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Catalytic Asymmetric Additions of in situ Generated Functionalized Zinc Reagents to Aldehydes

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Abstract
Enantioenriched secondary alcohols are ubiquitous moieties in natural products. The current methods to achieve their synthesis often times rely on complicated synthesis and isolation of fairly reactive and unstable organometallic reagents. To address these issues our group developed one-pot catalytic asymmetric methods toward the synthesis of E-allylic alcohols and diarylmethanols employing in situ synthesized functionalized Lewis acidic zinc reagents in the presence of chiral amino alcohols ligands. However, analogous methods for the synthesis of equally useful Z-allylic alcohols and diheteroaryl methanols were lacking. The reason why this task was more challenging is because en route toward the synthesis of the appropriate functionalized zinc reagents a Lewis acidic byproduct (lithium halide) was generated which would catalyze a racemic background reaction. The problem was addressed finding an additive, tetraethylethylenediamine (TEEDA), which could selectively inhibit the background reaction discriminating between the two Lewis acidic species present in the flask. The asymmetric addition could now take place giving the product in high yield and ee in one-pot. In the first chapter a novel catalytic asymmetric method for the synthesis of (Z)-disubstituted allylic alcohols is presented. Our one-pot procedure entails hydroboration of chloro alkynes and addition of a hydride source (t-BuLi), which results in formation of a (Z)-alkenylborane. Boron to zinc transmetalation of the alkenyl group with ZnEt2, addition of a chiral ligand, the inhibitor (TEEDA) and the substrate aldehyde results in formation of (Z)-allylic alcohols with excellent ee's. In the effort of streamlining the synthesis of compounds with multiple stereocenters, tandem protocols were devised to synthesize cyclopropyl- and epoxy-alcohols. Finally a brief study for the synthesis of racemic Z-trisubstituted allylic alcohols is presented. In the second chapter we describe a method for the synthesis of diarylmethanols generating the desired arylzinc reagent in situ and adding it to both aromatic and heteroaromatic aldehydes. The one pot procedure entails lithium/halogen exchange, transmetallation with a zinc species, with generation of undesired LiCl that can be sequestered in situ by an additive (TEEDA). The functionalized zinc reagent, in the presence of the chiral catalyst (–)-MIB, adds to a variety of aromatic and heteroaromatic aldehydes in excellent ee, thus enabling the formation of highly desirable diheteroarylmethanols as well as many other compounds.

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Luca Salvi

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Reader

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DEDICATION

This work is dedicated to all my family

ACKNOWLEDGEMENTS

I would like to thank everyone who helped me to achieve what only a few years ago would have been just simply a dream.

First of all I need to thank my adviser Patrick Walsh because if I have achieved anything in these years of research I owe it completely to him. His example, and his teaching had a tremendous impact in my education. It is interesting that I am writing this section after I already moved on for my postdoctoral assignment in Boston. In fact, it is evident now how I can stand my ground and feel confident about my work and my methods. Looking back into my experience however I can see that when I joined the research group of Pat, I was not the same person. It took his extreme ability to foster what he saw as a potential in me to make me able to express myself.

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Now I would like to take a minute to thank all the former members of the Walsh group who were the people I looked at when I first started. Dr. Alfred Wooten with whom I

learned how to work in the glove-box. Dr. Hongmei Li, Dr. Sang-Jin Jeon, Dr. Jeung Gon Kim, Dr. Hun-Young Kim, Dr. Michael Kerrigan and Dr. Ann Kelly. They taught me a lot and I honestly do not know what I would have done without them. Mike brought me up as an Eagles fan and I will be always thankful for this. I shared the cubicle with Ann Kelly until her graduation and even if "she was always busy" she always made time for my questions. Huny has been a terrific presence in the lab and all the cyclopropanation reactions I have done, I honestly owe it to her, who alone pioneered this direction in our lab. Sang-Jin and Jeung are two students who left some inheritance for me, and I moved my first and last steps in the same fields they were working on during their time in our lab.

I then need to thank all the current members of our lab who made my time in graduate school full of excitement. I still remember the lunches spent discussing papers at the board, followed by 3-4 run of espresso to feed the entire floor with the necessary amount of caffeine. In particular Petr Valenta with whom I shared the cubicle after Ann left. It has been an amazing time, and I may realize it more now that I am not there anymore and I miss our continuous share of ideas, bickering and biking. Then I need to thank Natalie Drucker who joined our lab to work on a project with Petr, but she came in lab always so positive that her smiles made my days being more positive!

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person in the whole lab. When you ask him something you know that he is going to do it for sure; I am sure this determination will be beneficial in the long run during graduate school. Finally I would like to spend a few words for Byeong-Seon Kim, a student who is an example to me. He came from South Korea to learn English before even going to school. He is a very brilliant chemist and I am still so impressed with his performance in the Cumulative Exams. I really feel like this group of people so different from each other but so passionate about their work will yield great fruits in the near future. I definitely would have been less of chemist without any of you!

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Thanks to everyone and sorry if I did not mention your name on the paper, but all of you who had touched my life in some ways you had an impact on it, and I will carry those memories with me in my heart!

Luca

ABSTRACT

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Professor Patrick J. Walsh

Supervisor of Dissertation

Enantioenriched secondary alcohols are ubiquitous moieties in natural products. The current methods to achieve their synthesis often times rely on complicated synthesis and isolation of fairly reactive and unstable organometallic reagents.

To address these issues our group developed one-pot catalytic asymmetric methods toward the synthesis of *E*-allylic alcohols and diarylmethanols employing *in situ* synthesized functionalized Lewis acidic zinc reagents in the presence of chiral amino alcohols ligands. *However, analogous methods for the synthesis of equally useful Z-allylic alcohols and diheteroaryl methanols were lacking*.

The reason why this task was more challenging is because *en route* toward the synthesis of the appropriate functionalized zinc reagents a Lewis acidic byproduct (lithium halide) was generated which would catalyze a racemic background reaction.

The problem was addressed finding an additive, tetraethylethylenediamine (TEEDA), which could selectively inhibit the background reaction discriminating between the two

Lewis acidic species present in the flask. The asymmetric addition could now take place giving the product in high yield and ee in one-pot.

In the first chapter a novel catalytic asymmetric method for the synthesis of (*Z*)-disubstituted allylic alcohols is presented. Our one-pot procedure entails hydroboration of chloro alkynes and addition of a hydride source (*t*-BuLi), which results in formation of a (Z)-alkenylborane. Boron to zinc transmetalation of the alkenyl group with $ZnEt_2$, addition of a chiral ligand, the inhibitor (TEEDA) and the substrate aldehyde results in formation of (Z)-allylic alcohols with excellent ee's. In the effort of streamlining the synthesis of compounds with multiple stereocenters, tandem protocols were devised to synthesize cyclopropyl- and epoxy-alcohols.

Finally a brief study for the synthesis of racemic *Z*-trisubstituted allylic alcohols is presented.

In the second chapter we describe a method for the synthesis of diarylmethanols generating the desired arylzinc reagent *in situ* and adding it to both aromatic and heteroaromatic aldehydes.

The one pot procedure entails lithium/halogen exchange, transmetallation with a zinc species, with generation of undesired LiCl that can be sequestered *in situ* by an additive (TEEDA). The functionalized zinc reagent, in the presence of the chiral catalyst (–)-MIB, adds to a variety of aromatic and heteroaromatic aldehydes in excellent ee, thus enabling the formation of highly desirable diheteroarylmethanols as well as many other compounds.

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Introduction

Asymmetric synthesis is a broad field, which overlaps with many other disciplines. The synthesis of molecules with high levels of stereocontrol is an essential requirement in the chemical industry and in academic laboratories. Applications are found in many processes involving pharmaceutical industry, agriculture, fragrance and material chemistry.

In the pharmaceutical industry, designing a new drug relies on the understanding of very subtle differences that are at the core of complicated recognition mechanisms. It is known that drug-receptor interactions involve chiral entities and that one enantiomer of a medication can interact with a receptor in the desired fashion, while the other enantiomer can interact with a different receptor and have a negative impact on the organism. In the case of thalidomide, one enantiomer had the desired effect while the other caused severe birth defects. Thus, it is crucial to develop practical, scalable methods for the synthesis of chiral entities as single enantiomers.

Asymmetric syntheses of chiral molecules have proven to be challenging. Considering only the instance in which a prochiral substrate is transformed into a chiral product, an asymmetric reaction uses a chiral auxiliary (the catalyst if it is used in much lower amount than the substrate), to form only one of the two possible enantiomers. Upon coordination of the catalyst to the prochiral substrate, the two diastereomeric reaction pathways leading to the product are now ideally much different in energy. This difference has to be >2 kcal to develop an efficient and practical process.

Ideally, asymmetric syntheses should be catalytic to reduce the amounts of very valuable reagents that are not going to be incorporated in the final product. Even today, however, industrial processes involve stoichiometric amounts of chiral auxiliaries, or kinetic resolutions of racemic mixtures. Fortunately, many catalytic processes have been

developed, but few have been applied to large scale synthetic application. One of the goals of our research is to develop scalable methods, which is why our new methods are conducted on at least 5 mmol scale (and in some cases up to 30 mmol are employed).

Designing an efficient catalyst for a specific reaction is still a daunting exercise. In fact, most new catalysts are developed by a trial and error process, which involves a number of optimization studies. The quest for a perfect match is thus approached in two ways: 1) seeking reactions that could potentially work with available catalysts, or 2) targeting a desired reaction and screening a library of different catalysts until one that gives promising enantioinduction is identified. The next step then calls for the synthesis of various derivatives of that catalyst. Ligand or catalyst modularity then become essential to perform this screening without spending most of the time synthesizing ligands rather than applying them to the targeted reactions.

The programs developed in our laboratory rely on organometallic catalysts. These catalysts have played an important role in asymmetric catalysis. Our group aim is not only to develop asymmetric reactions, but also to combine multiple steps in one flask, thus enabling the efficient synthesis of complex building blocks with minimal purifications. The key to succeed in such a task relies on the control of potential background reactions, caused both by the reagents and by-products generated *en route* to the desired product. Thus when the background reaction is either absent or slow, it is possible to synthesize relatively complicated molecules in high yield with regio- and stereocontrol from readily available materials.

The projects developed in the Walsh group involve the *in situ* generation of organozinc species, thus avoiding the need for cumbersome syntheses, isolation and storage of these reactive and pyrophoric compounds. In the past our group has developed several methods for the synthesis of (*E*)-vinylzinc species starting from terminal alkynes employing the procedure developed by Srebnik and Oppolzer.

The organozinc species thus generated are added to aldehydes in the presence of an enantioenriched amino alcohol ligand forming allylic zinc alkoxides, which provide

enantioenriched secondary alcohols after treatment with water in high yields and enantioselectivities.

Our group also explored the possibility of developing other functionalized zinc reagents *in situ* to use in asymmetric addition reactions. The problem we faced was that when employing either terminal halo alkynes or aryl- and heteroaryl bromides, necessary for the synthesis of either (*Z*)-vinylzinc or aryl- and heteroaryl species, a Lewis acidic by-product was generated such as LiCl, LiBr or EtZnBr. These Lewis acids promoted a background reaction that yields racemic products, even in the presence of the enantioenriched catalyst.

To develop a successful asymmetric reaction it is crucial that the byproduct promoted background reaction be suppressed. Employing TEEDA (tetraethylethylene diamine) or TMEDA (tetramethylethylene diamine) as an additive to inhibit the Lewis acidic by-products selectively provides an alternative to centrifugation or filtration of sensitive intermediates. Centrifugation and filtration have been used by others, but are impractical on large scale. Our approach is very remarkable considering that both the background and the catalyzed reactions are Lewis acid catalyzed. There are subtle difference between the Li and the Zn center that enable selective inhibition to be possible.

Having successfully developed methods for the asymmetric synthesis of allylic alcohols we wanted to investigate the possibility of increasing the complexity of the product maintaining the one-pot nature of our protocols. The synthesis of molecules with more than one stereocenter is a challenging problem. In most cases, the existing stereocenter in a molecule influences the substrate-reagent interactions, resulting in diastereomeric transition states and leading to the prevalent formation of one diastereomer. This is true in the instances in which the transformation occurs in the vicinity of the stereocenter, especially when the reaction is a directed reaction.[1] It is common practice to perform this operation in two steps, isolating first the enantioenriched product, and then subjecting the clean material to the diastereoselective transformation. Employing our methods for Oppolzer's syntheses of (*E*)-vinylzinc

species and additions to either aldehydes or ketones, our group developed tandem protocols not requiring isolation of the intermediates. The zinc alkoxide formed in the asymmetric addition controls the outcome of the diastereoselective reaction involving the allylic double bond.

In the projects herein presented, the possibility of performing tandem reactions was particularly challenging due to the presence of inorganic salts formed during the synthesis of the organozinc species, and also because of the presence of the inhibitor, which was not necessary in the earlier protocols.

Thus instead of stopping at the synthesis of the secondary alcohols by quenching the zinc allylic alkoxides, a directed epoxidation or cyclopropanation was successfully performed. In such a reaction, five synthetic steps were performed in one flask, generating up to three stereocenters with complete control over the enantio- and diastereoselectivity.

The present introduction aims to highlight the main factors in the field of asymmetric catalysis, along with a brief introduction to the research in the Walsh group, in order to prepare the reader for the more in depth discussion following in the next two chapters.

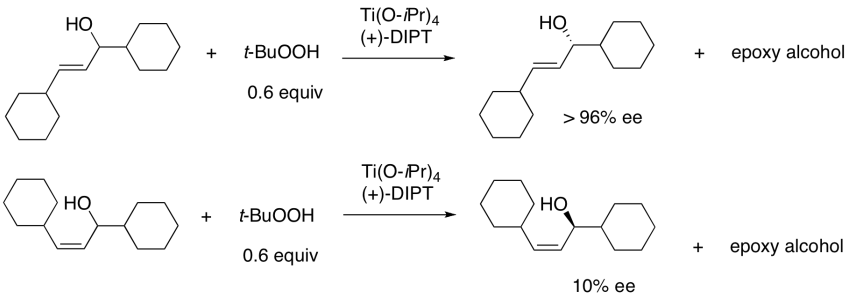
1. Usefulness of (*Z*)-Vinyl Organometallic Reagents

1.1. Catalytic Asymmetric Generation of (Z)-Disubstituted Allylic Alcohols

1.1.1. Introduction

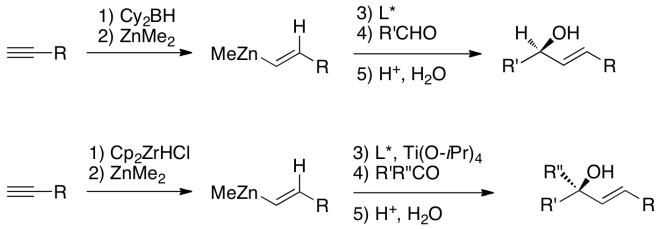
1.1.1.1. Synthesis of (*Z*)-Disubstituted Allylic Alcohols

Enantioenriched allylic alcohols are among the most commonly used chiral building blocks and have been widely applied in natural and non-natural product synthesis.[2-5] They are also precursors to enantioenriched epoxy alcohols,[2,5-11] allylic amines,[12] α- and β-amino acids,[13,14] and cyclopropyl alcohols.[15-18] Enantioenriched allylic alcohols are often isolated via kinetic resolution (KR) with the Sharpless-Katsuki asymmetric epoxidation catalyst.[5-8] Although (*E*)-allylic alcohols are excellent substrates for KR, (*Z*)-disubstituted allylic alcohols are not (Scheme 1-1).[5-8] Other drawbacks to KR include the need to separate the desired allylic alcohol from the epoxy alcohol product and a maximum yield of 50%.[19]



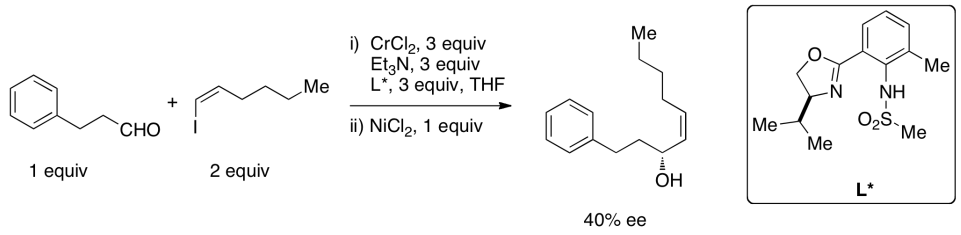
Scheme 1-1. Application of the Sharpless-Katsuki Catalyst to the Kinetic Resolution of (*E*)- and (*Z*)-Allylic Alcohols.

More efficient methods to prepare enantioenriched allylic alcohols include asymmetric vinylation of aldehydes[9-11,13,14,20-27] or ketones[28,29] (Scheme 1-2) and reductive coupling of alkynes and carbonyl compounds.[30-35] These methods simultaneously generate a C-C bond and a stereogenic center in a single step. Most vinylation methods are initiated by hydrometallation of terminal alkynes, via hydroboration[20-22,36] or hydrozirconation,[23,24,37] followed by addition of the resulting (*E*)-vinyl organometallic reagents to aldehydes or ketones to furnish (*E*)-allylic alcohols (Scheme 1-2). Similar methods to prepare (*Z*)-allylic alcohols would require *trans* hydrometallations, which are rarely observed.[38]



Scheme 1-2. Catalytic Asymmetric Vinylation of Aldehydes and Ketones via Hydrometallation of Terminal Alkynes, Transmetallation, and Addition.

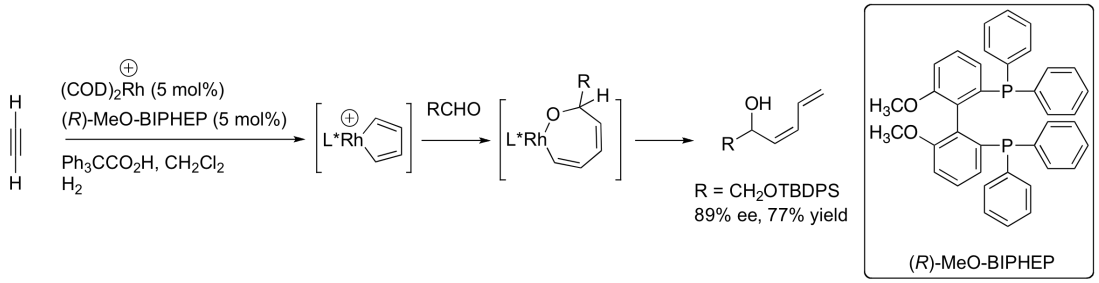
Only one direct (*Z*)-vinylation of aldehydes has been reported involving the Nozaki-Hiyama-Kishi reaction with (*Z*)-vinyl halides.



Scheme 1-3. Enantioselective (*Z*)-Allylic Alcohol from (*Z*)-Vinyl Iodide.

The single (*Z*)-vinyl halide substrate tested in this study, however, underwent addition with 40% enantioselectivity (Scheme 1-3).[39]

Progress toward the generation of enantioenriched (*Z*)-dienyl alcohols has recently been reported by the Krische group.[35] Employing acetylene gas and hydrogen in the presence of a rhodium catalyst and an aldehyde or α-ketoester, these researchers found that dienyl alcohols could be isolated in good yields (Scheme 1-4). The (*Z*)-geometry is believed to arise via reductive coupling of two acetylenes to generate a metallocyclopentadiene. Insertion of an aldehyde followed by protonation or hydrogenolysis of the metal carbon bond provides the observed (*Z*)-dienyl alcohol. Preliminary studies directed toward enantioselective versions of this dienylation reaction are promising.



Scheme 1-4. Generation of (*Z*)-Dienyl Alcohols and Proposed Intermediates by Krische and Coworkers.

1.1.1.2. Synthesis by the Walsh Group

We have been interested in the development and applications of vinyl organometallic reagents that enable the construction of di- and trisubstituted olefins and allylic alcohols.[9-

[11,13,14,18,28,29] Synthons for these species are shown in Figure 1-1. The synthon for the (*E*)-disubstituted vinyl groups represented in Scheme 1-2 (**A**, Figure 1-1) is readily derived from the hydrometallation of terminal alkynes. It contains one nucleophilic site *trans* to R^1. A synthon for a (*Z*)-di- or trisubstituted vinyl group (Figure 1-1, **B**), on the other hand, contains two reactive positions, a nucleophilic site *cis* to R^1 and an electrophilic site *trans* to R^1. For generation of (*Z*)-disubstituted allylic alcohols, the nucleophilic reagent that adds to the electrophilic site is a hydride. The increased functionality of this synthon provides greater flexibility and enables the formation of multiple bonds, potentially through synthetically efficient tandem reactions. In the development of reagents for synthon **B**, it is critical that the double bond stereochemistry be preserved during bond-forming processes.

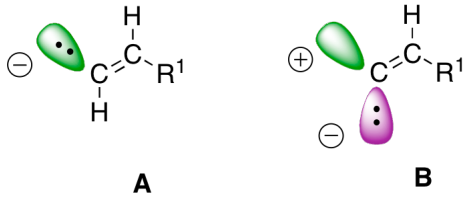
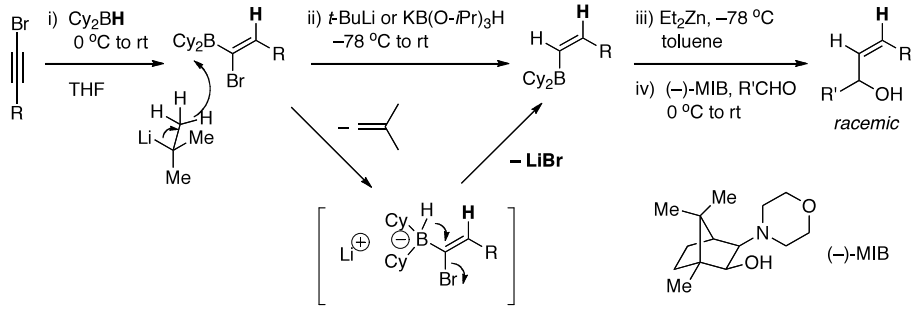


Figure 1-1. Synthon **A** Represents (*E*)-Disubstituted Vinyl Organometallics while Synthon **B** Represents (*Z*)-Di- or Trisubstituted Reagents.

We recently reported a one-pot stereospecific method for the synthesis of (*Z*)-disubstituted allylic alcohols based on synthon **B** (Scheme 1-5).[40] Initial hydroboration of 1-bromo-1-alkynes with dicyclohexylborane furnishes 1-bromo-1-alkenylboranes with excellent regioselectivity. It is known that nucleophiles react with 1-bromo-1-alkenylboron derivatives via addition of the nucleophile to the open coordination site on boron followed by migration of the nucleophile or a boron alkyl to the vinylic position

with inversion at the vinylic center.[41-46] In our investigations we chose to use *t*-BuLi, which had been shown to be an excellent hydride source by Molander[44] for the formation of (*Z*)-vinylboranes. Vinylboranes are fairly unreactive and have not been widely used in synthesis outside of Suzuki cross-coupling reactions. We envisioned that the (*Z*)-vinyl group would undergo boron to zinc transmetallation with dialkylzinc reagents to generate more reactive vinylzinc reagents. In fact, the increased reactivity of the vinylzinc reagent enabled additions to aldehydes to proceed smoothly to generate (*Z*)-allylic alcohols.[40] Using this method, a variety of racemic (*Z*)-allylic alcohols were prepared in high yields. Additions of (*Z*)-vinyl groups to enantioenriched protected α- and β-hydroxy aldehydes resulted in formation of (*Z*)-allylic alcohols with high diastereoselectivity.[40] Unfortunately, attempts at enantioselective versions of this transformation afforded only racemic allylic alcohol products. An additional problem with our original (*Z*)-vinylation of aldehydes was that it required a solvent switch from THF to toluene, which complicated the procedure.



Scheme 1-5. Our Stereospecific Method for the Synthesis of (*Z*)-Allylic Alcohols.

The next section describes the first general and direct catalytic asymmetric synthesis of (*Z*)-allylic alcohols. The application of this method to the one-pot preparation of highly functionalized epoxy alcohols and allylic epoxy alcohols is demonstrated in Section 1.2, while the application to the preparation of cyclopropyl alcohols is demonstrated in Section 1.3. These reactions lead to a rapid increase in molecular complexity and enable the synthesis of highly functionalized chiral building blocks.

1.1.2. Results and Discussion

1.1.2.1. Optimization of the Reaction Conditions

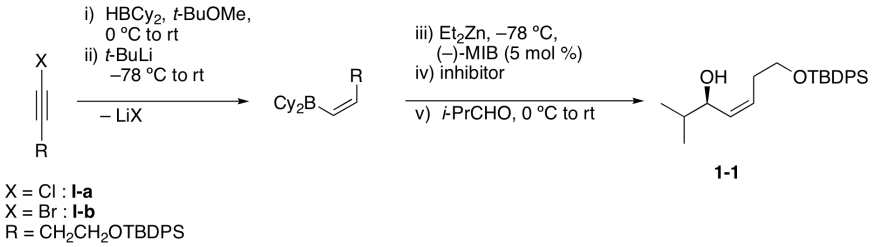
When our (*Z*)-vinylation of aldehydes (Scheme 1-5) was conducted in the presence of the amino alcohol-based catalyst derived from (–)-MIB, the (*Z*)-allylic alcohol product was isolated in good yields, but the product was found to be racemic. This result was surprising because the zinc-based catalyst derived from (–)-MIB is one of the most efficient and enantioselective amino alcohol-based catalysts known for carbonyl additions. The absence of enantioselectivity was attributed to the rapid addition reaction promoted by the liberated Lewis acid byproduct, LiBr (Scheme 1-5). Rather than attempt to remove the LiBr byproduct by filtration[47] or centrifugation,[48] which would be impractical on large scale, we attempted to deactivate it.

Our first attempts to inhibit the salt byproduct were based on observations reported by Bolm. In a study involving the addition of Ph_2Zn to aldehydes, Bolm and coworkers

emphasized the beneficial effect of dimethoxy poly(ethyleneglycol) (DiMPEG) on the reaction enantioselectivity.[47] They proposed that DiMPEG suppressed reactions catalyzed by trace achiral Lewis acids, including LiBr, allowing most of the arylation reaction to proceed via the ligand accelerated[49] Lewis acid catalyzed pathway.[50]

To suppress the LiBr-promoted vinyl addition to aldehydes, we employed DiMPEG as an inhibitor (Table 1-1). Addition of 5-7 mol of % DiMPEG (MW 2000 g/mol) proved most effective, with enantioselectivities in the (*Z*)-vinylation reaching 86% (Table 1-1, entries 1-4).

Table 1-1. Enantioselective Addition of (*Z*)-Vinylzinc Reagents to Aldehydes in the Presence of Various Inhibitors.



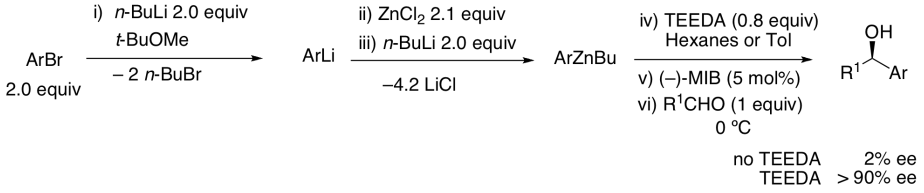
X = Cl : **I-a**
X = Br : **I-b**
R = $CH_2CH_2OTBDPS$

entry	additive (mol %)	X	ee (%)	entry	additive (mol %)	X	ee (%)
1	DiMPEG (5.5)	Br	75	10	none	Cl	0
2	DiMPEG (6)	Br	79	11	TEEDA (10)	Cl	82
3	DiMPEG (6.5)	Br	86	12	TEEDA (15)	Cl	89
4	DiMPEG (7)	Br	80	13	TEEDA (20)	Cl	90
5	tetraglyme (90)	Br	10	14	TEEDA (25)	Cl	90
6	tetraglyme (110)	Br	26	15	TEEDA (30)	Cl	90
7	tetraglyme (220)	Br	5	16	TEEDA (40)	Cl	45
8	TEEDA (20)	Br	10				
9	TEEDA (20)	Br	10				

Although this result was exciting and promising, we found that the reactions were very sensitive to the mol % DiMPEG and enantioselectivities were difficult to reproduce. Tetraglyme was used as a DiMPEG analog but was dramatically less effective at

inhibiting LiBr (Table 1-1, entries 5-7). After significant effort to identify reliable polyether inhibitors, this strategy was abandoned.

Instead, we turned to a diamine inhibitor that we had successfully used to solve a similar problem in our development of the first highly enantioselective one-pot asymmetric synthesis of enantioenriched diarylmethanols beginning from aryl bromides (Scheme 1-6).[51] Like the vinylation in Scheme 1-5, initial attempts at the asymmetric arylation reactions also resulted in formation of essentially racemic products. In the transmetallation reactions used to generate the aryl group donor, ArZn(*n*-Bu), over 4 equiv of LiCl were formed. As seen in the vinylation reactions, this Lewis acidic byproduct was significantly faster at promoting the aryl addition to provide diarylmethanols than the chiral amino alcohol-based catalyst, resulting in formation of racemic product. The key to the successful development of an asymmetric arylation system was inhibition of the LiCl byproduct with tetraethylethylene diamine (TEEDA). The diamine is believed to chelate LiCl to form a chloride-bridged dimer $[(TEEDA)LiCl]_2$ that is coordinatively saturated and catalytically inactive (Figure 1-2).[52,53] Using this technique, the racemic background reaction was completely suppressed, resulting in formation of diarylmethanols with enantioselectivities as high as 97%.



Scheme 1-6. Asymmetric Arylation of Aldehydes with TEEDA to Inhibit LiCl.

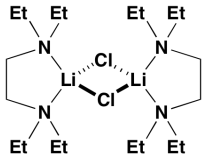


Figure 1-2. Possible Structure of the Coordinatively Saturated TEEDA Adduct of LiCl.

When the diamine-based strategy in Scheme 1-6 was applied to the synthesis of (*Z*)-allylic alcohols in Table 1-1, enantioselectivities peaked at 10% under our best conditions (Table 1-1, entries 8 and 9). These results suggested that inhibition of LiBr would be significantly different from inhibition of LiCl. It was speculated that the bromide analogs of $[(TEEDA)LiCl]_n$ (Figure 1-2) dissociate more readily to generate an open coordination site capable of aldehyde activation. Rather than search for a new inhibitor for LiBr, 1-chloro-1-alkynes were examined in this process, which would generate LiCl.

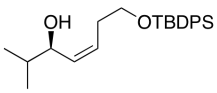
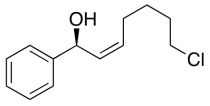
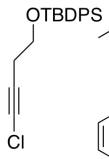
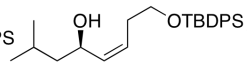
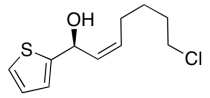
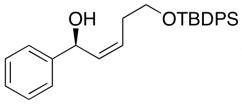
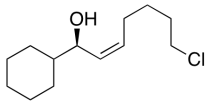
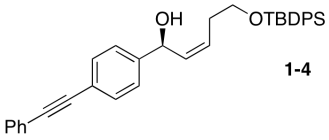
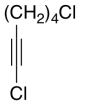
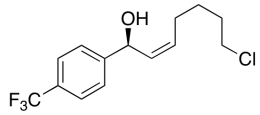
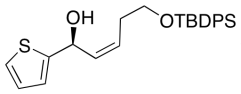
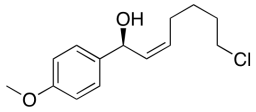
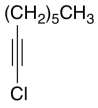
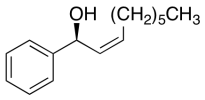
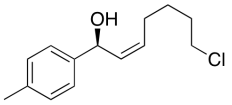
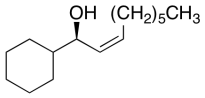
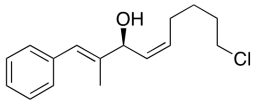
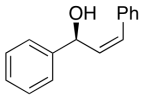
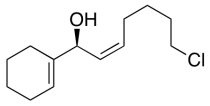
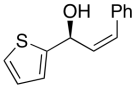
Examination of 1-chloro-1-alkynes was approached in a similar fashion to the optimization of 1-bromo-1-alkynes. When 1-bromo-1-alkynes were employed in a previous study[40] (Scheme 1-5), it was found to be necessary to perform the addition of *t*-BuLi in THF. A solvent switch was then needed, because the vinylzinc addition proceeds with low enantioselectivity in THF. Using the 1-chloro-1-alkynes, however, the entire reaction could be performed in *t*-BuOMe solvent, without the need to switch solvents. Hydroboration of 1-chloro-1-alkynes with Cy_2BH proceeds in 1 h at 0 ºC to room temperature with excellent regioselectivity. Reaction of the resulting 1-chloro-1-vinylborane with *t*-BuLi occurred with inversion at the vinylic center, generating the (*Z*)-vinylborane. Transmetallation with diethylzinc and addition to an aldehyde in the presence of the (–)-MIB-based catalyst provided the racemic allylic alcohol. Repeating

the sequence with the addition of increasing amounts of TEEDA resulted in the formation of enantioenriched (*Z*)-allylic alcohol products (Table 1-1, entries 10 - 16). The highest enantioselectivities were obtained with 20-30 mol % TEEDA. Further increases in the mol % diamine caused a decrease in both enantioselectivity and yield. This observation is likely due to inhibition of the chiral zinc-based catalyst by the diamine, allowing the uncatalyzed background reaction to become competitive with the catalyzed addition, eroding the product ee.

1.1.2.2. Catalytic Asymmetric Synthesis of (*Z*)-Disubstituted Allylic Alcohols

With the optimized conditions in Table 1-1, we examined the scope of the asymmetric vinylation (Table 1-2). Employing 20-30 mol % TEEDA, a variety of 1-chloro-1-alkynes and aldehydes underwent the addition with good yields (61-84%) and good-to-excellent enantioselectivities (76-98%). 1-Chloro-1-alkynes bearing a TBDPS-protected alcohol (entries 1 - 5), alkyl (entries 6 and 7), phenyl groups (entries 8 and 9) or chloroalkyl (entries 10 - 17) groups were successfully employed in the asymmetric vinylation reaction. Although aliphatic aldehydes with α-branching underwent addition with high enantioselectivity (84 – 90% ee, entries 1, 7, and 12), β-branched isovaleraldehyde was a more challenging substrate, undergoing addition with 76% enantiomeric excess (entry 2). α,β-Unsaturated aldehydes reacted to form dienols with 88-94% ee (entries 16 and 17). Aryl aldehydes were also good substrates for the vinylation reaction, providing benzylic alcohols with ee between 86 and 98%.

Table 1-2. Scope of the Catalytic Asymmetric Synthesis of (*Z*)-Allylic Alcohols.

entry	chloroalkyne	product	#	yield	ee (%)	entry	chloroalkyne	product	#	yield	ee (%)
1			**1-1**	61	90	10			**1-10**	84	88
2	 **1-a**		**1-2**	74	76	11			**1-11**	73	94
3			**1-3**	61	95	12			**1-12**	74	88
4			**1-4**	84	98	13			**1-13**	72	86
5			**1-5**	69	93	14	**1-d**		**1-14**	84	93
6			**1-6**	63	93	15			**1-15**	93	97
7	**1-b**		**1-7**	81	84	16			**1-16**	73	88
8			**1-8**	82	97	17			**1-17**	80	94
9	**1-c**		**1-9**	63	92						

The electron withdrawing trifluoromethyl benzaldehyde exhibited the lowest enantioselectivity of this class of substrates, possibly due to an earlier transition state with less bond formation and reduced steric bias. The heterocyclic aldehyde, 2-thiophene carboxaldehyde, proved to be an excellent substrate for (*Z*)-vinylations proceeding in 92-94% ee (entries 5, 9, and 11). This route to thiophene-containing allylic alcohols avoids potential problems with catalyst poisoning that can arise in the hydrogenation of

thiophene-containing propargylic alcohols. Similarly, the alkyne-bearing product in entry 4 would be difficult to prepare by selective Lindlar reduction.

1.1.2.3. Large Scale Application

The evaluation of scalability is essential in the development of practical methods with potential utility in target oriented synthesis. With this in mind, we examined the substrate combination in entry 15 using 5.0 mmol of the aldehyde. The desired (*Z*)-allylic alcohol was obtained in 79% yield at this scale with 96% ee. The high yield and enantioselectivity in this reaction bode well for large-scale applications of these asymmetric addition reactions.

Currently we are also preparing an *Organic Synthesis* paper employing chloro alkyne 1-d and tolualdehyde to generate **1-15**. The two runs necessary for publication were performed on a 30 mmol scale, yielding the product in 77% yield and 92% ee. Slight adjustments were necessary to obtain this result. As in any scale-up process, temperature needs to be monitored closely. For example, the addition of either *t*-BuLi or $ZnEt_2$ at −78 ºC needed to be performed dropwise while making sure that the temperature remained below −65 ºC. The aldehyde was diluted in 20 mL of hexanes and added slowly at 0 ºC with the aid of a syringe pump (5 mL/h) while maintaining the temperature at −10 ºC instead of 0 ºC as in the small scale reaction. Without these modifications, the product was obtained in 60% ee.

Additionally, the purity of the terminal chloro alkyne is crucial to provide the product in high purity. In fact, while preparing **1-d** in large amounts for this scale-up study, the

purification was performed by distillation of the crude chloro alkyne, which by ^{1}H NMR looked pure. However in the final product 3-5% of the (*E*)-allylic alcohol was detected by proton NMR.

To address this problem the (*E*)-allylic alcohol was synthesized separately to compare both the ^{1}H NMR and the retention times in the HPLC plot to those of the (*Z*)-product. Indeed traces of the (*E*)-allylic alcohol were present in the large scale reactions.

The possibilities were that the rearrangement upon *t*-BuLi addition was not 100% regioselective, or that the terminal chloro alkyne was contaminated by the terminal alkyne. By GC analysis we observed 3-5% of the terminal alkyne in the starting material used for this reaction, which could account for the observed formation of the (E)-allylic alcohol. The solution to this problem was found by purifying the terminal chloro alkyne by column chromatography while checking the purity of the fractions by GC analysis.

Using **1-d** purified in this way gave the desired (*Z*)-allylic alcohol in 77% yield and 92% ee. These results bode well for the use of this chemistry on large scale.

1.1.2.4. Outlook and Conclusions

The asymmetric synthesis of (Z)-allylic alcohols has been achieved utilizing 1-chloro alkynes as the precursor to provide the vinyl moiety. This method not only provides access to an important and challenging class of enantioenriched allylic alcohols, it also allows for a new synthon, which could be very useful in complex molecule synthesis.

Key to success in this endeavor is the discovery that TEEDA can inhibit the background reaction caused by LiCl, a by-product generated *en route* to the functionalized vinylzinc reagent. Most noteworthy is the fact that these additives do not inhibit the Zn-amino alcohol-based catalyst.

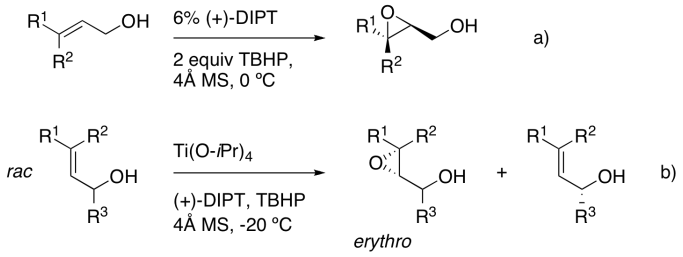
Some of the applications of the (*Z*)-allylic alcohols presented in this chapter will become evident in the next sections, in particular in Section 1.2 and Section 1.3. This work has been highlighted in the Organic Chemistry Portal edited by Professor Douglas Taber, and it has been cited already 8 times.

1.2. Developing a Diastereoselective One-Pot Epoxidation Protocol

1.2.1. Introduction

1.2.1.1. Synthesis of Epoxy Alcohols

Two of the most significant developments in the history of asymmetric catalysis were the introduction of the Sharpless-Katsuki asymmetric epoxidation of prochiral allylic alcohols[5,8,54] and the application of this reaction to the kinetic resolution of racemic allylic alcohols (Scheme 1-7).[6]



Scheme 1-7. a) Epoxidation of Prochiral Allylic Alcohols and b) Kinetic Resolution of Racemic Allylic Alcohols

The products of these processes, enantioenriched epoxy alcohols, are among the most valuable and versatile intermediates in organic synthesis[3] because they readily undergo regioselective ring-opening reactions.[7] As a result, the Sharpless-Katsuki asymmetric epoxidation has found extensive utility in the synthesis of natural products.[5]

Despite the enduring success of the Sharpless kinetic resolution, there remain significant limitations. If the desired product is the epoxy alcohol, the kinetic resolution must be quenched at low conversion to ensure product of high ee.[7] Alternatively, the resolved allylic alcohol is often isolated and epoxidized in a separate step. Of course, an inherent problem with kinetic resolutions is that the maximum yield is 50%.

In contrast to the synthesis of epoxy alcohols from achiral allylic alcohols, the direct synthesis of epoxy alcohols containing a stereogenic center at the carbanol carbon from achiral reagents requires that three contiguous stereocenters be established with high enantio- and diastereoselectivity. This transformation, therefore, is typically performed in a multistep procedure involving synthesis of a secondary allylic alcohol with high enantioselectivity, or racemic synthesis and resolution of the allylic alcohol, followed by a directed epoxidation reaction. The epoxidation of chiral secondary allylic alcohols is generally carried out using an organic peracid, such as *m*CPBA, or with a transition-metal catalyst in combination with a stoichiometric oxidant.[1] The diastereoselectivity of the directed epoxidation step ranges from poor to excellent, depending on the nature of the allylic alcohol.

Good to excellent diastereoselectivities have been achieved with cyclic allylic alcohols and with acyclic allylic alcohols having substitution on the olefin such that significant $A^{1,3}$ or $A^{1,2}$ strain exists in one of the diastereomeric transition states (Figure 1-3, Table 1-3). Thus, $A^{1,3}$ strain encountered in the transition state leading to the minor diastereomer can result in high diastereoselectivity for allylic alcohols that are *Z*-substituted with respect to the carbanol moiety (entries 1 and 2, Table 1-3). Likewise, substrates with substitution geminal to the carbanol group can exhibit $A^{1,2}$ strain in one of

the diastereomeric transition states and be epoxidized with high diastereoselectivity (entry 3, Table 1-3).

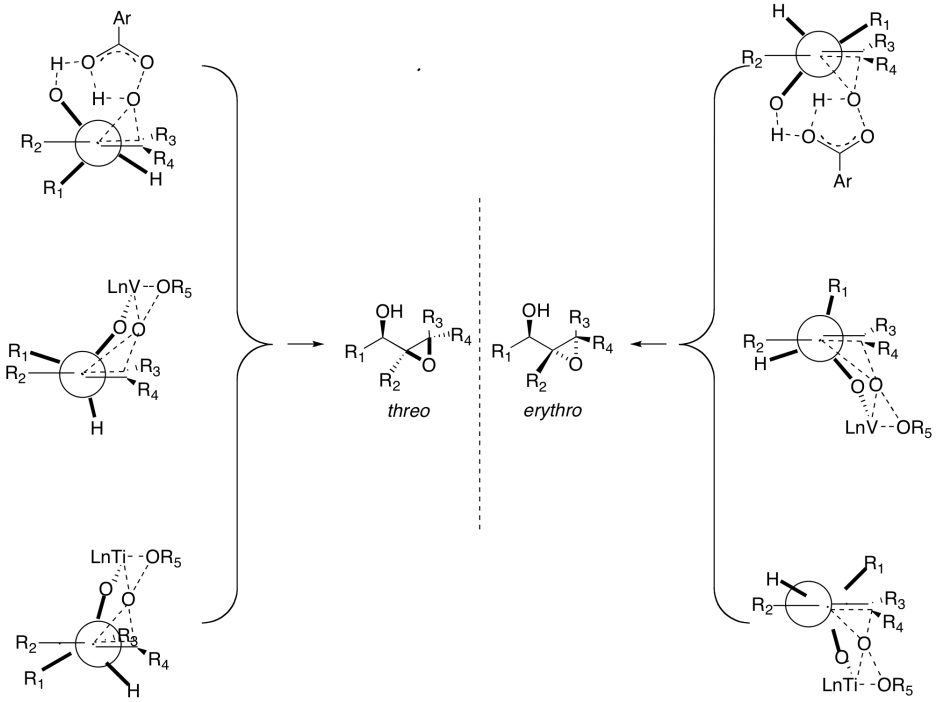
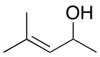
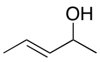


Figure 1-3. Transition States for the Directed Epoxidation of Chiral Allylic Alcohols via a Peracid or a Transition-Metal Peroxide

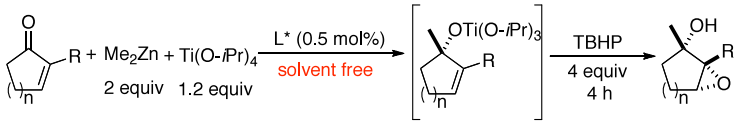
On the other hand, allylic alcohols containing disubstituted (*E*)-olefins are among the most difficult substrates for directed epoxidation. In the absence of significant $A^{1,3}$ and/or $A^{1,2}$ strain in the diastereomeric transition states, diastereoselectivities for these substrates are typically less than 2:1 with both peracid- and transition metal-catalyzed epoxidation reactions (entry 4, Table 1-3).[55-58]

Table 1-3. Diastereomeric Ratios for the Directed Epoxidation of Chiral Secondary Allylic Alcohols with Various Oxidizing Agents[59]

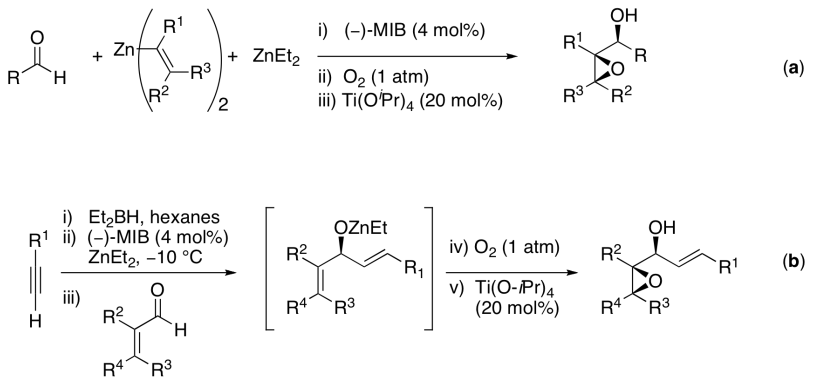
		Diastereomeric Ratios (*threo* : *erythro*		
entry	substrate	$Ti(O\text{-}iPr)_4$ *t*-BuOOH	$VO(acac)_2$ *t*-BuOOH	*m*-CPBA
1		10:1	2.4:1	19:1
2		19:1	6.1:1	19:1
3		1:3.5	1:19	1:1.2
4		1.9:1	1:2.4	1.8:1

1.2.1.2. Contributions from the Walsh Group

Having developed a viable method for the catalytic asymmetric synthesis of (*Z*)-disubstituted allylic alcohols, we wanted to examine briefly the potential application of this process in tandem addition/epoxidation reactions. We recently developed methods for tandem asymmetric alkylation of enones (Scheme 1-8)[60,61] and enals (Scheme 1-9)[9-11] followed by diastereoselective epoxidation of the resulting allylic alkoxides to provide epoxy alcohols with up to three contiguous stereogenic centers.[62] The oxidant in the epoxidation was a zinc peroxide generated upon reaction of either TBHP or dioxygen with dialkylzinc reagents.



Scheme 1-8. Tandem Asymmetric Alkylation/Epoxidation of Enones

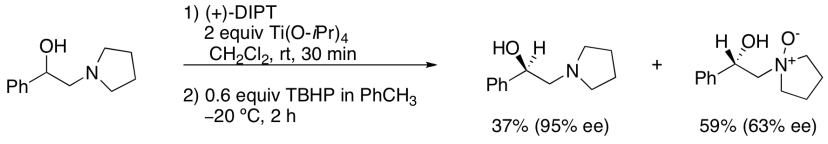


Scheme 1-9. (**a**) Tandem Asymmetric Alkylation/Epoxidation of Enals, (**b**) Vinylation/Epoxidation of Aldehydes

1.2.2. Results and Discussion

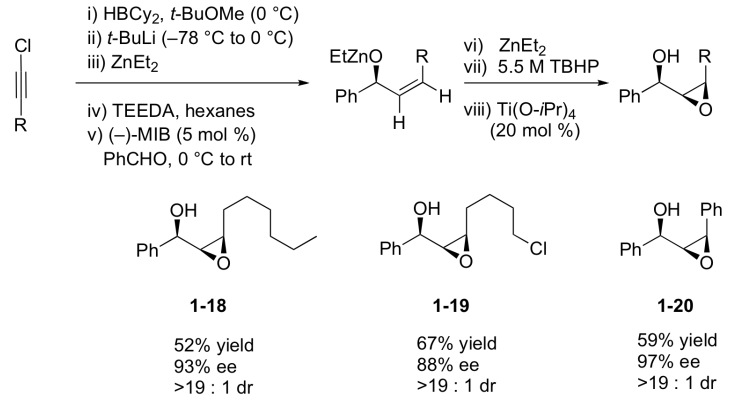
1.2.2.1. Developing an Enantioselective (Z)-Vinylation/Diastereoselective Epoxidation Tandem Protocol

Initially we were concerned that the reaction would be hampered by the presence of the TEEDA, due to its known coordination to titanium alkoxides[63] or oxidation to the *N*-oxide, as was observed in the KR of racemic β-amino alcohols by Sharpless (Scheme 1-10).[64] Fortunately, these side reactions did not interfere with the epoxidation.



Scheme 1-10. Sharpless *N*-Oxide KR of Nitrogen Containing Substrates

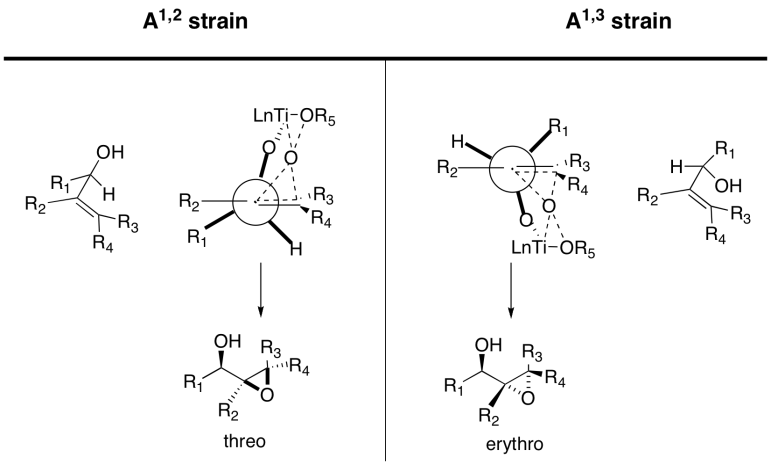
Adaptation of our addition/epoxidation method to the (*Z*)-vinylation reaction is illustrated in Scheme 1-11. The generation of the allylic zinc alkoxide was performed as outlined in Table 1-1. Rather than addition of water to quench the allylic alkoxide intermediate, however, 2 equiv of diethylzinc were injected into the flask. Dropwise addition of a 5.5 M solution of TBHP in decane was then followed by titanium tetraisopropoxide (20 mol %). The epoxidations were conducted at –20 ºC and stirred for 24 h before workup. The crude epoxy alcohols were chromatographed and isolated in 52 – 67% yield with excellent dr (>19:1 in each case, Scheme 1-11).



Scheme 1-11. Tandem Asymmetric Addition/Diastereoselective Epoxidation.

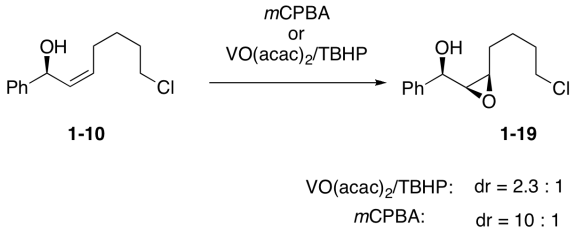
To aid in the assignment of the relative stereochemistry in the epoxy alcohol products in Scheme 1-11, we examined the diastereoselective epoxidation of an isolated allylic alcohol with the complementary epoxidizing agents *m*CPBA and $VO(acac)_2$/TBHP (Scheme 1-13). It is well known that $VO(acac)_2$/TBHP exhibits high diastereoselectivity with allylic alcohols that possess $A^{1,2}$ strain in one of the diastereomeric epoxidation transition states. In contrast, *m*CPBA is known to epoxidize with high

diastereoselectivity when allylic alcohols lead to an $A^{1,3}$ strain in one of the diastereomeric epoxidation transition states (Scheme 1-12).[4]



Scheme 1-12. Determining the Favored Diastereomer Formed According to the $A^{1,2}$ or $A^{1,3}$ Strain.

Subjecting the preformed allylic alcohol in Scheme 1-13 to the typical epoxidation conditions with $VO(acac)_2$/TBHP and *m*CPBA afforded the epoxy alcohols with 2.3 : 1 and 10 : 1 dr, respectively. The *m*CPBA epoxidation resulted in high stereoselectivity and formed the same diastereomer as our one-pot addition/epoxidation procedure.



Scheme 1-13. Epoxidation of the Isolated Allylic Alcohol with $VO(acac)_2$/TBHP and *m*CPBA.

This observation indicates that the *syn* diastereomer is formed in the tandem reaction, as shown in Scheme 1-11. Furthermore, the stereochemistry of **1-20** was assigned by derivatization with (–)-camphanic acid chloride to afford the expected ester, which was characterized by X-ray crystallography (Figure 1-4).

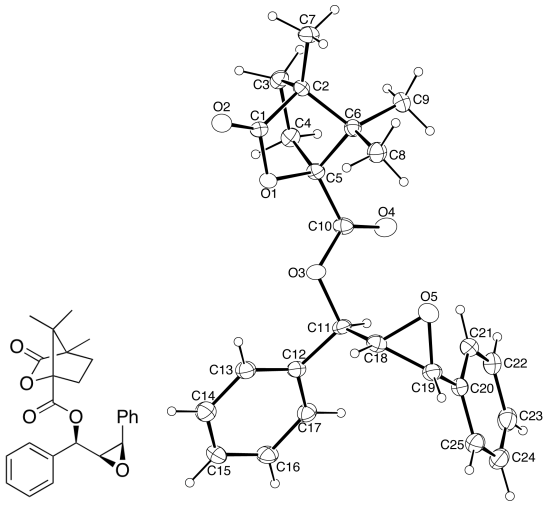
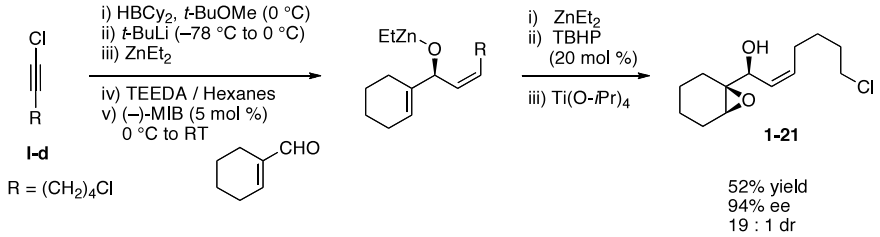


Figure 1-4. X-ray Structure of the Camphanic Ester of **1-20**.

1.2.2.2. Regioselectivity of Tandem Addition/Epoxidation Reactions

Having demonstrated that the epoxidation of the (*Z*)-allylic alkoxide could be performed in the tandem addition/epoxidation reaction, we wanted to explore the preferential epoxidation of a more substituted double bond in the presence of the (*Z*)-vinyl group. Thus, addition of the (*Z*)-vinylzinc reagent to cyclohexenecarboxaldehyde generated the intermediate dienyl alkoxide, which was subsequently exposed to zinc peroxide and titanium tetraisopropoxide. This reaction furnished the allylic epoxy

alcohol derived from oxidation of the more electron-rich trisubstituted double bond in 52% yield with 94% ee and 19 : 1 dr. The results in Scheme 1-11 and Scheme 1-14 highlight a unique feature of this epoxidation system: the ability to perform highly diastereoselective epoxidations with either $A^{1,2}$ or $A^{1,3}$ strain in one of the diastereomeric epoxidation transition states. In contrast, low diastereoselectivity is observed with *m*CPBA when selectivity is dependent on $A^{1,2}$ strain in one of the diastereomeric transition states and with $VO(acac)_2$/THBP or $Ti(O\textit{i}\text{-}Pr)_4$/TBHP when selectivity is dependent on $A^{1,3}$ strain.



Scheme 1-14. Tandem Asymmetric Addition/Diastereo- and Chemoselective Epoxidation.

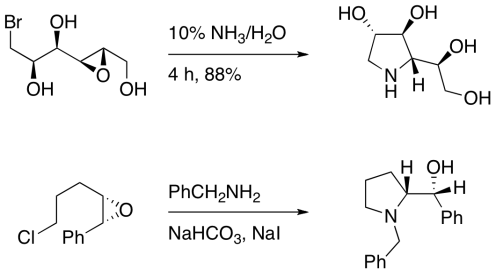
The apparent low yield for the synthesis of **1-21** in Scheme 1-14 needs further clarification. The overall sequence entails five synthetic steps in a tandem fashion. The 52% yield is the equivalent of an 88% yield for each individual transformations.

1.2.2.3. Future Directions

The asymmetric synthesis of epoxy alcohols was achieved in a simple protocol beginning from readily available starting materials. This method can provide new disconnections in the retrosynthetic analysis.

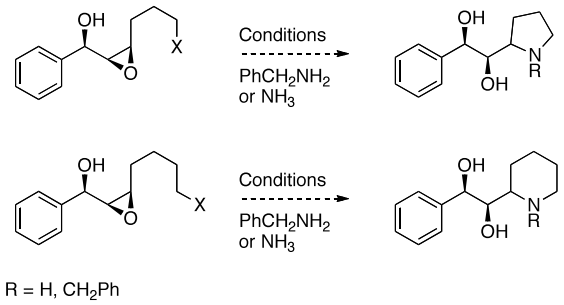
Currently, after succeeding in the synthesis of **1-15** on a 30 mmol scale, the synthesis of **1-19** is being attempted on the same scale. Preliminary results show that the tandem addition/epoxidation reaction needs a slightly different approach than the one used in the small scale reactions, because the generation of the Zn/peroxoalkyl reagent does not provide the same result on a 30 mmol scale. This result likely arises from precipitation of the zinc peroxide under the large scale conditions. Byeong-Seon Kim is testing other peroxide sources such as cumene hydroperoxide, which could be a more active and soluble reagent.

Moving into a different direction, epoxy alcohols with suitable functional groups such as halogens, generate *in situ* suitable species for intramolecular ring closing reactions. The epoxide serves as the internal electrophile upon treatment with ammonia or benzylamine (Scheme 1-15).[65,66]



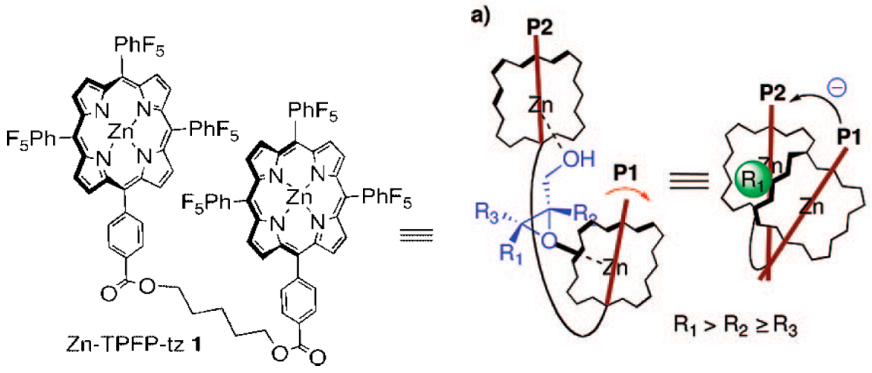
Scheme 1-15. Intramolecular Cyclization Reactions Employing the Epoxide as the Internal Electrophile.

The epoxy alcohols generated in this project could undergo a similar transformation providing either substituted pyrrolidine or piperidine depending on the length of the alkyl chain (Scheme 1-16).



Scheme 1-16. Proposed Ring Closing Reaction Employing the Epoxy Alcohols Described Herein.

The epoxy alcohols synthesized herein also appear to be suitable substrates for collaboration with professor Babak Borhan from Michigan State University. Their group has developed a porphyrin tweezer that would bind in a different way according to the absolute stereochemistry of the epoxy alcohol (Scheme 1-17).



Scheme 1-17. Borhan's Zinc Porphyrin Tweezers for Determination of Absolute Stereochemistry of Epoxy Alcohols.

Measuring the Exciton Coupled Circular Dichroism (ECCD) of the epoxy alcohol bound to the zinc porphyrin would provide the necessary information to determine the absolute stereochemistry without need for Mosher's ester analysis or other derivatization means.[67]

1.3. Developing Diastereoselective One-pot Cyclopropanation Protocols

1.3.1. Introduction

1.3.1.1. Background on the Cyclopropanation Reaction

Cyclopropane containing compounds often exhibit important biological activity[68-71] and are commonly encountered in natural products. These strained structural motifs are also valuable building blocks in organic chemistry that can be elaborated to provide functionalized cyclopropanes or ring-opened products.[72] The synthetic utility and medicinal properties of enantioenriched cyclopropanes have inspired many investigations into their preparation.[15,17,73-75] The need for the synthesis of chiral enantioenriched cyclopropyl alcohols to access natural products and biologically active compounds with control of stereochemistry, has driven the effort of many laboratories toward the development of enantioselective methods.

Three main methods have been widely utilized to synthesize cyclopropanes. The first two have seen a noteworthy development with regard to asymmetric catalytic synthesis, involving either organocatalytic cyclopropanation,[75-80] which proceeds via Michael-initiated ring-closure reactions,[81] or rhodium-catalyzed reactions of diazoesters and related precursors to afford enantio- and diastereoenriched cyclopropanes, although certain disubstituted alkenes remain challenging substrates.[75,82-84]

The Simmons-Smith cyclopropanation reaction, the third available method, was first discovered in 1959. Since then, it has been one of the premiere methods for the synthesis

of cylopropanes. In the first report, the active Cu/Zn couple was obtained by heating a mixture of zinc dust and cupric oxide to 500 ºC under an atmosphere of hydrogen. The resulting couple, which contained 90% zinc and 10% copper, gave reproducible results in the cyclopropane synthesis. Once the Cu/Zn couple was synthesized, it was added to a solution of iodine in diethyl ether. After the iodine color was observed to have faded, methylene diiodide and the olefin were added and refluxed for a period of up to three days.[73,85]

Since this first report, several modifications have been performed to improve the reaction's noticeably harsh conditions. In 1968, Furukawa was the first to employ $ZnEt_2$ and CH_2I_2 for the cyclopropanation reaction, resulting in higher yields with significantly milder conditions.[86] Subsequently, in 1985, Yamamoto introduced aluminum reagents to perform the cyclopropanation,[87] and in 1987 Molander successfully used samarium to obtain excellent diastereoselectivity in the cyclopropanation of allylic alcohols.[88,89]

In addition to improving reaction conditions, researchers were quick to understand the role of vicinal hydroxyl groups in enhancing both the rate of the reaction and the diastereoselectivity.[90-93] In particular Pereyre found that employing (*Z*)-allylic alcohols gave better diastereoselection than (*E*)-allylic alcohols.[94,95]

A significant contribution came from the laboratories of Charette, which enabled the synthesis of enantioenriched cyclopropyl alcohols starting from prochiral allylic alcohols, albeit with the need of stoichiometric amounts of a chiral auxiliary. Alternatively, employing previously synthesized chiral enantioenriched allylic alcohol, Charette demonstrated the possibility of performing highly diastereoselective cyclopropanation reactions with the addition of functionalized methylene groups.[96]

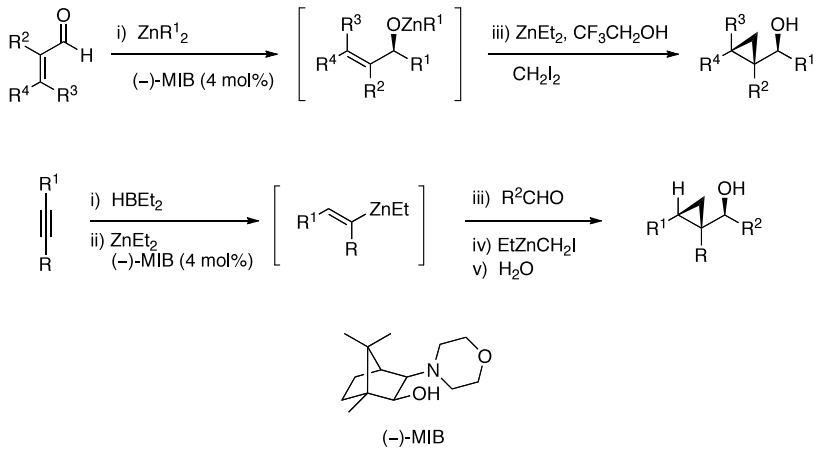
Despite these important improvements, there are still a number of limitations: 1) the need to isolate the allylic alcohol, which requires additional synthetic steps or 2) in the case of enantioselective synthesis, there is still the need for stoichiometric amounts of a chiral auxiliary.

Even though the Simmons-Smith-type cyclopropanation reaction has been known for half a century, many enantioselective methods are limited. These shortcomings prompted our group to attempt to address these problems using a different approach.

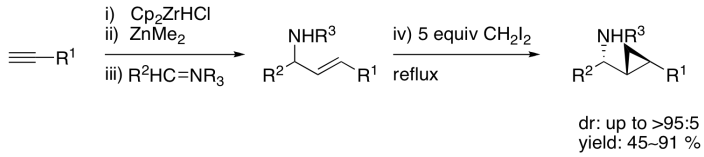
1.3.1.2. Walsh Group Contribution

Given the formidable challenge of developing catalytic enantioselective Simmons-Smith reactions, we considered alternative strategies for the catalytic enantio- and diastereoselective synthesis of cyclopropanes from *achiral* reagents. We envisioned a catalytic enantioselective carbonyl addition to generate an allylic zinc alkoxide intermediate followed by a diastereoselective cyclopropanation. Performing these reactions in tandem would enable the formation of three C-C bonds and stereocenters in a one-pot procedure with excellent stereoselectivity. Thus, the allylic zinc alkoxide would be formed via asymmetric alkyl addition to α,β-unsaturated aldehydes in the presence of 4 mol % of Nugent's (–)-MIB ligand (Scheme 1-18, route A),[97,98] or via an asymmetric addition of a vinyl group, generated by Oppolzer's method,[20] to saturated aldehydes (Scheme 1-18, route B). Subsequent cyclopropanation would be performed using modified Simmons-Smith type reagents. Wipf and coworkers recently reported a similar

procedure, vinyl addition/cyclopropanation with imines, to afford *anti*-cyclopropyl amines, however analogous reactions with aldehydes were reported to be unsuccessful (Scheme 1-19).[99]



Scheme 1-18. Two Tandem Asymmetric Addition/Diastereoselective Cyclopropanations.



Scheme 1-19. Formation of Allylic Amine and Diastereoselective Cyclopropanation by Wipf.

Although diastereoselective cyclopropanations of chiral allylic alcohols have been studied in the past, our work presents the first example of assembly of enantio- and diastereoenriched cyclopropyl alcohols from achiral precursors in a one-pot procedure.

1.3.2. Results and Discussion

1.3.2.1. Developing Tandem Protocols

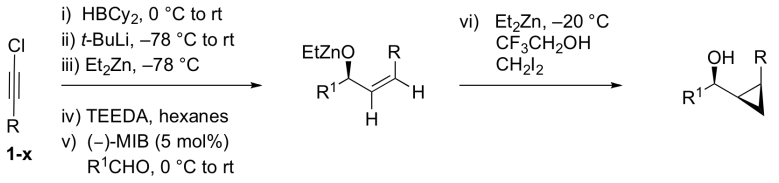
As introduced above, alkoxide-directed Simmons-Smith cyclopropanations of both (*E*)- and (*Z*)-chiral allylic alcohols are highly *syn* selective. The presence of a proximal hydroxy group plays a predominant role in assisting the delivery of the carbenoids. However, in most instances the enantioenriched chiral allylic alcohol is synthesized separately, and then subjected to diastereospecific cyclopropanation. The asymmetric synthesis of (*E*)-allylic alcohols is well documented as opposed to the synthesis of (*Z*)-allylic alcohols as we described earlier in Section 1.1.

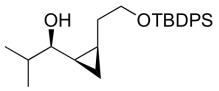
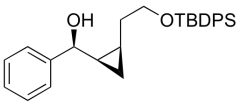
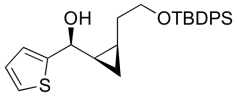
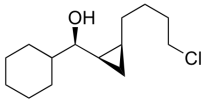
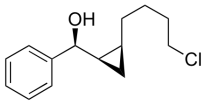
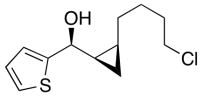
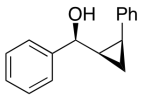
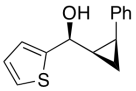
Our strategy to synthesize (*Z*)-cyclopropyl alcohols blends our one-pot synthesis of (*Z*)-disubstituted allylic alcohols with optimized cyclopropanation conditions developed in our laboratories.[18]

Upon generation of the allylic zinc alkoxide (performed as outlined in Table 1-1), instead of addition of water to quench the allylic alkoxide intermediate, 5 equiv of diethylzinc and 5 equivalents of CF_3CH_2OH are injected into the flask at 0 ºC. After 5 min of stirring, 5 equiv of CH_2I_2 are added and the flask is wrapped in aluminum foil to exclude light. The resulting solution is stirred at room temperature for 24 h (Table 1-4). The generation of a more reactive carbenoid employing diethylzinc and CF_3CH_2OH is crucial to the development of a synthetically useful method. This reagent was first devised by the Shi group[100] and then extensively studied by Dr. Hun-Young Kim a

former member of the Walsh group. Employing other less reactive species would yield a mixture of inseparable allylic alcohol and cyclopropyl alcohol.

