, 8.9, 3.7 Hz, 1 H), 1.06 (s, 3 H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 211.94, 169.66, 141.03, 114.72, 69.40, 51.77, 44.72, 34.58, 33.51, 32.66, 29.80, 25.45, 21.69; HRMS (ESI) calcd for $C_{13}H_{19}O_3^+$ [M + H^+] 223.1329, found 223.1328.

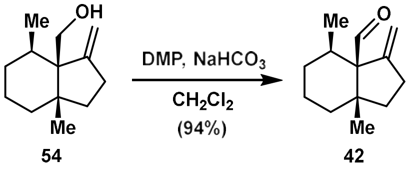


Ketone **27**: To a flame dried, 100 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added a solution of alkene **29** (1.12 g, 5.0 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (50 mL) followed by PtO_2 (83% Pt, 53.0 mg, 0.23 mmol, 4.6 mol %). The resultant system was then degassed with H_2 using a balloon, and the resulting black suspension was stirred at 23 °C for 2 h. Upon completion, the reaction mixture was concentrated directly to a volume of ~10 mL and diluted with hexanes (~20 mL). The resultant mixture was loaded directly on a column for purification by flash column chromatography (silica gel, Et_2O/hexanes, 1/6→1/3) to afford ketone **27** (0.849 g, 76% yield) as a white crystalline solid along with the undesired diastereomer **28** (0.279 g, 24% yield) as a colorless oil. **27**: $R_f = 0.48$ (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D^{23} = +41.2$ (c = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2963, 2942, 2926, 2870, 1735, 1715, 1455, 1433, 1411, 1265, 1238, 1221, 1202, 1116, 1064, 1033, 1009, 972, 585 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.51–2.36 (m, 2 H), 2.24 (td, J = 12.0, 8.8 Hz, 1 H), 1.87–1.76 (m, 1 H), 1.72–1.62 (m, 2 H), 1.62–1.60 (m, 1 H), 1.55–1.44 (m, 3 H), 1.39 (ddd, J = 12.9, 8.6, 2.5 Hz, 1 H), 0.94 (d, J = 6.4 Hz, 3 H), 0.94 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.88, 170.33, 65.59, 51.06, 42.68, 34.91, 32.83, 31.78, 29.46, 28.48, 26.91, 20.74, 16.21; HRMS (ESI) calcd for $C_{13}H_{21}O_3^+$ [M + H^+] 225.1485, found 225.1485. **28**: $R_f = 0.60$ (silica gel, hexanes/Et_2O, 2/1); $[\alpha]_D{}^{23} = +79.8$ (c = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2934, 2862, 2361, 2338, 1750, 1731, 1559, 1540, 1457, 1261, 1237, 1076, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.51 (ddd, *J* = 19.4, 10.1, 1.6 Hz, 1 H), 2.28 (dt, *J* = 19.1, 9.4 Hz, 1 H), 2.13 (dqd, *J* = 13.6, 6.9, 3.6 Hz, 1 H), 1.75 (dt, *J* = 13.0, 9.8 Hz, 1 H), 1.64–1.57 (m, 1 H), 1.52 (q, *J* = 3.1 Hz, 1 H), 1.47–1.37 (m, 2 H), 1.24 (dd, *J* = 13.7, 3.9 Hz, 1 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 1.10 (s, 3 H), 1.07 (dd, *J* = 13.2, 9.6 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.73, 171.77, 66.28, 51.68, 43.63, 35.97, 35.95, 33.63, 32.42, 30.4, 22.47, 21.79, 17.22; HRMS (ESI) calcd for $C_{13}H_{21}O_3^+$ [M + H$^+$] 225.1485, found 225.1487.



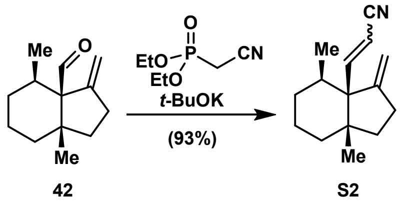
Alkene **26**: To a flame-dried, 500 mL round bottom flask at 23 °C in a glove box equipped with a magnetic stir bar was added KO*t*-Bu (6.80 g, 60.2 mmol, 9.0 equiv). The flask was then taken out of the glove box, charged with anhydrous toluene (100 mL), and heated to 110 °C until the solution became homogenous (typically in 10 minutes). Ph_3PCH_3Br (23.9 g, 66.9 mmol, 10 equiv) was then added in a single portion. The resulting bright yellow suspension was stirred at 110 °C for 1 h. Finally, a solution of ketone **27** (1.50 g, 6.69 mmol, 1.0 equiv) in anhydrous toluene (20 mL) was added, and stirring was continued for 12 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was then extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 15/1→8/1) to give the desired product **26** contaminated with Ph_3P, which was directly taken for the next step.

Alcohol 54: To a flame dried, 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added the previously obtained mixture of alkene **26** and Ph_3P (6.69 mmol, 100% yield assumed) and anhydrous CH_2Cl_2 (100 mL). The reaction solution was then cooled to –78 °C and then DIBAL-H (1.0 M solution in CH_2Cl_2, 16.7 mL, 16.7 mmol, 2.5 equiv) was added. The resulting mixture was stirred at –78 °C for 1 h. Upon completion, the cold bath was removed, and the mixture was stirred at 23 °C for 5 min. The reaction mixture was quenched by the slow addition of saturated aqueous Rochelle's salt (100 mL). The resultant slurry was stirred until clear (typically 1 h) and then transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 8/1→4/1) gave alcohol **54** (871 mg, 67% yield over two steps) as a white solid. **54**: R_f = 0.48 (silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{23}$ = +11.2 (*c* = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2932, 2361, 2337, 1685, 1653, 1643, 1559, 1457, 1372, 1070, 1044, 880 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (t, *J* = 2.3 Hz, 1 H), 4.75 (t, *J* = 2.6 Hz, 1 H), 3.70 (dd, *J* = 11.3, 8.4 Hz, 1 H), 3.53–3.39 (m, 1 H), 2.55–2.35 (m, 2 H), 1.91–1.80 (m, 1 H), 1.66–1.48 (m, 3 H), 1.47–1.31 (m, 6 H), 1.04 (d, *J* = 7.2 Hz, 3 H), 1.02 (s, 3vH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.30, 106.83, 61.69, 54.13, 43.69, 36.26, 35.04, 30.17 (2 C, confirmed by DEPT 135, COSY and HSQC), 28.40, 23.73, 19.06, 15.91; HRMS (ESI) calcd for $C_{13}H_{23}O^+$ [M + H$^+$] 195.1743, found 195.1742.

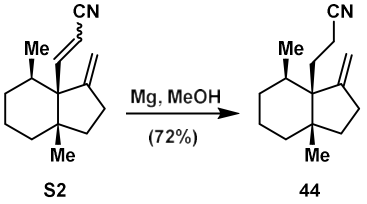


Aldehyde **42**: To a 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added alcohol **54** (0.871 g, 4.48 mmol, 1.0 equiv) and CH_2Cl_2 (100 mL) and then the contents were cooled down to 0 °C. Solid $NaHCO_3$ (5.00 g, 48.0 mmol, 10.7 equiv) and Dess–Martin periodinane (3.63 g, 8.60 mmol, 1.9 equiv) were then added sequentially as single portions. The resulting white suspension was stirred at 0 °C for 5 min and then at 23 °C for 2 h. Upon completion, the reaction mixture was diluted with hexanes (50 mL) and directly loaded onto a column. Flash column chromatography (silica gel, hexanes/Et_2O, 10/1→6/1) gave aldehyde **42** (0.813 g, 94% yield) as a white solid. **42**: $R_f = 0.58$ (silica gel, hexanes/EtOAc, 4/1); $[\alpha]_D^{23} = -95.0$ ($c = 0.1$, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 3074, 2934, 2877, 2716, 2361, 2337, 1717, 1684, 1675, 1646, 1559, 1540, 1457, 1437, 1419, 1376, 1249, 1223, 1062, 890, 704, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (d, J = 1.4 Hz, 1 H), 5.18 (t, J = 2.2 Hz, 1 H), 4.97 (t, J = 2.6 Hz, 1 H), 2.60–2.44 (m, 2 H), 2.09 (dt, J = 12.7, 9.9 Hz, 1 H), 1.72–1.65 (m, 1 H), 1.65–1.60 (m, 1 H), 1.60–1.53 (m, 2 H), 1.51 (q, J = 5.3, 4.8 Hz, 3 H), 1.19 (ddd, J = 12.4, 8.8, 3.1 Hz, 1 H), 0.95 (s, 3 H), 0.91 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.58, 152.38, 110.70, 64.14, 46.42, 33.93, 33.76, 32.76, 29.92, 28.59, 25.37, 21.03, 16.06; HRMS (ESI) calcd for $C_{13}H_{21}O^+$ [M + H^+] 193.1587, found 193.1589.

A one-pot procedure to convert alkene **26** into aldehyde **42** was also explored. To a flame dried, 25 mL round bottom flask at 23 °C equipped with a magnetic stir bar under an argon atmosphere was added a solution of the mixture containing alkene **26** (obtained by Wittig reaction from 60.0 mg **27**, 0.285 mmol, 1.0 equiv) and Ph_3P in anhydrous CH_2Cl_2 (5 mL). The reaction contents were then cooled to –78 °C and DIBAL-H (1.0 M solution in CH_2Cl_2, 0.570 mL, 0.570 mmol, 2.0 equiv relative to the assumed amount of **26**) was added. The reaction contents were then stirred at –78 °C for 1 h. Upon completion, the reaction contents were quenched at –78 °C by the slow addition of *t*-BuOH (1.27 g, 17.1 mmol, 30 equiv) and then warmed to 23 °C and stirred at that temperature for 1 h. Then, solid $NaHCO_3$ (0.300 g, 2.85 mmol, 10 equiv) was added followed by Dess–Martin periodinane (0.970 g, 2.28 mmol, 8.0 equiv). The mixture was then stirred at 23 °C for 1 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL). The reaction contents were transferred to a separatory funnel and diluted with Et_2O (15 mL) and H_2O (15 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 × 15 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/Et_2O, 10/1→6/1) to afford aldehyde **42** (30.1 mg, 55% yield overall) as a white solid.

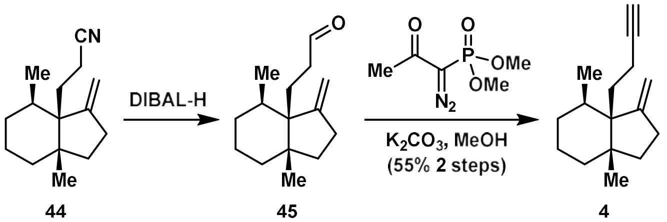


Unsaturated nitrile **S2**: To a flame dried, 100 mL round bottom flask at 23 °C inside a glove box and equipped with a magnetic stir bar was added *t*-BuOK (2.36 g, 21.0 mmol, 5.0 equiv). The reaction flask was then taken out of the glove box, charged with anhydrous THF (80 mL), and stirred until the solution became homogenous. Diethyl cyanomethylphosphonate (3.80 mL, 19.5 g, mmol, 4.6 equiv) was then added slowly, and the resulting pale yellow solution was stirred at 23 °C for 1 h. Finally, a solution of aldehyde **42** (0.813 g, 4.21 mmol, 1.0 equiv) in anhydrous THF (20 mL) was added and the resulting solution was heated to 65 °C and stirring was continued for 18 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was then extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, hexanes/Et_2O, 10/1→6/1) to afford **S2** (0.844 g, 93% yield, mixture of both diastereomers) as a colorless oil. **S2**: $R_f = 0.66$ and 0.54 (silica gel, hexanes/Et_2O, 4/1); ^{1}H NMR (500 MHz, $CDCl_3$, diagnostic peaks of crude material as a 1.7 : 1 mixture of *cis* : *trans* disposed diastereomers) *cis*: δ 6.34 (d, $J = 12.9$ Hz, 1 H); *trans*: δ 6.78 (d, $J = 17.0$ Hz, 1 H).



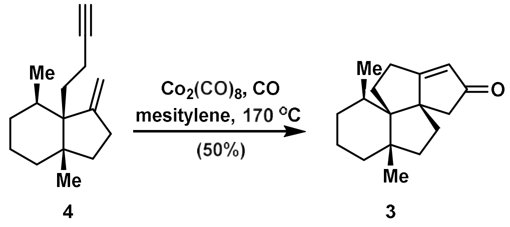
Nitrile **44**: To a flame dried, 500 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added unsaturated nitrile **S2** (0.820 g, 3.80 mmol, 1.0 equiv) and anhydrous MeOH (240 mL). The mixture was then cooled down to 0 °C and Mg turnings (activated with HCl washings, 2.90 g, 119 mmol, 31.4 equiv) were added. Stirring was continued at 0 °C for 15 min, at which point the cooling bath was removed and stirring was continued for another 3 h at 23 °C, during which time the Mg turnings disappeared, and a cloudy precipitate was formed. *CAUTION: The reaction was exothermic and required close monitoring.* Upon completion, the reaction mixture was cooled to 0 °C and quenched by slow addition of a 6 M aqueous solution of HCl (50 mL). The reaction mixture was diluted with Et_2O (100 mL) and H_2O (200 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL).

The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 8/1→6/1) afforded nitrile **44** (0.602 g, 72% yield) as a crystalline solid. **44**: $R_f = 0.54$ (silica gel, hexanes/Et_2OAc, 4/1); $[\alpha]_D^{23} = -12.6$ ($c = 0.1$, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2913, 2361, 2338, 2246, 1734, 1717, 1700, 1684, 1653, 1645, 1576, 1559, 1540, 1473, 1457, 1447, 886, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 (s, 1 H), 4.66 (s, 1 H), 2.47–2.34 (m, 2 H), 2.33–2.23 (m, 1 H), 2.15 (ddd, $J = 16.9$, 12.3, 4.8 Hz, 1 H), 1.95 (tdd, $J = 12.0$, 5.0, 2.5 Hz, 1 H), 1.82 (tq, $J = 7.5$, 3.9 Hz, 1 H), 1.65 (tt, $J = 12.5$, 4.2 Hz, 1 H), 1.56–1.45 (m, 3 H), 1.36–1.30 (m, 3 H), 1.27–1.20 (m, 2 H), 1.06 (s, 3 H), 1.05–1.01 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.70, 120.93, 107.47, 51.62, 44.31, 36.60, 35.87, 29.01, 28.64, 27.87, 26.75, 22.24, 17.64, 15.50, 11.82; HRMS (ESI) calcd for $C_{15}H_{24}N^+$ [M + H$^+$] 218.1903, found 218.1904.

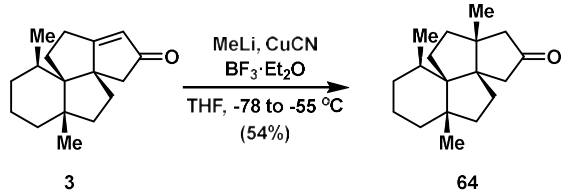


Alkyne **4**: To a flame dried, 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added nitrile **44** (0.602 g, 2.76 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (50 mL). After cooling the resultant solution to 0 °C, DIBAL-H (1.0 M in CH_2Cl_2, 5.00 mL, 5.00 mmol, 1.8 equiv) was added, and stirring was continued for 1 h at 0 °C. Upon completion, the mixture was quenched by the dropwise addition of saturated aqueous Rochelle's salt (50 mL). The slurry was stirred at 23 °C until clear (typically 1 h) before being transferred to a separatory funnel. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting crude product was dissolved in Et_2O (20 mL) and filtered through a short column of silica gel. The resultant crude **45** was directly used in the next step without further purification.

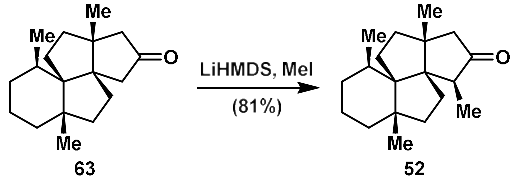
Next, to a 250 mL round bottom flask at 23 °C equipped with a magnetic stir bar, crude aldehyde (2.76 mmol, 100% yield assumed) and anhydrous MeOH (35 mL) were added under argon atmosphere. K_2CO_3 (0.95 g, 6.87 mmol, 2.5 equiv) and diethyl 1-diazo-2-oxopropylphosphonate (**22**) (0.80 g, 4.16 mmol, 1.5 equiv) were then added sequentially at 23 °C. The resulting yellow solution was then warmed to 30 °C and stirred at that temperature for 12 h. Upon completion, the reaction contents were quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (30 mL). The mixture was then diluted with Et_2O (30 mL) and H_2O (30 mL) and the contents were transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 1/0→30/1→10/1) afforded alkyne **4** (0.347 g, 58% yield) as a light yellow oil. **4**: R_f = 0.50 (silica gel, hexanes); $[\alpha]_D^{23} = -12.4$ (c = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 3311, 3071, 2937, 2361, 2337, 2118, 1646, 1559, 1540, 1458, 1448, 1385, 1374, 884, 668, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (t, J = 2.2 Hz, 1 H), 4.64 (t, J = 2.5 Hz, 1 H), 2.37 (ddt, J = 9.9, 5.0, 2.4 Hz, 2 H), 2.20–2.00 (m, 2 H), 1.93 (t, J = 2.6 Hz, 1 H), 1.87–1.77 (m, 2 H), 1.66 (tt, J = 12.6, 4.1 Hz, 1 H), 1.58–1.49 (m, 2 H), 1.45–1.37 (m, 1 H), 1.38–1.27 (m, 3 H), 1.21 (dtd, J = 12.9, 9.1, 8.1, 4.0 Hz, 2 H), 1.05 (s, 3 H), 1.03 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.62, 106.65, 85.83, 67.61, 51.79, 44.28, 36.71, 35.89, 30.08, 29.31, 29.12, 28.06, 22.48, 17.99, 15.61, 13.04; HRMS (ESI) calcd for $C_{16}H_{25}^+$ [M + H^+] 217.1951, found 217.1954.



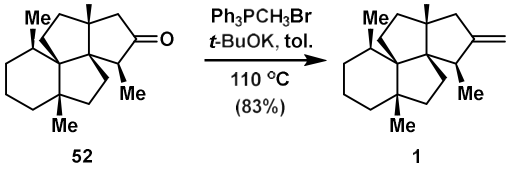
Tetracyclic enone **3**: To a flame dried, 100 mL round bottom flask at 23 °C equipped with a magnetic stir bar was added alkyne **4** (0.203 g, 0.94 mmol, 1.0 equiv). Fully degassed mesitylene (20 mL, 3 cycles of the freeze-pump-thaw method) was then added under an argon atmosphere. $Co_2(CO)_8$ (0.370 g, 1.07 mmol, 1.1 equiv, weighed out in a glove box and placed in a plastic microcentrifuge tube) and added to the reaction flask in a single portion at 23 °C. The resulting dark brown solution turned wine red after stirring for 2 h, at which point TLC analysis indicated full consumption of the starting material and the formation of a red complex. The reaction system was then degassed with CO and heated to 160 °C using a pre-heated oil bath. The solution was stirred at this temperature for an additional 24 h during which time a cobalt mirror formed along the walls. Upon completion, the reaction the mixture was directly loaded onto a column (silica gel) and eluted with hexanes to remove mesitylene. Subsequent flash column chromatography (silica gel, EtOAc/hexanes, 1/6→4/1) yielded tetracyclic enone **3** (0.115 g, 50% yield) as a brown oil. **3**: $R_f = 0.34$ (silica gel, hexanes/Et_2O, 3/1); $[\alpha]_D^{23} = -15.6$ (c = 0.1, $CHCl_3$, 92% *ee*); IR (film) ν_{max} 2942, 2868, 1712, 1636, 1463, 1412, 1386, 1196, 1168, 833 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.55 (t, J = 1.6 Hz, 1 H), 2.50 (d, J = 16.7 Hz, 1 H), 2.14 (d, J = 16.8 Hz, 1 H), 2.00–1.89 (m, 2 H), 1.68 (ddd, J = 13.9, 9.2, 4.7 Hz, 1H), 1.52–1.43 (m, 1 H), 1.35 (ddd, J = 13.4, 8.7, 4.3 Hz, 2 H), 1.26–1.14 (m, 4 H), 1.13–1.06 (m, 2 H), 1.06–0.99 (m, 3 H), 0.88 (s, 3 H), 0.70 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (126 MHz, C_6D_6) δ 208.72, 191.91, 120.54, 64.17, 56.55, 50.73, 45.04, 41.49, 38.72, 37.64, 33.41, 32.81, 30.38, 27.58, 24.59, 17.55, 17.08; HRMS (ESI) calcd for $C_{17}H_{25}O^+$ [M + H^+] 245.1900, found 245.1904.



Ketone **64** was synthesized via a slightly modified procedure used by the Lee group.[Ref.6] To a flame dried, 25 mL round bottom flask at 23 °C under an argon atmosphere and equipped with a magnetic stir bar was added CuCN (0.104 g, 1.16 mmol, 3.0 equiv) followed by anhydrous THF (5 mL). The solution was cooled to –78 °C and MeLi (1.6 M solution in Et_2O, 1.45 mL, 2.32 mmol, 6.0 equiv) was added. The cooling bath was removed and the reaction mixture was warmed to 23 °C and stirred for 10 min. The resultant colorless solution was then cooled to –78 °C and $BF_3{\bullet}Et_2O$ (100 μL, 132 mg, 0.93 mmol, 2.4 equiv) was added. A solution of tetracyclic enone **3** (94.7 mg, 0.387 mmol, 1.0 equiv) was then added slowly and the reaction system was moved to a –55 °C cooling bath and stirred for 2 h. The reaction contents were quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (5 mL). The reaction contents were then transferred to a separatory funnel and diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, Et_2O/hexanes, 1/8→1/6) yielded ketone **64** (54.8 mg, 54% yield) as a white crystalline solid. **64**: $R_f = 0.53$ (silica gel, hexanes/Et_2O, 3/1); $[\alpha]_D^{23} = +80.2$ ($c = 0.1$, $CHCl_3$, 82% *ee*); ^1H NMR and ^{13}C NMR spectra match those reported by the Lee group.



Ketone **52** was synthesized using a slightly modified procedure from the Lee group.[Ref.6] To a flame dried, 25 mL round bottom flask at 23 °C inside a glove box and equipped with a magnetic stir bar was added solid LiHMDS (70.4 mg, 0.420 mmol, 2.0 equiv). The flask was then taken out of the glove box and anhydrous THF (2 mL) was added. The reaction contents were then cooled to 0 °C and a solution of ketone **63** (54.8 mg, 0.210 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added slowly. Stirring was continued at 0 °C for 2 h before MeI (65.0 μL, 0.149 g, 1.05 mmol, 5.0 equiv) was added. The reaction contents were then warmed to 23 °C and stirred at that temperature for another 12 h. Upon completion, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl (5 mL). The contents were transferred to a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification of the resulting residue by flash column chromatography (silica gel, Et_2O/hexanes, 1/10→1/6) yielded ketone **52** (46.5 mg, 81% yield) as a yellow oil. **52**: $R_f = 0.59$ (silica gel, hexanes/Et_2O, 3/1); $[\alpha]_D^{23} = +22.8$ ($c = 0.1$, $CHCl_3$, 82% *ee*); ^1H NMR and ^{13}C NMR spectra match those reported by the Lee group.[Ref.6]

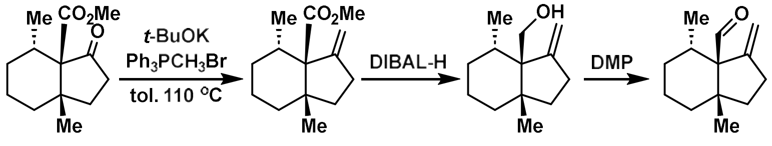


Waihoensene (**1**): To a flame dried, 10 mL round bottom flask at 23 °C inside a glove box and equipped with a magnetic stir bar was added KO*t*-Bu (0.172 g, 1.53 mmol, 9.0 equiv). The flask was then taken out of the glove box, charged with anhydrous toluene (3 mL), and heated at 110 °C until the solution became homogenous (typically in 5 minutes). Ph_3PCH_3Br (0.607 g, 1.70 mmol, 10 equiv) was then added in a single portion. The resulting bright yellow suspension was stirred at 110 °C for 1 h. Finally, a solution of ketone **52** (46.5 mg, 0.170 mmol, 1.0 equiv) in anhydrous toluene (2 mL) was added, and stirring was continued at 110 °C for another 1 h. Upon completion, the reaction contents were cooled to 23 °C and quenched by slow addition of saturated aqueous NH_4Cl (5 mL). The reaction contents were then transferred to a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by flash chromatography (silica gel, pentane) to give waihoensene (**1**, 38.4 mg, 83% yield) as a colorless oil. An analytical sample was prepared by reverse phase preparative TLC (Partisil® KC18, Whatman®, methanol, 91% recovery). **1**: R_f = 0.59 (silica gel, pentane); $[\alpha]_D^{23}$ = +40.6 (*c* = 0.1, $CHCl_3$, 82% *ee*); IR (film) ν_{max} 3068, 2931, 2867, 2361, 2338, 1734, 1717, 1700, 1684, 1653, 1559, 1540, 1521, 1507, 1472, 1457, 1375, 876, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (q, *J* = 1.9 Hz, 2 H), 2.71 (q, *J* = 7.4 Hz, 1 H), 2.22 (q, *J* = 2.1 Hz, 2 H), 1.78 (pd, *J* = 7.0, 3.6 Hz, 1 H), 1.64 (td, *J* = 13.7, 6.6 Hz, 1 H), 1.59–1.56 (m, 1 H), 1.56–1.54 (m, 1 H), 1.53–1.46 (m, 2 H), 1.46–1.42 (m, 1 H), 1.42–1.40 (m, 1 H), 1.40–1.36 (m, 1 H), 1.36–1.28 (m, 2 H), 1.28–1.25 (m, 1 H), 1.25–1.22 (m, 1 H), 1.18–1.14 (m, 1 H), 1.14–1.10 (m, 1 H), 1.04 (d, *J* = 7.3 Hz, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.64, 102.87, 68.18, 60.33, 52.45, 47.98, 44.62, 43.80, 41.95, 40.85, 35.88, 31.79, 30.41, 30.19, 28.65, 25.31, 24.95, 19.81, 19.14, 17.50; HRMS (ESI) calcd for $C_{20}H_{33}^{+}$ [M + H^{+}] 273.2577, found 273.2575.

^{1}H and ^{13}C NMR data comparison of synthetic and natural waihoensene (**1**)

^{1}H NMR		^{13}C NMR	
natural	synthetic	natural	synthetic
0.89 (d, *J* = 7 Hz, 3 H)	0.91 (d, *J* = 6.9 Hz, 3 H)	17.61	17.50
0.99 (s, 3 H)	1.01 (s, 3 H)	19.23	19.14
1.00 (s, 3 H)	1.02 (s, 3 H)	19.90	19.81
1.02 (d, *J* = 7 Hz, 3 H)	1.04 (d, *J* = 7.3 Hz, 3 H)	25.06	24.95
1.12 (m, 1 H)	1.14 – 1.10 (m, 1 H)	25.42	25.31
1.15 (m, 1 H)	1.18 – 1.14 (m, 1 H)	28.75	28.65
1.25 (m, 1 H)	1.25 – 1.22 (m, 1 H)	30.35	30.19
1.27 (m, 1 H)	1.28 – 1.25 (m, 1 H)	30.55	30.41
1.36 (m, 2 H)	1.36 – 1.28 (m, 2 H)	31.93	31.79
1.42 (m, 1 H)	1.40 – 1.36 (m, 1 H)	36.03	35.88
1.43 (m, 1 H)	1.42 – 1.40 (m, 1 H)	40.98	40.85
1.50 (m, 1 H)	1.46 – 1.42 (m, 1 H)	42.07	41.95
1.54 (m, 2 H)	1.53 – 1.46 (m, 2 H)	43.92	43.80
1.55 (m, 1 H)	1.56 – 1.54 (m, 1 H)	44.76	44.62
1.56 (m, 1 H)	1.59 – 1.56 (m, 1 H)	48.12	47.98
1.64 (m, 1 H)	1.64 (td, *J* = 13.7, 6.6 Hz, 1 H)	52.58	52.45
1.79 (ddq, *J* = 3, 7, 8 Hz, 1 H)	1.78 (pd, *J* = 7.0, 3.6 Hz, 1 H)	60.50	60.33
2.20 (br s, 2 H)	2.22 (q, *J* = 2.1 Hz, 2 H)	68.35	68.18
2.69 (q, *J* = 7 Hz, 1 H)	2.71 (q, *J* = 7.4 Hz, 1 H)	102.96	102.87
4.69 (d, *J* = 2 Hz, 2 H)	4.68 (d, *J* = 1.9 Hz, 2 H)	159.70	159.64

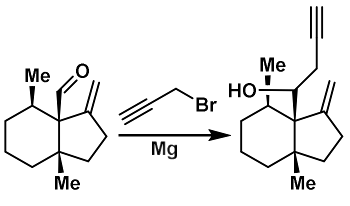
Selected Attempts Failed to Yield 1



Aldehyde **56**: Following the 3-step procedure described previously from **27** to **42**. Starting from **28** (259 mg, 1.23 mmol), alcohol **55** (154 mg, 64% over 2 steps) was obtained as a colorless oil. **55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (dtd, *J* = 7.3, 2.3, 0.9 Hz, 2H), 3.52 – 3.42 (m, 2H), 2.46

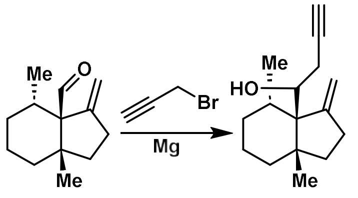
(pt, *J* = 9.2, 2.0 Hz, 1H), 2.35 (ddq, *J* = 17.8, 10.4, 2.6 Hz, 1H), 1.82 (dqd, *J* = 10.7, 7.2, 3.9 Hz, 1H), 1.67 – 1.59 (m, 2H), 1.53 – 1.35 (m, 5H), 1.30 (ddd, *J* = 12.6, 9.5, 2.8 Hz, 1H), 1.22 (d, *J* = 7.3 Hz, 3H), 1.17 – 1.11 (m, 1H), 0.96 (s, 3H).

Starting from alcohol **55** (15.5 mg, 1.23 mmol), aldehyde **56** (14.5 mg, 94%) was obtained as a colorless oil. **56**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 5.19 (t, *J* = 2.2 Hz, 1H), 5.08 (t, *J* = 2.5 Hz, 1H), 2.62 – 2.49 (m, 2H), 2.30 (dqd, *J* = 10.6, 7.2, 3.4 Hz, 1H), 1.61 – 1.32 (m, 7H), 1.22 – 1.15 (m, 1H), 1.09 (s, 3H), 1.07 (d, *J* = 7.9 Hz, 3H).



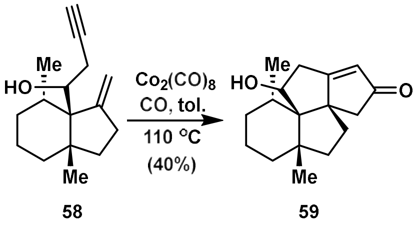
42 **57**

Enyne **57**: Allenylmagnesium bromide was first prepared. To a 25 mL round bottom flask equipped with a magnetic stir bar was charged magnesium turnings (activated by washing with 0.1 M HCl then dried, 120 mg, 5.0 mmol). The flask and its contents were flame dried under a vacuum, cooled, and backfilled with argon. $HgCl_2$ (0.5 mg, 0.002 mmol, 0.04 mol%) was added, followed by anhydrous Et_2O (3.0 mL). The flask was cooled to 0 ºC. Then propargyl bromide (80% mixture with toluene, 0.55 mL, 5.0 mmol) was added dropwise. The contents were stirred for 2 h at 0 ºC, during which time it slowly turns green, and the magnesium is consumed. The resultant solution containing allenylmagnesium bromide (100% yield assumed, ~1.5 M) was used immediately for the next step. In a separate 25 mL round bottom flask equipped with a magnetic stir bar was charged a solution of aldehyde **42** (19.3 mg, 0.10 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) under argon. The reaction mixture was cooled to 0 ºC, and freshly prepared allenylmagnesium bromide (0.10 mL, 0.15 mmol, 1.5 equiv) was added dropwise. The reaction was stirred at 0 ºC for 10 minutes, at which time TLC analysis showed the full consumption of **57**. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and warmed to 23 °C. The contents were then transferred to a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/Et_2O, 2/1) of the resultant residue gave enyne **57** (22.9 mg, 98% yield) as a colorless oil. **57**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (t, *J* = 2.2 Hz, 1H), 4.69 (t, *J* = 2.6 Hz, 1H), 4.05 (ddd, *J* = 10.3, 4.0, 2.3 Hz, 1H), 2.51 – 2.33 (m, 4H), 2.10 – 1.97 (m, 2H), 1.83 (d, *J* = 4.1 Hz, 1H), 1.78 (tp, *J* = 7.3, 3.5 Hz, 1H), 1.63 (tt, *J* = 12.8, 3.4 Hz, 1H), 1.58 – 1.47 (m, 1H), 1.31 – 1.25 (m, 5H), 1.23 (s, 3H), 1.05 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.74, 108.22, 82.89, 73.17, 70.70, 55.14, 45.18, 39.70, 39.32, 31.27, 31.05, 30.51, 22.67, 22.53, 17.67, 16.06.

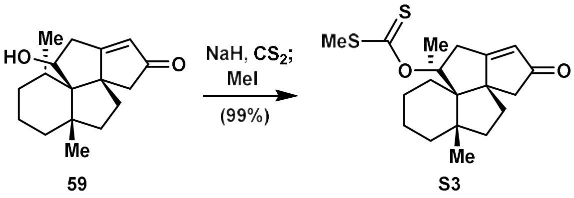


56 **58**

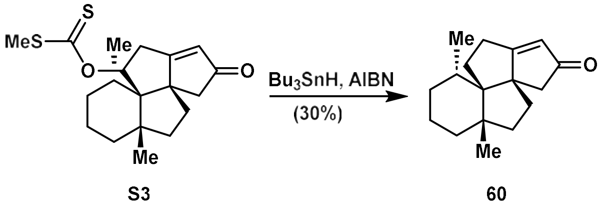
Enyne **58** was synthesized following the procedure described previously from **42** to **57**. Starting from aldehyde **56** (26.1 mg, 0.136 mmol), enyne **58** (31.6 mg, 100% yield) was obtained as a colorless oil. **58** was not fully characterized.



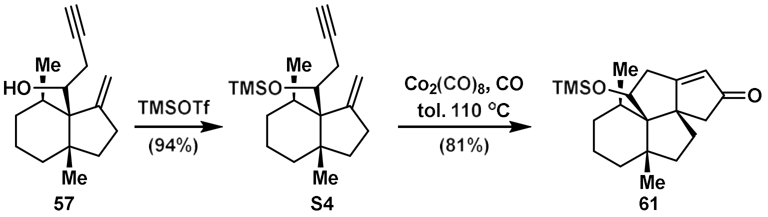
Tetracyclic enone **59** was synthesized following the procedure described previously from **8** to **23**. Starting from enyne **58** (21.7 mg, 0.093 mmol), tetracyclic enone **59** (9.6 mg, 40% yield) was obtained as a light-yellow oil. **59**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.70 (s, *J* = 2.0 Hz, 1H), 4.62 (dt, *J* = 11.6, 6.7 Hz, 1H), 3.40 (dd, *J* = 20.3, 10.3 Hz, 1H), 3.23 (d, *J* = 16.9 Hz, 1H), 2.61 (dd, *J* = 20.1, 7.3 Hz, 1H), 2.39 (dd, *J* = 16.9, 1.9 Hz, 1H), 2.10 (d, *J* = 7.3 Hz, 1H), 1.85 – 1.70 (m, 3H), 1.62 – 1.23 (m, 8H), 1.13 (d, *J* = 1.9 Hz, 3H), 0.87 (dd, *J* = 7.1, 1.9 Hz, 3H).



Xanthate **S3**: To a 10 mL round bottom flask equipped with a magnetic stir bar was charged a solution of tetracyclic enone **59** (4.0 mg, 0.015 mmol, 1.0 equiv) in anhydrous THF (1 mL) under argon. Carbon disulfide (18 μL, 22 mg, 0.30 mmol, 20 equiv) and sodium hydride (60% suspension in mineral oil, 3.0 mg, 0.075 mmol, 5.0 equiv) was sequentially added. The reaction mixture was stirred at 23 °C for 1.5 h, then iodomethane (22 μL, 50 mg, 0.36 mmol, 25.0 equiv) was added. The reaction mixture was continued stirring for 10 minutes, at which time TLC analysis showed the full consumption of **59**. The reaction mixture was quenched by the addition of saturated aqueous NH$_4$Cl (10 mL) and warmed to 23 °C. The contents were then transferred to a separatory funnel and diluted with Et$_2$O (10 mL) and H$_2$O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/Et_2O, 2/1) of the resultant residue gave xanthate **S3** (5.3 mg, 99% yield) as a yellow oil. **S3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 10.4, 7.0 Hz, 1H), 5.73 (t, *J* = 1.8 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.30 (d, *J* = 16.9 Hz, 1H), 2.59 (s, 3H), 2.55 (ddd, *J* = 20.2, 6.9, 1.0 Hz, 1H), 2.44 (d, *J* = 16.9 Hz, 1H), 2.23 (tq, *J* = 12.3, 5.9 Hz, 1H), 1.95 – 1.78 (m, 3H), 1.64 – 1.50 (m, 5H), 1.45 – 1.38 (m, 1H), 1.38 – 1.31 (m, 1H), 0.98 (s, 3H), 0.92 (d, *J* = 7.0 Hz, 3H).

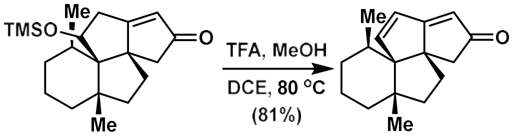


Tetracyclic enone **60**: To a 10 mL round bottom flask equipped with a magnetic stir bar was charged xanthate **S3** (5.3 mg, 0.015 mmol, 1.0 equiv). Stock solutions of azobisisobutyronitrile (0.015 M in toluene, 0.5 mL, 0.0015 mmol, 10 mol%) and tributyltin hydride (0.1 M in toluene, 0.30 mL, 0.03 mmol, 2.0 equiv) were added sequentially. The reaction mixture was purged with argon for 10 minutes before being heated to 80 °C and stirred at that temperature for 6 h. Upon completion, the reaction mixture was then cooled to 23 °C, diluted with hexanes (2 mL), and loaded onto a column. Flash column chromatography (silica gel, hexanes/Et_2O, 2/1) of the mixture gave tetracyclic enone **60** (1.4 mg, 30% yield) as a colorless oil. **60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, *J* = 1.8 Hz, 1H), 3.21 (d, *J* = 17.3 Hz, 1H), 2.71 – 2.64 (m, 2H), 2.38 (d, *J* = 17.4 Hz, 1H), 2.18 (dt, *J* = 14.5, 8.9 Hz, 1H), 1.85 (dtd, *J* = 14.9, 9.2, 5.3 Hz, 1H), 1.78 – 1.63 (m, 5H), 1.54 – 1.38 (m, 4H), 1.32 – 1.27 (m, 1H), 1.02 (s, 3H), 0.91 – 0.81 (m, 1H), 0.79 (d, *J* = 7.2 Hz, 3H).



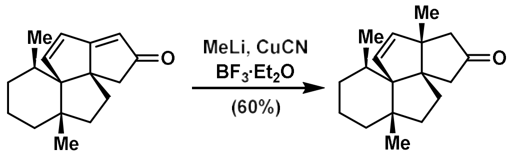
Silyl ether **S4**: To a 25 mL round bottom flask equipped with a magnetic stir bar was charged a solution of enyne **57** (14.1 mg, 0.061 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2.0 mL) under argon. The reaction mixture was cooled to 0 ºC before 2,6-lutidine (66 mg, 0.61 mmol, 10 equiv) and Trimethylsilyl trifluoromethanesulfonate (67 mg, 0.30 mmol, 5.0 equiv) was sequentially added. The reaction mixture was stirred at 0 ºC for 1 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and warmed to 23 °C. The contents were then transferred to a separatory funnel and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography (silica gel, hexanes/Et_2O, 8/1) of the resultant residue gave silyl ether **S4** (17.3 mg, 94% yield) as a colorless oil.

Tetracyclic enone **61** was synthesized following the procedure described previously from **8** to **23**. Starting from enol ether **S4** (17.3 mg, 0.057 mmol), tetracyclic enone **61** (14.0 mg, 74% yield) was obtained as a light-yellow oil. **61**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (d, *J* = 2.0 Hz, 1H), 4.05 (dd, *J* = 10.3, 6.8 Hz, 1H), 2.87 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.75 (d, *J* = 17.1 Hz, 1H), 2.67 – 2.56 (m, 1H), 2.28 (d, *J* = 17.2 Hz, 1H), 2.09 (ddd, *J* = 13.5, 11.1, 7.9 Hz, 1H), 1.80 (ddd, *J* = 12.4, 11.1, 8.7 Hz, 1H), 1.75 – 1.62 (m, 2H), 1.57 (tt, *J* = 13.4, 4.6 Hz, 1H), 1.51-1.32 (m, 6H), 1.42 (s, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 0.15 (s, 9H).



61 **62**

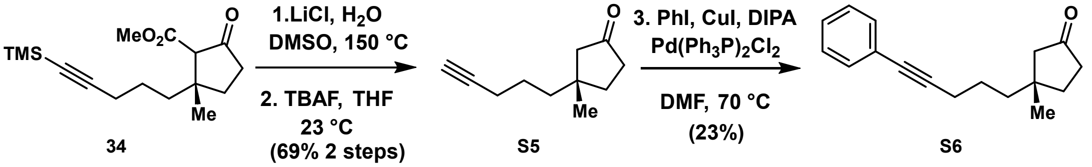
Diene **62**: To a 25 mL round bottom flask equipped with a magnetic stir bar was charged a solution of tetracyclic enone **61** (21.8 mg, 0.066 mmol, 1.0 equiv) in 1,2-dichloroethane (5.0 mL). Trifluoroacetic acid (0.30 mL) and methanol (0.25 mL) were sequentially added. The reaction flask was sealed and heated to 80 °C and stirred at that temperature for 16 h. Upon completion, the reaction mixture was then cooled to 23 °C, and all volatile contents are removed under vacuum. Flash column chromatography (silica gel, hexanes/Et_2O, 2/1) of the residue gave diene **62** (12.8 mg, 81% yield) as a light-yellow oil. **62**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, *J* = 5.8 Hz, 1H), 6.62 (d, *J* = 5.8 Hz, 1H), 5.65 (s, 1H), 2.65 (d, *J* = 15.9 Hz, 1H), 2.36 (d, *J* = 15.9 Hz, 1H), 1.95 (ddd, *J* = 13.7, 11.0, 8.0 Hz, 1H), 1.75 – 1.71 (m, 1H), 1.71 – 1.66 (m, 1H), 1.66 – 1.59 (m, 1H), 1.56 (s, 1H), 1.51 – 1.45 (m, 2H), 1.45 – 1.40 (m, 1H), 1.38 (dd, *J* = 13.7, 3.2 Hz, 1H), 1.36 – 1.32 (m, 1H), 1.23-1.15 (m, 1H), 1.20 (s, 3H), 1.05 (d, *J* = 7.3 Hz, 3H).



62 **63**

Alkene **63** was synthesized following the procedure described previously from **3** to **64**. Starting from diene **62** (2.2 mg, 0.0091 mmol), tetracyclic enone **63** (1.4 mg, 60% yield) was obtained as a light-yellow oil. **63**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (d, *J* = 6.0 Hz, 1H), 5.57 (d, *J* = 6.0 Hz, 1H), 2.88 (d, *J* = 18.8 Hz, 1H), 2.34 (d, *J* = 19.1 Hz, 1H), 2.29 – 2.25 (m, 2H), 1.98 (dd, *J* = 13.9, 6.7 Hz, 1H), 1.70 – 1.57 (m, 2H), 1.54 – 1.47 (m, 1H), 1.30 (m, 3H), 1.23-1.13 (m, 4H), 1.20 (s, 3H), 1.04 (s, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).

Preparation of compound S6 for HPLC analysis



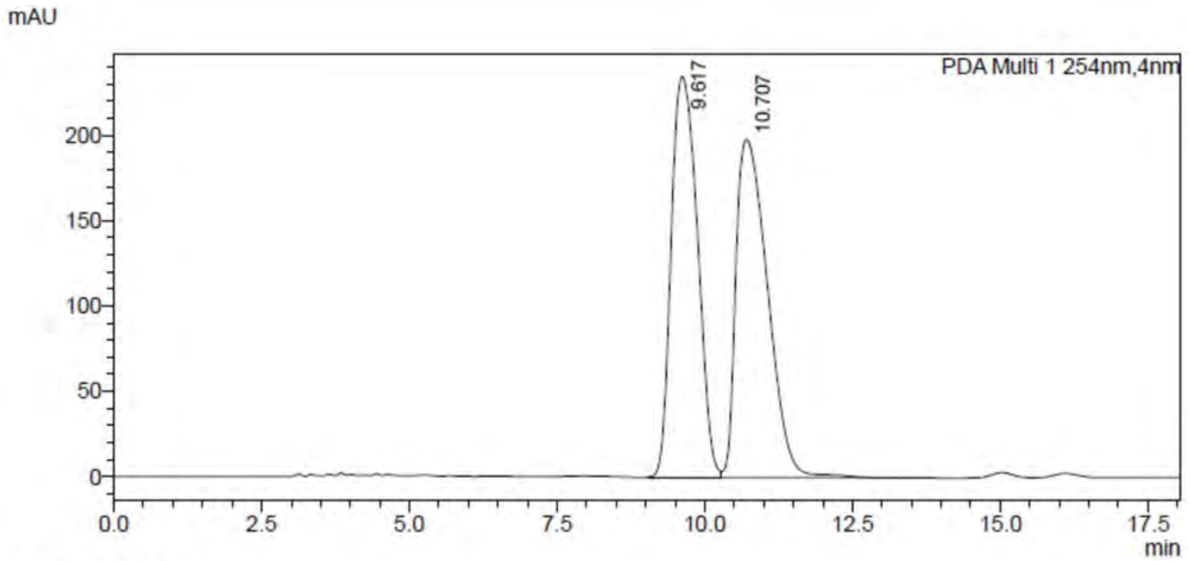
Alkyne **S5**: To a 10 mL round bottom flask equipped with a magnetic stir bar was added β-keto-ester **34** (60.0 mg, 0.203 mmol, 1.0 equiv), DMSO (0.5 mL), LiCl (18.0 mg, 0.406 mmol, 2.0 equiv) and H_2O (20.0 mg, 20.0 µL, 1.015 mmol, 5.0 equiv) at 23 °C. The resultant mixture was then heated to 150 °C and stirred for 3 h. Upon completion, the reaction was cooled to 23 °C and diluted by the addition of Et_2O (3 mL) and H_2O (3 mL). The contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford the crude deprotected ketone as a yellow oil (36.0 mg) which was directly used for the next step.

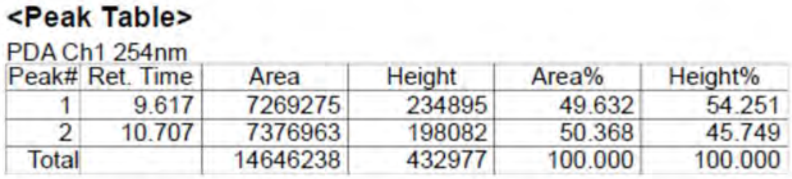
Next, to a flame dried, 10 mL round bottom flask equipped with a magnetic stir bar was added the previous deprotected ketone (36.0 mg, 0.154 mmol, 1.0 equiv) and anhydrous THF (0.75 mL) at 23 °C. TBAF (1.0 M in THF, 190 µL, 0.190 mmol, 1.2 equiv) was then added slowly and the solution was allowed to stir at 23 °C for 2 h. Upon completion, the reaction contents were quenched with H_2O (3 mL) and diluted with EtOAc (3 mL). The reaction contents were transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. Purification of the residue by flash column chromatography (silica gel, hexanes/EtOAc, 9/1) gave alkyne **S5** (23.0 mg, 69% overall yield) as a colorless oil. **S5**: $R_f = 0.28$ (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32–2.26 (m, 2 H), 2.20 (ddt, $J = 6.7, 4.0, 1.9$ Hz, 2 H), 2.11–2.00 (m, 2 H), 1.96 (t, $J = 2.6$ Hz, 1 H), 1.85–1.73 (m, 2 H), 1.65–1.45 (m, 4 H), 1.05 (s, 3 H).

Alkyne **S6**: Finally, to a flame dried, 10 mL round bottom flask at 23 °C and equipped with a magnetic stir bar was added $Pd(Ph_3P)_2Cl_2$ (6.6 mg, 9.12 mmol, 0.1 equiv), CuI (1.8 mg, 9.12 mmol, 0.1 eq), *i*-Pr_2NH (37.0 mg, 51.6 μL, 365.3 mmol, 4 equiv) and a solution of alkyne **S5** (15.0 mg, 91.3 mmol, 1.0 equiv) in DMF (0.7 mL). The resultant mixture was then heated to 70 °C and stirred for 4 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl solution (5 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with NH_4Cl (5 mL), H_2O (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated. Purification of the resultant residue by preparative TLC (silica gel, hexanes/EtOAc, 9/1, 2 runs) gave alkyne **S6** (5.1 mg, 23% yield) as a colorless oil. **S6**: $R_f = 0.20$ (silica gel, hexanes/EtOAc, 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.39 (m, 2 H), 7.34–7.29 (m, 3 H), 2.48–2.42 (m, 2 H), 2.36–2.30 (m, 2 H), 2.17–2.05 (m, 2 H), 1.91–1.78 (m, 2 H), 1.74–1.56 (m, 4 H), 1.11 (s, 3 H).

HPLC Traces of S6 (ChiralPak AD-H column, 99:1 hexanes/i-PrOH, 1mL/min, 254 nm)

Racemate:





<Peak Table>

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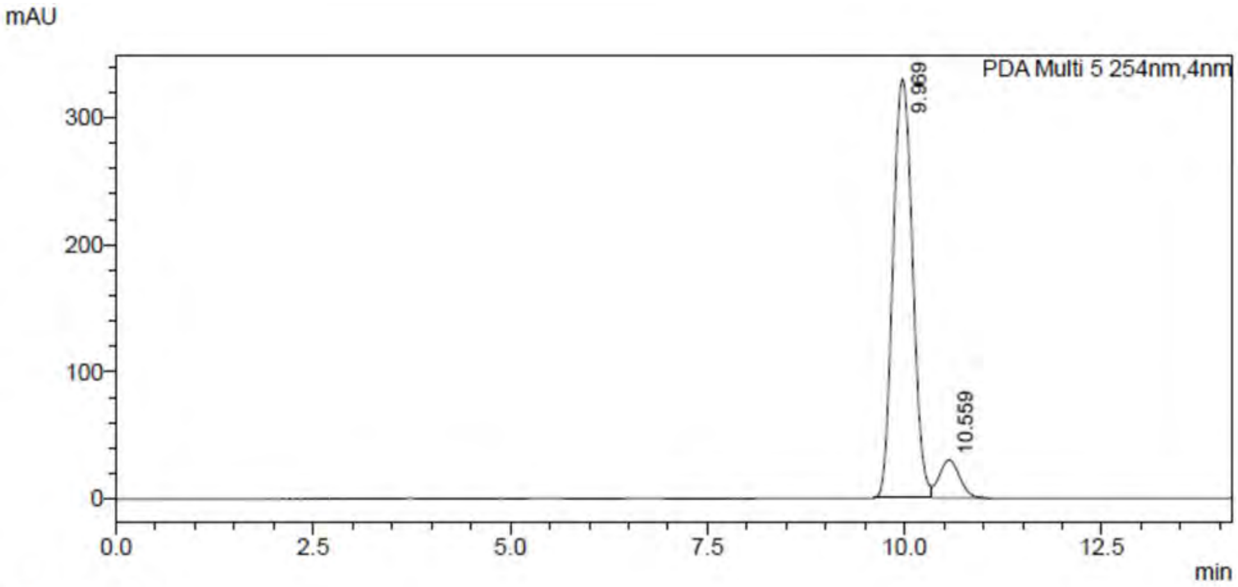
82% *ee*



<Peak Table>

PDA Ch5 254nm

Peak#	Ret. Time	Area	Height	Unit	Area%	Height%
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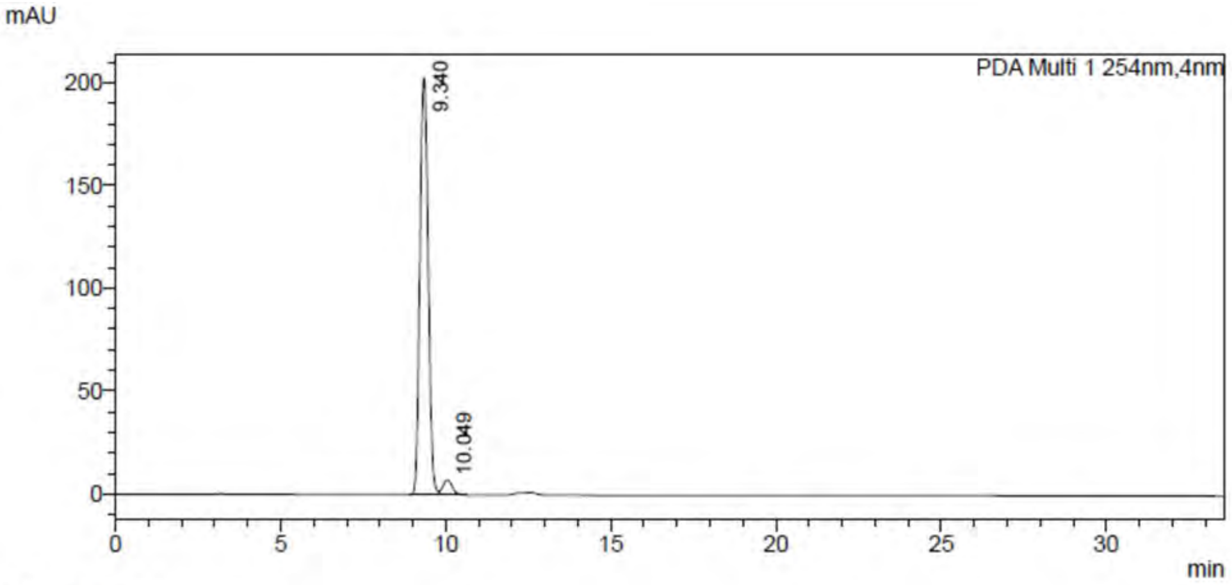
2	10.559	537369	29824		8.612	8.302
Total		6239801	359229		100.000	100.000

92% *ee*



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Height%
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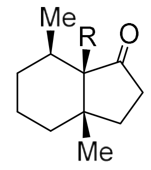
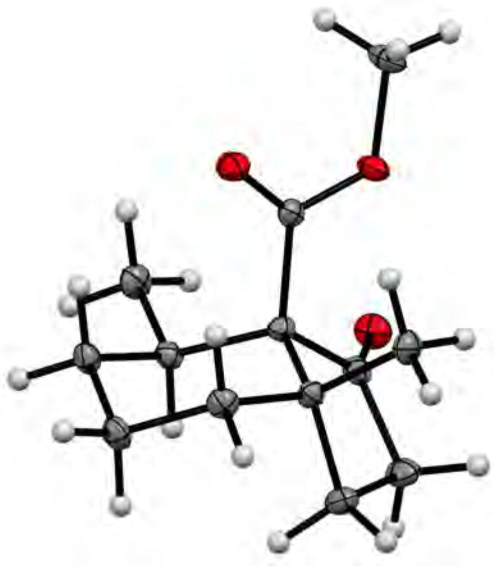
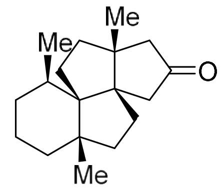
ORTEP structures of (±)-27 and (±)-64



27: R = CO_2Me

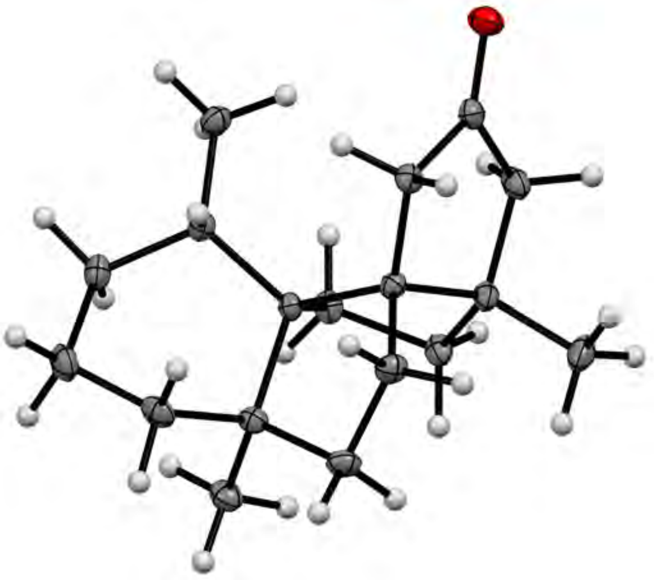
=



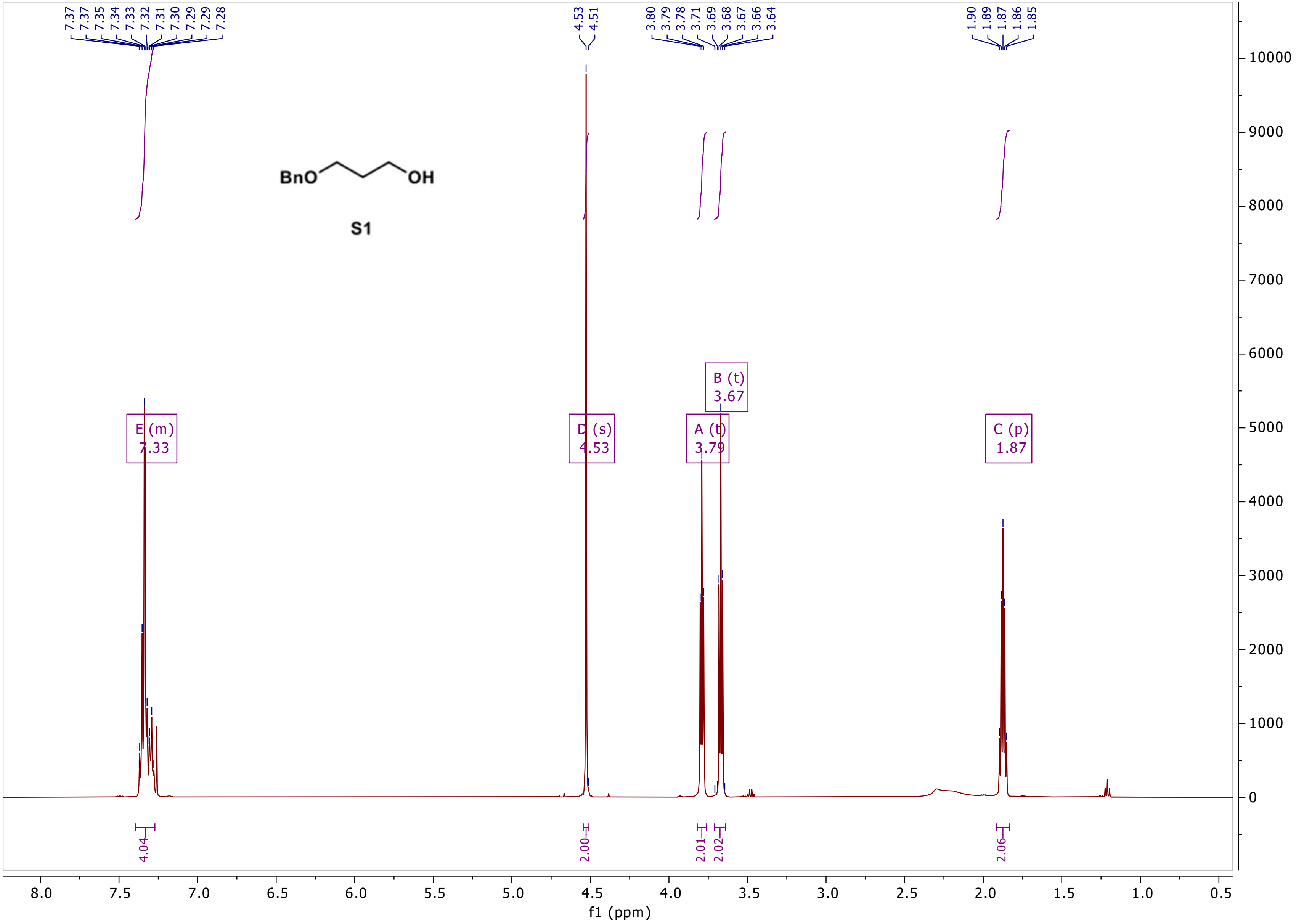


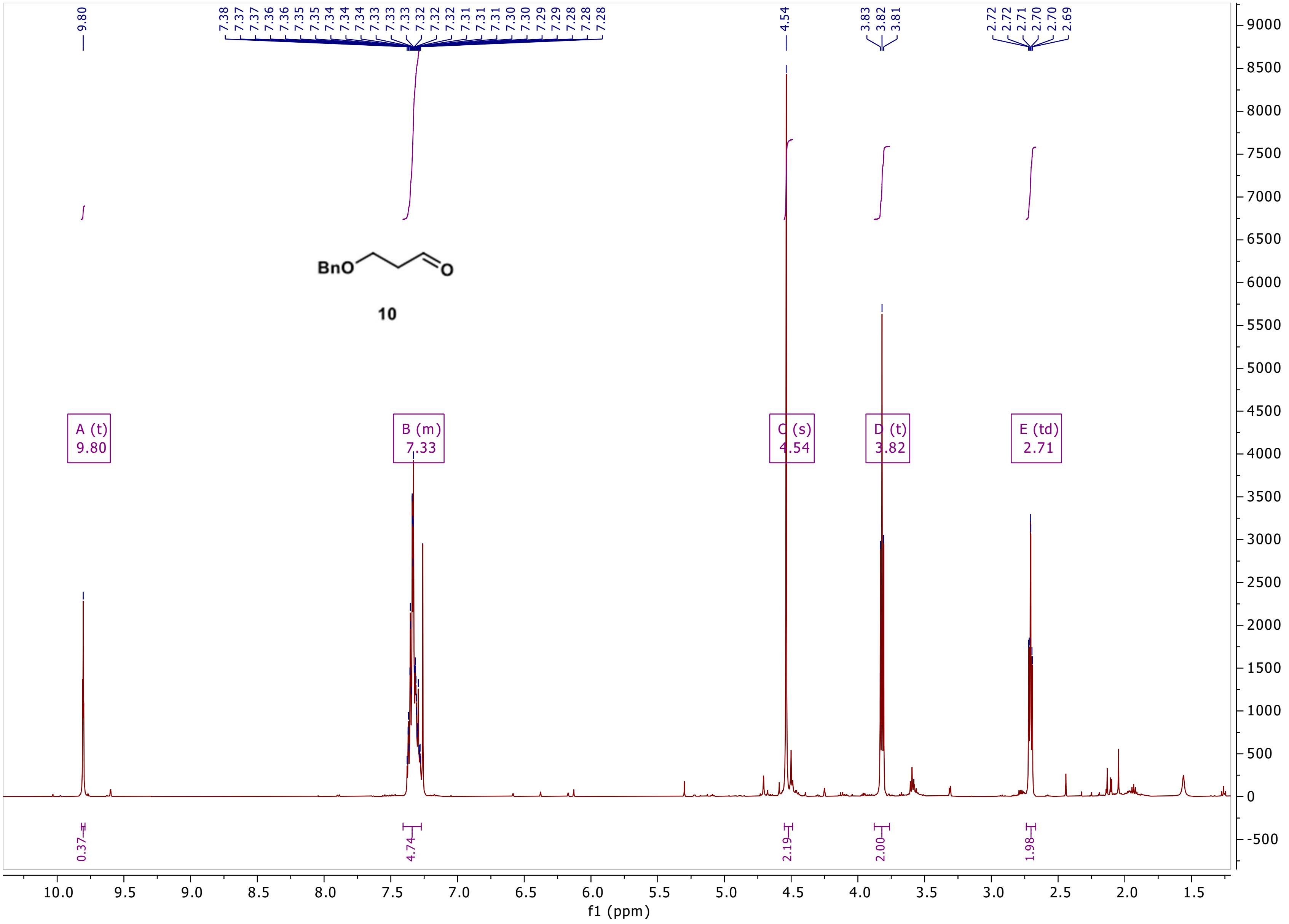
64

=



Selected NMR Spectrums




9.80
7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.31 7.30 7.29 7.29 7.28 7.28 7.28
4.54
3.83 3.82 3.81
2.72 2.72 2.71 2.70 2.70 2.69
BnO
O
A (t) 9.80
B (m) 7.33
C (s) 4.54
D (t) 3.82
E (td) 2.71
0.37
4.74
2.19
2.00
1.98
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
f1 (ppm)
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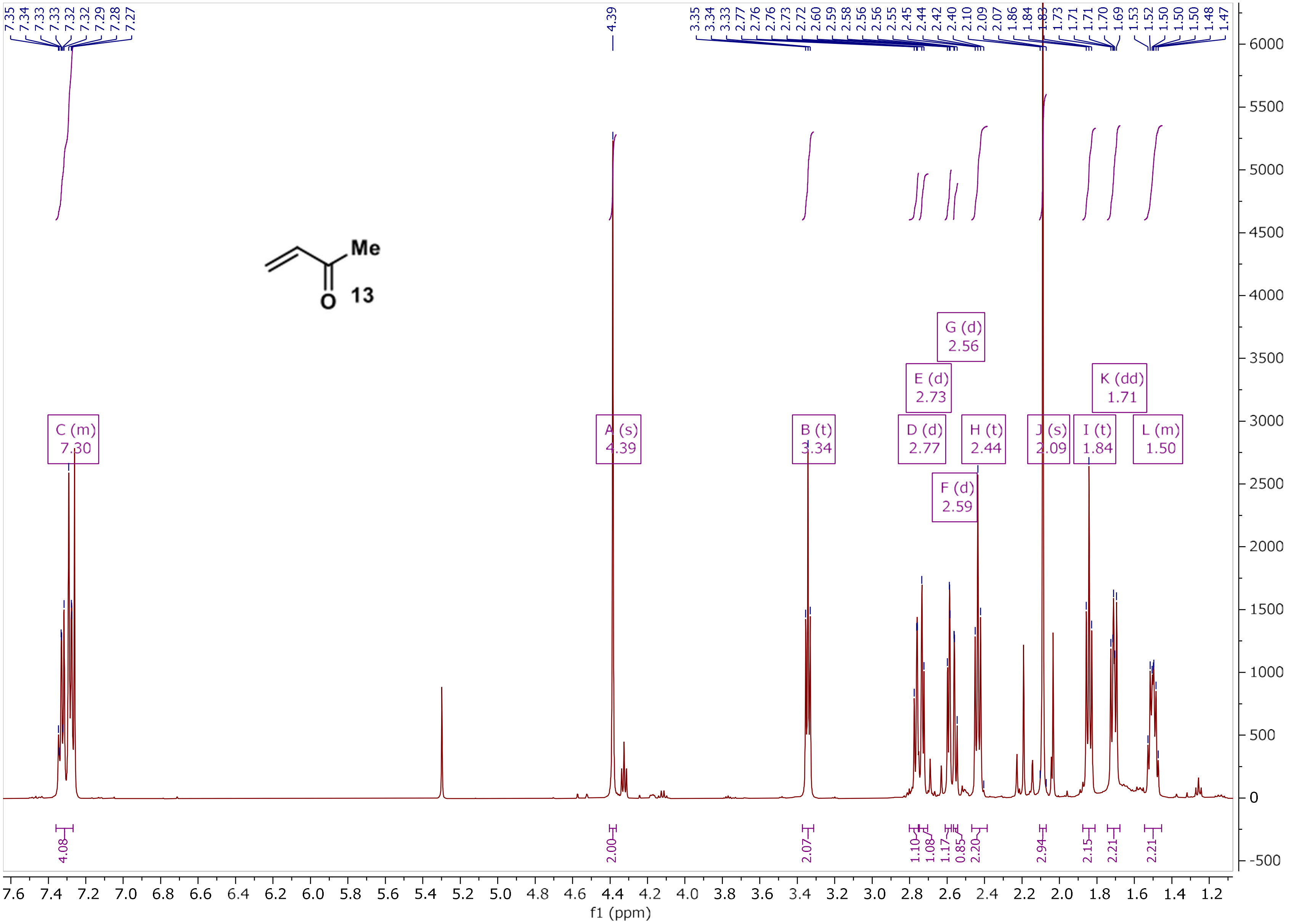
10



Me
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C (m) 7.30
A (s) 4.39
B (t) 3.34
D (d) 2.77
E (d) 2.73
F (d) 2.59
G (d) 2.56
H (t) 2.44
J (s) 2.09
I (t) 1.84
K (dd) 1.71
L (m) 1.50
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2.07
1.10
1.08
1.17
0.85
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2.94
2.15
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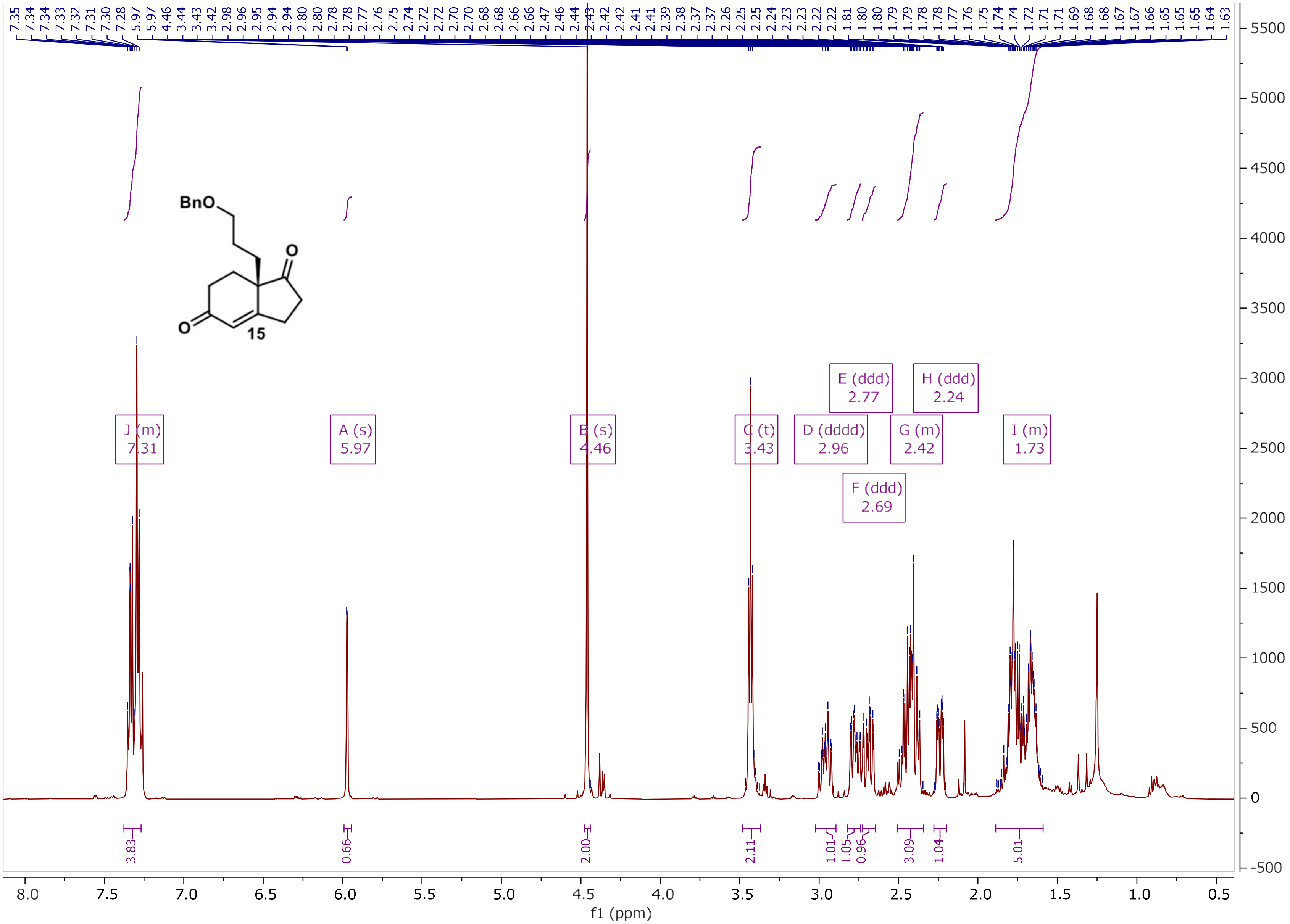
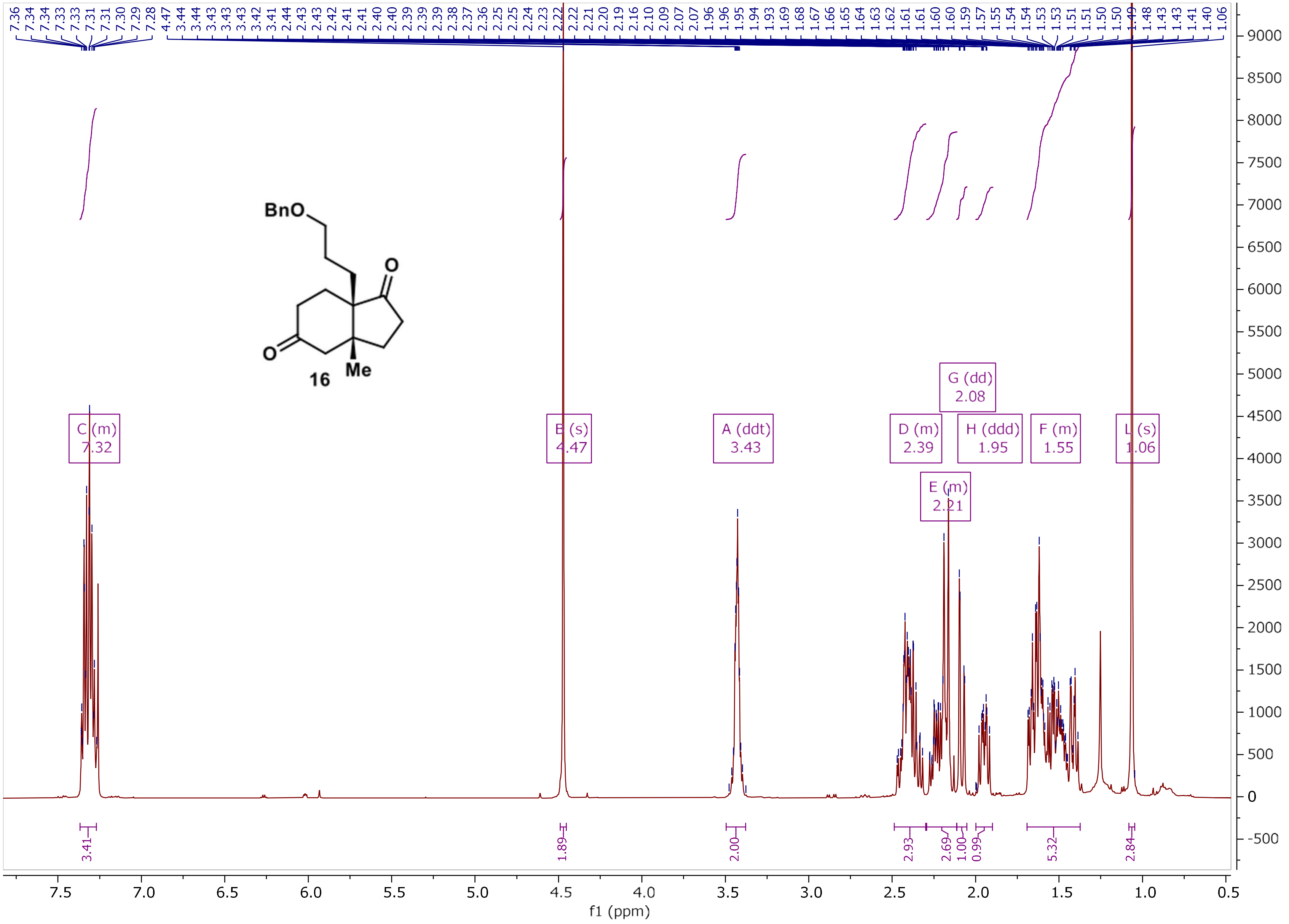
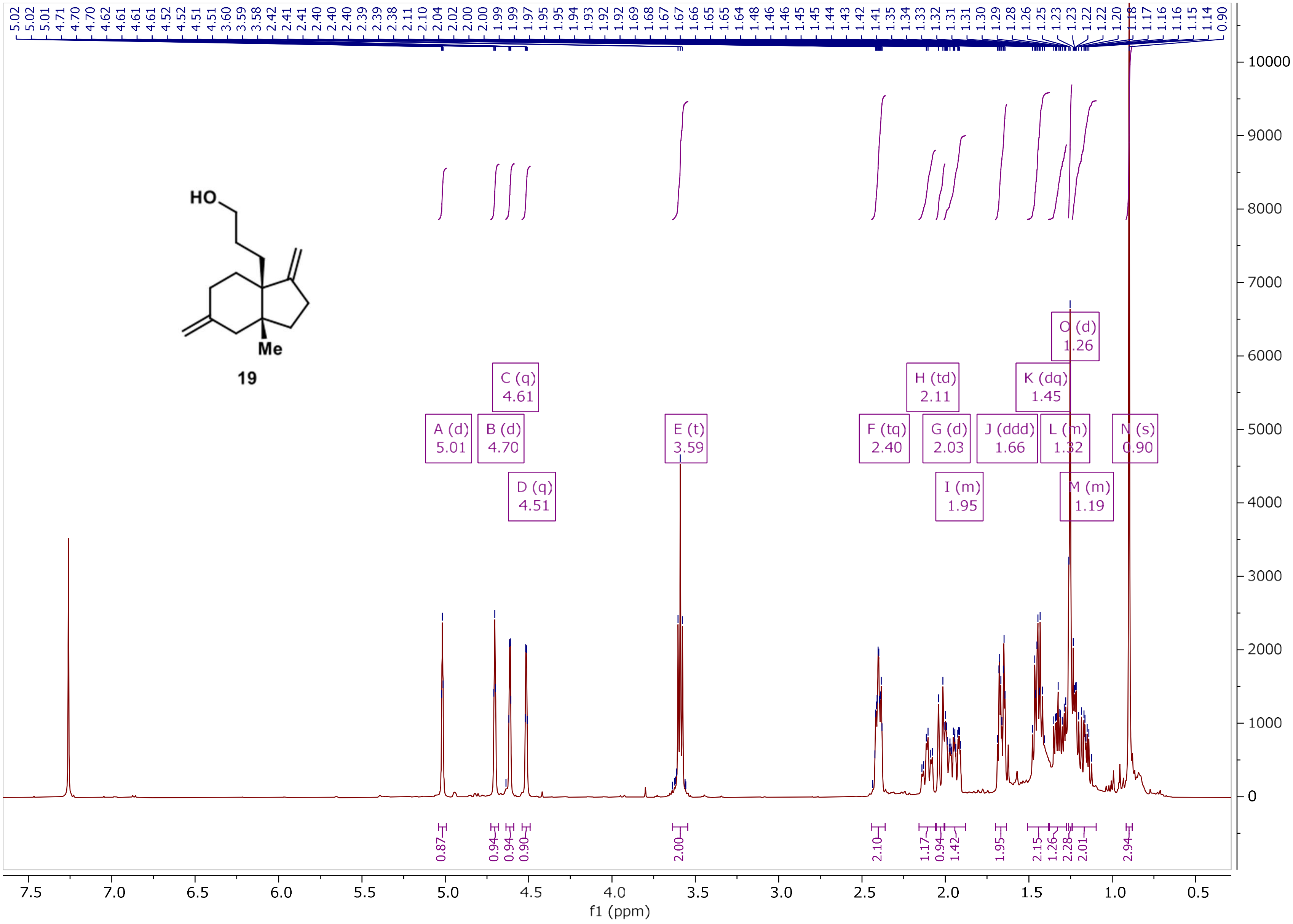
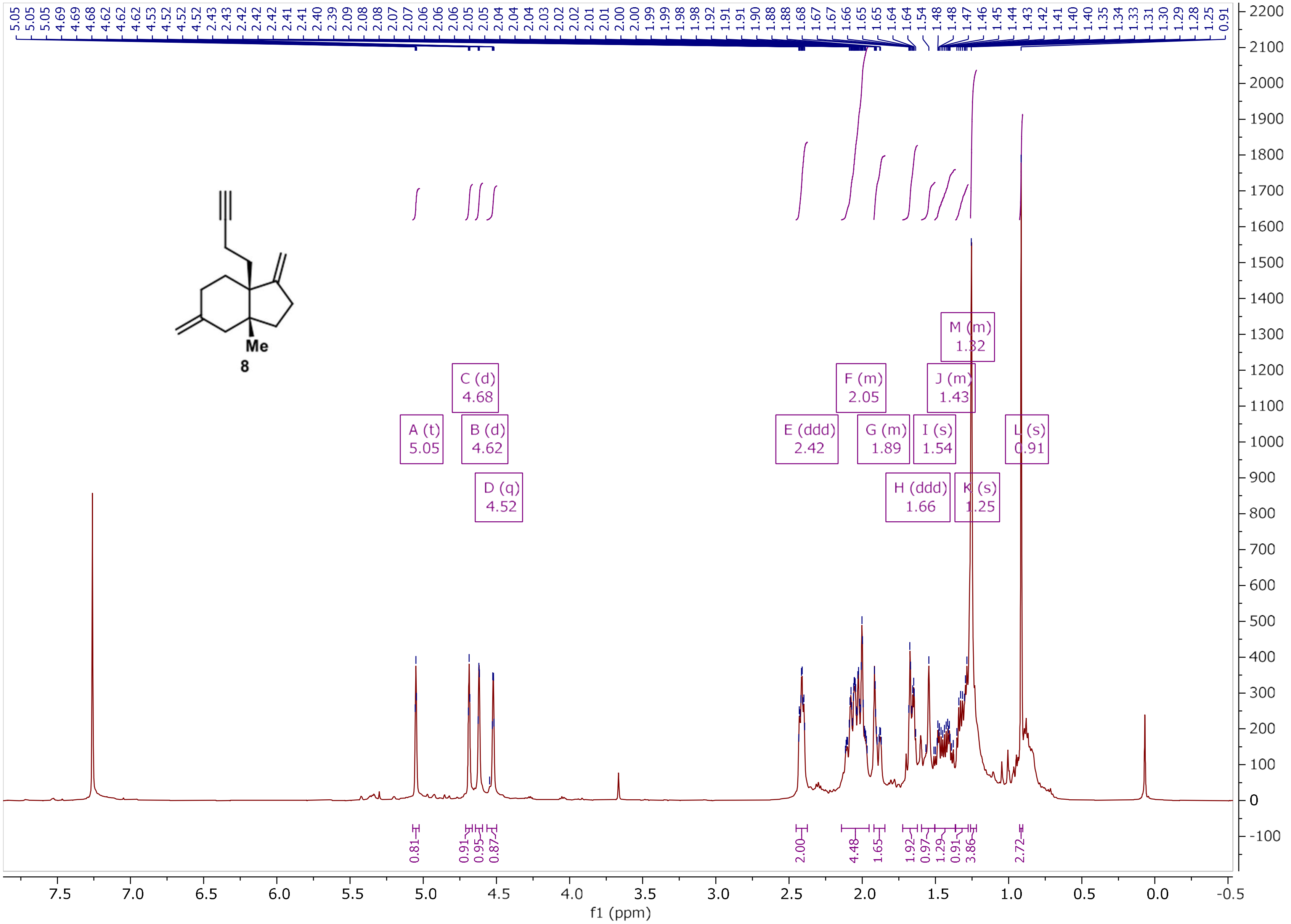
2.21
f1 (ppm)


7.35 7.34 7.34 7.33 7.32 7.31 7.30 7.28 5.97 5.97 4.46 3.44 3.43 3.42 2.98 2.96 2.95 2.94 2.94 2.80 2.80 2.78 2.77 2.76 2.75 2.74 2.72 2.72 2.70 2.70 2.68 2.68 2.66 2.66 2.47 2.46 2.44 2.43 2.42 2.42 2.41 2.41 2.39 2.38 2.37 2.37 2.26 2.25 2.25 2.24 2.23 2.23 2.22 2.22 1.81 1.80 1.80 1.79 1.79 1.78 1.78 1.77 1.76 1.75 1.74 1.74 1.72 1.72 1.71 1.71 1.69 1.68 1.68 1.67 1.67 1.66 1.65 1.65 1.65 1.64 1.63
BnO
O
O
15
J (m) 7.31
A (s) 5.97
B (s) 4.46
C (t) 3.43
D (dddd) 2.96
E (ddd) 2.77
F (ddd) 2.69
G (m) 2.42
H (ddd) 2.24
I (m) 1.73
3.83
0.66
2.00
2.11
1.01
1.05
0.96
3.09
1.04
5.01
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

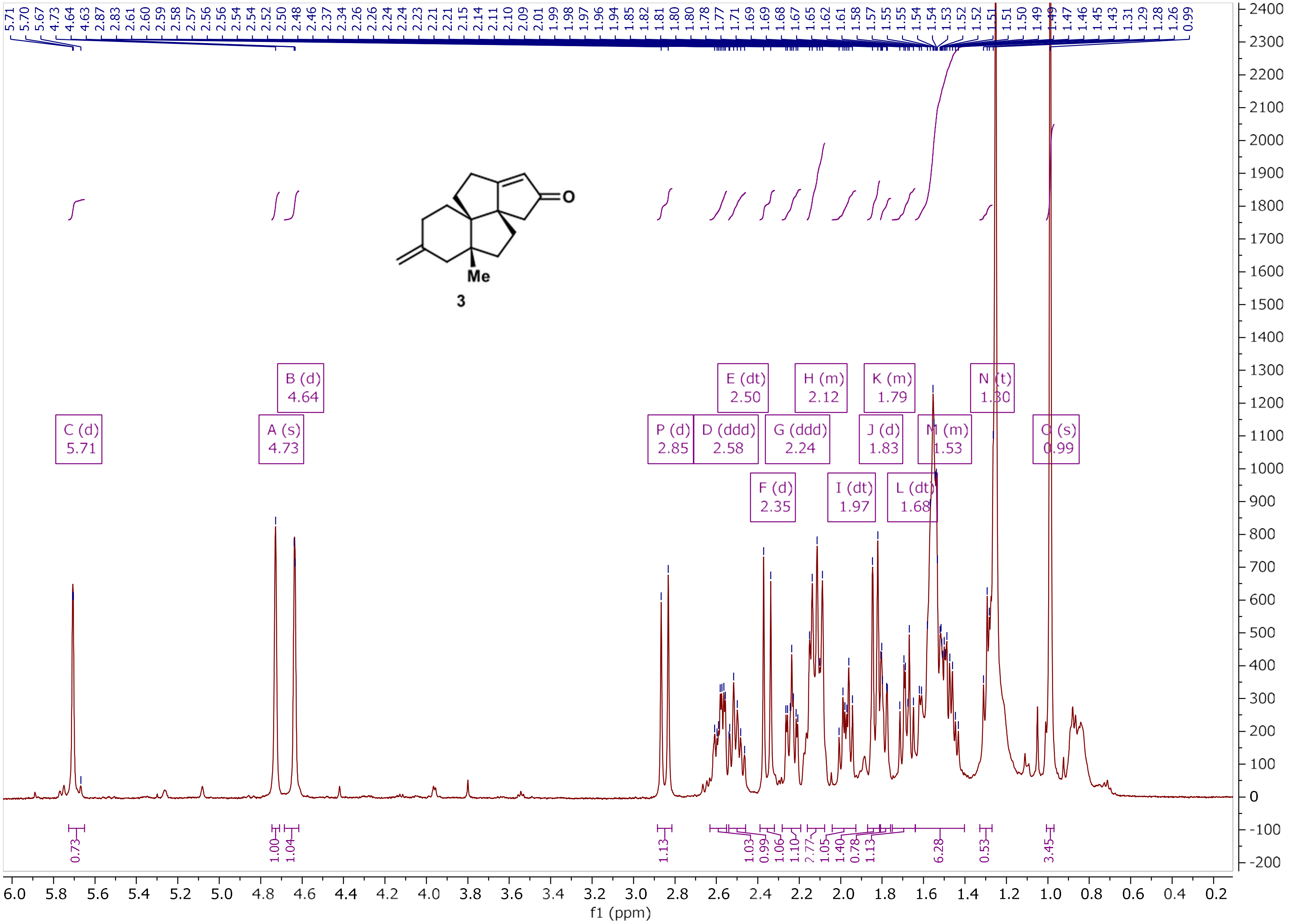

16

7.36 7.34 7.34 7.33 7.33 7.31 7.31 7.30 7.29 7.28 4.47 3.44 3.44 3.43 3.43 3.43 3.42 3.41 2.44 2.43 2.43 2.42 2.41 2.41 2.40 2.40 2.39 2.39 2.38 2.37 2.36 2.25 2.25 2.24 2.23 2.22 2.22 2.21 2.20 2.19 2.16 2.10 2.09 2.07 2.07 1.96 1.96 1.95 1.94 1.93 1.69 1.68 1.67 1.66 1.65 1.64 1.63 1.62 1.61 1.61 1.60 1.60 1.59 1.57 1.55 1.54 1.54 1.53 1.53 1.51 1.51 1.50 1.50 1.49 1.48 1.43 1.43 1.41 1.40 1.06
BnO
O
O
Me
C (m) 7.32
B (s) 4.47
A (ddt) 3.43
D (m) 2.39
E (m) 2.21
G (dd) 2.08
H (ddd) 1.95
F (m) 1.55
L (s) 1.06
3.41
1.89
2.00
2.93
2.69
1.00
0.99
5.32
2.84
9000 8500 8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500
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)

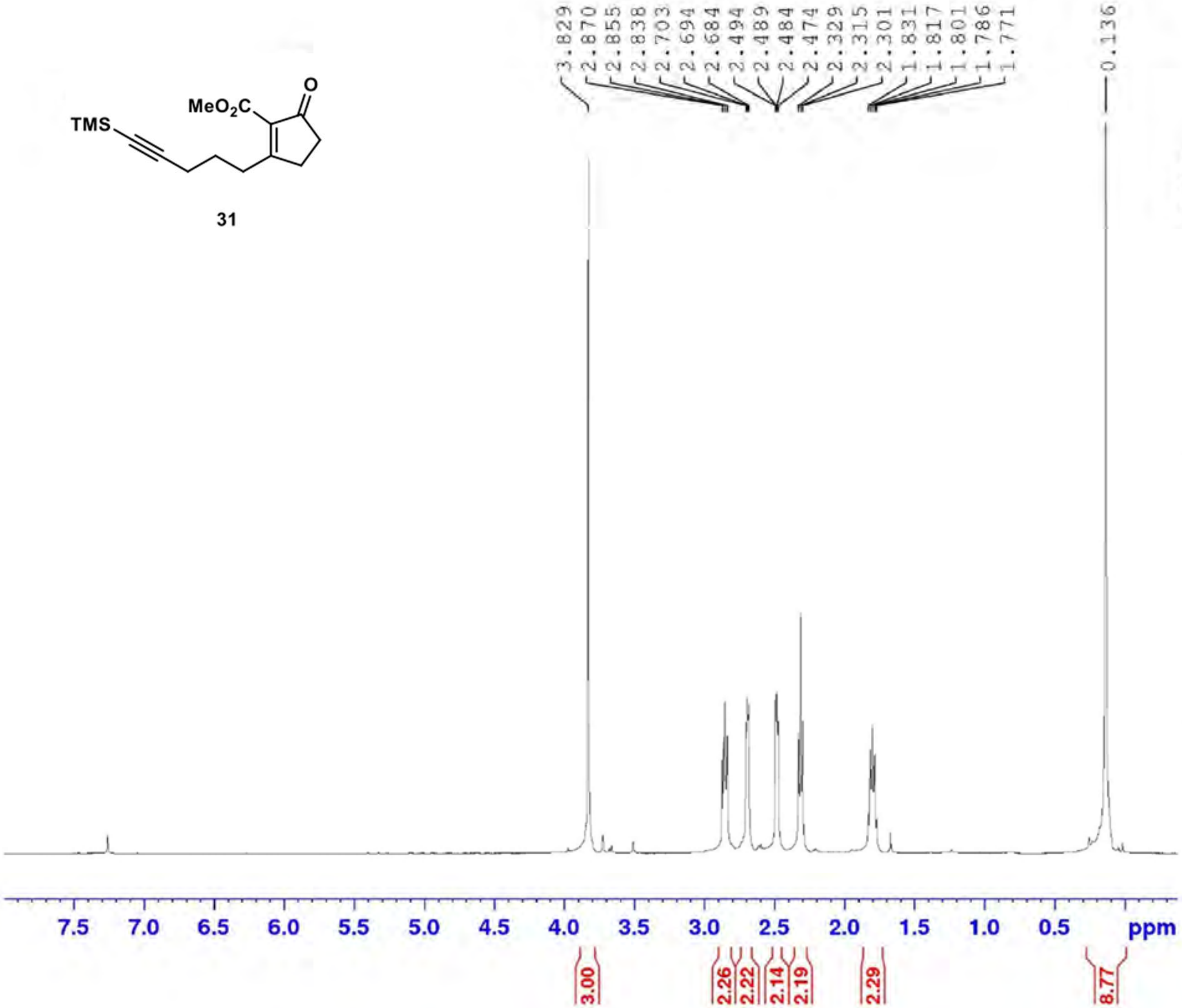

5.02 5.02 5.01 4.71 4.70 4.70 4.62 4.61 4.61 4.61 4.52 4.52 4.51 4.51 3.60 3.59 3.58 2.42 2.41 2.41 2.40 2.40 2.40 2.39 2.39 2.38 2.11 2.10 2.04 2.02 2.00 2.00 1.99 1.99 1.97 1.95 1.95 1.94 1.93 1.92 1.92 1.69 1.68 1.67 1.67 1.66 1.65 1.65 1.64 1.48 1.46 1.46 1.45 1.45 1.44 1.43 1.42 1.41 1.35 1.34 1.33 1.32 1.31 1.31 1.30 1.29 1.28 1.26 1.25 1.23 1.23 1.22 1.22 1.20 1.18 1.17 1.16 1.16 1.15 1.14 0.90
HO
Me
19
A (d) 5.01
B (d) 4.70
C (q) 4.61
D (q) 4.51
E (t) 3.59
F (tq) 2.40
G (d) 2.03
H (td) 2.11
I (m) 1.95
J (ddd) 1.66
K (dq) 1.45
L (m) 1.32
M (m) 1.19
N (s) 0.90
O (d) 1.26
0.87
0.94
0.94
0.90
2.00
2.10
1.17
0.94
1.42
1.95
2.15
1.26
2.28
2.01
2.94
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



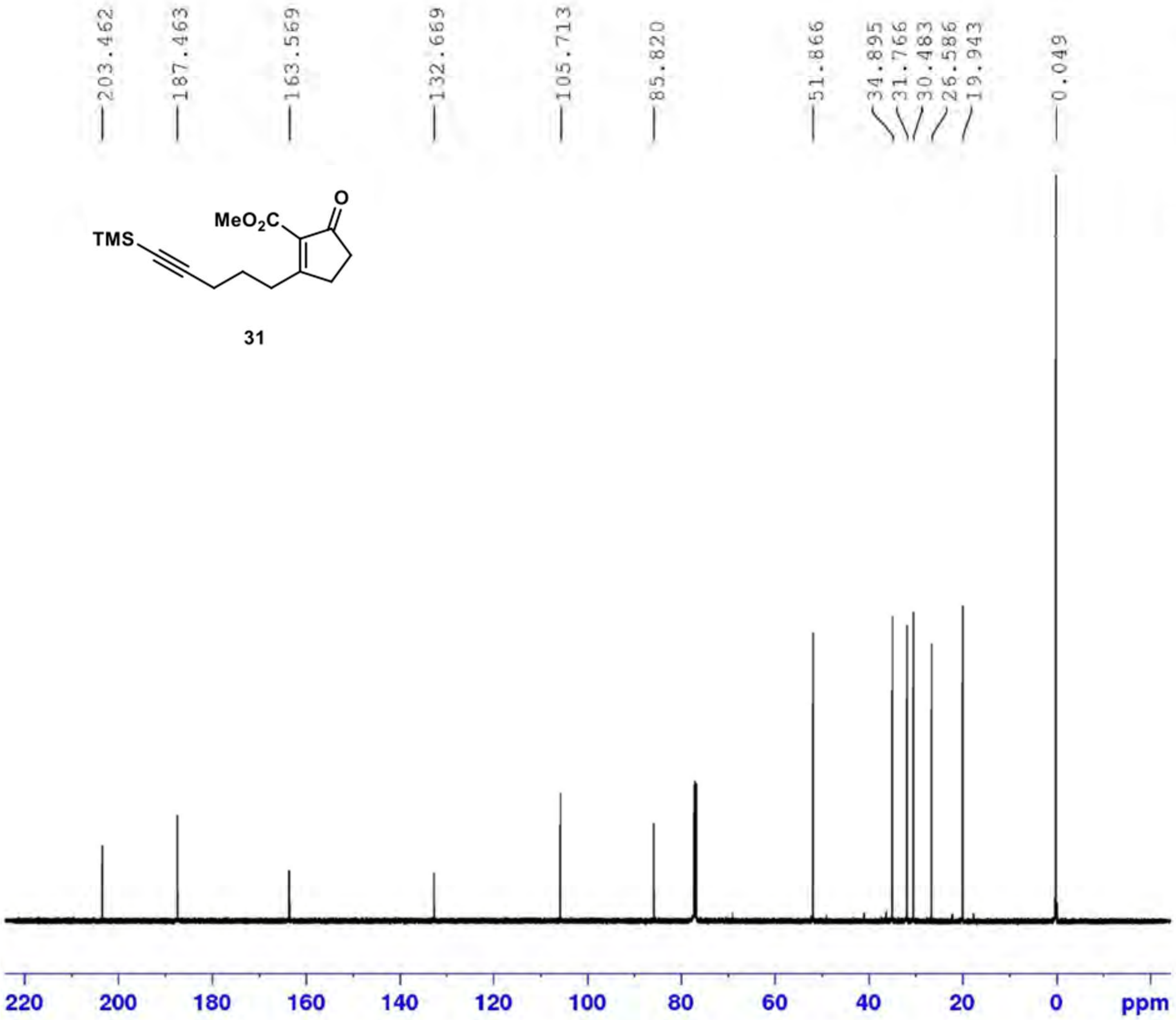
5.05
5.05
5.05
4.69
4.68
4.62
4.62
4.62
4.53
4.52
4.52
4.52
2.43
2.43
2.42
2.42
2.42
2.41
2.40
2.39
2.09
2.08
2.08
2.07
2.07
2.06
2.06
2.06
2.05
2.05
2.05
2.04
2.04
2.04
2.03
2.02
2.02
2.01
2.01
2.00
2.00
1.99
1.99
1.98
1.98
1.92
1.91
1.91
1.90
1.88
1.88
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.64
1.54
1.48
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.41
1.40
1.35
1.34
1.33
1.31
1.30
1.29
1.28
1.25
0.91
Me
8
A (t) 5.05
B (d) 4.62
C (d) 4.68
D (q) 4.52
E (ddd) 2.42
F (m) 2.05
G (m) 1.89
H (ddd) 1.66
I (s) 1.54
J (m) 1.43
K (s) 1.25
L (s) 0.91
M (m) 1.32
0.81
0.91
0.95
0.87
2.00
4.48
1.65
1.92
0.97
1.29
0.91
3.86
2.72
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)


5.71 5.70 5.67 4.73 4.64 4.63 2.87 2.83 2.61 2.60 2.59 2.58 2.57 2.56 2.56 2.54 2.54 2.52 2.50 2.48 2.46 2.37 2.34 2.26 2.26 2.24 2.24 2.23 2.21 2.21 2.15 2.14 2.11 2.10 2.09 2.01 1.99 1.98 1.97 1.96 1.94 1.85 1.82 1.81 1.80 1.80 1.78 1.77 1.71 1.69 1.69 1.68 1.67 1.65 1.62 1.61 1.58 1.57 1.55 1.55 1.54 1.54 1.53 1.52 1.52 1.51 1.51 1.50 1.49 1.49 1.47 1.46 1.45 1.43 1.31 1.29 1.28 1.26 0.99
O
Me
3
C (d) 5.71
A (s) 4.73
B (d) 4.64
P (d) 2.85
D (ddd) 2.58
E (dt) 2.50
F (d) 2.35
G (ddd) 2.24
H (m) 2.12
I (dt) 1.97
J (d) 1.83
K (m) 1.79
L (dt) 1.68
M (m) 1.53
N (t) 1.30
O (s) 0.99
0.73
1.00
1.04
1.13
1.03
0.99
1.06
1.10
2.77
1.05
1.40
0.78
1.13
6.28
0.53
3.45
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 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 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)

31

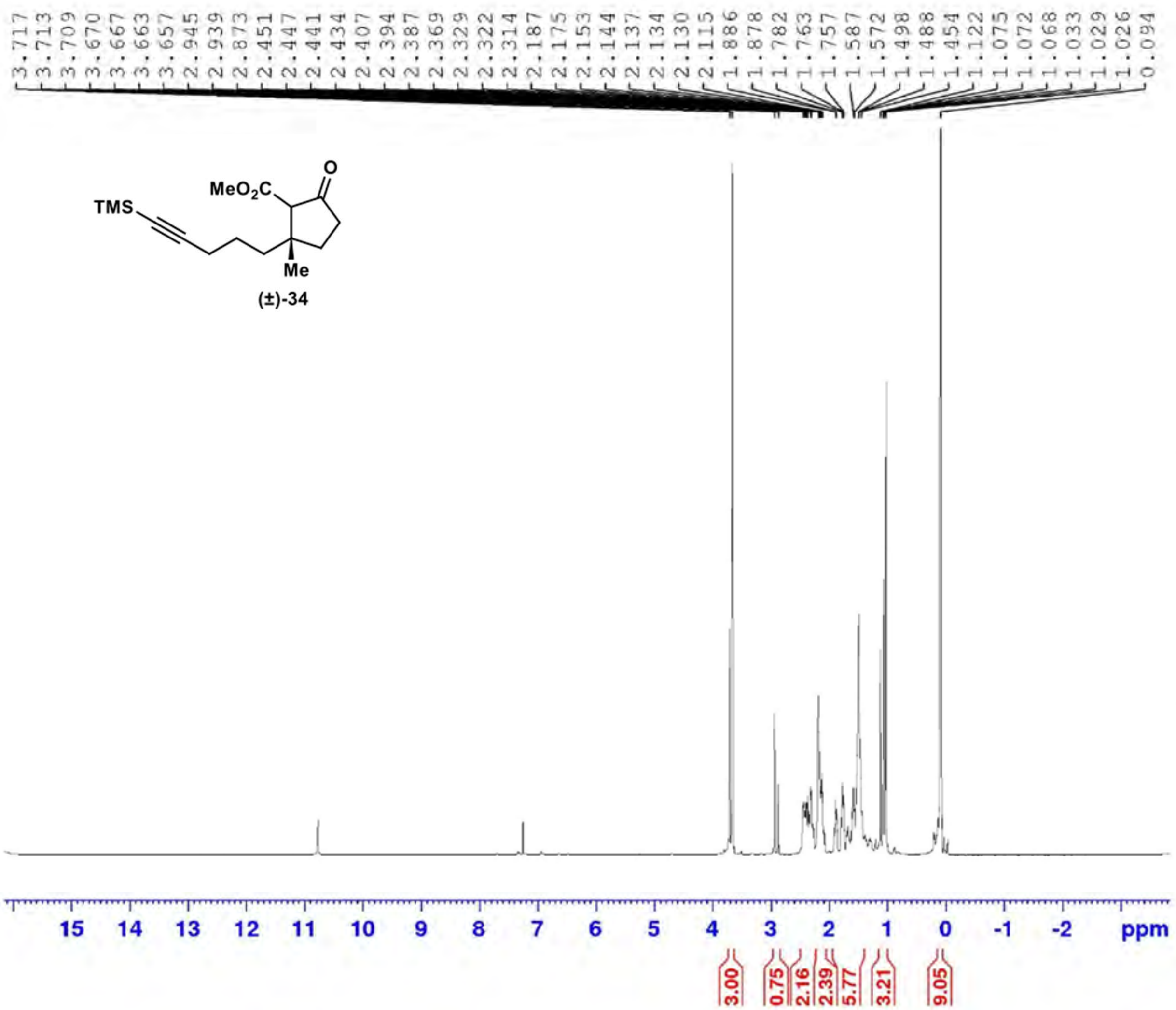


```
Current Data Parameters
NAME     pc-5-130-Collection
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20200306
Time                  18.25
INSTRUM               spect
PROBHD   5 mm PATXI 1H/
PULPROG                  zg
TD                    59998
SOLVENT               CDCl3
NS                        8
DS                        0
SWH             10000.000 Hz
FIDRES           0.166672 Hz
AQ              2.9999001 sec
RG                    46.36
DW                   50.000 usec
DE                    10.00 usec
TE                    294.4 K
D1               2.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                     1H
P1                     9.90 usec
PLW1          12.19999981 W

F2 - Processing parameters
SI                    65536
SF           500.1300134 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.00
```

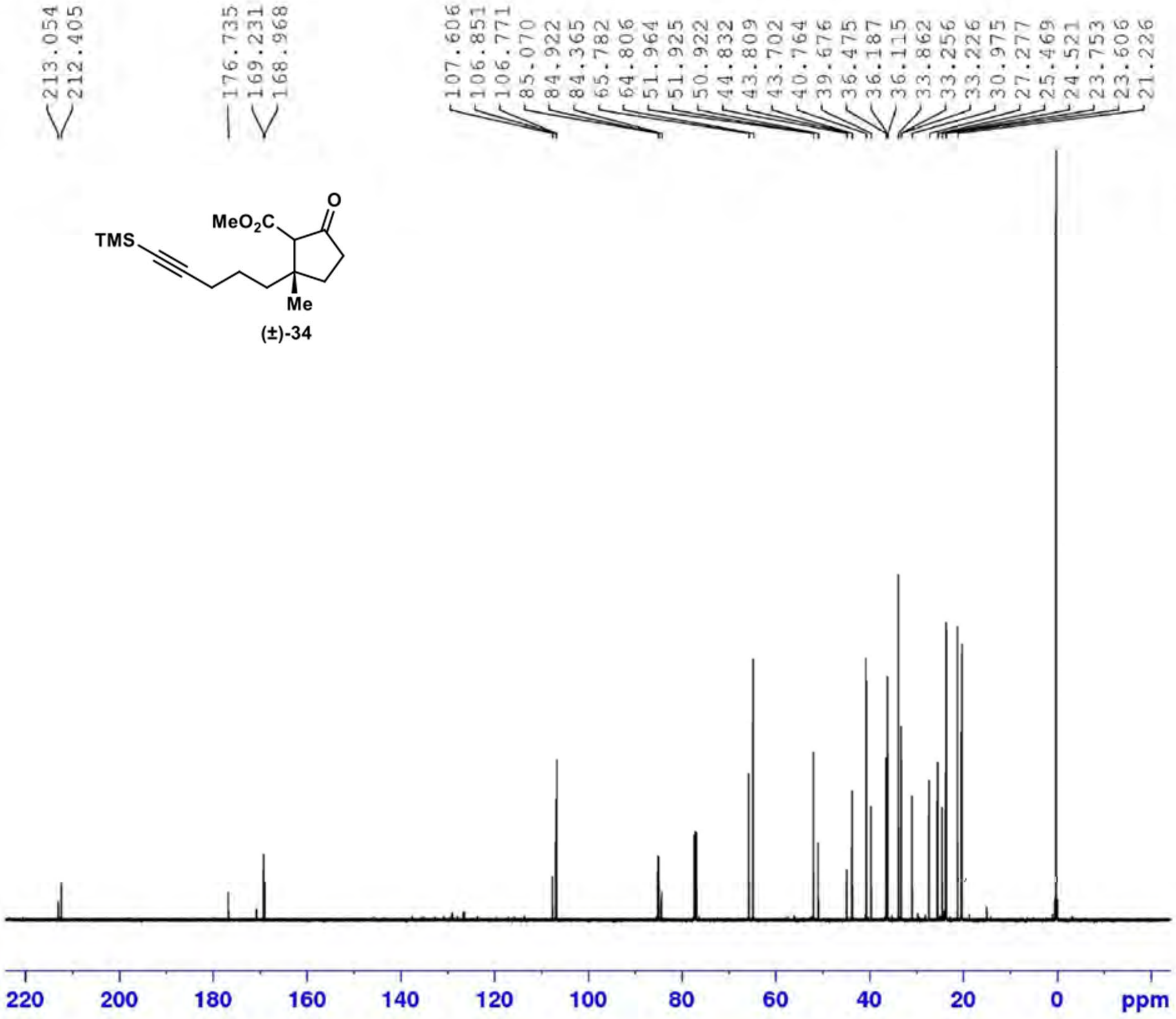


31

```
Current Data Parameters
NAME     PA-5-SAS-tetraenone
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20200307
Time                   2.10 h
INSTRUM               spect
PROBHD     Z113652_0187 (
PULPROG                zgdc
TD                   187496
SOLVENT               CDCl3
NS                      500
DS                        0
SWH               31250.000 Hz
FIDRES             0.333340 Hz
AQ                2.9999361 sec
RG                     2050
DW                   16.000 usec
DE                     6.50 usec
TE                    297.1 K
D1               3.00000000 sec
D11              0.03000000 sec
TD0                       1
SFO1            125.7049802 MHz
NUC1                    13C
P1                    10.00 usec
PLW1            72.83999634 W
SFO2            499.8724993 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 80.00 usec
PLW2            19.00000000 W
PLW12            0.29688001 W

F2 - Processing parameters
SI                  1048576
SF              125.6924178 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.40
```

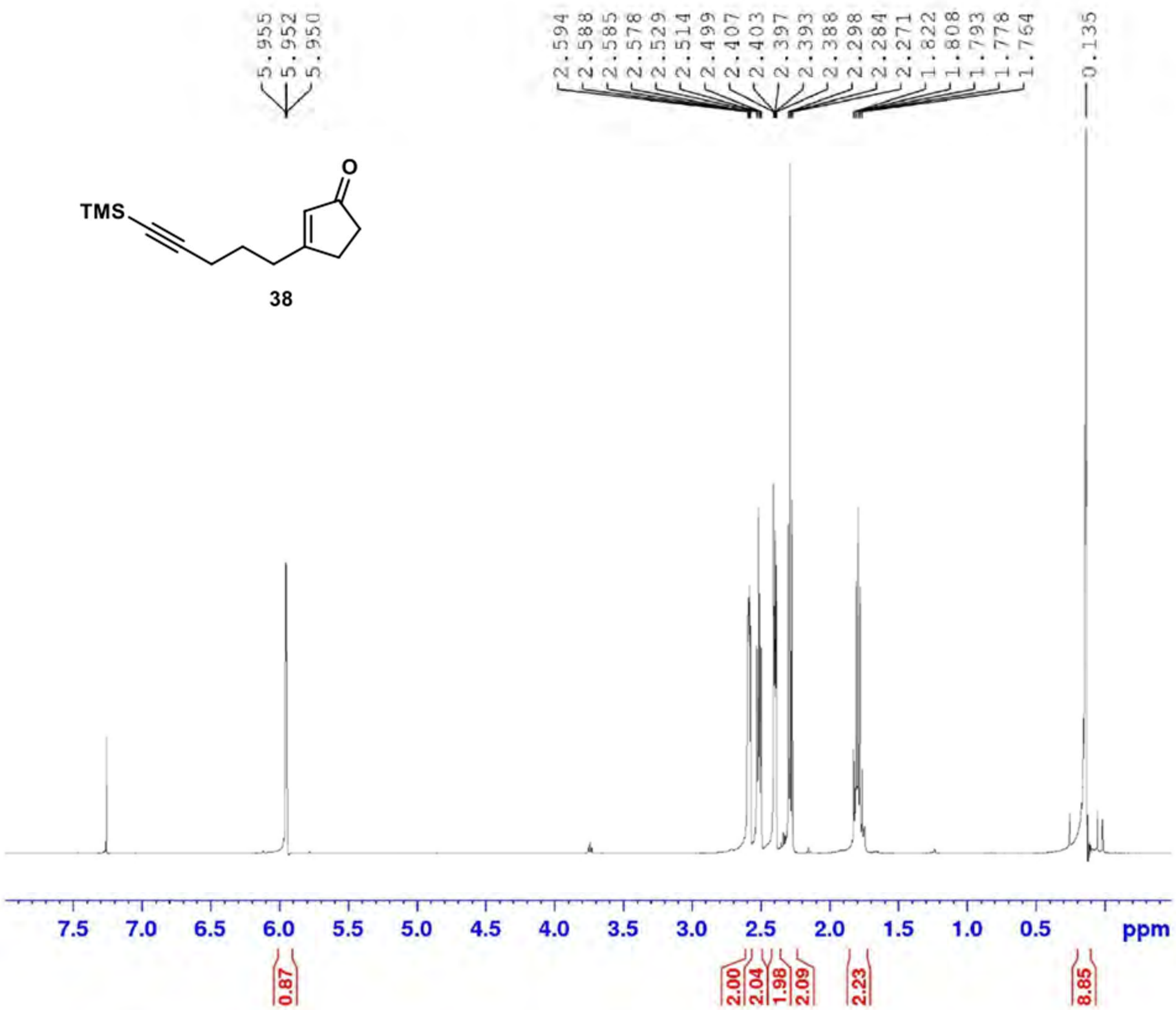


```
Current Data Parameters
NAME     PA-5-SAS-desiredregio
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_            20200307
Time                 0.11 h
INSTRUM             spect
PROBHD   Z113652_0187 (
PULPROG               zg
TD                 59998
SOLVENT            CDCl3
NS                     2
DS                     0
SWH            10000.000 Hz
FIDRES          0.333344 Hz
AQ             2.9999001 sec
RG                  5.21
DW                50.000 usec
DE                  6.50 usec
TE                 297.1 K
D1            3.00000000 sec
TD0                    1
SFO1         499.8730869 MHz
NUC1                  1H
P1                 10.75 usec
PLW1         18.25000000 W

F2 - Processing parameters
SI                 65536
SF           499.8700120 MHz
WDW                   EM
SSB        0
LB                  0.30 Hz
GB         0
PC                  1.00
```



(±)-34

```
Current Data Parameters
NAME      PA-5-SA5-desiredregio
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_             20200307
Time                  1.06 h
INSTRUM              spect
PROBHD   Z113652_0187 (
PULPROG               zgdc
TD                  187496
SOLVENT              CDCl3
NS                     500
DS                       0
SWH              31250.000 Hz
FIDRES            0.333340 Hz
AQ               2.9999361 sec
RG                    2050
DW                  16.000 usec
DE                    6.50 usec
TE                   297.1 K
D1              3.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           125.7049802 MHz
NUC1                   13C
P1                   10.00 usec
PLW1           72.83999634 W
SFO2           499.8724993 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           19.00000000 W
PLW12           0.29688001 W

F2 - Processing parameters
SI                 1048576
SF             125.6924037 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.40
```



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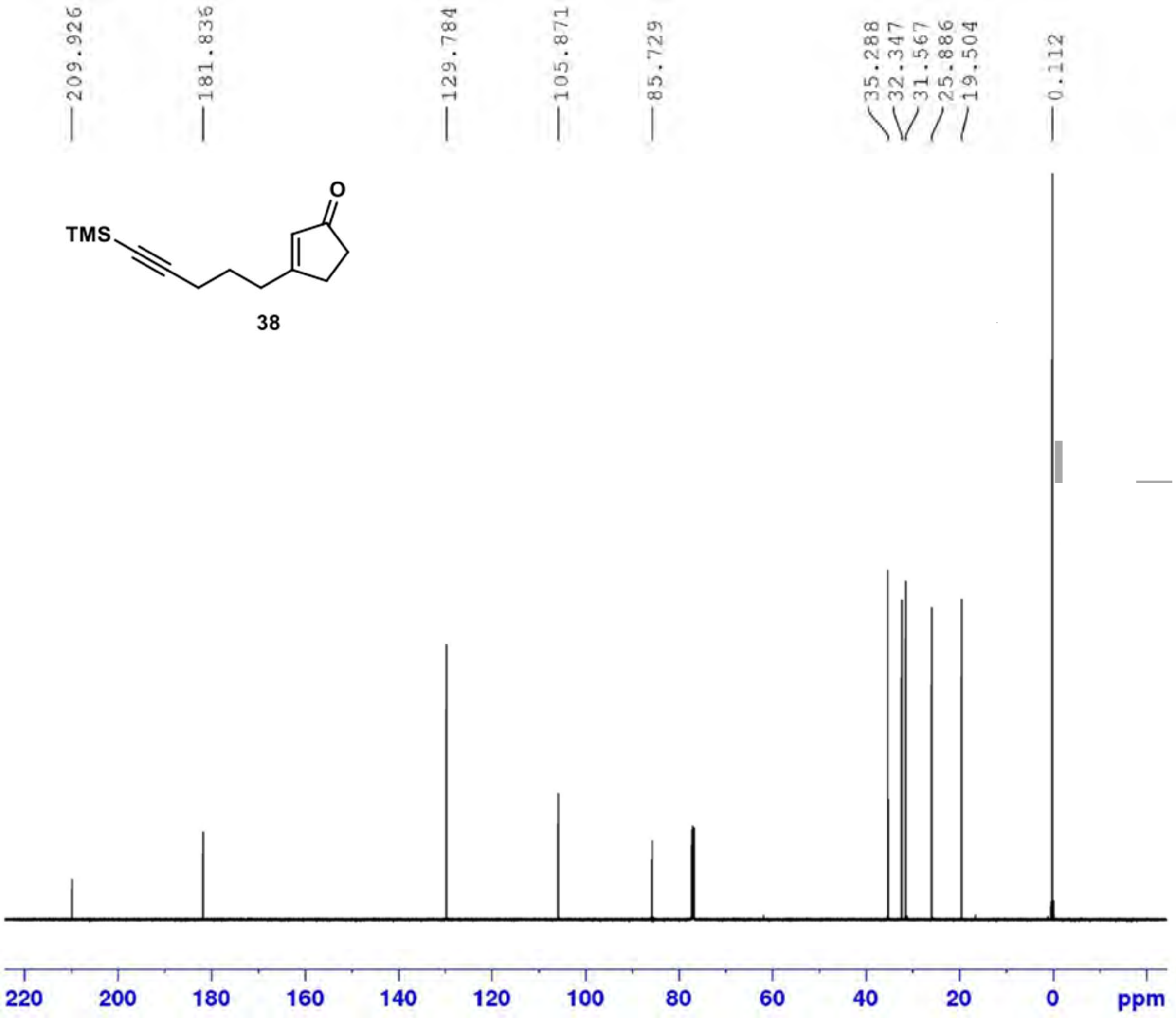
```
Current Data Parameters
NAME      PA-5-SAS-enone
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20200308
Time               20.27 h
INSTRUM            spect
PROBHD    Z113652_0187 (
PULPROG               zg
TD                 59998
SOLVENT            CDCl3
NS                     2
DS                     0
SWH            10000.000 Hz
FIDRES          0.333344 Hz
AQ             2.9999001 sec
RG                 25.24
DW                50.000 usec
DE                  6.50 usec
TE                 297.1 K
D1            3.00000000 sec
TD0                    1
SFO1         499.8730869 MHz
NUC1                  1H
P1                 10.75 usec
PLW1         18.25000000 W

F2 - Processing parameters
SI                 65536
SF           499.8700122 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```



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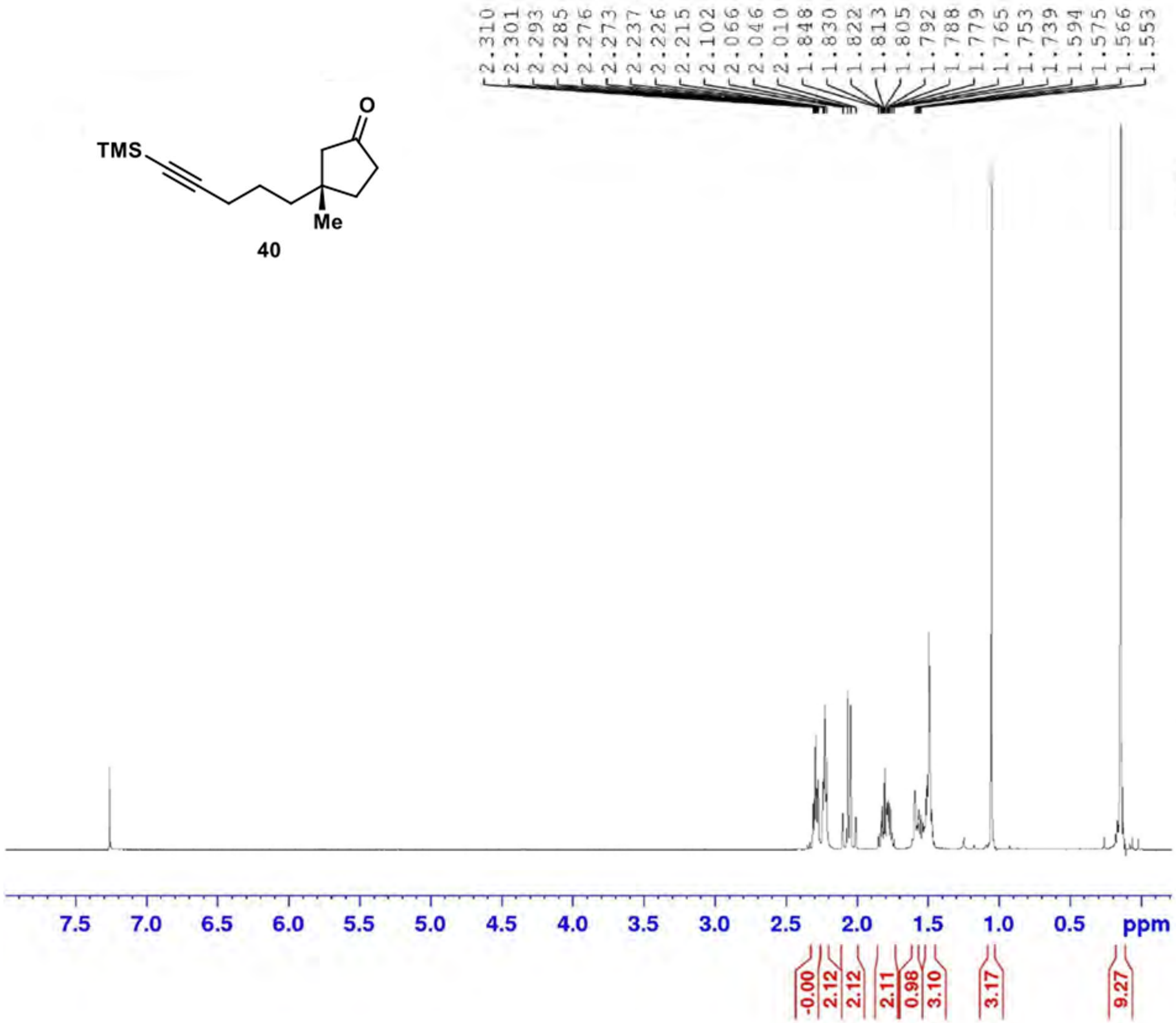
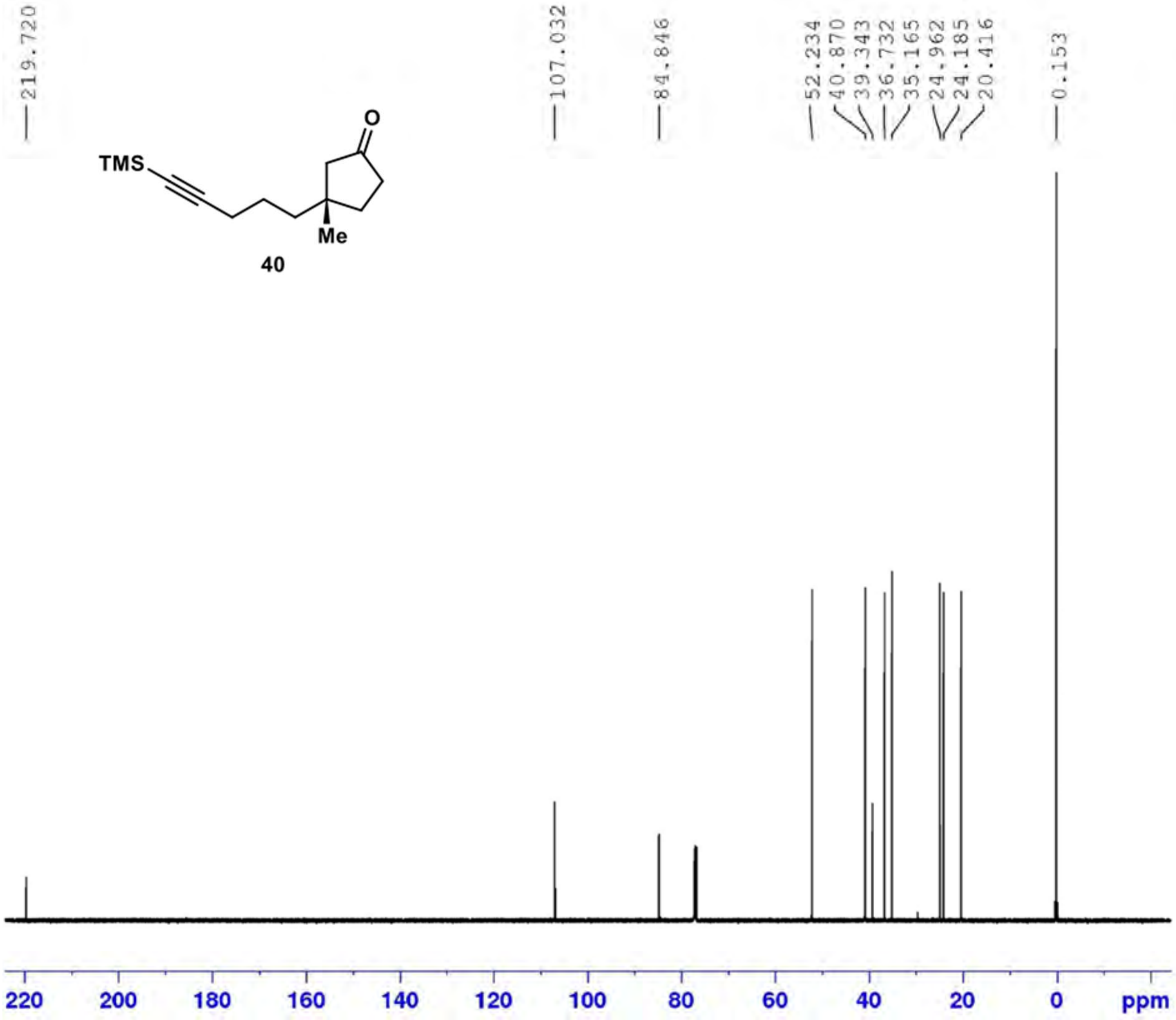
```
Current Data Parameters
NAME     PA-5-SAS-enone
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20200308
Time              21.19 h
INSTRUM           spect
PROBHD   Z113652_0187 (
PULPROG            zgdc
TD               187496
SOLVENT           CDCl3
NS                  500
DS                    0
SWH           31250.000 Hz
FIDRES         0.333340 Hz
AQ            2.9999361 sec
RG                 2050
DW               16.000 usec
DE                 6.50 usec
TE                297.1 K
D1           3.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        125.7049802 MHz
NUC1                13C
P1                10.00 usec
PLW1        72.83999634 W
SFO2        499.8724993 MHz
NUC2                 1H
CPDPRG[2        waltz16
PCPD2             80.00 usec
PLW2        19.00000000 W
PLW12        0.29688001 W

F2 - Processing parameters
SI              1048576
SF          125.6924182 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.40
```

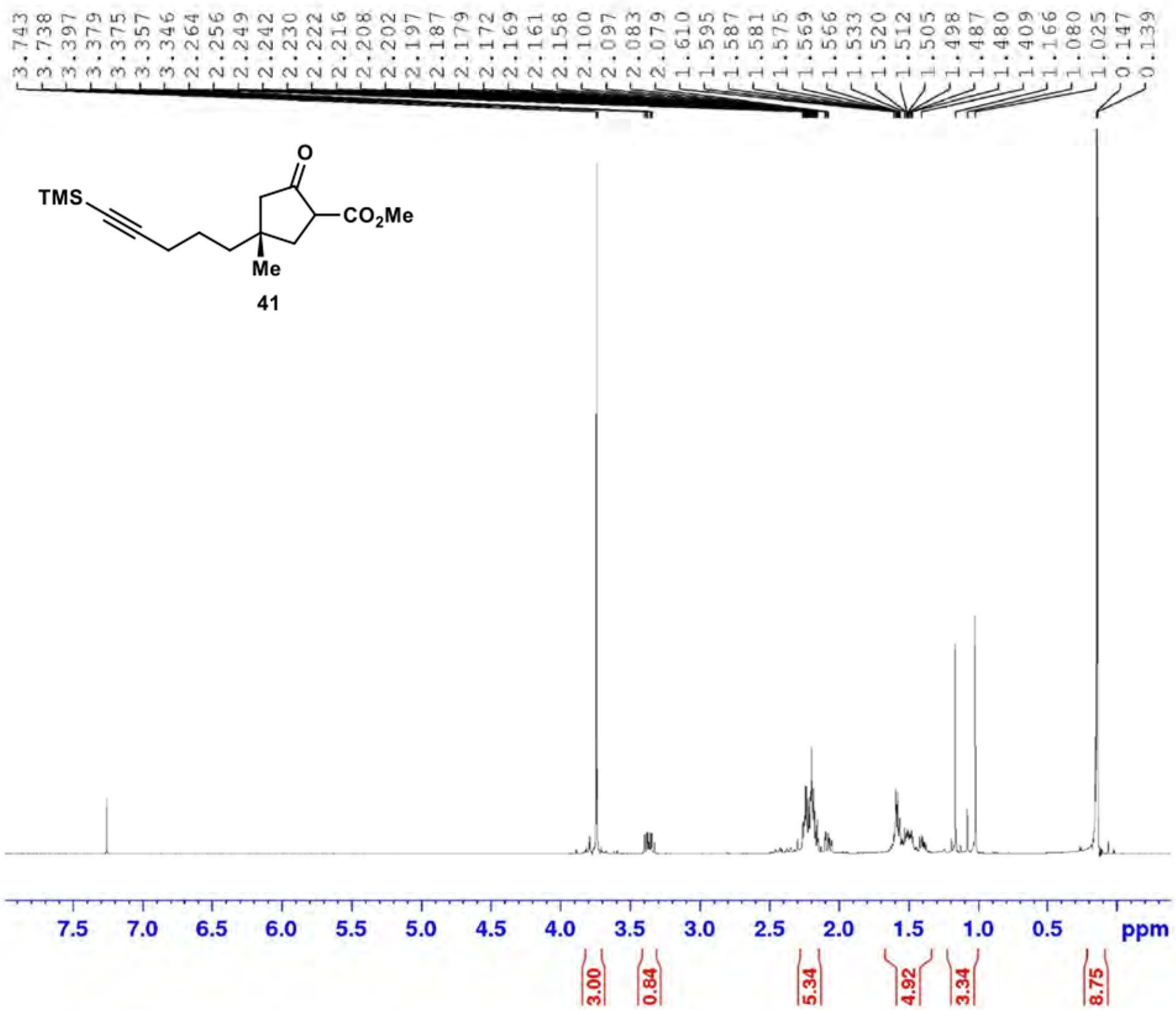
40



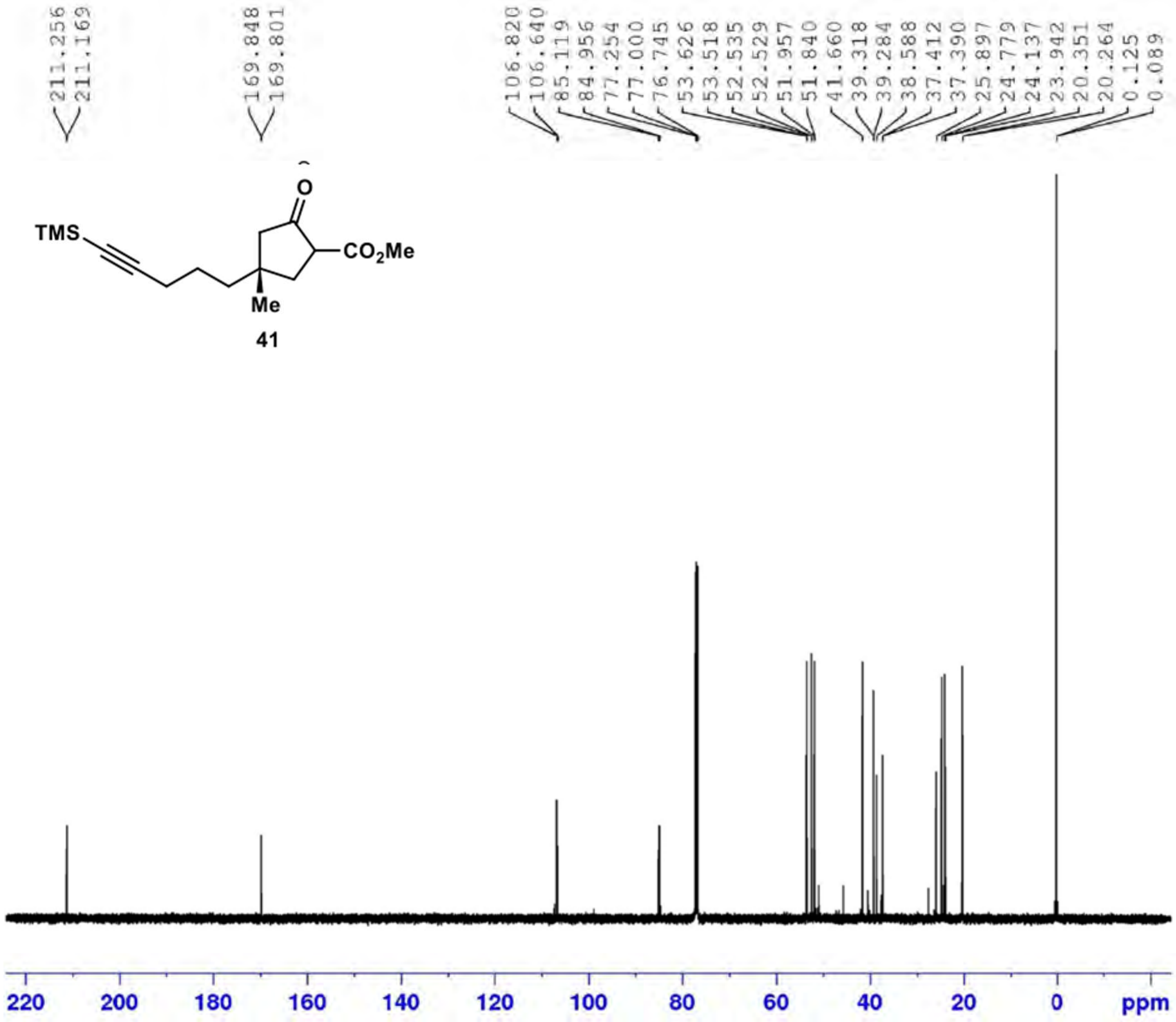
```
Current Data Parameters
NAME      PA-5-SAS-164-2
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20190913
Time               16.47
INSTRUM            spect
PROBHD   5 mm PATXI 1H/
PULPROG               zg
TD                 59998
SOLVENT            CDCl3
NS                     1
DS                     0
SWH            10000.000 Hz
FIDRES          0.166672 Hz
AQ             2.9999001 sec
RG                 87.71
DW                50.000 usec
DE                 10.00 usec
TE                 294.2 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.90 usec
PLW1         12.19999981 W

F2 - Processing parameters
SI                 65536
SF           500.1300133 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```



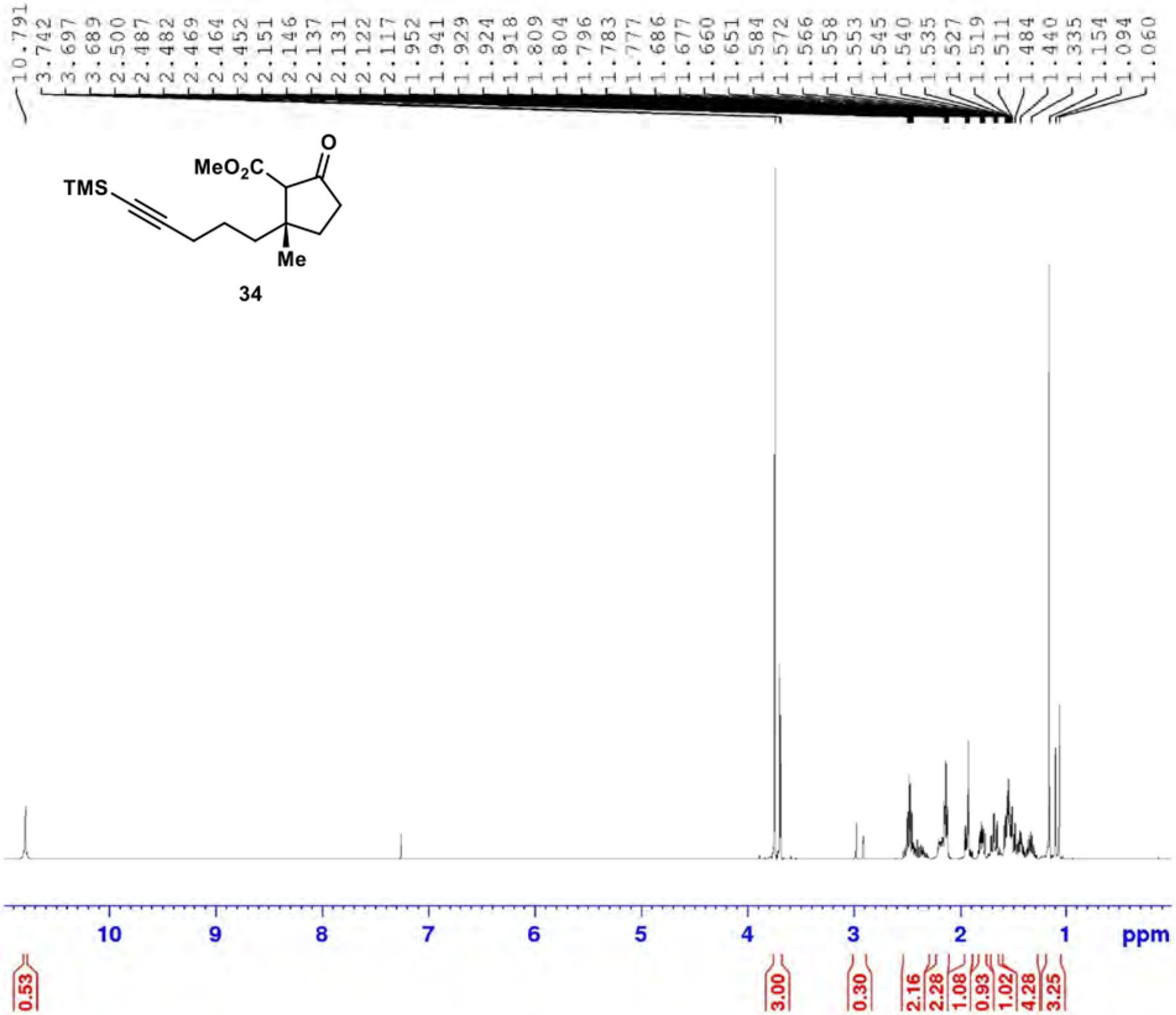
```
Current Data Parameters
NAME      PA-5-SAS-asymmetric
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_             20200305
Time                 17.19 h
INSTRUM              spect
PROBHD    2113652_0187 (
PULPROG               zgdc
TD                  187496
SOLVENT              CDCl3
NS                     161
DS                       0
SWH              31250.000 Hz
FIDRES            0.333340 Hz
AQ               2.9999361 sec
RG                    2050
DW                  16.000 usec
DE                    6.50 usec
TE                   297.1 K
D1              3.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           125.7049802 MHz
NUC1                   13C
P1                   10.00 usec
PLW1           72.83999634 W
SFO2           499.8724993 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           19.00000000 W
PLW12           0.29688001 W

F2 - Processing parameters
SI                 1048576
SF             125.6924183 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.40
```


41

```
Current Data Parameters
NAME     PA-5-SAS-undesiredregio
EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
Date_              20200311
Time                  19.04 h
INSTRUM               spect
PROBHD   Z113652_0187 (
PULPROG                  zg
TD                    59998
SOLVENT               CDCl3
NS                        2
DS                        0
SWH               10000.000 Hz
FIDRES             0.333344 Hz
AQ                2.9999001 sec
RG                    35.92
DW                   50.000 usec
DE                     6.50 usec
TE                    297.1 K
D1               3.00000000 sec
TD0                       1
SFO1            499.8730869 MHz
NUC1                     1H
P1                    10.75 usec
PLW1            18.25000000 W

F2 - Processing parameters
SI                    65536
SF              499.8700122 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.00
```



```
Current Data Parameters
NAME     PA-5-SAS-undesiredregio
EXPNO                          4
PROCNO                         1

F2 - Acquisition Parameters
Date_             20200311
Time                 19.57 h
INSTRUM              spect
PROBHD   Z113652_0187 (
PULPROG               zgdc
TD                  187496
SOLVENT              CDCl3
NS                     500
DS                       0
SWH              31250.000 Hz
FIDRES            0.333340 Hz
AQ               2.9999361 sec
RG                    2050
DW                  16.000 usec
DE                    6.50 usec
TE                   297.1 K
D1              3.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           125.7049802 MHz
NUC1                   13C
P1                   10.00 usec
PLW1           72.83999634 W
SFO2           499.8724993 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           19.00000000 W
PLW12           0.29688001 W

F2 - Processing parameters
SI                 1048576
SF             125.6924156 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.40
```



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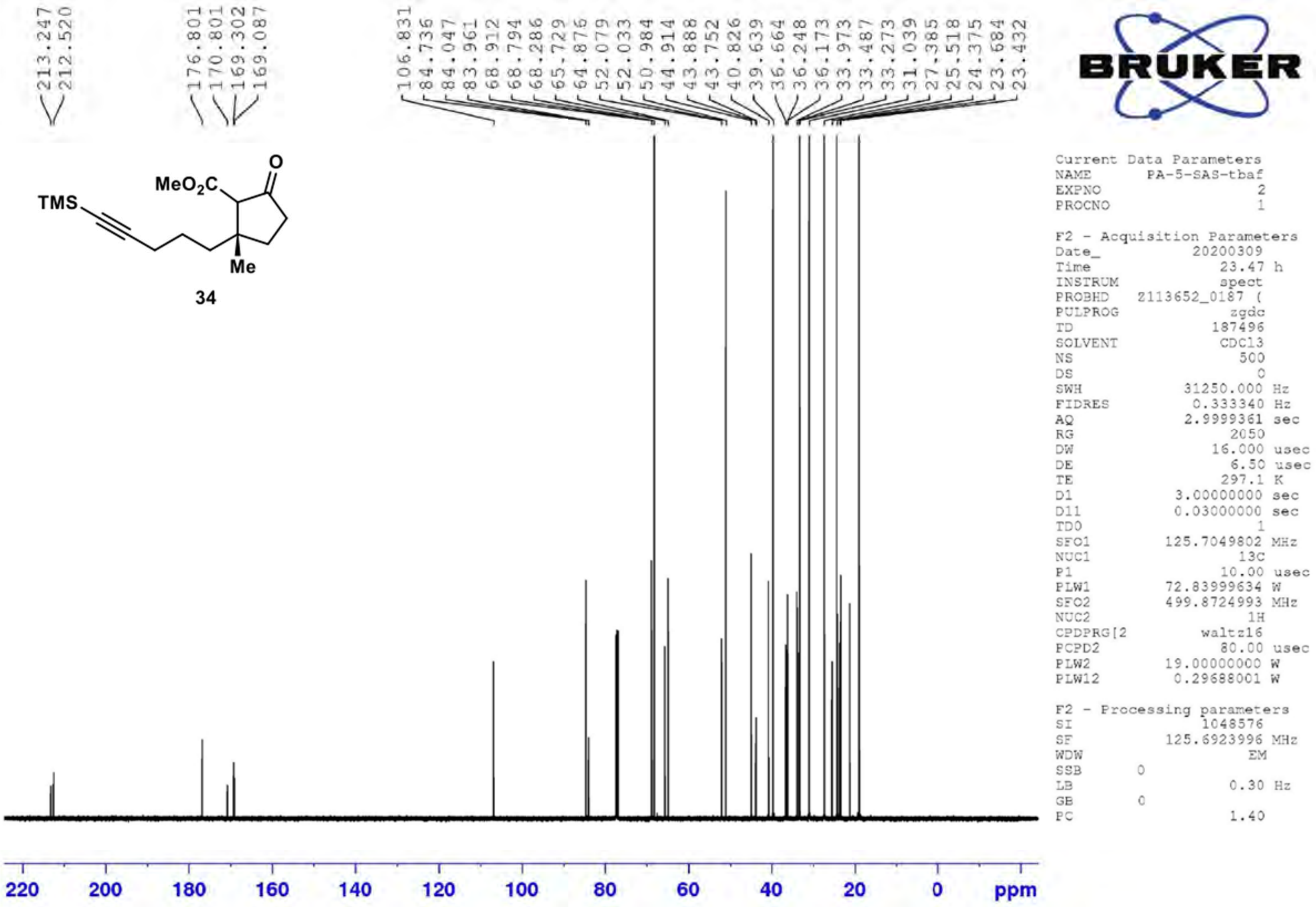
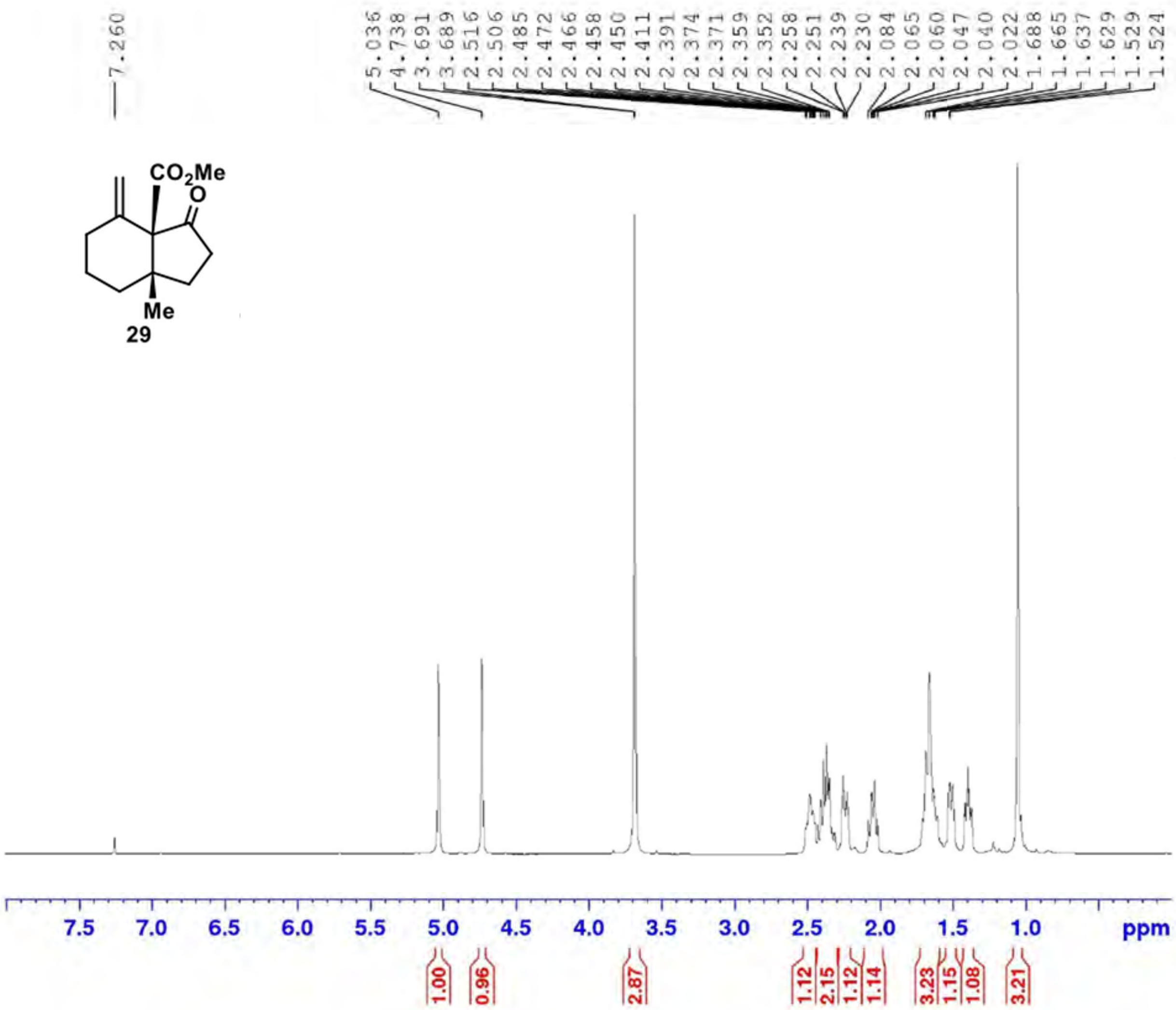
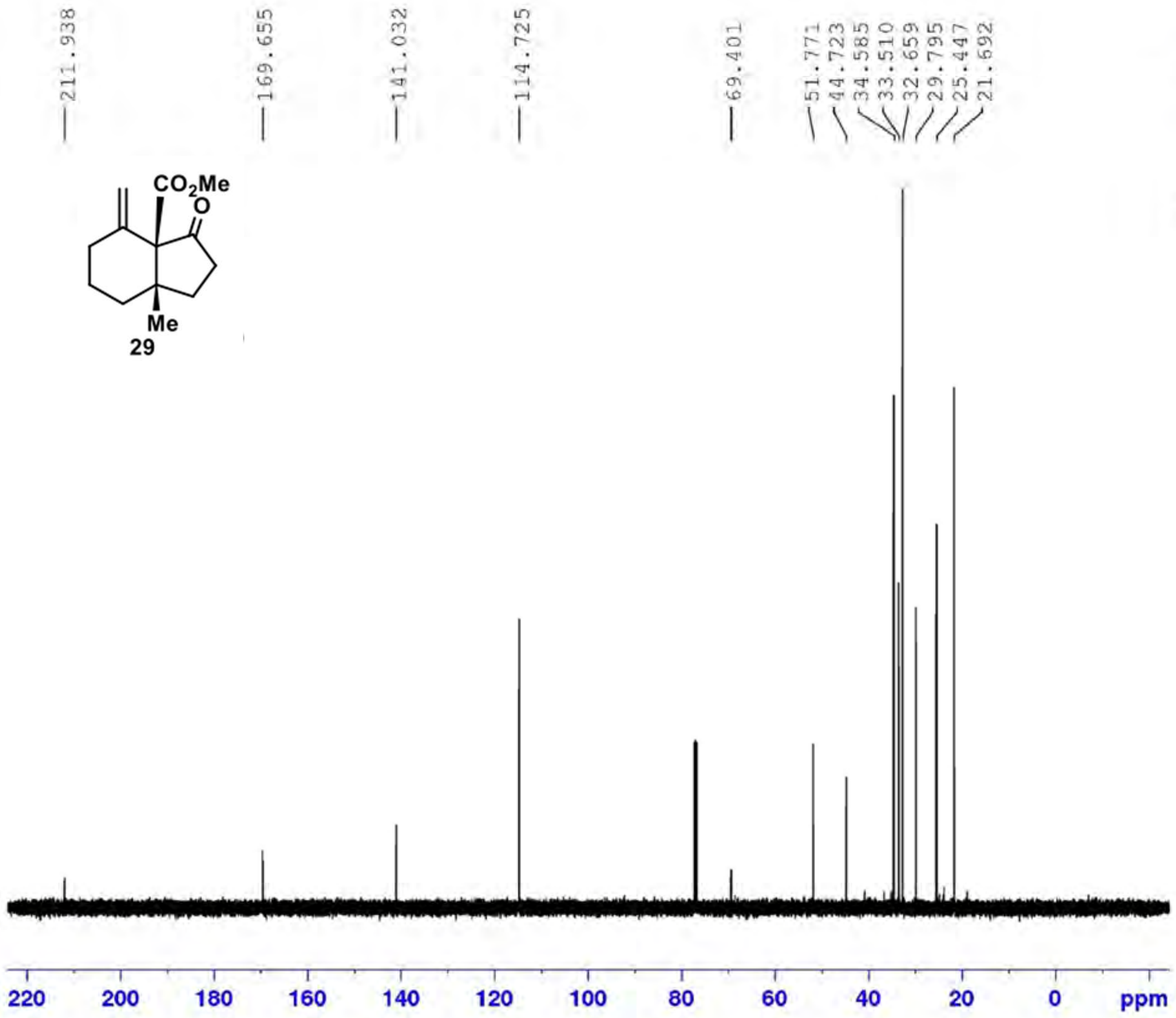
```
Current Data Parameters
NAME          PA-5-SAS-tbaf
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20200309
Time                  22.55 h
INSTRUM               spect
PROBHD   Z113652_0187 (
PULPROG                  zg
TD                    59998
SOLVENT               CDCl3
NS                        2
DS                        0
SWH               10000.000 Hz
FIDRES             0.333344 Hz
AQ                2.9999001 sec
RG                    13.94
DW                   50.000 usec
DE                     6.50 usec
TE                    297.1 K
D1               3.00000000 sec
TD0                       1
SFO1            499.8730869 MHz
NUC1                     1H
P1                    10.75 usec
PLW1            18.25000000 W

F2 - Processing parameters
SI                    65536
SF              499.8700121 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.00
```



```
Current Data Parameters
NAME       PA-5-SAS-tbaf
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20200309
Time               23.47 h
INSTRUM            spect
PROBHD    Z113652_0187 (
PULPROG             zgdc
TD                187496
SOLVENT            CDCl3
NS                   500
DS                     0
SWH            31250.000 Hz
FIDRES          0.333340 Hz
AQ             2.9999361 sec
RG                  2050
DW                16.000 usec
DE                  6.50 usec
TE                 297.1 K
D1            3.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         125.7049802 MHz
NUC1                 13C
P1                 10.00 usec
PLW1         72.83999634 W
SFO2         499.8724993 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         19.00000000 W
PLW12         0.29688001 W

F2 - Processing parameters
SI               1048576
SF           125.6923996 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.40
```



```
Current Data Parameters
NAME      pc-5-82-Collection
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_             20200304
Time                 21.44 h
INSTRUM              spect
PROBHD    Z113652_0187 (
PULPROG                 zg
TD                   59998
SOLVENT              CDCl3
NS                       8
DS                       0
SWH              10000.000 Hz
FIDRES            0.333344 Hz
AQ               2.9999001 sec
RG                   13.94
DW                  50.000 usec
DE                    6.50 usec
TE                   296.4 K
D1              3.00000000 sec
TD0                      1
SFO1           499.8730869 MHz
NUC1                    1H
P1                   10.75 usec
PLW1           18.25000000 W

F2 - Processing parameters
SI                   65536
SF             499.8700122 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.00
```



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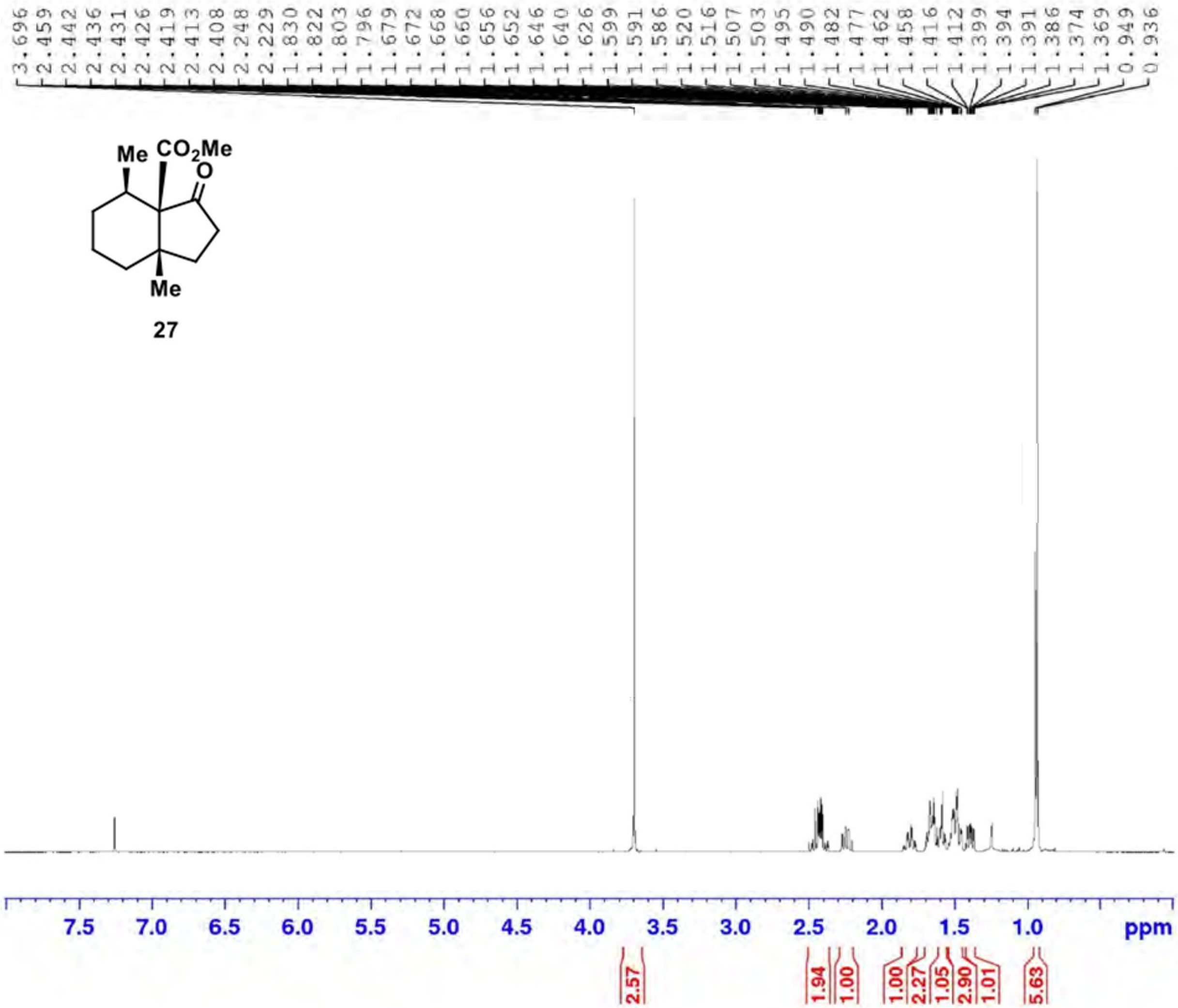
```
Current Data Parameters
NAME     pc-5-82-Collection
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20200304
Time                  21.50 h
INSTRUM               spect
PROBHD   2113652_0187 (
PULPROG                zgdc
TD                   187496
SOLVENT               CDCl3
NS                       40
DS                        0
SWH               31250.000 Hz
FIDRES             0.333340 Hz
AQ                2.9999361 sec
RG                     2050
DW                   16.000 usec
DE                     6.50 usec
TE                    296.3 K
D1               3.00000000 sec
D11              0.03000000 sec
TD0                       1
SFO1           125.7049802 MHz
NUC1                    13C
P1                    10.00 usec
PLW1            72.83999634 W
SFO2           499.8724993 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 80.00 usec
PLW2            19.00000000 W
PLW12            0.29688001 W

F2 - Processing parameters
SI                  1048576
SF             125.6924210 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.40
```

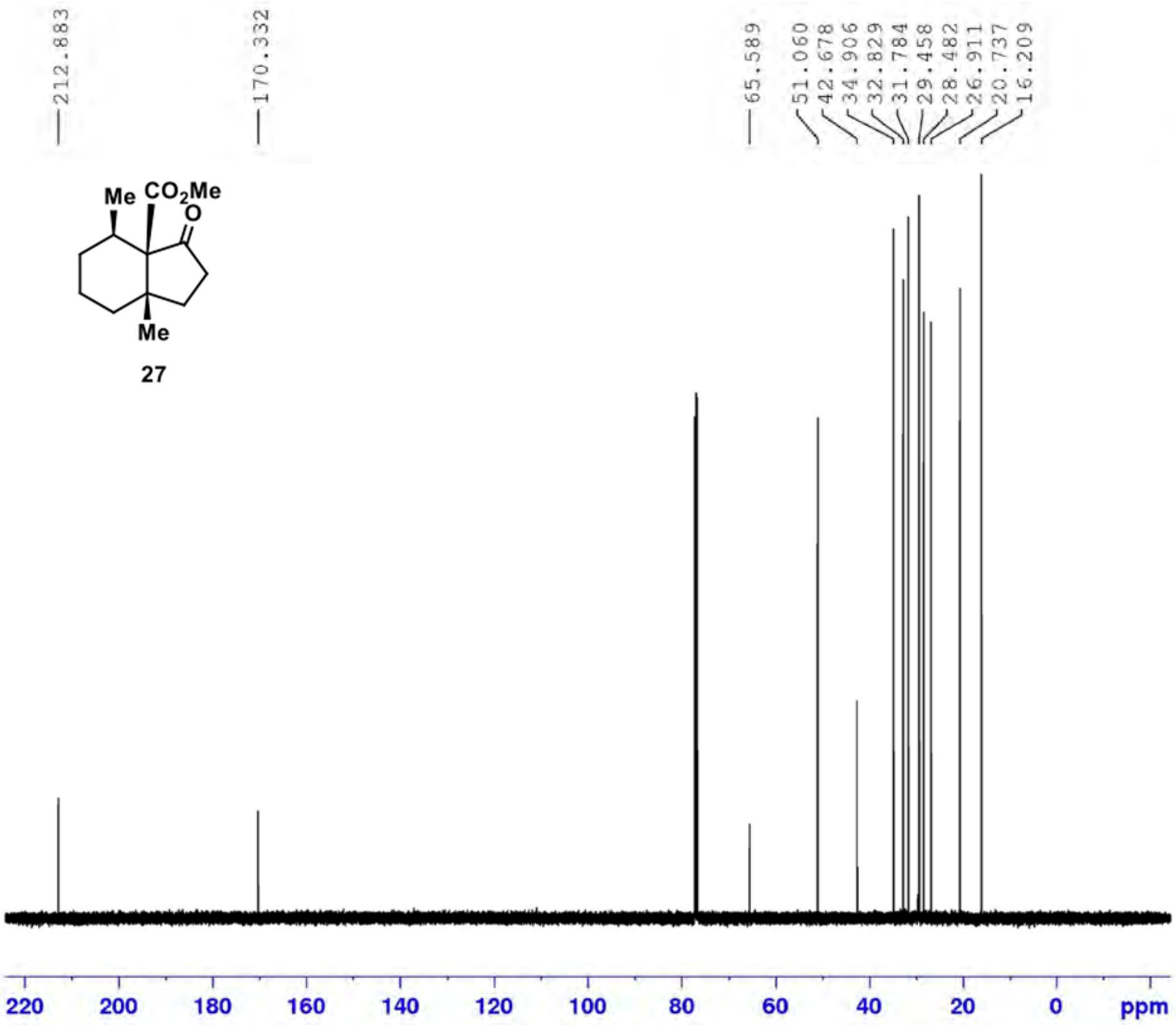


```
Current Data Parameters
NAME      pc-3-157-Collection-H2
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20190805
Time                  20.21
INSTRUM               spect
PROBHD   5 mm PABBO BB/
PULPROG                  zg
TD                    59998
SOLVENT               CDCl3
NS                       16
DS                        0
SWH            10000.000 Hz
FIDRES          0.166672 Hz
AQ             2.9999001 sec
RG                    51.11
DW               50.000 usec
DE                 6.50 usec
TE                298.1 K
D1           3.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1         499.8730869 MHz
NUC1                      1H
P1                 10.75 usec
PLW1         18.25000000 W

F2 - Processing parameters
SI                    65536
SF           499.8700122 MHz
WDW                      EM
SSB      0
LB                  0.30 Hz
GB       0
PC                     1.00
```



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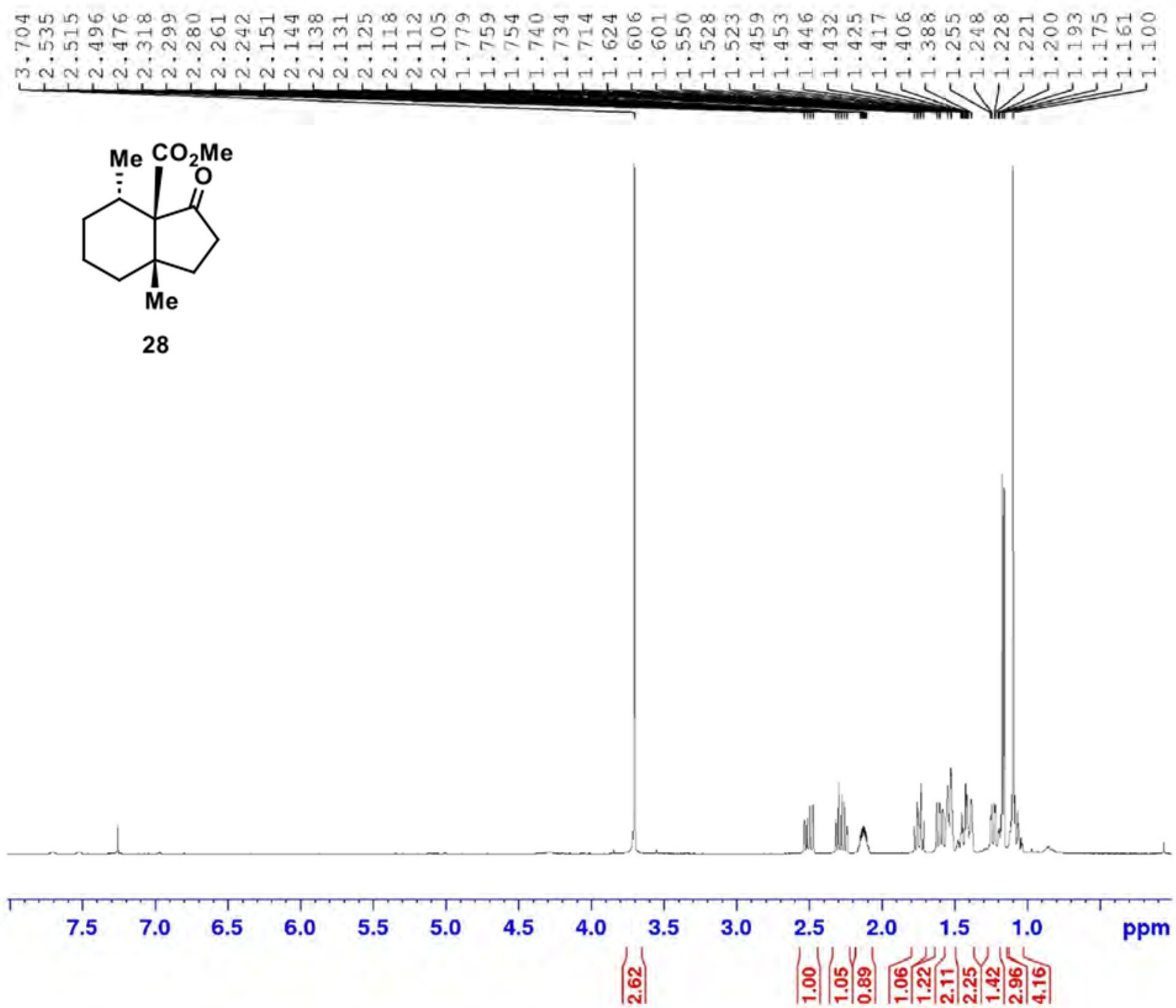
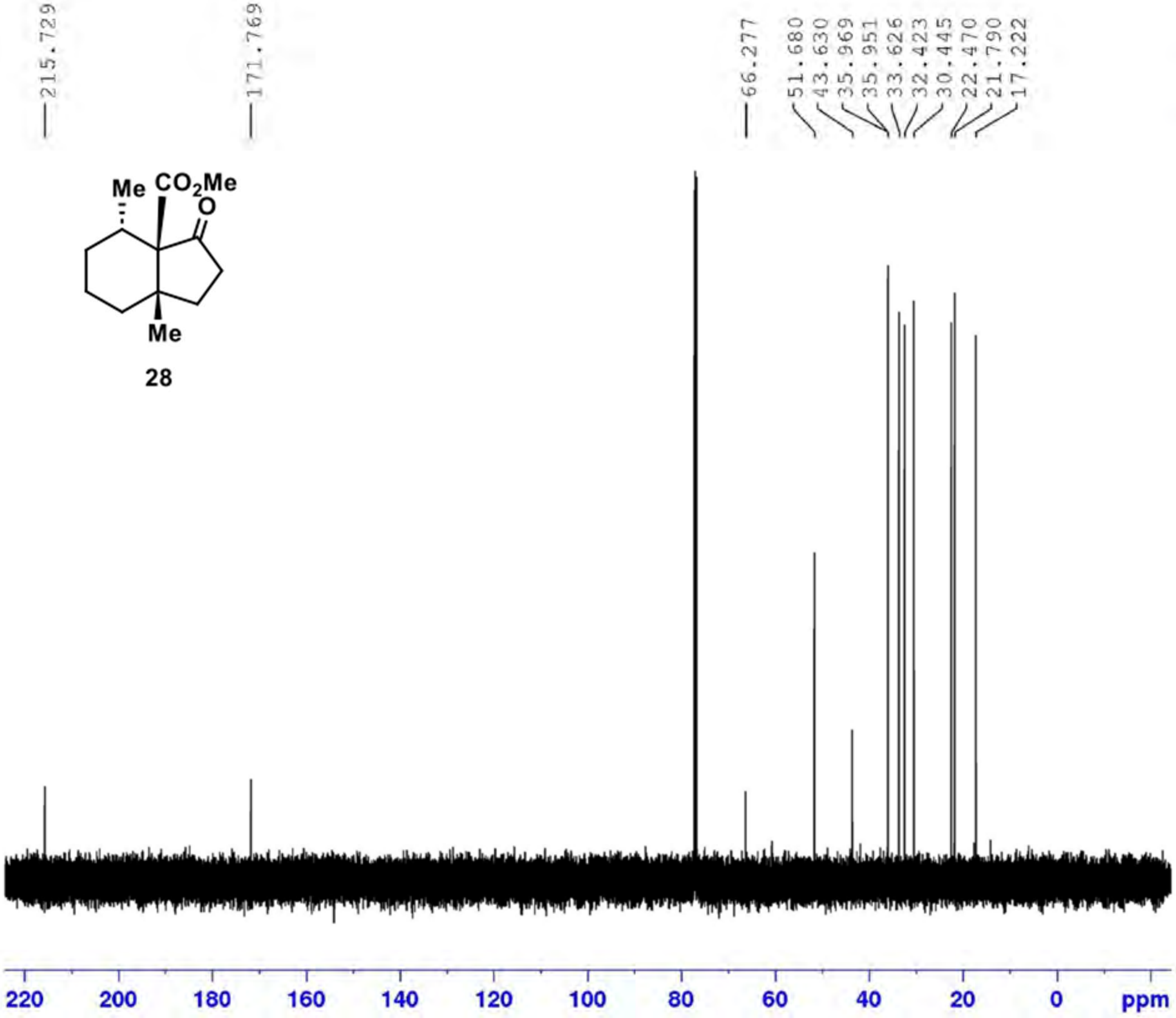
```
Current Data Parameters
NAME        pc-3-157-Collection-H2
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20190805
Time                 20.25
INSTRUM              spect
PROBHD      5 mm PABBO BB/
PULPROG               zgdc
TD                  187496
SOLVENT              CDCl3
NS                     529
DS                       0
SWH             31250.000 Hz
FIDRES           0.166670 Hz
AQ              2.9999361 sec
RG                    2050
DW                 16.000 usec
DE                   6.50 usec
TE                  298.4 K
D1             3.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          125.7049802 MHz
NUC1                   13C
P1                   10.00 usec
PLW1          72.83999634 W

======== CHANNEL f2 ========
SFO2          499.8724993 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2          19.00000000 W
PLW12          0.29688001 W

F2 - Processing parameters
SI                 1048576
SF            125.6924147 MHz
WDW                     EM
SSB         0
LB                    0.30 Hz
GB          0
PC                    1.40
```



