New Strategies for [2+2] Photocycloadditions of Aliphatic Alkenes

By

Christopher Shaw Gravatt

A dissertation submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

(Chemistry)

At the

UNIVERSITY OF WISCONSIN-MADISON

2020

Date of final oral examination: November 23rd, 2020

The dissertation is approved by the following members of the Final Oral Committee

Tehshik Yoon, Professor, Chemistry

Jennifer Schomaker, Professor, Chemistry

Randall Goldsmith, Associate Professor, Chemistry

Daniel Weix, Professor, Chemistry

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Christopher Shaw Gravatt

Under the Supervision of Professor Tehshik P. Yoon

At the University of Wisconsin-Madison

Abstract

Cyclobutanes are important targets in synthetic chemistry, due to their prominence in a diverse range of biologically active molecules displaying meaningful therapeutic properites. Among many methods for the synthesis of these strained rings, the most well-developed involves [2+2] photocycloaddition reactions of alkenes. To date, neither photoredox nor photosensitization processes have proven applicable to the activation of simple, unconjugated aliphatic alkenes. My doctoral research focused on solutions to this synthetic limitation through a range of photochemical tactics. Building upon early work from Salomon and Kochi on copper (I) catalyzed [2+2] photocycloadditions a more robust catalyst system for these reactions has been discovered and subsequently employed in the total synthesis of cyclobutane natural product (+)−sulcatine G.

Acknowledgements

I first would like to give special thanks to my advisor Professor Tehshik Yoon for his crucial role in my development as a scientist. Your approach to graduate school advising and true passion for the science has made obtaining my doctorate degree a truly life changing experience. I appreciate your constant guidance while at the same time allowing me to pursue my ideas and be very independent, which as an older slightly more mature student was very important to me. I further want to praise your patience not only with me but all your students, always being the voice of reason during times of high stress. I appreciate that you had enough confidence in me to have me to pursue research very much outside the scope of your program even a lengthy total synthesis project.

I want to thank the members of my committee for taking the time to see me off to the next steps. Professor Jennifer Schomaker, Professor Randal Goldsmith, and Professor Daniel Weix. I appreciate all of the productive input over the years and playing the parts you did in my scientific development. I also want to thank our outstanding support staff in the NMR, Mass Spec, and Crystallography facilities. Dr. Charlie Fry, Dr. Heike Hofstetter, Dr. Martha Vestling, and Dr. Ilia Guzei. I appreciate all the work you do and advice you readily give, my time here would not have been the same without all of you.

I want to thank all the past and present Yoon group members for too much to write about. You all made this experience truly unforgettable and I would not be where I am today without all of you. I want to give a special thanks to Bjung Joo Lee for being a constant friend and confidant your friendship made every day of graduate school a bit better. I also want to give special thanks to Andrew Maza of the Burke/Landis Group for taking so much time to discuss total synthesis, I really learned a lot from you, and I am a better synthetic chemist for it.

I want to give a special thanks to my ever-supportive family. My parents that listen to me talk about chemistry for hours even though they don’t know what I’m saying half the time. However, my wife Megan is the one that deserves a thanks I can do justice here but has been my rock throughout this whole process. She has deal with lack of vacations, late nights at work, and me not listening because I

am thinking about chemistry for five years and has not complained once! I would truly not been where I am today without her constant patience and understanding.

Chris

11/14/2020

Table of Contents

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

List of Schemes

Chapter 1

List of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 1. A Modern Synthetic Chemists Guide to Copper (I) Mediated [2+2] Photocycloadditions

1.1 Introduction

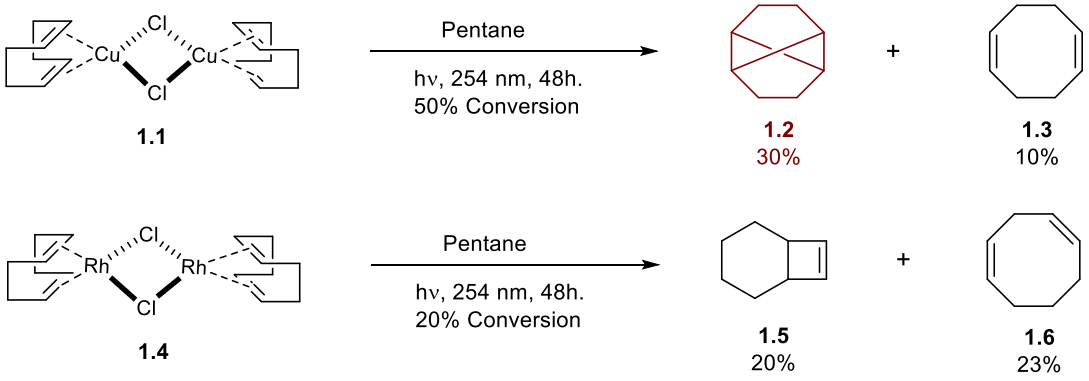
Cyclobutanes are important targets in synthetic chemistry.[1] They feature prominently in a surprisingly diverse range of bioactive natural products.[2] Many of the most well-developed strategies for the synthesis of cyclobutane rings involve photocycloaddition reactions.[3] The photoactivation strategies involved in these methods have included (*1*) direct photoexcitation of alkene compounds featuring conjugated pi systems with optical transitions in the visible or UV range[4] (*2*) photosensitization of conjugated pi systems with low-energy excited states accessible through facile energy transfer processes,[5] and (*3*) photoredox reactions that involve radical ion intermediates generated by photoinduced electron transfer.[6] None of these strategies, however, are generally applicable to the photoactivation of simple, unconjugated aliphatic alkenes. These substrates typically absorb only very short wavelengths (180–220 nm) that are not compatible with many common organic functional groups.[3a] They also possess high triplet energies (76–84 kcal/mol).[7] Simple alkenes possess electrochemical potentials[8] that lie outside of the range of most common photoredox catalysts.[9] The few methods that have been reported to mediate [2+2] cycloadditions of simple alkenes all involve a transition metal mediated radical redox event.[10]

The broadest of these methods for [2+2] cycloaddition of simple aliphatic alkenes is the CuOTf-catalyzed process originally developed by Kochi and Salomon.[11] This reaction involves the formation of a key 2:1 alkene–copper complex that absorbs at significantly longer wavelengths than isolated alkenes themselves. Excitation with UV light (254 nm) results in an inner-sphere charge transfer, which subsequently triggers cycloaddition. [11b] This method has enabled several total syntheses through [2+2] cycloadditions of aliphatic alkenes that could not be accomplished using direct photochemistry or through triplet sensitization. This chapter presents a review of what is known about its mechanism as well as other synthetic considerations that provide a guide to implementing this powerful reaction in a complex target-based setting.

1.2 Early Discovery

This initial discovery that copper was capable of catalyzing photochemical [2+2] cycloadditions came from experiments conducted by Srinivasan and co-workers in the 1960's involving irradiation of copper chloride cyclooctadiene dimer **1.1** with UV light.[12] Appreciable yields of the crossed [2+2] product **1.2** derived from cyclooctadiene were formed upon prolonged irradiation. It was also found that this reaction was specific to the copper complex as very different isomerization products were obtained upon irradiation of rhodium complex **1.4** (Scheme 1.1). Srinivasan and co-workers hypothesized that copper(I) might stabilize an electronic excited state of 1,5-cyclooctadiene that leads to the [2+2] product. Further investigation of this reaction conducted by Whitesides and co-workers suggested a different possibility involving initial formation of a coordination complex between copper(I) and free *cis,trans*- and *trans,trans*-1,5-cyclooctadiene formed during irradiation.[13] The authors suggest that this 1:1 complexation shifts the photoequilibrium towards the isomer that leads to product **1.2**. While Whitesides invokes a copper(I) olefin coordination complex, they hypothesized that the role of the transition metal was only to shift the position of the equilibrium rather than to act as a photocatalyst.

Scheme 1.1 Olefin dimerization Cuprous Chloride

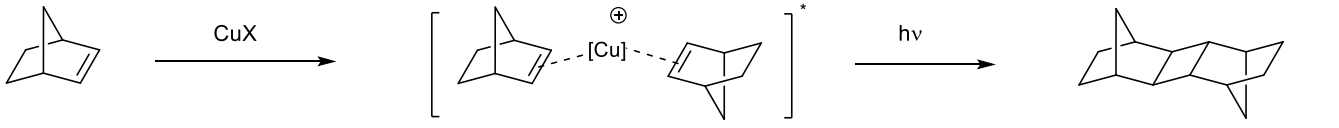


1.3 Copper Triflate and the Salomon – Kochi Reaction

Pioneering studies by Salomon and co-workers demonstrated that intermolecular dimerization of strained cyclic olefins, particularly norbornene **1.9,** could be accomplished by UV

irradiation in the presence of various copper (I) salts (Scheme 1.2).[11a] Interestingly, it was found that copper(I) triflate was a superior catalyst in these reactions giving much higher yields of the desired dimerization products.[11a] A thorough investigation of the mechanism of norbornene dimerization conducted by Salomon and Kochi revealed that the photoactive intermediate in this process was a 2:1 alkene:copper(I) complex whose absorption spectrum is substantially shifted to longer wavelengths in comparison with the free olefin.[11b] This observation also explains the rate increase when using CuOTf as triflate is far less coordinating than halide anions that would be more likely to disrupt olefin coordination to the copper(I) center.[11a] While this study clearly indicates the 2:1 complex as the photoactive species, the details of the actual bond-forming steps are proposed to involve charge transfer between the olefin and the metal center in the excited state.[11b] With this far more robust catalyst in hand and a much clearer understanding of the mechanism, Salomon subsequently reported a range of previously inaccessible [2+2] cycloadditions, making this a powerful synthetic strategy for synthesis of cyclobutane-containing products.

Scheme 1.2 Dimerization of Norbornene



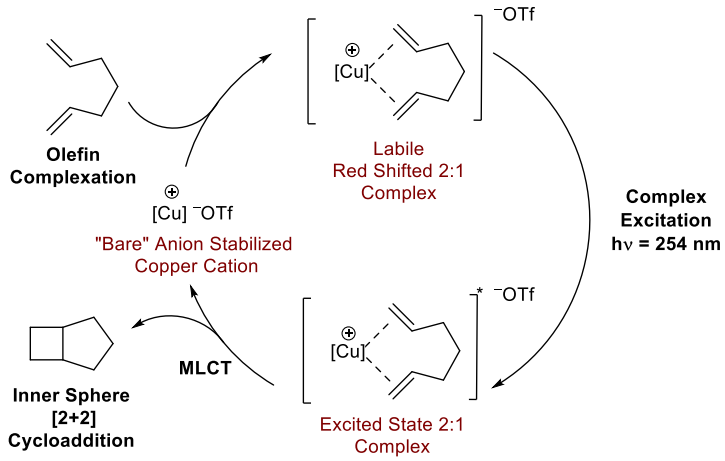
1.9 **2:1 Olefin: Cu Complex** **1.10**
CuBr = 38% Yield
CuOTf • C_6H_6 = 88% Yield

1.3.1 Mechanistic Proposals

The currently accepted mechanism for the transformation involves initial formation of a 2:1 alkene copper complex. This complex is red-shifted to wavelengths that are available using standard benchtop UV photoreactors (250–270 nm), while unbound simple unconjugated olefins absorb at much shorter wavelengths. This transition corresponds to an inner-sphere charge transfer that yields the desired cyclobutane product while regenerating your Cu(I) catalyst for

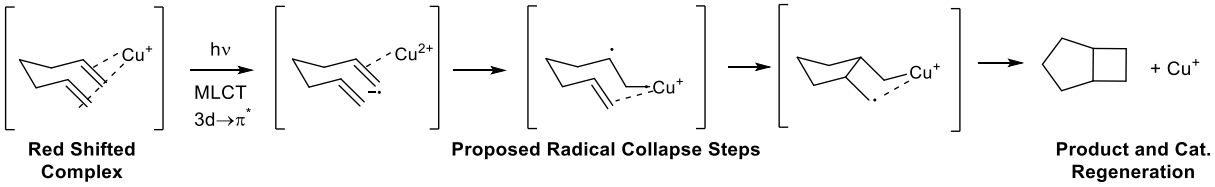
further turnovers (Figure 1.1). While this general mechanism is widely accepted, the details of the bond-forming steps themselves are still somewhat unclear.[11b]

Figure 1.1 Mechanistic Proposal of the Salomon and Kochi [2+2] Photocycloaddition



The most significant question has been whether the productive photochemical process involves metal-to-ligand charge transfer (MLCT) or ligand-to-metal charge transfer (LMCT). Computations conducted by Budzeller and co-workers suggest that the first step involves a 3d→π* MLCT. The resulting copper(II) alkene radical anion pair is then proposed to form a localized metal–carbon bond to fill its empty d orbital generating 1,3-biradical. Collapse of this biradical species by addition into the second alkene results in a net [2+2] cycloaddition and regeneration of the catalyst (Figure 1.2).[14]

Figure 1.2 Proposed Excitation and Bond Forming Steps via Computation



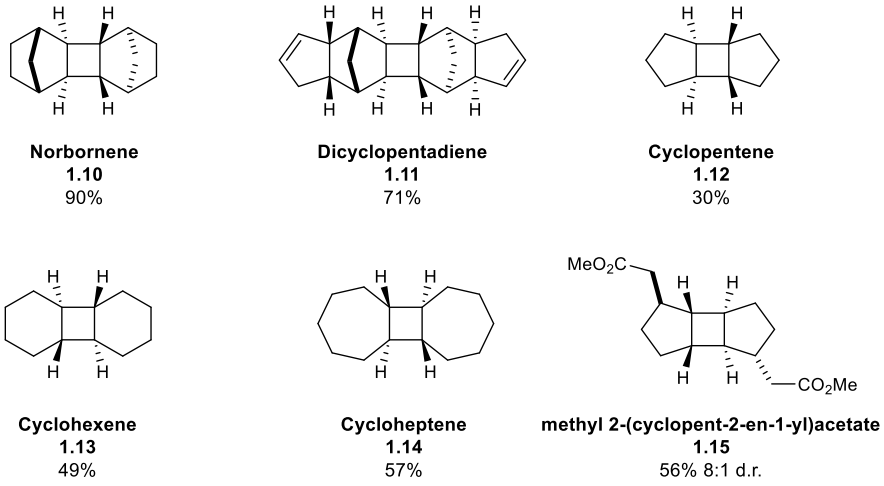
This computational proposal is further supported by flash photolysis experiments conducted by Ferraudi and co-workers in which spectral transformations associated with intermediates containing copper-alkyl bonds were observed upon photolysis of copper(I) ethylene complexes.[15] Though these studies support the computed pathway, there is to date no

direct evidence that provides insight into the nature of the carbon–carbon bond-forming steps (Figure 1.2).

1.3.2 Scope and Synthetic Utility

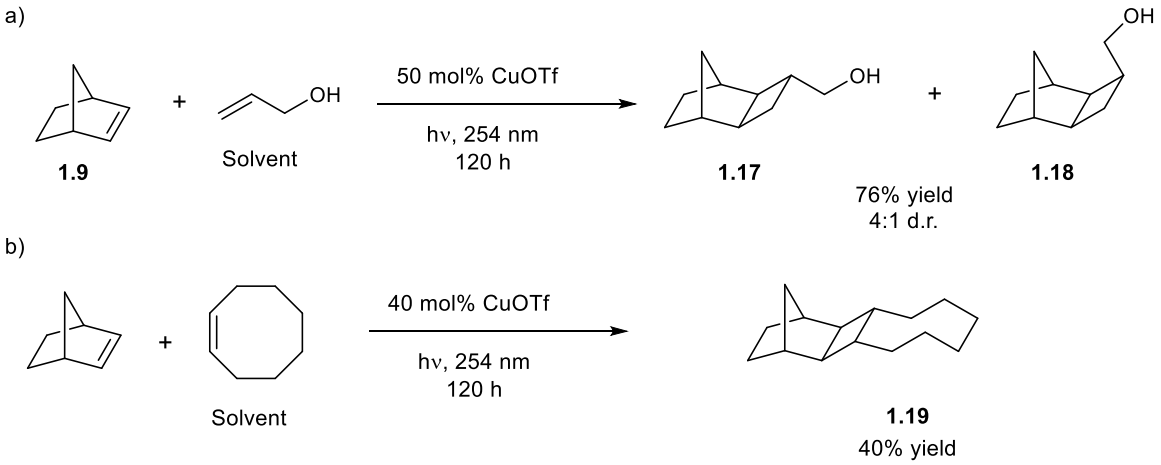
Salomon and Kochi's olefin dimerization conditions are applicable to a range of cyclic olefins (Table 1.1). Initial reports focused on dimerization of highly coordinating bicyclic alkenes such as norbornene and dicyclopentadiene, both yielding the *exo-trans-exo* isomers **1.10** and **1.11** respectively. This stereochemistry placing the bridge head carbons on opposing sides has been attributed to a preferred coordination geometry in the 2:1 norbornene copper complex. Less strained cyclopentene **1.12**, cyclohexane **1.13**, and cycloheptene **1.14** also can give serviceable yields. Interestingly, different ring sizes yield different stereochemistry: the cyclopentene dimer **1.12** displays *cis* stereochemistry while dimers of cyclohexene **1.13** and cycloheptene **1.14** display *trans* stereochemistry. It is proposed that copper-catalyzed E/Z isomerization in these larger rings occurs prior to cycloaddition and that the *trans*-isomers are more coordinating to copper.[16] Most examples are symmetric olefins that cannot result in regioisomers; however, a sole example of dimerization of substituted cyclopentene to give **1.15** suggests that high selectivity for one regioisomer has been reported.[17]

Table 1.1 Scope of Alkene Homodimerization



While a range of homodimerizations can be accomplished using the Salomon–Kochi reaction, heterodimerizations are rare, and only a few examples have been reported (Scheme 1.3). Both examples use norbornene **1.9** as the limiting coupling partner due to its strong coordination with copper(I). To prevent the known dimerization reaction, solvent quantities of the less coordinating coupling partner are employed to favor the mixed 2:1 alkene:copper complex. This has been accomplished using allyl alcohol to yield stereoisomers **1.17** and **1.18** and using cyclooctene to yield heterodimerization product **1.19.** These same reactions are also applicable to dicyclopentadiene in place of norbornene as the limiting coupling partner.[18] Presumably, systems involving two different alkenes with equal propensity to bind to the copper center would result in a mixture of products or dimerization of the most coordinating olefin.

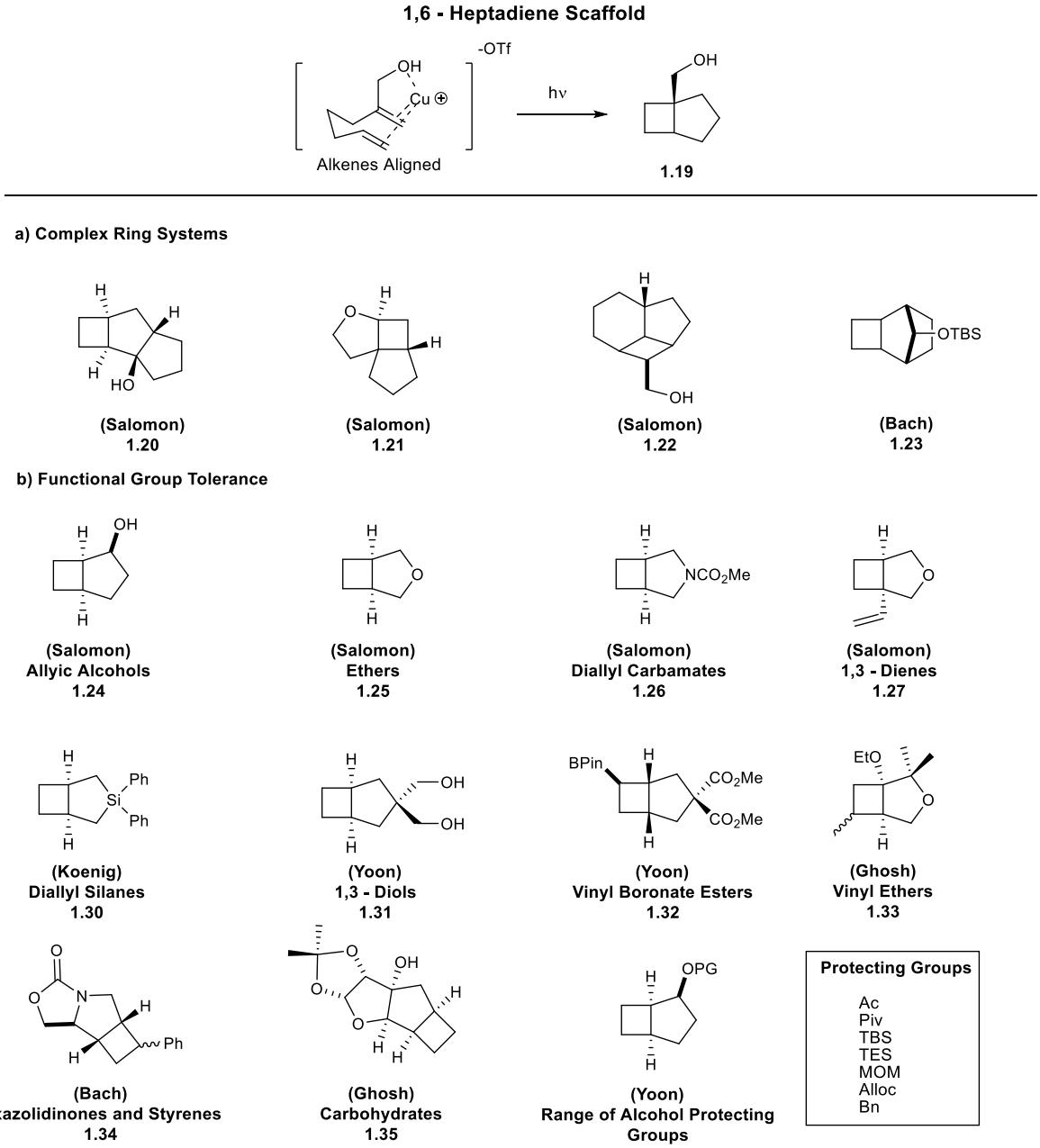
Scheme 1.3 Limited Scope of Heterodimerizations



While the Salomon and Kochi reaction was originally studied in the context of intermolecular dimerization reactions, its utility in synthesis has been derived from its application to the intramolecular cyclization of 1,6-heptadienes. Salomon and co-workers found that a wide range of dienes displaying a 1,6-diene substitution pattern could be cyclized to the corresponding bicyclo[3.2.0]heptanes, allowing for construction of complex cyclobutane containing carbocyclic scaffolds (Table 1.2a **1.20-1.23)**.[19] Furthermore, an exceptionally wide

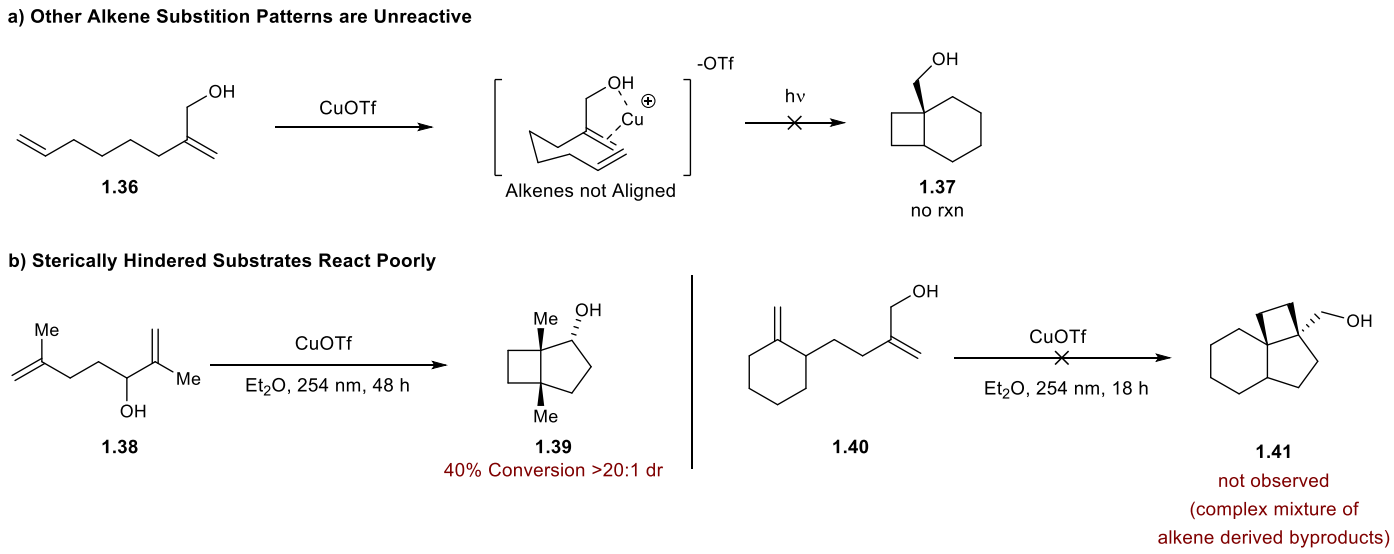
range of functional groups are tolerated, including allyic alcohols **1.24**[19a], ethers **1.25**[19c], carbamates **1.26**[20], 1,3-dienes **1.27**[21], silanes **1.28**[22], 1,3-diols **1.29**[23], vinyl boronate esters **1.30**[23], vinyl ethers **1.31**[24], styenes **1.32**[25], carbohydrates **1.33**[26], and a good selection of hydroxyl protecting groups[23] (Table 1.2b).

Table 1.2 Scope of Intramolecular Cyclization of 1,6-Heptadienes



While the scope of intramolecular cycloadditions of 1,6-heptadiene scaffolds is quite broad, the reaction has some clear limitations. Cyclization of any other substitution patterns has not been demonstrated in the Salomon and Kochi reaction. It has been proposed that the 1,6-diene pattern results in alignment of the alkenes thus allowing for unstrained coordination of both alkenes to the copper center, while other substitution patterns are poorly aligned and disfavor formation of the intramolecular 2:1 complex red (Scheme 1.4a).[19c] Also, sterically hindered substrates react poorly and lead to catalyst decomposition, likely due to inhibition of complex formation (Scheme 1.4b).[19a,19c]

Scheme 1.4 Limitations of Intramolecular [2+2] Cyclizations

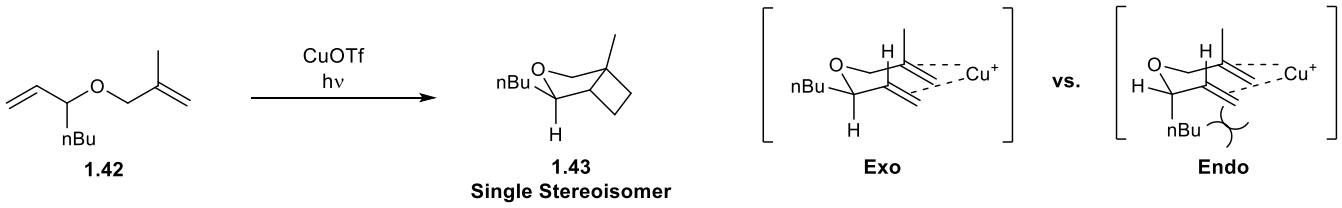


1.3.3 Factors Affecting Stereochemical Outcomes

While a wide range of 1,6-heptdiene scaffolds are readily cyclized using the Salomon and Kochi protocol, predicting the stereochemical outcomes of these intramolecular cyclization reactions presents a much more complex problem. Many different factors have been reported to greatly influence the stereochemistry of the resulting products including conformational strain, steric clash, and chelation. The stereochemistry is most often proposed to be controlled by the lowest energy conformation of the 2:1 olefin:copper complex.

Salomon and co-workers extensively studied many of these effects in their early publications regarding intramolecular cyclization of 1,6-heptadienes. Early observations revealed a strong preference for formation of the *exo* product **1.43**, which is easily rationalized by the fact that *exo* coordination places the larger alkyl group in the pseudoequatorial position, making it the thermodynamically preferred geometry (Scheme 1.5).[27] This demonstrates that for simple alkyl ethers and other linear 1,6-heptadienes lacking chelating functional groups, analysis of steric interactions in the two possible chair-like coordination states should give reliable predictions of stereochemical outcomes.

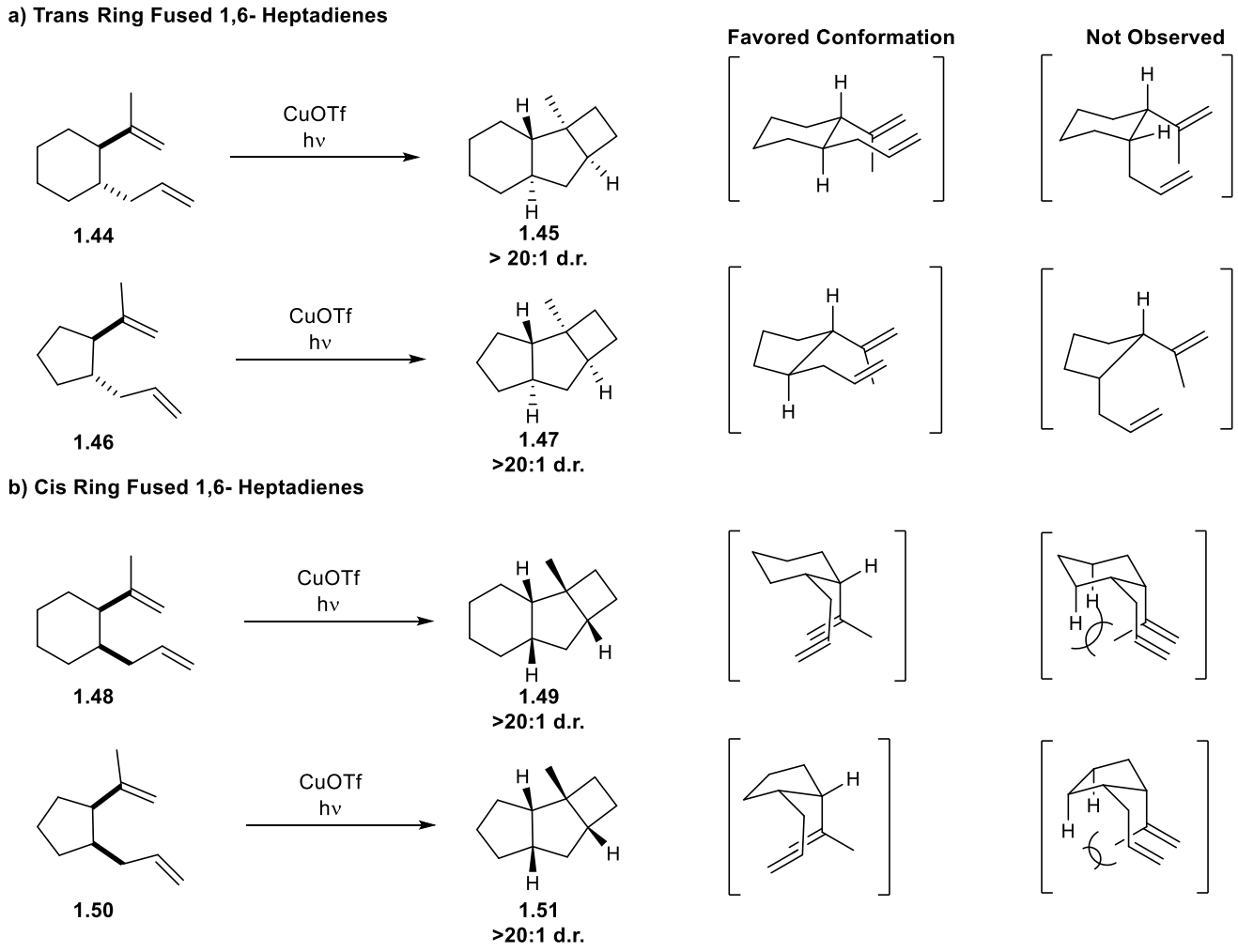
Scheme 1.5 Favoring the Least Sterically Hindered Coordination



While Salomon and co-workers studied the cyclization of a range of scaffolds containing multiple ring systems, this simplistic analysis based on steric interactions has been heavily relied upon for rationalization of the stereochemical outcomes observed with this reactivity. Bach and co-workers later conducted a study in conjunction with their efforts toward the total synthesis of (+/-)−kelsoene on the stereochemical outcomes of 1-methyl-substituted tricyclo[6.2.0.02,6]decanes and tricyclo[7.2.0.02,7]undecanes formed from [2+2] cycloadditions of both *cis* and *trans* ring-constrained 1,6-heptadienes. [28] They observed high degrees of selectivity for all these constrained 1,6-heptadienes further demonstrating the power of steric analysis previously employed by Salomon. Bach observed high selectivity for the *trans-anti-cis* products **1.45** and **1.47** in the case of *trans* substitution across the ring junction. This observation is easily rationalized by a strong preference for pseudoequatorial orientation of substituents to give the thermodynamically favored ring conformation when coordinating with copper (Scheme 1.6a). *Cis* substitution across the ring junction prevents any conformation in which both

substituents reside in an equatorial position. However, clear steric clash in orientations that place the methyl substituent below the ring system are highly disfavored, displaying high degrees of selectivity for the *cis-syn-cis* products **1.49** and **1.51** (Scheme 1.6b).

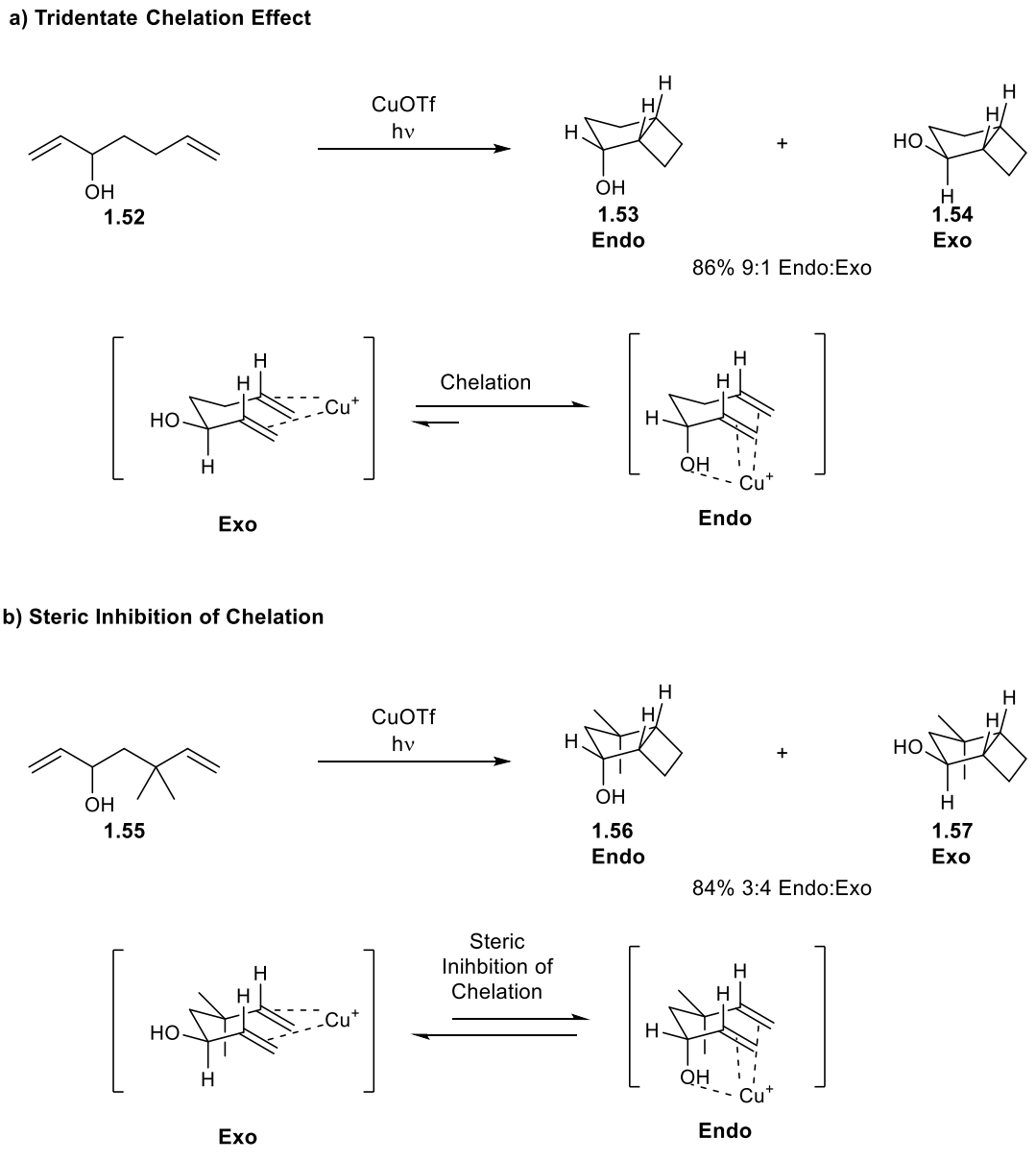
Scheme 1.6 Stereochemical Preferences for Ring Constrained 1,6- Heptadienes (Bach)



While conformation and steric analysis has proven to be a powerful predictor of stereochemical outcomes in these reactions, they are limited to systems that lack any Lewis basic functional groups. Early studies conducted by Salomon cyclizing 1,6-heptadien-3-ols discovered an interesting inversion in preference from the typical *exo* product **1.54** to in many cases highly favoring the higher energy endo product **1.53**. Salomon rationalized this selectivity by proposing that copper forms a tridentate complex with the two olefins and the allylic hydroxyl

group, necessitating the placement of the hydroxyl in the axial position and yielding the *endo* product **1.53** (1.7a).[19a] This suggests that the additional coordination of the hydroxyl group is stabilizing enough to override the increased steric congestion in the complex. However, increasing the steric strain in the *endo* coordination complex results in loss of stereochemical preference for the endo product (Scheme 1.7b).[19a]

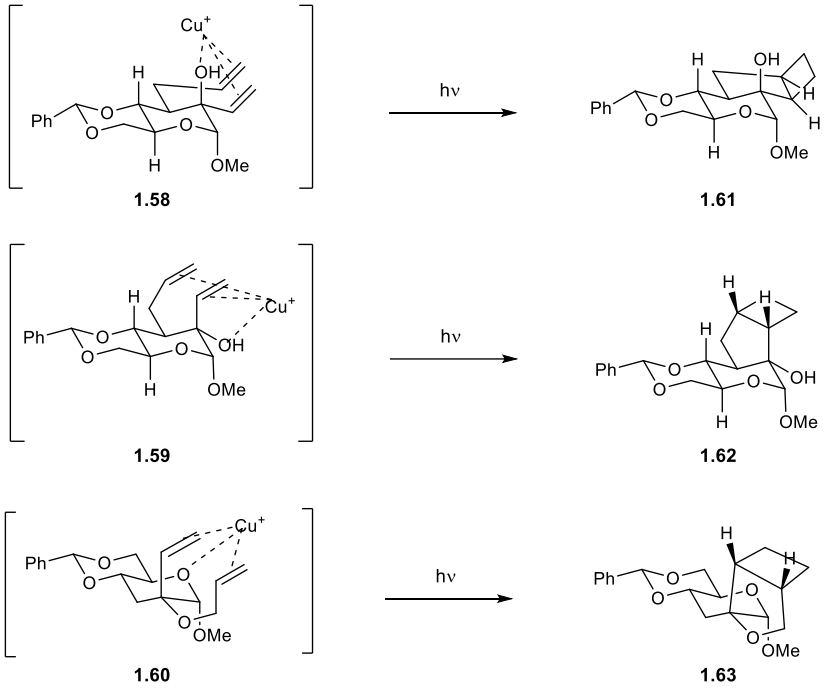
Scheme 1.7 Allylic Alcohol Chelation Effect on Stereochemical Outcomes



This chelation effect seems to be most general for allyic alcohols and ethers; however, more distal effects have been documented.[29] Ghosh and co-workers conducted a study on

complex carbohydrate derived scaffolds **1.58-1.60** demonstrating that both chelation to free hydroxyl groups and ethers are strong directing groups for the stereochemical outcomes in these reactions, giving high degrees of stereoselectivity for cyclobutane products **1.61-1.63** (Scheme 1.8). Furthermore, later studies conducted in our group demonstrate that a wide range of protected alcohols display this same chelating ability to varying degrees.[23]

Scheme 1.8 Allylic Alcohol Chelation and Diastereoselectivity in Complex Multi-Ring Systems

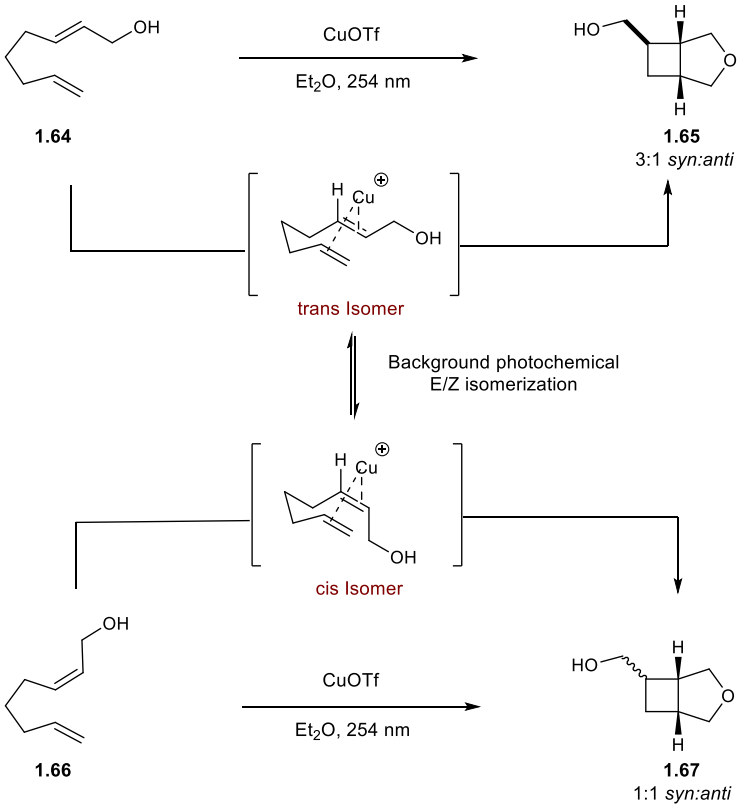


Until this point the discussion of stereochemistry has centered on *endo* vs. *exo* coordination of the catalyst because most examples employ terminal olefiins in which *endo* and *exo* are the only possible diastereomers. However, terminally substituted alkenes that result in a new stereocenter on one of the external cyclobutane carbons typically result in more complex mixture of diastereomers.

Salomon and co-workers observed that terminal substituted 1,6-heptdienes typically result in a 1:1 mixture of diastereomers. The authors attributed this observation to competitive copper-catalyzed photochemical *E*/*Z* isomerization scrambling the stereochemistry of an otherwise facially selective cycloaddition (Scheme 1.9).[19a] The authors also noted that

cyclization of the *trans* alkene **1.64** was notably faster and favored one diastereomer over the other in comparison to cyclization of the *cis* alkene, which gives a 1:1 mixture of the two diastereomers. Later studies conducted by our group verified these proposals with NMR time course experiments observing the isomerization during the cycloaddition that occurs at nearly the same rate as cycloaddition.[23] This phenomenon is unfortunate because in the absence of isomerization this reaction would be more modular allowing for selection of the desired diastereomer based on the alkene geometry displayed in the substrate.

Scheme 1.9 Terminally Substituted olefins and E/Z Isomerization



1.4 Application of the Salomon – Kochi Reaction to Total Synthesis

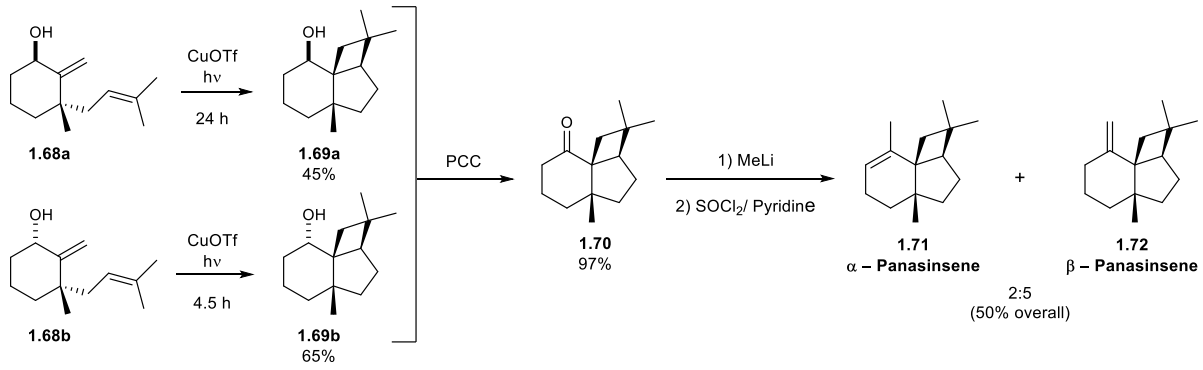
Because the Salomon and Kochi reaction is one of the few robust methods for the formation of complex cyclobutanes, it has been employed in numerous synthetic efforts towards cyclobutane natural products. Most products are retrosynthetically derived from a [2+2]

cycloaddition of simple aliphatic alkenes where direct excitation and triplet sensitization methods are not applicable. While both intramolecular and intermolecular cyclization using CuOTf have been employed in total synthesis, the vast majority of reports involve intramolecular cyclization of 1,6-heptadienes to form cores of natural products containing the bicyclo[2.2.1] heptyl moiety or to form bicyclo[2.2.1] heptyl intermediates that upon cleavage or rearrangement lead to the desired natural products. While not a common disconnection in total synthesis, the Salomon and Kochi reaction has been enabling in the synthesis of a range of largely aliphatic terpene and terpenoid cyclobutane containing natural products.

1.4.1 Natural Products Containing Bicyclo[2.2.1] Heptyl Moiety

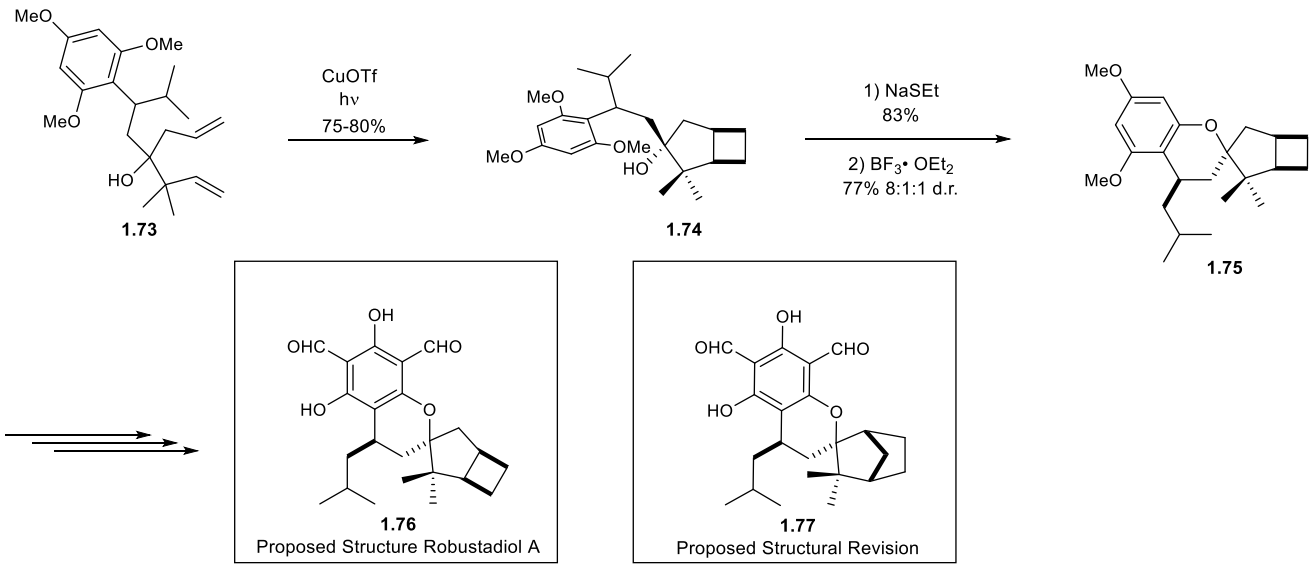
The earliest total synthesis employing the Salomon and Kochi reaction was the synthesis of α and β−panasinsene by McMurray and co-workers (Scheme 1.10).[30] [2+2] photocyclization of diene diastereomers **1.68a** and **1.68b** using CuOTf yields the desired core displaying all-*cis* stereochemistry. Interestingly this stereochemistry was obtained regardless of the orientation of the allylic alcohol. This observation suggests that chelation has little impact on the stereochemistry of the cycloaddition and that conformational bias instead governs the stereochemical outcomes displayed in cyclobutanes **1.69a** and **1.69b**. While chelation with the allylic alcohol had little impact on the stereochemical outcome, the authors report a substantial rate difference between the two diastereomers, suggesting that chelation in one diastereomer results in increased rates of reactivity. Oxidation of the two resulting cycloadducts yields ketone **1.70** that was found to be recalcitrant towards Wittig olefination. However, addition of methyl lithium followed by dehydration with thionyl chloride gave the two isomeric natural products **1.71** and **1.72** in a 2:5 ratio.

Scheme 1.10 Total Synthesis of Panasinene (McMurray)



The proposed structure of robustadiol A was synthesized by Salomon and co-workers by [2+2] cyclization of substituted 1,6-heptadiene scaffold **1.73** to give bicyclo[2.2.1] heptane **1.74** (Scheme 1.11)**.**[31] Subsequent selective monodemethylation directed by a remote neighboring group effect with the tertiary alcohol followed by Lewis acid mediated cyclization gave a 8:1:1 mixture of diastereomers favoring the desired pyran diastereomer **1.75** . Functionalization of the aromatic ring gives the proposed structure of robustadiol A **1.76**. However, the spectral data for this product did not match those of the reported isolated product. Salomon's confirmation that the original structural assignment was incorrect informed the proposal of an alternate structure **1.77** differing only by the connectivity of the bicyclic heptyl fragment.

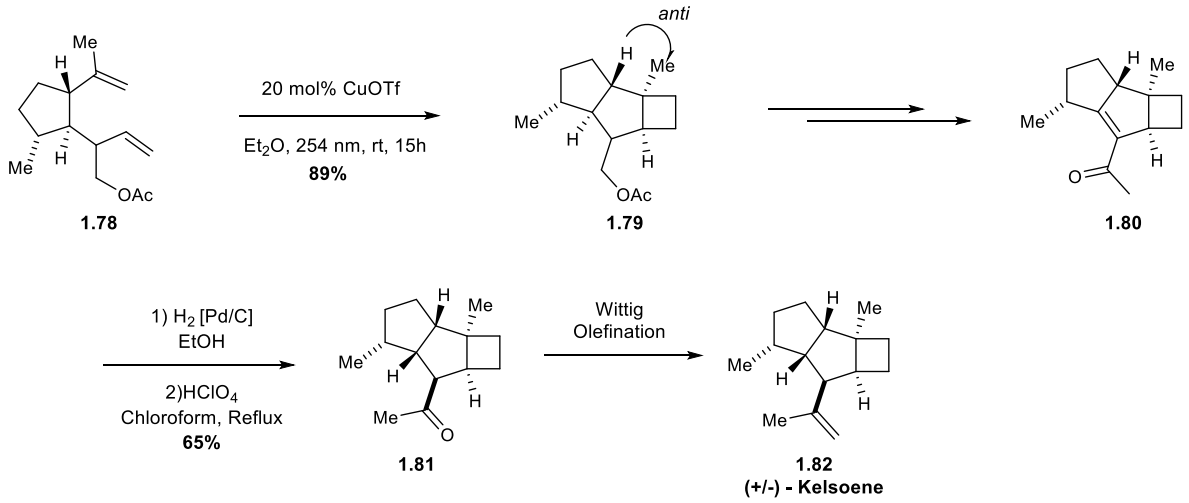
Scheme 1.11 Total Synthesis of Proposed Structure of Robustadiol A (Salomon)



Bach and co-workers employed the Salomon and Kochi reaction as the key step in their synthesis of (+/-)−kelsoene **1.82** to form the densely substituted tricyclo[6.2.0.0]decane core (Scheme 1.12).[32] Having conducted prior studies on the cyclization of both *trans*- and *cis*-substituted 2-allyl-1-(2-propen- yl)cyclopentanes, it was discovered that while kelsoene features a *cis* ring junction between the two cyclopentane rings, copper(I) catalyzed [2+2] cyclization of the *cis*-substituted 2-allyl-1-(2-propen-yl)cyclopentanes gives high selectivity for the undesired *cis-syn-cis* product.**Error! Bookmark not defined.** While these studies show that the *cis-anti-cis* t ricyclo[6.2.0.0]decane core cannot be accessed directly, Bach found that [2+2] photocyclization of *trans*-substituted cyclopentane scaffold **1.78** allowed the desired *anti* stereochemistry to be set on one side of the ring system in cycloadduct **1.79**. Subsequent transformation into cyclic enone **1.80** allowed facially selective hydrogenation, yielding the desired *cis-anti-cis* core. Acid-facilitated epimerization of the resulting ketone to its most stable isomer yielded ketone **1.81** as

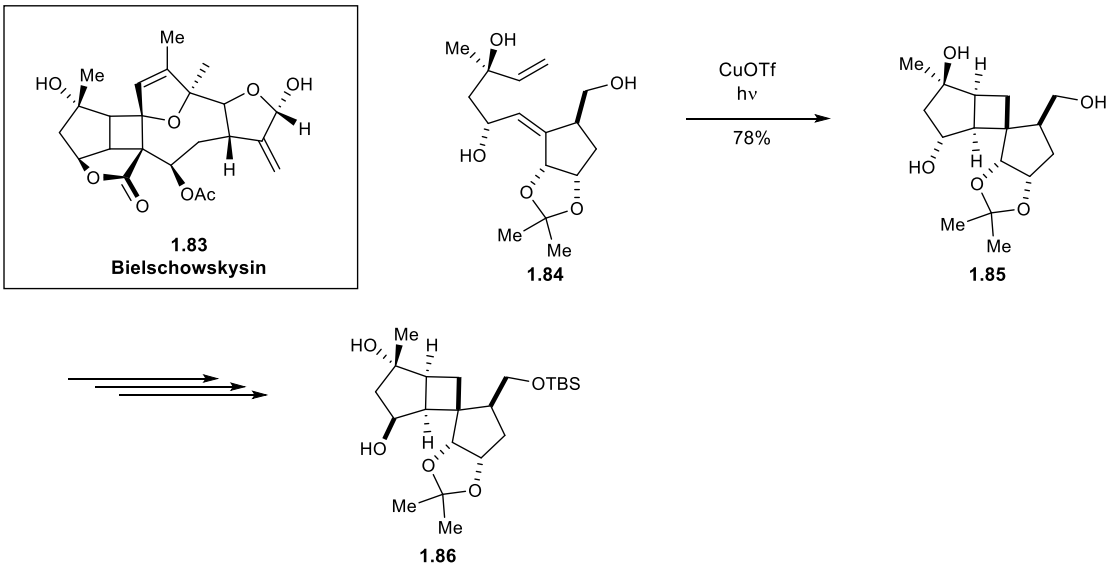
a single diastereomer. Ketone **1.81** was then converted to the natural product **1.82** using previously reported Wittig olefination conditions.

Scheme 1.12 Total Synthesis of (+/-) − Kelsoene (Bach)



Ghosh and co-workers have reported progress toward the total synthesis of bielschowskyin **1.83**, which is potentially the most complex natural product containing the bicyclo[2.2.1] heptyl moiety (Scheme 1.13).[33] There are no known synthesis of this product yet reported despite its very promising cytotoxicity towards lung cancer and renal cancer cell lines. Copper-catalyzed cyclization of 1,6-heptadiene **1.84** yields bicyclo[2.2.1]heptyl cycloadduct **1.85**. While this scaffold contains the proper connectivity found in the natural product, a substantial synthetic effort was required to obtain the proper stereochemistry. While a complete synthesis has yet to be reported, the ability to access bicyclo[2.2.1]heptyl scaffold **1.86** demonstrates the viability of using the Salomon and Kochi reaction as a key step in the synthesis of the western half of this molecule.

Scheme 1.13 Synthesis of the Bielschowskysin Core



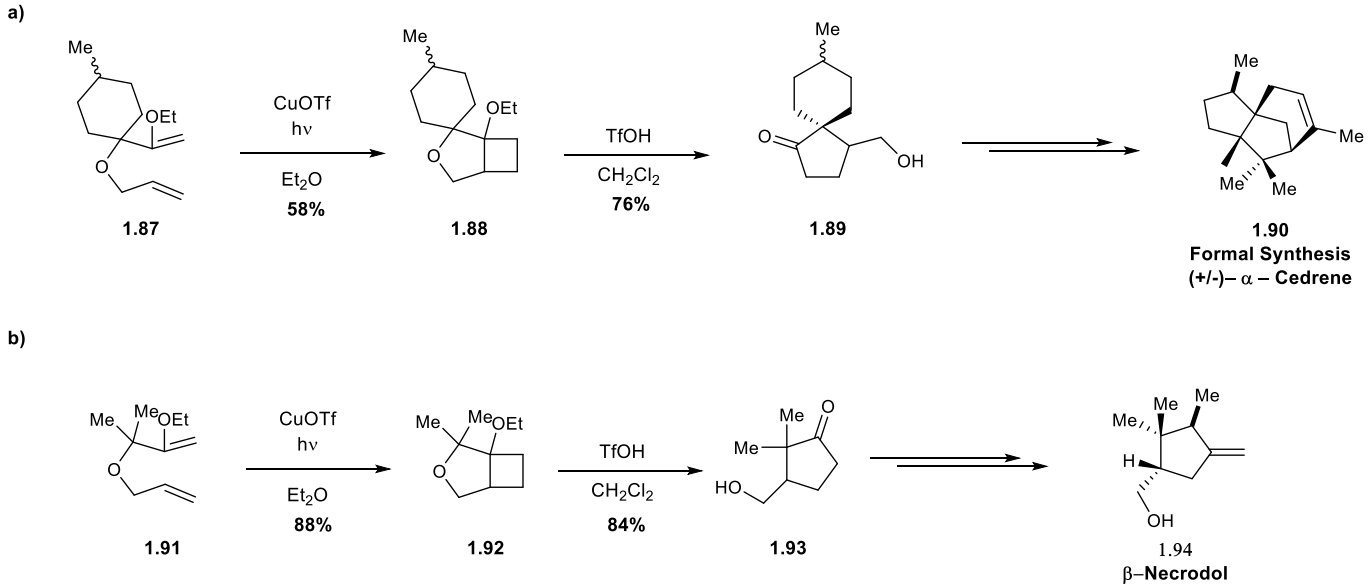
1.4.2 Products Derived from Intermediates Containing the Bicyclo[2.2.1] Heptyl Moiety

While the Salomon and Kochi reaction has proven to be a valuable strategy toward the synthesis of natural products containing the bicyclo[2.2.1] heptyl moiety, other syntheses have utilized this reactivity to form key intermediates towards other complex natural products. The cyclization of 1,6-heptadiene scaffolds typically proceeds with high facial selectivity that sets may stereocenters at once in a relatively reliable manner. This feature has been leveraged to form other complex carbocyclic scaffolds via cleavage or rearrangement of the rigid bicyclo[2.2.1] heptyl moiety.

Ghosh and co-workers reported syntheses of both (+/–)-cedrene[34] and β−necrodol[35] using a near identical strategy featuring the Salomon and Kochi reaction (Scheme 1.14). Cyclization of vinyl ether 1,6-heptadiene **1.87** gives ether bridgehead substituted bicyclo[2.2.1] heptane scaffold **1.88**. The authors found that treatment of **1.88** with acid resulted in expansion of the cyclobutane, furnishing spirocyclic cyclopentanone **1.89.** Subsequent synthetic modifications intercepted an intermediate in Stewart's previously reported synthesis to complete the formal synthesis. This same rearrangement strategy was used by Ghosh and coworkers

towards the synthesis of β−necrodol, accessing substituted cyclopentanone **1.93** as a key intermediate in the synthesis of **1.94**.

Scheme 1.14 Total Synthesis of (+/-) – Cedrene and β – Necrodol via Ring Expansion of Bicyclo[2.2.1] Heptyl Moiety (Ghosh)



Probably the most notable application of using the Salomon and Kochi reaction to set multiple stereocenters by deconstruction of the resulting bicyclo[2.2.1] heptane are the extensive studies conducted by Mattay and co-workers towards the synthesis of both (+) and (–)-grandisol,[36] a cyclobutane natural product that has been extensively studied as a benchmark for the utility of photochemical cycloaddition methods (Scheme 1.15). Mattay found that copper(I) catalyzed [2+2] photocycloaddition of (*S*)-2-heptadien-1-ol **1.94** gave a mixture of *endo* and *exo* diastereomers **1.95** and **1.96** that upon separation and ring opening gave two pure enantiomers displaying the required *cis*-stereochemistry across the cyclobutane core. Further elaboration of these products yields natural products **1.97** and **1.98** respectively (Scheme 1.15a).

While cyclization of the enantiopure **1.94** allowed for simple access to both enantiomers, the synthesis of **1.94** proved laborious. The authors then underwent an extensive study attempting to render the Salomon and Kochi reaction enantioselective allowing for employment of the much easier to access racemic material **1.99**. Initial attempts were aimed at employing

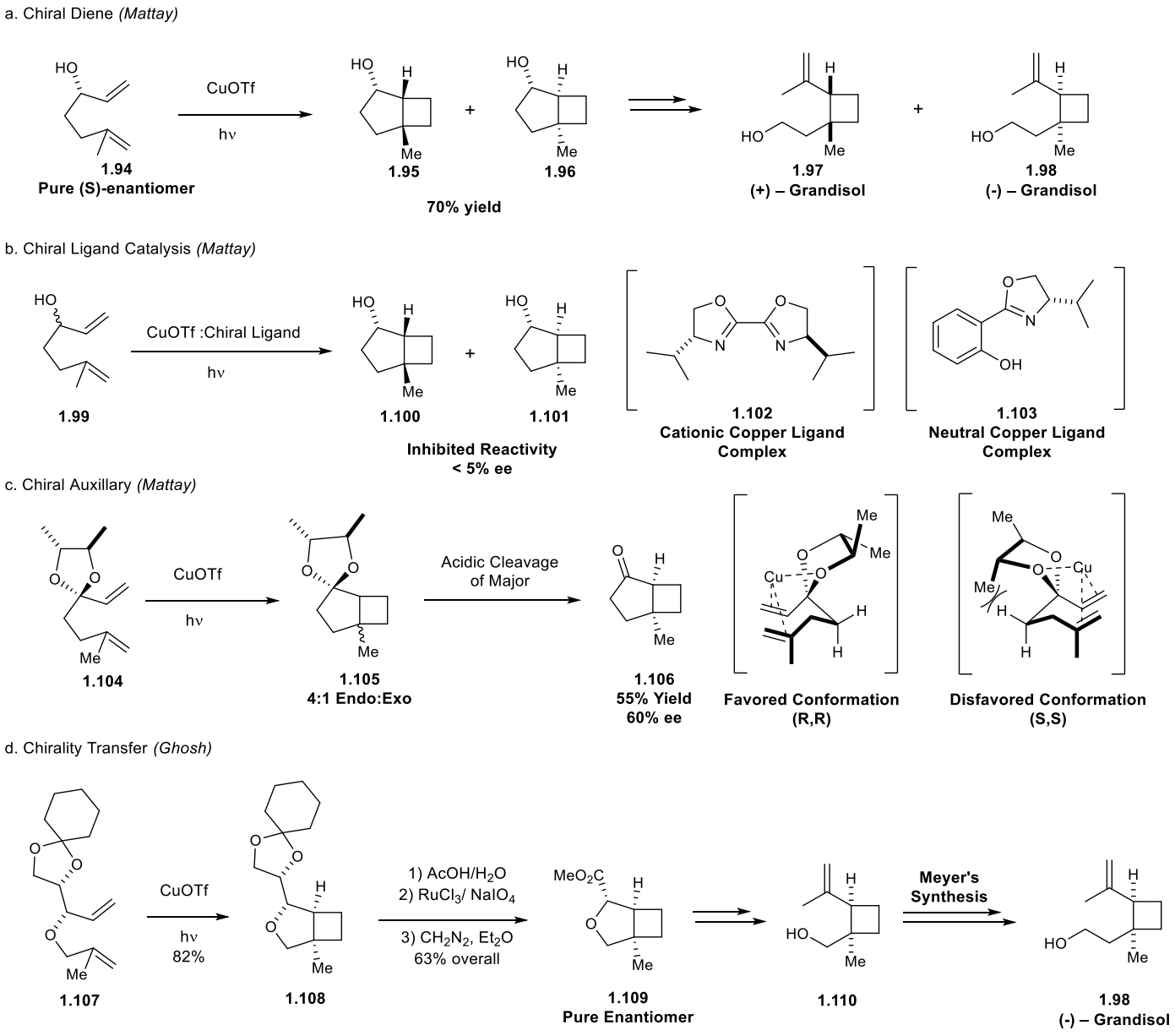
nitrogenous chiral ligands to occupy the other open coordination sites not required for olefin coordination (Scheme 1.15b). The authors found that using X-type ligand **1.103** resulted in neutral complexes that were unreactive catalysts for cycloaddition. CD spectral analysis also revealed that these neutral complexes do not coordinate to olefins as no spectral change was observed upon addition of diene substrate **1.99**. Employing L-type ligand **1.102** results in a cationic copper complex that shows clear CD-spectral changes upon addition of **1.99** and is capable of mediating the [2+2] cycloaddition reaction. Unfortunately, the reaction rates were substantially suppressed, and only low levels of enantioselectivity were observed. The authors suggest several potential explanations for these results. They proposed that the ligand might prevent binding, such that the reaction would be catalyzed predominantly by trace unligated copper(I) in solution. They also suggested that other charge transfer events associated with the chiral ligand could complete with the copper-to-alkene charge transfer transition necessary for successful cycloaddition.

The authors then turned to a chiral auxillary strategy, looking at a range of chiral protecting groups for the chelating allylic alcohol. The authors proposed that favoring one chiral tridentate copper(I) coordination geometry over another would result in preferential formation of one enantiomer over the other. Initial experiments involving chiral carboxylate esters and amino acid derivatives gave only low levels of enantioenrichment upon ring opening, suggesting that the chiral information is too distal from the metal center or that esters and amides are poorly coordinating to copper(I). Upon further exploration of chiral auxiliary options, the authors found that photocycloaddition of chiral ketal **1.104** yielded cycloadduct **1.105** as a 4:1 mixture of *endo*:*exo* cycloadducts demonstrating clear coordination to the copper center. Acidic cleavage of the major diastereomer resulted in ketone **1.106** in 60% ee for the (*R,R*) enantiomer. The authors envokes two potential *endo* coordination states, one of which is disfavored due to strong steric clash with the chiral ketal backbone (Scheme 1.15c). While valuable information was

gleaned from this study, a viable method for achieving high levels of enantioselectivity in this reaction has not yet been discovered.

Later studies conducted by Ghosh and co-workers approached this problem using a chiral relay strategy rather than an auxillary that requires coordination to the metal center (Scheme 1.15d).[37] First, chiral 1,6-heptadiene scaffold **1.107** is easily derived from readily available (*R*)-1,4-Dioxaspiro[4.5]decane-2-carboxaldehyde.[2+2] cyclization of chiral substrate **1.107** gives high levels of selectivity for the *exo* product **1.108** in the absence of allylic coordination to copper. Subsequent conversion of the chiral relay group to the methyl ester destroys the relay stereocenter and gives access to **1.109** as a pure enantiomer. Subsequent steps intercept known intermediate **1.110** of Meijer's synthesis of grandisol, completing the formal synthesis of 1.98. The authors suggest that the stepwise nature of this reaction allows for relay of chiral information to neighboring carbons during the first bond forming step and accounts for the high degree of selectivity observed without employing chiral tridentate coordination complexes as in Mattay's studies.

Scheme 1.15 Total Synthesis of Grandisol via Ring Cleavage of the Bicyclo[2.2.1] Heptyl Moiety

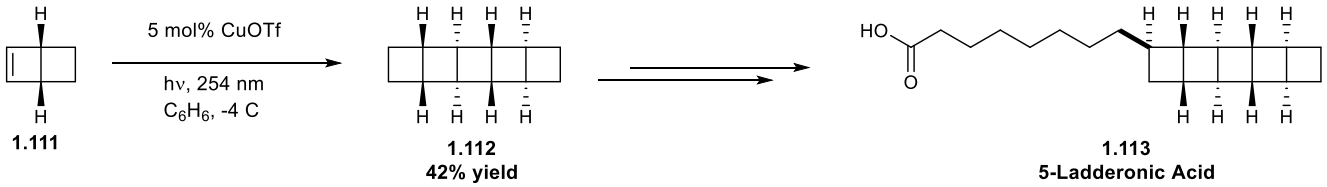


1.4.3 Natural Products Accessed via Copper (I) Photodimerization

While Cu(I) catalyzed intermolecular dimerization of strained alkenes has not been nearly as widely used in total synthesis as the intramolecular variants of this reaction, Burns and co-workers more recently reported the first total synthesis using the Salomon and Kochi

dimerization as the key step in their synthesis of the ionic 5-ladderonic acid (Scheme 1.16).[38] Copper(I) mediated dimerization of bicylcohexene **1.111** furnishes the exotic ladderane core **1.112**, the key synthetic challenge in this synthesis. Subsequent steps allowed for a synthesis of this natural product **1.113** in many fewer steps than previously reported. Interestingly this modest yielding reaction only gives serviceable yields of the ladderane core in benzene at –4°C at which the solvent is solid. These are very uncommon conditions for the Salomon and Kochi reaction as benzene absorbs UV light below 280 nm and usually prevents light absorption of the complex around 254 nm. More common conditions in ethereal and alkane solvents result in ring opening of the bicyclohexane rather than dimerization.

Scheme 1.16 Total Synthesis of 5−Ladderanoic Acid (Burns)

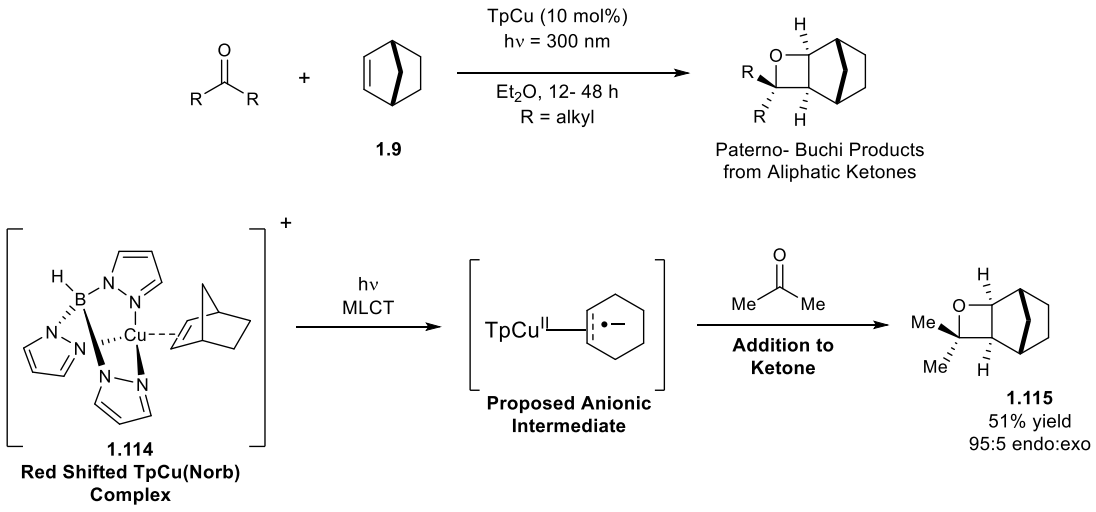


1.5 Modern Methods

Since the advent of this reactivity in the early 1970's the majority of work in this field has focused on application of Salomon's initial discoveries to complex molecule synthesis. Relatively little work has been published exploring new reactivity available via this copper olefin MLCT mechanism. Recently, Schmidt and co-workers reported an elegant solution to a longstanding limitation of the Paterno–Buchi [2+2] photocycloaddition via copper(I) olefin MLCT (Scheme 1.17).[39] The Paterno–Buchi reaction has always been limited to aryl ketones and other ketones with strong direct absorption of UV light and/or lower triplet energies. Aliphatic ketones such as acetone have not been documented to undergo a Paterno–Buchi reaction. Schmidt and co-workers proposed that rather than exciting the ketone, an anionic intermediate generated via Cu(I) MLCT to a coordinated olefin would productively add to these otherwise inert aliphatic ketones. Initial studies employing norbornene **1.9** as the alkene coupling partner and CuOTf as

the catalyst resulted in low yields and a mixture of Paterno–Buchi and dimerization products. The authors found that excitation of tris(pyrazolyl)borate copper(I) (TpCu) norbornene complex **1.114** in the presence of acetone gave only the desired oxetane product **1.115** likely due to the tridentate Tp ligand preventing formation of a 2:1 olefin copper complex. While the use of aliphatic ketones in the Paterno Buchi reaction by this inversion of reactivity is a significant advance these reactions were found to be entirely limited to norbornene **1.9** as the alkene coupling partner. This is potentially because norbornene is highly coordinating to copper(I) and because the increased hinderance of the tridentate ligand prevents complexation with less coordinating olefins.

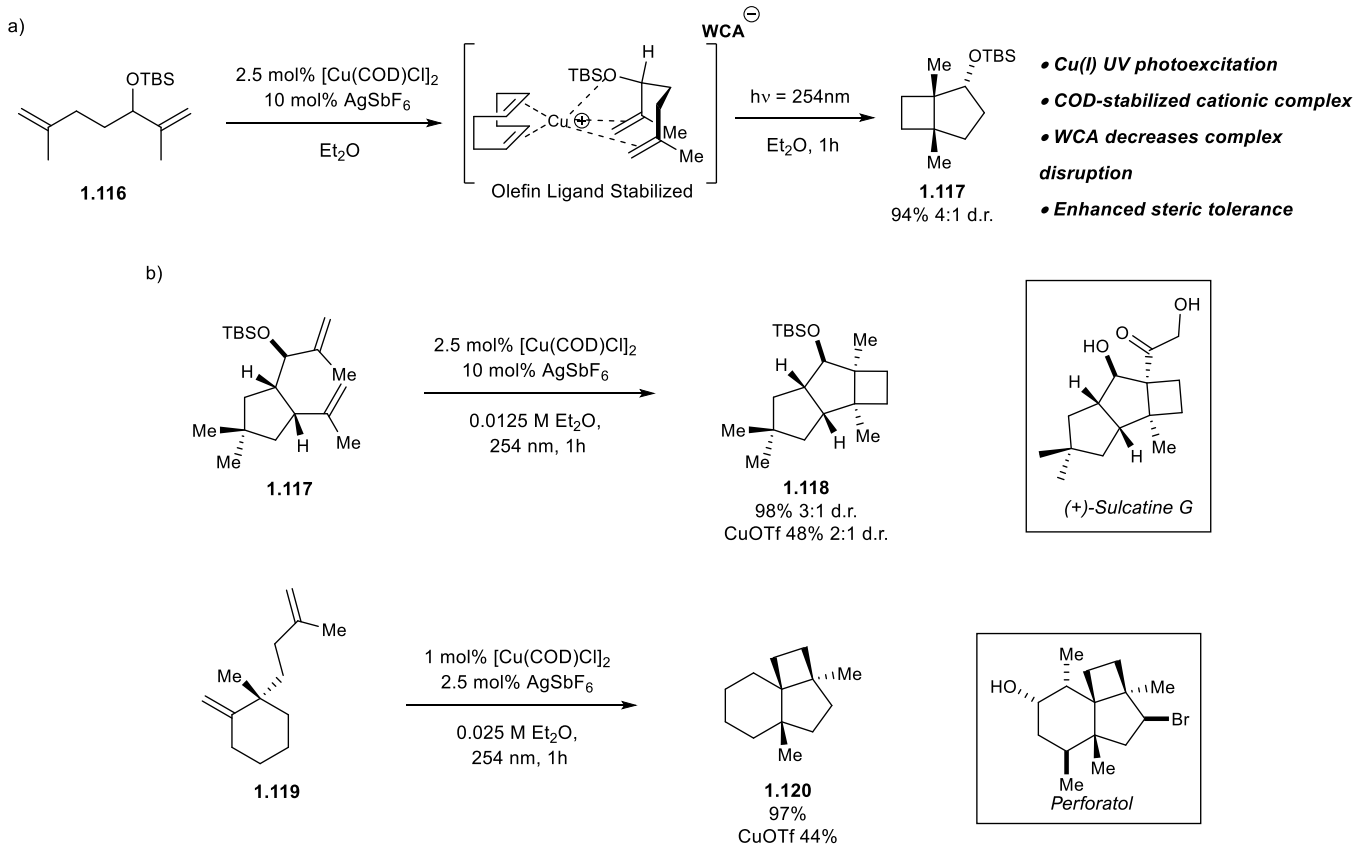
Scheme 1.17 Intermolecular 2 + 2 Carbonyl-Olefin Photocycloadditions Enabled by Cu(I)-Norbornene MLCT (Schmidt)



Our group has recently developed a new catalyst system that extends the useful scope of the Cu-catalyzed Salomon–Kochi photocycloaddition reaction, enabling the cycloaddition of sterically encumbered substituted alkenes.[23] Two features are critical to the success of this strategy. First, the use of a weakly coordinating SbF_6^- counteranion increases the reactivity of the catalyst by favoring the formation of the requisite copper:bis(alkene) complex. Second, while weakly coordinated cationic Cu(I) salts are prone to decomposition under the reaction

conditions, a COD ligand can stabilize the Cu(I) center without engendering the unproductive competitive low-energy LMCT transitions that would be introduced using more traditional nitrogen or phosphorous ligands. The optimal catalytic complex is capable of engaging hindered polysubstituted alkene substrates, can be generated from bench-stable precursors, and enjoys greater stability compared to the standard $[Cu(OTf)]_2$•benzene precatalyst (Scheme 1.17a). The preparation of the cores of the natural products sulcatine G and perforatol demonstrate the utility of this reaction in accessing structurally complex cyclobutane natural products (Scheme 1.17b).

Scheme 1.18 Olefin-Supported Cationic Copper Catalysts for Photochemical Synthesis of Structurally Complex Cyclobutanes (Yoon)



1.6 Conclusion and Outlook

The Salomon and Kochi [2+2] photocycloaddition has proven to be a powerful method for the construction of complex cyclobutanes from simple aliphatic olefins. It has been employed

in several total syntheses as a key transformation, allowing multiple stereocenters to be set in a single cycloaddition step. However, this reaction has been explored largely as a potential synthetic disconnect with little attention being given to catalyst optimization or other forms of reactivity accessible using this manifold. We believe that the base reactivity associated with this reaction allowing for generation of alkyl copper biradicals could potentially be exploited to access many different modes of reactivity. New catalyst design efforts could potentially unlock a broad array of transformations stemming from this alkyl copper biradical intermediate, as in Schmidt's work.[39] Also, research into catalysts that are more strongly coordinating towards alkenes could broaden the scope of this reaction to intermolecular [2+2] cycloadditions of linear alkenes and intramolecular cycloadditions of substitution patterns outside the 1,6-heptadiene scaffold.

Another avenue of research that is of great interest to our group is the development of enantioselective versions of these reactions. Chiral copper catalysts generated either by incorporation of chiral ligands or chiral counteranions could theoretically impart stereocontrol in these reactions, as highly organized coordination states with copper are already required for productive reactivity. A chiral copper catalyst for the Salomon and Kochi reaction would represent a new paradigm in enantioselective [2+2] photocycloaddition reactions, as chiral control derived from π-acidic metal complexes has yet to be demonstrated in alkene [2+2] photocycloadditions.

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Chapter 2. Aryl Vinyl Sulfides as Traceless Removable Redox Auxiliaries for Formal [2+2] Cycloadditions of Unactivated Alkenes

Portions of this work have been previously published:

Lin, S.; Lies, S. D.; Gravatt, C. S.; Yoon, T. P. “Radical Cation Cycloadditions Using Cleavable Redox Auxiliaries.” *Org. Lett.* **2017**, *19* (2), 368–371.

2.1 Introduction

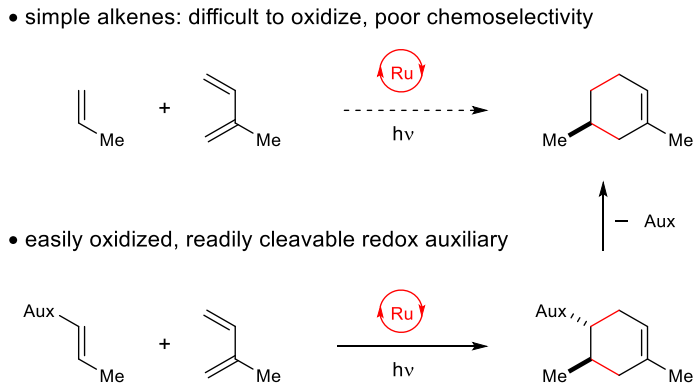
Alkene radical ions are open-shell reactive intermediates that participate in a wide variety of organic transformations. Many features of these reactions are synthetically attractive: they often proceed with very low activation barriers, and their regiochemical outcomes generally complement those involving closed-shell neutral alkenes.[1] Recently, there has been a renewed interest in the application of radical ion chemistry to synthesis, due in part to the recognition that photoredox catalysis offers a convenient means to access these odd-electron intermediates under relatively mild and convenient conditions, in comparison with harsh stiochometric single electron oxidants previously employed.[2] Recent reports of synthetic transformations involving photogenerated alkene radical cations *via* photoredox catalysis have included a variety of cycloaddition reactions[3] and anti-Markovnikov hydrofunctionalization reactions,[4] both of which are challenging to accomplish using alternate synthetic strategies.

One limitation common to all photoredox reactions is that reactivity is dictated by the thermodynamic feasibility of the photoinduced electron-transfer steps; substantially endergonic single-electron transfer (SET) steps result in poor overall reactivity. To address this, a large number of structurally varied photocatalysts spanning a range of excited state redox potentials can be exploited to broaden the scope of these reactions.[5] Nevertheless, a substrate's redox potential remains a fundamental thermodynamic constraint on the success of photoredox methods. For instance, simple mono- and disubstituted aliphatic alkenes have proven too difficult to oxidize (> +2.5 V vs SCE)[6] us with even the most powerfully oxidizing photoredox catalysts in common usage and have not successfully been engaged in photooxidatively triggered transformations.

We recently described the concept of a "redox auxiliary," which we defined as an easily removable moiety that can be temporarily installed on a substrate to enable its activation

by single-electron transfer processes.[7] Our initial demonstration of this concept was a radical anion [2+2] photoredox cycloaddition using 2-acylimidazoles as readily reducible analogues of enoate esters that would otherwise be resistant towards photoreductive activation.[7] We wondered if an analogous redox auxiliary strategy might be applied to facilitate *photooxidatively* initiated organic transformations. We hypothesized that the installation of an electron-rich redox auxiliary onto an otherwise unactivated alkene would facilitate its one-electron oxidation by lowering the redox potential; the resulting radical cations could subsequently undergo a number of characteristic alkene radical cation reactions, including Diels–Alder[3bfg] and [2+2] cycloadditions.[3ad] Subsequent cleavage of the redox auxiliary group would afford the products of formal cycloadditions involving unactivated alkene substrates (Figure 2.1).

Figure 2.1 Traceless redox auxiliary strategy for radical cation reactions.



Very recently, Cooke and co-workers described an intriguing first step towards an alternate oxidative redox auxiliary strategy, demonstrating that vinyl ferrocene is powerfully activated towards Diels–Alder and hydrothiolation reactions upon one-electron chemical oxidation.[8] This study verified that the incorporation of a reversibly oxidizable moiety onto an alkene can indeed be used to facilitate redox-promoted transformations. However, this strategy involves a separate activation step using

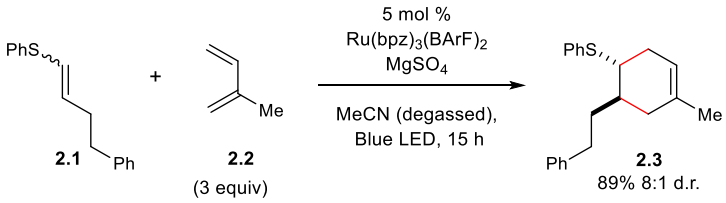
stoichiometric chemical oxidant rather than an in situ redox catalyst, and the requisite ferrocenyl moiety is not removable in a traceless fashion.

We imagined a different strategy utilizing a reversibly oxidizable sulfide moiety as a redox auxiliary. We were attracted to the use of vinyl sulfides in this context for a number of reasons. First, aryl vinyl sulfides generally possess oxidation potentials ranging from +1.1–1.4 V vs SCE,[9] which are readily accessible using the well-characterized Ru(II) polypyridyl photoredox catalysts that are increasingly being utilized in synthetic chemistry. Second, Bauld has studied chemically induced radical cation Diels–Alder cycloadditions of aryl vinyl sulfides using triarylaminium salts as chemical oxidants.[9,10] This valuable precedent demonstrates that vinyl sulfide radical cations are indeed activated towards cycloaddition reactions. Finally, C–S bonds are relatively weak, and a variety of mild, operationally facile methods for their cleavage have been utilized in the synthesis of complex molecules.[11] We imagined that successful development of this sequence would enable the preparation of formal cycloaddition products of simple alkenes that are not amenable to direct activation by photoredox catalysis and would also be challenging to engage in classical thermal cycloaddition methods.

2.2 Reaction Conditions and Scope

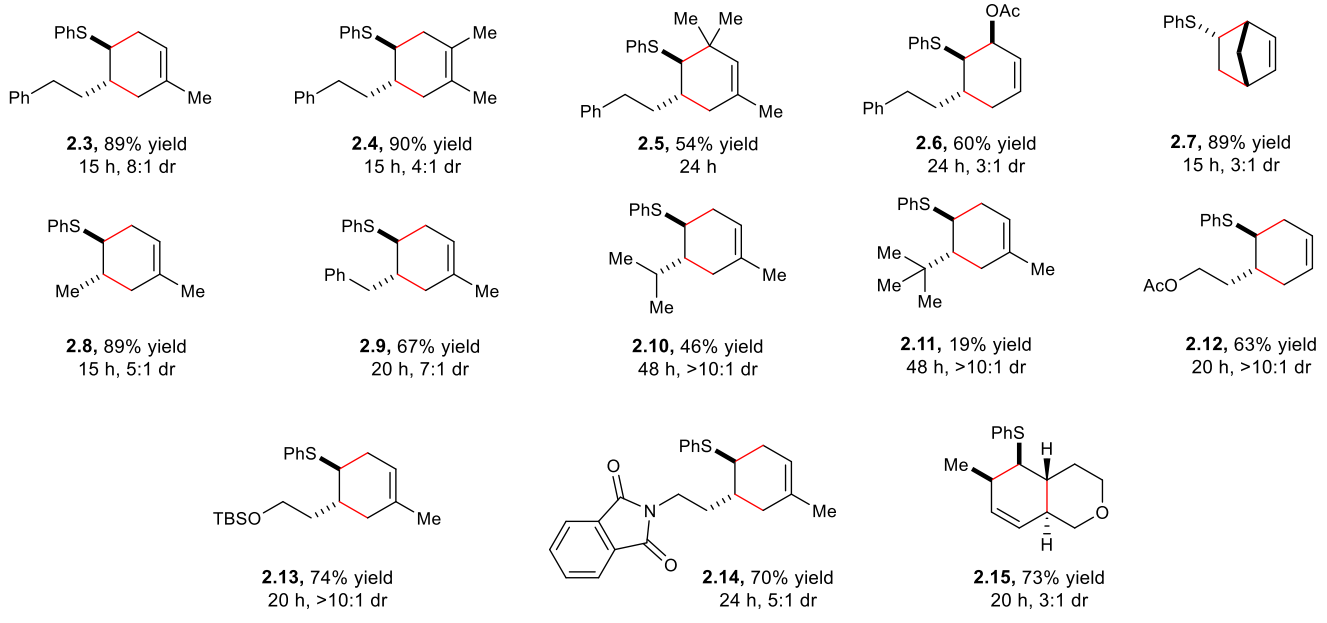
Optimal conditions were previously devised by colleague Dr. Shishi Lin for the [4+2] cycloaddition of aryl vinyl sulfide **2.1** with isoprene **2.2** utilizing highly oxidizing $Ru(bpz)_3(BArF)_2$ as the photocatalyst. The reaction was found to be sensitive to oxygen, requiring rigorous degassing by freeze-pump-thaw cycles to obtain optimal results. We hypothesize that this is due to the sensitivity of aryl vinylsulfides to oxygen-centered radical species. The reaction was also found to be highly water-sensitive, and addition of a dessicant $MgSO_4$ resulted in substantially higher yields (Scheme 2.1).

Scheme 2.1 Optimized Reaction Conditions



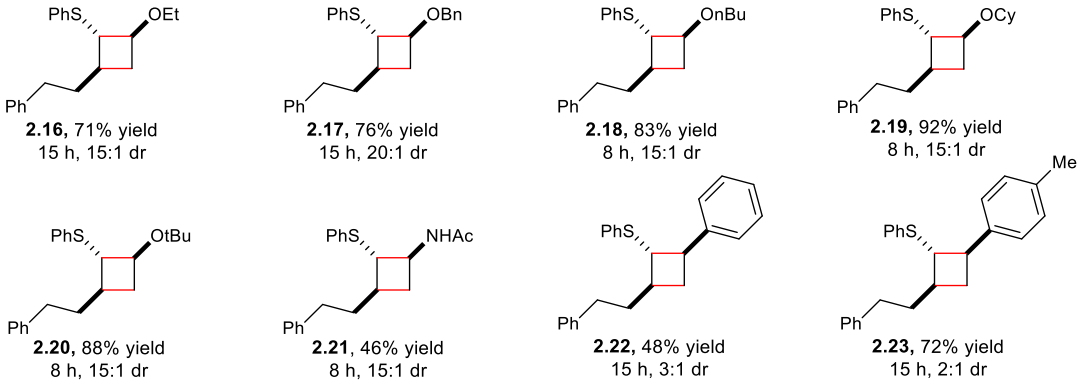
Studies examining the scope of the radical cation Diels–Alder cycloaddition of vinyl sulfides under optimized photocatalytic conditions are summarized in Figure 2.2. A range of simple cyclic and acyclic dienes participate readily in this process (**2.3–2.8**), though sterically bulky dienes require longer reaction times (**2.5**), and electron-rich dienes provide somewhat lower yields (**2.6**). Simple cyclic dienes (**2.7**), however, work well in this reaction. The structure of the vinyl sulfide partner can also be modified. An examination of simple alkyl-substituted dienophiles reveals a sensitivity to steric bulk; larger vinyl substituents result in substantially slower Diels–Alder reactions (**2.10** and **2.11**), and β,β-disubstituted vinyl sulfides do not provide any observable cycloadducts. On the other hand, the reaction tolerates various functional groups including esters, silyl ethers, and phthalimides (**2.12**–**2.14**). These conditions were also found to be applicable to intramolecular cycloadditions (**2.15**).

Table 2.1 Scope studies for aryl vinyl sulfide radical cation Diels–Alder cycloadditions



The goal of this project was to demonstrate that sulfide redox auxiliaries might be broadly applicable not only to Diels–Alder cycloadditions but also to a range of useful transformations involving alkene radical cations. To expand the scope beyond Deils-Alder cycloadditions, we next studied the use of vinyl sulfides in intermolecular [2+2] cycloaddition reactions. We had previously investigated the factors controlling the crossed selectivity of such reactions involving electron-rich styrenes and were pleased to observe that similar considerations are applicable to [2+2] radical cation cycloadditions of vinyl sulfides.[3d] Thus, when **2.1** is irradiated in the presence of electron rich monosubstituted alkenes, the corresponding unsymmetrical cyclobutanes are produced in good yield. Vinyl ethers were excellent reaction partners in this reaction, affording good yields and excellent selectivities regardless of the steric bulk of the ether substituent (**2.16**–**2.20**). An enamide also provided synthetically useful yields of the corresponding acetamide-substituted cyclobutane (**2.21**). Finally, although simple aliphatic olefins and vinyl esters did not participate in this reaction, styrenes are successful reaction partners (**2.22** and **2.23**), consistent with the stepwise radical mechanism expected for this cycloaddition.

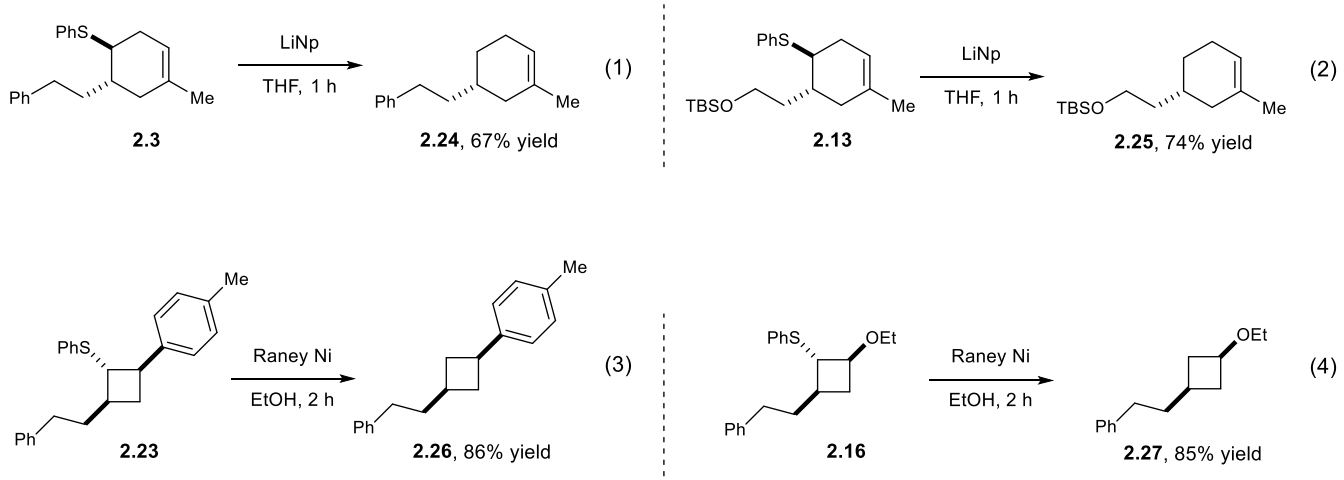
Table 2.2 Scope studies for aryl vinyl sulfide radical cation [2+2] cycloadditions



2.3 Product Derivatizations

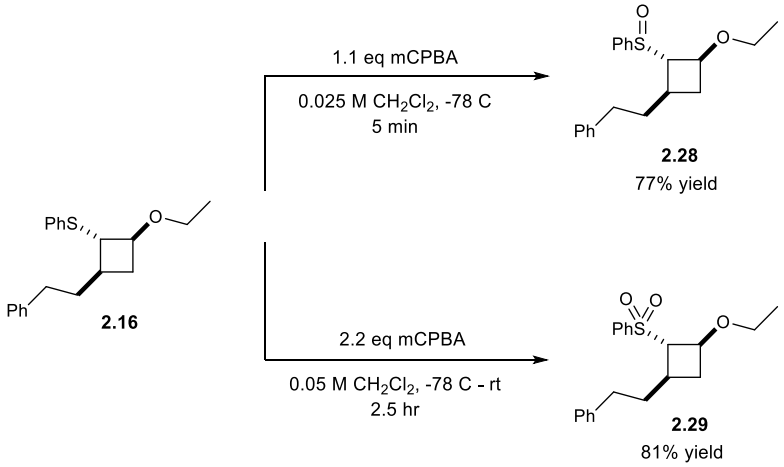
To fully demonstrate the utility of this redox auxiliary strategy, we intended to showcase the cleavage of the sulfide moiety, which was readily accomplished using various reductive protocols (Scheme 2.2). First, treatment of [4+2] cycloadduct **2.3** with freshly prepared lithium naphthalenide rapidly affords the corresponding desulfurized product without competitive reduction of the alkene moiety (eq 1). Importantly, the resulting cyclohexene **25** would not be directly accessible using alternate thermal or redox-promoted Diels–Alder methods. Similarly, cycloadduct **14** bearing a TBS-protected primary alcohol undergoes desulfurization to afford **26** without cleavage of the silyl protecting group (eq 2). The reduction of [2+2] cycloadduct **24** can readily be accomplished by treatment with Raney nickel (eq 3), and the diastereomer ratio of the resulting cyclobutane (**27**) is identical to that of the starting material, indicating that epimerization does not occur under these conditions. The desulfurization of functionalized cycloadduct **17** occurs without observable cleavage or elimination of the alkoxy substituent. Thus, removal of these sulfide auxiliary groups can be accomplished under relatively mild conditions that tolerate a variety of common functional groups.

Scheme 2.2 Reductive Cleavage of the Redox Auxiliary Group



Beyond reductive cleavage of the sulfide, oxidation of to the corresponding sulfoxides or sulfone derivatives could unlock other means of further functionalizing these products. Reaction of **2.16** with *meta*-chloroperoxybenzoic acid (mCPBA) was found to yield either the sulfoxide (**2.28**) or sulfone (**2.29**) selectively depending on the conditions applied. Synthetically useful yields of the sulfoxide could be obtained at low temperatures and very short reaction times. Longer reaction times with 2.2 equivalents of mCPBA were found to give the sulfone as the sole product.

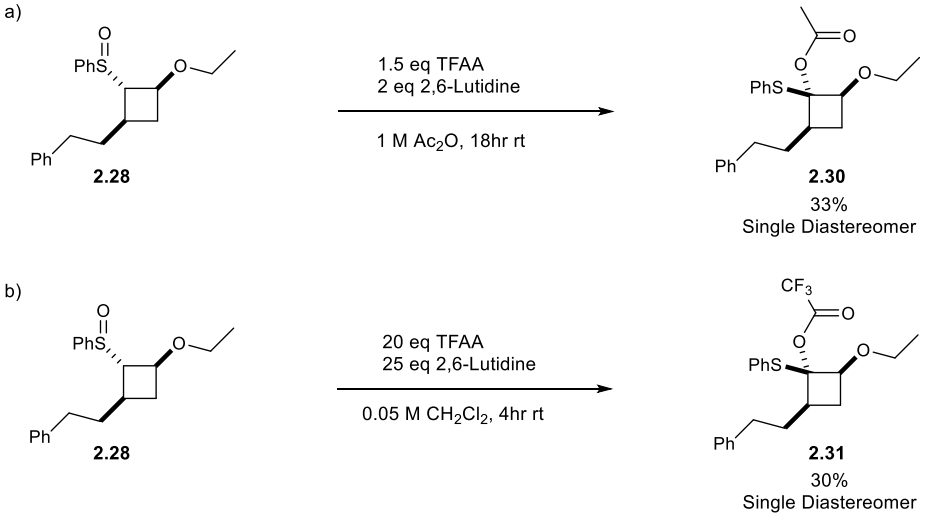
Scheme 2.3 Oxidation of the Aryl Vinyl Sulfide Auxiliary



Inspecting the structure of sulfoxide **2.28** we hypothesized it would be poised to undergo Pummerer rearrangement to yield α-substituted sulfide derivatives (Scheme 2.4). This transformation would open many synthetic routes to diverse cyclobutane based products, given the broad scope of the Pummerer rearrangement. A range of reported procedures were attempted with **2.28**; however, these largely resulted in decomposition. Utilizing a mixture of acetic and trifluoroacetic anhydrides in the presence of 2,6-lutidine as an exogenous base resulted in modest yields of only one of the two expected diastereomers **2.30** (Scheme 2.4a). Utilizing trifluoroacetic anhydride as the sole nucleophile as gave nearly identical results yielding **2.31** (Scheme 2.4b). These results suggested that only one of the two sulfoxide diastereomers was reactive towards the rearrangement. This could be due to an unfavourable deprotonation

event in one of the diastereomers and not the other. The harsh conditions required and the fact that only one of the sulfoxide diastereomers seemed to react resulted in abandoning furthers reaction development efforts.

Scheme 2.4 Pummerer rearrangement on sulfoxide cyclobutane product



2.4 Conclusion

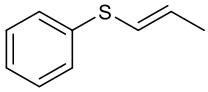
These studies indicate that vinyl sulfides are easily activated by catalytic photooxidation and subsequently undergo cycloddition reactions characteristic of alkene radical cations. The activating sulfide moiety can be tracelessly removed after the photoredox reaction to afford cycloadducts that could not be directly synthesized by reactions of simple unfunctionalized alkenes. These results, along with the reductive redox auxiliary strategy our group reported several years ago,[7] suggest that the use of redox auxiliary groups present a practical strategy to circumvent a fundamental limitation on the feasibility of photoredox reactions and could be used to significantly increase the scope of products that are available using this powerful mode of activation.

2.5 Experimentals

2.5.1 General Experimental Information

All organic reagents were purified prior to use. Styrenes were purified by basic extraction followed by distillation to remove trace radical inhibitors. $Ru(bpz)_3(BArF)_2$ was prepared according to our previously reported procedure.[12] MeCN, THF, Et_2O and CH_2Cl_2 were purified by elution through alumina as described by Grubbs.[13] A 23 W (1200 lumens) SLI Lighting Mini-Lynx compact fluorescent light bulb was used for the photoredox thiol-ene synthesis of the vinyl sulfide substrates. A 16 W (500 lumens) EagleLight blue PAR38 LED flood light was used for the Diels–Alder and [2+2] cycloadditions, unless otherwise stated. Flash column chromatography was performed with Silicycle 40–63 Å silica (230–400 mesh). Diastereomer ratios for all compounds were determined by ^{1}H NMR analysis of the unpurified reaction mixture. ^{1}H and ^{13}C NMR data for all previously uncharacterized compounds were obtained using Bruker Avance-500 spectrometer and are referenced to TMS (0.0 ppm) and $CDCl_3$ (77.0 ppm) respectively unless otherwise stated. IR spectral data was obtained using a Bruker Vector 22 spectrometer (thin film on NaCl). Mass spectrometry was performed with a Thermo Q Exactive Plus. These facilities are funded by the NSF (CHE-9974839, CHE-9304546), NIH (1S10 OD020022-1), and the University of Wisconsin.

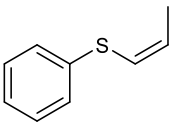
2.5.2 Synthesis of Alkyl Aryl Sulfide Cyclization Substrates



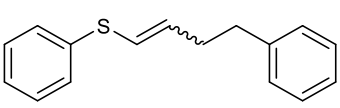
(*E*)-Phenyl(prop-1-enyl)sulfane. Prepared according to a modification of a previously reported procedure.[14] A flame-dried Schlenk tube was evacuated and charged with *i*-Pr_2NEt (474 µL, 2.72 mmol), $Pd_2(dba)_3$ (31 mg, 0.034 mmol), xantphos (39 mg, 0.068 mmol), and 1,4-dioxane (5 mL). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with nitrogen. Thiophenol (140 µL, 1.36 mmol) and *trans*-1-bromo-1-propene (94 µL, 1.09 mmol) were added under nitrogen. The reaction was heated at

110 °C for 16 h before being cooled to room temperature and subsequently passed through a plug of Celite with ether. Flash column chromatography (50:1 hexanes/EtOAc with 2% Et_3N) afforded 140 mg (0.93 mmol, 69% yield) of (*E*)-phenyl(prop-1-enyl)sulfane as a clear oil. All spectroscopic data were consistent with previously

reported values.[15]

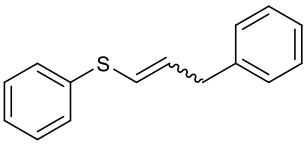


(*Z*)-Phenyl(prop-1-enyl)sulfane. Prepared according to a modification of a previously reported procedure.[14] A flame-dried Schlenk tube was evacuated and charged with *i*-Pr_2NEt (285 µL, 1.64 mmol), $Pd_2(dba)_3$ (19 mg, 0.021 mmol), xantphos (24 mg, 0.042 mmol) and 1,4-dioxane (3 mL). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with nitrogen. Thiophenol (90 µL, 0.87 mmol) and *cis*-1-bromo-1-propene (56 µL, 0.70 mmol) were added under nitrogen. The reaction was heated at 110 °C for 16 h before being cooled to room temperature and subsequently passed through a plug of celite with ether. Flash column chromatography (50:1 hexanes/EtOAc with 2% triethylamine) afforded 65 mg (0.433 mmol, 50% yield) of (*Z*)-phenyl(prop-1-enyl)sulfane as a clear oil. All spectroscopic data were consistent with previously reported values.[16]

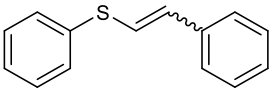


Phenyl(4-phenylbut-1-enyl)sulfane. Prepared according to a modification of a previously reported procedure.[17] A reaction vial was charged with $Ru(bpz)_3(PF_6)_2$ (4 mg 0.005 mmol), MeCN (4.5 mL), 4-phenyl-1-butyne (547 µL, 4.54 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography (gradient 50:1 to 9:1 hexanes/CH_2Cl_2) afforded 700 mg (2.91 mmol, 64% yield) of phenyl(4-phenylbut-1-enyl)sulfane as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (m, 4H), 7.20 (m, 6H), 6.21 (d, *J* = 9.2 Hz, 1H), 6.10 (d, *J* = 15.0 Hz, 1H), 6.00 (m, 1H), 5.83 (dt,

J = 9.1, 7.2 Hz, 1H), 2.76 (m, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 2.49 (q, *J* = 7.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.41, 141.22, 136.32, 136.25, 136.01, 132.22, 128.93, 128.88, 128.52, 128.50, 128.46, 128.38, 128.33, 126.20, 126.04, 125.95, 125.92, 123.60, 121.90, 35.35, 35.08, 34.76, 30.65. **HRMS** (EI) calculated for $[C_{16}H_{16}S]^+$ requires *m/z* 240.0968, found *m/z* 240.0966.

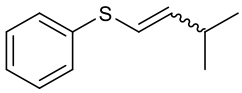


Phenyl(3-phenylprop-1-enyl)sulfane. Prepared according to a modification of a previously published procedure.[17] A reaction vial was charged with $Ru(bpz)_3(PF_6$2 (4 mg, 0.005 mmol), MeCN (4.5 mL), 3-phenyl-1-propyne (564 µL, 4.54 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography (gradient 50:1 to 9:1 hexanes/CH_2Cl_2) afforded 658 mg (2.91 mmol, 65% yield) of phenyl(3-phenylprop-1-enyl)sulfane as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (m, 6H), 7.22 (m, 4H), 6.34 (d, *J* = 9.2 Hz, 1H), 6.21 (d, *J* = 14.9 Hz, 1H), 6.10 (dt, *J* = 14.7, 6.8 Hz, 1H), 5.99 (dt, *J* = 9.1, 7.4 Hz, 1H), 3.62 (d, *J* = 7.3 Hz, 2H), 3.50 (d, *J* = 6.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.89, 139.28, 136.07, 135.98, 134.39, 131.55, 129.03, 128.99, 128.90, 128.55, 128.44, 126.37, 126.33, 126.32, 126.18, 123.95, 123.00, 39.30, 35.40. **HRMS** (EI) calculated for $[C_{15}H_{14}S]^+$ requires *m/z* 226.0811, found *m/z* 226.0813.

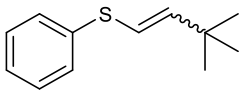


Phenyl(styryl)sulfane. Prepared according to a modification of a previously published procedure.[17] A reaction vial was charged with $Ru(bpz)_3(PF_6)_2$ (4 mg, 0.005 mmol), MeCN (4.5 mL), phenylacetylene (500 µL, 4.54 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography(gradient 50:1 to 9:1 hexanes/CH_2Cl_2) afforded 172 mg (0.81 mmol, 18% yield)

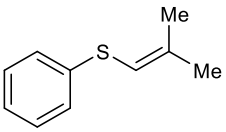
of phenyl(styryl)sulfane as a clear oil. All spectroscopic data were consistent with previously reported values.[18]



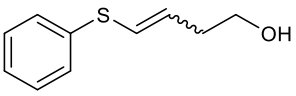
(3-Methylbut-1-enyl)(phenyl)sulfane. Prepared according to a modification of a previously published procedure.[17] A reaction vial was charged with $Ru(bpz)_3(PF_6)_2$ (4 mg, 0.005 mmol), MeCN (4.5 mL), 3-methyl-1-butyne (603 µL, 5.90 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography (gradient 50:1 to 25:1 hexanes/CH_2Cl_2) afforded 789 mg (4.42 mmol, 97% yield) of (3-methylbut-1-enyl)(phenyl)sulfane as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.25 Hz, 1H), 6.08 (d, *J* = 9.1 Hz, 1H), 5.67 (t, *J* = 9.2 Hz, 1H), 2.82 (m, 1H), 2.45 (m, 1H), 1.05 (s, 3H), 1.04 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.18, 140.75, 136.56, 128.93, 128.67, 128.36, 126.07, 120.27, 118.41, 77.01, 76.75, 31.94, 28.76, 22.43, 22.15. **HRMS** (EI) calculated for $[C_{11}H_{14}S]^+$ requires *m/z* 178.0811, found *m/z* 178.0808.



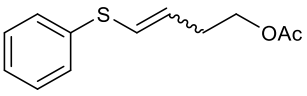
(3,3-Dimethylbut-1-enyl)(phenyl)sulfane. Prepared according to a modification of a previously published procedure.[17] A reaction vial was charged with $Ru(bpz)_3(PF_6)_2$ (4 mg, 0.005 mmol), MeCN (4.5 mL), 3,3-dimethyl- 1-butyne (727 µL, 5.90 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography (gradient 50:1 to 25:1 hexanes/CH_2Cl_2) afforded 681 mg (3.54 mmol, 78% yield) of (3,3-dimethylbut-1-enyl)(phenyl)sulfane as a clear oil. All spectroscopic data were consistent with previously reported values.[19]



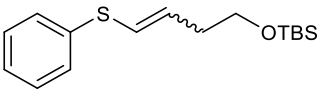
(2-Methylprop-1-enyl)(phenyl)sulfane. Prepared according to a modification of a previously published procedure.[14] A flame-dried Schlenk tube was evacuated and charged with *i*-Pr_2NEt (632 µL, 3.63 mmol), $Pd_2(dba)_3$ (42 mg, 0.045 mmol), xantphos (53 mg, 0.091 mmol) and 1,4-dioxane (7.3 mL). The reaction mixture was degassed by three freeze-pump-thaw cycles and backfilled with nitrogen. Thiophenol (186 µL , 1.82 mmol) and 1-bromo-2-methyl-1-propene (150 µL, 1.45 mmol) were added under nitrogen. The reaction was heated at 110 °C for 16 h before being cooled to room temperature and subsequently passed through a plug of Celite with ether. Flash column chromatography (50:1 hexanes/EtOAc with 2% Et_3N) afforded 215 mg (1.31 mmol, 72% yield) of (2-methylprop-1-enyl)(phenyl)sulfane as a clear oil. All spectroscopic data were consistent with previously reported values.[18]



4-(Phenylthio)but-3-en-1-ol. Prepared according to a modification of a previously published procedure.[17] A reaction vial was charged with $Ru(bpz)_3(PF_6)_2$ (4 mg, 0.005 mmol), MeCN (4.5 mL), 3-butyn-1-ol (343 µL, 4.54 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography (gradient 25:1 to 2:1 hexanes/EtOAc) afforded 650 mg (3.61 mmol, 79% yield) of 4-(phenylthio)but-3-en-1-ol as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (m, 4H), 7.21 (m, 1H), 6.36 (d, *J* = 9.3 Hz,1H), 6.28 (d, *J* = 15.0 Hz, 1H), 5.92 (dd, *J* = 14.9, 7.4 Hz, 1H), 5.85 (m, 1H), 3.75 (t, *J* =6.4 Hz, 2H), 3.70 (t, *J* = 6.3 Hz, 2H), 2.54 (q, *J* = 6.8 Hz, 2H), 2.43 (q, *J* = 6.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.88, 135.65, 132.68, 131.29, 129.85, 129.05, 129.02, 128.98, 128.46, 126.47, 126.43, 126.03, 124.71, 77.28, 77.02, 76.77, 61.87, 61.73, 36.40, 32.66. **HRMS** (EI) calculated for $[C_{10}H_{12}OS]^+$ requires *m/z* 180.0604, found *m/z* 180.0606.

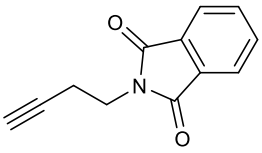


4-(Phenylthio)but-3-enyl acetate. A 25 mL round-bottomed flask was charged with 4-(phenylthio)but-3-en-1-ol (650 mg, 3.61 mmol), acetic anhydride (1.7 mL, 18.0 mmol) and pyridine (5.8 mL, 72 mmol). The reaction mixture was stirred under reflux for 14 h and subsequently poured onto water and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. Flash column chromatography (gradient 50:1 to 6:1 hexanes/EtOAc) afforded 441 mg (1.99 mmol, 55% yield) of 4-(phenylthio)but-3-enyl acetate as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 7.24 – 7.19 (m, 1H), 6.34 (dt, *J* = 9.3, 1.4 Hz, 1H), 5.80 (dt, *J* = 9.3, 7.2 Hz, 1H), 4.17 (t, *J* = 6.6 Hz, 2H), 2.60 (qd, *J* = 6.8, 1.4 Hz, 2H), 2.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.09, 135.83, 129.05, 127.79, 126.46, 126.11, 63.10, 28.66, 20.99.**HRMS** (EI) calculated for $[C_{12}H_{14}O_2S]^+$ requires *m/z* 222.0710, found *m/z* 222.0710.

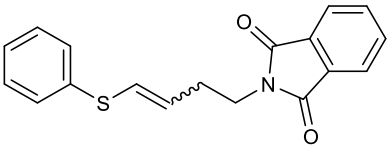


***tert*-Butyldimethyl(4-(phenylthio)but-3-enyloxy)silane**. A 10 mL round-bottomed flask was charged with 4-(phenylthio)but-3-en-1-ol (1.35 g, 7.49 mmol), *tert*-butyldimethylsilyl chloride (1.69 mg, 11.23 mmol), imidazole (1.02 mg, 14.98 mmol) and 4.5 mL DMF. After 10 h, the reaction was diluted with water and Et_2O. The phases were separated, and the aqueous phase was extracted two additional times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. Flash column chromatography (gradient, 50:1 to 4:1 hexanes/CH_2Cl_2) afforded 1.96 g (6.67 mmol, 89% yield) of *tert*-butyldimethyl(4-(phenylthio)but-3-enyloxy)silane as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (m, 4H), 7.12 (m, 1H), 6.20 (d, *J* = 9.3 Hz, 1H), 6.13 (d, *J* = 15.0 Hz, 1H), 5.88 (m, 1H), 5.80 (m, 1H), 3.62 (m, 2H), 2.41 (q, *J* = 6.5 Hz, 2H), 2.30 (q, *J* = 6.5 Hz, 2H), 0.83 (s, 9H), 0.82 (s, 9H), 0.00 (s, 6H), -0.02 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.31, 136.18, 133.20, 129.74, 128.93, 128.92, 128.84, 128.74, 126.18, 124.47, 123.01,

77.26, 77.01, 76.75, 62.40, 62.14, 36.61, 32.83, 25.95, 18.36, -5.25. **HRMS** (EI) calculated for $[C_{16}H_{26}OSSi]^+$ requires *m/z* 294.1469, found *m/z* 294.1464.

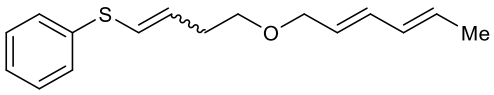


2-(But-3-ynyl)isoindoline-1,3-dione. Phthalic anhydride (1.07 g, 7.20 mmol) was placed in a 50 mL round-bottomed flask with CH_2Cl_2 (8.0 mL) and stirred to dissolve. After 15 min, 1-amino-3-butyne (500 mg, 7.20 mmol) was added dropwise, and the mixture stirred for 1 h more. The solvent was removed *in vacuo*. Acetic anhydride (2.4 mL, 25.3 mmol) and NaOAc (237 mg, 2.9 mmol) were added to the round-bottomed flask, which was then equipped with a reflux condenser. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the crude product recrystallized from EtOH to afford 951 mg (4.77 mmol, 52% yield) of the title compound as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.89 (t, *J* = 7.1 Hz, 2H), 2.62 (td, *J* = 7.1, 2.6 Hz, 2H), 1.96 (t, *J* = 2.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.03, 134.04, 131.98, 123.37, 80.26, 70.25, 36.53, 18.36. **HRMS** (EI) calculated for $[C_{12}H_9NO_2]^+$ requires *m/z* 199.0628, found *m/z* 199.0634.



2-(4-(Phenylthio)but-3-enyl)isoindoline-1,3-dione. Prepared according to a modification of a previously published procedure.[6] A reaction vial was charged with $Ru(bpz)_3(PF_6)_2$ (4 mg, 0.005 mmol), MeCN (4.5 mL), 2-(but-3-ynyl)isoindoline-1,3-dione (994 mg, 4.99 mmol) and thiophenol (467 µL, 4.54 mmol). The reaction mixture was stirred in front of a 23 W CFL bulb for 12 h and subsequently passed through a plug of silica with ether. Flash column chromatography (gradient 50:1 to 4:1 hexanes/EtOAc) afforded the crude product, which was recrystallized from EtOAc

and hexanes to afford 350 mg (1.41 mmol, 31% yield) of 2-(4-(phenylthio)but-3-enyl)isoindoline-1,3-dione as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.18 (m, 5H), 6.27 (d, *J* = 9.3 Hz, 1H), 6.20 (d, *J* = 15.0 Hz, 1H), 5.86 (m, 1H), 5.81 (m, 1H), 3.84 (t, *J* = 6.7 Hz, 2H), 3.79 (t, *J* = 7.1 Hz, 2H), 2.67 (q, *J* = 7.0 Hz, 2H), 2.55 (q, *J* = 7.1 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.37, 168.20, 135.69, 133.98, 133.84, 132.04, 130.37, 129.28, 128.93, 128.86, 128.09, 126.51, 126.28, 125.14, 123.29, 123.21, 37.23, 36.86, 32.06, 28.42. **HRMS** (EI) calculated for $[C_{18}H_{25}NO_2S]^+$ requires *m/z* 309.0819, found *m/z* 309.0819.

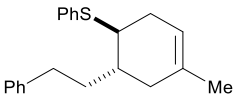


(4-((2*E*,4*E*)-Hexa-2,4-dienyloxy)but-1-enyl)(phenyl)sulfane. A flame-dried 50 mL round-bottomed flask was charged with 60% NaH (213 mg, 5.33 mmol) and 5 mL of dry THF. 4-(Phenylthio)but-3-en-1-ol (640 mg, 3.55 mmol) was added dropwise in 1 mL of THF, and the reaction was stirred for 30 min. The flask was cooled to 0 °C, and (2*E*,4*E*)-1-bromohexa-2,4-diene (686 mg, 4.26 mmol) was added dropwise in 1 mL THF. The mixture was gradually warmed to room temperature. After 12 h, the reaction was quenched by slow addition of saturated NH_4Cl. The phases were separated, and the aqueous phase was extracted two additional times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. Flash column chromatography (gradient, 50:1 to 10:1 hexanes/EtOAc) afforded 425 mg (1.63 mmol, 46% yield) of the title compound as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.21 (m, 1H), 6.21 (t, *J* = 16.4 Hz, 2H), .06 (m, 1H), 5.97 (dt, *J* = 14.8, 7.0 Hz, 1H), 5.67 (m, 2H), 4.00 (t, *J* = 7.2 Hz, 2H), 3.50 (dt, *J* = 13.3, 6.7 Hz, 2H), 2.45 (q, *J* = 6.8 Hz, 2H), 1.75 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.17, 133.18, 133.12, 132.85, 132.46, 130.82, 130.77, 130.05, 129.93, 129.44, 128.96, 128.94, 128.90, 128.71, 126.74, 126.62, 126.25, 126.18, 124.70, 123.18, 71.30, 71.18, 69.05, 68.80,

33.53, 29.72, 18.10. **HRMS** (EI) calculated for $[C_{16}H_{20}OS]^+$ requires *m/z* 260.1230, found *m/z* 260.1233.

2.5.3 [4+2] Photocycloadditions

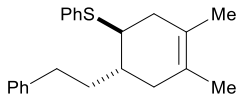
General Procedure: $Ru(bpz)_3(BArF)_2$ was dried over phosphrous pentoxide for 48 h in vacuo and stored under inert atmosphere prior to use. A dry 25 mL Schlenk tube was charged with anhydrous $MgSO_4$ (2 wt eq) and flame-dried under in vacuo. After cooling to room temperature, $Ru(bpz)_3(BArF)_2$ (0.05 eq), diene (3 eq), MeCN (0.05M) and a stock solution containing the dienophile (1 eq) in MeCN were added. The reaction was degassed by three freeze/pump/thaw cycles under nitrogen in the dark before back filling with nitrogen. The reaction was then allowed to stir while being irradiated by a 15 W (500 lumen) blue LED lamp. After a pre-determined time point, the reaction was eluted through a short pad of silica using Et_2O or EtOAc. After concentration by rotary evaporation, the pure cycloadduct was isolated by flash column chromatography. Structures and NMR data provided are representative of the major diastereomer.



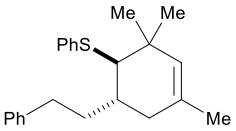
(4-Methyl-6-phenethylcyclohex-3-enyl)(phenyl)sulfane. (2.3)

Prepared according to the General Procedure using 80 mg (0.333 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 100 µL (0.999 mmol) isoprene, 38 mg (0.0165 mmol) $Ru(bpz)_3(BArF)_2$, 160 mg $MgSO_4$, 6.7 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 50:1 to10:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 92.5 mg of analytically pure cycloadduct as a clear oil (0.300 mmol, 90% yield, dr: 8:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.9 Hz, 1H),7.26 (m, 4H), 7.19 (m, 4H), 5.28 (s, 1H), 3.25 (q, *J* = 6.7 Hz, 1H), 2.73 (ddd, *J* = 15.7,10.4, 5.5 Hz, 1H), 2.59 (m, 1H), 2.39 (m, 2H), 2.13 (d, *J* = 19.9 Hz, 1H), 2.03 (m, 1H), 1.83 (m, 2H), 1.67 (s, 3H), 1.64 (m, 1H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.31, 135.39,132.60, 131.84, 131.53, 128.83, 128.78, 128.38, 128.36, 128.30, 126.59, 125.74,118.49, 47.38, 36.58, 35.38, 34.03, 32.91, 30.85, 23.61. **HRMS** (EI) calculated for $[C_{21}H_{24}S]^+$ requires *m/z* 308.1594, found *m/z* 308.1590.

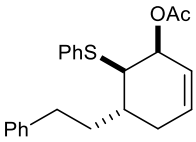


(3,4-Dimethyl-6-phenethylcyclohex-3-enyl)(phenyl)sulfane.**(2.4)** Prepared according to the General Procedure using 80 mg (0.333 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 113 µL (0.999 mmol) 2,3- dimethyl-1,3-butadiene, 38 mg (0.0165 mmol) $Ru(bpz)_3(BArF)_2$, 160 mg $MgSO_4$, 6.7 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 50:1 to 10:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 97 mg (0.300 mmol, 91% yield, dr: 4:1).of analytically pure cycloadduct as a clear oil. **^{1}H NMR** (500MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.9 Hz, 2H), 7.26 (m, 4H), 7.18 (m, 4H), 3.24 (m, 1H), 2.73 (m, 1H), 2.58 (ddd, *J* = 13.7, 10.3, 6.6 Hz, 1H), 2.34 (m, 2H), 2.09 (m, 2H), 1.95 (m, 1H), 1.81 (m, 2H), 1.62 (s, 3H), 1.56 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.41, 135.44,131.84, 131.57, 128.77, 128.40, 128.38, 126.55, 125.70, 124.21, 123.46, 49.25, 48.47, 37.57, 37.12, 36.10, 35.42, 32.92, 18.92, 18.69. **HRMS** (EI) calculated for $[C_{22}H_{26}S]^+$ requires *m/z* 322.1750, found *m/z* 322.1746.

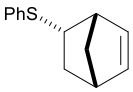


Phenyl(2,2,4-trimethyl-6-phenethylcyclohex-3-enyl)sulfane. **(2.5)** Prepared according to the General Procedure using 80 mg (0.333 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 129 µL (0.999 mmol) 2,4-dimethyl-1,3-pantadiene, 38 mg (0.0165 mmol) $Ru(bpz)_3(BArF)_2$, 160 mg $MgSO_4$, 6.7 mL MeCN and an irradiation time of 24 h. Purification by flash column chromatography (gradient, 50:1 to 10:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 56% (0.168 mmol) of cycloadduct as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ7.40 (d, *J* = 7.3 Hz, 1H), 7.23 (m, 4H), 7.12 (m, 4H), 5.20 (s, 1H), 2.93 (d, *J* = 11.9 Hz, m1H), 2.65 (m, 1H), 2.56 (m, 2H), 2.22 (dd, *J* = 17.2, 5.3 Hz, 1H), 1.93 (m, 1H),

1.81 (dd, *J* = 16.9, 10.9 Hz, 1H), 1.64 (s, 3H), 1.37 (m, 1H), 1.23 (s, 3H), 1.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.45, 139.45, 132.35, 130.15, 129.93, 128.77, 128.27, 128.19,125.67, 125.54, 64.09, 38.01, 37.61, 36.89, 36.09, 33.02, 30.03, 24.52, 23.15. **HRMS** (EI) calculated for $[C_{23}H_{28}S]^+$ requires *m/z* 336.1907, found *m/z* 336.1897.

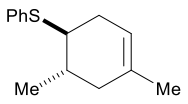


5-Phenethyl-6-(phenylthio)cyclohex-2-enyl acetate. **(2.6)** Prepared according to the General Procedure using 71 mg (0.300 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 101 mg (0.900 mmol) 1,3-acetoxybutadiene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 142 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 24 h. Purification by flash column chromatography (gradient, 50:1 to 10:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 70 mg (0.198 mmol, 66% yield, dr: 3:1) of analytically pure cycloadduct as a pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.41 – 7.37 (m, 2H), 7.34 – 7.14 (m, 8H), 5.92 (dt, *J* = 10.0, 3.3 Hz, 1H), 5.73 (ddt, *J* = 10.0, 4.2, 2.2 Hz, 1H), 5.41 (td, *J* = 4.1, 1.8 Hz, 1H), 3.50 (dd, *J* = 8.8, 4.0 Hz, 1H), 2.74 (ddd, *J* = 13.7, 10.3, 5.6 Hz, 1H), 2.62 (ddt, *J* = 12.2, 10.4, 5.0 Hz, 1H), 2.53 (dddt, *J* = 18.6, 5.8, 3.9, 2.0 Hz, 1H), 2.23 – 2.09 (m, 2H), 2.01 (s, 3H), 1.97 – 1.89 (m, 1H), 1.72 – 1.61 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.61, 141.94, 135.58, 132.05, 131.22, 129.00, 128.40, 128.36, 127.02, 125.86, 124.39, 68.57, 53.36, 35.19, 34.62, 32.84, 30.20, 21.00. **HRMS** (EI) calculated for $[C_{22}H_{24}O_2S]^+$ requires *m/z* 352.1492, found *m/z* 352.1480.

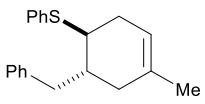


Bicyclo[2.2.1]hept-5-en-2-yl(phenyl)sulfane. **(2.7)** Prepared according to the General Procedure using 41 mg (0.300 mmol) phenyl vinyl sulfide, 75 µL (0.900 mmol) 1,3-cyclopentadiene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 82 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 50:1 to 10:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 50.4 mg (0.249 mmol,

83%, dr: 3:1) of analytically pure cycloadduct as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.17 (m, 1H), 6.27 (dd, *J* = 5.6, 3.0 Hz, 1H), 6.11 (dd, *J* = 5.7, 2.9 Hz, 1H), 3.69 (m, 1H), 3.09 (s, 1H), 2.92 (s, 1H), 2.29 (m, 1H), 1.56 (dd, *J* = 8.6, 2.4 Hz, 1H), 1.33 (d, *J* = 8.6 Hz, 1H), 0.97 (dt, *J* = 12.2, 3.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.25, 137.68, 137.47, 134.83, 132.97, 129.51, 129.25, 128.80, 128.77, 125.76, 48.87, 47.43, 46.48, 45.97, 45.70, 44.47, 42.61, 41.82, 34.53, 33.86. **HRMS** (EI) calculated for $[C_{13}H_{14}S]^+$ requires *m/z* 202.0811, found *m/z* 202.0817.

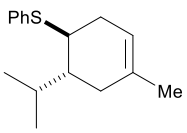


(4,6-Dimethylcyclohex-3-enyl)(phenyl)sulfane. **(2.8)** Prepared according to the General Procedure using 45 mg (0.300 mmol) phenyl(prop-1-enyl)sulfane, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 90 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 50:1 to 10:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 62 mg (0.282 mmol, 94%yield, dr: 5:1) of analytically pure cycloadduct as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 5.27 (s, 1H), 3.07 (td, *J* = 8.4, 5.3 Hz, 1H), 2.39 (d, *J* = 17.0 Hz, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 1.88 (dq, *J* = 14.4, 6.7, 6.3 Hz, 1H), 1.73 (dd, *J* = 17.5, 7.9 Hz, 1H), 1.64 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.49, 133.01, 131.96, 131.12, 128.79, 128.74, 126.57, 126.24, 118.93, 118.50, 49.45, 48.83, 37.79, 36.76, 33.01, 31.96, 31.54, 30.43, 23.60, 23.34, 20.21. **HRMS** (EI) calculated for $[C_{14}H_{18}S]^+$ requires *m/z* 218.1124, found *m/z* 218.1122.

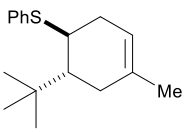


(6-Benzyl-4-methylcyclohex-3-enyl)(phenyl)sulfane.**(2.9)** Prepared according to the General Procedure using 68 mg (0.300 mmol) phenyl(3-phenylprop-1-enyl)sulfane, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 136 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 20 h. Purification by flash column

chromatography (gradient, 50:1 to 10:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 60 mg (0.204 mmol, 68% yield, dr: 7:1). of analytically pure cycloadduct as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.3 Hz, 2H), 7.27 (m, 4H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 7.1 Hz, 2H), 5.30 (s, 1H), 3.25 (q, *J* = 5.9 Hz, 1H), 3.06 (dd, *J* = 13.6, 5.5 Hz, 1H), 2.50 (dd, *J* = 13.6, 8.8 Hz, 2H), 2.16 (m, 3H), 1.70 (dd, *J* = 13.0, 2.9 Hz, 1H), 1.62 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.34, 135.47, 132.45, 131.40, 131.27, 129.10, 128.80, 128.27, 126.49, 125.98, 118.10, 46.35, 39.86, 38.77, 33.21, 30.35, 23.57. **HRMS** (EI) calculated for $[C_{20}H_{22}S]^+$ requires *m/z* 294.1437, found *m/z* 294.1441.

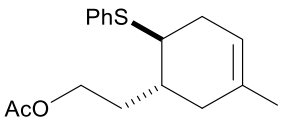


(6-Isopropyl-4-methylcyclohex-3-enyl)(phenyl)sulfane. **(2.10)** Prepared according to the General Procedure using 54 mg (0.300 mmol) (3-methylbut-1-enyl)(phenyl)sulfane, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 108 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 48 h. Purification by flash column chromatography (gradient, 50:1 to 20:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 34 mg (0.138 mmol, 46%, dr: >10:1) of analytically pure cycloadduct as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.27 (dd, *J* = 7.3, 7.2 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.26 (s, 1H), 3.28 (td, *J* = 8.6, 5.3 Hz, 1H), 2.36 (m, 1H), 2.21 (m, *J* = 6.8 Hz, 1H), 2.10 (m, 2H), 1.88 (dd, *J* = 17.6, 8.3 Hz, 1H), 1.69 (dd, *J* = 8.6, 5.3 Hz, 1H), 1.65 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.34, 132.27, 131.09, 127.73, 125.60, 117.92, 45.49, 42.03, 31.54, 28.19, 26.80, 22.51, 19.86, 15.68. **HRMS** (EI) calculated for $[C_{16}H_{22}S]^{[M+H]+}$ requires *m/z* 247.1515, found *m/z* 247.1511.

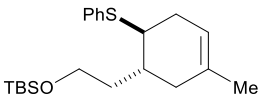


(6-*tert*-Butyl-4-methylcyclohex-3-enyl)(phenyl)sulfane. **(2.11)** Prepared according to the General Procedure using 58 mg (0.300 mmol) (3,3-dimethylbut-1-enyl)(phenyl)sulfane, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 116

mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 48 h. Purification by flash column chromatography (gradient, 50:1 to 20:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 15 mg (0.057 mmol,19%, dr: >10:1) of analytically pure cycloadduct as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.28 (m, 2H), 7.20 (m, 1H), 5.31 (s, 1H), 3.73 (m, 1H), 2.45 (ddt, *J* = 18.2, 5.4, 3.0 Hz, 1H), 2.36 (dd, *J* = 16.9, 7.1 Hz, 1H), 2.22 (m, 1H), 1.85 (d, *J* = 18.0 Hz, 1H), 1.71 (s, 3H), 1.68 (dd, *J* = 5.9, 3.5 Hz, 1H), 0.91 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.59, 133.99, 131.02, 128.83, 126.35, 117.55, 45.08, 44.14, 34.30, 29.03, 28.53, 27.87, 23.79. **HRMS** (EI) calculated for $[C_{17}H_{24}S]^+$ requires *m/z* 260.1600, found *m/z* 260.1594.

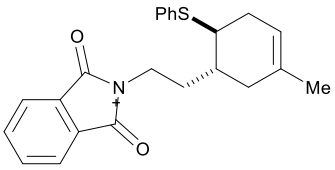


2-(3-Methyl-6-(phenylthio)cyclohex-3-enyl)ethyl acetate. **(2.12)** Prepared according to the General Procedure using 67 mg (0.300 mmol) 4-(phenylthio)but-3-enyl acetate, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 134 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 20 h. Purification by flash column chromatography (gradient, 50:1 to 7:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 56 mg (0.192 mmol, 64% yield, dr: >10:1) of analytically pure cycloadduct as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.28 (m, 2H), 7.22 (m, 1H), 5.30 (s, 1H), 4.14 (m, 2H), 3.21 (q, *J* = 6.3 Hz, 1H), 2.42 (m, 1H), 2.34 (m, 1H), 2.12 (m, 2H), 2.03 (s, 3H), 1.92 (m, 1H), 1.74 (dd, *J* = 19.2, 7.5 Hz, 1H), 1.66 (s, 3H), 1.60 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.13, 135.10, 132.23, 131.94, 131.48, 128.83, 126.78, 118.47, 62.38, 47.18, 34.01, 33.70, 32.34, 30.61, 23.54, 21.00. **HRMS** (EI) calculated for $[C_{17}H_{22}O_2S]^+$ requires *m/z* 290.1336, found *m/z* 290.1329.



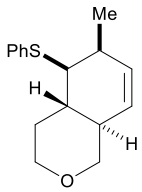
***tert*-Butyldimethyl(2-(3-methyl-6-(phenylthio)cyclohex-3-**

enyl)ethoxy)silane. **(2.13)** Prepared according to the General Procedure using 88 mg (0.300 mmol) *tert*-butyldimethyl (4-(phenylthio)but-3-enyloxy)silane, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 176 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 20 h. Purification by flash column chromatography (gradient, 50:1 to 25:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 83 mg (0.228 mmol, 76%, dr: >10:1) of analytically pure cycloadduct as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.23 (m, 2H), 7.16 (m, 1H), 5.25 (s, 1H), 3.65 (m, 2H), 3.23 (m, 1H), 2.36 (m, 2H), 2.10 (m, 1H), 1.97 (m, 1H), 1.88 (dtd, *J* = 13.9, 7.1, 4.7 Hz, 1H), 1.70 (dd, *J* = 17.4, 4.1 Hz, 1H), 1.62 (s, 3H), 1.44 (m, 1H), 0.85 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.61, 131.42, 131.26, 130.58, 128.99, 127.87, 127.74, 125.44, 125.24, 117.17, 60.08, 46.20, 35.52, 32.76, 32.49, 29.22, 24.94, 22.64, 17.27, -6.32. **HRMS** (EI) calculated for $[C_{21}H_{34}OSSi]^+$ requires *m/z* 362.2095, found *m/z* 362.2084.



2-(2-(3-Methyl-6-(phenylthio)cyclohex-3-enyl)ethyl)isoindoline-1,3-dione. **(2.14)** Prepared according to the General Procedure using 93 mg (0.300 mmol) 2-(4-(phenylthio)but-3-enyl)isoindoline-1,3-dione, 90 µL (0.900 mmol) isoprene, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 186 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 24 h. Purification by flash column chromatography (gradient, 50:1 to 2:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 79 mg (0.210 mmol, 70%, dr: 5:1) of analytically pure cycloadduct as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 5.29 (s, 1H), 3.75 (m, 2H), 3.23 (q, *J* = 6.0 Hz, 1H), 2.43 (t, *J* = 14.3 Hz, 2H), 2.12 (m, 2H), 1.84 (m, 2H), 1.69 (s, 3H), 1.64 (dd, *J* = 13.8, 5.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.32, 134.84, 133.88, 132.25, 132.13, 131.45, 128.76, 126.80,

123.21, 118.34, 47.17, 35.84, 34.47, 33.40, 32.32, 30.35, 23.63. **HRMS** (EI) calculated for $[C_{23}H_{23}NO_2S]^+$ requires *m/z* 377.1445, found *m/z* 377.1449.

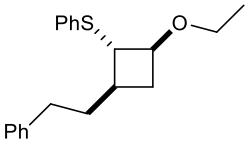


6-Methyl-5-(phenylthio)hexahydro-1H-isochromene. (2.15) Prepared according to the General Procedure using 78 mg (0.300 mmol) (4-((2*E*,4*E*)-hexa-2,4-dienyloxy)but-1-enyl)(phenyl)sulfane, 36 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 156 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 20 h. Purification by flash column chromatography (gradient, 50:1 to 20:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 58 mg (0.222 mmol, 74% yield, dr: 3:1) of analytically pure cycloadduct as an oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 5.75 (m, 1H), 5.56 (d, *J* = 10.0 Hz, 1H), 3.98 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.91 (d, *J* = 11.6 Hz, 1H), 3.70 (dd, *J* = 7.2, 3.5 Hz, 1H), 3.53 (dd, *J* = 11.5, 3.3 Hz, 1H), 3.22 (td, *J* = 11.6, 2.1 Hz, 1H), 2.66 (m, 1H), 2.24 (s, 1H), 2.12 (dq, *J* = 12.3, 4.0 Hz, 1H), 1.86 (qd, *J* = 12.5, 4.4 Hz, 1H), 1.74 (m, 1H), 1.20 (d, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.62, 131.45, 129.01, 127.36, 126.72, 72.15, 68.81, 52.30, 38.13, 36.33, 32.48, 29.70, 24.02, 17.40. **HRMS** (EI) calculated for $[C_{16}H_{20}OS]^+$ requires *m/z* 260.1230, found *m/z* 260.1232.

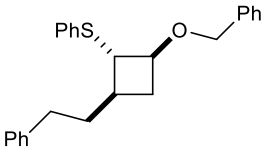
2.5.4 [2+2] Cycloadditions

General Procedure: A dry 25 mL Schlenk tube was charged with anhydrous $MgSO_4$ (2 wt eq) which was flame dried under in vacuo. After cooling to room temperature, $Ru(bpz)_3(BArF)_2$ (0.05 eq), terminal alkene (3 eq), and a stock solution of vinyl sulfide (1 eq) were added. The solution was then diluted with MeCN to give a 0.05 M solution with respect to the vinyl sulfide. The reaction was then degassed by three freeze/pump/thaw cycles under nitrogen in the dark before back filling with nitrogen. The reaction was then allowed to stir while being irradiated with a 15 W (500 lumen) blue LED lamp. After a pre-determined time point, the reaction was eluted

through a short pad of silica using Et_2O. After concentration by rotary evaporation, the pure cycloadduct was isolated by flash column chromatography.

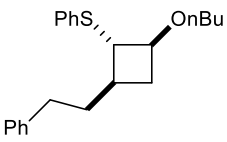


2-Ethoxy-4-phenethylcyclobutyl)(phenyl)sulfane. (2.16) Prepared according to the General Procedure using 24 mg (0.1 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 28.9 µL (0.3 mmol) ethyl vinyl ether, 11.5 mg (0.005 mmol) $Ru(bpz)_3(BArF)_2$, 48 mg $MgSO_4$, 2 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 22.2 mg of analytically pure cycloadduct as a clear oil (0.071 mmol, 71% yield, dr: 15:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.30 – 7.11 (m, 8H), 3.63 (q, *J* = 7.5 Hz, 1H), 3.47 (qq, *J* = 9.3, 7.0 Hz, 2H), 3.23 (dd, J = 8.1, 7.5 Hz 1H), 2.66 – 2.52 (m, 2H), 2.39 (dt, J= 15.1, 7.5 Hz, 1H), 1.98-1.89 (m,1H), 1.79 – 1.64 (m, 2H), 1.44 (ddd, J = 10.7, 9.3, 8.2 Hz, 1H), 1.17 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.93, 135.31, 131.47, 128.78, 128.35, 128.30, 126.63, 125.76, 77.16, 64.45, 53.74, 36.93, 33.73, 33.62, 33.39, 15.38. **HRMS** (ESI) calculated for $[C_{20}H_{24}OS]^{[M+H]+}$ requires *m/z* 313.1621, found *m/z* 313.1611.

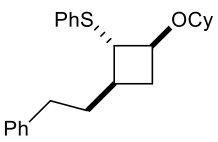


2-(Benzyloxy)-4-phenethylcyclobutyl)(phenyl)sulfane. (2.17) Prepared according to the General Procedure using 72 mg (0.3 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 124 µL (0.9 mmol) benzyl vinyl ether, 34.5 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 144 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 85.5 mg of analytically pure cycloadduct as a clear oil (0.23 mmol, 76% yield, dr: >20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47-7.11 (m, 15H), 4.46 (s, 2H), 3.75 (q, J = 7.4 Hz, 1H), 3.32 (dd, J = 8.4, 6.9 Hz, 1H), 2.68 – 2.53 (m, 2H), 2.38 (dt, J =

10.9, 7.3 Hz, 1H), 2.06 – 1.86 (m, 1H), 1.78-1.66 (m, 2H), 1.59 – 1.43 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.89, 138.04, 135.26, 131.53, 128.82, 128.36, 128.35, 128.30, 127.70, 127.62, 126.68, 125.77, 77.08, 70.87, 53.75, 36.94, 33.55, 33.51, 33.37. **HRMS** (ESI) calculated for $[C_{25}H_{26}OS]^{[M+NH4]+}$ requires *m/z* 392.2043, found *m/z* 392.2033.

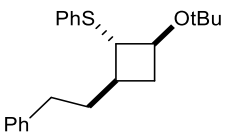


2-*n*-Butoxy-4-phenethylcyclobutyl)(phenyl)sulfane. (2.18) Prepared according to the General Procedure using 72.1 mg (0.3 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 120 µL (0.9 mmol) *n*-butyl vinyl ether, 34.5 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 144 mg $MgSO_4$, 6 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 84.9 mg of analytically pure cycloadduct as a clear oil (0.25 mmol, 83% yield, dr: 15:1).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.29 – 7.11 (m, 8H), 3.63 (q, *J* = 7.5 Hz, 1H), 3.38 (t, *J* = 6.6 Hz, 2H), 3.23 (dd, *J* = 8.4, 7.0 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.40 (dt, *J* = 11.0, 7.3 Hz, 1H), 1.98 – 1.88 (m, 1H), 1.78 – 1.64 (m, 2H), 1.57- 1.48 (m, 2H), 1.47-1.39 (m, 1H), 1.33 (dqd, J = 14.5, 7.3, 1.8 Hz 2H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.94, 135.50, 131.30, 128.76, 128.35, 128.29, 126.53, 125.75, 77.55, 68.80, 53.69, 36.97, 33.59, 33.57, 33.39, 31.89, 19.27, 13.89. **HRMS** (ESI) calculated for $[C_{22}H_{28}OS]^{[M+H]+}$ requires *m/z* 341.1934, found *m/z* 341.1929.

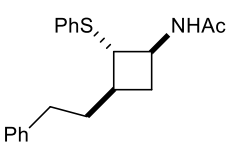


2-(Cyclohexyloxy)-4-phenethylcyclobutyl)(phenyl)sulfane. (2.19) Prepared according to the General Procedure using 72 mg (0.3 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 128 µL (0.9 mmol) cyclohexyl vinyl ether, 34.5 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 144 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 109.2 mg of analytically pure cycloadduct as a

clear oil (0.276 mmol, 92% yield, dr: 15:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.29 – 7.23 (m, 4H), 7.22 – 7.12 (m, 4H), 3.73 (q, *J* = 7.5 Hz, 1H), 3.31 – 3.21 (m, 2H), 2.59 (dq, *J* = 9.2, 3.0 Hz, 2H), 2.40 (dt, *J* = 10.8, 7.3 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.88 – 1.78 (m, 2H), 1.78 – 1.64 (m, 4H), 1.53 – 1.43 (m, 2H), 1.32 – 1.11 (m, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.99, 135.79, 131.01, 128.72, 128.36, 128.29, 126.35, 125.74, 76.85, 75.76, 54.13, 36.95, 35.04, 33.68, 33.44, 32.81, 32.77, 25.68, 24.15, 24.08. **HRMS** (ESI) calculated for $[C_{24}H_{30}OS]^{[M+NH4]+}$ requires *m/z* 384.2356, found *m/z* 384.2347.

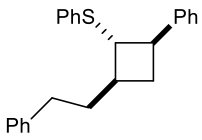


2-(*tert*-Butoxy)-4-phenethylcyclobutyl)(phenyl)sulfane. (2.20) Prepared according to the General Procedure using 72 mg (0.3 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 118 µL (0.9 mmol) tert-butyl vinyl ether, 34.5 mg (0.015 mmol) $Ru(bpz)_3(BArF)_2$, 144 mg $MgSO_4$, 6.0 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/EtOAc) and concentration by rotary evaporation afforded 96.0 mg of analytically pure cycloadduct as a clear oil (0.264 mmol, 88% yield, dr: 15:1).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 2H), 7.28 – 7.20 (m, 4H), 7.19 – 7.11 (m, 4H), 3.76 (q, *J* = 7.5 Hz, 1H), 3.26 (dd, *J* = 8.6, 7.3 Hz, 1H), 2.66 – 2.50 (m, 2H), 2.36 (dt, *J* = 10.7, 7.3 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.77-1.66 (m, 2H), 1.47 (ddd, *J* = 10.8, 9.4, 8.0 Hz, 1H), 1.16 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.00, 135.99, 130.67, 128.56, 128.34, 128.26, 126.07, 125.70, 73.88, 71.02, 54.14, 37.43, 36.87, 34.01, 33.47, 28.36. **HRMS** (ESI) calculated for $[C_{22}H_{28}OS]^{[M+H]+}$ requires *m/z* 341.1934, found *m/z* 341.1925.

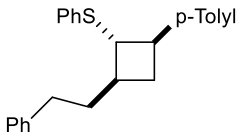


***N*-3-Phenethyl-2-(phenylthio)cyclobutyl)acetamide. (2.21)** Prepared according to the General Procedure using 24 mg (0.1 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 85 mg (1.0 mmol, 10 eq) N-vinylacetamide,11.5 mg (0.005 mmol) $Ru(bpz)_3(BArF)_2$, 48 mg $MgSO_4$, 2 mL MeCN and an irradiation time of 15 h. Purification by flash

column chromatography (gradient, 1:1 hexanes/Et_2O to 100% Et_2O) and concentration by rotary evaporation afforded 13.6 mg of analytically pure cycloadduct as a clear oil (0.04 mmol, 46% yield, dr: 20:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 – 7.05 (m, 10H), 5.66 (d, *J* = 8.1 Hz, 1H), 4.07 (p, *J* = 8.7 Hz, 1H), 3.08 (t, *J* = 8.9 Hz, 1H), 2.60 (t, *J* = 7.8 Hz, 2H), 2.40 (dt, *J* = 10.4, 8.1 Hz, 1H), 1.91 (s, 3H), 1.80 (dq, *J* = 17.3, 8.9 Hz, 1H), 1.67 (dq, J = 13.3, 7.6 Hz, 1H), 1.35 (q, *J* = 9.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.36, 141.79, 134.20, 132.89, 128.86, 128.34, 128.31, 127.84, 125.84, 77.28, 77.23, 77.03, 76.77, 54.70, 48.41, 36.68, 36.00, 34.12, 33.38, 23.32. **HRMS** (EI) calculated for $[C_{20}H_{23}NOS]^{[M+H]+}$ requires *m/z* 326.1573, found *m/z* 326.1571.



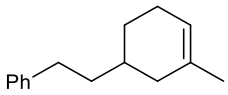
2-Phenethyl-4-phenylcyclobutyl)(phenyl)sulfane. (2.22) Prepared according to the General Procedure using 24 mg (0.1 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 34.3 µL (0.3 mmol) styrene, 11.5 mg (0.005 mmol) $Ru(bpz)_3(BArF)_2$, 48 mg $MgSO_4$, 2 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 6.6 mg of analytically pure cycloadduct as a clear oil (0.048 mmol, 48% yield, dr: 3:1).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.07 (m, 15H), 3.32 (t, *J* = 9.2 Hz, 1H), 3.19 (q, *J* = 9.4 Hz, 1H), 2.62 (tq, *J* = 13.8, 7.2 Hz, 2H), 2.44 (dt, *J* = 10.3, 8.4 Hz, 1H), 2.21 (dtd, J = 17.2, 8.9, 5.6 Hz, 1H), 1.96 (ddt, J = 12.8, 9.3, 6.8 Hz 1H), 1.81 – 1.61 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.92, 142.08, 134.24, 133.01, 128.71, 128.37, 128.35, 128.32, 127.12, 126.71, 126.42, 125.76, 54.82, 44.88, 40.13, 36.77, 33.26, 31.96. **HRMS** (ESI) calculated for $[C_{24}H_{24}S]^{[M+H]+}$ requires *m/z* 345.1672, found *m/z* 345.1669.



2-Phenethyl-4-(*p*-tolyl)cyclobutyl)(phenyl)sulfane. (2.23) Prepared according to the General Procedure using 24 mg (0.1 mmol) phenyl(4-phenylbut-1-enyl)sulfane, 39.6 µL (0.3 mmol) 4-methylstyrene, 11.5 mg (0.005 mmol)

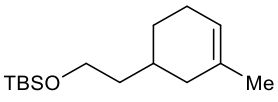
$Ru(bpz)_3(BArF)_2$, 48 mg $MgSO_4$, 2 mL MeCN and an irradiation time of 15 h. Purification by flash column chromatography (gradient, 10:1 to 4:1 hexanes/CH_2Cl_2) and concentration by rotary evaporation afforded 26.0 mg of analytically pure cycloadduct as a clear oil (0.072 mmol, 72% yield, dr: 2:1).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 6.99 (m, 14H), 3.29 (t, *J* = 9.2 Hz, 1H), 3.14 (q, *J* = 9.3 Hz, 1H), 2.61 (tq, *J* = 14.0, 7.3 Hz, 2H), 2.41 (dt, *J* = 10.2, 8.4 Hz, 1H), 2.32 (s, 3H), 2.20 (qd, *J* = 8.9, 5.7 Hz, 1H), 1.95 (ddt, *J* = 12.8, 9.3, 6.5 Hz, 1H), 1.78 – 1.58 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.11, 139.90, 135.95, 134.33, 133.01, 129.01, 128.69, 128.37, 128.30, 127.07, 126.60, 125.74, 54.88, 44.50, 40.13, 36.78, 33.26, 32.08, 21.05. **HRMS** (ESI) calculated for $[C_{25}H_{26}S]^{[M+H]+}$ requires *m/z* 359.1828, found *m/z* 359.1825.

2.5.5 Removal of the Redox Auxiliary

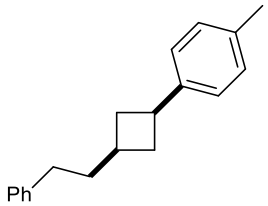


(2-(3-Methylcyclohex-3-en-1-yl)ethyl)benzene. (2.24) Prepared according to a modification of a previously published procedure.[20] An oven-dried 10 mL round bottom flask was charged with (4-ethyl-6-phenethylcyclohex-3-enyl)(phenyl)sulfane (26.8 mg, 0.087 mmol) and placed under N_2. 1 mL of a freshly prepared 0.5 M solution of lithium naphthalenide in THF (0.5 mmol) was added via syringe. The resulting dark brown solution was allowed to stir at room temperature. After one hour the reaction was quenched with $NaHCO_3$, then extracted with Et_2O (3 x 10mL). The combined organic layers were then washed with 10 mL of brine solution, dried with $MgSO_4$, and concentrated by rotary evaporation. Purification by flash column chromatography (100% pentane) and concentration by rotary evaporation afforded 11.7 mg of analytically pure cycloadduct as a clear oil (0.058 mmol, 67% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.14 (m, 3H), 5.38 (s, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.08 – 1.94 (m, 3H), 1.75 (ddt, *J* = 12.3, 4.1, 2.3 Hz, 1H), 1.70 – 1.55 (m, 6H), 1.17 (dtd, *J* = 12.5, 9.9, 6.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.00, 133.45, 128.35, 128.27, 125.56,

120.97, 38.55, 36.86, 33.58, 33.32, 28.63, 25.24, 23.80. **HRMS** (ASAP) calculated for [$C_{15}H_{20}$] $^{[M+H]+}$ requires *m/z* 201.1638, found *m/z* 201.1635.

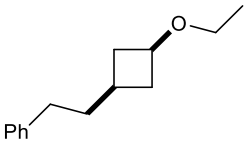


***tert*-Butyldimethyl(2-(3-methylcyclohex-3-en-1-yl)ethoxy)silane. (2.25)** Prepared according to a modification of a previously published procedure.[20] An oven-dried 10 mL round bottom flask was charged with, *tert*-Butyldimethyl(2-(3-methyl-6-(phenylthio)cyclohex-3-enyl)ethoxy)silane (70.8 mg, 0.195 mmol) and placed under N_2. 2 mL of a freshly prepared 0.5 M solution of lithium naphthalenide in THF (1 mmol) was added via syringe. The resulting dark brown solution was allowed to stir at room temperature. After 1 h the reaction was quenched with $NaHCO_3$, then extracted with Et_2O (3 x 10mL). The combined organic layers were then washed with 10 mL of brine solution, dried with $MgSO_4$, and concentrated by rotary evaporation. Purification by flash column chromatography (100:0 – 50:1 pentane/Et_2O gradient) and concentration by rotary evaporation afforded 37.1 mg of analytically pure cycloadduct as a clear oil (0.146 mmol, 74% yield) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.40 – 5.34 (m, 1H), 3.68 (t, *J* = 6.8 Hz, 2H), 2.06 – 1.91 (m, 3H), 1.69 (m, 1H), 1.66 – 1.58 (m, 4H), 1.50 (qd, *J* = 6.7, 1.5 Hz, 2H), 1.14 (ddq, *J* = 11.4, 7.2, 2.4 Hz, 1H), 0.90 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.47, 120.88, 77.26, 77.21, 77.00, 76.75, 61.25, 39.55, 36.91, 30.63, 28.64, 25.99, 25.17, 23.78, 18.37, -5.26. **HRMS** (ASAP) calculated for [$C_{15}H_{30}OSi$] $^{[M+H]+}$ requires *m/z* 255.2139, found *m/z* 255.2134.



1-Methyl-4-(3-phenethylcyclobutyl)benzene. (2.26) Prepared according to a modification of a previously reported procedure.[11a] A 25 mL round bottom flask was charged with 2-phenethyl-4-(p-tolyl)cyclobutyl)(phenyl)sulfane, 111.6 mg (0.31 mmol) in 6 mL of EtOH. The stirring solution was then treated with 4 mL of Raney Nickel solution and let stir at room temperature for 2 h.

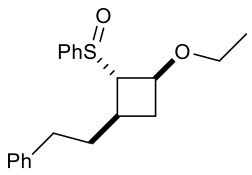
The resulting reaction mixture was diluted with 4 mL of distilled water and passed through a short Celite plug. The filtered reaction mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with 10 mL of brine solution, dried with $MgSO_4$, and concentrated by rotary evaporation. Purification by flash column chromatography (10:1 pentane/ DCM) and concentration by rotary evaporation afforded 66.7 mg of analytically pure cycloadduct as a clear oil (0.27 mmol, 86% yield, dr: 2:1). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.30 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 7.09 (s, 4H), 3.29 (tt, *J* = 10.0, 7.9 Hz, 1H), 2.58 – 2.53 (m, 2H), 2.51 – 2.43 (m, 2H), 2.31 (s, 3H), 2.23 (tt, *J* = 9.6, 7.4 Hz, 1H), 1.77 – 1.64 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.09, 142.59, 135.09, 128.83, 128.37, 128.23, 126.25, 125.59, 38.84, 36.08, 35.99, 33.51, 31.26, 20.98. **HRMS** (ASAP) calculated for $[C_{19}H_{22}]^+$ requires *m/z* 250.1716, found *m/z* 250.1715.



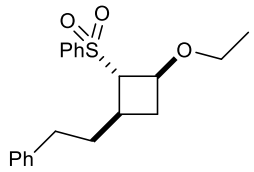
(2-(3-Ethoxycyclobutyl)ethyl)benzene. (2.27) Prepared according to a modification of a previously published procedure.[10] A 25 mL round bottom flask was charged with 2-ethoxy-4-phenethylcyclobutyl) (phenyl)sulfane (93.8 mg, 0.3 mmol) in 6 mL of EtOH. The stirring solution was then treated with 3 mL of Raney Nickel solution and let stir at room temperature for 30 min. The resulting reaction mixture was diluted with 2 mL of distilled water and passed through a short Celite plug. The filtered reaction mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with 10 mL of brine solution, dried with $MgSO_4$, and concentrated by rotary evaporation. Purification by flash column chromatography (10:1 hexanes/ EtOAc) and concentration by rotary evaporation afforded 52.3 mg of analytically pure cycloadduct as a clear oil (0.26 mmol, 85% yield, dr: 14:1) **^{1}H NMR** (500 MHz, CDCl3) δ 7.30 – 7.12 (m, 5H), 3.81 – 3.71 (m, 1H), 3.38 (q, *J* = 7.0 Hz, 2H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.38 (dddd, *J* = 11.6, 9.6, 5.6, 2.9 Hz, 2H), 1.79 – 1.68 (m, 3H), 1.53 (qd, *J* = 8.6, 2.8 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.39, 128.35,

128.24, 125.63, 69.53, 63.04, 38.82, 36.56, 33.70, 25.76, 15.36. **HRMS** (ESI) calculated for $[C_{14}H_{20}O]^{[M+H]+}$ requires *m/z* 205.1587, found *m/z* 205.1587.

2.5.6 Oxidation of Sulfide Cycloadduct



(2-(3-ethoxy-2-(phenylsulfinyl)cyclobutyl)ethyl)benzene (2.28) An oven dried 25 mL round bottom flask was charged with 43.9 mg (0.141 mmol, 1eq) 2-ethoxy-4-phenethylcyclobutyl)(phenyl) in 3 mL of anhydrous CH_2Cl_2. The reaction solution was then cooled to -78 C under N_2 atmosphere. The reaction solution was then treated with 34.7 mg (.155 mmol, 1.1 eq) mCPBA in 2.6 mL of anhydrous CH_2Cl_2 dropwise over twenty minutes. Five minutes post full addition of the oxidant the reaction was diluted with 10 mL CH_2Cl_2 and quenched with 10 mL of saturated $NaHCO_3$. The aqueous layer was then extracted with a further 20 mL of CH_2Cl_2. The pooled organic layers were dried with $MgSO_4$, and reconstituted. Purification by flash chromatography (2:1 Hex:EtOAc) and concentration by rotary evaporation afforded 35.5 mg of analytically pure oxidized cycloadduct as a clear oil (0.108 mmol, 77% yield, dr: 1:1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.65 – 7.41 (m, 4H), 7.37 – 7.09 (m, 4H), 6.94 – 6.83 (m, 1H), 4.12 (dq, *J* = 19.1, 7.5 Hz, 1H), 3.68 – 3.47 (m, 1H), 3.21 – 2.93 (m, 2H), 2.59 (td, *J* = 8.6, 6.7 Hz, 1H), 2.45 (ddt, *J* = 21.6, 10.7, 8.0 Hz, 1H), 2.30 (ddt, *J* = 12.9, 9.0, 4.3 Hz, 1H), 2.24 – 2.15 (m, 1H), 1.77 – 1.68 (m, 1H), 1.52 (dddd, *J* = 24.3, 10.6, 9.5, 7.7 Hz, 1H), 1.23 (t, *J* = 7.0 Hz, 2H), 1.21 – 1.13 (m, 1H), 0.87 (t, *J* = 7.0 Hz, 2H), 0.78 – 0.69 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.95, 141.59, 141.39, 141.31, 130.71, 130.66, 129.08, 128.98, 128.40, 128.37, 128.33, 128.22, 128.17, 125.97, 125.80, 124.22, 124.18, 123.63, 70.34, 69.19, 68.74, 66.68, 64.50, 64.35, 36.80, 36.68, 33.88, 33.33, 32.99, 32.85, 27.57, 22.62, 15.32, 15.00. HRMS (EI) calculated for $[C_{20}H_{24}O_2S]^{[M+H]+}$ requires *m/z* 329.1570, found *m/z* 329.1566.



(2-(3-ethoxy-2-(phenylsulfonyl)cyclobutyl)ethyl)benzene (2.29) An oven dried 50 mL round bottom flask was charged with 156 mg (0.5 mmol, 1eq) 2-ethoxy-4-phenethylcyclobutyl)(phenyl) in 2 mL of anhydrous CH_2Cl_2. The reaction solution was then cooled to -78 C under N_2 atmosphere. The reaction solution was then treated with 336 mg (1.5 mmol, 3 eq) mCPBA in 3 mL of anhydrous CH_2Cl_2 dropwise over five minutes. One hour post full addition of oxidant the reaction was diluted with 15 mL CH_2Cl_2 and quenched with 15 mL of saturated $NaHCO_3$. The aqueous layer was then extracted with a further 20 mL of CH_2Cl_2. The pooled organic layers were dried with $MgSO_4$, and reconstituted. Purification of crude by flash chromatography (2:1 Hex:EtOAc) and concentration by rotary evaporation afforded 127.4 mg of analytically pure oxidized cycloadduct as a clear oil (0.37 mmol, 74% yield, dr: 15:1).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 2H), 7.66 – 7.61 (m, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.20 – 7.14 (m, 1H), 7.04 – 6.98 (m, 2H), 4.20 (td, *J* = 7.8, 6.4 Hz, 1H), 3.48 (dq, *J* = 9.3, 7.0 Hz, 1H), 3.43 – 3.32 (m, 2H), 2.55 – 2.44 (m, 2H), 2.39 (dt, *J* = 13.8, 8.0 Hz, 1H), 2.23 (pd, *J* = 9.0, 5.2 Hz, 1H), 1.62 – 1.40 (m, 3H), 1.09 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.11, 138.85, 133.69, 129.27, 129.24, 129.22, 128.53, 128.43, 128.38, 128.34, 128.31, 128.29, 125.99, 70.48, 70.18, 64.81, 36.73, 33.20, 32.77, 28.93, 15.10. HRMS (EI) calculated for $[C_{20}H_{24}O_3S]^{[M+NH4]+}$ requires *m/z* 362.1784, found *m/z* 362.1776.

2.5.7 Relative Stereochemical Assignments: Representative NOE Data

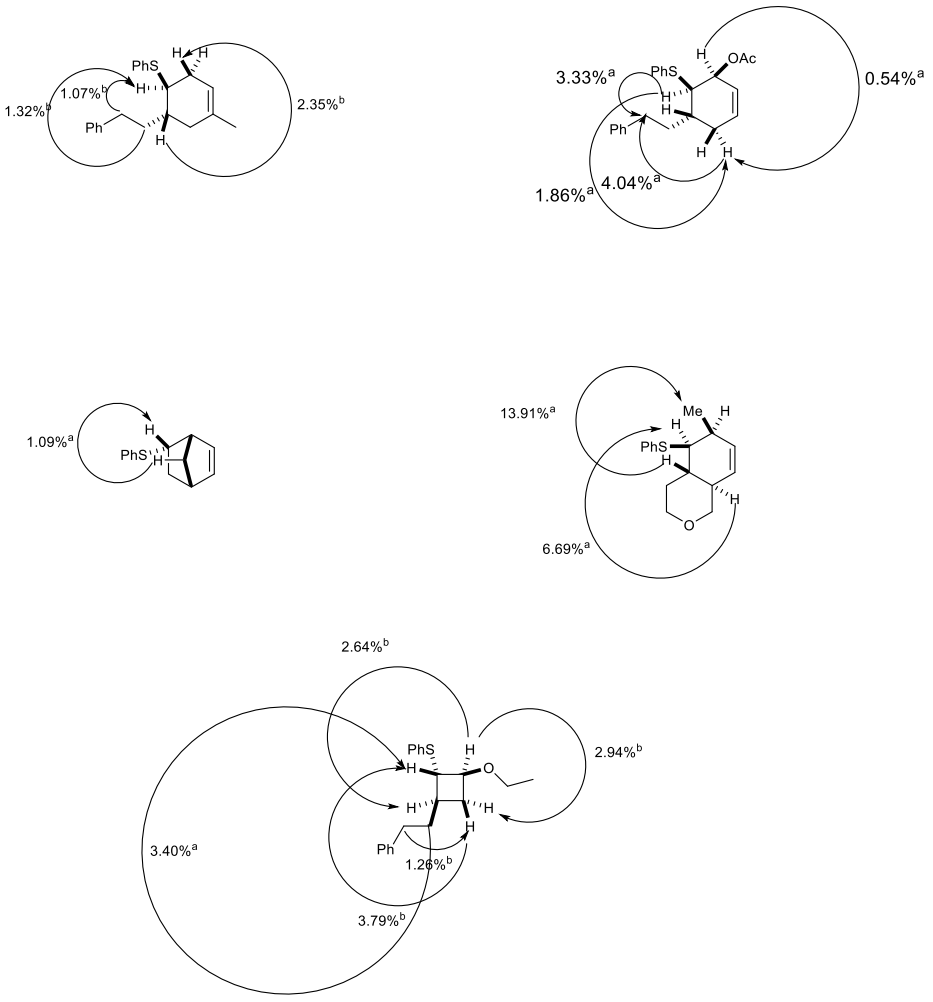


Figure 1: Analysis of relative stereochemistry via selective NOESY NMR experiments.
All NOE data collected on Bruker 500 MHz NMR. [a] NOE data collected in $CDCl_3$. [b] NOE data collected in d_6 *-benzene*

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Chapter 3. Olefin-Supported Cationic Copper Catalysts for Photochemical Synthesis of Structurally Complex Cyclobutanes

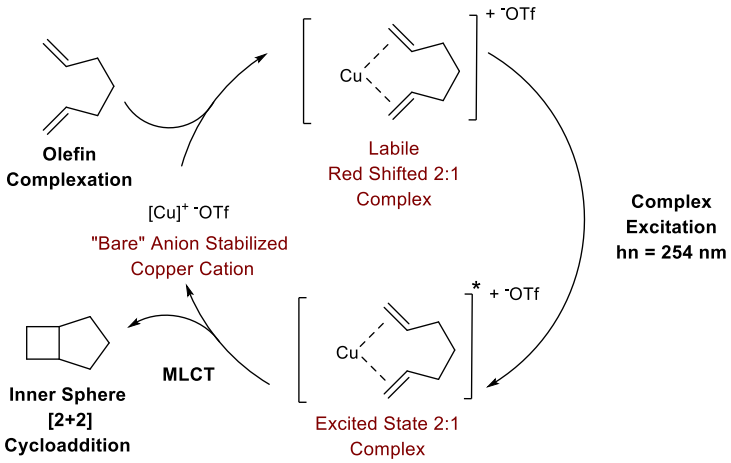
Portions or this work have been previously published Gravatt, C. S.; Melecio-Zambrano, L.; Yoon, T. P. "Olefin-Supported Cationic Copper Catalysts for Photochemical Synthesis of Structurally Complex Cyclobutanes." *Angew. Chem. Int. Ed.* **2020**. DOI: 10.1002/anie.202013067

3.1 Introduction

Cyclobutane rings feature in more than 2600 known natural products,[1] and the challenge of synthesizing these compounds has motivated the development of photochemical [2+2] cycloaddition reactions for many decades, as photochemical activation is considered the most direct access to these thermally forbidden processes. Numerous mechanistically distinct strategies for [2+2] photocycloadditions are known.[2] The most well-developed of these involve: (*1*) direct photoexcitation of olefinic compounds featuring optical transitions in the visible or near-UV range;[3] (*2*) triplet photosensitization of substrates with triplet state energies sufficiently low enough to enable Dexter energy transfer;[4] and (*3*) photoredox reactions of alkene radical ions generated via photoinduced electron transfer.[5] Notably, each of these activation modes is only amenable to alkene substrates with extended π conjugation, that have lower energy barriers to excitation and sensitization. Unconjugated aliphatic alkenes generally have short-wavelength optical transitions (<200 nm)[2a] that are not accessible with commercial UV photoreactors. They also feature high-energy triplet excited states (76–84 kcal/mol)[6] and electrochemical potentials[7] that lie outside of the range of most common photoredox catalysts.[8]

The sole method suitable for the [2+2] photocycloaddition of aliphatic alkenes is the Cu(OTf)-catalyzed process originally reported by Kochi and Salomon in 1973.[9] The key intermediate in this reaction, a 2:1 alkene-copper complex, absorbs at wavelengths that are accessible using standard benchtop UV reactors (ca. 270 nm). This absorbance corresponds to a metal-to-ligand charge transfer (MLCT) transition,[10] which initiates an inner-sphere bond-forming cascade that can convert simple aliphatic alkenes into cyclobutanes that are not accessible using any of the well-established direct, sensitized, or electron-transfer photochemistry (Figure 3.1).

Figure 3.1 General Mechanistic Proposal for Salomon and Kochi [2+2] Cycloaddition



Although the Salomon–Kochi photocycloaddition has featured in several total syntheses (Figure 3.2),[11] the conditions for this reaction have not been significantly reinvestigated since its early reports, and the utility of this method has been hampered by its narrow scope. A successful cycloaddition requires the formation of a Cu(I)-bis(alkene) complex that is relatively unstable, and a variety of common substrate structural features can destabilize the formation of this complex, thereby preventing the reaction from occurring. Most critically, sterically bulky alkenes disfavour the formation of the requisite 2:1 complex and thus are poor substrates for this strategy.[12] Consequently, many of the most interesting complex cyclobutane natural products bearing highly substituted cyclobutane cores (**3.10-3.12**) cannot be efficiently synthesized using the Salomon–Kochi protocol or indeed by any known photocycloaddition methodology (Figure 3.3). This represents a significant gap in chemists' ability to synthesize the diverse family of cyclobutane-containing natural products.