Table 1-4. Tandem Asymmetric Addition/Cyclopropanation



entry	product	#	ee (%)[a]	dr[b]	yield (%)
1		**1-22**	90	> 19:1	65
2		**1-23**	95	> 19:1	62
3		**1-24**	96	> 19:1	52
4		**1-25**	88	> 19:1	55
5		**1-26**	88	> 19:1	69
6		**1-27**	94	> 19:1	62
7		**1-28**	97	> 19:1	65
8		**1-29**	92	> 19:1	42

[a] ee's determined by HPLC. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

In prior optimized conditions, the volatile materials were removed under reduced pressure after the addition step was completed. This operation was performed in order to

increase the molarity of the reaction and to remove the volatile by-products. Employing this procedure however, the product was obtained, in low yield. In this current protocol, Cy_2BH is used in place of Et_2BH, thus leading us to reason that the removal of the volatile materials was not that important, at least for what concerns the removal of the volatile by-products. On a practical level it is not easy and desirable to remove large amount of solvent and volatiles when scaling-up the procedure. Employing the same reaction conditions without removing the volatile materials did indeed give the desired product in good yield and excellent dr. Aliphatic, aromatic and heteroaromatic aldehydes were suitable for asymmetric addition/diastereoselective cyclopropanation under these conditions (Table 1-4).

The *syn* diastereomer was expected to be formed based on our knowledge of Zn-alkoxy directed cyclopropanation reactions. [18,101] The stereochemistry of **1-28** was assigned as *syn* by derivatization with (–)-camphanic acid chloride to afford the expected ester, which was characterized by X-ray crystallography (Figure A-1).

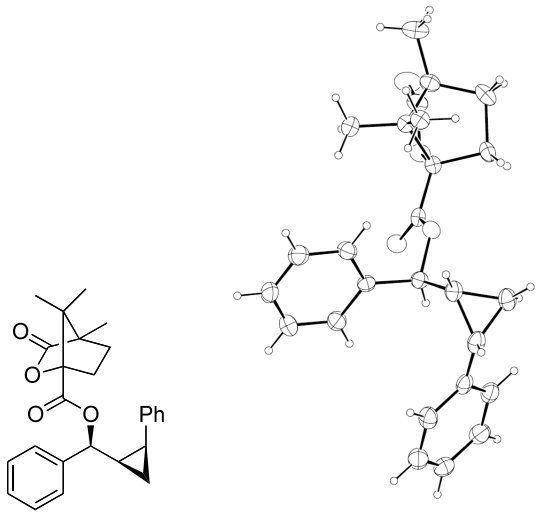


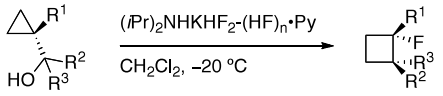
Figure 1-5. X-ray Structure of the Camphanic Ester of **1-28**.

1.3.2.2. Summary and Outlook

Employing the method developed in our laboratory for the asymmetric synthesis of (*Z*)-allylic alcohols, a tandem protocol for the diastereoselective synthesis of *cis* disubstituted cyclopropyl alcohols has been described. Given the rapid increase in molecular complexity with defined stereochemical outcome and the ease and efficiency of our one-pot procedures, we envision this procedure will be useful in enantioselective and in diversity-oriented synthesis.

The most important future studies with these substrates involve the possibility of performing the cyclopropanation reaction chemoselectively when more than one double bond is present in the substrate, which so far has been elusive.

Mahmud Hussain in our group is also investigating the possibility of opening the cyclopropyl ring employing both the (*Z*)- and the (*E*)-cyclopropyl alcohols. Since we have developed methods to synthesize both stereoisomers, these substrates would enable us to compare their reactivity in this process. Upon treatment with HF in pyridine the cyclopropyl ring could rearrange to form a cyclobutane ring (Scheme 1-20).[102]

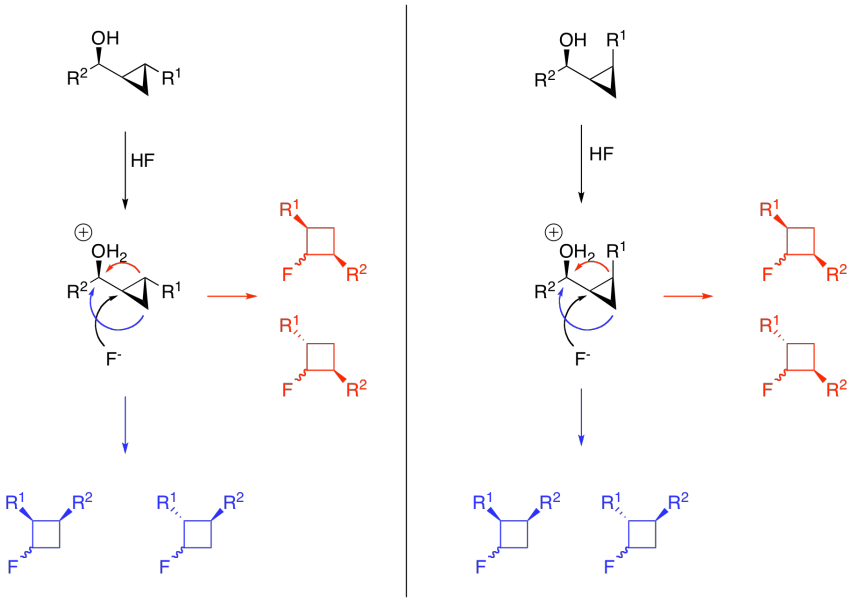


Scheme 1-20. Shimizu Ring Opening Reaction Mediated by HF.

Since the mechanism proceeds via formation of a carbocation, the stereocenter on the alcohol position would be racemized. However the other two stereocenters are expected

to be maintained in the product, which would be a very valuable building block (Scheme 1-21). In a similar fashion our group observed an excellent diastereoselectivity in the formation of cyclobutanones promoted by either Lewis or protic acid.[103]

Remaining questions include whether we would be able to obtain only one of the four possible diastereomers, and whether the (*E*)- and (*Z*)-cyclopropyl alcohol would provide the same or the opposite product, as depicted in Scheme 1-21, where all the possible products are drawn.



Scheme 1-21. Possible Diastereomers in the HF Mediated Ring Opening Reaction

1.4. Synthesis of (Z)-Trisubstituted Allylic Alcohols

1.4.1. Introduction

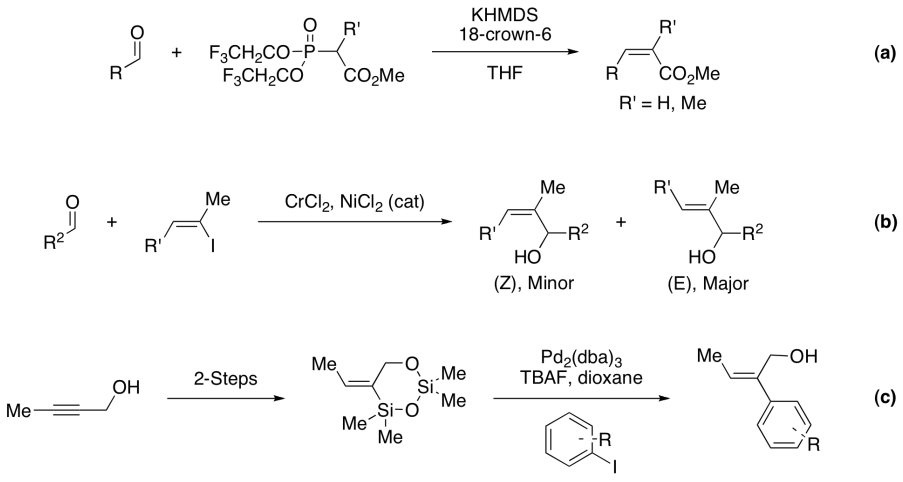
Allylic alcohols are exceptionally useful building blocks that can be readily transformed into numerous other valuable compounds, such as allylic amines,[12] amino acids,[13,14] cyclopropyl alcohols[15-18] and epoxy alcohols.[2,5-11] They are also prevalent in natural products.[2-5] As a result, much focus has been placed on their asymmetric synthesis, particularly through vinylzinc additions to aldehydes.[104] While significant progress has been made in the selective formation of *(E)*-di- and *(E)*-trisubstituted allylic alcohols,[13,20-22,30,105-107] and more recently *(Z)*-disubstituted allylic alcohols,[40,108] general methods for the direct, efficient, and stereoselecive synthesis of asymmetric *(Z)*-trisubstituted allylic alcohols remain sparse.[109]

1.4.1.1. Current Methods

One of the most common methods for synthesizing *(Z)*-trisubstituted allylic alcohols is the Still-Gennari modification of the Horner-Wadsworth-Emmons (HWE) olefination.[110] This popular method generates *(Z)*-trisubstituted α,β-unsaturated esters with good to excellent control of the double-bond geometry and yield (Scheme 1-22, a). However, this reaction is a two-carbon homologation and requires further functional group manipulation and additional steps to couple large fragments. Furthermore, the bis(trifluoroethyl)

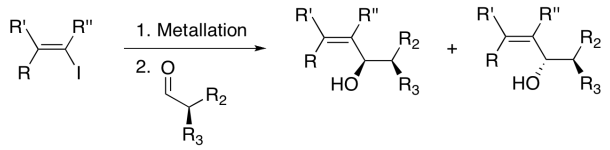
phosphonoester reagent, which is synthesized in 3-steps from trialkyl phosphite, requires up to 5 equiv of expensive and toxic 18-crown-6 to maximize the diastereoselectivity.

Additions of *(Z)*-vinylorganometallic reagents to aldehydes, such as the Nozaki-Hiyama-Kishi (NHK) reaction,[111] would appear to be a favorable method, but the difficulty in generating the requisite *(Z)*-alkenyliodide and the harsh reaction conditions often result in unfavorable mixtures of double bond isomers, which can be challenging to separate (Scheme 1-22, b). Denmark and coworkers devised a method for the generation of *(Z)*-trisubstituted allylic alcohols from 2-butyn-1-ol via silylation of the alcohol, platinum catalyzed *syn*-hydrosilation, and palladium catalyzed cross-coupling with aryl iodides (c).[112] While this three-step process gives fair to good yields and excellent control of the double bond geometry, 2-butyn-1-ol is the only substrate shown to work, significantly limiting the reaction scope. The only modulation is obtained through choice of the aryl iodide.



Scheme 1-22. Common methods for generating *(Z)*-trisubstituted allylic alcohols.

Of great interest to synthetic chemists is the development of methods to form chiral *(Z)*-trisubstituted allylic alcohols selectively and efficiently. Similar in principle to the NHK reaction, metallation of a *(Z)*-alkenyliodide with butyllithium or *i*-PrMgBr and addition to a chiral aldehyde yields diastereomeric mixtures of (*Z*)-allylic alcohols (Scheme 1-23).[113,114] The highly reactive nature of alkenyllithium and magnesium nucleophiles can frequently cause poor diasteroselectivity, thus softer nucleophiles (Zn, Al), additives and Lewis acids are often employed to increase the selectivity.[113-116] The overall efficiency of the process may be the larger issue as *(Z)*-alkenyliodides are precious and sensitive starting materials.



Scheme 1-23. Potential synthesis of enantioenriched *(Z)*-trisubstituted allylic alcohols.

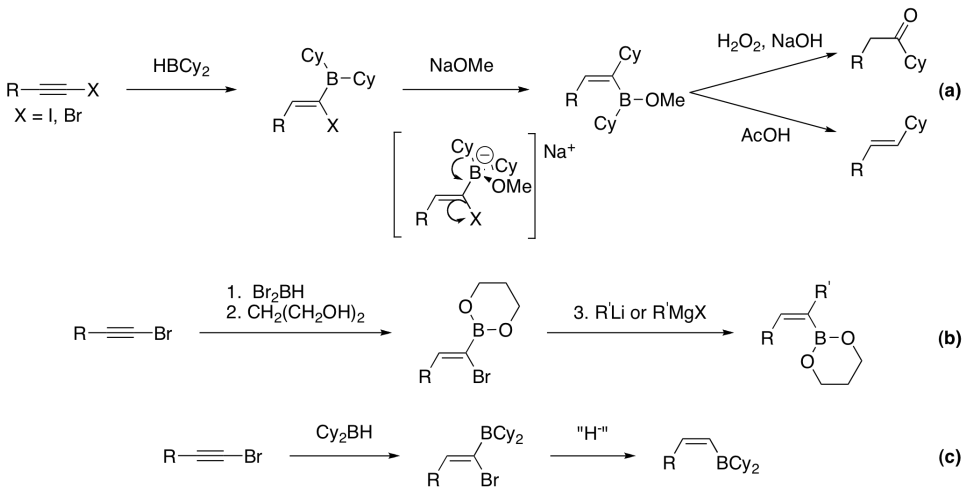
The ability to create molecular complexity rapidly in a single flask is of great importance to researchers. A great advantage to this chemistry would be the creation of both the *(Z)*-geometry as well as a new stereocenter in tandem using relatively simple starting materials. Dr. Young Chen, a former member of the Walsh group, first sought to develop a multicomponent C-C bond-forming reaction for the efficient and stereoselective synthesis of *(Z)*-trisubstituted allylic alcohols that would address the deficiencies in the state-of-the-art methods. Such a protocol would utilize an easily

accessible organometallic reagent with broad substrate scope and functional group tolerance as well as being capable of coupling large fragments to maximize efficiency.

1.4.2. Walsh Group Contribution

1.4.2.1. Development of a One-Pot Method for the Synthesis of (*Z*)-Trisubstituted Allylic Alcohols

This approach was largely based on the work of Zweifel,[41] who investigated the reactivity of the hydroborated 1-halo-1-alkynes with dicyclohexylborane (Scheme 1-24, a). The hydroboration step is highly regioselective, providing 1-halo-alken-1-ylborane as the only observed product by NMR.[117] Addition of sodium methoxide to 1-halo-alken-1-ylborane allowed the cyclohexyl group to undergo a 1,2-alkyl shift at the vinylic center, recently referred to as a 1,2-metallate rearrangement.[118,119] Other nucleophiles such as Grignard reagents,[45,120] alkyllithiums[45,120] (b), and hydrides[43,44,121] (c) have also permitted similar 1,2-metallate rearrangements to occur with 1-halo-1-alkenylboranes. This process is equivalent to performing a rare *trans*-hydrometallation on an internal alkyne regioselectively. The resulting *(E)*-vinylboranes are fairly unreactive toward nucleophilic addition, thus the vinylboranes were either oxidized to ketones or protodeborated with acid forming *trans*-alkenes.



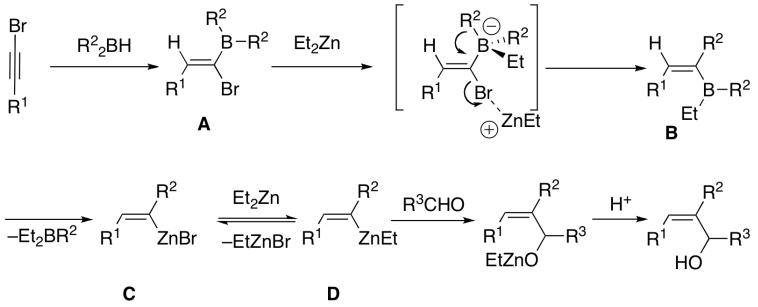
Scheme 1-24. 1,2-Metallate Rearrangements with 1-Halo-1-Alkenyl Boranes.

Since Zweifel first reported the synthesis of these *(E)*-alkenylboranes, Srebnik[36] and Oppolzer[20] have pioneered an alkenylboron-zinc transmetallation, generating a more reactive alkenylzinc species capable of adding to carbonyl groups. Based on these developments, our group sought to use these technologies in tandem to develop a stereoselective *(Z)*-trisubstituted alkenylzinc reagent capable of readily adding to aldehydes, thus directly coupling large fragments in a general and efficient manner.

1.4.2.2. Development of *(Z)*-Trisubstituted Alkenylzinc Additions to Aldehydes

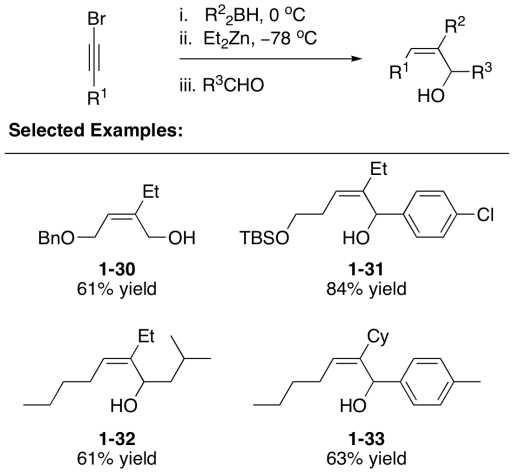
Dr. Young Chen attempted to generate a *(Z)*-trisubstituted alkenylzinc reagent *in situ* for the generation of (*Z*)-trisubstituted allylic alcohols.[46] Initially, hydroboration with diethyl- and dicyclohexylborane was investigated. Hydroboration of a 1-bromo-1-alkyne generated the 1-bromo-alk-1-enylborane as the only observed regioisomer (Scheme 1-25

- **A**). Addition of diethylzinc causes a 1,2-alkyl shift to occur with loss of halogen, forming an *(E)*-alkenylborane species (**B**). An additional equivalent of diethylzinc resulted in a boron-zinc transmetallation generating the *(Z)*-alkenylzinc reagent (**D**) and trialkylborane, which is observed at ~86 ppm by ^{11}B NMR. Addition of aldehyde furnishes *(Z)*-trisubstituted allylic alcohols in good yield as the only diastereomer observed (see Table 1-5 for selected examples).



Scheme 1-25. Proposed Mechanism for our *(Z)*-Trisubstituted Allylic Alcohol Synthesis.

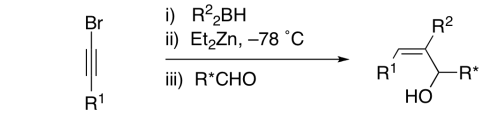
Table 1-5. Multicomponent Synthesis of (*Z*)-Trisubstituted Allylic Alcohols with Ethyl and Cyclohexyl Installation



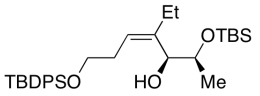
1.4.2.3. Diastereoselective Synthesis of Allylic Alcohols with Ethyl and Cyclohexyl Group Installation

Dr. Michael Kerrigan, now a former member of the Walsh group, employed the conditions used in Scheme 1-25 for the diastereoselective addition to enantioenriched aldehydes. The results were excellent as shown in Table 1-6 where it is evident that the ethyl alkenyl zinc group gives generally higher yields than when the reaction is performed with $HBCy_2$ (compare **1-34**, **1-38** and **1-39** against **1-36**).

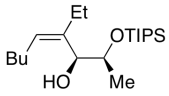
Table 1-6. Diastereoselective Synthesis of Allylic Alcohols with α-Ethyl and α-Cyclohexyl Substituents



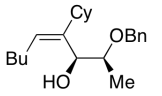
Selected Examples:



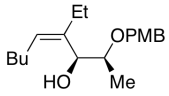
1-34 95% yield, 20 : 1 dr



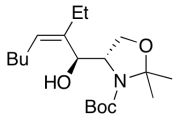
1-35 74% yield, 20 : 1 dr



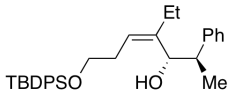
1-36 68% yield, 15 : 1 dr



1-37 71% yield, 20 : 1 dr



1-38 92% yield, 20 : 1 dr

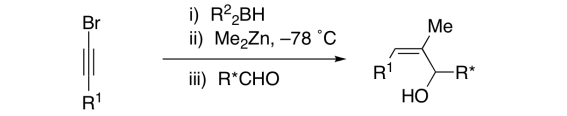


1-39 95% yield, 2 : 17 dr

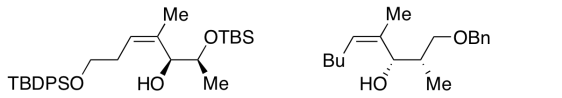
[a]Diastereomeric ratio (*anti*-Felkin : Felkin) based on ^1H NMR of crude product.

Methyl addition was more challenging. In fact, Dr. Michael Kerrigan had to employ Br_2BH or Cl_2BH for the initial hydroboration followed by addition of 4.5 equiv of Me_2Zn. In these cases, the dr's were generally very high, but the yields were lower than those obtained with ethyl and cyclohexyl installation (compare for example **1-38** versus **1-44**). It is possible that the lower yields in Table 1-7 relative to those in Table 1-6 are due to the reactivity and the Lewis acidity of the haloboranes, which are known to cleave ethers.

Table 1-7. Diastereoselective Synthesis of α-Methyl Substituted Allylic Alcohols

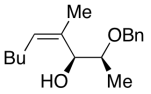


Selected Examples:

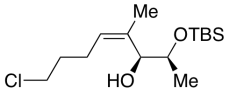


1-40 78% yield, 20 : 1 dr

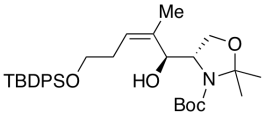
1-41 70% yield, 17 : 1 dr



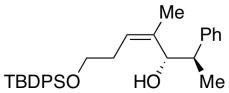
1-42 51% yield, 20 : 1 dr



1-43 67% yield, 20 : 1 dr



1-44 47% yield, 20 : 1 dr



1-45 55% yield, 1 : 4 dr

Diastereomeric ratio (*anti*-Felkin : Felkin) based on ^{1}H NMR of crude product.

To our surprise, almost all the compounds synthesized in Table 1-6 gave the *anti*-Felkin product. By varying the protecting groups on the α-hydroxy-aldehyde, it was expected that the TBS (**1-34**) protecting group would block chelation, thus giving the

Felkin product, while the Bn (**1-36**) and PMB (**1-37**) would allow chelation. This suggests that the alkylzinc halide byproduct might be a sufficiently Lewis acidic to chelate both alkyl and silyl ethers. After viewing this trend, use of the TIPS (**1-35**) protected derivative was employed; again the *anti*-Felkin product was observed in excellent diastereoselectivity. These puzzling results have been investigated further studying the role of the *in situ* generated alkyl zinc halides as possible Lewis acid coordinative center.[122]

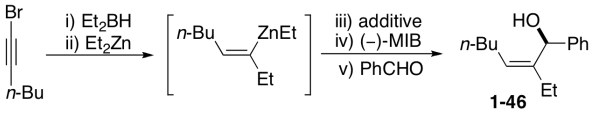
1.4.2.4. Catalytic Asymmetric *(Z)*-Trisubstituted Vinylzinc Additions to Aldehydes with Ethyl and Cyclohexyl Installation

Our group became interested in the asymmetric synthesis of *(Z)*-trisubstituted allylic alcohols due to our central focus of developing novel tandem and C-C bond forming reactions. We were curious as to whether our developed *(Z)*-trisubstituted alkenylzinc reagents[46,123] would be capable of participating in catalytic asymmetric additions to prochiral aldehydes in the presence of a chiral ligand. Compared to the number of chiral ligands capable of catalyzing the asymmetric addition of alkylzinc reagents to prochiral aldehydes, ligands capable of catalyzing asymmetric alkenylzinc additions to prochiral aldehydes are fairly rare.[20,23,24,124,125] Dr. Michael Kerrigan and Dr. Sang-Jin Jeon decided to tackle this problem using Nugent's chiral amino alcohol ligand (–)-MIB.[97,98] The zinc-based catalyst derived from (–)-MIB has been shown to exhibit excellent enantioselectivities in asymmetric alkenylzinc additions to aldehydes.[18,108,126]

The general procedure for the addition of our *(Z)*-trisubstituted alkenylzinc reagents to aldehydes now included addition of the chiral catalyst just prior to the addition of the aldehyde. With Nugent's (–)-MIB,[97,98] use of up to 20 mol % catalyst was investigated, rendering only racemic product (Table 1-8). After further consideration of the mechanism in Scheme 1-25, we postulated that the alkylzinc halide byproduct might promote a rapid background reaction.

It was also observed in Section 1.1.2.1 and in Chapter 2 that the addition of diamines in zinc vinylations and zinc arylation of aldehydes in the presence of *in situ* generated lithium halides significantly increased product ee's.

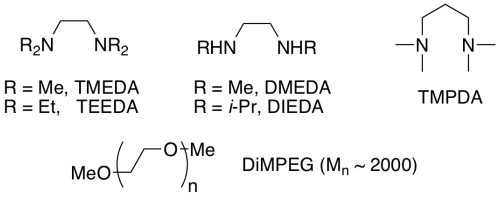
Table 1-8. Additive Screening in the Catalytic Asymmetric Formation of Allylic Alcohols by Dr. Sang-Jin Jeon.



1-46

entry	additive	equiv [a]	(-)-MIB (mol %)	ee (%)
1	none	–	5 - 20	0
2	DiMPEG	0.1 - 0.5	5 - 10	0
3	TMEDA	0.1	5	2
4	TMEDA	0.2	5	2
5	TMEDA	0.6	5	16
6	TMEDA	1	5	96
7	TEEDA	1	5	97
8	TMPDA	1	5	92
9	DIEDA	1	5	73
10	DMEDA	1	5	72

[a] with respect to equivalents of bromoalkynes used in the reaction.



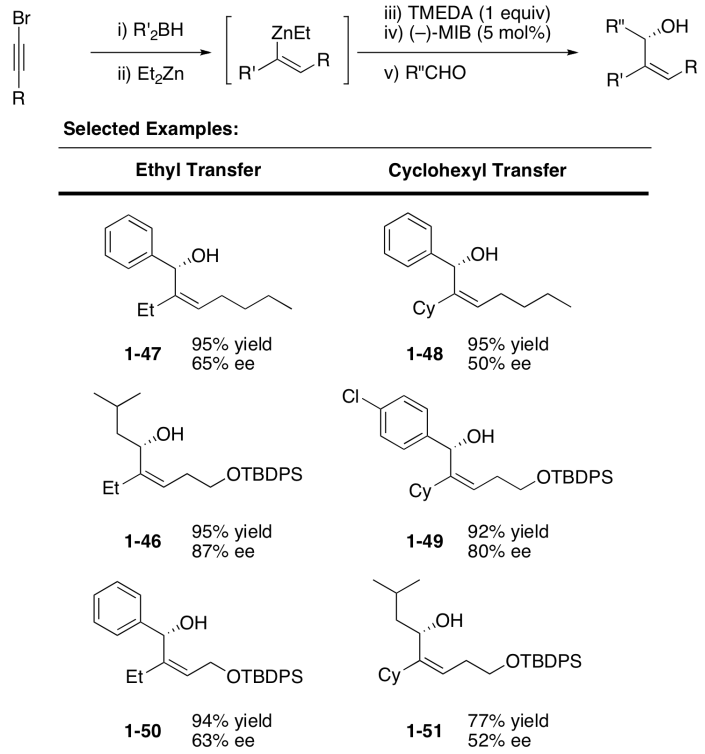
This increase in ee presumably arises by diamine binding to lithium salts, preventing them from catalyzing the background reactions.[51,108] Based on these precedents, Dr. Sang-Jin Jeon investigated several Lewis basic additives as inhibitors of these Lewis acidic materials. Additives were screened including the polymer DiMPEG and several diamines. In α-ethyl and cyclohexyl installed *(Z)*-trisubstituted alkenylzinc additions to benzaldehyde, one equivalent of either tetramethylethylenediamine (TMEDA) or tetraethylethylenediamine (TEEDA) resulted in greater than 95% ee with 5 mol % catalyst loading (Table 1-8, entries 6 and 7).

Following this initial lead, 1 equiv TMEDA was added just before addition of (–)-MIB and aldehyde in the general procedure. The resulting *(Z)*-trisubstituted allylic alcohols were generated in good to excellent yields and excellent enantioselectivity. Table 1-9

displays the compatibility of this chemistry to catalytic asymmetric conditions. Sang-Jin showed that alkyl substituted bromoalkynes and silyl protected propargylic and homopropargylic alcohols could be successfully applied to this chemistry in conjunction with alkyl, aryl, and α,β-unsaturated aldehydes. In the ethyl installation series (Table 1-9, compounds **1-46**, **1-47** and **1-50**), all substrates underwent addition with excellent ee and good to excellent yields. Cyclohexyl installation gave fair to excellent ee (Table 1-9, compounds **1-48**, **1-49** and **1-51**), but the yields varied significantly, as is often the trend with bulky reagents.

Attempts to adapt this procedure to the synthesis of α-methyl-substituted allylic alcohols with Br_2BH and Cl_2BH and varying amounts of DiMPEG or diamine inhibitor resulted in enantioselectivities below 30% and low yields (15–40%).

Table 1-9. α-Ethyl and Cyclohexyl Installation for the Synthesis of Enantioenriched *(Z)*-Trisubstituted Allylic Alcohols by Dr. Sang-Jin Jeon.



The hypothesis is that the low enantioselectivities arise from the additional 2 equiv of zinc halide byproduct generated when using X_2BH, as outlined in Scheme 6. Increasing the equivalents of diamine to inhibit the additional zinc halide (>300 mol %) also appeared to inhibit the Lewis acidic MIB-based catalyst (5–20 mol %).

Use of Me_2BH was plagued with problems. As in the synthesis of α-ethyl- and α-cyclohexyl-substituted allylic alcohols, use of Me_2BH generates only 1 equiv of zinc halide. The use of TMEDA was ineffective, however, and levels of enantioselectivity did not surpass 24%. The issue could be that the gaseous Me_2BH is generated as a solution in diethyl ether, which coordinates to the boron. Traces of Lewis basic solvent inhibit the MIB-based Lewis acid catalyst. Thus, it is believed that a different strategy will be

necessary for the enantioselective synthesis of α-methyl (*Z*)-trisubstituted allylic alcohols.

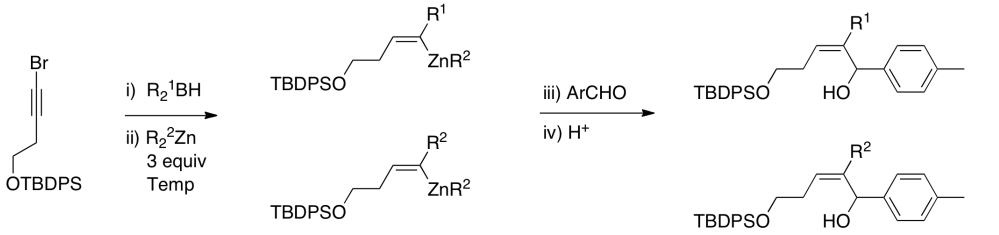
1.4.3. Results and Discussion

1.4.3.1. Zinc/Boron Alkyl Migration – Mechanistic Insight

The successful application of the method for the formation of (*Z*)-trisubstituted allylic alcohols relies on the migration of a single R group from the boron to the vinylic carbon. In the case of the ethyl installation both R groups are ethyls since Et_2BH and $ZnEt_2$ are employed. Substitution of dicyclohexylborane for diethylborane was next examined to generate the cyclohexyl-substituted product (Scheme 1-25, R^2 = Cy). Interestingly, hydroboration of the bromoalkyne with dicyclohexylborane followed by addition of diethylzinc at 0 °C and *p*-tolualdehyde led to the expected cyclohexylsubstituted product with up to 20% ethyl migration product (Table 1-10, entry 1, R^1 = Cy, R^2 = Et).

This result prompted a brief study of various hydroborating and transmetalating reagents to examine their impact on the product mixture and to identify conditions to more strongly favor migration of the B-alkyl over the Zn-alkyl. In contrast to addition of the diethylzinc at 0 °C, when the diethylzinc addition was performed at –78 °C, Cy:Et migration increased to a synthetically useful 14:1 ratio (Table 1-10, entry 2). When these conditions were used, the cyclohexyl-substituted allylic alcohols with *p*-tolualdehyde (**1-56**) was obtained in approximately 60% yield.

Table 1-10. Examination of the Impact of Dialkylborane and Dialkylzinc Reagents on the 1,2-Metalate Rearrangement

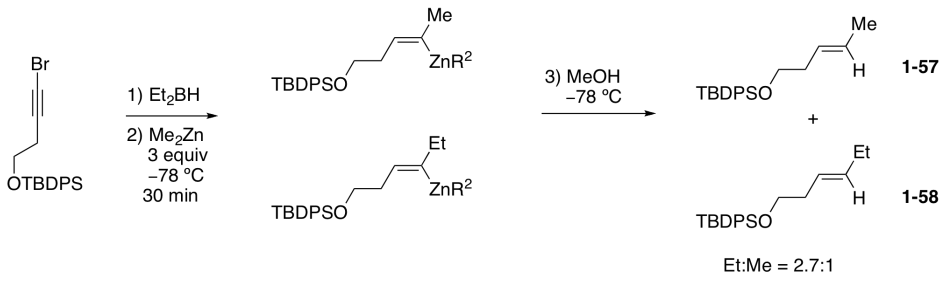


Ar=4-C_6H_4-Me

entry	R^1	additive	R^2	T (°C)	time	R^1 : R^2 ratio	**R^1:R^2 product**
1	Cy		Et	0	16 h	Cy:Et = 4:1	**1-56:1-53**
2	Cy		Et	–78	30 min	Cy:Et = 14:1	**1-56:1-53**
3	Et		*i*-Pr	–78	30 min	Et:*i*-Pr = 5:1	**1-53:1-54**
4	Et		*n*-Bu	–78	30 min	Et:*n*-Bu = 4:1	**1-53:1-55**
5	Et		Me	–78	30 min	Et:Me = 2.5:1	**1-53:1-52**
6	Cy		Me	–78	30 min	Cy:Me = 3:1	**1-56:1-52**
7*	Cy	*t*-BuLi	Et	–78	30 min	R^2 = only H	**1-3**

Next, the origin of the primary and secondary alkyl groups was reversed by using Et_2BH and (*i*-Pr)$_2$Zn with the dialkylzinc added at –78 °C (Table 1-10, entry 3). In this case, the ethyl migration product predominated (Et:*i*-Pr = 4:1 – **1-53**:**1-54**). Two primary alkyl group donors were used to compare groups with similar migratory aptitudes. In these experiments, hydroboration was performed with Et_2BH and transmetalation with (*n*-Bu)$_2$Zn (Table 1-10, entry 4) or Me_2Zn (entry 5) at –78 °C. With (*n*-Bu)$_2$Zn, the product contained a 4:1 mixture of Et:*n*-Bu substituted allylic alcohols (**1-53**:**1-55**). When Me_2Zn was employed, the ratio of Et:Me was closer to statistical (2.5:1, entry 5 – **1-53**:**1-52**). Use of Cy_2BH and $ZnMe_2$ resulted in a 3:1 ratio of cyclohexyl to methyl migration (entry 6 – **1-56**:**1-52**). Taken together, these results lead us to believe that a discrete trialkyl

alkenylboronate intermediate is involved in these processes. In this intermediate, migration of the alkyl group originally attached to boron (R^2 Scheme 1-25) is favored over the alkyl originating from the dialkylzinc. It is noteworthy that, when a hydride is added to the empty site on boron (from *t*-BuLi, for example),[44] only hydride migration to the vinylic center is observed and no alkyl migration is detected (Scheme 1-5 and Table 1-10, entry 7 – **1-3**).[108] Insight into the ease with which 1,2-metalate rearrangement and transmetalation occur was gained by hydroboration with Et_2BH and transmetalation at –78 °C with Me_2Zn followed by quenching the reaction mixture with methanol after 30 min at that temperature. The ethyl- and methyl-substituted (*Z*)-olefins were obtained in a 2.7:1 ratio (Scheme 1-26 – **1-58**:**1-57**). This result indicates that both the 1,2-metalate rearrangement and the transmetalation take place at a surprisingly low temperature. It is noteworthy that the protonolysis of vinylboranes is typically performed with acetic acid at 0 °C.[127,128]

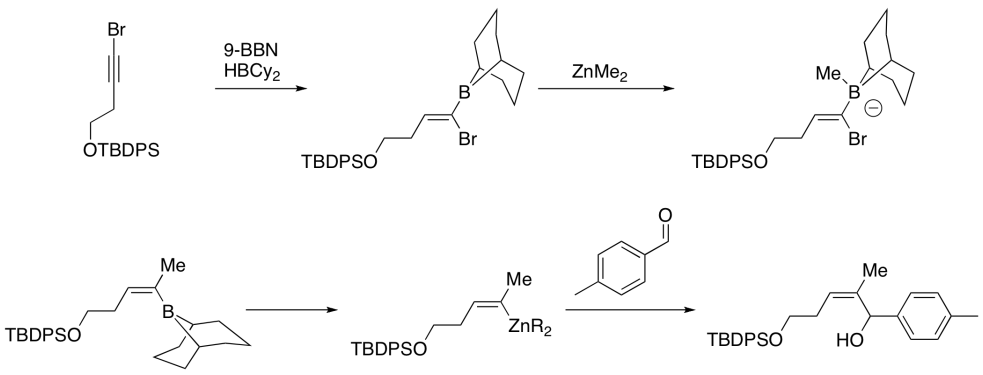


Scheme 1-26. Protonolysis of Intermediates in the Generation of Trisubstituted Vinylzinc Species

1.4.3.1. Summary and Outlook

Reported herein is a simple and efficient method for the *stereospecific* generation of (*Z*)-trisubstituted alkenylzinc reagents. Beginning with readily accessible 1-halo-1-alkynes, hydroboration with diethyl- or dicyclohexylborane provides 1-halo-1-alkenylboranes with excellent regioselectivity. The key to success of this method is our discovery that dialkylzinc reagents can both induce the 1,2-metalate rearrangement with formation of a C-C bond and promote the boron-to-zinc transmetalation to generate the requisite (*Z*)-trisubstituted alkenylzinc reagents. These reagents smoothly add to prochiral aldehydes to generate a variety of (*Z*)-trisubstituted allylic alcohols. It is noteworthy that no contamination by the thermodynamically more favorable (*E*)-allylic alcohols was observed by ^{1}H NMR spectroscopy.

The in depth understanding of the transmetalation-1,2 metalate rearrangement mechanism gained in this brief study opens up the possibility to address the problem of the synthesis of methyl trisubstituted alkenylzinc reagents. In fact, by blocking the migration of the alkyl groups on the boron using 9-BBN one could envision the 1,2 metalate rearrangement to occur with Me migration (Scheme 1-27). The final product of this reaction could be the (Z)-trisubstituted allylic alcohol with methyl installation. This, as we have seen in the previous sections, is a very challenging problem and we have not been able to develop an asymmetric version.



Scheme 1-27. Possible Route for the Methyl Installation

The initial studies in Scheme 1-27 have led to no addition product, but this is probably due to the lack of knowledge on how to perform the transmetallation of the alkenylborane bearing the BBN group quantitatively instead of diethyl or dicyclohexyl. More studies to develop a catalytic asymmetric synthesis of methyl trisubstituted allylic alcohols are being performed by Kevin Cheng, taking the results presented herein as the starting point.

1.5. Conclusions

Presented herein are the first general highly enantioselective addition of (*Z*)-alkenyl groups to aldehydes to afford enantioenriched (*Z*)-allylic alcohols.

Employing readily available 1-chloro-1-alkynes, hydroboration, addition of *t*-BuLi and transmetallation to zinc affords (*Z*)-disubstituted alkenylzinc intermediates. The resulting (*Z*)-alkenylzinc reagents undergo addition to aldehydes with high enantioselectivity in the presence of a zinc-based catalyst derived from MIB. A variety of enantioenriched (*Z*)-disubstituted allylic alcohols can be accessed in this simple one-pot procedure, including some that would be difficult to prepare using Lindlar hydrogenations of enantioenriched propargylic alcohols due to catalyst poisoning or functional group incompatibility.

Furthermore, in the attempt to increase molecular complexity, we have found the conditions for the (*Z*)-vinylation of aldehydes are compatible with both our diastereoselective epoxidation procedure and with our diastereoselective cyclopropanation procedure, allowing access to epoxy alcohols and allylic epoxy alcohols as well as cyclopropyl alcohols with three contiguous stereogenic centers with high ee and dr. Previous methods to prepare such compounds required several synthetic steps and purifications. Using the procedures introduced herein, such compounds can be readily synthesized in a single flask without isolation or purification of intermediates.

(*Z*)-Trisubstituted allylic alcohols have been synthesized with a simple and efficient method for the *stereospecific* generation of (*Z*)-trisubstituted alkenylzinc reagents. Beginning with readily accessible 1-halo-1-alkynes, hydroboration with diethyl- or

dicyclohexylborane provide 1-halo-1-alkenylboranes with excellent regioselectivity. The key to success of this method is our discovery that dialkylzinc reagents can both induce the 1,2-metallate rearrangement with formation of a C-C bond and promote the boron-to-zinc transmetallation to generate the requisite (*Z*)-trisubstituted alkenylzinc reagents. The understanding of the mechanism of this particular step gained by the survey of a combination of different dialkylborane and dialkyl sources, may provide potential new routes to address the problems of the catalytic asymmetric generation of α-methyl-trisubstituted allylic alcohols.

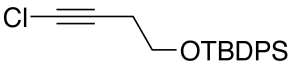
Given the rapid increase in molecular complexity with defined stereochemical outcome, we anticipate that these methods will be very useful in enantioselective synthesis.

1.6. Experimental Section

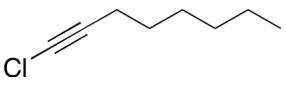
General Methods. All reactions were performed under a nitrogen atmosphere with oven-dried glassware using standard Schlenk or vacuum line techniques. The progress of all reactions was monitored by thin-layer chromatography which was performed on Whatman precoated silica gel 60 K6F plates and visualized by ultra-violet light or by staining with phosphomolybdic acid. *t*-BuOMe was distilled from Na/benzophenone and hexanes was dried through alumina columns. Tetraethylethylene diamine (TEEDA) was distilled and stored under nitrogen. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were obtained on a Brüker AM-500 Fourier transform NMR spectrometer at 500 and 125 MHz, respectively. ^{1}H NMR spectra were referenced to tetramethylsilane in $CDCl_3$ or residual protonated solvent; $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent. Analysis of enantiomeric excess was performed using a Hewlett-Packard 1100 Series HPLC and a chiral column specific for each compound. The optical rotations were recorded using a JASCO DIP-370. Infrared spectra were obtained using a Perkin-Elmer Spectrum 100 series spectrometer. All reagents were purchased from Aldrich or Acros unless otherwise described. 1-Bromo-1-alkynes[129] and 1-chloro-1-alkynes[130] were made according to known procedure. All commercially available aldehyde substrates were distilled prior to use. Silica gel (Silicaflash P60 40-63 μm, Silicycle) was used for air-flashed chromatography and deactivated silica gel was prepared by addition of 15 mL NEt_3 to 1 L of silica gel. Complete experimental procedures and characterization are located in the Supporting Information.

Caution. Dialkylzinc reagents and *t*-BuLi are pyrophoric. Care must be used when handling solutions of these reagents.

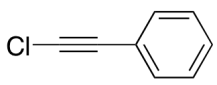
1.6.1. Characterization of 1-chloroalkynes



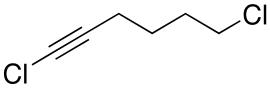
***tert*-Butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (1-a)**. Compound **1-a** was prepared from the corresponding alkyne[131] using the literature method.[130] It was purified by column chromatography on silica gel; (hexanes / EtOAc 95 / 5) to afford **1-a** (3.19 g, 48.6% yield) as a liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.14 (s, 9H), 2.49 (t, J = 6.7 Hz, 2H), 3.82 (t, J = 6.9 Hz, 2H), 7.46 (m, 5H), 7.75 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 19.4, 22.8, 27.0, 58.6, 62.4, 67.1, 128.0, 130.0, 133.8, 135.8 ppm; HRMS calcd for $C_{20}H_{24}O_1SiCl$ $(MH)^+$: 343.1285, found 343.1296.



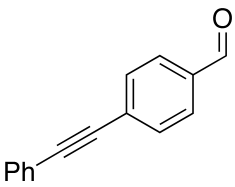
1-Chloro-oct-1-yne (1-b). Compound **1-b** was prepared using the literature method.[130] The crude product was purified by column chromatography on silica gel (pentane) to give **1-b** (1.80 g, 62% yield) as a liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (m, 3H), 1.26 (m, 6H), 1.81 (m, 2H), 2.12 (t, J = 7.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 14.2, 19.0, 22.7, 28.6, 28.7, 31.5, 57.1, 70.0 ppm.



Chloroethynyl-benzene (1-c). Compound **1-c** was prepared using the literature method.[130] The crude product was purified by column chromatography on silica gel (pentane) to give **1-c** (1.62 g, 59% yield) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 3H), 7.46 (m, 2H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 68.2, 69.6, 122.4, 128.6, 128.9, 132.2 ppm.



1,6-Dichloro-hex-1-yne (1-d). Compound **1-d** was prepared using the literature method.[130] The crude product was purified by column chromatography on silica gel (pentane) to give **1-d** (2.02 g, 67.4% yield) as a liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65 (qui, J = 7.3 Hz, 2H), 1.85 (qui, J = 7.0 Hz, 2H), 2.23 (t, J = 6.9 Hz, 2H), 3.56 (t, J = 6.9 Hz, 2H), ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 18.3, 25.7, 31.7, 44.6, 58.0, 69.0 ppm.

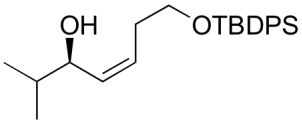


Characterization of 4-phenylethynyl-benzaldehyde (1-e). Compound **1-e** was prepared using the literature method.[132] The product was purified by chromatography in silica gel (hexanes/EtOAc 95/5) to give the product **1-e** (555.7 mg, 98.6% yield) as yellowish solid.[132] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 (m, 3H), 7.57 (m, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 10.03 (s, 1H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 89.0, 93.9, 122.9, 128.9, 129.4, 130.0, 132.2, 132.6, 135.8, 191.9 ppm; IR (neat): 3387, 3068, 3050, 2846, 2744, 2409, 1948, 1876, 1814, 1698, 1602, 1563, 1508, 1487, 1441, 1384, 1303, 1287, 1206, 1176, 1160 cm^{-1}; HRMS calcd for $C_{15}H_{10}O_1$ $(M)^+$: 206.0732 found 206.0721.

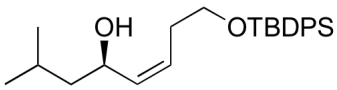
1.6.2. Catalytic Asymmetric Synthesis of (*Z*)-Disubstituted Allylic Alcohols

General Procedure A. Dicyclohexylborane (88 mg, 0.5 mmol) was weighed into a Schlenk flask under nitrogen and dry *t*-BuOMe (1 mL) was added. The 1-chloro-1-alkyne (0.5 mmol) was then added slowly to the reaction mixture at 0 °C. After 15 min, the reaction was warmed to room temperature and stirred for 45 min during which time the dicyclohexylborane dissolved leaving a clear solution. *t*-BuLi (0.365 mL, 0.55 mmol, 1.5 M pentane solution) was added dropwise at –78 °C and stirred for 60 min, warmed to room temperature and stirred for an additional 60 min. A precipitate formed during this time. Diethylzinc (0.275 mL, 0.55 mmol, 2 M hexanes solution) was slowly added to the reaction mixture at –78 °C and stirred for 20 min. Addition of TEEDA (14 μL, 0.066 mmol) and hexanes (4 mL) was next performed at –78 °C, followed by warming to 0 °C and addition of (–)-MIB (166 μL, 0.017 mmol) and neat aldehyde (0.333 mmol). The reaction was then slowly warmed to room temperature and stirred 12-16 h. After the reaction was complete by TLC analysis, it was diluted with 3 mL hexanes and quenched with water. The organic layer was next separated and the aqueous solution extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

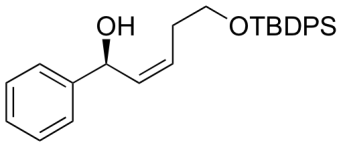
General Procedure B. This procedure is exactly the same as Procedure A except that the amount of TEEDA was adjusted to 30 mol %. Thus 21 μL (0.099 mmol) was used.



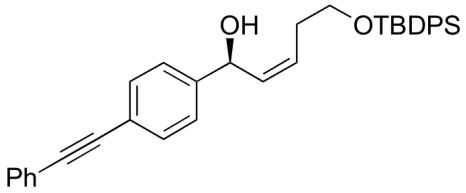
(*Z*)-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methyl-hept-4-en-3-ol (1-1). General Procedure A was applied to isobutyraldehyde (15 μL, 0.166 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (80 μL, 0.25 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-1** (38.0 mg, 61% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 15.0 min, t_r (2) = 16.7 min $[\alpha]_D^{20}$ = +2.79 (*c* = 0.045, $CHCl_3$, 90% ee). ^{1}H NMR and ^{13}C NMR spectra for this compound compare with previously reported literature data.[40]



(*Z*)-8-(*tert*-butyl-diphenyl-silanyloxy)-2-methyl-oct-5-en-4-ol (1-2). General Procedure A was applied to isovaleraldehyde (35 μL, 0.332 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-2** (97.9 mg, 74% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 14.9 min, t_r (2) = 16.9 min $[\alpha]_D^{20}$ = +10.20 (*c* = 0.039, $CHCl_3$, 76% ee). ^{1}H NMR and ^{13}C NMR spectra for this compound compare with previously reported literature data.[40]

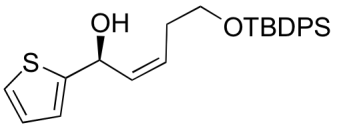


(*Z*)-5-(*tert*-butyl-diphenyl-silanyloxy)-1-phenyl-pent-2-en-1-ol (1-3). General Procedure A was applied to benzaldehyde (34 μL, 0.332 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-3** (83.8 mg, 61% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 38.2 min, t_r (2) = 44.6 min $[\alpha]_D^{20}$ = +131.11 (*c* = 0.001, $CHCl_3$, 95% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.12 (s, 9H), 2,20 (br, 1H), 2.45-2.51 (m, 1H), 2.58-2.65 (m, 1H), 3.73-3.80 (m, 2H), 5.50-5.51 (dd, *J* = 1.9, 8.0 Hz, 1H), 5.60-5.67 (dt, *J* = 7.8, 11.2 Hz, 1H), 5.77-5.81 (dd, *J* = 8.5, 10.9 Hz, 1H), 7.40 (m 10H), 7.71 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 19.4, 27.1, 31.4, 63.5, 69.9, 126.1, 127.6, 127.9, 128.7, 128.8, 129.9, 133.8, 134.5, 135.8, 143.7 ppm; IR (neat): 3369, 3069, 2931, 1958, 1890, 1824, 1656, 1589, 1472, 1427, 1389 cm^{-1}; HRMS calcd for $C_{27}H_{32}NaO_2Si$ $(M+Na)^+$: 439.2069, found 439.2054.



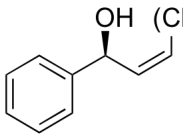
(*Z*)-5-(*tert*-Butyl-diphenyl-silanyloxy)-1-(4-phenylethynyl-phenyl)-pent-2-en-1-ol (1-4). General Procedure A was applied to 4-phenylethynyl-benzaldehyde (68.5 mg, 0.332 mmol, dissolved in 0.5 mL toluene) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). Upon addition of TEEDA, 3.5 mL of toluene were added instead of the 4 mL of hexanes to serve the same purpose. The crude product was purified by column chromatography on silica gel

(hexanes/EtOAc : 95/5) to give **1-4** (145.0 mg, 84% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 52.2 min, t_r (2) = 64.3 min $[\alpha]_D^{20}$ = +1.65 (*c* = 0.025, $CHCl_3$, 98% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 9H), 2,20 (br, 1H), 2.44-2.46 (m, 1H), 2.56-2.58 (m, 1H), 3.70-3.75 (m, 2H), 5.46-5.48 (d, *J* = 7.9 Hz, 1H), 5.63-5.67 (dt, *J* = 7.4, 11.2 Hz, 1H), 5.71-5.75 (dd, *J* = 9.0, 11.0 Hz, 1H), 7.35-7.57 (m, 15H), 7.70-7.73 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 19.4, 27.1, 31.4, 63.4, 69.5, 89.5, 89.6, 122.4, 123.5, 126.1, 127.9, 128.4, 128.6, 129.3, 130.0, 131.8, 132.0, 133.8, 134.2, 135.8, 143.9 ppm; IR (neat): 3393, 3070, 3050, 2957, 2930, 2857, 1597, 1486, 1427, 1361, 1111 cm^{-1}; HRMS calcd for $C_{35}H_{36}NaO_2Si$ $(M+Na)^+$: 539.2382, found 539.2394.

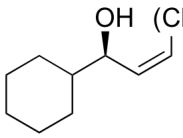


(*Z*)-5-(*tert*-butyl-diphenyl-silanyloxy)-1-phenyl-pent-2-en-1-ol (1-5). General Procedure A was applied to thiophenecarboxaldehyde (31 μL, 0.332 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-5** (98.8 mg, 69% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 20.0 min, t_r (2) = 28.4 min $[\alpha]_D^{20}$ = +55.97 (*c* = 0.093, $CHCl_3$, 93% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.08 (s, 9H), 2.27 (d, *J* = 4.0 Hz 1H), 2.39-2.46 (m, 1H), 2.49-2.56 (m, 1H), 3.69-3.78 (m, 2H), 5.65-5.70 (m, 2H), 5.82-5.86 (m, 1H), 6.93-6.97 (m, 2H), 7.24-7.27 (m, 1H), 7.39-7.46 (m, 5H), 7.68-7.71 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 19.4, 27.0, 31.3, 63.4,

66.3, 124.0, 125.0, 126.9, 127.9, 129.4, 129.9, 133.6, 133.8, 135.8, 147.7 ppm; IR (neat): 3390, 3070, 2930, 1960, 1891, 1826, 1656, 1589, 1471, 1427, 1389 cm^{-1}; HRMS calcd for $C_{25}H_{30}NaO_2SSi$ $(M+Na)^+$: 445.1633, found 445.1612.

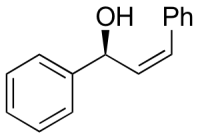


(*Z*)- 1-phenyl-non-2-en-1-ol (1-6). General Procedure A was applied to benzaldehyde (34 μL, 0.332 mmol) and 1-chloro-oct-1-yne (94 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-6** (45.5 mg, 63% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99.5:0.5, flow rate = 0.5 mL/min), t_r (1) = 26.0 min, t_r (2) = 29.0 min $[\alpha]_D^{20}$ = +143.56 (*c* = 0.060, $CHCl_3$, 93% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, 3H), 1.31 (br, 8H), 1.84 (d, *J* = 8.0 Hz, 1H), 2.22 (m, 2H), 5.59 (m, 3H), 7.26-7.30 (m, 1H) 7.34-7.42 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 14.3, 22.8, 28.0, 29.2, 29.8, 31.9, 70.0, 126.1, 127.6, 128.7, 132.1, 132.7, 144.0 ppm; IR (neat): 3340, 3085, 3063, 3028, 3012, 2956, 2926, 2855, 1655, 1603, 1492, 1452, 1378, 1282, 1192, 1079, 1023 cm^{-1}; HRMS calcd for $C_{15}H_{22}O$ $(M)^+$: 218.1671, found 218.1665.

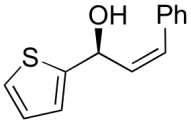


(*Z*)- 1-cyclohexyl-non-2-en-1-ol (1-7). General Procedure A was applied to cyclohexanecarboxaldehyde (40 μL, 0.332 mmol) and 1-chloro-oct-1-yne (94 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-7** (60.2 mg, 81% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column

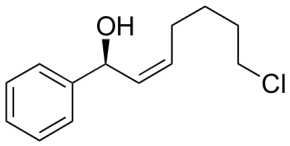
(hexanes:2-propanol = 99.5 : 0.5, flow rate = 0.5 mL/min), t_r (1) = 17.0 min, t_r (2) = 19.0 min $[\alpha]_D^{20}$ = +8.74 (*c* = 0.057, $CHCl_3$, 84% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.88 (m, 6H), 1.48 (br, 12H), 1.68 (br, 4H), 1.93 (m, 1H), 2.05 (m, 3H), 4.14 (t, *J* = 7.9 Hz, 1H), 5.37 (dd, *J* = 9.0, 11.1 Hz, 1H), 5.52 (dt, *J* = 7.6, 13.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 14.3, 22.8, 26.2, 26.4, 26.8, 28.0, 28.8, 29.0, 29.2, 29.9, 31.9, 44.2, 72.1, 131.2, 133.3 ppm; IR (neat): 3411, 3008, 2924, 2853, 2668, 1733, 1658, 1449, 1394, 1361, 1316, 1256, 1217, 1192, 1148, 1112, 1081, 1047, 1007 cm^{-1}; HRMS calcd for $C_{15}H_{27}O$ $(M-H)^+$: 223.2062, found 223.2056.



(*Z*)-1,3-diphenyl-prop-2-en-1-ol (1-8). General Procedure A was applied to benzaldehyde (34 μL, 0.332 mmol) and chloroethynyl-benzene (60 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc: 95/5) to give **1-8** (69.8 mg, 82% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AD column (hexanes:2-propanol = 97.5 : 2.5, flow rate = 0.5 mL/min), t_r (1) = 38.4 min, t_r (2) = 52.3 min $[\alpha]_D^{20}$ = +461.6 (*c* = 0.168, $CHCl_3$, 97% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.94 (d, *J* = 3.6 Hz, 1H), 5.58 (dd, *J* = 3.7, 9.4 Hz, 1H), 5.87 (dd, *J* = 9.4, 11.7 Hz, 1H), 6.63 (d, *J* = 11.0 Hz, 1H), 7.20-7.35 (m, 8H), 7.36-7.41 (m, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 70.2, 126.5, 127.7, 128.0, 128.6, 128.9, 129.0, 131.6, 133.4, 136.6, 143.4 ppm; IR (neat): 3543, 3346, 3081, 3059, 3026, 2923, 1952, 1888, 1810, 1761, 1639, 1600, 1575, 1493, 1447, 1403, 1336, 1261, 1220, 1193, 1157, 1079, 1043, 1028, 1005 cm^{-1}; HRMS calcd for $C_{15}H_{14}O$ $(M)^+$: 210.1045, found 210.1053.

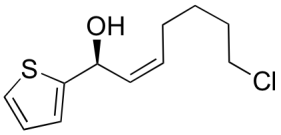


(*Z*)-3-phenyl-1-thiophen-2-yl-prop-2-en-1-ol (1-9). General Procedure A was applied to thiophenecarboxaldehyde (31 μL, 0.332 mmol) and chloroethynyl-benzene (60 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc: 95/5) to give **1-9** (45.0 mg, 63% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 97.5:2.5, flow rate = 0.5 mL/min), t_r (1) = 49.2 min, t_r (2) = 60.1 min $[\alpha]_D^{20}$ = +367.2 (*c* = 0.012, $CHCl_3$, 92% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.1 (d, *J* = 4.5 Hz, 1H), 5.79 (dd, *J* = 4.5, 9.4 Hz, 1H), 5.93 (dd, *J* = 9.7, 11.0 Hz, 1H), 6.66 (d, *J* = 11.0 Hz, 1H), 6.93 (m, 1H), 6.98 (m, 1H) 7.24 (m, 6H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 66.7, 124.6, 125.6, 127.1, 127.8, 128.6, 129.0, 131.8, 132.7 136.5, 147.8 ppm; IR (neat): 3554, 3443, 3103, 3060, 3025, 2923, 2853, 2626, 1952, 1886, 1800, 1725, 1644, 1599, 1576, 1493, 1447, 1413, 1352, 1286, 1265, 1229, 1204, 1178, 1036 cm^{-1}; HRMS calcd for $C_{13}H_{12}OS$ $(M)^+$: 216.0609, found 216.0611.

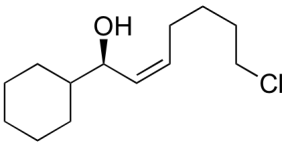


(*Z*)-7-chloro-1-phenyl-hept-2-en-1-ol (1-10). General Procedure B was applied to benzaldehyde (34 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-10** (62.4 mg, 84% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 52.0 min, t_r (2) = 59.5 min $[\alpha]_D^{20}$ = +101.3 (*c* = 0.203, $CHCl_3$, 88% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ

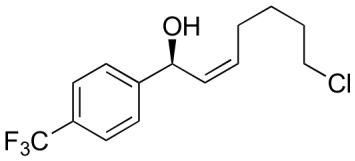
1.56 (m, 2H), 1.81 (m, 2H), 1.87 (d, J = 3.5 Hz, 1H), 2.26 (m, 2H), 3.54 (t, J = 6.60 Hz, 2H), 5.51-5.54 (dd, J = 3.6, 8.0 Hz, 1H), 5.55-5.59 (dt, J = 7.6, 10.7 Hz, 1H), 5.67 (dd, J = 8.9, 10.7 Hz, 1H), 7.27-7.31 (m, 1H), 7.34-7.42 (m, 4H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 26.9, 27.2, 32.3, 45.0, 70.0, 126.1, 127.8, 128.8, 131.6, 132.8, 143.8 ppm; IR (neat): 3352, 3062, 3012, 2937, 2864, 1951, 1881, 1810, 1654, 1602, 1492, 1451, 1384, 1300, 1276, 1191, 1076, 1036, 1009 cm^{-1}; HRMS calcd for $C_{13}H_{15}Cl$ $(M\text{-}H_2O)^+$: 206.0862, found 206.0851.



(*Z*)-7-chloro-1-thiophen-2-yl-hept-2-en-1-ol (1-11). General Procedure B was applied to thiophenecarboxaldehyde (31 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc: 95/5) to give **1-11** (56.0 mg, 73% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 84.0 min, t_r (2) = 93.0 min $[\alpha]_D^{20}$ = +167.9 (c = 0.031, $CHCl_3$, 94% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.57 (m, 2H), 1.79 (m, 2H), 1.99 (d, J = 3.3 Hz, 1H), 2.23 (m, 2H), 3.54 (t, J = 6.6 Hz, 2H), 5.61 (m, 1H), 5.75 (m, 2H), 6.98 (m, 2H), 7.27 (m, 1H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 26.9, 27.1, 32.2, 45.0, 66.3, 124.1, 125.3, 127.0, 132.0, 132.3 ppm; IR (neat): 3376, 3106, 3013, 2932, 2857, 2664, 1793, 1646, 1532, 1450, 1364, 1296, 1228, 1164, 1140, 1059, 1034 cm^{-1}; HRMS calcd for $C_{11}H_{14}ClS$ $(M\text{-}OH)^+$: 213.0505, found 213.0491.

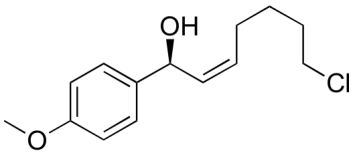


(*Z*)-7-chloro-1-cyclohexyl-hept-2-en-1-ol (1-12). General Procedure B was applied to cyclohexanecarboxaldehyde (40 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc: 95/5) to give **1-12** (57.1 mg, 74% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99.5:0.5, flow rate = 0.5 mL/min), t_r (1) = 35.8 min, t_r (2) = 39.3 min $[\alpha]_D^{20}$ = +21.4 (*c* = 0.040, $CHCl_3$, 88% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (m, 2H), 1.24 (m, 2H), 1.39 (m, 2H), 1.55 (m, 2H), 1.69 (m, 2H), 1.79 (m, 4H), 1.94 (d, *J* = 3.3 Hz, 1H), 2.12 (m, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 4.13 (t, *J* = 7.9 Hz, 1H), 5.41 (dd, *J* = 9.4, 11.1 Hz, 1H), 5.55 (dt, *J* = 7.5, 11.3 Hz, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 26.2, 26.3, 26.7, 27.1, 27.2, 28.8, 29.0, 32.3, 44.2, 45.0, 72.1, 131.9, 132.2 ppm; IR (neat): 3370, 3005, 2926, 2853, 2667, 1707, 1655, 1450, 1307, 1273, 1140, 1080, 1050 cm^{-1}; HRMS calcd for $C_{13}H_{21}Cl$ $(M\text{-}H_2O)^+$: 212.1332, found 212.1321.

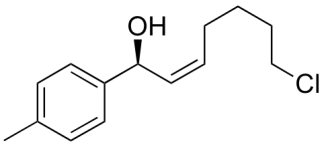


(*Z*)-7-chloro-1-(4-trifluoromethyl-phenyl)-hept-2-en-1-ol (1-13). General Procedure A was applied to *p*-trifluoromethyl-benzaldehyde (45 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-13** (70.4 mg, 72% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 48.0 min, t_r (2) = 55.8 min

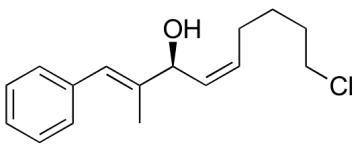
$[\alpha]_D^{20}$ = +119.9 (*c* = 0.01, $CHCl_3$, 86% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.58 (m, 3H), 1.83 (m, 2H), 2.28 (m, 2H), 3.56 (t, *J* = 6.5 Hz, 2H), 5.62 (m, 3H), 7.51 (d, *J* = 8.2 Hz, 2H) 7.62 (d, *J* = 8.2 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 26.9, 27.3, 32.3, 44.5, 69.4, 125.7 (q), 126.4, 130.0, 132.1, 132.7, 147.5 ppm; $^{19}F\{^1H\}$ NMR ($CDCl_3$, 282 MHz): δ -62.64 (s) ppm; IR (neat): 3350, 3014, 2939, 2866, 2360, 2097, 1924, 1807, 1654, 1619, 1588, 1446, 1417, 1266, 1164, 1125, 1067, 1046, 1016 cm^{-1}; HRMS calcd for $C_{14}H_{14}ClF_3$ $(M-H_2O)^+$: 274.0736, found 274.0724.



(*Z*)-7-chloro-1-(4-methoxy-phenyl)-hept-2-en-1-ol (1-14). General Procedure A was applied to *p*-methoxybenzaldehyde (40 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 90 / 10) to give **1-14** (71.1 mg, 84% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 95:5, flow rate = 0.5 mL/min), t_r (1) = 32.0 min, t_r (2) = 42.0 min $[\alpha]_D^{20}$ = +120.0 (*c* = 0.047, $CHCl_3$, 93% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.58 (m, 3H), 1.81 (m, 2H), 2.25 (m, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 5.49-5.52 (dd, *J* = 3.6, 8.3 Hz, 1H), 5.53-5.59 (dd, *J* = 8.0, 10.9 Hz, 1H), 5.71 (dd, *J* = 9.1, 11.0 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 2H) 7.34 (d, *J* = 8.7 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 26.9, 27.1, 32.3, 45.0, 55.5, 69.7, 114.2, 127.4, 131.2, 133.0, 136.1, 159.3 ppm; IR (neat): 3394, 2935, 1610, 1585, 1511, 1459, 1302, 1247, 1173, 1110, 1035 cm^{-1}; HRMS calcd for $C_{14}H_{17}ClO$ $(M-H_2O)^+$: 236.0968, found 236.0969.

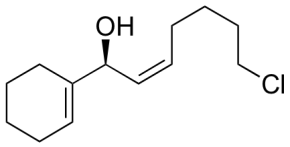


(*Z*)-7-chloro-1-p-tolyl-hept-2-en-1-ol (1-15). General Procedure A was applied to *p*-methylbenzaldehyde (39 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95 / 5) to give **1-15** (73.0 mg, 93% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99 : 1, flow rate = 0.5 mL/min), t_r (1) = 74.0 min, t_r (2) = 90.0 min $[\alpha]_D^{20}$ = +141.6 (*c* = 0.044, $CHCl_3$, 97% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.57 (m, 2H), 1.80 (m, 3H), 2.23 (m, 2H), 2.27 (s, 3H), 3.54 (t, *J* = 6.6 Hz, 2H), 5.48-5.52 (dd, *J* = 3.6, 8.7 Hz, 1H), 5.53 (dt, *J* = 7.8, 10.5 Hz, 1H), 5.67 (dd, *J* = 8.4, 10.7 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.28 (m, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 21.3, 26.9, 27.1, 32.3, 45.0, 69.9, 126.1, 129.5, 131.4, 132.9, 137.5, 140.1 ppm; IR (neat): 3368, 3012, 2932, 2861, 2361, 1903, 1654, 1512, 1452, 1230, 1193, 1177, 1111, 1039 cm^{-1}; HRMS calcd for $C_{14}H_{17}Cl$ $(M-H_2O)^+$: 220.1019, found 220.1027.