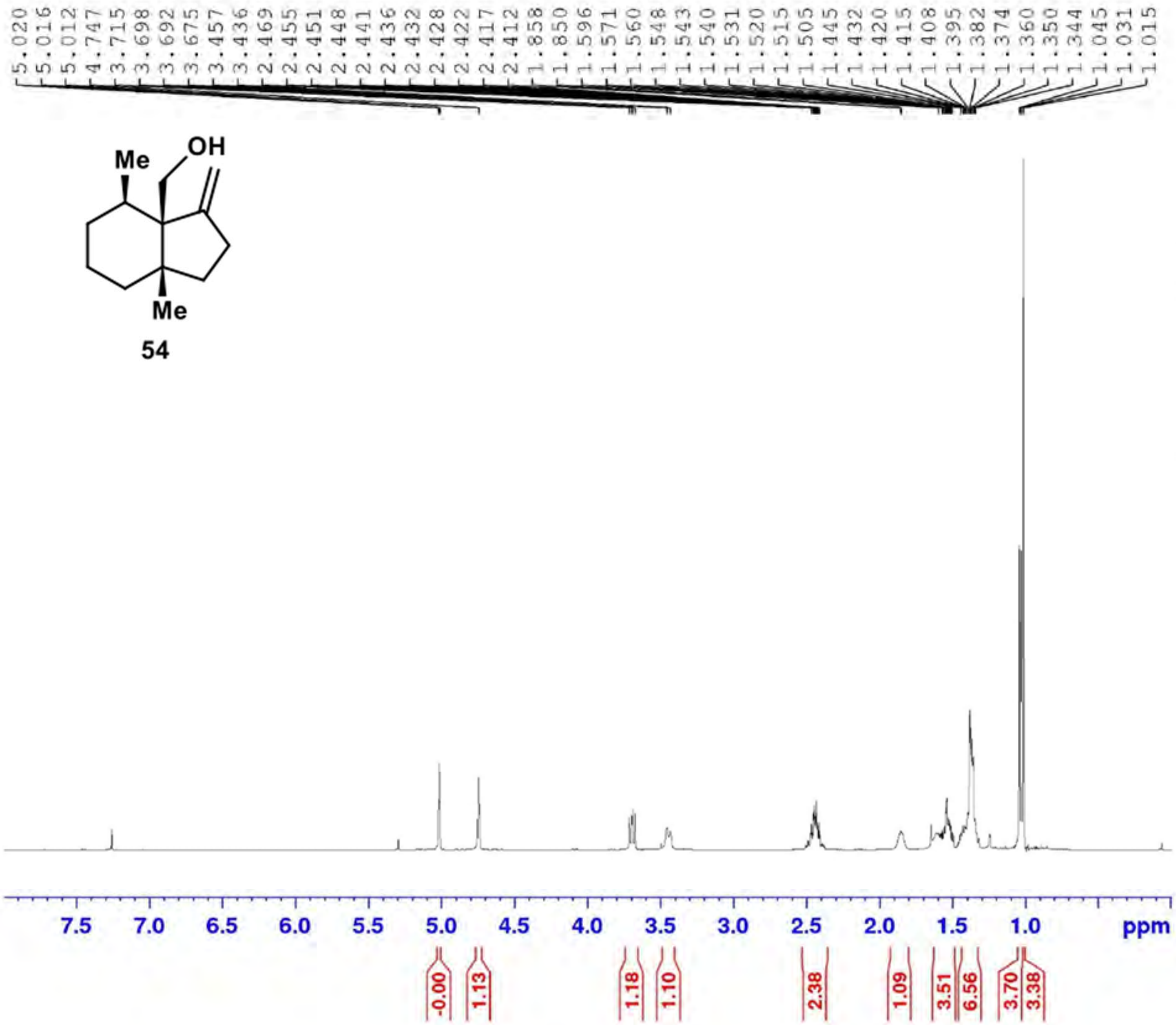
28

```
Current Data Parameters
NAME     pc-5-138-Collection-H2 minor
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20200309
Time              21.43 h
INSTRUM           spect
PROBHD   Z113652_0187 (
PULPROG              zg
TD                59998
SOLVENT           CDC13
NS                    8
DS                    0
SWH           10000.000 Hz
FIDRES         0.333344 Hz
AQ            2.9999001 sec
RG                35.92
DW               50.000 usec
DE                 6.50 usec
TE                297.1 K
D1           3.00000000 sec
TD0                   1
SFO1        499.8730869 MHz
NUC1                 1H
P1                10.75 usec
PLW1        18.25000000 W

F2 - Processing parameters
SI                65536
SF          499.8700124 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```



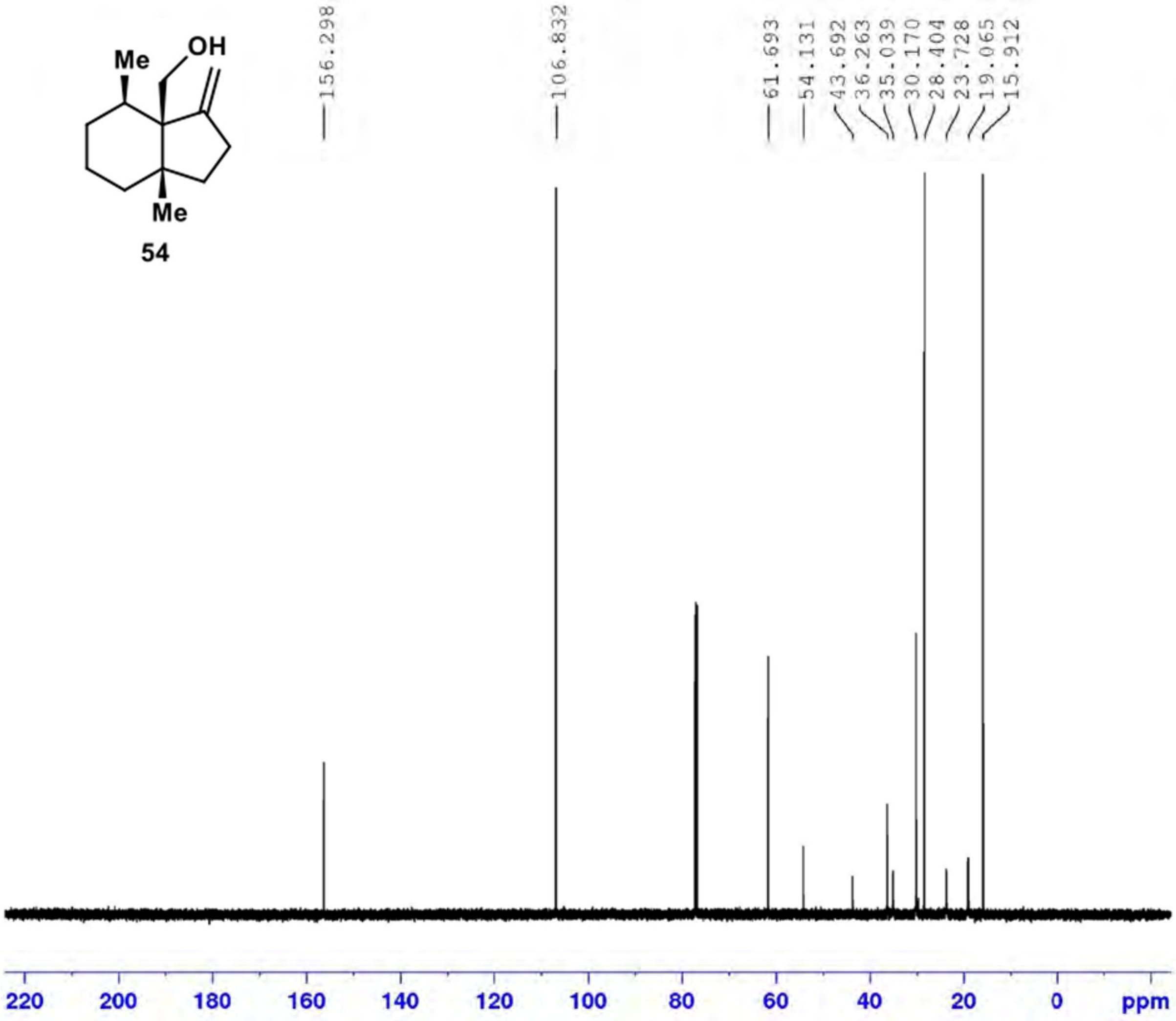
28

```
Current Data Parameters
NAME      pc-5-138-Collection-H2 minor
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20200309
Time                 21.47 h
INSTRUM              spect
PROBHD   Z113652_0187 (
PULPROG               zgdc
TD                  187496
SOLVENT              CDCl3
NS                      25
DS                       0
SWH              31250.000 Hz
FIDRES            0.333340 Hz
AQ               2.9999361 sec
RG                    2050
DW                  16.000 usec
DE                    6.50 usec
TE                   297.3 K
D1              3.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           125.7049802 MHz
NUC1                   13C
P1                   10.00 usec
PLW1           72.83999634 W
SFO2           499.8724993 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           19.00000000 W
PLW12           0.29688001 W

F2 - Processing parameters
SI                 1048576
SF             125.6924151 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.40
```



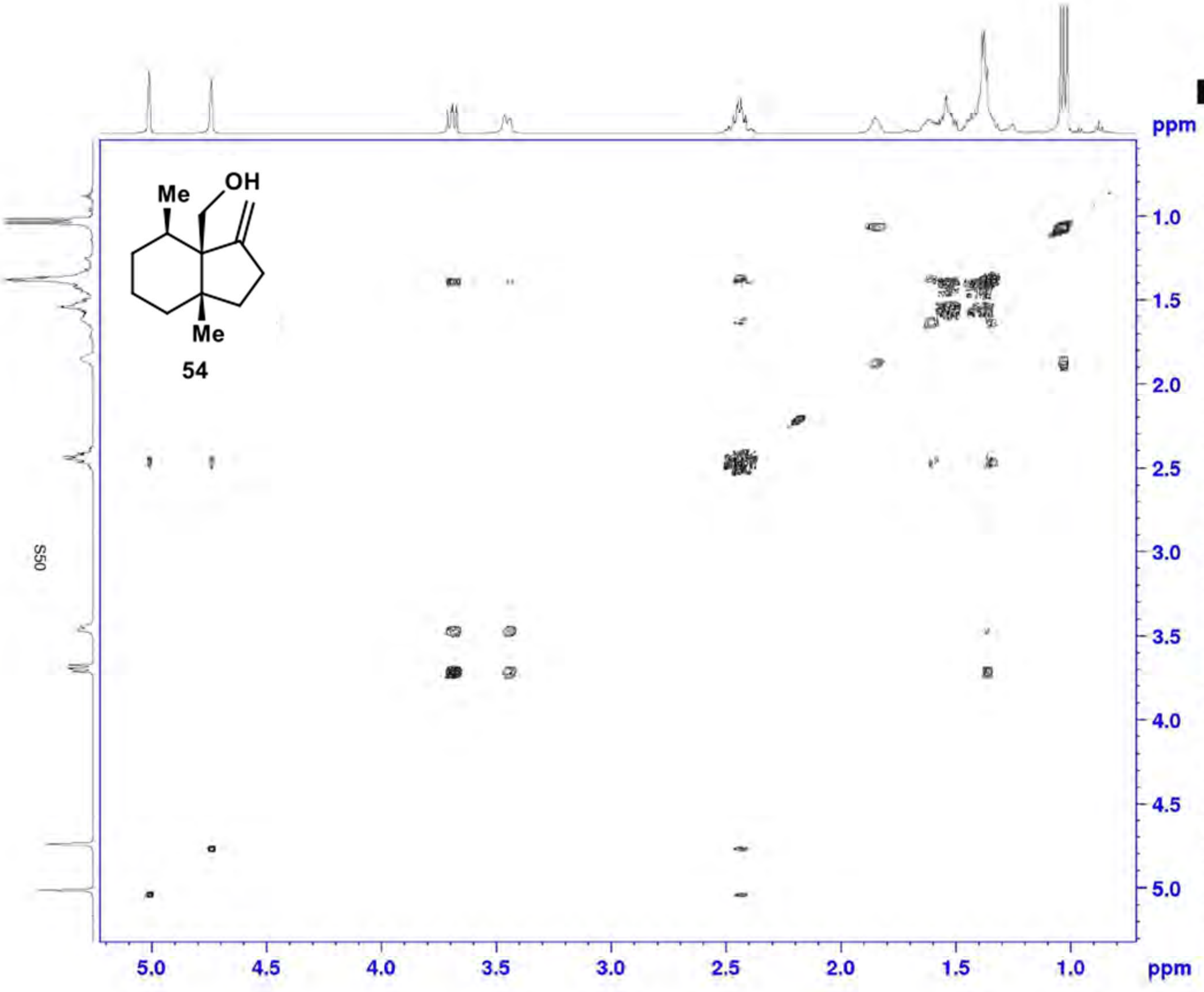
54

```
Current Data Parameters
NAME       pc-3-159-Collection DIBAL
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190806
Time                  16.10
INSTRUM               spect
PROBHD   5 mm PABBO BB/
PULPROG                  zg
TD                    59998
SOLVENT               CDCl3
NS                       16
DS                        0
SWH           10000.000 Hz
FIDRES         0.166672 Hz
AQ            2.9999001 sec
RG                    28.76
DW               50.000 usec
DE                 6.50 usec
TE                294.6 K
D1          3.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1        499.8730869 MHz
NUC1                     1H
P1                10.75 usec
PLW1        18.25000000 W

F2 - Processing parameters
SI                    65536
SF          499.8700122 MHz
WDW                      EM
SSB      0
LB                  0.30 Hz
GB       0
PC                     1.00
```



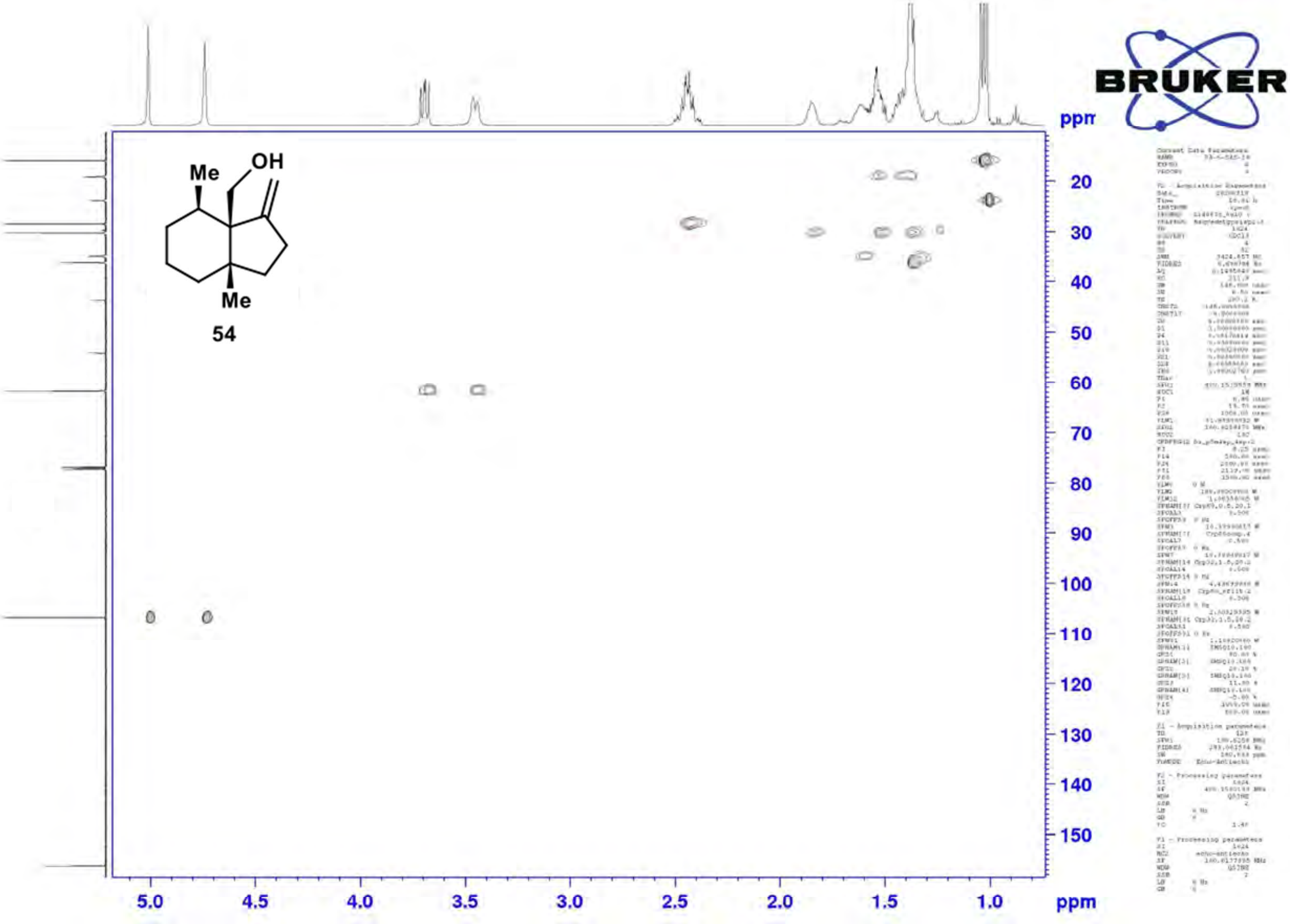
54

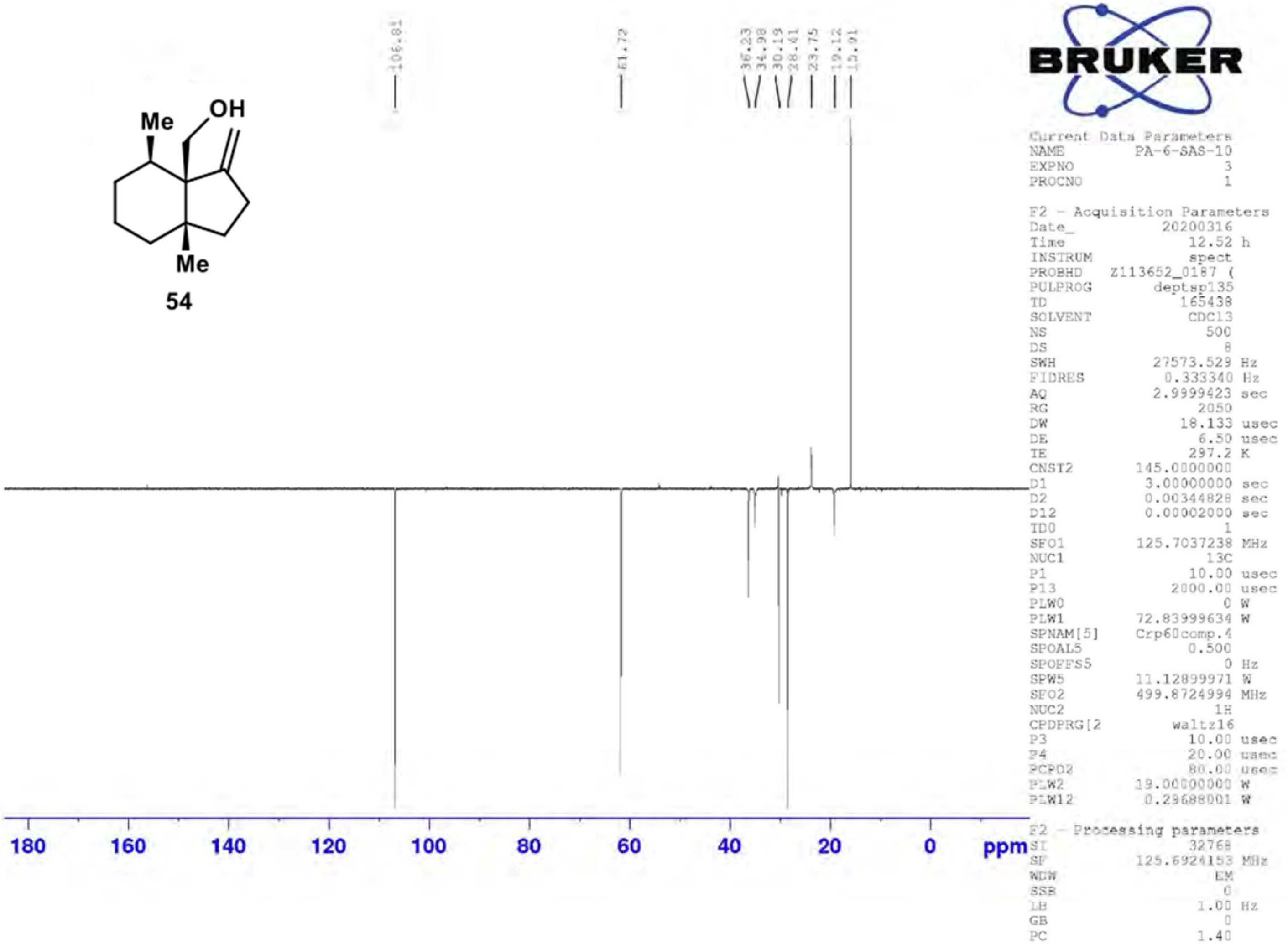
```
Current Data Parameters
NAME     pc-3-159-Collection DIBAL
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_              20190806
Time                  16.15
INSTRUM               spect
PROBHD   5 mm PABBO BB/
PULPROG                zgdc
TD                   187496
SOLVENT               CDCl3
NS                      245
DS                        0
SWH               31250.000 Hz
FIDRES             0.166670 Hz
AQ                2.9999361 sec
RG                     2050
DW                   16.000 usec
DE                     6.50 usec
TE                    295.2 K
D1               3.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            125.7049802 MHz
NUC1                    13C
P1                    10.00 usec
PLW1            72.83999634 W

======== CHANNEL f2 ========
SFO2            499.8724993 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 60.00 usec
PLW2            19.00000000 W
PLW12            0.29888001 W

F2 - Processing parameters
SI                  1048576
SF              125.6924161 MHz
WDW                      EM
SSB      0
LB                     0.30 Hz
GB       0
PC                     1.40
```



54

```
Current Data Parameters
NAME          FA-6-SAN-10
EXPNO                   5
PROCNO                  1

F2 - Acquisition Parameters
Date_            20200318
Time                14.13 h
INSTRUM              spect
PROBHD   Z8S1101_0001 (
PULPROG        cosygpmfqf
TD                   8192
SOLVENT             CDCl3
NS                      1
DS                      8
SWH              3125.000 Hz
FIDRES           0.762939 Hz
AQ              1.3107200 sec
RG                 196.79
DW                160.000 usec
DE                  10.00 usec
TE                  294.7 K
D0             0.00000300 sec
D1             1.50000000 sec
D13            0.00000400 sec
D16            0.00020000 sec
IN0            0.00032000 sec
TDav                    1
SFO1          500.1313763 MHz
NUC1                   1H
P1                   7.55 usec
PLW1          15.99600029 W
GPNAM[1]       SMSQ10.100
GPX1       0 %
GPY1       0 %
GPZ1                16.00 %
GPNAM[2]       SMSQ10.100
GPX2       0 %
GPY2       0 %
GPZ2                12.00 %
GPNAM[3]       SMSQ10.100
GPX3       0 %
GPY3       0 %
GPZ3                40.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    128
SFO1             500.1314 MHz
FIDRES          48.828125 Hz
SW                  6.248 ppm
FnMODE                 QF

F2 - Processing parameters
SI                   8192
SF            500.1300161 MHz
WDW                  SINE
SSB        0
LB         0 Hz
GB         0
PC                   1.40

F1 - Processing parameters
SI                   1024
MC2                    QF
SF            500.1300000 MHz
WDW                  SINE
SSB        0
LB         0 Hz
GB         0
```


Me
OH
Me
54
BRUKER
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



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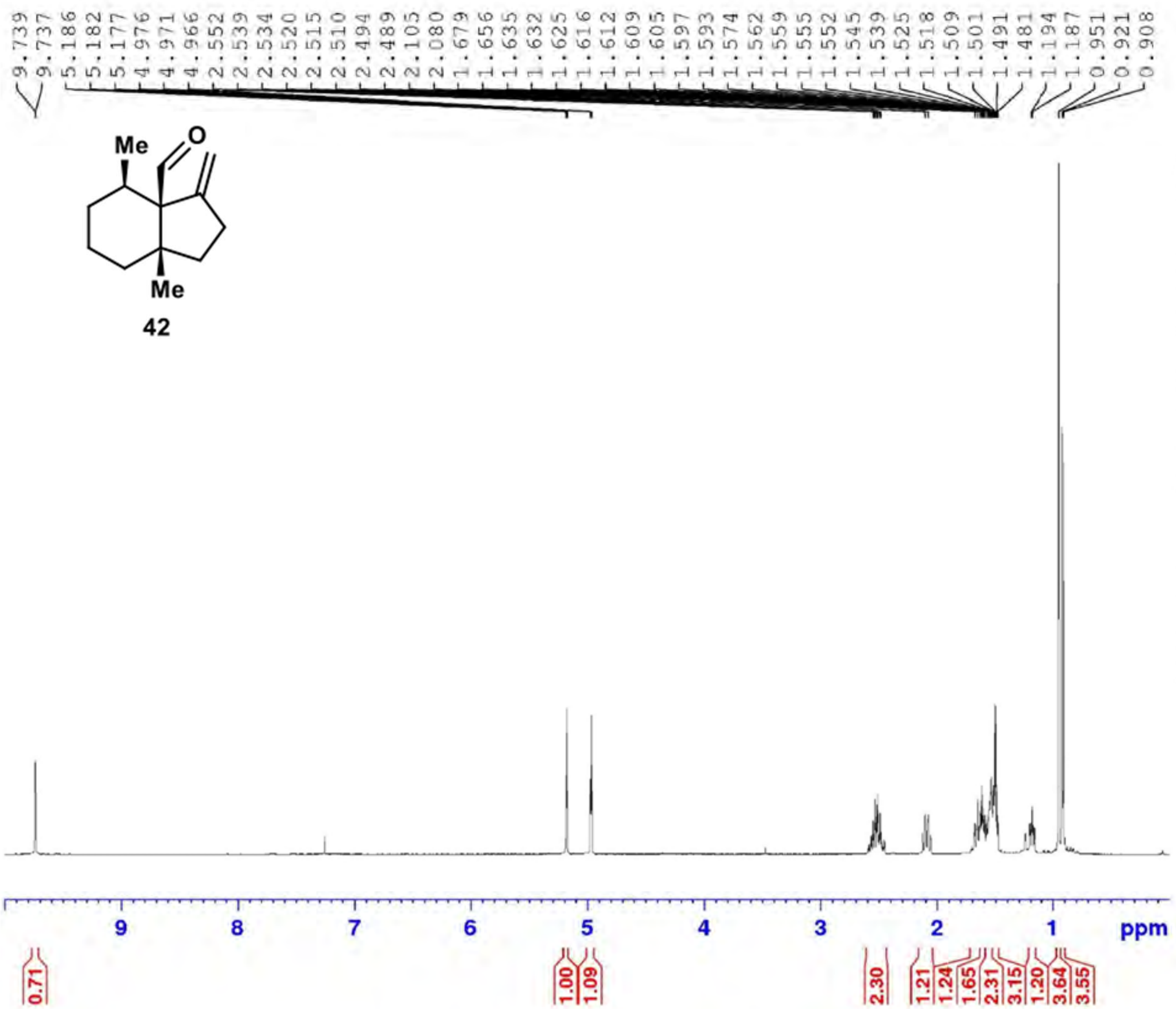
```
Current Data Parameters
NAME           PA-6-SAS-10
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_             20200316
Time                 12.52 h
INSTRUM              spect
PROBHD    Z113652_0187 (
PULPROG         deptsp135
TD                  165438
SOLVENT              CDCl3
NS                     500
DS                       8
SWH              27573.529 Hz
FIDRES            0.333340 Hz
AQ               2.9999423 sec
RG                    2050
DW                  18.133 usec
DE                    6.50 usec
TE                   297.2 K
CNST2          145.0000000
D1              3.00000000 sec
D2              0.00344828 sec
D12             0.00002000 sec
TD0                      1
SFO1           125.7037238 MHz
NUC1                   13C
P1                   10.00 usec
P13                2000.00 usec
PLW0                     0 W
PLW1           72.83999634 W
SPNAM[5]      Crp60comp.4
SPOAL5               0.500
SPOFFS5                  0 Hz
SPW5           11.12899971 W
SFO2           499.8724994 MHz
NUC2                    1H
CPDPRG[2           waltz16
P3                   10.00 usec
P4                   20.00 usec
PCPD2                80.00 usec
PLW2           19.00000000 W
PLW12           0.29688001 W

F2 - Processing parameters
SI                   32768
SF             125.6924153 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```



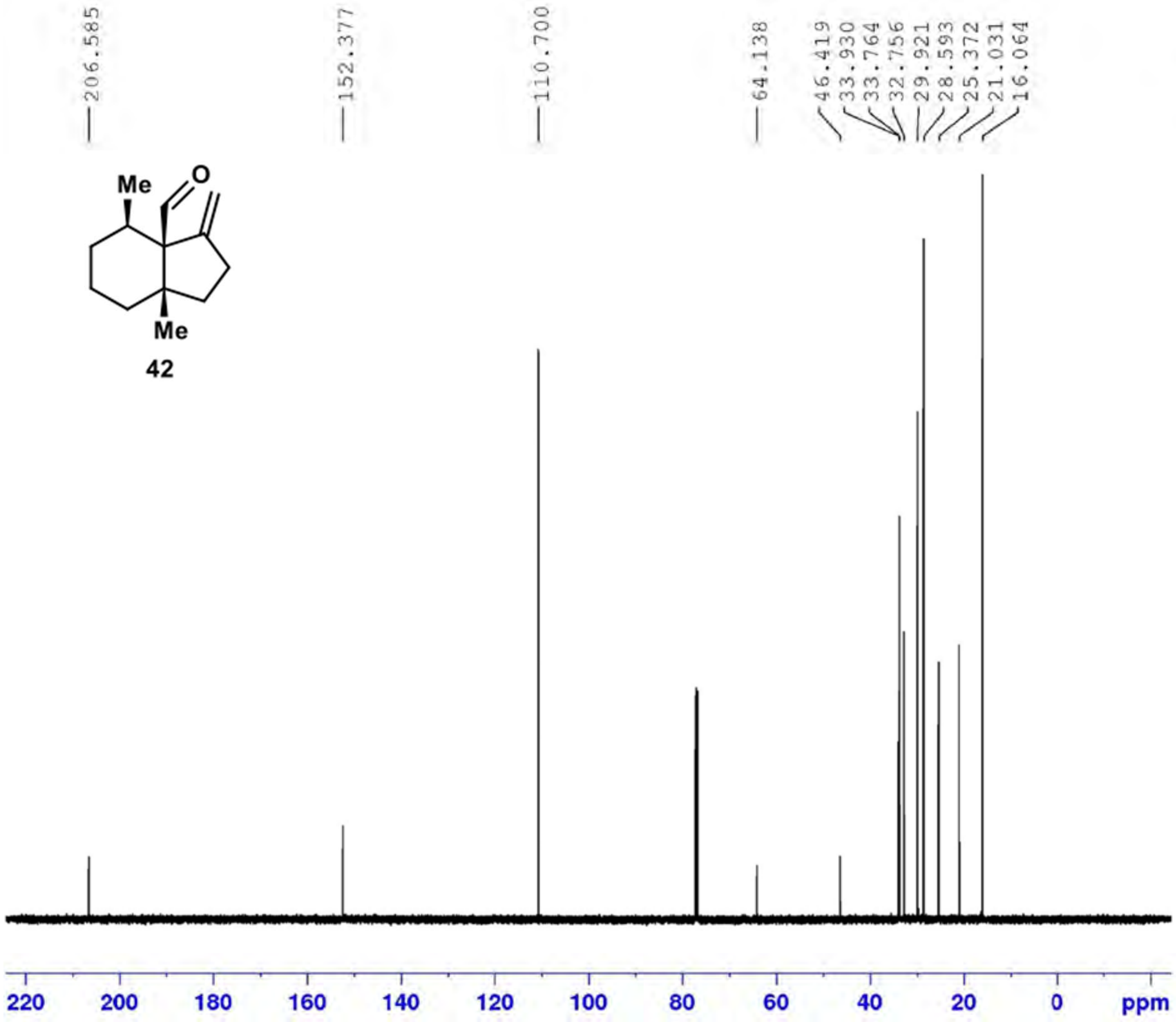
42

```
Current Data Parameters
NAME       pc-3-160-Collection DMP
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20190806
Time                 20.55
INSTRUM              spect
PROBHD   5 mm PABBO BB/
PULPROG                 zg
TD                   59998
SOLVENT              CDCl3
NS                      16
DS                       0
SWH              10000.000 Hz
FIDRES            0.166672 Hz
AQ               2.9999001 sec
RG                   28.76
DW                  50.000 usec
DE                    6.50 usec
TE                   294.0 K
D1              3.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1           499.8730869 MHz
NUC1                    1H
P1                   10.75 usec
PLW1           18.25000000 W

F2 - Processing parameters
SI                   65536
SF             499.8700122 MHz
WDW                     EM
SSB        0
LB                    0.30 Hz
GB         0
PC                    1.00
```



42

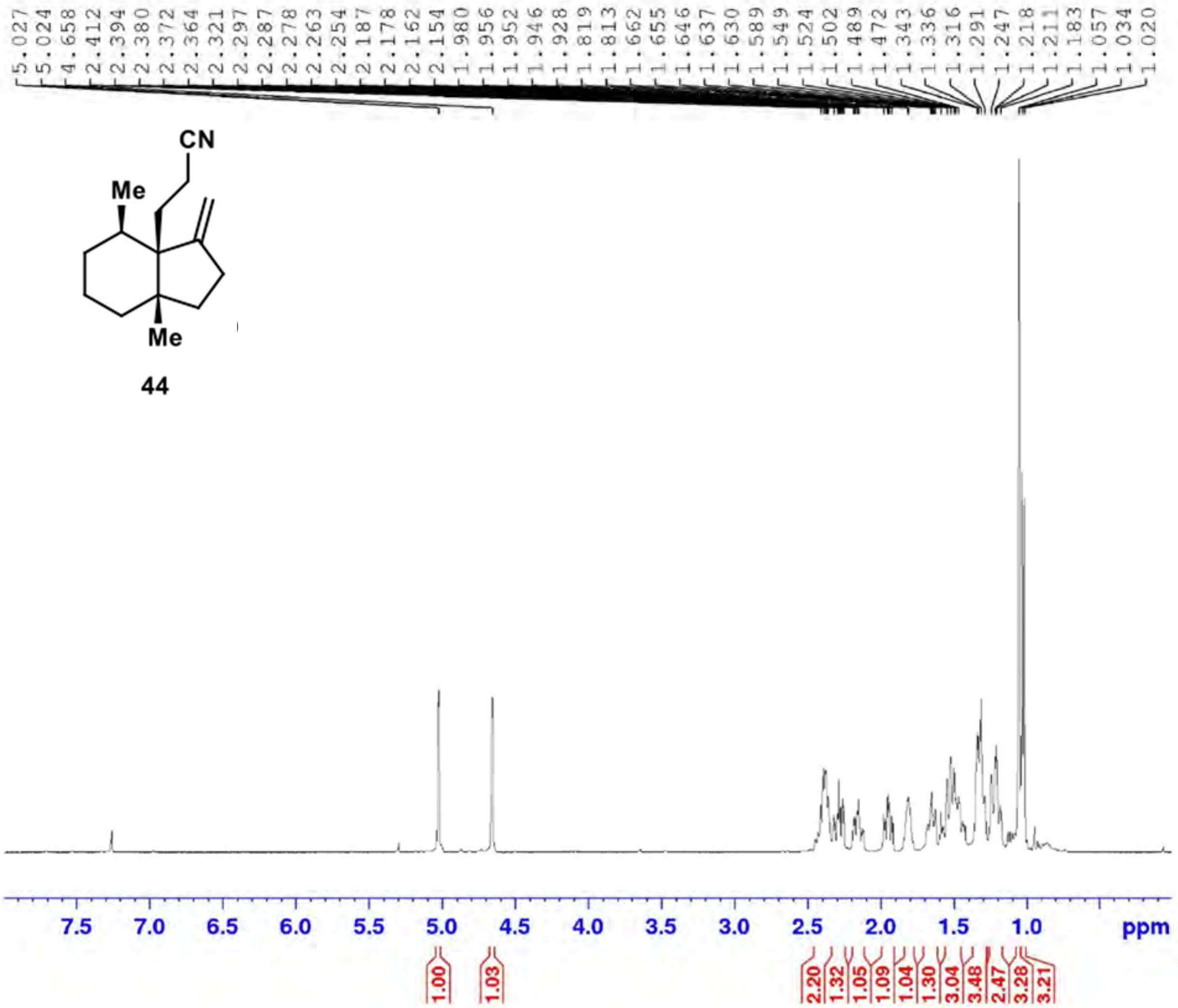
```
Current Data Parameters
NAME      pc-3-160-Collection DMP
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20190806
Time                20.58
INSTRUM             spect
PROBHD    5 mm PABBO BB/
PULPROG              zgdc
TD                 187496
SOLVENT             CDCl3
NS                    286
DS                      0
SWH             31250.000 Hz
FIDRES           0.166670 Hz
AQ              2.9999361 sec
RG                   2050
DW                 16.000 usec
DE                   6.50 usec
TE                  294.2 K
D1             3.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          125.7049802 MHz
NUC1                  13C
P1                  10.00 usec
PLW1          72.83999634 W

======== CHANNEL f2 ========
SFO2          499.8724993 MHz
NUC2                   1H
CPDPRG[2          waltz16
PCPD2               80.00 usec
PLW2          19.00000000 W
PLW12          0.29688001 W

F2 - Processing parameters
SI                1048576
SF            125.6924155 MHz
WDW                    EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.40
```



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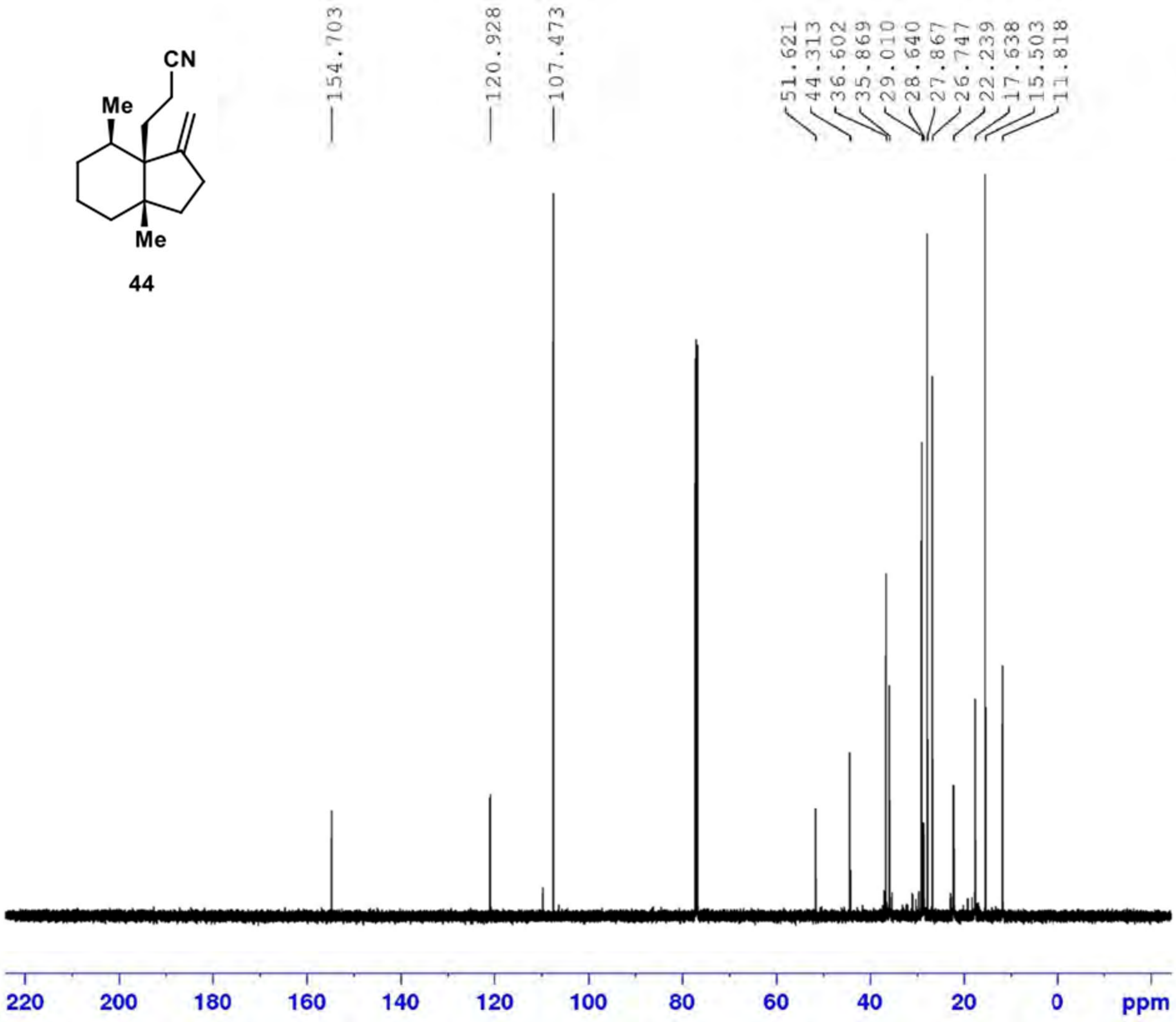
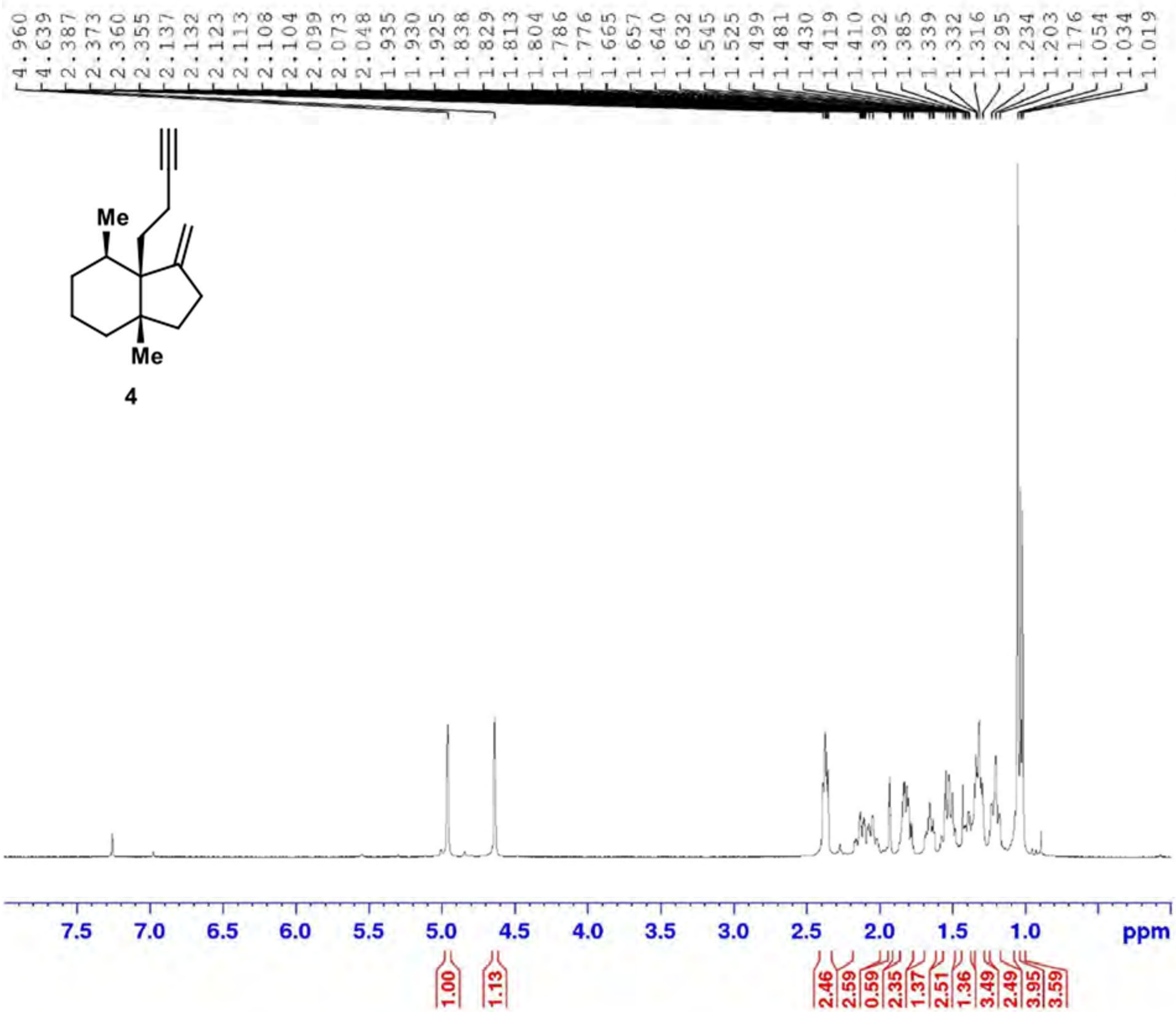
```
Current Data Parameters
NAME      pc-4-65-Collection Mg
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20190910
Time                17.13
INSTRUM             spect
PROBHD    5 mm PABBO BB/
PULPROG                zg
TD                  59998
SOLVENT             CDCl3
NS                     16
DS                      0
SWH             10000.000 Hz
FIDRES           0.166672 Hz
AQ              2.9999001 sec
RG                  22.37
DW                 50.000 usec
DE                   6.50 usec
TE                  294.1 K
D1             3.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          499.8730869 MHz
NUC1                   1H
P1                  10.75 usec
PLW1          18.25000000 W

F2 - Processing parameters
SI                  65536
SF            499.8700101 MHz
WDW                    EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```



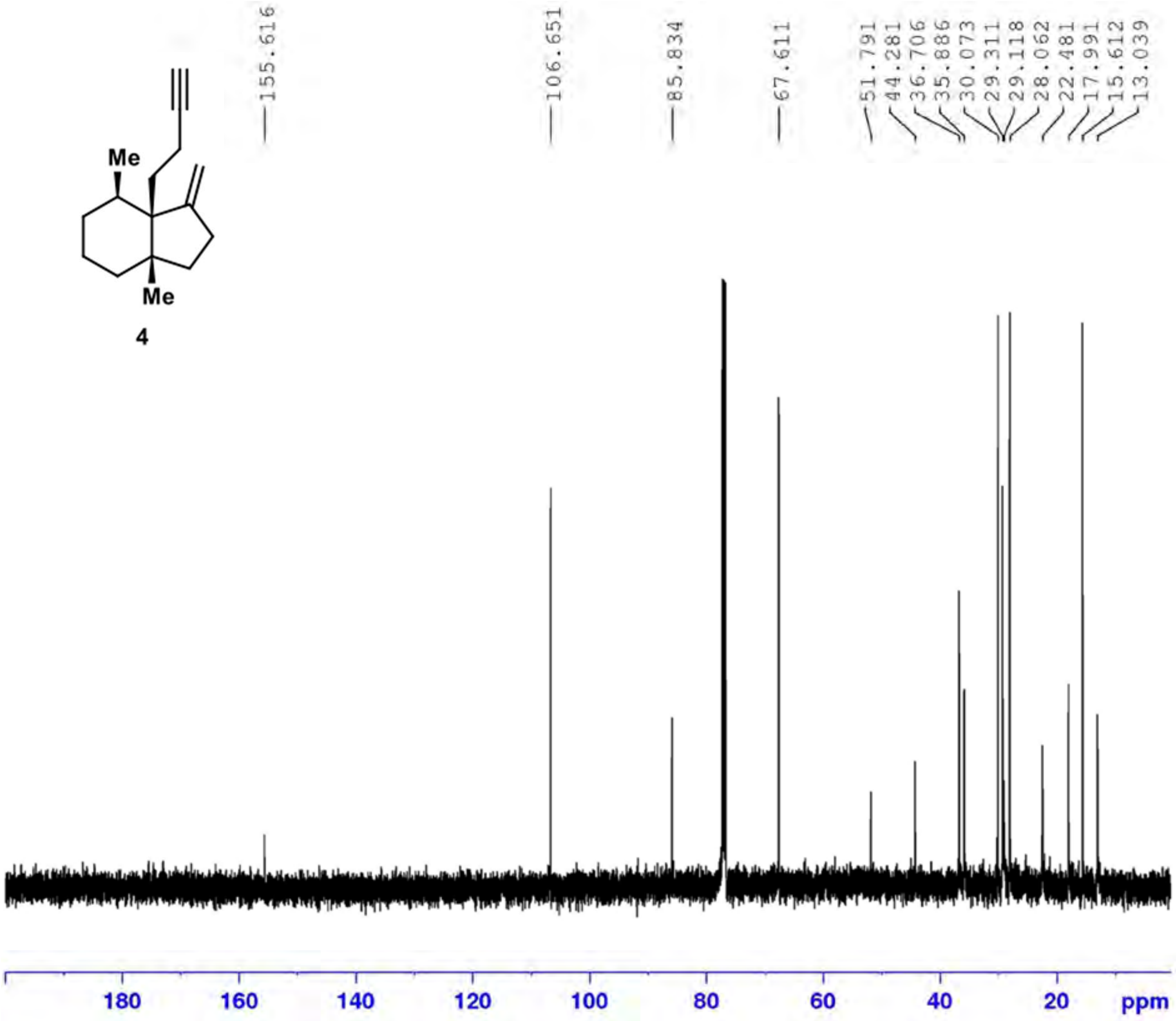
44

```
Current Data Parameters
NAME     pc-4-65-Collection Mg
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_           20190910
Time               17.17
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG             zgdc
TD                187496
SOLVENT            CDCl3
NS                   466
DS                     0
SWH            31250.000 Hz
FIDRES          0.166670 Hz
AQ             2.9999361 sec
RG                  2050
DW                16.000 usec
DE                  6.50 usec
TE                 294.1 K
D1            3.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.7049802 MHz
NUC1                 13C
P1                 10.00 usec
PLW1         72.83999634 W

======== CHANNEL f2 ========
SFO2         499.8724993 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         19.00000000 W
PLW12         0.29688001 W

F2 - Processing parameters
SI               1048576
SF           125.6924159 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.40
```



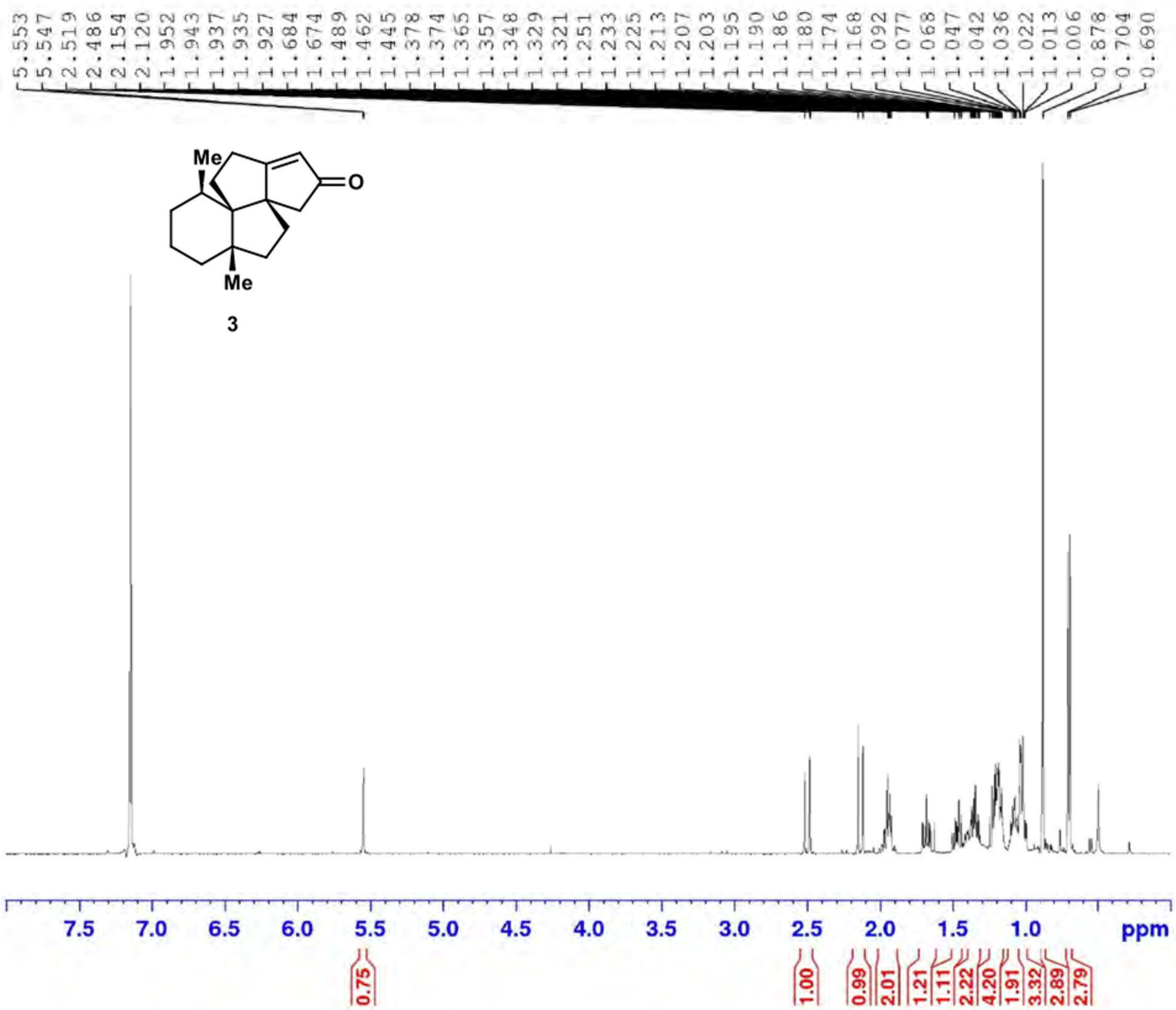
4

```
Current Data Parameters
NAME      pc-5-114-Collection-Alkyne
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_           20200303
Time                0.55
INSTRUM            spect
PROBHD   5 mm PATXI 1H/
PULPROG               zg
TD                 59998
SOLVENT            CDCl3
NS                     8
DS                     0
SWH            10000.000 Hz
FIDRES          0.166672 Hz
AQ             2.9999001 sec
RG                 52.86
DW                50.000 usec
DE                 10.00 usec
TE                 294.5 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                  1H
P1                  9.90 usec
PLW1         12.19999981 W

F2 - Processing parameters
SI                 65536
SF           500.1300134 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```



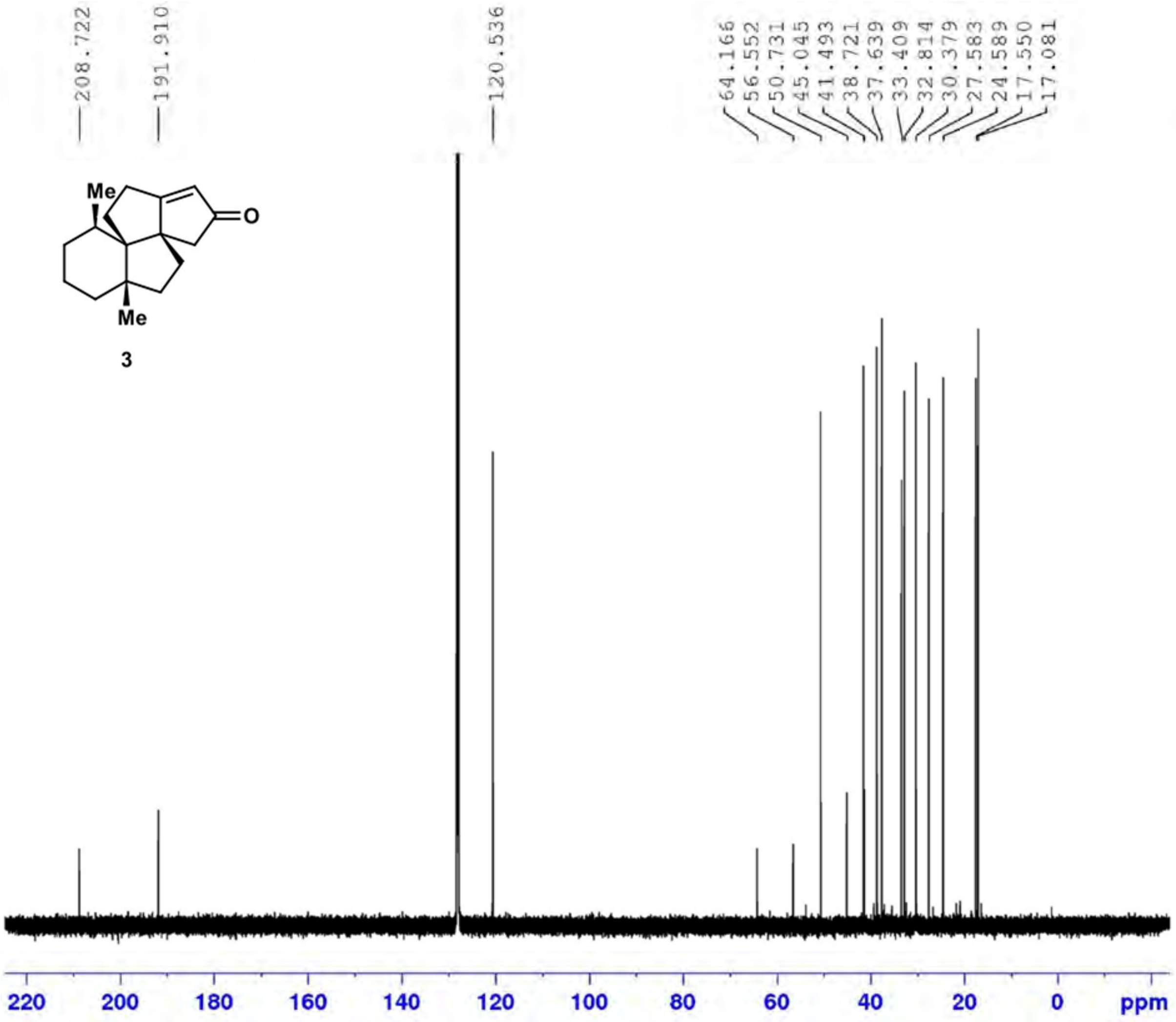
4

```
Current Data Parameters
NAME     pc-5-114-Collection-Alkyne
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20200303
Time                   0.57
INSTRUM               spect
PROBHD   5 mm PATXI 1H/
PULPROG                zgdc
TD                   178568
SOLVENT               CDCl3
NS                      353
DS                        0
SWH               29761.904 Hz
FIDRES             0.166670 Hz
AQ                2.9999423 sec
RG                   196.79
DW                   16.800 usec
DE                    10.00 usec
TE                    294.5 K
D1               3.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1            125.7703643 MHz
NUC1                    13C
P1                    15.50 usec
PLW1         170.00000000 W

======== CHANNEL f2 ========
SFO2            500.1320005 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 90.00 usec
PLW2            12.19999981 W
PLW12            0.20893000 W

F2 - Processing parameters
SI                   131072
SF              125.7577901 MHz
WDW                      EM
SSB      0
LB                     1.00 Hz
GB       0
PC                     1.40
```

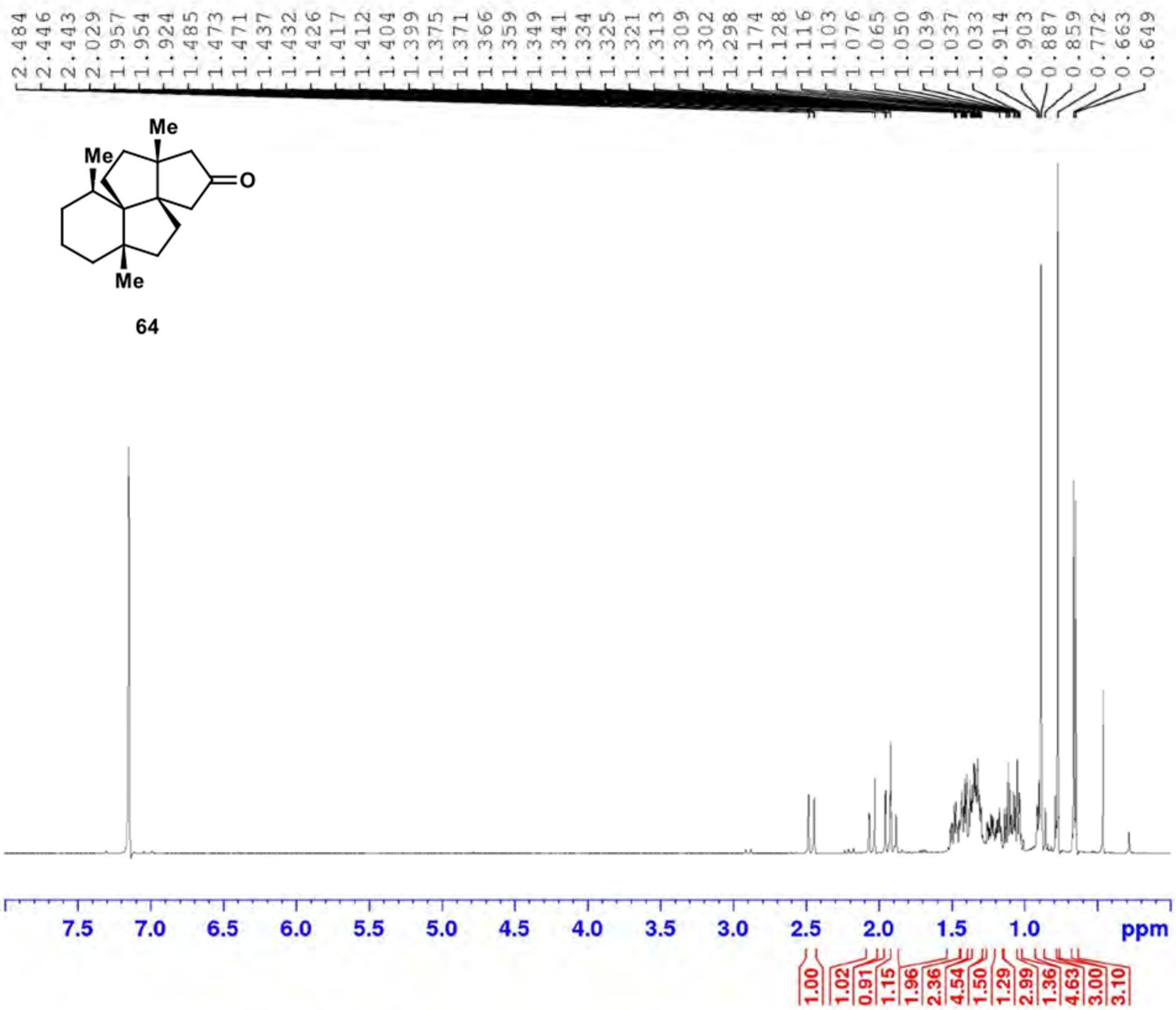


3

```
Current Data Parameters
NAME      pc-4-95-Collection PK
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20191008
Time               22.01 h
INSTRUM              spect
PROBHD    Z113652_0187 (
PULPROG                 zg
TD                   59998
SOLVENT               C6D6
NS                       1
DS                       0
SWH            10000.000 Hz
FIDRES          0.333344 Hz
AQ             2.9999001 sec
RG                   56.75
DW                  50.000 usec
DE                    6.50 usec
TE                   298.0 K
D1            3.00000000 sec
TD0                      1
SFO1         499.8730869 MHz
NUC1                    1H
P1                   10.75 usec
PLW1         18.25000000 W

F2 - Processing parameters
SI                   65536
SF           499.8700013 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.00
```

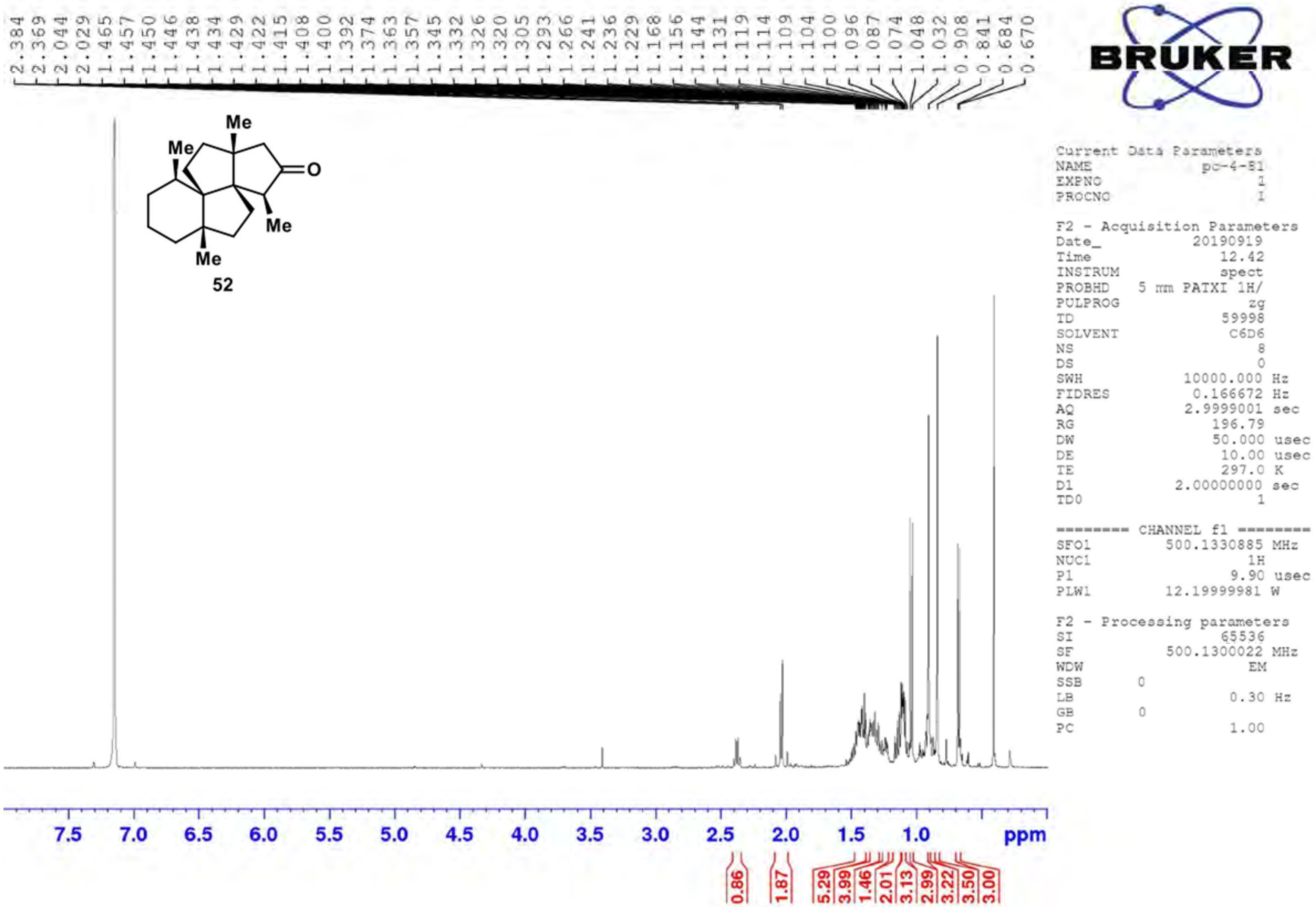


```
Current Data Parameters
NAME      pc-4-95-Collection PK
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20191008
Time               23.57 h
INSTRUM            spect
PROBHD    Z113652_0187 (
PULPROG             zgdc
TD                187496
SOLVENT             C6D6
NS                  1130
DS                     0
SWH            31250.000 Hz
FIDRES          0.333340 Hz
AQ             2.9999361 sec
RG                  2050
DW                16.000 usec
DE                  6.50 usec
TE                 298.2 K
D1            3.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         125.7049802 MHz
NUC1                 13C
P1                 10.00 usec
PLW1         72.83999634 W
SFO2         499.8724993 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         19.00000000 W
PLW12         0.29688001 W

F2 - Processing parameters
SI               1048576
SF           125.6923655 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.40
```



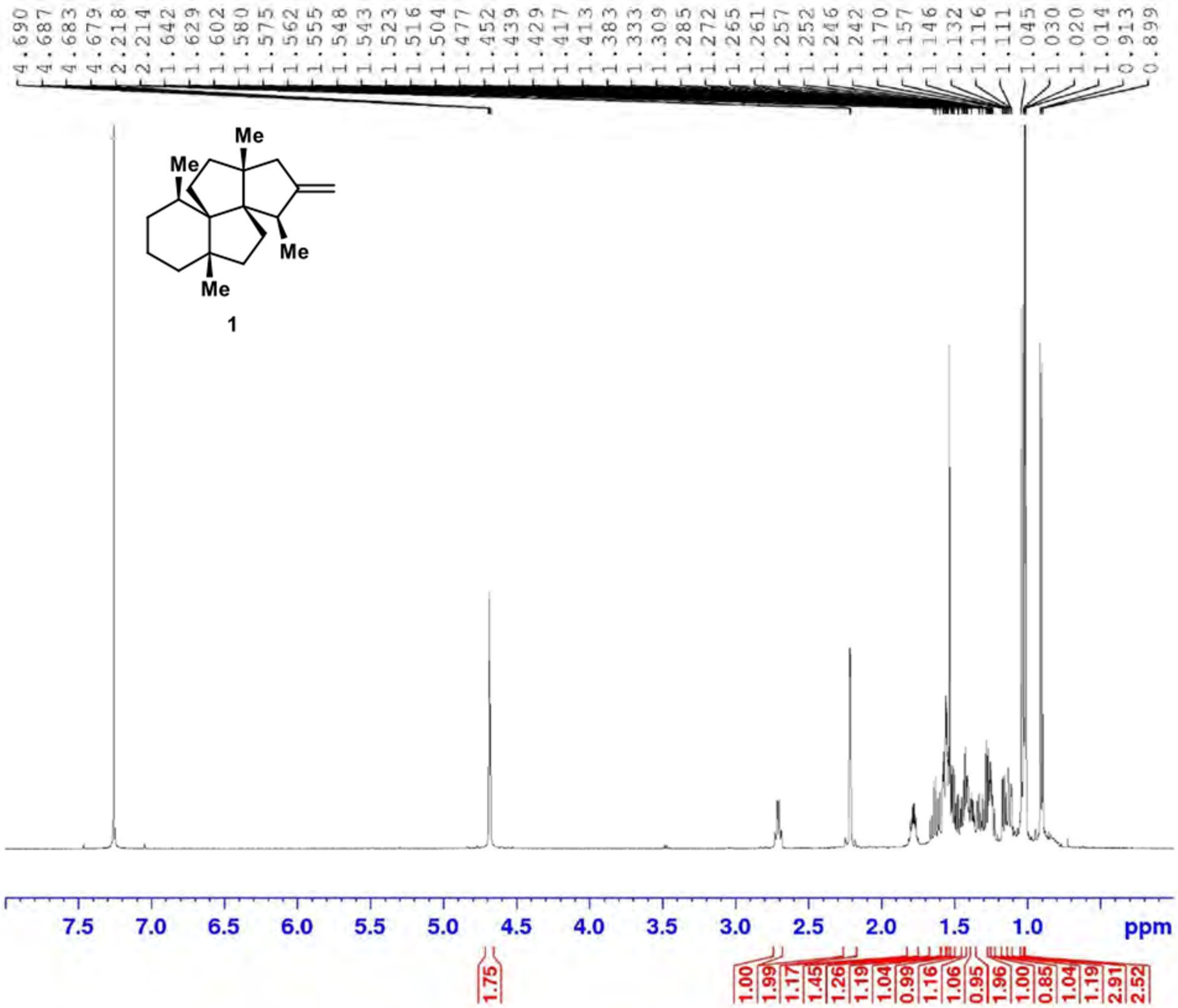
64

```
Current Data Parameters
NAME                pc-4-79
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20190918
Time                  18.30
INSTRUM               spect
PROBHD   5 mm PATXI 1H/
PULPROG                  zg
TD                    59998
SOLVENT                C6D6
NS                        8
DS                        0
SWH            10000.000 Hz
FIDRES          0.166672 Hz
AQ             2.9999001 sec
RG                    97.37
DW                50.000 usec
DE                 10.00 usec
TE                 297.1 K
D1            2.00000000 sec
TD0                       1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                     1H
P1                  9.90 usec
PLW1         12.19999981 W

F2 - Processing parameters
SI                    65536
SF           500.1300021 MHz
WDW                      EM
SSB      0
LB                  0.30 Hz
GB       0
PC                     1.00
```

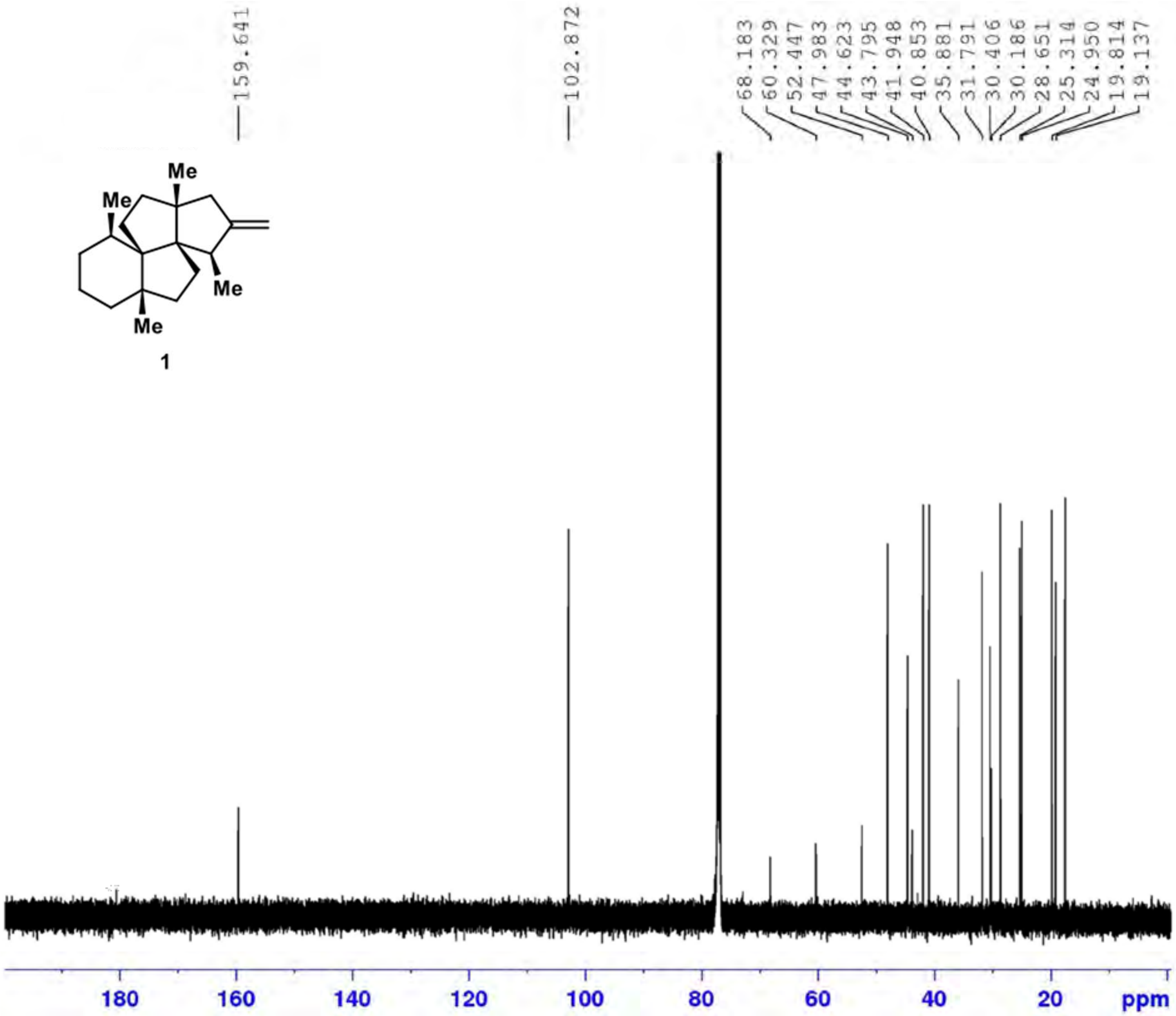


52

```
Current Data Parameters
NAME              pc-4-81
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20190919
Time                12.42
INSTRUM             spect
PROBHD   5 mm PATXI 1H/
PULPROG                zg
TD                  59998
SOLVENT              C6D6
NS                      8
DS                      0
SWH             10000.000 Hz
FIDRES           0.166672 Hz
AQ              2.9999001 sec
RG                 196.79
DW                 50.000 usec
DE                  10.00 usec
TE                  297.0 K
D1             2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         500.1330885 MHz
NUC1                   1H
P1                    9.90 usec
PLW1         12.19999981 W

F2 - Processing parameters
SI                  65536
SF           500.1300022 MHz
WDW                    EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```

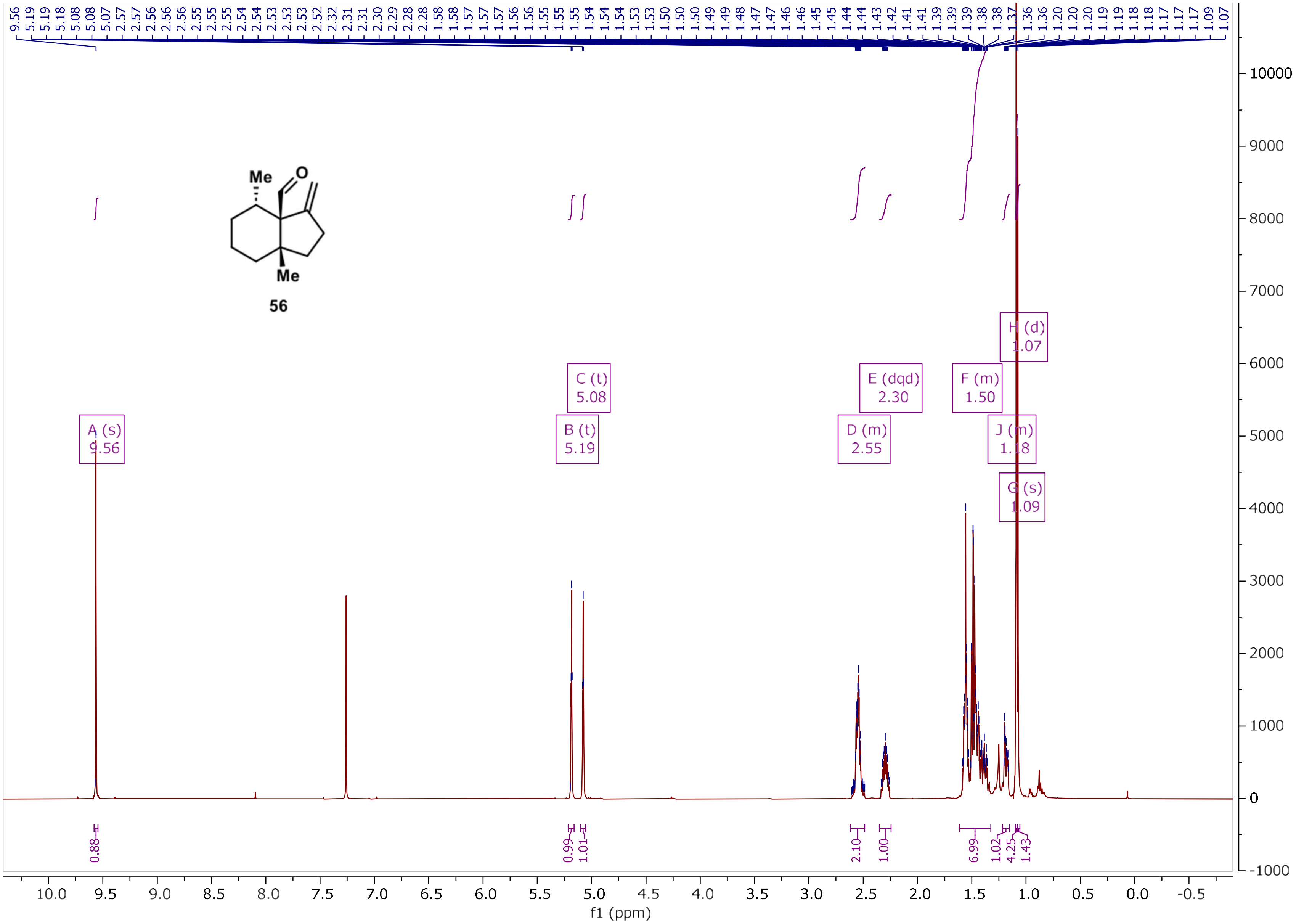


```
Current Data Parameters
NAME      pc-5-146-Purified
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_            20200312
Time                23.32 h
INSTRUM             spect
PROBHD    Z113652_0187 (
PULPROG                zg
TD                  59998
SOLVENT             CDCl3
NS                     32
DS                      0
SWH             10000.000 Hz
FIDRES           0.333344 Hz
AQ              2.9999001 sec
RG                  70.49
DW                 50.000 usec
DE                   6.50 usec
TE                  297.1 K
D1             3.00000000 sec
TD0                     1
SFO1          499.8730869 MHz
NUC1                   1H
P1                  10.75 usec
PLW1          18.25000000 W

F2 - Processing parameters
SI                  65536
SF            499.8700124 MHz
WDW                    EM
SSB      0
LB                   0.30 Hz
GB       0
PC                   1.00
```

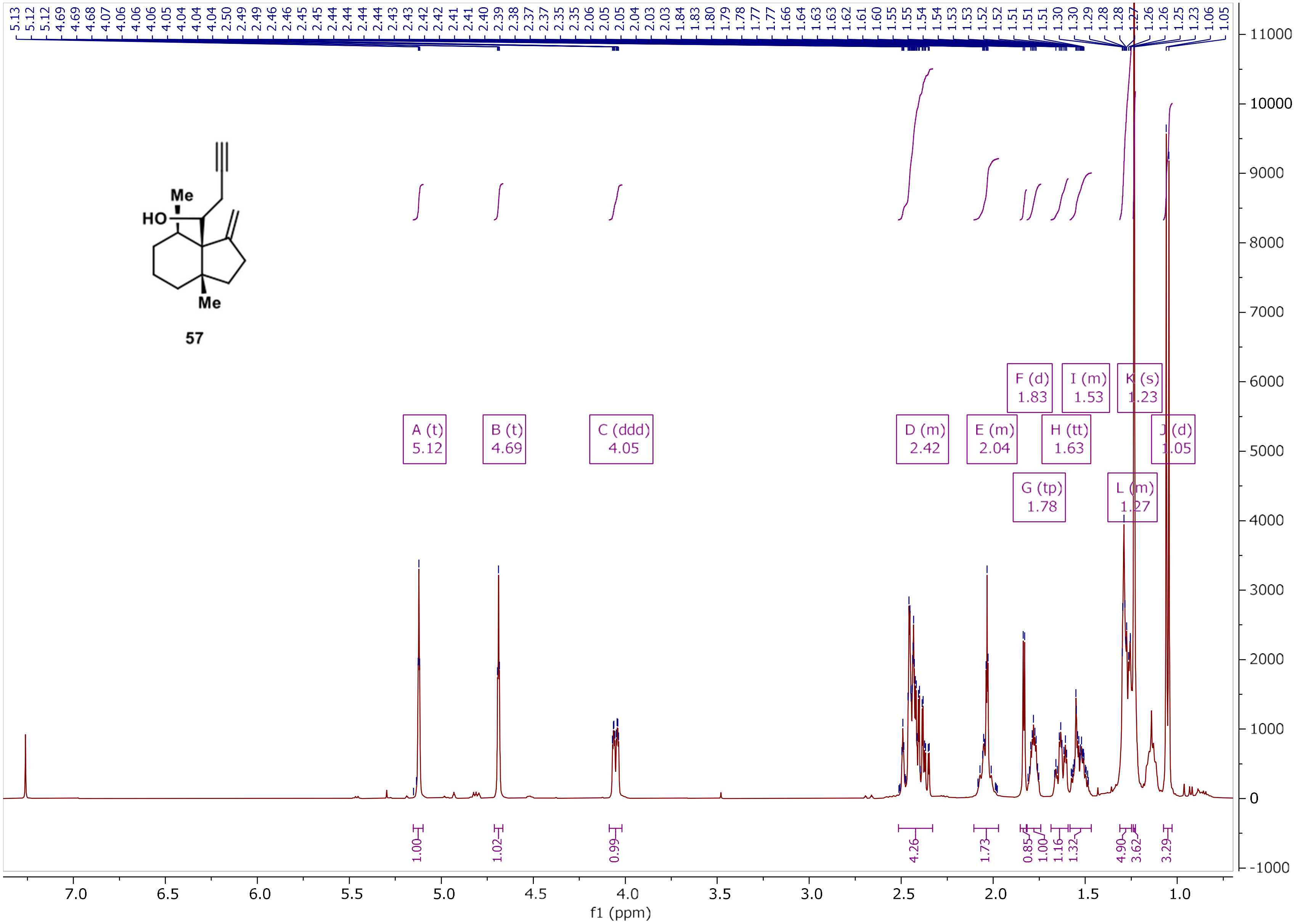


1

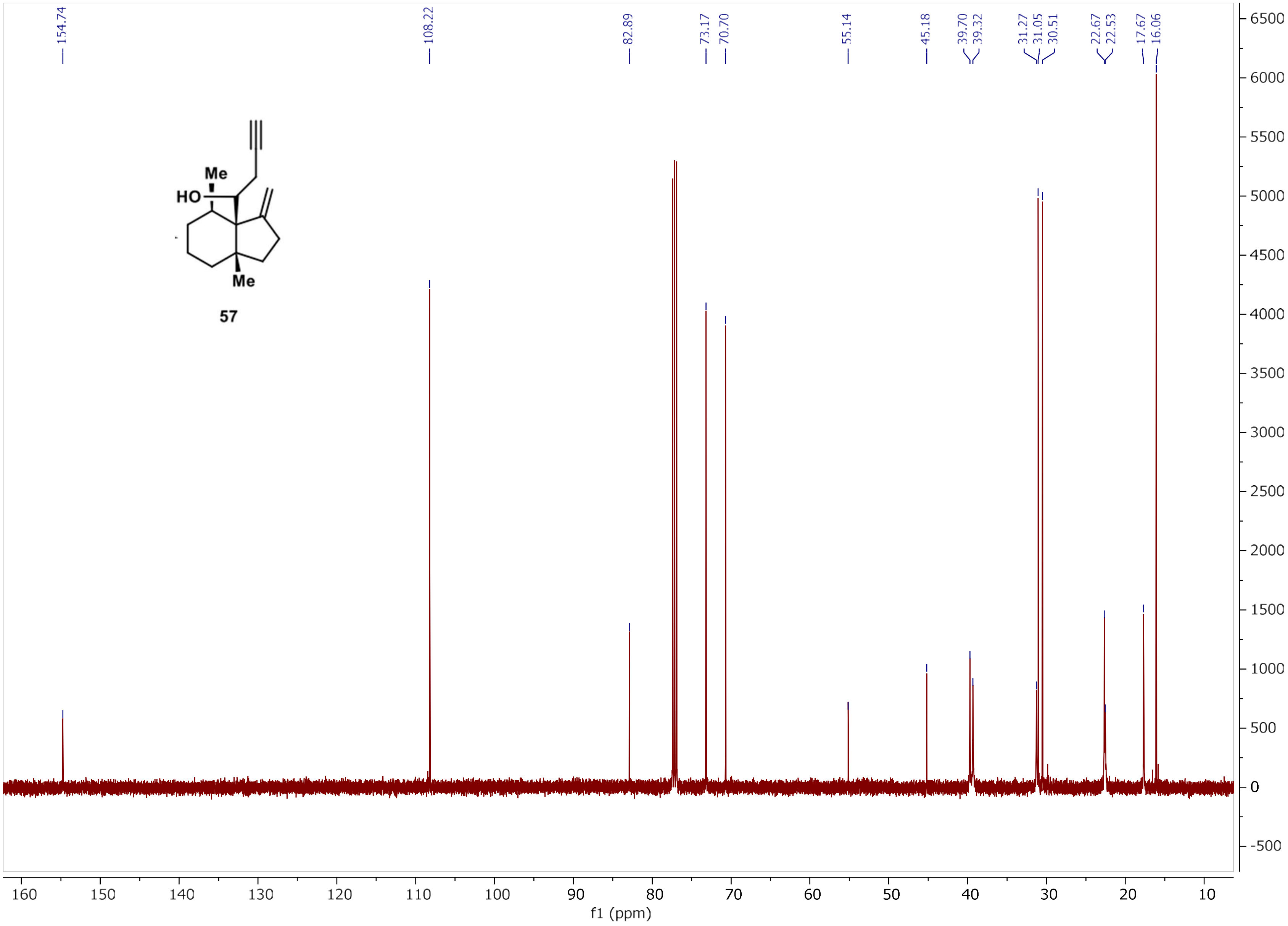
```
Current Data Parameters
NAME      pc-5-146-Purified
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_             20200313
Time                  9.37 h
INSTRUM              spect
PROBHD    Z113652_0187 (
PULPROG               zgdc
TD                  187496
SOLVENT              CDCl3
NS                    5966
DS                       0
SWH              31250.000 Hz
FIDRES            0.333340 Hz
AQ               2.9999361 sec
RG                    2050
DW                  16.000 usec
DE                    6.50 usec
TE                   297.3 K
D1              3.00000000 sec
D11             0.03000000 sec
TD0                      1
SFO1           125.7049802 MHz
NUC1                   13C
P1                   10.00 usec
PLW1           72.83999634 W
SFO2           499.8724993 MHz
NUC2                    1H
CPDPRG[2           waltz16
PCPD2                80.00 usec
PLW2           19.00000000 W
PLW12           0.29688001 W