Figure 3.2 The Salomon and Kochi Reaction and Total Synthesis

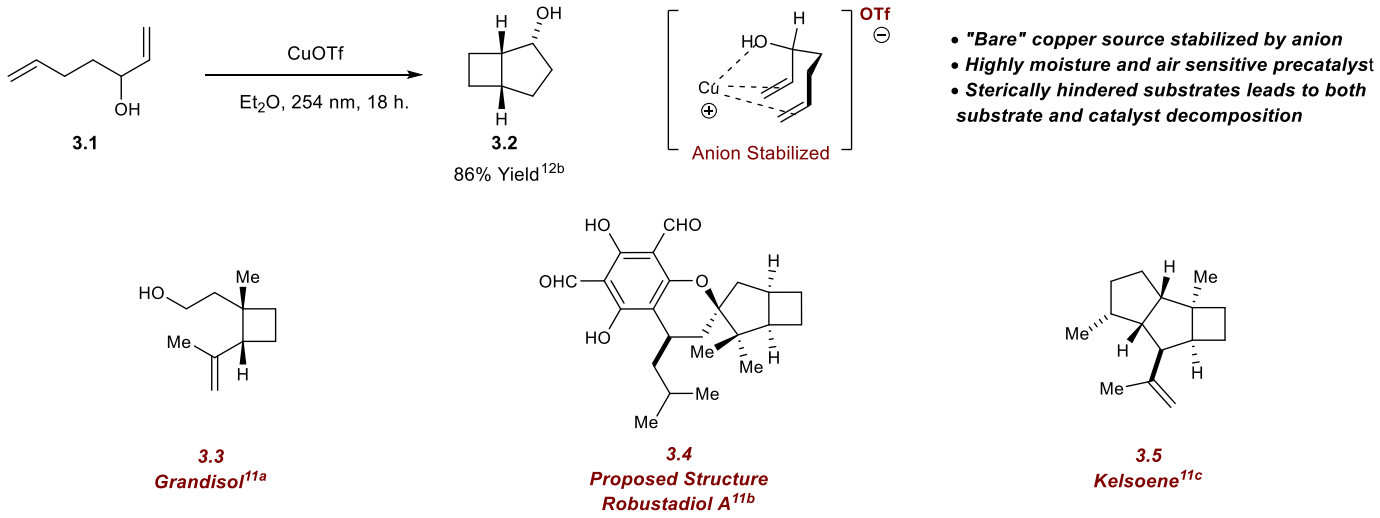
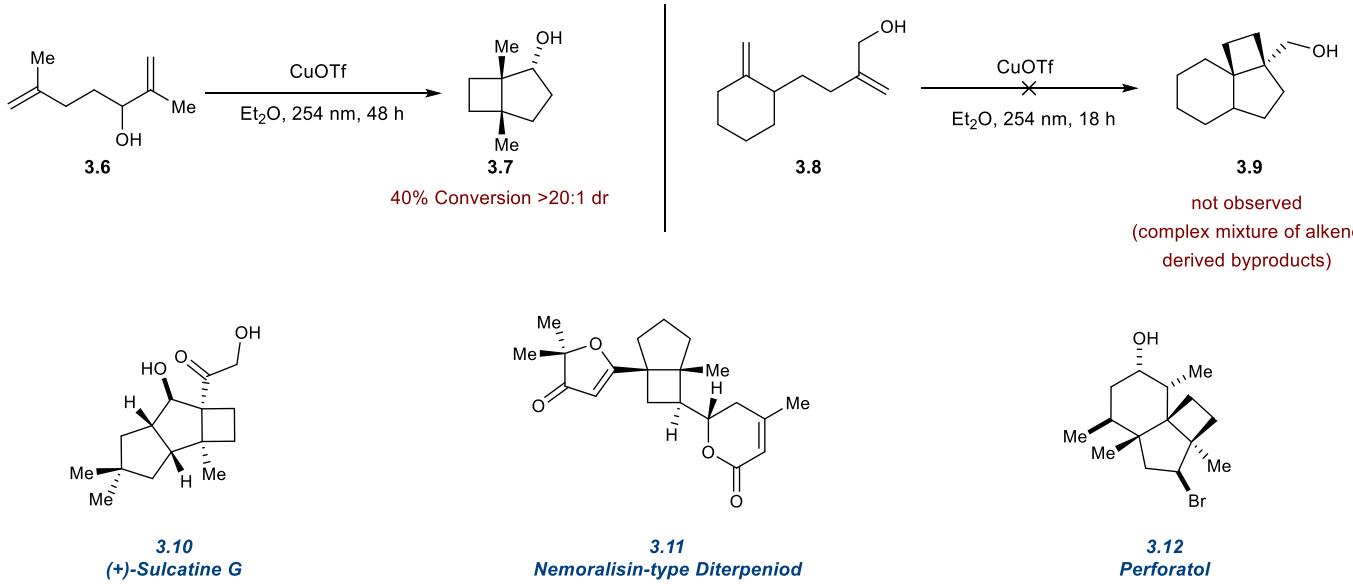


Figure 3.3 Steric Inhibition Problem and Motivation for Catalyst Improvement



A notable consequence of the relative instability of the cationic copper bis(alkene) intermediate is a strong dependence on the coordinating ability of the counteranion. Salomon reported that photocycloadditions catalyzed by CuOTf occur at least an order of magnitude faster than those conducted using CuCl.[9] This observation was attributed to the ability of more nucleophilic counteranions to displace the labile olefin ligands. Considering this trend, we hypothesized that complexes bearing even more weakly coordinating counteranions (WCAs)

than triflate would result in a more electrophilic Cu(I) metal center that could productively engage bulky alkenes in this reaction.

It has been recently demonstrated that triflate anions are intimately coordinated to the Cu(I) center in 1,5,9-cyclododecatriene complexes in the solid state.[13] We imagined that improvement of this catalyst system could be achieved by developing Cu(I) catalysts bearing even more weakly coordinating anions (WCA's). However, generating such a "bare" copper center presents significant challenges. In exploratory studies, we attempted to synthesize CuX•benzene complexes featuring a range of WCAs and observed rapid oxidative decomposition upon attempts to isolate them. One obvious solution is to employ the wide range of ligands that have been developed for Cu(I) catalysis to generate a stabilized cationic Cu(I) species; however nitrogen based ligands have been shown to substantially inhibit this reaction.[14] Furthermore, phosphine and nitrogen based ligands bound to Cu(I) have well documented charge transfer states upon UV irradiation that would potentially undermine the desired MLCT to the olefin substrate.[15,16] This presented a unique challenge of how to generate a catalytically stable, coordinatively unsaturated copper center *in situ* that rapidly binds weakly coordinating olefins without disruption from either the anion or ancillary precatalyst ligands.

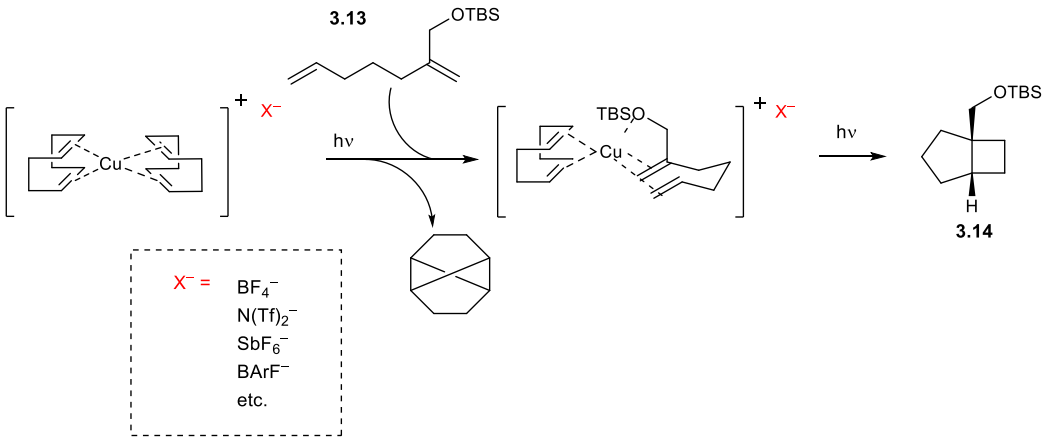
3.2 Catalyst Design and Reaction Optimization

The CuOTf•benzene catalyst has many advantages in this transformation. First, it bears a relatively weakly coordinating anion, preventing unwanted anion disruption during formation of the alkene copper complex.[9] Furthermore, the ancillary supporting benzene ligands are highly labile and are easily replaced by an alkene substrate.[9] These two properties render this complex as highly active catalyst for alkene [2+2] cycloaddition reactions. However, these same

properties result in a very unstable catalyst prone to decomposition both during storage and during the reaction. To develop a catalyst that more strongly coordinates olefins due to a less stabilizing anion, a new strategy must be devised for opening coordination sites on the copper center *in situ* from a more stable precatalyst that could be easily manipulated on the benchtop under ambient conditions.

Whitesides demonstrated that irradiation of Cu(I) 1,5-cyclooctadiene (COD) complexes with 254 nm light results in a crossed [2+2] cycloaddition of COD, liberating it from the coordination sphere of copper.[17] We wondered if a copper(I) COD complex bearing a weakly coordinating anion would catalyze the Salomon–Kochi [2+2] reaction after the initial cyclization the ancillary COD ligand (Scheme 3.1). We further wondered if COD might stabilize the resulting highly electron-deficient Cu(I) center without engendering competitive low-energy charge-transfer states.

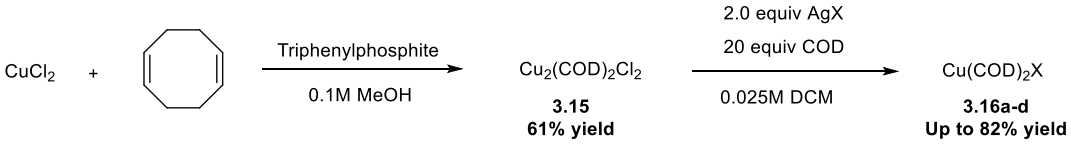
Scheme 3.1 Copper (I) COD Cyclization Strategy



Prior to our work, Cu(I) COD complexes bearing anions less coordinating then triflate were generally unknown. Thus, a synthetic procedure had to be devised to access the desired catalyst bearing different anions from a common inexpensive intermediate. It was found that $[Cu(COD)Cl]_2$, in the presence of excess COD, was prone to chloride abstraction salt metathesis with Ag(I) salts of various weakly coordinating anions. This dimer is easily obtained in high purity

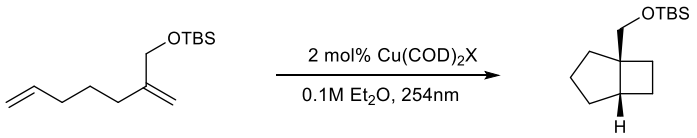
by reduction of Cu(II) chloride with triphenylphosphite in the presence of COD.[18] The tetracoordinate Cu(I) COD complexes are isolated as bench-stable white solids in typically high yield (Scheme 3.4). Characterization of Cu(I) bis(COD) hexafluoroantimonate complex **3.16c** by NMR and MS confirmed the proposed structure and analogous complexes bearing different anions were assumed to have the same general structure.

Scheme 3.2 Synthesis of Copper (I) COD Complexes



Next, these complexes were tested in a model reaction previously reported by Salomon. All complexes were found to be competent catalysts; however, different reaction rates were observed depending on the counterion (Table 3.1). To our delight, less coordinating anions, as denoted by the calculated gas phase acidity constants, result in increased reaction rates, with SbF_6^- being superior anion in this reaction compared to triflate (entries 2-4). The only result that devated from this trend was $B(C_6F_5)_4^-$ (entry 5). This anion can directly absorb light at the reaction wavelength. This may result in competitive light absorption, which could lead to catalyst decomposition. Shortening the reaction time to 1 h showed that $Cu(COD)_2SbF_6$ had only slightly faster reaction rates in comparison with CuOTf (entries 6 and 7).

Table 3.1 Testing Copper (I) COD Complexes



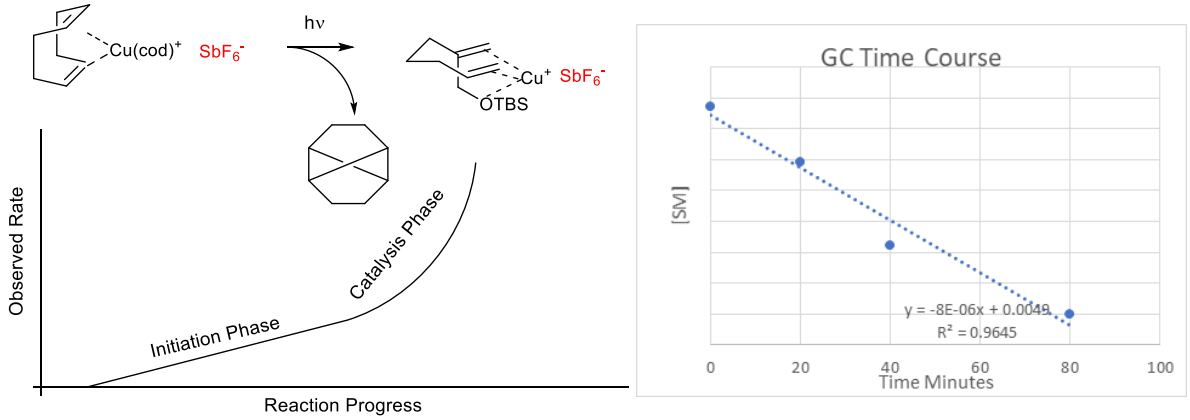
3.13 **3.14**

Entry	Copper Cat.	Time (h)	Conversion.	% yield[a,b]
1	$[CuOTf]_2 \cdot C_6H_6$	3	100%	74%
2	**3.16a** $Cu(COD)_2OTf$ (299.5)[c]	3	50%	46%
3	**3.16b** $Cu(COD)_2N(Tf)_2$ (286.5)[c]	3	80%	53%
4	**3.16c** $Cu(COD)_2SbF_6$ (255.5)[c]	3	100%	73%
5	**3.16d** $Cu(COD)_2B(C_6F_5)_4$ (<250.0)[c]	3	50%	35%
6	$Cu(COD)_2SbF_6$	1	50%	47%
7	$[CuOTf]_2 \cdot C_6H_6$	1	40%	35%

[a] Reactions conducted in quartz tubes equipped with a cold finger. Irradiation took place in a Rayonet RP-100 photoreactor with 254 nm bulbs. [b] NMR yields taken with TMS-Ph as internal standard [c] Gas phase acidity constants(ΔG_{acid}) of anions corresponding acid.

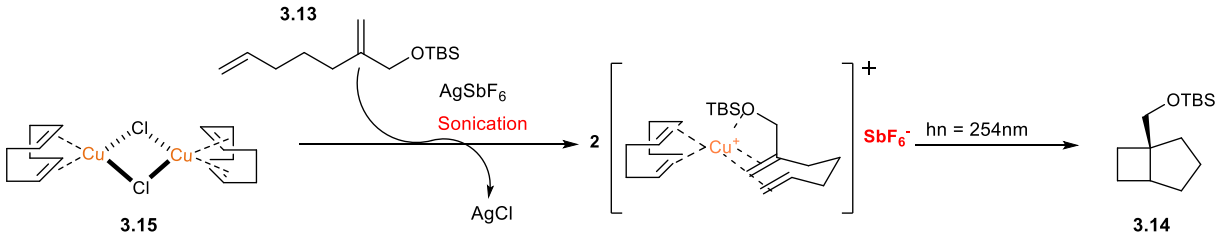
A direct comparison between the reactivity of $[Cu(OTf)]_2(C_6H_6)$ and $[Cu(COD)_2]OTf$ revealed a second important factor to consider for catalyst design: the ancillary ligand. We expected that the COD ligand would undergo cyclization to open coordination sites for alkene binding. However, the time scale for cyclization of COD demonstrated by Whitesides is much longer than the reaction times required for cyclization of 1,6-heptadienes, due to COD undergoing unproductive isomerization reactions that do not result in cyclization.[17] A time course study of this reaction was found to be linear and lacked an induction phase feature that would otherwise be expected if COD was cyclizing to open coordination sites (Figure 3.4). It was clear from this study that the hypothesized anion effect is likely operative, but the rate of the reaction is substantially retarded by the ancillary ligand. This could be due to several possible effects: (1) the benzene complex may be poorly soluble, and only a small portion of the catalyst is active, (2) the COD ligand may not be undergoing cyclization on the reaction time scale, and catalysis is inhibited by the unfavorable ligand exchange between COD and substrate. Because SbF_6 was found to be a superior anion to triflate, further optimization of the catalyst focused around Cu(I) SbF_6 complexes.

Figure 3.4 Reaction Time Course



Because displacement of a COD ligand by a less conformationally rigid bis(alkene) substrate was found to be thermodynamically unfavorable, $Cu(COD)_2^+$ complexes were deemed unsuitable precatalysts. Alternatively, we hypothesized that coordinatively unsaturated Cu(I) complexes could be generated *in situ* by anion metathesis of dimeric $[Cu(COD)Cl]_2$ with Ag(I) salts of WCAs (Scheme 3.3). This strategy would enable use of bench-stable catalyst precursors instead of the air- and moisture-sensitive $[Cu(OTf)]_2$•benzene complex that has been the catalyst of choice for this reaction for decades.

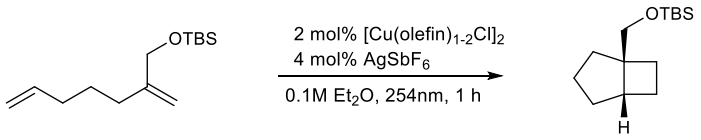
Scheme 3.3 *In Situ* Chloride Abstraction Strategy



Indeed, initial experiments using the $[Cu(COD)Cl]_2$ dimer togetehr with $AgSbF_6$ gave very promising results, affording 54% conversion in 1 h (Table 3.2, entry 1). While dimeric $[Cu(COD)Cl]_2$ was an obvious initial choice for precatalyst as it is highly bench stable and is both commercially and easily prepared from $CuCl_2$, we wondered if similar dimers bearing different

olefin supporting ligands would potentially be more reactive catalysts. It was found that a wide range of copper chloride olefin dimers could be isolated using Cooke's previously reported procedure.[18] While the structures of these complexes were not characterized, we assumed that they would likely have copper coordination spheres analogous to the well-characterized $[Cu(COD)Cl]_2$ dimer. Testing these complexes revealed that all complexes were viable catalysts giving similar conversions (Entries 2–8). Many of them, however, proved to be air sensitive and prone to decomposition. For these reasons, we elected to continue using the more robust $[Cu(COD)Cl]_2$ dimer as the optimal catalyst for further study.

Table 3.2 Survey of Possible $[Cu(Olefin)Cl]_2$ Dimers as Precatalysts



3.13 **3.14**

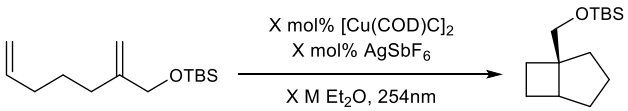
Entry	Copper Dimer	Conversion.
1	$[Cu(1,5\text{-Cyclooctadiene})Cl]_2$	54%
2	$[Cu(1,5\text{-Dimethyl-1,5-cyclooctadiene})Cl]_2$	46%
3	$[Cu(Cyclooctene)_2Cl]_2$	58%
4	$[Cu(Cyclohexene)_2Cl]_2$	43%
5	$[Cu(1,1,3,3\text{-Tetramethyl-1,3-divinyldisiloxane})Cl]_2$	29%
6	$[Cu(Benzene)Cl]_2$	41%
7	$[Cu(Diallyl\ Ether)Cl]_2$	32%
8	$[Cu(Pentamethylcyclopentadiene)Cl]_2$	37%

[a] Reactions conducted in quartz tubes equipped with a cold finger. Irradiation took place in a Rayonet RP-100 photoreactor with 254 nm bulbs.

Initial reaction concentrations and catalyst loadings we optimized first. It was found that both copper and silver loadings have little effect on reactivity as long as sufficient equivalencies of silver are present to ensure full abstraction of chloride (entries 1–3). A slightly excess of silver relative to Cu was beneficial, as the reactions are found to be more reproducible. The rate of the reaction proved to be highly concentration-dependent, which is typical of photoreactions requiring high photonic input: increasing the concentration resulted in substantially slower rates

of cyclization (entry 4). The rate improved linearly with decreasing concentration, and 0.025 M was selected as optimal, giving full conversion to the desired product in 80% yield in 30 min (entries 5–7). With simple reaction conditions developed, we next tested this methodology on a more sterically hindered scaffold to test the original motivations for the development of this catalyst system (i.e., to generate a catalyst with greater steric tolerance).

Table 3.3 Optimization of Loadings and Concentration *In-Situ* Chloride Abstraction



3.13 3.14

Entry	$[Cu(COD)Cl]_2$	$AgSbF_6$	Conc.	Time (h)	% yield[a,b]
1	1 $mol\%_6$	4 mol%	0.1 M	1	47%
2	2.5 mol%	10 mol%	0.1 M	1	29%
3	1 mol%	10 mol%	0.1 M	1	49%
4	1 mol%	10 mol%	0.25 M	1	18%
5	1 mol%	10 mol%	0.05 M	1	57%
6	1 mol%	10 mol%	0.025 M	1	77%
7	1 mol%	10 mol%	0.025 M	0.5	80%

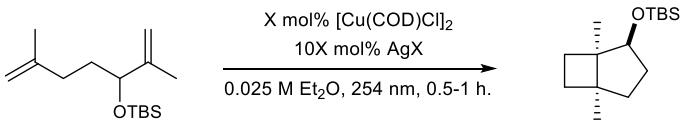
[a] Reactions conducted in quartz tubes equipped with a cold finger. Irradiation took place in a Rayonet RP-100 photoreactor with 254 nm bulbs. [b] NMR yields taken with TMS-Ph as internal standard

We thus examined the photocycloaddition of diene **3.17**, which Salomon had reported is a poor substrate under his conditions.[12a, 12b] Consistent with this precedent, standard Salomon-Kochi conditions (1 mol% $[Cu(OTf)]_2$•benzene) afforded only 28% of cyclobutane product (Table 1, entry 1). This reaction does not proceed to completion upon extended irradiation times, and the observation of Cu^0 depositing in the reaction vessel indicated significant catalyst decomposition (entry 2). As a control, we first treated $[Cu(COD)Cl]_2$ with AgOTf *in situ*, and the resulting complex performed similarly to the standard $[Cu(OTf)]_2$•benzene catalyst (entry 3). However, extended irradiation results in complete conversion, demonstrating that diene ligands are indeed able to stabilize the highly electron-deficient cationic Cu(I) center without attenuating its photoactivity (entry 4). We next examined the use of a series of WCAs in this reaction and

were delighted to observe increased reactivity, with a correlation between the calculated gas-phase acidities[19] of the WCA conjugate acids and the yield of the cycloaddition (entries 5–8), with exception of carborane $CB_{11}H_{12}^-$ (entry 7). As before with the BArF anion, this can be attributed to competitive absorption by the anion, which inhibits the reaction (See Experimental 3.5.5). The optimal SbF_6^- complex afforded 94% yield of the [2+2] cycloadduct in just 1 h. Indeed, the reaction proceeds essentially to completion in only 30 min (entry 8), highlighting the substantial rate improvement using this optimal catalyst over the canonical triflate salt. Interestingly nearly all catalysts tested gave near identical diastereoselectivity for the endo product except for the carborane and triflimide anions both displaying an increase in diastereoselectivity for the *endo* product albeit at slower reactions rates in comparison to the optimal hexafluoroantimonate catalyst (entries 6 and 7).

To test the importance of the Cu(I):COD stoichiometry, we next independently prepared $[Cu(COD)_2]SbF_6$ and found it to be a less effective catalyst (entry 10), consistent with the expected slow rate of exchange of the COD ligand with substrate. Presumably the two active catalysts are identical barring the necessity for ligand exchange based on the diastereoselectivity observed. To further demonstrate the deleterious effects of excess strongly chelating olefin ligand, addition of 50 mol% of COD resulted in complete loss of reactivity (entry 11). However, 1:1 copper:COD stoichiometry is also important as the use of CuCl as a precatalyst in the absence of COD ligand proved ineffective (entry 12). In this experiment, we observed the formation of Cu^0 precipitate, consistent with the propensity of the unstabilized cationic $CuSbF_6$ complex to decompose. Finally, control experiments excluding the Cu catalyst, silver salt, or light source resulted in no observable consumption of the substrate (entries 13–15), demonstrating the necessity of each of these reaction components.

Table 3.4 *In- Situ* Chloride Abstraction Strategy Anion Survey and Control Reactions



3.17 3.18

Entry	Copper Cat.	Ag Salt (Gas Phase Acidity)	Time (h)	% yield[a,b]
1	1 mol%[CuOTf]$_2$ • C_6H_6	-	1	28% 4:1 d.r.
2	1 mol%[CuOTf]$_2$ • C_6H_6	-	18	42% 4:1 d.r.
3	1 mol% [Cu(COD)Cl]$_2$	AgOTf (299.5 kcal/mol)[c]	1	33% 4:1 d.r.
4	1 mol% [Cu(COD)Cl]$_2$	AgOTf	18	91% 4:1 d.r.
5	1 mol% [Cu(COD)Cl]$_2$	$AgBF_4$ (288 kcal/mol)[c]	1	52% 4:1 d.r.
6	1 mol% [Cu(COD)Cl]$_2$	$AgNTf_2$ (286.5 kcal/mol)[c]	1	57% 8:1 d.r.
7	1 mol% [Cu(COD)Cl]$_2$	$AgCB_{11}H_{12}$ (260.4 kcal/mol)[c]	1	14% 6:1 d.r.
8	1 mol% [Cu(COD)Cl]$_2$	$AgSbF_6$ (255.5 kcal/mol)[c]	1	94% 4:1 d.r.
9	1 mol% [Cu(COD)Cl]$_2$	$AgSbF_6$	0.5	81% 4:1 d.r.
10	2 mol% $Cu(COD)_2SbF_6$	-	0.5	18% 4:1 d.r.
11[d]	1 mol% [Cu(COD)Cl]$_2$	$AgSbF_6$	0.5	0%
12	2 mol% CuCl	$AgSbF_6$	0.5	9%
13	1 mol% [Cu(COD)Cl]$_2$	-	0.5	0%
14	-	$AgSbF_6$	0.5	0%
15[e]	1 mol% [Cu(COD)Cl]$_2$	$AgSbF_6$	0.5	0%

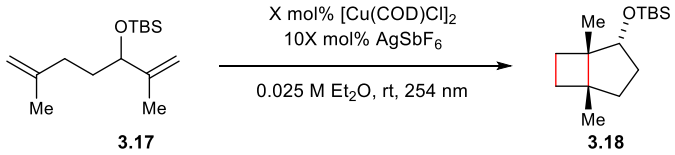
[a] Reactions conducted in quartz tubes equipped with a cold finger. Irradiation took place in a Rayonet RP-100 photoreactor with 254 nm bulbs. [b] NMR yields taken with TMS-Ph as internal standard. [c] Gas phase acidity constants (ΔG_{acid}) of corresponding acid. [d] Addition of 50 mol% 1,6-cyclooctadiene (COD) [e] No UV irradiation

3.3 Reaction Scope and Stereoselectivity Studies

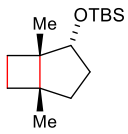
Studies examining the scope of the photocycloaddition using this new catalyst system are summarized in Table 3.5. We first examined the reactivity of variously substituted 1,6-heptadienes (**3.18**–**3.23**). As expected, the optimized [Cu(COD)Cl]$_2$/$AgSbF_6$ catalyst system outperforms the standard [Cu(OTf)]$_2$•benzene catalyst in all cases examined. This advantage became more evident with greater steric bulk on the alkene, consistent with our catalyst design strategy. Cyclization of naturally occurring terpenes linalool and nerolidol demonstrate tolerance both for a free hydroxyl group and pendant substituted olefins (**3.24**–**3.25**). Interestingly, nerolidol cycloadduct **3.25** was isolated as a 1:1 mixture of diastereomers, despite the well-defined geometry of the starting alkene. Even with the increased Lewis acidity of the reactive

Cu(I) center, a range of Lewis basic functional groups including amides, ethers, and alcohols are readily tolerated (**3.26**–**3.30**). The rate of reaction slowed using a chelating 1,3-diol-containing substrate (**3.31**), which required longer reaction time and higher catalyst loading. Protection of the diol, however, fully restores reactivity (**3.32**). Vinyl boronate esters also cyclize in good yield (**3.33**) without any observed unproductive deborylation, providing a synthetic handle for further derivatization. A range of common alcohol protecting groups were also investigated (**3.34**–**3.38**). A base-sensitive pivalate protecting group (**3.34**) is well tolerated. An acid-sensitive TES group can be utilized in place of TBS (**3.35**), albeit with somewhat diminished *endo* diastereoselectivity. Highly chelating MOM protecting groups are well tolerated (**3.36**). Furthermore, allyl carbonate with a third alkene binding site gives good yields without decomposition of the protecting group (**3.37**). Interestingly, benzyl protecting groups are uniquely tolerated by the new catalyst system; we observed complete decomposition of this substrate when the reaction was conducted using CuOTf (**3.38**). For ease of synthesis, many of the substrates examined bear oxygen substituents in the allylic position. Regardless of the alkene substitution or the identity of the allylic coordinating functional group, the cycloaddition preferentially results in the formation of the thermodynamically less favourable *anti*-cycloadduct. This result is consistent with Salomon's observations using allylic alcohol substrates, suggesting a chelating interaction with the Cu(I) center in the reactive complex.[12b] Finally, these reaction conditions were found to be readily scalable: a batch reaction conducted on gram-scale afforded **3.14** in 89% yield after 5 h of irradiation.

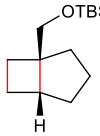
Table 3.5 Reaction Scope 1,6- Heptadienes



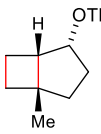
3.17 **3.18**



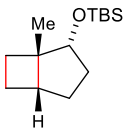
3.18
1 mol% 1 h,
yield = 94% 4:1 d.r.[a]
CuOTf yield = 28% 4:1 d.r.[a]



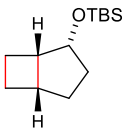
3.14
1 mol% 30 min,
yield = 95%[a], 89%[b,c]
CuOTf yield = 39%[a]



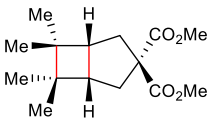
3.19
1 mol% 30 min,
yield = 94% >20:1 d.r.[a]
CuOTf yield = 43% >20:1 d.r.[a]



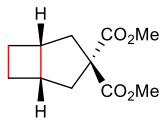
3.20
1 mol% 30 min,
yield = 91% >20:1 d.r.[a]
CuOTf yield = 17% >20:1 d.r.[a]



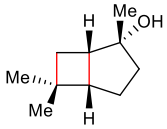
3.21
1 mol% 1 h,
yield = 89% >20:1 dr[a]
CuOTf yield = 85% >20:1[a]



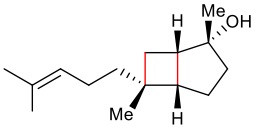
3.22
1 mol% 6 h,
yield = 42%[a]
CuOTf yield = 4%[a]



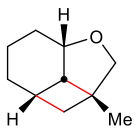
3.23
1 mol% 1 h,
yield = 90%[a]
CuOTf yield = 51%[a]



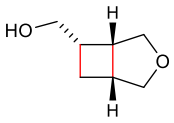
3.24
1 mol% 3 h,
yield = 68%[b]



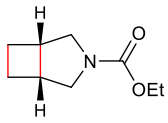
3.25
1 mol% 3 h,
yield = 87% 1:1 d.r.[b]
CuOTf yield = 28 1.5:1 d.r.%[a]



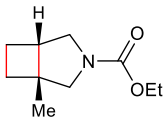
3.26
1 mol% 8 h,
yield = 48%[a]
CuOTf yield = 16%[a]



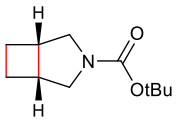
3.27
1 mol% 1 h,
yield = 84% 1.5:1 d.r.[b]
CuOTf yield = 62% 1:1 d.r.[a]



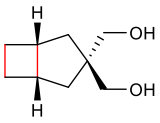
3.28
2.5 mol% 20 h,
yield = 74%[a]
CuOTf yield = 23%[a]



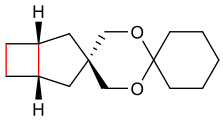
3.29
2.5 mol% 20 h,
yield = 97%[a]



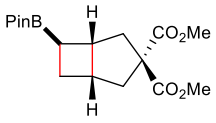
3.30
2.5 mol% 20 h,
yield = 64%[a]



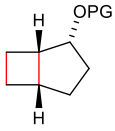
3.31
2.5 mol% 7 h,
yield = 86%[a]



3.32
1 mol% 1 h,
yield = 92% [a]



3.33
1 mol% 3 h,
yield = 76% 2.5:1 d.r.[b]



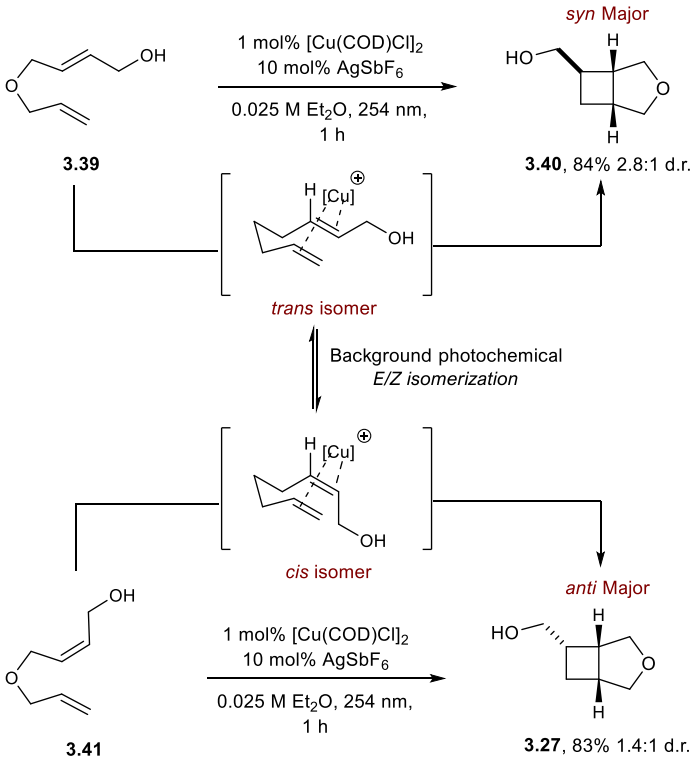
19-23
1 mol%

PG= Piv **3.34** 5 h, 97% 5:1 d.r.[b]
TES **3.35** 2 h, 80% 2:1 d.r.[a,d]
MOM **3.36** 3 h, 77% 6:1 d.r.[a]
Alloc **3.37** 5 h, 85% 5:1 d.r.[b]
Bn **3.38** 5 h, 64% >20:1 d.r.[b] (CuOTf <5%)[a]

[a] NMR Yields based on TMS-Ph internal standard; $[Cu(OTf)]_2$•benzene yields at same catalyst loading, concentration and timepoint; [b] Isolated yields; [c] gram-scale reaction;. [d] 2.5 mol% $AgSbF_6$, 0.0125 M in Et_2O.

Given the observation that geometrically well-defined alkene substrates result in the formation of diastereomeric products, we became interested in the origin of the loss of stereochemical integrity. To assess this, we prepared the *trans* and *cis* isomers of *O*-allyl but-2-ene-1,4-diol (**3.39** and **3.41**) and irradiated them under the optimized reaction conditions. Both afford a mixture of diastereomers in good yields. However, the identity of the major diastereomer differs (Scheme 3.4). To gain deeper insight, we conducted a time-course experiment using *cis* isomer **3.41**. We observed the formation of *trans* alkene **3.39** over the course of this experiment, and the rate of its formation is competitive with the production of the cycloadducts. Furthermore, the alkene isomerization occurs only upon irradiation. We conclude, therefore, that the cycloaddition itself is stereospecific, and that the loss of stereochemical fidelity is due to an alternate Cu-catalyzed photoreaction that scrambles the geometry of the starting alkene. Time course data and NMR analysis can be found in experimental section 3.5.4.

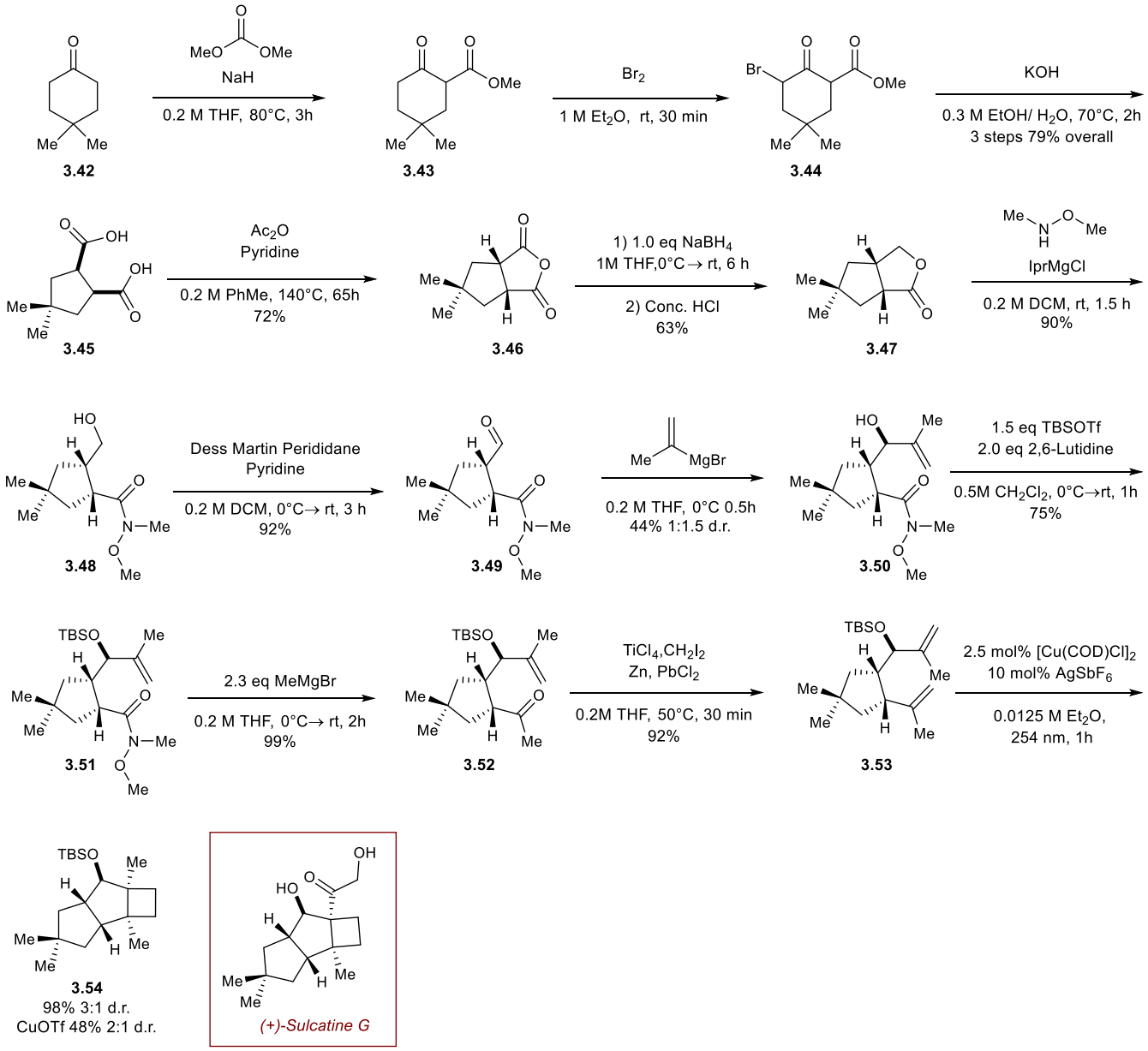
Scheme 3.4 Origins of observed diastereoselectivity



3.4 Application of Methodology to Complex Natural Product Cores

The enhanced reactivity of this new catalyst system, particularly towards substituted alkene substrates, significantly expands the applicability of photocycloaddition methodology to the synthesis of a broader class of complex cyclobutane natural products. To highlight this potential, we used this new method to prepare the core of the natural product sulcatine G, a tricyclic sesquiterpene isolated from cultures of the Basidiomycetes fungus *Laurilia sulcate* (Scheme 3.6).[20] Synthesis of this began with a known 4 step sequence to prepare anhydride **3.46** from 4,4-dimethylcyclohexanone.[21] While a known process conditions for the Favorski rearrangement of **3.44** and the dehydration of **3.45** were optimized substantially to give this precursor in high yield. Reduction of anhydride **3.46** gave lactone **3.47** which was then ring-opened to give *cis*-Weinreb amide **3.48**. Oxidation with pyridine-buffered Dess–Martin periodate yielded aldehyde **3.49**. Grignard addition with isopropenyl magnesium bromide resulted in a 1:1.5 mixture of diastereomers in modest yield. The minor diastereomer was determined to be the desired stereochemistry via NOE analysis of the cyclized lactone of the major diastereomer resulting from prolonged storage. TBS protection of the minor diastereomer with TBSOTf and 2,6-lutidine gave protected allylic alcohol **3.51** no longer prone to spontaneous lactonization. Methylation of the amide with methyl magnesium bromide gave ketone **3.52** in high yield. Lombardo olefination of ketone **3.52** gave diene cycloaddition precursor **3.53** without any epimerization as was observed under Wittig type conditions. Cyclization of **3.53** under the newly developed conditions gave the desired sulcatine core **3.54** in 98% yield. As expected, the improved method provides significantly superior results compared to [Cu(OTf)]•benzene. Importantly, this reaction favors formation of the highly sterically disfavored *anti* configuration of the bridgehead substituents due to allylic hydroxyl coordination, a key structural feature of this molecule.

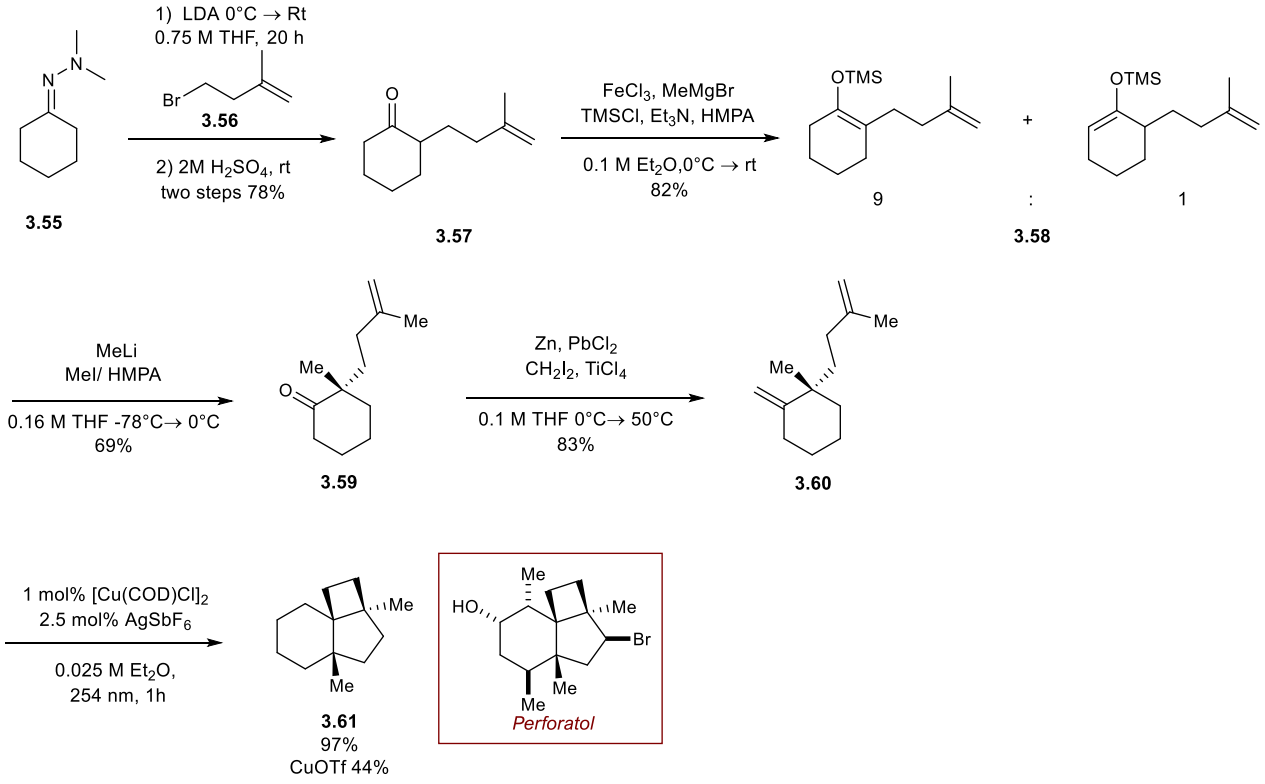
Scheme 3.5 Synthesis of Sulcatine G Core



The densely functionalized core of another natural product perforatol, a compound isolated from the toxic sea hare *Aplysia punctate* could also be readily accessed using this new methodology. Synthesis of the perforatol (Scheme 3.7)[22] core began by alkylation of cyclohexyl N,N dimethylhydrazone **3.55** with alkylbromide **3.56**. Subsequent acidic cleavage of the hydrazone furnished 2-substituted cyclohexanone **3.57**. A enolate trapping procedure using Fe(0) as an *in situ* generated base gave the highest selectivity for the more substituted silyl enol ether **3.58**.[23] This proved crucially important as purification of the regioisomeric products in the

proceeding step was very challenging. A second alkylation using MeI was achieved from TMS enolate **3.58** furnishing 2,2-disubstituted cyclohexanone **3.59**. It is important to note that the order of the two alkylation steps is key to this synthesis as efforts to engage alkyl bromide **3.56** in this reaction failed. Lombardo olefination gives diene [2+2] precursor **3.60**, that upon cyclization under optimal conditions gave the perforatol core **3.61** in high yield as a single diastereomer, again giving higher yields in comparison with CuOTf.

Scheme 3.6 Synthesis of Perforatol Core



3.4 Conclusion and Outlook

In summary, we have developed a new catalyst system that extends the useful scope of the Cu-catalyzed Salomon–Kochi photocycloaddition reaction, enabling the cycloaddition of sterically encumbered substituted alkenes. Key features of this strategy include the *in situ* generation of a COD-supported cationic Cu(I) complex bearing a weakly coordinating SbF_6^- counteranion. This more reactive complex is capable of engaging hindered polysubstituted alkene substrates, can be generated from bench-stable precursors, and enjoys greater stability

compared to the standard $[Cu(OTf)]_2$•benzene precatalyst. The preparation of the cores of the natural products sulcatine G and perforatol demonstrate the utility of this reaction in accessing structurally complex cyclobutane natural products.

3.5 Experimental

3.5.1 General Experimental Information

All organic reagents were purified prior to use. $[Cu(COD)Cl]_2$ was prepared according to the previously reported procedure by Cooke.[18] CuOTf was obtained from Sigma Aldrich. THF, Et_2O, DMF and CH_2Cl_2 were purified by elution through alumina as described by Grubbs.[24] UV irradiation was conducted using a Rayonet RP-200 Photoreactor with 2540 Å bulbs. Flash column chromatography was performed with Silicycle 40–63 Å silica (230–400 mesh). Diastereomer ratios for all compounds were determined by ^1H NMR analysis of the unpurified reaction mixture. ^1H and ^{13}C NMR data for all previously uncharacterized compounds were obtained using Bruker Avance-500 spectrometer and are referenced to TMS (0.0 ppm) and $CDCl_3$ (77.0 ppm) respectively unless otherwise stated. Mass spectrometry was performed with a Thermo Q Exactive Plus. These facilities are funded by the NSF (CHE-1048642), NIH (1S10 OD020022-1), and a generous gift from the Paul J. and Margaret M. Bender Fund.

3.5.2 Catalyst Synthesis

$Cu(cod)_2SbF_6$ $[Cu(COD)Cl]_2$ (1 mmol, 414.4 mg) was dispensed into a flame-dried 100 mL round-bottomed flask and suspended in CH_2Cl_2 (40 mL). The reaction was placed under N_2, and 1,5-cyclooctadiene (40 mmol, 4.9 mL) was added via syringe resulting in clearing of the solution to a translucent yellow. $AgSbF_6$ (2 mmol, 687.2 mg) was then added as a solution in CH_2Cl_2 and acetone (5 mL, 3 mL), and the reaction was stirred at room temperature for 1 h. The reaction was filtered to remove AgCl, and the filtrate was reconstituted to approximately 10 mL of CH_2Cl_2. Addition of hexane (40 mL) resulted in formation of a white powder precipitate, which was then collected on a filter frit to yield 466 mg (0.90 mmol, 90%) of desired productfter drying under high vac. **^1H NMR** (500 MHz, CD_2Cl_2) δ 5.84 (t, *J* = 3.4 Hz, 8H), 2.47 (d, *J* = 130.0 Hz, 16H). **^{13}C NMR** (126 MHz, CD_2Cl2) δ 123.34, 28.47. **^{19}F NMR** (377 MHz, CD_2Cl_2) δ -111.2, -114.3, -116.4,

-120.0, -121.7, -122.9, -125.6, -126.9, -128.7, -132.1, -134.2, -137.3. **HRMS** (EI) calculated for $[C_{16}H_{24}Cu]^+$ requires *m/z* 279.1169 , found *m/z* 279.1167.

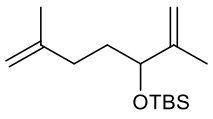
3.5.3 Synthesis of Substrates

General procedure for synthesis of 3-Hydroxy-1,6-heptadienes.

3-Hydroxy-1,6-heptadienes were prepared according to Salomon's previously reported procedure.[12b] Aldehyde was dispensed into a flame-dried round-bottomed flask and dissolved in THF to give a 0.5 M solution. The solution was placed under nitrogen, cooled to –78 °C, and treated dropwise with Grignard reagent (1.5 eq). The reaction was warmed to room temperature and stirred until TLC ($KMnO_4$ stain) indicated completion. The reaction was then quenched with saturated NH_4Cl solution, extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated to give crude desired product. This was carried on without further purification.

General TBS protection procedure.

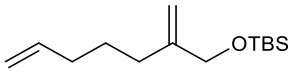
3-Hydroxy-1,6-heptadiene was dispensed into a flame-dried round-bottomed flask and dissolved in dimethylformamide to give a 0.5 M solution. The solution was then treated with 2 equiv of imidazole and 1.5 equiv of TBS-Cl, then placed under nitrogen. The reaction was then stirred 18–48 h at room temperature until TLC indicated completion. The reaction was then quenched with water and extracted with diethyl ether. The organic layer was then washed with water and brine, dried with $MgSO_4$, and concentrated to give a crude oil. Purification via flash chromatography gave analytically pure TBS protected 3-hydroxy-1,6- heptadienes as clear oils.



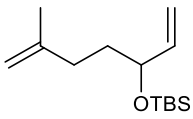
***tert*-Butyl((2,6-dimethylhepta-1,6-dien-3-yl)oxy)dimethylsilane(3.17)**

Prepared according to the general procedure with 2,6-dimethyl-1,6-heptadien-3-ol**Error! Bookmark not defined.** (3.1 mmol, 434.7 mg), TBS-Cl (4.7 mmol, 708.3 mg), i midazole (6.2 mmol, 422.1 mg), and DMF (6 mL). Purification on silica gel (9:1 pentanes:CH_2Cl_2) afforded 761.3 mg of product (2.99 mmol, 97%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-

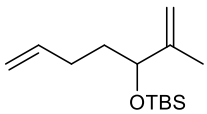
d) δ 4.84 (s, 1H), 4.75 (t, *J* = 1.8 Hz, 1H), 4.70 – 4.67 (m, 1H), 4.67 – 4.64 (m, 1H), 4.02 (t, *J* = 6.2 Hz, 1H), 1.96 (dddd, *J* = 44.9, 15.1, 10.4, 5.7 Hz, 2H), 1.70 (s, 3H), 1.66 (s, 3H), 1.65 – 1.52 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.7, 146.0, 110.7, 109.5, 76.4, 34.3, 33.6, 25.9, 22.7, 18.2, 17.1, -4.7, -5.0. **HRMS** (EI) calculated for $[C_{15}H_{30}OSi + H]^+$ requires *m/z* 255.2139, found *m/z* 255.2135.



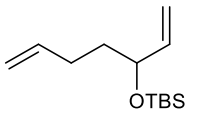
***tert*-Butyldimethyl((2-methylenehept-6-en-1-yl)oxy)silane (3.13)** Prepared according to the general procedure with 2-(hydroxymethyl)-1,6-heptadiene[25] (7.2 mmol, 907.8 mg), TBS-Cl (10.8 mmol, 1.62 g), imidazole (14.4 mmol, 980 mg), and DMF (14 mL) Purification on silica gel (9:1 pentanes:CH_2Cl_2) afforded 1.48 g of product (6.2 mmol, 86%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.05 – 4.98 (m, 2H), 4.96 (ddt, *J* = 10.1, 2.2, 1.3 Hz, 1H), 4.82 (s, 1H), 4.07 (d, *J* = 1.5 Hz, 2H), 2.12 – 1.97 (m, 4H), 1.55 (p, *J* = 7.7 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.5, 138.7, 114.6, 108.5, 65.9, 33.5, 32.1, 27.1, 25.9, 18.4, -5.4. **HRMS** (EI) calculated for $[C_{14}H_{28}OSi + H]^+$ requires *m/z* 241.1982, found *m/z* 241.1979.



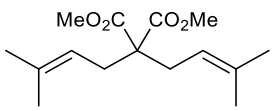
***tert*-Butyldimethyl((6-methylhepta-1,6-dien-3-yl)oxy)silane (S1)** Prepared according to the general procedure with 6-methyl-1,6-heptadien-3-ol[12b] (2.0 mmol, 250 mg), TBS-Cl (3.0 mmol, 447.6 mg), imidazole (4.0 mmol, 269.6 mg), and DMF (4 mL) Purification on silica gel (9:1 pentanes:CH_2Cl_2) afforded 390 mg of product (1.62 mmol, 82%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.80 (ddd, *J* = 16.7, 10.4, 6.1 Hz, 1H), 5.15 (dt, *J* = 17.1, 1.6 Hz, 1H), 5.03 (dt, *J* = 10.4, 1.5 Hz, 1H), 4.68 (ddd, *J* = 13.6, 2.5, 1.4 Hz, 2H), 4.10 (q, *J* = 6.2 Hz, 1H), 2.03 (qdd, *J* = 14.9, 9.9, 5.9 Hz, 2H), 1.72 (s, 3H), 1.69 – 1.56 (m, 2H), 0.90 (s, 9H), 0.04 (d, *J* = 10.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.9, 141.6, 113.7, 109.6, 73.5, 36.1, 33.3, 25.9, 22.6, 18.3, -4.3, -4.8. **HRMS** (EI) calculated for $[C_{14}H_{28}OSi + H]^+$ requires *m/z* 241.1982, found *m/z* 241.1980.



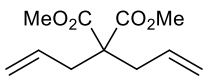
***tert*-Butyldimethyl((2-methylhepta-1,6-dien-3-yl)oxy)silane (S2)** Prepared according to the general procedure with 2-methyl-1,6-heptadien-3-ol[12b] (1.98 mmol, 250 mg), TBS-Cl (3.0 mmol, 452 mg), imidazole (4.0 mmol, 269 mg), and DMF (4 mL). Purification on silica gel (9:1 pentanes:CH_2Cl_2) afforded 328.9 mg of product (1.36 mmol, 69%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.82 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.00 (dq, *J* = 17.2, 1.8 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.3, 1.4 Hz, 1H), 4.85 (dt, *J* = 2.1, 1.0 Hz, 1H), 4.76 (p, *J* = 1.7 Hz, 1H), 4.06 – 4.01 (m, 1H), 2.12 – 1.95 (m, 2H), 1.67 (s, 3H), 1.61 (dddd, *J* = 13.2, 9.6, 7.2, 5.9 Hz, 1H), 1.56 – 1.48 (m, 1H), 0.89 (s, 9H), 0.02 (d, *J* = 18.2 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.7, 138.8, 114.3, 110.7, 76.2, 35.4, 29.8, 25.9, 18.2, 17.1, -4.7, -5.0. **HRMS** (EI) calculated for $[C_{14}H_{28}OSi + H]^+$ requires *m/z* 241.1982, found *m/z* 241.1975.



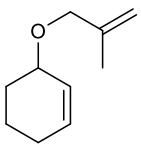
***tert*-Butyl(hepta-1,6-dien-3-yloxy)dimethylsilane (S3)** Prepared according to the general procedure with 1,6-heptadien-3-ol[12b] (2.23 mmol, 250 mg), TBS-Cl (3.35 mmol, 504.9 mg), imidazole (4.46 mmol, 303.6 mg), and DMF (4.6 mL). Purification on silica gel (9:1 pentanes:CH_2Cl_2) afforded 412.6 mg of product (1.82 mmol, 82%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.88 – 5.74 (m, 2H), 5.14 (dt, *J* = 17.1, 1.6 Hz, 1H), 5.06 – 4.97 (m, 2H), 4.95 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.11 (q, *J* = 6.1 Hz, 1H), 2.16 – 2.01 (m, 2H), 1.66 – 1.49 (m, 2H), 0.90 (s, 9H), 0.04 (d, *J* = 10.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.6, 138.7, 114.4, 113.7, 73.3, 37.3, 29.4, 25.9, 18.3, -4.3, -4.8. **HRMS** (EI) calculated for $[C_{13}H_{26}OSi + H]^+$ requires *m/z* 227.1826, found *m/z* 227.1823.



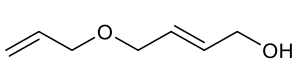
Dimethyl 2,2-bis(3-methylbut-2-en-1-yl) malonate (S4) was prepared according to a previously reported procedure.[26] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.94 (t, *J* = 7.4 Hz, 2H), 3.70 (s, 6H), 2.58 (d, *J* = 7.4 Hz, 4H), 1.68 (s, 6H), 1.59 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.9, 135.5, 117.8, 57.8, 52.3, 30.9, 26.0, 17.8. Spectral data matched those previously reported.



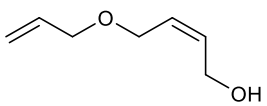
Diallylmalonate (S5) was prepared according to previously reported procedure.[27] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.65 (ddt, *J* = 18.9, 9.4, 7.4 Hz, 2H), 5.13 – 5.11 (m, 2H), 5.09 (d, *J* = 1.1 Hz, 2H), 3.72 (s, 6H), 2.64 (dt, *J* = 7.4, 1.2 Hz, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.2, 132.2, 119.3, 57.6, 52.4, 36.9. Spectral data matched those previously reported.



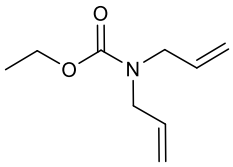
3-((2-Methylallyl)oxy)cyclohex-1-ene (S6) A flame-dried 50 mL round-bottomed flask was charged with $NaHCO_3$ (20 mmol, 1.71 g) and β-methallyl alcohol (40 mmol, 3.4 mL). The reaction was placed under N_2, cooled to 0 °C, and stirred vigorously. 3-bromocyclohexene (10 mmol, 1.15 mL) was added dropwise via a syringe, and the reaction was warmed to room temperature and stirred for 36 h under N_2. The reaction was then filtered, and the filtrate was extracted with Et_2O (3 x 30 mL), dried with $MgSO_4$, and concentrated to give the crude product. Purification on silica gel (20:1 pentanes: Et_2O) afforded 1.28 g of product (8.4 mmol, 84%) as a pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.85 (dtd, *J* = 10.2, 3.6, 1.2 Hz, 1H), 5.78 (dq, *J* = 10.1, 2.4 Hz, 1H), 4.99 – 4.97 (s, 1H), 4.89 – 4.86 (s, 1H), 3.94 (q, *J* = 12.6 Hz, 2H), 3.87 (tdt, *J* = 4.9, 3.2, 1.5 Hz, 1H), 2.05 (ddddd, *J* = 16.3, 7.5, 5.6, 3.7, 2.0 Hz, 1H), 1.95 (dddd, *J* = 18.0, 9.7, 3.7, 1.6 Hz, 1H), 1.85 – 1.74 (m, 5H), 1.69 (dtd, *J* = 11.9, 6.3, 3.4 Hz, 1H), 1.55 (dddd, *J* = 17.4, 7.1, 5.9, 2.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.9, 130.8, 127.9, 111.8, 72.1, 71.9, 28.4, 25.2, 19.6, 19.3. **HRMS** (EI) calculated for $[C_{10}H_{16}O + H]^+$ requires *m/z* 153.1274, found *m/z* 153.1274.



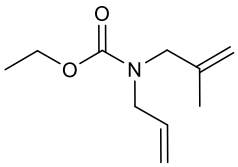
1,4-Bis(allyloxy)-trans-2-butene (3.39) was prepared according to a previously reported procedure.[28] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.97 – 5.87 (m, 2H), 5.83 (dtt, *J* = 15.5, 5.7, 1.3 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.19 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.17 (dd, *J* = 5.2, 1.2 Hz, 2H), 4.00 (dq, *J* = 5.7, 1.5 Hz, 4H), 1.53 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.6, 132.1, 127.8, 117.1, 71.3, 70.0, 63.0. Spectral data matched those previously reported.



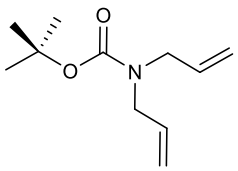
1,4-Bis(allyloxy)-cis-2-butene (3.41) was prepared according to a previously reported procedure.[28] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.81 (dtt, *J* = 11.2, 6.3, 1.5 Hz, 1H), 5.70 (dtt, *J* = 11.2, 6.3, 1.4 Hz, 1H), 5.29 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.19 (dd, *J* = 6.6, 1.2 Hz, 2H), 4.06 (dd, *J* = 6.3, 1.3 Hz, 2H), 4.00 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.31 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.4, 132.3, 128.2, 117.5, 71.4, 65.7, 58.7. Spectral data matched those previously reported.



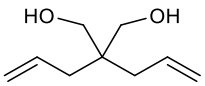
Ethyl diallylcarbamate (S7) was prepared according to a previously reported procedure.[12c] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.77 (ddt, *J* = 16.4, 11.4, 5.7 Hz, 2H), 5.18 – 5.08 (m, 4H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.85 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 133.7, 117.0, 116.5, 61.4, 48.9, 48.4, 14.7. Spectral data matched those previously reported.



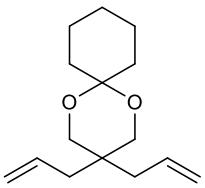
Ethyl allyl(2-methylallyl)carbamate (S8) was prepared according to a previously reported procedure.[12c] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.87 – 5.66 (m, 1H), 5.12 (m, 2H), 4.86 (s, 1H), 4.77 (m , 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.82 (m, 4H), 1.68 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 141.1, 133.5, 116.8 (d, J = 56.3 Hz), 111.9 (d, J = 42.5 Hz), 61.4, 51.6 (d, J = 59.4 Hz), 48.3 (d, J = 58.8), 19.9, 14.7. Spectral data matched those previously reported.



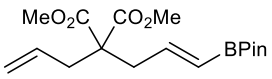
tert-Butyl diallylcarbamate (S9) was prepared according to a previously reported procedure.[29] **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.76 (ddt, *J* = 16.8, 11.7, 6.0 Hz, 2H), 5.17 – 5.02 (m, 4H), 3.80 (d, *J* = 26.0 Hz, 4H), 1.46 (s, 8H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.4, 134.0, 116.4 (d, *J* = 51.9 Hz), 79.6, 48.7, 28.4. Spectral data matched those previously reported.



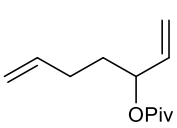
2,2-Diallylpropane-1,3-diol (S10) A flame-dried 25 mL round-bottomed flask was charged with Et_2O (5 mL) and $LiAlH_4$ (5 mmol, 190 mg), then placed under N_2. The reaction was then cooled to 0 °C, and diallylmalonate (2 mmol, 424.5 mg) was added dropwise as a solution in Et_2O (3 mL) over 15 min. The resulting suspension was stirred 1 h at room temperature. The reaction was then poured into Et_2O (30 mL), quenched sequentially dropwise with H_2O (0.19 mL), 15% NaOH solution (0.19 mL), and H_2O (0.57 mL), and dried over $MgSO_4$. Concentration of the filtrate gave crude product. Purification on silica gel (100% Et_2O) afforded 271.7 mg of product (1.74 mmol, 87%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.93 – 5.77 (m, 2H), 5.15 – 5.08 (m, 4H), 3.59 (d, *J* = 3.7 Hz, 4H), 2.38-2.26 (m, 2H), 2.09 (dt, *J* = 7.5, 1.2 Hz, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.9, 118.1, 68.3, 42.1, 36.1. **HRMS** (EI) calculated for $[C_9H_{16}O_2 + Na]^+$ requires *m/z* 179.0143 , found *m/z* 179.0143.



3,3-Diallyl-1,5-dioxaspiro[5.5]undecane (S11) was prepared according to a modification of a previously reported procedure.[30] A flame-dried 25 mL round-bottomed flask was charged with 2,2-diallylpropane-1,3-diol (3 mmol, 468.7 mg), cyclohexanone (2 mmol, 0.2 mL), $(EtO)_3CH$ (2 mmol, 0.33 mL), and CH_2Cl_2 (6 mL). The vessel was flushed with N_2, and $ZrCl_4$ (0.06 mmol, 14 mg) was added in one portion. The reaction was quickly placed back under N_2 and stirred at room temperature for 18 h. The reaction was quenched with 10% NaOH (10 mL) and extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers where washed with brine, dried over Na_2SO_4, and concentrated to give crude product. Purification on silica gel (9:1 pentanes: Et_2O) afforded 428.1 mg of product (1.82 mmol, 91%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.84 – 5.73 (m, 2H), 5.11 (s, *J* = 2H), 5.10 – 5.07 (m, 2H), 3.58 (s, 4H), 2.14 (dt, *J* = 7.6, 1.1 Hz, 4H), 1.74 (t, *J* = 6.0 Hz, 4H), 1.51 (p, *J* = 6.0 Hz, 4H), 1.40 (tt, *J* = 8.8, 4.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.2, 118.3, 98.0, 66.4, 36.8, 35.6, 32.6, 25.7, 22.6. **HRMS** (EI) calculated for $[C_{15}H_{24}O_2 + H]^+$ requires *m/z* 237.1849 , found *m/z* 237.1848.

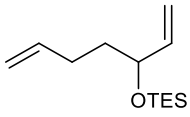


Dimethyl (*E*)-2-allyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl) malonate (S12) A flame-dried 25 mL round-bottomed flask was charged with dimethyl 2-allyl-2-(prop-2-ynyl)malonate[31] (3.47 mmol, 827 mg) and neat pinacolborane (3.82 mmol, 0.55 mL), then placed under N_2. Cp_2ZrHCl (1.04 mmol, 268.1 mg) was then added in one portion followed by triethylamine (1.04 mmol, 0.15 mL). The reaction was quickly placed back under N_2, wrapped in tin foil to exclude light, and heated to 60 °C for 18 h. Upon completion, the reaction was diluted with hexanes and filtered through celite to remove solids. Concentration of the filtrate yielded crude product. Purification on boron doped silica gel (9:1 Hexanes: EtOAc) afforded 1.04 g of product (3.1 mmol, 89%) as a pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 6.39 (dt, *J* = 17.7, 7.3 Hz, 1H), 5.65 (ddt, *J* = 17.5, 10.2, 7.4 Hz, 1H), 5.52 (dt, *J* = 17.7, 1.4 Hz, 1H), 5.15 – 5.04 (m, 2H), 3.71 (s, 6H), 2.75 (dd, *J* = 7.3, 1.4 Hz, 2H), 2.64 (dt, *J* = 7.5, 1.2 Hz, 2H), 1.25 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.0, 146.8, 132.2, 124.1, 119.4, 83.2, 57.5, 52.4, 39.0, 37.0, 24.8. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 29.7. **HRMS** (EI) calculated for $[C_{17}H_{27}BO_6 + H]^+$ requires *m/z* 339.1974, found *m/z* 339.1972.

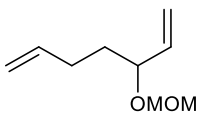


Hepta-1,6-dien-3-yl pivalate (S13) A flame-dried 100 mL round-bottomed flask was charged with1,6-heptadien-3-ol[12b] (4.46 mmol, 500 mg), DMAP (0.22 mmol, 27.2 mg), and 10 mL of CH_2Cl_2. The solution was placed under N_2, cooled to 0 °C, treated with triethylamine (44.6 mmol, 6.2 mL), stirred 15 min at 0 °C, and then treated with pivoyl chloride (5.4 mmol, 0.66 mL) dropwise via syringe. The reaction was then warmed to room temperature and stirred for 18 h. Upon completion, the reaction was quenched with MeOH (6 mL) and H_2O (20 mL) and then extracted with Et_2O (3 x 30 mL). The organic layer was washed with 1 M HCl (50 mL), 1 M NaOH (50 mL), and brine (50 mL), and then dried with $MgSO_4$ and concentrated to give the crude product. Purification on silica gel (9:1 pentanes: Et_2O) afforded 806 mg of product (2.27 mmol, 92%) as a pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.86 – 5.73

(m, 2H), 5.27 – 5.19 (m, 2H), 5.15 (dt, *J* = 10.6, 1.2 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.98 (dq, *J* = 10.2, 1.5 Hz, 1H), 2.18 – 1.98 (m, 2H), 1.81 – 1.63 (m, 2H), 1.22 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.7, 137.6, 136.6, 116.2, 115.1, 73.6, 38.9, 33.5, 29.3, 27.2. **HRMS** (EI) calculated for $[C_{12}H_{20}O_2 + H]^+$ requires *m/z* 197.1536, found *m/z* 197.1532.

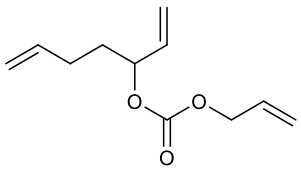


Triethyl(hepta-1,6-dien-3-yloxy)silane (S14) A flame-dried 50 mL round-bottomed flask was charged with1,6-heptadien-3-ol[12b] (2 mmol, 224 mg) and dissolved into 8 mL CH_2Cl_2. The reaction was placed under N_2, cooled to 0 °C, and treated with 2,6-lutidine (4 mmol, 0.5 mL). The reaction was then treated dropwise with TESOTf (3 mmol, 0.7 mL) and stirred 1 h at 0 °C. The reaction was then diluted with CH_2Cl_2, quenched with H_2O, and extracted with CH_2Cl_2. The organic layers where washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to give the crude product. Purification on silica gel (50:1 pentanes: CH_2Cl_2) afforded 312 mg of product (1.4 mmol, 70%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.82 (dddd, *J* = 16.8, 12.1, 10.2, 6.4 Hz, 2H), 5.14 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.06 – 4.98 (m, 2H), 4.95 (ddt, *J* = 10.2, 2.0, 1.3 Hz, 1H), 4.10 (q, *J* = 6.3 Hz, 1H), 2.16 – 2.02 (m, 2H), 1.68 – 1.50 (m, 2H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.7 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.6, 138.7, 114.4, 113.9, 73.3, 37.3, 29.4, 6.9, 5.0. **HRMS** (EI) calculated for $[C_{13}H_{26}OSi + H]^+$ requires *m/z* 227.1826, found *m/z* 227.1825.

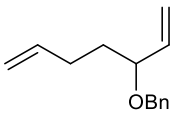


3-(Methoxymethoxy)hepta-1,6-diene (S15). A flame-dried 50 mL round-bottomed flask was charged with1,6-heptadien-3-ol[12b] (2.5 mmol, 280.4 mg) and dissolved into 25 mL CH_2Cl_2. The reaction was placed under N_2, cooled to 0 °C, and treated sequentially with Hünig's base (5 mmol, 0.9 mL) and MOMCl (3.75 mmol, 0.3 mL). Reaction was then warmed to room temperature and stirred for 48 h. The reaction was then quenched with aqueous NH_4Cl, extracted with CH_2Cl_2, dried with $MgSO_4$, filtered and concentrated to give

the crude product. Purification on silica gel (20:1 pentanes: Et_2O) afforded 355 mg of product (2.27 mmol, 91%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.83 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.68 (ddd, *J* = 17.7, 10.3, 7.6 Hz, 1H), 5.25 – 5.16 (m, 2H), 5.08 – 4.93 (m, 2H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 1H), 3.38 (s, 3H), 2.23 – 2.04 (m, 2H), 1.77 – 1.57 (m, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.2, 138.2, 117.4, 114.8, 93.8, 76.8, 55.5, 34.6, 29.6. **HRMS** (EI) calculated for $[C_9H_{16}O_2 + H]^+$ requires *m/z* 157.1223, found *m/z* 157.1224.



Allyl hepta-1,6-dien-3-yl carbonate (S16). A flame-dried 50 mL round-bottomed flask was charged with1,6-heptadien-3-ol[12b] (2.23 mmol, 253.6 mg) and in 5 mL CH_2Cl_2. The reaction solution was placed under N_2, cooled to 0 °C and treated with pyridine (4.46 mmol, 0.36 mL). Reaction was stirred 15 min at 0 °C and then treated with allyl chloroformate (3.66 mmol, 0.39 mL) dropwise via syringe. The reaction was warmed to room temperature and stirred for 18 h. Upon completion, the reaction was diluted with CH_2Cl_2 (15 mL), quenched with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated to give the crude product. Purification on silica gel (18:1 pentanes: Et_2O) afforded 333.6 mg of product (1.7 mmol, 76%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.94 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.85 – 5.75 (m, 2H), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.32 (dt, J= 17.2, 1.2 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.23 (dt, *J* = 10.5, 1.2 Hz, 1H), 5.08 (qd, *J* = 6.5, 6.0, 1.1 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.99 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.62 (dt, *J* = 5.8, 1.4 Hz, 2H), 2.13 (dtq, *J* = 8.2, 6.7, 1.5 Hz, 2H), 1.82 (ddd, *J* = 14.2, 8.2, 6.9 Hz, 1H), 1.75 – 1.67 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.4, 137.3, 135.8, 131.7, 118.8, 117.7, 115.3, 78.5, 68.3, 33.3, 29.2. **HRMS** (EI) calculated for $[C_{11}H_{16}O_3 + NH_4]^+$ requires *m/z* 214.1438, found *m/z* 214.1434



((Hepta-1,6-dien-3-yloxy)methyl)benzene (S17). A flame-dried 50 mL round-bottomed flask was charged with NaH (8.2 mmol, 328 mg) and THF (8 mL). The reaction was placed under N_2, 1,6-heptadien-3-ol[12b] (6.28 mmol, 704.8 mg) was added as a solution in THF (5 mL), and the reaction was allowed to stir 30 min at room temperature. Benzyl bromide (12.6 mmol, 1.49 mL) was added, and the reaction was refluxed at 80 °C for 14 h. Upon completion, the reaction was diluted with Et_2O (20 mL), quenched with H_2O (5 mL), and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated to give the crude product. Purification on silica gel (6:1 pentanes:CH_2Cl_2) afforded 969.3 mg of product (4.79 mmol, 76%) as a yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 4.4 Hz, 4H), 7.30 – 7.23 (m, 1H), 5.86 – 5.69 (m, 2H), 5.27 – 5.17 (m, 2H), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 3.75 (td, *J* = 7.5, 5.9 Hz, 1H), 2.23 – 2.03 (m, 2H), 1.76 (dddd, *J* = 13.4, 9.0, 7.3, 6.1 Hz, 1H), 1.63 – 1.54 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.9, 138.8, 138.4, 128.3, 127.8, 127.4, 117.2, 114.7, 79.9, 70.1, 34.7, 29.6. **HRMS** (EI) calculated for $[C_{14}H_{18}O + H]^+$ requires *m/z* 203.1430, found *m/z* 203.1429.

3.5.3 [2+2] Photocycloadditions

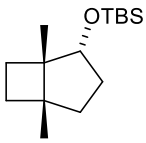
General Procedure:

A quartz reaction tube is charged with $[Cu(COD)Cl]_2$ (1–2.5 mol%), and the 1,6-heptadiene substrate is then added as a solution in Et_2O (1 mL/ 0.2 mmol). The reaction is then sonicated 1 min, diluted to 0.05 M and stirred under N_2 for 5 min. $AgSbF_6$ (10–25 mol%) is then added as a solution in Et_2O to give a 0.025 M solution, and the reaction is further stirred for 15 min under N_2. Once the reaction has cleared and AgCl has fully precipitated, the reaction is fit with a water-recirculating coldfinger and irradiated at 254 nm in a Rayonet RPR-200 photoreactor. After the indicated time point, the reaction is treated with 7 M NH_3 in MeOH (1 mL) and eluted through a

plug of silica with Et_2O. Concentration on rotovap gives crude product mixtures. Sensitive substrates can be passed thru silica without the NH_3 quench and Cu(I) impurities can be removed during further purification. Products were purified via flash chromatography; however, the yields of products that were very difficult to quantitatively isolate either due to visualization difficulty or volatility were determined using Quantitative ^1H NMR using TMS-Ph or 1-methylnapthalene as an internal standard.

CuOTf Comparison Procedure

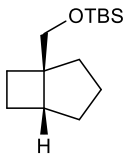
In an inert-atmosphere glovebox, CuOTf was weighed into a vial and dissolved in Et_2O. This was transferred to a quartz vessel containing a solution of diene substrate under N_2. This solution was diluted to 0.025 M and prestirred for 15 min. The reaction was then fit with a water-recirculating coldfinger and irradiated at 254 nm in a Rayonet photoreactor for the indicated time. Workup is identical to the general procedure above.



***tert*-Butyl((1,5-dimethylbicyclo[3.2.0]heptan-2-yl)oxy)dimethylsilane (3.18).** Prepared according to the general procedure with **3.17** (0.2 mmol, 50.9 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (8 mL). Irradiation time = 1 h, NMR yield (94%, 0.188 mmol, 5:1 dr), internal standard (17.0 mg TMS-Ph). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil.

Prepared according to CuOTf comparison procedure with **3.17** (0.2 mmol, 50.9 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). **Experiment 1**, Irradiation time = 1 h, NMR yield (28%, 0.056 mmol, 5:1 dr), internal standard (18.5 mg TMS-Ph). **Experiment 2**, Irradiation time = 18 h, NMR yield (44%, 0.088 mmol, 5:1 dr), internal standard (19.9 mg TMS-Ph). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.59 (t, *J* = 8.3 Hz, 1H), 2.04 (ddd, *J* = 12.6, 10.4, 6.8 Hz, 1H), 1.80 (dtd, *J* = 9.2, 5.1, 4.6, 2.7 Hz, 2H), 1.68 (tdd, *J* = 11.8, 6.9, 1.1 Hz, 1H), 1.54 (ddd, *J* = 11.9, 10.4,

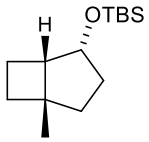
6.3 Hz, 1H), 1.45 – 1.40 (m, 1H), 1.33 – 1.17 (m, 2H), 0.98 (d, *J* = 0.9 Hz, 6H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 81.0, 46.9, 43.1, 36.7, 32.4, 29.6, 25.7, 23.3, 21.5, 20.7, 18.1, -4.31, -4.80. **HRMS** (EI) calculated for $[C_{15}H_{30}OSi + H]^+$ requires *m/z* 255.2139, found *m/z* 255.2137.



((Bicyclo[3.2.0]heptan-1-yl)methoxy)(tert-butyl)dimethylsilane (3.14). Prepared according to the general procedure with **3.13** (0.2 mmol, 48.0 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (95%, 0.19 mmol), internal standard (17.7 mg TMS-Ph). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.54 (d, *J* = 9.8 Hz, 1H), 3.48 (d, *J* = 9.8 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.06 – 1.89 (m, 3H), 1.81 (dddd, *J* = 12.3, 7.5, 5.0, 2.4 Hz, 1H), 1.55 – 1.44 (m, 3H), 1.39 – 1.25 (m, 4H), 0.91 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 68.7, 50.5, 39.2, 35.7, 33.4, 25.9, 25.6, 21.1, 18.3, -5.4, -5.4. **HRMS** (EI) calculated for $[C_{14}H_{28}OSi + H]^+$ requires *m/z* 241.1982, found *m/z* 241.1981.

Scale-up: Prepared according to the general procedure in a 500 mL quartz round bottom instead of tube. **S1** (4.16 mmol, 1.0 g), $[Cu(COD)Cl]_2$ (0.042 mmol, 17.4 mg), $AgSbF_6$ (0.21 mmol, 72.2 mg), and Et_2O (166 mL). Irradiation time = 5 h. Purification on silica gel (20:1 pentanes:CH_2Cl_2) afforded 887.4 mg of product (3.7 mmol, 89%) as a clear oil.

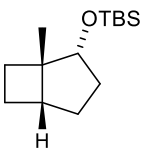
Comparison: Prepared according to CuOTf comparison procedure with **3.13** (0.2 mmol, 50.9 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (39%, 0.078 mmol), internal standard (16.8 mg TMS-Ph).



***tert*-Butyldimethyl((5-methylbicyclo[3.2.0]heptan-2-yl)oxy)silane (3.19).** Prepared according to the general procedure with **S1** (0.2 mmol, 48.0 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (8 mL).

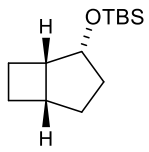
Irradiation time = 30 min, NMR yield (94%, 0.188 mmol, >20:1 dr), internal standard (17.0 mg TMS-Ph). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.18 (dt, *J* = 10.1, 6.8 Hz, 1H), 2.17 (dq, *J* = 9.6, 5.9, 5.0 Hz, 1H), 1.96 (m, 1H), 1.91 – 1.85 (m, 2H), 1.80 – 1.65 (m, 3H), 1.40 (dd, *J* = 12.7, 6.5 Hz, 1H), 1.23 (td, *J* = 12.9, 6.3 Hz, 1H), 1.15 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 75.0, 46.6, 43.1, 37.1, 33.8, 31.3, 27.3, 25.9, 18.2, 12.4, -4.8. **HRMS** (EI) calculated for $[C_{14}H_{28}OSi + H]^+$ requires *m/z* 241.1982, found *m/z* 241.1983.

Comparison: Prepared according to CuOTf comparison procedure with **S1** (0.2 mmol, 48 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (45%, 0.09 mmol), internal standard (10 µL of 1-methylnapthalene).



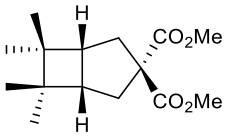
***tert*-Butyldimethyl((1-methylbicyclo[3.2.0]heptan-2-yl)oxy)silane (3.20).** Prepared according to the general procedure with **S2** (0.2 mmol, 48 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (91%, 0.182 mmol, 7:1 dr), internal standard (23.3 mg TMS-Ph). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.62 (dd, *J* = 10.0, 6.2 Hz, 1H), 2.22 – 2.08 (m, 3H), 1.95 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.59 (tt, *J* = 13.2, 6.7 Hz, 1H), 1.40 – 1.28 (m, 3H), 1.13 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 80.9, 46.2, 41.4, 33.4, 28.5, 25.9, 24.9, 23.4, 21.3, 18.1, -4.4, -4.8. **HRMS** (EI) calculated for $[C_{14}H_{28}OSi + H]^+$ requires *m/z* 241.1982, found *m/z* 241.1980.

Comparison: Prepared according to CuOTf comparison procedure with **S2** (0.2 mmol, 48 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (17%, 0.03 mmol), internal standard (10 µL of 1-methylnapthalene).



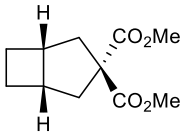
((Bicyclo[3.2.0]heptan-2-yl)oxy)(*tert*-butyl)dimethylsilane (3.21). Prepared according to the general procedure with **S3** (0.2 mmol, 45.3 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (8 mL). Irradiation time = 1 h, NMR yield (89%, 0.178 mmol, 20:1 dr), internal standard (15.8 mg TMS-Ph). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.13 (dt, *J* = 10.1, 6.4 Hz, 1H), 2.62 (dtd, *J* = 8.8, 4.5, 2.1 Hz, 2H), 2.29 – 2.18 (m, 1H), 2.05 – 1.91 (m, 2H), 1.89 – 1.74 (m, 2H), 1.60 – 1.43 (m, 2H), 1.39 (dd, *J* = 12.9, 6.7 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 3H), -0.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 75.6, 40.8, 36.1, 32.1, 29.6, 25.9, 24.9, 18.2, 16.2, -4.8. **HRMS** (EI) calculated for $[C_{13}H_{26}OSi + H]^+$ requires *m/z* 227.1826, found *m/z* 227.1823.

Comparison: Prepared according to CuOTf comparison procedure with **S3** (0.2 mmol, 45 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (85%, 0.17 mmol), internal standard (10 µL of 1-methylnapthalene).



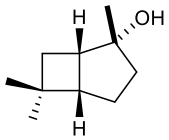
Dimethyl-6,6,7,7-tetramethylbicyclo[3.2.0]heptane-3,3-dicarboxylate (3.22). Prepared according to the general procedure with **S4** (0.2 mmol, 53.6 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (4 mL). Irradiation time = 6 h, NMR yield (42%, 0.084 mmol), internal standard (16.8 mg TMS-Ph). **Note**: 0.05 M instead of 0.025 M. Purification on silica gel (100% CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.73 (s, 3H), 3.70 (s, 3H), 2.41 – 2.27 (m, 4H), 2.14 (dd, *J* = 13.1, 4.8 Hz, 2H), 1.00 (s, 6H), 0.88 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.0, 172.5, 64.3, 52.6, 52.5, 45.5, 37.4, 35.3, 27.1, 21.7. **HRMS** (EI) calculated for $[C_{11}H_{16}O_4 + H]^+$ requires *m/z* 269.1747, found *m/z* 269.1742.

Comparison: Prepared according to CuOTf comparison procedure with **S4** (0.2 mmol, 53.6 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (4 mL). Irradiation time = 30 min, NMR yield (4 %, 0.007 mmol), internal standard (16.6 mg TMS-Ph).

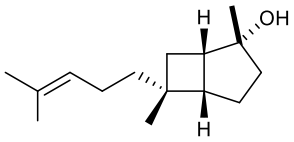


Dimethyl-bicyclo[3.2.0]heptane-3,3-dicarboxylate (3.23) Prepared according to the general procedure with **S5** (0.3 mmol, 63.7 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.3 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 1 h, NMR yield (90%, 0.27 mmol), internal standard (16.8 mg TMS-Ph). Purification on silica gel (20:1 pentanes: Et_2O, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.77 (d, *J* = 0.8 Hz, 3H), 3.70 (d, *J* = 0.8 Hz, 3H), 2.83 (dp, *J* = 7.6, 3.7 Hz, 2H), 2.43 – 2.37 (m, 2H), 2.32 (dd, *J* = 13.3, 3.0 Hz, 2H), 2.20 – 2.12 (m, 2H), 1.60 (dddd, *J* = 8.7, 6.4, 4.7, 2.0 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.0, 172.9, 63.8, 52.7, 52.5, 41.7, 38.6, 24.3. **HRMS** (EI) calculated for $[C_{11}H_{16}O_4 + H]^+$ requires *m/z* 213.1121, found *m/z* 213.1120.

Comparison: Prepared according to CuOTf comparison procedure with **S5** (0.2 mmol, 43 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). Irradiation time = 30 min, NMR yield (51%, 0.1 mmol), internal standard (10 µL of 1-methylnapthalene).

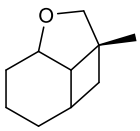


(1*S*,2*R*,5*S*)-2,6,6-Trimethylbicyclo[3.2.0]heptan-2-ol (3.24). Prepared according to the general procedure with L–linalool (0.75 mmol, 115.7 mg), $[Cu(COD)Cl]_2$ (0.0075 mmol, 3.1 mg), $AgSbF_6$ (0.075 mmol, 25.8 mg), and Et_2O (30 mL). Irradiation time = 5 h. Purification on silica gel (4:1 pentanes: Et_2O, $KMnO_4$ stain) afforded 55 mg of product (0.51 mmol, 68%) as a white crystalline solid, giving a full spectral match with the previous report.[12] **HRMS** (EI) calculated for $[C_{10}H_{18}O + H]^+$ requires *m/z* 155.1430, found *m/z* 155.1428.



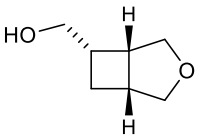
2,6-Dimethyl-6-(4-methylpent-3-en-1-yl)bicyclo[3.2.0]heptan-2-ol (3.25). Prepared according to the general procedure with nerolidol (0.3 mmol, 66.7 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.3 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 3 h. Purification on silica gel (4:1 pentanes: Et_2O, $KMnO_4$ stain) afforded 55 mg of product (0.25 mmol, 82%, 1:1 dr) as a yellow oil. Mixture of diastereomers matched previously reported spectra[32] and were not separated. **HRMS** (EI) calculated for $[C_{15}H_{26}O + H]^+$ requires *m/z* 223.2056, found *m/z* 223.2052.

Prepared according to CuOTf comparison procedure with nerolidol (0.3 mmol, 66.7 mg), $[CuOTf]_2$ C_6H_6 (0.003 mmol, 1.5 mg), and Et_2O (12 mL). Irradiation time = 3 hr NMR yield (28%, 0.084 mmol, 1:1 dr), internal standard (18.3 mg TMS-Ph).



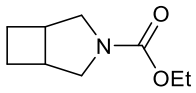
2a-Methyloctahydro-2H-cyclobuta[cd]benzofuran (3.26). Prepared according to the general procedure with **S6** (0.3 mmol, 45.7 mg), $[Cu(COD)Cl]_2$ (1 mol%, 0.003 mmol, 1.3 mg), $AgSbF_6$ (10 mol% 0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 8 h, NMR yield (48%, 0.14 mmol), internal standard (15.9 mg TMS-Ph). Purification on silica gel (4:1 pentanes:Et_2O, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.05 (dt, *J* = 6.5, 2.9 Hz, 1H), 3.63 (d, *J* = 8.6 Hz, 1H), 3.23 (d, *J* = 8.6 Hz, 1H), 2.45 (dddd, *J* = 11.6, 9.9, 6.5, 1.7 Hz, 1H), 2.09 (td, *J* = 7.8, 3.1 Hz, 1H), 2.02 – 1.93 (m, 2H), 1.92 – 1.83 (m, 1H), 1.62 (ddd, *J* = 11.3, 10.1, 3.1 Hz, 1H), 1.46 – 1.26 (m, 4H), 1.24 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 78.6, 76.5, 43.8, 43.2, 31.9, 27.5, 26.2, 23.0, 20.0, 14.3. **HRMS** (EI) calculated for $[C_{10}H_{16}O + H]^+$ requires *m/z* 153.1274, found *m/z* 153.1273.

Comparison: Prepared according to CuOTf comparison procedure with **S6** (0.3 mmol, 45.7 mg), $[CuOTf]_2$ C_6H_6 (0.003 mmol, 1.5 mg), and Et_2O (12 mL). Irradiation time = 8 hr, NMR yield (16%, 0.048 mmol), internal standard (15.7 mg TMS-Ph).



(3-Oxabicyclo[3.2.0]heptan-6-yl)methanol (3.27). Prepared according to the general procedure with **3.41** (0.3 mmol, 38.5 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.3 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 1 h. Purification on silica gel (100 % Et_2O, $KMnO_4$ stain) afforded 32.5 mg of product (0.252 mmol, 84 %, 1.4:1 dr) as a yellow oil. Diastereomers were separated on silica gel (4:1 pentanes:acetone) with the major diastereomer eluting first. **Major Diastereomer: ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.16 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 9.1 Hz, 1H), 3.70 – 3.62 (m, 2H), 3.41 (dt, *J* = 10.1, 6.3 Hz, 2H), 3.01 (q, *J* = 7.7 Hz, 1H), 2.91 (tt, *J* = 8.1, 5.4 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.24 (dddd, *J* = 12.3, 10.4, 8.7, 1.5 Hz, 1H), 1.77 (s, 1H), 1.49 (ddd, *J* = 12.9, 7.4, 6.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 74.2, 69.2, 62.4, 39.8, 35.7, 33.8, 26.4. **Minor Diastereomer: ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.88 (dd, *J* = 12.5, 9.2 Hz, 2H), 3.66 (tt, *J* = 10.8, 7.9 Hz, 2H), 3.50 (ddd, *J* = 9.1, 5.4, 3.4 Hz, 2H), 2.86 (ddd, *J* = 13.4, 8.3, 5.3 Hz, 1H), 2.68 (dt, *J* = 8.5, 5.0 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.88 – 1.75 (m, 2H), 1.32 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 74.5, 74.0, 66.8, 41.7, 39.1, 35.8, 26.4. **HRMS** (EI) calculated for $[C_7H_{12}O_2 + H]^+$ requires *m/z* 129.0910, found *m/z* 129.0910.

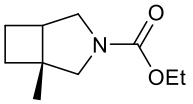
Comparison: Prepared according to CuOTf comparison procedure with **3.41** (0.2 mmol, 25.6 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1.0 mg), and Et_2O (8 mL). Irradiation time = 1 h, NMR yield (62%, 0.12 mmol), internal standard (19.6 mg TMS-Ph).



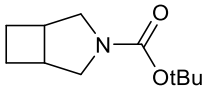
Ethyl 3-azabicyclo[3.2.0]heptane-3-carboxylate (3.28). Prepared according to the general procedure with **S7** (0.3 mmol, 50.8 mg), $[Cu(COD)Cl]_2$ (2.5 mol%, 0.0075 mmol, 3.1 mg), $AgSbF_6$ (25 mol% 0.075 mmol, 25.8 mg), and Et_2O (12 mL). Irradiation time = 20 hr, NMR yield (74%, 0.22 mmol), internal standard (19.2 mg TMS-Ph). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.56 (d, *J* = 32.5 Hz, 2H), 3.27 (s, 2H), 2.90 (dt, *J* = 8.4, 4.5 Hz, 2H), 2.18 (ddd, *J* = 8.8, 6.0, 3.3 Hz, 2H), 1.71 (dq, *J* = 10.8, 7.0, 6.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 155.9, 60.9, 53.0 (d, *J* = 35.4 Hz),

37.6 (d, *J* = 117.5 Hz), 24.6, 14.9. **HRMS** (EI) calculated for $[C_9H_{15}NO_2 + H]^+$ requires *m/z* 170.1176, found *m/z* 170.1175.

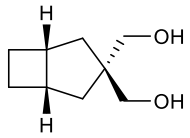
Comparison: Prepared according to CuOTf comparison procedure with **S7** (0.2 mmol, 33.8 mg), $[CuOTf]_2$ C_6H_6 (0.005 mmol, 2.5 mg), and Et_2O (8 mL). Irradiation time = 20 h, NMR yield (23%, 0.046 mmol), internal standard (19.2 mg TMS-Ph).



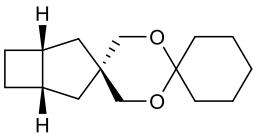
Ethyl-1-methyl-3-azabicyclo[3.2.0]heptane-3-carboxylate (3.29). Prepared according to the general procedure with **S8** (0.2 mmol, 37 mg), $[Cu(cod)Cl]_2$ (2.5 mol%, 0.0075 mmol, 3.1 mg), $AgSbF_6$ (10 mol% 0.02 mmol, 25.8 mg), and Et_2O (12 mL). Irradiation time = 20 h, NMR yield (97%, 0.19 mmol), internal standard (10 µL of 1-methylnapthalene). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.47 (m, 2H), 3.37 (d, *J* = 9.7 Hz, 1H), 2.97 (d, *J* = 14.1 Hz, 1H), 2.40 (q, *J* = 7.0 Hz, 1H), 2.15 (dddd, *J* = 12.1, 10.4, 8.5, 6.6 Hz, 1H), 1.94 (q, *J* = 10.2, 9.8 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.59 (dp, *J* = 11.3, 5.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 60.9, 59.1 (d, *J* = 30.97 Hz), 53.0 (d, *J* = 40.67 Hz), 44.9 (d, *J* = 121.7 Hz), 43.1 (d, *J* = 123.11Hz), 30.8, 24.1, 21.3, 14.8.**HRMS** (EI) calculated for $[C_{10}H_{17}NO_2 + H]^+$ requires *m/z* 184.1332, found *m/z* 184.1332.



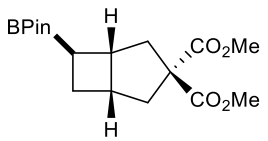
***tert*-Butyl 3-azabicyclo[3.2.0]heptane-3-carboxylate (3.30).** Prepared according to the general procedure with **S9** (0.3 mmol, 59.1 mg), $[Cu(COD)Cl]_2$ (2.5 mol%, 0.0075 mmol, 3.1 mg), $AgSbF_6$ (25 mol% 0.075 mmol, 25.8 mg), and Et_2O (12 mL). Irradiation time = 20 h, NMR yield (64%, 0.19 mmol), internal standard (17.1 mg TMS-Ph). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.53 (d, *J* = 39.5 Hz, 2H), 3.24 (s, 1H), 2.88 (p, *J* = 3.2 Hz, 2H), 2.18 (tt, *J* = 6.2, 3.4 Hz, 2H), 1.72 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4, 79.1, 53.1, 52.8, 38.1, 37.2, 28.6, 24.6. **HRMS** (EI) calculated for $[C_{11}H_{19}NO_2 + H]^+$ requires *m/z* 198.1489, found *m/z* 198.1487.



(Bicyclo[3.2.0]heptane-3,3-diyl)dimethanol (3.31) . Prepared according to the general procedure with **S10** (0.3 mmol, 46.9 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 3.1 mg), $AgSbF_6$ (0.03 mmol, 25.7 mg), and Et_2O (12 mL). Irradiation time = 7 h, NMR yield (86%, 0.258 mmol), internal standard (18.1 mg TMS-Ph). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.84 (d, *J* = 4.0 Hz, 2H), 3.46 (d, *J* = 4.3 Hz, 2H), 2.73 (ddd, *J* = 10.6, 5.3, 3.1 Hz, 2H), 2.33 – 2.14 (m, 4H), 1.95 – 1.85 (m, 2H), 1.67 – 1.60 (m, 2H), 1.48 – 1.38 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 71.9, 69.3, 54.3, 39.7, 38.2, 26.0. **HRMS** (EI) calculated for $[C_9H_{16}O_2 + H]^+$ requires *m/z* 157.1223 , found *m/z* 157.1224.

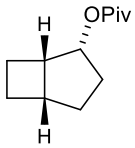


Dispiro[bicyclo[3.2.0]heptane-3,5'-[1,3]dioxane-2',1''-cyclohexane] (3.32). Prepared according to the general procedure with **S11** (0.3 mmol, 70.9 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.3 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 1 h, NMR yield (93%, 0.279 mmol), internal standard (16.7 mg TMS-Ph). Purification on silica gel (20:1 pentanes:Et_2O, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.85 (s, 2H), 3.46 (s, 2H), 2.78 – 2.66 (m, 2H), 2.22 (dq, *J* = 10.0, 6.1 Hz, 2H), 1.96 – 1.84 (m, 2H), 1.76 (t, *J* = 6.0 Hz, 4H), 1.67 – 1.55 (m, 2H), 1.55 – 1.45 (m, 6H), 1.41 (p, *J* = 5.9 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 97.8, 68.8, 68.0, 47.4, 41.6, 38.0, 32.7, 25.9, 22.6. **HRMS** (EI) calculated for $[C_{15}H_{24}O_2 + H]^+$ requires *m/z* 237.1849 , found *m/z* 237.1847.

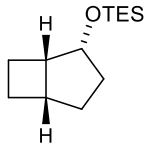


Dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.2.0] heptane-3,3-dicarboxylate (3.33). Prepared according to the general procedure with **S12** (0.3 mmol, 63.7 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.3 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 2 h. Purification on boron doped silica gel (4:1 pentanes: Et_2O) afforded 77.9 mg of product (0.23 mmol, 76%, 2.5:1 dr) as a yellow oil. Separation of diastereomers was performed on CombiFlash Rf 200 equipped

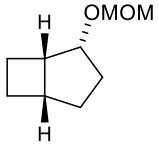
with 340CF ELSD detector (Teledyne Isco). The first round of purification was performed on a silica 24 g gold column with a gradient of 0–20% hexane/EtOAc to afford the pure major isomer. The semi-pure minor obtained was further purified on a silica 12g gold column with a gradient of 0–15% hexane/EtOAc to get the pure minor diastereomer. Note under these conditions the minor diastereomer elutes first. **Major Diastereomer**: **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.76 (s, 3H), 3.70 (s, 3H), 2.83 (m, 2H), 2.45 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.39 – 2.33 (m, 3H), 2.21 – 2.08 (m, 1H), 1.75 (ddd, *J* = 12.2, 10.7, 4.0 Hz, 1H), 1.48 (ddd, *J* = 10.9, 7.3, 4.7 Hz, 1H), 1.25 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.0, 172.8, 83.1, 63.5, 52.7, 52.6, 42.5, 41.7, 39.9, 38.2, 25.9, 24.7. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 34.3. **Minor Diastereomer**: **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 3.73 (s, 3H), 3.68 (s, 3H), 2.85 (tdd, *J* = 16.5, 8.4, 6.2 Hz, 2H), 2.57 – 2.46 (m, 2H), 2.41 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.09 – 1.97 (m, 2H), 1.80 (ddd, *J* = 11.8, 9.3, 6.1 Hz, 1H), 1.26 (d, *J* = 3.4 Hz, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.7, 172.4, 83.2, 76.8, 64.3, 52.6, 52.5, 41.7, 40.0, 39.3, 38.5, 28.0, 25., 24.9. **^{11}B NMR** (128 MHz, $CDCl_3$) δ 33.1. **HRMS** (EI) calculated for $[C_{17}H_{27}BO_6 + H]^+$ requires *m/z* 339.1974, found *m/z* 339.1973.



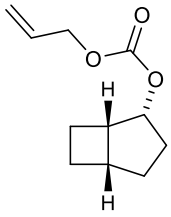
Bicyclo[3.2.0]heptan-2-yl pivalate (3.34). Prepared according to the general procedure with **S13** (0.6 mmol, 117.7 mg), $[Cu(COD)Cl]_2$ (0.006 mmol, 2.5 mg), $AgSbF_6$ (0.06 mmol, 20.6 mg), and Et_2O (24 mL). Irradiation time = 4 h. Purification on silica gel (25:1 pentanes: Et_2O, $KMnO_4$ stain) afforded 113.7 mg of product (0.51 mmol, 85%) as a yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.93 (q, *J* = 7.8 Hz, 1H), 2.97 – 2.89 (m, 1H), 2.77 – 2.67 (m, 1H), 2.32 – 2.22 (m, 1H), 2.11 – 2.04 (m, 2H), 1.93 – 1.80 (m, 2H), 1.70 – 1.59 (m, 1H), 1.53 (dddt, *J* = 17.3, 12.8, 8.5, 4.8 Hz, 2H), 1.19 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 178.4, 77.1, 38.8, 38.5, 36.1, 29.6, 28.7, 27.2, 24.7, 16.3. **HRMS** (EI) calculated for $[C_{12}H_{20}O_2 + H]^+$ requires *m/z* 197.1536, found *m/z* 197.1536.



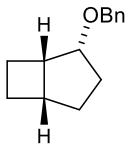
((Bicyclo[3.2.0]heptan-2-yl)oxy)triethylsilane (3.35). Prepared according to the general procedure with **S14** (0.2 mmol, 45 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 1 mg), $AgSbF_6$ (0.005mmol, 45 mg), and Et_2O (8 mL). Irradiation time = 1 h. NMR yield (80%, 2:1 d.r., 0.279 mmol), internal standard (10 µL of 1-methylnapthalene). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **Major Diastereomer ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.13 (dt, *J* = 10.2, 6.4 Hz, 1H), 2.68 – 2.55 (m, 2H), 2.30 – 2.16 (m, 1H), 2.07 – 1.93 (m, 2H), 1.91 – 1.75 (m, 2H), 1.61 – 1.42 (m, 2H), 1.39 (dd, *J* = 13.0, 6.7 Hz, 1H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.56 (qd, *J* = 7.9, 2.2 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 75.4, 40.8, 36.1, 32.0, 29.6, 24.9, 16.3, 6.8, 4.8. **HRMS** (EI) calculated for $[C_{13}H_{26}OSi + H]^+$ requires *m/z* 227.1826, found *m/z* 227.1825. Purification of minor diastereomer away from the mixed proved to be challenging, and only the major diastereomer was fully characterized.



2-(Methoxymethoxy)bicyclo[3.2.0]heptane (3.36). Prepared according to the general procedure with **S15** (0.3 mmol, 47 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.2 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 3 h. NMR yield (77%, 6:1 d.r., 0.279 mmol), internal standard (10 µL of 1-methylnapthalene). Purification on silica gel (20:1 pentanes:Et_2O, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.62 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.01 (dt, *J* = 9.7, 7.1 Hz, 1H), 3.35 (s, 3H), 2.87 – 2.78 (m, 1H), 2.72 – 2.64 (m, 1H), 2.33 – 2.21 (m, 1H), 2.09 – 1.84 (m, 4H), 1.64 – 1.42 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 95.8, 80.2, 55.3, 38.6, 35.9, 29.5, 29.3, 24.9, 16.5. **HRMS** (EI) calculated for $[C_9H_{16}O_2 + H]^+$ requires *m/z* 157.1223, found *m/z* 157.1224.



Allyl-(bicyclo[3.2.0]heptan-2-yl) carbonate (3.37). Prepared according to the general procedure with **S16** (0.6 mmol, 117.6 mg), $[Cu(COD)Cl]_2$ (0.006 mmol, 2.5 mg), $AgSbF_6$ (0.06 mmol, 20.6 mg), and Et_2O (24 mL). Irradiation time = 4 h. Purification on silica gel (25:1 pentanes: Et_2O, $KMnO_4$ stain) afforded 100.2 mg of product (0.51 mmol, 85%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.94 (ddt, *J* = 16.5, 10.2, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.91 (dt, *J* = 9.1, 7.5 Hz, 1H), 4.61 (dd, *J* = 5.7, 1.5 Hz, 2H), 2.96 (p, *J* = 7.1 Hz, 1H), 2.72 (ddd, *J* = 11.5, 9.4, 5.7 Hz, 1H), 2.29 (dq, *J* = 12.6, 9.2 Hz, 1H), 2.16 (ddd, *J* = 11.3, 9.2, 5.4 Hz, 2H), 1.93 (td, *J* = 9.1, 8.5, 7.1 Hz, 2H), 1.66 (tt, *J* = 12.1, 7.5 Hz, 1H), 1.60 – 1.49 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 131.7, 118.8, 81.0, 68.2, 38.3, 35.9, 29.5, 28.6, 24.6, 16.4. **HRMS** (EI) calculated for $[C_{11}H_{16}O_3 + H]^+$ requires *m/z* 197.1172, found *m/z* 197.1171.



2-(Benzyloxy)bicyclo[3.2.0]heptane (3.38). Prepared according to the general procedure with **S17** (0.3 mmol, 61.3 mg), $[Cu(COD)Cl]_2$ (0.003 mmol, 1.3 mg), $AgSbF_6$ (0.03 mmol, 10.3 mg), and Et_2O (12 mL). Irradiation time = 5 h, NMR yield (65%, 0.188 mmol), internal standard (19.2 mg TMS-Ph). Purification on silica gel (20:1 pentanes:CH_2Cl_2, I_2 stain) afforded product for characterization as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 4.39 (q, *J* = 11.7 Hz, 2H), 3.91 (dt, *J* = 10.1, 6.9 Hz, 1H), 2.84 (ddd, *J* = 12.1, 9.7, 5.9 Hz, 1H), 2.73 – 2.65 (m, 1H), 2.27 (tdd, *J* = 11.8, 9.3, 6.7 Hz, 1H), 2.09-1.99 (m, 3H), 1.88 (tdd, *J* = 11.9, 9.1, 6.2 Hz, 1H), 1.61 – 1.48 (m, 2H), 1.48 – 1.41 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.9, 128.3, 127.7, 127.4, 81.8, 71.4, 38.1, 36.1, 29.6, 29.4, 24.8, 16.0. **HRMS** (EI) calculated for $[C_{14}H_{18}O + H]^+$ requires *m/z* 203.1430, found *m/z* 203.1428.

Comparison: Prepared according to CuOTf comparison procedure with S15 (0.3 mmol, 61.3 mg), $[CuOTf]_2$ C_6H_6 (0.003 mmol, 1.5 mg), and Et_2O (12 mL). Irradiation time = 5 h, NMR yield (No product; only alkene-based decomposition products), internal standard (22.9 mg TMS-Ph).

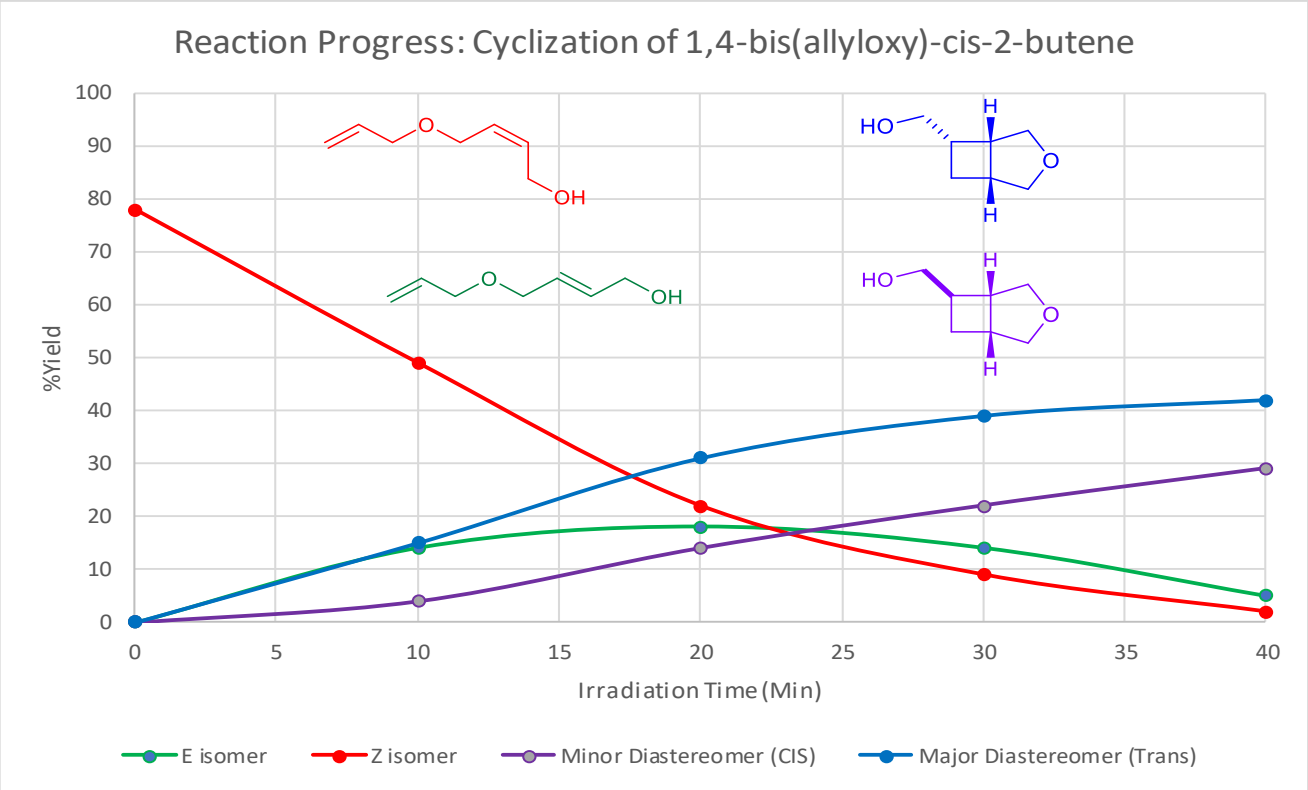
3.5.4 E/Z Isomerization Study

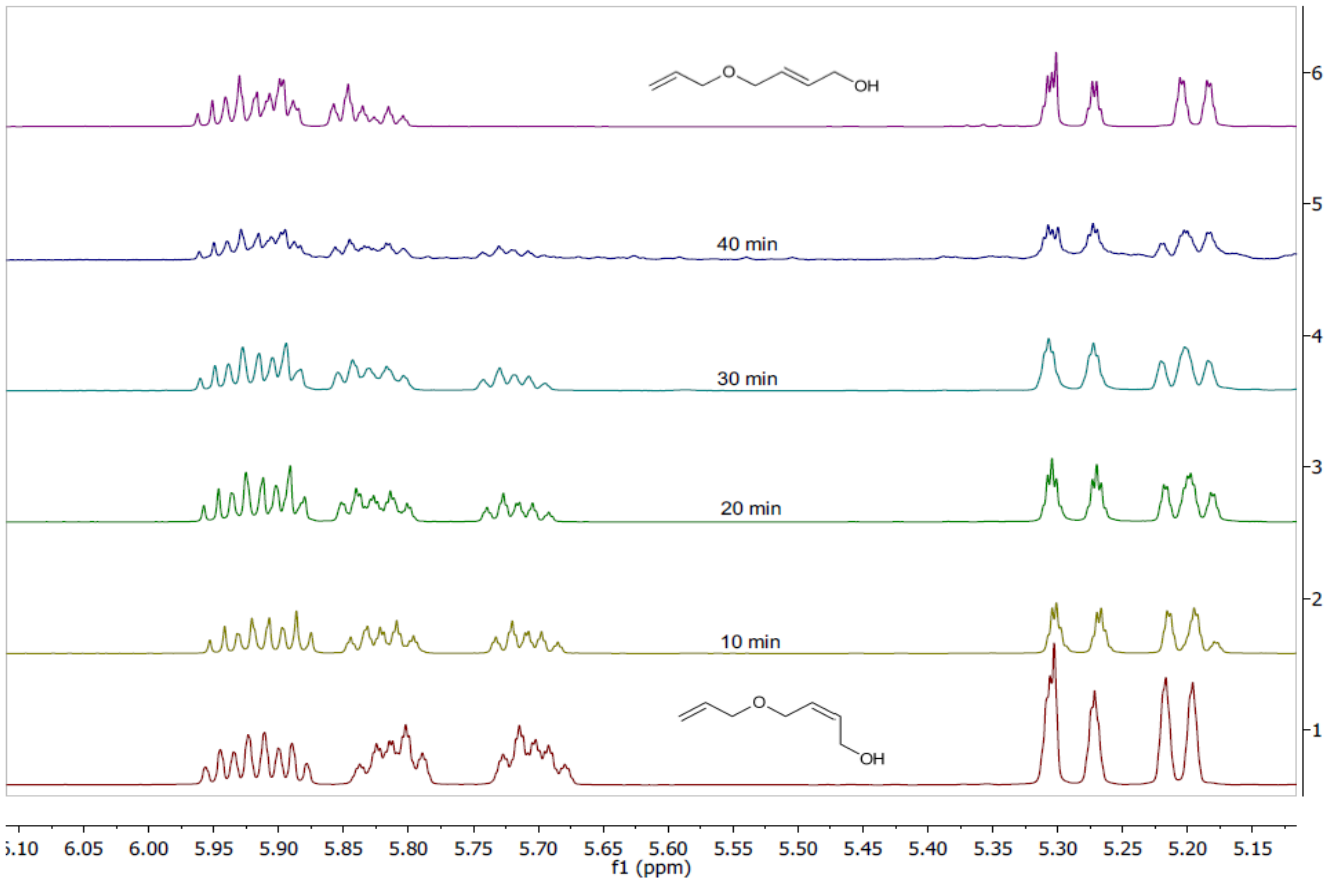
3.39 **3.40**

1 hr: 84% 2.8:1 dr

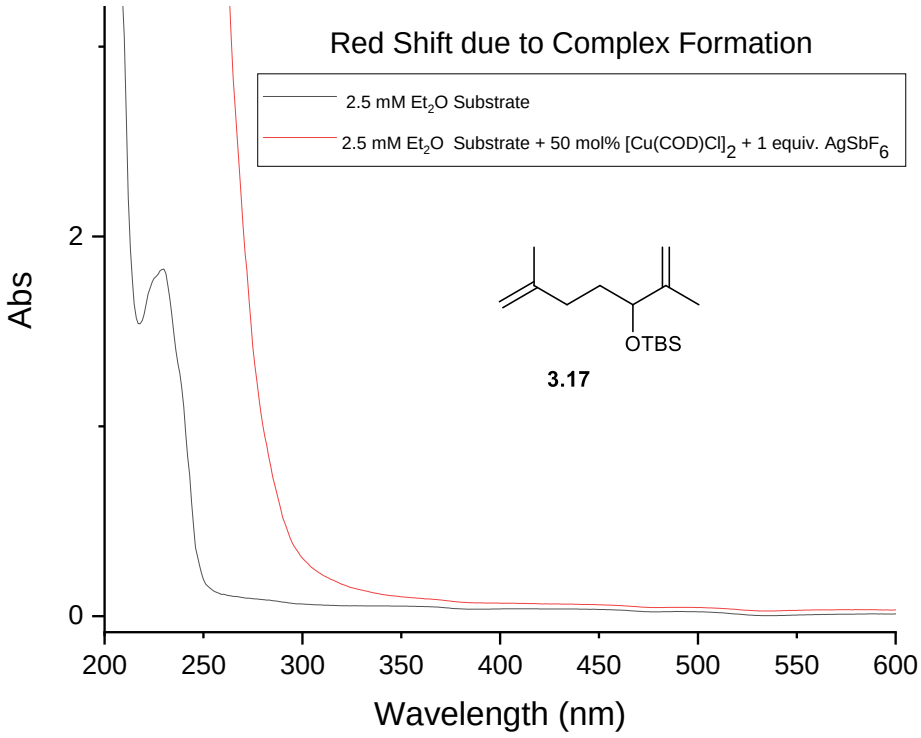
30 min: 61% 3.4:1 dr RSM: E= 19% Z=9%

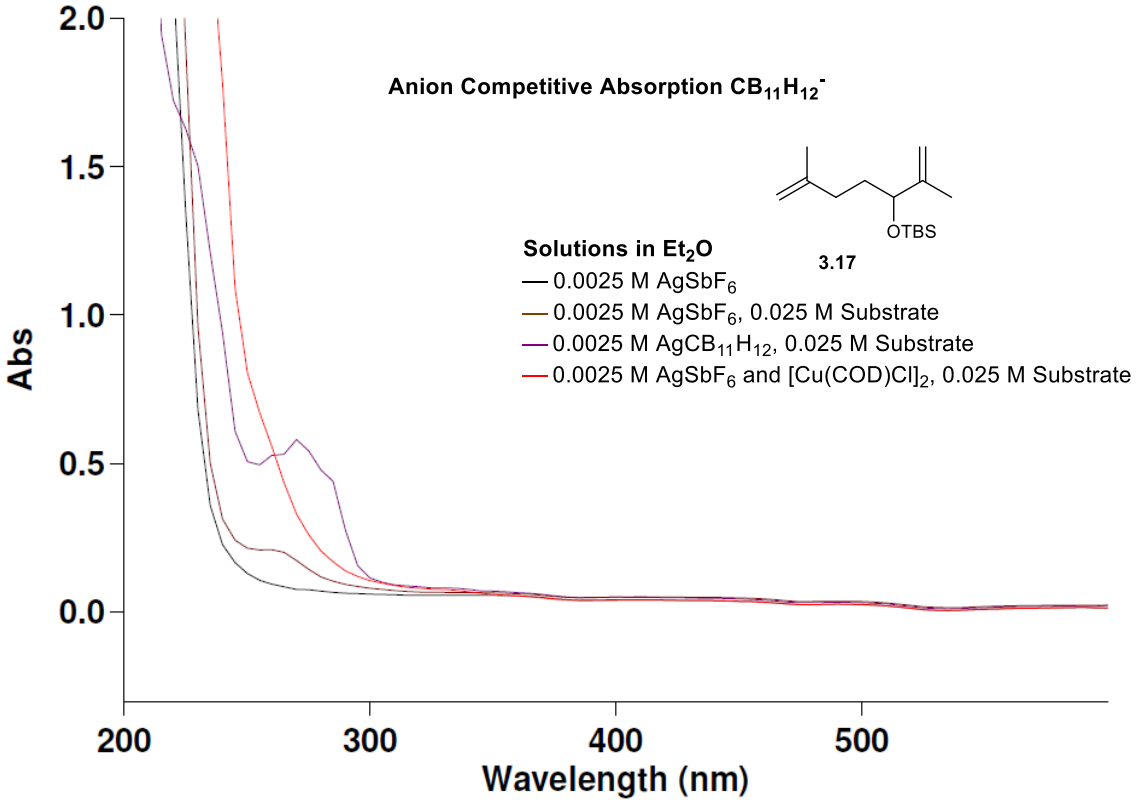
Prepared according to the general procedure with **26** (0.2 mmol, 25.6 mg), $[Cu(COD)Cl]_2$ (0.002 mmol, 0.8 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), and Et_2O (12 mL). **Experiment 1**: Irradiation time = 1 h. NMR yield (84%, 0.14 mmol, 2.8:1 dr), internal standard (22.6 mg TMS-Ph). **Experiment 2**: Irradiation time = 0.5 h. NMR yield (61%, 0.14 mmol, 3.4:1 dr), internal standard (22.6 mg TMS-Ph). ^{1}H NMR (500 MHz, Chloroform-*d*). Diastereomers were separated on silica gel (4:1 Pentanes: Acetone) with the major diastereomer eluting second. **Major Diastereomer: ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.88 (dd, *J* = 12.5, 9.2 Hz, 2H), 3.66 (tt, *J* = 10.8, 7.9 Hz, 2H), 3.50 (ddd, *J* = 9.1, 5.4, 3.4 Hz, 2H), 2.86 (ddd, *J* = 13.4, 8.3, 5.3 Hz, 1H), 2.68 (dt, *J* = 8.5, 5.0 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.88 – 1.75 (m, 2H), 1.32 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 74.5, 74.0, 66.8, 41.7, 39.1, 35.8, 26.4. **Minor Diastereomer: ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.16 (d, *J* = 10.1 Hz, 1H), 3.80 (d, *J* = 9.1 Hz, 1H), 3.70 – 3.62 (m, 2H), 3.41 (dt, *J* = 10.1, 6.3 Hz, 2H), 3.01 (q, *J* = 7.7 Hz, 1H), 2.91 (tt, *J* = 8.1, 5.4 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.24 (dddd, *J* = 12.3, 10.4, 8.7, 1.5 Hz, 1H), 1.77 (s, 1H), 1.49 (ddd, *J* = 12.9, 7.4, 6.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 74.2, 69.2, 62.4, 39.8, 35.7, 33.8, 26.4. **HRMS** (EI) calculated for $[C_7H_{12}O_2 + H]^+$ requires *m/z* 129.0910, found *m/z* 129.0910.


Reaction Progress: Cyclization of 1,4-bis(allyloxy)-cis-2-butene
%Yield
Irradiation Time (Min)
E isomer
Z isomer
Minor Diastereomer (CIS)
Major Diastereomer (Trans)

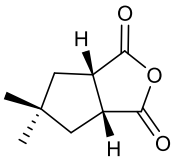

40 min
30 min
20 min
10 min
f1 (ppm)

3.5.5 UV-Vis Studies

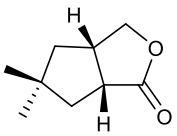




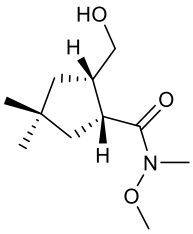
3.5.6 Sulcatine G and Perforatol Cores Experimentals



5,5-Dimethyltetrahydro-1H-cyclopenta[c]furan-1,3(3aH)-dione (3.46) Prepared using previously known procedures via a 4-step protocol from 4,4-dimethylcyclohexanone involving a Favorskii rearrangement and dehydration of the resulting diacid. All spectral data matched those previously reported.[21]

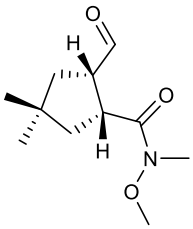


5,5-Dimethylhexahydro-1H-cyclopenta[c]furan-1-one (3.47) $NaBH_4$ (48.3 mmol, 1.83g) was dispensed into a flame-dried 250 mL round-bottomed flask containing THF (10 mL). The reaction was placed under N_2, cooled to 0 °C, and treated slowly via syringe with a solution of anhydride **3.46** in THF (40 mL). The reaction was warmed to rt and stirred under N_2 for 6 h. The reaction was then cooled back to 0 °C and treated dropwise with 6 M HCl (20 mL). Once quenched, the reaction mixture was partially concentrated *in vaccuo*, then extracted with Et_2O. The extracted organics were washed sequentially with H_2O, $NaHCO_3$ (aq), and brine. The organics were then dried over $MgSO_4$, filtered, and concentrated to yield lactone (4.67g, 63%) as a clear yellow oil that was taken on to the next step without further purification. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.43 (dd, *J* = 9.3, 7.1 Hz, 1H), 4.10 (dd, *J* = 9.3, 2.1 Hz, 1H), 3.11 – 3.01 (m, 2H), 1.93 (ddd, *J* = 13.3, 9.7, 1.6 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.79 (dd, *J* = 13.4, 4.8 Hz, 1H), 1.40 (dd, *J* = 12.8, 7.8 Hz, 1H), 1.08 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 181.4, 72.7, 47.4, 44.3, 43.7, 41.7, 39.6, 28.3, 28.1. **IR** (cm^{-1}) 2954, 2868, 1758, 1464, 1369, 1306, 1164, 1124. **HRMS** (EI) calculated for $[C_9H_{14}O_2 + H]^+$ requires *m/z* 155.1067, found *m/z* 155.1065.

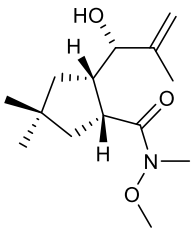


2-(Hydroxymethyl)-*N*-methoxy-*N*,4,4-trimethylcyclopentane-1-carboxamide (3.48). A solution of **3.47** (4.61g, 30.3mmol) and *N,O*-dimethylhydroxylamine hydrochloride (4.73 g, 48.5 mmol) in DCM (150 mL) was placed under N_2 and cooled to 0 ºC. The reaction was then treated dropwise

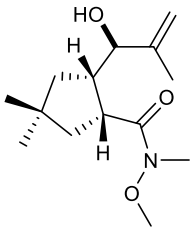
with 2 M solution *i*-propylmagnesium chloride in THF (45.5 mL, 53.2 mmol) over approx. 15 min. The reaction was stirred a further 45 min at rt then quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and reconstituted to give crude desired product. Purification on silica gel (1:1 Hexane: EtOAc) afforded **3.48** (5.88g, 90%) as a clear yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.73 (s, 3H), 3.56-3.48 (m, 3H), 3.21 (s, 3H), 2.88 (t, *J* = 6.2 Hz, 1H), 2.56 (qt, *J* = 8.3, 5.0 Hz, 1H), 1.91 (t, *J* = 11.8 Hz, 1H), 1.59 – 1.52 (m, 2H), 1.14 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.2, 63.9, 61.7, 44.5, 43.8, 43.0, 41.3, 38.3, 32.4, 29.4, 28.6. **HRMS** (EI) calculated for $[C_{11}H_{21}NO_3 + H]^+$ requires *m/z* 216.1594, found *m/z* 216.1593.



2-Formyl-*N*-methoxy-*N*,4,4-trimethylcyclopentane-1-carboxamide (3.49). To a solution of **3.48** (1.09 g, 5.1 mmol) in CH_2Cl_2 (30 mL) was added pyridine (3.3 mL, 40.5 mmol) followed by addition of Dess–Martin periodinane (2.57g, 6.07 mmol) in one portion. The reaction was placed under N_2 and stirred for 3 h at room temperature. The reaction was then concentrated removing all DCM and some pyridine. Passing through a celite plug with hexanes removed DMP byproducts. Concentration *in vaccuo* gave largely clean desired product (995mg, 92%) that was used without further purification due to this compound's sensitivity to acid catalyzed epimerization on silica. **^{1}H NMR** (500 MHz, Benzene-d_6) δ 9.76 (d, *J* = 2.4 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.03 (s, 3H), 2.81 (s, 3H), 2.72 (q, *J* = 8.9, 8.3 Hz, 1H), 1.98 – 1.93 (m, 1H), 1.91 (dd, *J* = 12.9, 10.0 Hz, 1H), 1.55 (dd, *J* = 12.9, 8.5 Hz, 1H), 1.36 (ddt, *J* = 12.8, 7.8, 1.2 Hz, 1H), 0.98 (s, 3H), 0.74 (s, 3H). **^{13}C NMR** (126 MHz, C_6D6) δ 201.0, 174.5, 128.0, 71.3, 60.4, 52.7, 44.4, 42.8, 41.1, 38.7, 28.7, 28.0. **HRMS** (EI) calculated for $[C_{11}H_{19}NO_3 + H]^+$ requires *m/z* 214.1438 found *m/z* 214.1437.



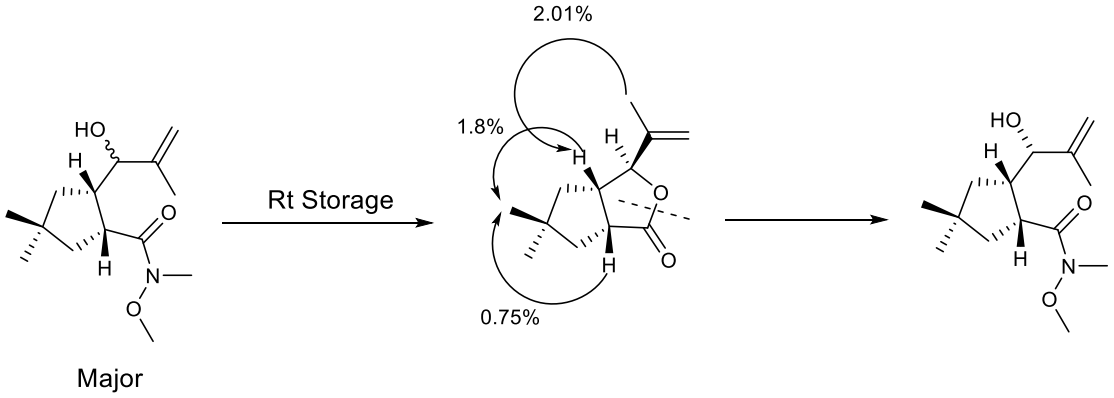
Major

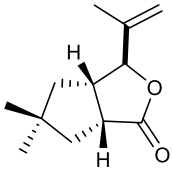


Minor

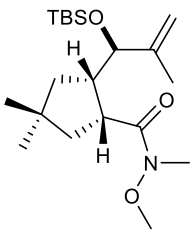
2-(1-Hydroxy-2-methylallyl)-*N*-methoxy-*N*,4,4-trimethyl-cyclopentane-1-carboxamide (3.50) A solution of **3.49** (995 mg, 4.7 mmol) in THF (50 mL) was placed under N_2, cooled to 0 °C and treated dropwise over 10 min with 0.5 M isopropenyl magnesium bromide solution (9.7 mL, 4.9 mmol). The reaction was monitored by TLC until full consumption of aldehyde (approx. 30 min). Upon completion, the reaction was quenched with saturated NH_4Cl solution, extracted with Et_2O, dried with $MgSO_4$, filtered and concentrated to give a crude mixture of diastereomers (1.5:1 d.r.). Purification on silica gel (4:1 Hexane: EtOAc) afforded **3.50** (202.3 mg (17% minor): 323.9 mg (27% major), Overall 44%) as a clear yellow oil, eluting the desired minor diastereomer first. **Minor Diastereomer ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.02 (dt, *J* = 2.3, 1.2 Hz, 1H), 4.82 (dt, *J* = 2.6, 1.4 Hz, 1H), 4.05 (s, 1H), 3.83 (d, *J* = 2.6 Hz, 1H), 3.73 (s, 3H), 3.61 (td, *J* = 11.3, 6.9 Hz, 1H), 3.24 (s, 3H), 2.64 (q, *J* = 10.4 Hz, 1H), 1.89 (t, *J* = 12.0 Hz, 1H), 1.83 (dd, *J* = 13.0, 9.2 Hz, 1H), 1.70 – 1.67 (m, 3H), 1.53 (ddd, *J* = 12.2, 7.1, 1.8 Hz, 1H), 1.34 (ddd, *J* = 13.0, 8.3, 1.8 Hz, 1H), 1.14 (s, 3H), 0.99 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.5, 145.3, 110.6, 74.1, 61.6, 45.4, 44.4, 41.6, 38.9, 38.2, 32.3, 29.0, 28.3, 20.0. **Major Diastereomer ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.91 (dt, *J* = 2.0, 0.9 Hz, 1H), 4.81 (p, *J* = 1.6 Hz, 1H), 4.09 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.72 (s, 3H), 3.53 (d, *J* = 9.4 Hz, 1H), 3.16 (s, 3H), 2.65 – 2.54 (m, 2H), 1.86 (dd, *J* = 12.8, 9.2 Hz, 1H), 1.71 (t, *J* = 1.2 Hz, 3H), 1.64 (ddd, *J* = 12.7, 7.9, 1.7 Hz, 1H), 1.54 (t, *J* = 11.8 Hz, 1H), 1.34 (ddd, *J* = 12.6, 7.2, 1.7 Hz, 1H), 1.12 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.89, 146.46, 112.64, 76.81, 61.64, 45.30, 45.20, 44.24, 39.64, 38.53, 32.54, 29.32, 28.46, 17.21. **IR** (cm^{-1}) 3431, 2951, 2866, 1770, 1644, 1463, 1445, 1385, 1368, 1328, 1251, 1183, 1117 **HRMS** (EI) calculated for $[C_{14}H_{25}NO_3 + H]^+$ requires *m/z* 256.1907, found *m/z* 256.1903. (Note: Trace peaks in the carbon spectra are a result of lactonization of the NMR sample prior to acquiring ^{13}C)

Stereochemistry Determination NOE on Cyclized Lactone



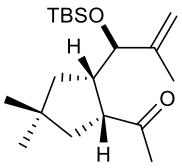


5,5-Dimethyl-3-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-1-one (S18). **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.00 (d, *J* = 1.4 Hz, 1H), 4.88 (d, *J* = 1.7 Hz, 1H), 4.58 (d, *J* = 2.9 Hz, 1H), 3.12 (td, *J* = 9.9, 6.1 Hz, 1H), 2.78 (qd, *J* = 8.2, 3.0 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.78 (dd, *J* = 13.4, 6.1 Hz, 1H), 1.74 (t, *J* = 1.1 Hz, 3H), 1.48 (dd, *J* = 12.9, 8.1 Hz, 1H), 1.10 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 180.8, 143.1, 111.6, 87.6, 47.7, 44.8, 44.4, 43.7, 41.7, 28.2, 28.0, 17.6. **HRMS** (EI) calculated for $[C_{12}H_{18}O_2 + H]^+$ requires *m/z* 195.1380, found *m/z* 195.1380.

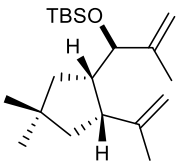


2-(1-((*tert*-Butyldimethylsilyl)oxy)-2-methylallyl)-N-methoxy-N,4,4-trimethyl-cyclopentane-1-carboxamide (3.51) A solution of **3.50** (190.2 mg, 0.74 mmol) in CH_2Cl_2 (1.5 mL) was placed under N_2, cooled to 0 °C, and treated sequentially with 2,6-lutadine (0.17 mL, 1.49 mmol) then TBSOTf (0.26 mL, 1.12 mmol). The reaction was then warmed to rt and stirred for 30 min. Upon completion, the reaction was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried with Na_2SO_4, filtered and concentrated. Purification on silica gel (9:1 Hexane:EtOAc) afforded **3.51** (204.2 mg, 75%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.75 – 4.67 (m, 2H), 4.39 (d, *J* = 9.6 Hz, 1H), 3.58 (s, 3H), 3.22-3.12 (m, 1H), 2.45 (dtd, *J* = 12.2, 9.1, 6.7 Hz, 1H), 1.84 (t, *J* = 12.1 Hz, 1H), 1.76 (ddd, *J* = 13.2, 9.0, 1.3 Hz, 1H), 1.71 – 1.63 (m, 5H), 1.11 (s, 3H), 1.03 (s, 3H), 0.86 (s, 9H),

0.05 (s, 3H), -0.02 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.1, 146.8, 112.8, 78.0, 61.2, 47.0, 46.3, 45.9, 39.4, 38.3, 31.8, 30.2, 30.0, 25.9, 18.2, 16.3, -4.6, -4.8. **IR** (cm^{-1}) 2953, 2930,2897,2858, 1775, 1719, 1662, 1462,1415,1385,1323, 1250,1175, 1108. **HRMS** (EI) calculated for $[C_{20}H_{39}NO_3Si + H]^+$ requires *m/z* 370.2772, found *m/z* 370.2769.

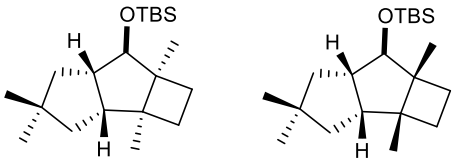


2-(1-((*tert*-Butyldimethylsilyl)oxy)-2-methylallyl)-4,4-dimethylcyclopentyl)ethan-1-one (3.52). A solution of **3.51** (400.5 mg, 1.08 mmol) in THF (10 mL) was placed under N_2, cooled to 0 °C, and treated dropwise with 3.0 M methyl magnesium bromide (0.83 mL, 2.49 mmol). The reaction was then warmed to rt and stirred for 3 h until complete by TLC. Upon completion, the reaction was quenched with saturated NH_4Cl solution , extracted with Et_2O, dried with $MgSO_4$, filtered and concentrated to afford **3.52** (345.5 mg, 99%) as a clear oil without further purification necessary. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.73 (dq, *J* = 2.9, 1.5 Hz, 1H), 4.66 (q, *J* = 1.1 Hz, 1H), 4.36 (d, *J* = 9.6 Hz, 1H), 2.85 (td, *J* = 8.4, 4.4 Hz, 1H), 2.35 (ddt, *J* = 12.1, 9.6, 7.2 Hz, 1H), 2.00 (s, 3H), 1.83 – 1.72 (m, 2H), 1.69 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.65 (dd, *J* = 12.1, 6.9 Hz, 1H), 1.53 (dd, *J* = 13.4, 4.5 Hz, 1H), 1.05 (s, 3H), 1.02 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), -0.02 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.2, 147.2, 113.0, 77.5, 51.6, 47.6, 45.2, 44.9, 38.2, 32.1, 30.8, 30.6, 25.9, 18.2, 16.2, -4.6, -4.8. **IR** (cm^{-1}) 2953, 2929, 2857, 1711, 1462, 1364, 1250, 1118, 1103. **HRMS** (EI) calculated for $[C_{19}H_{36}O_2Si + H]^+$ requires *m/z* 325.2557, found *m/z* 325.2555.



***tert*-Butyl((1-(4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylallyl)oxy) dimethylsilane (3.53).** To a suspension of Zn powder (333.5 mg, 5.1 mmol) and $PbCl_2$ (14.1mg, 0.051 mmol) in degassed THF (2.5 mL) under N_2 was added CH_2I_2 (0.21 mL, 2.55 mmol), and the reaction mixture was stirred at rt for 1 h. The reaction was then cooled to 0

°C and treated with a solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 0.51 mL, 0.51 mmol). The reaction was then warmed to rt and stirred for 2 h. The reaction was again cooled to 0 °C and treated with a solution of **3.52** (165 mg, 0.51 mmol) in degassed THF (2.5 mL), and the resulting solution was heated at 50 °C for 1 h. Upon completion, the reaction was quenched with saturated $NaHCO_3$ (6 mL) and filtered through a pad of Celite. To the filtrate was added saturated aqueous $Na_2S_2O_3$ solution (6 mL), and this mixture was extracted with Et_2O, dried with $MgSO_4$, filtered and concentrated. Purification on silica gel (100:1 Pentane: Et_2O) to afford product (151 mg, 92%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.79 (d, *J* = 2.0 Hz, 1H), 4.78 (t, *J* = 1.8 Hz, 1H), 4.70 (q, *J* = 1.7 Hz, 2H), 4.05 (d, *J* = 5.0 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.29 (qd, *J* = 8.3, 5.0 Hz, 1H), 1.82 (dd, *J* = 13.0, 7.9 Hz, 1H), 1.76 – 1.71 (s, 3H), 1.71 – 1.63 (m, 4H), 1.54 – 1.42 (m, 2H), 1.12 (s, 3H), 1.00 (s, 3H), 0.89 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.0, 146.0, 111.8, 111.6, 76.3, 48.4, 45.4, 45.2, 41.8, 36.9, 30.6, 30.2, 26.1, 23.6, 18.3, 17.9, -4.1, -4.5. **HRMS** (EI) calculated for $[C_{20}H_{38}OSi+ H]^+$ requires *m/z* 323.2765, found *m/z* 323.2761.

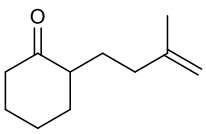


***tert*-Butyldimethyl((2a,4,4,6a-tetramethyldecahydrocyclobuta-[a]pentalen-6-yl)oxy)silane (3.54).** Prepared according to the general procedure with **S16** (0.25 mmol, 81 mg), $[Cu(COD)Cl]_2$ (2.5 mol%, 0.0075 mmol, 3.1 mg), $AgSbF_6$ (25 mol% 0.075 mmol, 25.8 mg), and Et_2O (12 mL). Irradiation time = 1 h. Analysis of the crude reaction showed full conversion to a 3:1 mixture of diastereomers. Purification of the crude on silica gel (100% Pentane) afforded **30** (76.7 mg, 3:1 d.r., 95%). **Major Diastereomer ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.90 (d, *J* = 4.3 Hz, 1H), 2.78 (ddt, *J* = 10.7, 7.2, 3.8 Hz, 2H), 2.38 – 2.30 (m, 1H), 2.29 – 2.20 (m, 1H), 1.65 – 1.59 (m, 1H), 1.52 – 1.47 (m, 1H), 1.43 – 1.38 (m, 1H), 1.33 (dd, *J* = 13.1, 6.8 Hz, 1H), 1.27 – 1.19 (m, 5H), 1.07 (s, 3H), 1.05 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.00 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 80.3, 58.2, 55.3, 47.7,

45.1, 44.7, 39.0, 34.5, 34.3, 29.4, 28.7, 26.0, 23.9, 21.3, 18.3, -4.7, -4.9. **Minor Diastereomer** **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.97 (d, *J* = 6.9 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.31 (ddd, *J* = 11.6, 10.0, 8.4 Hz, 1H), 1.88 (dt, *J* = 11.5, 8.7 Hz, 1H), 1.71 (ddd, *J* = 12.4, 8.3, 1.6 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.33 – 1.23 (m, 4H), 1.09 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.82 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 90.2, 54.8, 54.0, 51.8, 49.6, 47.7, 43.6, 41.3, 29.3, 28.2, 28.0, 26.9, 25.9, 23.5, 18.1, 15.7, -4.3, -4.4. **HRMS** (EI) calculated for $[C_{20}H_{38}OSi+ H]^+$ requires *m/z* 323.2765, found *m/z* 323.2764.

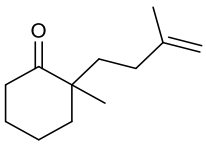
Comparison: Prepared according to CuOTf comparison procedure with **3.53** (0.1 mmol, 31 mg), $[CuOTf]_2$ C_6H_6 (0.0025 mmol, 1.5 mg), and Et_2O (8 mL). Irradiation time = 1 h, NMR yield **3.54** (49%, 2:1 d.r., 0.05 mmol), internal standard (17.9 mg TMS-Ph).

See Section 3.5.7 for NOE Analysis



2-(3-Methylbut-3-en-1-yl)cyclohexan-1-one (3.57). *n*-Buli (2.5 M in hexanes, 9.5 mL, 23.7 mmol) was added dropwise to a solution of diisopropylamine (3.6 mL, 25.7 mmol) in THF (30 mL) at 0 °C. The reaction was stirred 10 min, then warmed to rt and stirred for 20 min. The reaction was cooled back to 0 °C, 2-cyclohexylidene-1,1-dimethylhydrazine **3.55** (3.0 g, 21.5 mmol) was added, and the reaction was stirred 3 h more at rt. The reaction was then cooled back to 0 °C, 4-bromo-2-methylbut-1-ene **3.56** (3.8 g, 25.7 mmol) was added, and the reaction was stirred for 18 h slowly warming to rt. Upon completion, the reaction was diluted with Et_2O (20 mL) and poured into 40 mL of 2 M H_2SO_4 and 40 mL of Et_2O. The reaction was stirred 1 h, then extracted with Et_2O. The organics were washed with brine, dried over $MgSO_4$, filtered and reconstituted to yield crude product. Purification on silica gel (20:1 hexane:Et_2O) afforded **3.57** (2.79 g, 78%) as a pale yellow clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.70 (t, *J* = 1.8 Hz, 1H), 4.68 – 4.65 (m, 1H), 2.39 (dtd, *J* = 13.5, 4.1, 1.4 Hz, 1H), 2.35 – 2.22 (m, 2H), 2.17 – 2.07 (m, 1H), 2.08 – 1.92 (m, 4H), 1.91 – 1.80 (m, 1H), 1.71

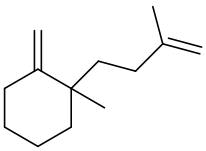
(d, *J* = 1.2 Hz, 3H), 1.70 – 1.61 (m, 2H), 1.45 – 1.35 (m, 1H), 1.35 – 1.24 (m, 1H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 213.2, 145.7, 110.0, 50.0, 42.1, 35.2, 34.0, 28.1, 27.2, 25.0, 22.4. **HRMS** (EI) calculated for $[C_{11}H_{18}O+ H]^+$ requires *m/z* 167.1430, found *m/z* 167.1429.



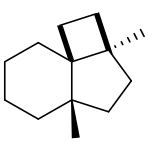
2-Methyl-2-(3-methylbut-3-en-1-yl)cyclohexan-1-one (3.59). $FeCl_3$ (1.44 g, 8.9 mmol) was dispensed into a dry 250 mL round-bottomed flask in a glovebox then capped under N_2 atmosphere. Solid was suspended in Et_2O (65 mL), cooled to 0 °C, treated with 3.0 M MeMgBr solution in Et_2O (8.9 mL, 26.7 mmol), then warmed to rt and stirred 1 h under N_2. **3.57** (1.34 g, 8.04 mmol) was then added as a solution in Et_2O (15 mL), and the reaction was stirred 15 min at rt. The reaction was then treated sequentially with TMSCl (3.4 mL, 26.7 mmol), Et_3N (3.8 mL, 27.6 mmol), and HMPA (1.55 mL, 8.9 mmol). The reaction was then stirred for 22 h at rt. Upon completion, the reaction was diluted with Et_2O, washed with $NaHCO_3$ (aq), dried over $MgSO_4$, filtered and concentrated to give crude silyl enol ether **3.58** (1.58 g, 82%) as a 9:1 mixture of regioisomers favoring the thermodynamic enolate, which was bought forward without further purification.

Silyl enol ether **3.58** (1.58g, 6.6 mmol) was dispensed into a 250 mL flame-dried round-bottomed flask with 45 mL of THF. The reaction was placed under N_2, cooled to 0 °C, and treated rapidly with 1.25 M MeLi (5.3 mL, 6.6 mmol). The reaction was stirred 15 min at 0 °C then cooled to –78 °C. Reaction was then treated rapidly with a solution of MeI (2.05 mL, 33 mmol) in 5.85 mL of HMPA. The reaction was then stirred at -78ºC for 30 min until complete by TLC. Reaction was then diluted with Et_2O and poured into DI H_2O and extracted with Et_2O. Organics were washed with brine, dried over $MgSO_4$, filtered, and reconstituted to give crude alkylation product. Purification on silica gel (40:1 pentane:Et_2O) afforded **3.59** (824.2 mg, 69%) as a clear colorless oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.70 (d, *J* = 2.0 Hz, 1H), 4.69 – 4.66 (m, 1H), 2.46 – 2.30 (m, 2H), 2.05 – 1.64 (m, 11H), 1.56 (dtd, *J* = 22.3, 12.9, 12.2, 4.7 Hz, 2H), 1.07 (s, 3H). **^{13}C**

NMR (126 MHz, $CDCl_3$) δ 215.8, 146.0, 109.7, 48.4, 39.4, 38.8, 35.7, 31.9, 27.5, 22.7, 22.5, 21.1. **HRMS** (EI) calculated for $[C_{12}H_{20}O+ H]^+$ requires *m/z* 181.1587, found *m/z* 181.1586.



1-Methyl-1-(3-methylbut-3-en-1-yl)-2-methylenecyclohexane) (3.60) To a suspension of Zn powder (2.16 g, 33 mmol) and $PbCl_2$ (61 mg, 0.22 mmol) in degassed THF (11 mL) under N_2 was added CH_2I_2 (1.33 mL, 16.5 mmol), and the reaction mixture was stirred at rt for 1 h. The reaction was then cooled to 0 °C and treated with a solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 3.3 mL, 3.3 mmol). The reaction was then warmed to rt and stirred for 1 h. The reaction was again cooled to 0 °C and treated with a solution of 2-methyl-2-(3-methylbut-3-en-1-yl)cyclohexan-1-one **3.59** (400 mg, 2.2 mmol) in degassed THF (11 mL), and the resulting solution was heated at 50 °C for 1 h. Upon completion, the reaction was quenched with saturated $NaHCO_3$ (6 mL) and filtered through a pad of Celite. To the filtrate was added saturated aqueous $Na_2S_2O_3$ solution (6 mL), this mixture was extracted with Et_2O, dried with $MgSO_4$, filtered and concentrated. Purification on silica gel (100% pentane) afforded 1-methyl-1-(3-methylbut-3-en-1-yl)-2-methylenecyclohexane) (327 mg, 83%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.83 (dt, *J* = 2.2, 1.1 Hz, 1H), 4.81 (d, *J* = 1.8 Hz, 2H), 4.71 – 4.68 (m, 1H), 2.14 – 2.02 (m, 2H), 1.99 – 1.80 (m, 3H), 1.68 (t, *J* = 1.0 Hz, 3H), 1.63 – 1.46 (m, 2H), 1.44-1.36 (m, 2H), 1.34 – 1.20 (m, 3H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 146.7, 109.8, 107.5, 41.0, 39.5, 35.8, 33.5, 32.7, 28.9, 25.7, 22.9, 22.3. **HRMS** (EI) calculated for $[C_{13}H_{22}+ H]^+$ requires *m/z* 179.1794, found *m/z* 179.1793.

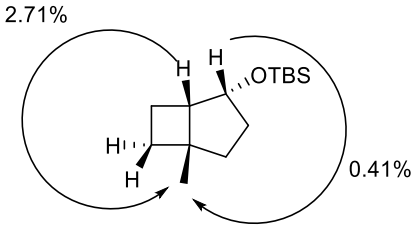


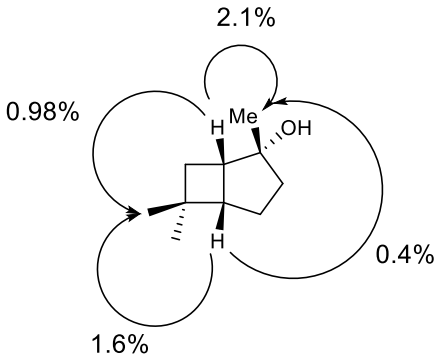
2a,4a-Dimethyldecahydrocyclobuta[c]indene (3.61) Prepared according to the general procedure with **3.60** (0.2 mmol, 18 mg), $[Cu(COD)Cl]_2$ (1 mol%, 0.002 mmol, 1.0 mg), $AgSbF_6$ (5 mol% 0.075 mmol, 25.8 mg), and Et_2O (8 mL). Irradiation time = 1 h. NMR yield (93%, 0.186 mmol), internal standard (10 µL 1-methylnapthalene 0.07 mmol). Purification of this product proved very difficult with both normal and reverse phase silica. A second experiment was run to complete conversion and NMR yield was not taken to give

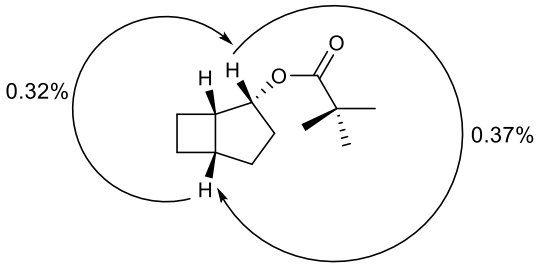
analytically clean product for characterization as a white solid single diastereomer after silica plug work up. ^{1}H NMR (500 MHz, Benzene-d_6) δ 1.87 – 1.73 (m, 3H), 1.71 – 1.59 (m, 2H), 1.51 (dd, J = 13.0, 7.8 Hz, 1H), 1.47 – 1.07 (m, 13H), 0.88 (s, 3H). ^{13}C NMR (126 MHz, C_6D6) δ 50.3, 45.0, 42.2, 38.1, 38.0, 34.2, 29.7, 28.1, 24.7, 24.3, 23.6, 21.1, 18.0. **HRMS** (EI) calculated for $[C_{13}H_{22}+ H]^+$ requires *m/z* 179.1794, found *m/z* 179.1794.

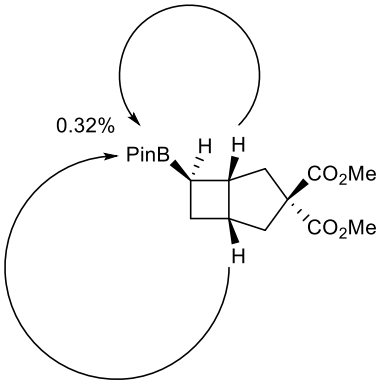
Comparison: Prepared according to CuOTf comparison procedure with **3.60** (0.2 mmol, 36 mg), $[CuOTf]_2$ C_6H_6 (0.002 mmol, 1 mg), and Et_2O (8 mL). Irradiation time = 1 hr, NMR yield **3.61** (46%, 0.09 mmol), internal standard (10 µL 1-methylnapthalene 0.07 mmol).

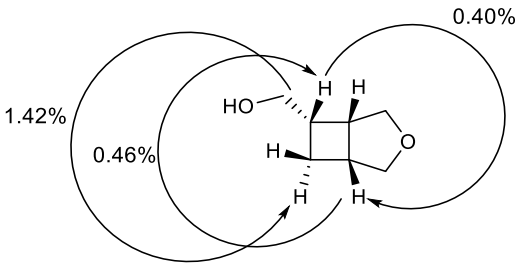
3.5.7: NOE Data







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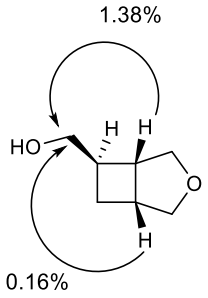
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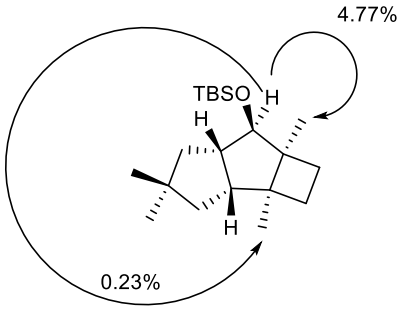
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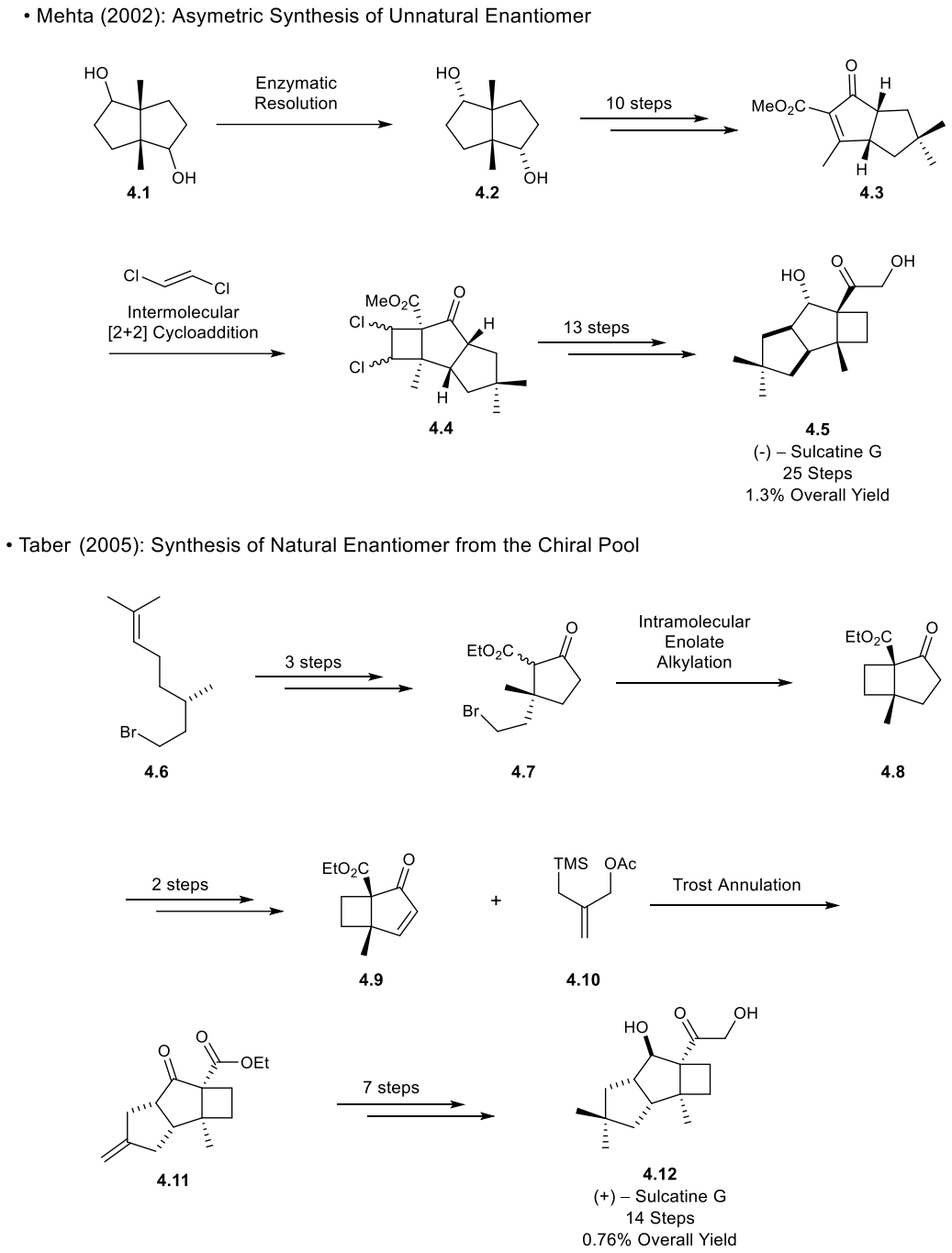
Chapter 4. Progress Toward a Concise Asymmetric Total Synthesis of (+) – Sulcatine G via Copper(I) Templated Intramolecular [2+2] Cycloaddition.

4.1 Introduction

Sulcatine G is a tricyclic sesquiterpene isolated from cultures of the Basidiomycetes fungus *Laurilia sulcata*.[1] Sulcatine G possesses an unusual *cis-anti-cis*-tricyclo[6.2.0.02,6]decane skeleton, which has drawn attention from the total synthesis community for the synthetic challenge of constructing this densely substituted multicyclic scaffold. A key feature of sulcatine G is the highly functionalized cyclobutane ring containing adjacent quaternary carbons. Previous syntheses have heavily relied on distinct cycloaddition strategies to individually form each ring of the core individually, requiring multiple steps and preinstallation of functional groups not present in the natural product (Scheme 4.1). Mehta and co-workers' synthesis of (−)–sulcatine G employed an enzymatic resolution of *endo,endo-cis*-bicyclo[3.3.0]octane-2,6-diol **4.1** to obtain the enantiopure core **4.2**, which was further elaborated to substrate **4.3** that would allow for installation of the cyclobutane. Intermolecular [2+2] cycloaddition with dichloroethylene stereoselectively forms the final cyclobutane ring, giving the fully formed core **4.4** which could be further elaborated to give the unnatural enantiomer (−)−sulcatine G **4.5** and confirming the absolute stereochemistry of the natural product.[2]

While [2+2] cycloaddition is an obvious disconnect, a very different approach was later taken by Taber and co-workers starting from (*S*)-(+)-citronellyl bromide **4.6**. Cyclopentane **4.7** can be accessed utilizing Taber's previously developed Rh-mediated intramolecular C−H insertion strategy. Intermolecular enolate alkylation of **4.7** forms the key cyclobutane core **4.8**, constructing the second of the three fused rings. Ensuing steps install the second cyclopentane ring by way of *exo*-face-selective Trost annulation between elimination product **4.9** and functionalized alkene **4.10,** giving the desired *cis-anti-cis*-tricyclo[6.2.0.02,6]decane skeleton **4.11**. Subsequent functional group conversions of **4.11** furnished natural product **4.12**. While relatively low yielding overall, Taber's synthesis is far more concise and is the sole report accessing the natural enantiomer (+)–sulcatine G.

Scheme 4.1 Previous Total Synthesis of Sulcatine G



While both syntheses represent elegant solutions for formation of the core of this natural product, a common feature of these two strategies is the sequential formation of each ring of the core, requiring the presence of functional groups to enable the key ring forming-steps that are not present in the natural product. Both assemble the core skeleton at an early phase of the synthesis, and most of the subsequent steps are redox manipulations required to furnish the peripheral functional groups of **4.5** and **4.12**. For example, in both synthesis the key full formed

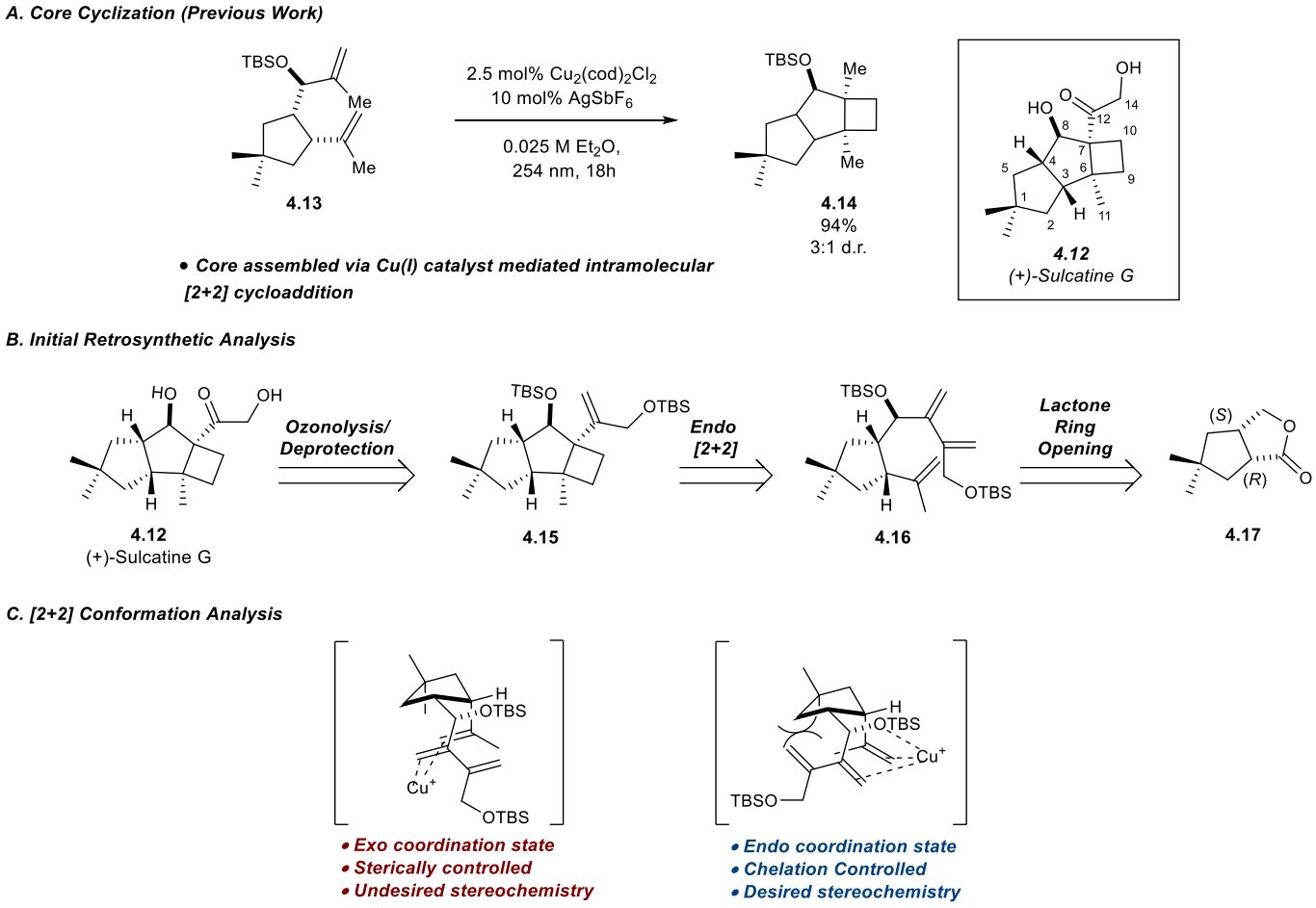
cores **4.4** and **4.11** are accessed as ketones, requiring reduction to the secondary alcohol displayed in the natural product. This reduction is not selective, as bulky reductants favor the incorrect diastereomer preventing steric control. Furthermore, both syntheses require multiple steps to access the α-hydroxy ketone moiety from a common ester intermediate.

4.2 Synthetic Analysis

We proposed a substantially different strategy towards (+)–sulcatine G involving a copper(I) catalyzed intramolecular [2+2] cycloaddition that would form two ring systems simultaneously in a stereoselective manner (Scheme 4.2). This strategy also requires no prefunctionalization as the cycloaddition occurs on simple olefin substrates.

One challenge of an intramolecular [2+2] cyclization strategy using the Salomon–Kochi reaction is the formation of the quaternary carbon centers at the C6−C7 cyclobutane ring junction.[2] Previously, this steric encumbrance would have prevented the use of the Salomon-Kochi intramolecular [2+2] cycloaddition as a key step, due to CuOTf's poor catalytic efficiency with sterically hindered substrates.[3] Recently, our group reported a new, more reactive catalyst system for the Salomon and Kochi [2+2] cycloaddition that displays greater steric tolerance due to the employment of a more weakly coordinating anion. This allowed for the cyclization of **4.13** to furnish the core of sulcatine G **4.14** in high yield favoring the desired *cis-anti-cis* stereochemistry, demonstrating the viability of the key cycloaddition (Scheme 4.2a).[4]

Scheme 4.2 Previous Model Substrate and Synthetic Analysis



Retrosynthetically, we proposed that copper-mediated [2+2] cycloaddition of 2-vinyl substituted 1,6-heptadiene **4.16** would yield *endo* diastereomer **4.15 (**Scheme 4.2B). The stereochemistry in this step would be controlled by copper complexation with the allylic alcohol. This chelation favors the sterically disfavored *endo* coordination geometry that yields the desired *cis-anti-cis*-tricyclo[6.2.0.02,6]decane skeleton **(**Scheme 4.2C).[3b] Chelation control of the stereochemical outcome is the crux of this synthetic strategy, as it not only sets the stereochemistry of the ring system but simultaneously sets the hydroxyl stereocenter at position C8. With the core of the natural product assembled, subsequent oxidation of the resulting 1,1-disubstituted **4.15** olefin by either ozonolysis or known dihydroxylation–elimination procedures to its corresponding ketone followed by global deprotection would give the natural product **4.12**

in just 2-3 steps after successful cyclization. We imagined **4.16** could be derived from ring-opening of enantiopure lactone **4.17** to obtain the required *cis*-stereochemistry on the cyclopentane ring.

This proposed cycloaddition would be a further challenge of our newly developed methodology. Not only is this the most hindered, conformationally constrained substrate attempted with this system, this would be the first instance of employing this method on a substrate containing an internal 1,3-diene that will undergo direct absorption at 254 nm. Furthermore, formation of the required ring system requires that the cycloaddition gives some amount of the *endo* product to obtain the unique *cis-anti-cis* stereochemistry. Previous studies conducted by Bach using CuOTf showed that without the allyic alcohol moiety *cis*-2-allyl-1-(2-propenyl)-substituted cyclopentanes proceed with high facial diastereoselectivities yielding the *cis-syn-cis* product.[5] However, the less hindered model substrate **4.13** bearing the coordinating allylic alcohol favoured the desired stereoisomer, suggesting that oxygen complexation can overcome the intrinsic steric bias against the desired diastereomer.[4]

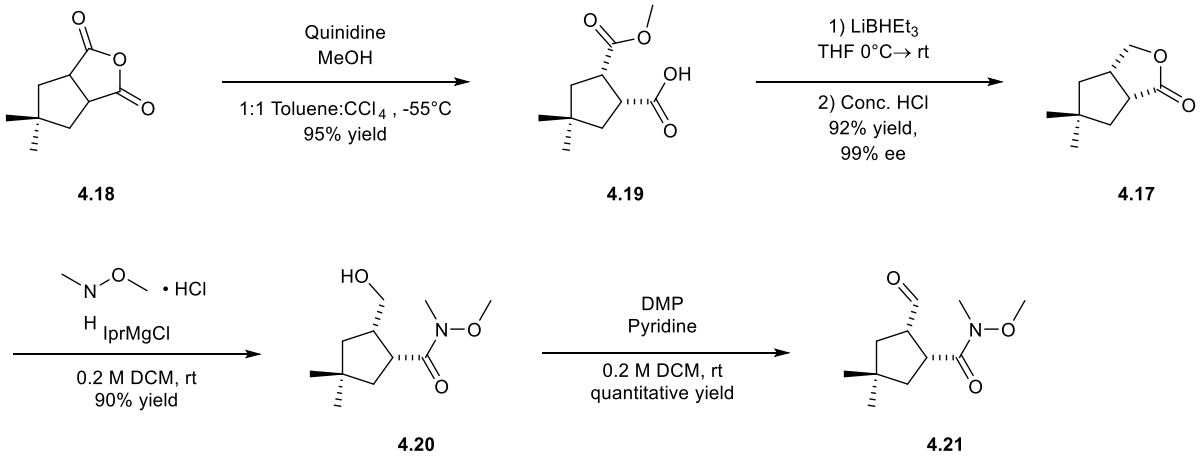
One potential concern initially overlooked when designing **4.16** as the cycloaddition precursor is the presence of a less hindered primary alcohol lacking in model substrate **4.13,** installed early in the synthesis to easy late stage access to the α-hydroxy ketone, could preferentially bind with the metal. This could potentially impact the rate Salomon previously demonstrated; coordination at that position should not result in productive reactivity because [2+2] cycloadditions of 1,7-octadienes are outside the scope of this reaction, due to misalignment of the alkenes preventing formation of the 2:1 alkene copper complex.[3b]

4.3 Results and Discussion

The first challenge of the synthesis was envisioned to be setting the unfavourable *cis*-stereochemistry displayed across the C3−C4 positions of the cyclopentane ring in **4.16** (Scheme

4.3). We began the synthesis from *cis*-anhydride **4.18**, easily prepared on 50 g scale using a Favorskii rearrangement sequence from 4,4-dimethyl cyclohexanone.[6] Asymmetric ring opening using Bolm's cinchona alkaloid desymmetrization[7] procedure yields hemiacetal **4.19**, which can be reduced with $LiBHEt_3$ followed by acid promoted cyclization[8b] to furnish enantiopure (*S*,*R*)-lactone **4.17** in high yield and enantioselectivity (92% yield, 99% ee). Catalytic procedures for desymmetrization developed by Deng and coworkers were also attempted but resulted in lower enantioselectivity.[8] Ring-opening of lactone **4.17** with the Weinreb amine as a soft nucleophile gave alcohol **4.20**, setting the unfavorable *cis* stereochemistry about the cyclopentane ring.[9] Subsequent pyridine-buffered Dess-Martin oxidation affords aldehyde **4.21**, which is primed for further elaboration. Non-buffered Dess−Martin conditions result in substantial epimerization to the *trans* product. It is important to note that aldehyde **4.21** is highly sensitive to both acid and base catalysed epimerization, which prevented silica chromatography purification and highly limited the reaction conditions that could be tolerated in the subsequent steps.