(*Z*)-9-chloro-2-methyl-1-phenyl-nona-1,4-dien-3-ol (1-16). General Procedure B was applied to α-methyl *trans* cinnamaldehyde (46 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-16** (64.6 mg, 73% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 67.0 min, t_r (2) = 73.5 min $[\alpha]_D^{20}$ = +167.9 (*c* = 0.03, $CHCl_3$, 88% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.58 (qui, *J* =

7.4 Hz, 2H), 1.64 (d, *J* = 3.3 Hz, 1H), 1.82 (m, 2H), 1.88 (d, *J* = 1.3 Hz, 3H), 2.24 (m, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 4.99 (dd, *J* = 3.0, 7.5 Hz, 1H), 5.58 (m, 2H), 6.61 (s, 1H), 7.28 (m, 5H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 14.3, 26.9, 27.3, 32.3, 45.0, 73.5, 125.4, 126.7, 128.3, 129.2, 131.2, 132.5, 137.8, 139.8 ppm; IR (neat): 3370, 3020, 2937, 2861, 1949, 1886, 1654, 1599, 1575, 1491, 1444, 1413, 1383, 1360, 1300, 1180, 1010 cm^{-1}; HRMS calcd for $C_{16}H_{21}OCl$ $(M)^+$: 264.1281, found 264.1278.



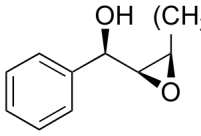
(*Z*)-7-chloro-1-cyclohex-1-enyl-hept-2-en-1-ol (1-17). General Procedure A was applied to cyclohexenecarboxaldehyde (38 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **1-17** (61.1 mg, 80% yield) as an oil. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 97.5:2.5, flow rate = 0.5 mL/min), t_r (1) = 28.2 min, t_r (2) = 32.9 min $[\alpha]_D^{20}$ = +88.55 (*c* = 0.078, $CHCl_3$, 94% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45 (d, *J* = 3.2 Hz, 1H), 1.52-1.67 (m, 6H), 1.80 (m, 2H), 2.04 (m, 4H), 2.16 (m, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 1H), 5.48 (m, 2H), 5.75 (m, 1H) ppm; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 22.7, 22.8, 24.4, 25.2, 26.9, 27.1, 32.3, 45.1, 72.2, 122.7, 131.6, 131.7, 139.7 ppm; IR (neat): 3350, 2929, 2858, 1655, 1437, 1268, 1137, 1006 cm^{-1}; HRMS calcd for $C_{13}H_{19}Cl$ $(M\text{-}H_2O)^+$: 210.1175, found 210.1176.

1.6.3. Asymmetric Addition/Diastereoselective Epoxidation Reactions

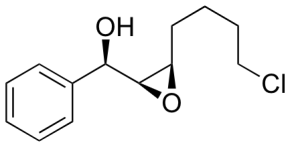
General procedure C. Dicyclohexylborane (88 mg, 0.5 mmol) was weighed into a Schlenk flask under nitrogen and dry *t*-BuOMe (1 mL) was added. The 1-chloroalkyne (0.5 mmol) was then added slowly to the reaction mixture at 0 °C. After 15 min the reaction mixture was warmed to room temperature and stirred for 45 min resulting in a clear solution. *t*-BuLi (0.365 mL, 0.55 mmol, 1.5 M pentane solution) was added dropwise at –78 °C and stirred for 60 min. The solution was warmed to room temperature and stirred for an additional 60 min during which time a precipitate formed. Diethylzinc (0.275 mL, 0.55 mmol, 2 M hexanes solution) was slowly added to the reaction mixture at –78 °C and stirred for 20 min. Addition of TEEDA (14 μL, 0.066 mmol) and hexanes (4 mL) was performed while at –78 °C. The solution was warmed to 0 °C. (–)-MIB (166 μL, 0.017 mmol) and neat aldehyde (0.333 mmol) were then added. The reaction mixture was then slowly warmed to room temperature and stirred 12-16 h. After the reaction was complete by TLC analysis, the temperature was lowered to –20 °C and $ZnEt_2$ (0.275 mL, 0.55 mmol, 2 M solution in hexanes) was added. The solution was stirred for 30 min and TBHP (0.300 mL, 1.68 mmol, 5.5 M solution in decanes) was added. After 30 min the $Ti(O\text{-}iPr)_4$ (48 μL, 0.067 mmol, 1.4 M solution in hexanes) was added and the reaction was stirred until completion (about 16 h). The reaction was quenched with 2 mL saturated aq. NH_4Cl, allowed to stir for 30 minutes at room temperature, and poured into a separatory funnel with a solution of aq. $Na_2S_2O_3$. The organic and aqueous layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were then washed with 5 mL

brine, 5 mL H_2O and then dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography on deactivated silica gel. Analysis of diastereomeric excess was performed *via* NMR before purification. The relative stereochemistry was determined by comparison of NMR data for known epoxidation methods (vide **1-19**) and by derivatization and single crystal X-ray analysis.

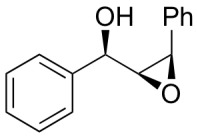
General Procedure D. This procedure is exactly the same as procedure C except that the amount of TEEDA necessary to obtain optimum results was adjusted to 30 mol %. Thus, 21 μL (0.099 mmol) were used.



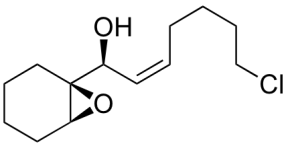
(3-Hexyl-oxiranyl)-phenyl-methanol (1-18). General Procedure C was applied to benzaldehyde (34 μL, 0.332 mmol) and 1-chloro-oct-1-yne (94 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 90/10) to give **1-18** (40.1 mg, 52% yield) as an oil. $[\alpha]_D^{20}$ = +35.9 (*c* = 0.026, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.92 (t, *J* = 7.1 Hz 3H), 1,37 (m, 8H), 1,71 (m, 2H), 2.53 (br, 1H), 3.09 (dt, *J* = 4.7, 7.7 Hz, 1H), 3.21 (dd, *J* = 4.3, 8.2 Hz, 1H), 4.60 (d, *J* = 8.0 Hz, 1H), 7.43 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 14.2, 22.7, 27.0, 28.8, 29.3, 31.9, 58.7, 61.5, 72.4, 126.4, 128.4, 128.9, 140.3 ppm; IR (neat): 3415, 3087, 3063, 3031, 2955, 2857, 1604, 1494, 1454, 1378, 1267, 1234, 1194, 1145, 1080, 1042 cm^{-1}; HRMS calcd for $C_{15}H_{21}O$ $(M\text{-}OH)^+$: 217.1592, found 217.1586.



[3-(4-Chloro-butyl)-oxiranyl]-phenyl-methanol (1-19). General Procedure D was applied to benzaldehyde (34 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 90/10) to give **1-19** (53.6 mg, 67% yield) as an oil. $[\alpha]_D^{20}$ = +56.0 (*c* = 0.041, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.64 (m, 6H), 2.46 (d, *J* = 2.9 Hz, 1H), 3.1 (m, 1H), 3.20 (dd, *J* = 4.4, 8.4 Hz, 1H), 3.56 (t, *J* = 6.8 Hz, 2H), 4.58 (dd, *J* = 2.8, 8.0 Hz, 1H), 7.31 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 24.5, 28.0, 32.3, 44.9, 58.3, 61.4, 72.5, 126.4, 128.6, 129.0, 140.1 ppm; IR (neat): 3419, 3062, 3031, 2955, 2866, 1807, 1604, 1492, 1454, 1278, 1195, 1040 cm^{-1}; HRMS calcd for $C_{13}H_{16}OCl$ $(M\text{-}OH)^+$: 223.0889, found 223.0888.



(*Z*)-phenyl-(3-phenyl-oxiranyl)-methanol (1-20). General Procedure C was applied to benzaldehyde (33 μL, 0.327 mmol) and chloroethynyl-benzene (60 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 90/10) to give **1-20** (43.5 mg, 59% yield) as an oil. $[\alpha]_D^{20}$ = +60.5 (*c* = 0.026, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.42 (d, *J* = 2.3 Hz, 1H), 3.44 (dd, *J* = 4.5, 8.5 Hz, 1H), 4.26 (d, *J* = 4.4 Hz, 1H), 4.30 (dd, *J* = 1.9, 8.5 Hz, 1H), 6,97 (m, 2H), 7.28 (m, 3H), 7.40 (m, 5H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 58.3, 63.4, 71.9, 126.1, 126.6, 128.3, 128.4, 128.6, 128.7, 135.0, 139.4 ppm; IR (neat): 3412, 3031, 2980, 2923, 1956, 1888, 1815, 1604, 1495, 1453, 1254, 1199 cm^{-1}; HRMS calcd for $C_{15}H_{18}NO_2$ $(M+NH_4)^+$: 244.1338, found 244.1326.



(*Z*)-7-Chloro-1-(7-oxa-bicyclo[4.1.0]hept-1-yl)-hept-2-en-1-ol (1-21). General Procedure C was applied to cyclohexenecarboxaldehyde (76 μL, 0.667 mmol) and 1,6-dichloro-hex-1-yne (132 μL, 1.0 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 90/10) to give **1-21** (85.7 mg, 52% yield) as an oil. $[\alpha]_D^{20}$ = +43.8 (*c* = 0.016, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.27 (m, 2H), 1.58 (m, 4H), 1.81 (m, 5H), 1.99 (m, 1H), 2.20 (m, 3H), 3.30 (d, *J* = 2.8 Hz, 1H), 3.56 (d, *J* = 7.0 Hz, 2H), 4.40 (d, *J* = 9.2 Hz, 1H), 5.33 (dd, *J* = 9.3, 10.9 Hz, 1H), 5.68 (dt, *J* = 7.3, 10.9 Hz, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 19.7, 20.2, 24.5, 25.0, 26.7, 27.2, 32.1, 44.8, 54.9, 62.1, 67.5, 128.1, 135.0 ppm; IR (neat): 3438, 2936, 2861, 2673, 1715, 1659, 1446, 1434, 1359, 1344, 1298, 1275, 1192, 1177, 1164, 1108, 1078, 1047 cm^{-1}; HRMS calcd for $C_{13}H_{21}O_2NaCl$ $(M+Na)^+$: 267.1128, found 267.1136.

1.6.4. Determination of Absolute Configuration of Secondary Alcohols

The configuration of the secondary alcohols from addition reactions was determined by X-ray diffraction analysis. In the case of the epoxy alcohol epoxidation reagents with known diastereoselectivity were employed and the products compared by ^{1}H NMR spectrometry.

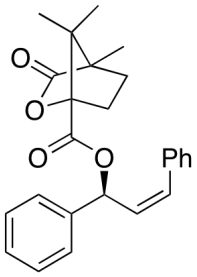
Epoxidation with *m*CPBA. To a solution of **1-10** (168 mg, 0.748 mmol) dissolved in CH_2Cl_2 (2 mL) *m*CPBA (142 mg, 0.823 mmol) was added. The solution was stirred

magnetically at room temperature and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was quenched by addition of 0.50 g of K_2CO_3 generating a suspension that was stirred another 30 min. The suspension was removed by filtration, the filtrate washed with saturated aq. $NaHCO_3$ (3 × 5 mL) and water (2 × 5 mL), the organic phase dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography on deactivated silica gel. Analysis of diastereomeric excess was performed by ^{1}H NMR spectroscopy. The epoxy alcohol **1-19** was obtained as a mixture of diastereomers (10:1).

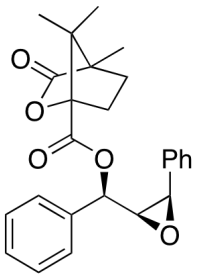
Epoxidation with VO(acac)$_2$/*t*-BuOOH. To a solution of **1-10** (180 mg, 0.8 mmol) in CH_2Cl_2 (2 mL) was added $VO(acac)_2$ (21 mg, 0.08 mmol). After stirring for 5 min at room temperature, *t*-BuOOH was added (0.73 mL, 4 mmol, 5.5 M in decane) and the mixture changed from blue to red. The reaction progress was monitored by TLC until completion. The reaction was then quenched with 1M $Na_2S_2O_3$, diluted with EtOAc (3 mL) and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* giving a crude product that was purified by chromatography on deactivated silica gel. Analysis of diastereomeric excess was performed by ^{1}H NMR spectroscopy before purification. The epoxy alcohol **1-19** was obtained as a mixture of diastereomers (2.3:1).

1.6.5. Derivatization of alcohols for X-ray Diffraction Analysis.

General procedure E. A solution of the desired alcohol (0.42 mmol) and (dimethylamino)pyridine (DMAP) (103 mg, 0.84 mmol) in 2 mL dichloromethane was treated with (–)-camphanic acid chloride (136 mg, 0.63 mmol), and the mixture was allowed to stand at room temperature for 2 h. The crude product was purified by column chromatography on silica gel to give the title compound. Clear crystals suitable for an X-ray diffraction study were formed by a slow vapor diffusion of dry hexanes into a THF solution of the compound.



(*Z*)-4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid 1,3-diphenyl-allyl ester (derivative of 1-8). General procedure E was applied to 1-8 (90 mg, 0.42 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give the derivate of **1-8** (125 mg, 74% yield) as an oil. $[\alpha]_D^{20}$ = +42.5 (*c* = 0.016, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.91 (s, 3H), 1.01 (s, 3H), 1.10 (s, 3H), 1.67 (m, 1H), 1.90 (m, 1H), 2.01 (m, 1H), 2.40 (m, 1H), 5.99 (dd, *J* = 9.7, 11.3 Hz, 1H), 6.74 (d, *J* = 11.2 Hz, 1H), 6.84 (d, *J* = 9.8 Hz, 1H), 7.37 (m, 10H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 9.9, 16.9, 17.0, 29.2, 30.7, 54.5, 55.0, 74.0, 91.2, 127.3, 128.0, 128.6, 128.7, 128.8, 128.9, 129.0, 133.1, 136.1, 139.2, 166.7, 178.4; IR (neat): 3060, 3028, 2969, 2876, 1955, 1888, 1790, 1751, 1664, 1601, 1576, 1494, 1448, 1397, 1378, 1356, 1318, 1264, 1228, 1168, 1125, 1102, 1061, 1017 cm^{-1}; HRMS calcd for $C_{25}H_{26}O_4$ $(M)^+$: 390.1831, found 390.1827.



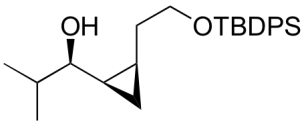
Preparation of 4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid phenyl-(3-phenyl-oxiranyl)-methyl ester (derivative of 1-20). General Procedure E was applied to 1-20 (95 mg, 0.42 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc: 95/5) to give the derivate of **1-20** (120 mg, 70% yield) as an oil. $[\alpha]_D^{20}$ = –5.78 (*c* = 0.038, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.08 (s, 3H), 1.11 (s, 3H), 1.15 (s, 3H), 1.70 (m, 1H), 1.94 (m, 1H), 2.05 (m, 1H), 2.48 (m, 1H), 3.57 (dd, *J* = 4.3, 8.7 Hz, 1H), 4.20 (d, *J* = 4.3 Hz, 1H), 5.62 (d, *J* = 8.7 Hz, 1H), 6.89 (m, 2H), 7.25 (m, 3H), 7.40 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 10.1, 17.0, 17.1, 29.3, 30.9, 54.8, 55.2, 57.7, 60.9, 75.7, 91.6, 126.7, 126.8, 128.7, 128.8, 128.9, 129.1, 134.2, 135.7, 166.9, 178.8 ppm; IR (neat): 3110, 3063, 3034, 2974, 2935, 2874, 2337, 1959, 1901, 1789, 1732, 1606, 1587, 1497, 1454, 1396, 1379, 1360, 1343, 1322, 1269, 1223, 1165, 1125, 1099, 1064, 1022 cm^{-1}; HRMS calcd for $C_{25}H_{26}O_5Na$ $(M + Na)^+$: 429.1678, found 429.1698.

1.6.6. Asymmetric Addition/Diastereoselective Cyclopropanation Reactions

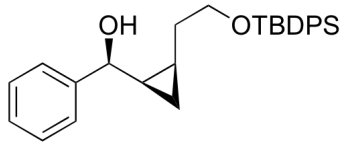
General procedure F. Dicyclohexylborane (88 mg, 0.5 mmol) was weighed into a Schlenk flask under nitrogen and dry *t*-BuOMe (1 mL) was added. The 1-chloroalkyne (0.5 mmol) was then added slowly to the reaction mixture at 0 °C. After 15 min the reaction mixture was warmed to room temperature and stirred for 45 min resulting in a clear solution. *t*-BuLi (0.365 mL, 0.55 mmol, 1.5 M pentane solution) was added dropwise at –78 °C and stirred for 60 min. The solution was warmed to room

temperature and stirred for an additional 60 min during which time a precipitate formed. Diethylzinc (0.275 mL, 0.55 mmol, 2 M hexanes solution) was slowly added to the reaction mixture at –78 °C and stirred for 20 min. Addition of TEEDA (14 μL, 0.066 mmol) and hexanes (4 mL) was performed while at –78 °C. The solution was warmed to 0 °C. (–)-MIB (166 μL, 0.017 mmol) and neat aldehyde (0.333 mmol) were then added. The reaction mixture was then slowly warmed to room temperature and stirred 12-16 h. After the reaction was complete by TLC analysis, the temperature was lowered to 0 °C and $ZnEt_2$ (0.83 mL, 1.66 mmol, 2 M solution in hexanes) was added. CF_3CH_2OH (120 μL, 1.65 mmol) was then added dropwise. After stirring at 0 ºC for 10 min, CH_2I_2 (135 μL, 1.67 mmol) was added. The reaction continued to stir with light exclusion at room temperature for 24 h. It was then quenched with saturated solution of NH_4Cl. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were then washed with brine and dried over $MgSO_4$. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography on deactivated silica gel. Analysis of diastereomeric excess was performed *via* NMR before purification.

General Procedure G. This procedure is exactly the same as General Procedure E except that the amount of TEEDA necessary to obtain optimum results was adjusted to 30 mol %. Thus, 21 μL (0.099 mmol) were used.

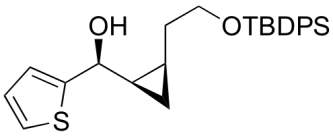


(*Z*)-1-(2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)cyclopropyl)-2-methylpropan-1-ol (1-22). General Procedure F was applied to isobutyraldehyde (30 μL, 0.332 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-22** (92.1 mg, 70% yield) as an oil. $[\alpha]_D^{20}$ = +4.41 (*c* = 0.026, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.05 (m, 1H), 0.67 (m, 1H), 0.93 (m, 2H), 0.98 (t, *J* = 7.9 Hz, 6H), 1.1 (m, 9H), 1.23 (m, 1H), 1.3 (d, *J* = 3.6 Hz, 1H), 1.74 (m, 1H), 1.91 (m, 1H), 2.96 (m, 1H), 3.76 (m, 2H), 7.42 (m, 6H), 7.7 (m, 4H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 8.9, 14.8, 17.6, 19.2, 19.4, 21.1, 27.1, 32.8, 34.7, 64.5, 76.7, 127.8, 129.8, 134.2, 135.8 ppm; IR (neat): 3599, 3411, 3134, 3070, 3050, 3013, 2952, 2912, 2895, 2858, 2739, 2319, 1958, 1888, 1823, 1589, 1486, 1471, 1428, 1362, 1331, 1306, 1260, 1235, 1187, 1157, 1110 1029, 1007 cm^{-1}; HRMS calcd for $C_{25}H_{36}O_2NaSi$ $(M+Na)^+$: 419.2382, found 419.2377.

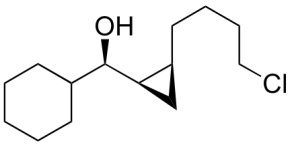


(*Z*)-(2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)cyclopropyl) (phenyl)methanol (1-23). General Procedure F was applied to benzaldehyde (34 μL, 0.332 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-23** (88.1 mg, 62% yield) as an oil. $[\alpha]_D^{20}$ = +35.4 (*c* = 0.023, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.27 (dd, *J* = 5.4, 10.5 Hz, 1H), 0.83 (dt, *J* = 5.4, 8.3 Hz, 1H), 1.05 (s, br, 10H), 1.26 (m, 1H), 1.40 (m, 1H), 1.83 (d, *J* = 3.4 Hz, 1H), 1.86 (m, 1H), 3.66 (t, *J* = 6.6 Hz, 2H), 4.20 (dd, *J* = 3.4,

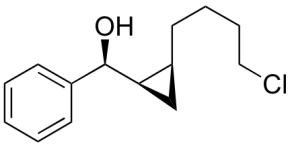
10.5 Hz, 1H), 7.34 (m, 11H), 7.63 (m, 4H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 9.9, 13.6, 19.1, 23.6, 26.8 32.3, 64.1, 74.7, 126.1, 127.5, 128.4, 129.5, 133.9, 135.5, 144.2; IR (neat): 3564, 3365, 3069, 3029, 2997, 2955, 2892, 2857, 2318, 1958, 1888, 1823, 1774, 1660, 1602, 1589, 1567, 1557, 1487, 1471, 1461, 1427, 1361, 1322, 1302, 1287, 1232, 1190, 1157, 1110, 1030, 992 cm^{-1}; HRMS calcd for $C_{28}H_{34}O_2NaSi$ $(M+Na)^+$: 453.2226, found 453.2229.



(*Z*)-(2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)cyclopropyl) (thiophen-2-yl)methanol (1-24). General Procedure F was applied to 2-thiopenecarboxaldehyde (31 μL, 0.332 mmol) and *tert*-butyl-(4-chloro-but-3-ynyloxy)-diphenyl-silane (160 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-24** (69.0 mg, 48% yield) as an oil. $[\alpha]_D^{20}$ = +26.6 (*c* = 0.022, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.27 (dd, *J* = 6.9, 11.4 Hz, 1H), 0.87 (m, 1H), 0.98 (m, 1H), 1.05 (s, 9H), 1.12 (m, 1H), 1.35 (m, 2H), 1.99 (d, *J* = 4.4 Hz, 1H), 3.7 (t, *J* = 6.9 Hz, 2H), 4.45 (dd, *J* = 4.4, 9.7 Hz, 1H), 6.98 (m, 2H), 7.25 (m, 1H), 7.40 (m, 6H), 7.66 (m, 4H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 10.4, 13.9, 19.4, 24.1, 27.1, 32.3, 64.3, 71.1, 124.0, 124.9, 127.8, 129.8, 134.2, 135.8, 148.4; IR (neat): 3374, 3070, 3049, 3012, 2929, 2857, 2739, 1959, 1889, 1825, 1778, 1729, 1656, 1589, 1471, 1462, 1446, 1389, 1306, 1264, 1230, 1188, 1157, 1107, 1030, 1008, 997 cm^{-1}; HRMS calcd for $C_{26}H_{31}O_2SSi$ $(M-H)^+$: 435.1811, found 435.1814.

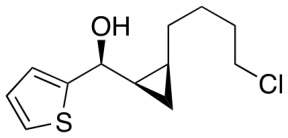


(*Z*)-(2-(4-chlorobutyl)cyclopropyl)(cyclohexyl)methanol (1-25). General Procedure G was applied to cyclohexanecarboxaldehyde (40 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-25** (57.1 mg, 70% yield) as an oil. $[\alpha]_D^{20}$ = +17.1 (*c* = 0.086, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.20 (dd, *J* = 5.4, 10.7 Hz, 1H), 0.69 (m, 1H), 0.86 (m, 1H), 0.99 (m, 2H), 1.05 (m, 3H), 1.23 (m, 2H), 1.30 (d, *J* = 3.8 Hz, 1H), 1.39 (m, 1H), 1.53 (m, 2H), 1.64 (m, 2H), 1.77 (m, 5H), 1.91 (d, *J* = 12.7 Hz, 1H), 2.94 (m, 1H), 3.52 (t, *J* = 6.4 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 8.8, 17.4, 21.4, 26.2, 26.4, 26.5, 27.2, 28.1, 28.8, 29.2, 32.3, 44.7, 45.0, 76.0; IR (neat): 3390, 3062, 2991, 2922, 2852, 2667, 2044, 1634, 1448, 1416, 1309, 1262, 1220, 1188, 1150, 1099, 1084, 1069, 1025, 982 cm^{-1}; HRMS calcd for $C_{14}H_{24}Cl$ $(M\text{-}OH)^+$: 227.1567, found 227.1574.

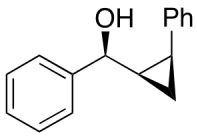


(*Z*)-(2-(4-chlorobutyl)cyclopropyl)(phenyl)methanol (1-26). General Procedure G was applied to cyclohexenecarboxaldehyde (34 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-26** (55.8 mg, 70% yield) as an oil. $[\alpha]_D^{20}$ = +53.8 (*c* = 0.037, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.29 (d, *J* = 5.3 Hz, 1H), 0.89 (m, 2H), 1.19 (m, 1H), 1.28 (m, 1H), 1.40 (m, 1H), 1.48 (m, 1H), 1.56 (m, 1H), 1.74 (m, 2H), 1.87 (br, 1H), 3.47 (t, *J* = 6.7 Hz, 2H), 4.24 (d, *J* = 9.6 Hz, 1H), 7.28 (m, 1H), 7.35

(m, 2H), 7.43 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 10.5, 17.0, 24.2, 27.6, 28.8, 32.6, 45.2, 75.0, 126.5, 127.9, 128.7, 144.5; IR (neat): 3367, 3062, 3029, 2993, 2932, 2858, 2048, 1950, 1882, 1809, 1758, 1603, 1492, 1454, 1408, 1307, 1195, 1140, 1031, 915 cm^{-1}; HRMS calcd for $C_{14}H_{18}Cl$ $(M\text{-}OH)^+$: 221.1097, found 221.1097.

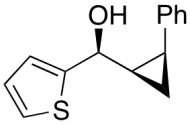


(*Z*)-(2-(4-chlorobutyl)cyclopropyl)(thiophen-2-yl)methanol (1-27). General Procedure G was applied to 2-thiophenecarboxaldehyde (31 μL, 0.332 mmol) and 1,6-dichloro-hex-1-yne (66 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-27** (50.3 mg, 62% yield) as an oil. $[\alpha]_D^{20}$ = +78.4 (*c* = 0.063, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.30 (dd, *J* = 5.4, 10.4 Hz, 1H), 0.90 (m, 1H), 0.97 (m, 1H), 1.15 (m, 1H), 1.35 (m, 1H), 1.52 (m, 3H), 1.76 (m, 2H), 1.98 (d, *J* = 3.9 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 2H), 4.47 (dd, *J* = 3.9, 9.6 Hz, 1H), 6.96 (m, 1H), 7.04 (dd, *J* = 3.4, 5.1 Hz, 1H), 7.26 (dd, *J* = 1.1, 5.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 10.5, 16.7, 24.2, 27.2, 28.2, 32.3, 44.9, 70.8, 123.8, 124.7, 126.5, 148.2; IR (neat): 3364, 3105, 3068, 2993, 2934, 2857, 2051, 1794, 1729, 1645, 1543, 1455, 1393, 1359, 1300, 1267, 1229, 1167, 1136, 1106, 1073 1031 cm^{-1}; HRMS calcd for $C_{12}H_{16}SCl$ $(M\text{-}OH)^+$: 227.0661, found 227.0668.



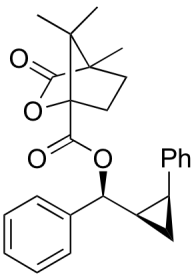
(*Z*)-phenyl(2-phenylcyclopropyl)methanol (1-28). General Procedure F was applied to benzaldehyde (34 μL, 0.332 mmol) and chloroethynyl-benzene (60 μL, 0.5 mmol). The crude product was purified by column

chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-28** (48.2 mg, 65% yield) as an oil. $[\alpha]_D^{20}$ = +47.2 (*c* = 0.045, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.18 (dt, *J* = 5.7, 8.3 Hz, 1H), 1.28 (dd, *J* = 5.7, 11.5 Hz, 1H), 1.60 (m, 1H), 1.71 (d, *J* = 3.3 Hz, 1H), 2.29 (m, 1H), 3.91 (dd, *J* = 2.5, 9.4 Hz, 1H), 6.97 (m, 2H), 7.12 (m, 2H), 7.22 (m, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 8.0, 21.5, 26.8, 73.9, 126.0, 126.1, 127.4, 127.9, 128.1, 128.9, 137.8, 143.6; IR (neat): 3360, 3061, 3028, 3005, 2923, 2851, 2245, 1948, 1882, 1807, 1754, 1602, 1582, 1541, 1495, 1454, 1411, 1384, 1335, 1285, 1256, 1224, 1197, 1137, 1108, 1083, 1015, 971, 920 cm^{-1}; HRMS calcd for $C_{16}H_{15}$ $(M\text{-}OH)^+$: 207.1174, found 207.1168.



(*Z*)-(2-phenylcyclopropyl)(thiophen-2-yl)methanol (1-29). General Procedure F was applied to 2-thiophenecarboxaldehyde (31 μL, 0.332 mmol) and chloroethynyl-benzene (60 μL, 0.5 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give **1-29** (31.6 mg, 42% yield) as an oil. 24.4 mg of the allylic alcohol were recovered accounting for the relatively low yield. $[\alpha]_D^{20}$ = +28.7 (*c* = 0.061, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.20 (dt, *J* = 5.5, 8.3 Hz, 1H), 1.26 (dd, *J* = 5.5, 11.8 Hz, 1H), 1.66 (m, 1H), 1.85 (d, *J* = 4.0 Hz, 1H), 2.35 (m, 1H), 4.12 (dd, *J* = 4.0, 9.3 Hz, 1H), 6.55 (m, 1H), 6.85 (dd, *J* = 3.5, 5.0 Hz, 1H), 7.13 (m, 2H), 7.18 (m, 2H), 7.21 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 8.2, 21.5, 26.8, 70.2, 123.7, 124.4, 126.2, 126.3, 128.0, 128.9, 137.4, 147.4; IR (neat): 3928, 3824, 3363, 3106, 3064, 3026, 3006, 2922, 2850, 2340, 2067, 1947, 1885,

1799, 1728, 1652, 1602, 1580, 1535, 1497, 1446, 1372, 1301, 1259, 1230, 1165, 1134, 1083, 1011 cm^{-1}; HRMS calcd for $C_{14}H_{14}ONaS$ $(M+Na)^+$: 253.0663, found 263.0656.

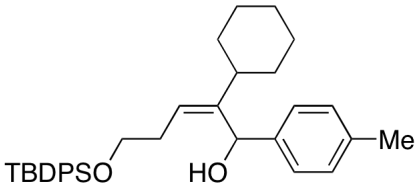


(*Z*)-(1*S*)-phenyl(2-phenylcyclopropyl)methyl 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (derivative of 1-28). General Procedure E was applied to **1-28** (106.7 mg, 0.476 mmol). The crude product was purified by column chromatography on deactivated silica gel (hexanes/EtOAc : 95/5) to give derivative of 1-28 (70.0 mg, 36% yield) as a solid. 50.0 mg of 1-28 were recovered accounting for the low yield. $[\alpha]_D^{20}$ = –32.9 (*c* = 0.031, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.94 (s, 3H), 1.05 (s, 3H), 1.09 (s, 3H), 1.16 (dd, *J* = 5.6, 8.2 Hz, 1H), 1.34 (q, *J* = 5.9 Hz, 1H), 1.65 (m, 1H), 1.75 (m, 1H), 1.88 (m, 1H), 1.97 (m, 1H), 2.36 (m, 2H), 5.31 (d, *J* = 5.4 Hz, 1H), 6.89 (m, 2H), 7.12 (m, 2H), 7.19 (m, 4H), 7.25 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 9.0, 9.6, 16.6, 16.7, 21.9, 24.7, 28.9, 30.4, 54.0, 54.7, 78.1, 91.0, 126.3, 126.6, 127.9, 128.0 128.1, 128.2, 128.5, 128.7, 136.9, 139.1,166.8, 178.1; IR (in CH_2Cl_2): 3944, 3756, 3689, 3554, 3055, 2975, 2935, 2877, 2685, 2522, 2410, 2305, 2126, 1952, 1884, 1788, 1744, 1603, 1497, 1450, 1422, 1397, 1383, 1359, 1319, 1265, 1217, 1169, 1125, 1103, 1062 cm^{-1}; HRMS calcd for $C_{26}H_{28}O_4Na$ $(M+Na)^+$: 427.1885, found 427.1874.

1.6.7. Synthesis of (Z)-Trisubstituted Allylic Alcohols

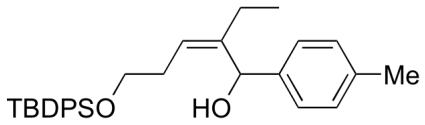
Compounds 1-30 to 1-51 were presented to display the entire process but were already reported in Michael Kerrigan thesis.

1.6.7.1. Examination of the Impact of Dialkylborane and Dialkylzinc Reagents on the 1,2-Metallate Rearrangement (Table 1-10).



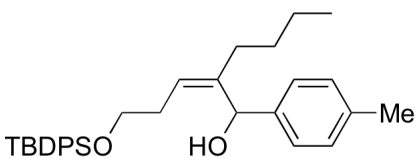
(*Z*)-5-(tert-butyldiphenylsilyloxy)-2-cyclohexyl-1-p-tolylpent-2-en-1-ol (1-56). A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 (g) three times, was charged with dicyclohexylborane (1 mmol) and toluene (1 mL) under a nitrogen atmosphere. The solution was cooled to 0 ºC followed by addition of (4-bromobut-3-ynyloxy)(*tert*-butyl)diphenylsilane (386.4 mg, 1 mmol). The reaction was stirred for 5 min, warmed to room temperature, and stirred for 15 min. The solution was cooled to –78 °C and diethylzinc (3 mL, 3 mmol, 1.0 M in toluene) was added. After stirring for 20 min, the reaction flask was warmed to 0 ºC. Under a steady flow of N_2 (g), the rubber septum was replaced with a glass stopper coated with silicon grease and high vacuum was gradually applied to remove the volatile contents. The resulting vinylzinc reagent was redissolved in toluene (1 mL) followed by addition of *p*-tolualdehyde (0.67 mmol). The reaction mixture was gradually warmed to ambient temperature and stirred until no aldehyde remained by TLC (usually 7-16 h). Quenching by saturated aq. NH_4Cl (2 mL), followed by addition of 2 N HCl (1 mL) and 5 mL of

EtOAc. The organic layer was separated and the aqueous layer was extracted successively with EtOAc (2 × 10 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel to yield a mixture of 1-56 (173 mg, 50.7%) and (*Z*)-5-(tert-butyldiphenylsilyloxy)-2-ethyl-1-p-tolylpent-2-en-1-ol (1-53) (11.0 mg, 3.6%) in a 14:1 ratio, respectively. When diethylzinc was added to the reaction solution at 0 °C, the ratio changed to 4:1. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (m, 4H), 7.44 (m, 6H), 7.31 (d, J = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.54 (d, 4.0 Hz, 1H), 5.48 (t, *J* = 7.8 Hz, 1H), 3.69 (m, 2H), 2.61 (m, 1H), 2.37 (s, 3H), 1.96 (m, 1H), 1.79 (m, 2H), 1.68 (m, 2H), 1.51 (d, *J* = 9.4 Hz, 1H), 1.28 (m, 2H), 1.11 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 149.9, 140.5, 136.4, 135.9, 133.7, 129.9, 128.9, 127.9, 126.1, 123.2, 72.6, 63.9, 41.6, 34.6, 34.3, 31.4, 27.2, 26.5, 21.3, 19.4 ppm; HRMS-CI calcd for $C_{34}H_{44}O_2SiCl$ $(M+Cl)^-$: 547.2797, found 547.2799.



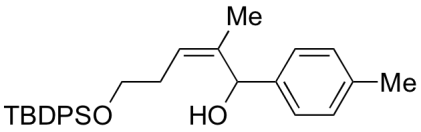
(*Z*)-5-(tert-butyldiphenylsilyloxy)-2-ethyl-1-p-tolylpent-2-en-1-ol (1-53). A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 (g) three times, was charged with (4-bromobut-3-ynyloxy)(*tert*-butyl)diphenylsilane (128.13 mg, 0.33 mmol) and toluene (1 mL) under a nitrogen atmosphere. The solution was cooled to 0 ºC followed by slow addition of diethylborane (0.33 mL, 1.0 M in toluene, 0.33 mmol). The reaction was stirred for 5 min, warmed to room temperature, and stirred for 15 min. The

solution was cooled to –78 °C and diisopropylzinc (1 mL, 1.0 M in toluene 1 mmol) was added. After stirring for 20 min, the reaction flask was warmed to 0 ºC. Under a steady flow of N_2 (g), the rubber septum was replaced with a glass stopper coated with silicon grease and high vacuum was gradually applied to remove the volatile contents. The resulting vinylzinc reagent was redissolved in toluene (1 mL) followed by addition of *p*-tolualdehyde (0.22 mmol). The reaction mixture was gradually warmed to ambient temperature and stirred until no aldehyde remained by TLC (usually 7-16 hrs). It was quenched with saturated aq. NH_4Cl (2 ml), followed by the addition of 2 N HCl (1 mL) and 5 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted successively with EtOAc (2 × 10 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel to yield a mixture of 1-53 (48 mg, 47.5%) and (*Z*)-5-(tert-butyldiphenylsilyloxy)-2-isopropyl-1-p-tolylpent-2-en-1-ol (1-54) (10.0 mg, 9.6%) in a 5:1 ratio, respectively. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (d, *J* = 7.8 Hz, 4H), 7.44 (m, 6H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.63 (d, *J* = 3.0 Hz, 1H), 5.42 (t, *J* =7. 6 Hz, 1H), 3.74 (t, *J* = 6.4 Hz, 2H), 2.6 (m, 1H), 2.51 (m, 1H), 2.37 (s, 3H), 2.30 (d, *J* = 3.5 Hz, 1H), 2.10 (m, 1H), 1.87 (m, 1H), 1.10 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 144.9, 140.0, 136.6, 133.8, 129.9, 129.0, 127.9, 126.7, 126.0, 122.8, 72.1, 64.0, 31.2, 27.1, 24.6, 21.3, 19.4, 13.0 ppm.



(*Z*)-2-(3-(tert-butyldiphenylsilyloxy)propylidene)-1-p-tolylhexan-1-ol (1-55). A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 (g) three times, was charged with (4-bromobut-3-ynyloxy)(*tert*-butyl)diphenylsilane (386.4 mg, 1 mmol) and toluene (1 mL) under a nitrogen atmosphere. The solution was cooled to 0 ºC followed by slow addition of diethylborane (1 mL, 1.0 M in toluene, 1 mmol). The reaction was stirred for 5 min, warmed to room temperature, and stirred for 15 min. The solution was cooled to –78 °C and dibutylzinc (3 mL, 1.0 M in heptane, 3 mmol) was added. After stirring for 20 min, the reaction flask was warmed to 0 ºC. Under a steady flow of N_2 (g), the rubber septum was replaced with a glass stopper coated with silicon grease and high vacuum was gradually applied to remove the volatile contents. The resulting vinylzinc reagent was redissolved in toluene (1 mL) followed by addition of *p*-tolualdehyde (0.67 mmol). The reaction mixture was gradually warmed to ambient temperature and stirred until no aldehyde remained by TLC (usually 7-16 hrs). It was quenched with saturated aq. NH_4Cl (2 ml), followed by the addition of 2 N HCl (1 mL) and 5 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted successively with EtOAc (2 × 10 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel to yield a mixture of 1-55 (55 mg, 15.7%) and 1-53 (205 mg, 62%) in a 1:4 ratio, respectively. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71 (d, *J* = 7.6 Hz, 4H), 7.42 (m, 6H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 5.59 (d, *J*

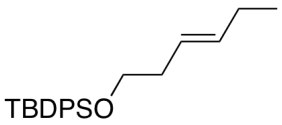
= 2.7 Hz, 1H), 5.42 (t, *J* = 7.4 Hz, 1H), 3.73 (t, *J* = 6.2 Hz, 2H), 2.59 (m, 1H), 2.49 (m, 1H), 2.36 (s, 3H), 2.29 (d, 3.5 Hz, 1H), 2.03 (m, 1H), 1.88 (m, 1H), 1.29 (m, 4H), 1.09 (s, 9H), 0.86 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 143.6, 140.0, 136.6, 135.9, 133.8, 129.9, 129.0, 127.9, 126.0, 123.9, 72.2, 64.0, 31.9, 31.3, 31.2, 27.1, 22.9, 21.3, 19.4, 14.2.



(*Z*)-5-(tert-butyldiphenylsilyloxy)-2-methyl-1-p-tolylpent-2-en-1-ol (1-52). A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 (g) three times, was charged with (4-bromobut-3-ynyloxy)(*tert*-butyl)diphenylsilane (386.4 mg, 1 mmol) and toluene (1 mL) under a nitrogen atmosphere. The solution was cooled to 0 ºC followed by slow addition of diethylborane (1 mL, 1.0 M in toluene, 1 mmol). The reaction was stirred for 5 min, warmed to room temperature, and stirred for 15 min. The solution was cooled to –78 °C and dimethylzinc (3 mL, 1.0 M, in toluene, 3 mmol) was added. After stirring for 20 min, the reaction flask was warmed to 0 ºC. Under a steady flow of N_2 (g), the rubber septum was replaced with a glass stopper coated with silicon grease and high vacuum was gradually applied to remove the volatile contents. The resulting vinylzinc reagent was redissolved in toluene (1 mL) followed by addition of *p*-tolualdehyde (0.67 mmol). The reaction mixture was gradually warmed to ambient temperature and stirred until no aldehyde remained by TLC (usually 7-16 hrs). It was quenched by saturated aq. NH_4Cl (2 mL), followed by the addition of 2 N HCl (1 mL) and 5 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted successively with

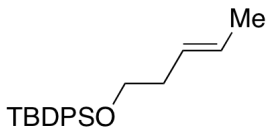
EtOAc (2 × 10 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel to yield a mixture of 1-52 (67.6 mg, 23%) and 1-53 (172.2 mg, 56.7%) in a 1:2.5 ratio, respectively. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, *J* = 7.1 Hz, 4H), 7.45 (m, 6H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.62 (s, 1H), 5.40 (t, *J* = 7.4 Hz, 1H), 3.76 (m, 2H), 2.55 (dt, *J* = 6.7 Hz, 6.4 Hz, 2H), 2.37 (s, 3H), 2.08 (d, *J* = 3.1 Hz, 1H), 1.62 (s, 3 H), 1.12 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 139.6, 139.1, 136.6, 135.8, 133.9, 129.9, 129.1, 127.9, 125.9, 124.7, 71.5, 64.0, 31.3, 27.1, 21.3, 19.4, 18.5 ppm; HRMS-CI calcd for $C_{29}H_{36}O_2SiCl$ ($M+Cl^+$): 479.2195, found 479.2189.

1.6.7.2. Protonolysis of Intermediates in the Generation of Trisubstituted Vinylzinc Species (Scheme 1-26).



(*E*)-*tert*-butyl(hex-3-enyloxy)diphenylsilane (1-58). A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 (g) three times, was charged with (4-bromobut-3-ynyloxy)(*tert*-butyl)diphenylsilane (386.4 mg, 1 mmol) and toluene (1 mL) under a nitrogen atmosphere. The solution was cooled to 0 ºC followed by slow addition of diethylborane (1mL, 1.0 M in toluene, 1 mmol). The reaction was stirred for 5 min, warmed to room temperature, and stirred for 15 min. The solution was cooled to –78 ºC and dimethylzinc (3 mL, 1.0 M, in toluene, 3 mmol) was added. After stirring for 20 min, the reaction was quenched with MeOH. Warming to ambient temperature, saturated aq. NH_4Cl (2 ml) was

added and 5 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted successively with EtOAc (2 x 10 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel to yield a mixture of 1-58 and (*E*)-*tert*-butyl(pent-3-enyloxy)diphenylsilane (1-57) in a 1:2.7 ratio, respectively. For comparison, (*E*)-*tert*-butyl(hex-3-enyloxy)diphenylsilane was also prepared using the same procedure and diethylzinc in the place of dimethylzinc. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, *J* = 6.5 Hz, 4H), 7.41 (m, 6H), 5.52 (dt, *J* = 15.3, 6.1 Hz, 1H), 5.41 (dt, *J* = 15.3, 6.7 Hz, 1H), 3.70 (t, *J* = 6.7 Hz, 2H), 2.28 (dt, *J* = 6.5, 6.7 Hz, 2H), 2.02 (dq, *J* = 6.5, 7.0 Hz, 2H), 1.08 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 135.8, 134.4, 134.3, 129.7, 127.8, 125.7, 64.3, 36.2, 27.1, 25.9, 19.5, 14.0 ppm.



(*E*)-*tert*-butyl(pent-3-enyloxy)diphenylsilane (1-57). For comparison the title compound was synthesized separately. A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 (g) three times, was charged with bromoalkyne (1 mmol) and toluene (1 mL) under a nitrogen atmosphere. The solution was cooled to 0 ºC followed by slow addition of either $Br_2BH•SMe_2$ (166 μL, 1 mmol). The reaction was stirred for 5 min, warmed to room temperature, and stirred for 15 min. The solution was cooled to −78 ºC and Me_2Zn (2.25 mL, 2.0 M in PhMe) was added. After stirring at this temperature for 20 min, the reaction flask was warmed to 0 ºC. Under a steady flow of N_2 (g), the rubber septum was

replaced with a glass stopper coated with silicon grease and high vacuum was gradually applied to remove the volatile contents. The resulting vinylzinc reagent was redissolved in toluene (1 mL) followed by addition of *p*-tolualdehyde (78.5 μL, 0.67 mmol). The reaction mixture was gradually warmed to ambient temperature and stirred until no aldehyde remained by TLC (usually ~16 hrs). Quenching by saturated aq. NH_4Cl (2 ml), followed by addition of 2 N HCl (1 mL) and 5 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted successively with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ followed by saturated NaCl, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on silica gel to yield 1-57. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, J = 7.8 Hz, 4H), 7.41 (m, 6H), 5.45 (m, 2H), 3.69 (t, J = 6.8 Hz, 2H), 2.27 (dt, J = 6.6, 6.3 Hz, 2H), 1.66 (d, 5.4 Hz, 3H), 1.07 (s, 9H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 135.8, 134.3, 129.7, 127.9, 127.8, 127.2, 64.2, 36.2, 27.1, 19.4, 18.2 ppm.

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2. Practical Catalytic Asymmetric Synthesis of Diaryl-, Aryl Heteroaryl- and Diheteroarylmethanols

2.1. Introduction

Enantioenriched diaryl-, aryl heteroaryl-, and diheteroarylmethanols are important intermediates and structural motifs in medicinal chemistry. Diarylmethanols form the core of several biologically active compounds, including (*R*)-neobenodine, (*R*)-orphenadrine and (*S*)-cetrizine.[1-6] The 1-benzofuran derivatives **2-1a-c** are intermediates in the synthesis of chiral azoles (**2-2a-c**, Figure 2-1). Compounds **2-2a-c** were initially examined as antifungal agents[7] and have been found to be powerful nonsteroidal aromatase inhibitors.[8-13] They are indicated in the treatment of hormone-dependent breast cancer.[14] Likewise, diheteroarylmethanols have received recent attention. For example, chiral dithienylmethanols have been evaluated as antiallergic and antiischemic agents (**2-3**, Figure 2-1).[15] Furthermore, enantioenriched diarylmethanols can be converted into diarylmethane derivatives via S_N2 substitution at the C-O bond without loss of ee.[1] The diarylmethane motif is found in antimuscarinics,[16] antidepressants,[17] and endothelin antagonists.[18]

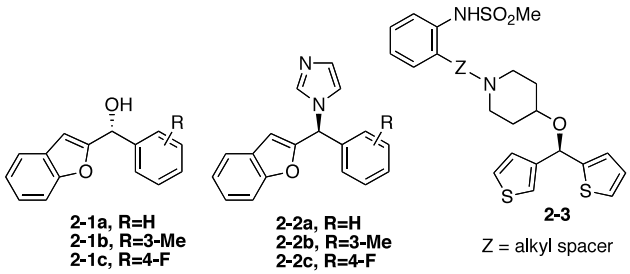
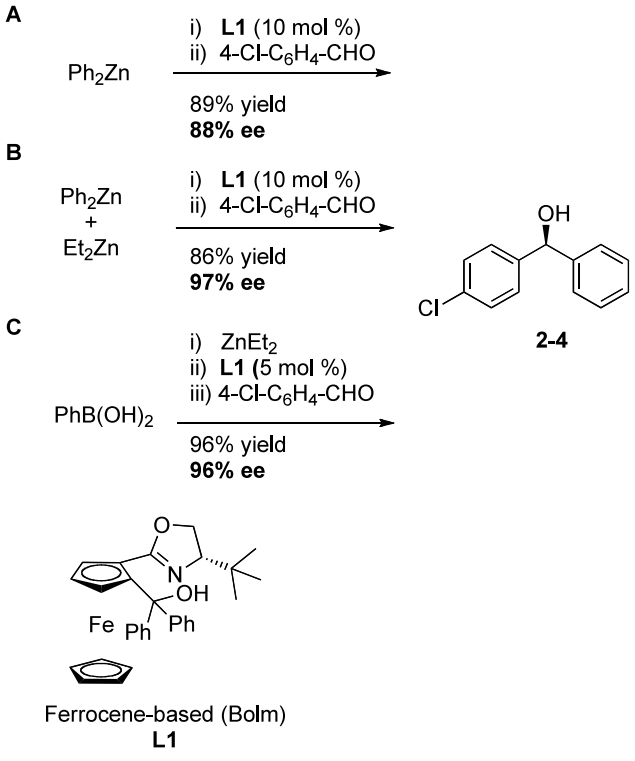


Figure 2-1. Biologically active heteroaryl- and diheteroarylmethanols.

The catalytic enantioselective synthesis of diarylmethanols has been the focus of many studies.[19] The most efficient approach to their preparation is the arylation of aromatic aldehydes to generate a C-C bond and stereocenter in a single step. Early studies by Seebach and coworkers employed Ph-Ti(O-*i*Pr)$_3$, generated from Cl-Ti(O-*i*Pr)$_3$ and PhLi, in combination with TADDOL-based titanium catalysts.[20-22] To achieve high enantioselectivity, it was necessary to remove the LiCl byproduct formed during salt metathesis by centrifugation.

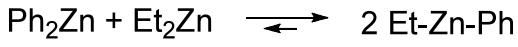
Pioneering studies by Fu and coworkers[23] with a planar-chiral catalyst, diphenylzinc, and 4-chlorobenzaldehyde furnished the diarylmethanol product with 57% ee. A highly enantioselective catalyst was reported by Pu shortly thereafter.[24]



Scheme 2-1. Asymmetric Arylation of 4-Chlorobenzaldehyde with Ph_2Zn (A) and PhZnEt Generated from Ph_2Zn and Et_2Zn (B) or from $PhB(OH)_2$ and Et_2Zn (C).

These works inspired many subsequent investigations using diphenylzinc, as exemplified in Scheme 2-1A.[25-30]

Despite the large number of studies with diphenylzinc, significant drawbacks remained. Diphenylzinc is prohibitively expensive and limited to phenyl transfer.[25,31-34] Furthermore, unlike dialkylzinc additions to aldehydes, which exhibit slow background reactions, the uncatalyzed addition of diphenylzinc to aldehydes is sufficiently rapid to compete with most catalyzed additions.[34-36] The latter problem was addressed by Bolm and coworkers, who discovered that the mixed reagent EtZnPh[33] exhibited a slower background reaction than diphenylzinc. EtZnPh also resulted in higher enantioselectivities with the same catalysts (Scheme 2-1B), in part from the reduced contribution of the background reaction.[37-42] EtZnPh is easily generated by combining Ph_2Zn and Et_2Zn (Equation 2-1).



Equation 2-1

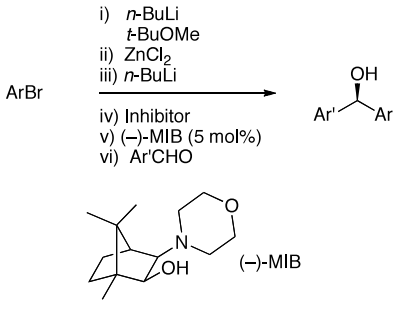
The development of methods for the enantioselective transfer of substituted aryl groups to aldehydes remained a challenge for several years. Although diarylzinc reagents can be easily prepared from ArLi or ArMgX and zinc halides (ZnX_2), the salt byproducts LiX and MgX_2 are Lewis acidic and readily promote the background reaction in the presence of enantioenriched catalysts, resulting in diarylmethanols with little or no ee. To bypass this problem, Bolm and coworkers introduced a method whereby arylboronic acid derivatives underwent transmetallation with dialkylzinc reagents to provide access to salt-

free arylzinc reagents, ArZnEt (Scheme 2-1C).[30,42-48] In this procedure,[44] 2.4 equiv of the aryl boronic acid was heated with 7.2 equiv of diethylzinc for 12 h to generate ArZnEt. Dimethyl (polyethylene glycol) (DiMPEG, 10 mol %, MW~2,000) was used as an additive to inhibit the background reaction caused by achiral Lewis acidic $ZnPh_2$ or $ZnBr_2$.[43,49,50] Further study and optimization by the groups of Pericàs and Magnus significantly reduced the transmetallation time.[51,52] Braga demonstrated that the acceleration could be achieved by microwave irradiation.[53] Based on Bolm's breakthrough, several arylboron derivatives, such as triarylboranes[42,43,50,54-57] and boroxines,[52,58,59] were successfully employed in the asymmetric arylation of aldehydes. Highly enantioselective late transition metal-based catalysts can also be employed with boronic acid derivatives.[60-62]

Main group metals other than zinc have been applied to the asymmetric arylation of aldehydes. In 2008 Muramatsu and Harada[63] introduced a method wherein Grignard reagents (1.2 equiv) could be added to titanium tetraisopropoxide (3 equiv) in the presence of 2 mol % 3-(3,5-Ph_2-C_6H_3)-H_8-BINOL and aldehydes to provide diarylmethanols with high ee. In a similar vein, Gau and coworkers employed salt-free Ar_3Al•THF reagents in combination with titanium tetraisopropoxide and either H_8-BINOL[64] or sulfonamide alcohol-based ligands,[65] which led to diarylmethanols with high enantioselectivities. These reactions may proceed via an Ar-Ti intermediate.[66]

At the outset of our research into the arylation of aldehydes in 2005, two major limitations existed. The first was the necessity for salt-free arylzinc reagents. The second was the use of costly aryl sources such as Ph_2Zn and arylboronic acids, which are synthesized from aryl halides. To address these problems, we deemed the following

criteria essential to a practical, cost effective and scalable protocol: 1) to use readily available aryl bromides, and 2) to avoid filtration or centrifugation[20-22,43,67] of metal halide byproducts from the aryl organometallic reagent. Herein we report the full details of the successful development of a method that fulfills these criteria.[68] Thus, metallation of an aryl bromide with *n*-BuLi, transmetallation to zinc, and enantioselective addition to aldehydes in the presence of the MIB-based[69,70] catalyst can now be performed in a one-pot procedure (Equation 2-2).[68] To circumvent the need for tedious sublimation, filtration, or centrifugation of the intermediate arylzinc reagents, we introduced a method to sequester the LiCl byproduct, enabling the generation of diarylmethanols with high levels of enantioselectivity in the presence of lithium chloride. Unfortunately, this procedure was unsuccessful when applied to the generation of enantioenriched diheteroarylmethanols. Therefore, an alternative procedure for heteroaryl additions to aldehydes was developed. To our knowledge, these studies represent the first highly enantioselective catalytic asymmetric synthesis of enantioenriched diheteroarylmethanols.



Equation 2-2

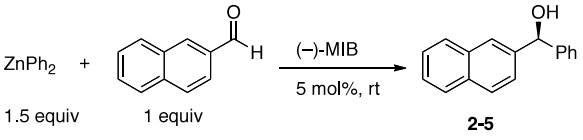
2.2. Prior Work in the Walsh Group

The ultimate goal of these investigations was to develop a practical method for the addition of aryl and heteroaryl groups to aldehydes using readily available aryl and heteroaryl bromides. Asymmetric additions with commercial diphenylzinc were used to evaluate catalyst enantioselectivity and for comparison with reactions using bromobenzene.

2.2.1. Phenylation with Ph2Zn and MIB.

Our first priority was to determine the enantioselectivity of the (–)-MIB-based catalyst in phenyl additions to aldehydes. The substrate selected for these studies conducted by Dr. Jeung Gon Kim was 2-naphthaldehyde (Table 2-1), which was used with commercial $ZnPh_2$ and 5 mol % (–)-MIB.

Table 2-1. Solvent Screen in the Asymmetric Phenyl Addition to 2-Naphthaldehyde.



entry	solvent	ee (%)
1	toluene	94
2	Et_2O	60
3	*t*-BuOMe	88
4	*t*-BuOMe/Hex (1:3)	89
5	*t*-BuOMe/Hex (1:3)	92[a]
6	2 PhLi + $ZnCl_2$ in *t*-BuOMe/Hex (1:3)	2

[a] Reaction conducted at 0° C.

The phenyl addition proceeded with 94% ee in toluene and 60% ee in diethyl ether (entries 1 and 2). Diethyl ether most likely binds to the MIB-based zinc catalyst, reducing its activity and, therefore, enantioselectivity. When less coordinating *tert*-butyl methyl ether (TBME) was used, the diarylmethanol was obtained with 88% ee (entry 3). In the mixed solvent composed of 1:3 TBME:hexanes, 89% ee was observed at room temperature (entry 4) and 92% ee at 0 ºC (entry 5). Of the solvents examined, only TBME was suitable for the salt metathesis of PhLi with $ZnCl_2$.

To evaluate the possibility of beginning with aryl bromides, we next generated $ZnPh_2$ by metallation of 4.5 equiv PhBr with 4 equiv *n*-BuLi in TBME followed by transmetallation with 2 equiv $ZnCl_2$. After addition of hexanes to precipitate additional LiCl, the *in situ*-generated Ph_2Zn solution was used in place of the commercial Ph_2Zn under otherwise identical conditions (Table 2-1, entry 6). The expected alcohol product was isolated, but withs only 2% ee. We hypothesized that the Lewis acidic LiCl, generated en route to $ZnPh_2$, promoted the addition to form the racemate faster than the amino alcohol-based Lewis acid catalyst promoted the asymmetric addition. Other researchers have had varying degrees of success employing either filtration or centrifugation of LiCl and MgX_2 byproducts.[20-22,33,67] These salt byproducts are often produced as a fine particulate and are difficult to remove. Although these procedures are useful on laboratory scale, filtration or centrifugation of highly air-sensitive materials is less practical on large scale. To overcome this problem, our strategy was to inhibit the LiCl byproduct rather than remove it. A similar approach was devised by Bolm and coworkers involving the addition of Ph_2Zn to aldehydes. These researchers observed a beneficial effect of dimethoxypoly(ethylene glycol) (DiMPEG) on the catalyst

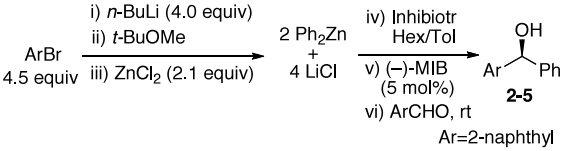
enantioselectivity[43,50] and proposed that DiMPEG suppressed reactions catalyzed by trace achiral Lewis acids, including $ZnBr_2$ and LiBr, allowing the arylation reaction to proceed via the ligand-accelerated[71] pathway.[19] Although selectivities reached 93% ee, yields ranged from 8-31% when Ph_2Zn was generated from PhLi and $ZnBr_2$.[43] Furthermore, we had difficulties with reproducibility using DiMPEG in combination with the MIB-based catalyst for enantioselective vinylation of aldehydes.[72,73]

2.2.2. Development of a Lithium Chloride Selective Inhibitor.

The lack of enantioselectivity with Ph_2Zn generated from PhBr in Table 2-1 (entry 6) suggested that the achiral LiCl is a more active Lewis acid than the (–)-MIB-based zinc catalyst. There are three important differences between the lithium and zinc Lewis acids: 1) the lithium is more electropositive and probably the stronger Lewis acid, 2) the lithium center is less sterically saturated than the zinc center in the MIB-based catalyst and 3) the lithium chloride *has at least two available coordination sites* while the MIB-based zinc catalyst has only one accessible site. Based on this analysis, our strategy was to employ bidentate inhibitors that would chelate lithium and bind tightly, but coordinate in a monodentate fashion to the chiral zinc catalyst. Support for this approach was gained through structures of $[TMEDA{\bullet}LiCl]_n$, which contain four-coordinate lithium centers with bridging chlorides.[74,75]

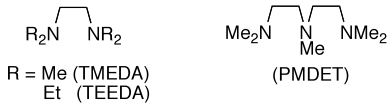
On the basis of this proposal, multidentate amines were screened by Dr. Jeung Gon Kim as LiCl inhibitors in the catalytic enantioselective phenylation of 2-naphthaldehyde with *in situ* prepared $ZnPh_2$ (Table 2-2).

Table 2-2. Examination of Possible LiCl Inhibitors.



entry	inhibitor	equiv.	ee (%)	
1	none	–	2	
2	TEEDA	0.2	55	
3	TEEDA	0.4	76	
4	TEEDA	0.8	83	
5	TEEDA	1.0	83	
6	TEEDA	1.2	77	low conversion
7	TEEDA	0.8	89	*t*-BuOMe/Tol = 1:5
8	TEEDA	0.8	92[b]	*t*-BuOMe/Tol = 1:5
9	TMEDA	0.8	81	
10	TMEDA	1.0	81	
11	PMDET	0.1	51	
12	PMDET	0.2	80	
13	PMDET	0.4	71	

[a] Solvent = *t*-BuOMe/Hex = 1:3 unless noted. [b] Addition conducted at 0 °C



N,N,N',N'-Tetraethylethylenediamine (TEEDA) was first examined, because the amino groups are slightly more hindered than the tetramethyl analog TMEDA. Use of 0.2 equiv TEEDA resulted in an improvement from 2% ee in the absence of diamine to 55% ee (Table 2-2, entries 1 and 2). Increasing the amount of TEEDA from 0.2–0.8 and 1.0 equiv resulted in product enantioselecitvity of up to 83% ee. A further increase in TEEDA to 1.2 equiv, however, resulted in a slower reaction and a decrease in the product ee to 77%, probably due to inhibition of the MIB-based zinc catalyst by the diamine. It

was found that addition of 5 equiv toluene (or hexanes) relative to TBME after transmetallation led to higher enantioselectivity (up to 89% ee, entry 7). When the temperature of the addition was lowered from rt (entry 7) to 0 °C (entry 8) the enantioselectivity increased to 92% ee. It is noteworthy that the same enantioselectivity was obtained with commercial Ph_2Zn in Table 2-1 (entry 5), indicating that TEEDA is an excellent inhibitor of LiCl. For comparison, TMEDA was examined in Table 2-2 (entries 9 and 10) and found to be nearly as effective as TEEDA. Pentamethyldiethylenetriamine inhibited LiCl at lower concentrations (0.2 equiv, 80% product ee, entry 12).

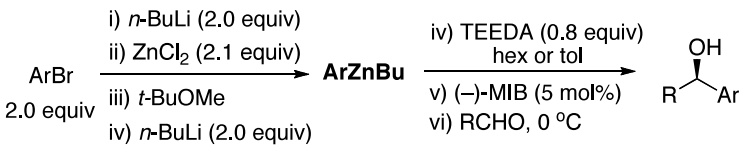
2.2.3. Generation and Application of Mixed Aryl Alkyl Zinc Reagents

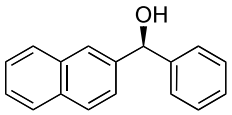
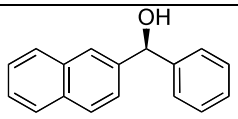
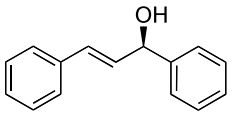
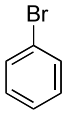
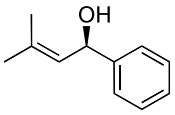
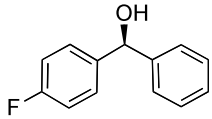
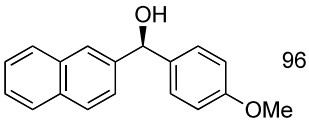
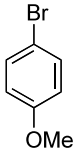
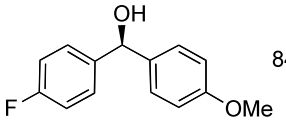
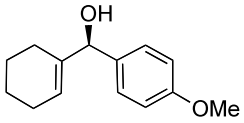
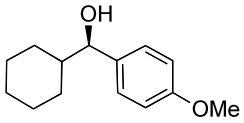
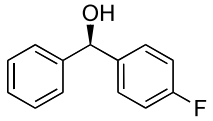
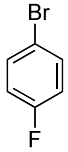
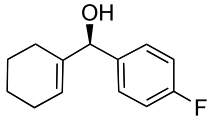
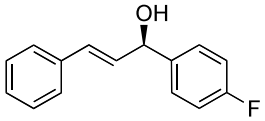
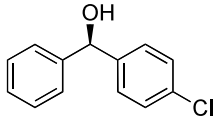
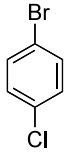
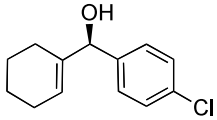
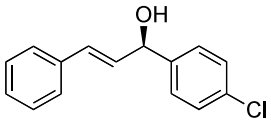
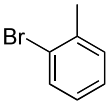
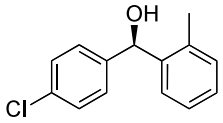
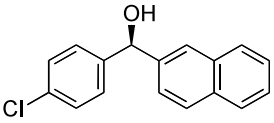
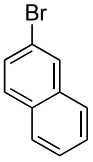
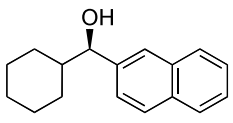
As outlined in the Introduction 2.1, the background reaction of diarylzinc reagents with aldehydes is often competitive with, or faster than the ligand accelerated pathway[71] with amino alcohol-based catalysts. On the basis of the successful application of mixed aryl alkyl zinc reagents by Bolm and co-workers,[33] we desired to develop an in situ route to these species to increase enantioselectivities in the aldehyde arylations. To determine the benefit of the mixed organozinc reagents with MIB, our initial experiments involved conproportionation of a 1:1 ratio of commercial Ph_2Zn and Et_2Zn to generate PhZnEt (Equation 2-1) followed by addition of (–)-MIB and 2-naphthaldehyde at 0 ºC. Under these conditions, the enantioselectivity increased from 92% ee with Ph_2Zn (entry 5, Table 2-1 and entry 8, Table 2-2) to 97% ee with the mixed PhZnEt (Table 2-3, entry 1).

To prepare the mixed aryl alkyl zinc reagents in situ we choose to avoid the use of dialkylzinc reagents, focusing on the more readily available alkyllithiums. Thus, metallation of PhBr with *n*-BuLi (2 equiv each) and addition of 2.1 equiv $ZnCl_2$ resulted in the generation of PhZnCl. A second dose of *n*-BuLi (2 equiv) was then added to produce PhZnBu, which was used in combination with 0.8 equiv TEEDA in the asymmetric addition reaction (Table 2-3, entry 2). Gratifyingly, the enantioselectivity with the in situ generated PhZnBu (97%) was equal to the salt-free PhZnEt, despite the 4 equiv of LiCl in the reaction vessel.

To determine the generality of this method, Dr. Jeung Gon Kim emplyed a series of aryl bromides and aldehydes (Table 2-3). Bromobenzene and 4-substituted aryl bromides bearing OMe, F and Cl were used in the arylation of benzaldehyde derivatives with 93–97% enantioselectivity. 2-Bromotoluene and 2-bromonaphthalene were added to benzaldehydes with ≥93% ee. Aryl additions to α,β-unsaturated aldehydes occurred with 81–90% ee (entries 3, 4, 8, 11, 12, 14 and 15). The aliphatic substrate, cyclohexanecarboxaldehyde, underwent aryl addition with 78–82% ee (entries 9 and 18). The examples in Table 2-3 are the first examples of aldehyde arylation beginning with aryl bromides.[68]

Table 2-3. Catalytic Asymmetric Aryl Additions to Aldehydes with ArZnBu Generated from Aryl Bromides



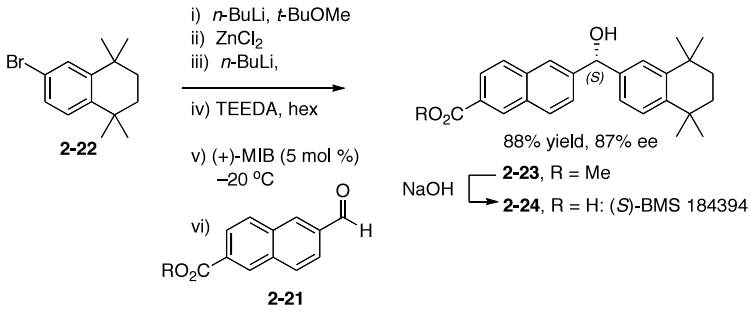
#	ArBr with Ar=	product	yield	ee (%)
2-5	Ph_2Zn/Et_2Zn		--	97
2-5			90	97
2-6			95	88
2-7			75	90
2-8			80	96
2-9			96	93
2-10			84	93
2-11			82	83
2-12			84	78
2-13			75	97
2-14			64	88
2-15			74	84
2-4			78	95
2-16			55	87
2-17			68	81
2-18			73	95
2-19			79	96
2-20			76	82

Subsequent to our initial communication,[68] a related report appeared by Pu[76] employing aryl iodides, and two examples were reported by Harada.[63,77] Woodward also developed a method using arylzinc halides in combination with trimethylaluminum based on the Schlenk equilibrium.[78]

2.2.4. Formal Synthesis of (S)-BMS 184394.

One example of a biologically active diarylmethanol is BMS 184394 (**2-24**, Scheme 2-2), an RAR γ selective retinoid with activity against skin diseases and cancers, in particular breast cancer and acute promyelocytic leukemia.[79-81] It was found that the (*S*)-enantiomer is significantly more potent than the (*R*)-enantiomer.[80] The enantioselective route to this drug candidate employed two sequential enzymatic kinetic resolutions that required 2 and 3.5 days (43% yield and 95% ee).[80] Asymmetric reduction of the requisite diaryl ketone would likely be challenging due to the similar environments of the carbonyl lone pairs.[82-84]

Using conditions outlined in Table 2-3 Dr. Jeung Gon Kim performed the synthesis of BMS 184394. 3.0 Equiv of aryl bromide **2-22** (Scheme 2-2) was employed to generate the mixed aryl butyl zinc reagent. TEEDA (1.5 equiv) and hexanes were added followed by (+)-MIB (5 mol %) and aldehyde **2-21**. The addition product **2-23** was produced with 87% ee in 88% yield (Scheme 2-2). Conversion to (*S*)-BMS 184394 can be accomplished by saponification of the ester.[80]



Scheme 2-2. Synthesis of Enantioenriched **2-23**, the Key Intermediate in the Synthesis of (*S*)-BMS 184394.