F2 - Processing parameters
SI                 1048576
SF             125.6924143 MHz
WDW                     EM
SSB      0
LB                    0.30 Hz
GB       0
PC                    1.40
```


9.56
5.19
5.19
5.18
5.08
5.08
5.07
2.57
2.57
2.56
2.56
2.56
2.55
2.55
2.55
2.54
2.54
2.53
2.53
2.53
2.52
2.32
2.31
2.31
2.30
2.29
2.28
2.28
1.58
1.58
1.57
1.57
1.57
1.56
1.56
1.55
1.55
1.55
1.54
1.54
1.54
1.53
1.53
1.50
1.50
1.50
1.49
1.49
1.48
1.47
1.47
1.46
1.46
1.45
1.45
1.44
1.44
1.43
1.42
1.41
1.41
1.39
1.39
1.39
1.38
1.38
1.37
1.36
1.36
1.20
1.20
1.19
1.19
1.19
1.18
1.18
1.17
1.17
1.17
1.09
1.07
Me
O
Me
A (s)
9.56
B (t)
5.19
C (t)
5.08
D (m)
2.55
E (dqd)
2.30
F (m)
1.50
J (m)
1.18
G (s)
1.09
H (d)
1.07
0.88
0.99
1.01
2.10
1.00
6.99
1.02
4.25
1.43
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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)

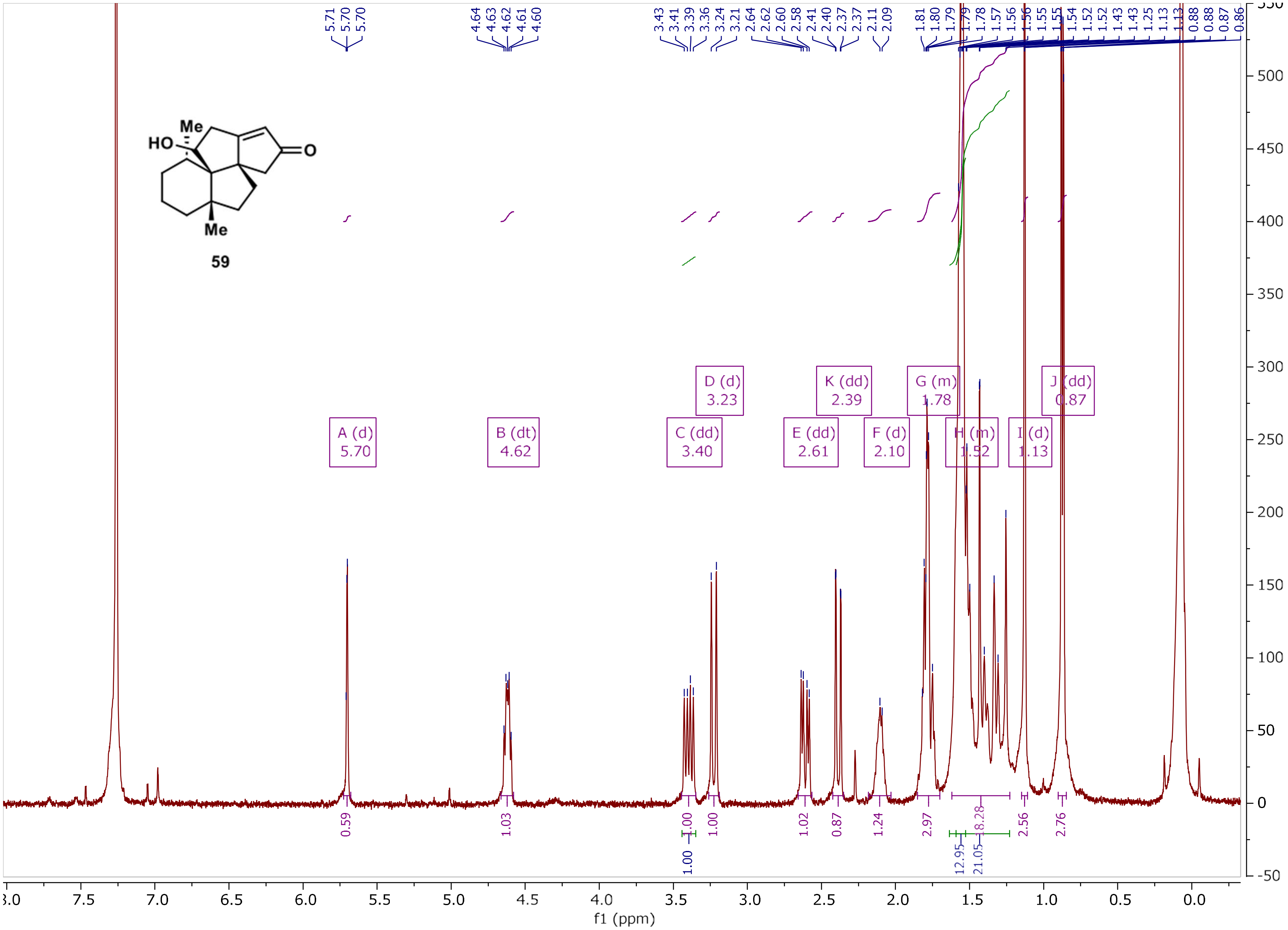
56

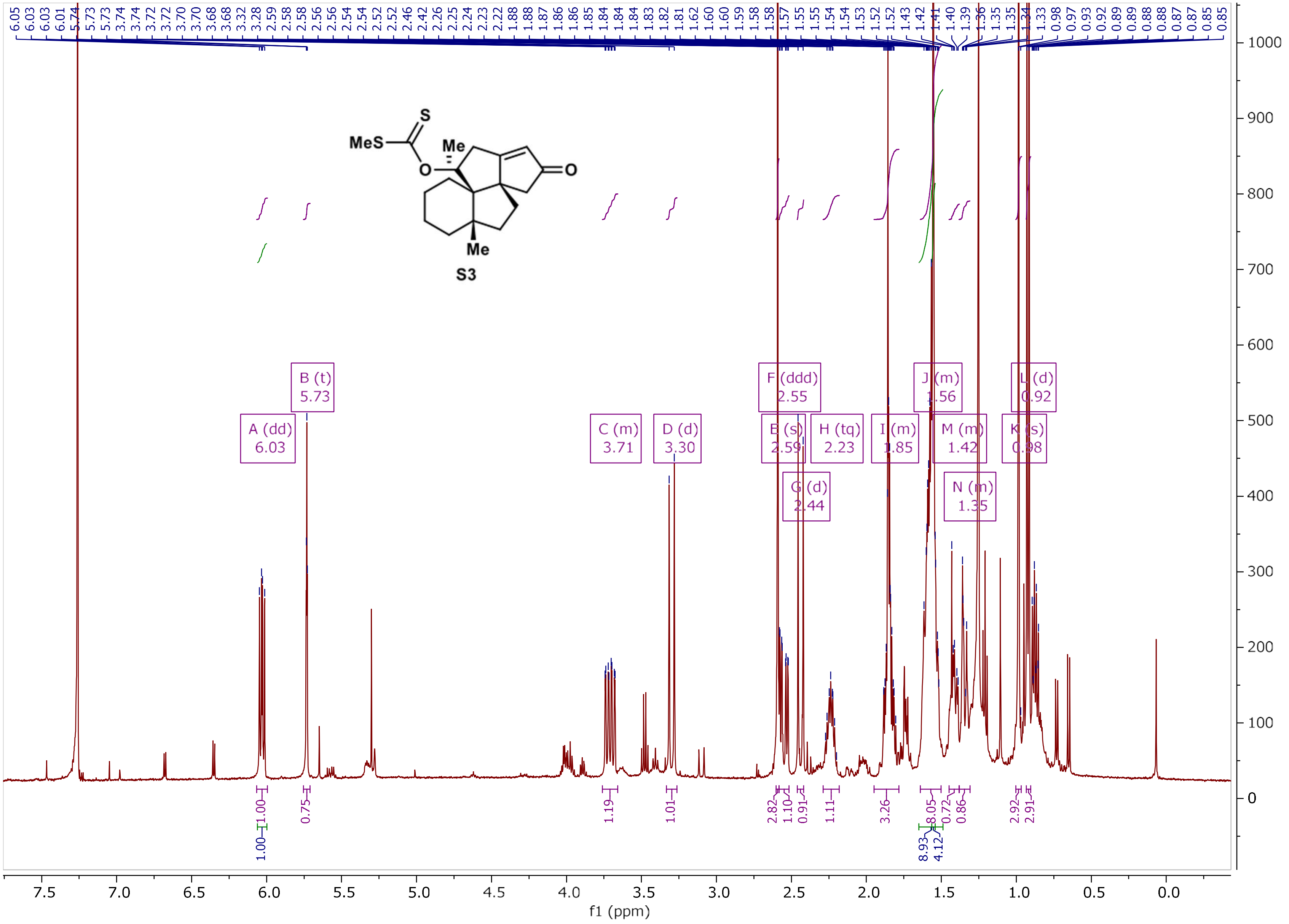


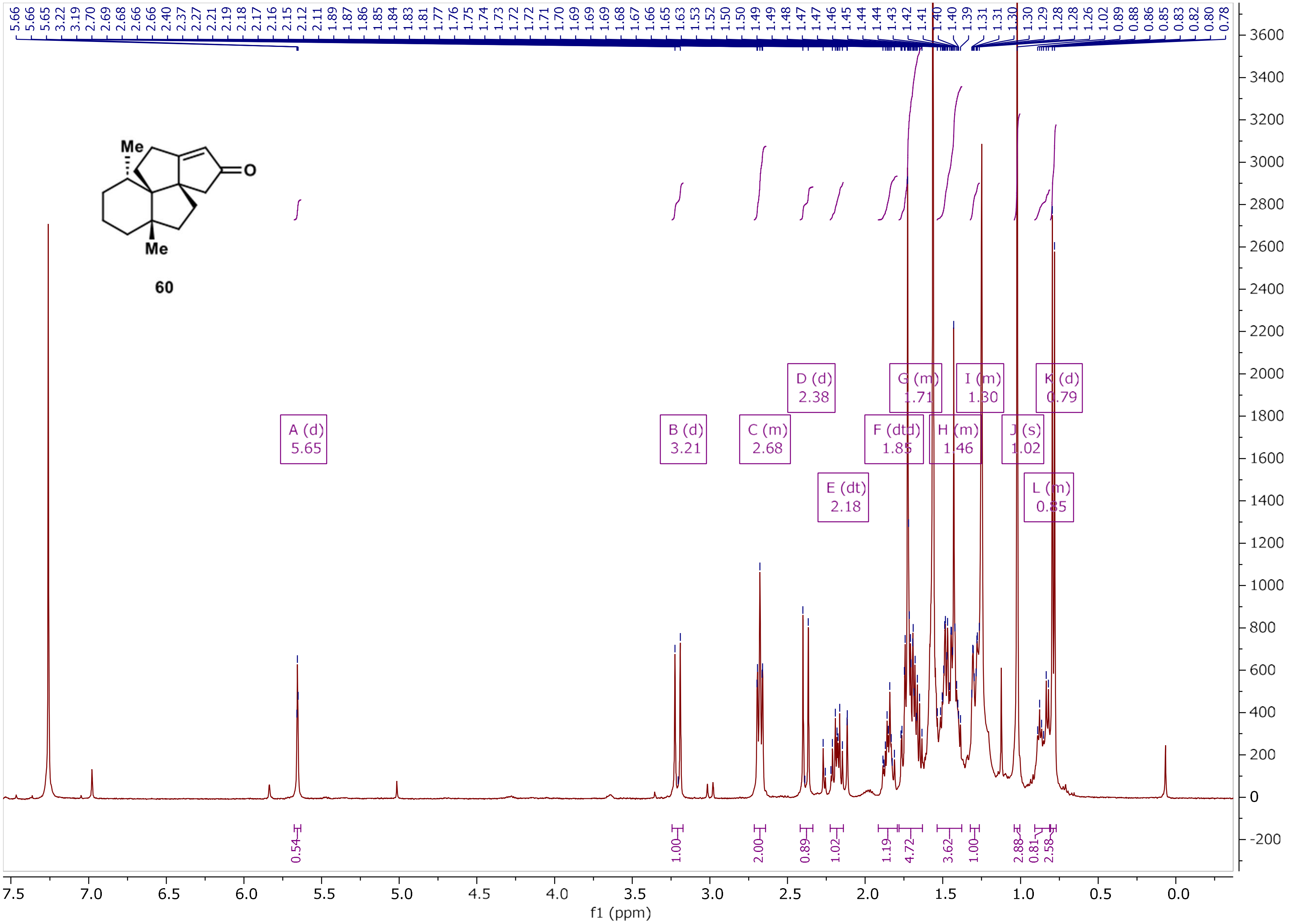
5.13 5.12 5.12 4.69 4.69 4.68 4.07 4.06 4.06 4.06 4.05 4.04 4.04 4.04 2.50 2.49 2.49 2.46 2.46 2.45 2.45 2.44 2.44 2.44 2.44 2.44 2.43 2.43 2.42 2.42 2.42 2.41 2.41 2.40 2.39 2.38 2.37 2.37 2.35 2.35 2.06 2.05 2.05 2.04 2.03 2.03 1.84 1.83 1.80 1.79 1.78 1.77 1.77 1.66 1.64 1.63 1.63 1.62 1.61 1.60 1.55 1.55 1.54 1.54 1.53 1.53 1.52 1.52 1.51 1.51 1.51 1.30 1.30 1.29 1.28 1.28 1.27 1.26 1.26 1.25 1.23 1.06 1.05
Me
HO
Me
57
A (t) 5.12
B (t) 4.69
C (ddd) 4.05
D (m) 2.42
E (m) 2.04
F (d) 1.83
G (tp) 1.78
H (tt) 1.63
I (m) 1.53
J (d) 1.05
K (s) 1.23
L (m) 1.27
1.00
1.02
0.99
4.26
1.73
0.85
1.00
1.16
1.32
4.90
3.62
3.29
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)
11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000

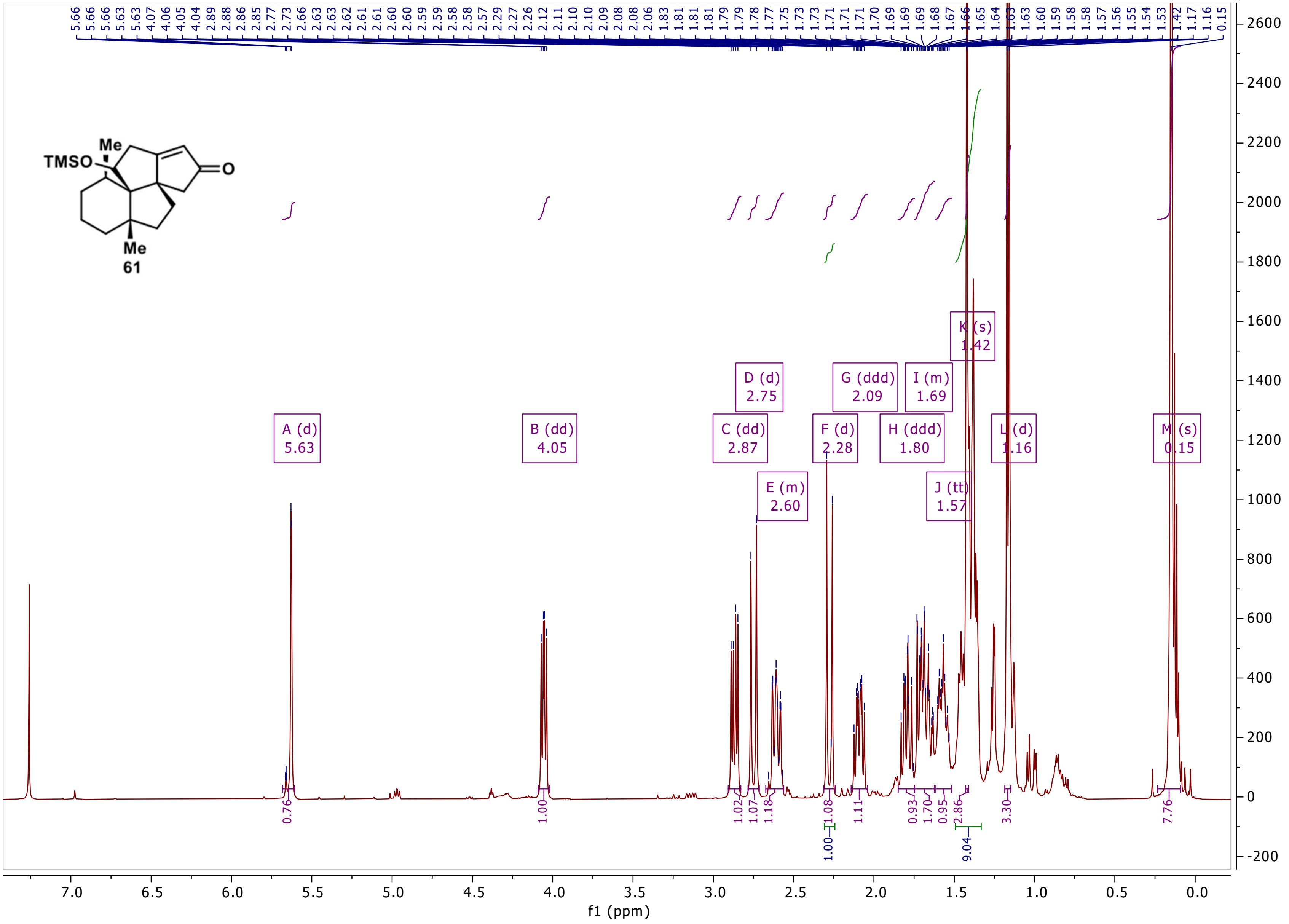

154.74
108.22
82.89
73.17
70.70
55.14
45.18
39.70
39.32
31.27
31.05
30.51
22.67
22.53
17.67
16.06
Me
HO
Me
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

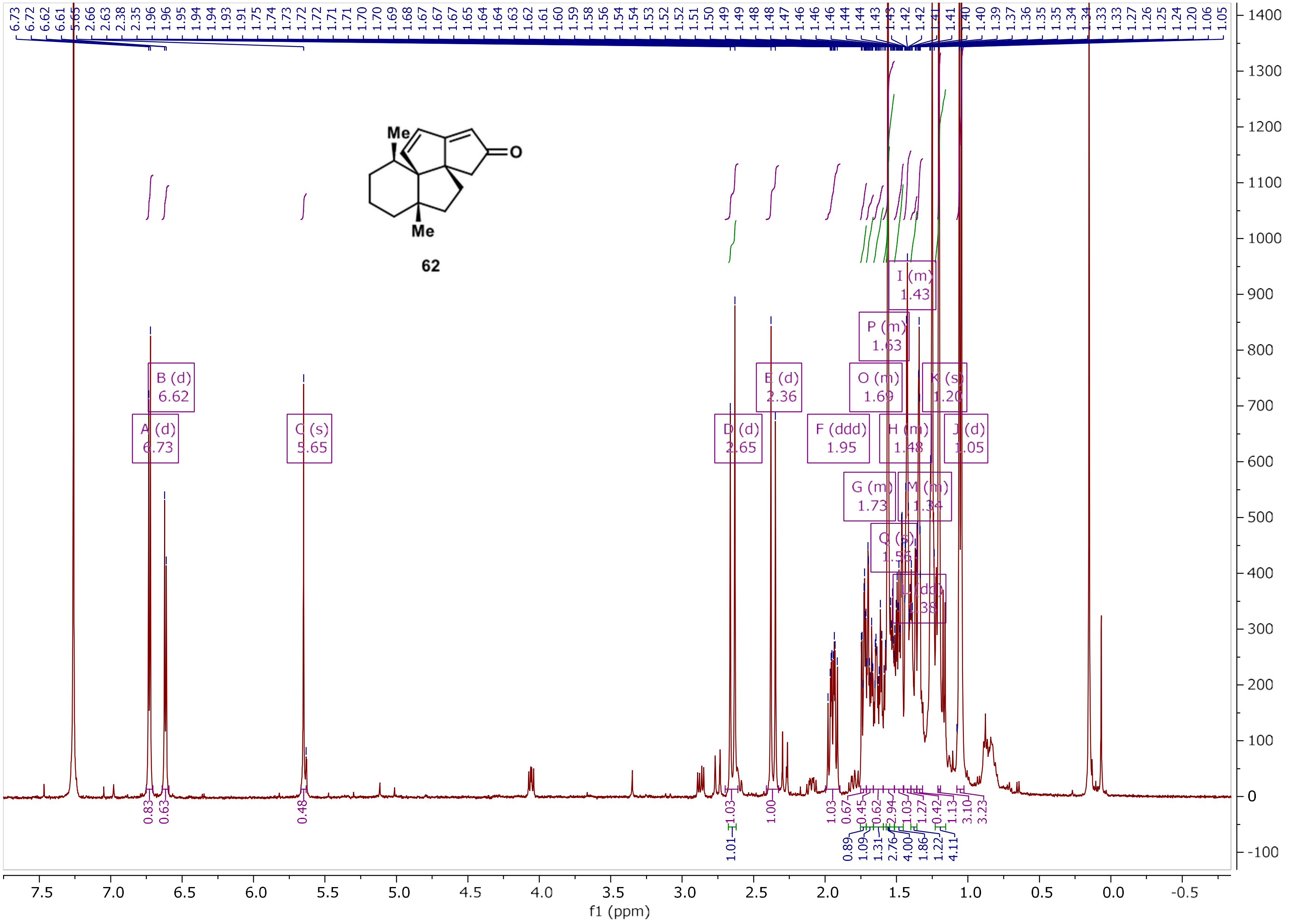
57


HO
Me
Me
O
59
5.71
5.70
5.70
4.64
4.63
4.62
4.61
4.60
3.43
3.41
3.39
3.36
3.24
3.21
2.64
2.62
2.60
2.58
2.41
2.40
2.37
2.37
2.11
2.09
1.81
1.80
1.79
1.79
1.78
1.57
1.56
1.56
1.55
1.55
1.54
1.52
1.52
1.43
1.43
1.25
1.13
1.13
0.88
0.88
0.87
0.86
A (d) 5.70
B (dt) 4.62
C (dd) 3.40
D (d) 3.23
E (dd) 2.61
K (dd) 2.39
F (d) 2.10
G (m) 1.78
H (m) 1.52
I (d) 1.13
J (dd) 0.87
0.59
1.03
1.00
1.00
1.00
1.02
0.87
1.24
2.97
12.95
21.05
8.28
2.56
2.76
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)
550
500
450
400
350
300
250
200
150
100
50
0
-50

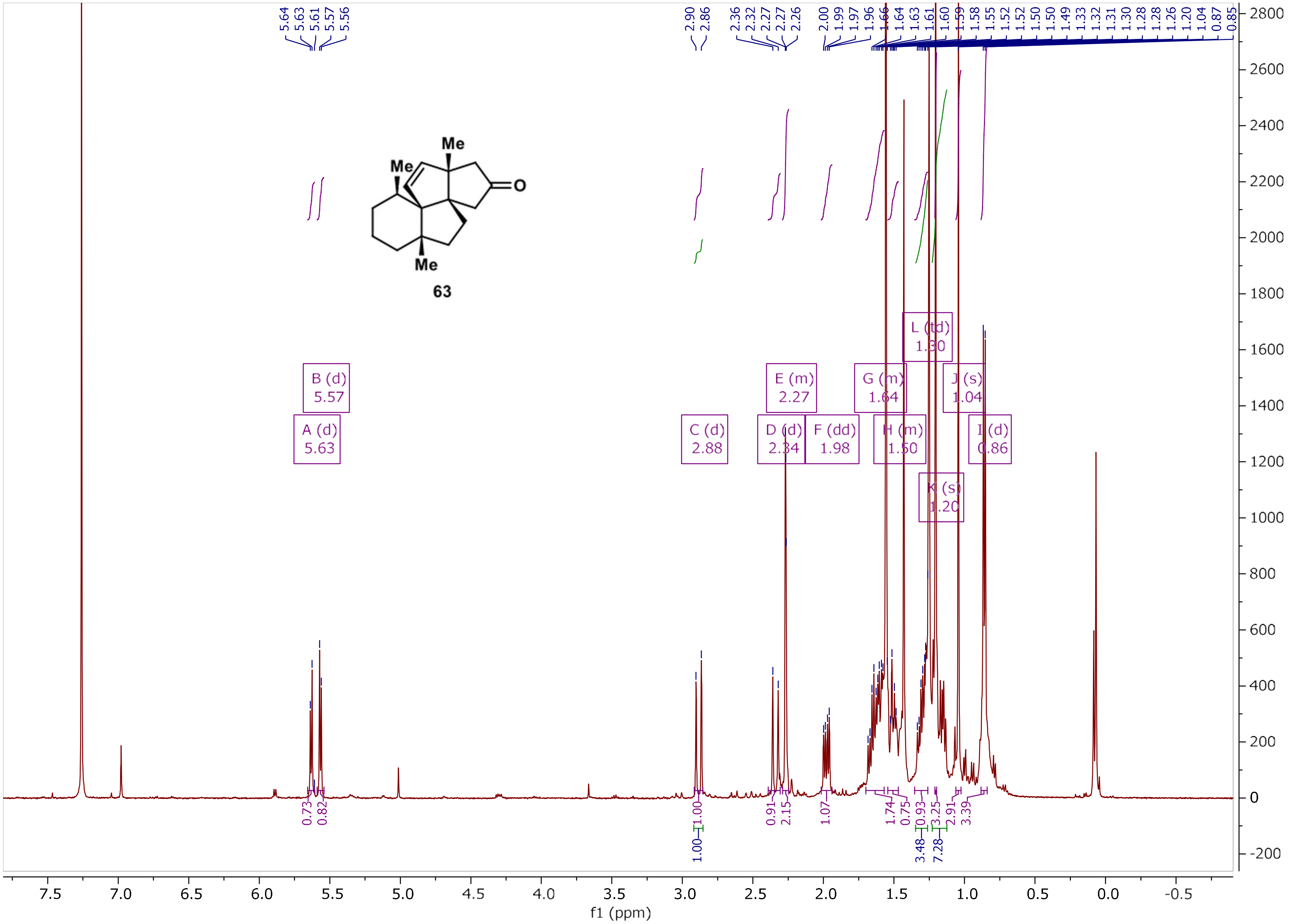

6.05 6.03 6.03 6.01 5.74 5.73 5.73 3.74 3.74 3.72 3.72 3.70 3.70 3.68 3.68 3.32 3.28 2.59 2.58 2.58 2.56 2.56 2.54 2.54 2.52 2.52 2.46 2.42 2.26 2.25 2.24 2.23 2.22 1.88 1.88 1.87 1.86 1.86 1.85 1.84 1.84 1.84 1.83 1.82 1.81 1.62 1.60 1.60 1.59 1.58 1.58 1.57 1.55 1.55 1.54 1.54 1.53 1.52 1.52 1.43 1.42 1.41 1.40 1.39 1.36 1.35 1.35 1.34 1.33 0.98 0.97 0.93 0.92 0.89 0.89 0.88 0.88 0.87 0.87 0.85 0.85
MeS
S
O
Me
O
Me
S3
A (dd) 6.03
B (t) 5.73
C (m) 3.71
D (d) 3.30
F (ddd) 2.55
E (s) 2.59
G (d) 2.44
H (tq) 2.23
I (m) 1.85
J (m) 1.56
M (m) 1.42
N (m) 1.35
K (s) 0.98
L (d) 0.92
1.00
1.00
0.75
1.19
1.01
2.82
1.10
0.91
1.11
3.26
8.93
8.05
4.12
0.72
0.86
2.92
2.91
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)
1000 900 800 700 600 500 400 300 200 100 0


5.66
5.66
5.65
3.22
3.19
2.70
2.69
2.68
2.66
2.66
2.40
2.37
2.27
2.21
2.19
2.18
2.17
2.16
2.15
2.12
2.11
1.89
1.87
1.86
1.85
1.84
1.83
1.81
1.77
1.76
1.75
1.74
1.73
1.72
1.72
1.71
1.70
1.69
1.69
1.69
1.68
1.67
1.66
1.65
1.63
1.53
1.52
1.50
1.50
1.49
1.49
1.48
1.47
1.47
1.46
1.45
1.44
1.44
1.43
1.42
1.41
1.40
1.40
1.39
1.31
1.31
1.30
1.30
1.29
1.28
1.28
1.26
1.02
0.89
0.88
0.86
0.85
0.83
0.82
0.80
0.78
Me
O
Me
60
A (d) 5.65
B (d) 3.21
C (m) 2.68
D (d) 2.38
E (dt) 2.18
F (dtd) 1.85
G (m) 1.71
H (m) 1.46
I (m) 1.30
J (s) 1.02
K (d) 0.79
L (m) 0.85
0.54
1.00
2.00
0.89
1.02
1.19
4.72
3.62
1.00
2.88
0.81
2.58
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)
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200


5.66
5.66
5.66
5.63
4.07
4.06
4.05
4.04
2.89
2.88
2.86
2.85
2.77
2.73
2.66
2.63
2.63
2.62
2.61
2.61
2.60
2.59
2.59
2.58
2.58
2.57
2.29
2.27
2.26
2.12
2.11
2.10
2.10
2.09
2.08
2.08
2.06
1.83
1.81
1.81
1.81
1.79
1.79
1.78
1.77
1.75
1.73
1.73
1.71
1.71
1.71
1.70
1.69
1.69
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.63
1.60
1.59
1.58
1.58
1.57
1.56
1.55
1.54
1.53
1.42
1.17
1.16
0.15
TMSO
Me
O
Me
61
A (d) 5.63
B (dd) 4.05
C (dd) 2.87
D (d) 2.75
E (m) 2.60
F (d) 2.28
G (ddd) 2.09
H (ddd) 1.80
I (m) 1.69
J (tt) 1.57
K (s) 1.42
L (d) 1.16
M (s) 0.15
0.76
1.00
1.02
1.07
1.18
1.08
1.00
1.11
0.93
1.70
0.95
2.86
9.04
3.30
7.76
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)


Me
Me
O
A (d) 6.73
B (d) 6.62
C (s) 5.65
D (d) 2.65
E (d) 2.36
F (ddd) 1.95
G (m) 1.73
O (m) 1.69
P (m) 1.63
Q (s) 1.56
H (m) 1.48
I (m) 1.43
L (ddd) 1.38
M (m) 1.34
K (s) 1.20
J (d) 1.05
f1 (ppm)

62



5.64
5.63
5.61
5.57
5.56
2.90
2.86
2.36
2.32
2.27
2.27
2.26
2.00
1.99
1.97
1.96
1.66
1.64
1.63
1.61
1.60
1.59
1.58
1.55
1.52
1.52
1.50
1.50
1.49
1.33
1.32
1.31
1.30
1.28
1.28
1.26
1.20
1.04
0.87
0.85
Me
Me
O
Me
63
L (td) 1.30
B (d) 5.57
E (m) 2.27
G (m) 1.64
J (s) 1.04
A (d) 5.63
C (d) 2.88
D (d) 2.34
F (dd) 1.98
H (m) 1.50
I (d) 0.86
K (s) 1.20
0.73
0.82
1.00
1.00
0.91
2.15
1.07
1.74
0.75
0.93
3.25
2.91
3.39
3.48
7.28
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

References

---

[1] For reviews on syntheses of natural products with contiguous all-carbon quaternary stereocenters, see: (a) Büschleb, M.; Dorich, S.; Hanessian, S.; Tao, D. J.; Schenthal, K. B.; Overman, L. E. Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms. *Angew. Chem., Int. Ed.* **2016**, *55*, 4156–4186. (b) Long, R.; Huang, J.; Gong, J.; Yang, Z. Direct Construction of Vicinal All-Carbon Quaternary Stereocenters in Natural Product Synthesis. *Nat. Prod. Rep.* **2015**, *32*, 1584–1601.

[2] For a review on syntheses of polyquinane natural products, see: Mehta, G.; Adusumilli Srikrishna. Synthesis of Polyquinane Natural Products: An Update. *Chem. Rev.* **1997**, *97*, 671–720.

[3] Clarke, D. B.; Hinkley, S. F. R.; Weavers, R. T. Waihoensene. A New Laurenene-Related Diterpene from Podocarpus Totara Var Waihoensis. *Tetrahedron Lett.* **1997**, *38*, 4297–4300.

[4] For the isolation of laurenene, see: (a) Corbett, R. E.; Lauren, D. R.; Weavers, R. T. The Structure of Laurenene, a New Diterpene from the Essential Oil of Dacrydium Cupressinum. Part 1. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1774–1790. (b) Corbett, R. E.; Couldwell, C. M.; Lauren, D. R.; Weavers, R. T. The Structure of Laurenene, a New Diterpene from the Essential Oil of Dacrydium Cupressinum. Part 2. Crystal Structure. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1791–1794. For syntheses of laure-nene, see: (c) Crimmins, M. T.; Gould, L. D. Intramolecular Photocycloaddition-Cyclobutane Fragmentation: Total Synthesis of (.+-.)-Laurenene. *J. Am. Chem. Soc.* **1987**, *109*, 6199–6200. (d) Paquette, L. A.; Okazaki, M. E.; Jean-Claude Caille. A Formal Total Synthesis of (.+-.)-Laurenene. *J. Org. Chem.* **1988**, *53*, 477–481. (e) Wender, P. A.; Thomas; Levine, B. Synthetic Studies on Arene-Olefin Cycloadditions. 10. A Concise, Stereocontrolled Total Synthesis of (.+-.)-Laurenene. *J. Am. Chem. Soc.* **1988**, *110*, 4858–4860. (f) Mehta, G.; Kasibhatla Srinivas Rao. Transannulation Route to the [5.5.5.7]-Fenestrane Ring System of Laurenene. *J. Org. Chem.* **1988**, *53*, 425–427.

[5] Jens-Kerim Ergüden; Moore, H. W. A New Tandem Route to Angular Tetraquinanes. Synthesis of the Waihoensene Ring System. *Org. Lett.* **1999**, *1*, 375–378.

[6] Lee, H.-S.; Taek Won Kang; Lee, H.-Y. Total Synthesis of (±)-Waihoensene. *Angew. Chem., Int. Ed.* **2017**, *56*, 8254–8257.

[7] Zhang, Y.; Zheng, T.-L.; Cheng, F.; Dai, K.-L.; Zhang, K.; Ma, A.-J.; Zhang, F.-M.; Zhang, X.-M.; Wang, S.-H.; Tu, Y.-Q. Facile Access to Diverse All-Carbon Quaternary Center Containing Spirobicycles by Exploring a Tandem Castro–Stephens Coupling/Acyloxy Shift/Cyclization/Semipinacol Rearrangement Sequence. *Chem. Sci.* **2020**, *11*, 3878–3884.

[8] (a) Snyder, S. A.; Wespe, D. A.; von Hof, J. M. A Concise, Stereocontrolled Total Synthesis of Rippertenol. *J. Am. Chem. Soc.* **2011**, *133*, 8850–8853. (b) Hu, P.; Snyder, S. A. Enantiospecific Total Synthesis of the Highly Strained (−)-Presilphiperfolan-8-Ol via a Pd-Catalyzed Tandem Cyclization *J. Am. Chem. Soc.* **2017**, *139*, 5007–5010. (c) Hu, P.; Chi, H. M.; DeBacker, K. C.; Gong, X.; Keim, J. H.; Hsu, I. T.; Snyder, S. A. Quaternary-Centre-Guided Synthesis of Complex Polycyclic Terpenes. *Nature* **2019**, *569*, 703–707. (d) Yi, H.; Hu, P.; Snyder, S. A. Development and Elucidation of a Pd-Based Cyclization–Oxygenation Sequence for Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 2674–2678.

[9] Piyush Arya, *Ph.D. Dissertation*, **2020**, the University of Chicago.

[10] For original reports on the Pauson–Khand reaction, see: (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyldicobalt Complexes, (R1C2R2)Co2(CO)6, with Norbornene and Its

---

Derivatives. *J. Chem. Soc. Perkin Trans. 1* **1973***, 977 – 981*. (b) Pauson, P. L. The Khand Reaction. *Tetrahedron* **1985**, *41*, 5855–5860. For examples of Pauson –Khand reactions forming angular triquinane structures, see: (c) Ishizaki, M.; Iwahara, K.; Kyoumura, K.; Hoshino, O. An Effective Synthesis of Angular Tricyclic Compounds Having Two Contiguous Quaternary Centers by Intramolecular Pauson-Khand Reaction of Exocyclic Enynes. *Synlett* **1999**, *1999*, 587–589. (d) Renaud, J.-L.; Aubert, C.; Malacria, M. Cobalt-Mediated Cycloisomerization of δ-Substituted ε-Acetylenic β-Ketoesters Construction of Angular Triquinane by a Sequence Ene/Pauson-Khand Reactions. *Tetrahedron* **1999**, *55*, 5113–5128. (e) Ishizaki, M.; Iwahara, K.; Niimi, Y.; Satoh, H.; Hoshino, O. Investigation of the Synthesis of Angular Tricyclic Compounds by Intramolecular Pauson–Khand Reaction of Exo- and Endo-Cyclic Enynes. *Tetrahedron* **2001**, *57*, 2729–2738.

[11] Hajos, Z. G.; Parrish, D. R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *The J. Org. Chem.* **1974**, *39*, 1615–1621.

[12] Ramachary, D. B.; Kishor, M. Direct Amino Acid-Catalyzed Cascade Biomimetic Reductive Alkylations: Application to the Asymmetric Synthesis of Hajos–Parrish Ketone Analogues. *Org. Biomol. Chem.* **2008**, *6*, 4176-4187.

[13] Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. Dichloromethane Activation. Direct Methylenation of Ketones and Aldehydes with CH_2Cl_2 Promoted by Mg/$TiCl_4$/THF. *Org. Lett.* **2004**, *6*, 4961–4963.

[14] (a) Ikemoto, N.; Schreiber, S. L. Total Synthesis of (-)-Hikizimycin Employing the Strategy of Two-Directional Chain Synthesis. *J. Am. Chem. Soc.* **1992**, *114*, 2524–2536. (b) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. Highly Stereoselective and Efficient Total Synthesis of (+)-Laurencin. *Org. Lett.* **2005**, *7*, 75–77.

[15] Omura, K.; Swern, D. Oxidation of Alcohols by “Activated” Dimethyl Sulfoxide. A Preparative, Steric and Mechanistic Study. *Tetrahedron* **1978**, *34*, 1651–1660.

[16] (a) Ohira, S. Methanolysis of Dimethyl (1-Diazo-2-Oxopropyl) Phosphonate: Generation of Dimethyl (Diazomethyl) Phosphonate and Reaction with Carbonyl Compounds. *Synth. Commun.* **1989**, *19*, 561–564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. An Improved One-Pot Procedure for the Synthesis of Alkynes from Aldehydes. *Synlett* **1996**, *1996*, 521–522. (c) Roth, G.; Liepold, B.; Müller, S.; Bestmann, H. Further Improvements of the Synthesis of Alkynes from Aldehydes. *Synthesis* **2003**, *2004*, 59–62.

[17] Shambayani, S.; Crowe, W. E.; Schreiber, S. L. N-Oxide Promoted Pauson-Khand Cyclizations at Room Temperature. *Tetrahedron Lett.* **1990**, *31*, 5289–5292.

[18] Koga, Y.; Kobayashi, T.; Koichi Narasaka. Rhodium-Catalyzed Intramolecular Pauson-Khand Reaction. *Chemistry Lett.* **1998**, *27*, 249–250.

[19] (a) Iwasaki, K.; Wan, K. K.; Oppedisano, A.; Crossley, S. W. M.; Shenvi, R. A. Simple, Chemoselective Hydrogenation with Thermodynamic Stereocontrol. *J. Am. Chem. Soc.* **2014**, *136*, 1300–1303. (b) Obradors, C.; Martinez, R. M.; Shenvi, R. A. Ph(*I*-PrO)SiH_2: An Exceptional Reductant for Metal-Catalyzed Hydrogen Atom Transfers. *J. Am. Chem. Soc.* **2016**, *138* (14), 4962–4971.

[20] Computational analysis by Cooper Taylor from the Snyder group using m062x/cc-PVDZ.

[21] Kennedy-Smith, J. J.; Staben, S. T.; F. Dean Toste. Gold(I)-Catalyzed Conia-Ene Reaction of β-Ketoesters with Alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527.

[22] Hird, A.; Hoveyda, A. H. Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989.

---

[23] Eagan, J. M.; Hori, M.; Wu, J.; Kanyiva, K. S.; Snyder, S. A. Synthesis and Applications of Hajos-Parrish Ketone Isomers. *Angew. Chem. Int., Ed.* **2015**, *54*, 7842–7846.

[24] (a) May, T. L.; Brown, M. A.; Hoveyda, A. H. Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl and Aryl Aluminum Reagents to Five-, Six-, and Seven-Membered-Ring β-Substituted Cyclic Enones. *Angew. Chem. Int., Ed.* **2008**, *47*, 7358–7362. (b) Brown, M. A.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene. *Angew. Chem. Int., Ed.* **2007**, *46*, 1097–1100.

[25] Posner, G. H.; Lentz, C. M. A Directing Effect of Neighboring Aromatic Groups on the Regiochemistry of Formation and Stereochemistry of Alkylation and Bromination of Ketone Lithium Enolates. Evidence for Lithium-Arene Coordination and Dramatic Effect of Copper(I) in Controlling Stereochemistry and Limiting Polyalkylation. *J. Am. Chem. Soc.* **1979**, *101*, 934–946.

[26] Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P. Synthetic Applications and Mechanism Studies of the Decarbalkoxylations of Geminal Diesters and Related Systems Effected in Dimethyl Sulfoxide by Water And/or by Water with Added Salts. *J. Org. Chem.* **1978**, *43*, 138–147.

[27] Crabtree, R. H.; Davis, M. W. Directing Effects in Homogeneous Hydrogenation with [Ir(Cod)(PCy3)(Py)]PF6. *The J. Org. Chem.* **1986**, *51*, 2655–2661.

[28] Wadsworth, W. S. Synthetic Applications of Phosphoryl-Stabilized Anions. *Org. React.* **1977**, 73–253.

[29] Pfaffenbach, M.; Gaich, T. A Flexible Route to Indole Scaffolds - Formal Synthesis of (±)-Mersicarpine. *Eur. J. Org. Chem.* **2015**, *2015*, 3427–3429.

[30] For selected reviews on the Pauson–Khand reaction, see: (a) Kurti, L., Czako, B. *Strategic Applications of Named Reactions in Organic Chemistry*, **2005**, *pp. 334-335.* (b) Geis, O.; Schmalz, H.-G. New Developments in the Pauson-Khand Reaction. *Angew. Chem. Int. Ed.* **1998**, *37*, 911–914. (c) Brummond, K. M.; Kent, J. L. Recent Advances in the Pauson–Khand Reaction and Related [2+2+1] Cycloadditions. *Tetrahedron* **2000**, *56*, 3263–3283. (d) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. The Pauson–Khand Reaction, a Powerful Synthetic Tool for the Synthesis of Complex Molecules. *Chem. Soc. Rev.* **2004**, *33*, 32–42. (e) Boñaga, L. V. R.; Krafft, M. E. When the Pauson–Khand and Pauson–Khand Type Reactions Go Awry: A Plethora of Unexpected Results. *Tetrahedron* **2004**, *60*, 9795–9833.

[31] (a) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. Effects of Lewis Acids on Higher Order, Mixed Cuprate Couplings. *Tetrahedron Lett.* **1984**, *25*, 5959–5962. (b) Luc Van Hijfte; R. Daniel Little; Petersen, J. L.; Moeller, K. D. Intramolecular 1,3-Diyl Trapping Reactions. Total Synthesis of (.+-.)-Hypnophilin and (.+-.)-Coriolin. Formation of the Trans-Fused Bicyclo[3.3.0]Octane Ring System. *J. Org. Chem.* **1987**, *52*, 4647–4661.

[32] (a) Petasis, N. A.; Bzowej, E. I. Titanium-Mediated Carbonyl Olefinations. 1. Methylenations of Carbonyl Compounds with Dimethyltitanocene. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394.

[33] Barton, D. H. R.; McCombie, S. W. A New Method for the Deoxygenation of Secondary Alcohols. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574-1585.

[34] Pasto, D. J.; Richard. Reduction with Diimide. *Org. React.* **2004**, 91–155.

[35] Corey, E. J.; Kirst, H. A. Position-Specific Alkylation of Lithio-1-Trimethylsilylpropyne, a Useful New Route to Acetylenes and 1, 5-Dienes. *Tetrahedron Lett.* **1968**, *9*, 5041–5043.

[36] Myers, A. G.; Movassaghi, M. Highly Efficient Methodology for the Reductive Coupling of Aldehyde Tosylhydrazones with Alkyllithium Reagents. *J. Am. Chem. Soc.* **1998**, *120*, 8891–8892.

---

[37] Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. Asymmetric Total Synthesis of (+)-Waihoensene. *J. Am. Chem. Soc.* **2020**, *142*, 6511–6515.

[38] Rosenbaum, L.-C.; Maximilian Häfner; Gaich, T. Total Synthesis of the Diterpene Waihoensene. *Angew. Chem., Int. Ed.* **2021**, *60*, 2939–2942.

[39] Wang, Y.-P.; Fang, K.; Tu, Y.-Q.; Yin, J.-J.; Zhao, Q.; Ke, T. An Efficient Approach to Angular Tricyclic Molecular Architecture via Nazarov-like Cyclization and Double Ring-Expansion Cascade. *Nature Commun.* **2022**, *13*, 2335.

Chapter 3 Studies Toward the Strategic Syntheses of Bipolarolides A and B

3.1 Introduction

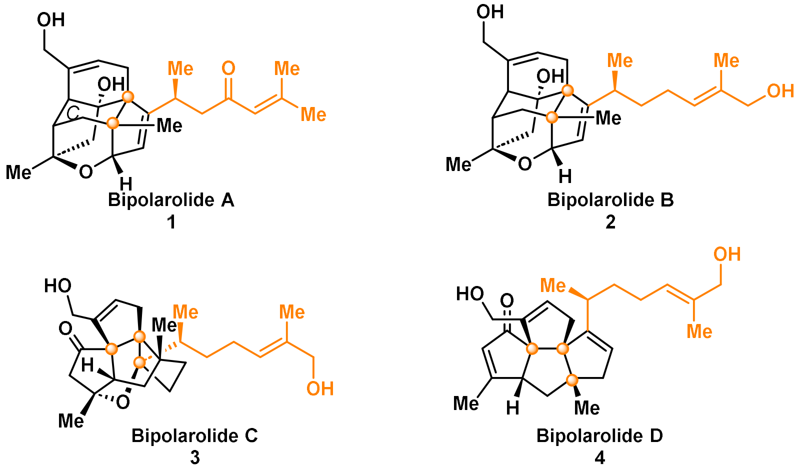


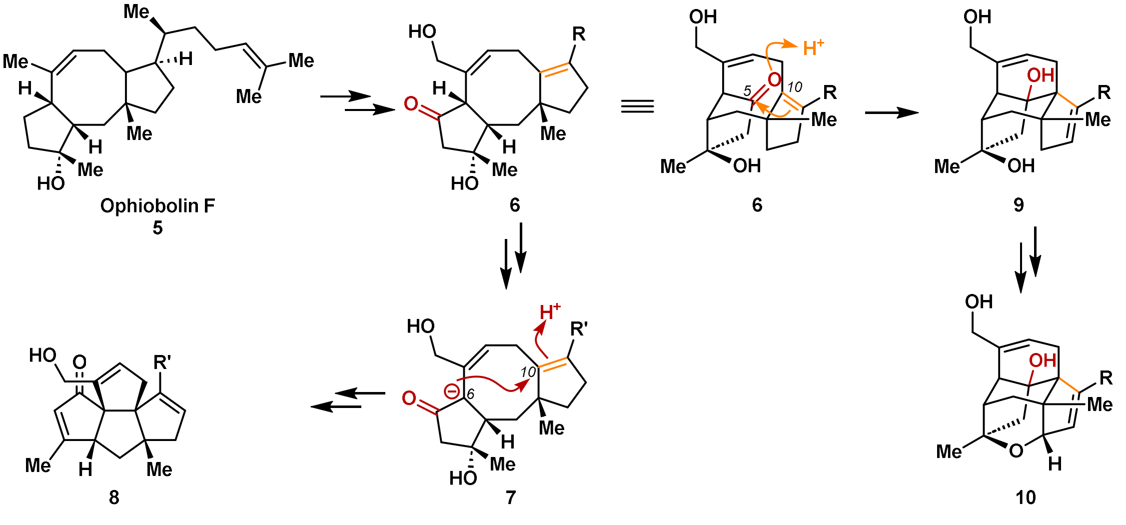
Figure 3.1. The structures of bipolarolides A-D.

Bipolarolides A-G were isolated from fungus *Bipolaris sp.* TJ403-B1 by the Yonghui Zhang group in 2019[1]. While all 7 sesterterpenes were proposed to derive from the ophiobolin family, they bear three different types of frameworks, two of which drew particular attention to our group: the unprecedented pentacyclic caged framework with 2 contiguous quaternary centers of bipolarolides A-B (**1** and **2**), and the tetraquinane framework with 3 contiguous quaternary centers of bipolarolides C-D (**3** and **4**). It was proposed by the isolation team that, on intermediates with the hallmark 5/8/5 fused ring system of the ophiobolin family, the electrophilic attack of C-5 into C-10 results **10**, which bears the pentacyclic framework of **1** and **2**; while the nucleophilic attach of C-6 into C-10 results into **8**, which bears the tetraquinane framework of **3** and **4**.

The potential biological target of bipolarolides A-G were screened *in silico* by the isolation team by utilizing the Swiss Target Prediction tool. HMG-CoA reductase (HMGR) was identified as the most likely target for the natural product family. An *in vitro* assay further revealed that bipolarolide

A (**1**) has the best inhibitory potency, with an IC_{50} value of 2.46 ± 0.07 μM. The hypolipidemic effect of **1** was further evaluated in HepG2 cells, showing that **1** dose-dependently suppressed oleic-acid-dependent lipid accumulation with an efficiency comparable to that of pravastatin[2], a popular hypocholesterol medication marketed by Bristol-Myers Squibb, at the concentration of 100 nM.

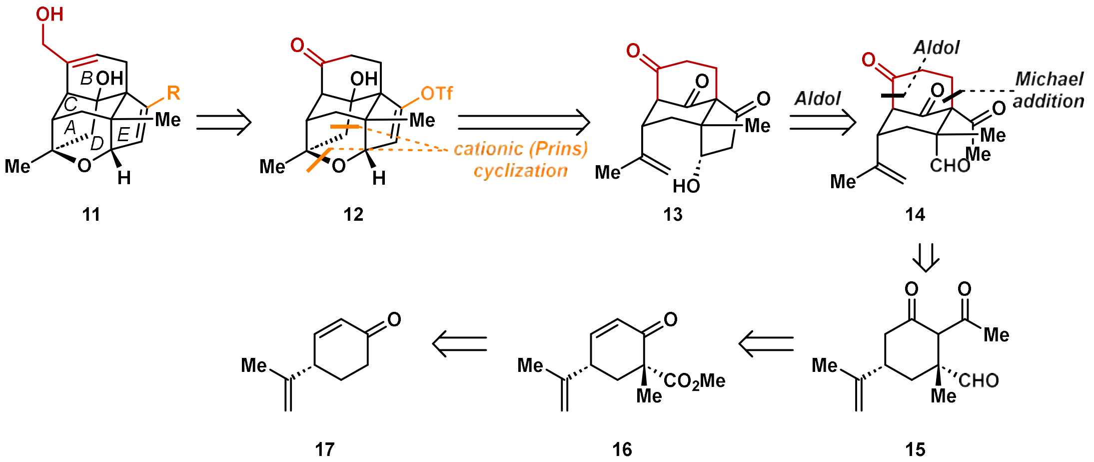
The caged skeleton of **1** and **2** deeply impressed us with its high levels of congestion and strain. The highly substituted central *C* ring, with all 6 carbons as stereocenters, bears 5 axial C-C bonds, in addition to a [4.3.0], two [3.3.1]'s, and a [3.2.1] bridgecyclic system attached to it. Fascinated by their biological activities, unique structures, and the potential challenges they may bring, we initiated our synthetic studies of this natural product family focusing on **1** and **2**. During our explorations, we also delightedly found a new method that could lead to bipolarolides C and D (**3** and **4**) as well.



Scheme 3.1. The proposed biological synthesis of **1-4**.

3.2 Early Attempts

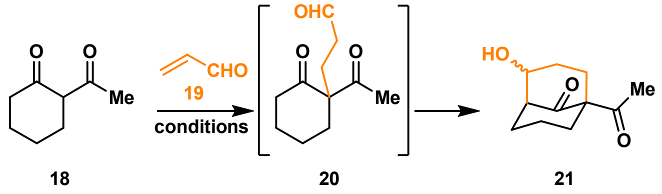
3.2.1 First-Generation Retrosynthetic Analysis Based on A Prins Cyclization Reaction



Scheme 3.2. Retrosynthetic analysis based on a Prins cyclization reaction.

In our retrosynthesis, a different strategy than nature was taken. To access both **1** and **2**, we disconnected the side chain to a vinyl triflate, hoping we could diversify at a later stage. The allyl alcohol on the *B* ring was traced back to a ketone in **12**. To access the hallmark caged structure, we disconnected the *A* and *D* rings at the same time, leading to **13**. We projected a cationic cyclization cascade initiating from the *C* ring ketone, with the isopropenyl group reacting as the initial nucleophile in a Prins reaction manner, and the *E* ring hydroxyl group as the terminal nucleophile. Then the *E* ring was disconnected through an aldol condensation reaction, tracing back to **14**. With the bicyclic [3.3.1] ring system left, we determined it was strategic to start from the more substituted *C* ring. We proposed that the three-carbons unit of the *B* ring could simply come from acrolein (**19**) through a condensation sequence similar to a Robinson annulation reaction. Finally, we proposed that **15** could be synthesized asymmetrically from enone **17**, which was reported to come from (-)-perillaldehyde (**22**) through a 3-step sequence[3].

3.2.2 A Model Study of the Tandem Michael-Addition/Aldol-Condensation Reactions Giving the [3.3.1] bicyclic ring system

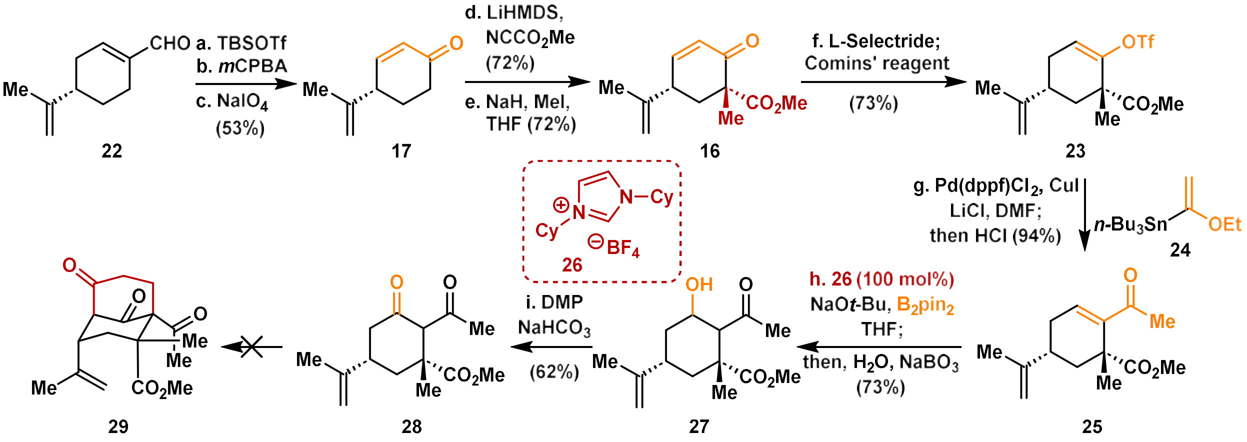


Entry	Condition	Result
1	TfOH, DCM, -78 to 0 ºC	Decomposed
2	TFA, DCM, rt.	N.R.
3	TMSOTf, DCM, -78 ºC to 0 ºC	42%
4	TMSOTf, MeOH, DCM, **19** (slow add.)	74%
5	Et_3N, MeCN, 40 ºC; then, DCM, TfOH, 0 ºC	55%

Table 3.1. Screen of conditions for the Tandem Michael-Addition/Aldol-Condensation Reactions Giving the bicyclic [3.3.1] ring system.
Entry 4: TMSOTf (0.30 equiv), MeOH (0.30 equiv), CH_2Cl_2, **19** (solution in CH_2Cl_2, 1.2 equiv, added over 2 h), 74%.

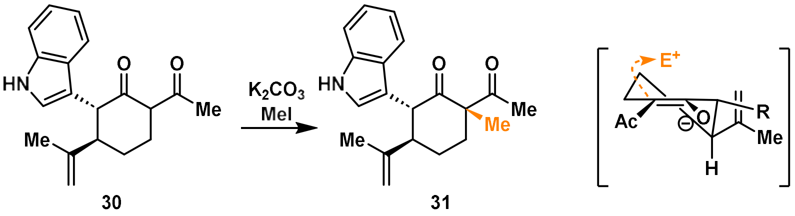
To quickly justify our proposed Michael-addition/aldol-condensation sequence to access the [3.3.1] bicyclic ring system, we conducted a quick model study on commercially available compound **18**. During initial literature research, we found that the Nicolaou group has attempted a similar conversion in their synthetic studies toward hyperforin family natural products[4]. A replica of their condition (entry 1) proved unsuccessful, possibly due to the instability of acrolein under the strong acidic condition. Despite the setback, we continued to pursue other acidic conditions for the conversion. A weaker acid, namely TFA, was not able to catalyze the Michael addition (entry 2). However, when switching the acidic catalyst to TMSOTf, we observed a 42% yield of the desired bicyclic product **21** (entry 3). It is uncertain whether TMSOTf catalyzed the conversions as a Lewis acid or the reaction simply proceeds because of the trace TfOH as a result of the hydrolysis of TMSOTf. Notably, the reaction requires multiple equivalents of acrolein, with the significant decomposition of acrolein observed, possibly by oligomerization. After some screenings, we found the optimal condition (entry 4) to be catalyzed by in-situ generated TfOH from TMSOTf and MeOH, with the slow addition of acrolein (**19**) to the reaction system. A more robust 2-step procedure was also found (entry 5): the initial Michael addition could be catalyzed by Et_3N, then all volatile contents were removed, and the residue containing intermediate **20** was treated with TfOH to give **21** in 55% yield.

3.2.3 Challenges in Translating the Model System into The Real System



Scheme 3.3. The synthesis of 1,3-diketone **28**, and the failure of converting it into the [3.3.1] bicyclic system. (a)-(c) See Ref.3. (d) LiHMDS (1.2 equiv), THF, -78 ºC, 30 min; then Mander's reagent (1.3 equiv), 30 min, 72%. (e) NaH (1.1 equiv), THF, 0 ºC, 30 min; then MeI (1.2 equiv), 23 ºC, 5 h, 72%. (f) L-selectride (1.1 equiv), THF, -78 ºC, 30 min; then Comins' reagent (1.0 equiv), 1 h, 73%. (g) LiCl (5.0 equiv), CuI (10 mol%), tributyl(1-ethoxyvinyl)tin (1.5 equiv), $Pd(dppf)Cl_2$ (10 mol%), DMF, 40 ºC, 12 h; then Et_2O (25 V%), 6 N HCl (25 V%), 23 ºC, 2 h, 94%. (h) 1,3-dicyclohexylimidazolium tetrafluoroborate salt (1.0 equiv), bis(pinacolato)diboron (1.1 equiv), NaO*t*-Bu (1.0 equiv), THF, 23 ºC, 48 h; then H_2O (33 V%), $NaBO_3 \cdot H_2O$ (5.0 equiv), 18 h, 73%, unoptimized. (i) Dess-Martin periodinane (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 ºC, 2 h, 62%, unoptimized.

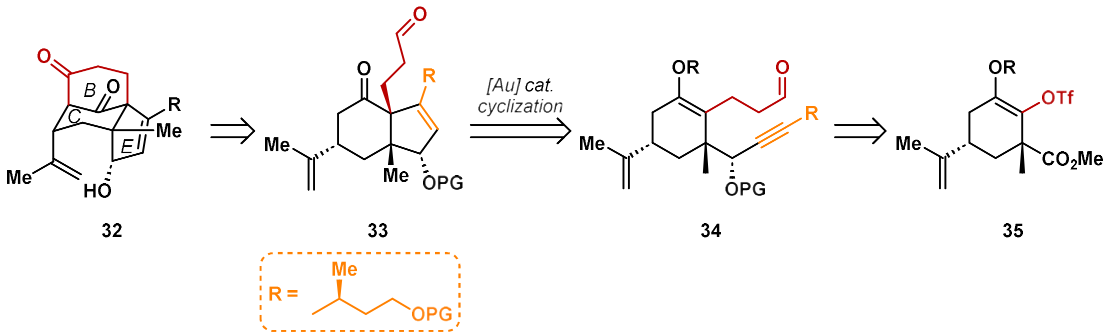
With the support of the key reaction in the model system, we moved on to the synthesis of 1,3-diketone **28**. Starting with (-)-perillaldehyde (**22**), we followed the reported procedure to prepare enone **17** on a decagram scale. Deprotonation of **17** with LDA, followed by the treatment of Mander's reagent gave a β-keto ester. A second deprotonation by NaH and the treatment of MeI gave enone **16** as a single diastereomer. A selective 1,4-reduction of the enone moiety and the subsequent trapping of the resultant enolate with Comins' reagent gave vinyl triflate **23**. A Stille coupling was then carried out with Tributyl(1-ethoxyvinyl)stannane followed by acidic hydrolysis[5], to give enone **25**. A formal hydroxyl 1,4-addition was achieved by a N-hetero carbene (NHC) mediated hydroboration of enone[6] and subsequent oxidation, to give **27**. Stoichiometric NHC was required for a faster conversion rate, albeit the reaction could theoretically run with catalytic NHC. Multiple other conditions for the hydroboration step were not successful, including some copper(I)-catalyzed conditions[7]. After Dess-Martin oxidation, the desired 1,3-diketone **28** was synthesized in 9 steps.



Scheme 3.4. An alkylation reaction in a similar system showing undesired diastereoselectivity, and the proposed model based on Fürst-Plattner Rule.

Unfortunately, any tandem Michael-Addition/aldol-Condensation conditions we attempted on **28** failed to yield any bicyclic product **29**. All conditions from Table 1 gave recovered **28**. We attribute the unsuccess mainly to the fact that the projected conversion is forming a second quaternary center next to an existing one. Thus, the initial Michael addition was too slow to outcompete the oligomerization of acrolein. While more conditions could be screened, an example we found of a similar system eventually put this approach into the grave. During the synthetic study of hapalindole-type alkaloids by the Zhou group[8], methylation on a similar 1,3-diketone **30** was found to react from the same face to the isopropenyl substitution, which could be explained by the Fürst-Plattner Rule[9] for the substitutions of cyclohexenes. Despite the differences in substitutional patterns, the isopropenyl group in both molecules should adopt the equatorial position, hence determining the stereoselectivity of the substitution of the 1,3-diketone. Our proposed approach unfortunately could not progress any further with such undesired selectivity.

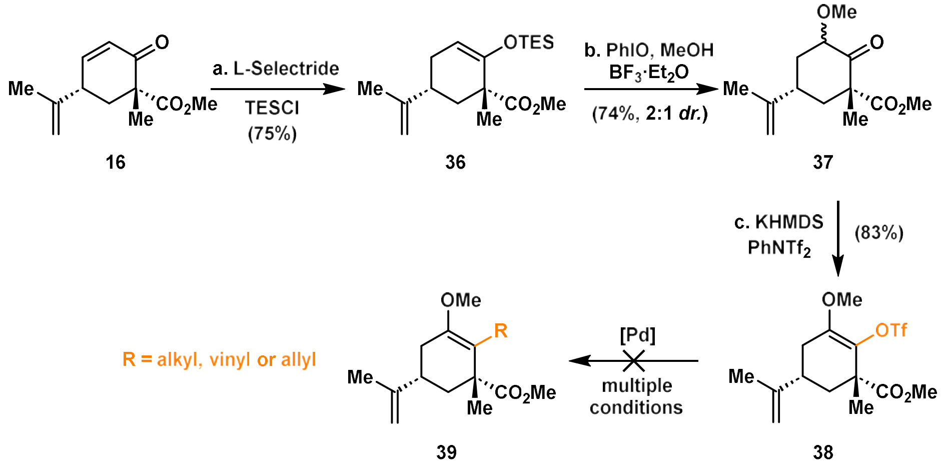
3.2.4 A Revised Route Based on a Gold-Catalyzed Cyclization Reaction



32 33 34 35

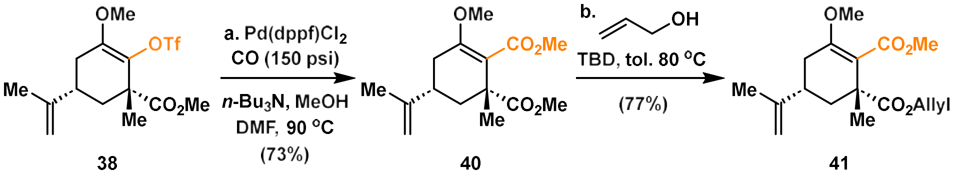
Scheme 3.5. A revised retro-synthetic analysis based on gold-catalyzed cyclization reaction.

Based on the challenges we described before, we amended our synthetic proposal, mainly in the parts involving the formation of the *E* ring. This time, we proposed to disconnect the *B* ring before the *E* ring. We think this is more strategic in two aspects: 1) in the *cis* 6/5 ring system of **33**, the angular substitution, namely the aldehyde-containing side chain, is forced towards a more axial-like position, hence making the subsequent aldol cyclization kinetically more favorable; and 2) the *E* ring formation step is now made into an intramolecular reaction, which is more favorable for a quaternary-center-forming step than intermolecular reactions, and will ensure the formation of the kinetically favored *cis* 6/5 ring system, solving both the reactivity and stereoselectivity issues. Plus, we were delighted to see the possibility of utilizing the trusty gold-cyclized cyclization reaction[10] for the formation of the *E* ring. Another benefit of this disconnection is that a chiral side chain (the R group in **32**) could be carried from the starting materials[11], thus avoiding a late-stage coupling reaction on a reaction chiral center. Finally, we projected the synthesis of **34** from vinyl triflate **35**, which is closely related to the synthetic approach described earlier.



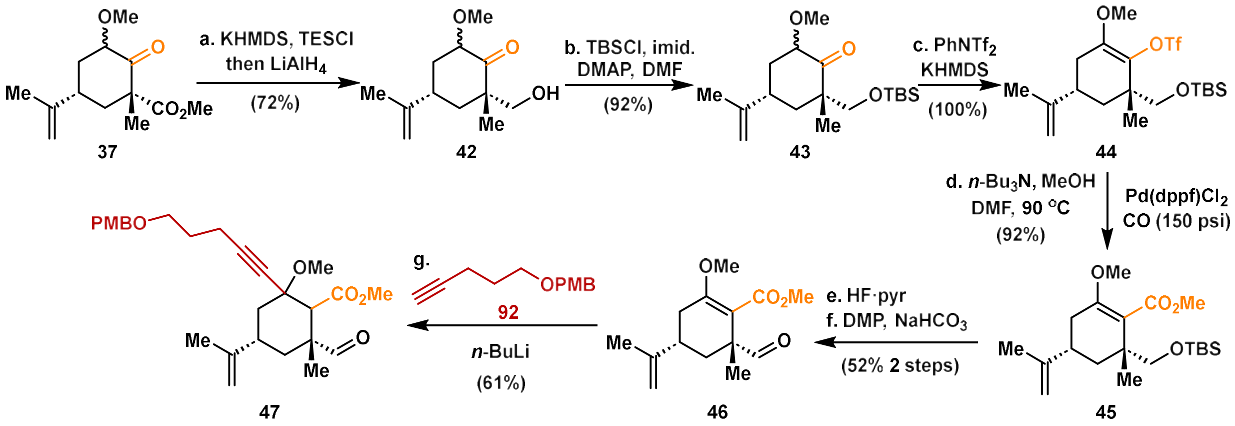
Scheme 3.6. The synthesis of vinyl triflate **38**, and its failure in cross-coupling reactions. (a) L-selectride (1.1 equiv), THF, -78 ºC, 30 min; then TESCl (1.2 equiv), 1 h, 75%. (b) Iodosobenzene (3.0 equiv), $BF_3 \cdot OEt_2$ (5.0 equiv), MeOH, -78 to 0 ºC, 3 h, 74%, 2:1 *dr.* (c) KHMDS (2.4 equiv), THF, -78 ºC, 30 min; then *N*-Phenyl-bis(trifluoromethanesulfonimide) (1.5 equiv), 30 min, 83%.

From enone **16**, a similar 1,4-reduction by l-selectride followed by trapping the resultant enolate with TESCl gave silyl enol ether **36**. Treatment of the latter compound with iodosobenzene and boron trifluoride etherate in methanol[12] gave the oxidized product **37** as a pair of diastereomers. The desired vinyl triflate **38** was then formed by deprotonation of **37** with KHMDS and subsequent treatment with $PhNTf_2$. Unfortunately, the projected coupling reaction on **38** proved to be very challenging. We attribute the unsuccess to two reasons: 1) the vinyl triflate is extremely electron-rich, and thus is hard to undergo oxidative addition with transition metals; 2) the reaction center is next to a quaternary center, hence is sterically challenging.



Scheme 3.7. The synthesis of ester **41** by carbonylative coupling reaction, and its selective transesterification. (a) Tributylamine (2.0 equiv), $Pd(dppf)Cl_2$ (10 mol%), DMF/MeOH 1/2, CO (150 psi), 90 ºC, 16 h, 73%. (b) Triazabicyclodecene (1.6 equiv), allyl alcohol/toluene 1/10, 80 ºC, 16 h, 77%.

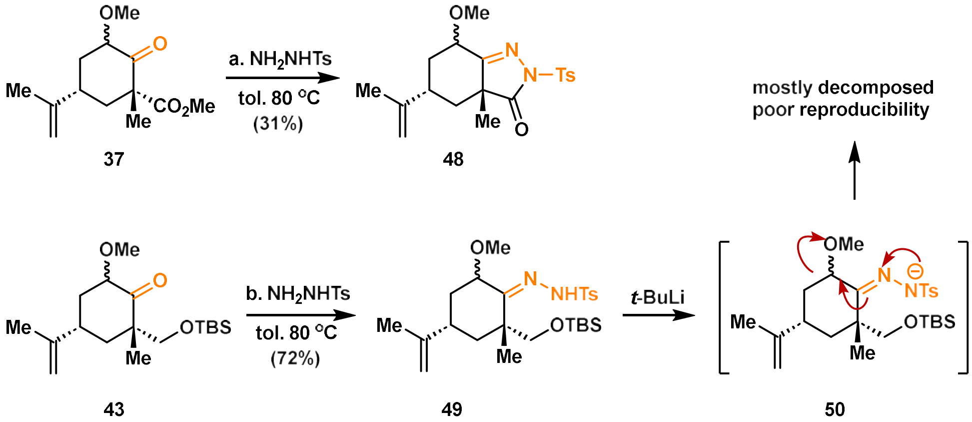
After a thorough literature review, the only example we found of a C-C bond coupling reaction on a 2-methoxy vinyl triflate moiety was a carbonylation condition reported by the Overman group[13]. We replicated their condition under high pressure of CO, and the reaction did proceed to give bis-ester **40**. We then attempted to differentiate the two ester groups in the molecule. Ideally, we would like to selectively convert the unsaturated ester to an allyl ester through a transesterification reaction, and further obtain **39** (R = allyl) by a decarboxylative allylation reaction. However, upon treating with excess allyl alcohol and catalytic TBD (triazabicyclodecene)[14], we only observed the transesterification to happen on the more sterically hindered saturated ester, possibly due to the lowered reactivity of the other ester group through conjugation.



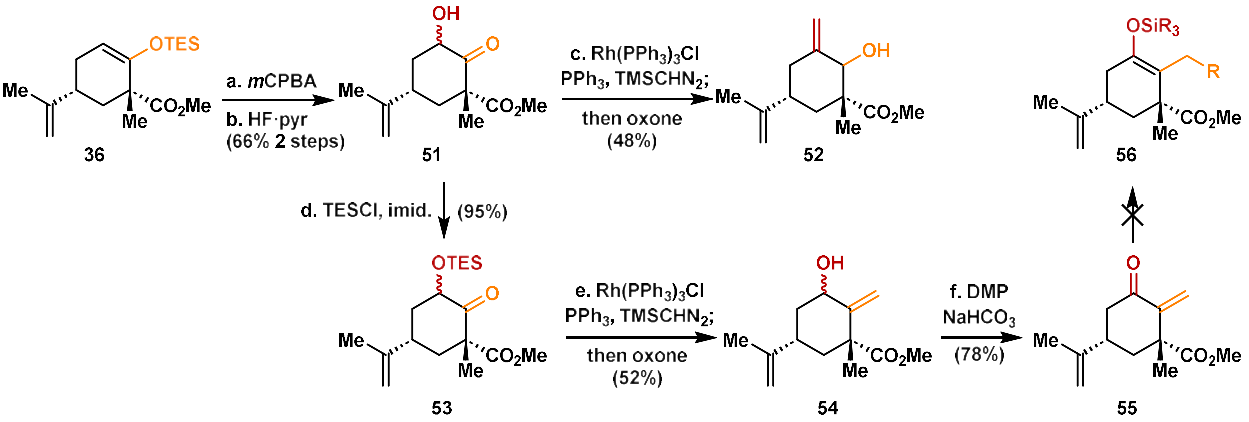
Scheme 3.8. Synthesis of aldehyde **46**, and its reaction with alkynyl lithium reagents. (a) KHMDS (1.2 equiv), THF, 0 °C, 30 min; then TESCl (1.5 equiv), 30 min; then $LiAlH_4$ (2.0 equiv), 30 min, 72%. (b) Imidazole (10.0 equiv), DMAP (1.2 equiv), TBSCl (3.0 equiv), DMF, 0 to 23 °C, 16 h, 92%. (c) KHMDS (2.4 equiv), THF, -78 °C, 30 min; then *N*-Phenyl-bis(trifluoromethanesulfonimide) (1.5 equiv), 30 min, 100%. (d) Tributylamine (2.0 equiv), Pd(dppf)Cl_2 (10 mol%), DMF/MeOH 1/2, CO (150 psi), 90 °C, 16 h, 92%. (e) HF·pyridine complex (10 V%), THF, 23 °C, 16 h. (f) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 2 h, 52% over 2 steps, unoptimized. (g) Alkyne (1.8 equiv), *n*-BuLi (1.2 equiv), THF, 0 °C, 30 min; then **46**, 30 min, 61%, unoptimized.

To avoid the problem of differentiating the two ester groups, we selectively reduced the ester group in **37**. **37** was first treated with KHMDS and TESCl to give a silyl enol ether, then $LiAlH_4$ was added to reduce the ester group and transform the silyl enol ether back into an enolate. It is uncertain whether the silyl group was removed through reduction by aluminum hydride species or hydrolysis mediated by hydroxide impurities contained in the reagents. Similar conditions involving deprotonation only, but no TES protection resulted in poor selectivity in reduction. The resultant primary alcohol **42** was protected by the formation of silyl ether **43**. Then, a similar sequence as described before was used for the formation of unsaturated ester **45**. The silyl group was then removed by hydrogen fluoride-pyridine complex, and the oxidation of the resultant primary alcohol was oxidized by Dess-Martin periodinane to give aldehyde **46**. Surprisingly, treating aldehyde **46** with alkynyl lithium reagent only resulted in the alkylation from the β-position of the unsaturated ester with the aldehyde untouched.

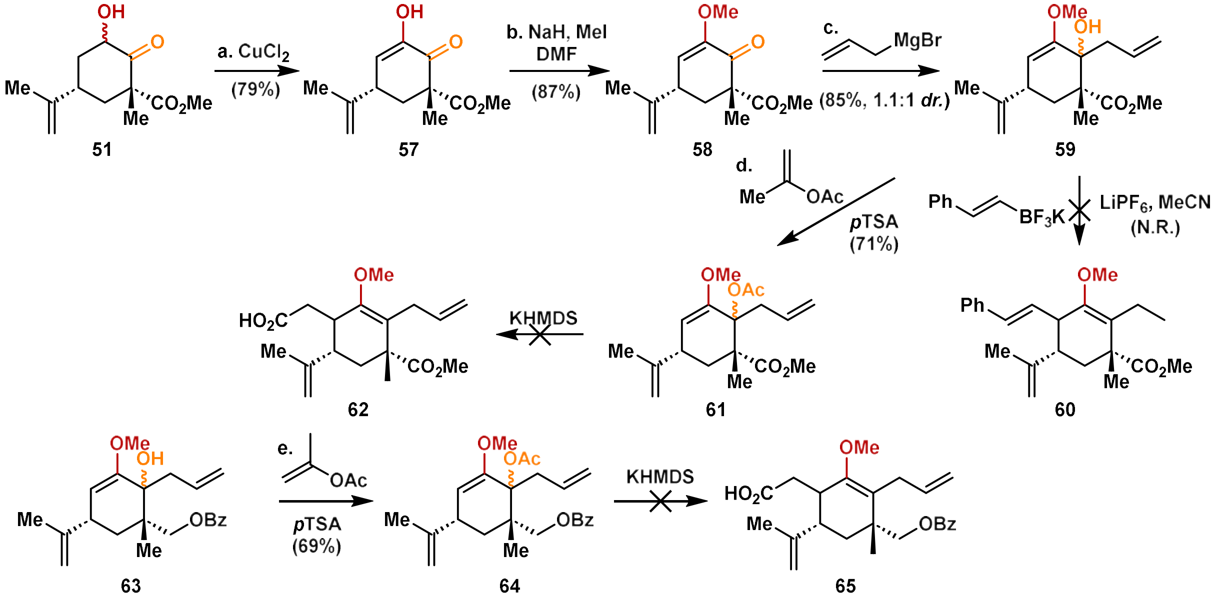
We also envisioned using a Shapiro reaction[15] to form a carbon-carbon bond and access the structure of **39**. Directly treating ketone **37** with tosylhydrazine resulted in the formation of pyrazolone **48**. Using **43** which has the ester group reduced and protected, we successfully accessed hydrazone **49**. However, the treatment of **49** with base only resulted in a complex mixture of products, possibly due to the elimination of the methoxy group.



Scheme 3.9. Synthesis of hydrazone **49** and its failure in Shapiro reactions. (a) and (b): *p*-toluenesulfonyl hydrazide (1.1 equiv), toluene, 80 °C, 16 h.



Scheme 3.10. The synthesis of enone **55**, and its failure in 1,4-addition reactions. (a) *m*CPBA (1.1 equiv), Et_2O/sat. aq. $NaHCO_3$ 1/1, 23 °C, 30 min. (b) HF·pyridine complex (10 V%), THF, 23 °C, 16 h, 66% 2 steps. (c) $Rh(PPh_3)_3Cl$ (5 mol%), PPh_3 (3.0 equiv), $TMSCHN_2$ (10 equiv), 1,4-dioxane/*i*-PrOH 10/1, 60 °C, 1 h; then H_2O (50 V%), oxone (3.0 equiv), 1 h, 48%. (d) Imidazole (5.0 equiv), TESCl (1.2 equiv), CH_2Cl_2, 23 °C, 30 min, 95%. (e) Same condition as (c), 52%. (f) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 2 h, 78%.



Scheme 3.11. Synthesis of tertiary alcohol **59**, and failures to convert it further. (a) $CuCl_2$ (2.2 equiv), THF, reflux, 2 h, 79%. (b) NaH (1.5 equiv), DMF, 0 °C, 30 min; then MeI (2.0 equiv), 1 h, 87%. (c) Allylmagnesium bromide (1.2 equiv), THF, -20 °C, 30 min, 85%, 1.1:1 *dr.* (d) *p*-Toluenesulfonic acid (10 mol%), isopropenyl acetate, 100 °C, 16 h, 71%. (e) Same as (d), 69%.

We also proposed to synthesize enone **55** and use a 1,4-addition reaction to access enol ether **56**. We started with a Rubottom oxidation[16] of **36**, accessing α-hydroxy ketone **51** as a pair of diastereomers. While multiple Wittig conditions we screened on **51** failed to give the desired product, due to a combination of the poor reactivity of the ketone and the low stability of **51** under basic conditions, we found that a rhodium-catalyzed condition reported by the Paquet group[17] was successful in this case. Unlike the conventional conditions that generate methylenetriphenylphosphorane ylide under strong basic conditions, this condition uses a mild rhodium-catalyzed condition to generate the same intermediate, and the reaction can be heated to enhance the reactivity. However, upon a careful characterization of the methylenation product obtained from **51**, we found that the methylenation happened with wrong regioselectivity, giving **52** as the only product. We propose that α-hydroxy ketone **51** can automatically tautomerize under the reaction condition, and the methylenation reaction rate of the isomerized ketone is significantly faster than **51** due to the lack of steric hindrance. To solve this problem, we protected **51** with TES group and treated product **53** with a similar Wittig condition. A workup by Oxone removed the extra PPh_3 in the reaction mixture and removed the TBS group to give **54**. Benzoyl (Bz) protecting group resulted in a mixture of regioisomers through protection group shift. Upon oxidation, enone **55** was obtained. However, no 1,4-addition condition was found to give the desired structure **56**.

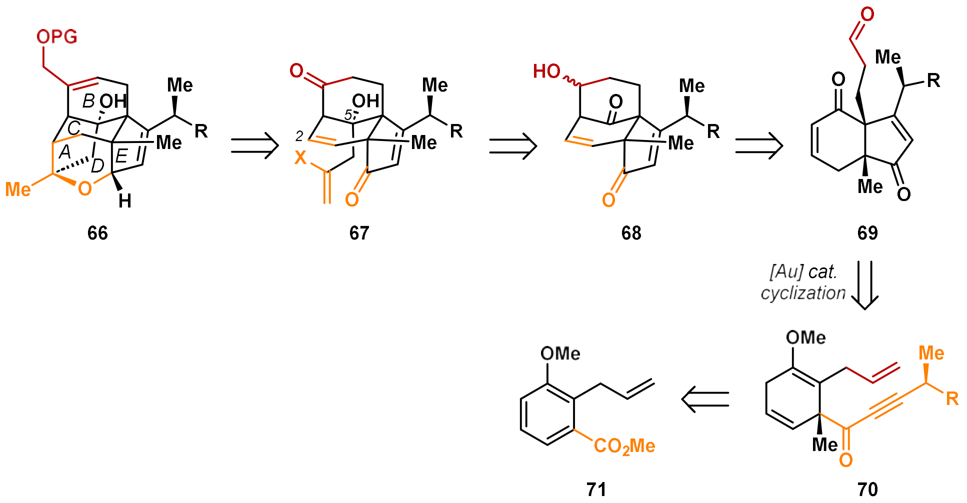
α-Hydroxy ketone **51** could be oxidized by $CuCl_2$[18] to give **57**, in a form of an α-hydroxy enone, and could be protected by forming enol ether **58**. The addition of allylmagnesium bromide gave tertiary alcohol **59** as a pair of diastereomers. To access the desired functionalities for our future synthesis, a formal S_N2' substitution reaction through oxylallyl cation reported by the May group[19] was tested but failed to yield product **60**. In addition, we transformed **59** into acetate **61**. Due to the high steric hindrance at the hydroxyl group in **59**, regular acetate formation conditions all failed to give any product. The only successful condition was found to be refluxing the substrate in isopropenyl acetate with a catalytic amount of *p*TSA[20]. It was proposed that acetate **61** could undergo an Ireland-Claisen rearrangement reaction[21] to give carboxylic acid **62**, although, in practice, we only observed by-products related to the nucleophilic attack of the acetate into the ester group. We then attempted a similar reaction on benzoate **64** but also failed to observe any desired product.

3.2.5 Discussions on the Early Attempts

As described earlier, we have thoroughly explored the possibility to synthesize **39** or related structures as the substrate for the key gold-catalyzed cyclization reaction. Although we have several other proposals that can lead to such structures, at this point we determined that a different strategy is needed for multiple reasons. (1) Despite the chiral pool strategy's benefit of incorporating asymmetry from natural product **22**, it constrains us from strategically designing a concise and modular route and limits us from using many reactions. (2) A thorough literature investigation reveals that such cationic cyclizations forming a [3.2.1] bicycle is not easy[22], partly due to the orbital geometry, which is described as a disfavored 5-*endo* cyclization according to the Baldwin's rules[23]. (3) Computational studies reveal that in the stable conformation of **32**, the *C* ring may adopt a boat conformation, to leave the bulky isopropenyl group on the equatorial position, which makes the proposed cationic cyclization reaction more challenging.

3.3 A Strategic Second-Generation Retrosynthetic Analysis

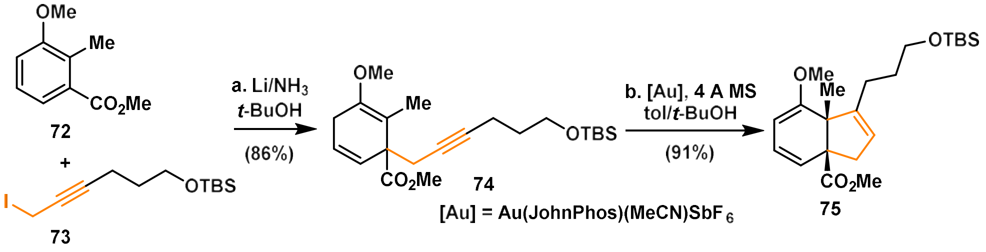
Nevertheless, we still believe in several key designs of our retrosynthetic analysis. We wanted to keep the order of ring formations. Since the [3.2.1] bicycle is the most strained bicyclic system in the molecule, we once again disconnected the *A* and *D* rings first, hoping the rigid conformation of the *BCE* ring system could help the formation of them. To avoid the possibility of a bulky substitution at C-2 forcing the *C* ring into a boat conformation, we took a different approach by tracing **66** back to **67**, which bears a synthetic handle on C-5. And we envisioned installing this synthetic handle onto **68** by a facially selective 1,2-addition reaction. As discussed in 3.2.4., we think it is strategic to form the *CE* ring system before the formation of the *B* ring. Finally, without the limit from a set starting material, we quickly identified that **70** could come from aromatic compound **71** by Birch reduction[24].



Scheme 3.12. A revised retrosynthetic analysis.

3.4 A Concise Synthesis of the *BCE* Ring System

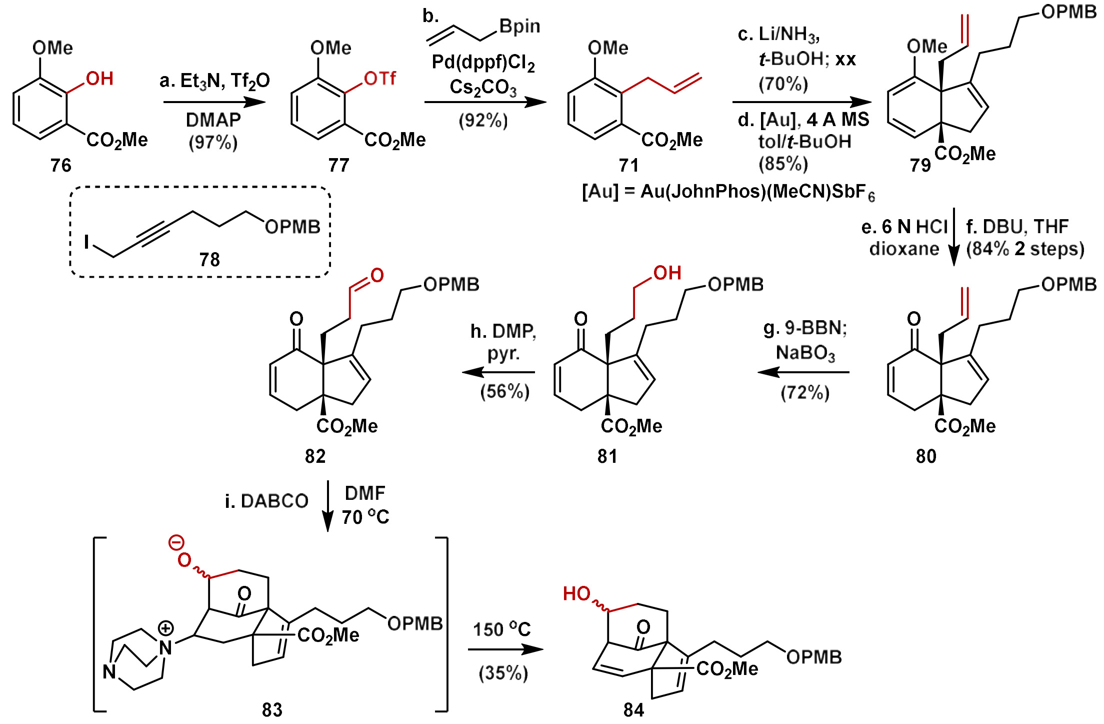
3.4.1 A Model Study of the formation of the *BCE* Ring System



Scheme 3.13. A model study of the gold-catalyzed cyclization reaction for forming the *CE* ring system. (a) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH_3 1/5, -78 ºC, 30 min; then 2,3-dimethyl-1,3-butadiene; then **73**, 30 min, 86%. (b) 4 Å molecular sieves, Au(JohnPhos)(MeCN)(SbF_6) (10 mol%), toluene/*t*-BuOH 10/1, 23 ºC, 20 min, 91%.

To quickly test the envisioned gold-catalyzed cyclization reaction, we treated commercially available compound **72** with lithium in ammonia, followed by propargyl iodide **73**, to give alkyne **74**. After some screens, we found the best condition for the gold-catalyzed cyclization to be conducted in a mixed solvent of toluene and *tert*-butyl alcohol, with the presence of 4 A molecular sieves, which prevents the formation of acids from the gold catalyst's hydrolysis. Unexpectedly, product **75** contains an enol ether moiety that did not undergo solvolysis. This result has led us to a design of a tandem gold-catalyzed cyclization reaction, which will be discussed in detail in chapChapter

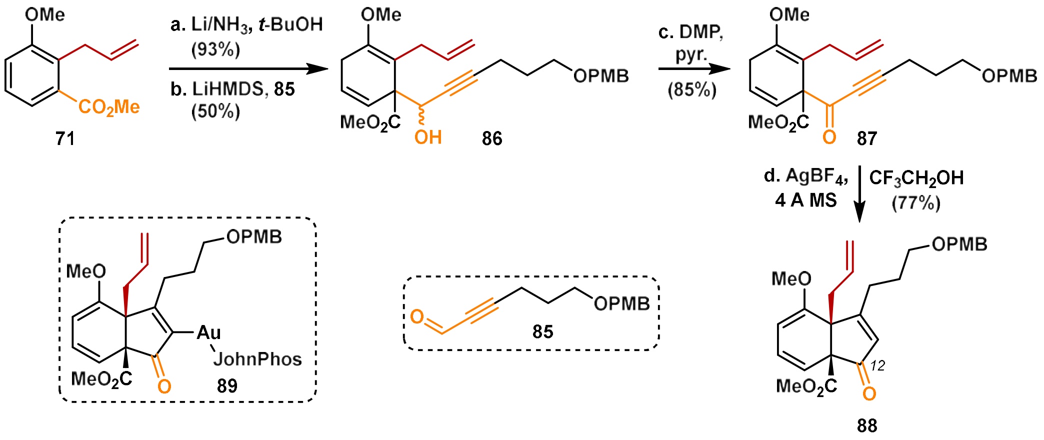
Phenol **76** was transformed into triflate **77**, which was then coupled with allylboronic acid pinacol ester to give alkene **71**. A similar sequence was followed to afford enol ether **79** with an allyl sidechain. Upon hydrolysis, enone **80** was obtained. To install the proper functionality for the envisioned aldol condensation reaction, we performed a hydroboration-oxidation reaction in one pot to give **81** in good yield, with the enone unreduced. Dess-Martin oxidation then afforded aldehyde **82**. Recognizing the similarity of our projected conversion to a Baylis-Hillman Reaction[25], we treated **82** with DABCO in DMF. The substrate was fully consumed at 70 ºC within 20 minutes, however, no product spot was detected on thin-layer chromatography. It was rationalized that the Baylis-Hillman was interrupted by the formation of a bridge-cycle intermediate **83** that cannot be deprotonated from the α-position of the ketone. Thus, we further heated the reaction mixture to 150 ºC, at which temperature a Hofmann elimination was possible to give tricyclic compound **84**.



Scheme 3.14. A model study of the formation of the *BCE* Ring System. (a) Et_3N (5.0 equiv), DMAP (0.10 equiv), Tf_2O (1.0 equiv), CH_2Cl_2, -78 to 23 °C, 18 h, 97%. (b) Allylboronic acid pinacol ester (3.0 equiv), Cs_2CO_3 (2.0 equiv), $Pd(dppf)Cl_2$ (1 mol%), DMF, 80 °C, 16 h, 92%. (c) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH_3 1/5, -78 °C, 30 min; then 2,3-dimethyl-1,3-butadiene; then **78**, 30 min, 70%. (d) 4 Å molecular sieves, $Au(JohnPhos)(MeCN)SbF_6$ (10 mol%), toluene/*t*-BuOH 10/1, 23 °C, 20 min, 85%. (e) 1,4-dioxane/6 N HCl 10/1, 23 °C, 1.5 h. (f) DBU (3.0 equiv), THF, 23 °C, 16 h, 84% overall. (g) 9-BBN (5.0 equiv), THF, 23 °C, 5 h; then H_2O (50 V%), $NaBO_3{\cdot}H_2O$ (10.0 equiv), 18 h, 72%, unoptimized. (h) Dess-Martin periodinane (2.5 equiv), pyridine (5.0 equiv), CH_2Cl_2, 23 °C, 2 h, 56%, unoptimized. (i) DABCO (0.50 equiv), DMF, 70 °C, 2 h; then 150 °C, 48 h, 35%, unoptimized.

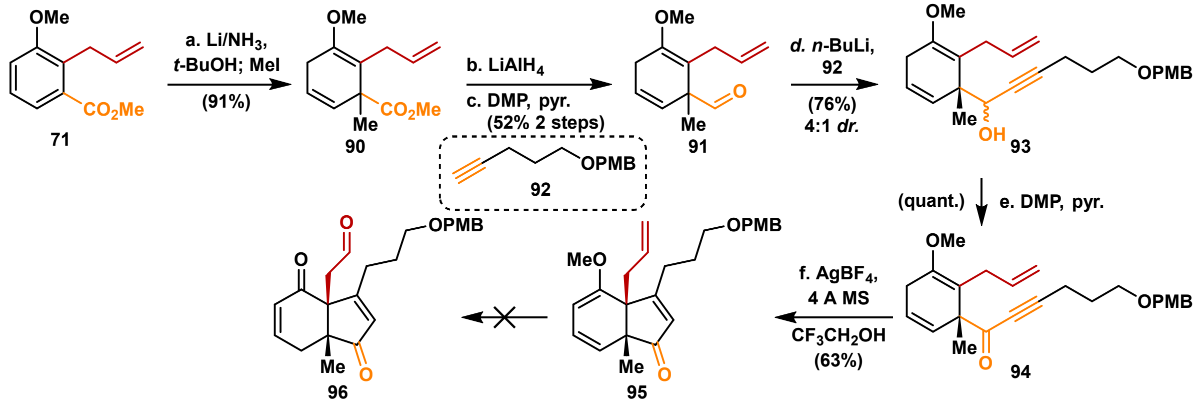
3.4.2 Challenges in Translating the Model System into The Real System

Noting that in **1** and **2**, the C-12 position is oxidized. To quickly test the gold-catalyzed cyclization reaction with the proper oxidative state, we separately conducted the Birch reduction of **71**, followed by an aldol condensation reaction with aldehyde **85**. We subjected **86** to the gold-catalyzed cyclization reaction in its unprotected or trimethylsilyl-protected form but failed to obtain any product. Inspired by our group's synthesis of chalcitrin$^{\text{ref. 10b}}$, we intended to test the cyclization reaction on the MOM ether of **86**. However, the secondary alcohol was unreactive to various MOM protection conditions due to its proximity to a quaternary center. We then attempted to oxidize alcohol **86** to ketone **87** to further test the projected cyclization reaction. With similar gold-catalyzed conditions, the only product we obtained was gold complex **89**, which was stable on column chromatography and confirmed by high-resolution mass spectroscopy. This result indicates the gold catalyst was not turned over, possibly because the α-gold enone complex is too stable to undergo a proto-demetallation step. Various ligands and solvents have been tested but no turnover was observed. We then turned our attention to metals with a similar reactivity, but have a lower affinity to carbon (namely a harder Lewis acid). With some screenings, we found that silver trifluoroborate was able to catalyze the desired transformation. A similar example was reported in our group's synthesis of arboridinine[26], where the nucleophile for the reaction was an indole moiety.



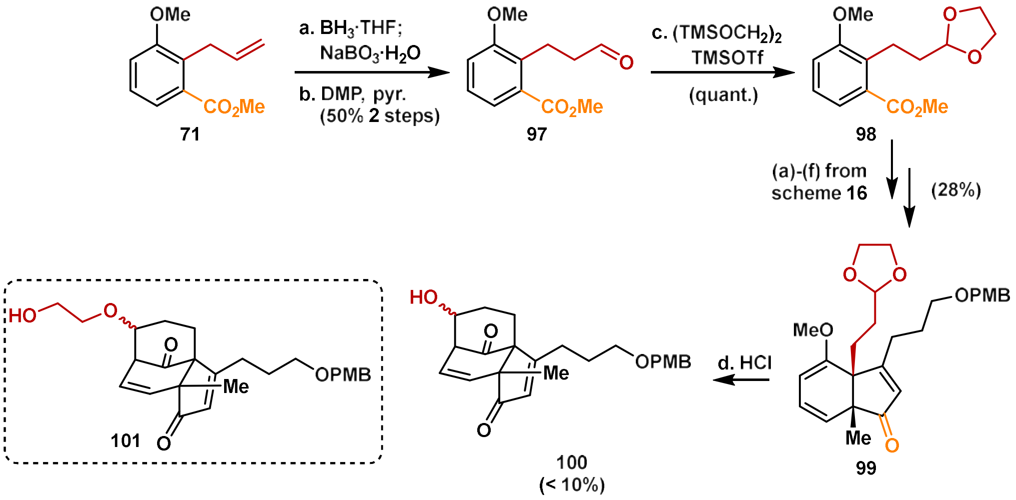
Scheme 3.15. Silver-catalyzed cyclization enabling the synthesis of the C-12-keto enol ether **88**. (a) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH_3 1/5, -78 ºC, 30 min; then 2,3-dimethyl-1,3-butadiene, 93%. (b) LiHMDS (1.1 equiv), THF, 0 ºC, 30 min; then **85** (1.2 equiv), 30 min, 50%, 3:1 *dr.*, unoptimized. (c) Dess-Martin periodinane (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2, 23 ºC, 2 h, 85%. (d) 4 Å molecular sieves, $AgBF_4$ (20 mol%), CF_3CH_2OH, 23 ºC, 30 min, 89%.

To move forward with our synthesis, we coupled the Birch reduction of **91** with a methylation reaction to give **90**. Then the ester group was transformed into ketone **94** in a 4-step sequence. Notable that the Dess-Martin oxidation steps gave inconsistent yields, which were unoptimized at this time and will be discussed later. The silver-catalyzed condition once again successfully gave bicyclic compound **95**. We first attempted similar conditions we used for the transformation from **79** to **82**, anticipating the formation of aldehyde **96** for the proposed aldol cyclization reaction. However, hydroboration of related compounds led to rapid reduction of the C-12 ketone, followed by complex reaction pathways leading to multiple products. Wacker oxidation[27], ozonolysis, or dihydroxylation conditions also could not afford any desirable products.



Scheme 3.16. The synthesis of enol ether **95** and the challenges of further conversion. (a) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH$_3$ 1/5, -78 °C, 30 min; then 2,3-dimethyl-1,3-butadiene; then MeI, 30 min, 91%. (b) LiAlH$_4$ (1.0 equiv), THF, 0 °C, 30 min. (c) Dess-Martin periodinane (1.4 equiv), pyridine (2.8 equiv), CH$_2$Cl$_2$, 23 °C, 2 h, 52% 2 steps, unoptimized. (d) **92** (1.4 equiv), *n*-BuLi (1.3 equiv), THF, 0 °C, 30 min; then **91**, 30 min, 76%, 4:1 *dr*. (e) Dess-Martin periodinane (1.5 equiv), pyridine (3.0 equiv), CH$_2$Cl$_2$, 23 °C, 2 h, 100%. (f) 4 Å molecular sieves, AgBF$_4$ (20 mol%), CF$_3$CH$_2$OH, 23 °C, 30 min, 63%.

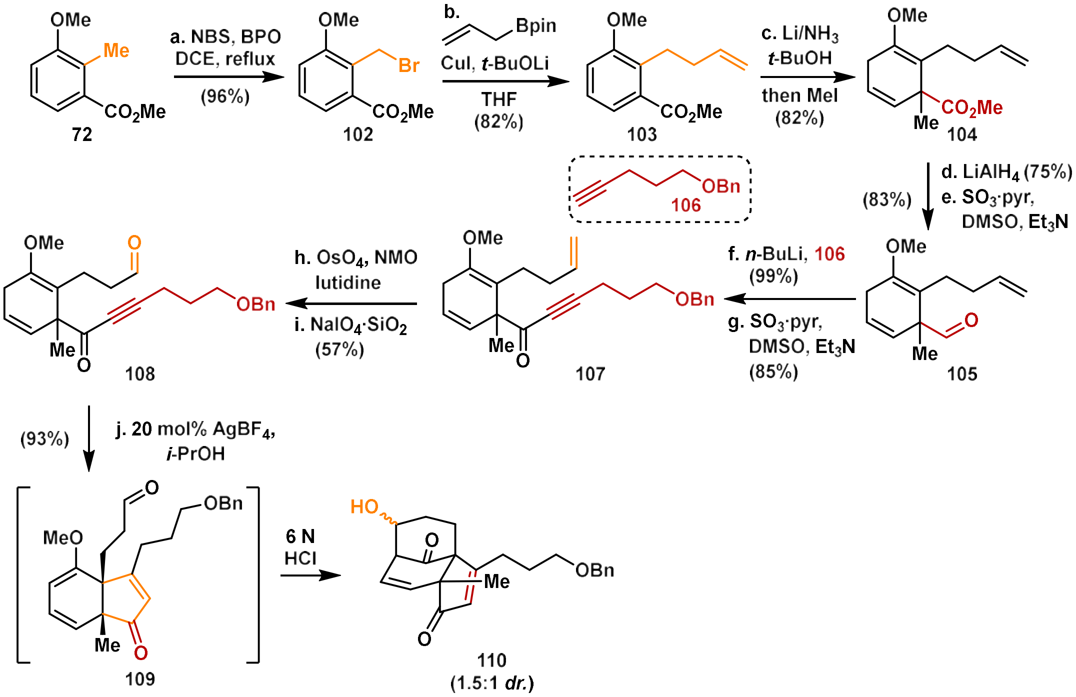
We then turned our attention to incorporating an aldehyde from an earlier stage in the form of an acetal. Hydroboration/oxidation of **71**, followed by Dess-Martin oxidation and acetal protection afforded acetal **98**. A similar sequence was followed for the synthesis of **99**. Noting that both the acetal group and the enol ether moiety can be hydrolyzed, various acidic conditions were tested but failed to give any selectivity. With stronger acidic conditions, no **96** was observed, however, 2 more polar products were isolated in low yield and were characterized as the diastereomers of tricyclic alcohol **100**. We hypothesized that the major product formed was tricyclic compound **101** resulting from the partial hydrolysis of the acetal group, which was very polar and lost during purification. It was also found that the PMB-protecting group was not completely stable under the strong acidic condition. Therefore, a benzyl-protecting group was instead used henceforth.



Scheme 3.17. The synthesis of enol ether **99** with an acetal group, and its conversion to tricyclic alcohol **100**. (a) BH_3·THF (0.5 equiv), THF, 0 ºC, 1.5 h; then H_2O (50 V%), $NaBO_3$·H_2O (2.0 equiv), 2 h. (b) Dess-Martin periodinane (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2, 23 ºC, 2 h, 50% 2 steps. (c) $(TMSOCH_2)_2$ (1.5 equiv), TMSOTf (0.20 equiv), CH_2Cl_2, -78 ºC, 1 h, 100%. (d) 6 N HCl (10 V%), various solvents.

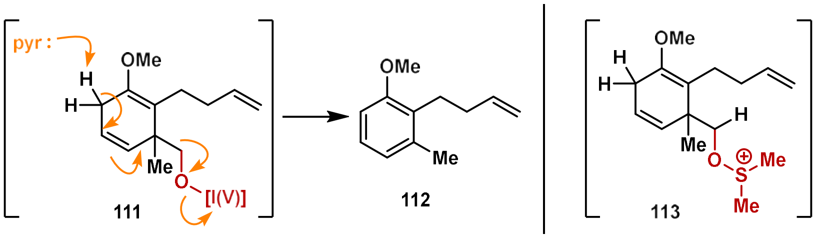
3.4.3 The Enabling Synthesis of Tricyclic Compound 110

The optimized route successfully leading to tricyclic compound **110** was described in Scheme 18. Commercially available benzyl bromide **102** was synthesized in lab on decagram scale by an improved procedure. A benzyl-allyl coupling reaction using a slightly different condition from the Xu group[28] lead to alkene **103**. Birch reduction and methylation smoothly afforded ester **104**. After reducing the ester group, a Parikh–Doering oxidation[29] was found to be the optimal condition for the synthesis of aldehyde **105**. Dess-Martin oxidation led to the formation of arene **112**, possibly via a remote deprotonation of intermediate **111**. Swern oxidation gave the product in inconsistent yields, possibly due to the instability of intermediate **113** upon standing in the reaction mixture (noting that in Swern oxidation, intermediate **113** was pre-formed before the addition of triethylamine). Despite that Parikh–Doering oxidation proceeds through the same intermediate **113**, the triethylamine in the presence of the reaction mixture immediately converted the **113** to aldehyde **105**. Alkynylation followed by another Parikh–Doering oxidation afforded ketone **107** in good yield. Lemieux–Johnson oxidation[30] then afforded aldehyde **108**. Aldehyde **108** was then cyclized smoothly under the silver-catalyzed condition into **109**, at which stage of the reaction a small amount of tricyclic product **110** was observed, possibly due to the trace acid formed from the hydrolysis or solvolysis of $AgBF_4$. To push the reaction to completion, we worked up the reaction with 6 N HCl and isolated **110** in excellent yield as a pair of diastereomers. Overall, this route was proven to be reliable on multi-gram scales and only required 7 columns. A reliable supply of **110** was ensured for the next stage of the synthesis.



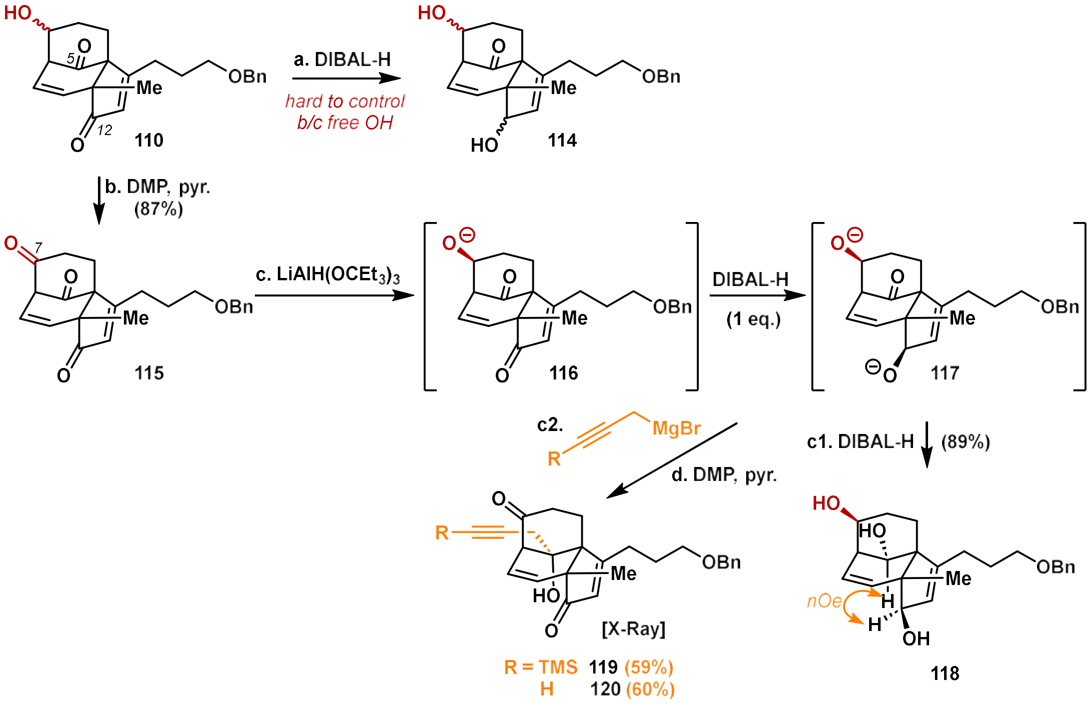
Scheme 3.18. The enabling synthesis of tricyclic alcohol **110**. (a) NBS (1.1 equiv), BPO (0.05 equiv), DCE, 80 ºC, 5 h, 96%. (b) *t*-BuOLi (2.0 equiv), allylboronic acid pinacol ester (2.0 equiv), CuI (0.10 equiv), THF, 23 ºC, 12 h, columned, 82%. (c) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH_3 1/5, -78 ºC, 30 min; then 2,3-dimethyl-1,3-butadiene; then MeI, 30 min, 82%. (d) $LiAlH_4$ (1.0 equiv), THF, 0 ºC, 30 min, columned, 75%. (e) Et_3N (5.0 equiv), sulfur trioxide pyridine complex (4.0 equiv), DMSO/DCM 1/4, 0 to 23ºC, 4 h, columned, 83%. (f) **106** (1.4 equiv), *n*-BuLi (1.2 equiv), THF, 0 ºC, 30 min; then **105**, 30 min, 99%, 4:1 *dr*. (g) Et_3N (5.0 equiv), sulfur trioxide pyridine

complex (4.0 equiv), DMSO/DCM 1/4, 0 to 23°C, 18 h, columned, 85%. (h) 2,6-lutidine (3.0 equiv), NMO (1.3 equiv), OsO_4 (2 mol%), dioxane/H_2O 10/1, 23°C, 16h. (i) $NaIO_4$ on silica (3.0 equiv), CH_2Cl_2, 23 °C, 30 min, columned, 57% over 2 steps. (j) $AgBF_4$ (0.20 equiv), *i*-PrOH, 23 °C, 2 h; then 6 N HCl (20 V%), 18 h, columned, 93%, (*7R*):(*7S*)=1.5:1.



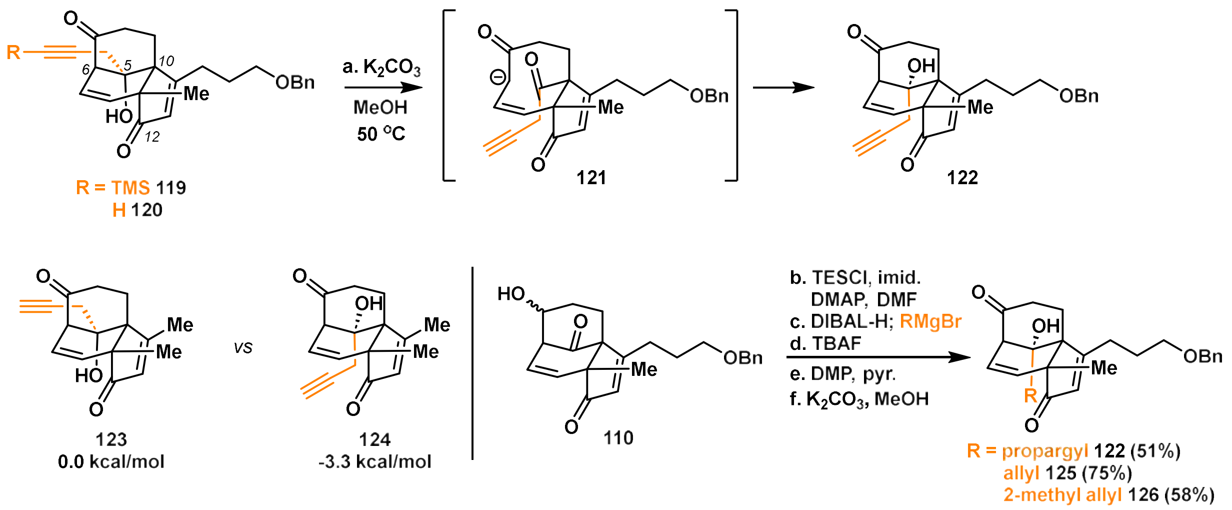
Scheme 3.19. The proposed side reaction pathway of the Dess-Martin oxidation giving **112**, and the structure of intermediate **113**.

3.5 The Facial-selective Functionalization of the C-5 Carbonyl



Scheme 3.20. Selective functionalization of the C-5 ketone. (a) DIBAL-H (2.0 equiv), THF, 0 ºC, 30 min, inconsistent yields. (b) Dess-Martin periodinane (1.5 equiv), pyridine (3.0 equiv), CH_2Cl_2, 23 ºC, 2 h, 87%. (c1) $LiAlH(OCEt_3)_3$ (2.1 equiv), THF, 0 ºC, 30 min; then DIBAL-H (3.7 equiv), 30 min, 89%, unoptimized. (c2) $LiAlH(OCEt_3)_3$ (1.2 equiv), THF, 0 ºC, 30 min; then DIBAL-H (1.2 equiv), 30 min; then 3-trimethylsilyl-propargylmagnesium bromide (3.0 equiv), 30 min. (d) Dess-Martin periodinane (5.0 equiv), pyridine (10 equiv), CH_2Cl_2, 23 ºC, 2 h, **119**: 59% over 2 steps; **120**: 60% over 2 steps, unoptimized.

The selective functionalization of the C-5 carbonyl was then studied. The chemoselectivity between the C-5 and C-12 ketones was achieved by treating **110** with 2 equivalents of DIBAL-H, giving **114** as the major product. However, this condition gave inconsistent yields on scale, possibly due to the competition between deprotonation and C-5 reduction. Adding NaH before the addition of DIBAL-H did not improve the yield. Grignard reagent selectively reacts with the C-12 ketone first. $NaBH_4$ reduces both ketones. Other reducing reagents such as $LiAlH_4$, Red-Al, and 9-BBN were not chemoselective, while L-selectride and $LiAlH(OCEt_3)_3$ were not reactive to **110**.



Scheme 3.21. The epimerization of the C-5 tertiary alcohol and a reliable procedure for the synthesis of diketones **122**, **125**, and **126**. (a) K_2CO_3 (3.0 equiv), MeOH, 50 °C, 2 h, 57% from **119**, 48 % from **120**, unoptimized. (b) Imidazole (4.0 equiv), DMAP (1.0 equiv), TESCl (3.0 equiv), DMF, 0-23 °C, 16 h, 98%. (c) DIBAL-H (1.05 equiv), THF, 0 °C, 30 min; RMgBr (3.0 equiv), 30 min. (d) TBAF (3.0 equiv), THF, 23 °C, 16 h. (e) Dess-Martin periodinane (3.0 equiv), pyridine (4.0 equiv), CH_2Cl_2, 23 °C, 2 h. (f) K_2CO_3 (3.0 equiv), MeOH, 50 °C, 30 min, **122**: 51%, **125**: 75%, **126**: 58%. The energy difference between **123** and **124** was calculated using DFT B3LYP/6-31g(d',p').

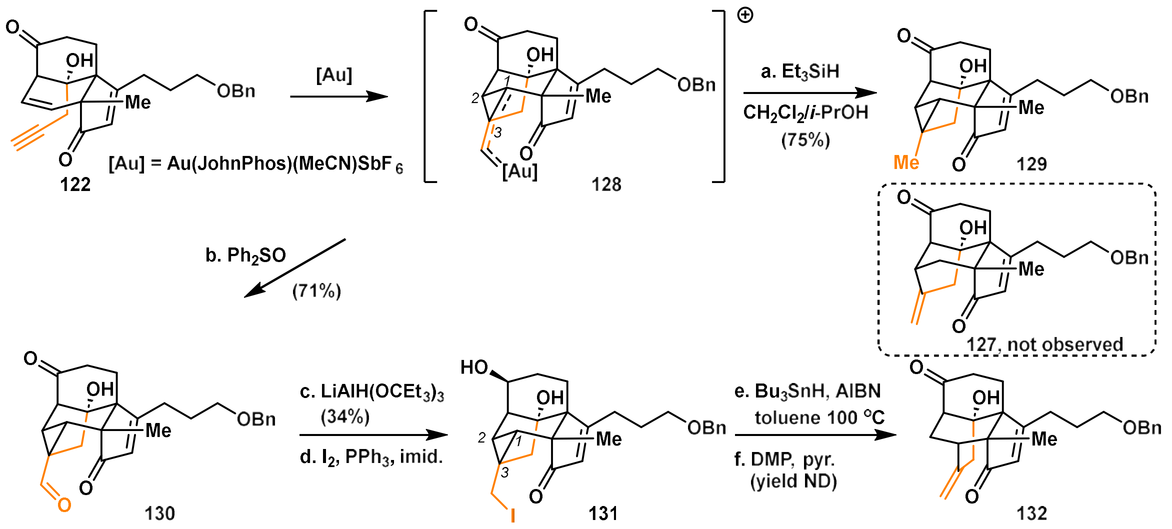
One reliable method for the selective reduction was achieved by (1) the oxidation of **110** to triketone **115**; (2) the selective reduction of the C-7 ketone by $LiAlH(OCEt_3)_3$, forming intermediate **116**; (3) the addition of 1 equivalent of DIBAL-H in one-pot to reduce the C-5 ketone, forming bis-anionic intermediate **117**. At this stage, if excess DIBAL-H was added, the reduction of C-12 ketone resulted in triol **118**, which shows a strong nOe correlation between the C-5 and the C-12 protons, indicating that the C-5 ketone reduction occurred from the *Si* face. To intermediate **117**, if propargyl Grignard reagents were added, followed by a separate Dess-Martin oxidation reaction, diketones **119** and **120** were isolated respectively as major products. The structures were confirmed by single crystal XRD, showing that the alkylation happened from the *Re* face. The discrepancy in the facial selectivity was not fully understood.

When studying the deprotection of **119** with K_2CO_3 in MeOH, we surprisingly found the initially formed alkyne **120** was further converted into a different product **122**. With full NMR characterizations, we determined that **122** is the C-5 epimer of **120**, bearing the desired stereochemistry. We hypothesized that the epimerization went through a retro-aldol/aldol reactions sequence, possibly by the cleavage of the C-5/C-6 bond. However, both the C-7 and the C-12 ketones must be present for the transformation to be successful. Of note, it is also possible that the epimerization occurred through the C-5/C-10 bond cleavage, which correlates to the proposed biosynthetic pathway of the natural products. Computational studies revealed that **124** was 3.3 kcal/mol more stable than **123**, which indicates that the equilibrium is thermodynamically controlled. Based on these results, a 5-step procedure was developed to convert **110** into **122**, **125**, or **126**, requiring only 2 columns after steps a and e, in consistent descent yields. This procedure proves to be more reliable on scale.

3.6 The Construction of the *AD* Ring System

3.6.1 Attempts Based on Gold-Catalyzed Enyne Cyclizations

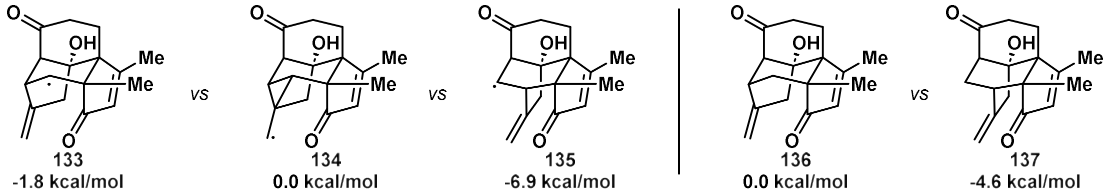
It was soon identified that enyne **122** could be a good substrate for a gold-catalyzed enyne cyclization reaction to form the A ring. We anticipated that after the initial coordination of the gold complex to the alkyne, the C-2/C-3 bond would preferentially form first, which can be rationalized by the Baldwin's rules. Given the cationic nature of the cyclization process, we proposed that the resultant C-1 carboncation could be reduced by triethylsilane to form alkene **127** with the [3.2.1] bridge cycle skeleton. However, we only observed the formation of cyclopropane **129** in good yield. This result could be explained by the formation of a delocalized gold-carbene intermediate **128**[31], which was formed by C-1/C-3 bond formation before the reduction happened on the gold-carbene. A broad screening of reducing agents and solvents was unfruitful to find a condition leading to alkene **127**. Realizing that the formation of the cyclopropane was inevitable, we attempted several acidic conditions trying to open the cyclopropane ring but failed.



Scheme 3.22. Attempts to construct the *AD* ring system based on gold-catalyzed enyne cyclizations. (a) Et$_3$SiH (5.0 equiv), Au(JohnPhos)(MeCN)SbF$_6$ (0.50 equiv), CH$_2$Cl$_2$/i-PrOH 10/1, 23 °C, 18 h, 75%, unoptimized. (b) Ph$_2$SO (3.0 equiv), Au(JohnPhos)(MeCN)SbF$_6$ (10 mol%), CH$_2$Cl$_2$, 23 °C, 18 h, 71%. (c) LiAlH(OCEt$_3$)$_3$ (4.0 equiv), THF, 0 °C, 30 min, 34%, unoptimized. (d) Imidazole (1.5 equiv), PPh$_3$ (1.2 equiv), I$_2$ (1.3 equiv), CH$_2$Cl$_2$, 0 °C, 30 min. (e) Bu$_3$SnH (2.8 equiv), AIBN (0.5 equiv), toluene, 100 °C, 3.5 h. (f) Dess-Martin periodinane (3.0 equiv), pyridine (5.0 equiv), CH$_2$Cl$_2$, 23 °C, 2 h, unoptimized, yield not determined.

Instead of being reduced by triethylsilane, intermediate **128** was able to be oxidized by diphenyl sulfoxide instead[32], to form aldehyde **130**. We realized that the aldehyde group could serve as a great handle for opening the cyclopropane ring through a radical pathway. Direct treatment of aldehyde **130** with SmI$_2$[33] yielded a complex mixture of products. Thus, aldehyde **130** was converted to iodide **131** by a sequence of a reduction by LiAlH(OCEt$_3$)$_3$ and an Appel reaction[34]. No condition was found to selectively reduce the aldehyde group without touching the C-7 ketone.

Treating iodide **131** with a reductive radical condition resulted in the opening of the cyclopropane ring. To simplify the product mixture, a Dess-Martin oxidation reaction was conducted in sequence to yield **132** as the only product. After careful NMR examinations, we determined the structure of the product to be **132** with a [2.2.2] bicycle, instead of the desired structure **127**.

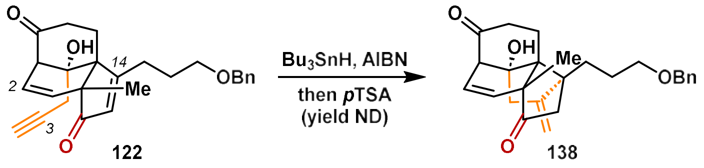


Scheme 3.23. Calculations of energy differences among radical intermediates **133-135**, and between diketone **136** and **137**. All results were calculated using DFT B3LYP/6-31g(d',p').

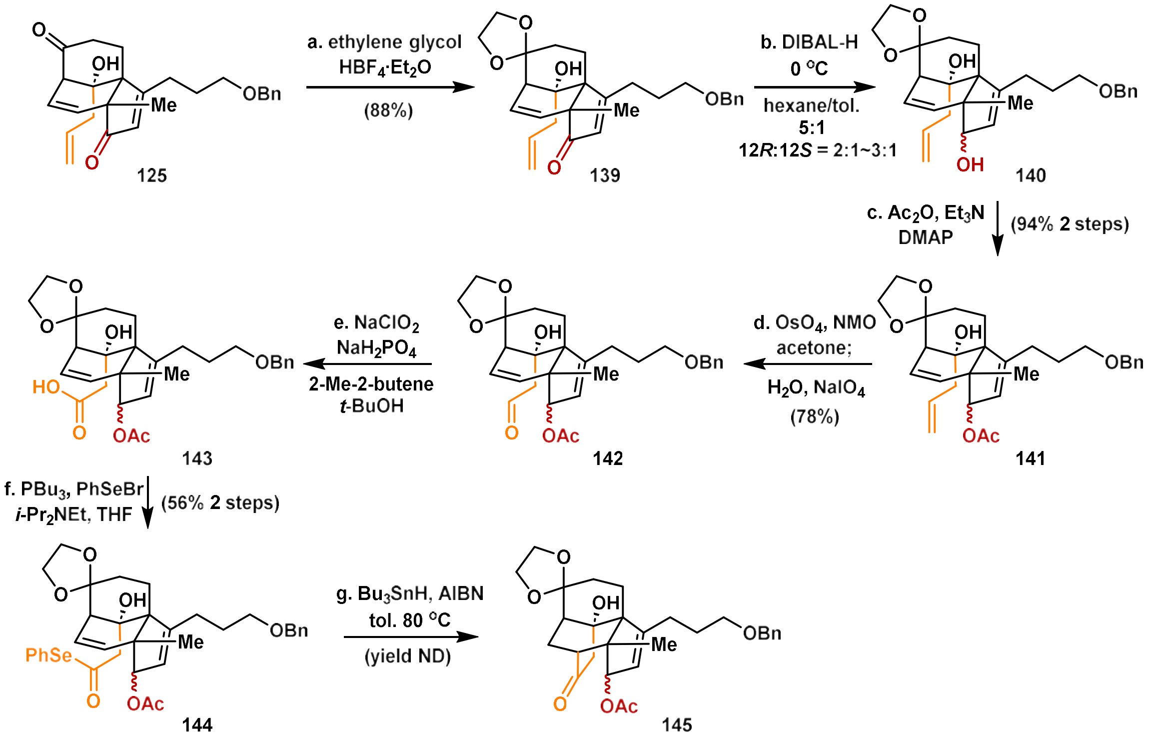
To further understand the selectivity in forming **132**, some computational studies were conducted. We found that radical **133** with the [3.2.1] bicycle to be 1.8 kcal/mol more stable than cyclopropylmethyl radical **134**, but 5.1 kcal/mol less stable than radical **135** with the [2.2.2] bicycle. This is presumably due to the ring strain from the [3.2.1] bicyclic system. Assuming the equilibrium among the three radicals is fast, this could explain the exclusive formation of alkene **132**. We also compare the energy between alkene **136** and **137**, showing that the [2.2.2] bicycle **137** is 4.6 kcal/mol more stable than the desired [3.2.1] bicycle **136**, adding some concerns to our synthesis.

3.6.2 Attempts Based on Radical Cyclizations

Radical-based cyclizations have also been thoroughly explored. We started by directly treating enyne **122** with Bu_3SnH and AIBN[35], which condition generates $Bu_3Sn\cdot$ radical that adds into the alkyne to generate a C-3 vinyl radical. Upon hydrolysis of the stannyl group, the only product isolated was **138**, formed through the addition of the C-3 radical into the cyclopentenone moiety.

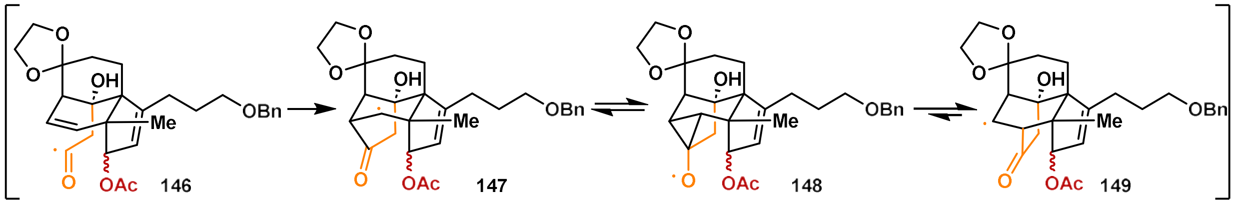