Scheme 4.3 Synthesis of Enantiopure cis – Cyclopentane Carboxaldehyde

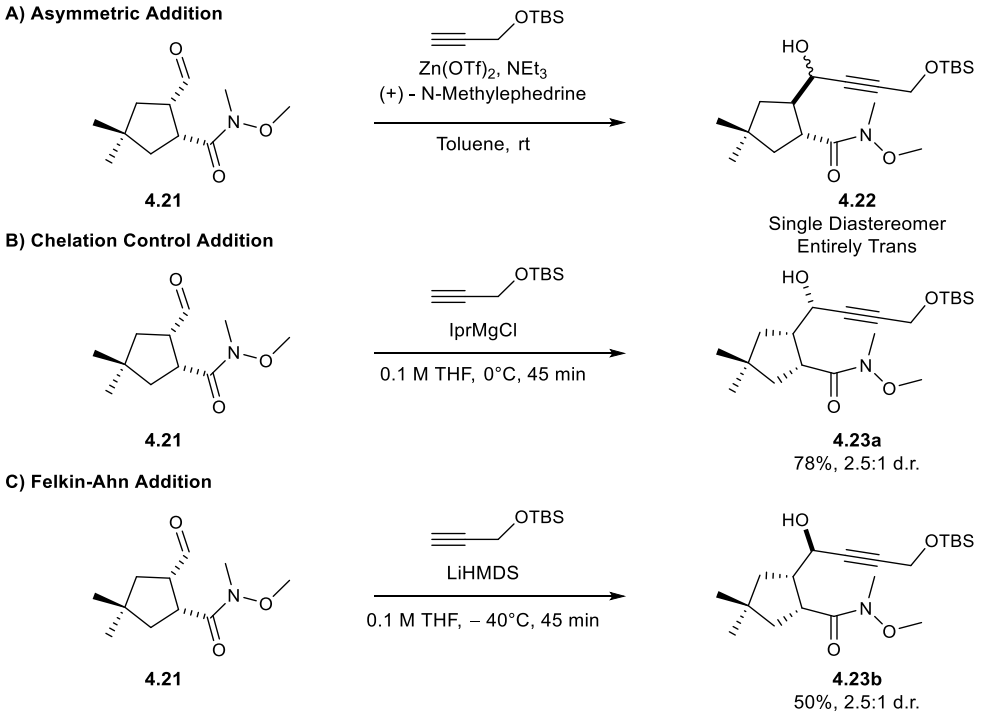


With the first challenge of setting the *cis*-stereochemistry on the first cyclopentane ring completed, we next explored strategies for installation of the 1,3-diene motif via aldehyde addition. We saw this motif as a retron for an intermolecular enyne metathesis from a

propargylic alcohol, as direct addition of a 1,3-diene coupling partner is far less developed in comparison with addition of terminal alkynes to aldehydes. However, a range of asymmetric alkyne addition conditions were attempted on aldehyde **4.21** to achieve selectivity for the desired Felkin–Anh diastereomer. Carreira's asymmetric alkyne addition using $Zn(OTf)_2$ seemed like a promising avenue as it has been shown to be highly selective for a single diastereomer in complex settings.[10] Unfortunately, these even mildly basic conditions led to complete epimerization to the *trans* cyclopentane ring prior to addition to give **4.22** (Scheme 4.4A).[11] Epimerization under Carriera conditions was later found to have been documented on a similar *cis*-cyclopentane carboxaldehyde scaffold.[12] Several BINOL-derived asymmetric conditions were also attempted, all either resulting in epimerization prior to addition or no addition to the aldehyde.[13]

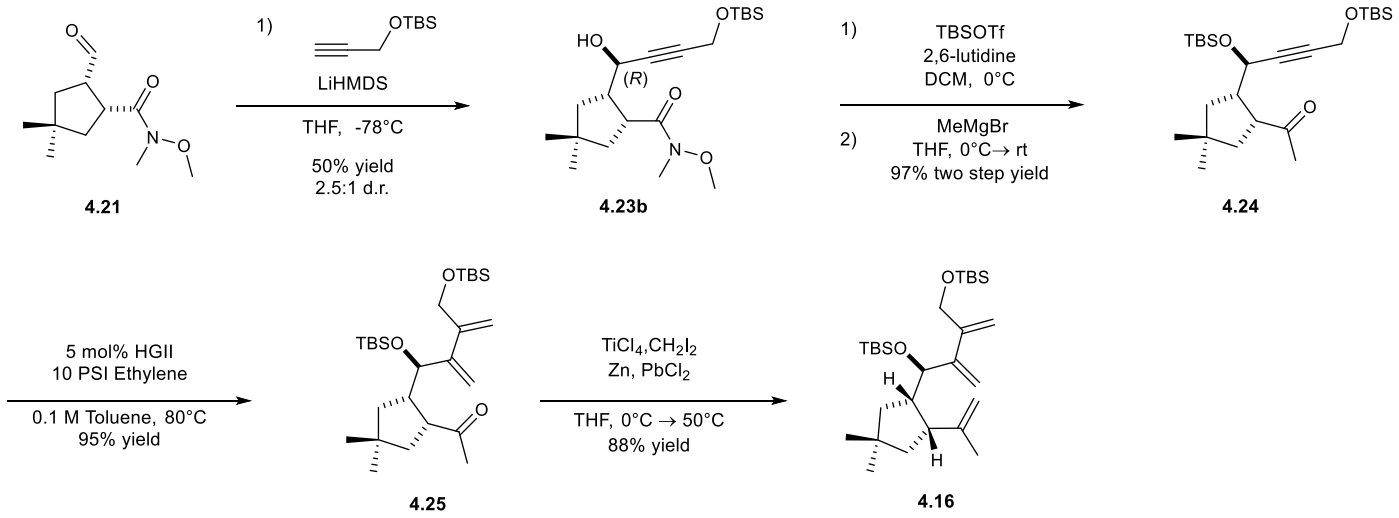
With asymmetric conditions exhausted, we turned to traditional organometallic alkynyl nucleophiles with hopes of achieving the desired selectivity by finding conditions favouring the Felkin–Anh product. Grignard-type nucleophiles were found to favor the undesired chelate control product **4.23a** (Scheme 4.4B). It was found the LiHMDS at low temperatures gave the desired addition product in modest yield favouring the requisite Felkin–Anh product **4.23b** 2.5:1(Scheme 4.4C). This product was found to be sensitive to lactonization upon storage; however, this enabled determination of the stereochemistry of the alkyne addition using NOE analysis on the rigidified lactone derived from the minor diastereomer (See section 4.5.2 for NOE Analysis).

Scheme 4.4 Optimization of Stereoselective Alkyne Addition and Stereochemical Determination



With conditions for a modestly selective alkyne addition yielding the correct diastereomer, the construction of cycloaddition precursor **4.16** proceeded as follows (Scheme 4.5). TBS protection of **4.23b** prevents lactonization and allows for clean methylation of the Weinreb amide with MeMgBr to give disubstituted alkyne **4.24**, which is poised to undergo enyne metathesis to generate the requisite 1,3-diene moiety. Being a very sterically hindered substrate for intermolecular enyne metathesis, this reaction required some optimization. Initial trials involving less reactive catalysts (GI, GII) showed little promise.[14] It was found that 1,3-diene **4.23** could be cleanly generated with the more activated Hoveyda–Grubbs second-generation catalyst[15] in toluene at elevated temperatures. Finally, non-basic Lombardo olefination yielded the proposed scaffold **4.16** without epimerization to trans as was observed with Wittig type procedures. With **4.16** in hand, we next tested the validity of the proposed key [2+2] cycloaddition step.

Scheme 4.5 Synthesis of [2+2] Precursor 4.16

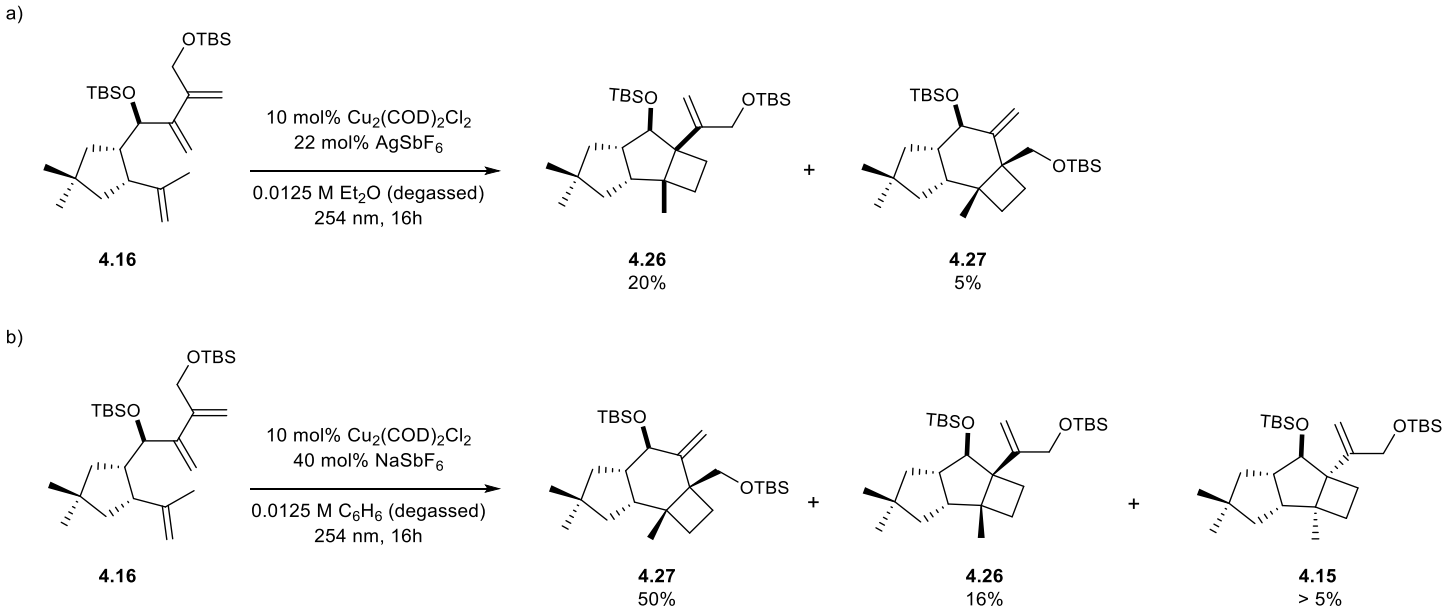


Cyclization of **4.16** under the previously developed conditions revealed some clear problems with the design of this scaffold (Scheme 4.6). Under typical ethereal conditions, large amounts of decomposition occurred resulting in low yields. This could be attributed to two different factors. Direct absorption by the 1,3-diene moiety may be leading to excited-state intermediates that result in substrate decomposition. Secondly, we proposed that silver-catalyzed processes, either thermal or photochemical in nature, could also be leading to the observed decomposition. Changing reaction conditions through substantial optimization, it was found that the overall yield could be increased by using benzene as the solvent to absorb short wavelengths (< 280 nm) and $NaSbF_6$ in place of the $AgSbF_6$ to eliminate the reactive silver cation in solution.

However, the more intractable issue was the selectivity of these reactions when compared to the model substrate. Ethereal conditions previously employed give almost solely the *exo* product **4.26**. Interestingly formation of the six-membered ring product **4.27** was observed. This was extremely surprising as Salomon has previously proposed that 1,6-heptadiene substitution patterns are required due to conformational alignment of the alkenes and other substitution patterns are too constraned to form the 2:1 alkene copper complex.[3b] Switching to the latter developed benzene/$NaSbF_6$ conditions, this unexpected six-membered

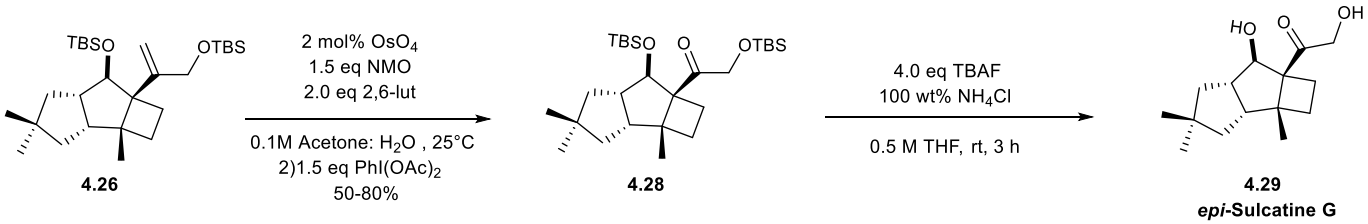
cycloadduct becomes the dominant product in much higher yield. One can only speculate as to the reason for this inversion in selectivity, but it may be related to an increased propensity for coordination with the allylic alcohols in less polar solvent, and coordination to the primary alcohol leads to unexpected six-membered ring product **4.27**. All conditions attempted on this scaffold resulted in at most trace yield of the desired *endo* product **4.15**.

Scheme 4.6 Key [2+2] Photocycloaddition of 4.16



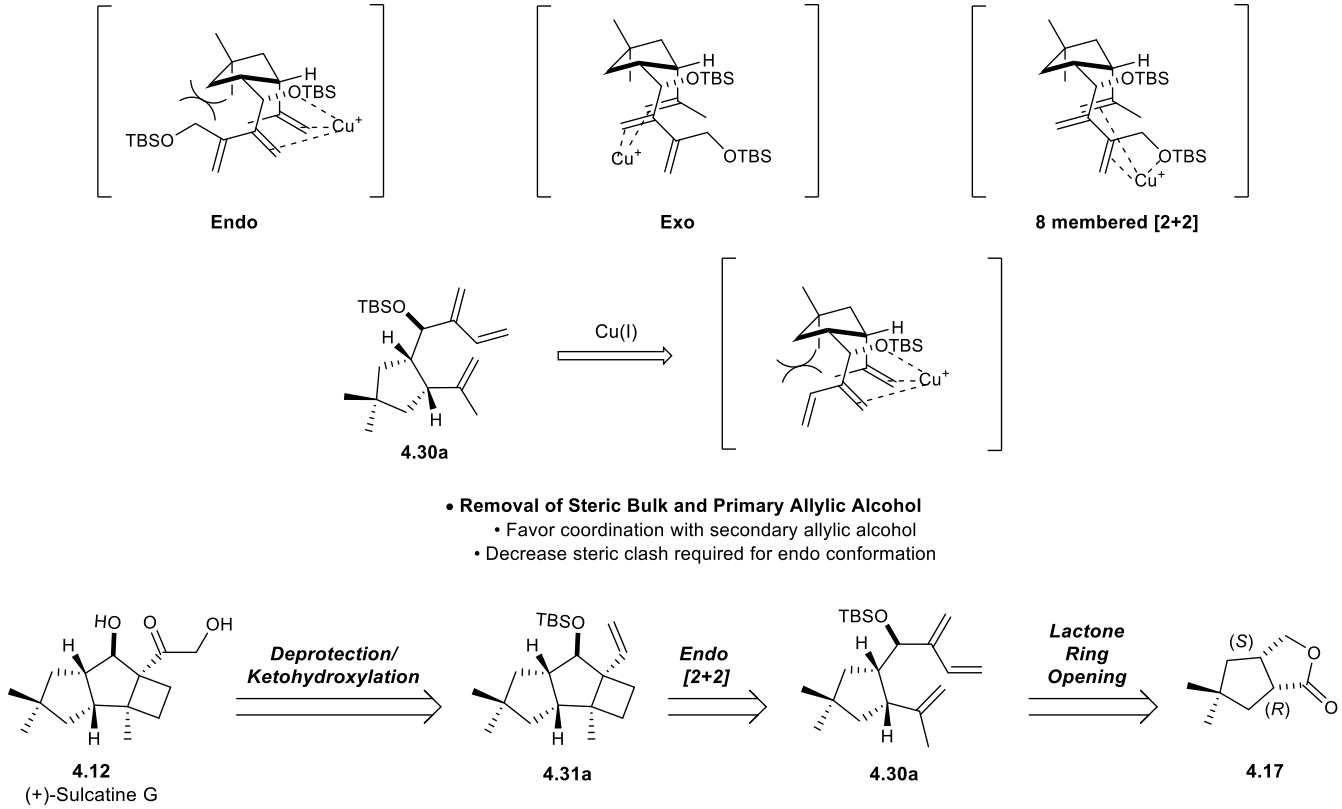
While the [2+2] cycloaddition reactions conducted on this scaffold were unsuccessful oxidation/ deprotection conditions were developed to access *epi*– Sulcatine G **4.29** (Scheme 4.7). One pot dihydroxylation/ elimination of **4.26** using Nicolaou's procedure[16] yielded protected α-hydroxy ketone **4.28** that could be globally deprotected using buffered TBAF conditions developed during Taber's synthesis of (+)-Sulcatine**Error! Bookmark not defined.** giving *epi* – sulcatine G **4.29** which was confirmed as the cis-syn-cis product by NOE analysis (See 4.5.2 for NOE analysis).

Scheme 4.7 Synthesis of *epi* – Sulcatine G



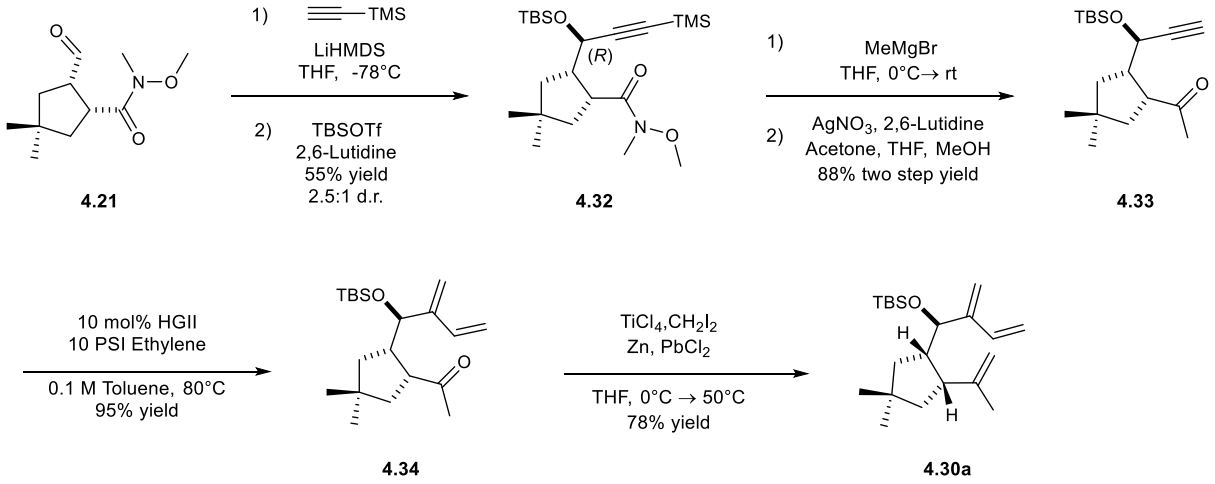
The results of this initially devised route lead us to believe that two major factors were inhibiting formation of the *endo* product. Steric bulk on the internal position of the 1,3−diene leads to substantial clash with the cyclopentane ring in the desired *endo* conformation. This overrides the stabilization arising from coordination with the secondary allylic alcohol, thus favoring the *exo* conformation. Second, the less sterically hindered primary allylic alcohol might preferentially coordinate and could be the reason the six membered ring is the favored conformation involving alcohol coordination rather than the *endo* conformation. With these hypotheses in mind, we proposed that removal of the CH_2OTBS group from the 1,3-diene would solve both problems by decreasing steric bulk in the transition state and removing the problematic coordinating alcohol (Figure 4.1). We then proposed a very similar retrosynthesis strategy to the generation one synthesis to access the new cycloaddition precursor **4.28a**. However**,** deprotection and ketohydroxylation of the resulting terminal alkene would furnish **4.12** from cycloadduct **4.29a**.

Figure 4.1 Conformational Analysis Cyclization of 4.14 and Proposed Structure Changes



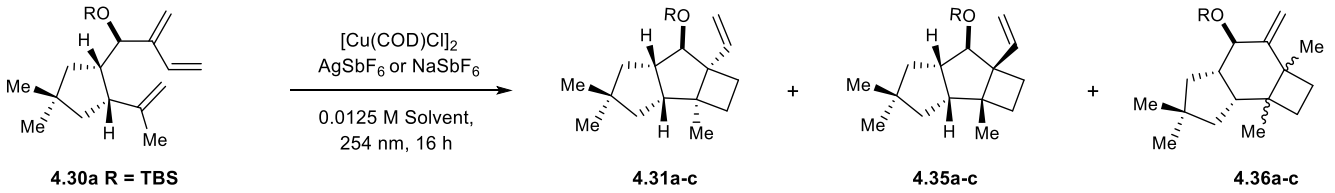
Synthesis of **4.30a** could be achieved using an almost identical strategy as employed for the synthesis of its counterpart **4.16** from aldehyde **4.21** (Scheme 4.8). Alkyne addition using the previously developed Felkin-selective conditions with TMS acetylene gave similar selectivity yielding **4.32** after *in-situ* TBS protection in modest yield and d.r. as an inseparable mixture of diastereomers. The free alcohol is substantially more prone to lactonization upon work up and purification than **4.23b**, and high yields were obtained *via* this *in situ* protection method. Methylation of the amide followed by silver mediated TMS cleavage[17] gave terminal alkyne **4.33.** It is worth noting here that standard K_2CO_3 conditions for TMS cleavage result in complete epimerization of the α–keto stereocenter, while TBAF conditions resulted in unselective cleavage of both silyl-protecting groups. Isolation of the major diastereomer and submitting to already optimized conditions for the enyne metathesis on **4.24** worked equally well on the terminal alkyne giving 1,3-diene **4.32** in high yield. Lombardo olefination furnishes **4.30a** in good yield again without any epimerization.

Scheme 4.8 Synthesis of 4.30a



With [2+2] precursor **4.30a** constructed, we next tested the cycloaddition under the two previously utilized systems studied with **4.14** (Table 4.1). Cyclization of **4.30a** under ethereal conditions, unfortunately, gave a low yield of the undesired *exo* product **4.35a** was the sole product (entry 1). The alternate benzene/$NaSbF_6$ conditions showed only slightly more positive results, yielding 8% of the desired product **4.31a**; however, *exo* product **4.35a** and six-membered cycloadduct **4.36a** are still the dominant products (entry 2). We proposed that increasing the coordinating ability of the allylic alcohol could enhance selectivity for the endo product. The more coordinating free alcohol **4.30b** and benzyl protected **4.30c** were found to be lower yielding and displayed similar diastereoselectivity favoring the undesired cycloadducts (entries 3 and 4).

Table 4.1 Key [2+2] Photocycloaddition of 4.5b-d



4.30a R = TBS
4.30b R = H
4.30c R = Bn

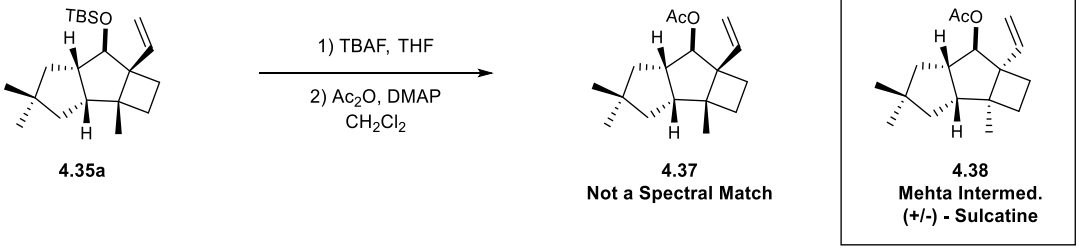
4.31a-c **4.35a-c** **4.36a-c**

Entry	Sub.	*[Cu] Loading*	*Anion Source*	*Solvent*	4.29a-c	*4.33a-c*	4.34a-c
1	4.30a	10 mol %	10 mol % AgSbF6	Et_2O	N.D.	20%	N.D.
2	4.30a	10 mol %	40 mol % NaSbF6	C_6H_6	8%	41%	25% > 20:1 d.r.
3	4.30b	10 mol %	40 mol % NaSbF6	C_6H_6	8%	20%	9% > 20:1 d.r.
4	4.30c	10 mol %	40 mol % NaSbF6	C_6H_6	2%	22%	20% > 20:1 d.r.

[a] Reactions conducted in quartz tubes equipped with a cold finger. Irradiation took place in a Rayonet RP-100 photoreactor with 254 nm bulbs. [b] NMR yields taken with TMS-Ph as internal standard.

Confirmation of the stereochemistry of the products **4.31a** and **4.35a** was achieved by spectral comparison with **4.38,** a previously reported intermediate in Mehta's synthesis of (+/-)–sulcatine (Scheme 4.9).[2b] TBAF deprotection of the major diastereomer **4.35a** followed by acetate protection with acetic anhydride furnished compound **4.37,** which upon comparison with known intermediate **4.38** displayed clear differences in coupling constants and chemical shifts confirming that **4.35a** is not the desired *endo* product. Furthermore, comparison of the spectra of **4.36** with **4.31b** gave a near-perfect spectral match for diagnostic downfield alkene protons suggesting **4.31a-c** are the desired endo products.

Scheme 4.9 Stereochemical Determination by Spectral Comparison



4.35a

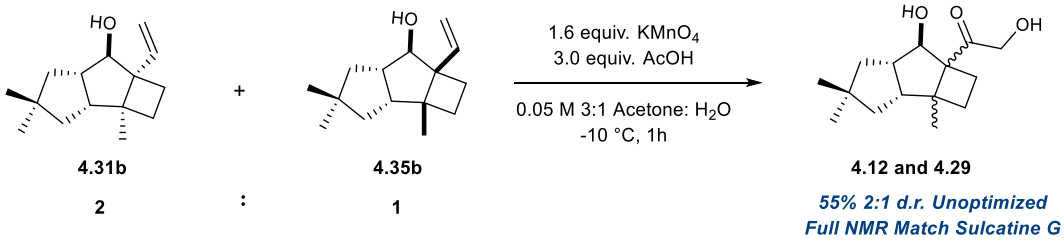
4.37
Not a Spectral Match

4.38
Mehta Intermed.
(+/-) - Sulcatine

.

The hypothesis about the stereochemistry of **4.31a-c** and **4.35a-c** was further confirmed by submitting a 2:1 mixture of the diastereomers **4.31b** and **4.35b** to $KMnO_4$-mediated ketohydroxylation[18] conditions resulting in a 2:1 mixture of **4.12** and **4.29**. The major diastereomer from this reaction gave a full NMR spectral match with the natural product (Scheme 4.10).

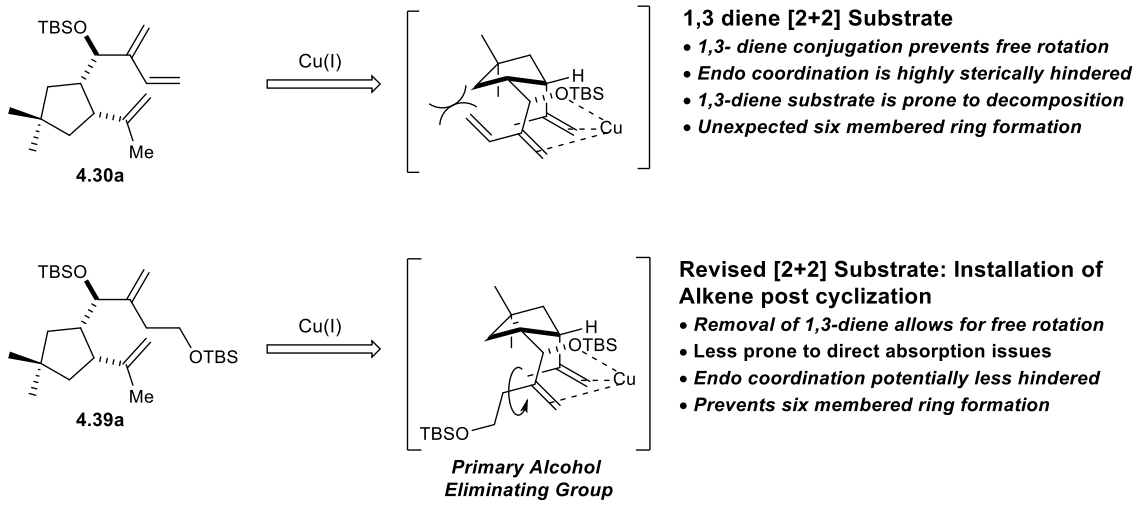
Scheme 4.10 Accessing Sulcatine as a Mixture of Diastereomers via Ketohydroxylation



While scaffold **4.30a** successfully allowed for access to sulcatine G, the key cycloaddition step does not give synthetically useful enough yields of the desired diastereomer for this to be a viable route to the natural product in comparison to other strategies. With the initial strategy of cyclization of a 1,3-diene being unsuccessful, we decided that installation of the terminal olefin could potentially be achieved post-cyclization. This would remove the problematic 1,3-diene moiety, the key difference between model substrate **4.13** and **4.30a**. This could be advantageous for a number of reasons (Figure 4.2). (*1*) 1,3-dienes are conjugated, more rigid, and prefer the *trans* configuration in the absence of other substituents. This inhibits conformational changes required to adopt different coordination states with copper(I). (*2*) Without the 1,3-diene, previously observed issues with direct excitation related decomposition are prevented as simple alkenes are UV inactive. (*3*) Deletion of the 1,3-diene motif entirely prevents the formation of the six-membered ring product. We proposed that scaffold **4.37a** would provide a UV-inactive scaffold with increased stability under the reaction conditions that would more easily adopt the requisite *endo* coordination state as observed in the model substrate **4.10**.

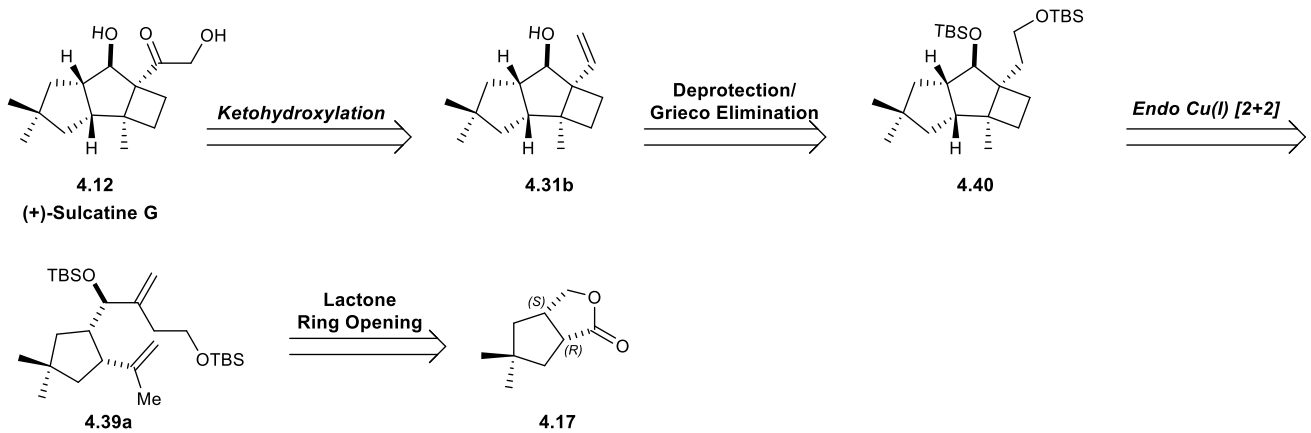
Furthermore, a range of well-developed strategies for elimination of primary alcohols in complex settings can be employed to access the desired terminal olefin intermediate **4.29b** post cyclization of **4.37a**.

Figure 4.2 Conformational Analysis Cyclization 4.30a and Proposed Structure Changes



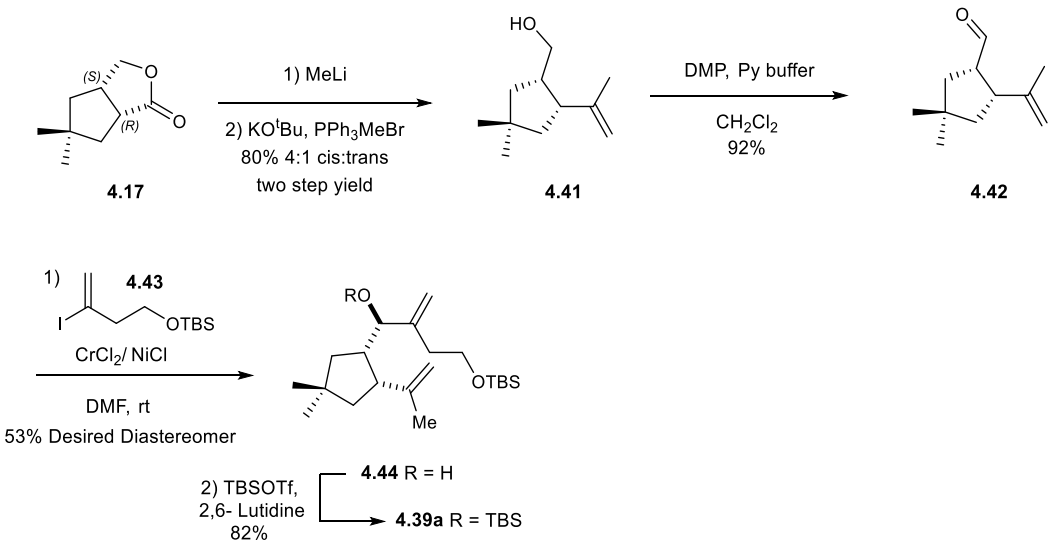
Retrosynthetically, we already knew that natural product **4.12** could be accessed by ketohydroxylation of **4.31b.** Key intermediate **4.31b** we envisioned deriving from **4.38** by a global deprotection followed by primary alcohol selective Grieco–Sharpless elimination. We imagined that [2+2] precursor **4.39a** could be constructed using a similar strategy ring involving opening of enantiopure lactone **4.17** (Scheme 4.11).

Scheme 4.11 Reroute Retrosynthetic Analysis



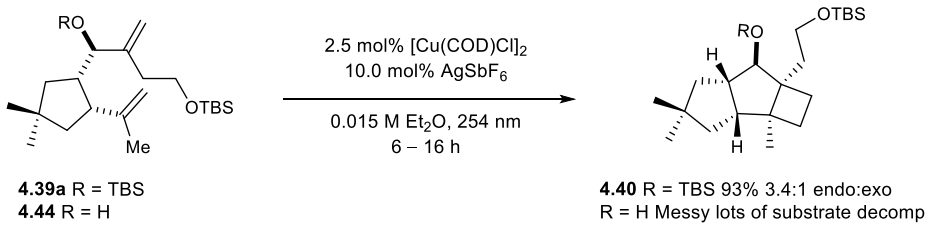
Synthesis of [2+2] precursor **4.39a** permitted a different route involving early installation of 1,1-disubstituted alkene prior to the aldehyde addition (Scheme 4.12). In previous routes this moiety was incompatible with the enyne metathesis step as HG II unlike less active metathesis catalysts can interact with sterically hindered olefins an would likely result in intramolecular cyclization over intermolecular enyne metathesis.[19] MeLi addition to lactone **4.17** resulted in formation of the corresponding methyl lactol in quantitative yield. Wittig olefination at high loadings of ylide gave alcohol **4.41** as a 3:1 mixture of *cis* and *trans* isomers that could be separated using flash chromatography to obtain pure *cis* product. Oxidation using previously employed pyridine-buffered Dess–Martin periodinane conditions gives aldehyde **4.42** in high yield with no observed epimerization. Kishi coupling[20] conditions were employed to affect the addition of vinyl iodide **4.43** to aldehyde **4.42** furnishing **4.44** as a 2:1 mixture of diastereomers with the minor component consisting of a combination of three diastereomers (one *cis* and two *trans*) resulting from epimerization of the aldehyde during the reaction. Kishi conditions were chosen for this transformation as they are known to favor the desired Felkin–Ahn product as diastereoselectivity is purely sterically driven.[21] Attempting this coupling under more typical *tert*-butyl lithium conditions results in a complex mixture of products producing only trace amounts of the desired diastereomer. While surprisingly some epimerization occurs under these typically very mild conditions, the addition as expected favors the correct diastereomer and gives serviceable yields of the desired [2+2] precursor. Further optimization of these reaction conditions are underway to improve the yield and selectivity of this reaction. TBS protection of **4.42** with TBSOTf gives **4.37a** to test in the key [2+2] cycloaddition step.

Scheme 4.12 Synthesis of 4.27



Cyclization of **4.39a** under the optimal conditions developed for cyclization of model substrate **4.13** gave **4.40** in high yield as a 3:1 ratio of diastereomers favoring the desired *cis-anti-cis* configuration. The current stereochemical assignments of these diastereomers is based on spectral comparison with the model substrate. Attempts to increase the *endo* selectivity by way of cyclization of free hydroxyl **4.44** resulted in significant decomposition suggesting that TBS protection of the allylic alcohol prevents unwanted elimination and fragmentation pathways (Scheme 4.13).

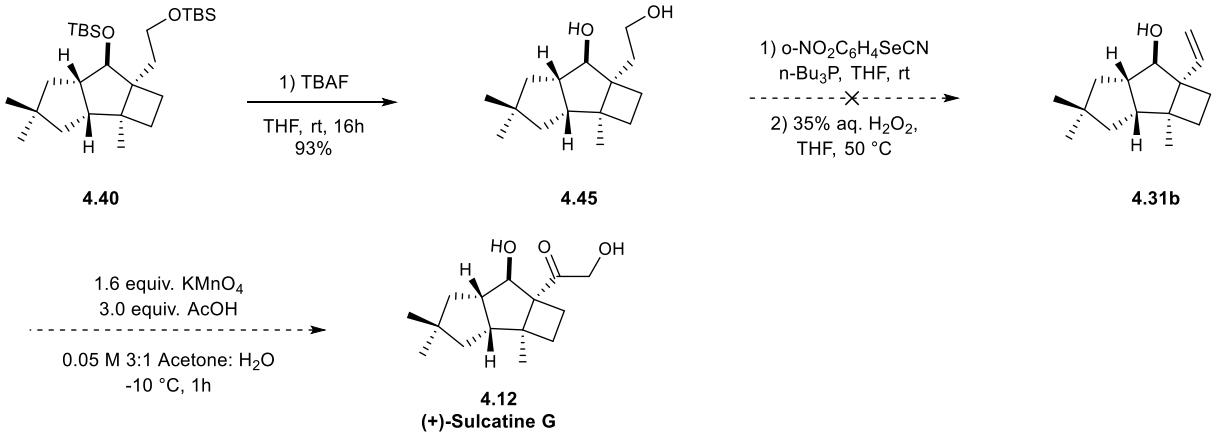
Scheme 4.13 Cyclization of 4.25



With optimal conditions for the photocycloaddition in hand furnishing the required *cis-anti-cis*-tricyclo[6.2.0.02,6]decane skeleton in good yield, several steps are required to complete the synthesis of (+)–sulcatine G (Scheme 4.14). Global TBS deprotection of **4.40** reveals unprotected diol **4.45** cleanly. Subsequent dehydration of the primary alcohol via a two-step

Grieco–Sharpless elimination protocol[22] failed to give previously isolated sulcatine precursor **4.31b** resulting in substrate decomposition. If a protocol for the elimination of **4.45** was developed subsequent ketohydroxylation of **4.31b** should give (+) – Sulcatine G in much higher projected overall yield in fewer linear steps, than previous synthesis.

Scheme 4.14 Planned Finishing Steps and (+) – Sulcatine G



The Greico elimination seemed to be the most likely avenue towards a high yielding elimination as it has been used to mediate eliminations of primary alcohols in complex settings containing other more hindered free hydroxyl groups.[23] However, a wide array of different elimination protocols have been reported to give the desired product.[24] Selective deprotection of the primary alcohol has proven unsuccessful under many standard conditions so an elimination ideally needs to take place from the globally deprotected diol **4.45.**

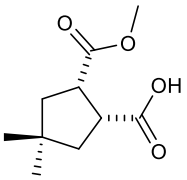
4.4 Conclusions

Upon successful completion of this synthesis, this route would constitute the first total synthesis of natural enantiomer **4.12** not leveraging the chiral pool, and the projected overall yield should be much higher than previous syntheses. More importantly this study uniquely demonstrates that structural optimization of the diene precursor can have substantial impact on the stereoselectivity of this key cycloaddition. Through structural analysis and substrate optimization the intrinsic bias of these scaffolds towards the exo product can be overridden by

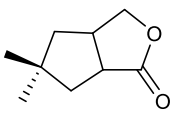
chelation to the allylic alcohol to give the previously deemed inaccessible cis-anti-cis tricyclo [6.2.0.02,6] decane core.

4.5 Experimentals

4.51 Procedures and Characterization
Synthesis of [2+2] Precurser

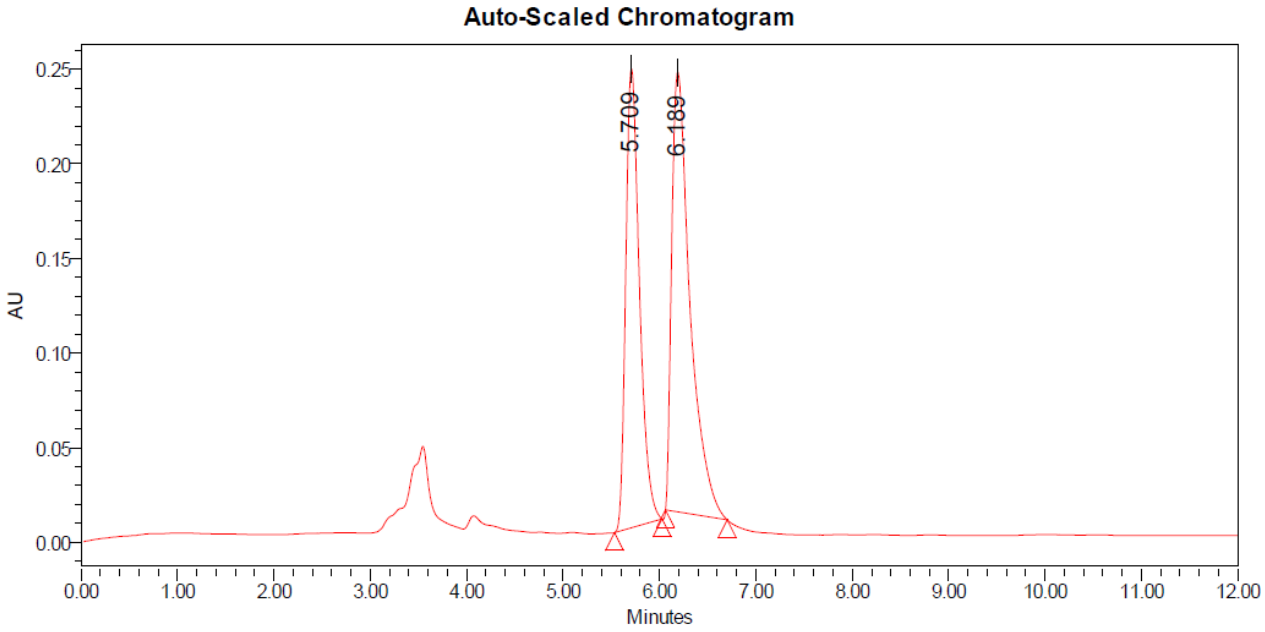


(1R,2S)-2-(methoxycarbonyl)-4,4-dimethylcyclopentane-1-carboxylic acid (4.19) A solution of Anhydride **S1** (8.2 g, 48.7 mmol) in 1:1 Toluene/CCl_4 (200 mL) and Quinidine (17.4 g, 53.6 mmol) was placed under argon, and cooled to -55 ºC in a controlled temperature chiller. Reaction was then treated dropwise with dry methanol (5.9 mL, 146.1 mmol) and stirred for 87 hr at -55 ºC. Upon completion the reaction was reconstituted *in vacu* to dryness. The resulting crude was dissolved in Et_2O and washed with 2M HCl to extract Quinidine for recycling. The aqueous HCl layer was extracted with Et_2O (2 x 40 mL). The organic phase was extracted with saturated $NaHCO_3$ (3 x 50 mL). The basic aqueous layer was then acidified with conc. HCl then extracted with CH_2Cl_2 (3 x 100 mL). Organics were dried with Na_2SO_4, filtered, and reconstituted to afford **32** (9.2 g, 95%) as a clear oil without further purification necessary. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.66 (s, 3H), 3.30 – 3.16 (m, 2H), 1.92 (ddd, *J* = 13.5, 8.4, 5.1 Hz, 2H), 1.83 – 1.76 (m, 2H), 1.13 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.96, 174.48, 51.76, 45.98, 43.45, 38.64, 29.38, 28.72. **HRMS** (EI) calculated for $[C_{10}H_{16}O_4 - H]^-$ requires *m/z* 199.0976, found *m/z* 199.0979. **IR** (cm^{-1}) 2953, 2869, 1734, 1702, 1436, 1368, 1317, 1279, 1201, 1159, 1121, 1041. **$[\alpha]^{22}_D$** + 8.2° (c 0.73, CH_2Cl_2).



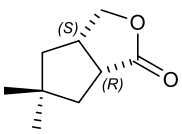
5,5-dimethylhexahydro-1H-cyclopenta[c]furan-1-one $NaBH_4$ (48.3 mmol, 1.83 g) was dispensed into a flame dried 250 mL roundbottom flask containing THF (10 mL). Reaction was placed under N_2, cooled to 0℃, and treated slowly via syringe with a solution of anhydride **S1** (48.3 mmol, 8.12 g) in THF (40 mL). Reaction was warmed to rt and stirred under N_2 for 6h. Reaction was then cooled back to 0℃ and treated dropwise with 6 M HCl (20 mL). Once quenched reaction was partially concentrated *in vacu* then extracted with

Et_2O. Extracted organics where washed sequentially with H_2O, $NaHCO_{3(aq)}$, and brine. Organics were then dried over $MgSO_4$, filtered and reconstituted to yield lactone **S2** (4.67g, 63%) as a clear yellow oil which was brought on to the next step without further purification. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.43 (dd, *J* = 9.3, 7.1 Hz, 1H), 4.10 (dd, *J* = 9.3, 2.1 Hz, 1H), 3.11 – 3.01 (m, 2H), 1.93 (ddd, *J* = 13.3, 9.7, 1.6 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.79 (dd, *J* = 13.4, 4.8 Hz, 1H), 1.40 (dd, *J* = 12.8, 7.8 Hz, 1H), 1.08 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 181.38, 72.71, 47.42, 44.26, 43.70, 41.68, 39.56, 28.25, 28.10. **IR** (cm^{-1}) 2954, 2868, 1758, 1464, 1369, 1306, 1164, 1124. **HRMS** (EI) calculated for $[C_9H_{14}O_2 + H]^+$ requires *m/z* 155.1067, found *m/z* 155.1065.



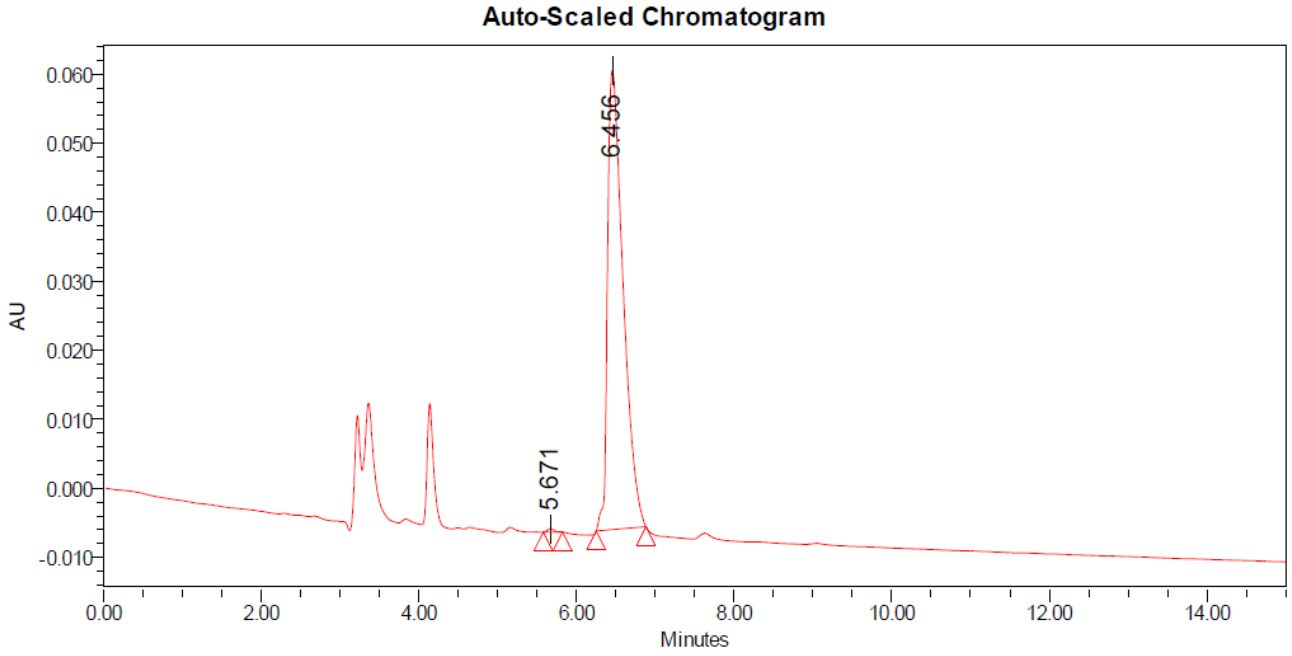
Peak Results

	RT	Area	Height	% Area
1	5.709	2401230	242576	43.92
2	6.189	3066374	232241	56.08



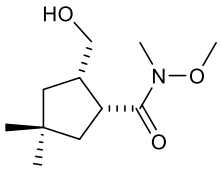
(3aS,6aR)-5,5-dimethylhexahydro-1H-cyclopenta[c]furan-1-one(4.17) A flame dried roundbottom flask was charged with 1 M $LiBHEt_3$ in THF (100 mL, 100 mmol) under argon. The reaction was cooled to 0 ºC and treated dropwise with a solution

of **32** (5.0 g, 25 mmol) in THF (35 mL) via an addition funnel over 20 min. Upon complete addition reaction was stirred 1 hr at 0 ºC then warmed to rt, and stirred a further 4 hr. Reaction was then cooled back to 0 ºC and slowly quenched with 6 M HCl (120 mL) and the resulting mixture was stirred overnight then extracted with Et_2O. Combined organics were washed with 10% H_2O_2, water, and brine then dried with $MgSO_4$, filtered and reconstituted to give crude lactone **30**. Purification on silica gel (4:1 Hexane: Et_2O) afforded **30** (3.55 g, 92 %) as a clear light yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.43 (dd, *J* = 9.3, 7.1 Hz, 1H), 4.10 (dd, *J* = 9.3, 2.1 Hz, 1H), 3.11 – 3.01 (m, 2H), 1.93 (ddd, *J* = 13.3, 9.7, 1.6 Hz, 1H), 1.87 – 1.81 (m, 1H), 1.79 (dd, *J* = 13.4, 4.8 Hz, 1H), 1.40 (dd, *J* = 12.8, 7.8 Hz, 1H), 1.08 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 181.38, 72.71, 47.42, 44.26, 43.70, 41.68, 39.56, 28.25, 28.10. **IR** (cm^{-1}) 2954, 2868, 1758, 1464, 1369, 1306, 1164, 1124. **HRMS** (EI) calculated for $[C_9H_{14}O_2 + H]^+$ requires *m/z* 155.1067, found *m/z* 155.1065. **$[\alpha]^{22}_D$** - 99.6° (c 0.55, CH_2Cl_2)

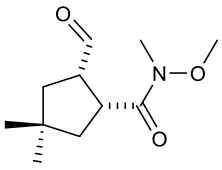


Peak Results

	RT	Area	Height	% Area
1	5.671	3057	516	0.33
2	6.456	913661	66545	99.67

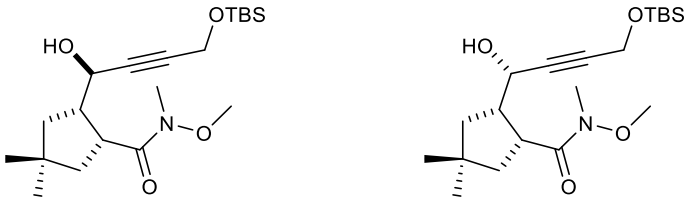


(1R,2S)-2-(hydroxymethyl)-N-methoxy-N,4,4-trimethylcyclopentane-1-carboxamide (4.20) To a solution of **4.17** (3.19 g, 20.7 mmol) in DCM (100 mL) was added *N,O*-dimethylhydroxylamine hydrochloride (3.2 g, 33.1 mmol) was placed under N_2, and cooled to 0 ºC. Reaction was then treated dropwise with 2M in THF *i*-propylmagnesium chloride solution (31 mL, 62.1 mmol), when the addition was completed, all the solids dissolved and the solution turned light yellow (1h). Reaction was then quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and reconstituted to give crude desired product. Purification on silica gel (2:1 Hexane: EtOAc) afforded **4.20** (6.36 4.02 g, 90%) as a white amorphous solid. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 3.73 (s, 3H), 3.56-3.48 (m, 3H), 3.21 (s, 3H), 2.88 (t, *J* = 6.2 Hz, 1H), 2.56 (qt, *J* = 8.3, 5.0 Hz, 1H), 1.91 (t, *J* = 11.8 Hz, 1H), 1.59 – 1.52 (m, 3H), 1.14 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.15, 63.87, 61.69, 44.48, 43.84, 42.98, 41.25, 38.29, 32.41, 29.36, 28.64. **IR** (cm^{-1}) 3425, 2952, 2866, 1639, 1463, 1422, 1386, 1366, 1326, 1178, 1116 **HRMS** (EI) calculated for $[C_{11}H_{21}NO_3 + H]^+$ requires *m/z* 216.1594, found *m/z* 216.1593. **$[\alpha]^{22}_D$** - 14.8° (c 0.61, CH_2Cl_2)



(1R,2S)-2-formyl-N-methoxy-N,4,4-trimethylcyclopentane-1-carboxamide (4.21) To a solution of **33** (2.03 g, 9.4 mmol) in CH_2Cl_2 (100 mL) was added pyridine (6.1 mL, 75.2 mmol). To this solution was added Dess-Martin Periodate (DMP) portionwise. Reaction was then placed under nitrogen and stirred at rt for 3 h. Upon completion reaction was partially concentrated to approximately 25 mL and diluted with 1:1 Pentane: Et_2O (200 mL) and stirred for 15 min. Solution was then filtered thru a plug of celite and filtrate was washed with 1 M $CuSO_4$ solution (3 X 50 mL) and brine (2 X 50 mL). Washed organics were then dried with $MgSO_4$, filtered and reconstituted to afford crude **34** (2.00 g, 100%) as a clear yellow oil. Product is extremely sensitive to both acid and base catalyzed epimerization so is carried on crude to next reaction. Store under nitrogen at -4 °C. **^{1}H NMR** (500 MHz, Benzene-d_6) δ 9.76 (d, *J* = 2.4 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.03 (s, 3H), 2.81 (s, 3H),

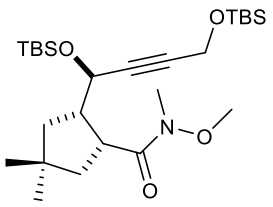
2.72 (q, *J* = 8.9, 8.3 Hz, 1H), 1.98 – 1.93 (m, 1H), 1.91 (dd, *J* = 12.9, 10.0 Hz, 1H), 1.55 (dd, *J* = 12.9, 8.5 Hz, 1H), 1.36 (ddt, *J* = 12.8, 7.8, 1.2 Hz, 1H), 0.98 (s, 3H), 0.74 (s, 3H). **^{13}C NMR** (126 MHz, C_6D6) δ 200.97, 174.47, 127.98, 71.30, 60.41, 52.73, 44.41, 42.80, 41.05, 38.66, 28.67, 27.99. **HRMS** (EI) calculated for $[C_{11}H_{19}NO_3 + H]^+$ requires *m/z* 214.1438 found *m/z* 214.1437.



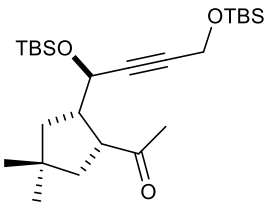
(1R,2S)-2-(4-((tert-butyldimethylsilyl)oxy)-1-hydroxybut-2-yn-1-yl)-N-methoxy-N,4,4-trimethylcyclopentane-1-carboxamide (4.23a and 4.23b) LiHMDS (1.46 g, 8.5 mmol) was weighed out in a glovebox into a dry 250 mL roundbottom flask. Reaction was then removed from the glovebox and placed under a stream of nitrogen and 45 mL of dry THF was added. Reaction was then cooled to -78 °C and tert-butyldimethyl(prop-2-yn-1-yloxy)silane was added as a solution in 45 mL of THF. Reaction was stirred for 5 minutes then warmed to – 40 °C and a solution of aldehyde **4.21** was added dropwise and the reaction was stirred for 45 min and – 40 °C until complete consumption of the aldehyde by TLC. Reaction was then quenched with NH_4Cl, diluted with 100 mL H_2O. and extracted with Et_2O (3 X 50 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to give crude mixture of diastereomers. Purification on silica gel (4:1 Hexane: EtOAc) afforded **4.23a** and **4.23b** (1.6 g, 64% 2:1 d.r.) as a viscous clear yellow oil. **Major 4.23b ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.52 (td, *J* = 3.7, 1.9 Hz, 1H), 4.32 (d, *J* = 1.8 Hz, 2H), 3.83 (d, *J* = 3.7 Hz, 1H), 3.72 (s, 3H), 3.59 (q, *J* = 10.0 Hz, 1H), 3.23 (s, 3H), 2.70 – 2.57 (m, 1H), 2.02 (dd, *J* = 13.0, 9.1 Hz, 1H), 1.85 (t, *J* = 11.9 Hz, 1H), 1.69 (ddd, *J* = 12.9, 8.1, 1.7 Hz, 1H), 1.56 (ddd, *J* = 12.3, 7.2, 1.6 Hz, 1H), 1.16 (s, 3H), 1.01 (s, 3H), 0.90 (s, 9H), 0.11 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.86, 84.89, 82.37, 63.20, 61.73, 51.78, 47.85, 45.63, 41.34, 40.49, 38.28, 32.35, 28.97, 28.36, 25.82, 18.29, -5.14, -5.16. **IR** (cm^{-1}) 3404, 2954, 2931, 2900, 2859, 1634, 1422, 1388, 1367, 1330, 1254, 1179, 1127. **HRMS** (EI)

calculated for $[C_{20}H_{37}NO_4Si + H]^+$ requires *m/z* 384.2565 found *m/z* 384.2561. **$[\alpha]^{22}_D$** + 17.1 ° (c 0.7, CH_2Cl_2)

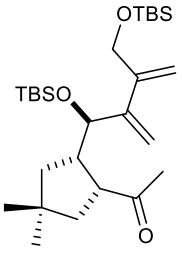
Minor 4.23a ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.41 (t, *J* = 7.7 Hz, 1H), 4.32 (d, *J* = 1.9 Hz, 2H), 3.98 (d, *J* = 8.5 Hz, 1H), 3.74 (s, 3H), 3.60 (q, *J* = 9.4 Hz, 1H), 3.20 (s, 3H), 2.64 (ddd, *J* = 17.2, 10.2, 7.3 Hz, 1H), 1.85 – 1.75 (m, 2H), 1.63 (dddd, *J* = 28.9, 12.7, 7.6, 1.8 Hz, 3H), 1.13 (s, 3H), 1.01 (s, 3H), 0.90 (s, 10H), 0.10 (s, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 177.66, 85.80, 82.84, 63.24, 61.65, 51.77, 48.13, 45.91, 43.85, 39.82, 38.58, 32.53, 29.17, 28.04, 25.83, 18.31, -5.13, -5.15.



(1R,2S)-N-methoxy-N,4,4-trimethyl-2-((R)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-yn-5-yl)cyclopentane-1-carboxamide A solution of crude propargyl alcohol **4.23b** (1.05 g, 2.75 mmol) in CH_2Cl_2 (10 mL) was placed under N_2, cooled to 0 ℃, and treated sequentially with 2,6-Lutadine (0.63 mL, 5.5 mmol) then TBSOTf (0.94 mL, 4.1 mmol). Reaction was then stirred for 30 min at 0 ℃ until complete by TLC. Upon completion reaction was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried with Na_2SO_4, filtered and reconstituted. Purification on silica gel (25:1 Hexane: EtOAc) afforded TBS protected propargyl alcohol (1.34 g, 98 %) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.62 (dt, *J* = 9.2, 1.5 Hz, 1H), 4.28 (d, *J* = 1.5 Hz, 2H), 3.68 (d, *J* = 1.4 Hz, 3H), 3.56 – 3.41 (m, 1H), 3.15 (s, 3H), 2.58 (p, *J* = 9.1 Hz, 1H), 1.72 (d, *J* = 8.2 Hz, 2H), 1.67 (d, *J* = 9.1 Hz, 2H), 1.10 (s, 3H), 1.00 (s, 3H), 0.89 (m, 18H), 0.13 (s, 3H), 0.10 – 0.08 (m, 9H). **13C NMR** (126 MHz, CDCl3) δ 176.42, 86.40, 82.64, 64.26, 61.31, 51.74, 49.47, 45.78, 45.10, 40.29, 38.58, 32.28, 29.68, 28.86, 25.87, 25.79, 18.25, 18.18, -4.29, -4.91, -5.20. **IR** (cm^{-1}) 2953, 2929, 2896, 2857, 1661, 1463, 1413, 1386, 1363, 1327, 1252, 1176 **HRMS** (EI) calculated for $[C_{20}H_{37}NO_4Si + H]^+$ requires *m/z* found *m/z*. **$[\alpha]^{22}_D$** +25.7 ° (c 1.075, CH_2Cl_2)

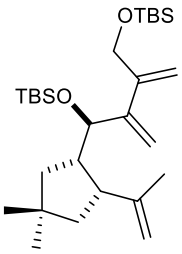


1-((1R,2S)-4,4-dimethyl-2-((R)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-yn-5-yl)cyclopentyl)ethan-1-one (4.24) A solution of (1R,2S)-N-methoxy-N,4,4-trimethyl-2-((R)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-yn-5-yl)cyclopentane-1-carboxamide (1.34 g, 2.69 mmol) in THF (27 mL) was placed under N_2, cooled to 0℃, and treated dropwise with 3.0 M methyl magnesium bromide (2.06 mL, 6.2 mmol). Reaction was then warmed to rt and stirred for 2 hr until complete by TLC. Upon completion reaction was quenched with saturated NH_4Cl solution (40 mL), extracted with Et_2O, dried with $MgSO_4$, filtered and reconstituted to afford **4.25** (1.19 g, 98%) as a clear oil without further purification necessary. **Major ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.57 (dt, *J* = 8.4, 1.7 Hz, 1H), 4.30 (d, *J* = 1.7 Hz, 2H), 3.21 (q, *J* = 8.3 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.19 (s, 3H), 1.75 – 1.58 (m, 4H), 1.08 (s, 3H), 0.98 (s, 3H), 0.89 (d, *J* = 4.2 Hz, 18H), 0.12 (s, 3H), 0.10 (d, *J* = 3.0 Hz, 6H), 0.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.19, 86.27, 83.27, 63.81, 51.90, 51.67, 49.73, 44.95, 44.25, 38.43, 32.04, 29.76, 29.21, 25.85, 25.78, 18.25, 18.19, -4.32, -4.92, -5.20, -5.24. **IR** (cm^{-1}) 2953, 2929, 2858, 1709, 1472, 1463, 1362, 1252. **HRMS** (EI) calculated for $[C_{25}H_{48}O_3Si_2 + H]^+$ requires *m/z* 453.3215 found *m/z* 453.3219.



1-((1R,2S)-4,4-dimethyl-2-((R)-2,2,3,3,10,10,11,11-octamethyl-6,7-dimethylene-4,9-dioxa-3,10-disiladodecan-5-yl)cyclopentyl)ethan-1-one (4.25) A 100 mL pressure vessel was charged with HGII (82.3 mg, 0.13 mmol) and **4.24** (1.19 g, 2.63 mmol) in toluene (20 mL). Reaction was sparged for 5 min with nitrogen and fit with a pressure head. Vessel was then pressurized with ethlyene to 60 PSI and vented back to atmospheric pressure. This process was repeated 5 times with rapid stirring of the solution to saturate with ethylene. Reaction was then vented to 10 PSI of ethylene and heated at 75 ºC for 20 h. Reaction was then cooled to rt, opened to air, and isocyanate was added (0.1

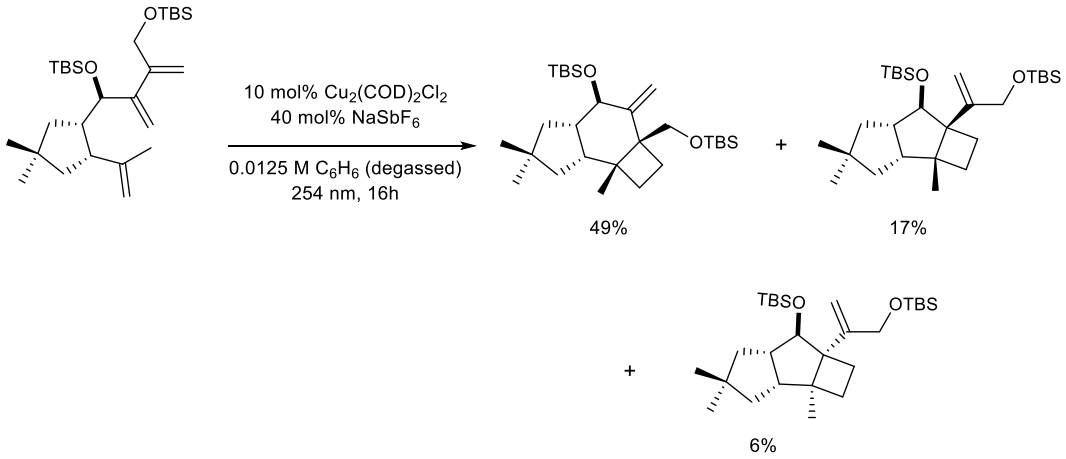
mL). Reaction was stirred for 15 minutes then reconstituted *in vacu.* The crude reaction mixture was then dissolved in 4:1 Hexane:Et_2O and passed thru a silica plug to remove ruthenium isocyanate adducts. Purification on silica gel (50:1 Hexane: EtOAc) afforded **4.25** (1.20 g, 95%) as a clear pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.40 (t, *J* = 1.8 Hz, 1H), 5.34 (q, *J* = 2.0 Hz, 1H), 5.03 (d, *J* = 1.7 Hz, 1H), 4.94 (d, *J* = 1.6 Hz, 1H), 4.63 (d, *J* = 8.5 Hz, 1H), 4.38 (dt, *J* = 14.7, 1.7 Hz, 1H), 4.20 (dt, *J* = 14.8, 1.7 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.46 (ddt, *J* = 11.7, 8.6, 7.3 Hz, 1H), 2.02 (s, 3H), 1.81 (t, *J* = 11.9 Hz, 1H), 1.71 (ddd, *J* = 13.2, 8.8, 0.9 Hz, 1H), 1.62 – 1.54 (m, 2H), 1.05 (s, 3H), 0.99 (s, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.08 (s, 6H), 0.06 (s, 3H), -0.04 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.94, 148.93, 145.44, 114.43, 112.59, 64.74, 52.02, 48.15, 44.85, 44.05, 37.72, 31.57, 30.76, 30.53, 25.95, 18.44, 18.12, -4.14, -4.85, -5.34, -5.36. **IR** (cm^{-1}) 2954, 2929, 2895, 2857, 1710, 1664, 1471, 1463, 1408, 1387, 1363, 1252, 1167 **HRMS** (EI) calculated for $[C_{27}H_{52}O_3Si_2 + H]^+$ requires *m/z* 481.3528 found *m/z* 481.3530. **$[\alpha]^{22}_D$** +34.7 ° (c 0.905, CH_2Cl_2)



(R)-5-((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2,2,3,3,10,10,11,11-octamethyl-6,7-dimethylene-4,9-dioxa-3,10-disiladodecane (4.16) To a suspension of Zn powder (1.35 g,20.7 mmol) and $PbCl_2$ (78 mg, 0.28 mmol) in degassed THF(sparge with N_2) (7 mL) under N_2 was added diiodomethane (0.84 mL, 10.4 mmol), and the reaction mixture was stirred at rt for 1h. The reaction was then cooled to 0 ℃ and treated with a solution of $TiCl_4$ 1.0 M in CH_2Cl_2 (2.1 mL, 2.1 mmol). Reaction was then warmed to rt and stirred for 2 h. Reaction was again cooled to 0 ℃ and treated with a solution of **4.25** (661.4 mg, 1.38 mmol) in degassed THF (7mL) and the resulting solution was heated at 50 ℃ for 1h until complete by TLC. Reaction was quenched slowly with saturated $NaHCO_3$ (6 mL) and filtered thru a pad of celite. To the filtrate was added saturated aqueous $Na_2S_2O_3$ solution (10 mL) and this mixture was extracted with Et_2O, dried

with $MgSO_4$, filtered and reconstituted. Purification on silica gel (200:1 Hexane: EtOAc) to afford 571.5 mg of **4.16** (571.5 mg, 87%) as a clear oil**. ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.31 (q, *J* = 1.9 Hz, 1H), 5.17 (q, *J* = 1.7 Hz, 1H), 5.08 (d, *J* = 1.3 Hz, 1H), 5.00 (d, *J* = 1.5 Hz, 1H), 4.81 (dt, *J* = 2.4, 1.1 Hz, 1H), 4.73 (d, *J* = 1.7 Hz, 1H), 4.44 – 4.35 (m, 1H), 4.28 – 4.17 (m, 2H), 2.67 – 2.57 (m, 1H), 2.31 (tdd, *J* = 8.8, 7.1, 3.8 Hz, 1H), 1.80 – 1.71 (m, 4H), 1.43 – 1.30 (m, 2H), 1.12 (s, 3H), 0.96 (s, 3H), 0.92 (d, *J* = 7.1 Hz, 18H), 0.08 (s, 6H), 0.02 (s, 3H), -0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.93, 145.91, 145.18, 112.62, 111.84, 110.63, 73.36, 64.59, 48.29, 45.04, 44.46, 40.29, 36.45, 30.41, 30.19, 26.24, 25.94, 23.52, 18.42, 18.22, -3.15, -4.29, -5.37 **HRMS** (EI) calculated for $[C_{28}H_{54}O_2Si_2 + H]^+$ requires *m/z* 479.3735 found *m/z* 479.3738. **$[\alpha]^{22}_D$** +35.3 ° (c 0.64, CH_2Cl_2)

Key [2+2] Cycloaddition



A quartz reaction vial was charged with $[Cu(COD)Cl]_2$ (2.1 mg, 0.005 mmol) and $NaSbF_6$ (6 mg, 0.01 mmol) placed under N_2. **4.16** (24.5 mg, 0.05 mmol) was then added as a solution in 4 mL of degassed Et_2O (degassed by 30 min N_2 sparge). The reaction was then sonicated for 1 min then prestirred for 25 minutes under nitrogen. Reaction was then fit with a cold finger and irradiated at 254 nm for 16 h. Reaction was then passed through a pad of silica with Et_2O and reconstituted *in vacu* to give crude mixture of cycloadducts as a clear oil. NMR analysis of the crude reaction mixture gave yields of 49% **4.27**, 17% **4.26**, and 6% **4.15** with TMSPh (8.9 mg)

as an internal standard. Scaling this reaction up to 0.375 mmol and purification on silica gel (50:1 Hexane: CH_2Cl_2) allowed for isolation of each product for characterization.

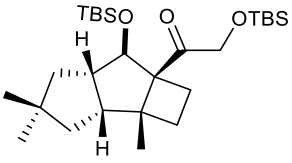
tert-butyl(((2aS,4R,4aS,7aR,7bR)-4-((tert-butyldimethylsilyl)oxy)-6,6,7b-trimethyl-3-methylenedecahydro-2aH-cyclobuta[e]inden-2a-yl)methoxy)dimethylsilane (4.27) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.15 (t, *J* = 1.8 Hz, 1H), 4.83 (t, *J* = 1.6 Hz, 1H), 4.49 (dt, *J* = 9.0, 1.6 Hz, 1H), 3.80 (q, *J* = 10.3 Hz, 2H), 2.18 (tdd, *J* = 11.4, 9.0, 7.2 Hz, 1H), 2.06 (ddd, *J* = 11.7, 10.1, 7.9 Hz, 1H), 1.88 – 1.76 (m, 3H), 1.64 – 1.54 (m, 1H), 1.50 – 1.41 (m, 2H), 1.22 (t, *J* = 11.7 Hz, 1H), 1.14 (s, 3H), 1.06 (s, 4H), 0.94 (s, 9H), 0.90 (s, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 – 0.02 (m, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.09, 103.31, 74.52, 64.03, 47.97, 47.93, 47.89, 44.39, 43.98, 42.24, 37.06, 28.26, 27.43, 26.06, 24.97, 24.82, 23.63, 23.11, 17.36, 17.05, -5.38, -5.74, -6.62, -6.74.

tert-butyl((2-((2aR,2bR,5aS,6R,6aR)-6-((tert-butyldimethylsilyl)oxy)-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)allyl)oxy)dimethylsilane (4.26) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.27 (q, *J* = 2.1 Hz, 1H), 4.70 (q, *J* = 1.9 Hz, 1H), 4.35 (dt, *J* = 14.3, 2.0 Hz, 1H), 4.17 (d, *J* = 7.2 Hz, 1H), 3.93 (dt, *J* = 14.3, 1.6 Hz, 1H), 2.58 (ddt, *J* = 12.5, 9.7, 7.9 Hz, 1H), 2.44 (ddd, *J* = 12.3, 9.7, 8.2 Hz, 1H), 2.14 (td, *J* = 10.6, 9.1 Hz, 1H), 1.91 – 1.77 (m, 2H), 1.69 – 1.61 (m, 1H), 1.32 (ddd, *J* = 12.4, 8.2, 1.9 Hz, 1H), 1.28 – 1.17 (m, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H), 0.92 (s, 9H), 0.82 (s, 9H), 0.06 (d, *J* = 2.1 Hz, 6H), -0.02 (s, 3H), -0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.48, 107.89, 90.15, 63.21, 62.78, 54.99, 52.27, 51.58, 48.37, 43.61, 39.88, 27.95, 26.60, 26.01, 25.00, 24.83, 23.86, 21.76, 17.41, 16.94, -5.22, -5.52, -6.30, -6.33.

tert-butyl((2-((2aS,2bR,5aS,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)allyl)oxy)dimethylsilane (4.15) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.37 (q, *J* = 1.8 Hz, 1H), 4.89 (q, *J* = 1.5 Hz, 1H), 4.13 (dt, *J* =

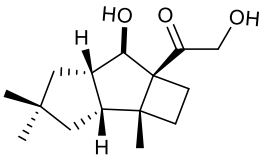
13.9, 1.6 Hz, 1H), 4.05 (dt, *J* = 14.1, 1.7 Hz, 1H), 3.92 (d, *J* = 8.4 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.23 – 2.10 (m, 2H). Diagnostic downfield signals only.

See section 4.5.2 for NOE analysis of **4.26** and **4.27**



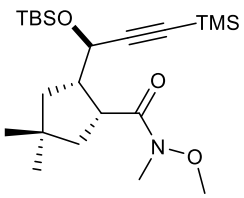
2-((tert-butyldimethylsilyl)oxy)-1-((2aR,2bR,5aS,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)ethan-1-one

(4.28) Cycloadduct **36** (105 mg, 0.22 mmol) was dispensed into a 25 mL roundbottom and dissolved in 4.5 mL of a 10:1 Acetone: H_2O. This solution was treated with N-methylmorpholine oxide NMO (38.8 mg, 0.33 mmol) then 2,6-Lutidine (0.05 mL, 0.44 mmol) followed by OsO_4 4wt% in H_2O (0.05 mL, 0.01 mmol) and allowed to stir for 12 hours. $PhI(OAc)_2$ (106.3 mg, 0.33 mmol) was then added in one portion and the reaction was stirred for 1 hour. The reactions was then quenched with aqueous $Na_2S_2O_3$ and extracted with ethyl acetate. The organic layer was washed with $CuSO_4$ and brine, dried with Na_2SO_4, filtered and concentrated to give crude product. Purification on silica gel (50:1 Hex:EtOAc) gave ketone **4.28** (81 mg, 76%) as a clear oil. ^{1}H NMR (500 MHz, Acetone-d_6) δ 4.57 (d, *J* = 17.2 Hz, 1H), 4.43 (d, *J* = 7.2 Hz, 1H), 4.33 (d, *J* = 17.3 Hz, 1H), 2.96 (dddd, *J* = 12.3, 9.7, 8.2, 7.1 Hz, 1H), 2.40 (ddd, *J* = 11.1, 10.2, 8.9 Hz, 1H), 1.84 (ddd, *J* = 12.3, 8.3, 1.8 Hz, 1H), 1.68 (ddd, *J* = 11.1, 8.2, 1.7 Hz, 1H), 1.43 (dd, *J* = 12.3, 9.6 Hz, 1H), 1.37 (ddd, *J* = 12.3, 8.3, 1.8 Hz, 1H), 1.35 – 1.25 (m, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.92 (s, 11H), 0.85 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (126 MHz, Acetone) δ 205.88, 90.73, 69.18, 68.89, 55.97, 53.90, 53.44, 48.31, 44.70, 40.49, 28.28, 26.99, 26.31, 25.42, 25.33, 22.57, 21.95, 18.21, 17.56, -5.18, -5.63, -5.78.



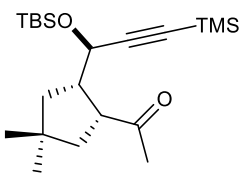
2-hydroxy-1-((2aR,2bR,5aS,6R,6aS)-6-hydroxy-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)ethan-1-one (4.29) A solution of **4.28** (22.9 mg, 0.05 mmol) was dissolved in 0.4 mL of THF. Solid NH_4Cl (25 mg) was added followed by treatment with 1.0 M TBAF solution in THF (0.2 mmol, 0.2 mL). The reaction was stirred for 3 hours then quenched with 2 M HCl and extracted with EtOAc. The organic layers were washed with aqueous NH_4Cl and brine, filtered and concentrated to give crude product. Purification on silica gel (2:1 Hexanes:EtOAc) gave clean desired product for characterization. As this was a probe scale reaction no isolated yield was obtained.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.42 (dd, *J* = 19.1, 4.0 Hz, 1H), 4.29 (d, *J* = 6.9 Hz, 1H), 4.17 (dd, *J* = 19.1, 4.0 Hz, 1H), 3.20 (t, *J* = 4.8 Hz, 1H), 2.86 (dq, *J* = 12.0, 8.4 Hz, 1H), 2.63 (ddd, *J* = 12.0, 10.2, 8.1 Hz, 1H), 2.35 (dt, *J* = 11.3, 9.3 Hz, 1H), 2.09 (dt, *J* = 11.6, 8.9 Hz, 1H), 1.92 (ddd, *J* = 10.8, 8.3, 2.1 Hz, 1H), 1.86 (ddd, *J* = 12.7, 8.3, 1.9 Hz, 1H), 1.43 (ddd, *J* = 11.4, 9.1, 2.1 Hz, 1H), 1.35 (ddq, *J* = 11.8, 9.0, 3.5, 2.7 Hz, 2H), 1.26 (t, *J* = 11.3 Hz, 1H), 1.12 (s, 3H), 1.09 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.39, 90.47, 68.52, 67.68, 56.20, 55.38, 52.94, 47.58, 44.96, 40.86, 29.11, 27.75, 26.67, 23.54, 21.61. See section 4.5.2 for NOE analysis



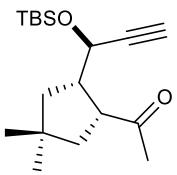
(1R,2S)-2-((R)-1-((tert-butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-N-methoxy-N,4,4-trimethylcyclopentane-1-carboxamide (4.32) TMS Acetylene (9.0 mmol, 1.25 mL) was added to a dry 200 mL roundbottom flask and diluted in 50 mL of THF. Reaction was placed under nitrogen, cooled to -20 °C, and treated with LiHMDS 1.0 M in THF (8.3 mmol, 8.3 mL). Reaction was stirred for 15 min at -20 °C, then cooled to -78°C followed by addition of aldehyde **4.10** (7.5 mmol, 1.61 g) as a solution

in 25 mL of THF. Reaction was then stirred for 45 minutes until complete by TLC. The reaction was then treated with 2,6-Lutidine (15.0mmol, 1.74 mL) followed by TBSOTf (11.27 mmol, 2.6 mL) then stirred for 30 minutes allowing to warm to room temperature. Reaction was then quenched with saturated $NaHCO_3$ then extracted with EtOAc (3 X 30 mL). Organic layer was then washed with saturated $CuSO_4$ (25 mL) and Brine (25 mL), filtered, dried with Na_2SO_4 and concentrated to yield crude mixture of diastereomers. Purification on silica gel (25:1 Hex: EtOAc) gave **4.32** as a 2.5:1 mixture of diastereomers (1.59 g, 50% 2.5:1 d.r.) **Major** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.61 (d, *J* = 9.3 Hz, 1H), 3.68 (s, 3H), 3.15 (s, 3H), 2.57 (p, *J* = 9.2 Hz, 1H), 1.79 – 1.65 (m, 4H), 1.10 (s, 3H), 1.00 (s, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 8H), 0.10 (s, 3H). **Minor** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.80 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.41 (s, 1H), 3.11 (s, 3H), 2.62 – 2.50 (m, 1H), 1.81 – 1.65 (m, 3H), 1.59 (ddd, *J* = 12.4, 7.0, 1.3 Hz, 1H), 1.09 (s, 3H), 1.03 (s, 3H), 0.88 (s, 9H), 0.18 (s, 3H), 0.15 (s, 9H), 0.05 (s, 3H). Stereochemistry was determined by NOE analysis of the lactonization product derived from storage of the unprotected free hydroxyl major diastereomer (see 4.5.2).

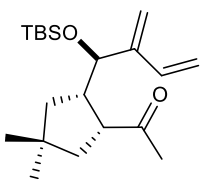


1-((1R,2S)-2-((R)-1-((tert-butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-4,4-dimethylcyclopentyl)ethan-1-one A solution of diastereomers **4.32** (3.52 g, 8.3 mmol) in THF (80 mL) was placed under N_2, cooled to 0℃, and treated dropwise with 3.0 M methyl magnesium bromide (6.35 mL, 19.05 mmol). Reaction was then warmed to rt and stirred for 2 hr until complete by TLC. Upon completion reaction was quenched with saturated NH_4Cl solution (40 mL), extracted with Et_2O, dried with $MgSO_4$, filtered and reconstituted to afforded ketone (3.0 g, 96%) as a mixture of diastereomers without further purification necessary. **Major** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.51 (d, *J* = 8.8 Hz, 1H), 3.22 (q, *J* = 8.3 Hz, 1H), 2.54 (dtd, *J* = 11.0, 8.7, 7.2 Hz, 1H), 2.18 (s, 3H), 1.75 – 1.58 (m, 4H), 1.08 (s, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.14 (s, 9H), 0.12 (s, 3H),

0.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.18, 107.82, 89.31, 64.34, 51.84, 49.69, 45.05, 44.41, 38.55, 32.24, 29.76, 29.21, 25.85, 18.26, -0.24, -4.40, -4.86.

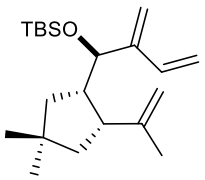


1-((1R,2S)-2-((R)-1-((tert-butyldimethylsilyl)oxy)prop-2-yn-1-yl)-4,4-dimethylcyclopentyl)ethan-1-one (4.33) In a 500 mL round bottom flask 1-((1R,2S)-2-((R)-1-((tert-butyldimethylsilyl)oxy)-3-(trimethylsilyl)prop-2-yn-1-yl)-4,4-dimethylcyclopentyl)ethan-1-one (3.0 g, 7.95 mmol) was dissolved in 100 mL of THF. Reaction was then treated with H_2O (100 mL), EtOH (100 mL) and 2,6-Lutidine (10 mL). $AgNO_3$ was then added in a single portion (13.5 g, 79.5 mmol) and the resulting white suspension was stirred for 4 hours at room temperature. Reaction was then quenched by addition of 100 mL of saturated Na_2PO_4 stirring for 15 minutes. The quenched reaction mixture was then filtered through celite and extracted with Et_2O (3 X 50 mL). Organic layer was then washed with sat. $CuSO_4$, Brine, dried with $MgSO_4$, filtered and concentrated to give compound **4.33** as a mixture of diastereomers (2.28 g, 93%). Diastereomers could be separated via flash chromatography (75:1 Hex: EtoAc) allowing for isolation of pure major and minor diastereomers of **4.33. Major** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.60 (dd, *J* = 8.5, 2.1 Hz, 1H), 3.23 (q, *J* = 8.3 Hz, 1H), 2.56 (dtd, *J* = 10.9, 8.6, 7.3 Hz, 1H), 2.37 (d, *J* = 2.1 Hz, 1H), 2.18 (s, 3H), 1.74 (ddd, *J* = 12.8, 8.4, 1.3 Hz, 1H), 1.71 – 1.59 (m, 4H), 1.08 (s, 3H), 0.99 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H). **Minor** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.63 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.17 (q, *J* = 8.0 Hz, 1H), 2.58 (dq, *J* = 10.8, 8.1 Hz, 1H), 2.39 (d, *J* = 2.1 Hz, 1H), 2.17 (s, 3H), 1.76 – 1.57 (m, 4H), 1.08 (s, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H).



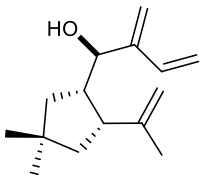
1-((1R,2S)-2-((R)-1-((tert-butyldimethylsilyl)oxy)-2-methylenebut-3-en-1-yl)-4,4-dimethylcyclopentyl)ethan-1-one (4.34) A 100 mL pressure vessel was charged with HGII (100 mg, 0.16 mmol) and **37** (510 mg, 1.65 mmol) in toluene (16 mL). Reaction was sparged for 5 min with nitrogen and fit with a pressure head.

Vessel was then pressurized with ethlyene to 60 PSI and vented back to 10 PSI pressure. This process was repeated 5 times with rapid stirring of the solution to saturate with ethylene. Reaction was then vented to 10 PSI of ethylene and heated at 80 ºC for 20 h. Reaction was then cooled to rt, opened to air, and isocyanate was added (0.1 mL). Reaction was stirred for 15 minutes then reconstituted *in vacu.* The crude reaction mixture was then dissolved in 4:1 Hexane:Et_2O and passed thru a silica plug to remove ruthenium isocyanate adducts. Purification on silica gel (50:1 Hexane: EtOAc) afforded **36** (523 mg, 94%) as a clear pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 6.30 (ddd, *J* = 17.6, 11.1, 0.8 Hz, 1H), 5.56 (dd, *J* = 17.7, 1.7 Hz, 1H), 5.12 – 5.08 (m, 2H), 4.85 (d, *J* = 1.9 Hz, 1H), 4.58 (d, *J* = 8.8 Hz, 1H), 2.84 (ddd, *J* = 9.0, 7.6, 5.1 Hz, 1H), 2.47 (ddt, *J* = 11.6, 8.8, 7.3 Hz, 1H), 2.01 (s, 3H), 1.81 (t, *J* = 12.0 Hz, 1H), 1.73 (ddd, *J* = 13.3, 9.0, 1.0 Hz, 1H), 1.64 (dd, *J* = 12.3, 7.1 Hz, 1H), 1.60 – 1.54 (m, 1H), 1.05 (s, 3H), 1.01 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), -0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.07, 148.90, 135.13, 115.65, 114.70, 75.35, 51.95, 48.26, 44.94, 44.36, 37.94, 31.66, 30.76, 30.56, 25.88, 18.15, -4.44, -4.85.

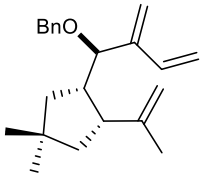


tert-butyl(((R)-1-((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylenebut-3-en-1-yl)oxy)dimethylsilane (4.30a) To a suspension of Zn powder (1.42 g, 21.8 mmol) and $PbCl_2$ (81 mg, 0.29 mmol) in degassed THF(sparge with N_2) (7.5 mL) under N_2 was added diiodomethane (0.88 mL, 10.9 mmol), and the reaction mixture was stirred at rt for 1h. The reaction was then cooled to 0℃ and treated with a solution of $TiCl_4$ 1.0 M in CH_2Cl_2 (2.2 mL, 2.2 mmol). Reaction was then warmed to rt and stirred for 2 h. Reaction was again cooled to 0℃ and treated with a solution of **4.34** (487.2 mg, 1.45 mmol) in degassed THF (7.5 mL) and the resulting solution was heated at 50℃ for 1h until complete by TLC. Reaction was quenched slowly with saturated $NaHCO_3$ (6 mL) and filtered thru a pad of celite. To the filtrate was added saturated aqueous $Na_2S_2O_3$ solution (10 mL) and this mixture was extracted with Et_2O, dried with $MgSO_4$, filtered and reconstituted.

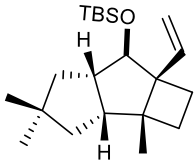
Purification on silica gel (200:1 Hexane: EtOAc) to afford **29** (377.7 mg, 78%) as a clear oil**. ^{1}H NMR** (500 MHz, Chloroform-*d*) δ 6.27 (ddd, *J* = 17.7, 11.1, 0.9 Hz, 1H), 5.34 (dd, *J* = 17.8, 1.4 Hz, 1H), 5.09 – 5.05 (m, 2H), 5.07 – 5.00 (m, 1H), 4.82 (dq, *J* = 2.3, 1.1 Hz, 1H), 4.74 (dt, *J* = 2.2, 1.2 Hz, 1H), 4.37 (dd, *J* = 4.4, 0.8 Hz, 1H), 2.64 (dt, *J* = 9.9, 7.4 Hz, 1H), 2.35 (tdd, *J* = 8.5, 7.3, 4.4 Hz, 1H), 1.81 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.79 – 1.77 (m, 3H), 1.74 (dd, *J* = 12.2, 10.8 Hz, 1H), 1.48 – 1.39 (m, 2H), 1.12 (s, 3H), 0.98 (s, 3H), 0.90 (s, 9H), 0.01 (s, 3H), -0.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.27, 145.41, 136.62, 115.01, 113.72, 111.83, 72.53, 48.29, 45.24, 40.91, 36.55, 30.44, 30.28, 26.16, 23.75, 18.22, -3.50, -4.42.



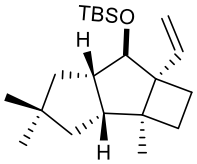
(R)-1-((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylenebut-3-en-1-ol (4.30b) A 10 mL roundbottom flask was charged with **4.30a** (100.4 mg, 0.3 mmol) in 1.5 mL of THF. Reaction was then treated with 1.0 M TBAF in THF (0.6 mL, 0.6 mmol) then stirred for 8 hours at room temperature. Reaction was then quenched with 2 M HCl and extracted with Et_2O. The organic layer was then washed with aqueous NH_4Cl and brine, dried with $MgSO_4$, filtered and reconstituted to give crude deprotected product. Purification on silica gel (50:1 Hexanes: EtOAc) gave **4.30b** (63.6 mg, 96%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 6.27 (dd, *J* = 17.8, 11.2 Hz, 1H), 5.24 (q, *J* = 1.6 Hz, 1H), 5.16 (dd, *J* = 17.9, 0.9 Hz, 1H), 5.14 – 5.10 (m, 1H), 5.04 (dq, *J* = 11.1, 1.0 Hz, 1H), 4.99 (h, *J* = 1.4 Hz, 1H), 4.93 (d, *J* = 1.9 Hz, 1H), 4.56 – 4.51 (m, 1H), 2.85 (ddd, *J* = 14.1, 9.7, 6.1 Hz, 1H), 2.54 (tdd, *J* = 9.3, 7.1, 2.2 Hz, 1H), 1.96 – 1.90 (m, 3H), 1.84 (d, *J* = 3.5 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.64 (dd, *J* = 13.3, 7.2 Hz, 1H), 1.37 (ddd, *J* = 11.8, 6.1, 1.7 Hz, 1H), 1.26 (ddd, *J* = 13.3, 9.0, 1.7 Hz, 1H), 1.12 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.99, 147.40, 137.13, 114.72, 113.03, 110.37, 69.55, 47.50, 45.00, 42.73, 38.46, 36.74, 29.67, 28.77, 24.65.



((((R)-1-((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylenebut-3-en-1-yl)oxy)methyl)benzene (4.30c) A 10 mL roundbottom flask containing 0.5 mL of THF was charged with NaH 60 wt% (9.6 mg, 0.24 mmol). A solution of **4.30b** (40 mg, 0.18 mmol) in 1.2 mL of THF was added and the reaction was stirred for 30 minutes under N_2 at room temperature. Benzyl bromide (0.04 mL, 0.36 mmol) was then added and the reaction was refluxed at 80°C for 48 hours. The reaction was then quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, filtered and reconstituted to give crude benzyl protected product. Purification on silica gel (100% Hexanes → 100:1 Hexanes: EtOAc) gave **4.30c** (26 mg, 47%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.34 – 7.31 (m, 5H), 6.35 (dd, *J* = 17.9, 11.2 Hz, 1H), 5.29 – 5.21 (m, 2H), 5.17 (d, *J* = 2.0 Hz, 1H), 5.06 (d, *J* = 11.2 Hz, 1H), 4.90 (t, *J* = 1.8 Hz, 1H), 4.80 – 4.74 (m, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.20 (d, *J* = 11.3 Hz, 1H), 4.14 – 4.08 (m, 1H), 2.84 – 2.74 (m, 1H), 2.44 (tdd, *J* = 8.9, 6.0, 2.3 Hz, 1H), 1.93 (t, *J* = 12.2 Hz, 1H), 1.83 (s, 3H), 1.79 (dd, *J* = 13.4, 6.0 Hz, 1H), 1.33 (ddd, *J* = 16.7, 12.6, 7.7 Hz, 2H), 1.08 (s, 3H), 0.97 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.78, 145.13, 139.33, 137.67, 128.44, 128.32, 128.08, 127.09, 126.93, 115.29, 113.28, 110.98, 77.70, 69.83, 48.59, 44.86, 44.06, 39.58, 36.83, 30.03, 23.88.



Major 4.35a



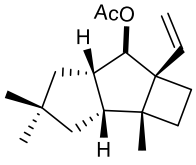
Minor 4.31a

Table 4.1, entry 2 (4.35a and 4.31a): A quartz reaction vessel was charged with $[Cu(COD)Cl)_2$ (8.3 mg, 0.02 mmol) and $NaSbF_6$ (20.7 mg, 0.08 mmol) and placed under N_2. A solution of **4.31a** in 16 mL of benzene was added and the reaction was sonicated for 1 minute, then prestirred for 15 minutes. Reaction was fit with a coldfinger and irradiated and 254 nm for 17 hours. The reaction was then flush through a pad of silica with Et_2O and concentrated to give crude mixture of products that upon NMR analysis with TMSPh (28.2 mg) as an internal standard gave a 50% yield as a 5:1 mixture of

diastereomers. Diastereomers were separated for clean characterization by purification of silica gel (100% Hexane).

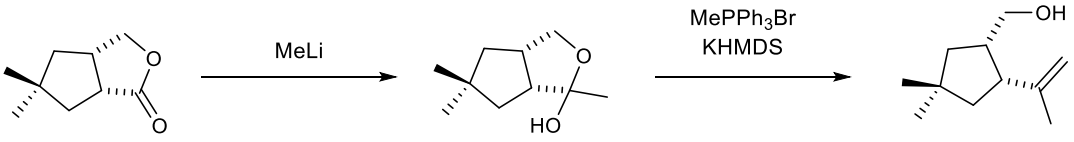
tert-butyldimethyl(((2aR,2bR,5aS,6R,6aS)-2a,4,4-trimethyl-6a-vinyldecahydrocyclobuta[a]pentalen-6-yl)oxy)silane Major ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.89 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.09 (dd, *J* = 10.8, 2.1 Hz, 1H), 4.87 (dd, *J* = 17.4, 2.1 Hz, 1H), 4.09 (d, *J* = 7.3 Hz, 1H), 2.78 – 2.63 (m, 1H), 2.40 (ddd, *J* = 11.9, 10.0, 8.3 Hz, 1H), 2.13 (dt, *J* = 11.0, 9.2 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.80 – 1.71 (m, 2H), 1.33 – 1.24 (m, 4H), 1.10 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H), 0.84 (s, 9H), -0.00 (s, 3H), -0.05 (s, 3H).

tert-butyldimethyl(((2aS,2bR,5aS,6R,6aR)-2a,4,4-trimethyl-6a-vinyldecahydrocyclobuta[a]pentalen-6-yl)oxy)silane Minor ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.75 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.13 (dd, *J* = 10.6, 1.6 Hz, 1H), 4.97 (dd, *J* = 17.3, 1.6 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 2.61 (q, *J* = 8.1 Hz, 1H), 2.21 – 2.04 (m, 2H), 1.87 – 1.59 (m, 5H), 1.55 (dd, *J* = 13.8, 2.3 Hz, 1H), 1.34 (dd, *J* = 12.4, 7.0 Hz, 1H), 1.06 (d, *J* = 9.9 Hz, 1H),1.12 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H), 0.83 (s, 9H), 0.01 (s, 3H), -0.08 (s, 3H).



(2aR,2bR,5aS,6R,6aS)-2a,4,4-trimethyl-6a-vinyldecahydrocyclobuta[a]pentalen-6-yl acetate (4.37) A 10 mL round bottom flask was charged with **4.31a** (33.5 mg, 0.1 mmol) in 0.5 mL of THF. The reaction was then treated with 1.0 M TBAF in THF (0.4 mL, 0.4 mmol) then stirred at 60°C for 8 hours. The reaction was then cooled to room temperature and quenched with 2M HCl and extracted with EtOAc. The organic layer was washed with aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered and reconstituted to give crude TBS deprotected product. This crude product was then dissolved in 1 mL of DCM and treated with DMAP (18.3 mg, 0.15 mmol) and Ac_2O (14 µL, 0.15 mmol) and allowed to stir at room temperature for 13 hours. The reaction was then quenched with 2M HCl and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give crude acetate protected product. Purification on

silica gel (50:1 Hexanes: EtOAc) gave **4.37** (10.4 mg, 40%) as a clear oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.78 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.11 (dd, *J* = 10.7, 1.9 Hz, 1H), 5.07 (d, *J* = 7.5 Hz, 1H), 4.91 (dd, *J* = 17.3, 1.9 Hz, 1H), 2.97 (dt, *J* = 12.5, 4.4 Hz, 1H), 2.87 (dddd, *J* = 11.9, 9.2, 8.3, 7.5 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.14 (dt, *J* = 10.7, 9.1 Hz, 1H), 1.96 (s, 3H), 1.79 – 1.73 (m, 2H), 1.42 – 1.27 (m, 5H), 1.11 (s, 3H), 0.94 (d, *J* = 2.7 Hz, 6H), 0.07 (s, 6H). Does not match Mehta's intermediate.[2b]

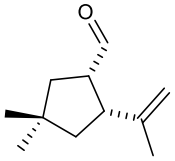


((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)methanol (4.41) A dry 250 mL roundbottom flask was charged with lactone **4.17** (3.83 g, 24.9 mmol) in 125mL of dry THF. The reaction was placed under N_2, cooled to -78°C, and treated dropwise with a 1.1 M solution of MeLi in THF (22.6 mL, 24.9 mmol). The reaction was then allowed to warm to 0°C and stir for 45 minutes then was quenched with aqueous NH_4Cl solution. The reaction mixture was then extracted with Et_2O, washed with brine, dried with $MgSO_4$, filtered and concentrated to yield 3.27 g methyl lactol as an opaque white semi solid (79%, 19.7 mmol). Further purification was not necessary, and this material was bought forward crude.

A dry 500 mL roundbottom was charged with methyltriphenylphosphonium bromide (55.4 g, 155 mmol) in 300 mL of THF. The reaction was cooled to 0°C and treated with potassium tert-butoxide (14.1 g, 126 mmol) as a solid in one portion, then placed under nitrogen. The reaction was then stirred for 2 hours slowly warming to room temperature. The reaction was then fit with an addition funnel and a solution of methyl lactol (3.27 g, 19.4 mmol) in 100 mL THF was added dropwise over 30 minutes. The reaction was then stirred a further 30 minutes at room temperature until complete by TLC. Upon completion reaction was quenched with H_2O and extracted with Et_2O. Organic layers where washed with brine, dried

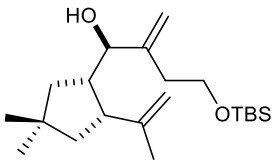
over $MgSO_4$, filtered and concentrated to give crude alcohol product**.** Purification on silica gel (9:1 Hexane: EtOAc) afforded **4.41** (2.42 g, 76%, 3.5:1 cis : trans) as a clear pale yellow oil. Further purification on silica gel (4:1 Chloroform: Hexane) allowed for separation of pure cis isomer to bring forward.

CIS Major ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.85 (d, *J* = 2.1 Hz, 1H), 4.79 (s, 1H), 3.55 (ddd, *J* = 11.6, 6.8, 5.0 Hz, 1H), 3.34 (dt, *J* = 11.2, 6.9 Hz, 1H), 2.75 (dt, *J* = 13.5, 7.2 Hz, 1H), 2.42 (dddd, *J* = 14.9, 8.1, 6.9, 4.8 Hz, 1H), 1.84 (d, *J* = 1.0 Hz, 3H), 1.69 – 1.61 (m, 2H), 1.52 (dd, *J* = 7.0, 5.3 Hz, 1H), 1.44 (dd, *J* = 12.4, 6.3 Hz, 1H), 1.38 (dd, *J* = 13.4, 4.9 Hz, 1H), 1.11 (s, 3H), 1.02 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.99, 110.17, 64.68, 47.42, 43.81, 43.72, 43.38, 36.97, 31.13, 30.23, 23.80. **HRMS** (EI) calculated for $[C_{11}H_{20}O + H]^+$ requires *m/z* 169.1587 found *m/z* 169.1587. **$[\alpha]^{22}_D$** +27.9 ° (c 0.58, CH_2Cl_2)

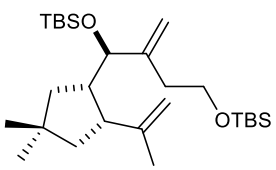


(1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentane-1-carbaldehyde (4.42)

A dry 100 mL round bottom flask was charged with alcohol **4.41** (613.2 mg, 3.67 mmol) in 18 mL of DCM. Reaction was then treated with pyridine (1.3 mL, 14.7 mmol) then des-martin periodate (2.33 g, 5.5 mmol). The reaction was stirred 1h at room temperature then concentrated in vac. The crude was then dissolved in 2:1 pentanes: Et_2O and flushed thru a plug of silica. Eluent was then washed with $CuSO_4$ (2 X 15 mL) and brine, dried over $MgSO_4$, filtered and reconstituted to give g of pure aldehyde **4.42** (560 mg, 92%) with no further purification necessary. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.53 (d, *J* = 3.2 Hz, 1H), 4.85 (q, *J* = 1.4 Hz, 1H), 4.81 (t, *J* = 1.3 Hz, 1H), 3.06 – 2.93 (m, 2H), 1.84 (dd, *J* = 13.7, 5.1 Hz, 1H), 1.78 (t, *J* = 1.0 Hz, 3H), 1.69 – 1.53 (m, 4H), 1.16 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.19, 143.53, 111.47, 52.57, 47.89, 44.45, 40.20, 38.05, 30.07, 29.45, 22.97. **HRMS** (EI) calculated for $[C_{11}H_{18}O + H]^+$ requires *m/z* 167.1430 found *m/z* 167.1431.

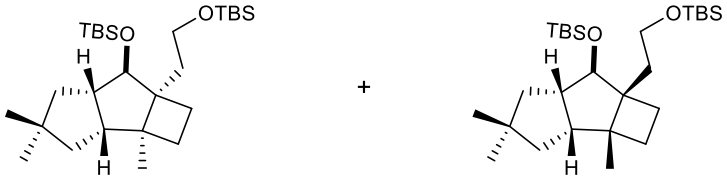


(R)-4-((tert-butyldimethylsilyl)oxy)-1-((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylenebutan-1-ol (4.44) A dry 250 mL roundbottom was charged with $CrCl_2$ (1.12 g, 9.0 mmol) and $NiCl_2$ (1.1 mg) in a nitrogen filled glovebox. Reaction was sealed and removed from the glovebox and placed under argon, then 25mL of dry DMSO was added followed by a mixture of aldehyde **4.42** (248 mg, 1.5 mmol) and tert-butyl((3-iodobut-3-en-1-yl)oxy)dimethylsilane[Ref] **4.43** (1.42g, 4.5 mmol) in 12.5 mL of DMSO. The reaction was then stirred for 16 hours at room temperature then quenched by addition of chloroform and aqueous NH_4Cl. The mixture was then extracted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated to give crude mixture of diastereomers. Purification on silica (50:1 Hexanes: EtOAc) yields the pure desired major diastereomer **4.44** (173mg, 33%), remaining aldehyde **4.42** (52 mg, 21%) and an inseparable mixture of 3 diastereomers one the cis minor the other two resulting from epimerization of aldehyde prior to addition (79mg, 15%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.06 (t, *J* = 1.7 Hz, 1H), 4.92 (d, *J* = 2.1 Hz, 1H), 4.88 – 4.83 (m, 2H), 4.11 (d, *J* = 3.3 Hz, 1H), 3.76 – 3.66 (m, 2H), 2.82 (ddd, *J* = 12.6, 9.1, 6.3 Hz, 2H), 2.52 (tdd, *J* = 9.6, 7.2, 2.8 Hz, 1H), 2.25 (dt, *J* = 14.5, 7.3 Hz, 1H), 2.21 (d, *J* = 3.7 Hz, 1H), 2.14 (dt, *J* = 14.3, 6.9 Hz, 1H), 1.86 (t, *J* = 0.9 Hz, 3H), 1.72 (t, *J* = 12.3 Hz, 1H), 1.62 (dd, *J* = 13.2, 7.2 Hz, 1H), 1.45 – 1.30 (m, 2H), 1.11 (s, 3H), 0.99 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.78, 147.55, 110.76, 110.45, 73.00, 63.18, 47.47, 44.84, 42.23, 38.98, 36.86, 36.62, 29.70, 29.17, 25.94, 24.42, 18.37, -5.34. **HRMS** (EI) calculated for $[C_{21}H_{40}O_2Si + H]^+$ requires *m/z* 353.2870 found *m/z* 353.2865. **$[\alpha]^{22}_D$**



(R)-5-((1S,2R)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2,2,3,3,10,10,11,11-octamethyl-6-methylene-4,9-dioxa-3,10-disiladodecane (4.39a) A 50 mL roundbottom flask was charged with **4.44** (234 mg, 0.66 mmol) in 4 mL DCM. Reaction was placed under N_2, cooled to 0°C, and treated

with 2,6- lutidine (0.15 mL, 1.3 mmol). The reaction was then treated with TBSOTf (0.23mL, 0.99 mmol) dropwise. The reaction was then stirred for 30 minutes at 0°C before being quenched with aqueous sodium bicarbonate. The mixture was then extracted with DCM, washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification on silica gel (10:1 Hexanes: DCM) yielded **4.39a** (248.1 mg, 81%) as a clear colorless oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 4.92 (s, 1H), 4.77 (s, 1H), 4.75 (d, *J* = 1.7 Hz, 1H), 4.69 (s, 1H), 4.05 (d, *J* = 5.2 Hz, 1H), 3.74 (t, *J* = 7.5 Hz, 2H), 2.62 (q, *J* = 8.5 Hz, 1H), 2.35 – 2.23 (m, 2H), 2.18 (dt, *J* = 15.1, 7.5 Hz, 1H), 1.79 – 1.72 (m, 4H), 1.67 (dd, *J* = 12.4, 9.8 Hz, 1H), 1.47 (ddd, *J* = 12.0, 7.8, 3.1 Hz, 2H), 1.11 (s, 3H), 0.99 (s, 3H), 0.89 (d, *J* = 7.4 Hz, 18H), 0.06 (s, 6H), 0.00 (s, 3H), -0.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.48, 145.88, 111.74, 76.39, 62.61, 48.21, 45.56, 44.87, 41.68, 36.81, 34.54, 30.51, 30.19, 26.13, 25.99, 23.65, 18.38, 18.23, -3.56, -4.45, -5.24. **HRMS** (EI) calculated for $[C_{11}H_{18}O + H]^+$ requires *m/z* 467.3735 found *m/z* 467.3734. **$[\alpha]^{22}_D$** +21.6 ° (c 0.73, CH_2Cl_2)



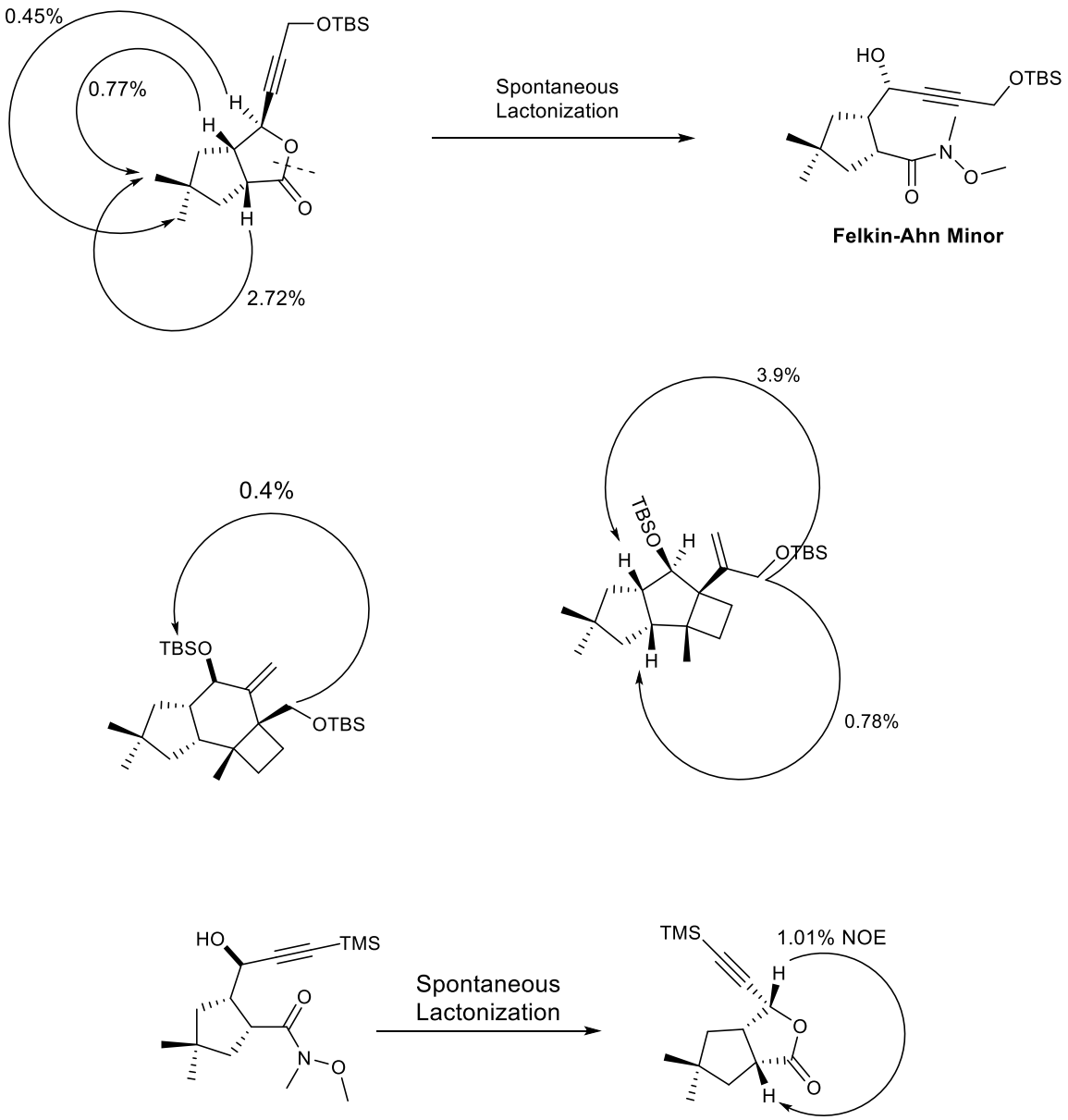
tert-butyl(2-((2aS,2bR,5aS,6R)-6-((tert-butyldimethylsilyl)oxy)-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)ethoxy)dimethylsilane (4.40) A quartz vessel was charged with $[Cu(COD)Cl]_2$ (1 mg, 0.0025 mmol) and placed under N_2. Diene **4.39a** (47.8 mg, 0.1 mmol) was then added as a solution in 3.25 mL of Et_2O and the reaction was sonicated 1 minute and stirred for 5 minutes. A solution of $AgSbF_6$ (3.4 mg, 0.01 mmol) in 3.25 mL of Et_2O and the reaction was stirred for 20 minutes under N_2. The reaction was then fit with a coldfinger and irradiated at 254 nm for 6 hours. The reaction was then flushed through a pad of silica with Et_2O and concentrated to give a crude mixture of diastereomers 3.5:1 d.r. Purification on silica (10:1 Hexanes:DCM) allowed for isolation of **4.40 Major** (29.7 mg, 62%) and **4.40 Minor** (8.7 mg, 18%).

4.40 Major tert-butyl(2-((2aS,2bR,5aS,6R,6aR)-6-((tert-butyldimethylsilyl)oxy)-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)ethoxy)dimethylsilane

^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.20 (td, *J* = 9.4, 6.4 Hz, 1H), 3.96 (d, *J* = 4.1 Hz, 1H), 3.60 (td, *J* = 9.7, 3.9 Hz, 1H), 2.85 (td, *J* = 7.5, 3.5 Hz, 2H), 2.36 (td, *J* = 9.1, 6.5 Hz, 1H), 2.29 – 2.17 (m, 2H), 1.88 (ddd, *J* = 10.2, 6.6, 1.2 Hz, 1H), 1.83 (dddd, *J* = 13.1, 9.2, 4.0, 1.0 Hz, 1H), 1.60 (dd, *J* = 12.6, 6.8 Hz, 1H), 1.54 (s, 3H), 1.38 (ddd, *J* = 9.8, 6.4, 1.2 Hz, 1H), 1.34 (dd, *J* = 13.0, 6.9 Hz, 1H), 1.25 – 1.19 (m, 1H), 1.11 (d, *J* = 1.1 Hz, 3H), 1.05 (s, 3H), 0.91 (s, 4H), 0.90 (s, 8H), 0.88 (s, 9H), 0.06 (s, 6H), 0.01 (d, *J* = 2.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 81.19, 62.44, 57.96, 57.19, 48.67, 46.77, 45.29, 44.83, 38.74, 37.59, 34.14, 29.99, 29.71, 29.35, 28.66, 26.16, 26.10, 24.86, 18.41, -4.59, -4.60, -5.00, -5.12. **$[\alpha]^{22}_{D}$** +34.1 ° (c 1.49, CH_2Cl_2)

4.40 Minor tert-butyl(2-((2aR,2bR,5aS,6R,6aS)-6-((tert-butyldimethylsilyl)oxy)-2a,4,4-trimethyloctahydrocyclobuta[a]pentalen-6a(1H)-yl)ethoxy)dimethylsilane ^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.03 (d, *J* = 6.8 Hz, 1H), 3.77 – 3.70 (m, 1H), 3.63 – 3.55 (m, 1H), 2.45 (dddd, *J* = 12.2, 9.6, 8.1, 6.8 Hz, 1H), 2.34 (ddd, *J* = 12.1, 9.8, 8.2 Hz, 1H), 1.83 (dt, *J* = 11.5, 8.7 Hz, 1H), 1.75 – 1.63 (m, 5H), 1.54 – 1.50 (m, 1H), 1.32 – 1.27 (m, 2H), 1.21 (q, *J* = 11.8, 11.3 Hz, 3H), 1.08 (s, 6H), 0.92 (s, 3H), 0.89 (d, *J* = 0.9 Hz, 18H), 0.04 – 0.03 (m, 9H), 0.02 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 90.27, 60.71, 56.93, 54.95, 52.59, 50.53, 48.53, 43.91, 40.97, 35.40, 29.71, 29.10, 27.19, 27.11, 26.06, 25.95, 23.28, 18.37, 18.02, -4.23, -4.28, -5.12, -5.15.

4.5.2 NOE Data


0.45%
0.77%
OTBS
H
H
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H
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Spontaneous
Lactonization
HO
OTBS
N
O
O
Felkin-Ahn Minor
3.9%
TBSO
H
H
OTBS
H
0.78%
0.4%
TBSO
OTBS
HO
TMS
O
N
O
Spontaneous
Lactonization
TMS
1.01% NOE
H
O
O
H

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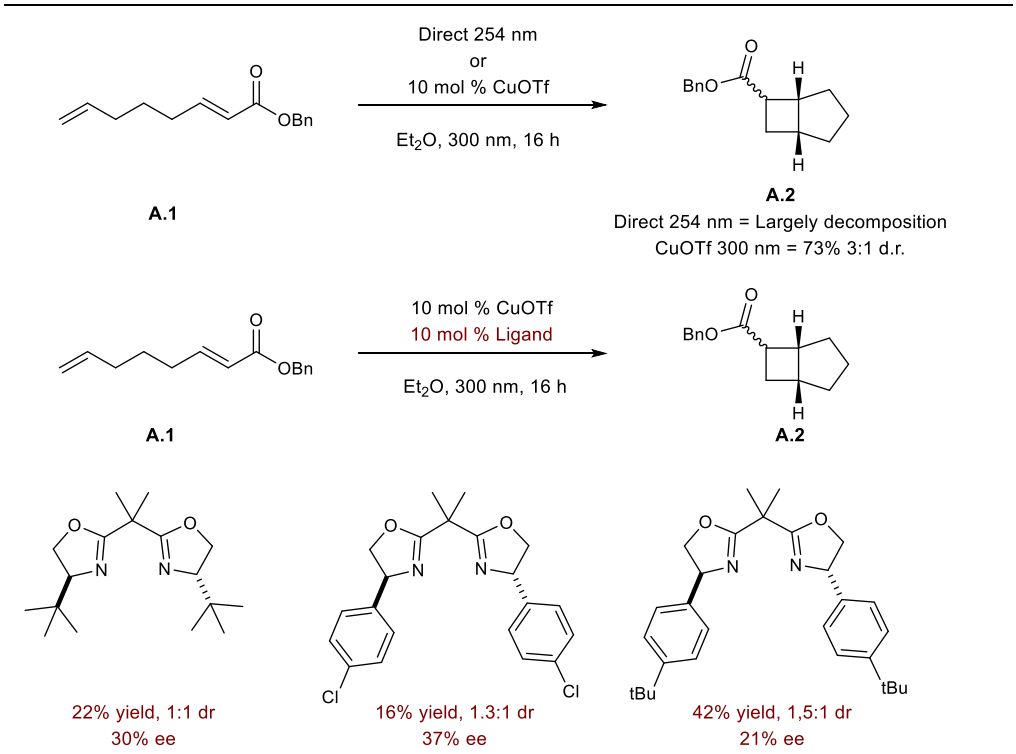
Appendix A. Cu(I) Catalyzed [2+2] Cycloaddition of Electron Deficient 1,6 - Heptadienes and Progress Towards Enantioselective Catalysis.

A.1 Discussion

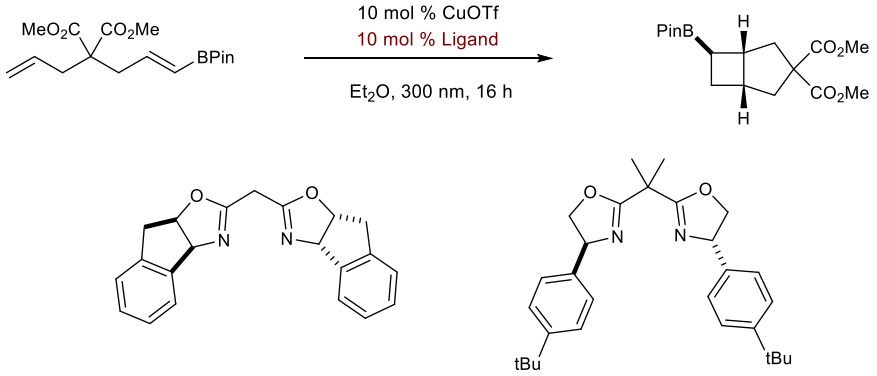
While exploring the scope of the racemic Salomon–Kochi reaction, we wondered if it might be applicable to substrates that decompose upon direct irradiation at 254 nm if simply a longer wavelength were to be employed. UV–vis experiments revealed that enones and other electron-deficient olefins undergo a similar red shift when coordinated to copper, giving compounds that can be photoexcited at longer wavelengths (300 nm). Irradiation at 300 nm under typical Salomon–Kochi conditions gave the desired product in good yield without the decomposition observed at 254 nm (Scheme A.1). With this result in hand, we wondered if electron-deficient olefins would better tolerate a more electron rich ligated copper catalyst than the previous neutral olefins. We hypothesized that π backdonation from the metal to the electron deficient olefin could be a much larger component of olefin coordination in this system, leading us to believe that chiral BOX type ligands could be employed where they have previously failed on electron-neutral alkenes.

Scheme A.1 Progress Towards Cu(I) Templated Enantioselective Intramolecular [2+2] of Electron Deficient 1,6-Heptadienes



We were delighted to see that not only did BOX type ligands not shut down the reaction, they also resulted in substantial enantioenrichment of cycloadducts. NMR analysis of the 1:1 Cu(I) chiral ligand complexes suggests that the dominant interaction is still olefin coordination because of the disappearance of the terminal olefin carbon signals upon coordination with the catalyst. If this is true this chemistry should not only be limited to enones, but rather a wide variety of electron deficient olefin coupling partners. This is demonstrated by cyclization of vinyl boronate ester using this same strategy. While no enantiomeric excess was obtained for this experiment, the fact the diastereoselectivity is much different in the presence of the chiral ligand suggests the ligand has an impact on the stereochemistry-determining steps of the reaction. These results are highly preliminary, but they represent a potentially new mode of catalysis in asymmetric [2+2] photocycloadditions, using the π-system itself to coordinate to the chiral catalyst.

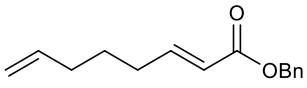
Scheme A.2 Expanding Method to Other Electron Deficient 1,6-Heptadienes



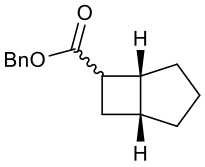
17% yield, 1.6:1 dr

42% yield, 2.3:1 dr

A.2 Experimental



benzyl (E)-octa-2,7-dienoate (A.1) A 25 mL roundbottom was charged with benzyl 2-(triphenyl-l5-phosphaneylidene)acetate (2.5 g, 6.1 mmol) in 5 mL of DCM. Reaction was placed under N_2 and treated with a solution of hex-5-enal (402 mg, 4.1 mmol). The reaction was then stirred for 24 hours then concentrated to give crude product. Purification on silica gel (9:1 Pentanes: Et_2O) gave **A.1** (562 mg, 60%) as a clear pale yellow oil. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.40 – 7.30 (m, 5H), 7.01 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.88 (dt, *J* = 15.6, 1.6 Hz, 1H), 5.78 (ddt, *J* = 16.9, 10.2, 6.8 Hz, 1H), 5.30 (s, 1H), 5.18 (s, 2H), 5.05 – 4.94 (m, 2H), 2.27 – 2.18 (m, 2H), 2.12 – 2.04 (m, 3H), 1.62 – 1.51 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.47, 149.69, 137.97, 136.13, 128.54, 128.19, 128.16, 121.18, 115.13, 66.03, 33.07, 31.56, 27.09.



benzyl-bicyclo[3.2.0]heptane-6-carboxylate (A.2)

Racemic Procedure

A quartz vessel was charged with **A.1** (46.1 mg, 0.2 mmol) in 4 mL of Et_2O. The reaction was placed under N_2 and treated with a solution of CuOTf (5 mg, 0.01 mmol) in 4 mL of Et_2O. After stirring for 15 minutes the reaction was fit with a coldfinger and irradiated at 300 nm for 18 hours. The reaction was then flushed through a pad of silica with Et_2O and concentrated to give crude cycloadducts (75% NMR Yield with 16.7 mg of TMSPh internal standard, 3.5:1 d.r.). Purification on silica gel (40:1 Pentanes: Et_2O) allowed for characterization of the major diastereomer. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.41 – 7.28 (m, 5H), 5.13 (s, 2H), 2.98 – 2.89 (m, 1H), 2.79 – 2.67 (m, 1H), 2.59 (dddd, *J* = 9.7, 6.0, 4.9, 1.0 Hz, 1H), 2.49 – 2.40 (m, 1H), 1.88

– 1.78 (m, 2H), 1.66 (dddd, *J* = 14.8, 7.2, 4.3, 1.7 Hz, 2H), 1.60 – 1.38 (m, 2H), 1.35 – 1.21 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.10, 136.32, 132.84, 128.51, 128.06, 128.02, 66.06, 42.07, 40.61, 34.94, 32.91, 26.95, 24.67, 22.34, 14.06.

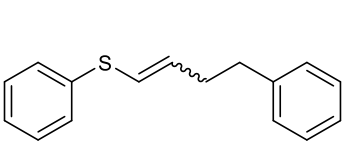
Asymmetric General Procedure

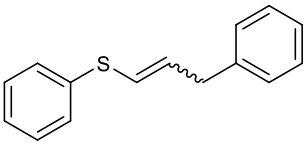
A quartz vessel was charged with chiral ligand (0.01 mmol) and **A.1** (46.1 mg, 0.2 mmol) in 4 mL of Et_2O. The reaction was placed under N_2 and treated with a solution of CuOTf (5 mg, 0.01 mmol) in 4 mL of Et_2O. After stirring for 15 minutes the reaction was fit with a coldfinger and irradiated at 300 nm for 18 hours. The reaction was then flushed through a pad of silica with Et_2O and concentrated to give crude cycloadducts (75% NMR Yield with 16.7 mg of TMSPh internal standard, 3.5:1 d.r.). Purification on silica gel (40:1 Pentanes: Et_2O) allowed for characterization of the major diastereomer. HPLC Method: OJ-H, Gradient_10_30MTBE

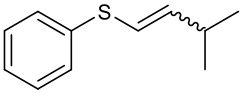
Appendix B ^{1}H and ^{13}C NMR Spectra for New Compounds