2.3. Results and Discussion

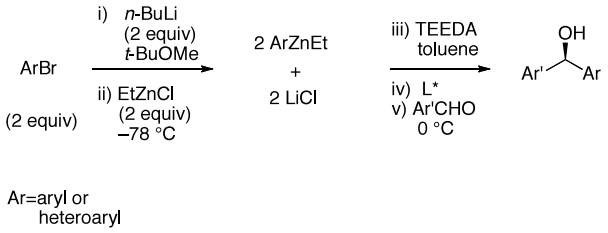
2.3.1. Attempted Heteroaryl Additions to Aldehydes.

General, highly enantioselective additions of heteroaryl groups to aldehydes have not been developed. To our knowledge, the only examples of highly enantioselective heteroaryl additions were published in 2008 by Gau and involved the addition of 2-furyl aluminum reagents to ketones.[85] Heteroaryl groups are among the most important pharmacophores in medicinal chemistry and diheteroarylmethanols have been identified as biologically active structural motifs.[15] Thus, not only would methods for heteroaryl additions to aldehydes increase the classes of enantioenriched diarylmethanols accessible, it would enable the catalytic asymmetric synthesis of diheteroarylmethanols that are currently not directly accessible.

With the goal of introducing asymmetric heteroaryl additions to aldehydes, we applied our arylation procedure to metallation of 3-bromothiophene followed by addition to

benzaldehyde. The only modification was to maintain the temperature of the heteroaryllithium at –78 °C. Unfortunately, no addition product was observed. When the aryl bromides were used under the conditions outlined in Table 2-3, the salt metathesis was conducted at room temperature for 4.5 h.[68] At this temperature the (3-thienyl)Li readily decomposes.

We hypothesized that the absence of product was due to decomposition of the heteroaryllithium in the transmetallation step, which was complicated by the limited solubility of $ZnCl_2$ in TBME at low temperature. To address this problem, we envisaged a more soluble zinc source might undergo transmetallation at lower temperature. Our choice of EtZnCl was based on the large reactivity difference of sp^2 hybridized Zn-C bonds over their sp^3 counterparts. Another advantage of EtZnCl is that only a single equivalent of LiCl forms during the metathesis, whereas $ZnCl_2$ produces two equivalents (Scheme 2-3). Lower levels of salt byproduct facilitate inhibition of the LiCl-promoted background reaction.



Scheme 2-3. Metathesis with EtZnCl for the Aryl and Heteroaryl Additions to Aldehydes.

The synthesis of EtZnCl was initially performed following the method of Woodward and coworkers by combination of $ZnCl_2$ and $ZnEt_2$ in THF followed by removal of the

solvent under reduced pressure.[86] Using EtZnCl prepared in this manner, the transmetallation proceeded at –78 °C and the desired heteroaryl addition products were obtained. Unfortunately, product yields and ee's varied greatly from run to run. Our unsuccessful attempts to develop asymmetric heteroaryl additions convinced us to first focus on development of a low temperature transmetallation and then revisit enantioselective heteroaryl additions.

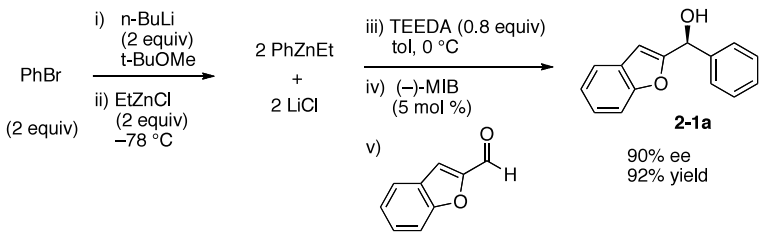
2.3.2. Development of Low Temperature Transmetallation Conditions and Synthesis of Biologically Active 2-2a.

Momentarily stepping away from the more challenging enantioenriched diheteroarylmethanols, we concentrated on developing low temperature conditions for lithium to zinc transmetallations. We attributed the inconsistencies in the previously described heteroaryl additions to the presence of residual zinc-bound THF in the EtZnCl, which was observed by ^{1}H NMR spectroscopy.[86] THF is known to inhibit the MIB-based zinc Lewis acid catalyst. On the basis of this hypothesis, an alternative synthesis of EtZnCl was pursued.[87-89] Using toluene in place of THF required heating $ZnEt_2$ and sparingly soluble $ZnCl_2$ at 60 °C for 72 h, after which the solution was filtered to remove any unreacted $ZnCl_2$. The volatiles were then removed under reduced pressure to afford EtZnCl as a white solid that could be stored under nitrogen for months.

The THF-free EtZnCl was first employed with bromobenzene (Equation 2-3). The transmetallation was conducted at –78 °C to generate PhZnEt, and the addition to 2-benzofurancarbaldehyde was performed at 0 °C. After 12 h, the reaction mixture was

quenched with water, worked up, and purified on deactivated silica. We were pleased to isolate the desired addition product **2-1a** in 92% yield with 90% ee (Equation 2-3). Compound **2-1a** was converted to the promising breast cancer treatment candidate **2-2a** (Figure 2-1) without loss of ee in 41% unoptimized yield (84% based on recovered **2-1a** of 90% ee) via a Mitsunobu reaction with imidazole.[90] S_N2 substitutions of this type are known to be very difficult.[1] Alternative methods for this transformation also appear potentially useful.[92-95]

Recently promising diarylmethanes have been examined as possible inhibitors and receptor agonist candidates, but due to limited methods to synthesize the diarylmethanols enantioselectively, most of the studies employed racemic material.[11,96,97] Synthesis of **2-1a** with 90% ee suggests that this procedure can be used to prepare diarylmethanols and their derivatives with high ee.



Equation 2-3

2.3.3. Enantioselective Addition of Heteroaryl Groups to Aldehydes.

The heteroaryl addition was attempted with 3-bromothiophene under the conditions employed with bromobenzene to generate **2-1a** in Equation 2-3. Thus, after metallation of 3-bromothiophene with *n*-BuLi, transmetallation was performed at –78 °C with THF-

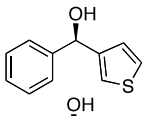
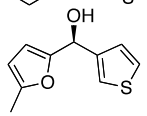
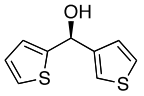
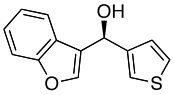
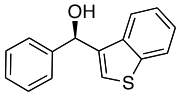
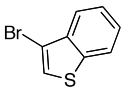
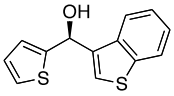
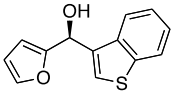
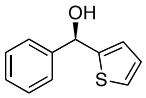
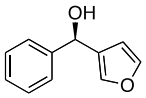
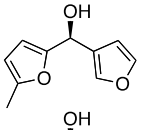
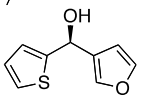
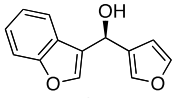
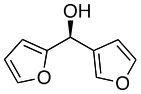
free EtZnCl. The resulting solution was then warmed to 0 °C and TEEDA, (–)-MIB, and benzaldehyde were added (Table 2-4). After stirring 12 h, followed by workup and purification, we were pleased to isolate the desired heteroaryl addition product in 68% yield with 90% ee (Table 2-4, entry 1). These revised conditions led to reproducible product ee's and yields.

To explore the enantioselective synthesis of diheteroarylmethanols, the optimized conditions for addition of (3-thienyl)ZnEt to benzaldehyde were employed with heteroaromatic aldehydes. Thus, addition to 5-methyl-2-furan carboxaldehyde, 2-thiophenecarboxaldehyde and 3-benzofurancarboxaldehyde occurred with 92–94% enantioselectivity in 60–83% yield (Table 2-4, entries 2–4). The differences in yields in entries 1–4 probably arise from a combination of the instability of the heteroaryl organometallic reagents and diminished electrophilicity of the heteroaromatic aldehydes. To develop practical and useful methods, scalability must be demonstrated. Thus, for the synthesis of **2-27**, precursor to potential drug candidate **2-3** (Figure 2-1), the asymmetric addition was scaled to produce 820 mg (83% yield and 93% ee, entry 3).

Other heterocycles such as 3-bromobenzothiophene can also be used in the addition with very good enantioselectivities (81–88% ee, entries 5–7). Employing 2-bromothiophene and benzaldehyde afforded diarylmethanol in 90% ee and 57% yield (entry 8). In a similar fashion 3-furanyl ethyl zinc can be added to benzaldehyde (93% ee, 86% yield, entry 9) and heteroaromatic aldehydes with excellent enantioselectivities (89–99% ee, entries 11–13). 5-Methyl-2-furan carboxaldehyde gave addition product of 80% ee (entry 10). Attempts to add 2-furanylzinc reagents to aldehydes, however,

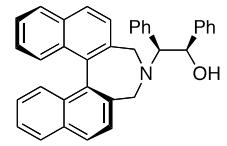
resulted in poor enantioselectivities, probably due to the presence of the coordinating oxygen in close proximity to zinc.

Table 2-4. Synthesis of Aryl Heteroaryl- and Diheteroarylmethanols using 5 mol % (–)-MIB (unless noted below).

entry	ArheteroBr	product	#	yield	ee (%)
1			**2-25**	68	90
2[a]			**2-26**	72	92
3			**2-27**	83	93
4			**2-28**	60	94
5[a]			**2-29**	65	88
6[a]			**2-30**	70	81
7[a]			**2-31**	70	82
8[a]			**2-32**	57	90
9			**2-33**	86	93
10[a]			**2-34**	67	80
11			**2-35**	60	99
12			**2-36**	79	94
13			**2-37**	61	89

a 10 mol % MIB. See SI for details.

To determine if our method for addition of heteroaromatic groups to aldehydes could be extended to other catalysts, we examined the use of Chan's ligand (**L2**, Figure 2-2)[48,98] with 3-bromothiophene and benzaldehyde under the conditions listed in Table 2-4, which led to product of 90% ee and 70% yield. These results are virtually identical to those in entry 1 (Table 2-4) with MIB, indicating that our strategy employing TEEDA to inhibit LiCl is applicable to other amino alcohol-based catalysts.



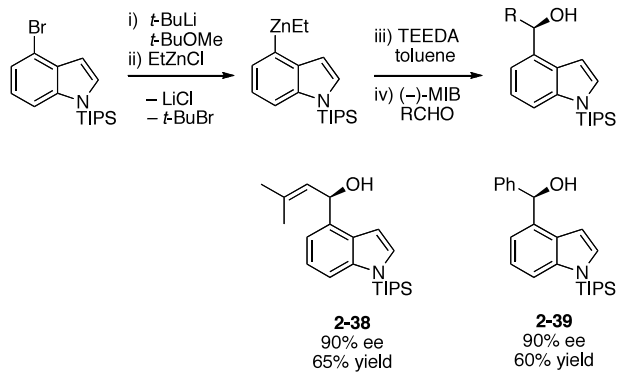
(1S_a,2*S*,3*R*)binaphthyl
L2

Figure 2-2. Structure of Chan's ligand (**L2**).

2.3.4. Synthesis of Indole Methanols

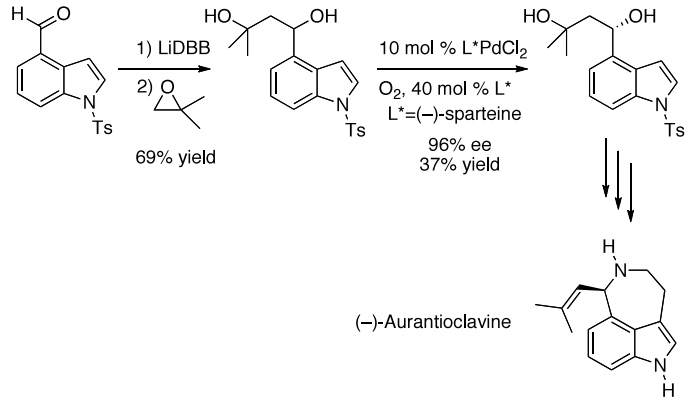
Indoles are regarded as privileged structures in medicinal chemistry and are substructures of an enormous variety of natural products.[99,100] We therefore turned our attention toward the synthesis of enantioenriched diarylmethanols containing the indole motif. Metallation of *N*-silyl-protected 4-bromoindole with *n*-BuLi was unsuccessful under a variety of conditions, including those in Table 2-4, most likely due to the electron rich nature of the heterocyclic π-system. More challenging metal-halogen exchange reactions are generally performed with two equiv *t*-BuLi.[101] In these reactions, the first equiv undergoes the metal-halogen exchange with the aryl bromide generating *t*-BuBr and the second drives the equilibrium by promoting elimination of the liberated *t*-BuBr to produce isobutylene and LiBr. Unfortunately, diamines that inhibit LiCl had little impact when LiBr was formed. Although we do not understand the intimate differences between LiCl and LiBr at this time, we speculate that weaker bridging Li-Br interactions in $[(\text{diamine})\text{LiBr}]_n$ facilitate dissociation of the oligomers, opening a coordination site on lithium. To avoid production of LiBr, a 1:1 ratio of 4-bromoindole to *t*-BuLi was

employed, furnishing indole-based diarylmethanols with 90% ee and 60–65% yield (Equation 2-4).



Equation 2-4.

It is noteworthy that enantioenriched indole **2-38** is a potential intermediate for the synthesis of (–)-aurantioclavine, which is illustrated in Scheme 2-4 along with related intermediates in the elegant synthesis of this alkaloid by Stoltz and coworkers.[102]

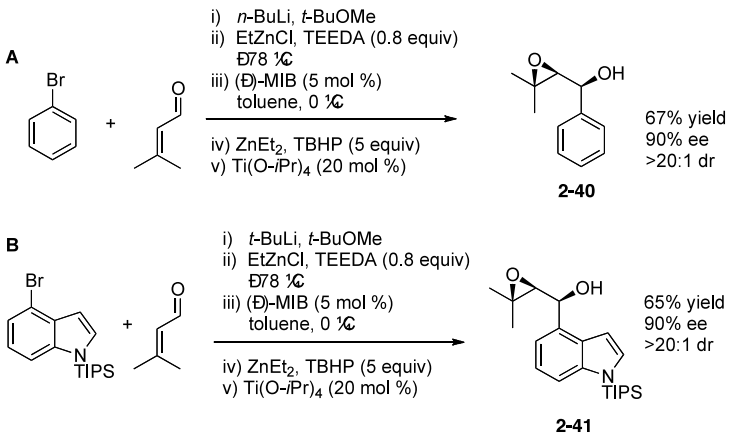


Scheme 2-4. Structure of (–)-Aurantioclavine and Intermediates in its Synthesis by Stoltz and Coworkers.[102]

2.3.5. Tandem Asymmetric Aryl Addition/Diastereoselective Epoxidation.

We recently developed a series of tandem reactions involving the asymmetric addition of alkyl,[103-105] vinyl,[73,103,106,107] or allyl[108] groups to aldehydes and ketones followed by diastereoselective epoxidation to provide epoxy alcohols with three contiguous stereogenic centers.[109] These one-pot procedures rapidly increase molecular complexity in a synthetically efficient fashion. To explore the possibility of performing arylation and heteroarylation of enals followed by diastereoselective epoxidation, we examined asymmetric phenyl addition/oxidation with 3-methyl-2-butenal. As shown in Scheme 2-5A, using the conditions outlined in Table 2-4 the catalytic asymmetric phenyl addition was performed. The resulting enantioenriched zinc allylic alkoxide was then treated with Et_2Zn (1 equiv), TBHP (*tert*-butylhydroperoxide, 5 equiv), and 20 mol % titanium tetraisopropoxide at 0 ºC. The epoxidation reached completion in 3 h, after which the reaction mixture was quenched, worked up, and the product purified by chromatography to afford the epoxy alcohol in 67% yield with 90% ee and >20:1 dr (as determined by ^1H NMR). The heteroarylation/epoxidation was examined with the TIPS protected 4-bromoindole (Scheme 2-5B). Metallation with *t*-BuLi, transmetallation with EtZnCl, and asymmetric addition as performed in Equation 2-4 was followed by addition of Et_2Zn, TBHP and 20 mol % titanium tetraisopropoxide at 0 ºC. Following workup and purification, the enantioenriched indole epoxy alcohol was isolated in 65% yield with 90% ee and >20:1 dr. Interestingly, attempted epoxidation of the isolated indole allylic alcohol product in Equation 2-4 with *m*-CPBA resulted in formation of the epoxy alcohol in low yield accompanied by several side products. The examples in Scheme 2-5 indicate

that the asymmetric arylation and heteroarylation are compatible with our tandem diastereoselective epoxidation conditions and could be used to prepare an array of functionalized epoxy alcohols.

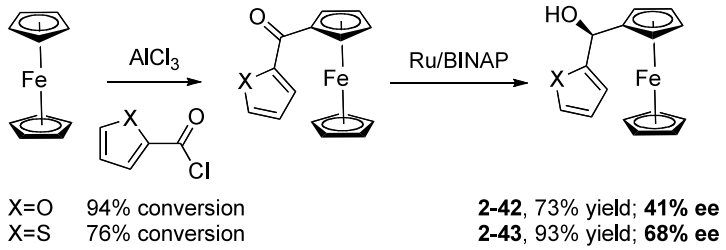


Scheme 2-5. Tandem Asymmetric Arylation of Aldehydes/Diastereoselective Epoxidation.

2.3.6. Synthesis of Ferrocenylzinc and Applications to Asymmetric Additions.

Having developed successful methods for the enantioselective addition of aryl and heteroaryl groups to aldehydes, we focused on the generation of the ferrocenylzinc reagent, (Fc)ZnEt. Highly enantioselective additions of ferrocenylzinc reagents to aromatic and heteroaromatic aldehydes would provide rapid access to heteroaryl ferrocenyl methanols. Related motifs[110,111] are precursors to important enantioenriched ferrocene-based ligands such as BoPhoz,[112] Josiphos,[113] FERRIPHOS,[114,115] Pigiphos,[116,117] PPFA,[118] Walphos,[119] Taniaphos[120] and Trap.[112,121,122] The ferrocenyl methanol scaffold is often synthesized by CBS (Corey-Bakshi-Shibata)[123-125] or Ru/BINAP (Noyori

asymmetric hydrogenation) reduction of ferrocenyl ketones.[4,122,126] Asymmetric reduction of heteroaromatic ketone derivatives, however, resulted in only moderate enantioselectivity (X=O, 41% ee; X=S, 68% ee, Equation 2-5).[127]



Equation 2-5.

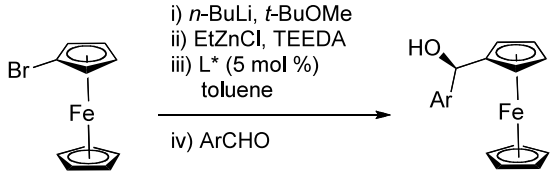
Beginning with ferrocenyl bromide (FcBr) and applying the conditions used in Table 2-4 to the generation and addition of (Fc)ZnEt to benzaldehyde with (–)-MIB provided product with a disappointing 50% ee (Table 2-5, entry 1).

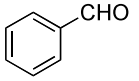
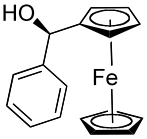
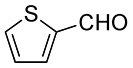
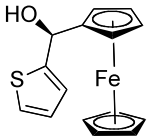
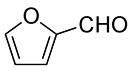
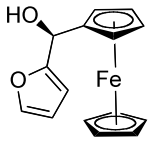
Inspired by the importance of functionalized ferrocenyl methanols, we screened other amino alcohol ligands. Fortunately, use of Chan's[48,98] amino alcohol **L2** (Figure 2-2) with benzaldehyde provided the desired product in 86% yield with 98% ee (Table 2-5, entry 2). Use of 2-thiophenecarboxaldehyde and 2-furfural in combination with **L2** provided the ferrocene-based ligand precursors with enantioselectivities of 96% and yields of 95% (entries 3 and 4).

It is known that substitution of furyl groups for phenyl can lead to an increase in catalyst enantioselectivity.[128]

The high yields and stereochemical purity of functionalized ferrocenes make them attractive building blocks for the construction of new ferrocene-based ligands for asymmetric catalysis.

Table 2-5. Asymmetric Addition of (Fc)ZnEt to Aldehydes.



entry	ligand	ArCHO	product	#	yield	ee (%)
1	(Đ)-MIB			**2-44**	75	50
2	**L2**				86	98
3	**L2**			**2-43**	95	96
4	**L2**			**2-42**	95	96

2.4. Summary and Outlook

Herein we described versatile methods for the generation of diaryl- aryl heteroaryl-, and diheteroarylmethanols with high levels of enantioselectivity. The significance of these methods is that asymmetric arylation of aldehydes can now be initiated with aryl bromides, many of which are readily available. Key to the success of our procedures was

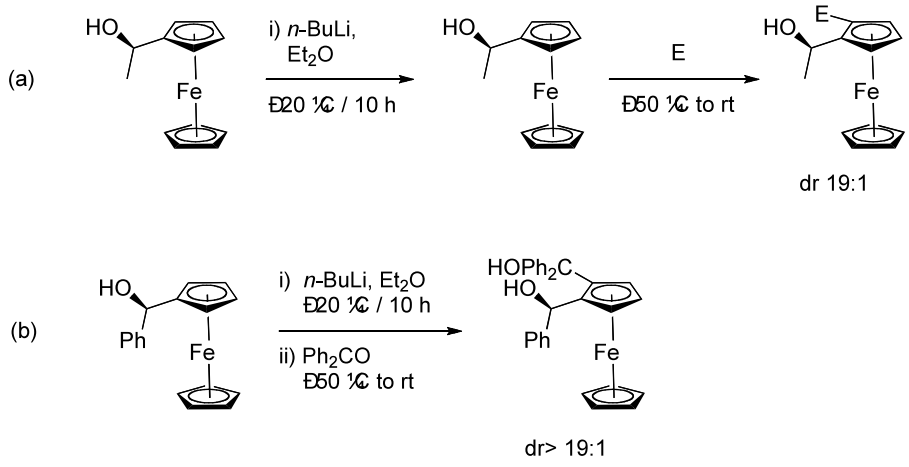
the introduction of a diamine, such as TEEDA. In the absence of TEEDA the addition reaction was promoted by LiCl, generating racemic products. The TEEDA inhibited the LiCl byproduct, allowing the asymmetric addition to proceed via the ligand accelerated pathway.[71,129] Importantly, in the presence of the diamine it was not necessary to filter,[43] centrifuge,[67] or isolate the pyrophoric arylzinc reagents as was required with previous procedures, making our method suitable for large scale applications.

We also developed the first method for the synthesis of highly enantioenriched diheteroarylmethanols from readily available heteroaryl bromides. A crucial feature of this approach was the use of EtZnCl in the transmetallation step with the heteroaryllithium at –78 °C, at which temperature decomposition of the heteroaryl organometallic species was minimized. Use of EtZnCl in place of $ZnCl_2$ also halves the amount of LiCl byproduct, which had been detrimental to the enantioselectivity in the asymmetric addition and which must be inhibited by diamine. This method was also shown to be applicable to the tandem asymmetric addition/diastereoselective epoxidation to generate epoxy alcohols with two stereogenic centers in high enantio- and diastereoselectivity.

The straightforward methods introduced herein make possible the synthesis of functionalized, previously inaccessible enantioenriched diheteroarylmethanols. We anticipate that these methods will be useful in medicinal chemistry and asymmetric catalysis.

Finally, we also described the first examples of generation and highly enantioselective addition of ferrocenyl zinc reagents to aldehydes, opening the door to new enantioenriched ferrocene-based ligands. In particular we wanted to investigate the

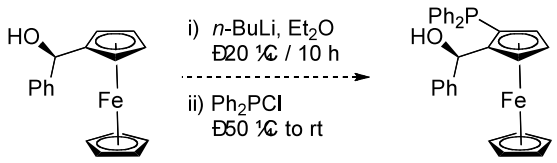
possibility of synthesizing new ligands *via* ortho lithiation of ferrocenyl alcohols. The Ueberbacher group recently published a report in which they were able to perform the ortho lithiation employing the free ferrocenyl alcohol. Upon quenching with an electrophile they obtained the functionalized ferrocenyl methanols with excellent dr's. Most of their examples employed the methyl-ferrocenyl methanol, but they also had one example employing phenyl ferrocenyl methanol (the racemic mixture of 2-44 reported herein in Table 2-5) where the electrophile used was benzophenone (Scheme 2-6).[130]



Scheme 2-6. Ortho-Lithiation of a) Free Methyl Ferrocenyl Alcohols and b) Free Phenyl Ferrocenyl Alcohols.

What we would like to do with the compounds synthesized in Table 2-5 is to use them as a scaffold for the synthesis of new chiral ligands. The reaction of 2-44 using the method outlined above, followed by quenching with Ph_2PCl was our first attempt. Unfortunately the desired product was not observed and the starting material could not be

recovered (Scheme 2-7). More studies are necessary to solve this problem that could provide access to a new class of enantioenriched chiral ligands.



Scheme 2-7. Designing Ferrocenyl Phosphorous Ligand *via* Ortho Lithiation of Free Ferrocenyl Phenyl Methanol.

2.5. Experimental Section

General Considerations

All reactions were performed under a nitrogen atmosphere with oven-dried glassware using standard Schlenk or vacuum-line techniques. The progress of reactions was monitored by thin-layer chromatography (TLC) performed on Whatman precoated silica gel 60 Å K6F plates and visualized by ultra-violet light or by staining with cerium-ammonium-molybdate. *t*-BuOMe was distilled from Na/benzophenone and toluene was dried through alumina columns. TEEDA was distilled and stored under nitrogen. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra were obtained on a Brüker Fourier transform NMR spectrometer at either 300 or 500 and 75 or 125 MHz, respectively. ^{1}H NMR spectra were referenced to tetramethylsilane in $CDCl_3$ or residual protonated solvent; $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent. Analysis of enantiomeric excess was performed using a Hewlett-Packard 1100 Series HPLC and a chiral column. Alternatively, a Berger SFC PioNTo™ ® was employed when the compounds could not be resolved by HPLC. The optical rotations were recorded using a JASCO DIP-370. Infrared spectra were obtained using a Perkin-Elmer Spectrum 100 Series spectrometer. All reagents were purchased from Aldrich or Acros unless otherwise described. 3-Benzofurancarboxaldehyde was synthesized according to known procedure starting from commercially available 3-methylbenzofuran.[131] Binaphthyl amino alcohol ligand was synthesized according to Chan's procedure.[48,98] EtZnCl was synthesized following

Guerrero's method.[87,132] All aldehyde substrates were distilled prior to use. Silica gel (Silicaflash P60 40-63 μm, Silicycle) was used for air-flashed chromatography.

Caution. Dialkylzinc and alkyl lithium reagents are pyrophoric. Care and appropriate laboratory equipment must be used when handling these reagents.

2.5.1. Arylation of Aldehydes.

Preparation of (4-Fluoro-phenyl)-(4-methoxy-phenyl)-methanol (2-10): A nitrogen purged Schlenk flask was charged with 4-bromoanisole (100.1 μL, 0.8 mmol) and *t*-BuOMe (1 mL) and cooled to –78 ºC. *n*-BuLi (0.32 mL, 2.5 M in hexanes, 0.8 mmol) was added dropwise and the solution was stirred for 1 h and the temperature raised to 0 ºC. $ZnCl_2$ (114.5 mg, 0.84 mmol) was added to the reaction mixture and it was stirred for 30 min. Additional *n*-BuLi (0.32 mL, 2.5 M in hexanes, 0.8 mmol) was added to the reaction mixture and the resulting solution was allowed to warm to rt and stirred 4.5 h. Toluene (5 mL) and TEEDA (68 μL, 0.32 mmol) were added to the reaction vessel and the solution was stirred. After 1 h (–)-MIB (4.8 mg, 0.02 mmol) was added and the reaction vessel was cooled to 0 ºC for 30 min. Finally, 4-fluorobenzaldehyde (43 μL, 0.4 mmol) was added and reaction mixture was stirred at 0 ºC and monitored by TLC. After completion (12 h), the reaction mixture was quenched with H_2O (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by

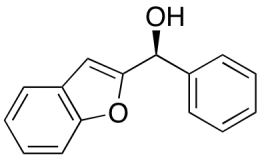
column chromatography on silica gel (hexanes:EtOAc, 95:5) to give **2-10** (77.7 mg, 84% yield) as a white crystalline solid (m. p. = 52 ºC). The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 95:5, flow rate = 0.5 mL/min), t_r (1) = 20.0 min, t_r (2) = 22.1 min, $[\alpha]_D^{20}$ = +13.8 (*c* = 0.195, THF, 93% ee); ^{1}H NMR (C_6D_6, 300 MHz): δ 2.17 (s, 1H), 3.38 (s, 3H), 5.50 (s, 1H), 6.81-6.95 (m, 4H), 7.17-7.29 (m, 4H); ^{13}C{^{1}H} NMR (C_6D_6, 75 MHz): δ 55.0, 75.3, 114.3, 115.4 (d, *J* = 21.2 Hz), 128.4, 128.7 (d, *J* = 8.0 Hz), 136.9, 141.0 (d, *J* = 3.0 Hz), 159.7, 162.6 (d, *J* = 243 Hz); IR (neat): 831, 1033, 1248, 1504, 1609, 2837, 2957, 3422 cm^{-1}; HRMS calcd for $C_{14}H_{13}FO_2$ $(M)^+$: 232.0900, found: 232.0900.

2.5.2. Synthesis and characterization of Heteroaryl- and Diheteroarylmethanols

General Procedure A. A nitrogen purged Schlenk flask was charged with 3-bromofuran (67.0 μL 0.75 mmol) and *t*-BuOMe (1 mL) and cooled to –78 °C. *n*-BuLi (0.3 mL, 2.5 M in hexanes, 0.75 mmol) was then added dropwise and the solution was stirred for 1 h at this temperature. During this time a white precipitate formed. EtZnCl (97.0 mg, 0.75 mmol) was added to the reaction flask as a solid at –78 °C followed by toluene (3 mL). The heterogeneous solution was stirred at –78 °C for 30 min and then warmed at 0 °C. TEEDA (64 μL, 0.30 mmol) was added and the solution stirred for an additional 30 min. (–)-MIB (190 μL, 0.1 M solution in hexanes, 0.019 mmol) was added to the reaction flask and the solution was stirred for 5 min before 2-thiophenecarboxaldehyde (35 μL, 0.37 mmol, dissolved in 1.5 mL of toluene) was added

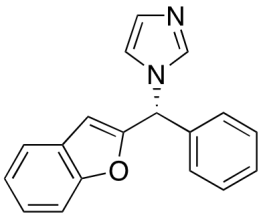
over 1.5 h by syringe pump. The reaction mixture was stirred at 0 °C and monitored by TLC until completion (approximately 10 h). The reaction mixture was diluted with 3 mL EtOAc and quenched with water (5 mL). The organic layer was separated and the aqueous solution extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica gel.

General Procedure B. This procedure is exactly the same as General Procedure A except that the catalyst loading was 10% mol.



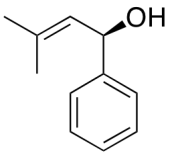
Benzofuran-2-yl(phenyl)methanol (2-1a). General Procedure A was applied to 2-benzofurancarboxaldehyde (36.5 mg, 0.25 mmol) and bromobenzene (53 μL, 0.50 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-1a** (51.7 mg, 92% yield) as a yellow solid. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 98:2, flow rate = 0.5 mL/min), t_r (1) = 44.6 min, t_r (2) = 48.4 min, $[\alpha]_D^{20}$ = +3.5 (c = 0.041, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.49 (d, J = 4.5 Hz, 1H), 5.97 (d, J = 4.5 Hz, 1H), 6.54 (s, 1H), 7.18-7.24 (m, 3H), 7.33-7.44 (m, 3H), 7.49-7.53 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 70.9, 104.3, 111.6, 121.4, 123.1, 124.5, 127.0, 128.3, 128.6, 128.9, 140.0, 155.3, 158.0; IR (neat): 3389, 3019, 2960, 2925, 2873, 1706, 1597, 1496, 1452, 1264, 1200,

1124 cm^{-1}; HRMS calcd for $C_{15}H_{11}O$ $(M\text{-}OH)^+$: 207.0810, found 207.0802. The data collected are in agreement with previously published results.[133,134]

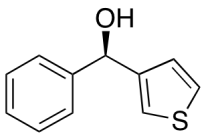


1-(benzofuran-2-yl(phenyl)methyl)-1*H*-imidazole (2-2a). A 10 mL Schlenk flask was charged with benzofuran-2-yl(phenyl)methanol (43.5 mg, 0.19 mmol) and THF (1 mL). PPh_3 (66.0 mg, 0.25 mmol) and imidazole (17.2 mg, 0.25 mmol) were quickly weighted into the flask and stirred at 0 °C for 5 min. Finally DIAD (diisopropyl azodicarboxylate) (50 μL, 0.25 mmol) was added and the reaction stirred at room temperature for 12 h. The volatile materials were removed *in vacuo* and the oil thus obtained was dissolved in DCM (5 mL) and washed with water (3 mL). The water layer was then extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine (5 mL) dried over $MgSO_4$, filtered, and the volatile material were removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica gel (hexanes/2-propanol : 95/5) to give **2-2a** (22 mg, 41% yield) as a yellow solid. 18 mg of **1** (0.08 mmol) were recovered unreacted but with no loss of ee. Thus the yield based on recovered starting material was 84%. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 90:10, flow rate = 0.5 mL/min), t_r (1) = 24.6 min, t_r (2) = 32.6 min, $[\alpha]_D^{20}$ = –2.7 (*c* = 0.027, $CHCl_3$, 90% ee); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.51 (t, *J* = 0.9 Hz, 1H), 6.62 (s, 1H), 6.99 (t, *J* = 1.2 Hz, 1H), 7.14 (t, *J* = 1.2 Hz, 1H), 7.20-7.28 (m, 4H), 7.30-7.35 (m, 1H), 7.39-7.42 (m, 3H) 7.45-7.49 (m, 1H) 7.53-7.57 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75

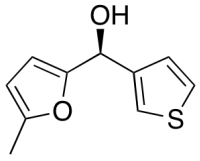
MHz): δ 59.5, 107.4, 111.7, 119.1, 121.5, 123.4, 125.3, 127.6, 129.1, 129.2, 129.7, 136.8, 137.2, 154.1, 155.4; IR (neat): 3442, 3191, 3146, 3056, 2980, 2930, 1968, 1899, 1821, 1721, 1590, 1483, 1453, 1437, 1373, 1310, 1279, 1254, 1226, 1196, 1120, 1072, 1028, 997 cm^{-1}; HRMS calcd for $C_{18}H_{15}N_2O$ $(MH)^+$: 275.1184, found 275.1184. The data collected are in agreement with previously published results.[8]



3-Methyl-1-phenylbut-2-en-1-ol (2-7). General Procedure A was applied to 3-methyl-2-butenal (24.2 μL, 0.25 mmol) and bromobenzene (53.0 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-7** (35.1 mg, 85.9% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 55.1 min, t_r (2) = 60.9 min, $[\alpha]_D^{20}$ = –118.3 (*c* = 0.106, $CHCl_3$, 90% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.74 (d, *J* = 1.1 Hz, 3H), 1.80 (d, *J* = 1.1 Hz, 3H), 1.86 (d, *J* = 2.9 Hz, 1H), 5.40 (dt, *J* = 1.1, 8.8 Hz, 1H), 5.45 (dd, *J* = 3.0, 8.8 Hz, 1H), 7.22-7.27 (m, 1H), 7.31-7.39 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 18.2, 25.8, 70.7, 125.8, 127.2, 127.7, 128.4, 135.2, 144.2; IR (neat): 3335, 3085, 3062, 3029, 2972, 2913, 2792, 1948, 1880, 1806, 1674, 1602, 1492, 1450, 1375, 1332, 1281, 1249, 1195, 1109, 1075 cm^{-1}; HRMS calcd for $C_{11}H_{14}ONa$ $(M+Na)^+$: 185.0966, found 185.0948. The data collected are in agreement with previously published results.[135]

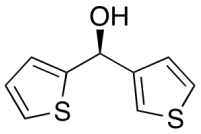


Phenyl(thiophen-3-yl)methanol (2-25). General Procedure A was applied to benzaldehyde (38 μL, 0.38 mmol) and 3-bromothiophene (70 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-25** (44.0 mg, 68% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 65.5 min, t_r (2) = 69.0 min, $[\alpha]_D^{20}$ = –19.5 (*c* = 0.026, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.18 (d, *J* = 4.3 Hz, 1H), 5.88 (d, *J* = 4.3 Hz, 1H), 6.98 (dd, *J* = 1.5, 4.3 Hz, 1H), 7.16 (m, 1H), 7.24-7.29 (m, 2H), 7.32-7.39 (m, 5H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 72.8, 121.6, 126.1, 126.3, 126.4, 127.7, 128.5, 143.3, 145.2; IR (neat): 3944, 3756, 3691, 3595, 3054, 2987, 2685, 2522, 2411, 2372, 2305, 2126, 2055, 1603, 1551, 1493, 1421, 1265, 1149, 1080, 1020 cm^{-1}; HRMS calcd for $C_{11}H_9S$ $(M\text{-}OH)^+$: 173.0425, found 173.0430. The data collected are in agreement with previously published results.[136,137]

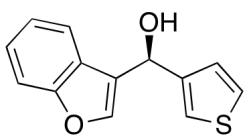


(5-methylfuran-2-yl)(thiophen-3-yl)methanol (2-26). General Procedure B was applied to 5-methyl-2-furancarboxaldehyde (37 μL, 0.37 mmol) and 3-bromothiophene (70 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-26** (52.0 mg, 72% yield) as a yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 98:2, flow rate = 0.5 mL/min), t_r (1) = 57.8 min, t_r (2) = 62.8 min, $[\alpha]_D^{20}$ = +11.5 (*c* = 0.024, $CHCl_3$, 92% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30 (m, 4H), 5.85 (d, *J* = 5.1 Hz, 1H), 5.91 (m 1H), 6.04

(d, J = 3.7 Hz, 1H), 7.12 (m, 1H), 7.31 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): δ 13.8, 66.8, 106.4, 108.5, 122.4, 126.2, 126.7, 142.4, 152.6, 154.0; IR (neat): 3370, 3105, 2920, 1560, 1420, 1262, 1218, 1148, 1018 cm^{-1}; HRMS calcd for $C_{10}H_{10}O_2Na$ $(M+Na)^+$: 217.0299, found 217.0302.

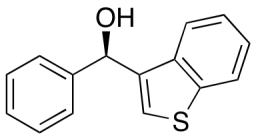


Thiophen-2-yl(thiophen-3-yl)methanol (2-27). General Procedure A was applied to 2-thiophenecarboxaldehyde (470 μL, 0.37 mmol) and 3-bromothiophene (940 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-27** (820 mg, 83% yield) as a solid. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 97:3, flow rate = 0.5 mL/min), t_r (1) = 43.6 min, t_r (2) = 48.9 min, $[\alpha]_D^{20}$ = +5.0 (c = 0.015, $CHCl_3$, 93% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.35 (d, J = 4.5 Hz, 1H), 6.15 (d, J = 4.5 Hz, 1H), 6.96-6.98 (m 2H), 7.10-7.12 (m, 1H), 7.28-7.29 (m, 1H), 7.31-7.33 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): δ 69.1, 122.1, 125.1, 125.6, 126.4, 126.6, 126.9, 144.8, 147.7; IR (neat): 3234, 3108, 2957, 2923, 1438, 1417, 1362, 1291, 1274,1227, 1215, 1177, 1134, 1075, 1024 cm^{-1}; HRMS calcd for $C_9H_9OS_2$ $(MH)^+$: 197.0095, found 197.0095. The title compound was observed as a byproduct but not fully characterized in the work of Ravikanth, thus a full characterization is herein reported.[138]



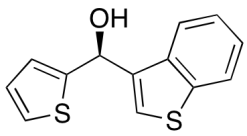
Benzofuran-3-yl(thiophen-3-yl)methanol (2-28). General Procedure A was applied to 3-benzofurancarboxaldehyde (36.5 mg,

0.25 mmol) and 3-bromothiophene (47 μL, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-28** (18.0 mg, 60% yield) as a thick oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 97.5:2.5, flow rate = 0.5 mL/min), t_r (1) = 76.2 min, t_r (2) = 83.9 min, $[\alpha]_D^{20}$ = +29.5 (*c* = 0.010, $CHCl_3$, 94% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.26 (d, *J* = 5.0 Hz, 1H), 6.16 (d, *J* = 4.0 Hz, 1H), 7.13-7.15 (m, 1H), 7.20-7.24 (m, 1H), 7.29-7.38 (m, 3H), 7.49-7.52 (m, 2H), 7.58 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 65.7, 111.6, 120.6, 122.2, 122.8, 123.4, 124.6, 126.0, 126.3, 126.4, 142.3, 143.7, 155.8; IR (DCM): 3944, 3756, 3691, 3594, 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2126, 2054, 1579, 1551, 1421, 1265, 1135, 1105, 1075, 1010 cm^{-1}; HRMS calcd for $C_{13}H_{10}O_2S$ $(M)^+$: 230.0402, found 230.0406.

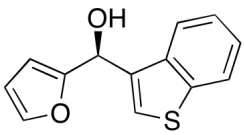


Benzo[*b*]thiophen-3-yl(phenyl)methanol (2-29). General Procedure B was applied to benzaldehyde (37.8 μL, 0.37 mmol) and 3-bromobenzothiophene (98 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-29** (57 mg, 65% yield) as a white solid. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 98:2, flow rate = 0.5 mL/min), t_r (1) = 50.7 min, t_r (2) = 54.0 min, $[\alpha]_D^{20}$ = +7.0 (*c* = 0.020, $CHCl_3$, 88% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (d, *J* = 4.2 Hz, 1H), 6.18 (d, *J* = 4.2 Hz, 1H), 7.27-7.39 (m, 6H), 7.45-7.48 (m, 2H), 7.71-7.75 (m, 1H), 7.83-7.86 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 72.5, 122.9, 123.1, 124.1, 124.3, 124.7, 127.1, 128.3, 128.9, 137.5, 138.8, 141.2, 142.4;

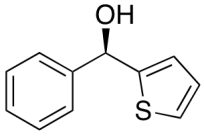
IR (neat): 3351, 3061, 3028, 2955, 2880, 1949, 1903, 1732, 1602, 1562, 1524, 1493, 1455, 1428, 1366, 1334, 1288, 1256, 1196, 1174, 1156, 1110, 1089, 1055, 1018, 1004 cm^{-1}; HRMS calcd for $C_{15}H_{11}S$ $(M\text{-}OH)^+$: 223.0581, found 223.0565. The data collected are in agreement with previously published results.[134]



Benzo[*b*]thiophen-3-yl(thiophen-2-yl)methanol (2-30). General Procedure B was applied to 2-thiophenecarboxaldehyde (35 μL, 0.37 mmol) and 3-bromobenzothiophene (98 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 90/10) to give **2-30** (64.5 mg, 70% yield) as an oil. The enantiomeric excess was determined by SFC with a Chiralcel AS-H column (2-propanol:CO_2:MeOH 30-80%, flow rate 2% min; oven temperature: 40 ºC, detection: 220 nm), t_r (1) = 5.87 min, t_r (2) = 6.39 min, $[\alpha]_D^{20}$ = +9.8 (*c* = 0.017, $CHCl_3$, 81% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47 (d, *J* = 4.2 Hz, 1H), 6.42 (dt, *J* = 0.9, 4.2 Hz, 1H), 6.97 (dd, *J* = 3.3, 4.8 Hz, 1H), 7.02 (ddd, *J* = 0.6, 1.2, 3.6 Hz, 1H), 7.30 (dd, *J* = 1.2, 4.8 Hz, 1H), 7.32-7.36 (m, 2H), 7.53 (d, *J* = 0.9 Hz, 1H), 7.74-7.77 (m, 1H), 7.86-7.89 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 68.4, IR (neat): 3931, 3819, 3360, 3104, 3072, 2956, 2923, 2867, 2299, 1944, 1908, 1791, 1667, 1609, 1562, 1524, 1459, 1428, 1366, 1290, 1263, 1228, 1174, 1137, 1120, 1088, 1053, 1036, 1020 cm^{-1}; HRMS calcd for $C_{13}H_9S_2$ $(M\text{-}OH)^+$: 229.0137, found 229.0146.

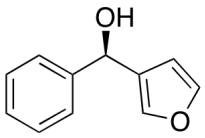


Benzo[*b*]thiophen-3-yl(furan-2-yl)methanol (2-31). General Procedure B was applied to furfural (31 μL, 0.37 mmol) and 3-bromobenzothiophene (98 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 90/10) to give **2-31** (60.2 mg, 70% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 97.5:2.5, flow rate = 0.5 mL/min), t_r (1) = 60.2 min, t_r (2) = 71.1 min, $[\alpha]_D^{20}$ = +17.6 (*c* = 0.017, $CHCl_3$, 82% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.46 (d, *J* = 4.8 Hz, 1H), 6.20 (d, *J* = 4.8 Hz, 1H), 6.23 (dt, *J* = 0.6, 3.3 Hz, 1H), 6.35 (dd, *J* = 1.8, 3.3 Hz, 1H), 7.34-7.37 (m, 2H), 7.43 (dd, *J* = 0.6, 1.2 Hz, 1H), 7.50 (d, *J* = 0.9 Hz, 1H), 7.75-7.79 (m, 1H), 7.86-7.89 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 66.2, 108.0, 110.6, 122.7, 123.1, 124.3, 124.4, 124.7, 136.0, 137.3, 141.1, 142.8, 154.9; IR (neat): 3937, 3418, 3115, 3060, 2924, 2634, 2303, 2082, 1945, 1910, 1713, 1562, 1523, 1501, 1426, 1428, 1346, 1264, 1151, 1095 cm^{-1}; HRMS calcd for $C_{13}H_9OS$ $(M\text{-}OH)^+$: 213.0374, found 213.0371.

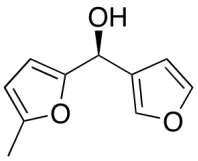


Phenyl(thiophen-2-yl)methanol (2-32). General Procedure B was applied to benzaldehyde (37.8 μL, 0.37 mmol) and 2-bromothiophene (72.5 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-32** (39.4 mg, 57% yield) as a white solid. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 65.0 min, t_r (2) = 71.9 min, $[\alpha]_D^{20}$ = –9.0 (*c* = 0.030, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.41 (d, *J* = 4.2

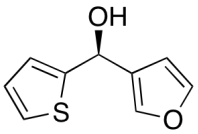
Hz, 1H), 6.11 (d, J = 4.2 Hz, 1H), 6.93-6.95 (m, 1H), 6.98-7.01 (m, 1H), 7.31-7.33 (m, 1H), 7.36-7.45 (m, 3H), 7.49-7.52 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): δ 72.7, 125.2, 125.7, 126.6, 126.9, 128.3, 128.8, 143.2, 148.0; IR (DCM): 3944, 3757, 3691, 3589, 3054, 2987, 2831, 2685, 2521, 2410, 2305, 2126, 2054, 1602, 1551, 1421, 1265, 1156, 1016 cm^{-1}; HRMS calcd for $C_{13}H_{10}O_2S$ $(M\text{-}OH)^+$: 173.0425, found 173.0430. The data collected are in agreement with previously published results.[139]



Furan-3-yl(phenyl)methanol (2-33). General Procedure A was applied to benzaldehyde (37.8 μL, 0.37 mmol) and 3-bromofuran (67 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-33** (56.6 mg, 86% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 61.6 min, t_r (2) = 67.2 min, $[\alpha]_D^{20}$ = –2.7 (c = 0.033, $CHCl_3$, 93% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.10 (d, J = 4.0 Hz, 1H), 5.80 (d, J = 4.0 Hz, 1H), 6.34-6.35 (m, 1H), 7.31-7.33 (m, 2H), 7.36-7.39 (m, 3H), 7.41-7.43 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 69.8, 109.4, 126.6, 128.1, 128.8, 129.2, 140.0, 143.2, 143.7; IR (neat): 3944, 3756, 3691, 3595, 3054, 2987, 2685, 2521, 2410, 2305, 2126, 2054, 1601, 1551, 1492, 1421, 1265, 1157, 1024 cm^{-1}; HRMS calcd for $C_{11}H_{10}O_2Na$ $(M+Na)^+$: 197.0578, found 197.0577. The data collected are in agreement with previously published results.[140]

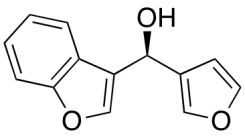


Furan-3-yl(5-methylfuran-2-yl)methanol (2-34). General Procedure B was applied to 5-methyl-2-furalaldehyde (37 μL, 0.37 mmol) and 3-bromofuran (67 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 90/10) to give **2-34** (44.4 mg, 67% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 46.8 min, t_r (2) = 51.5 min, $[\alpha]_D^{20}$ = +4.0 (*c* = 0.024, $CHCl_3$, 80% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21 (d, *J* = 5.1 Hz, 1H), 2.30 (s, 3H), 5.73 (d, *J* = 5.1 Hz, 1H), 5.91-5.93 (m, 1H), 6.10-6.11 (m, 1H), 6.47-6.48 (m, 1H), 7.41-7.42 (m, 1H), 7.47-7.48 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 13.8, 63.5, 106.4, 108.3, 109.6, 126.3, 140.3, 143.5, 152.6, 153.7; IR (neat): 3401, 3132, 2923, 1714, 1622, 1562, 1505, 1383, 1218, 1156, 1021 cm^{-1}; HRMS calcd for $C_{10}H_{10}O_3Na$ $(M+Na)^+$: 201.0528, found 201.0531.

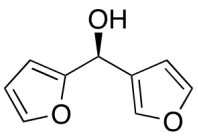


Furan-3-yl(thiophen-2-yl)methanol (2-35). General Procedure A was applied to 2-thiophenecarboxaldehyde (35 μL, 0.37 mmol) and 3-bromofuran (67 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-35** (44.4 mg, 60% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 97:3, flow rate = 0.5 mL/min), t_r (1) = 40.4 min, t_r (2) = 47.1 min, $[\alpha]_D^{20}$ = +18.2 (*c* = 0.032, $CHCl_3$, 99% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.27 (d, *J* = 5.0 Hz, 1H), 6.04 (d, *J* = 5.0 Hz, 1H), 6.44-6.45 (m, 1H), 6.97-6.99 (m, 1H), 7.01-7.02 (m, 1H), 7.30 (dd, *J* = 1.5, 5.0 Hz, 1H) 7.41 (t, *J* = 1.5 Hz, 1H), 7.45-7.46 (m, 1H);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 65.8, 109.3, 125.0, 125.6, 126.9, 128.6, 140.1, 143,7, 147.4; IR (neat): 3410, 3108, 2924, 2855, 1759, 1672, 1614, 1507, 1416, 1264, 1230, 1156, 1022 cm^{-1}; HRMS calcd for $C_9H_7O_2S$ $(M-H)^+$: 179.0167, found 179.0169.



Benzofuran-3-yl(furan-3-yl)methanol (2-36). General Procedure A was applied to 3-benzofuranecarboxaldehyde (19 mg, 0.13 mmol) and 3-bromofuran (23.5 μL, 0.26 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-36** (21.9 mg, 79% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 97.5:2.5, flow rate = 0.5 mL/min), t_r (1) = 54.6 min, t_r (2) = 69.5 min, $[\alpha]_D^{20}$ = +12.9 (*c* = 0.010, $CHCl_3$, 94% ee); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (d, *J* = 4.5 Hz, 1H), 6.05 (d, *J* = 4.5 Hz, 1H), 6.44-6.45 (m, 1H), 7.21-7.34 (m, 2H), 7.42-7.43 (m, 1H), 7.48-7.52 (m, 2H), 7.54-7.57 (m, 1H), 7.59-7.60 (m, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): δ 62.6, 109.4, 111.8, 120.8, 122.9, 123.3, 124.8, 126.2, 127.6, 140.2, 142.4, 143.9; IR (neat): 3367, 3148, 3060, 2962, 2923, 2874, 1901, 1783, 1702, 1596, 1579, 1502, 1477, 1452, 1333, 1276, 1216, 1184, 1158, 1103, 1075, 1024, 1009, 959 cm^{-1}; HRMS calcd for $C_{13}H_{10}O_3$ $(M)^+$: 214.0630, found 214.0622.



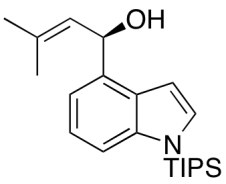
Furan-2-yl(furan-3-yl)methanol (2-37). General Procedure A was applied to furfural (31 mg, 0.37 mmol) and 3-bromofuran (67 μL, 0.75 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-37** (37.5 mg, 61% yield) as an oil. The enantiomeric

excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 97:3, flow rate = 0.5 mL/min), t_r (1) = 35.6 min, t_r (2) = 38.6 min, $[\alpha]_D^{20}$ = –1.2 (*c* = 0.023, $CHCl_3$, 89% ee); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.21 (d, *J* = 5.1 Hz, 1H), 5.80 (d, *J* = 5.0 Hz, 1H), 6.25 (dt, *J* = 0.9, 3.3 Hz, 1H), 6.35 (dd, *J* = 0.3, 3.3 Hz, 1H), 6.47 (dd, *J* = 0.3, 0.9 Hz, 1H), 7.42-7.43 (m, 2H), 7.47-7.48 (m, 1H), 7.48-7.52 (m, 2H), 7.54-7.57 (m, 1H), 7.59-7.60 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 63.5, 107.3, 109.5, 110.5, 126.2, 140.3, 142.7, 143.6, 155.5; IR (neat): 3401, 3148, 2924, 1722, 1626, 1568, 1504, 1466, 1391, 1315, 1222, 1158, 1072, 1014 cm^{-1}; HRMS calcd for $C_9H_9O_3$ $(M\text{-}OH)^+$: 165.0538, found 165.0546.

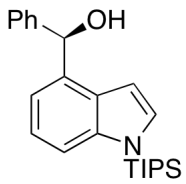
2.5.3. Synthesis of Indole Methanols

General Procedure C. A nitrogen purged Schlenk flask was charged with 4-bromo-1-TIPS indole (106.5 mg, 0.3 mmol) and *t*-BuOMe (1 mL) and cooled to –78 °C. *t*-BuLi (0.18 mL, 1.7 M in pentane, 0.3 mmol) was then added dropwise and the solution was stirred for 1 h at this temperature. During this time a white precipitate formed. EtZnCl (39.6 mg, 0.3 mmol) was added to the reaction flask as a solid at –78 °C followed by toluene (3 mL). The heterogeneous solution was stirred at –78 °C for 30 min and then warmed at 0 °C. TEEDA (26 μL, 0.12 mmol) was added and the solution stirred for an additional 30 min. (–)-MIB (150 μL, 0.1 M solution in hexanes, 0.015 mmol) was added to the reaction flask and the solution was stirred for 5 min before 3-methyl-2-butenal (14.7 μL, 0.15 mmol, dissolved in 1.5 mL of toluene) was added over 1.5 h by syringe

pump. The reaction mixture was stirred at 0 °C and monitored by TLC until completion (approximately 10 h). The reaction mixture was diluted with 3 mL EtOAc and quenched with water (5 mL). The organic layer was separated and the aqueous solution extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica gel.



3-Methyl-1-(1-(triisopropylsilyl)-1*H*-indol-4-yl)but-2-en-1-ol (2-38). General Procedure C was applied to 3-methyl-2-butenal (14.5 μL, 0.15 mmol) and 4-bromo-1-TIPS indole (106.5 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-38** (37.1 mg, 65% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 44.2 min, t_r (2) = 47.3 min, $[\alpha]_D^{20}$ = –61.5 (*c* = 0.049, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.13 (d, *J* = 7.33 Hz, 18H), 1.69 (sept, *J* = 7.3 Hz, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.86 (d, *J* = 1.3 Hz, 3H), 1.88 (d, *J* = 3.0 Hz, 1H), 5.66 (d apparent quintet, 1.3 Hz, 8.8 Hz, 1H), 5.81 (d, *J* = 8.8 Hz, 1H) 6.76 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.16 (m, 1H), 7.25 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 12.8, 18.1, 18.2, 25.8, 70.2, 103.2, 113.2, 116.5, 121.2, 127.2, 128.8, 130.9, 135.1, 135.7, 141.2; IR (neat): 3392, 2948, 2868, 1669, 1599, 1514, 1464, 1426, 1384, 1279, 1204, 1148, 1123, 1071 cm^{-1}; HRMS calcd for $C_{22}H_{34}NSi$ $(M\text{-}OH)^+$: 340.2451, found 340.2461.

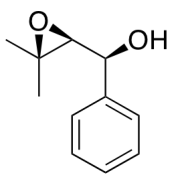


Phenyl(1-(triisopropylsilyl)-1*H*-indol-4-yl)methanol (2-39). General Procedure C was applied to benzaldehyde (15 μL, 0.15 mmol) and 4-bromo-1-TIPS indole (106.5 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-39** (34.1 mg, 60% yield) as an oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 99:1, flow rate = 0.5 mL/min), t_r (1) = 79.9 min, t_r (2) = 89.9 min, $[\alpha]_D^{20}$ = +24.4 (*c* = 0.047, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.12 (d, *J* = 7.1 Hz, 18H), 1.68 (sept, *J* = 7.1 Hz, 3H), 2.30 (d, *J* = 3.6 Hz, 1H), 6.24 (d, *J* = 3.0 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 7.10 (m, 2H), 7.23 (m, 2H), 7.32 (t, *J* = 7.1 Hz, 2H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 12.7, 18.1, 74.9, 103.0, 113.5, 117.5, 121.2, 126.6, 127.1, 128.2, 129.3, 131.2, 135.3, 141.1, 143.5; IR (neat): 3402, 3060, 3028, 2948, 2868, 2728, 1946, 1892, 1807, 1715, 1601, 1582, 1514, 1493, 1478, 1463, 1453, 1427, 1391, 1368, 1279, 1203, 1148, 1123, 1071 cm^{-1}; HRMS calcd for $C_{24}H_{32}NSi$ $(M\text{-}OH)^+$: 362.2304, found 362.2305.

2.5.4. Diastereoselective Addition/Epoxidation Reaction

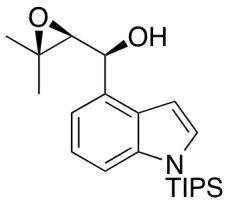
General Procedure D. A nitrogen purged Schlenk flask was charged with 4-bromo-1-TIPS indole (106.5 mg, 0.3 mmol) and *t*-BuOMe (1 mL) and cooled to –78 °C. Alkyl lithium (*n*-BuLi or *t*-BuLi, see below, 0.3 mmol) was added dropwise and the solution was stirred for 1 h. EtZnCl (39.6 mg, 0.3 mmol) was delivered to the reaction flask as a

solid at –78 °C. Toluene (3 mL) was next added giving a heterogenous mixture. The solution was warmed to –10 °C and stirred at that temperature for 3 h. Then TEEDA (26 μL, 0.12 mmol) was added and the solution was stirred for an additional 30 min. (–)-MIB (150 μL, 0.1 M solution in hexanes, 0.015 mmol) was added to the reaction flask and the solution was stirred for 5 min before 3-methyl-2-butenal (14.7 μL, 0.15 mmol, dissolved in 1.5 mL of toluene) was delivered over 1.5 h by syringe pump. The reaction mixture was stirred at –10 °C and monitored by TLC until completion. Upon completion of the reaction the solution was warmed to 0 ºC. $ZnEt_2$ (0.15 mL, 1 M in hexanes, 0.15 mmol) was added followed by TBHP (0.14 mL, 5.5 M in decane, 0.77 mmol). After stirring for 5 min Ti(O-*i*Pr)$_4$ (30 μL, 1 M in hexanes, 0.03 mmol) was added and the reaction stirred until the epoxidation reached completion (approximately 3 h). After the reaction was complete by TLC analysis, it was diluted with 3 mL EtOAc and quenched with water (5 mL). The organic layer was separated and the aqueous solution extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and the volatile materials were removed under reduced pressure. The crude product was purified by column chromatography on deactivated silica gel.



(3,3-Dimethyloxiran-2-yl)(phenyl)methanol (2-40). General Procedure D was applied to 3-methyl-2-butenal (24.2 μL, 0.25 mmol), bromobenzene (53.0 μL, 0.5 mmol) and *n*-BuLi (0.2 mL, 2.5 M in hexanes, 0.5 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 90/10) to give **2-40** (30.3 mg, 67.8% yield) as an oil. The

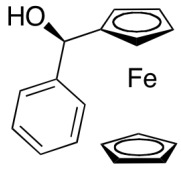
diastereomeric ratio was determined by ^{1}H NMR of the crude product (dr > 20:1); $[\alpha]_D^{20}$ = –23.1 (*c* = 0.043, $CHCl_3$, 90% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.29 (s, 3H), 1.43 (s, 3H), 2.60 (d, *J* = 2.9 Hz, 1H), 2.97 (d, *J* = 8.1 Hz, 1H), 4.55 (dd, *J* = 2.9, 8.1 Hz, 1H), 7.29-7.34 (m, 1H), 7.36-7.39 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 19.6, 24.8, 60.0, 68.0, 72.6, 125.9, 128.0, 128.6, 140.1; IR (neat): 3417, 3063, 3032, 2964, 2927, 2741, 1955, 1888, 1812, 1764, 1634, 1604, 1586, 1494, 1455, 1427, 1380, 1323, 1282, 1248, 1193, 1130, 1075 cm^{-1}; HRMS calcd for $C_{11}H_{14}ONa$ $(M+Na)^+$: 201.0891, found 201.0885.



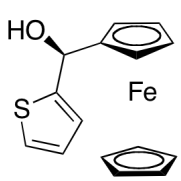
(3,3-Dimethyloxiran-2-yl)(1-(triisopropylsilyl)-1*H*-indol-4-yl)methanol (2-41). General Procedure D was applied to 3-methyl-2-butenal (14.5 μL, 0.15 mmol), 4-bromo-1-TIPS indole (106.5 mg, 0.3 mmol) and *t*-BuLi (0.18 mL, 1.7 M in pentane, 0.3 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 90/10) to give **2-41** (36.6 mg, 64.9% yield) as an oil. The diastereomeric ratio was determined by ^{1}H NMR of the crude product (dr > 20:1); $[\alpha]_D^{20}$ = –6.1 (*c* = 0.041, $CHCl_3$, 90% ee); 1.13 (d, *J* = 7.6 Hz, 18H), 1.29 (s, 3H), 1.43 (s, 3H), 1.69 (sept, *J* = 7.6 Hz, 3H), 2.48 (d, *J* = 3.0 Hz, 1H), 3.31 (d, *J* = 8.1 Hz, 1H), 4.89 (dd, *J* = 3.0, 8.1 Hz, 1H), 6.80 (d, *J* = 3.3 Hz, 1H), 7.10-7.14 (m, 1H), 7.30 (d, *J* = 3.3 Hz, 1H), 7.47 (dd, *J* = 2.8, 6.9 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 12.8, 18.0, 19.5, 24.8, 60.1, 67.3, 72.2, 103.3, 113.9, 117.6, 121.1, 129.2, 131.5, 141.3; IR (neat): 3445, 3135, 3081, 3048, 2948, 2892, 2868, 2760, 2729, 2625, 2559, 2361, 2343, 2246, 2150, 2074, 1892, 1824, 1740, 1675, 1599, 1514, 1463,

1428, 1378, 1345, 1323, 1280, 1248, 1209, 1150, 1124, 1096, 1073 cm^{-1}; HRMS calcd for $C_{22}H_{35}NO_2NaSi$ $(M+Na)^+$: 396.2335, found 396.2321.

2.5.5. Synthesis of Ferrocenyl Derivatives

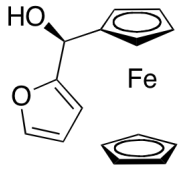


Phenyl(ferrocenyl)methanol (2-44). General Procedure A was applied to benzaldehyde (19 μL, 0.188 mmol), bromoferrocene (99 mg, 0.37 mmol) and Chan's ligand **L2** (94 μL, 0.1 M in toluene, 0.0094 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-44** (47 mg, 86% yield) as a red solid. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 93:7, flow rate = 0.5 mL/min), t_r (1) = 26.7 min, t_r (2) = 45.2 min, $[\alpha]_D^{20}$ = –94.4 (*c* = 0.016, $CHCl_3$, 98% ee); ^1H NMR ($CDCl_3$, 360 MHz): δ 2.42 (d, *J* = 3.24 Hz, 1H), 4.22 (s, 9H), 5.46 (d, *J* = 3.24 Hz, 1H), 7.30-7.40 (m, 5H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 66.2, 67.7, 68.3, 68.4, 68.7, 72.3, 94.5, 126.4, 127.7, 128.4, 143.5; IR (DCM): 3944, 3757, 3691, 3584, 3054, 2987, 2685, 2521, 2410, 2305, 2126, 2054, 1602, 1550, 1493, 1421, 1383, 1265, 1172, 1105, 1079, 1045, 1016, 1002, 896 cm^{-1}; HRMS calcd for $C_{17}H_{16}O_1Fe$ $(M)^+$: 292.0550, found 292.0559. The data collected are in agreement with previously published results.[44,141,142]



Thienyl(ferrocenyl)methanol (2-43). General Procedure A was applied to 2-thiophenecarboxaldehyde (17.5 μL, 0.188 mmol),

bromoferrocene (99 mg, 0.37 mmol) and Chan's ligand **L2** (94 μL, 0.1 M in toluene, 0.0094 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-43** (52.9 mg, 95% yield) as a red solid. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexanes:2-propanol = 95:5, flow rate = 0.5 mL/min), t_r (1) = 42.7 min, t_r (2) = 51.0 min, $[\alpha]_D^{20}$ = –73.3 (*c* = 0.023, $CHCl_3$, 98% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.55 (d, *J* = 3.5 Hz, 1H), 4.25 (s, 9H), 5.73 (d, *J* = 3.5 Hz, 1H), 6.94-6.95 (m, 2H), 7.24-7.25 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 66.5, 67.5, 68.4, 68.5, 68.6, 68.9, 93.6, 124.6, 124.9, 126.5 147.5; IR (neat): 3928, 3542, 3435, 3096, 2972, 2927, 2867, 2253, 2054, 1666, 1532, 1437, 1411, 1393, 1292, 1260, 1231, 1191, 1158, 1106, 1041, 1002 cm^{-1}; HRMS calcd for $C_{15}H_{14}O_1SFe$ $(M)^+$: 298.0115, found 298.0104. The data collected are in agreement with previously published results.[142]



Furanyl(ferrocenyl)methanol (2-42). General Procedure A was applied to furfural (15.5 μL, 0.188 mmol), bromoferrocene (99 mg, 0.37 mmol) and Chan's ligand **L2** (94 μL, 0.1 M in toluene, 0.0094 mmol). The crude product was purified by column chromatography on silica gel (hexanes/EtOAc : 95/5) to give **2-42** (50 mg, 95% yield) as a yellow oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexanes:2-propanol = 95:5, flow rate = 0.5 mL/min), t_r (1) = 37.6 min, t_r (2) = 45.2 min, $[\alpha]_D^{20}$ = –30.0 (*c* = 0.022, $CHCl_3$, 96% ee); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.36 (d, *J* = 5.1 Hz, 1H), 4.18 (s, 7H), 4.26-4.29 (m, 2H), 5.48 (d, *J* = 5.1 Hz, 1H), 6.23-6.24 (m, 1H), 6.33-6.35 (m, 1H), 6.40-6.41 (m,

1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz): δ 66.3, 67.2, 67.5, 68.4, 68.5, 68.9, 90.7, 106.7, 110.3, 142.1, 155.8; IR (neat): 3928, 3401, 3095, 2920, 1637, 1504, 1467, 1411, 1301, 1211, 1170, 1147, 1105, 1043, 1002 cm^{-1}; HRMS calcd for $C_{15}H_{14}O_2NaFe$ $(M+Na)^+$: 305.0241, found 305.0244. The data collected are in agreement with previously published results.[142,143]

2.6. References

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3. Appendix A: ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectra

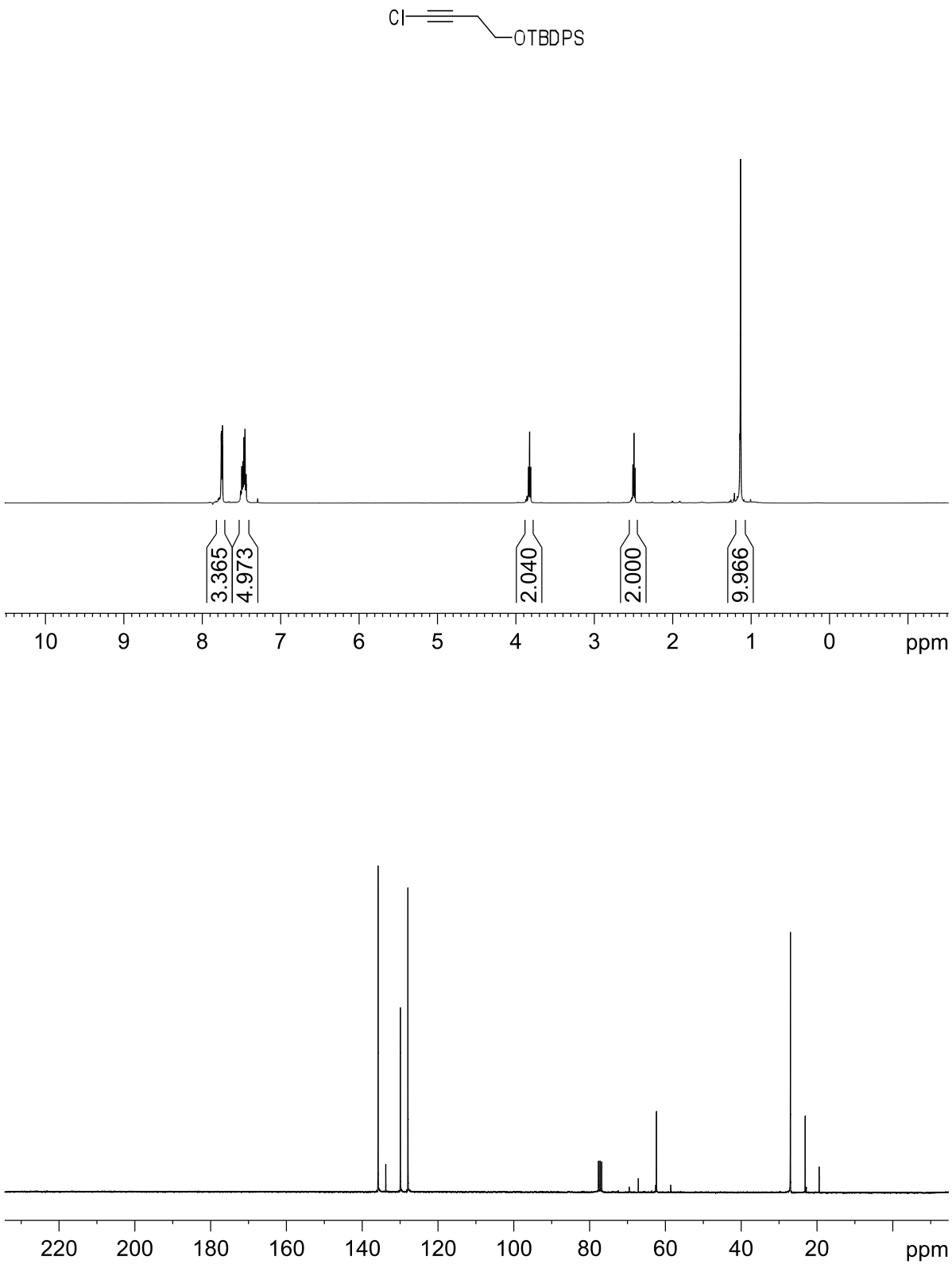


Figure 3-1. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-a** in $CDCl_3$.