Scheme 3.24. Radical cyclization of alkyne **122**. Bu_3SnH (3.0 equiv), AIBN (0.5 equiv), toluene, 100 ºC, 2 h; then *p*TSA (5.0 equiv), CH_2Cl_2, 23 ºC, 2 h, yield not determined.



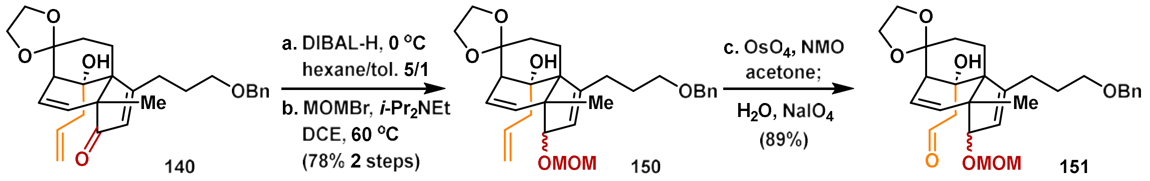
Scheme 3.25. The synthesis of selenoester **144** and its radical cyclization. (a) $HBF_4{\cdot}Et_2O$ (0.5 equiv), ethylene glycol/CH_2Cl_2 1/1, 23 ºC, 16 h, 88%. (b) DIBAL-H (3.0 equiv), hexane/toluene 5/1, 0 ºC, 30 min, typically 2:1~3:1 *dr.* (c) Et_3N (4.0 equiv), DMAP (1.0 equiv), Ac_2O (3.0 equiv), CH_2Cl_2, 23 ºC, 1 h, 94% over 2 steps. (d) OsO_4 (5 mol%), NMO (1.5 equiv), acetone, 23 ºC, 16 h; then H_2O (100 V%), $NaIO_4$ (5.0 equiv), 30 min, 78%. (e) $NaClO_2$ (10.0 equiv), NaH_2PO_4 (6.0 equiv), H_2O, 2-methyl-2-butene/*t*-BuOH 1/5, 23 ºC, 16 h. (f) *i*-Pr_2Net (3.9 equiv), Bu_3P (2.7 equiv), PhSeBr (2.7 equiv), THF, 23 ºC, 16 h, 56% over 2 steps, unoptimized. (g) Bu_3SnH (5.0 equiv), AIBN (0.5 equiv), toluene, 80 ºC, 2 h, yield not determined, unoptimized.

It was not surprising to us that a vinyl radical would preferentially attack the most electron-deficient alkene in the molecule. However, noticing that the attack of the C-2 position is sterically more favored than the C-14 position, we anticipated that reducing the enone would reverse the selectivity. Another problem with this design is, according to the results described in scheme 23, the addition of the C-3 vinyl radical into the C-2/C-1 double bond will result in a radical similar to **134**, which will very likely to rearrange into an undesired [2.2.2] bicyclic product. Therefore, we continued our explorations with alkene **125**. The C-7 ketone was selectively protected by the treatment of ethylene glycol and catalytic protic acid (HBF_4). The 1,2-reduction of the enone moiety in **139** turned out to be very challenging, with the substrate being inert to multiple conditions involving $LiAlH_4$ or $NaBH_4$. DIBAL-H was found to react with **139**, however, with THF, CH_2Cl_2, or toluene as solvent, a significant amount of 1,4-reduction product was observed. Eventually, it was found that hexanes were a superior solvent for the conversion, although 20% toluene was needed to help dissolve the substrate. Acetyl protection of the crude product from the reduction reaction produced esters **141** as a pair of diastereomers in excellent yield. A Lemieux–Johnson oxidation was then applied to afford aldehydes **142**. We initially anticipated to generate the C-3 radical required for the cyclization from a phenyl selenoester[36]. Pinnick oxidation[37] of **142** followed by careful acidification afforded carboxylic acid **143**. A substitution reaction optimized from a procedure reported by Crich[38] then yielded selenoester **144**. Treating **144** with Bu_3SnH and AIBN, we delightedly saw the C-3 radical selectively added into the C-2/C-1 double bond. However, after careful examination of NMRs, we determined that the product is **145**, again, bearing an undesired [2.2.2] bicycle.

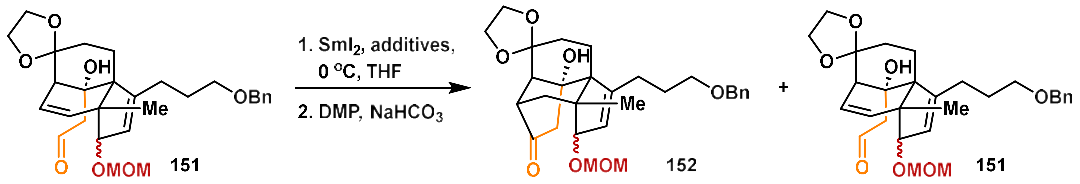


Scheme 3.26. The proposed mechanism of the formation of ketone **145**.

Based on our previous discussions, there are two possible pathways for the formation of **145**: (1) the C-3 radical directly attacks C-1, forming radical **149**, which was reduced by Bu_3SnH to give **145**; or (2) the C-3 radical initially attacks C-2, forming radical **147**, which then rearranges through cyclopropoxy radical **148** to radical **149**. According to the Baldwin's rule, we hypothesized that the second pathway was more likely. Several pieces of literature have also been found to thoroughly discuss the process in similar systems, all of which support the second pathway[39]. Therefore, we anticipated the rearrangement pathway could be completely avoided by using a saturated C-3 radical, which can be generated by treating aldehyde **142** with SmI_2.



Scheme 3.27. Synthesis of aldehyde **142**. (a) DIBAL-H (3.0 equiv), hexane/toluene 5/1, 0 °C, 30 min, typically 2:1~3:1 *dr.* (b) i-Pr_2NEt (5.0 equiv), MOMBr (3.0 equiv), 1,2-dichloroethane, 60 °C, 72 h, 78% over 2 steps. (c) OsO_4 (5 mol%), NMO (1.5 equiv), acetone, 23 °C, 16 h; then H_2O (100 V%), $NaIO_4$ (5.0 equiv), 30 min, 89%.



Entry	HMPA	H source	Result [a,b]
1	-	none	Decomposition
2	-	t-BuOH or MeOH (1.2 equiv)	**151** only
3	+	t-BuOH or MeOH (10% V)	Decomposition + dimerization[c]
4	+	PhSH (1.2 equiv)	**152** : **151**= 1 : 2.4
5	+	$(2,6\text{-}Me_2C_6H_3)SH$ (1.2 equiv)	**152** : **151** = 1 : 1.3
6	+	$(2,4,6\text{-}i\text{-}Pr_3C_6H_2)SH$ (1.2 equiv)	**152** only, (74% yield)

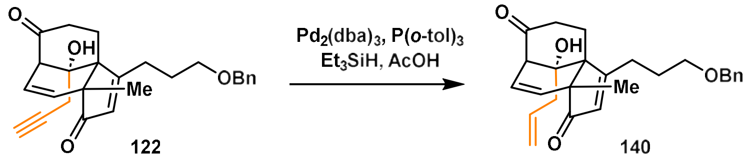
Table 3.2. Screen of conditions of the SmI_2-mediated radical cyclization reaction

[a] Full consumption of **151** was observed after step 1 for all entries. [b] Total yield not determined for entries 2-5, product ratio determined by NMR. [c] In some cases, dimerization products are observed, see SI for details. Entry 6: (1) 2,4,6-Triisopropylbenzenethiol (1.2 equiv), SmI_2-HMPA (1:8 complex, 2-3 equiv), THF, 0 °C, 15 min. (2) Dess-Martin periodinane (3.0 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 16 h, 74% over 2 steps.

During our explorations, it was found that the Ac (acetate) protecting group was not inert to the SmI_2 conditions. Silyl groups were also less than ideal since they do not provide extra coordination to the samarium complex. Aldehyde **142** with a MOM ether moiety was synthesized in good yield and later identified to be the best substrate for the SmI_2-mediated radical cyclization reaction.

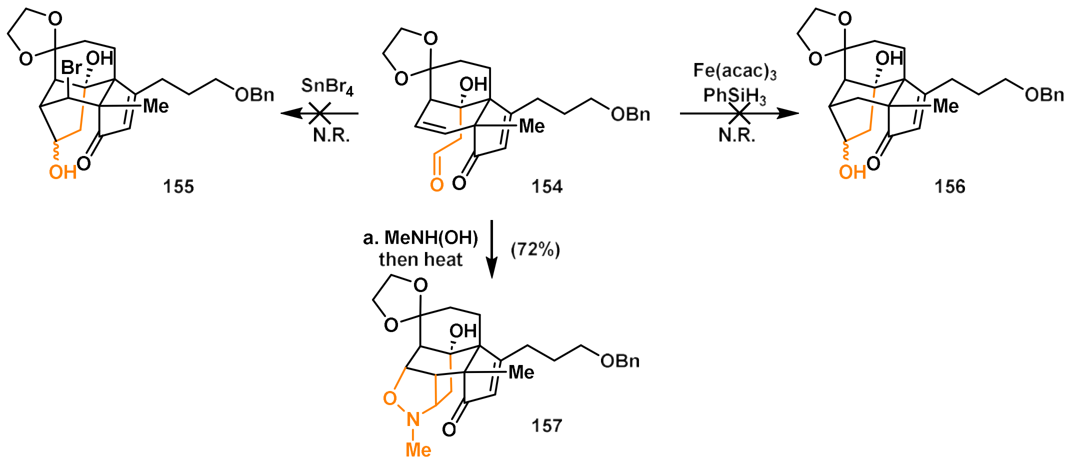
A thorough screening of conditions was conducted for the SmI_2-induced radical cyclization reaction, with the major results shown in Table 2. Treatment of aldehyde **151** with SmI_2 without any other additive (entry 1) resulted in decomposition. Noteworthy, in the vast majority of SmI_2-induced radical cyclization reactions reported to date, the samarium-stabilized radical anion will add into an electron-deficient alkene, forming an α-radical to an electron-withdrawing group, which was then further reduced by SmI_2 to generate a stabilized carbonanion to terminate the reaction. However, this pathway was not viable in our system due to the inactivated nature of the alkene. Thus, our proposed reaction could not be properly terminated without a hydrogen-atom donor. The addition of methanol or *t*-BuOH into the reaction (entry 2) lead to the direct reduction of the aldehyde **151** into a primary alcohol, which after Dess-Martin oxidation gave aldehyde **151** back. These results suggest that the samarium-stabilized radical anion reacted with the hydrogen-atom donors before its cyclization into the alkene. It was then hypothesized that the addition of ligands such as HMPA could coordinate with Sm^{2+}, to surround the samarium-stabilized radical anion and block it from the hydrogen-atom donors. However, adding HMPA to the reaction system (entry 3) again led to a complex mixture of products. Several attempts were made in the system. In one particular case, a dimeric product was formed by the dimerization of the C-1 radical (see SI for details), which supported that the addition of HMPA successfully protected the samarium-stabilized radical anion from direct reduction, however, a stronger hydrogen-atom donor is needed to terminate the C-1 radical. After a thorough literature review, we identified that thiophenol was reported as a superior hydrogen-atom donor for similar reactions [40]. With HMPA and 1.2 equivalents of thiophenol (entry 4), we observed a clean reaction profile, yielding a mixture of products of product **152** and recycled aldehyde **151** (1 : 2.4) after Dess-Martin oxidation. We further optimized the results by adding more steric hindrance to the thiophenol (entry 5-6), hoping to make it harder to approach the samarium-stabilized radical anion. Eventually, 2,4-6-trisisopropyl thiophenol was found to be the superior hydrogen-atom donor, giving **152** as the only product in good yield.

3.6.3 Attempts Based on Other Miscellaneous Mechanisms



Scheme 3.28. Palladium-catalyzed reduction of **122** giving **140**.

Some selected attempts that failed to lead to the A ring formation are described here. Applying the palladium-catalyzed reductive enyne cyclization condition reported by Trost[41], we only observed the formation of alkene **140**, which presumably resulted from the direct reduction of the C-3 vinyl palladium intermediate after the initial hydrometallation step. Due to the lack of reactivity of the C-3 vinyl palladium species against migratory insertion into the C-2/C-1 alkene, we did not further attempt any other conditions based on similar mechanisms.

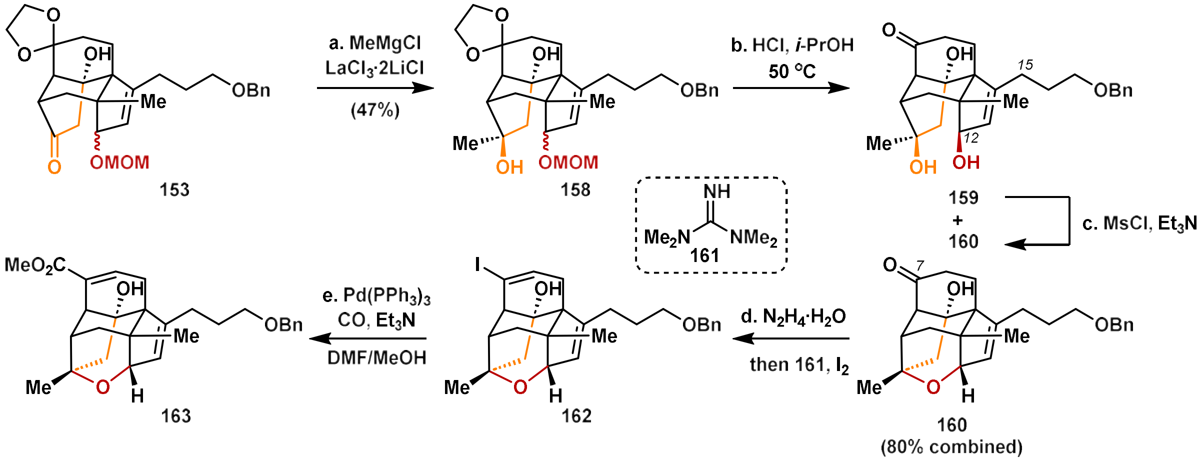


Scheme 3.29. Miscellaneous attempts on the cyclization of aldehyde **154**. (a) MeNH(OH)·HCl (11 equiv), Et_3N (20 equiv), MeOH, 23 °C, 16 h; then concentrated, toluene/MeOH 1/1, 100 °C, 2 h, 72%.

Some other cyclization strategies have been tested on aldehyde **154**. A Prins-type cyclization induced by $SnBr_4$[42] failed to lead to any cyclized product. Metal-hydride hydrogen atom transfer (MHAT) conditions[43] failed to react with the alkene. A [3+2] cycloaddition of an oxime derived from **154** led to pentacyclic product **157** with undesired C-3/C-1 bond formation.

3.6.4 Formation of the *D* Ring

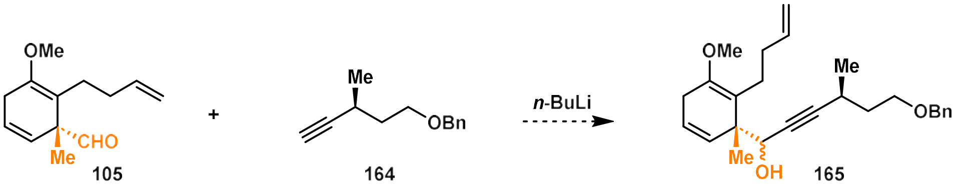
With the successful synthesis of **153**, we further explored the formation of the *D* ring. Methylmagnesium chloride, combined with $LaCl_3 \cdot 2LiCl$[44] reacted with **153** to yield **158** as a pair of diastereomers. The absence of Lewis acid promoters led to other unidentified side products that failed to be transformed further. Noteworthy, the condition resulted in significant hydrolysis of THF into 4-chlorobutan-1-ol, thus column chromatography was preferred after the step. Treatment of **158** with HCl in isopropanol afforded diol **159** as the minor product, together with the pentacyclic product **160** with the *D* ring closed as the major product. Based on the product distribution, we hypothesized that the (12*R)*-isomer cyclized into **160** via an S_N1 reaction at C-3, while the (12*S*)-isomer was stuck at the stage of diol **159**. It was then found that diol **159** could be converted into pentacyclic product **160** via the C-12 methanesulfonate, which supported our hypothesis. Noteworthy, when **158** is treated with aqueous HCl, elimination of the C-12 alcohol was observed as a major side reaction. We proposed that isopropanol serves as a bulkier conjugate base than water, hence avoiding the deprotonation at C-15.



Scheme 3.30. The synthesis of pentacyclic compound **163**. (a) $LaCl_3 \cdot 2LiCl$ (6.0 equiv), THF, 23 ºC, 30 min; then MeMgCl (5.0 equiv), 16 h, 47%. (b) HCl (~0.5 M in *i*-PrOH), 50 ºC, 12 h, 53%. (c) MsCl (1.5 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 23 ºC, 1 h, 26% from **158**. (d) $N_2H_4 \cdot H_2O$ (excess), MeOH, 60 ºC, 12 h; then concentrated, Et_2O, I_2 (3.0 equiv), **161** (3.0 equiv), 30 min, yield not determined. (e) Et_3N (2.0 equiv), $Pd(PPh_3)_3$ (0.10 equiv), CO (balloon pressure), DMF/MeOH 2/1, 60 ºC, 16 h, yield not determined.

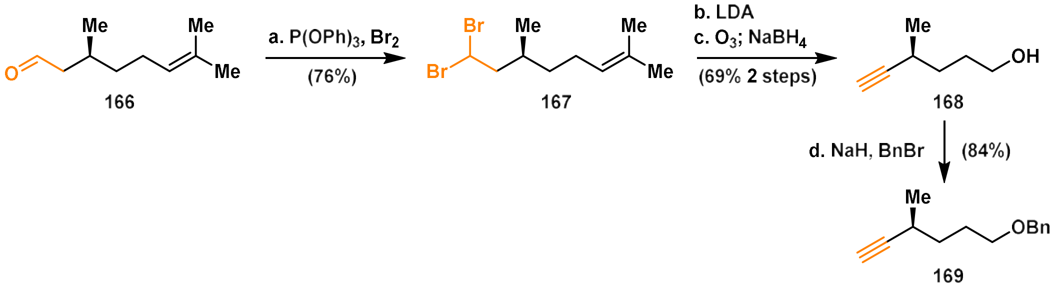
To test the possibility of a late-stage derivatization at the C-7 position, ketone **160** was converted into vinyl iodide **162** by Barton's vinyl iodide synthesis[45]. Attempts to synthesize the corresponding vinyl triflate were not successful, which result is in accord with the general instability of the framework to strong basic conditions. Finally, a carbonylative coupling reaction transformed vinyl iodide **162** into unsaturated ester **163**. No further attempts were made to push **163** forward into more complex structures, as an asymmetric solution is required for the synthesis of **1** and **2**.

3.7 Asymmetric Synthesis



Scheme 3.31. The proposed step to combine asymmetric partners **105** and **164**.

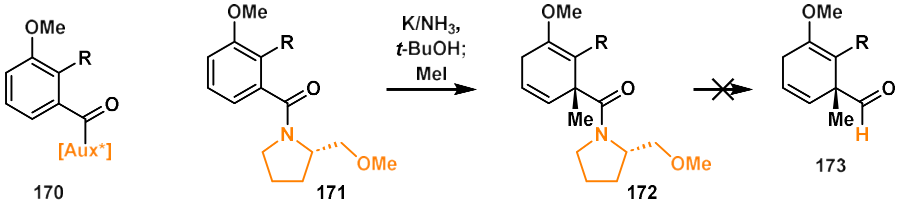
As part of our proposal, we plan to introduce the C-15 stereocenter from chiral starting material. To realize this design, both building blocks **105** and **164** have to be made chiral.



Scheme 3.32. The synthesis of alkyne **169**. (a) diisopropylamine (4.0 equiv), *n*-BuLi (3.5 equiv), THF, -78 to 0 °C, 1 h; then **167**, 23 °C, 16 h. (c) O_3, CH_2Cl_2, -78 °C; MeOH (100 V%), $NaBH_4$ (0.85 equiv), 23 °C, 16 h, 69% 2 steps. (d) NaH (1.5 equiv), THF, 0 °C, 30 min; BnBr (1.2 equiv), 23 °C, 16 h, 84%.

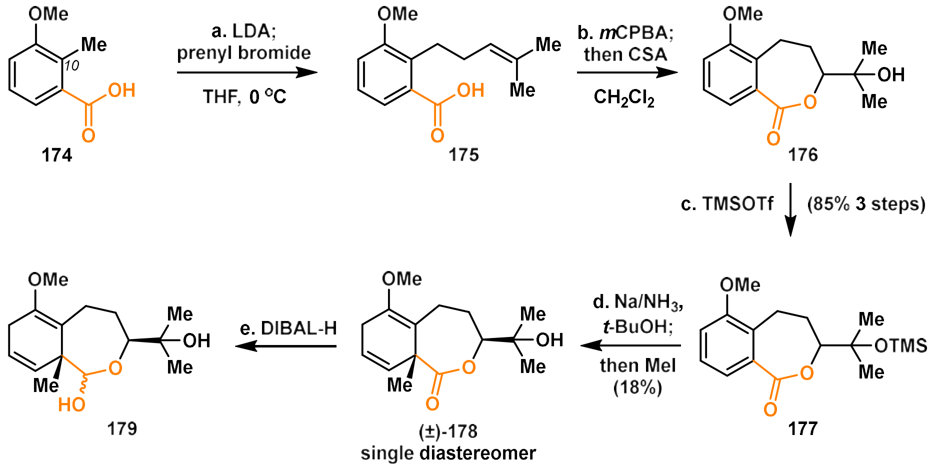
Alkyne **164** has been synthesized by Martin and co-workers through a 3-step procedure involving an Evans auxiliary$^{\text{ref.11}}$. Albeit our success in replicating the procedure, we found it less than ideal for large-scale synthesis, partly due to the involvement of a careful column chromatography step. Instead, starting from (−)-citronellal (**166**), we took a 4-step protocol inspired by Shenvi's synthesis of Jiadifenolide[46] to produce benzyl ether **169** on decagram scale. The involvement of a homologated side chain is also desirable for the late-stage diversification towards both bipolarolides A and B.

To introduce asymmetry to the core moiety, namely aldehyde **105**, an asymmetric reductive alkylation step was required. Noticing the similarity of this conversion to a carbonyl α-substitution reaction, we proposed to use a chiral auxiliary to control the stereochemistry outcome. After thorough literature research, we found the most common method for such conversions involves a 2-(Methoxymethyl)pyrrolidine amide[47]. Treating amide **171** with potassium in ammonia, followed by iodomethane, we delightfully observed product **172** as a single diastereomer. However, significant challenges were met when we attempted to convert **172** into the desired aldehyde **173**. Reduction conditions either lead to no reaction or the reduction of amide into an amine. The only method reported in the literature to convert such functional groups further is by hydrolysis under strong acidic conditions, which in our case will also hydrolyze the enol-ether moiety required for the silver-catalyzed cyclization reaction. Some other auxiliaries were also tested without any positive results. A menthol ester gave an 1:1 mixture of inseparable diastereomers in the reductive alkylation reaction. A recent report by the Vanderwal group[48] shows the unlikelihood of the 8-phenylmenthol ester of our substrate to be successful in offering good diastereoselectivity. Evans auxiliaries, containing a carbamate functional group, could not survive the Birch reduction condition.



Scheme 3.33. The proposed asymmetric synthesis of aldehyde **105** via chiral auxiliaries.

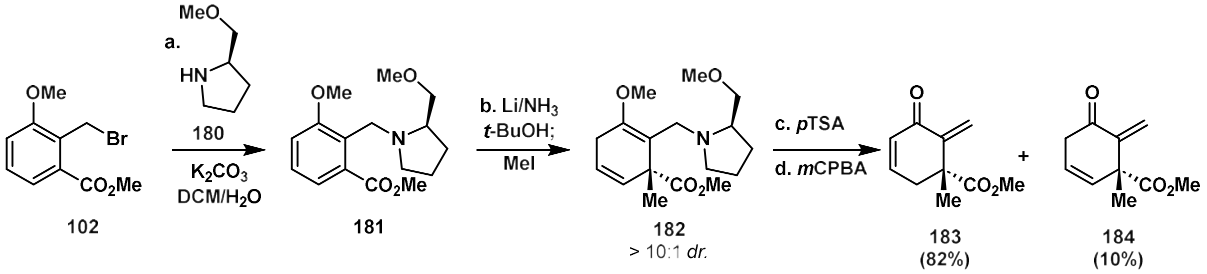
To further utilize the C-10 substation to assist the asymmetric step, we came up with a proposal involving a 7-membered lactone. Starting from commercially available carboxylic acid **174**, directed deprotonation at the benzylic position and subsequent treatment of prenyl bromide afforded alkene **175**[49]. Epoxidation of the alkene followed by epoxide-opening induced by camphorsulfonic acid gave 7-membered lactone **176**[50]. In the future, we were planning to utilize the Shi asymmetric epoxidation[51] for the synthesis of **176** in enantio-pure form. The tertiary alcohol must be protected in the form of a trimethylsilyl ether for the subsequent reductive alkylation step. Upon screening, it was found that Na was the only metal (among itself, Li, and K) that successfully gave the reductive alkylation product **178**. Reduction of the lactone carbonyl was observed with Li or K. Although more optimizations may be conducted, we moved forward with **178** obtained in 18% yield as a single diastereomer[52]. Direct treatment of **178** with alkynyl lithium yielded no conversion. Reduction of **178** by DIBAL-H afforded hemiacetal **179**, which was also inert to alkynyl lithium addition. We concluded that the poor reactivity to be a result of the combination of the inherent inertness of lactones and hemiacetals, the hindrance brought by the α-quaternary center, and the low reactivity of alkynyl lithium reagents. Therefore, we moved away from this proposal.



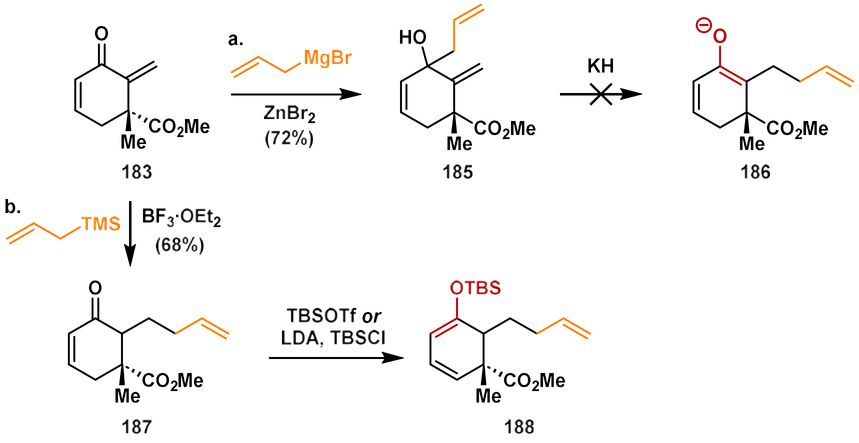
Scheme 3.34. Attempted asymmetric synthesis via 7-membered lactone **176**. (a) See ref. 49. (b) *m*CPBA (1.2 equiv), CH_2Cl_2, 23 °C, 1 h; then (±)-camphorsulfonic acid (0.1 equiv), 16 h. (c) TMSOTf (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, 85% over 3 steps. (d) *t*-BuOH (1.0 equiv), Na (2-3 equiv), THF/NH_3 1/2, -78 °C, 30 min; then

2,3-dimethyl-1,3-butadiene; then MeI (1.2 equiv), 30 min, 18%, single diastereomer. (e) DIBAL-H (3.0 equiv), THF, 0 ºC, 1 h, yield not determined.

During literature research, we found the enantiomer of dienone **183** was synthesized by the Schultz group from benzyl bromide **102** from a 4-steps protocol[53]. Realizing the close relationship of **183** to our desired structure, we replicated their procedure and obtained dienone **183** in 87% yield over 4 steps, along with skip-enone **184** in 11% yield.

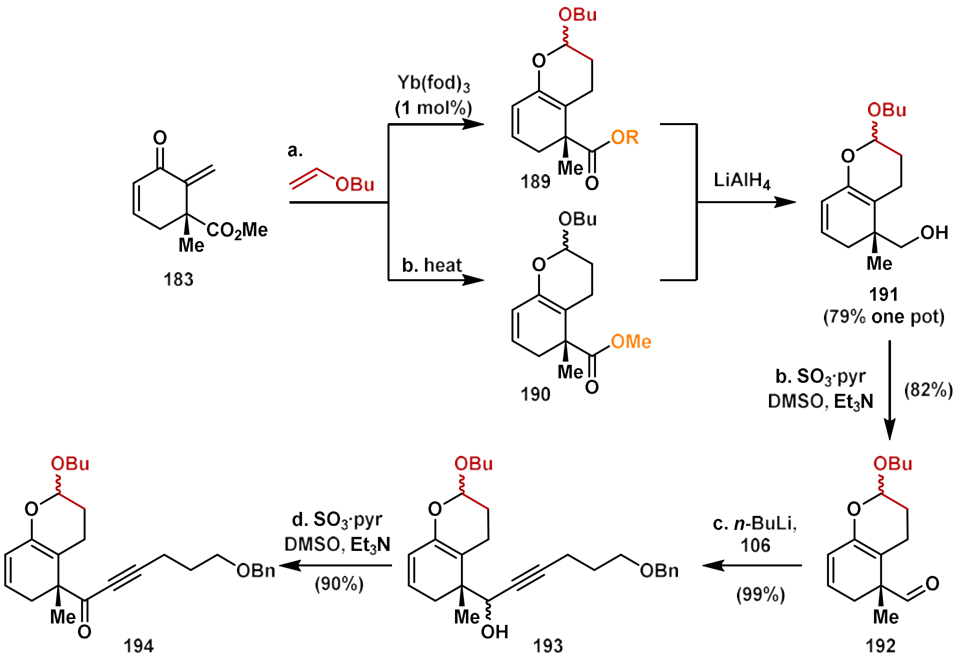


Scheme 3.35. The synthesis of dienone **183**, and skip-enone **184**. (a) **102** (1.0 equiv), **180** (1.05 equiv), K_2CO_3 (1.5 equiv), CH_2Cl_2/H_2O 5/1. (b) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH_3 1/5, -78 ºC, 30 min; then 2,3-dimethyl-1,3-butadiene; then MeI (1.2 equiv), 30 min. (c) *p*TSA (1.1 equiv), toluene, 80 ºC, 1 h. (d) *m*CPBA (1.2 equiv), CH_2Cl_2, 23 ºC, 30 min, 82% **183**, 10% **184**.



Scheme 3.36. Some failed attempts to convert **183** into substrates that can undergo the desired gold-catalyzed cyclization reaction. (a) AllylMgBr (2.4 equiv), $ZnBr_2$ (1.2 equiv), THF, 0 ºC, 10 min, then **183**, 30 min, 72%. (b) $BF_3 \cdot OEt_2$ (1.2 equiv), allyltrimethylsilane (1.2 equiv), CH_2Cl_2, -78 to 23 ºC, 68%.

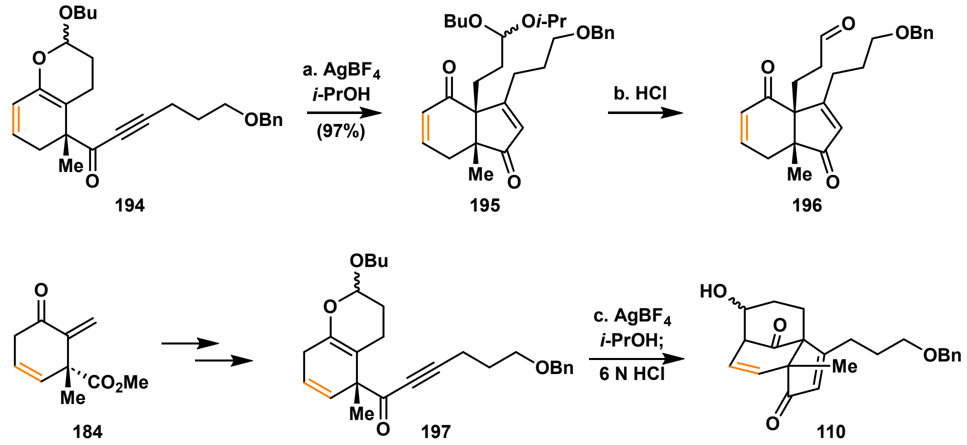
Treatment of dienone **183** by allyl cuprate reagents resulted in only 1,2-addition into the carbonyl. Realizing the possibility of converting the 1,2-addition product to the desired enol-ether structure by an oxy-Cope rearrangement reaction[54], we intentionally synthesized **185** by the treatment of dienone **183** with allylzinc bromide. However, various basic conditions were attempted without giving any desired product. Inspired by Yang's synthesis of waihoensene[55], we found a Sakurai-type reaction could selectively functionalize the external alkene to give **187**. However, various enol-ether formation conditions only gave the undesired regioisomer **188**.



Scheme 3.37. The synthesis of dihydropyran **194** by hetero Diels-Alder reaction. (a) One pot from **183** to **191**: butyl vinyl ether (solvent, 0.5 M concentration), Yb(fod)$_3$ (1.0 mol%), 23 °C, 16 h; then THF (100 V%), 0 °C, LiAlH$_4$ (1.2 equiv), 15 min, 79%. (b) Et$_3$N (5.0 equiv), sulfur trioxide pyridine complex (4.0 equiv), DMSO/DCM 1/4, 0 to 23 °C, 4 h, 82%. (c) **106** (1.4 equiv), *n*-BuLi (1.2 equiv), THF, 0 °C, 30 min; then **191**, 30 min, 99%. (d) Et$_3$N (5.0 equiv), sulfur trioxide pyridine complex (4.0 equiv), DMSO/DCM 1/4, 0 to 23 °C, 4 h, 90%.

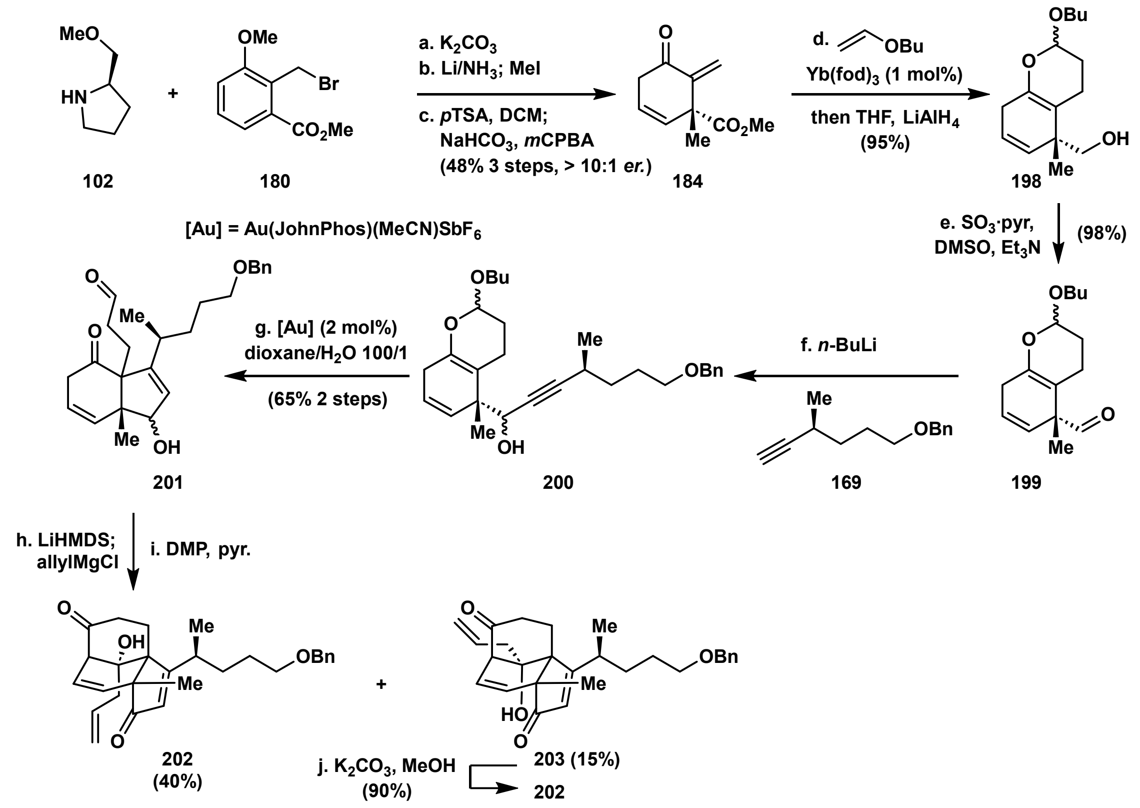
So far, we have been focusing on synthesizing structures related to alkene **105** asymmetrically. However, noticing that what we ultimately need is aldehyde **108**, we investigated the possibilities of synthesizing structures more closely related to the later compound. We thus proposed a hetero-

Diels-Alder reaction[56] to convert dienone **183** into dihydropyran **190** bearing an acetal moiety, which has the same oxidative state as aldehyde **108**. Heating dienone **183** in vinyl butyl ether successfully gave the desired dihydropyran **190**. The same transformation was successful with a milder condition under the catalysis of $Yb(fob)_3$, however, a transesterification occurred at the same time, giving product **189** as an unidentified ester. After reduction by $LiAlH_4$ in situ, alcohol **191** was obtained in 79% yield. The catalytical condition was adopted in material pushing due to its mildness and higher time efficiency. Parikh–Doering oxidation, homologation, and a second Parikh–Doering oxidation gave ketone **194** in good yields.



Scheme 3.38. The silver-catalyzed cyclization reaction of **194**, the failure of aldol condensation reaction of **195**, and the asymmetric synthesis of tricyclic alcohol **110** from skip-enone **184**. (a) $AgBF_4$ (0.20 equiv), *i*-PrOH, 23 ºC, 2 h, 97%. (b) 6 N HCl (20 V%), *i*-PrOH, 18 h, yield not determined. (c) $AgBF_4$ (0.20 equiv), *i*-PrOH, 23 ºC, 2 h; then 6 N HCl (20 V%), 18 h, yield not determined.

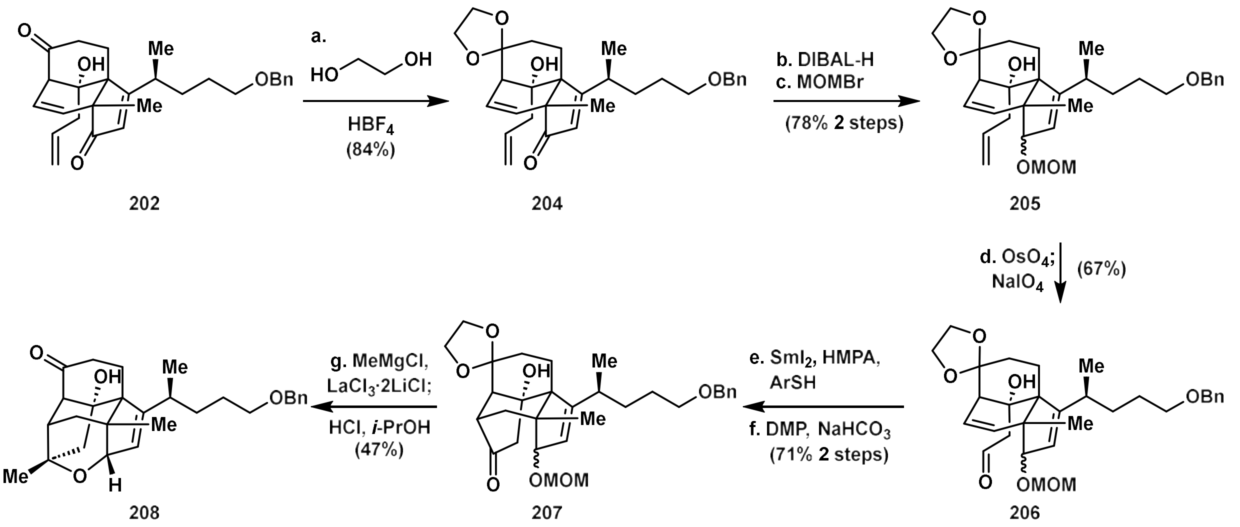
The silver-catalyzed cyclization reaction was then evaluated in the new system. Instead of enol-ether products similar to **109**, mixed acetal **195** was obtained as the initial product. We hypothesized that the cationic intermediate after the initial cyclization preferentially breaks the glycoside bond. Upon treating **195** with acid, only aldehyde **196** was observed, without any further aldol condensation product detected. Although a basic condition was possible in converting aldehyde **196** further into the tricyclic product **110**, we wanted to avoid using it due to the possibility of the epimerization of the C-15 stereocenter under basic conditions. We then started from the skip enone byproduct **184** and synthesized ketone **197** through a similar sequence. This time, treatment of **197** with $AgBF_4$ followed by acidic work-up gave the cyclized product **110**. Therefore, we hypothesized that the acid-catalyzed aldol condensation reaction would only work with a skip enone structure, which was also likely in the case of the reaction from **108** to **110**.



Scheme 3.39. The asymmetric synthesis of **202** via a gold-catalyzed cyclization reaction. (a) **102** (1.0 equiv), **180** (1.05 equiv), K_2CO_3 (3.0 equiv), CH_2Cl_2/H_2O 5/1. (b) *t*-BuOH (1.0 equiv), Li (2-3 equiv), THF/NH_3 1/5, -78 °C, 30 min; then 2,3-dimethyl-1,3-butadiene; then MeI (1.2 equiv), 30 min. (c) *p*TSA (2.0 equiv), CH_2Cl_2, 23 °C, 4 h; then $NaHCO_3$ (sat. aq., 100 V%), *m*CPBA (1.2 equiv), 30 min, 48% over 3 steps. (d) butyl vinyl ether (solvent, 0.5 M concentration), $Yb(fod)_3$ (1.0 mol%), 23 °C, 16 h; then THF (100 V%), 0 °C, $LiAlH_4$ (1.2 equiv), 15 min, 95%. (e) Et_3N (5.0 equiv), sulfur trioxide pyridine complex (4.0 equiv), DMSO/DCM 1/4, 0 to 23°C, 4 h, 98%. (f) **169** (1.3 equiv), *n*-BuLi (1.2 equiv), THF, 0 °C, 30 min; then **198**, 30 min. (g) $Au(JohnPhos)(MeCN)SbF_6$ (2.0 mol%), $dioxane/H_2O$ 100/1, 23 °C, 30 min, 65% over 2 steps. (h) LiHMDS (3.0 equiv), THF, 0 °C, 30 min; then allylMgCl (3.0 equiv), 2 h. (i) Dess-Martin periodinane (5.0 equiv), pyridine (10 equiv), CH_2Cl_2, 23 °C, 16 h, 40% **202**, 15% **203**. (j) K_2CO_3 (3.0 equiv), MeOH, 50 °C, 30 min, 90%.

To preferentially produce skip enone **184**, we found that hydrolyzing reductive alkylation product **182** with *p*TSA in CH_2Cl_2 at 23 ºC, followed by the Cope elimination in one pot was optimal, giving **184** in 68% yield. Generally, it was found that the alkene shift reaction of **184** into **183** was very slow under acidic conditions at low temperatures. However, the same transformation was considerably easier under basic conditions. A worse selectivity in **184** over **183** was observed when the acidic hydrolysis and the Cope elimination reactions were conducted separately (with the reaction worked up and concentrated in between), likely because **182** itself contains a basic tertiary amine moiety.

Alcohol **200** was successfully synthesized following a similar sequence using asymmetric materials. Noticing the repeated oxidations and reductions of the C-12 position, included in the 5-steps sequence from **110** to **125**, make the route less than efficient, we further explored the possibility of a gold-catalyzed cyclization reaction directly on alcohol **200**. Although a similar enyne cyclization was not successful as described before, we anticipated the extra driving force from the breaking of the glycoside bond would help facilitating the reaction in this case. After some screenings, we found the reaction successfully yielded aldehyde **201** in decent yield in a mixed solvent of 1,4-dioxane and water. Treating **201** with LiHMDS, we observed the formation of the tricyclic system. Allylmagnesium bromide was then added in one pot to selectively functionalize the C-5 ketone. After a global oxidation, we surprisingly found that the major product observed was the desired (5*R*) isomer of **202**, matching most NMR peaks with **125**. It was so far unclear about the reason for the differences in selectivity. A small amount of **203** was also observed as a minor product, which could be isomerized to **202** using the basic retro-aldol/aldol condition described earlier.



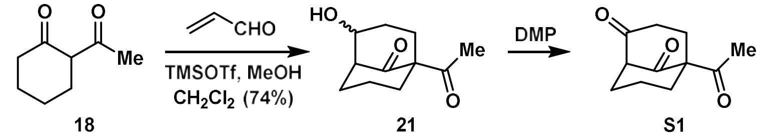
Scheme 3.40. The synthesis of **208** with the pentacyclic core of bipolarolides A and B. (a) $HBF_4·Et_2O$ (0.5 equiv), ethylene glycol/CH_2Cl_2 1/1, 23 ºC, 16 h, 84%. (b) DIBAL-H (3.0 equiv), hexane/toluene 5/1, 0 ºC, 30 min, typically 2:1~3:1 *dr.* (c) *i*-Pr_2NEt (5.0 equiv), MOMBr (3.0 equiv), 1,2-dichloroethane, 60 ºC, 72 h, 78% over 2 steps. (d) OsO_4 (5 mol%), NMO (1.5 equiv), acetone, 23 ºC, 16 h; then H_2O (100 V%), $NaIO_4$ (5.0 equiv), 30 min, 67%. (e) 2,4,6-Triisopropylbenzenethiol (1.2 equiv), SmI_2-HMPA (1:8 complex, 2-3 equiv), THF, 0 ºC, 15 min. (f) Dess-Martin periodinane (3.0 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 ºC, 16 h, 71% over 2 steps. (g) $LaCl_3·2LiCl$ (6.0 equiv), THF, 23 ºC, 30 min; then MeMgCl (5.0 equiv), 16 h; HCl (~0.5 M in *i*-PrOH), 50 ºC, 2 h, 47%.

A similar sequence used in the transformation from **125** to **160** was followed to convert **202** into **208** bearing the pentacyclic core. The addition of the exocyclic stereocenter and the homologated side chain proof to have minimal effect in the overall efficiency of the route.

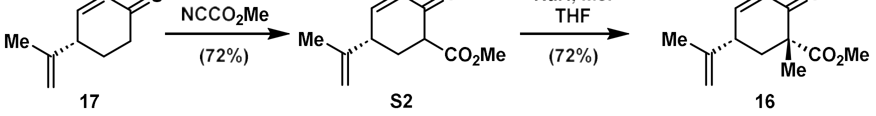
3.8 Summary

In a brief summary, we evolved a concise synthetic route to form the full core skeleton of caged natural products bipolarolides A and B, guided by the careful design of the order of ring formations and the information we receive from the challenges we met during the synthetic study. As of the finalization of this dissertation, we are actively working on transforming **208** into bipolarolides A and B.

Supporting Information

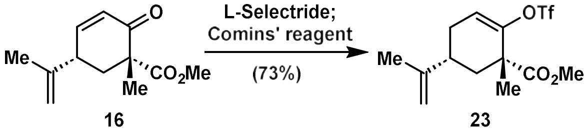


Alcohol **21**: 50 mL round bottom flask equipped with a magnetic stir bar was added diketone **18** (43.9 mg, 0.313 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous CH_2Cl_2 (5.0 mL), TMSOTf (21 mg, 0.094 mmol, 0.30 equiv), and MeOH (4 µL, 3 mg, 0.3 equiv) were sequentially added. A solution of acrolein (35 mg, 0.626 mmol, 2.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL) was added slowly via syringe pump (~0.30 mL/h). After 2 h, TLC analysis showed the complete consumption of **18**, at which time about 0.6 mL acrolein solution (~1.2 equiv) was added. The reaction was then quenched by the addition of saturated $NaHCO_3$ (5 mL). The reaction contents were then transferred to a separatory funnel, diluted with CH_2Cl_2 (5 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave alcohol **21** (45.3 mg, 74% yield) as a colorless oil. The structure of **21** was confirmed after Dess-Martin oxidation. **S1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.13 (t, *J* = 3.9 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.50 – 2.39 (m, 2H), 2.36 (td, *J* = 13.7, 5.3 Hz, 1H), 2.30 (s, 3H), 2.14 – 2.01 (m, 2H), 1.86 – 1.73 (m, 2H), 1.66 (qt, *J* = 14.0, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.26, 208.74, 206.20, 63.08, 61.83, 39.67, 37.98, 34.94, 27.61, 23.56, 18.87.



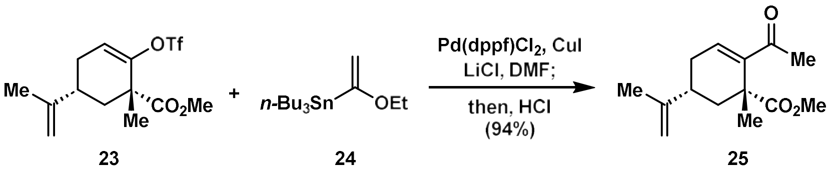
β-Keto ester **S2**: to a 500 mL round bottom flask equipped with a magnetic stir bar was added enone **17** (2.43 g, 17.8 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (175 mL) was added. The reaction flask was cooled to -78 ºC before LiHMDS (1.3 M in THF, 16.5 mL, 21.4 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at -78 ºC for 30 min, and Mander's reagent (1.97 g, 23.1 mmol, 1.3 equiv) was added. The reaction mixture was continued stirred at -78 ºC for another 30 min, at which time TLC analysis showed the complete consumption of **17**. The reaction was then quenched by the addition of saturated $NaHCO_3$ (50 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave β-Keto ester **S2** (2.49 g, 72% yield) as a yellow oil.

Enone **16**: to a 500 mL round bottom flask equipped with a magnetic stir bar was added β-Keto ester **S2** (2.49 g, 13.8 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (120 mL) was added. The reaction flask was cooled to 0 ºC before NaH (60% suspension in mineral oil, 0.61 g, 15.2 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at 0 ºC for 30 min, and MeI (1.2 mL, 2.6 g, 18 mmol, 1.2 equiv) was added. The reaction mixture was warmed up to 23 ºC and stirred at that temperature for 5 h, at which time TLC analysis showed the complete consumption of **S2**. The reaction was then quenched by the careful addition of saturated NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave enone **16** (1.93 g, 72% yield) as a light yellow oil. **16**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (ddd, *J* = 10.2, 2.8, 1.4 Hz, 1H), 6.06 (dd, *J* = 10.2, 2.6 Hz, 1H), 4.94 – 4.90 (m, 1H), 4.81 – 4.79 (m, 1H), 3.70 (s, 3H), 3.10 (ddt, *J* = 10.2, 5.4, 2.7 Hz, 1H), 2.55 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.02 (ddd, *J* = 13.6, 5.1, 1.5 Hz, 1H), 1.82 (s, 3H), 1.43 (s, 3H).

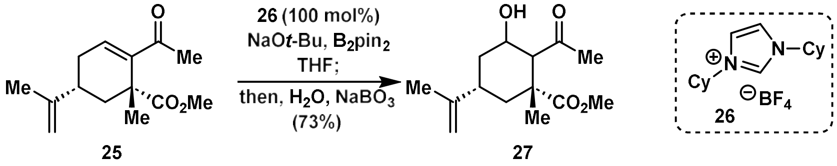


Vinyl triflate **23**: to a 500 mL round bottom flask equipped with a magnetic stir bar was added enone **16** (1.93 g, 9.27 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (150 mL) was added. The reaction flask was cooled to -78 °C before l-selectride (1.0 M in THF, 9.8 mL, 9.8 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min, and Comins' reagent (3.65 g, 9.27 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added. The reaction mixture was continued stirred at -78 °C for another 1 h, at which time TLC analysis showed the complete consumption of **16**. The reaction was then quenched by the addition of saturated $NaHCO_3$ (50 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel saturated with Et_3N, hexanes/EtOAc, 10/1→4/1) gave vinyl triflate **23** (2.32 g, 73% yield) as a colorless oil. **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dd, *J* =

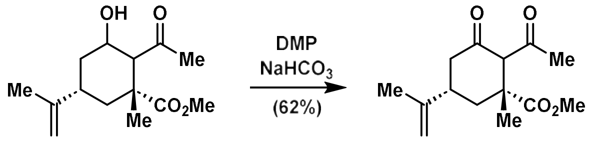
5.9, 2.5 Hz, 1H), 4.83 – 4.79 (m, 1H), 4.76 (s, 1H), 3.74 (s, 3H), 2.41 – 2.29 (m, 2H), 2.28 – 2.19 (m, 1H), 2.07 (t, *J* = 12.5 Hz, 1H), 1.89 (s, 1H), 1.74 (s, 3H), 1.48 (s, 3H).



Enone **25**: to a 250 mL round bottom flask equipped with a magnetic stir bar was added LiCl (1.44 g, 33.9 mmol, 5.0 equiv). The flask and its contents were flame-dried under vacuum and backfilled with argon upon cooling. CuI (0.13 g, 0.68 mmol, 10 mol%), anhydrous DMF (70 mL), tributyl(1-ethoxyvinyl)tin (**24**) (3.67 g, 10.2 mmol, 1.5 equiv), a solution of triflate **23** (2.32 g, 6.78 mmol, 1.0 equiv) in anhydrous DMF (10 mL), and Pd(dppf)Cl_2 (0.50 g, 0. 68 mmol, 10 mol%) was sequentially added to the flask. The reaction system was degassed and backfilled with argon three times and heated to 40 ºC. After stirring at 40 ºC for 12 h, TLC analysis showed the complete consumption of **23**. Upon cooling to 23 ºC, Et_2O (20 mL), and HCl (6 N solution, 20 mL) was added, and the reaction mixture was continued stirred for 2 h. The reaction contents were then transferred to a separatory funnel, diluted with Et_2O (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave enone **25** (1.50 g, 94% yield) as a colorless oil. **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 5.6, 2.5 Hz, 1H), 4.80 (s, 1H), 4.77 (s, 1H), 3.63 (s, 3H), 2.44 (dtd, *J* = 18.8, 5.8, 1.6 Hz, 1H), 2.37 (ddd, *J* = 16.0, 11.6, 3.7 Hz, 1H), 2.29 (s, 3H), 2.25 (ddd, *J* = 18.7, 8.5, 2.3 Hz, 1H), 1.79 (ddd, *J* = 12.7, 3.3, 1.8 Hz, 1H), 1.75 (s, 3H), 1.72 (d, *J* = 12.4 Hz, 1H), 1.40 (s, 3H).



β-Hydroxy ketone **27**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added 1,3-dicyclohexylimidazolium tetrafluoroborate salt (**26**) (28 mg, 0.087 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (2.0 mL) was added. The flask was then moved into a nitrogen-filled glove box, where bis(pinacolato)diboron (25 mg, 0.096 mmol, 1.1 equiv) and sodium *tert*-butoxide (8.5 mg, 0.087 mmol, 1.0 equiv) was sequentially added. The reaction flask was then moved out of the glove box, and a solution of enone **25** (20.6 mg, 0.087 mmol, 1.0 equiv) in anhydrous THF (1.0 mL) was added. The reaction mixture was stirred at 23 °C for 48 h, at which time TLC analysis showed the complete consumption of **25**. H_2O (1.0 mL) and $NaBO_3 \cdot H_2O$ (45 mg, 0.44 mmol, 5.0 equiv) were added sequentially, and the reaction mixture was stirred vigorously for 18 h. The reaction contents were then diluted with H_2O (5 mL) and EtOAc (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na$_2$SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/2) gave β-Hydroxy ketone **27** (16.2 mg, 73% yield) as a colorless oil. **27**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (t, *J* = 1.6 Hz, 1H), 4.73 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.44 (q, *J* = 3.0 Hz, 1H), 3.72 (s, 3H), 3.07 (d, *J* = 2.7 Hz, 1H), 2.59 (tt, *J* = 12.7, 3.3 Hz, 1H), 2.21 (s, 3H), 2.06 – 1.96 (m, 1H), 1.84 – 1.77 (m, 1H), 1.74 (t, *J* = 1.0 Hz, 3H), 1.59 (t, *J* = 12.8 Hz, 1H), 1.49 (s, 3H), 1.40 (ddd, *J* = 13.8, 12.4, 2.9 Hz, 1H).



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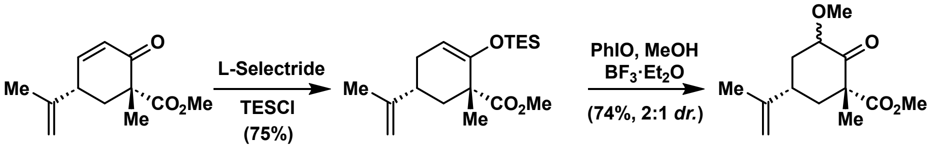
28

1,3-Diketone **28**: to a 25 mL vial charged with alcohol **27** (16.2 mg, 0.069 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (2.0 mL), $NaHCO_3$ (36 mg, 0.34 mmol, 5.0 equiv), and Dess-Martin periodinane (36 mg, 0.083 mmol, 1.2 equiv). The reaction mixture was stirred at 23 °C for 2 h, at which time TLC analysis showed the complete consumption of **27**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→2/1) gave 1,3-diketone **28** (10.2 mg, 62% yield) as a colorless oil. **28**: diagnostic peaks on ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75-4.84 (2 H, alkenes); 3.68, 3.70, 3.71 (3 s, 3 H, methyl ester); 2.01 (s, methyl ketone); 1.73-1.77 (3 H, allyl Me); 1.53-1.56 (3 H, Me).



16

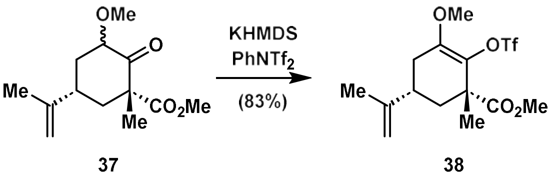
36

37

Silyl enol ether **36**: to a 50 mL round bottom flask equipped with a magnetic stir bar was added enone **16** (172 mg, 0.83 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (10 mL) was added. The reaction flask was cooled to -78 ºC before l-selectride (1.0 M in THF, 0.91 mL, 0.91 mmol, 1.1 equiv) was added dropwise. The reaction mixture was stirred at -78 ºC for 30 min, and chlorotriethylsilane (150 mg, 1.00 mmol, 1.2 equiv) was added. The reaction mixture was continued stirred at -78 ºC for another 1 h, at which time TLC analysis showed the complete consumption of **16**. The reaction was then quenched by the addition of saturated $NaHCO_3$ (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10/1) gave silyl enol ether **36** (201 mg, 75% yield) as a colorless oil.

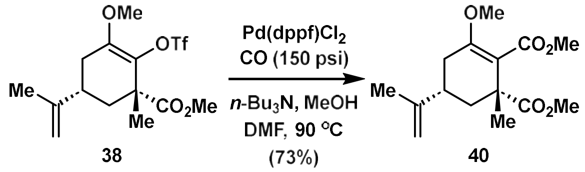
α-Methoxy ketone **37**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added iodosobenzene (409 mg, 1.86 mmol, 3.0 equiv). The flask was degassed and backfilled with argon, and anhydrous MeOH (5.0 mL) was added. The reaction flask was cooled to -78 ºC before boron trifluoride etherate (0.38 mL, 440 mg, 3.10 mmol, 5.0 equiv) was added. After stirring at -78 ºC for 5 min, a solution of silyl enol ether **36** (201 mg, 0.62 mmol, 1.0 equiv) in anhydrous MeOH (3.0 mL) was added, and the reaction was allowed to warm up to 0 ºC. After stirring at 0 ºC for 3 h, TLC analysis showed the complete consumption of **36**. The reaction was then quenched by the addition of saturated $NaHCO_3$ (5 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (5 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→2/1) gave α-Methoxy ketone **37** (110 mg, 74%

yield, 2:1 *dr.*) as a colorless oil. **37**: Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.83 (s, 1H), 4.00 (t, *J* = 6.4 Hz, 1H), 3.71 (s, 3H), 3.39 (s, 3H), 2.60 (dt, *J* = 9.6, 5.1 Hz, 1H), 2.50 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.14 (ddd, *J* = 14.5, 9.0, 5.8 Hz, 1H), 2.04 (dddd, *J* = 13.9, 7.0, 5.1, 2.0 Hz, 1H), 1.94 – 1.84 (m, 1H), 1.79 (s, 3H), 1.50 (s, 3H). Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 2H), 4.06 (dd, *J* = 12.6, 6.1 Hz, 1H), 3.77 (s, 3H), 3.45 (s, 3H), 2.69 – 2.59 (m, 1H), 2.42 – 2.31 (m, 2H), 1.87 (dt, *J* = 13.6, 3.4 Hz, 1H), 1.77 (s, 3H), 1.73 (d, *J* = 12.6 Hz, 1H), 1.54 (s, 3H).

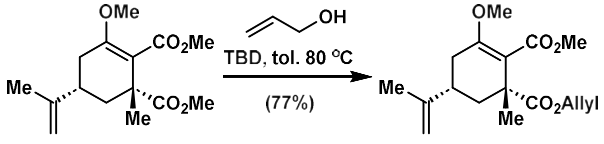


Vinyl triflate **38**: to a 50 mL round bottom flask equipped with a magnetic stir bar was added α-Methoxy ketone **37** (350.5 mg, 1.46 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (15 mL) was added. The reaction flask was cooled to -78 °C before KHMDS (1.0 M in THF, 3.5 mL, 3.5 mmol, 2.4 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 30 min and a solution of *N*-Phenyl-bis(trifluoromethanesulfonimide) (782 mg, 2.19 mmol, 1.5 equiv) in anhydrous THF (1.0 mL) was added. The reaction mixture was continued stirred at -78 °C for another 30 min, at which time TLC analysis showed the complete consumption of **37**. The reaction was then quenched by the addition of saturated $NaHCO_3$ (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel saturated with

Et_3N, hexanes/EtOAc, 10/1→4/1) gave vinyl triflate **38** (452 mg, 83% yield) as a colorless oil. **38**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.79 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 2.50 – 2.43 (m, 2H), 2.35 (dd, *J* = 17.2, 11.9 Hz, 1H), 2.05 (t, *J* = 12.4 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.76 (s, 3H), 1.45 (s, 3H).

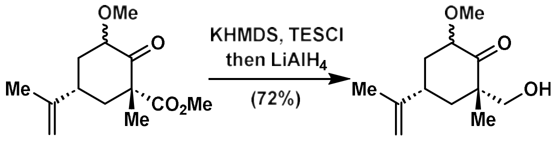


Ester **40**: A solution of triflate **38** (61.2 mg, 0.164 mmol, 1.0 equiv) in anhydrous MeOH (1.0 mL) and anhydrous DMF (0.50 mL) was transferred to a 30 mL Q-Tube™. A magnetic stir bar, tributylamine (61 mg, 0.328 mmol, 2.0 equiv), and $Pd(dppf)Cl_2$ (12 mg, 0.016 mmol, 10 mol%) were sequentially added. The tube was charged with argon (150 psi) and vacated 10 times, then charged with CO (150 psi). The tube was sealed and heated to 90 °C, and the reaction mixture was stirred at that temperature for 16 h. Upon completion, the tube was cooled to 23 °C, and carefully vacated. The reaction was then quenched by the addition of saturated $NaHCO_3$ (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave ester **40** (33.8 mg, 73% yield) as a yellow oil. **40**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 – 4.81 (m, 1H), 4.81 (s, 1H), 3.74 (s, 3H), 3.30 (s, 3H), 3.15 (s, 3H), 2.68 (tt, *J* = 12.9, 3.4 Hz, 1H), 2.42 – 2.31 (m, 2H), 1.82 (dt, *J* = 13.6, 3.3 Hz, 1H), 1.78 (s, 3H), 1.74 (dd, *J* = 13.7, 12.7 Hz, 1H), 1.57 (s, 3H).



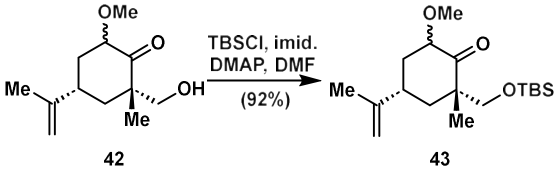
40 **41**

Allyl ester **41**: to a 10 mL round bottom flask containing ester **40** (2.6 mg, 0.0092 mmol, 1.0 equiv) was sequentially added a magnetic stir bar, toluene (0.50 mL), allyl alcohol (0.05 mL), and triazabicyclodecene (2.0 mg, 0.014 mol, 1.6 equiv). The reaction flask was sealed and heated to 80 °C and the contents were stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **40**. Upon cooling to 23 °C, the magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave ester **41** (2.2 mg, 77% yield) as a light yellow oil. **41**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.92 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.82 (t, *J* = 1.5 Hz, 1H), 4.81 (s, 1H), 4.65 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.64 (dd, *J* = 2.8, 1.4 Hz, 1H), 3.30 (s, 3H), 3.15 (s, 3H), 2.75 – 2.60 (m, 1H), 2.43 – 2.34 (m, 2H), 1.83 (dt, *J* = 13.4, 3.2 Hz, 1H), 1.78 (s, 3H), 1.76 – 1.71 (m, 1H), 1.58 (s, 3H).

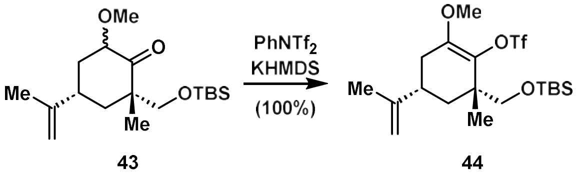


37 **42**

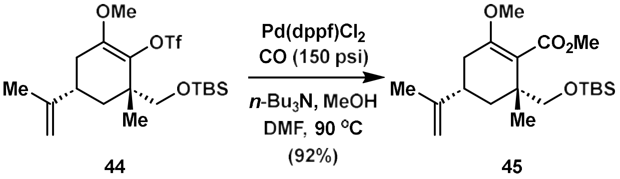
Alcohol **42**: to a 50 mL round bottom flask equipped with a magnetic stir bar was added α-methoxy ketone **37** (257.1 mg, 1.07 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (11 mL) was added. The reaction flask was cooled to 0 ºC before KHMDS (1.0 M in THF, 1.3 mL, 1.3 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at 0 ºC for 30 min and TESCl (242 mg, 1.60 mmol, 1.5 equiv) was added. The reaction mixture continued due stirred at 0 ºC for another 30 min, at which time TLC analysis showed the complete consumption of **37**. $LiAlH_4$ (1.0 M in THF, 2.2 mL, 2.2 mmol, 2.0 equiv) was added. After stirring at 0 ºC for another 30 minutes, the reaction was then quenched by the addition of saturated aqueous Rochelle's salt (10 mL) dropwise (note that the temporary TES protecting group was cleaved in the reduction step in this case, thus no acidic workup is needed). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave alcohol **42** (163.8 mg, 72% yield) as a colorless oil. **42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 – 4.70 (m, 2H), 3.59 (d, *J* = 11.4 Hz, 1H), 3.53 (t, *J* = 3.5 Hz, 1H), 3.34 (d, *J* = 12.3 Hz, 1H), 3.30 (s, 3H), 2.89 (tt, *J* = 12.7, 3.5 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.20 (dq, *J* = 14.2, 3.4 Hz, 1H), 1.82 (t, *J* = 13.1 Hz, 1H), 1.76 (s, 3H), 1.69 (ddd, *J* = 14.3, 12.5, 3.7 Hz, 1H), 1.58 (dt, *J* = 13.3, 3.4 Hz, 1H), 1.32 (s, 3H).



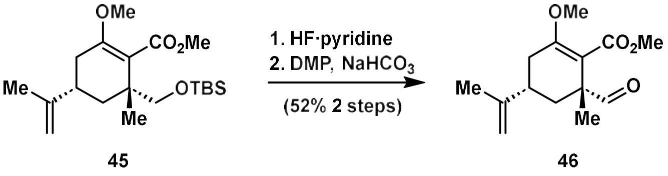
α-Methoxy ketone **43**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added alcohol **42** (112 mg, 0.528 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous DMF (5.0 mL), imidazole (360 mg, 5.28 mmol, 10.0 equiv), and DMAP (78 mg, 0.64 mmol, 1.2 equiv) were sequentially added. The reaction flask was cooled to 0 °C before TBSCl (239 mg, 1.58 mmol, 3.0 equiv) was added in one portion. The reaction mixture was allowed to warm up to 23 °C and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **42**. The reaction was then quenched by the addition of methanol (1 mL), and was stirred at 23 °C for 1 h before saturated aqueous $NaHCO_3$ (10 mL) was added. The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) gave α-methoxy ketone **43** (158 mg, 92% yield) as a colorless oil.



Vinyl triflate **44** was synthesized following the procedure described from **37** to **38**, starting from α-methoxy ketone **43** (158 mg, 0.485 mmol), giving vinyl triflate **44** (222 mg, 100% yield) as a colorless oil. **44**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 – 4.80 (m, 1H), 4.79 – 4.78 (m, 1H), 3.59 (s, 3H), 3.57 (d, *J* = 9.7 Hz, 1H), 3.28 (d, *J* = 9.6 Hz, 1H), 2.51 – 2.37 (m, 2H), 2.18 – 2.11 (m, 1H), 1.91 (t, *J* = 12.9 Hz, 1H), 1.76 (s, 3H), 1.48 (dt, *J* = 13.0, 2.3 Hz, 1H), 1.07 (s, 3H), 0.87 (s, 9H), 0.03 – 0.02 (m, 6H).

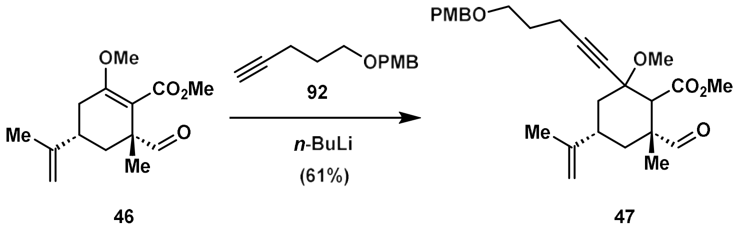


Ester **45** was synthesized following the procedure described from **38** to **40**, starting from vinyl triflate **44** (60.4 mg, 0.132 mmol), giving ester **45** (44.9 mg, 92% yield) as a light yellow oil. **45**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.81 – 4.75 (m, 2H), 3.82 (d, *J* = 9.6 Hz, 1H), 3.35 (d, *J* = 9.6 Hz, 1H), 3.28 (s, 3H), 3.11 (s, 3H), 2.71 (tt, *J* = 12.9, 3.2 Hz, 1H), 2.35 (dt, *J* = 13.3, 3.2 Hz, 1H), 1.87 (t, *J* = 13.3 Hz, 1H), 1.78 (t, *J* = 1.1 Hz, 3H), 1.69 (dt, *J* = 13.5, 3.3 Hz, 1H), 1.55 (t, *J* = 13.0 Hz, 1H), 1.20 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H).

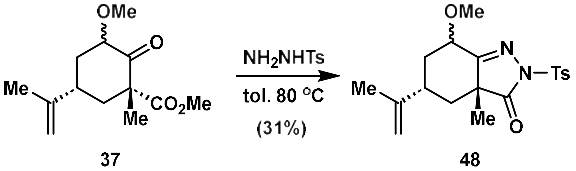


Aldehyde **46**: to a 25 mL plastic vial with a magnetic stir bar was added a solution of ester **45** (28.6 mg, 0.078 mmol, 1.0 equiv) in anhydrous THF (2.0 mL). HF·pyridine complex (0.20 mL, 10 V%) was added, and the resultant mixture was stirred at 23 °C for 16 h, at which time TLC analysis showed the complete consumption of **45**. The reaction contents were diluted with H_2O (5 mL) and EtOAc (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. The resultant crude product was transferred to a 25 mL vial for the next step without further purification. To the reaction vial was added a magnetic stir bar, CH_2Cl_2 (1.0 mL), $NaHCO_3$ (24 mg, 0.28 mmol, 5.0 equiv), and Dess-Martin periodinane (36 mg, 0.083 mmol, 1.5 equiv). The reaction mixture was stirred at 23 °C for 2 h, at which time TLC analysis showed the complete consumption of the deprotection product. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→2/1) gave aldehyde **46** (10.3 mg, 52% yield over 2 steps) as a colorless oil.

46: ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 4.84 (t, *J* = 1.5 Hz, 1H), 4.82 (s, 1H), 3.31 (s, 3H), 3.17 (s, 3H), 2.82 – 2.72 (m, 1H), 2.42 (dt, *J* = 13.7, 3.2 Hz, 1H), 2.01 (t, *J* = 13.2 Hz, 1H), 1.78 (t, *J* = 1.1 Hz, 3H), 1.72 – 1.61 (m, 2H), 1.48 (s, 3H).

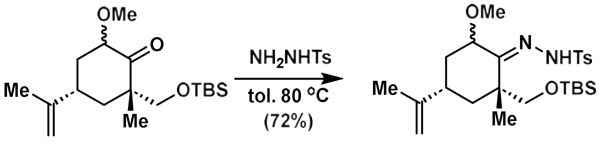


Aldehyde **47**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added alkyne **92** (102 mg, 0.50 mmol). The flask was degassed and backfilled with argon. Anhydrous THF (1.0 mL) was added, and the reaction flask was cooled to 0 ºC. *n*-BuLi (1.6 M in hexanes, 0.21 mL, 0.33 mmol) was added dropwise, and the reaction mixture was stirred at 0 ºC for 30 min, to give a 0.28 M solution of alkynyl lithium. In a separate 10 mL round bottom flask with a magnetic stir bar was added aldehyde **46** (5.2 mg, 0.021 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (1.0 mL) was added, and the reaction flask was cooled to 0 ºC. The previous alkynyl lithium solution (0.09 mL, 0.025 mmol, 1.2 equiv) was added dropwise. The reaction mixture was continued stirred at 0 ºC for another 30 min, at which time TLC analysis showed the complete consumption of aldehyde **46**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (5 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (5 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave aldehyde **47** (5.7 mg, 61% yield) as a colorless oil. **47**: diagnostic peaks on ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H, aldehyde), 7.24 (m, 2H, aromatic), 6.90 – 6.85 (m, 2H, aromatic), 4.80 – 4.73 (m, 2H, alkene), 4.42 (s, *J* = 3.8 Hz, 2H, benzyl), 3.80 (s, 3H, ester), 3.51 (t, *J* = 6.1 Hz, 2H, CH_2OPMB), 3.44 (s, 3H, aromatic-OMe), 3.32 (s, 3H, OMe), 1.75 – 1.73 (m, 3H, allylic Me), 1.23 (s, 3H, Me).



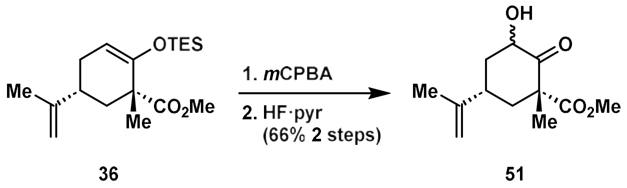
37 **48**

Pyrazolone **48**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added α-methoxy ketone **37** (10.5 mg, 0.044 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous toluene (1.0 mL) and *p*-toluenesulfonyl hydrazide (9.0 mg, 0.048 mmol, 1.1 equiv) was sequentially added. The resultant mixture was heated to 80 ºC and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **37**. The reaction mixture was diluted with hexanes (2 mL), and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/2) to give pyrazolone **48** (5.2 mg, 31% yield) as a colorless oil. **48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.33 (m, 2H), 4.78 – 4.74 (m, 1H), 4.66 (d, *J* = 1.8 Hz, 1H), 4.17 (t, *J* = 3.0 Hz, 1H), 3.27 (s, 3H), 2.68 (t, *J* = 12.7 Hz, 1H), 2.44 (s, 3H), 2.23 (dq, *J* = 14.3, 2.9 Hz, 1H), 1.94 (dt, *J* = 13.1, 2.9 Hz, 1H), 1.75 (d, *J* = 13.5 Hz, 1H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.41 (s, 3H), 1.39 – 1.35 (m, 1H).

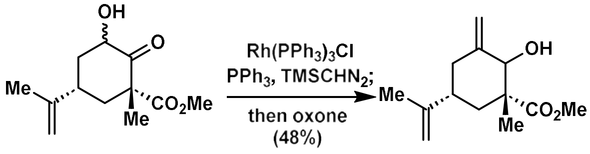


43 **49**

Hydrazone **49** was synthesized following the procedure described from **37** to **48**. Starting from α-methoxy ketone **43** (14.2 mg, 0.043 mmol), giving hydrazone **49** (15.3 mg, 72% yield) as a colorless oil. **49**: diagnostic peaks on ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 2H, aromatic), 7.33 – 7.22 (m, 2H, aromatic), 4.79 – 4.70 (m, 1H, alkene), 4.69 – 4.63 (m, 1H, alkene), 3.38 – 3.28 (2s, 3H, OMe), 2.42 (m, 3H, aromatic Me).

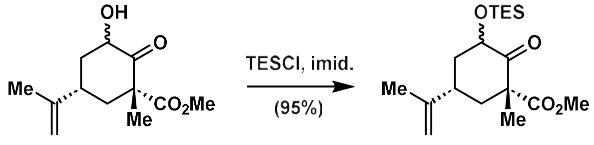


α-Hydroxy ketone **51**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added a solution of silyl enol ether **36** (960 mg, 2.96 mmol, 1.0 equiv) in Et_2O (30 mL). Saturated aqueous $NaHCO_3$ (30 mL) was added, followed by *m*CPBA (77% mixture with H_2O, 750 mg, 3.26 mmol, 1.1 equiv). The reaction mixture was stirred vigorously for 30 min, at which time TLC analysis showed the complete consumption of **36**. The reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with Et_2O (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. The resultant crude product was dissolved in anhydrous THF (25 mL) and transferred to a 50 mL plastic centrifugation tube. A magnetic stir bar was added, followed by HF·pyridine complex (2.5 mL, 10 V%). The resultant mixture was stirred at 23 °C for 16 h. The reaction contents were diluted with H_2O (10 mL) and EtOAc (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, $2/1\rightarrow1/1$) gave α-hydroxy ketone **51** (443 mg, 66% yield over 2 steps) as a colorless oil. **51**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.89 (d, *J* = 1.4 Hz, 1H), 4.85 – 4.75 (m, 1H), 3.64 (s, 3H), 2.78 (ddd, *J* = 14.2, 5.6, 2.3 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.48 – 2.40 (m, 1H), 1.83 – 1.80 (m, 3H), 1.79 – 1.71 (m, 2H), 1.39 (s, 3H).

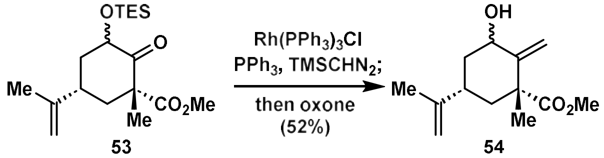


51 **52**

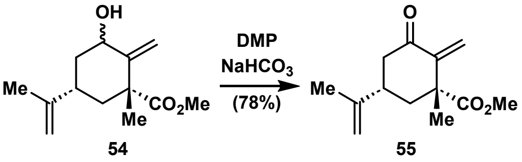
Alcohol **52**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added $Rh(PPh_3)_3Cl$ (5.2 mg, 0.057 mmol, 5 mol%) and PPh_3 (45 mg, 0.171 mmol, 3.0 equiv). The flask was degassed and backfilled with argon, and anhydrous 1,4-dioxane (1.0 mL) was added. The reaction mixture was heated to 60 ºC, and all solid contents were dissolved. Anhydrous *i*-PrOH (0.2 mL, 10 V%), a solution of α-hydroxy ketone **51** (25.6 mg, 0.113 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (1.0 mL), and trimethylsilyldiazomethane (2 M in hexanes, 0.56 mL, 1.13 mmol, 10 equiv) was sequentially added. The reaction mixture was stirred at 60 ºC for 1 h, at which point TLC analysis showed the complete consumption of **51**. H_2O (1 mL) and oxone (105 mg, 0.339 mmol, 3.0 equiv) were added, and the resultant mixture was continued stirred at 60 ºC for 1 h. The reaction contents were diluted with Et_2O (10 mL) and H_2O, transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$, and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave alcohol **52** (12.2 mg, 48% yield) as a yellow oil. **52**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (q, *J* = 1.9 Hz, 1H), 4.96 (q, *J* = 1.9 Hz, 1H), 4.75 (t, *J* = 1.5 Hz, 1H), 4.74 – 4.69 (m, 1H), 4.49 (s, 1H), 3.74 (s, 3H), 2.41 (ddd, *J* = 13.0, 3.8, 2.6 Hz, 1H), 2.21 (tt, *J* = 12.8, 3.7 Hz, 1H), 2.03 – 1.95 (m, 1H), 1.89 (dt, *J* = 13.4, 3.1 Hz, 1H), 1.72 (t, *J* = 1.1 Hz, 3H), 1.67 (t, *J* = 13.0 Hz, 1H), 1.15 (s, 3H).



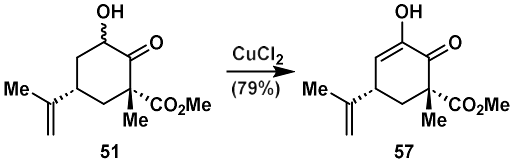
TES-Ether **53**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added α-hydroxy ketone **51** (17.3 mg, 0.076 mmol, 1.0 equiv). Anhydrous CH_2Cl_2 (2.0 mL), imidazole (26 mg, 0.382 mmol, 5.0 equiv), and TESCl (14 mg, 0.091 mmol, 1.2 equiv) were sequentially added. The reaction mixture was stirred at 23 °C for 30 min, at which point TLC analysis showed the complete consumption of **51**. Methanol (0.1 mL) was added to quench the reaction. The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) gave TES-ether **53** (24.5 mg, 95% yield) as a colorless oil. **53**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 – 4.83 (m, 1H), 4.82 (s, 1H), 4.59 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.67 (s, 3H), 2.65 – 2.49 (m, 2H), 2.24 – 2.08 (m, 1H), 2.02 – 1.91 (m, 1H), 1.79 (s, 3H), 1.78 – 1.69 (m, 1H), 1.46 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 7.8 Hz, 6H).



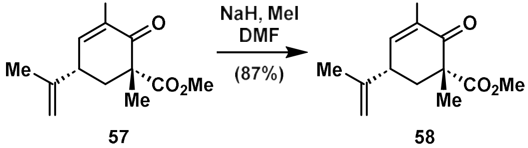
Alcohol **54** was synthesized following the procedure described from **51** to **52**. Starting from TES-ether **53** (24.5 mg, 0.072 mmol) giving alcohol **54** (8.5 mg, 52% yield) as a yellow oil. **54**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (s, 1H), 4.81 (s, 1H), 4.78 – 4.74 (m, 2H), 4.54 (t, *J* = 4.4 Hz, 1H), 3.70 (s, 3H), 2.62 (tdt, *J* = 12.0, 8.0, 3.3 Hz, 1H), 2.13 (dd, *J* = 13.3, 11.4 Hz, 1H), 1.92 (dtd, *J* = 13.6, 4.3, 1.9 Hz, 1H), 1.78 – 1.75 (m, 3H), 1.75 – 1.70 (m, 1H), 1.65 (ddd, *J* = 13.2, 3.7, 2.0 Hz, 1H), 1.56 (s, 3H).



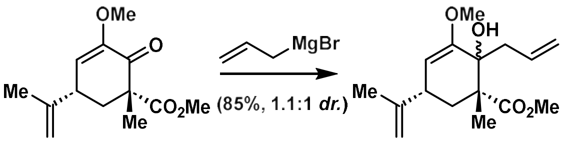
Enone **55**: to a 25 mL vial containing alcohol **54** (8.5 mg, 0.038 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (1.0 mL), $NaHCO_3$ (20 mg, 0.19 mmol, 5.0 equiv), and Dess-Martin periodinane (24 mg, 0.057 mmol, 1.5 equiv). The reaction mixture was stirred at 23 °C for 2 h, at which time TLC analysis showed the complete consumption of **54**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→2/1) gave enone **55** (6.6 mg, 78% yield) as a colorless oil. **55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.28 (d, *J* = 3.7 Hz, 1H), 4.80 (q, *J* = 1.5 Hz, 1H), 4.75 (q, *J* = 1.1 Hz, 1H), 3.69 (s, 3H), 2.63 – 2.56 (m, 1H), 2.53 (dt, *J* = 12.3, 3.8 Hz, 1H), 2.36 (dd, *J* = 16.2, 12.2 Hz, 1H), 2.29 (dd, *J* = 13.5, 11.8 Hz, 1H), 1.82 (dt, *J* = 13.5, 3.0 Hz, 1H), 1.74 (t, *J* = 1.1 Hz, 3H), 1.42 (s, 3H).



α-Hydroxy enone **57**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added α-hydroxy ketone **51** (158 mg, 0.700 mmol, 1.0 equiv), THF (7.0 mL), and $CuCl_2$ (208 mg, 1.54 mmol, 2.2 equiv). The reaction flask was adapted with a reflux condenser, and the reaction mixture was stirred under reflux for 2 h, at which point TLC analysis showed the complete consumption of **51**. The reaction contents were diluted with EtOAc (10 mL) and H_2O, transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave α-hydroxy enone **57** (125 mg, 79% yield) as a green oil. **57**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 3.6, 1.0 Hz, 1H), 5.95 (s, 1H), 4.89 (p, *J* = 1.5 Hz, 1H), 4.82 (dt, *J* = 1.6, 0.8 Hz, 1H), 3.69 (s, 3H), 3.18 (dt, *J* = 8.7, 4.4 Hz, 1H), 2.52 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.02 (ddd, *J* = 13.6, 5.0, 1.1 Hz, 1H), 1.81 (t, *J* = 1.1 Hz, 3H), 1.46 (s, 3H).

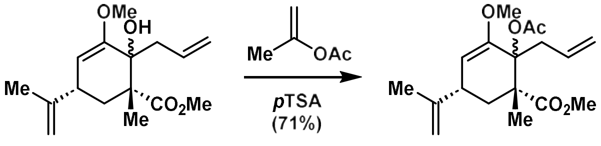


α-Methoxy enone **58**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added α-hydroxy enone **57** (125 mg, 0.556 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous DMF (6.0 mL) was added, and the reaction flask was cooled to 0 °C. NaH (60% suspension in mineral oil, 24 mg, 0.835 mmol, 1.5 equiv) was added, and the reaction mixture was stirred at 0 °C for 30 min. Iodomethane (158 mg, 1.11 mmol, 2.0 equiv) was added, and the resultant mixture was continued stirred at 0 °C for 1 h, at which point TLC analysis showed the complete consumption of **57**. The reaction was then quenched by the careful addition of saturated aqueous NH_4Cl (10 mL). The reaction contents were diluted with Et_2O (10 mL) and H_2O, transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave α-methoxy enone **58** (116 mg, 87% yield) as a yellow oil. **58**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (dd, *J* = 3.4, 1.0 Hz, 1H), 4.89 (p, *J* = 1.5 Hz, 1H), 4.87 – 4.82 (m, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.20 (dt, *J* = 8.7, 4.3 Hz, 1H), 2.49 (dd, *J* = 13.5, 9.3 Hz, 1H), 1.97 (ddd, *J* = 13.5, 5.0, 1.1 Hz, 1H), 1.81 (t, *J* = 1.0 Hz, 3H), 1.44 (s, 3H).



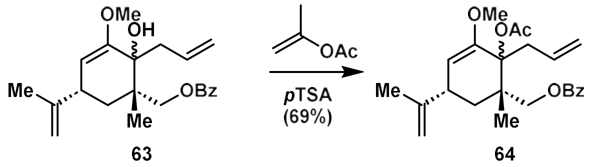
58 **59**

Alcohol **59**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added α-methoxy enone **58** (116 mg, 0.486 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (5.0 mL) was added, and the reaction flask was cooled to -20 °C. Allylmagnesium bromide (1.0 M in THF, 0.59 mL, 0.59 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at -20 °C for 30 min, at which point TLC analysis showed the complete consumption of **58**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The reaction contents were diluted with Et_2O (10 mL) and H_2O, transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave alcohol **59** (116 mg, 85% yield, 1.1:1 *dr.*) as a colorless oil. **59** (selected isomer): ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.4, 10.2, 7.3 Hz, 1H), 4.95 – 4.86 (m, 2H), 4.76 (dt, *J* = 1.9, 0.8 Hz, 1H), 4.71 – 4.68 (m, 1H), 4.42 (dd, *J* = 2.7, 1.1 Hz, 1H), 3.66 (s, 3H), 3.47 (s, 3H), 2.85 (ddd, *J* = 11.3, 6.5, 2.7 Hz, 1H), 2.41 (ddt, *J* = 14.0, 7.5, 1.2 Hz, 1H), 2.29 (ddt, *J* = 14.0, 7.2, 1.3 Hz, 1H), 1.90 (dd, *J* = 14.3, 11.2 Hz, 1H), 1.79 (ddd, *J* = 14.3, 6.4, 1.2 Hz, 1H), 1.67 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.32 (d, *J* = 0.6 Hz, 3H).

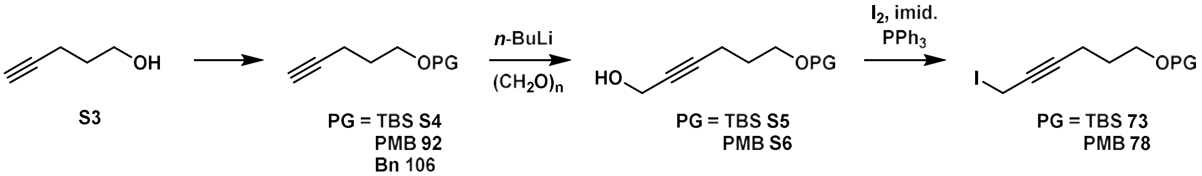


59 **61**

Acetate **61**: to a 10 mL round bottom flask containing alcohol **59** (11.8 mg, 0.042 mmol, 1.0 equiv) was sequentially added a magnetic stir bar, isopropenyl acetate (1.0 mL), and *p*-toluenesulfonic acid (0.8 mg, 0.004 mol, 10 mol%). The reaction flask was sealed and heated to 100 ºC and the contents were stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **59**. Upon cooling to 23 ºC, the magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave acetate **61** (9.6 mg, 71% yield) as a light yellow oil. **61**: diagnostic peaks on ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.78 (m, 1H, allyl, internal), 4.99 – 4.94 (m, 1H, alkene), 4.89 – 4.80 (m, 1H, alkene), 4.79 – 4.73 (m, 1H, alkene), 4.71 – 4.58 (m, 1H, alkene), 3.70 (s, 3H, CO_2Me), 3.55 – 3.49 (2 s, 3H, OMe), 2.06 – 1.91 (2 s, 3H, acetate), 1.75 – 1.72 (2 s, 3H, allylic Me), 1.36 – 1.30 (2 s, 3H, Me).



Acetate **64** was synthesized following the procedure described from **59** to **61**. Starting from benzoate **63** (6.9 mg, 0.019 mmol), giving acetate **64** (5.3 mg, 69% yield) as a light yellow oil. **64**: diagnostic peaks on ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 2H, aromatic), 7.50 – 7.38 (m, 2H, aromatic), 6.08 – 5.77 (m, 1H, allyl, internal), 5.13 – 4.99 (m, 1H, alkene), 4.88 – 4.82 (m, 1H, alkene), 4.78 – 4.74 (m, 1H, alkene), 4.72 – 4.67 (m, 1H, alkene), 4.51 – 4.44 (m, 1H, CH_2OBz), 4.37 – 4.22 (m, 1H, CH_2OBz), 3.57 – 3.51 (2 s, 3H, OMe), 2.03 – 1.93 (2 s, 3H, acetate), 1.72 (m, 3H, allylic Me).



TBS-ether **S4**: to a 100 mL round bottom flask equipped with a magnetic stir bar were sequentially added alcohol **S3** (1.73 g, 20.6 mmol, 1.0 equiv), CH_2Cl_2 (50 mL), imidazole (2.81 g, 41.2 mmol, 2.0 equiv), DMAP (0.25 g, 2.06 mmol, 0.10 equiv), and TBSCl (3.72 g, 24.7 mmol, 1.2 equiv). The reaction mixture was stirred for 30 minutes, at which time TLC analysis showed the complete consumption of **S4**. Methanol (1.0 mL) was added to quench the reaction. The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) gave TBS-ether **S4** (3.79 g,93% yield) as a colorless oil. **S4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (t, *J* = 6.0 Hz, 2H), 2.27 (td, *J* = 7.1, 2.7 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.73 (tt, *J* = 7.1, 6.0 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

PMB-ether **92** was prepared following the procedure reported by Krishna and co-workers[57]. NMR matches the reported.