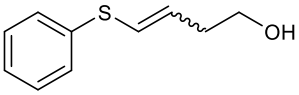
List of Compounds Chapter 2

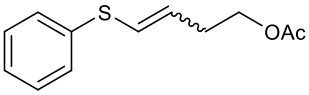
Aryl Vinyl Sulfides

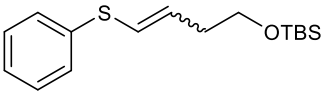


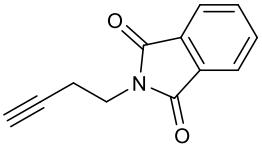


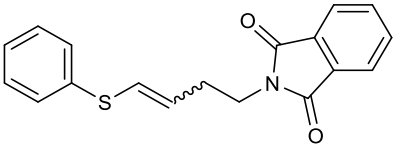


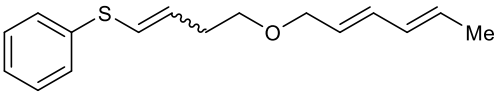




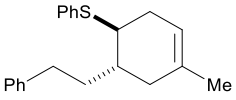


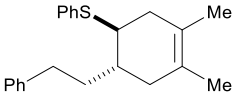


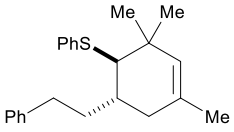


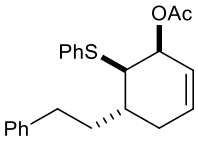


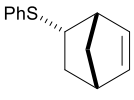
[4+2] Cycloadducts

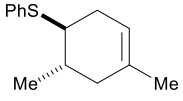


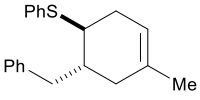


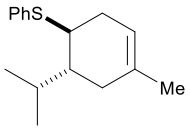


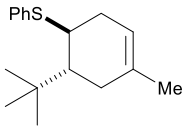


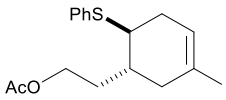


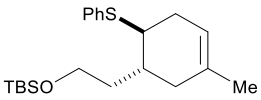


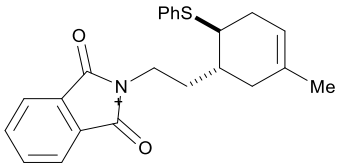


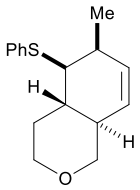




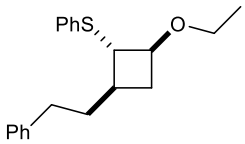


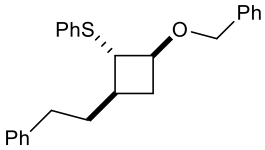


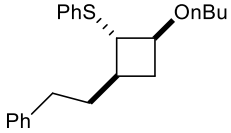


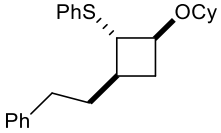


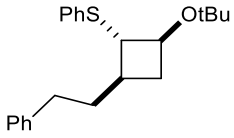
[2+2] Cycloadducts

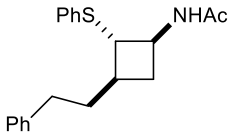


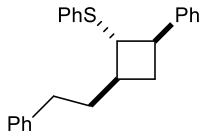


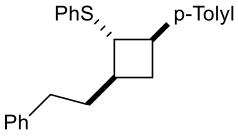




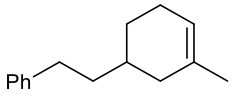


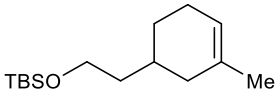


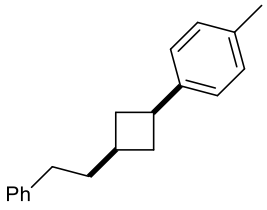


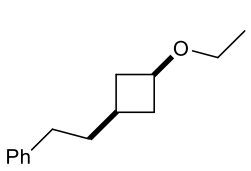


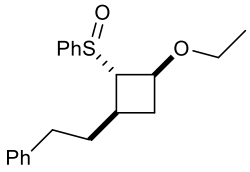
Product Derivatizations

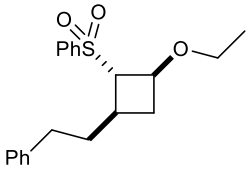


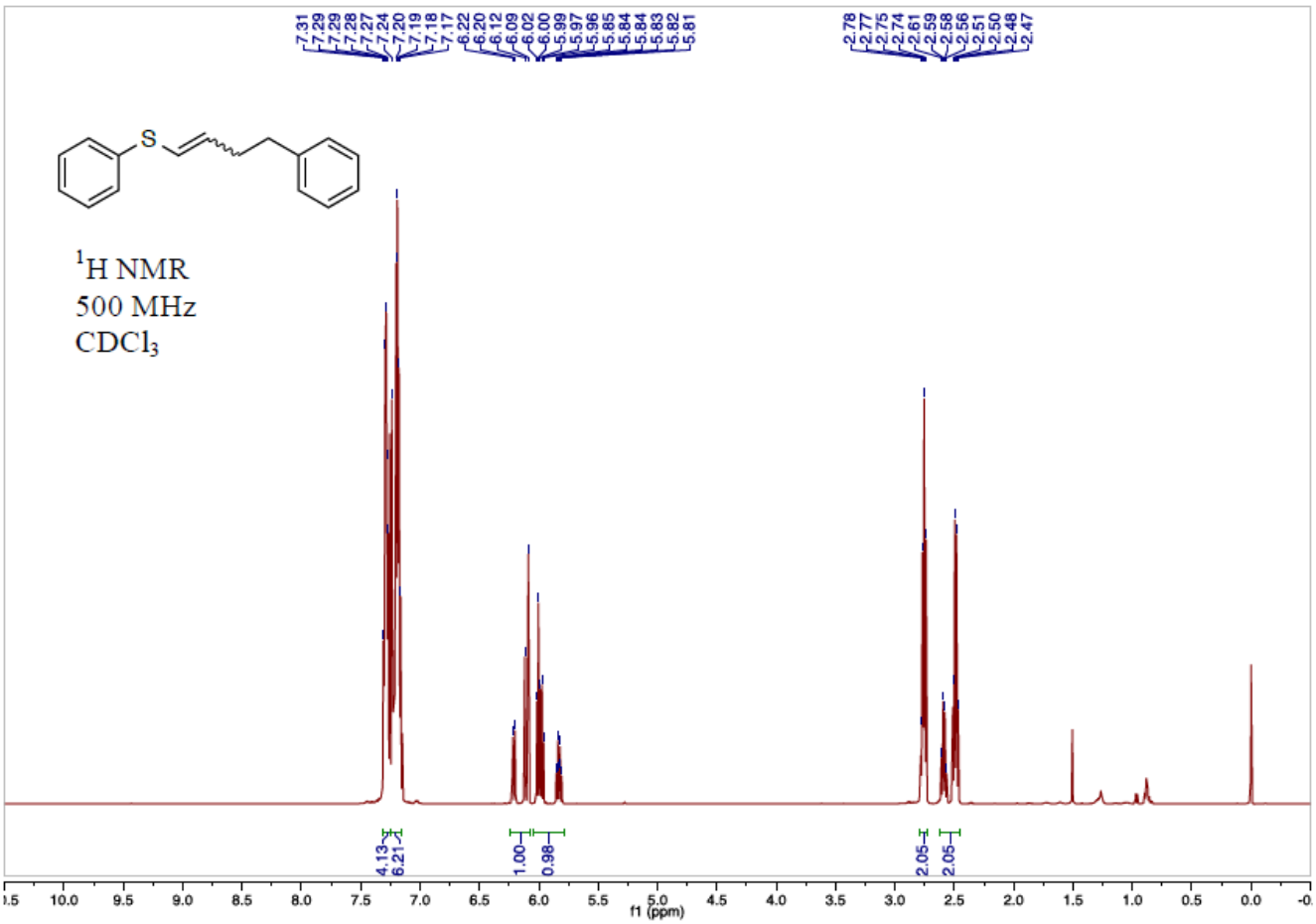








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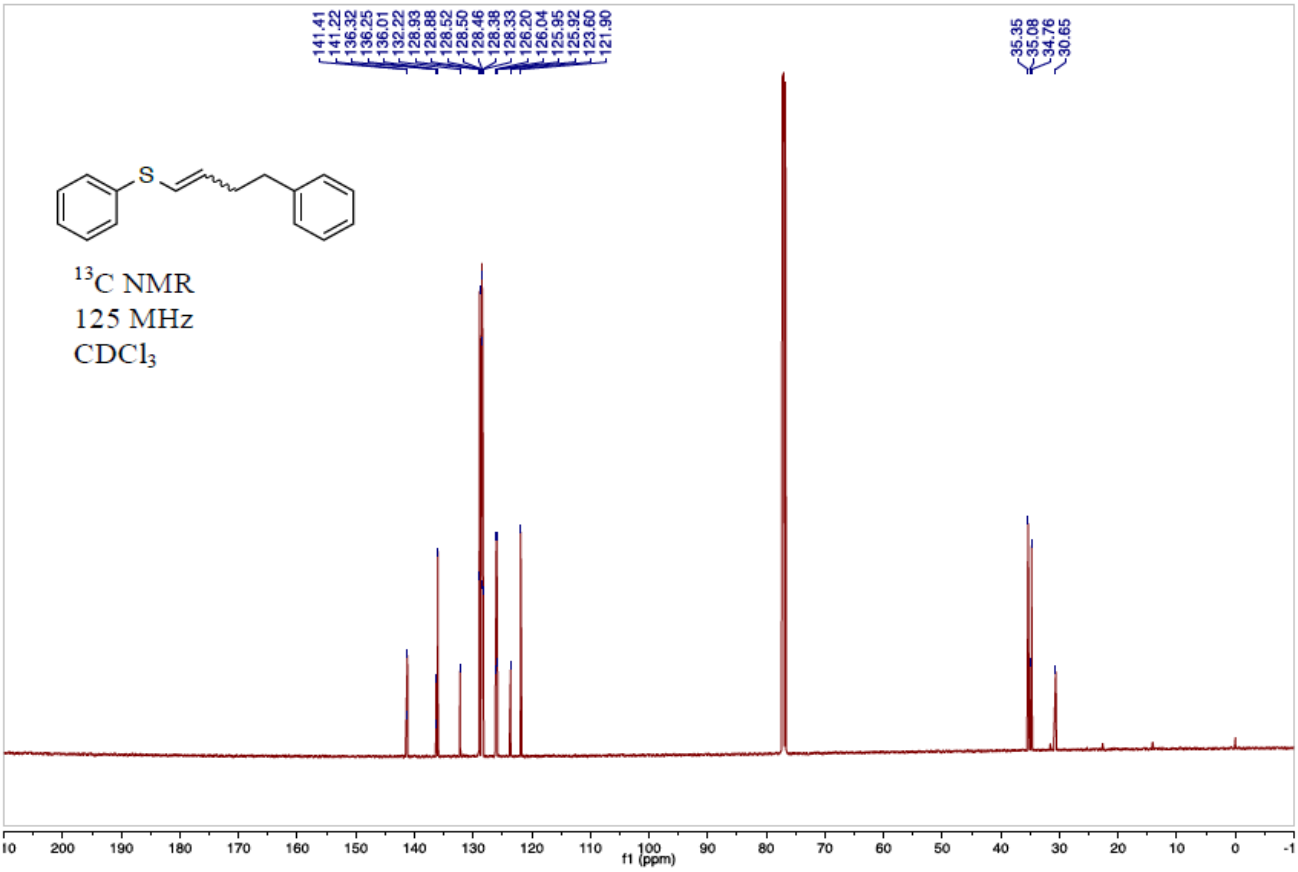
6.09
6.02
6.00
5.99
5.97
5.96
5.85
5.84
5.84
5.83
5.82
5.81
2.78
2.77
2.75
2.74
2.61
2.59
2.58
2.56
2.51
2.50
2.48
2.47
S
^{1}H NMR
500 MHz
$CDCl_3$
4.13
6.21
1.00
0.98
2.05
2.05
f1 (ppm)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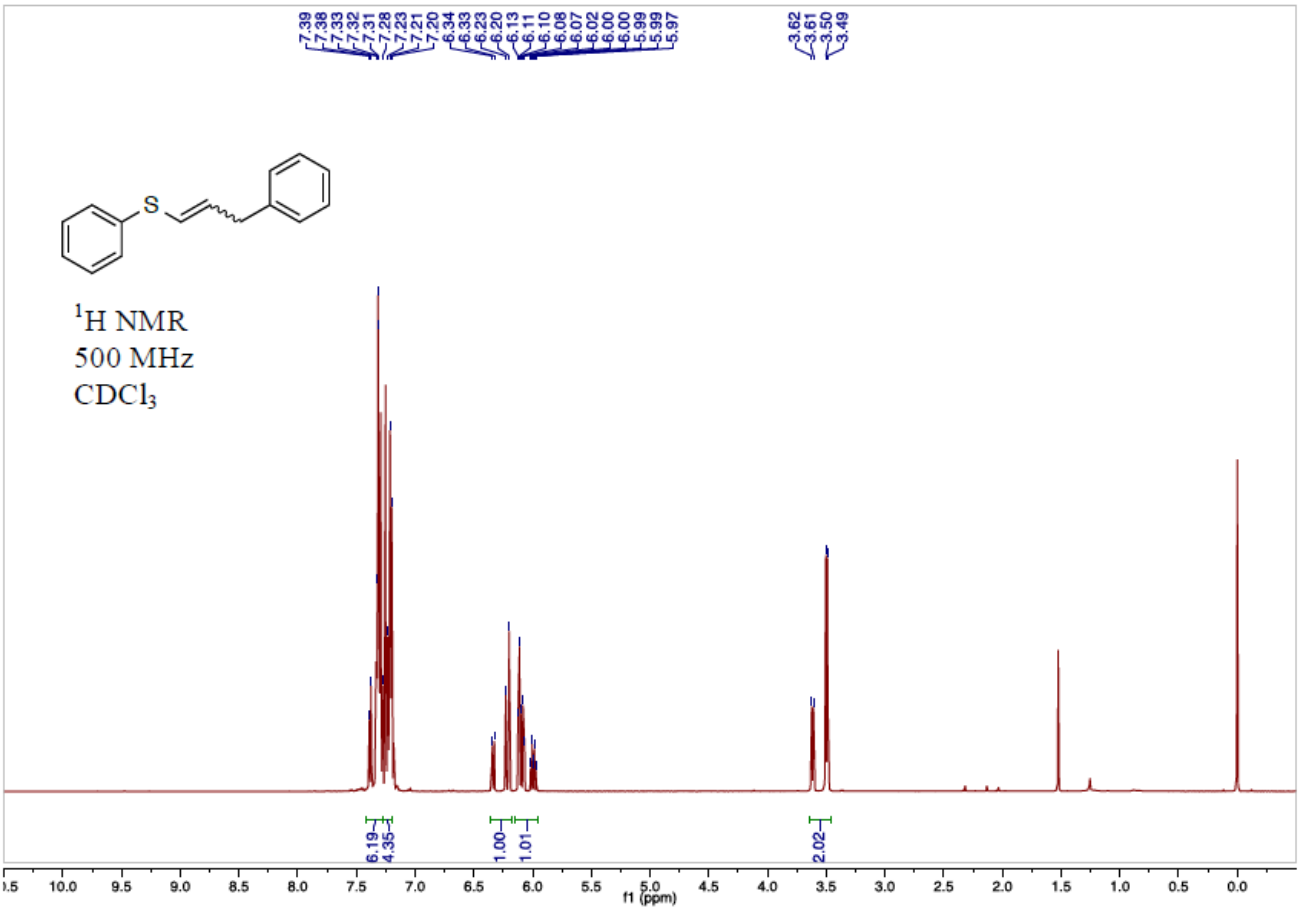
128.38
128.33
126.20
126.04
125.95
125.92
123.60
121.90
35.35
35.08
34.76
30.65
S
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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7.21
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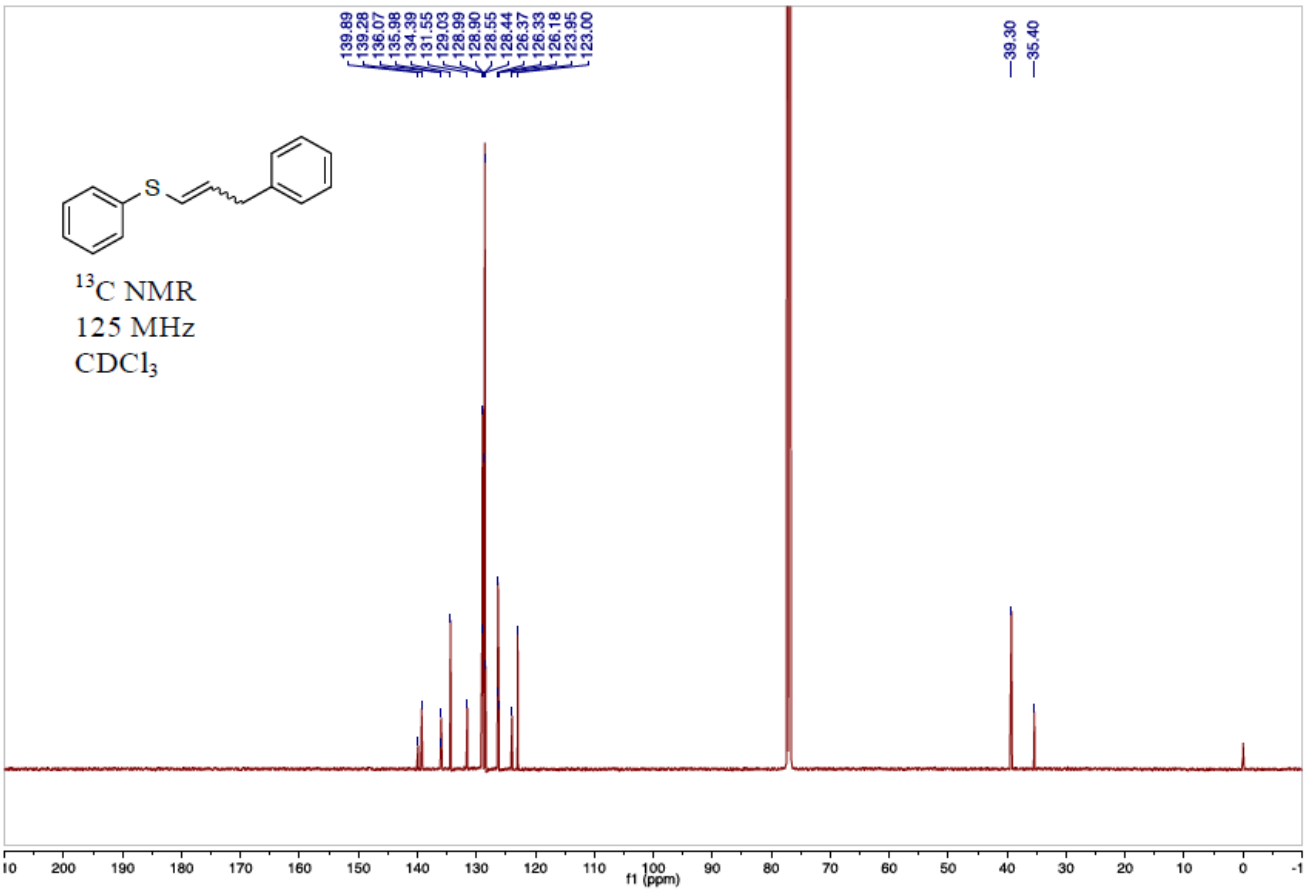
6.23
6.20
6.13
6.11
6.10
6.08
6.07
6.02
6.00
6.00
5.99
5.99
5.97
3.62
3.61
3.50
3.49
S
1H NMR
500 MHz
CDCl3
6.19
4.35
1.00
1.01
2.02
f1 (ppm)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139.28
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135.98
134.39
131.55
129.03
128.99
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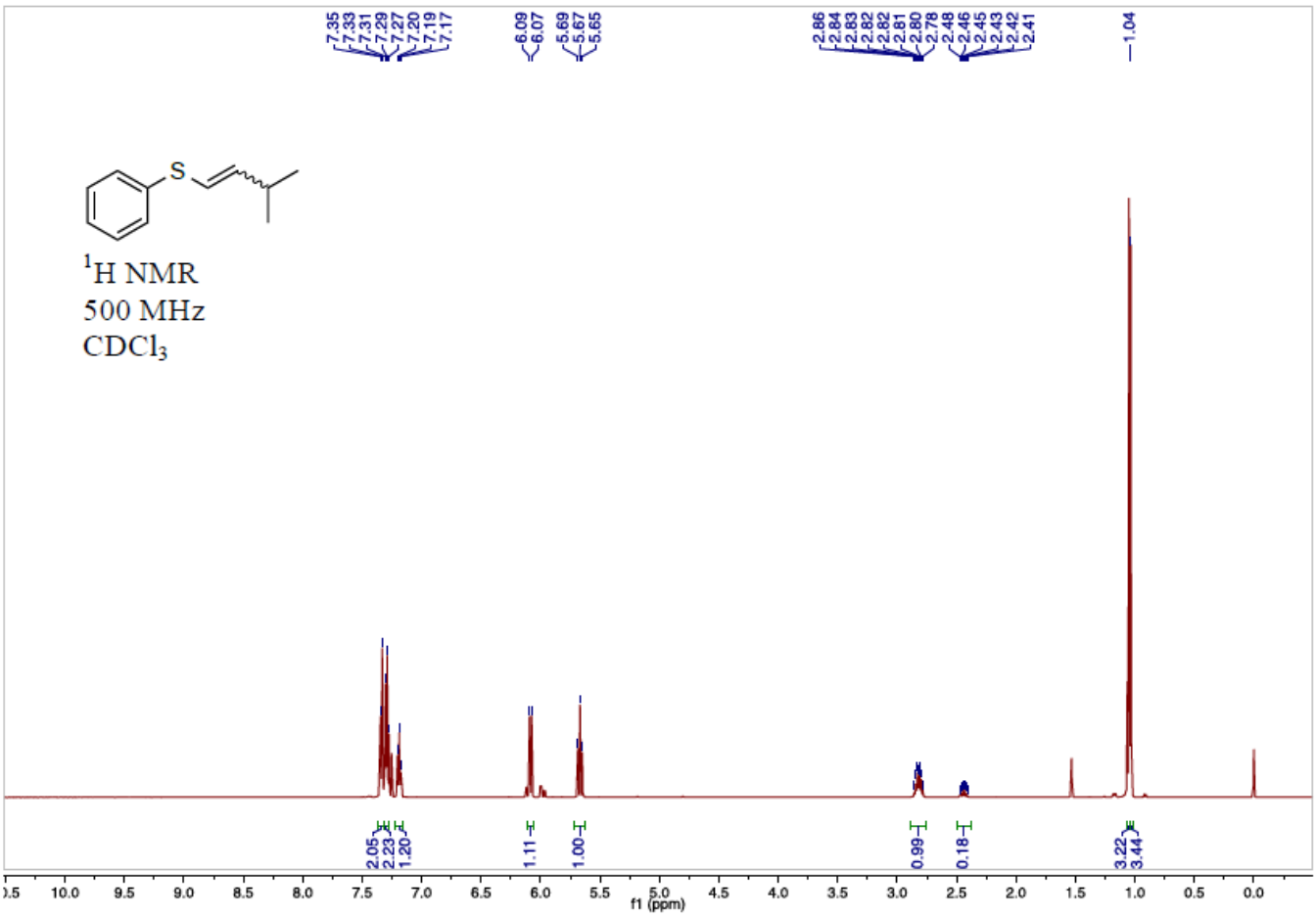
128.55
128.44
126.37
126.33
126.18
123.95
123.00
39.30
35.40
S
13C NMR
125 MHz
CDCl3
f1 (ppm)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7.20
7.19
7.17
6.09
6.07
5.69
5.67
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2.86
2.84
2.83
2.82
2.82
2.81
2.80
2.78
2.48
2.46
2.45
2.43
2.42
2.41
1.04
S
1H NMR
500 MHz
CDCl3
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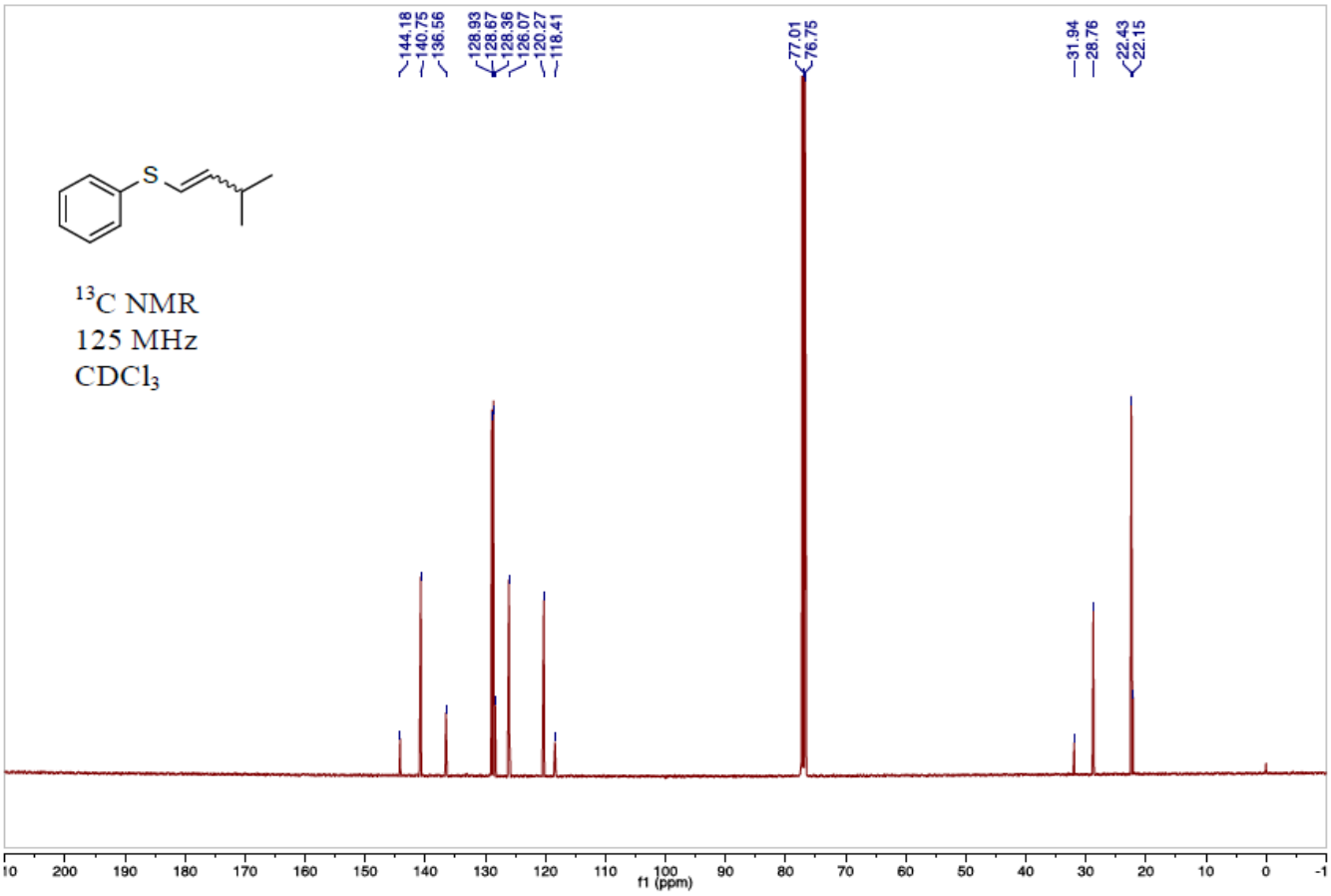
2.23
1.20
1.11
1.00
0.99
0.18
3.22
3.44
f1 (ppm)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128.67
128.36
126.07
120.27
118.41
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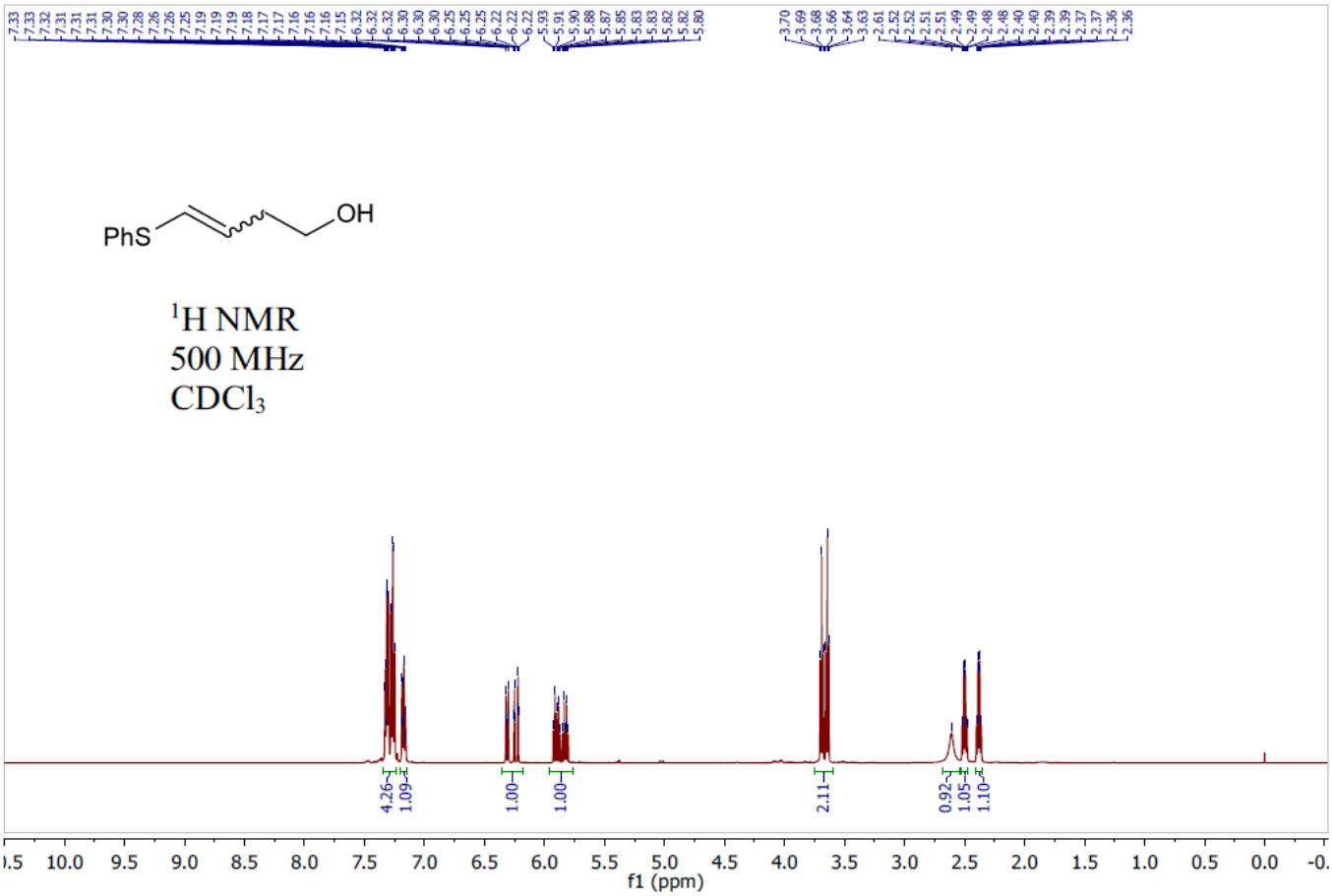
76.75
31.94
28.76
22.43
22.15
S
13C NMR
125 MHz
CDCl3
f1 (ppm)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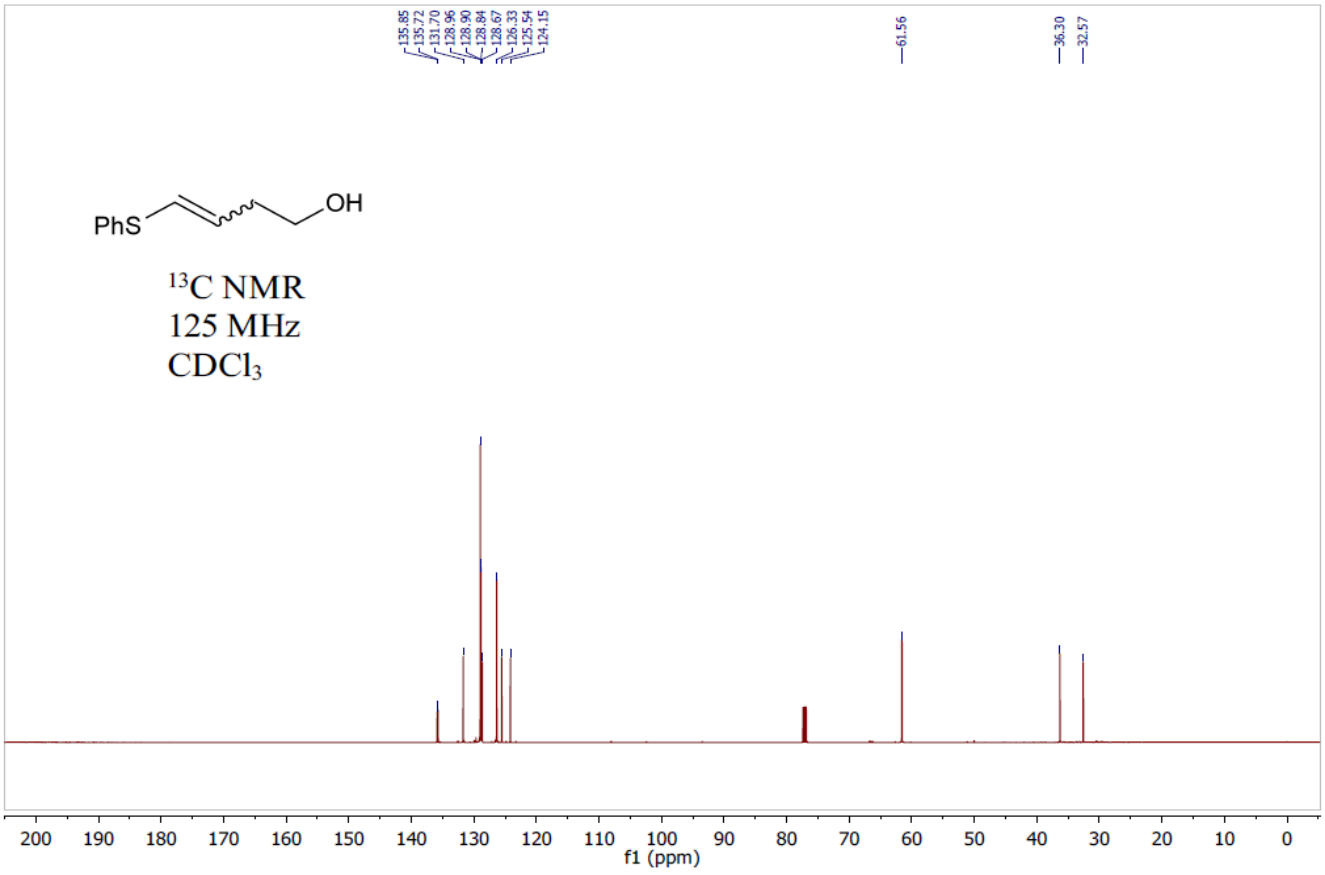
OH
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)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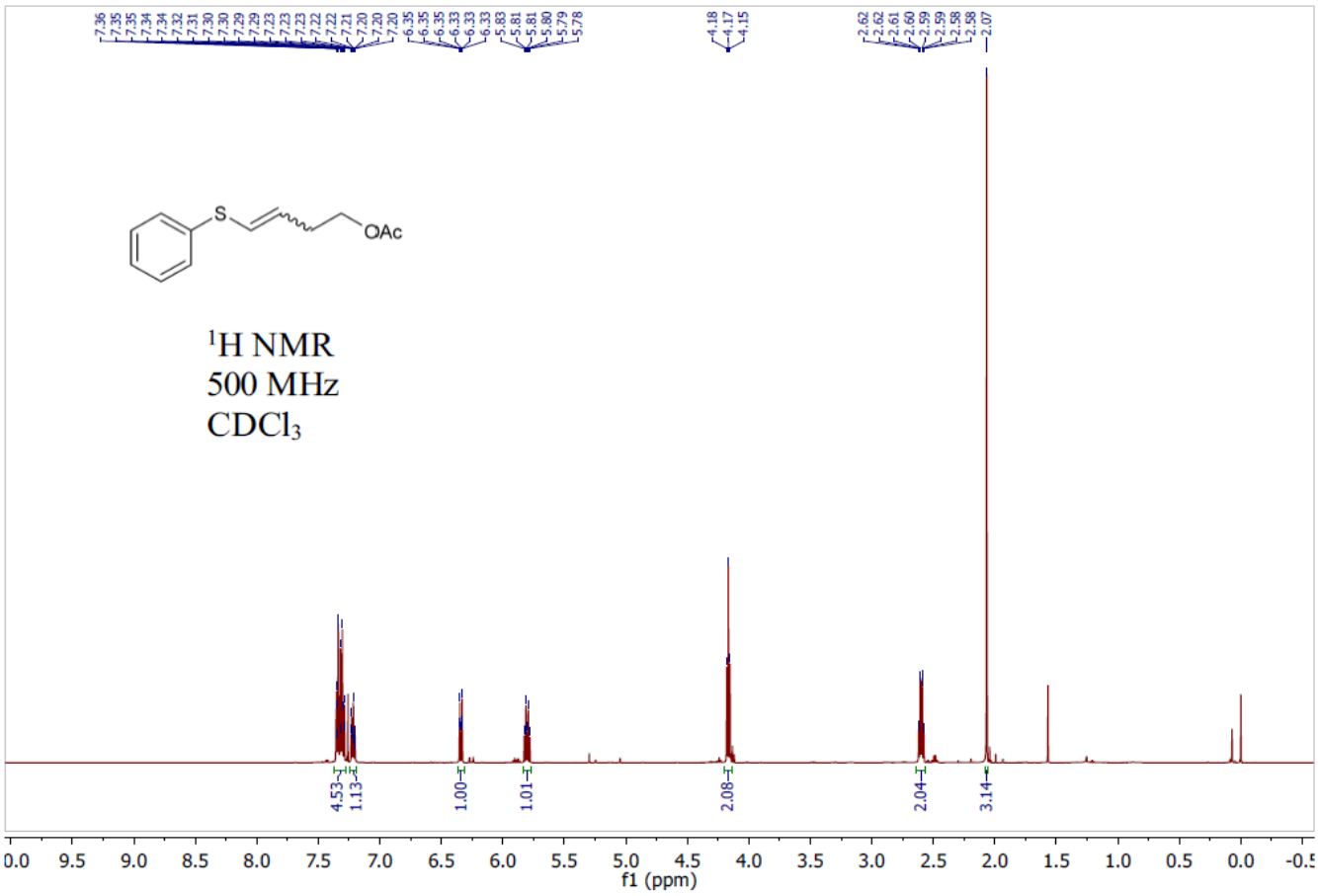
OH
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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OAc
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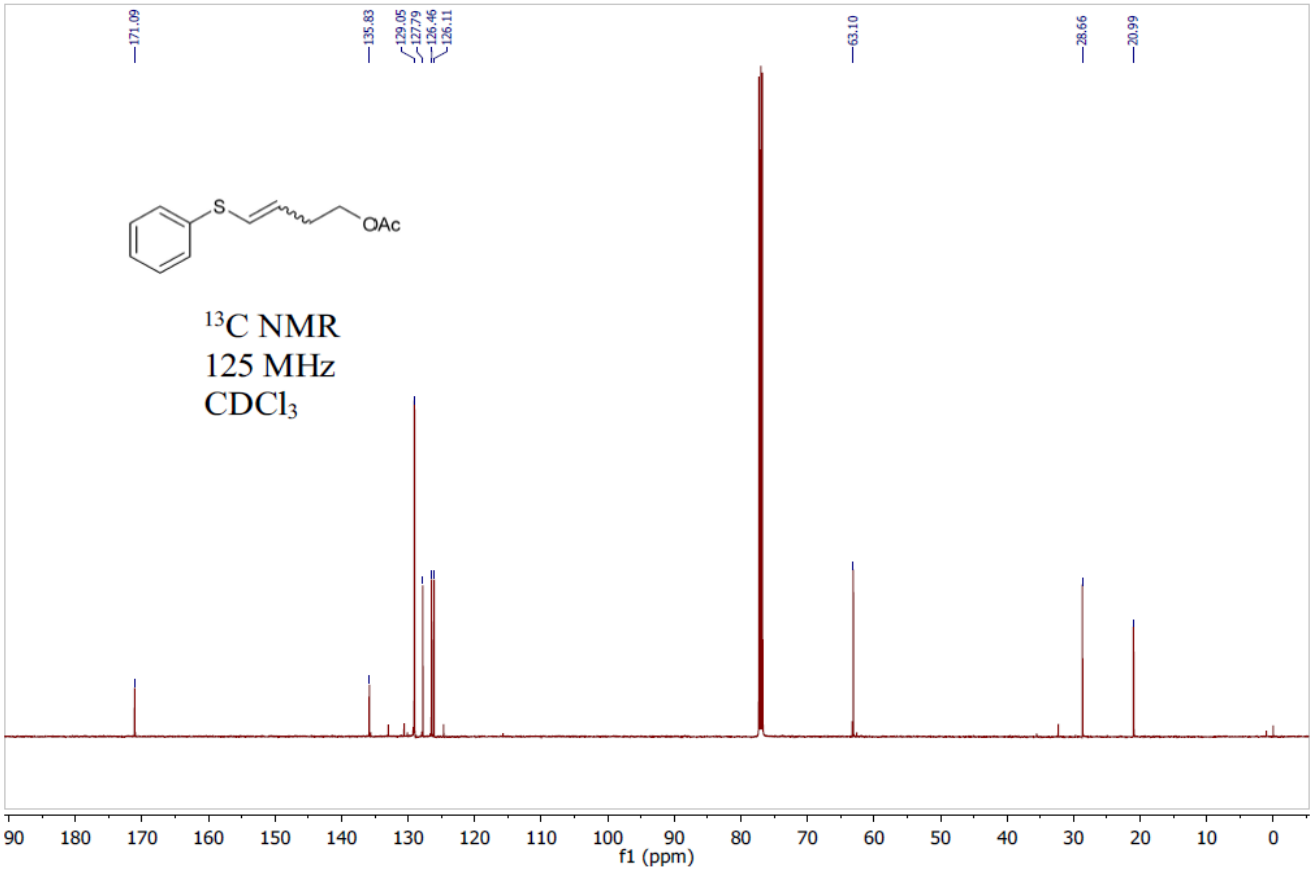
500 MHz
$CDCl_3$
f1 (ppm)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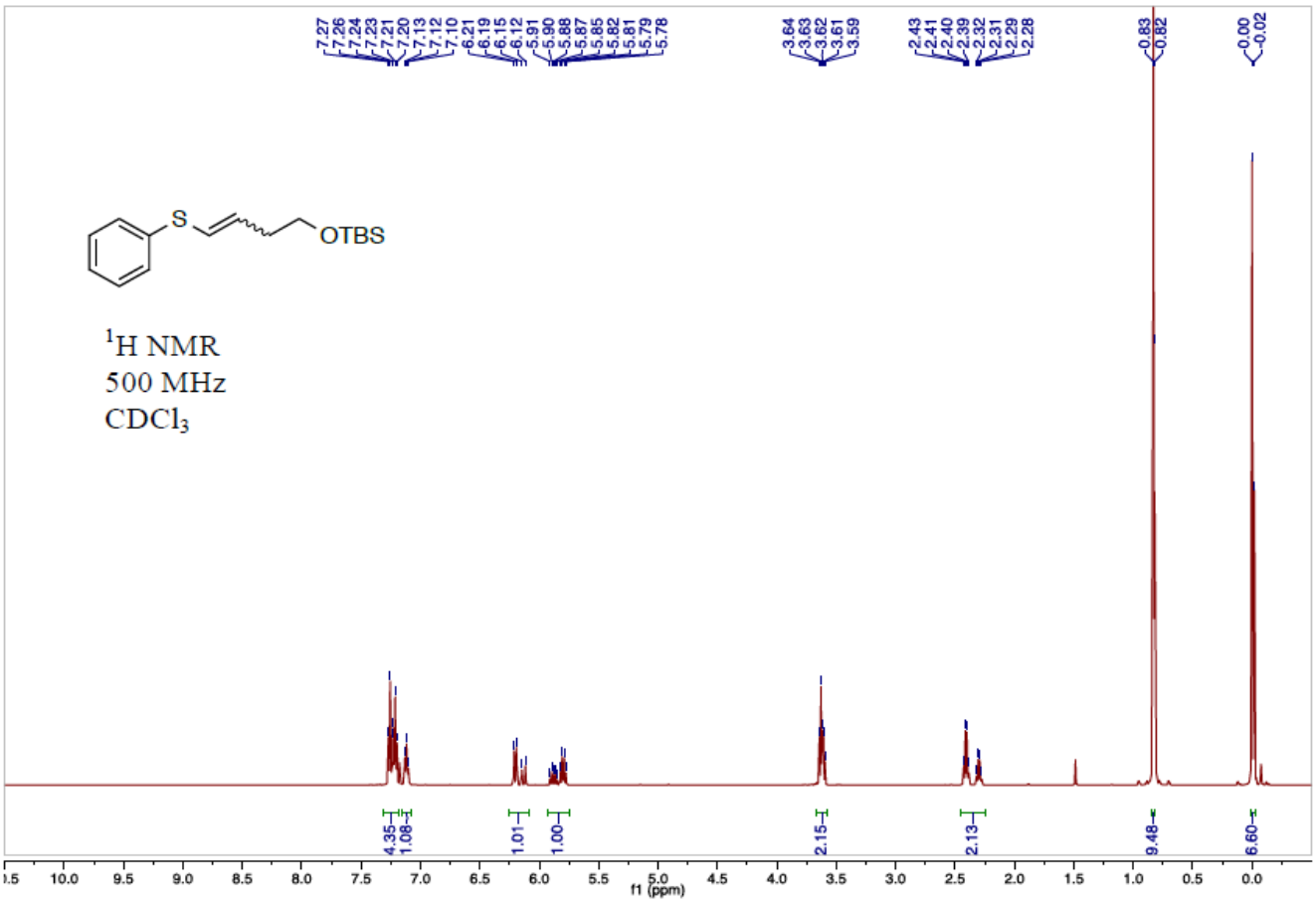
OAc
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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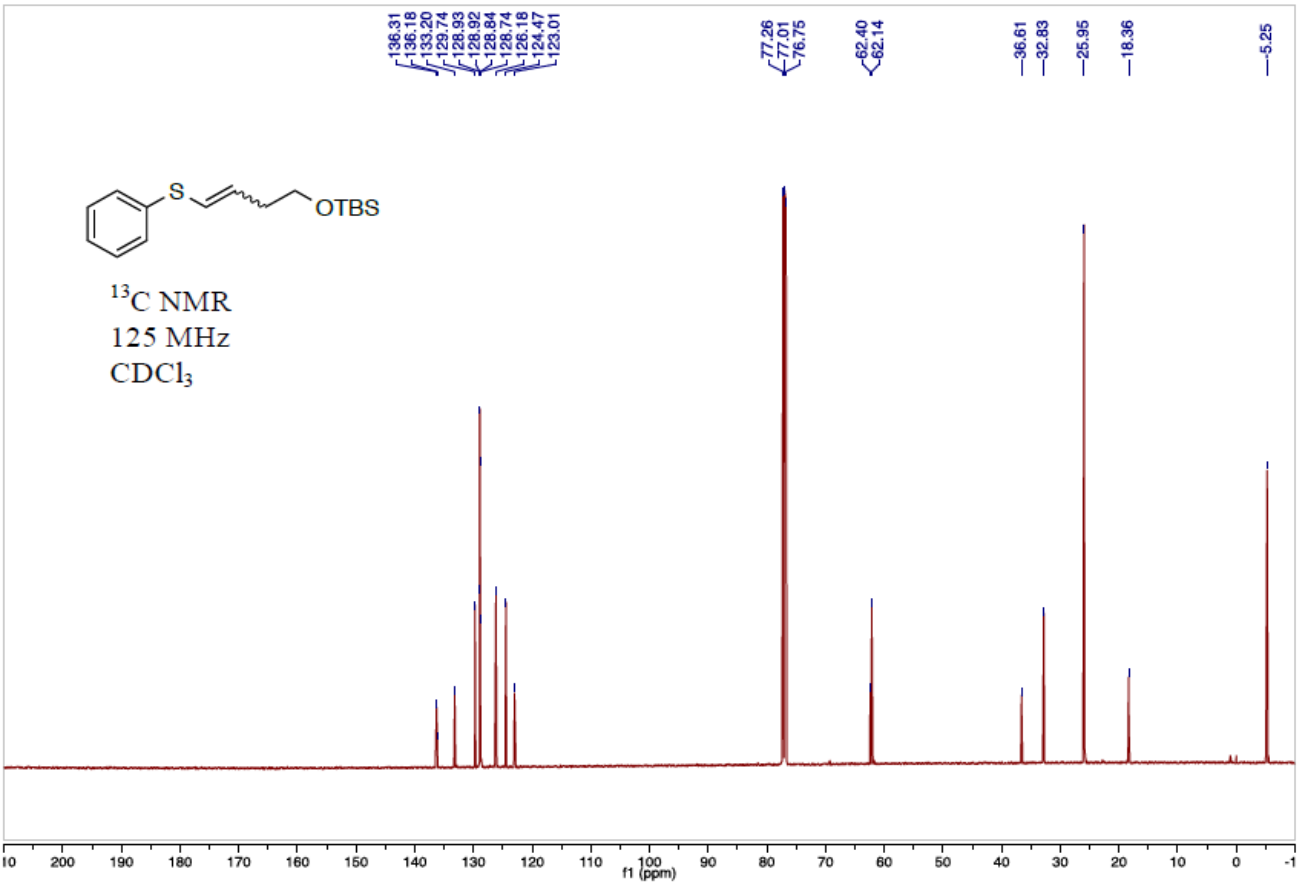
OTBS
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)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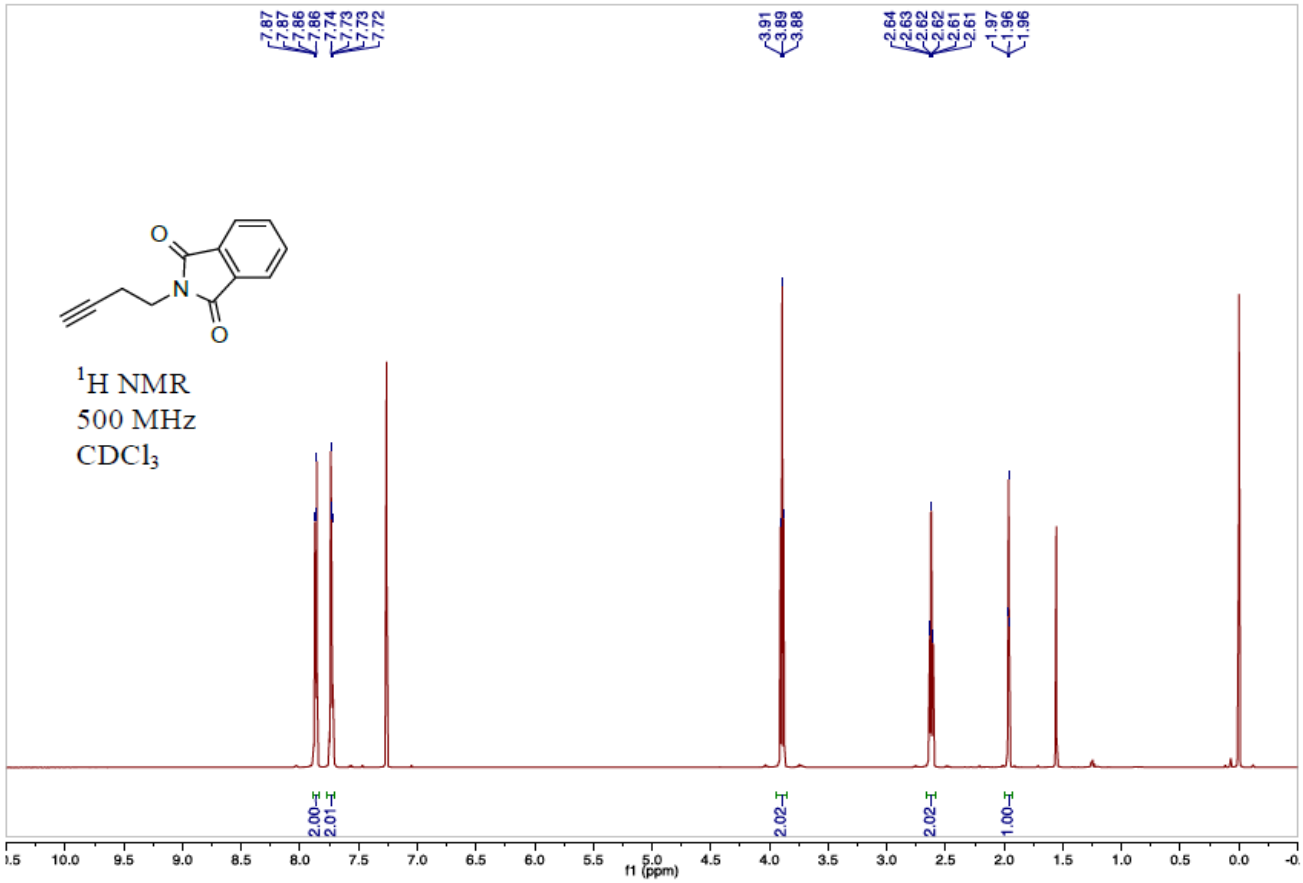
OTBS
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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3.88
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2.63
2.62
2.62
2.61
2.61
1.97
1.96
1.96
O
N
O
^{1}H NMR
500 MHz
$CDCl_3$
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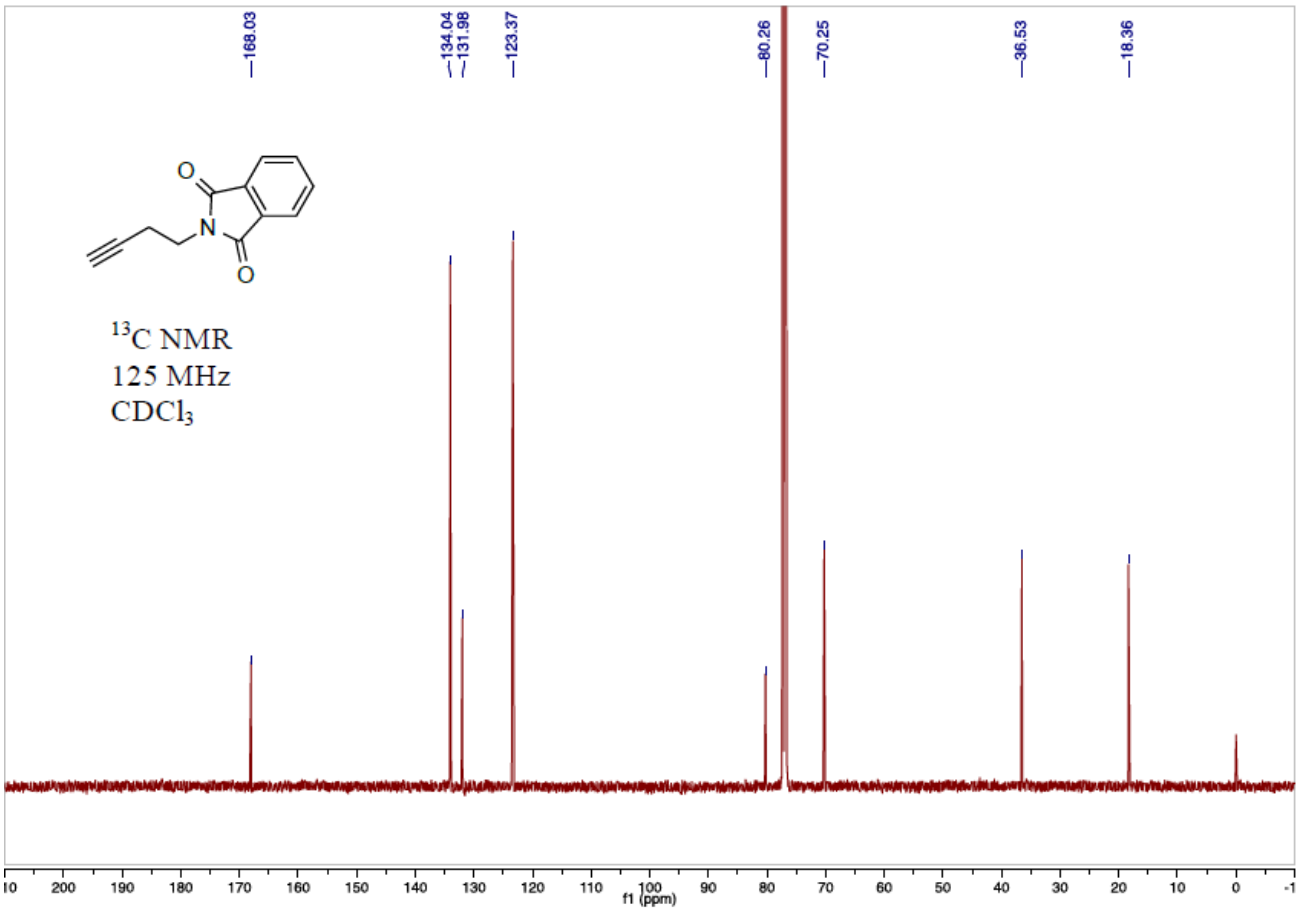
2.02
2.02
1.00
f1 (ppm)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134.04
131.98
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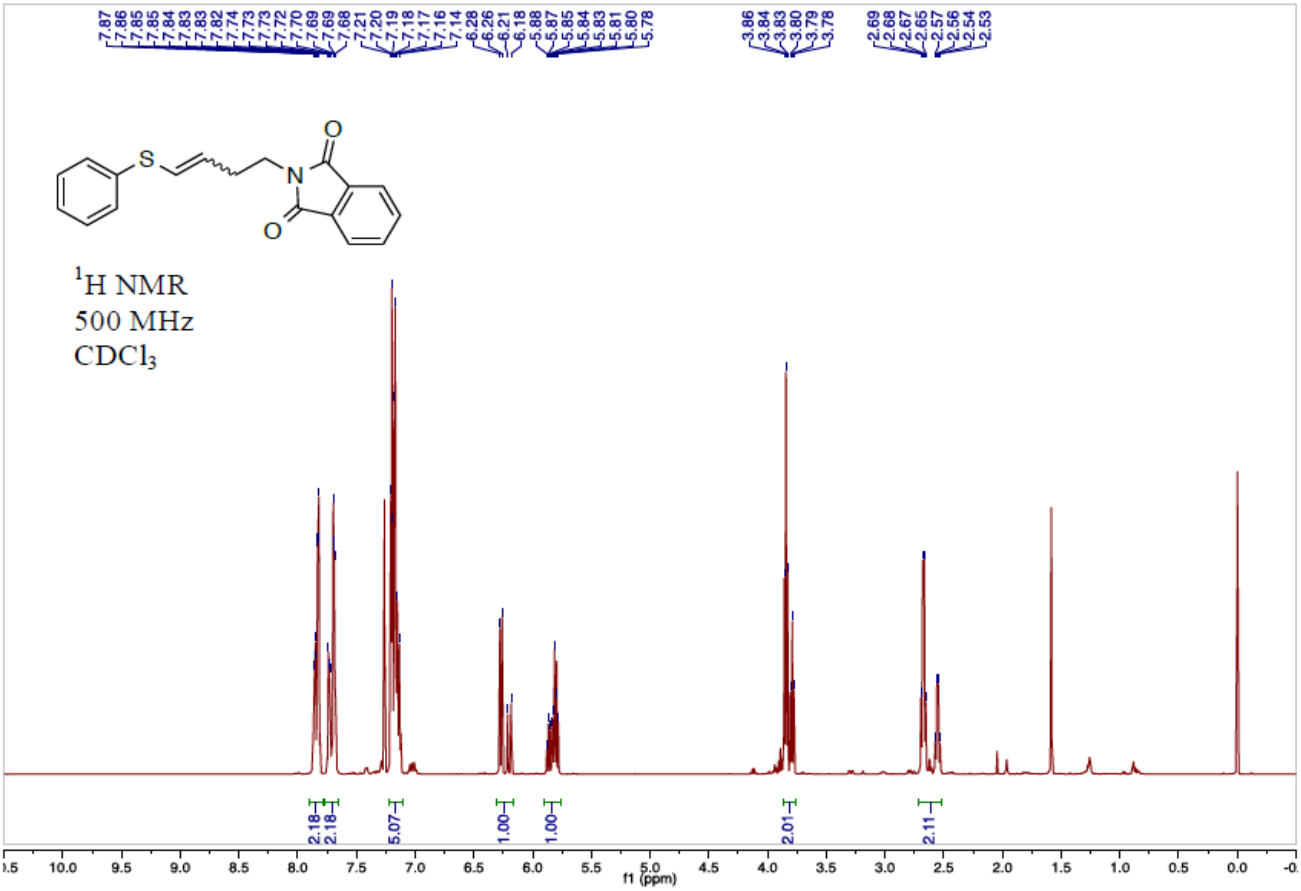
80.26
70.25
36.53
18.36
O
N
O
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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7.69
7.68
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7.17
7.16
7.14
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6.26
6.21
6.18
5.88
5.87
5.85
5.84
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3.80
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3.78
2.69
2.68
2.67
2.65
2.57
2.56
2.54
2.53
S
N
O
O
1H NMR
500 MHz
CDCl3
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2.18
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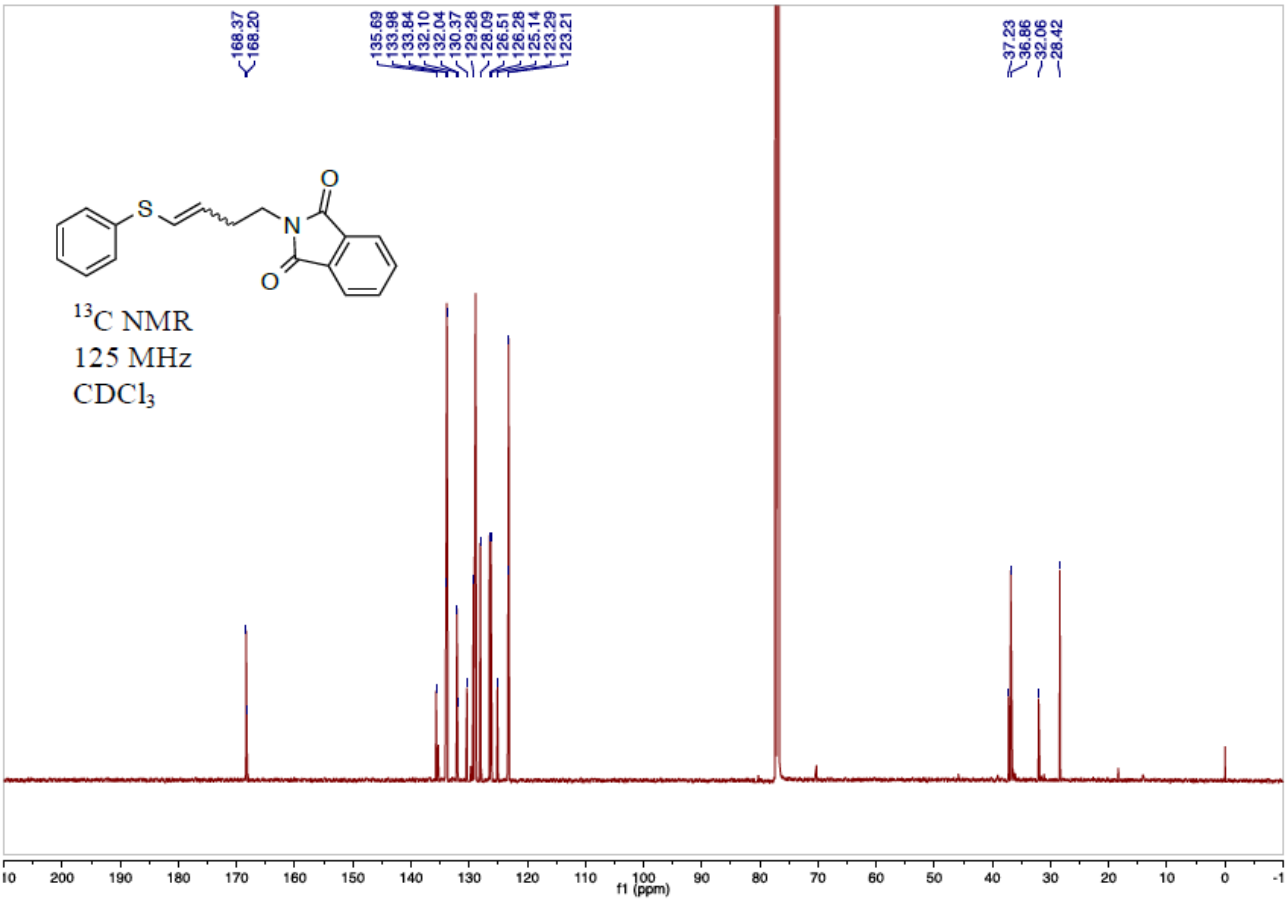
1.00
1.00
2.01
2.11
f1 (ppm)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168.20
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132.10
132.04
130.37
129.28
128.09
126.51
126.28
125.14
123.29
123.21
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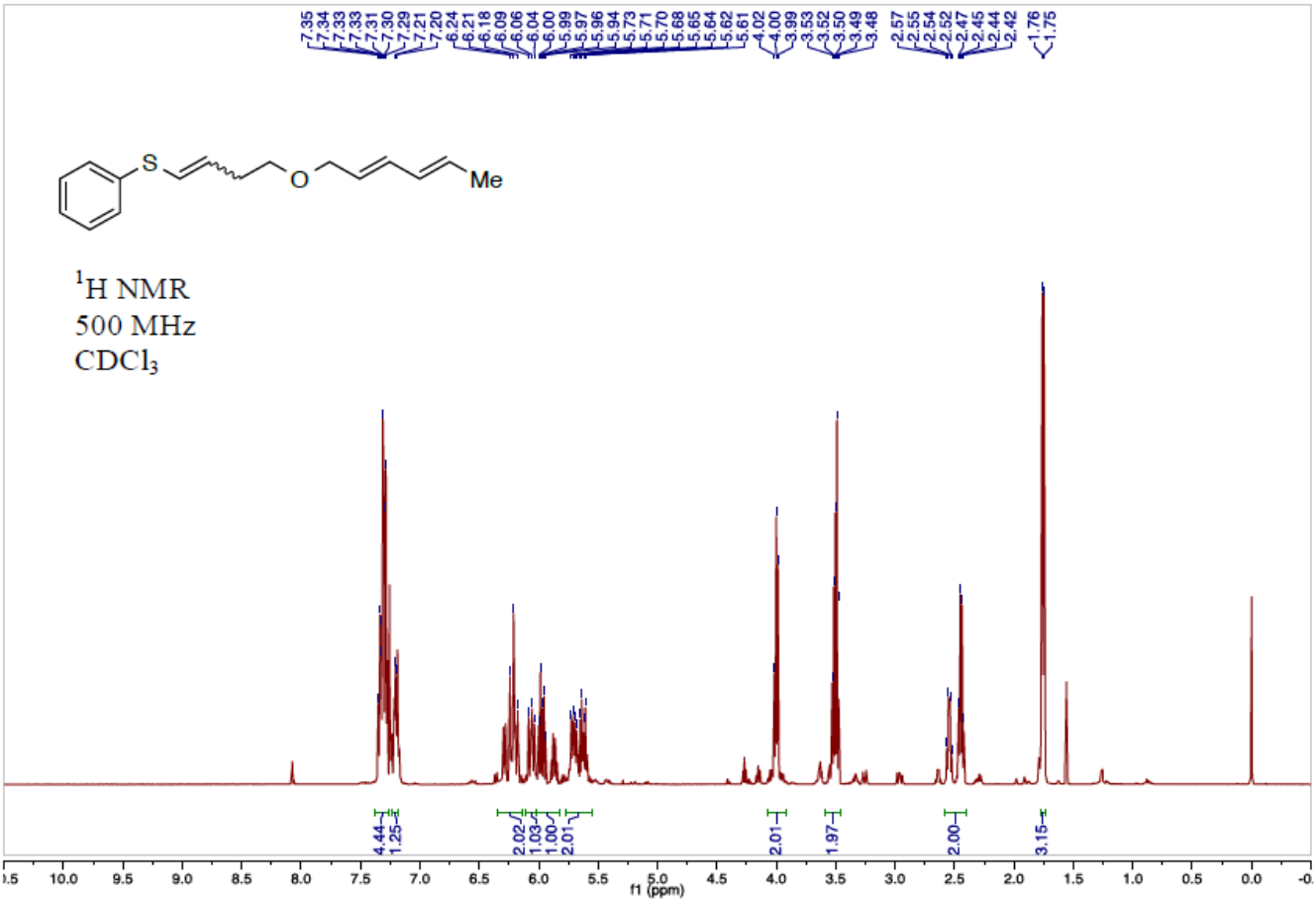
36.86
32.06
28.42
S
N
O
O
13C NMR
125 MHz
CDCl3
f1 (ppm)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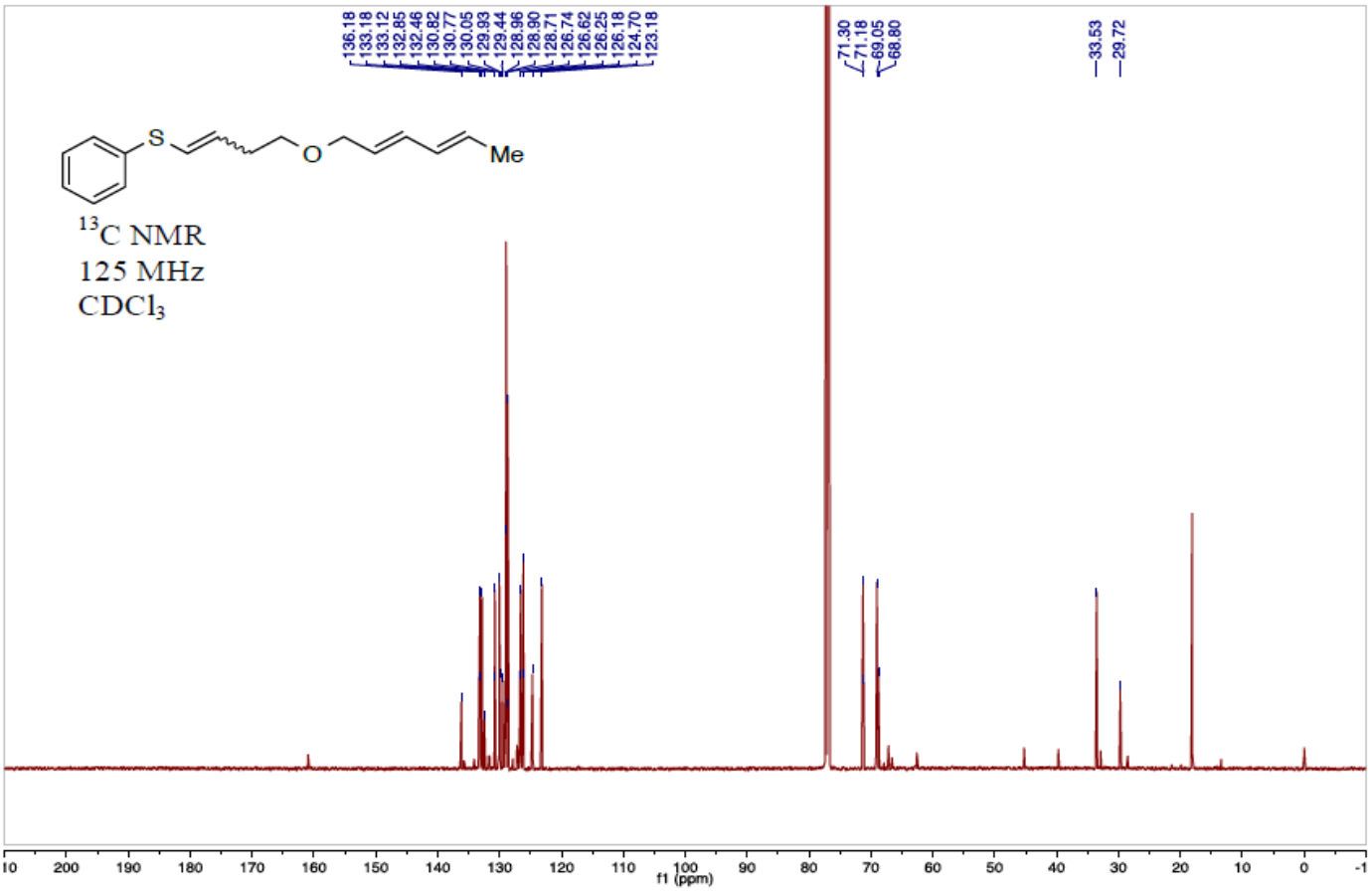
O
Me
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)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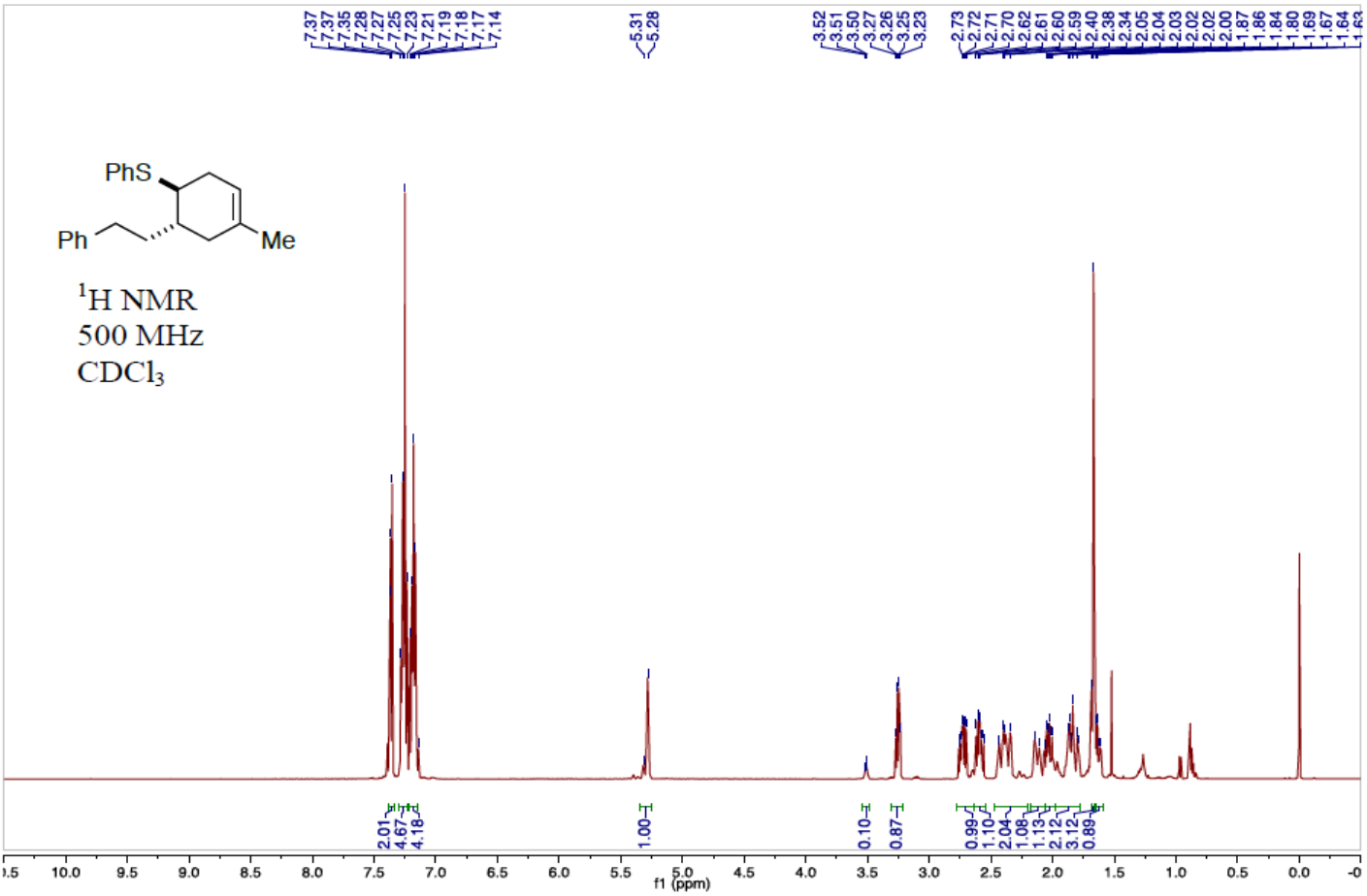
O
Me
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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Ph
Me
^{1}H NMR
500 MHz
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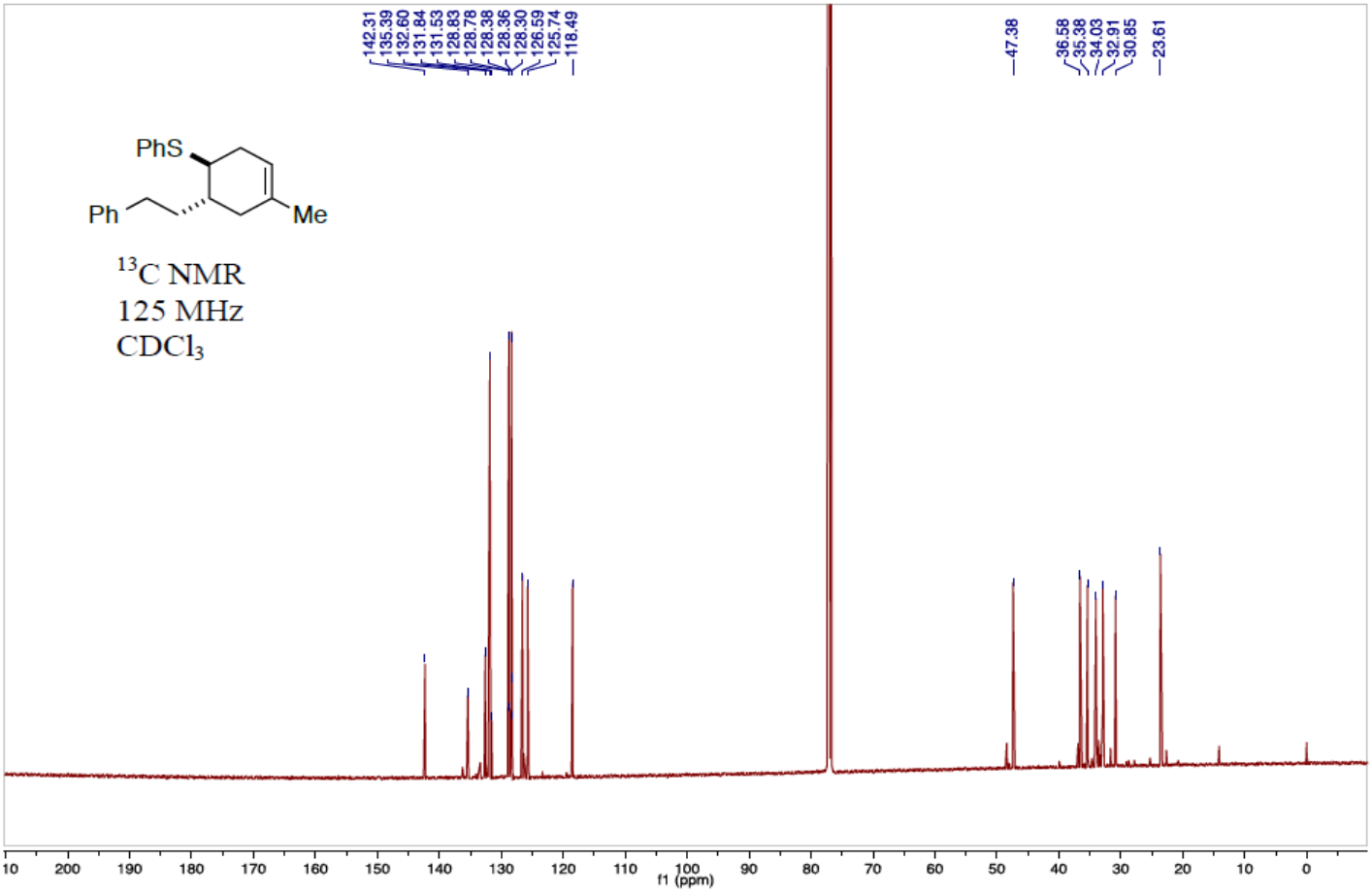
f1 (ppm)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Ph
Me
^{13}C NMR
125 MHz
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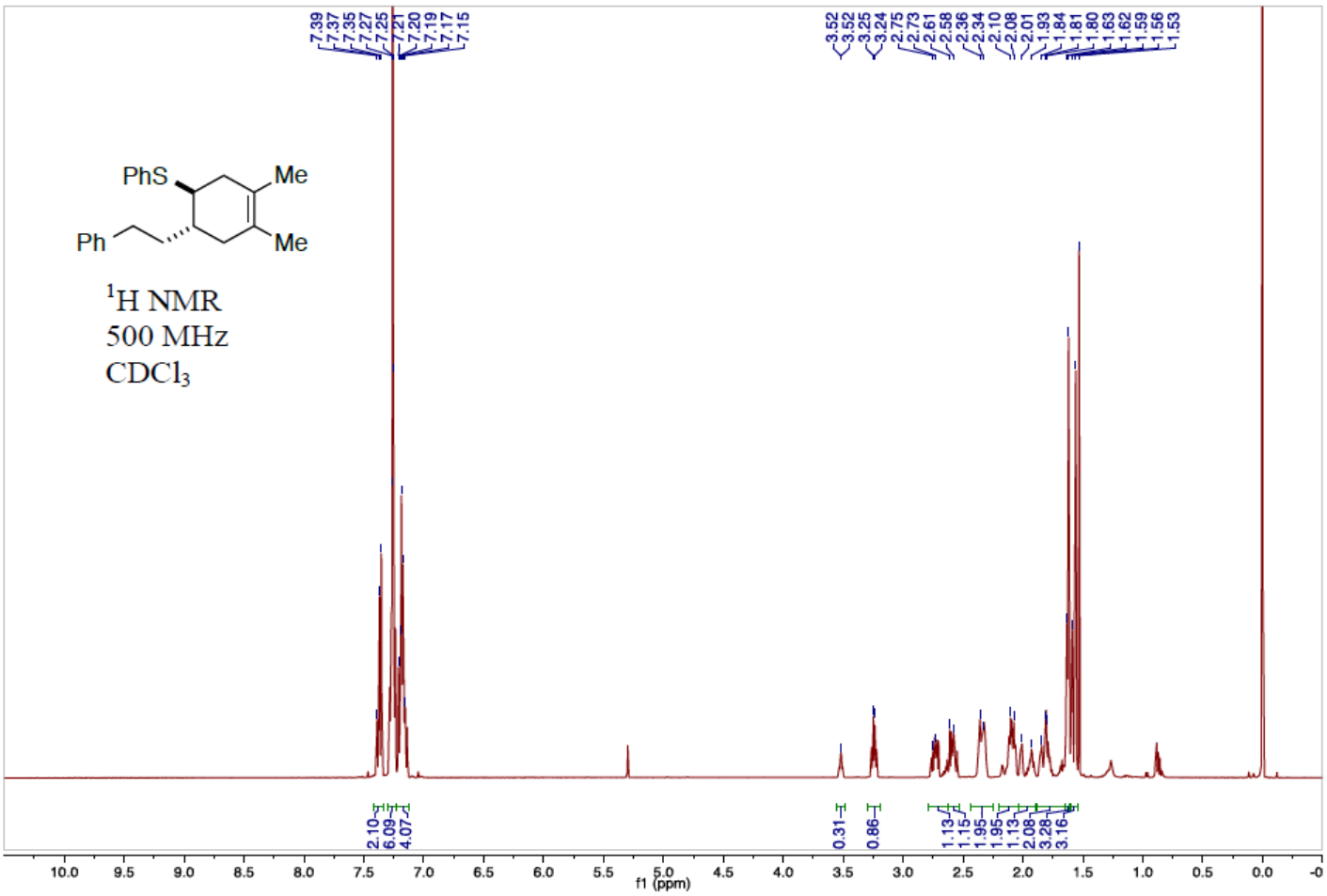
f1 (ppm)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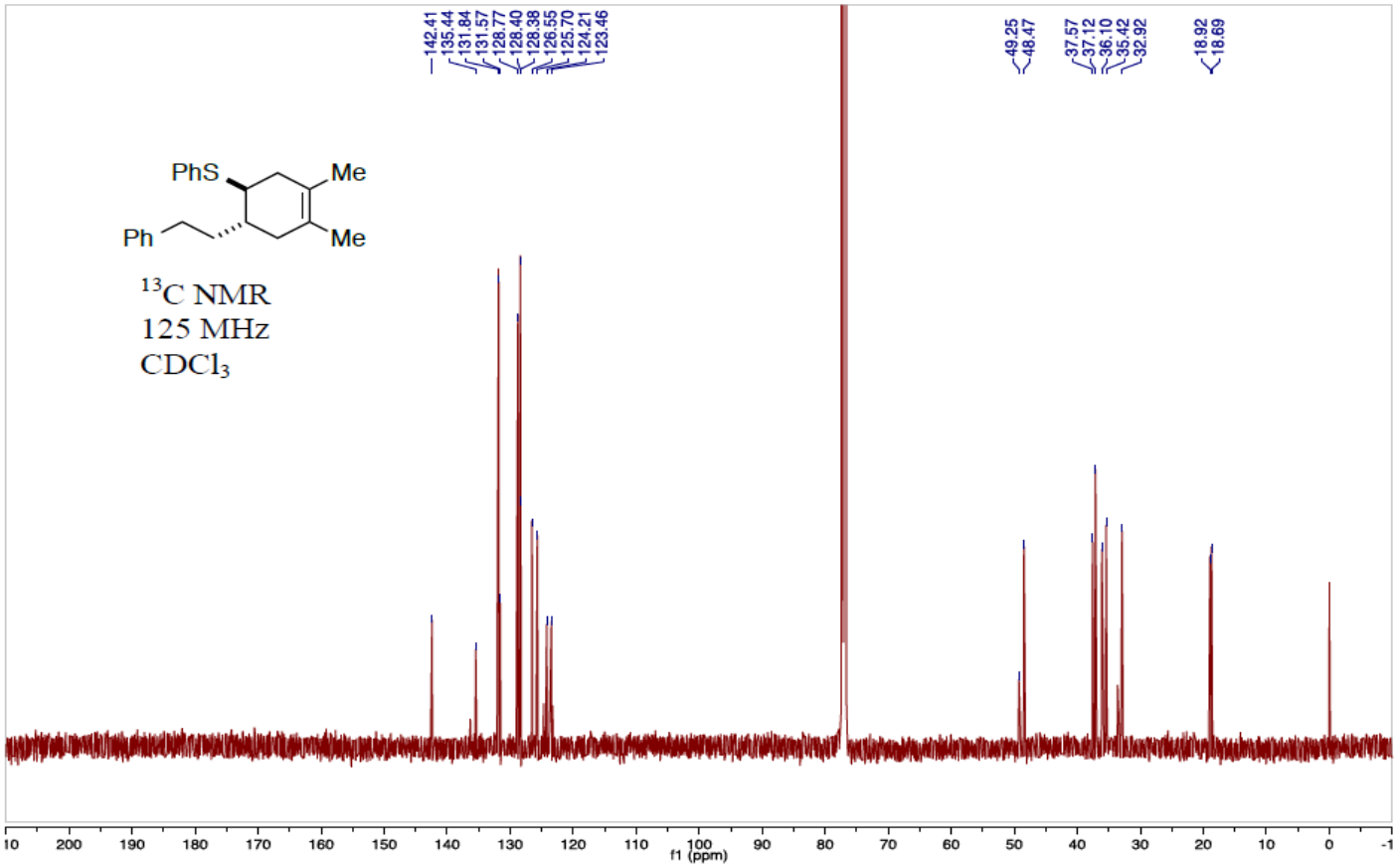
Me
Ph
Me
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)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Me
Ph
Me
^{13}C NMR
125 MHz
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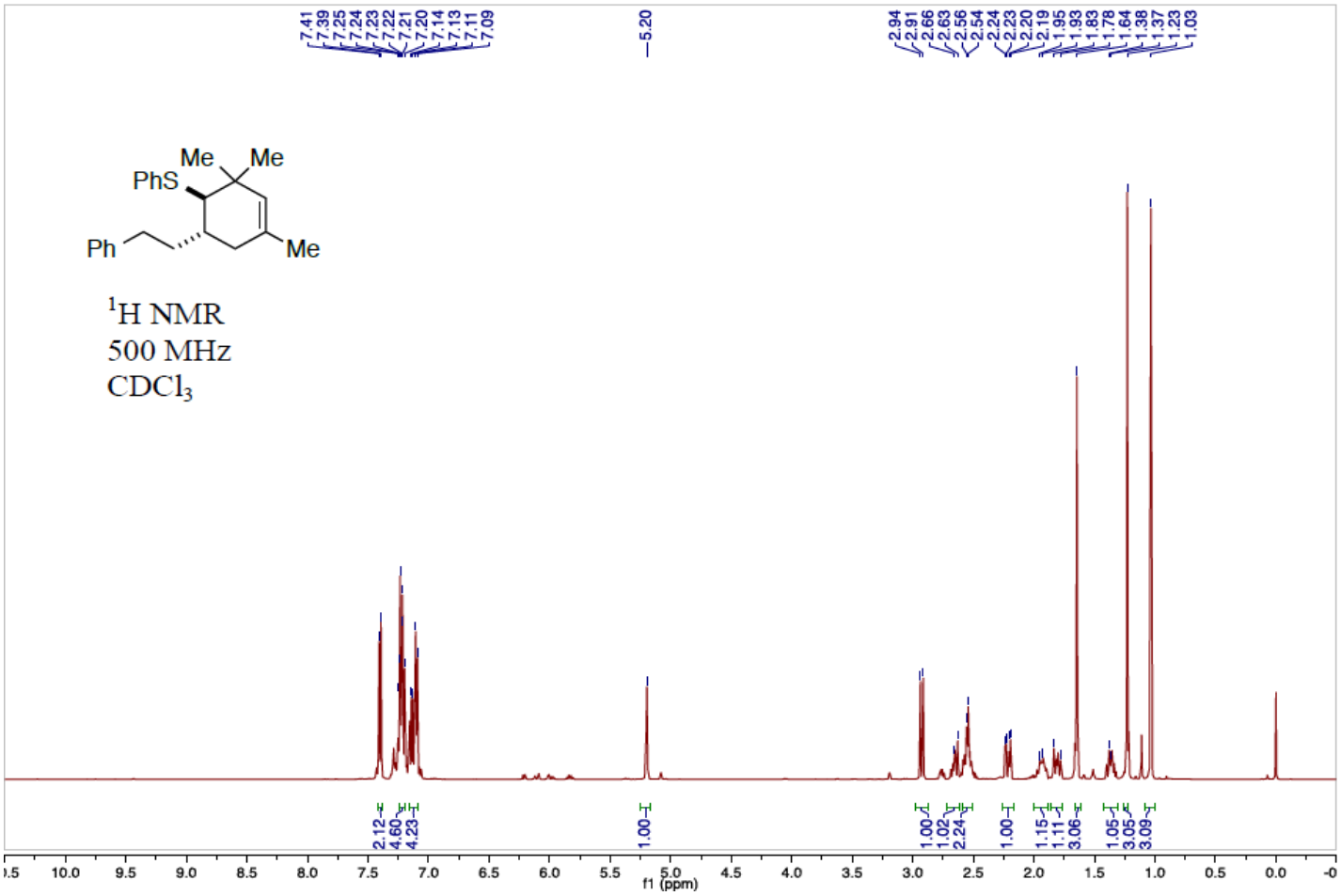
f1 (ppm)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7.39
7.25
7.24
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7.20
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7.13
7.11
7.09
5.20
2.94
2.91
2.66
2.63
2.56
2.54
2.24
2.23
2.20
2.19
1.95
1.93
1.83
1.78
1.64
1.38
1.37
1.23
1.03
Me
Me
PhS
Ph
Me
1H NMR
500 MHz
CDCl3
2.12
4.60
4.23
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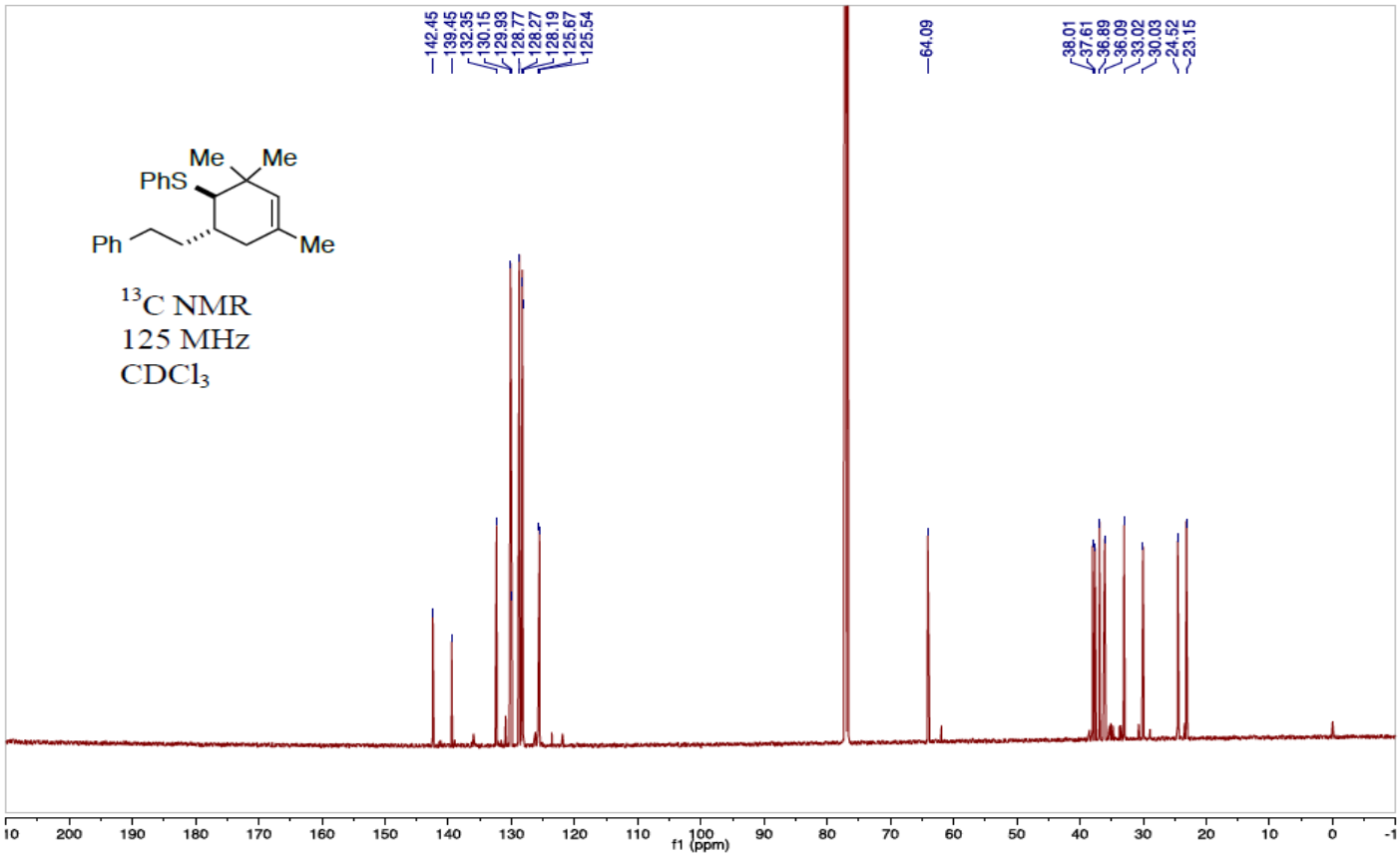
1.00
1.15
1.11
3.06
1.05
3.05
3.09
f1 (ppm)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128.77
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128.19
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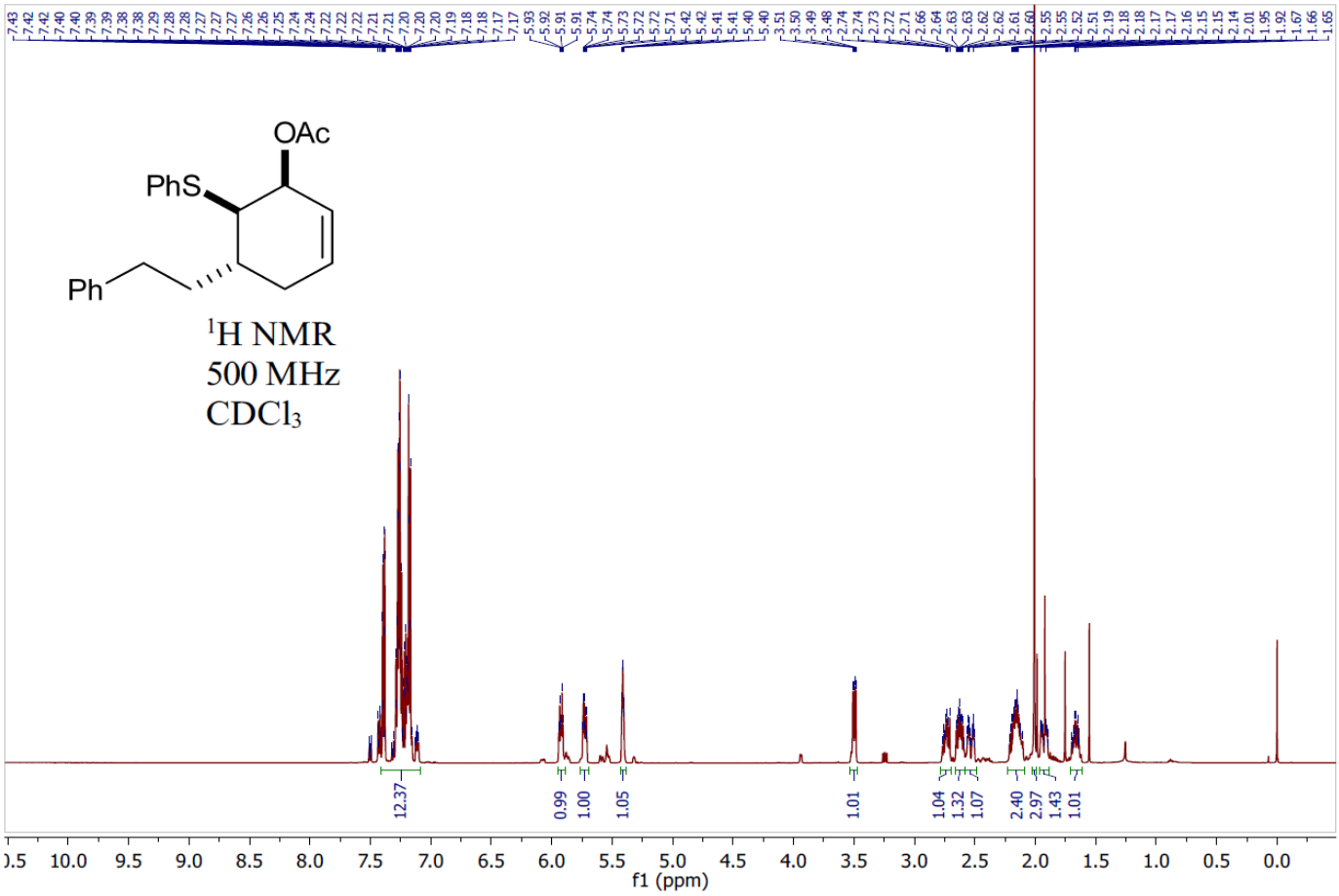
125.54
64.09
38.01
37.61
36.89
36.09
33.02
30.03
24.52
23.15
Me
Me
PhS
Ph
Me
13C NMR
125 MHz
CDCl3
f1 (ppm)


OAc
PhS
Ph
^{1}H NMR
500 MHz
$CDCl_3$
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1.01
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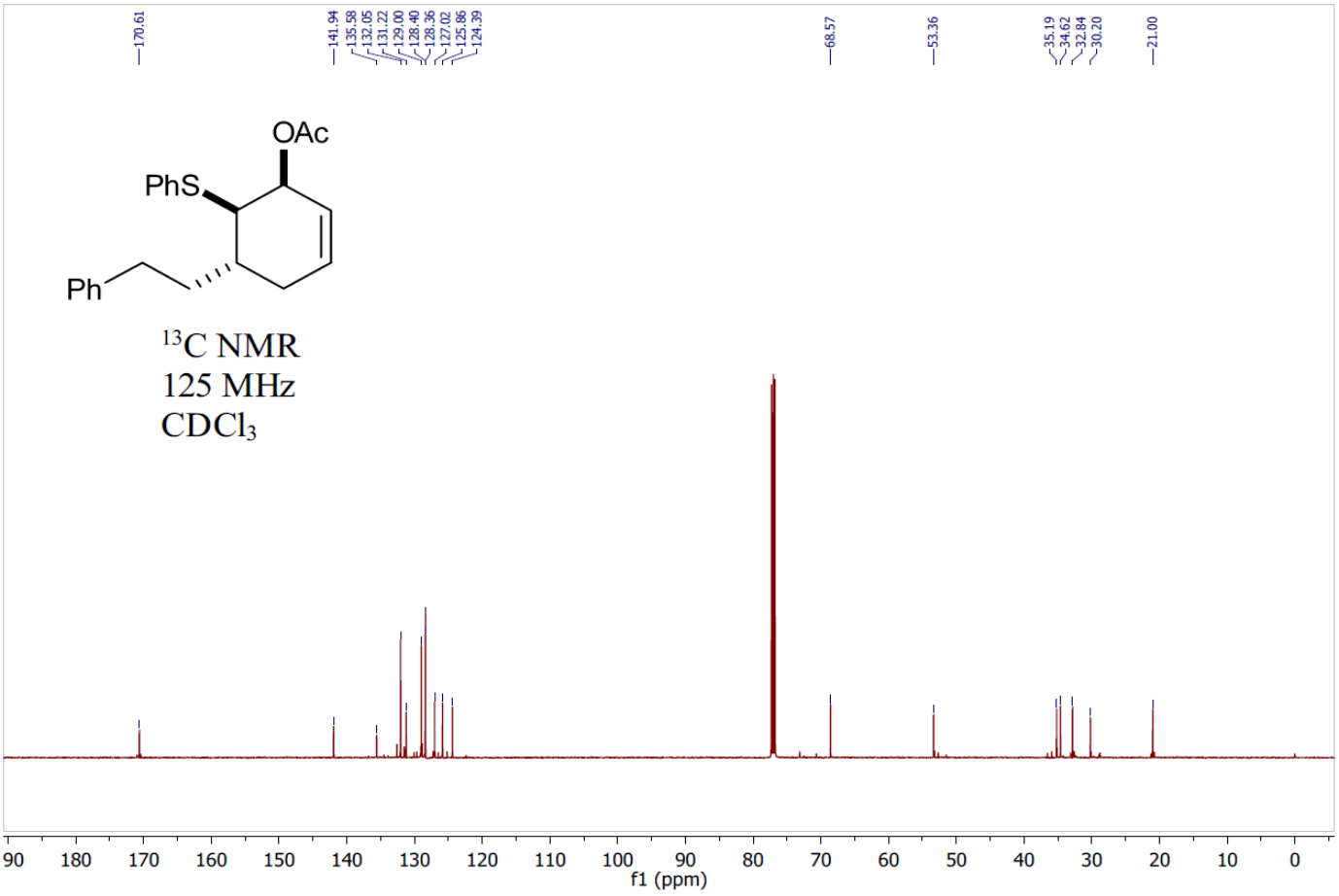
1.32
1.07
2.40
2.97
1.43
1.01
f1 (ppm)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129.00
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128.36
127.02
125.86
124.39
68.57
53.36
35.19
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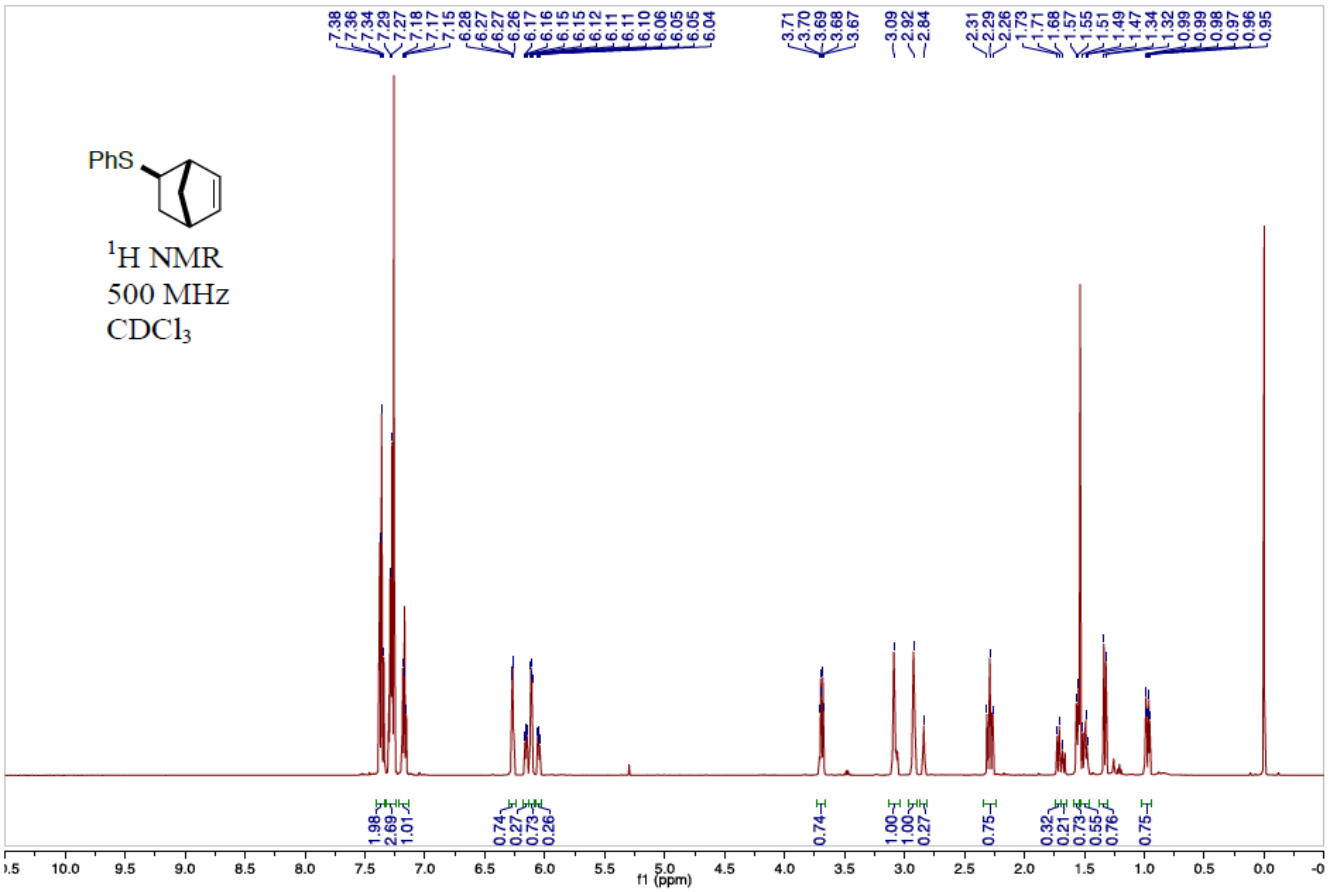
30.20
21.00
OAc
PhS
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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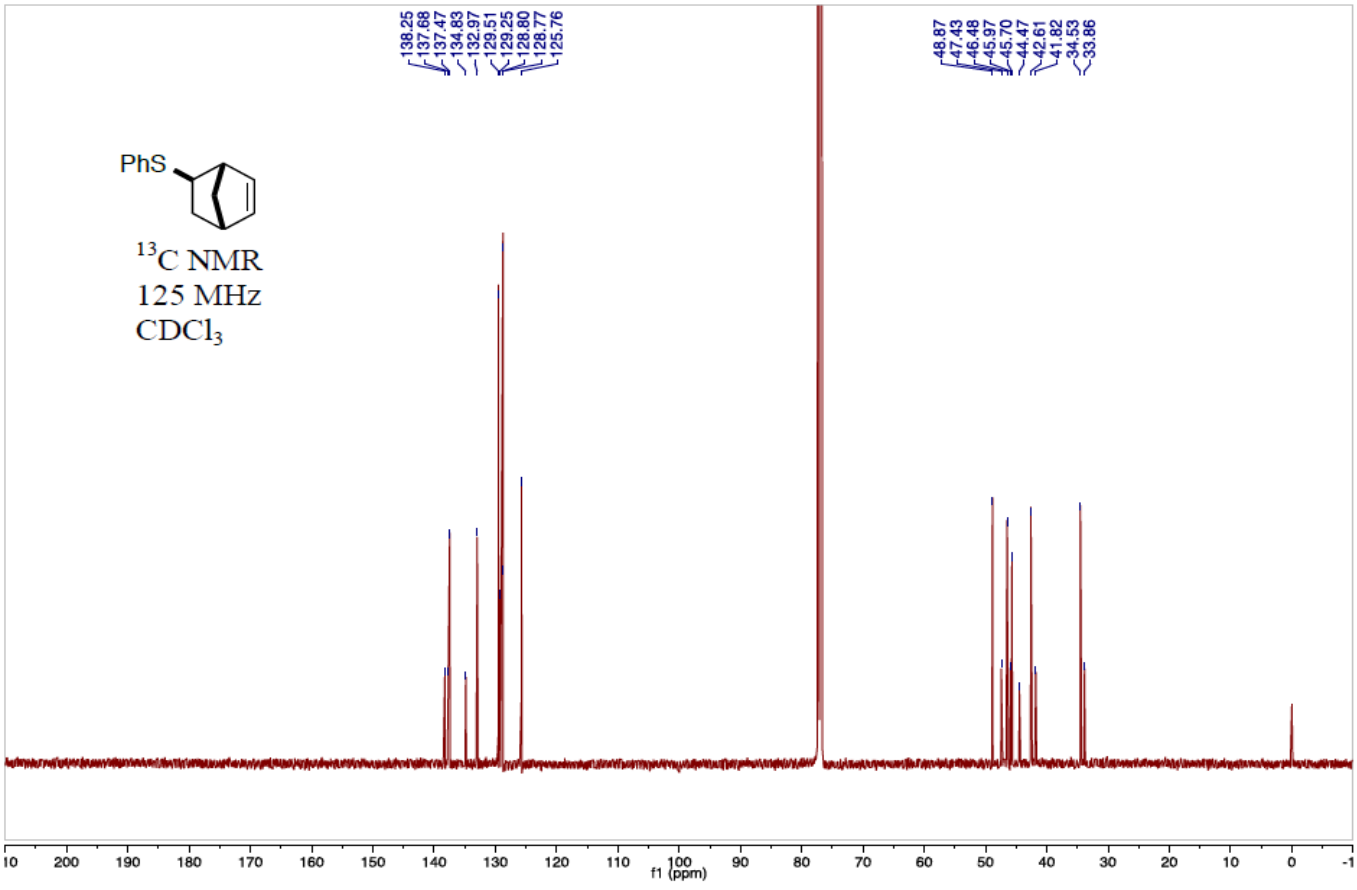
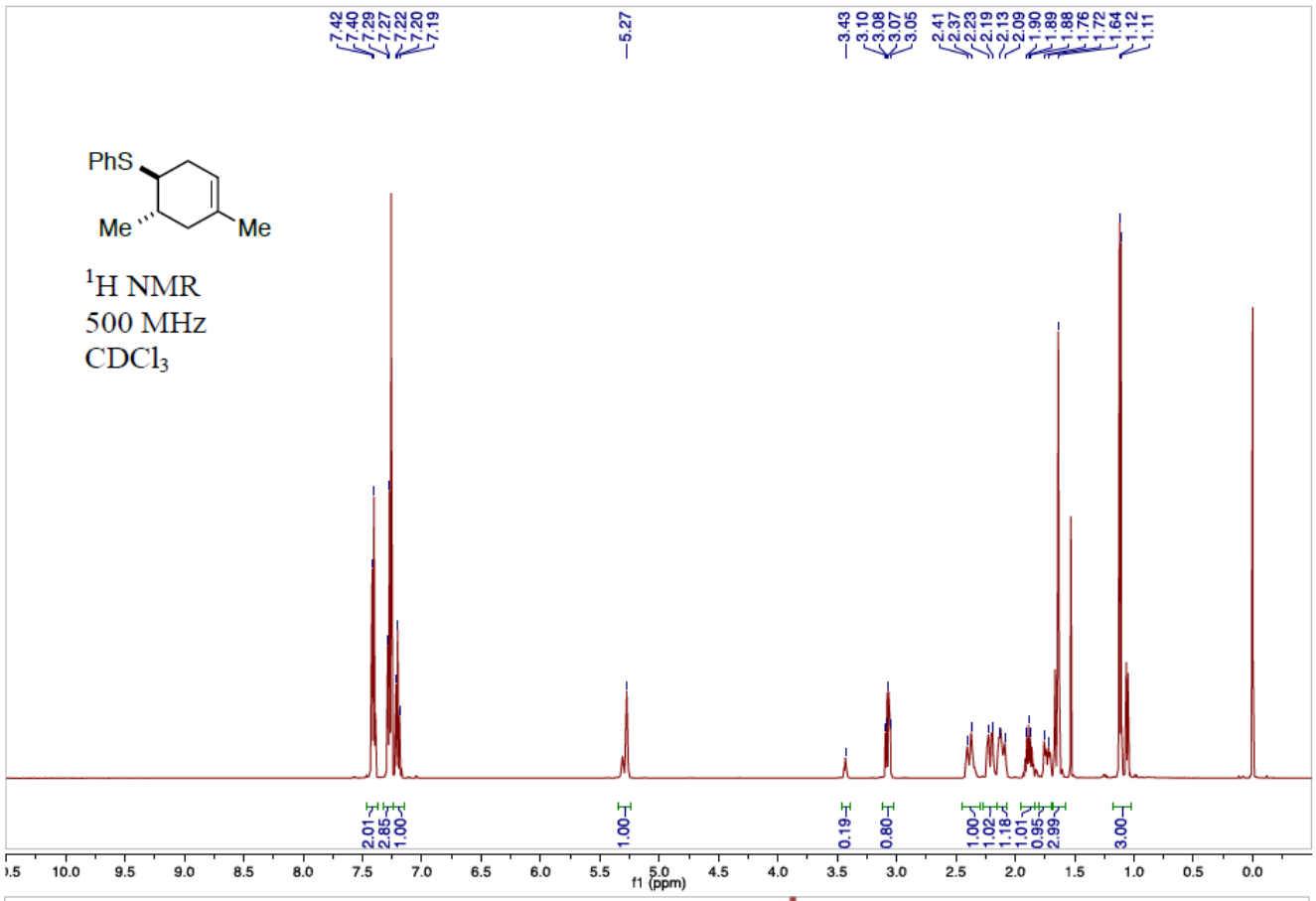
500 MHz
$CDCl_3$
f1 (ppm)


PhS
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)


PhS
Me
Me
^{1}H NMR
500 MHz
$CDCl_3$
7.42
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7.22
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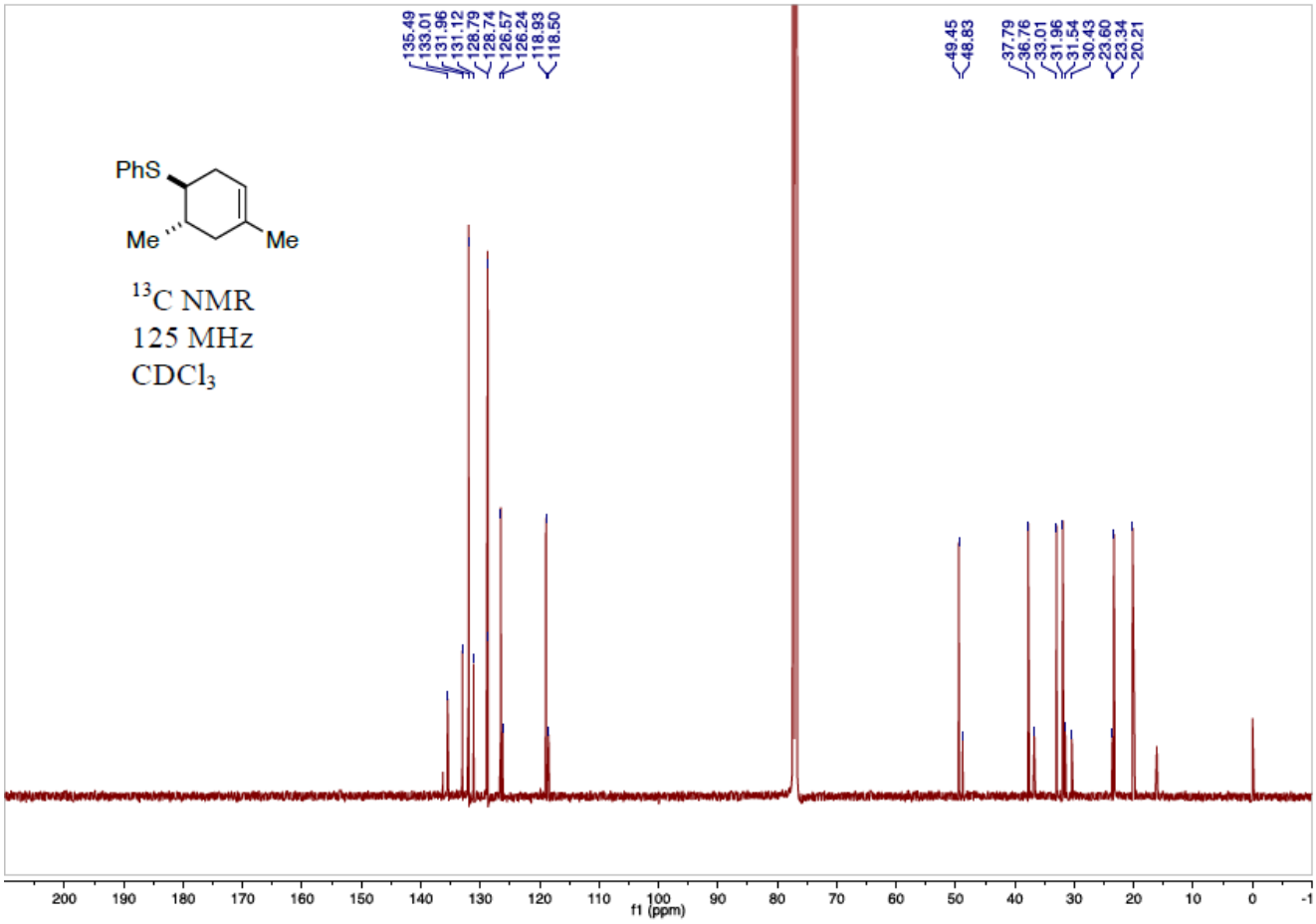
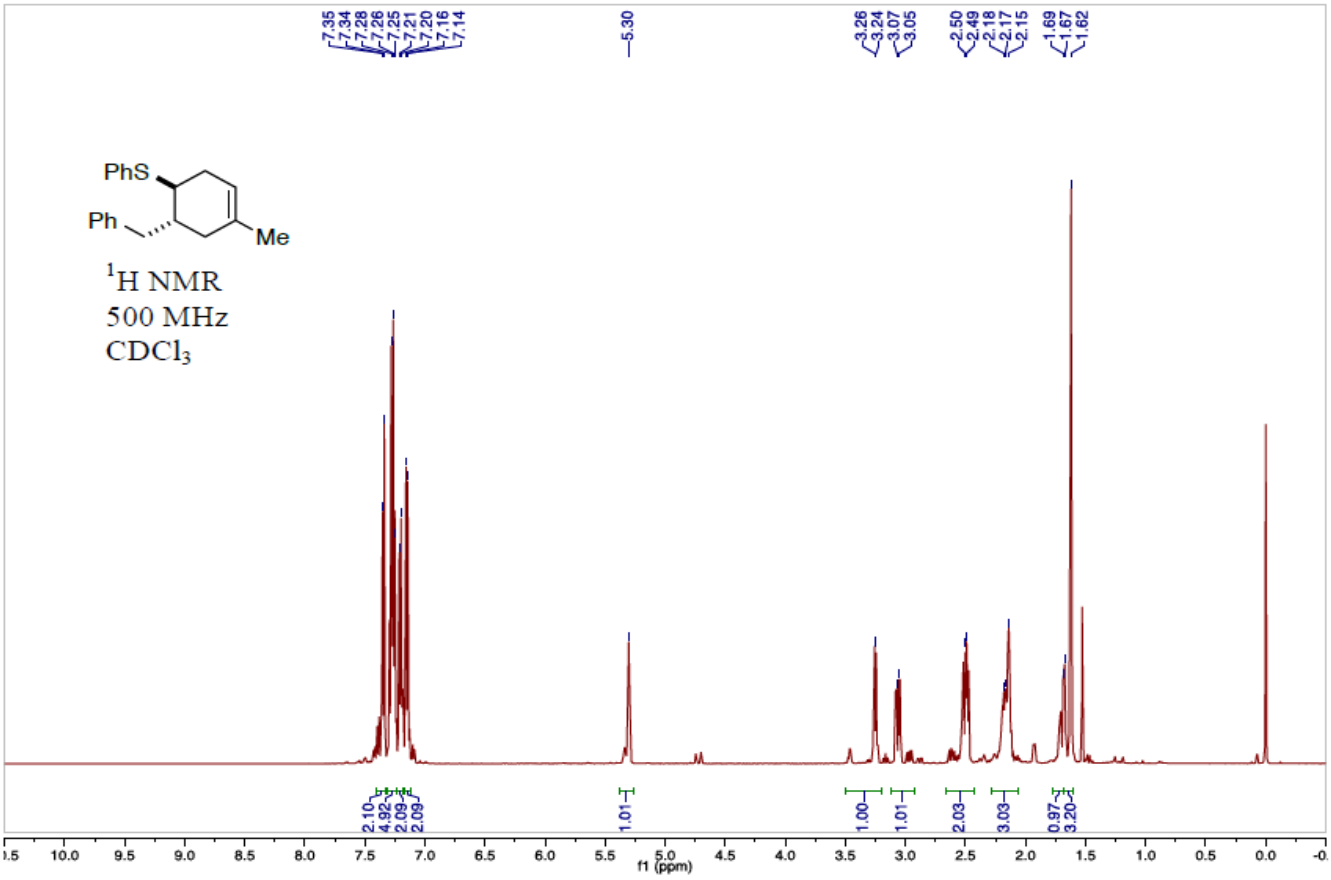
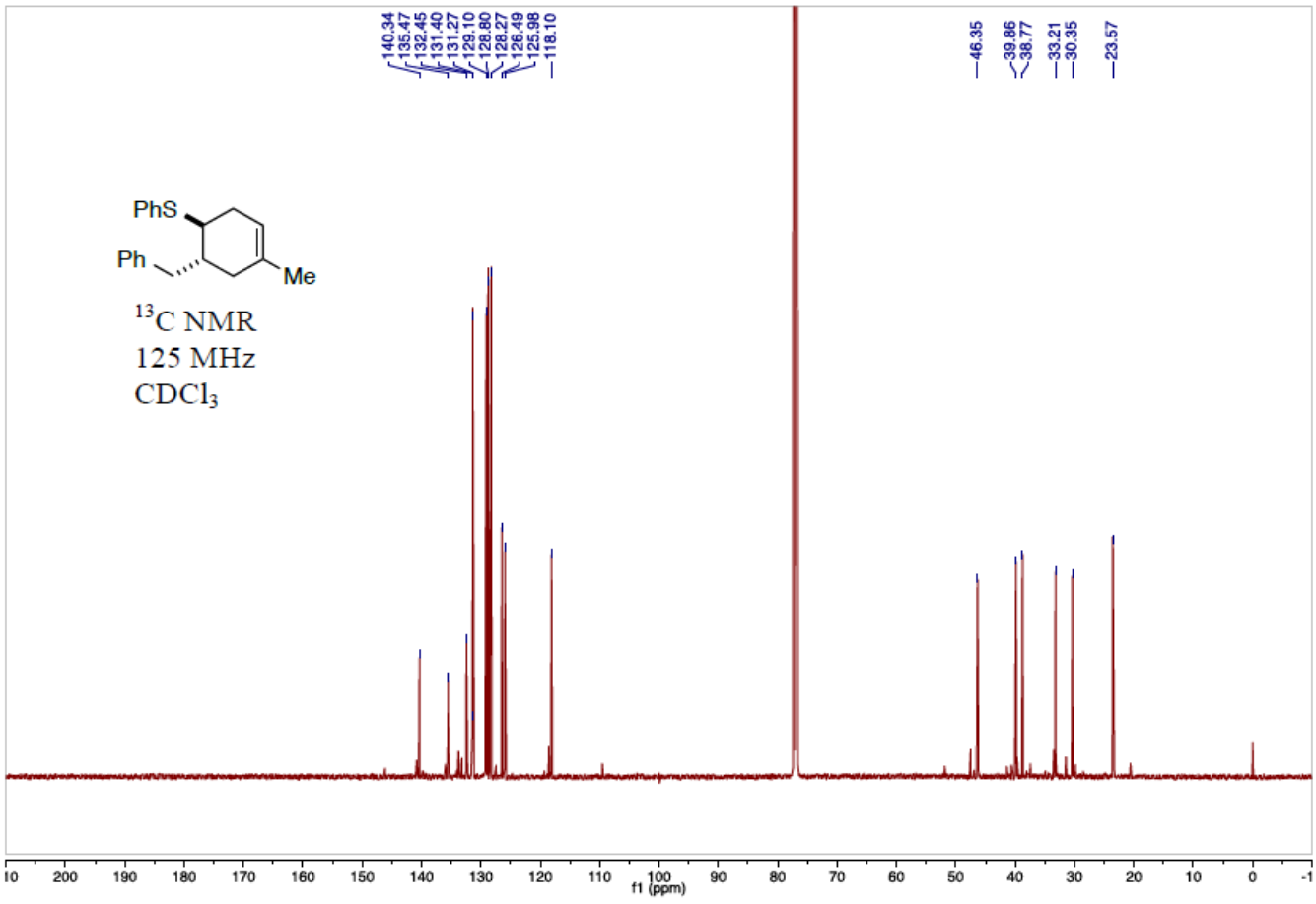
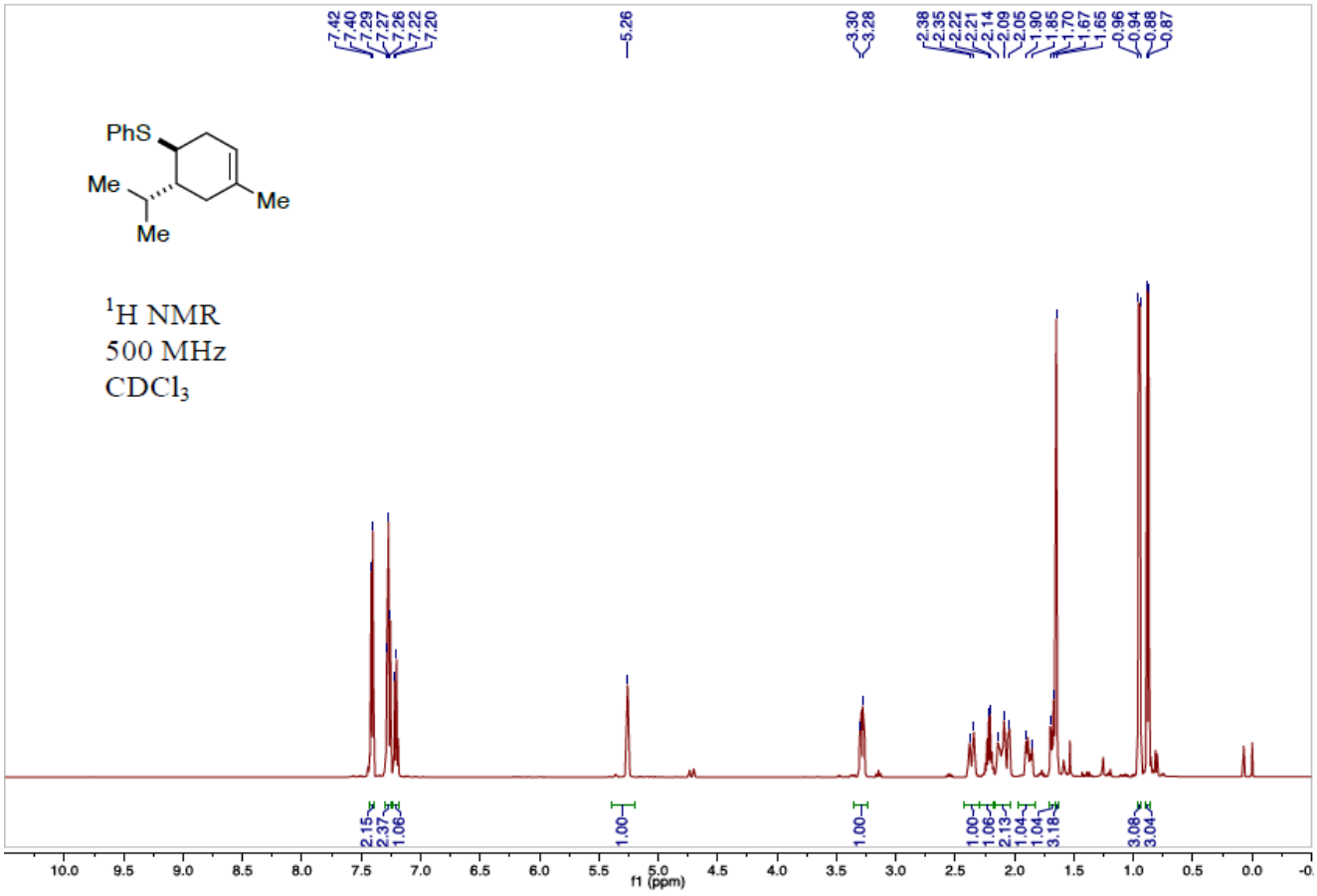
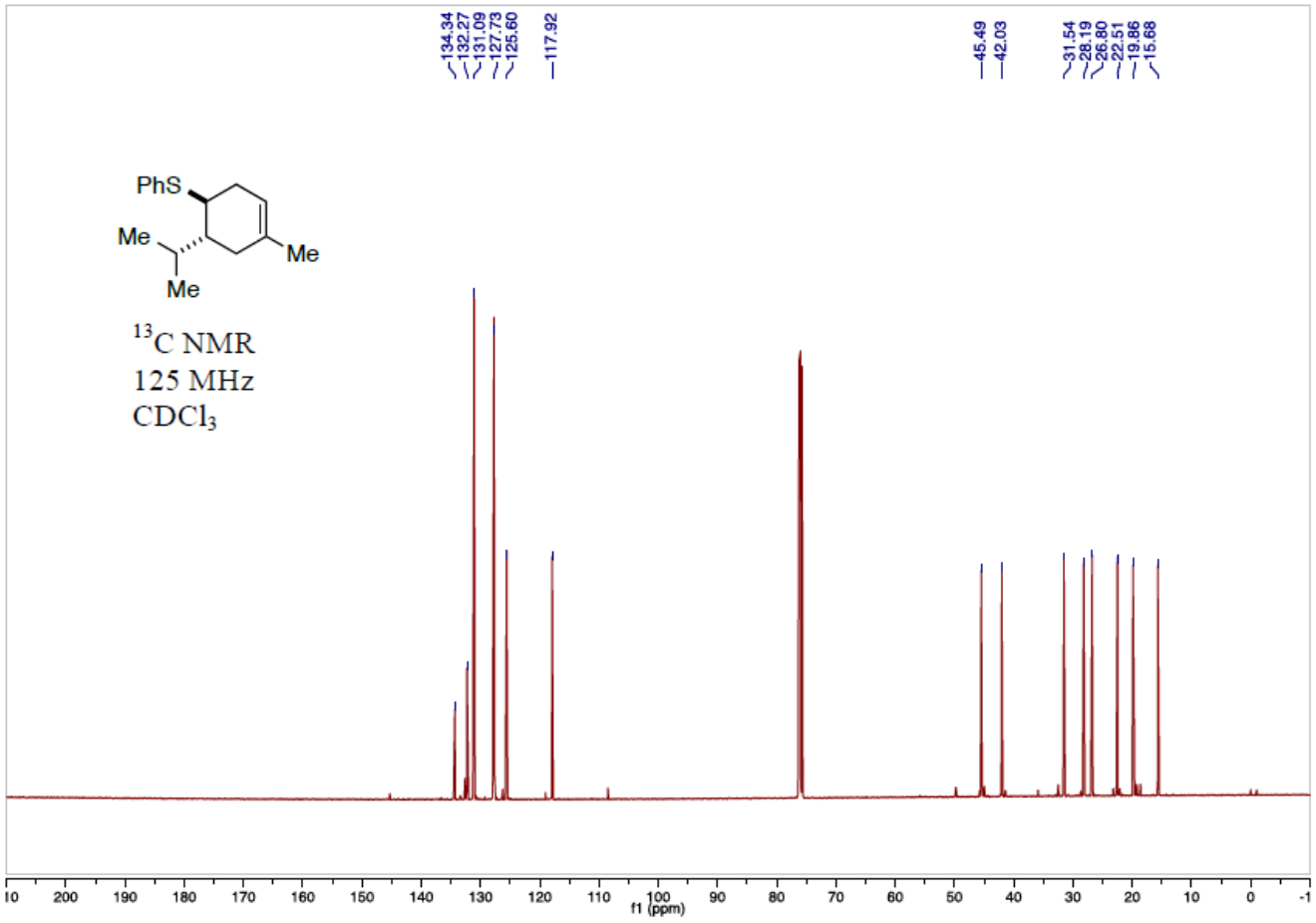
7.19
5.27
3.43
3.10
3.08
3.07
3.05
2.41
2.37
2.23
2.19
2.13
2.09
1.90
1.89
1.88
1.76
1.72
1.64
1.12
1.11
2.01
2.85
1.00
1.00
0.19
0.80
1.00
1.02
1.18
1.01
0.95
2.99
3.00
f1 (ppm)

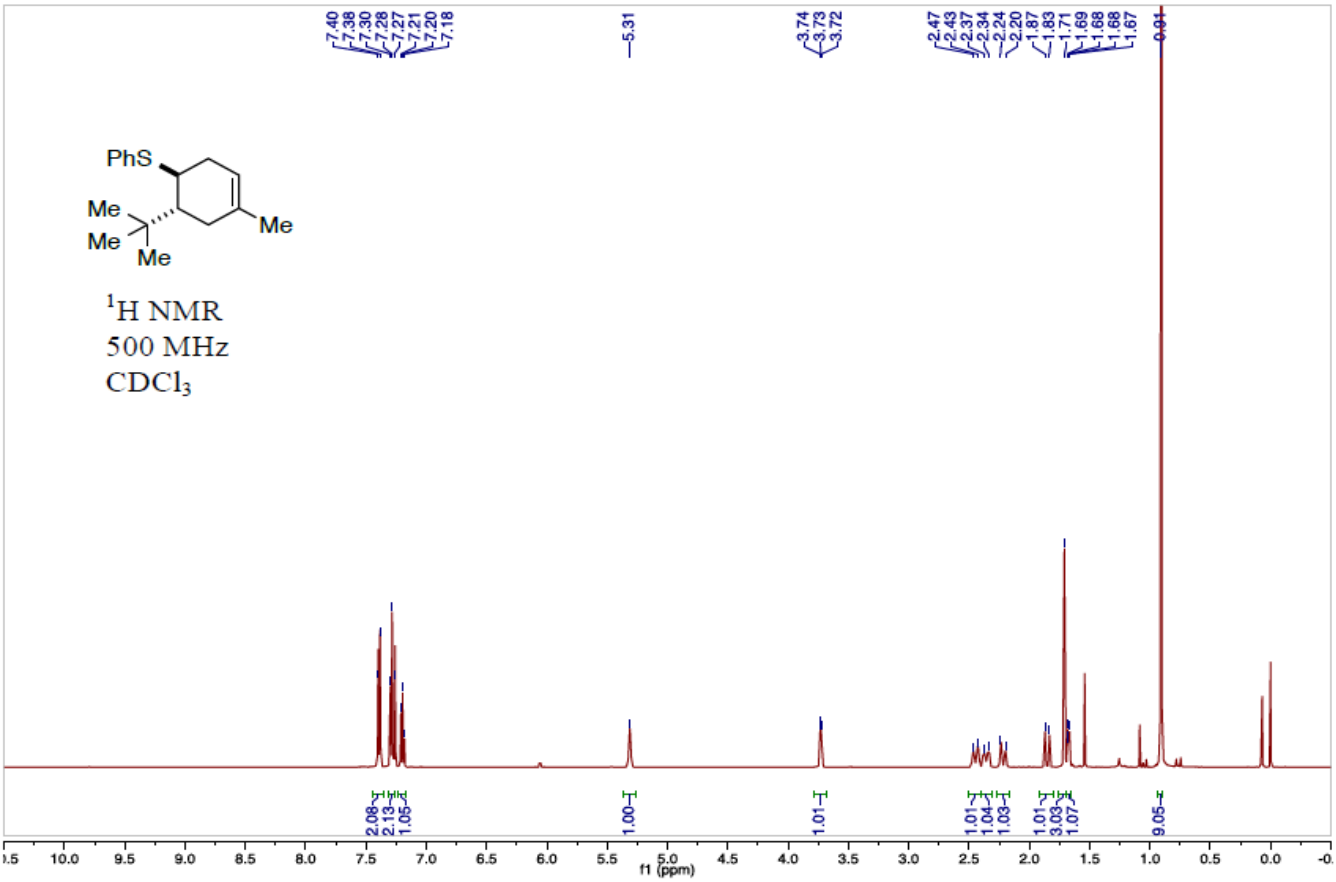

PhS
Me
Me
^{13}C NMR
125 MHz
$CDCl_3$
135.49
133.01
131.96
131.12
128.79
128.74
126.57
126.24
118.93
118.50
49.45
48.83
37.79
36.76
33.01
31.96
31.54
30.43
23.60
23.34
20.21
f1 (ppm)

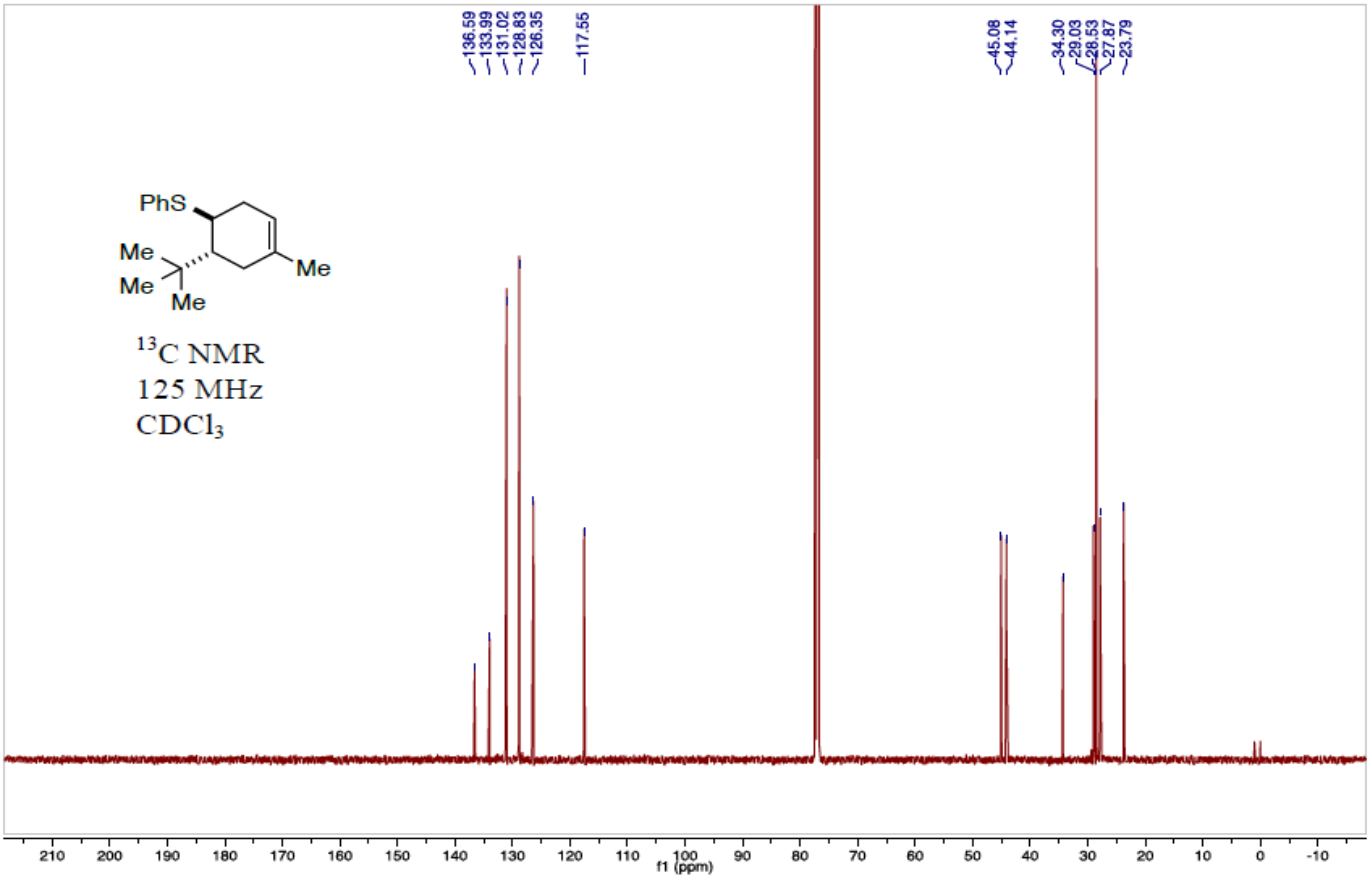

PhS
Ph
Me
^{1}H NMR
500 MHz
$CDCl_3$
7.35
7.34
7.28
7.26
7.25
7.21
7.20
7.16
7.14
5.30
3.26
3.24
3.07
3.05
2.50
2.49
2.18
2.17
2.15
1.69
1.67
1.62
2.10
4.92
2.09
2.09
1.01
1.00
1.01
2.03
3.03
0.97
3.20
f1 (ppm)

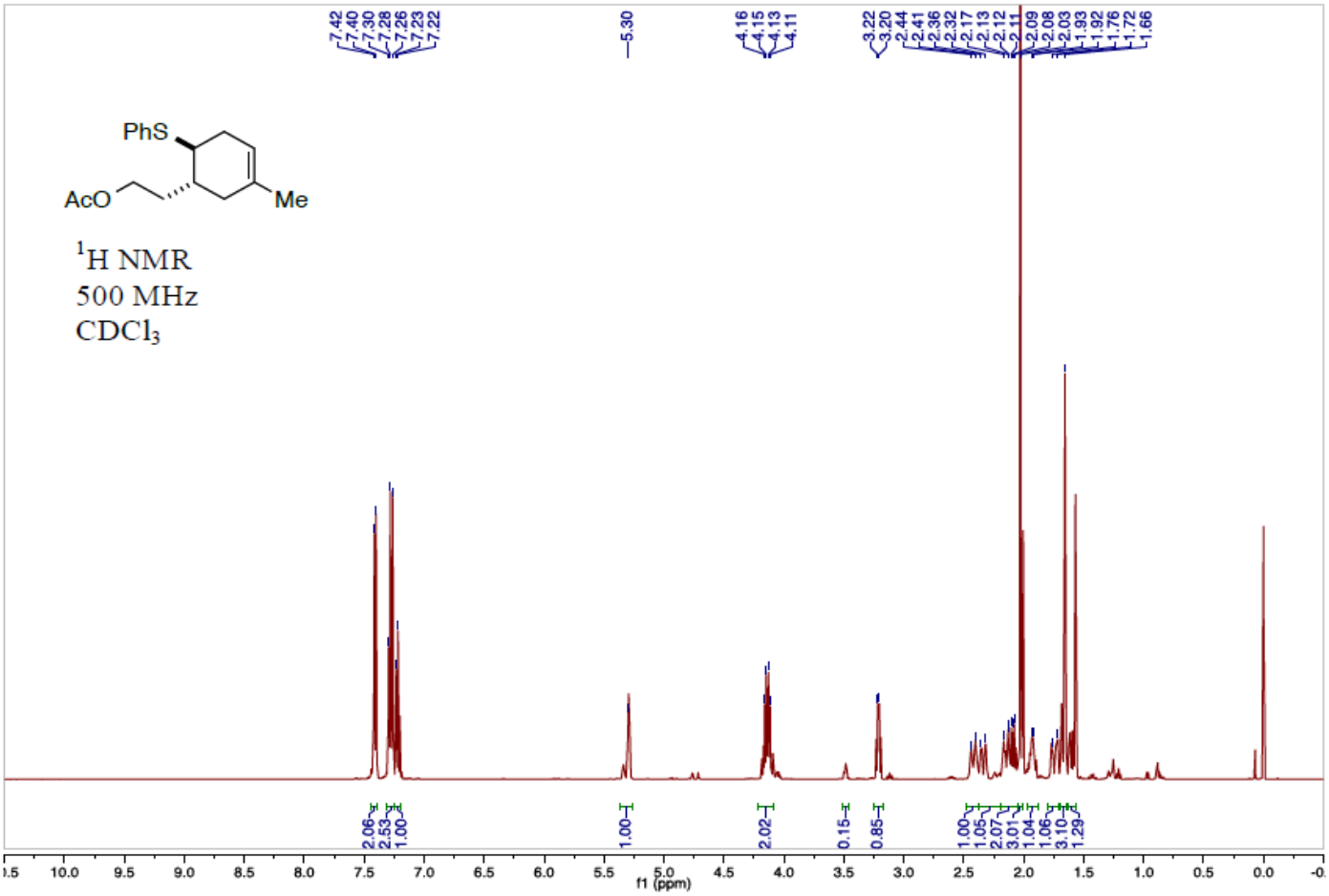

PhS
Ph
Me
^{13}C NMR
125 MHz
$CDCl_3$
140.34
135.47
132.45
131.40
131.27
129.10
128.80
128.27
126.49
125.98
118.10
46.35
39.86
38.77
33.21
30.35
23.57
f1 (ppm)

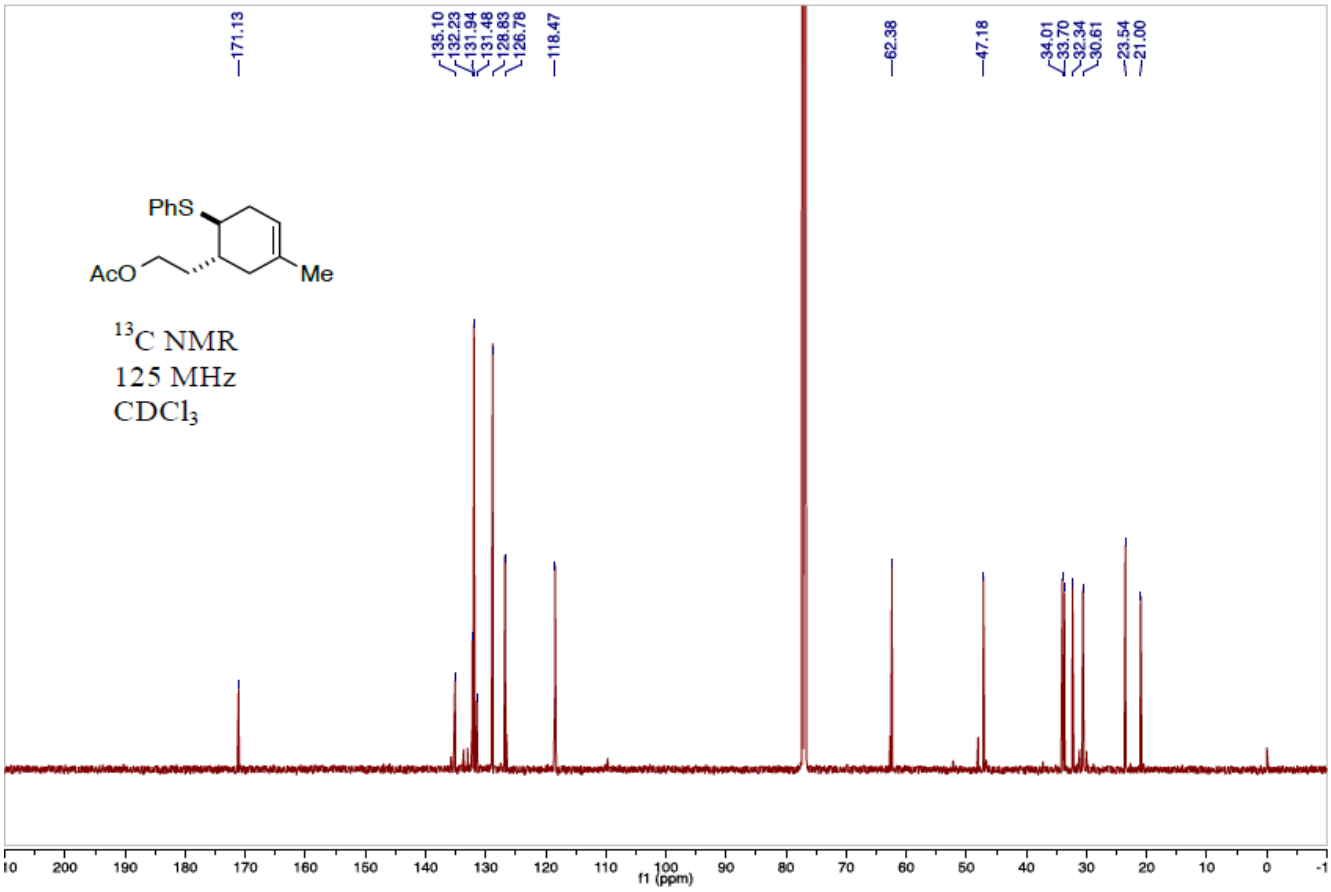

7.42
7.40
7.29
7.27
7.26
7.22
7.20
5.26
3.30
3.28
2.38
2.35
2.22
2.21
2.14
2.09
2.05
1.90
1.85
1.70
1.67
1.65
0.96
0.94
0.88
0.87
PhS
Me
Me
Me
1H NMR
500 MHz
CDCl3
2.15
2.37
1.06
1.00
1.00
1.00
1.06
2.13
1.04
1.04
3.18
3.08
3.04
f1 (ppm)

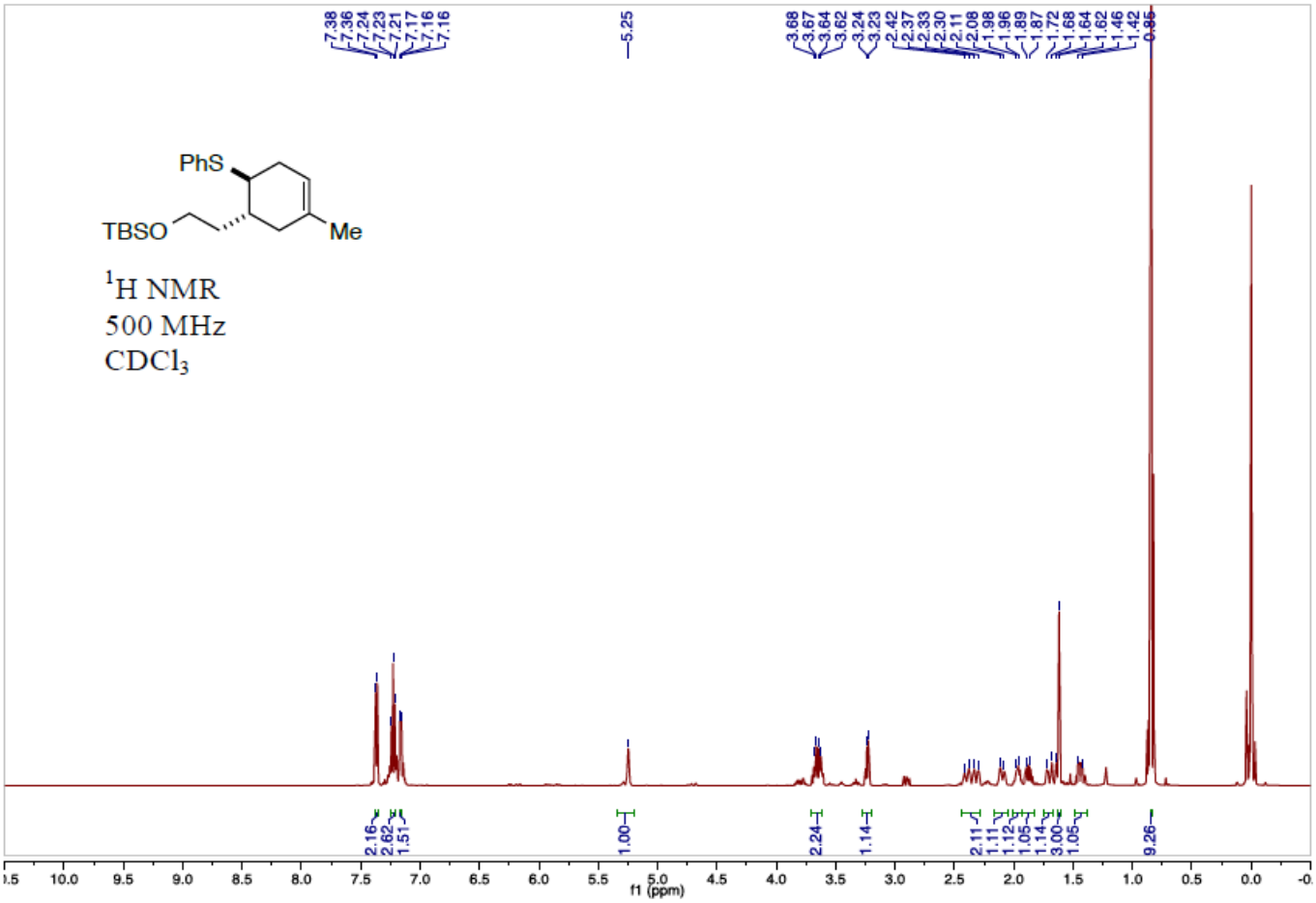

134.34
132.27
131.09
127.73
125.60
117.92
45.49
42.03
31.54
28.19
26.80
22.51
19.86
15.68
PhS
Me
Me
Me
13C NMR
125 MHz
CDCl3
f1 (ppm)

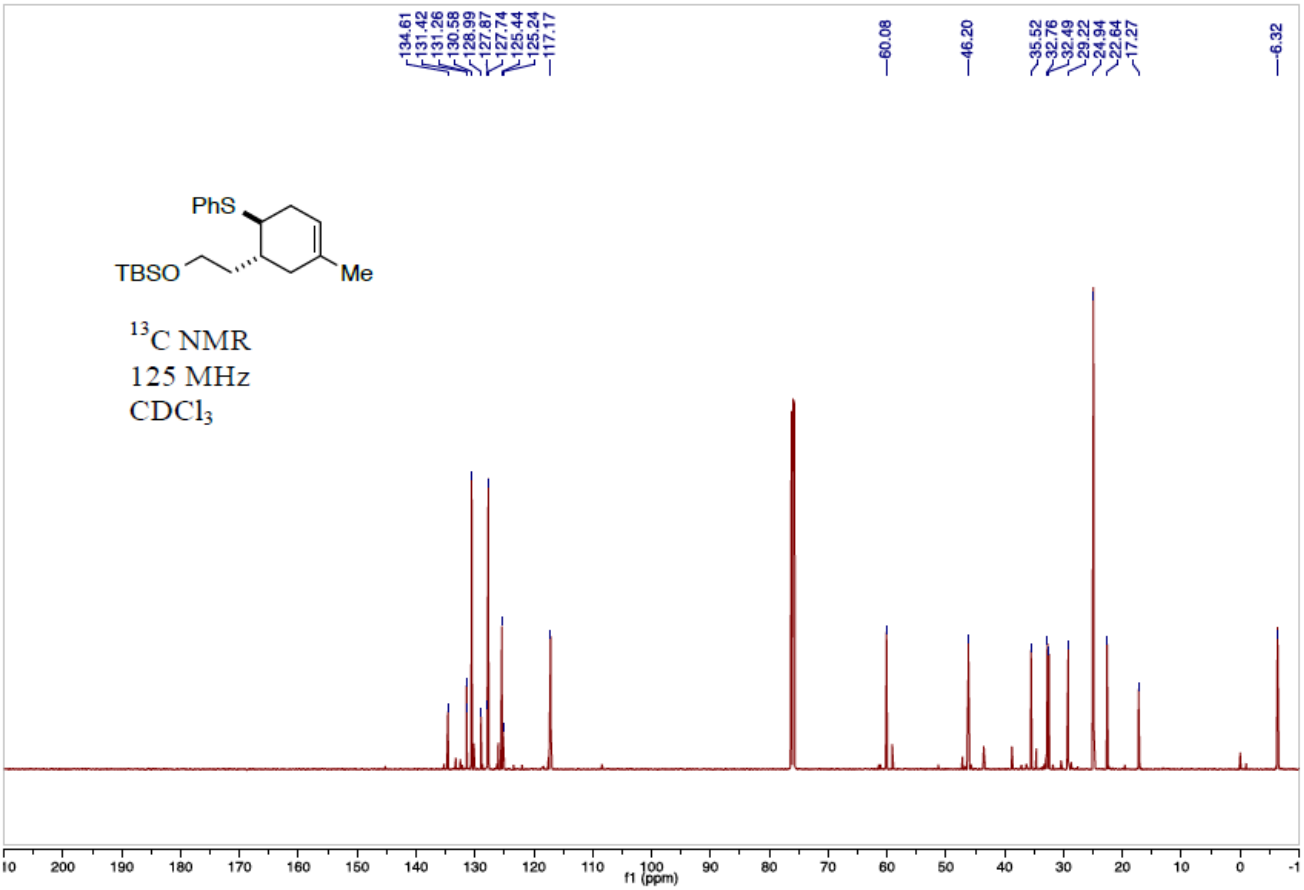

PhS
Me
Me
Me
Me
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

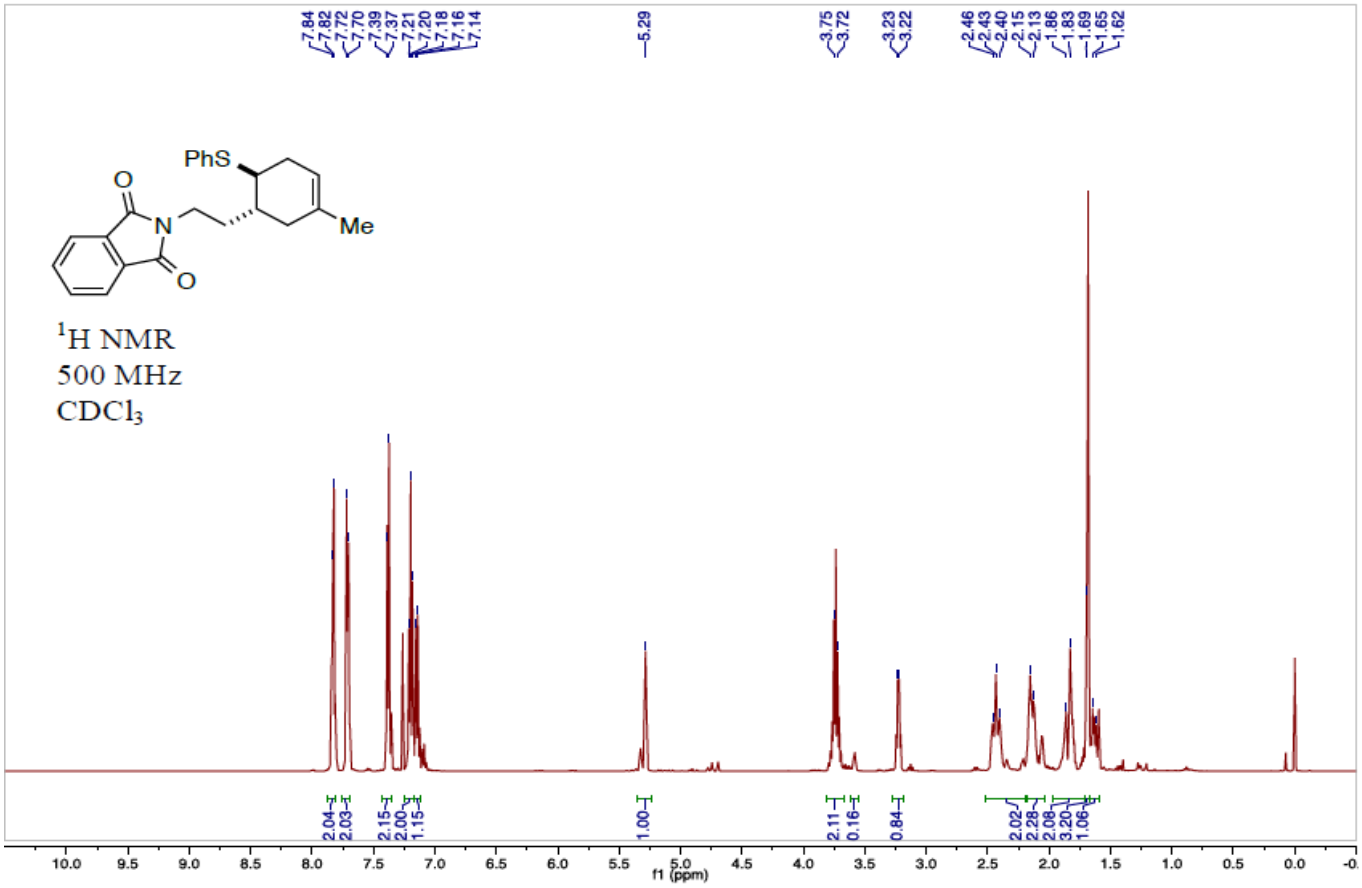

PhS
Me
Me
Me
Me
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

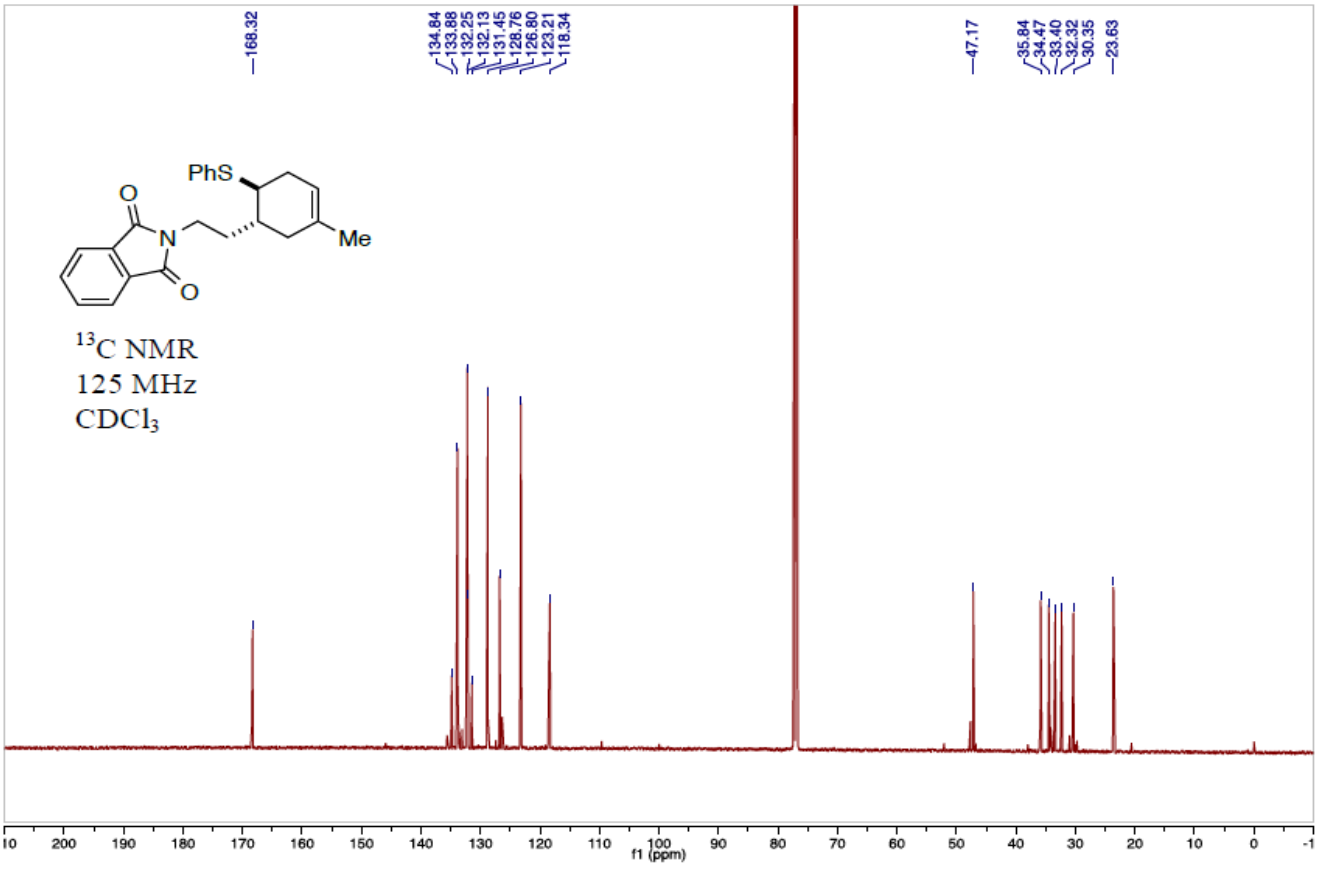

PhS
AcO
Me
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

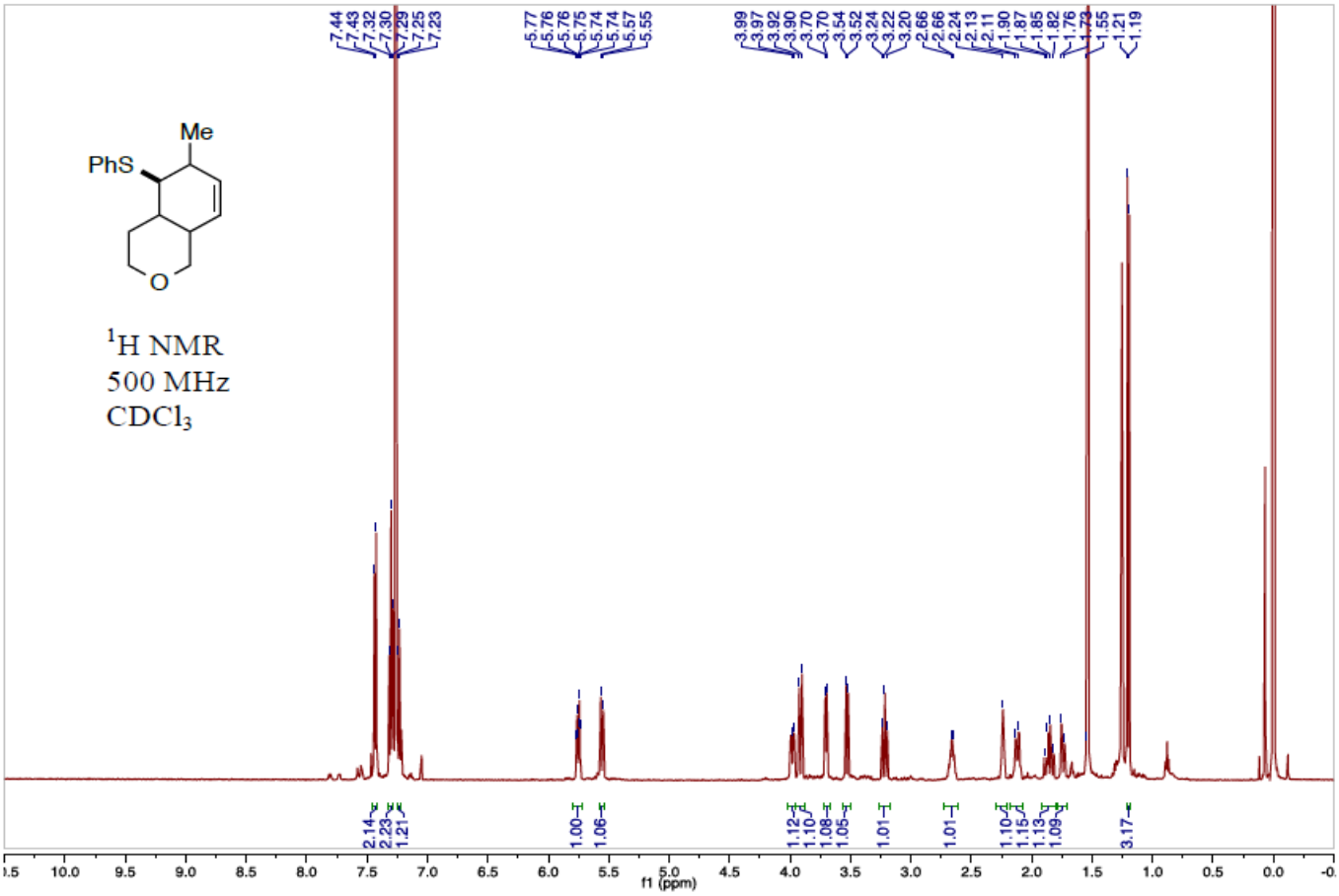

PhS
AcO
Me
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

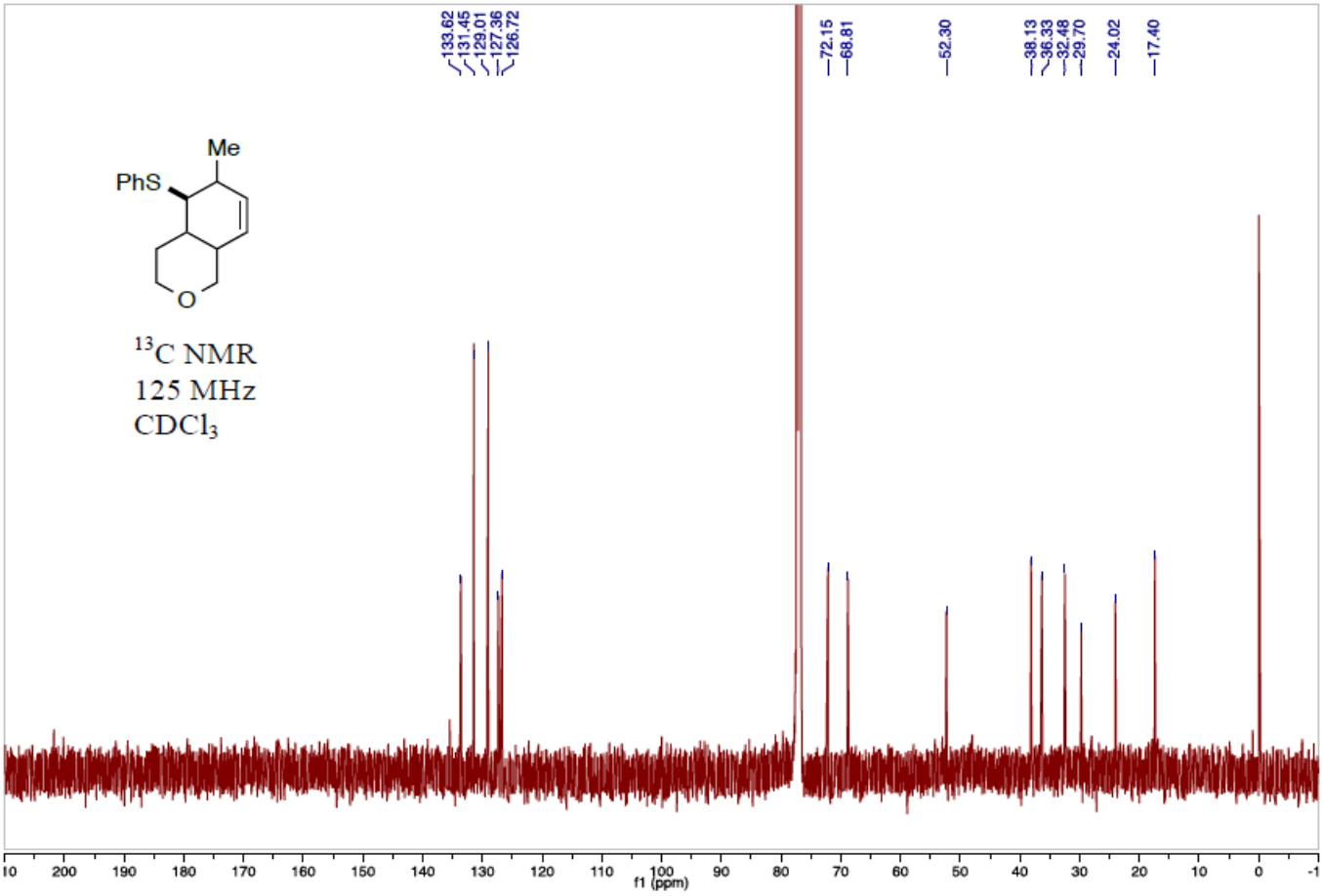

PhS
TBSO
Me
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

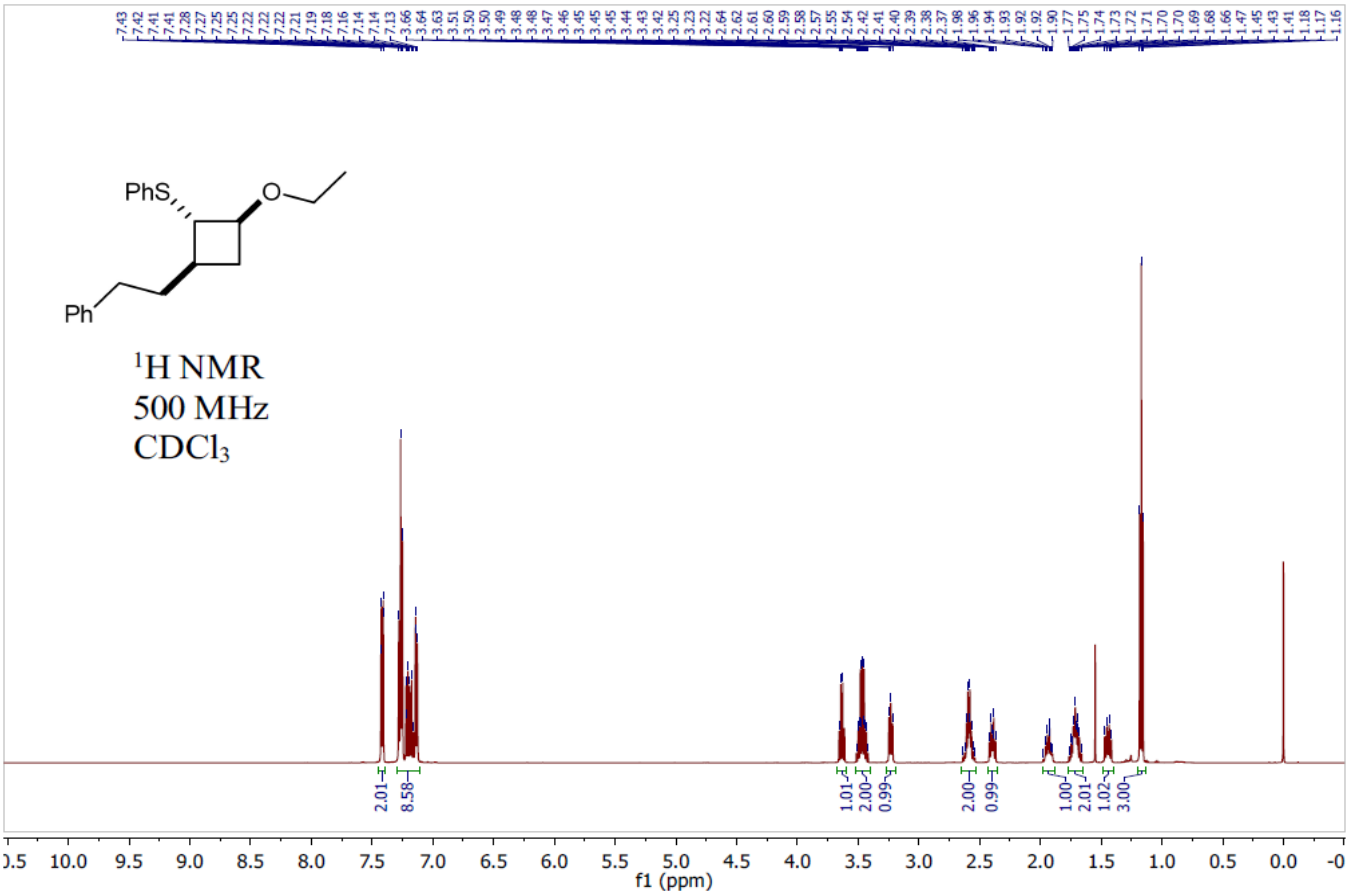

PhS
TBSO
Me
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

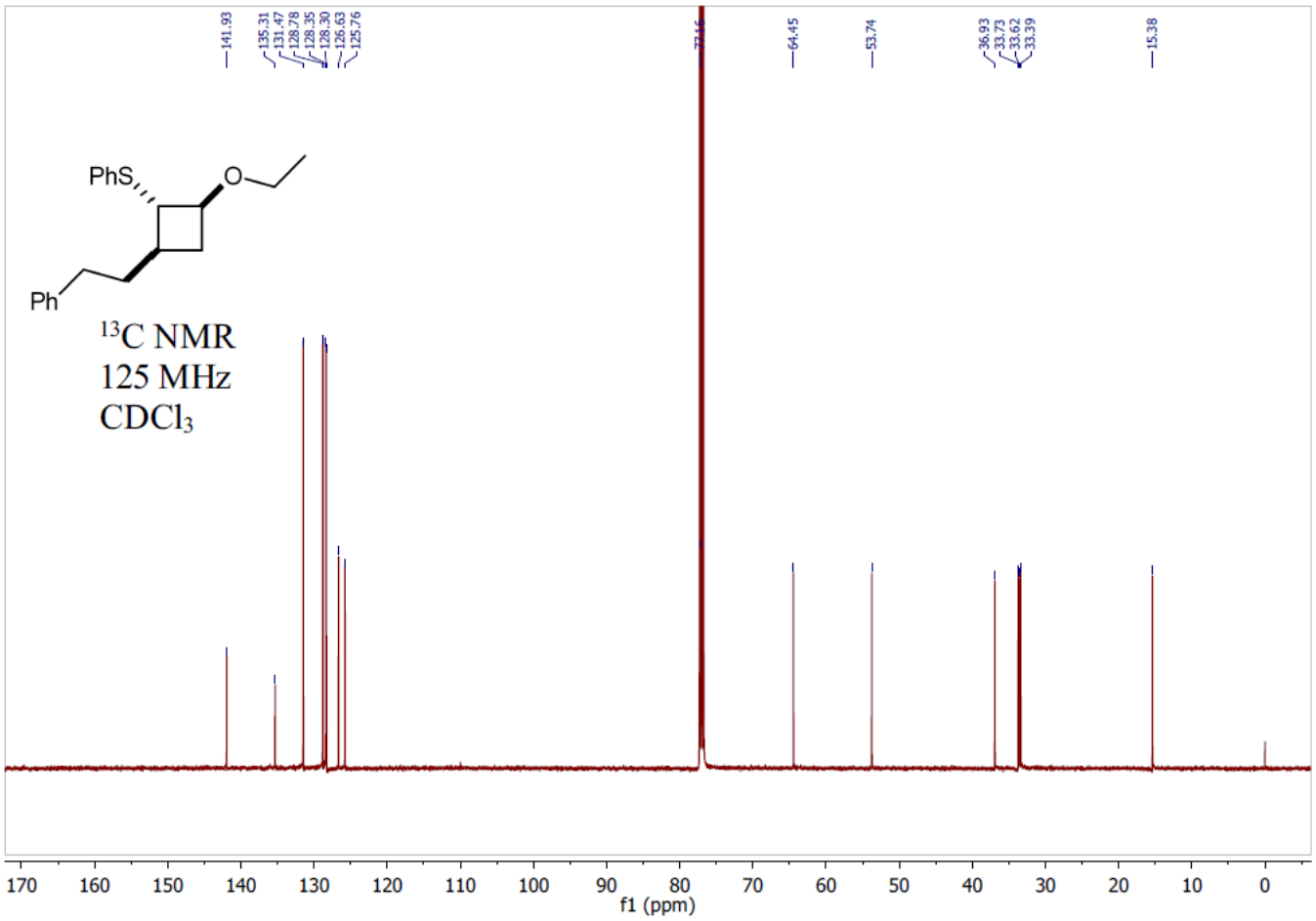

7.84
7.82
7.72
7.70
7.39
7.37
7.21
7.20
7.18
7.16
7.14
5.29
3.75
3.72
3.23
3.22
2.46
2.43
2.40
2.15
2.13
1.86
1.83
1.69
1.65
1.62
PhS
O
N
O
Me
1H NMR
500 MHz
CDCl3
2.04
2.03
2.15
2.00
1.15
1.00
2.11
0.16
0.84
2.02
2.28
2.08
3.20
1.06
f1 (ppm)

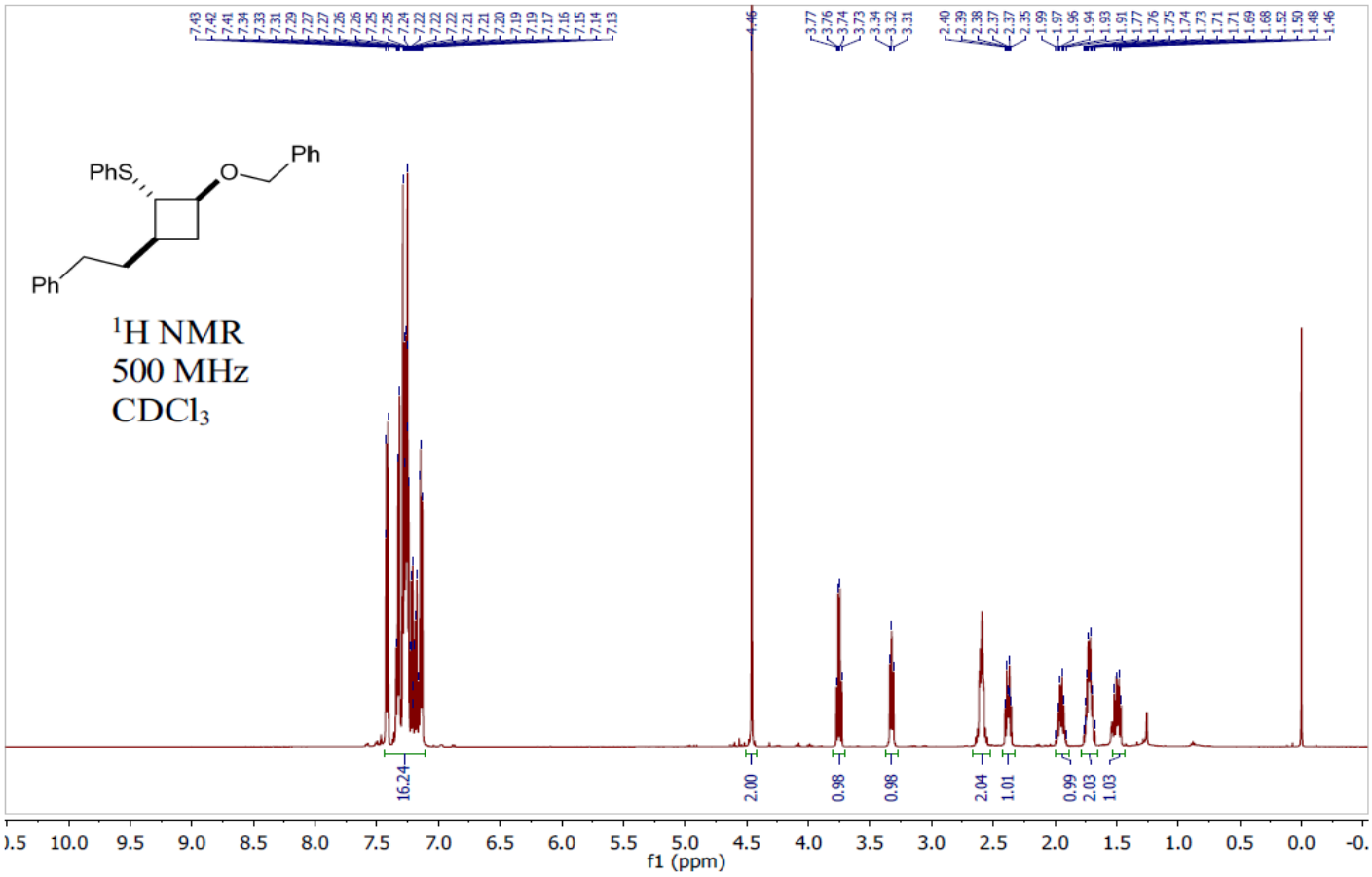

168.32
134.84
133.88
132.25
132.13
131.45
128.76
126.80
123.21
118.34
47.17
35.84
34.47
33.40
32.32
30.35
23.63
PhS
O
N
O
Me
13C NMR
125 MHz
CDCl3
f1 (ppm)

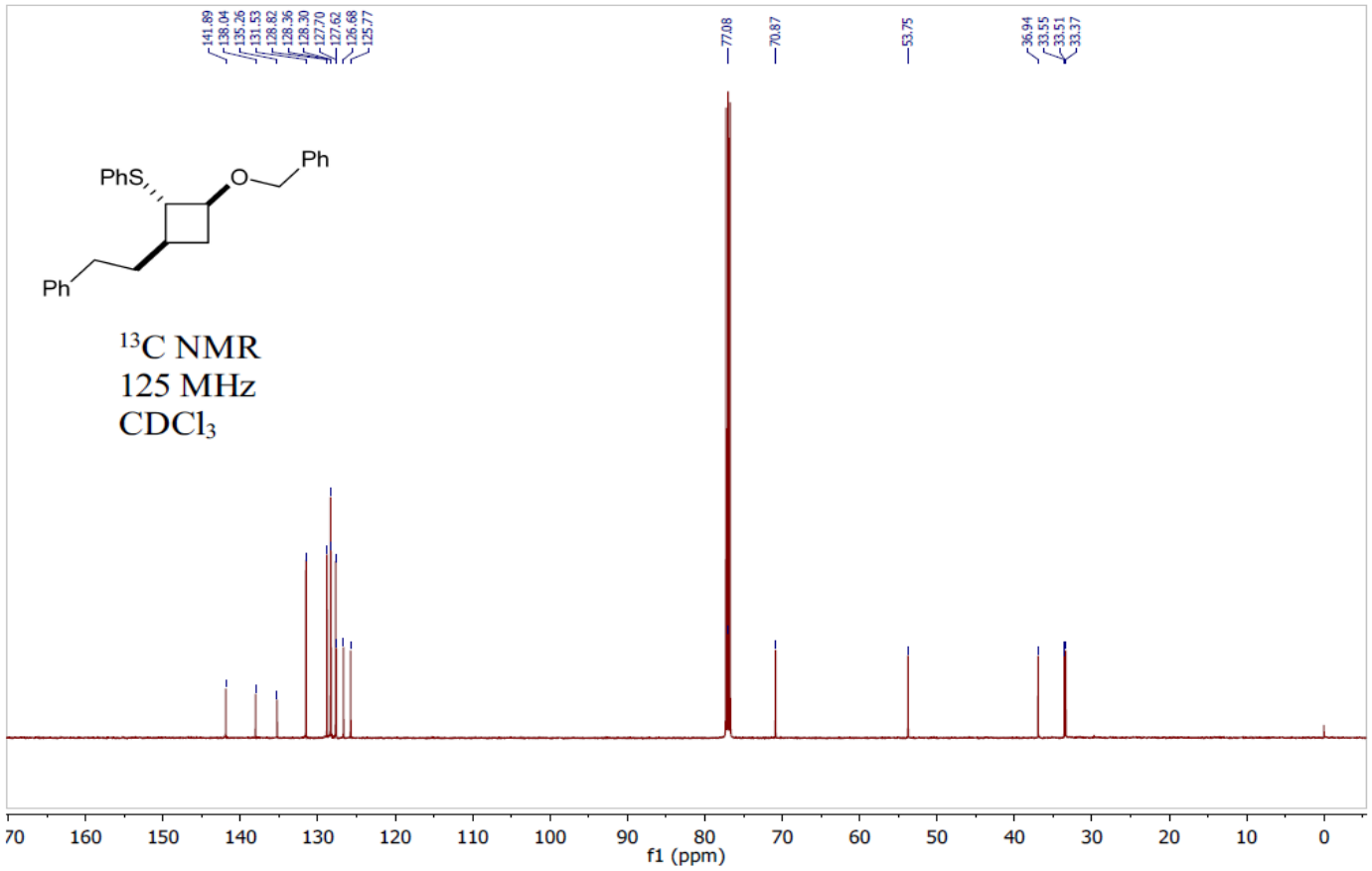

Me
PhS
O
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

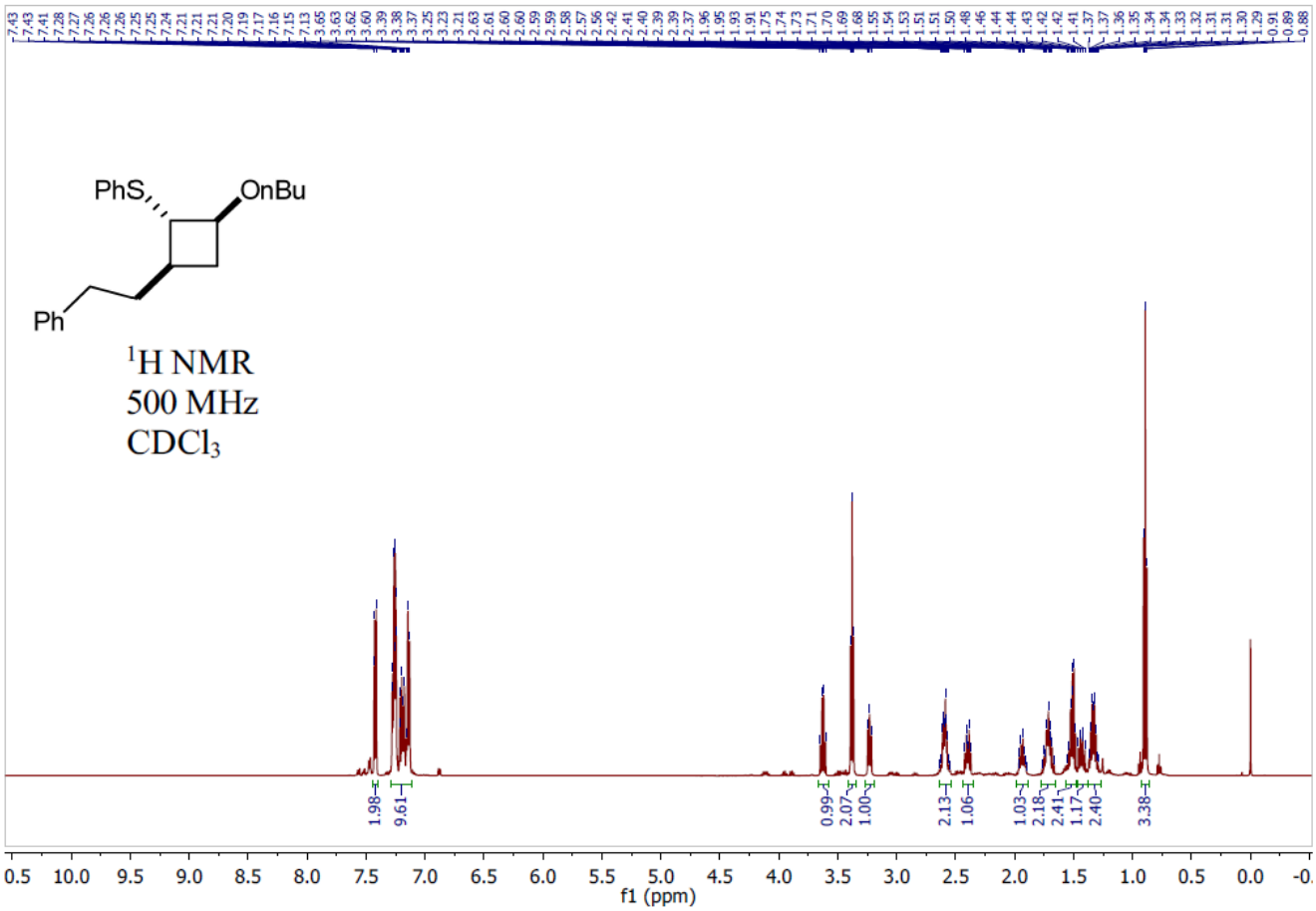

Me
PhS
O
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

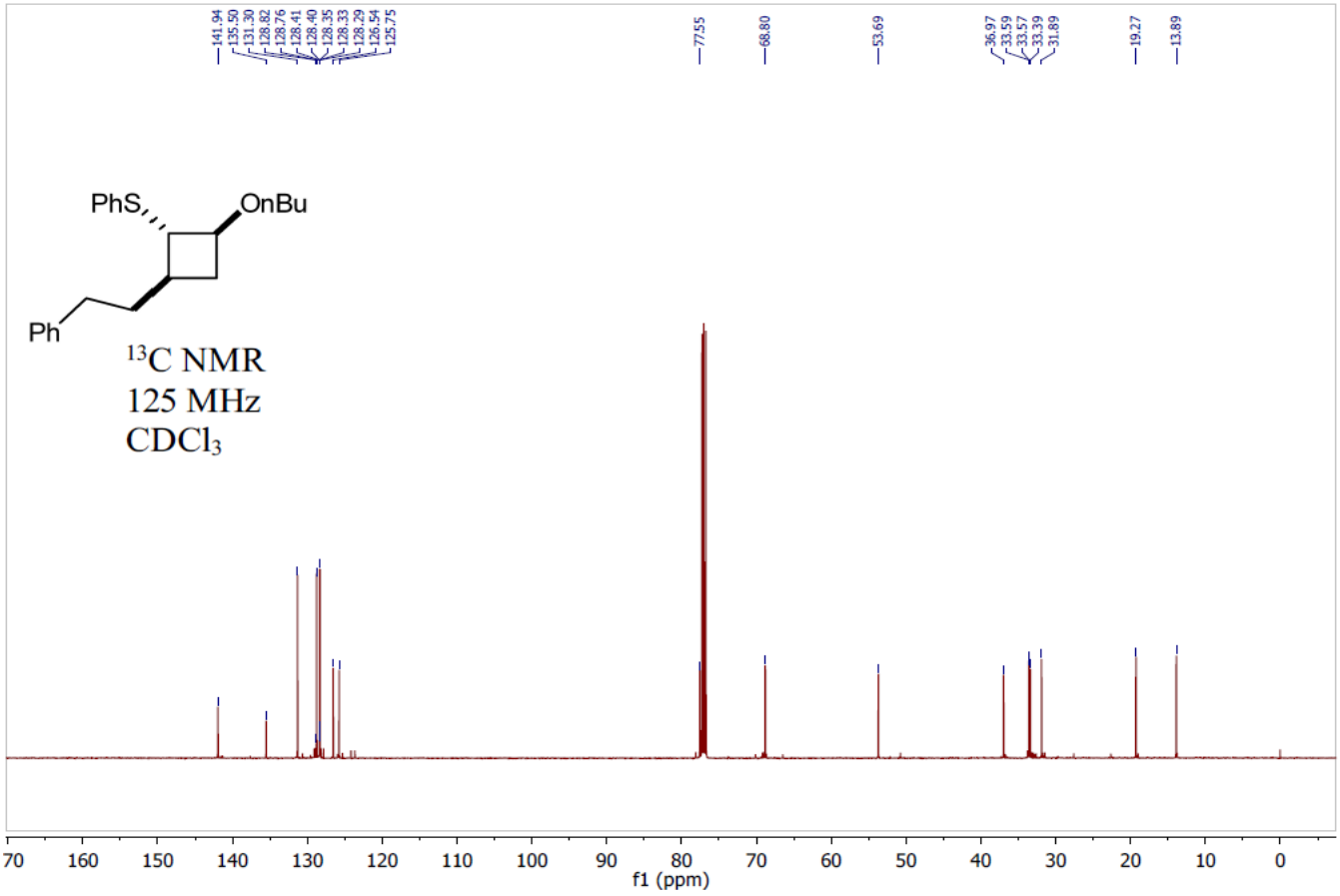

PhS
O
Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

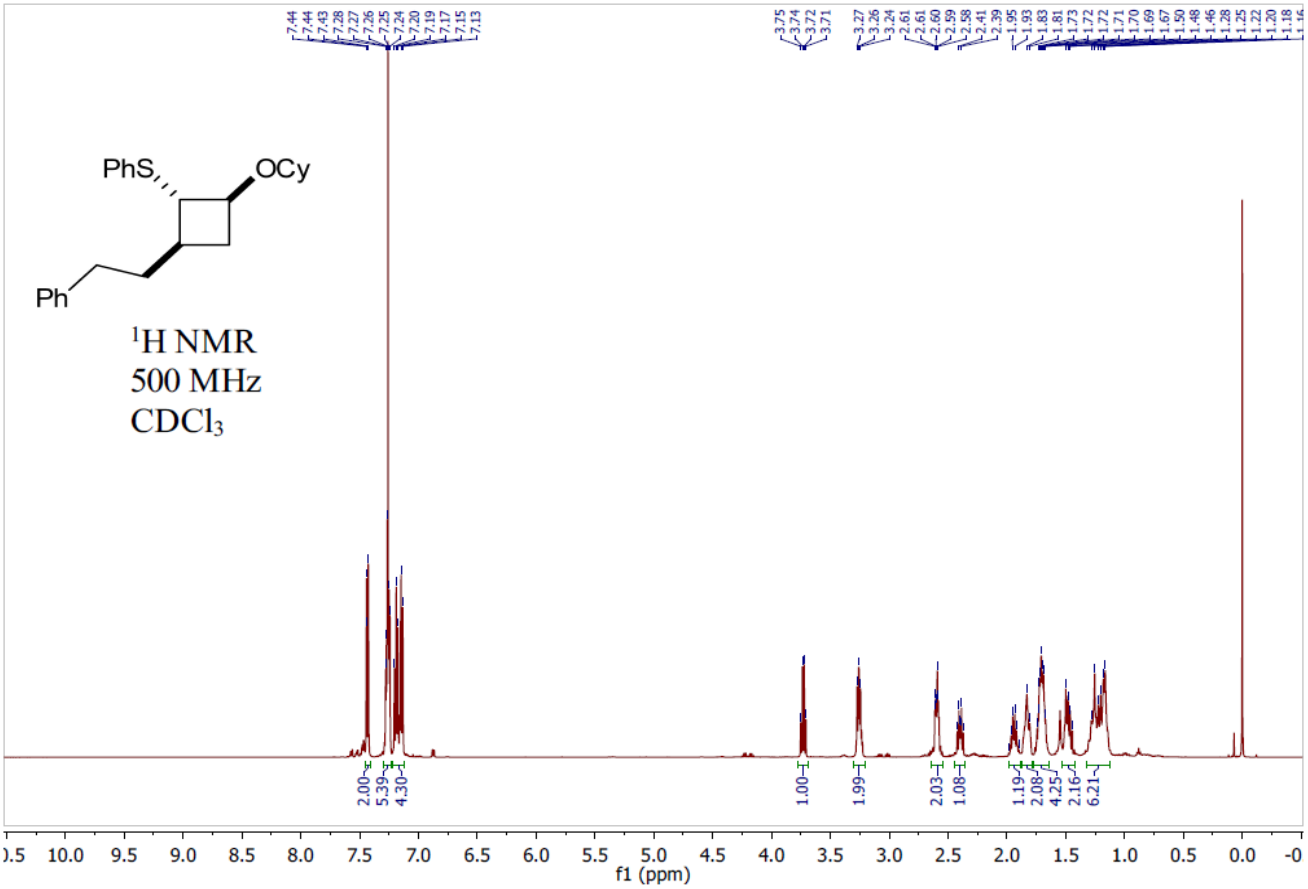

PhS
O
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

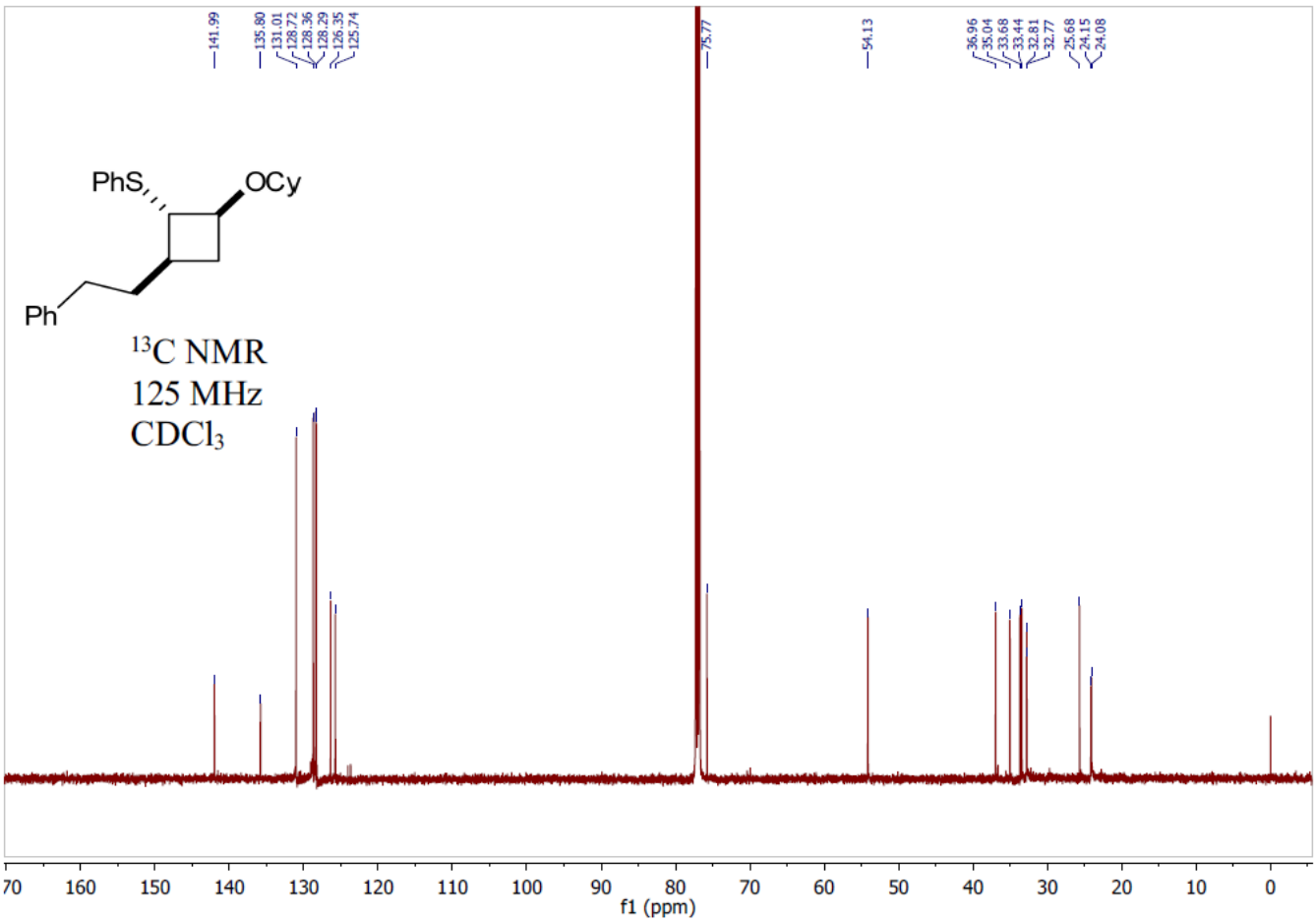

PhS
O
Ph
Ph
^{1}H NMR
500 MHz
$CDCl_3$
16.24
2.00
0.98
0.98
2.04
1.01
0.99
2.03
1.03
f1 (ppm)

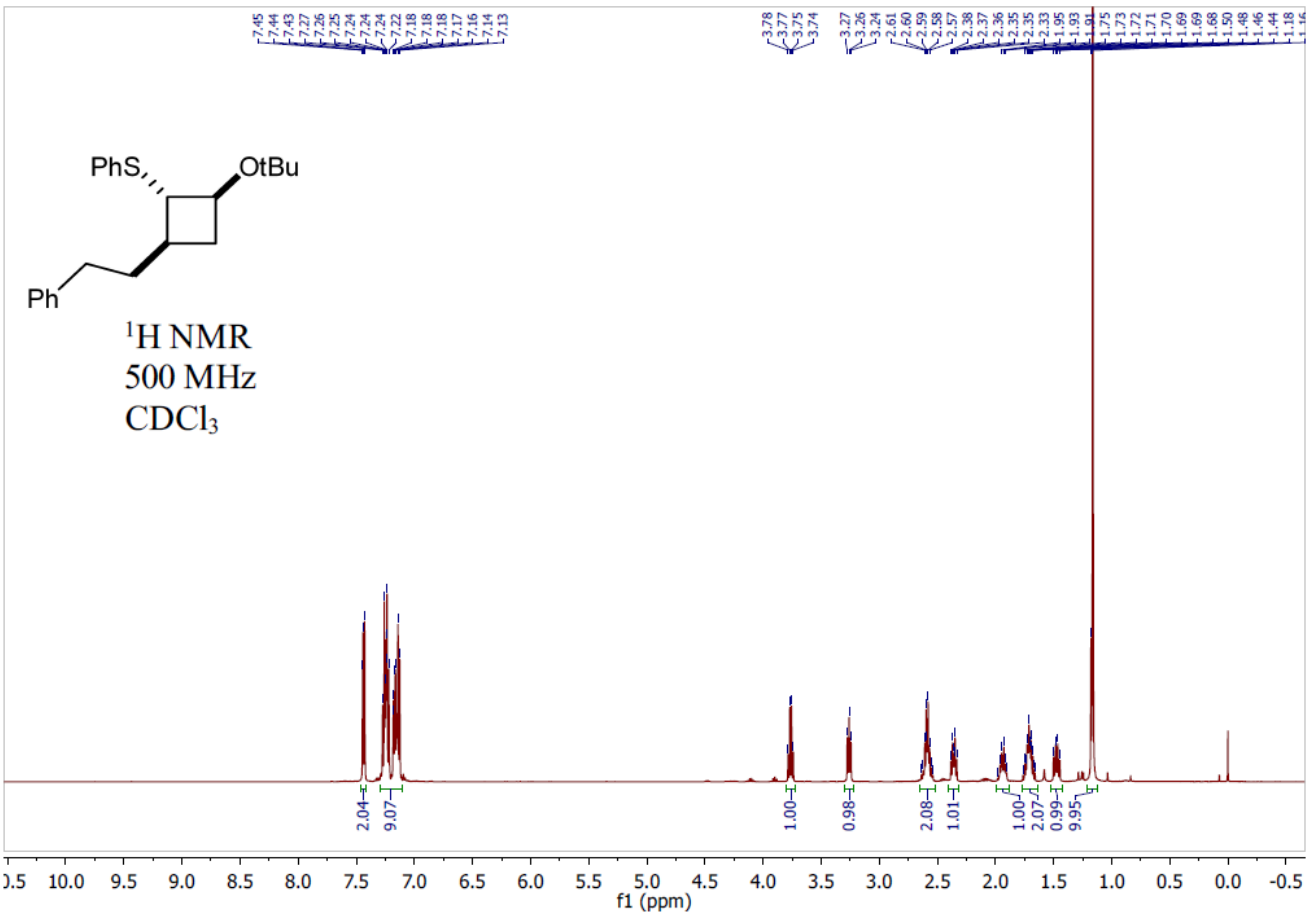

PhS
O
Ph
Ph
^{13}C NMR
125 MHz
$CDCl_3$
77.08
70.87
53.75
f1 (ppm)

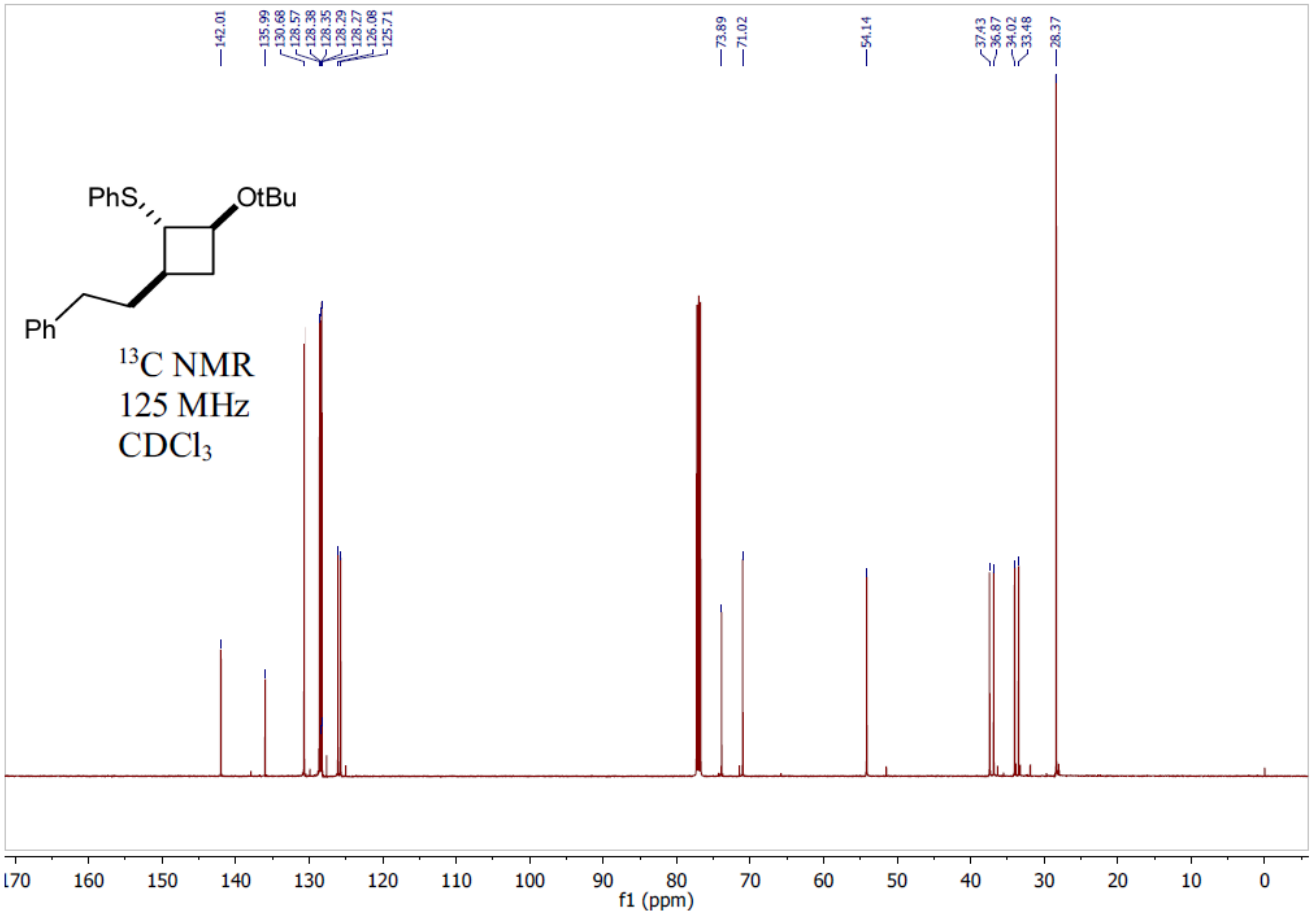

PhS
OnBu
Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

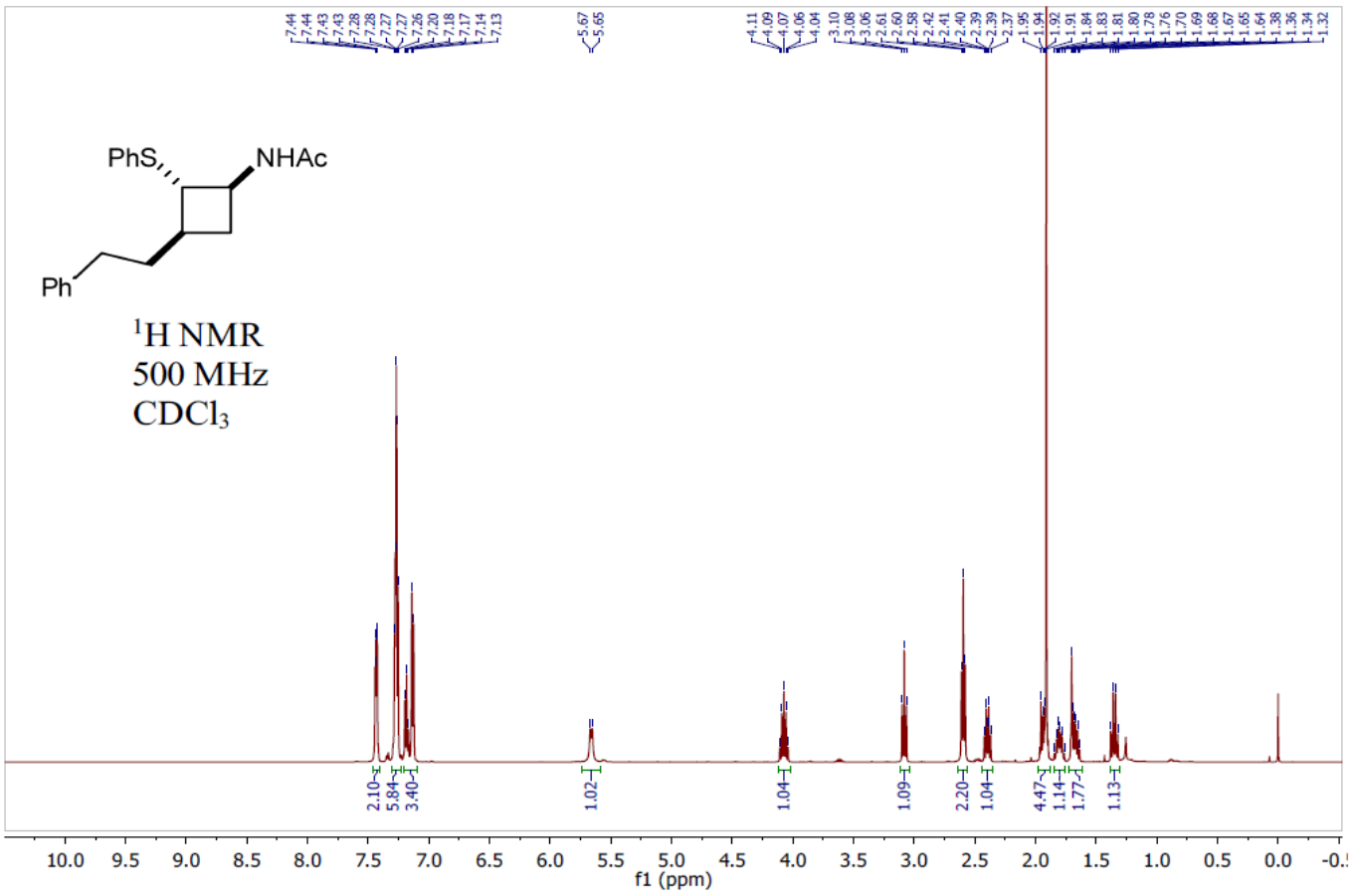

PhS
OnBu
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)


PhS
OCy
Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)


PhS
OCy
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)


PhS
OtBu
Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)