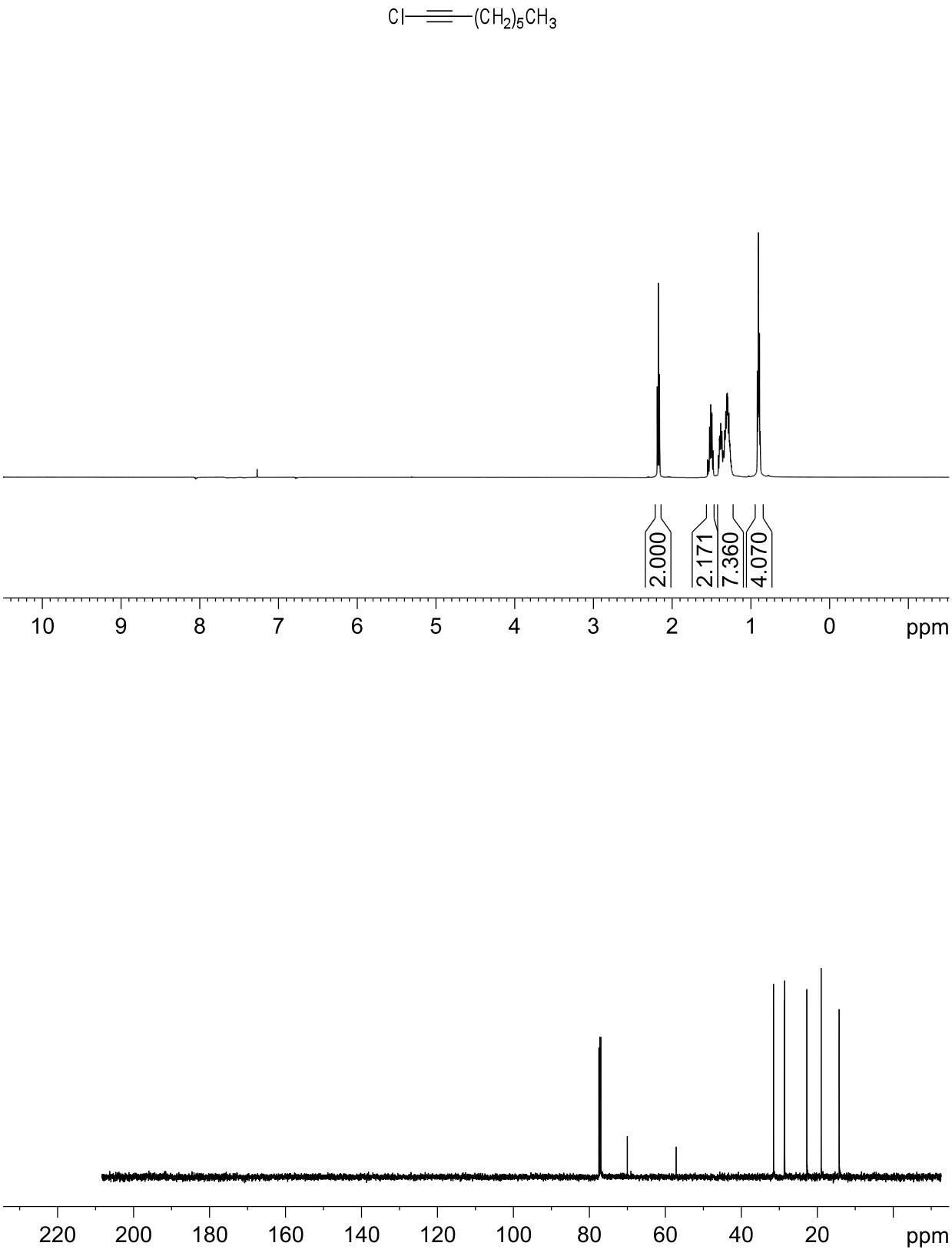


Figure 3-2. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-b** in $CDCl_3$.

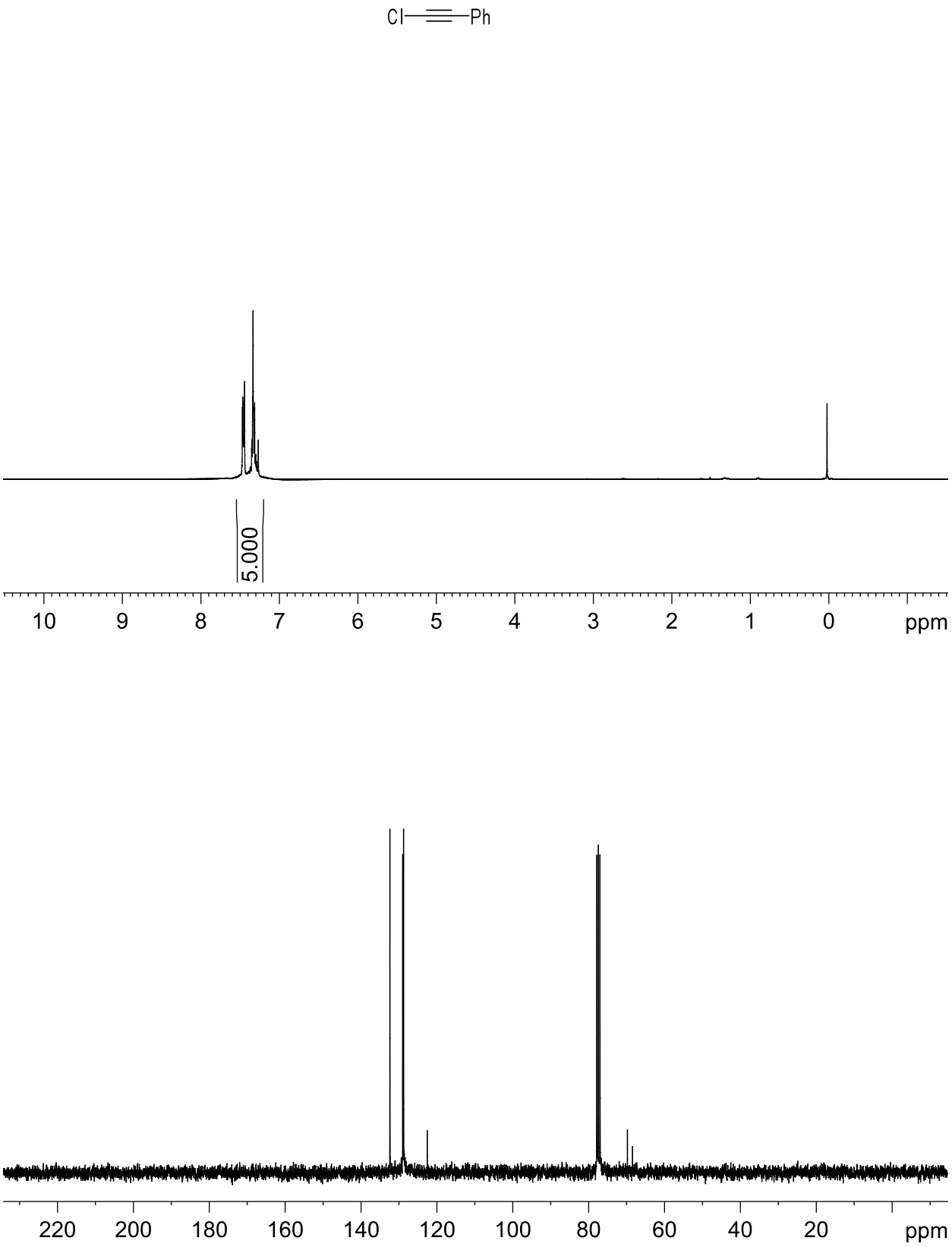


Figure 3-3. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-c** in $CDCl_3$.

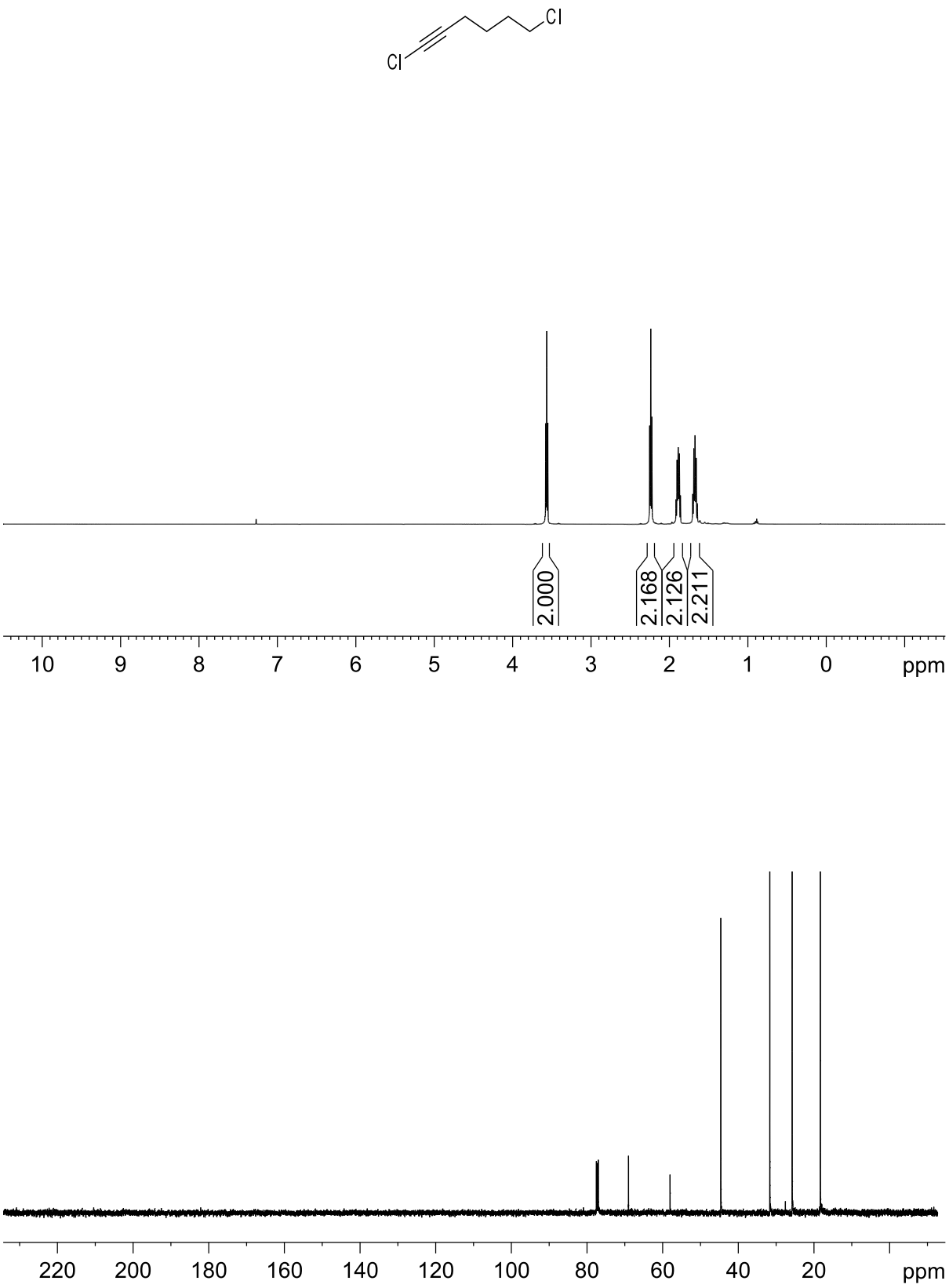


Figure 3-4. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-d** in $CDCl_3$.

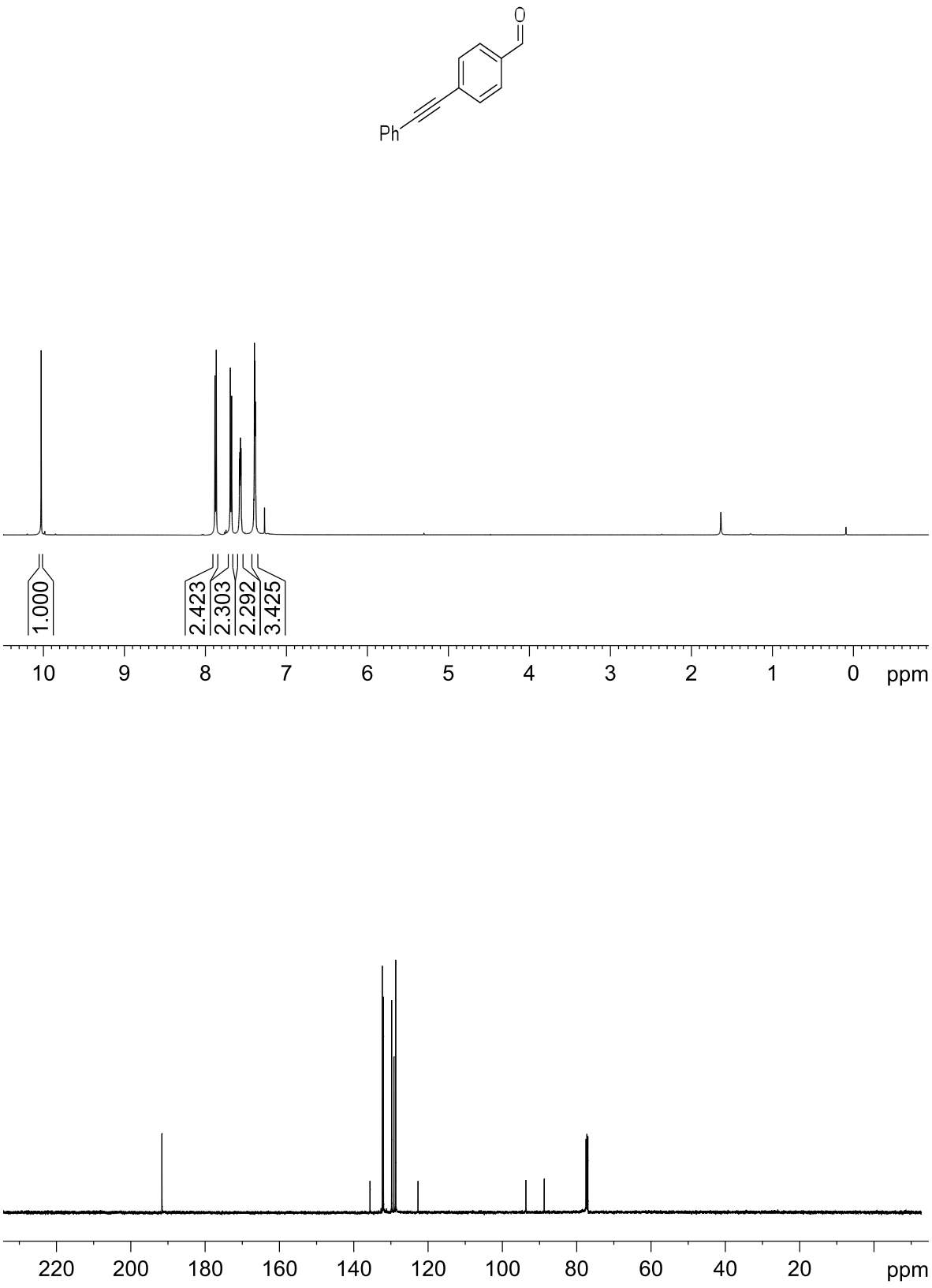


Figure 3-5. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-e** in $CDCl_3$.

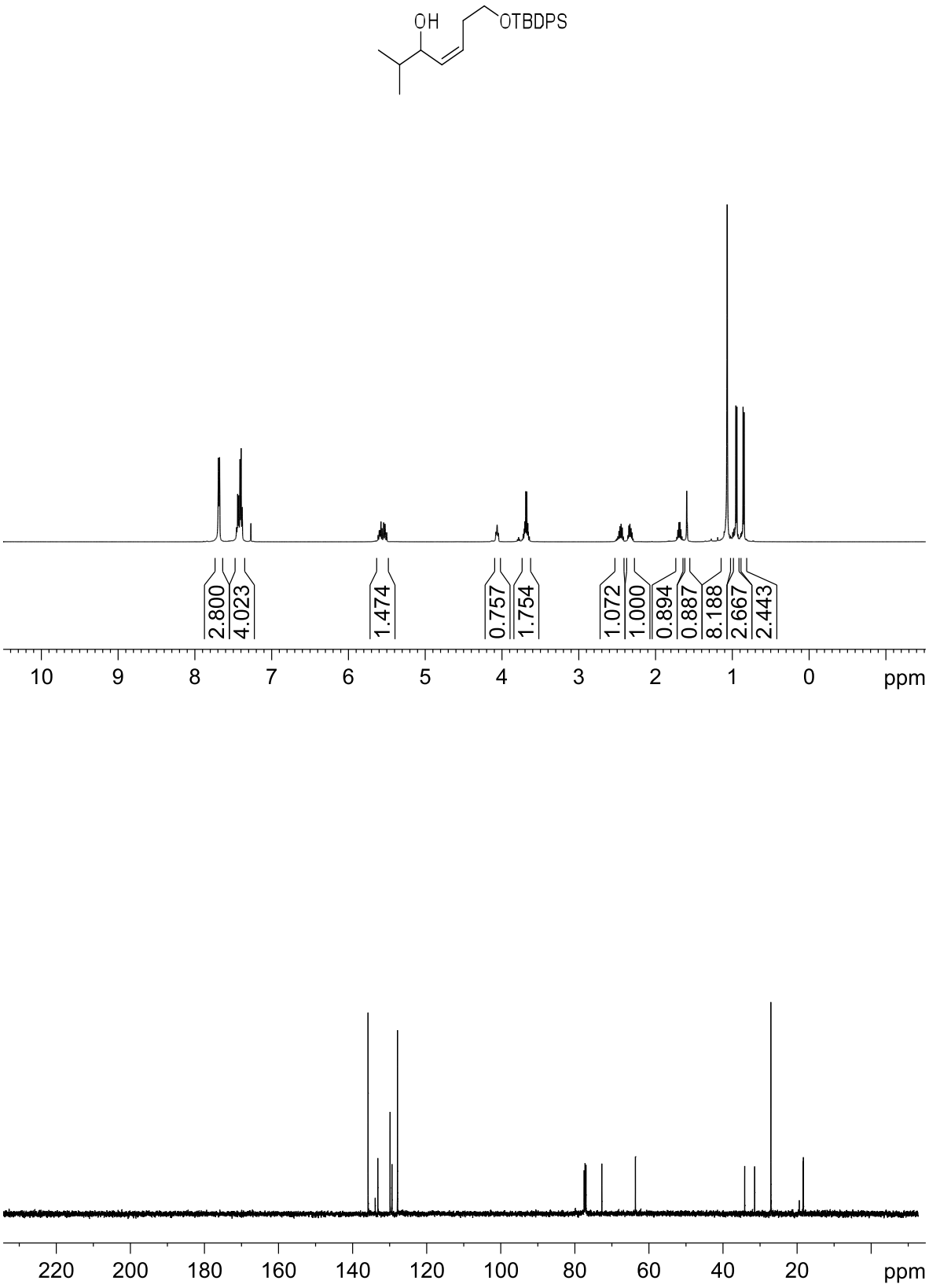


Figure 3-6. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-1** in $CDCl_3$.

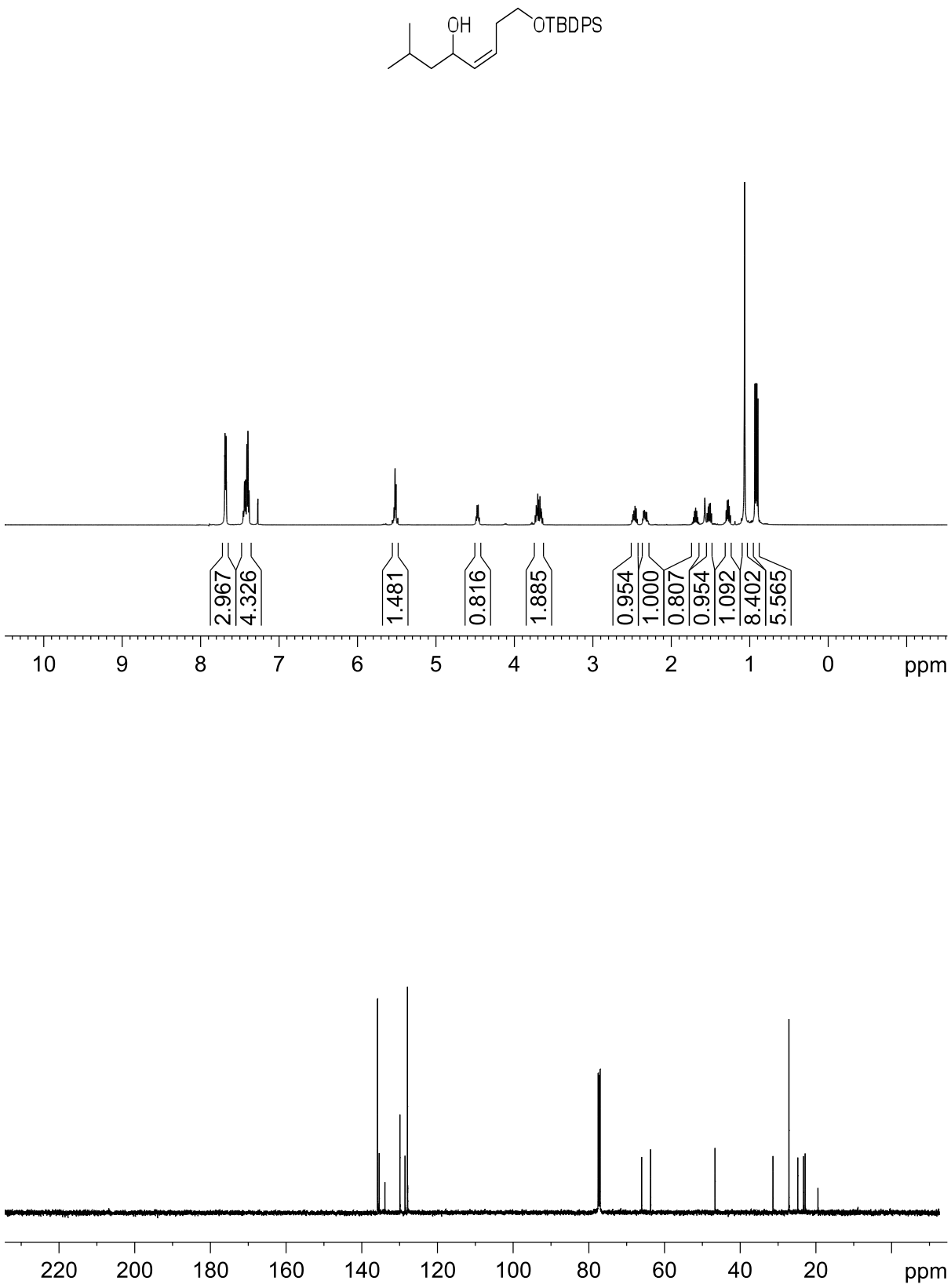


Figure 3-7. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-2** in $CDCl_3$.

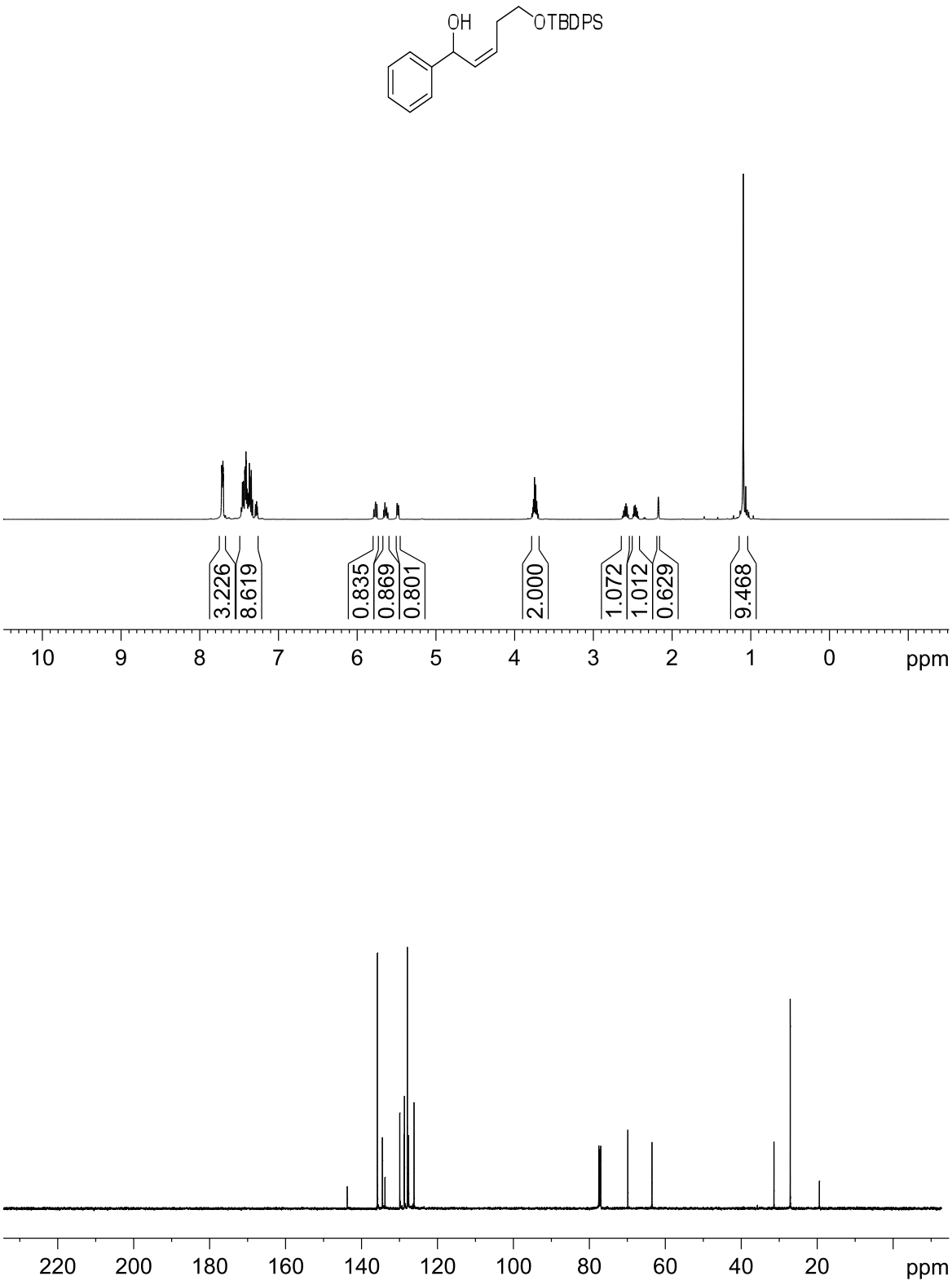


Figure 3-8. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-3** in $CDCl_3$.

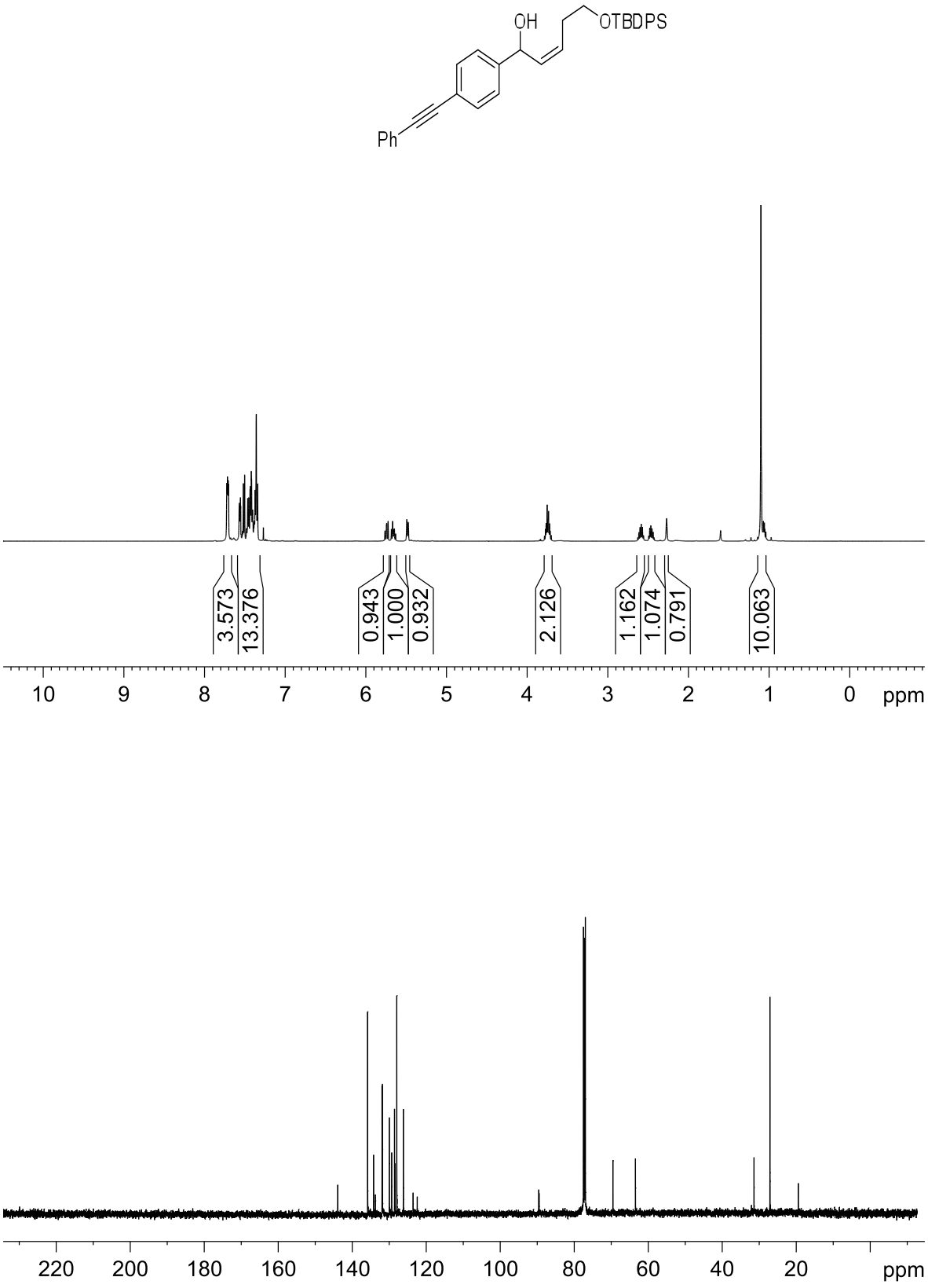


Figure 3-9. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-4** in $CDCl_3$.

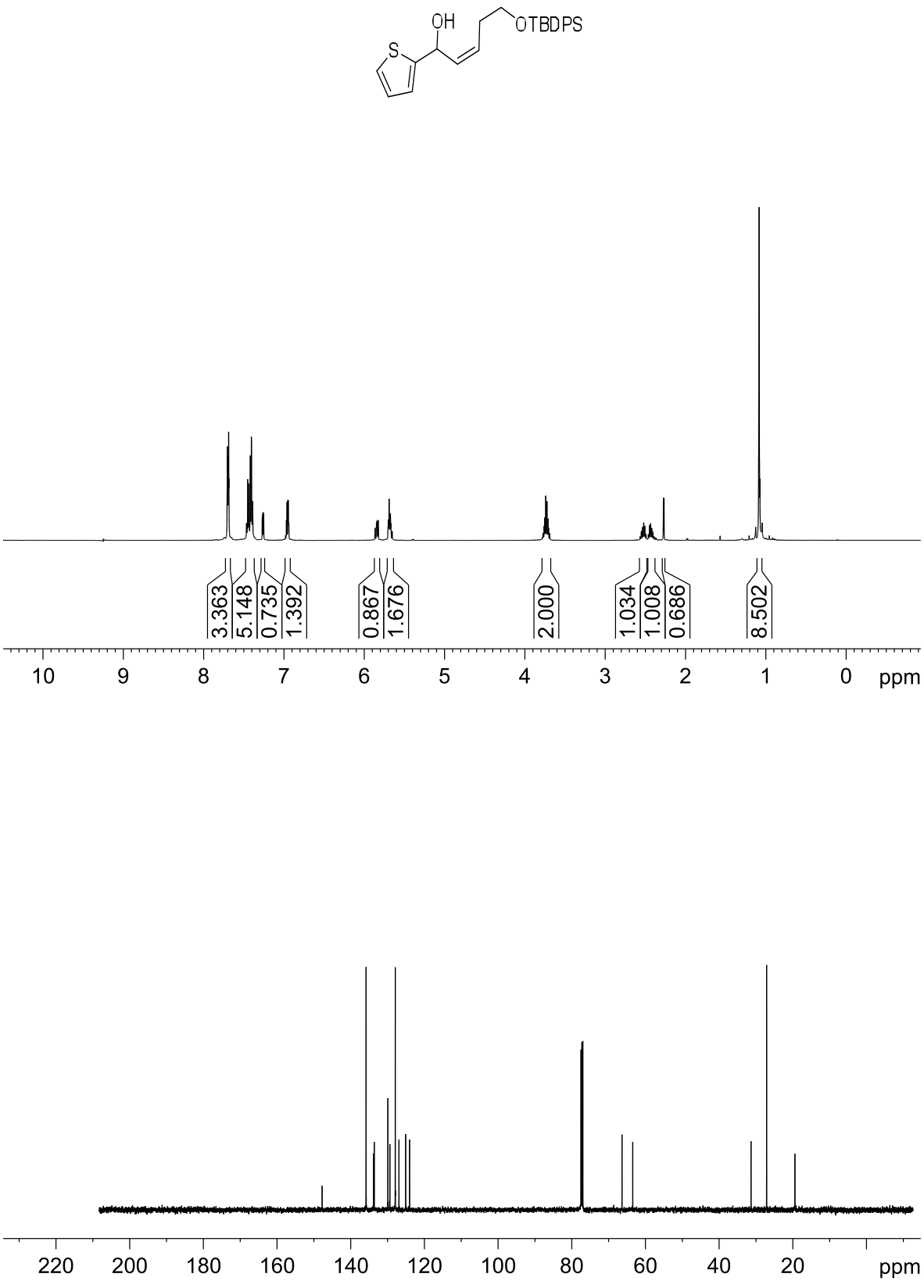


Figure 3-10. 500 MHz ^{1}Hand 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-5** in $CDCl_3$.

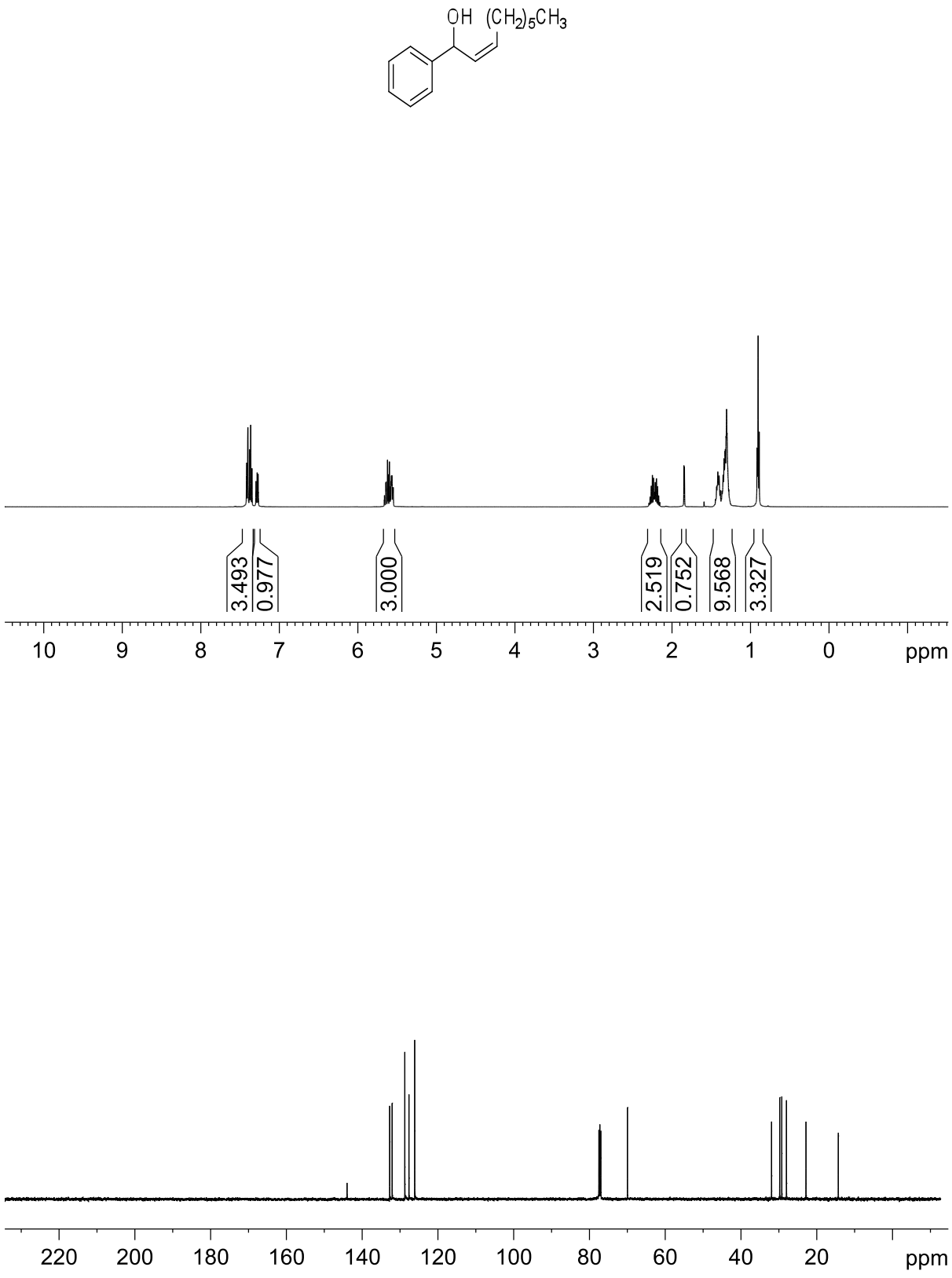


Figure 3-11. 500 MHz ^{1}Hand 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-6** in $CDCl_3$.

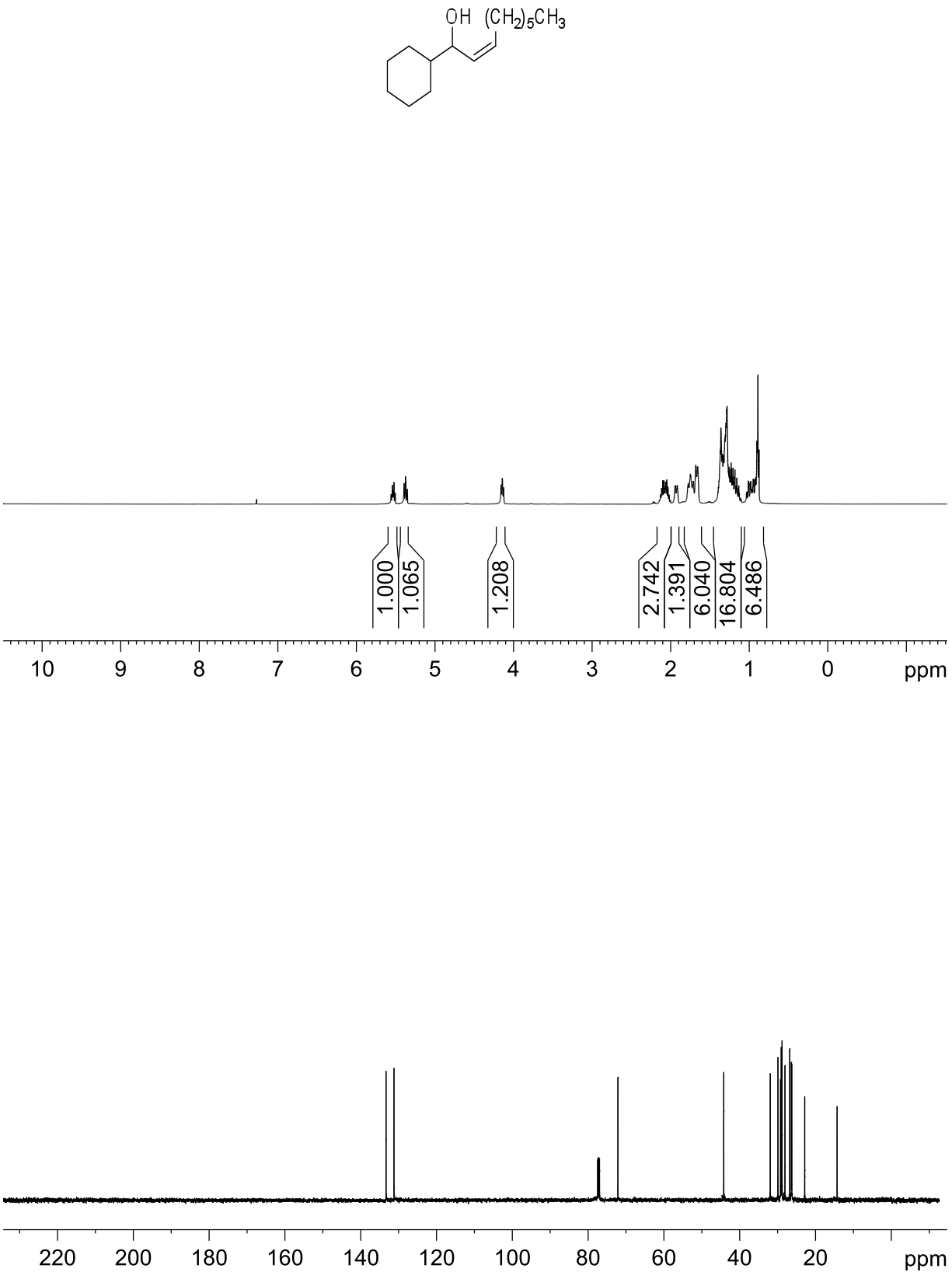


Figure 3-12. 500 MHz ^{1}Hand 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-7** in $CDCl_3$.

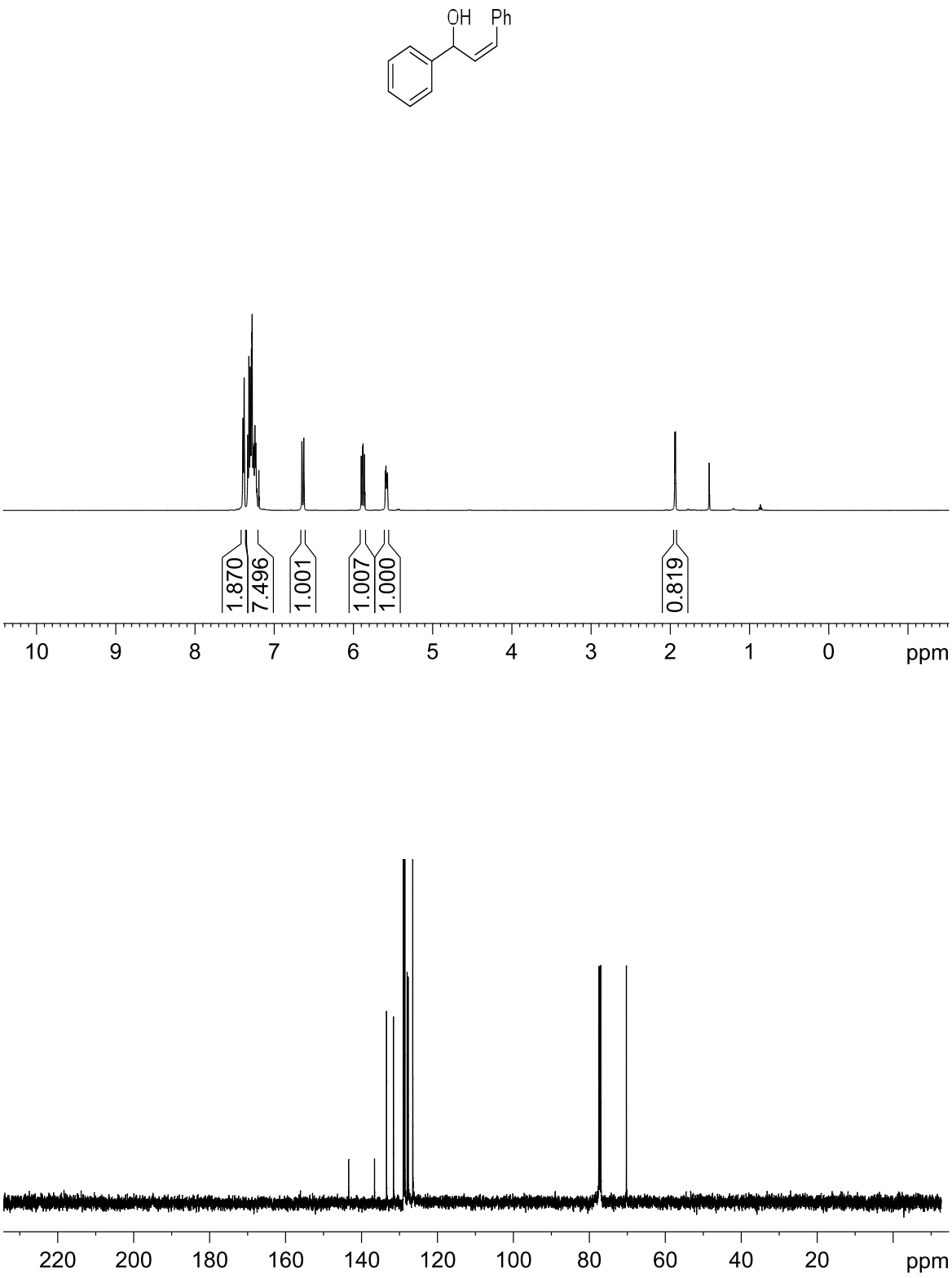


Figure 3-13. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-8** in $CDCl_3$.

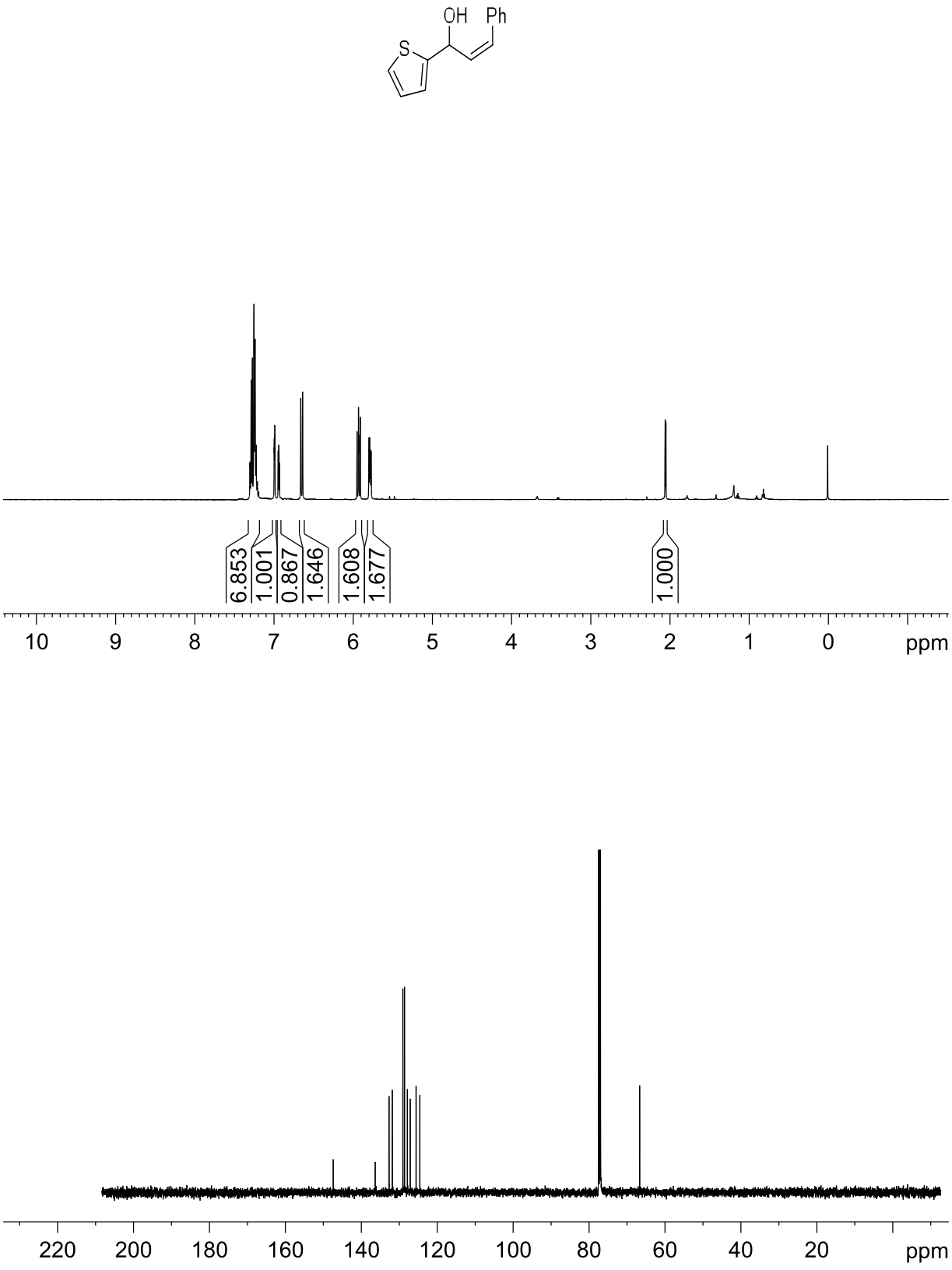


Figure 3-14. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-9** in $CDCl_3$.

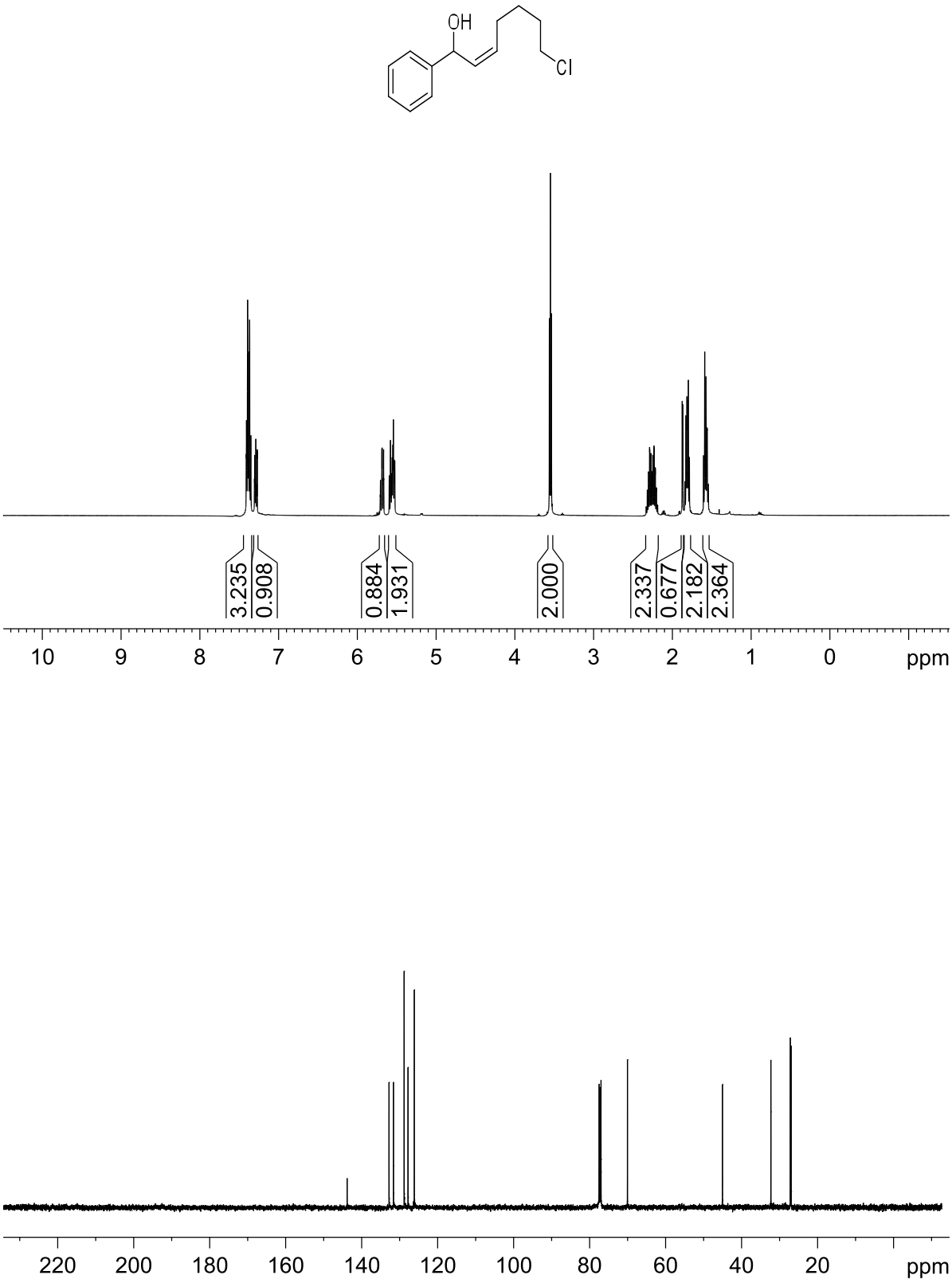


Figure 3-15. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-10** in $CDCl_3$.

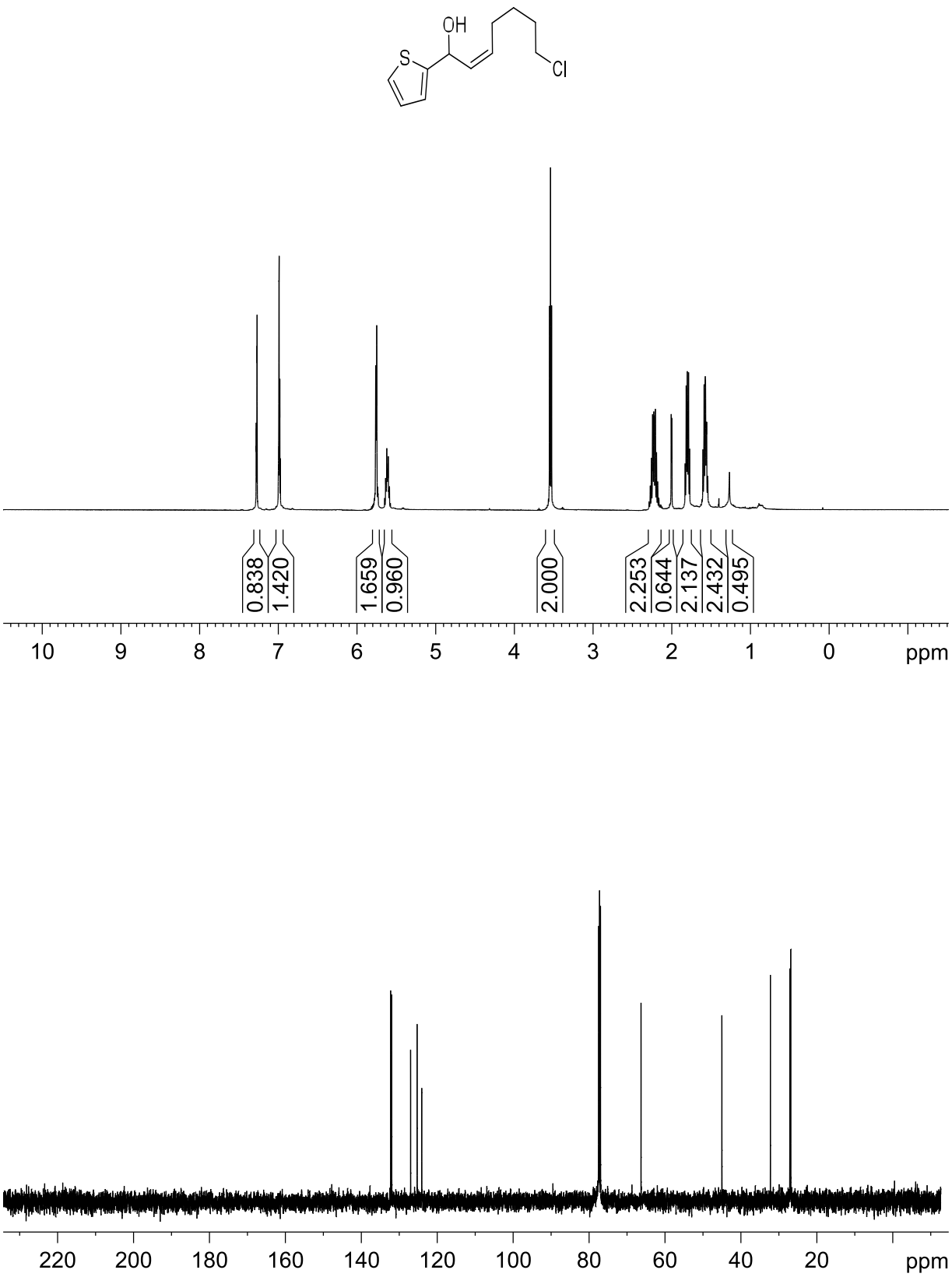


Figure 3-16. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-11** in $CDCl_3$.

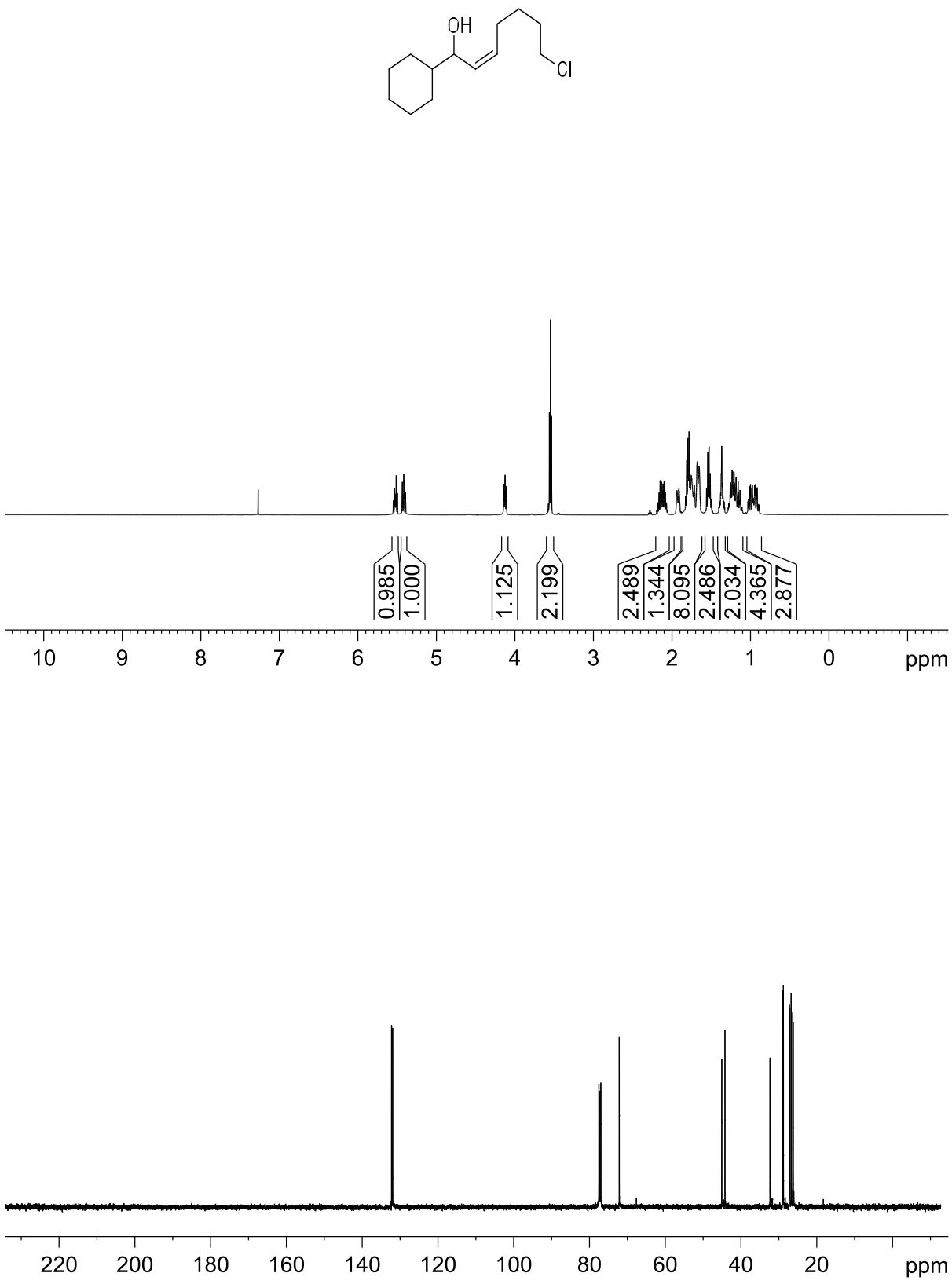


Figure 3-17. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-12** in $CDCl_3$.

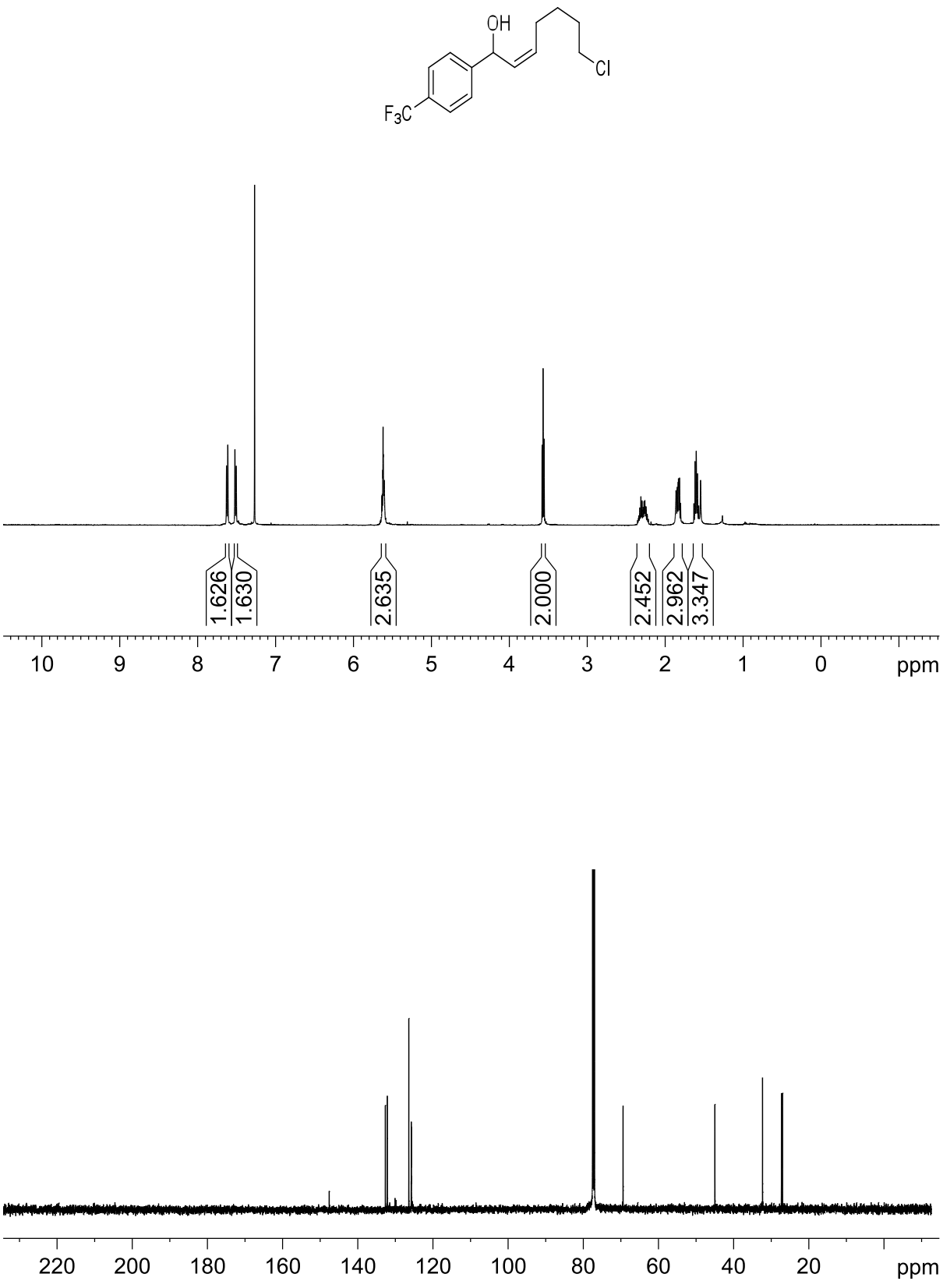


Figure 3-18. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-13** in $CDCl_3$.