Benzyl ether **106**: to a 1000 mL round bottom flask equipped with a magnetic stir bar was added alcohol **S3** (10.0 g, 119 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (500 mL) was added, and the reaction mixture was cooled to 0 ºC. Under vigorous stirring, NaH (60% suspension in mineral oil, 7.16 g, 178 mmol, 1.5 equiv) was carefully added portion-wise. The resultant suspension was stirred at 0 ºC for 30 minutes before benzyl bromide (24.4 g, 143 mmol, 1.2 equiv) was added. The reaction mixture was warmed up to 23 ºC and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **S3**. Methanol (10.0 mL) was added to quench the reaction. The reaction contents were then transferred to a separatory funnel, diluted with saturated aqueous $NaHCO_3$ (300 mL) and EtOAc (100 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated to afford benzyl ether **106** containing ~10% benzyl methyl ether as a colorless oil. **106**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 4.52 (s, 2H), 3.58 (t, *J* = 6.2 Hz, 2H), 2.33 (td, *J* = 7.1, 2.6 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.84 (tt, *J* = 7.2, 6.2 Hz, 2H).

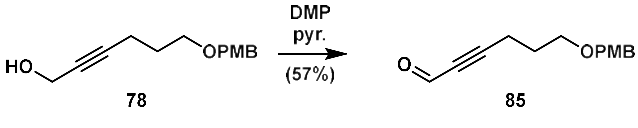
Propargyl alcohol **S5**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added TBS-ether **S3** (3.45 g, 17.4 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (50 mL) was added, and the reaction mixture was cooled to 0 ºC. *n*-BuLi (2.5 M solution in hexanes, 10.5 mL, 26.1 mmol, 1.5 equiv) was added dropwise, and the resultant solution was stirred at 0 ºC for 30 min. Paraformaldehyde (1.1 g, 34.8 mmol CH_2O, 2.0 equiv) was added in one portion. The reaction mixture was allowed to warm up to 23 ºC and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **S3**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (30 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave propargyl alcohol **S5** (3.00 g,74% yield) as a colorless oil. **S5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (dt, *J* = 6.1, 2.2 Hz, 2H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.30 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.71 (ddd, *J* = 13.3, 7.2, 6.1 Hz, 2H), 1.44 (td, *J* = 6.1, 1.0 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H).

Propargyl alcohol **S6** was prepared following the procedure from **S3** to **S5**, starting from PMB-ether **S4** (1.47 g, 7.20 mmol), giving propargyl alcohol **S6** (1.32 g, 78% yield) as a colorless oil. **S6**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.44 (s, 2H), 4.23 (dt, *J* = 6.0, 2.2 Hz, 2H), 3.81 (s, 3H), 3.53 (t, *J* = 6.2 Hz, 2H), 2.33 (tt, *J* = 7.0, 2.2 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.54 (s, 3H).

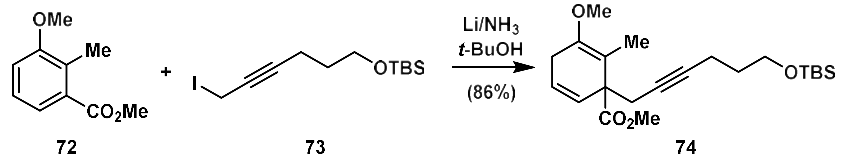
Propargyl iodide **73**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added propargyl alcohol **S5** (1.08 g, 4.73 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous CH_2Cl_2 (30 mL) was added, and the reaction mixture was cooled to 0 ºC.

Imidazole (0.48 g, 7.10 mmol, 1.5 equiv), PPh_3 (1.49 g, 5.68 mmol, 1.2 equiv), and iodine (1.56 g, 6.15 mmol, 1.3 equiv) were sequentially added. The reaction was stirred at 0 ºC for 30 min, at which time TLC analysis showed the complete consumption of **S5**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2OAc, 10/1→4/1) gave propargyl iodide **73** (1.31 g,73% yield) as a colorless oil. **73**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.70 (t, *J* = 2.5 Hz, 2H), 3.68 (t, *J* = 6.1 Hz, 2H), 2.28 (tt, *J* = 7.1, 2.5 Hz, 2H), 1.70 (apparent p, *J* = 6.5 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

Propargyl iodide **78** was prepared following the procedure from **S5** to **73**, starting from propargyl alcohol **S6** (1.32 g, 5.63 mmol), giving propargyl iodide **78** (1.49 g, 77% yield) as a colorless oil. **78**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.45 (s, 2H), 3.81 (s, 3H), 3.68 (t, *J* = 2.5 Hz, 2H), 3.52 (t, *J* = 6.2 Hz, 2H), 2.31 (tt, *J* = 7.0, 2.5 Hz, 2H), 1.83 – 1.74 (m, 2H).

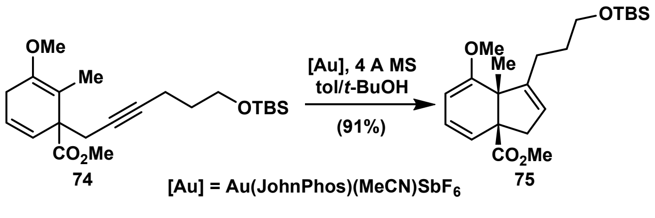


Aldehyde **85**: to a 25 mL vial charged with propargyl alcohol **78** (371 mg, 1.58 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (10 mL), pyridine (370 mg, 4.74 mmol, 3.0 equiv), and Dess-Martin periodinane (1.01 g, 2.38 mmol, 1.5 equiv). The reaction mixture was stirred at 23 °C for 2 h, at which time TLC analysis showed the complete consumption of **78**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6/1→2/1) gave aldehyde **85** (212 mg, 57% yield) as a colorless yellow oil.

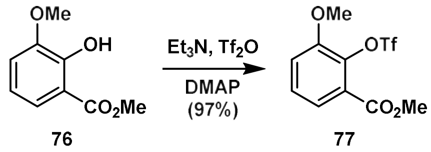


Alkyne **74**: to a 25 mL 2-neck flask equipped with a magnetic stir bar was adapted a Dewar condenser. The system was purged by dry nitrogen for 5 minutes, before being sealed and adapted with a nitrogen balloon. A solution of aromatic ester **72** (62 mg, 0.34 mmol, 1.0 equiv) and *t*-BuOH (25 mg, 0.34 mmol, 1.0 equiv) in anhydrous THF (2.0 mL) was transferred to the reaction flask via syringe. The reaction flask was then cooled to –78 ºC by a dry-ice/acetone bath, and the Dewar condenser was also filled with dry ice and acetone. Ammonia gas was then carefully passed into the system from the top of the Dewar condenser until approximately 10 mL of liquid ammonia was collected. Lithium wire that was cut into small pieces and rinsed with hexanes was added to the reaction mixture under vigorous stirring. The reaction solution turned dark blue upon the lithium metal dissolved and immediately turned bright yellow upon diffusion. Lithium metal was kept added piecewise until the blue color of the reaction solution persisted for 30 minutes.

Approximately 2-3 equivalents of lithium metal are typically needed. 2,3-dimethyl-1,3-butadiene was then added dropwise until the reaction solution turned bright yellow, to quench the excess solvated electron. Propargyl iodide **73** (144 mg, 0.377 mmol, 1.1 equiv) in anhydrous THF (1.0 mL) was then added dropwise. The reaction mixture turned colorless or light yellow and was stirred for another 30 minutes. The reaction was then quenched by the addition of solid NH_4Cl (approximately 1 g) and $Na_2S_2O_3{\cdot}5H_2O$ (approximately 100 mg). The Dewar condenser and the cooling bath were removed, allowing the ammonia to slowly evaporate overnight. The resultant solid mixture was picked up by H_2O (10 mL) and EtOAc (10 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) gave alkyne **74** (116 mg, 86% yield) as a colorless oil. **74**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 9.9, 3.5 Hz, 1H), 5.57 (dt, *J* = 9.8, 2.1 Hz, 1H), 3.67 (s, 3H), 3.64 (t, *J* = 6.2 Hz, 2H), 3.57 (s, 3H), 2.85 (dt, *J* = 3.8, 1.9 Hz, 2H), 2.65 (ddt, *J* = 21.8, 16.6, 2.5 Hz, 2H), 2.17 (tt, *J* = 7.0, 2.4 Hz, 2H), 1.64 – 1.61 (m, 2H), 1.60 (t, *J* = 1.8 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

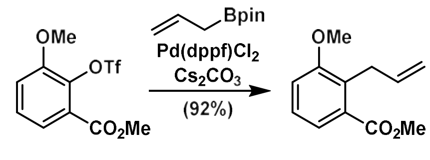


Enol ether **75**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added molecular sieves (4 Å, powdered, 32 mg, 200 wt%). The flask was flame-dried under vacuum, cooled to 23 °C, and backfilled with argon. A solution of alkyne **74** (15.9 mg, 0.040 mmol, 1.0 equiv) in anhydrous toluene (1.0 mL) and *t*-BuOH (0.10 mL) was transferred to the reaction flask via syringe. The resultant mixture was stirred for 5 minutes before Au(JohnPhos)(MeCN)SbF_6 (3.1 mg, 0.0040 mmol, 10 mol%) was added in one portion. The reaction mixture was stirred for 20 minutes, at which time TLC analysis showed the complete consumption of **74**. The reaction mixture was diluted with hexanes (2 mL), and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) to give enol ether **75** (14.5 mg, 91% yield) as a colorless oil. **75**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.39 (dq, *J* = 3.7, 1.9 Hz, 1H), 5.03 (d, *J* = 9.5 Hz, 1H), 4.91 (d, *J* = 6.4 Hz, 1H), 3.66 (s, 3H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.58 (s, 3H), 3.08 (dt, *J* = 15.9, 3.0 Hz, 1H), 2.33 (d, *J* = 15.8 Hz, 1H), 2.03 – 1.85 (m, 1H), 1.75 – 1.60 (m, 3H), 1.12 (s, 3H), 0.88 (d, *J* = 1.5 Hz, 9H), 0.03 (s, 6H).



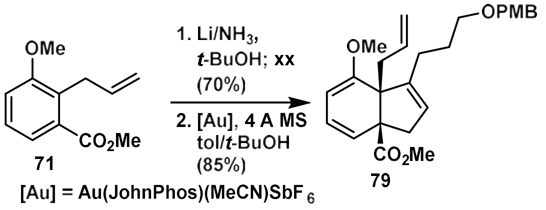
Triflate **77**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added phenol **76** (1.00 g, 5.49 mmol, 1.0 equiv), DMAP (67 mg, 0.55 mmol, 0.10 equiv) and CH_2Cl_2 (30 mL). The reaction flask was adapted with a balloon filled with argon and cooled to -78 °C. Triethylamine (4.0 mL, 2.7 g, 27.4 mmol, 5.0 equiv) and trifluoromethanesulfonic anhydride (0.92 mL, 1.55 g, 5.49 mmol, 1.0 equiv) were sequentially added. The reaction mixture was allowed to 23 °C and stirred at this temperature for 18 h, at which time TLC analysis showed the complete consumption of **76**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated.

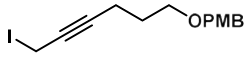
The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated to afford triflate **76** (1.68 g, 97% yield) as a light brown oil. **76**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.9, 1.6 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.21 (dd, J = 8.3, 1.6 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H).



77 **71**

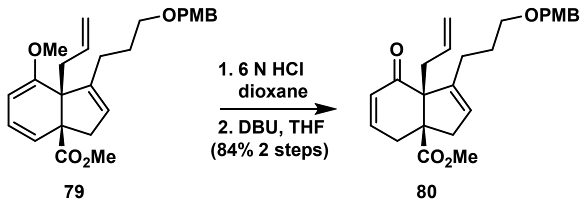
Alkene **71**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added triflate **77** (1.48 g, 4.71 mmol, 1.0 equiv) and anhydrous DMF (25 mL) under argon atmosphere. Cs_2CO_3 (3.07 g, 9.42 mmol, 2.0 equiv), allylboronic acid pinacol ester (2.37 g, 14.1 mmol, 3.0 equiv), and Pd(dppf)$_2$Cl$_2$ (35 mg, 0.047 mmol, 1 mol%) were sequentially added. The reaction was heated to 80 ºC and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **77**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and diluted with Et_2O (30 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with water and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) gave alkene **71** (896 mg, 92% yield) as a thick yellow oil. **71**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 5.97 (ddd, J = 16.6, 10.5, 5.8 Hz, 1H), 5.01 – 4.92 (m, 2H), 3.87 (d, J = 1.6 Hz, 3H), 3.85 (s, 3H), 3.73 (d, J = 6.2 Hz, 2H).





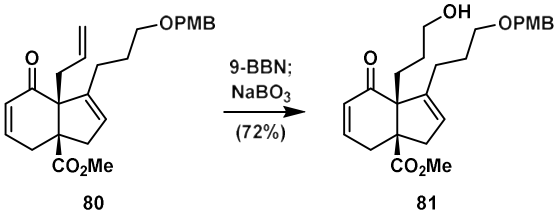
78

Enol ether **79**: following the 2-step procedure described previously from **72** to **75**. Starting from alkene **71** (430 mg, 2.09 mmol), enol ether **79** (522 mg, 60% over 2 steps) was obtained as a colorless oil. **79**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.87 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.73 (dddd, *J* = 16.9, 10.2, 7.9, 6.6 Hz, 1H), 5.52 (dq, *J* = 3.6, 1.9 Hz, 1H), 5.07 (d, *J* = 9.4 Hz, 1H), 4.95 (d, *J* = 6.3 Hz, 1H), 4.94 – 4.90 (m, 1H), 4.42 (s, 2H), 3.81 (s, 3H), 3.62 (s, 3H), 3.58 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.01 (dq, *J* = 16.1, 2.6 Hz, 1H), 2.63 (ddt, *J* = 14.8, 7.8, 1.3 Hz, 1H), 2.53 (ddt, *J* = 14.8, 6.7, 1.5 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.13 – 2.02 (m, 1H), 2.02 – 1.93 (m, 1H), 1.84 – 1.71 (m, 2H).

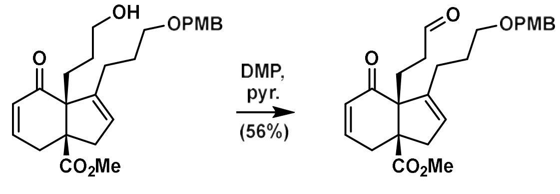


Enone **80**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added a solution of enol ether **79** (205 mg, 0.483 mmol, 1.0 equiv) in 1,4-dioxane (5.0 mL). 6 N HCl (0.50 mL) was added, and the reaction mixture was stirred at 23 ºC for 1.5 h, at which time TLC analysis showed the complete consumption of **79** and a weakly UV-active product spot. The reaction was then quenched by the careful addition of saturated aqueous NaHCO$_3$ (10 mL) and diluted with

Et_2O (10 mL). The reaction contents were then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. To the crude residue was added a magnetic stir bar, THF (5.0 mL), and 1,8-Diazabicyclo[5.4.0]undec-7-ene (221 mg, 1.45 mmol, 3.0 equiv). The reaction mixture was stirred at 23 ºC for 16 h, at which time TLC analysis showed a strongly UV-active product spot. The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave enone **80** (167 mg, 84% yield) as a colorless oil. **80**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.86 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.72 (dddd, *J* = 16.9, 10.2, 7.9, 6.6 Hz, 1H), 5.51 (dq, *J* = 3.7, 1.9 Hz, 1H), 5.06 (d, *J* = 9.4 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.62 (s, 3H), 3.57 (s, 3H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.00 (dq, *J* = 16.2, 2.6 Hz, 1H), 2.62 (ddt, *J* = 14.8, 7.9, 1.3 Hz, 1H), 2.52 (ddt, *J* = 14.6, 6.6, 1.5 Hz, 1H), 2.34 – 2.25 (m, 1H), 2.16 – 2.03 (m, 1H), 2.02 – 1.90 (m, 1H), 1.77 (dddd, *J* = 13.4, 11.7, 6.6, 3.1 Hz, 2H).



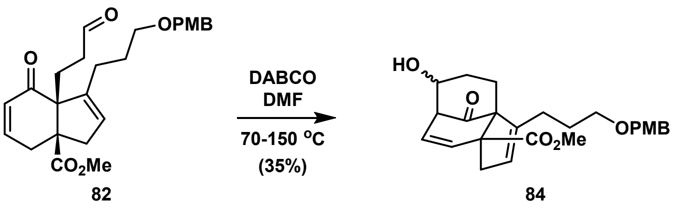
Alcohol **81**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added enone **80** (45.9 mg, 0.112 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (2.0 mL) was added, followed by 9-BBN (0.5 M solution in THF, 1.1 mL, 0.56 mmol, 5.0 equiv.). The reaction mixture was stirred at 23 ºC for 5 h, at which time TLC analysis showed the complete consumption of **80**. H_2O (1.0 mL) and $NaBO_3 \cdot H_2O$ (112 mg, 1.12 mmol, 10.0 equiv) were added sequentially, and the reaction mixture was stirred vigorously for 18 h. The reaction contents were diluted with H_2O (10 mL) and EtOAc (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 1/1→1/2) gave alcohol **81** (34.8 mg, 72% yield) as a colorless oil. **81**: diagnostic peaks on ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.2 Hz, 2H, aromatic), 6.88 (m, *J* = 8.3 Hz, 3H, aromatic and enone-β), 6.19 (d, *J* = 10.3 Hz, 1H, enone α), 5.55 (m, 1H, alkene), 4.41 (s, 2H, benzyl), 3.80 (s, 3H, ester), 3.67 (s, 3H, OMe.



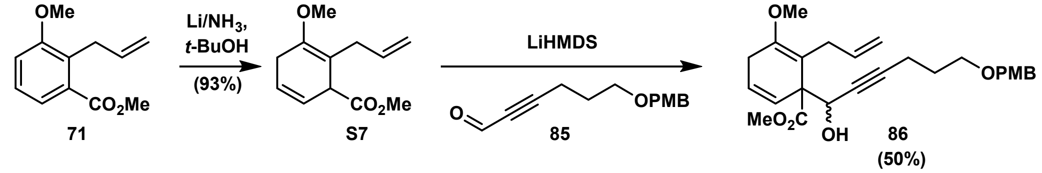
81 **82**

Aldehyde **82**: to a 25 mL vial charged with alcohol **81** (34.8 mg, 0.081 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (2.0 mL), pyridine (32 mg, 0.41 mmol, 5.0 equiv), and Dess-Martin periodinane (86 mg, 0.203 mmol, 2.5 equiv). The reaction mixture was stirred at 23 ºC for 2 h, at which time TLC analysis showed the complete consumption of **81**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried

(Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave aldehyde **82** (19.5 mg, 56% yield) as a yellow oil. **82**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 – 9.63 (m, 1H), 7.25 (d, *J* = 9.1 Hz, 2H), 6.91 – 6.83 (m, 3H), 6.20 – 6.14 (m, 1H), 5.61 – 5.57 (m, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.93 (dd, *J* = 16.5, 2.5 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.58 – 2.44 (m, 2H), 2.32 (ddd, *J* = 16.4, 11.1, 5.5 Hz, 1H), 2.25 (dd, *J* = 16.5, 2.3 Hz, 1H), 2.21 – 2.13 (m, 1H), 2.12 – 2.05 (m, 1H), 2.00 – 1.95 (m, 1H), 1.91 (ddd, *J* = 15.1, 10.9, 4.8 Hz, 1H), 1.72 (apparent p, *J* = 7.0 Hz, 2H).

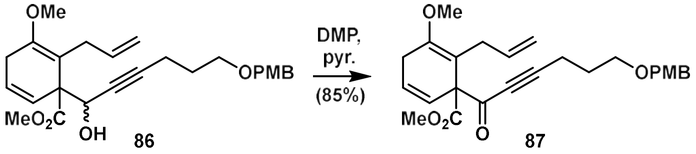


Alcohol **84**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added aldehyde **82** (9.1 mg, 0.021 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (1.0 mL) was added, followed by 1,4-diazabicyclo[2.2.2]octane (1.2 mg, 0.50 equiv). The reaction mixture was heated to 70 °C and stirred at that temperature for 2 h, at which time TLC analysis showed the complete consumption of **82**. The reaction was further heated to 150 °C and stirred at that temperature for 48 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (10 mL). The reaction contents were transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave alcohol **84** (3.2 mg, 35% yield) as a colorless yellow oil. **84**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.14 (d, *J* = 9.8 Hz, 1H), 5.80 (dd, *J* = 9.7, 6.5 Hz, 1H), 5.58 – 5.54 (m, 1H), 4.44 (d, *J* = 2.4 Hz, 2H), 4.35 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.58 – 3.44 (m, 2H), 2.91 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.65 (d, *J* = 15.9 Hz, 1H), 2.38 – 2.33 (m, 2H), 2.24 – 2.10 (m, 2H), 2.01 (d, *J* = 9.2 Hz, 2H), 1.89 – 1.80 (m, 3H).



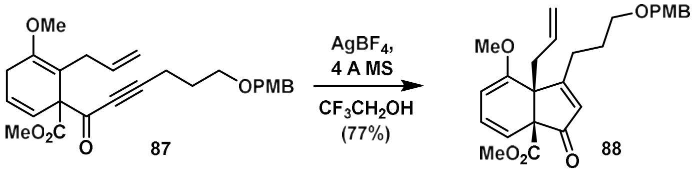
Triene **S7** was synthesized following the procedure described from **72** to **74**, omitting the addition of alkyl iodide. Starting from alkene **71** (2.08 g), giving triene **S7** (1.94 g, 93% yield) as a colorless oil.

Alcohol **86**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added triene **S7** (27.5 mg, 0.132 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (1.5 mL) was added. The reaction flask was cooled to 0 ºC, and purged with argon for 5 minutes. LiHMDS (1.0 M solution in THF, 0.15 mL, 0.15 mmol, 1.1 equiv) was added, and the reaction mixture was stirred at 0 ºC for 30 min. A solution of aldehyde **85** (37.0 mg, 0.159 mmol, 1.2 equiv) in anhydrous THF (1.0 mL) was added to the reaction mixture, which was stirred for another 30 min at 0 ºC. At this time, TLC analysis showed the complete consumption of **S7**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave alcohol **86** (29.1 mg, 50% yield, 3:1 *dr.*) as a colorless oil. **86**: diagnostic peaks on ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H, aromatic), 6.87 (d, *J* = 8.6 Hz, 2H, aromatic), 6.09 – 6.00 (m, 1H, alkene), 5.92 – 5.82 (m, 1H, alkene), 5.79 – 5.65 (m, 1H, allyl, internal), 5.05 – 4.84 (m, 2H, allyl, terminal), 4.42 (m, 2H, benzyl), 3.80 (s, 3H, ester), 3.65 (s, 3H), 3.56 (s, 3H).

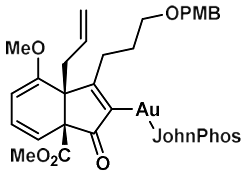


Ketone **87**: to a 25 mL vial charged with alcohol **86** (14.9 mg, 0.034 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (1.0 mL), pyridine (8.0 mg, 0.102 mmol, 3.0 equiv), and Dess-Martin periodinane (22 mg, 0.051 mmol, 1.5 equiv). The reaction mixture was stirred at 23 ºC for 2 h, at which time TLC analysis showed the complete consumption of **86**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave ketone **87** (12.5 mg, 85% yield) as a colorless oil. **87**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.00 (dt, *J* = 9.9, 3.6 Hz, 1H), 5.83 (dt, *J* = 9.9, 2.2 Hz, 1H), 5.74 (ddt, *J* = 16.5, 10.1, 6.1 Hz, 1H), 4.94 – 4.83 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 3.60 (s, 3H), 3.50 (t, *J* =

6.0 Hz, 2H), 3.09 (dd, *J* = 15.5, 5.8 Hz, 1H), 2.97 (dt, *J* = 22.0, 1.7 Hz, 1H), 2.90 (dt, *J* = 22.3, 2.1 Hz, 1H), 2.82 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.47 (apparent t, *J* = 7.1 Hz, 2H), 1.82 (apparent p, *J* = 6.6 Hz, 2H).

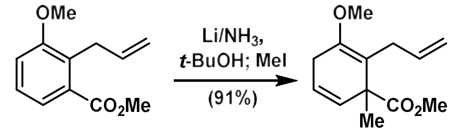


Enol ether **88**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added molecular sieves (4 Å, powdered, 14 mg, 200 wt%). The flask was flame-dried under vacuum, cooled to 23 ºC, and backfilled with argon. A solution of ketone **87** (6.9 mg, 0.016 mmol, 1.0 equiv) in CF_3CH_2OH (1.0 mL) was transferred to the reaction flask via syringe. The resultant mixture was stirred for 5 minutes before $AgBF_4$ (0.6 mg, 0.0031 mmol, 20 mol%) was added in one portion. The reaction mixture was stirred for 30 minutes, at which time TLC analysis showed the complete consumption of **87**. The reaction mixture was diluted with hexanes (2 mL), and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) to give enol ether **88** (5.3 mg, 77% yield) as a brown oil. **88**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.16 (t, *J* = 1.5 Hz, 1H), 5.94 (dd, *J* = 9.5, 6.5 Hz, 1H), 5.56 (dddd, *J* = 16.3, 10.6, 7.9, 5.3 Hz, 1H), 5.46 (d, *J* = 9.6 Hz, 1H), 5.30 (s, 1H), 5.11 (d, *J* = 6.6 Hz, 1H), 4.99 (dt, *J* = 3.3, 1.3 Hz, 1H), 4.98 – 4.93 (m, 1H), 4.44 (s, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H), 3.49 (t, *J* = 6.2 Hz, 2H), 3.08 – 2.99 (m, 1H), 2.63 – 2.56 (m, 2H), 2.42 (dd, *J* = 15.1, 8.0 Hz, 1H), 1.85 (apparent p, *J* = 6.1 Hz, 2H).



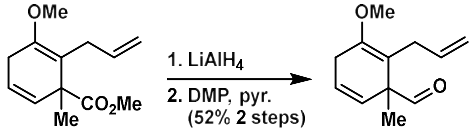
89

Gold-complex **89** was obtained as the only product, starting from ketone **87**, following the procedure described from **74** to **75**. **89**: ^{1}H NMR (500 MHz, CDCl3) δ 7.90 – 7.83 (m, 1H), 7.49 – 7.39 (m, 2H), 7.27 – 7.19 (m, 5H), 7.16 – 7.06 (m, 3H), 6.85 (d, J = 8.6 Hz, 2H), 5.91 (dd, J = 9.5, 6.5 Hz, 1H), 5.63 – 5.52 (m, 1H), 5.44 (d, J = 9.6 Hz, 1H), 5.09 (d, J = 6.5 Hz, 1H), 5.00 – 4.91 (m, 2H), 4.38 (s, 2H), 3.79 (s, 3H), 3.63 (s, 3H), 3.57 (s, 3H), 3.36 (t, J = 6.7 Hz, 2H), 3.19 – 3.07 (m, 1H), 2.42 – 2.28 (m, 3H), 1.92 – 1.80 (m, 1H), 1.71 (td, J = 11.9, 5.8 Hz, 1H), 1.38 (dd, J = 14.5, 3.4 Hz, 18H). HRMS: calcd for $C_{46}H_{56}AuO_6P^+$ $[M + H]^+$ 933.3553, found 933.3581.



71 **90**

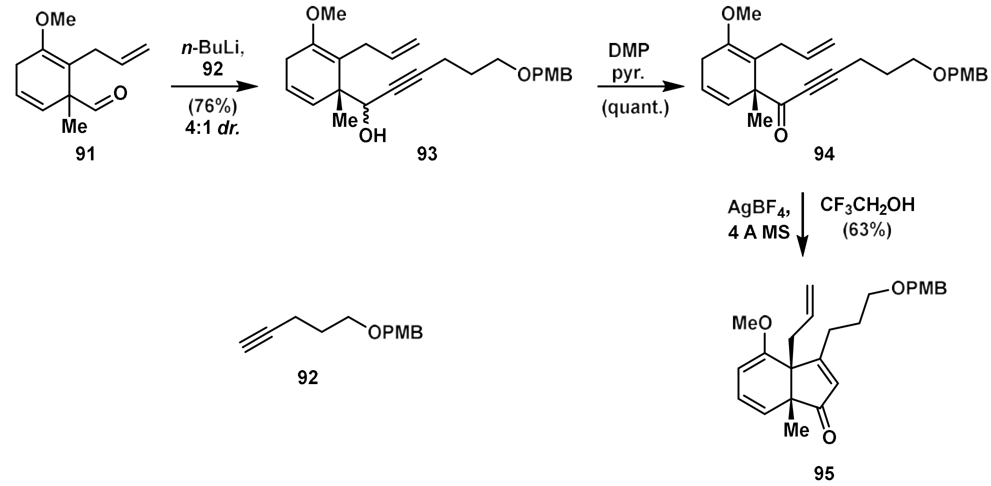
Triene **90** was synthesized following the procedure described from **72** to **74**, substituting the addition of propargyl iodide **73** into iodomethane. **90**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 – 7.83 (m, 1H), 7.49 – 7.39 (m, 2H), 7.27 – 7.19 (m, 5H), 7.16 – 7.06 (m, 3H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.91 (dd, *J* = 9.5, 6.5 Hz, 1H), 5.63 – 5.52 (m, 1H), 5.44 (d, *J* = 9.6 Hz, 1H), 5.09 (d, *J* = 6.5 Hz, 1H), 5.00 – 4.91 (m, 2H), 4.38 (s, 2H), 3.79 (s, 3H), 3.63 (s, 3H), 3.57 (s, 3H), 3.36 (t, *J* = 6.7 Hz, 2H), 3.19 – 3.07 (m, 1H), 2.42 – 2.28 (m, 3H), 1.92 – 1.80 (m, 1H), 1.71 (td, *J* = 11.9, 5.8 Hz, 1H), 1.38 (dd, *J* = 14.5, 3.4 Hz, 18H).



90 **91**

Aldehyde **91**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added propargyl triene **90** (44.8 mg, 0.202 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (2.0 mL) was added. The reaction flask was cooled to 0 ºC before $LiAlH_4$ (1.0 M in THF, 0.20 mL, 0.20 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 ºC for 30 min, at which time TLC analysis showed the complete consumption of **90**. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (10 mL). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude primary alcohol was transferred to a 25 mL vial for the next step without further purification. A magnetic stir bar, CH_2Cl_2 (4.0 mL), pyridine (43 mg, 0.552 mmol, 2.8 equiv), and Dess-Martin periodinane (117 mg, 0.278 mmol, 1.4 equiv) was added to the vial. The reaction mixture was stirred at 23 ºC for 2 h, at which time TLC analysis showed the complete consumption of the primary alcohol. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave aldehyde **91** (20.0 mg, 52%

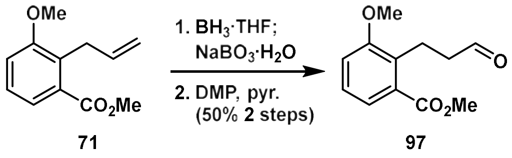
yield) as a colorless oil. **91**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 5.95 (dt, *J* = 9.8, 3.5 Hz, 1H), 5.73 (ddt, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.21 (dt, *J* = 9.8, 2.1 Hz, 1H), 4.99 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.94 (dq, *J* = 10.0, 1.6 Hz, 1H), 3.61 (s, 3H), 2.99 – 2.94 (m, 2H), 2.89 – 2.80 (m, 1H), 2.66 (dd, *J* = 15.0, 6.2 Hz, 1H), 1.25 (s, 3H).



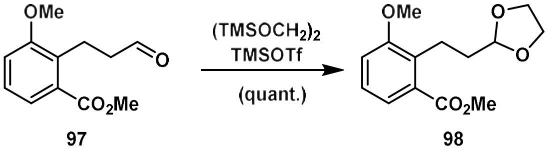
Alcohol **93**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added alkyne **92** (458 mg, 2.24 mmol, 1.4 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (20 mL) was added, and the reaction flask was cooled to 0 ºC. *n*-BuLi (2.5 M in hexanes, 0.84 mL, 2.08 mmol, 1.3 equiv) was added dropwise, and the reaction mixture was stirred at 0 ºC for 30 min. A solution of aldehyde **91** (307 mg, 1.60 mmol, 1.0 equiv) in anhydrous THF (3.0 mL) was added to the reaction mixture via syringe. The reaction mixture was continued stirred for another 30 min, at which time TLC analysis showed the complete consumption of aldehyde **91**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6/1→2/1) gave alcohol **93** (481 mg, 76% yield, 4:1 *dr.*) as a colorless oil.

Ketone **94**: to a 25 mL vial charged with alcohol **93** (481 mg, 1.21 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (10 mL), pyridine (284 mg, 3.64 mmol, 3.0 equiv), and Dess-Martin periodinane (772 mg, 1.82 mmol, 1.5 equiv). The reaction mixture was stirred at 23 °C for 2 h, at which time TLC analysis showed the complete consumption of **93**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) gave ketone **94** (482 mg, 100% yield) as a colorless oil.

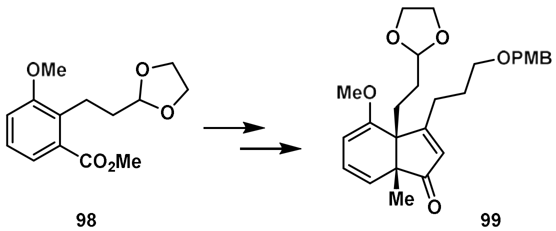
Enol ether **95** was synthesized following the procedure described from **87** to **88**. Starting from ketone **94** (482 mg, 1.21 mmol), to give enol ether **95** (305 mg, 63% yield) as a yellow oil. **95**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.10 (d, *J* = 1.6 Hz, 1H), 5.73 (dd, *J* = 9.4, 6.5 Hz, 1H), 5.52 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.08 (d, *J* = 6.4 Hz, 1H), 5.06 – 4.93 (m, 3H), 4.42 (s, 2H), 3.81 (s, 3H), 3.60 (s, 3H), 2.67 – 2.60 (m, 2H), 2.44 (ddt, *J* = 8.2, 5.7, 1.9 Hz, 2H), 1.81 (apparent p, *J* = 6.4 Hz, 2H), 1.17 (s, 3H).



Aldehyde **97**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added alkene **71** (105 mg, 0.509 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous THF (5.0 mL) was added, and the reaction mixture was cooled to 0 ºC, before BH_3·THF (1.0 M solution in THF, 0.26 mL, 0.26 mmol, 0.50 equiv) was added. The reaction mixture was stirred at 0 ºC for 1.5 h, at which time TLC analysis showed the complete consumption of **71**. H_2O (2.5 mL) and $NaBO_3 \cdot H_2O$ (102 mg, 1.02 mmol, 2.0 equiv) were added sequentially, and the reaction mixture was stirred vigorously for 2 h. The reaction contents were diluted with saturated aqueous $Na_2S_2O_3$ (10 mL) and EtOAc (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude primary alcohol product was transferred to a 25 mL vial for the next step without further purification. A magnetic stir bar, CH_2Cl_2 (5.0 mL), pyridine (119 mg, 1.53 mmol, 3.0 equiv), and Dess-Martin periodinane (324 mg, 0.764 mmol, 1.5 equiv) was added to the vial. The reaction mixture was stirred at 23 ºC for 2 h, at which time TLC analysis showed the complete consumption of the primary alcohol. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) gave aldehyde **97** (56.1 mg, 50% yield over 2 steps) as a colorless oil. **97**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.82 (t, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.23 (t, *J* = 7.6 Hz, 2H), 2.76 – 2.69 (m, 2H).

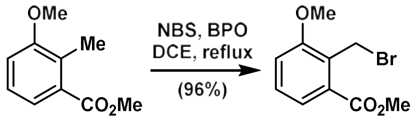


Acetal **98**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added aldehyde **97** (56.1 mg, 0.252 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous CH$_2$Cl$_2$ (3.0 mL) was added, and the reaction mixture was cooled to -78 ºC before 1,2-Bis(trimethylsiloxy)ethane (78 mg, 0.38 mmol, 1.5 equiv) and TMSOTf (11 mg, 0.050 mmol, 0.20 equiv) were sequentially added. The reaction mixture was stirred at -78 ºC for 1 h, at which time TLC analysis showed the complete consumption of **97**. The reaction was then quenched by the addition of saturated aqueous NaHCO$_3$ (5 mL). The reaction contents were diluted with CH$_2$Cl$_2$ (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ and brine, dried (Na$_2$SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) gave acetal **98** (67.3 mg, 100% yield) as a colorless oil. **98**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 4.94 (t, *J* = 4.8 Hz, 1H), 4.04 – 3.95 (m, 2H), 3.89 (s, 3H), 3.88 – 3.85 (m, 2H), 3.85 (s, 3H), 3.06 – 2.99 (m, 2H), 1.97 – 1.89 (m, 2H).



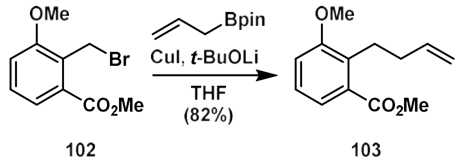
98 **99**

Enol ether **99** was synthesized following the 6-step procedure described from **71** to **95**. **99** (17.0 mg, 28% yield over 6 steps) was obtained as a colorless oil. **99**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.25 (d, *J* = 9.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.10 (s, 1H), 5.73 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.07 (d, *J* = 2.9 Hz, 1H), 5.05 (s, 1H), 4.80 (t, *J* = 4.6 Hz, 1H), 4.42 (s, 2H), 4.03 – 3.81 (m, 4H), 3.81 (s, 3H), 3.58 (s, 3H), 3.46 (t, *J* = 6.4 Hz, 2H), 2.52 – 2.45 (m, 2H), 1.98 – 1.89 (m, 2H), 1.87 – 1.77 (m, 2H), 1.54 – 1.46 (m, 2H), 1.18 (s, 3H).

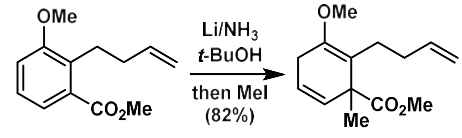


72 **102**

Bromide **102**: to a 1000 mL two-neck flask equipped with a magnetic stir bar was added ester **72** (18.6 g, 103 mmol, 1.0 equiv), benzoyl peroxide (1.3 g, 5.17 mmol, 0.05 equiv) and 1,2-dichloroethane (300 mL). The flask was adapted with a reflux condenser. The system was purged with nitrogen, before being heated to 80 ºC. N-Bromosuccinimide (20.3 g, 113.8 mmol, 1.1 equiv) was added portion-wise under a positive flow of nitrogen while maintaining the system mildly refluxing. After the completion of addition, the reaction was stirred at 80 ºC for 5 h. Upon cooling to 23 ºC, the reaction was quenched by the addition of saturated aqueous NaHCO$_3$ (100 mL). The reaction contents were diluted with CH$_2$Cl$_2$ (100 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated to give bromide **102** (25.7 g, 96%) as a pale yellow crystalline solid. Recrystallization can be performed in CH_2Cl_2/hexanes to reach a higher purity but is not required for the next step.



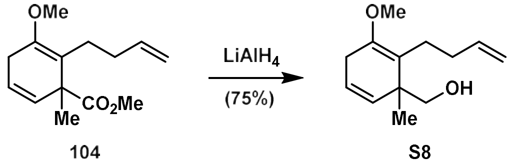
Alkene **103**: to a 1000 mL two-neck flask equipped with a magnetic stir bar under argon atmosphere was added bromide **102** (9.74 g, 33.7 mmol, 1.0 equiv). CuI (0.64 g, 0.34 mmol, 0.10 equiv) and lithium *tert*-butoxide (5.40 g, 67.4 mmol, 2.0 equiv) were weighed out from a nitrogen-filled glove box and added to the reaction flask. The flask was then degassed and backfilled with argon three times, before allylboronic acid pinacol ester (11.4 g, 67,4 mmol, 2.0 equiv) and anhydrous THF (350 mL) were added. The reaction was stirred at 23 °C for 12 h, at which time TLC analysis showed the complete consumption of bromide **102**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (100 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 6/1→2/1) gave alkene **103** (5.67 g, 82% yield) as a colorless oil. **103**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 8.1 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.04 – 6.95 (m, 1H), 5.98 – 5.85 (m, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 3.88 (s, 3H), 3.85 (d, *J* = 2.6 Hz, 3H), 3.02 – 2.97 (m, 2H), 2.30 (d, *J* = 7.8 Hz, 2H), 1.54 (s, 3H).



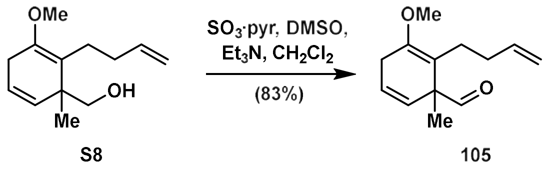
103

104

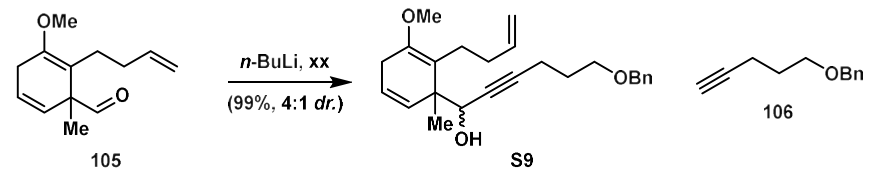
Triene **104**: to a 500 mL 2-neck flask equipped with a magnetic stir bar was adapted a Dewar condenser. The system was purged by dry nitrogen for 5 minutes, before being sealed and adapted with a nitrogen balloon. A solution of alkene **103** (5.67 g, 27.5 mmol, 1.0 equiv) and *t*-BuOH (2.24 g, 30.2 mmol, 1.1 equiv) in anhydrous THF (50 mL) was transferred to the reaction flask via syringe. The reaction flask was then cooled to –78 ºC by a dry-ice/acetone bath, and the Dewar condenser was also filled with dry ice and acetone. Ammonia gas was then carefully passed into the system from the top of the Dewar condenser until approximately 10 mL of liquid ammonia was collected. Lithium wire that was cut into small pieces and rinsed with hexanes was added to the reaction mixture under vigorous stirring. The reaction solution turned dark blue upon the lithium metal dissolved and immediately turned bright yellow upon diffusion. Lithium metal was kept added piecewise until the blue color of the reaction solution persisted for 30 minutes. Approximately 2-3 equivalents of lithium metal is typically needed. 2,3-dimethyl-1,3-butadiene was then added dropwise until the reaction solution turned bright yellow, to quench the excess solvated electron. Iodomethane (2.1 mL, 4.7 g, 33 mmol, 1.2 equiv) was then added dropwise. The reaction mixture turned colorless or light yellow and was stirred for another 30 minutes. The reaction was then quenched by the addition of solid NH_4Cl (approximately 5 g) and $Na_2S_2O_3 \cdot 5H_2O$ (approximately 1 g). The Dewar condenser and the cooling bath were removed, allowing the ammonia to slowly evaporate overnight. The resultant solid mixture was picked up by H_2O (100 mL) and EtOAc (100 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was then extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give triene **104** (4.99 g, 82% yield) as a colorless oil, which was used in the next step without further purification.



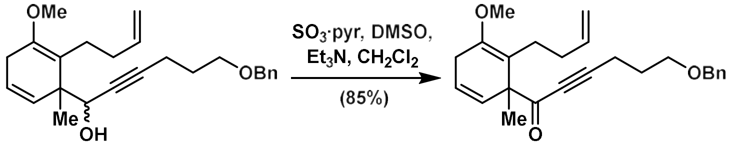
Alcohol **S8**: to a 1000 mL round bottom flask equipped with a magnetic stir bar was added triene **104** (4.99 g, 22.5 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (250 mL) was added. The reaction flask was cooled to 0 ºC before $LiAlH_4$ (0.86 g, 22.5 mmol, 1.0 equiv) was added in one portion. The reaction mixture was stirred at 0 ºC for 30 min, at which time TLC analysis showed the complete consumption of **104**. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (100 mL). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (100 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6/1→2/1) gave alcohol **S8** (3.51 g, 75% yield) as a colorless oil. **S8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.79 (m, 1H), 5.78 – 5.74 (m, 1H), 5.55 – 5.48 (m, 1H), 4.99 (d, *J* = 17.1 Hz, 1H), 4.92 (d, *J* = 10.3 Hz, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 2.91 (d, *J* = 21.7 Hz, 1H), 2.84 (d, *J* = 19.5 Hz, 1H), 2.24 – 2.06 (m, 3H), 1.97 (d, *J* = 14.1 Hz, 1H), 1.36 (s, 3H).



Aldehyde **105**: to a 250 mL round bottom flask equipped with a magnetic stir bar was added alcohol **S8** (3.51 g, 16.9 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous CH_2Cl_2 (160 mL), anhydrous DMSO (40 mL, 25V%), and anhydrous triethylamine (12.3 mL, 8.6 g, 84.5 mmol, 5.0 equiv) were sequentially added. The reaction flask was cooled to 0 ºC before sulfur trioxide pyridine complex (10.8 g, 67.6 mmol, 4.0 equiv) was added in one portion. The reaction mixture was allowed to warm up to 23 ºC and stirred at that temperature for 4 h, at which time TLC analysis showed the complete consumption of **S8**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→6/1) gave aldehyde **105** (2.92 g, 83% yield) as a colorless oil. **105**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 5.95 (dt, *J* = 9.8, 3.6 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.21 (dt, *J* = 9.8, 2.1 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.61 (s, 3H), 2.95 (ddt, *J* = 3.4, 2.1, 1.0 Hz, 2H), 2.23 – 2.07 (m, 2H), 2.05 – 1.97 (m, 1H), 1.94 – 1.84 (m, 1H), 1.26 (s, 3H).

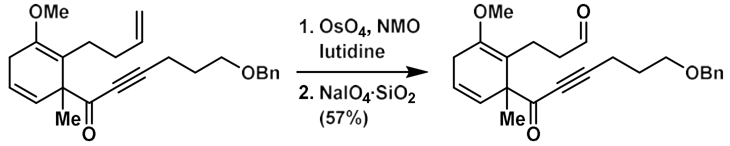


Alcohol **S9**: to a 250 mL round bottom flask equipped with a magnetic stir bar was added alkyne **106** (3.45 g, 19.8 mmol, 1.4 equiv, containing ~10% benzyl methyl ether). The flask was degassed and backfilled with argon. Anhydrous THF (140 mL) was added, and the reaction flask was cooled to 0 °C. *n*-BuLi (2.5 M in hexanes, 6.8 mL, 17.0 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min. A solution of aldehyde **105** (2.92 g, 14.2 mmol, 1.0 equiv) in anhydrous THF (20 mL) was added to the reaction mixture via syringe. The reaction mixture was continued stirred for another 30 min, at which time TLC analysis showed the complete consumption of aldehyde **105**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 6/1→2/1) gave alcohol **S9** (5.31 g, 99% yield, 4:1 *dr.*) as a colorless oil. **S9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.96 – 5.82 (m, 1H), 5.80 (dt, *J* = 10.0, 3.5 Hz, 1H), 5.50 (dt, *J* = 9.9, 2.1 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.93 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.50 (s, 2H), 4.22 – 4.16 (m, 1H), 3.54 (s, 3H), 3.52 (t, *J* = 6.1 Hz, 2H), 2.87 – 2.78 (m, 2H), 2.30 (td, *J* = 7.1, 2.1 Hz, 2H), 1.80 – 1.74 (m, 2H), 1.24 (s, 3H).



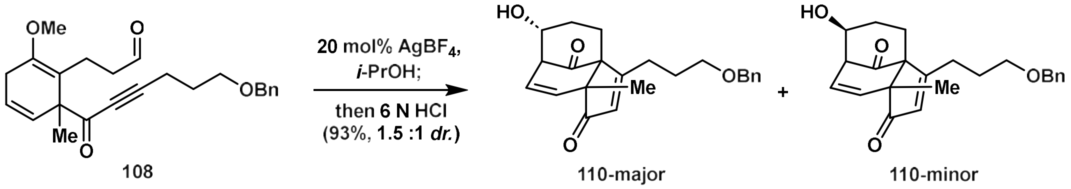
S9 **107**

Ketone **107** was synthesized following the procedure described from **S8** to **105**, except by stirring the reaction mixture for 18 h. Starting from alcohol **S9** (5.31 g, 14.0 mmol), giving ketone **107** (4.53 g, 85% yield) as a colorless oil. **107**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 – 7.27 (m, 5H), 5.87 – 5.77 (m, 2H), 5.32 (dt, *J* = 9.8, 2.1 Hz, 1H), 4.98 (dq, *J* = 17.2, 1.6 Hz, 1H), 4.94 – 4.89 (m, 1H), 4.50 (s, 2H), 3.57 (s, 3H), 3.53 (t, *J* = 6.1 Hz, 2H), 2.90 (td, *J* = 4.0, 2.0 Hz, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.29 (s, 3H).

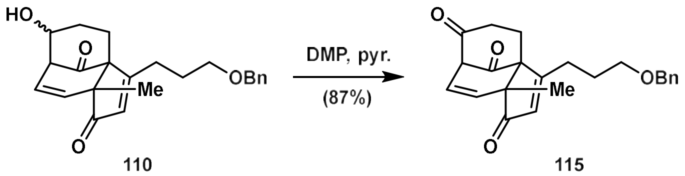


107 **108**

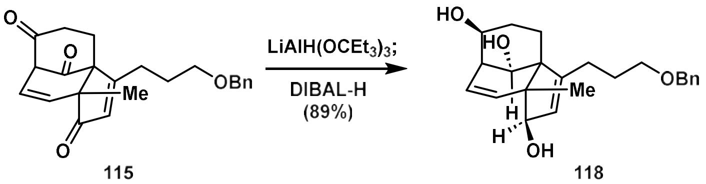
Aldehyde **108**: to a 250 mL round bottom flask equipped with a magnetic stir bar was added ketone **107** (4.53 g, 12.0 mmol, 1.0 equiv), 1,4-dioxane (120 mL), H$_2$O (12 mL, 10 V%), *N*-Methylmorpholine *N*-oxide (1.82 g, 15.6 mmol, 1.3 equiv) and 2,6-lutidine (3.85 g, 35.9 mmol, 3.0 equiv). OsO$_4$ (4% in H$_2$O, 1.6 mL, 0.24 mmol, 2 mol%) was added dropwise to the reaction mixture under stirring. The reaction mixture was stirred at 23 °C for 16 h, at which time TLC analysis showed the complete consumption of ketone **107**. The reaction was then quenched by the addition of saturated aqueous NaHCO$_3$ (50 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (50 mL). The reaction contents were diluted with EtOAc (100 mL) and H$_2$O, transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. The residue was transferred to a 250 mL round bottom flask, a magnetic stir bar, and CH_2Cl_2 (120 mL) was added. $NaIO_4$ on silica (prepared by the procedure described in ref.30b, 0.68 mmol/g, 52.4 g, 35.9 mmol, 3.0 equiv) was added to the reaction under stirring, and the resultant suspension was stirred at 23 °C for 30 min. The magnetic stir bar was then extracted, and the reaction mixture was concentrated under reduced pressure until a total volume of ~20 mL is left. The residue was diluted with hexanes (20 mL), and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) to give aldehyde **108** (2.61 g, 57% yield) as a light brown oil. **108**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (t, *J* = 1.8 Hz, 1H), 7.42 – 7.27 (m, 5H), 5.83 (dt, *J* = 9.8, 3.6 Hz, 1H), 5.35 (dt, *J* = 9.8, 2.1 Hz, 1H), 4.50 (s, 2H), 3.55 (s, 3H), 3.53 (t, *J* = 6.1 Hz, 2H), 2.92 – 2.87 (m, 2H), 2.52 – 2.39 (m, 5H), 2.12 – 2.03 (m, 1H), 1.83 (apparent p, *J* = 6.7 Hz, 2H), 1.28 (s, 3H).



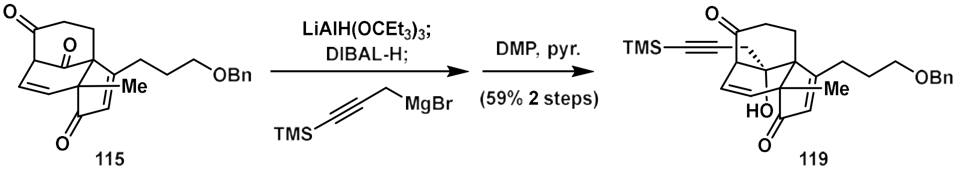
Tricyclic alcohol **110**: to a 250 mL round bottom flask equipped with a magnetic stir bar was added aldehyde **108** (2.61 g, 6.86 mmol, 1.0 equiv). The flask was degassed and backfilled with argon before anhydrous isopropanol (70 mL) was added. $AgBF_4$ (212 mg, 1.37 mmol, 0.20 equiv) was added in one portion, and the reaction mixture was stirred at 23 °C for 2 h. At this time, TLC analysis showed the complete consumption of aldehyde **108**. 6 N HCl (14 mL, 20 V%) was added, resulting in a white suspension, which was stirred at 23 °C for 18 h. The reaction contents were then diluted with EtOAc (50 mL) and H_2O (50 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$ (which will remove any AgCl precipitate), and brine; dried (Na_2SO4); filtered; and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/4) gave alcohol **110** (2.44 g, 93% yield, 1.5:1 *dr.*) as a colorless oil. **110** (major isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.01 (d, *J* = 9.7 Hz, 1H), 5.95 (t, *J* = 1.7 Hz, 1H), 5.76 (dd, *J* = 9.7, 6.3 Hz, 1H), 4.52 (apparent d, *J* = 3.0 Hz, 2H), 4.40 – 4.35 (m, 1H), 3.65 – 3.48 (m, 2H), 2.92 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.68 – 2.49 (m, 2H), 2.49 – 2.34 (m, 1H), 2.20 (tdd, *J* = 14.2, 4.5, 3.0 Hz, 1H), 2.07 – 1.88 (m, 4H), 1.86 – 1.76 (m, 1H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.25, 205.67, 178.99, 138.43, 134.13, 128.56, 127.90, 127.80, 126.69, 125.26, 74.18, 73.25, 69.60, 64.19, 60.77, 56.25, 27.73, 27.09, 25.81, 25.78, 23.24. HRMS: calcd for $C_{23}H_{27}O_4^+$ $[M + H]^+$, 367.1904, found 367.1902. **110** (Minor isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.13 (d, *J* = 9.8 Hz, 1H), 5.95 (t, *J* = 1.7 Hz, 1H), 5.78 (dd, *J* = 9.8, 6.1 Hz, 1H), 4.51 (apparent d, *J* = 3.2 Hz, 2H), 4.06 (dq, *J* = 10.5, 5.3 Hz, 1H), 3.64 – 3.47 (m, 2H), 3.25 (t, *J* = 5.4 Hz, 1H), 2.52 (dddd, *J* = 17.7, 9.9, 6.0, 1.8 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.10 – 1.75 (m, 7H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.43, 205.54, 178.35, 138.41, 134.50, 128.58, 127.89, 127.84, 126.96, 123.74, 73.25, 73.20, 69.50, 62.83, 60.89, 56.06, 27.79, 27.47, 27.07, 24.64, 23.65. HRMS: calcd for $C_{23}H_{27}O_4^+$ $[M + H]^+$, 367.1904, found 367.1903.



Triketone **115**: to a 25 mL vial charged with alcohol **110** (71.4 mg, 0.188 mmol, 1.0 equiv) was added a magnetic stir bar, CH_2Cl_2 (3 mL), pyridine (44 mg, 0.56 mmol, 3.0 equiv), and Dess-Martin periodinane (120 mg, 0.282 mmol, 1.5 equiv). The reaction mixture was stirred at 23 °C for 2 h, at which time TLC analysis showed the complete consumption of **110**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave triketone **115** (61.7 mg, 87% yield) as a colorless oil. **115**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 6.08 (d, J = 9.3 Hz, 1H), 6.04 (t, J = 1.7 Hz, 1H), 5.82 (dd, J = 9.3, 6.9 Hz, 1H), 4.52 (apparent d, J = 4.3 Hz, 2H), 3.81 (dd, J = 7.0, 1.4 Hz, 1H), 3.61 (dt, J = 9.3, 5.6 Hz, 1H), 3.53 (ddd, J = 9.3, 7.4, 5.4 Hz, 1H), 3.06 (ddd, J = 16.6, 14.1, 7.4 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.45 – 2.34 (m, 1H), 2.20 (ddd, J = 14.1, 7.4, 1.7 Hz, 1H), 2.09 (td, J = 14.1, 5.4 Hz, 1H), 2.03 – 1.89 (m, 2H), 1.41 (s, 3H).

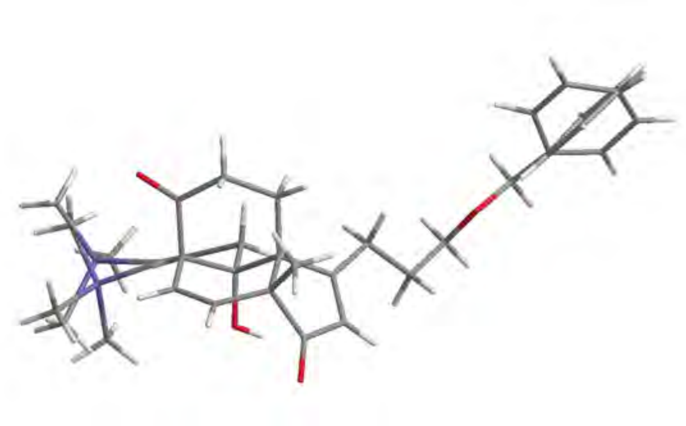


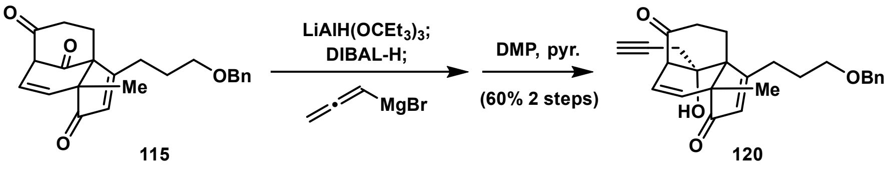
Triol **118**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added triketone **115** (8.9 mg, 0.024 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (1.0 mL) was added. The reaction flask was cooled to 0 ºC before $LiAlH(OCEt_3)_3$ (0.5 M in THF, 0.05 mL, 0.05 mmol, 2.1 equiv) was added dropwise. The reaction mixture was stirred at 0 ºC for 30 min, at which time TLC analysis showed the complete consumption of **115**. DIBAL-H (1.0 M in toluene, 0.09 mL, 0.09 mmol, 3.7 equiv) was then added dropwise, and the reaction was stirred at 0 ºC for another 30 min. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (3 mL). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 1/1→1/4) gave triol **118** (8.0 mg, 89% yield) as a colorless oil. **118**: diagnostic peaks on ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 5H, aromatic), 5.98 (d, *J* = 9.9 Hz, 1H, C-1 alkene), 5.65 (dd, *J* = 9.9, 6.3 Hz, 1H, C-2 alkene), 5.34 – 5.28 (m, 1H, C-13 alkene), 4.64 (s, 1H, C-12), 4.49 (s, 2H, benzyl), 4.19 (dt, *J* = 10.5, 5.0 Hz, 1H, C-7), 3.92 – 3.87 (m, 1H, C-5), 3.61 – 3.43 (m, 2H, CH_2OBn), 0.98 (s, 3H, Me).



Alkyne **119**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added triketone **115** (69.0 mg, 0.182 mmol, 1.0 equiv). The flask was degassed and backfilled with argon, and anhydrous THF (3.0 mL) was added. The reaction flask was cooled to 0 ºC before $LiAlH(OCEt_3)_3$ (0.5 M in THF, 0.44 mL, 0.22 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at 0 ºC for 30 min, at which time TLC analysis showed the complete consumption of **115**. DIBAL-H (1.0 M in toluene, 0.22 mL, 0.22 mmol, 1.2 equiv) was then added dropwise, and the reaction was stirred at 0 ºC for another 30 min. 3-trimethylsilyl-propargylmagnesium bromide (1.4 M in Et_2O, prepared freshly through the procedure described in the waihoensene synthesis, 0.39 mL, 0.55 mmol, 3.0 equiv) was then added, and the reaction was stirred at 0 ºC for another 30 min. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (5 mL) and NH_4Cl (5 mL). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude product was then transferred to a 25 mL vial for the next step without further purification. A magnetic stir bar, CH_2Cl_2 (3.0 mL), pyridine (142 mg, 1.82 mmol, 10 equiv), and Dess-Martin periodinane (386 mg, 0.91 mmol, 5.0 equiv) were added to the vial. The reaction mixture was stirred at 23 ºC for 2 h, at which time TLC analysis showed the complete consumption of the primary alcohol. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/2) gave alkyne **119** (51.0 mg, 59% yield over 2 steps) as a yellow crystalline solid. The structure was confirmed by single crystal XRD.

X-Ray structure of **119**:



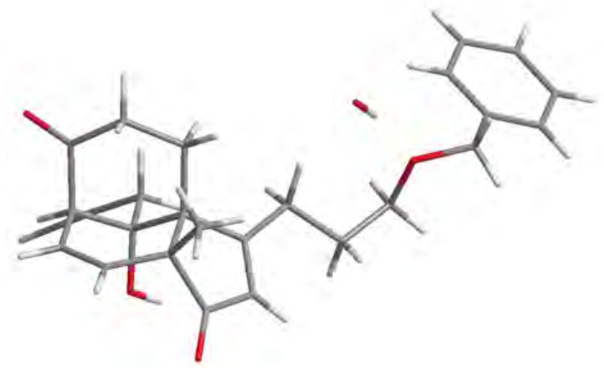


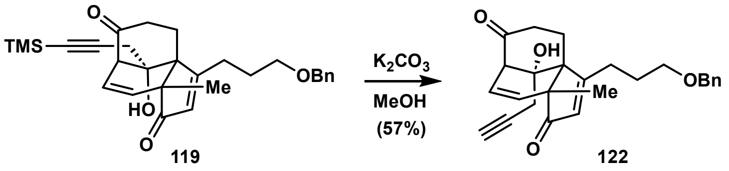
115

120

Alkyne **120** was synthesized following the procedure described from **115** to **119**, except using allenylmagnesium bromide instead of trimethylsilyl-propargylmagnesium bromide, giving alkyne **120** (60% yield) as a white crystalline solid. **120**: ^{1}H NMR (500 MHz, CDCl3) δ 7.40 – 7.28 (m, 5H), 6.27 (d, J = 9.6 Hz, 1H), 6.14 (d, J = 1.7 Hz, 1H), 5.67 (dd, J = 9.7, 6.5 Hz, 1H), 4.56 – 4.46 (m, 2H), 3.55 (ddd, J = 11.0, 9.4, 5.3 Hz, 3H), 2.75 (ddd, J = 15.8, 13.4, 8.0 Hz, 1H), 2.63 (dd, J = 16.6, 2.7 Hz, 1H), 2.56 – 2.45 (m, 2H), 2.45 – 2.34 (m, 1H), 2.29 (dd, J = 15.8, 5.9 Hz, 1H), 2.24 – 2.12 (m, 3H), 2.11 – 2.02 (m, 1H), 1.99 – 1.85 (m, 2H), 1.24 (s, 3H). The structure was confirmed by single crystal XRD.

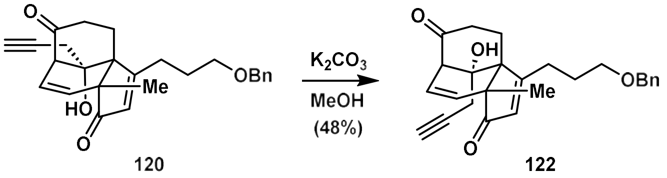
X-Ray structure of **120**:



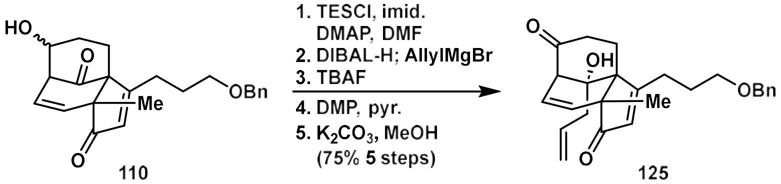


Alkyne **122**: To a 25 mL vial charged with alkyne **119** (40.9 mg, 0.0859 mmol, 1.0 equiv) was added a magnetic stir bar, methanol (2.0 mL), and K_2CO_3 (36 mg, 0.26 mmol, 3.0 equiv). The reaction mixture was heated to 50 ºC and was stirred vigorously at that temperature for 2 h, at which time TLC analysis showed the complete consumption of **119**. The reaction was cooled to 23 ºC, before being diluted with H_2O (5 mL) and EtOAc (5 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave alkyne **122** (19.8 mg, 57% yield) as a yellow oil. **122**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.12 (d, *J* = 9.7 Hz, 1H), 6.03 (t, *J* = 1.8 Hz, 1H), 5.68 (dd, *J* = 9.7, 7.0 Hz, 1H), 4.52 (apparent d, *J* = 1.9 Hz, 2H), 3.61 – 3.48 (m, 2H), 3.42 (d, *J* = 6.8 Hz, 1H), 2.82 (td, *J* = 13.0, 5.8 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.68 – 2.62 (m, 1H), 2.56

– 2.43 (m, 1H), 2.41 – 2.31 (m, 1H), 2.26 (dd, *J* = 16.6, 2.6 Hz, 1H), 2.13 (t, *J* = 2.7 Hz, 1H), 2.04 (dd, *J* = 16.6, 2.7 Hz, 1H), 1.95 – 1.83 (m, 3H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.62, 207.76, 180.21, 138.31, 134.75, 128.61, 127.90 (2C), 127.35, 123.01, 78.54, 77.31, 74.31, 73.34, 69.41, 59.09, 56.86, 55.67, 34.11, 28.26, 27.76, 27.34, 23.91, 23.75.



Alkyne **120** was transformed into **122** following the procedure described from **119** to **122**. Starting from **120** (9.9 mg, 0.025 mmol), giving **122** (4.8 mg, 48% yield) as a yellow oil.



Alkene **125**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added alcohol **110** (479 mg, 1.26 mmol, 1.0 equiv). The flask was degassed and backfilled with argon. Anhydrous DMF (7.0 mL), imidazole (344 mg, 5.04 mmol, 4.0 equiv), and DMAP (154 mg, 1.26 mmol, 1.0 equiv) were sequentially added. The reaction flask was cooled to 0 °C before TESCl (0.72 mL, 569 mg, 3.78 mmol, 3.0 equiv) was added in one portion. The reaction mixture was allowed to warm up to 23 °C and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **110**. The reaction was then quenched by the addition of methanol (1 mL) and was stirred at 23 °C for 1 h before saturated aqueous $NaHCO_3$ (10 mL) was added. The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. The resultant residue was filtered through a short silica column (hexanes/Et_2O, 2:1) to give TES-protected product (632 mg, 1.24 mmol, 98% yield) as a colorless oil, which was transferred to a 50 mL round bottom flask for the next step.

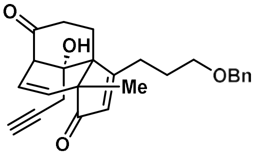
To the flask containing the TES-protected product (1.24 mmol) was added a magnetic stir bar. The flask was degassed and backfilled with argon before anhydrous THF (13 mL) was added. The reaction mixture was cooled to 0 °C, and DIBAL-H (1.0 M in toluene, 1.30 mL, 1.30 mmol, 1.05 equiv) was added dropwise. The reaction was stirred at 0 °C for 15 min, at which time TLC analysis showed only products with no UV absorptions. Allylmagnesium bromide (2.0 M in THF, 1.85 mL, 3.7 mmol, 3.0 equiv) was added dropwise, and the reaction mixture was continued stirred at 0 °C for 15 min. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (10 mL) and NH_4Cl (10 mL). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude product was then transferred to a 25 mL plastic vial for the next step without further purification.

To the 25 mL plastic vial containing the previous product was added a magnetic stir bar, THF (13 mL), and TBAF·$3H_2O$ (1.18 g, 3.72 mmol, 3.0 equiv). The reaction mixture was stirred at 23 °C for 16 h, and quenched by the addition of saturated aqueous NH_4Cl (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude product was then transferred to a 25 mL vial for the next step without further purification.

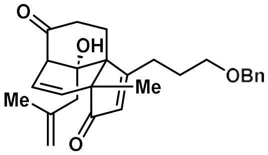
To the 25 mL vial containing the previous product was added a magnetic stir bar, CH_2Cl_2 (13 mL), pyridine (388 mg, 4.96 mmol, 4.0 equiv), and Dess-Martin periodinane (1.58 g, 3.72 mmol, 3.0 equiv). The reaction mixture was stirred at 23 °C for 2 h before being quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. The crude product was then transferred to a 25 mL plastic vial for the next step without further purification.

To the 25 mL vial containing the previous product was added a magnetic stir bar, methanol (13 mL), and K_2CO_3 (515 mg, 3.72 mmol, 3.0 equiv). The reaction mixture was heated to 50 °C and was stirred vigorously at that temperature for 30 min, at which time TLC analysis showed only one major spot. The reaction was cooled to 23 °C, before being diluted with H_2O (5 mL) and EtOAc (5 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave alkene **125** (388 mg, 77% yield from **110**) as a light yellow oil. **125**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 6.15 (d, J = 9.7 Hz, 1H), 6.05 (t, J = 1.8 Hz, 1H), 5.64 (dd, J = 9.7, 7.0 Hz, 1H), 5.61 – 5.52 (m, 1H), 5.19 (dd, J = 10.1, 1.9 Hz, 1H), 5.03 (dt, J = 17.0, 1.6 Hz, 1H), 4.52

(apparent d, *J* = 2.2 Hz, 2H), 3.56 (td, *J* = 6.2, 2.1 Hz, 2H), 3.00 (dd, *J* = 7.0, 1.3 Hz, 1H), 2.82 (td, *J* = 13.1, 5.8 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.69 – 2.61 (m, 1H), 2.56 – 2.42 (m, 1H), 2.34 (ddt, *J* = 15.8, 5.9, 1.4 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.01 – 1.78 (m, 3H), 1.65 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.46, 208.20, 180.24, 138.29, 135.27, 131.68, 128.61, 127.90, 127.86, 127.45, 122.40, 121.77, 78.21, 73.26, 69.34, 59.18, 56.99, 56.25, 40.33, 34.16, 28.03, 27.29, 23.97, 23.85. HRMS: calcd for $C_{26}H_{31}O_4^+$ $[M + H]^+$, 407.2217, found 407.2208.



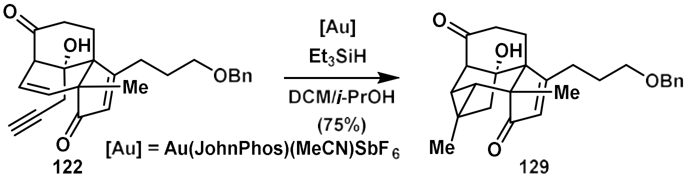
122



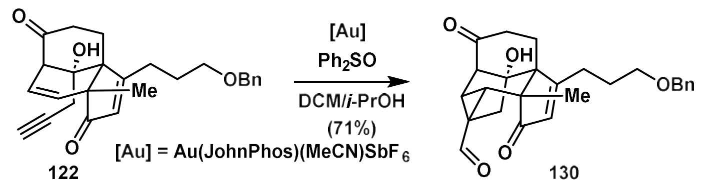
126

Alkyne **122** was synthesized following the 5-step procedure described from **110** to **125**, substituting the addition of allylmagnesium bromide into freshly prepared 3-trimethylsilyl-propargylmagnesium bromide. Starting from **110** (218 mg, 0.576 mmol), giving **122** (120 mg, 51% yield).

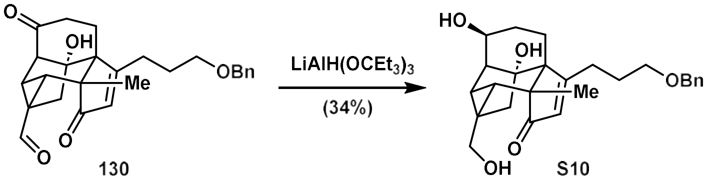
Alkene **126** was synthesized following the 5-step procedure described from **110** to **125**, substituting the addition of allylmagnesium bromide into 2-methylallylmagnesium bromide. Starting from **110** (93.1 mg, 0.246 mmol), giving **126** (60.3 mg, 58% yield) **126**: diagnostic peaks on ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H, aromatic), 6.15 (d, *J* = 9.7 Hz, 1H, C-1 alkene), 6.06 – 6.02 (m, 1H, enone), 5.63 (dd, *J* = 9.6, 7.0 Hz, 1H, C-2 alkene), 4.94 (s, 1H, terminal alkene), 4.65 (s, 1H, terminal alkene), 4.52 (apparent d, *J* = 3.3 Hz, 2H, benzyl), 2.95 (d, *J* = 7.0 Hz, 1H, C-6), 1.67 (s, 3H, allylic Me), 1.33 (s, 3H, Me).



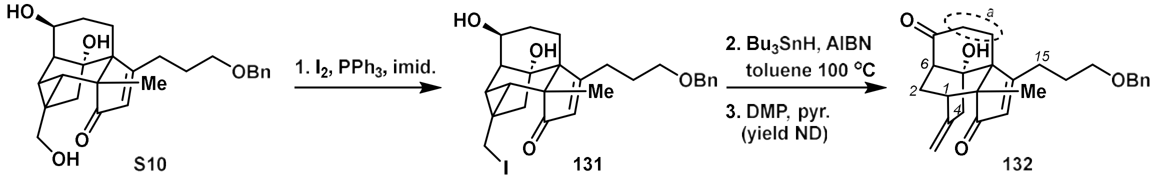
Cyclopropane **129**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added alkyne **122** (6.1 mg, 0.015 mmol, 1.0 equiv). The flask was degassed and back filled with argon. Anhydrous CH_2Cl_2 (1.0 mL), anhydrous *i*-PrOH (0.10 mL), triethylsilane (8.8 mg, 0.075 mmol, 5.0 equiv), and Au(JohnPhos)(MeCN)SbF_6 (5.7 mg, 0.0074 mmol, 50 mol%) was added sequentially. The reaction mixture was stirred for 18 h, at which time TLC analysis showed the complete consumption of **122**. The reaction mixture was diluted with hexanes (2 mL) and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) to give cyclopropane **129** (4.6 mg, 75% yield) as a colorless oil. **129**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 6.18 (t, *J* = 1.6 Hz, 1H), 4.47 (apparent q, *J* = 12.0 Hz, 2H), 3.52 (qd, *J* = 6.4, 3.6 Hz, 2H), 2.82 – 2.79 (m, 1H), 2.78 – 2.68 (m, 1H), 2.63 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.52 – 2.35 (m, 2H), 1.99 – 1.86 (m, 2H), 1.82 – 1.75 (m, 1H), 1.73 (d, *J* = 12.6 Hz, 1H), 1.31 (s, 3H), 1.28 (dd, *J* = 14.2, 3.5 Hz, 3H), 1.11 (s, 3H), 1.01 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.77, 212.74, 182.56, 137.75, 129.18, 128.64, 128.10, 128.08, 83.11, 73.24, 68.50, 60.47, 55.07, 53.91, 40.37, 36.03, 27.46, 27.24, 26.69, 26.50, 24.27, 22.74, 22.58, 19.87. HRMS: calcd for $C_{26}H_{31}O_4^+$ $[M + H]^+$ 407.2217, found 407.2221.



Aldehyde **130**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added alkyne **122** (31.2 mg, 0.077 mmol, 1.0 equiv). The flask was degassed and back filled with argon. Anhydrous CH_2Cl_2 (2.0 mL), diphenyl sulfoxide (47 mg, 0.231 mmol, 3.0 equiv), and Au(JohnPhos)(MeCN)SbF_6 (6.0 mg, 0.0077 mmol, 10 mol%) was added sequentially. The reaction mixture was stirred for 18 h, at which time TLC analysis showed the complete consumption of **122**. The reaction mixture was diluted with hexanes (2 mL) and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/Et_2O, 4/1→1/1) to give aldehyde **130** (23.1 mg, 71% yield) as a colorless oil. **130**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.38 – 7.28 (m, 5H), 6.18 (d, *J* = 1.6 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.59 – 3.48 (m, 2H), 3.18 (s, 1H), 2.86 – 2.78 (m, 2H), 2.75 – 2.65 (m, 2H), 2.64 – 2.52 (m, 1H), 2.48 – 2.38 (m, 1H), 2.29 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.04 (d, *J* = 7.8 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.89 (d, *J* = 13.2 Hz, 1H), 1.83 (td, *J* = 7.4, 5.2 Hz, 1H), 1.78 (d, *J* = 13.2 Hz, 1H), 1.40 (s, 3H).



Diol **S10**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added aldehyde **130** (8.9 mg, 0.021 mmol, 1.0 equiv). The flask was degassed and back filled with argon, and anhydrous THF (1.0 mL) was added. The reaction flask was cooled to 0 °C before $LiAlH(OCEt_3)_3$ (0.5 M in THF, 0.17 mL, 0.085 mmol, 4.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min, at which time TLC analysis showed the complete consumption of **130**. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (2 mL). The resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (5 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→0/1) gave diol **S10** (3.1 mg, 34% yield) as a colorless oil. **S10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 6.13 (d, *J* = 1.6 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.06 (dt, *J* = 11.0, 5.2 Hz, 1H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.51 (qt, *J* = 9.6, 5.2 Hz, 2H), 3.30 (d, *J* = 11.3 Hz, 1H), 2.80 – 2.70 (m, 2H), 2.46 (t, *J* = 3.8 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.13 (td, *J* = 14.1, 4.0 Hz, 1H), 1.97 – 1.85 (m, 3H), 1.83 (d, *J* = 12.7 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.64 – 1.61 (m, 1H), 1.51 (dt, *J* = 13.9, 3.4 Hz, 1H), 1.46 (dd, *J* = 7.4, 2.7 Hz, 1H), 1.34 (d, *J* = 12.7 Hz, 1H), 1.24 (s, 3H), 1.03 (d, *J* = 7.3 Hz, 1H).

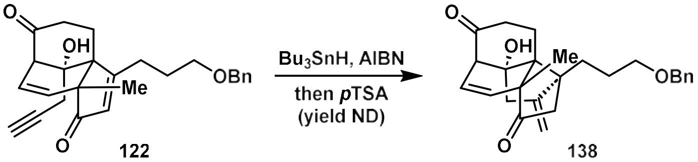


Iodide **131**: to a 10 mL round bottom flask containing diol **S10** (3.1 mg, 0.0073 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous CH_2Cl_2 (1.0 mL), imidazole (0.8 mg, 0.011 mmol, 1.5 equiv), and PPh_3 (2.3 mg, 0.0088 mmol, 1.2 equiv) were sequentially added. The reaction flask was cooled to 0 ºC before iodine (2.4 mg, 0.0095 mmol, 1.3 equiv) was added. The reaction mixture was stirred at 0 ºC for 30 min, at which time the reaction contents turned brown, and TLC analysis showed the complete consumption of **S10**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/2) gave iodide **131** as a mixture with $POPh_3$, which was used in the next step without further purification.

Diketone **132**: To a 10 mL round bottom flask containing iodide **131** was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous toluene (1.0 mL), Bu_3SnH (2 drops, ca. 6.0 mg, 2.8 equiv), and AIBN (0.6 mg, 0.004 mmol, 0.5 equiv) was sequentially added. The reaction system was purged with argon for 10 minutes before being heated to 100 ºC. After stirring at 100 ºC for 3.5 h, TLC analysis showed the complete consumption of **131**. Upon cooling to 23 ºC, the reaction mixture was diluted with hexanes (2 mL) and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 1/1→0/1) to give the cyclization product, which was subjected to Dess-Martin oxidation for a cleaner NMR profile.

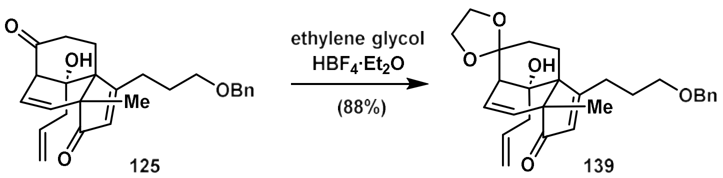
The previous product was transferred to a 25 mL vial, a magnetic stir bar, CH_2Cl_2 (1.0 mL), pyridine (1 drop, ca. 3.0 mg, 0.037 mmol, 5.0 equiv), and Dess-Martin periodinane (9.3 mg, 0.0219 mmol, 3.0 equiv) was sequentially added. The reaction mixture was stirred at 23 ºC for 2 h before being quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous

$Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave diketone **132** as a colorless oil. **132**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (ddt, *J* = 11.6, 8.2, 5.9 Hz, 5H), 6.12 (s, 1H), 4.84 (s, 1H), 4.63 (s, 1H), 4.50 (d, *J* = 3.5 Hz, 2H), 3.56 – 3.50 (m, 2H), 2.88 – 2.72 (m, 2H, 1H C-15, 1H region a), 2.67 (td, *J* = 12.6, 6.7 Hz, 1H region a), 2.54 – 2.43 (m, 1H C-15, 1H region a, 1H C-1 or C-6), 2.37 (t, *J* = 2.8 Hz, 1H C-6 or C-1), 2.32 (dt, *J* = 16.9, 2.6 Hz, 1H C-4), 2.06 – 1.98 (m, 1H C-4, 2H C-2), 1.96 – 1.87 (m, 2H), 1.71 (dd, *J* = 13.6, 7.8 Hz, 1H region a), 1.31 (s, 3H).



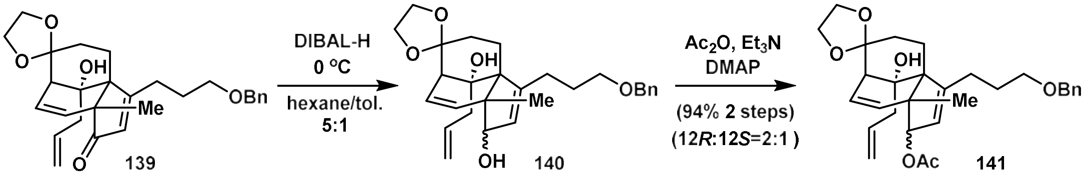
Diketone **138**: To a 10 mL round bottom flask containing alkyne **122** (4.3 mg, 0.0106 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous toluene (1.0 mL), Bu_3SnH (3 drops, ca. 9.0 mg, 3.0 equiv), and AIBN (0.8 mg, 0.005 mmol, 0.5 equiv) was sequentially added. The reaction system was purged with argon for 10 minutes before being heated to 100 °C. After stirring at 100 °C for 2 h, TLC analysis showed the complete consumption of **122**. Upon cooling to 23 °C, and reaction mixture was concentrated under reduced pressure. CH_2Cl_2 (1.0 mL) and *p*-Toluenesulfonic acid monohydrate (10 mg, 0.053 mmol, 5.0 equiv) were added, and the reaction mixture was stirred at 23 °C for 2 h, at which time

TLC analysis showed only one spot with no UV absorption. The reaction mixture was then diluted with hexanes (2 mL) and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) to give diketone **138** (yield ND). **138**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 6.06 (d, *J* = 9.7 Hz, 1H), 5.67 (dd, *J* = 9.7, 7.1 Hz, 1H), 5.07 – 5.06 (m, 1H), 5.04 (d, *J* = 3.0 Hz, 1H), 4.52 (s, 2H), 3.50 (apparent t, *J* = 5.4 Hz, 2H), 3.12 (d, *J* = 5.1 Hz, 1H), 3.09 (d, *J* = 3.6 Hz, 1H), 2.64 (dt, *J* = 15.7, 2.7 Hz, 1H), 2.60 – 2.45 (m, 2H), 2.38 – 2.30 (m, 1H), 2.18 (d, *J* = 15.8 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.87 (d, *J* = 9.5 Hz, 3H), 1.84 – 1.71 (m, 1H), 1.40 (s, 3H).



Ketal **139**: to a 50 mL equipped with a magnetic stir bar was added alkene **125** (261 mg, 0.642 mmol, 1.0 equiv), anhydrous CH_2Cl_2 (5.0 mL), ethylene glycol (5.0 mL), and $HBF_4{\cdot}Et_2O$ (52 mg, 0.321 mmol, 0.50 equiv). The biphasic mixture was stirred vigorously for 16 h before being quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The reaction contents were diluted with CH_2Cl_2 (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave ketal **139** (255 mg, 88% yield) as a light yellow oil. **139**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.02 (d, *J* = 9.9 Hz, 1H), 5.97 (t, *J* = 1.7 Hz, 1H), 5.76 (dddd, *J* = 17.2, 10.2, 8.9, 5.0 Hz, 1H), 5.64 (dd, *J* = 9.9, 6.8 Hz, 1H), 5.03 – 4.96 (m, 1H), 4.94 – 4.88 (m, 1H), 4.85 (d, *J* = 2.0 Hz, 1H), 4.52 (apparent d, *J* =