PhS
OtBu
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)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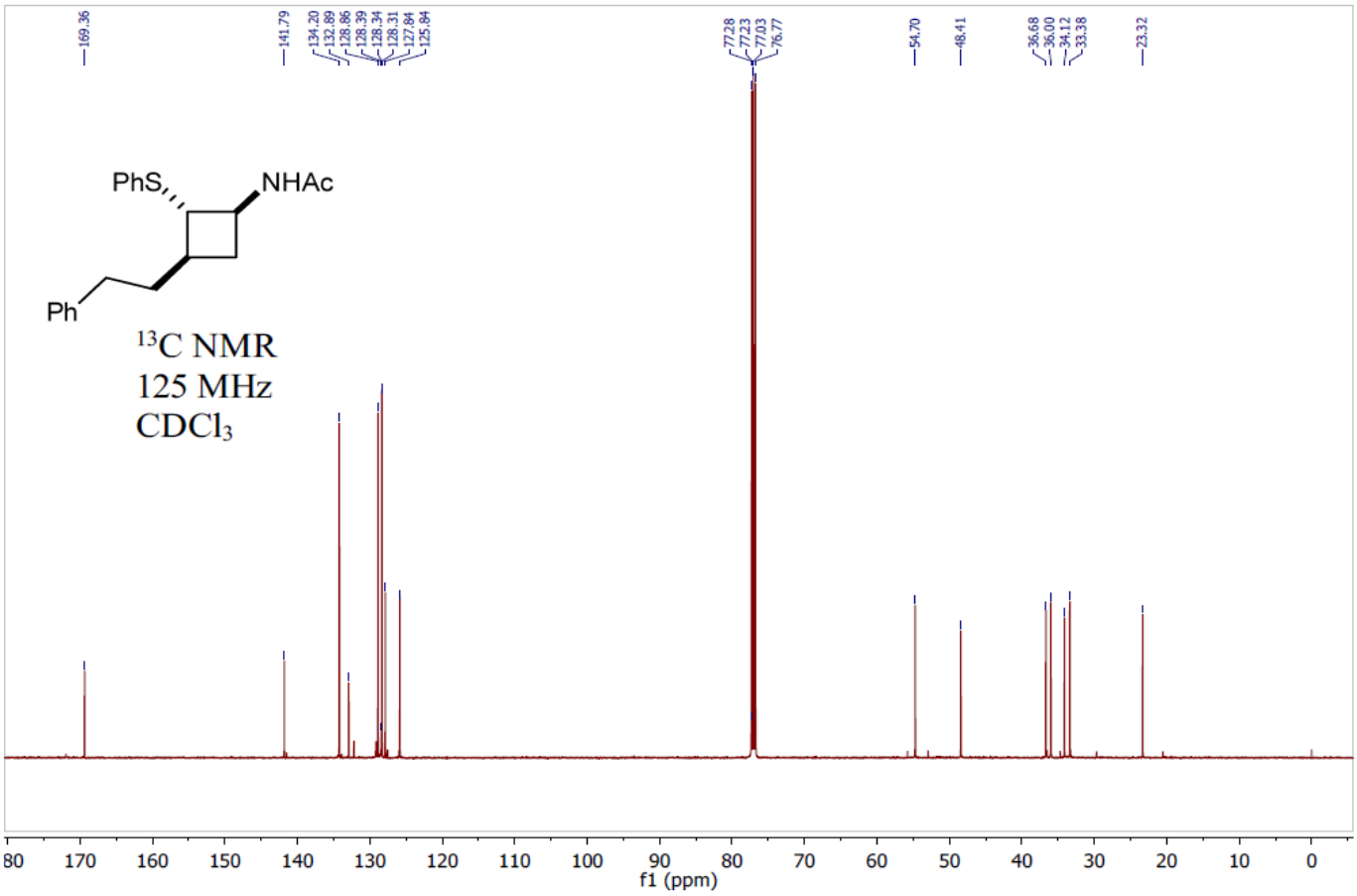
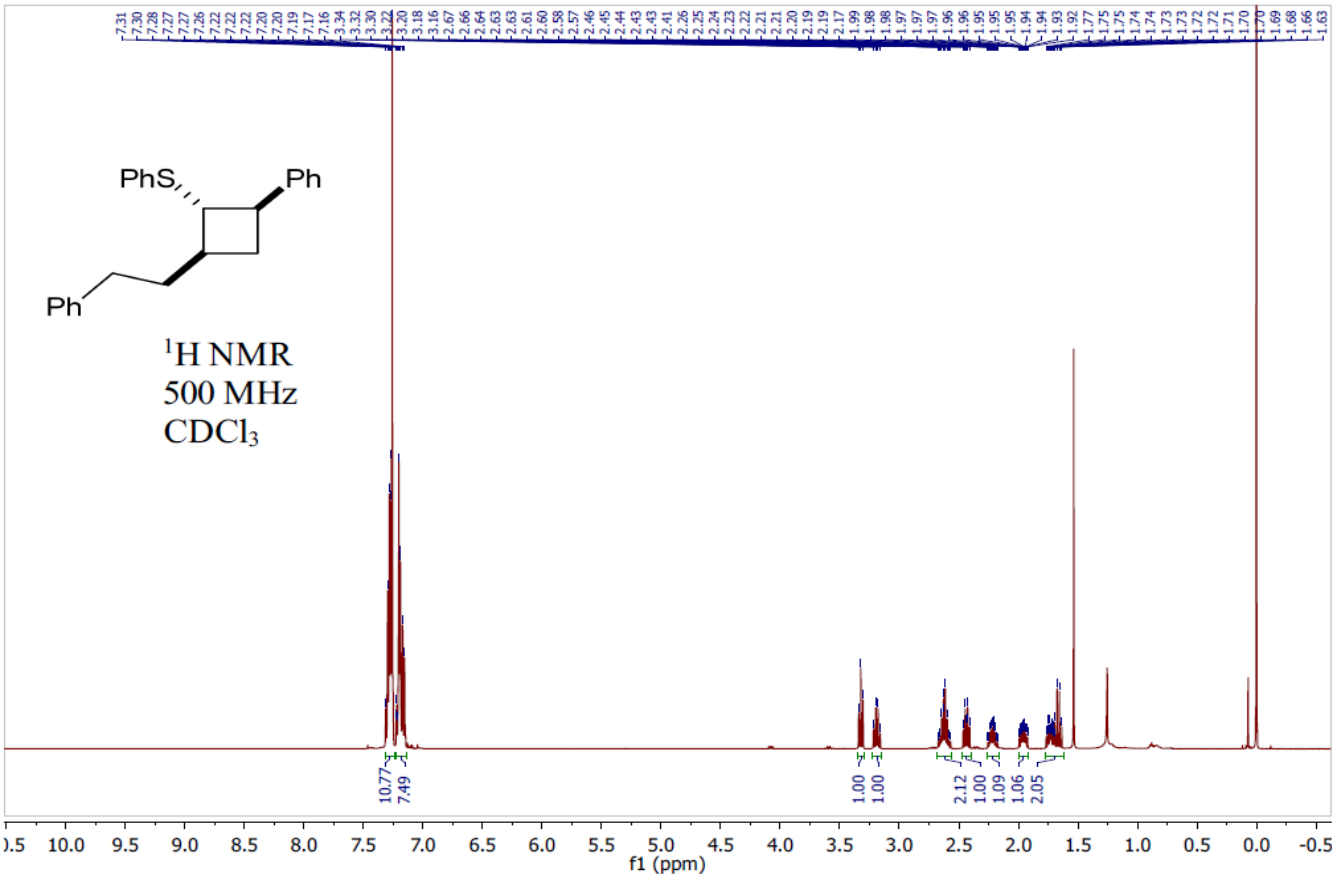
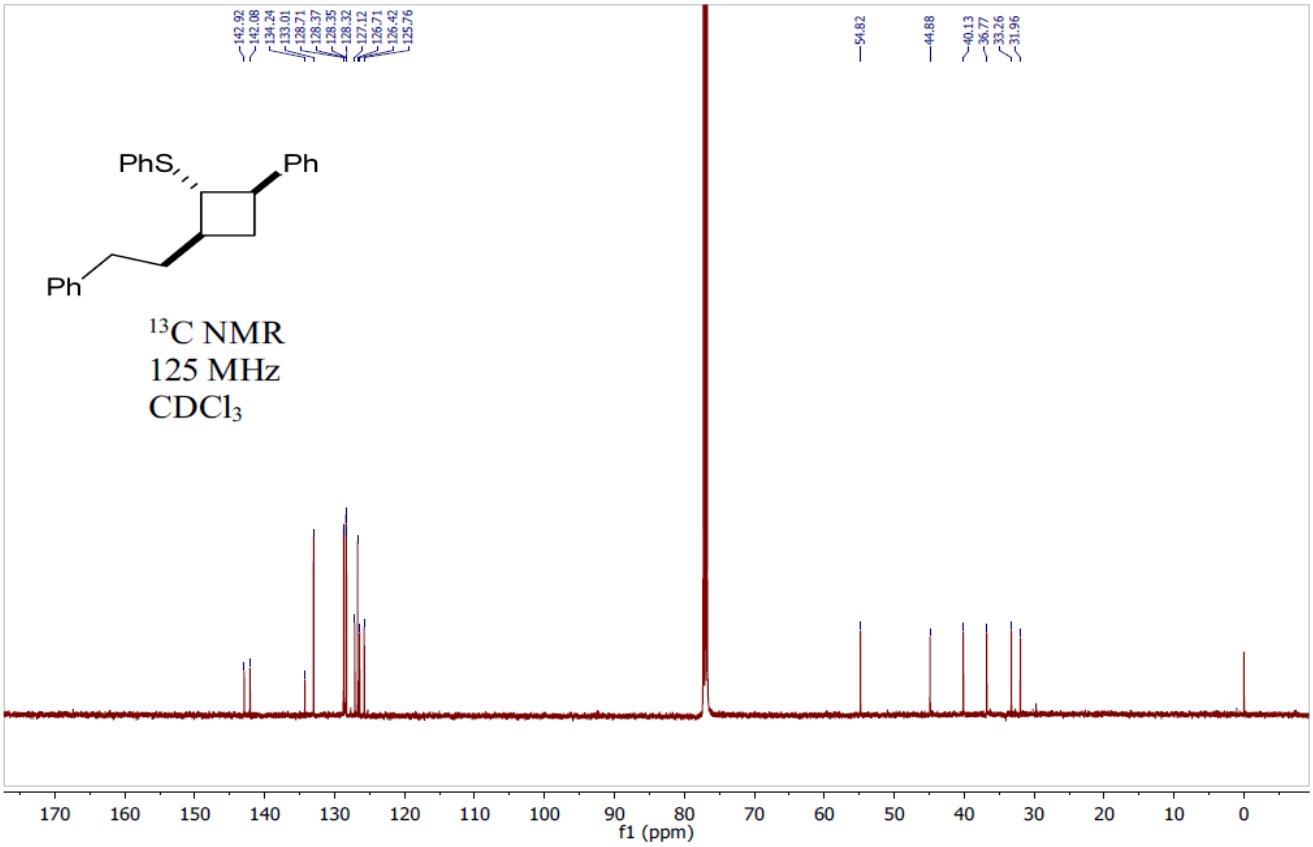
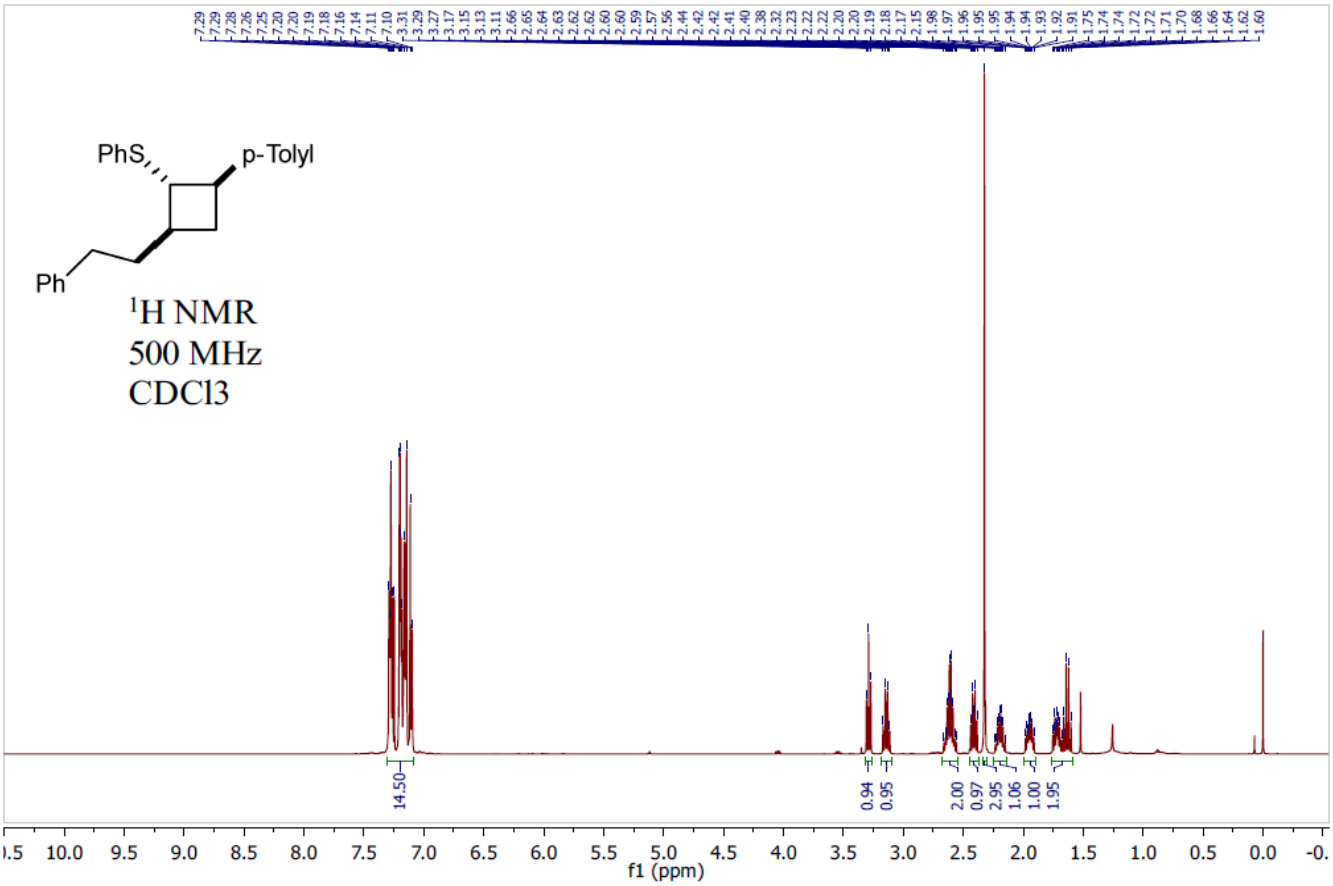
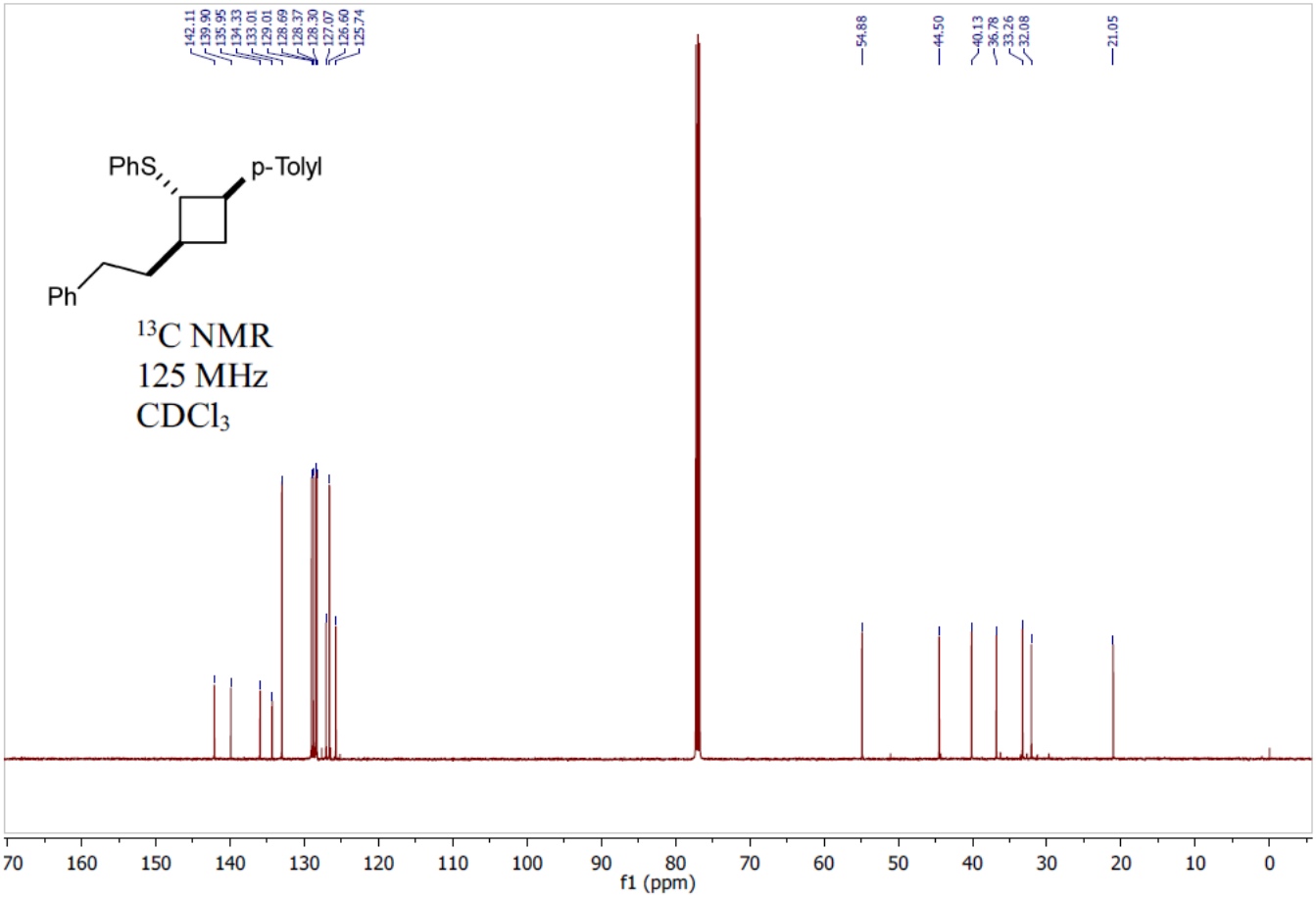
NHAc
Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

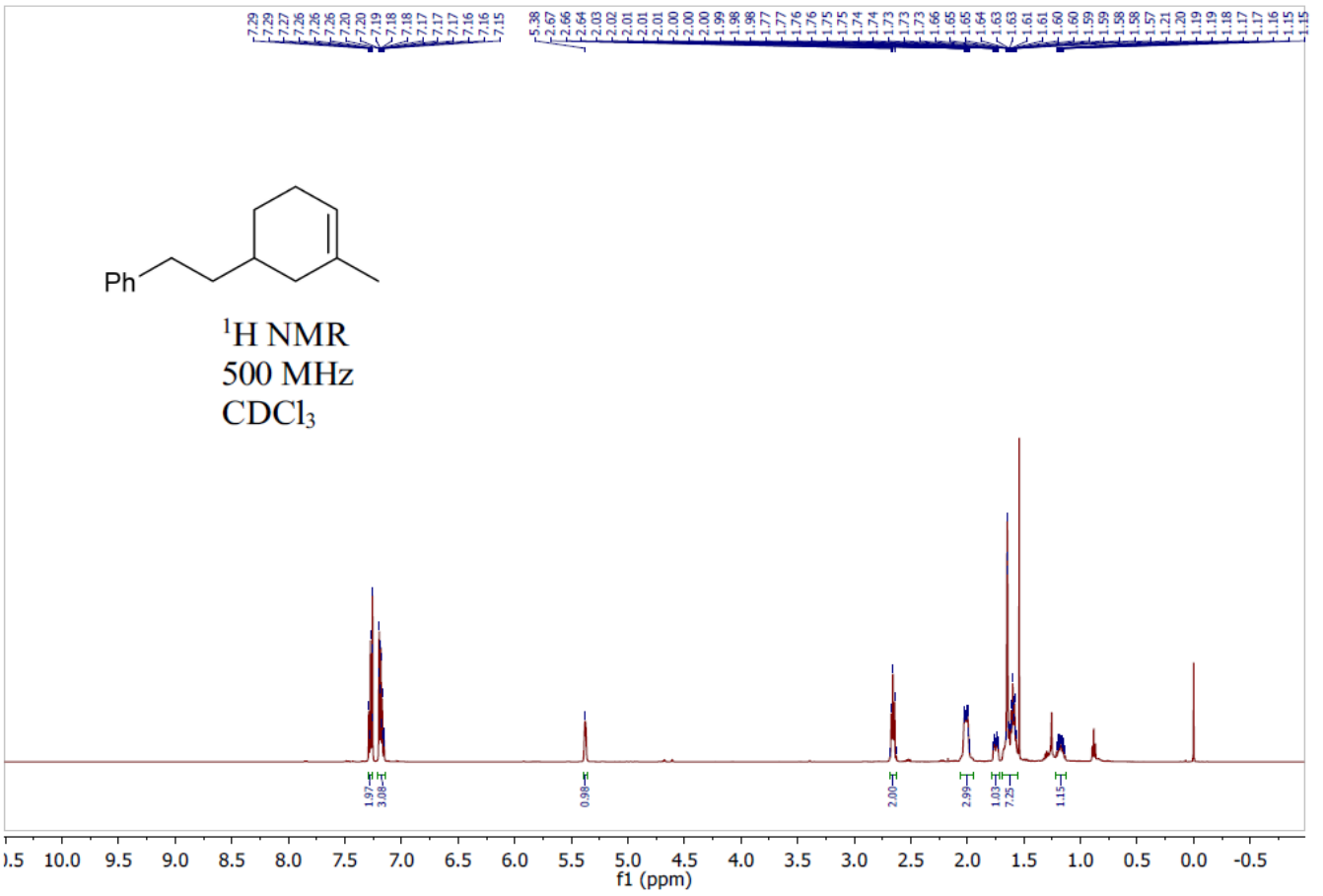

PhS
NHAc
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

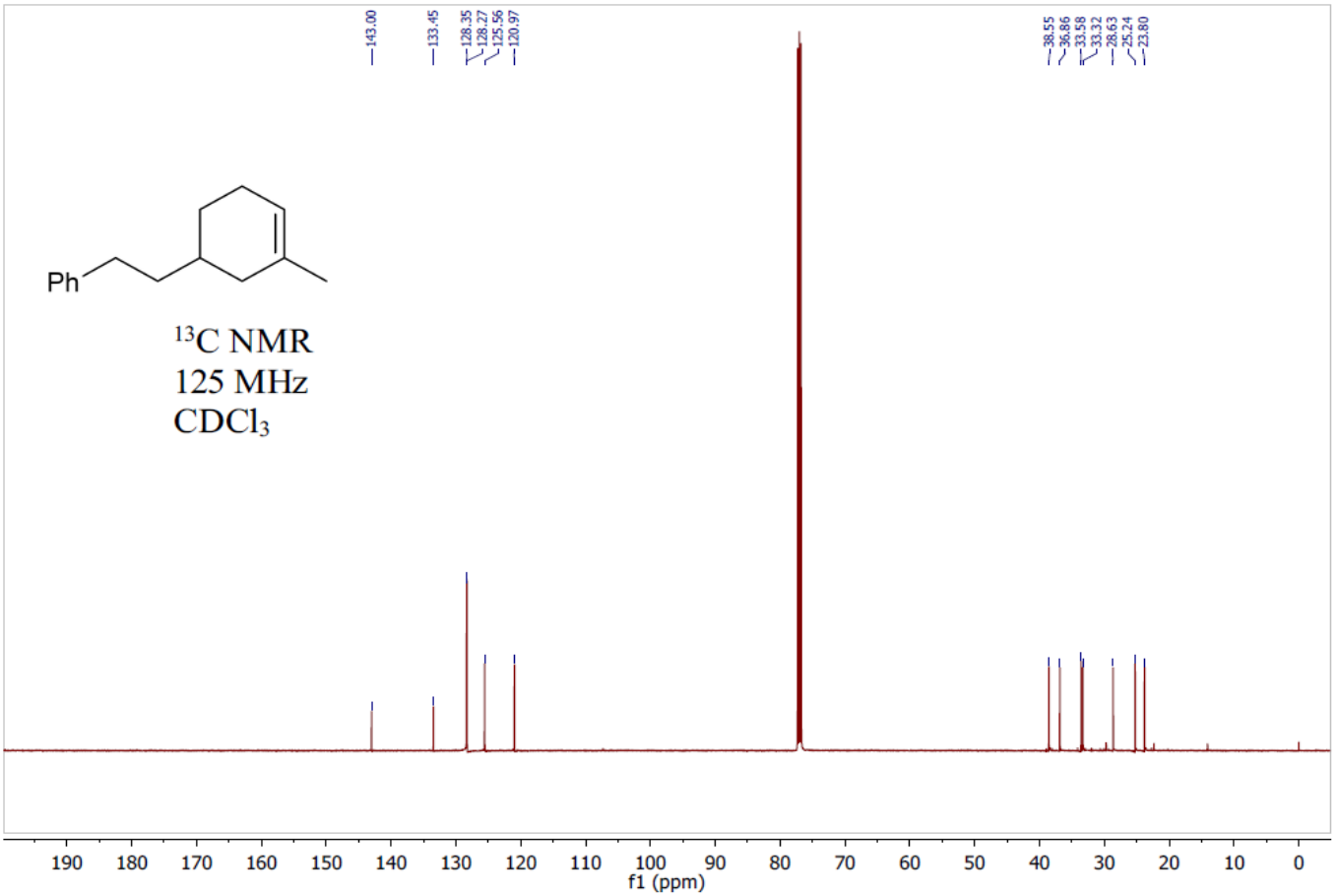

PhS
Ph
Ph
^{1}H NMR
500 MHz
$CDCl_3$
10.77
7.49
1.00
1.00
2.12
1.00
1.09
1.06
2.05
f1 (ppm)

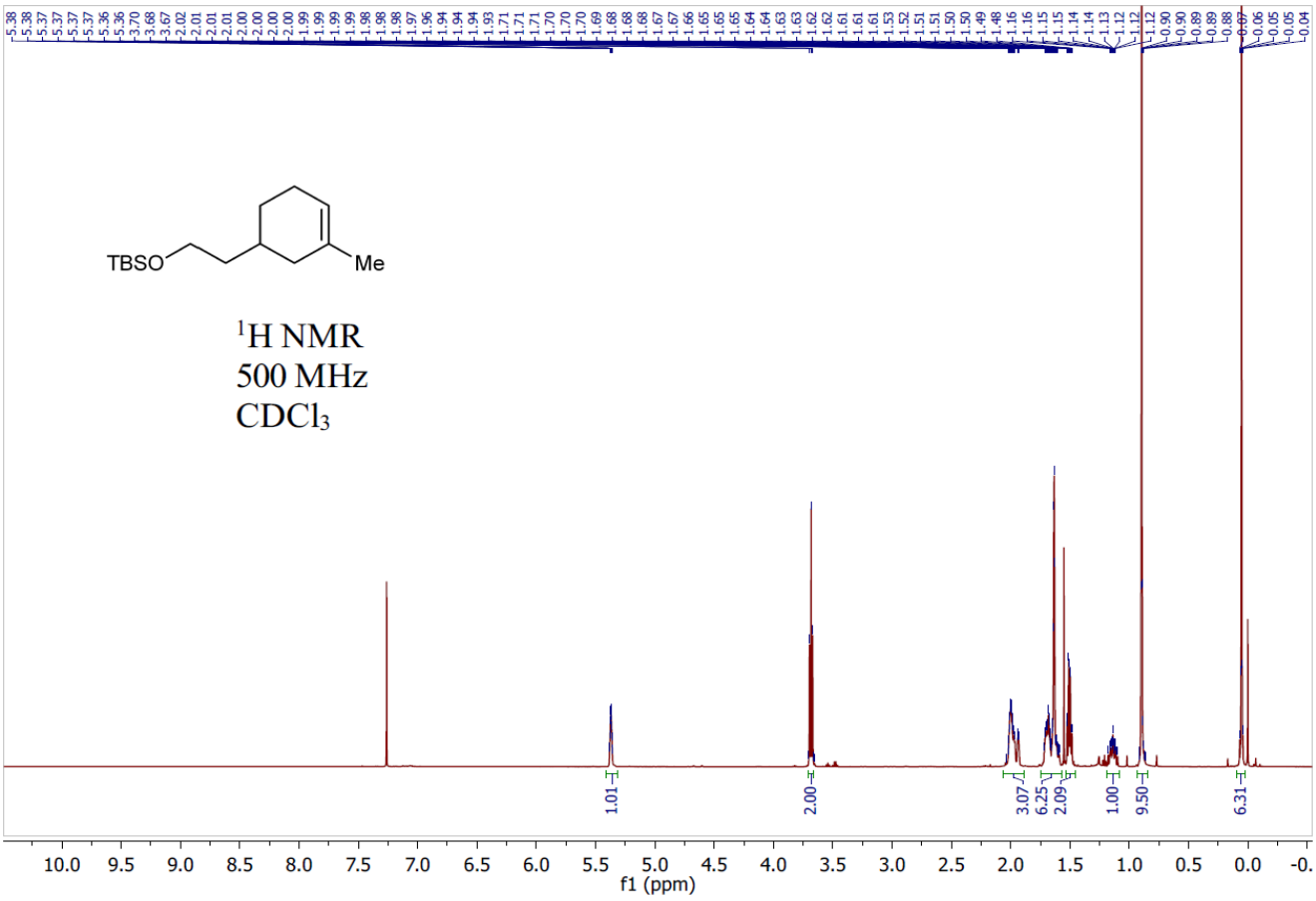

PhS
Ph
Ph
^{13}C NMR
125 MHz
$CDCl_3$
142.92
142.08
134.24
133.01
128.71
128.37
128.35
128.32
127.12
126.71
126.42
125.76
54.82
44.88
40.13
36.77
33.26
31.96
f1 (ppm)

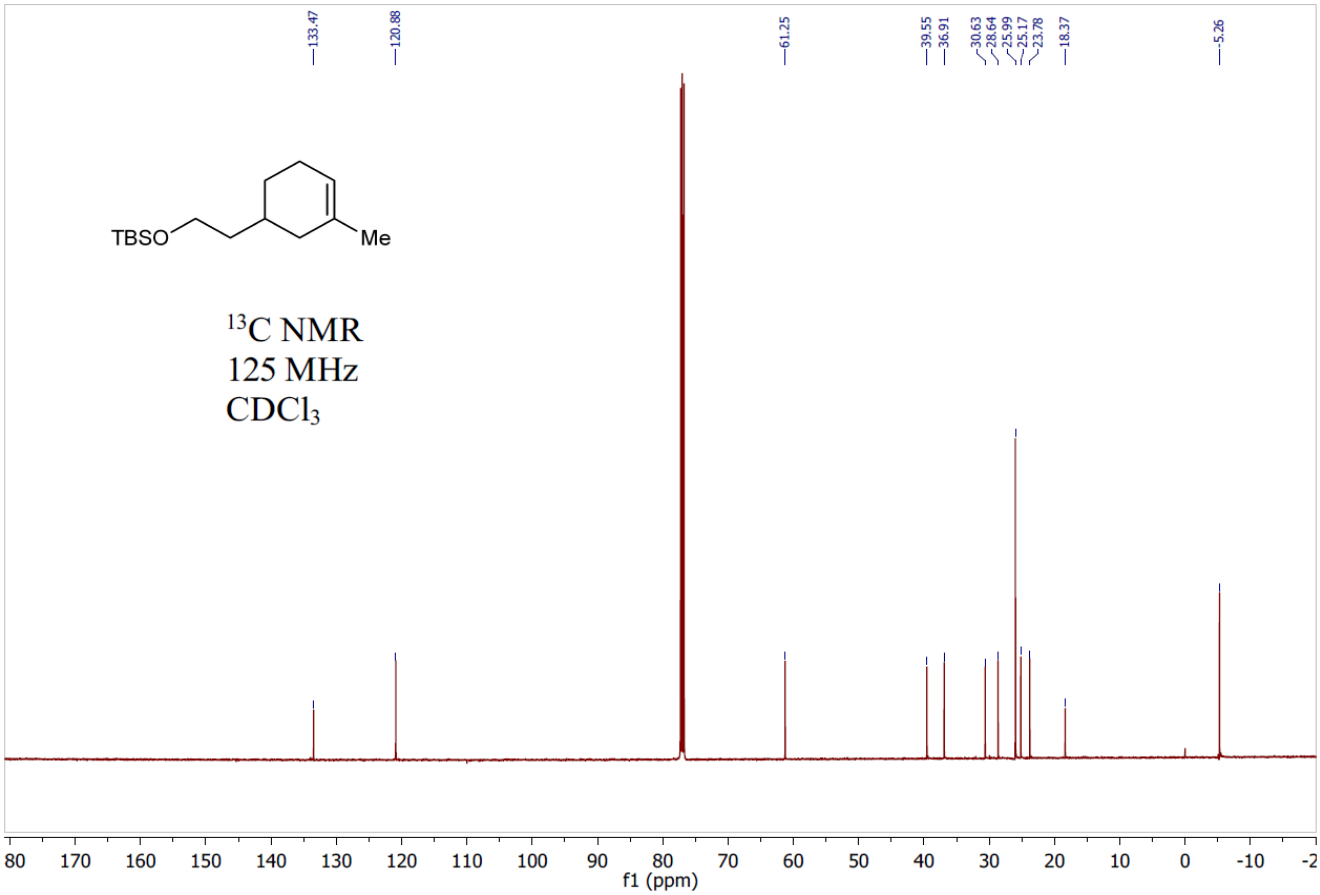

PhS
p-Tolyl
Ph
1H NMR
500 MHz
CDCl3
14.50
0.94
0.95
2.00
0.97
2.95
1.06
1.00
1.95
f1 (ppm)

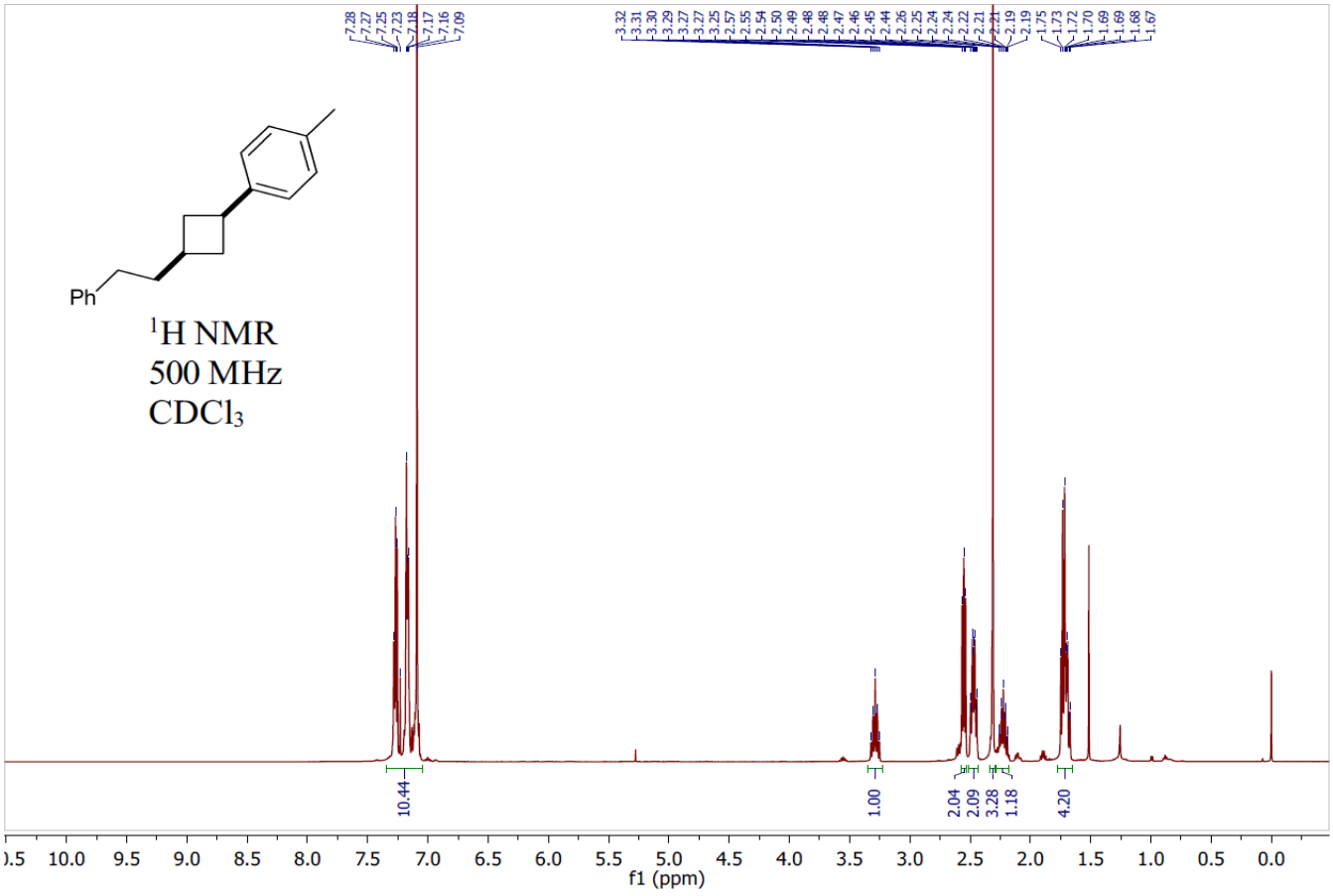

PhS
p-Tolyl
Ph
13C NMR
125 MHz
CDCl3
f1 (ppm)

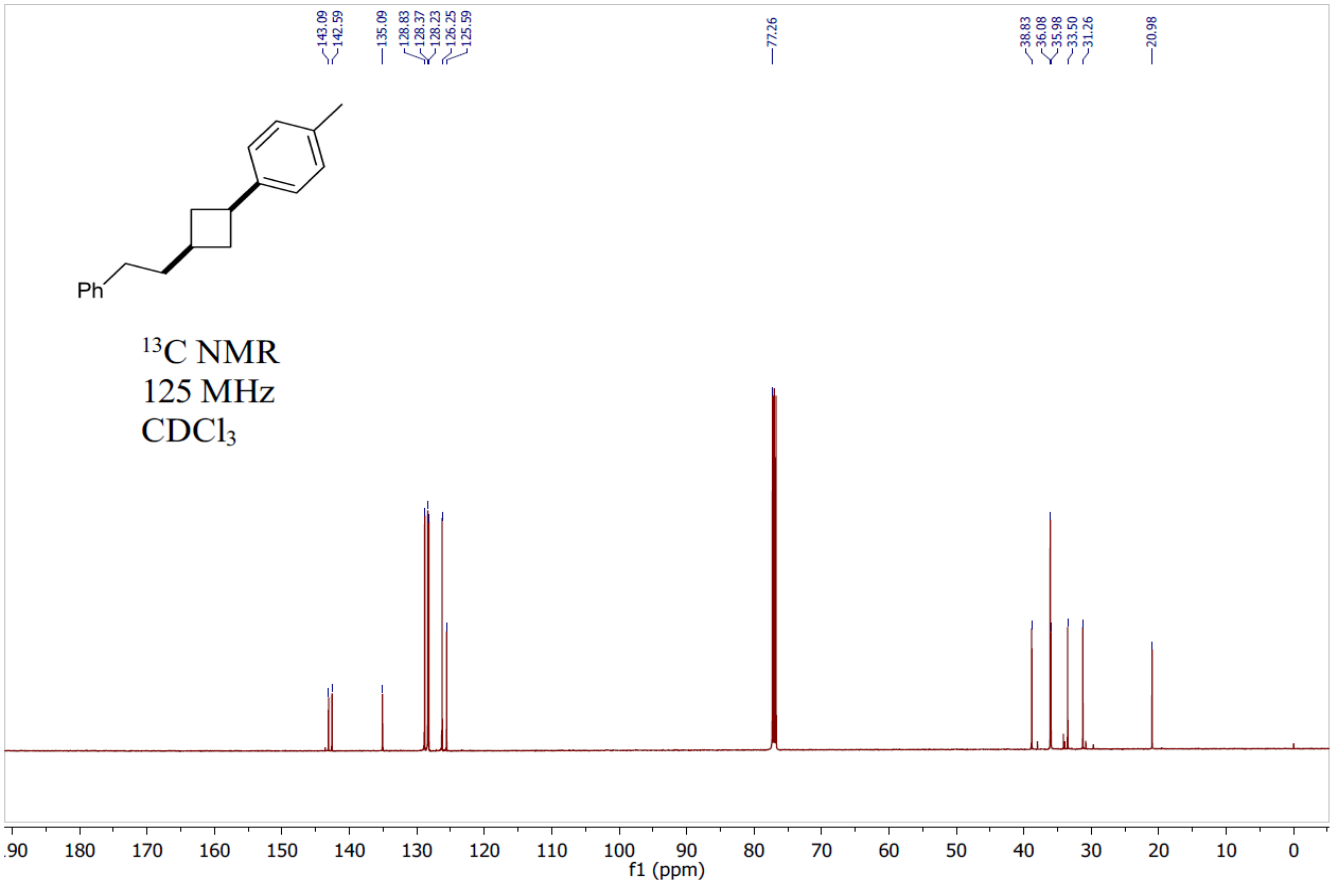

Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

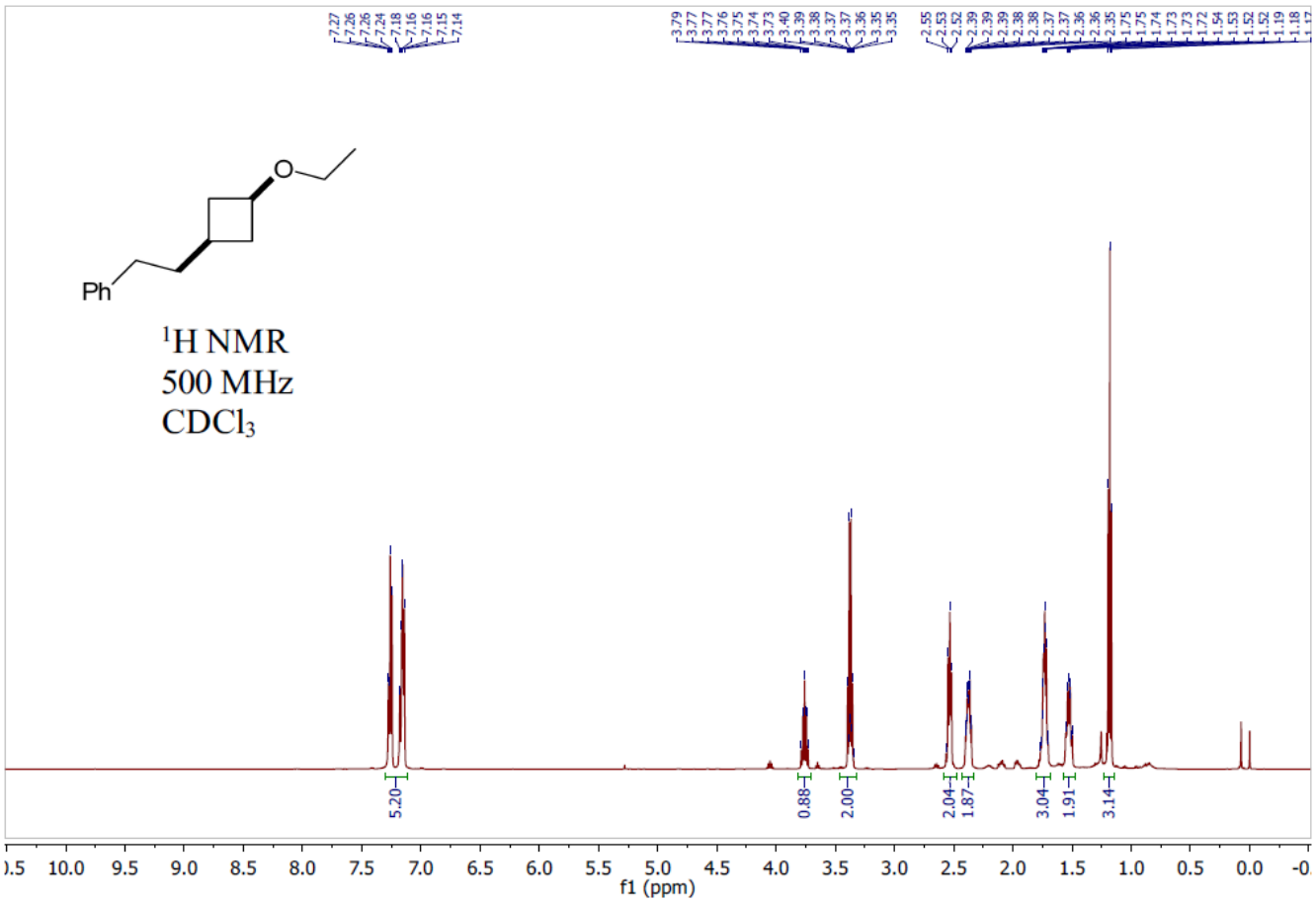

Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

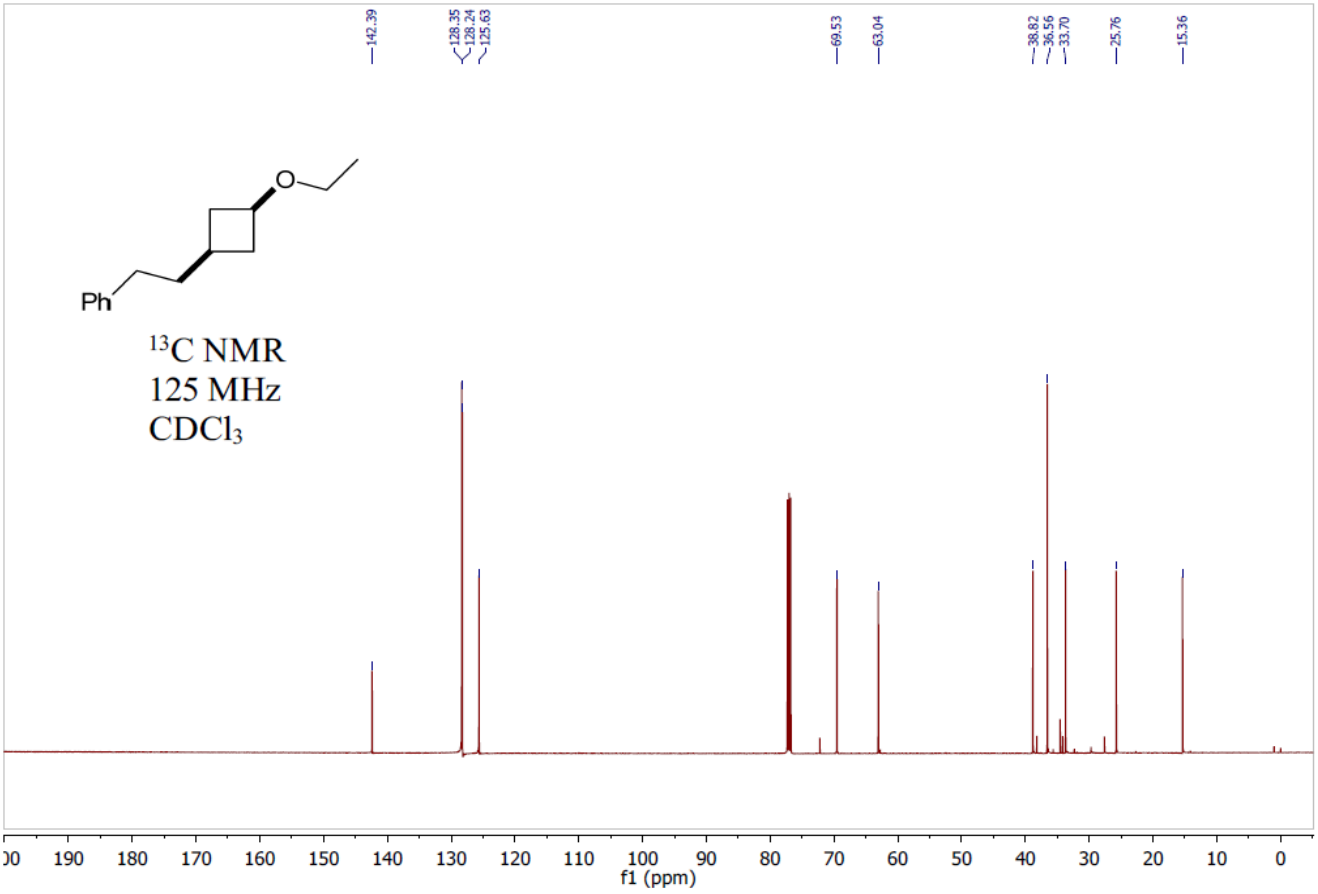

TBSO
Me
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

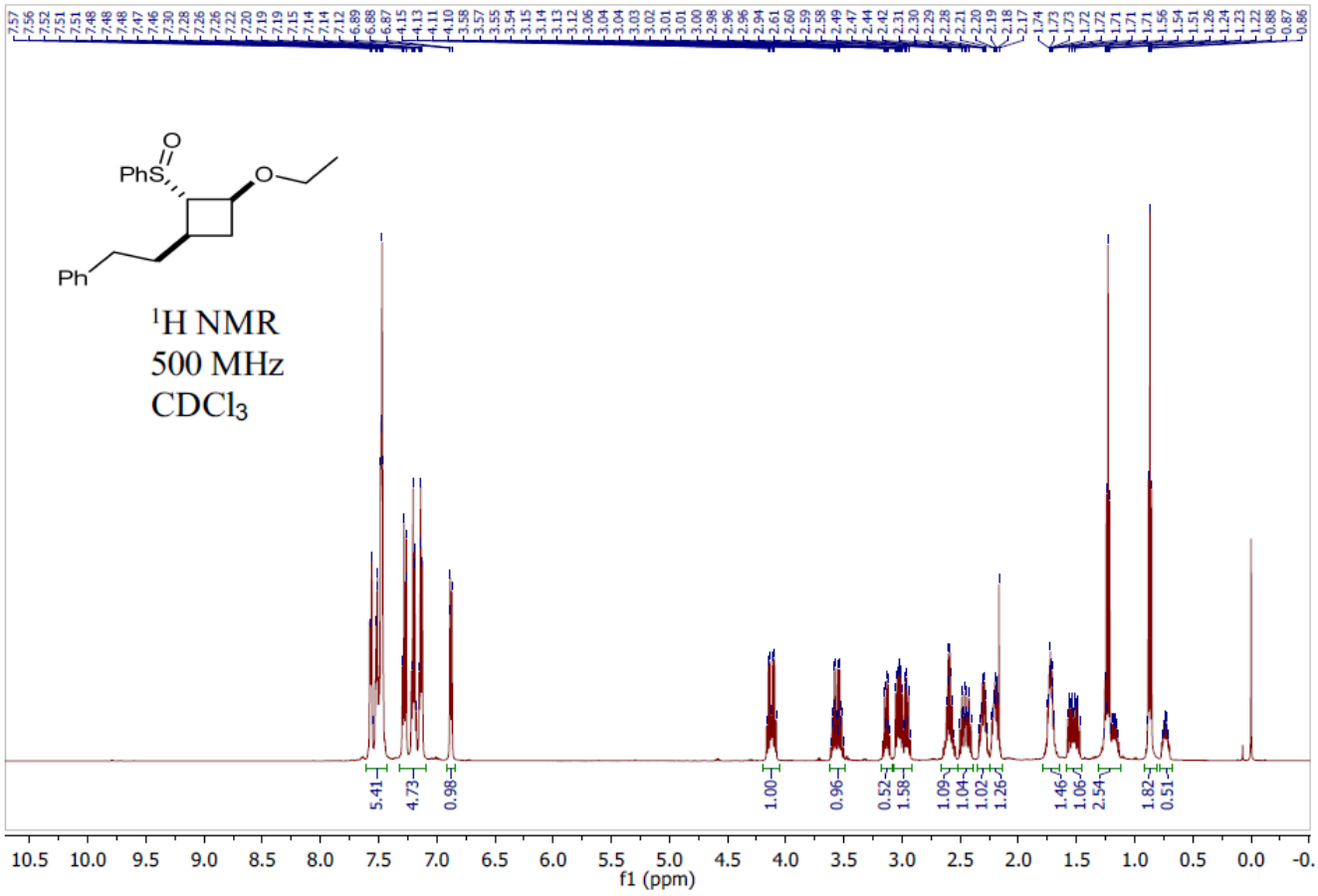

TBSO
Me
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

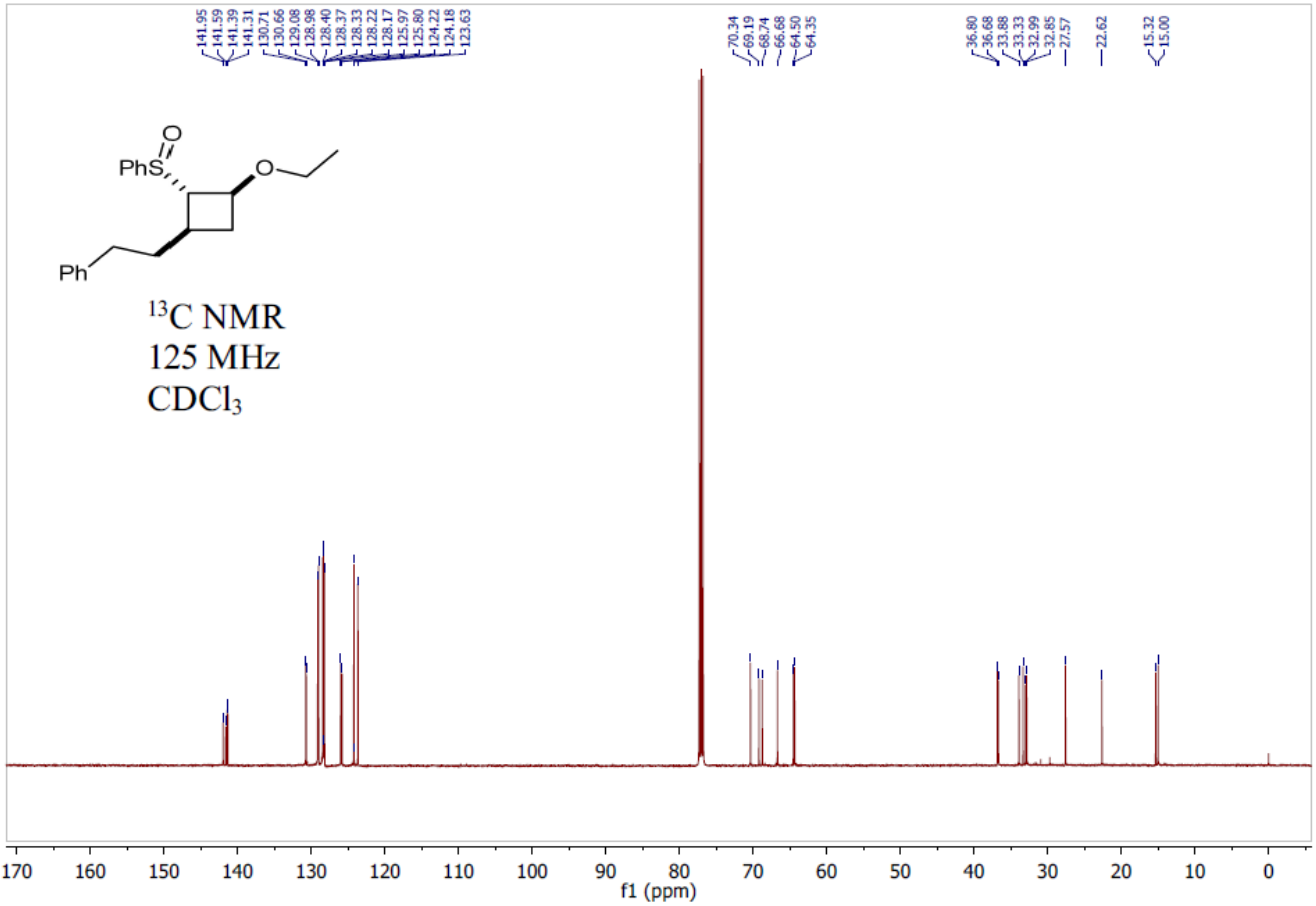

Ph
^{1}H NMR
500 MHz
$CDCl_3$
10.44
1.00
2.04
2.09
3.28
1.18
4.20
f1 (ppm)

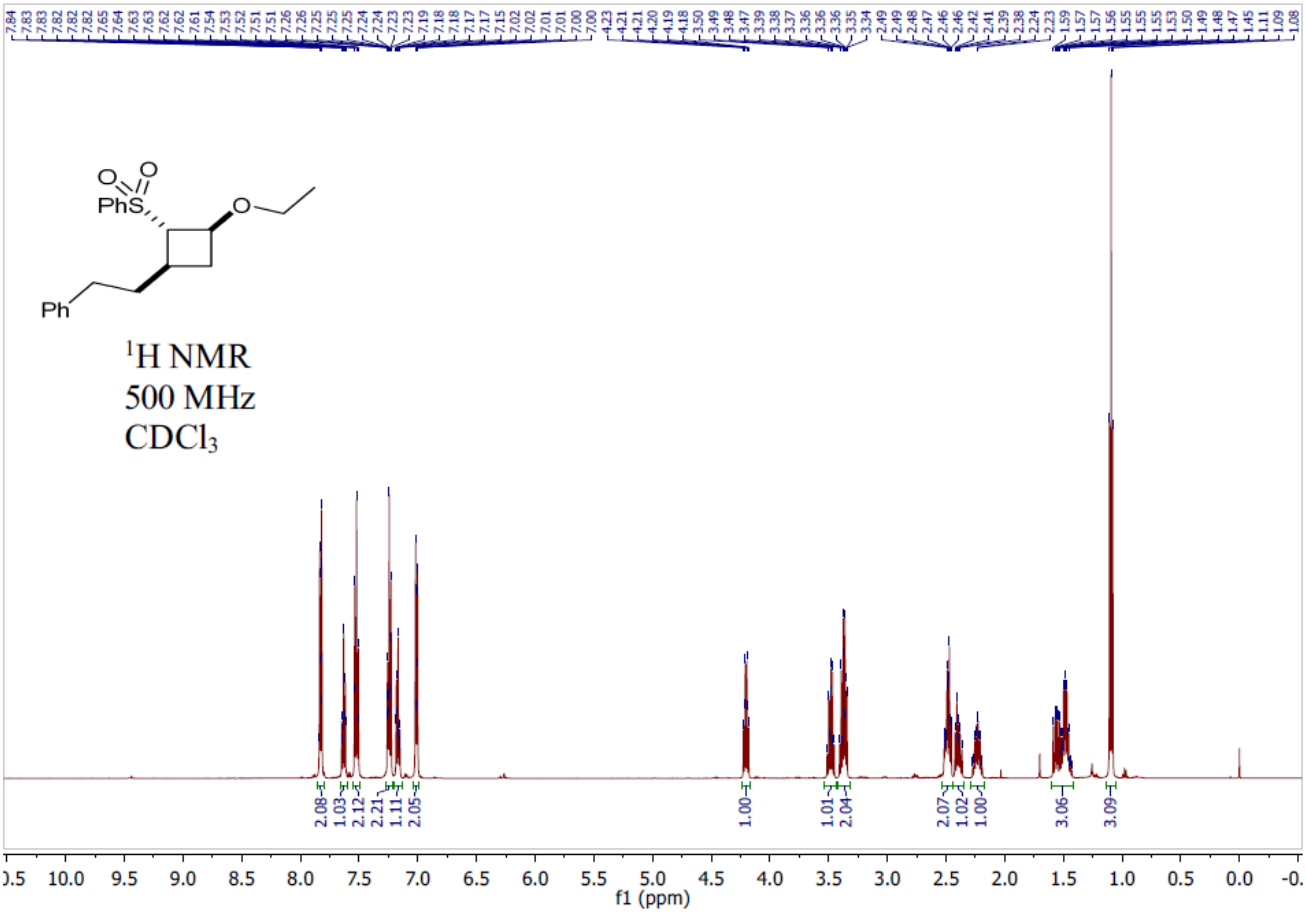

Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

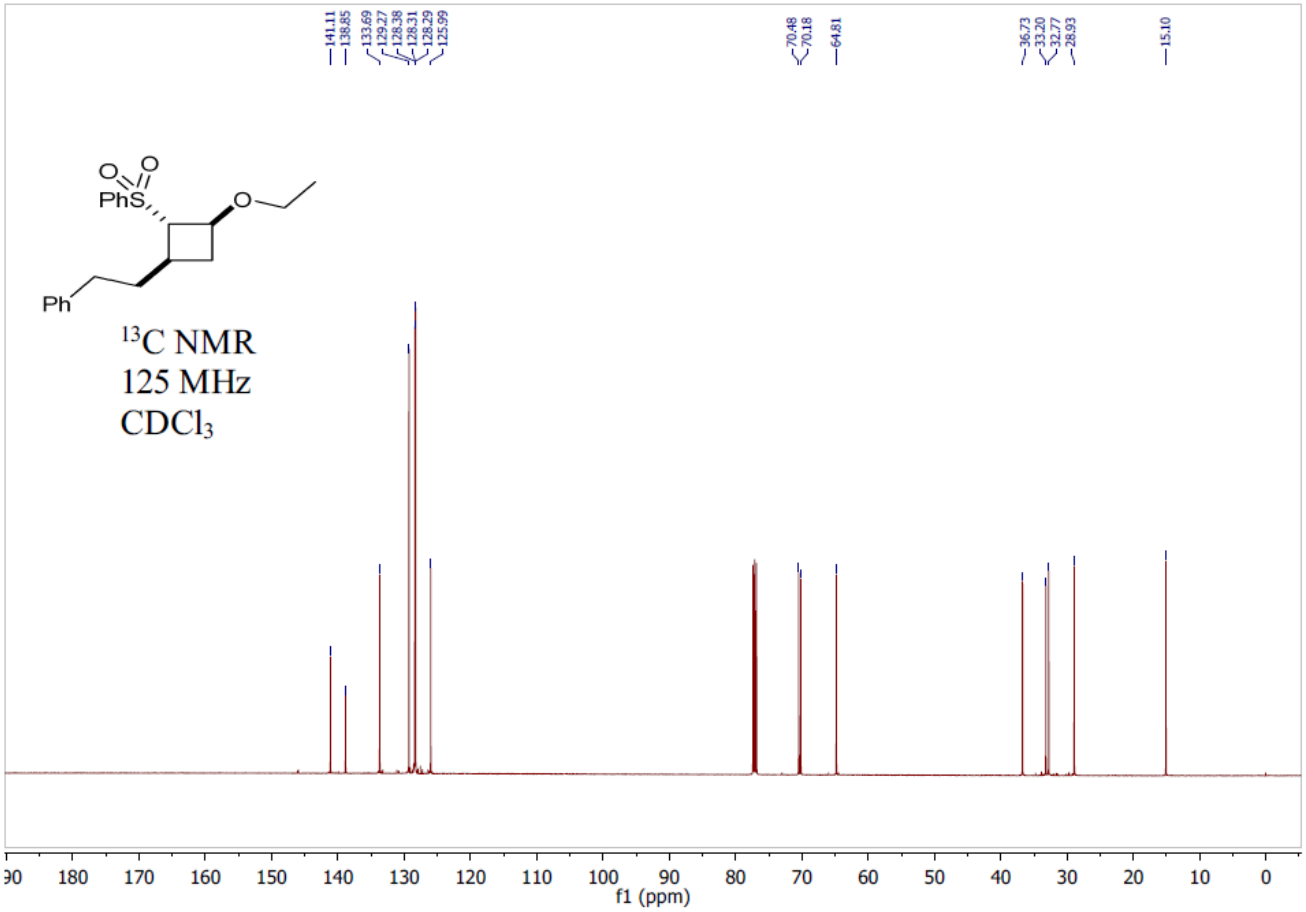

Ph
O
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)


Ph
O
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)


PhS
O
O
Ph
^{1}H NMR
500 MHz
$CDCl_3$
5.41
4.73
0.98
1.00
0.96
0.52
1.58
1.09
1.04
1.02
1.26
1.46
1.06
2.54
1.82
0.51
f1 (ppm)


PhS
O
O
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)


PhS
O
O
Ph
^{1}H NMR
500 MHz
$CDCl_3$
f1 (ppm)

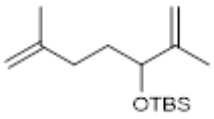

PhS
O
O
Ph
^{13}C NMR
125 MHz
$CDCl_3$
f1 (ppm)

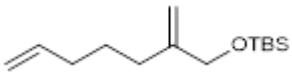
List of Compounds Chapter 3

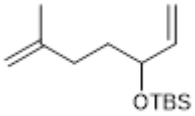
Catalyst

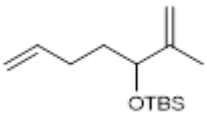
$Cu(COD)_2SbF_6$

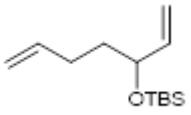
[2+2] Cycloaddition Precursors

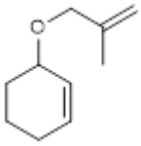


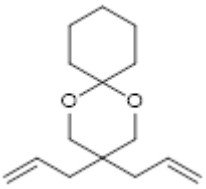


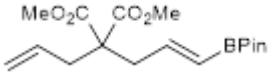


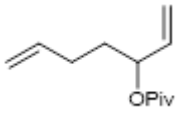


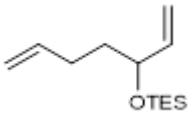


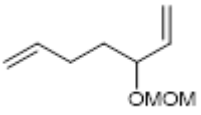


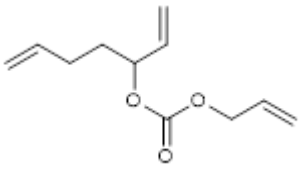


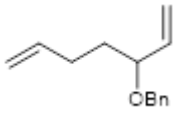




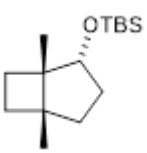


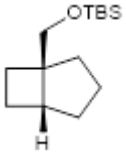


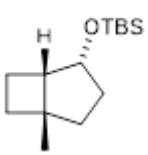


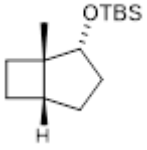


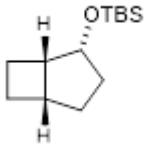
[2+2] Cycloadducts

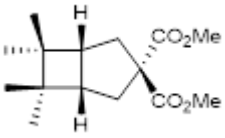


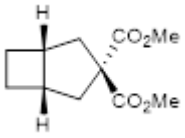


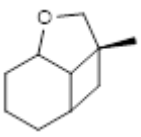


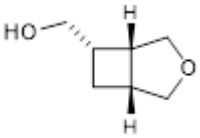


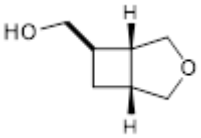


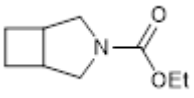


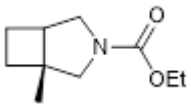


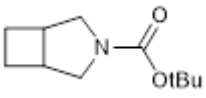


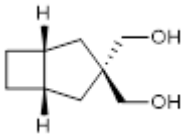


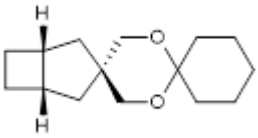


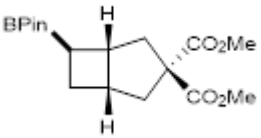


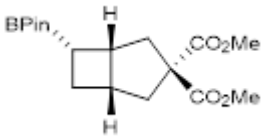


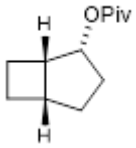


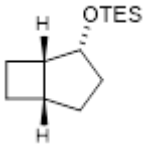


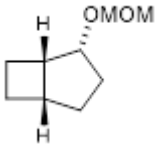


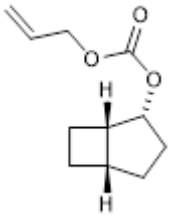


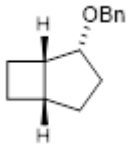




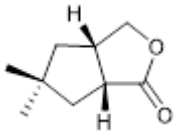


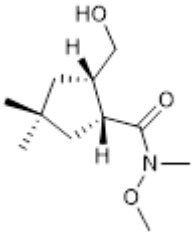


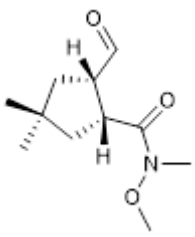


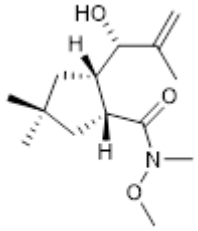


Synthesis of Sulcatine G Core









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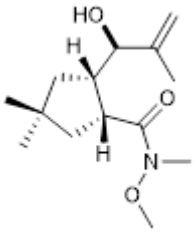
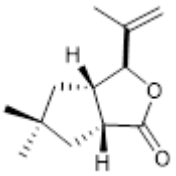
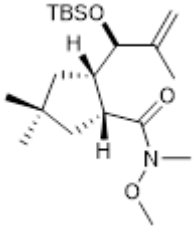
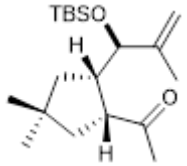
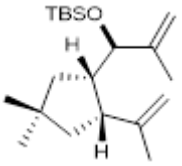


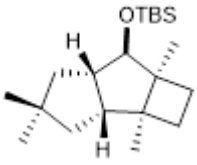
Minor

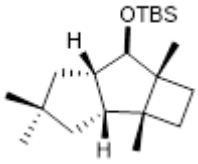




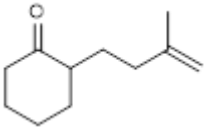


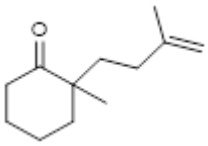


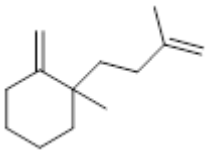


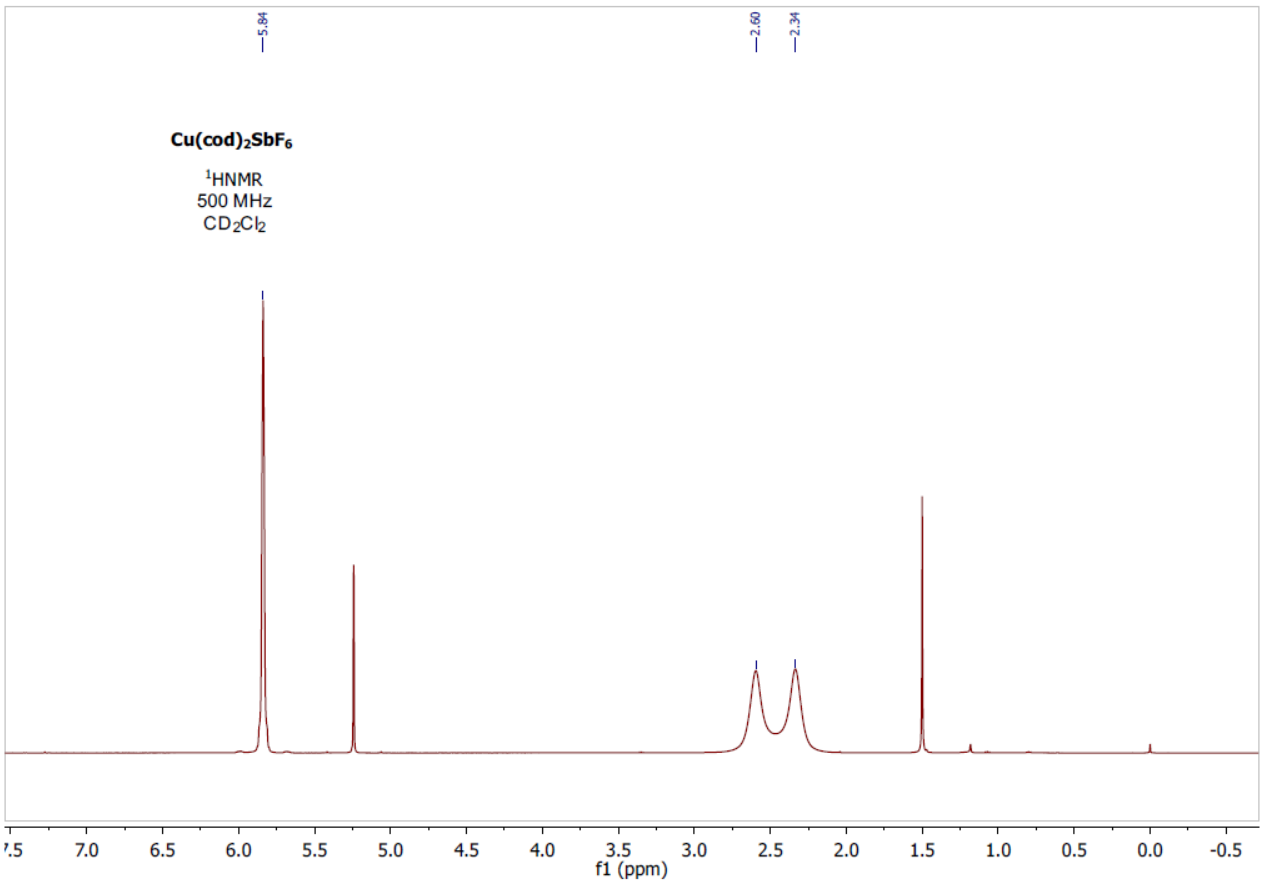


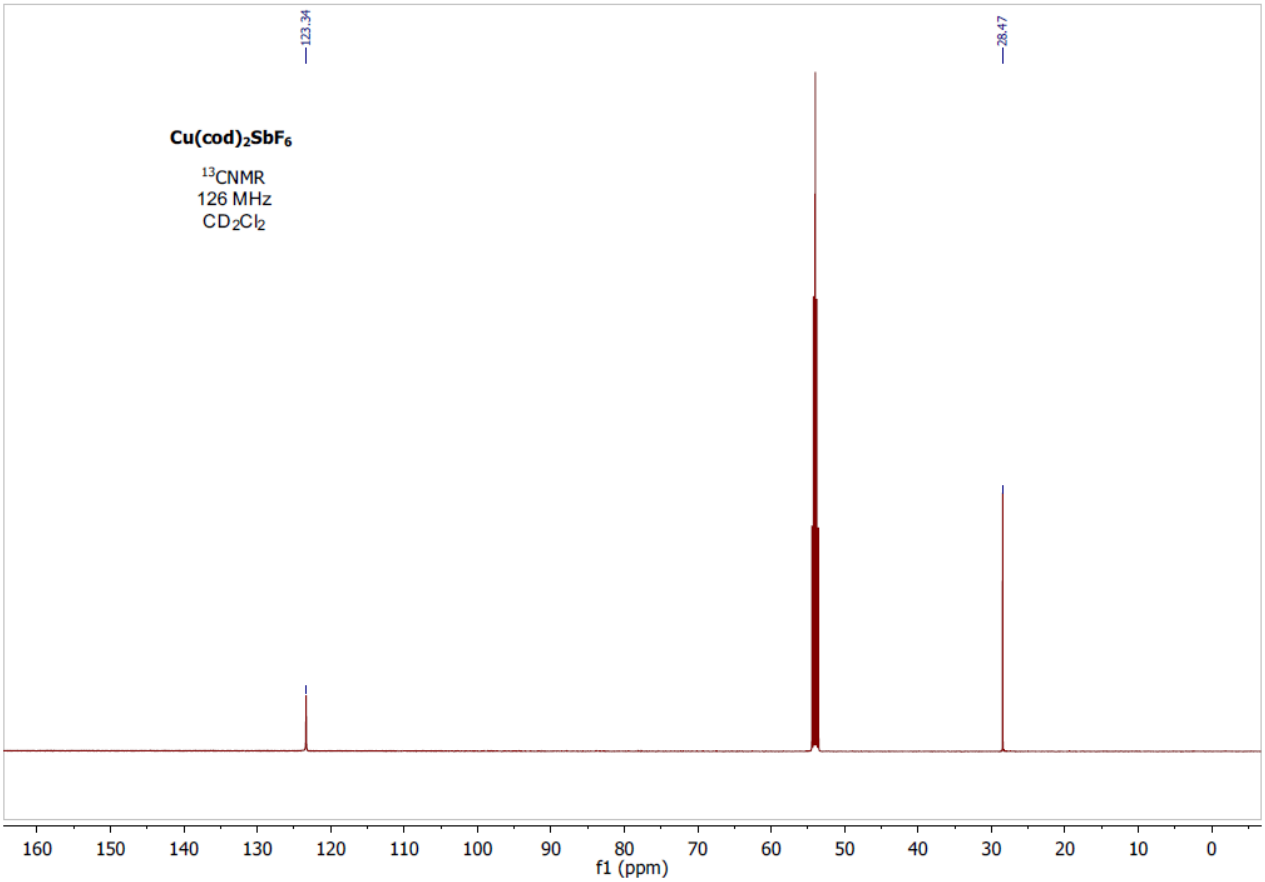
Synthesis of Perforatol Core

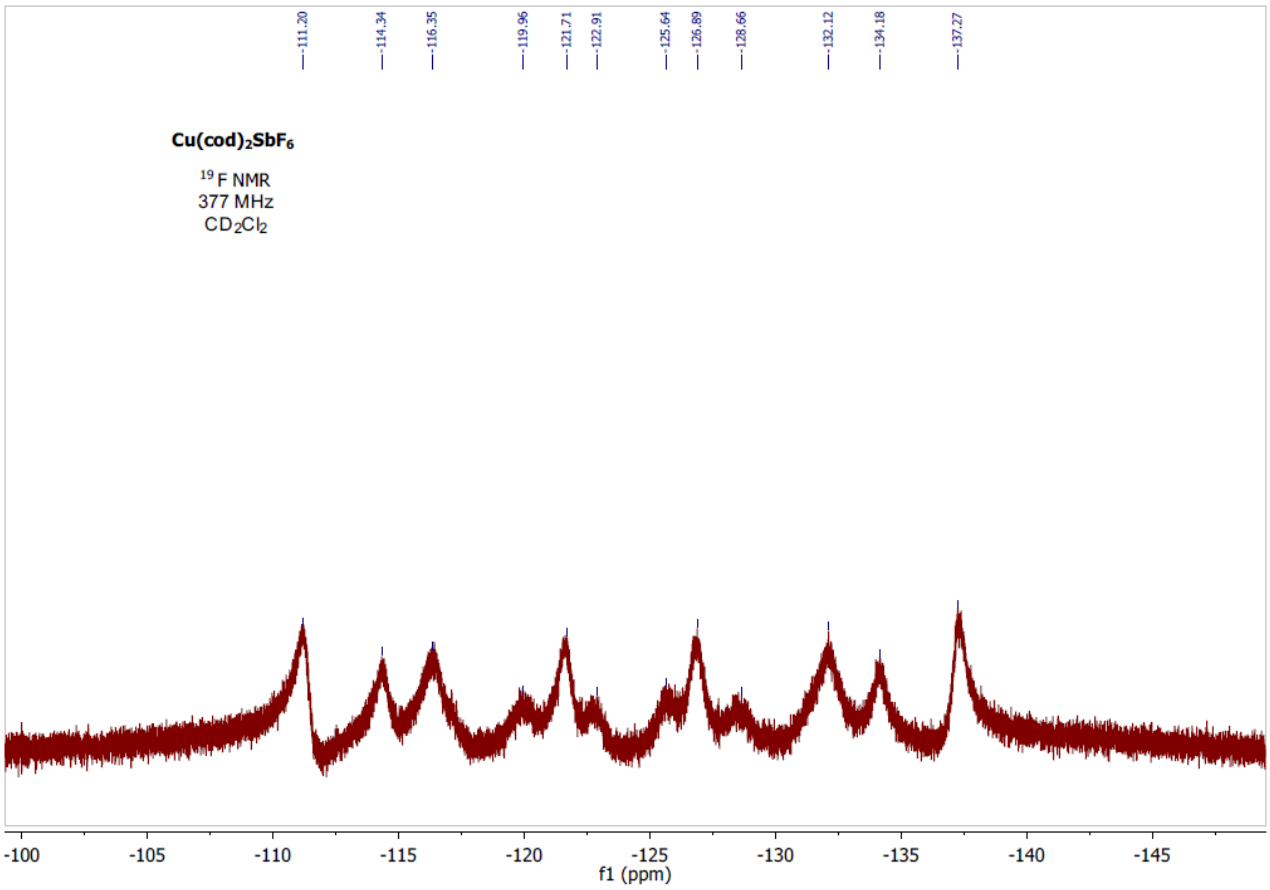


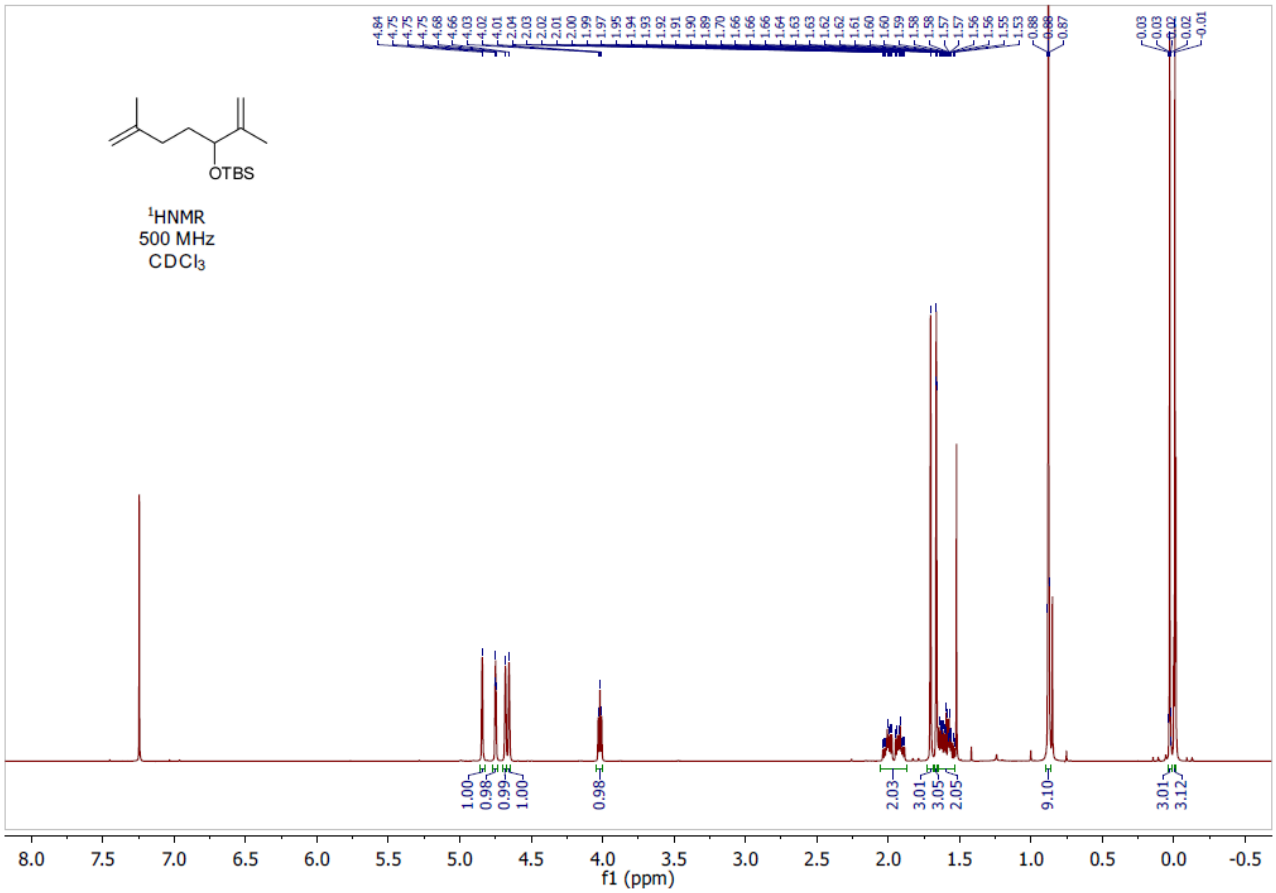


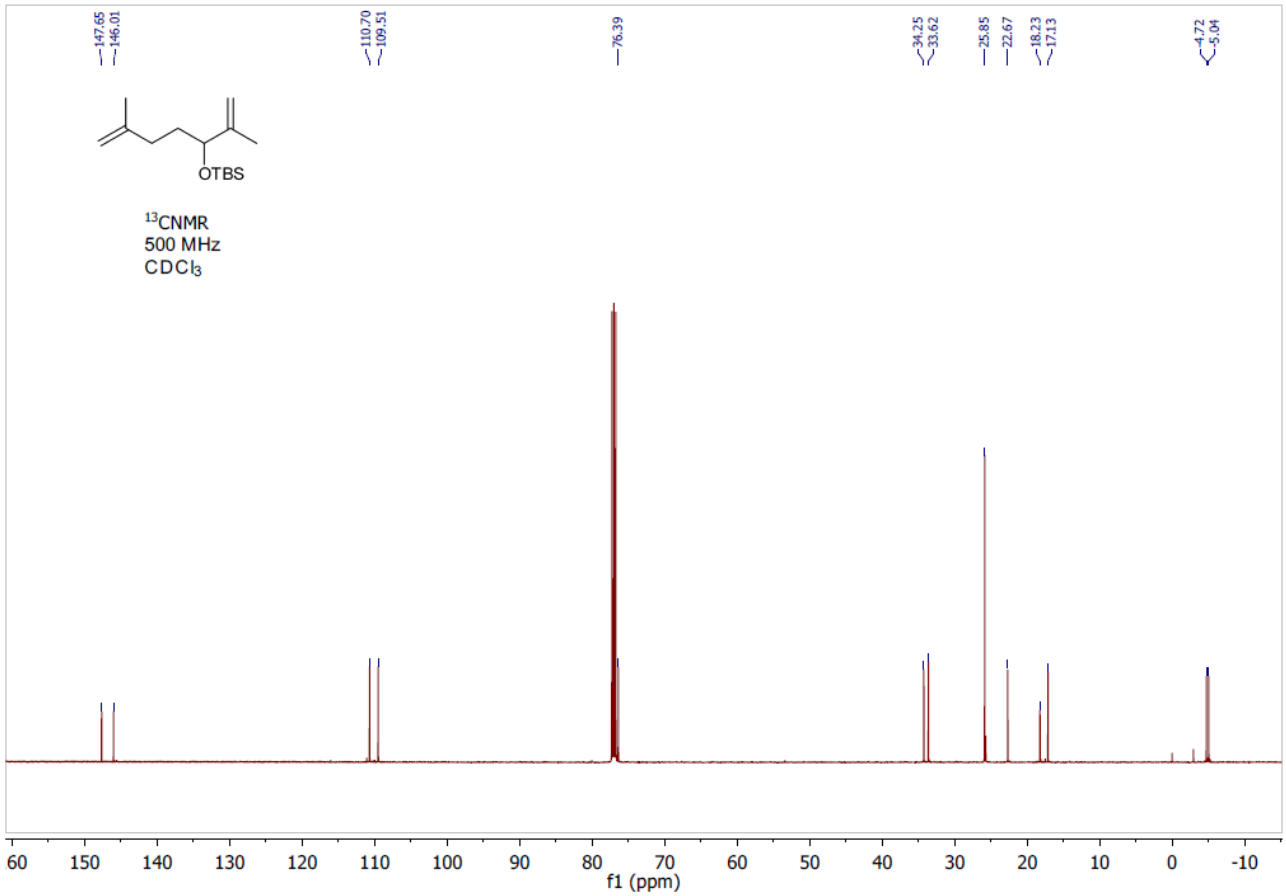


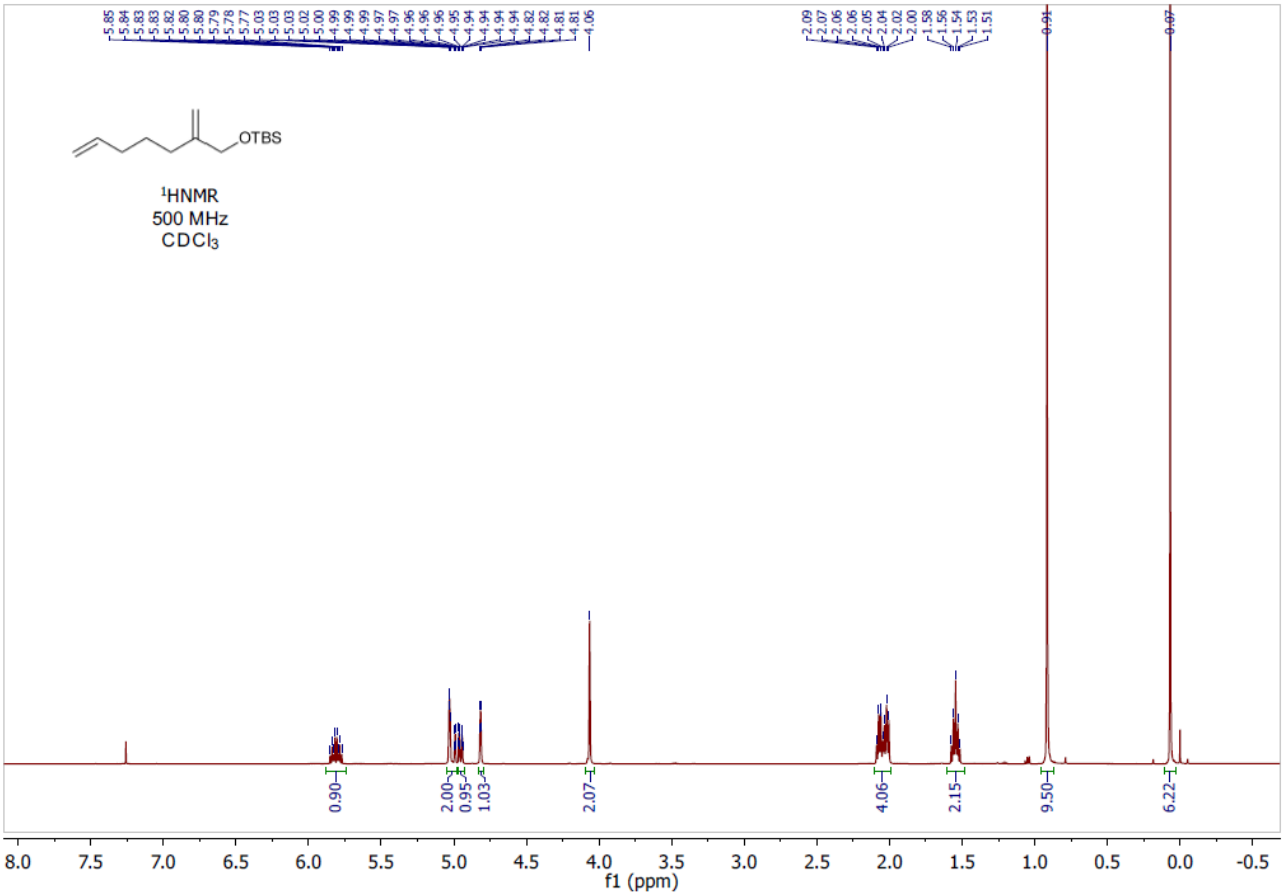

5.84
2.60
2.34
Cu(cod)2SbF6
1HNMR
500 MHz
CD2Cl2
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

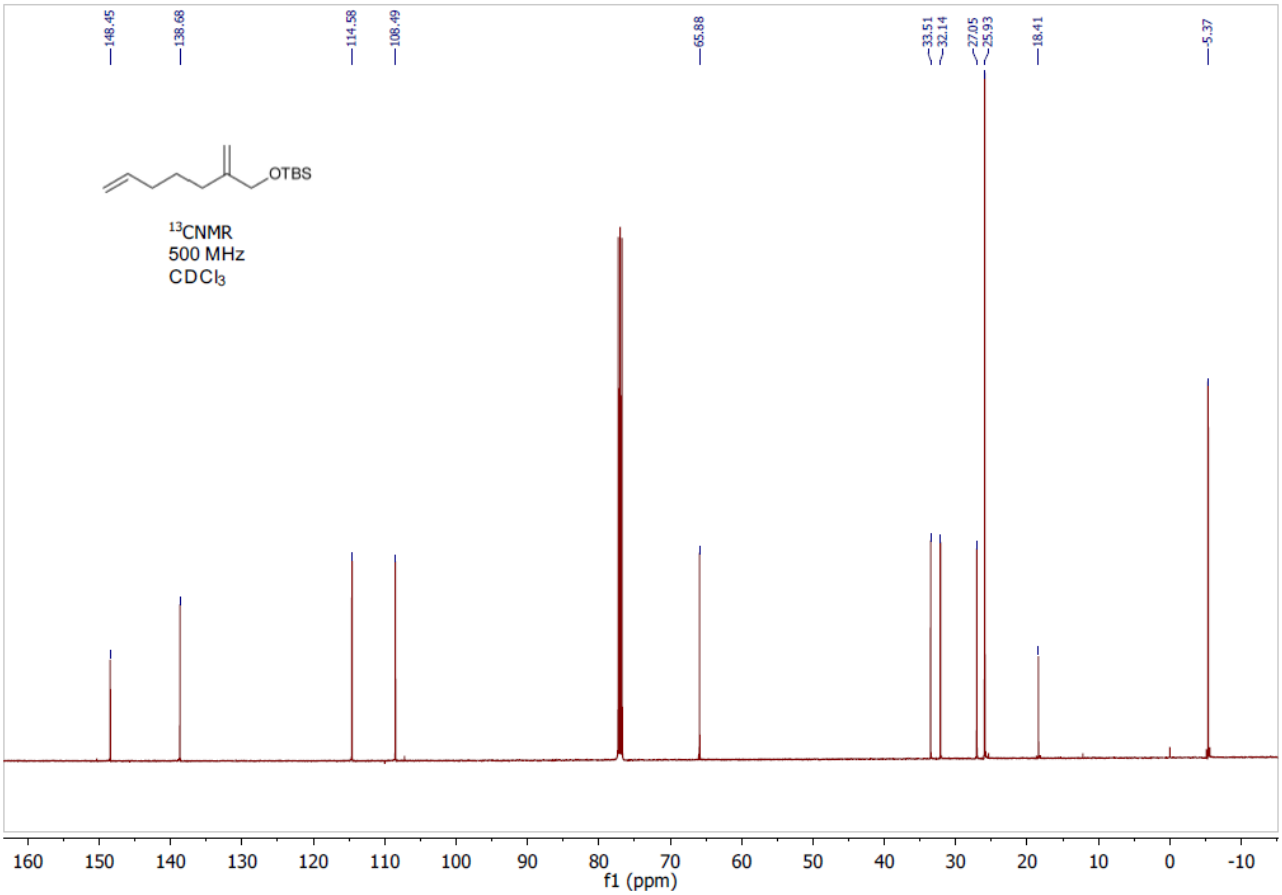

123.34
28.47
Cu(cod)2SbF6
13CNMR
126 MHz
CD2Cl2
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

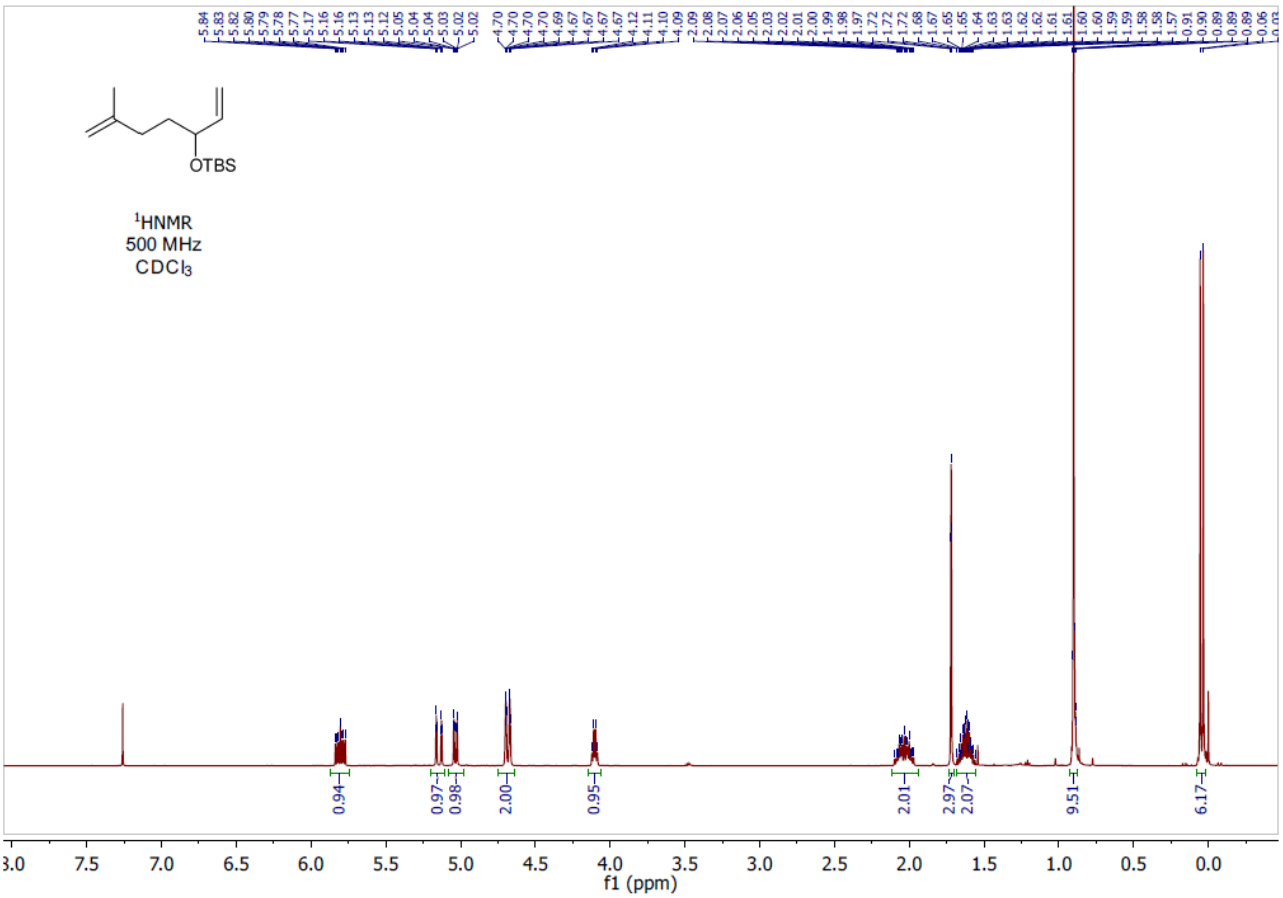

111.20
114.34
116.35
119.96
121.71
122.91
125.64
126.89
128.66
132.12
134.18
137.27
Cu(cod)2SbF6
19F NMR
377 MHz
CD2Cl2
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

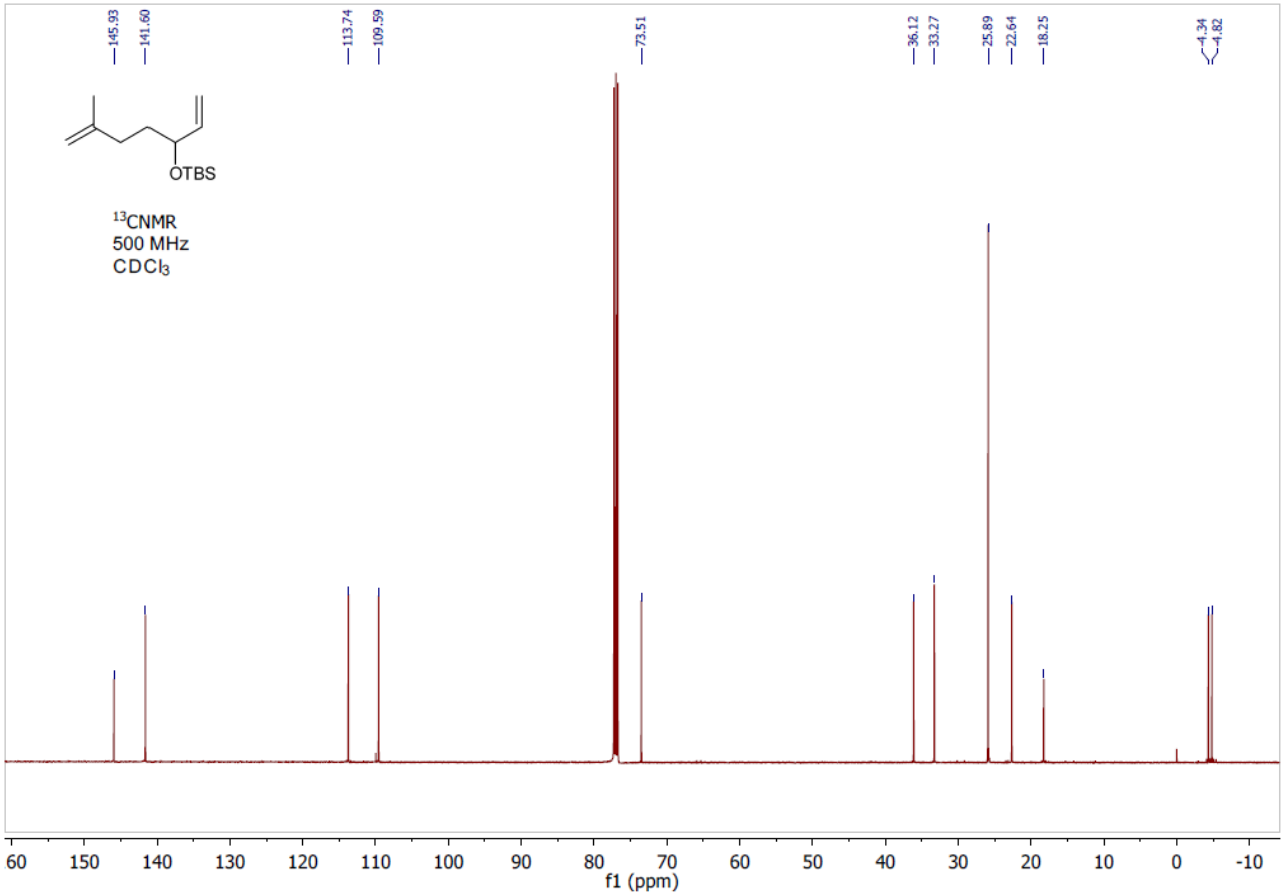

OTBS
1HNMR
500 MHz
CDCl3
f1 (ppm)

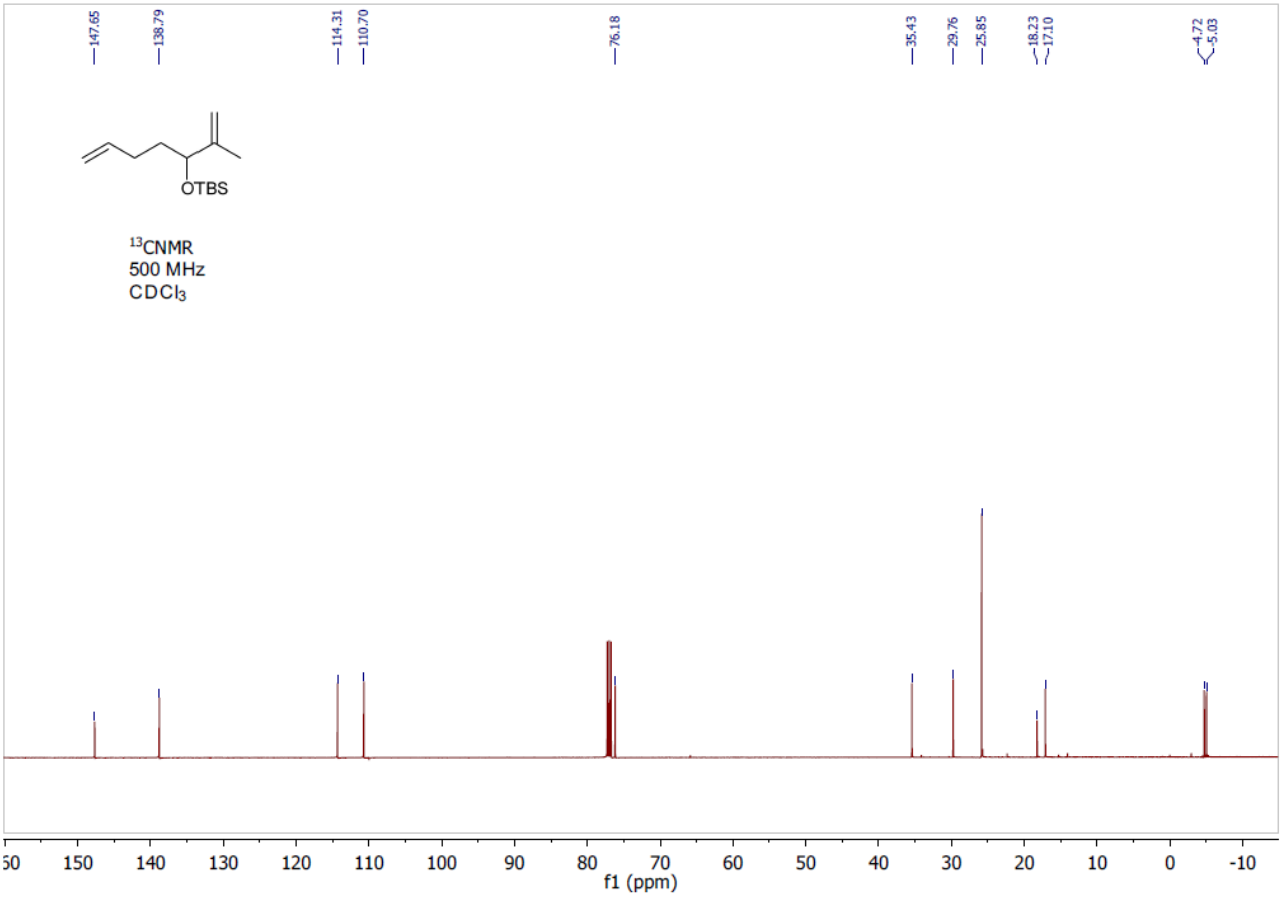

OTBS
13CNMR
500 MHz
CDCl3
f1 (ppm)

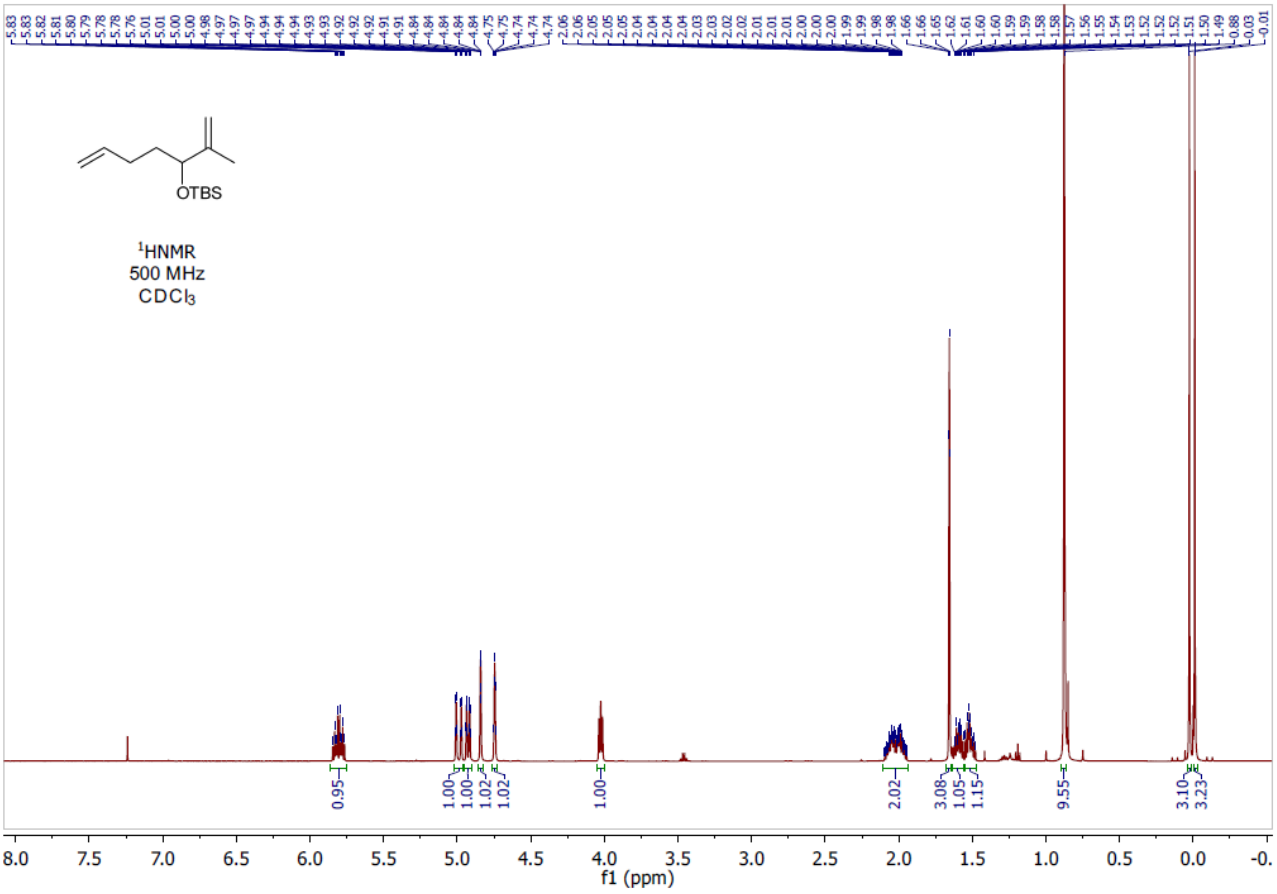

OTBS
1HNMR
500 MHz
CDCl3
f1 (ppm)

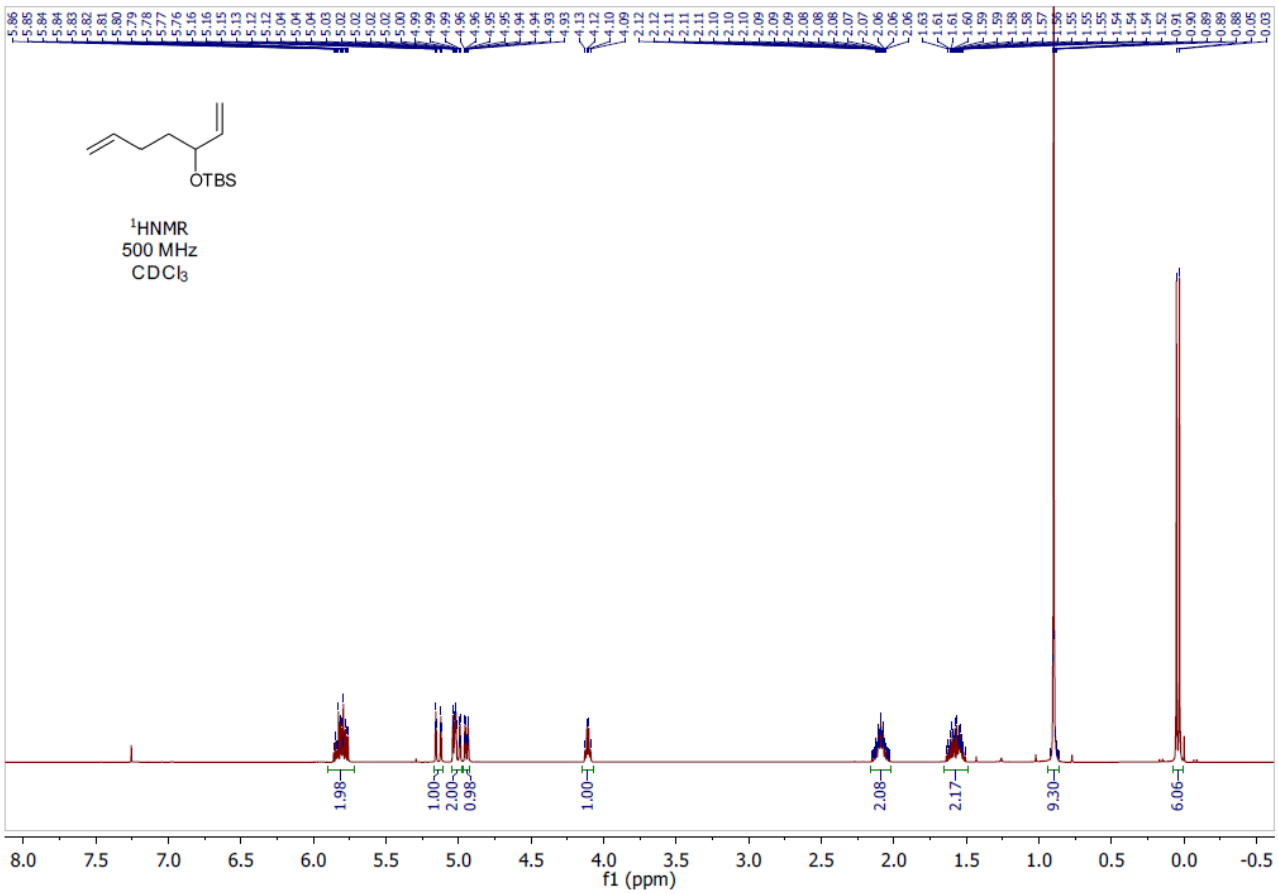

OTBS
13CNMR
500 MHz
CDCl3
f1 (ppm)

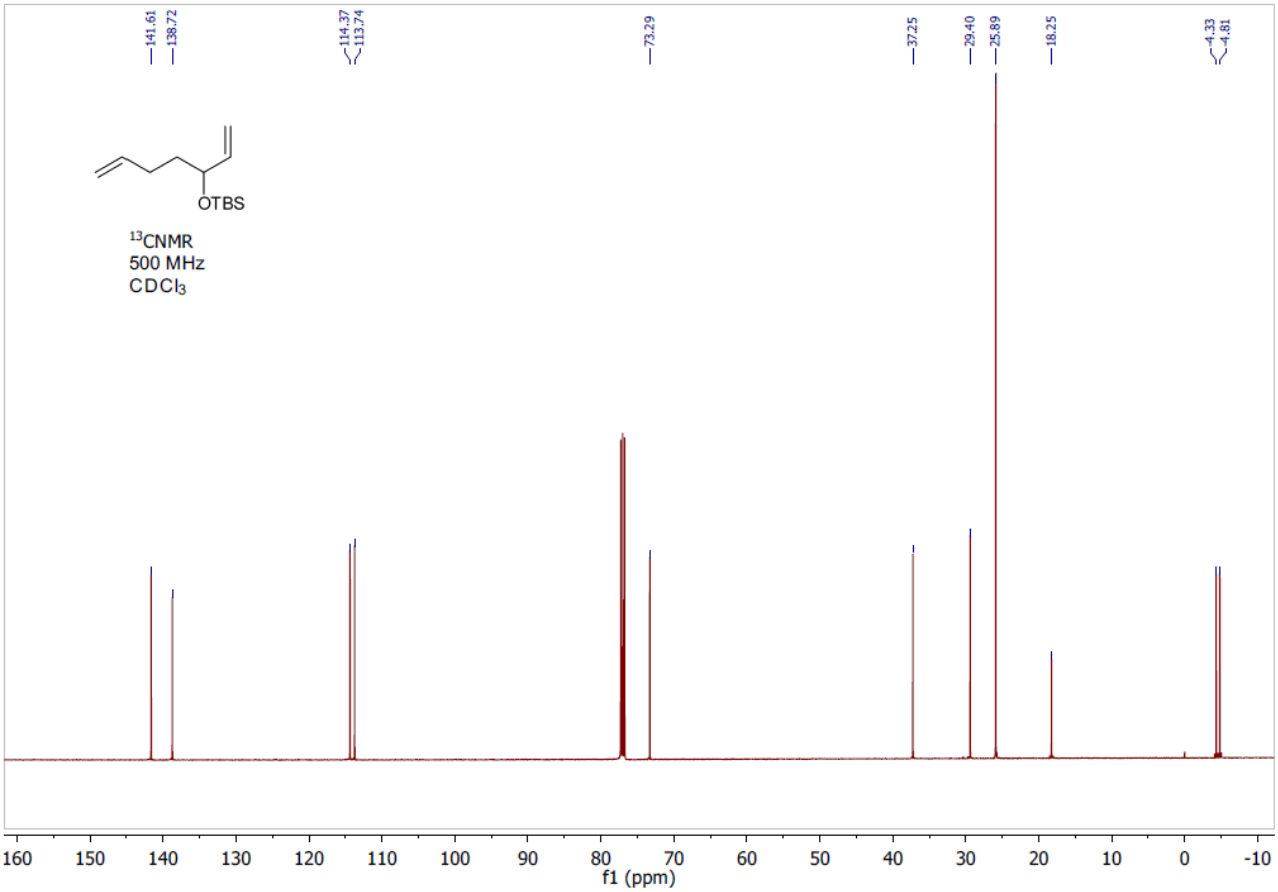

OTBS
1HNMR
500 MHz
CDCl3
0.94
0.97
0.98
2.00
0.95
2.01
2.97
2.07
9.51
6.17
f1 (ppm)

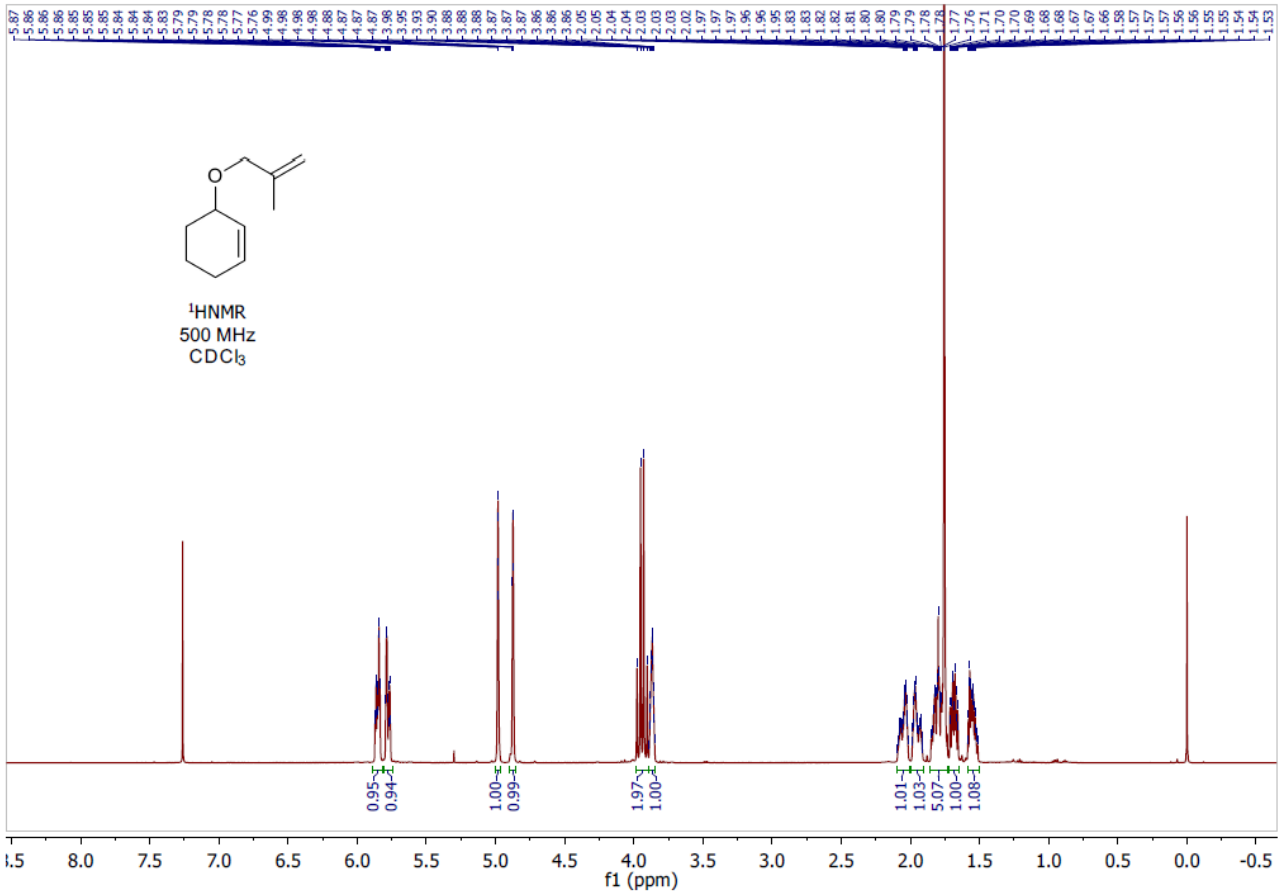

OTBS
13CNMR
500 MHz
CDCl3
145.93
141.60
113.74
109.59
73.51
36.12
33.27
25.89
22.64
18.25
-4.34
-4.82
f1 (ppm)

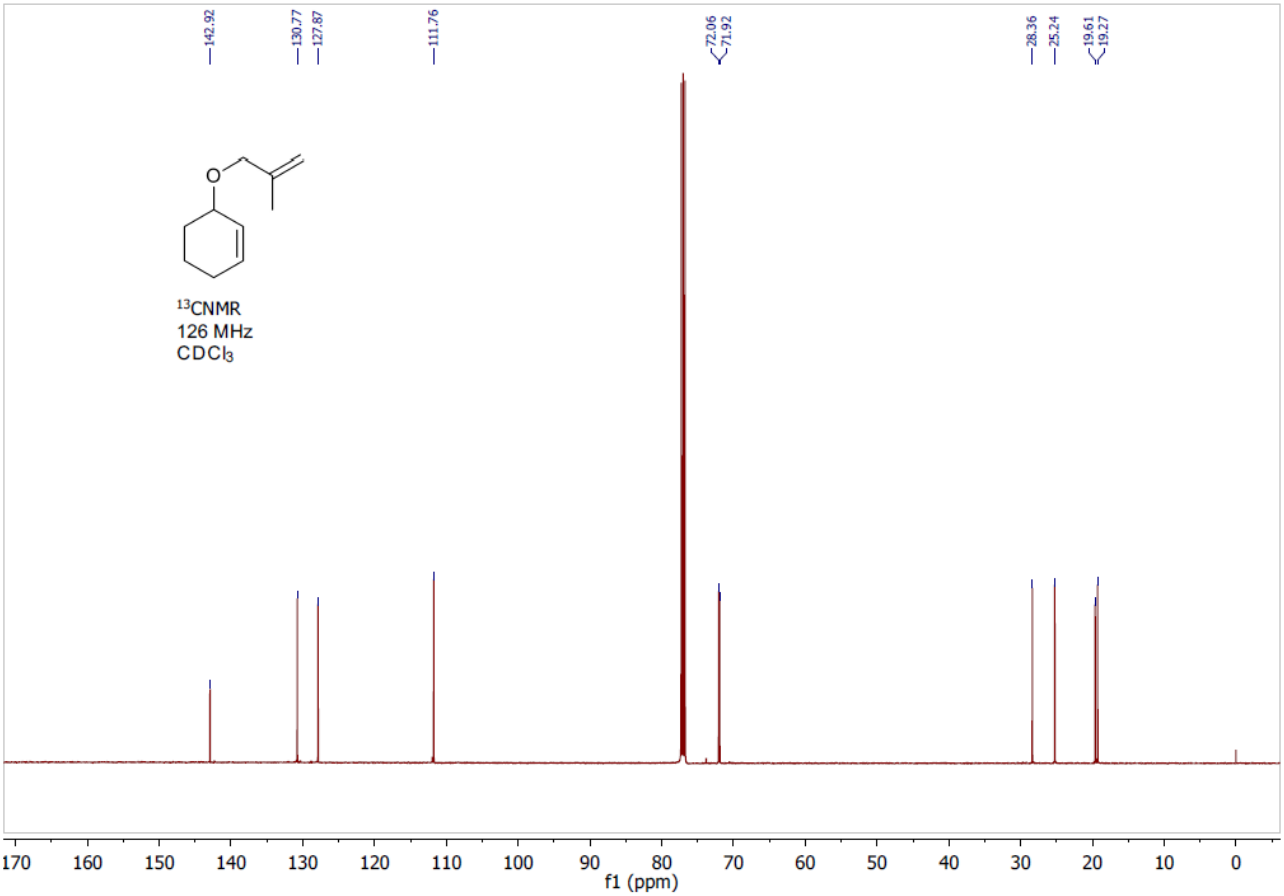

147.65
138.79
114.31
110.70
76.18
35.43
29.76
25.85
18.23
17.10
-4.72
-5.03
OTBS
13CNMR
500 MHz
CDCl3
f1 (ppm)

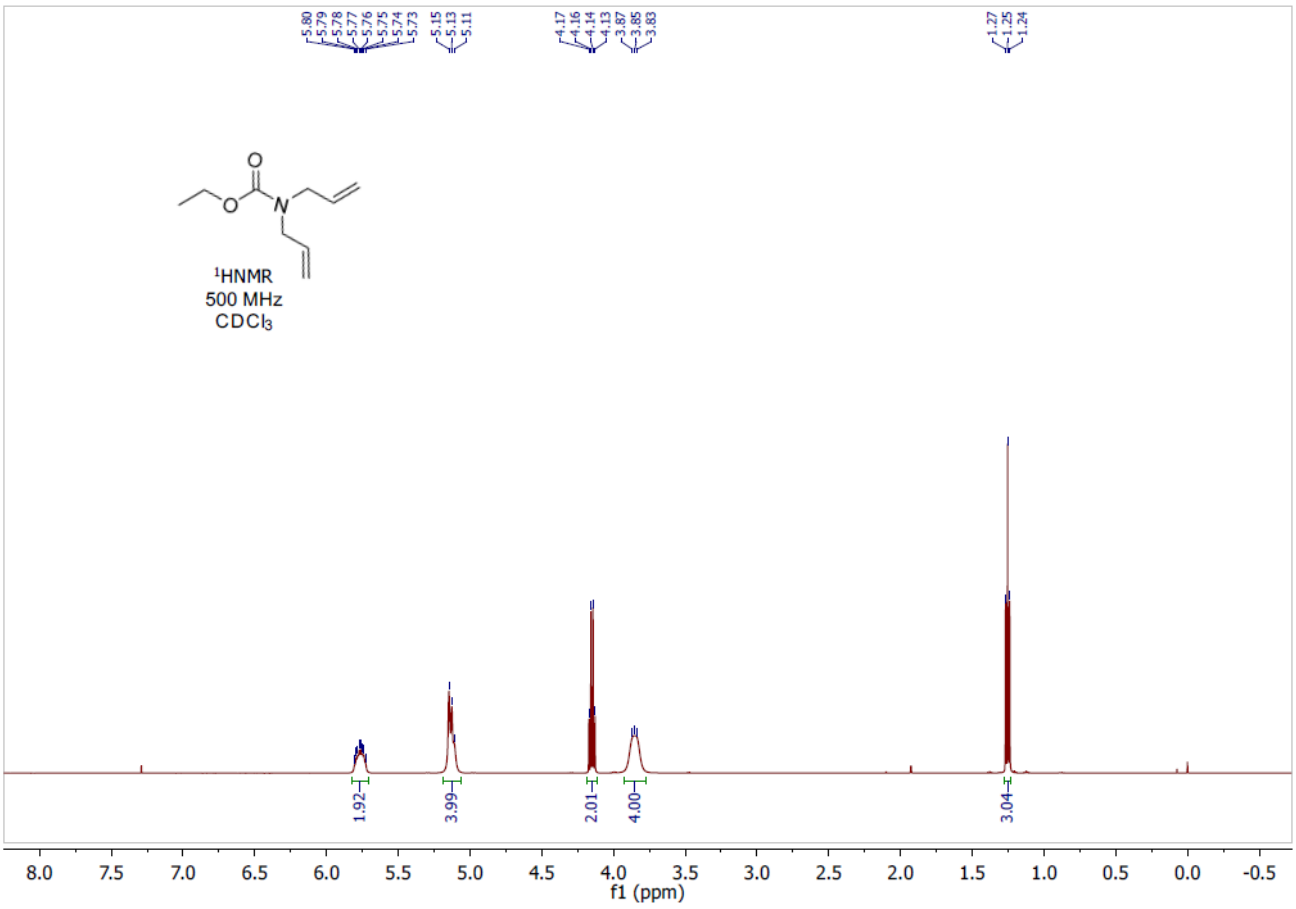

OTBS
1HNMR
500 MHz
CDCl3
f1 (ppm)

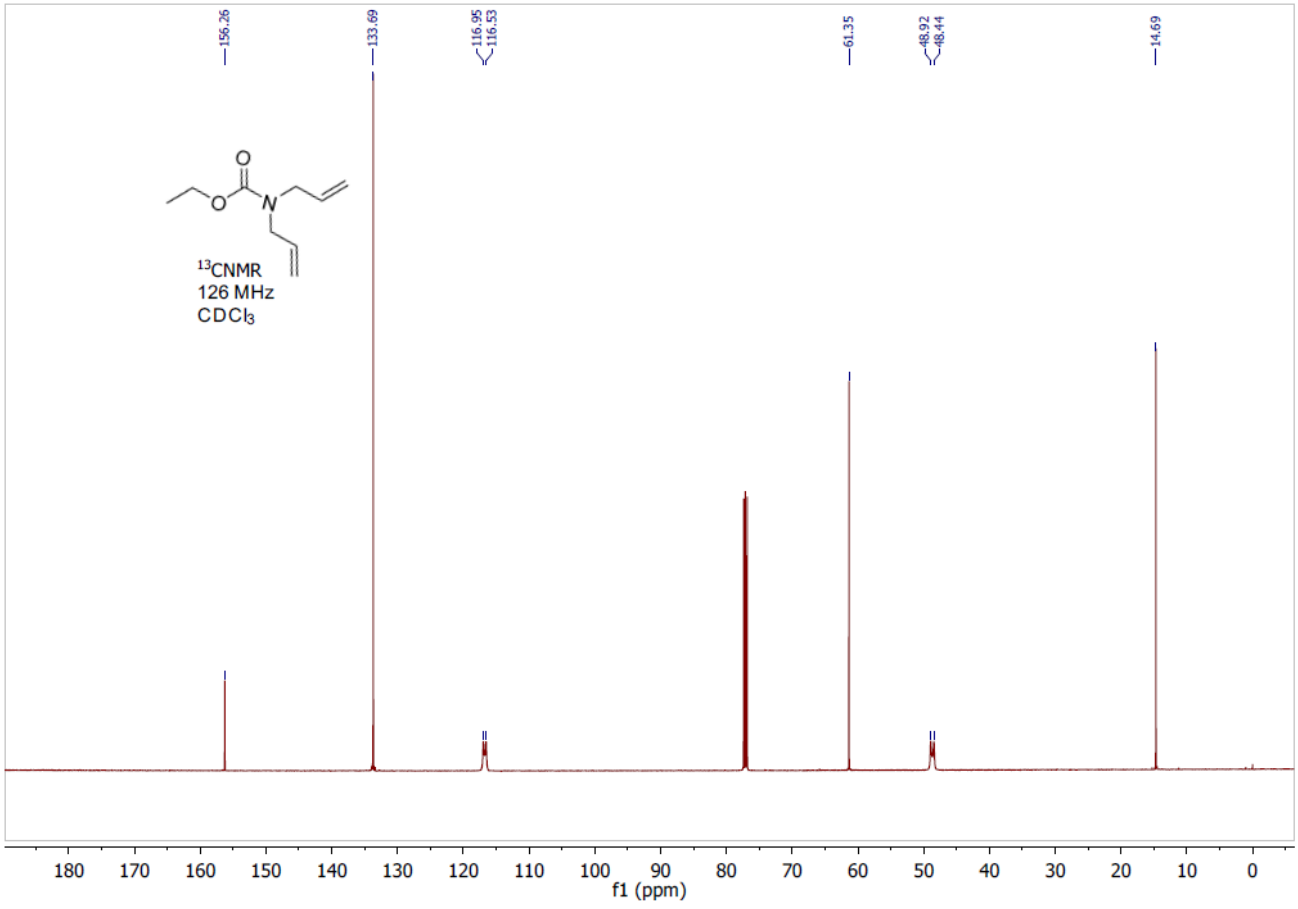

OTBS
1HNMR
500 MHz
CDCl3
1.98
1.00
2.00
0.98
1.00
2.08
2.17
9.30
6.06
f1 (ppm)

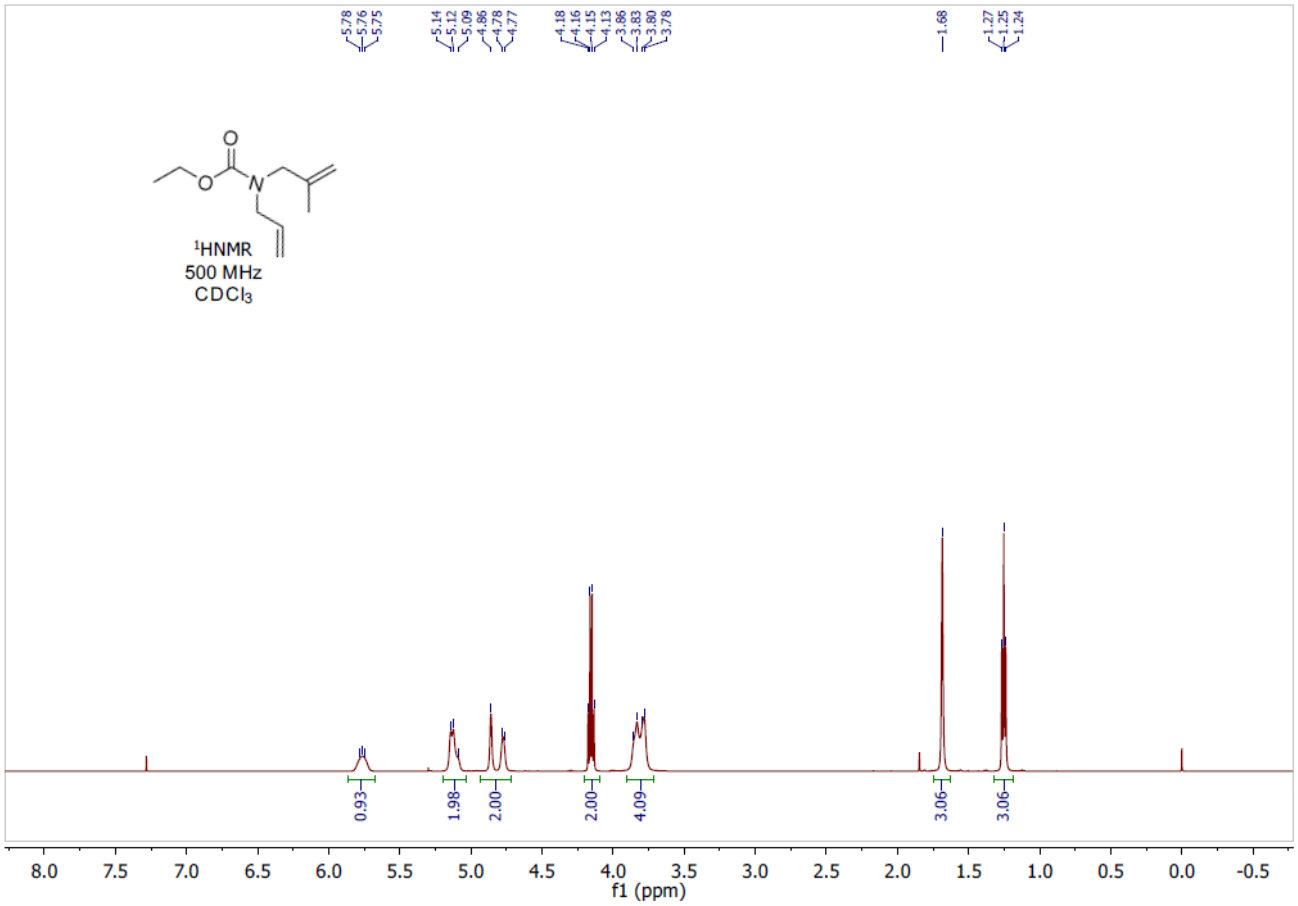

141.61
138.72
114.37
113.74
73.29
37.25
29.40
25.89
18.25
-4.33
-4.81
OTBS
13CNMR
500 MHz
CDCl3
f1 (ppm)

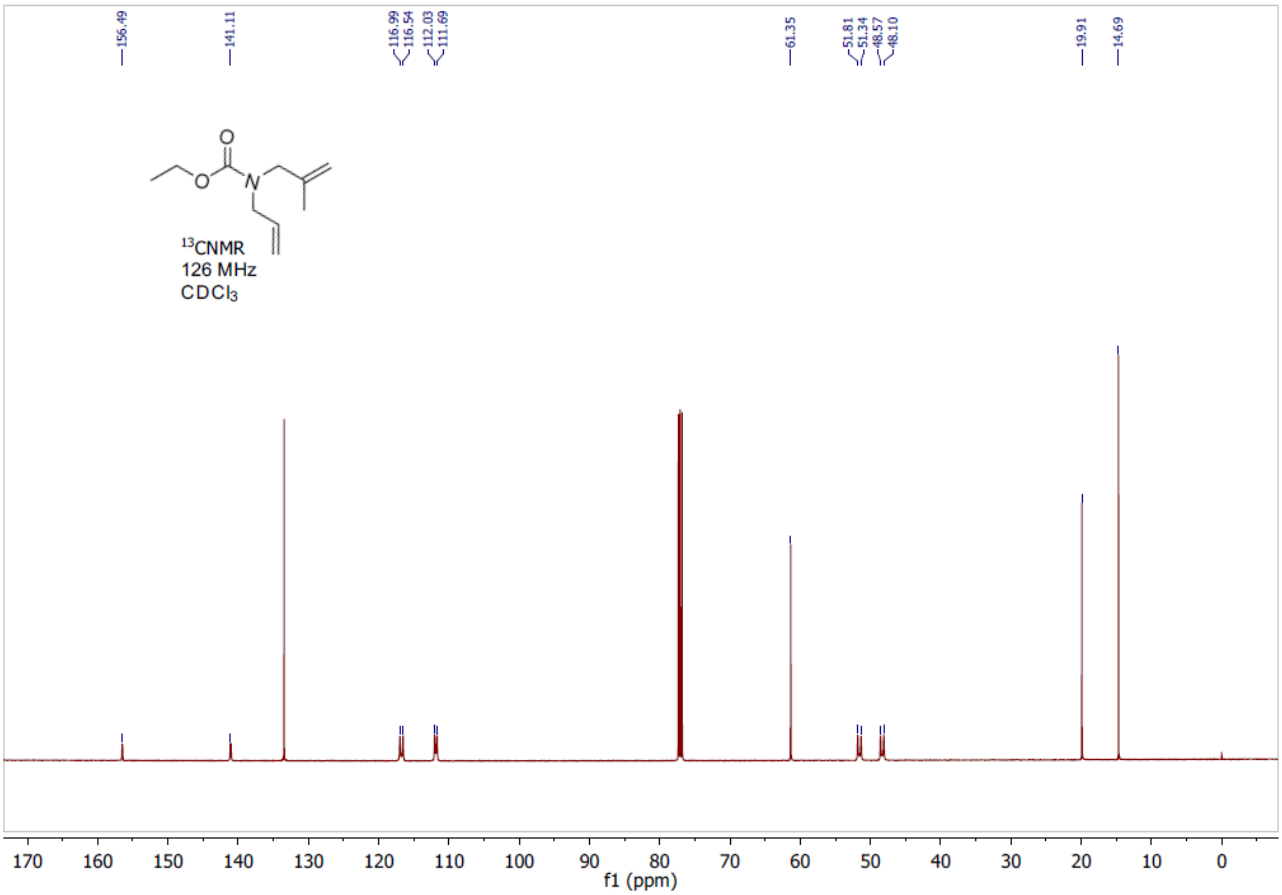

^{1}HNMR
500 MHz
$CDCl_3$
0.95
0.94
1.00
0.99
1.97
1.00
1.01
1.03
5.07
1.00
1.08
f1 (ppm)

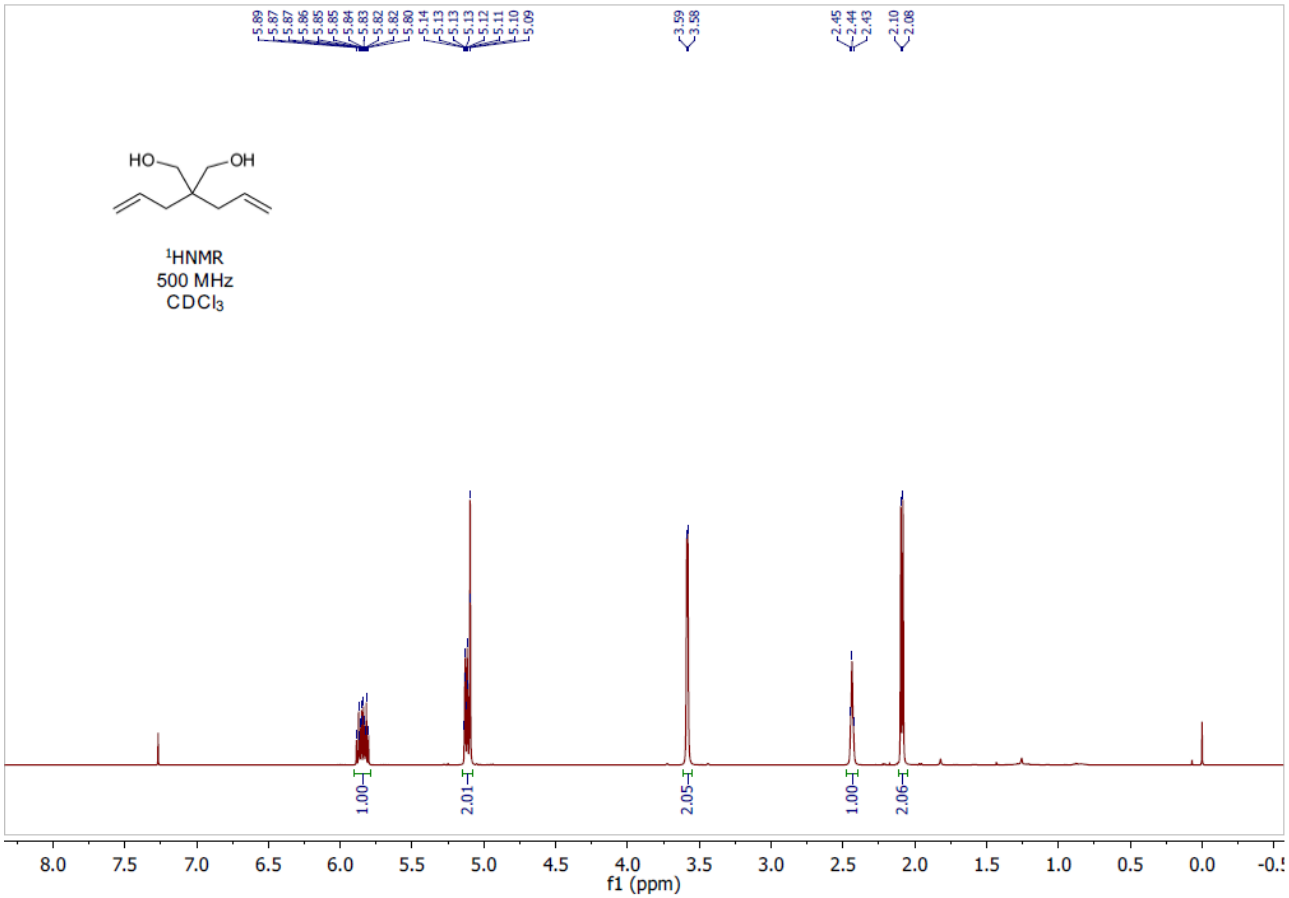

142.92
130.77
127.87
111.76
72.06
71.92
28.36
25.24
19.61
19.27
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

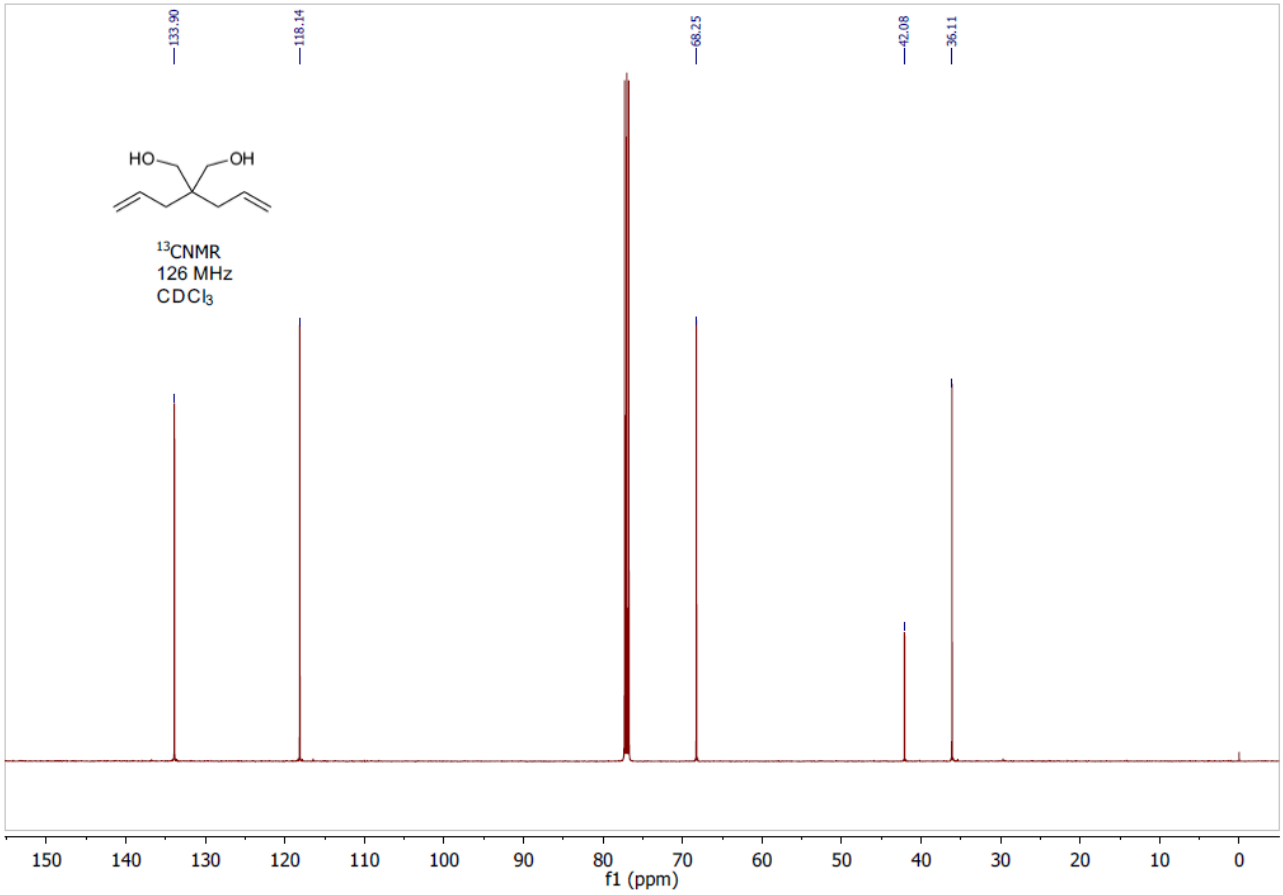

5.80
5.79
5.78
5.77
5.76
5.75
5.74
5.73
5.15
5.13
5.11
4.17
4.16
4.14
4.13
3.87
3.85
3.83
1.27
1.25
1.24
O
O
N
¹HNMR
500 MHz
CDCl3
1.92
3.99
2.01
4.00
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

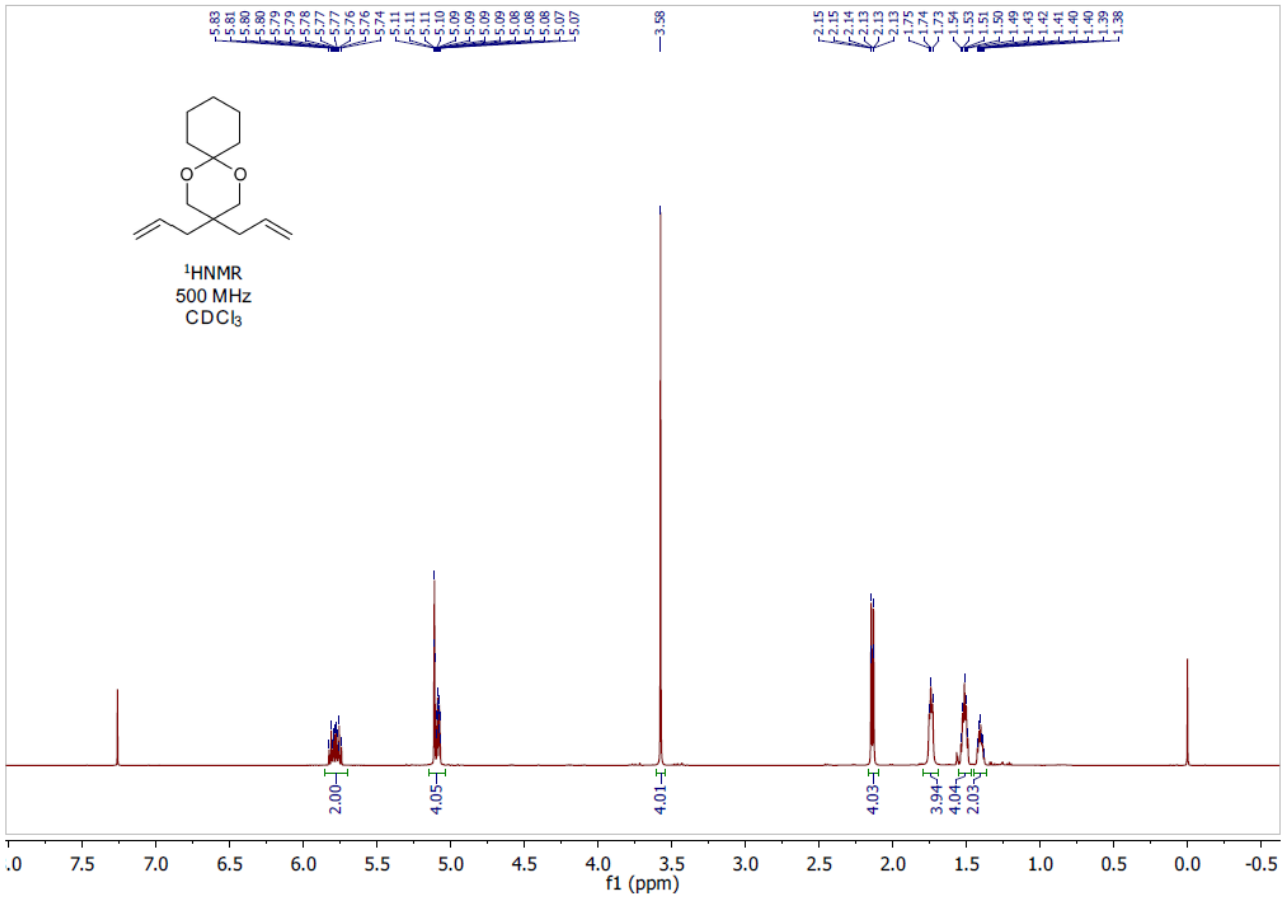

156.26
133.69
116.95
116.53
61.35
48.92
48.44
14.69
O
O
N
¹³CNMR
126 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

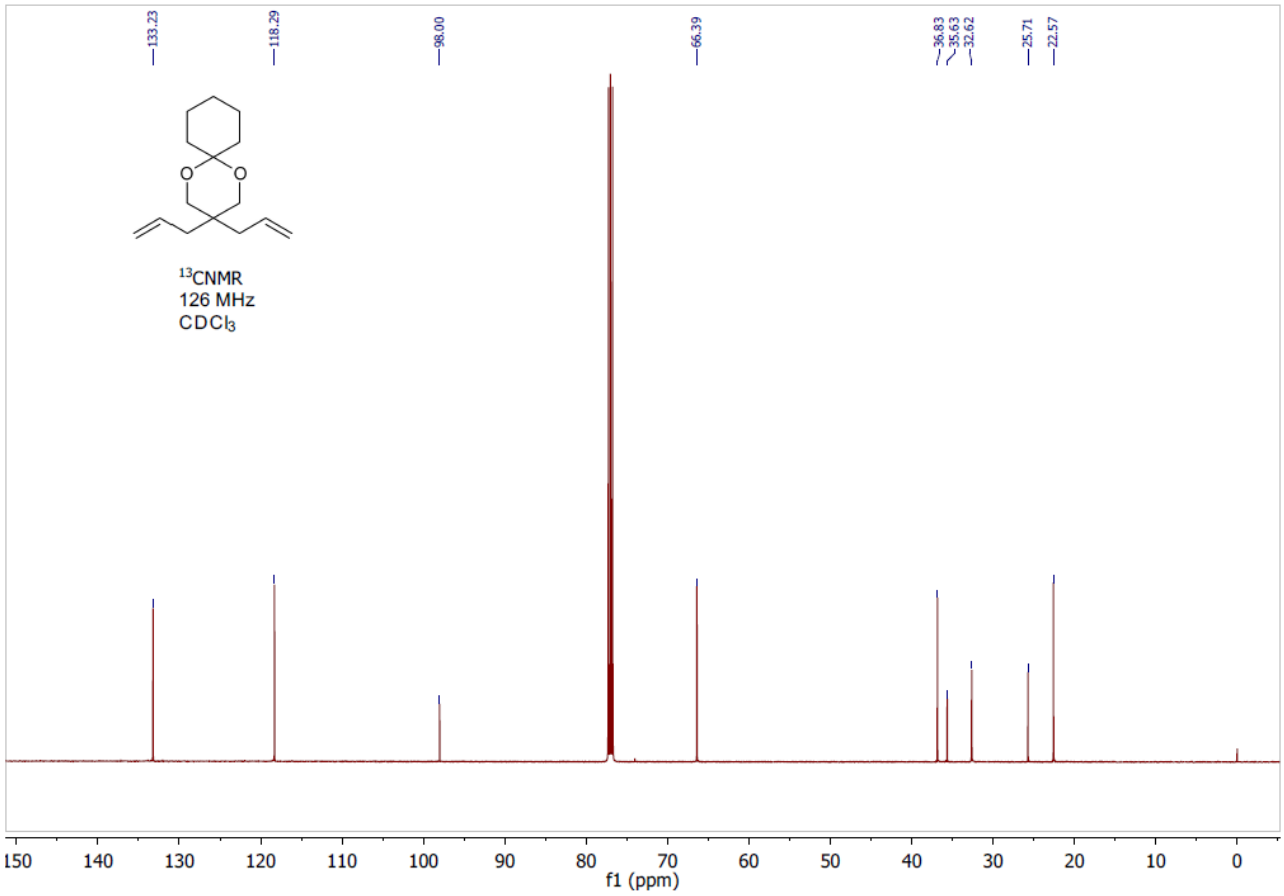

5.78
5.76
5.75
5.14
5.12
5.09
4.86
4.78
4.77
4.18
4.16
4.15
4.13
3.86
3.83
3.80
3.78
1.68
1.27
1.25
1.24
O
O
N
^{1}HNMR
500 MHz
$CDCl_3$
0.93
1.98
2.00
2.00
4.09
3.06
3.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

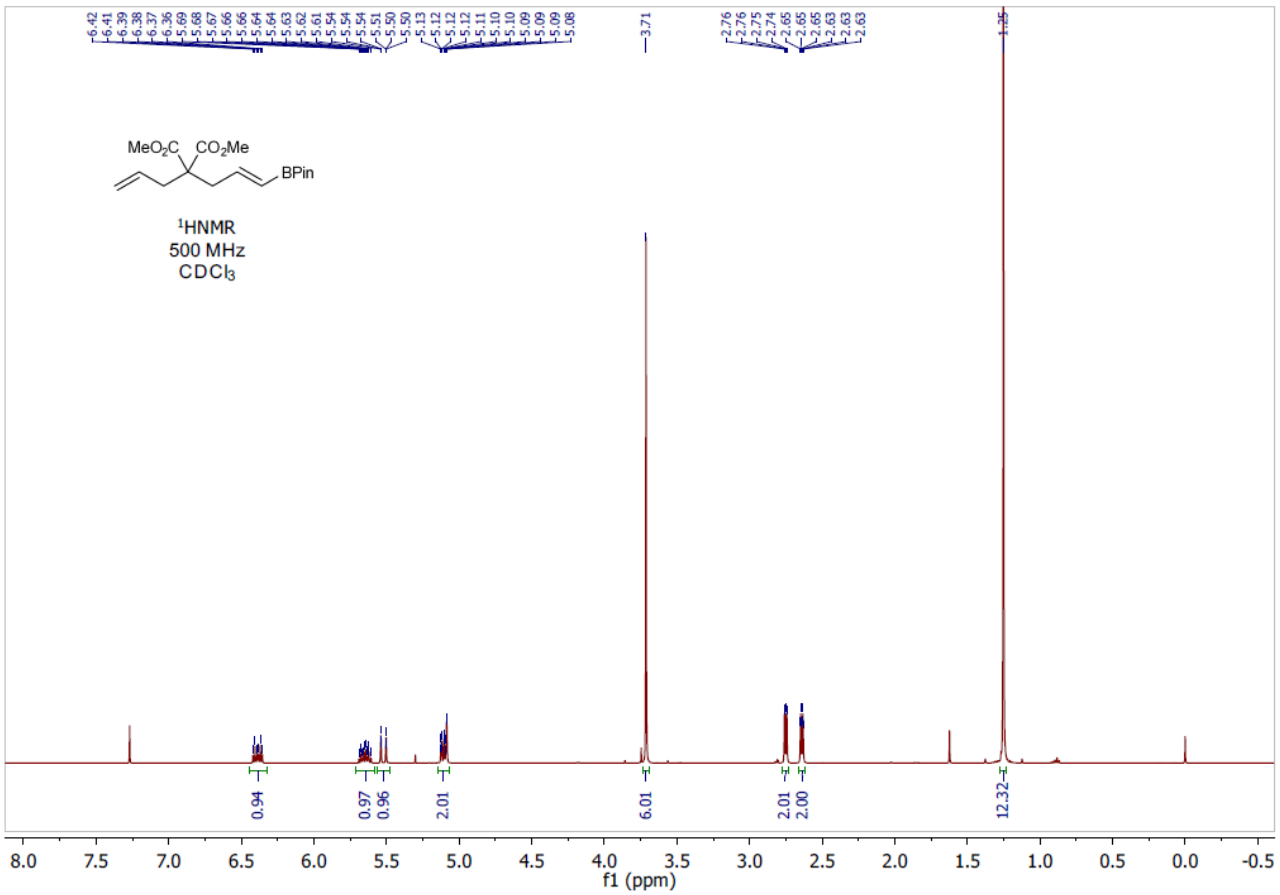

156.49
141.11
116.99
116.54
112.03
111.69
61.35
51.81
51.34
48.57
48.10
19.91
14.69
O
O
N
^{13}CNMR
126 MHz
$CDCl_3$
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

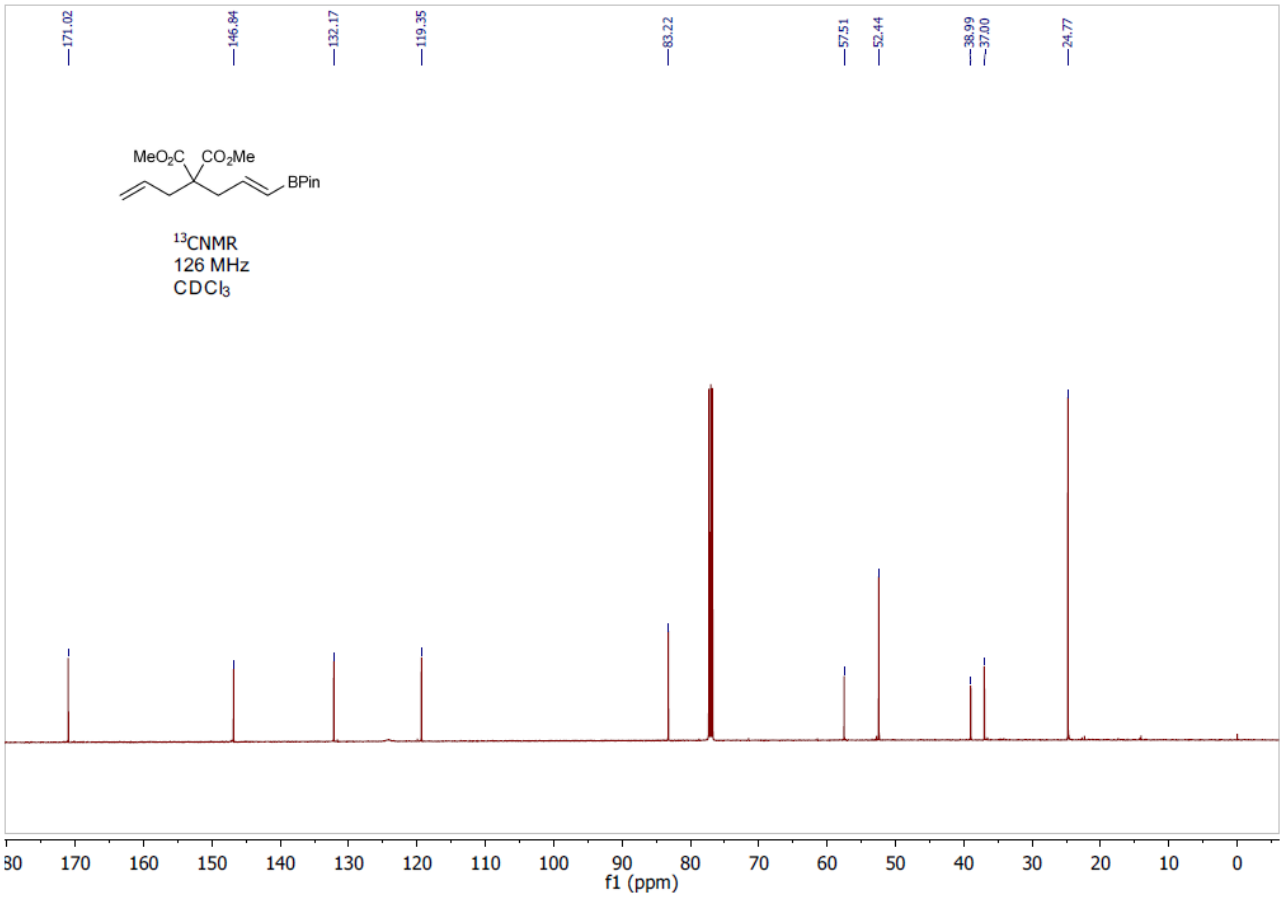

5.89
5.87
5.87
5.86
5.85
5.85
5.84
5.83
5.82
5.82
5.80
5.14
5.13
5.13
5.13
5.12
5.11
5.10
5.09
3.59
3.58
2.45
2.44
2.43
2.10
2.08
HO
OH
1HNMR
500 MHz
CDCl3
1.00
2.01
2.05
1.00
2.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

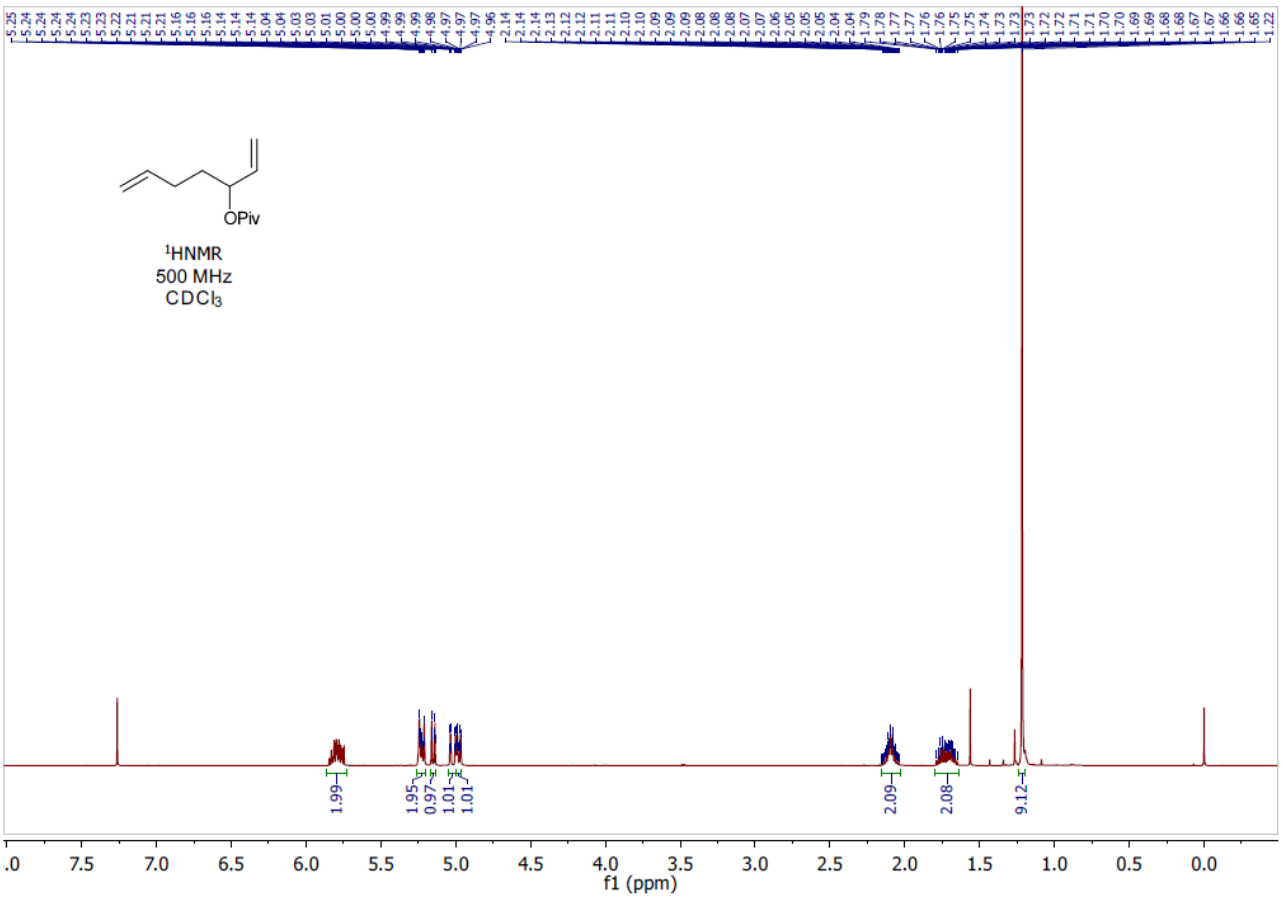

133.90
118.14
68.25
42.08
36.11
HO
OH
13CNMR
126 MHz
CDCl3
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

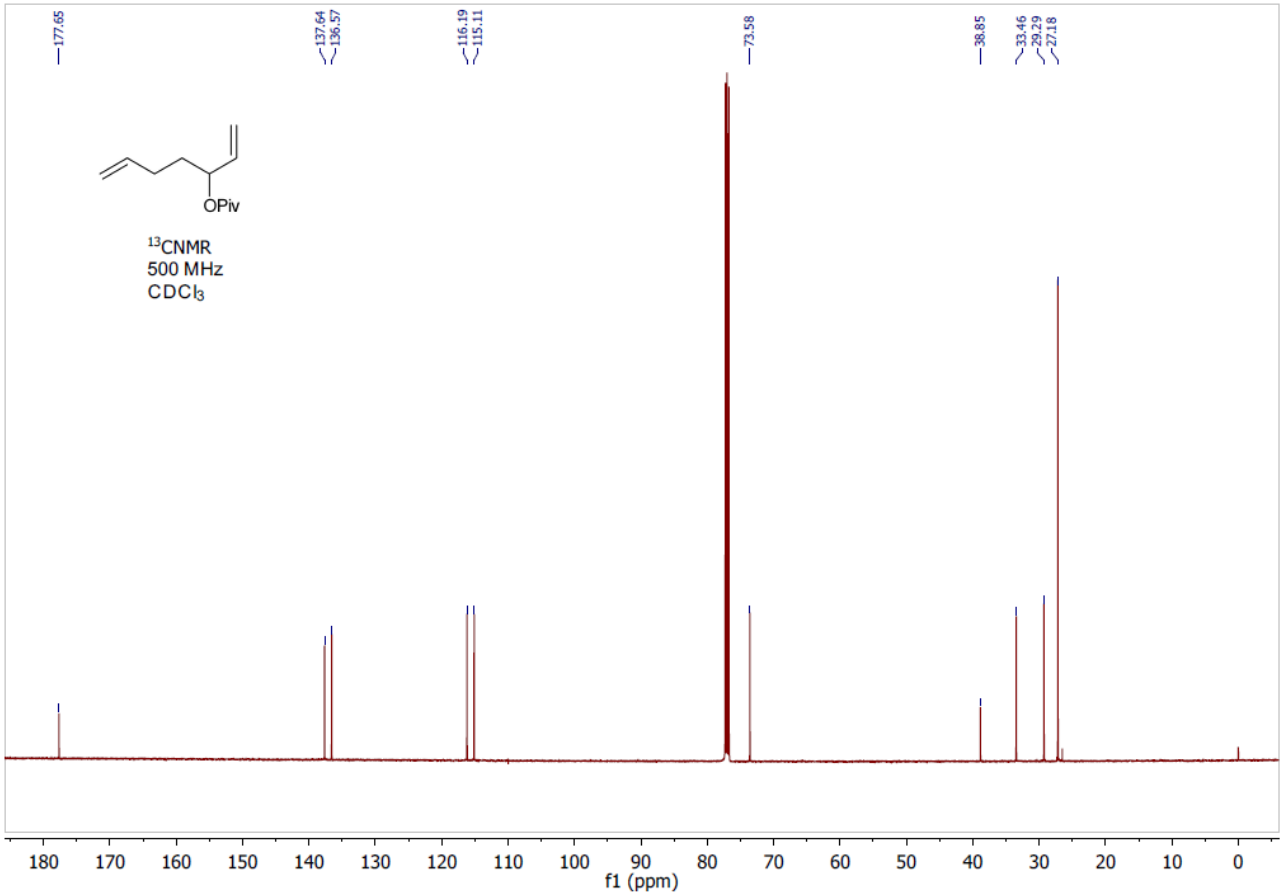

5.83
5.81
5.80
5.80
5.79
5.79
5.78
5.77
5.77
5.76
5.76
5.74
5.11
5.11
5.10
5.09
5.09
5.09
5.09
5.08
5.08
5.07
5.07
3.58
2.15
2.15
2.14
2.13
2.13
2.13
1.75
1.74
1.73
1.54
1.53
1.51
1.50
1.49
1.43
1.42
1.41
1.40
1.40
1.39
1.38
O
O
^{1}HNMR
500 MHz
$CDCl_3$
2.00
4.05
4.01
4.03
3.94
4.04
2.03
7.5
7.0
6.5
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
-0.5
f1 (ppm)

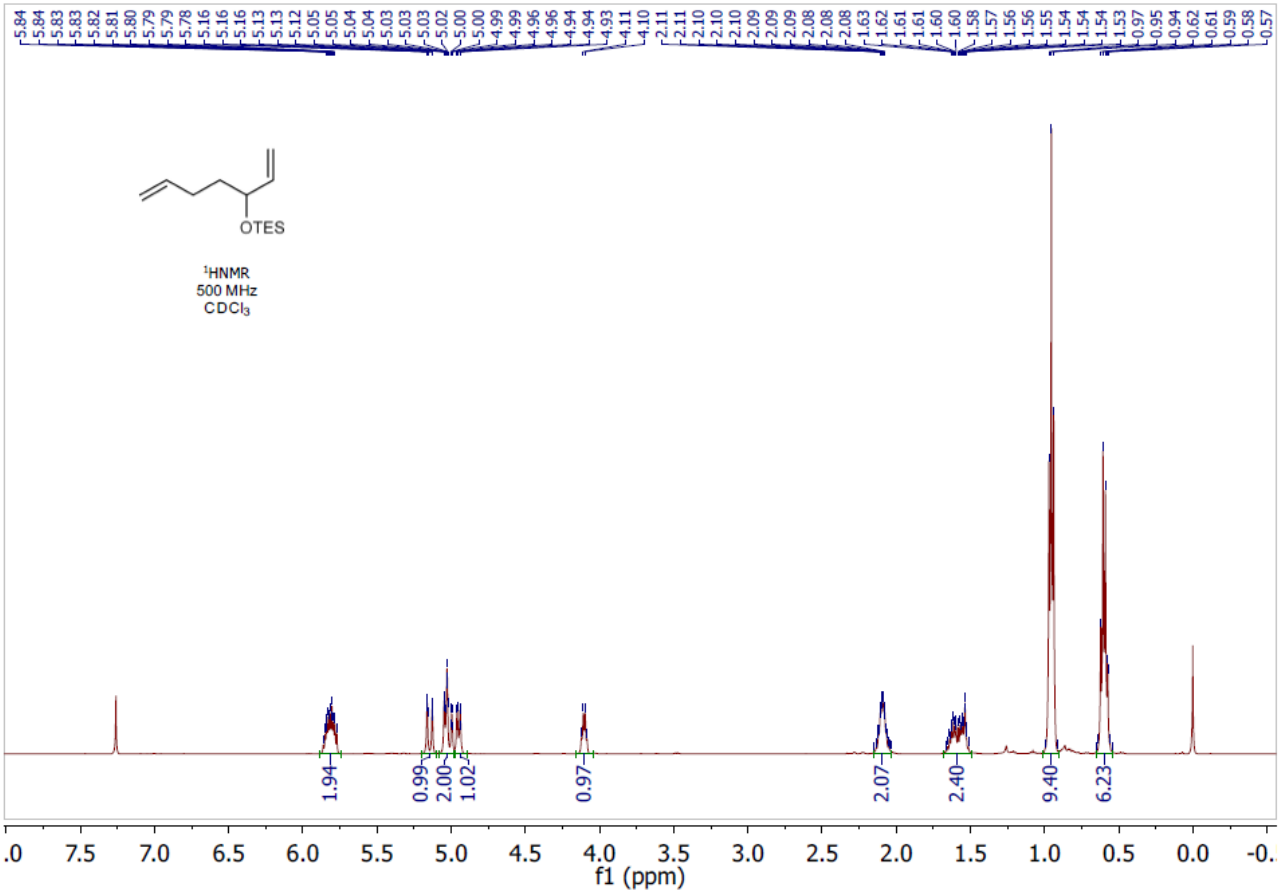

133.23
118.29
98.00
66.39
36.83
35.63
32.62
25.71
22.57
O
O
^{13}CNMR
126 MHz
$CDCl_3$
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

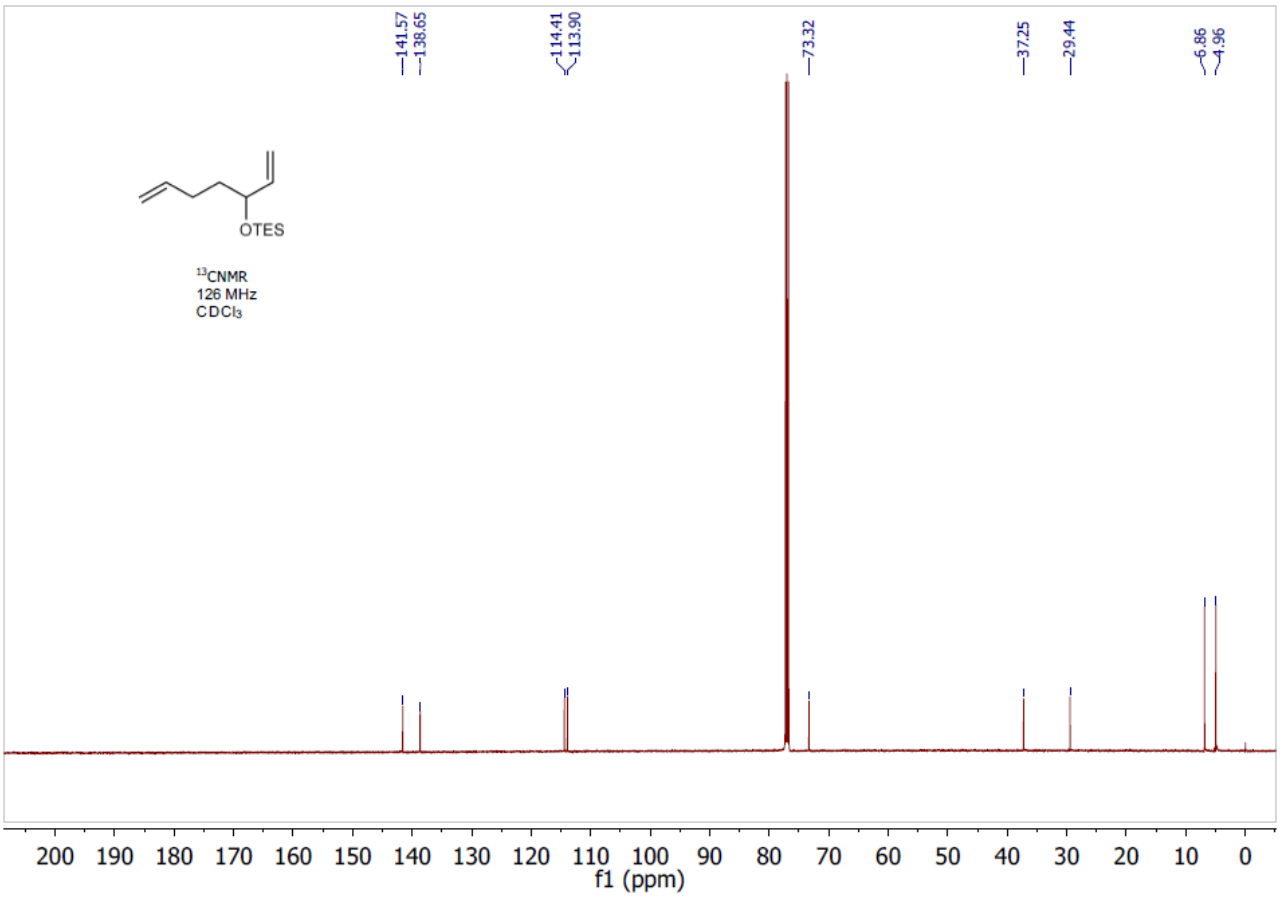

MeO2C CO2Me
BPin
1HNMR
500 MHz
CDCl3
f1 (ppm)