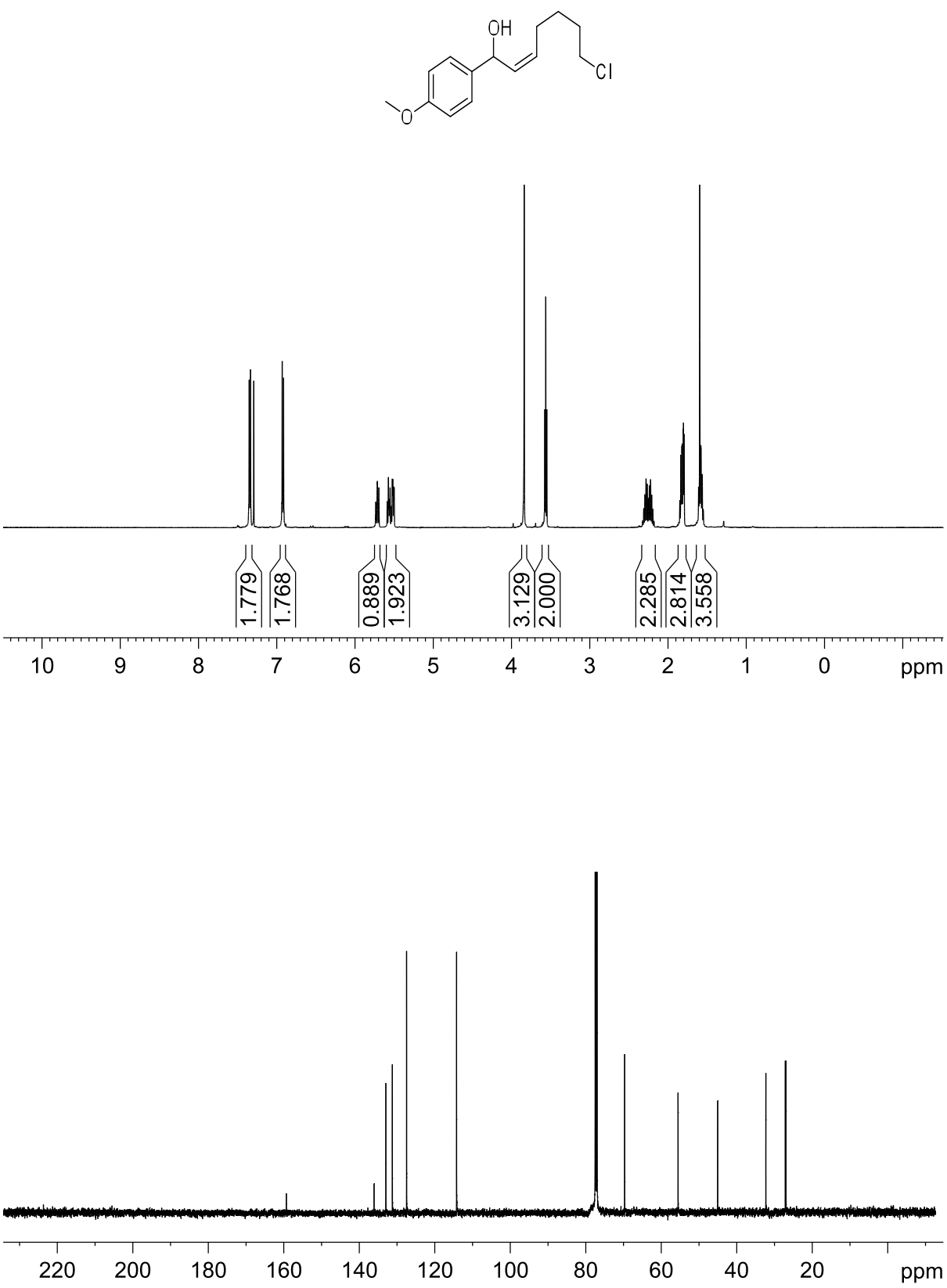


Figure 3-19. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-14** in $CDCl_3$.

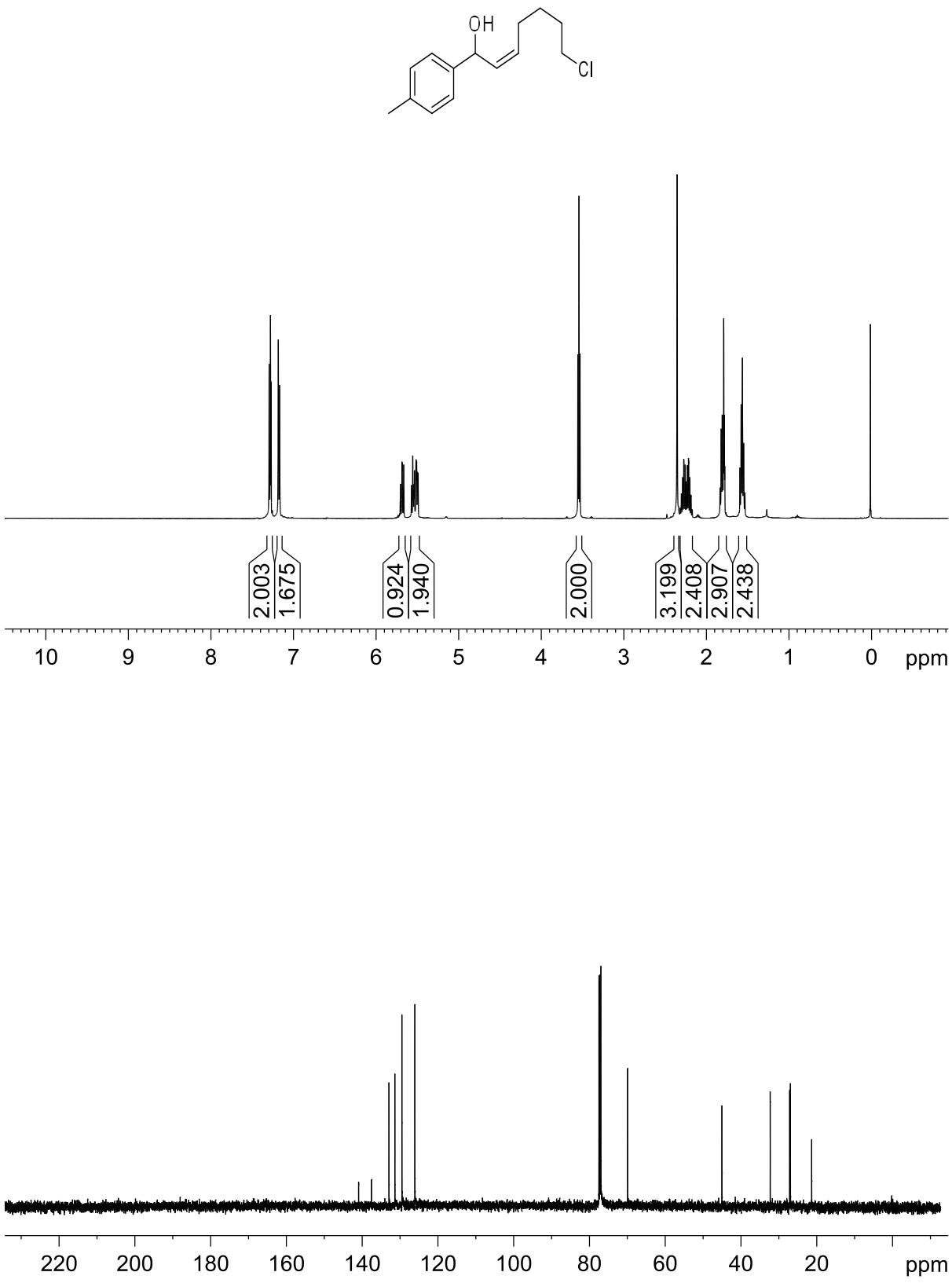


Figure 3-20. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-15** in $CDCl_3$.

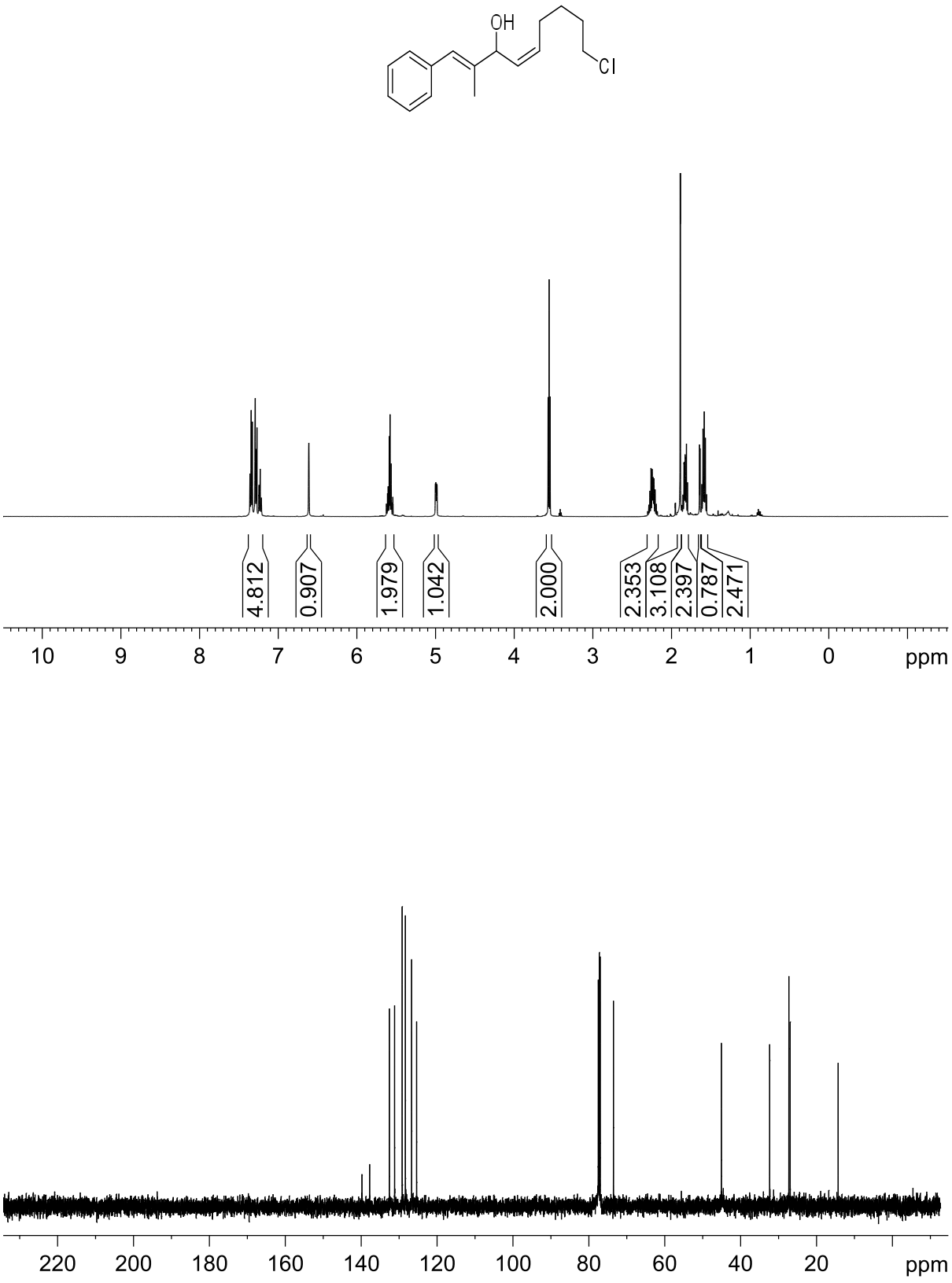


Figure 3-21. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-16** in $CDCl_3$.

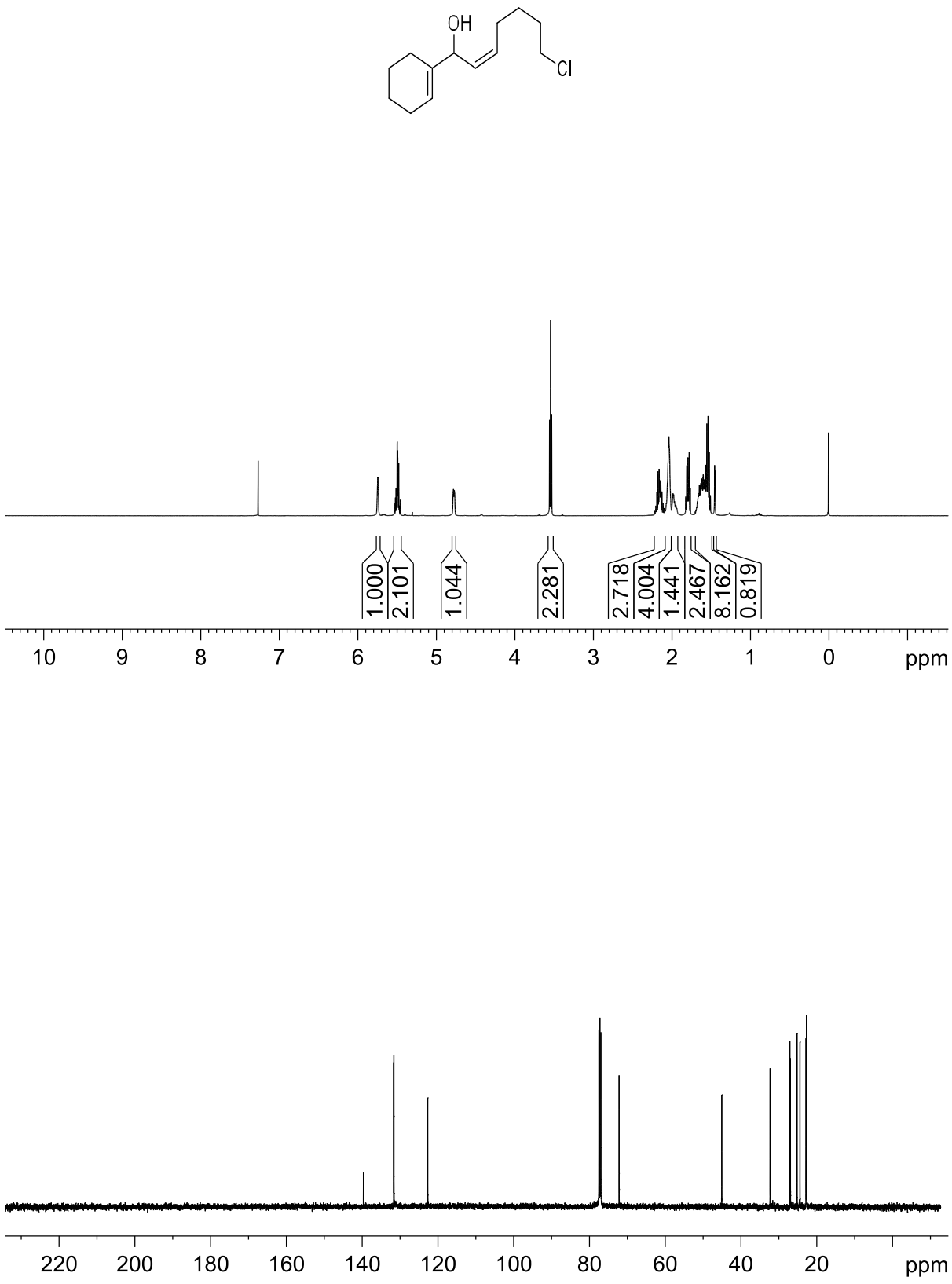


Figure 3-22. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-17** in $CDCl_3$.

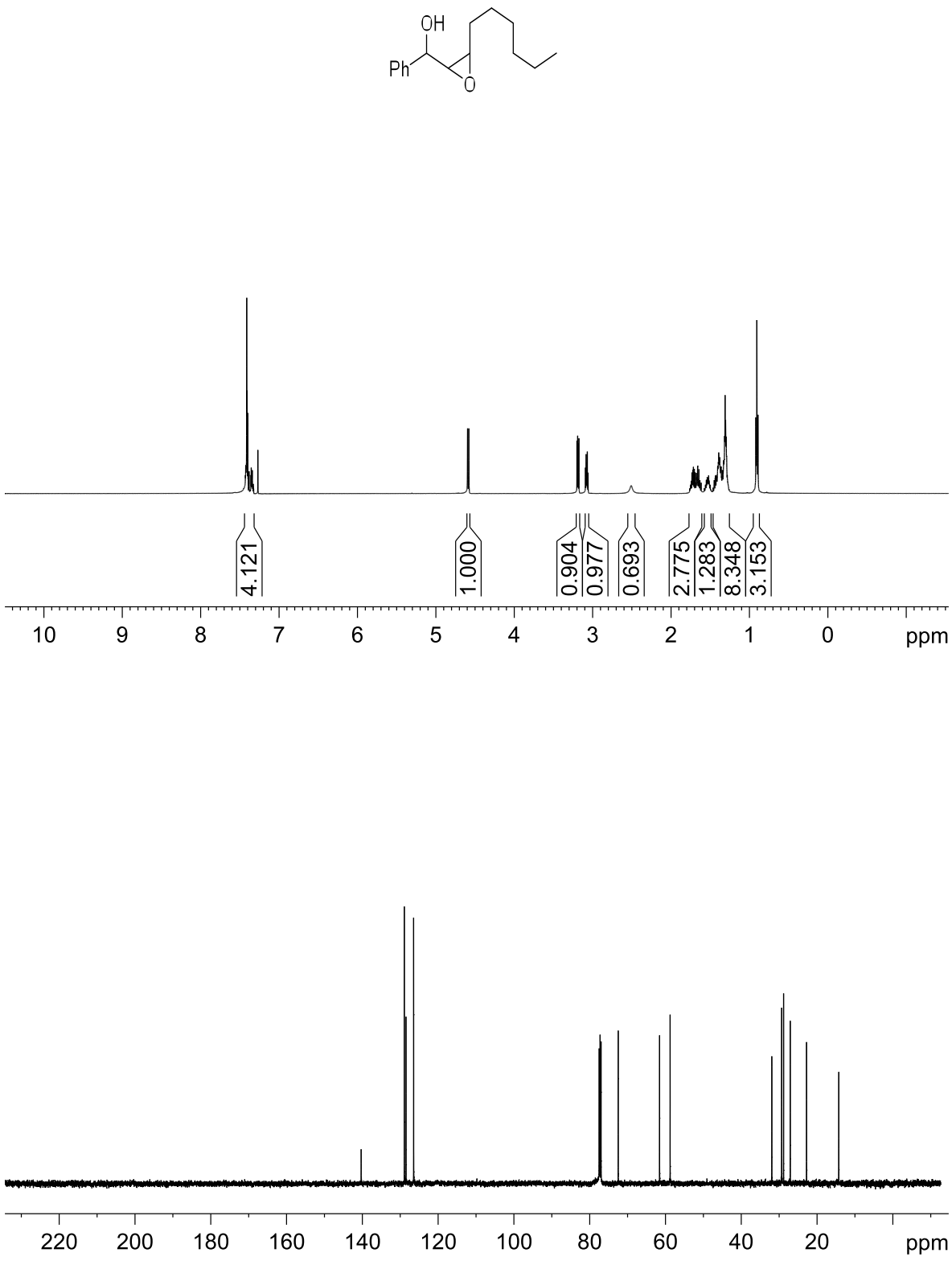


Figure 3-23. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-18** in $CDCl_3$.

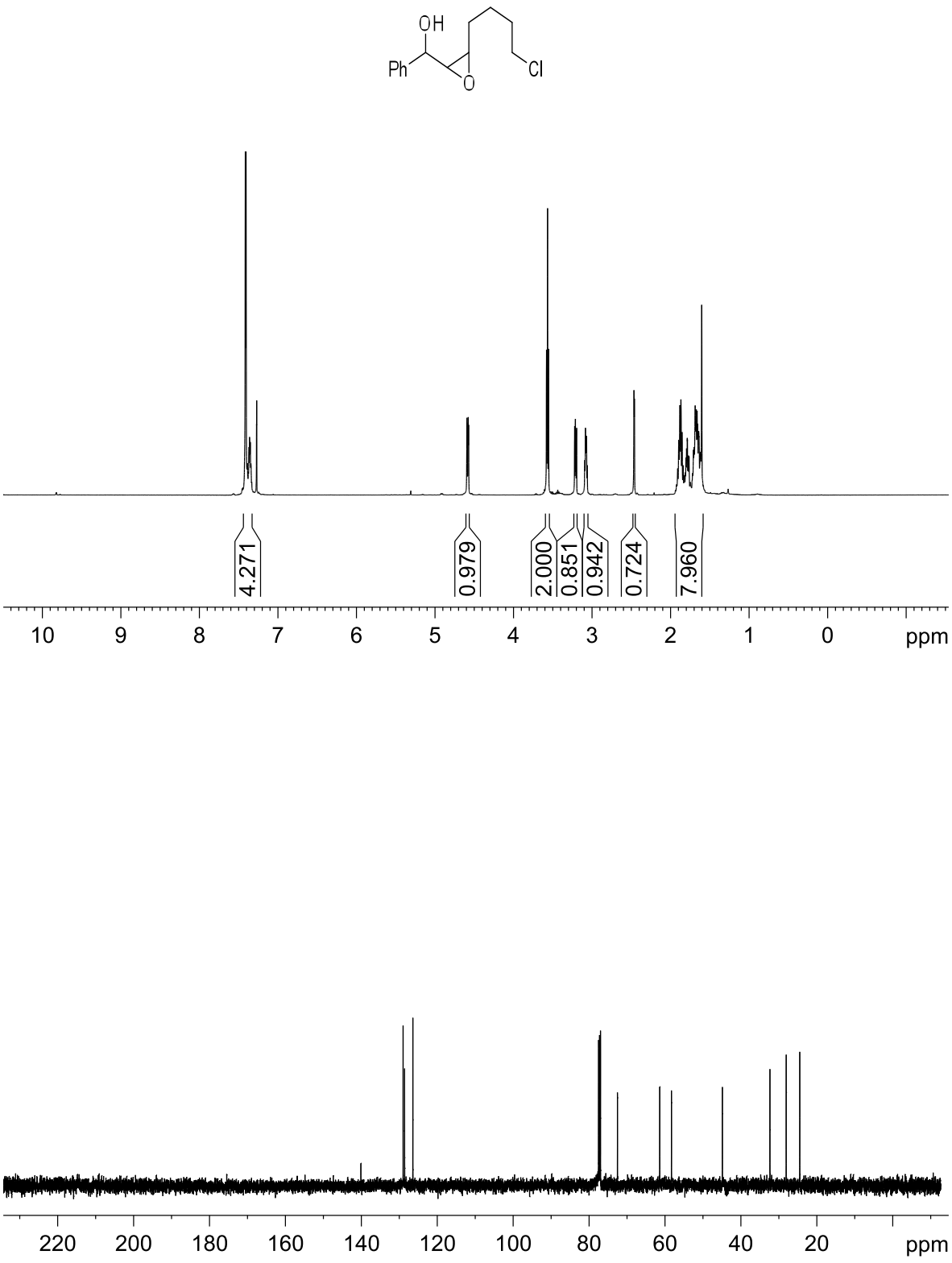


Figure 3-24. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-19** in $CDCl_3$.

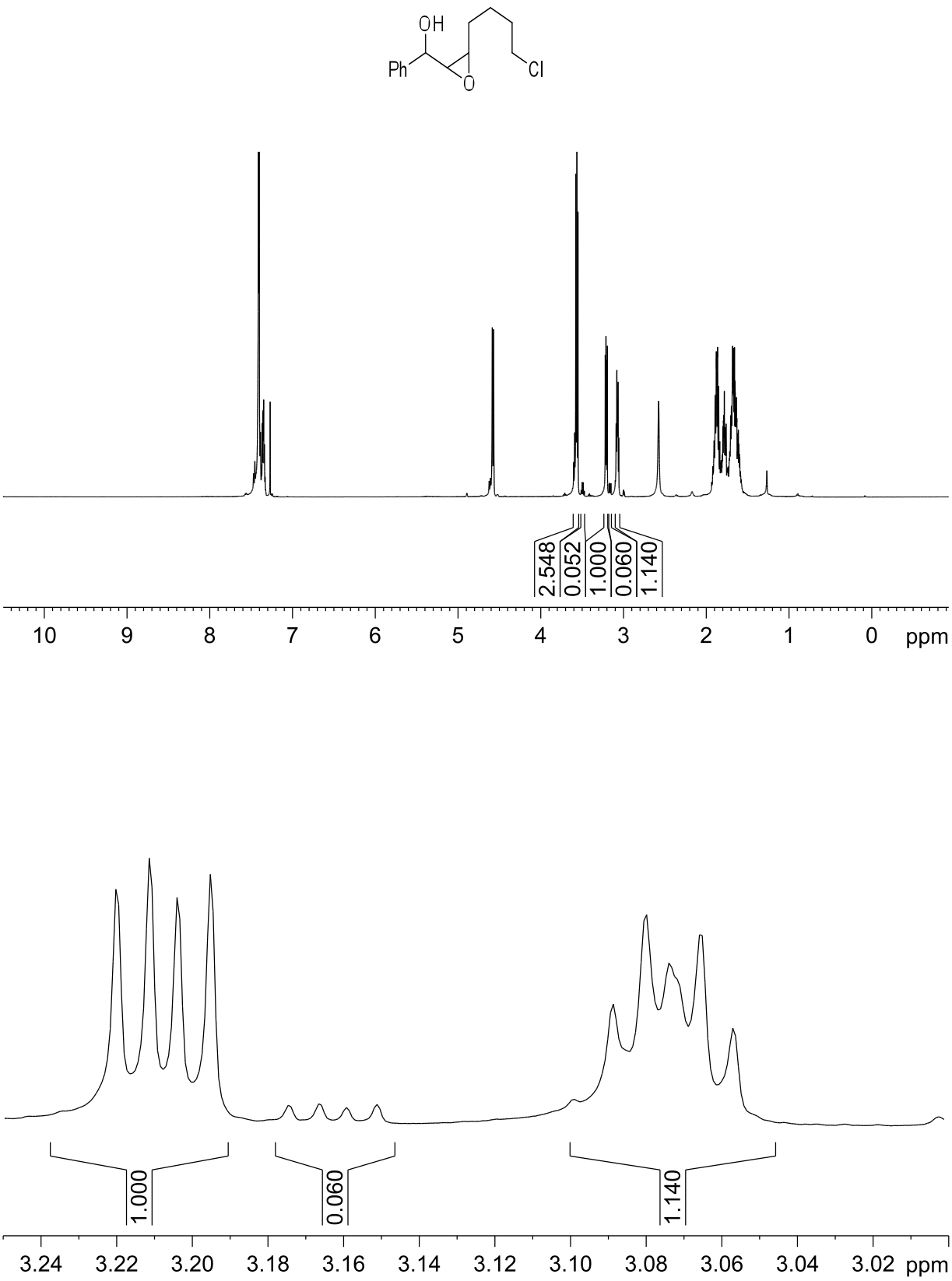


Figure 3-25. 500 MHz ^{1}H NMR of Compound **1-19** in $CDCl_3$ - generated with *m*CPBA.

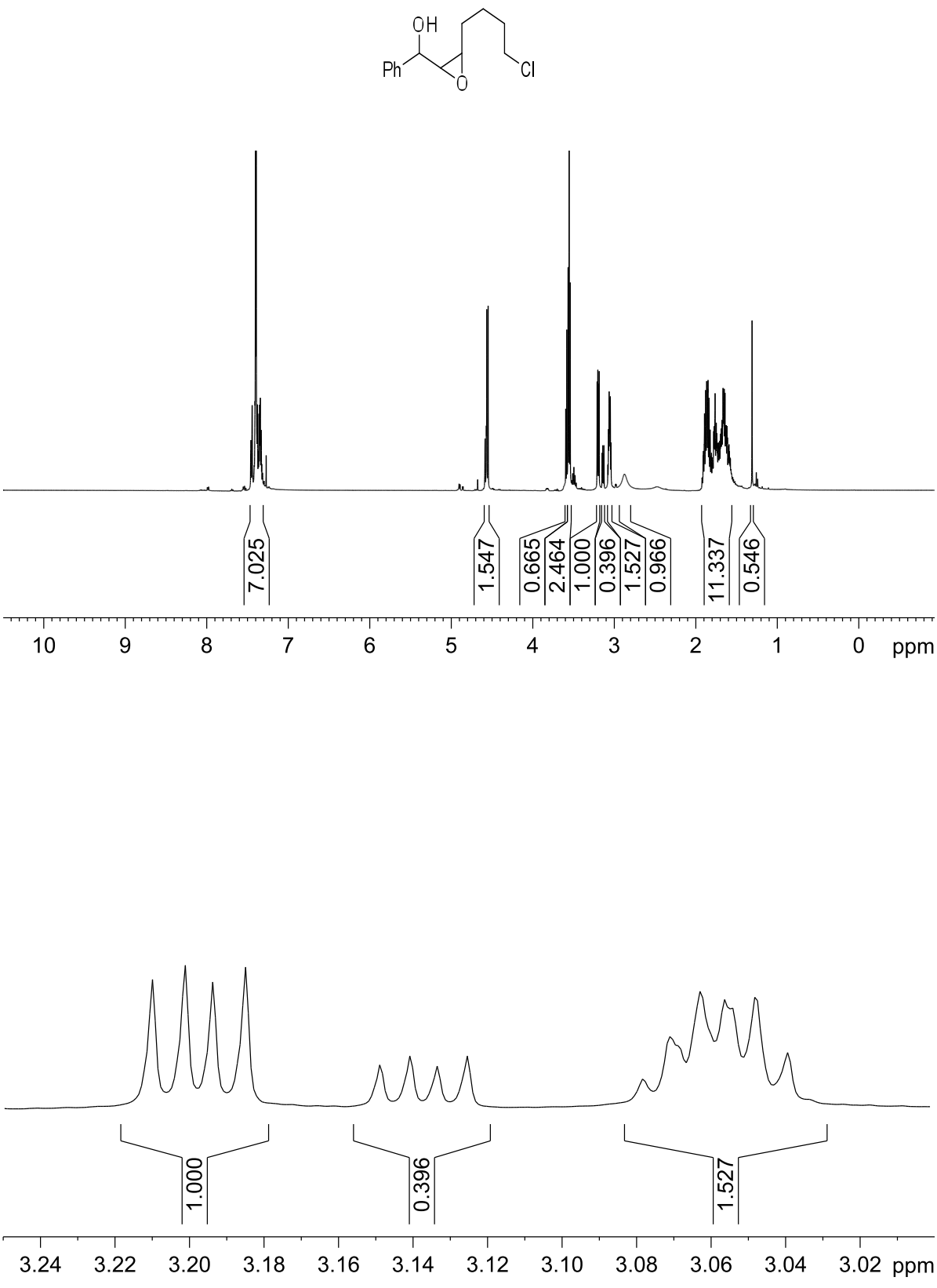


Figure 3-26. 500 MHz ^{1}H NMR of Compound **1-19** in $CDCl_3$ - generated with $VO(acac)_2$.

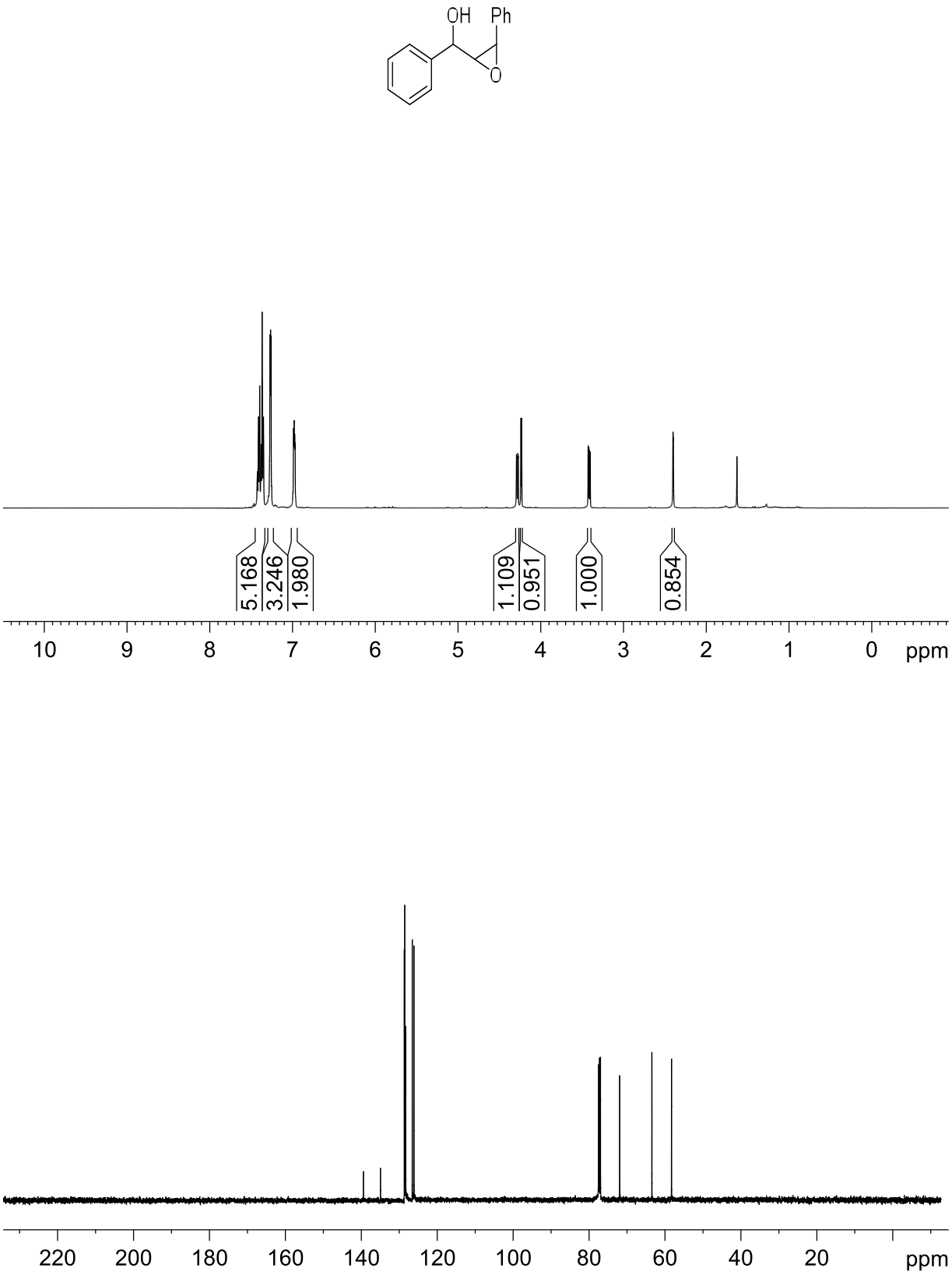


Figure 3-27. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-20** in $CDCl_3$.

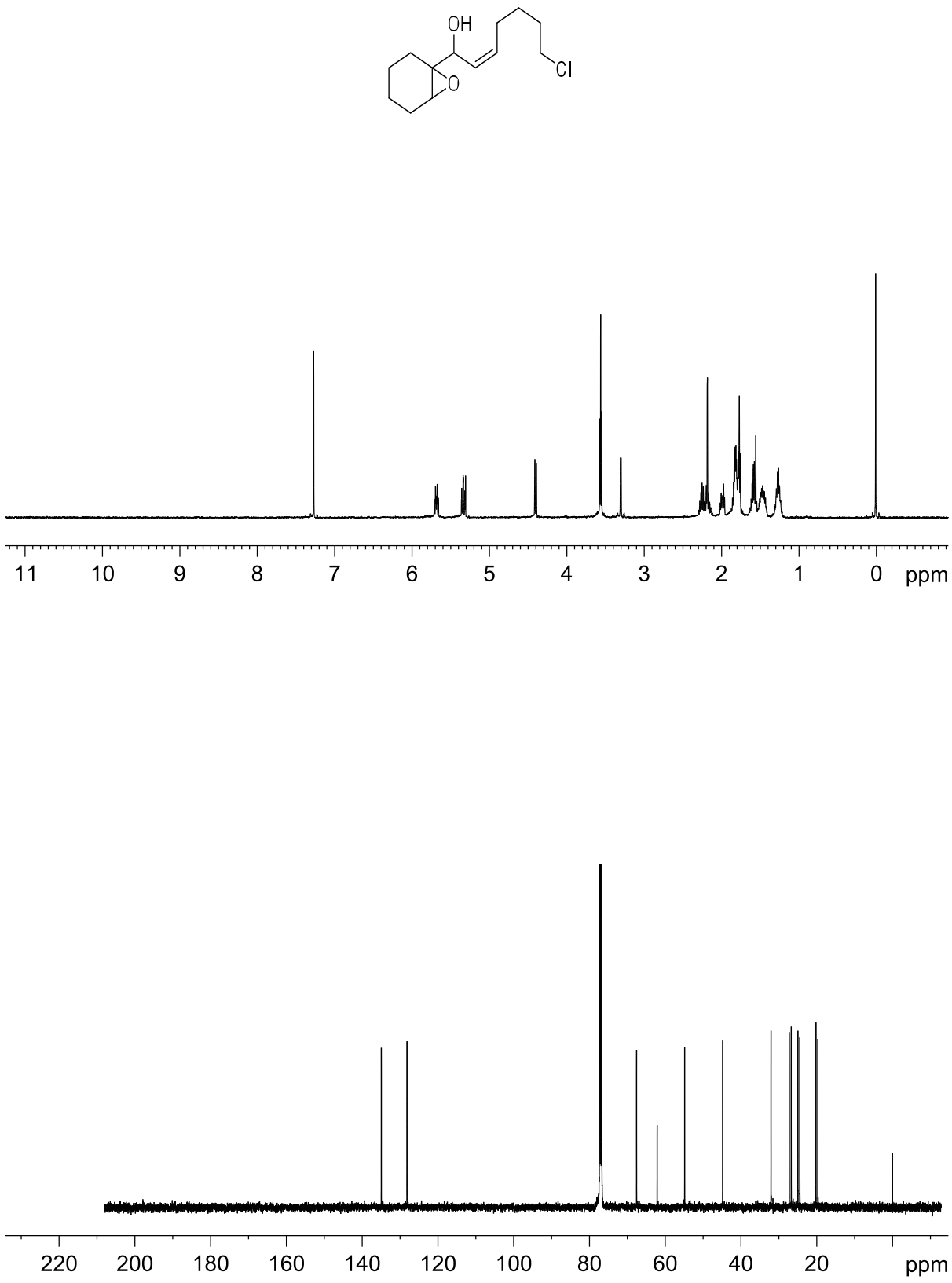


Figure 3-28. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-21** in $CDCl_3$.

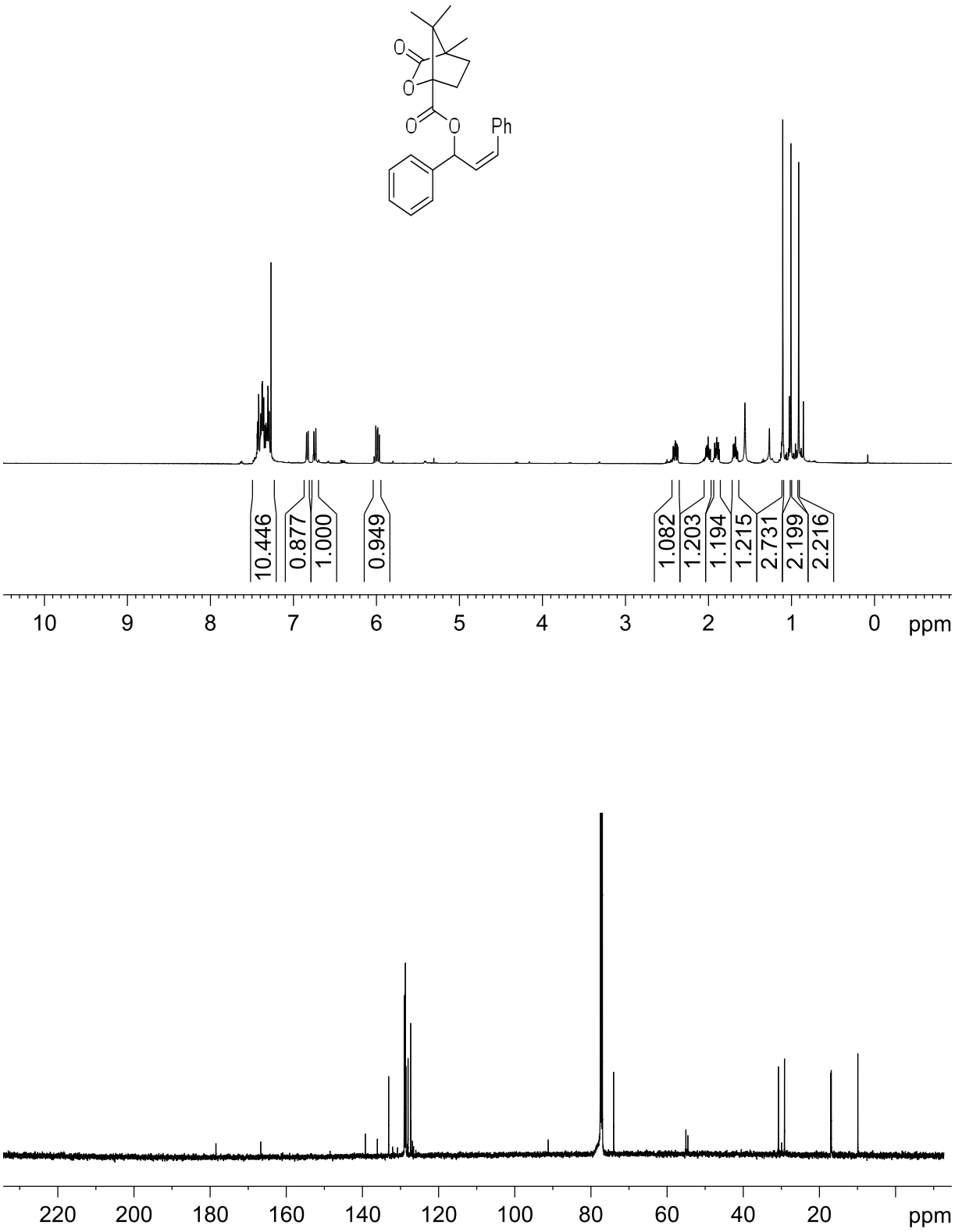


Figure 3-29. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Derivative of Compound **1-8** in $CDCl_3$.

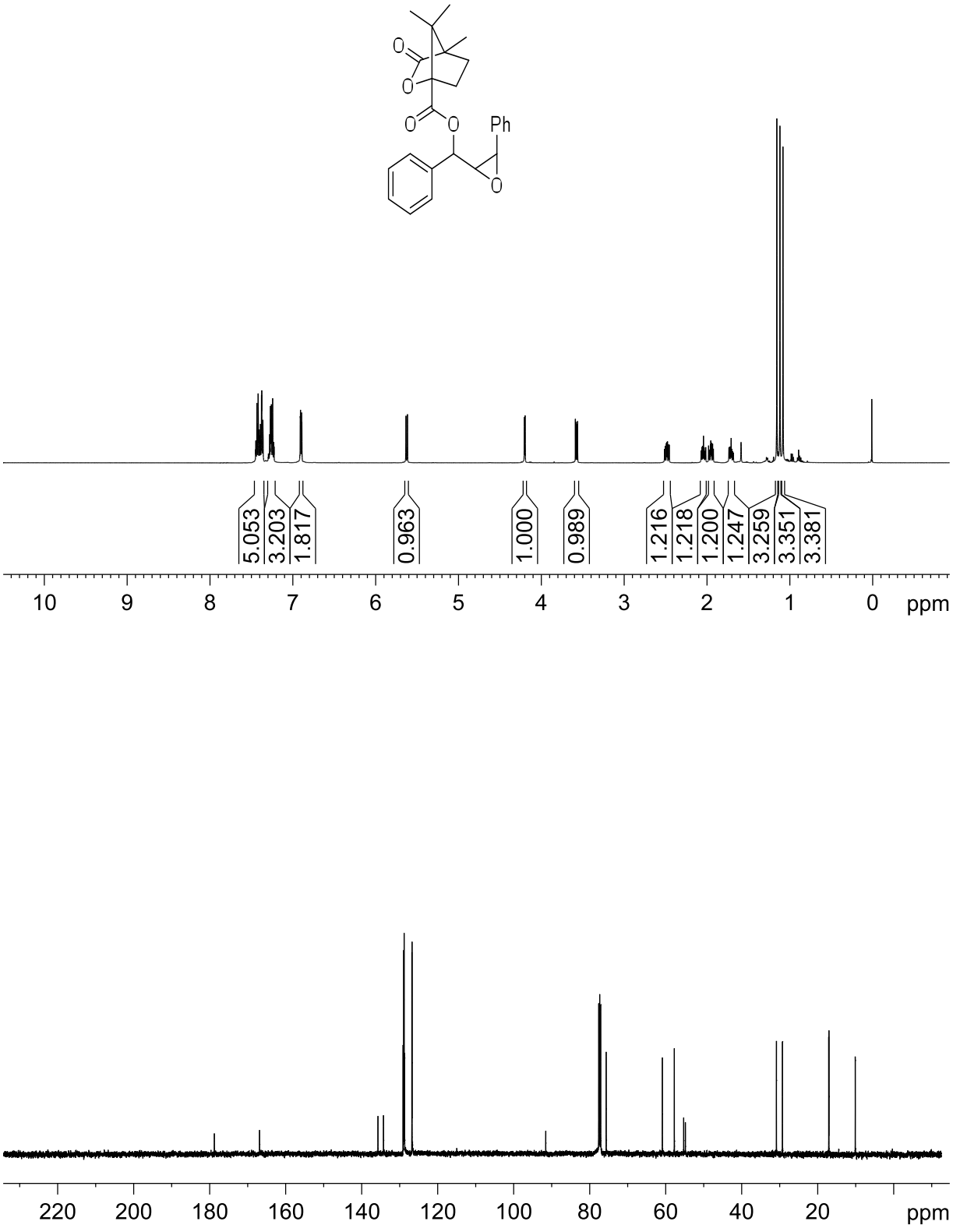


Figure 3-30. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Derivative of Compound **1-20** in $CDCl_3$.

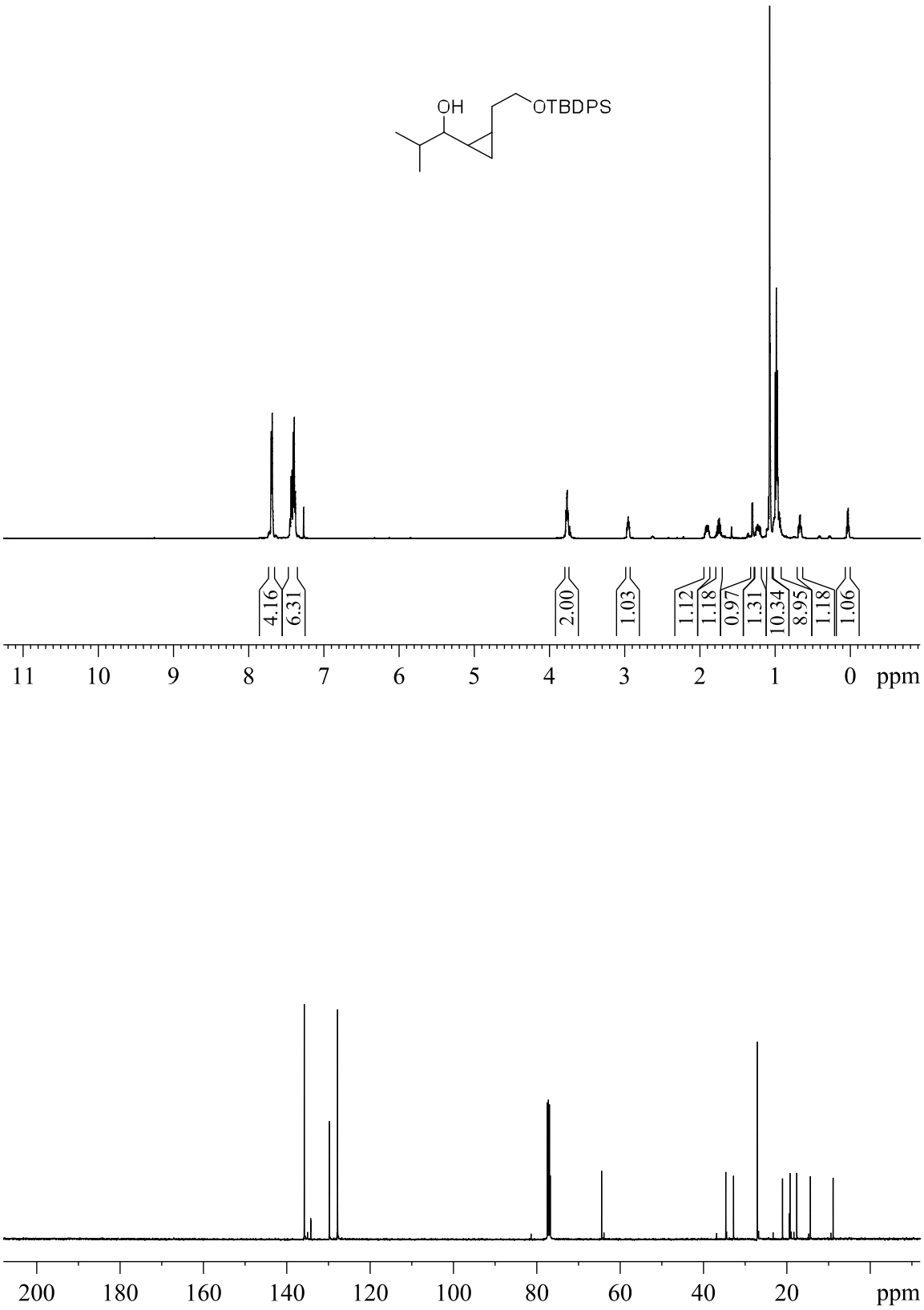


Figure 3-31. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-22** in $CDCl_3$.

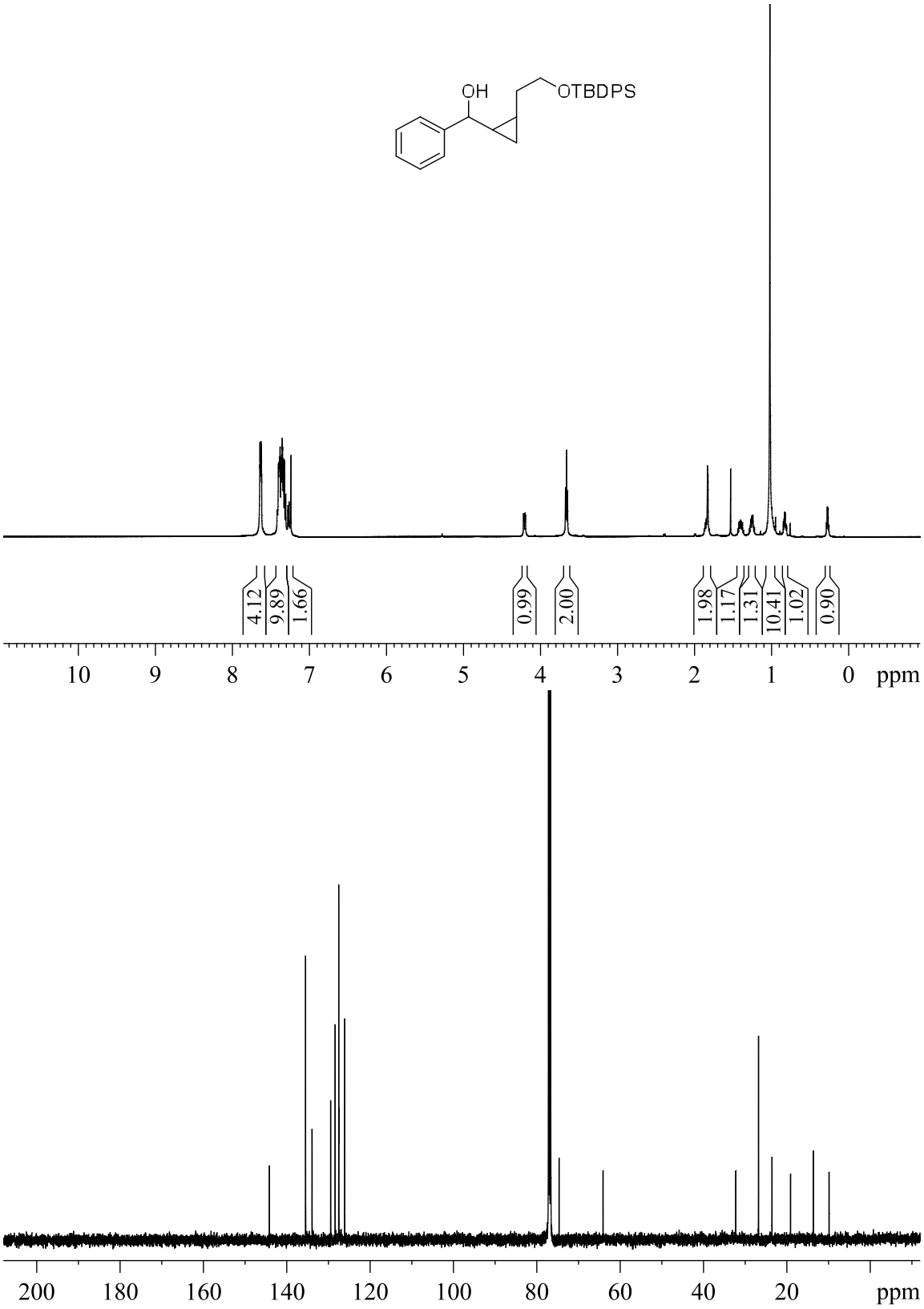


Figure 3-32. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-23** in $CDCl_3$.

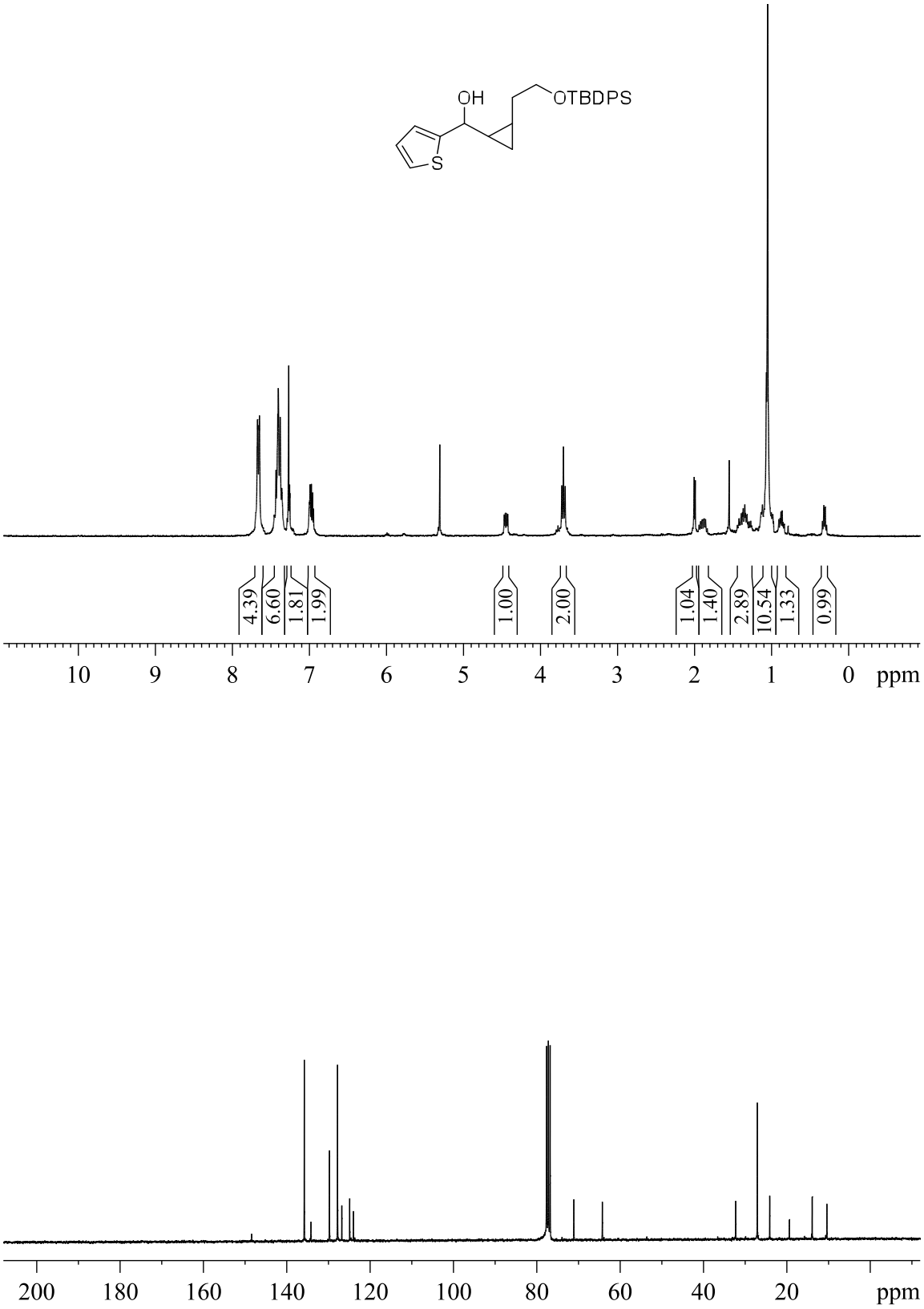


Figure 3-33. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-24** in $CDCl_3$.

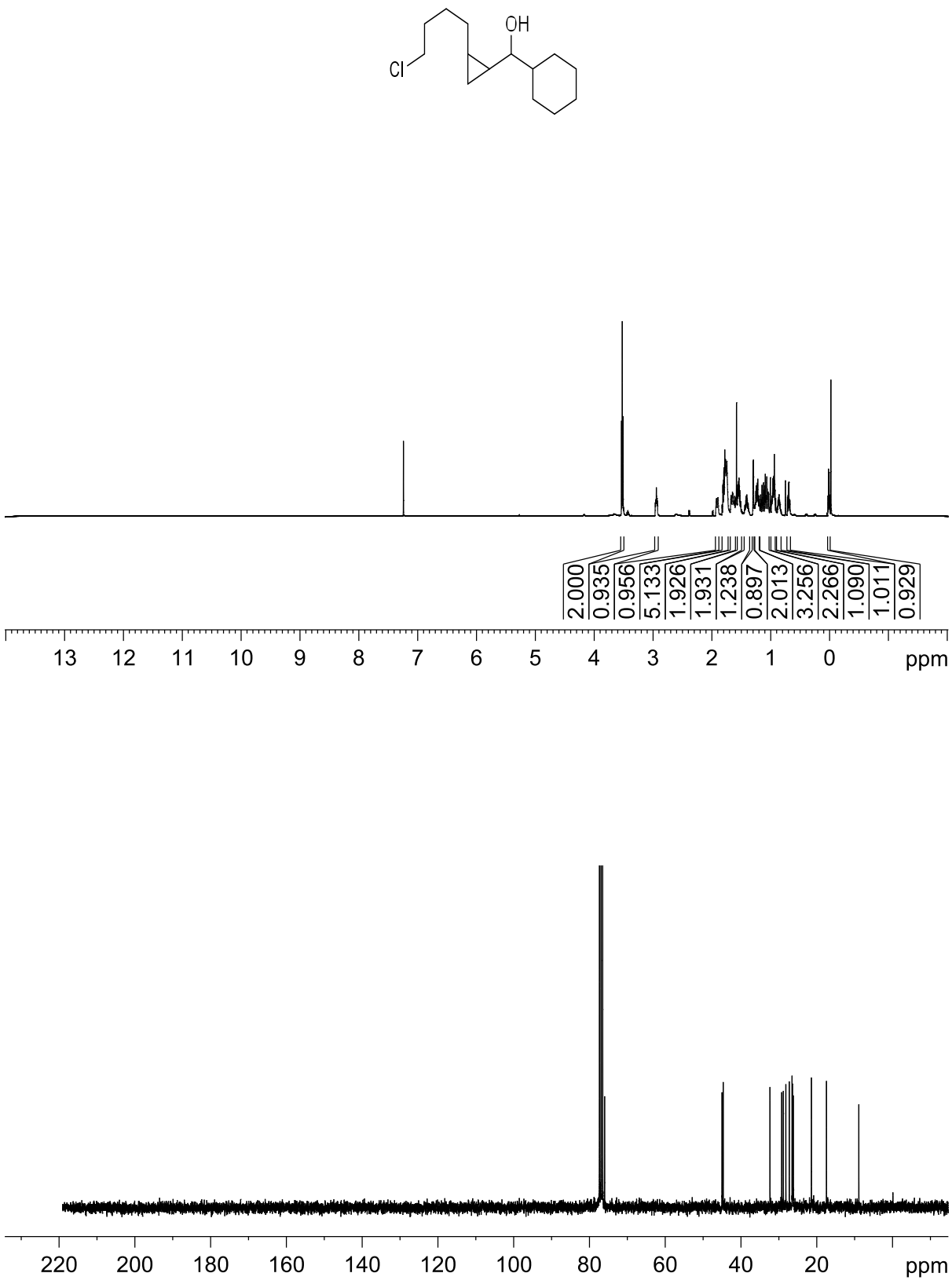


Figure 3-34. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-25** in $CDCl_3$.

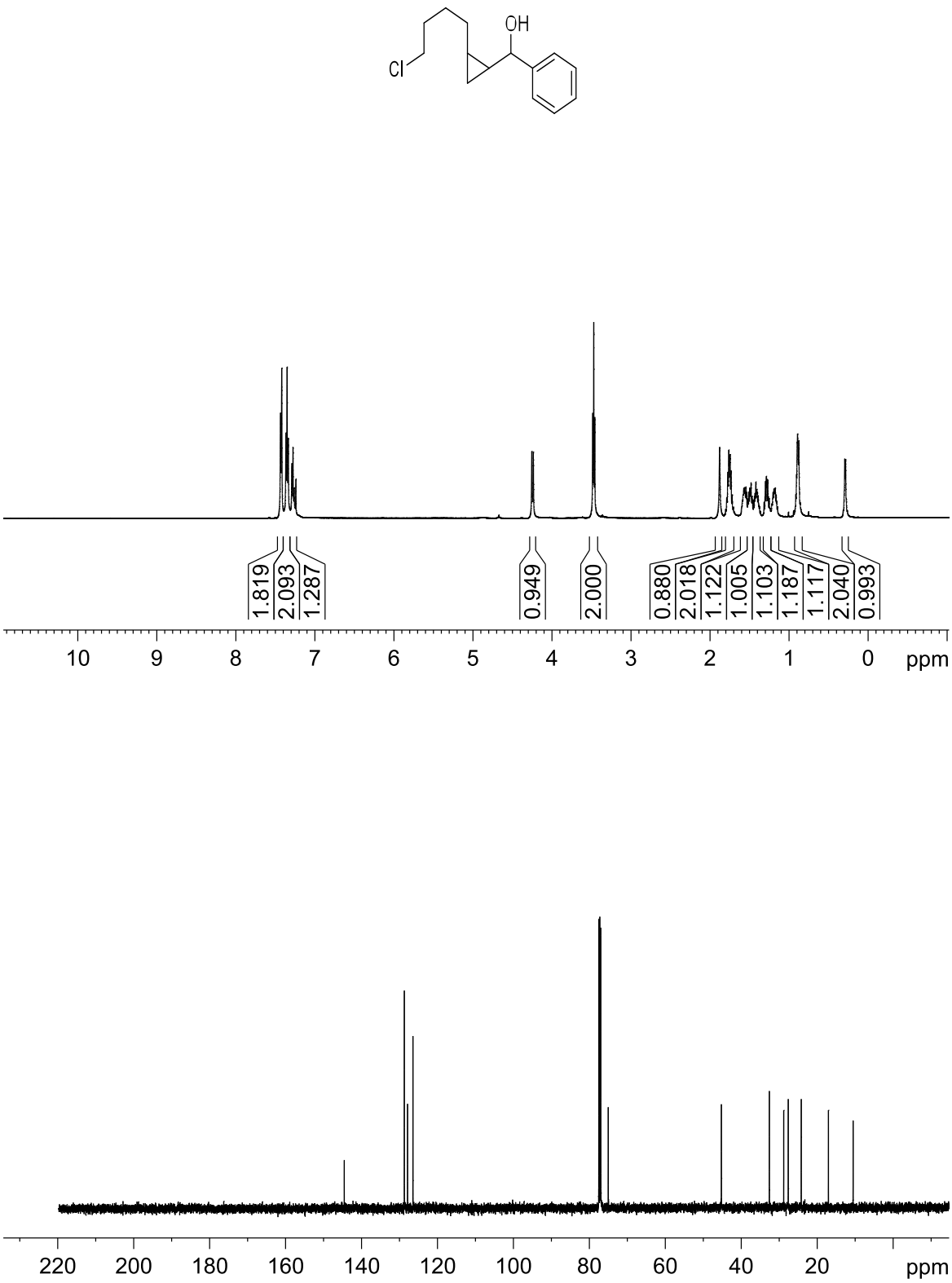


Figure 3-35. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-26** in $CDCl_3$.

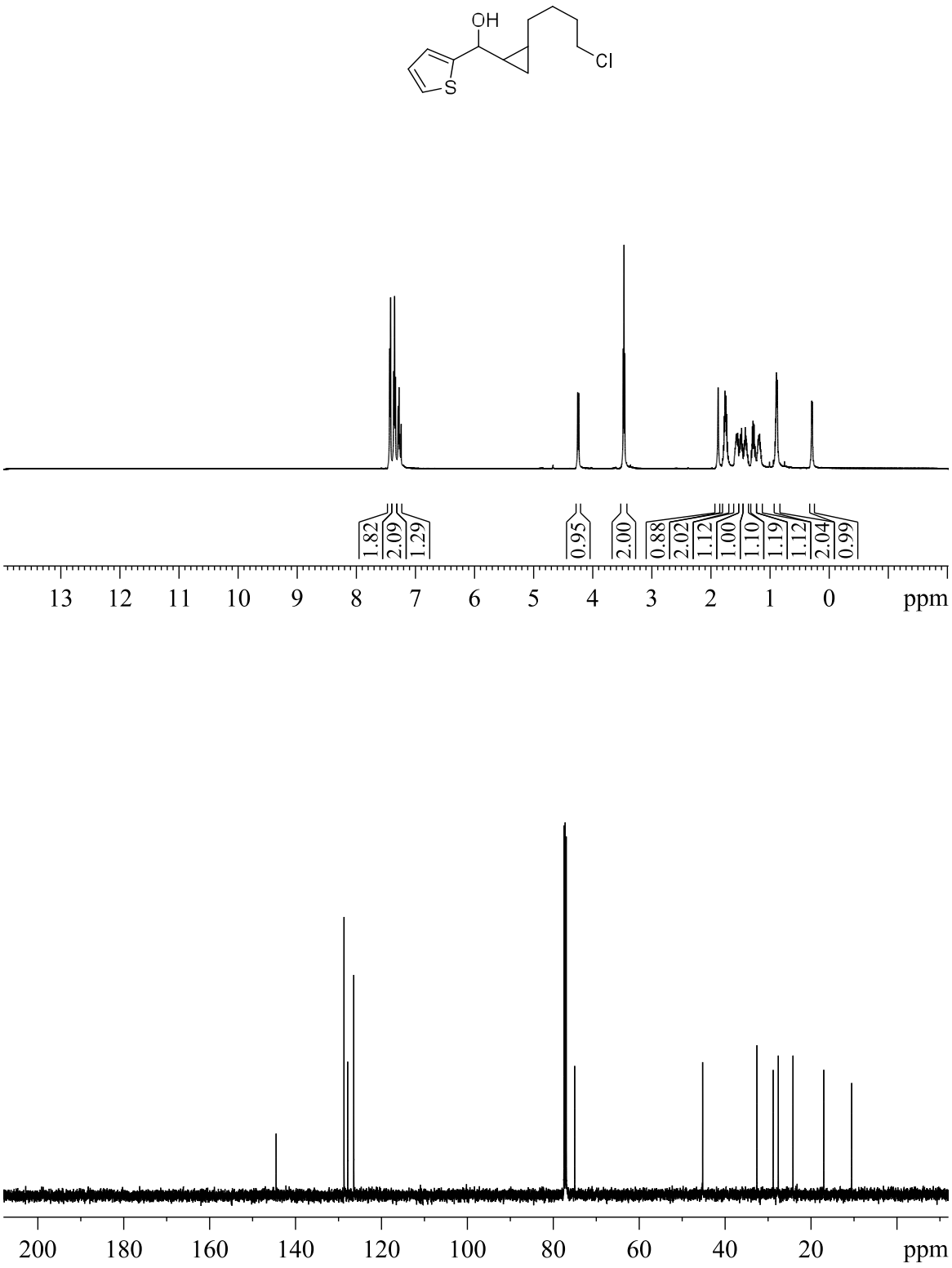


Figure 3-36. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-27** in $CDCl_3$.