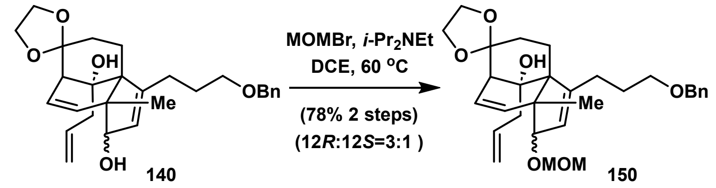
2.0 Hz, 2H), 4.18 – 3.90 (m, 4H), 3.64 – 3.48 (m, 2H), 2.89 – 2.76 (m, 1H), 2.53 – 2.39 (m, 2H), 2.34 (dd, *J* = 6.9, 1.6 Hz, 1H), 2.09 – 1.97 (m, 1H), 1.93 – 1.86 (m, 2H), 1.85 – 1.74 (m, 2H), 1.64 (ddt, *J* = 13.4, 5.2, 2.3 Hz, 2H), 1.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.48, 181.40, 138.41, 134.25, 134.16, 128.46, 127.80, 127.68, 126.60, 124.68, 117.84, 112.02, 77.42, 73.16, 69.72, 64.90, 64.03, 56.91, 56.89, 46.01, 41.15, 28.85, 27.92, 27.20, 23.84, 22.10. HRMS: calcd for $C_{28}H_{35}O_5^+$ $[M + H]^+$ 451.2479, found 407.2472.



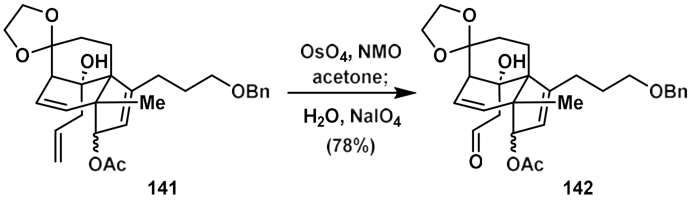
Diol **140**: to a 25 mL round bottom flask containing ketal **139** (33.8 mg, 0.0750 mmol) was added a magnetic stir bar. The flask was degassed and back filled with argon before anhydrous toluene (0.3 mL) was added. After the starting material dissolves, hexanes (1.5 mL) were added, and the reaction mixture was cooled to 0 °C. DIBAL-H (1.0 M in toluene, 0.23 mL, 0.23 mmol, 3.0 equiv) was added dropwise. The reaction was stirred at 0 °C for 15 min, at which time TLC analysis showed only products with no UV absorptions. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (5 mL) and the resulting biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated to give crude diol as a colorless oil that was used for the next step without further purification. Analytical samples of each diastereomer were prepared from preparative TLC (silica, hexanes/EtOAc, 1/1). Major product (12*R*)-**140**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 5.96 – 5.82 (m, 1H), 5.79 (d, *J* = 10.0 Hz, 1H), 5.67 (dd, *J* = 10.0, 6.9 Hz, 1H), 5.58 – 5.51 (m, 1H), 5.08 – 4.90 (m, 2H), 4.62 (d, *J* = 2.0 Hz, 1H), 4.50 (s, 2H), 4.18 (s, 1H), 4.13 – 3.88 (m, 4H), 3.60 – 3.43 (m, 2H), 2.86 – 2.76 (m, 1H), 2.48 (dt, *J* = 17.1, 8.1 Hz, 1H), 2.40 – 2.27 (m, 2H), 2.08 (tt, *J* = 14.4, 7.3 Hz, 3H), 1.94 (dd, *J* = 14.3, 4.6 Hz, 1H), 1.83 (dq, *J* = 9.3, 6.3 Hz, 2H), 1.62 (s, 1H), 1.42 – 1.32 (m, 1H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.00, 138.75, 136.29, 136.26, 128.50, 127.88, 127.64, 125.90, 124.21, 117.10, 112.64, 83.84, 76.26, 73.12, 70.50, 64.83, 63.88, 57.66, 51.54, 44.96, 41.64, 29.97, 28.04, 25.85, 25.64, 23.41. HRMS: calcd for $C_{28}H_{36}O_5Na^+$ $[M + Na]^+$ 475.2455, found 475.2451. Minor product (12*S*)-**140**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 5.99 – 5.80 (m, 2H), 5.64 – 5.53 (m, 1H), 5.40 (q, *J* = 1.8 Hz, 1H), 5.06 – 4.98 (m, 1H), 4.98 – 4.88 (m, 1H), 4.74 (s, 1H), 4.62 (d, *J* = 1.7 Hz, 1H), 4.50 (d, *J* = 1.6 Hz, 2H), 4.10 – 3.88 (m, 4H), 3.51 (dddd, *J* = 16.2, 14.3, 9.2, 6.8 Hz, 2H), 2.40 – 2.23 (m, 5H), 2.18 – 1.97 (m, 2H), 1.88 – 1.76 (m, 2H), 1.59 – 1.40 (m, 3H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.13, 138.76, 136.91, 135.81, 128.50, 127.89, 127.65, 126.90, 124.16, 117.16, 112.54, 80.87, 77.54, 73.13, 70.48, 64.83, 63.91, 58.30, 53.84, 45.66, 40.54, 28.96, 27.93, 25.81, 24.24, 16.55. HRMS: calcd for $C_{28}H_{36}O_5Na^+$ $[M + Na]^+$ 475.2455, found 475.2449.

Acetate **141**: the previous crude product was transferred to a 25 mL vial. A magnetic stir bar was added, followed by anhydrous CH_2Cl_2 (1.5 mL), anhydrous triethyl amine (31 mg, 0.30 mmol, 4.0 equiv), DMAP (10 mg, 0.075 mmol, 1.0 equiv), and acetic anhydride (23 mg, 0.225 mmol, 3.0 equiv). The reaction mixture was stirred at 23 ºC for 1 h, at which time TLC analysis showed the complete consumption of diol **140**. The reaction was then quenched by the addition of MeOH (0.1 mL). The reaction contents were concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave acetate **141** (34.7 mg, 94% over 2 steps, 2.6:1 *dr.*) as a colorless oil. **141**: diagnostic peaks on ^{1}H NMR (500

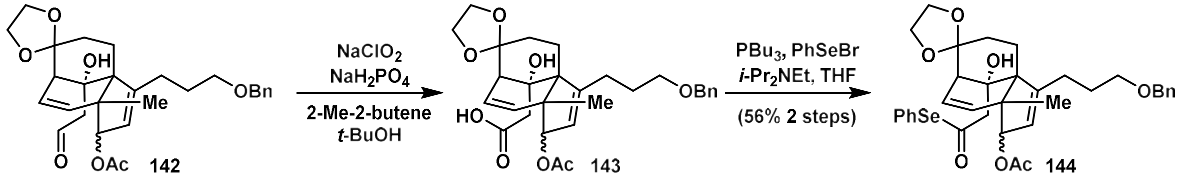
MHz, CDCl$_3$) δ 5.48 – 5.38 (2 s, 1H, cyclopentene), 5.18 (s, 1H, allylic major), 4.95 (s, 1H, allylic minor), 4.50 (d, *J* = 1.9 Hz, 2H, benzyl), 2.04 (s, 3H, acetate minor), 2.03 (s, 3H, acetate major).



MOM-Ether **150**: to a 25 mL round bottom flask containing crude diol **140** synthesized following the procedure described above from ketal **139** (61.8 mg, 0,137 mmol) was sequentially added a magnetic stir bar, 1,2-dichloroethane (2.0 mL), anhydrous *i*-Pr$_2$Net (70 mg, 0.54 mmol, 5.0 equiv), and bromomethyl methyl ether (41 mg, 0.32 mmol, 3.0 equiv). The reaction flask was sealed and heated to 60 °C. After stirring at 60 °C for 72 h, TLC analysis showed the complete consumption of **140**. Upon cooling to 23 °C, the reaction was quenched by the addition of MeOH (0.5 mL). The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave MOM-ether **150** (52.9 mg, 78% over 2 steps, 3:1 *dr.*) as a colorless oil. **150**: diagnostic peaks on ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.86 (d, *J* = 9.9 Hz, 1H, C-1 minor), 5.77 (d, *J* = 10.0 Hz, 1H, C-1 major), 4.68 (d, *J* = 3.2 Hz, 1H, allylic minor), 4.65 (d, *J* = 2.9 Hz, 1H, allylic major), 4.50 (apparent d, *J* = 1.5 Hz, 2H, benzyl), 3.40 (s, 3H, methoxy minor), 3.32 (s, 3H, Me minor), 1.12 (s, 3H, Me major), 1.08 (s, 3H, Me minor). ^{13}C NMR (126 MHz, CDCl$_3$) δ 152.32, 148.52, 138.77, 138.74, 137.28, 136.82, 136.65, 135.79, 128.47, 127.85, 127.83, 127.60, 127.59, 125.44, 124.58, 124.20, 123.29, 117.20, 116.66, 112.70, 112.54, 96.91, 96.64, 90.48, 86.95, 77.52, 76.75, 73.10, 73.06, 70.53, 70.50, 64.79, 63.88, 63.84, 58.10, 57.33, 55.93, 55.58, 55.45, 53.79, 51.07, 45.54, 45.01, 44.98, 41.08, 40.43, 29.88, 29.02, 28.06, 27.92, 26.12, 25.81, 25.79, 24.12, 23.23, 17.56. HRMS: calcd for $C_{30}H_{40}O_6Na^+$ $[M + Na]^+$ 519.2717, found 519.2702.



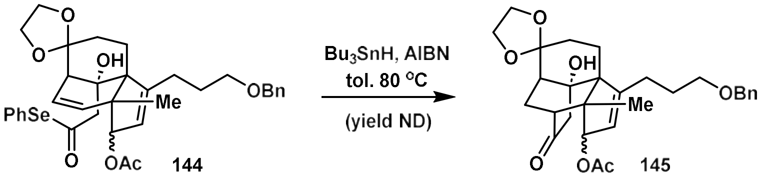
Aldehyde **142**: to a 25 mL vial containing acetate **141** (34.7 mg, 0.0702 mmol) was sequentially added a magnetic stir bar, acetone (1.5 mL), *N*-Methylmorpholine *N*-oxide (13 mg, 0.105 mmol, 1.5 equiv), and OsO_4 (4% in H_2O, 0.02 mL, ca. 0.03 mmol, 0.05 equiv). The reaction mixture was stirred at 23 °C for 16 h, at which time TLC analysis showed the complete consumption of **141**. H_2O (1.5 mL, 100 V%) was added, followed by $NaIO_4$ (75 mg, 0.35 mmol, 5.0 equiv). The resultant mixture was stirred vigorously at 23 °C for 30 min, and quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave aldehyde **142** (27.0 mg, 78% yield, 2.5:1 *dr.*) as a colorless oil. **142**: diagnostic peaks on ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.7 Hz, 1H, aldehyde major), 9.78 (t, *J* = 2.6 Hz, 1H, aldehyde minor), 1.18 (s, 3H, Me major), 0.99 (s, 3H, Me minor).



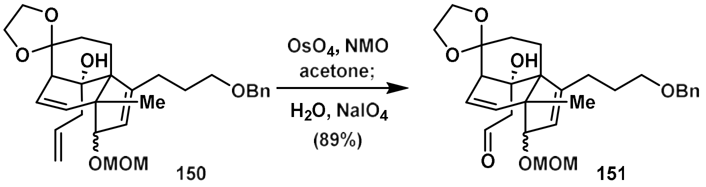
Carboxylic acid **143**: To a 25 mL vial containing aldehyde **142** (8.9 mg, 0.0179 mmol, 1.0 equiv) was sequentially added a magnetic stir bar, 2-methyl-2-butene (0.2 mL, 20 V%) and *t*-BuOH (1.0 mL). To a separate vial, $NaClO_2$ (17 mg, 0.180 mmol, 10.0 equiv) and $NaH_2PO_4 \cdot 2H_2O$ (17 mg, 0.108 mmol, 6.0 equiv) were dissolved in a minimal volume of H_2O (ca. 0.1 mL). The aqueous solution of the salts was transferred to the reaction vial via syringe. The resultant mixture was stirred at 23 °C for 16 h, at which time TLC analysis showed the complete consumption of **142**. 10% aqueous solution of citric acid (2 mL) was added to acidify the reaction mixture to pH 3. The reaction contents were diluted with CH_2Cl_2 (5 mL) and H_2O, transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated to give crude carboxylic acid **143** as a colorless oil, which was transferred to a 10 mL round bottom flask for the next step without further purification.

Selenoester **144**: to the flask containing crude **143** was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous THF (1.0 mL), *i*-Pr_2Net (9 mg, 0.071 mmol, 3.9 equiv), tributylphosphine (10 mg, 0.048 mmol, 2.7 equiv), and PhSeBr (13 mg, 0.048 mmol, 2.7 equiv) was sequentially added. The resultant mixture was stirred at 23 °C for 16 h, at which time TLC analysis showed the complete consumption of **143**. The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) gave selenoester **144** (6.6 mg, 56% over 2 steps) as a yellow oil. **144**: diagnostic peaks on ^1H NMR (500 MHz, $CDCl_3$) δ

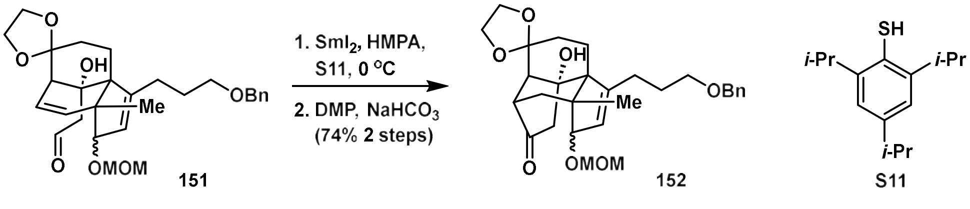
7.55 – 7.27 (m, 10H, aromatic), 5.55 (s, br, 1H, cyclopentene), 5.19 (s, br, 1H, allylic), 4.57 – 4.48 (m, 2H, benzyl), 3.44 (d, *J* = 15.5 Hz, 1H, selenoester-α), 2.75 (d, *J* = 15.5 Hz, 1H, selenoester-α), 1.19 (s, 3H, Me).



Ketone **145**: To a 10 mL round bottom flask containing selenoester **144** (6.6 mg, 0.0101 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous toluene (1.0 mL), Bu_3SnH (5 drops, ca. 15 mg, 5.0 equiv), and AIBN (0.8 mg, 0.005 mmol, 0.5 equiv) was sequentially added. The reaction system was purged with argon for 10 minutes before being heated to 80 °C. After stirring at 80 °C for 2 h, TLC analysis showed the complete consumption of **144**. Upon cooling to 23 °C, and reaction mixture was diluted with hexanes (2 mL) and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/2) to give ketone **145** (yield ND). An analytical sample was prepared by preparative TLC (silica, hexanes/EtOAc, 1/1) **145**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.51 (q, *J* = 1.8 Hz, 1H), 5.30 (d, *J* = 2.1 Hz, 1H), 4.82 (s, 1H), 4.51 (d, *J* = 1.5 Hz, 2H), 4.12 – 3.85 (m, 4H), 3.59 – 3.43 (m, 2H), 2.79 (d, *J* = 18.2 Hz, 1H), 2.53 (ddd, *J* = 16.6, 10.7, 5.6 Hz, 1H), 2.31 – 2.09 (m, 3H), 2.08 – 1.98 (m, 2H), 1.95 (s, 3H), 1.98 – 1.69 (m, 5H), 1.47 – 1.36 (m, 1H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.77, 171.48, 155.58, 138.70, 128.51, 127.84, 127.68, 123.09, 111.78, 87.71, 75.48, 73.08, 70.31, 65.15, 63.84, 55.60, 50.25, 49.56, 48.28, 41.77, 29.64, 28.65, 26.25, 24.46, 23.08, 21.34, 21.10.



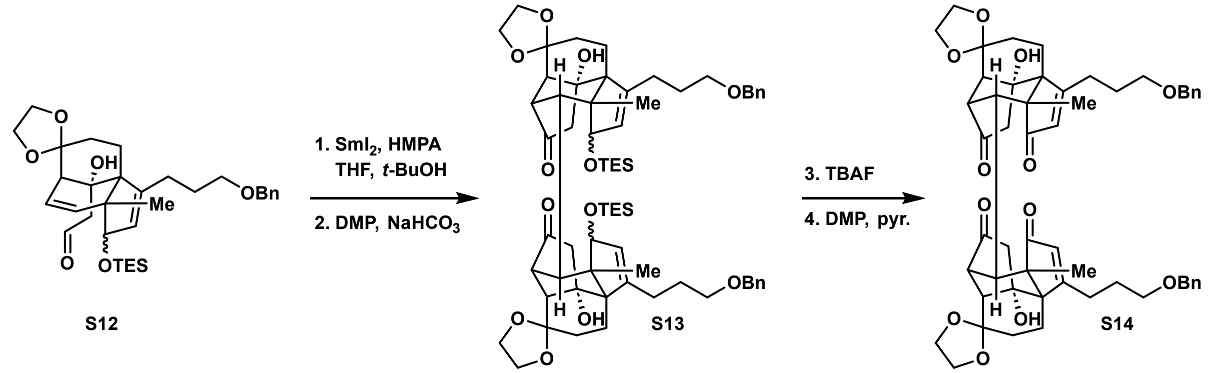
Aldehyde **151** was synthesized following the procedure described from **141** to **142**. Starting from MOM-ether **150** (38.1 mg, 0.0767 mmol), giving aldehyde **151** (34.4 mg, 89%, 3:1 *dr.*) as a colorless oil. **151**: diagnostic peaks on ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.81 (dd, *J* = 3.2, 2.2 Hz, 1H, aldehyde major), 9.79 (t, *J* = 1.9 Hz, 1H, aldehyde minor), 5.88 (d, *J* = 9.9 Hz, 1H, C-1 minor), 5.78 (d, *J* = 10.0 Hz, 1H, C-1 major), 1.11 (s, 3H, Me major), 1.07 (s, 3H, Me minor). ^{13}C NMR (126 MHz, CDCl$_3$) δ 205.75, 203.96, 152.24, 148.21, 138.70, 138.67, 137.36, 136.71, 128.48, 127.84, 127.81, 127.64, 127.62, 126.52, 124.59, 124.16, 123.99, 112.23, 112.10, 96.96, 96.45, 89.49, 86.51, 77.57, 76.76, 73.12, 73.06, 70.33, 64.90, 64.03, 63.98, 57.90, 57.19, 55.62, 55.50, 53.92, 51.09, 51.06, 51.03, 50.05, 47.81, 47.20, 29.51, 28.70, 28.02, 27.86, 25.98, 25.91, 25.64, 23.58, 22.77, 17.24. HRMS: calcd for $C_{29}H_{39}O_7^+$ [M + H]$^+$ 499.2690, found 499.2672.



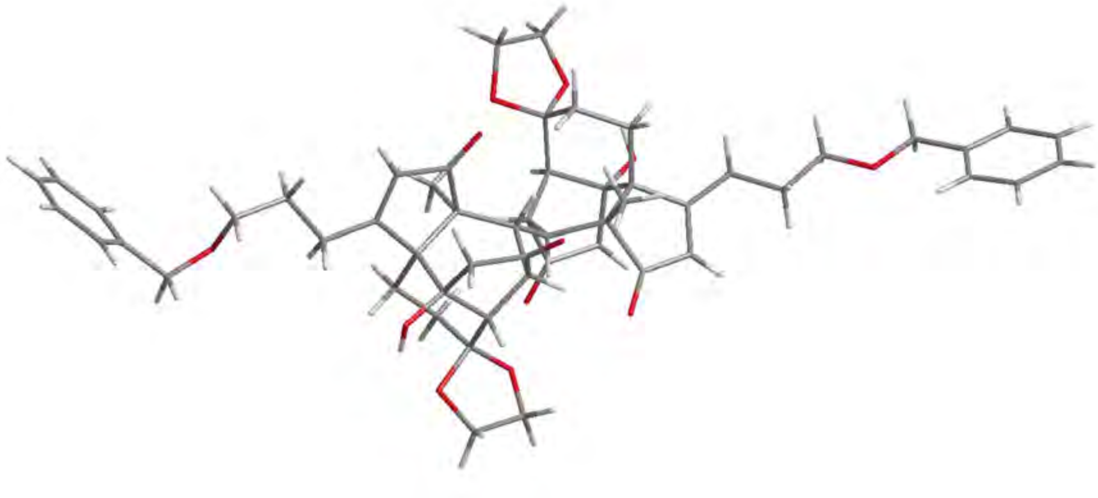
SmI$_2$-HMPA complex was prepared freshly: to a 25 mL round bottom flask equipped with a magnetic stir bar was added Sm (freshly filed powder, 150 mg, 1.00 mmol) and 1,2-diiodoethane (washed as a CH$_2$Cl$_2$ solution by saturated aqueous NaHCO$_3$, concentrated and dried, 141 mg, 0.50 mmol). The flask was degassed and back filled with argon. Anhydrous THF (5.0 mL) was added, and the resultant mixture was stirred vigorously at 23 ºC for 2 h, giving a dark-blue solution. The solution can be stored under argon atmosphere for 5 days without a significant drop in reactivity. Before being used for the radical cyclization reaction, HMPA (0.70 mL, 717 mg, 4.0 mmol) was added. The resultant mixture was stirred for 5 minutes, giving a purple solution, which was used as a 0.086 M solution of the SmI_2-HMPA complex.

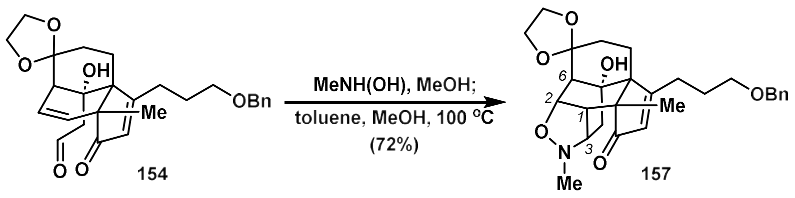
Ketone **152**: To a 10 mL round bottom flask containing aldehyde **151** (18.6 mg, 0.0373 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous THF (3.5 mL) and 2,4,6-Triisopropylbenzenethiol (**S11**) (10.6 mg, 0.0448 mmol, 1.2 equiv) were sequentially added. The reaction system was cooled to 0 ºC and purged with argon for 10 minutes. Under stirring, SmI_2-HMPA complex (0.086 M solution in THF) was added dropwise via syringe until the reaction solution kept its purple color for at least 5 minutes. Typically 2-3 equivalents of the SmI_2-HMPA complex is needed. After stirring at 0 ºC for 15 min, TLC analysis showed the complete consumption of **151**. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (5 mL) and the resulting biphasic mixture was stirred vigorously for 15 min. The reaction contents were then transferred to a separatory funnel, diluted with Et_2O (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed three times with 1/1 brine/H_2O, once with brine, dried (Na_2SO4), filtered, and concentrated to give the crude product as a yellow oil that was transferred to a 25 mL vial for the next step without further purification.

To the 25 mL vial containing the previous product was added a magnetic stir bar, CH_2Cl_2 (1.0 mL), $NaHCO_3$ (16 mg, 0.19 mmol, 5.0 equiv), and Dess-Martin periodinane (48 mg, 0.112 mmol, 3.0 equiv). The reaction mixture was stirred at 23 ºC for 16 h before being quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave ketone **152** (13.8 mg, 74% over 2 steps) as a light-yellow oil. Analytical samples of each diastereomer were prepared from preparative TLC (silica, hexanes/EtOAc, 1/1). Major product (12*R*)-**152**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.75 – 5.65 (m, 1H), 4.58 – 4.43 (m, 4H), 4.08 – 3.93 (m, 4H), 3.90 (s, 1H), 3.67 (d, *J* = 2.8 Hz, 1H), 3.50 (dtd, *J* = 15.8, 9.2, 6.6 Hz, 2H), 3.31 (s, 3H), 3.14 – 3.03 (m, 1H), 2.57 (s, 1H), 2.43 (dt, *J* = 16.9, 7.7 Hz, 1H), 2.32 (td, *J* = 14.1, 5.1 Hz, 1H), 2.15 – 1.96 (m, 4H), 1.91 (dd, *J* = 16.0, 2.7 Hz, 1H), 1.88 – 1.78 (m, 1H), 1.68 (dd, *J* = 15.0, 5.3 Hz, 1H), 1.53 (dd, *J* = 14.9, 4.3 Hz, 1H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.69, 152.59, 138.66, 128.52, 127.87, 127.69, 125.13, 109.34, 96.54, 89.64, 78.57, 73.12, 70.16, 64.90, 64.53, 57.13, 55.68, 52.32, 50.44, 49.91, 46.35, 32.48, 31.36, 29.00, 28.13, 25.88, 22.75. HRMS: calcd for $C_{29}H_{38}O_7Na^+$ $[M + Na]^+$ 521.2510, found 521.2488. Minor product (12*S*)-**152**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H), 5.58 (s, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.50 (d, *J* = 3.2 Hz, 2H), 4.10 – 3.95 (m, 5H), 3.50 (q, *J* = 6.4 Hz, 2H), 3.33 (s, 3H), 2.67 (s, 1H), 2.63 – 2.54 (m, 1H), 2.31 (td, *J* = 14.4, 5.8 Hz, 2H), 2.17 (d, *J* = 19.8 Hz, 1H), 2.15 (d, *J* = 10.7 Hz, 1H), 2.13 – 1.77 (m, 5H), 1.68 (td, *J* = 15.2, 4.8 Hz, 2H), 1.32 (d, *J* = 6.9 Hz, 1H), 1.25 – 1.20 (m, 1H), 1.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.88, 149.30, 138.68, 128.52, 127.86, 127.69, 126.60, 109.18, 97.29, 88.17, 80.17, 73.08, 70.16, 64.94, 64.55, 57.26, 55.54, 51.40, 51.17, 51.11, 50.68, 33.47, 31.57, 27.88, 25.73, 23.31, 20.78. HRMS: calcd for $C_{29}H_{39}O_7^+$ $[M + H]^+$ 499.2690, found 499.2687.

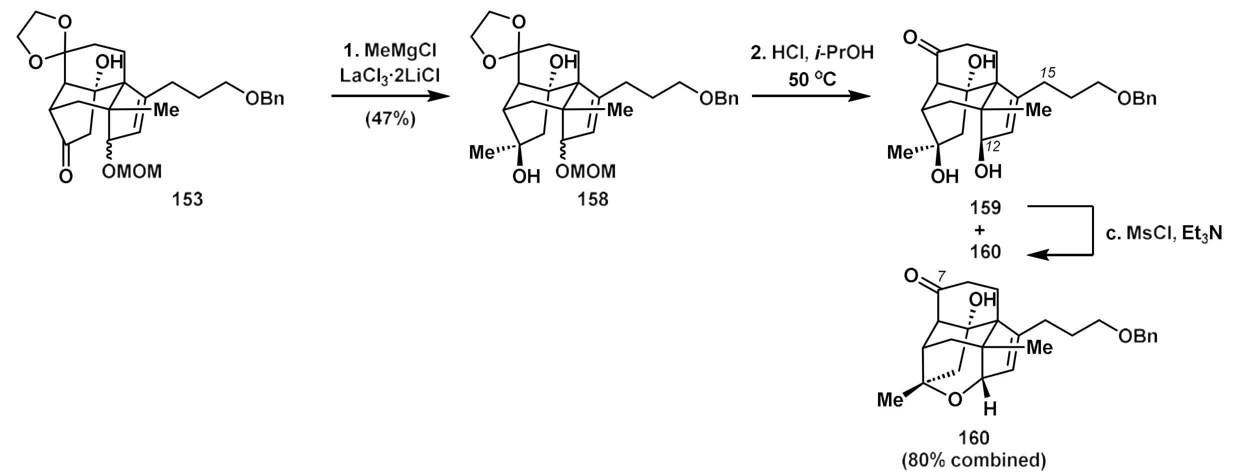


A *meso*-dimer was obtained from TES-ether **S12**, using the conditions in entry 3 of Table 2. The structure of the dimeric product was confirmed after deprotection and oxidation. The X-Ray structure of **S14**:





157: To a 4 mL vial was charged a magnetic stir bar, aldehyde **154** (26.8 mg, 0.0592 mmol, 1.0 equiv), MeOH (2.0 mL), MeNHOH·HCl (52.9 mg, 0.633 mmol, 10.7 equiv), and Et_3N (164 µL, 1.18 mmol, 20 equiv). The mixture was stirred at 23 °C for 16 hours. The reaction mixture was then transferred to a 50 mL RBF, concentrated, and azeotropically dried with toluene (5 mL). The resulting residue was transferred to a microwave vial using MeOH (2.0 mL). This solution was concentrated. MeOH (1.0 mL) and toluene (3.0 mL) were charged to the vial. Next, the vial was degassed with argon before being heated to 100 °C. The reaction mixture was then stirred at that temperature for 2 hours. Upon completion, H_2O (3 mL) was charged and the mixture was extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was passed through a silica plug, eluting with CH_2Cl_2/MeOH (9/1), then concentrated. Purification of the resultant residue by flash column chromatography (silica gel, Hexanes/EtOAc 1/3 → EtOAc with 2% Et_3N) gave **157** (20.5 mg, 72% yield) as a colorless oil. **157**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 6.08 (t, *J* = 1.6 Hz, 1H), 4.63 (s, 1H), 4.50 (apparent d, *J* = 1.8 Hz, 2H), 4.40 (d, *J* = 4.6 Hz, 1H, C-2), 4.16 – 3.97 (m, 4H), 3.61 – 3.43 (m, 2H), 2.95 (dd, *J* = 8.4, 5.1 Hz, 1H, C-3), 2.88 – 2.74 (m, 1H), 2.64 (s, 3H), 2.55 (t, *J* = 4.9 Hz, 1H, C-1), 2.52 – 2.40 (m, 1H), 2.32 (td, *J* = 14.0, 6.0 Hz, 1H), 1.95 (d, *J* = 2.0 Hz, 1H, C-6), 1.94 – 1.72 (m, 5H), 1.58 – 1.44 (m, 2H), 1.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.94, 186.06, 138.43, 128.53, 127.88, 127.86, 127.76, 109.41, 75.95, 73.21, 71.75, 69.74, 65.01, 64.33, 61.12, 54.50, 54.33, 49.44, 47.10, 44.50, 39.37, 30.46, 28.51, 27.82, 22.25, 21.35. HRMS: calcd for $C_{28}H_{36}NO_6^+$ $[M + H]^+$, 482.2537, found 482.2541.

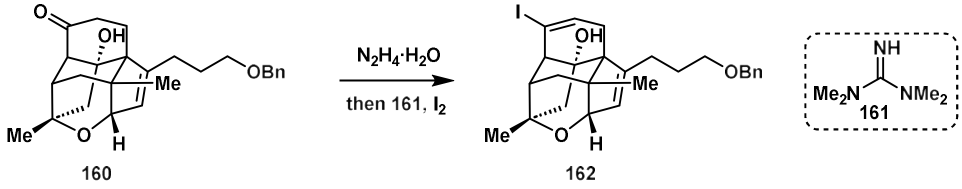


Pentacyclic ketone **160**: To a 10 mL round bottom flask containing ketone **153** (64.2 mg, 0.129 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and backfilled with argon. Anhydrous THF (3.0 mL) and $LaCl_3 \cdot 2LiCl$ (0.6 M in THF, 1.1 mL, 0.64 mmol, 6.0 equiv) was added. The resultant solution was stirred at 23 °C for 15 min. MeMgCl (3.0 M in THF, 0.26 mmol, 5.0 equiv) was added slowly. The reaction mixture was then heated to 50 °C and stirred at that temperature for 30 min, at which time TLC analysis showed the complete consumption of **160**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (5 mL) and Na_2EDTA. The resultant biphasic mixture was stirred vigorously for 15 min. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave **158** (31.2 mg, 47% yield) as a pair of diastereomers.

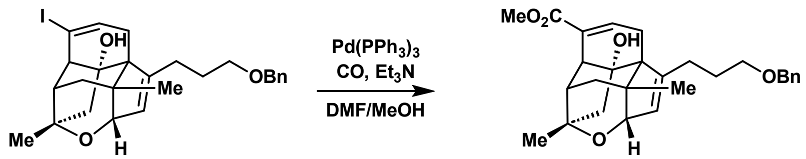
158 was then transferred to a 25 mL round bottom flask. A magnetic stir bar, *i*-PrOH (1.5 mL), and HCl (4-6 M in *i*-PrOH, 0.30 mL, 20V%) were sequentially added. The resultant solution was heated to 50 ºC and stirred at that temperature for 12 h. The reaction contents were then concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave pentacyclic ketone **160** (13.1 mg, 53% yield) as a colorless oil. A more polar spot was isolated and tentatively assigned as **159** (9.2 mg, 36% yield).

159 was then transferred to a 25 mL round bottom flask. A magnetic stir bar, anhydrous CH_2Cl_2 (1.0 mL), Et_3N (7 mg, 0.06 mmol, 3.0 equiv), and MsCl (4 mg, 0.03 mmol, 1.5 equiv) were sequentially added. The resultant mixture was stirred at 23 ºC for 30 min, at which time TLC analysis showed the complete consumption of **159**. The reaction was quenched by the addition of MeOH (0.5 mL). The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→2/1) gave **160** (6.5 mg, 26% yield from **158**) as a colorless oil.

Ketone **160**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 5.86 (d, *J* = 2.6 Hz, 1H), 4.55 – 4.43 (m, 2H), 3.92 (d, *J* = 2.9 Hz, 1H), 3.64 – 3.46 (m, 2H), 2.64 (dq, *J* = 15.7, 8.0 Hz, 3H), 2.47 – 2.40 (m, 2H), 2.36 (d, *J* = 12.9 Hz, 1H), 2.23 (ddd, *J* = 16.6, 8.7, 7.0 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.98 – 1.76 (m, 4H), 1.71 (dd, *J* = 13.8, 4.4 Hz, 1H), 1.46 – 1.36 (m, 2H), 1.26 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.79, 154.10, 138.24, 128.60, 128.02, 127.91, 126.91, 85.96, 82.01, 79.27, 73.13, 69.25, 62.21, 58.01, 51.21, 48.67, 44.99, 37.64, 31.64, 29.09, 27.11, 26.18, 24.69, 20.43.

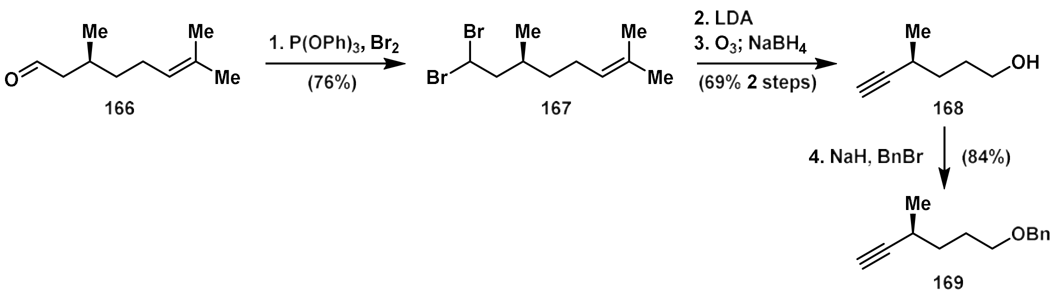


Vinyl iodide **162**: To a 10 mL round bottom flask containing **160** 1.8 mg, 0.0044 mmol, 1.0 equiv) was sequentially added a magnetic stir bar, MeOH (1.0 mL), and $N_2H_4 \cdot H_2O$ (1 drop, excess). The reaction flask was sealed. The contents were stirred at 60 ºC for 12 h, at which time TLC analysis showed the complete consumption of **160**. The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. The crude hydrazone was re-dissolved in anhydrous Et_2O (1.0 mL). To a separate 10 mL round bottom flask with a magnetic stir bar was added iodine (4 mg, 0.013 mmol, 3.0 equiv) and anhydrous Et_2O (1.0 mL). The flask was cooled to 0 ºC before tetramethylguanidine **161** (1.5 mg, 0.013 mmol, 3.0 equiv) was added. The reaction contents were stirred at 0 ºC for 15 min. The solution of the crude hydrazone was transferred to the reaction flask via syringe. The reaction was allowed to warm up to 23 ºC and stirred at that temperature for 30 minutes before quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with Et_2O (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→2/1) gave vinyl iodide **162** (yield not determined) as a light-yellow oil. Diagnostic peak on ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, J = 5.9, 2.1 Hz, 1H, vinyl iodide).



162 **163**

Ester **163**: A solution of vinyl iodide **162** (100% yield assumed, 0.0044 mmol, 1.0 equiv) in anhydrous MeOH (1.0 mL) and anhydrous DMF (0.50 mL) was transferred to a 10 mL round bottom flask. A magnetic stir bar, triethylamine (1 drop, excess), and $Pd(PPh_3)_4$ (0.3 mg, 0.0004 mmol, 10 mol%) was sequentially added. The flask was then degassed and backfilled with CO. The reaction mixture was heated to 60 °C and stirred at that temperature for 16 h. Upon completion, the reaction mixture was cooled to 23 °C, and quenched by the addition of saturated $NaHCO_3$ (10 mL). The reaction contents were then transferred to a separatory funnel, diluted with Et_2O (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by preparative TLC (silica gel, hexanes/EtOAc, 2/1) gave ester **163** (yield not determined) as a colorless oil. Diagnostic peaks on ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 6H, aromatic, unsaturated ester), 5.79 (m, 1H, alkene), 4.49 (d, *J* = 1.7 Hz, 2H, benzylic), 3.85 (m, 1H, allyl ether), 3.74 (s, 3H, methyl ester), 3.52 (q, *J* = 6.5 Hz, 1H), 2.85 (d, *J* = 6.9 Hz, 1H), 2.75 (d, *J* = 19.1 Hz, 1H), 2.41 – 2.32 (m, 1H), 2.30 – 2.16 (m, 2H), 1.84 (d, *J* = 8.2 Hz, 3H), 1.34 (s, 3H), 0.86 (s, 3H).

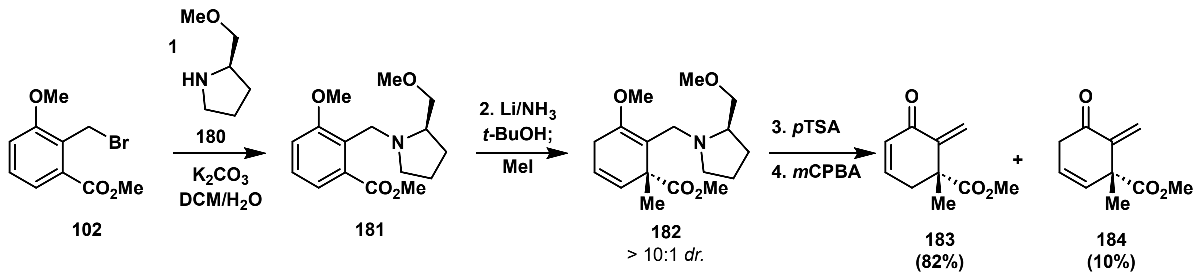


Dibromide **167**: To a 2 L round bottom flask was sequentially charged a magnetic stir bar, triphenyl phosphite (75 mL, 270 mmol, 1.5 equiv) and CH_2Cl_2 (1000 mL). The flask was degassed and backfilled with argon. The reaction mixture was cooled to -78 °C before Br_2 (12.0 mL, 234 mmol, 1.3 equiv) was added over 10 minutes. Then, anhydrous triethylamine (75 mL, 540 mmol, 3.0 equiv) was added over 25 minutes using an addition funnel. (-)-citronellal (27.8 g, 180 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (100 mL) and was charged over about an hour using an addition funnel. The resulting solution was slowly allowed to warm to 23 °C and stirred at that for 16 hours. Upon completion, the reaction mixture was concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes) gave **167** (41.02 g, 76% yield) as an yellow oil. NMR of **166** matches the reported.

Alcohol **168**: to a 2 L round bottom flask was sequentially charged a magnetic stir bar, diisopropylamine (78 mL, 550 mmol, 4.0 equiv) and anhydrous THF (240 mL). The flask was degassed and backfilled with argon. The reaction mixture was cooled to -78 °C before *n*-BuLi (1.6 M in hexanes, 300 mL, 480 mmol, 3.5 equiv) was charged over one hour using an addition funnel. Following addition, the mixture was warmed to 0 °C and stirred at that temperature for 1 hour. Then, the reaction mixture was cooled to -78 °C, and dibromide **167** (41.0 g, 138 mmol, 1.0 equiv) in anhydrous THF (240 mL) and was charged over about 1 hour using an addition funnel. The mixture was slowly warmed to 23 °C and stirred at that temperature for 16 hours. The reaction mixture was then quenched with water and extracted with hexanes (100 mL x 2). The combined organics were washed with brine, dried over Na_2SO_4, and filtered. The resulting mixture was concentrated with a bath temperature of 4 ºC to give the title compound which was used without further purification.

The previous product was transferred as a solution in CH_2Cl_2 (300 mL) to a 2 L round bottom flask equipped with a magnetic stir bar. The mixture was cooled to -78 ºC. Ozone was sparged through the reaction mixture until the reaction was complete by TLC analysis. Upon completion, MeOH (300 mL) was slowly charged at -78 ºC then $NaBH_4$ (4.43 g, 117 mmol, 0.85 equiv) was charged portion-wise over about 5 minutes. The mixture was allowed to slowly warm to 23 ºC and stirred at that temperature for 16 hours. The reaction mixture was then quenched with saturated aqueous ammonium chloride then was diluted with water. The mixture was extracted with CH_2Cl_2 (50 mL x 3). Then, the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1:1 Hexanes / Et_2O) gave **168** (10.7 g, 69% over 2 steps). **168**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.68 (apparent td, *J* = 6.4, 1.2 Hz, 2H), 2.53 – 2.42 (m, 1H), 2.05 (t, *J* = 1.9 Hz, 1H), 1.83 – 1.64 (m, 2H), 1.58 – 1.48 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H).

Benzyl ether **169** was synthesized following the procedure described from **S3** to **106**. Starting from alcohol **168** (18.26 g, 163 mmol), to give benzyl ether **169** (27.6 g, 84% yield). **169**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.30 (m, 5H), 4.58 – 4.53 (m, 2H), 3.61 – 3.49 (m, 2H), 2.56 – 2.46 (m, 1H), 2.10 (d, *J* = 2.5 Hz, 1H), 1.89 (dtdt, *J* = 13.0, 8.2, 6.5, 2.9 Hz, 1H), 1.78 (ddp, *J* = 14.6, 8.4, 2.1 Hz, 1H), 1.68 – 1.51 (m, 2H), 1.25 (dt, *J* = 7.0, 1.3 Hz, 3H).



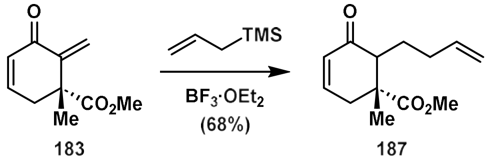
Enones **183** and **184**: A slightly modified procedure from reference 53 was applied. To a 100 mL round bottom flask was sequentially added a magnetic stir bar, **102** (770 mg, 2.97 mmol, 1.0 equiv), CH_2Cl_2 (10 mL), H_2O (2 mL, 20 V%), K_2CO_3 (648 mg, 4.69 mmol, 1.5 equiv), and **180** (360 mg, 3.13 mmol, 1.05 equiv). The biphasic reaction mixture was stirred vigorously at 23 °C for 16 h, at which time TLC analysis showed the complete consumption of **102**. The reaction contents were then transferred to a separatory funnel, diluted with CH_2Cl_2 (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated to give crude **181** as a colorless oil. The NMR of the crude product matches the reported.

The crude **181** was directly used in the following step without further purification. To a 500 mL 2-neck flask equipped with a magnetic stir bar was adapted a Dewar condenser. The system was purged by dry nitrogen for 5 minutes, before being sealed and adapted with a nitrogen balloon. A solution of crude **181** and *t*-BuOH (258 mg, 3.47 mmol, 1.1 equiv) in anhydrous THF (6 mL) was transferred to the reaction flask via syringe. The reaction flask was then cooled to –78 °C by a dry-ice/acetone bath, and the Dewar condenser was also filled with dry ice and acetone. Ammonia gas was then carefully passed into the system from the top of the Dewar condenser, until approximately 30 mL of liquid ammonia was collected. Lithium wire that was cut into small pieces and rinsed by hexanes was added to the reaction mixture under vigorous stirring. The reaction solution turned dark blue upon the lithium metal dissolved, and immediately turned bright yellow upon diffusion.

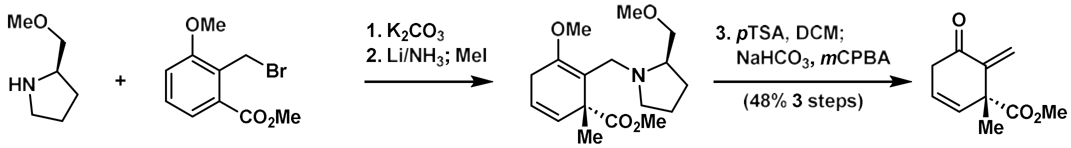
Lithium metal was kept added piecewise until the blue color of the reaction solution persisted for 30 minutes. Approximately 2-3 equivalents of lithium metal is typically needed. 2,3-dimethyl-1,3-butadiene was then added dropwise until the reaction solution turned bright yellow, to quench the excess solvated electron. Iodomethane (0.24 mL, 537 mg, 3.78 mmol, 1.2 equiv) was then added dropwise. The reaction mixture turned colorless or light yellow, and was stirred for another 30 minutes. The reaction was then quenched by the addition of solid NH_4Cl (approximately 5 g) and $Na_2S_2O_3·5H_2O$ (approximately 1 g). The Dewar condenser and the cooling bath were removed, allowing the ammonia to slowly evaporate overnight. The resultant solid mixture was picked up by H_2O (20 mL) and EtOAc (20 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give crude **182** as a yellow oil. The NMR of the crude product matches the reported and indicates a diastereomeric ratio of ~ 10:1 (^{1}HNMR in $CDCl_3$, desired isomer δ 1.46, undesired isomer δ 1.37).

The crude **182** was transferred into a 100 mL round bottom flask for the following step without further purification. To the flask was sequentially added a magnetic stir bar, toluene (15 mL), and *p*-toluenesulfonic acid monohydrate (632 mg, 3.32 mmol, 1.1 equiv). A reflux condenser was attached before the reaction flask was heated to 80 ºC. The reaction mixture was stirred at that temperature for another 1 h before quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The reaction contents were diluted with EtOAc (20 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude product was then dissolved in CH_2Cl_2 (15 mL) in a 100 mL round bottom flask with a magnetic stir bar. *m*-Chloroperoxybenzoic acid (77% suspension in water, 744 mg, 3.32 mmol, 1.2

equiv) was added in one portion. The resultant mixture was stirred at 23 °C for 30 min before quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (20 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 4/1→1/2) gave enones **183** (436 mg, 82% yield) and **184** (53 mg, 10% yield) as white crystalline solids. NMR of **183** matches the reported. **184**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, *J* = 2.3 Hz, 1H), 5.93 (dt, *J* = 10.3, 2.5 Hz, 1H), 5.70 (d, *J* = 10.0 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 3.66 (s, 3H), 3.19 (dq, *J* = 22.6, 3.0 Hz, 1H), 3.00 (dt, *J* = 22.3, 2.0 Hz, 1H), 1.57 (d, *J* = 2.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.08, 173.91, 145.20, 130.95, 125.21, 122.38, 52.80, 49.56, 38.02, 23.79. HRMS: calcd for $C_{10}H_{13}O_3^+$ $[M + H]^+$ 181.0859, found 181.0842.



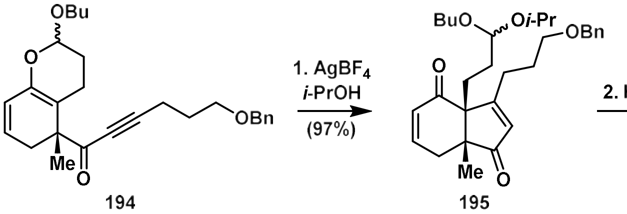
Alkene **187**: to a 25 mL round bottom flask containing enone **183** (12.7 mg, 0.0705 mmol) was added a magnetic stir bar. The flask was degassed and back filled with argon before anhydrous CH_2Cl_2 (1.5 mL) and allyltrimethylsilane (10 mg, 0.085 mmol, 1.2 equiv) was sequentially added. The reaction solution was cooled to -78 °C, and $BF_3{\cdot}Et_2O$ (12 μL, 12 mg, 0.085 mmol, 1.2 equiv) was added. The resultant solution was allowed to slowly warm up to 23 °C and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **183**. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 4/1→1/2) gave alkene **187** (10.6 mg, 2:1 *dr.*, 68% yield) as a colorless oil. **187**: diagnostic peaks on ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (ddd, *J* = 10.2, 5.3, 2.8 Hz, 1H), 5.94 (dq, *J* = 10.1, 1.5 Hz, 1H), 5.85 – 5.66 (m, 1H), 5.05 – 4.93 (m, 2H), 3.70 (2 s, 3H), 2.96 – 2.86 (m, 2H), 1.30 and 1.22 (2 s, 3H).



102 **180** **182** > 10:1 *dr.* **184**

Selective synthesis of enone **184**: A solution of crude **182** (synthesized following the procedure described before, from 1.00 g **102**, 8.68 mmol) in CH_2Cl_2 (16 mL) was transferred to a 100 mL round bottom flask. A magnetic stir bar and *p*-toluenesulfonic acid monohydrate (3.0 g, 17.4 mmol, 2.0 equiv) was added. The resultant solution was stirred at 23 °C for 4 h. Then, saturated aqueous $NaHCO_3$ solution (16 mL, 100 V%) was carefully added, followed by *m*-Chloroperoxybenzoic acid (77% suspension in water, 2.33 g, 10.4 mmol, 1.2 equiv). The biphasic mixture was stirred vigorously at 23 °C for 1 h before quenched by the addition of saturated aqueous $Na_2S_2O_3$ (50 mL). The reaction contents were diluted with CH_2Cl_2 (50 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated.

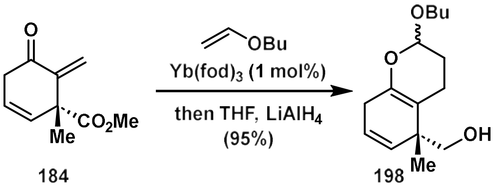
Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 4/1→1/2) gave enone **184** (751 mg, 48% yield) as a white crystalline solid.



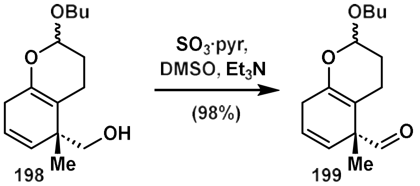
Acetal **195**: to a 25 mL round bottom flask equipped with a magnetic stir bar was added ketone **194** (synthesized following a similar procedure described below from **184** to **200**, 72.3 mg, 0.171 mmol, 1.0 equiv). The flask was degassed and back filled with argon before anhydrous isopropanol (3 mL) was added. $AgBF_4$ (7.0 mg, 0.034 mmol, 0.20 equiv) was added in one portion, and the reaction mixture was stirred at 23 °C for 2 h. At this time, TLC analysis showed the complete consumption of ketone **194**. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (5 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave acetal **195** (78.5 mg, 3:1 *dr.*, 97% yield) as a colorless oil. **187**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 6.85 (ddd, *J* = 10.4, 6.4, 2.0 Hz, 1H), 6.02 (d, *J* = 1.7 Hz, 1H), 5.94 (dd, *J* = 10.2, 2.3 Hz, 1H), 4.52 (d, *J* = 2.9 Hz, 2H), 4.50 – 4.44 (m, 1H), 3.92 – 3.74 (m, 1H), 3.61 – 3.33 (m, 4H), 2.99 – 2.90 (m, 1H), 2.72 (dddd, *J* = 17.5, 10.5, 5.3, 1.6 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.42 (ddd, *J* = 14.4, 12.0, 4.2 Hz, 1H), 2.34 – 2.24 (m, 1H), 1.90

(dtd, *J* = 13.0, 7.1, 3.8 Hz, 1H), 1.85 – 1.73 (m, 1H), 1.72 – 1.59 (m, 2H), 1.58 – 1.49 (m, 3H), 1.38 (ddd, *J* = 15.3, 7.8, 6.4 Hz, 2H), 1.22 – 1.17 (2 d, *J* = 6.1 Hz, 3H), 1.16 (2 s, 3H), 1.13 (2 d, *J* = 6.1 Hz, 3H), 0.97 – 0.85 (2 t, *J* = 7.1 Hz, 3H).

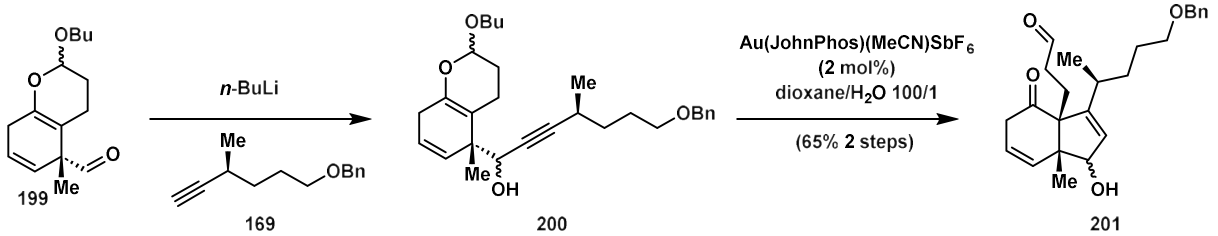
Aldehyde **196** was synthesized following the procedure described from **108** to **110**. Starting from **194** (36.1 mg, 0.0854 mmol), giving **196** (17.8 mg, 55% yield) as a colorless oil. **196**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.2 Hz, 1H), 7.40 – 7.27 (m, 5H), 6.89 (ddd, *J* = 10.2, 6.3, 2.1 Hz, 1H), 6.06 (d, *J* = 1.7 Hz, 1H), 5.98 (ddd, *J* = 10.1, 2.6, 1.1 Hz, 1H), 4.56 – 4.46 (m, 2H), 3.63 – 3.44 (m, 2H), 3.03 – 2.94 (m, 1H), 2.79 – 2.65 (m, 2H), 2.55 (dddd, *J* = 15.4, 12.0, 5.1, 1.8 Hz, 1H), 2.47 – 2.32 (m, 2H), 2.28 – 2.20 (m, 1H), 1.91 (qdd, *J* = 14.0, 7.3, 3.3 Hz, 2H), 1.84 – 1.73 (m, 1H), 1.11 (s, 3H).



Alcohol **198**: to a 100 mL round bottom flask containing enone **184** (466 mg, 2.59 mmol) was added a magnetic stir bar. The flask was degassed and back filled with argon before butyl vinyl ether (5.0 mL) and $Yb(fod)_3$ (27 mg, 0.026 mmol, 1.0 mol%) was sequentially added. The resultant solution was stirred at 23 ºC for 16 h, at which time TLC analysis showed the complete consumption of **184**. The reaction mixture was then cooled to 0 ºC. Anhydrous THF (5.0 mL, 100 V%) was added. $LiAlH_4$ (1.0 M in THF, 3.1 mL, 3.1 mmol, 1.2 equiv) was then added carefully. The reaction mixture was stirred at 0 ºC for 15 min, at which time TLC analysis showed the complete consumption of the hetero-Diels-Alder adduct. The reaction was then quenched by the dropwise addition of saturated aqueous Rochelle's salt (50 mL) and the resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 4/1→1/2) gave the mixed isomers of alcohol **198** (622 mg, 95% yield) as a colorless oil. The pure fractions of each isomers are used as analytical samples. Major isomer: ^1H NMR (400 MHz, C_6D_6) δ 5.59 (dt, *J* = 10.0, 3.4 Hz, 1H), 5.30 (dt, *J* = 10.0, 2.1 Hz, 1H), 4.84 (t, *J* = 2.7 Hz, 1H), 3.74 (dt, *J* = 9.5, 6.6 Hz, 1H), 3.45 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.35 (dt, *J* = 9.5, 6.3 Hz, 1H), 3.17 (dd, *J* = 10.4, 7.6 Hz, 1H), 2.80 – 2.62 (m, 2H), 2.14 – 2.00 (m, 1H), 1.78 (ddd, *J* = 12.7, 6.5, 3.2 Hz, 1H), 1.72 – 1.58 (m, 2H), 1.56 – 1.40 (m, 2H), 1.38 – 1.26 (m, 3H), 0.90 (s, 3H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 144.48, 133.72, 123.49, 106.31, 96.56, 68.40, 67.81, 43.13, 32.24, 29.38, 27.46, 23.04, 19.69, 15.26, 13.98. Minor isomer: ^1H NMR (400 MHz, C_6D_6) δ 5.58 (dt, *J* = 10.0, 3.4 Hz, 1H), 5.22 (dt, *J* = 10.0, 2.1 Hz, 1H), 4.86 (dd, *J* = 3.3, 2.5 Hz, 1H), 3.79 (dt, *J* = 9.6, 6.6 Hz, 1H), 3.44 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.38 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.11 (dd, *J* = 10.5, 3.7 Hz, 1H), 2.80 – 2.61 (m, 2H), 2.10 (dddd, *J* = 16.9, 9.1, 5.0, 2.3 Hz, 1H), 1.83 – 1.76 (m, 1H), 1.75 – 1.60 (m, 2H), 1.59 – 1.40 (m, 2H), 1.40 – 1.23 (m, 2H), 1.13 – 1.05 (m, 1H), 0.87 (s, 3H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 144.13, 133.38, 124.15, 106.22, 96.73, 68.48, 67.70, 43.17, 32.20, 29.34, 27.54, 22.52, 19.67, 15.38, 13.97.

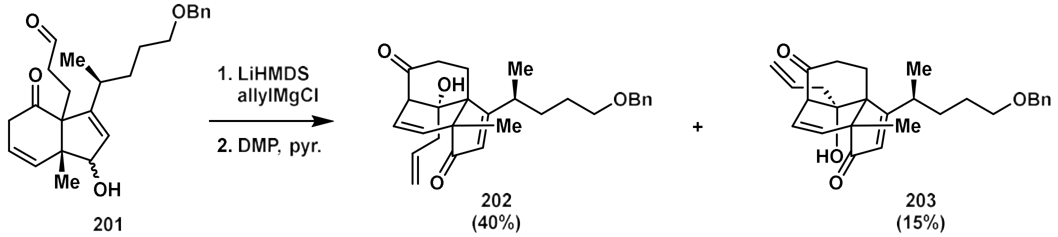


Aldehyde **199**: to a 100 mL round bottom flask equipped with a magnetic stir bar was added alcohol **198** (622 mg, 2.47 mmol, 1.0 equiv). The flask was degassed and back filled with argon. Anhydrous CH_2Cl_2 (25 mL), anhydrous DMSO (5 mL, 20V%) and anhydrous triethylamine (1.8 mL, 1.4 g, 12.4 mmol, 5.0 equiv) were sequentially added. The reaction flask was cooled to 0 ºC before sulfur trioxide pyridine complex (1.58 g, 9.88 mmol, 4.0 equiv) was added in one portion. The reaction mixture was allowed to warm up to 23 ºC and stirred at that temperature for 4 h, at which time TLC analysis showed the complete consumption of **198**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→6/1) gave the mixed diastereomers of aldehyde **199** (608 mg, 98% yield) as a colorless oil. **199**: ^{1}H NMR (400 MHz, C_6D_6) δ 9.25 – 9.21 (2 s, 1H, aldehyde), 5.56 – 5.51 (2 dt, 1H, alkene), 5.08 – 5.01 (2 dt, alkene), 4.80 and 4.73 (t and dd, 1H, glycoside), 3.78 – 3.68 (2 dt, 1H, butyl ether), 3.36 – 3.30 (2 dt, 1H, butyl ether), 2.70 – 2.59 (m, 2H, allylic), 1.79 – 1.25 (m, 8H, butyl and dihydropyrane), 1.22 and 1.24 (2s, 3H, Me), 0.84 – 0.79 (2t, 3H, butyl terminal Me). ^{13}C NMR (151 MHz, C_6D_6) δ 197.44, 197.41, 145.46, 144.97, 127.57, 127.34, 126.92, 126.80, 102.88, 102.67, 97.54, 96.73, 67.96, 67.81, 54.65, 54.25, 32.15, 32.07, 29.35, 29.30, 27.61, 27.05, 19.65, 19.61, 18.85, 18.31, 17.27, 16.38, 13.95, 13.93.



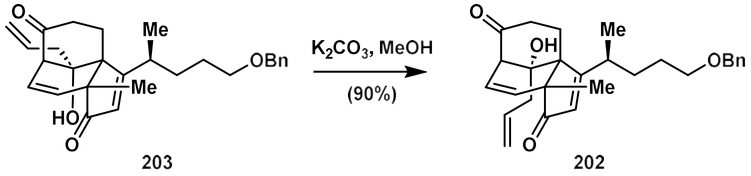
Alcohol **200**: to a 50 mL round bottom flask equipped with a magnetic stir bar was added alkyne **169** (640 mg, 3.16 mmol, 1.3 equiv). The flask was degassed and back filled with argon. Anhydrous THF (20 mL) was added, and the reaction flask was cooled to 0 ºC. *n*-BuLi (2.5 M in hexanes, 1.2 mL, 2.9 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was stirred at 0 ºC for 30 min. A solution of aldehyde **199** (608 mg, 2.43 mmol, 1.0 equiv) in anhydrous THF (5.0 mL) was added to the reaction mixture via syringe. The reaction mixture was continue stirred for another 30 min, at which time TLC analysis showed the complete consumption of aldehyde **199**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (20 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/Et_2O, 4/1→1/1) gave the mixed diastereomers of alcohol **200** as a colorless oil. Due to the complexity of the mixed isomers, no further characterization was made at this time.

Aldehyde **201**: to a 100 mL round bottom flask containing alcohol **200** (100% yield assumed, 2.43 mmol) was sequentially added a magnetic stir bar, 1,4-dioxane (25 mL), H_2O (0.25 mL, 1 V%), and Au(JohnPhos)(MeCN)SbF_6 (40 mg, 0.051 mmol, 2.0 mol%). The resultant solution was stirred at 23 ºC for 30 min, at which time TLC analysis showed the complete consumption of **201**. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/2) gave the mixed diastereomers of aldehyde **201** (628 mg, 65% over 2 steps) as a colorless oil. Noting that aldehyde **201** was not stable on silica gel, due to its tendency to undergo aldol condensation reaction, no attempts were made to separate the isomers of **201**. While a fast column purification resulted in minimal lost of the product, crude **201** could also be used in the following step to give a similar overall yield.

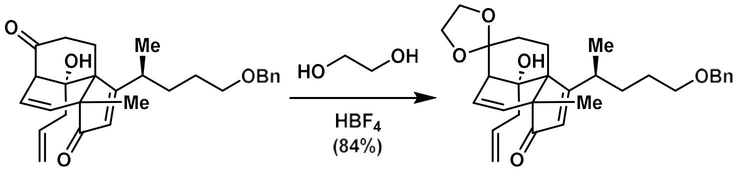


Tricyclic alkene **202** and **203**: to a 100 mL round bottom flask containing aldehyde **201** (628 mg, 1.58 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and backfilled with argon. Anhydrous THF (30 mL, 0.05 M substrate concentration due to solubility of the dianion species) was added. The reaction mixture was cooled to 0 ºC before LiHMDS (1.0 M in THF, 4.0 mL, 4.0 mmol, 2.5 equiv) was added. The resultant mixture was stirred at 0 ºC for 30 min, at which time TLC analysis showed the complete consumption of aldehyde **201**. Allylmagnesium chloride (2.0 M in THF, 4.8 mL, 6.0 mmol, 3.0 equiv) was added. The reaction mixture was allowed to warm up to 23 ºC and stirred at that temperature for 1 h. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (50 mL). The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (50 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude product was transferred to a 50 mL round bottom flask as a solution in CH_2Cl_2 (15 mL). A magnetic stir bar, pyridine (0.62 mL, 617 mg, 7.90 mmol, 5.0 equiv), Dess-Martin periodinane (2.01 g, 4.74 mmol, 3.0 equiv) were sequentially added. The reaction mixture was stirred at 23 °C for 16 h before quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (20 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated, and azeotrope with toluene. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave **202** (353 mg, 40% yield) and **203** (132 mg, 15% yield) as colorless oil. **202**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 6.14 (d, *J* = 9.7 Hz, 1H), 6.10 (s, 1H), 5.64 (dd, *J* = 9.6, 7.1 Hz, 1H), 5.62 – 5.51 (m, 1H), 5.22 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.49 (s, 2H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.00 (d, *J* = 6.9 Hz, 1H), 2.90 – 2.85 (m, 1H), 2.82 (dt, *J* = 13.2, 6.7 Hz, 1H), 2.67 (ddd, *J* = 15.9, 13.0, 7.4 Hz, 1H), 2.30 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.19 (dd, *J* = 13.8, 6.4 Hz, 1H), 1.93 (dd, *J* = 13.3, 7.4 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.67 – 1.55 (m, 3H), 1.39 (qd, *J* = 10.9, 4.6 Hz, 1H), 1.33 (s, 3H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.58, 208.29, 186.08, 138.52, 135.35, 131.74, 128.55, 127.79, 127.78, 127.55, 122.65, 121.99, 78.75, 73.19, 70.09, 59.26, 56.94, 56.89, 40.36, 34.53, 33.95, 33.45, 27.60, 24.04, 23.95, 19.33. **203**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H), 6.25 (d, *J* = 9.7 Hz, 1H), 6.13 (s, 1H), 5.87 – 5.70 (m, 1H), 5.60 (ddd, *J* = 9.6, 6.6, 2.9

Hz, 1H), 5.24 – 5.16 (m, 1H), 5.10 – 5.01 (m, 1H), 4.48 (s, 2H), 3.47 (td, *J* = 5.9, 2.2 Hz, 2H), 3.34 (d, *J* = 6.6 Hz, 1H), 2.68 (ddd, *J* = 17.4, 14.8, 8.4 Hz, 1H), 2.49 (dtd, *J* = 10.2, 6.6, 3.3 Hz, 1H), 2.38 – 2.15 (m, 4H), 2.10 (dd, *J* = 13.6, 8.3 Hz, 1H), 1.82 – 1.54 (m, 4H), 1.38 (d, *J* = 15.3 Hz, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.23 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.89, 181.06, 138.44, 136.95, 131.43, 128.59, 128.54, 128.45, 127.87, 127.79, 121.84, 120.69, 75.50, 73.23, 69.93, 58.76, 58.21, 56.30, 39.79, 35.26, 34.02, 33.26, 27.34, 22.82, 22.78, 18.39.

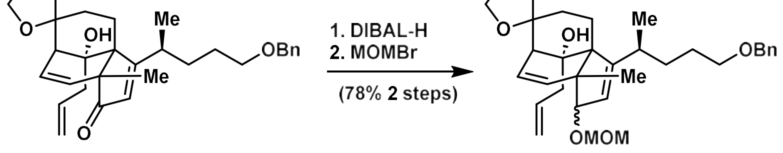


Tricyclic alkene **202**: To a 25 mL vial charged with alkene **203** (10.5 mg, 0.0242 mmol, 1.0 equiv) was added a magnetic stir bar, methanol (1.0 mL), and K_2CO_3 (10 mg, 0.0725 mmol, 3.0 equiv). The reaction mixture was heated to 50 ºC and was stirred vigorously at that temperature for 30 min, at which time TLC analysis showed the complete consumption of **202**. The reaction was cooled to 23 ºC, before diluted with H_2O (5 mL) and EtOAc (5 mL). The reaction contents were then transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave alkene **202** (9.4 mg, 90% yield) as a colorless oil.



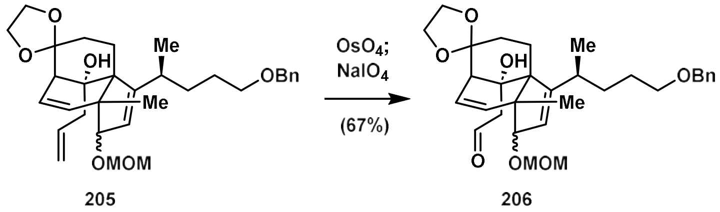
202 204

Ketal **204**: to a 50 mL equipped with a magnetic stir bar was added alkene **202** (243 mg, 0.559 mmol, 1.0 equiv), anhydrous CH_2Cl_2 (5.0 mL), ethylene glycol (5.0 mL, 100 V%), and $HBF_4 \cdot Et_2O$ (45 mg, 0.280 mmol, 0.50 equiv). The biphasic mixture was stirred vigorously for 16 h before quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave ketal **204** (225 mg, 84% yield) as a light yellow oil. **204**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 6.02 (s, 1H), 6.00 (d, *J* = 9.9 Hz, 1H), 5.76 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.62 (dd, *J* = 9.9, 6.8 Hz, 1H), 4.99 (dd, *J* = 10.3, 2.3 Hz, 1H), 4.89 (dd, *J* = 17.4, 2.2 Hz, 1H), 4.81 (s, 1H), 4.49 (s, 2H), 4.05 (dt, *J* = 8.7, 6.7 Hz, 2H), 3.97 (tt, *J* = 14.1, 7.2 Hz, 2H), 3.46 (t, *J* = 6.2 Hz, 2H), 2.88 (dt, *J* = 13.4, 7.0 Hz, 1H), 2.48 (td, *J* = 14.3, 4.7 Hz, 1H), 2.33 (d, *J* = 6.7 Hz, 1H), 2.02 (td, *J* = 13.7, 4.8 Hz, 1H), 1.82 (d, *J* = 7.1 Hz, 1H), 1.73 – 1.65 (m, 1H), 1.64 – 1.52 (m, 5H), 1.44 – 1.32 (m, 1H), 1.22 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H).

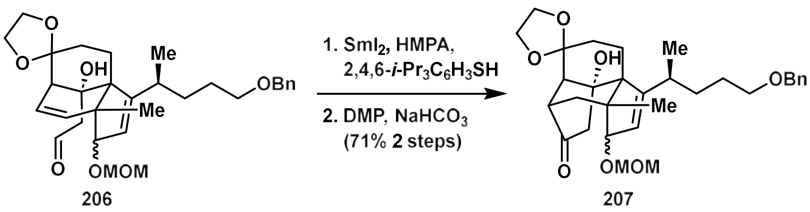


204 205

MOM-ether **205**: to a 25 mL round bottom flask containing ketal **204** (225 mg, 0.470 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and back filled with argon before anhydrous toluene (1.0 mL) was added. After the starting material dissolves, hexanes (5.0 mL) was added, and the reaction mixture was cooled to 0 ºC. DIBAL-H (1.0 M in toluene,1.4 mL, 1.4 mmol, 3.0 equiv) was added dropwise. The reaction was stirred at 0 ºC for 15 min, at which time TLC analysis showed only products with no UV absorptions. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (10 mL) and the resultant biphasic mixture was stirred vigorously for 1 h. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated to give a brown oil. The crude product was transferred to a 25 mL round bottom flask. A magnetic stir bar, 1,2-dichloroethane (4.0 mL), anhydrous *i*-Pr_2Net (0.33 mL, 230 mg, 1.76 mmol, 3.7 equiv), and bromomethyl methyl ether (132 mg, 1.05 mmol, 2.2 equiv) were sequentially added. The reaction flask was sealed and heated to 60 ºC. After stirring at 60 ºC for 72 h, TLC analysis showed the complete consumption of the reduction product. Upon cooling to 23 ºC, the reaction was quenched by the addition of MeOH (0.5 mL). The magnetic stir bar was extracted, and the reaction mixture was concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 8/1→4/1) gave MOM-ether **205** (193 mg, 78% over 2 steps, ~3:1 *dr.*) as a colorless oil.



Aldehyde **205**: to a 25 mL vial containing acetate **205** (193 mg, 0.368 mmol, 1.0 equiv) was sequentially added a magnetic stir bar, acetone (4.0 mL), *N*-Methylmorpholine *N*-oxide (65 mg, 0.552 mmol, 1.5 equiv), and OsO_4 (4% in H_2O, 0.12 mL, ca. 0.0184 mmol, 0.05 equiv). The reaction mixture was stirred at 23 ºC for 16 h, at which time TLC analysis showed the complete consumption of **205**. H_2O (4.0 mL, 100 V%) was added, followed by $NaIO_4$ (394 mg, 1.84 mmol, 5.0 equiv). The resultant mixture was stirred vigorously at 23 ºC for 30 min, and quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave aldehyde **206** (129 mg, 67% yield) as a colorless oil.

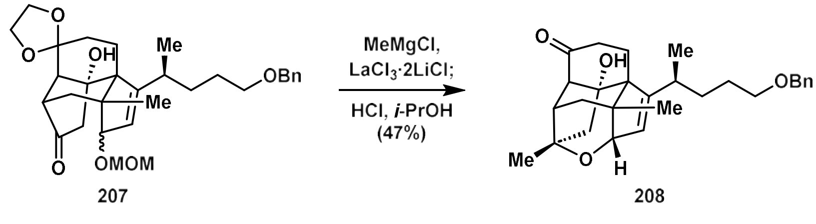


SmI_2-HMPA complex was prepared freshly: to a 50 mL round bottom flask equipped with a magnetic stir bar was added Sm (freshly filed powder, 300 mg, 2.0 mmol) and 1,2-diiodoethane (washed as a CH_2Cl_2 solution by saturated aqueous $NaHCO_3$, concentrated and dried, 282 mg, 1.0 mmol). The flask was degassed and back filled with argon. Anhydrous THF (10 mL) was added, and the resultant mixture was stirred vigorously at 23 °C for 2 h, giving a dark-blue solution. The solution can be stored under argon atmosphere for 5 days without significant drop in reactivity. Before used for the radical cyclization reaction, HMPA (1.40 mL, 1.42 g, 8.0 mmol) was added. The resultant mixture was stirred for 5 minutes, giving a purple solution, which was used as a 0.086 M solution of SmI_2-HMPA complex.

Ketone **207**: To a 10 mL round bottom flask containing aldehyde **206** (129 mg, 0.245 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and back filled with argon. Anhydrous THF (20 mL) and 2,4,6-Triisopropylbenzenethiol (**S11**) (70 mg, 0.294 mmol, 1.2 equiv) was sequentially added. The reaction system was cooled to 0 °C and purged with argon for 10 minutes. Under stirring, SmI_2-HMPA complex (0.086 M solution in THF) was added dropwise via syringe until the reaction solution kept its purple color for at least 5 minutes. Typically 2-3 equivalents of SmI_2-HMPA complex is needed. After stirring at 0 °C for 15 min, TLC analysis showed the complete consumption of **206**. The reaction was then quenched by the addition of saturated aqueous Rochelle's salt (5 mL) and the resultant biphasic mixture was stirred vigorously for 15 min. The reaction contents were then transferred to a separatory funnel, diluted with Et_2O (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed three times with 1/1 brine/H_2O, once with brine, dried (Na_2SO4), filtered, and concentrated to give crude product as a yellow oil that was transferred to a 25 mL vial for the next step without further purification.

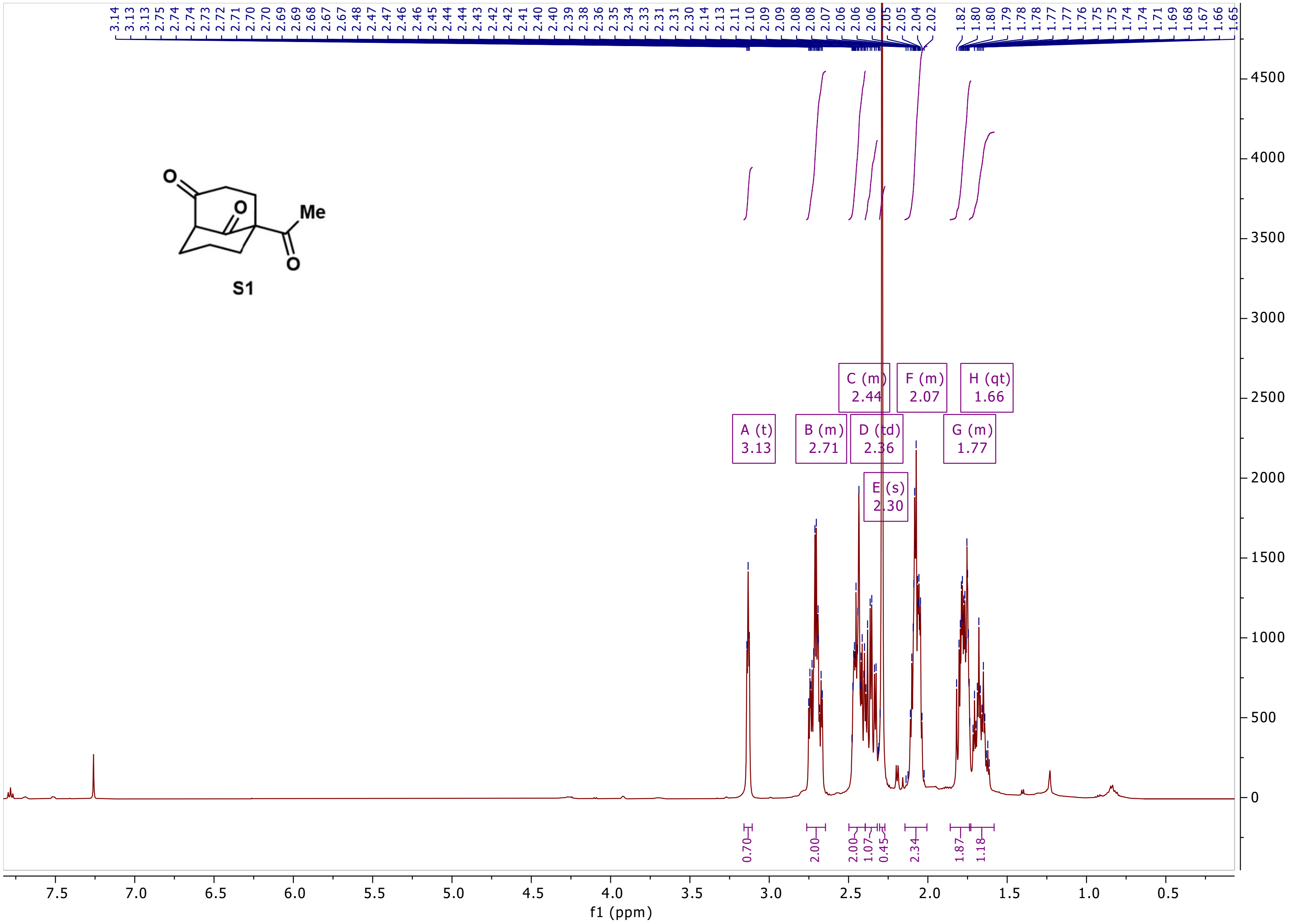
To the 25 mL vial containing the previous product was added a magnetic stir bar, CH_2Cl_2 (5 mL), $NaHCO_3$ (103 mg, 1.23 mmol, 5.0 equiv), and Dess-Martin periodinane (312 mg, 0.735 mmol, 3.0

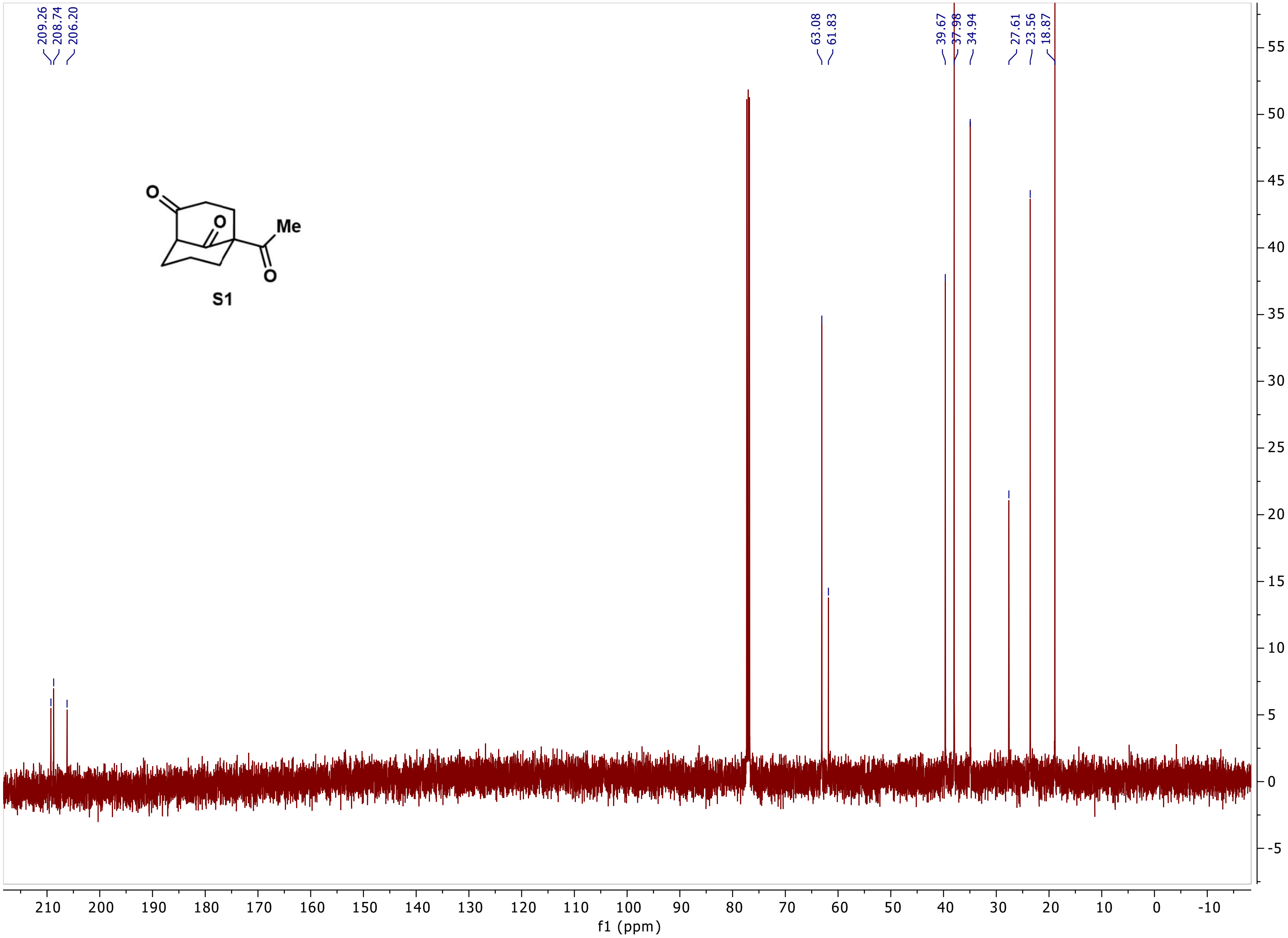
equiv). The reaction mixture was stirred at 23 °C for 16 h before quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction contents were diluted with CH_2Cl_2 (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO4), filtered, and concentrated. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 4/1→1/1) gave ketone **207** (91 mg, 71% over 2 steps) as a light-yellow oil. An analytical sample of the major diastereomer was prepared from preparative TLC (silica, hexanes/EtOAc, 1/1). Ketone **207** (major isomer): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.77 (d, *J* = 2.8 Hz, 1H), 4.53 (s, 2H), 4.49 (s, 2H), 4.06 – 3.95 (m, 4H), 3.70 (d, *J* = 2.8 Hz, 1H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.32 (d, *J* = 1.5 Hz, 3H), 3.07 (d, *J* = 19.4 Hz, 1H), 2.58 – 2.55 (m, 1H), 2.40 (q, *J* = 6.9 Hz, 1H), 2.31 (td, *J* = 14.4, 4.9 Hz, 1H), 2.07 – 1.97 (m, 3H), 1.91 – 1.86 (m, 2H), 1.67 (dd, *J* = 15.1, 5.3 Hz, 1H), 1.64 – 1.49 (m, 4H), 1.44 (tt, *J* = 11.7, 6.1 Hz, 1H), 1.35 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.07 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 214.72, 159.07, 138.79, 128.50, 127.77, 127.66, 125.33, 109.38, 96.57, 89.91, 78.60, 73.05, 70.74, 64.92, 64.50, 57.38, 55.68, 52.22, 50.46, 50.00, 46.19, 35.66, 32.38, 32.18, 31.47, 29.13, 28.16, 22.52, 21.56.



Pentacyclic ketone **208**: To a 10 mL round bottom flask containing ketone **207** (71.4 mg, 0.136 mmol, 1.0 equiv) was added a magnetic stir bar. The flask was degassed and backfilled with argon. Anhydrous THF (3.0 mL) and $LaCl_3 \cdot 2LiCl$ (0.6 M in THF, 1.4 mL, 0.82 mmol, 6.0 equiv) was added. The resultant solution was stirred at 23 ºC for 15 min. MeMgCl (3.0 M in THF, 0.23 mL, 0.68 mmol, 5.0 equiv) was added slowly. The reaction mixture was then heated to 50 ºC and stirred at that temperature for 30 min, at which time TLC analysis showed the complete consumption of **207**. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (5 mL) and Na_2EDTA. The resultant biphasic mixture was stirred vigorously for 15 min. The reaction contents were then transferred to a separatory funnel, diluted with EtOAc (10 mL) and H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO4), filtered, and concentrated. The crude product was then transferred to a 25 mL round bottom flask. A magnetic stir bar, *i*-PrOH (3.0 mL), and HCl (4-6 M in *i*-PrOH, 0.6 mL, 20 V%) were sequentially added. The resultant solution was heated to 50 ºC and stirred at that temperature for 12 h. The reaction contents were then concentrated under reduced pressure. Purification of the resultant residue by flash column chromatography (silica gel, hexanes/EtOAc, 2/1→1/1) gave pentacyclic ketone **208** (27.7 mg, 47% yield) as a colorless oil. **208**: diagnostic peaks on ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (d, *J* = 3.0 Hz, 1H, alkene), 4.49 (apparent d, *J* = 9.1 Hz, 2H, benzylic), 3.93 (d, *J* = 3.0 Hz, 1H, allyl ether), 3.44 (t, *J* = 6.3 Hz, 2H, benzyl ether).

Selected NMR Spectrums

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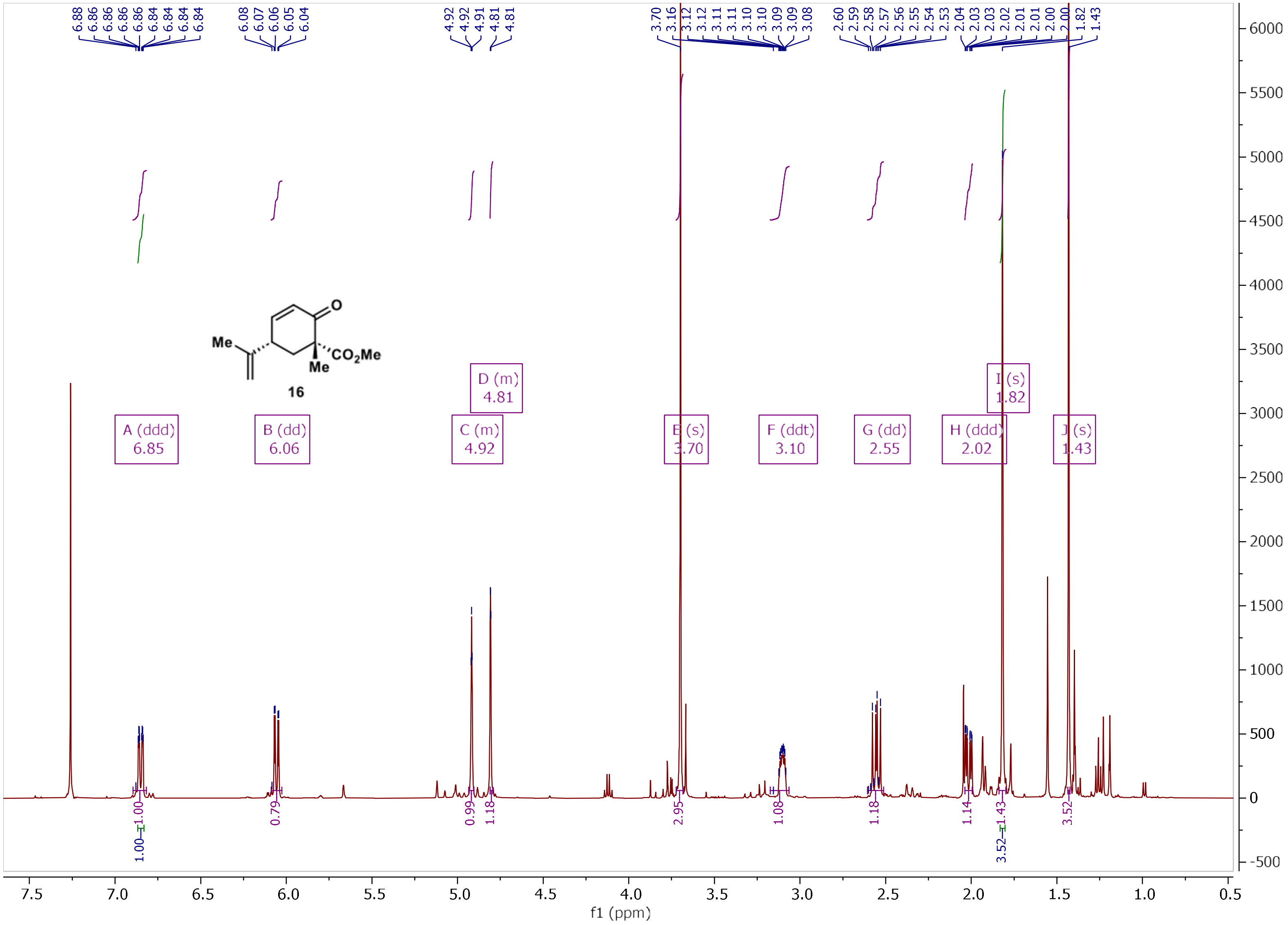
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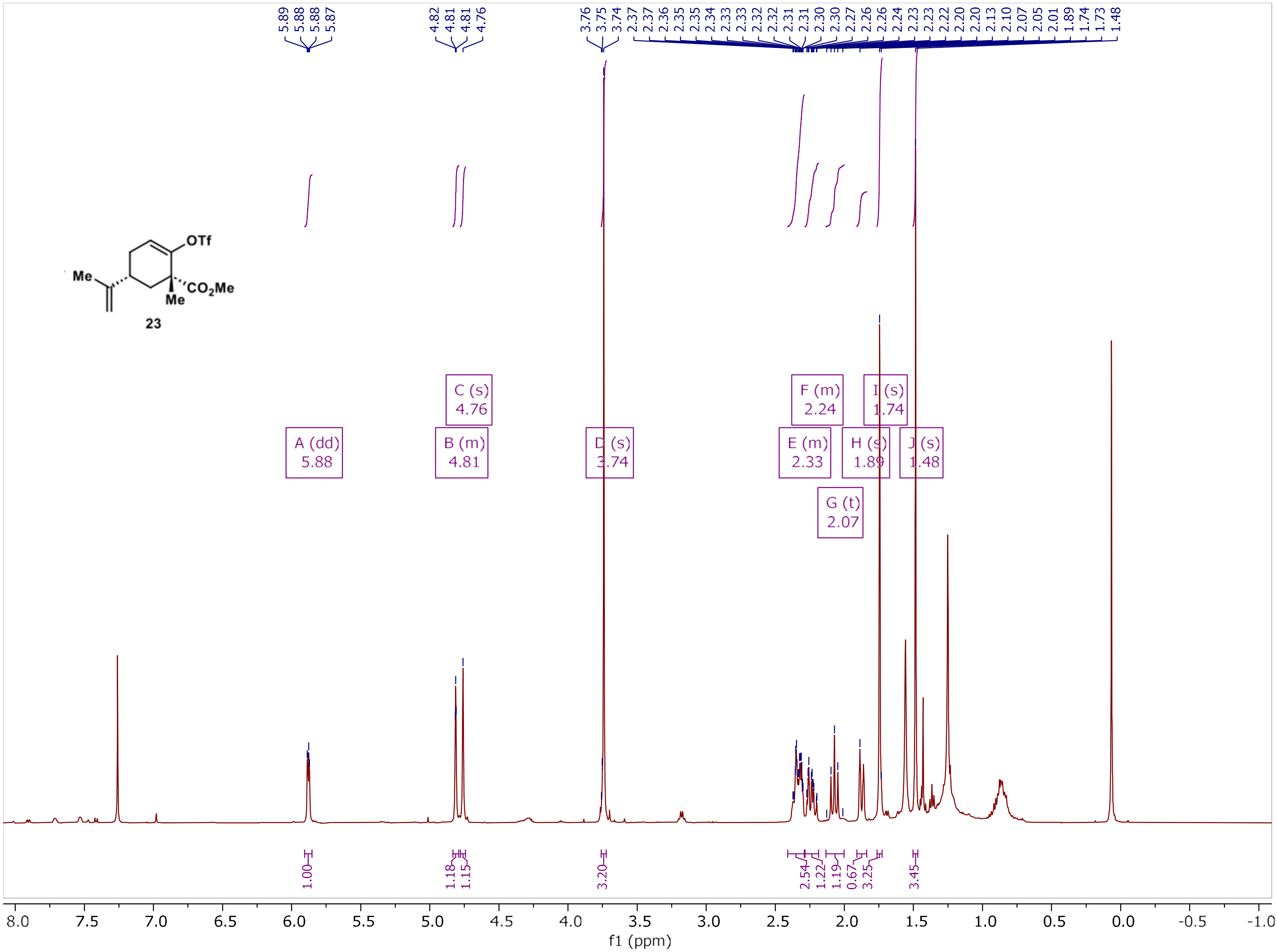

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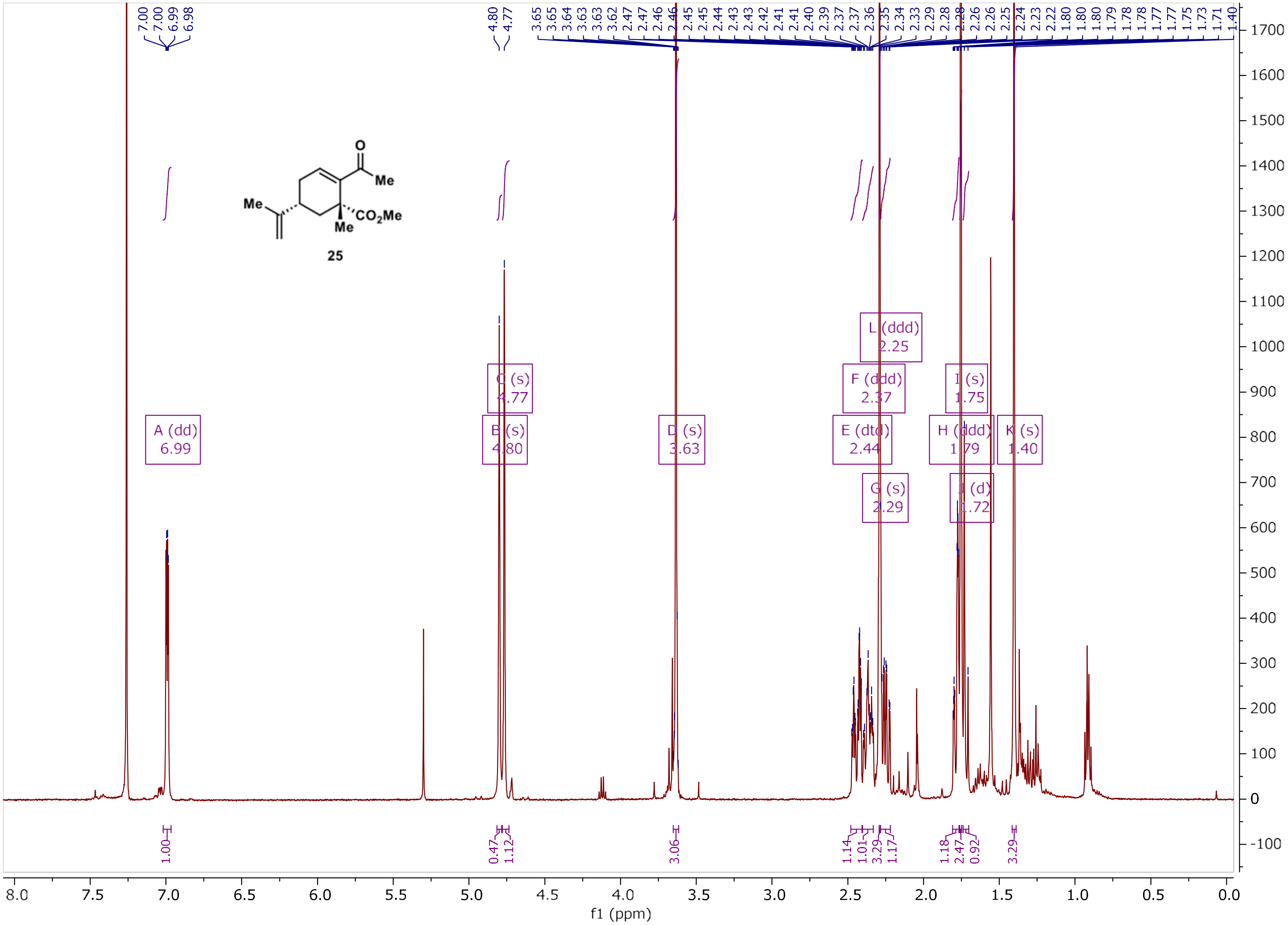
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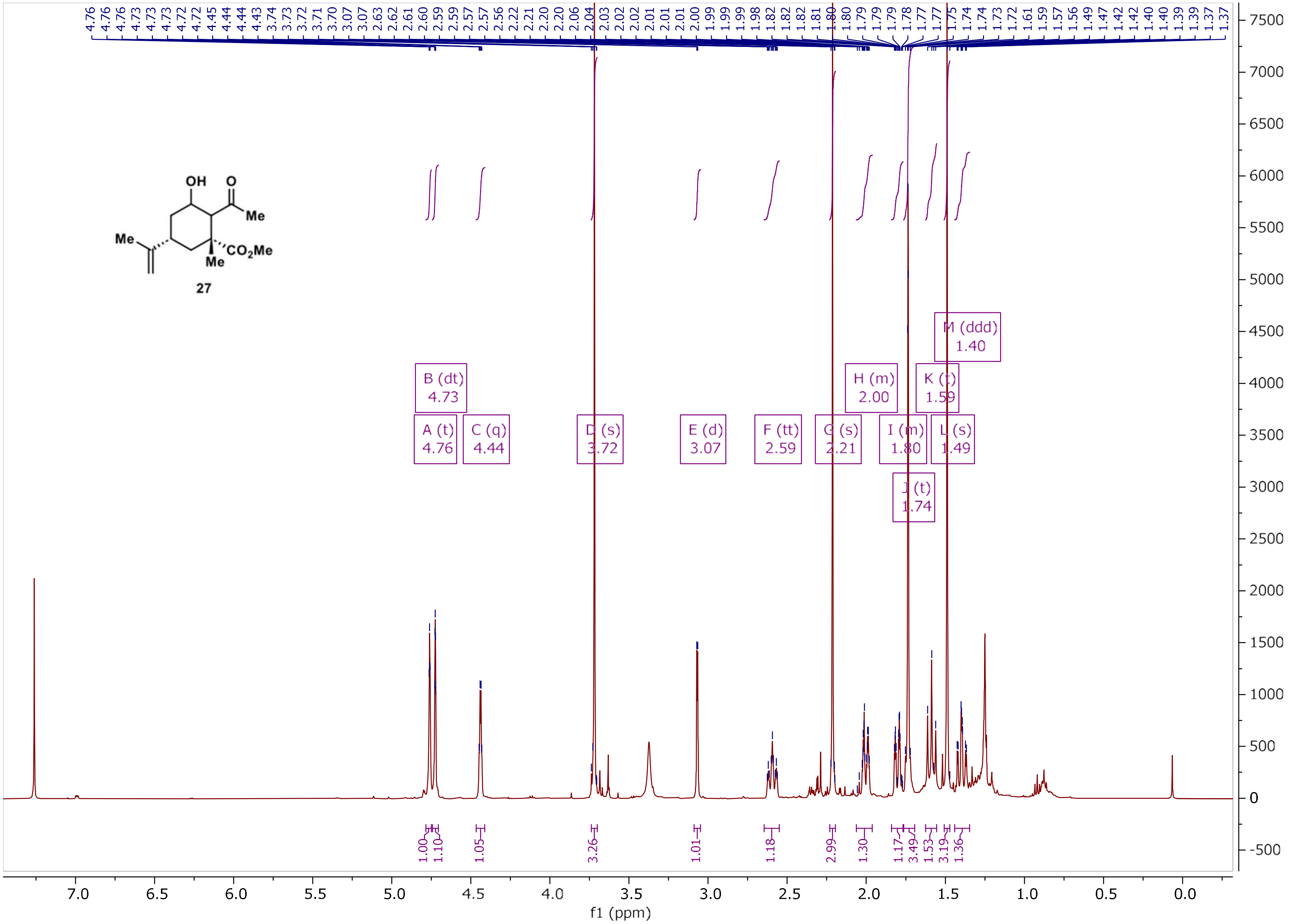
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Me
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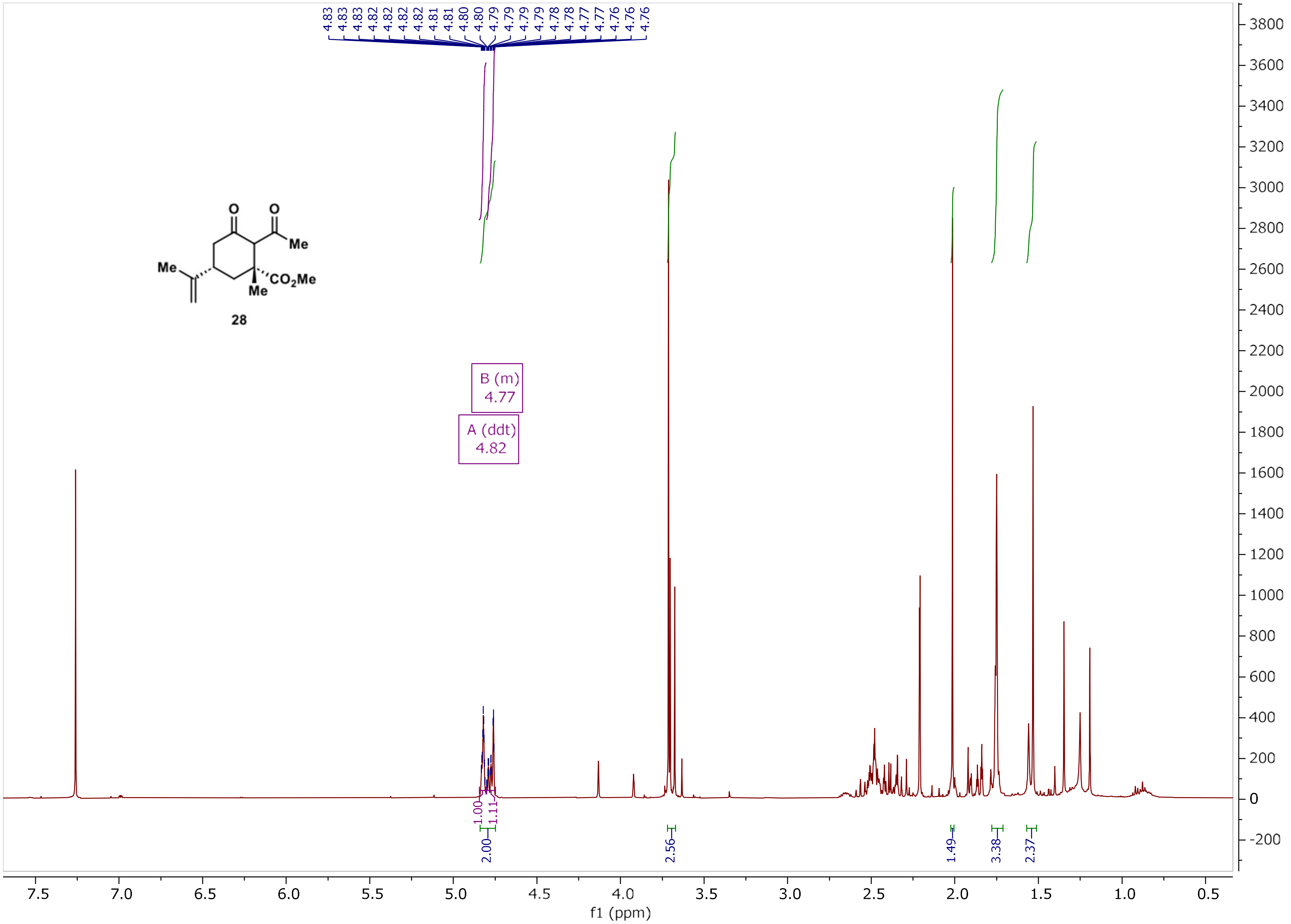

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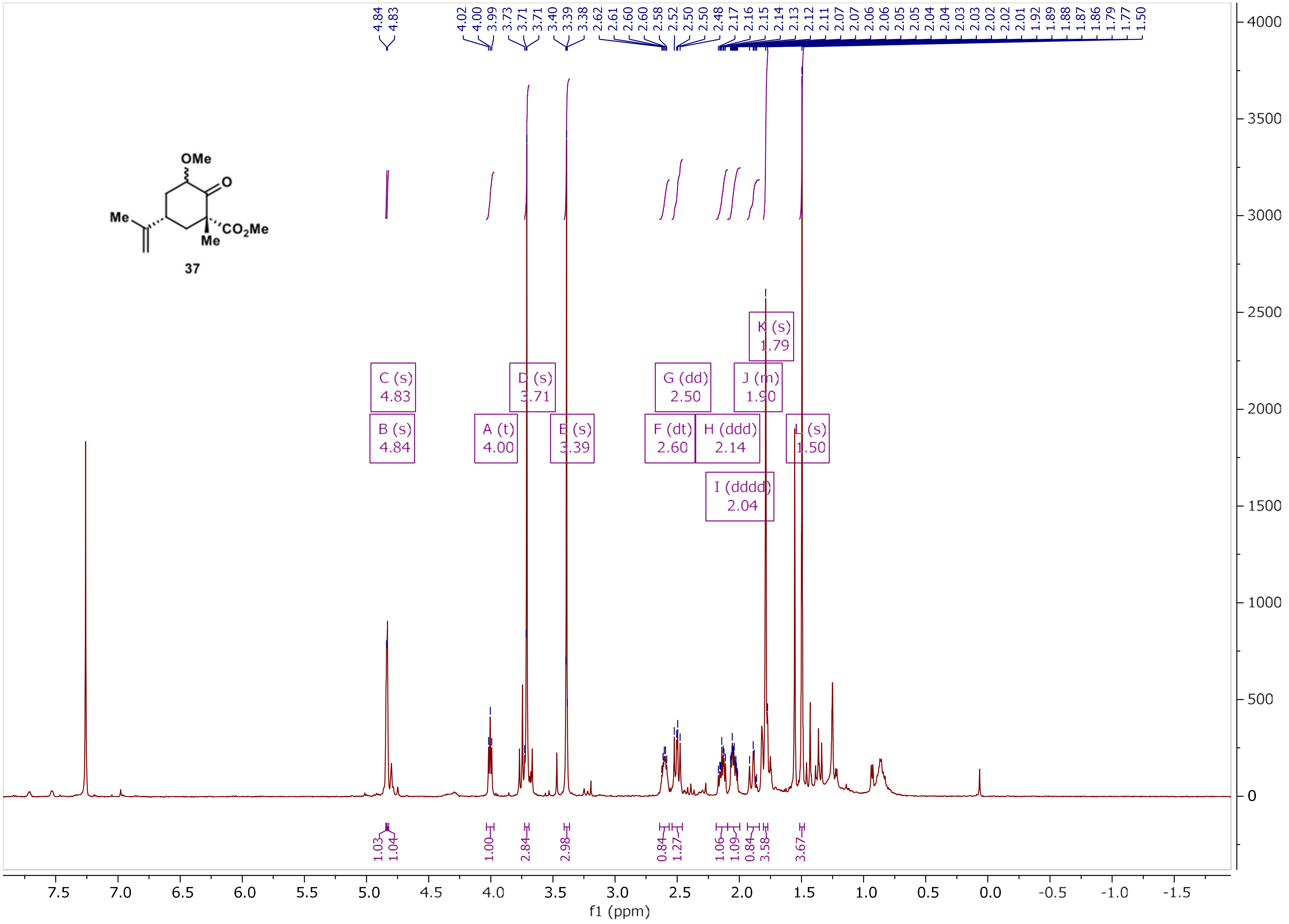OMe
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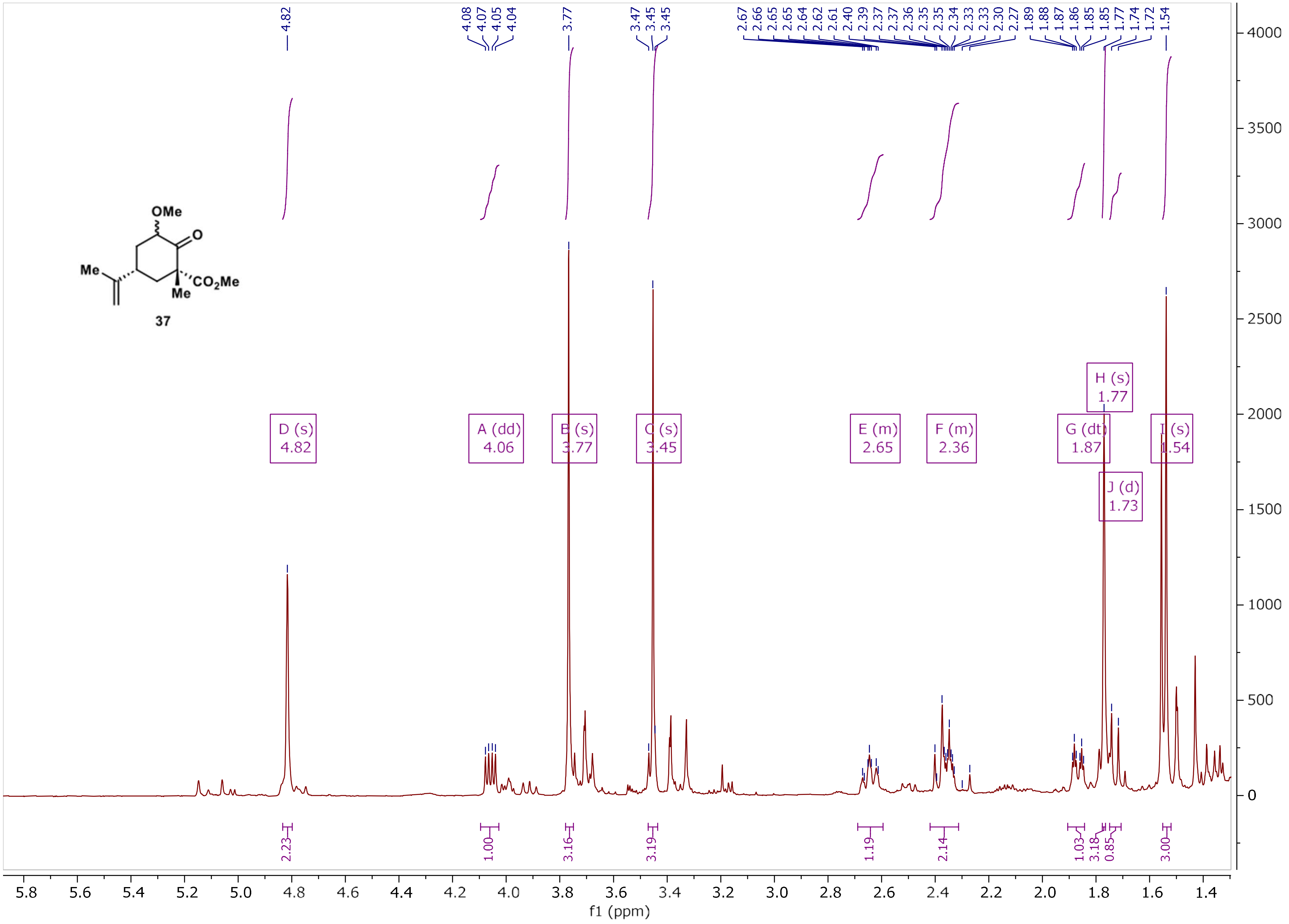
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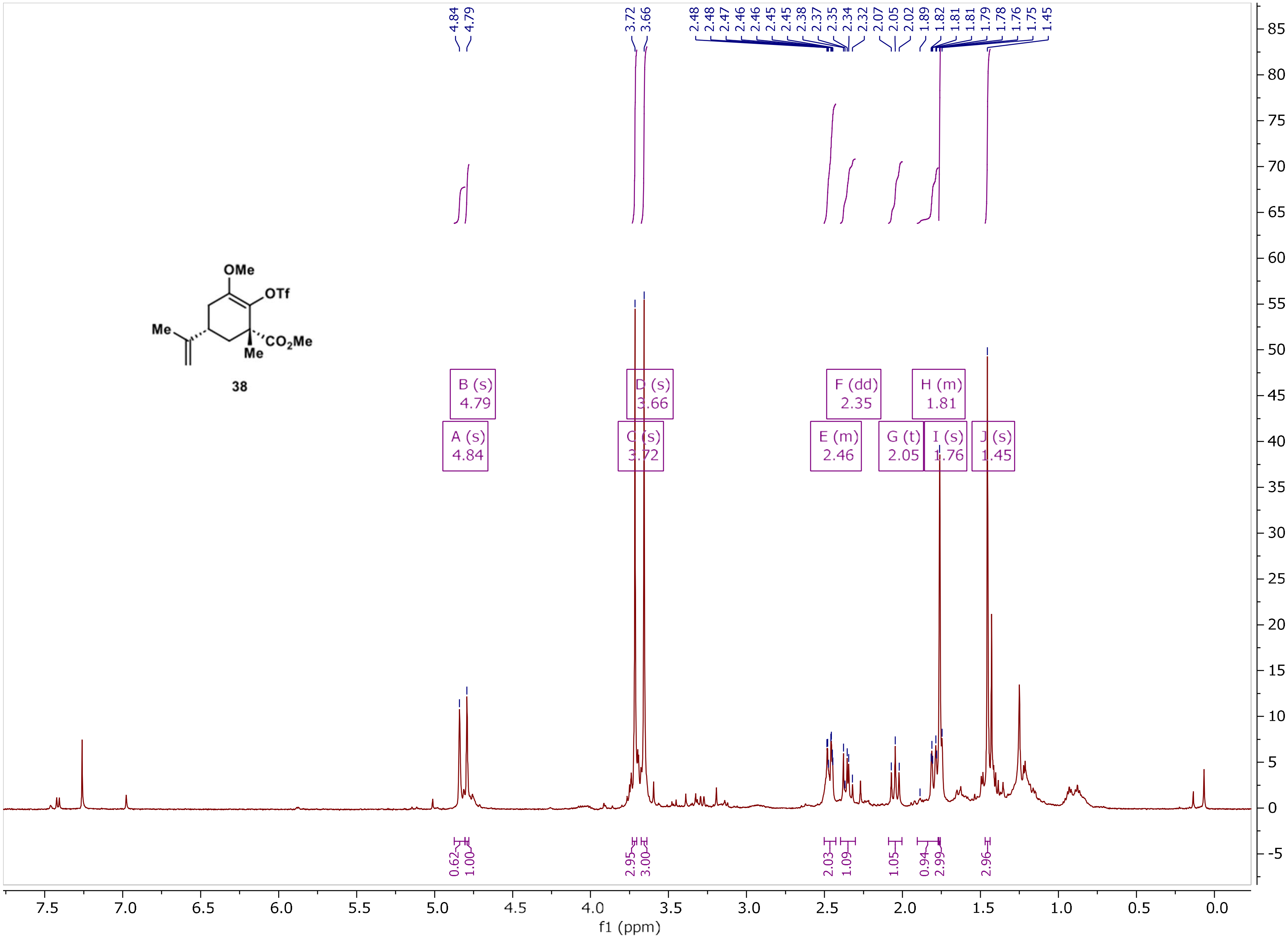
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C (s) 3.72
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H (m) 1.81
G (t) 2.05
I (s) 1.76
J (s) 1.45
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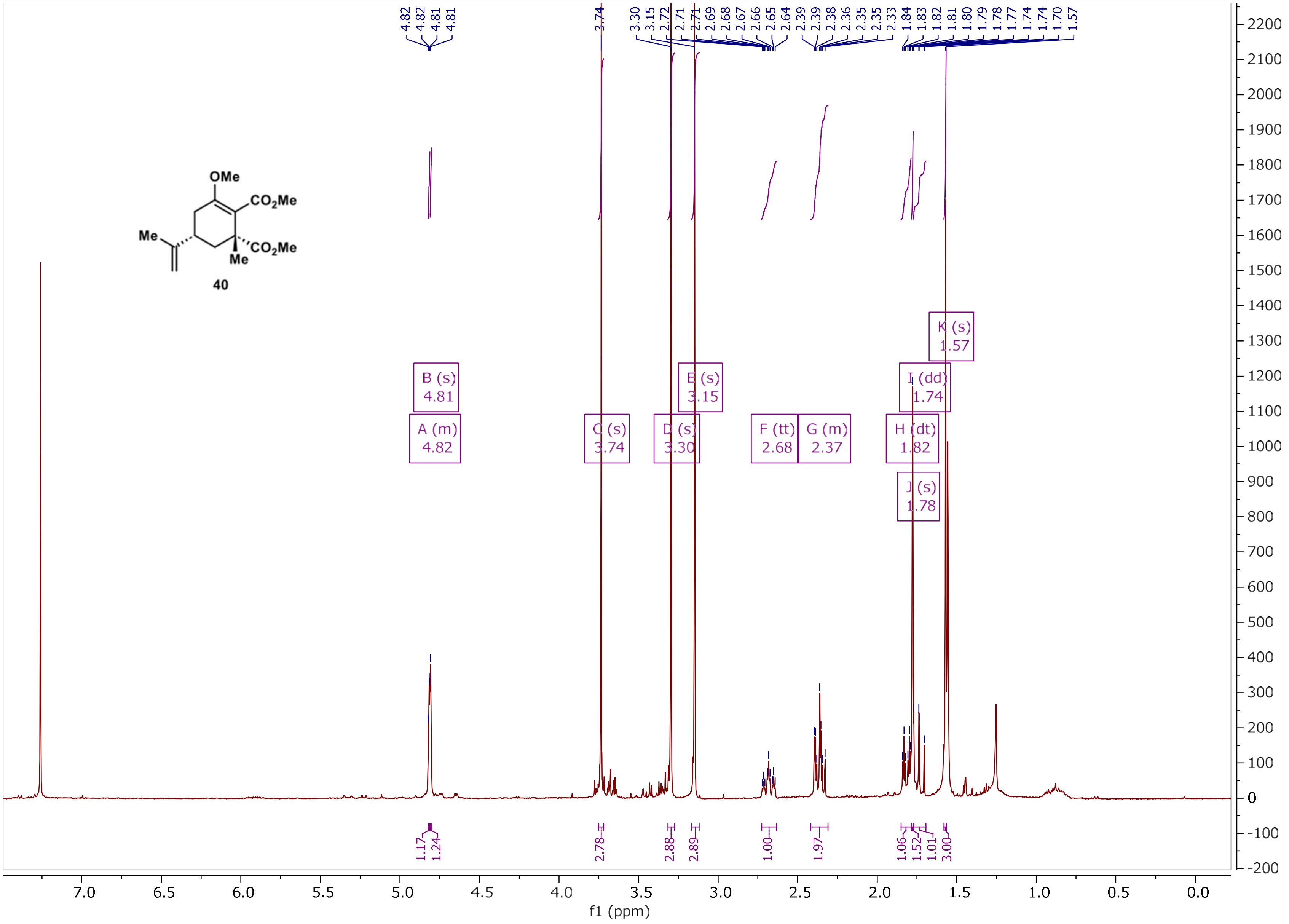
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1.74
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1.57
B (s) 4.81
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C (s) 3.74
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K (s) 1.57
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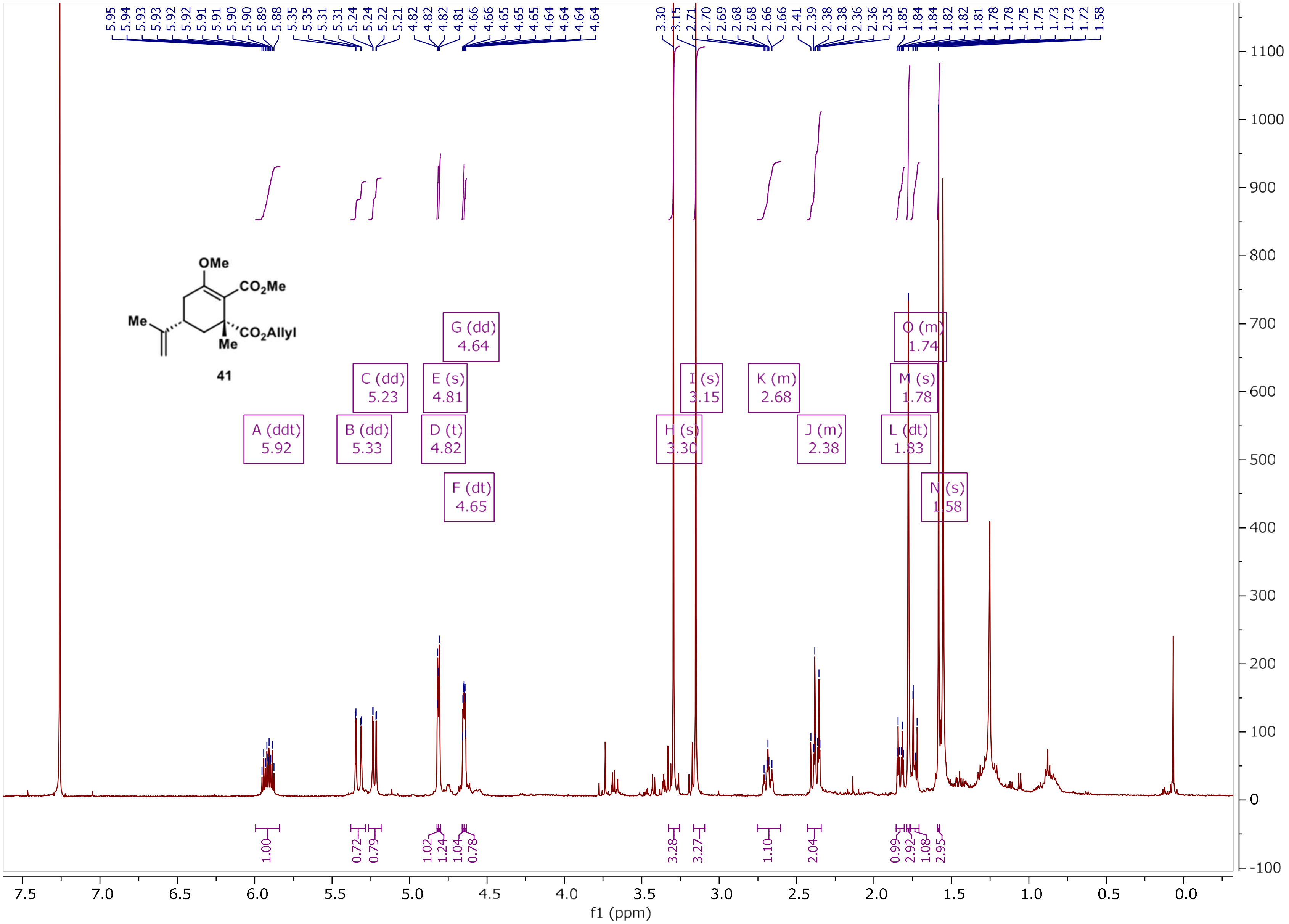
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3.30 3.15 2.71 2.70 2.69 2.68 2.68 2.66 2.66 2.41 2.39 2.38 2.38 2.36 2.36 2.35 1.85 1.84 1.84 1.82 1.82 1.81 1.78 1.78 1.75 1.75 1.73 1.73 1.72 1.58
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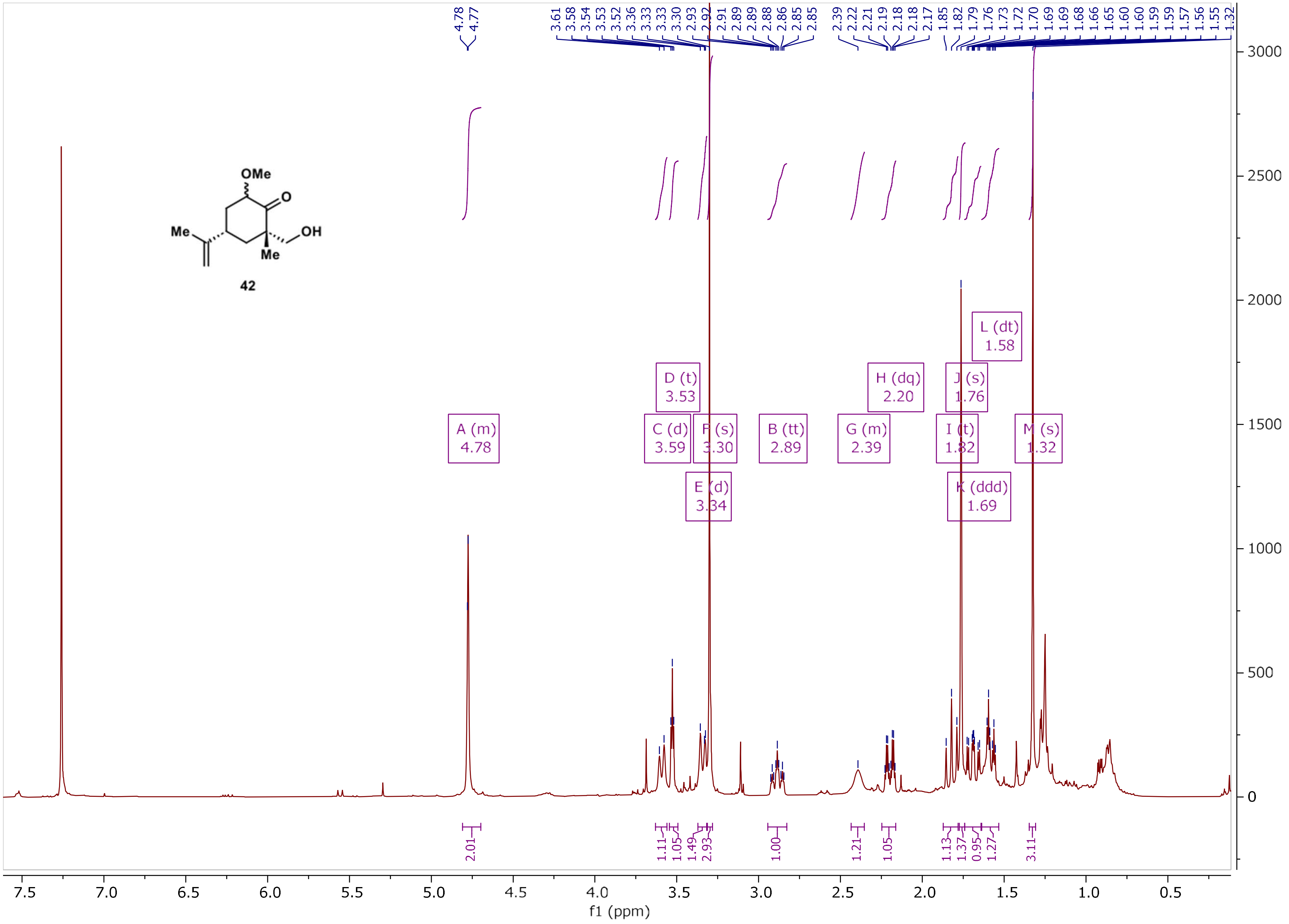
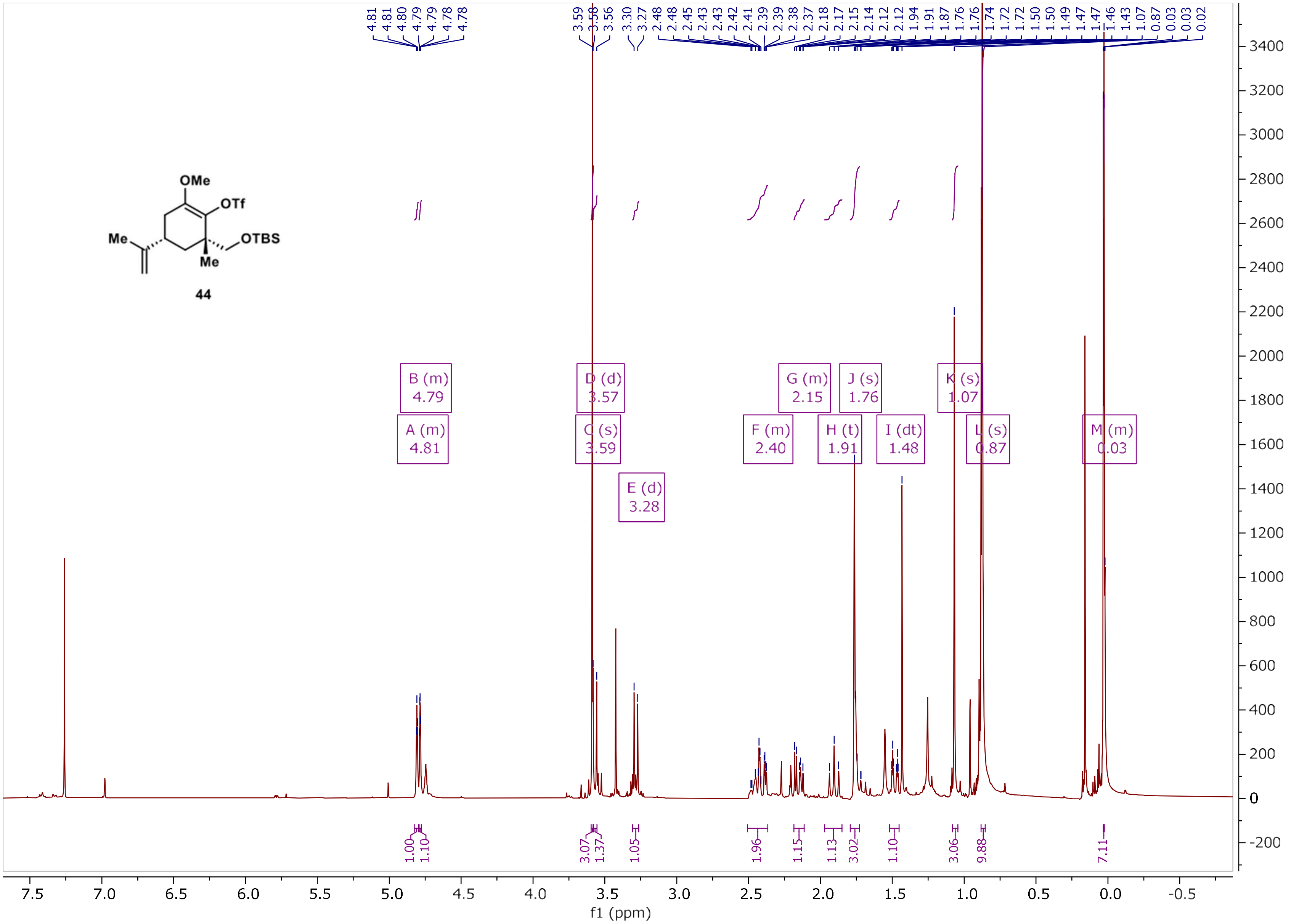
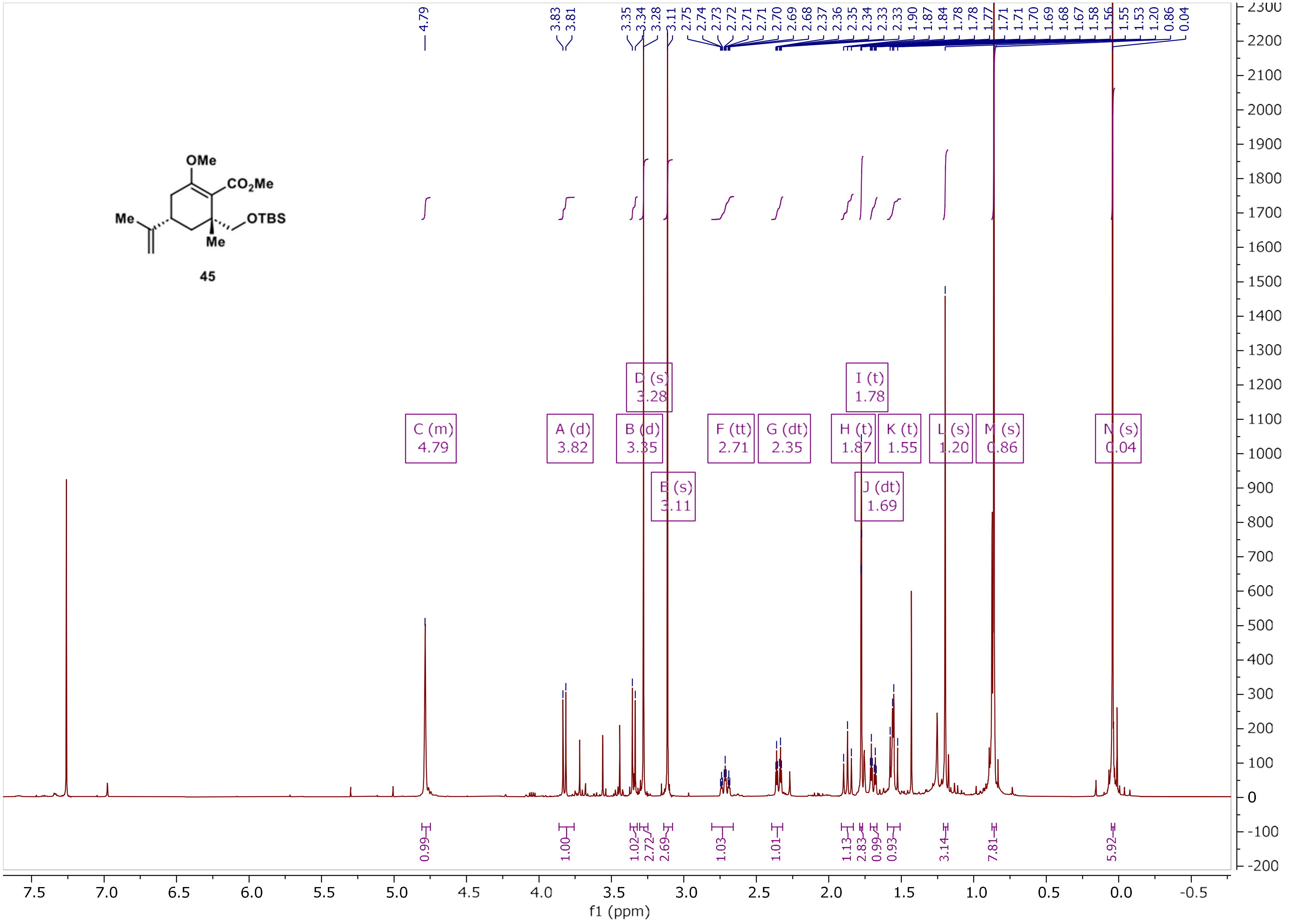
C (dd) 5.23
D (t) 4.82
E (s) 4.81
F (dt) 4.65
G (dd) 4.64
H (s) 3.30
I (s) 3.15
K (m) 2.68
J (m) 2.38
L (dt) 1.83
M (s) 1.78
N (s) 1.58
O (m) 1.74
1.00
0.72
0.79
1.02
1.24
1.04
0.78
3.28
3.27
1.10
2.04
0.99
2.92
1.08
2.95
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
1100 1000 900 800 700 600 500 400 300 200 100 0 -100

41

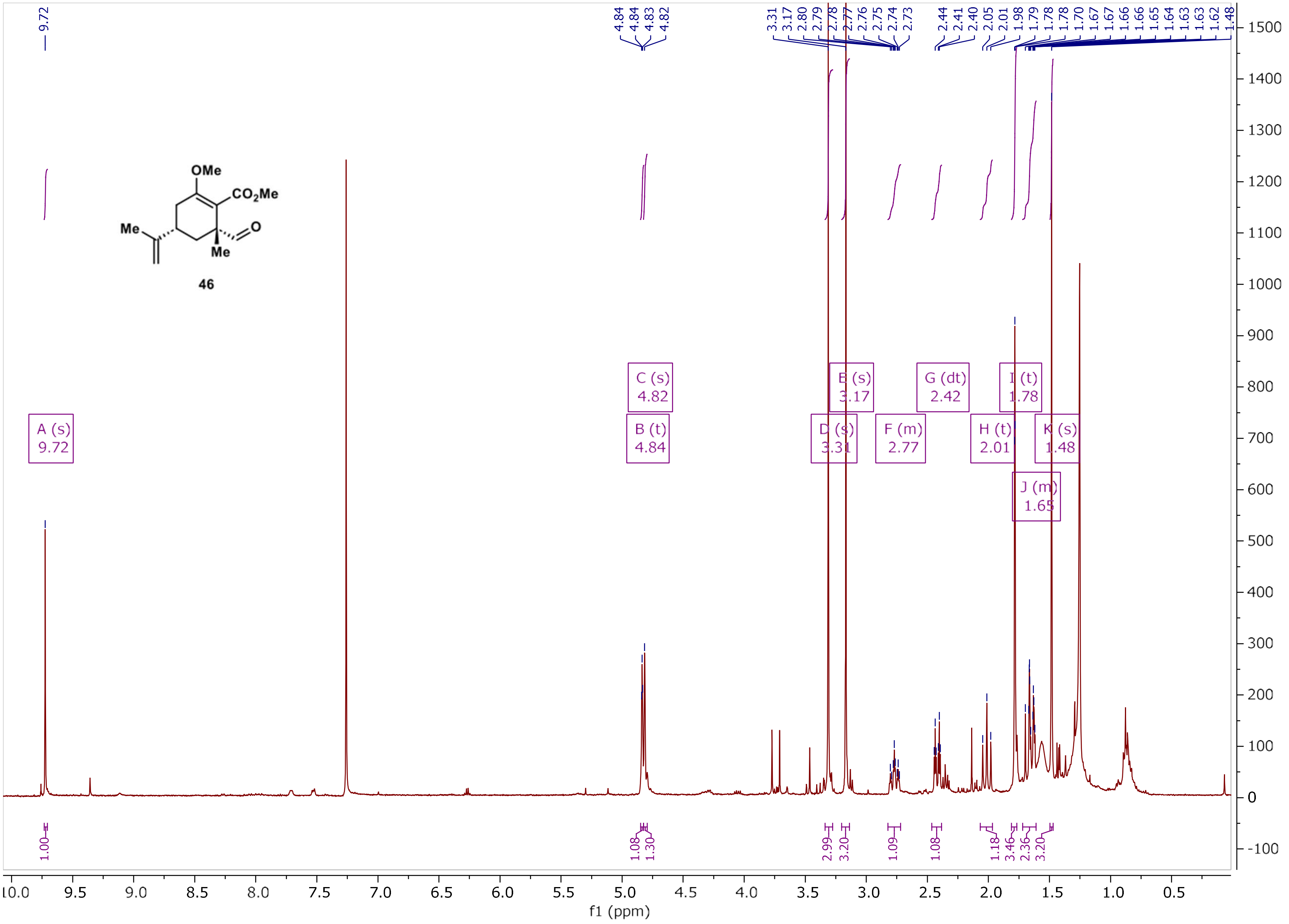

OMe
O
OH
Me
Me
42
4.78
4.77
3.61
3.58
3.54
3.53
3.52
3.36
3.33
3.33
3.30
2.93
2.92
2.91
2.89
2.89
2.88
2.86
2.85
2.85
2.39
2.22
2.21
2.19
2.18
2.18
2.17
1.85
1.82
1.79
1.76
1.73
1.72
1.70
1.69
1.69
1.68
1.66
1.65
1.60
1.60
1.59
1.59
1.57
1.56
1.55
1.32
A (m)
4.78
C (d)
3.59
D (t)
3.53
E (d)
3.34
F (s)
3.30
B (tt)
2.89
G (m)
2.39
H (dq)
2.20
I (t)
1.82
J (s)
1.76
K (ddd)
1.69
L (dt)
1.58
M (s)
1.32
2.01
1.11
1.05
1.49
2.93
1.00
1.21
1.05
1.13
1.37
0.95
1.27
3.11
3000
2500
2000
1500
1000
500
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



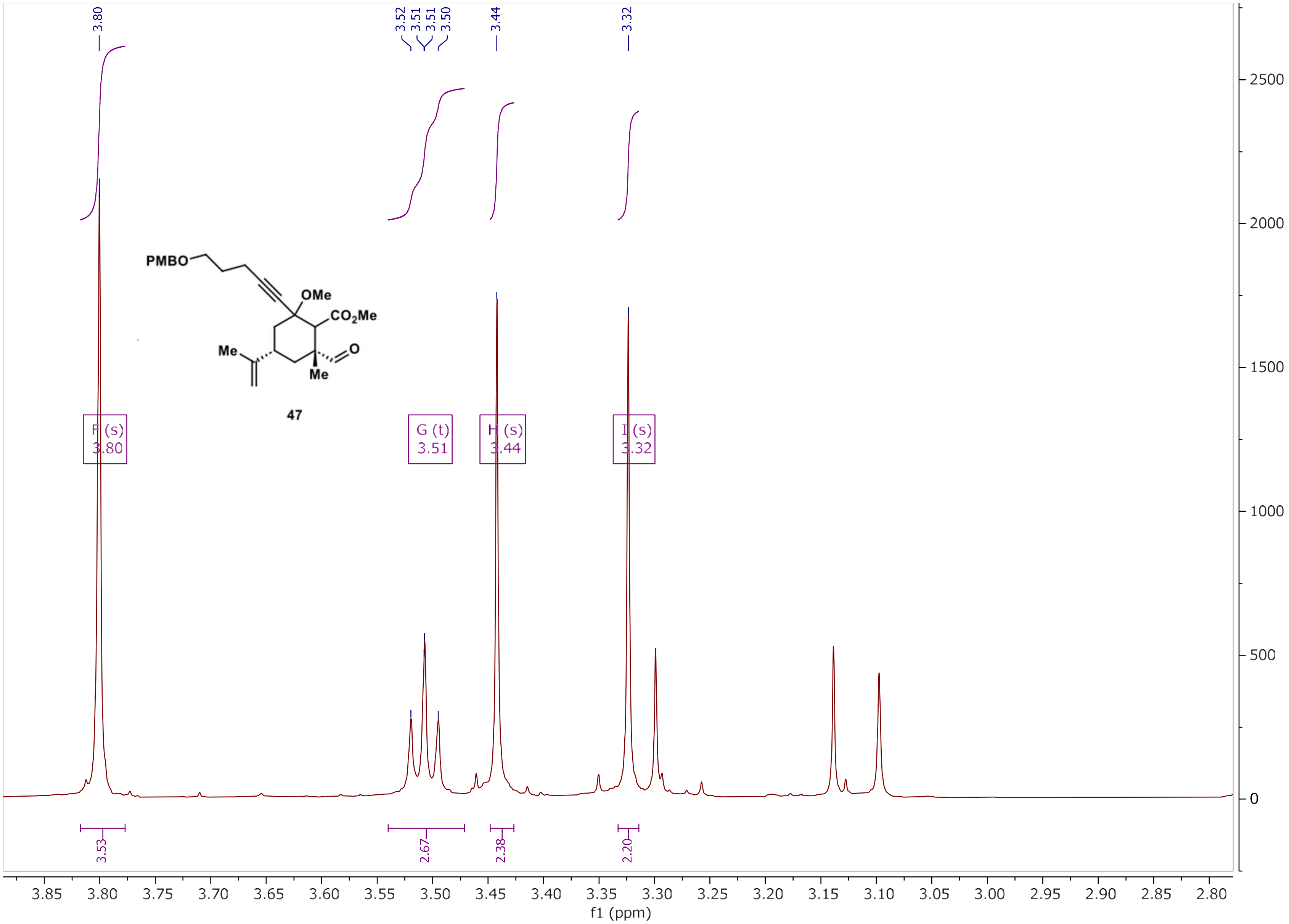
4.81
4.81
4.80
4.79
4.79
4.78
4.78
3.59
3.58
3.56
3.30
3.27
2.48
2.48
2.45
2.43
2.43
2.42
2.41
2.39
2.39
2.38
2.37
2.18
2.17
2.15
2.14
2.12
2.12
1.94
1.91
1.87
1.76
1.76
1.74
1.72
1.72
1.50
1.50
1.49
1.47
1.47
1.46
1.43
1.07
0.87
0.03
0.03
0.02
OMe
OTf
Me
OTBS
Me
44
B (m) 4.79
A (m) 4.81
D (d) 3.57
C (s) 3.59
E (d) 3.28
G (m) 2.15
F (m) 2.40
J (s) 1.76
H (t) 1.91
I (dt) 1.48
K (s) 1.07
L (s) 0.87
M (m) 0.03
1.00
1.10
3.07
1.37
1.05
1.96
1.15
1.13
3.02
1.10
3.06
9.88
7.11
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
f1 (ppm)
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

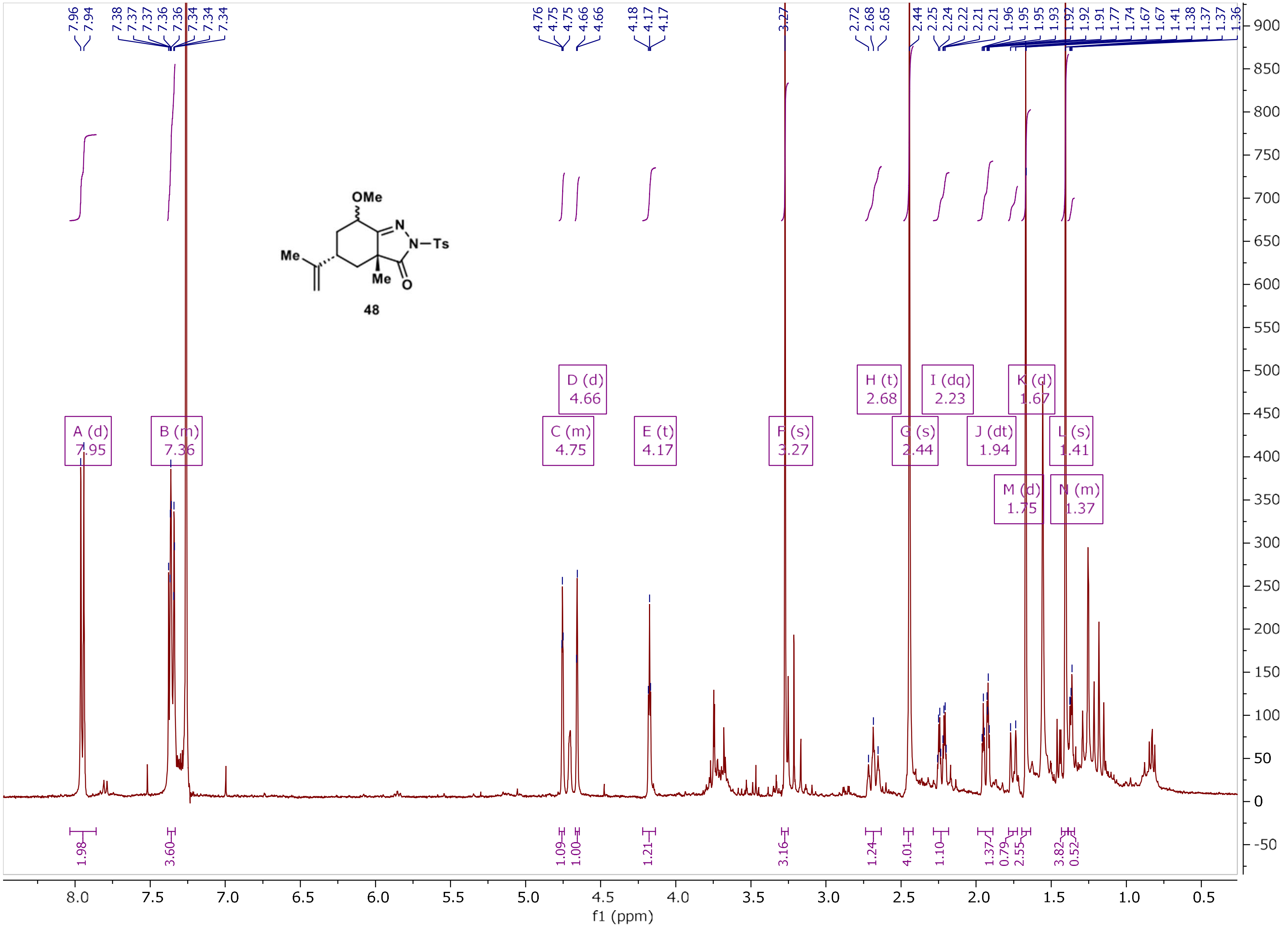


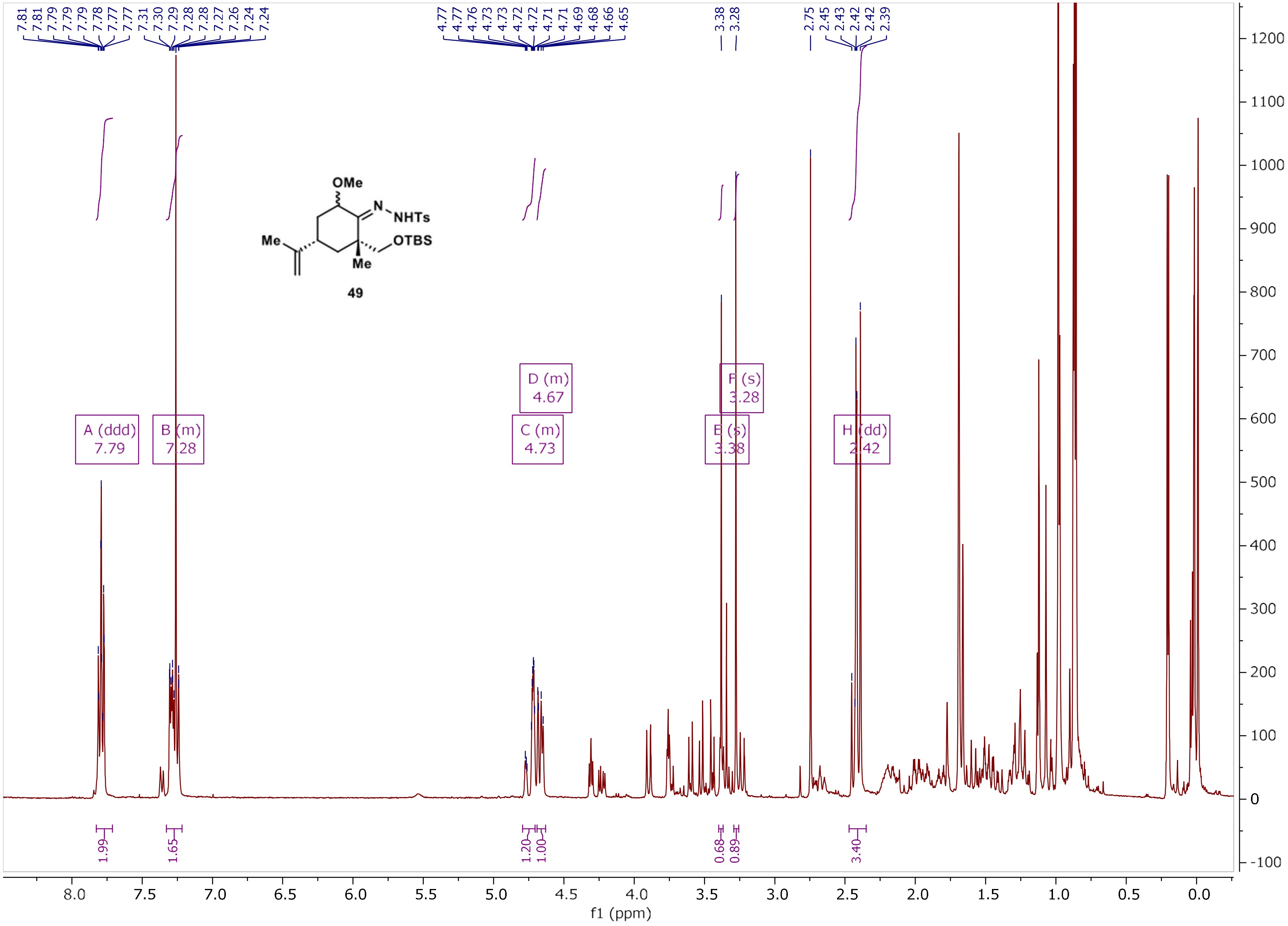
OMe
CO$_2$Me
Me
OTBS
Me
45
4.79
3.83
3.81
3.35
3.34
3.28
3.11
2.75
2.74
2.73
2.72
2.71
2.71
2.70
2.69
2.68
2.37
2.36
2.35
2.34
2.33
2.33
1.90
1.87
1.84
1.78
1.78
1.77
1.71
1.71
1.70
1.69
1.68
1.67
1.58
1.56
1.55
1.53
1.20
0.86
0.04
C (m) 4.79
A (d) 3.82
B (d) 3.35
D (s) 3.28
E (s) 3.11
F (tt) 2.71
G (dt) 2.35
H (t) 1.87
I (t) 1.78
J (dt) 1.69
K (t) 1.55
L (s) 1.20
M (s) 0.86
N (s) 0.04
0.99
1.00
1.02
2.72
2.69
1.03
1.01
1.13
2.83
0.99
0.93
3.14
7.81
5.92
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)
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

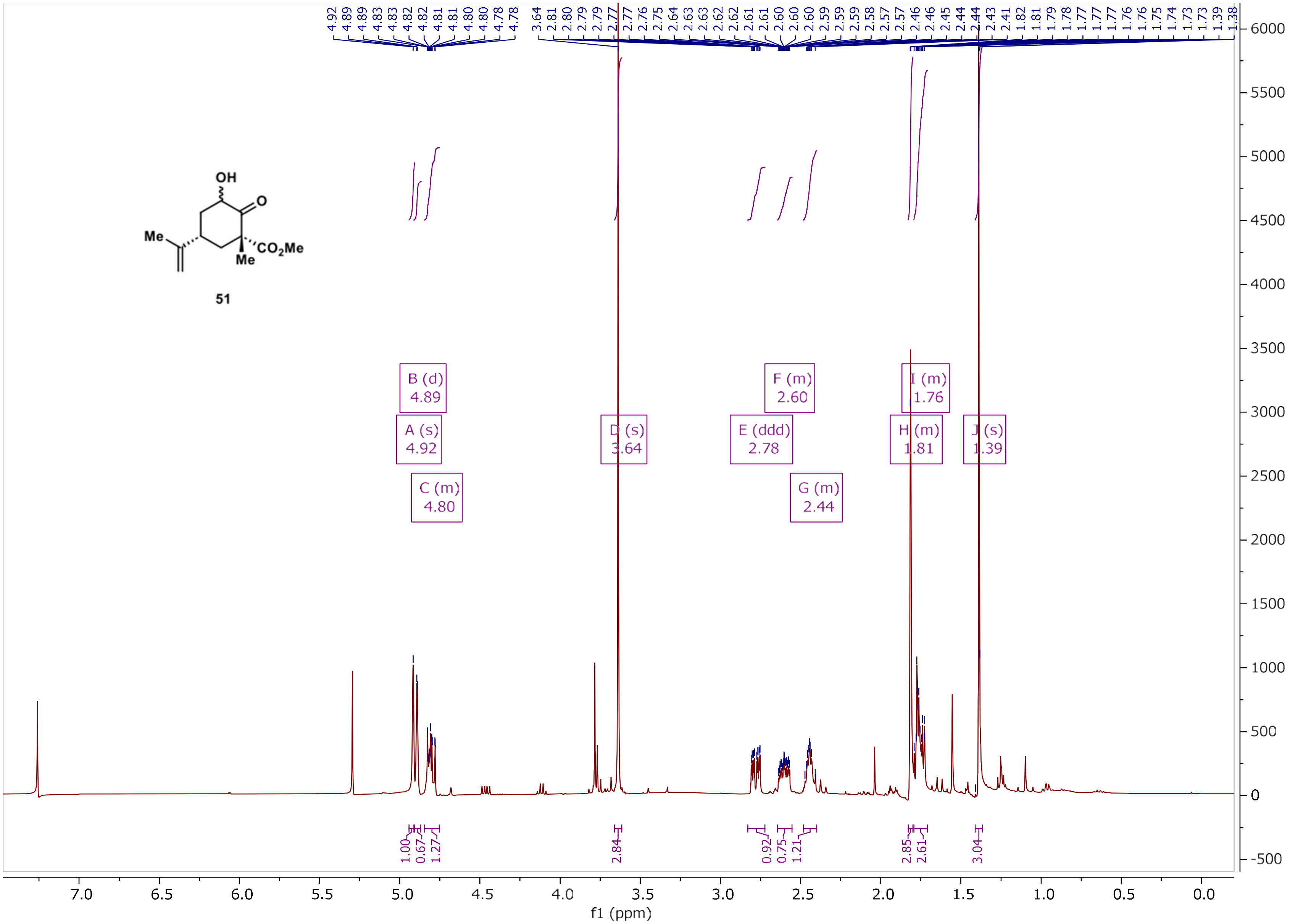


9.72
4.84
4.84
4.83
4.82
3.31
3.17
2.80
2.79
2.78
2.77
2.76
2.75
2.74
2.73
2.44
2.41
2.40
2.05
2.01
1.98
1.79
1.78
1.78
1.70
1.67
1.67
1.66
1.66
1.65
1.64
1.63
1.63
1.62
1.48
OMe
CO2Me
Me
O
Me
46
A (s) 9.72
B (t) 4.84
C (s) 4.82
D (s) 3.31
E (s) 3.17
F (m) 2.77
G (dt) 2.42
H (t) 2.01
I (t) 1.78
J (m) 1.65
K (s) 1.48
1.00
1.08
1.30
2.99
3.20
1.09
1.08
1.18
3.46
2.36
3.20
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
f1 (ppm)
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

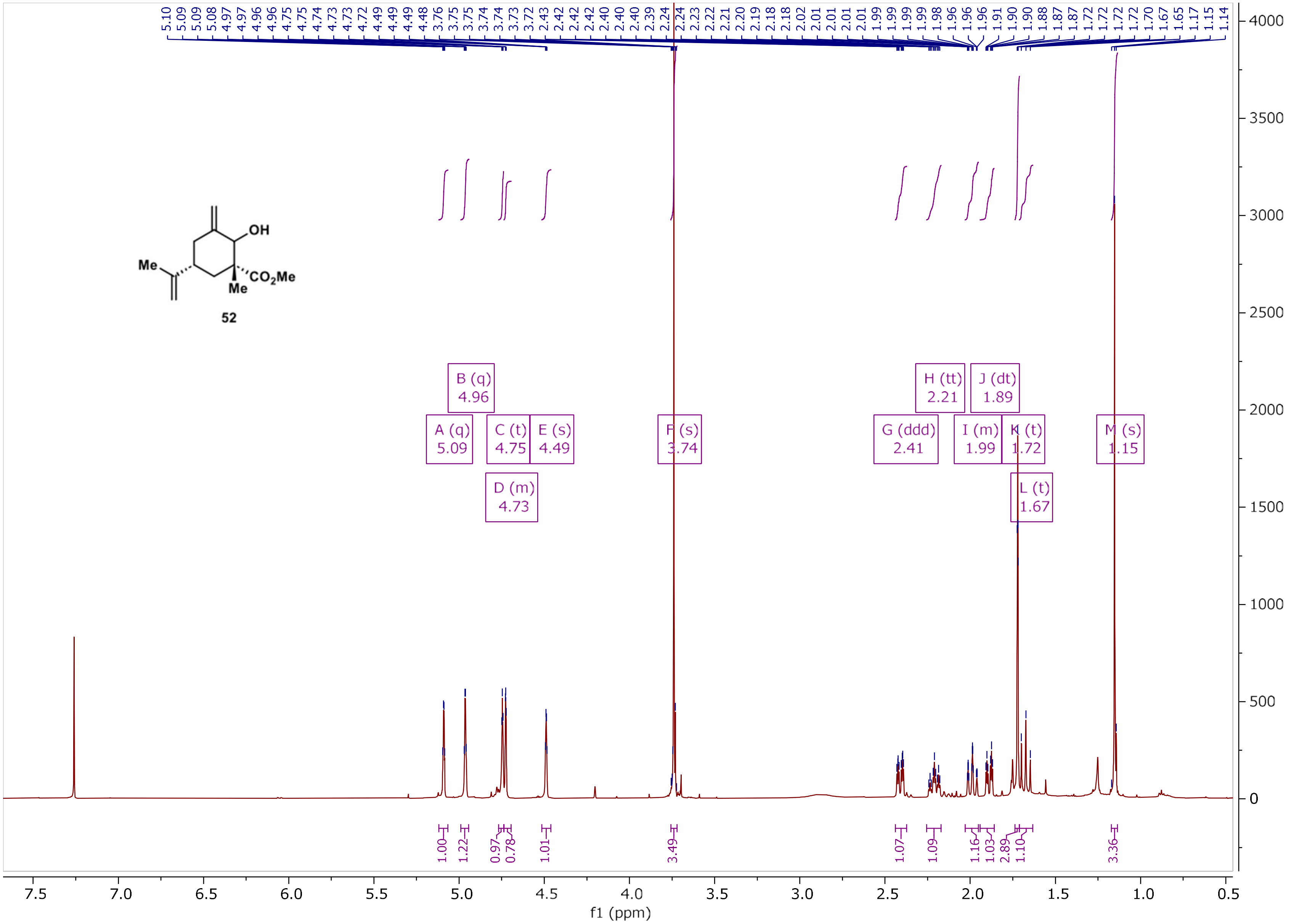

3.80
3.52
3.51
3.51
3.50
3.44
3.32
PMBO
OMe
CO2Me
Me
O
Me
47
F (s)
3.80
G (t)
3.51
H (s)
3.44
I (s)
3.32
3.53
2.67
2.38
2.20
3.85
3.80
3.75
3.70
3.65
3.60
3.55
3.50
3.45
3.40
3.35
3.30
3.25
3.20
3.15
3.10
3.05
3.00
2.95
2.90
2.85
2.80
f1 (ppm)
2500
2000
1500
1000
500
0


7.96
7.94
7.38
7.37
7.37
7.36
7.36
7.34
7.34
7.34
4.76
4.75
4.75
4.66
4.66
4.18
4.17
4.17
3.27
2.72
2.68
2.65
2.44
2.25
2.24
2.22
2.21
2.21
1.96
1.95
1.95
1.93
1.92
1.92
1.91
1.77
1.74
1.67
1.67
1.41
1.38
1.37
1.37
1.36
OMe
N
N—Ts
Me
Me
O
Me
48
A (d)
7.95
B (m)
7.36
C (m)
4.75
D (d)
4.66
E (t)
4.17
F (s)
3.27
G (s)
2.44
H (t)
2.68
I (dq)
2.23
J (dt)
1.94
K (d)
1.67
L (s)
1.41
M (d)
1.75
N (m)
1.37
1.98
3.60
1.09
1.00
1.21
3.16
1.24
4.01
1.10
1.37
0.79
2.55
3.82
0.52
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

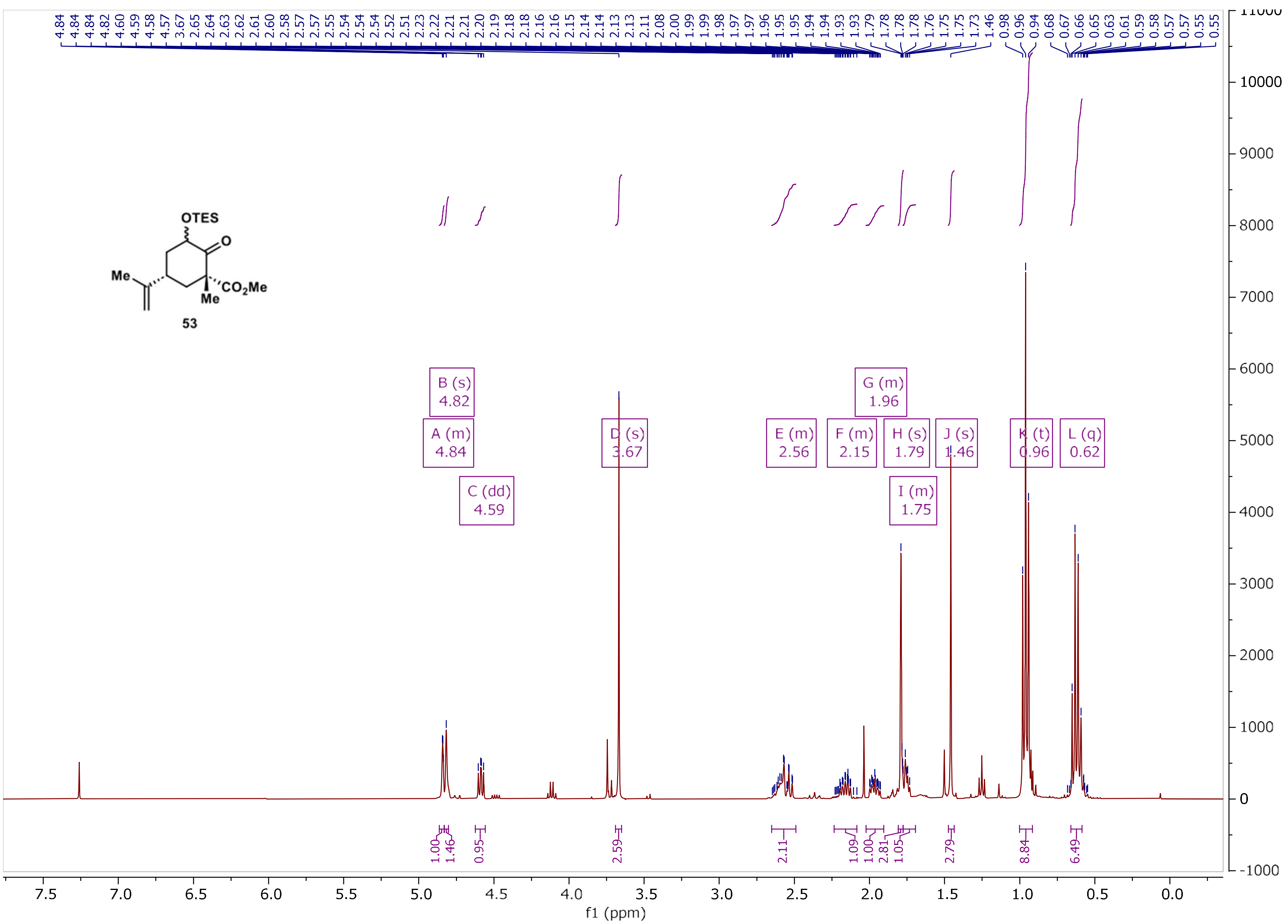

7.81
7.81
7.79
7.79
7.79
7.78
7.77
7.77
7.31
7.30
7.29
7.28
7.28
7.27
7.26
7.24
7.24
4.77
4.77
4.76
4.73
4.73
4.72
4.72
4.71
4.71
4.69
4.68
4.66
4.65
3.38
3.28
2.75
2.45
2.43
2.42
2.42
2.39
OMe
N
NHTs
Me
OTBS
Me
49
A (ddd)
7.79
B (m)
7.28
C (m)
4.73
D (m)
4.67
E (s)
3.38
F (s)
3.28
H (dd)
2.42
1.99
1.65
1.20
1.00
0.68
0.89
3.40
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)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

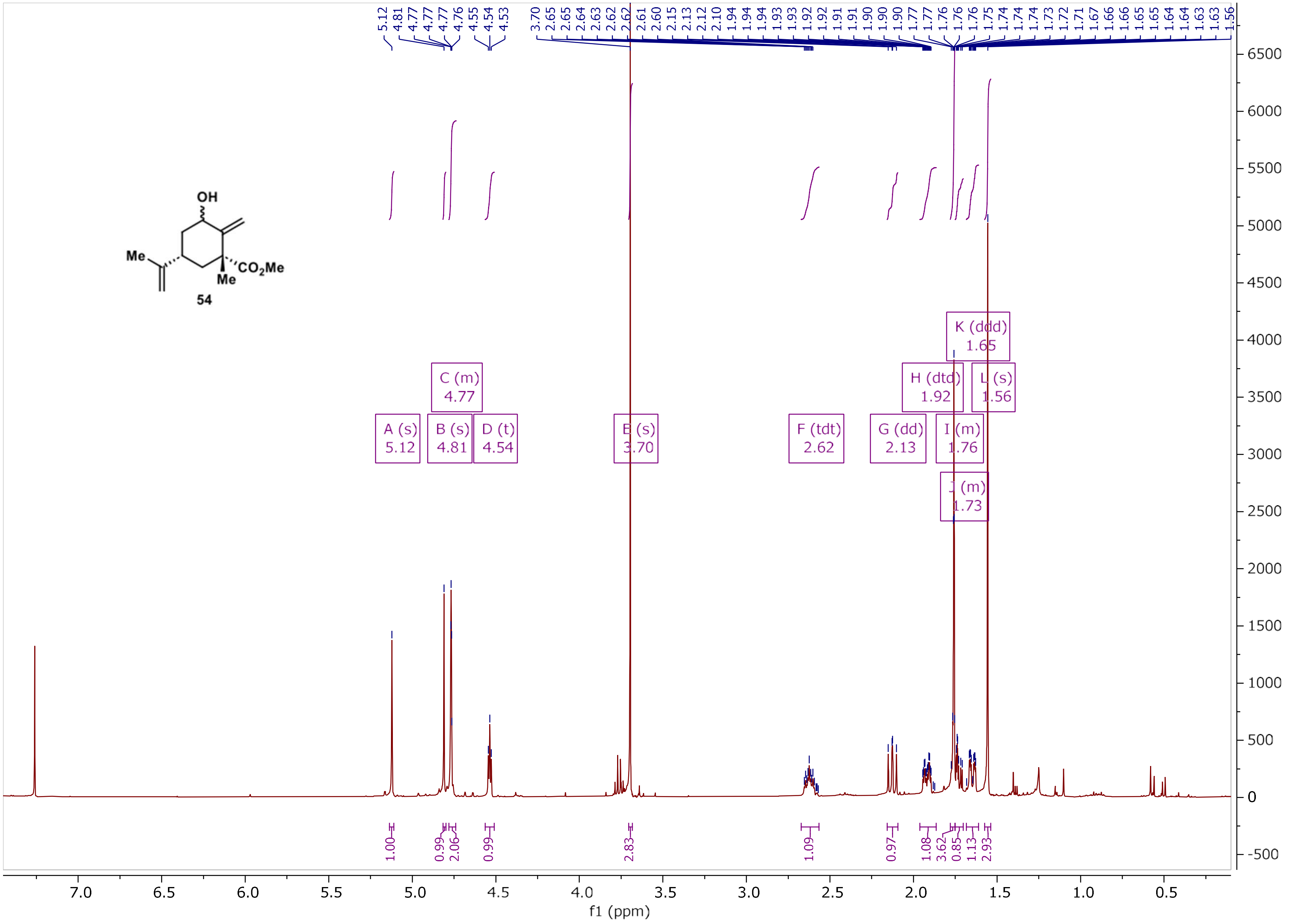


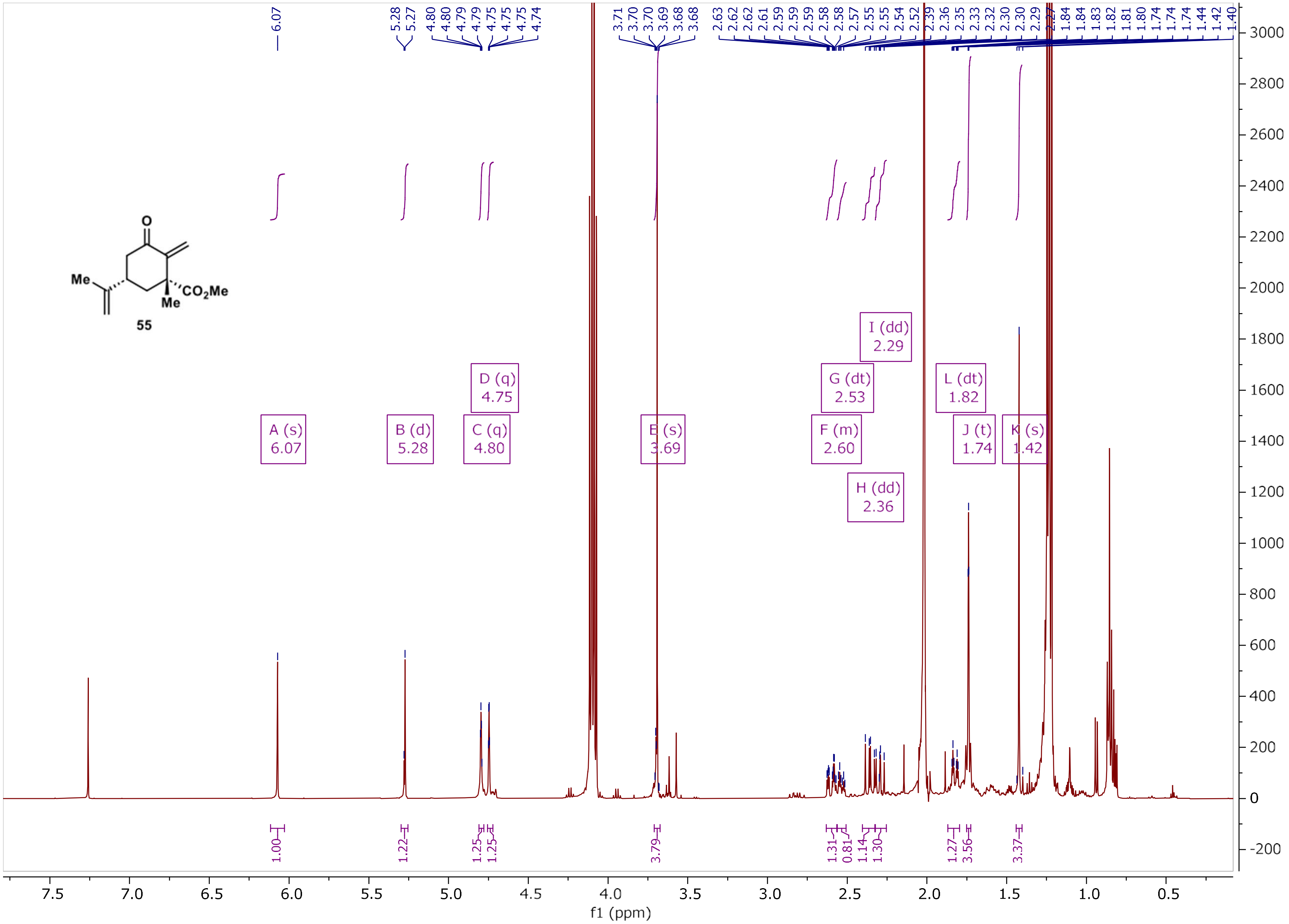
4.92 4.89 4.89 4.83 4.83 4.82 4.82 4.81 4.81 4.80 4.80 4.78 4.78
3.64 2.81 2.80 2.79 2.79 2.77 2.77 2.76 2.75 2.64 2.63 2.63 2.62 2.62 2.61 2.61 2.60 2.60 2.60 2.59 2.59 2.59 2.58 2.57 2.57 2.46 2.46 2.45 2.44 2.44 2.43 2.41 1.82 1.81 1.79 1.78 1.77 1.77 1.77 1.76 1.76 1.75 1.74 1.73 1.73 1.39 1.38
OH
O
Me
CO2Me
Me
51
B (d) 4.89
A (s) 4.92
C (m) 4.80
D (s) 3.64
E (ddd) 2.78
F (m) 2.60
G (m) 2.44
H (m) 1.81
I (m) 1.76
J (s) 1.39
1.00
0.67
1.27
2.84
0.92
0.75
1.21
2.85
2.61
3.04
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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)



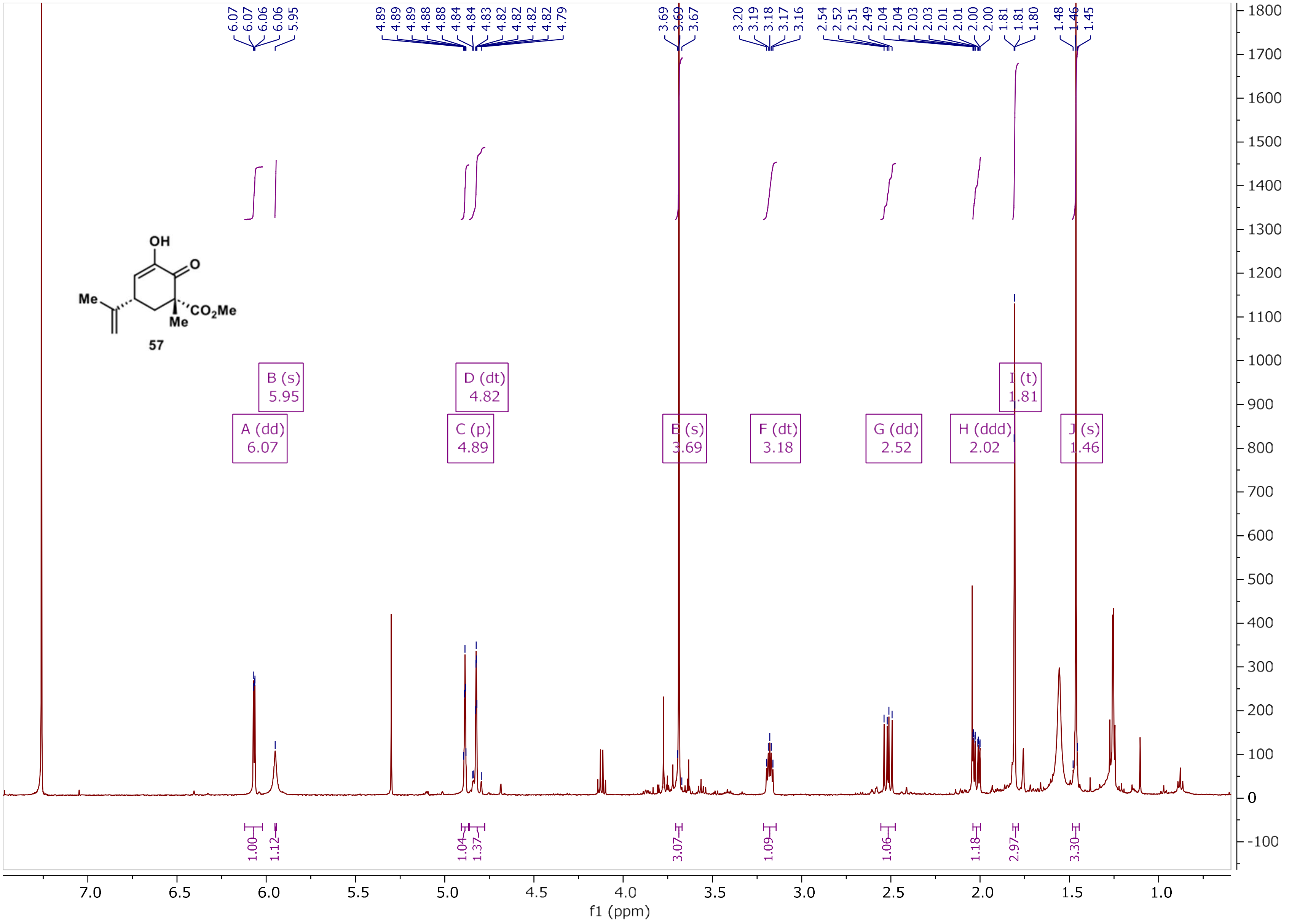
5.10 5.09 5.09 5.08 4.97 4.97 4.96 4.96 4.75 4.75 4.74 4.73 4.73 4.72 4.49 4.49 4.49 4.48 3.76 3.75 3.75 3.74 3.74 3.73 3.72 2.43 2.42 2.42 2.42 2.40 2.40 2.40 2.39 2.24 2.24 2.23 2.22 2.21 2.20 2.19 2.18 2.18 2.02 2.01 2.01 2.01 2.01 1.99 1.99 1.99 1.99 1.98 1.96 1.96 1.96 1.91 1.90 1.90 1.88 1.87 1.87 1.72 1.72 1.72 1.70 1.67 1.65 1.17 1.15 1.14
OH
Me
CO2Me
Me
52
A (q) 5.09
B (q) 4.96
C (t) 4.75
D (m) 4.73
E (s) 4.49
F (s) 3.74
G (ddd) 2.41
H (tt) 2.21
I (m) 1.99
J (dt) 1.89
K (t) 1.72
L (t) 1.67
M (s) 1.15
1.00
1.22
0.97
0.78
1.01
3.49
1.07
1.09
1.16
1.03
2.89
1.10
3.36
4000
3500
3000
2500
2000
1500
1000
500
0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

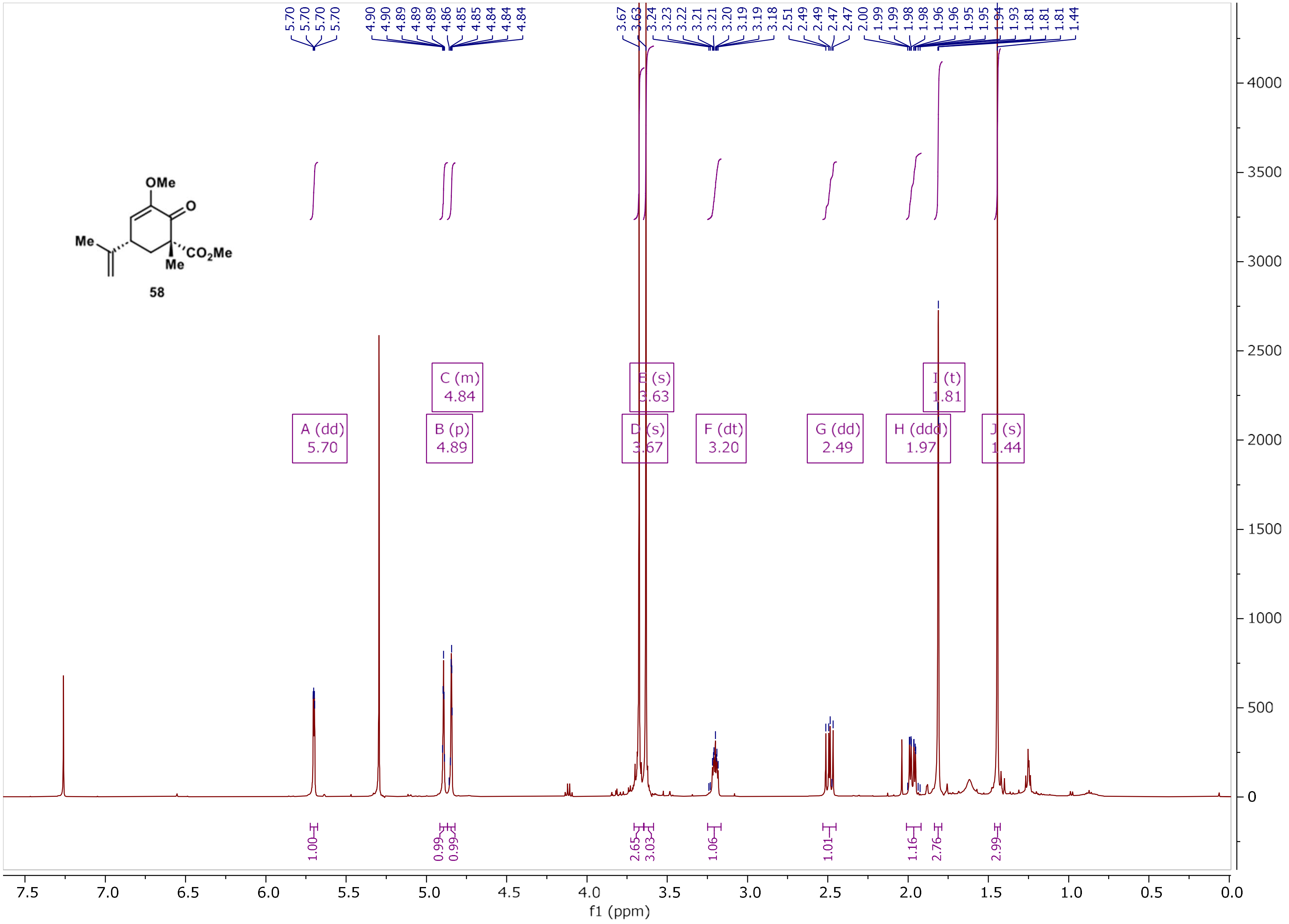