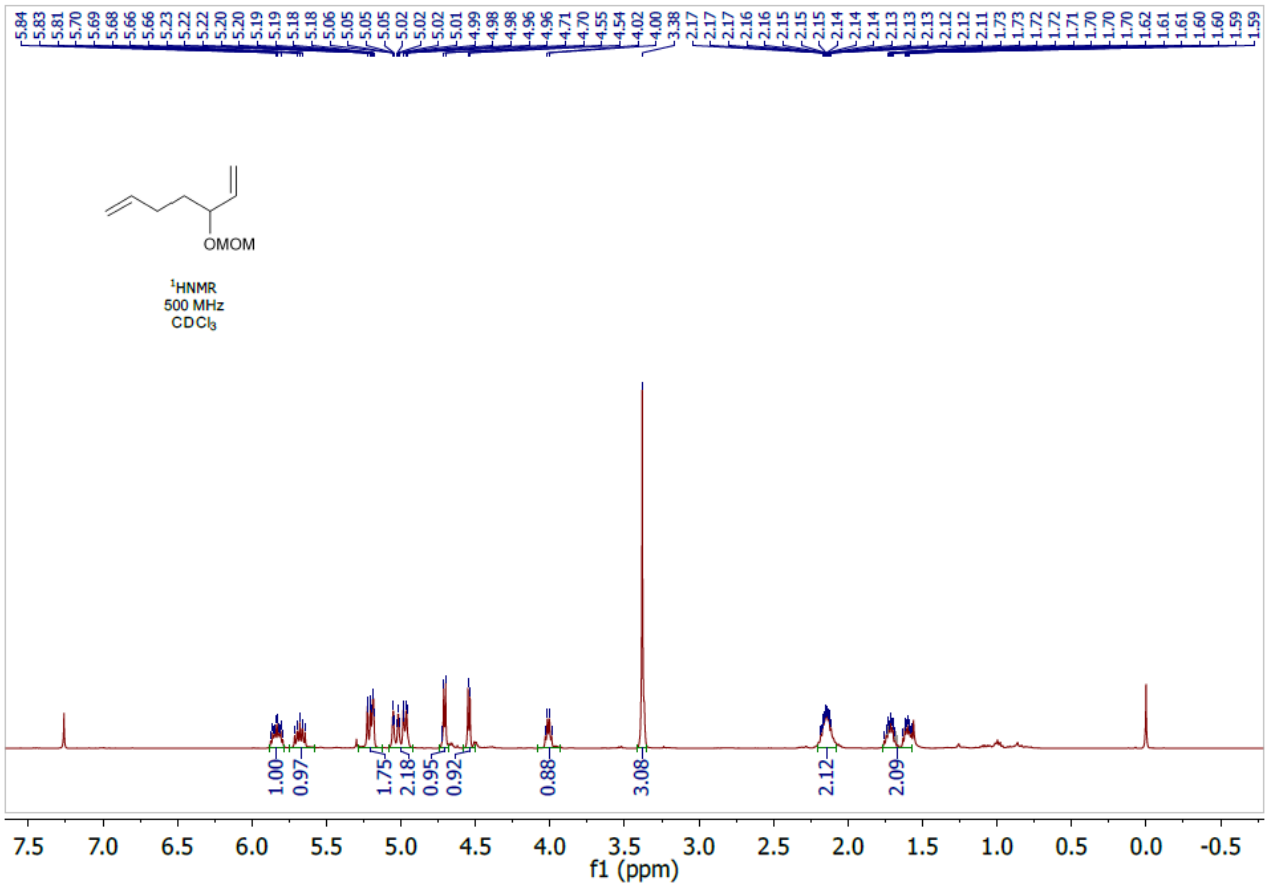

MeO2C CO2Me
BPin
13CNMR
126 MHz
CDCl3
f1 (ppm)

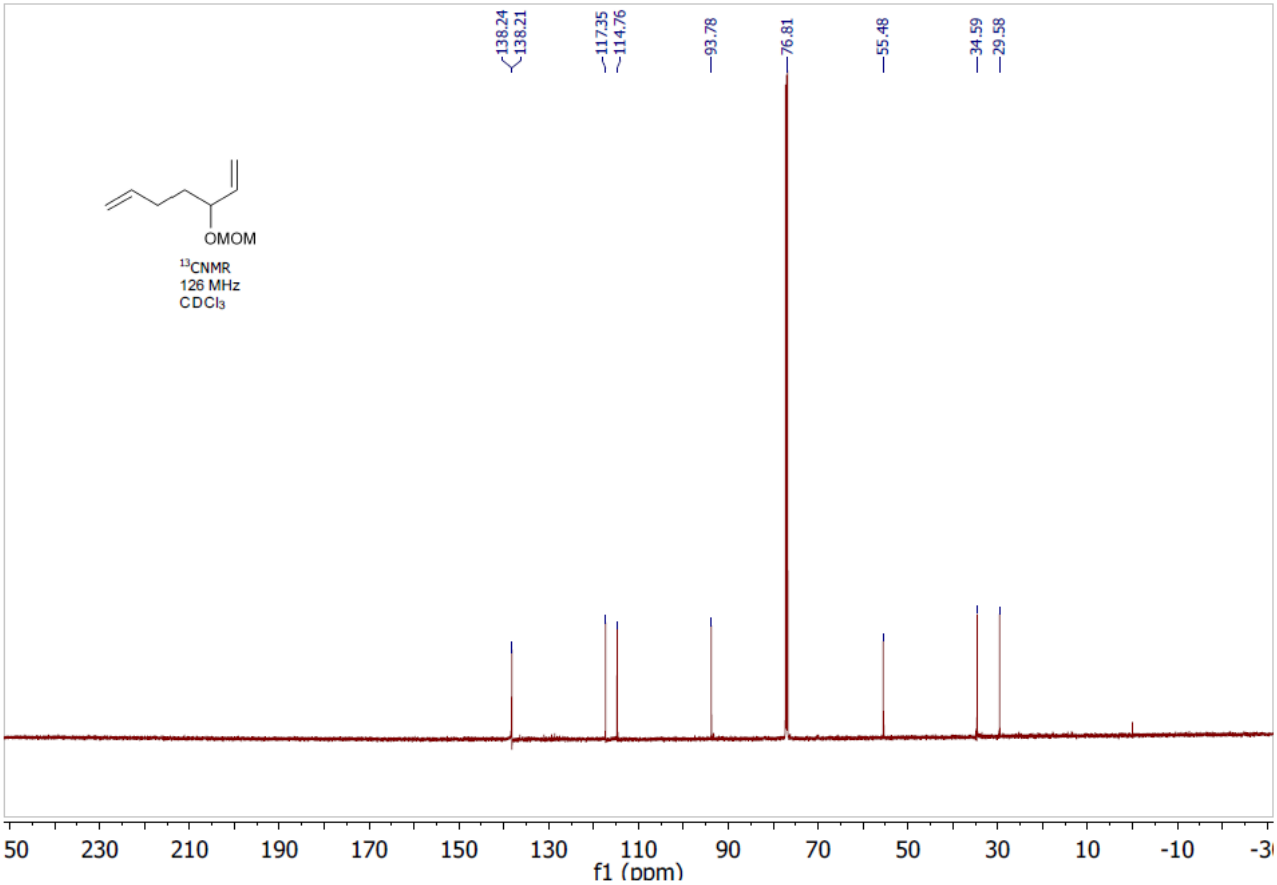

OPiv
1HNMR
500 MHz
CDCl3
1.99
1.95
0.97
1.01
1.01
2.09
2.08
9.12
f1 (ppm)

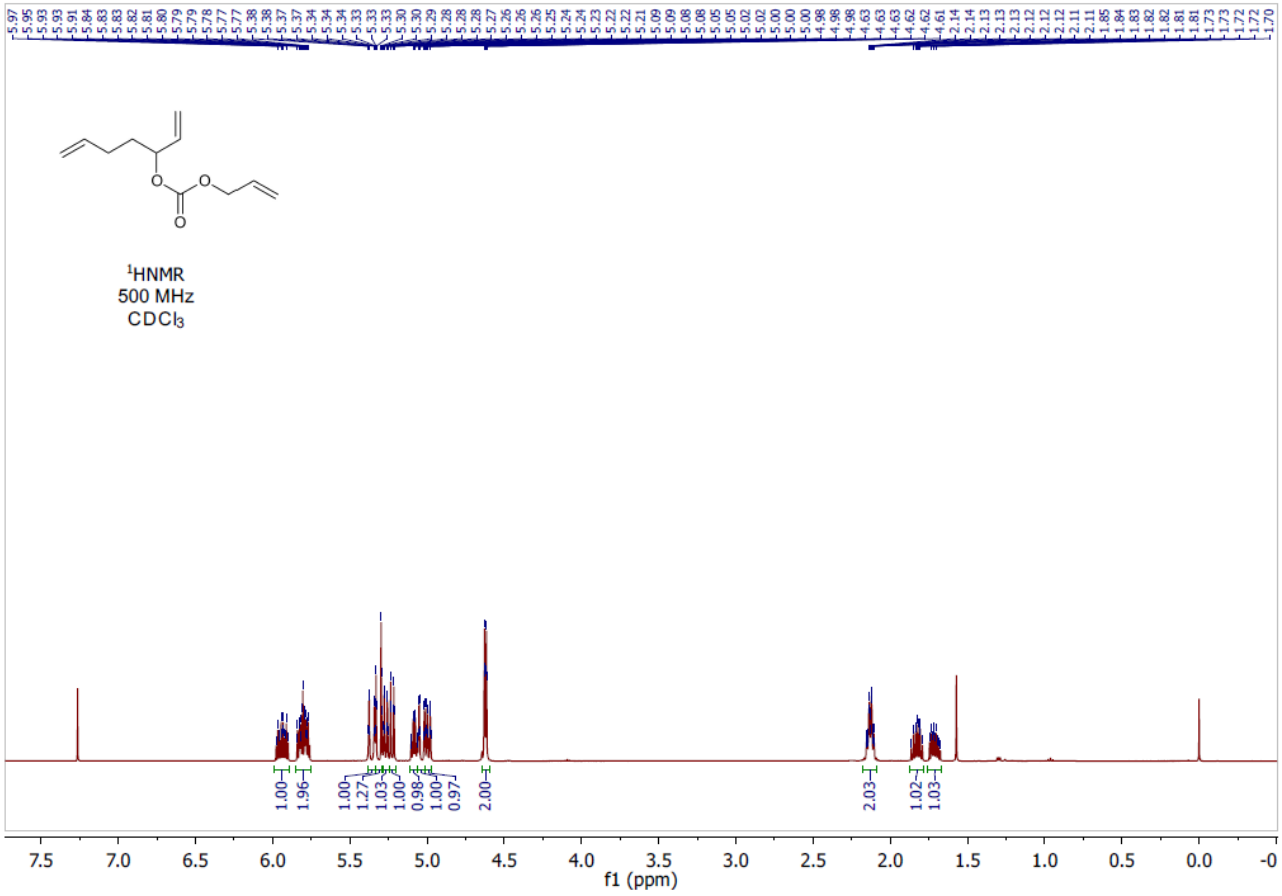

177.65
137.64
136.57
116.19
115.11
73.58
38.85
33.46
29.29
27.18
OPiv
13CNMR
500 MHz
CDCl3
f1 (ppm)

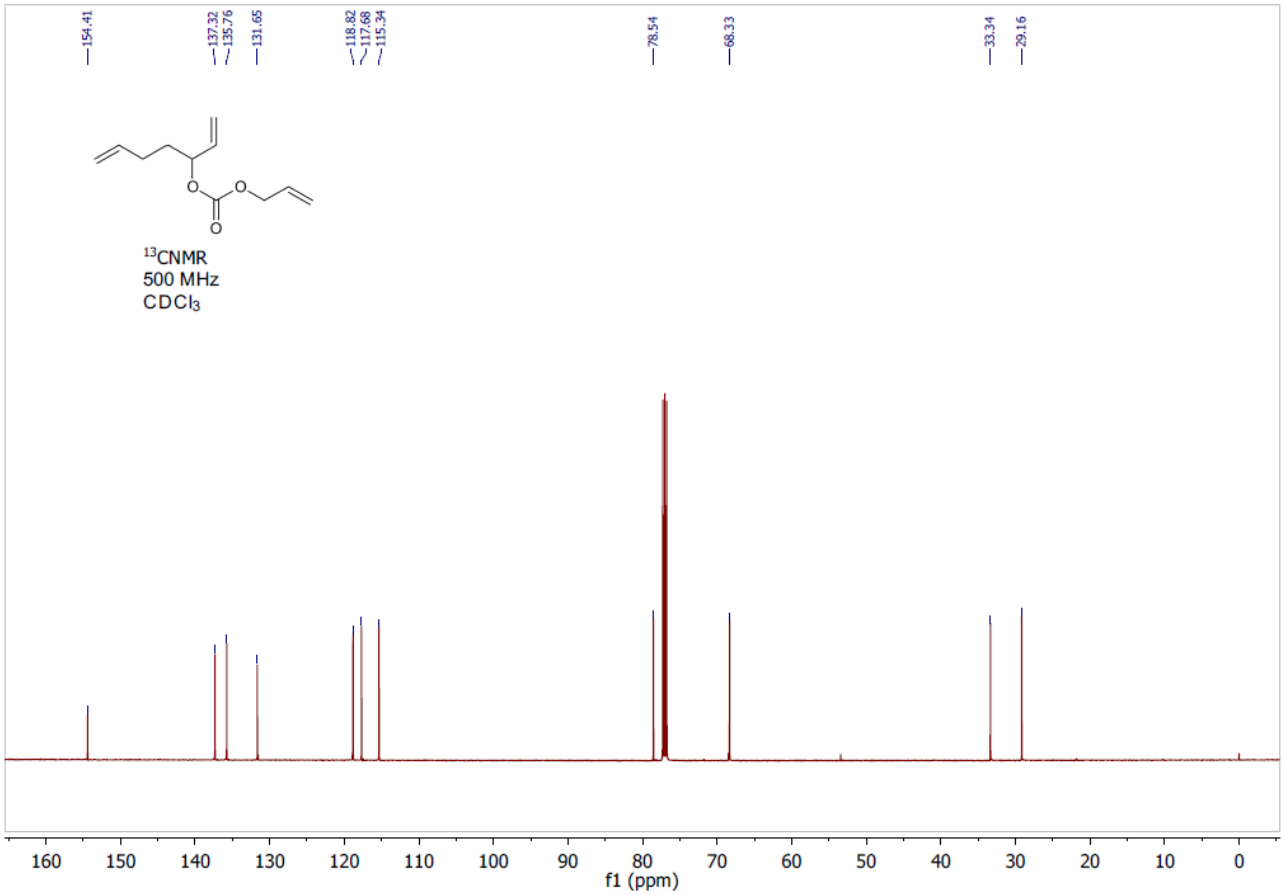

OTES
^{1}HNMR
500 MHz
$CDCl_3$
1.94
0.99
2.00
1.02
0.97
2.07
2.40
9.40
6.23
f1 (ppm)

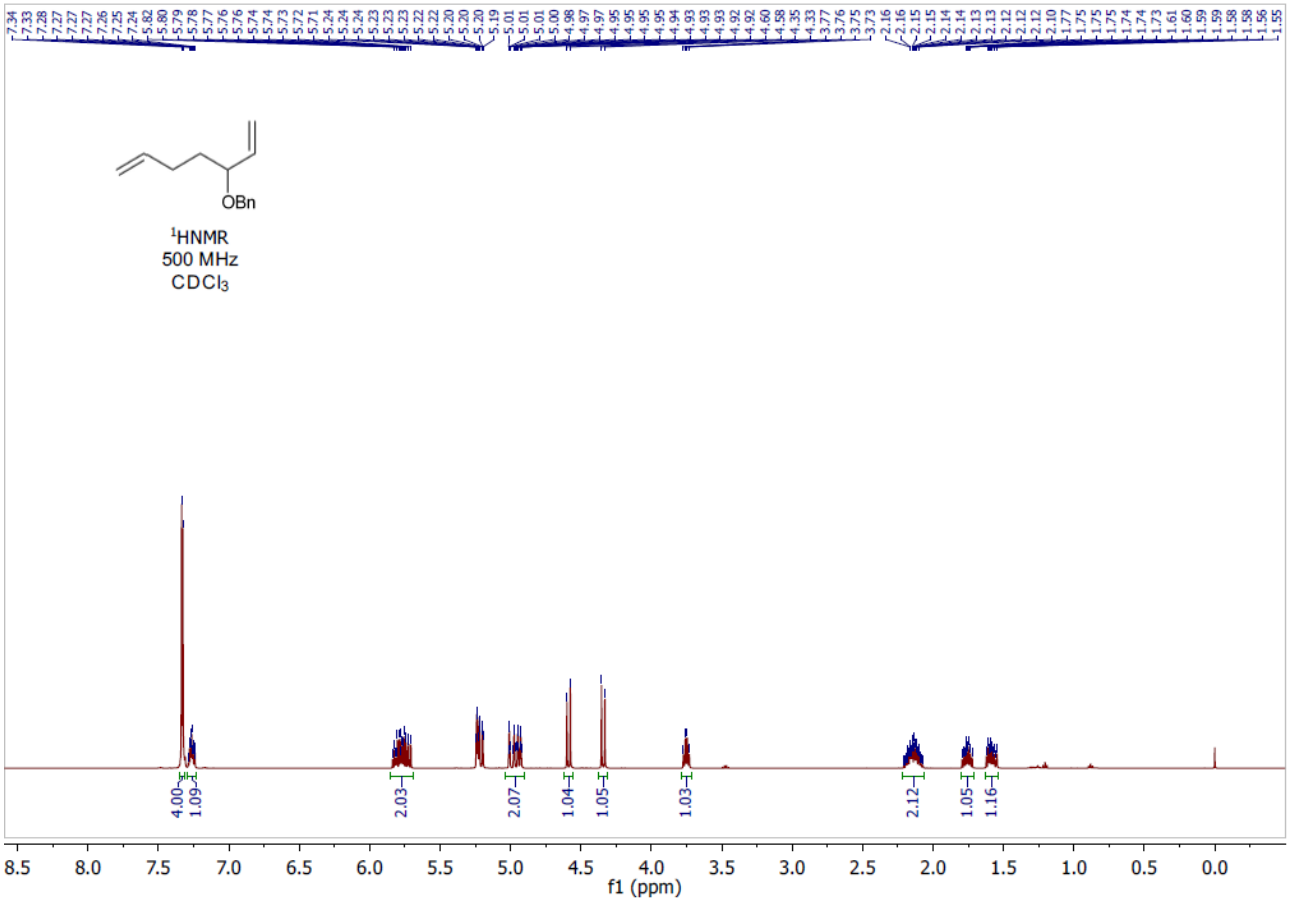

OTES
^{13}CNMR
126 MHz
$CDCl_3$
141.57
138.65
114.41
113.90
73.32
37.25
29.44
6.86
4.96
f1 (ppm)

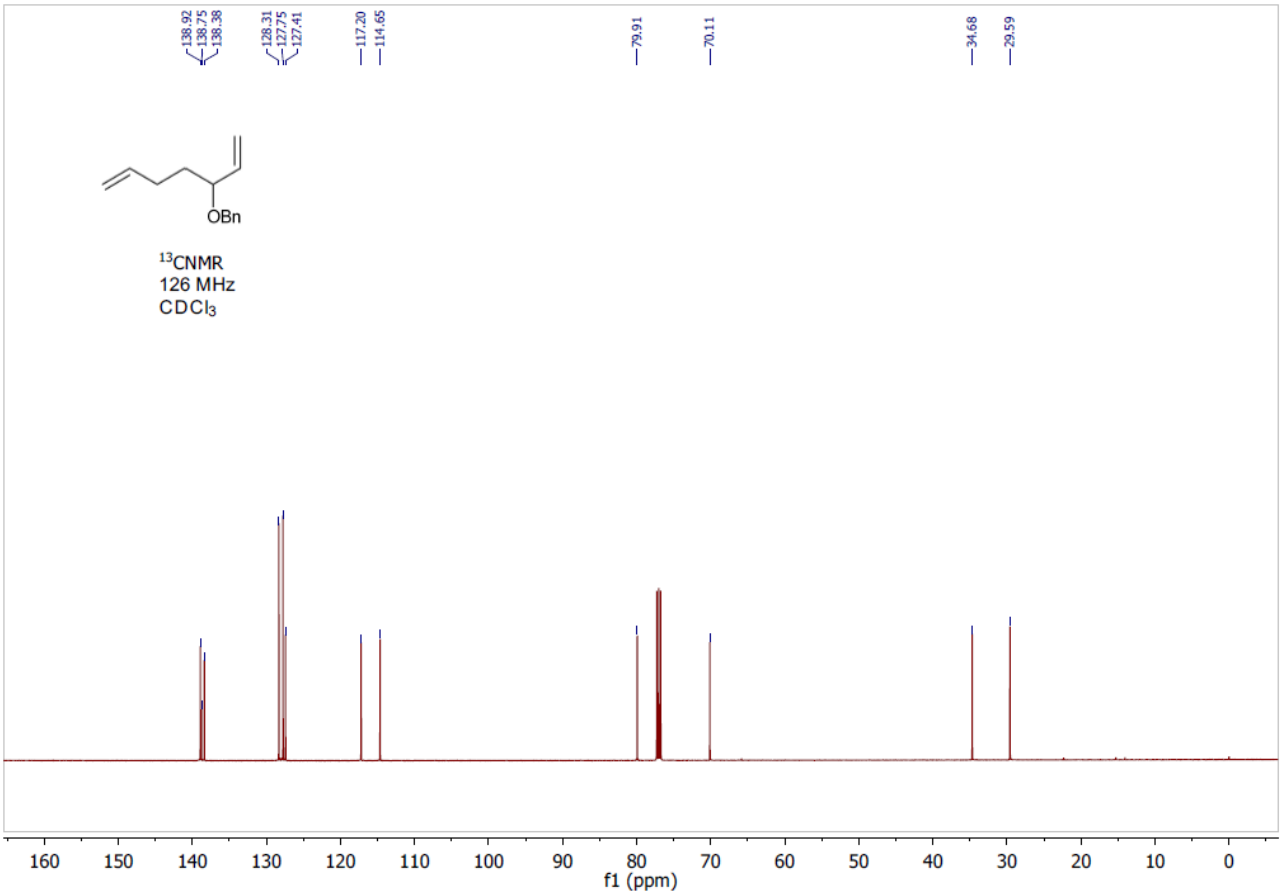

OMOM
1HNMR
500 MHz
CDCl3
1.00
0.97
1.75
2.18
0.95
0.92
0.88
3.08
2.12
2.09
f1 (ppm)

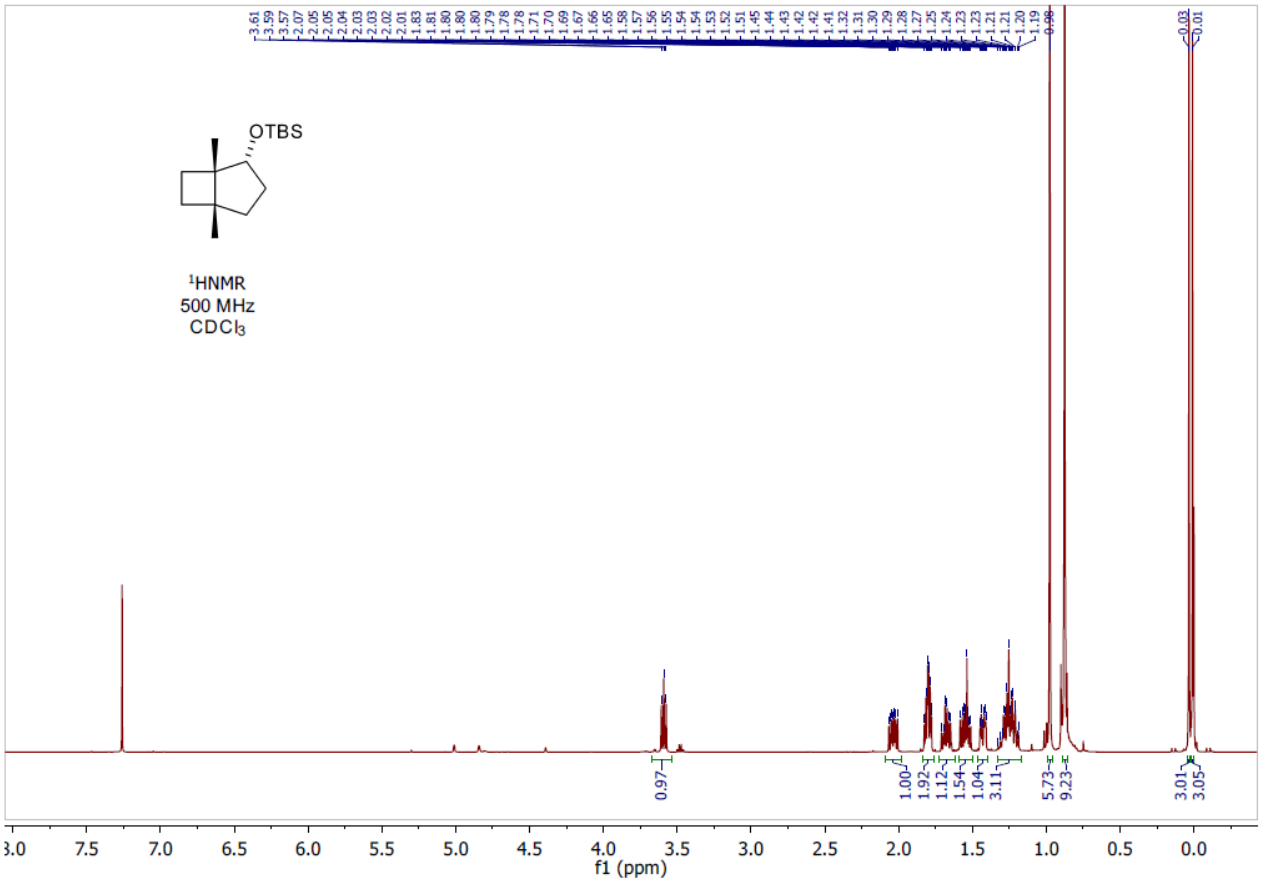

OMOM
13CNMR
126 MHz
CDCl3
138.24
138.21
117.35
114.76
93.78
76.81
55.48
34.59
29.58
f1 (ppm)

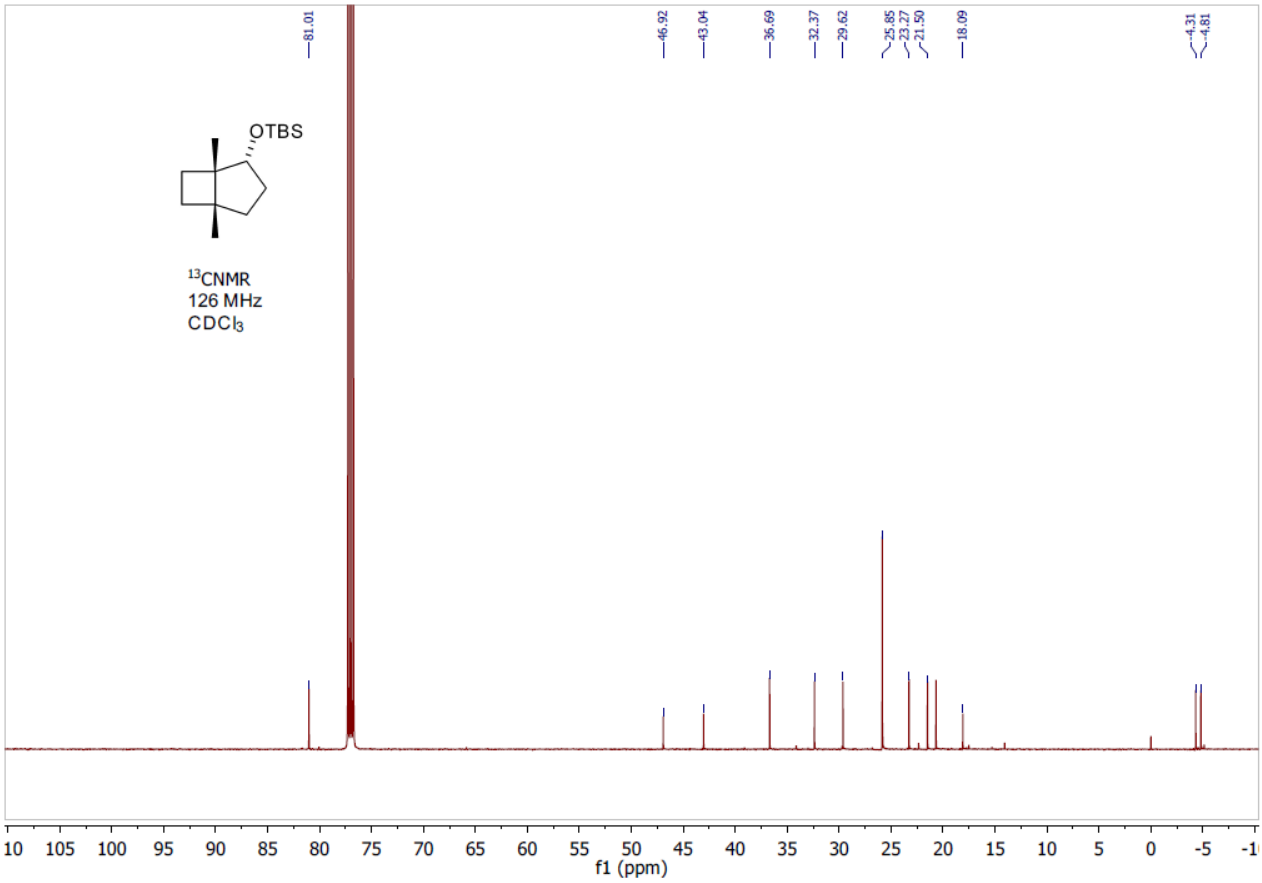

^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

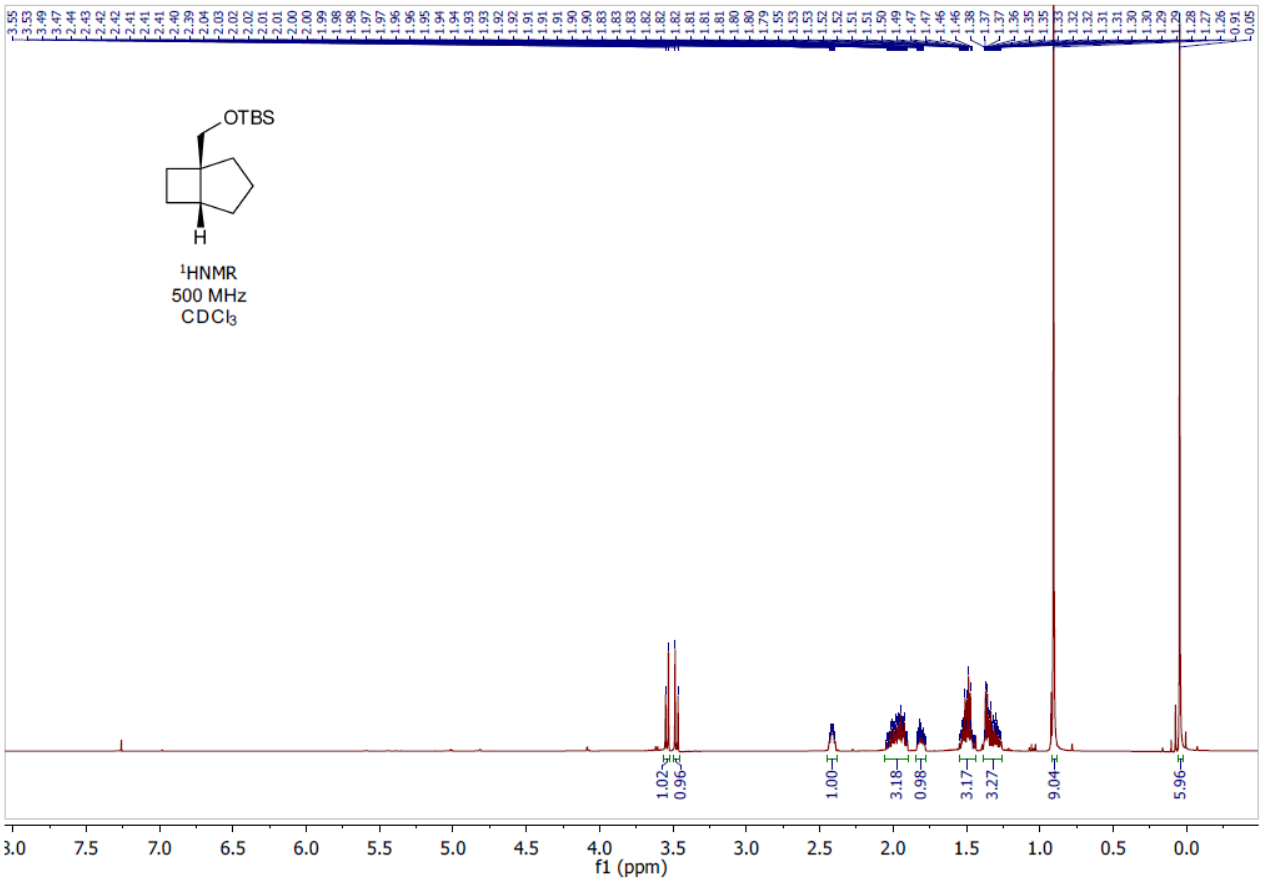

^{13}CNMR
500 MHz
$CDCl_3$
f1 (ppm)

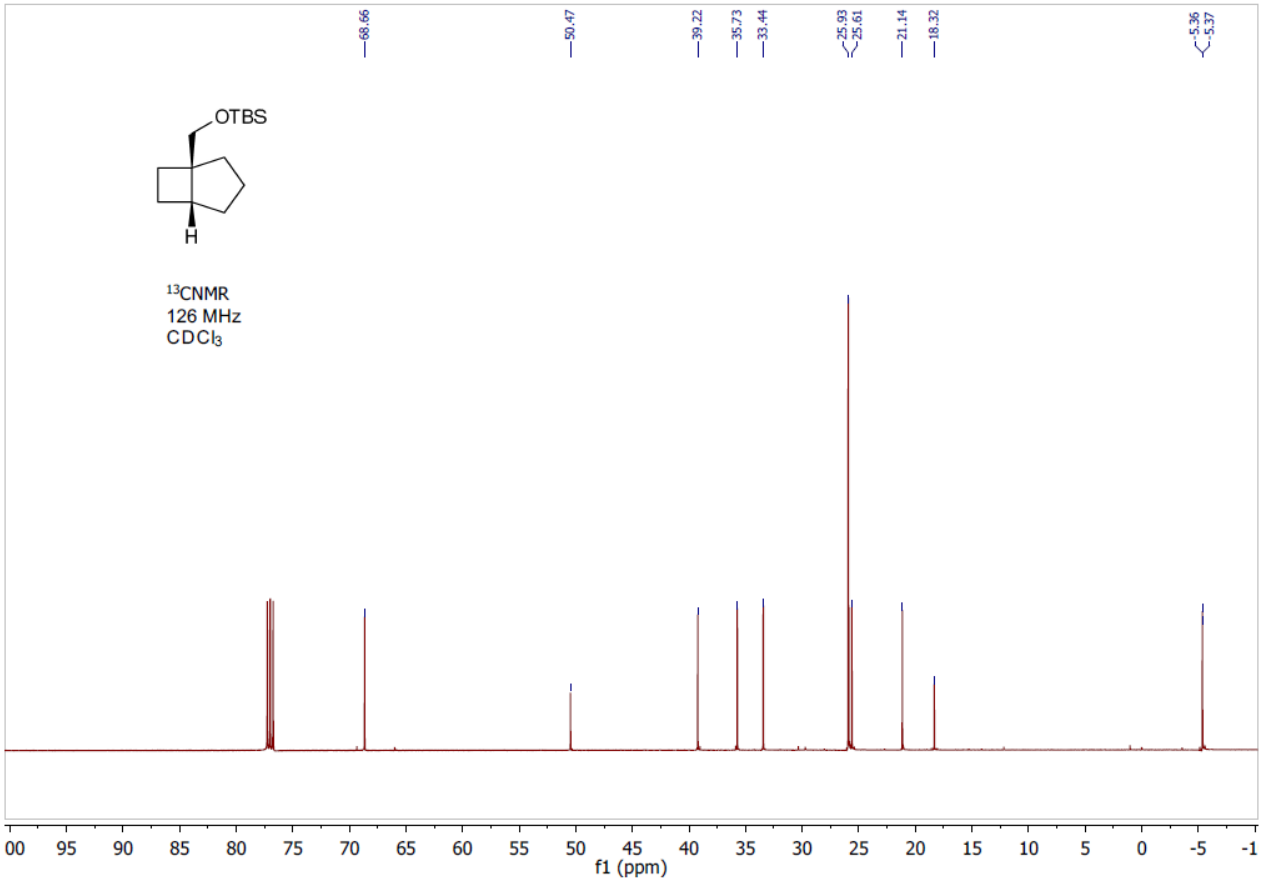

OBn
1HNMR
500 MHz
CDCl3
4.00
1.09
2.03
2.07
1.04
1.05
1.03
2.12
1.05
1.16
f1 (ppm)

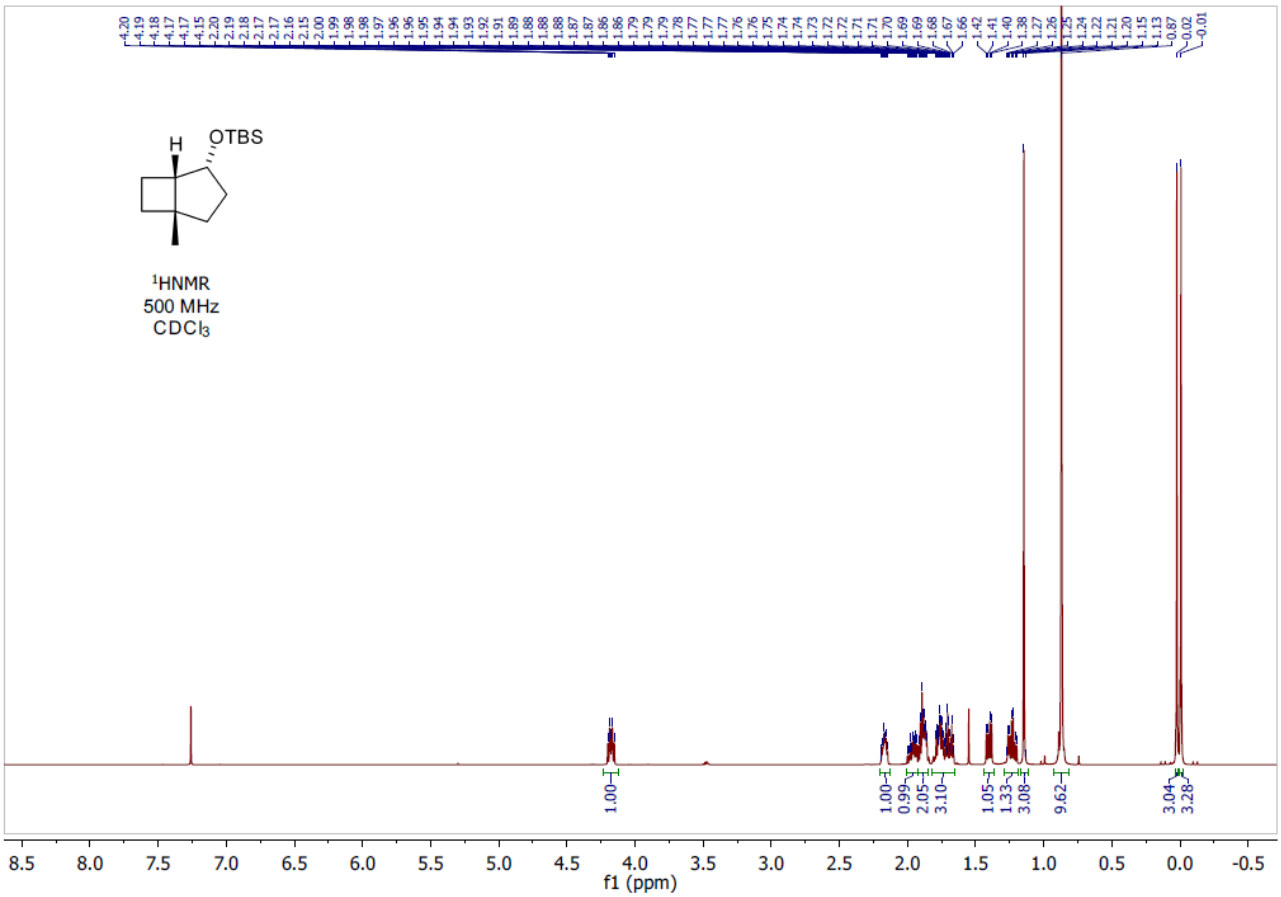

OBn
13CNMR
126 MHz
CDCl3
f1 (ppm)

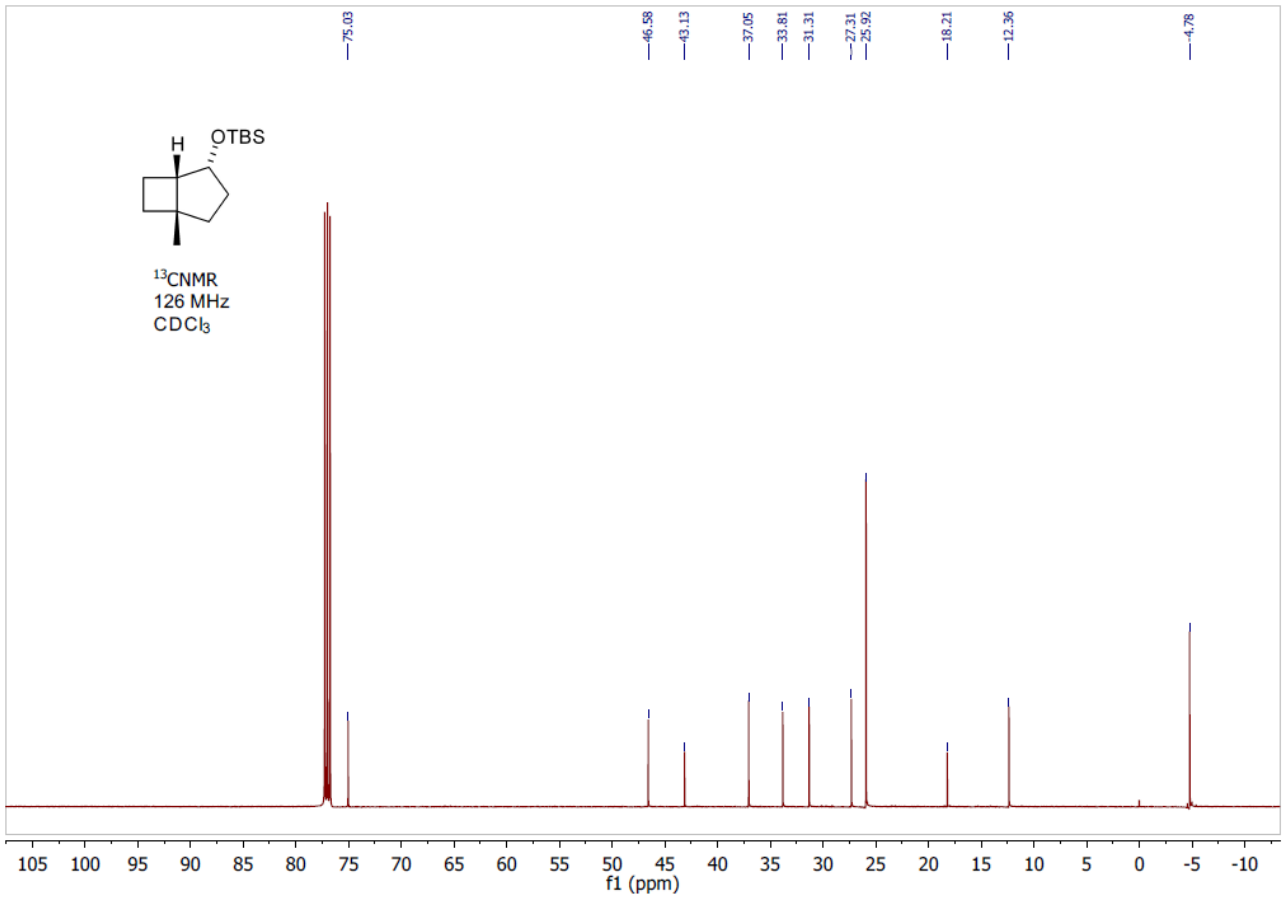

OTBS
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

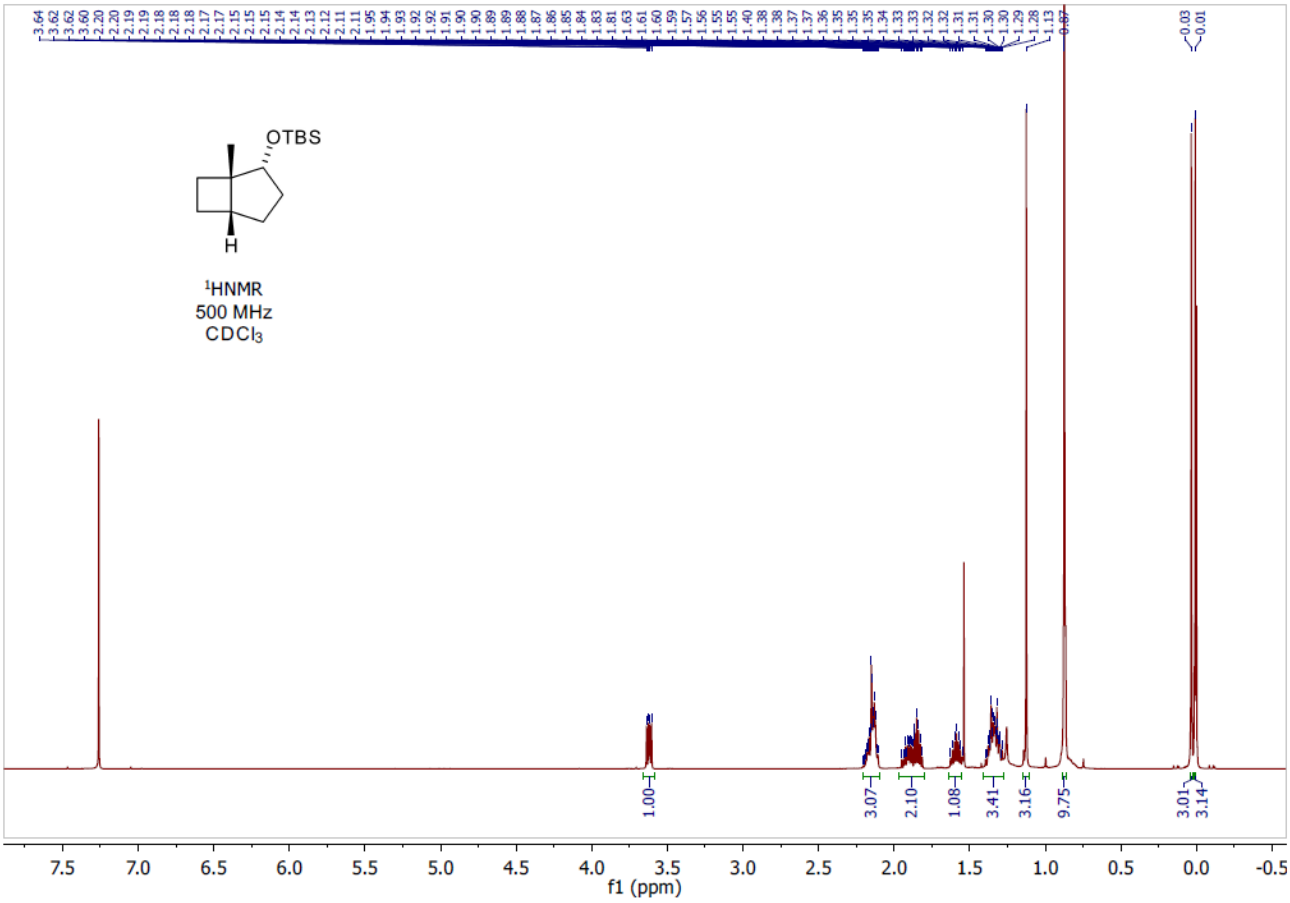

OTBS
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

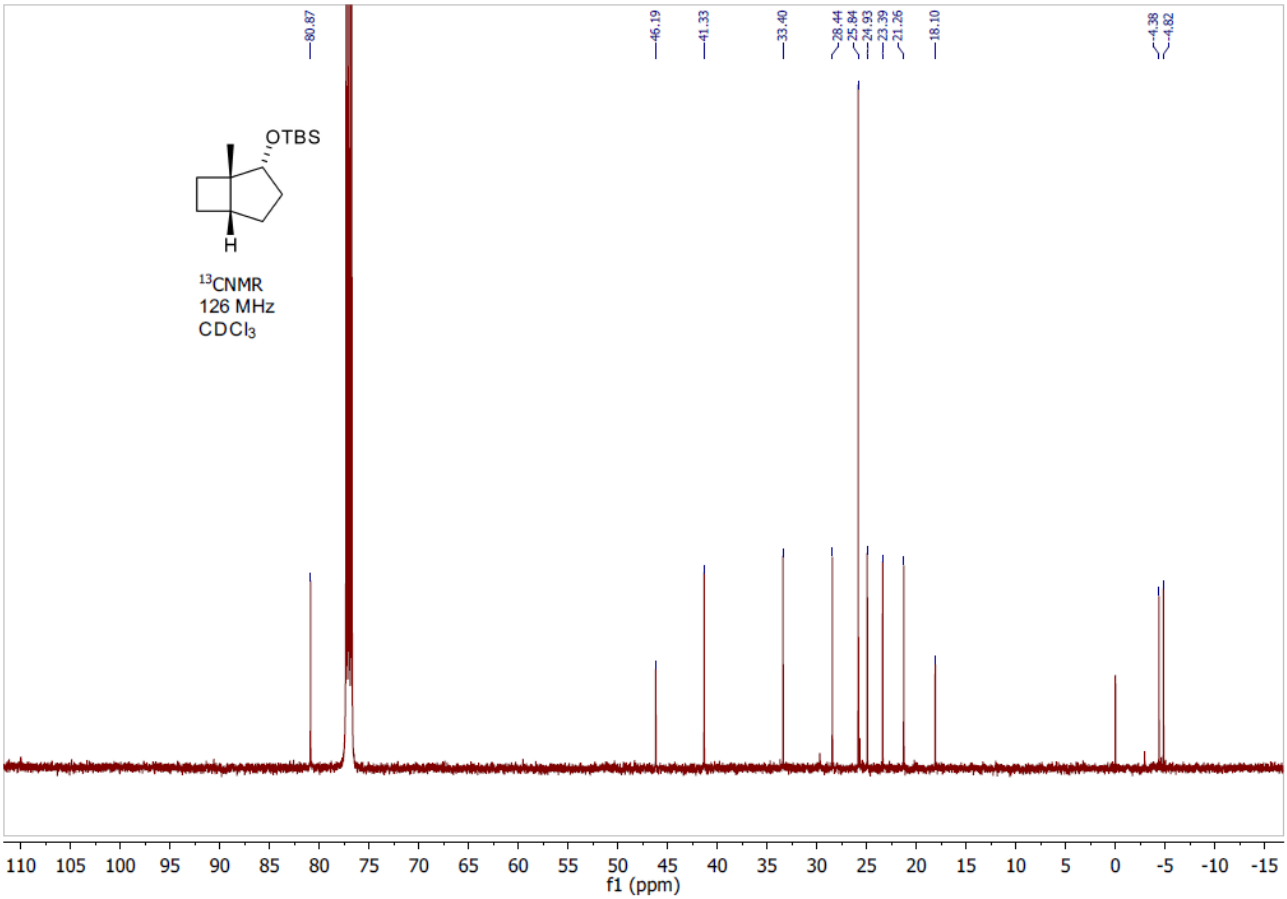

OTBS
H
1HNMR
500 MHz
CDCl3
1.02
0.96
1.00
3.18
0.98
3.17
3.27
9.04
5.96
f1 (ppm)

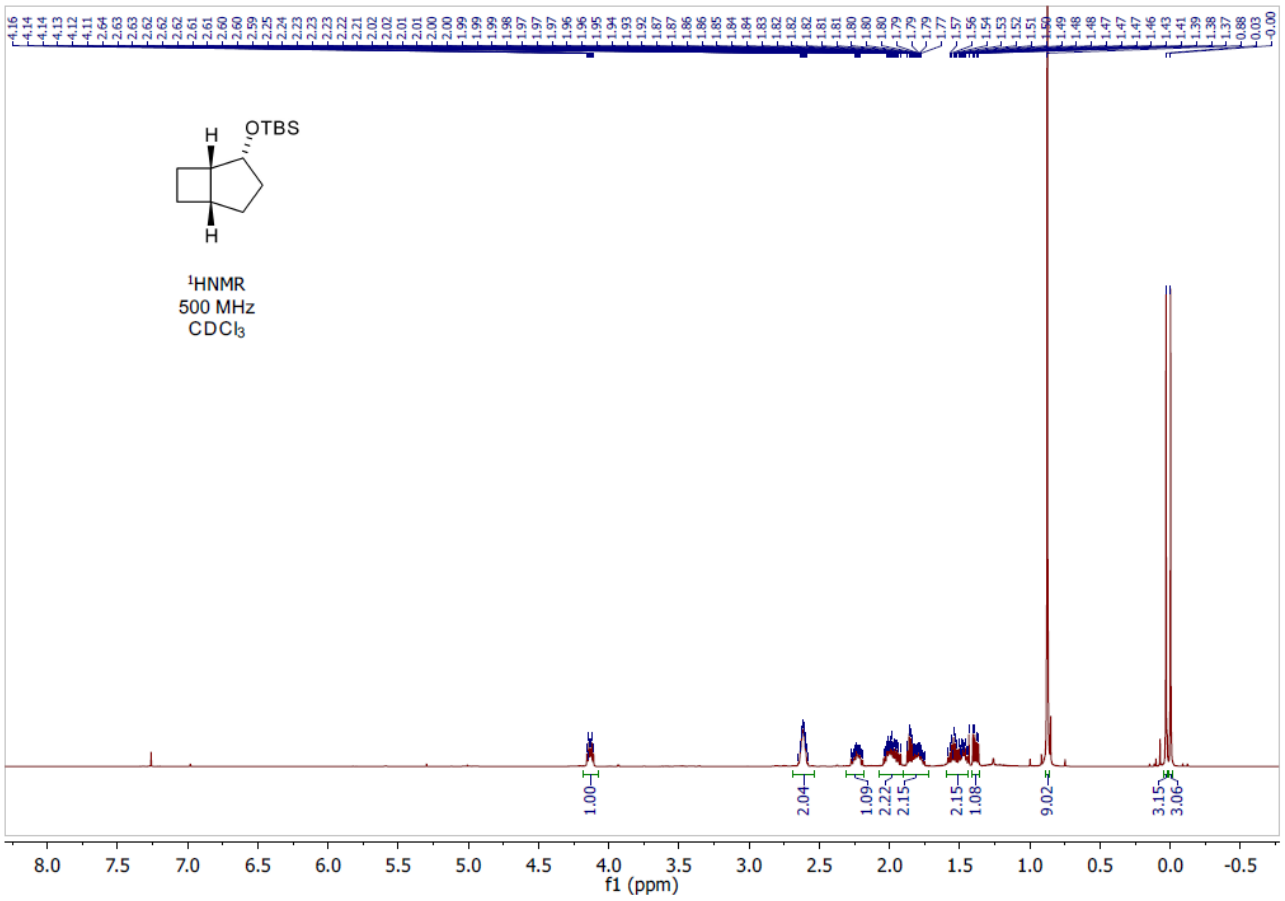

68.66
50.47
39.22
35.73
33.44
25.93
25.61
21.14
18.32
5.36
5.37
OTBS
H
13CNMR
126 MHz
CDCl3
f1 (ppm)

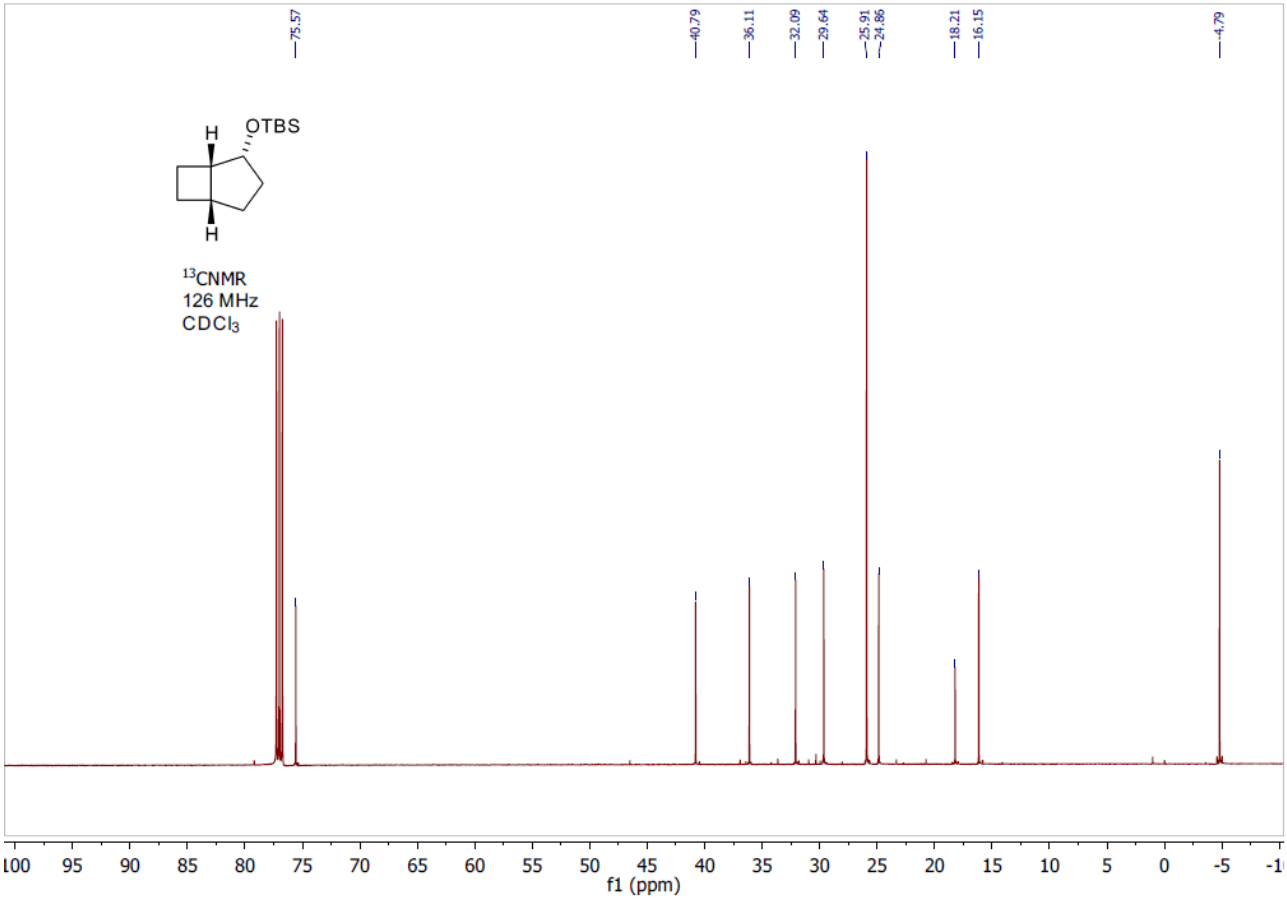

H
OTBS
¹HNMR
500 MHz
CDCl3
f1 (ppm)

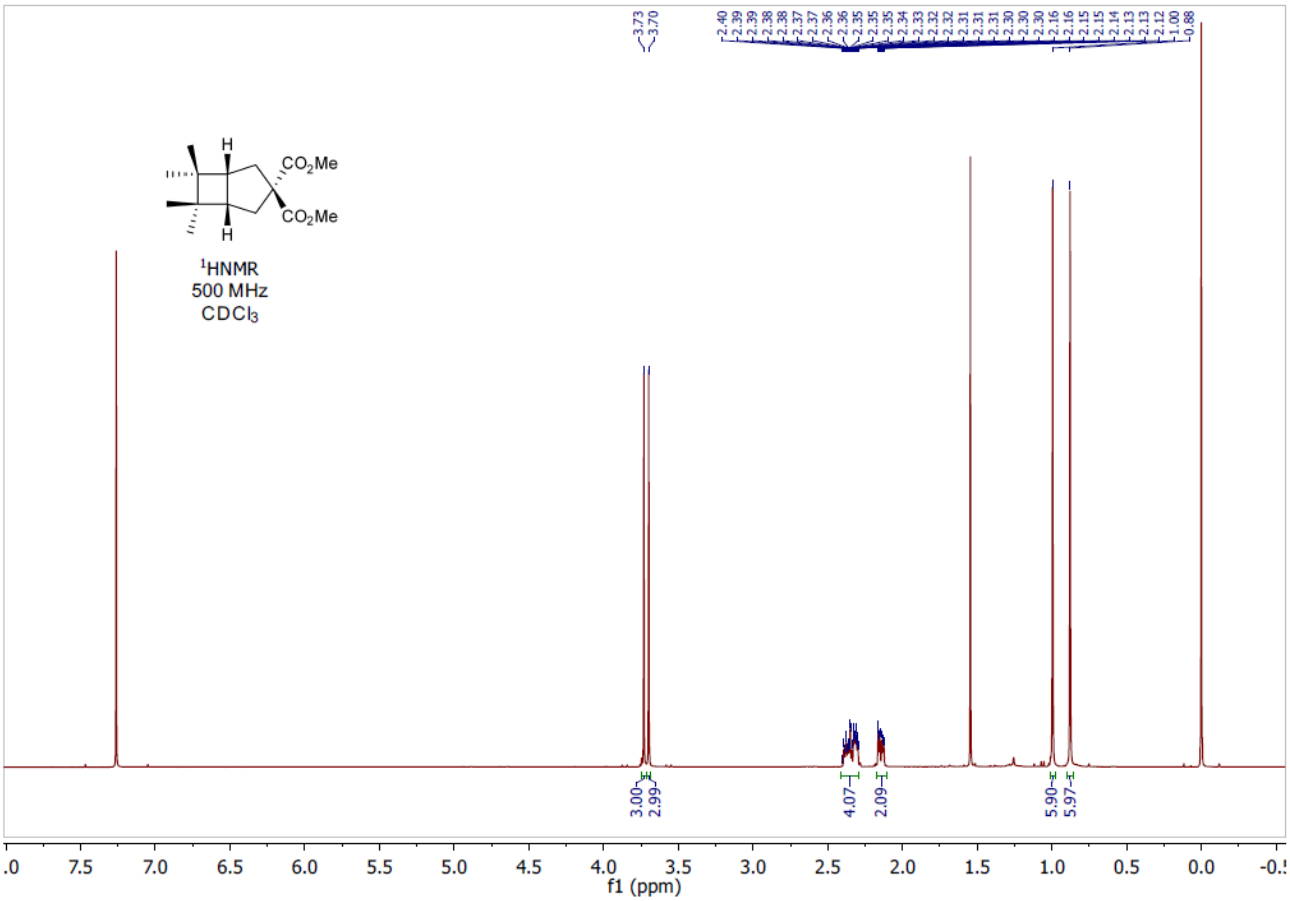

H
OTBS
¹³CNMR
126 MHz
CDCl3
f1 (ppm)

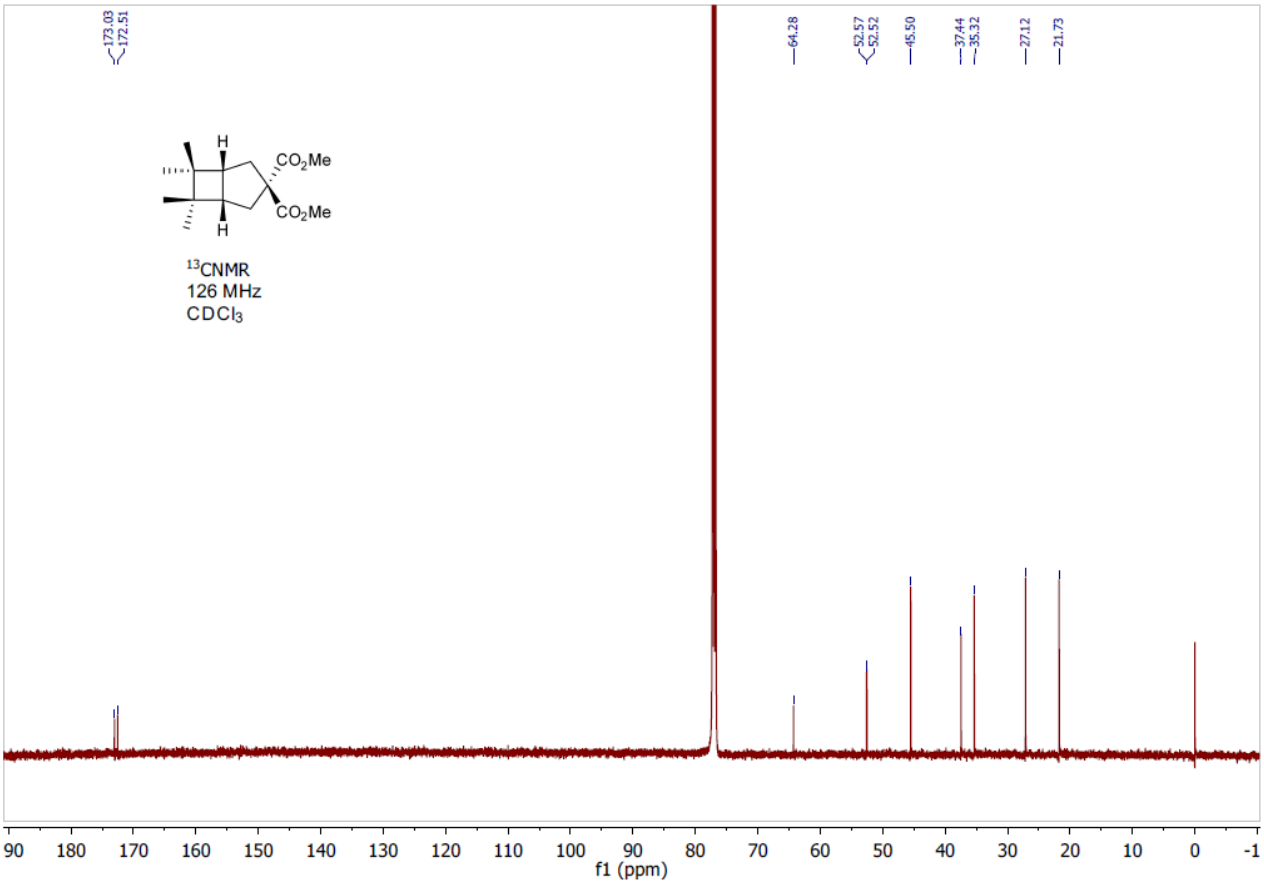

OTBS
H
^{1}HNMR
500 MHz
$CDCl_3$
1.00
3.07
2.10
1.08
3.41
3.16
9.75
3.01
3.14
f1 (ppm)

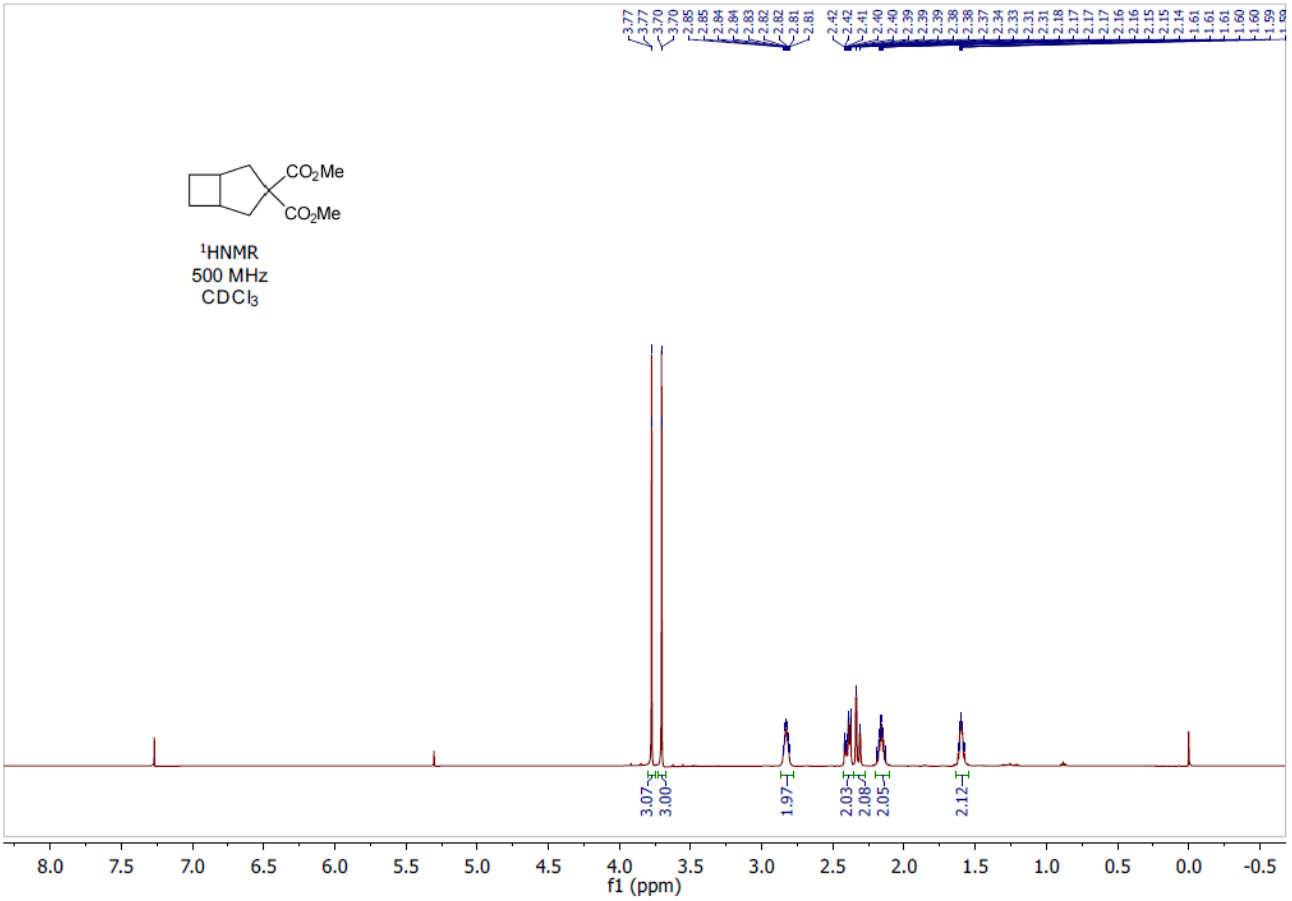

OTBS
H
^{13}CNMR
126 MHz
$CDCl_3$
80.87
46.19
41.33
33.40
28.44
25.84
24.93
23.39
21.26
18.10
-4.38
-4.82
f1 (ppm)

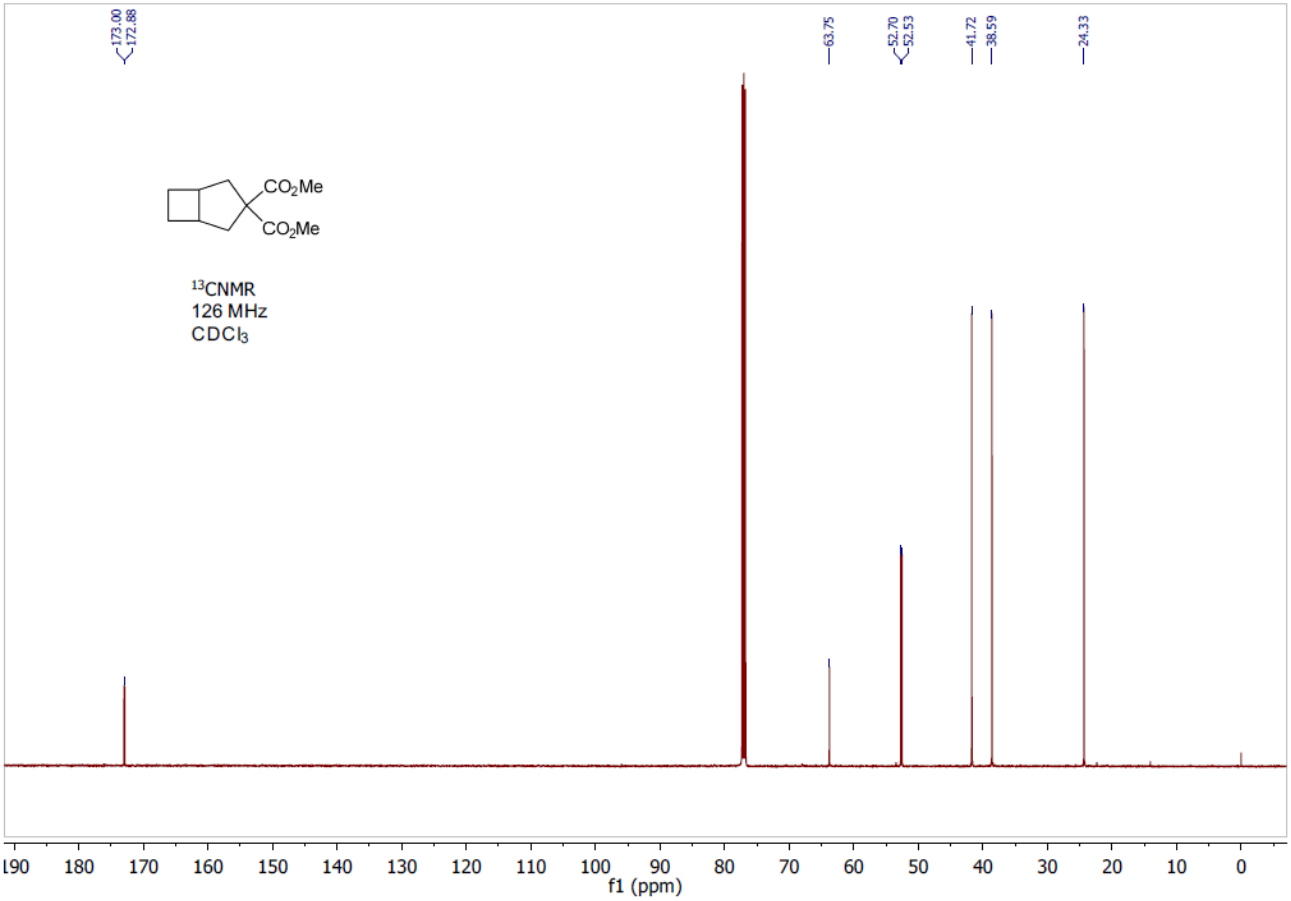

OTBS
H
H
^{1}HNMR
500 MHz
$CDCl_3$
1.00
2.04
1.09
2.22
2.15
2.15
1.08
9.02
3.15
3.06
f1 (ppm)

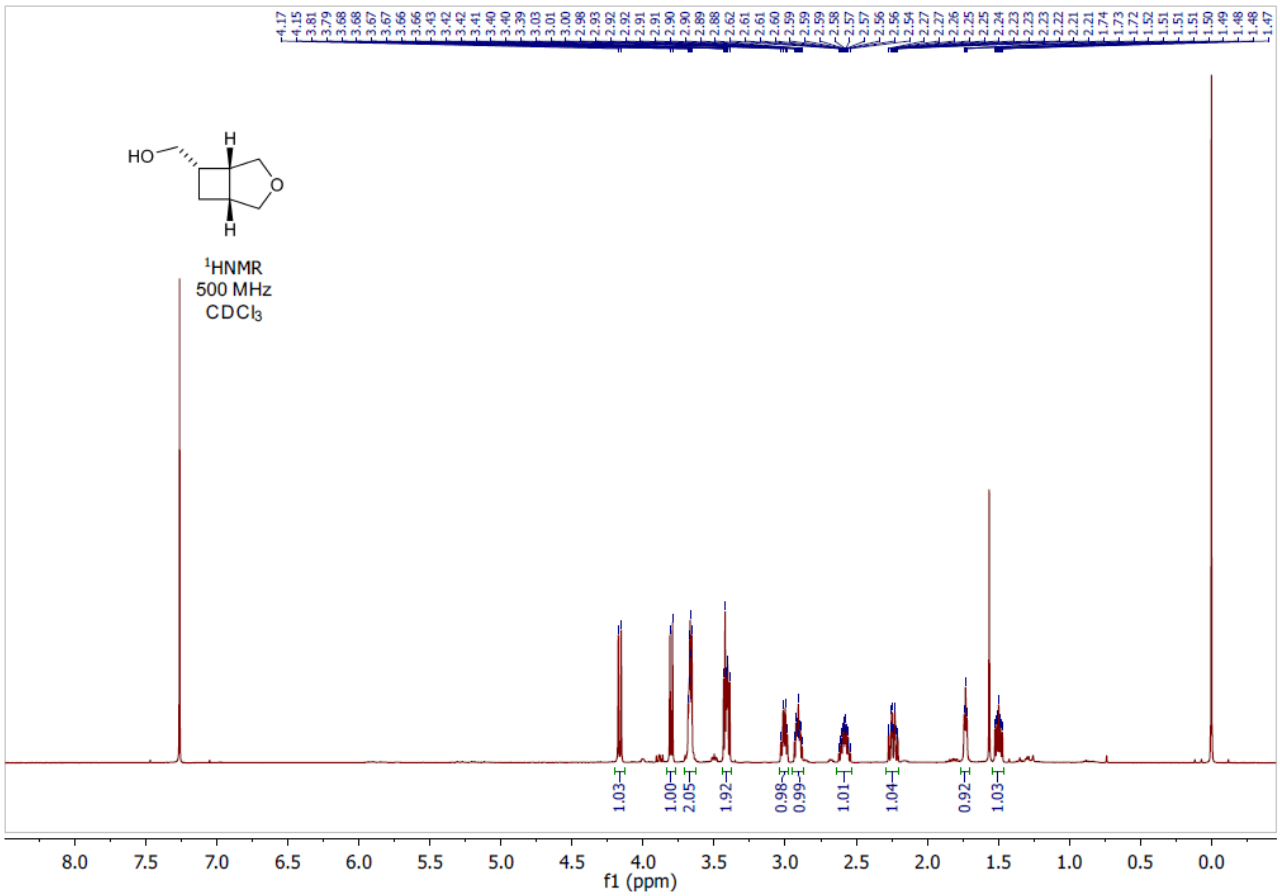

75.57
40.79
36.11
32.09
29.64
25.91
24.86
18.21
16.15
4.79
OTBS
H
H
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

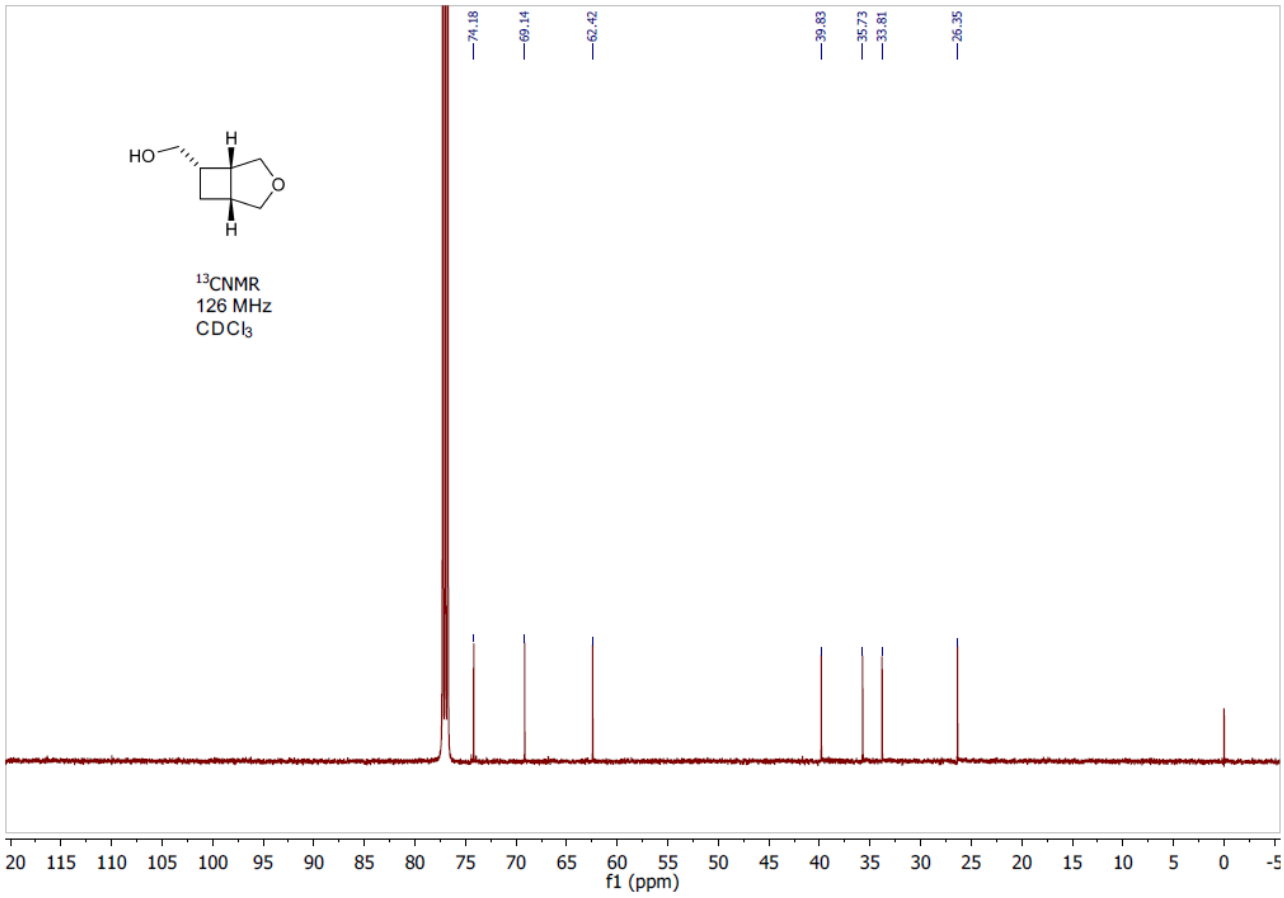

H
CO2Me
CO2Me
H
1HNMR
500 MHz
CDCl3
3.73
3.70
3.00
2.99
4.07
2.09
5.90
5.97
f1 (ppm)

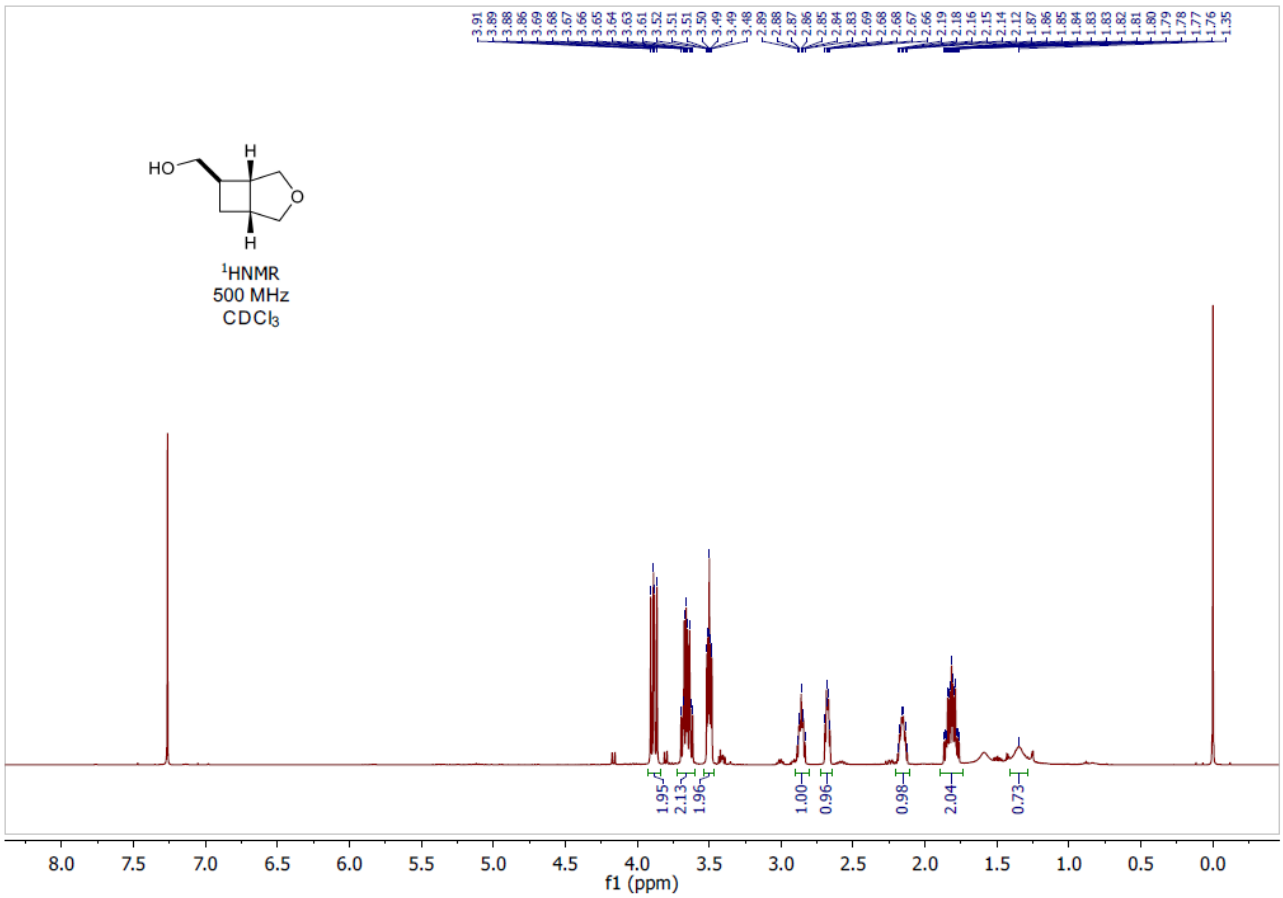

173.03
172.51
64.28
52.57
52.52
45.50
37.44
35.32
27.12
21.73
H
CO2Me
CO2Me
H
13CNMR
126 MHz
CDCl3
f1 (ppm)

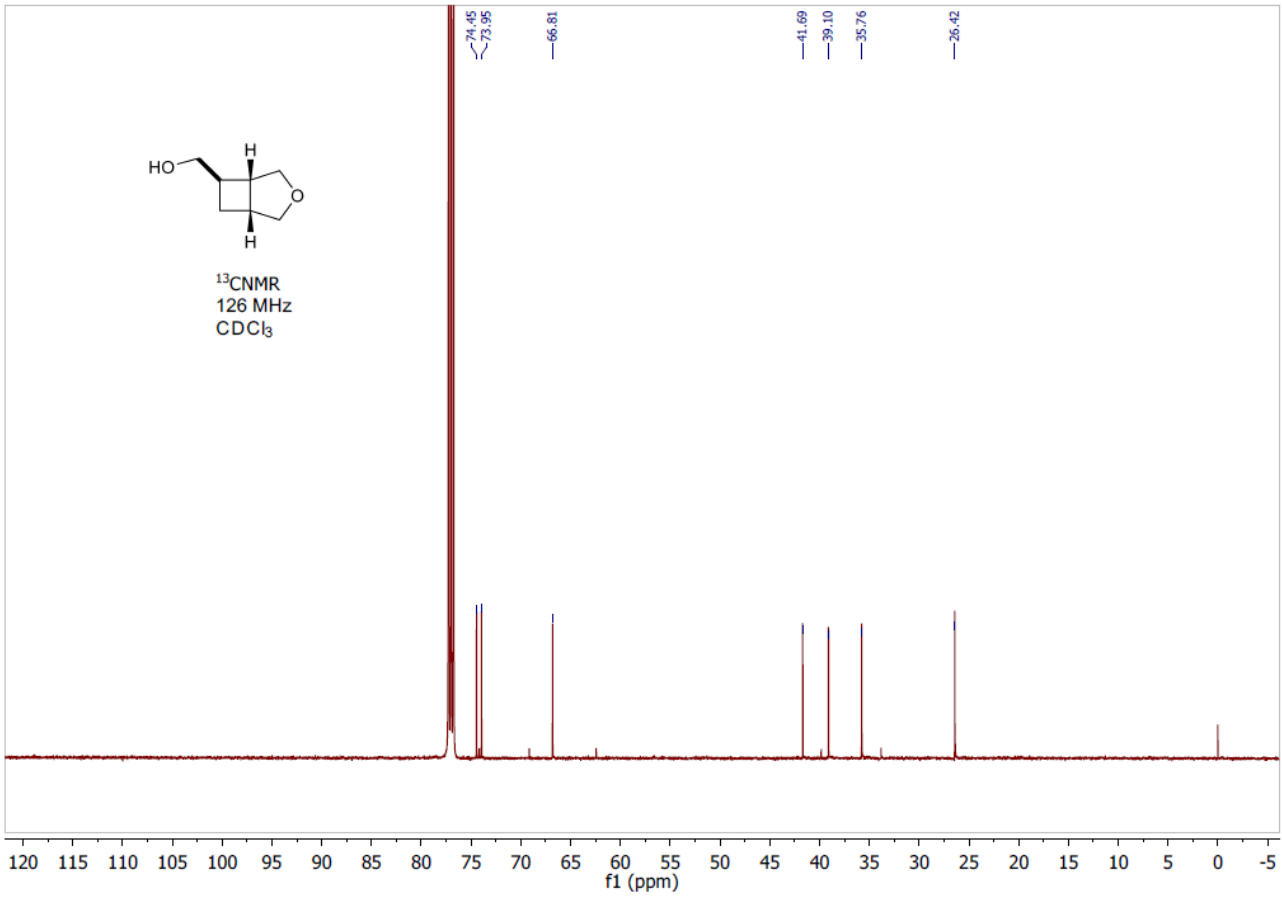

CO2Me
CO2Me
1HNMR
500 MHz
CDCl3
3.07
3.00
1.97
2.03
2.08
2.05
2.12
f1 (ppm)

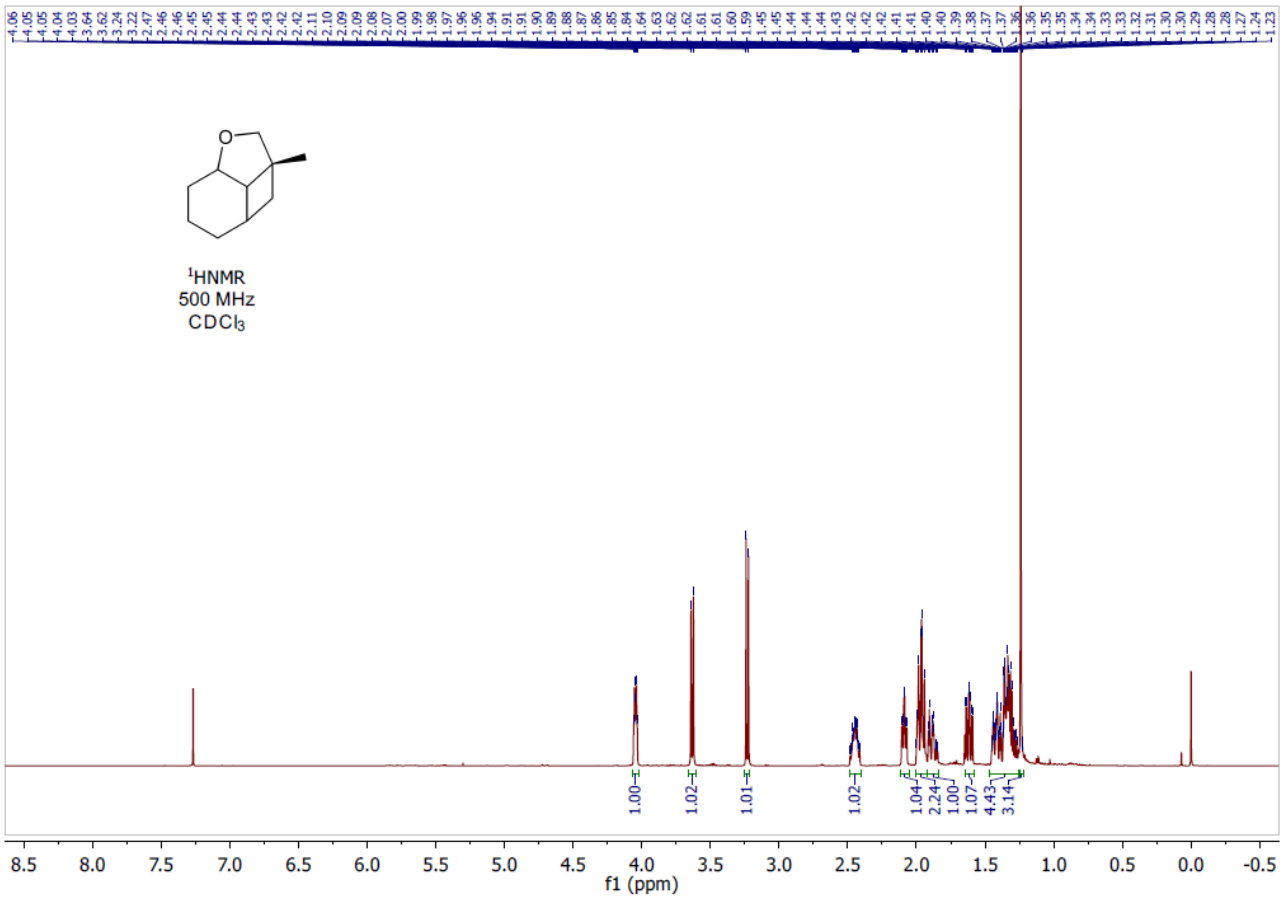

CO2Me
CO2Me
13CNMR
126 MHz
CDCl3
f1 (ppm)

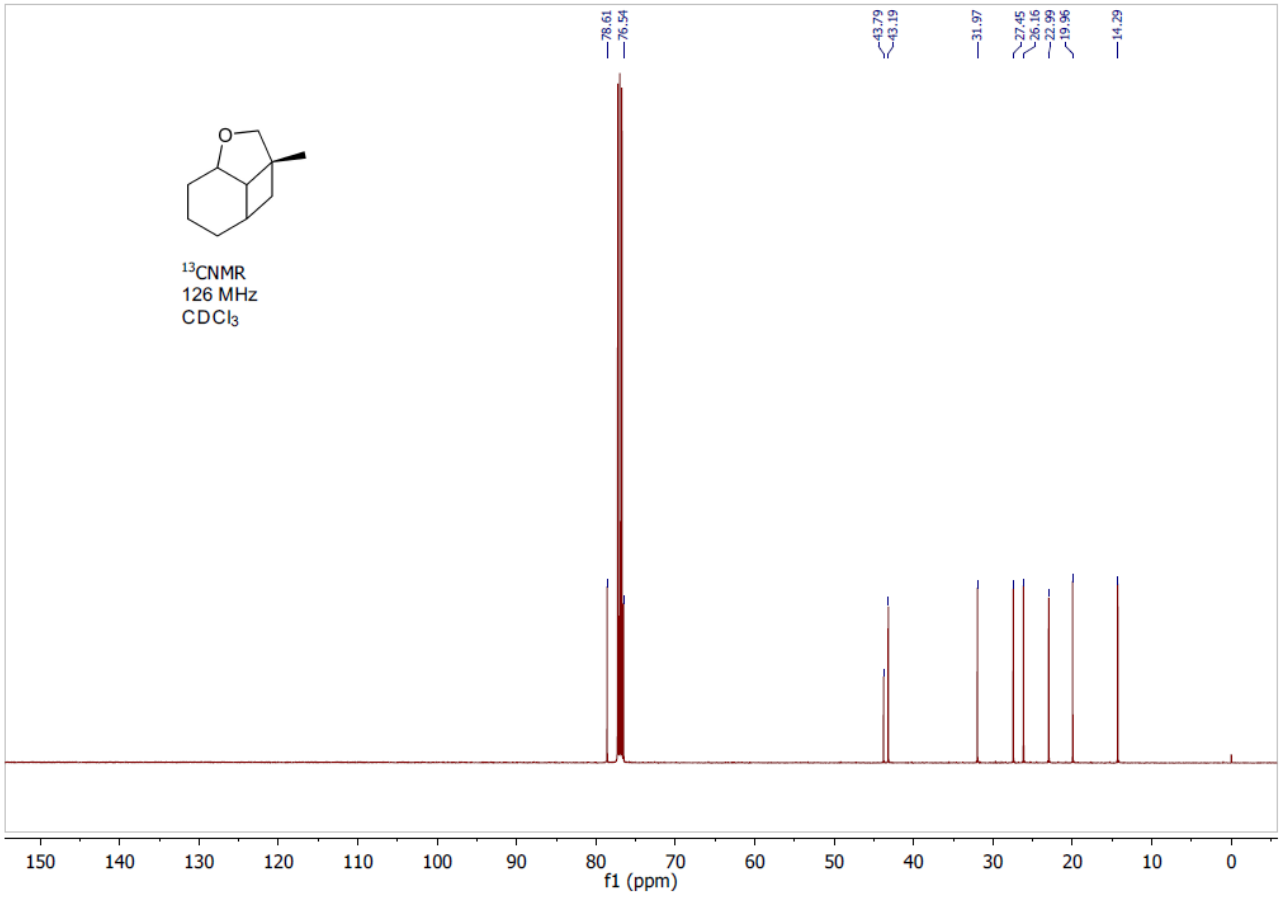

HO
H
H
O
^{1}HNMR
500 MHz
$CDCl_3$
1.03
1.00
2.05
1.92
0.98
0.99
1.01
1.04
0.92
1.03
f1 (ppm)

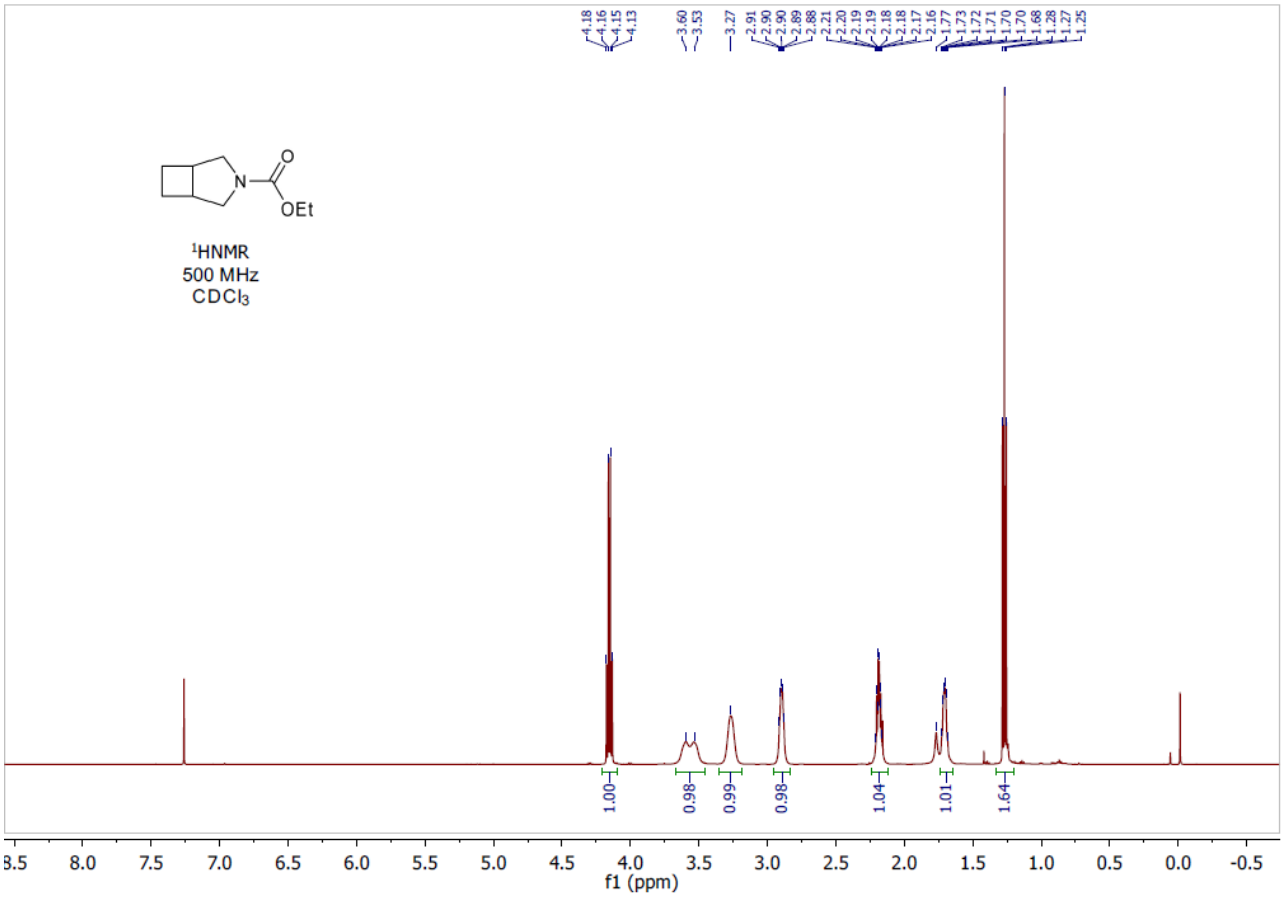

74.18
69.14
62.42
39.83
35.73
33.81
26.35
HO
H
H
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

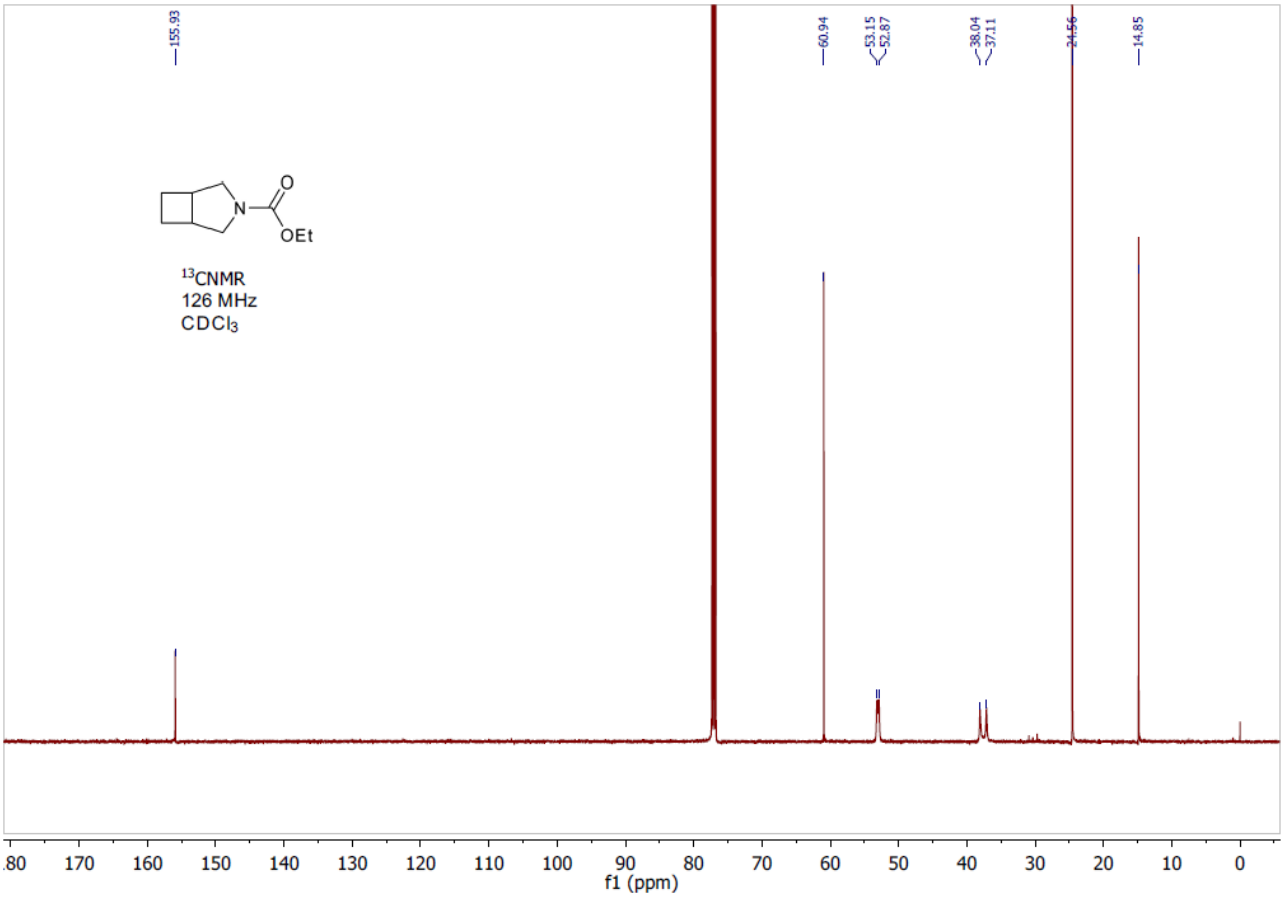

HO
H
O
H
^{1}HNMR
500 MHz
$CDCl_3$
1.95
2.13
1.96
1.00
0.96
0.98
2.04
0.73
f1 (ppm)

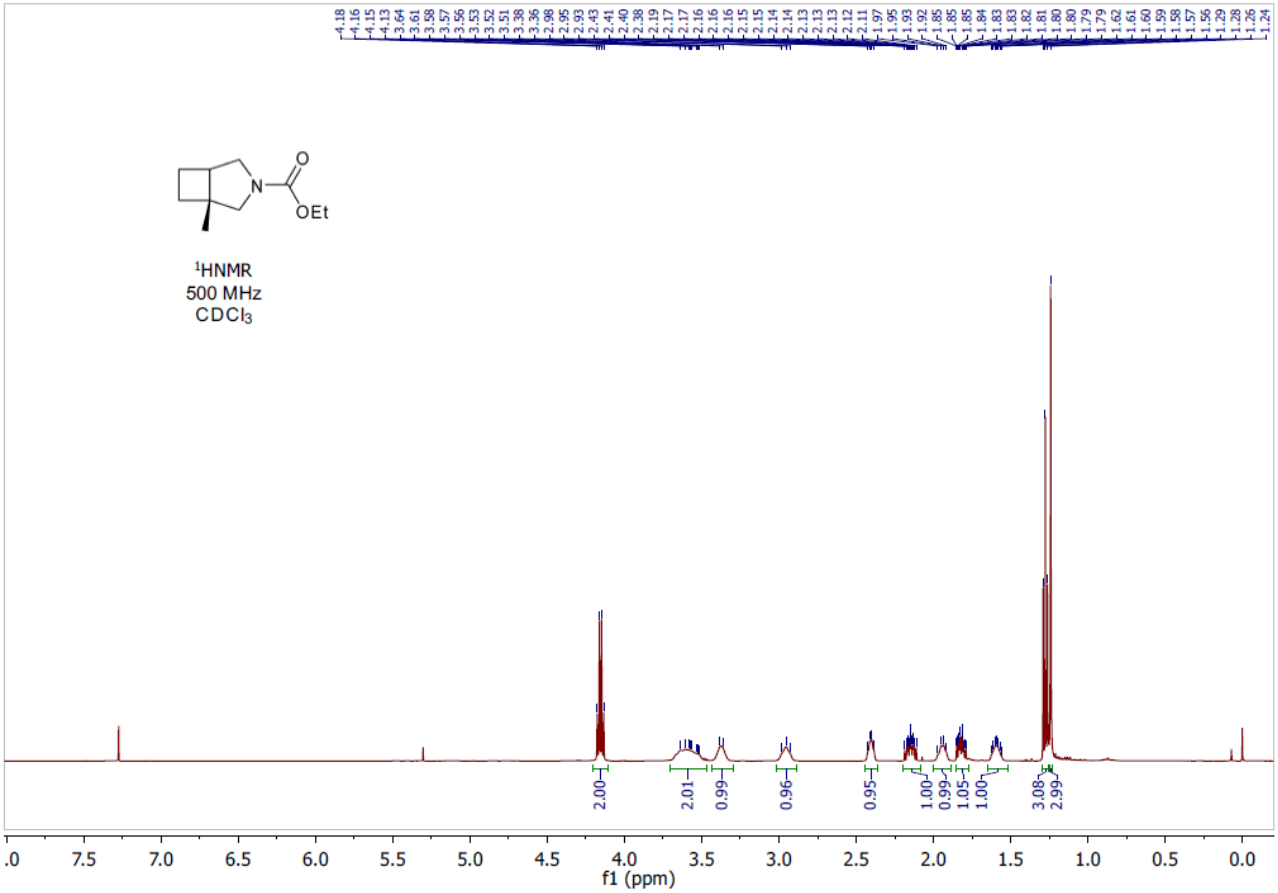

HO
H
O
H
^{13}CNMR
126 MHz
$CDCl_3$
74.45
73.95
66.81
41.69
39.10
35.76
26.42
f1 (ppm)

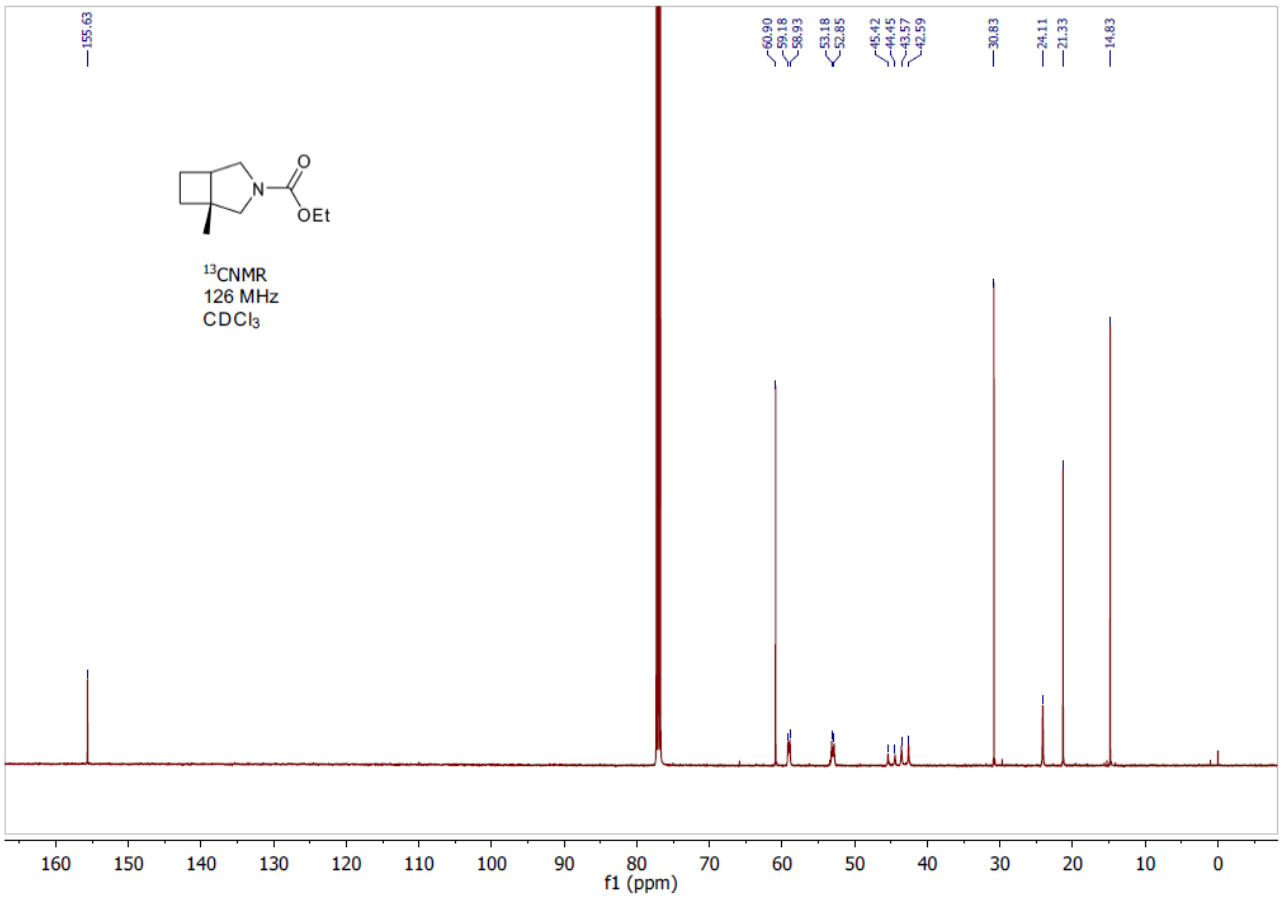

^{1}HNMR
500 MHz
$CDCl_3$
1.00
1.02
1.01
1.02
1.04
2.24
1.00
1.07
4.43
3.14
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

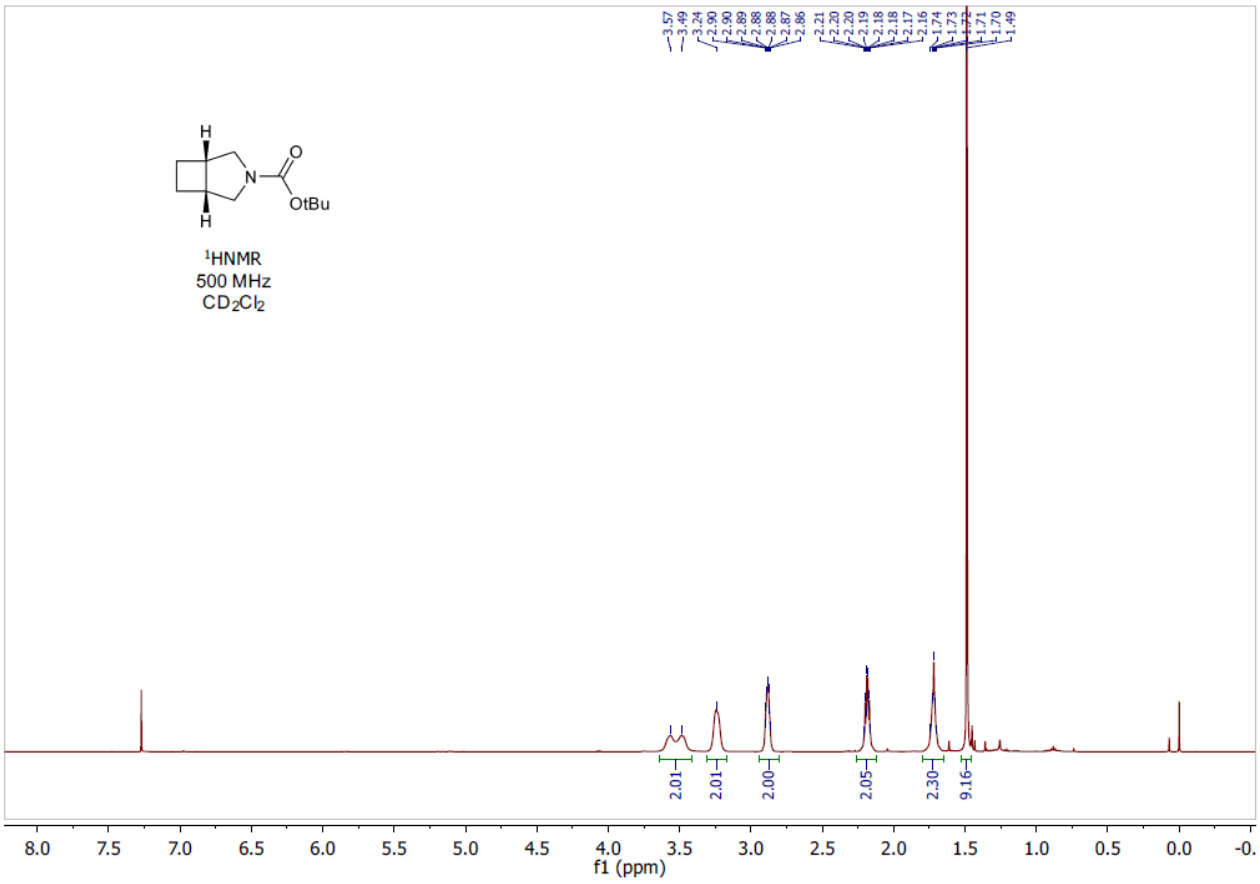

^{13}CNMR
126 MHz
$CDCl_3$
78.61
76.54
43.79
43.19
31.97
27.45
26.16
22.99
19.96
14.29
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

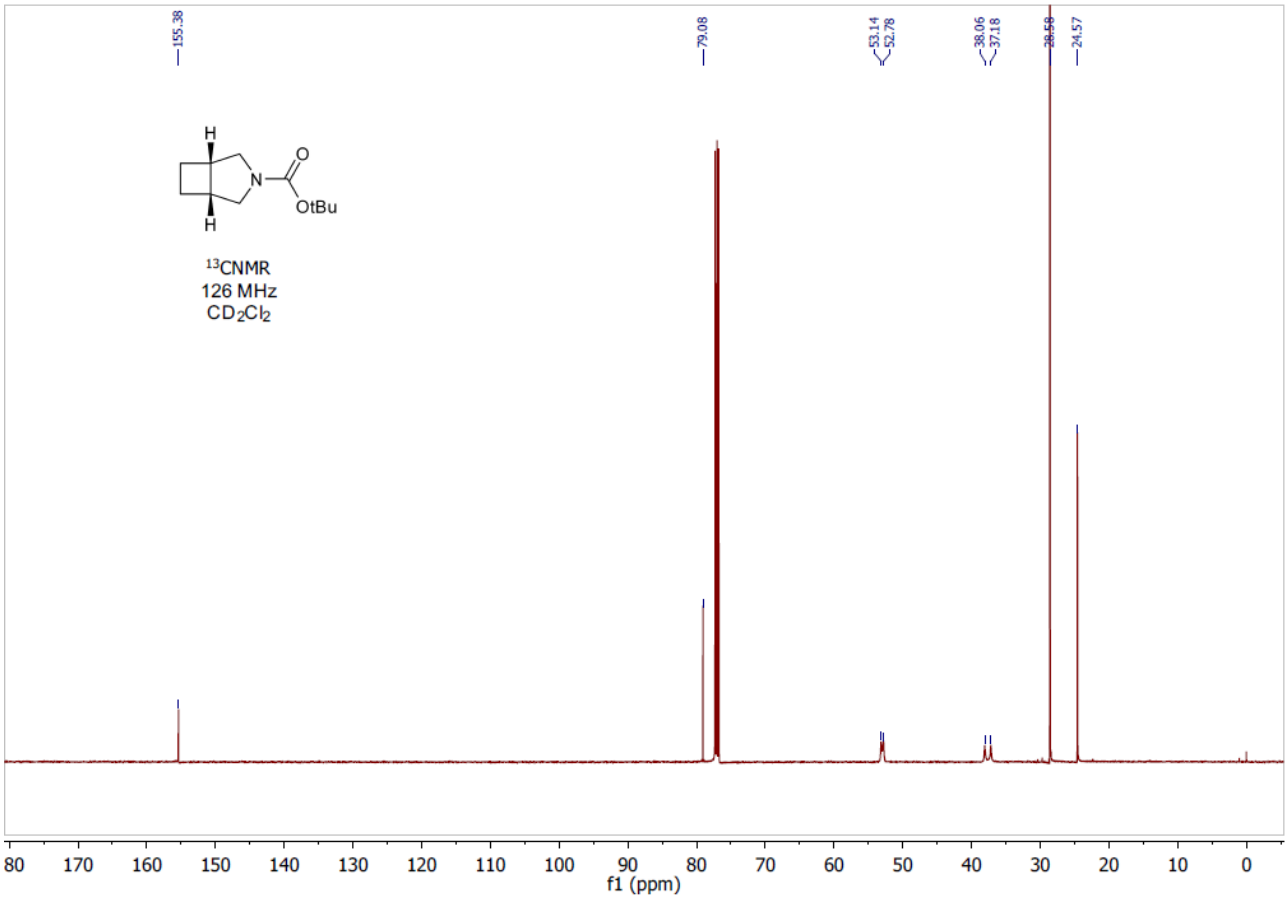

4.18
4.16
4.15
4.13
3.60
3.53
3.27
2.91
2.90
2.90
2.89
2.88
2.21
2.20
2.19
2.19
2.18
2.18
2.17
2.16
1.77
1.73
1.72
1.71
1.70
1.70
1.68
1.28
1.27
1.25
N
O
OEt
1HNMR
500 MHz
CDCl3
1.00
0.98
0.99
0.98
1.04
1.01
1.64
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

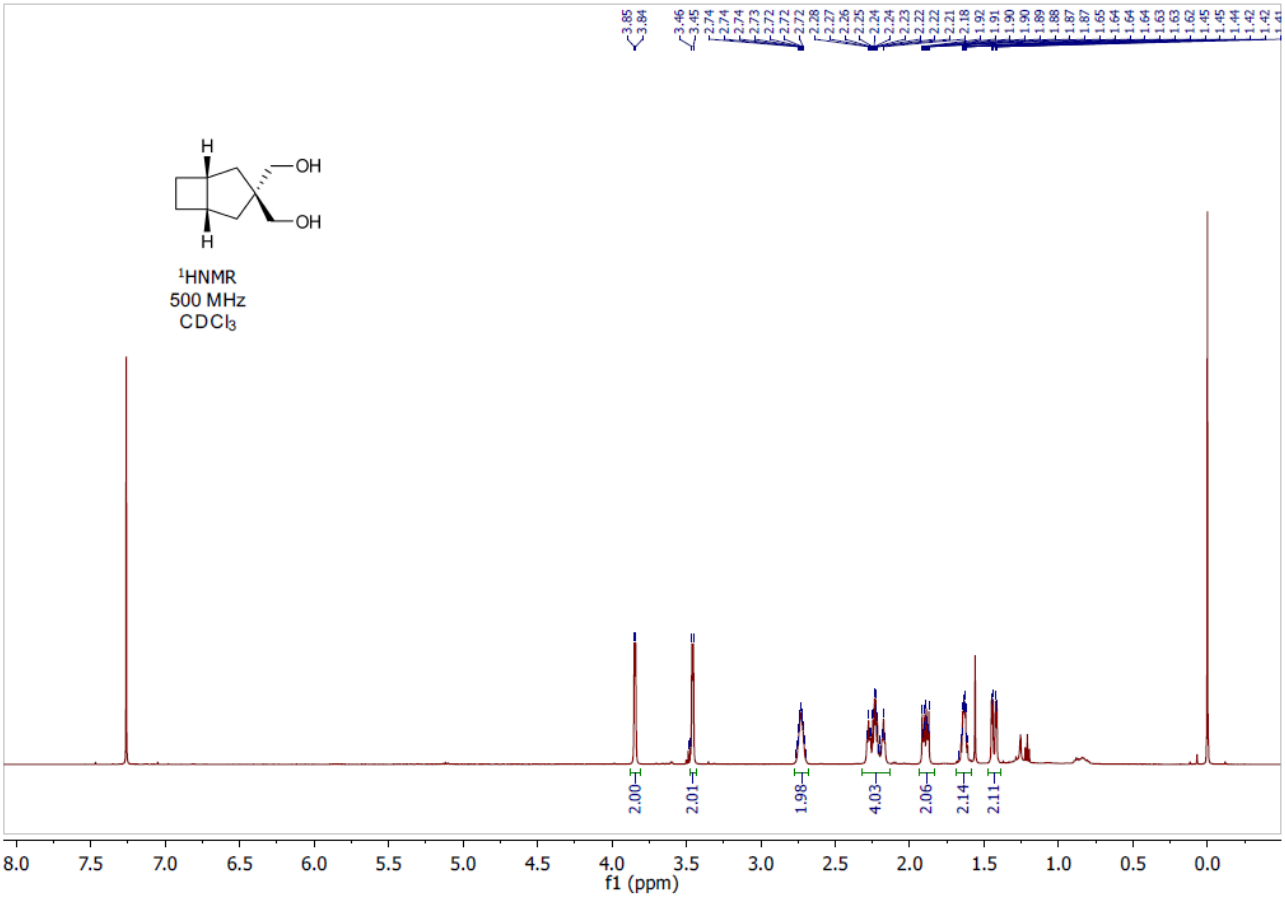

155.93
60.94
53.15
52.87
38.04
37.11
24.66
14.85
N
O
OEt
13CNMR
126 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

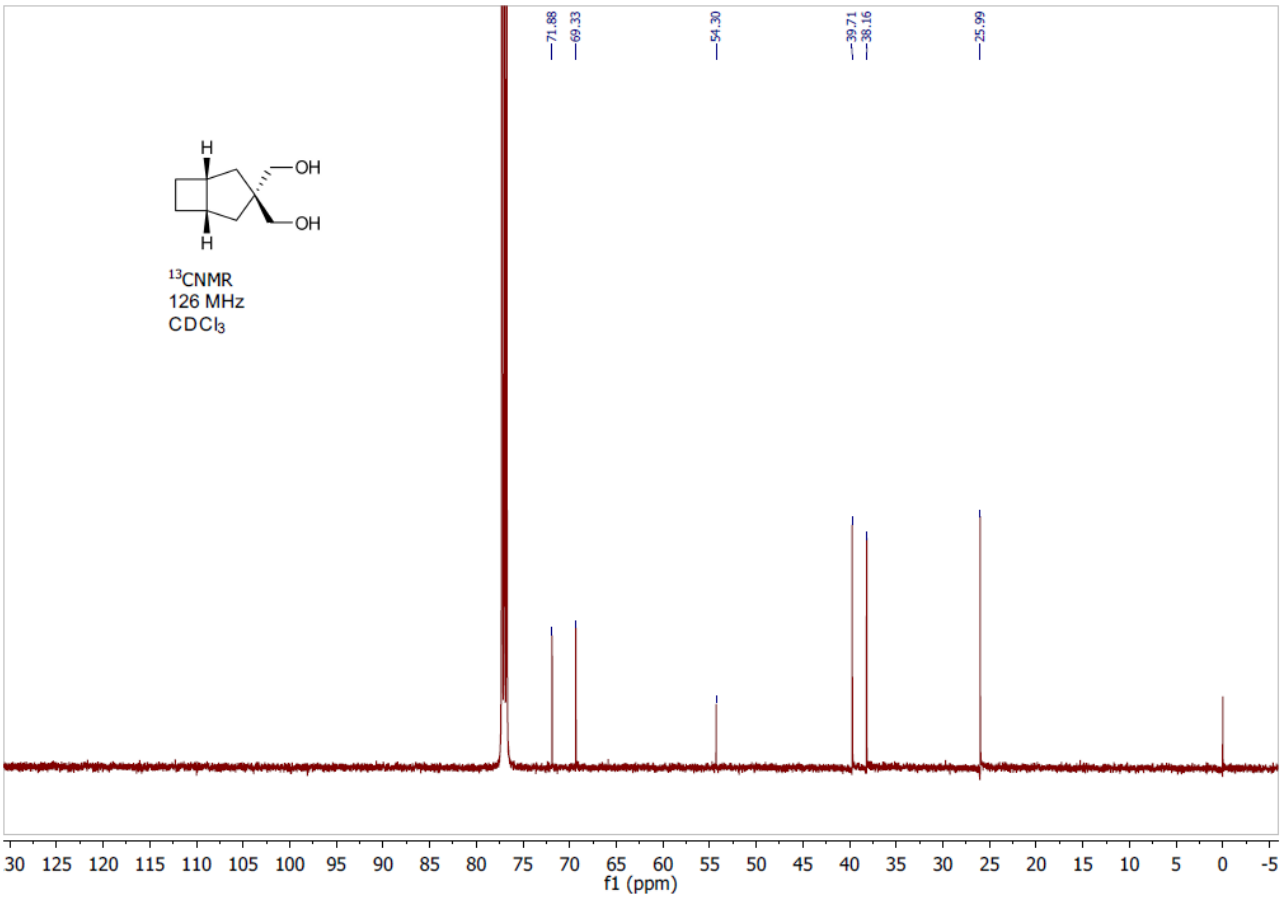

OEt
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

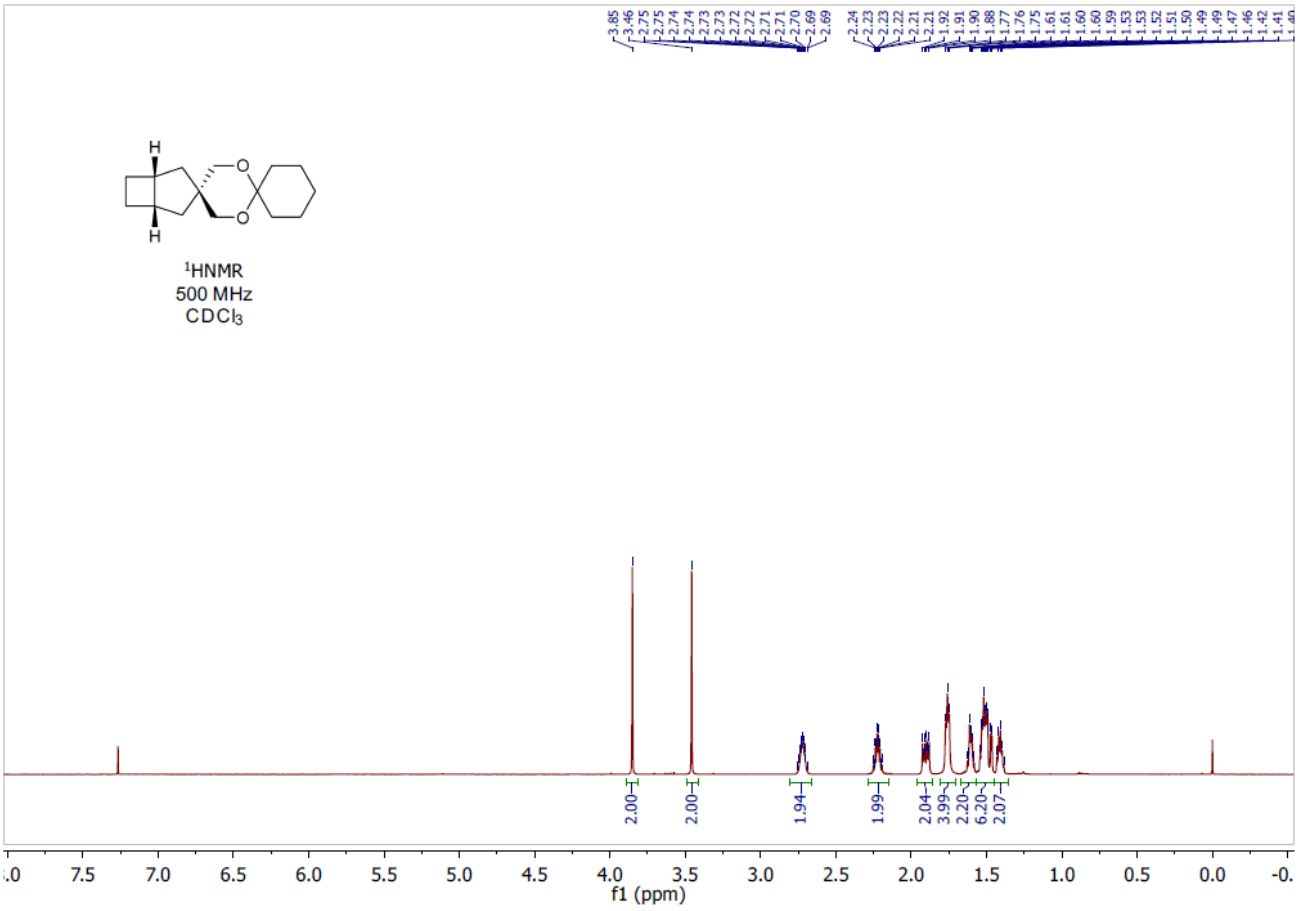

OEt
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

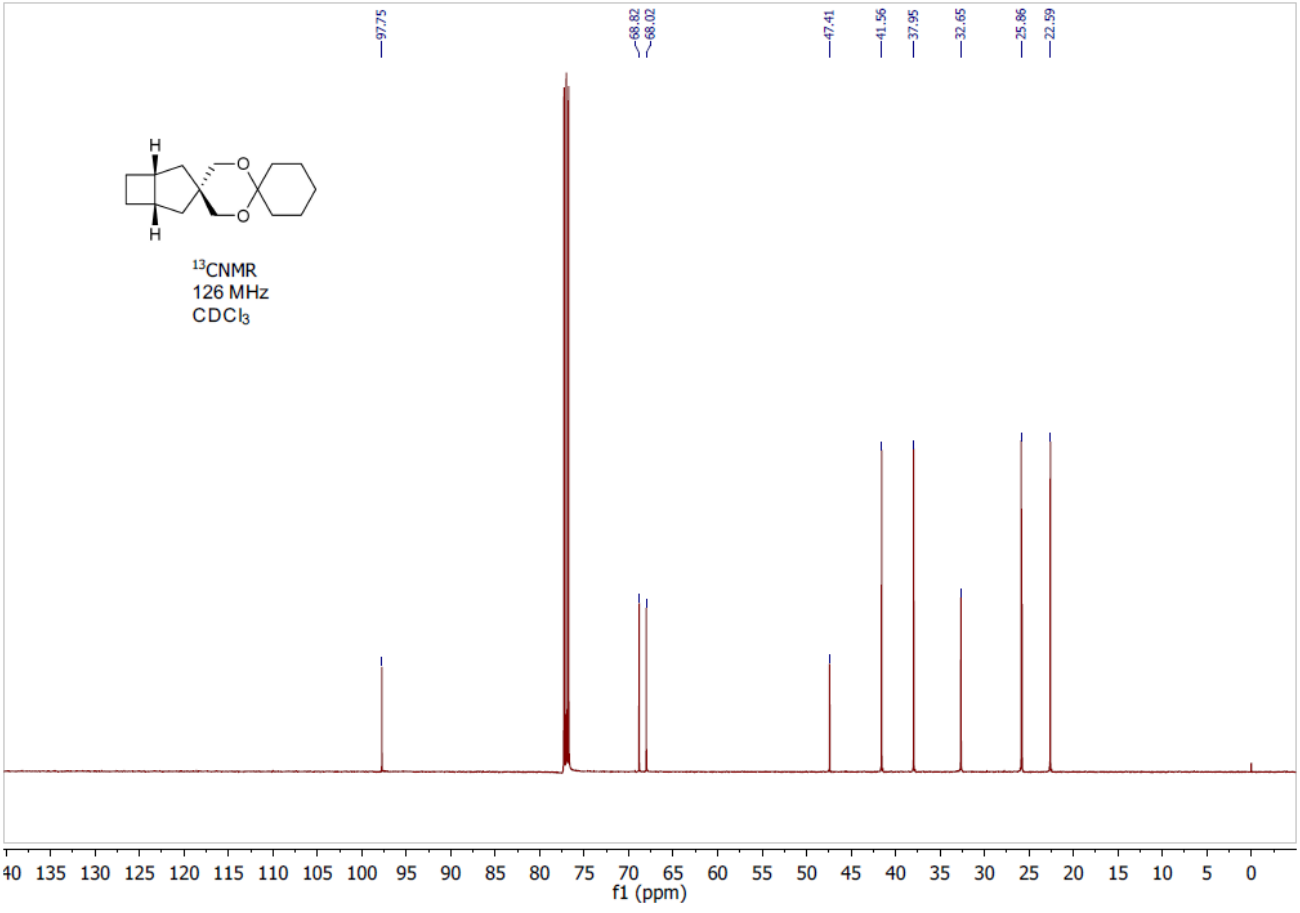

H
N
O
OtBu
H
^{1}HNMR
500 MHz
CD_2Cl_2
3.57
3.49
3.24
2.90
2.89
2.88
2.87
2.86
2.21
2.20
2.19
2.18
2.17
2.16
1.74
1.73
1.72
1.71
1.70
1.49
2.01
2.01
2.00
2.05
2.30
9.16
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

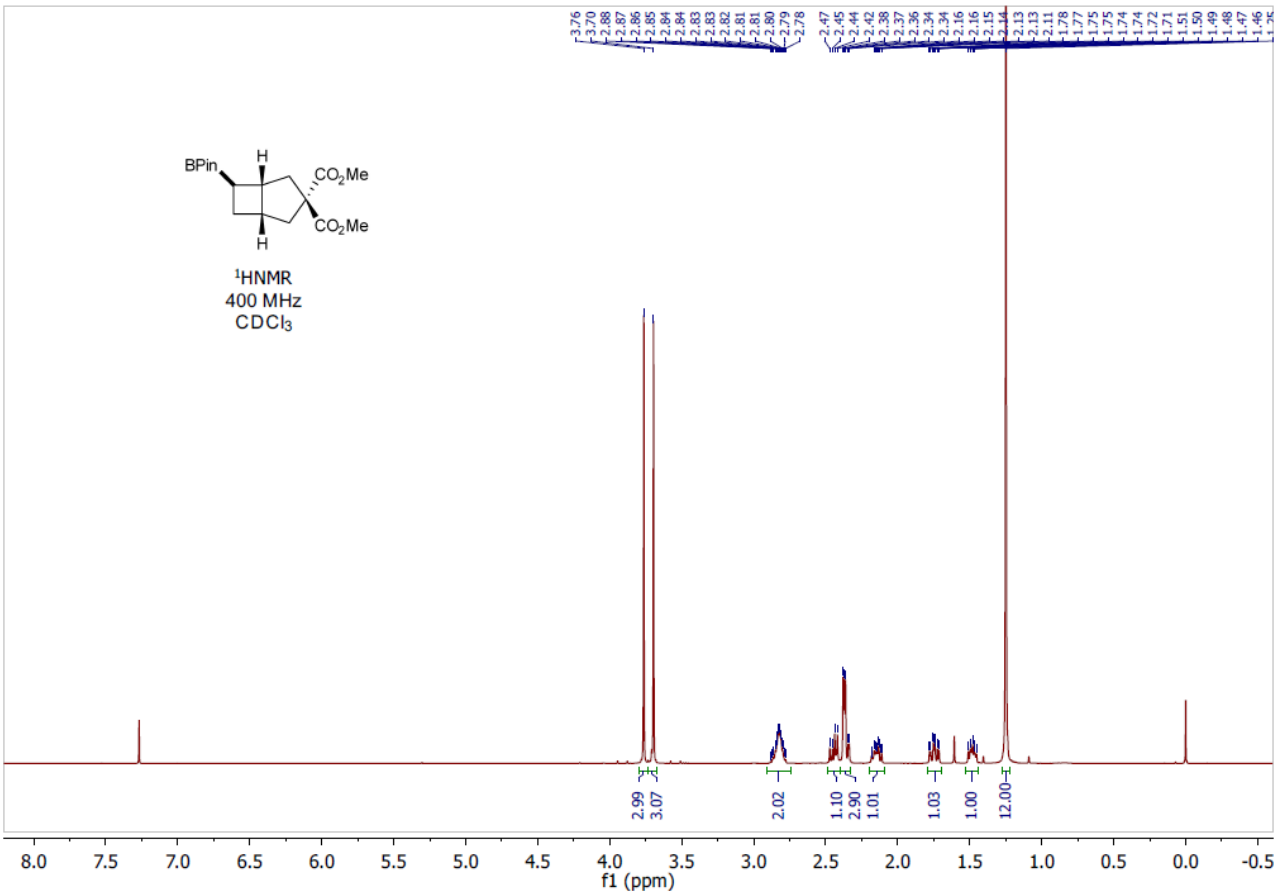

155.38
79.08
53.14
52.78
38.06
37.18
28.58
24.57
H
N
O
OtBu
H
^{13}CNMR
126 MHz
CD_2Cl_2
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

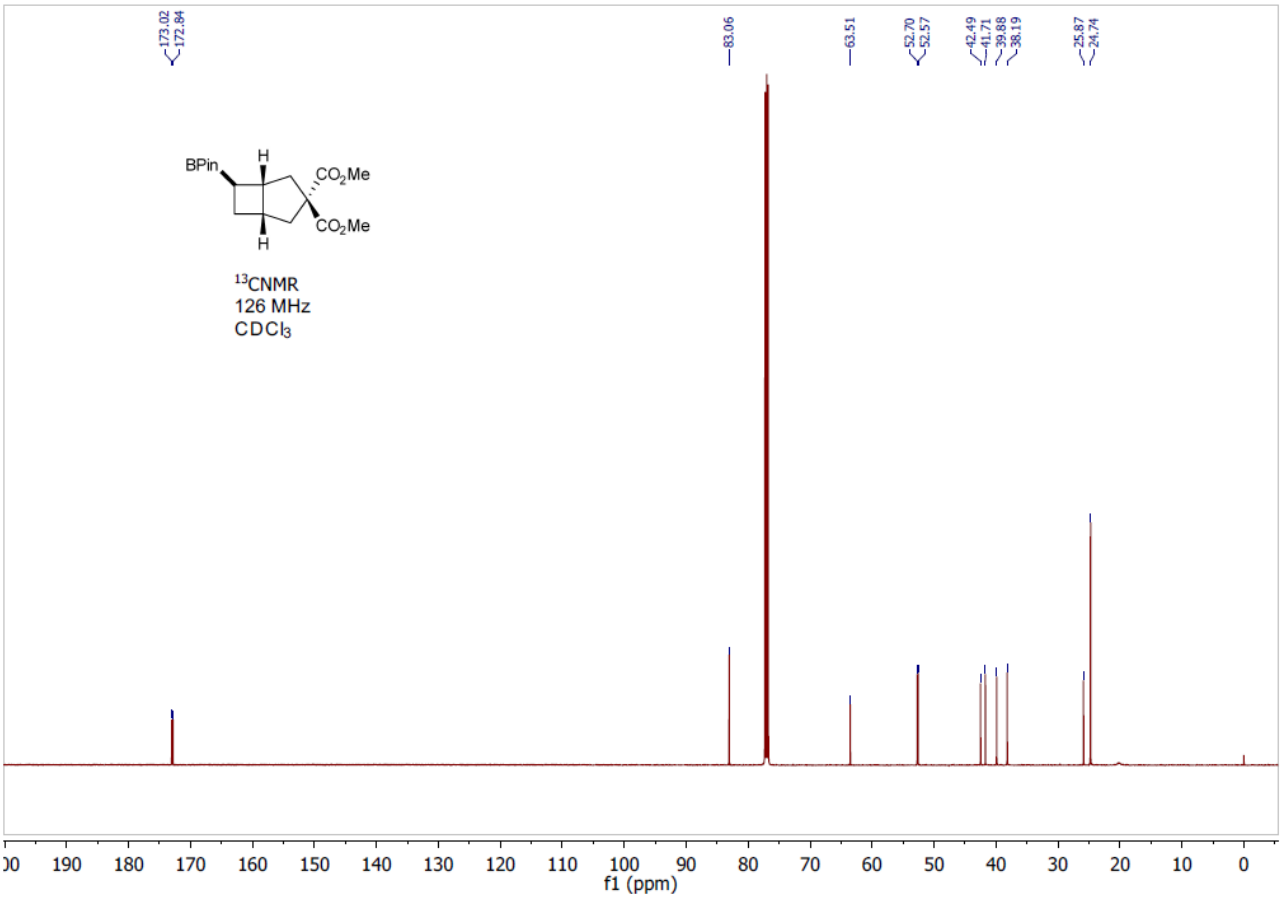

H
OH
OH
H
^{1}HNMR
500 MHz
$CDCl_3$
3.85
3.84
3.46
3.45
2.74
2.74
2.74
2.74
2.73
2.72
2.72
2.72
2.28
2.27
2.26
2.25
2.24
2.24
2.23
2.22
2.22
2.21
2.18
1.92
1.91
1.90
1.90
1.89
1.88
1.87
1.87
1.65
1.64
1.64
1.64
1.63
1.63
1.62
1.45
1.45
1.44
1.42
1.42
1.41
2.00
2.01
1.98
4.03
2.06
2.14
2.11
8.0 7.5 7.0 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)

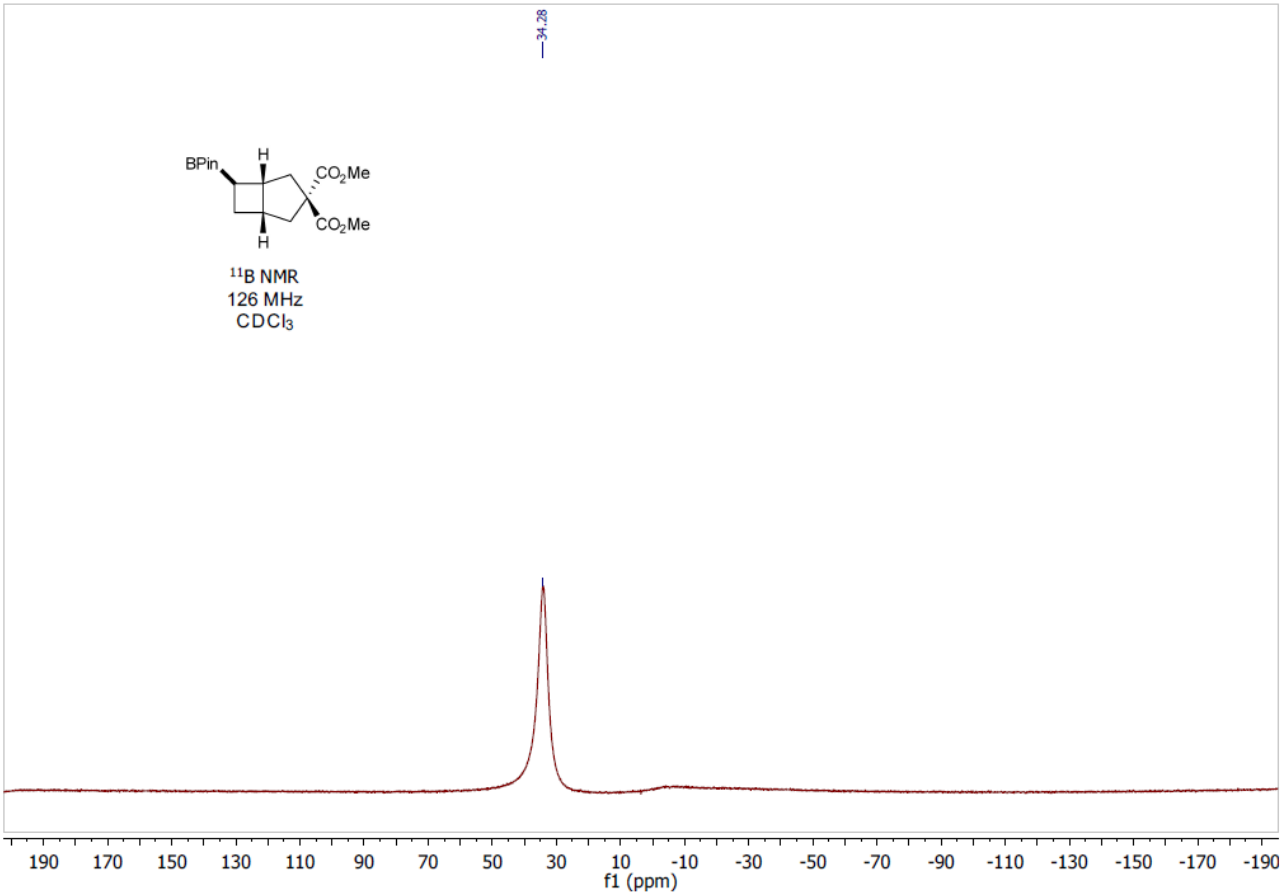

H
OH
OH
H
^{13}CNMR
126 MHz
$CDCl_3$
71.88
69.33
54.30
39.71
38.16
25.99
30 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5
f1 (ppm)

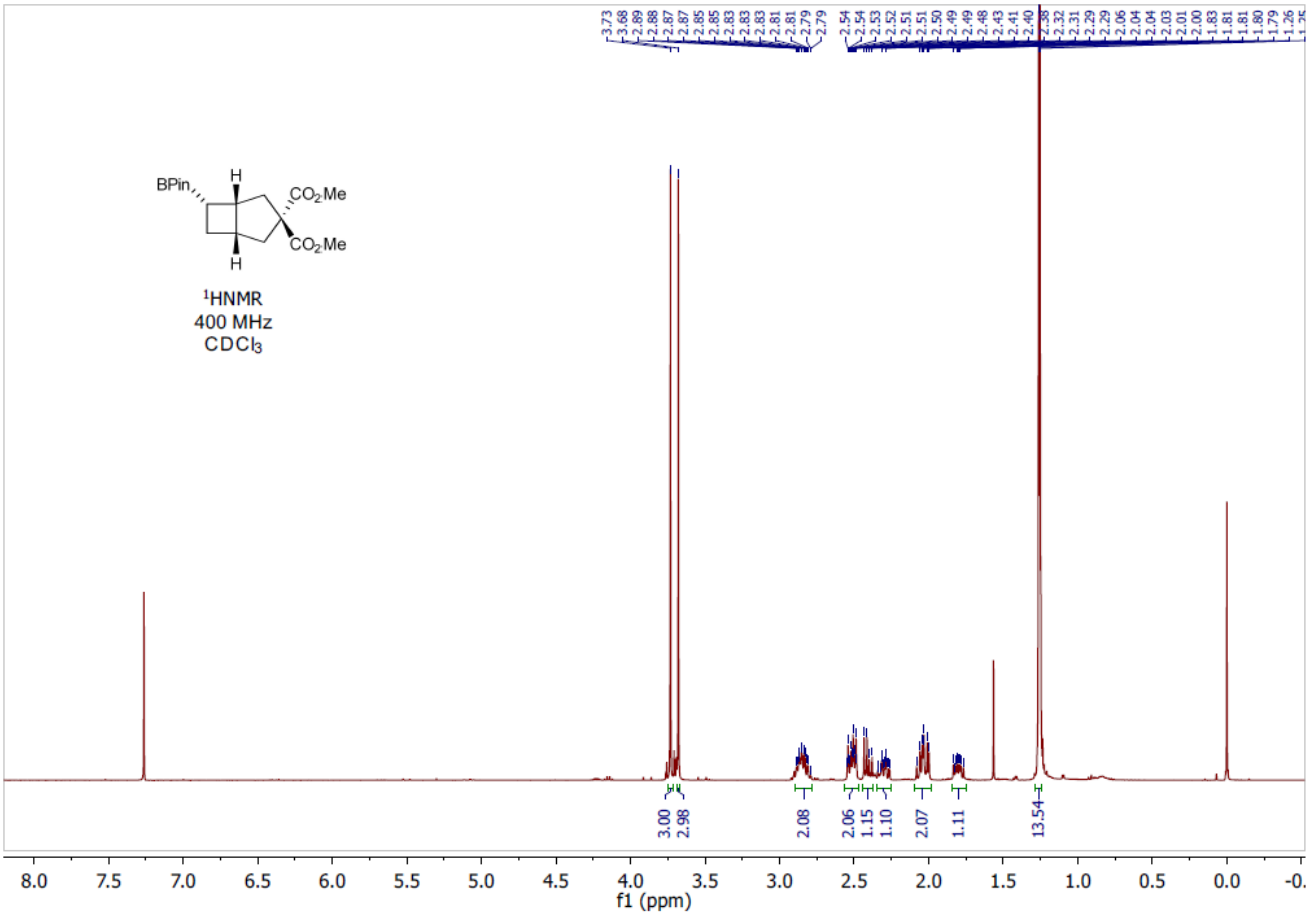

H
H
O
O
^{1}HNMR
500 MHz
$CDCl_3$
2.00
2.00
1.94
1.99
2.04
3.99
2.20
6.20
2.07
f1 (ppm)

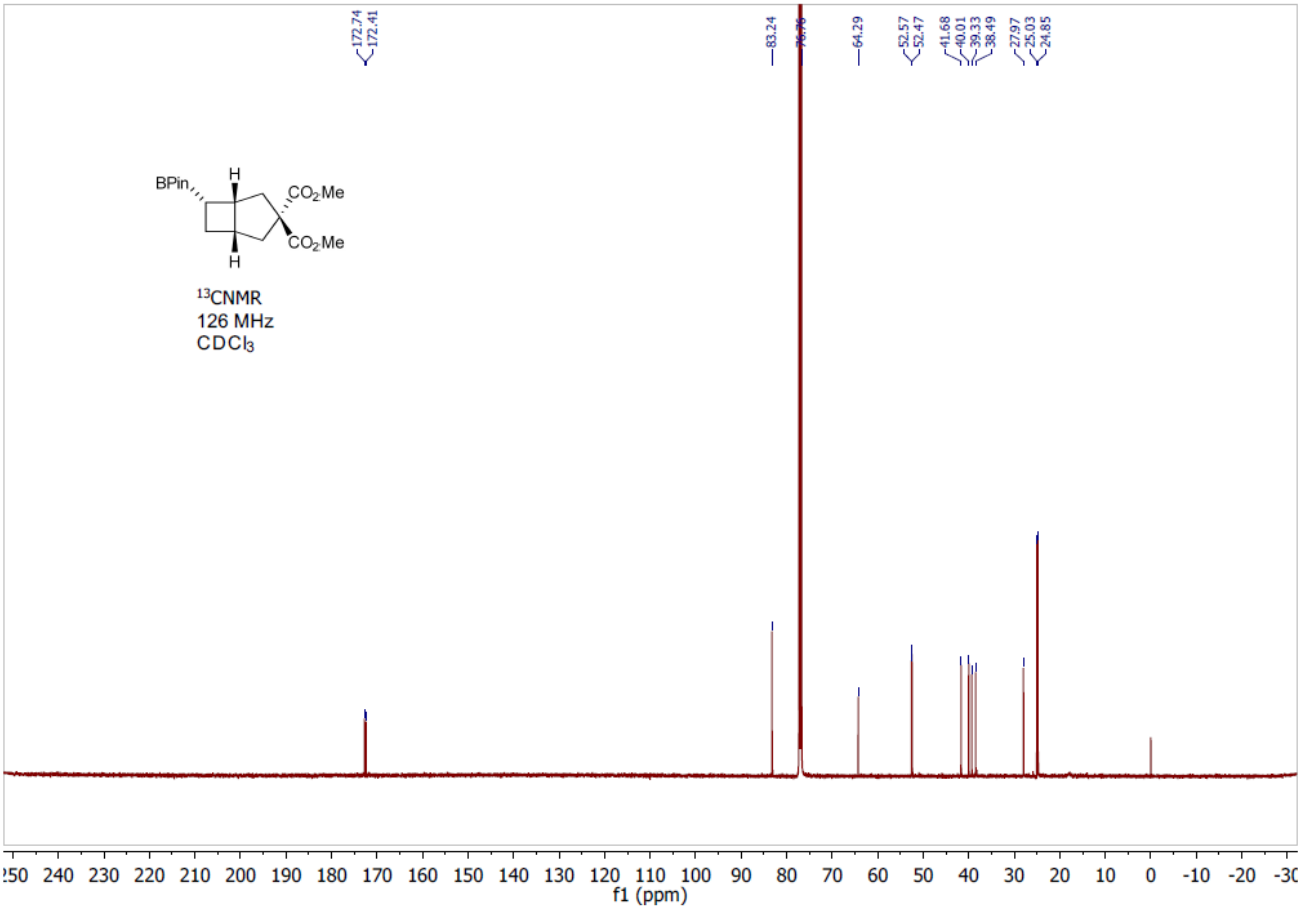

97.75
68.82
68.02
47.41
41.56
37.95
32.65
25.86
22.59
H
H
O
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

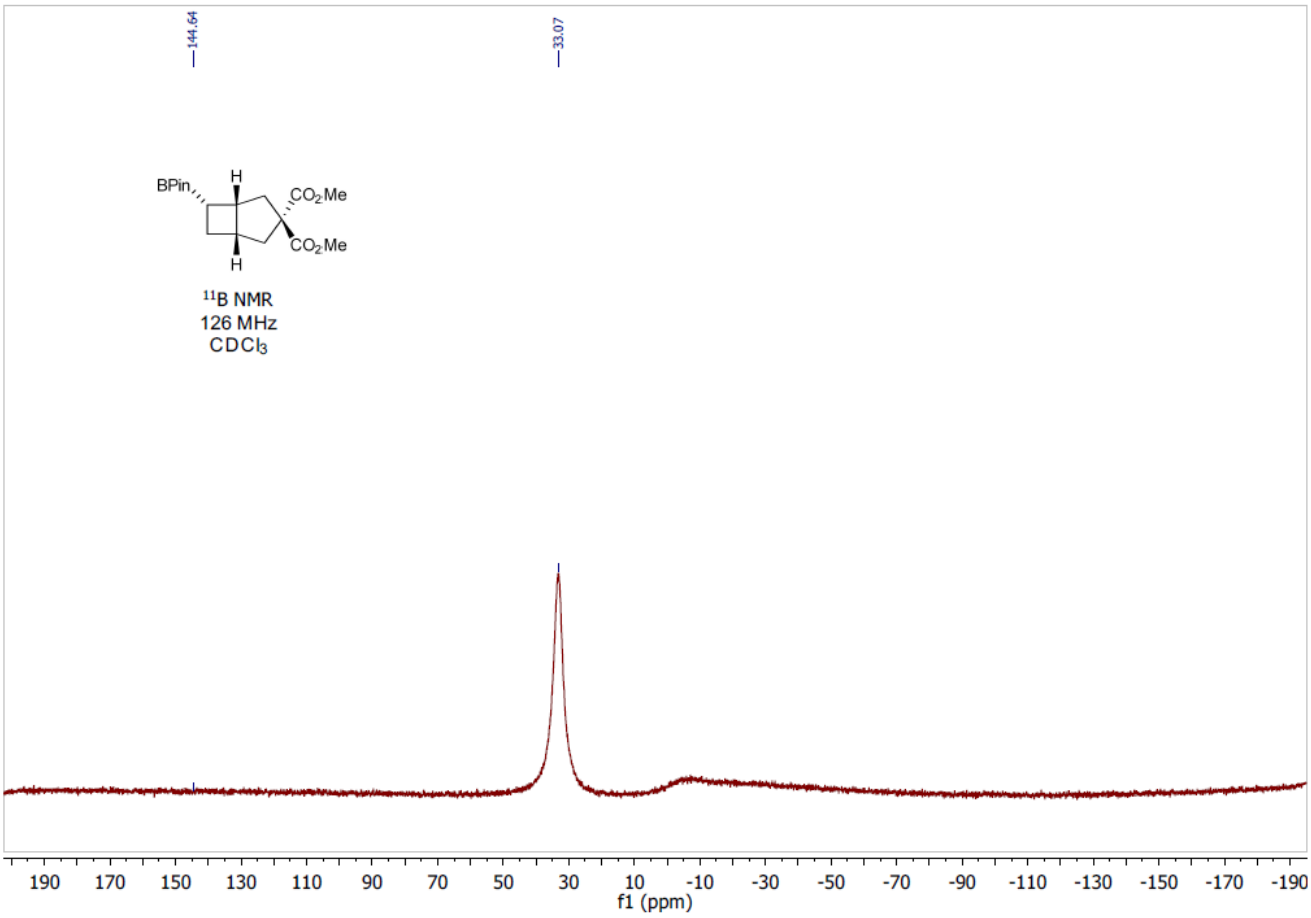

BPin
H
CO2Me
CO2Me
H
1HNMR
400 MHz
CDCl3
f1 (ppm)

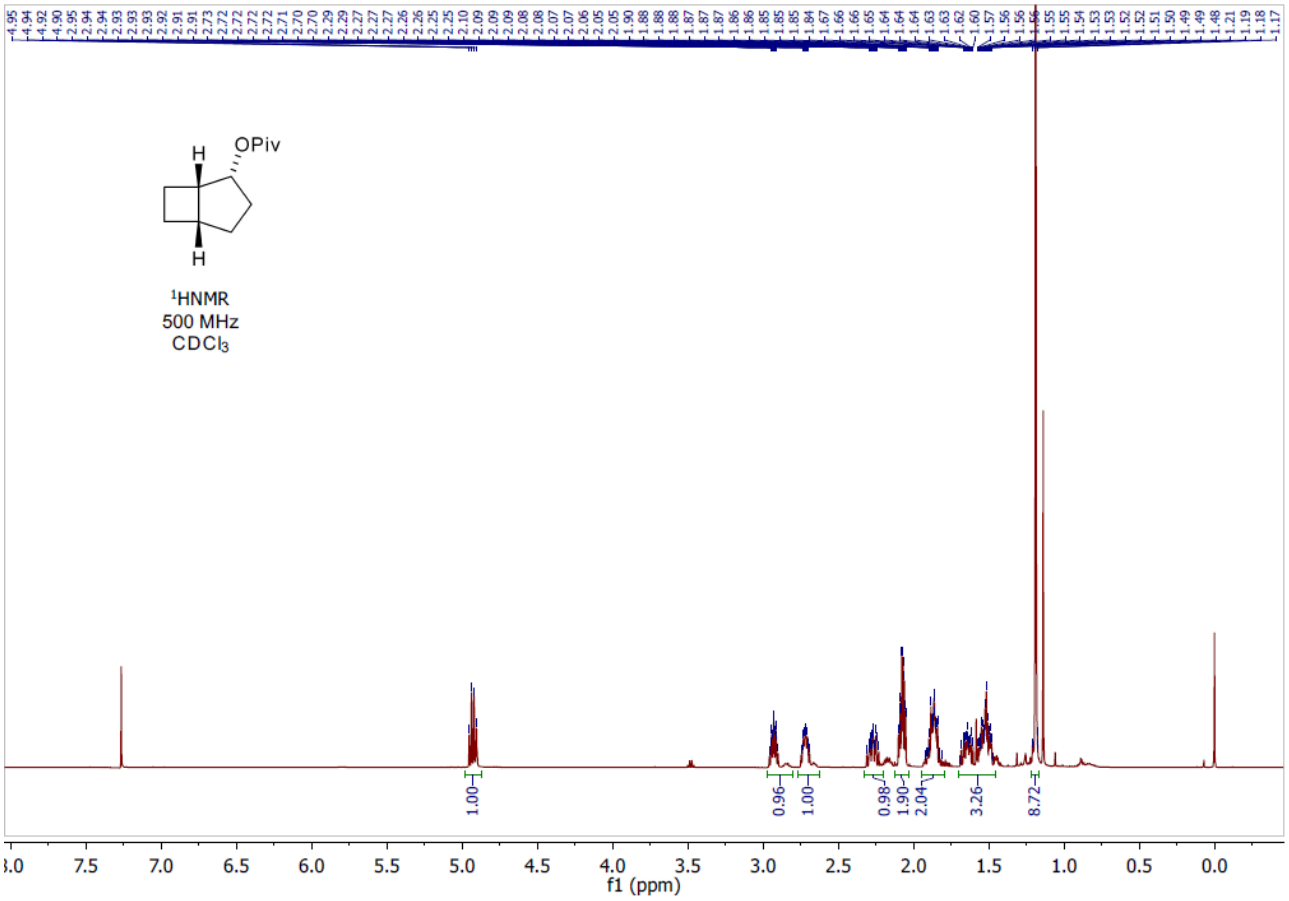

BPin
H
CO2Me
CO2Me
H
13CNMR
126 MHz
CDCl3
f1 (ppm)

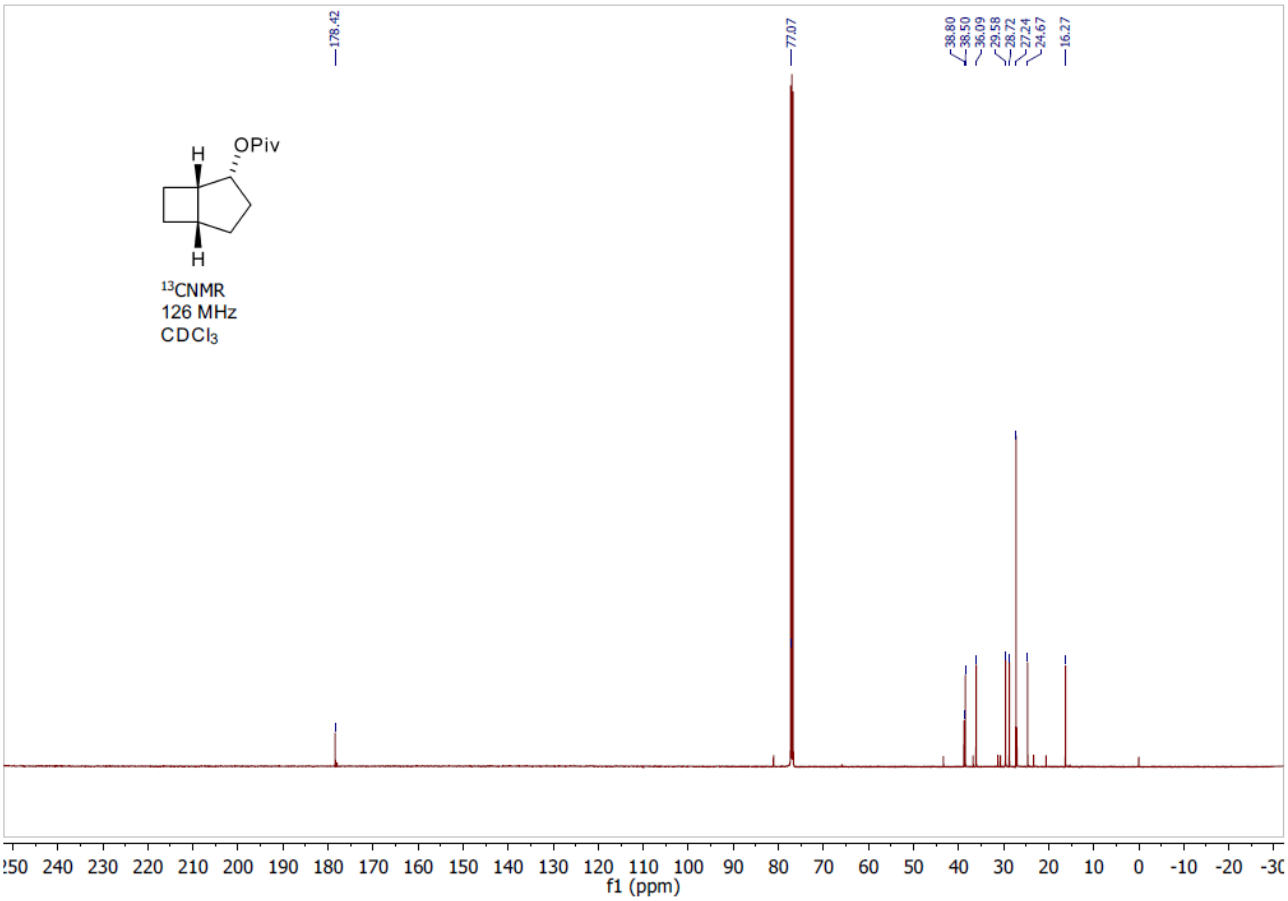

34.28
BPin
H
CO2Me
CO2Me
H
11B NMR
126 MHz
CDCl3
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

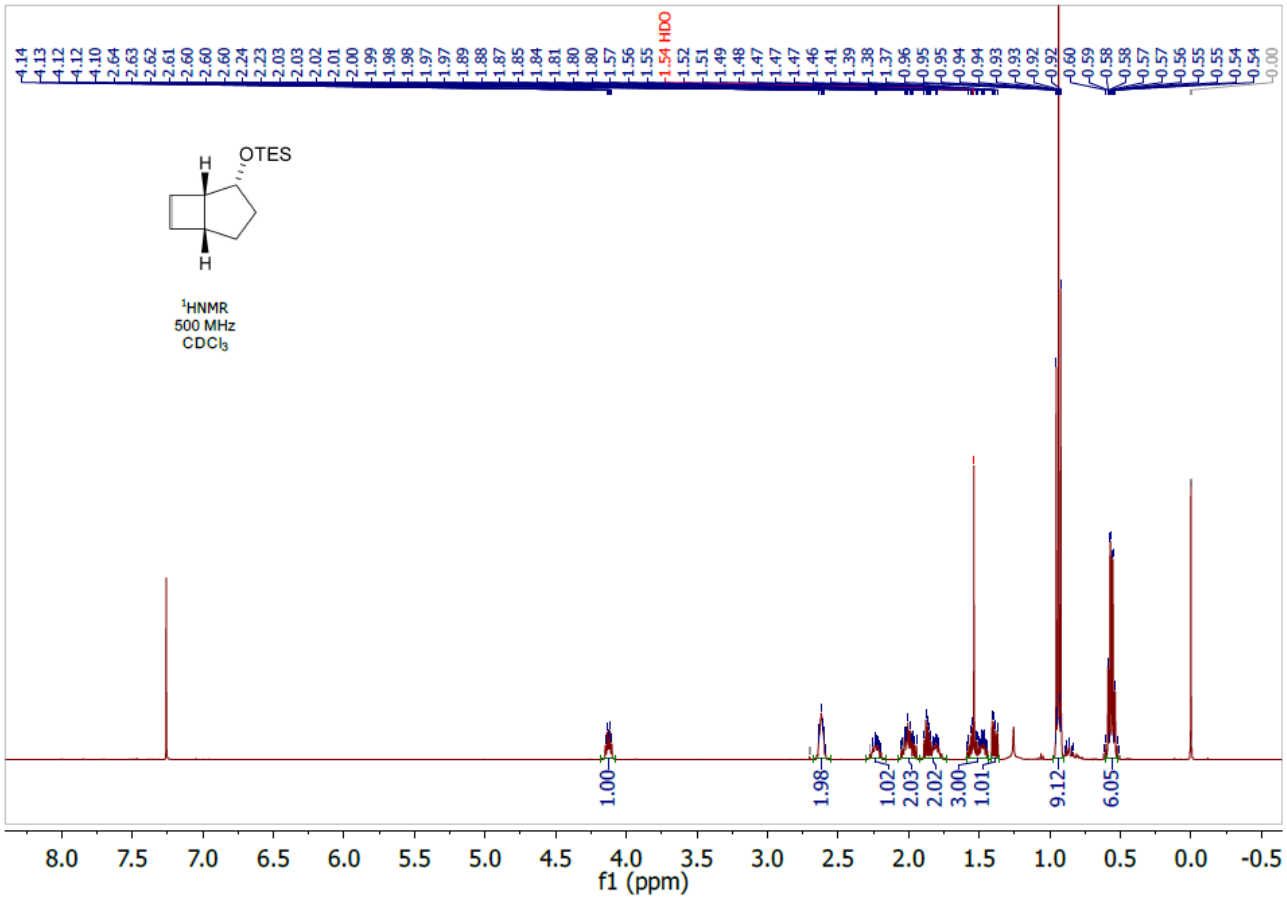

BPin
H
CO2Me
CO2Me
H
1HNMR
400 MHz
CDCl3
3.00
2.98
2.08
2.06
1.15
1.10
2.07
1.11
13.54
f1 (ppm)

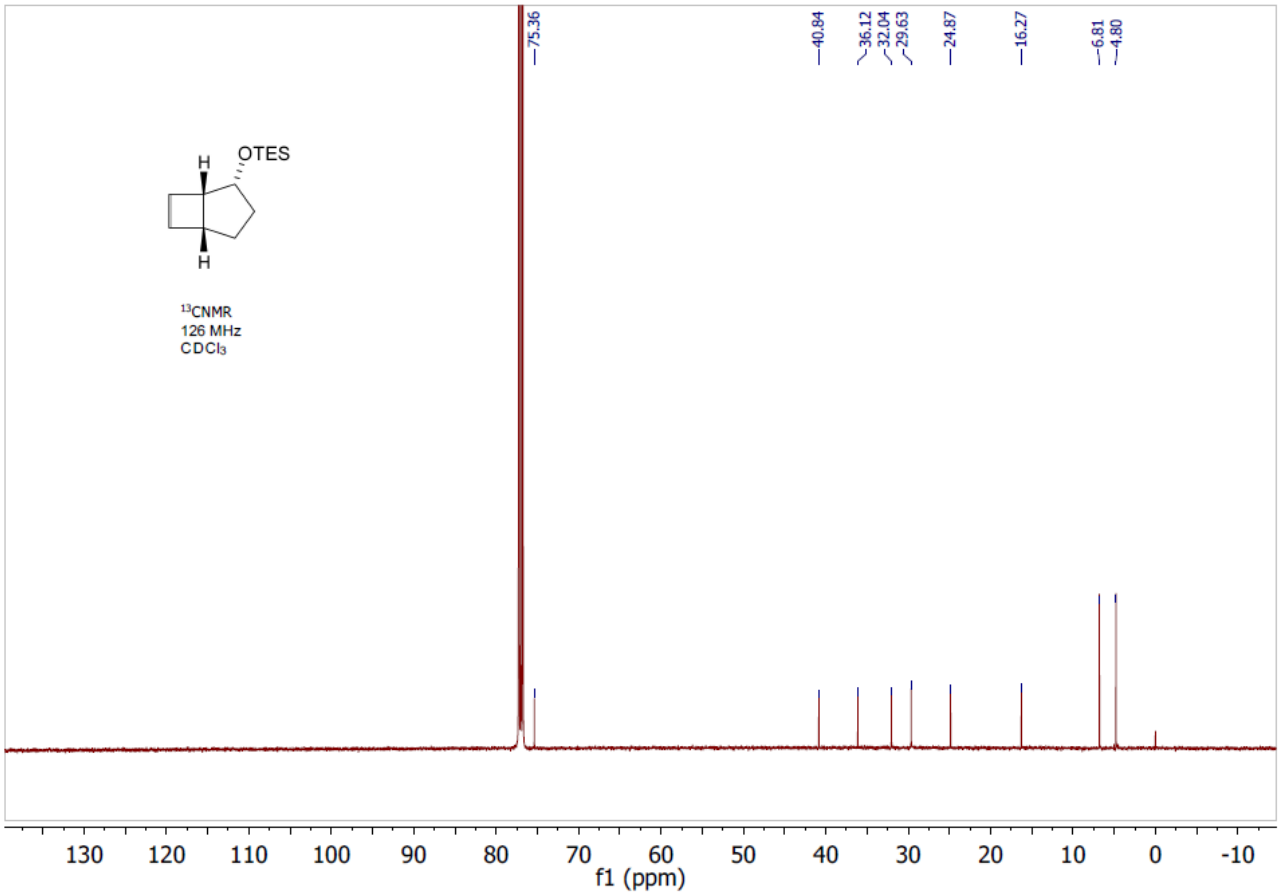

172.74
172.41
83.24
79.76
64.29
52.57
52.47
41.68
40.01
39.33
38.49
27.97
25.03
24.85
BPin
H
CO2Me
CO2Me
H
13CNMR
126 MHz
CDCl3
f1 (ppm)