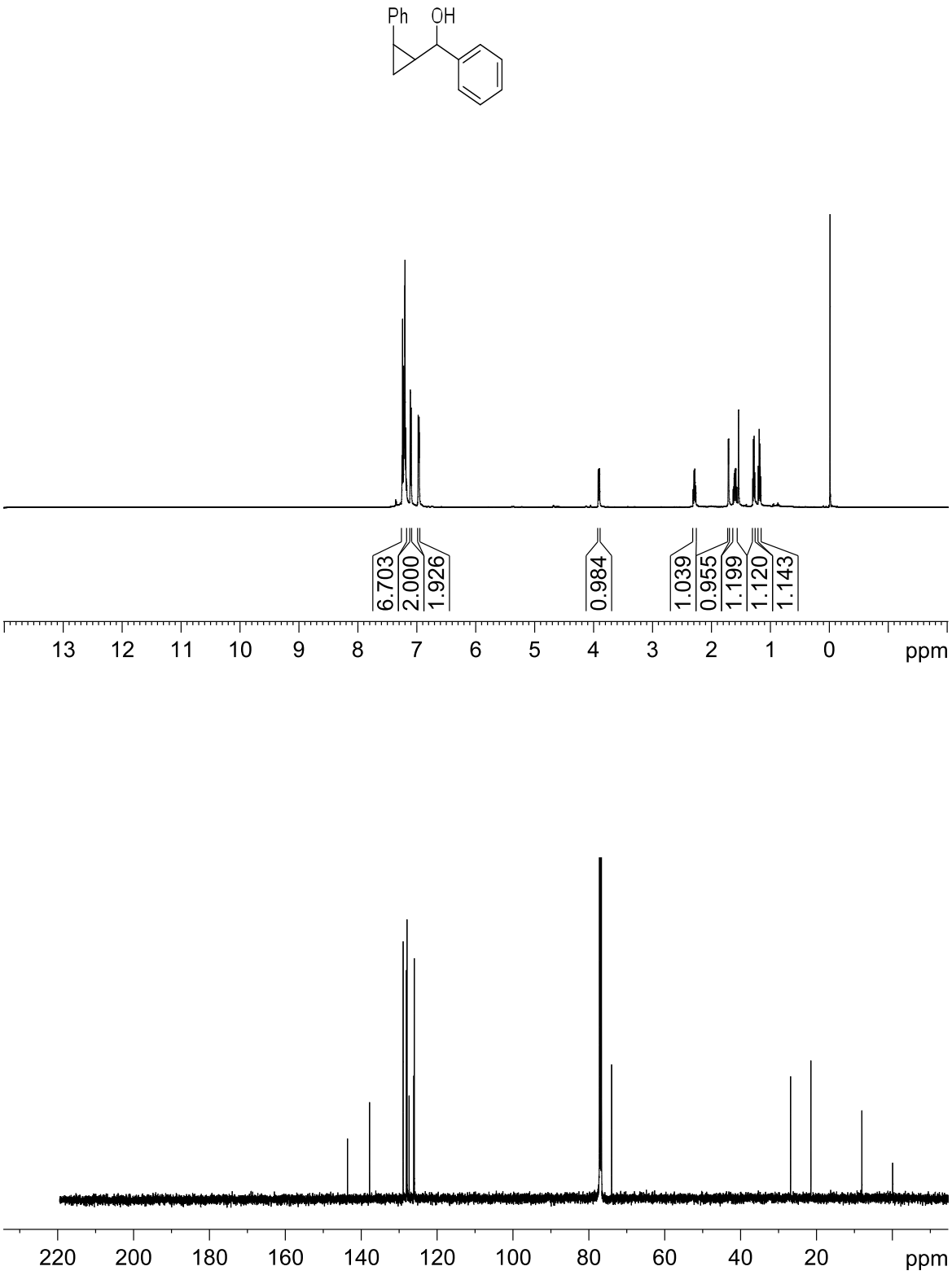


Figure 3-37. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-28** in $CDCl_3$.

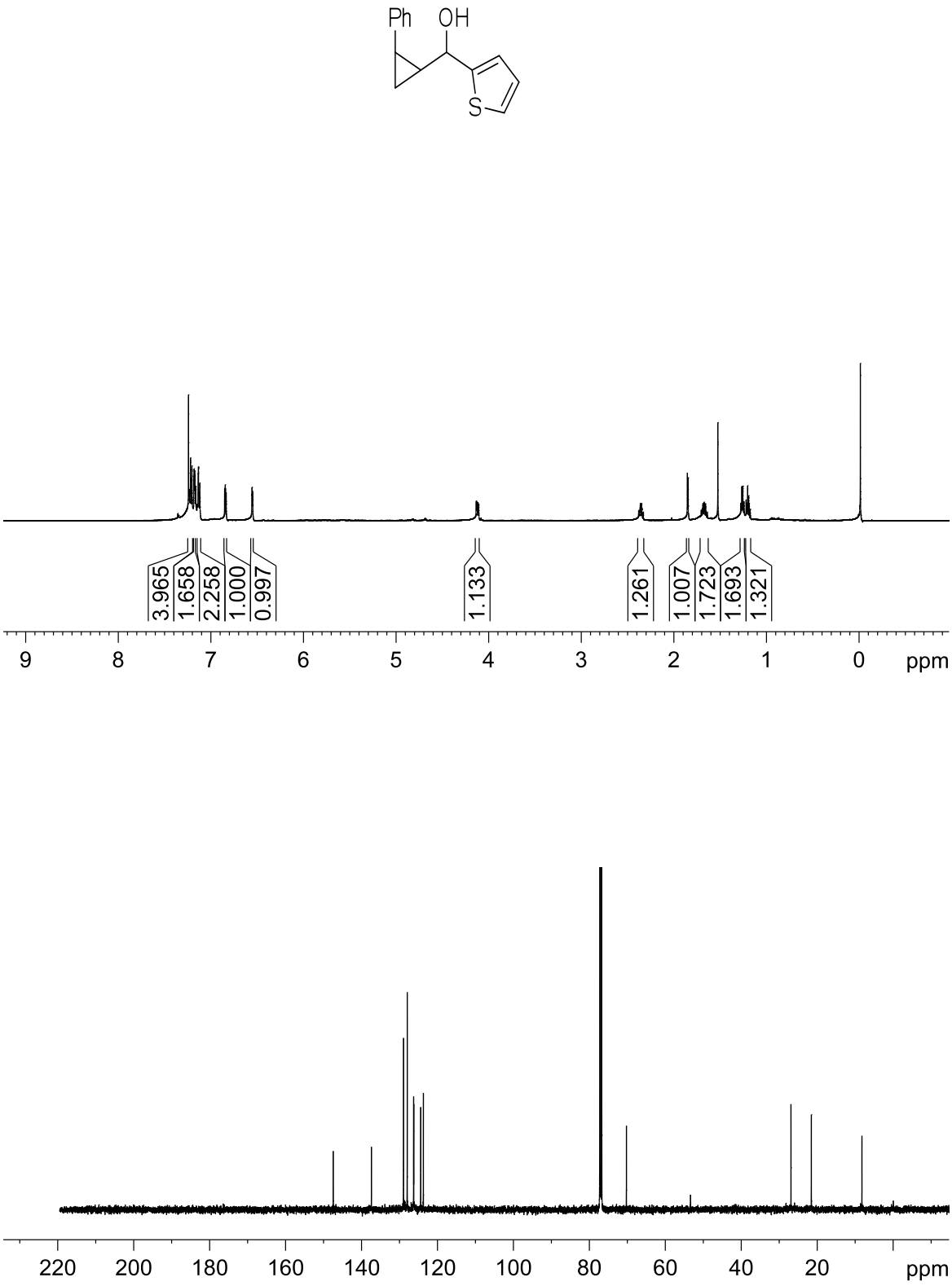


Figure 3-38. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-29** in $CDCl_3$.

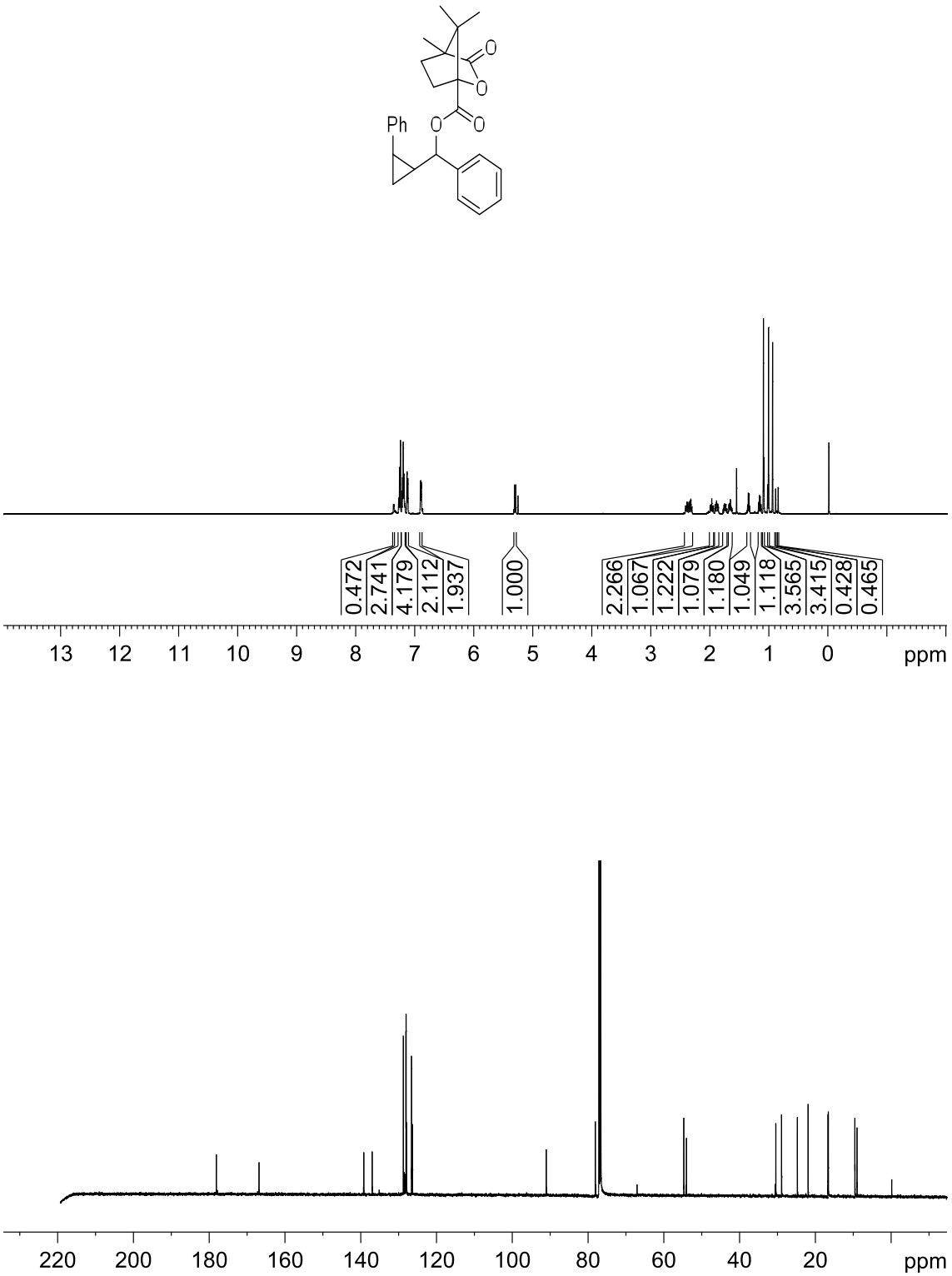


Figure 3-39. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Derivative of Compound **1-28** in $CDCl_3$.

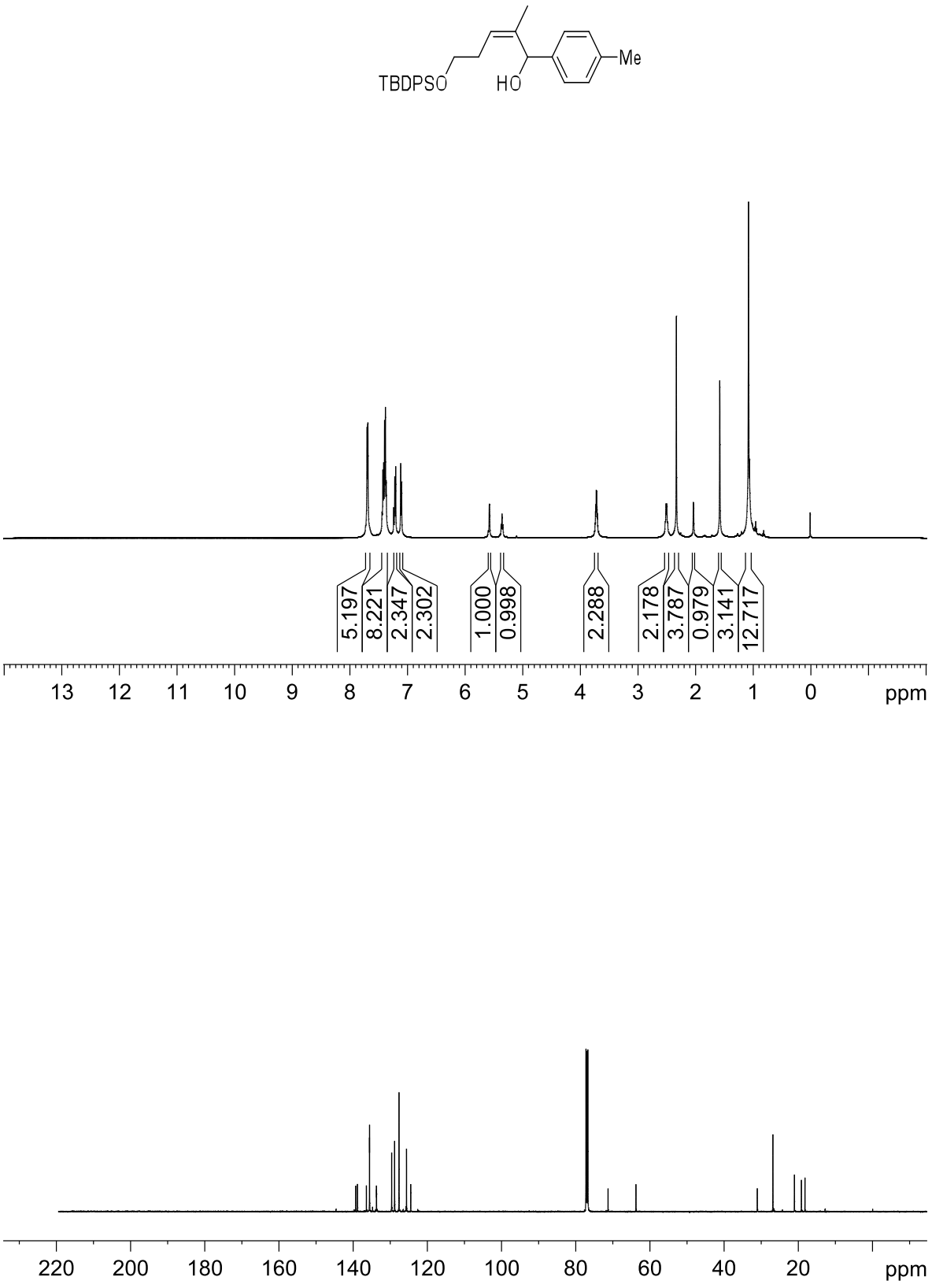


Figure 3-40. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-49** in $CDCl_3$.

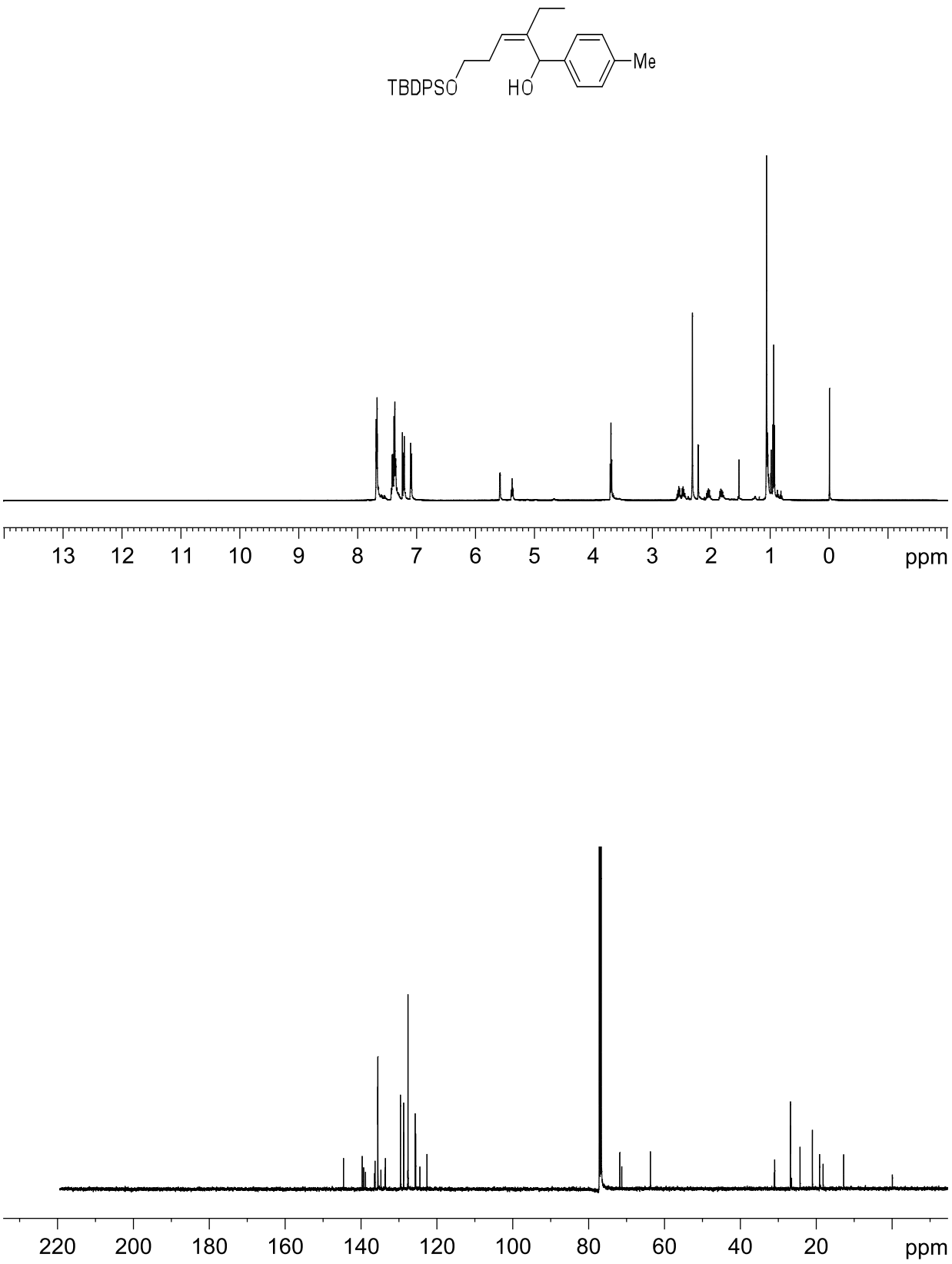


Figure 3-41. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-50** in $CDCl_3$.

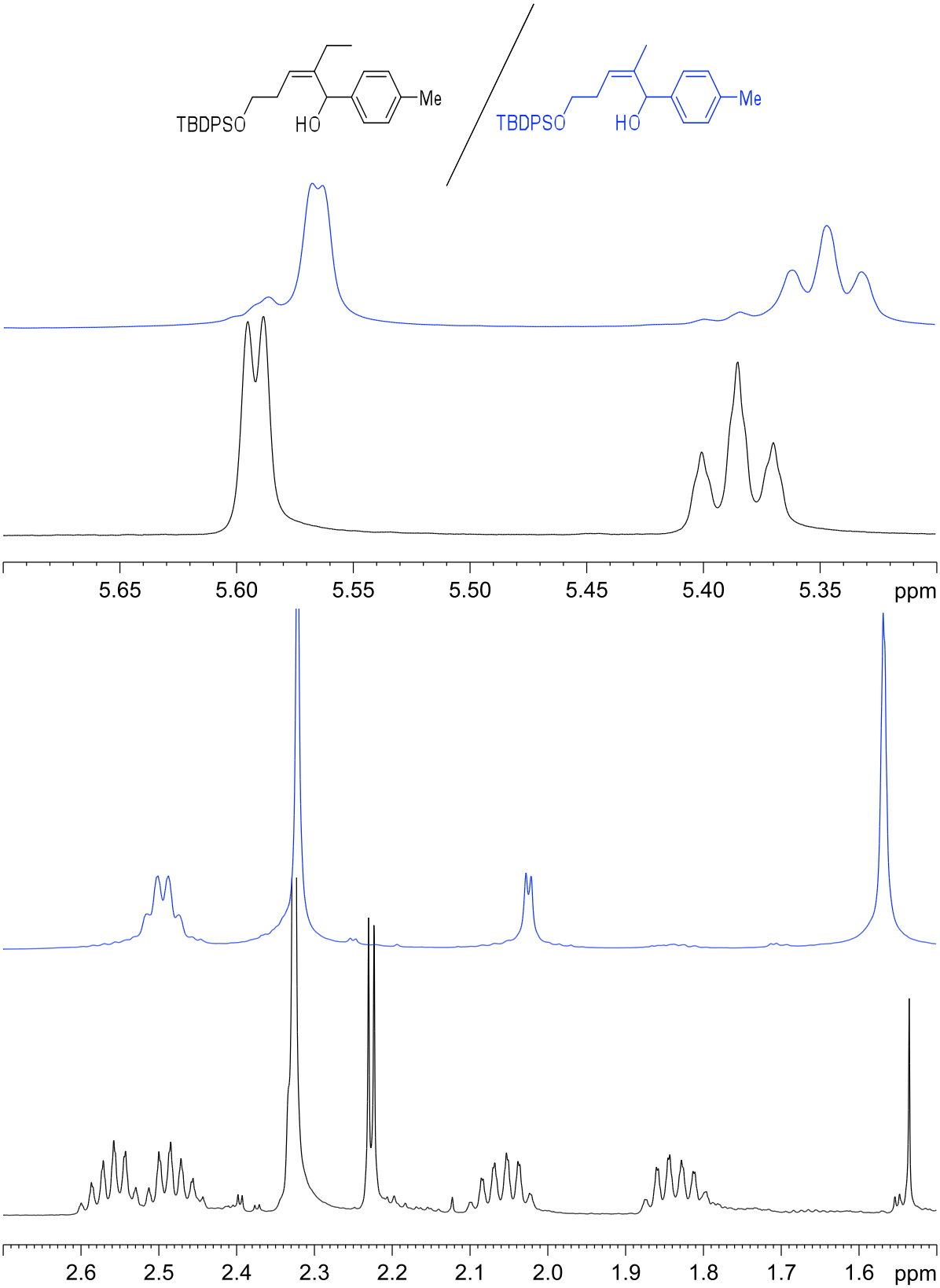


Figure 3-42. 500 MHz ^{1}H NMR of Compound **1-49** and **1-50** in a mixture in $CDCl_3$.

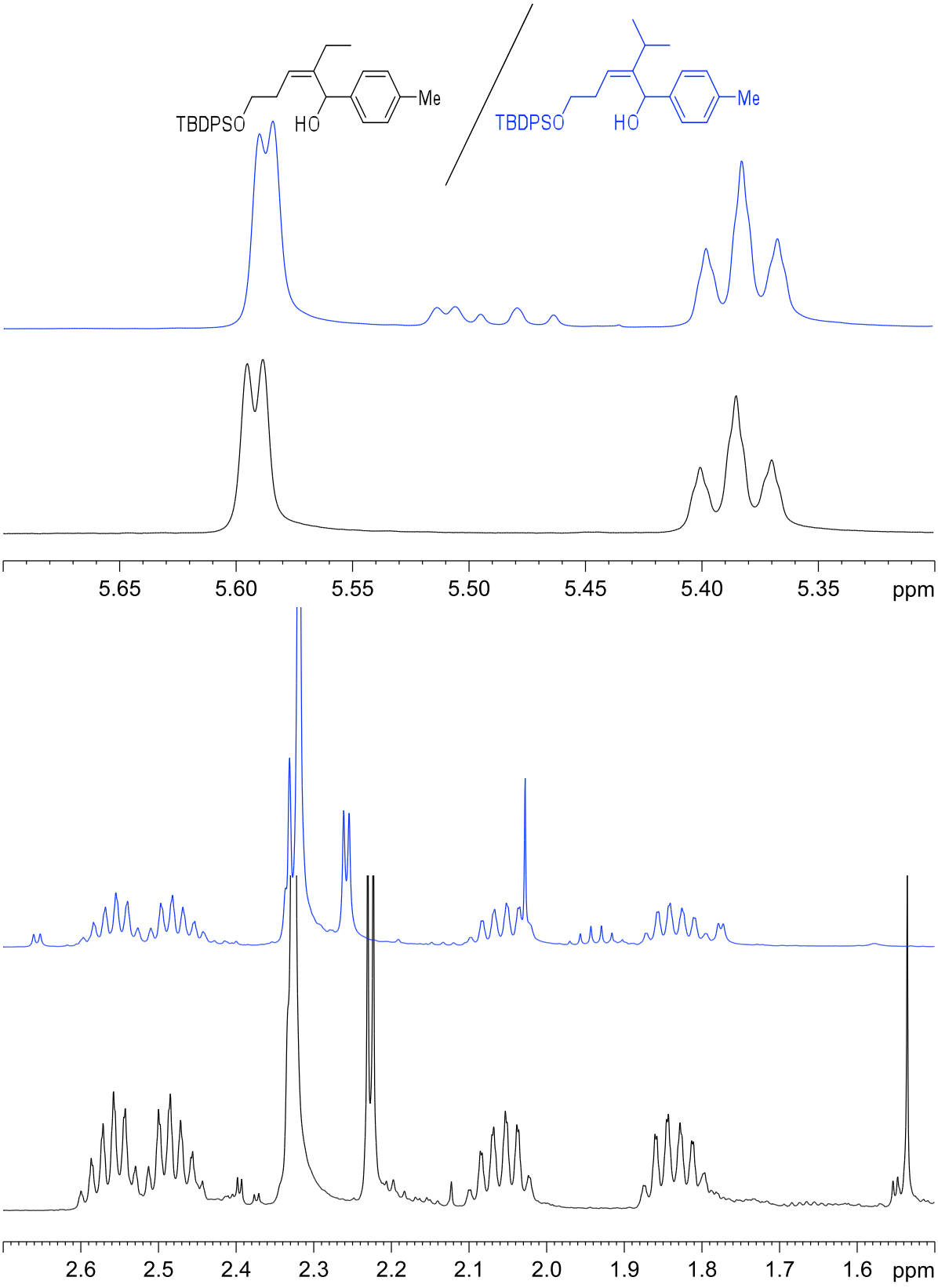


Figure 3-43. 500 MHz ^{1}H NMR of Compound **1-50** and **1-51** in a mixture in $CDCl_3$.

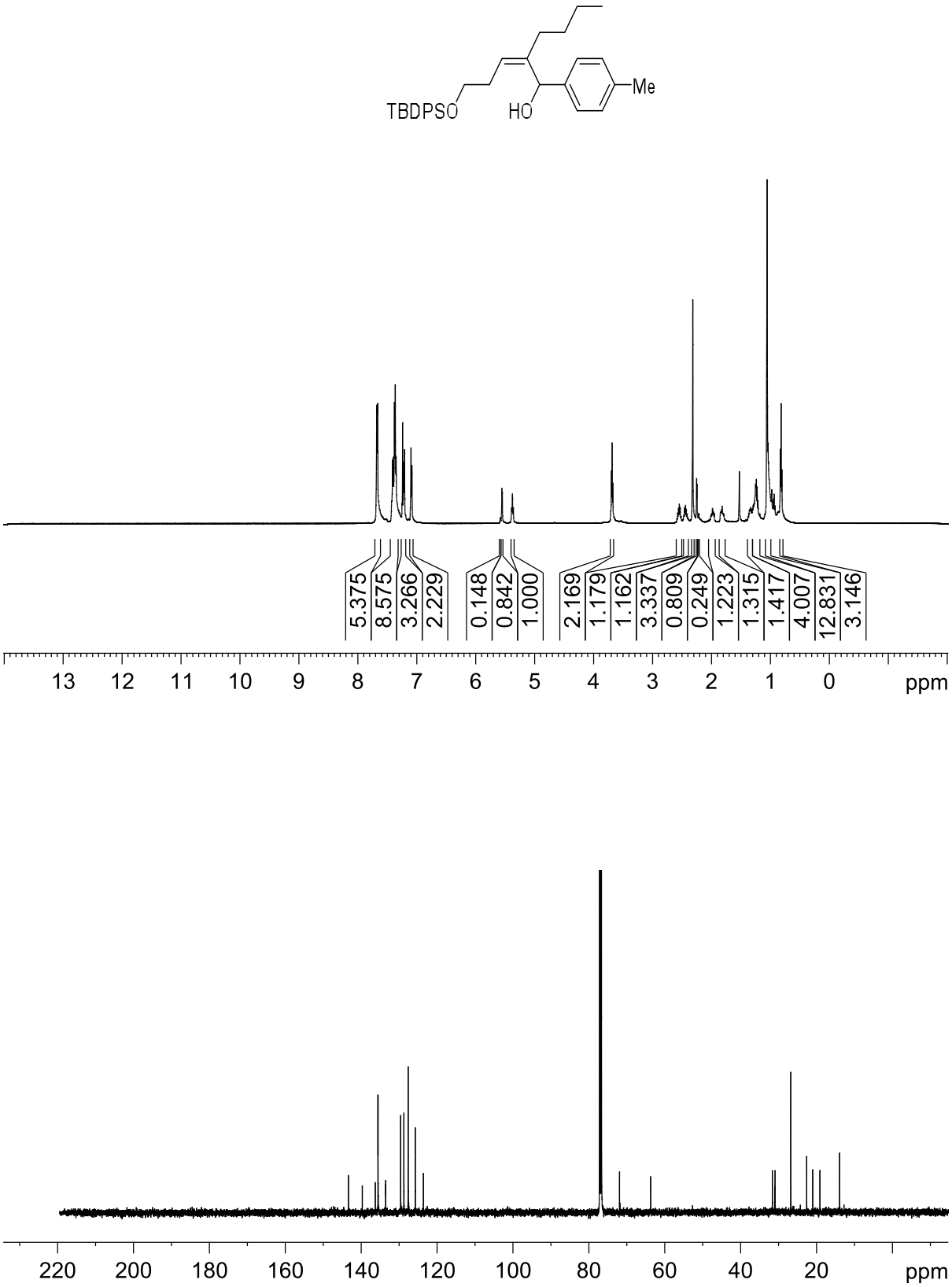


Figure 3-44. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-52** in $CDCl_3$.

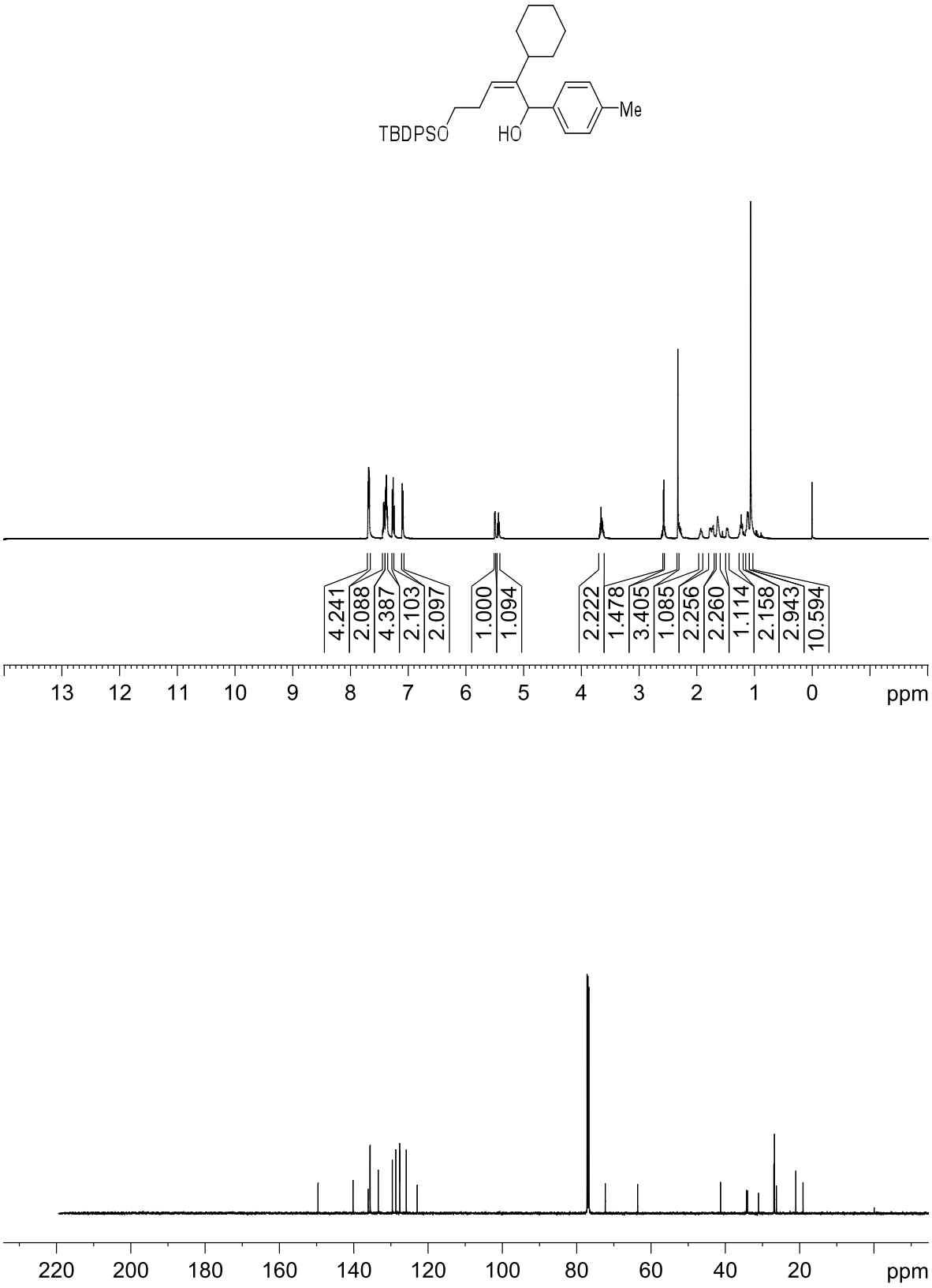


Figure 3-45. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-53** in $CDCl_3$.

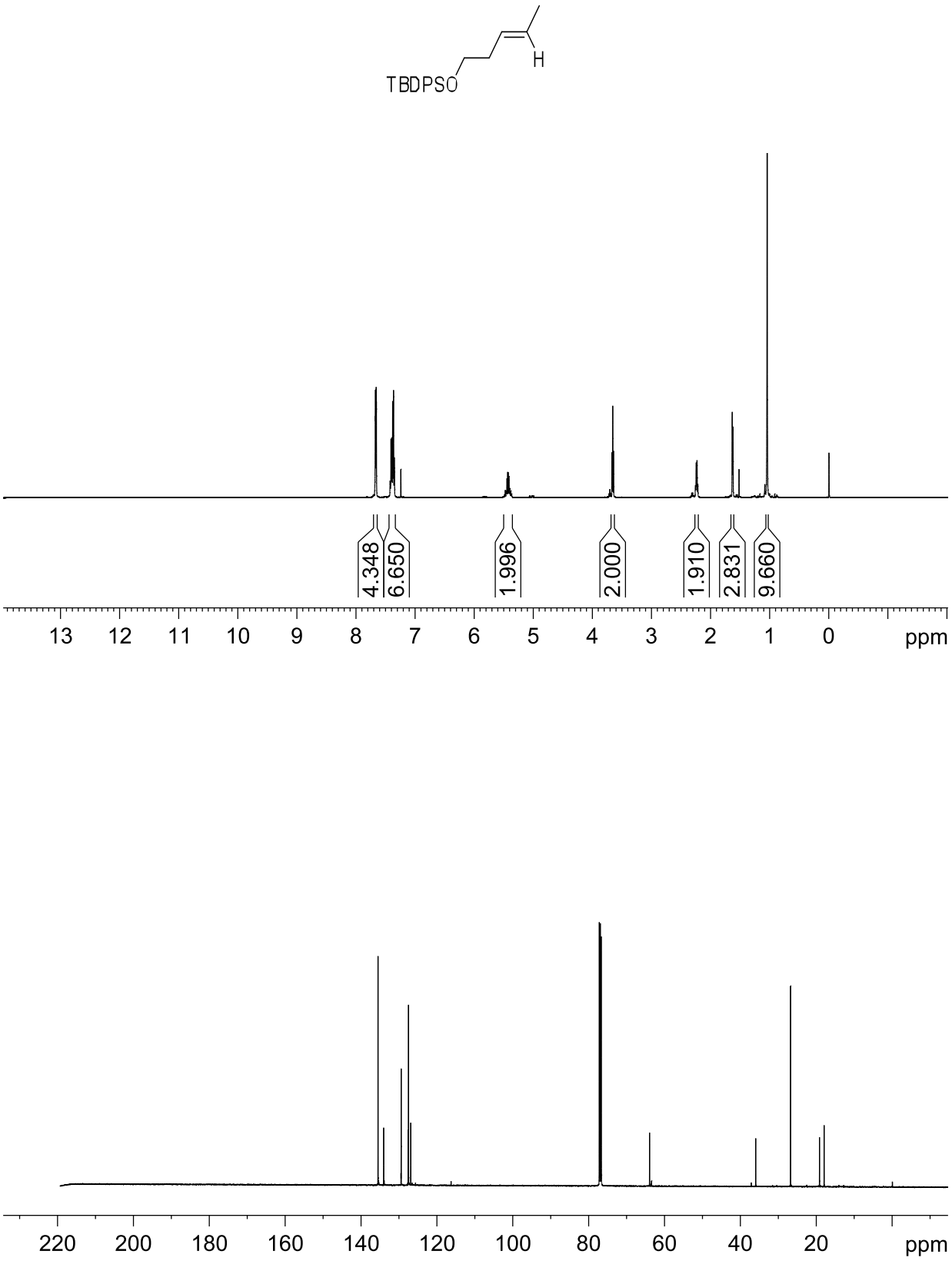


Figure 3-46. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-54** in $CDCl_3$.

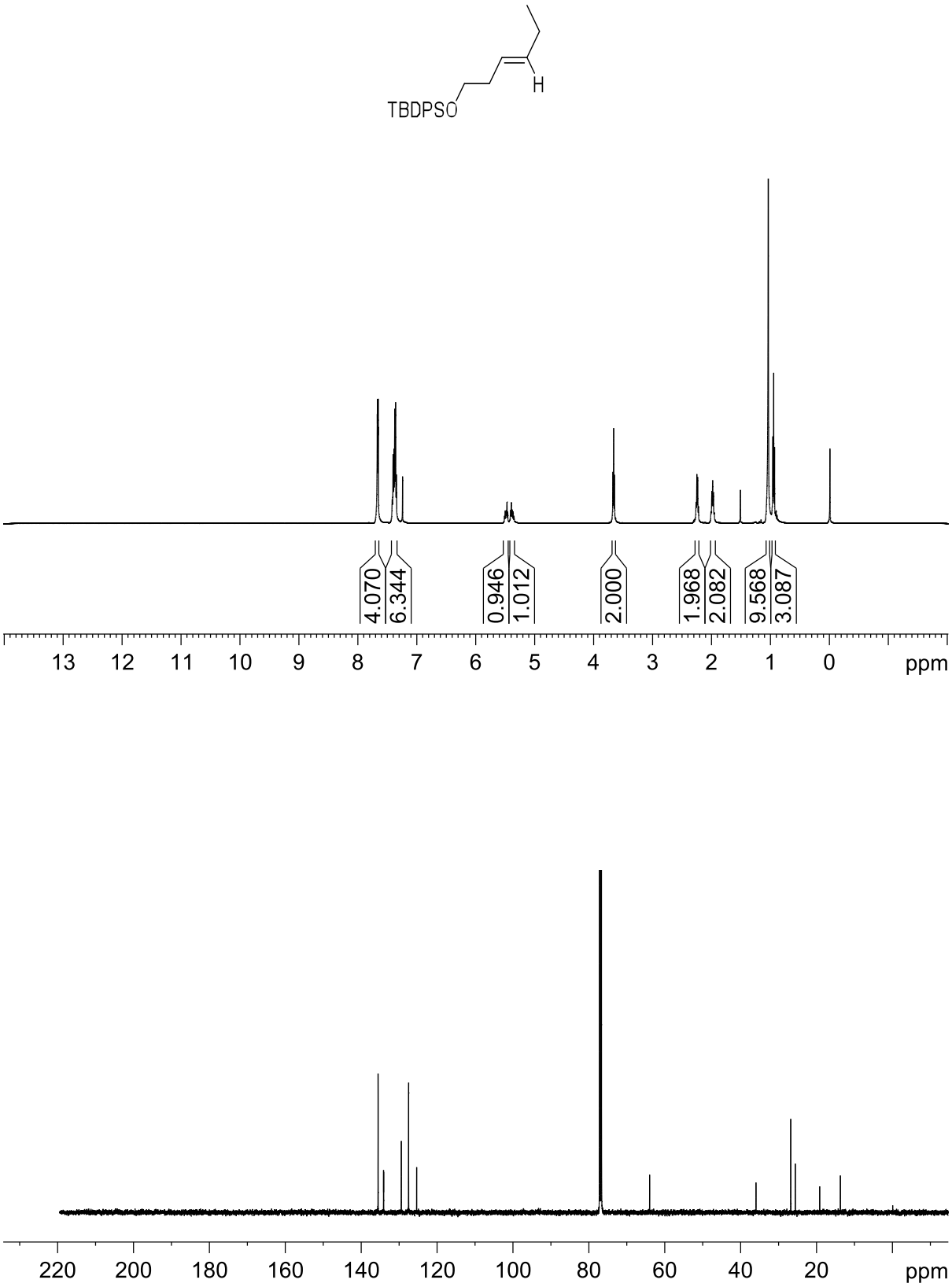


Figure 3-47. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **1-55** in $CDCl_3$.

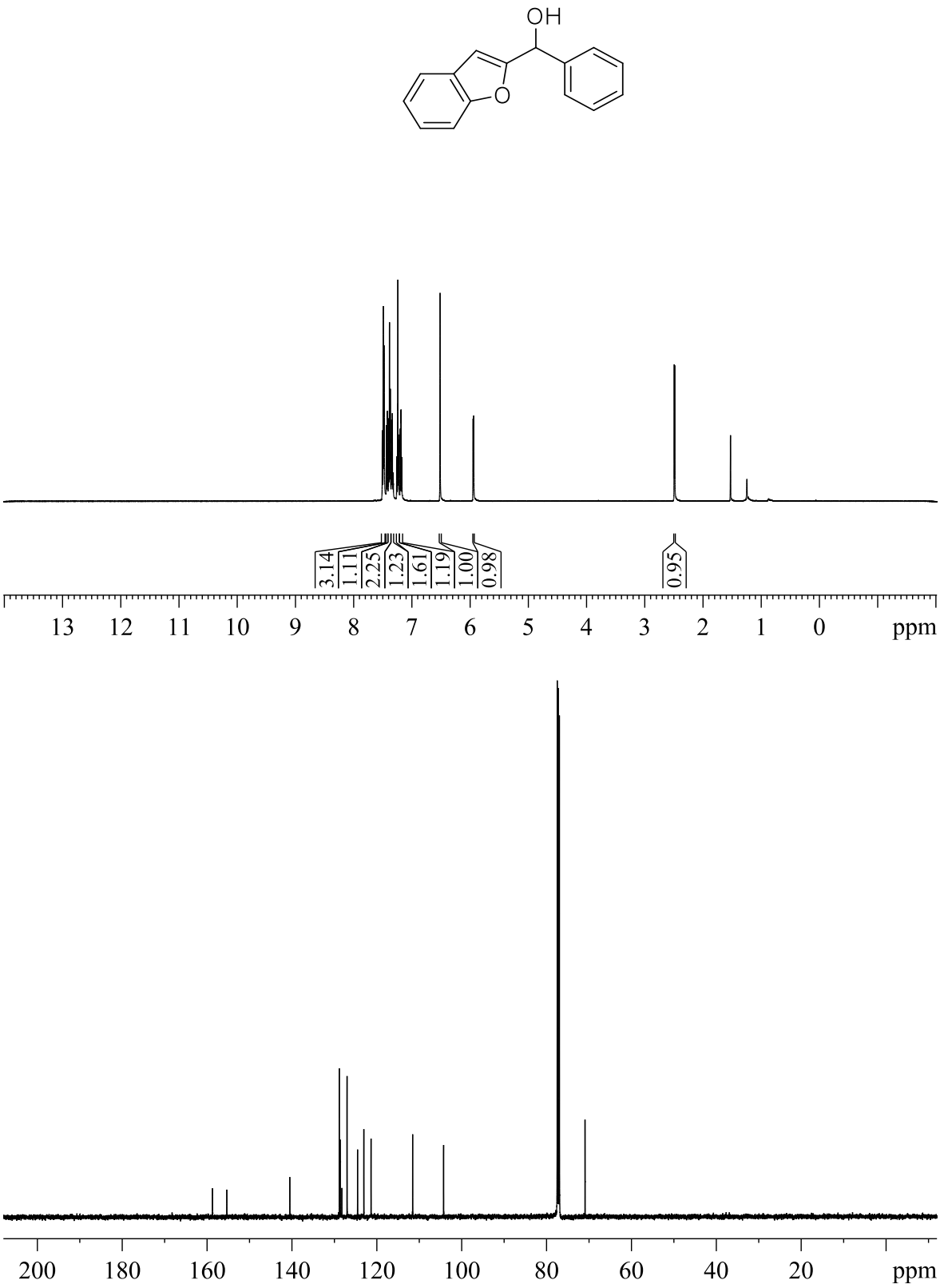


Figure 3-48. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-1a** in $CDCl_3$.

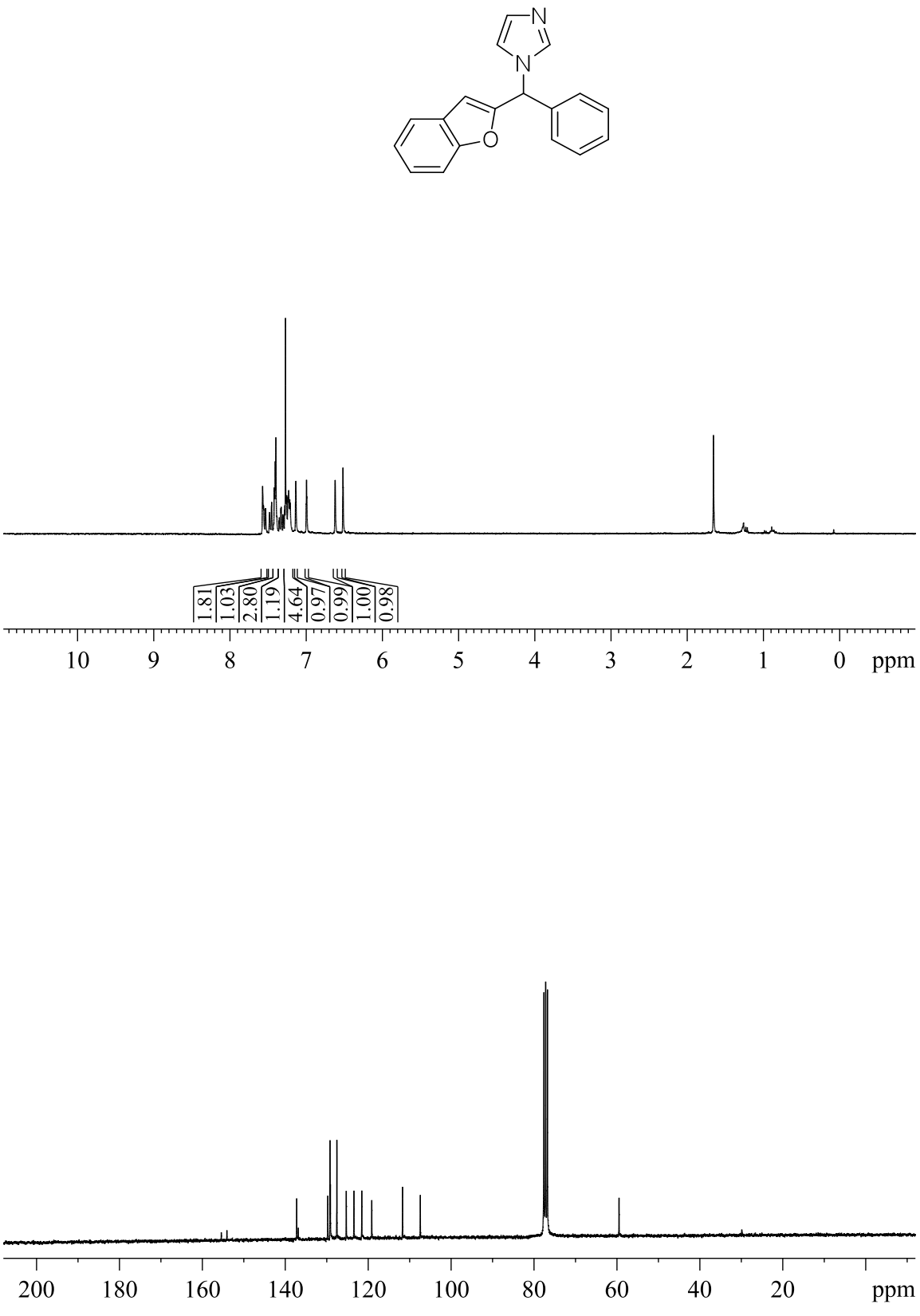


Figure 3-49. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-2a** in $CDCl_3$.

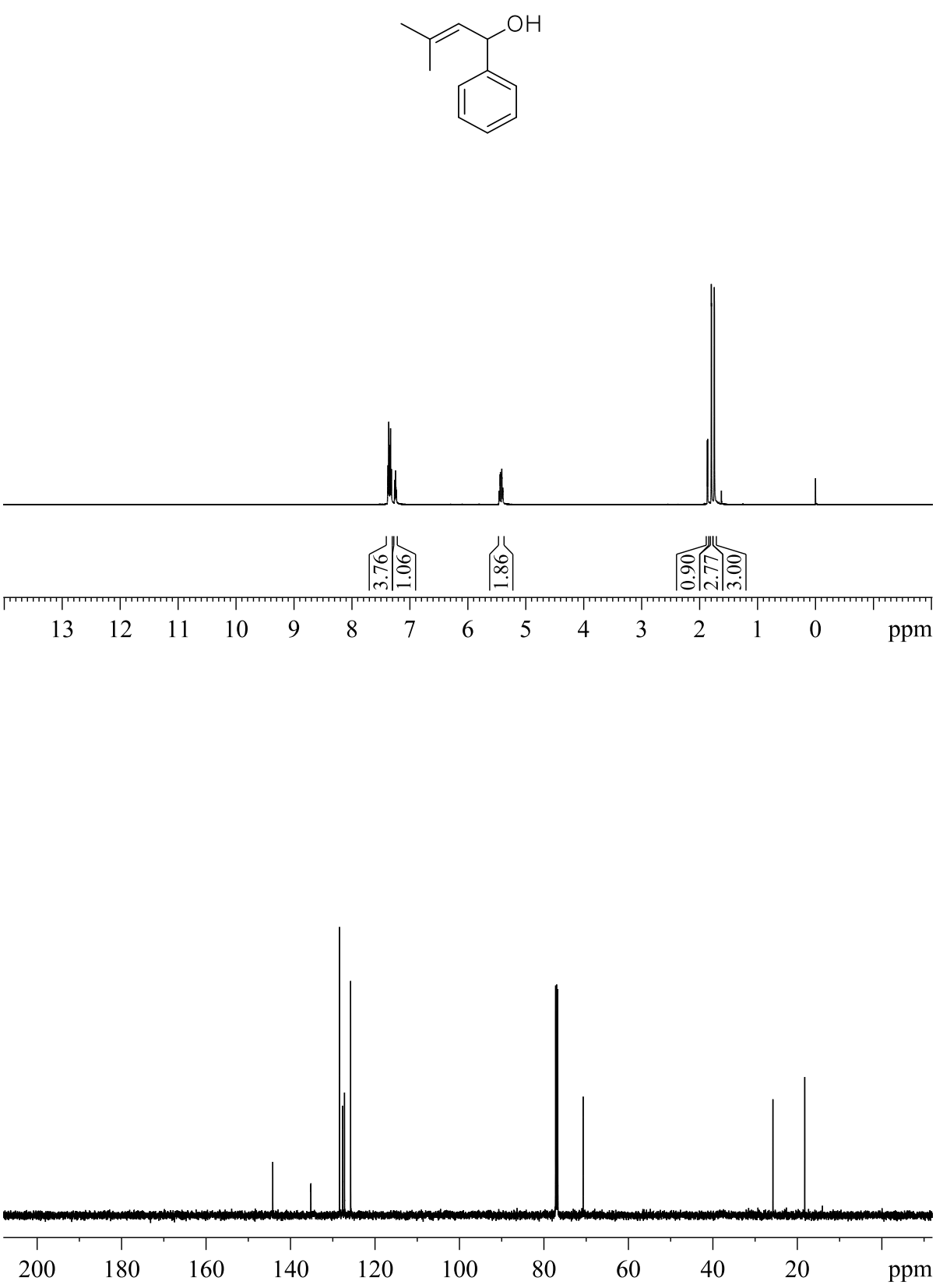


Figure 3-50. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-7** in $CDCl_3$.

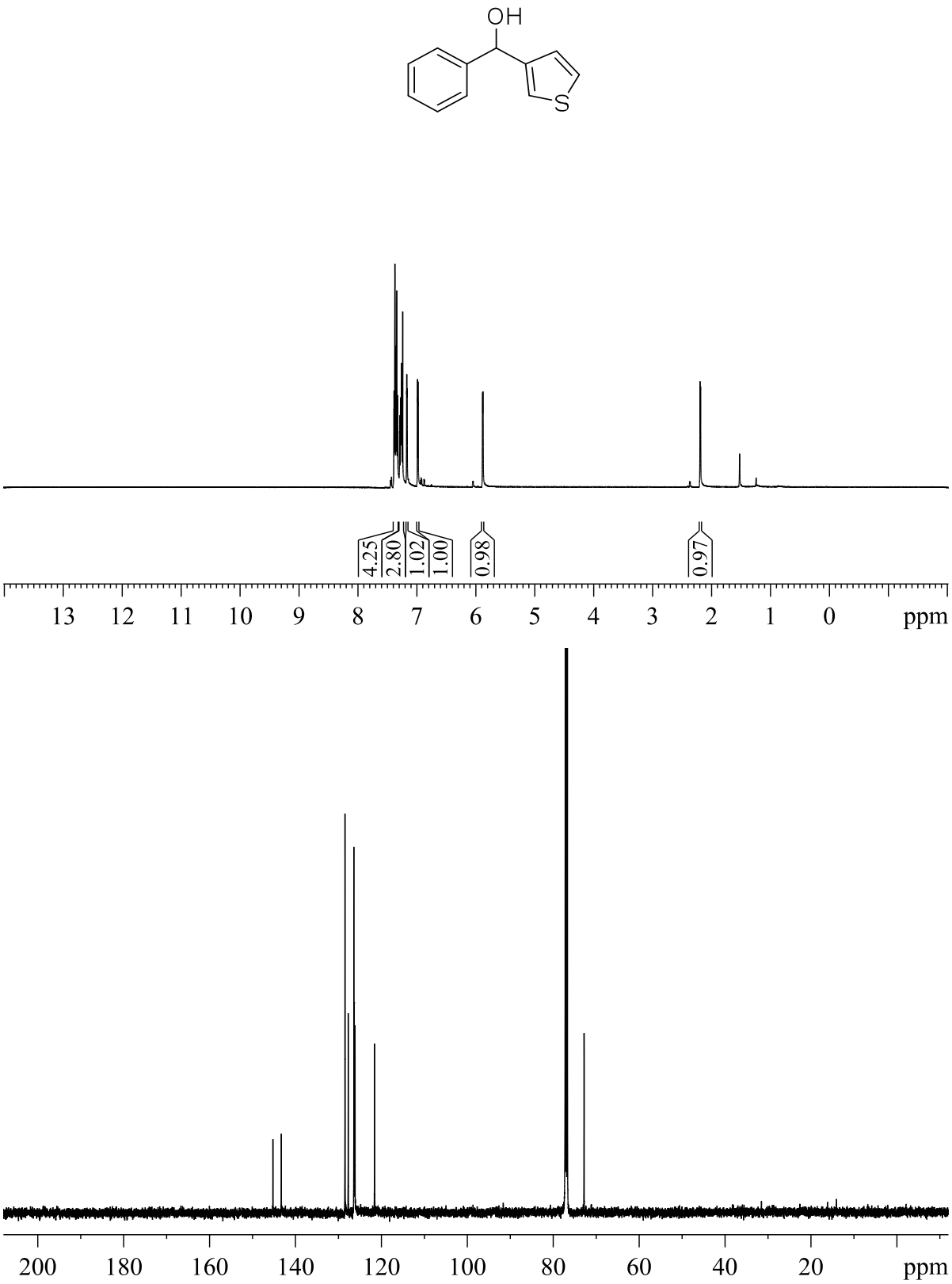


Figure 3-51. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-25** in $CDCl_3$.

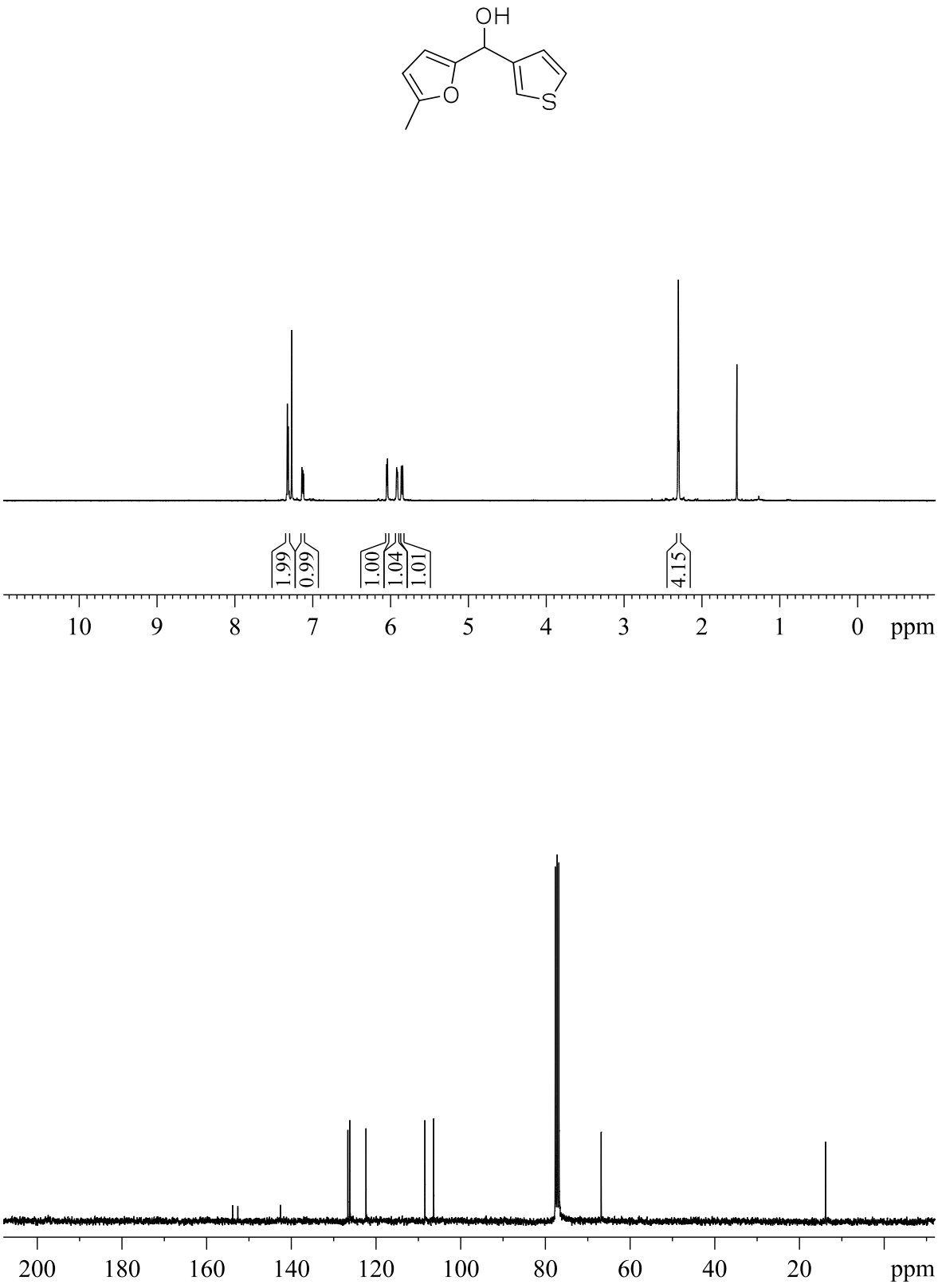


Figure 3-52. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-26** in $CDCl_3$.

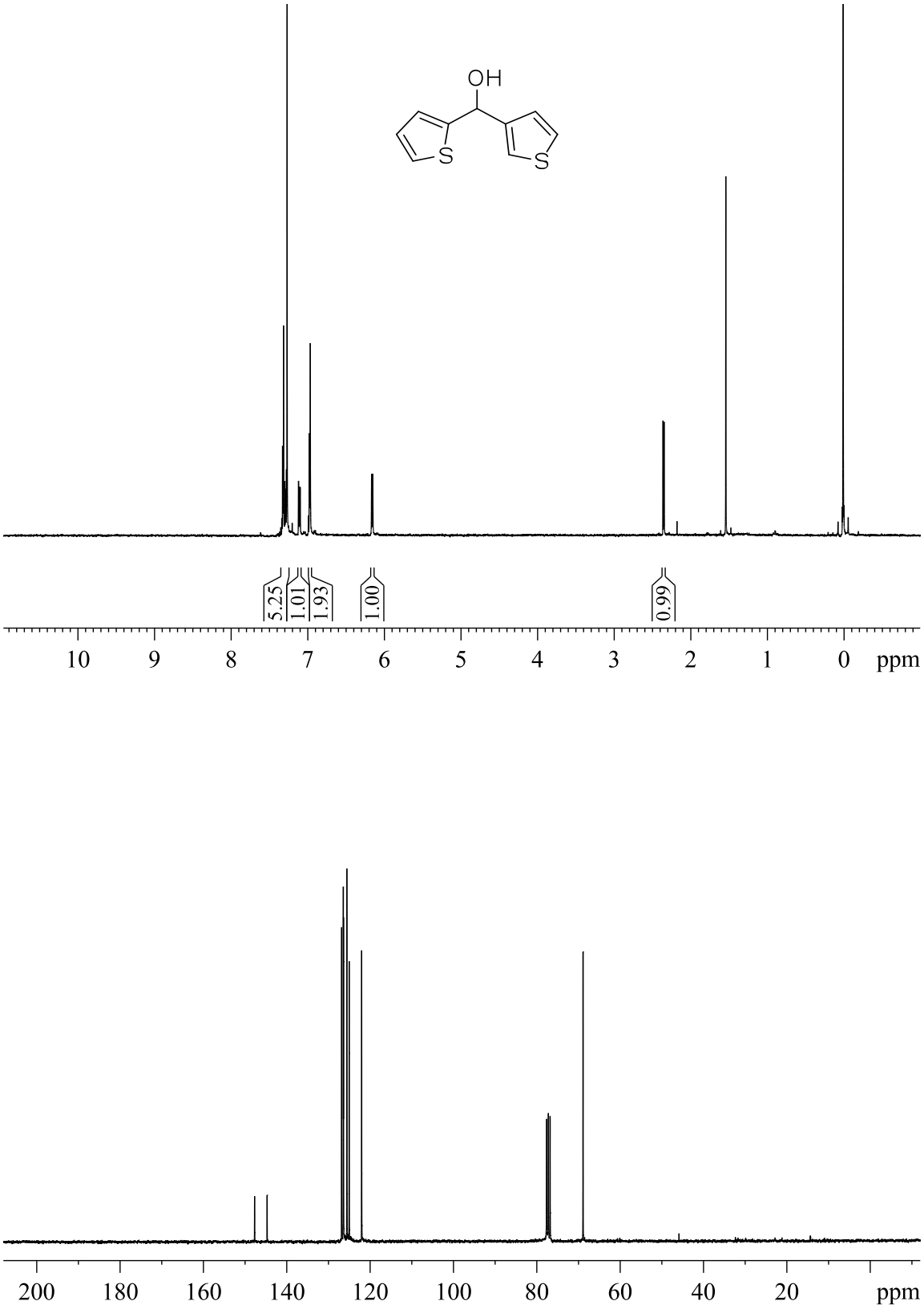


Figure 3-53. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-27** in $CDCl_3$.

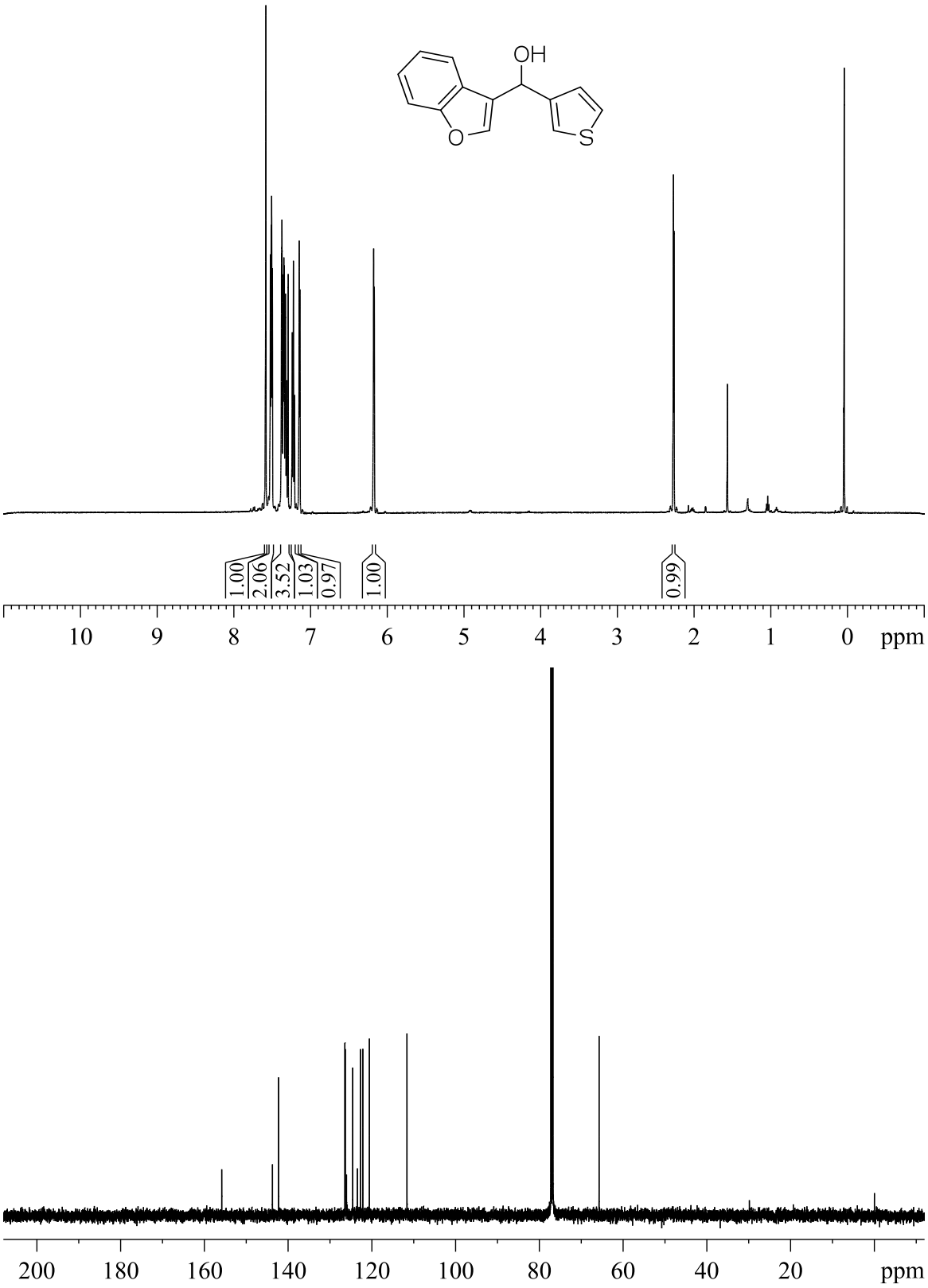


Figure 3-54. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-28** in $CDCl_3$.