4.84 4.84 4.84 4.82 4.60 4.59 4.58 4.57 3.67 2.65 2.64 2.63 2.62 2.61 2.60 2.58 2.57 2.57 2.55 2.54 2.54 2.54 2.52 2.51 2.23 2.22 2.21 2.21 2.20 2.19 2.18 2.18 2.16 2.16 2.15 2.14 2.14 2.13 2.13 2.11 2.08 2.00 1.99 1.99 1.98 1.97 1.97 1.96 1.95 1.95 1.94 1.94 1.93 1.93 1.79 1.78 1.78 1.78 1.76 1.75 1.75 1.73 1.46 0.98 0.96 0.94 0.68 0.67 0.66 0.65 0.63 0.61 0.59 0.58 0.57 0.55 0.55
OTES
O
Me
CO2Me
Me
53
B (s) 4.82
A (m) 4.84
C (dd) 4.59
D (s) 3.67
E (m) 2.56
F (m) 2.15
G (m) 1.96
H (s) 1.79
I (m) 1.75
J (s) 1.46
K (t) 0.96
L (q) 0.62
1.00
1.46
0.95
2.59
2.11
1.09
1.00
2.81
1.05
2.79
8.84
6.49
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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)


5.12
4.81
4.77
4.77
4.77
4.76
4.55
4.54
4.53
3.70
2.65
2.65
2.64
2.63
2.62
2.62
2.61
2.60
2.15
2.13
2.12
2.10
1.94
1.94
1.94
1.93
1.93
1.92
1.92
1.91
1.91
1.90
1.90
1.90
1.77
1.77
1.76
1.76
1.76
1.75
1.74
1.74
1.74
1.73
1.72
1.71
1.67
1.66
1.65
1.65
1.64
1.63
1.63
1.56
OH
Me
CO_2Me
Me
54
A (s) 5.12
B (s) 4.81
C (m) 4.77
D (t) 4.54
E (s) 3.70
F (tdt) 2.62
G (dd) 2.13
H (dtd) 1.92
I (m) 1.76
J (m) 1.73
K (ddd) 1.65
L (s) 1.56
1.00
0.99
2.06
0.99
2.83
1.09
0.97
1.08
3.62
0.85
1.13
2.93
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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)



6.07
5.28
5.27
4.80
4.80
4.79
4.79
4.75
4.75
4.75
4.74
3.71
3.70
3.70
3.69
3.68
3.68
2.63
2.62
2.62
2.61
2.59
2.59
2.59
2.58
2.58
2.57
2.55
2.55
2.55
2.54
2.52
2.39
2.36
2.35
2.33
2.32
2.30
2.30
2.29
2.27
1.84
1.84
1.83
1.82
1.81
1.80
1.74
1.74
1.74
1.44
1.42
1.40
O
Me
CO2Me
Me
55
A (s) 6.07
B (d) 5.28
C (q) 4.80
D (q) 4.75
E (s) 3.69
F (m) 2.60
G (dt) 2.53
H (dd) 2.36
I (dd) 2.29
J (t) 1.74
K (s) 1.42
L (dt) 1.82
1.00
1.22
1.25
1.25
3.79
1.31
0.81
1.14
1.30
1.27
3.56
3.37
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)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200


OH
O
Me
CO2Me
Me
57
6.07 6.07 6.06 6.06 5.95
4.89 4.89 4.89 4.88 4.88 4.84 4.84 4.83 4.82 4.82 4.82 4.82 4.79
3.69 3.69 3.67
3.20 3.19 3.18 3.17 3.16
2.54 2.52 2.51 2.49 2.04 2.04 2.03 2.03 2.01 2.01 2.00 2.00
1.81 1.81 1.80
1.48 1.46 1.45
A (dd) 6.07
B (s) 5.95
C (p) 4.89
D (dt) 4.82
E (s) 3.69
F (dt) 3.18
G (dd) 2.52
H (ddd) 2.02
I (t) 1.81
J (s) 1.46
1.00
1.12
1.04
1.37
3.07
1.09
1.06
1.18
2.97
3.30
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)
1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100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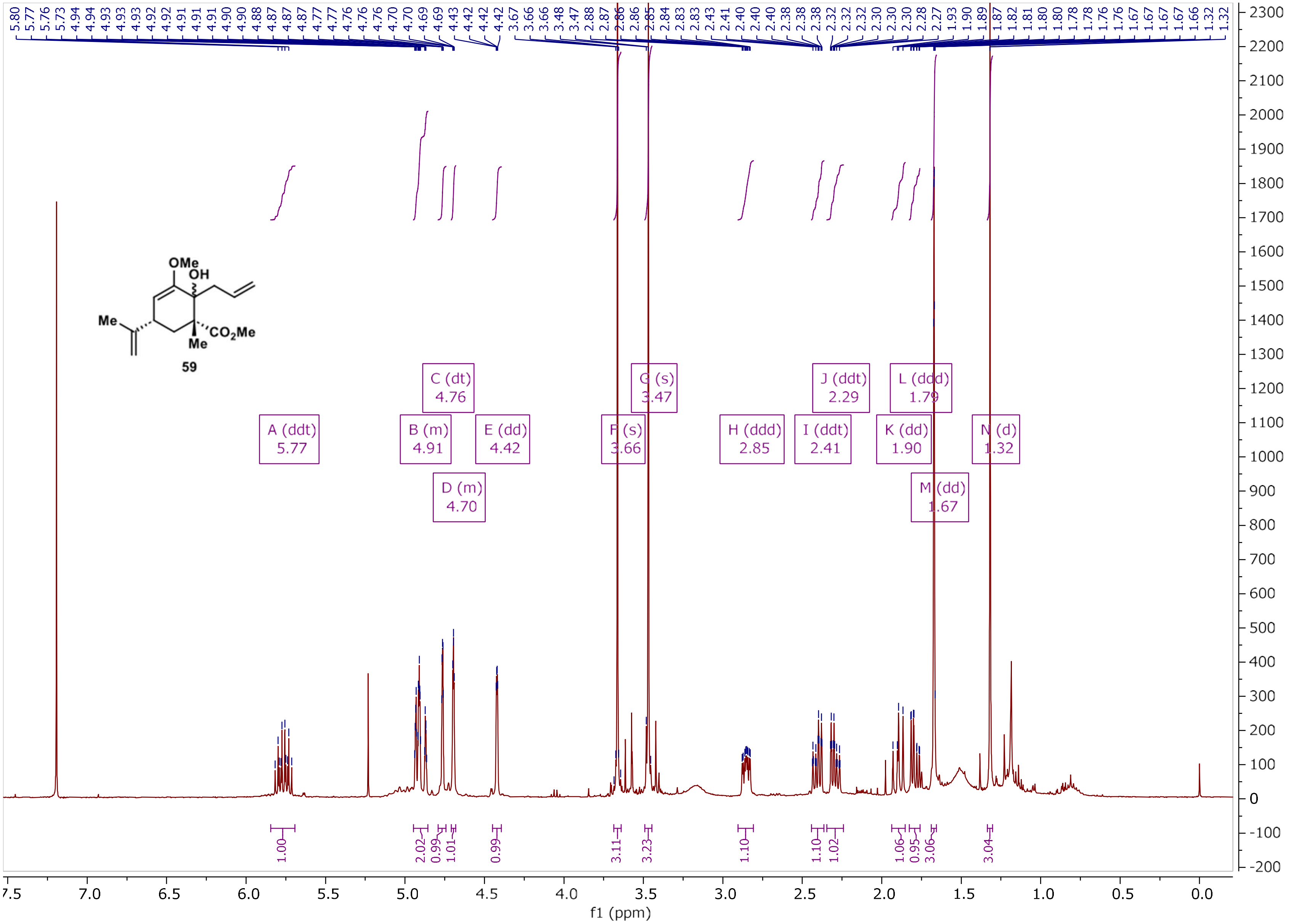
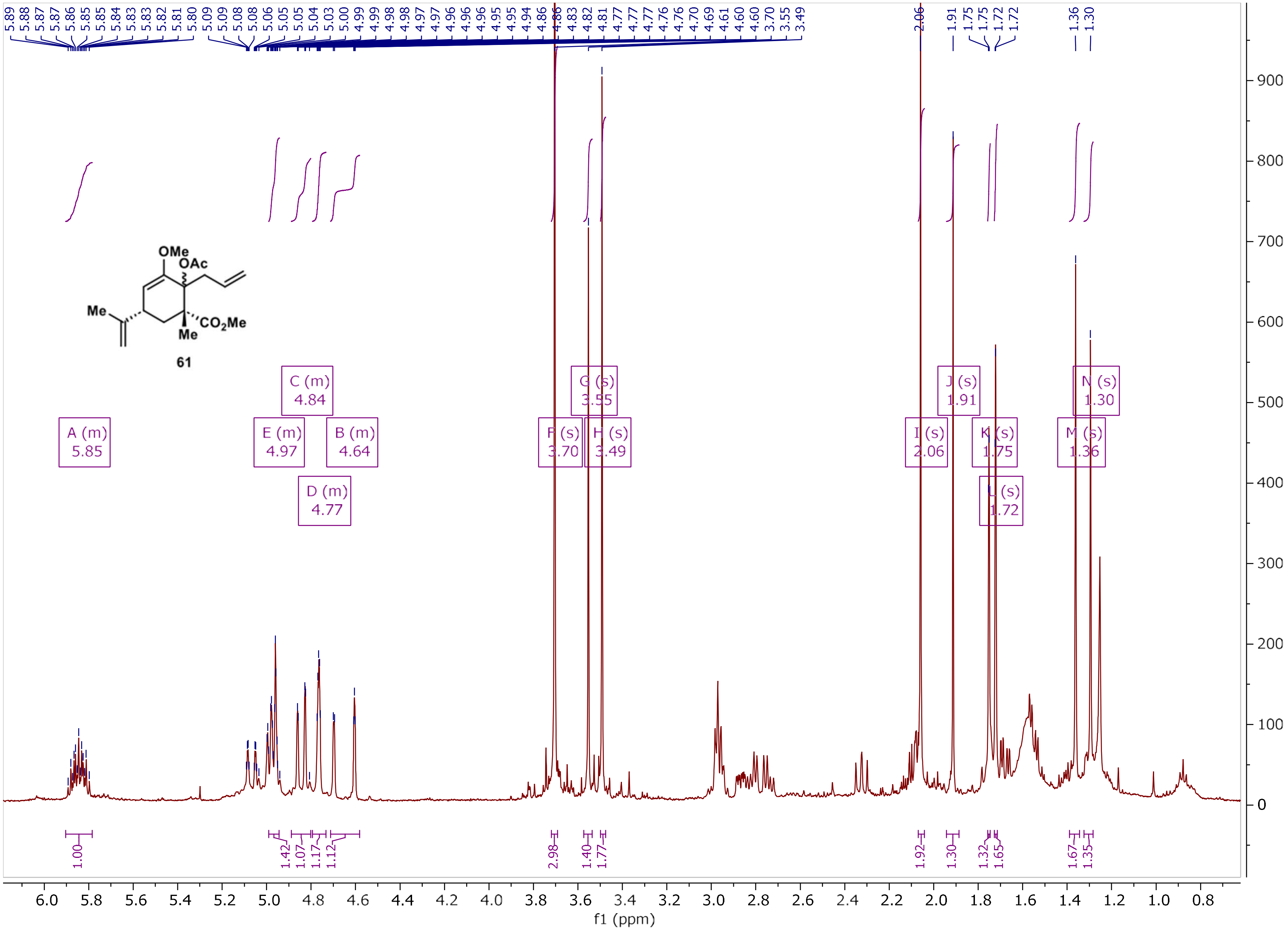
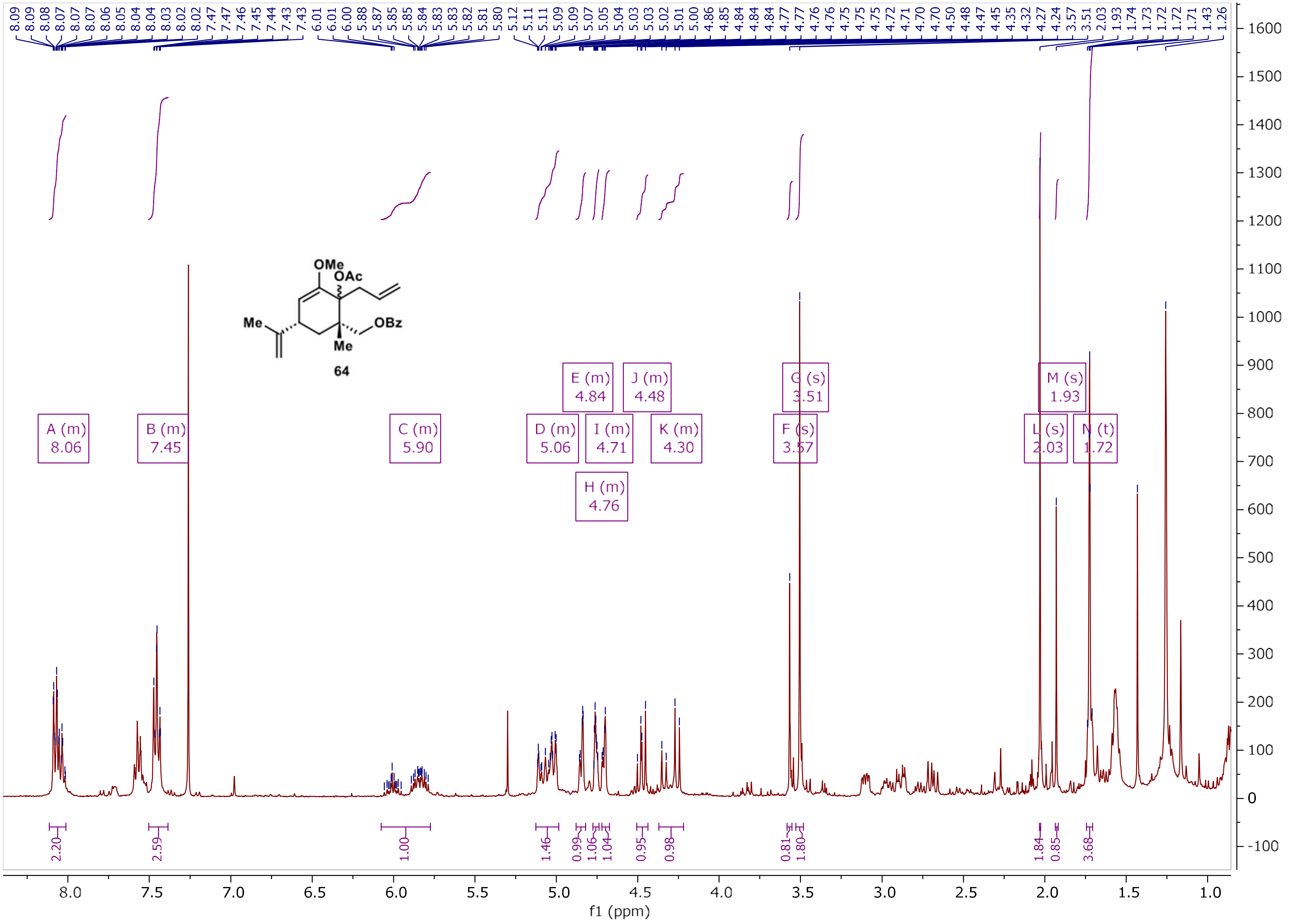
4.85
4.84
4.84
4.84
3.67
3.63
3.24
3.23
3.22
3.21
3.21
3.20
3.19
3.19
3.18
2.51
2.49
2.49
2.47
2.47
2.00
1.99
1.99
1.98
1.98
1.96
1.96
1.95
1.95
1.94
1.93
1.81
1.81
1.81
1.44
OMe
O
Me
CO2Me
Me
58
A (dd)
5.70
B (p)
4.89
C (m)
4.84
D (s)
3.67
E (s)
3.63
F (dt)
3.20
G (dd)
2.49
H (ddd)
1.97
I (t)
1.81
J (s)
1.44
1.00
0.99
0.99
2.65
3.03
1.06
1.01
1.16
2.76
2.99
4000
3500
3000
2500
2000
1500
1000
500
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)

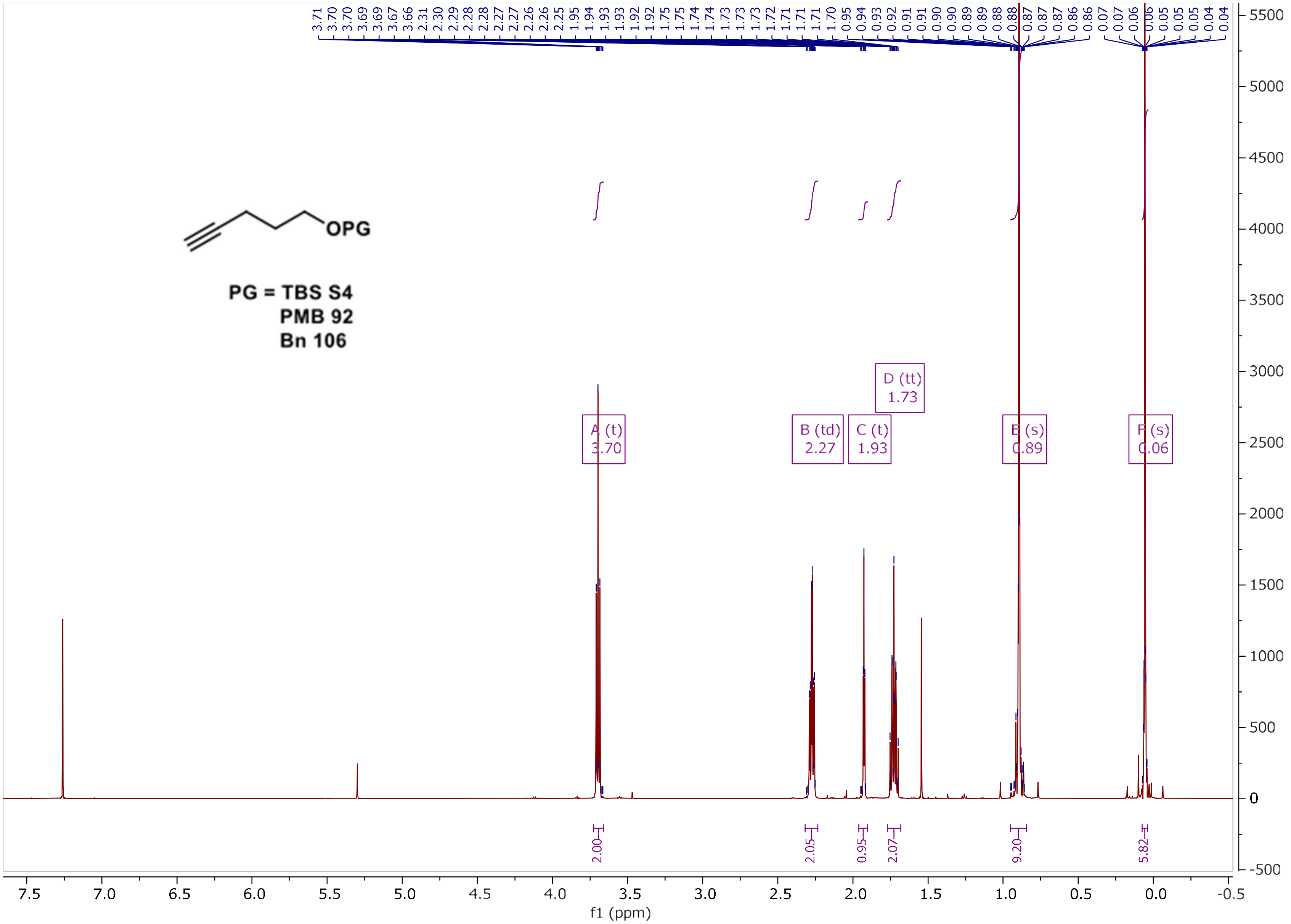

59

5.80 5.77 5.76 5.73 4.94 4.94 4.93 4.93 4.93 4.92 4.92 4.91 4.91 4.91 4.90 4.90 4.88 4.87 4.87 4.87 4.77 4.77 4.76 4.76 4.76 4.70 4.70 4.69 4.69 4.43 4.42 4.42 4.42 3.67 3.66 3.66 3.48 3.47 2.88 2.87 2.86 2.86 2.85 2.84 2.83 2.83 2.43 2.41 2.40 2.40 2.40 2.38 2.38 2.38 2.32 2.32 2.32 2.30 2.30 2.30 2.28 2.27 1.93 1.90 1.89 1.87 1.82 1.81 1.80 1.80 1.78 1.78 1.76 1.76 1.67 1.67 1.67 1.67 1.66 1.32 1.32
OMe
OH
Me
CO2Me
Me
A (ddt) 5.77
B (m) 4.91
C (dt) 4.76
D (m) 4.70
E (dd) 4.42
F (s) 3.66
G (s) 3.47
H (ddd) 2.85
I (ddt) 2.41
J (ddt) 2.29
K (dd) 1.90
L (ddd) 1.79
M (dd) 1.67
N (d) 1.32
1.00
2.02
0.99
1.01
0.99
3.11
3.23
1.10
1.10
1.02
1.06
0.95
3.06
3.04
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)
2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200


5.89 5.88 5.87 5.87 5.86 5.85 5.85 5.84 5.83 5.83 5.82 5.81 5.80 5.09 5.09 5.08 5.08 5.06 5.05 5.05 5.04 5.03 5.00 4.99 4.99 4.98 4.98 4.97 4.96 4.96 4.96 4.95 4.95 4.94 4.86 4.86 4.83 4.82 4.81 4.77 4.77 4.77 4.76 4.76 4.70 4.69 4.61 4.60 4.60 3.70 3.55 3.49
2.06 1.91 1.75 1.75 1.72 1.72 1.36 1.30
OMe
OAc
Me
CO2Me
Me
61
A (m) 5.85
E (m) 4.97
C (m) 4.84
D (m) 4.77
B (m) 4.64
F (s) 3.70
G (s) 3.55
H (s) 3.49
I (s) 2.06
J (s) 1.91
K (s) 1.75
L (s) 1.72
M (s) 1.36
N (s) 1.30
1.00
1.42
1.07
1.17
1.12
2.98
1.40
1.77
1.92
1.30
1.32
1.65
1.67
1.35
900
800
700
600
500
400
300
200
100
0
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 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 1.2 1.0 0.8
f1 (ppm)



8.09 8.09 8.08 8.07 8.07 8.07 8.06 8.05 8.04 8.04 8.03 8.02 8.02 7.47 7.47 7.46 7.45 7.44 7.43 7.43 6.01 6.01 6.00 5.88 5.87 5.85 5.85 5.84 5.83 5.83 5.82 5.81 5.80 5.12 5.11 5.11 5.09 5.09 5.07 5.05 5.04 5.03 5.03 5.02 5.01 5.00 4.86 4.85 4.84 4.84 4.84 4.77 4.77 4.76 4.76 4.75 4.75 4.75 4.72 4.71 4.70 4.70 4.50 4.48 4.47 4.45 4.35 4.32 4.27 4.24 3.57 3.51 2.03 1.93 1.74 1.73 1.73 1.72 1.72 1.71 1.43 1.26
OMe
OAc
Me
OBz
Me
64
A (m) 8.06
B (m) 7.45
C (m) 5.90
D (m) 5.06
E (m) 4.84
H (m) 4.76
I (m) 4.71
J (m) 4.48
K (m) 4.30
F (s) 3.57
G (s) 3.51
L (s) 2.03
M (s) 1.93
N (t) 1.72
2.20
2.59
1.00
1.46
0.99
1.06
1.04
0.95
0.98
0.81
1.80
1.84
0.85
3.68
1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100
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
f1 (ppm)


OPG
PG = TBS S4
PMB 92
Bn 106
3.71 3.70 3.70 3.69 3.69 3.67 3.66 2.31 2.30 2.29 2.28 2.28 2.27 2.27 2.26 2.26 2.25 1.95 1.94 1.93 1.93 1.92 1.92 1.75 1.75 1.74 1.74 1.73 1.73 1.73 1.72 1.71 1.71 1.71 1.70 0.95 0.94 0.93 0.92 0.91 0.91 0.90 0.90 0.89 0.89 0.88 0.88 0.87 0.87 0.87 0.87 0.86 0.86 0.07 0.07 0.06 0.06 0.05 0.05 0.05 0.04 0.04
A (t) 3.70
B (td) 2.27
C (t) 1.93
D (tt) 1.73
E (s) 0.89
F (s) 0.06
2.00
2.05
0.95
2.07
9.20
5.82
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)
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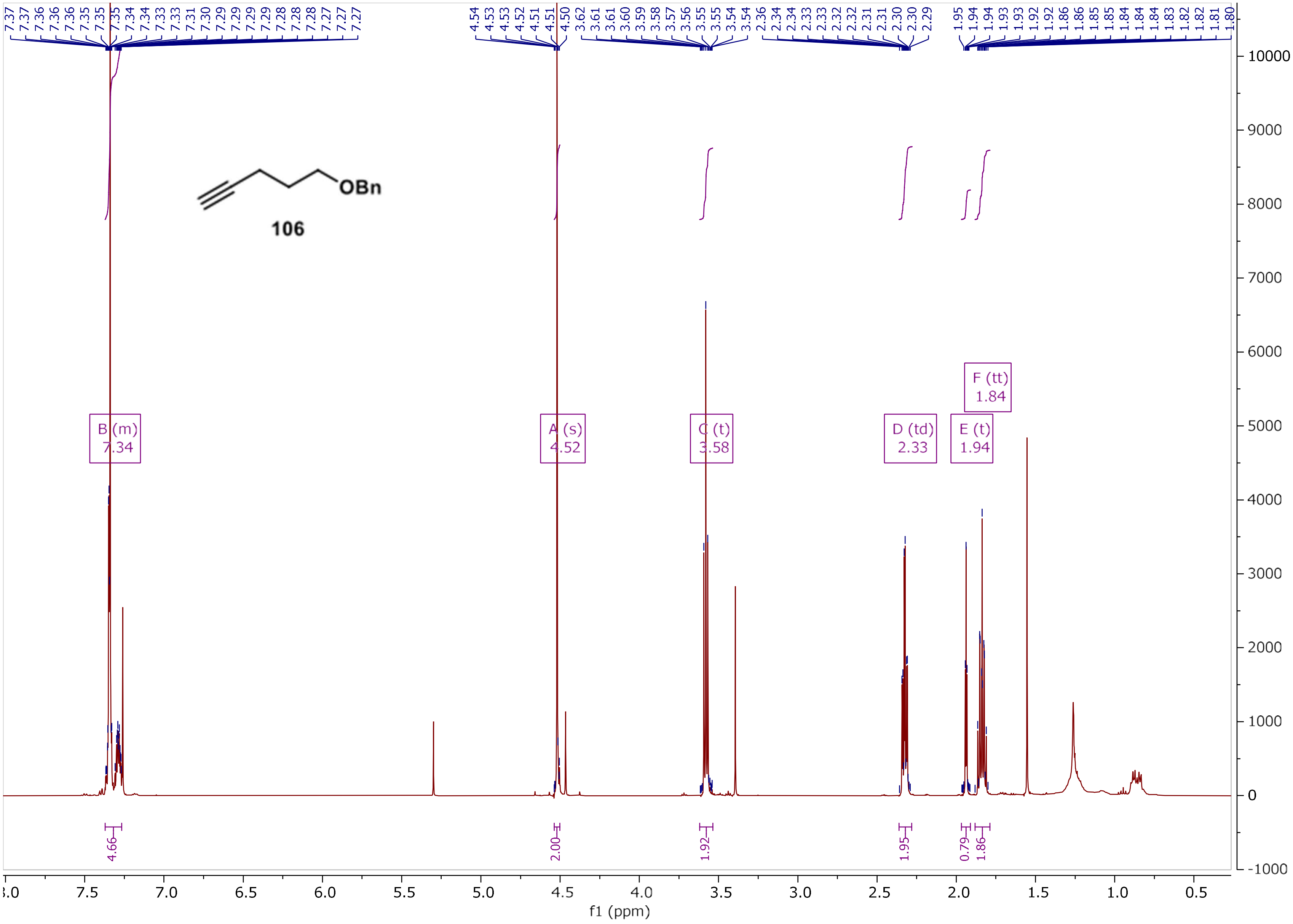
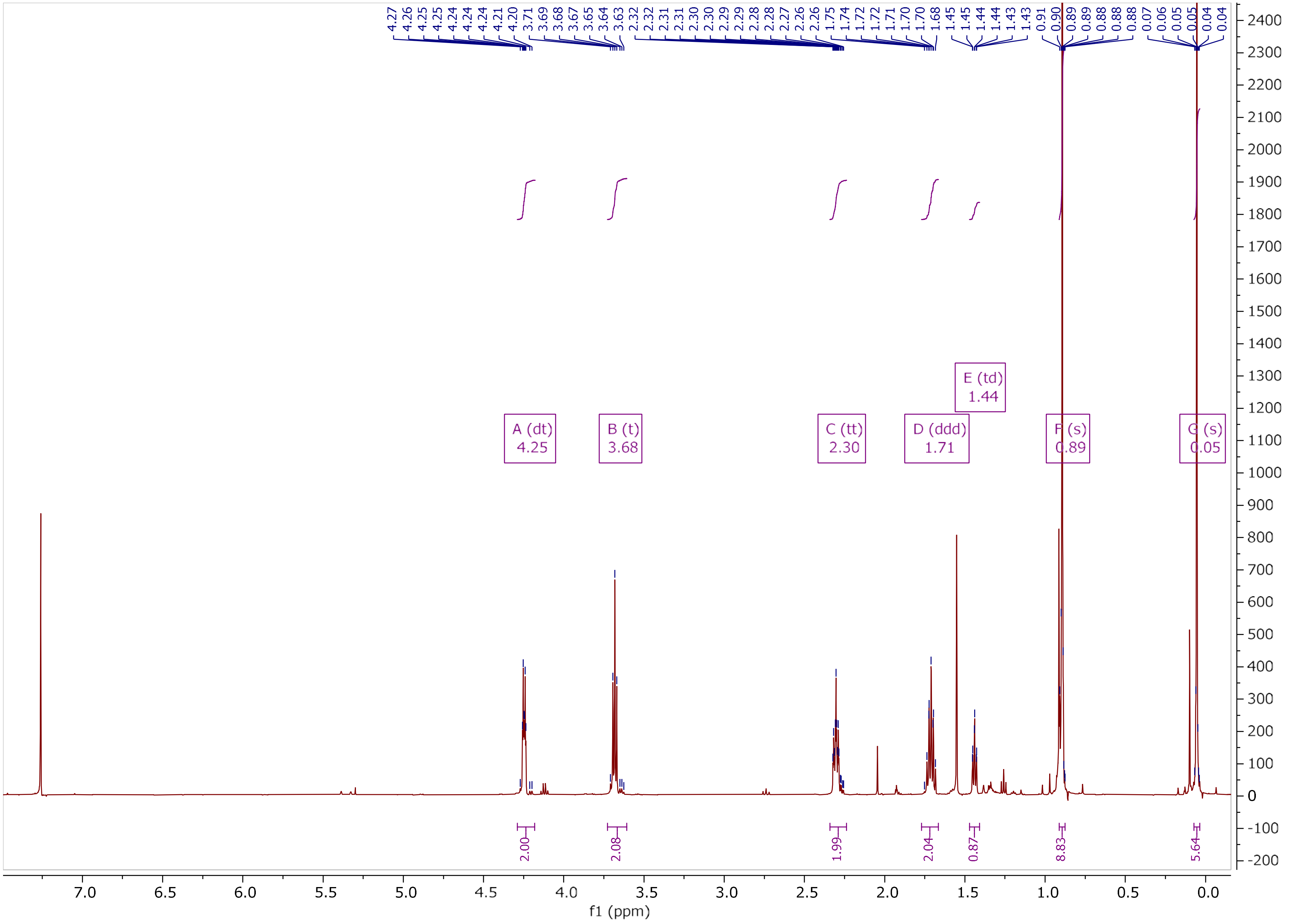

OBn
106
7.37 7.37 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.33 7.33 7.31 7.30 7.29 7.29 7.29 7.29 7.28 7.28 7.28 7.27 7.27 7.27
4.54 4.53 4.53 4.52 4.51 4.51 4.50
3.62 3.61 3.61 3.60 3.59 3.58 3.57 3.56 3.55 3.55 3.54 3.54
2.36 2.34 2.34 2.33 2.33 2.32 2.32 2.31 2.31 2.30 2.30 2.29
1.95 1.94 1.94 1.93 1.93 1.92 1.92 1.86 1.86 1.85 1.85 1.84 1.84 1.84 1.83 1.82 1.82 1.81 1.80
B (m)
7.34
A (s)
4.52
C (t)
3.58
D (td)
2.33
E (t)
1.94
F (tt)
1.84
4.66
2.00
1.92
1.95
0.79
1.86
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



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4.26
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4.25
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4.24
4.24
4.21
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3.71
3.69
3.68
3.67
3.65
3.64
3.63
2.32
2.32
2.31
2.31
2.30
2.30
2.29
2.29
2.28
2.28
2.27
2.26
2.26
1.75
1.74
1.72
1.72
1.71
1.70
1.70
1.68
1.45
1.45
1.44
1.44
1.43
1.43
0.91
0.90
0.89
0.89
0.88
0.88
0.88
0.07
0.06
0.05
0.05
0.04
0.04
A (dt) 4.25
B (t) 3.68
C (tt) 2.30
D (ddd) 1.71
E (td) 1.44
F (s) 0.89
G (s) 0.05
2.00
2.08
1.99
2.04
0.87
8.83
5.64
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
7.0
6.5
6.0
5.5
5.0
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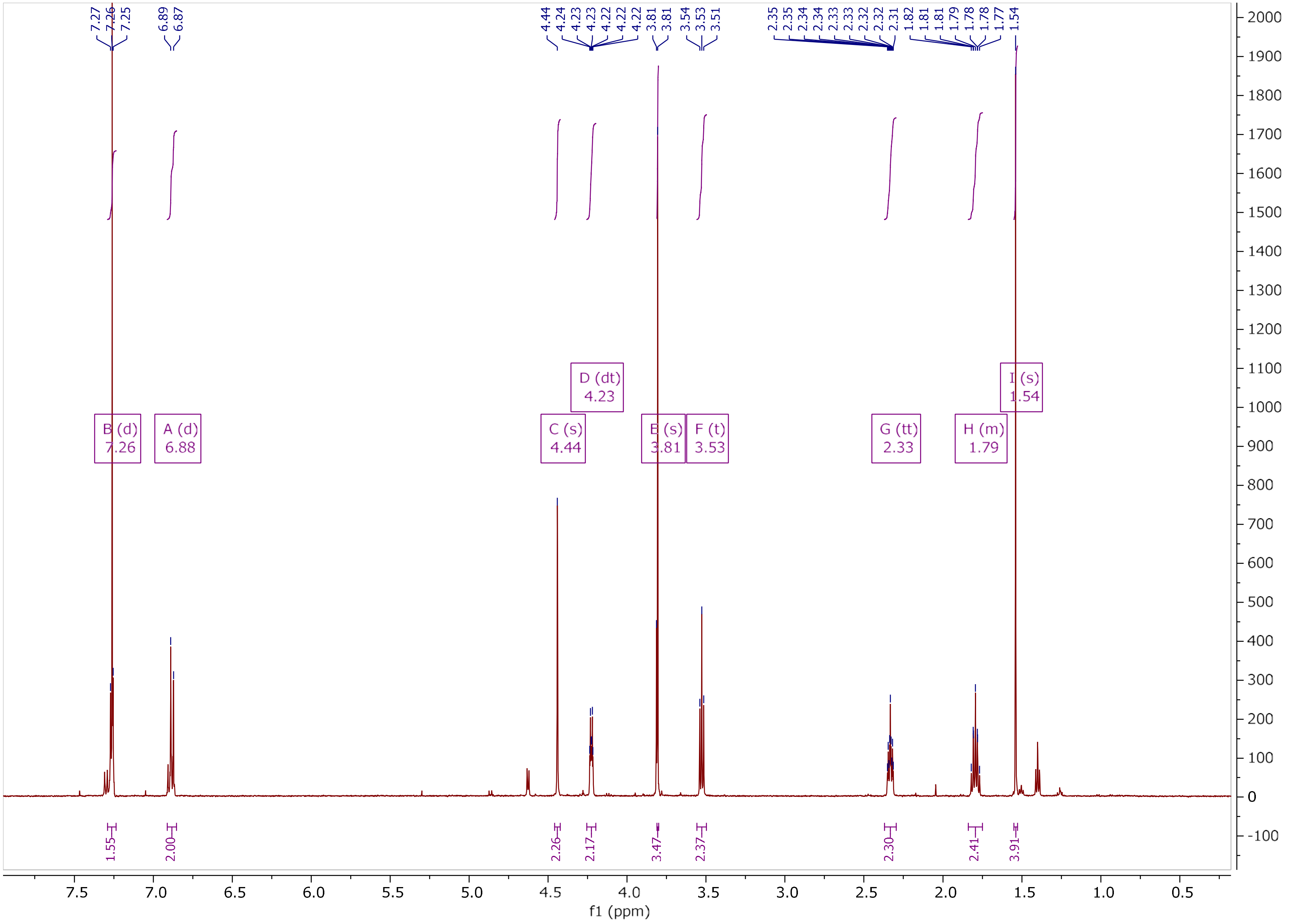
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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4.24
4.23
4.23
4.22
4.22
4.22
3.81
3.81
3.54
3.53
3.51
2.35
2.35
2.34
2.33
2.33
2.32
2.32
2.31
1.82
1.81
1.81
1.79
1.78
1.78
1.77
1.54
B (d)
7.26
A (d)
6.88
C (s)
4.44
D (dt)
4.23
E (s)
3.81
F (t)
3.53
G (tt)
2.33
H (m)
1.79
I (s)
1.54
1.55
2.00
2.26
2.17
3.47
2.37
2.30
2.41
3.91
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
7.5
7.0
6.5
6.0
5.5
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4.5
4.0
3.5
3.0
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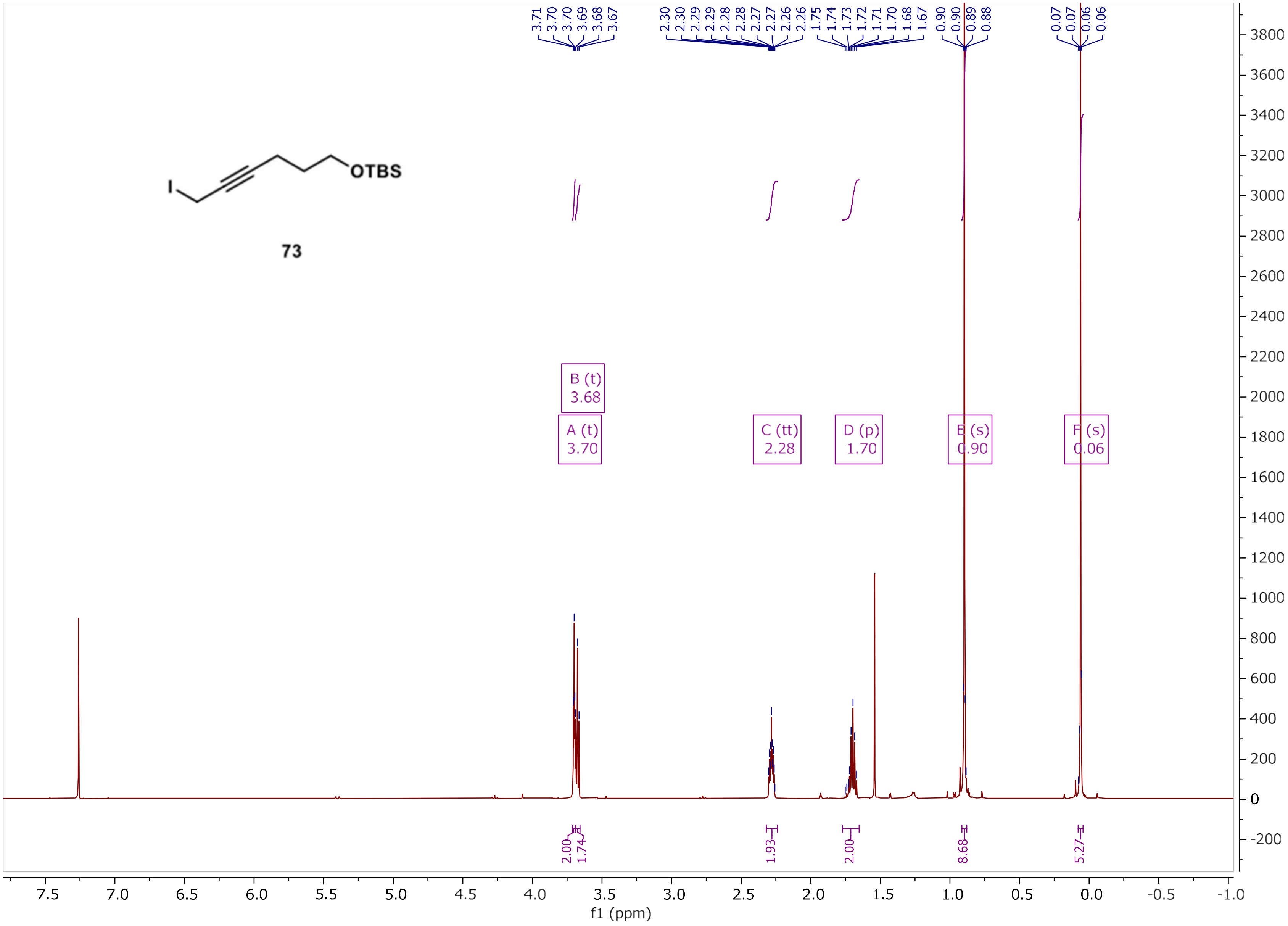
2.0
1.5
1.0
0.5
f1 (ppm)

3.71
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2.28
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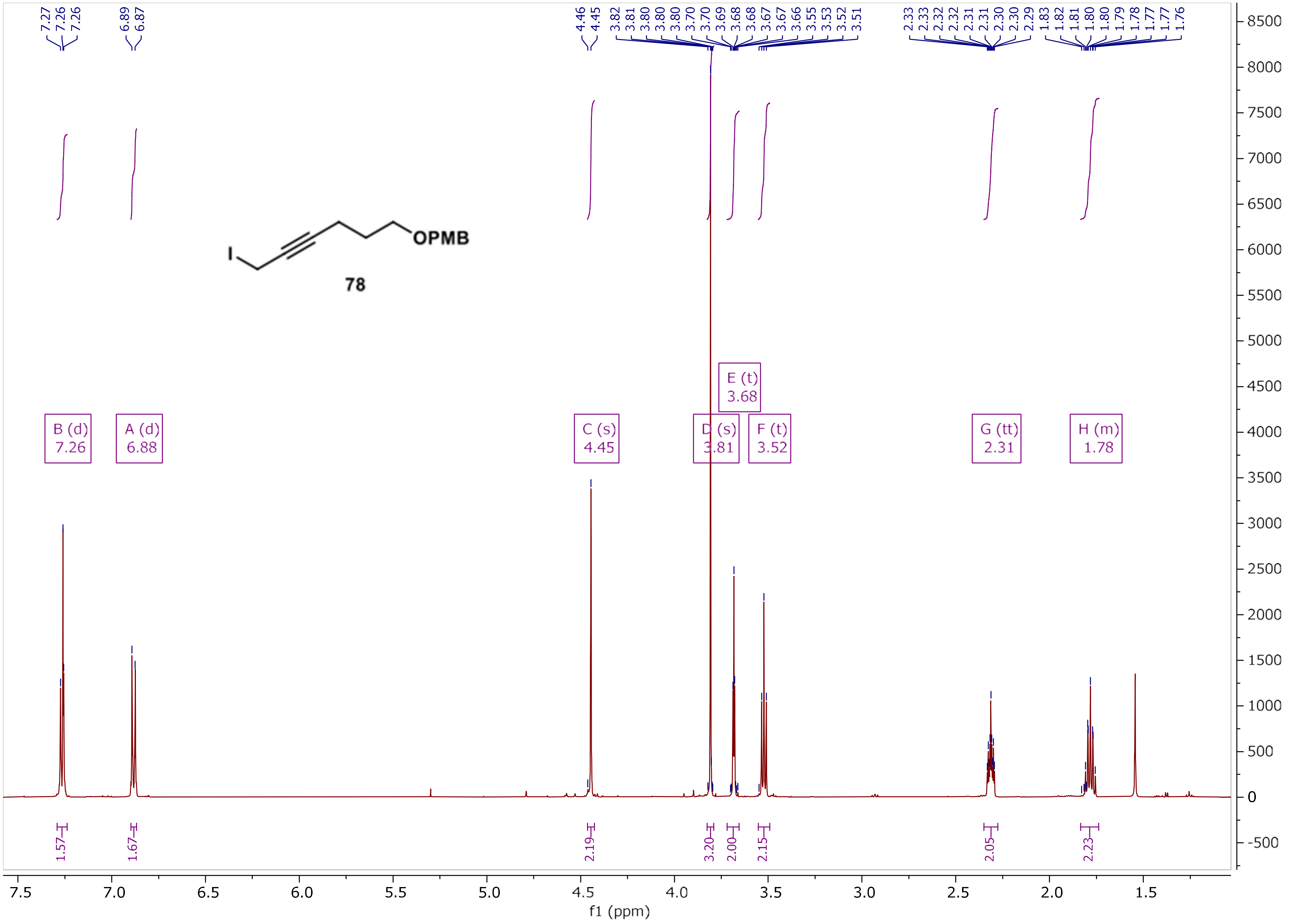
2.27
2.26
2.26
1.75
1.74
1.73
1.72
1.71
1.70
1.68
1.67
0.90
0.90
0.89
0.88
0.07
0.07
0.06
0.06
I
OTBS
73
B (t)
3.68
A (t)
3.70
C (tt)
2.28
D (p)
1.70
E (s)
0.90
F (s)
0.06
2.00
1.74
1.93
2.00
8.68
5.27
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
7.5
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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4.45
3.82
3.81
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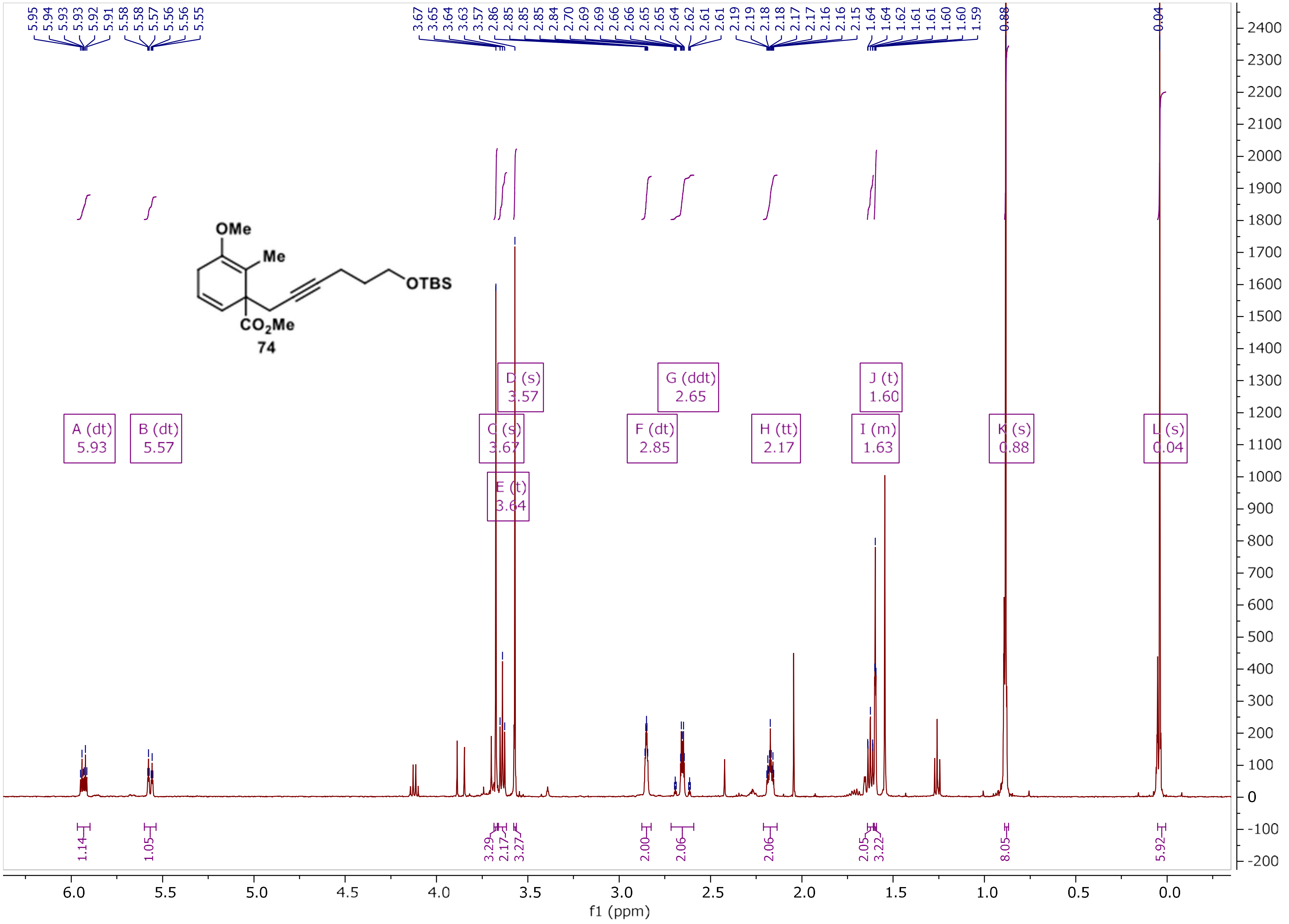
3.70
3.69
3.68
3.68
3.67
3.67
3.66
3.55
3.53
3.52
3.51
2.33
2.33
2.32
2.32
2.31
2.31
2.30
2.30
2.29
1.83
1.82
1.81
1.80
1.80
1.79
1.78
1.77
1.77
1.76
I
OPMB
78
B (d) 7.26
A (d) 6.88
C (s) 4.45
D (s) 3.81
E (t) 3.68
F (t) 3.52
G (tt) 2.31
H (m) 1.78
1.57
1.67
2.19
3.20
2.00
2.15
2.05
2.23
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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)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5.57
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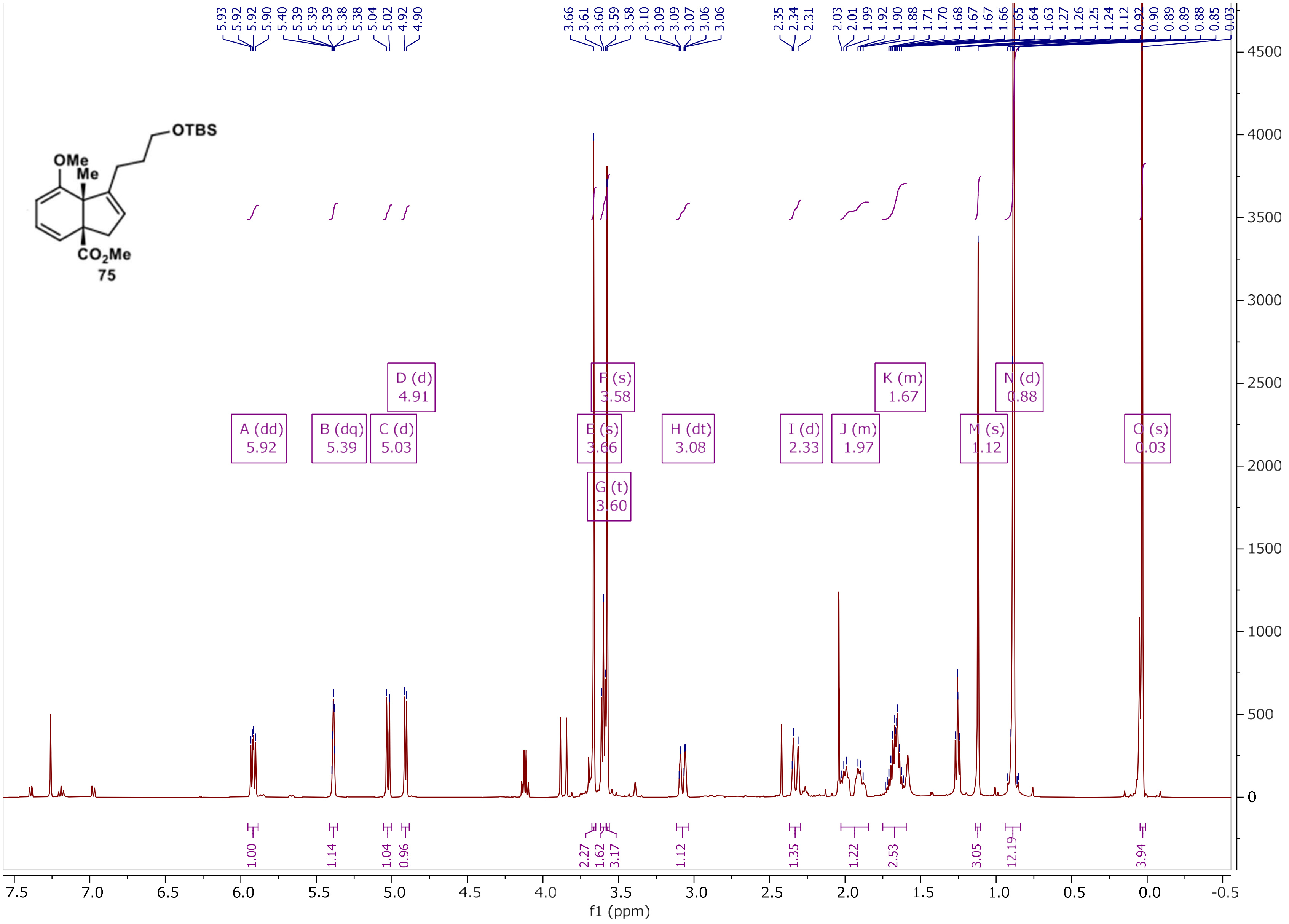
3.64
3.63
3.57
2.86
2.85
2.85
2.85
2.84
2.70
2.69
2.69
2.66
2.66
2.65
2.65
2.64
2.62
2.61
2.61
2.19
2.19
2.18
2.17
2.17
2.16
2.16
2.15
1.64
1.64
1.62
1.61
1.61
1.60
1.59
0.88
0.04
OMe
Me
OTBS
CO$_2$Me
74
A (dt) 5.93
B (dt) 5.57
C (s) 3.67
D (s) 3.57
E (t) 3.64
F (dt) 2.85
G (ddt) 2.65
H (tt) 2.17
I (m) 1.63
J (t) 1.60
K (s) 0.88
L (s) 0.04
1.14
1.05
3.29
2.17
3.27
2.00
2.06
2.06
2.05
3.22
8.05
5.92
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)
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200


OTBS
OMe
Me
CO2Me
75
5.93
5.92
5.92
5.90
5.40
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5.39
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5.38
5.38
5.04
5.02
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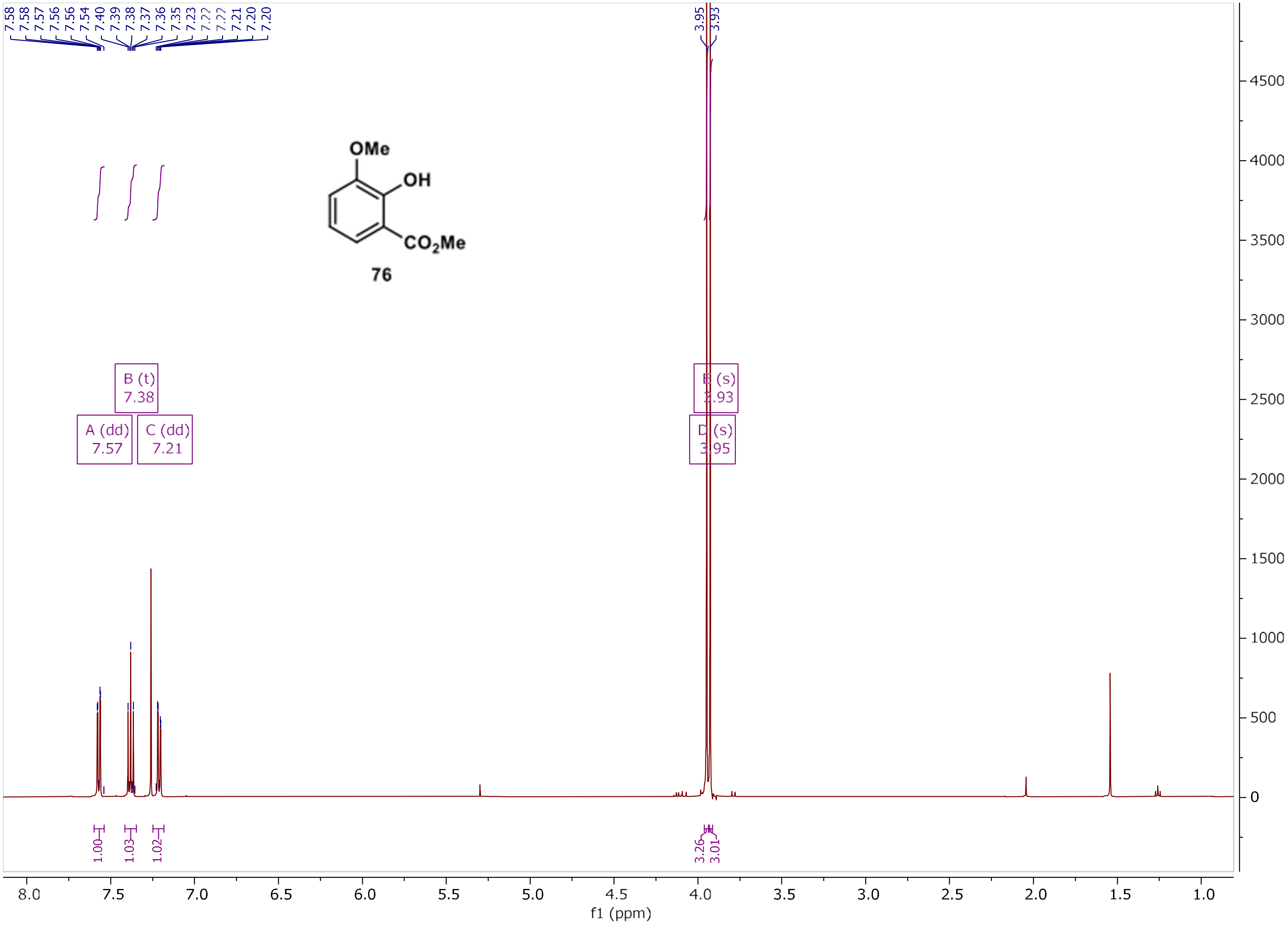
4.90
3.66
3.61
3.60
3.59
3.58
3.10
3.09
3.09
3.07
3.06
3.06
2.35
2.34
2.31
2.03
2.01
1.99
1.92
1.90
1.88
1.71
1.70
1.68
1.67
1.67
1.66
1.65
1.64
1.63
1.27
1.26
1.25
1.24
1.12
0.92
0.90
0.89
0.89
0.88
0.85
0.03
A (dd) 5.92
B (dq) 5.39
C (d) 5.03
D (d) 4.91
E (s) 3.66
F (s) 3.58
G (t) 3.60
H (dt) 3.08
I (d) 2.33
J (m) 1.97
K (m) 1.67
M (s) 1.12
N (d) 0.88
O (s) 0.03
1.00
1.14
1.04
0.96
2.27
1.62
3.17
1.12
1.35
1.22
2.53
3.05
12.19
3.94
4500
4000
3500
3000
2500
2000
1500
1000
500
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)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7.56
7.54
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7.39
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7.37
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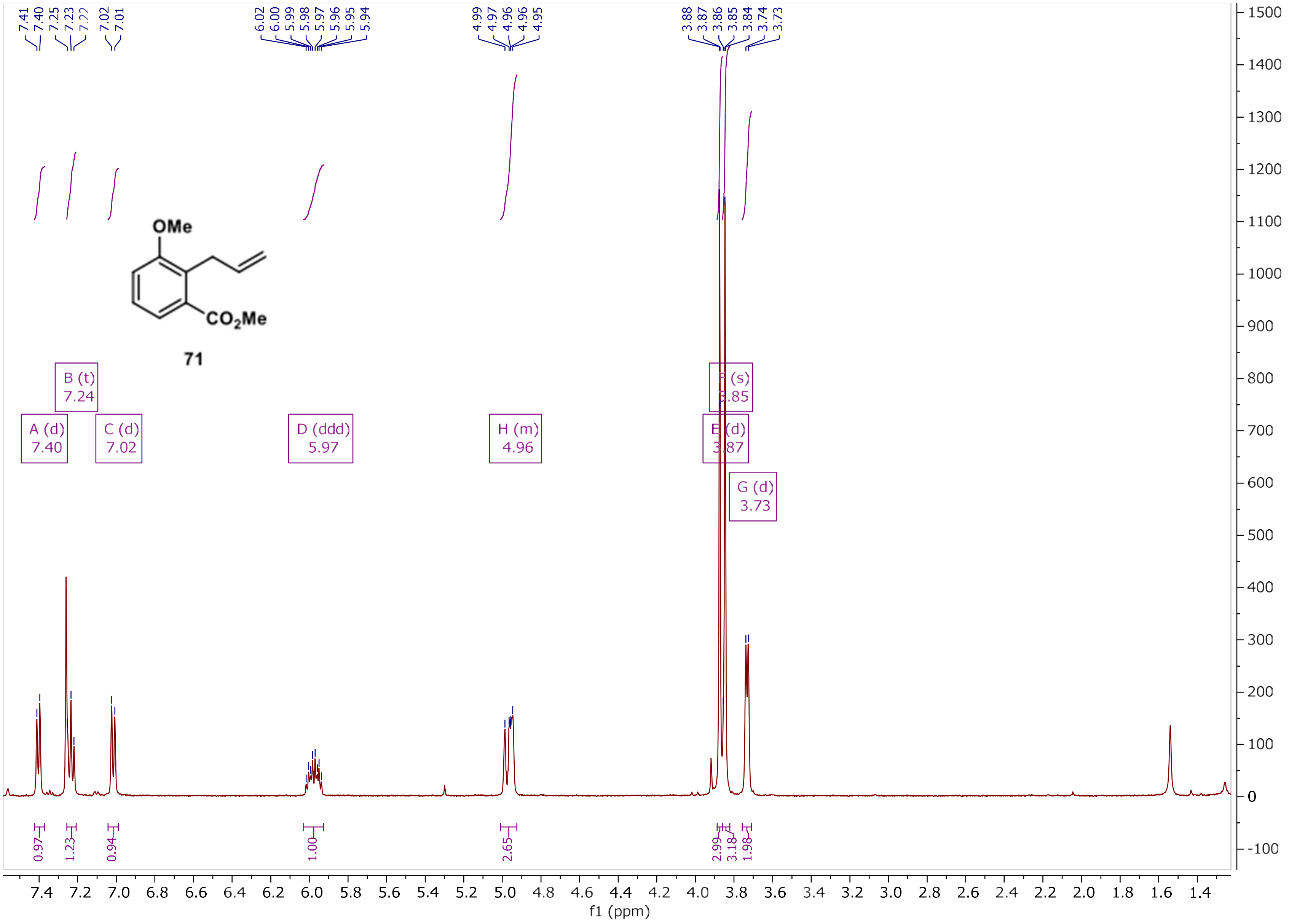
7.35
7.23
7.22
7.22
7.21
7.20
7.20
3.95
3.93
OMe
OH
CO2Me
76
B (t)
7.38
A (dd)
7.57
C (dd)
7.21
E (s)
3.93
D (s)
3.95
1.00
1.03
1.02
3.26
3.01
4500
4000
3500
3000
2500
2000
1500
1000
500
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)



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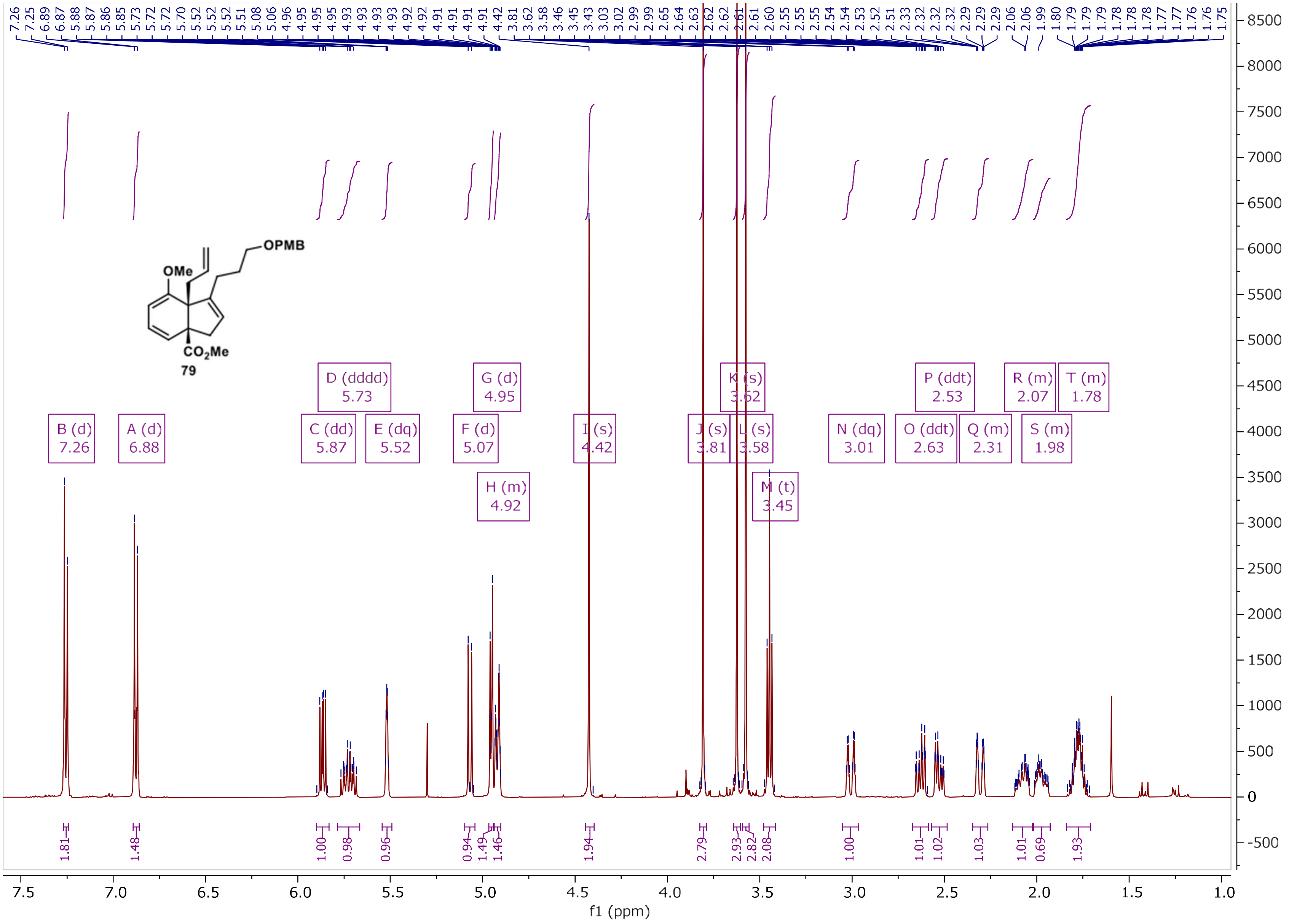
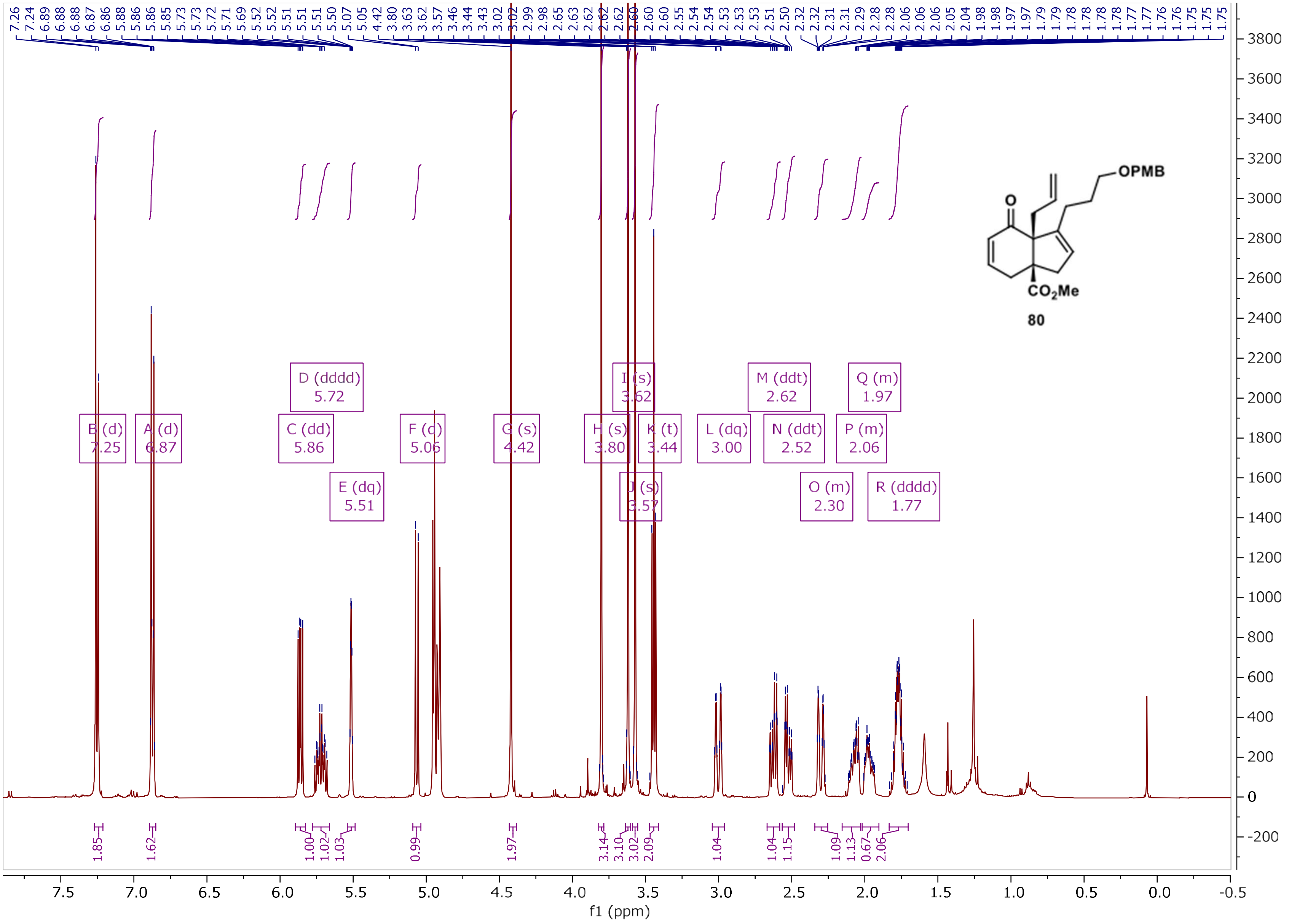
6.02
6.00
5.99
5.98
5.97
5.96
5.95
5.94
4.99
4.97
4.96
4.96
4.95
3.88
3.87
3.86
3.85
3.84
3.74
3.73
OMe
CO2Me
71
A (d)
7.40
B (t)
7.24
C (d)
7.02
D (ddd)
5.97
H (m)
4.96
F (s)
3.85
E (d)
3.87
G (d)
3.73
0.97
1.23
0.94
1.00
2.65
2.99
3.18
1.98
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
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
f1 (ppm)
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100


7.26 7.25 6.89 6.87 5.88 5.87 5.86 5.85 5.73 5.72 5.72 5.70 5.52 5.52 5.52 5.51 5.08 5.06 4.96 4.95 4.95 4.93 4.93 4.93 4.93 4.92 4.92 4.91 4.91 4.91 4.91 4.42 3.81 3.62 3.58 3.46 3.45 3.43 3.03 3.02 2.99 2.99 2.65 2.64 2.63 2.62 2.62 2.61 2.61 2.60 2.55 2.55 2.55 2.54 2.54 2.53 2.52 2.51 2.33 2.32 2.32 2.32 2.29 2.29 2.29 2.06 2.06 1.99 1.80 1.79 1.79 1.79 1.78 1.78 1.78 1.77 1.77 1.76 1.76 1.75
OMe
OPMB
CO2Me
79
B (d) 7.26
A (d) 6.88
D (dddd) 5.73
C (dd) 5.87
E (dq) 5.52
G (d) 4.95
F (d) 5.07
H (m) 4.92
I (s) 4.42
J (s) 3.81
K (s) 3.62
L (s) 3.58
M (t) 3.45
N (dq) 3.01
P (ddt) 2.53
O (ddt) 2.63
Q (m) 2.31
R (m) 2.07
S (m) 1.98
T (m) 1.78
1.81 1.48 1.00 0.98 0.96 0.94 1.49 1.46 1.94 2.79 2.93 2.82 2.08 1.00 1.01 1.02 1.03 1.01 0.69 1.93
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)
8500 8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500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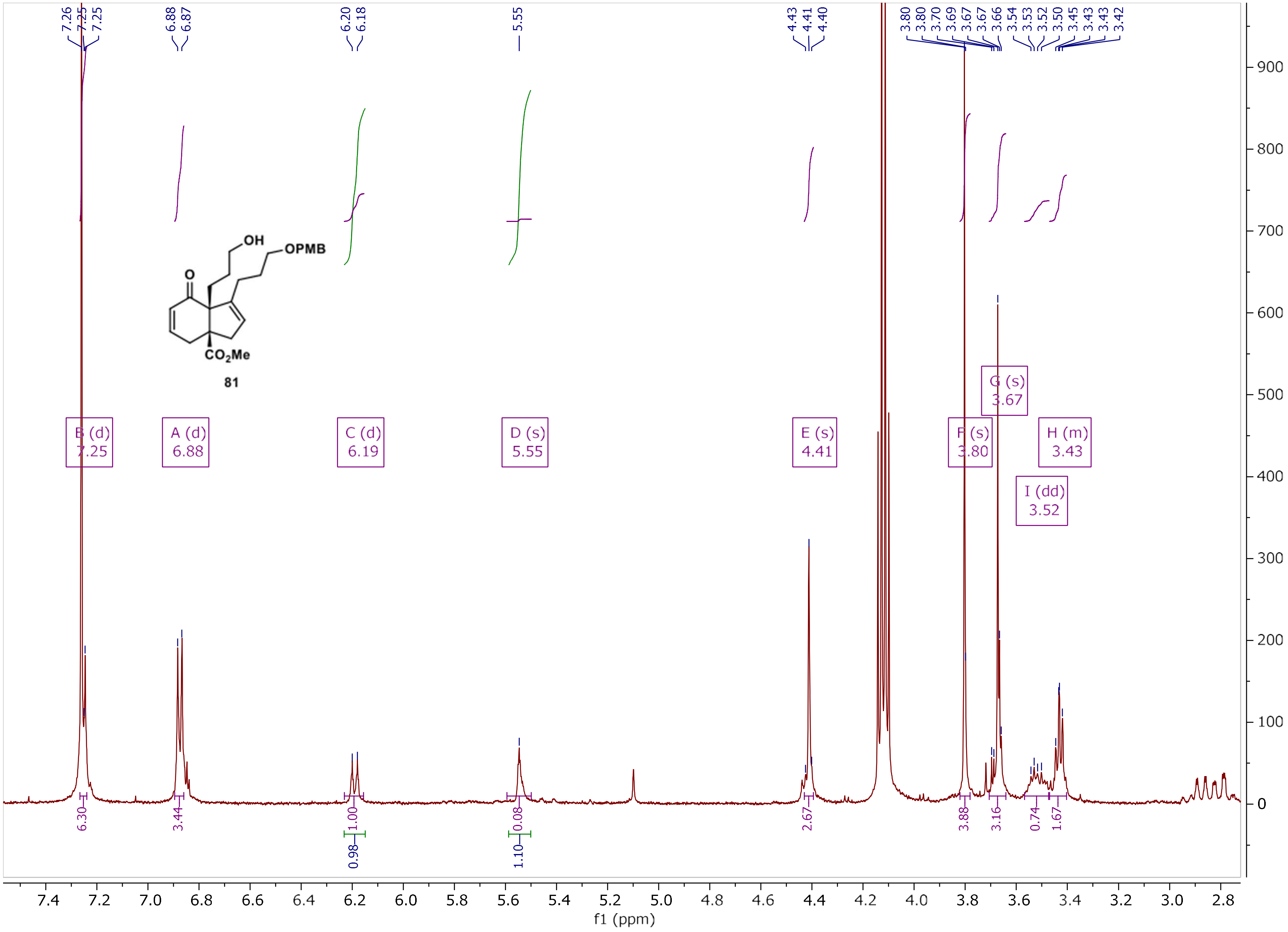
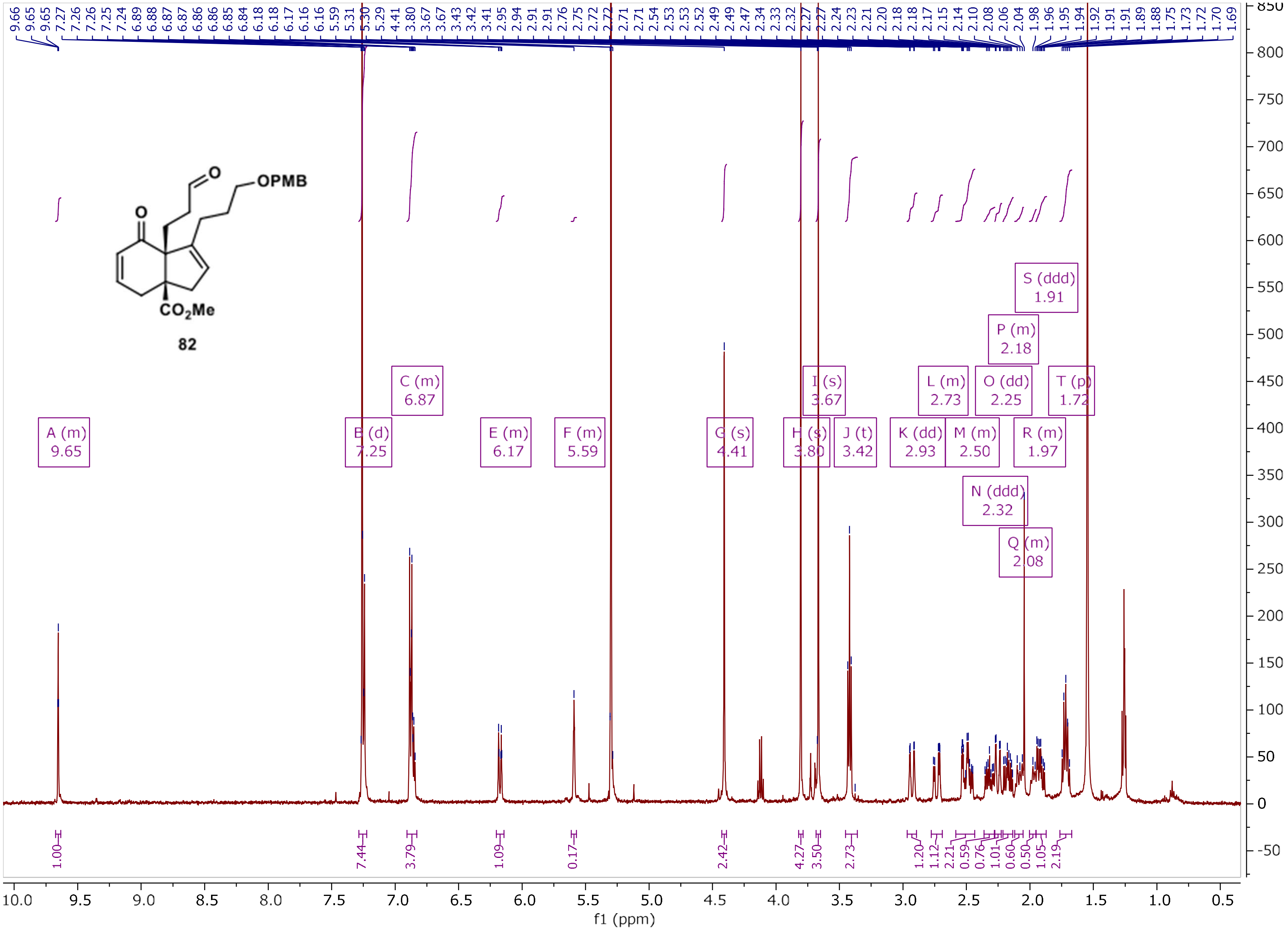
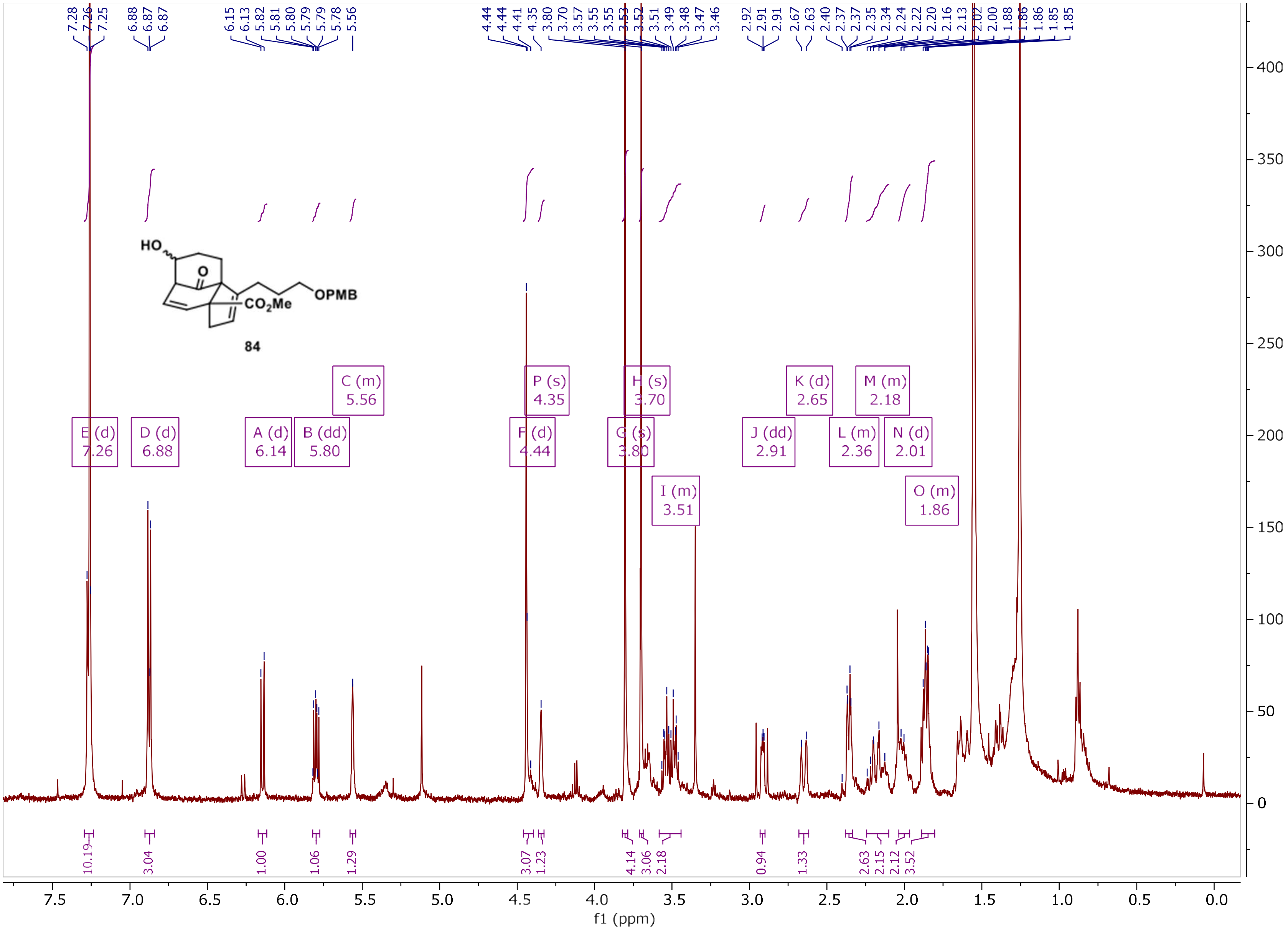
B (d) 7.25
A (d) 6.87
D (dddd) 5.72
C (dd) 5.86
E (dq) 5.51
F (d) 5.06
G (s) 4.42
H (s) 3.80
I (s) 3.62
J (s) 3.57
K (t) 3.44
L (dq) 3.00
M (ddt) 2.62
N (ddt) 2.52
O (m) 2.30
P (m) 2.06
Q (m) 1.97
R (dddd) 1.77
1.85
1.62
1.00
1.02
1.03
0.99
1.97
3.14
3.10
3.02
2.09
1.04
1.04
1.15
1.09
1.13
0.67
2.06
O
OPMB
CO2Me
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

80


7.26
7.25
7.25
6.88
6.87
6.20
6.18
5.55
4.43
4.41
4.40
3.80
3.80
3.70
3.69
3.67
3.67
3.66
3.54
3.53
3.52
3.50
3.45
3.43
3.43
3.42
OH
OPMB
O
CO2Me
81
B (d)
7.25
A (d)
6.88
C (d)
6.19
D (s)
5.55
E (s)
4.41
F (s)
3.80
G (s)
3.67
H (m)
3.43
I (dd)
3.52
6.30
3.44
1.00
0.98
0.08
1.10
2.67
3.88
3.16
0.74
1.67
900
800
700
600
500
400
300
200
100
0
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
f1 (ppm)



OPMB
O
O
CO2Me
82
A (m) 9.65
B (d) 7.25
C (m) 6.87
E (m) 6.17
F (m) 5.59
G (s) 4.41
H (s) 3.80
I (s) 3.67
J (t) 3.42
K (dd) 2.93
L (m) 2.73
M (m) 2.50
N (ddd) 2.32
O (dd) 2.25
P (m) 2.18
Q (m) 2.08
R (m) 1.97
S (ddd) 1.91
T (p) 1.72
9.66 9.65 9.65 7.27 7.26 7.26 7.25 7.24 6.89 6.88 6.87 6.87 6.86 6.86 6.85 6.84 6.18 6.18 6.17 6.16 6.16 5.59 5.31 5.30 5.29 4.41 3.80 3.67 3.67 3.43 3.42 3.41 2.95 2.94 2.91 2.91 2.76 2.75 2.72 2.72 2.71 2.71 2.54 2.53 2.53 2.52 2.49 2.49 2.47 2.34 2.33 2.32 2.27 2.27 2.24 2.23 2.21 2.20 2.18 2.18 2.17 2.15 2.14 2.10 2.08 2.06 2.04 1.98 1.96 1.95 1.94 1.92 1.91 1.91 1.89 1.88 1.75 1.73 1.72 1.70 1.69
1.00 7.44 3.79 1.09 0.17 2.42 4.27 3.50 2.73 1.20 1.12 2.21 0.59 0.76 1.01 0.60 0.50 1.05 2.19
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
850 800 750 700 650 600 550 500 450 400 350 300 250 200 150 100 50 0 -50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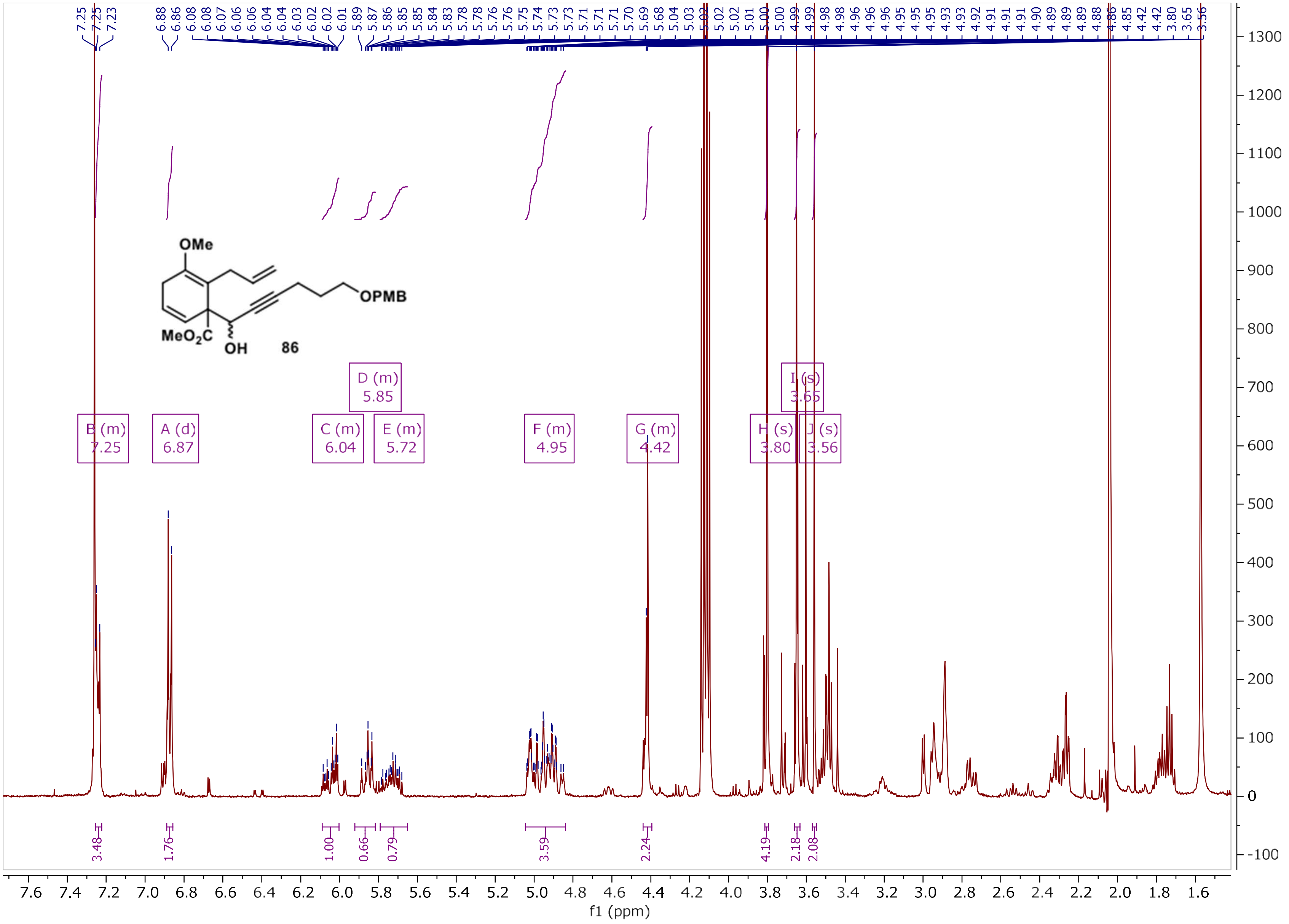
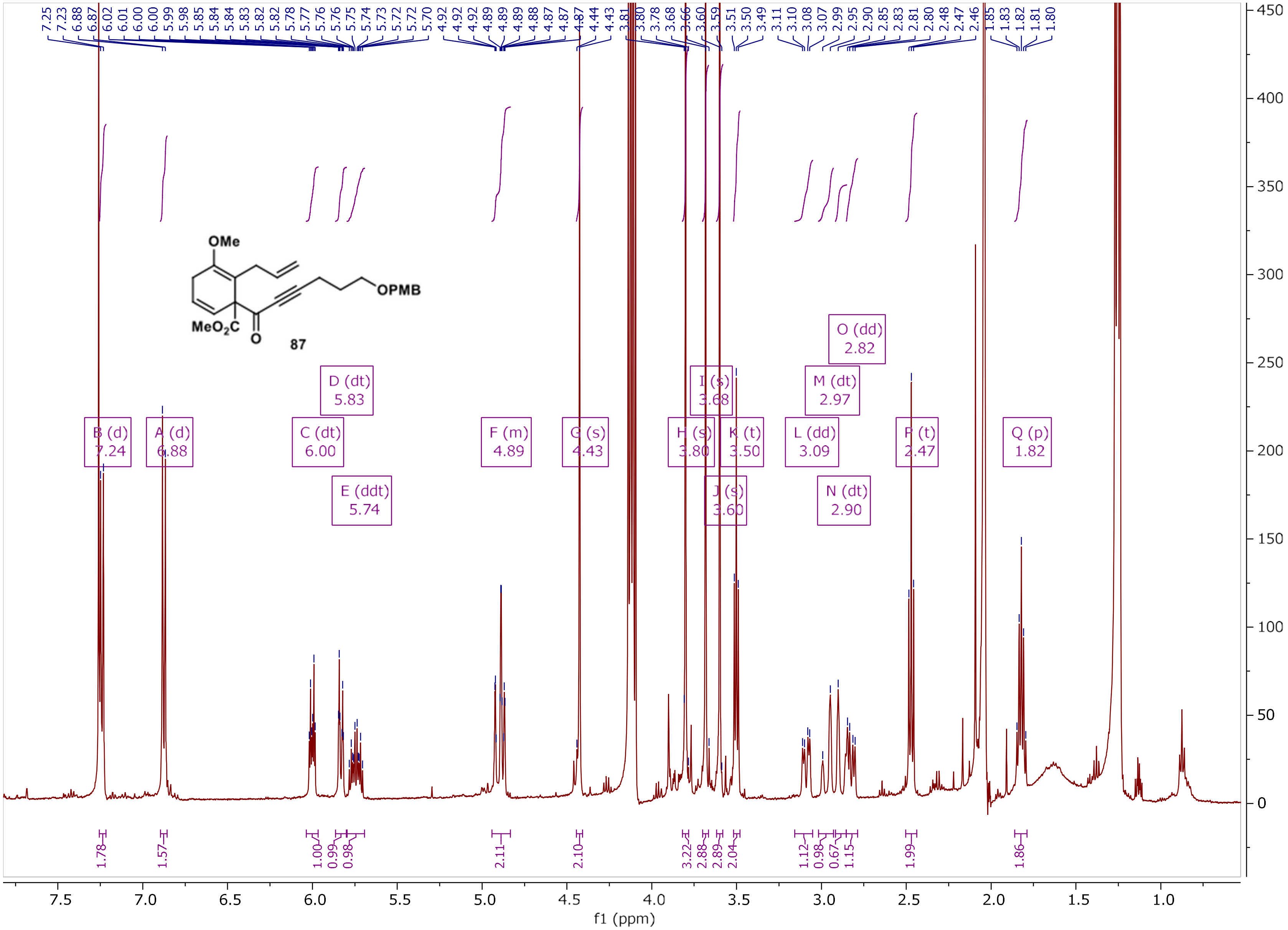
7.26
7.25
6.88
6.87
6.87
6.15
6.13
5.82
5.81
5.80
5.79
5.79
5.78
5.56
4.44
4.44
4.41
4.35
3.80
3.70
3.57
3.55
3.55
3.53
3.52
3.51
3.49
3.48
3.47
3.46
2.92
2.91
2.91
2.67
2.63
2.40
2.37
2.37
2.35
2.34
2.24
2.22
2.20
2.16
2.13
2.02
2.00
1.88
1.86
1.86
1.85
1.85
HO
O
CO2Me
OPMB
84
C (m) 5.56
P (s) 4.35
H (s) 3.70
K (d) 2.65
M (m) 2.18
E (d) 7.26
D (d) 6.88
A (d) 6.14
B (dd) 5.80
F (d) 4.44
G (s) 3.80
J (dd) 2.91
L (m) 2.36
N (d) 2.01
I (m) 3.51
O (m) 1.86
10.19
3.04
1.00
1.06
1.29
3.07
1.23
4.14
3.06
2.18
0.94
1.33
2.63
2.15
2.12
3.52
400
350
300
250
200
150
100
50
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.25
7.25
7.23
6.88
6.86
6.08
6.08
6.07
6.06
6.06
6.04
6.04
6.03
6.02
6.02
6.01
5.89
5.87
5.86
5.85
5.85
5.84
5.83
5.78
5.78
5.76
5.75
5.74
5.73
5.73
5.71
5.71
5.70
5.69
5.68
5.04
5.03
5.02
5.02
5.02
5.01
5.00
5.00
4.99
4.99
4.98
4.98
4.96
4.96
4.95
4.95
4.95
4.93
4.93
4.92
4.91
4.91
4.91
4.90
4.89
4.89
4.89
4.88
4.86
4.85
4.42
4.42
3.80
3.65
3.56
OMe
OPMB
MeO2C
OH
86
B (m) 7.25
A (d) 6.87
C (m) 6.04
D (m) 5.85
E (m) 5.72
F (m) 4.95
G (m) 4.42
H (s) 3.80
I (s) 3.65
J (s) 3.56
3.48
1.76
1.00
0.66
0.79
3.59
2.24
4.19
2.18
2.08
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
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
f1 (ppm)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100


7.25
7.23
6.88
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6.01
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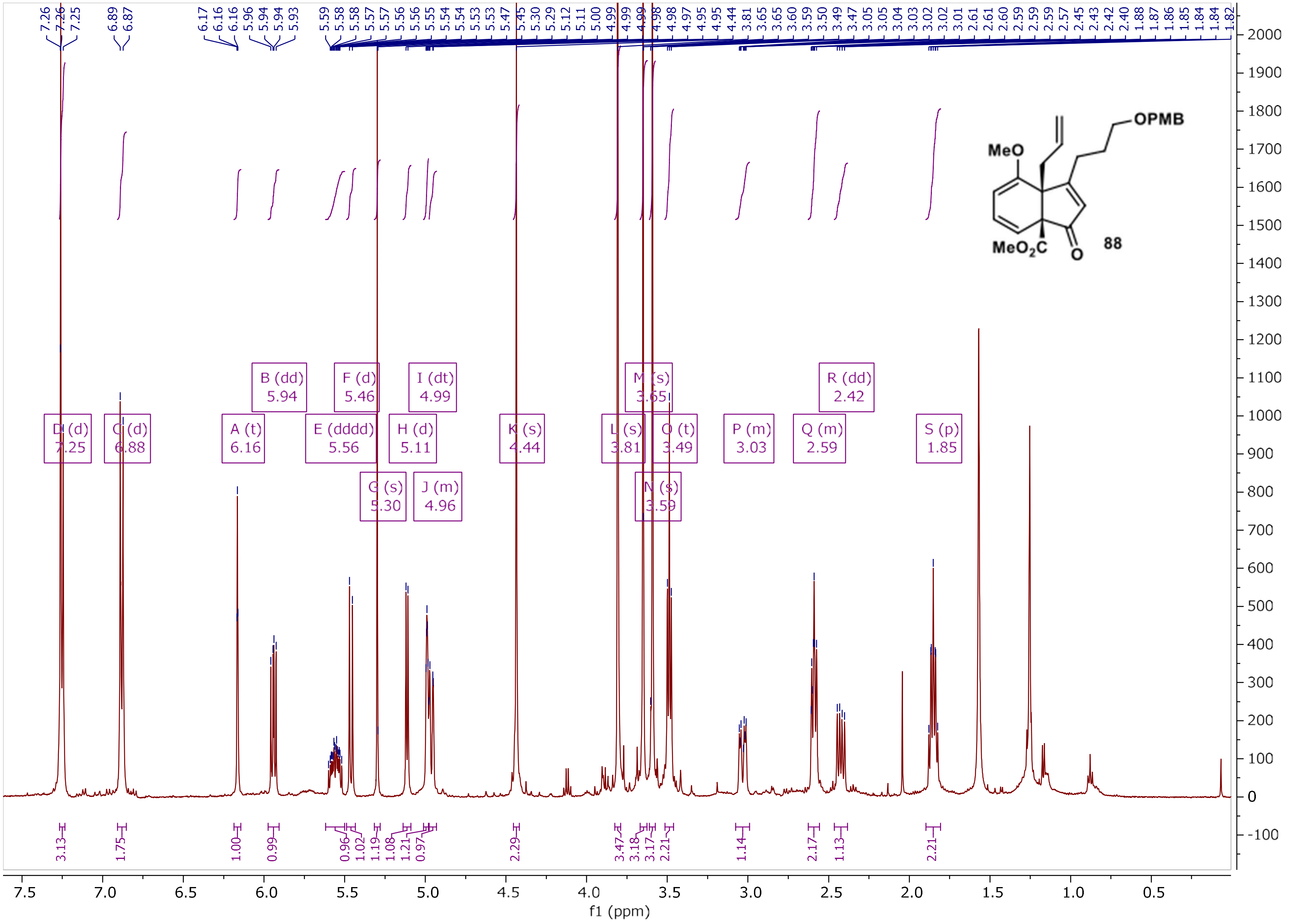
6.00
5.99
5.98
5.85
5.84
5.84
5.83
5.82
5.82
5.78
5.77
5.76
5.76
5.75
5.74
5.73
5.72
5.72
5.70
4.92
4.92
4.92
4.89
4.89
4.89
4.88
4.87
4.87
4.87
4.44
4.43
3.81
3.80
3.78
3.68
3.66
3.60
3.59
3.51
3.50
3.49
3.11
3.10
3.08
3.07
2.99
2.95
2.90
2.85
2.83
2.81
2.80
2.48
2.47
2.46
1.85
1.83
1.82
1.81
1.80
OMe
OPMB
MeO$_2$C
O
87
B (d) 7.24
A (d) 6.88
C (dt) 6.00
D (dt) 5.83
E (ddt) 5.74
F (m) 4.89
G (s) 4.43
H (s) 3.80
I (s) 3.68
J (s) 3.60
K (t) 3.50
L (dd) 3.09
M (dt) 2.97
N (dt) 2.90
O (dd) 2.82
P (t) 2.47
Q (p) 1.82
1.78
1.57
1.00
0.99
0.98
2.11
2.10
3.22
2.88
2.89
2.04
1.12
0.98
0.67
1.15
1.99
1.86
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
f1 (ppm)
450
400
350
300
250
200
150
100
50
0


7.26
7.26
7.25
6.89
6.87
6.17
6.16
6.16
5.96
5.94
5.94
5.93
5.59
5.58
5.58
5.57
5.57
5.56
5.56
5.55
5.54
5.54
5.53
5.53
5.47
5.45
5.30
5.29
5.12
5.11
5.00
4.99
4.99
4.99
4.98
4.98
4.97
4.95
4.95
4.44
3.81
3.65
3.60
3.59
3.50
3.49
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3.05
3.05
3.04
3.03
3.02
3.01
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2.61
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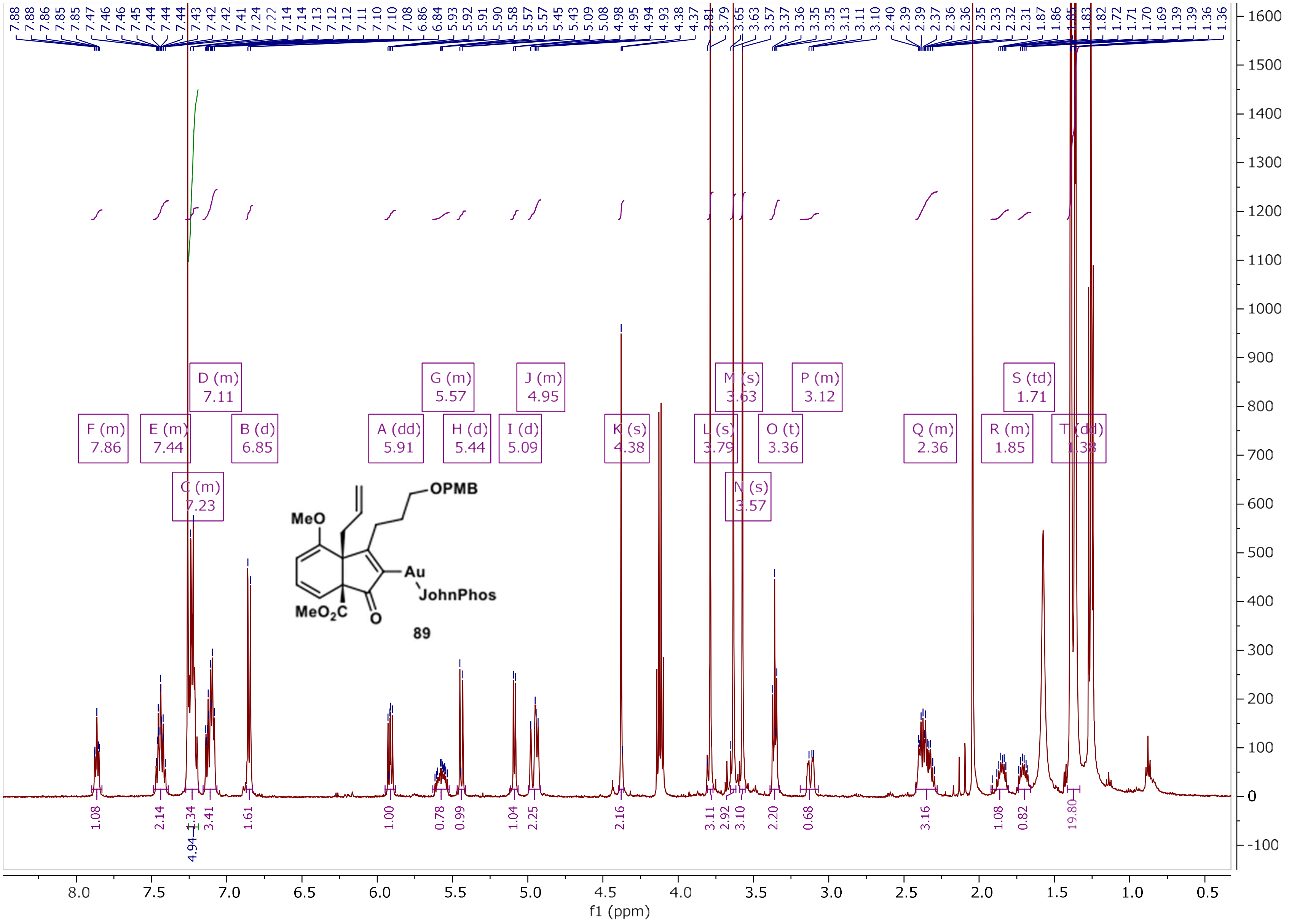
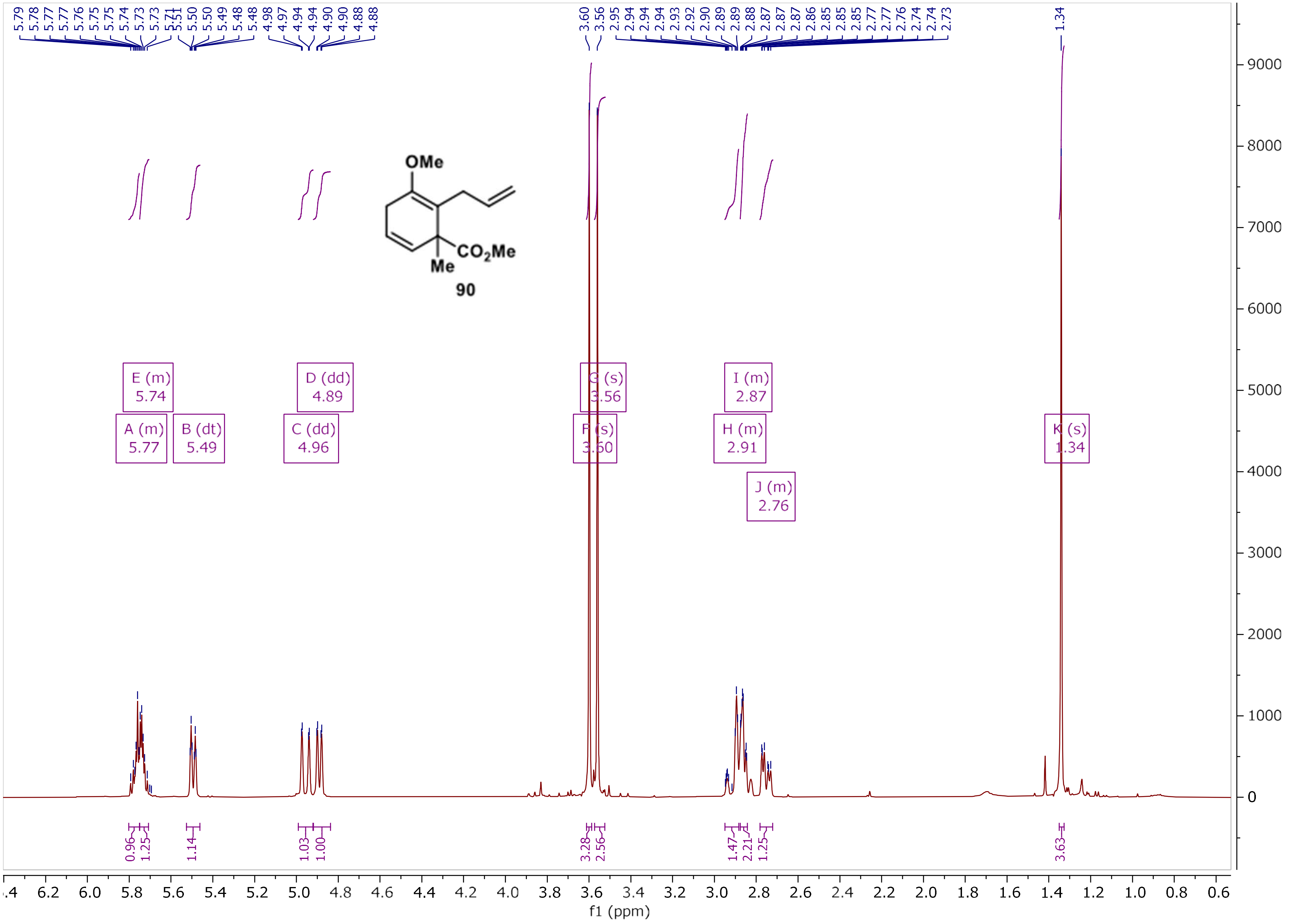
2.59
2.59
2.59
2.57
2.45
2.43
2.42
2.40
1.88
1.87
1.86
1.85
1.84
1.82
MeO
OPMB
MeO2C
O
88
D (d) 7.25
C (d) 6.88
A (t) 6.16
B (dd) 5.94
E (dddd) 5.56
F (d) 5.46
G (s) 5.30
H (d) 5.11
I (dt) 4.99
J (m) 4.96
K (s) 4.44
L (s) 3.81
M (s) 3.65
N (s) 3.59
O (t) 3.49
P (m) 3.03
Q (m) 2.59
R (dd) 2.42
S (p) 1.85
3.13
1.75
1.00
0.99
0.96
1.02
1.19
1.08
1.21
0.97
2.29
3.47
3.18
3.17
2.21
1.14
2.17
1.13
2.21
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


7.88 7.88 7.86 7.85 7.85 7.47 7.46 7.45 7.44 7.44 7.43 7.42 7.42 7.41 7.24 7.22 7.14 7.14 7.13 7.12 7.12 7.11 7.10 7.10 7.08 6.86 6.84 5.93 5.92 5.91 5.90 5.58 5.57 5.57 5.45 5.43 5.09 5.08 4.98 4.95 4.94 4.93 4.38 4.37 3.81 3.79 3.65 3.63 3.57 3.37 3.36 3.35 3.35 3.13 3.11 3.10 2.40 2.39 2.39 2.37 2.36 2.36 2.35 2.33 2.32 2.31 1.87 1.86 1.85 1.83 1.82 1.72 1.71 1.70 1.69 1.39 1.39 1.36 1.36
F (m) 7.86
E (m) 7.44
D (m) 7.11
C (m) 7.23
B (d) 6.85
A (dd) 5.91
G (m) 5.57
H (d) 5.44
I (d) 5.09
J (m) 4.95
K (s) 4.38
L (s) 3.79
M (s) 3.63
N (s) 3.57
O (t) 3.36
P (m) 3.12
Q (m) 2.36
R (m) 1.85
S (td) 1.71
T (dd) 1.38
MeO
OPMB
Au
JohnPhos
MeO2C
O
89
1.08 2.14 1.34 3.41 1.61 1.00 0.78 0.99 1.04 2.25 2.16 3.11 2.92 3.10 2.20 0.68 3.16 1.08 0.82 19.80
4.94
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100


5.79
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5.75
5.75
5.74
5.73
5.73
5.71
5.51
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5.50
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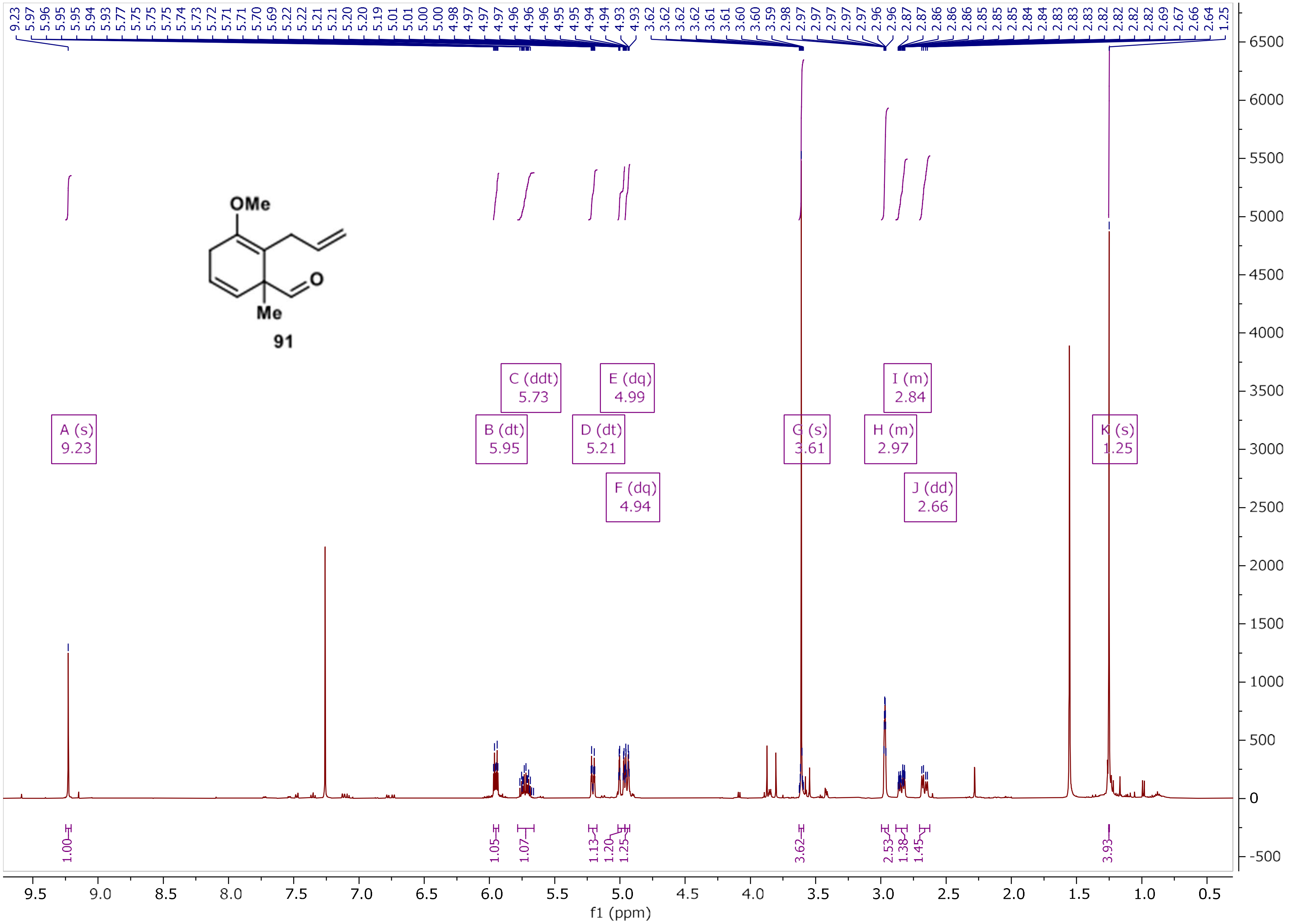
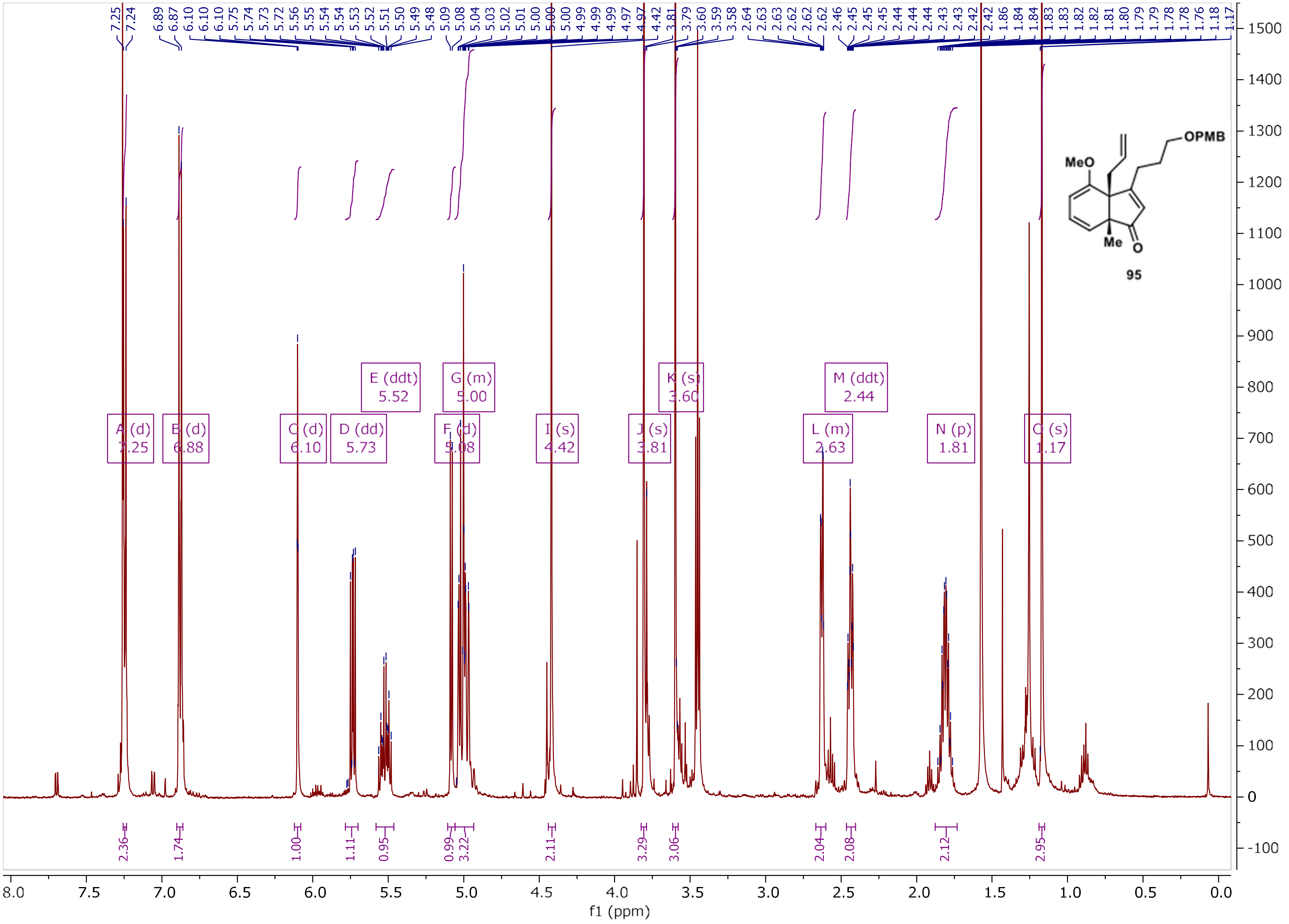
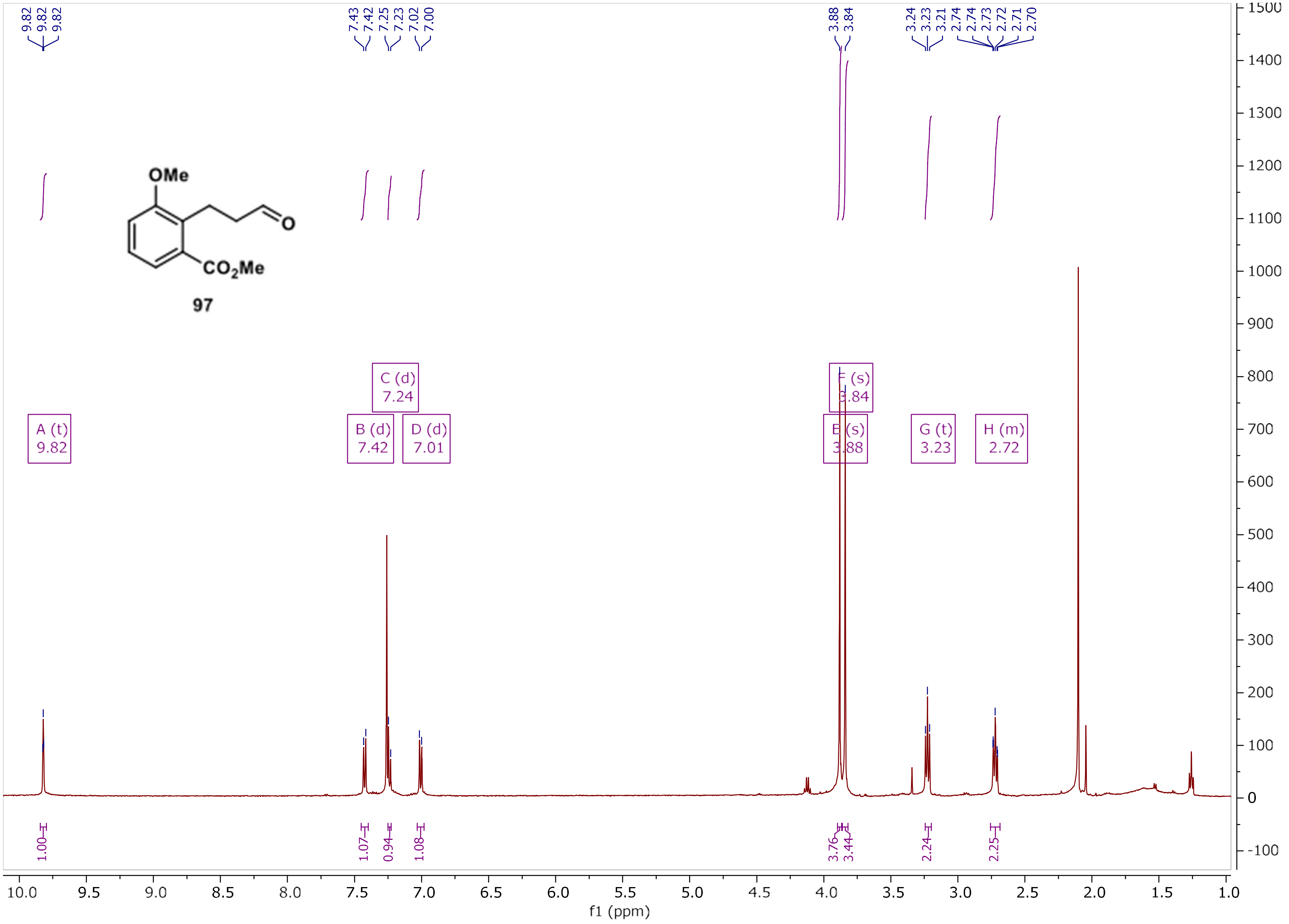
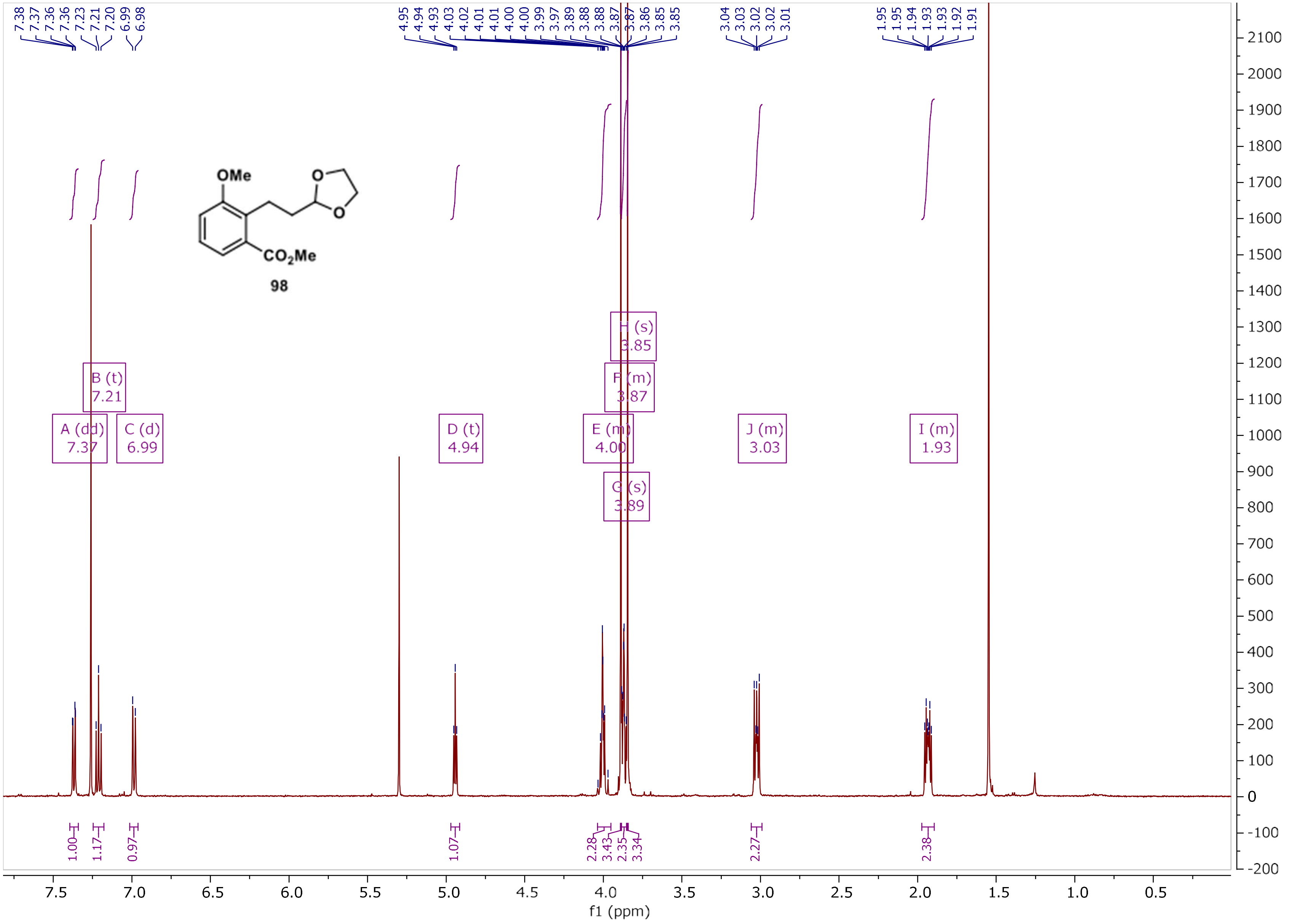
5.48
5.48
4.98
4.97
4.94
4.94
4.90
4.90
4.88
4.88
3.60
3.56
2.95
2.94
2.94
2.94
2.93
2.92
2.90
2.89
2.89
2.88
2.87
2.87
2.86
2.85
2.85
2.85
2.77
2.77
2.76
2.74
2.74
2.73
1.34
OMe
CO_2Me
Me
90
E (m) 5.74
A (m) 5.77
B (dt) 5.49
D (dd) 4.89
C (dd) 4.96
G (s) 3.56
F (s) 3.60
I (m) 2.87
H (m) 2.91
J (m) 2.76
K (s) 1.34
0.96
1.25
1.14
1.03
1.00
3.28
2.56
1.47
2.21
1.25
3.63
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
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
1.2
1.0
0.8
0.6
f1 (ppm)


9.23 5.97 5.96 5.95 5.95 5.94 5.93 5.77 5.75 5.75 5.75 5.74 5.73 5.72 5.71 5.71 5.70 5.69 5.22 5.22 5.21 5.21 5.20 5.20 5.19 5.01 5.01 5.00 5.00 4.98 4.97 4.97 4.97 4.96 4.96 4.96 4.95 4.95 4.94 4.94 4.93 4.93 3.62 3.62 3.62 3.62 3.61 3.61 3.60 3.59 2.98 2.97 2.97 2.97 2.97 2.97 2.96 2.96 2.87 2.87 2.87 2.86 2.86 2.86 2.85 2.85 2.85 2.84 2.84 2.83 2.83 2.83 2.82 2.82 2.82 2.82 2.69 2.67 2.66 2.64 1.25
OMe
O
Me
91
A (s) 9.23
B (dt) 5.95
C (ddt) 5.73
D (dt) 5.21
E (dq) 4.99
F (dq) 4.94
G (s) 3.61
H (m) 2.97
I (m) 2.84
J (dd) 2.66
K (s) 1.25
1.00
1.05
1.07
1.13
1.20
1.25
3.62
2.53
1.38
1.45
3.93
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



7.25
7.24
6.89
6.87
6.10
6.10
5.75
5.74
5.73
5.72
5.56
5.55
5.54
5.54
5.53
5.52
5.51
5.50
5.49
5.48
5.09
5.08
5.04
5.03
5.02
5.01
5.00
5.00
5.00
4.99
4.99
4.99
4.97
4.97
4.42
3.81
3.79
3.60
3.59
3.58
2.64
2.63
2.62
2.62
2.62
2.46
2.45
2.45
2.44
2.44
2.44
2.43
2.43
2.42
2.42
1.86
1.84
1.84
1.83
1.83
1.82
1.82
1.81
1.80
1.79
1.79
1.78
1.78
1.76
1.18
1.17
A (d) 7.25
B (d) 6.88
C (d) 6.10
D (dd) 5.73
E (ddt) 5.52
F (d) 5.08
G (m) 5.00
I (s) 4.42
J (s) 3.81
K (s) 3.60
L (m) 2.63
M (ddt) 2.44
N (p) 1.81
O (s) 1.17
2.36
1.74
1.00
1.11
0.95
0.99
3.22
2.11
3.29
3.06
2.04
2.08
2.12
2.95
MeO
OPMB
Me
O
95
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)
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100


9.82
9.82
9.82
7.43
7.42
7.25
7.23
7.02
7.00
3.88
3.84
3.24
3.23
3.21
2.74
2.74
2.73
2.72
2.71
2.70
OMe
O
CO2Me
97
A (t) 9.82
B (d) 7.42
C (d) 7.24
D (d) 7.01
E (s) 3.88
F (s) 3.84
G (t) 3.23
H (m) 2.72
1.00
1.07
0.94
1.08
3.76
3.44
2.24
2.25
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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
f1 (ppm)


7.38
7.37
7.36
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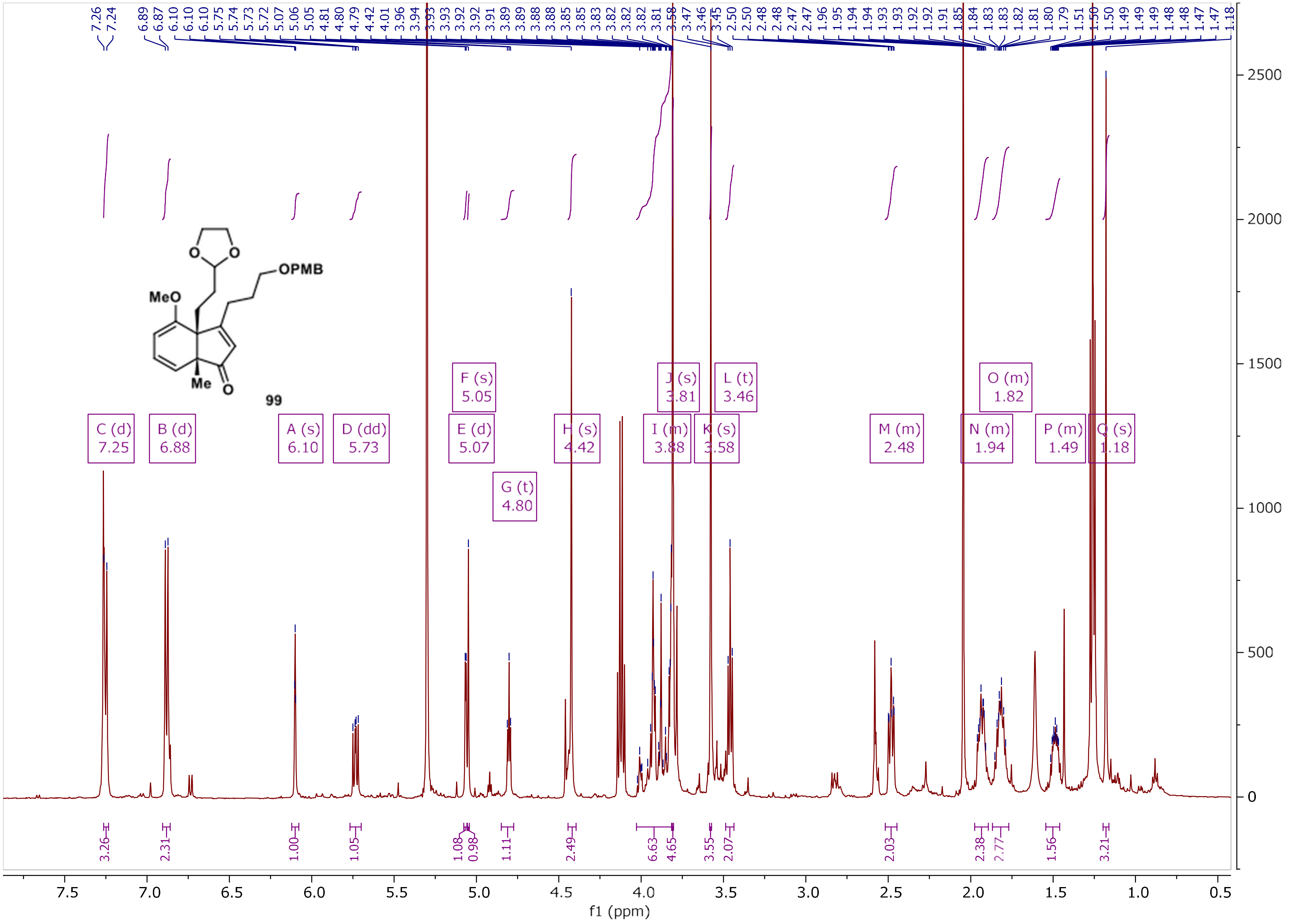
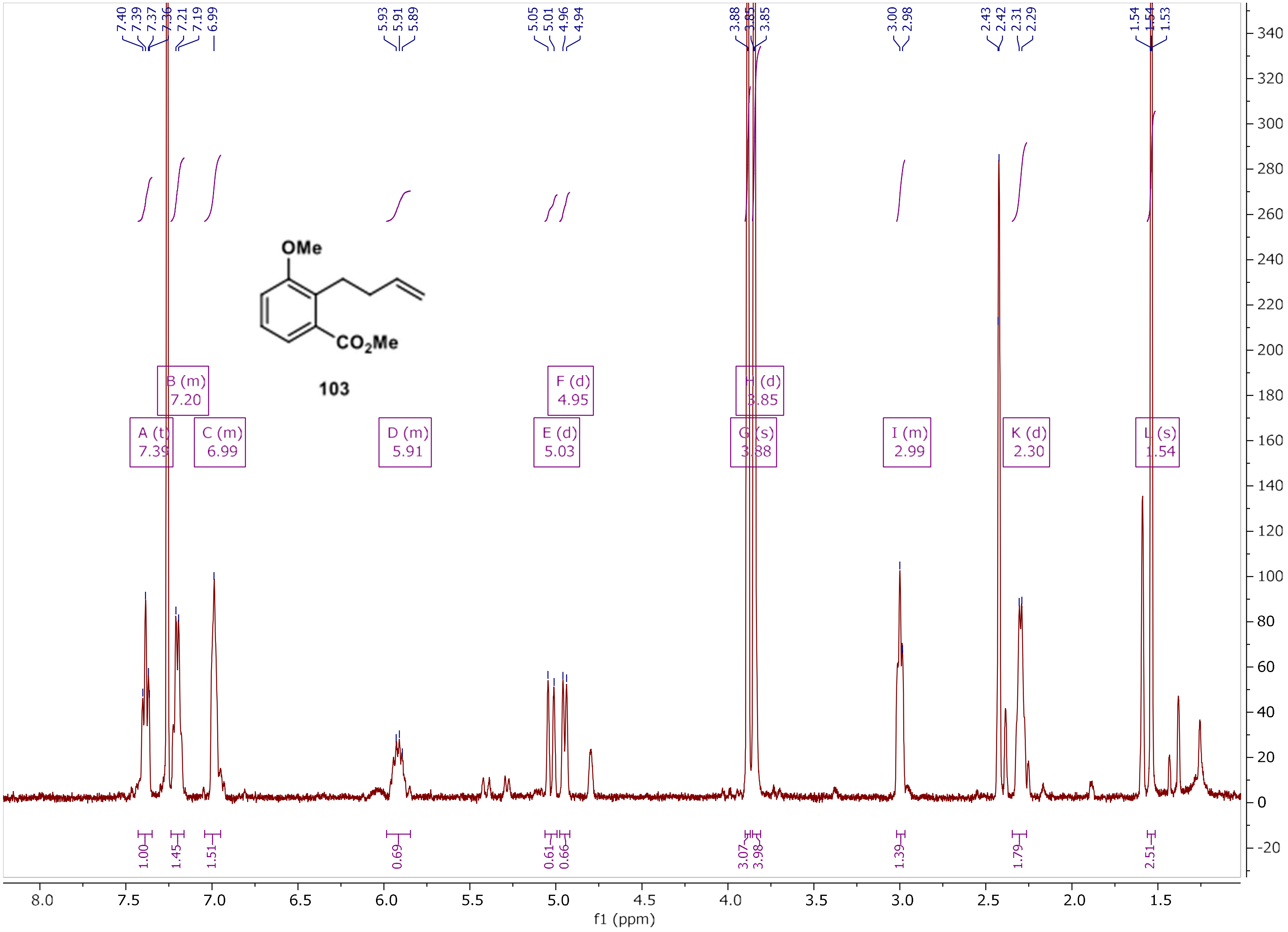
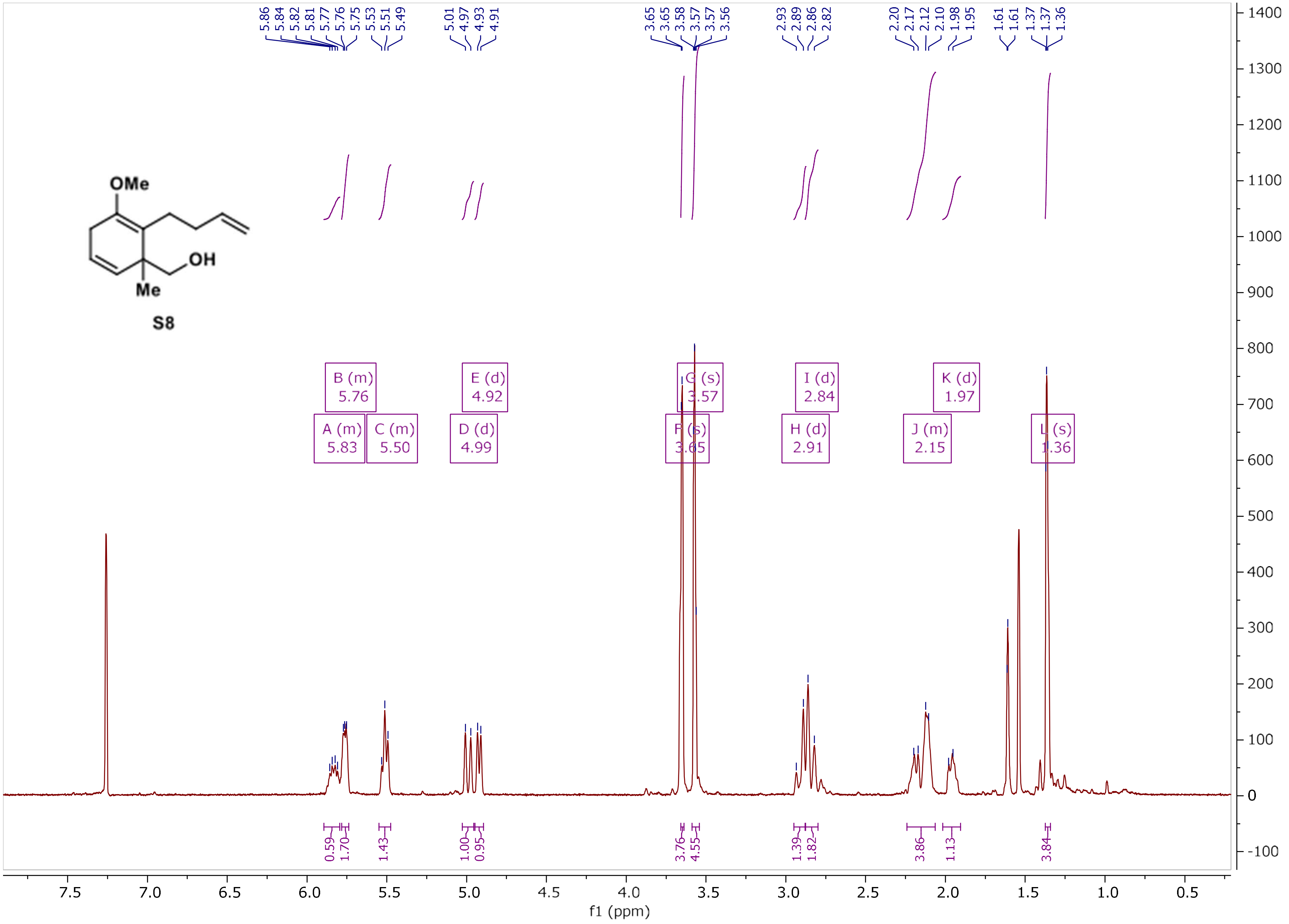
7.21
7.20
6.99
6.98
4.95
4.94
4.93
4.03
4.02
4.01
4.01
4.00
4.00
3.99
3.97
3.89
3.88
3.88
3.87
3.87
3.86
3.85
3.85
3.04
3.03
3.02
3.02
3.01
1.95
1.95
1.94
1.93
1.93
1.92
1.91
OMe
O
O
CO2Me
98
H (s)
3.85
B (t)
7.21
F (m)
3.87
A (dd)
7.37
C (d)
6.99
D (t)
4.94
E (m)
4.00
J (m)
3.03
I (m)
1.93
G (s)
3.89
1.00
1.17
0.97
1.07
2.28
3.43
2.35
3.34
2.27
2.38
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)
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

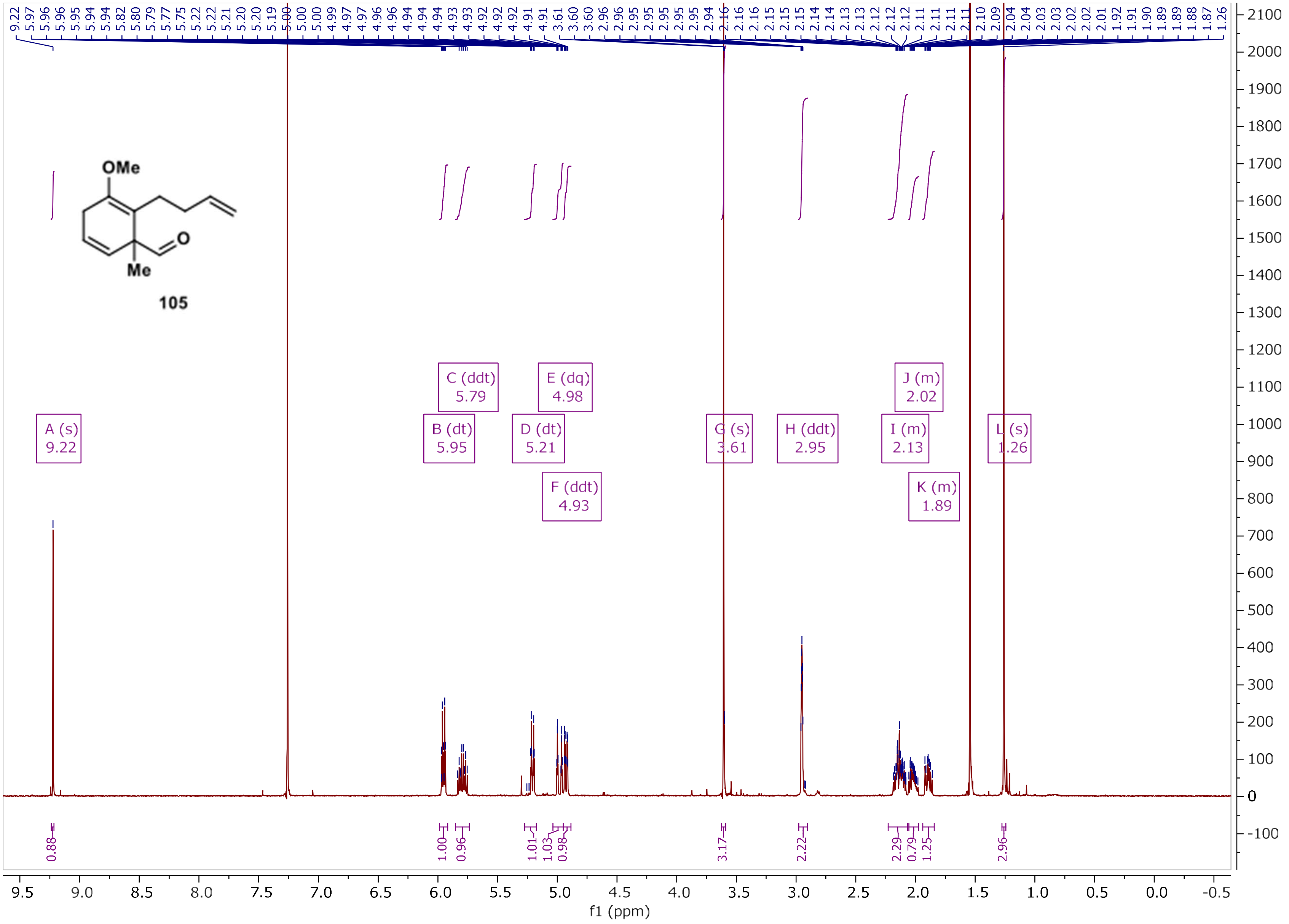

7.26
7.24
6.89
6.87
6.10
6.10
6.10
5.75
5.74
5.73
5.72
5.07
5.06
5.05
4.81
4.80
4.79
4.42
4.01
3.96
3.94
3.93
3.93
3.92
3.92
3.91
3.89
3.89
3.88
3.88
3.85
3.85
3.83
3.82
3.82
3.82
3.81
3.58
3.47
3.46
3.45
2.50
2.50
2.48
2.48
2.47
2.47
1.96
1.95
1.94
1.94
1.93
1.93
1.92
1.92
1.91
1.85
1.84
1.83
1.83
1.82
1.81
1.80
1.79
1.51
1.50
1.50
1.49
1.49
1.49
1.48
1.48
1.47
1.47
1.18
O
O
OPMB
MeO
Me
O
F (s) 5.05
J (s) 3.81
L (t) 3.46
O (m) 1.82
C (d) 7.25
B (d) 6.88
A (s) 6.10
D (dd) 5.73
E (d) 5.07
H (s) 4.42
I (m) 3.88
K (s) 3.58
M (m) 2.48
N (m) 1.94
P (m) 1.49
Q (s) 1.18
G (t) 4.80
3.26
2.31
1.00
1.05
1.08
0.98
1.11
2.49
6.63
4.65
3.55
2.07
2.03
2.38
2.77
1.56
3.21
2500
2000
1500
1000
500
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

99

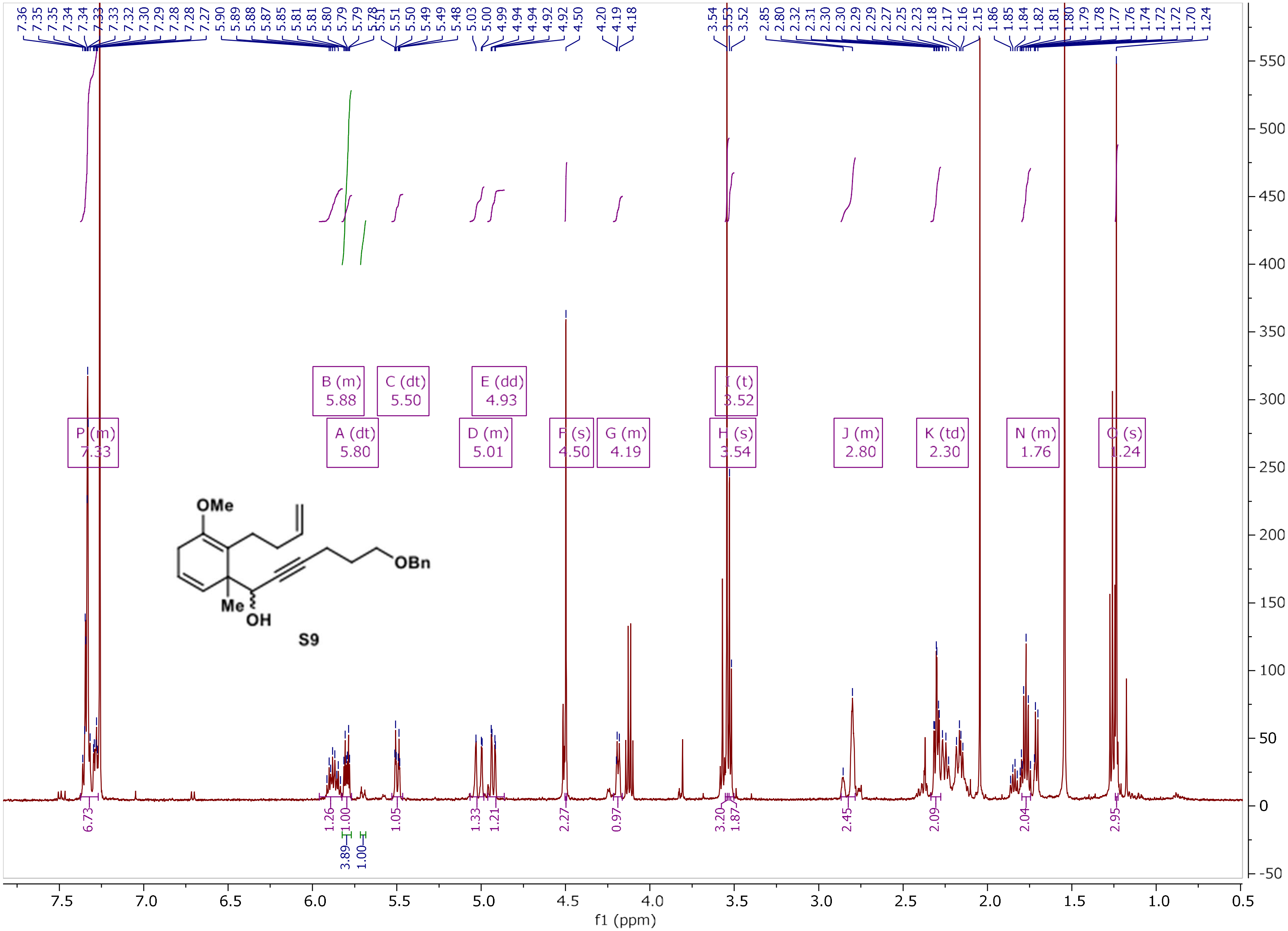

103

7.40
7.39
7.37
7.36
7.21
7.19
6.99
5.93
5.91
5.89
5.05
5.01
4.96
4.94
3.88
3.85
3.85
3.00
2.98
2.43
2.42
2.31
2.29
1.54
1.54
1.53
OMe
CO2Me
A (t) 7.39
B (m) 7.20
C (m) 6.99
D (m) 5.91
E (d) 5.03
F (d) 4.95
G (s) 3.88
H (d) 3.85
I (m) 2.99
K (d) 2.30
L (s) 1.54
1.00
1.45
1.51
0.69
0.61
0.66
3.07
3.98
1.39
1.79
2.51
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
f1 (ppm)
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

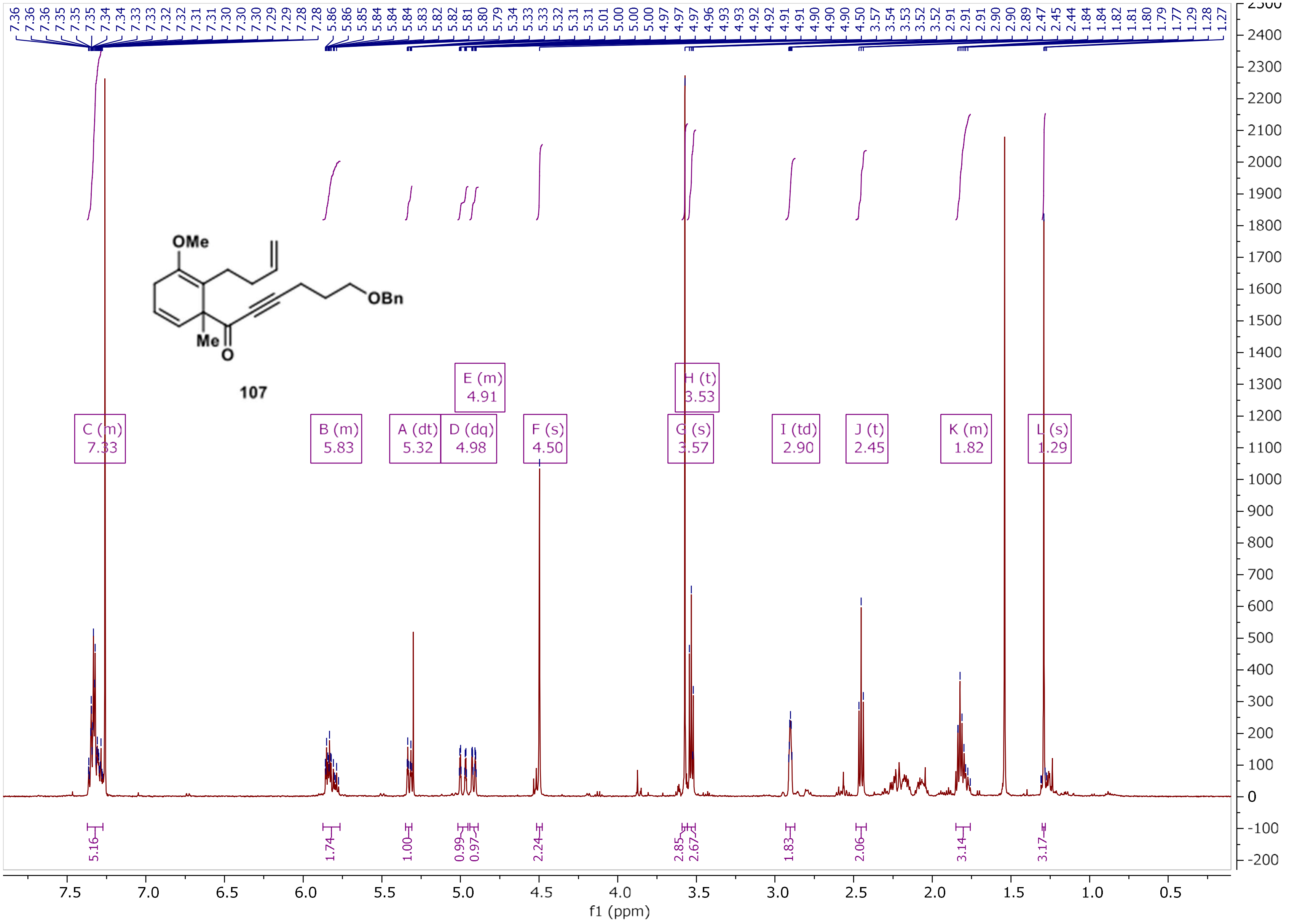

5.86
5.84
5.82
5.81
5.77
5.76
5.75
5.53
5.51
5.49
5.01
4.97
4.93
4.91
3.65
3.65
3.58
3.57
3.57
3.56
2.93
2.89
2.86
2.82
2.20
2.17
2.12
2.10
1.98
1.95
1.61
1.61
1.37
1.37
1.36
OMe
OH
Me
S8
B (m) 5.76
A (m) 5.83
C (m) 5.50
E (d) 4.92
D (d) 4.99
G (s) 3.57
F (s) 3.65
I (d) 2.84
H (d) 2.91
K (d) 1.97
J (m) 2.15
L (s) 1.36
0.59
1.70
1.43
1.00
0.95
3.76
4.55
1.39
1.82
3.86
1.13
3.84
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)


105

9.22 5.97 5.96 5.96 5.95 5.94 5.94 5.82 5.80 5.79 5.77 5.75 5.22 5.22 5.21 5.20 5.20 5.19 5.00 5.00 5.00 4.99 4.97 4.97 4.96 4.96 4.94 4.94 4.94 4.93 4.93 4.92 4.92 4.92 4.91 4.91 3.61 3.60 2.96 2.96 2.95 2.95 2.95 2.95 2.95 2.94 2.16 2.16 2.15 2.15 2.15 2.14 2.14 2.13 2.13 2.12 2.12 2.12 2.11 2.11 2.11 2.11 2.10 2.09 2.04 2.04 2.03 2.03 2.02 2.02 2.01 1.92 1.91 1.90 1.89 1.89 1.88 1.87 1.26
OMe
O
Me
A (s) 9.22
B (dt) 5.95
C (ddt) 5.79
D (dt) 5.21
E (dq) 4.98
F (ddt) 4.93
G (s) 3.61
H (ddt) 2.95
I (m) 2.13
J (m) 2.02
K (m) 1.89
L (s) 1.26
0.88
1.00
0.96
1.01
1.03
0.98
3.17
2.22
2.29
0.79
1.25
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 -0.5
f1 (ppm)
2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100



OMe
OBn
Me
OH
S9
P (m) 7.33
B (m) 5.88
A (dt) 5.80
C (dt) 5.50
D (m) 5.01
E (dd) 4.93
F (s) 4.50
G (m) 4.19
H (s) 3.54
I (t) 3.52
J (m) 2.80
K (td) 2.30
N (m) 1.76
O (s) 1.24
6.73
1.26
1.00
3.89
1.00
1.05
1.33
1.21
2.27
0.97
3.20
1.87
2.45
2.09
2.04
2.95
7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.30 7.29 7.28 7.28 7.27
5.90 5.89 5.88 5.87 5.85 5.81 5.81 5.80 5.79 5.79 5.78 5.51 5.51 5.50 5.49 5.49 5.48
5.03 5.00 4.99 4.94 4.94 4.92 4.92 4.50
4.20 4.19 4.18
3.54 3.53 3.52
2.85 2.80 2.32 2.31 2.30 2.30 2.29 2.29 2.27 2.25 2.23 2.18 2.17 2.16 2.15
1.86 1.85 1.84 1.82 1.81 1.80 1.79 1.78 1.77 1.76 1.74 1.72 1.72 1.70 1.24
550
500
450
400
350
300
250
200
150
100
50
0
-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
f1 (ppm)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7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.31
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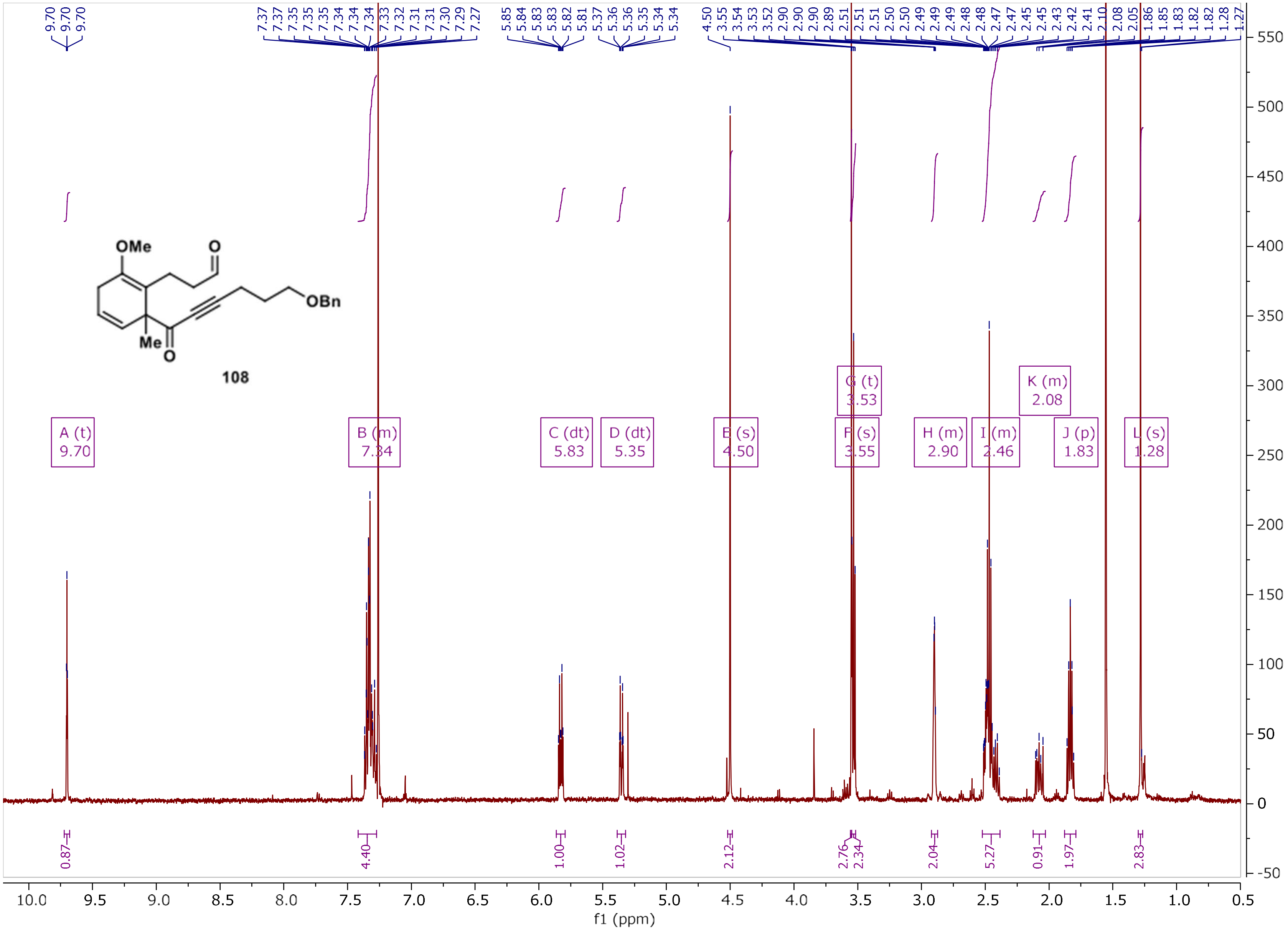
7.30
7.30
7.30
7.29
7.29
7.28
7.28
5.86
5.86
5.85
5.84
5.84
5.84
5.83
5.82
5.82
5.81
5.80
5.79
5.34
5.33
5.33
5.32
5.31
5.31
5.01
5.00
5.00
5.00
4.97
4.97
4.97
4.96
4.93
4.93
4.92
4.92
4.91
4.91
4.90
4.90
4.90
4.50
3.57
3.54
3.53
3.52
3.52
2.91
2.91
2.91
2.90
2.90
2.89
2.47
2.45
2.44
1.84
1.84
1.82
1.81
1.80
1.79
1.77
1.29
1.28
1.27
OMe
OBn
Me
O
107
C (m) 7.33
B (m) 5.83
A (dt) 5.32
D (dq) 4.98
E (m) 4.91
F (s) 4.50
G (s) 3.57
H (t) 3.53
I (td) 2.90
J (t) 2.45
K (m) 1.82
L (s) 1.29
5.16
1.74
1.00
0.99
0.97
2.24
2.85
2.67
1.83
2.06
3.14
3.17
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)
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

9.70
9.70
9.70
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7.35
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7.33
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7.31
7.31
7.30
7.29
7.27
5.85
5.84
5.83
5.83
5.82
5.81
5.37
5.36
5.36
5.35
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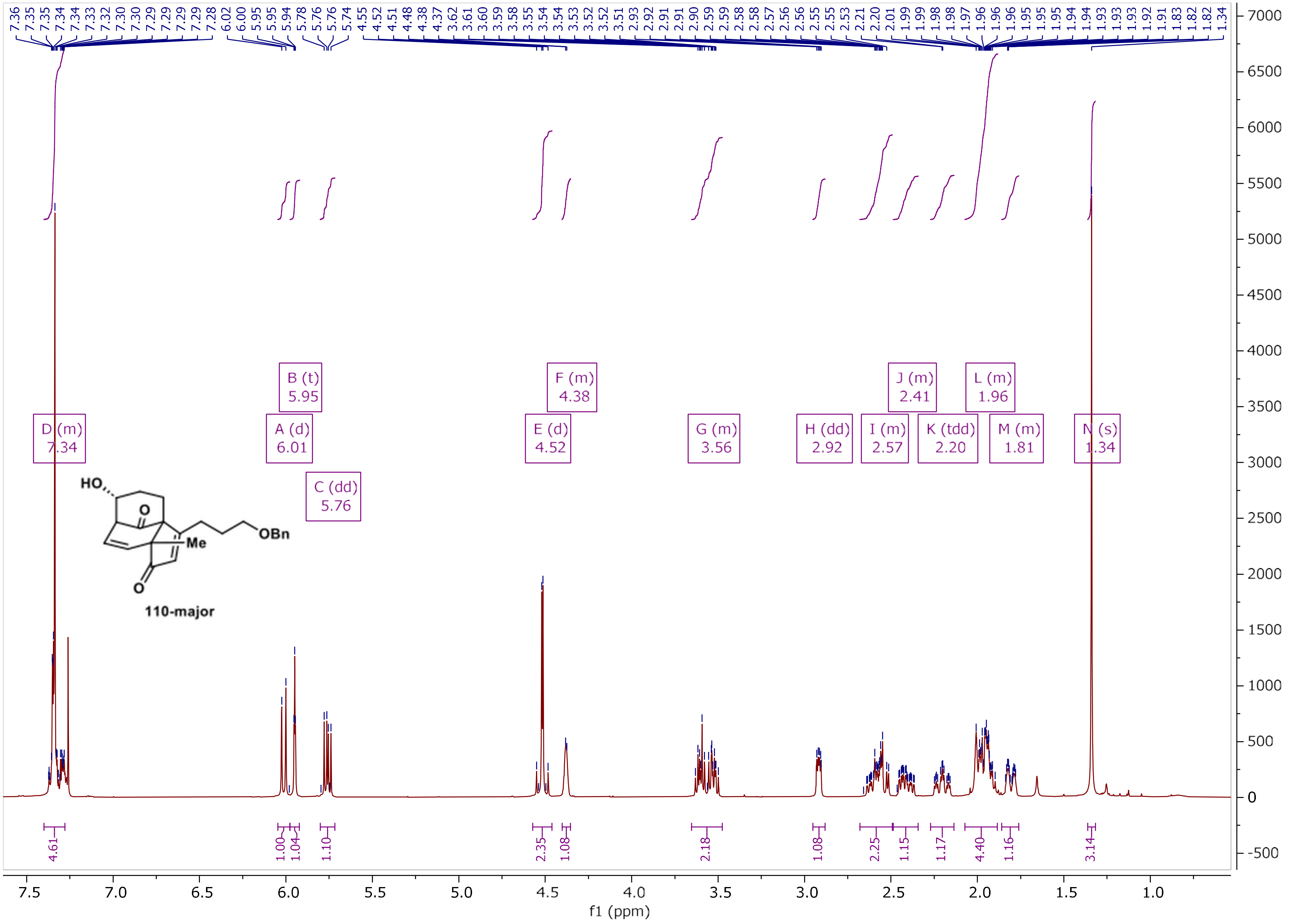
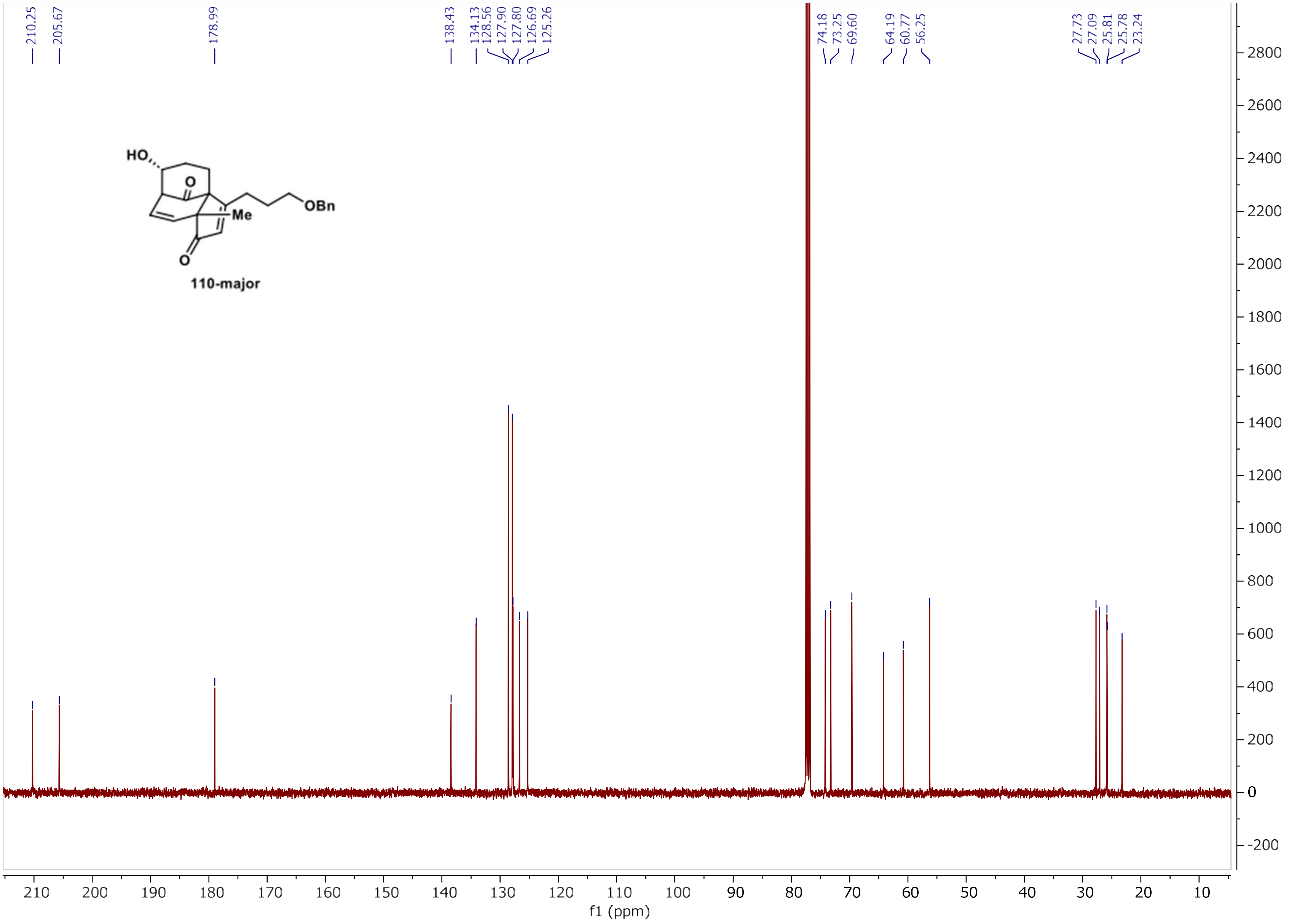
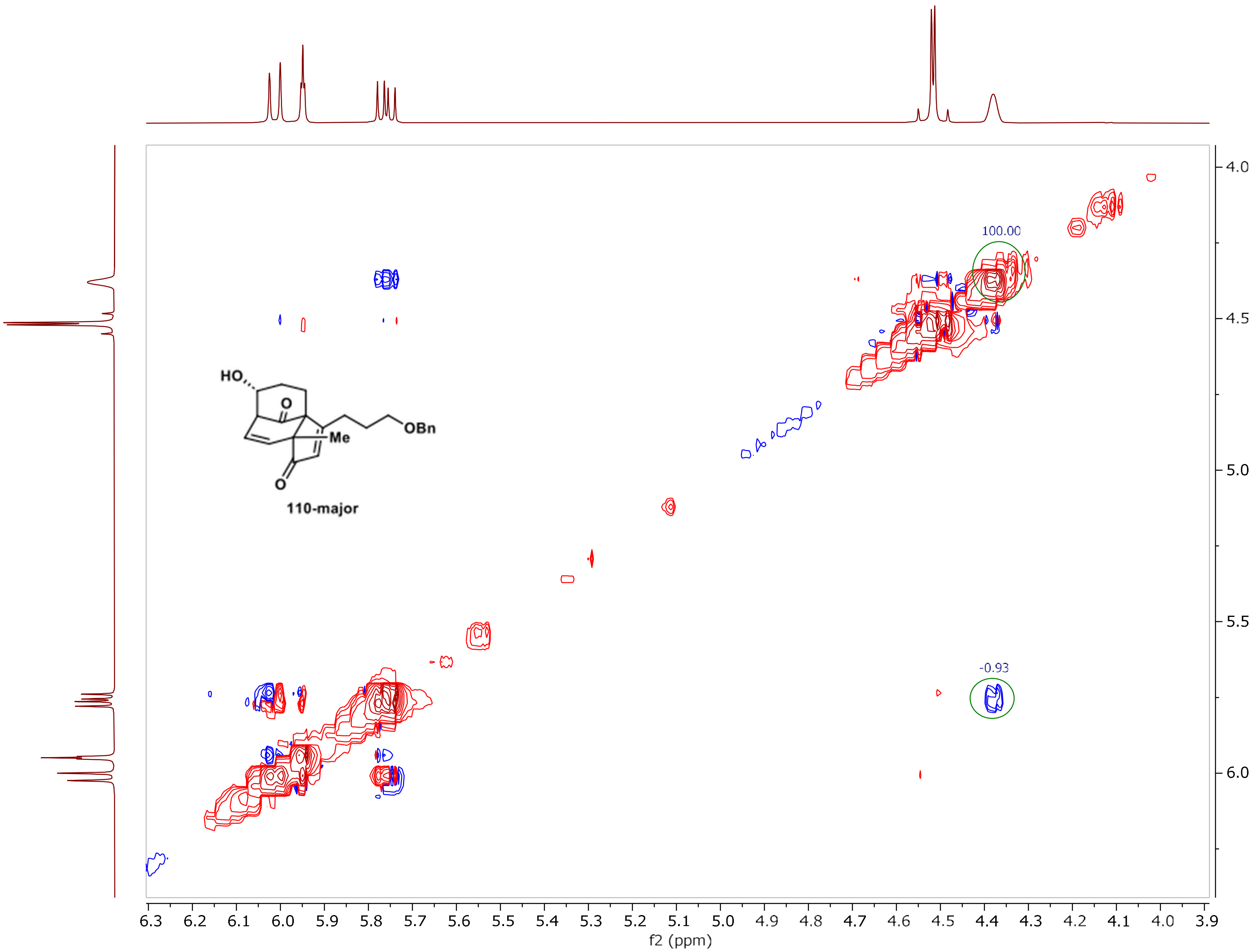
5.34
4.50
3.55
3.54
3.53
3.52
2.90
2.90
2.90
2.89
2.51
2.51
2.51
2.50
2.50
2.49
2.49
2.49
2.48
2.48
2.47
2.47
2.45
2.45
2.43
2.42
2.41
2.10
2.08
2.05
1.86
1.85
1.83
1.82
1.82
1.28
1.27
OMe
O
OBn
Me
O
108
A (t)
9.70
B (m)
7.34
C (dt)
5.83
D (dt)
5.35
E (s)
4.50
G (t)
3.53
F (s)
3.55
H (m)
2.90
I (m)
2.46
K (m)
2.08
J (p)
1.83
L (s)
1.28
0.87
4.40
1.00
1.02
2.12
2.76
2.34
2.04
5.27
0.91
1.97
2.83
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

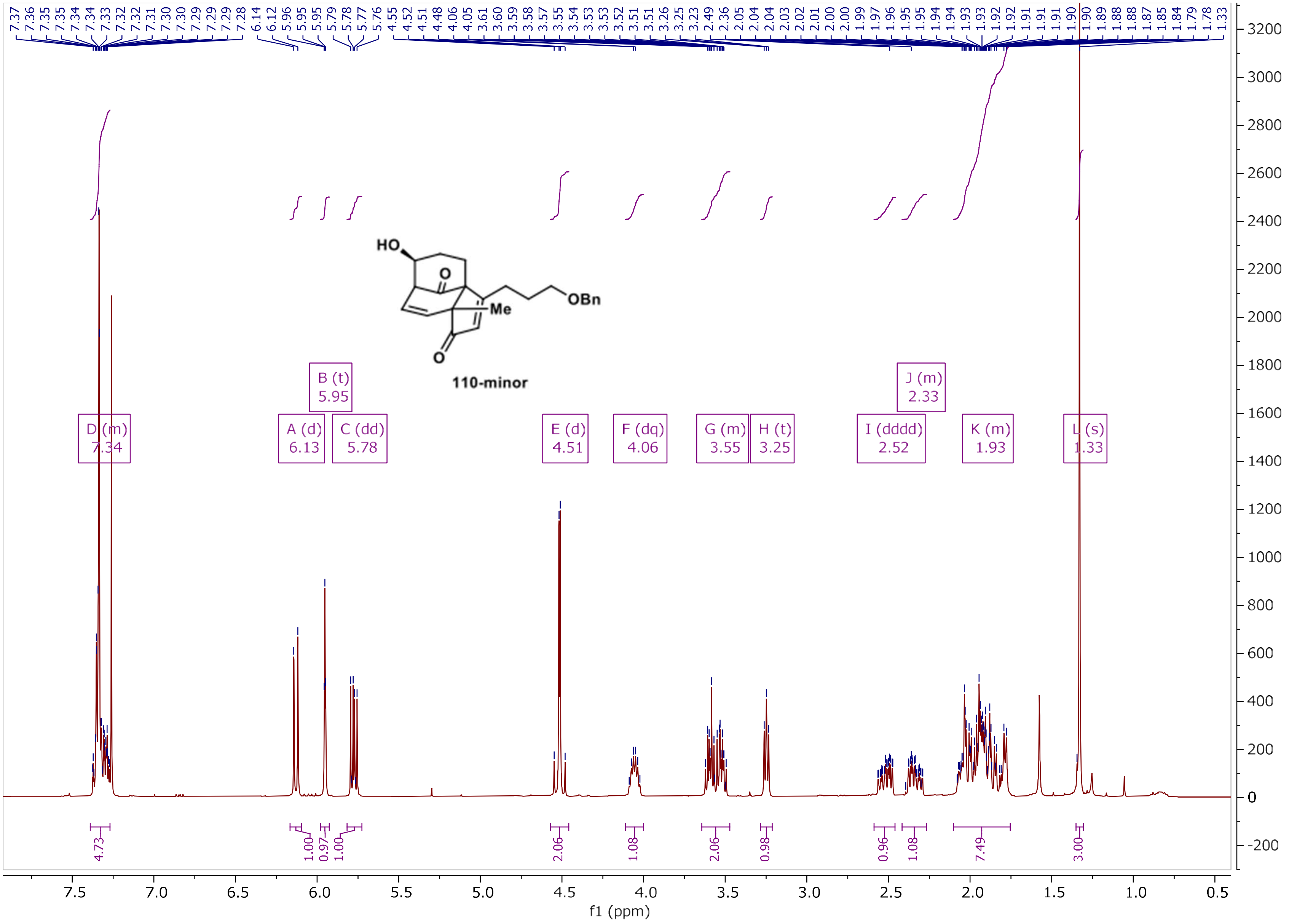

7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.30
7.30
7.29
7.29
7.29
7.29
7.28
6.02
6.00
5.95
5.95
5.94
5.78
5.76
5.76
5.74
4.55
4.52
4.51
4.48
4.38
4.37
3.62
3.61
3.60
3.59
3.58
3.55
3.54
3.54
3.53
3.52
3.52
3.51
2.93
2.92
2.91
2.91
2.90
2.59
2.59
2.58
2.58
2.57
2.56
2.56
2.55
2.55
2.53
2.21
2.20
2.01
1.99
1.99
1.98
1.98
1.97
1.96
1.96
1.96
1.95
1.95
1.95
1.94
1.94
1.93
1.93
1.93
1.92
1.91
1.83
1.82
1.82
1.34
D (m) 7.34
B (t) 5.95
A (d) 6.01
C (dd) 5.76
F (m) 4.38
E (d) 4.52
G (m) 3.56
H (dd) 2.92
J (m) 2.41
I (m) 2.57
K (tdd) 2.20
L (m) 1.96
M (m) 1.81
N (s) 1.34
HO
O
Me
OBn
O
4.61
1.00
1.04
1.10
2.35
1.08
2.18
1.08
2.25
1.15
1.17
4.40
1.16
3.14
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)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

110-major

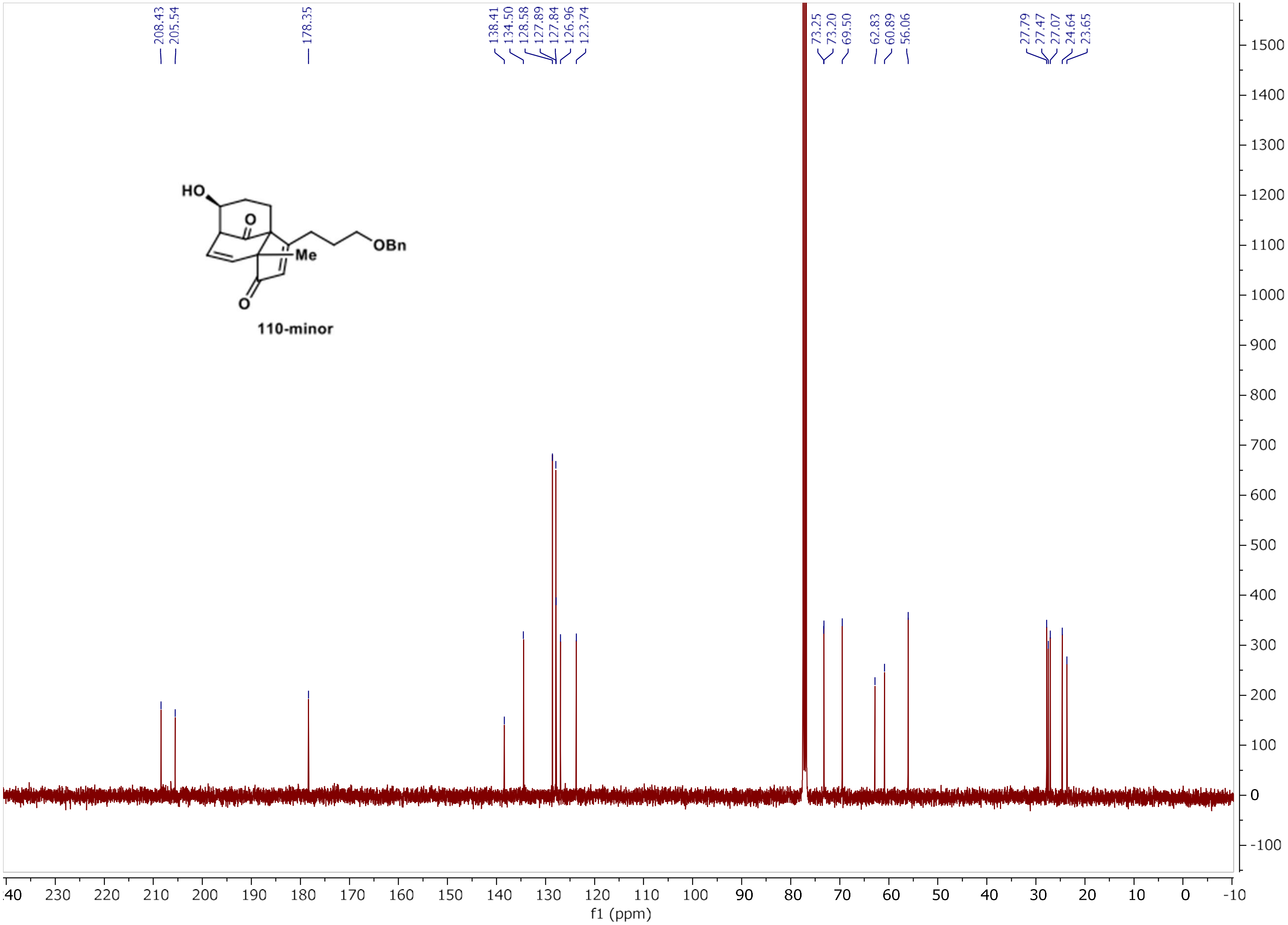

210.25
205.67
178.99
138.43
134.13
128.56
127.90
127.80
126.69
125.26
74.18
73.25
69.60
64.19
60.77
56.25
27.73
27.09
25.81
25.78
23.24
HO
O
O
Me
OBn
110-major
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


HO
O
Me
OBn
O
100.00
-0.93
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
f2 (ppm)
4.0
4.5
5.0
5.5
6.0
f1 (ppm)

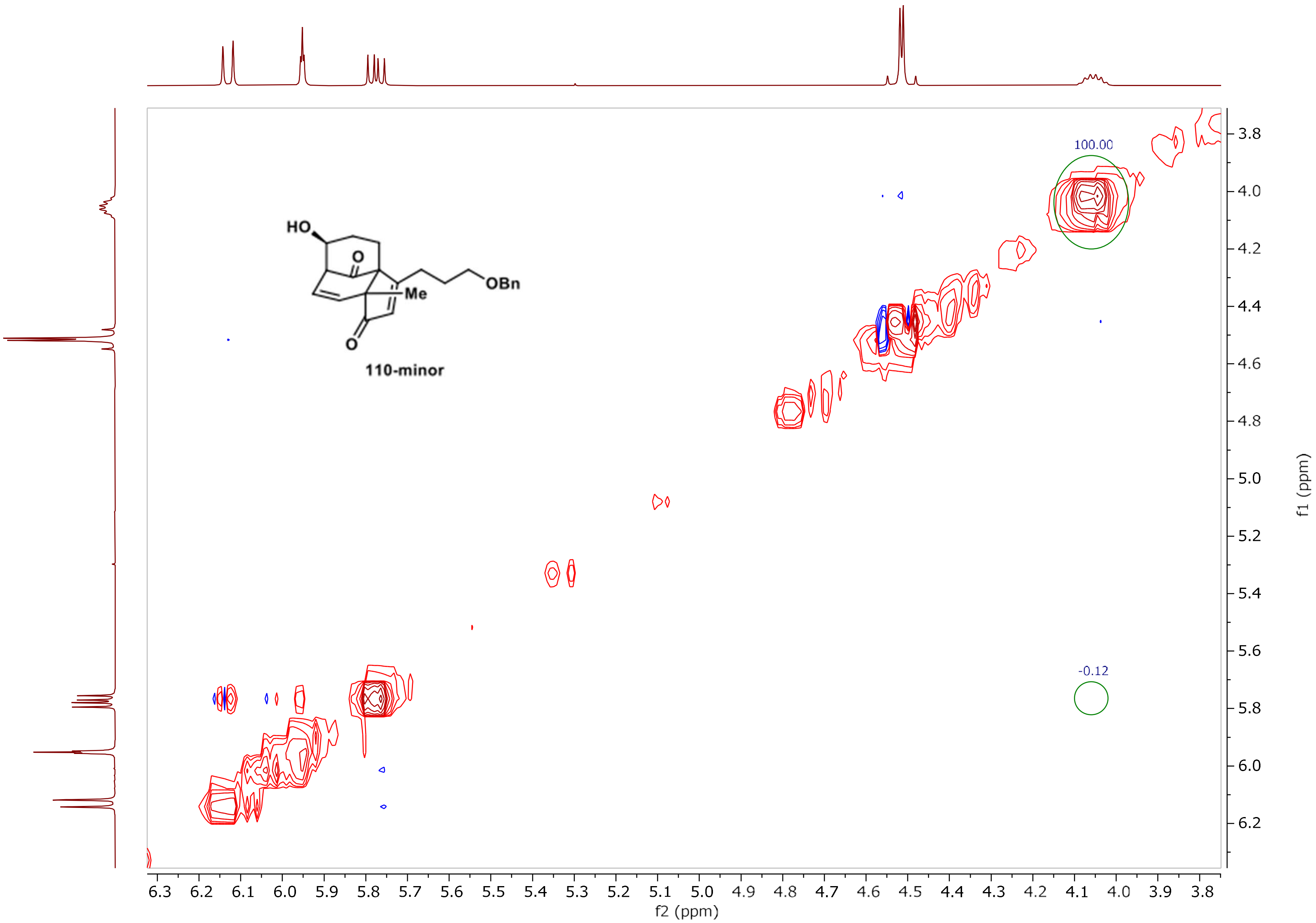
110-major

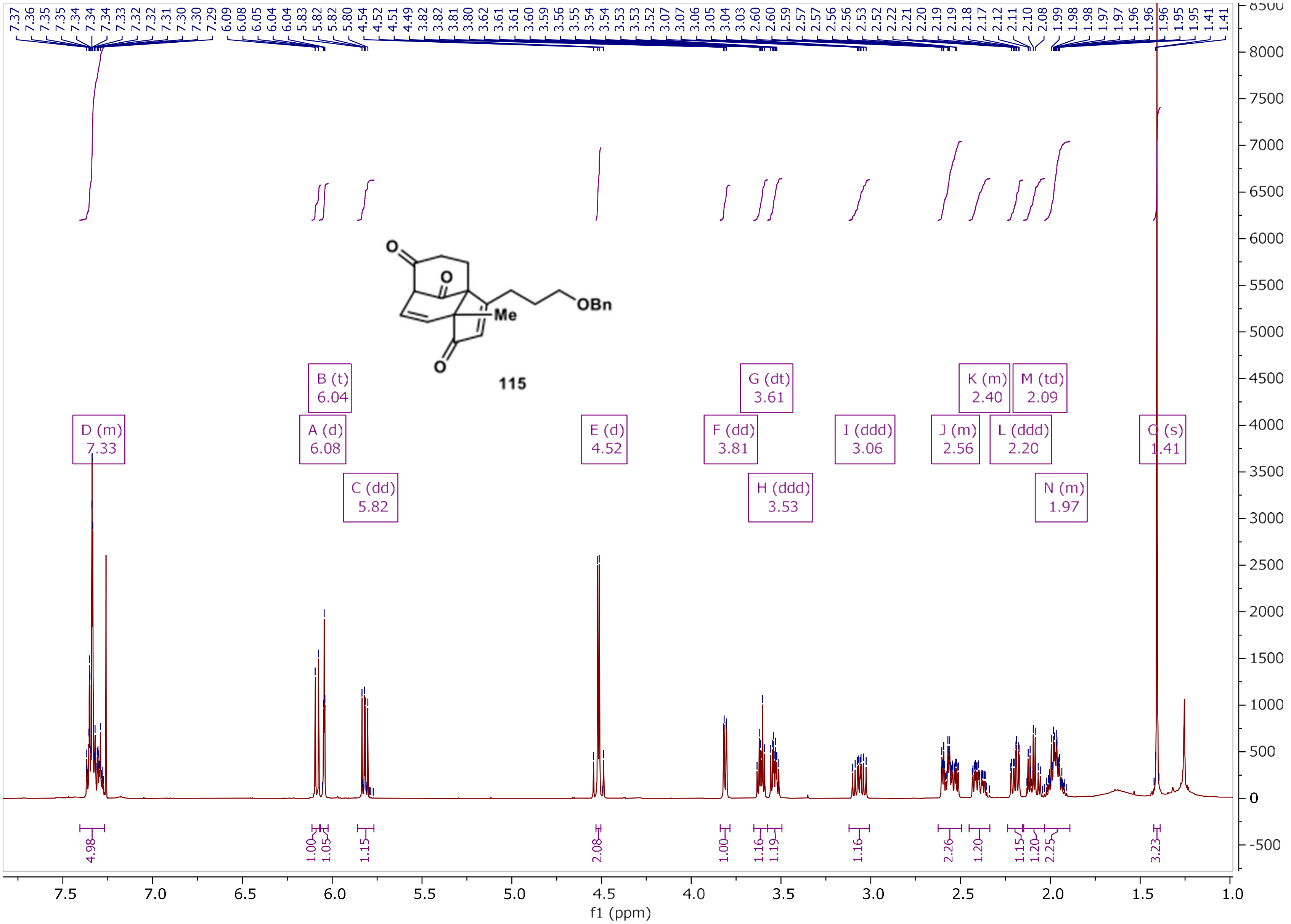

7.37 7.36 7.35 7.35 7.34 7.34 7.33 7.32 7.32 7.31 7.30 7.29 7.29 7.29 7.28 6.14 6.12 5.96 5.95 5.95 5.79 5.78 5.77 5.76 4.55 4.52 4.51 4.48 4.06 4.05 3.61 3.60 3.59 3.58 3.57 3.55 3.54 3.53 3.53 3.52 3.51 3.51 3.26 3.25 3.23 2.49 2.36 2.05 2.04 2.04 2.03 2.02 2.01 2.00 2.00 1.99 1.97 1.96 1.95 1.95 1.94 1.94 1.93 1.93 1.92 1.92 1.91 1.91 1.91 1.90 1.90 1.89 1.88 1.88 1.87 1.85 1.84 1.79 1.78 1.33
HO
O
Me
OBn
O
B (t) 5.95
J (m) 2.33
D (m) 7.34
A (d) 6.13
C (dd) 5.78
E (d) 4.51
F (dq) 4.06
G (m) 3.55
H (t) 3.25
I (dddd) 2.52
K (m) 1.93
L (s) 1.33
4.73
1.00
0.97
1.00
2.06
1.08
2.06
0.98
0.96
1.08
7.49
3.00
3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200
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)

110-minor

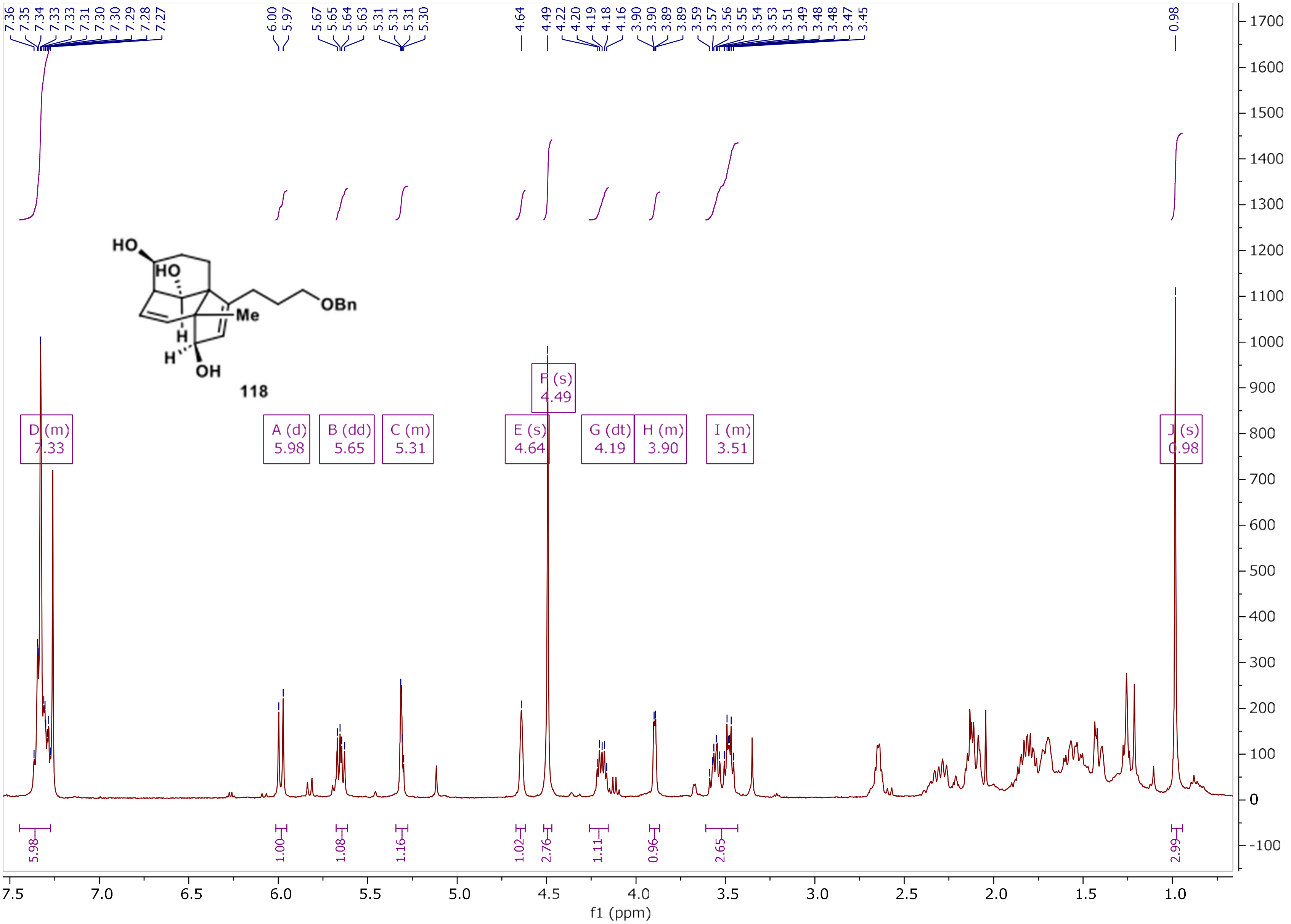


208.43
205.54
178.35
138.41
134.50
128.58
127.89
127.84
126.96
123.74
73.25
73.20
69.50
62.83
60.89
56.06
27.79
27.47
27.07
24.64
23.65
HO
O
Me
OBn
O
110-minor
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

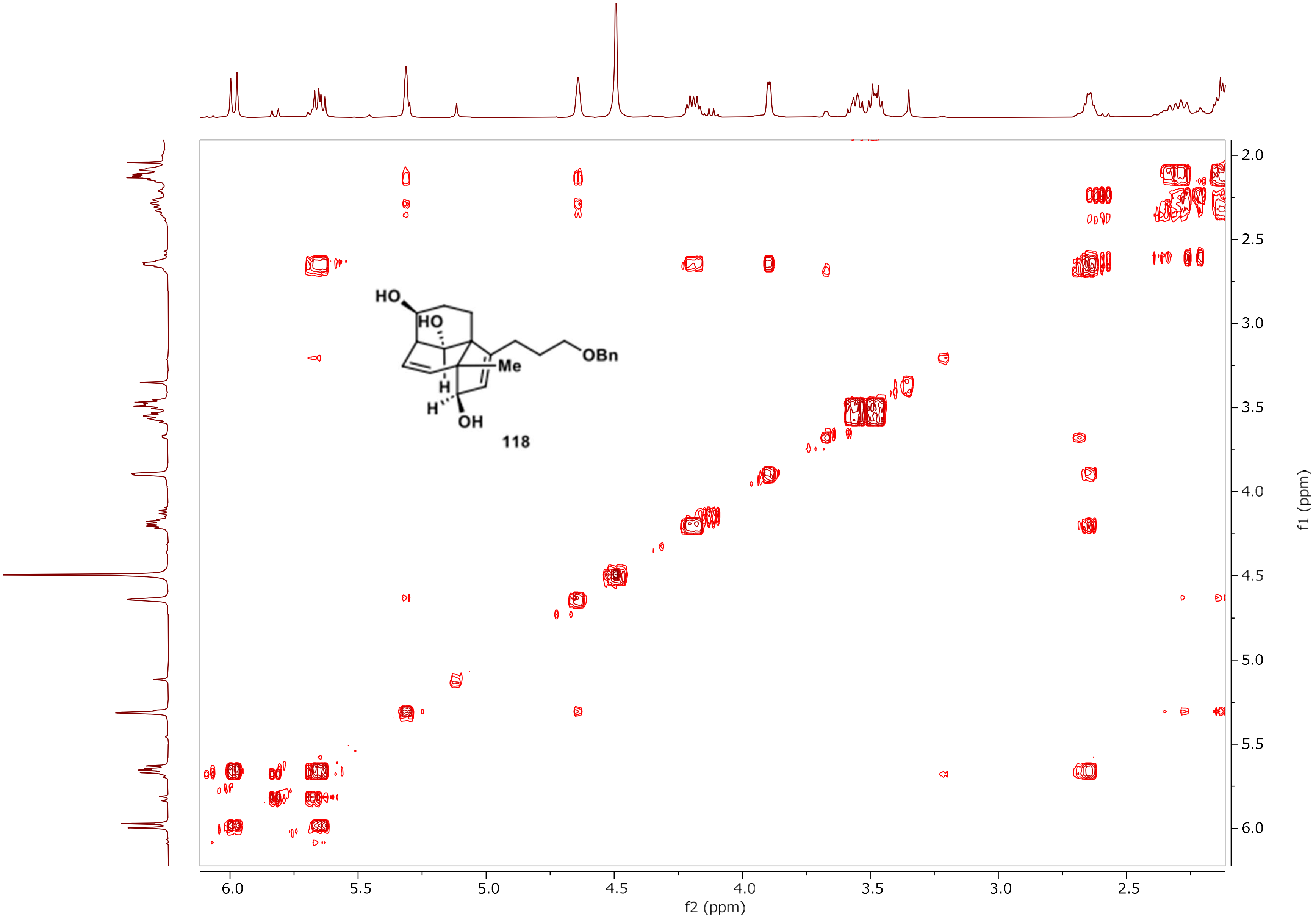

HO
O
OBn
Me
O
110-minor
100.00
-0.12
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
f2 (ppm)
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
5.8
6.0
6.2
f1 (ppm)


7.37 7.36 7.35 7.35 7.34 7.34 7.34 7.33 7.32 7.32 7.31 7.30 7.29 6.09 6.08 6.05 6.04 6.04 5.83 5.82 5.82 5.80 4.54 4.52 4.51 4.49 3.82 3.82 3.81 3.80 3.62 3.61 3.61 3.60 3.59 3.56 3.55 3.54 3.54 3.53 3.53 3.52 3.07 3.07 3.06 3.05 3.04 3.03 2.60 2.60 2.59 2.57 2.57 2.56 2.56 2.53 2.52 2.22 2.21 2.20 2.19 2.19 2.18 2.17 2.12 2.11 2.10 2.08 1.99 1.98 1.98 1.97 1.97 1.96 1.96 1.96 1.95 1.95 1.41 1.41
O
O
O
Me
OBn
D (m) 7.33
B (t) 6.04
A (d) 6.08
C (dd) 5.82
E (d) 4.52
F (dd) 3.81
G (dt) 3.61
H (ddd) 3.53
I (ddd) 3.06
J (m) 2.56
K (m) 2.40
L (ddd) 2.20
M (td) 2.09
N (m) 1.97
O (s) 1.41
4.98
1.00
1.05
1.15
2.08
1.00
1.16
1.19
1.16
2.26
1.20
1.15
1.20
2.25
3.23
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
f1 (ppm)
8500 8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

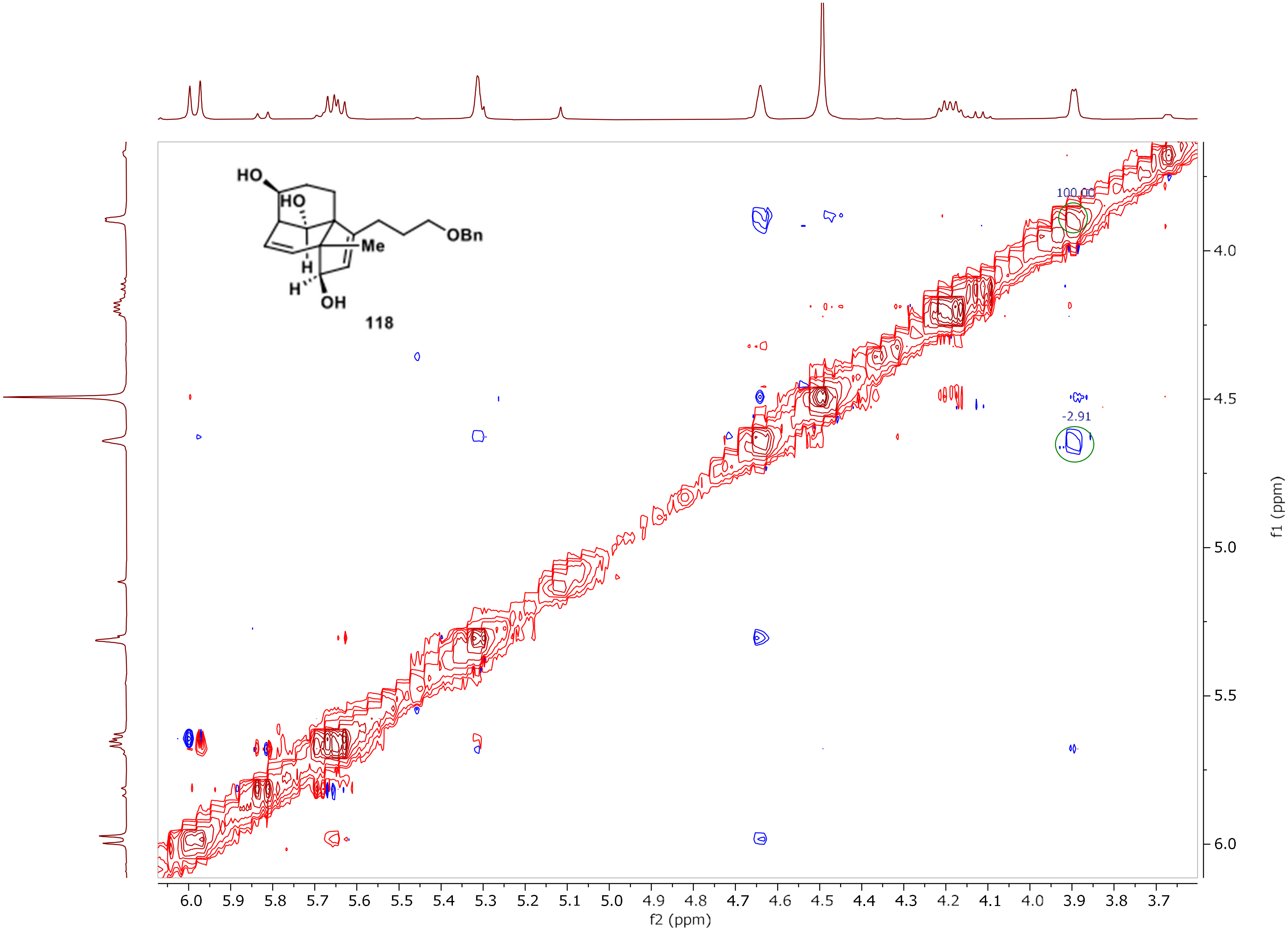
115


7.36 7.35 7.34 7.33 7.33 7.31 7.30 7.29 7.28 7.27
6.00 5.97
5.67 5.65 5.64 5.63
5.31 5.31 5.31 5.30
4.64
4.49
4.22 4.20 4.19 4.18 4.16
3.90 3.90 3.89 3.89
3.59 3.57 3.56 3.55 3.54 3.53 3.51 3.49 3.48 3.48 3.47 3.45
0.98
HO
HO
Me
OBn
H
H
OH
D (m) 7.33
A (d) 5.98
B (dd) 5.65
C (m) 5.31
E (s) 4.64
F (s) 4.49
G (dt) 4.19
H (m) 3.90
I (m) 3.51
J (s) 0.98
5.98
1.00
1.08
1.16
1.02
2.76
1.11
0.96
2.65
2.99
1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100
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)

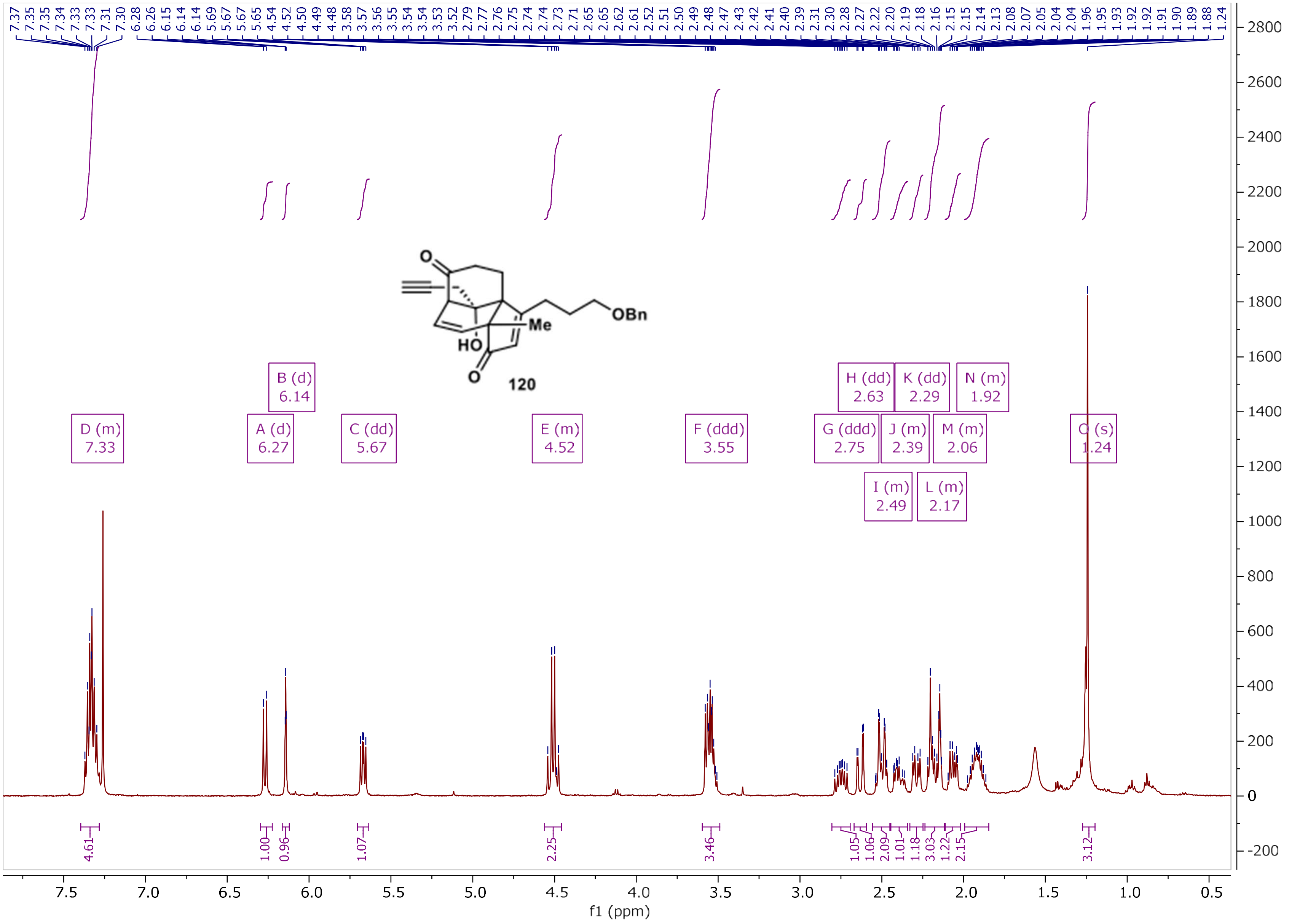
118

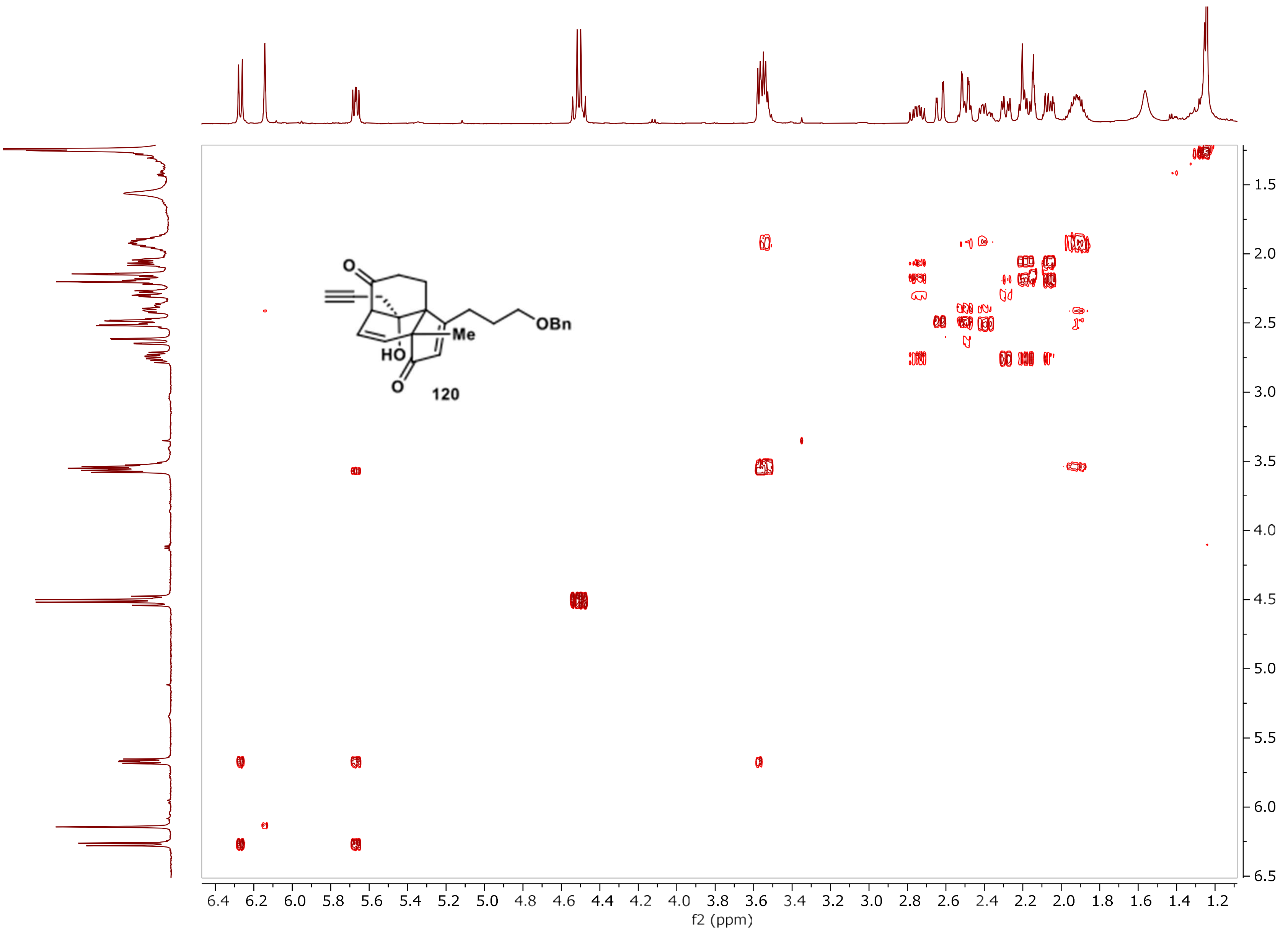

HO
HO
Me
OBn
H
H
OH
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
f1 (ppm)

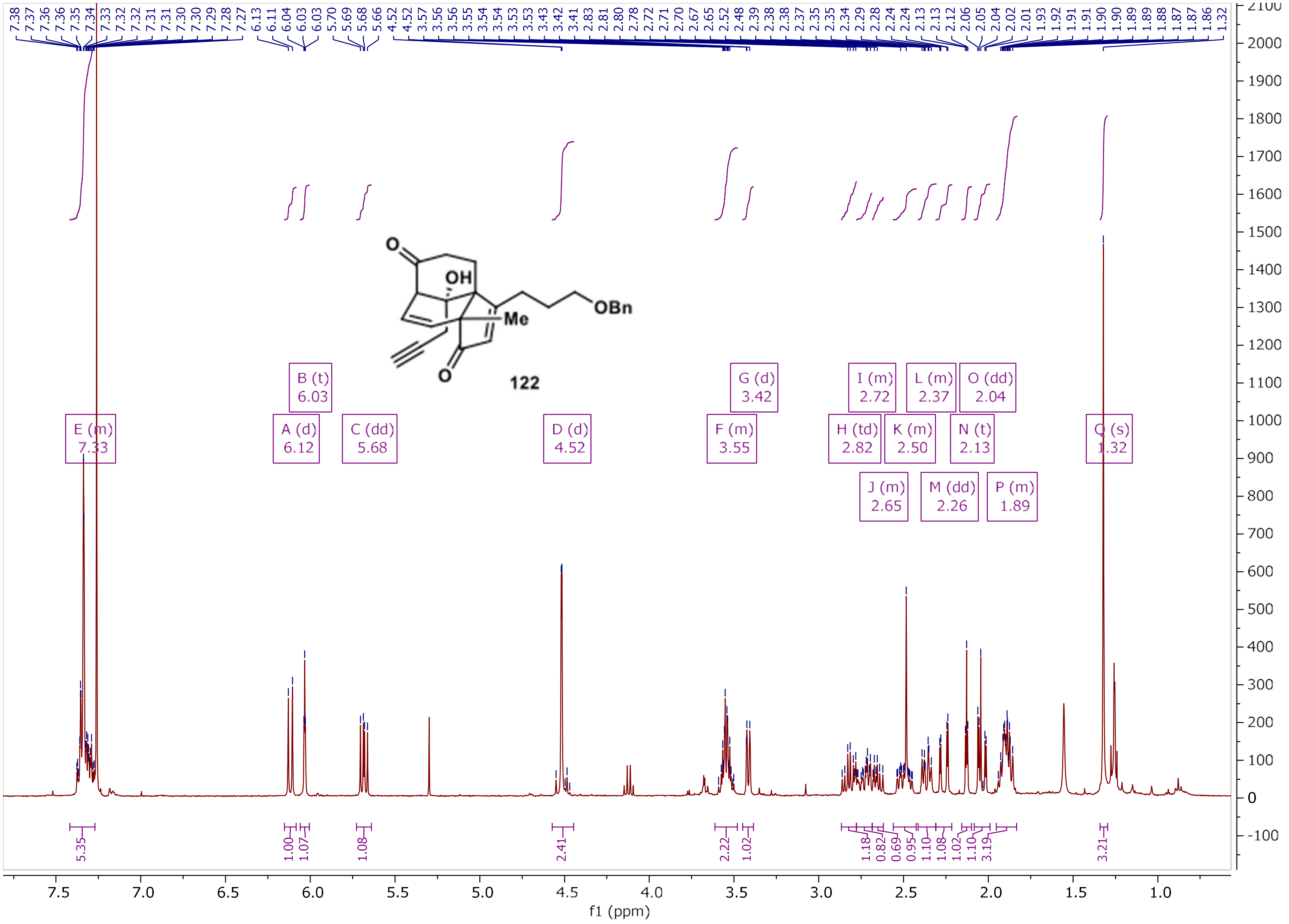
118



HO
HO
Me
OBn
H
H
OH
118
100.00
-2.91
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
f2 (ppm)
4.0
4.5
5.0
5.5
6.0
f1 (ppm)

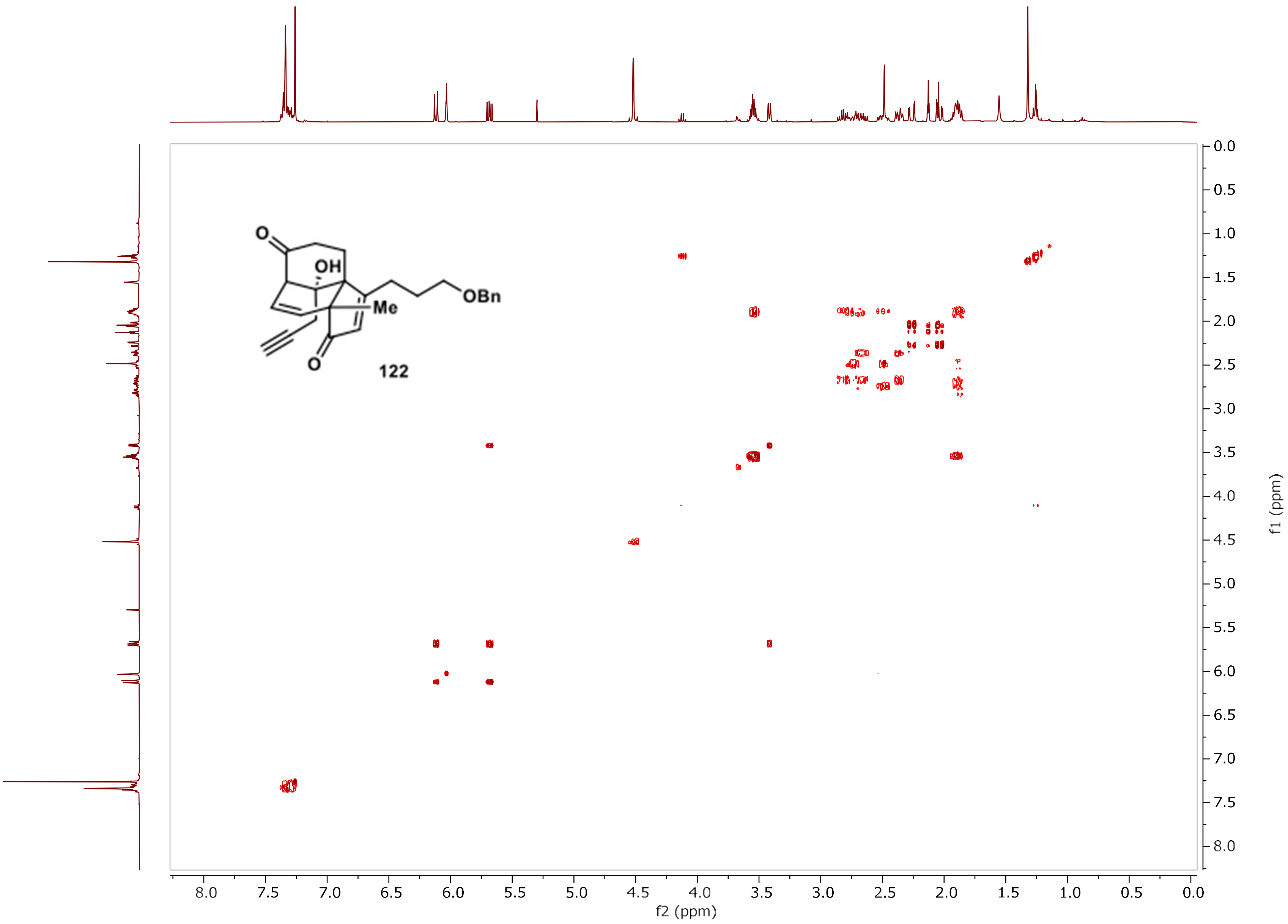

7.37 7.35 7.35 7.34 7.33 7.33 7.31 7.30 6.28 6.26 6.15 6.14 5.69 5.67 5.67 5.65 4.54 4.52 4.50 4.49 4.48 3.58 3.57 3.56 3.55 3.54 3.54 3.53 3.52 2.79 2.77 2.76 2.75 2.74 2.74 2.73 2.71 2.65 2.65 2.62 2.61 2.52 2.51 2.50 2.49 2.48 2.47 2.43 2.42 2.41 2.40 2.39 2.31 2.30 2.28 2.27 2.22 2.20 2.19 2.18 2.16 2.15 2.15 2.14 2.13 2.08 2.07 2.05 2.04 2.04 1.96 1.95 1.93 1.92 1.92 1.91 1.90 1.89 1.88 1.24
O
OBn
Me
HO
O
120
D (m) 7.33
A (d) 6.27
B (d) 6.14
C (dd) 5.67
E (m) 4.52
F (ddd) 3.55
G (ddd) 2.75
H (dd) 2.63
I (m) 2.49
J (m) 2.39
K (dd) 2.29
L (m) 2.17
M (m) 2.06
N (m) 1.92
O (s) 1.24
4.61
1.00
0.96
1.07
2.25
3.46
1.05
1.06
2.09
1.01
1.18
3.03
1.22
2.15
3.12
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
f1 (ppm)
2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200

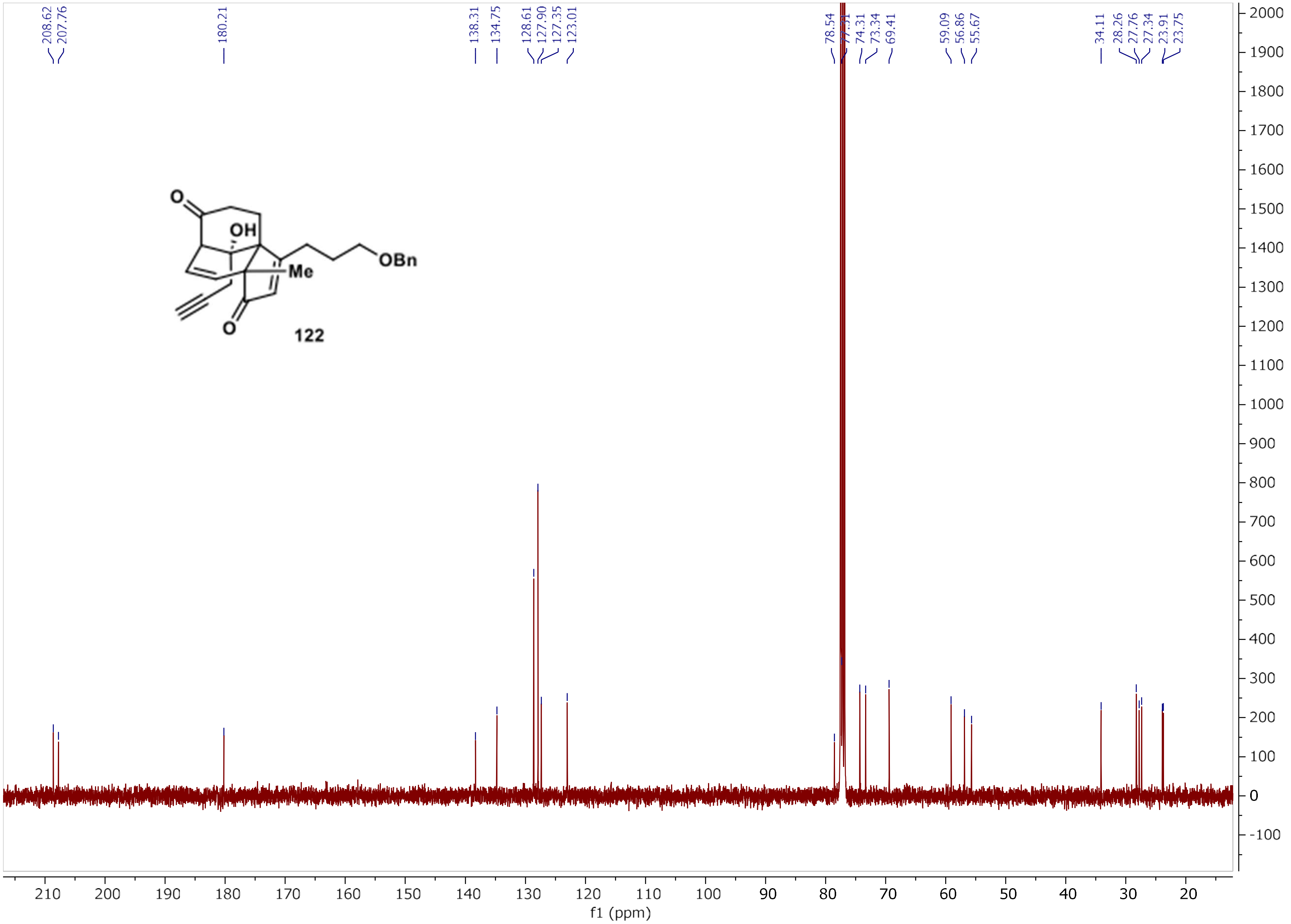

O
OBn
Me
HO
O
120
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
f2 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
f1 (ppm)

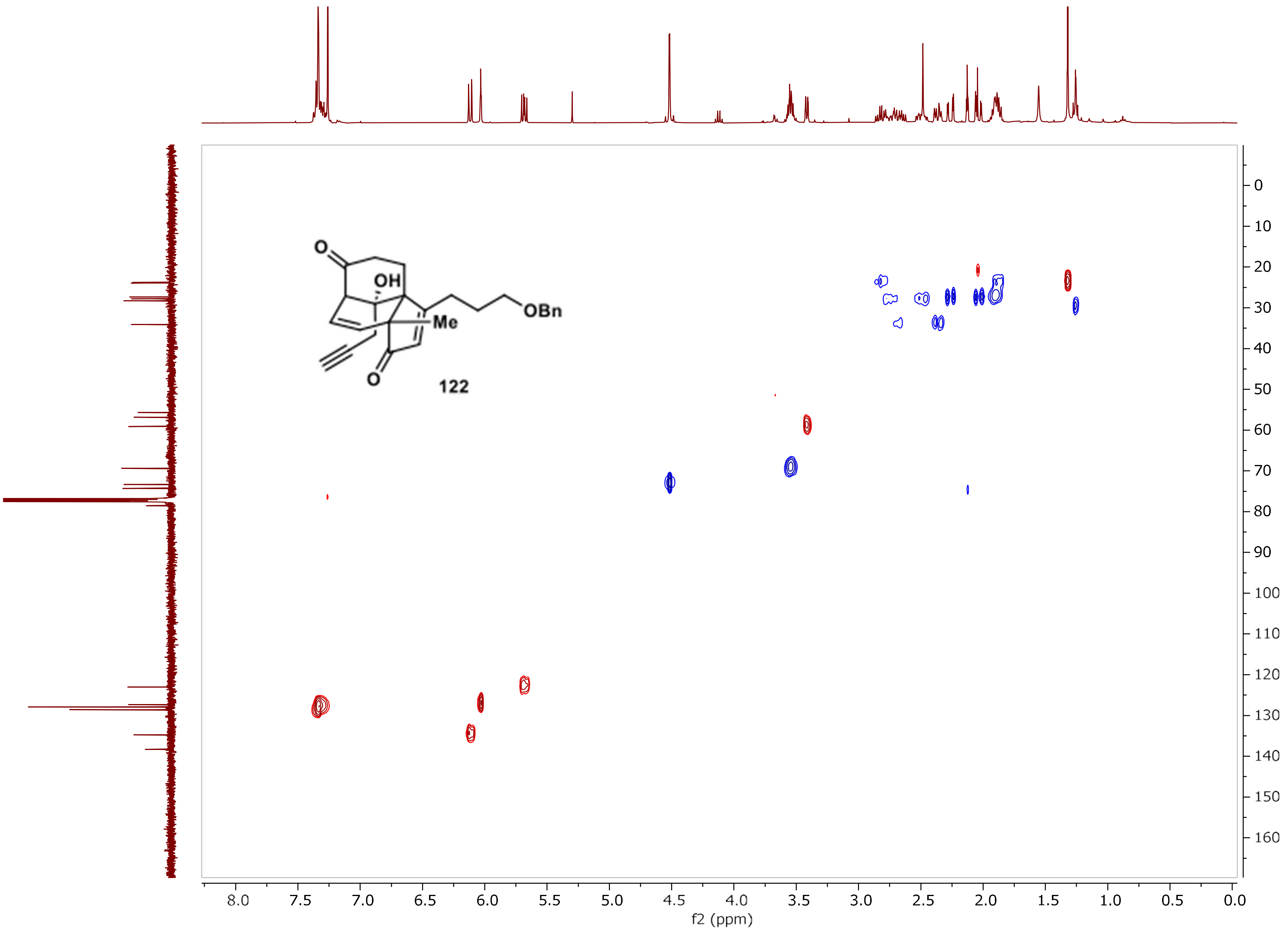


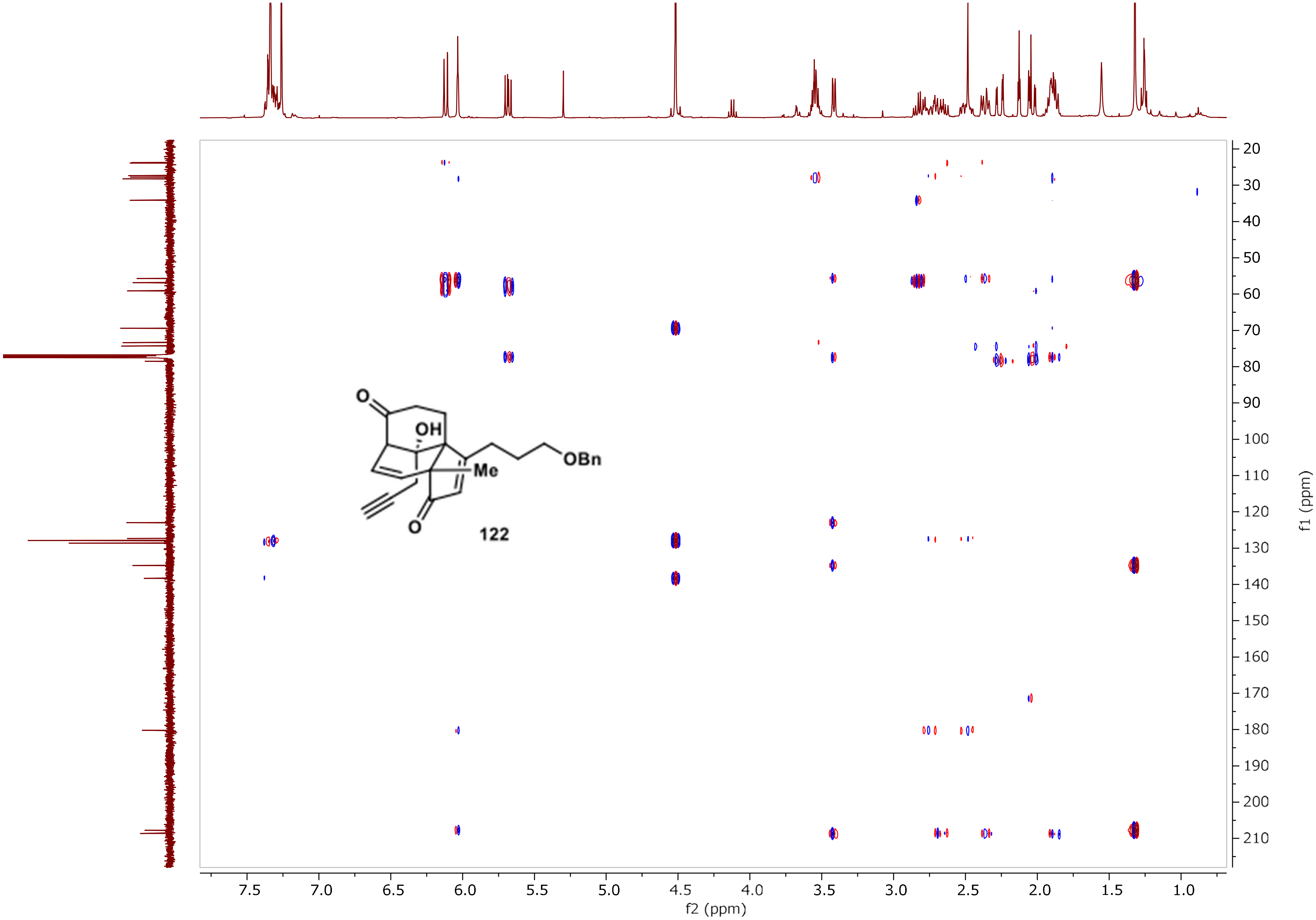
122

7.38 7.37 7.36 7.36 7.35 7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.29 7.28 7.27 6.13 6.11 6.04 6.03 6.03 5.70 5.69 5.68 5.66 4.52 4.52 3.57 3.56 3.56 3.55 3.54 3.54 3.53 3.53 3.43 3.42 3.41 2.83 2.81 2.80 2.78 2.72 2.71 2.70 2.67 2.65 2.52 2.48 2.39 2.38 2.38 2.37 2.35 2.35 2.34 2.29 2.28 2.24 2.24 2.13 2.13 2.12 2.06 2.05 2.04 2.02 2.01 1.93 1.92 1.91 1.91 1.90 1.90 1.89 1.89 1.88 1.87 1.87 1.86 1.32
O
OH
Me
OBn
O
E (m) 7.33
A (d) 6.12
B (t) 6.03
C (dd) 5.68
D (d) 4.52
F (m) 3.55
G (d) 3.42
H (td) 2.82
I (m) 2.72
J (m) 2.65
K (m) 2.50
L (m) 2.37
M (dd) 2.26
N (t) 2.13
O (dd) 2.04
P (m) 1.89
Q (s) 1.32
5.35
1.00
1.07
1.08
2.41
2.22
1.02
1.18
0.82
0.69
0.95
1.10
1.08
1.02
1.10
3.19
3.21
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)


O
OH
Me
OBn
O
122
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
f2 (ppm)
f1 (ppm)

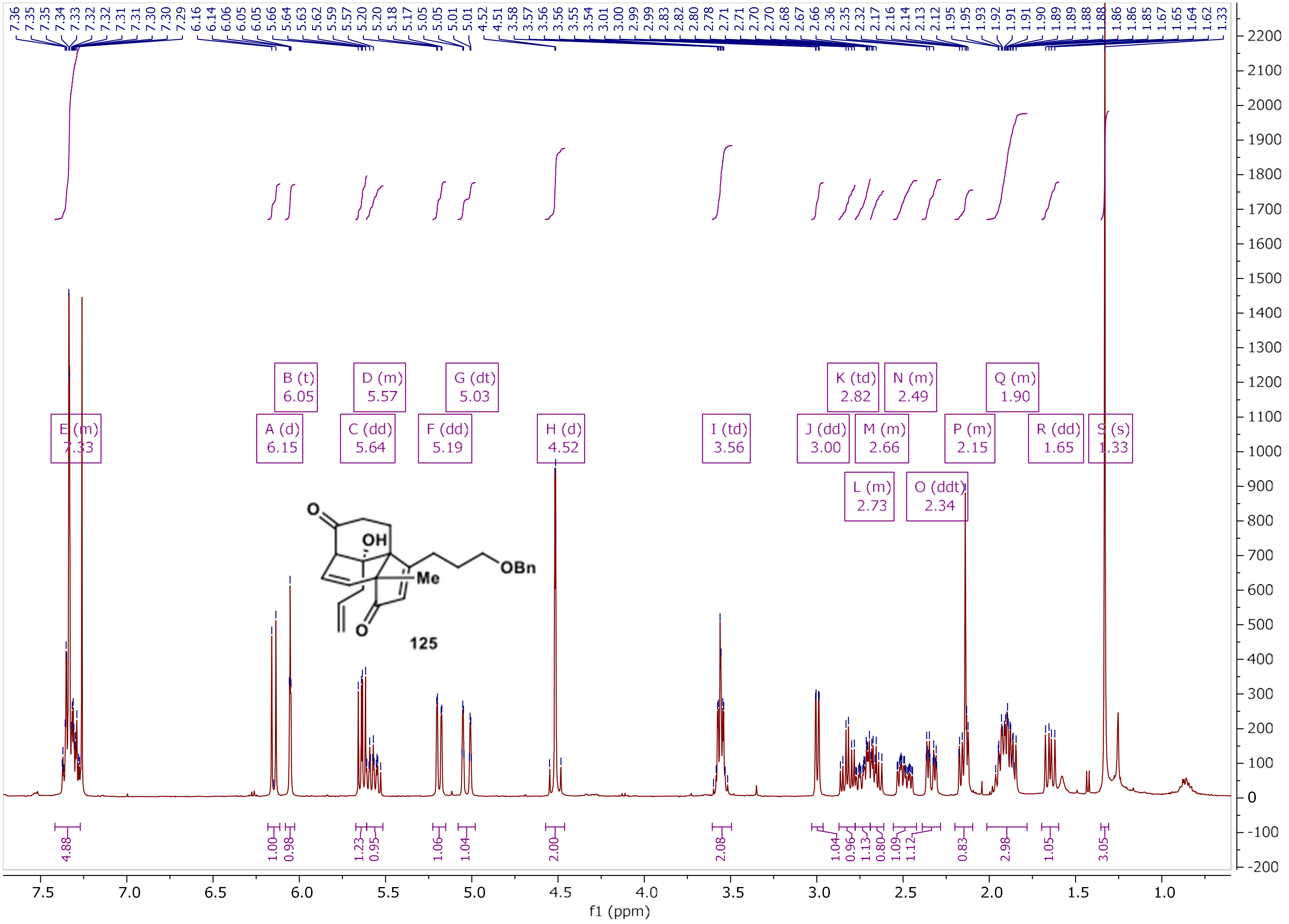

208.62
207.76
180.21
138.31
134.75
128.61
127.90
127.35
123.01
78.54
77.31
74.31
73.34
69.41
59.09
56.86
55.67
34.11
28.26
27.76
27.34
23.91
23.75
O
OH
Me
OBn
O
122
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

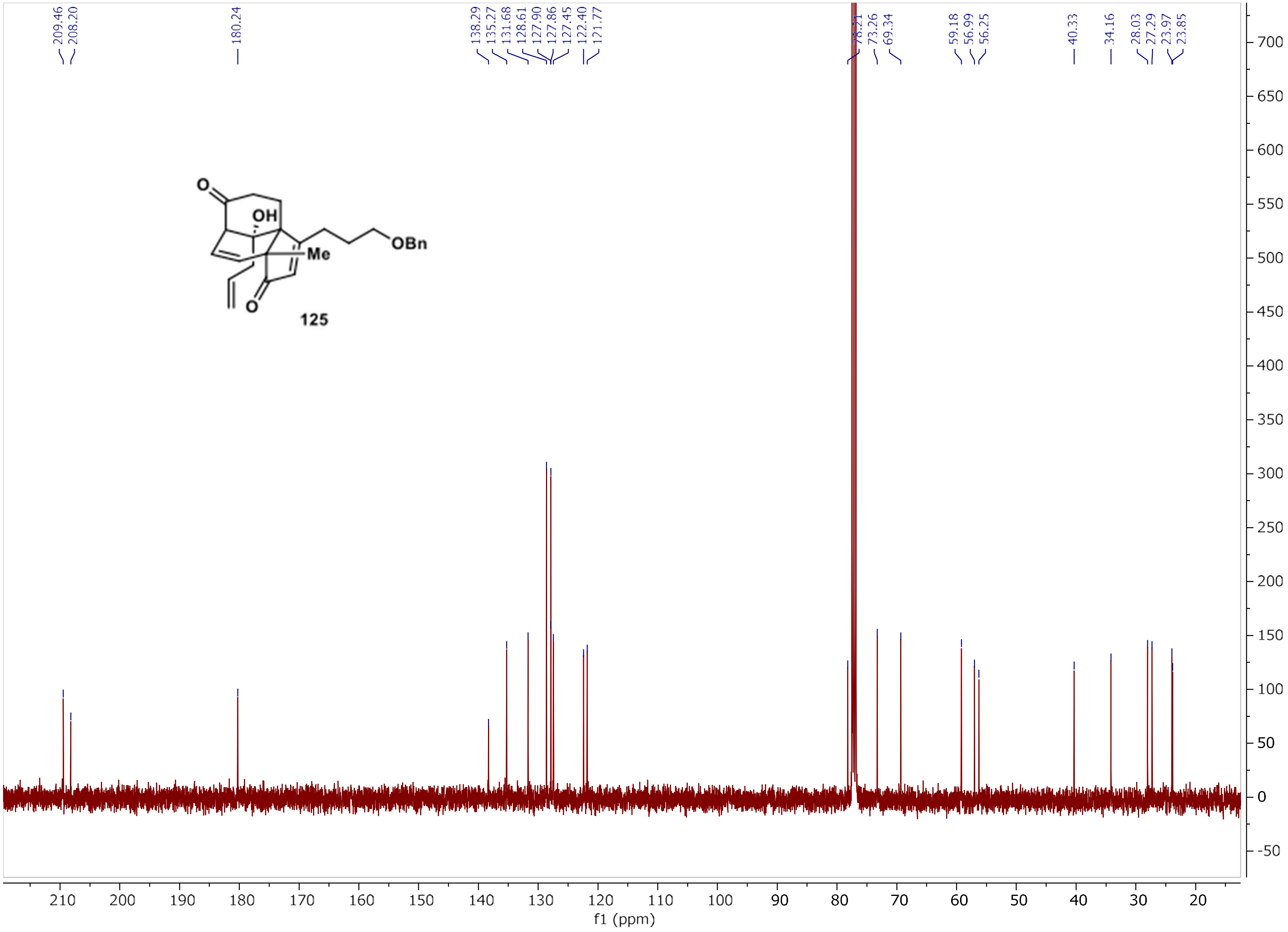

O
OH
Me
OBn
O
122
f2 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160



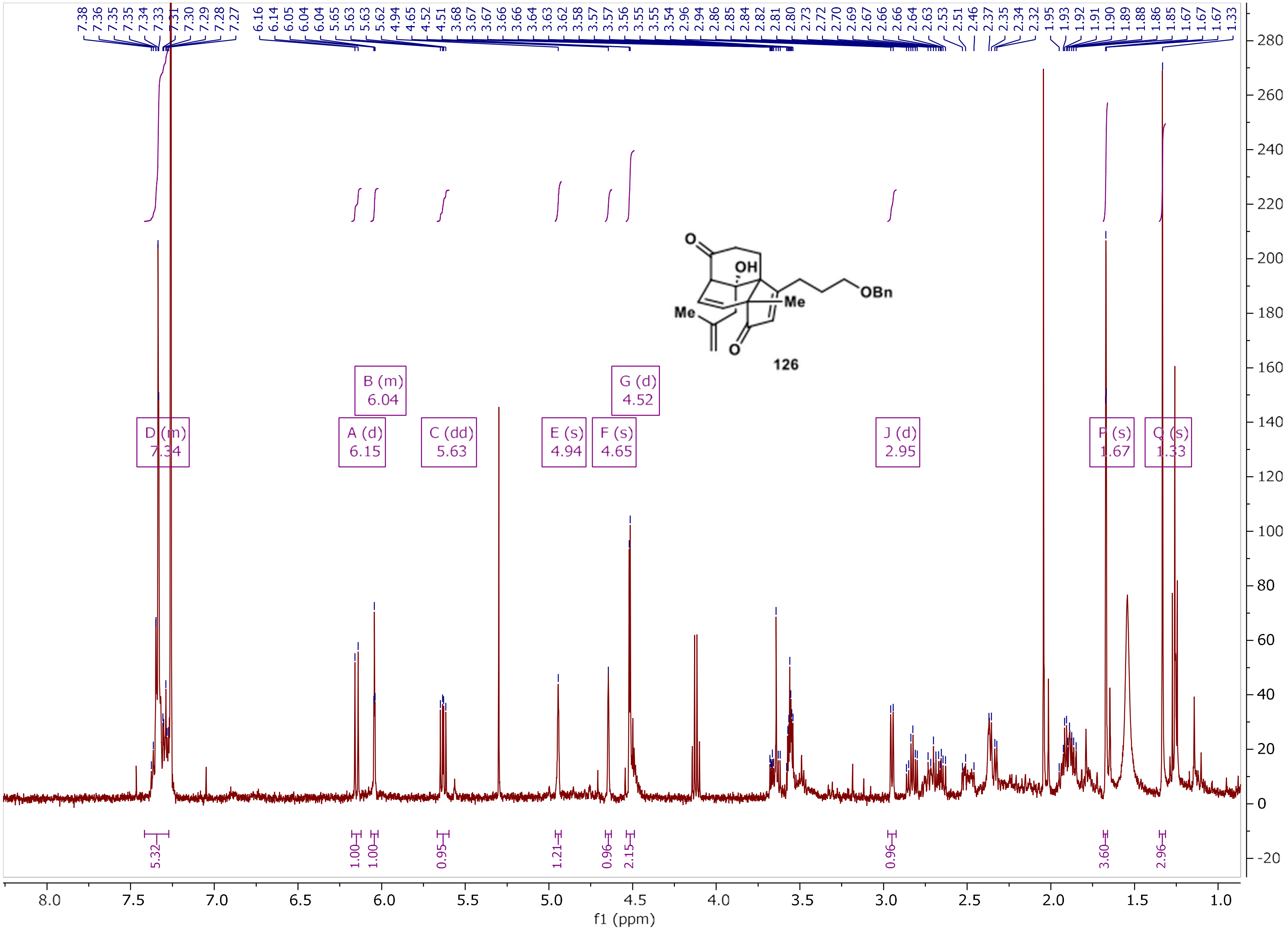
O
OH
Me
OBn
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

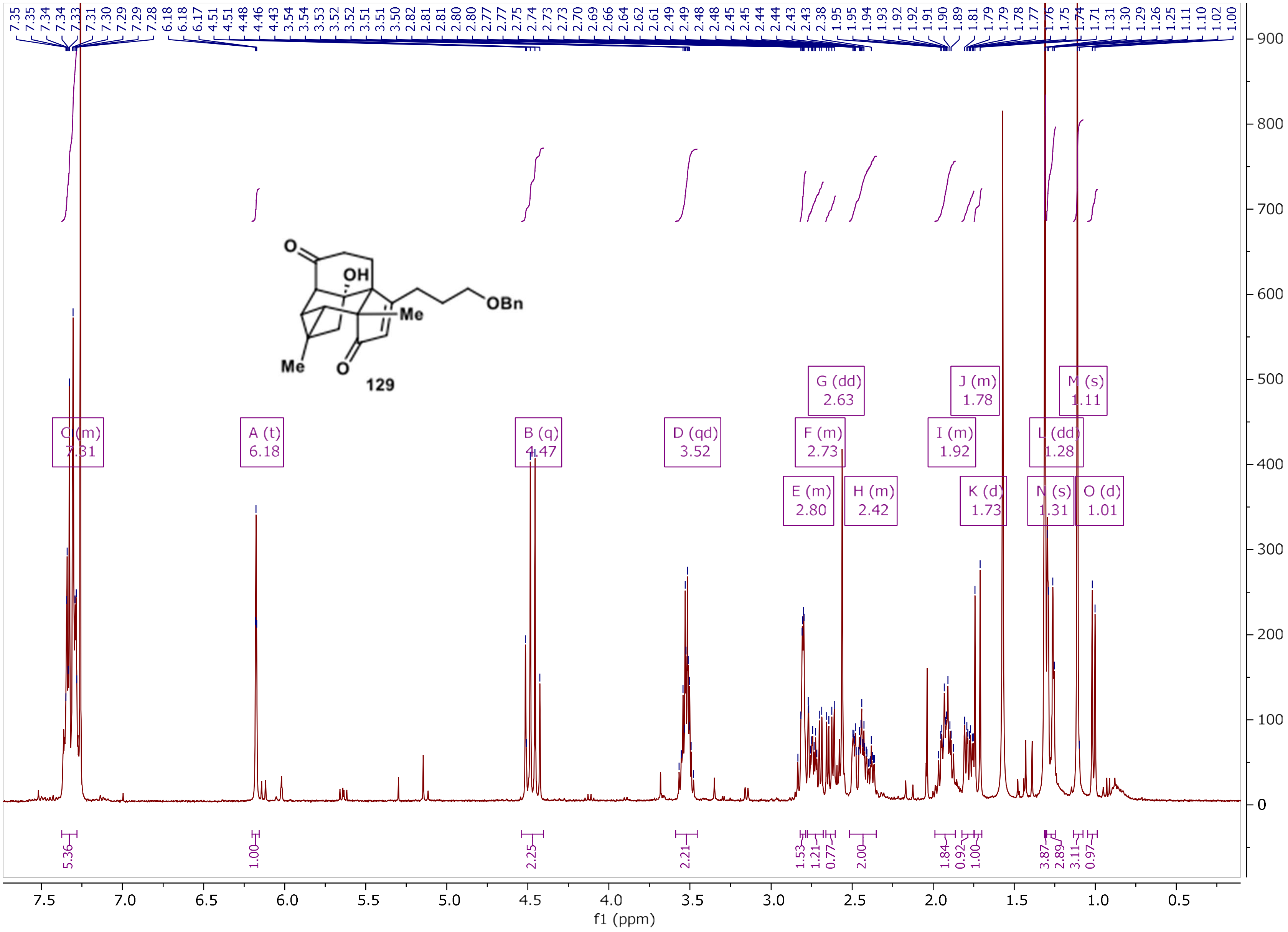
122

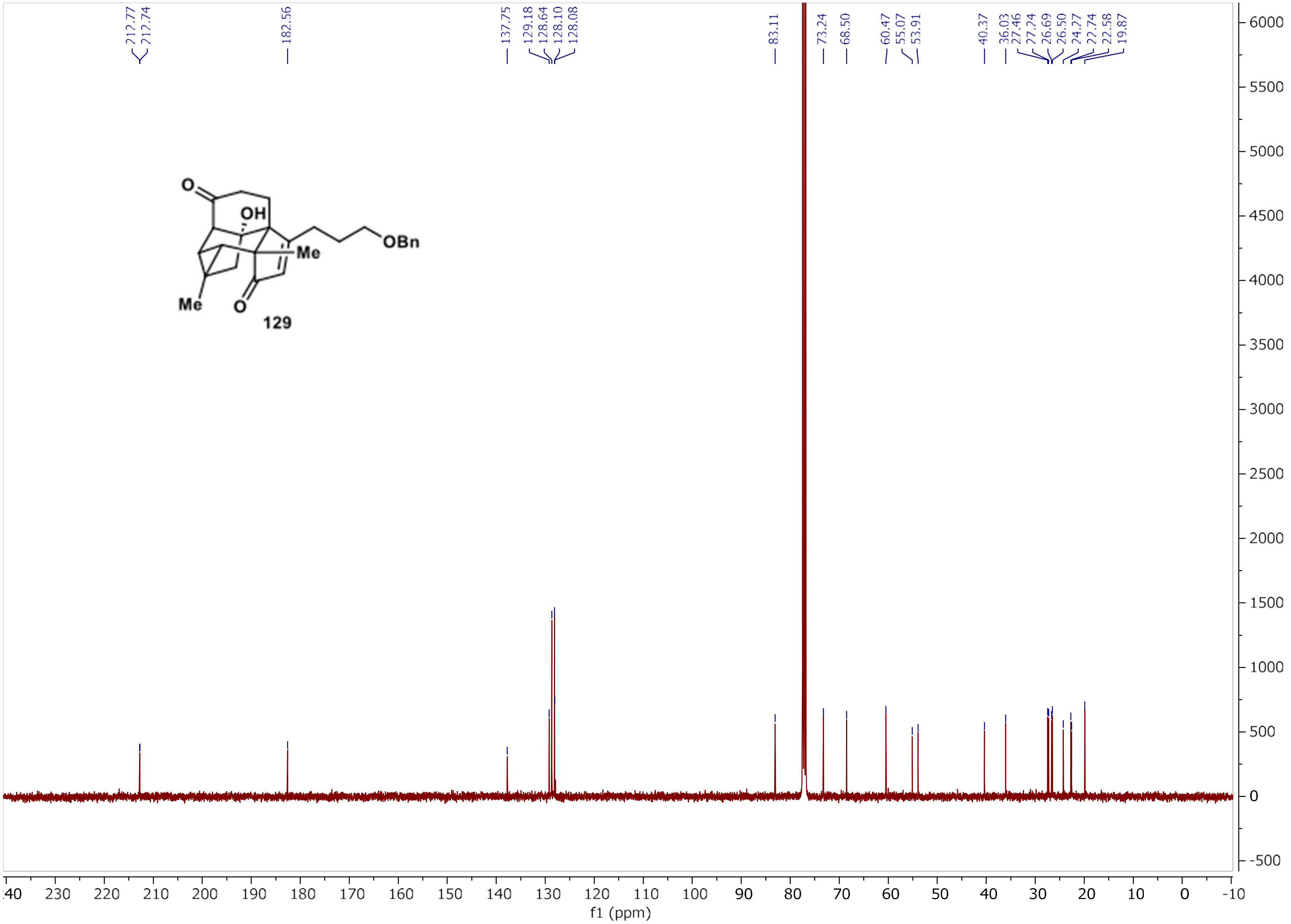

7.36 7.35 7.35 7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 6.16 6.14 6.06 6.05 6.05 5.66 5.64 5.63 5.62 5.59 5.57 5.20 5.20 5.18 5.17 5.05 5.05 5.01 5.01 4.52 4.51 3.58 3.57 3.56 3.56 3.55 3.54 3.01 3.00 2.99 2.99 2.83 2.82 2.80 2.78 2.71 2.71 2.70 2.70 2.68 2.67 2.66 2.36 2.35 2.32 2.17 2.16 2.14 2.13 2.12 1.95 1.95 1.93 1.92 1.91 1.91 1.90 1.89 1.89 1.88 1.88 1.86 1.86 1.85 1.67 1.65 1.64 1.62 1.33
E (m) 7.33
A (d) 6.15
B (t) 6.05
C (dd) 5.64
D (m) 5.57
F (dd) 5.19
G (dt) 5.03
H (d) 4.52
I (td) 3.56
J (dd) 3.00
K (td) 2.82
L (m) 2.73
M (m) 2.66
N (m) 2.49
O (ddt) 2.34
P (m) 2.15
Q (m) 1.90
R (dd) 1.65
S (s) 1.33
4.88
1.00
0.98
1.23
0.95
1.06
1.04
2.00
2.08
1.04
0.96
1.13
0.80
1.09
1.12
0.83
2.98
1.05
3.05
O
OH
Me
OBn
O
125
2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200
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)


209.46
208.20
180.24
138.29
135.27
131.68
128.61
127.90
127.86
127.45
122.40
121.77
78.21
73.26
69.34
59.18
56.99
56.25
40.33
34.16
28.03
27.29
23.97
23.85
O
OH
Me
OBn
O
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

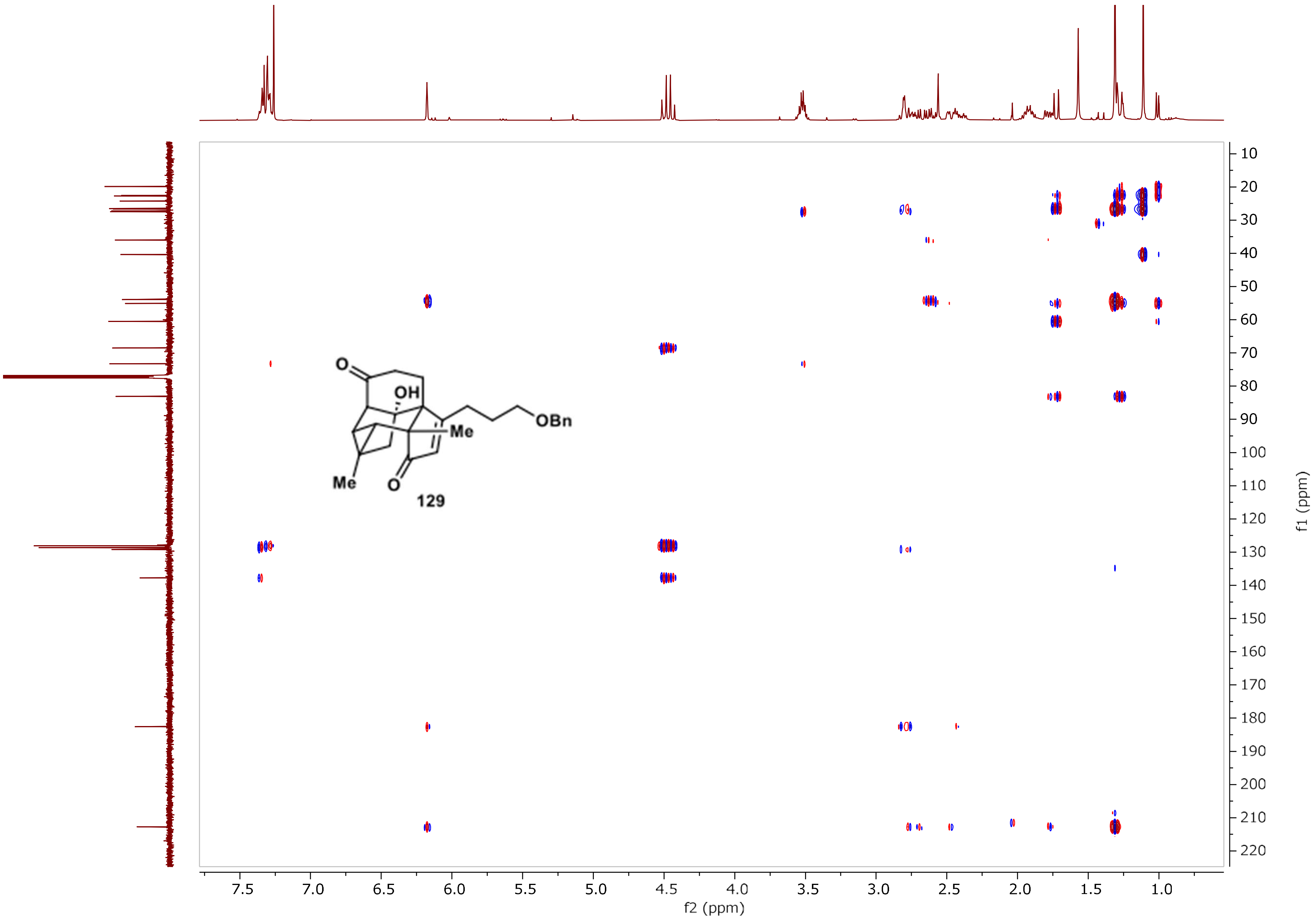
125

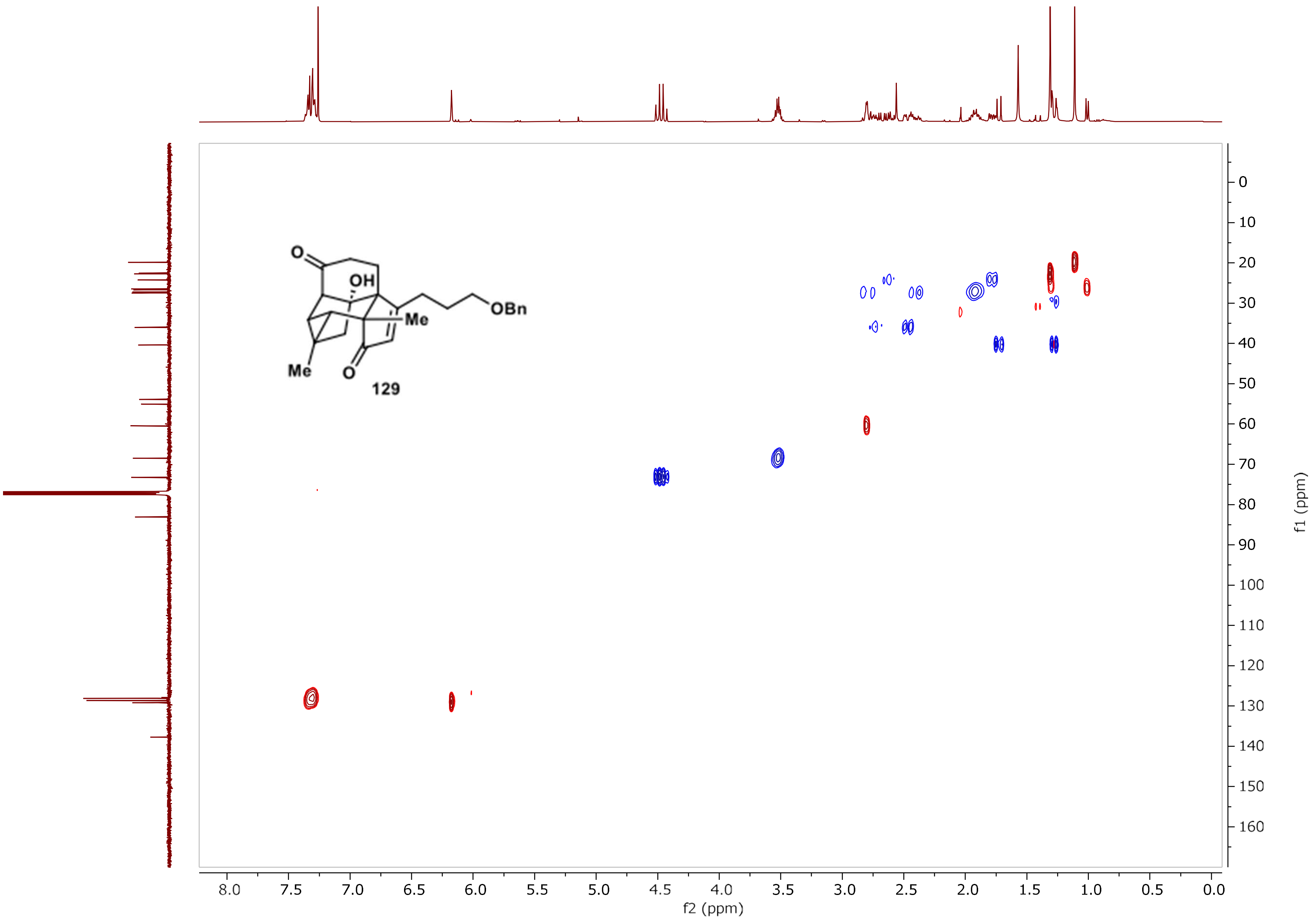

7.38
7.36
7.35
7.35
7.34
7.33
7.31
7.30
7.29
7.28
7.27
6.16
6.14
6.05
6.04
6.04
5.65
5.63
5.63
5.62
4.94
4.65
4.52
4.51
3.68
3.67
3.67
3.66
3.64
3.63
3.62
3.58
3.57
3.57
3.56
3.55
3.55
3.54
2.96
2.94
2.86
2.85
2.84
2.82
2.81
2.80
2.73
2.72
2.70
2.69
2.67
2.66
2.66
2.64
2.63
2.53
2.51
2.46
2.37
2.35
2.34
2.32
1.95
1.93
1.92
1.91
1.90
1.89
1.88
1.86
1.85
1.67
1.67
1.67
1.33
O
OH
OBn
Me
Me
O
126
D (m)
7.34
B (m)
6.04
A (d)
6.15
C (dd)
5.63
E (s)
4.94
F (s)
4.65
G (d)
4.52
J (d)
2.95
P (s)
1.67
Q (s)
1.33
5.32
1.00
1.00
0.95
1.21
0.96
2.15
0.96
3.60
2.96
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
f1 (ppm)
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20


7.35
7.35
7.34
7.34
7.32
7.31
7.30
7.29
7.29
7.28
6.18
6.18
6.17
4.51
4.51
4.48
4.46
4.43
3.54
3.54
3.53
3.52
3.52
3.51
3.51
3.50
2.82
2.81
2.81
2.80
2.80
2.77
2.77
2.75
2.74
2.73
2.73
2.70
2.69
2.66
2.64
2.62
2.61
2.49
2.49
2.48
2.48
2.45
2.45
2.44
2.44
2.43
2.43
2.38
1.95
1.95
1.94
1.93
1.92
1.92
1.91
1.90
1.89
1.81
1.79
1.79
1.78
1.77
1.76
1.75
1.74
1.71
1.31
1.30
1.29
1.26
1.25
1.11
1.10
1.02
1.00
O
OH
OBn
Me
Me
O
129
C (m) 7.31
A (t) 6.18
B (q) 4.47
D (qd) 3.52
G (dd) 2.63
F (m) 2.73
E (m) 2.80
H (m) 2.42
J (m) 1.78
I (m) 1.92
K (d) 1.73
M (s) 1.11
L (dd) 1.28
N (s) 1.31
O (d) 1.01
5.36
1.00
2.25
2.21
1.53
1.21
0.77
2.00
1.84
0.92
1.00
3.87
2.89
3.11
0.97
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
f1 (ppm)
900
800
700
600
500
400
300
200
100
0

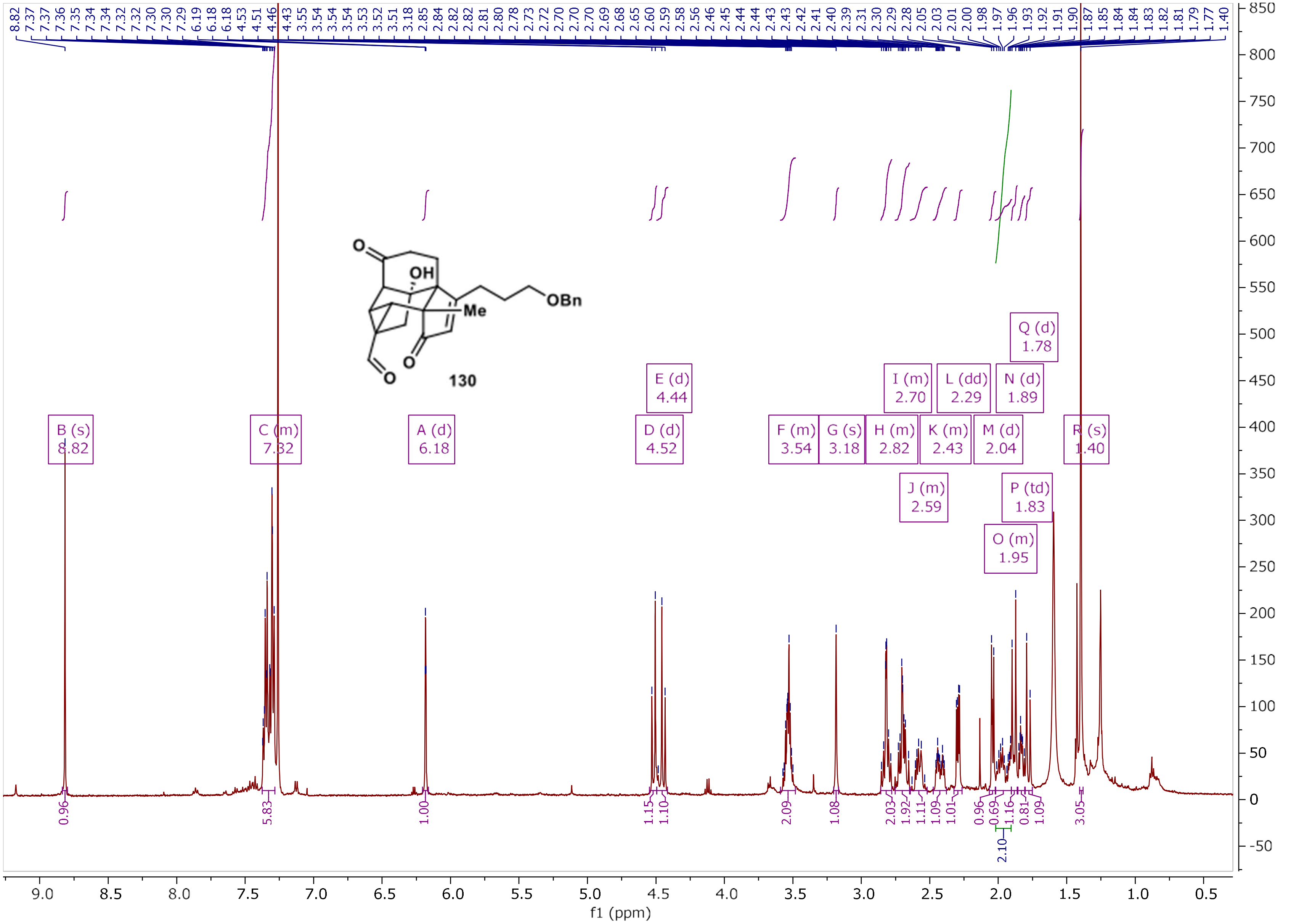


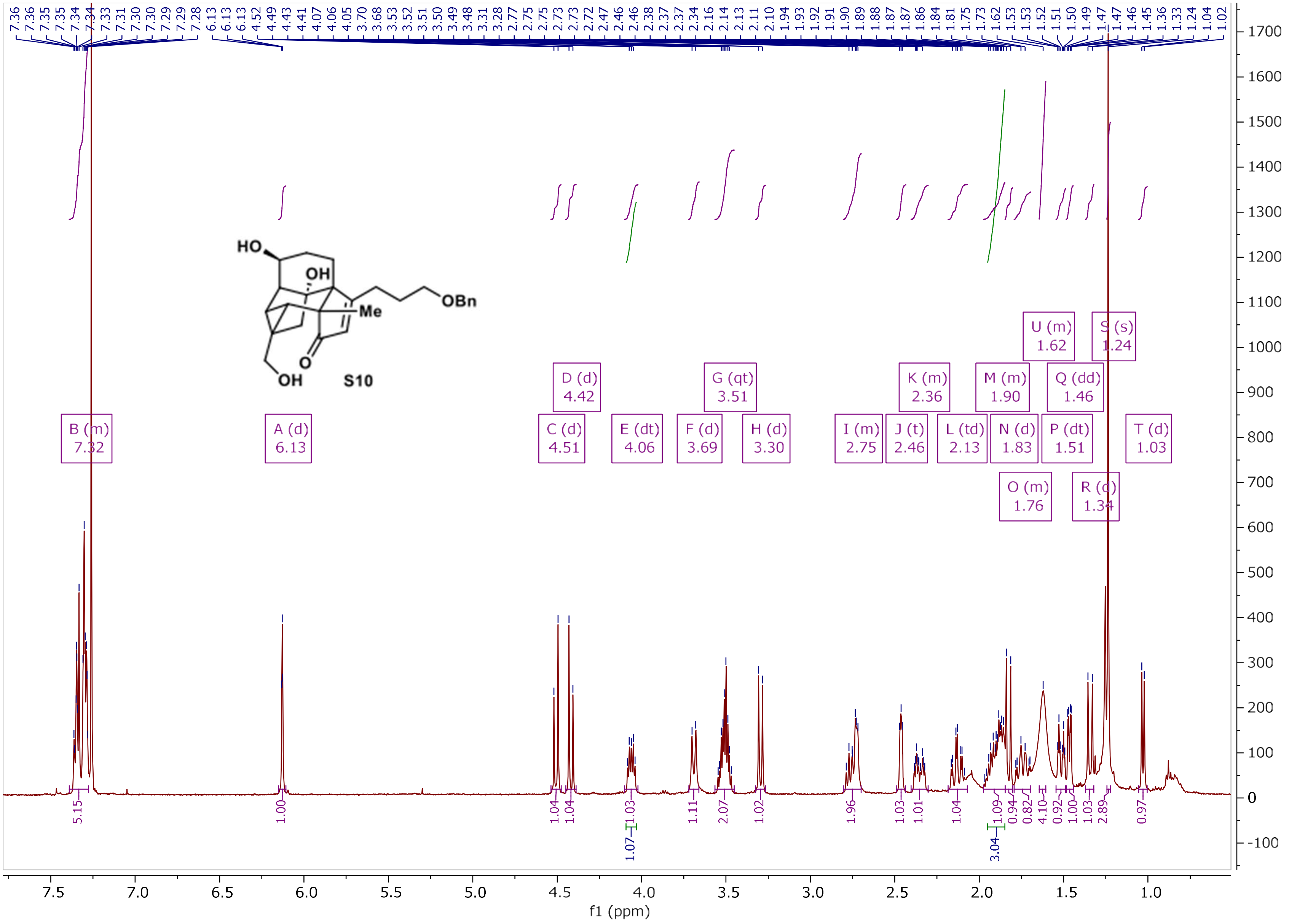
212.77
212.74
182.56
137.75
129.18
128.64
128.10
128.08
83.11
73.24
68.50
60.47
55.07
53.91
40.37
36.03
27.46
27.24
26.69
26.50
24.27
22.74
22.58
19.87
O
OH
OBn
Me
Me
O
129
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

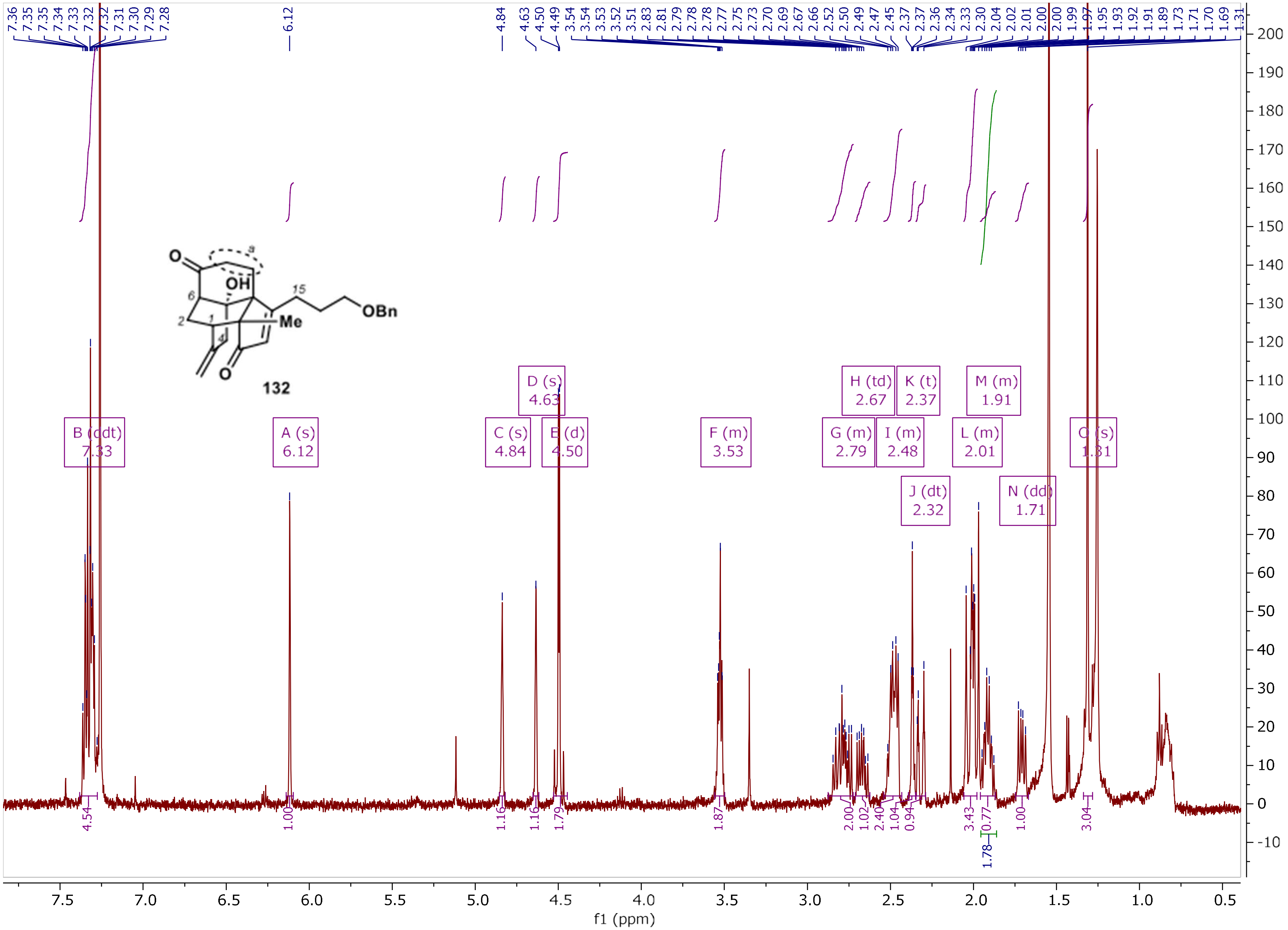

O
OH
Me
OBn
Me
O
129
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

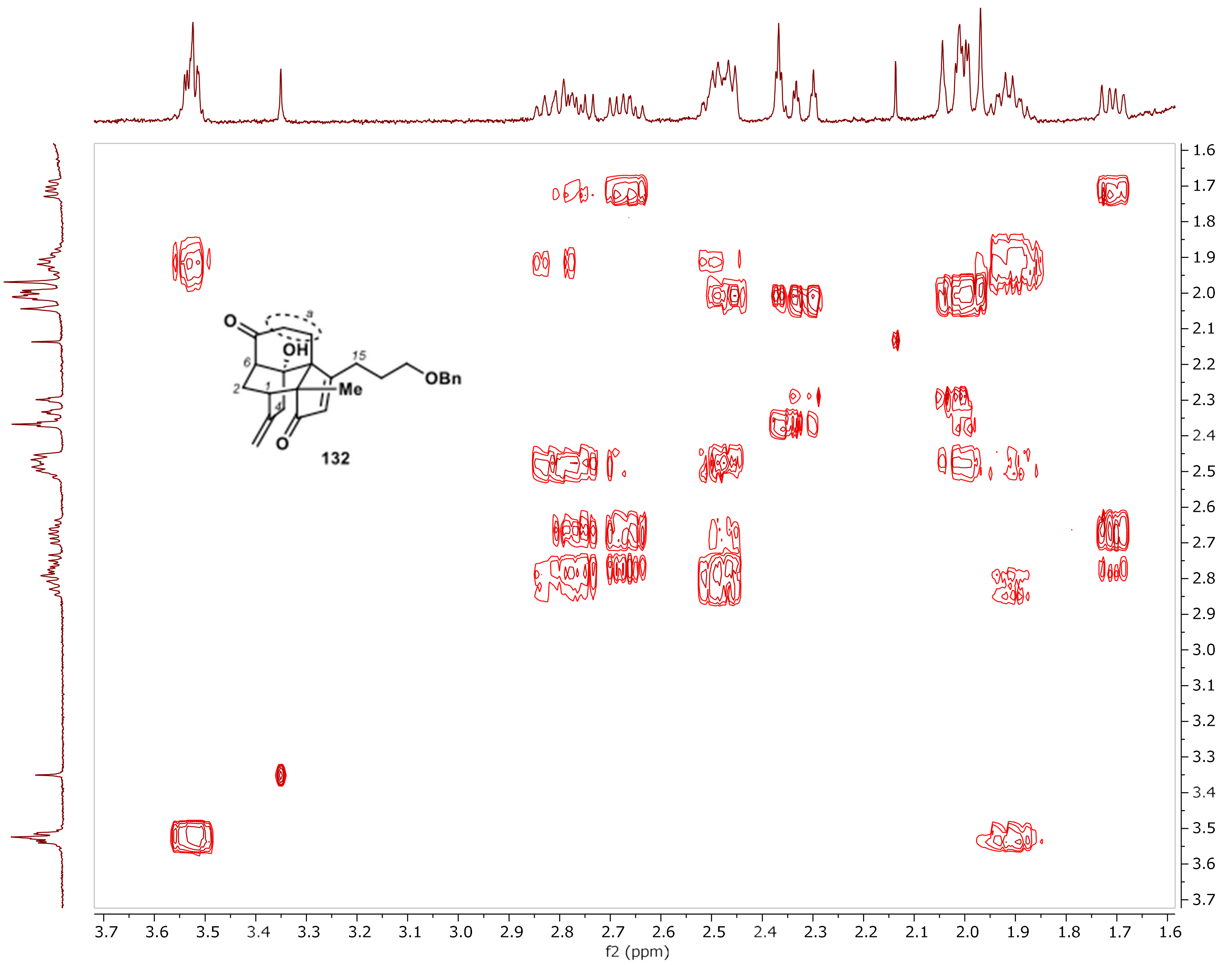

OH
O
Me
OBn
Me
O
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

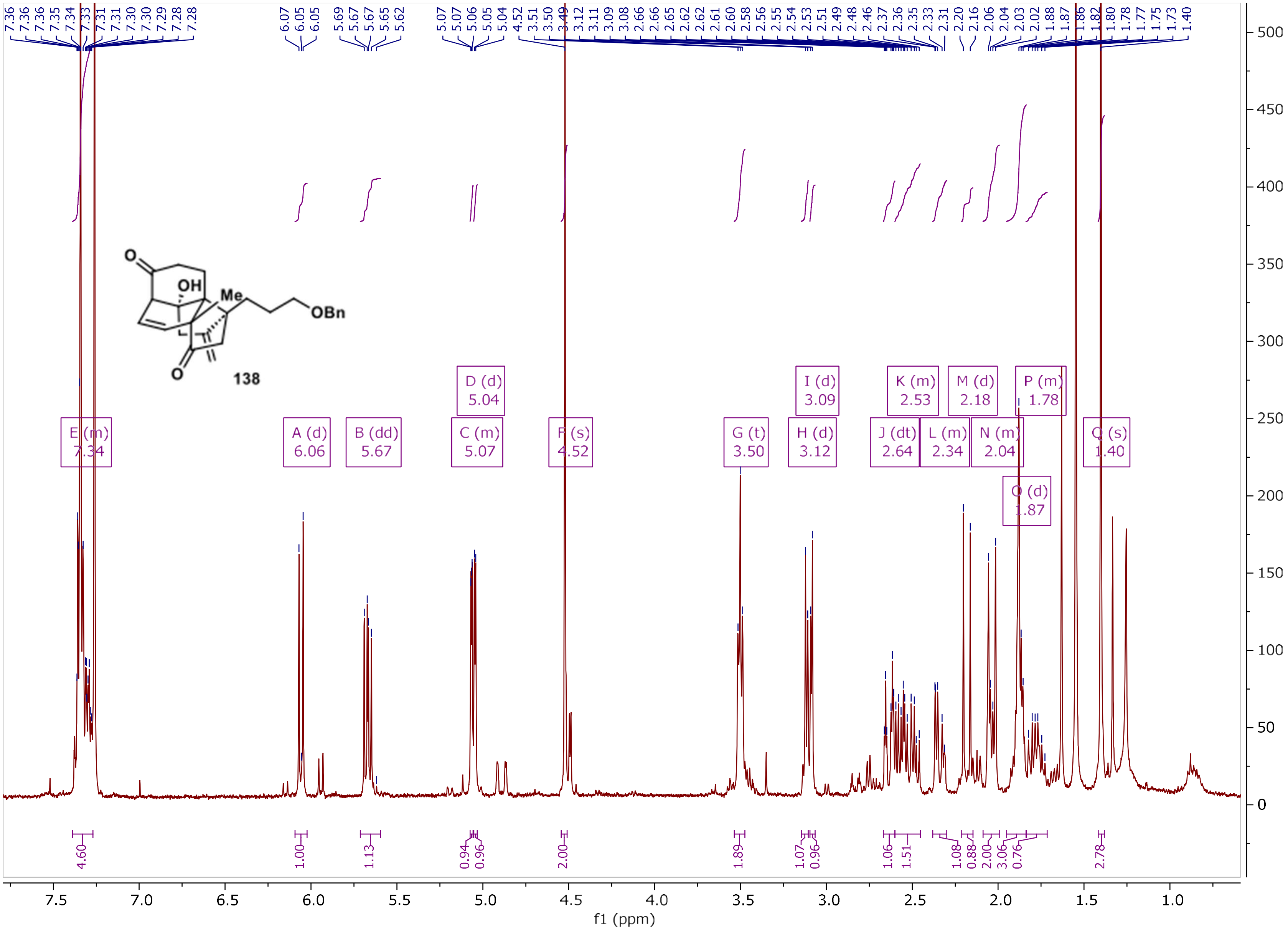
129

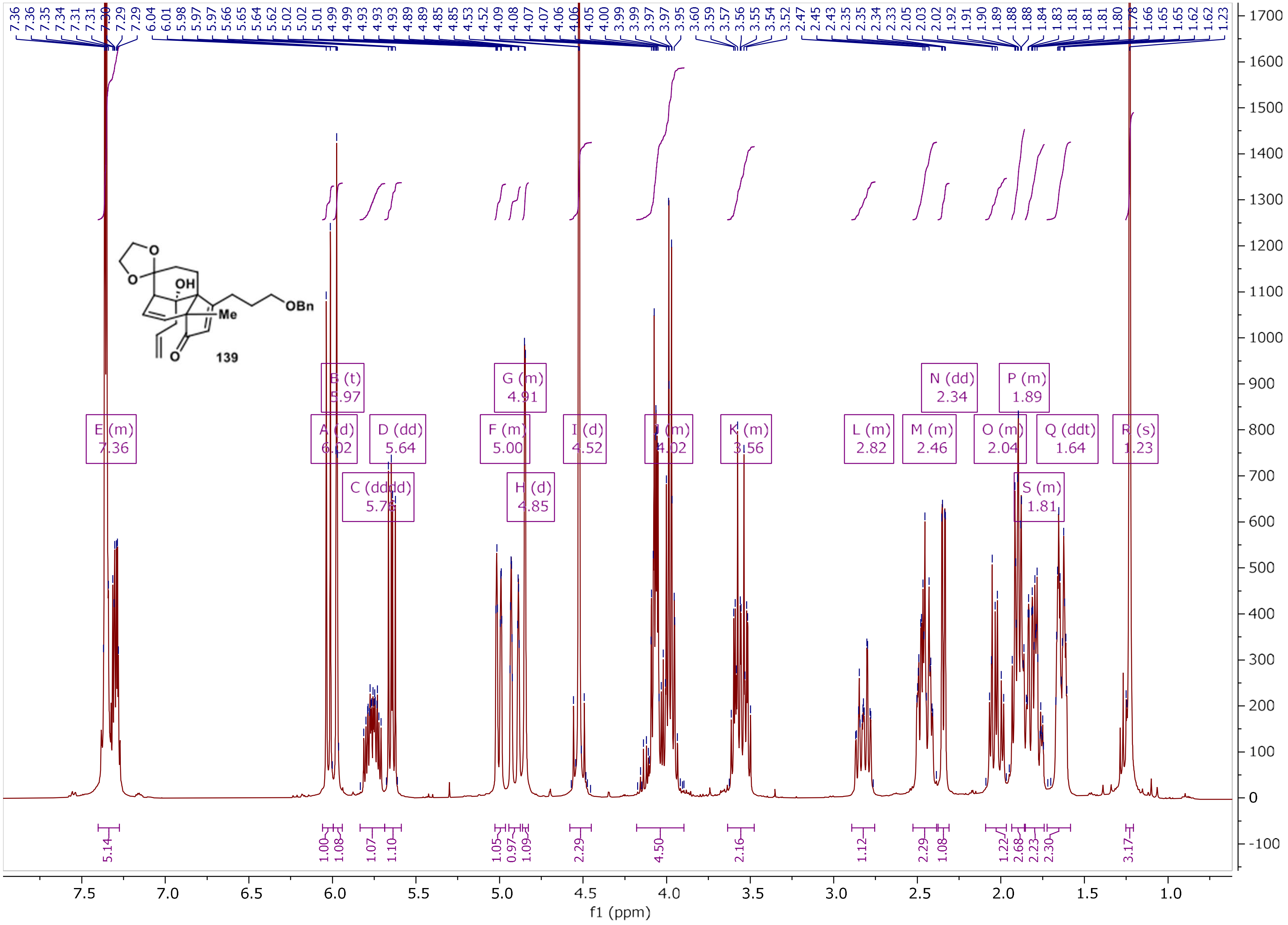

8.82
7.37
7.37
7.36
7.35
7.34
7.34
7.32
7.32
7.30
7.30
7.29
6.19
6.18
6.18
4.53
4.51
4.46
4.43
3.55
3.54
3.54
3.54
3.53
3.52
3.51
3.18
2.85
2.84
2.82
2.82
2.81
2.80
2.78
2.73
2.72
2.70
2.70
2.69
2.68
2.65
2.60
2.59
2.58
2.56
2.46
2.45
2.44
2.44
2.43
2.43
2.42
2.41
2.40
2.39
2.31
2.30
2.29
2.28
2.05
2.03
2.01
2.00
1.98
1.97
1.96
1.93
1.92
1.91
1.90
1.87
1.85
1.84
1.84
1.83
1.82
1.81
1.79
1.77
1.40
O
OH
OBn
Me
O
O
130
B (s) 8.82
C (m) 7.32
A (d) 6.18
E (d) 4.44
D (d) 4.52
F (m) 3.54
G (s) 3.18
H (m) 2.82
I (m) 2.70
J (m) 2.59
K (m) 2.43
L (dd) 2.29
M (d) 2.04
N (d) 1.89
O (m) 1.95
P (td) 1.83
Q (d) 1.78
R (s) 1.40
0.96
5.83
1.00
1.15
1.10
2.09
1.08
2.03
1.92
1.11
1.09
1.01
0.96
0.69
1.16
0.81
1.09
2.10
3.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

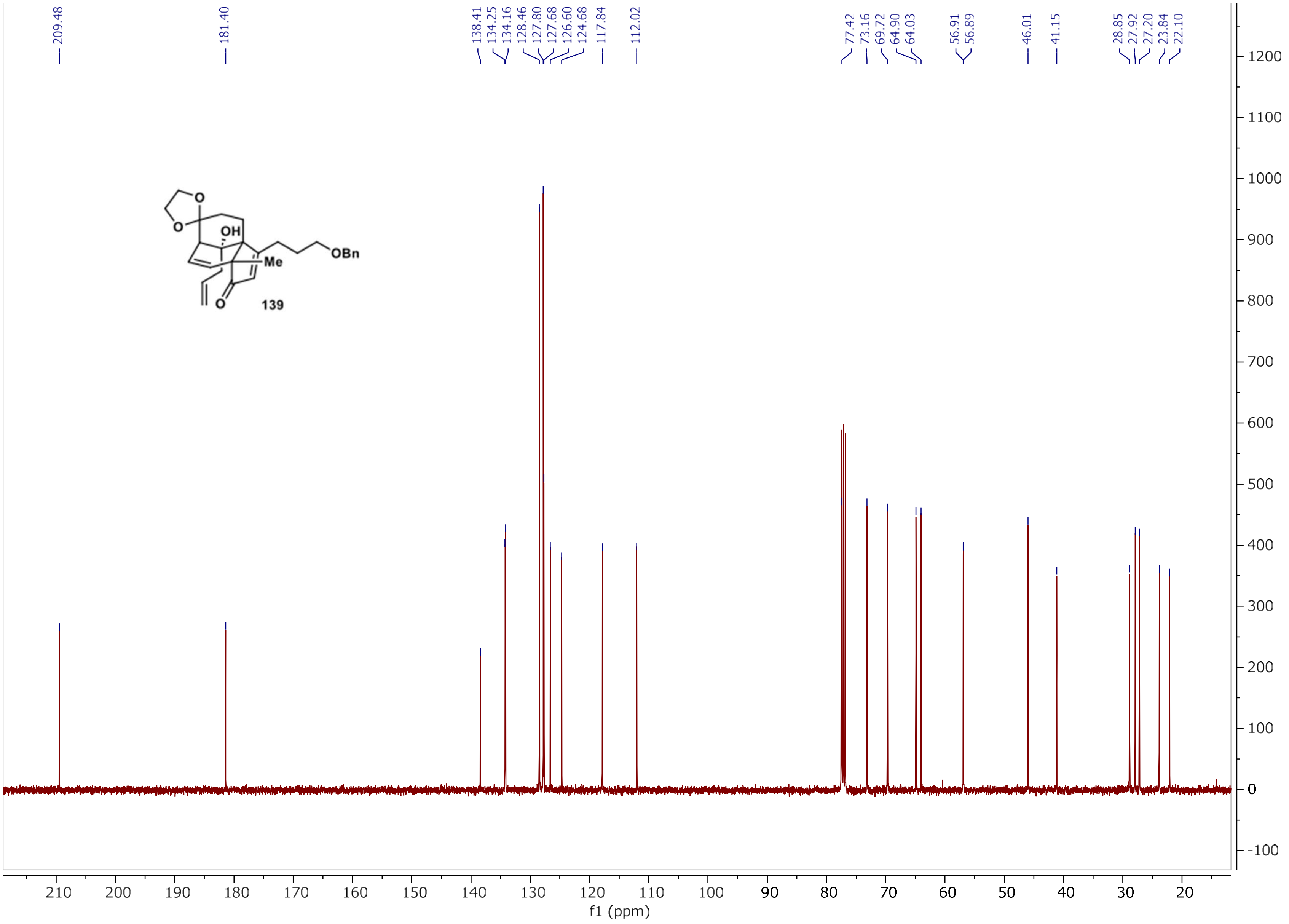

7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.31 7.30 7.30 7.29 7.29 7.28 6.13 6.13 6.13 6.13 4.52 4.49 4.43 4.41 4.07 4.06 4.05 3.70 3.68 3.53 3.52 3.51 3.50 3.49 3.48 3.31 3.28 2.77 2.75 2.75 2.73 2.73 2.72 2.47 2.46 2.38 2.37 2.37 2.34 2.16 2.14 2.13 2.11 2.10 1.94 1.93 1.92 1.91 1.90 1.89 1.88 1.87 1.87 1.86 1.84 1.81 1.75 1.73 1.62 1.53 1.53 1.52 1.51 1.50 1.49 1.47 1.47 1.46 1.45 1.36 1.33 1.24 1.04 1.02
HO
OH
OBn
Me
O
OH
S10
B (m) 7.32
A (d) 6.13
D (d) 4.42
C (d) 4.51
E (dt) 4.06
G (qt) 3.51
F (d) 3.69
H (d) 3.30
I (m) 2.75
K (m) 2.36
J (t) 2.46
L (td) 2.13
M (m) 1.90
N (d) 1.83
O (m) 1.76
U (m) 1.62
Q (dd) 1.46
P (dt) 1.51
S (s) 1.24
R (d) 1.34
T (d) 1.03
5.15 1.00 1.04 1.04 1.03 1.07 1.11 2.07 1.02 1.96 1.03 1.01 1.04 1.09 3.04 0.94 0.82 4.10 0.92 1.00 1.03 2.89 0.97
1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100
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)


7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.31
7.30
7.29
7.28
6.12
4.84
4.63
4.50
4.49
3.54
3.54
3.53
3.52
3.51
2.83
2.81
2.79
2.78
2.78
2.77
2.75
2.73
2.70
2.69
2.67
2.66
2.52
2.50
2.49
2.47
2.45
2.37
2.37
2.36
2.34
2.33
2.30
2.04
2.02
2.01
2.00
1.99
1.97
1.95
1.93
1.92
1.91
1.89
1.73
1.71
1.70
1.69
1.31
O
OH
a
6
15
2
1
4
Me
OBn
O
132
B (ddt) 7.33
A (s) 6.12
C (s) 4.84
D (s) 4.63
E (d) 4.50
F (m) 3.53
G (m) 2.79
H (td) 2.67
I (m) 2.48
K (t) 2.37
J (dt) 2.32
L (m) 2.01
M (m) 1.91
N (dd) 1.71
O (s) 1.31
4.54
1.00
1.16
1.16
1.79
1.87
2.00
1.02
2.40
1.04
0.94
3.43
0.77
1.78
1.00
3.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-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
f1 (ppm)


O
OH
a
6
2
1
4
15
Me
OBn
O
132
f2 (ppm)
f1 (ppm)
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
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


7.36 7.36 7.35 7.34 7.33 7.31 7.31 7.30 7.30 7.29 7.28 7.28
6.07 6.05 6.05
5.69 5.67 5.67 5.65 5.62
5.07 5.07 5.06 5.05 5.04
4.52 3.51 3.50 3.49 3.12 3.11 3.09 3.08 2.66 2.66 2.65 2.62 2.62 2.61 2.60 2.58 2.56 2.55 2.54 2.53 2.51 2.49 2.48 2.46 2.37 2.36 2.35 2.33 2.31 2.20 2.16 2.06 2.04 2.03 2.02 1.88 1.87 1.86 1.82 1.80 1.78 1.77 1.75 1.73 1.40
O
OH
Me
OBn
O
138
E (m) 7.34
A (d) 6.06
B (dd) 5.67
D (d) 5.04
C (m) 5.07
F (s) 4.52
G (t) 3.50
I (d) 3.09
H (d) 3.12
K (m) 2.53
J (dt) 2.64
L (m) 2.34
M (d) 2.18
N (m) 2.04
P (m) 1.78
O (d) 1.87
Q (s) 1.40
4.60
1.00
1.13
0.94
0.96
2.00
1.89
1.07
0.96
1.06
1.51
1.08
0.88
2.00
3.06
0.76
2.78
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)
500 450 400 350 300 250 200 150 100 50 0


7.36
7.36
7.35
7.34
7.31
7.31
7.30
7.29
7.29
6.04
6.01
5.98
5.97
5.97
5.66
5.65
5.64
5.62
5.02
5.01
4.99
4.99
4.93
4.93
4.93
4.89
4.85
4.85
4.53
4.52
4.09
4.08
4.07
4.07
4.06
4.06
4.05
4.00
3.99
3.99
3.97
3.97
3.95
3.60
3.59
3.57
3.56
3.55
3.54
3.52
2.47
2.45
2.43
2.35
2.35
2.34
2.33
2.05
2.03
2.02
1.92
1.91
1.90
1.89
1.88
1.88
1.84
1.83
1.81
1.81
1.81
1.80
1.78
1.66
1.65
1.65
1.62
1.62
1.23
O
O
OH
OBn
Me
O
139
E (m) 7.36
A (d) 6.02
B (t) 5.97
C (dddd) 5.76
D (dd) 5.64
F (m) 5.00
G (m) 4.91
H (d) 4.85
I (d) 4.52
J (m) 4.02
K (m) 3.56
L (m) 2.82
M (m) 2.46
N (dd) 2.34
O (m) 2.04
P (m) 1.89
S (m) 1.81
Q (ddt) 1.64
R (s) 1.23
5.14
1.00
1.08
1.07
1.10
1.05
0.97
1.09
2.29
4.50
2.16
1.12
2.29
1.08
1.22
2.68
2.23
2.30
3.17
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)
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100


209.48
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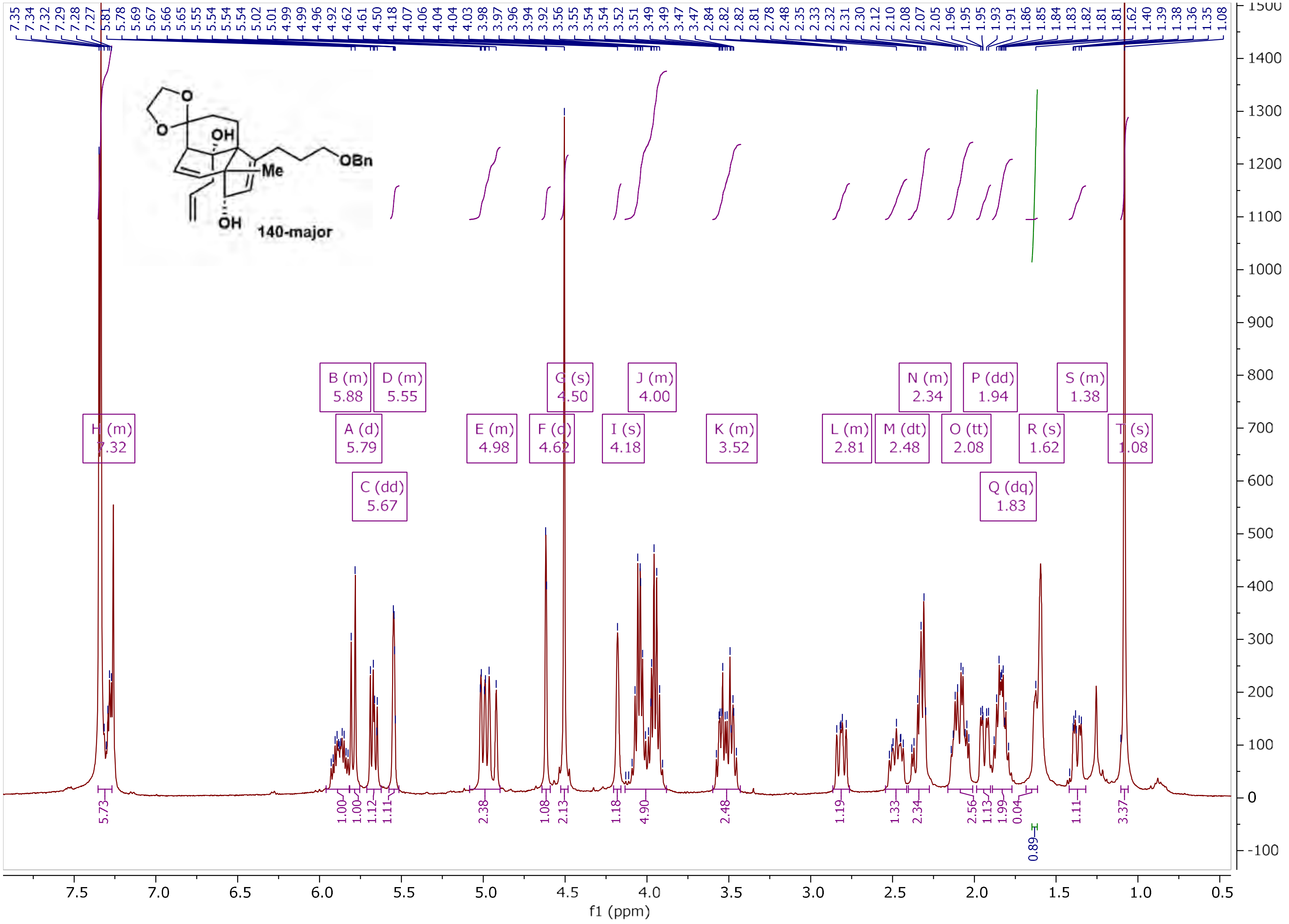
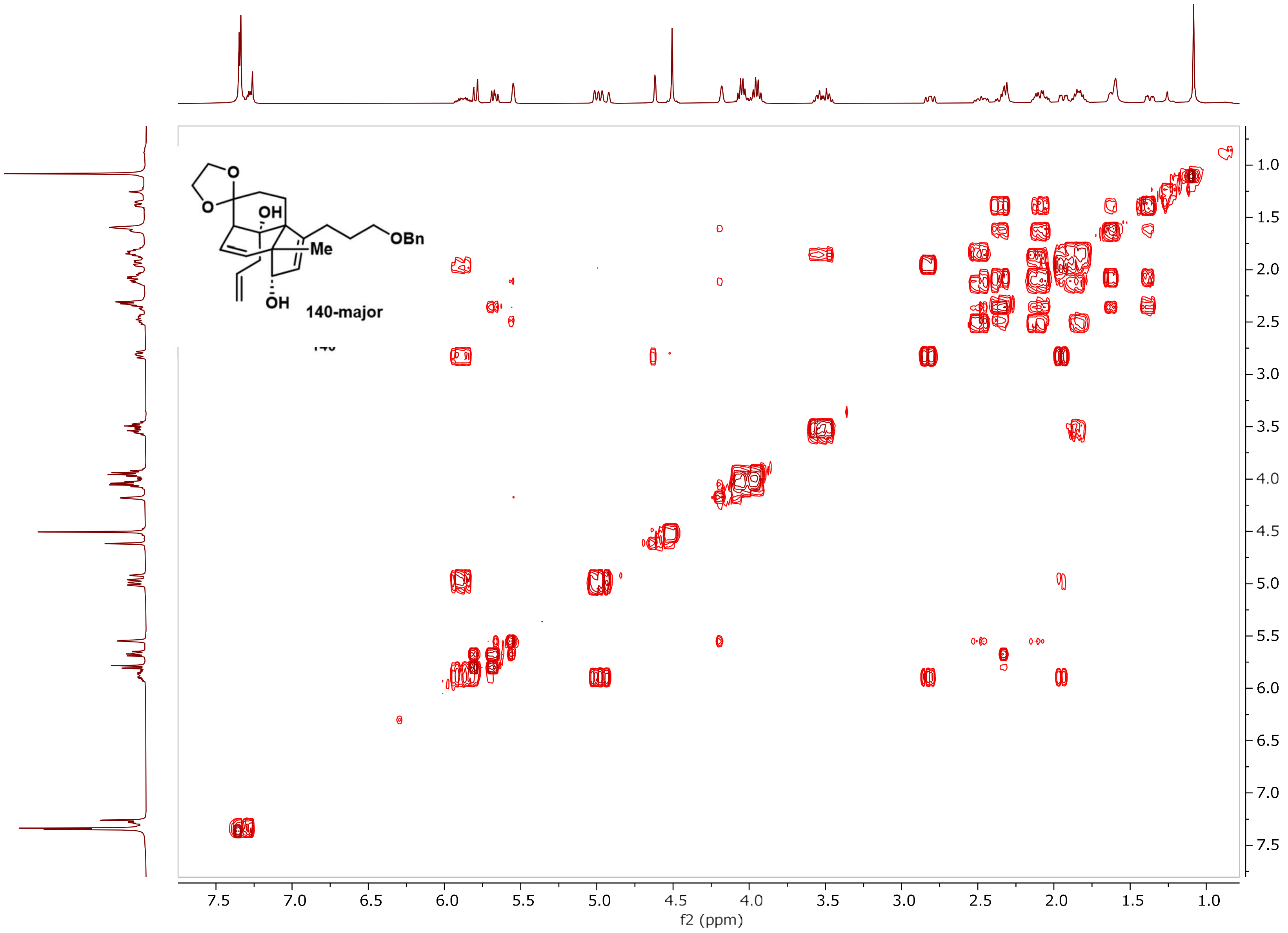
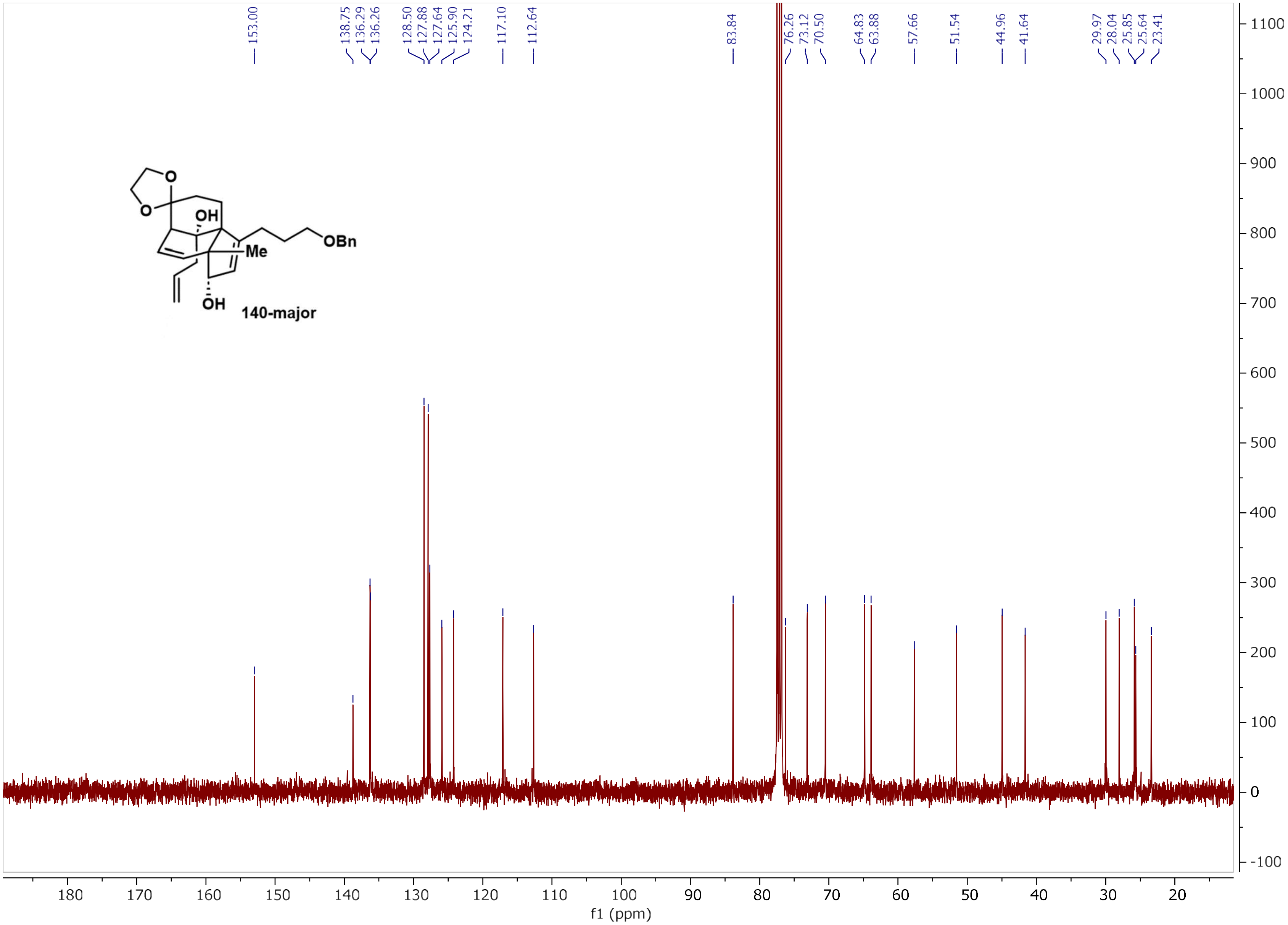
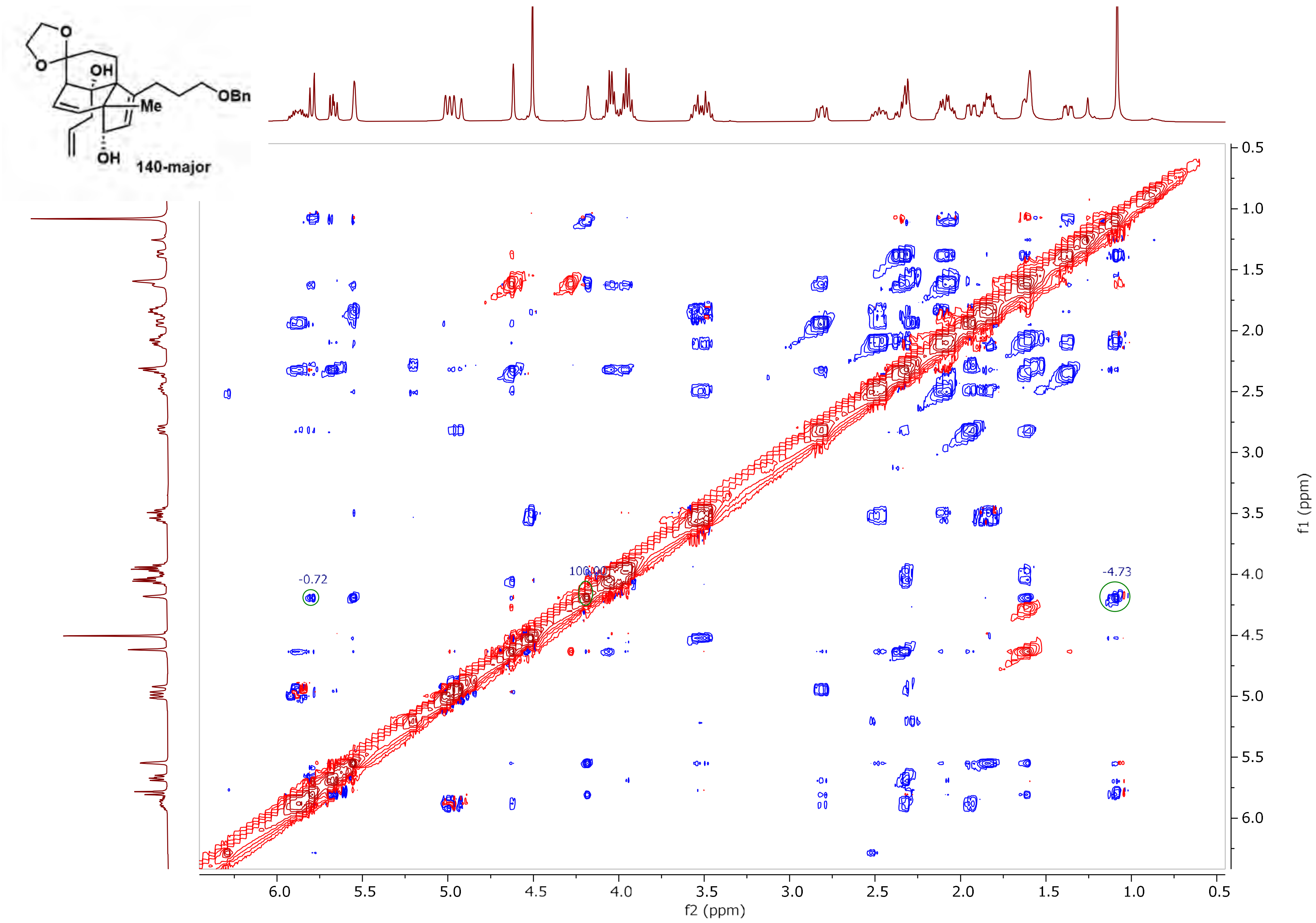
134.25
134.16
128.46
127.80
127.68
126.60
124.68
117.84
112.02
77.42
73.16
69.72
64.90
64.03
56.91
56.89
46.01
41.15
28.85
27.92
27.20
23.84
22.10
O
O
OH
Me
OBn
O
139
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

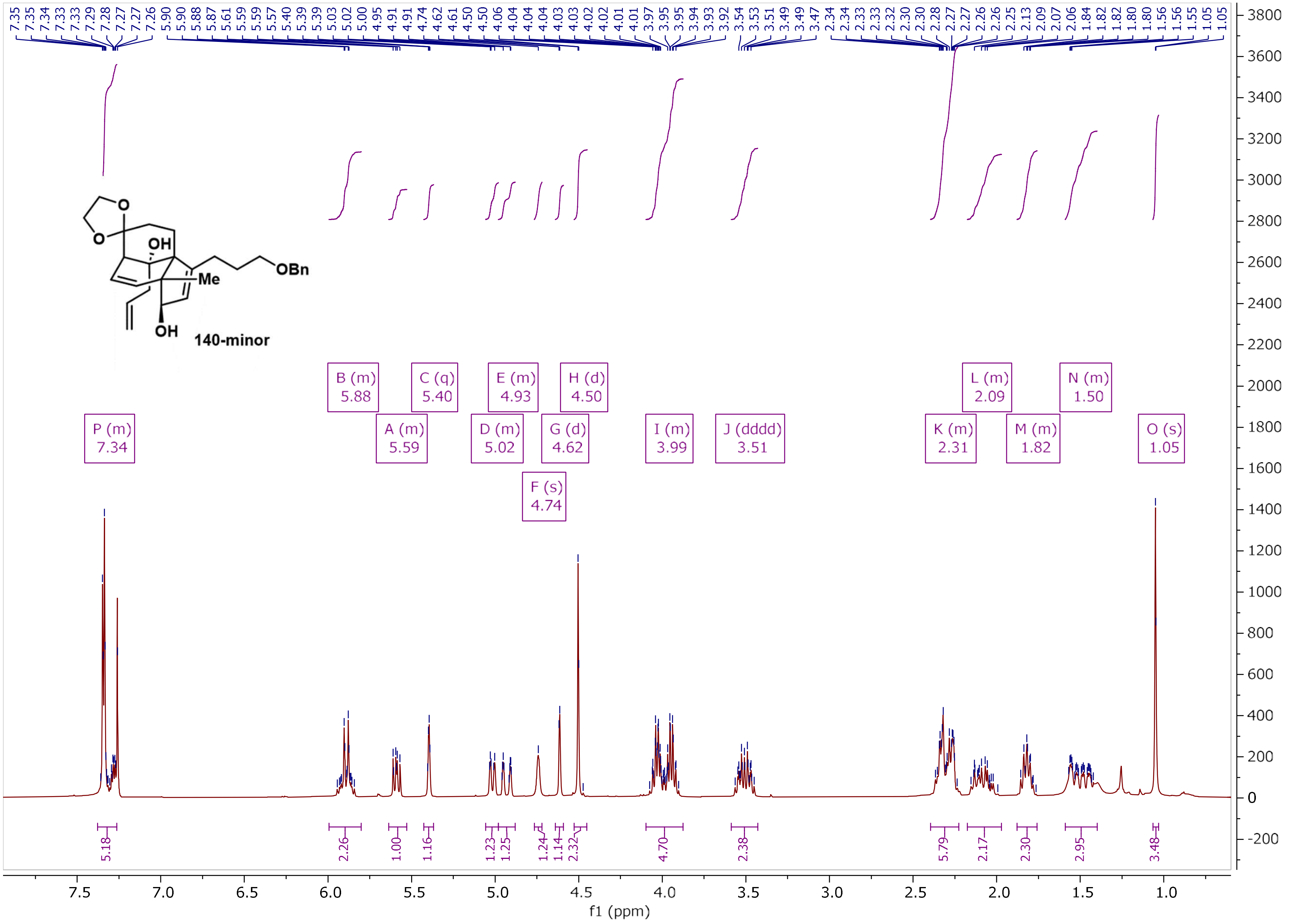
7.35
7.34
7.32
7.29
7.28
7.27
5.81
5.78
5.69
5.67
5.66
5.65
5.55
5.54
5.54
5.54
5.02
5.01
4.99
4.99
4.96
4.92
4.62
4.61
4.50
4.18
4.07
4.06
4.04
4.04
4.03
3.98
3.97
3.96
3.94
3.92
3.56
3.55
3.54
3.54
3.52
3.51
3.49
3.49
3.47
3.47
2.84
2.82
2.82
2.81
2.78
2.48
2.35
2.33
2.32
2.31
2.30
2.12
2.10
2.08
2.07
2.05
1.96
1.95
1.95
1.93
1.91
1.86
1.85
1.84
1.83
1.82
1.81
1.81
1.62
1.40
1.39
1.38
1.36
1.35
1.08
O
O
OH
OBn
Me
OH
140-major
B (m) 5.88
D (m) 5.55
G (s) 4.50
J (m) 4.00
N (m) 2.34
P (dd) 1.94
S (m) 1.38
H (m) 7.32
A (d) 5.79
E (m) 4.98
F (d) 4.62
I (s) 4.18
K (m) 3.52
L (m) 2.81
M (dt) 2.48
O (tt) 2.08
R (s) 1.62
T (s) 1.08
C (dd) 5.67
Q (dq) 1.83
5.73
1.00
1.00
1.12
1.11
2.38
1.08
2.13
1.18
4.90
2.48
1.19
1.33
2.34
2.56
1.13
1.99
0.04
0.89
1.11
3.37
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)


O
O
OH
Me
OBn
OH
140-major
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)
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
f2 (ppm)

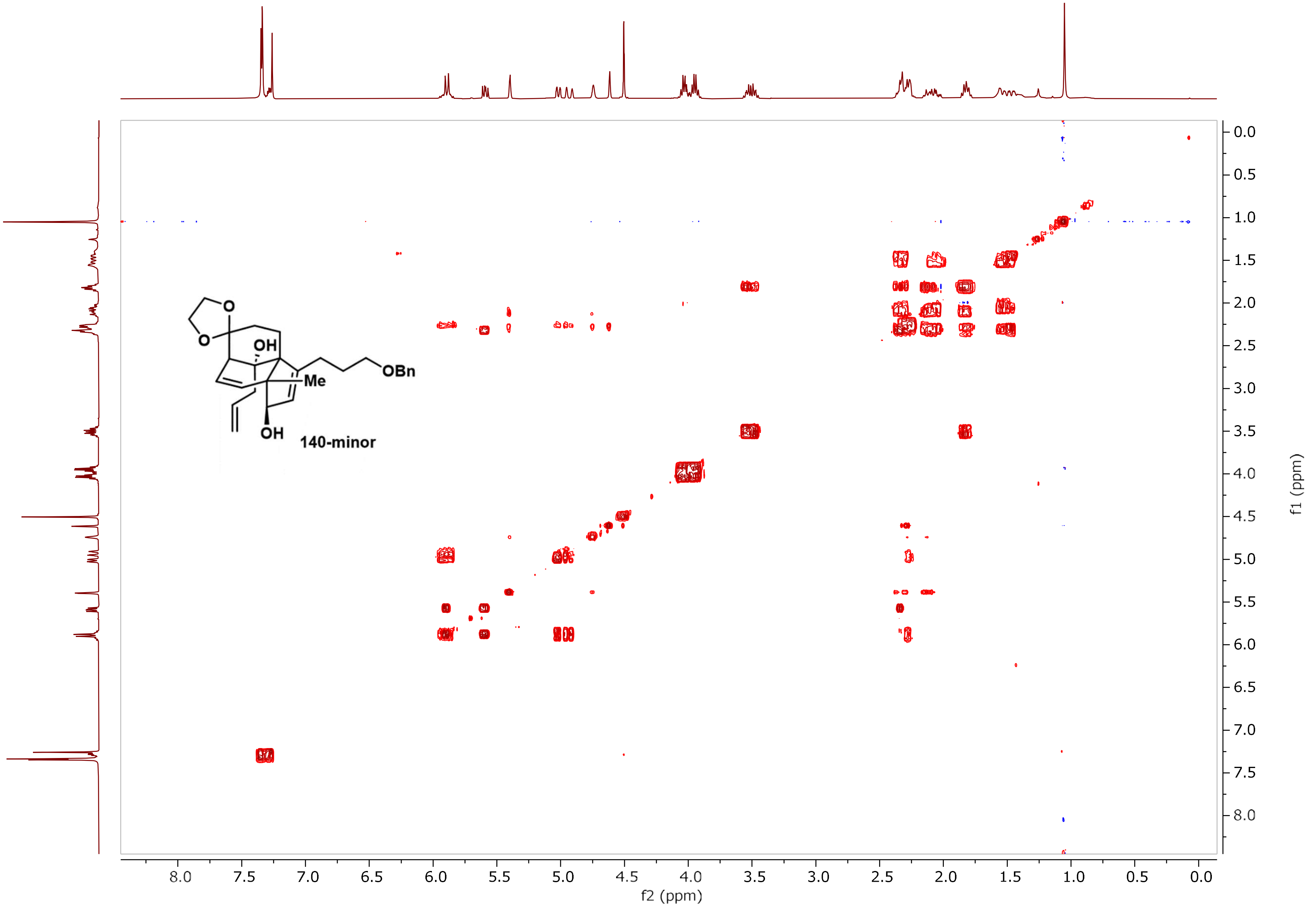

153.00
138.75
136.29
136.26
128.50
127.88
127.64
125.90
124.21
117.10
112.64
83.84
76.26
73.12
70.50
64.83
63.88
57.66
51.54
44.96
41.64
29.97
28.04
25.85
25.64
23.41
O
O
OH
OBn
Me
OH
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

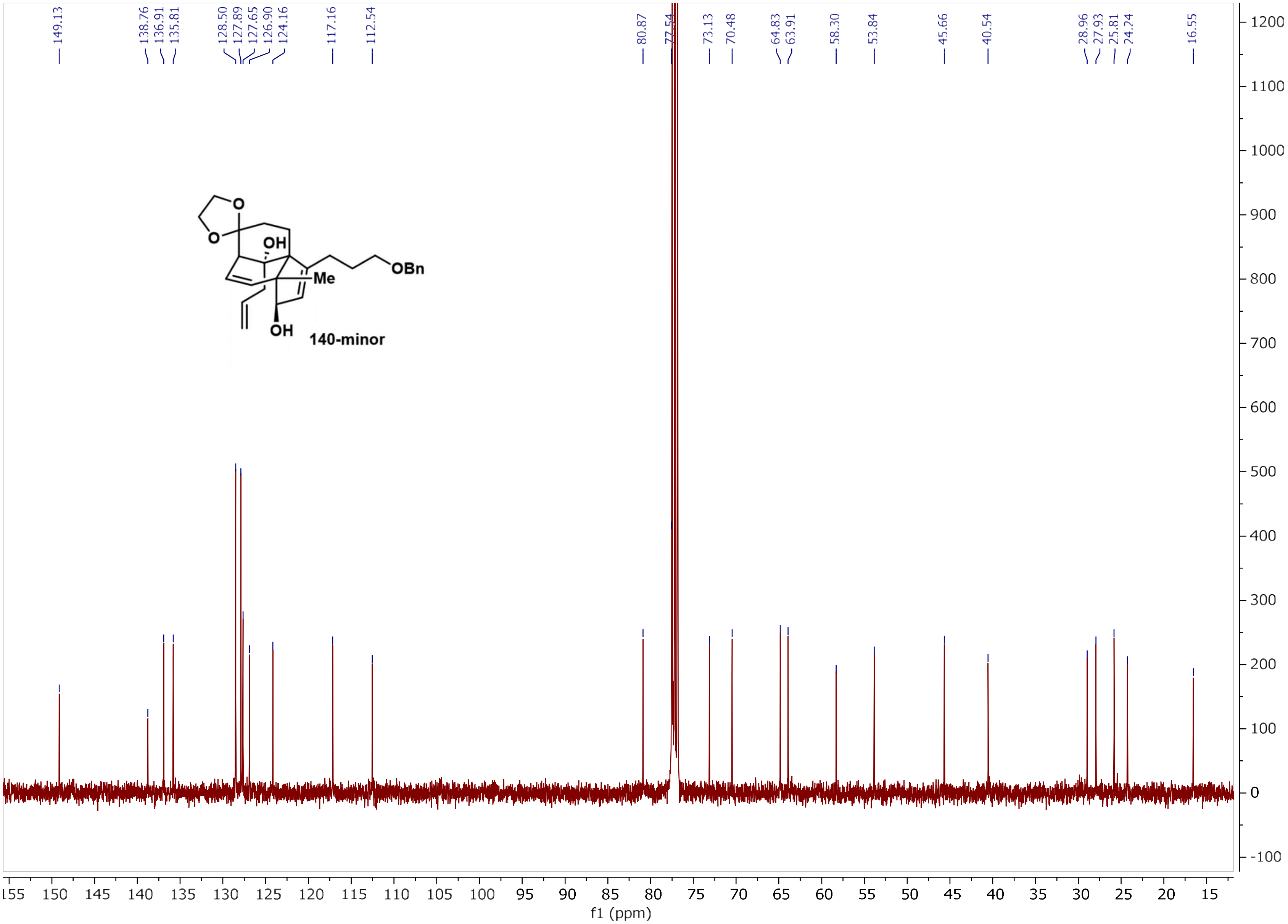
140-major

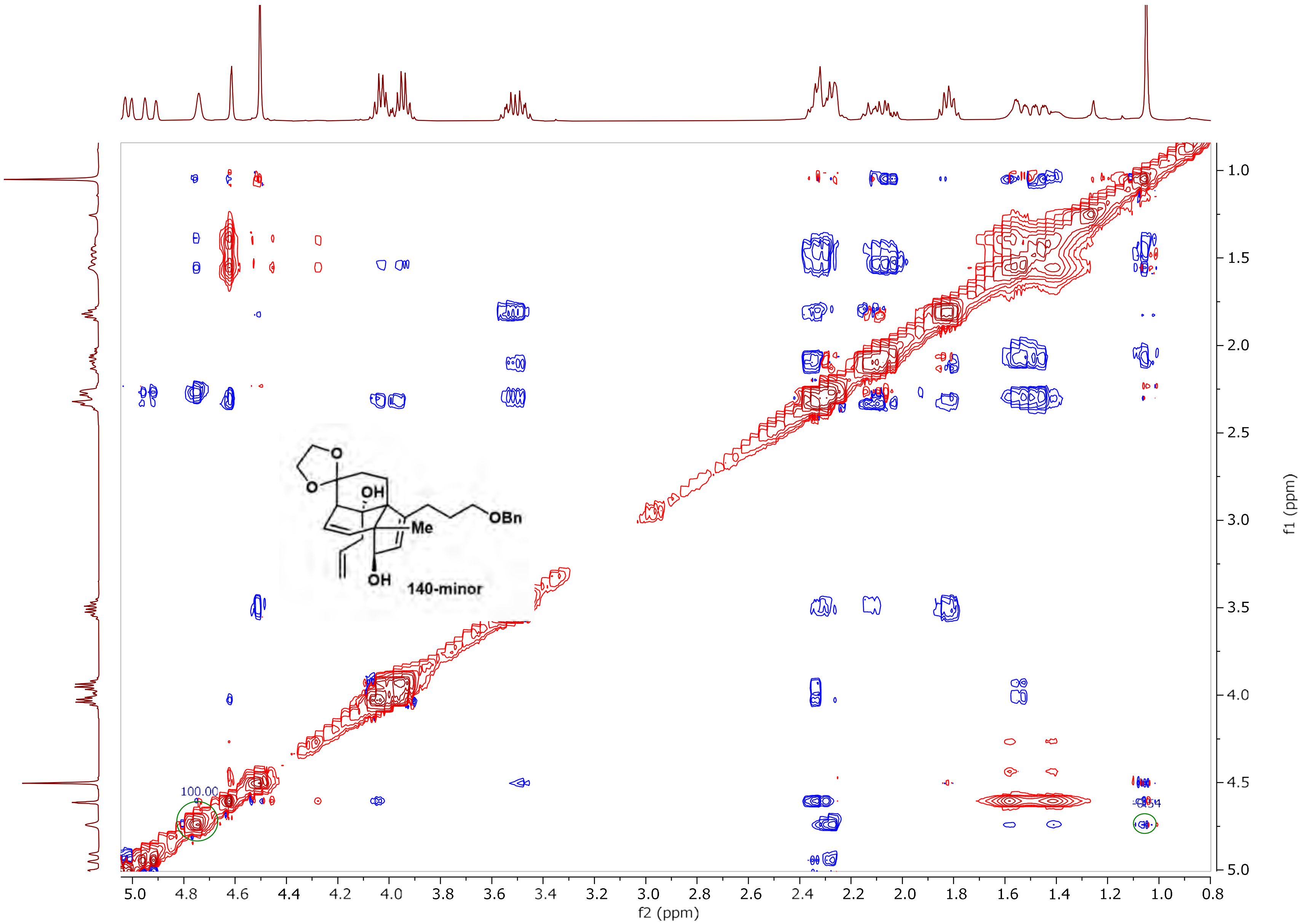

O
O
OH
Me
OBn
OH
140-major
-0.72
100.00
-4.73
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
f1 (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

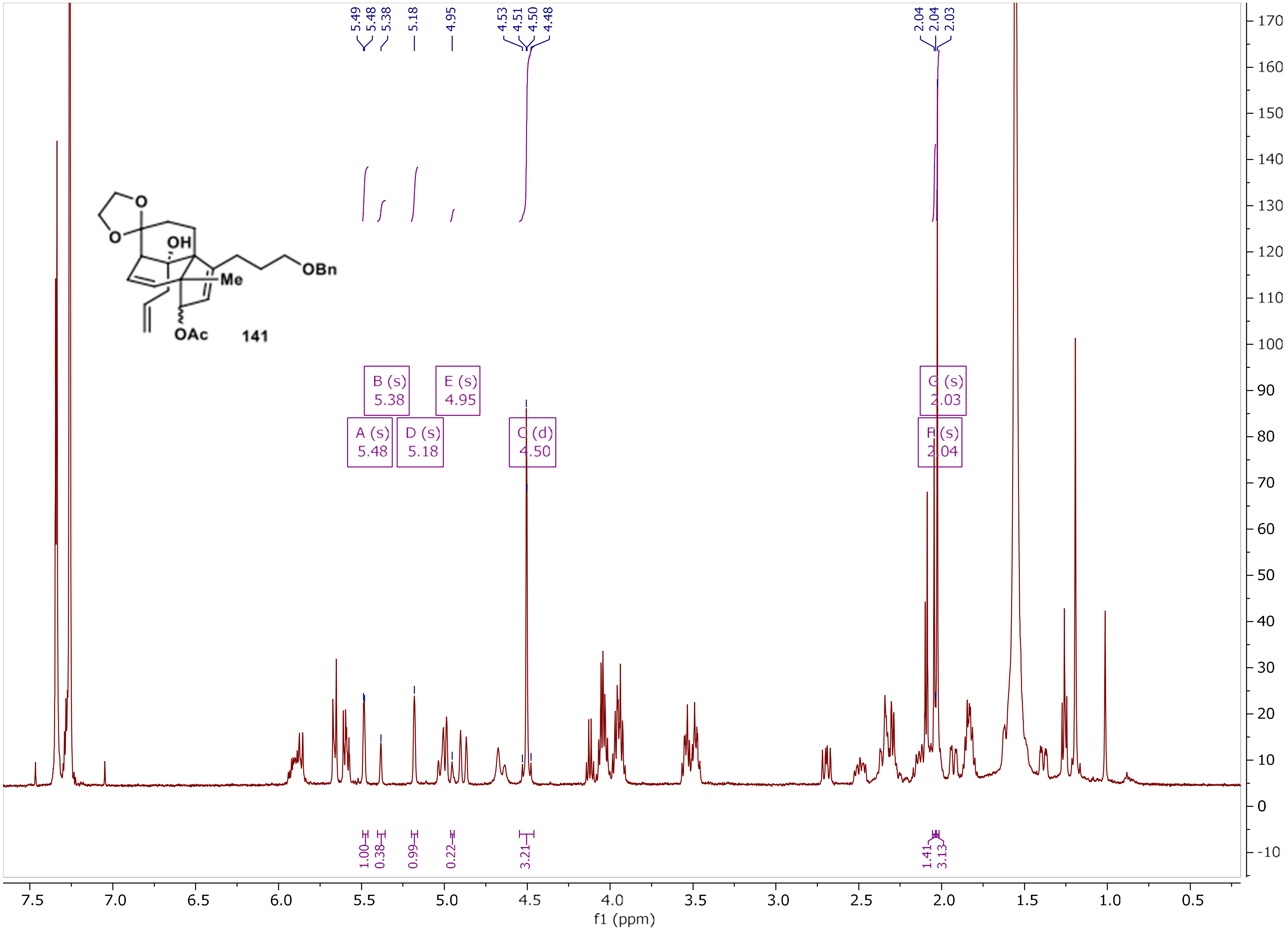

7.35 7.35 7.34 7.33 7.33 7.29 7.28 7.27 7.27 7.26 5.90 5.90 5.88 5.87 5.61 5.59 5.59 5.57 5.40 5.39 5.39 5.03 5.02 5.00 4.95 4.91 4.91 4.74 4.62 4.61 4.50 4.50 4.06 4.04 4.04 4.03 4.03 4.02 4.02 4.01 4.01 3.97 3.95 3.95 3.94 3.93 3.92 3.54 3.53 3.51 3.49 3.49 3.47 2.34 2.34 2.33 2.33 2.32 2.30 2.30 2.28 2.27 2.27 2.26 2.26 2.25 2.13 2.09 2.07 2.06 1.84 1.82 1.82 1.80 1.80 1.56 1.56 1.55 1.05 1.05
OH
O
O
Me
OBn
OH
P (m) 7.34
B (m) 5.88
A (m) 5.59
C (q) 5.40
D (m) 5.02
E (m) 4.93
F (s) 4.74
G (d) 4.62
H (d) 4.50
I (m) 3.99
J (dddd) 3.51
K (m) 2.31
L (m) 2.09
M (m) 1.82
N (m) 1.50
O (s) 1.05
5.18
2.26
1.00
1.16
1.23
1.25
1.24
1.14
2.32
4.70
2.38
5.79
2.17
2.30
2.95
3.48
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
f1 (ppm)
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

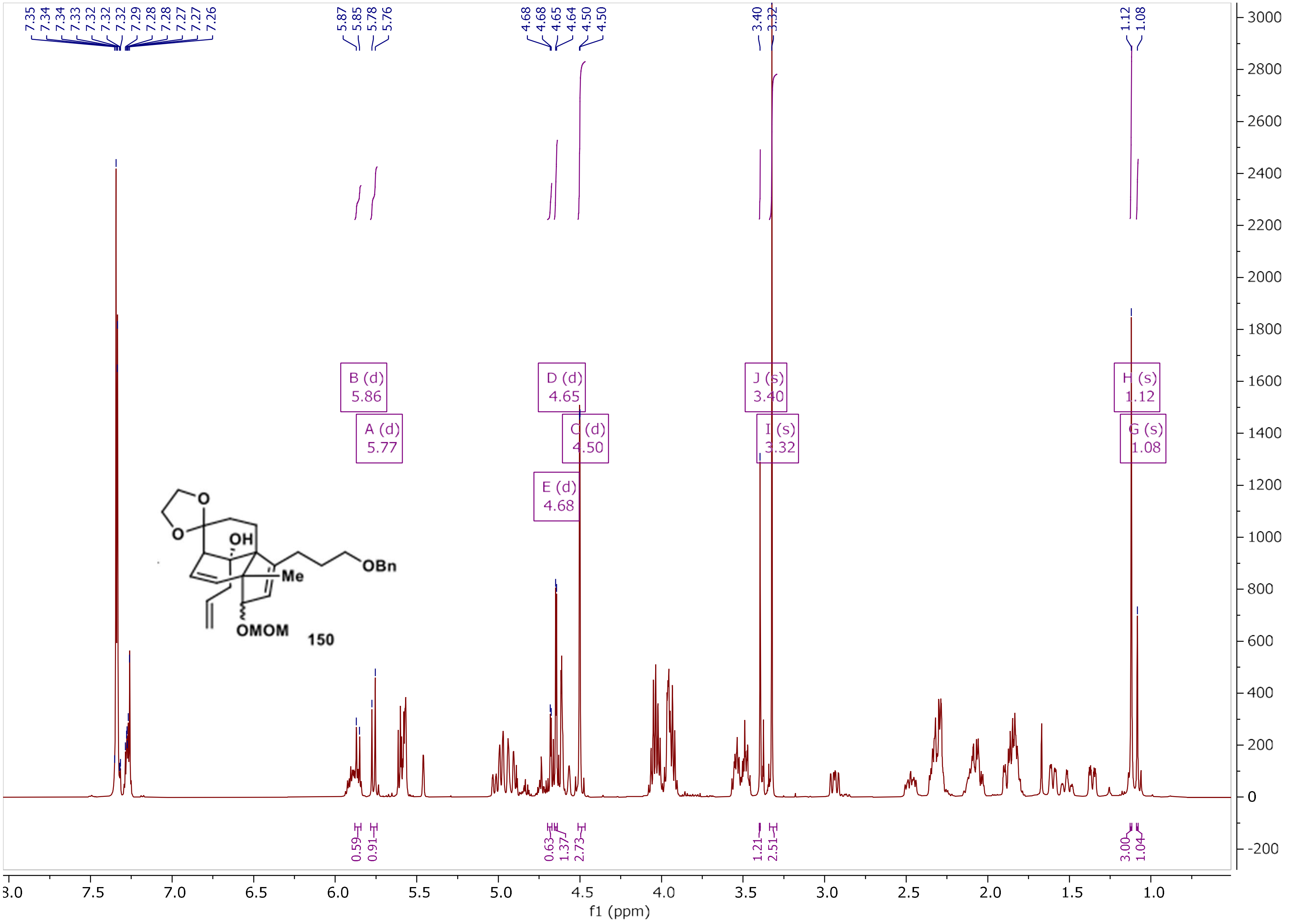
140-minor

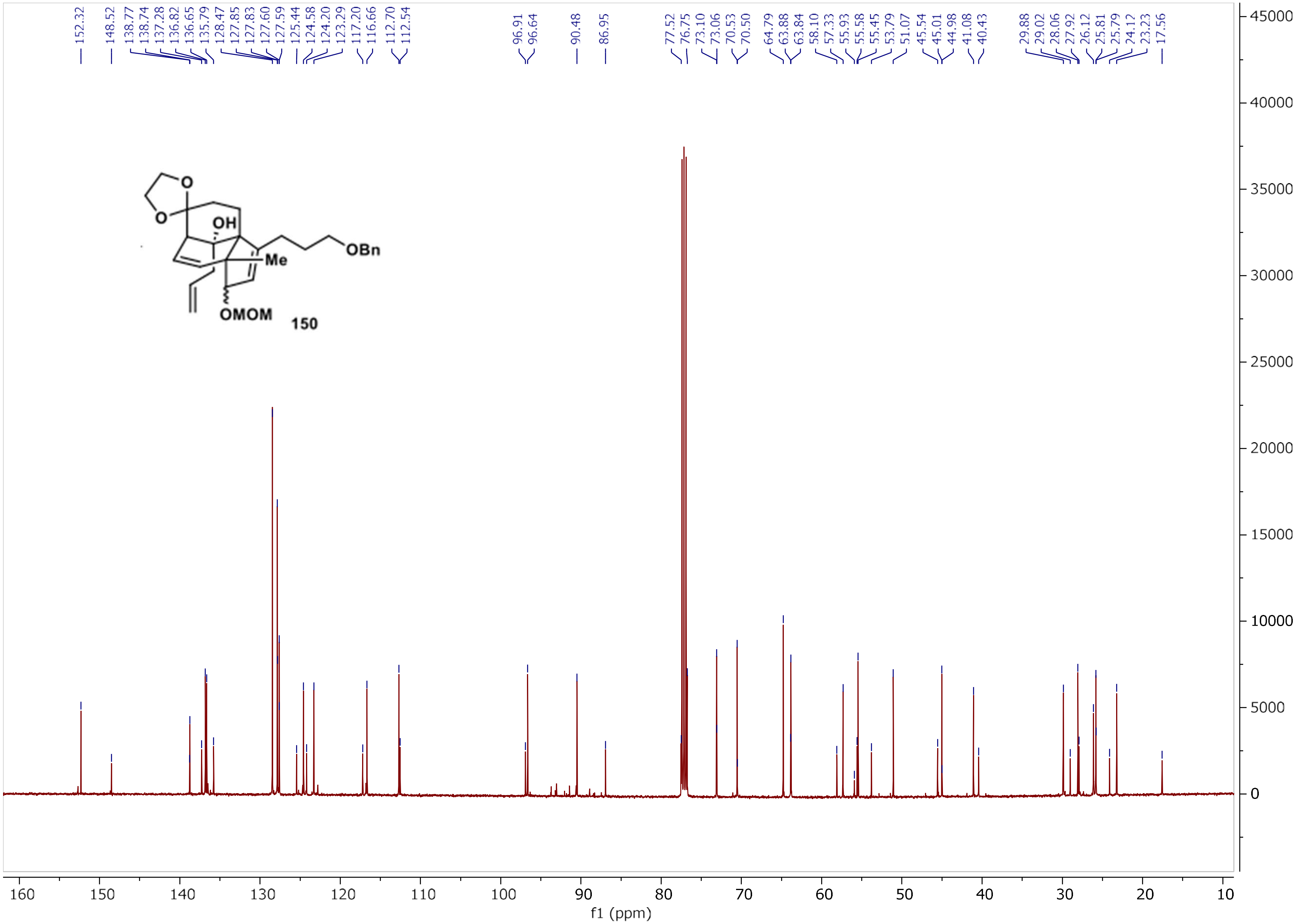

OH
OH
Me
OBn
O
O
140-minor
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

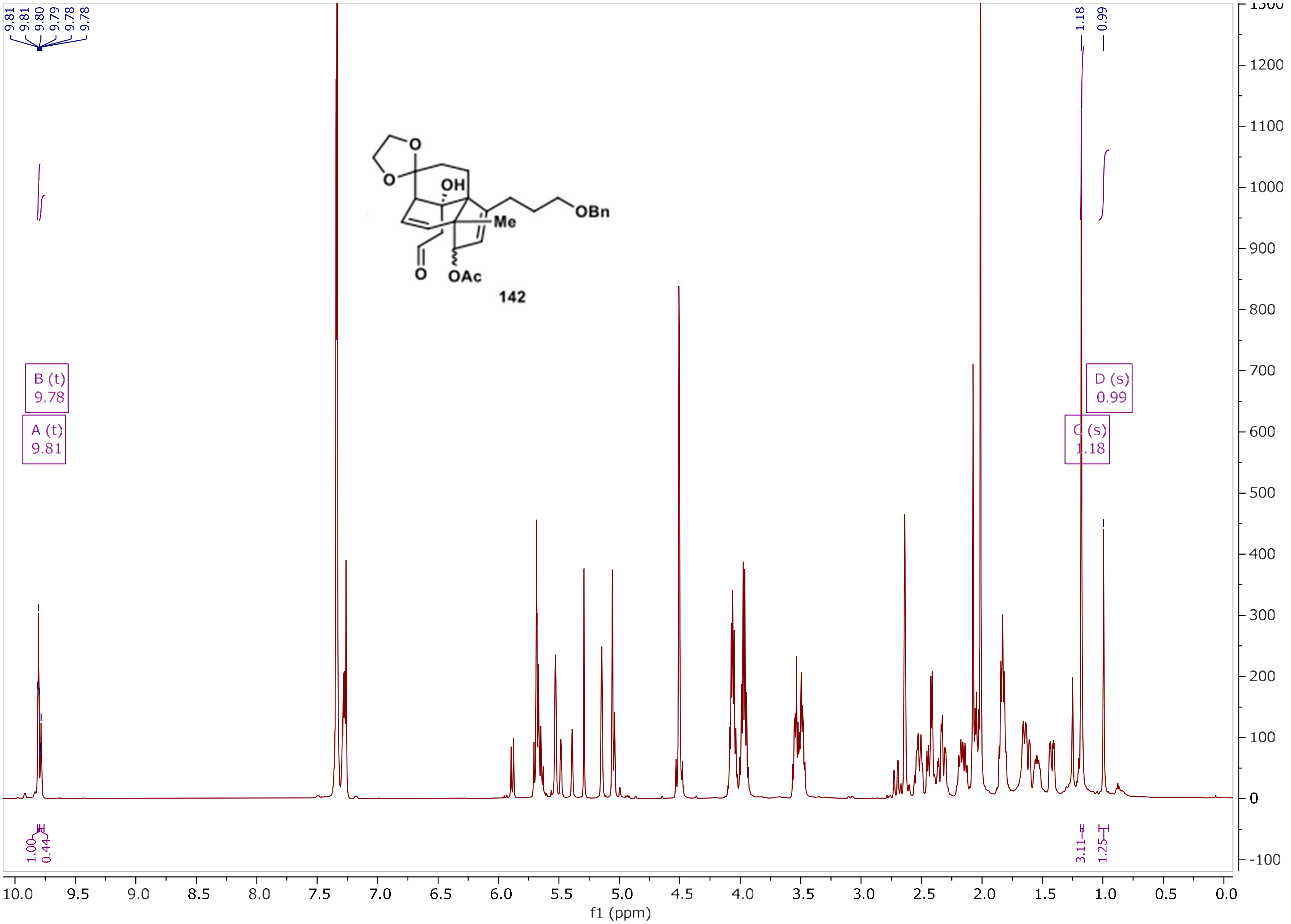

149.13
138.76
136.91
135.81
128.50
127.89
127.65
126.90
124.16
117.16
112.54
80.87
77.54
73.13
70.48
64.83
63.91
58.30
53.84
45.66
40.54
28.96
27.93
25.81
24.24
16.55
O
O
OH
OBn
Me
OH
140-minor
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)


O
O
OH
Me
OBn
OH
140-minor
100.00
5.0
4.8
4.6
4.4
4.2
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
1.2
1.0
0.8
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
f1 (ppm)

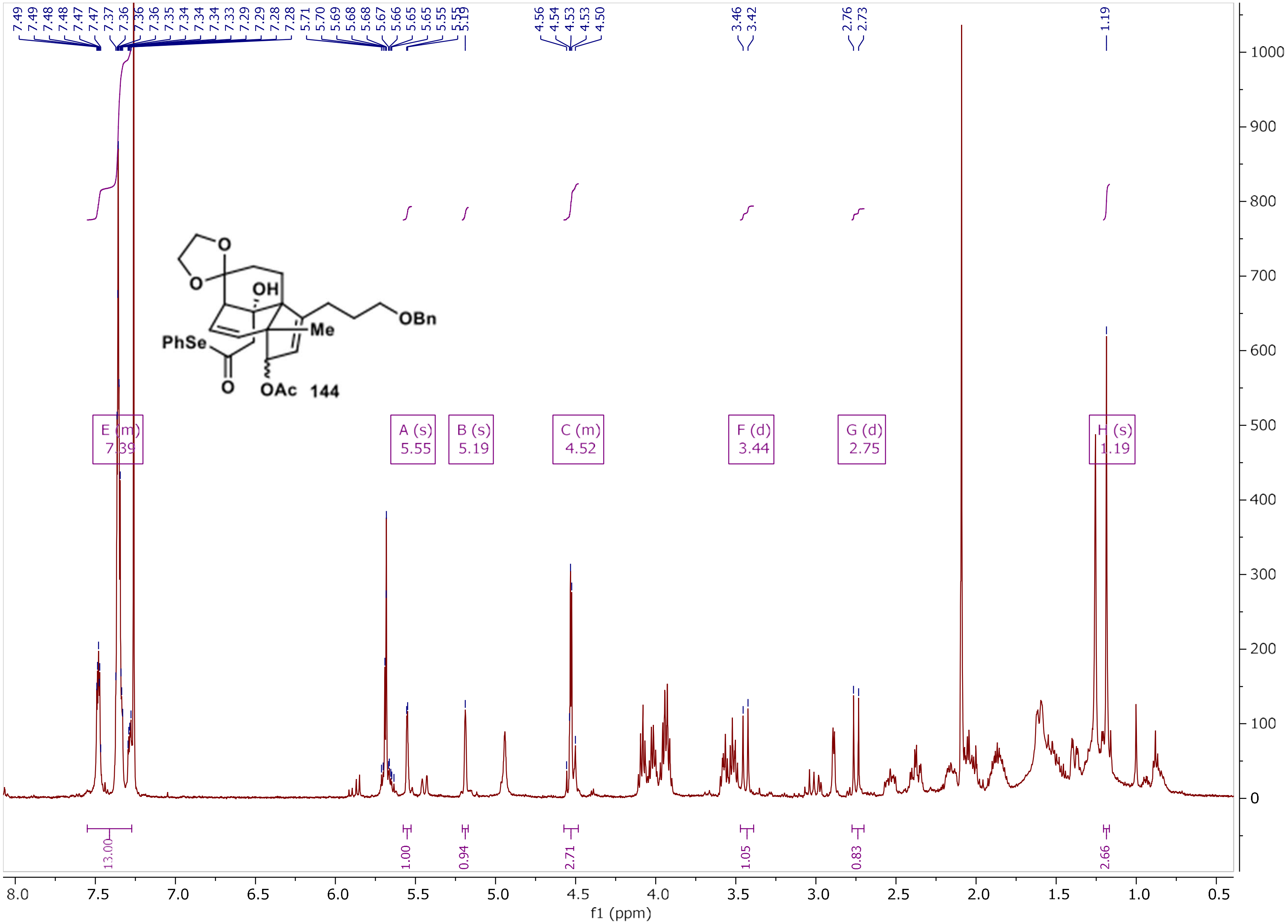

5.49
5.48
5.38
5.18
4.95
4.53
4.51
4.50
4.48
2.04
2.04
2.03
O
O
OH
Me
OBn
OAc
141
A (s)
5.48
B (s)
5.38
D (s)
5.18
E (s)
4.95
C (d)
4.50
G (s)
2.03
F (s)
2.04
1.00
0.38
0.99
0.22
3.21
1.41
3.13
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

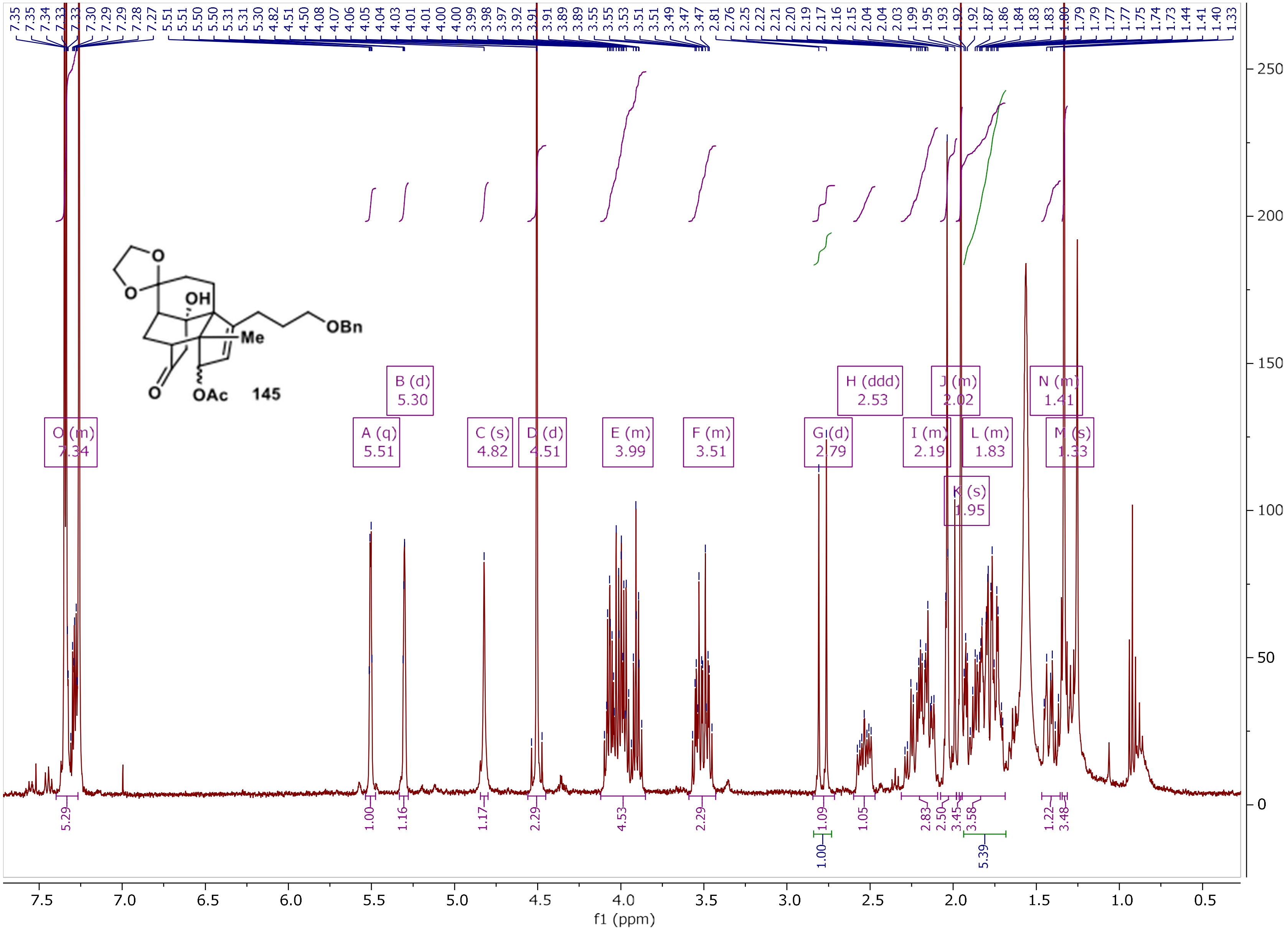

7.35 7.34 7.34 7.33 7.32 7.32 7.32 7.29 7.28 7.28 7.27 7.27 7.26
5.87 5.85 5.78 5.76
4.68 4.68 4.65 4.64 4.50 4.50
3.40 3.32
1.12 1.08
B (d) 5.86
A (d) 5.77
D (d) 4.65
C (d) 4.50
E (d) 4.68
J (s) 3.40
I (s) 3.32
H (s) 1.12
G (s) 1.08
O
O
OH
Me
OBn
OMOM
150
0.59
0.91
0.63
1.37
2.73
1.21
2.51
3.00
1.04
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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
f1 (ppm)

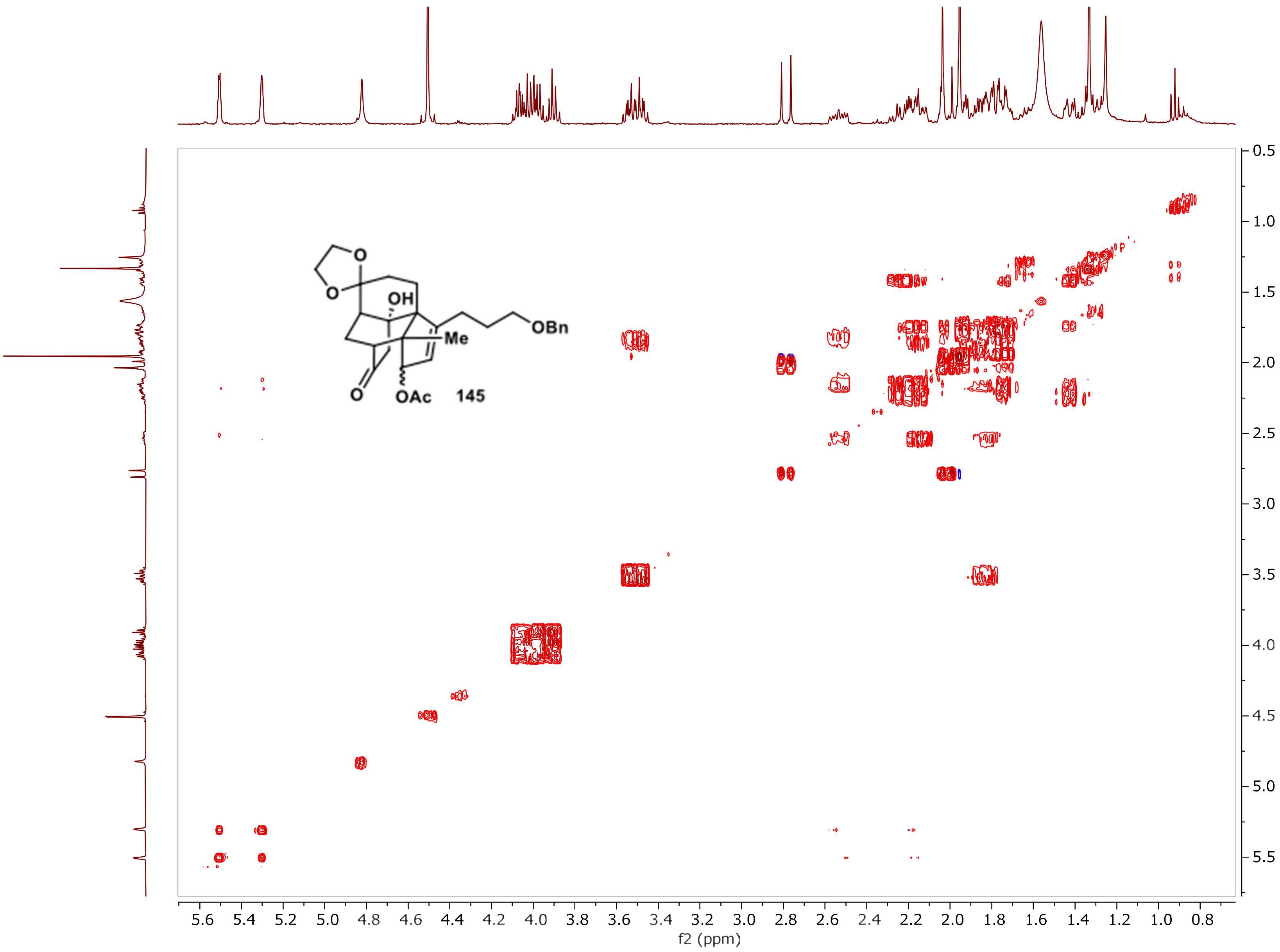

152.32
148.52
138.77
138.74
137.28
136.82
136.65
135.79
128.47
127.85
127.83
127.60
127.59
125.44
124.58
124.20
123.29
117.20
116.66
112.70
112.54
96.91
96.64
90.48
86.95
77.52
76.75
73.10
73.06
70.53
70.50
64.79
63.88
63.84
58.10
57.33
55.93
55.58
55.45
53.79
51.07
45.54
45.01
44.98
41.08
40.43
29.88
29.02
28.06
27.92
26.12
25.81
25.79
24.12
23.23
17.56
O
O
OH
Me
OBn
OMOM
150
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

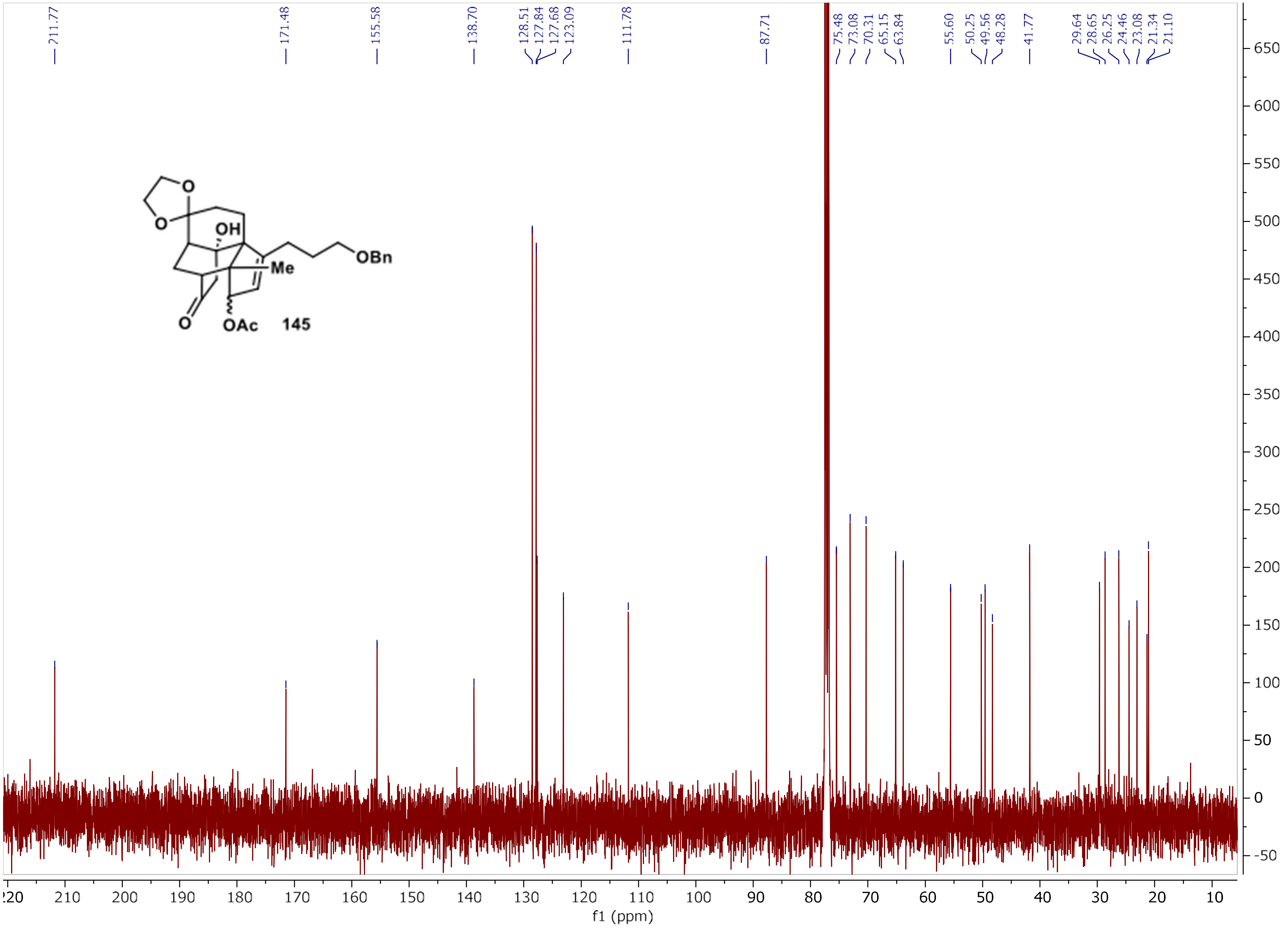

9.81
9.81
9.80
9.79
9.78
9.78
1.18
0.99
B (t)
9.78
A (t)
9.81
C (s)
1.18
D (s)
0.99
1.00
0.44
3.11
1.25
OH
Me
OBn
O
O
O
OAc
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

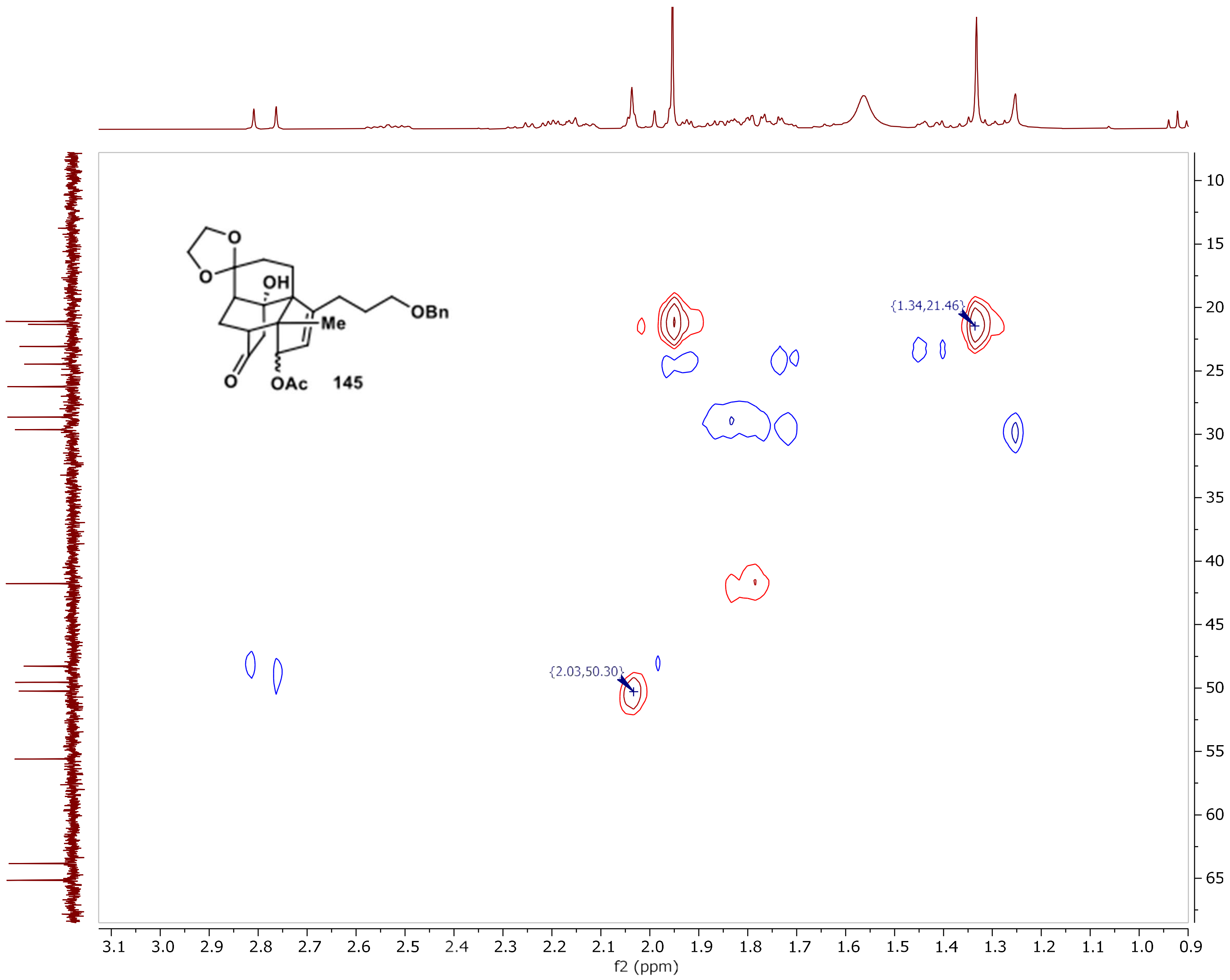
142


7.49
7.49
7.48
7.48
7.47
7.47
7.37
7.36
7.36
7.36
7.35
7.34
7.34
7.34
7.33
7.29
7.29
7.28
7.28
5.71
5.70
5.69
5.68
5.68
5.67
5.66
5.65
5.65
5.55
5.55
5.19
4.56
4.54
4.53
4.53
4.50
3.46
3.42
2.76
2.73
1.19
PhSe
O
O
O
OH
Me
OBn
O
OAc
144
E (m)
7.39
A (s)
5.55
B (s)
5.19
C (m)
4.52
F (d)
3.44
G (d)
2.75
H (s)
1.19
13.00
1.00
0.94
2.71
1.05
0.83
2.66
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
1000
900
800
700
600
500
400
300
200
100
0

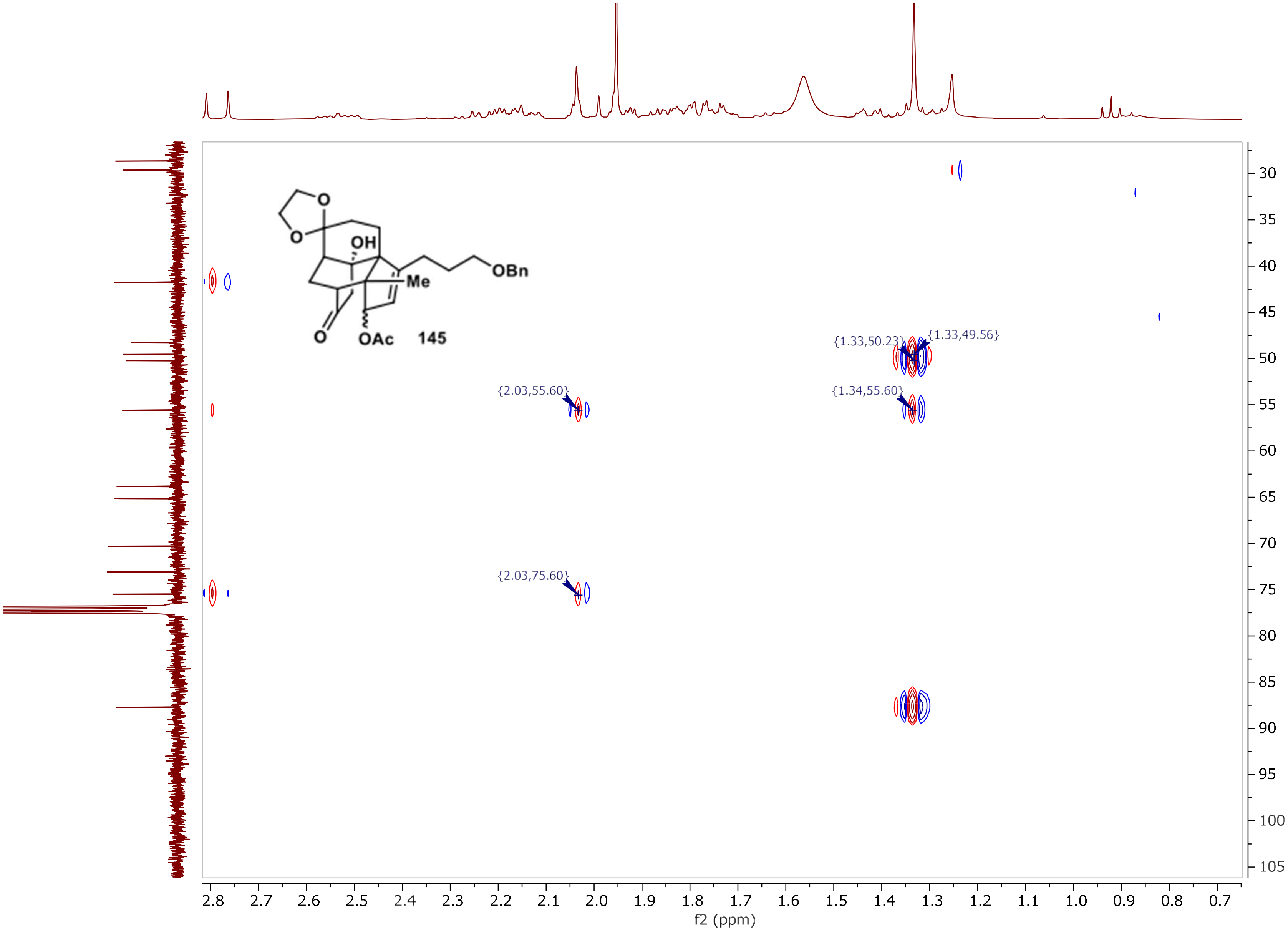

7.35 7.35 7.34 7.33 7.32 7.30 7.29 7.29 7.28 7.27 5.51 5.51 5.50 5.50 5.31 5.31 5.30 4.82 4.51 4.50 4.08 4.07 4.06 4.05 4.04 4.03 4.01 4.01 4.00 4.00 3.99 3.98 3.97 3.92 3.91 3.91 3.89 3.89 3.55 3.53 3.51 3.51 3.49 3.47 3.47 2.81 2.76 2.25 2.22 2.21 2.20 2.19 2.17 2.16 2.15 2.04 2.04 2.03 1.99 1.95 1.93 1.92 1.87 1.86 1.84 1.83 1.83 1.80 1.79 1.77 1.77 1.75 1.74 1.73 1.44 1.41 1.40 1.33
O
O
OH
Me
OBn
O
OAc
145
O (m) 7.34
A (q) 5.51
B (d) 5.30
C (s) 4.82
D (d) 4.51
E (m) 3.99
F (m) 3.51
G (d) 2.79
H (ddd) 2.53
I (m) 2.19
J (m) 2.02
K (s) 1.95
L (m) 1.83
N (m) 1.41
M (s) 1.33
5.29
1.00
1.16
1.17
2.29
4.53
2.29
1.09
1.00
1.05
2.83
2.50
3.45
3.58
5.39
1.22
3.48
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
f1 (ppm)
250
200
150
100
50
0


O
O
OH
Me
OBn
O
OAc
145
f2 (ppm)
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
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
1.2
1.0
0.8
f1 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

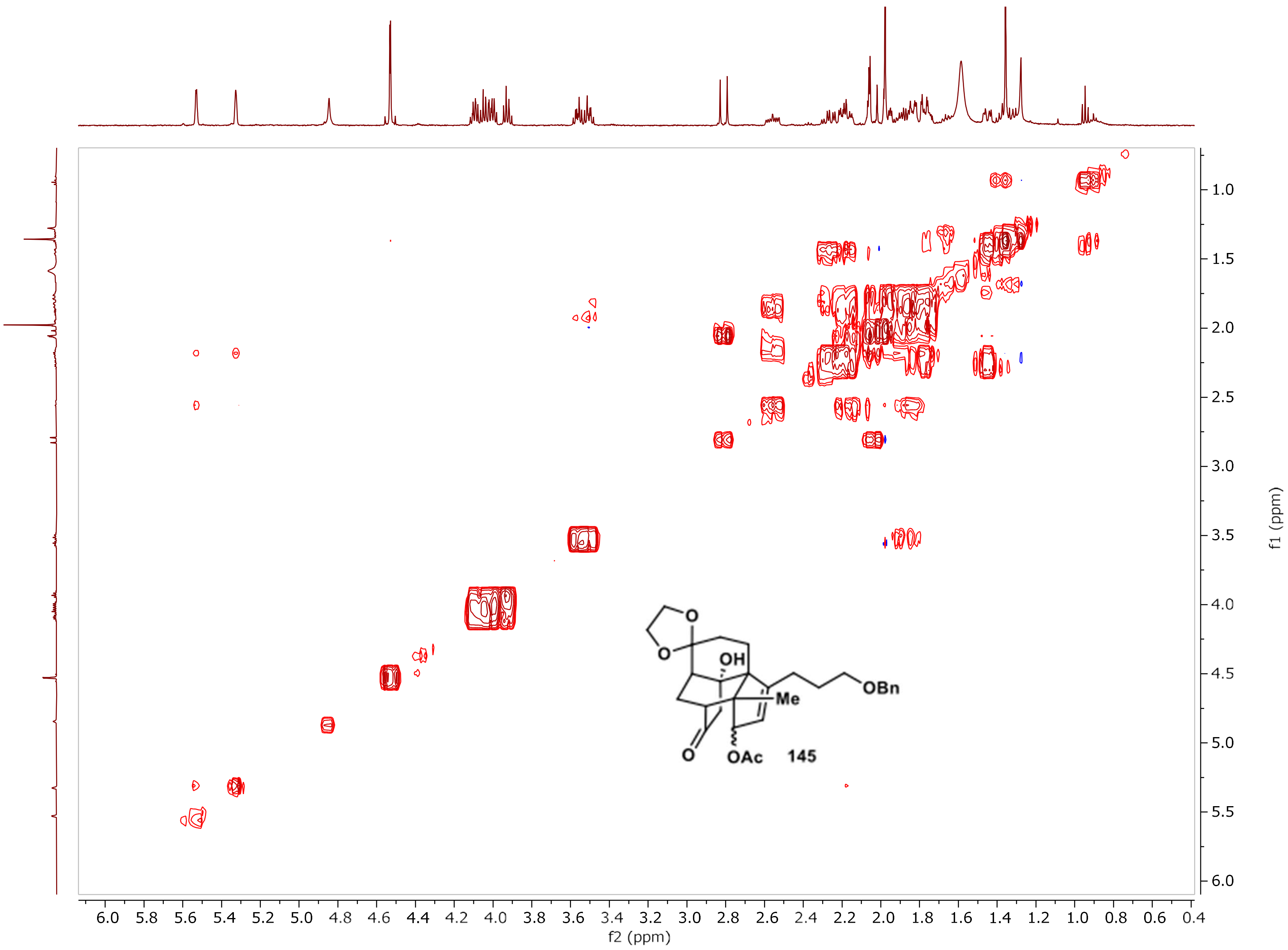

211.77
171.48
155.58
138.70
128.51
127.84
127.68
123.09
111.78
87.71
75.48
73.08
70.31
65.15
63.84
55.60
50.25
49.56
48.28
41.77
29.64
28.65
26.25
24.46
23.08
21.34
21.10
O
O
OH
Me
OBn
O
OAc
145
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



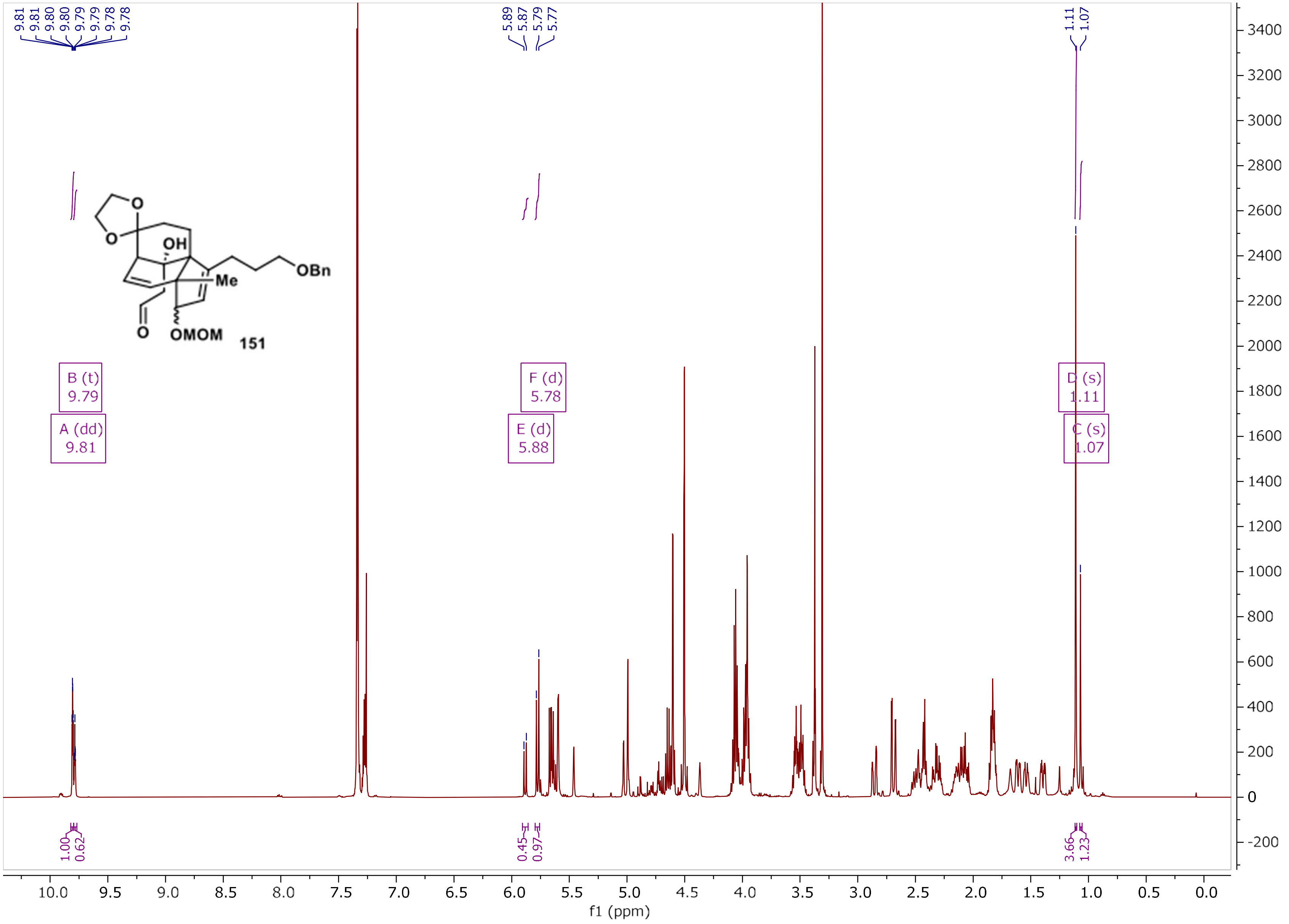
O
O
OH
Me
OBn
O
OAc
145
{1.34,21.46}
{2.03,50.30}
f2 (ppm)
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
f1 (ppm)
10
15
20
25
30
35
40
45
50
55
60
65

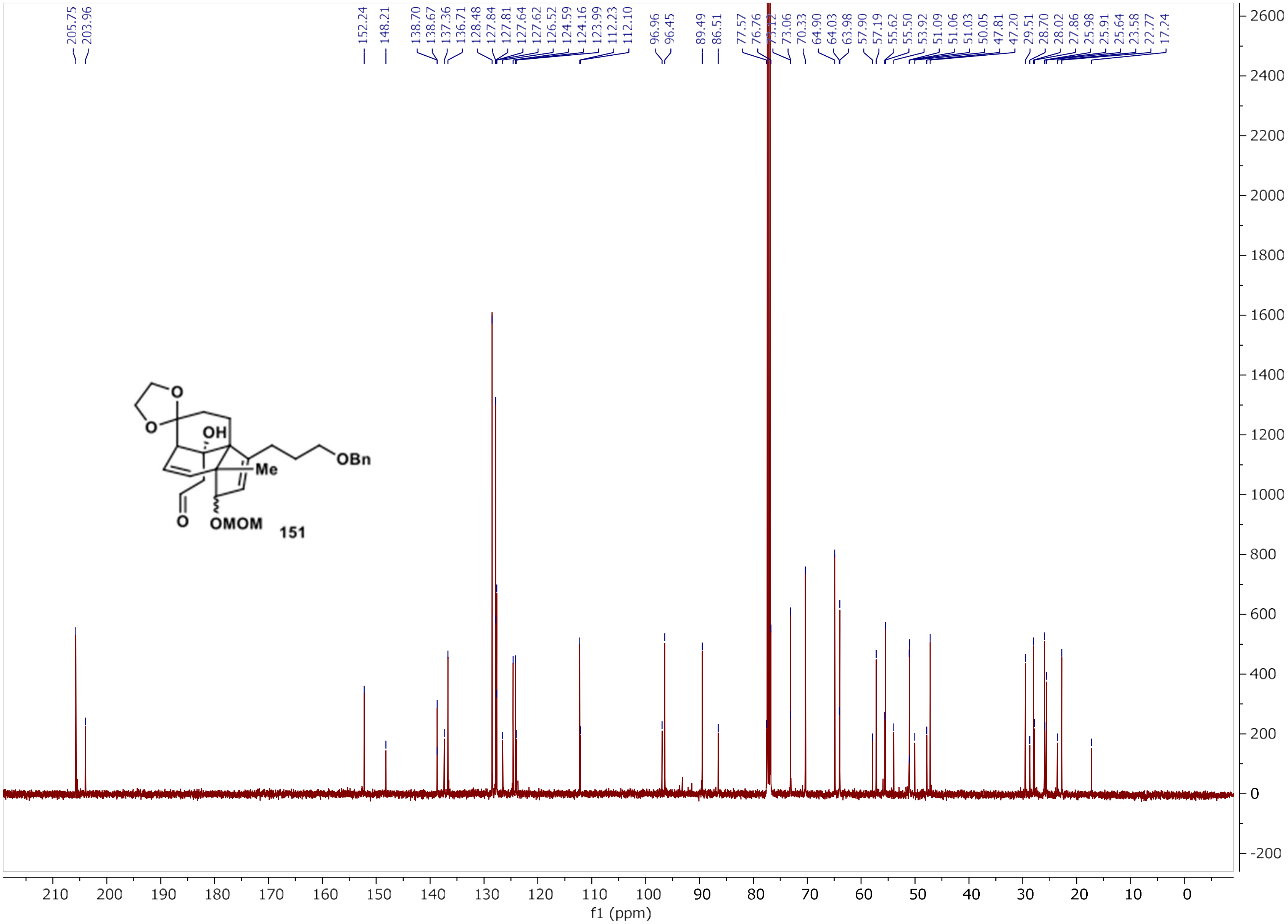


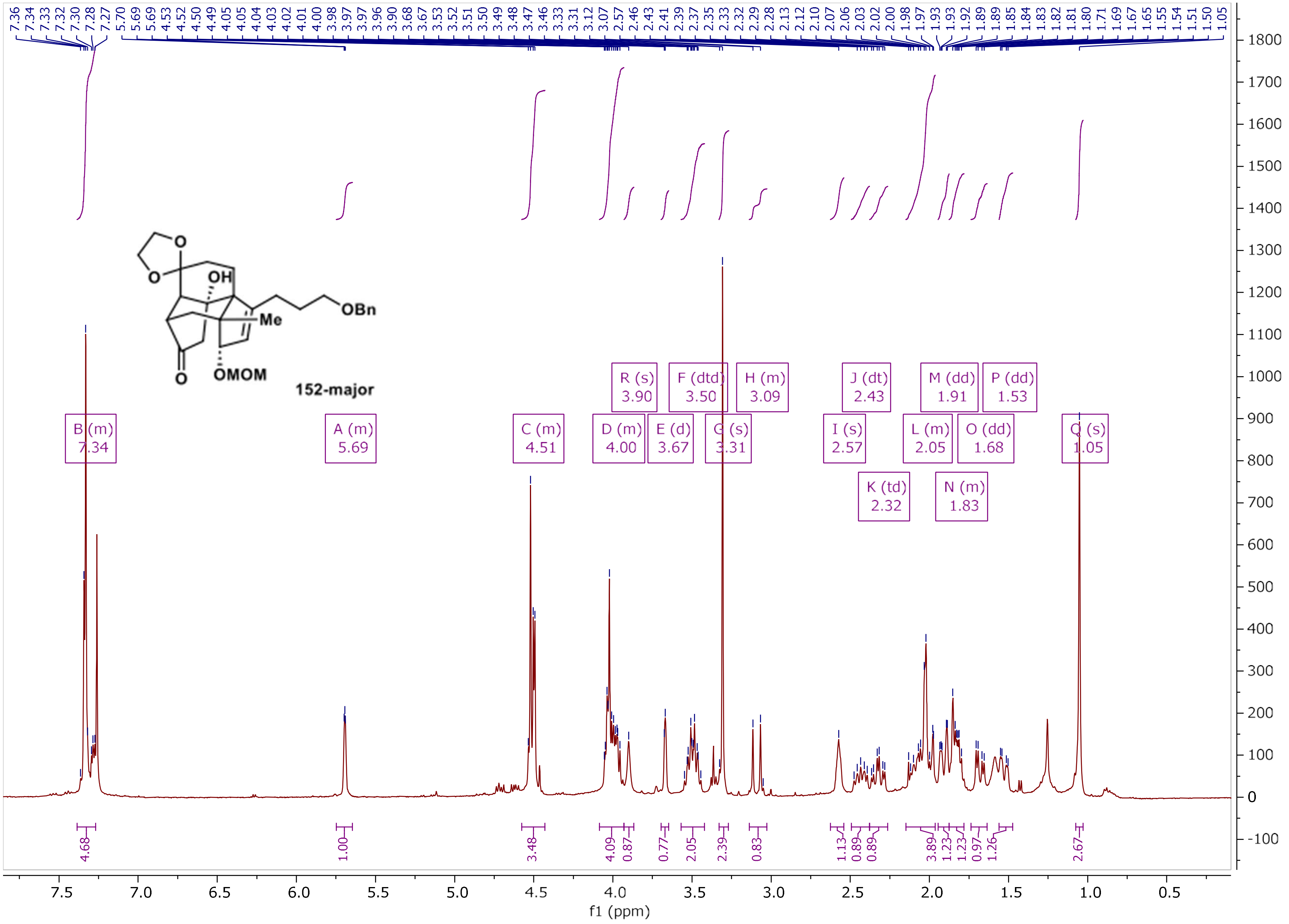
O
O
OH
Me
OBn
O
OAc
145
{1.33,50.23}
{1.33,49.56}
{2.03,55.60}
{1.34,55.60}
{2.03,75.60}
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
f2 (ppm)
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
f1 (ppm)



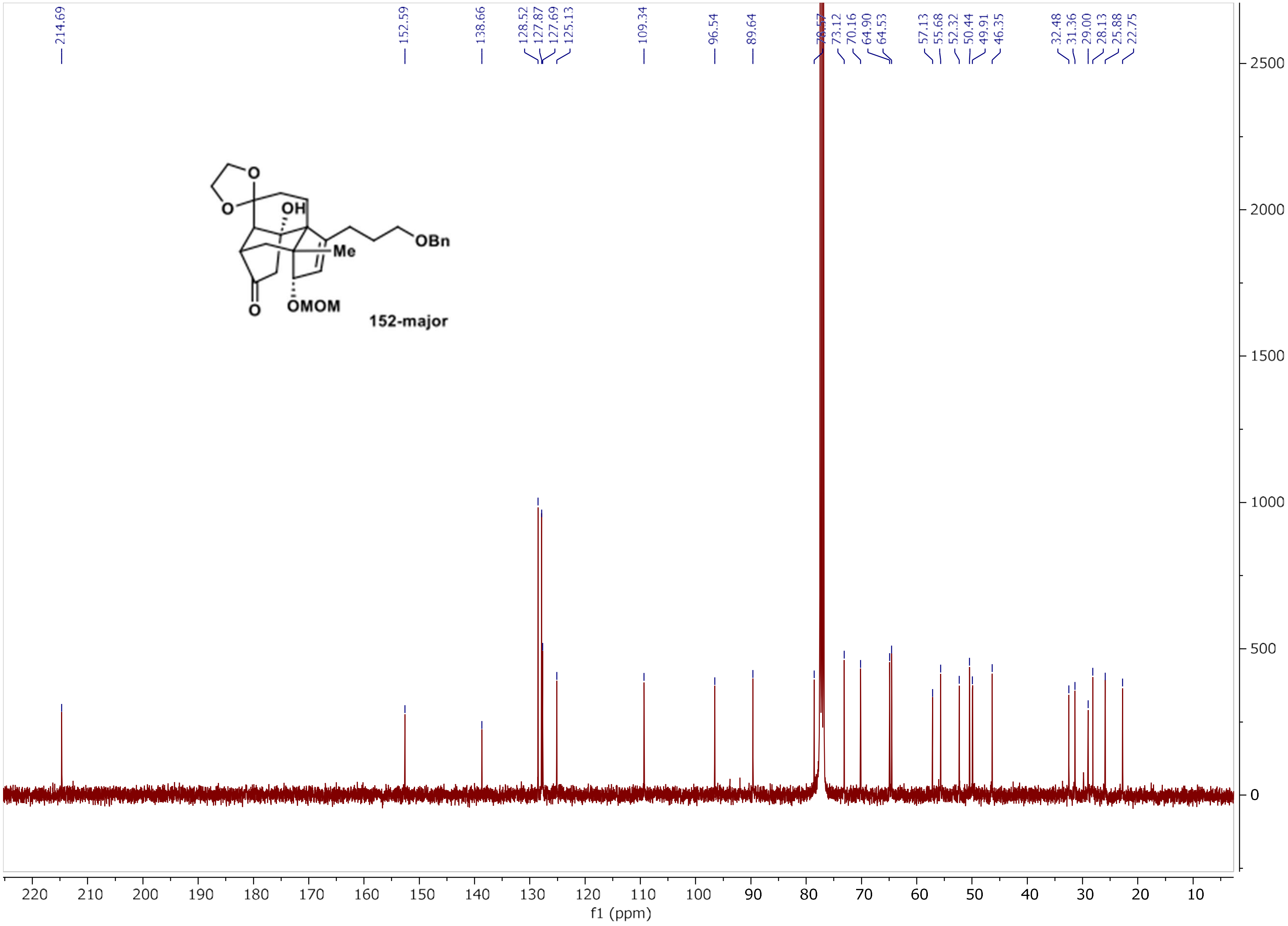
OH
Me
OBn
O
O
O
OAc
145
f2 (ppm)
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
f1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0

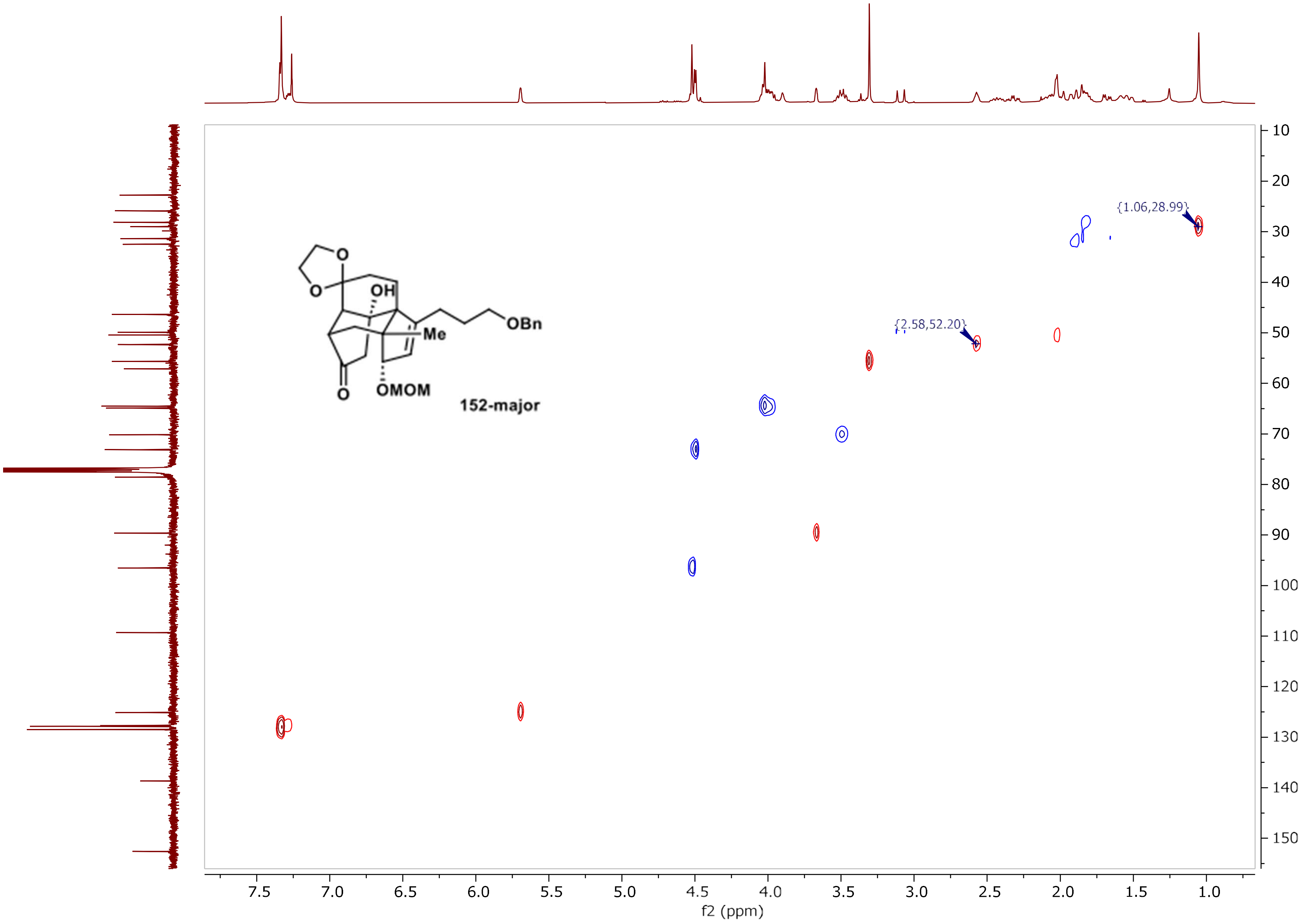

9.81
9.81
9.80
9.80
9.79
9.79
9.78
9.78
5.89
5.87
5.79
5.77
1.11
1.07
O
O
OH
Me
OBn
O
OMOM
151
B (t)
9.79
A (dd)
9.81
F (d)
5.78
E (d)
5.88
D (s)
1.11
C (s)
1.07
1.00
0.62
0.45
0.97
3.66
1.23
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10.0
9.5
9.0
8.5
8.0
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)


205.75
203.96
152.24
148.21
138.70
138.67
137.36
136.71
128.48
127.84
127.81
127.64
127.62
126.52
124.59
124.16
123.99
112.23
112.10
96.96
96.45
89.49
86.51
77.57
76.76
73.12
73.06
70.33
64.90
64.03
63.98
57.90
57.19
55.62
55.50
53.92
51.09
51.06
51.03
50.05
47.81
47.20
29.51
28.70
28.02
27.86
25.98
25.91
25.64
23.58
22.77
17.24
O
O
OH
OBn
Me
O
OMOM
151
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

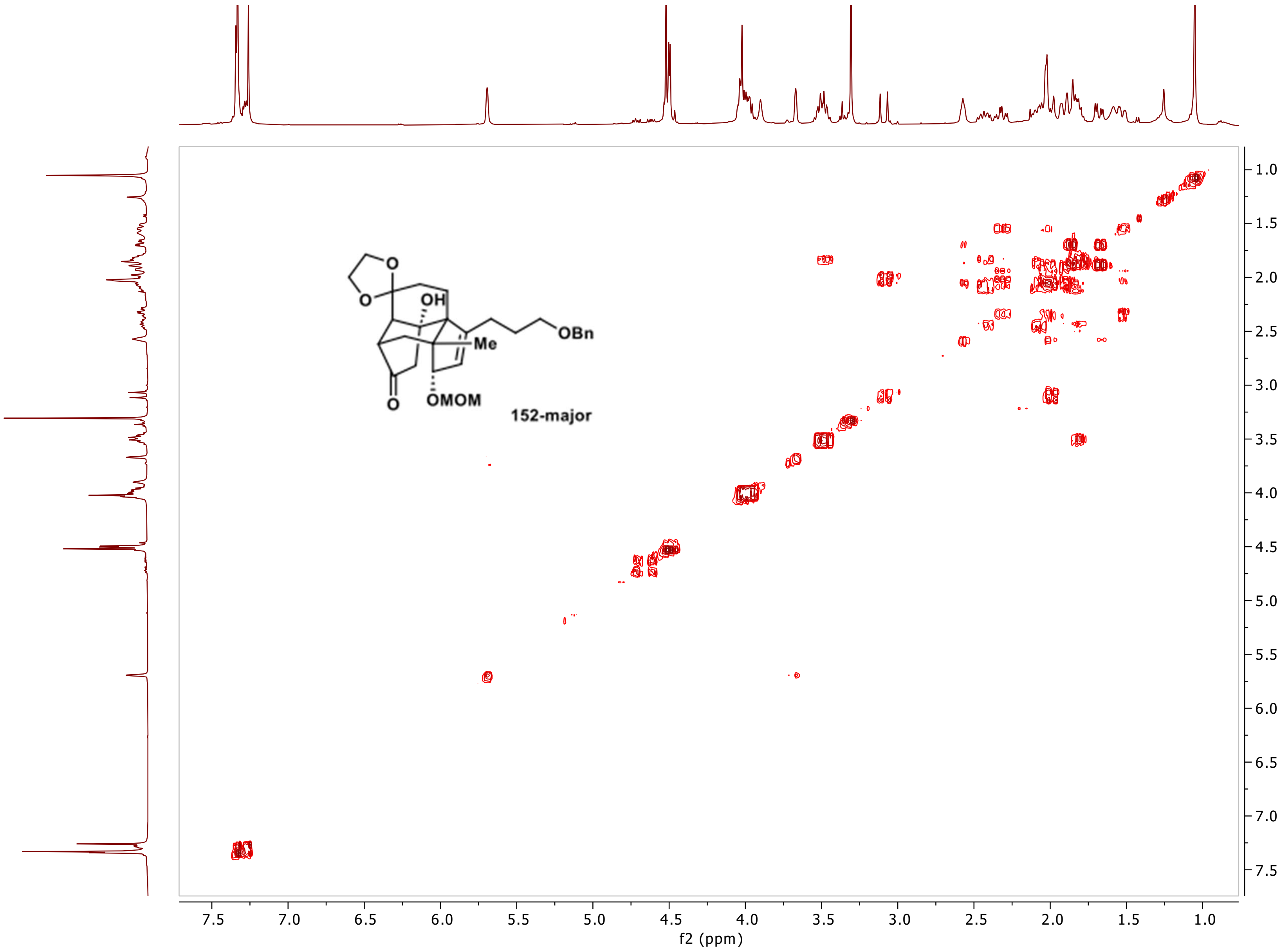

7.36 7.34 7.33 7.32 7.30 7.28 7.27 5.70 5.69 5.69 4.53 4.52 4.50 4.49 4.05 4.05 4.04 4.03 4.02 4.01 4.00 3.98 3.97 3.96 3.90 3.68 3.67 3.53 3.52 3.51 3.50 3.49 3.48 3.47 3.46 3.33 3.31 3.12 3.07 2.57 2.46 2.43 2.41 2.39 2.37 2.35 2.33 2.32 2.29 2.28 2.13 2.12 2.10 2.07 2.06 2.03 2.02 2.00 1.98 1.97 1.93 1.93 1.92 1.89 1.89 1.85 1.84 1.83 1.82 1.81 1.80 1.71 1.69 1.67 1.65 1.55 1.54 1.51 1.50 1.05
O
O
OH
Me
OBn
O
OMOM
B (m) 7.34
A (m) 5.69
C (m) 4.51
D (m) 4.00
R (s) 3.90
E (d) 3.67
F (dtd) 3.50
G (s) 3.31
H (m) 3.09
I (s) 2.57
J (dt) 2.43
K (td) 2.32
L (m) 2.05
M (dd) 1.91
N (m) 1.83
O (dd) 1.68
P (dd) 1.53
Q (s) 1.05
4.68
1.00
3.48
4.09
0.87
0.77
2.05
2.39
0.83
1.13
0.89
0.89
3.89
1.23
1.23
0.97
1.26
2.67
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)
1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

152-major

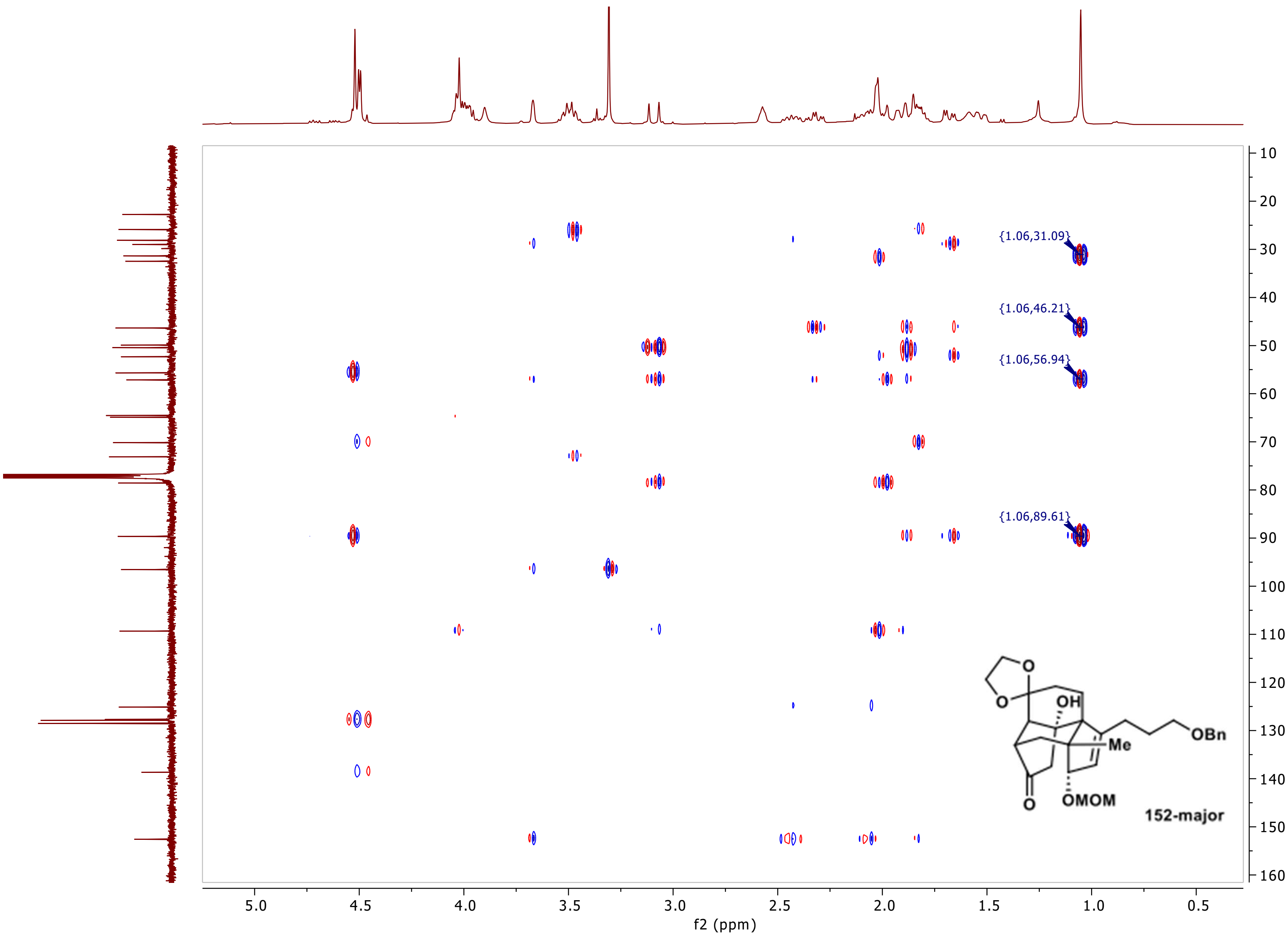

214.69
152.59
138.66
128.52
127.87
127.69
125.13
109.34
96.54
89.64
78.57
73.12
70.16
64.90
64.53
57.13
55.68
52.32
50.44
49.91
46.35
32.48
31.36
29.00
28.13
25.88
22.75
O
O
OH
Me
OBn
O
OMOM
152-major
2500
2000
1500
1000
500
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
O
OH
Me
OBn
O
OMOM
{1.06,28.99}
{2.58,52.20}
f2 (ppm)
f1 (ppm)
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
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

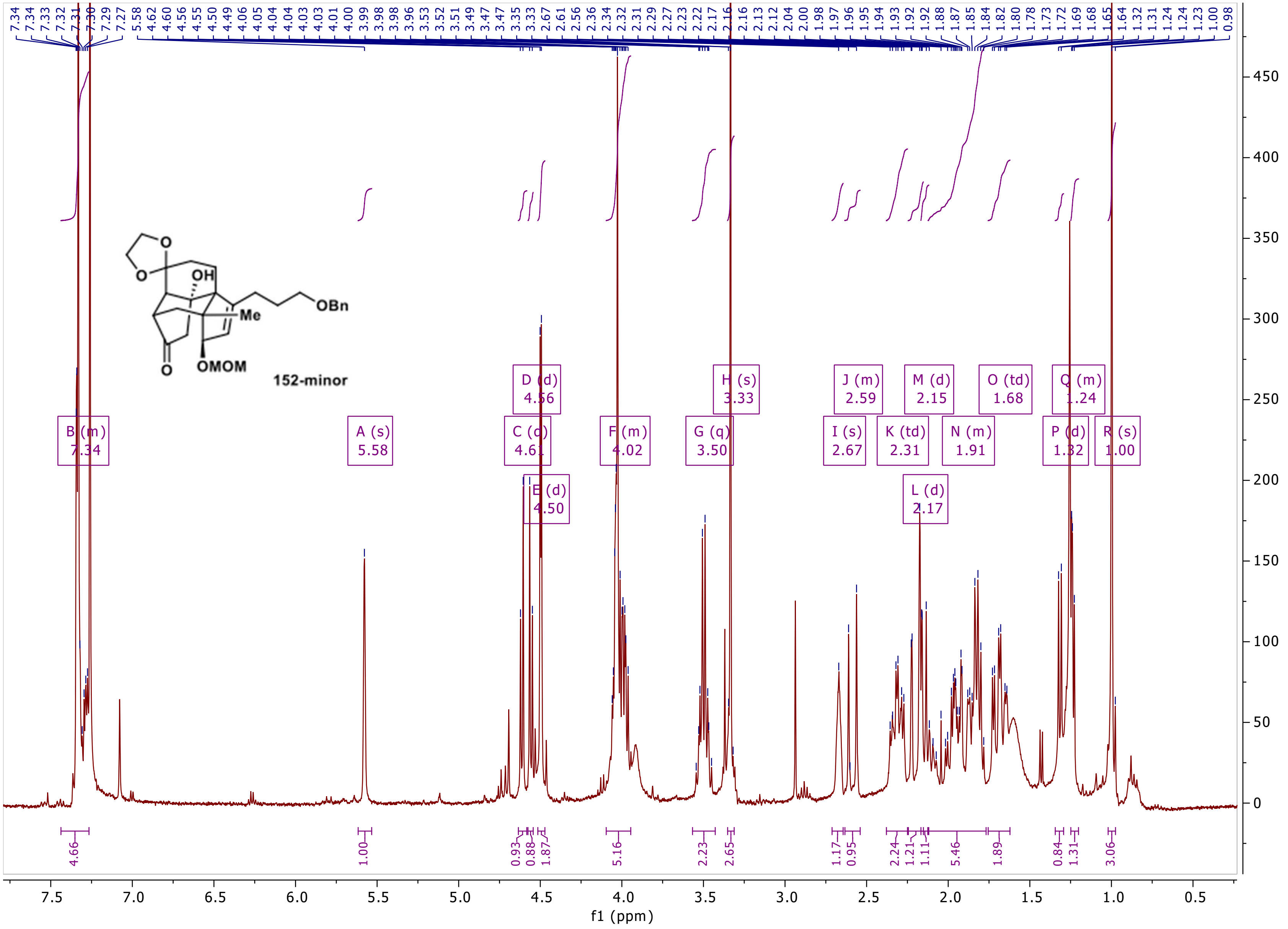
152-major


OH
Me
OBn
O
O
O
OMOM
f2 (ppm)
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)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

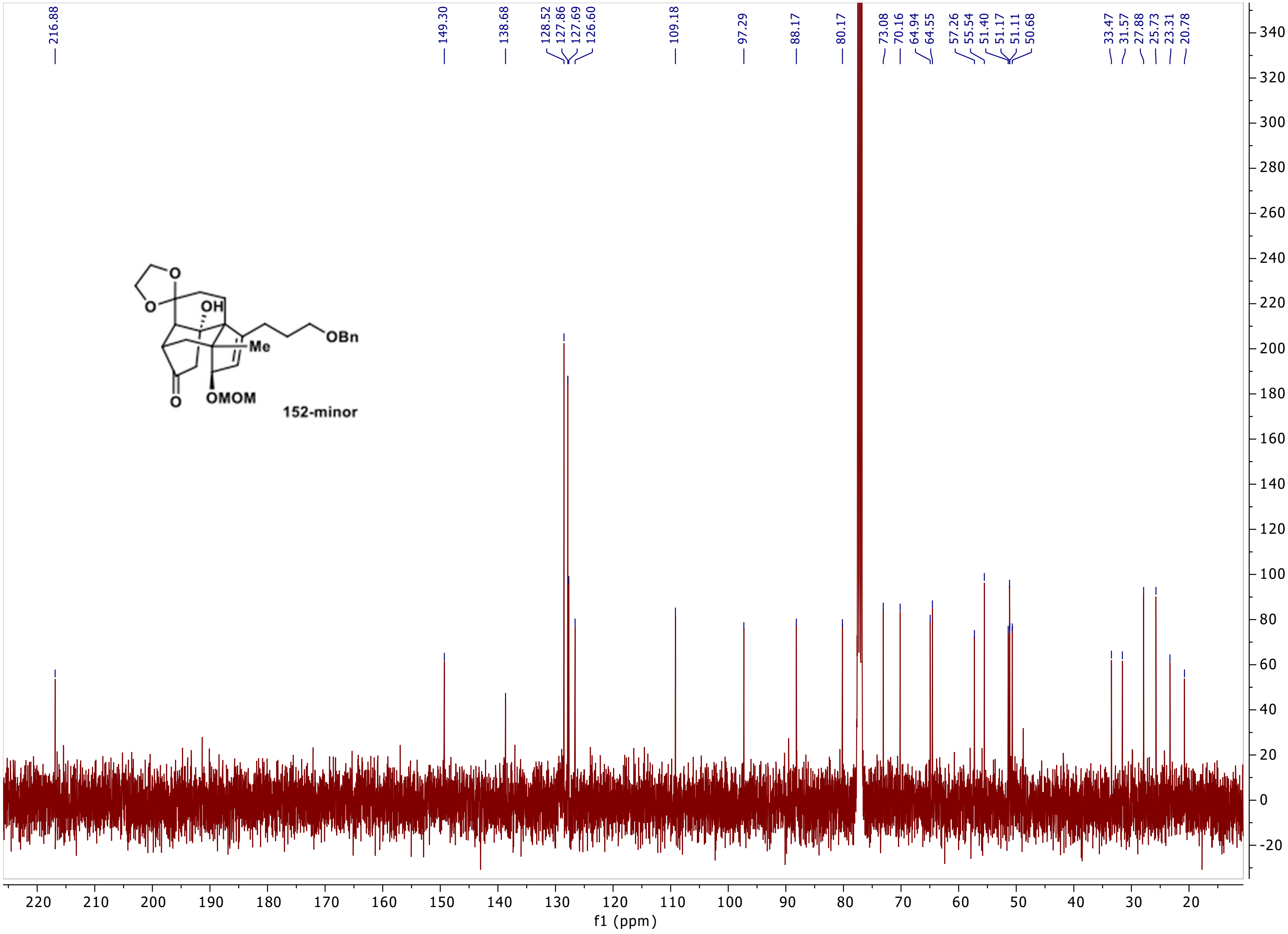
152-major

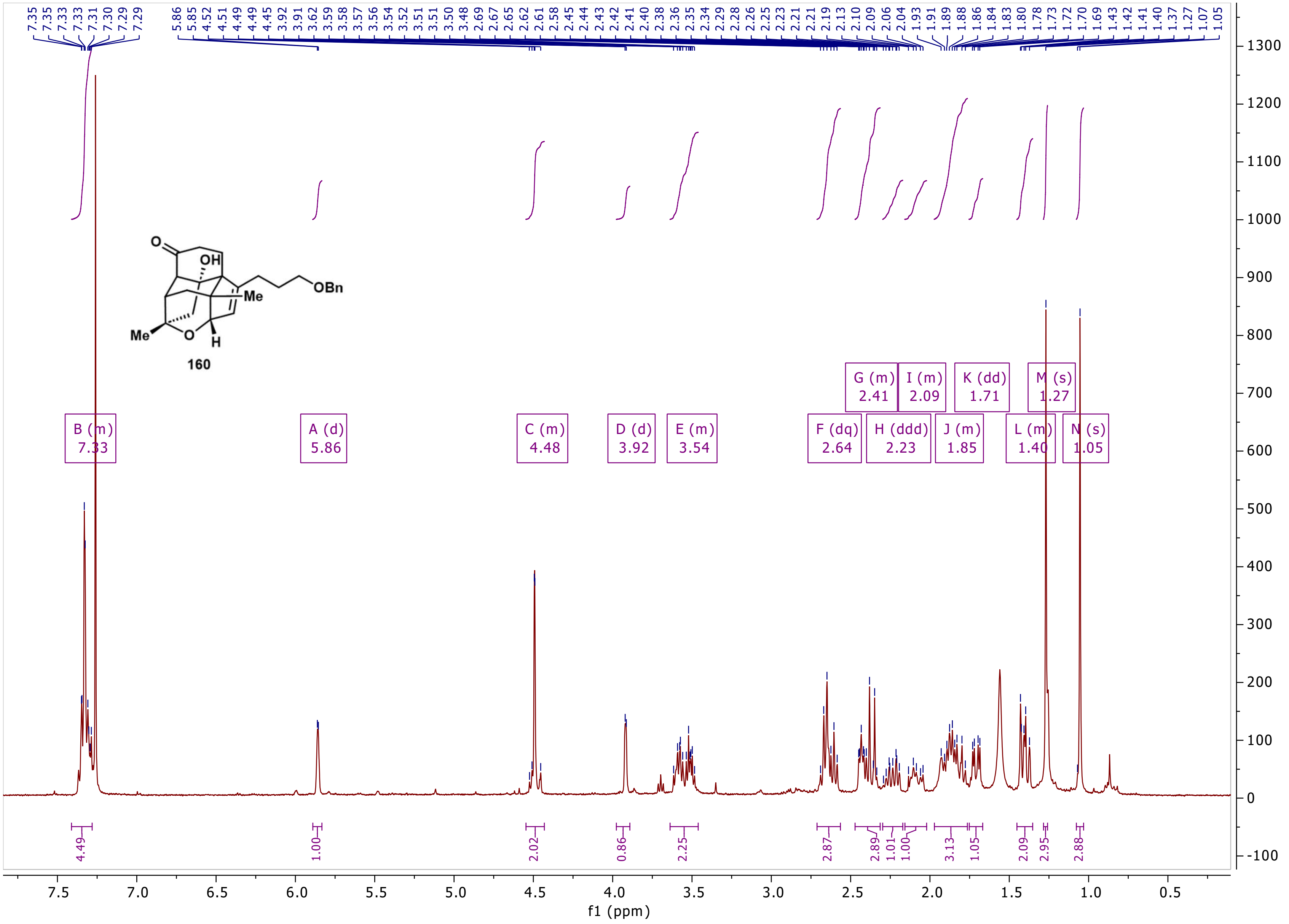


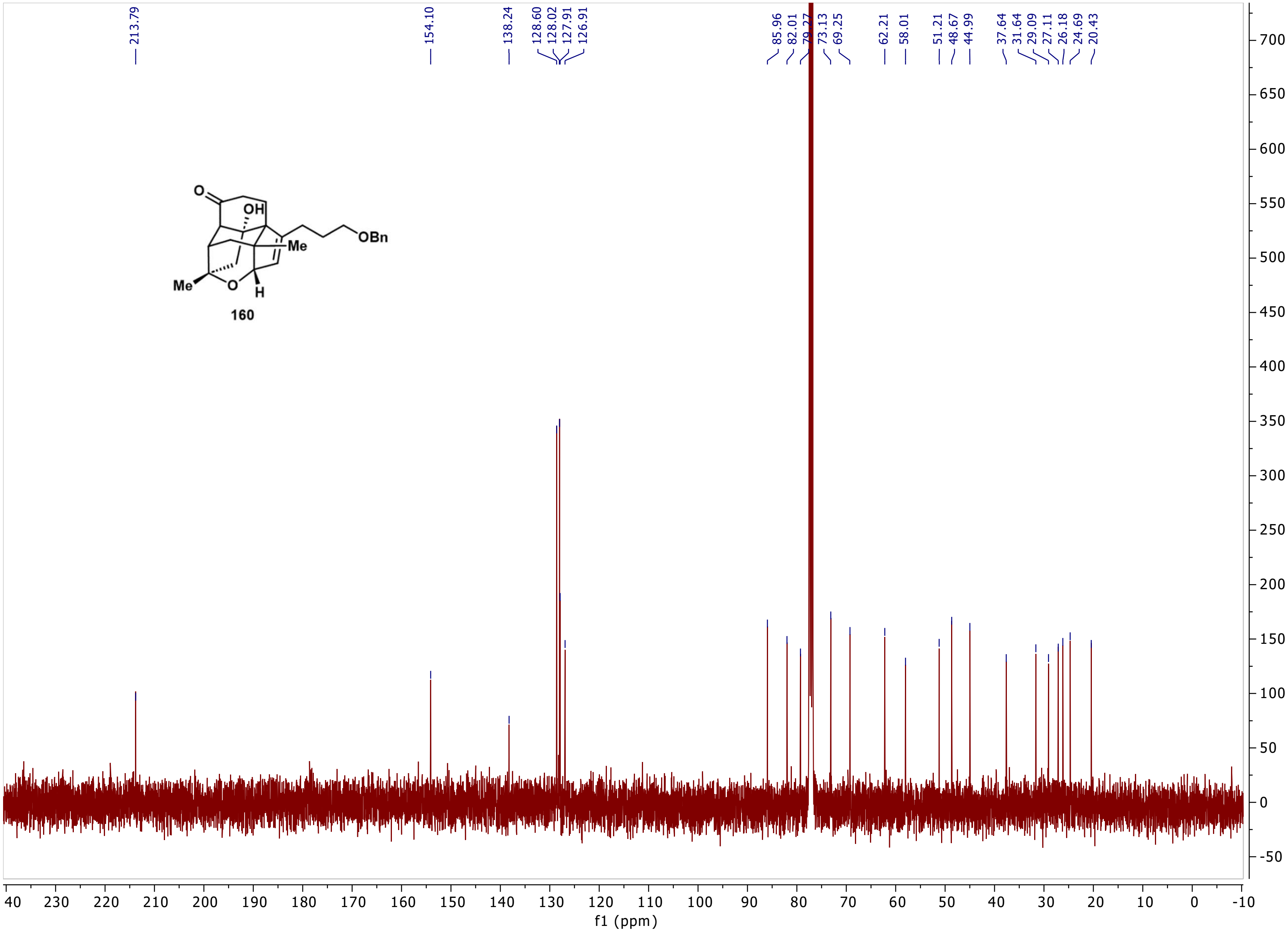
{1.06,31.09}
{1.06,46.21}
{1.06,56.94}
{1.06,89.61}
O
O
OH
Me
OBn
O
OMOM
152-major
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
f1 (ppm)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

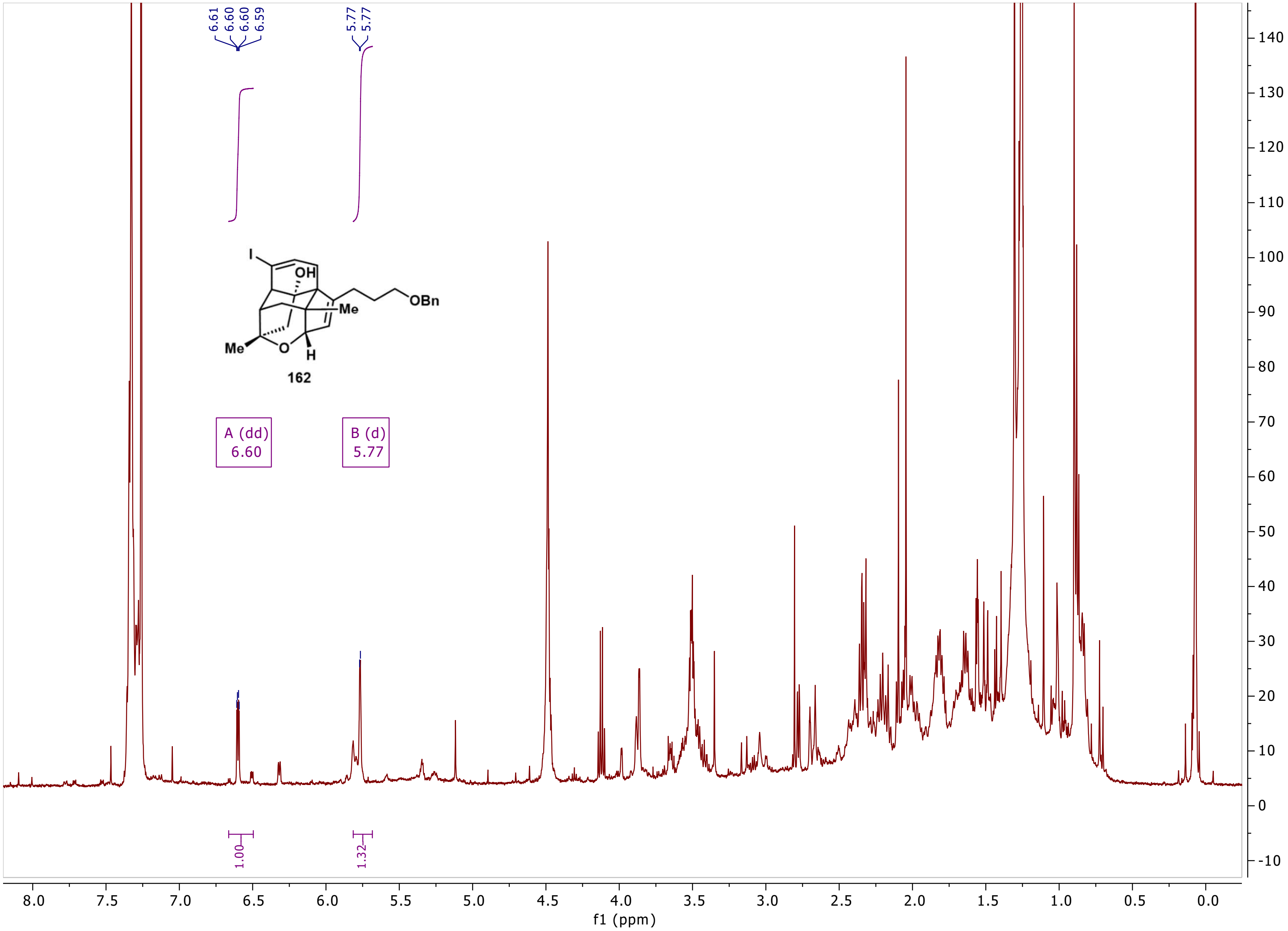

7.34 7.34 7.33 7.32 7.31 7.30 7.29 7.27 5.58 4.62 4.60 4.56 4.55 4.50 4.49 4.06 4.05 4.04 4.04 4.03 4.03 4.01 4.00 3.99 3.98 3.98 3.96 3.53 3.52 3.51 3.49 3.47 3.35 3.33 2.67 2.61 2.56 2.36 2.34 2.32 2.31 2.29 2.27 2.23 2.22 2.17 2.16 2.16 2.13 2.12 2.04 2.00 1.98 1.97 1.96 1.95 1.94 1.93 1.92 1.92 1.88 1.87 1.85 1.84 1.82 1.80 1.78 1.73 1.72 1.69 1.68 1.65 1.64 1.32 1.31 1.24 1.24 1.23 1.00 0.98
O
O
OH
Me
OBn
O
OMOM
B (m) 7.34
A (s) 5.58
D (d) 4.56
C (d) 4.61
E (d) 4.50
F (m) 4.02
G (q) 3.50
H (s) 3.33
J (m) 2.59
I (s) 2.67
K (td) 2.31
M (d) 2.15
L (d) 2.17
N (m) 1.91
O (td) 1.68
P (d) 1.32
Q (m) 1.24
R (s) 1.00
4.66
1.00
0.93
0.88
1.87
5.16
2.23
2.65
1.17
0.95
2.24
1.21
1.11
5.46
1.89
0.84
1.31
3.06
450
400
350
300
250
200
150
100
50
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

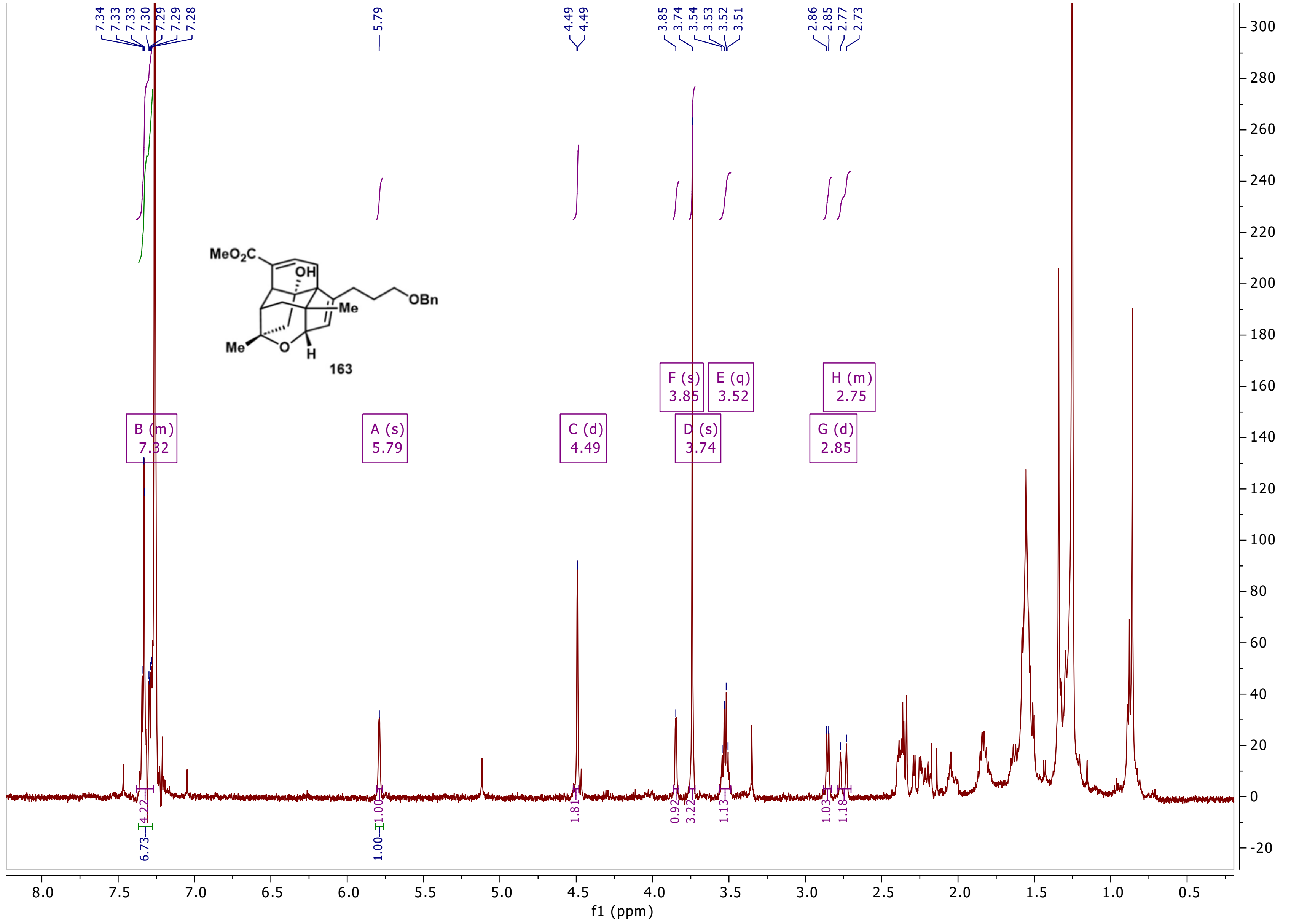
152-minor

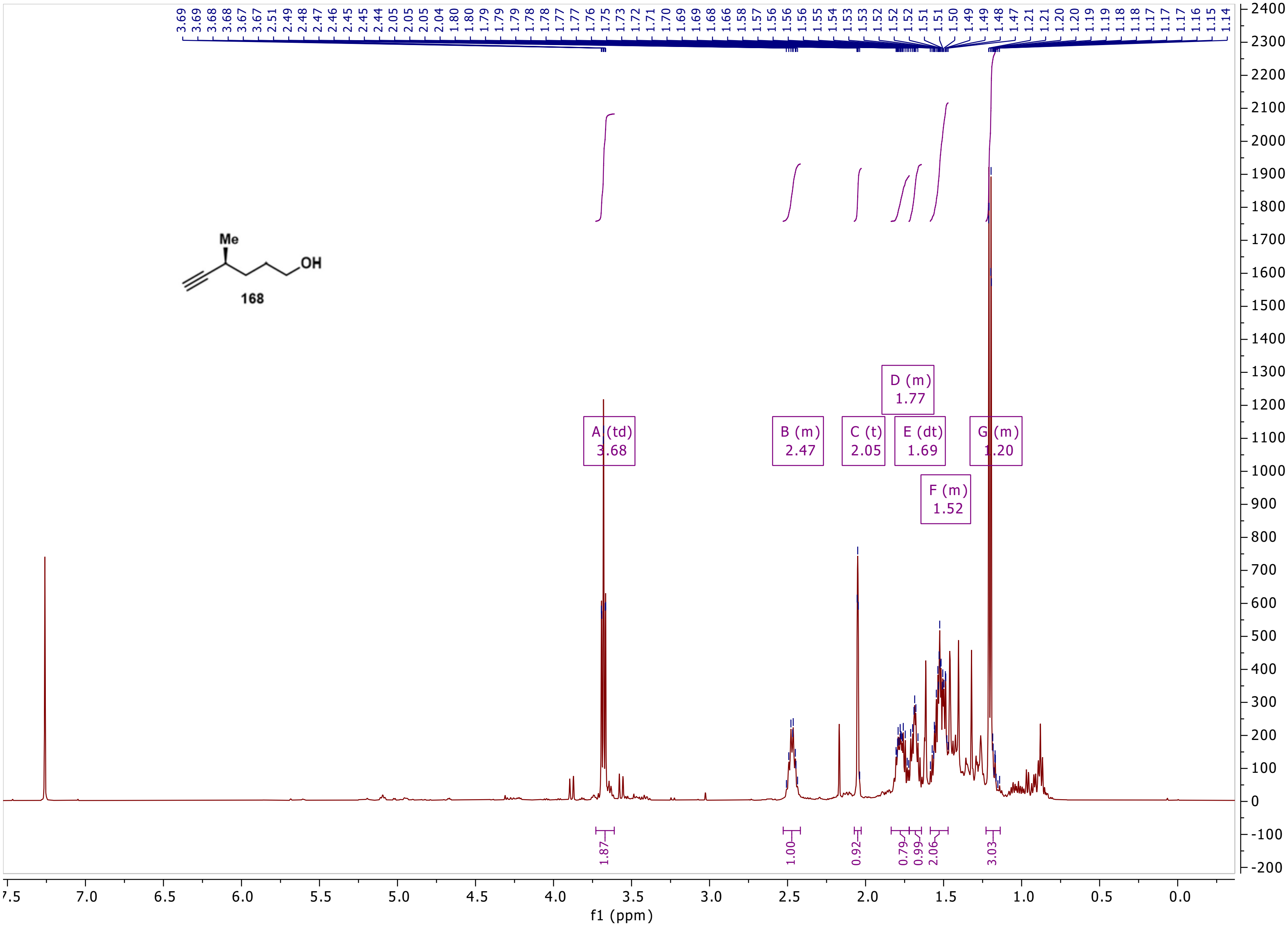

216.88
149.30
138.68
128.52
127.86
127.69
126.60
109.18
97.29
88.17
80.17
73.08
70.16
64.94
64.55
57.26
55.54
51.40
51.17
51.11
50.68
33.47
31.57
27.88
25.73
23.31
20.78
O
O
OH
Me
OBn
O
OMOM
152-minor
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

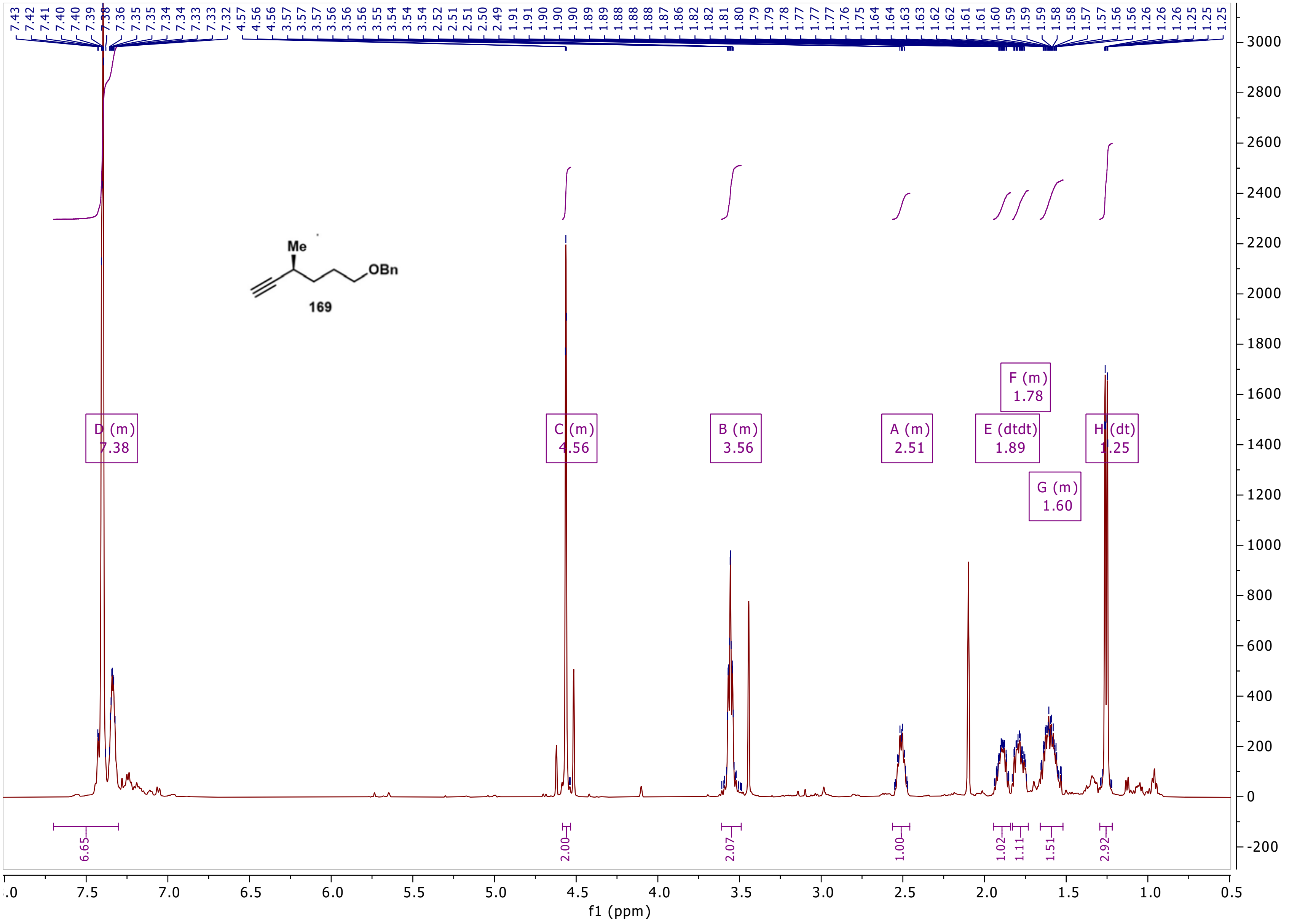

7.35 7.35 7.33 7.33 7.31 7.30 7.29 7.29
5.86 5.85 4.52 4.51 4.49 4.49 4.45 3.92 3.91 3.62 3.59 3.58 3.57 3.56 3.54 3.52 3.51 3.51 3.50 3.48 2.69 2.67 2.65 2.62 2.61 2.58 2.45 2.44 2.43 2.42 2.41 2.40 2.38 2.36 2.35 2.34 2.29 2.28 2.26 2.25 2.23 2.21 2.21 2.19 2.13 2.10 2.09 2.06 2.04 1.93 1.91 1.89 1.88 1.86 1.84 1.83 1.80 1.78 1.73 1.72 1.70 1.69 1.43 1.42 1.41 1.40 1.37 1.27 1.07 1.05
O
OH
OBn
Me
Me
O
H
160
B (m) 7.33
A (d) 5.86
C (m) 4.48
D (d) 3.92
E (m) 3.54
F (dq) 2.64
G (m) 2.41
H (ddd) 2.23
I (m) 2.09
J (m) 1.85
K (dd) 1.71
L (m) 1.40
M (s) 1.27
N (s) 1.05
4.49
1.00
2.02
0.86
2.25
2.87
2.89
1.01
1.00
3.13
1.05
2.09
2.95
2.88
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
f1 (ppm)
1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

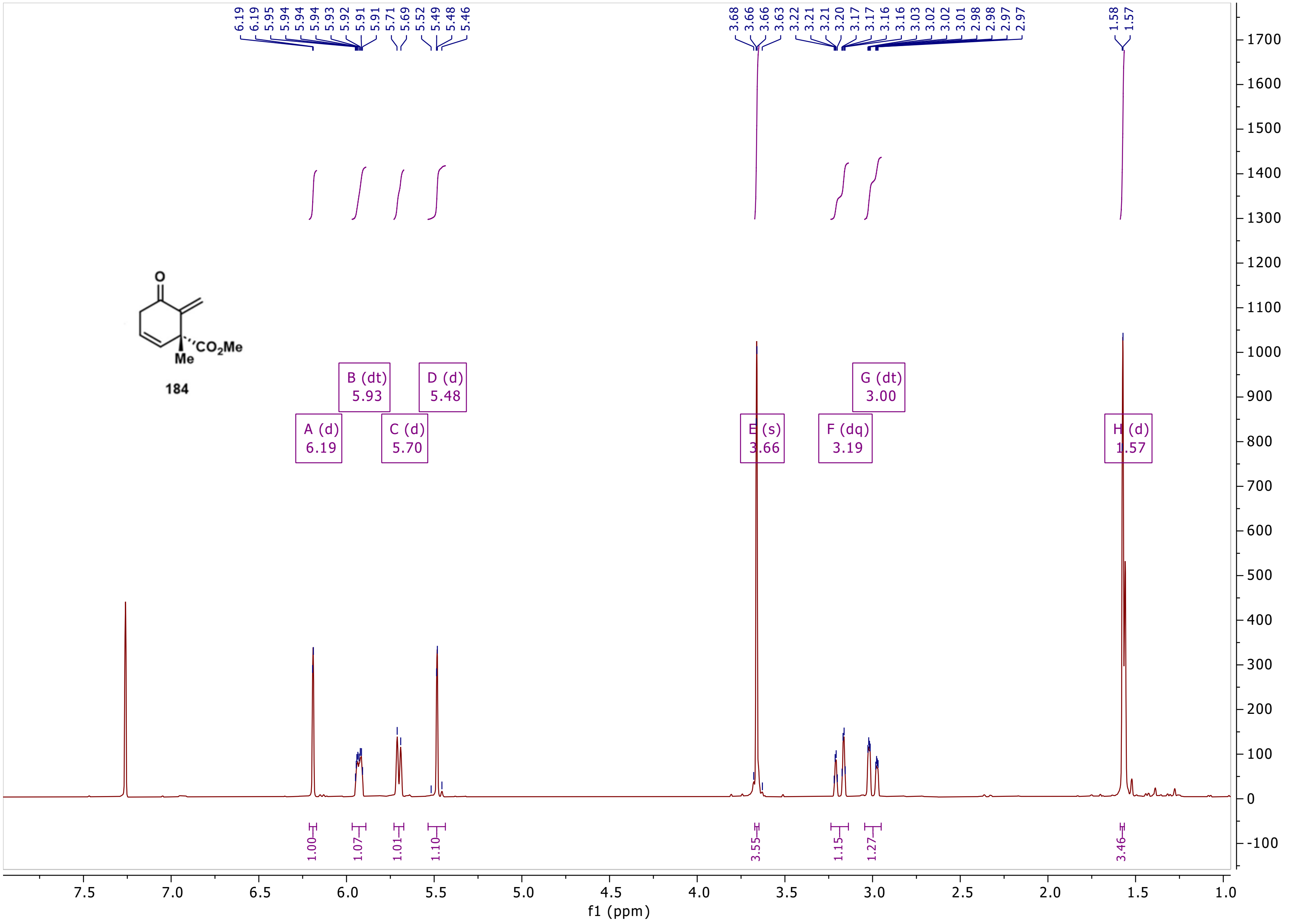

213.79
154.10
138.24
128.60
128.02
127.91
126.91
85.96
82.01
79.27
73.13
69.25
62.21
58.01
51.21
48.67
44.99
37.64
31.64
29.09
27.11
26.18
24.69
20.43
O
OH
Me
OBn
Me
O
H
160
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


6.61
6.60
6.60
6.59
5.77
5.77
I
OH
Me
OBn
Me
O
H
162
A (dd)
6.60
B (d)
5.77
1.00
1.32
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


7.34
7.33
7.33
7.30
7.29
7.29
7.28
5.79
4.49
4.49
3.85
3.74
3.54
3.53
3.52
3.51
2.86
2.85
2.77
2.73
MeO2C
OH
OBn
Me
Me
O
H
163
B (m) 7.32
A (s) 5.79
C (d) 4.49
F (s) 3.85
D (s) 3.74
E (q) 3.52
G (d) 2.85
H (m) 2.75
4.22
6.73
1.00
1.00
1.81
0.92
3.22
1.13
1.03
1.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20

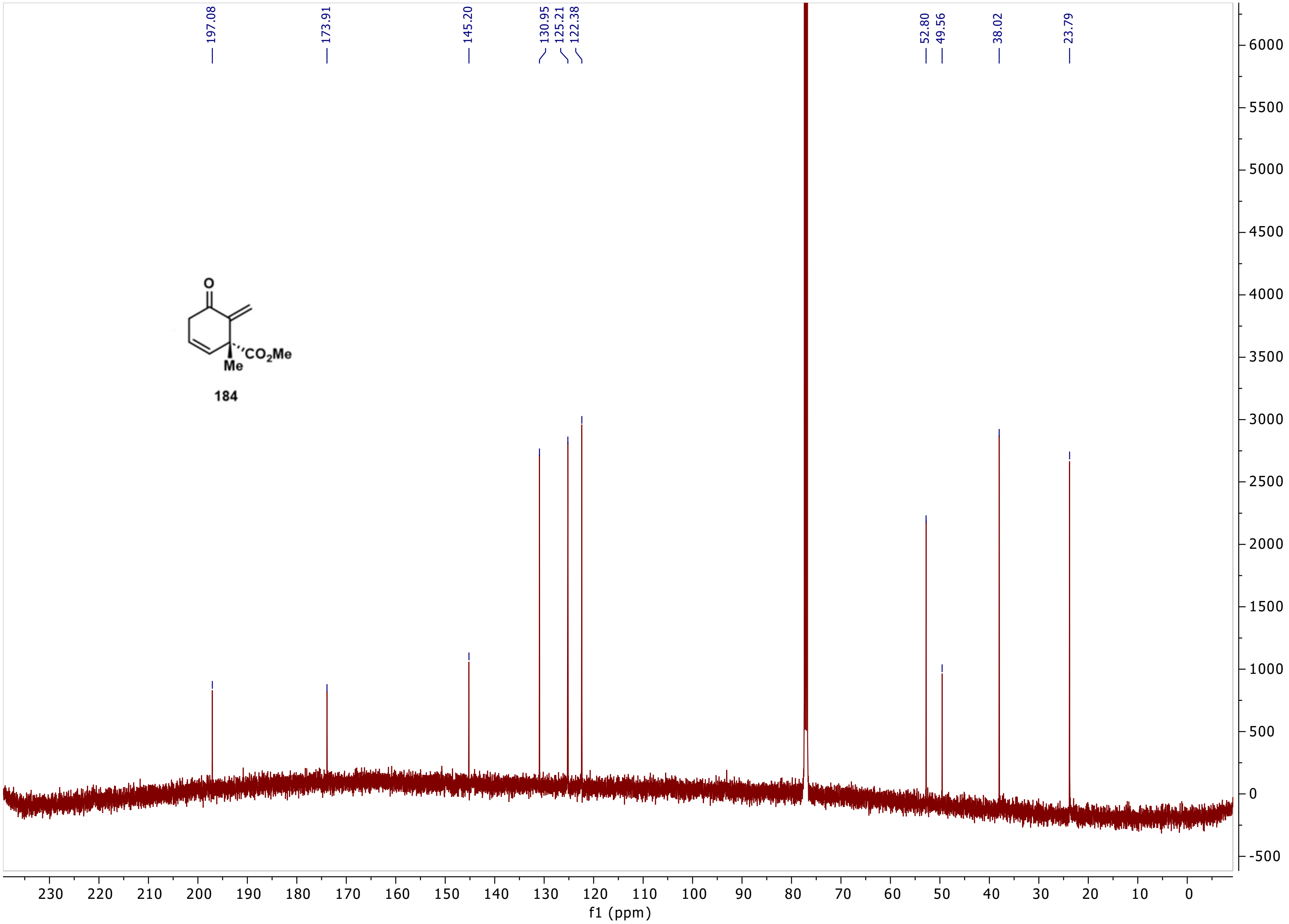

3.69 3.69 3.68 3.68 3.67 3.67 2.51 2.49 2.48 2.47 2.46 2.45 2.45 2.44 2.05 2.05 2.05 2.04 1.80 1.80 1.79 1.79 1.79 1.79 1.78 1.78 1.77 1.77 1.76 1.75 1.73 1.72 1.71 1.70 1.69 1.69 1.68 1.66 1.58 1.57 1.56 1.56 1.56 1.55 1.54 1.53 1.53 1.52 1.52 1.52 1.51 1.51 1.50 1.49 1.49 1.48 1.47 1.21 1.21 1.20 1.20 1.19 1.19 1.18 1.18 1.17 1.17 1.17 1.16 1.15 1.14
Me
OH
168
A (td)
3.68
B (m)
2.47
C (t)
2.05
D (m)
1.77
E (dt)
1.69
F (m)
1.52
G (m)
1.20
1.87
1.00
0.92
0.79
0.99
2.06
3.03
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)
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200

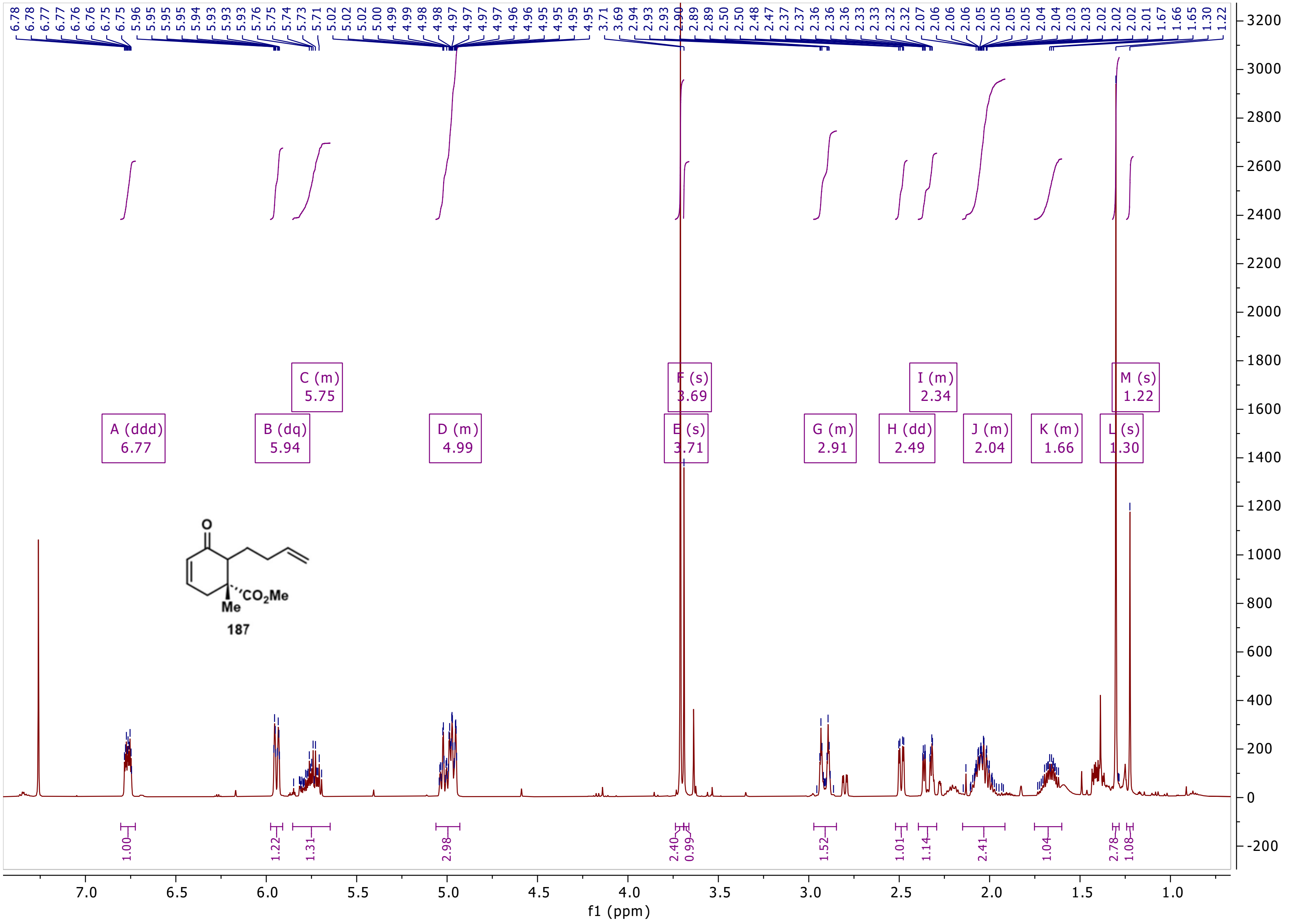

7.43 7.42 7.41 7.40 7.40 7.39 7.38 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 4.57 4.56 4.56 3.57 3.57 3.57 3.56 3.56 3.56 3.55 3.54 3.54 3.54 2.52 2.51 2.51 2.50 2.49 1.91 1.91 1.90 1.90 1.90 1.89 1.89 1.88 1.88 1.88 1.87 1.86 1.82 1.82 1.81 1.80 1.79 1.79 1.78 1.77 1.77 1.77 1.76 1.75 1.64 1.64 1.63 1.63 1.62 1.62 1.61 1.61 1.60 1.59 1.59 1.59 1.58 1.58 1.57 1.57 1.56 1.56 1.26 1.26 1.26 1.25 1.25 1.25
Me
OBn
169
D (m) 7.38
C (m) 4.56
B (m) 3.56
A (m) 2.51
E (dtdt) 1.89
F (m) 1.78
G (m) 1.60
H (dt) 1.25
6.65
2.00
2.07
1.00
1.02
1.11
1.51
2.92
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



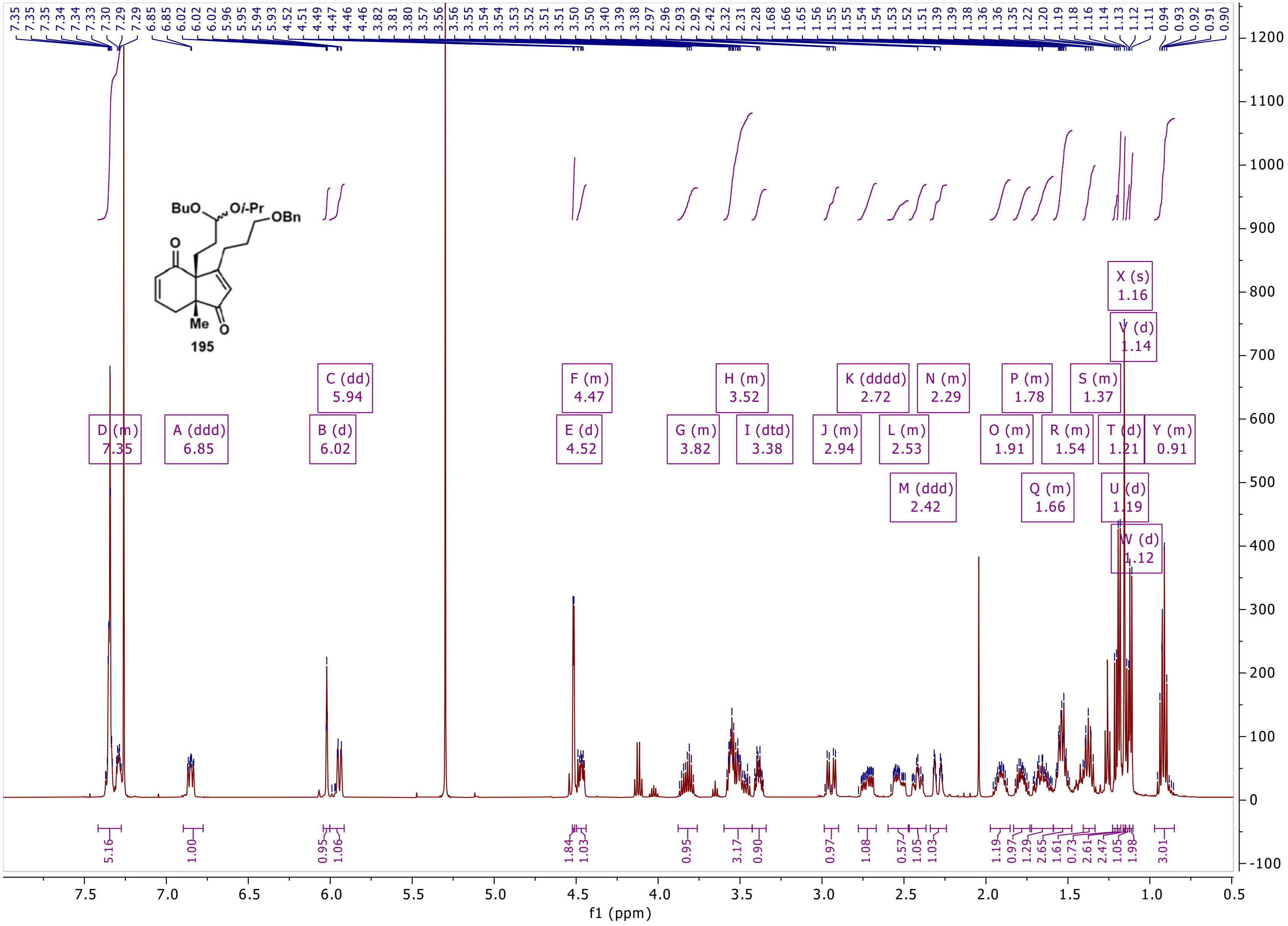
6.19
6.19
5.95
5.94
5.94
5.94
5.93
5.92
5.91
5.91
5.71
5.69
5.52
5.49
5.48
5.46
3.68
3.66
3.66
3.63
3.22
3.21
3.21
3.20
3.17
3.17
3.16
3.03
3.02
3.01
2.98
2.98
2.97
2.97
1.58
1.57
O
CO2Me
Me
A (d) 6.19
B (dt) 5.93
C (d) 5.70
D (d) 5.48
E (s) 3.66
F (dq) 3.19
G (dt) 3.00
H (d) 1.57
1.00
1.07
1.01
1.10
3.55
1.15
1.27
3.46
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)

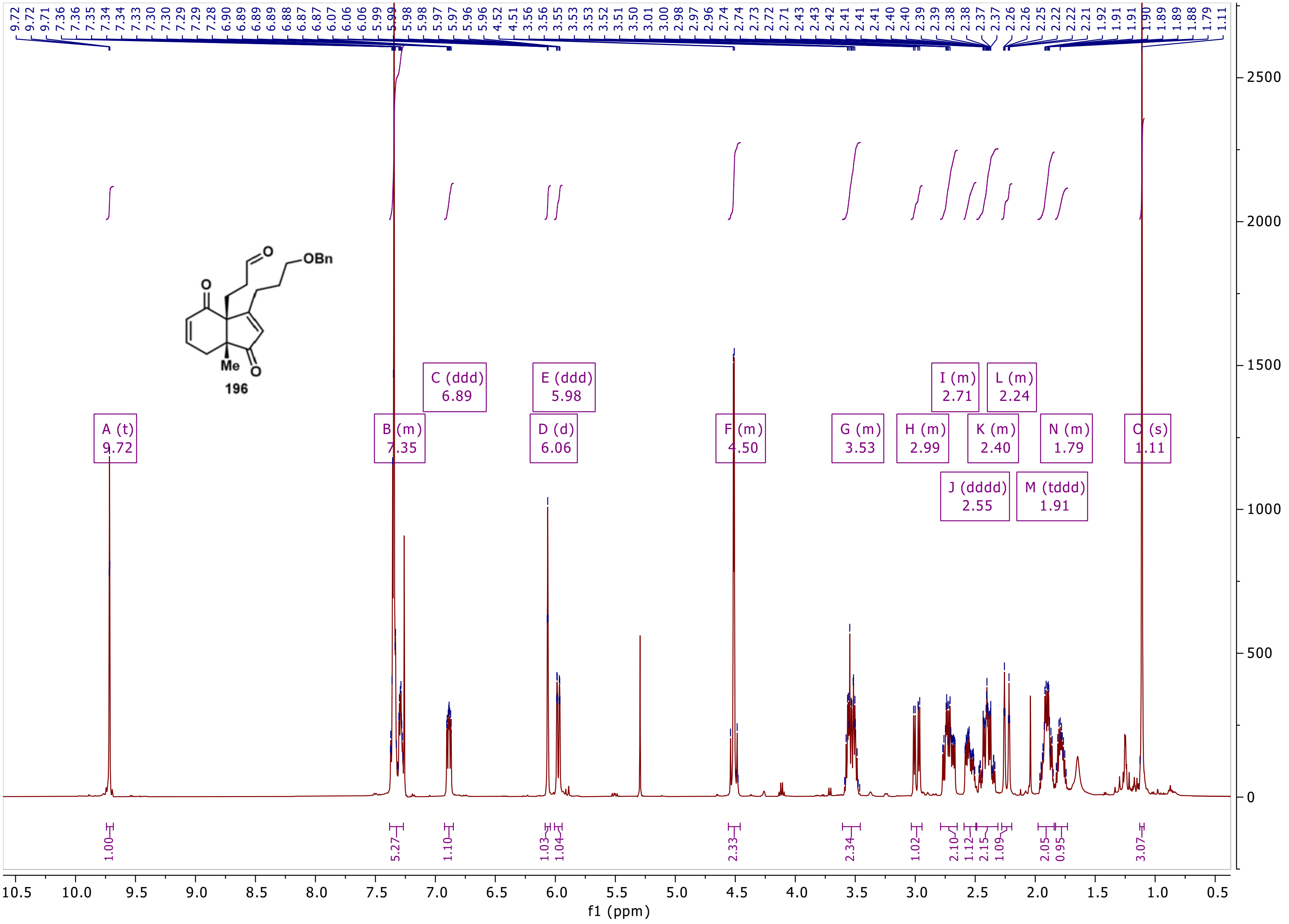
184

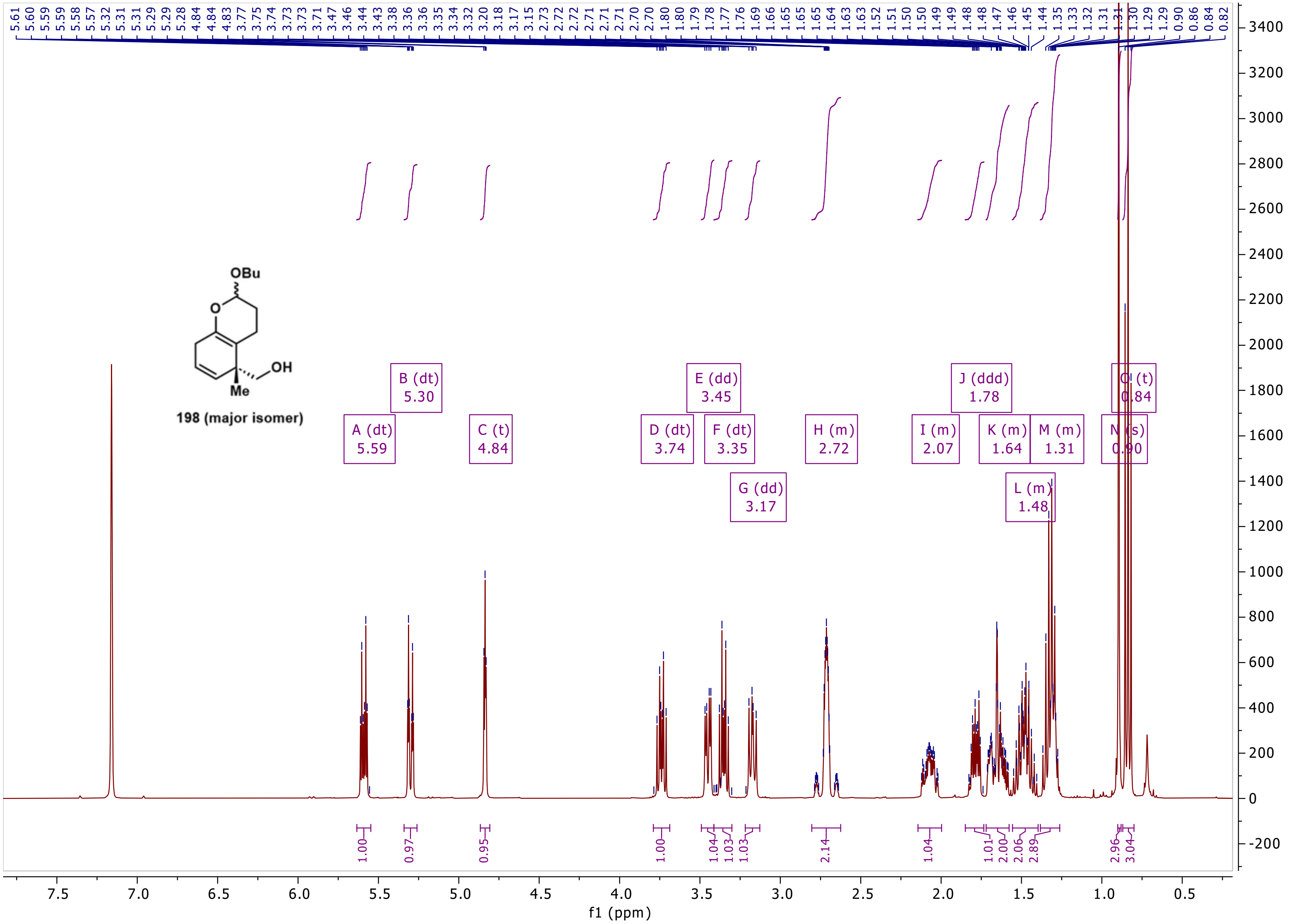

197.08
173.91
145.20
130.95
125.21
122.38
52.80
49.56
38.02
23.79
O
CO2Me
Me
184
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


6.78 6.78 6.77 6.77 6.76 6.76 6.75 6.75 5.96 5.95 5.95 5.94 5.93 5.93 5.93 5.76 5.75 5.74 5.73 5.71 5.02 5.02 5.00 4.99 4.99 4.98 4.98 4.97 4.97 4.97 4.97 4.96 4.95 4.95 4.95 3.71 3.69 2.94 2.93 2.93 2.90 2.89 2.89 2.50 2.50 2.48 2.47 2.37 2.37 2.36 2.36 2.36 2.33 2.33 2.32 2.32 2.07 2.06 2.06 2.06 2.05 2.05 2.05 2.05 2.04 2.04 2.03 2.03 2.02 2.02 2.02 2.02 2.01 1.67 1.66 1.65 1.30 1.22
A (ddd) 6.77
B (dq) 5.94
C (m) 5.75
D (m) 4.99
E (s) 3.71
F (s) 3.69
G (m) 2.91
H (dd) 2.49
I (m) 2.34
J (m) 2.04
K (m) 1.66
L (s) 1.30
M (s) 1.22
1.00
1.22
1.31
2.98
2.40
0.99
1.52
1.01
1.14
2.41
1.04
2.78
1.08
O
CO2Me
Me
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)
3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200

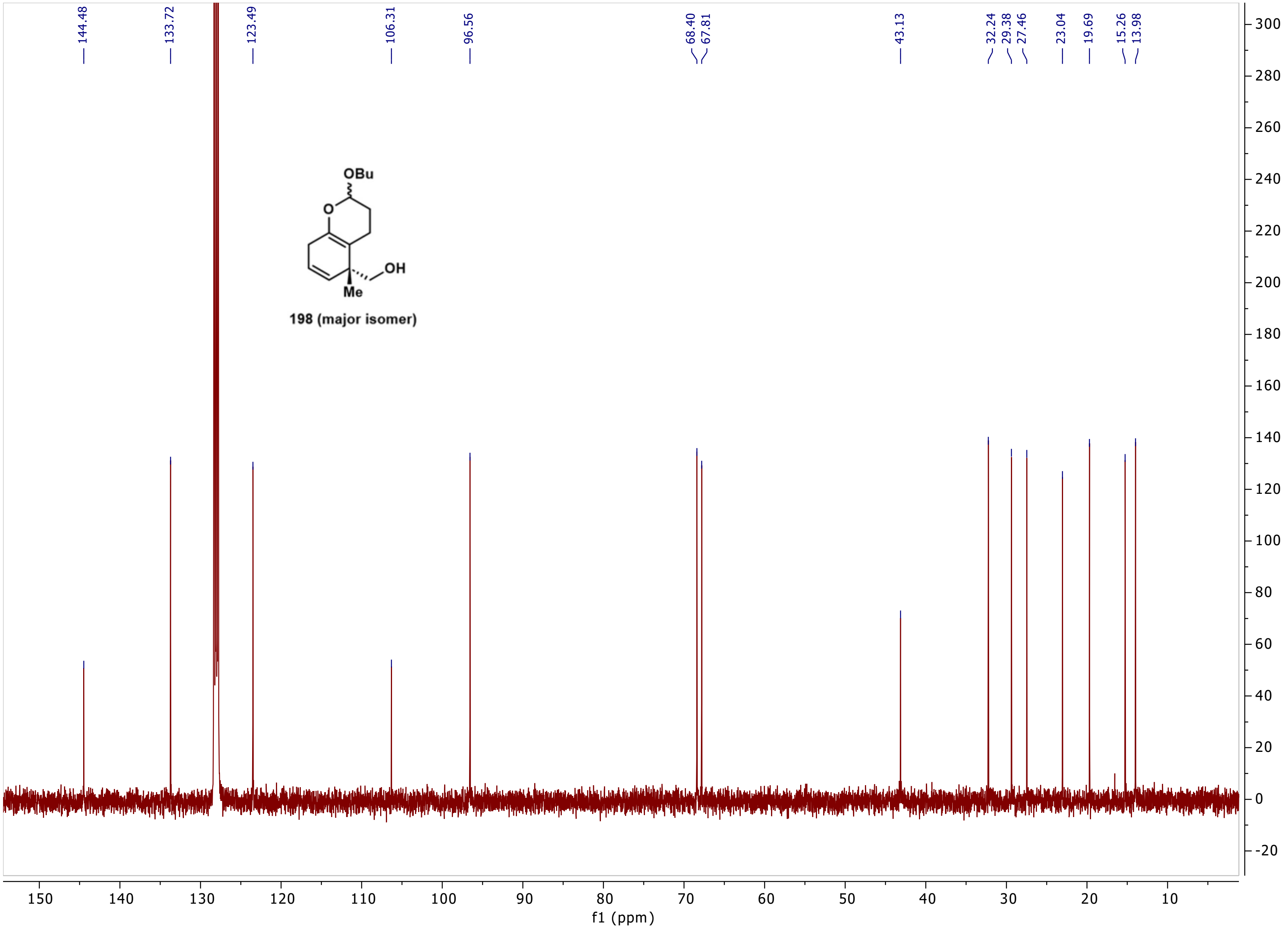
187

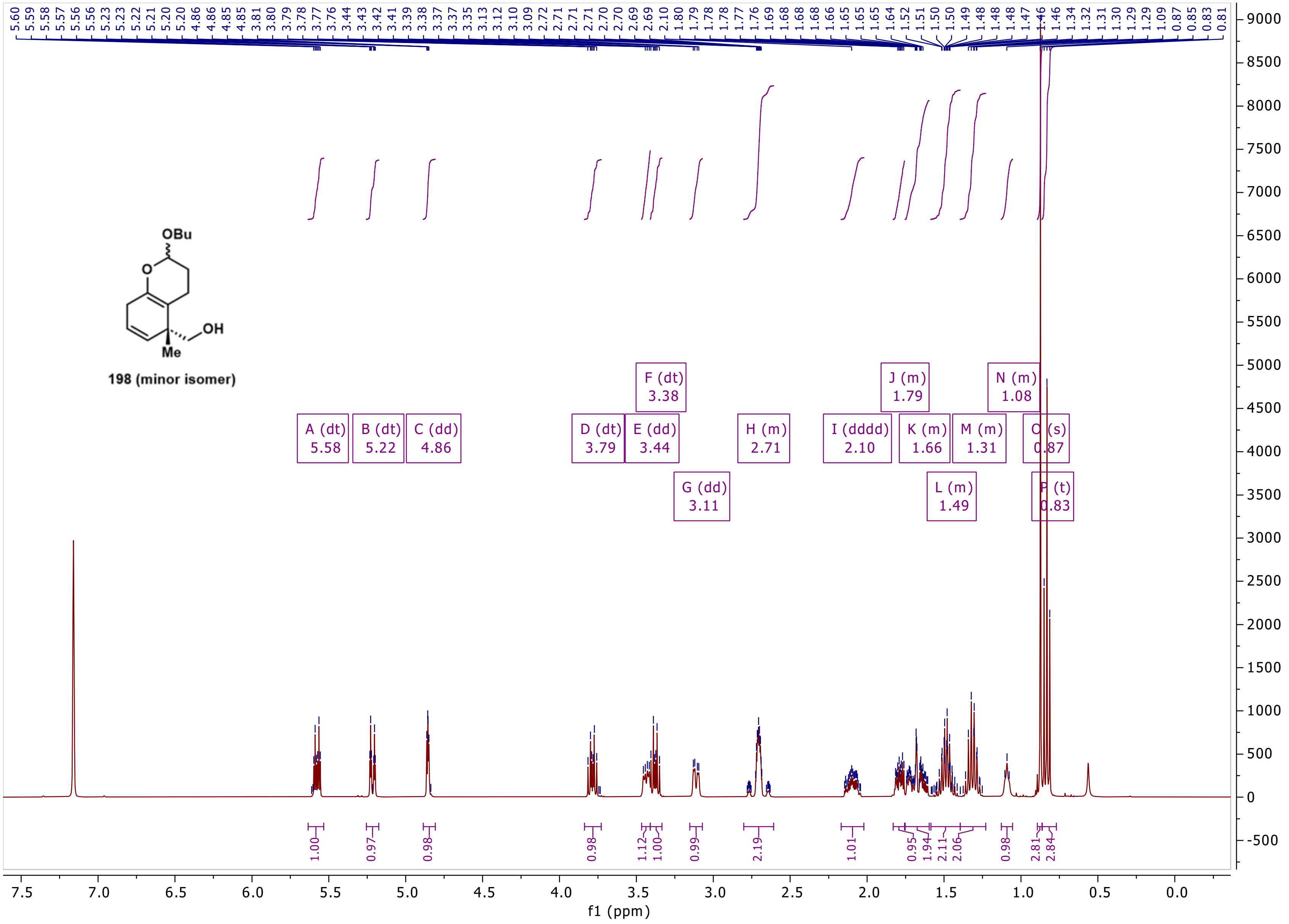

7.35 7.35 7.35 7.34 7.34 7.33 7.30 7.29 7.29 6.85 6.85 6.02 6.02 5.96 5.95 5.94 5.93 4.52 4.51 4.49 4.47 4.46 4.46 3.82 3.81 3.80 3.57 3.56 3.56 3.55 3.54 3.54 3.53 3.52 3.51 3.51 3.50 3.50 3.40 3.39 3.38 2.97 2.96 2.93 2.92 2.42 2.32 2.31 2.28 1.68 1.66 1.65 1.56 1.55 1.55 1.54 1.54 1.53 1.52 1.51 1.39 1.39 1.38 1.36 1.36 1.35 1.22 1.20 1.19 1.18 1.16 1.14 1.13 1.12 1.11 0.94 0.93 0.92 0.91 0.90
BuO
O*i*-Pr
OBn
O
Me
O
195
D (m) 7.35
A (ddd) 6.85
B (d) 6.02
C (dd) 5.94
E (d) 4.52
F (m) 4.47
G (m) 3.82
H (m) 3.52
I (dtd) 3.38
J (m) 2.94
K (dddd) 2.72
L (m) 2.53
M (ddd) 2.42
N (m) 2.29
O (m) 1.91
P (m) 1.78
Q (m) 1.66
R (m) 1.54
S (m) 1.37
T (d) 1.21
U (d) 1.19
X (s) 1.16
V (d) 1.14
W (d) 1.12
Y (m) 0.91
5.16
1.00
0.95
1.06
1.84
1.03
0.95
3.17
0.90
0.97
1.08
0.57
1.05
1.03
1.19
0.97
1.29
2.65
1.61
0.73
2.61
2.47
1.05
1.98
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
f1 (ppm)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

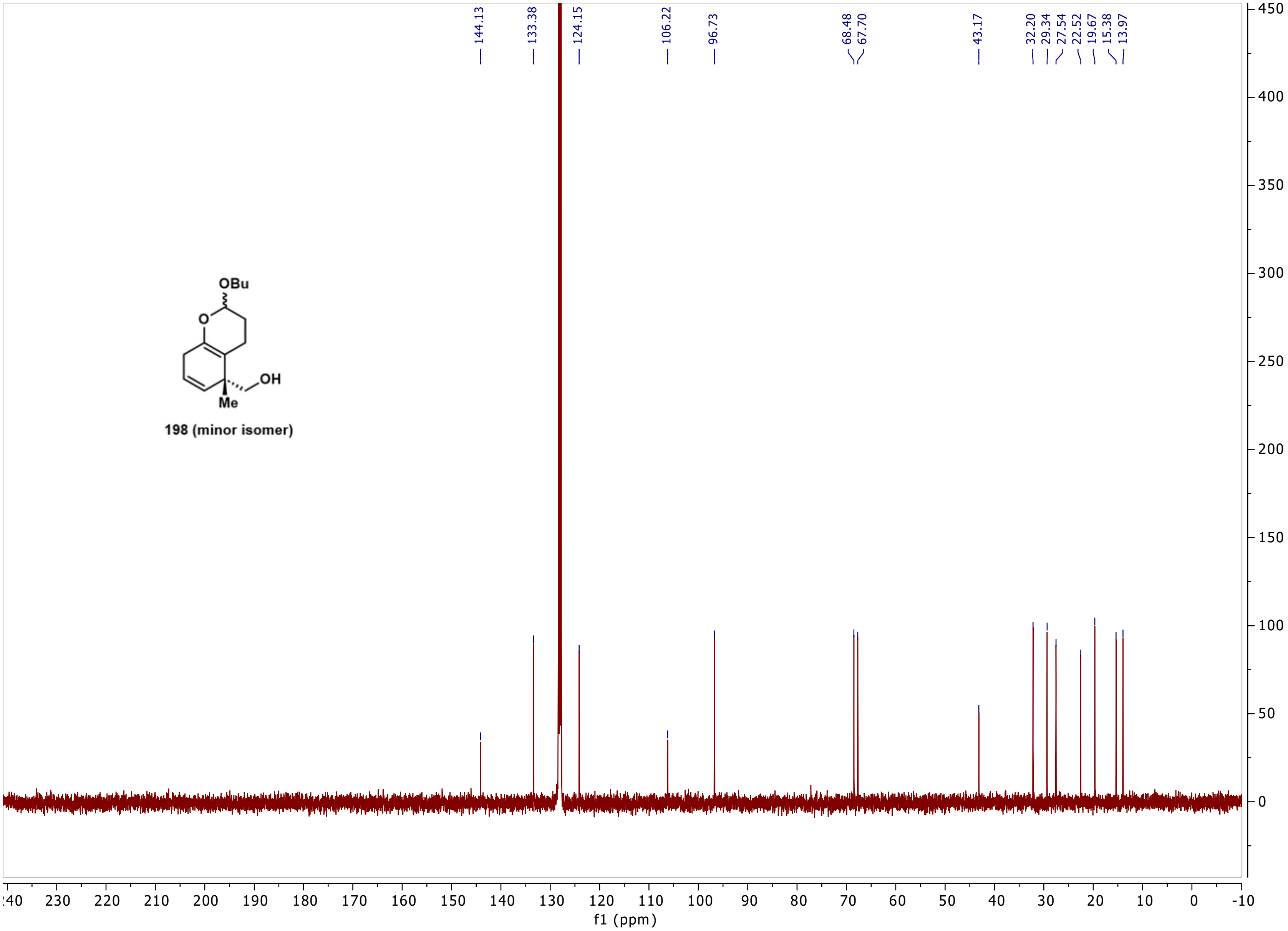

9.72 9.72 9.71 7.36 7.35 7.34 7.34 7.33 7.30 7.30 7.29 7.29 7.28 6.90 6.89 6.89 6.89 6.88 6.87 6.87 6.07 6.06 5.99 5.99 5.98 5.98 5.97 5.97 5.96 5.96 4.52 4.51 3.56 3.56 3.55 3.53 3.53 3.52 3.51 3.50 3.01 3.00 2.98 2.97 2.96 2.74 2.74 2.73 2.72 2.71 2.43 2.43 2.42 2.41 2.41 2.41 2.40 2.39 2.39 2.38 2.38 2.37 2.37 2.26 2.26 2.25 2.22 2.22 2.21 1.92 1.91 1.91 1.90 1.89 1.89 1.88 1.79 1.11
OBn
O
O
O
Me
196
A (t) 9.72
B (m) 7.35
C (ddd) 6.89
D (d) 6.06
E (ddd) 5.98
F (m) 4.50
G (m) 3.53
H (m) 2.99
I (m) 2.71
J (dddd) 2.55
K (m) 2.40
L (m) 2.24
M (tddd) 1.91
N (m) 1.79
O (s) 1.11
1.00
5.27
1.10
1.03
1.04
2.33
2.34
1.02
2.10
1.12
2.15
1.09
2.05
0.95
3.07
2500
2000
1500
1000
500
0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



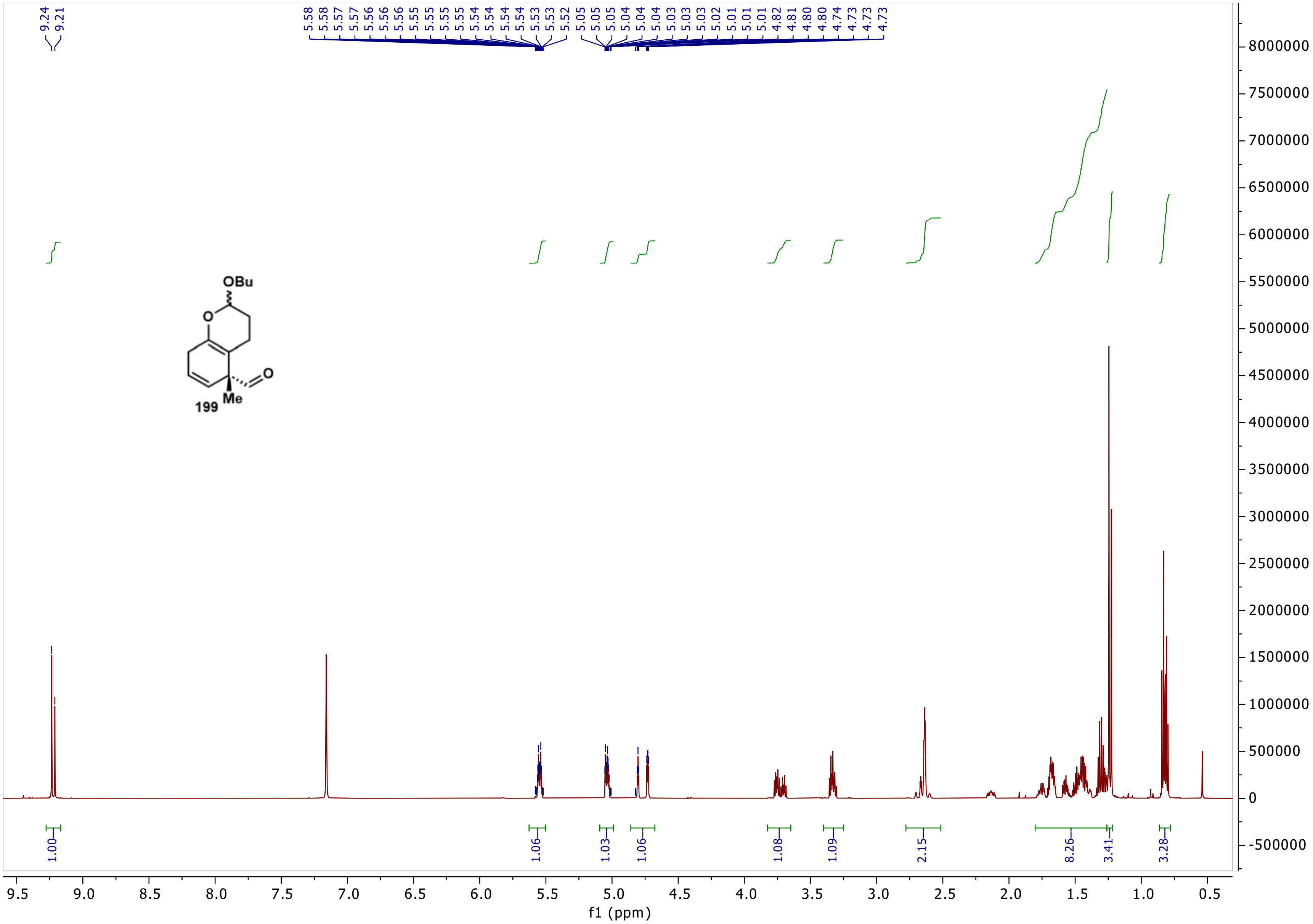
198 (major isomer)

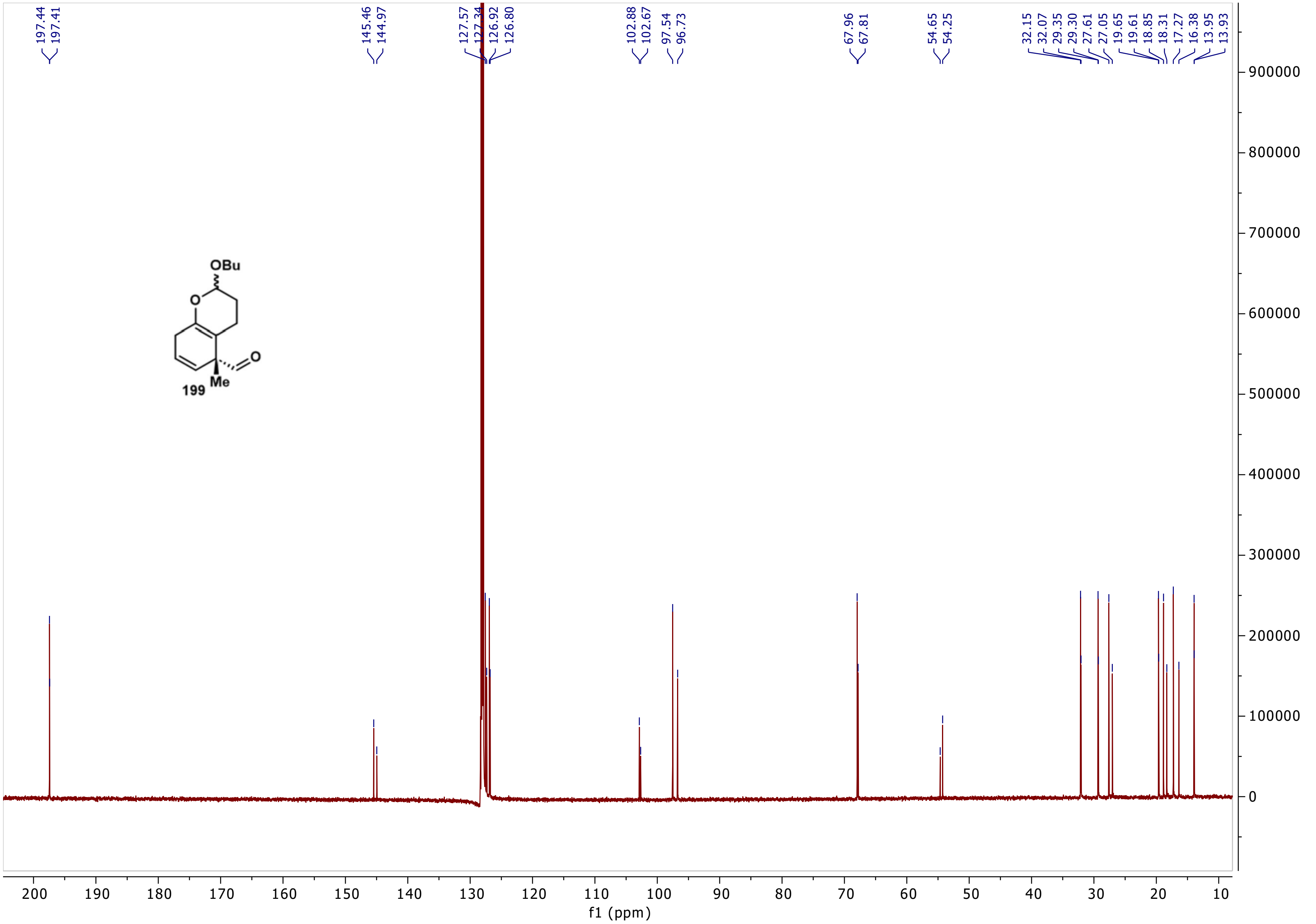

198 (major isomer)

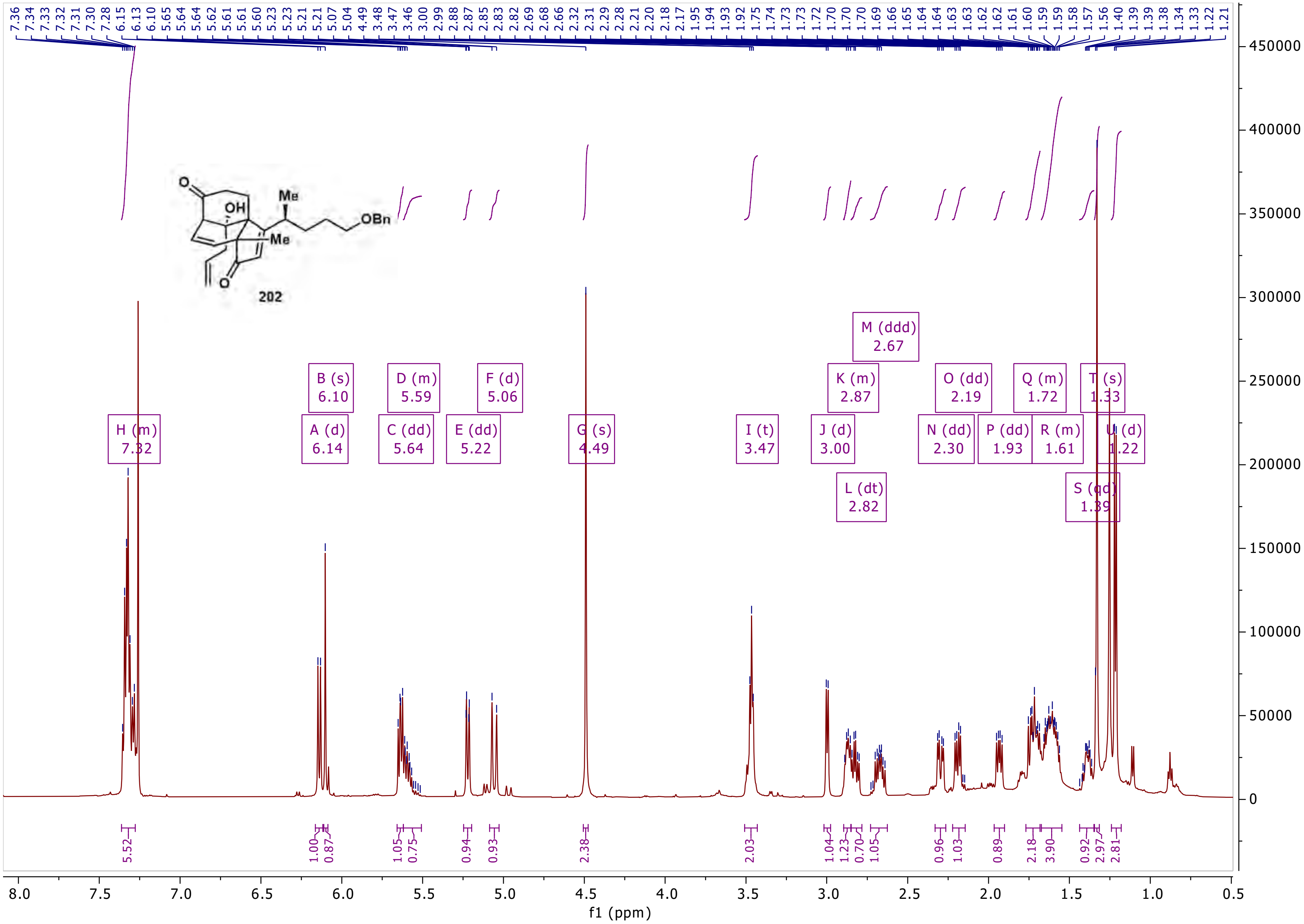

198 (minor isomer)

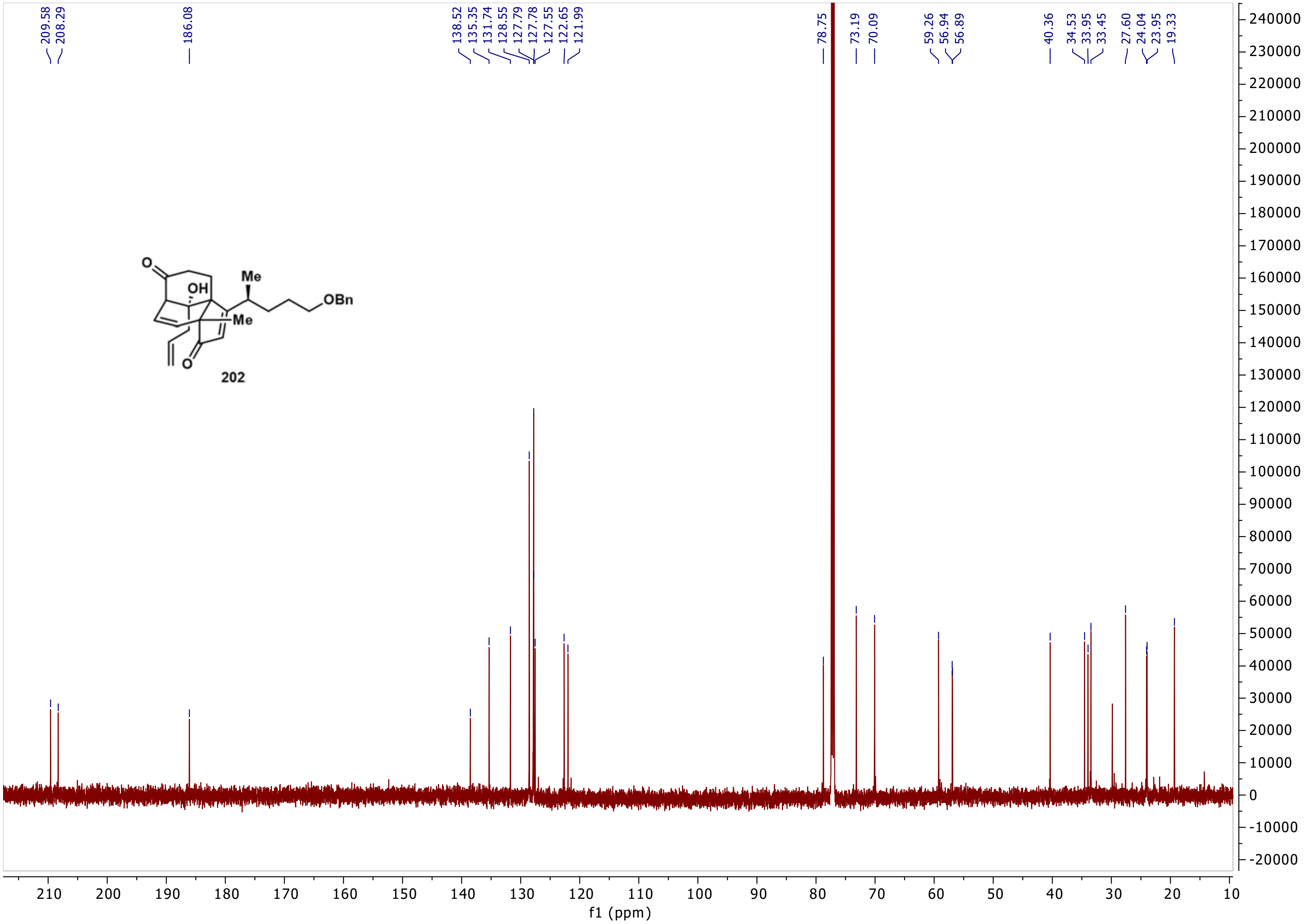


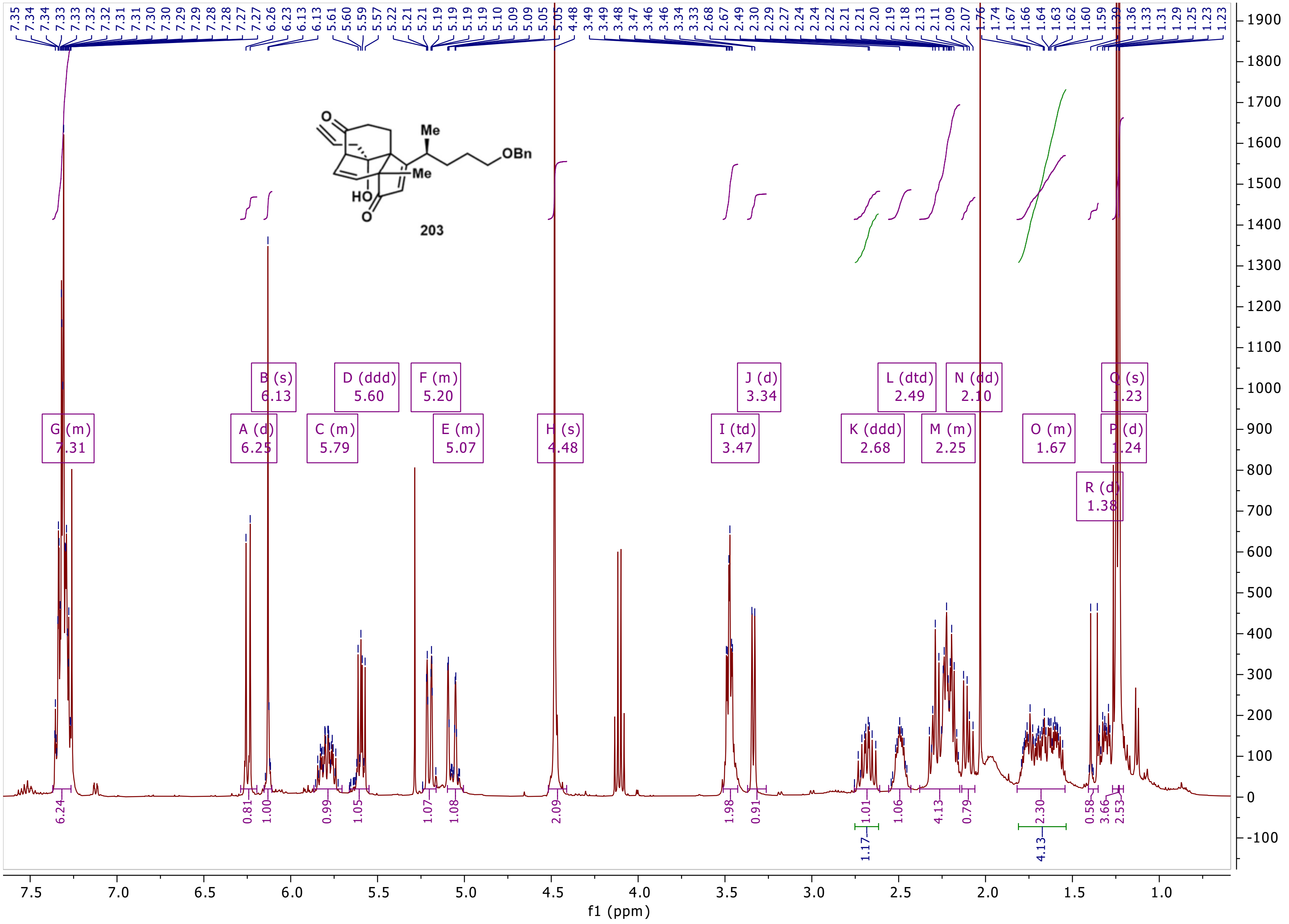
198 (minor isomer)

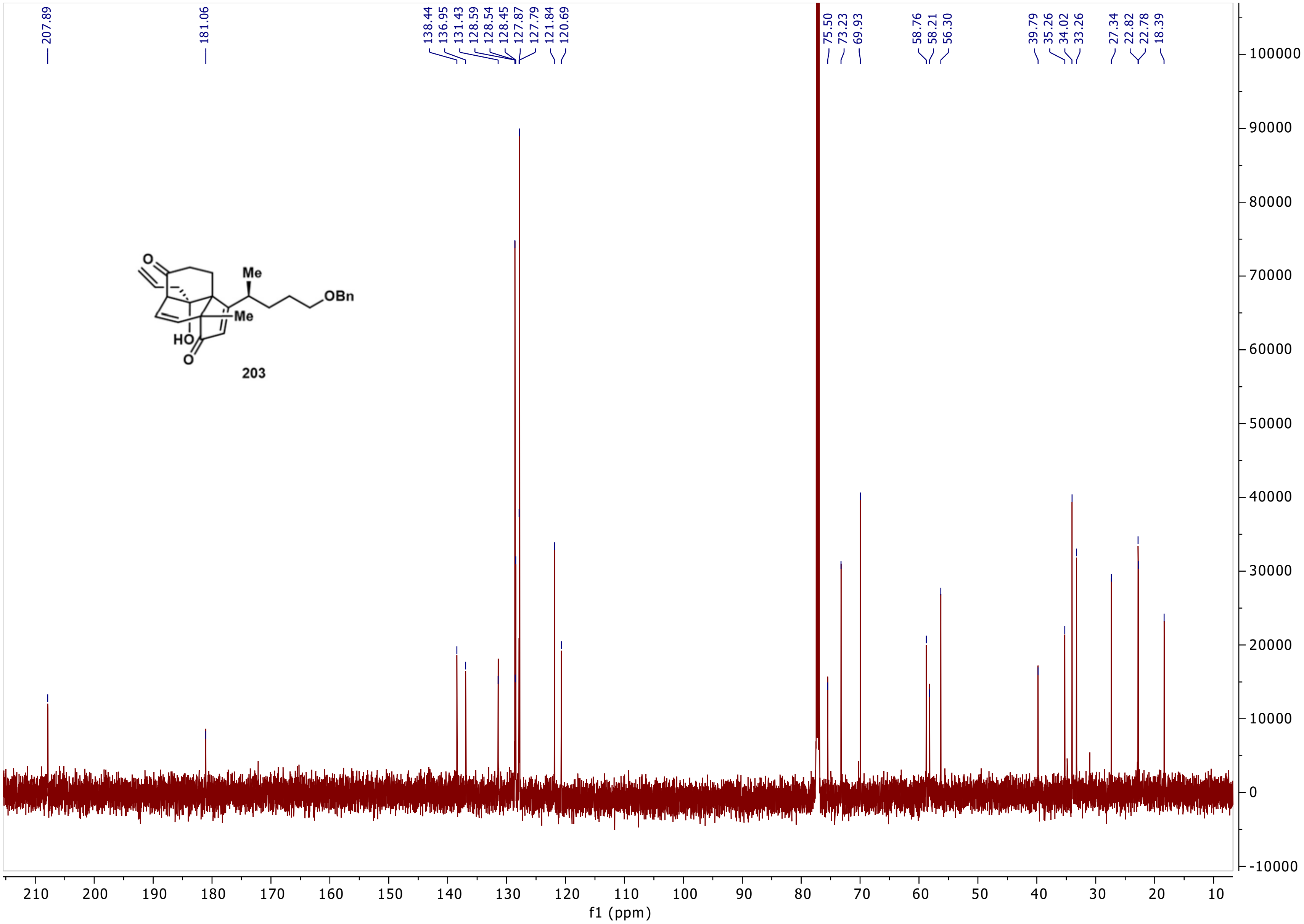

9.24
9.21
5.58
5.58
5.57
5.57
5.56
5.56
5.56
5.55
5.55
5.55
5.55
5.54
5.54
5.54
5.54
5.53
5.53
5.52
5.05
5.05
5.05
5.04
5.04
5.04
5.03
5.03
5.03
5.02
5.01
5.01
5.01
4.82
4.81
4.80
4.80
4.74
4.73
4.73
4.73
OBu
O
O
Me
199
1.00
1.06
1.03
1.06
1.08
1.09
2.15
8.26
3.41
3.28
8000000
7500000
7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

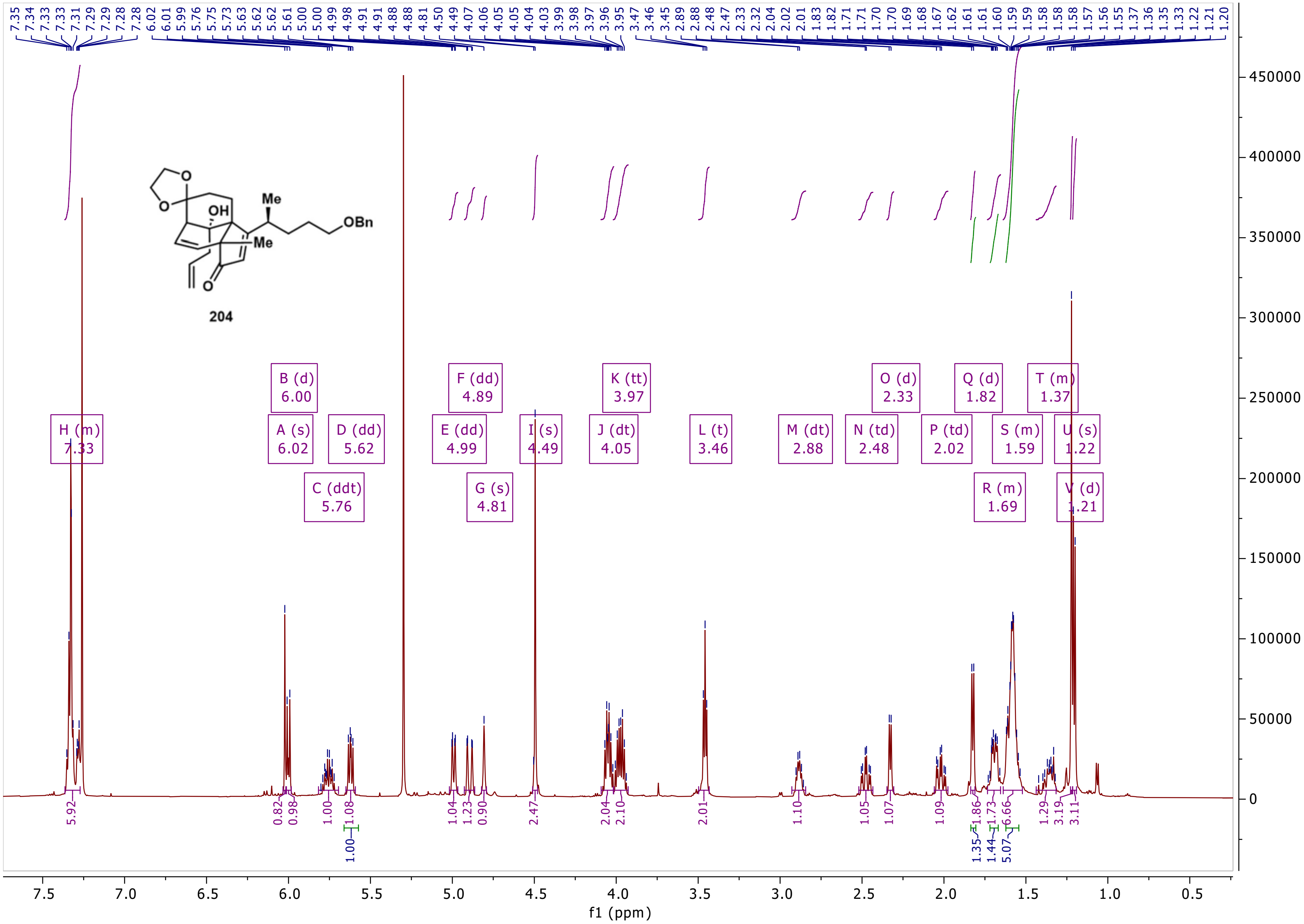

197.44
197.41
145.46
144.97
127.57
127.34
126.92
126.80
102.88
102.67
97.54
96.73
67.96
67.81
54.65
54.25
32.15
32.07
29.35
29.30
27.61
27.05
19.65
19.61
18.85
18.31
17.27
16.38
13.95
13.93
OBu
O
O
Me
199
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.36
7.34
7.33
7.32
7.31
7.30
7.28
6.15
6.13
6.10
5.65
5.64
5.62
5.61
5.61
5.60
5.23
5.23
5.21
5.21
5.07
5.04
4.49
3.48
3.47
3.46
3.00
2.99
2.88
2.87
2.85
2.83
2.82
2.69
2.68
2.66
2.32
2.31
2.29
2.28
2.21
2.20
2.18
2.17
1.95
1.94
1.93
1.92
1.75
1.74
1.73
1.73
1.72
1.70
1.70
1.70
1.69
1.66
1.65
1.64
1.64
1.63
1.63
1.62
1.62
1.61
1.60
1.59
1.59
1.58
1.57
1.56
1.40
1.39
1.39
1.38
1.34
1.33
1.22
1.21
O
OH
Me
Me
OBn
O
202
H (m) 7.32
A (d) 6.14
B (s) 6.10
C (dd) 5.64
D (m) 5.59
E (dd) 5.22
F (d) 5.06
G (s) 4.49
I (t) 3.47
J (d) 3.00
K (m) 2.87
L (dt) 2.82
M (ddd) 2.67
N (dd) 2.30
O (dd) 2.19
P (dd) 1.93
Q (m) 1.72
R (m) 1.61
S (qd) 1.39
T (s) 1.33
U (d) 1.22
5.52
1.00
0.87
1.05
0.75
0.94
0.93
2.38
2.03
1.04
1.23
0.70
1.05
0.96
1.03
0.89
2.18
3.90
0.92
2.97
2.81
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

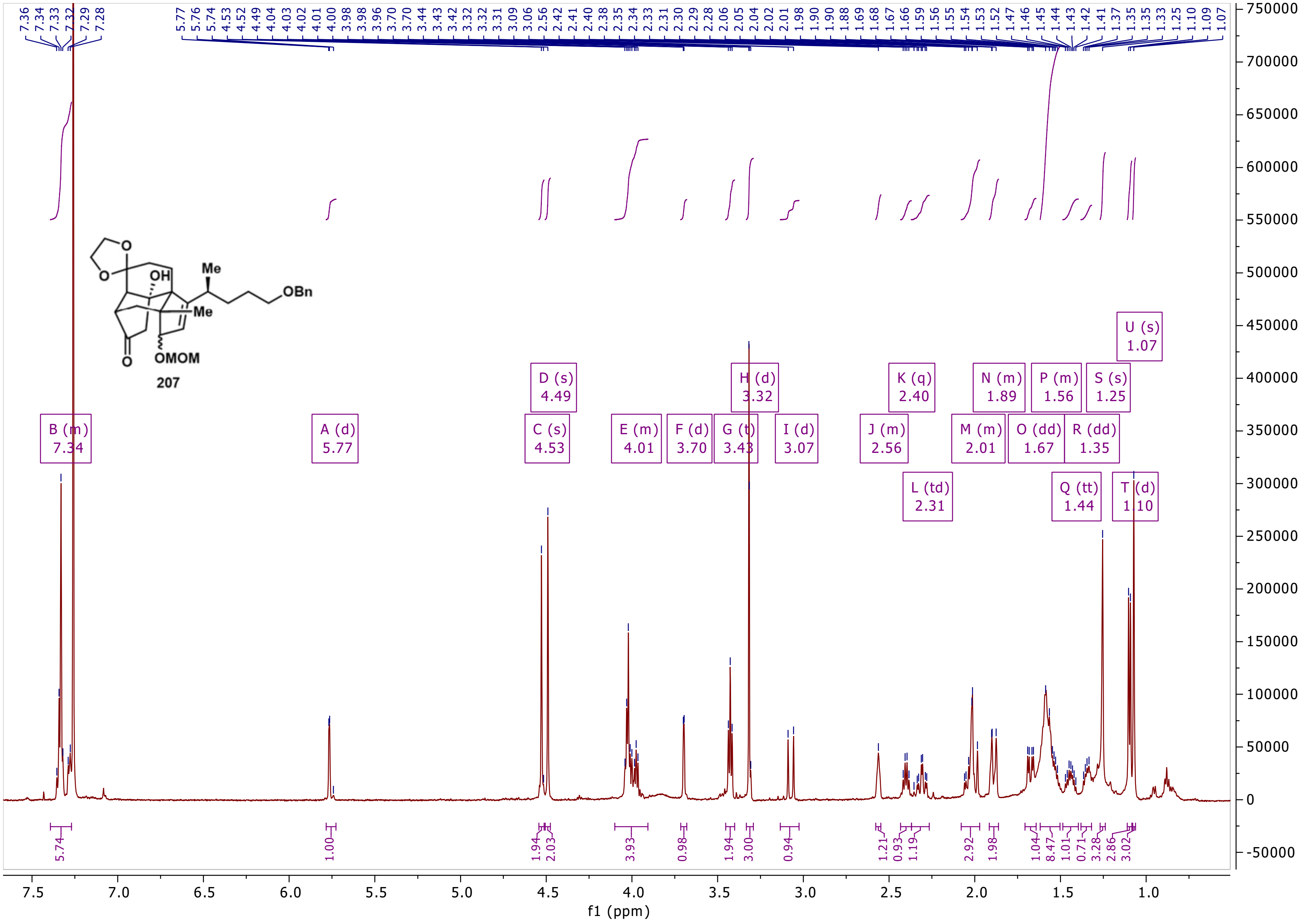

209.58
208.29
186.08
138.52
135.35
131.74
128.55
127.79
127.78
127.55
122.65
121.99
78.75
73.19
70.09
59.26
56.94
56.89
40.36
34.53
33.95
33.45
27.60
24.04
23.95
19.33
O
OH
Me
OBn
Me
O
202
240000