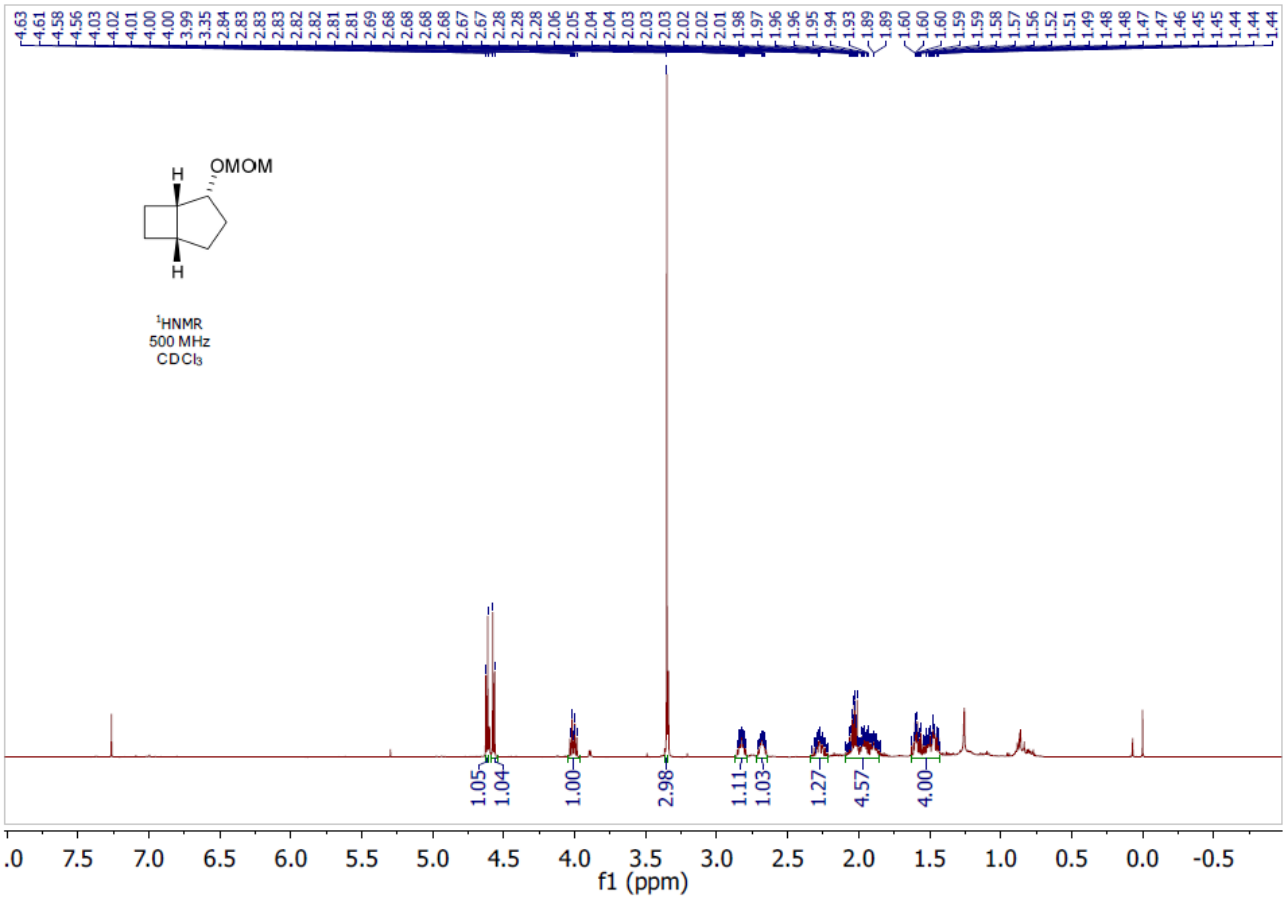

144.64
33.07
BPin
H
CO2Me
CO2Me
H
11B NMR
126 MHz
CDCl3
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

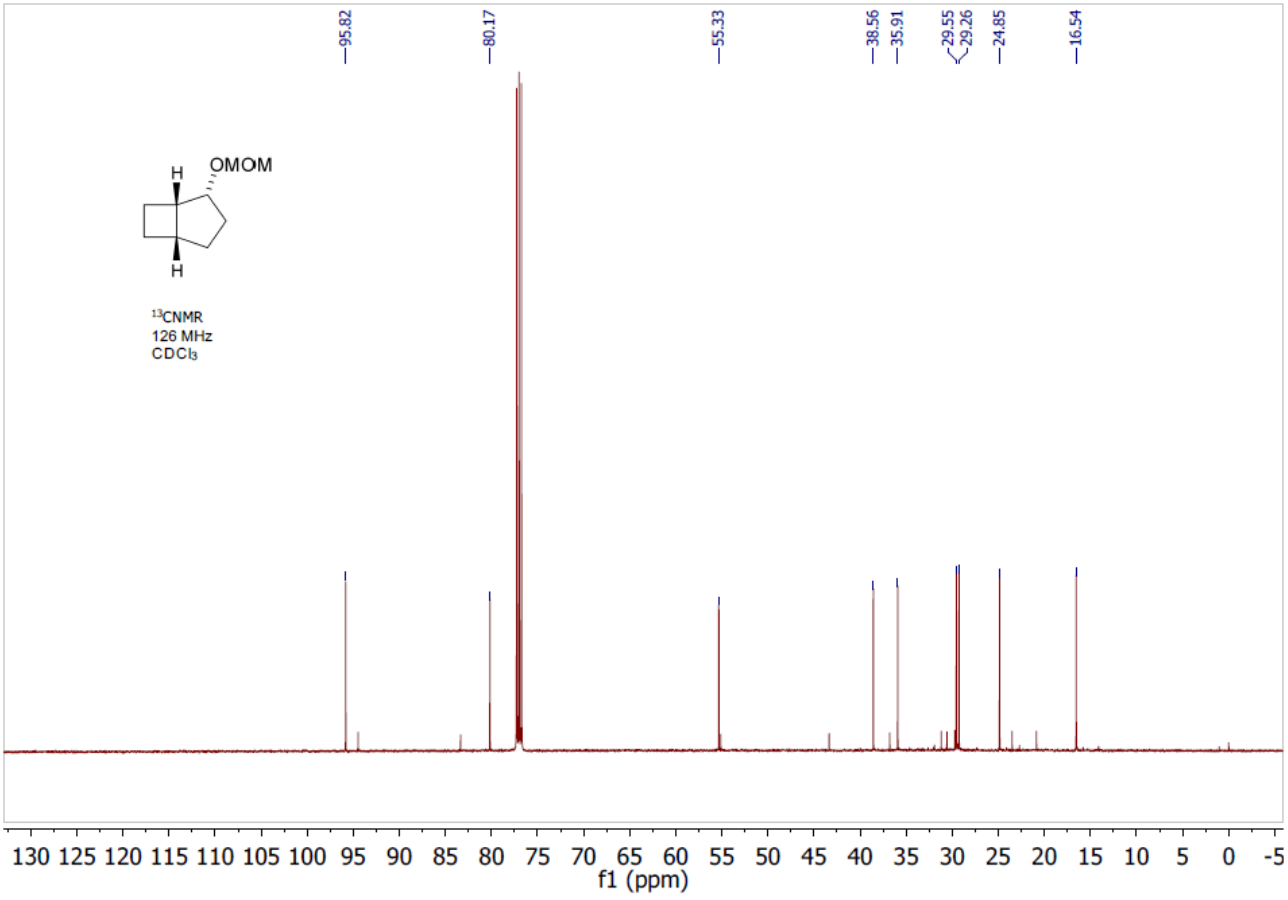

OPiv
H
H
^{1}HNMR
500 MHz
$CDCl_3$
1.00
0.96
1.00
0.98
1.90
2.04
3.26
8.72
f1 (ppm)

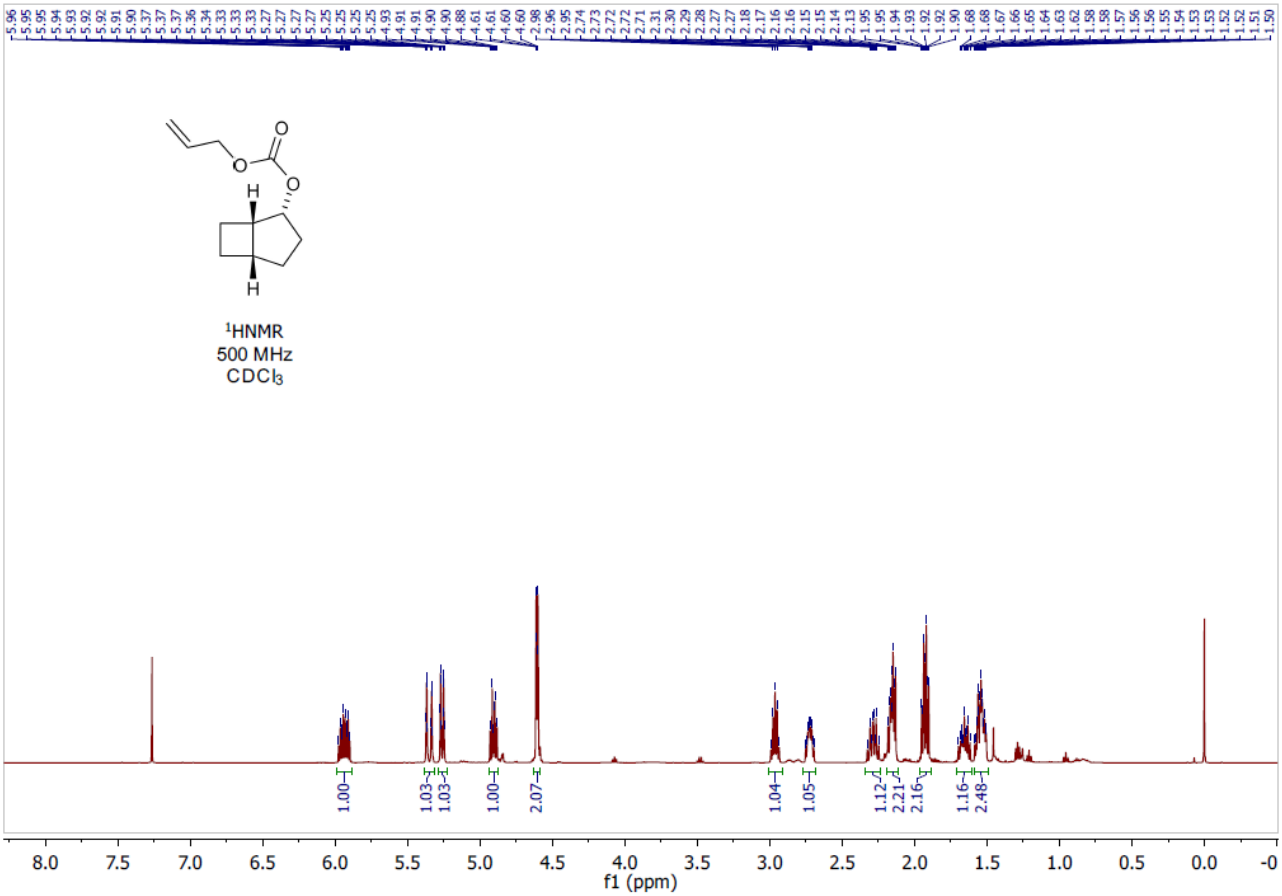

178.42
77.07
38.80
38.50
36.09
29.58
28.72
27.24
24.67
16.27
OPiv
H
H
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

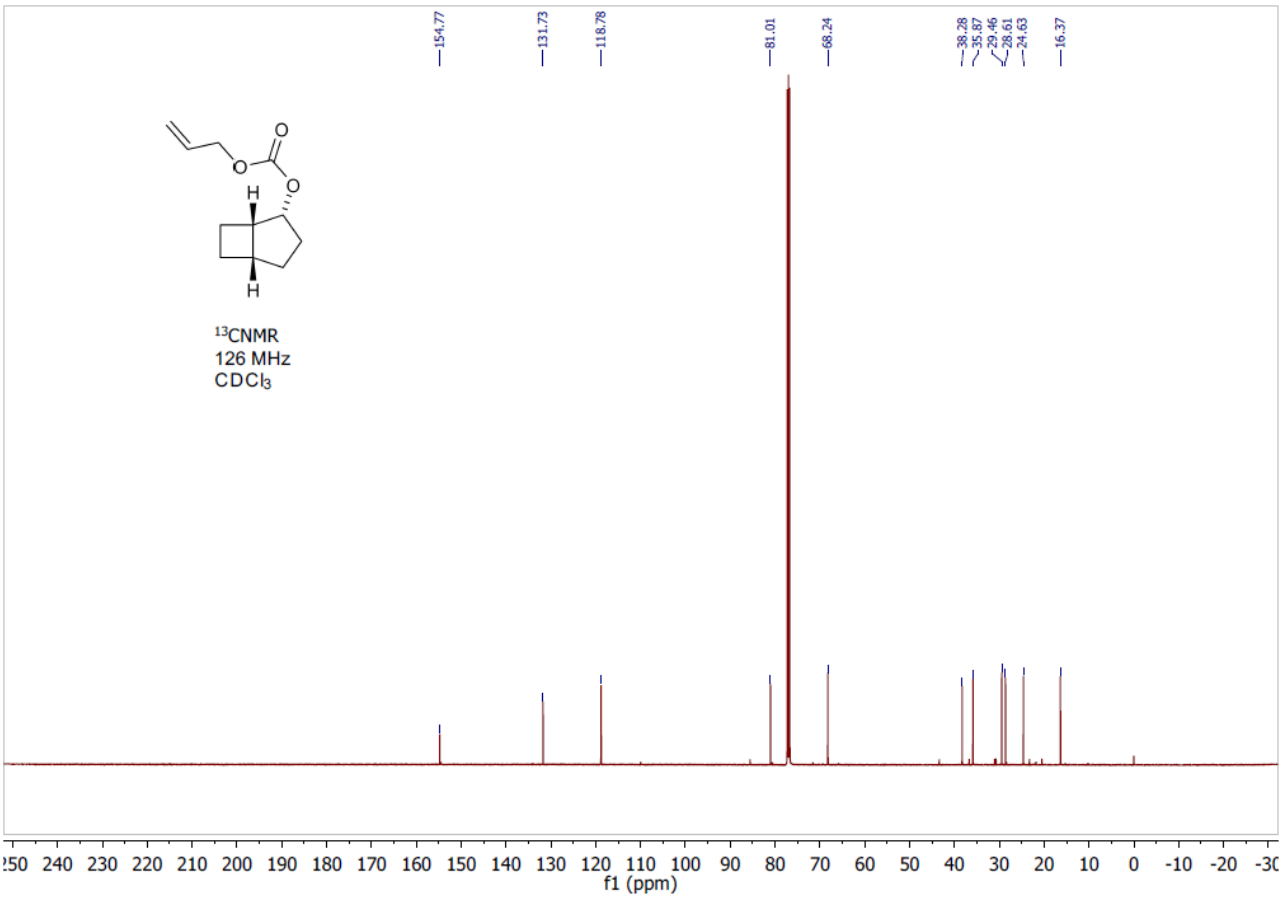

OTES
H
H
^{1}HNMR
500 MHz
$CDCl_3$
HDO
1.00
1.98
1.02
2.03
2.02
3.00
1.01
9.12
6.05
f1 (ppm)

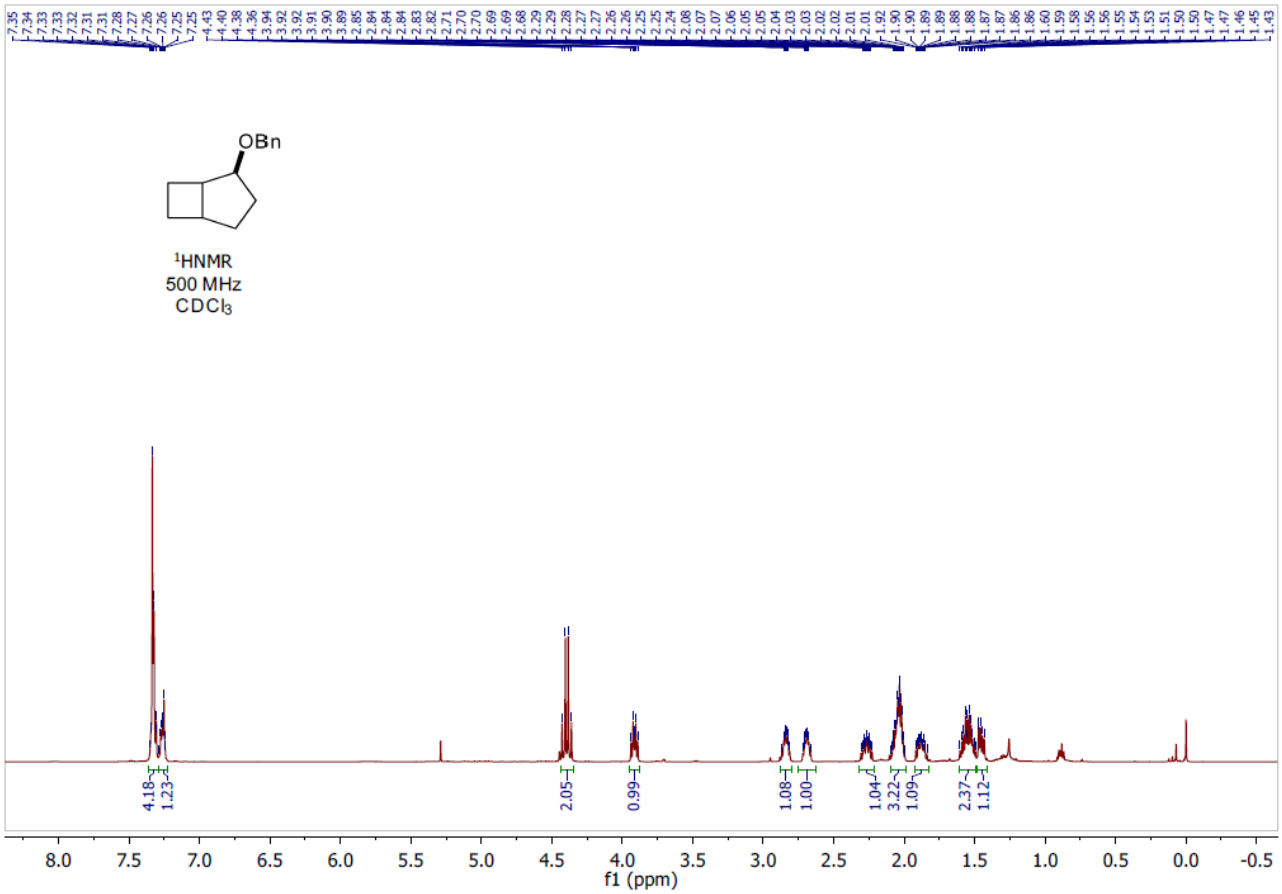

OTES
H
H
^{13}CNMR
126 MHz
$CDCl_3$
75.36
40.84
36.12
32.04
29.63
24.87
16.27
6.81
4.80
f1 (ppm)

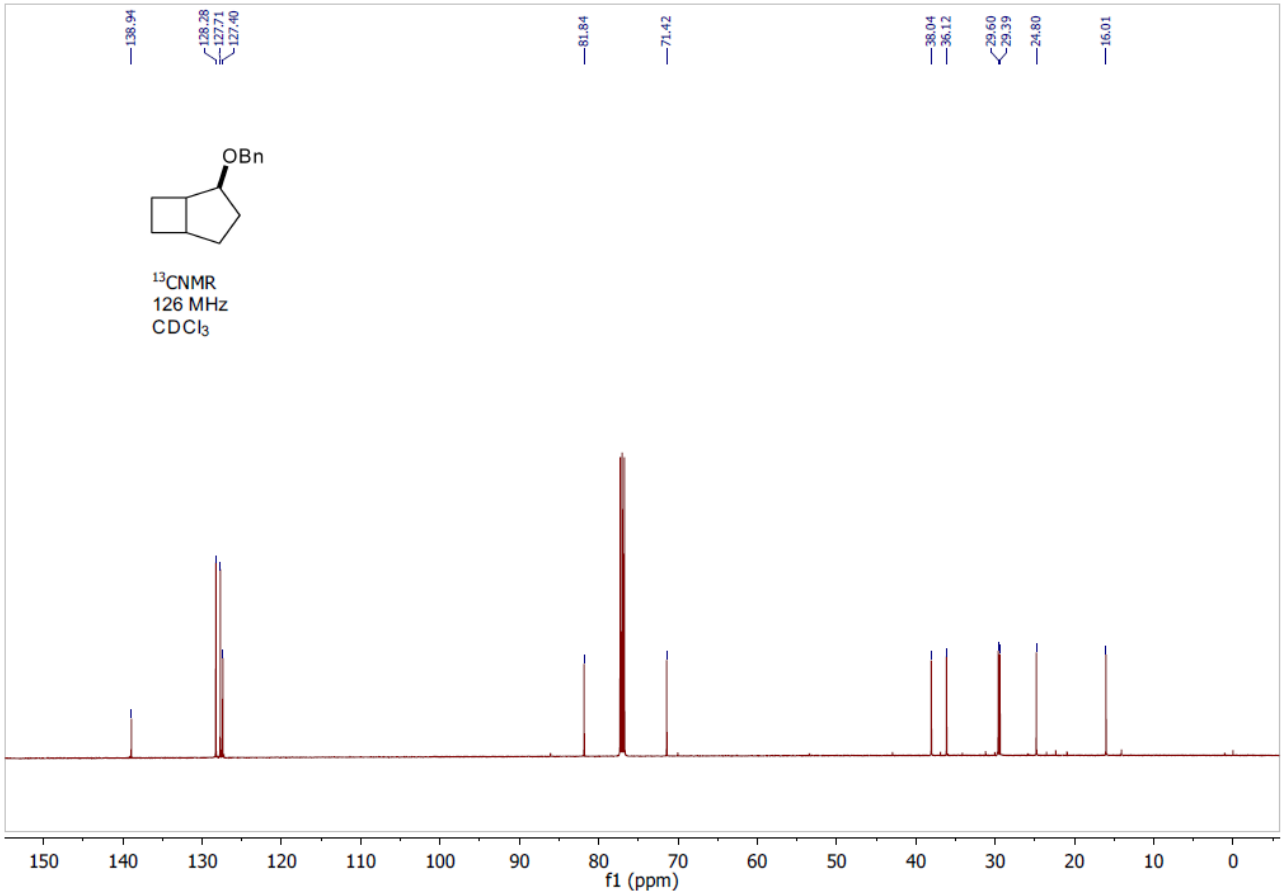

OMOM
H
H
^{1}HNMR
500 MHz
CDCl$_3$
1.05
1.04
1.00
2.98
1.11
1.03
1.27
4.57
4.00
f1 (ppm)

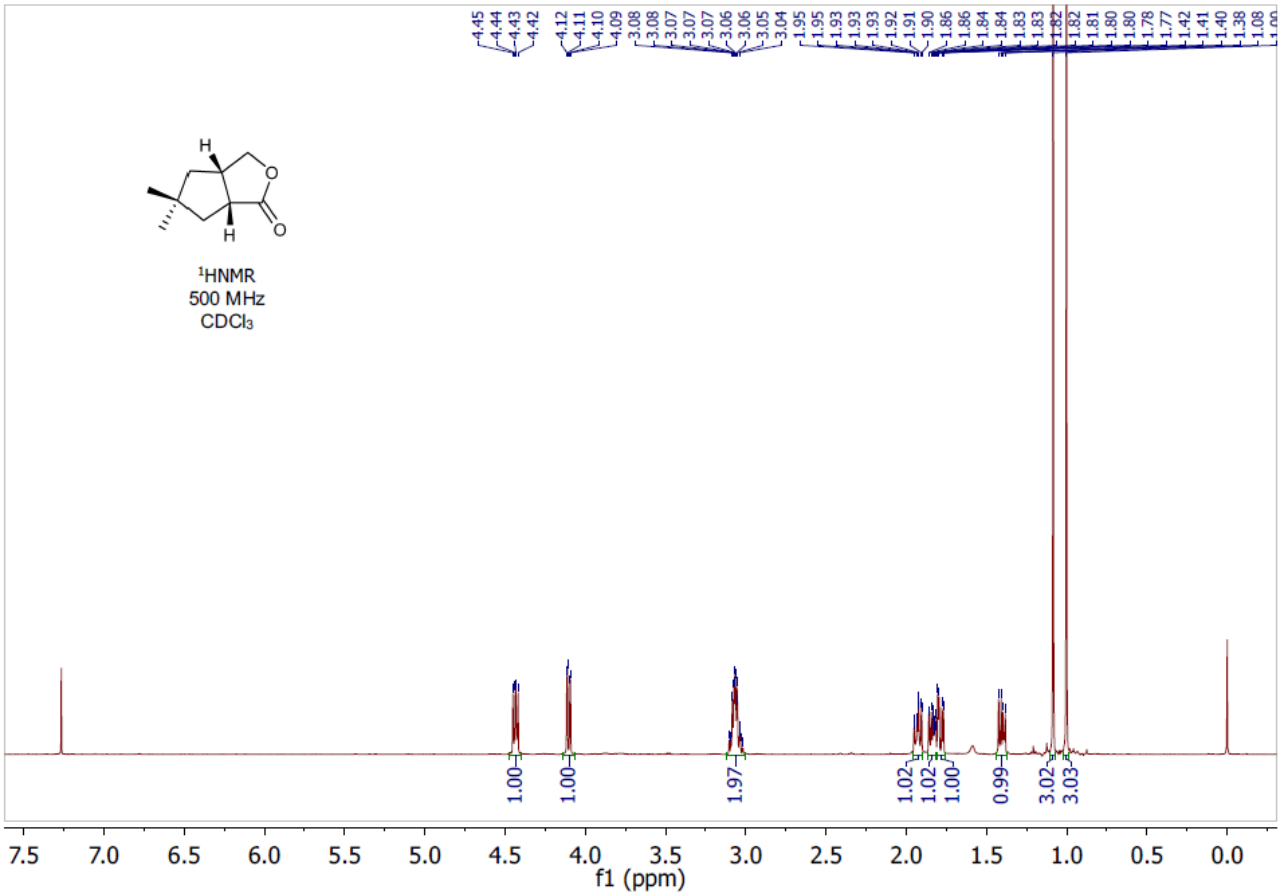

95.82
80.17
55.33
38.56
35.91
29.55
29.26
24.85
16.54
OMOM
H
H
^{13}CNMR
126 MHz
CDCl$_3$
f1 (ppm)

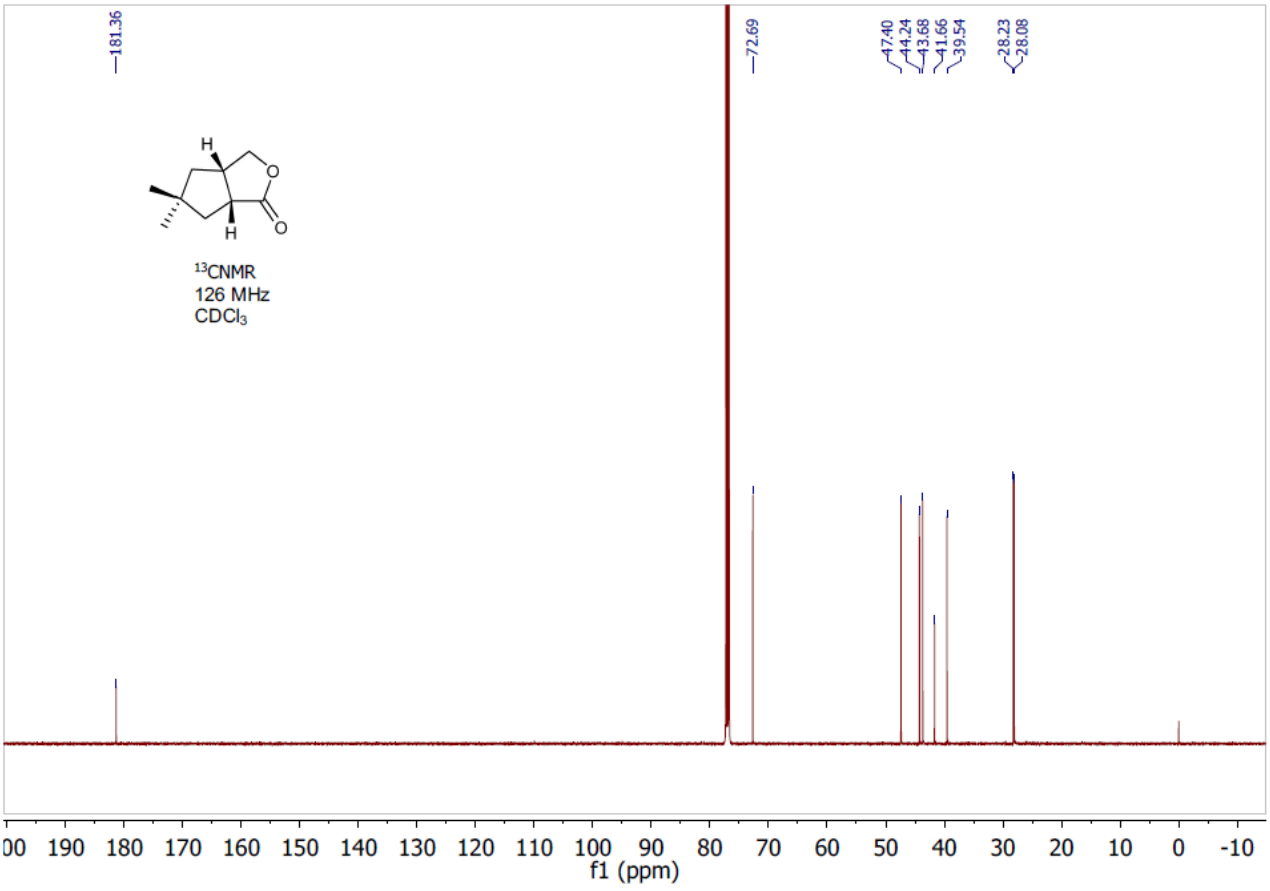

1HNMR
500 MHz
CDCl3
1.00
1.03
1.03
1.00
2.07
1.04
1.05
1.12
2.21
2.16
1.16
2.48
f1 (ppm)

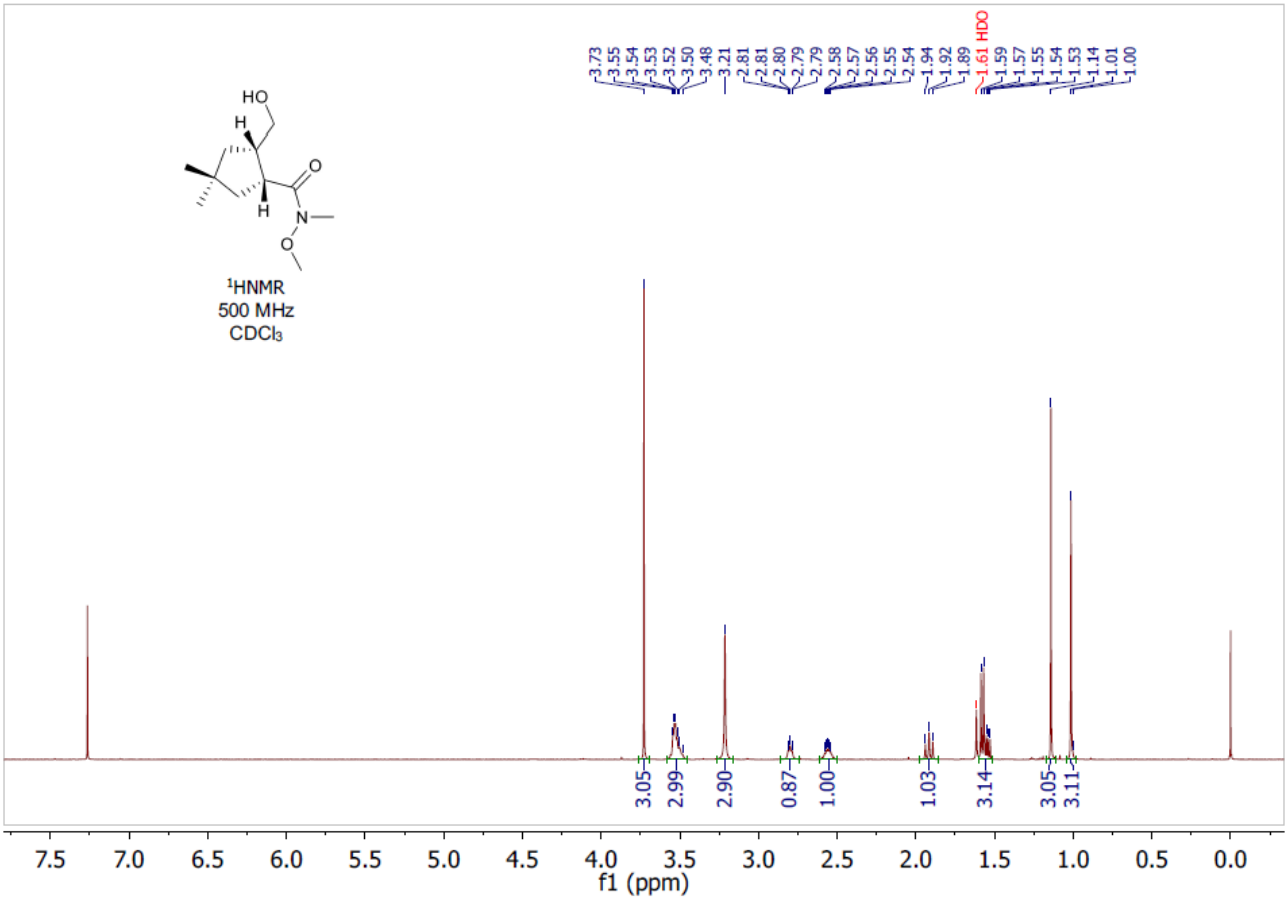

154.77
131.73
118.78
81.01
68.24
38.28
35.87
29.46
28.61
24.63
16.37
13CNMR
126 MHz
CDCl3
f1 (ppm)

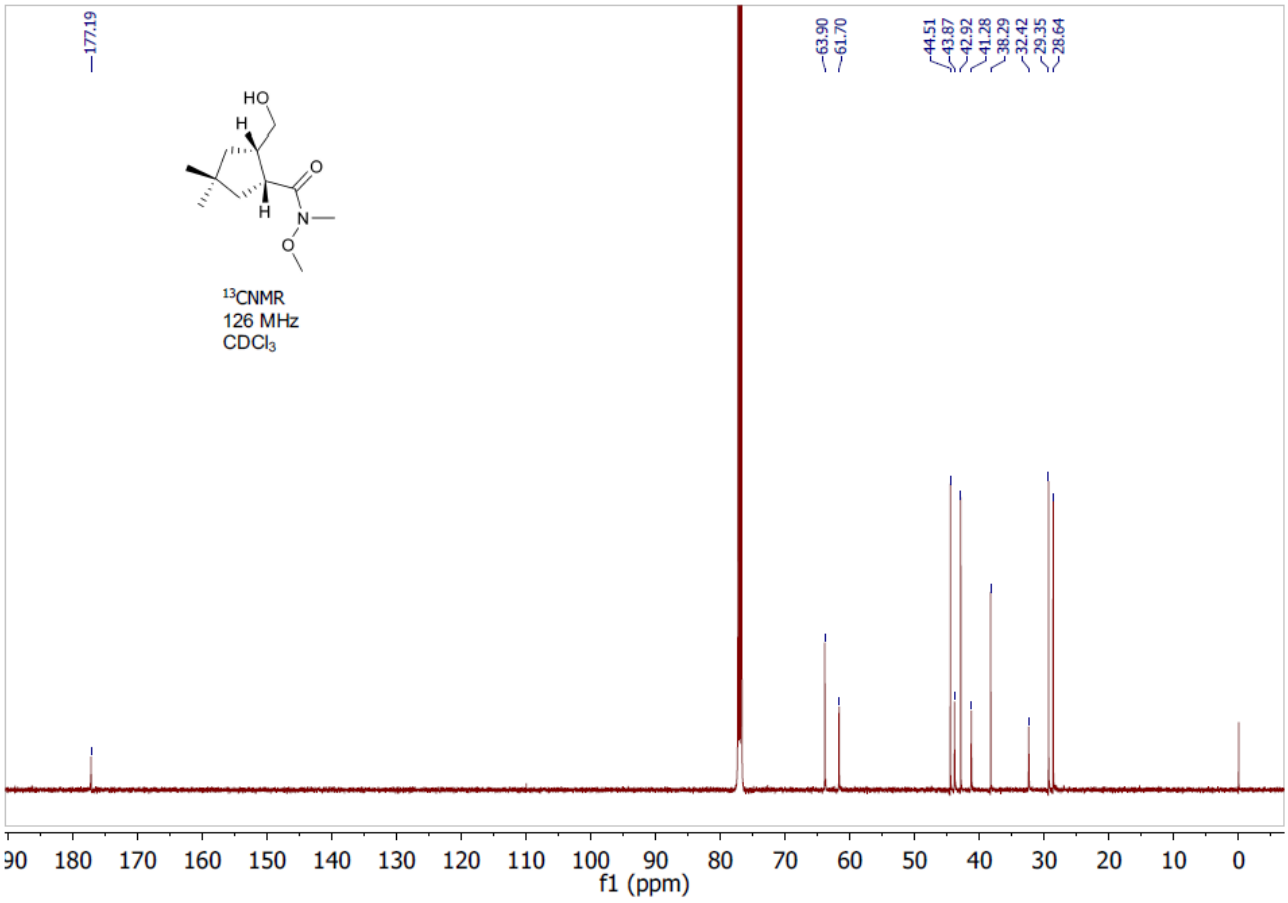

OBn
¹HNMR
500 MHz
CDCl₃
4.18
1.23
2.05
0.99
1.08
1.00
1.04
3.22
1.09
2.37
1.12
f1 (ppm)

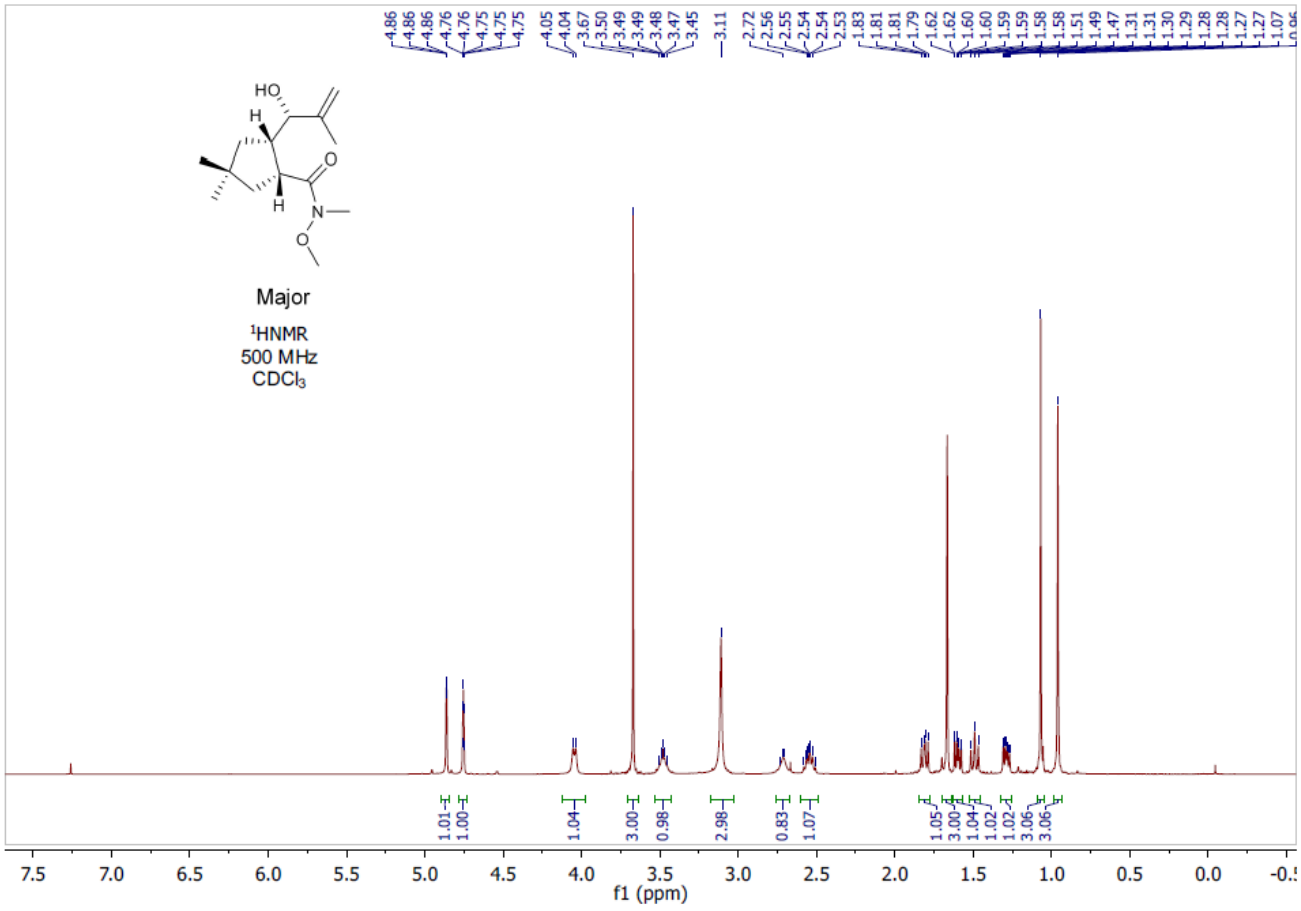

138.94
128.28
127.71
127.40
81.84
71.42
38.04
36.12
29.60
29.39
24.80
16.01
OBn
¹³CNMR
126 MHz
CDCl₃
f1 (ppm)

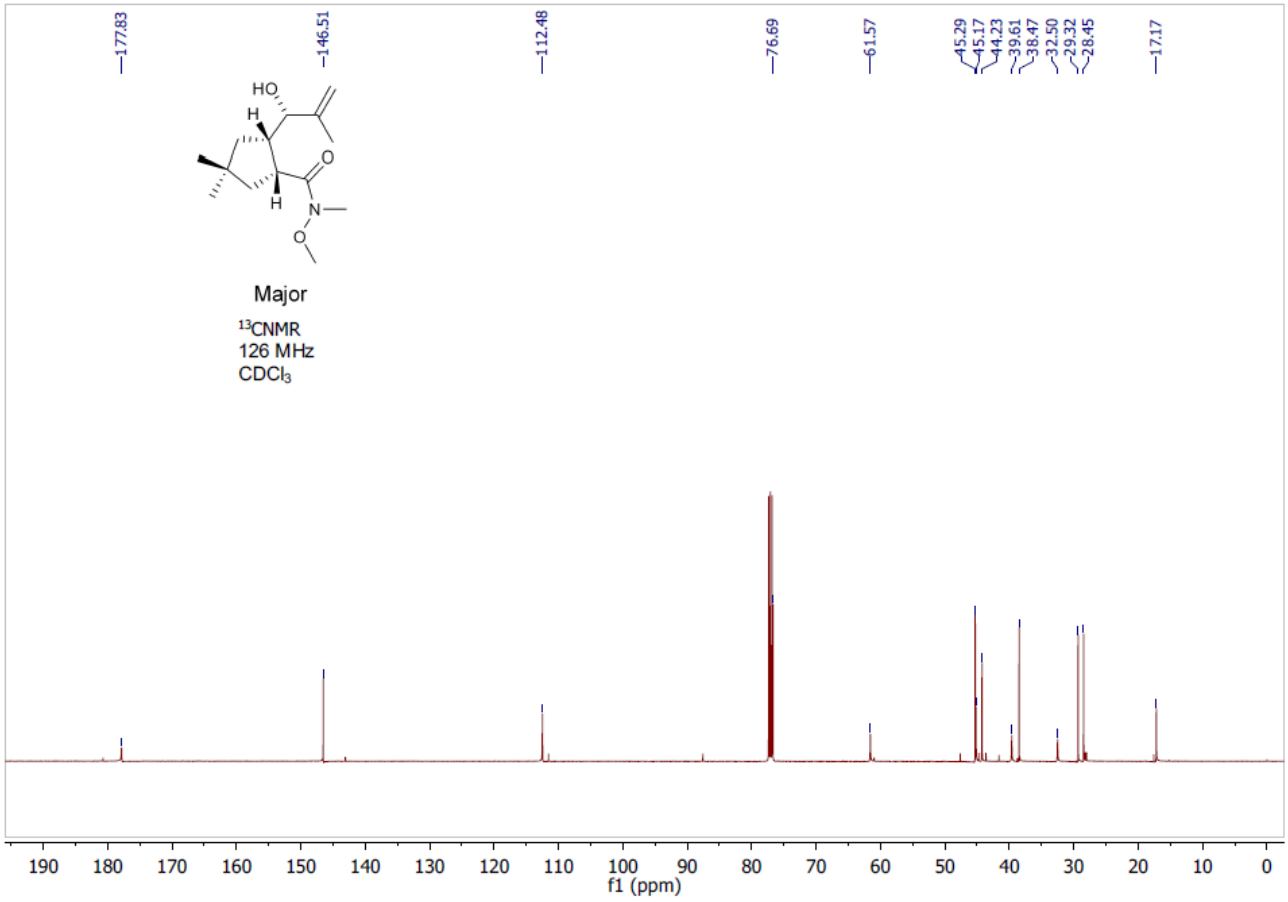

^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

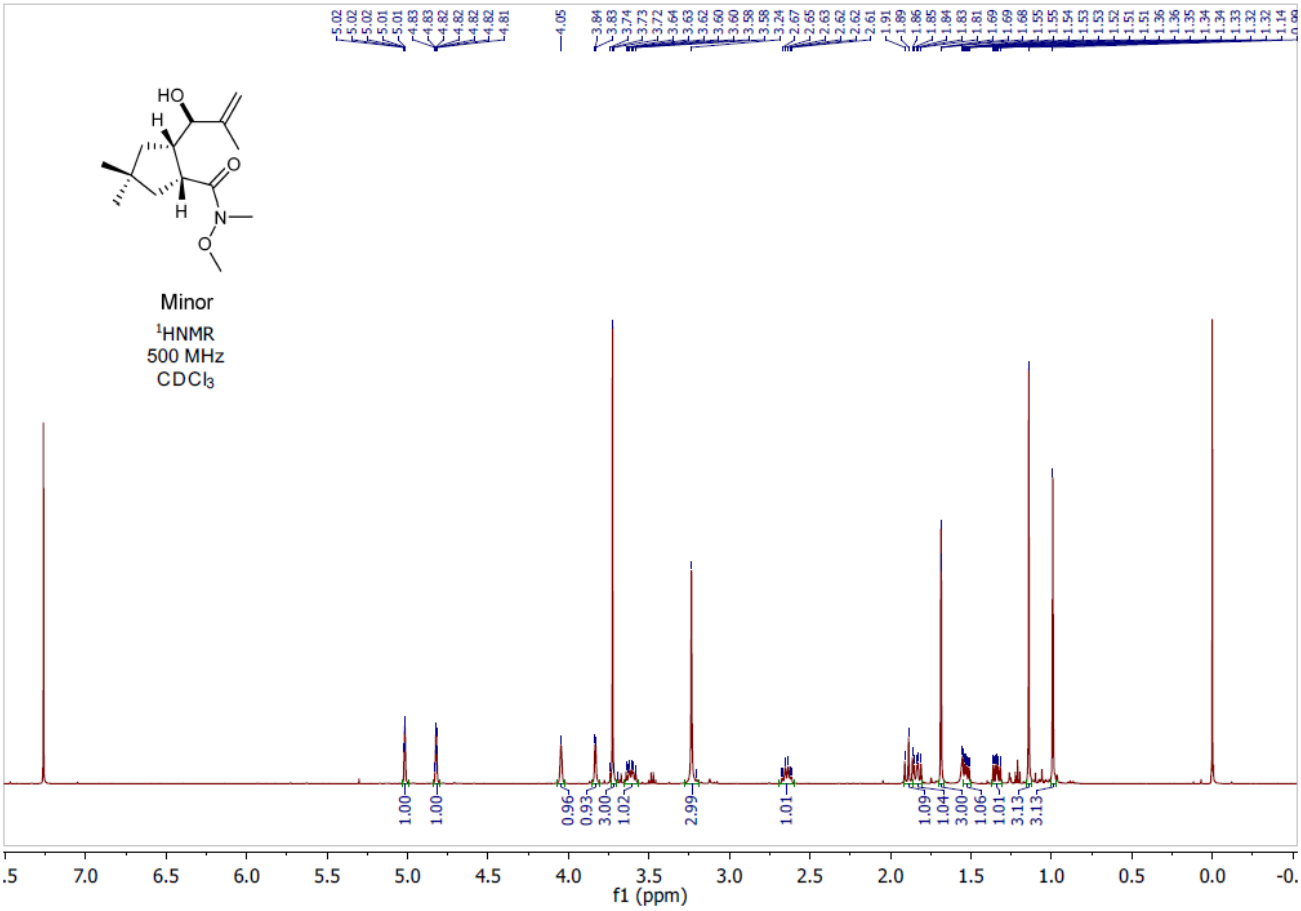

^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

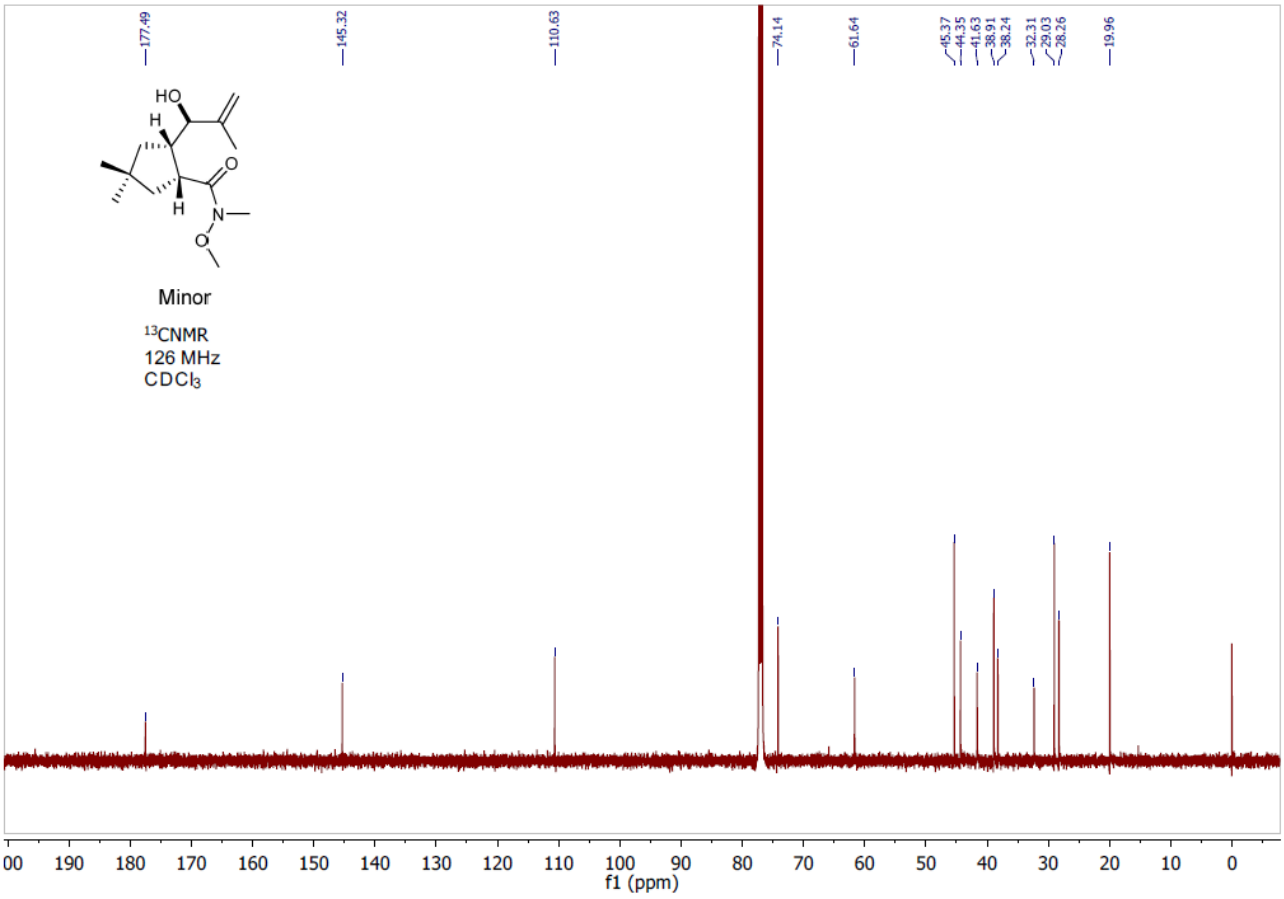

HO
H
H
O
N
O
^{1}HNMR
500 MHz
CDCl$_3$
3.73
3.55
3.54
3.53
3.52
3.50
3.48
3.21
2.81
2.80
2.79
2.58
2.57
2.56
2.55
2.54
1.94
1.92
1.89
1.61 HDO
1.59
1.57
1.55
1.54
1.53
1.14
1.01
1.00
3.05
2.99
2.90
0.87
1.00
1.03
3.14
3.05
3.11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

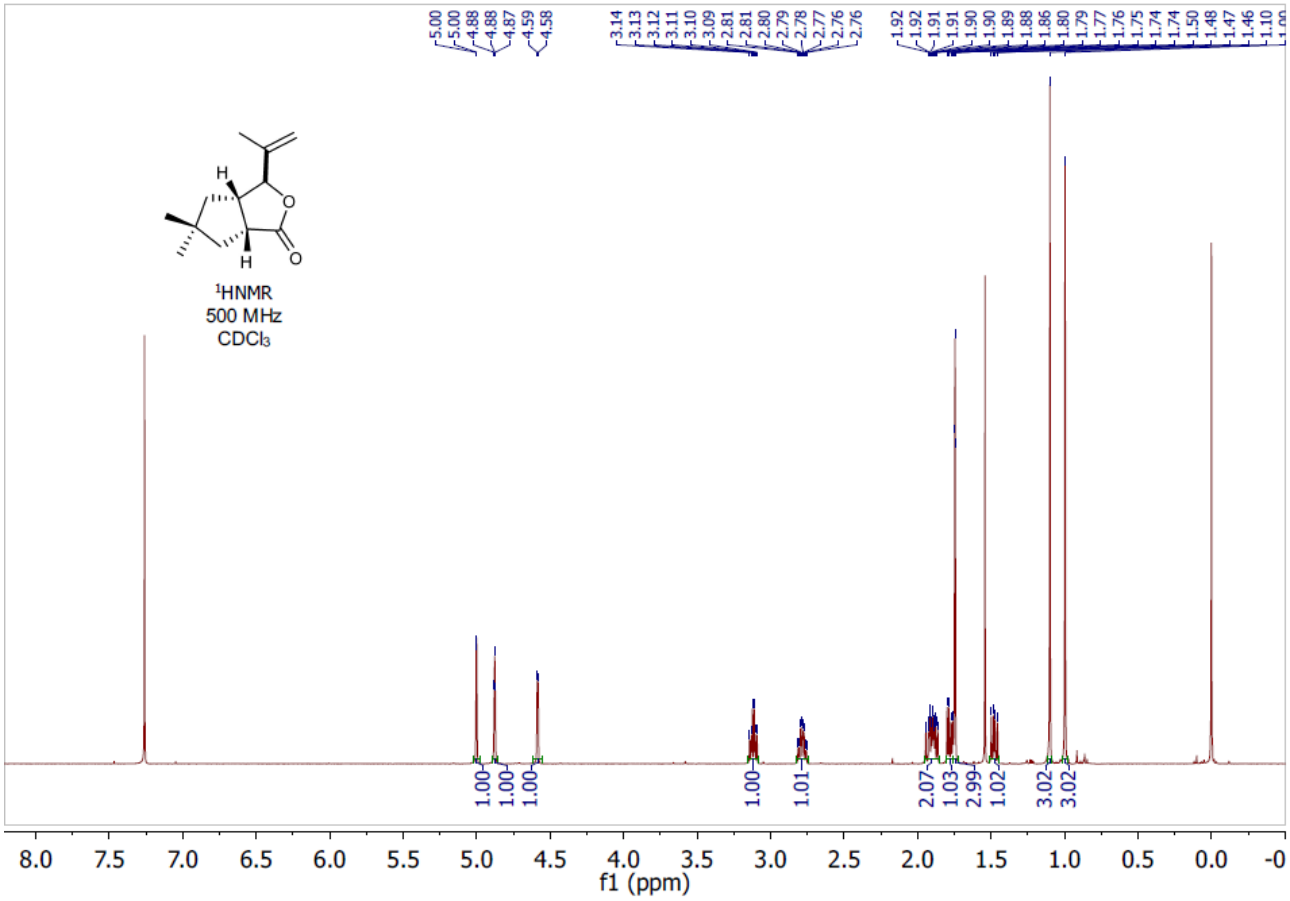

177.19
63.90
61.70
44.51
43.87
42.92
41.28
38.29
32.42
29.35
28.64
HO
H
H
O
N
O
^{13}CNMR
126 MHz
CDCl$_3$
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

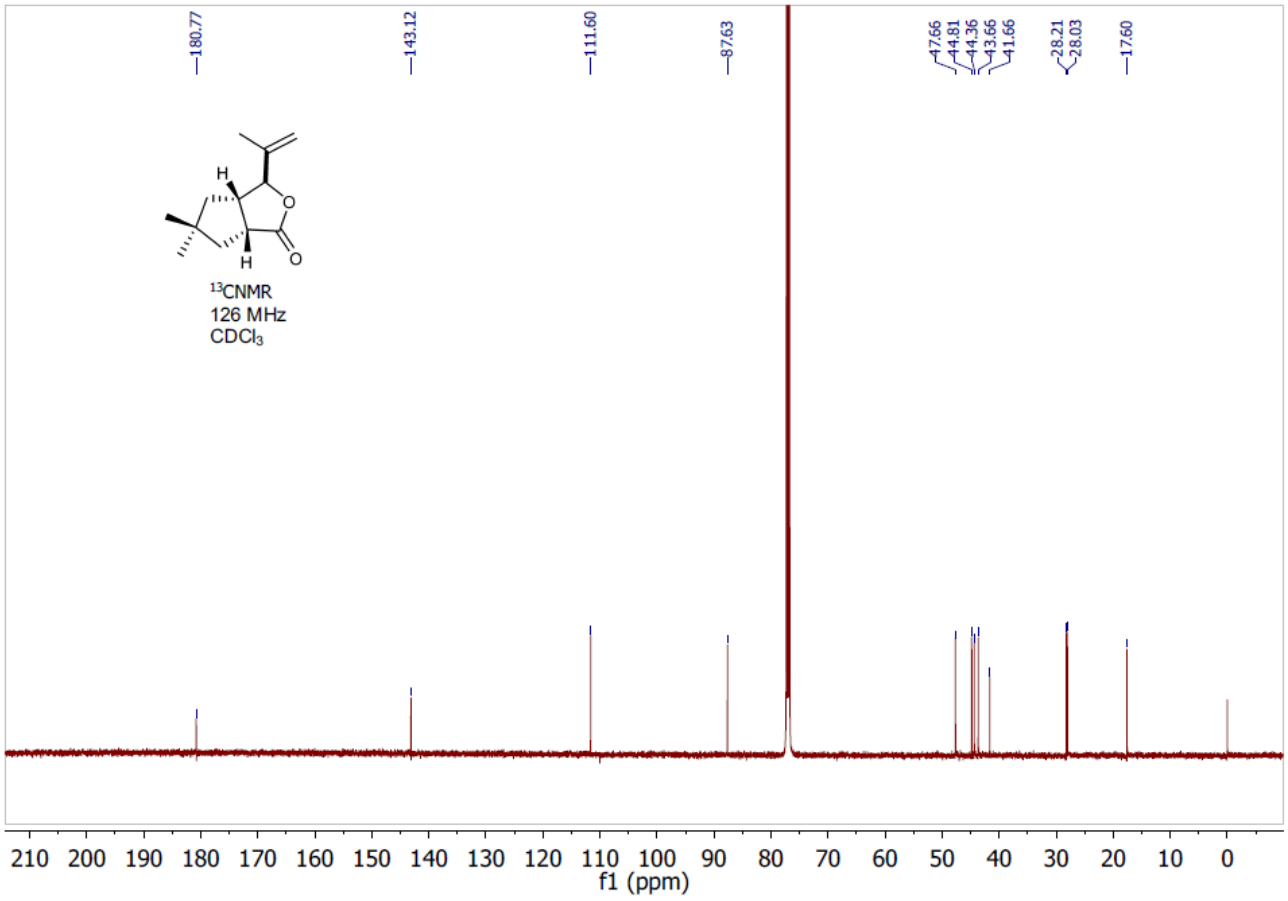

Major
1HNMR
500 MHz
CDCl3
f1 (ppm)

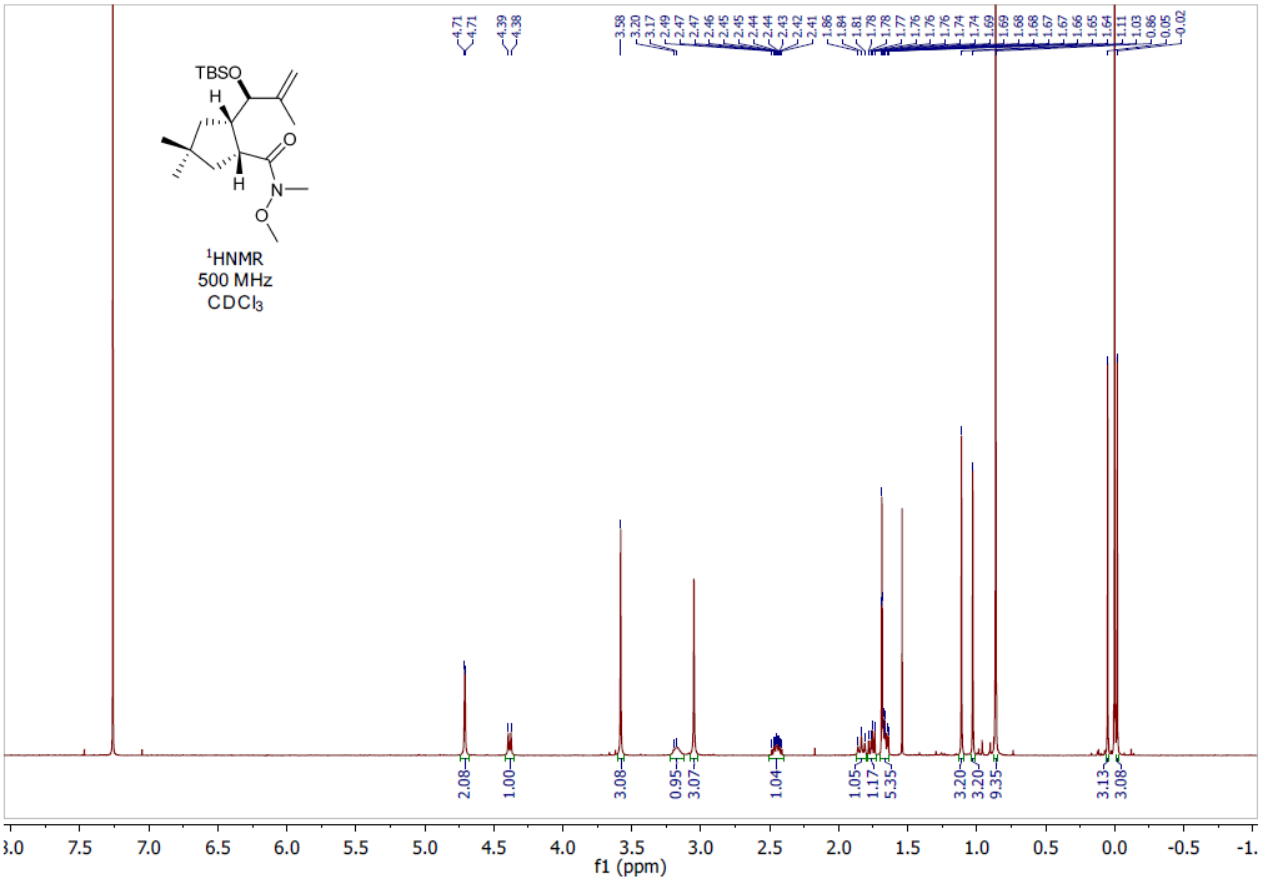

Major
13CNMR
126 MHz
CDCl3
f1 (ppm)

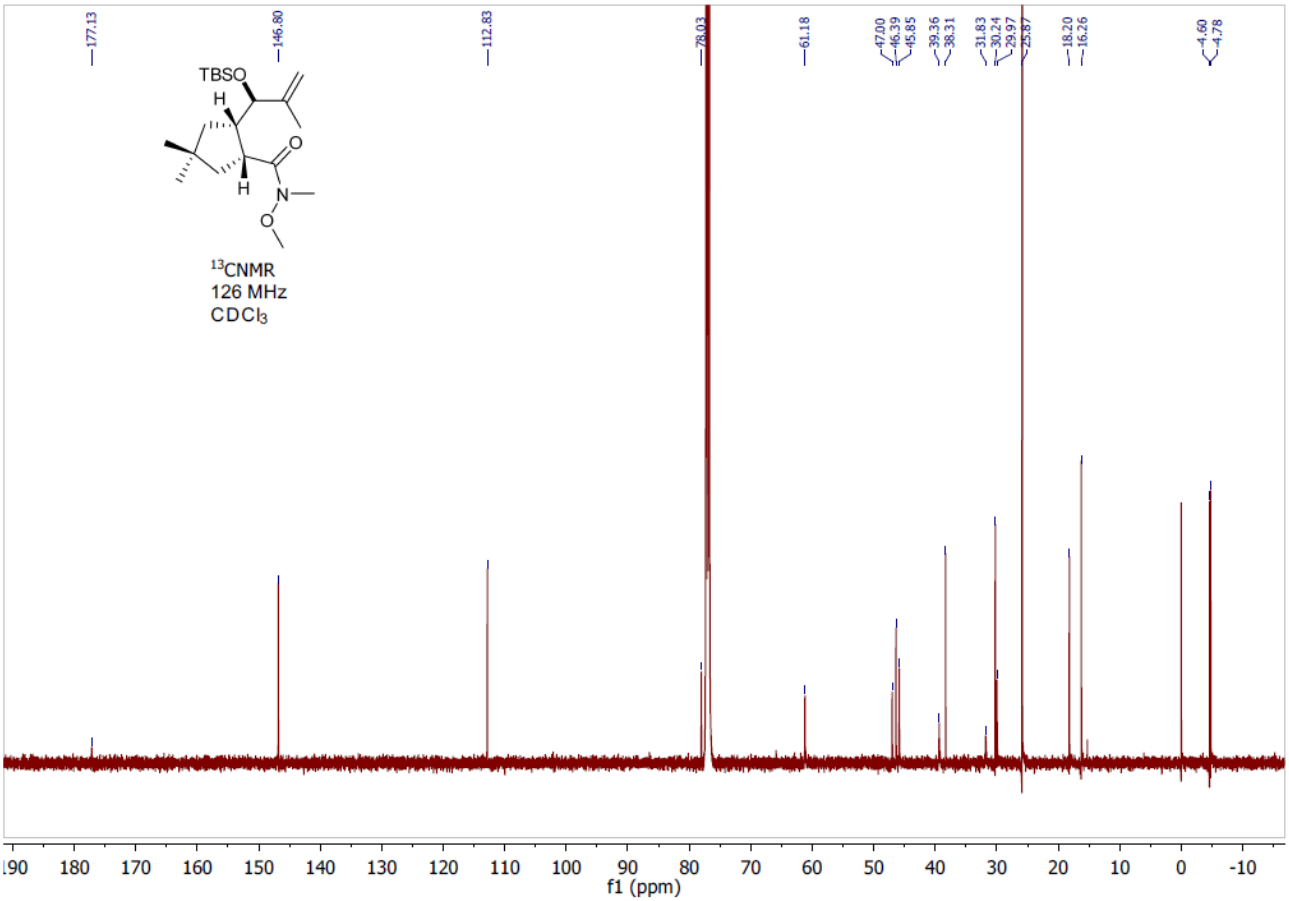

Minor
1HNMR
500 MHz
CDCl3
f1 (ppm)

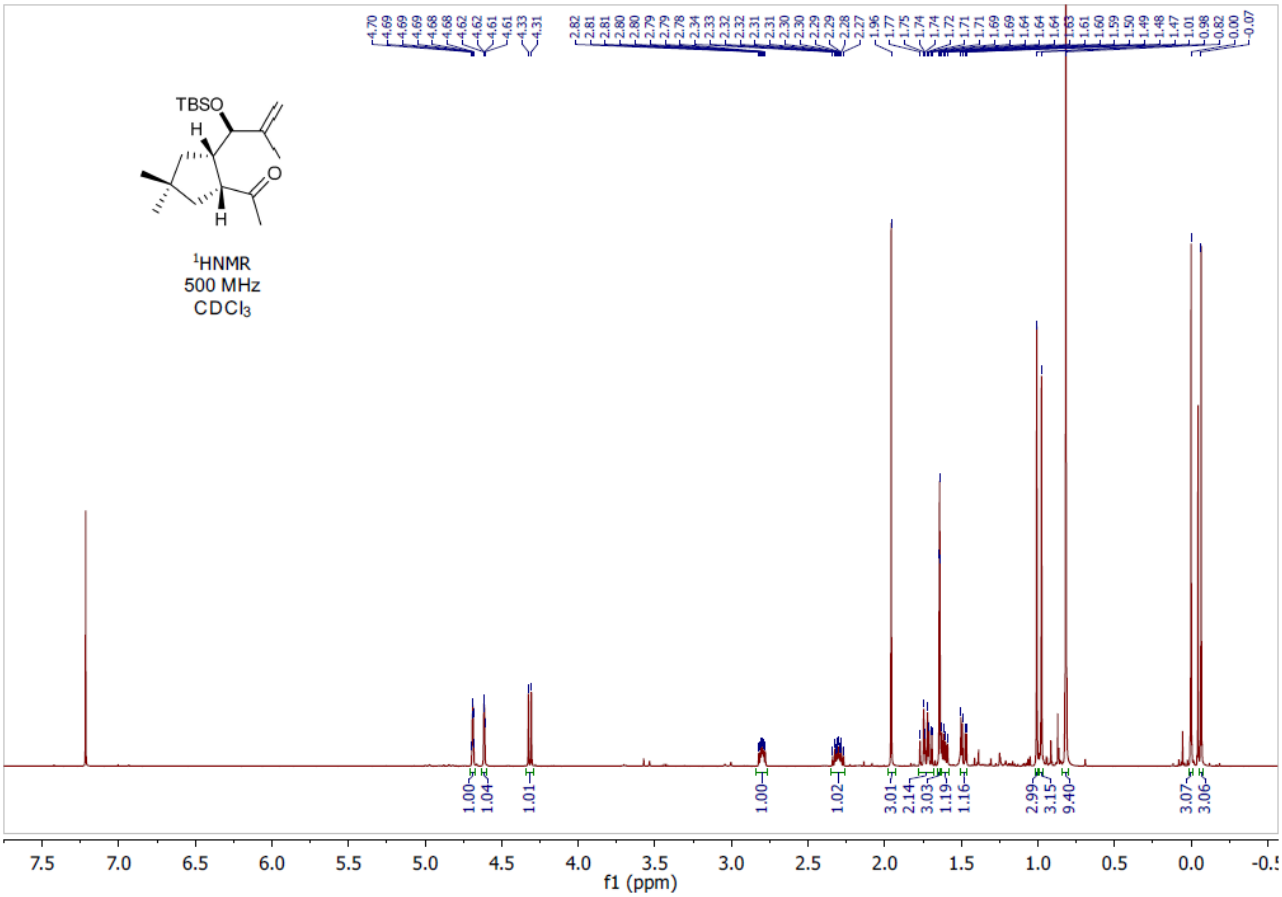

Minor
13CNMR
126 MHz
CDCl3
f1 (ppm)

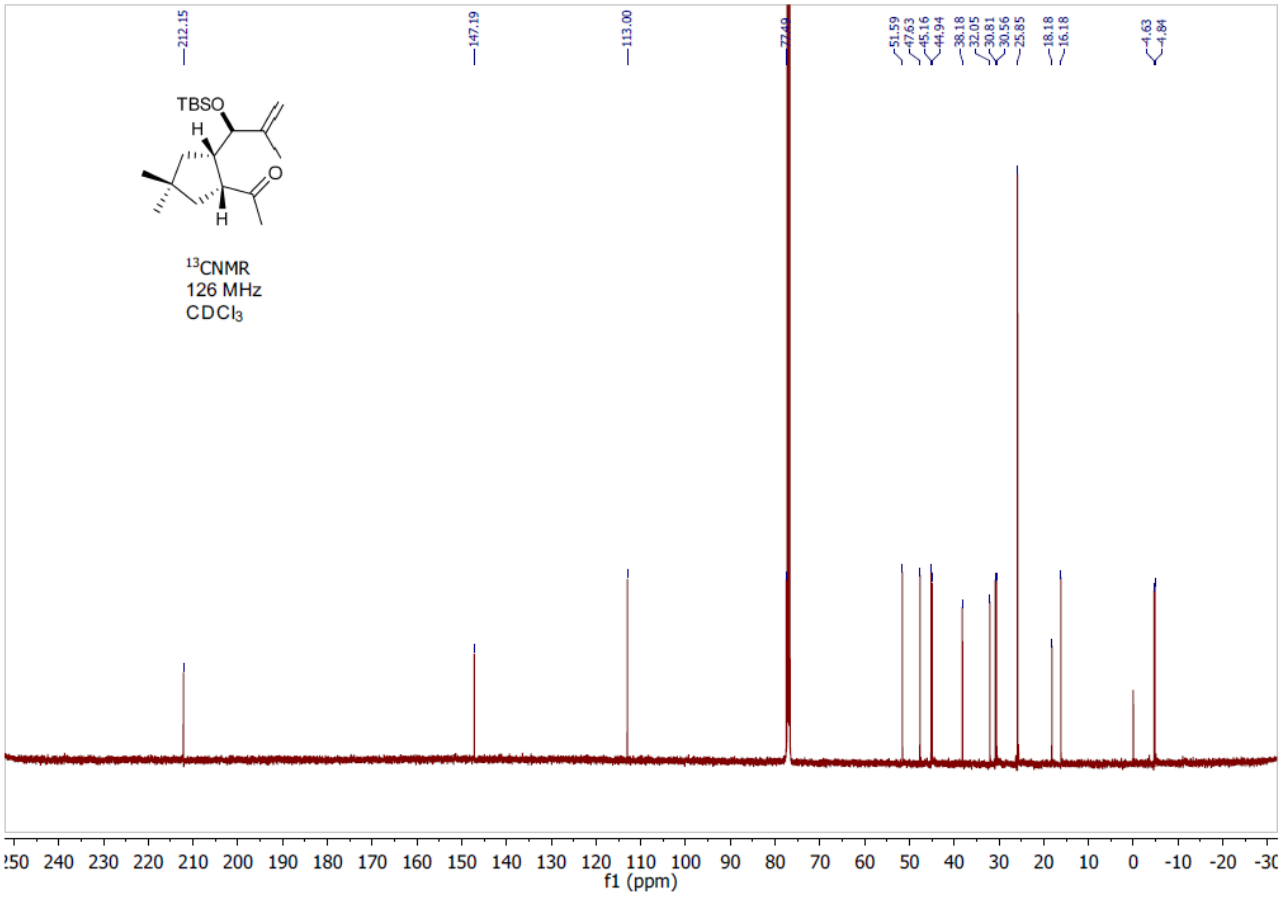

5.00
5.00
4.88
4.88
4.87
4.59
4.58
3.14
3.13
3.12
3.11
3.10
3.09
2.81
2.81
2.80
2.79
2.78
2.77
2.76
2.76
1.92
1.92
1.91
1.91
1.90
1.90
1.89
1.88
1.86
1.80
1.79
1.77
1.76
1.75
1.74
1.74
1.50
1.48
1.47
1.46
1.10
H
O
O
H
1HNMR
500 MHz
CDCl3
1.00
1.00
1.00
1.00
1.01
2.07
1.03
2.99
1.02
3.02
3.02
8.0 7.5 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
f1 (ppm)

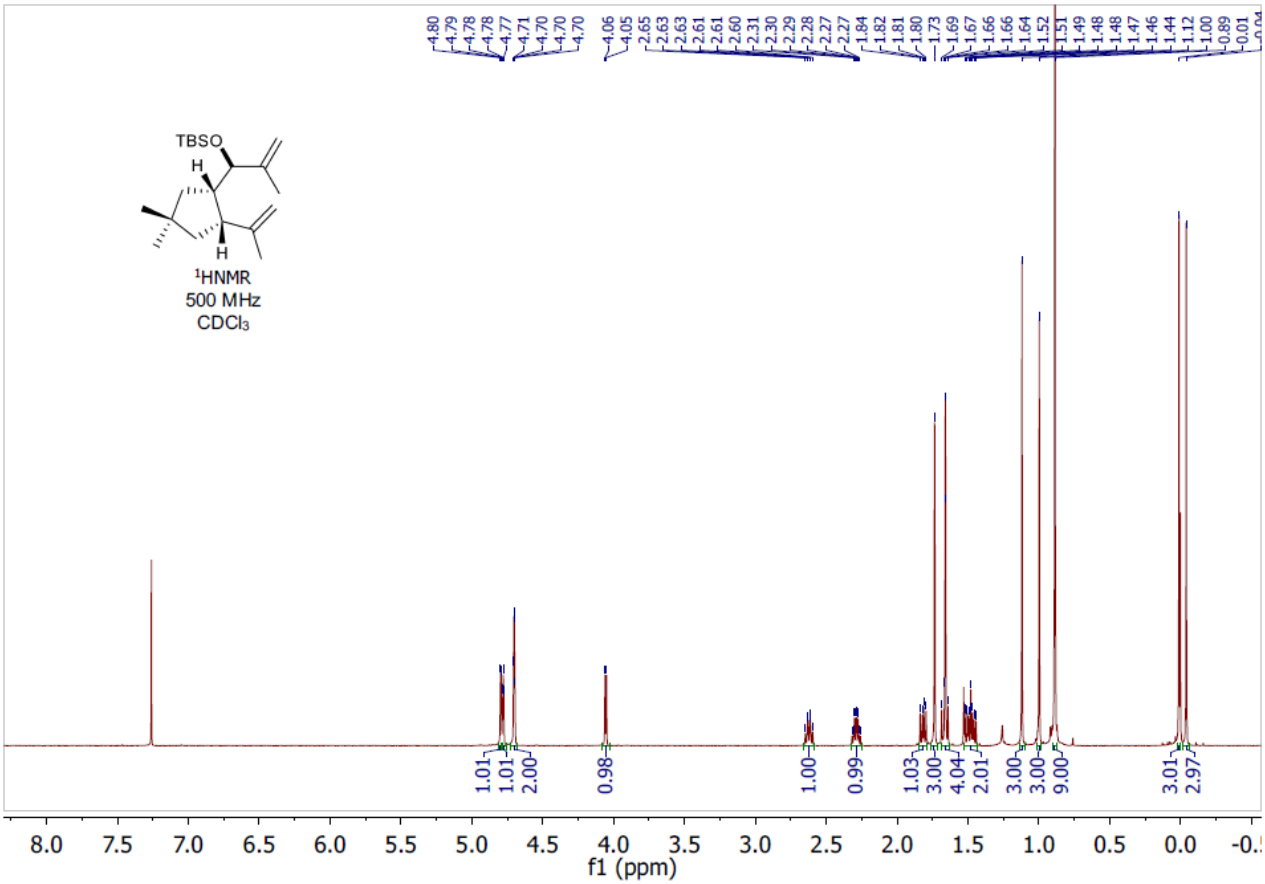

180.77
143.12
111.60
87.63
47.66
44.81
44.36
43.66
41.66
28.21
28.03
17.60
H
O
O
H
13CNMR
126 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

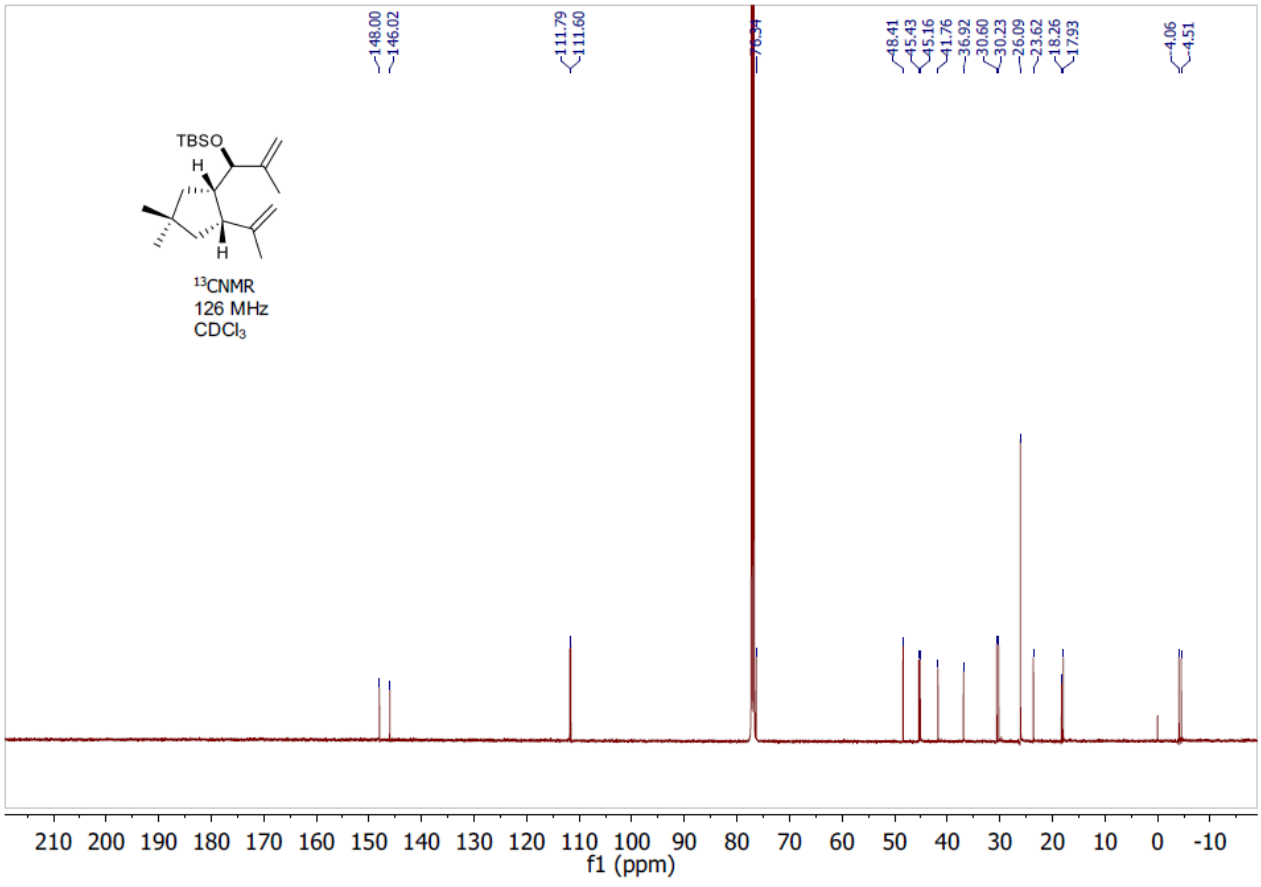

TBSO
H
H
O
N
O
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

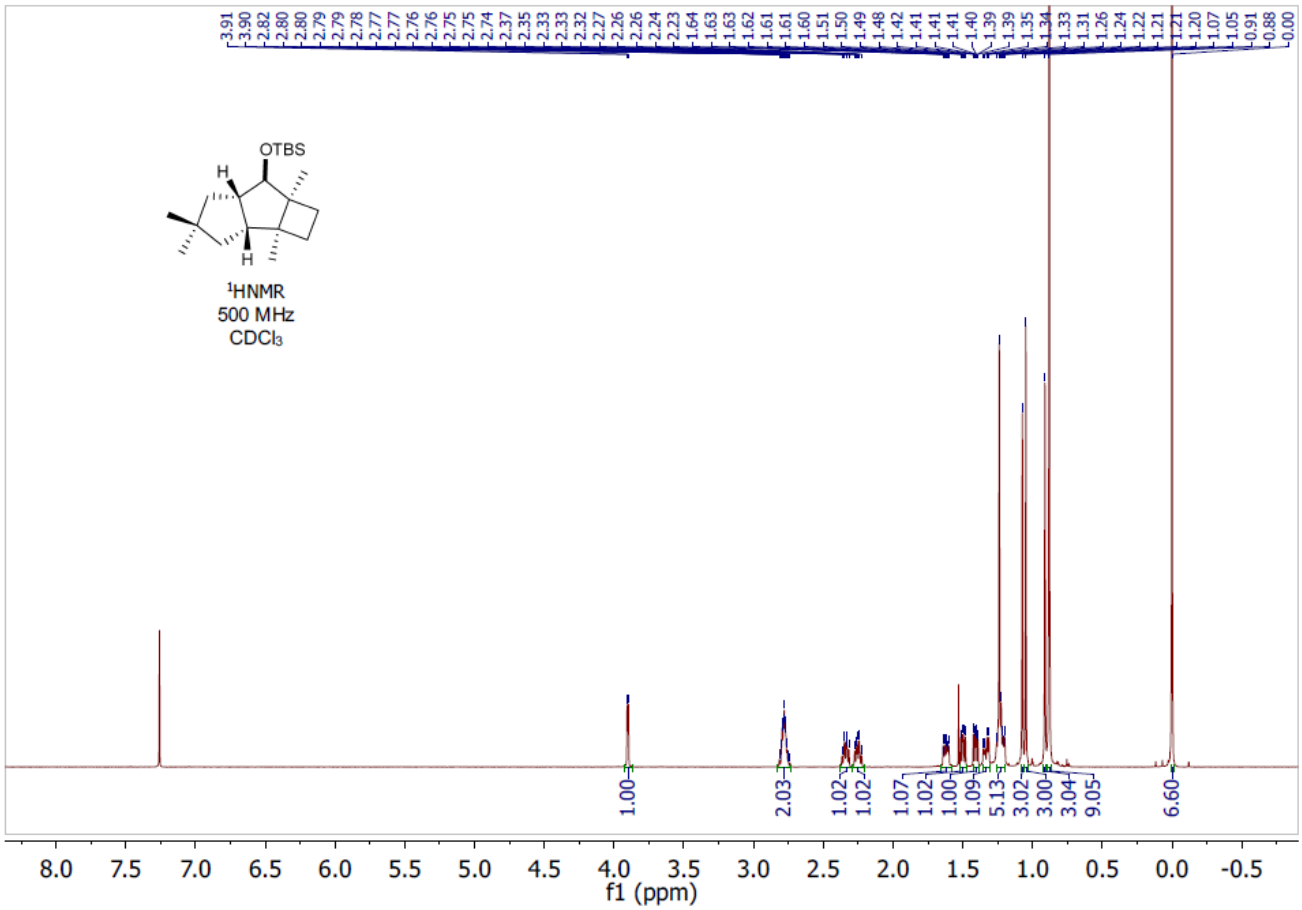

TBSO
H
H
O
N
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

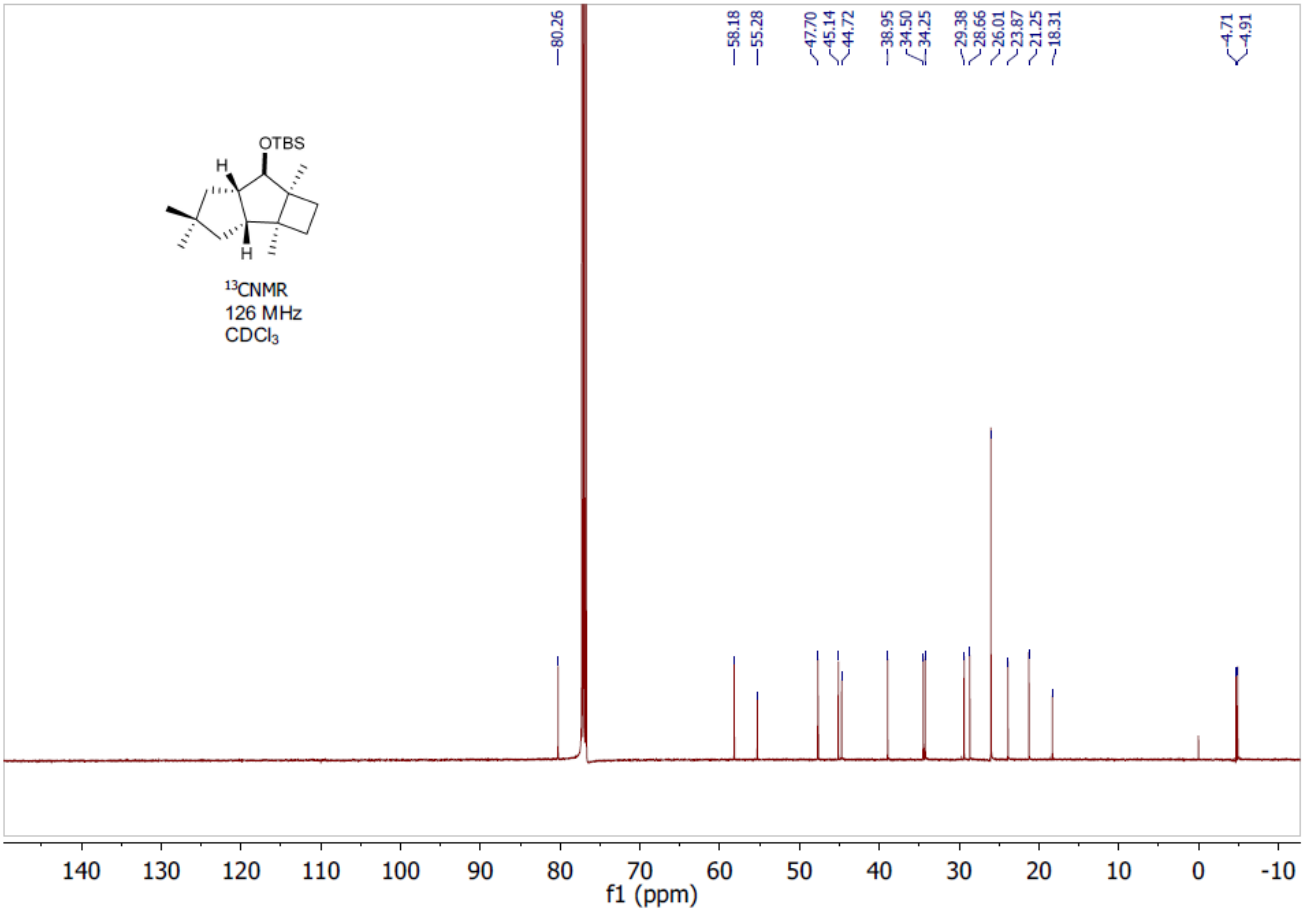

TBSO
H
O
H
1HNMR
500 MHz
CDCl3
f1 (ppm)

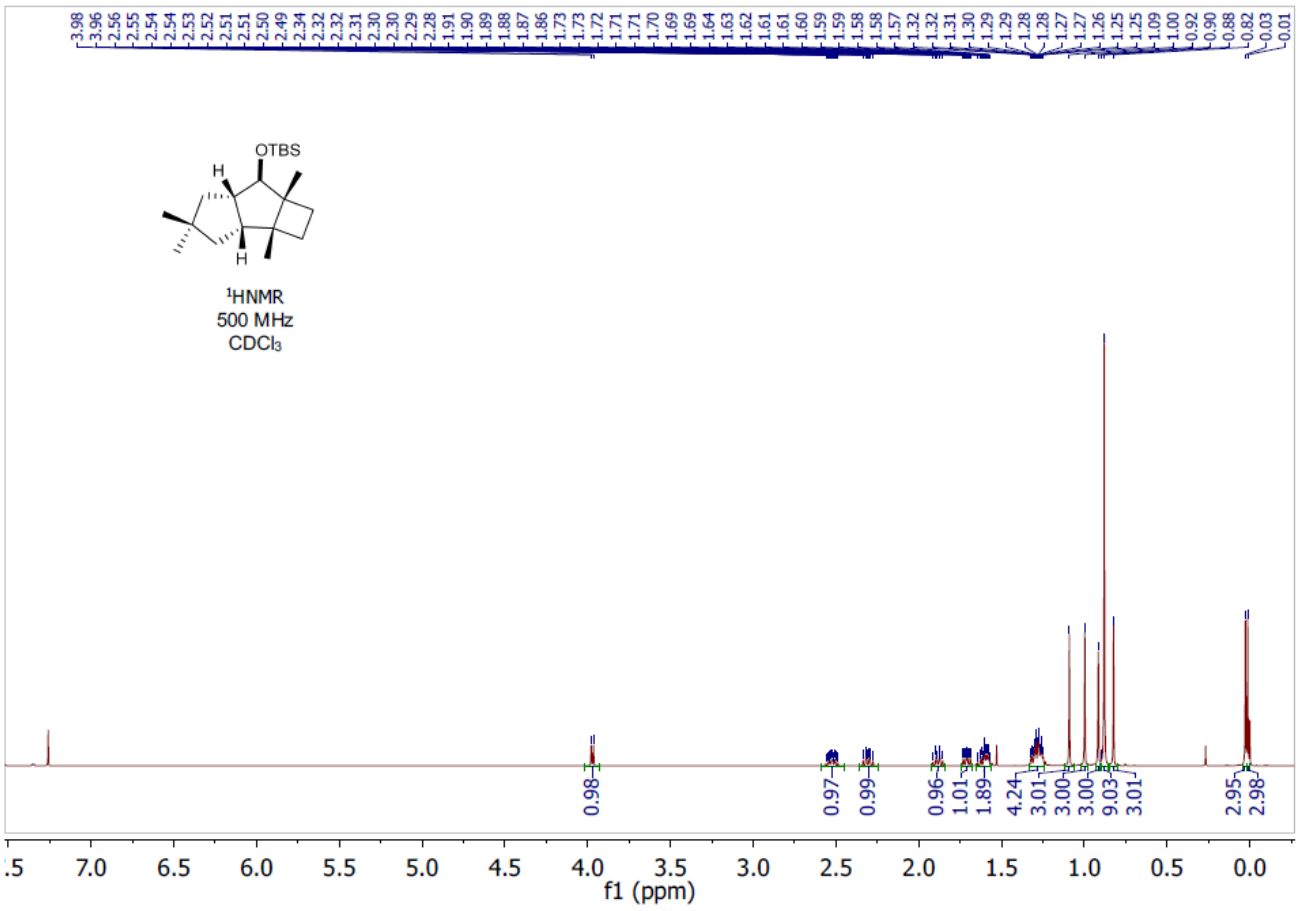

TBSO
H
O
H
13CNMR
126 MHz
CDCl3
f1 (ppm)

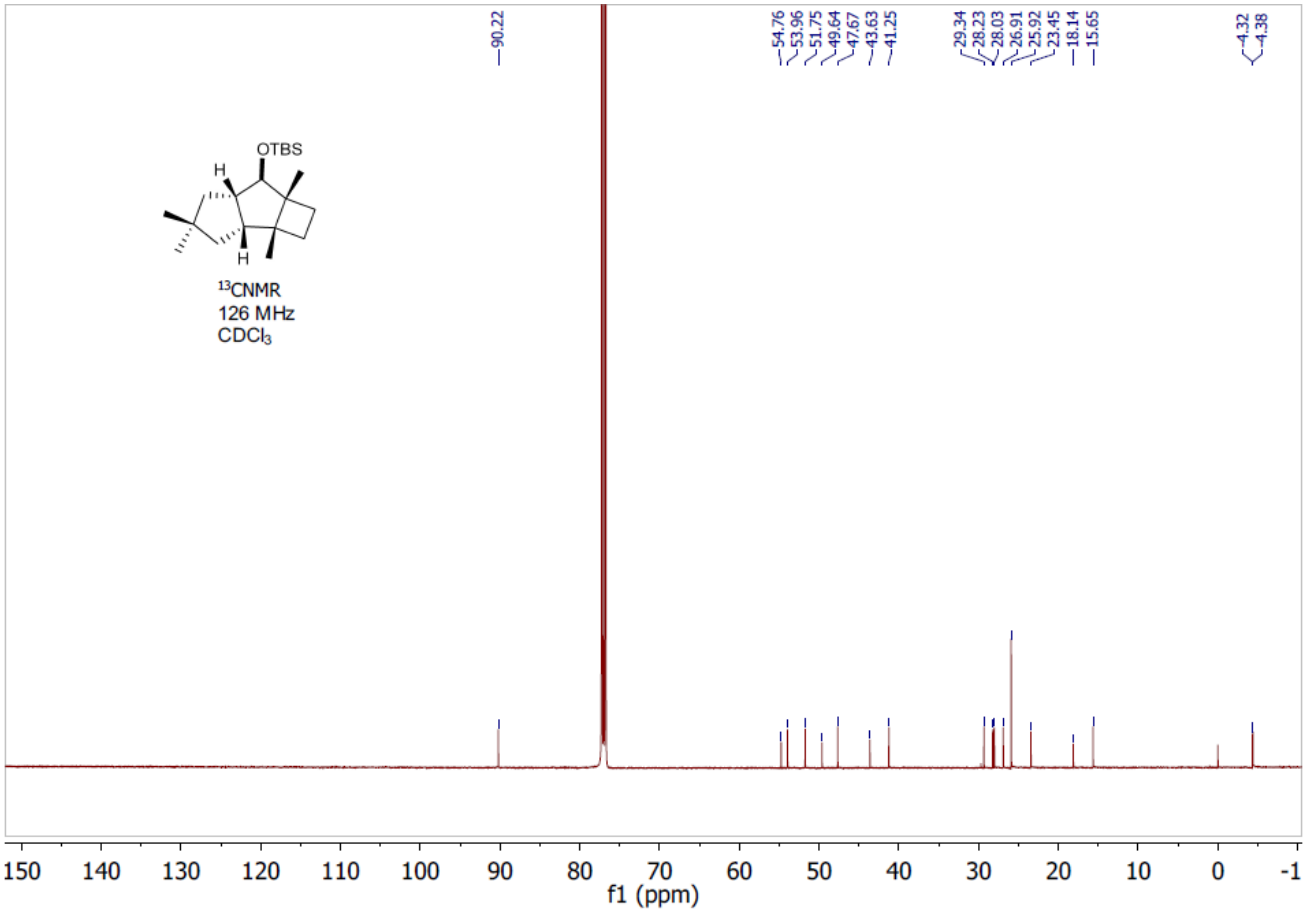

TBSO
H
H
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

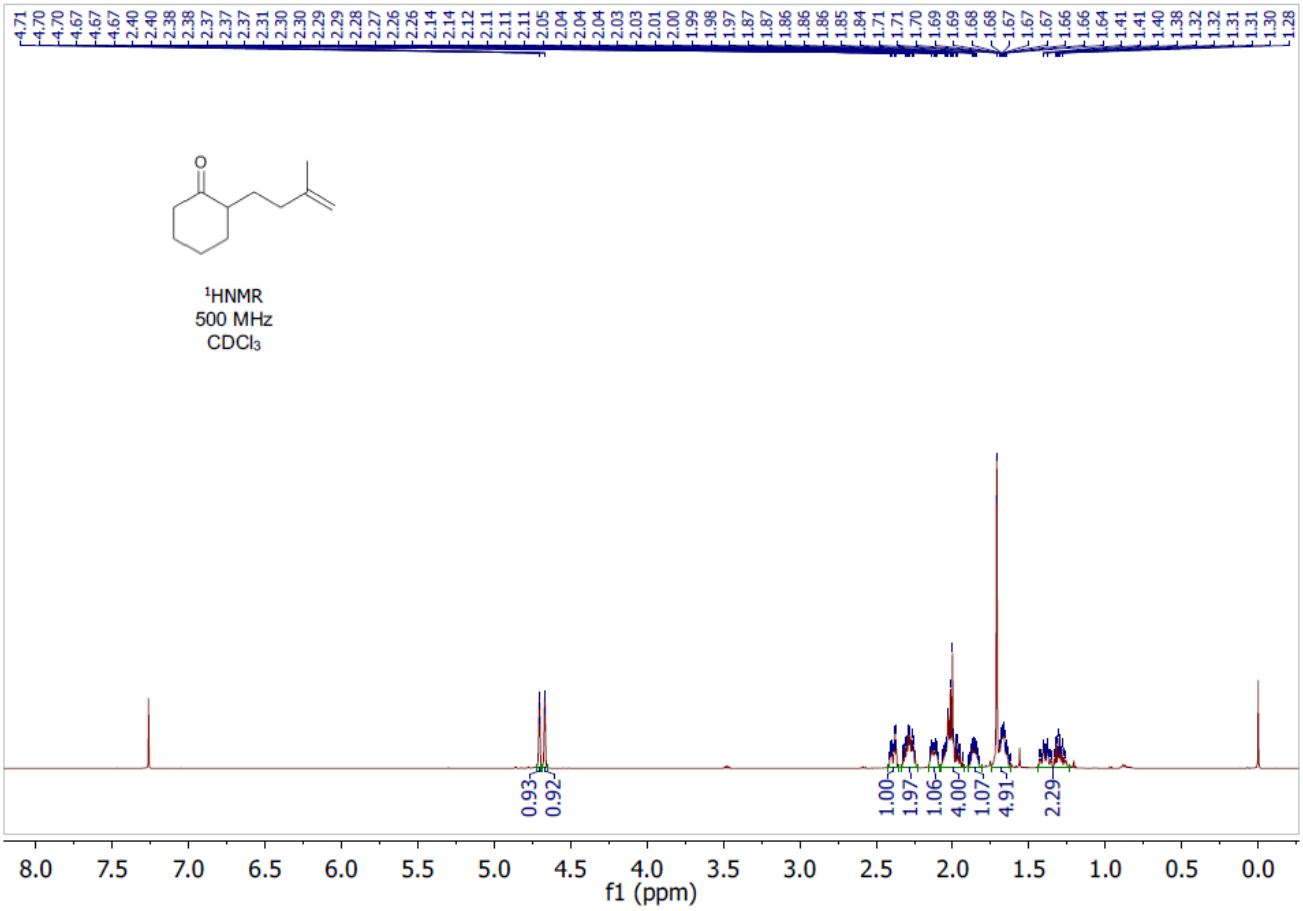

TBSO
H
H
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

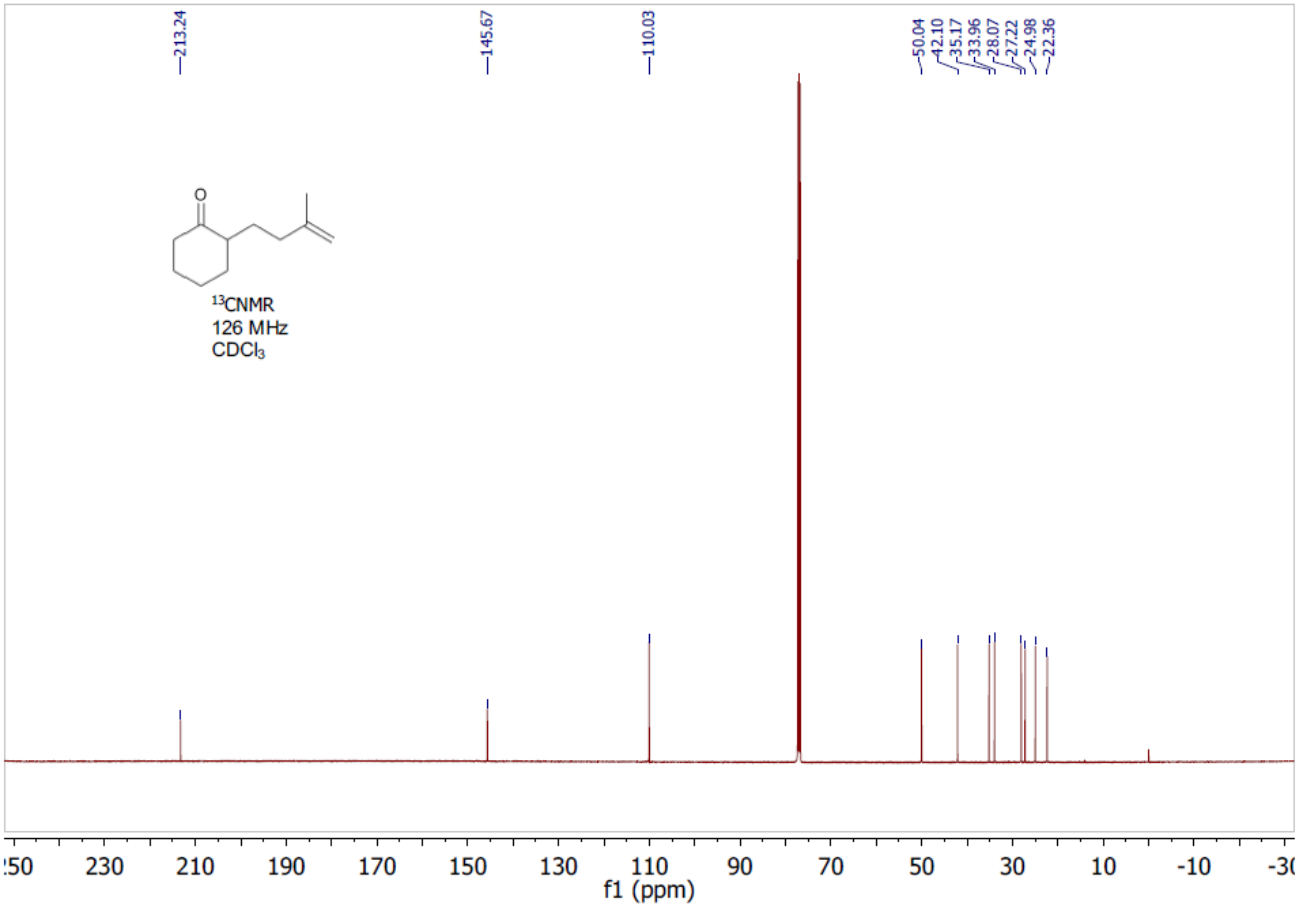

OTBS
H
H
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

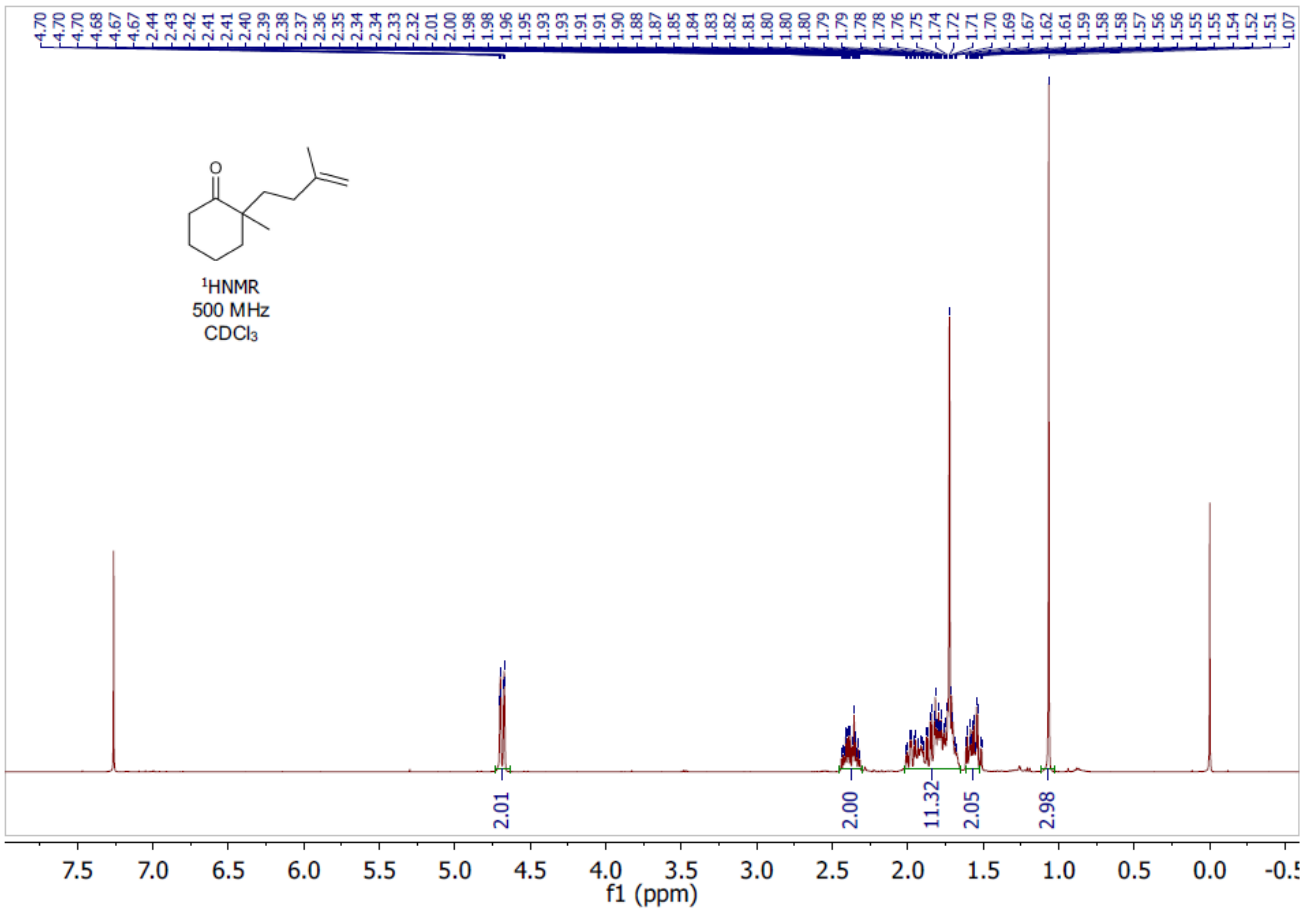

OTBS
H
H
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

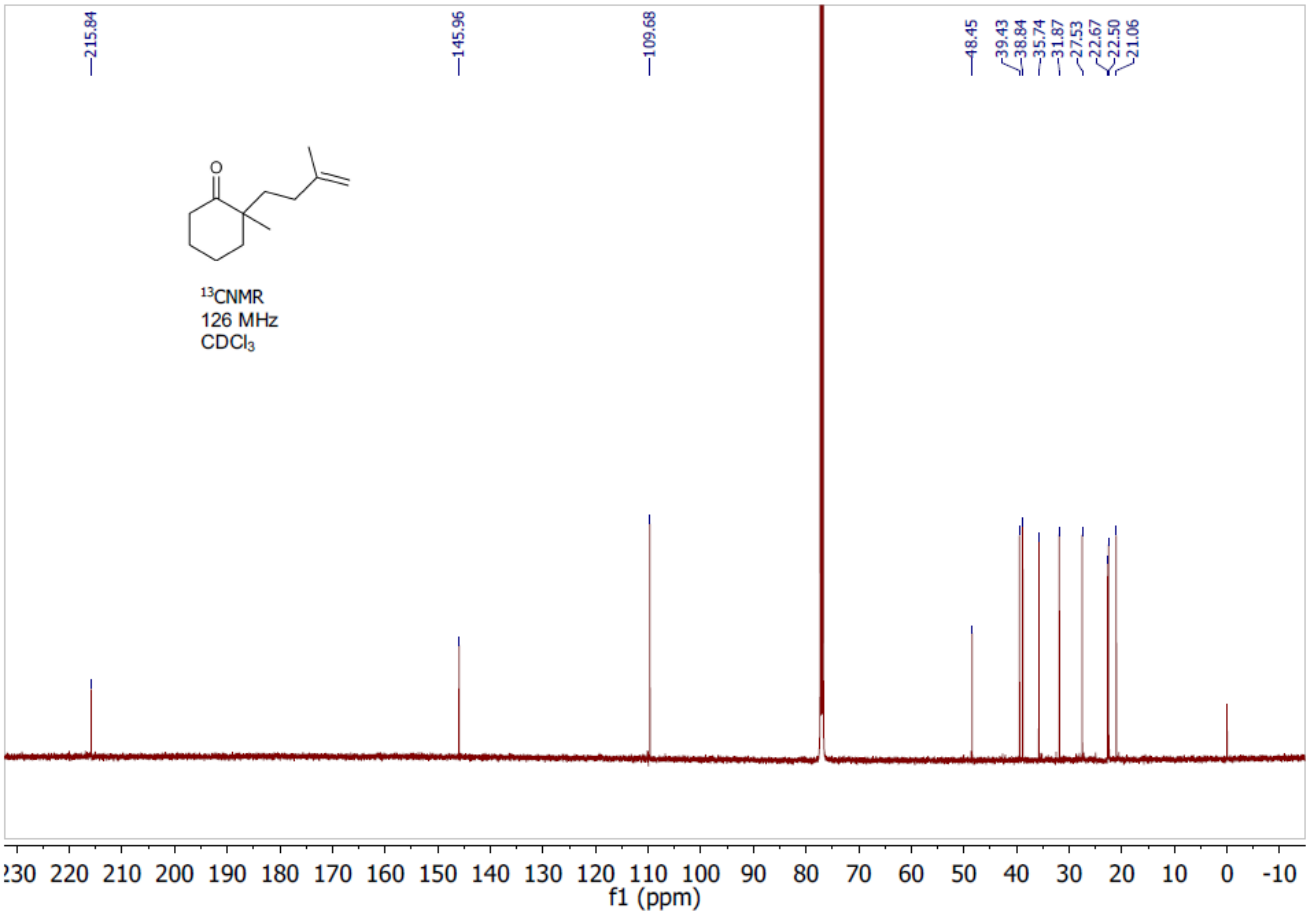

OTBS
H
H
1HNMR
500 MHz
CDCl3
f1 (ppm)

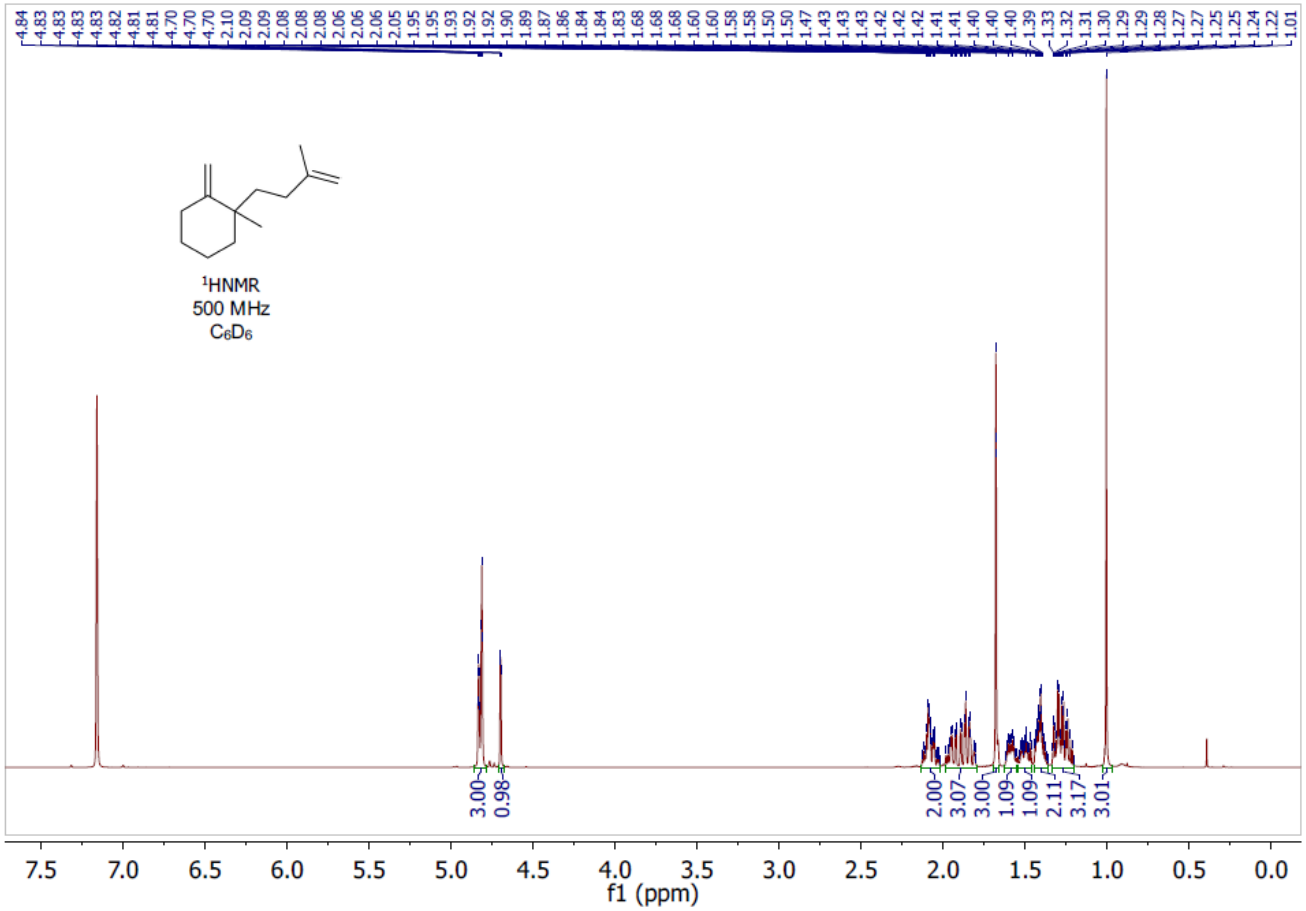

OTBS
H
H
13CNMR
126 MHz
CDCl3
f1 (ppm)

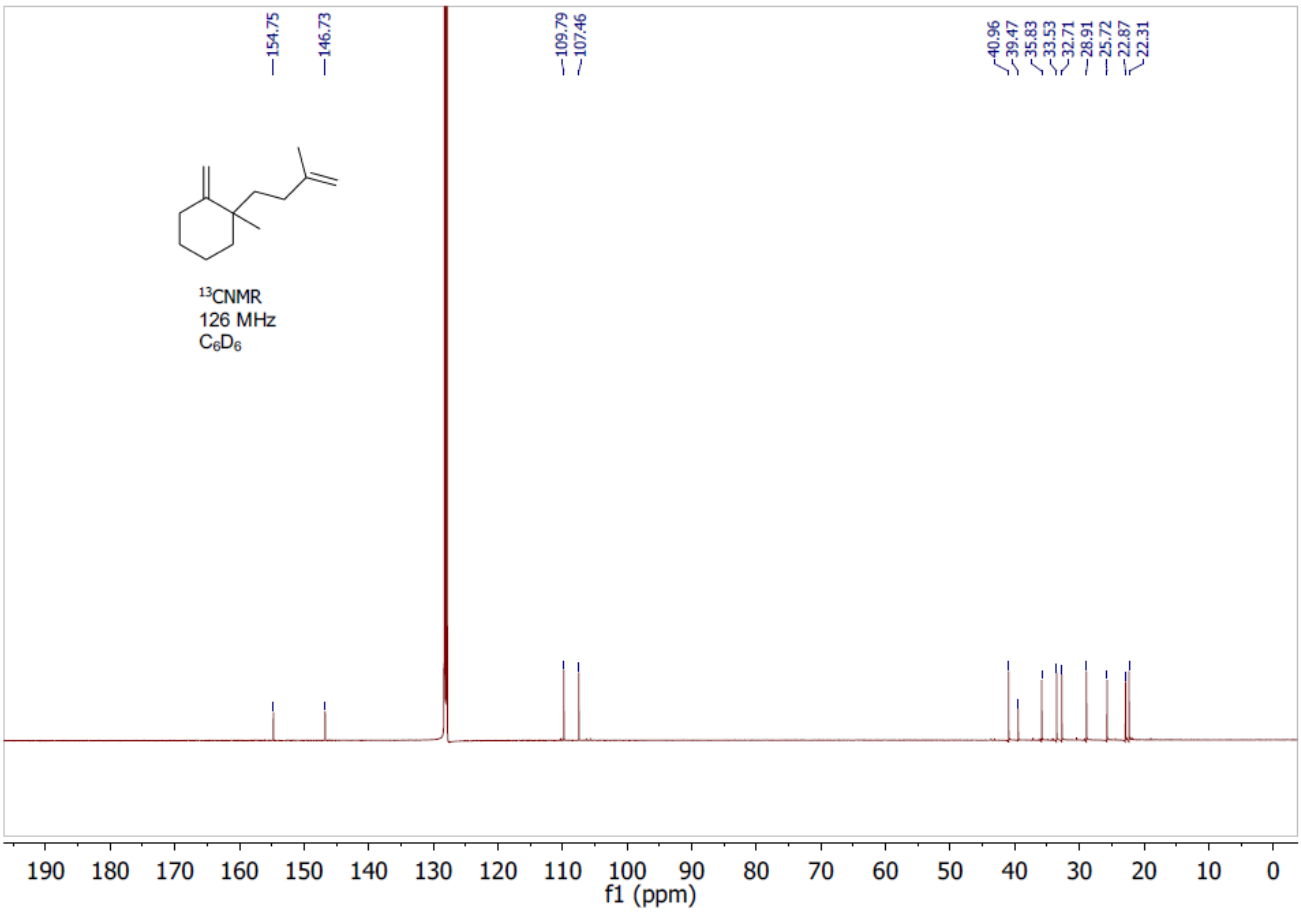

4.71 4.70 4.70 4.67 4.67 4.67 2.40 2.40 2.38 2.38 2.37 2.37 2.37 2.31 2.30 2.30 2.29 2.29 2.28 2.27 2.26 2.26 2.14 2.14 2.12 2.11 2.11 2.11 2.05 2.04 2.04 2.04 2.03 2.03 2.01 2.00 1.99 1.98 1.97 1.87 1.87 1.86 1.86 1.86 1.85 1.84 1.71 1.71 1.70 1.69 1.69 1.68 1.68 1.67 1.67 1.67 1.66 1.66 1.64 1.41 1.41 1.40 1.38 1.32 1.32 1.31 1.31 1.30 1.28
O
1HNMR
500 MHz
CDCl3
0.93
0.92
1.00
1.97
1.06
4.00
1.07
4.91
2.29
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)

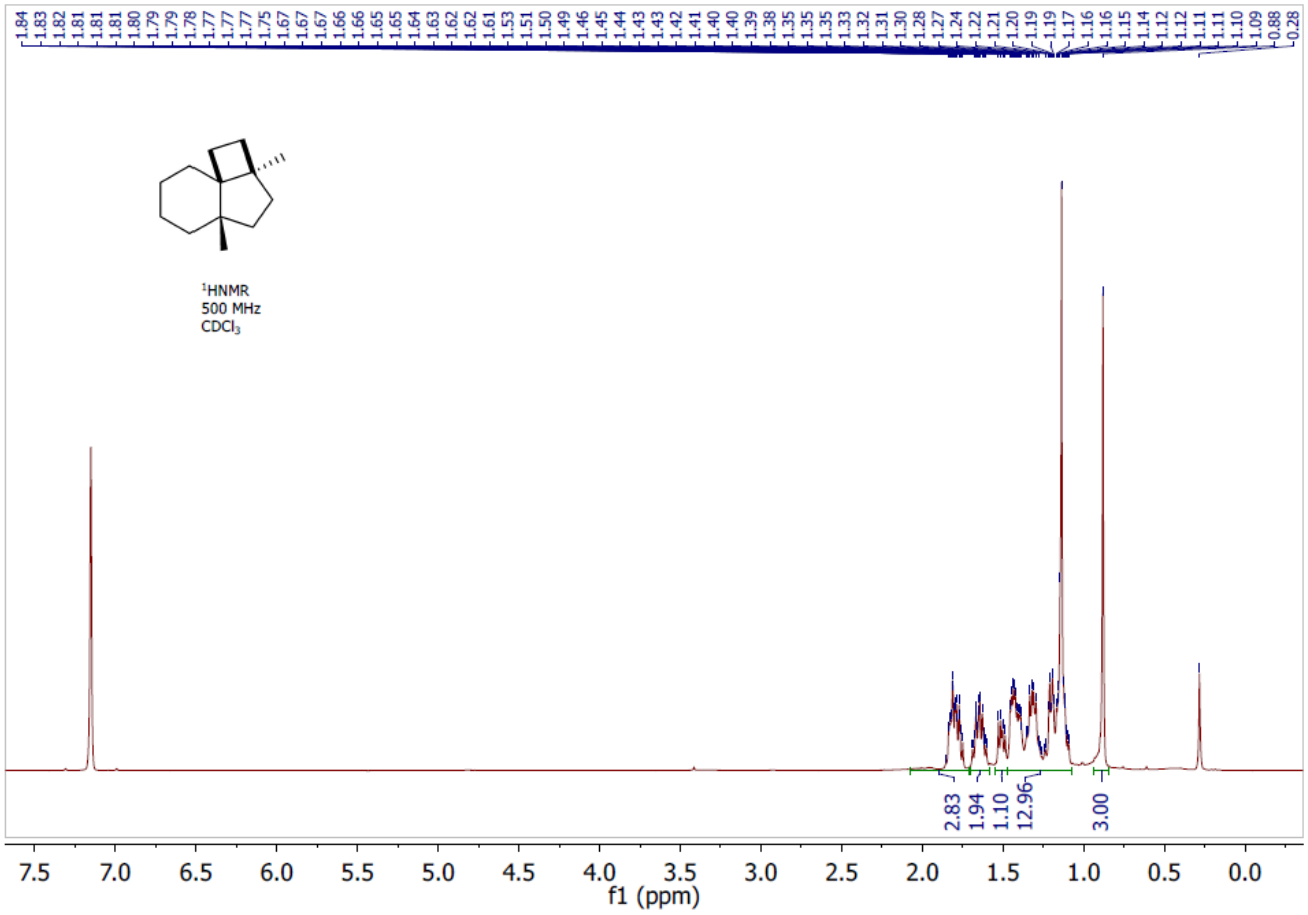

213.24
145.67
110.03
50.04
42.10
35.17
33.96
28.07
27.22
24.98
22.36
O
13CNMR
126 MHz
CDCl3
250 230 210 190 170 150 130 110 90 70 50 30 10 -10 -30
f1 (ppm)

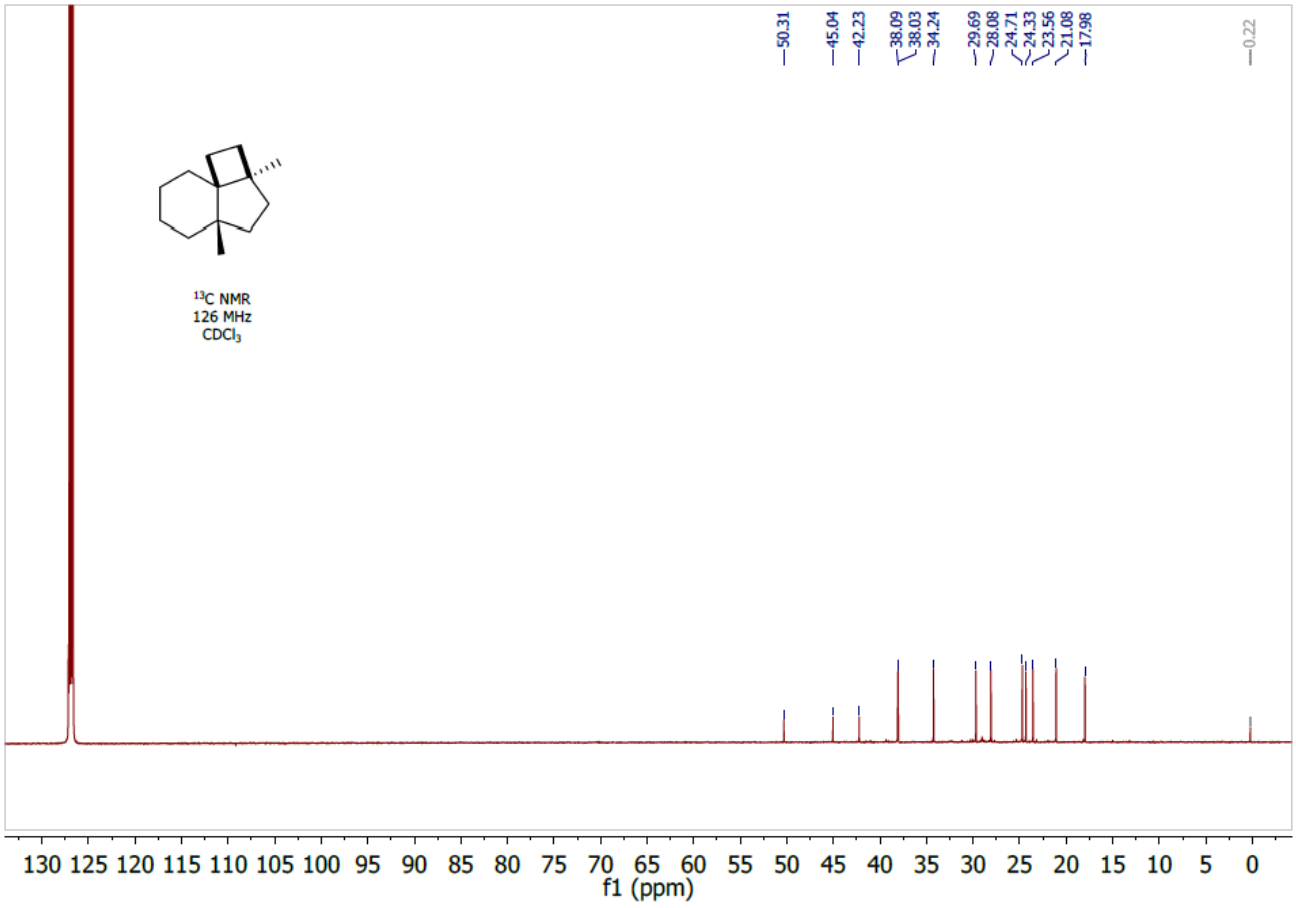

^{1}HNMR
500 MHz
$CDCl_3$
2.01
2.00
11.32
2.05
2.98
f1 (ppm)


215.84
145.96
109.68
48.45
39.43
38.84
35.74
31.87
27.53
22.67
22.50
21.06
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

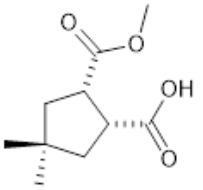

^{1}HNMR
500 MHz
C_6D_6
3.00
0.98
2.00
3.07
3.00
1.09
1.09
2.11
3.17
3.01
f1 (ppm)

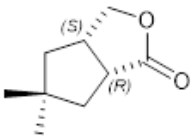

154.75
146.73
109.79
107.46
40.96
39.47
35.83
33.53
32.71
28.91
25.72
22.87
22.31
^{13}CNMR
126 MHz
C_6D_6
f1 (ppm)

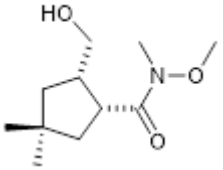

^{1}HNMR
500 MHz
$CDCl_3$
2.83
1.94
1.10
12.96
3.00
f1 (ppm)

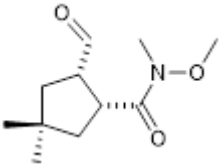

^{13}C NMR
126 MHz
$CDCl_3$
50.31
45.04
42.23
38.09
38.03
34.24
29.69
28.08
24.71
24.33
23.56
21.08
17.98
0.22
f1 (ppm)

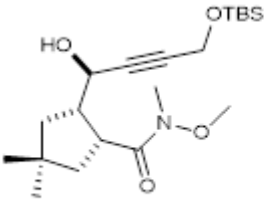
List of Compounds Chapter 4



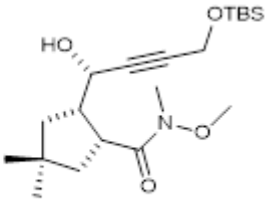


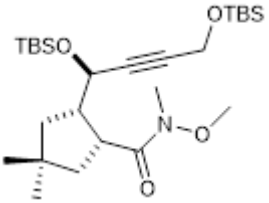


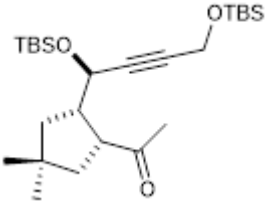


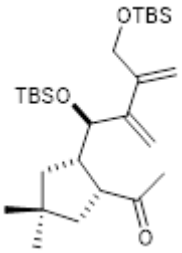


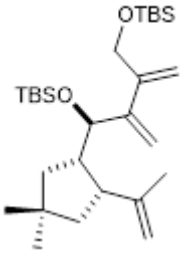
2 : **1**

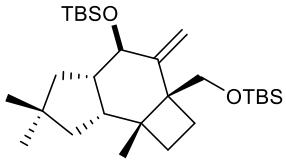


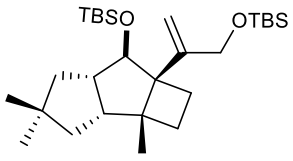


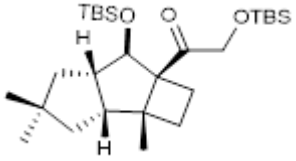


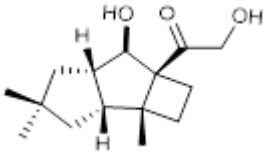


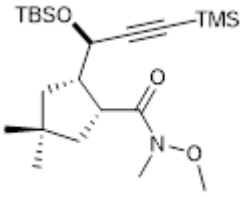


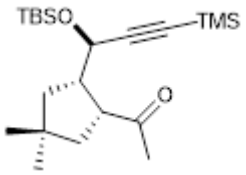









TBSO
TMS
O
N
O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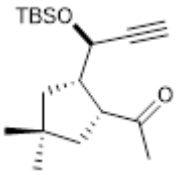
TMS
O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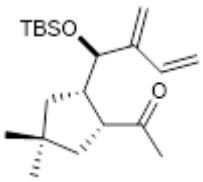
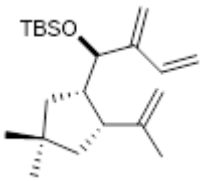
O


TBSO
O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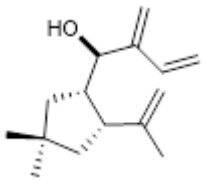
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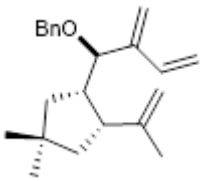
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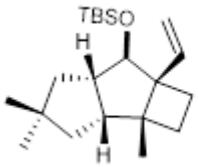
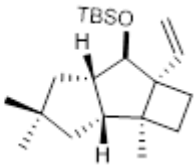

TBSO
H
H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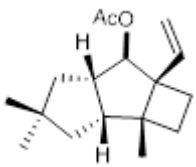
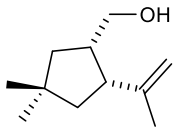
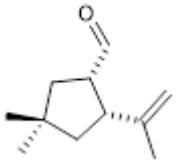
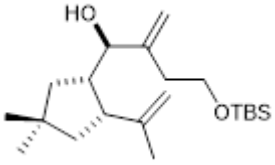
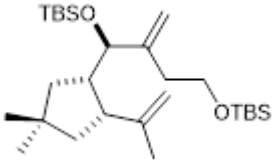
H
H

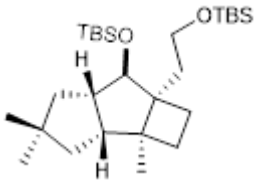

AcO
H
H

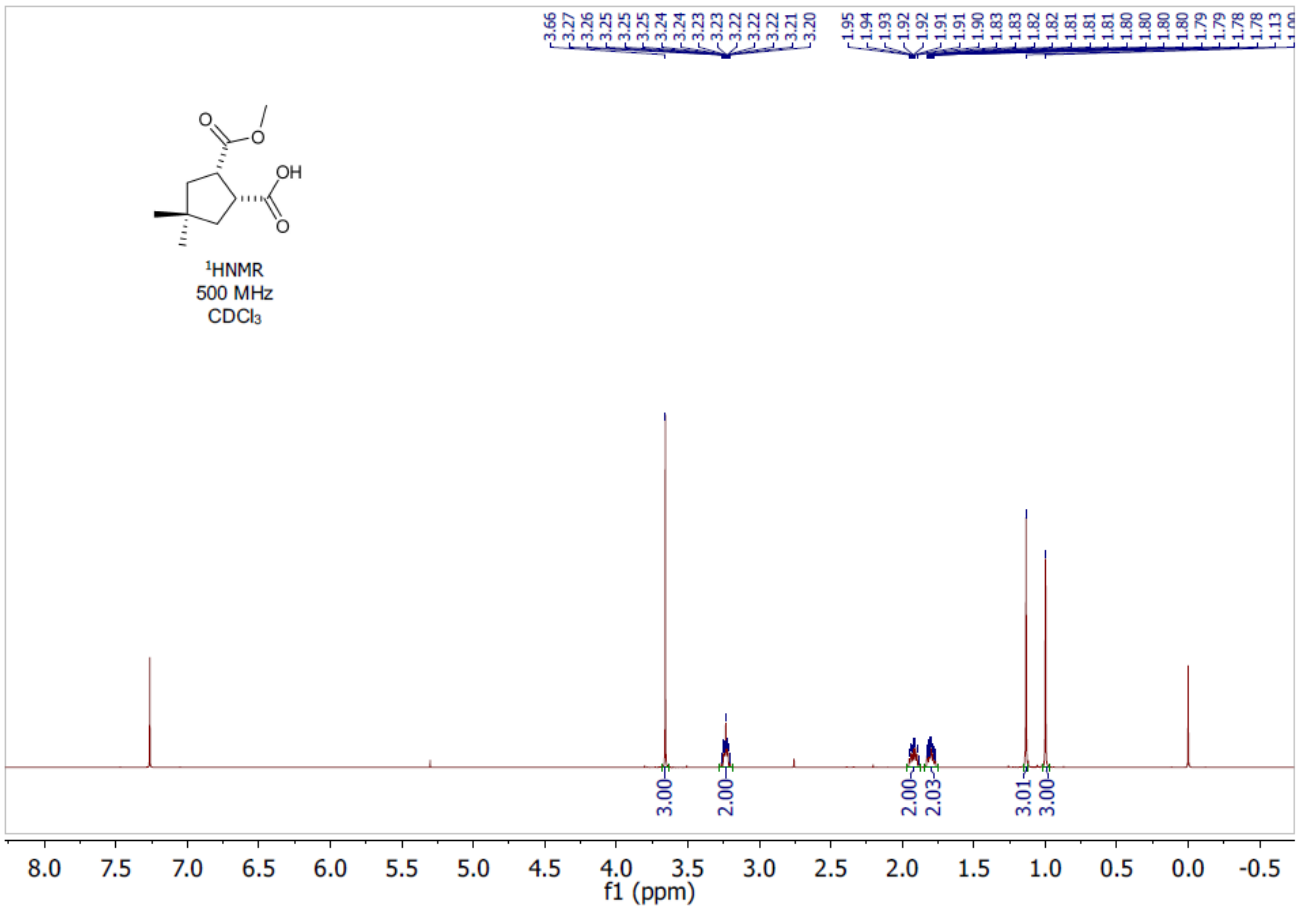

OH

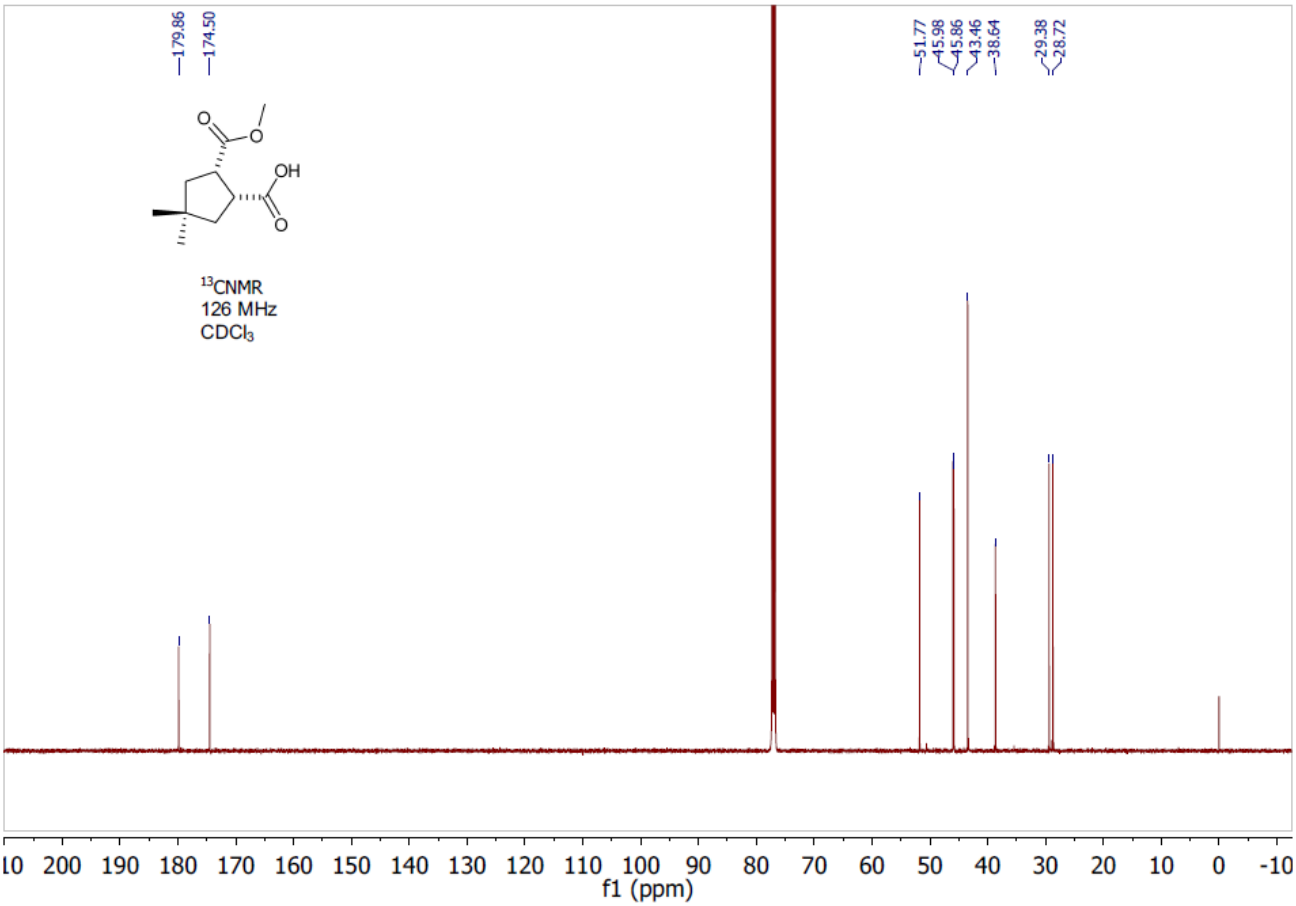

O

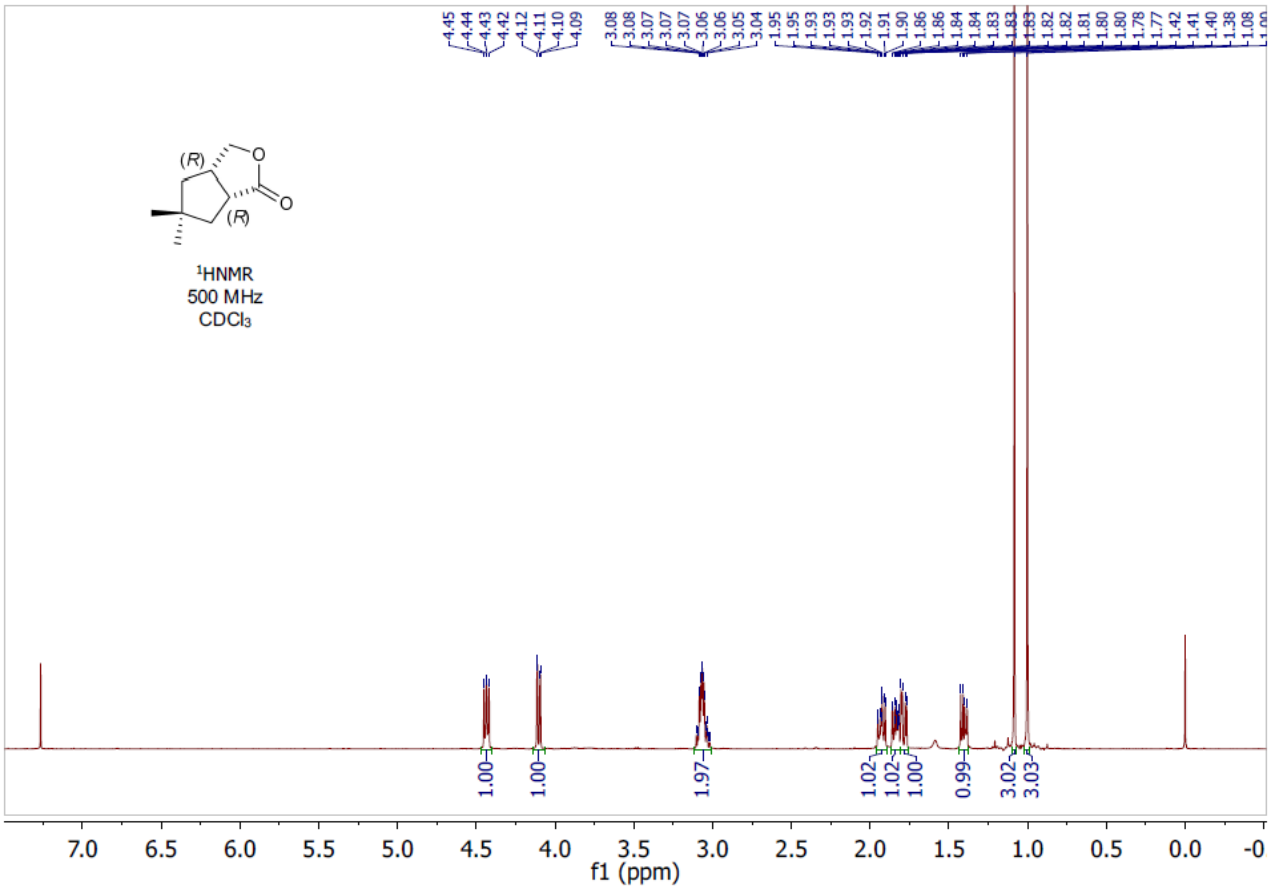

HO
OTBS

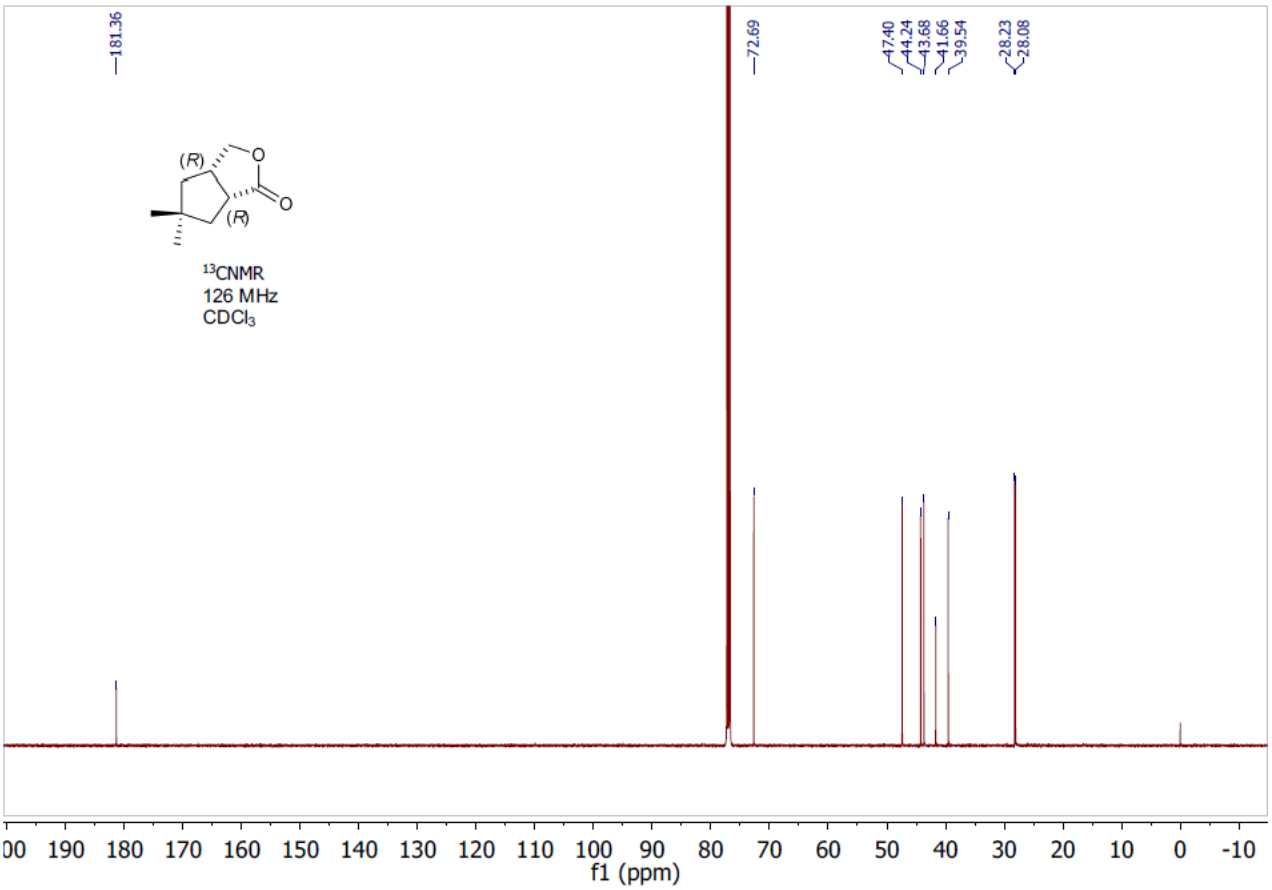

TBSO
OTBS

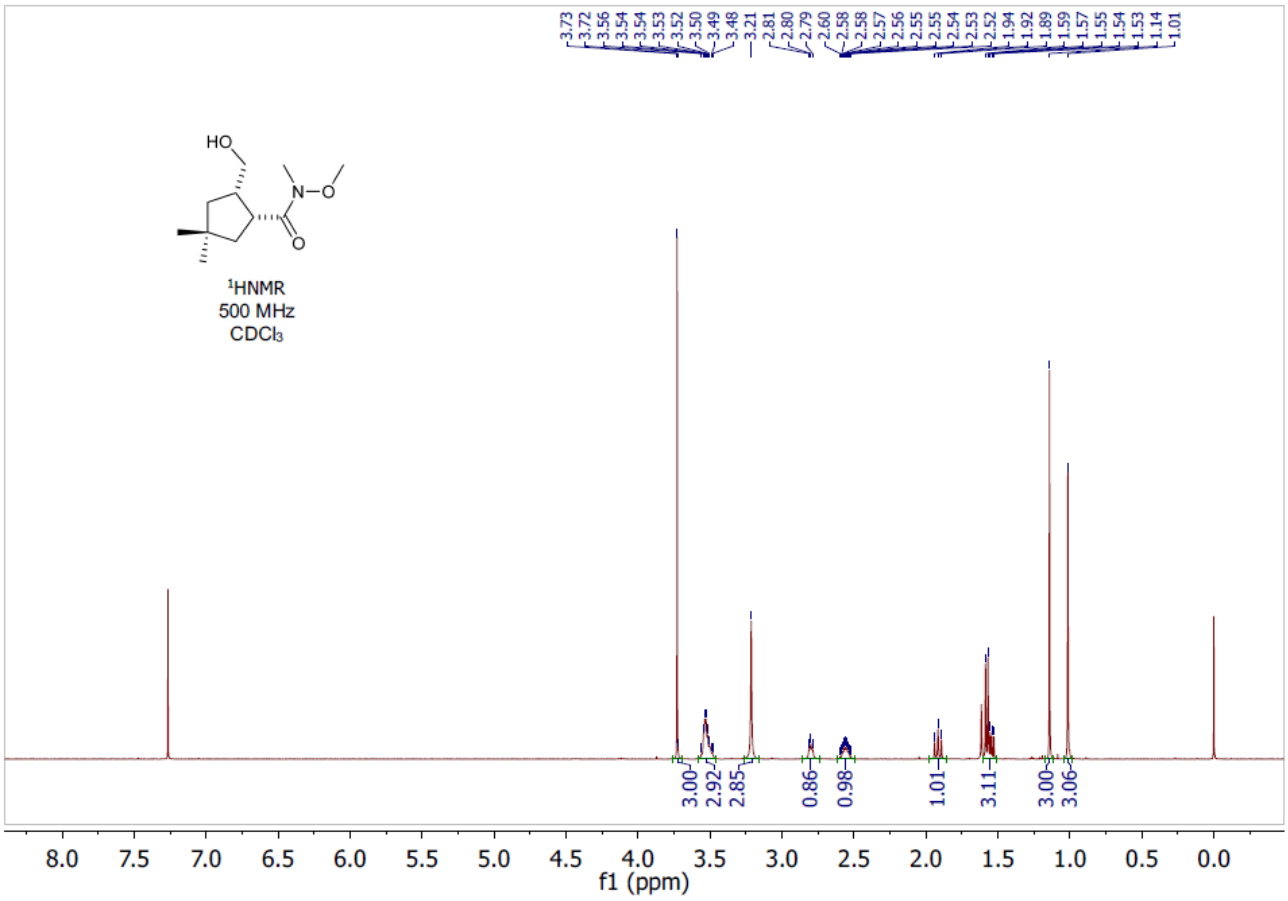

TBSO
OTBS
H
H

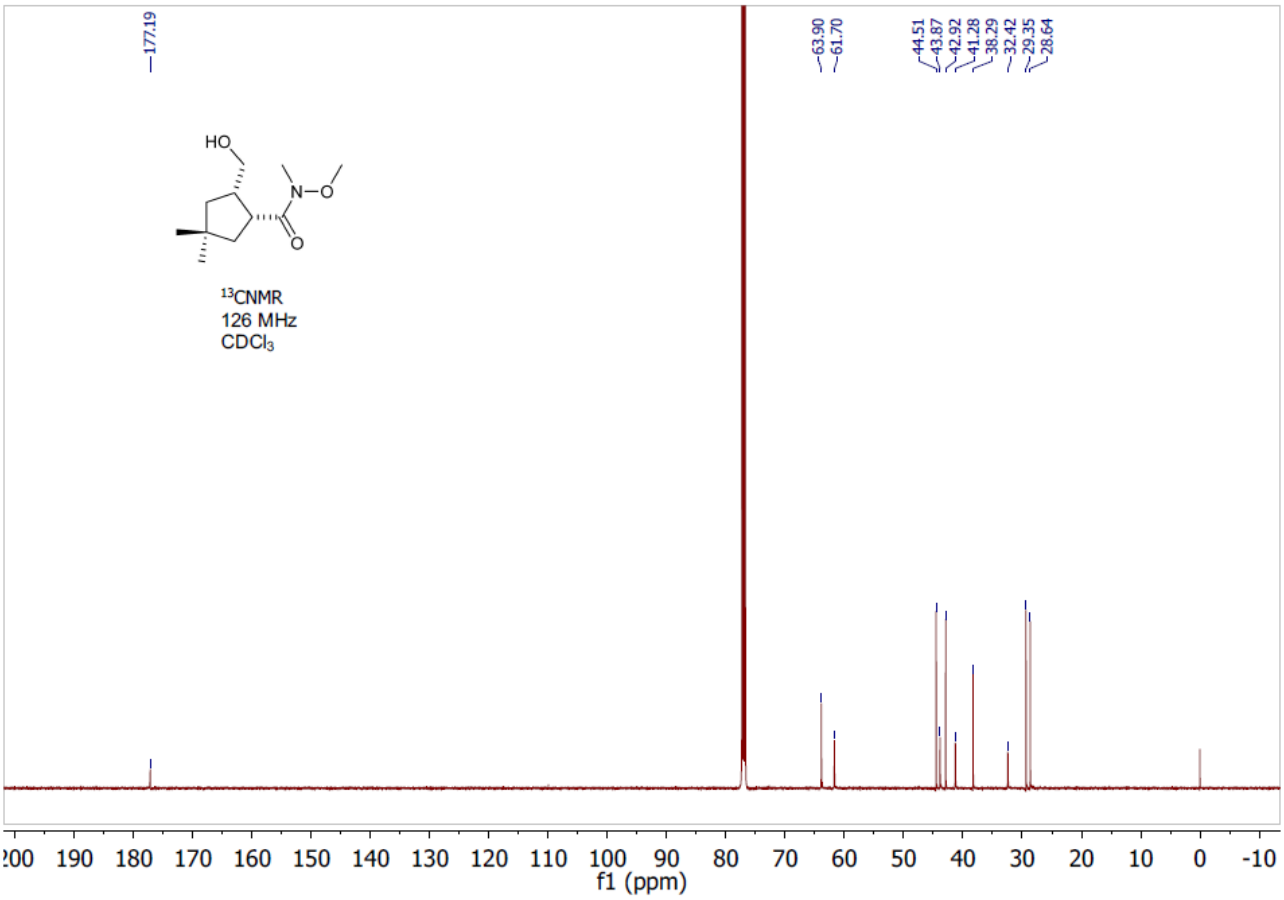

3.66
3.27
3.26
3.25
3.25
3.25
3.24
3.24
3.23
3.23
3.22
3.22
3.22
3.21
3.20
1.95
1.94
1.93
1.92
1.92
1.91
1.91
1.90
1.83
1.83
1.82
1.82
1.81
1.81
1.81
1.80
1.80
1.80
1.80
1.79
1.79
1.78
1.78
1.13
O
O
OH
O
1HNMR
500 MHz
CDCl3
3.00
2.00
2.00
2.03
3.01
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

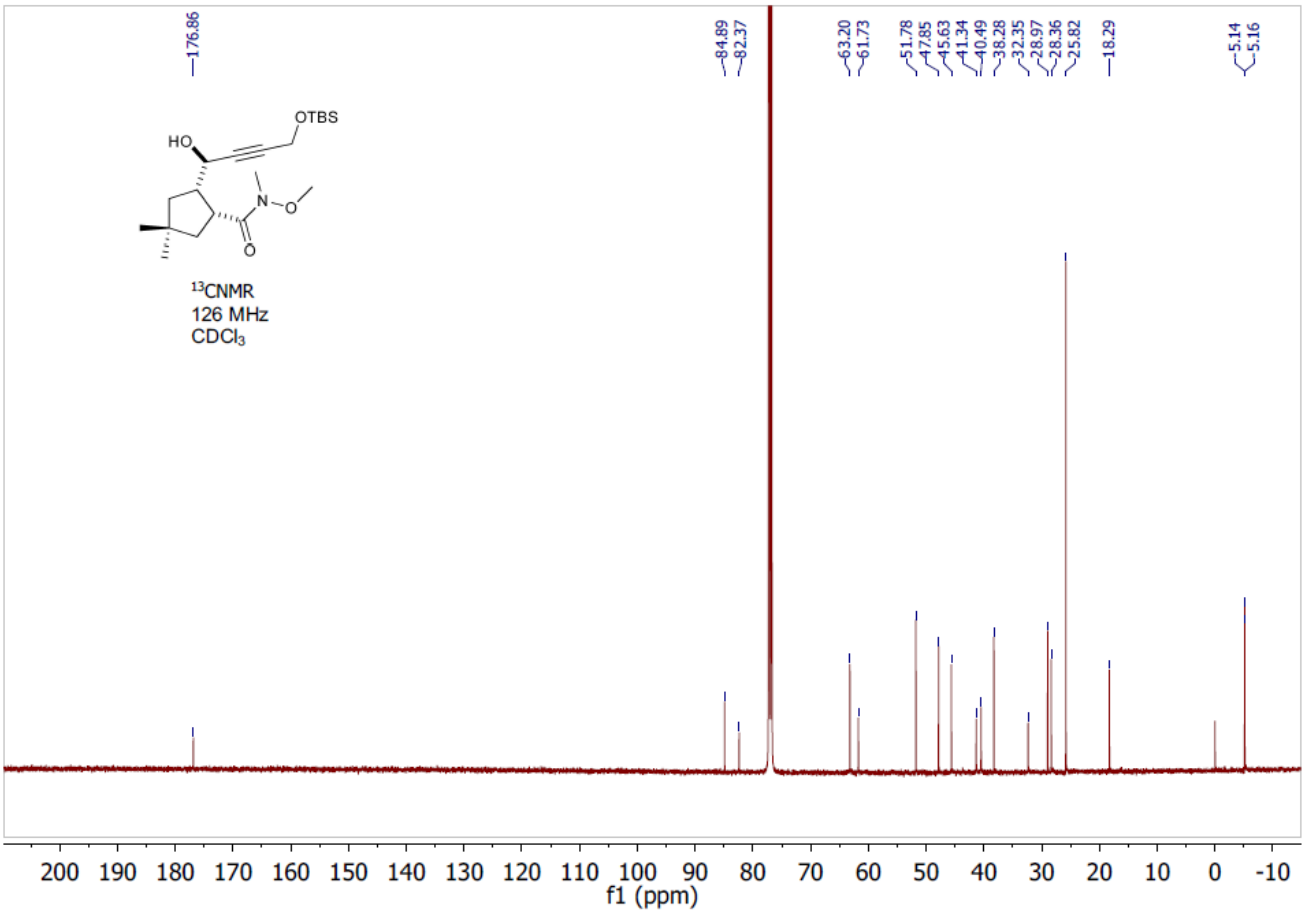

179.86
174.50
51.77
45.98
45.86
43.46
38.64
29.38
28.72
O
O
OH
O
13CNMR
126 MHz
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

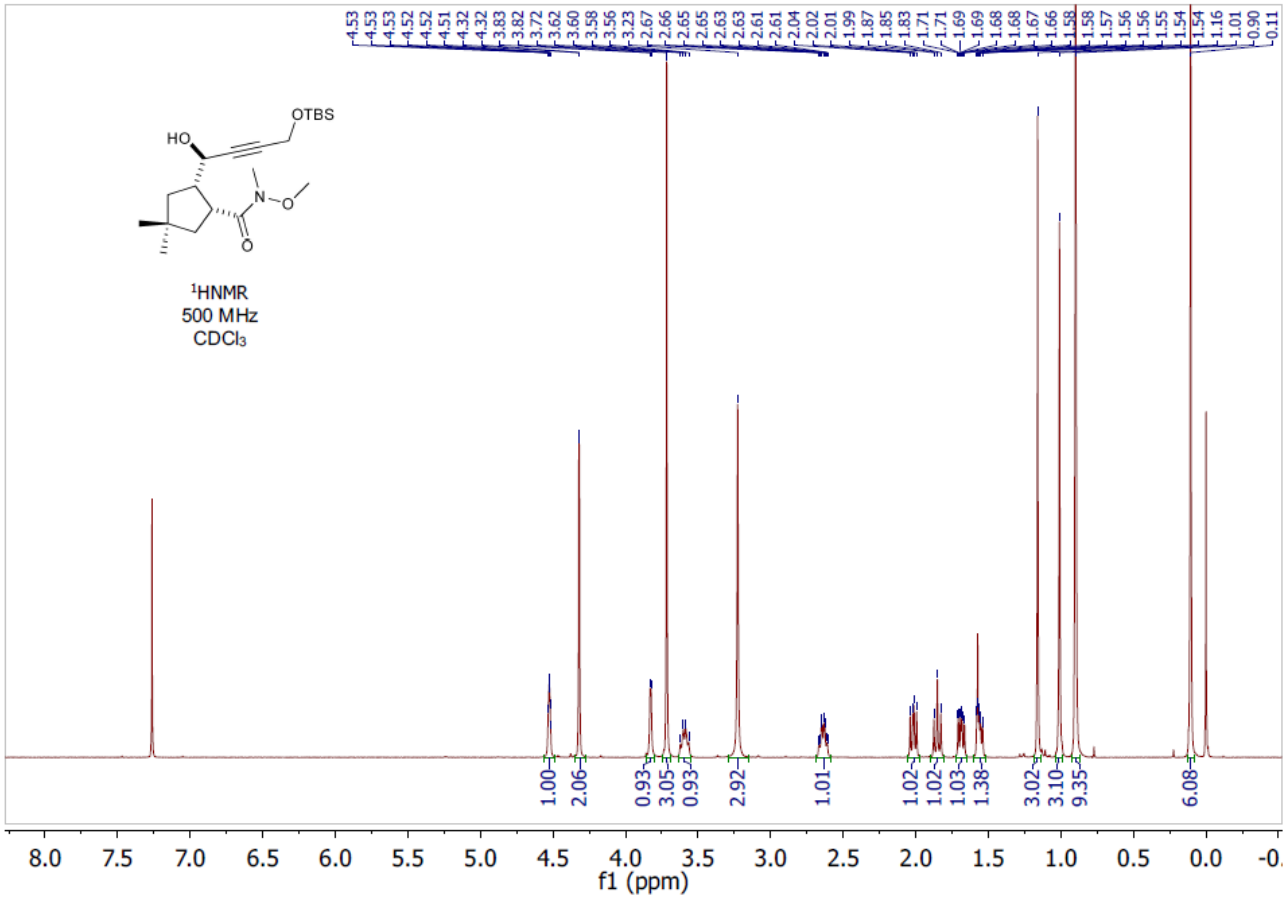

(R)
O
O
(R)
1HNMR
500 MHz
CDCl3
4.45
4.44
4.43
4.42
4.12
4.11
4.10
4.09
3.08
3.08
3.07
3.07
3.07
3.06
3.06
3.05
3.04
1.95
1.95
1.93
1.93
1.92
1.91
1.90
1.86
1.86
1.84
1.84
1.83
1.83
1.83
1.82
1.82
1.81
1.80
1.80
1.78
1.77
1.42
1.41
1.40
1.38
1.08
1.00
1.00
1.97
1.02
1.02
1.00
0.99
3.02
3.03
7.0
6.5
6.0
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
f1 (ppm)

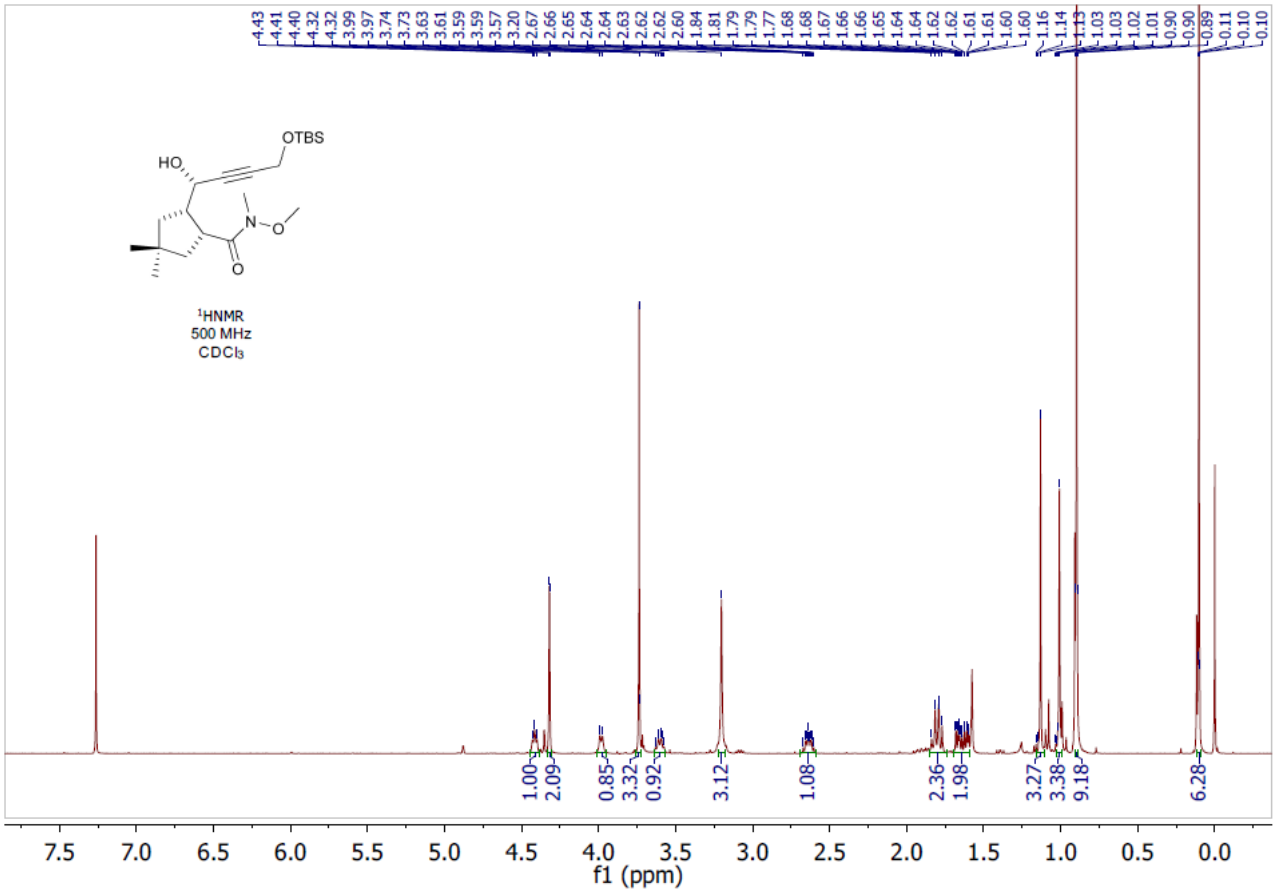

181.36
72.69
47.40
44.24
43.68
41.66
39.54
28.23
28.08
(R)
O
O
(R)
13CNMR
126 MHz
CDCl3
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