230000
220000
210000
200000
190000
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.27 6.26 6.23 6.13 6.13 5.61 5.60 5.59 5.57 5.22 5.21 5.21 5.19 5.19 5.19 5.19 5.10 5.09 5.09 5.05 5.05 4.48 3.49 3.49 3.48 3.47 3.46 3.46 3.34 3.33 2.68 2.67 2.49 2.30 2.29 2.27 2.24 2.24 2.22 2.21 2.21 2.20 2.19 2.18 2.13 2.11 2.09 2.07 1.76 1.74 1.67 1.66 1.64 1.63 1.62 1.60 1.59 1.39 1.36 1.33 1.31 1.29 1.25 1.23 1.23
O
Me
OBn
Me
HO
O
203
G (m) 7.31
A (d) 6.25
B (s) 6.13
C (m) 5.79
D (ddd) 5.60
F (m) 5.20
E (m) 5.07
H (s) 4.48
I (td) 3.47
J (d) 3.34
K (ddd) 2.68
L (dtd) 2.49
M (m) 2.25
N (dd) 2.10
O (m) 1.67
R (d) 1.38
P (d) 1.24
Q (s) 1.23
6.24
0.81
1.00
0.99
1.05
1.07
1.08
2.09
1.98
0.91
1.01
1.17
1.06
4.13
0.79
2.30
4.13
0.58
3.66
2.53
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)
1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

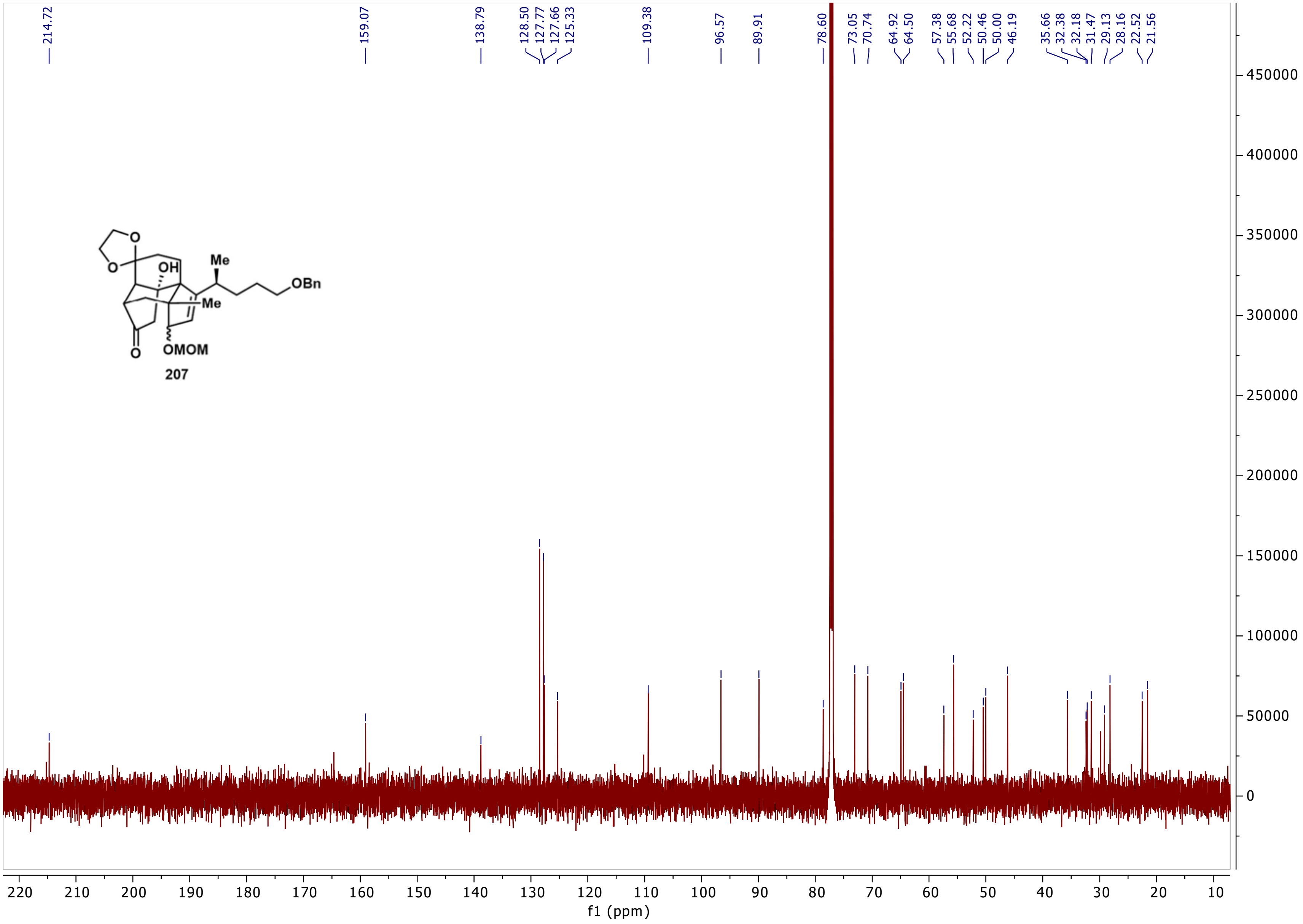

207.89
181.06
138.44
136.95
131.43
128.59
128.54
128.45
127.87
127.79
121.84
120.69
75.50
73.23
69.93
58.76
58.21
56.30
39.79
35.26
34.02
33.26
27.34
22.82
22.78
18.39
O
Me
OBn
Me
HO
O
203
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

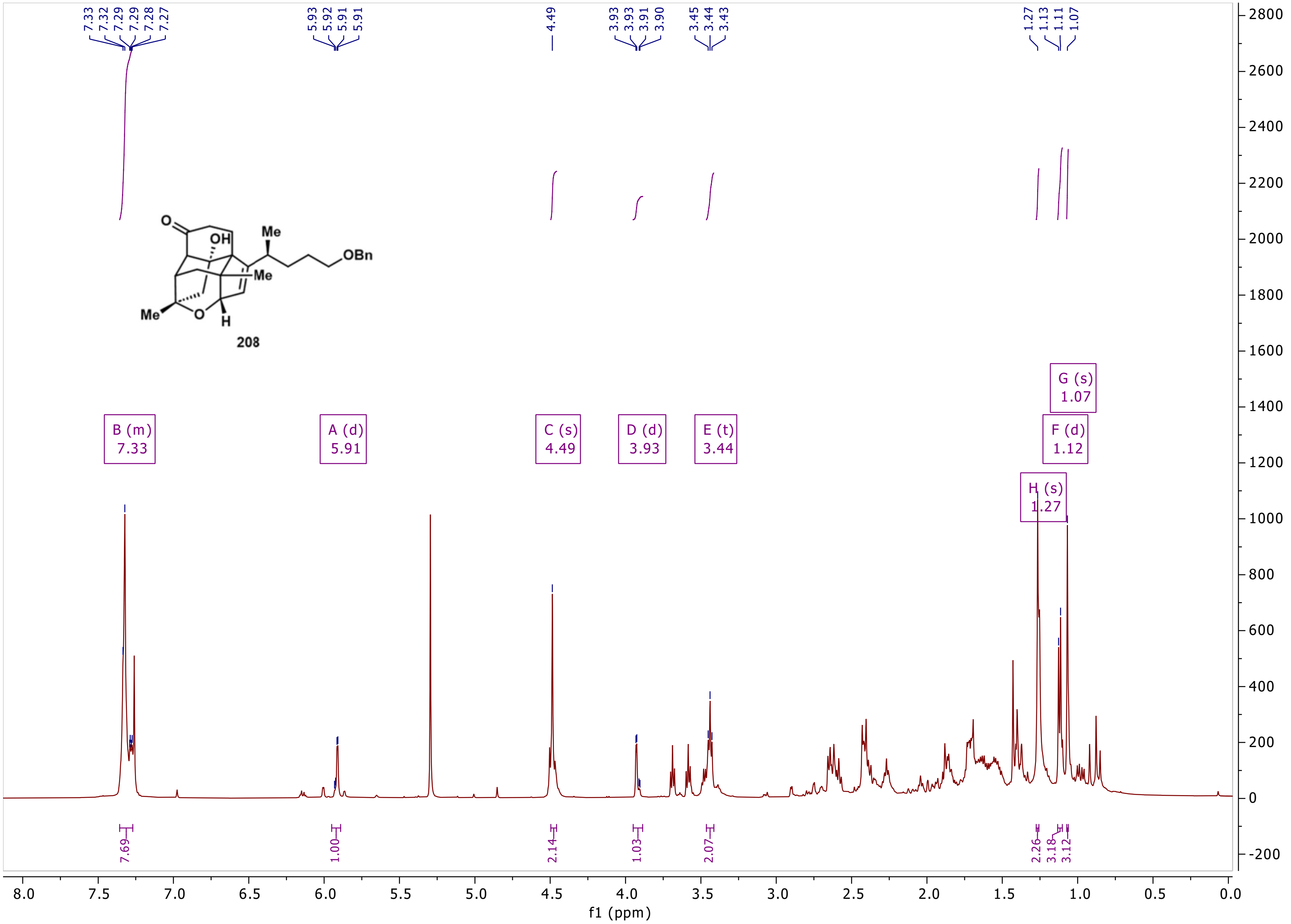


OH
Me
Me
OBn
O
O
O
204
H (m) 7.33
A (s) 6.02
B (d) 6.00
C (ddt) 5.76
D (dd) 5.62
E (dd) 4.99
F (dd) 4.89
G (s) 4.81
I (s) 4.49
J (dt) 4.05
K (tt) 3.97
L (t) 3.46
M (dt) 2.88
N (td) 2.48
O (d) 2.33
P (td) 2.02
Q (d) 1.82
R (m) 1.69
S (m) 1.59
T (m) 1.37
U (s) 1.22
V (d) 1.21
5.92
0.82
0.98
1.00
1.08
1.00
1.04
1.23
0.90
2.47
2.04
2.10
2.01
1.10
1.05
1.07
1.09
1.86
1.73
6.66
1.35
1.44
5.07
1.29
3.19
3.11
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
f1 (ppm)
450000
400000
350000
300000
250000
200000
150000
100000
50000
0


7.36
7.34
7.33
7.32
7.29
7.28
5.77
5.76
5.74
4.53
4.52
4.49
4.04
4.03
4.02
4.01
4.00
3.98
3.96
3.70
3.44
3.43
3.42
3.32
3.32
3.31
3.09
3.06
2.56
2.42
2.41
2.40
2.38
2.35
2.34
2.33
2.31
2.30
2.29
2.28
2.06
2.05
2.04
2.02
2.01
1.98
1.90
1.90
1.88
1.69
1.68
1.67
1.66
1.59
1.56
1.55
1.54
1.53
1.52
1.47
1.46
1.45
1.44
1.43
1.42
1.41
1.37
1.35
1.35
1.33
1.25
1.10
1.09
1.07
O
O
OH
Me
OBn
Me
O
OMOM
B (m) 7.34
A (d) 5.77
D (s) 4.49
C (s) 4.53
E (m) 4.01
F (d) 3.70
G (t) 3.43
H (d) 3.32
I (d) 3.07
J (m) 2.56
K (q) 2.40
L (td) 2.31
M (m) 2.01
N (m) 1.89
O (dd) 1.67
P (m) 1.56
Q (tt) 1.44
R (dd) 1.35
S (s) 1.25
T (d) 1.10
U (s) 1.07
5.74
1.00
1.94
2.03
3.93
0.98
1.94
3.00
0.94
1.21
0.93
1.19
2.92
1.98
1.04
8.47
1.01
0.71
3.28
2.86
3.02
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)
750000
700000
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000

207


214.72
159.07
138.79
128.50
127.77
127.66
125.33
109.38
96.57
89.91
78.60
73.05
70.74
64.92
64.50
57.38
55.68
52.22
50.46
50.00
46.19
35.66
32.38
32.18
31.47
29.13
28.16
22.52
21.56
OH
Me
OBn
Me
O
O
O
OMOM
207
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



7.33
7.32
7.29
7.29
7.28
7.27
5.93
5.92
5.91
5.91
4.49
3.93
3.93
3.91
3.90
3.45
3.44
3.43
1.27
1.13
1.11
1.07
O
OH
Me
OBn
Me
Me
O
H
B (m)
7.33
A (d)
5.91
C (s)
4.49
D (d)
3.93
E (t)
3.44
G (s)
1.07
F (d)
1.12
H (s)
1.27
7.69
1.00
2.14
1.03
2.07
2.26
3.18
3.12
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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

References

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[1] Liu, M.; Sun, W.; Shen, L.; He, Y.; Liu, J.; Wang, J.-P.; Hu, Z.; Zhang, Y. Bipolarolides A–G: Ophiobolin-Derived Sesterterpenes with Three New Carbon Skeletons from *Bipolaris* Sp. TJ403-B1. *Angew. Chem., Int. Ed.* **2019**, *58*, 12091–12095.

[2] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Pravachol NDA 019898/S-061 approval letter, May 18, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/019898Orig1s061.pdf.

[3] Siegel, C.; Gordon, P.; Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. Synthesis of Racemic and Optically Active .DELTA.9-Tetrahydrocannabinol (THC) Metabolites. *J. Org. Chem.* **1991**, *56*, 6865–6872.

[4] Nicolaou, K. C.; Giacomo; Valer Jeso. Construction of Highly Functionalized Medium-Sized Rings: Synthesis of Hyperforin and Perforatumone Model Systems. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895–3899.

[5] (a) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. Total Syntheses of Cyanthiwigins B, F, and G. *Chem. - Eur. J.* **2011**, *17*, 9957. (b) Xu, J.; Rawal, V. H. Total Synthesis of (−)-Ambiguine P. *J. Am. Chem. Soc.* **2019**, *141*, 4820–4823.

[6] (a) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. Metal-Free Catalytic Enantioselective C–B Bond Formation: (Pinacolato)Boron Conjugate Additions to α,β-Unsaturated Ketones, Esters, Weinreb Amides, and Aldehydes Promoted by Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2012**, *134*, 8277–8285. (b) Radomkit, S.; Hoveyda, A. H. Enantioselective Synthesis of Boron-Substituted Quaternary Carbon Stereogenic Centers through NHC-Catalyzed Conjugate Additions of (Pinacolato)Boron Units to Enones. *Angew. Chem., Int. Ed.* **2014**, *53*, 3387–3391. (c) Wu, H.; Garcia, J. M.; Haeffner, F.; Suttipol Radomkit; Zhugralin, A. R.; Hoveyda, A. H. Mechanism of NHC-Catalyzed Conjugate Additions of Diboron and Borosilane Reagents to α,β-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 10585–10602.

[7] Mun, S.; Lee, J.; Yun, J. Copper-Catalyzed β-Boration of α,β-Unsaturated Carbonyl Compounds: Rate Acceleration by Alcohol Additives. *Org. Lett.* **2006**, *8*, 4887–4889.

[8] Liu, Y.; Cheng, L.-J.; Yue, H.-T.; Che, W.; Xie, J.-H.; Zhou, Q.-L. Divergent Enantioselective Synthesis of Hapalindole-Type Alkaloids Using Catalytic Asymmetric Hydrogenation of a Ketone to Construct the Chiral Core Structure. *Chem. Sci.* **2016**, *7*, 4725–4729.

[9] Furst, A.; Plattner, P. A. Über Steroide Und Sexualhormone. 160. Mitteilung. 2α, 3α- Und 2β, 3β-Oxido-Chlolestane; Konfiguration Der 2-Oxy-Cholestane. *Helv. Chim. Acta* **1949**, *32*, 275–283.

[10] For the original discovery of a gold-catalyzed cyclization reaction between a silyl-enol ether and an alkyne, see: (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; F. Dean Toste. Gold(I)-Catalyzed Cyclizations of Silyl Enol Ethers: Application to the Synthesis of (+)-Lycopladine A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991–5994. For our group's previous works utilizing similar transformations, see: (b) Yang, M.; Yin, F.; Fujino, H.; Snyder, S. A. The Total Synthesis of Chalcitrin. *J. Am. Chem. Soc.* **2019**, *141*, 4515–4520. (c) Peng, C.; Arya, P.; Zhou, Z.; Snyder, S. A. A Concise Total Synthesis of (+)-Waihoensene Guided by Quaternary Center Analysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 13521–13525. (d) Qu, P.; Snyder, S. A. Concise and Stereoselective Total Syntheses of Annotinolides C, D, and E. *J. Am. Chem. Soc.* **2021**, *143*, 11951–11956.

---

[11] Kummer, D. A.; Brenneman, J. B.; Martin, S. F. Domino Intramolecular Enyne Metathesis/Cross Metathesis Approach to the Xanthanolides. Enantioselective Synthesis of (+)-8-Epi-Xanthatin. *Tetrahedron* **2006**, *62*, 11437–11449.

[12] Moriarty, R. M.; Prakash, O.; Duncan, M. J.; Vaid, R. K.; Musallam, H. A. Hypervalent Iodine Oxidation of Silyl Enol Ethers under Lewis-Acid Conditions in Methanol. A General Route to .alpha.-Methoxy Ketones. *J. Org. Chem.* **1987**, *52*, 150–153.

[13] Madin, A.; O'Donnell, C. A.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. H. Use of the Intramolecular Heck Reaction for Forming Congested Quaternary Carbon Stereocenters. Stereocontrolled Total Synthesis of (±)-Gelsemine. *J. Am. Chem. Soc.* **2005**, *127*, 18054–18065.

[14] Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. Triazabicyclodecene: A Simple Bifunctional Organocatalyst for Acyl Transfer and Ring-Opening Polymerization of Cyclic Esters. *J. Am. Chem. Soc.* **2006**, *128*, 4556–4557.

[15] Shapiro, R. Alkenes from Tosylhydrazones. *Org. React.* **2011**, 405–507.

[16] (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. Peracid Oxidation of Trimethylsilyl Enol Ethers: A Facile α-Hydroxylation Procedure. *Tetrahedron Lett.* **1974**, *15*, 4319–4322. (b) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. α-Hydroxylation of Enolates and Silyl Enol Ethers. *Org. React.* **2004**, 1–356.

[17] (a) Lebel, H.; Paquet, V. E. Rhodium-Catalyzed Methylenation of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 320–328. (b) Lebel, H.; Guay, D.; Paquet, V. E.; Huard, K. Highly Efficient Synthesis of Terminal Alkenes from Ketones. *Org. Lett.* **2004**, *6*, 3047–3050.

[18] Weiss, M.; Appel, M. The Catalytic Oxidation of Benzoin to Benzil. *J. Am. Chem. Soc.* **1948**, *70*, 3666–3667.

[19] Nguyen, T. Q.; Krit Setthakarn; May, J. A. Oxyallyl Cation Capture via Electrophilic Deborylation of Organoboronates: Access to *α*,*α'*-Substituted Cyclic Ketones. *Org. Lett.* **2019**, *21*, 7837–7840.

[20] (a) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G. L.; McQuire, L.; DeLuca, M.; Merritt, A.; Chung Yong Kim; Vicker, N. Synthesis of Strychnine and the Wieland-Gumlich Aldehyde. *J. Am. Chem. Soc.* **1993**, *115*, 8116–8129. (b) Crimmins, M. T.; Mans, M. C.; Rodríguez, A. D. Total Synthesis of the Proposed Structure of Briarellin J. *Org. Lett.* **2010**, *12*, 5028–5031. (c) Wuts, P. G. M., *Greene's Protective Groups in Organic Synthesis, 5th Edition*. **2014**, pp. 278.

[21] Ireland, R. E.; Mueller, R. E. Claisen Rearrangement of Allyl Esters. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

[22] Cernijenko, A.; Risgaard, R.; Baran, P. S. 11-Step Total Synthesis of (−)-Maoecrystal V. *J. Am. Chem. Soc.* **2016**, *138*, 9425–9428.

[23] Baldwin, J. E.; Lusch, M. J. Rules for Ring Closure: Application to Intramolecular Aldol Condensations in Polyketonic Substrates. *Tetrahedron* **1982**, *38*, 2939–2947.

[24] (a) Birch, A. J. 117. Reduction by Dissolving Metals. Part I. *J. Chem. Soc.* **1944**, 430–436. (b) Rabideau, P. W.; Marcinow, Z. The Birch Reduction of Aromatic Compounds. *Org. React.* **1992**, 1–334.

[25] (a) Baylis, A. B.; Hillman, M. E. D. Reaction of acrylic type compounds with aldehydes and certain ketones. German patent 2155113, **1972**. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Recent Advances in the Baylis−Hillman Reaction and Applications. *Chem. Rev.* **2003**, *103*, 811–892. (c) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. Recent Contributions from the Baylis−Hillman Reaction to Organic Chemistry. *Chem. Rev.* **2010**, *110*, 5447–5674.

---

[26] Gan, P.; Pitzen, J.; Qu, P.; Snyder, S. A. Total Synthesis of the Caged Indole Alkaloid Arboridinine Enabled by *Aza*-Prins and Metal-Mediated Cyclizations. *J. Am. Chem. Soc.* **2018**, *140*, 919–925.

[27] (a) Michel, B. W.; Steffens, L. D.; Sigman, M. S. Wacker Oxidation, The. *Org. React.* **2014**, 75–414. (b) Kim, K. H.; Li, J.-M.; Grubbs, R. H.; Stoltz, B. M. Catalytic Anti-Markovnikov Transformations of Hindered Terminal Alkenes Enabled by Aldehyde-Selective Wacker-Type Oxidation. *J. Am. Chem. Soc.* **2016**, *138*, 13179–13182.

[28] Wang, G.-Z.; Jiang, J.; Bu, X.-S.; Dai, J.; Xu, J.; Fu, Y.; Xu, H.-J. Copper-Catalyzed Cross-Coupling Reaction of Allyl Boron Ester with 1°/2°/3°-Halogenated Alkanes. *Org. Lett.* **2015**, *17*, 3682–3685.

[29] Parikh, J. R.; Doering, W. v. E. Sulfur Trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[30] (a) Pappo, R.; Allen, Jr., D. S.; Lemieux, R. U.; Johnson, W. S. Notes - Osmium Tetroxide-Catalyzed Periodate Oxidation of Olefinic Bonds. *J. Org. Chem.* **1956**, *21*, 478–479. For the improved procedure using silica gel-supported $NaIO_4$, see: (b) Zhong, Y.-L.; Shing, T. K. M. Efficient and Facile Glycol Cleavage Oxidation Using Improved Silica Gel-Supported Sodium Metaperiodate. *J. Org. Chem.* **1997**, *62*, 2622–2624.

[31] For reviews on the diverse reaction outcome through this intermediate, see: (a) Dorel, R.; Echavarren, A. M. Gold-Catalyzed Reactions via Cyclopropyl Gold Carbene-like Intermediates. *J. Org. Chem.* **2015**, *80*, 7321–7332. (b) Jiménez-Núñez, E.; Echavarren, A. M. Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. *Chem. Rev.* **2008**, *108*, 3326–3350.

[32] Witham, C. A.; Mauleón, P.; Shapiro, N. I.; Sherry, B. D.; F. Dean Toste. Gold(I)-Catalyzed Oxidative Rearrangements. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

[33] Nivlet, A.; Guen, V. L.; Dechoux, L.; Gall, T. L.; Mioskowski, C. Reductive Opening of Cyclopropylogous α-Hydroxy Aldehydes and Ketones by Samarium(II) Iodide. *Tetrahedron Lett.* **1998**, *39*, 2115–2118.

[34] Castro, B. Replacement of Alcoholic Hydroxyl Groups by Halogens and Other Nucleophiles via Oxyphosphonium Intermediates. *Org. React.* **1983**, 1–162.

[35] Stork, G.; Mook, R. A. Vinyl Radical Cyclizations Mediated by the Addition of Stannyl Radicals to Triple Bonds. *J. Am. Chem. Soc.* **1987**, *109*, 2829–2831.

[36] Boger, D. L.; Mathvink, R. J. Phenyl Selenoesters as Effective Precursors of Acyl Radicals for Use in Intermolecular Alkene Addition Reactions. *J. Org. Chem.* **1989**, *54*, 1777–1779.

[37] Bal, B. S.; Childers, W. E.; Pinnick, H. W. Oxidation of α,β-Un Saturated Aldehydes. *Tetrahedron* **1981**, *37*, 2091–2096.

[38] Batty, D.; Crich, D. An Improved Procedure for the Formation OfSe-Phenyl Selenoesters. *Synthesis* **1990**, *1990*, 273–275.

[39] For some detailed discussions of the regioselectivity of a similar system, see: Toyota, M.; Yokota, M.; Ihara, M. Construction of Bicyclo[2.2.2]Octane Ring System via Homoallyl-Homoallyl Radical Rearrangement. *Tetrahedron Lett.* **1999**, *40*, 1551–1554.

[40] (a) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. Chemoenzymatic Total Syntheses of the Sesquiterpene (−)-Patchoulenone. *New J. Chem.* **2003**, *27*, 50–59. (b) Molander, G. A.; Czako, B.; Rheam, M. Construction of Bicyclic Ring Systems via a Transannular SmI_2-Mediated Ketone−Olefin Cyclization Strategy. *J. Org. Chem.* **2007**, *72*, 1755–1764.

[41] Trost, B. M.; Rise, F. Reductive Cyclization of 1,6- and 1,7-Enynes. *J. Am. Chem. Soc.* **1987**, *109*, 3161–3163.

---

[42] Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. Synthesis of (−)-Centrolobine by Prins Cyclizations That Avoid Racemization. *Org. Lett.* **2002**, *4*, 3919–3922.

[43] (a) Saladrigas, M.; Bosch, C.; Saborit, G. V.; Josep Bonjoch; Bradshaw, B. Radical Cyclization of Alkene-Tethered Ketones Initiated by Hydrogen-Atom Transfer. *Angew. Chem., Ind. Ed.* **2018**, *57*, 182–186. (b) Saladrigas, M.; Puig, J.; Josep Bonjoch; Bradshaw, B. Iron-Catalyzed Radical Intermolecular Addition of Unbiased Alkenes to Aldehydes. *Org. Lett.* **2020**, *22*, 8111–8115.

[44] Arkady Krasovskiy; Kopp, F. K.; Knochel, P. Soluble Lanthanide Salts (LnCl3·2 LiCl) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chem., Ind. Ed.* **2006**, *45*, 497–500.

[45] Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. An Improved Preparation of Vinyl Iodides. *Tetrahedron Lett.* **1983**, *24*, 1605–1608.

[46] Lu, H.-H.; Martinez, M. D.; Shenvi, R. A. An Eight-Step Gram-Scale Synthesis of (−)-Jiadifenolide. *Nature Chem.* **2015**, *7*, 604–607.

[47] (a) Schultz, A. G.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. The Enantioselective Conversion of Ortho-Substituted Benzoic Acids to Chiral Cyclohexane Derivatives. *Tetrahedron Lett.* **1985**, *26*, 4575–4578. (b) Schultz, A. G.; Macielag, M. J.; Padmanabhan Sundararaman; Taveras Arthur G; Welch, M. An Enantioselective Method for Reductive Alkylation of Aromatic Carboxylic Acid Derivatives. Examination of the Factors That Provide Stereoselectivity. *J. Am. Chem. Soc.* **1988**, *110*, 7828–7841.

[48] Kozlowski, R. A.; Nguyen, H. T.; Lehman, M. E.; Vanderwal, C. D. Stereocontrolled Access to Quaternary Centers by Birch Reduction/Alkylation of Chiral Esters of Salicylic Acids. *J. Org. Chem.* **2023**, *88* (9), 6232–6236.

[49] Chuc, L. T. N.; Chen, C.-S.; Lo, W.-S.; Shen, P.-C.; Hsuan, Y.-C.; Tsai, H.-H. G.; Shieh, F.-K.; Hou, D.-R. Long-Range Olefin Isomerization Catalyzed by Palladium(0) Nanoparticles. *ACS Omega* **2017**, *2*, 698–711.

[50] Zhao, J.; Dong, H.-B.; Yang, M.-Y.; Du, J.; Jiang, J.-Z.; Wang, M.-A. Synthesis and Antifungal Activity of 7-Methyl-7-Hydroxy-2,3-Benzo[C]Octa-1,6-Olide. *J. Asian Nat. Prod. Res.* **2014**, *16*, 312–317.

[51] Tu, Y.; Wang, Z.-X.; Shi, Y. An Efficient Asymmetric Epoxidation Method for *Trans*-Olefins Mediated by a Fructose-Derived Ketone. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.

[52] For a detailed study on the alkylation of 7-membered lactones, see: Lavinda, O.; Witt, C. H.; Woerpel, K. A. Origin of High Diastereoselectivity in Reactions of Seven-Membered-Ring Enolates. *Angew. Chem., Int. Ed.* **2022**, *61*, e202114183.

[53] Schultz, A. G.; Richard. Diastereoselective Ester Enolate Alkylations. Asymmetric Syntheses of 3-Alkyl-3-Carbomethoxy-2-Exo-Methylene-5-Cyclohexen-1-Ones. *J. Am. Chem. Soc.* **1992**, *114*, 3937–3943.

[54] Wilson, S. D. Anion-Assisted Sigmatropic Rearrangements. *Org. React.* **2004**, 93–250.

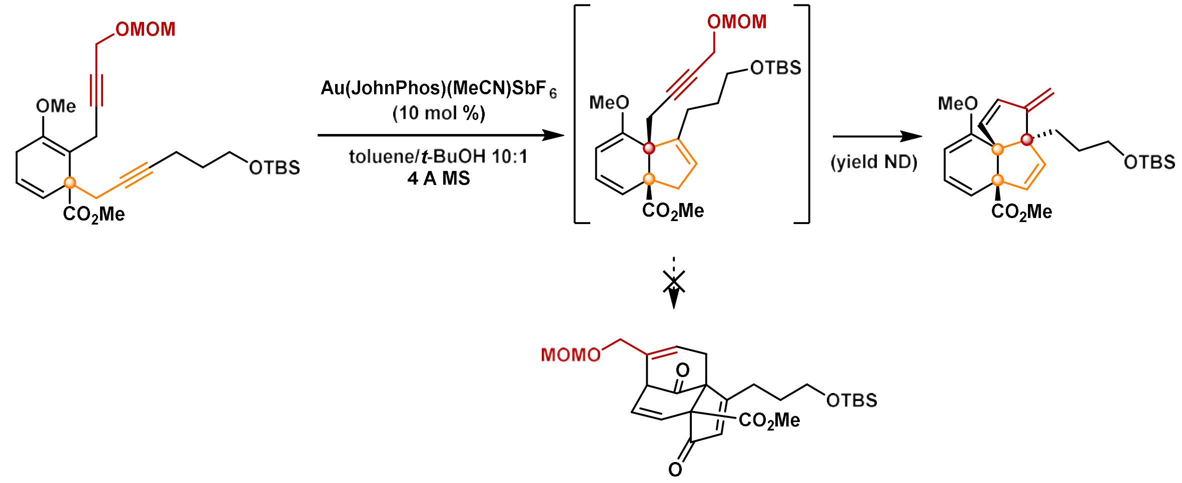
[55] Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. Asymmetric Total Synthesis of (+)-Waihoensene. *J. Am. Chem. Soc.* **2020**, *142*, 6511–6515.

[56] (a) Danishefsky, S.; Bednarski, M. Lanthanide Catalysis of Cycloadditions of Heterodienes with Enol Ethers. *Tetrahedron Lett.* **1984**, *25*, 721–724. For a similar application of such reaction, see: (b) Yokoshima, S.; Watanabe, S.; Ishikawa, M.; Nomura, T.; Fukuyama, T. Total Synthesis of Lycoposerramine-R. *Synlett* **2018**, *29*, 2377–2380.

[57] Dumpala, M.; Theegala, S.; Palakodety, R. K. Total Synthesis of Distaminolyne A. *Tetrahedron Lett.* **2017**, *58*, 1273–1275.

Chapter 4 The Application of Gold(I) Catalysis in the Formation of Polycyclic Systems with Contiguous All-carbon Quaternary Stereocenters

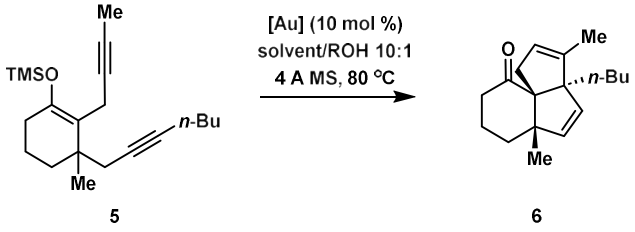
4.1 Background on the Discovery of the Methodology



Scheme 4.1. The discovery of a tandem gold-catalyzed cyclization reaction to form angular tricyclic systems with 3 contiguous quaternary centers.

As discussed in section 3.4.1, the gold-catalyzed cyclization reaction unexpectedly left the enol ether moiety unhydrolyzed in the product. Given this outcome, we ambitiously designed a tandem cyclization sequence, hoping the enol ether would further react with a second alkyne in substrate **1**, to directly give tricyclic product **4** desired in the synthesis of bipolarolides A and B. Upon testing the reaction, we found that the first cyclization happened as we proposed, to give intermediate **2**, while the second cyclization occurred between the second alkyne and the freshly formed, electron-neutral alkene on the 5-membered ring, to give angular tricyclic compound **3** with the methoxymethyl ether eliminated. This outcome can be attributed to the highly strained transition state in the formation of **4**. We became very excited about this transformation since **3** bears 3 contiguous all-carbon quaternary centers, with 2 of which formed in the reaction event. Plus, angular product **3** is highly related to the structure of waihoensene. Thus, further investigations into this reaction were initiated, mainly under the conduct of Seth Freedman, a younger graduate student in our group.

4.2 A Brief Summary of the Developments in Progress



Entry	solvent	ROH	[Au]	NMR yield[a]
1[b]	toluene	*t*-BuOH	Au(JohnPhos)(MeCN)SbF_6	85%
2	toluene	*t*-BuOH	Au(SPhos)(MeCN)SbF_6	70%
3	toluene	*t*-BuOH	Ph_3PAuCl, $AgSbF_6$	22%
4	1,2-DCE	*t*-BuOH	Au(JohnPhos)(MeCN)SbF_6	14%
5	toluene[c]	*t*-BuOH	Au(JohnPhos)(MeCN)SbF_6	66%
6	toluene	*i*-PrOH	Au(JohnPhos)(MeCN)SbF_6	60%
7	toluene	MeOH	Au(JohnPhos)(MeCN)SbF_6	46%

Table 4.1. Screen of conditions of the gold-catalyzed tandem cyclization reaction of **5**

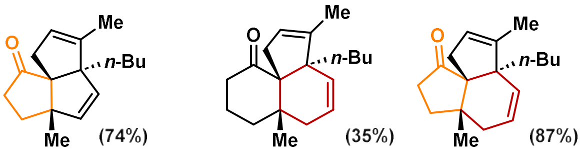
[a] NMR yields determined using methyl 3,5-dinitrobenzoate as the internal standard.

[b] Optimal condition: 4 A MS (200 wt% to **5**), toluene/*t*-BuOH 10/1, 23 °C, 10 min; then Au(JohnPhos)(MeCN)SbF_6 (10 mol %), 80 °C, 16 h, 85%.

[c] No 4 A MS.

To further simplify the system, we conducted our initial optimizations on substrate **5** (synthesis not shown here). Table 1 summarizes some selected results. A screen of a variety of gold pre-catalysts shows that biaryl phosphine ligands are more optimal than simple phosphine ligands and NHC ligands (entries 2-3, results with NHC ligands not shown). Toluene as the major solvent behaves better than other commonly used solvents in similar reactions, such as 1,2-DCE (entry 4), MeCN, and THF (not shown). The addition of molecular sieves is critical to the success, as the acidic species from the hydrolysis of the gold pre-catalyst may result in the decomposition of the silyl enol ether part of **5**. A clear trend was observed when different alcohols were used as co-solvents (entries 6-7), with more hindered alcohols being favored.

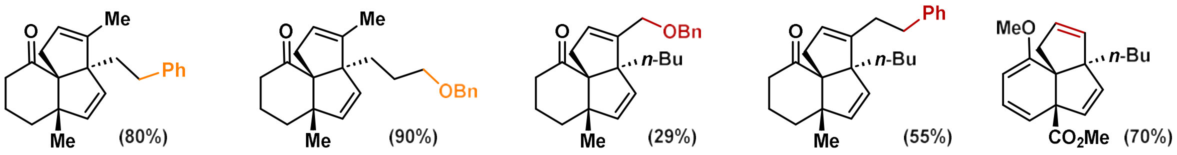
The scope of this reaction was further studied. First off, we tested the reaction in the formation of different ring systems (figure 1). Starting with a 5-membered ring shows minimal impact on the reaction's yield (**7**). The formation of a 6/6 fused ring system is not optimal (**8**), while the formation of a 5/6 fused ring system is undisruptive (**9**), similar to an observation by Barriault and co-workers[1].



7 **8** **9**

Figure 4.1. Products of different ring sizes.

The reaction is also compatible with a variety of substitutions (figure 2). A phenyl substitution (**10**) or a benzyl ether (**11**) on the side-chain shows minimal impact. A propargyl benzyl ether next to the second reactive alkyne was not favorable (**12**). Unwanted coordinations in the substrate or elimination side reactions similar to the initial discovery (scheme 1) may be at fault. 2-phenyl-ethyl substituted product **13** was obtained in decent yield. Dienoether **14** with a similar substitutional pattern to **3** could also be obtained in good yield.



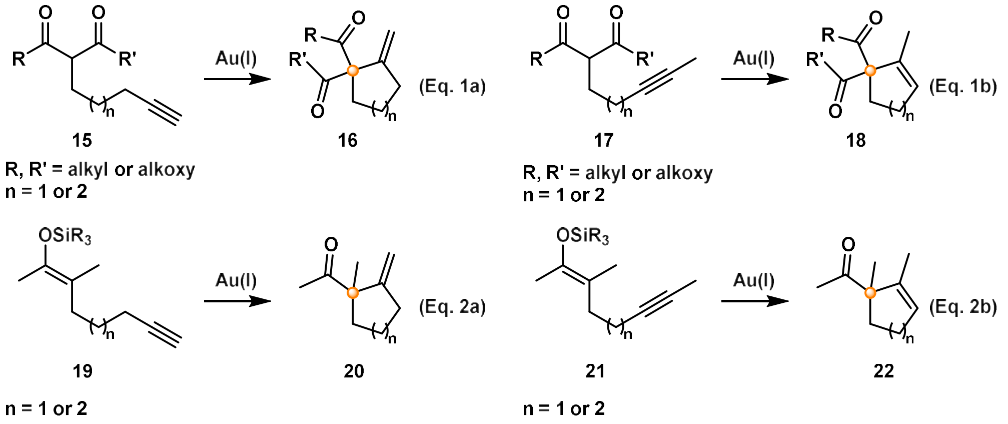
10 **11** **12** **13** **14**

Figure 4.2. Products with different substitutional patterns.

4.3 The Application of Gold(I) Catalysis in the Formation of All-carbon Quaternary Stereocenters: A Review of Literature

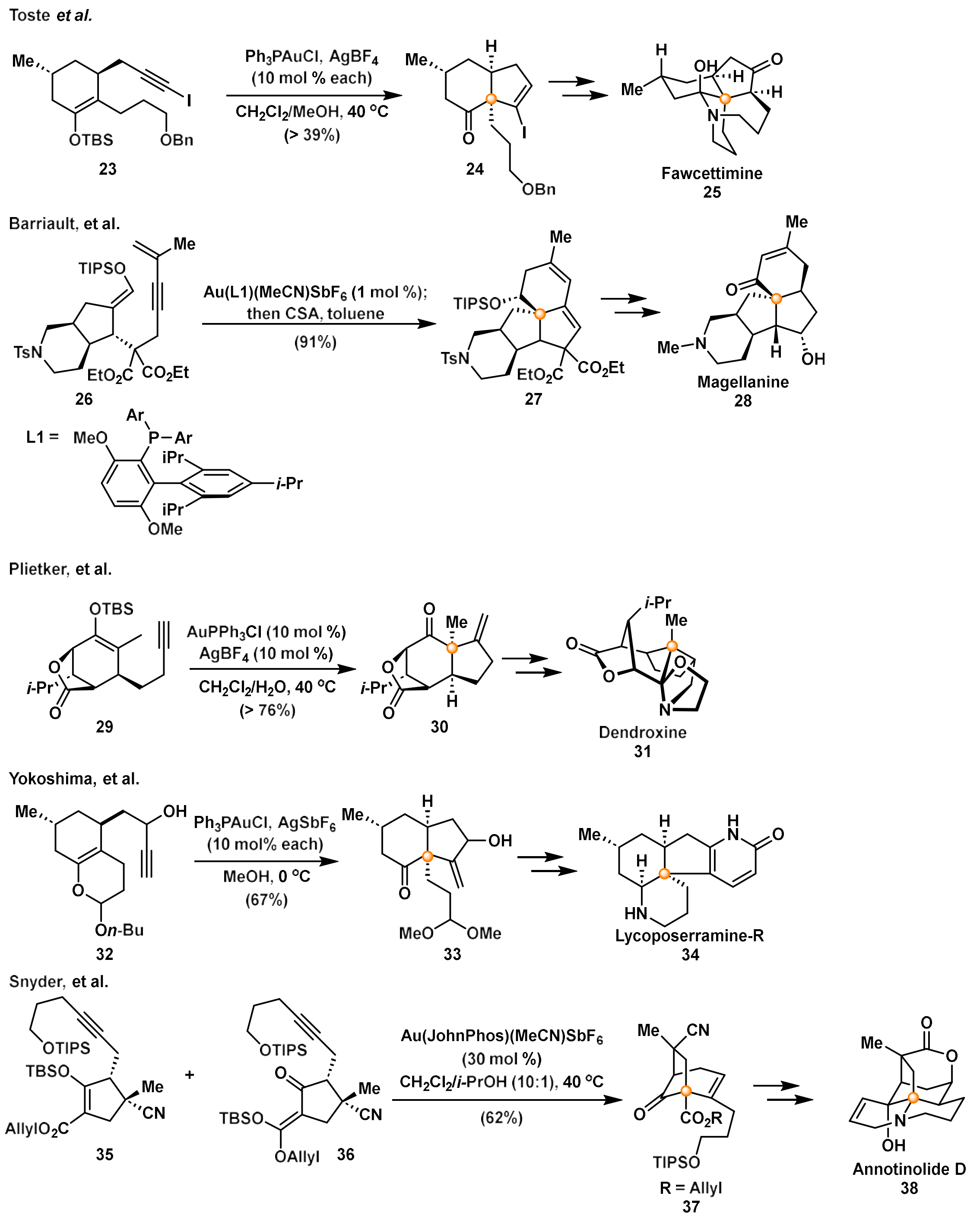
4.3.1 Cycloisomerization-related Transformations

Perhaps the most useful gold-catalyzed transformation leading to the formation of all-carbon quaternary centers is related to the cycloisomerization, typically of enynes and ene-allenes (including acetylenic dicarbonyl compounds). Noteworthy, all gold-catalyzed reactions we discussed in this dissertation fall into this category, including the Conia-ene-type reaction in waihoensene synthesis in section 2.4.2, the *E* ring formation in the bipoloarolides A and B in section 3.7, the cyclopropane-forming reaction in section 3.6.1, and both steps of the tandem gold-catalyzed cyclization reaction discussed earlier in this chapter. This section summarizes pioneering works and applications of such transformations in natural product syntheses.



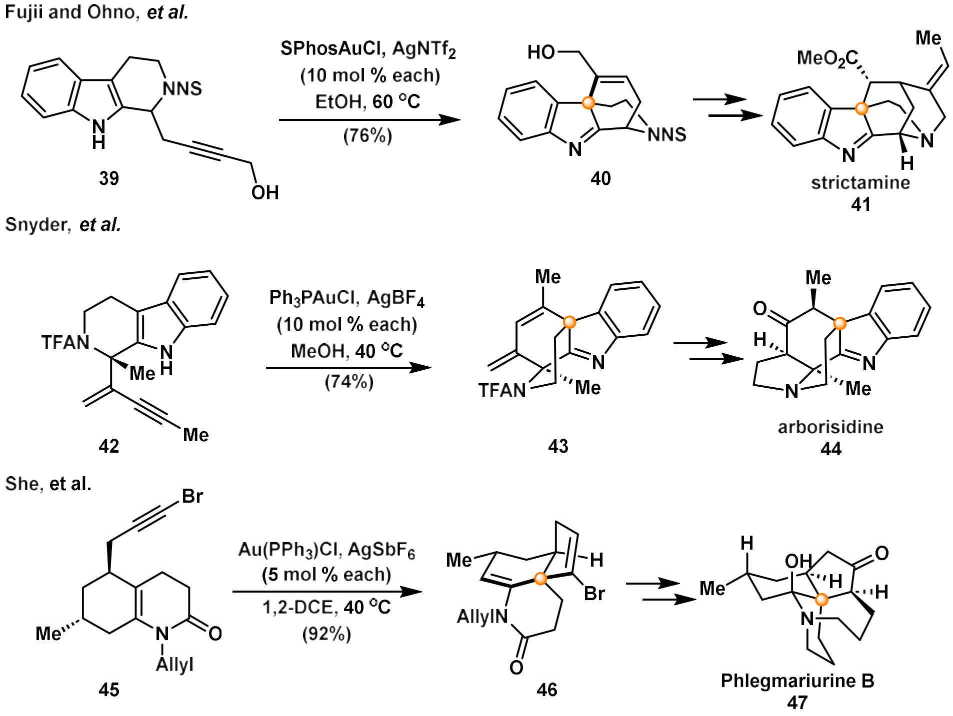
Scheme 4.2. Generalized pathways of gold-catalyzed cycloisomerization reactions that can lead to the formation of all-carbon quaternary centers with 1,3-dicarbonyl compounds or silyl enol ethers as nucleophiles.

In 2004, the Toste group published the lead discovery of this class of transformations. Acetylenic dicarbonyl compounds were found to undergo Conia-ene-type reactions to generate products with

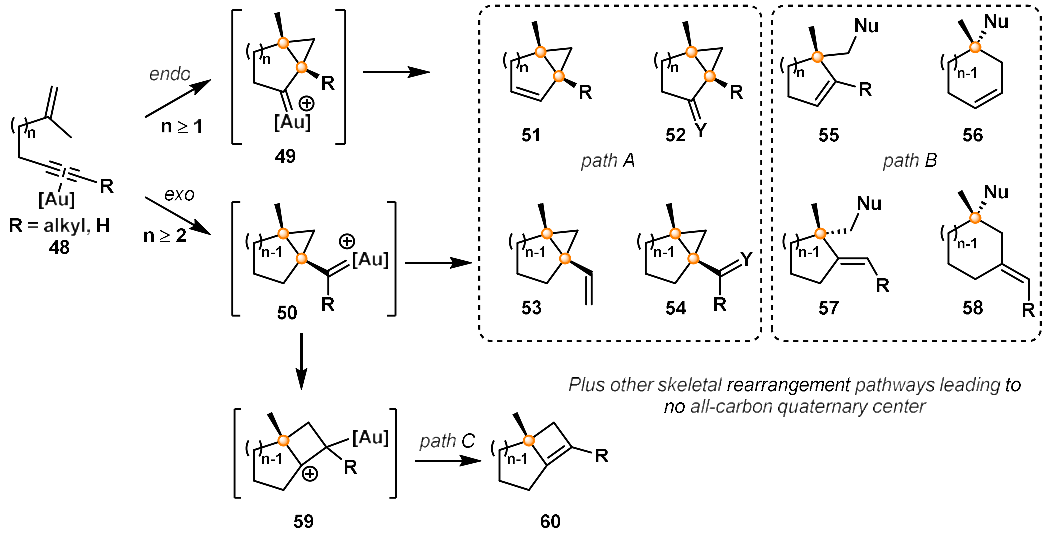


Scheme 4.3. A summary of natural product syntheses using gold-catalyzed cycloisomerization reactions that use 1,3-dicarbonyl compounds or silyl enol ethers as nucleophiles, with all-carbon quaternary centers formed in the step.

an all-carbon quaternary center[2] (scheme 2, Eq. 1a and 1b). Later, the same group expanded the scope of the nucleophile to silyl enol ethers (Eq 2a and 2b) and applied the reaction in the synthesis of lycopladine A and fawcettimine (**25**)[3]. Other notable total synthesis works applying such transformations include, Barriault's synthesis of magellanine(**28**)[4] (which includes a tandem cyclization), Plietker's syntheses of picrotoxane alkaloids (represented by **31**)[5], Yokoshima's synthesis of lycoposerramine-R (**34**)[6], and our group's syntheses of waihoensene (chapter 2) and annotinolides (represented by **38**)[7]. Indoles or enamines can also be as the nucleophile, inspiring Fujii and Ohno's formal synthesis of strictamine (**41**)[8], our group's synthesis of arborisidine (**44**)[9], and She's collective syntheses of *Lycopodium* alkaloids (represented by **47**, uses enamine as the nucleophile)[10].



Scheme 4.4. A summary of natural product syntheses using gold-catalyzed cycloisomerization reactions that use indoles or enamines as nucleophiles, with all-carbon quaternary centers formed in the step.

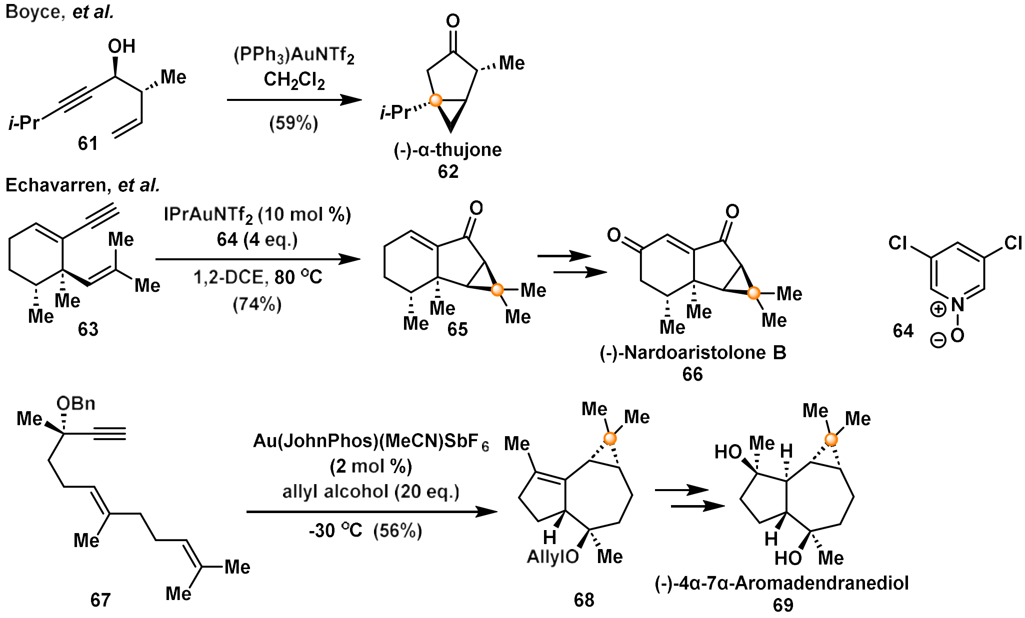


Scheme 4.5. Generalized pathways of gold-catalyzed cycloisomerization reactions that can lead to the formation of all-carbon quaternary centers with electron-neutral alkenes as nucleophiles.

When an electron-neutral alkene is used as the nucleophile for the transformation, the Toste group[11] and the Echavarren group[12] observed on 1,5- and 1,6-enynes, respectively, the formation of cyclopropane-containing products with all-carbon quaternary centers. The Echavarren group thoroughly studied the mechanism of the reaction, concluding that the reaction proceeds through a delocalized cyclopropyl gold carbene-like intermediate **49** and **50**[3, 13, 14]. Scheme 5 generalizes all pathways from these intermediates that can lead to products with all-carbon quaternary centers. It should be noted that the selectivity among these pathways is both substrate and condition dependent, and often can be tuned by either changing the reaction conditions or modifying the substrate.

Elimination or direct trapping of intermediates **49** and **50** without further skeletal rearrangement can lead to the formation of products containing cyclopropane rings (Scheme 5, path A). Elimination product **51** can be observed when *endo* intermediate **59** is formed under conditions with no presence of terminal nucleophiles[ref.12, 15]. One notable application of such conversion is

Boyce's synthesis of (+)- and (−)-α-thujone (**62**)[16], where path A further benefits from the additional driving force of the elimination product enol tautomerizing into a ketone. Oxidative trapping of intermediate **49** can lead to **52** (Y = O), which was applied in Echavarren's synthesis of (−)-Nardoaristolone B (**66**)[17]. However, similar pathways are significantly less common for *exo* intermediate **50**, which generally prefers further skeletal rearrangements to form products with no all-carbon quaternary centers. As we have shown in section 3.6.1, terminal oxidative[18] or reductive[19] agents can be added to trap intermediate **50**, forming products with the structure of **54** (Y = O or H_2).

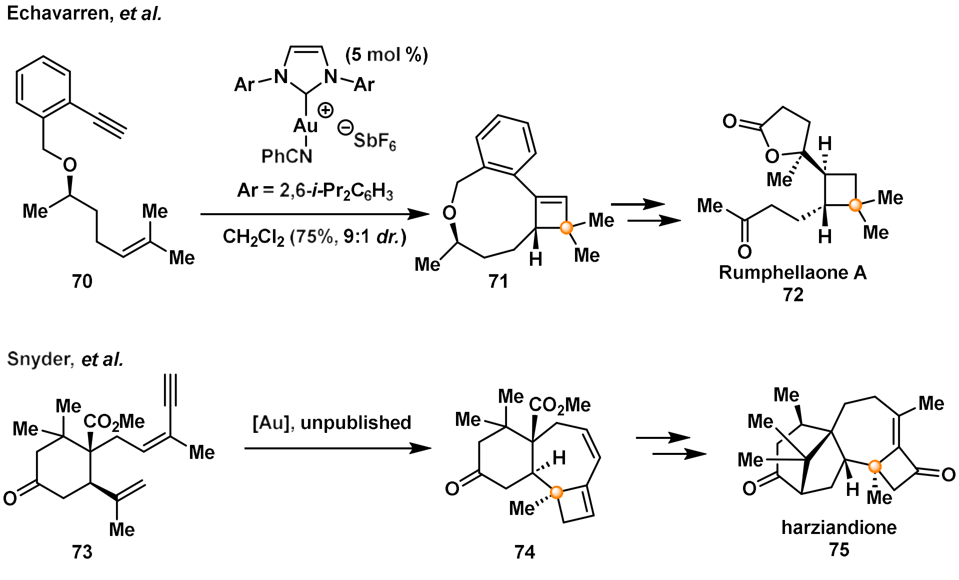


Scheme 4.6. A summary of total syntheses using gold-catalyzed cycloisomerization reactions in forming all-carbon quaternary centers with electron-neutral alkenes as nucleophiles.

The nucleophilic opening of the gold carbene intermediate **49** and **50** are less common in the context of natural product syntheses, perhaps due to the lack of inherent regioselectivity in the substrate's electron-neutral alkene. The Echavarren group[ref.12] first reported the trapping of *endo* intermediate **49** with alkoxyl nucleophiles, to give products with the structure of **55** and **56**.

Subsequently, the addition of nitrogen[20] and carbon[21] nucleophiles has been reported. The most notable application of such transformations, however, involves the nucleophilic opening of *exo* intermediate **50** in Echavarren's syntheses of Epiglobulol and Aromadendranediols (represented by **69**)[22].

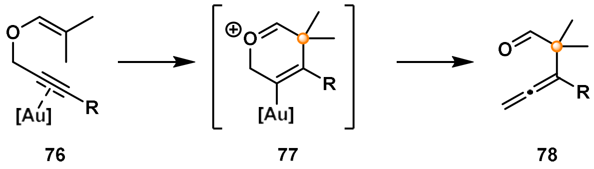
Additionally, intermediates **49** and **50** can undergo a ring-expanding rearrangement (path C) to generate cyclobutene product **60**, completing a formal [2+2] reaction between the alkene and the alkyne. This was originally discovered by the Echavarren group[ref.13a], who later expanded the reaction scope to intermolecular systems[23]. Mechanism studies by the same group[24] and several other works[25] suggest the formation of cyclobutene is favored when the alkyne is electron rich or intermediate **59** is stabilized. In addition, biaryl phosphine ligands are generally preferred. This transformation was applied in Echavarren's syntheses of rumphellaone A (**72**) and hushinone and inspired the Yang group's synthetic studies[ref.25b] and our group's unpublished syntheses[26] of harziane diterpenes (represented by **75**).



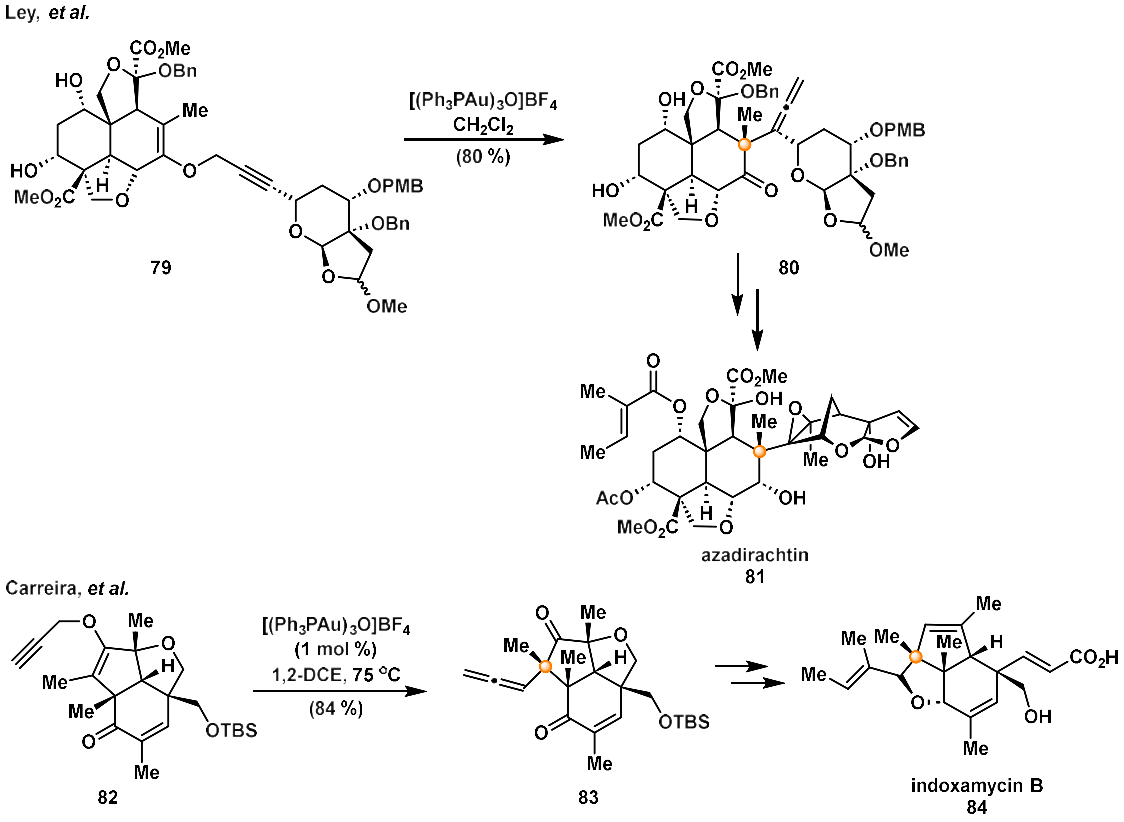
Scheme 4.7. A summary of total syntheses using gold-catalyzed enyne formal [2+2] reaction in forming all-carbon quaternary centers.

Similar transformations have also been reported on allenes, but will not be reviewed here.

4.3.2 All-carbon Quaternary Center Formation by [3.3]-Sigmatropic Rearrangements



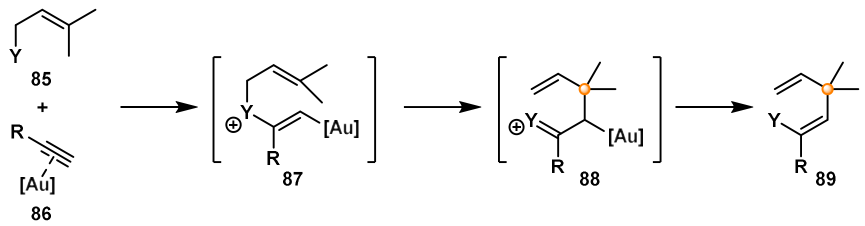
Scheme 4.8. Gold-catalyzed Claisen rearrangement of propargyl vinyl ethers.



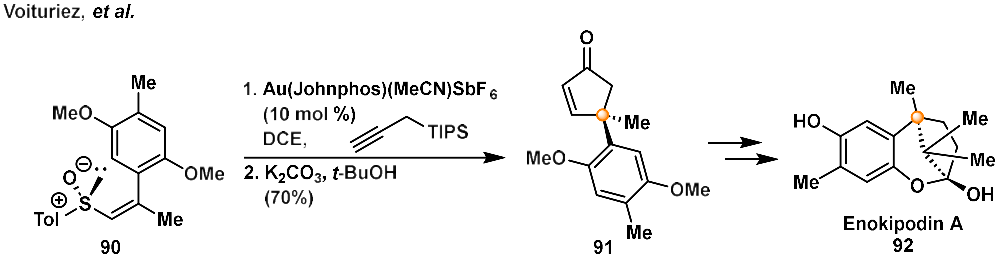
Scheme 4.9. A summary of total syntheses using gold-catalyzed Claisen rearrangement of propargyl vinyl ethers in forming all-carbon quaternary centers.

In 2004, the Toste group reported the first examples of gold(I)-catalyzed Claisen rearrangement of propargyl vinyl ethers (**76**) to give allenes (**78**)^{27}. The rearrangement reaction was applied by the

Ley group in their synthesis of azadirachtin (**81**) and by the Carreira group in their synthesis of indoxamycin B (**84**)[28].



Scheme 4.10. [3.3]-sigmatropic rearrangements of alkyne adducts **87** under gold catalysis.

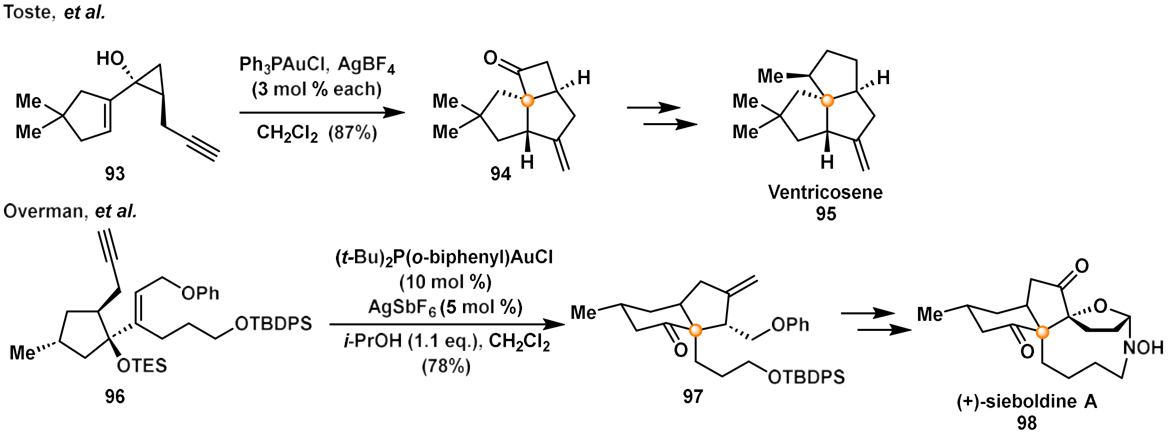


Scheme 4.11. Voituriez's synthesis of enokipodin A (**92**).

Another class of transformations involves a nucleophilic atom adding into an alkyne activated by gold, then cationic intermediate **87** undergoes a [3.3]-sigmatropic rearrangement to give product **89** that may potentially contain an all-carbon quaternary center. In 2007, the Gagosz group first reported such transformation with a tertiary amine as the nucleophile (Y = NR_2), giving 2,3-disubstituted pyrroles with all-carbon quaternary centers in the 2-substitution[29]. The same group later reported a similar reaction with an ether as the nucleophile (Y = OR), to give furans with similar substitutional patterns[30]. Multiple other works report the successful transformation with ethers, alcohols, or sulfides as the nucleophile (Y = OR, OH, or SR)[31]. Inspired by the works from the Toste[32], Ujaque, and Asensio groups[33], the Voituriez group reported a transformation using vinyl sulfoxide as the nucleophile for the efficient synthesis of cyclopentenones with C-4-all-carbon quaternary centers and applied the reaction in the total synthesis of several sesquiterpenoids (represented by **92**)[34].

Another unique example of a gold-catalyzed Cope rearrangement was reported on cyclopropylidenes bearing 1,5-dienes, which benefits from the strain release of the substrate[35].

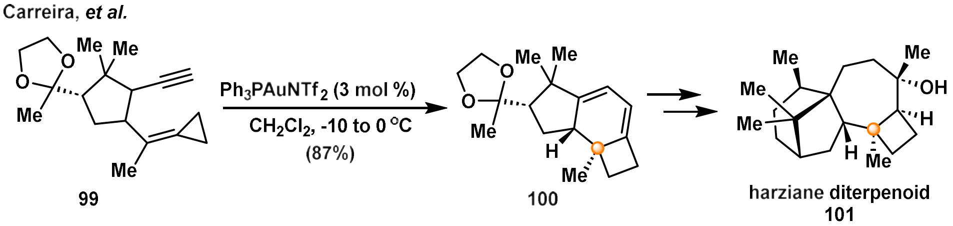
4.3.3 All-carbon Quaternary Center Formation by Wagner-Meerwein shift



Scheme 4.12. A summary of total syntheses using gold-catalyzed cationic ring expansion in forming all-carbon quaternary centers.

The cationic nature of gold(I) catalysis also means that the carbocation-like intermediates can undergo Wagner-Meerwein shift to generate skeletal rearranged products. The Toste group observed the semi-pinacol-type ring expansion rearrangement of 1-propargyl cyclopropanols and cyclobutanols under gold-catalysis[36]. Later, the same group expanded the scope of the cationic intermediate to those generated from gold-catalyzed enyne cycloisomerizations, to generate products with all-carbon quaternary centers, including **94**, a precursor that led to the total synthesis of angular-triquinane-bearing natural product, ventricosene (**95**)[37]. A similar transformation was undertaken by the Overman group as the key step in their synthesis of sieboldine A (**98**)[38]. Multiple other reports also show the possibility of designing semi-pinacol-type rearrangements in tandem with more complicated gold-catalyzed transformations, that can potentially lead to the formation of all-carbon quaternary centers[39].

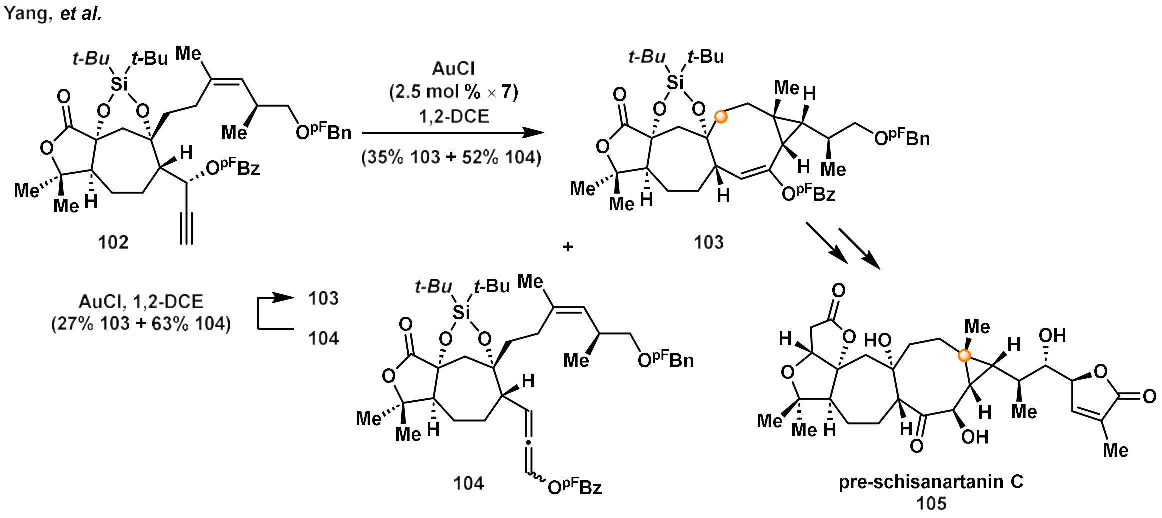
One interesting example by the Gagne group showed the possibility of a Wagner-Meerwein shift driven merely by strain release[40] to form products with cyclobutane rings. The Carreira group in 2020, reported their total synthesis of harziane diterpenoid (**101**) utilizing the reaction as a key transformation[41].



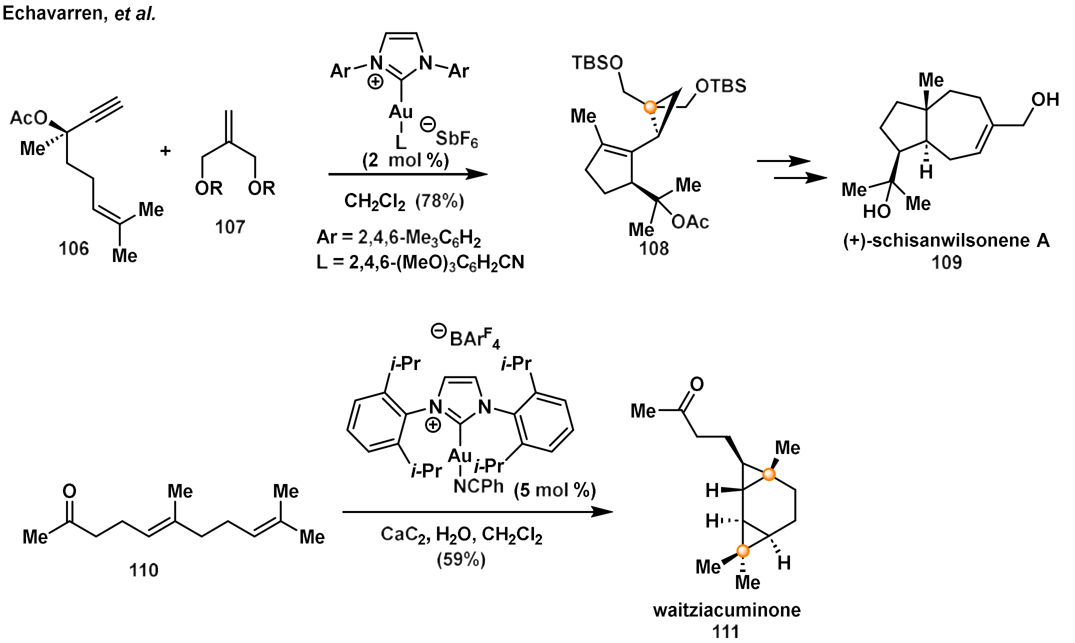
Scheme 4.13. Carreira's synthesis of harziane diterpenoid (**101**).

4.3.4 All-carbon Quaternary Center Formation by Gold-carbene-mediated Cyclopropanation

Multiple transformations we have discussed so far involve the formation of gold carbene intermediates. The Toste group, in 2005, first demonstrated that gold carbenes generated from 1,2-acyl shift of propargyl esters can be intercepted by alkenes to form cyclopropane[42]. Intramolecular versions of this transformation were found to be powerful in constructing medium-sized rings[43]. Inspired by these works, the Yang group applied the reaction in building the bicyclo-[6.1.0] system with an angular all-carbon quaternary center in pre-schisanartanin C (**105**)[44]. A significant amount of allene side-product **104** from a Meyer–Schuster rearrangement was isolated and was resubjected to the same gold-catalyzed condition to give the desired product **103**.



Scheme 4.14. Yang's synthesis of pre-schisanartanin C (**105**).

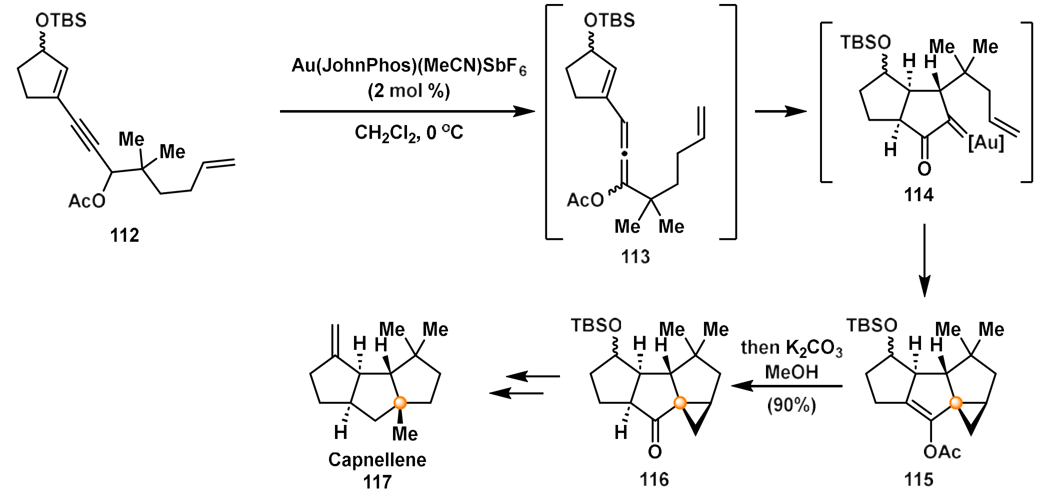


Scheme 4.15. Echavarren's syntheses of (+)-schisanwilsonene A (**109**) and waitziacuminone (**111**).

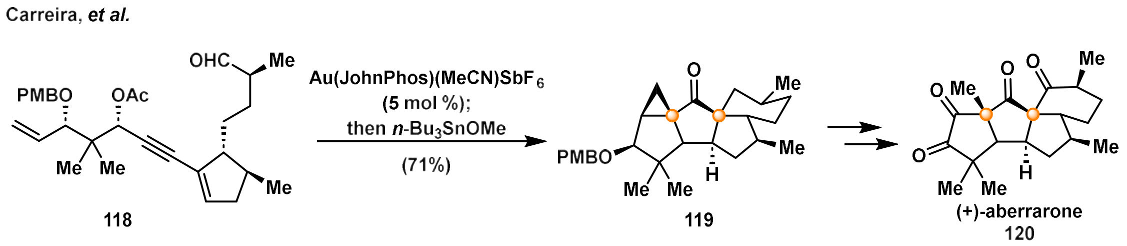
In 2006, the Echavarren group found that gold carbenes generated from enyne cycloisomerization processes (intermediates **49** and **50**) could also undergo cyclopropanation reaction with alkenes[45].

The same group then applied this transformation in the syntheses of (+)-schisanwilsonene A (**109**)[46] and waitziacuminone (**111**), both of which bear all-carbon quaternary centers[47].

A unique gold-catalyzed cascade of Meyer–Schuster rearrangement/ Nazarov cyclization/ cyclopropanation was reported by the Malacria group in 2007. The conjugated enyne part of substrate **112** was rearranged into allene **113**, which undergoes a Nazarov cyclization[48] to generate gold carbene intermediate **114**, and further reacts with the remote alkene to give the cyclopropanation products (represented by **115**).[49] The same group thoroughly studied the mechanism of the reaction and applied it in the synthesis of linear triquinane natural product capnellene (**117**)[50]. In 2022, the Carreira group applied the same transformation in their synthesis of (+)-aberrarone.[51] In both syntheses, the cyclopropane products were reduced to generate the angular methyl groups next to all-carbon quaternary centers.



Scheme 4.16. Malacria's synthesis of capnellene (**117**) using a gold-catalyzed cascade of Meyer–Schuster rearrangement/ Nazarov cyclization/ cyclopropanation.



Scheme 4.17. Carreira's synthesis of (+)-aberrarone (**120**).

4.3.5 Discussions

In the previous sections, we have shown the power of gold(I)-catalysis in the formation of all-carbon quaternary centers. The Gorin and Toste review has explained the exceptional reactivity of gold(I)-catalysis in allene- and alkyne-bearing systems in detail. To further explain the outstanding reactivity in all-carbon quaternary center forming systems, we think the linear nature of gold(I)-complexes plays an important role. Although methodologists who are interested in asymmetric catalysis may complain about the ligand being pointed away from the reaction center, this geometry is highly desirable for the formation of all-carbon quaternary centers. In fact, bulky biaryl phosphine ligands are often the most desirable in many gold(I)-catalyzed transformations[52] to stabilize the catalyst. In some difficult systems, special bulky ligands have been used to create confined reaction sites[53]. In addition, the common electrophilic components for such reactions, alkynes, are also linear. Thus, the reaction system overall is less sensitive to the bulkiness of the nucleophilic component, which can explain the success of our tandem gold-catalyzed cyclization forming contiguous all-carbon quaternary centers.

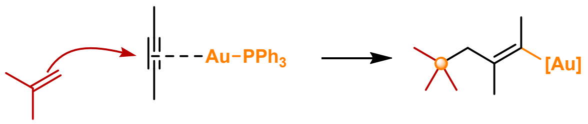
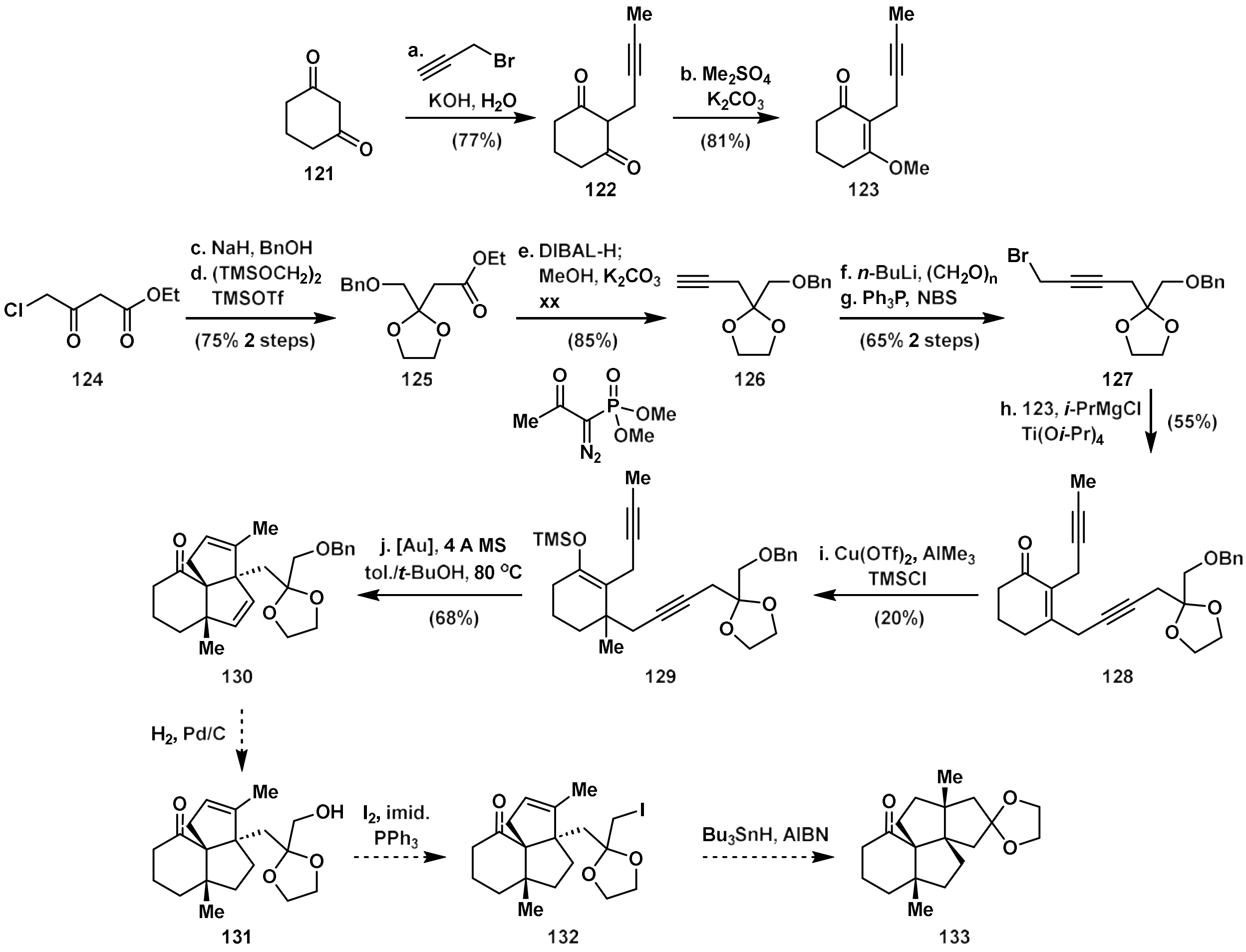


Figure 4.3. The desirable linear conformations of alkynes and gold complexes for forming all-carbon quaternary centers.

4.4 Proposals for Applying the Transformation in Natural Product Synthesis

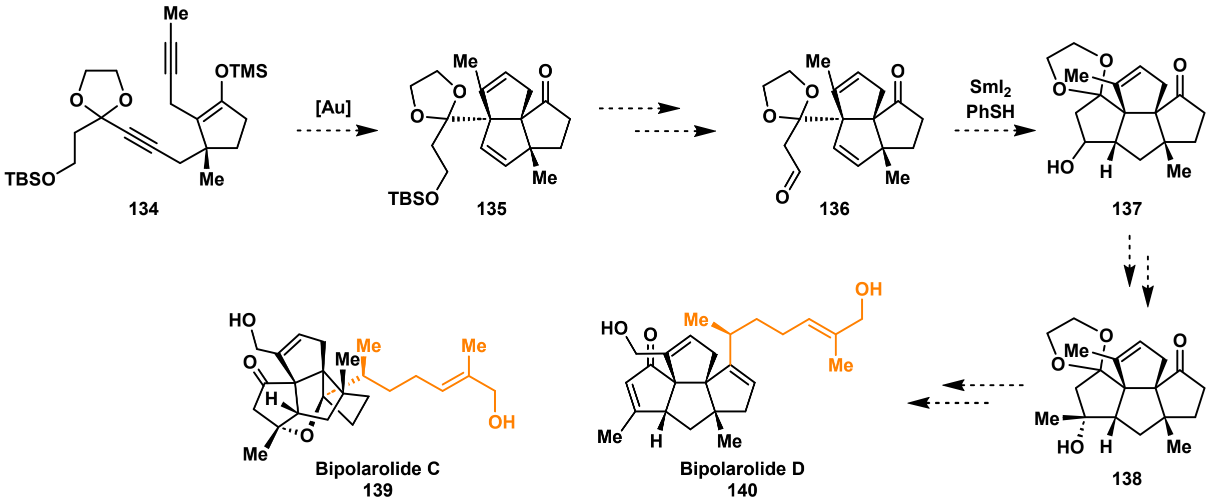
4.4.1 Waihoensene



Scheme 4.18. The proposed formal synthesis of waihoensene. (a) **121** (1.2 equiv), 1-bromo-2-butyne (1.0 equiv), KOH (1.5 equiv), H_2O, 23 °C, 16 h, 77%. (b) K_2CO_3 (3.0 equiv), Me_2SO_4 (1.1 equiv), acetone, 50 °C, 2 h, 81%. (c) NaH (2.0 equiv), BnOH (1.1 equiv), THF, 23 °C, 16 h (d) 1,2-Bis(trimethylsiloxy)ethane (1.25 equiv), TMSOTf (0.2 equiv), CH_2Cl_2, 23 °C, 16 h, 75% (2 steps). (e) DIBAL-H (1.2 equiv), CH_2Cl_2, -78 °C, 15 min; then MeOH, Ohira-Bestmann reagent (2.0 equiv), K_2CO_3 (3.0 equiv), 23 °C, 16 h, 85%. (f) *n*-BuLi (1.2 equiv), THF, -78 °C, 1 h; then $(CH_2O)_n$, 23 °C, 16 h, 72%. (g) Triphenylphospine (1.2 equiv). NBS (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 90%. (h) **123** (1.0 equiv), **127** (2.0 equiv), Ti(O*i*Pr)$_4$ (2.0 equiv), *i*PrMgCl (4.0 equiv), CH_2Cl_2, -78 °C, 16 h, 55%. (i) $Cu(OTf)_2$ (0.2 equiv), $AlMe_3$ (3.0 equiv), TMSCl (4.0 equiv), THF, -78 °C, 1 h; then 23 °C, 5 h, 20%, unoptimized. (j)Au(JohnPhos)(MeCN)SbF_6 (0.10 equiv), toluene/*t*-BuOH, 4 Å MS, 80 °C, 16 h, 68%, unoptimized.

Realizing the similarity between the structure of **11** and that of waihoensene, we began our pursuit toward a more concise formal of waihoensene. Starting from chloroacetylacetate **124**, a 3-steps sequence including a one-pot reduction and Ohira-Bestmann homologation from Stockdill and co-workers[54] gave alkyne **126**. Deprotonation and subsequent reaction with paraformaldehyde, followed by an Appel bromination afforded propargyl bromide **127**. Next, a titanium-mediated condition[55] was effective in connecting the alkyne to vinylogous ester **123**. Methyl cuprate 1,4-addition and subsequent capping by TMSCl successfully afforded silyl enol ether **129**, albeit in poor yield. Further optimization of the step is underway. The gold-catalyzed tandem cyclization reaction then successfully gave tricyclic compound **130**. Future plans that are being investigated involve: (1) a selective reduction of the di-substituted alkene and the benzyl ether to give **131**; (2) an Appel reaction to give iodide **132**; and (3) a Giese-type radical cyclization reaction to give tetracyclic compound **133**, which is an intermediate in Yang's synthesis of waihoensene[56].

4.4.2 Bipolarolides C and D



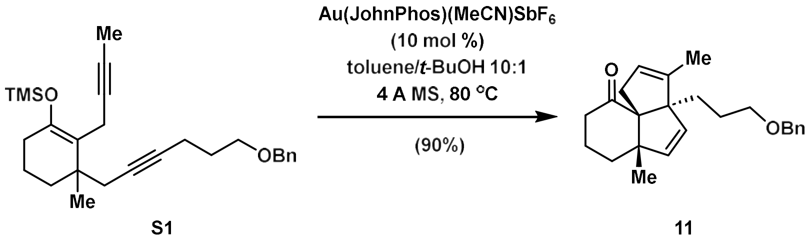
Scheme 4.19. The proposed synthesis of bipolarolide C and D.

We have also proposed to synthesize bipolarolides C and D (**139** and **140**) using the gold-catalyzed tandem cyclization reaction. As shown in section 4.2, the transformation is compatible with 5-membered ring starting materials. We project to apply a such transformation on diyne **134** to give tricyclic compound **135** bearing 3 contiguous all-carbon quaternary centers. Then, a SmI_2-

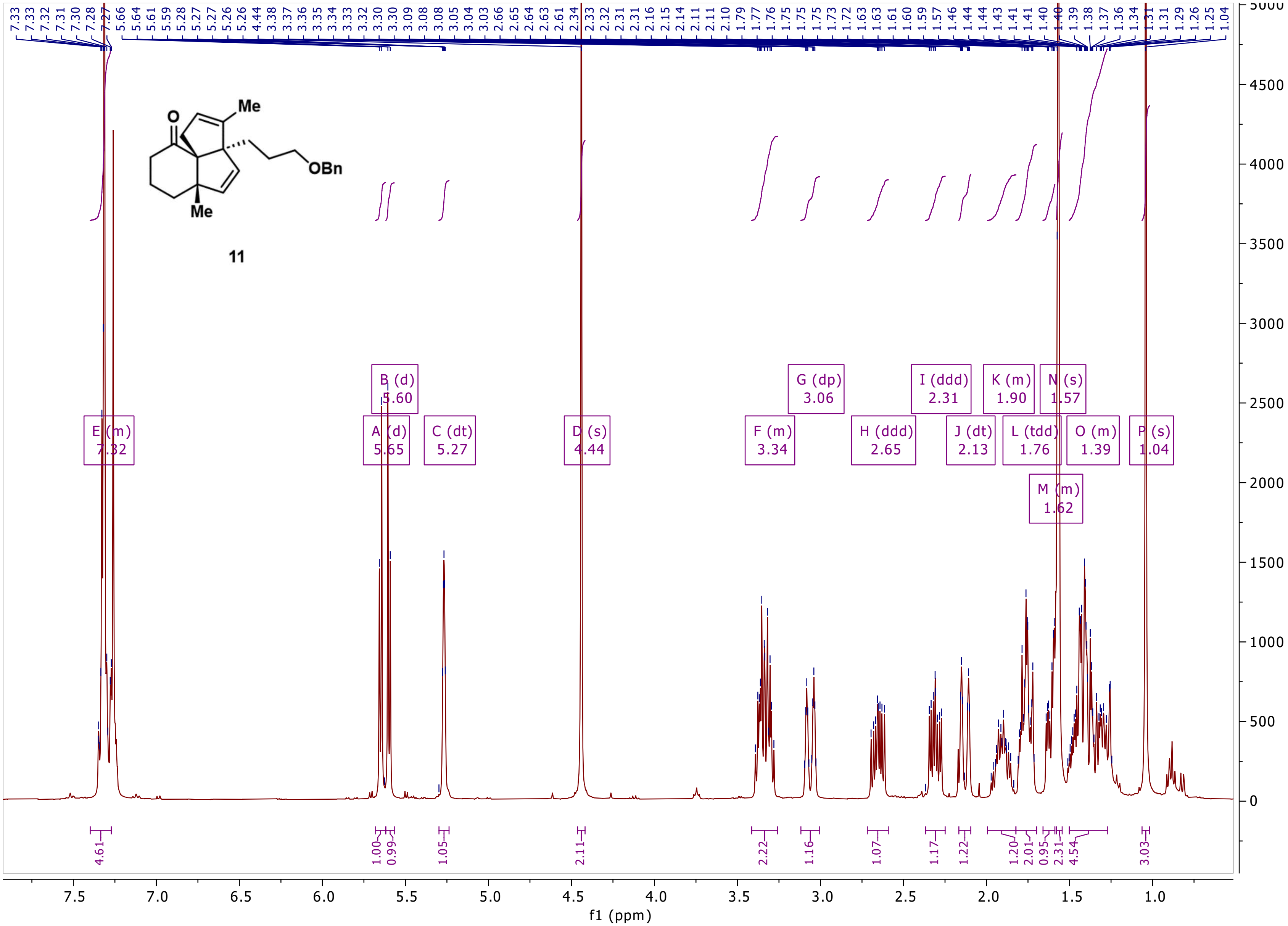
mediated reductive radical cyclization reaction similar to the one we described in the synthetic studies toward bipolarolides A and B was proposed to construct the fourth cyclopentane ring. Subsequent functional group manipulations should afford **139** and **140** concisely.

Supporting Information

General procedure for the tandem gold-catalyzed cyclization reaction:



Tricyclic ketone **11**: to a 10 mL round bottom flask equipped with a magnetic stir bar was added molecular sieves (4 Å, powdered, 60 mg, 200 wt%). The flask was flame-dried under vacuum, cooled to 23 ºC, and backfilled with argon. A solution of alkyne **S1** (29.5 mg, 0.0698 mmol, 1.0 equiv) in anhydrous toluene (1.4 mL) and *t*-BuOH (0.14 mL) was transferred to the reaction flask via syringe. The resultant mixture was stirred for 5 minutes before Au(JohnPhos)(MeCN)SbF$_6$ (5.4 mg, 0.0070 mmol, 10 mol%) was added in one portion. The reaction mixture was heated to 80 ºC and stirred at that temperature for 16 h, at which time TLC analysis showed the complete consumption of **S1**. The reaction mixture was diluted with hexanes (2 mL), and loaded directly onto a silica column for purification by flash column chromatography (silica gel, hexanes/EtOAc, 10/1→4/1) to give tricyclic ketone **11**(22.0 mg, 90% yield) as a colorless oil. **11**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.27 (m, 5H), 5.65 (d, *J* = 5.7 Hz, 1H), 5.60 (d, *J* = 5.7 Hz, 1H), 5.27 (dt, *J* = 3.1, 1.7 Hz, 1H), 4.44 (s, 2H), 3.41 – 3.26 (m, 2H), 3.06 (dp, *J* = 17.1, 2.6 Hz, 1H), 2.65 (ddd, *J* = 15.2, 11.0, 6.2 Hz, 1H), 2.31 (ddd, *J* = 15.2, 9.6, 4.3 Hz, 1H), 2.13 (dt, *J* = 17.0, 2.3 Hz, 1H), 1.99 – 1.82 (m, 1H), 1.76 (tdd, *J* = 12.1, 6.3, 2.7 Hz, 2H), 1.66 – 1.59 (m, 1H), 1.57 (s, 3H), 1.50 – 1.27 (m, 4H), 1.04 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 215.01, 140.71, 139.55, 138.90, 134.57, 128.42, 127.67, 127.51, 124.05, 72.76, 72.71, 70.98, 70.96, 56.26, 37.62, 35.11, 33.74, 30.95, 25.12, 24.41, 19.71, 13.29.

7.33 7.33 7.32 7.31 7.30 7.28 7.27 5.66 5.64 5.61 5.59 5.28 5.27 5.27 5.26 4.44 3.38 3.37 3.36 3.35 3.34 3.33 3.32 3.30 3.30 3.09 3.08 3.08 3.05 3.04 3.03 2.66 2.65 2.64 2.63 2.61 2.34 2.33 2.32 2.31 2.31 2.16 2.15 2.14 2.11 2.11 2.10 1.79 1.77 1.76 1.75 1.75 1.75 1.73 1.72 1.63 1.63 1.61 1.60 1.59 1.57 1.46 1.44 1.44 1.43 1.41 1.41 1.40 1.40 1.39 1.38 1.37 1.36 1.34 1.31 1.31 1.29 1.26 1.25 1.04
O
Me
OBn
Me
11
E (m) 7.32
B (d) 5.60
A (d) 5.65
C (dt) 5.27
D (s) 4.44
F (m) 3.34
G (dp) 3.06
H (ddd) 2.65
I (ddd) 2.31
J (dt) 2.13
K (m) 1.90
L (tdd) 1.76
M (m) 1.62
N (s) 1.57
O (m) 1.39
P (s) 1.04
4.61
1.00
0.99
1.05
2.11
2.22
1.16
1.07
1.17
1.22
1.20
2.01
0.95
2.31
4.54
3.03
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
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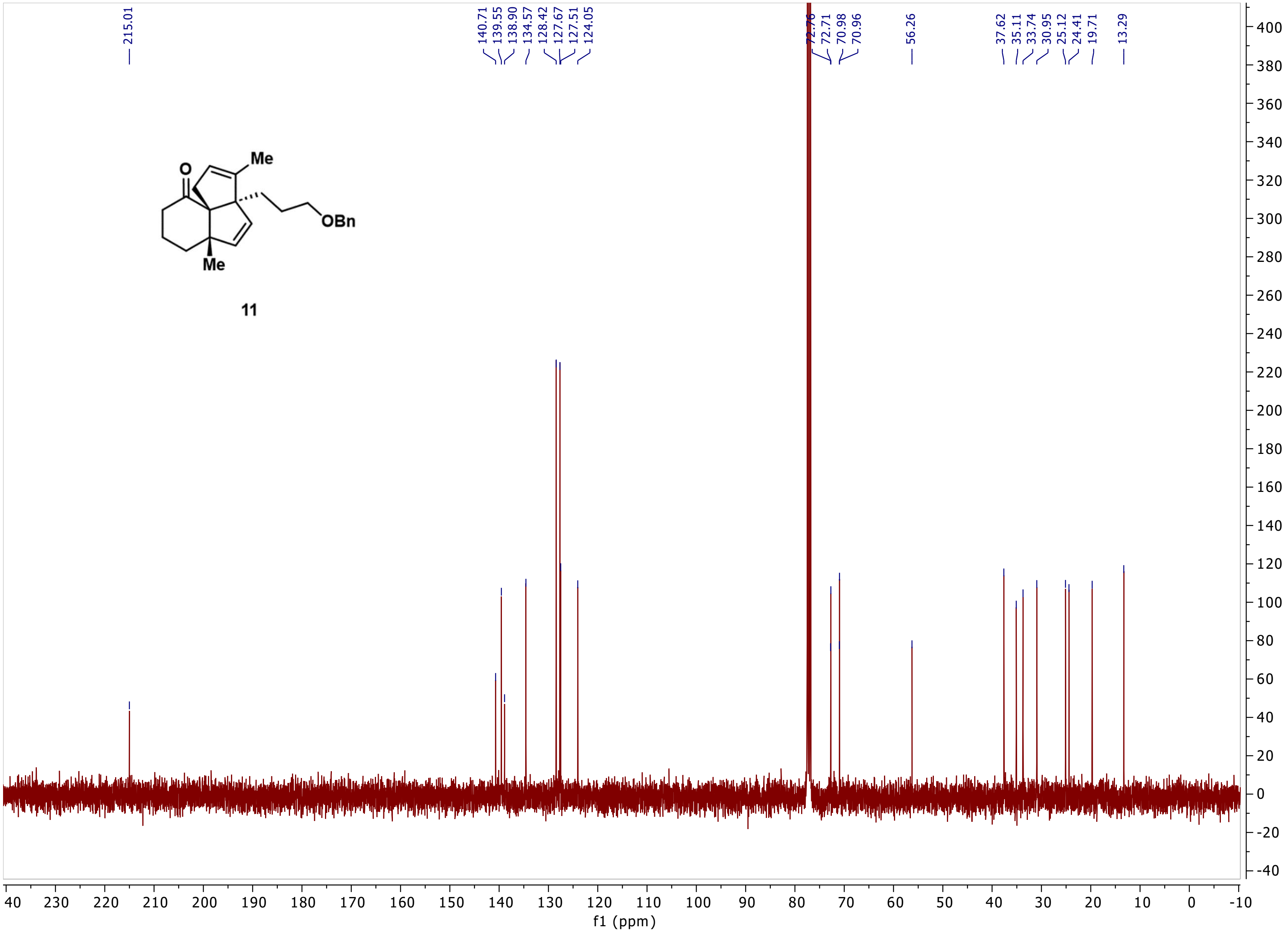
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)


215.01
140.71
139.55
138.90
134.57
128.42
127.67
127.51
124.05
72.76
72.71
70.98
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56.26
37.62
35.11
33.74
30.95
25.12
24.41
19.71
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O
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400
380
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340
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260
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220
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180
160
140
120
100
80
60
40
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0
-20
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230
220
210
200
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130
120
110
100
90
80
70
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50
40
30
20
10
0
-10
f1 (ppm)

11

References

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[1] Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. Synthesis of Fused Carbocycles via a Selective 6-*Endo* Dig Gold(I)-Catalyzed Carbocyclization. *Org. Lett.* **2011**, *13*, 5580–5583.

[2] (a) Kennedy-Smith, J. J.; Staben, S. T.; F. Dean Toste. Gold(I)-Catalyzed Conia-Ene Reaction of β-Ketoesters with Alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. Gold(I)-Catalyzed 5-Endo-Dig Carbocyclization of Acetylenic Dicarbonyl Compounds. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352.

[3] Linghu, X.; Kennedy-Smith, Joshua J.; Toste, F. Dean. Total Synthesis of (+)-Fawcettimine. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671–7673.

[4] McGee, P.; Bétournay, G.; Barabé, F.; Barriault, L. An 11-Steps Total Synthesis of Magellanine through a Gold(I)-Catalyzed Dehydro Diels-Alder Reaction. *Angew. Chem., Int. Ed.* **2017**, *56*, 6280–6283.

[5] Guo, L.; Frey, W.; Plietker, B. Catalytic Enantioselective Total Synthesis of the Picrotoxane Alkaloids (−)-Dendrobine, (−)-Mubironine B, and (−)-Dendroxine. *Org. Lett.* **2018**, *20*, 4328–4331.

[6] Yokoshima, S.; Watanabe, S.; Ishikawa, M.; Nomura, T.; Fukuyama, T. Total Synthesis of Lycoposerramine-R. *Synlett* **2018**, *29*, 2377–2380.

[7] Qu, P.; Snyder, S. A. Concise and Stereoselective Total Syntheses of Annotinolides C, D, and E. *J. Am. Chem. Soc.* **2021**, *143*, 11951–11956.

[8] Nishiyama, D.; Ohara, A.; Chiba, H.; Kumagai, H.; Oishi, S.; Fujii, N.; Ohno, H. Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization. *Org. Lett.* **2016**, *18*, 1670–1673.

[9] Zhou, Z.; Gao, A. X.; Snyder, S. A. Total Synthesis of (+)-Arborisidine. *J. Am. Chem. Soc.* **2019**, *141*, 7715–7720.

[10] He, F.; Feng, S.; Zhao, Y.; Shi, H.; Duan, X.; Li, H.; Xie, X.; She, X. Collective Total Syntheses of Five *Lycopodium* Alkaloids. *Angew. Chem., Int. Ed.* **2022**, *61*, e202205439.

[11] Luzung, M. R.; Markham, J. P.; Toste, F. D. Catalaytic Isomerization of 1,5-Enynes to Bicyclo[3.1.0]Hexenes. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859.

[12] Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. Cationic Gold(I) Complexes: Highly Alkynophilic Catalysts for the *exo*- And *endo*-Cyclization of Enynes. *Angew. Chem., Int. Ed.* **2004**, *116*, 2456–2460.

[13] (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. Divergent Mechanisms for the Skeletal Rearrangement and [2+2] Cycloaddition of Enynes Catalyzed by Gold. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146–6148. (b) Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. On the Mechanism of the Puzzling "Endocyclic" Skeletal Rearrangement of 1,6-Enynes. *Eur. J. Org. Chem.* **2007**, *2007*, 4217–4223. (c) López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. Nature of the Intermediates in Gold(I)-Catalyzed Cyclizations of 1,5-Enynes. *Chem. Eur. J.* **2011**, *17*, 10972–10978.

[14] For reviews on the diverse reaction outcome: (a) Dorel, R.; Echavarren, A. M. Gold-Catalyzed Reactions via Cyclopropyl Gold Carbene-like Intermediates. *J. Org. Chem.* **2015**, *80*, 7321–7332. (b) Jiménez-Núñez, E.; Echavarren, A. M. Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. *Chem. Rev.* **2008**, *108*, 3326–3350. For a review of other-metals-catalyzed processes involving such intermediates, see: (c) Echavarren, A. M.; Nevado, C. Non-

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Stabilized Transition Metal Carbenes as Intermediates in Intramolecular Reactions of Alkynes with Alkenes. *Chem. Soc. Rev.* **2004**, *33*, 431.

[15] (a) Gagosz, F. Unusual Gold(I)-Catalyzed Isomerization of 3-Hydroxylated 1,5-Enynes: Highly Substrate-Dependent Reaction Manifolds. *Org. Lett.* **2005**, *7*, 4129–4132. (b) Watson, I. D. G.; Ritter, S.; Toste, F. D. Asymmetric Synthesis of Medium-Sized Rings by Intramolecular Au(I)-Catalyzed Cyclopropanation. *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057.

[16] Weeks, K. L.; Williams, J. D.; Boyce, G. R. A Three-Step Enantioselective Synthesis of (+)- and (−)-α-Thujone. *Org. Biomol. Chem.* **2021**, *19*, 8018–8020.

[17] Homs, A.; Muratore, M. E.; Echavarren, A. M. Enantioselective Total Synthesis of (−)-Nardoaristolone B via a Gold(I)-Catalyzed Oxidative Cyclization. *Org. Lett.* **2015**, *17*, 461–463.

[18] (a) Witham, C. A.; Mauleón, P.; Shapiro, N. I.; Sherry, B. D.; F. Dean Toste. Gold(I)-Catalyzed Oxidative Rearrangements. *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839.

[19] The only example of this transformation to our knowledge is our example described in section 3.6.1.

[20] Gimeno, A.; Rodríguez-Gimeno, A.; Cuenca, A. B.; Ramírez de Arellano, C.; Medio-Simón, M.; Asensio, G. Gold(I)-Catalysed Cascade Reactions in the Synthesis of 2,3-Fused Indole Derivatives. *Chem. Commun.* **2015**, *51*, 12384–12387.

[21] Toullec, P.; Michelet, V.; Pradal, A.; Chen, Q.; Faudot dit Bel, P. Gold-Catalyzed Cycloisomerization of Functionalized 1,5-Enynes - an Entry to Polycyclic Framework. *Synlett* **2011**, *2012*, 74–79.

[22] Carreras, J.; Livendahl, M.; McGonigal, P. R.; Echavarren, A. M. Gold(I) as an Artificial Cyclase: Short Stereodivergent Syntheses of (−)-Epiglobulol and (−)-4β,7α- and (−)-4α,7α-Aromadendranediols. *Angew. Chem., Int. Ed.* **2014**, *53*, 4896–4899.

[23] (a) López-Carrillo, V.; Echavarren, A. M. Gold(I)-Catalyzed Intermolecular [2+2] Cycloaddition of Alkynes with Alkenes. *J. Am. Chem. Soc.* **2010**, *132* (27), 9292–9294. (b) de Orbe, M. E. Intermolecular [2+2] Cycloaddition of Alkynes with Alkenes Catalyzed by Gold(I). *Org. Synth.* **2016**, *93*, 115–126.

[24] (a) de Orbe, M. E.; Amenós, L.; Kirillova, M. S.; Wang, Y.; López-Carrillo, V.; Maseras, F.; Echavarren, A. M. Cyclobutene vs 1,3-Diene Formation in the Gold-Catalyzed Reaction of Alkynes with Alkenes: The Complete Mechanistic Picture. *J. Am. Chem. Soc.* **2017**, *139* (30), 10302–10311. (b) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. The Role of Cyclobutenes in Gold(I)-Catalysed Skeletal Rearrangement of 1,6-Enynes. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111.

[25] (a) Odabachian, Y.; Gagosz, F. Cyclobutenes as Isolable Intermediates in the Gold(I)-Catalysed Cycloisomerisation of 1,8-Enynes. *Adv. Synth. Cat.* **2009**, *351*, 379–386. (b) Tu, Q.; Wang, Z.; Zhang, Z.; Huang, J.; Yang, Z. Synthetic Strategy for Construction of Highly Congested Tetracyclic Core (6–5–7–4) of Harziane Diterpenoids. *Org. Lett.* **2021**, *23*, 4088–4093.

[26] (a) Zhiyao Zhou, *Ph.D. Dissertation*, **2020**, the University of Chicago. (b) Philipp Gemmel, *Ph.D. Dissertation*, **2022**, the University of Chicago.

[27] (a) Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Propargyl Claisen Rearrangement. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979. (b) Mauleón, P.; Krinsky, J. L.; Toste, F. D. Mechanistic Studies on Au(I)-Catalyzed [3,3]-Sigmatropic Rearrangements Using Cyclopropane Probes. *J. Am. Chem. Soc.* **2009**, *131*, 4513–4520.

[28] Jeker, O. F.; Carreira, E. M. Total Synthesis and Stereochemical Reassignment of (±)-Indoxamycin B. *Angew. Chem., Int. Ed.* **2012**, *51*, 3474–3477.

---

[29] Istrate, F. M.; Gagosz, F. Synthesis of Functionalized Pyrroles via Gold(I)-Catalyzed Aza-Claisen-Type Rearrangement. *Org. Lett.* **2007**, *9*, 3181–3184.

[30] Istrate, F. M.; Gagosz, F. Gold(I)-Catalyzed Formation of Furans by a Claisen-Type Rearrangement of Ynenyl Allyl Ethers. *Beilstein J. Org. Chem.* **2011**, *7*, 878–885.

[31] (a) Cheong, J. Y.; Im, D.; Lee, M.; Lim, W.; Rhee, Y. H. Gold(I)-Catalyzed Synthesis of γ-Hydroxyketones from 5-Allyloxy-1-Ynes. *J. Org. Chem.* **2010**, *76*, 324–327. (b) Jun, J.; Yeom, H.-S.; An, J.-H.; Shin, S. Gold-Catalyzed Intermolecular Coupling of Sulfonylacetylene with Allyl Ethers: [3,3]- and [1,3]-Rearrangements. *Beilstein J. Org. Chem.* **2013**, *9*, 1724–1729. (c) Ketcham, J. M.; Biannic, B.; Aponick, A. The Tandem Intermolecular Hydroalkoxylation/Claisen Rearrangement. *Chem. Commun.* **2013**, *49*, 4157–4159. (d) Hashmi, A. S. K.; Graf, K.; Ackermann, M.; Rominger, F. Gold(I)-Catalyzed Domino Reaction of Allyl 2-En-4-Ynyl Ethers to 1,3,6-Trien-4-Yl Ketones. *ChemCatChem* **2013**, *5*, 1200–1204. (e) Park, S. R.; Kim, C.; Kim, D.; Thrimurtulu, N.; Yeom, H.-S.; Jun, J.; Shin, S.; Rhee, Y. H. Entry to β-Alkoxyacrylates via Gold-Catalyzed Intermolecular Coupling of Alkynoates and Allylic Ethers. *Org. Lett.* **2013**, *15*, 1166–1169. (f) Ackermann, M.; Bucher, J.; Rappold, M.; Graf, K.; Rominger, F.; Hashmi, A. S. K. [3,3]-Sigmatropic Rearrangement Step in the Gold-Catalyzed Cyclization of Allyl-(*Ortho*-Alkinylphenyl)Methyl Ethers. *Chem. Asian J.* **2013**, *8*, 1786–1794. (g) Wu, H.; Zi, W.; Li, G.; Lu, H.; Toste, F. D. Gold(I)-Catalyzed Desymmetrization of 1,4-Dienes by an Enantioselective Tandem Alkoxylation/Claisen Rearrangement. *Angew. Chem., Int. Ed.* **2015**, *54*, 8529–8532. (h) Kim, H.; Jang, J.; Shin, S. Gold-Catalyzed Asymmetric Thioallylation of Propiolates via Charge-Induced Thio-Claisen Rearrangement. *J. Am. Chem. Soc.* **2020**, *142*, 20788–20795.

[32] Shapiro, N. D.; Toste, F. D. Rearrangement of Alkynyl Sulfoxides Catalyzed by Gold(I) Complexes. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161.

[33] Cuenca, A. B.; Montserrat, S.; Hossain, K. M.; Mancha, G.; Lledós, A.; Medio-Simón, M.; Ujaque, G.; Asensio, G. Gold(I)-Catalyzed Intermolecular Oxyarylation of Alkynes: Unexpected Regiochemistry in the Alkylation of Arenes. *Org. Lett.* **2009**, *11*, 4906–4909.

[34] (a) Zhou, W.; Voituriez, A. Gold(I)-Catalyzed Synthesis of Highly Substituted 1,4-Dicarbonyl Derivatives via Sulfonium [3,3]-Sigmatropic Rearrangement. *Org. Lett.* **2020**, *23*, 247–252. (b) Zhou, W.; Voituriez, A. Synthesis of Cyclopentenones with C4-Quaternary Stereocenters via Stereospecific [3,3]-Sigmatropic Rearrangement and Applications in Total Synthesis of Sesquiterpenoids. *J. Am. Chem. Soc.* **2021**, *143*, 17348–17353.

[35] Felix, R. J.; Weber, D.; Gutierrez, O.; Tantillo, D. J.; Gagné, M. R. A Gold-Catalysed Enantioselective Cope Rearrangement of Achiral 1,5-Dienes. *Nature Chemistry* **2012**, *4* (5), 405–409.

[36] Markham, J. P.; Staben, S. T.; Toste, F. D. Gold(I)-Catalyzed Ring Expansion of Cyclopropanols and Cyclobutanols. *J. Am. Chem. Soc.* **2005**, *127*, 9708–9709.

[37] Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. Au(I)-Catalyzed Ring Expanding Cycloisomerizations: Total Synthesis of Ventricosene. *Org. Lett.* **2008**, *10*, 4315–4318.

[38] Canham, S. M.; France, D. J.; Overman, L. E. Total Synthesis of (+)-Sieboldine A. *J. Am. Chem. Soc.* **2010**, *132* (23), 7876–7877.

[39] (a) Zheng, T.-L.; Zhang, Y.; Gou, A-Long.; Cheng, F.; Liu, S.-Z.; Yu, L.; Cui, M.-Y.; Xu, X.-T.; Zhang, K.; Wang, S.-H. Au(I)-Catalyzed Cyclization/Semipinacol Rearrangement Reaction of Allenes to Construct Quaternary Carbon-Containing Scaffolds. *Org. Lett.* **2020**, *22*, 7073–7077. (b) Zhang, Y.; Zheng, T.-L.; Cheng, F.; Dai, K.-L.; Zhang, K.; Ma, A.-J.; Zhang, F.-M.; Zhang, X.-M.; Wang, S.-H.; Tu, Y.-Q. Facile Access to Diverse All-Carbon Quaternary Center Containing Spirobicycles by Exploring a Tandem Castro–Stephens Coupling/Acyloxy

---

Shift/Cyclization/Semipinacol Rearrangement Sequence. *Chem. Sci.* **2020**, *11*, 3878–3884. (c) Pitaval, A.; Leboeuf, D.; Ceccon, J.; Echavarren, A. M. Access to the Protoilludane Core by Gold-Catalyzed Allene-Vinylcyclopropane Cycloisomerization. *Org. Lett.* **2013**, *15*, 4580–4583.

[40] (a) Felix, R. J.; Gutierrez, O.; Tantillo, D. J.; Gagné, M. R. Gold(I)-Catalyzed Formation of Bicyclo[4.2.0]Oct-1-Enes. *The Journal of Organic Chemistry* **2013**, *78* (11), 5685–5690. (b) Zheng, H.; Felix, R. J.; Gagné, M. R. Gold-Catalyzed Enantioselective Ring-Expanding Cycloisomerization of Cyclopropylidene Bearing 1,5-Enynes. *Org. Lett.* **2014**, *16*, 2272–2275.

[41] Hönig, M.; Carreira, E. M. Total Synthesis and Structural Revision of a Harziane Diterpenoid. *Angew. Chem., Int. Ed.* **2019**, *59*, 1192–1196.

[42] Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. Gold(I)-Catalyzed Stereoselective Olefin Cyclopropanation. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003.

[43] (a) Boyer, F.-D.; Le Goff, X.; Hanna, I. Gold(I)-Catalyzed Cycloisomerization of 1,7- and 1,8-Enynes: Application to the Synthesis of a New Allocolchicinoid. *J. Org. Chem.* **2008**, *73*, 5163–5166. (b) Watson, I. D. G.; Ritter, S.; Toste, F. D. Asymmetric Synthesis of Medium-Sized Rings by Intramolecular Au(I)-Catalyzed Cyclopropanation. *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057. (c) Moreau, X.; Hours, A.; Fensterbank, L.; Goddard, J.-P.; Malacria, M.; Thorimbert, S. Use of Ionic Liquids in the Platinum- and Gold-Catalyzed Cycloisomerization of Enyne Systems. *J. Organomet. Chem.* **2009**, *694*, 561–565.

[44] Jiang, Y.; Yu, H.; Li, Y.; Pei Hua Qu; Han, Y.; Chen, J.; Yang, Z. Asymmetric Total Synthesis of Pre-Schisanartanin C. *Jo J. Am. Chem. Soc.* **2020**, *142* (1), 573–580.

[45] López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. Gold(I)-Catalyzed Intermolecular Cyclopropanation of Enynes with Alkenes: Trapping of Two Different Gold Carbenes. *Angew. Chem., Int. Ed.* **2006**, *118*, 6175–6178.

[46] Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J.; Echavarren, A. M. Synthesis of (+)-Schisanwilsonene a by Tandem Gold-Catalyzed Cyclization/1,5-Migration/Cyclopropanation. *Angew. Chem., Int. Ed.* **2013**, *52*, 6396–6399.

[47] Both the gold-catalyzed steps in the syntheses of (+)-schisanwilsonene A and waitziacuminone form an all-carbon quaternary center, albeit in the earlier case the quaternary center was eliminated during skeletal rearrangements with a new quaternary center formed.

[48] For the discovery of a similar gold-catalyzed Nazarov cyclization, see: Shi, X.; Gorin, D. J.; Toste, F. D. Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.

[49] Gilles Lemière; Gandon, V.; Cariou, K.; Fukuyama, T.; Anne-Lise Dhimane; Fensterbank, L.; Malacria, M. Tandem Gold(I)-Catalyzed Cyclization/Electrophilic Cyclopropanation of Vinyl Allenes. *Org. Lett.* **2007**, *9*, 2207–2209.

[50] Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. Generation and Trapping of Cyclopentenylidene Gold Species: Four Pathways to Polycyclic Compounds *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006.

[51] Amberg, W. M.; Carreira, E. M. Enantioselective Total Synthesis of (+)-Aberrarone. *J. Am. Chem. Soc.* **2022**, *144*, 15475–15479.

[52] Ranieri, B.; Escofet, I.; Echavarren, A. M. Anatomy of Gold Catalysts: Facts and Myths. *Org. Biomol. Chem.* **2015**, *13*, 7103–7118.

[53] (a) Ochida, A.; Ito, H.; Sawamura, M. Using Triethynylphosphine Ligands Bearing Bulky End Caps to Create a Holey Catalytic Environment: Application to Gold(I)-Catalyzed Alkyne Cyclizations. *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487. (b) Muratov, K.; Gagosz, F.

Confinement-Induced Selectivities in Gold(I) Catalysis—the Benefit of Using Bulky Tri-(*Ortho* - Biaryl)Phosphine Ligands. *Angew. Chem., Int. Ed.* **2022**, *61,* e2022034.

[54] Lopez, A.; Ibrahim, A.; Rosenhauer, G.; Sirinimal, H.; Stockdill, J. Tin-Free Access to the ABC Core of the Calyciphylline A Alkaloids and Unexpected Formation of a D-Ring-Contracted Tetracyclic Core. *Org. Lett.* **2018**, *20*, 2216-2219.

[55] (a) Nakagawa, T.; Kasatkin, A.; Sato, F. Highly Efficient Synthesis of Propargyl- and Allenyltitanium Reagents from Propargyl Halides or Propargyl Alcohol Derivatives. Practical Synthesis of Allenyl and Homopropargyl Alcohols. *Tetrahedron Lett.* **1995**, *36*, 3207–3210. (b) Nakayama, Y.; Maser, M. R.; Okita, T.; Dubrovskiy, A. V.; Campbell, T. L.; Reisman, S. E. Total Synthesis of Ritterazine B. *J. Am. Chem. Soc.* **2021**, *143*, 4187–4192.

[56] Qu, Y.; Wang, Z.; Zhang, Z.; Zhang, W.; Huang, J.; Yang, Z. Asymmetric Total Synthesis of (+)-Waihoensene. *J. Am. Chem. Soc.* **2020**, *142*, 6511–6515.