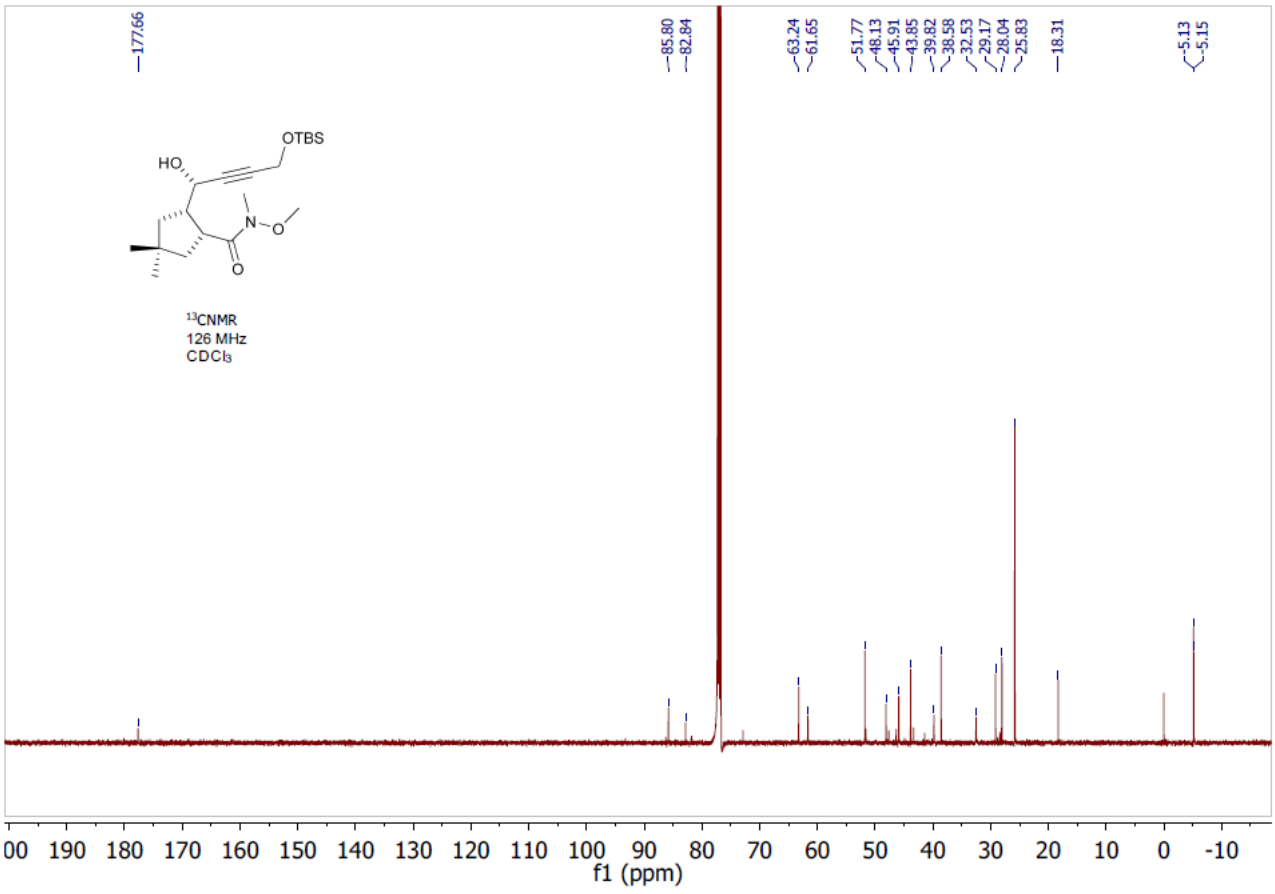

HO
N–O
O
^{1}HNMR
500 MHz
$CDCl_3$
3.73
3.72
3.56
3.54
3.54
3.53
3.52
3.50
3.49
3.48
3.21
2.81
2.80
2.79
2.60
2.58
2.58
2.57
2.56
2.55
2.55
2.54
2.53
2.52
1.94
1.92
1.89
1.59
1.57
1.55
1.54
1.53
1.14
1.01
3.00
2.92
2.85
0.86
0.98
1.01
3.11
3.00
3.06
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

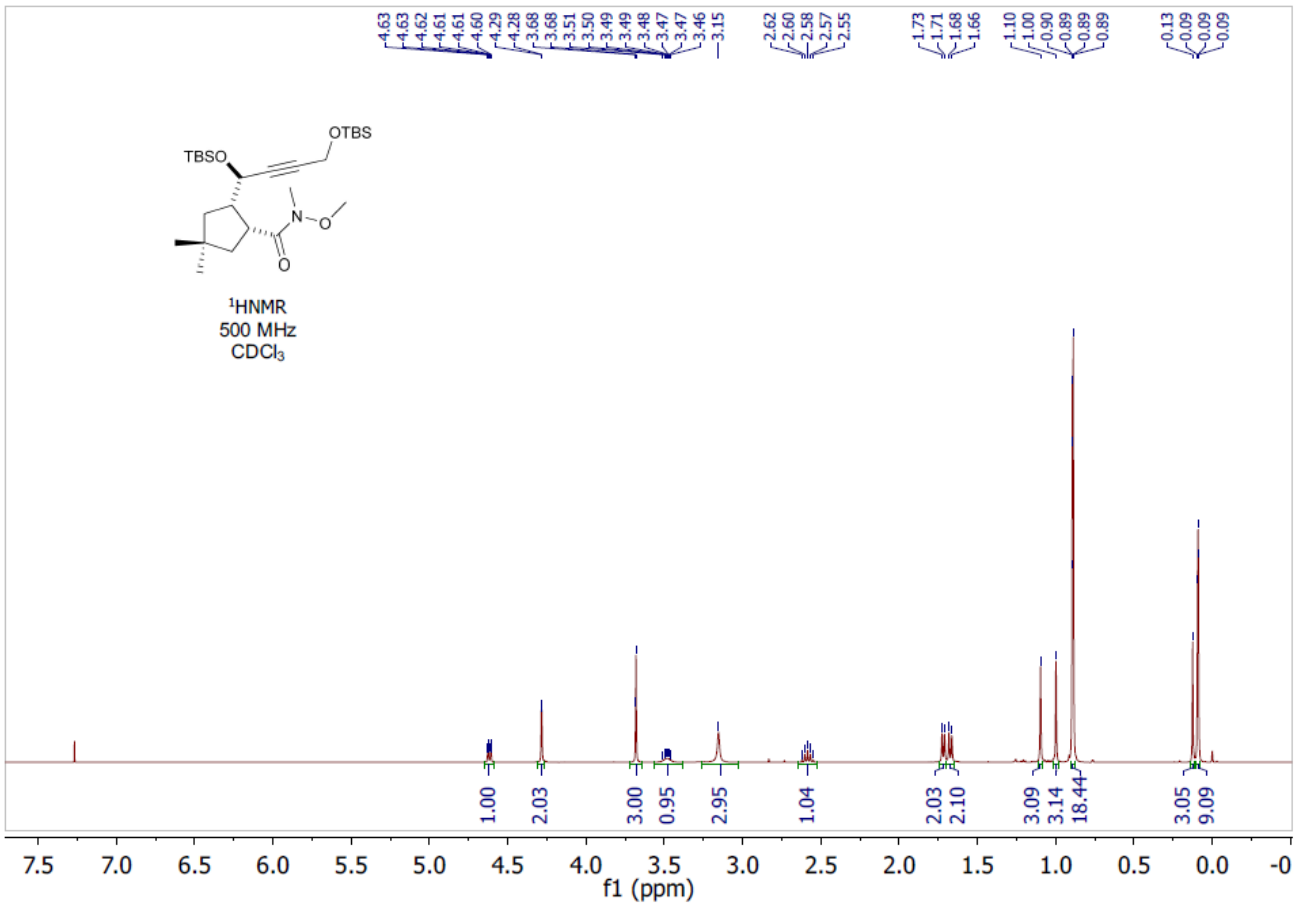

177.19
63.90
61.70
44.51
43.87
42.92
41.28
38.29
32.42
29.35
28.64
HO
N–O
O
^{13}CNMR
126 MHz
$CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

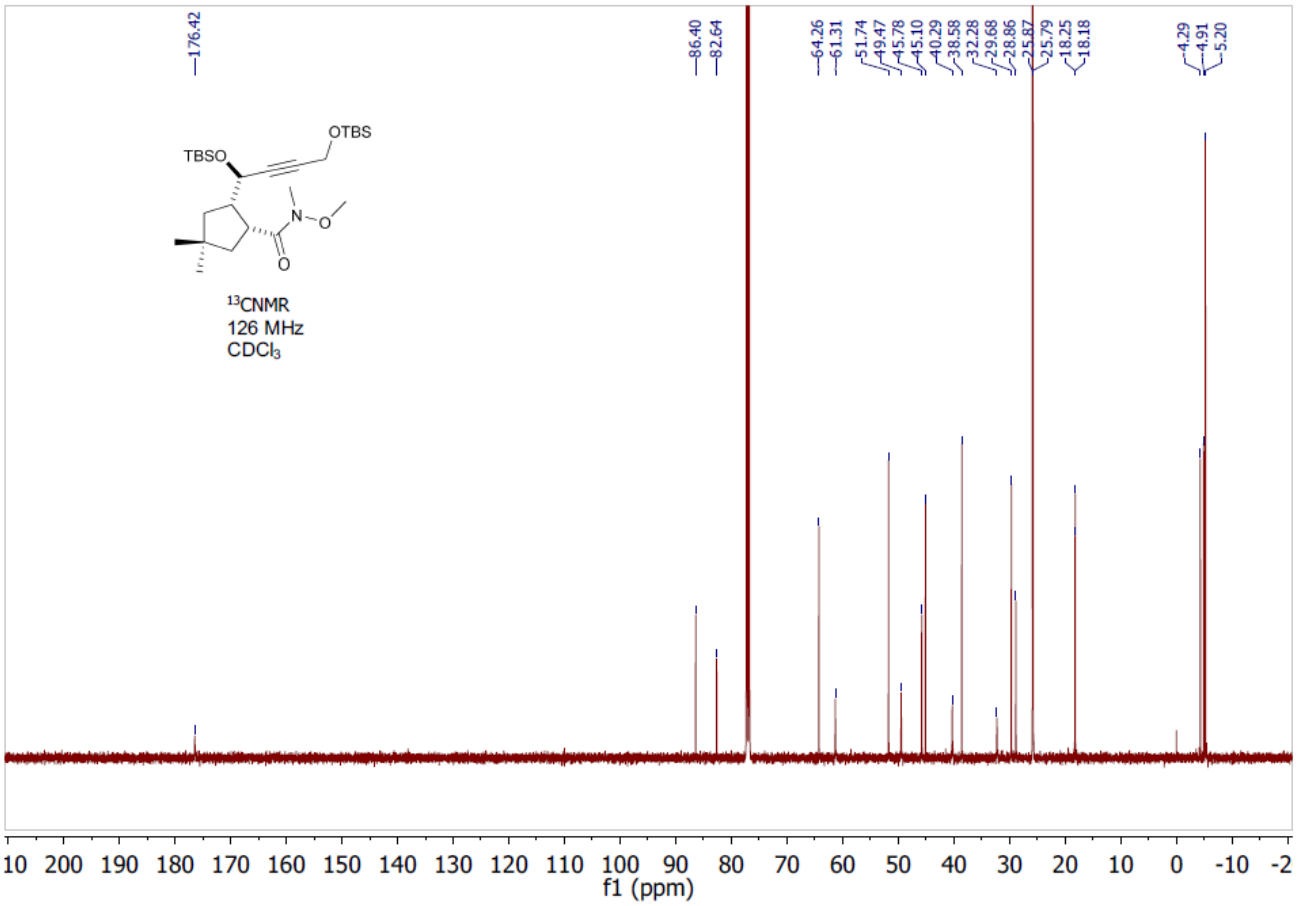

176.86
84.89
82.37
63.20
61.73
51.78
47.85
45.63
41.34
40.49
38.28
32.35
28.97
28.36
25.82
18.29
5.14
5.16
OTBS
HO
N
O
O
13CNMR
126 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

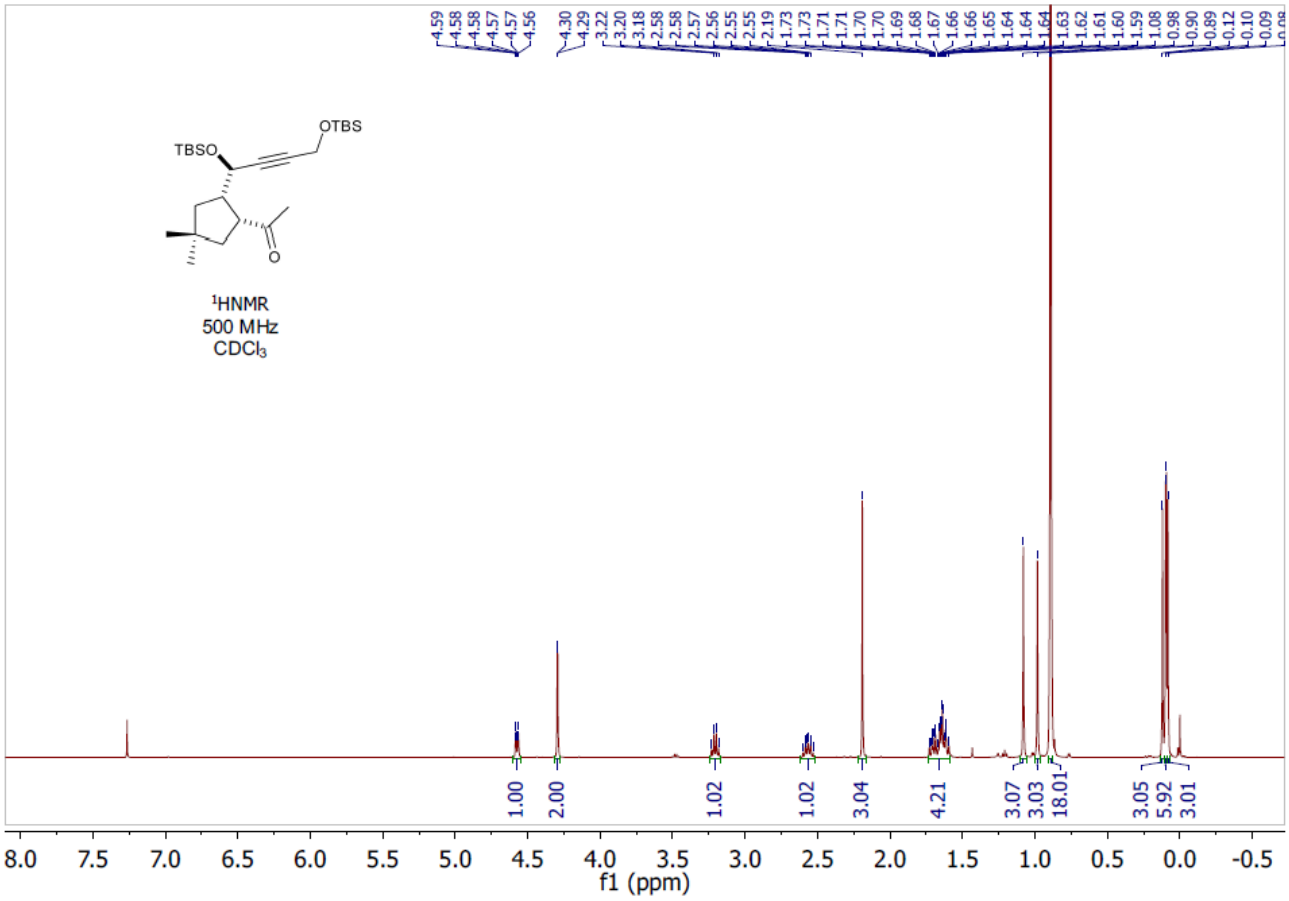

OTBS
HO
N
O
O
1HNMR
500 MHz
CDCl3
1.00
2.06
0.93
3.05
0.93
2.92
1.01
1.02
1.02
1.03
1.38
3.02
3.10
9.35
6.08
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

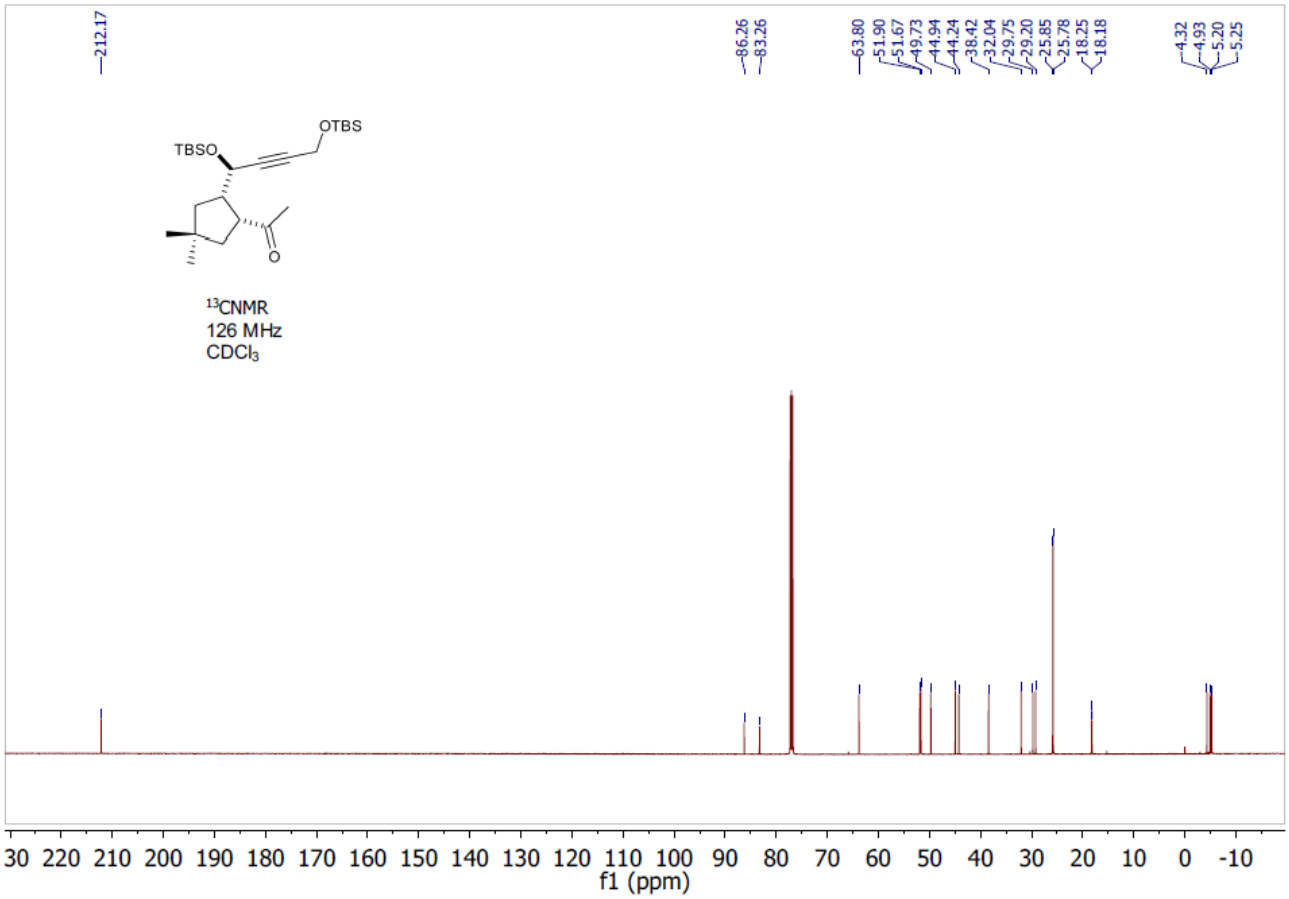

OTBS
HO
N
O
O
^{1}HNMR
500 MHz
CDCl$_3$
f1 (ppm)

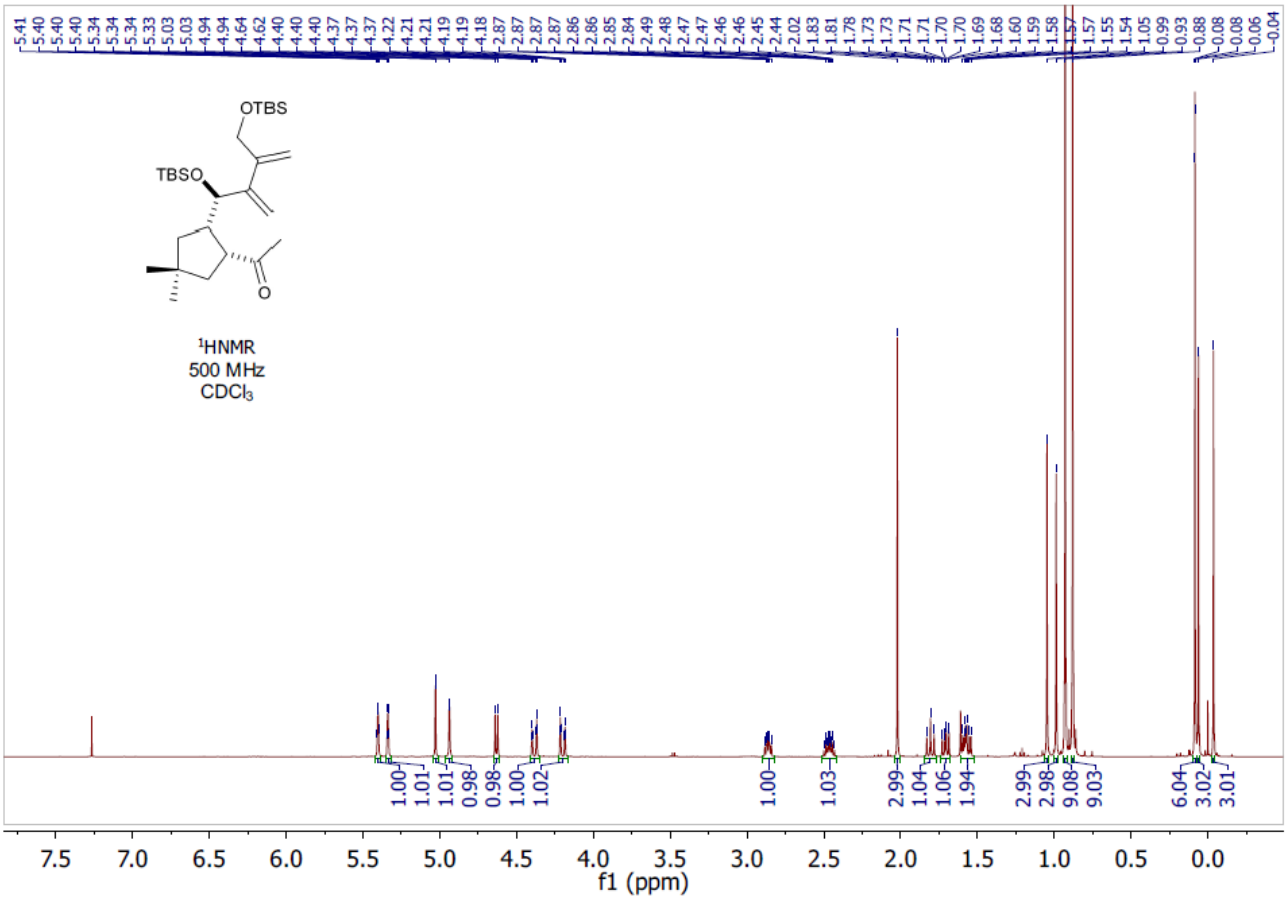

OTBS
HO
N
O
O
^{13}CNMR
126 MHz
CDCl$_3$
f1 (ppm)

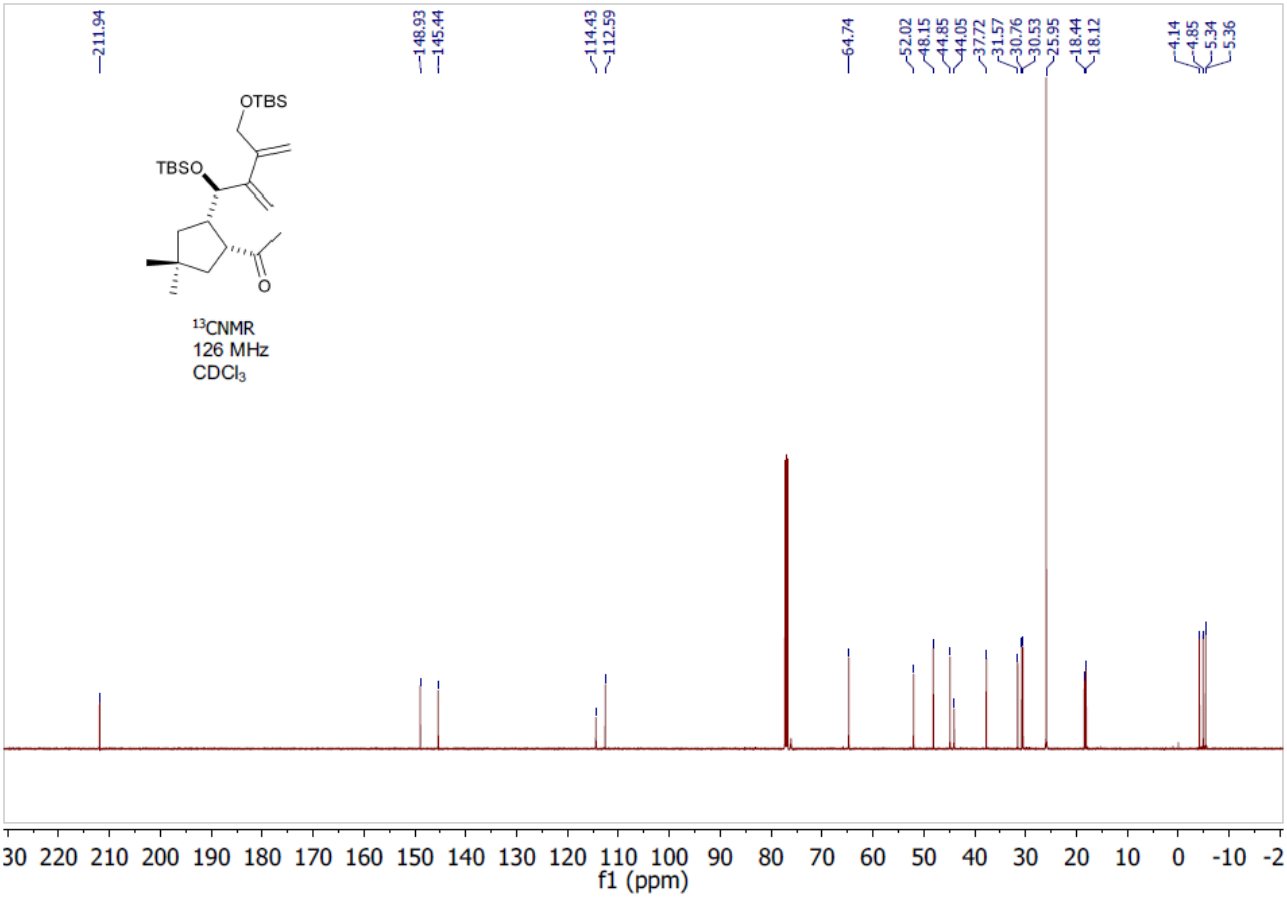

4.63
4.63
4.62
4.61
4.61
4.60
4.29
4.28
3.68
3.68
3.51
3.50
3.49
3.49
3.48
3.47
3.47
3.46
3.15
2.62
2.60
2.58
2.57
2.55
1.73
1.71
1.68
1.66
1.10
1.00
0.90
0.89
0.89
0.89
0.13
0.09
0.09
0.09
TBSO
OTBS
N
O
O
1HNMR
500 MHz
CDCl3
1.00
2.03
3.00
0.95
2.95
1.04
2.03
2.10
3.09
3.14
18.44
3.05
9.09
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

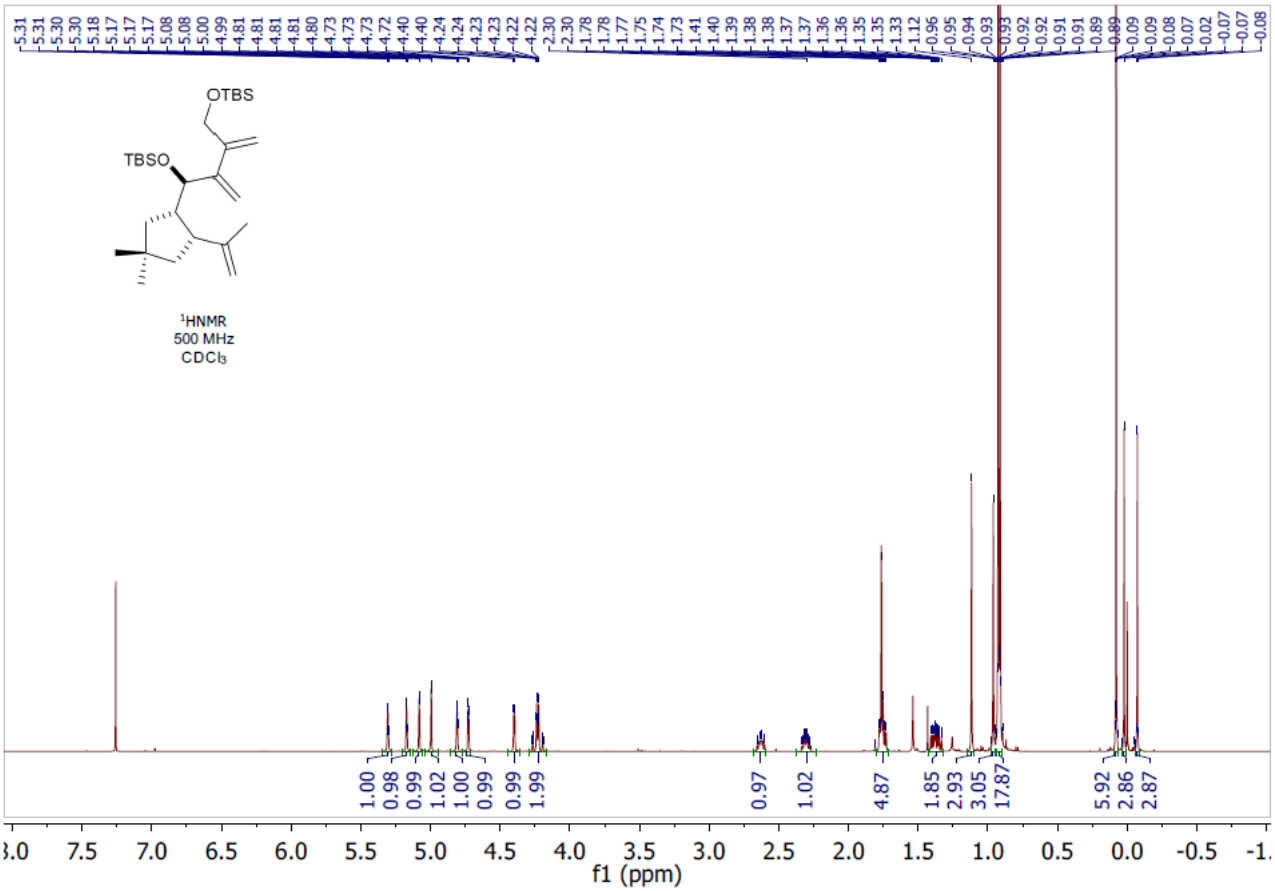

176.42
86.40
82.64
64.26
61.31
51.74
49.47
45.78
45.10
40.29
38.58
32.28
29.68
28.86
25.87
25.79
18.25
18.18
4.29
4.91
5.20
TBSO
OTBS
N
O
O
13CNMR
126 MHz
CDCl3
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)

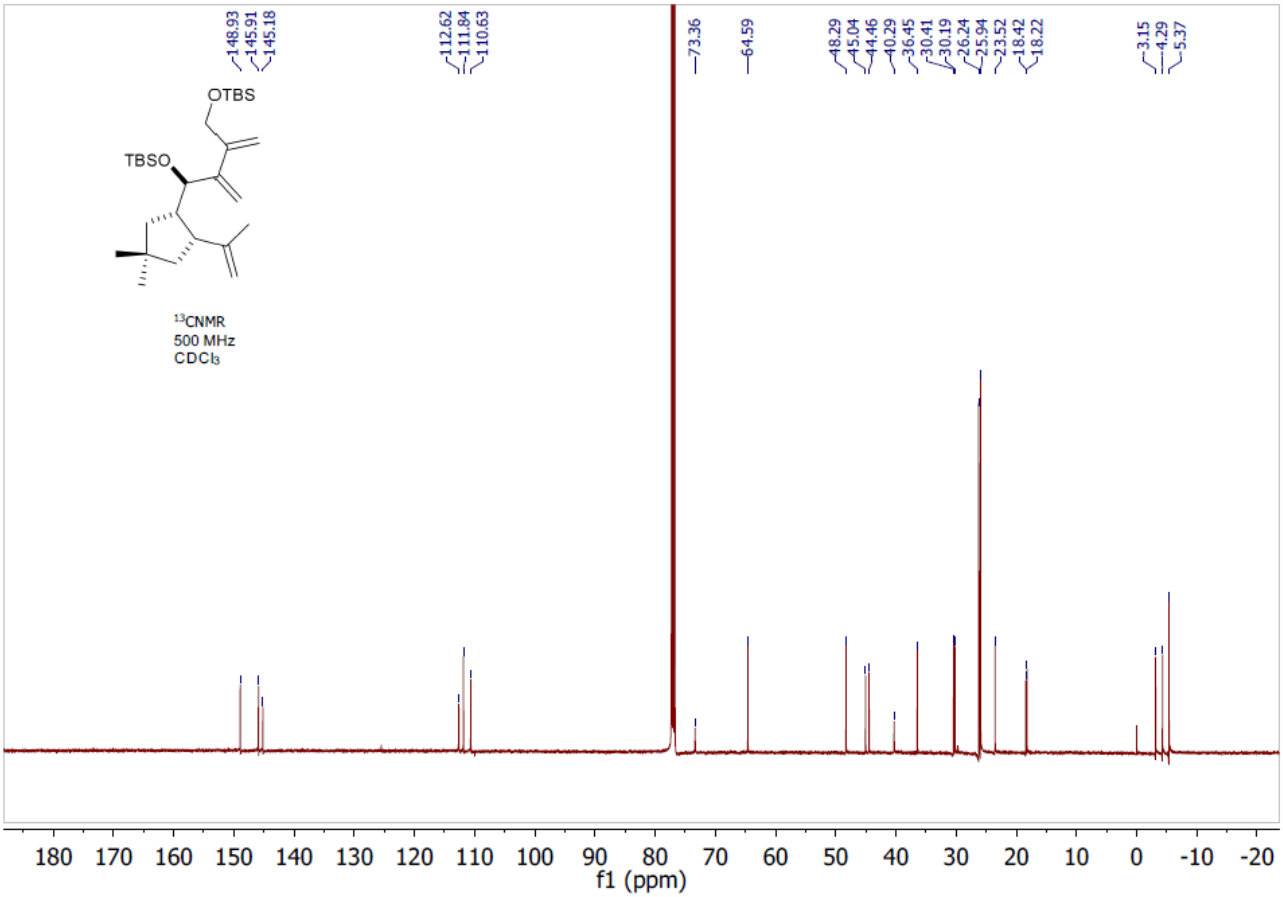

TBSO
OTBS
O
^{1}HNMR
500 MHz
$CDCl_3$
1.00
2.00
1.02
1.02
3.04
4.21
3.07
3.03
18.01
3.05
5.92
3.01
f1 (ppm)

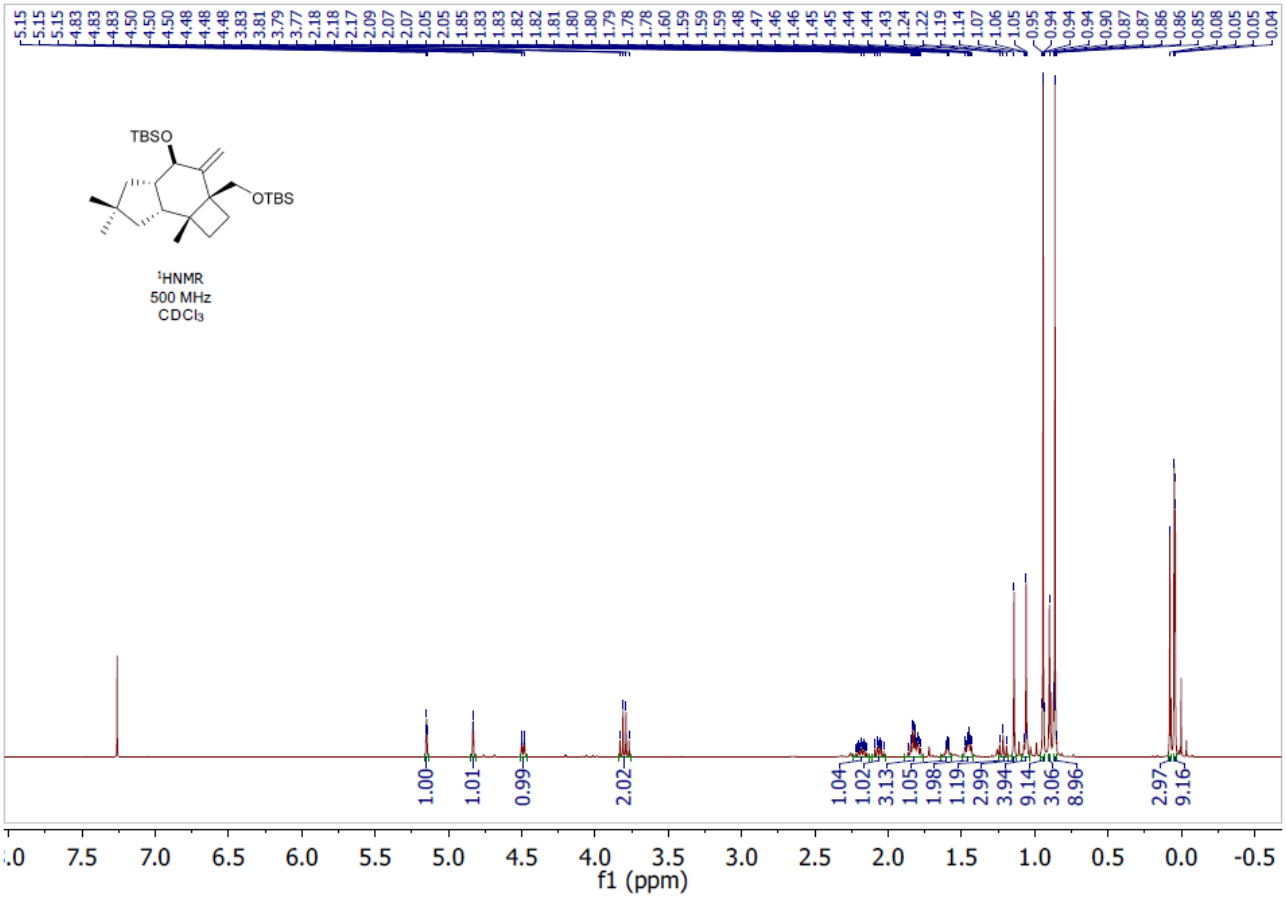

TBSO
OTBS
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

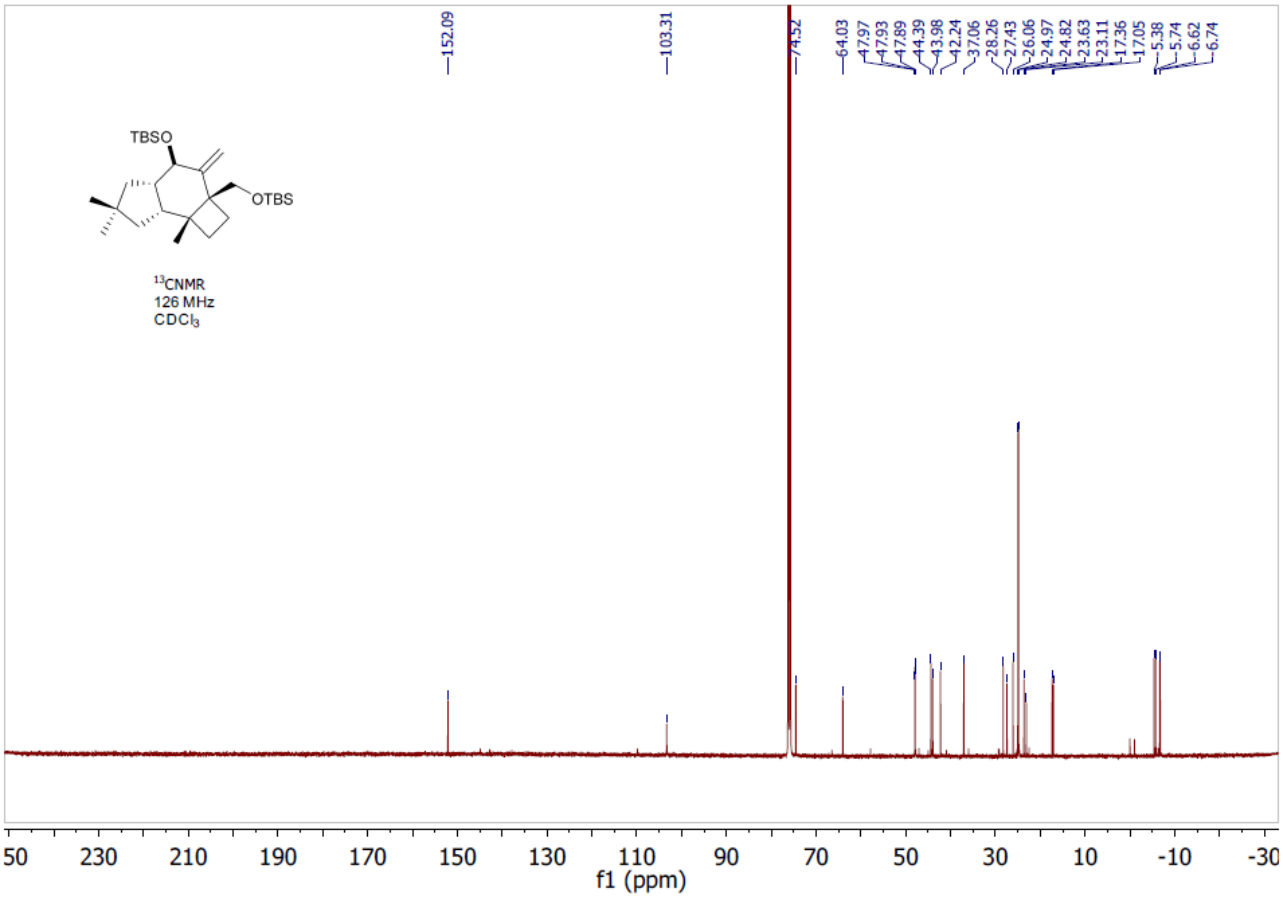

OTBS
TBSO
O
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

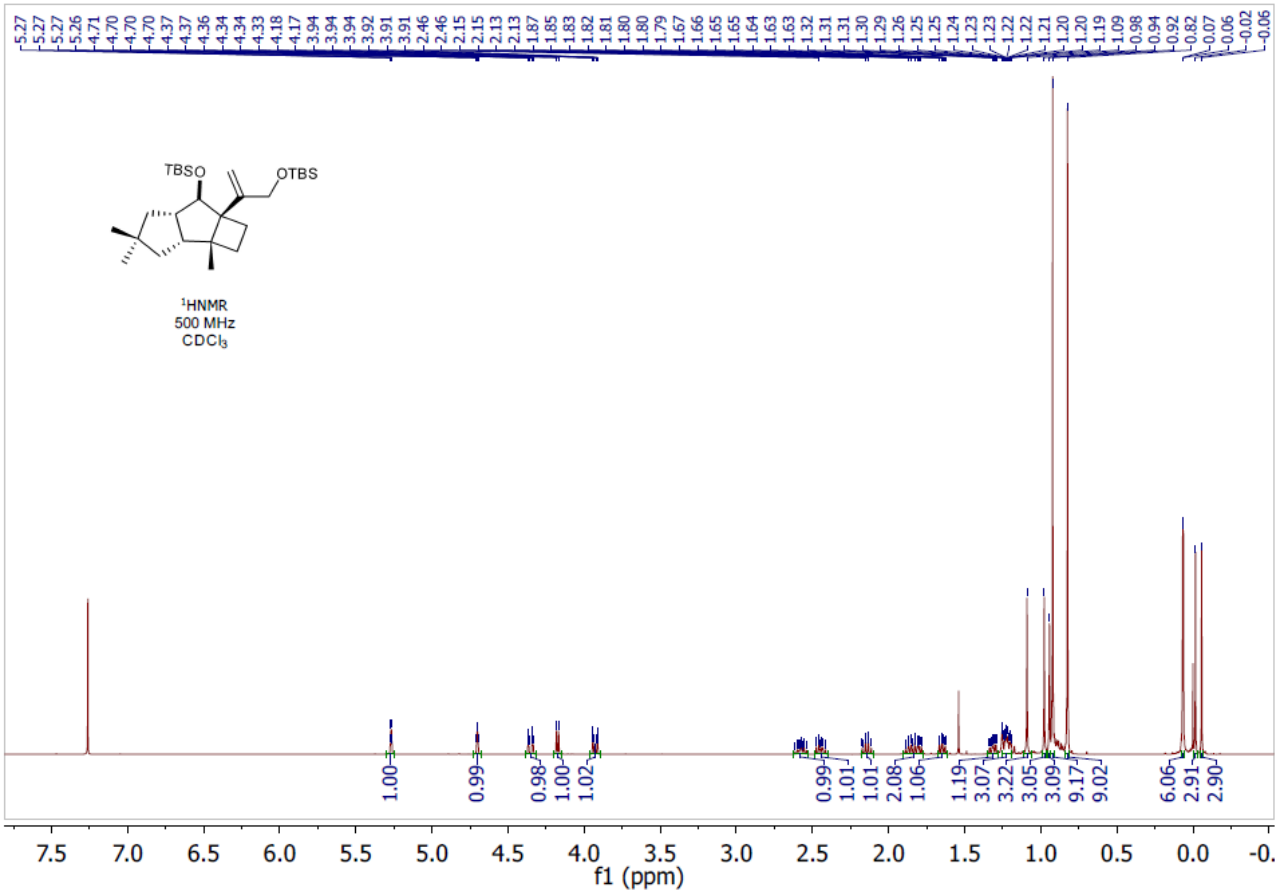

OTBS
TBSO
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

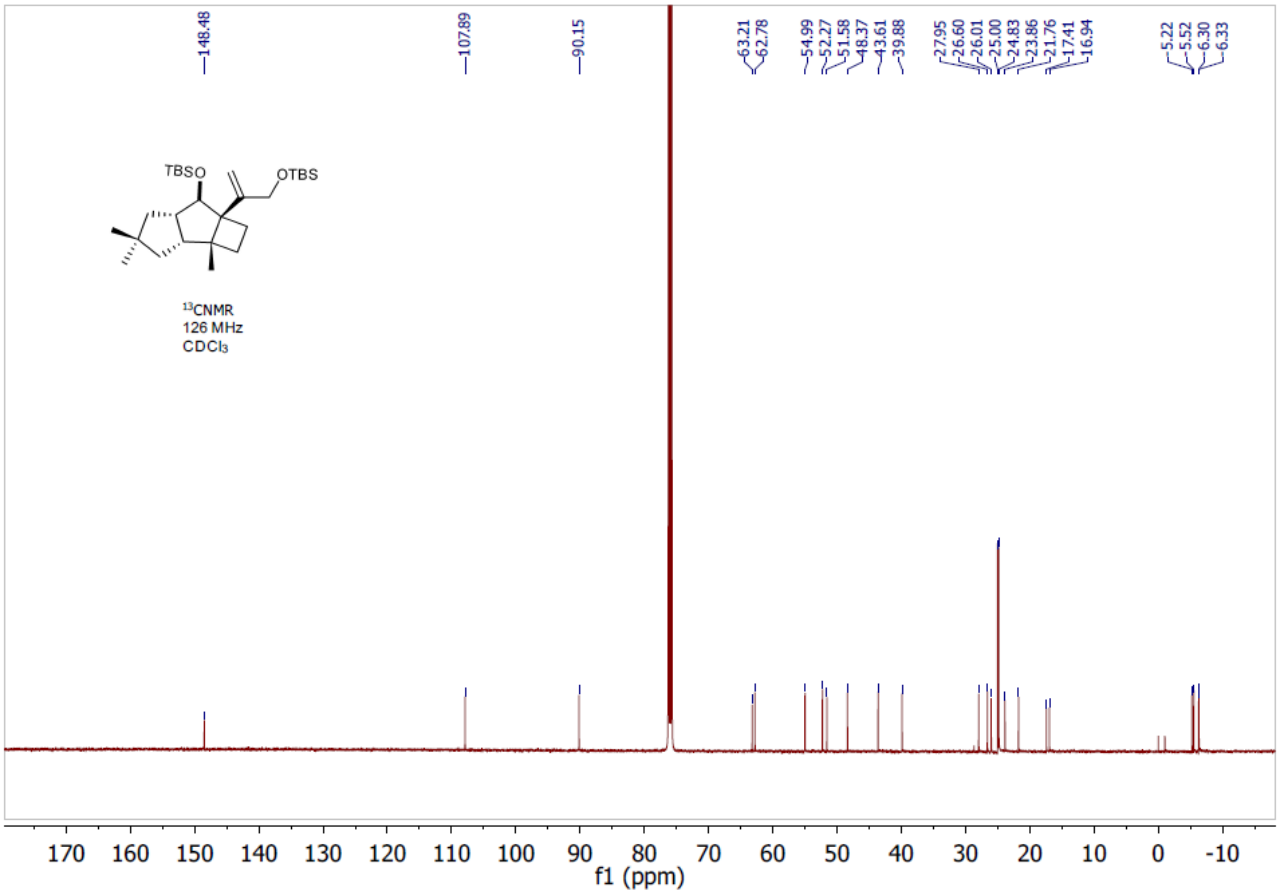

OTBS
TBSO
1HNMR
500 MHz
CDCl3
f1 (ppm)

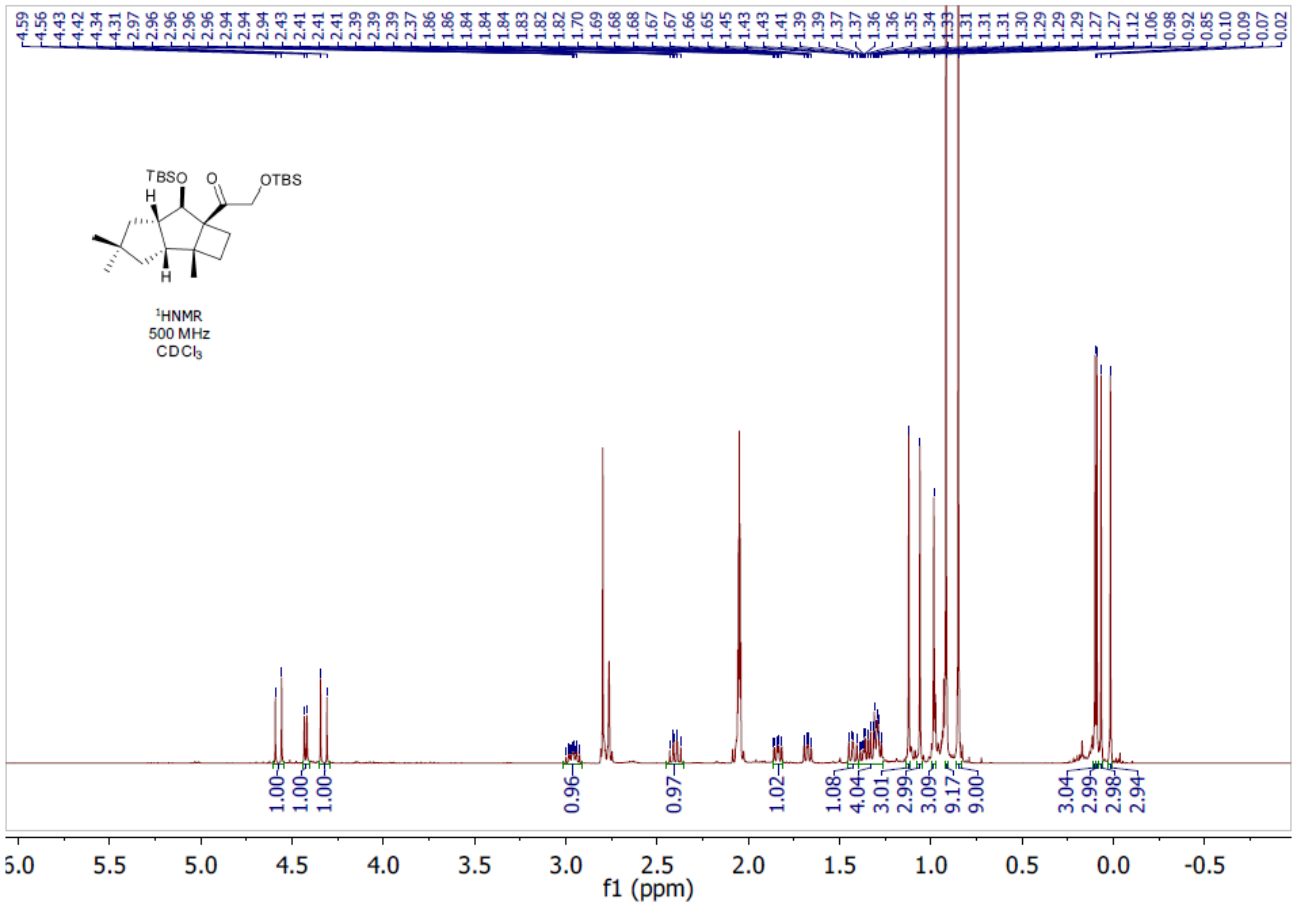

OTBS
TBSO
13CNMR
500 MHz
CDCl3
f1 (ppm)

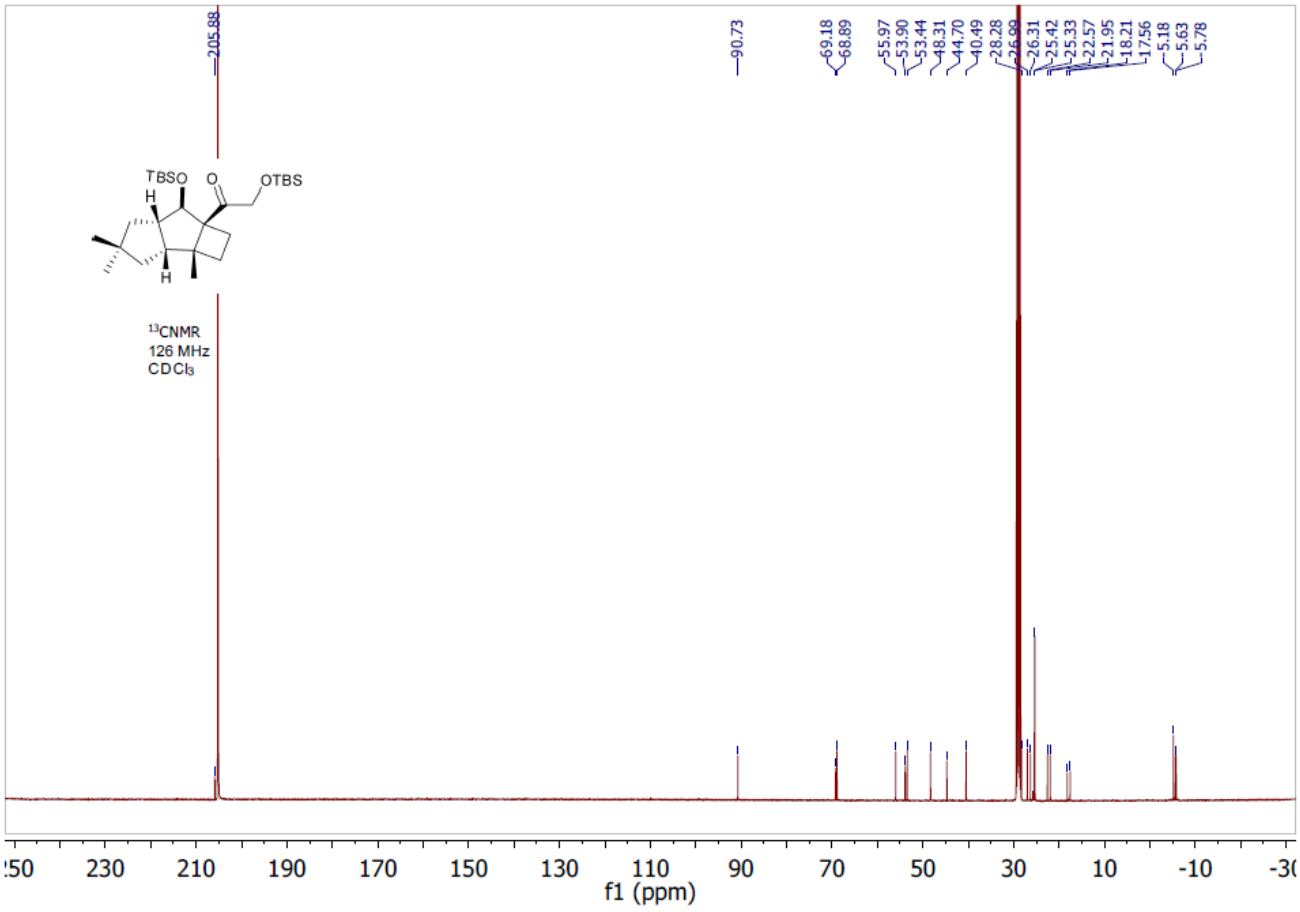

TBSO
OTBS
^{1}HNMR
500 MHz
$CDCl_3$
1.00
1.01
0.99
2.02
1.04
1.02
3.13
1.05
1.98
1.19
2.99
3.94
9.14
3.06
8.96
2.97
9.16
f1 (ppm)

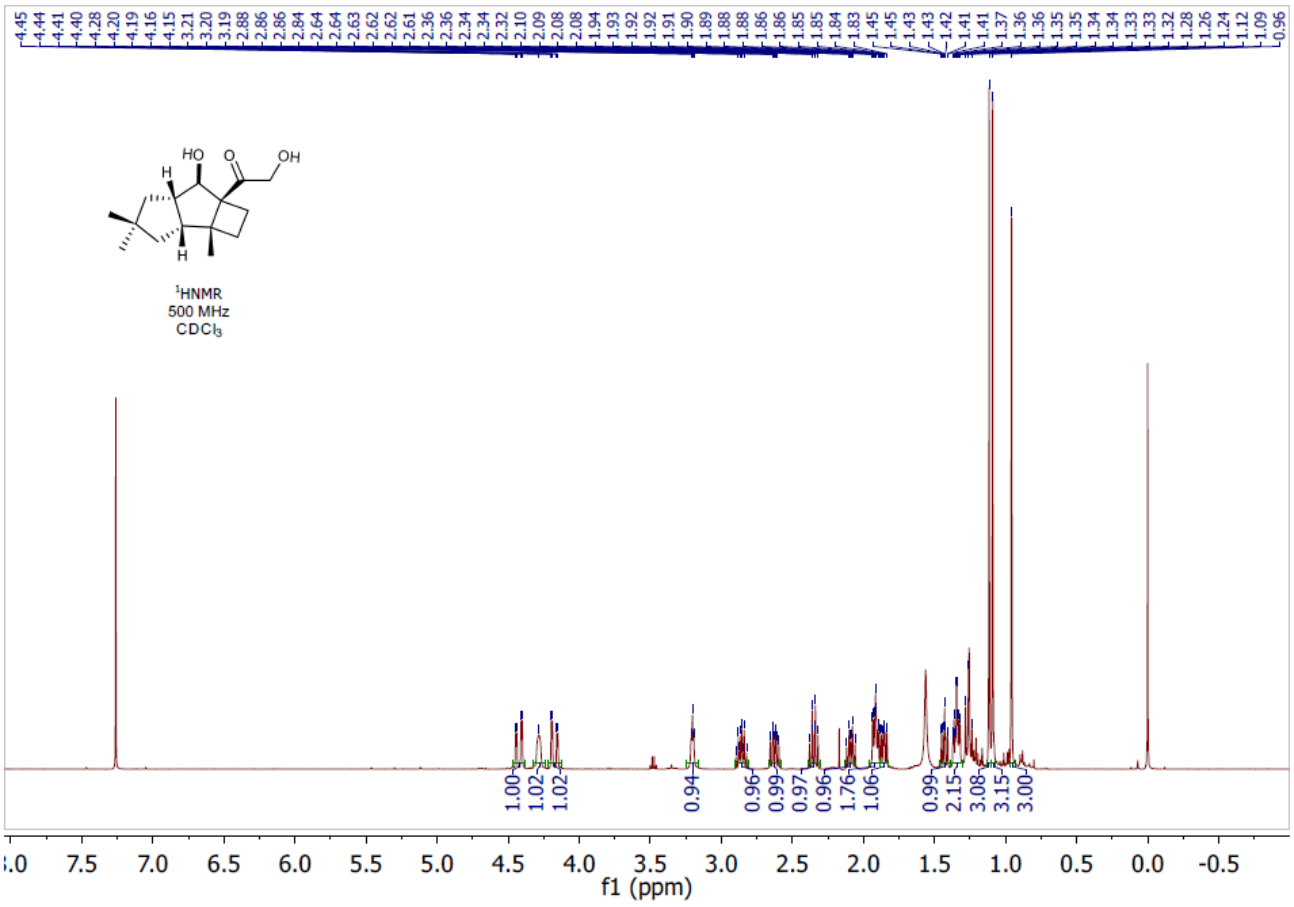

152.09
103.31
74.52
64.03
47.97
47.93
47.89
44.39
43.98
42.24
37.06
28.26
27.43
26.06
24.97
24.82
23.63
23.11
17.36
17.05
5.38
5.74
6.62
6.74
TBSO
OTBS
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

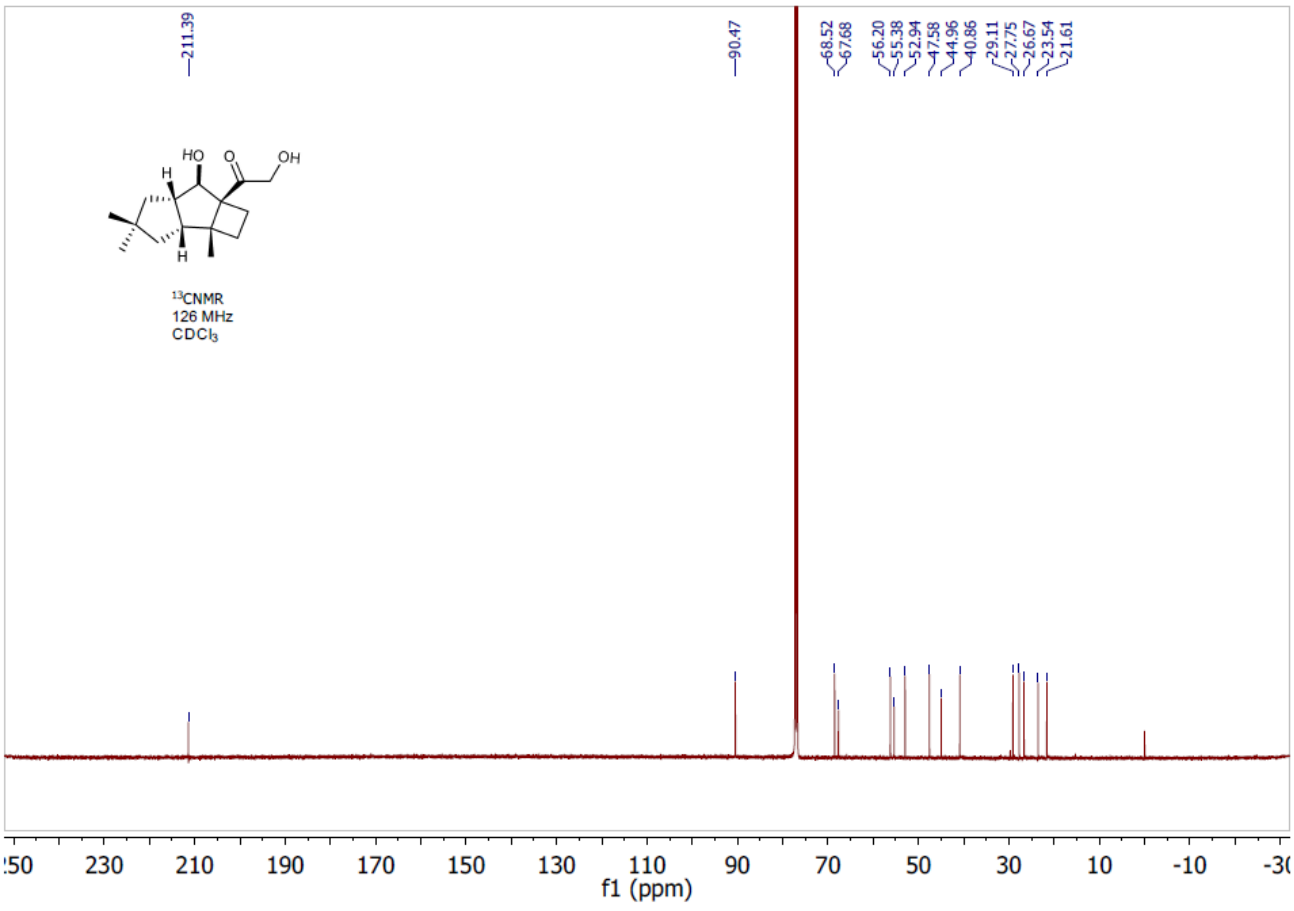

TBSO
OTBS
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

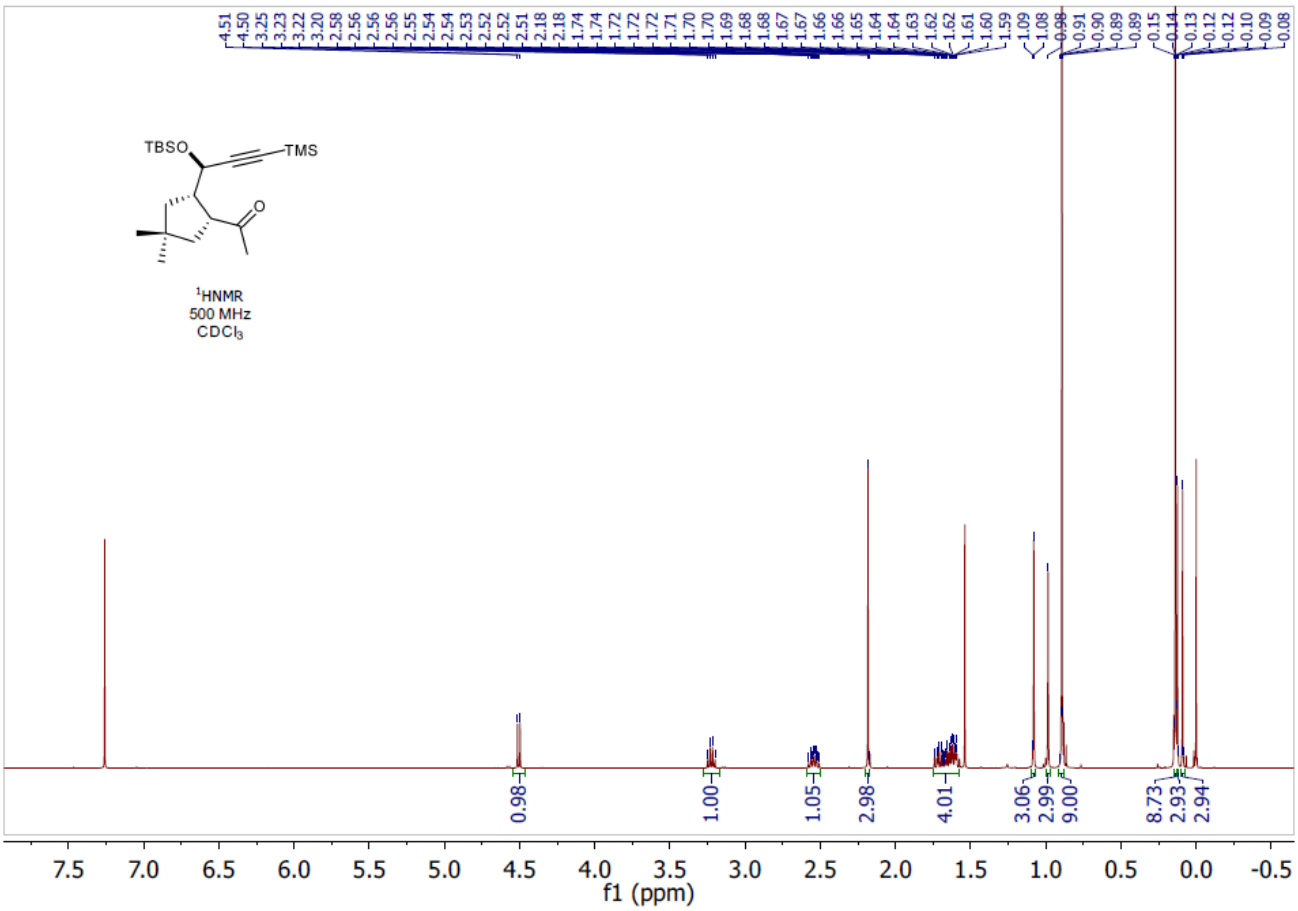

TBSO
OTBS
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

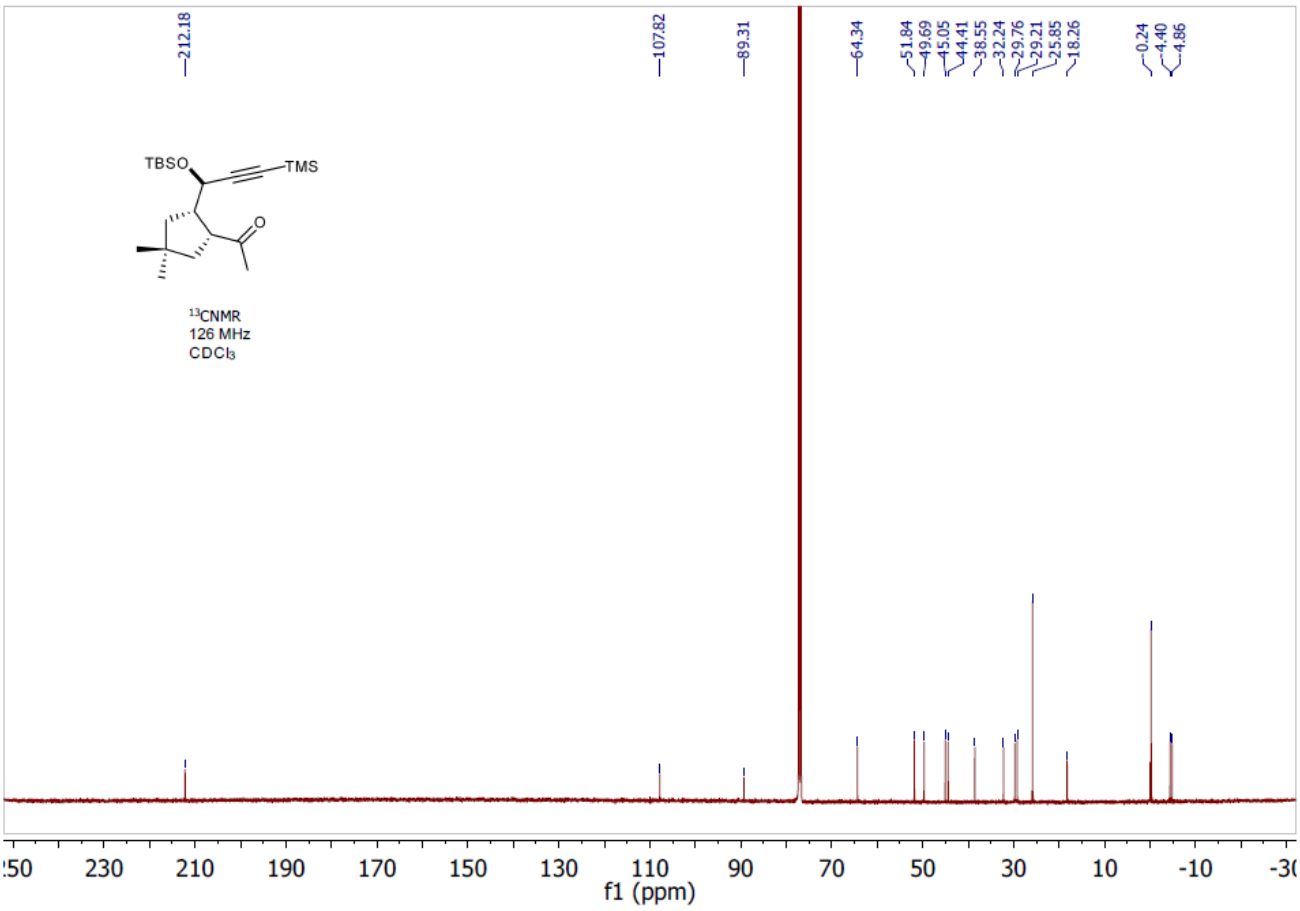

TBSO
OTBS
H
H
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

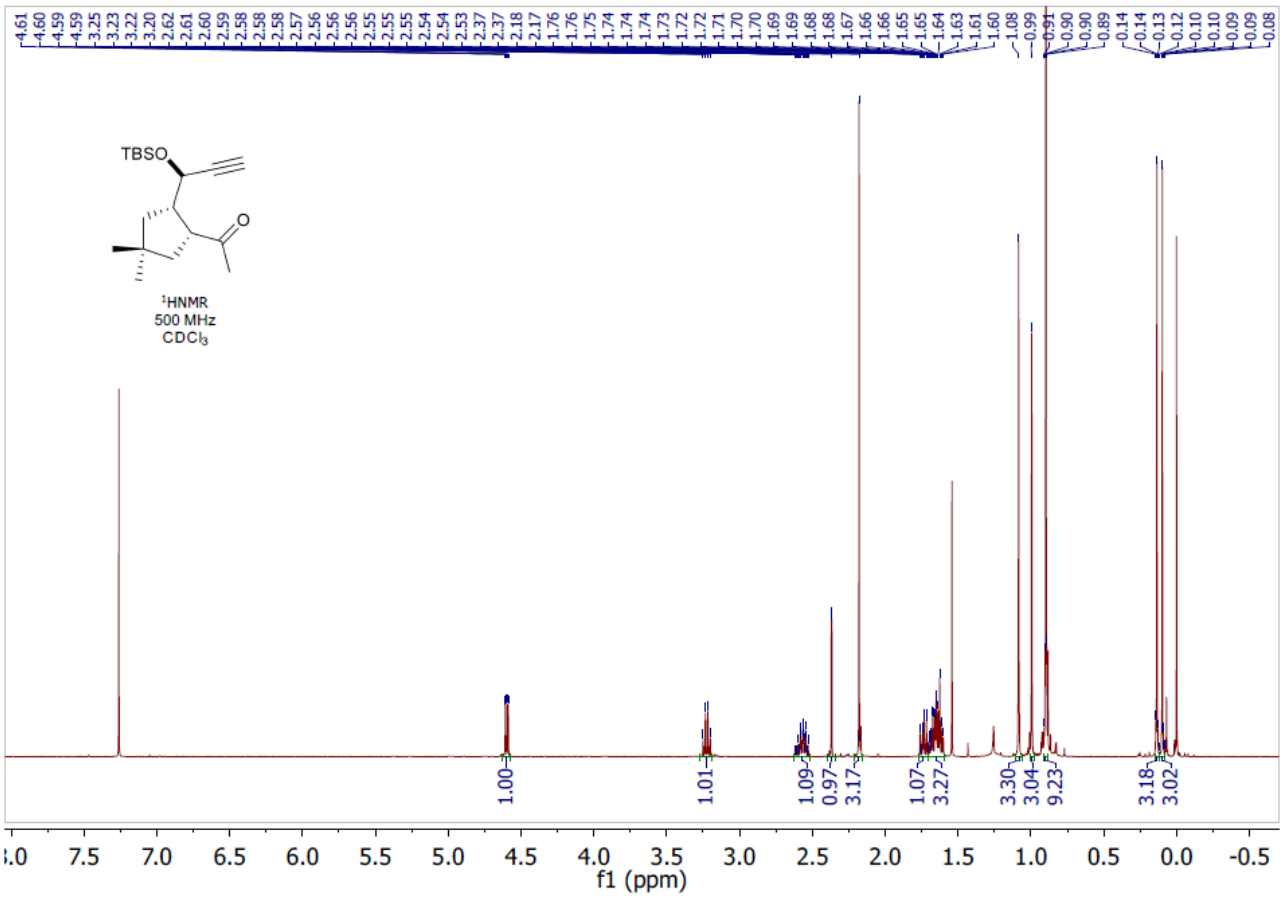

TBSO
OTBS
H
H
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

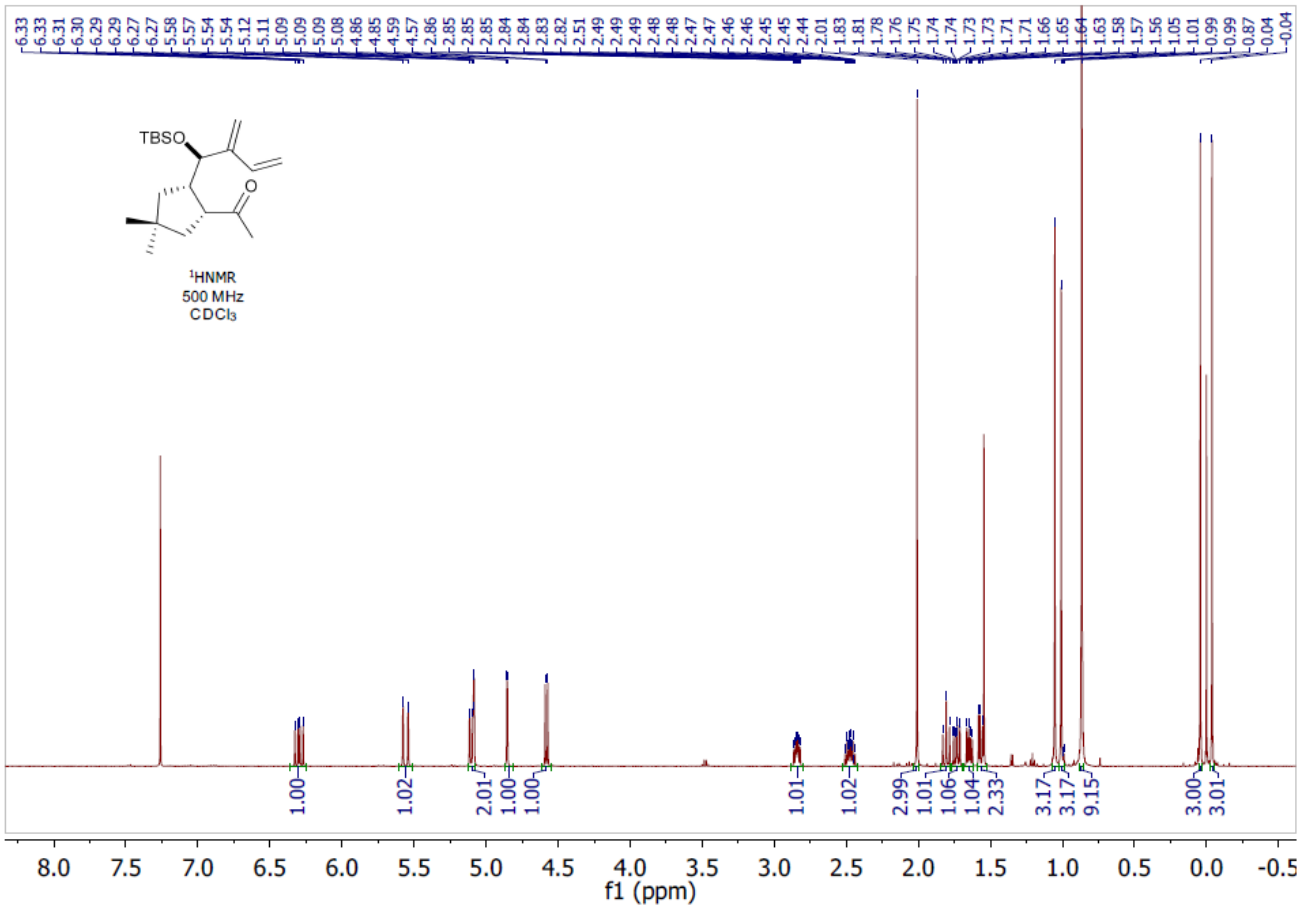

HO
O
OH
H
H
^{1}HNMR
500 MHz
$CDCl_3$
1.00
1.02
1.02
0.94
0.96
0.99
0.97
0.96
1.76
1.06
0.99
2.15
3.08
3.15
3.00
f1 (ppm)

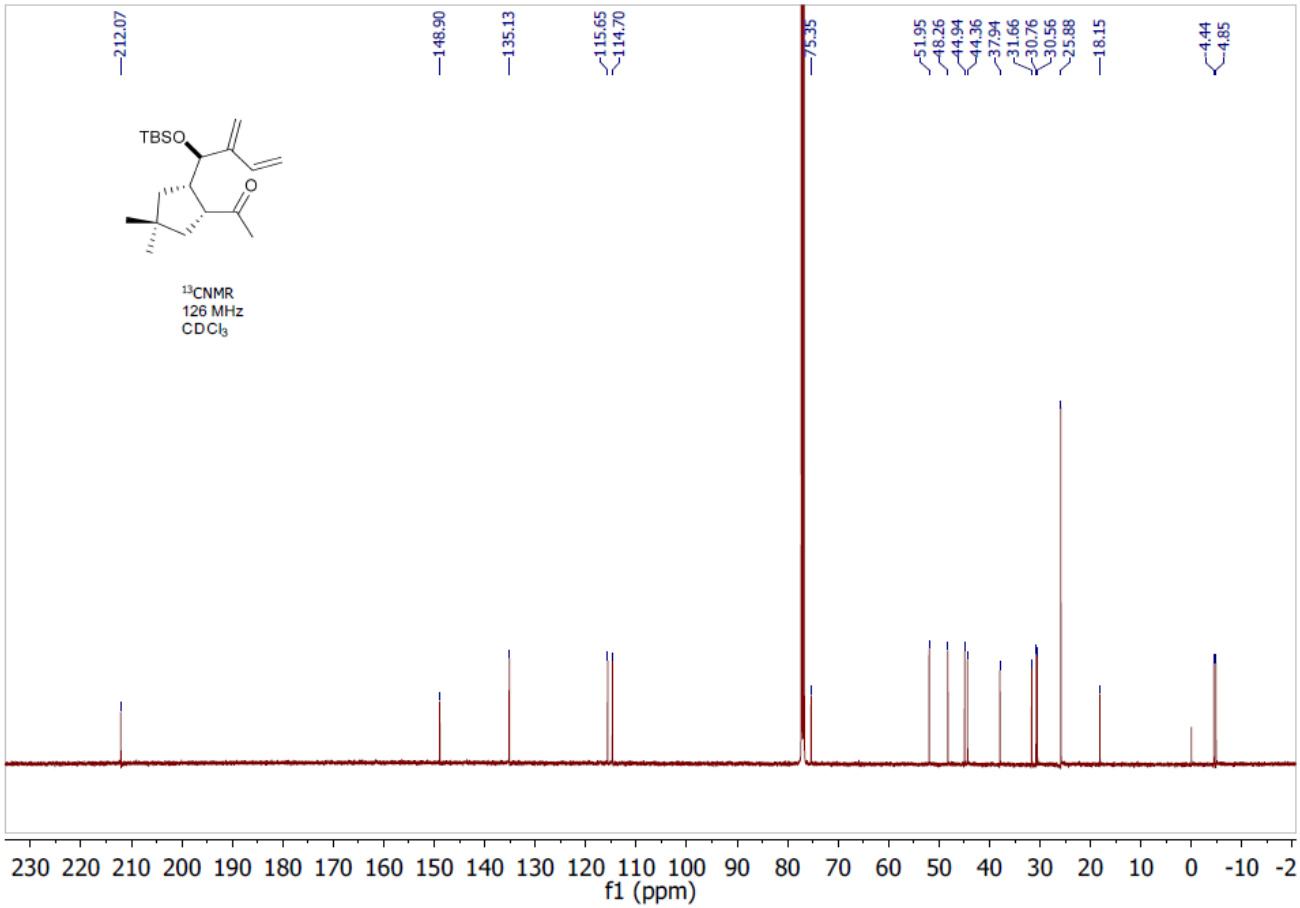

211.39
90.47
68.52
67.68
56.20
55.38
52.94
47.58
44.96
40.86
29.11
27.75
26.67
23.54
21.61
HO
O
OH
H
H
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

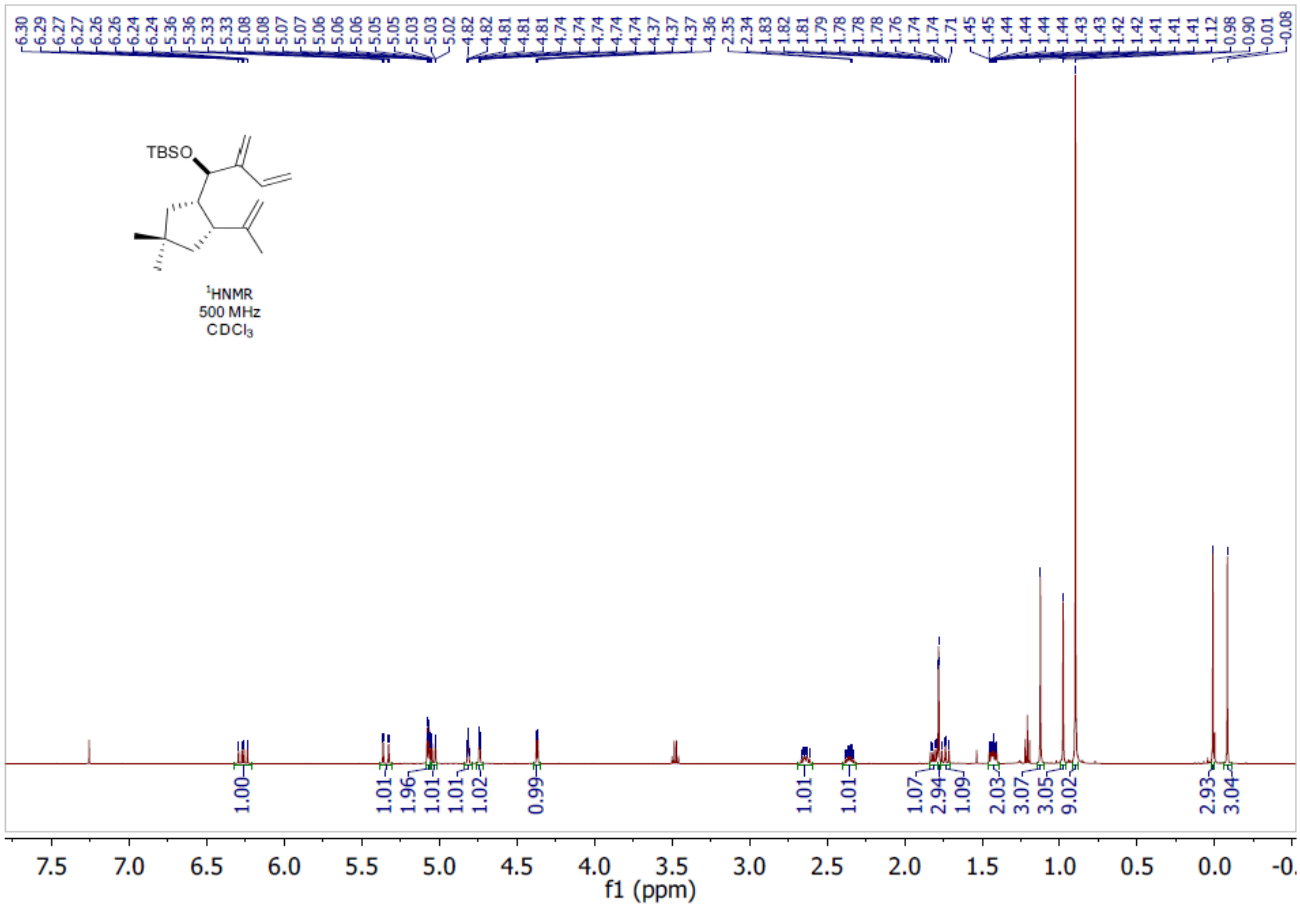

TBSO
TMS
O
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

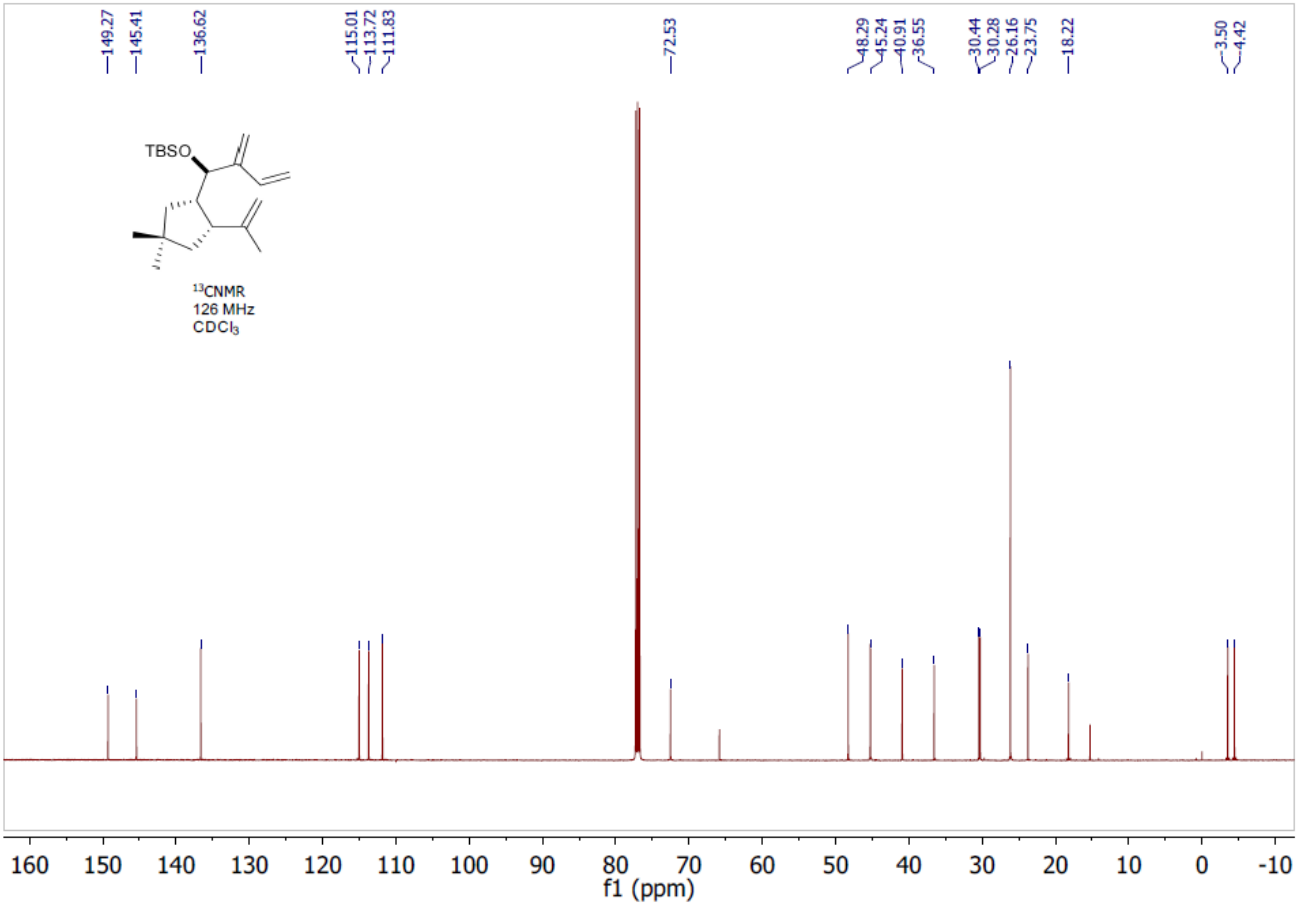

TBSO
TMS
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

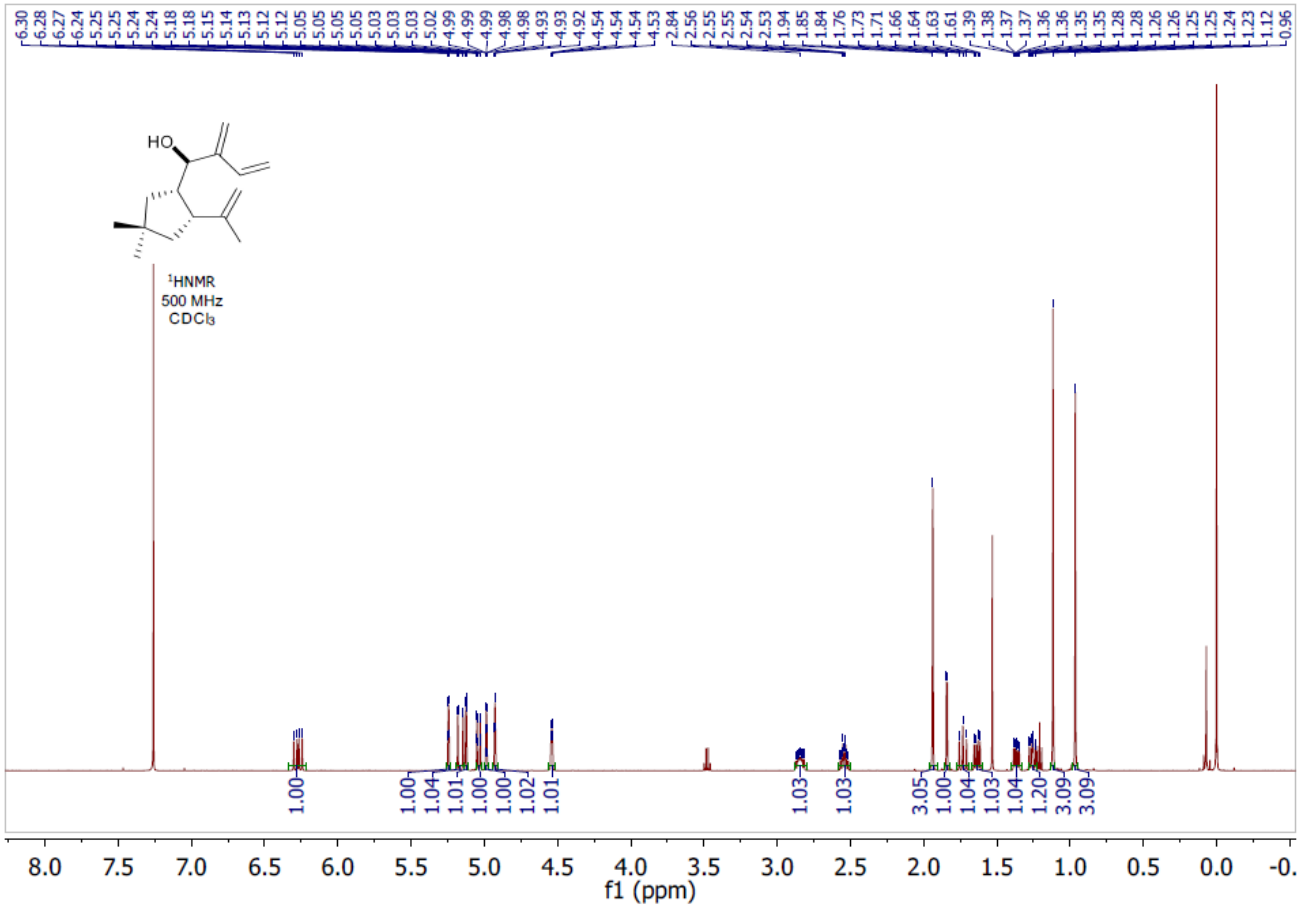

TBSO
O
^{1}HNMR
500 MHz
$CDCl_3$
1.00
1.01
1.09
0.97
3.17
1.07
3.27
3.30
3.04
9.23
3.18
3.02
f1 (ppm)

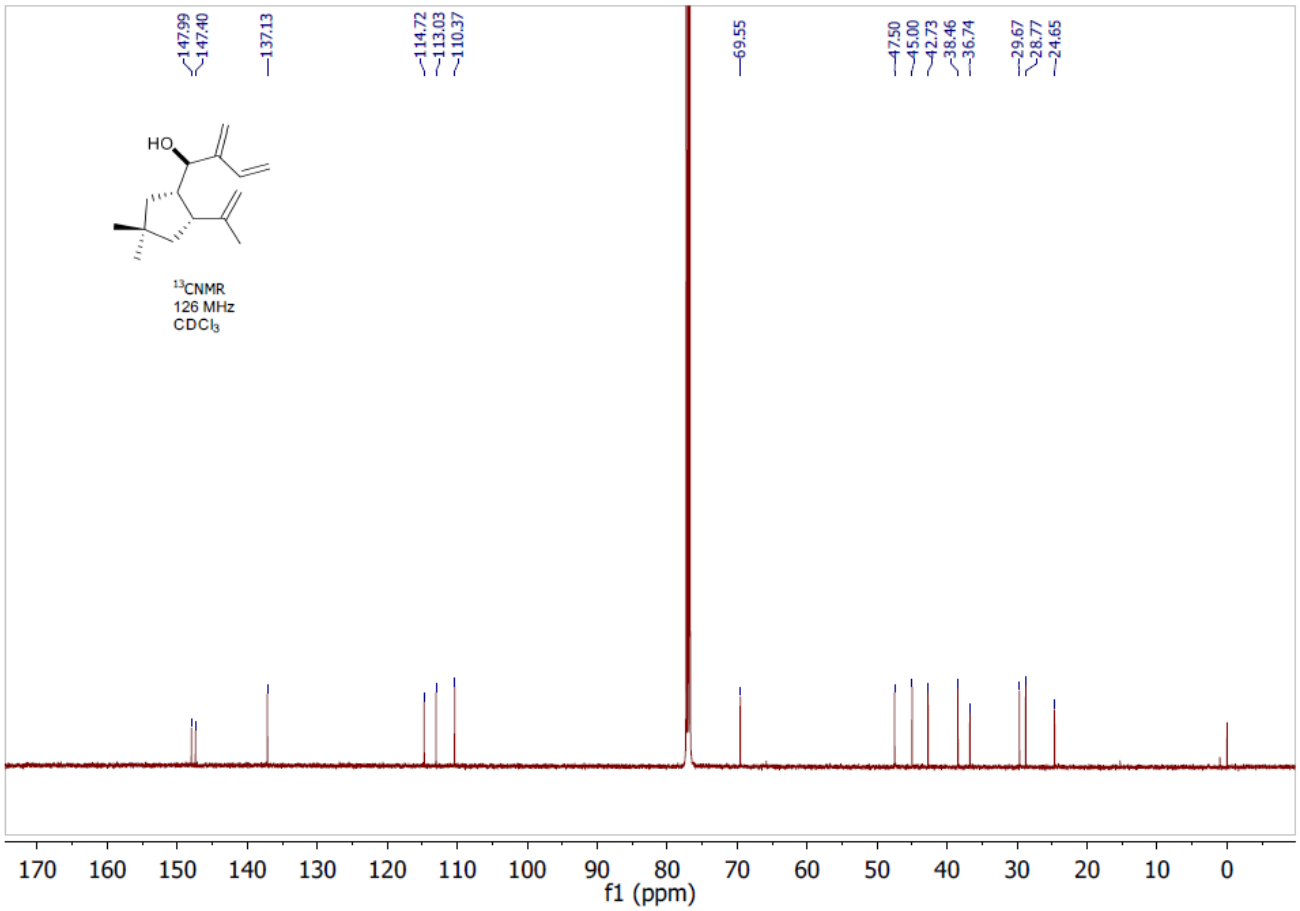

TBSO
O
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

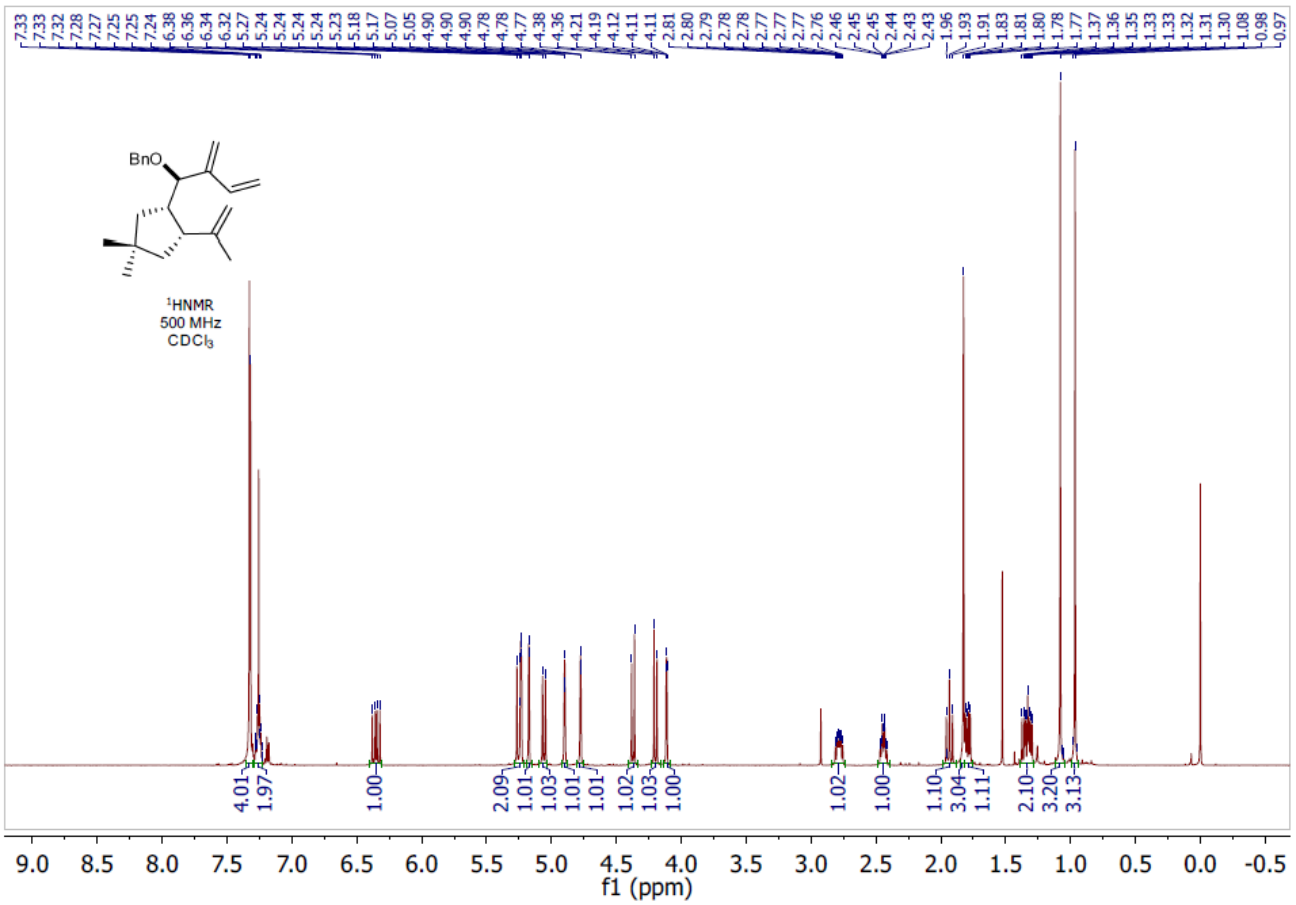

TBSO
O
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

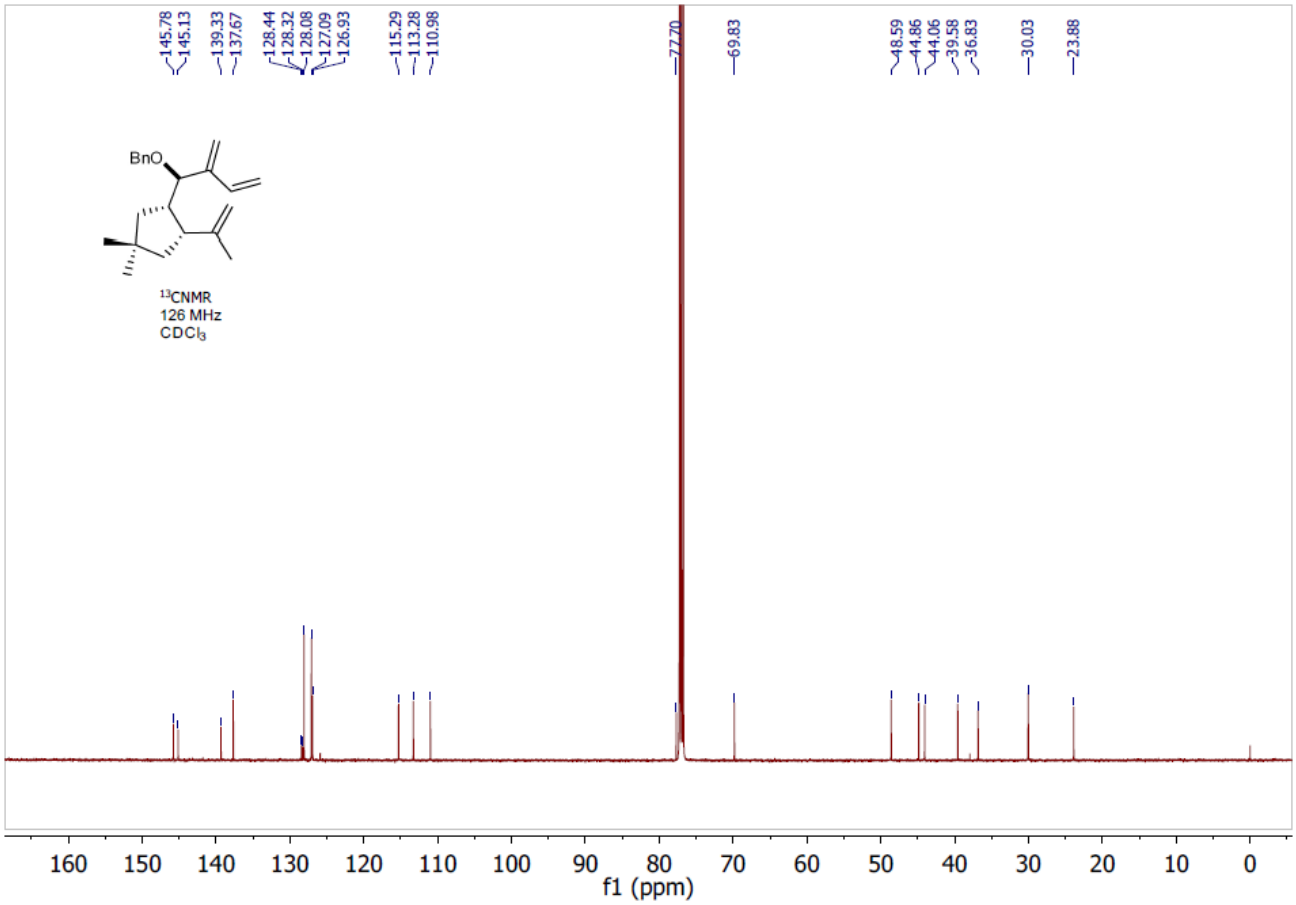

TBSO
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

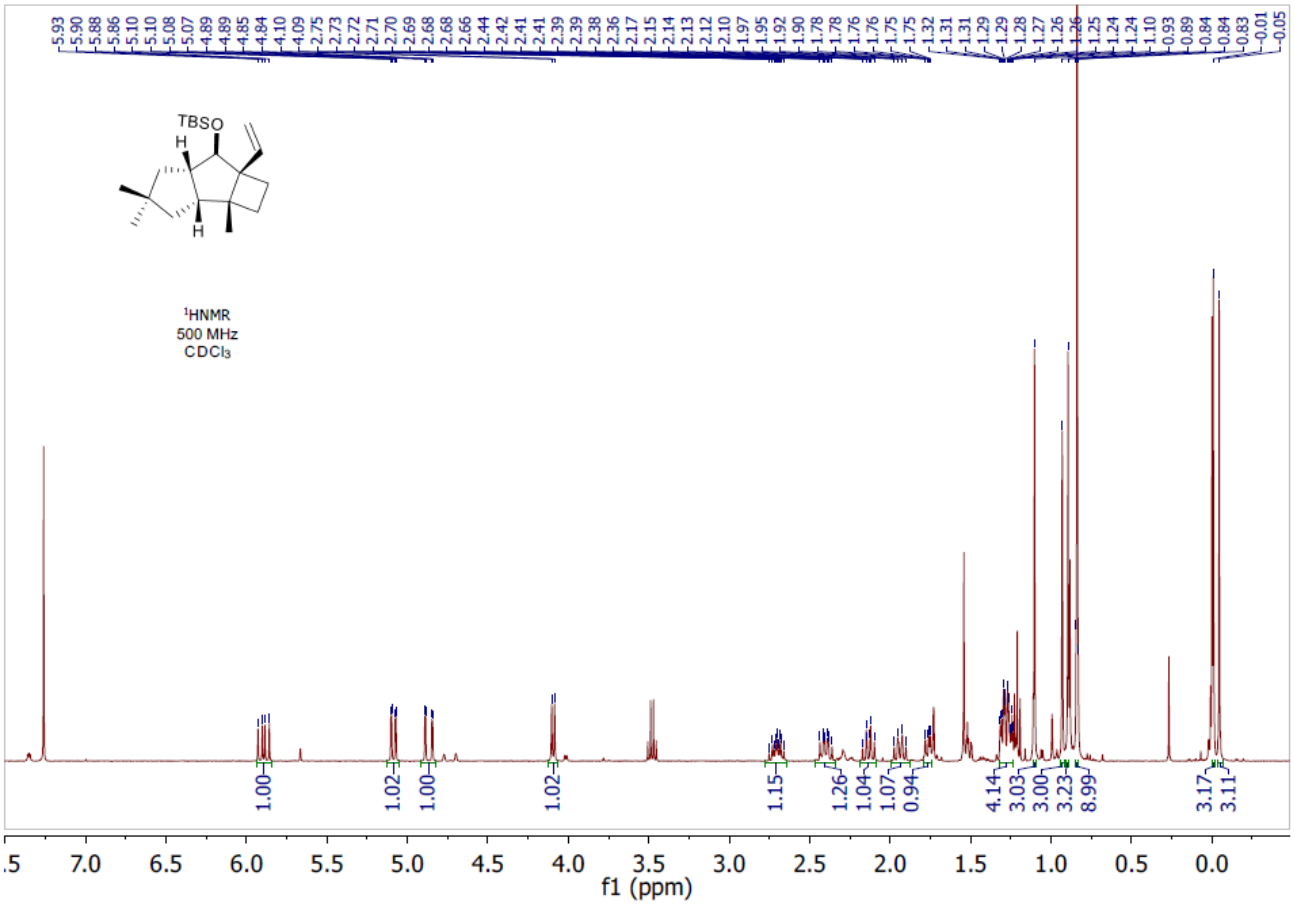

TBSO
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

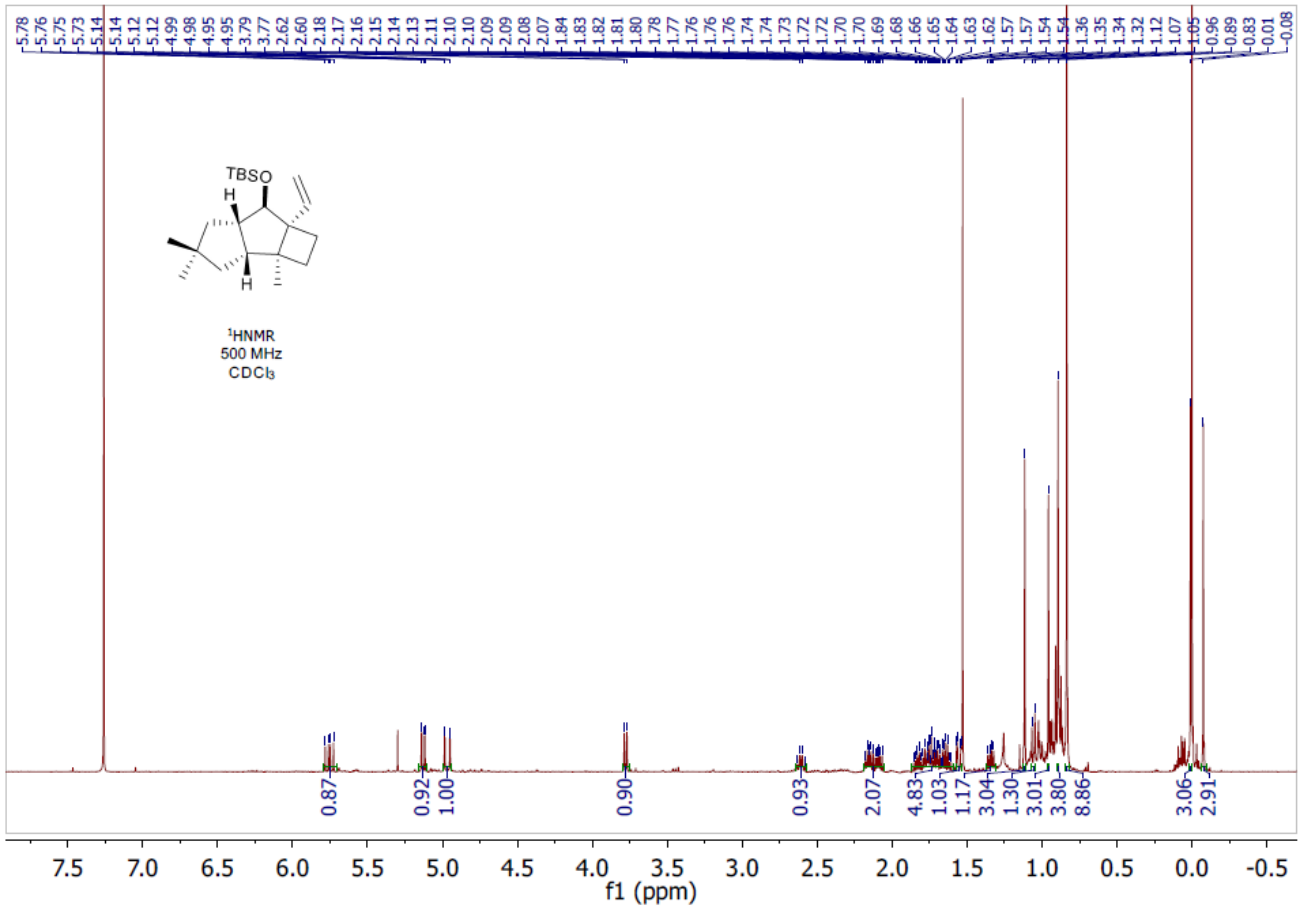

HO
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

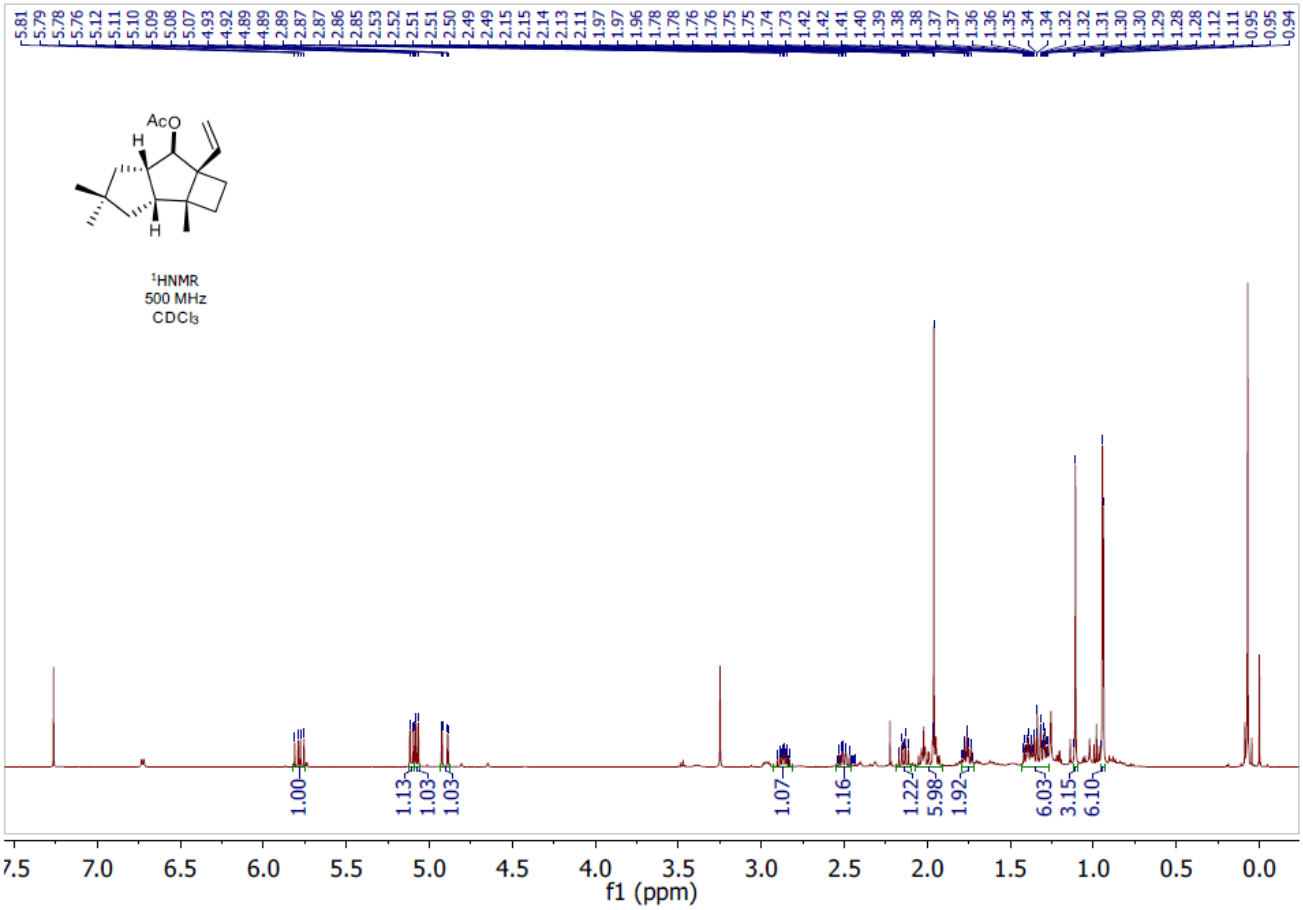

HO
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

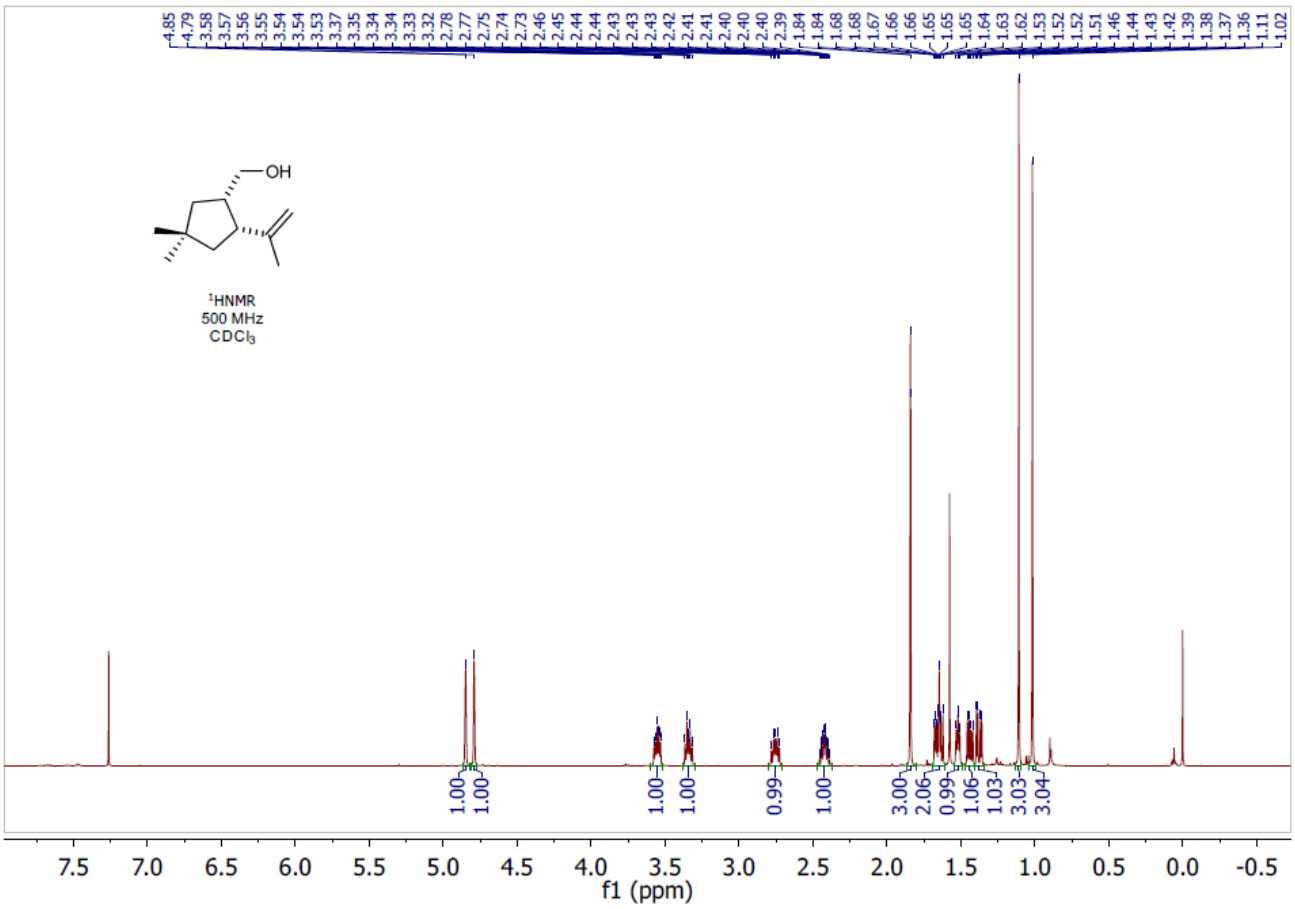

BnO
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

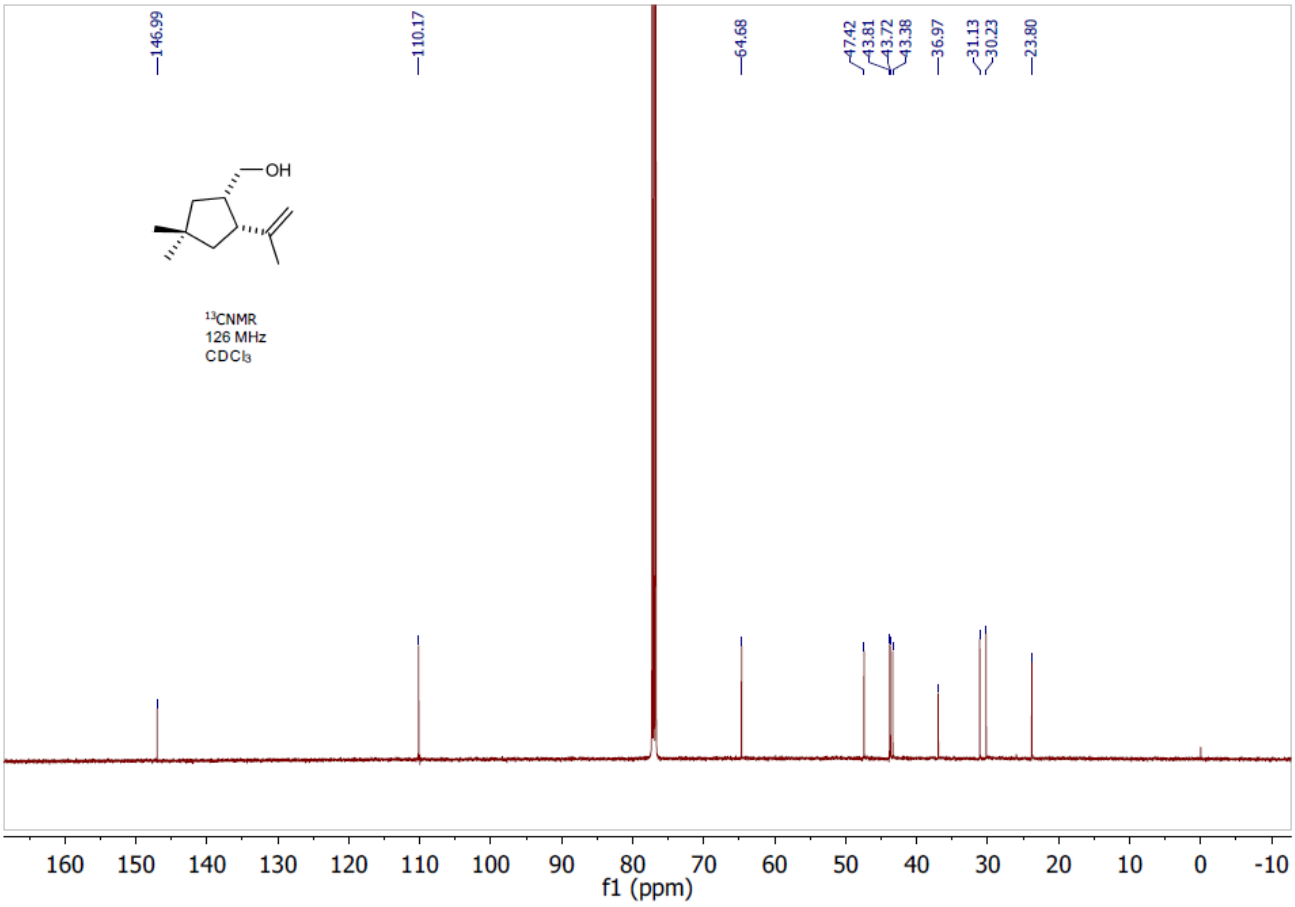

BnO
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

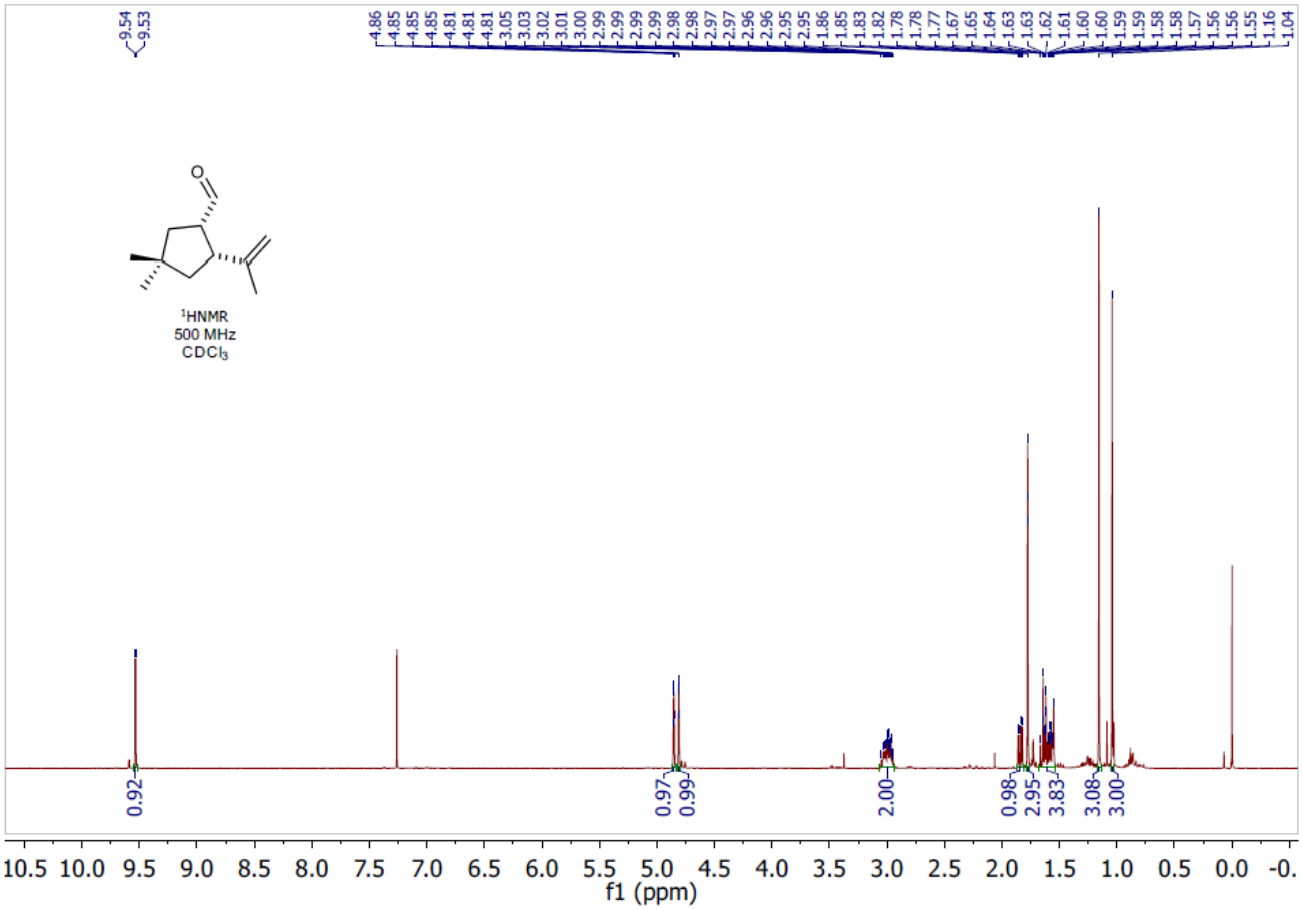

TBSO
H
H
¹HNMR
500 MHz
CDCl₃
1.00
1.02
1.00
1.02
1.15
1.26
1.04
1.07
0.94
4.14
3.03
3.00
3.23
8.99
3.17
3.11
f1 (ppm)

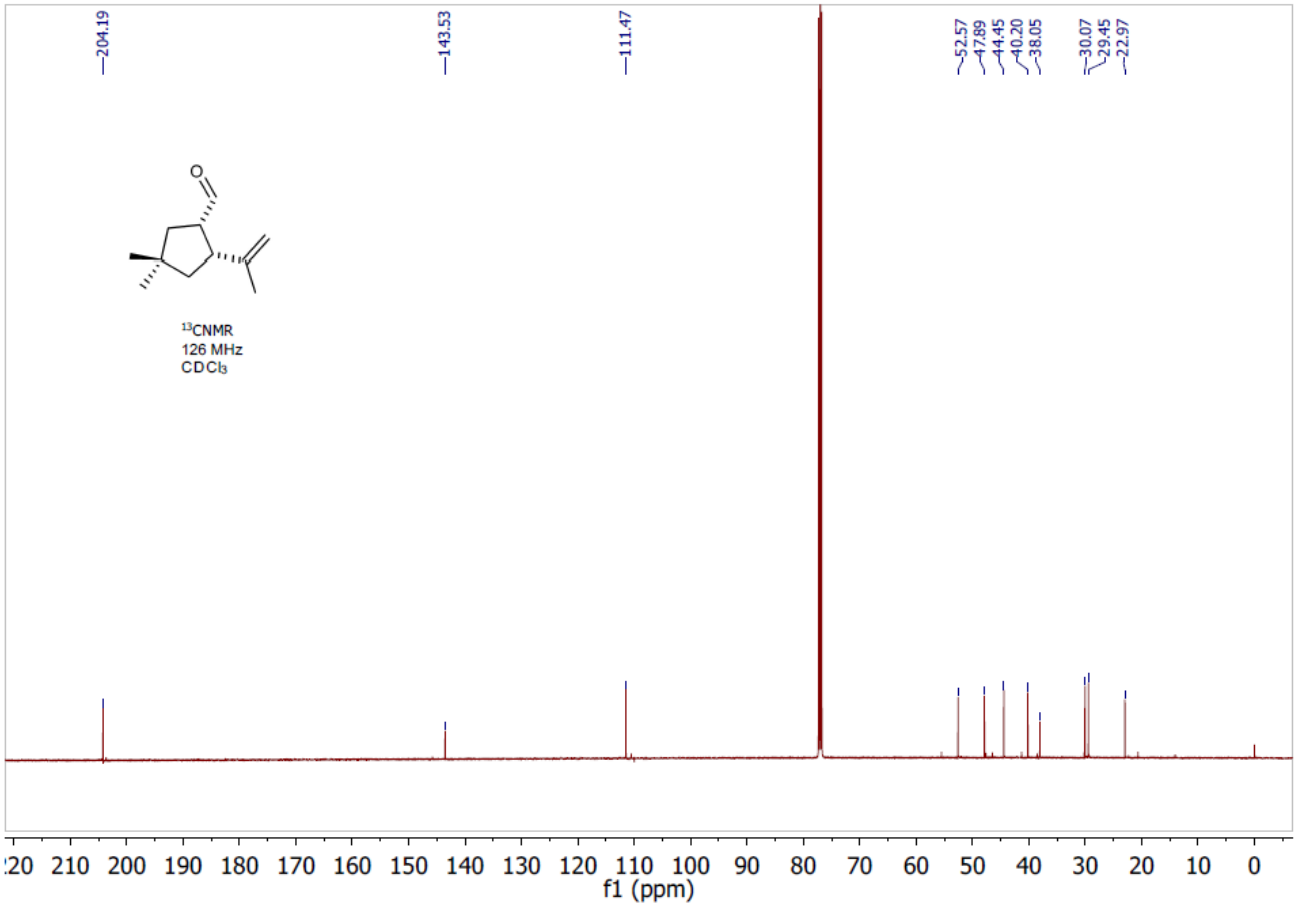

TBSO
H
H
¹HNMR
500 MHz
CDCl₃
0.87
0.92
1.00
0.90
0.93
2.07
4.83
1.03
1.17
3.04
1.30
3.01
3.80
8.86
3.06
2.91
f1 (ppm)

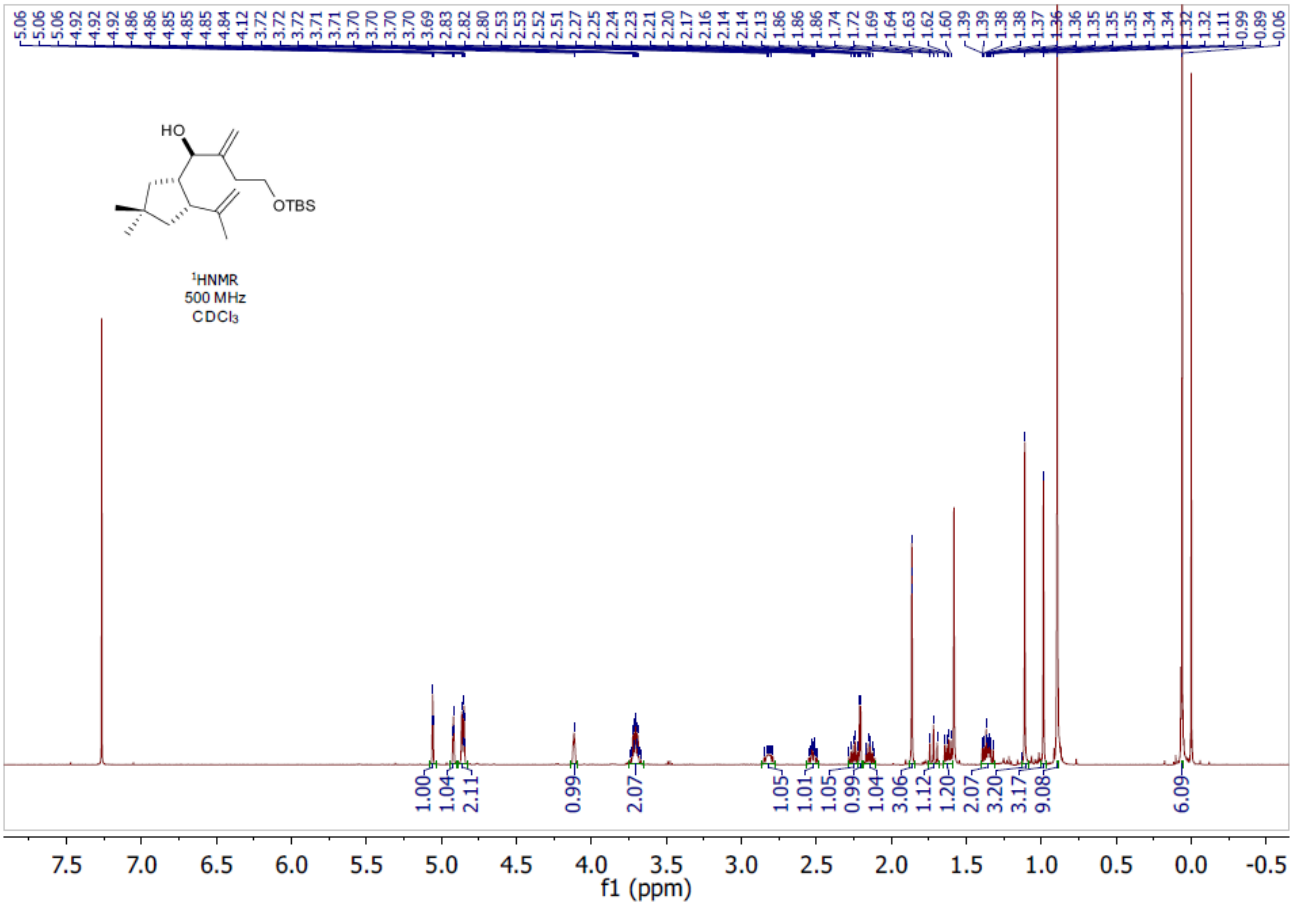

AcO
H
H
¹HNMR
500 MHz
CDCl3
1.00
1.13
1.03
1.03
1.07
1.16
1.22
5.98
1.92
6.03
3.15
6.10
f1 (ppm)

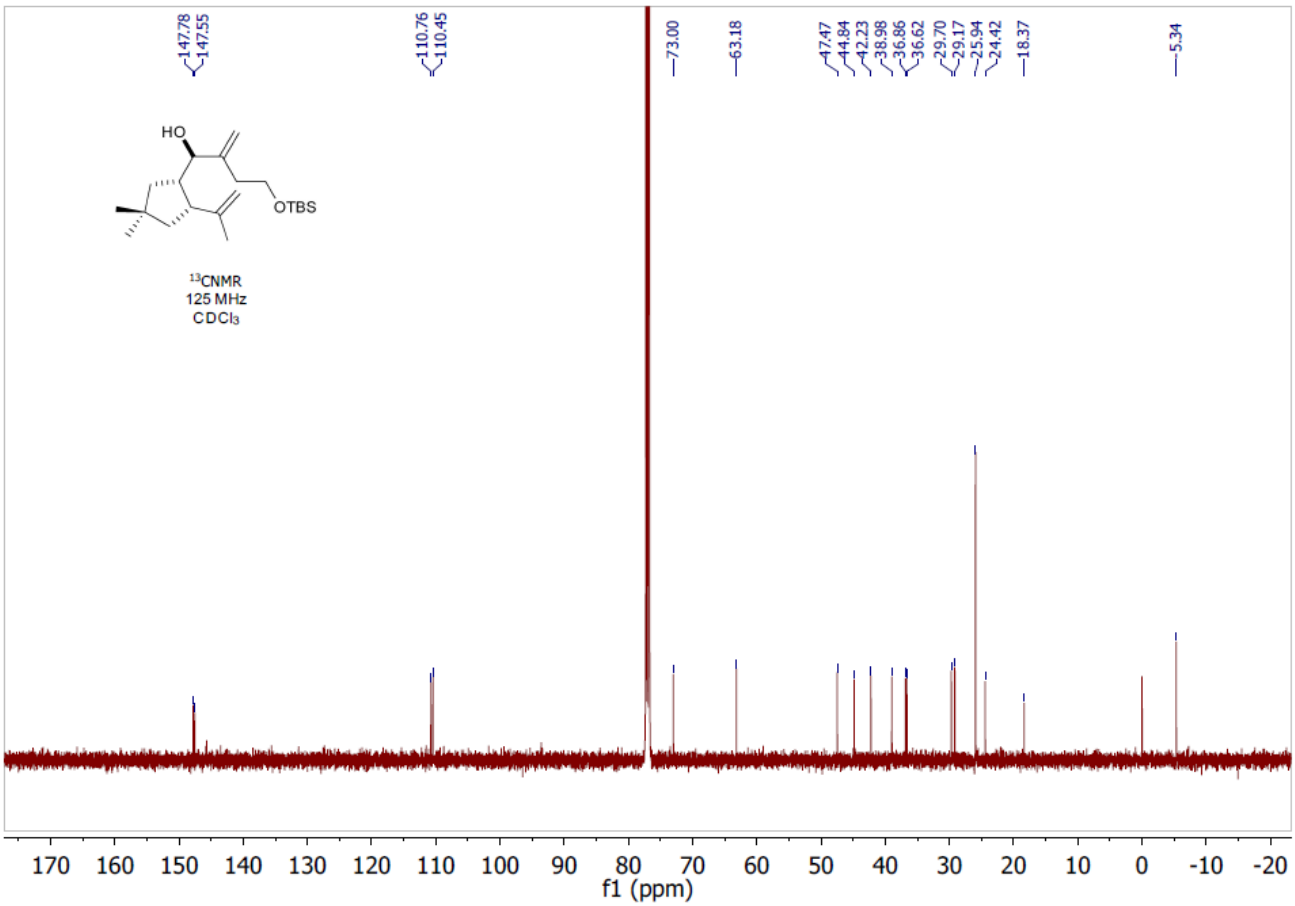

OH
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

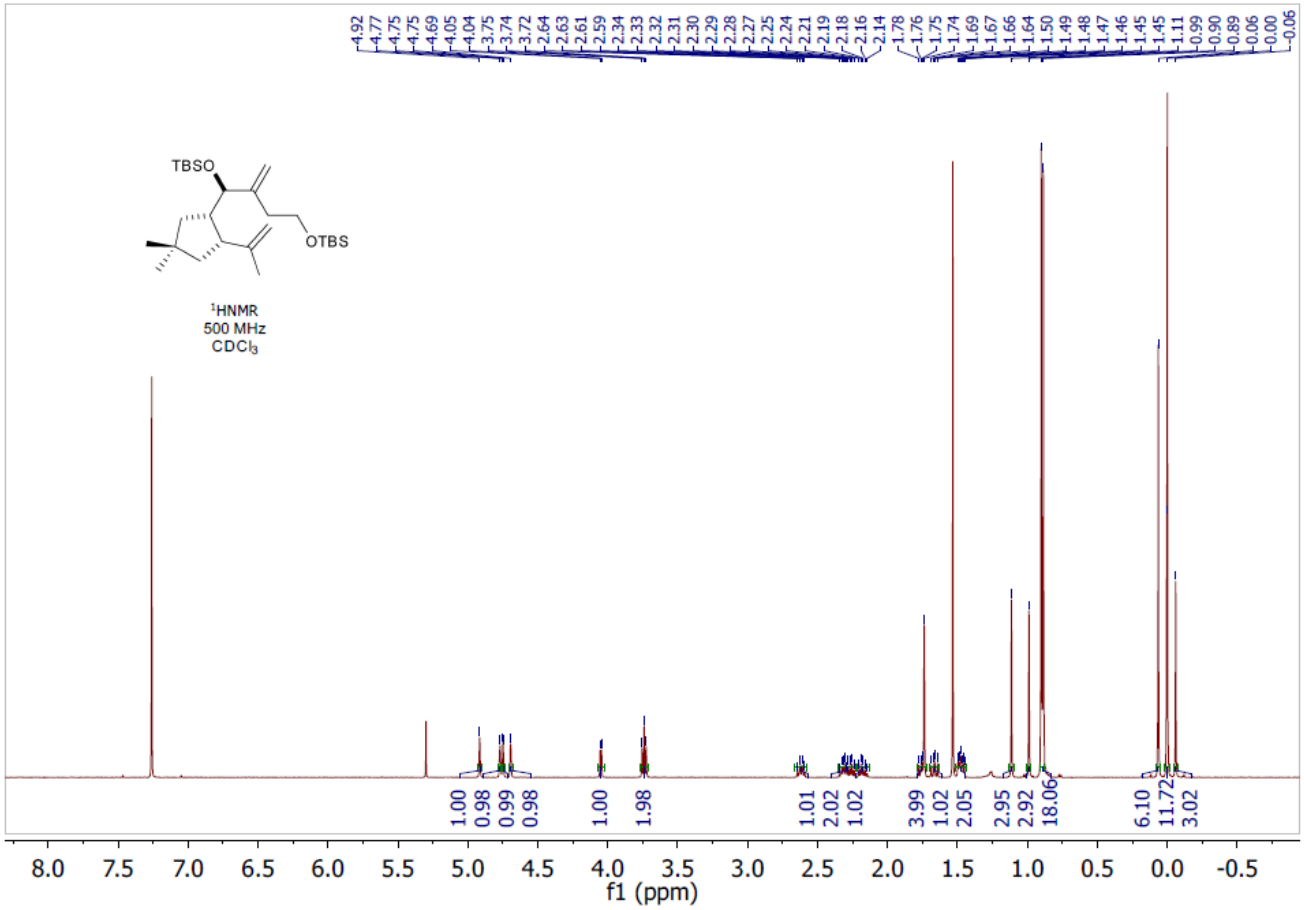

OH
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

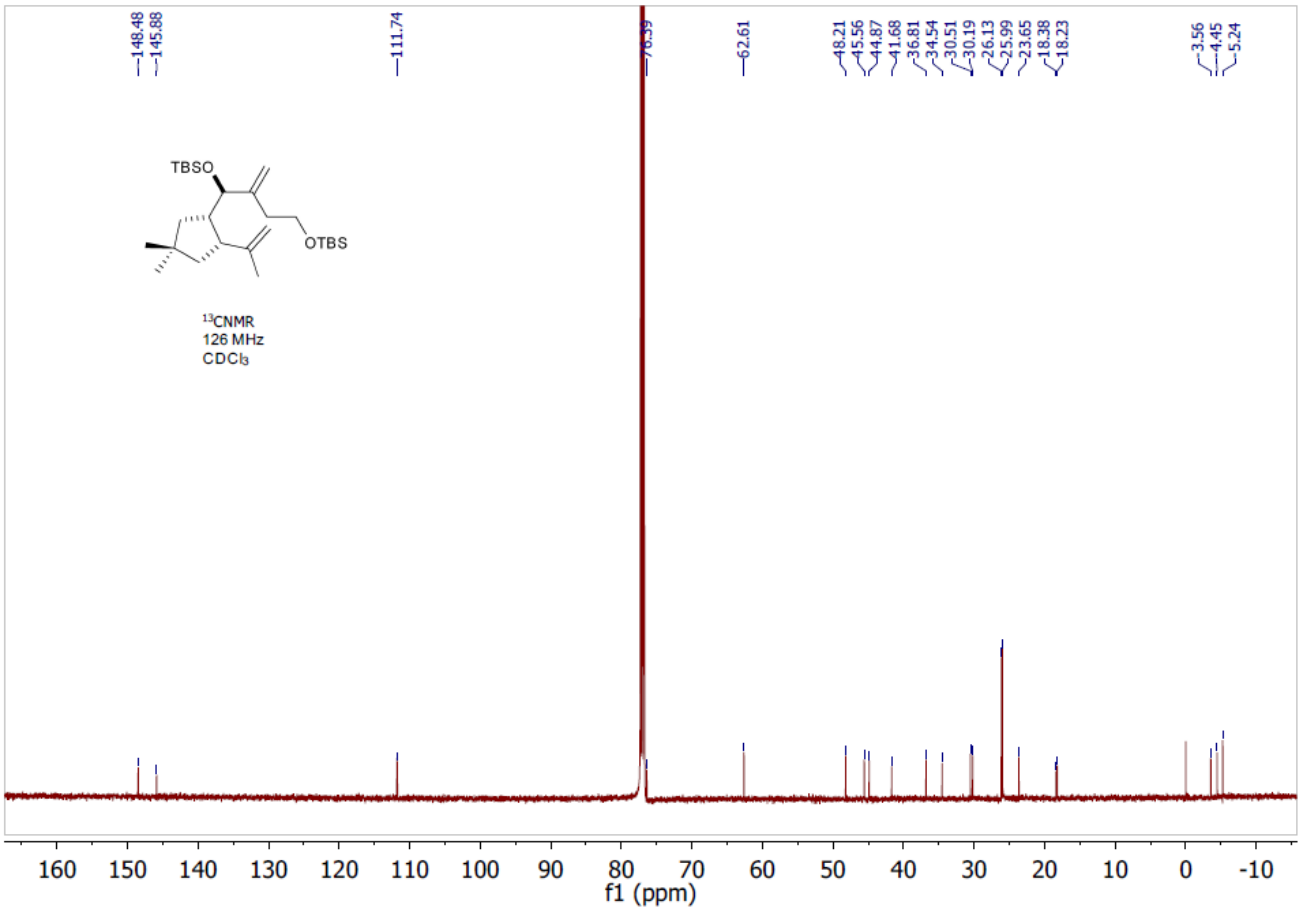

9.54
9.53
4.86
4.85
4.85
4.85
4.81
4.81
4.81
3.05
3.03
3.02
3.01
3.00
2.99
2.99
2.99
2.99
2.98
2.98
2.97
2.97
2.96
2.96
2.95
2.95
1.86
1.85
1.83
1.82
1.78
1.78
1.77
1.67
1.65
1.64
1.63
1.63
1.62
1.61
1.60
1.60
1.59
1.59
1.58
1.58
1.57
1.56
1.56
1.55
1.16
1.04
O
1HNMR
500 MHz
CDCl3
0.92
0.97
0.99
2.00
0.98
2.95
3.83
3.08
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

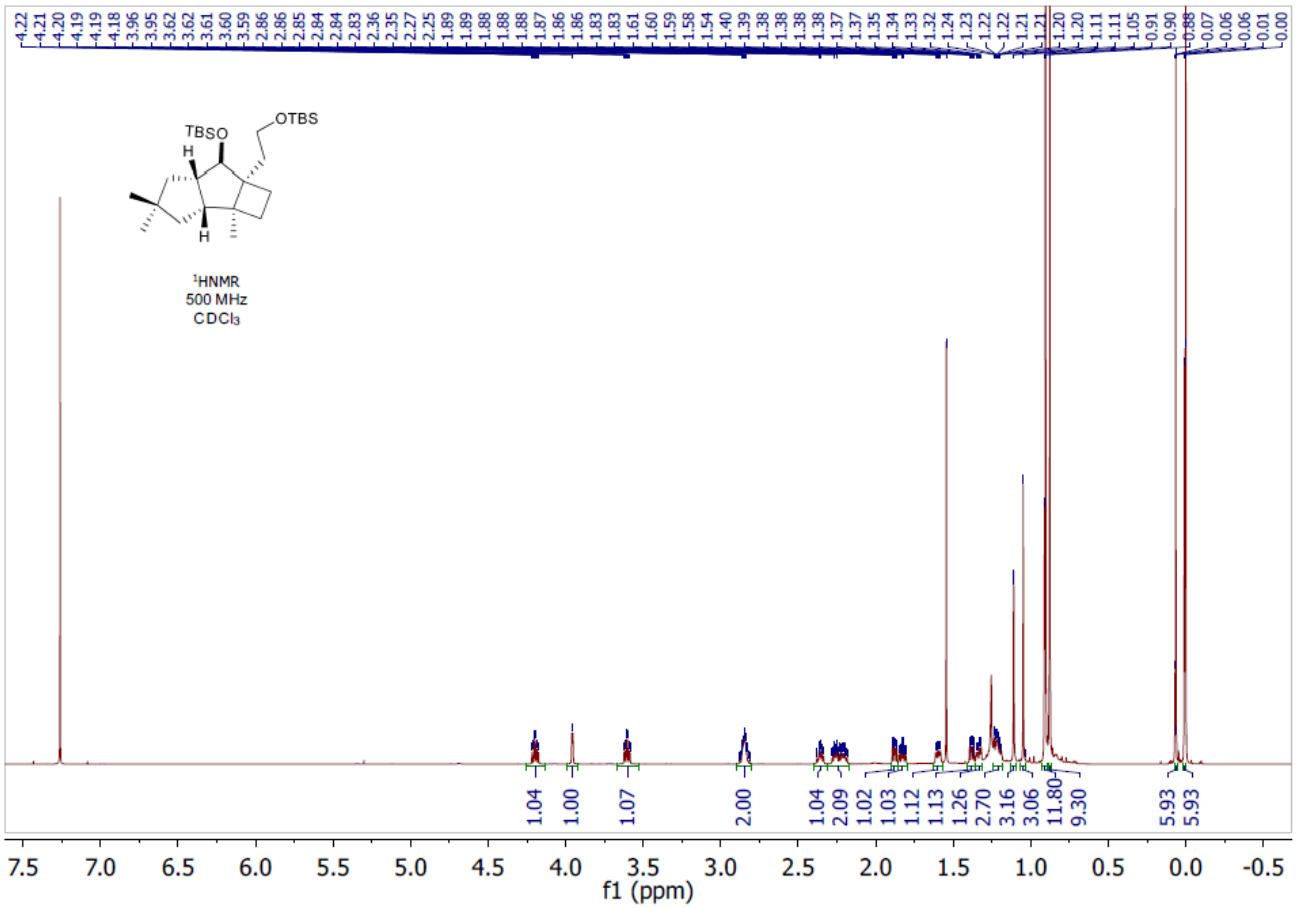

204.19
143.53
111.47
52.57
47.89
44.45
40.20
38.05
30.07
29.45
22.97
O
13CNMR
126 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

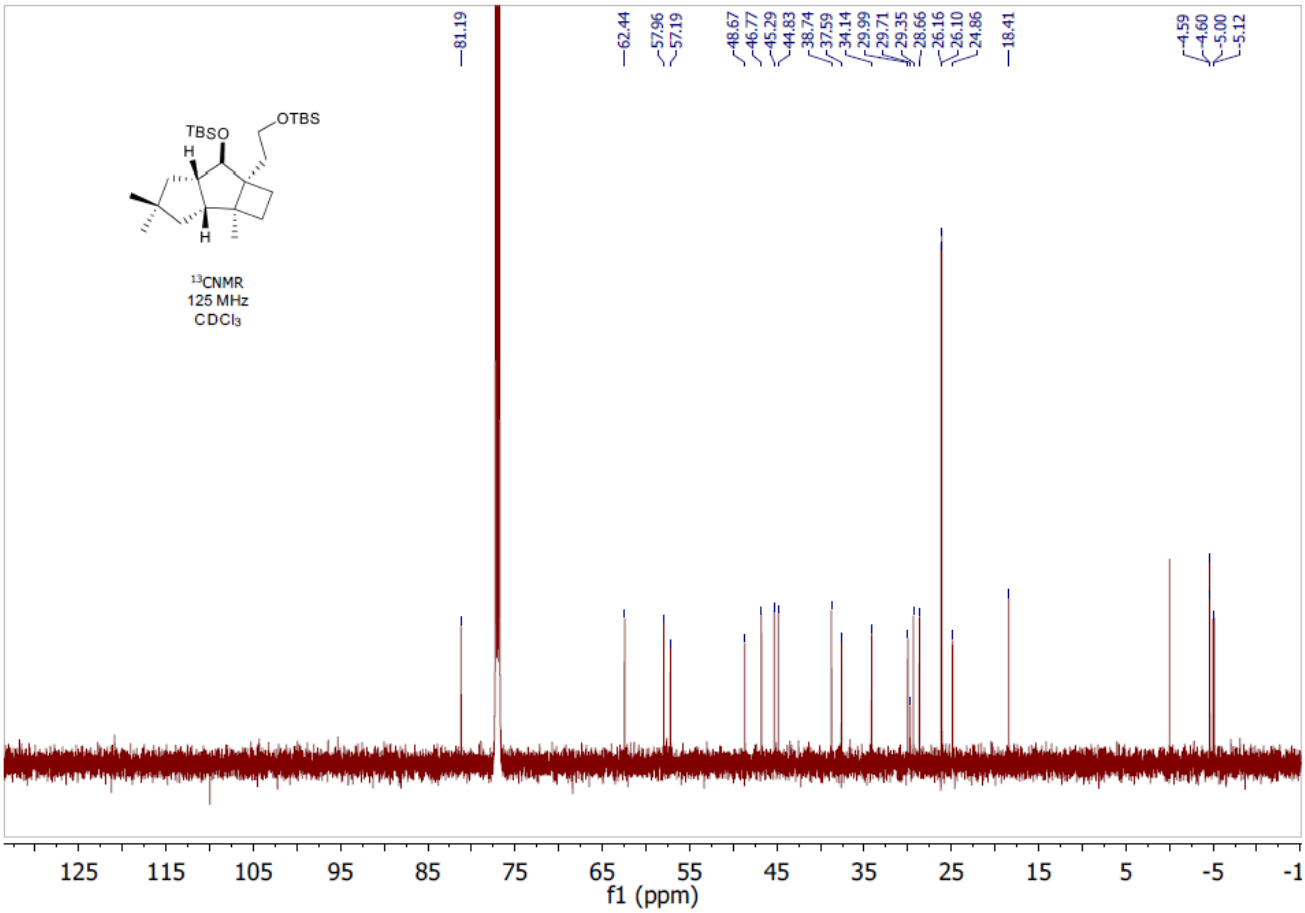

HO
OTBS
1HNMR
500 MHz
CDCl3
f1 (ppm)


HO
OTBS
13CNMR
125 MHz
CDCl3
f1 (ppm)

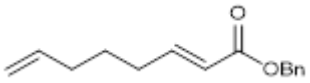

TBSO
OTBS
^{1}HNMR
500 MHz
$CDCl_3$
f1 (ppm)

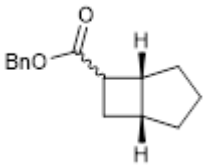

TBSO
OTBS
^{13}CNMR
126 MHz
$CDCl_3$
f1 (ppm)

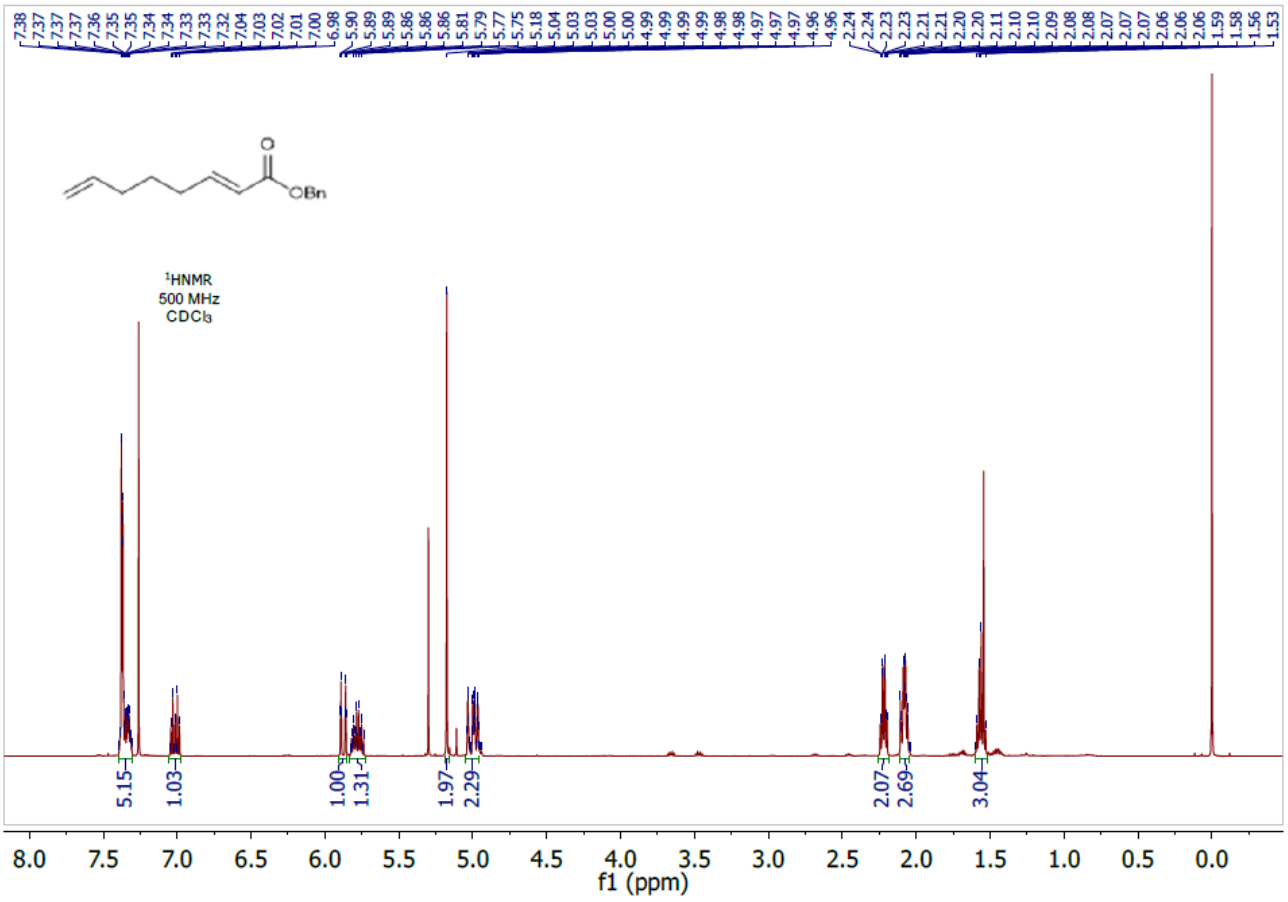

TBSO
OTBS
H
H
^{1}HNMR
500 MHz
CDCl$_3$
1.04
1.00
1.07
2.00
1.04
2.09
1.02
1.03
1.12
1.13
1.26
2.70
3.16
3.06
11.80
9.30
5.93
5.93
f1 (ppm)

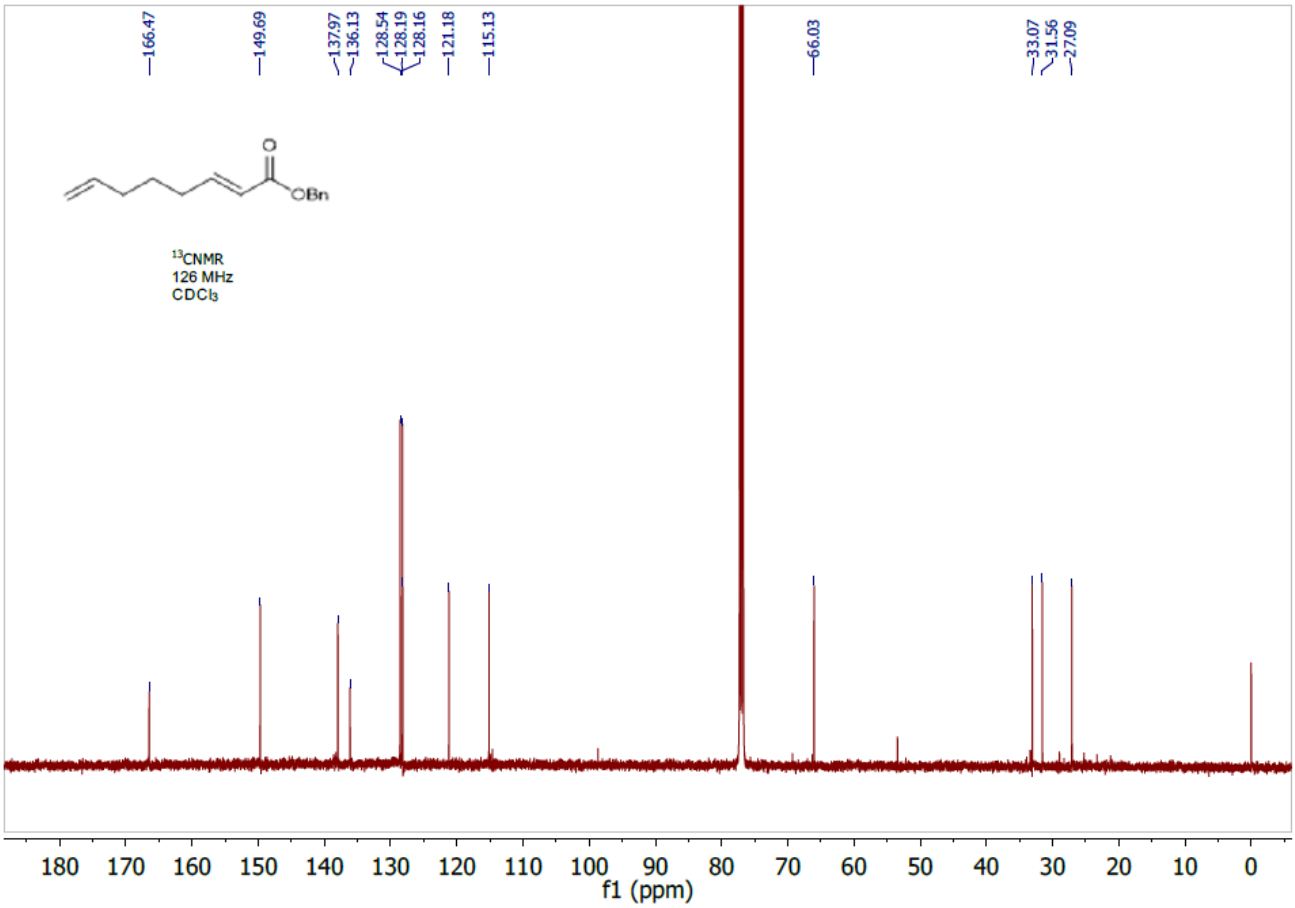

TBSO
OTBS
H
H
^{13}CNMR
125 MHz
CDCl$_3$
81.19
62.44
57.96
57.19
48.67
46.77
45.29
44.83
38.74
37.59
34.14
29.99
29.71
29.35
28.66
26.16
26.10
24.86
18.41
-4.59
-4.60
-5.00
-5.12
f1 (ppm)

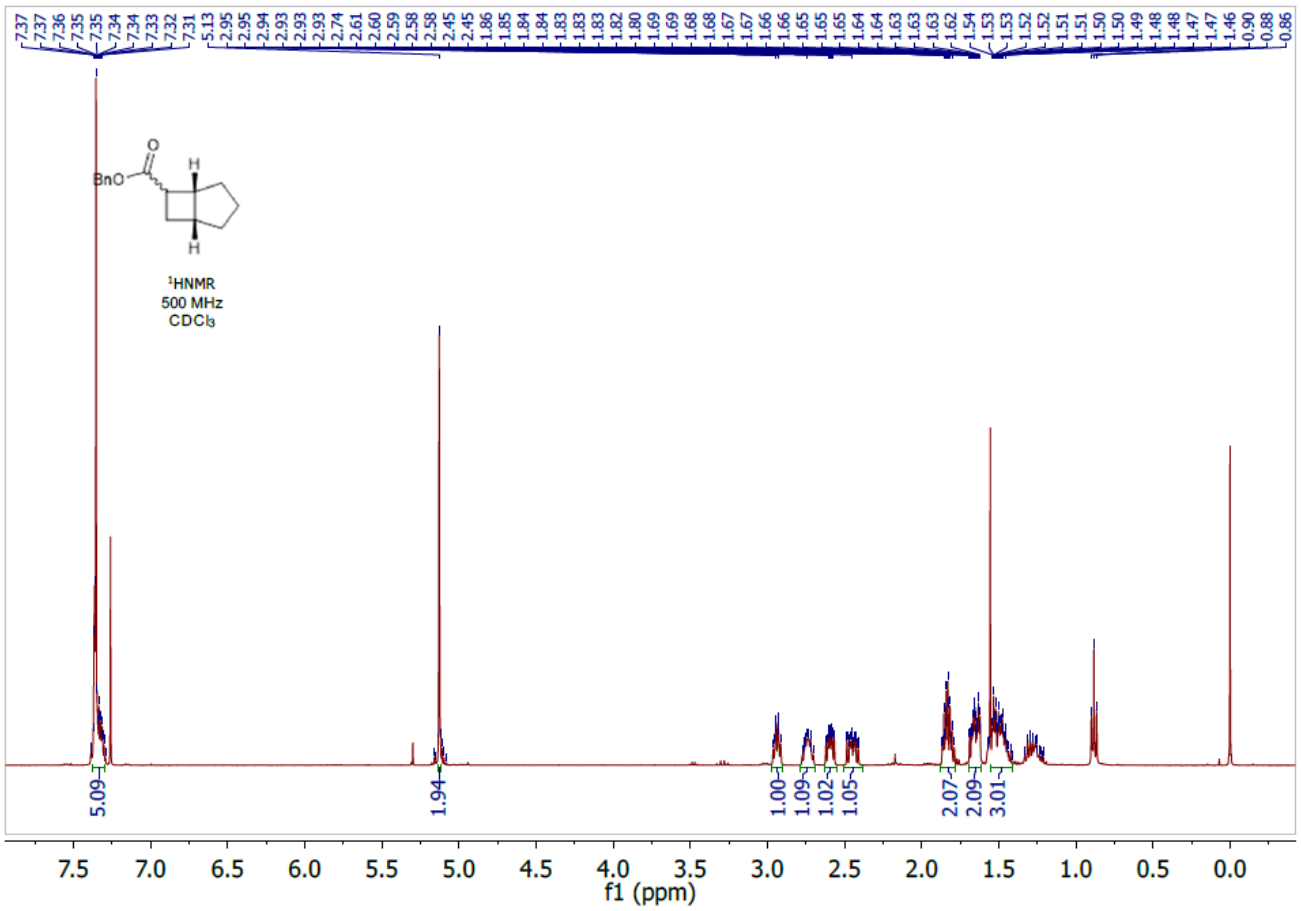
List of Compounds Appendix A

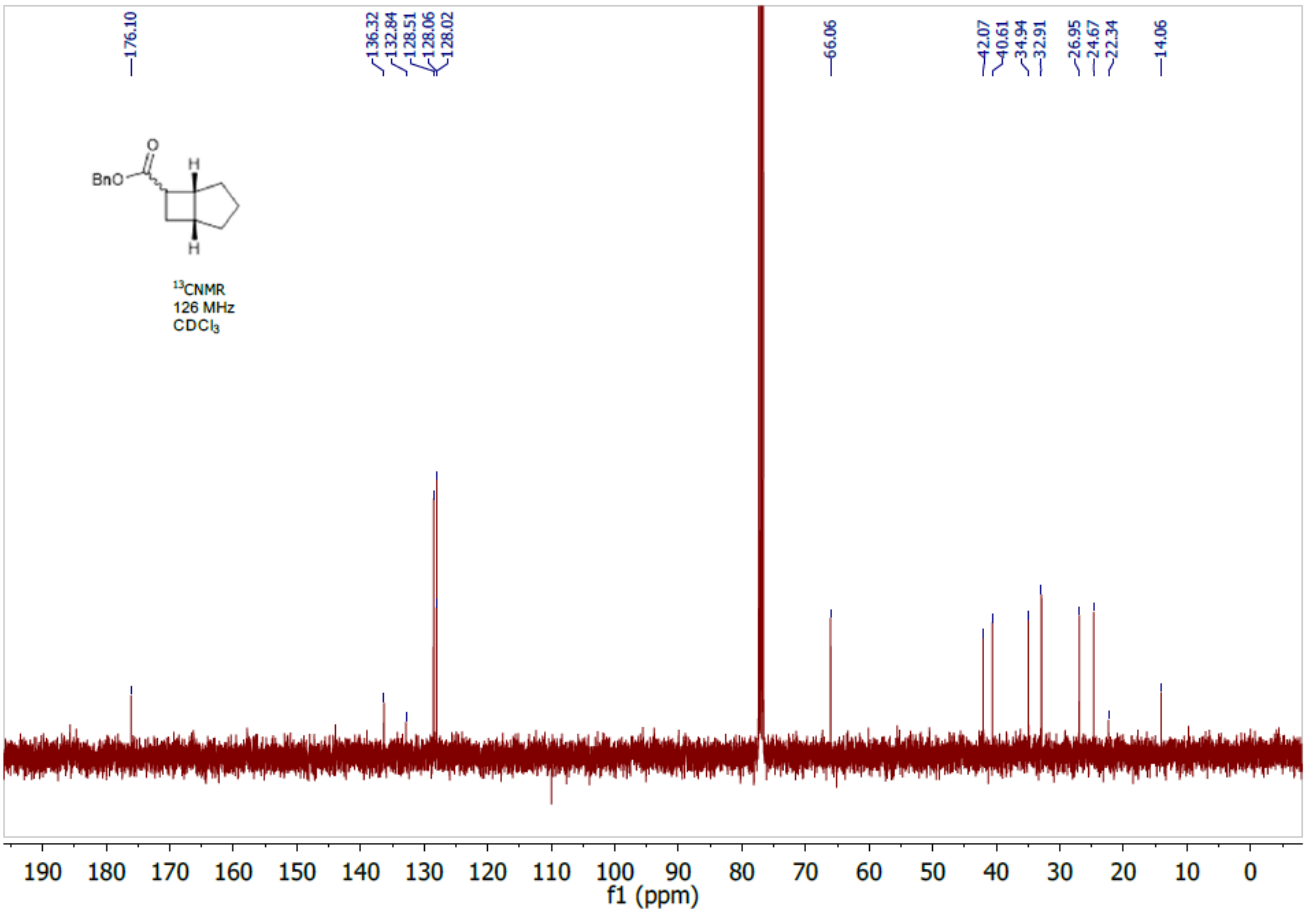





OBn
^{1}HNMR
500 MHz
CDCl3
5.15
1.03
1.00
1.31
1.97
2.29
2.07
2.69
3.04
f1 (ppm)


166.47
149.69
137.97
136.13
128.54
128.19
128.16
121.18
115.13
66.03
33.07
31.56
27.09
OBn
^{13}CNMR
126 MHz
CDCl3
f1 (ppm)


BnO
H
H
O
^{1}HNMR
500 MHz
CDCl$_3$
5.09
1.94
1.00
1.09
1.02
1.05
2.07
2.09
3.01
f1 (ppm)


176.10
136.32
132.84
128.51
128.06
128.02
66.06
42.07
40.61
34.94
32.91
26.95
24.67
22.34
14.06
BnO
H
H
O
^{13}CNMR
126 MHz
CDCl$_3$
f1 (ppm)