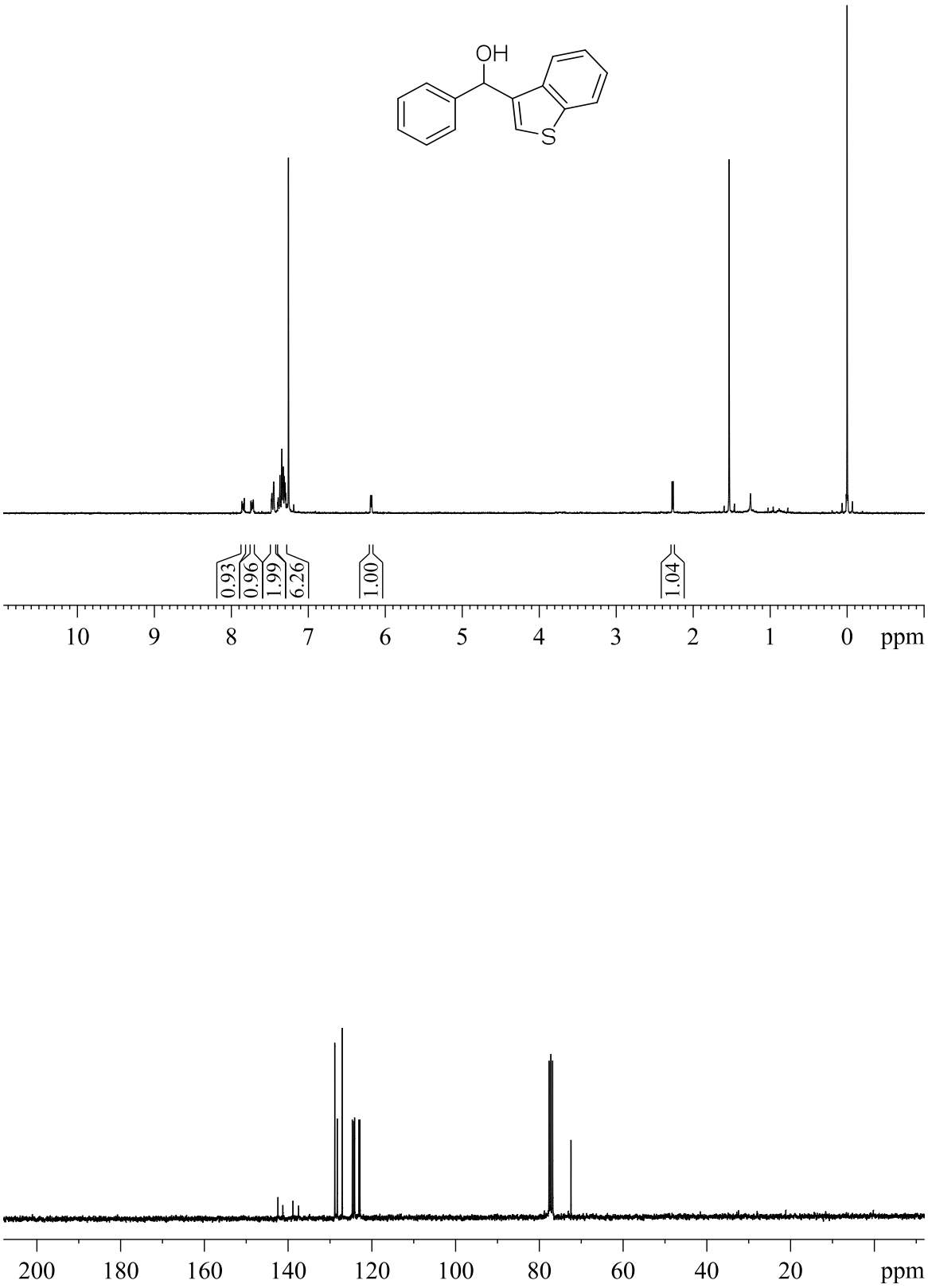


Figure 3-55. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-29** in $CDCl_3$.

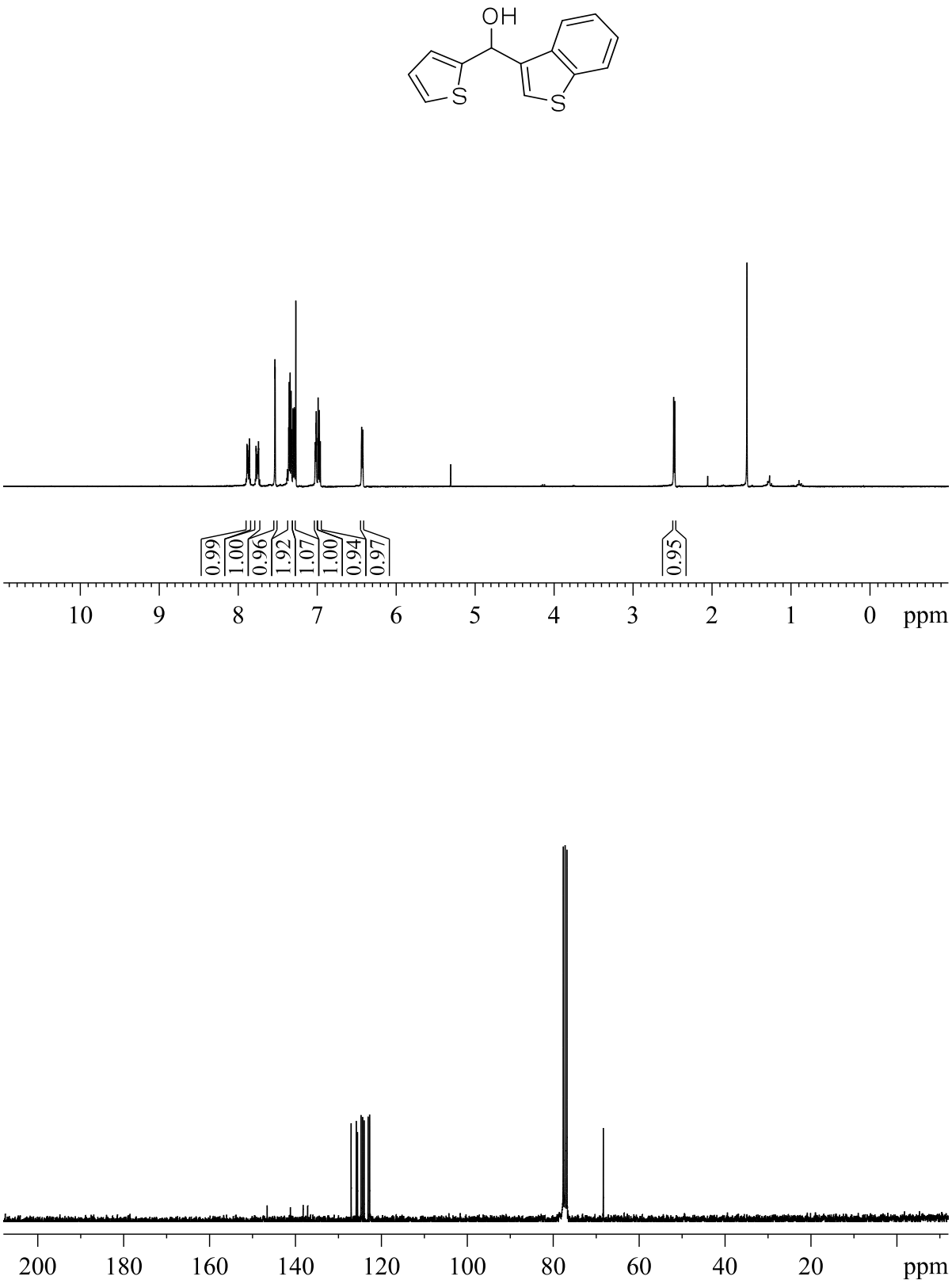


Figure 3-56. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-30** in $CDCl_3$.

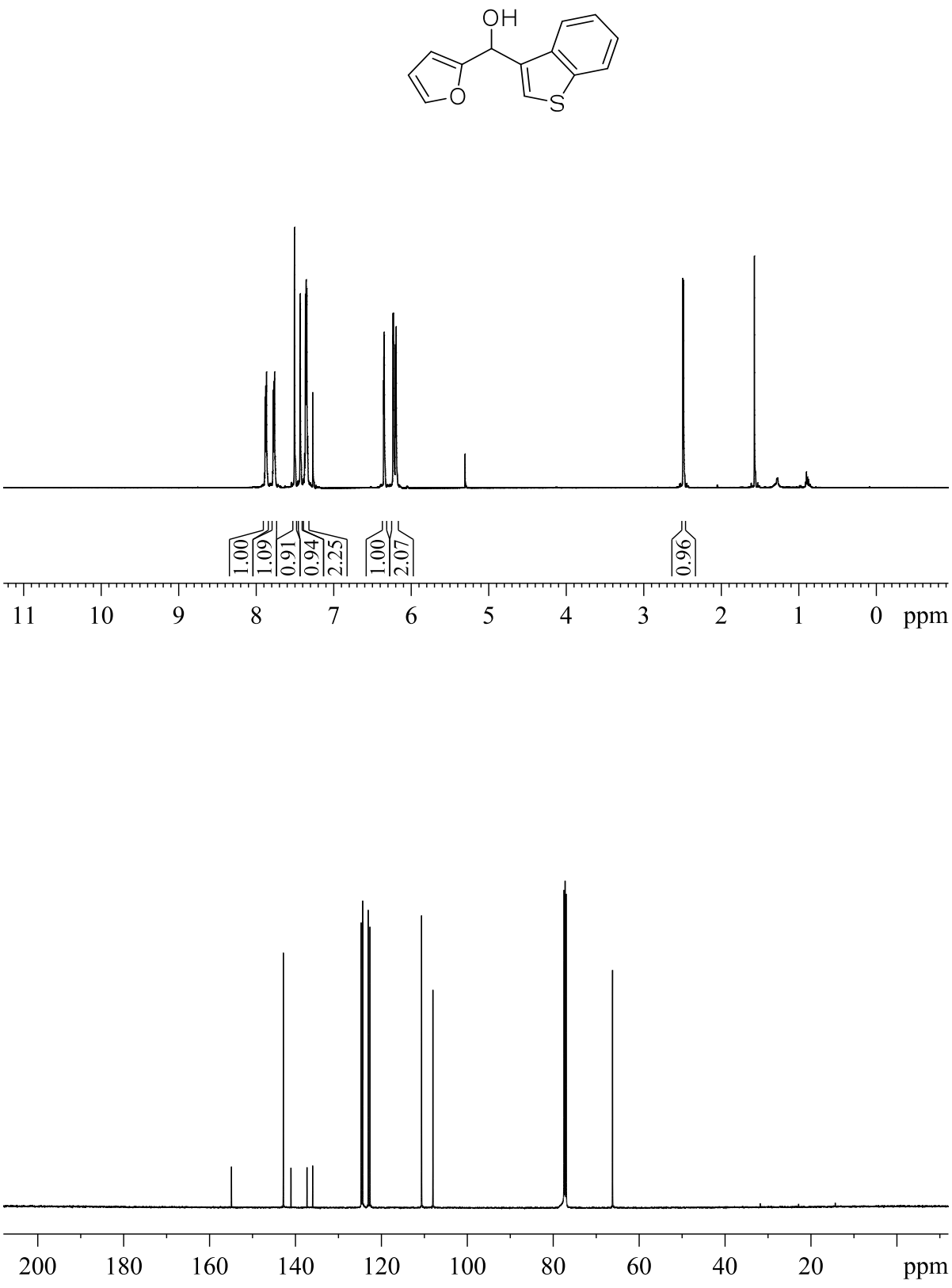


Figure 3-57. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-31** in $CDCl_3$.

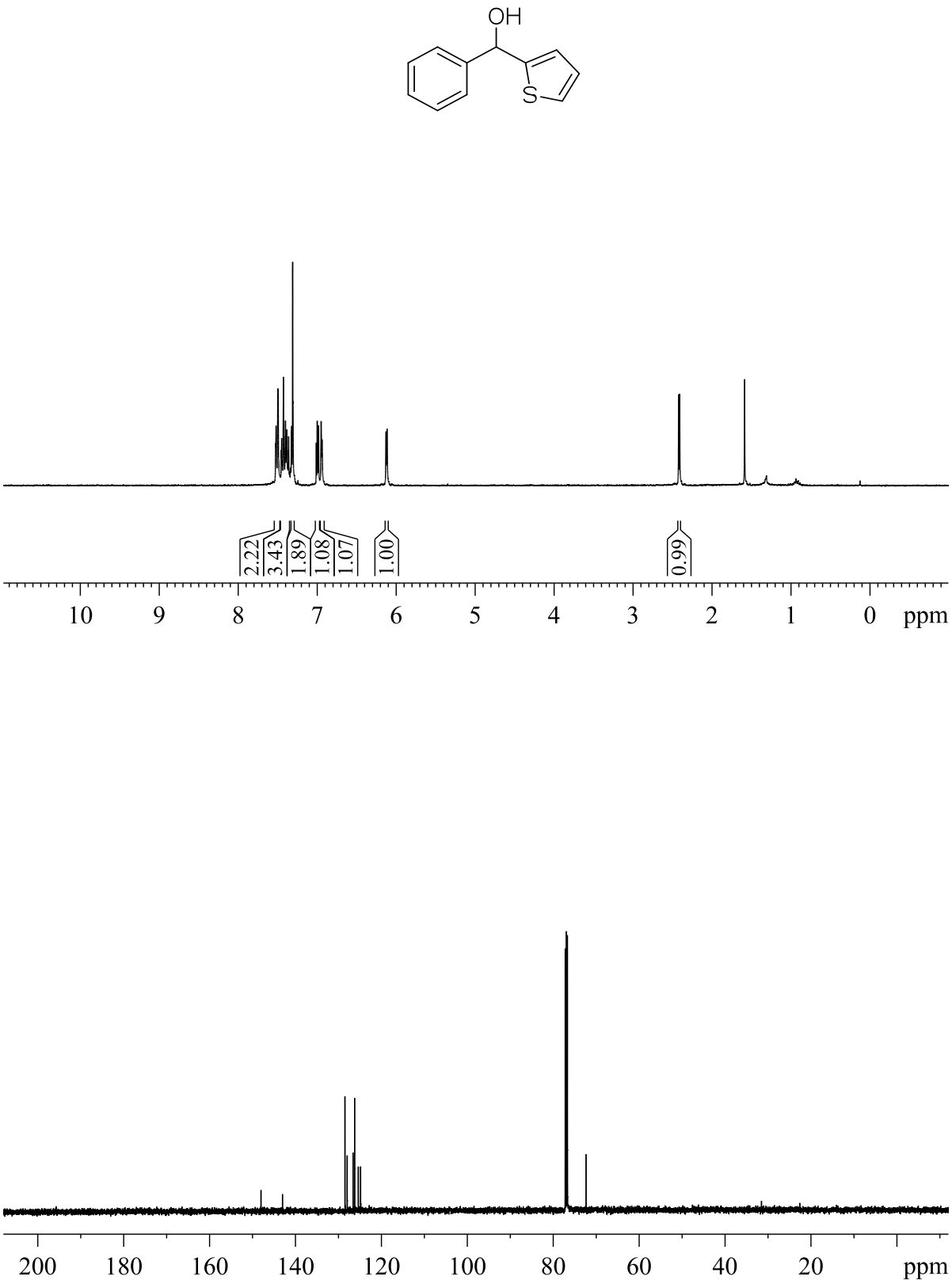


Figure 3-58. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-32** in $CDCl_3$.

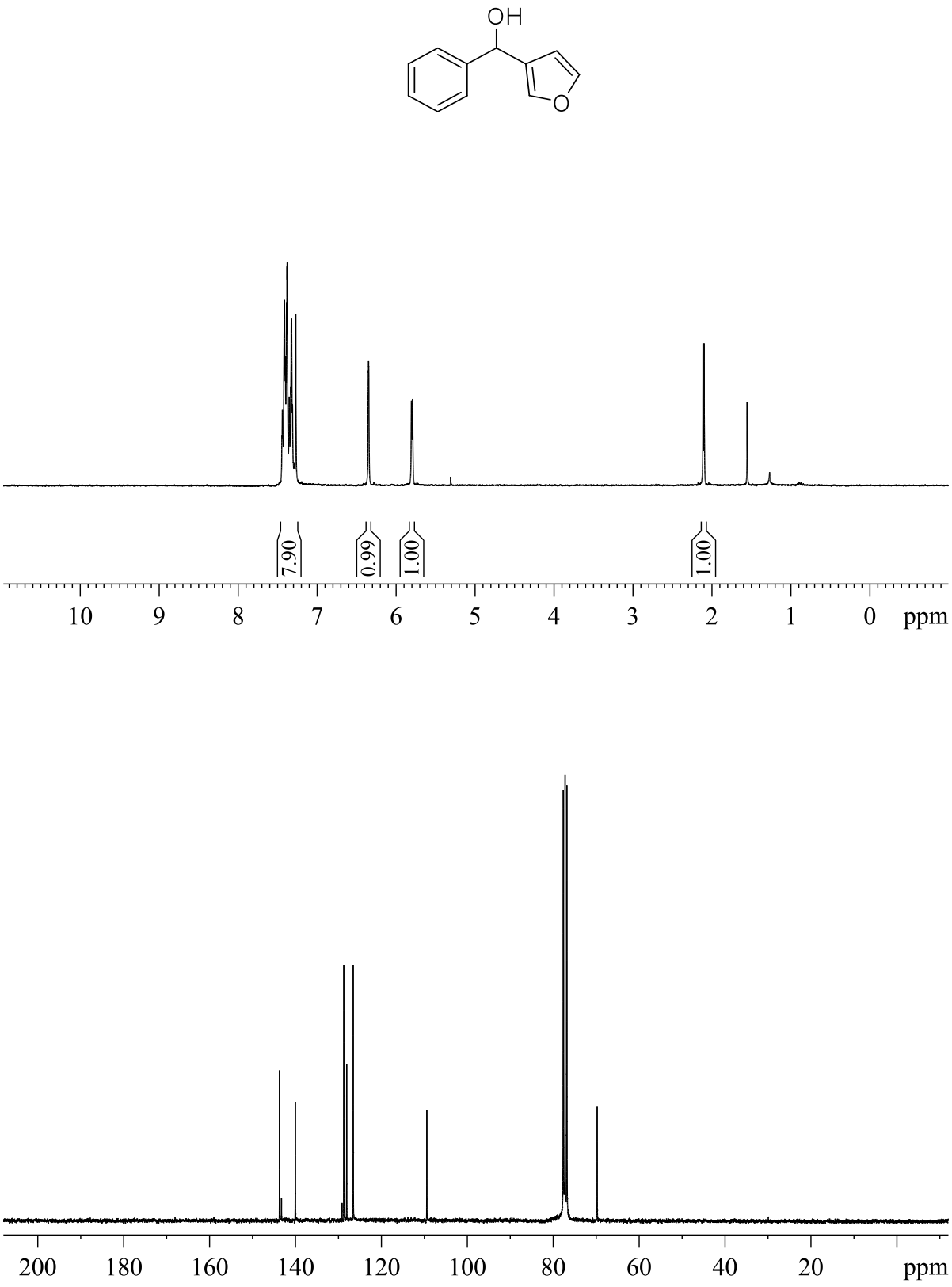


Figure 3-59. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-33** in $CDCl_3$.

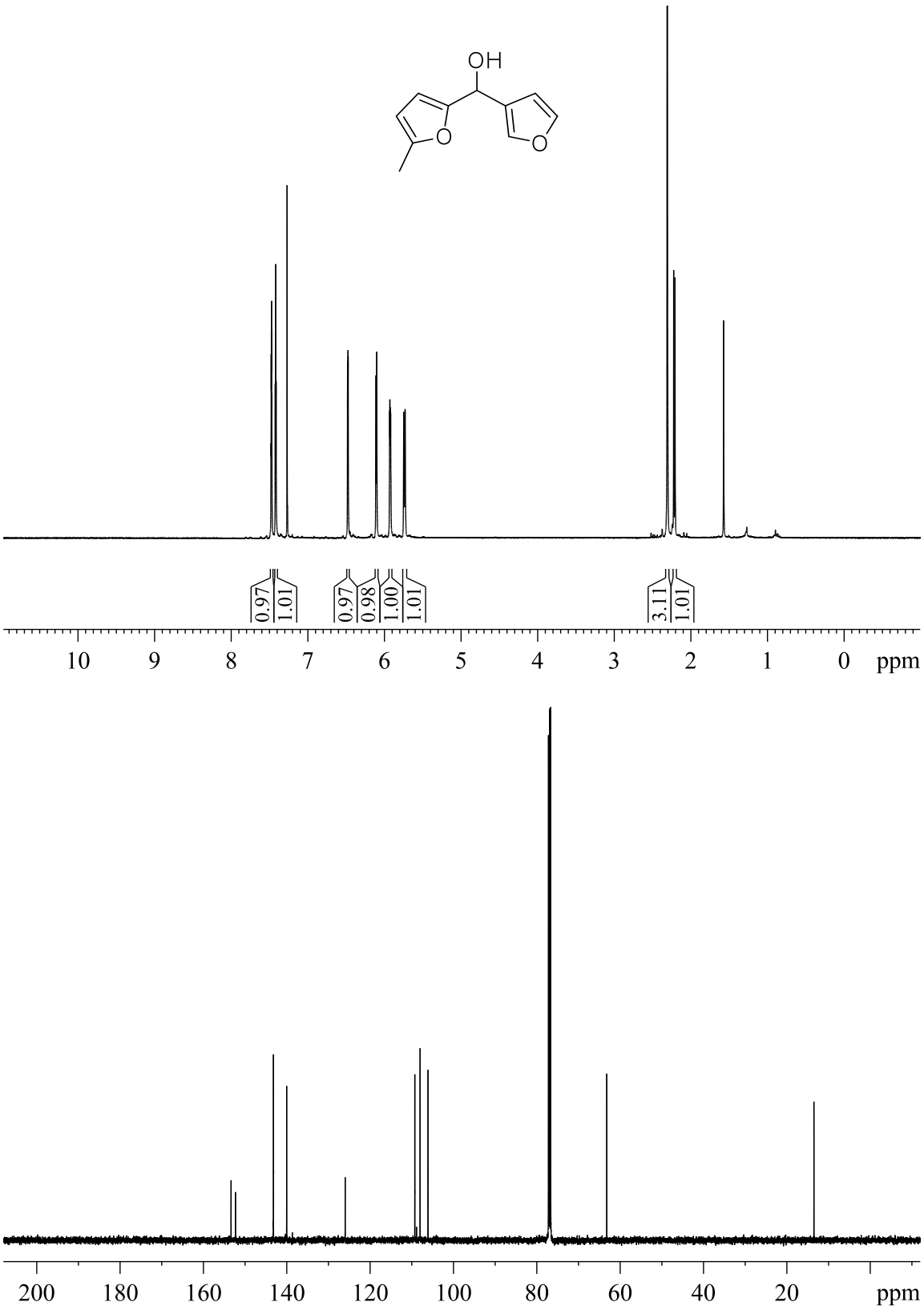


Figure 3-60. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-34** in $CDCl_3$.

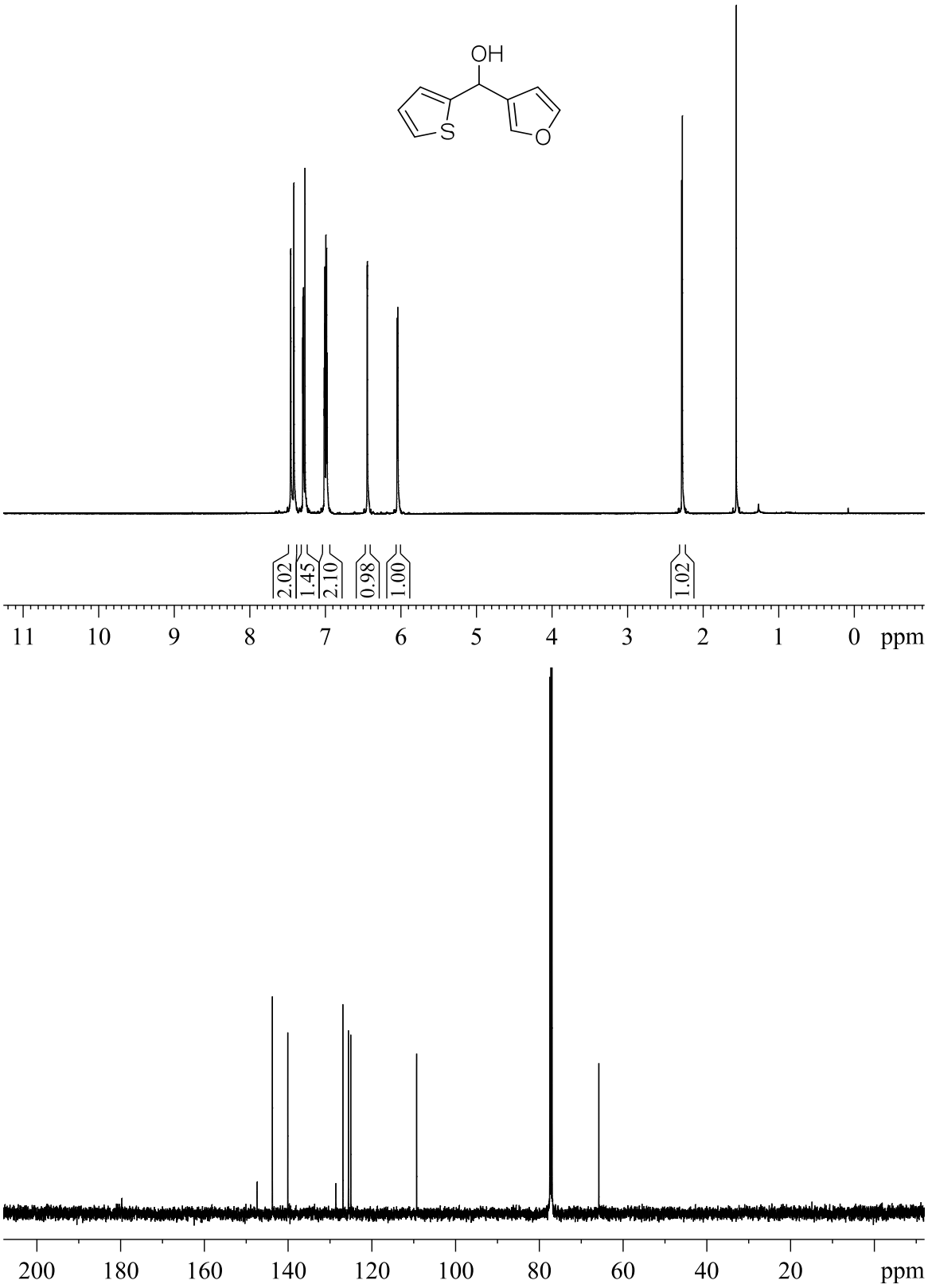


Figure 3-61. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-35** in $CDCl_3$.

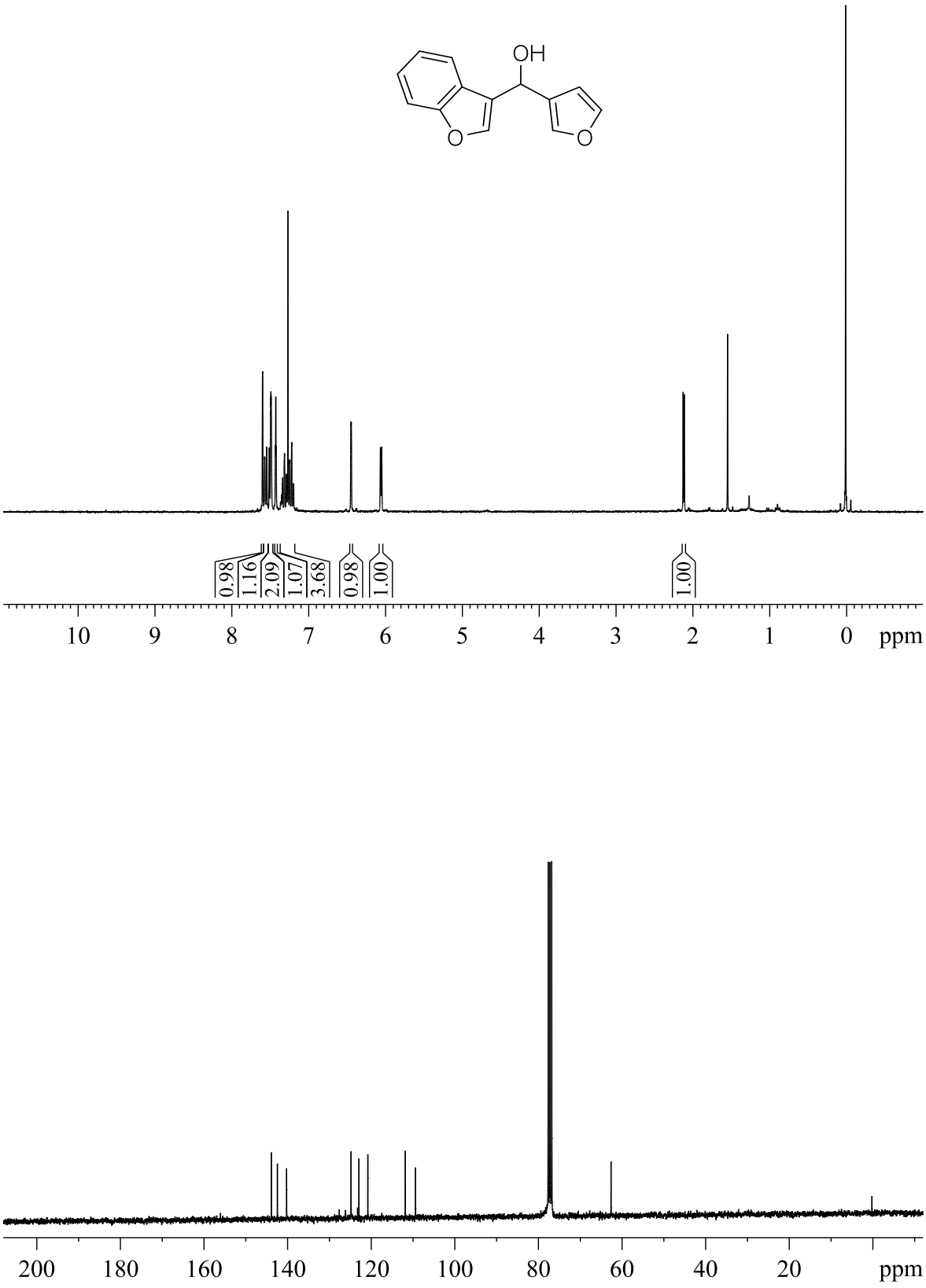


Figure 3-62. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-36** in $CDCl_3$.

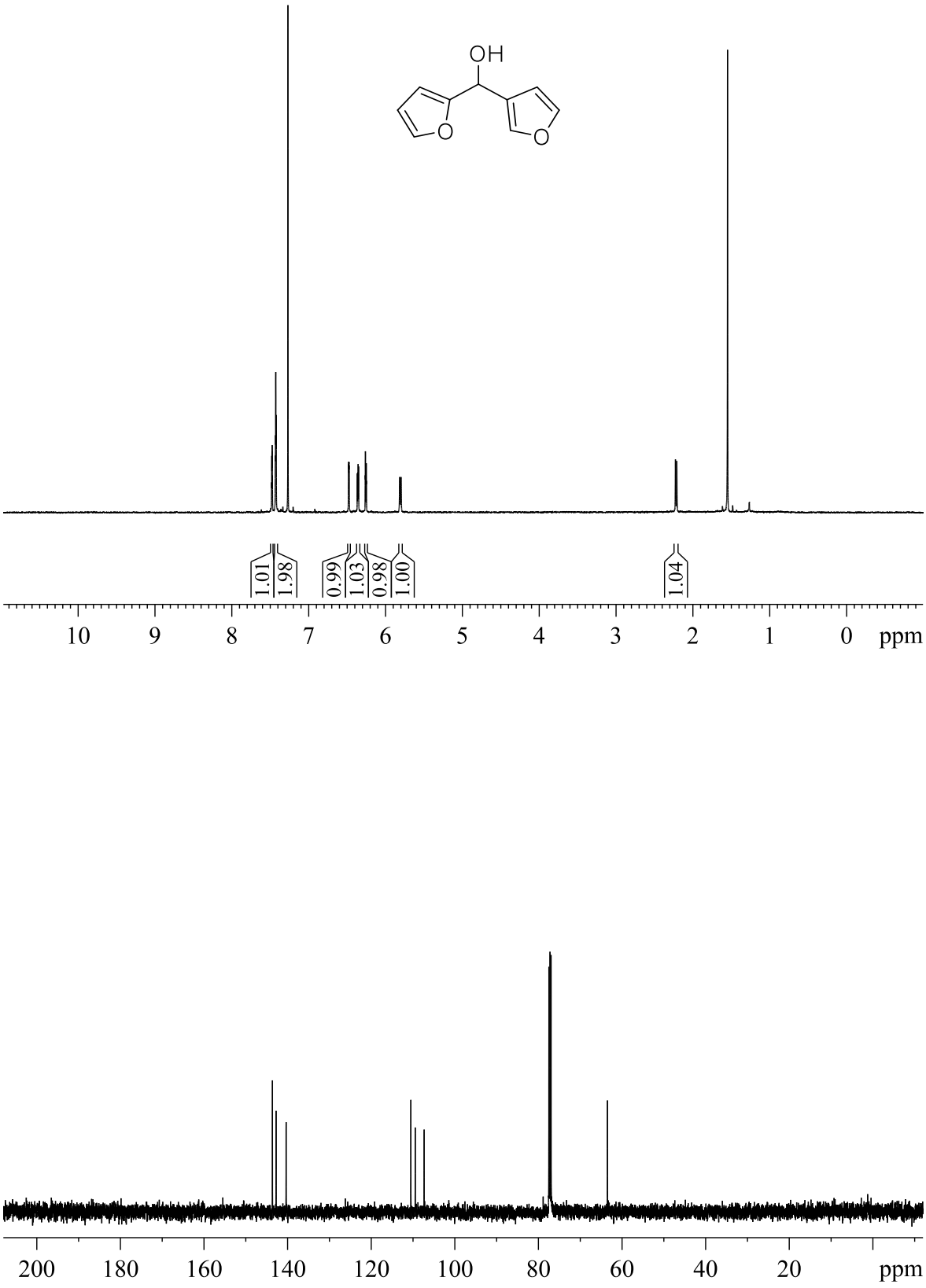


Figure 3-63. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-37** in $CDCl_3$.

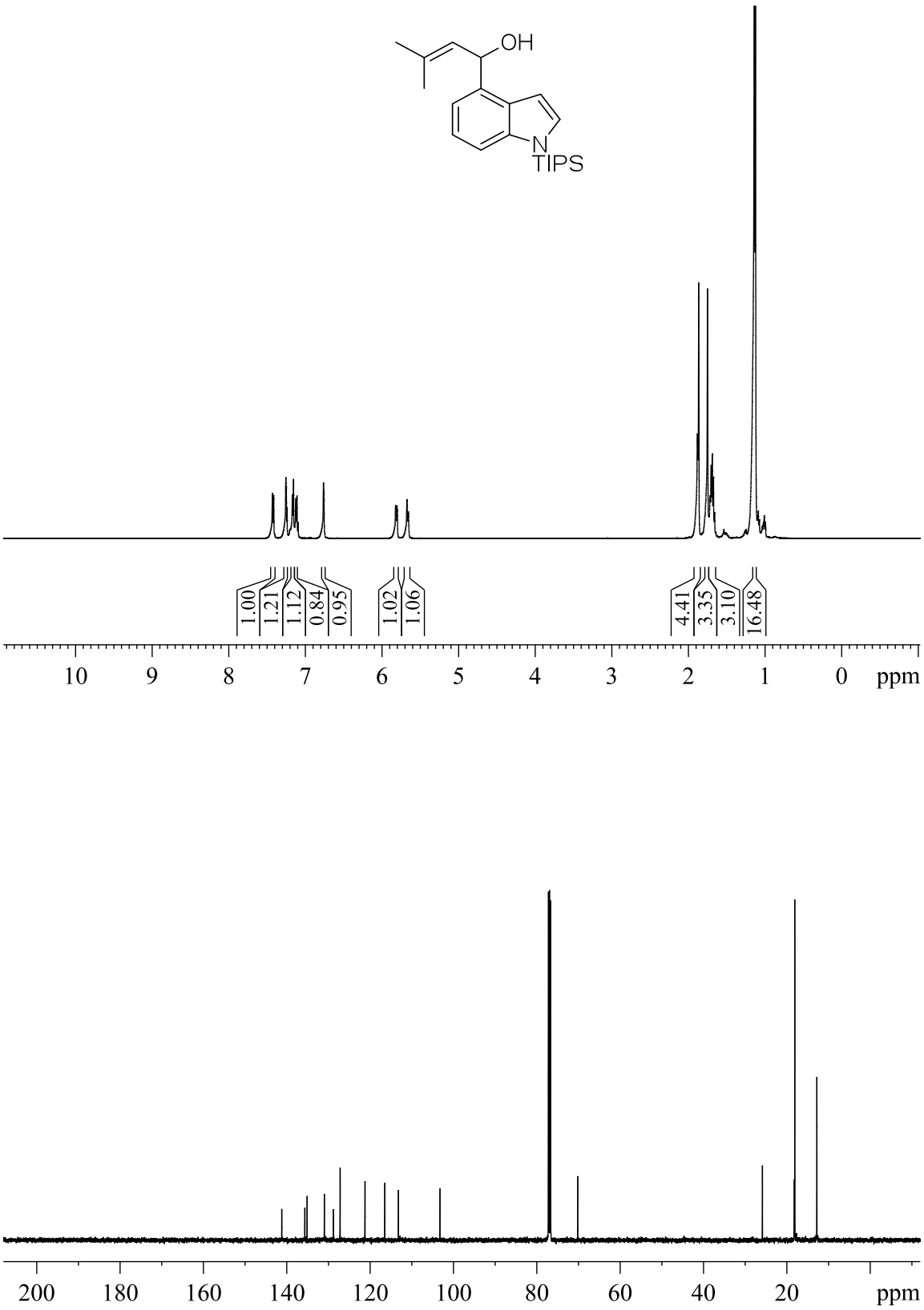


Figure 3-64. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-38** in $CDCl_3$.

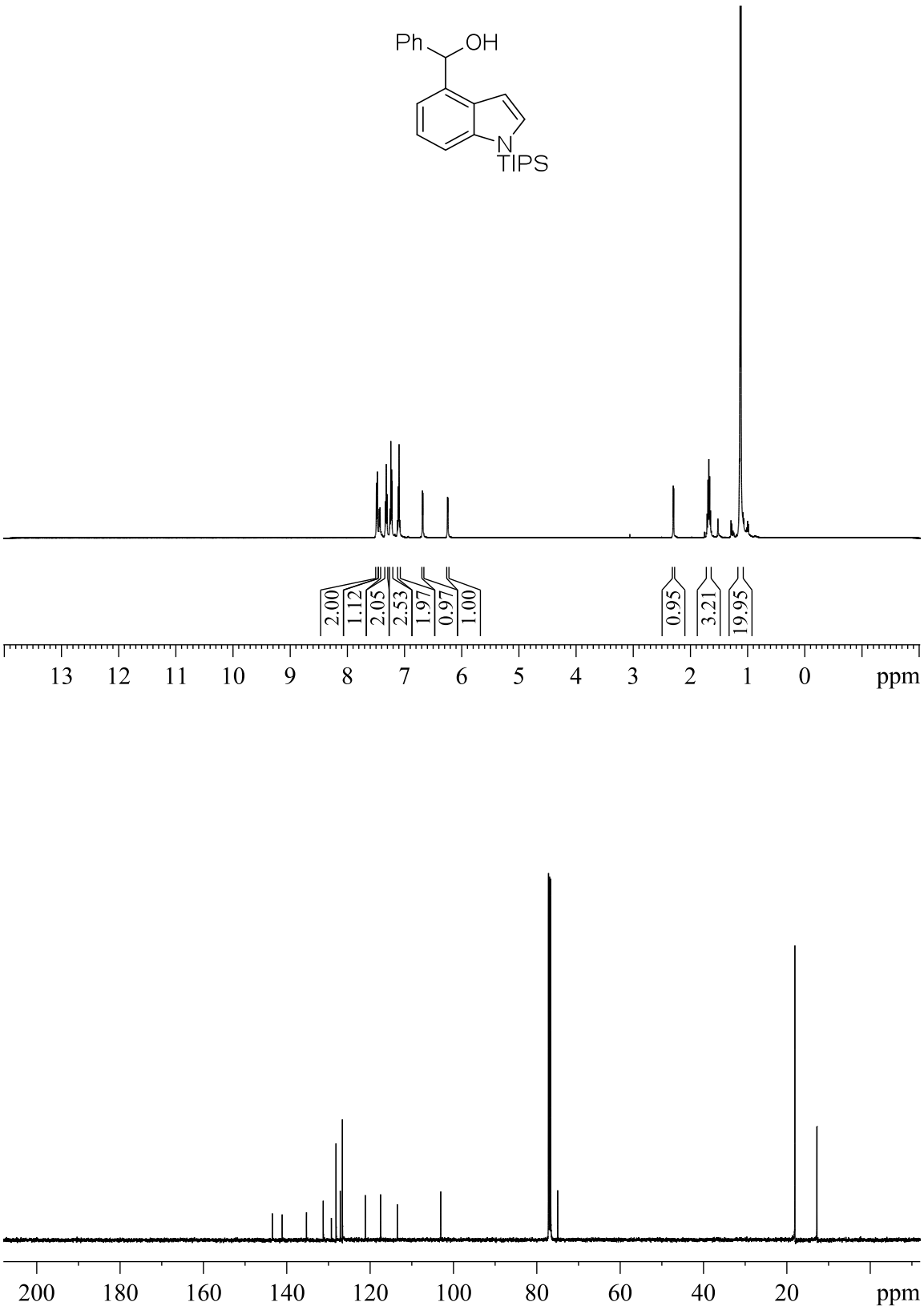


Figure 3-65. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-39** in $CDCl_3$.

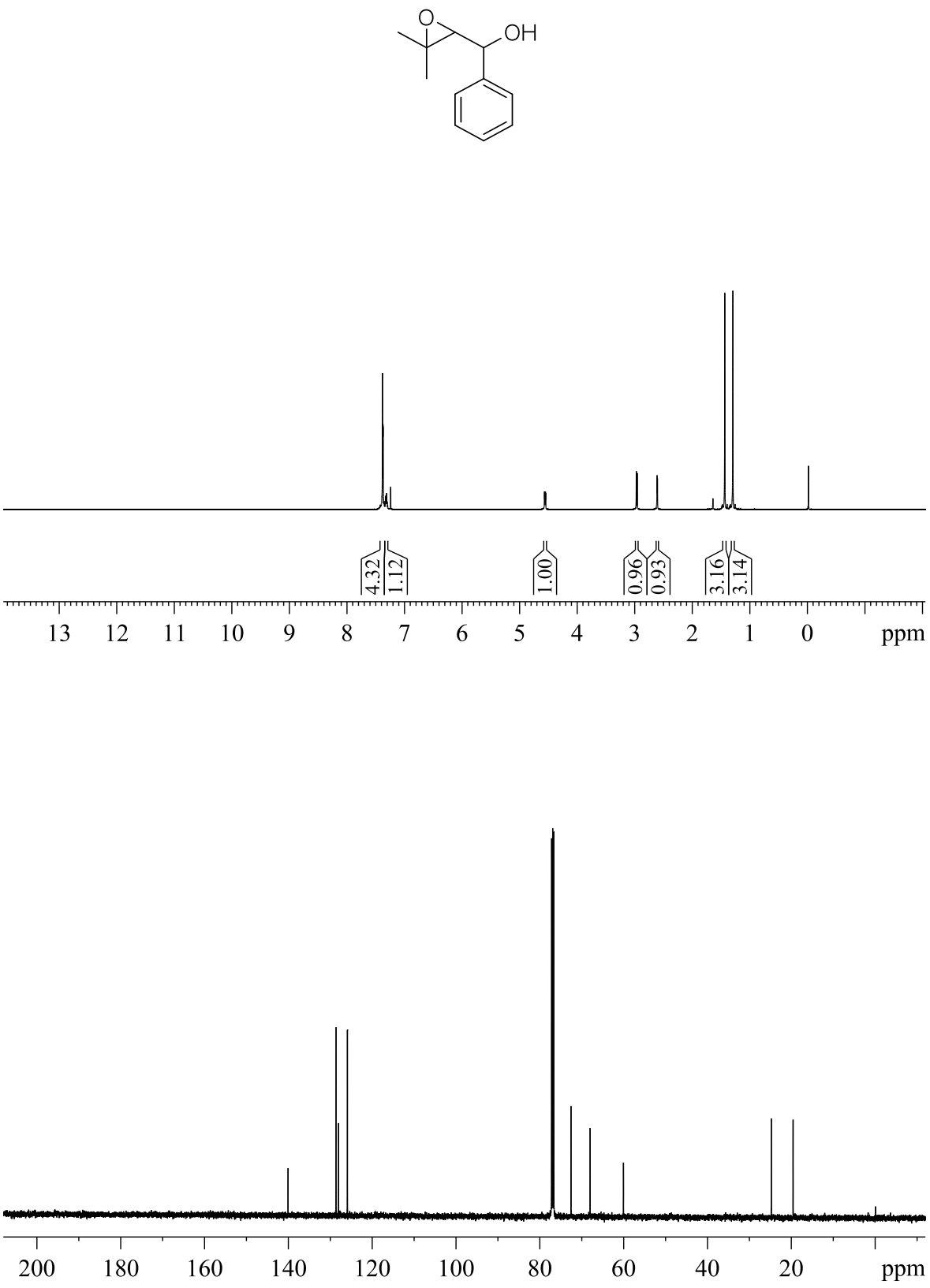


Figure 3-66. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-40** in $CDCl_3$.

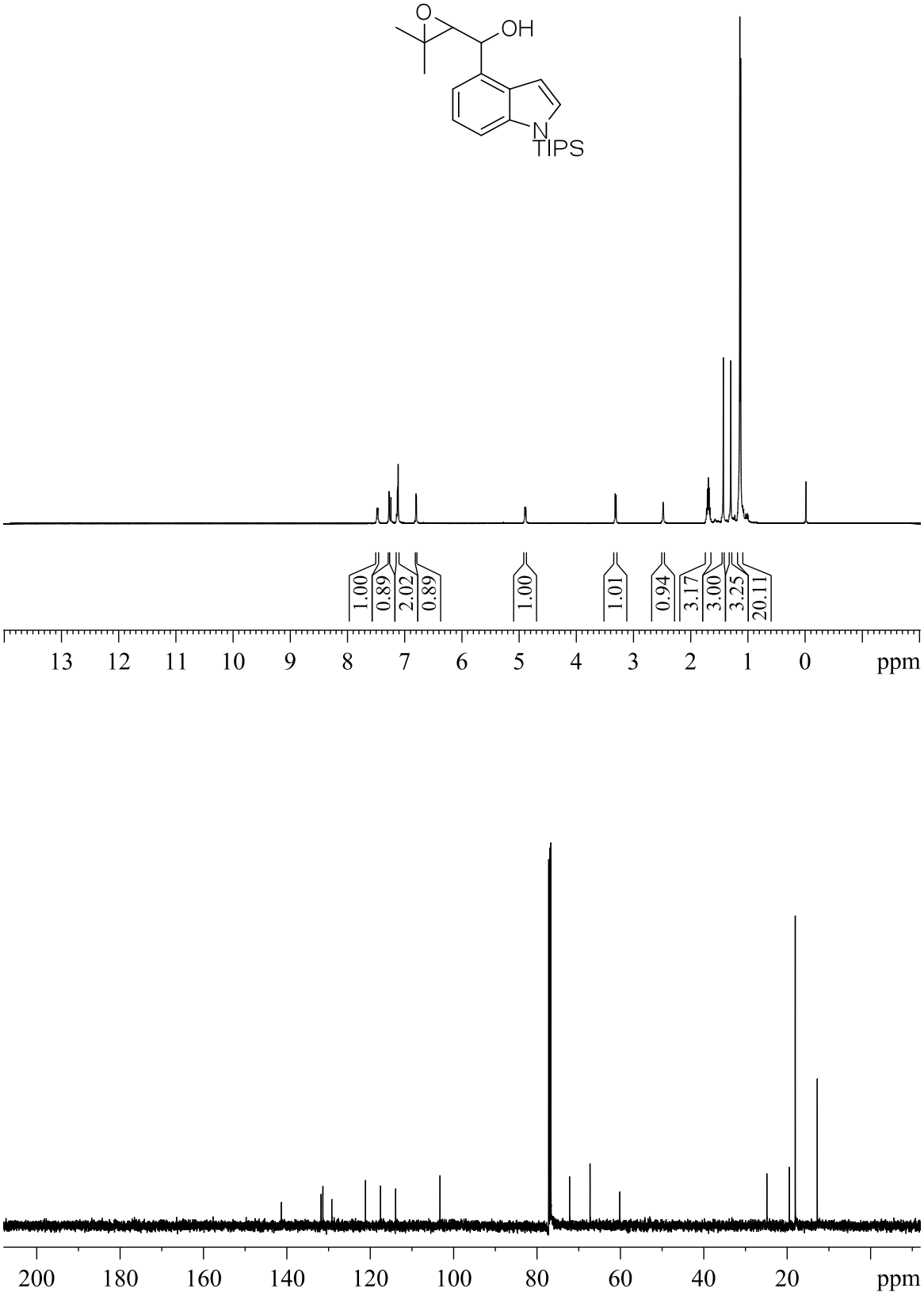


Figure 3-67. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-41** in $CDCl_3$.

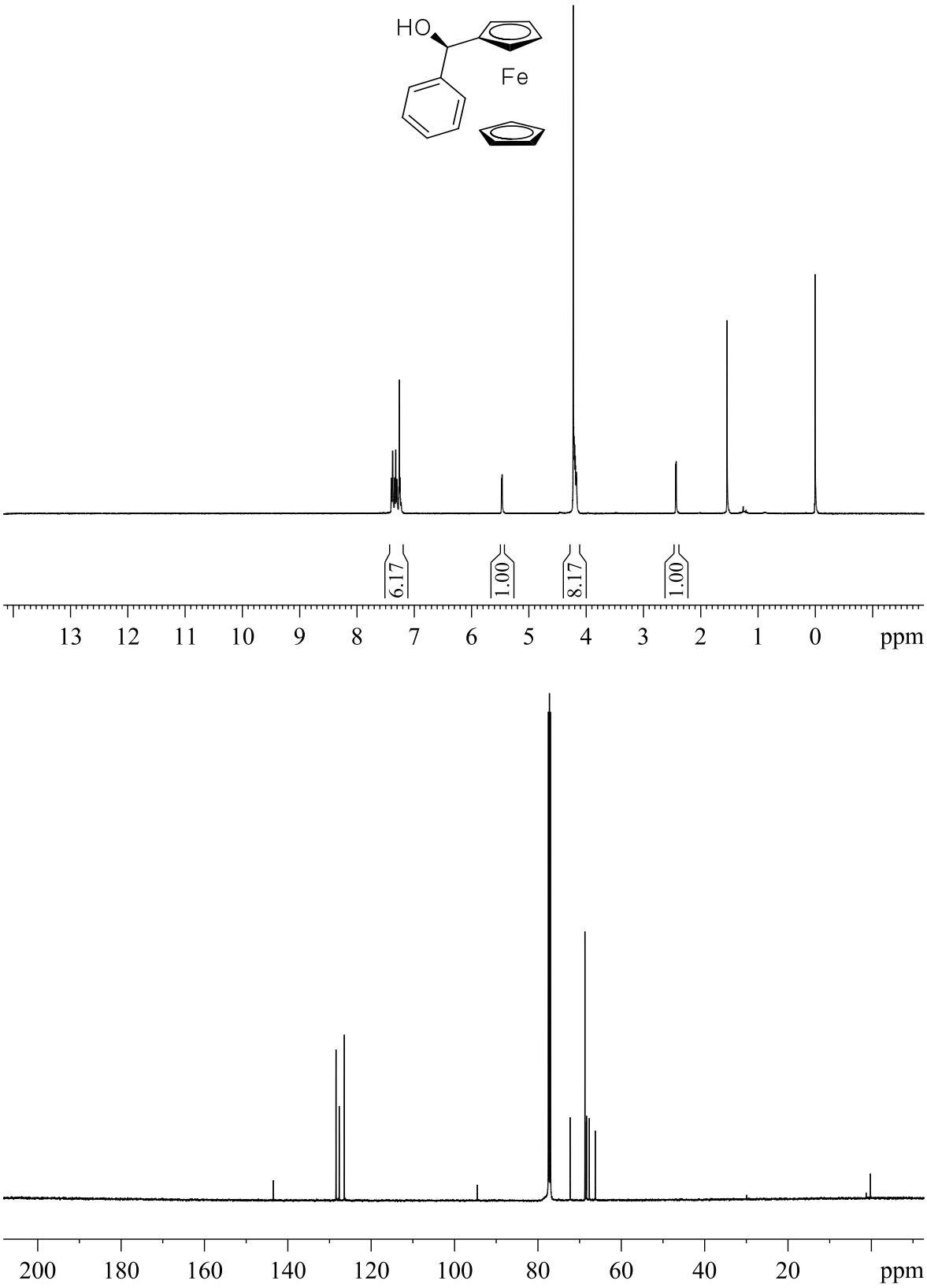


Figure 3-68. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-44** in $CDCl_3$.

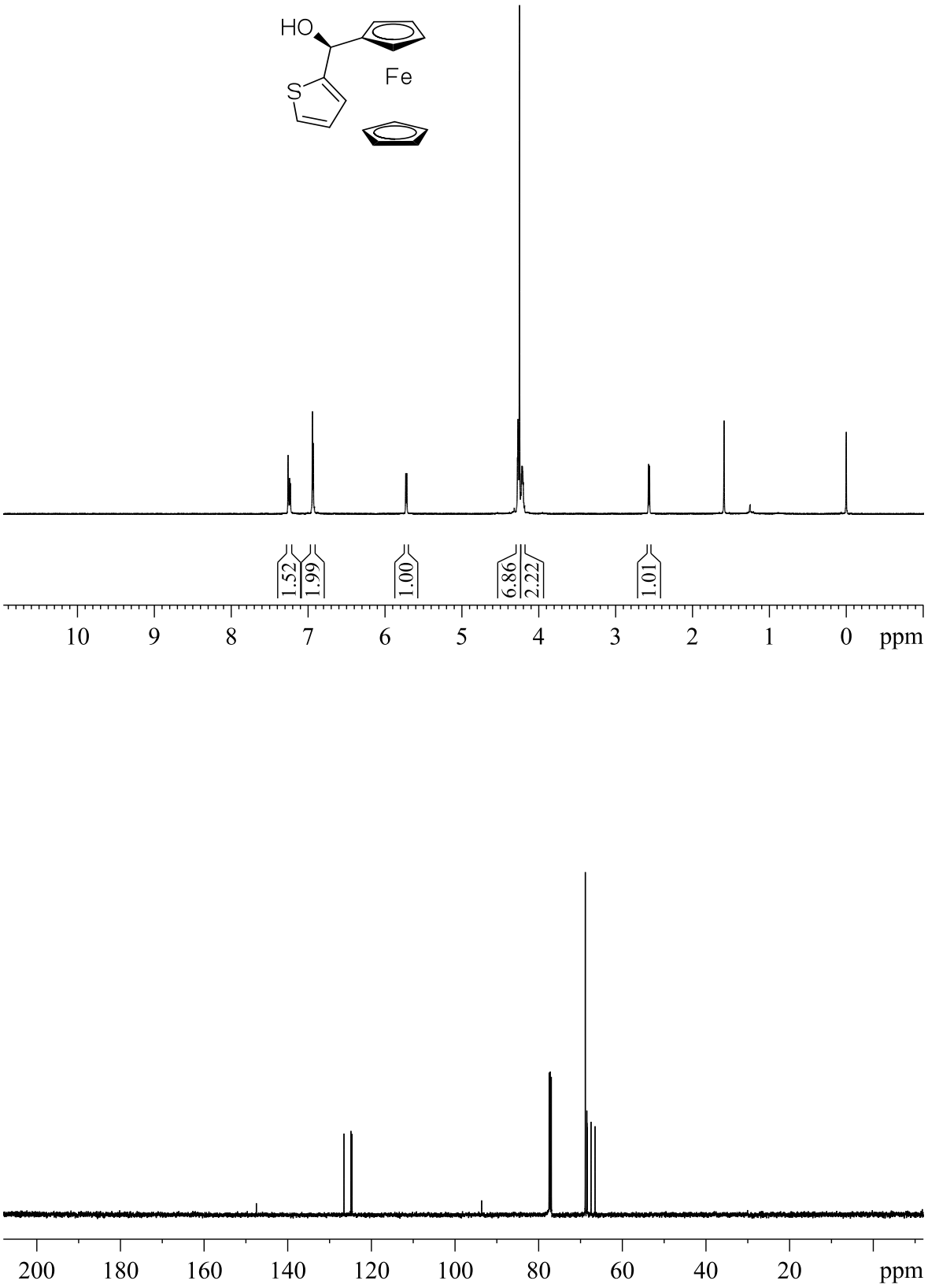


Figure 3-69. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-43** in $CDCl_3$.

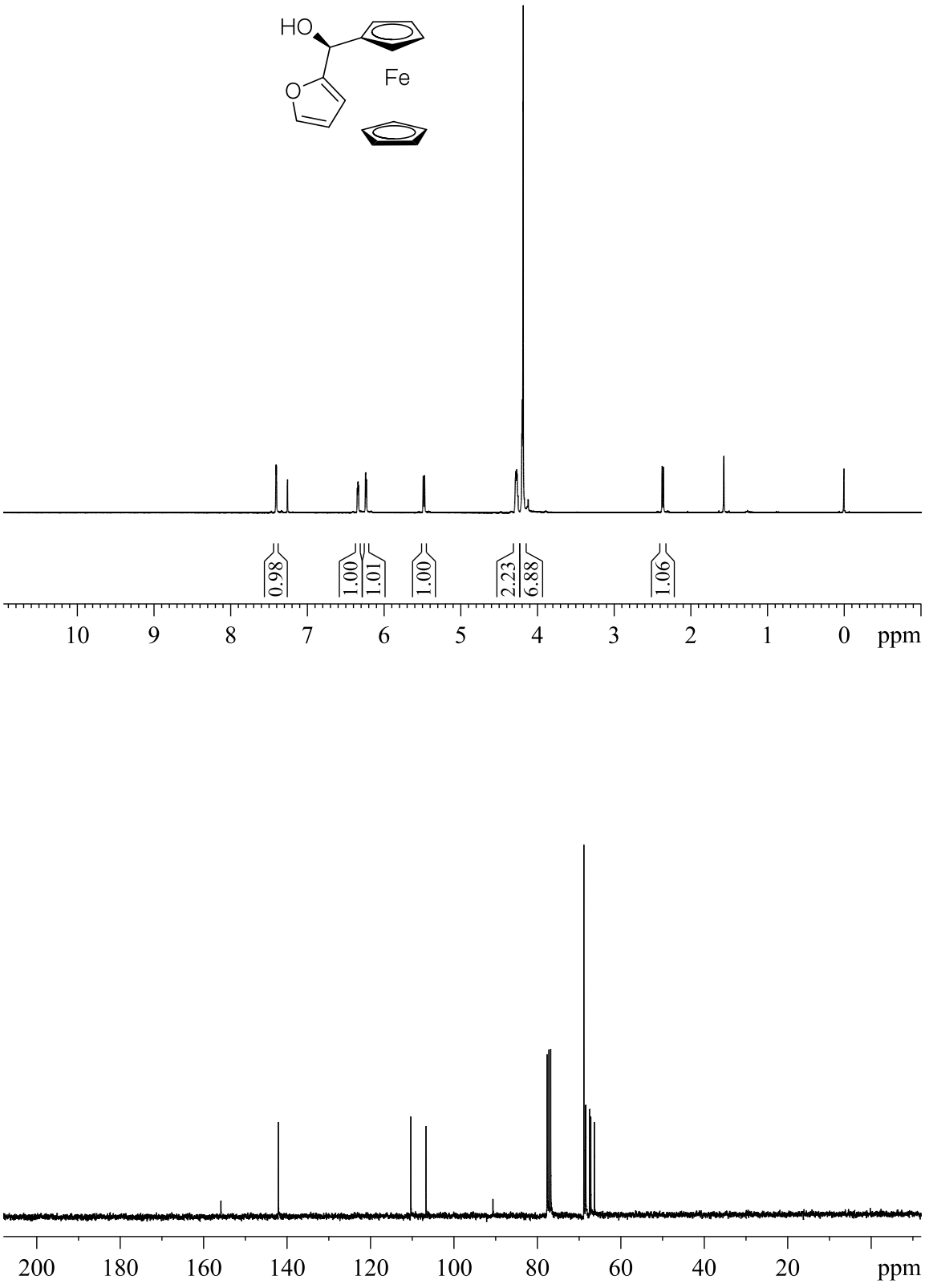
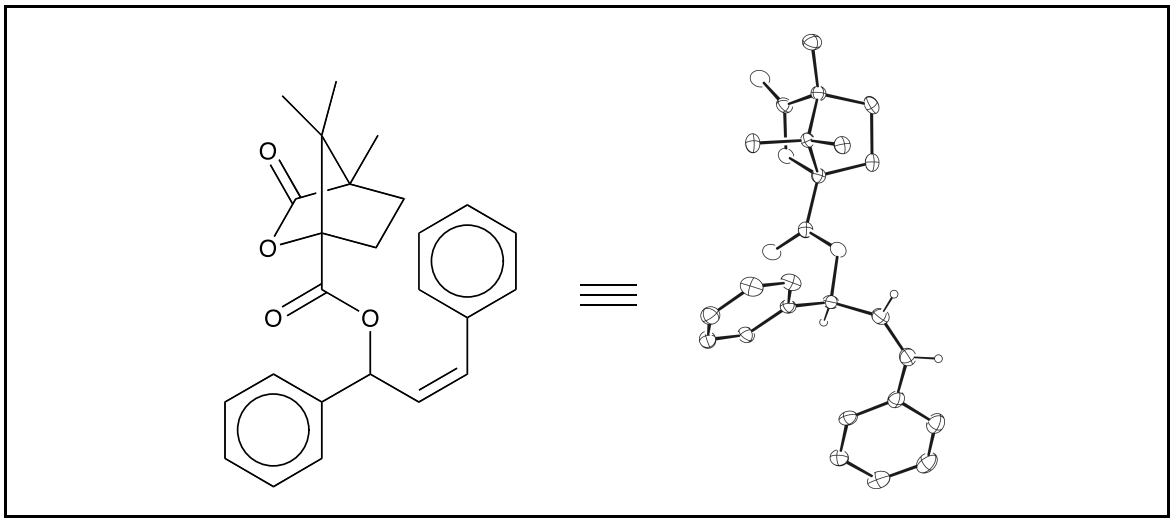


Figure 3-70. 500 MHz ^{1}H and 125 MHz $^{13}C\{^{1}H\}$ NMR of Compound **2-42** in $CDCl_3$.

4. Appendix B: X-Ray Structures' Report

X-ray Structure Determination of Derivative of 1-8 (#6122)



Compound 6122, $C_{25}H_{26}O_4$, crystallizes in the monoclinic space group $P2_1$ (systematic absences 0k0: k=odd) with a=12.631(3)Å, b=6.1265(13)Å, c=13.649(3)Å, β=91.167(5)°, V=1056.0(4)Å^3, Z=2 and d_{calc}=1.228 g/cm^3. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-K_α radiation (λ=0.71069 Å) at a temperature of 143K. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A total of 350 rotation images were collected with a crystal to detector distance of 35 mm, a 2θ swing angle of -12°, rotation widths of 0.5° and exposures of 15 seconds: scan no. 1 was a ϕ-scan from 0° to 150° at ω = 10° and χ = 20°; scan no. 2 was an ω-scan from -20° to 5° at χ = -90° and ϕ = 225°. Rotation images were processed using CrystalClear[i], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the CrystalStructure[ii] program package for further processing and structure solution on a Dell Pentium III computer. A total of 4760 reflections were measured over the ranges 5.98 ≤ 2θ ≤ 50 °, -14 ≤ h ≤ 15, -5 ≤ k ≤ 7, -16 ≤ l ≤ 14 yielding 2967 unique reflections (R_{int} = 0.0253). The intensity data were corrected for Lorentz and polarization effects and for absorption using REQAB[iii] (minimum and maximum transmission 0.768, 1.000).

The structure was solved by direct methods (SIR97[iv]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97[v]. All reflections were used during refinement (F^2's that were experimentally negative were replaced by $F^2 = 0$). The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ 0.0407P^2 + 0.1112P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a "riding" model. Refinement converged to R_1=0.0437 and wR_2=0.0888 for 2538 reflections for which $F > 4\sigma(F)$ and R_1=0.0542, wR_2=0.0971 and GOF = 1.099 for all 2967 unique, non-zero reflections and 266 variables[vi]. The maximum Δ/σ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.164 and -0.193 e/Å^3.

Table 4-1 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 4-2. Anisotropic thermal parameters are in Table 4-3. Table 4-4 and Table 4-5 list bond distances and bond angles. Figure 4-1 is an ORTEP[vii] representation of the molecule with 30% probability thermal ellipsoids displayed.

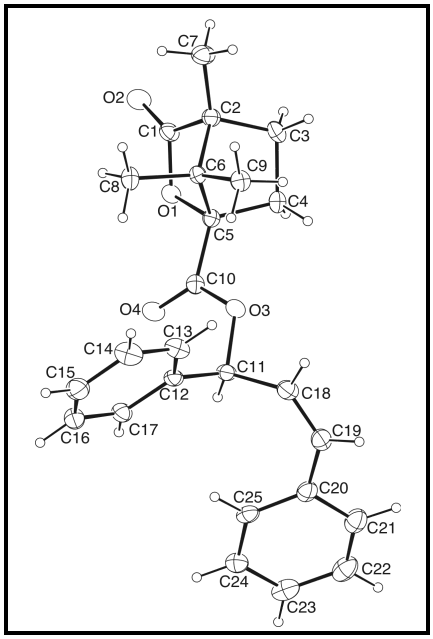


Figure 4-1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 4-1. Summary of Structure Determination of Compound 6122

Formula:	$C_{25}H_{26}O_4$
Formula weight:	390.46
Crystal class:	monoclinic
Space group:	$P2_1$ (#4)
Z	2
Cell constants:	
a	12.631(3)Å
b	6.1265(13)Å
c	13.649(3)Å
β	91.167(5)°
V	1056.0(4)Å^3
μ	0.82 cm^{-1}
crystal size, mm	0.38 x 0.14 x 0.08
D_{calc}	1.228 g/cm^3
F(000)	416
Radiation:	Mo-K_α (λ=0.71073Å)
2θ range	5.98 – 50 °
hkl collected:	-14≤ h ≤15; -5≤ k ≤7; -16≤ l ≤14
No. reflections measured:	4760
No. unique reflections:	2967 (R_{int}=0.0253)
No. observed reflections	2538 (F>4σ)
No. reflections used in refinement	2967
No. parameters	266
R indices (F>4σ)	R_1=0.0437
	wR_2=0.0888
R indices (all data)	R_1=0.0542
	wR_2=0.0971
GOF:	1.099
Final Difference Peaks, e/Å^3	+0.164, -0.193

Table 4-2. Refined Positional Parameters for Compound 6122

Atom	x	y	z	U_{eq}, Å^2
C1	0.1932(2)	0.5140(5)	0.5653(2)	0.0309(7)
C2	0.2235(2)	0.7517(5)	0.5711(2)	0.0289(6)
C3	0.1200(2)	0.8712(5)	0.5399(2)	0.0329(7)
H3a	0.0606	0.8190	0.5773	0.044
H3b	0.1269	1.0276	0.5493	0.044
C4	0.1049(2)	0.8154(5)	0.4299(2)	0.0305(7)
H4a	0.0380	0.7420	0.4170	0.041
H4b	0.1089	0.9448	0.3892	0.041
C5	0.1988(2)	0.6632(4)	0.4140(2)	0.0248(6)
C6	0.2905(2)	0.7670(5)	0.4762(2)	0.0249(6)
C7	0.2735(2)	0.8255(5)	0.6671(2)	0.0408(8)
H7a	0.2258	0.7972	0.7194	0.061
H7b	0.2882	0.9790	0.6640	0.061
H7c	0.3384	0.7470	0.6787	0.061
C8	0.3905(2)	0.6233(5)	0.4797(2)	0.0355(7)
H8a	0.4209	0.6181	0.4159	0.053
H8b	0.3720	0.4783	0.4998	0.053
H8c	0.4410	0.6838	0.5257	0.053
C9	0.3211(2)	0.9980(5)	0.4486(2)	0.0318(7)
H9a	0.3658	1.0589	0.4993	0.048
H9b	0.2583	1.0853	0.4410	0.048
H9c	0.3584	0.9959	0.3881	0.048
C10	0.2244(2)	0.5988(5)	0.3108(2)	0.0276(6)
C11	0.2660(2)	0.7544(5)	0.1550(2)	0.0311(7)
H11	0.2237	0.6383	0.1241	0.041
C12	0.3830(2)	0.7013(5)	0.1490(2)	0.0295(7)
C13	0.4585(2)	0.8482(6)	0.1855(2)	0.0408(8)
H13	0.4371	0.9785	0.2139	0.054
C14	0.5659(2)	0.7993(6)	0.1793(2)	0.0494(9)
H14	0.6161	0.8962	0.2046	0.066
C15	0.5980(2)	0.6076(7)	0.1359(2)	0.0453(8)
H15	0.6698	0.5761	0.1313	0.060
C16	0.5235(2)	0.4629(6)	0.0993(2)	0.0421(8)
H16	0.5450	0.3342	0.0696	0.056
C17	0.4168(2)	0.5092(5)	0.1067(2)	0.0347(7)
H17	0.3670	0.4096	0.0828	0.046
C18	0.2378(2)	0.9703(5)	0.1107(2)	0.0355(7)
H18	0.2606	1.0926	0.1455	0.047
C19	0.1841(2)	1.0093(6)	0.0274(2)	0.0374(7)
H19	0.1721	1.1559	0.0132	0.050
C20	0.1412(2)	0.8544(5)	-0.0450(2)	0.0355(7)
C21	0.0472(2)	0.9079(6)	-0.0960(2)	0.0462(9)
H21	0.0148	1.0414	-0.0842	0.061
C22	0.0020(2)	0.7668(7)	-0.1632(2)	0.0505(9)
H22	-0.0608	0.8050	-0.1955	0.067
C23	0.0492(2)	0.5689(6)	-0.1829(2)	0.0476(10)
H23	0.0178	0.4728	-0.2275	0.063
C24	0.1434(2)	0.5149(6)	-0.1359(2)	0.0407(8)

H24	0.1765	0.3832	-0.1498	0.054
C25	0.1887(2)	0.6571(5)	-0.0680(2)	0.0345(8)
H25	0.2524	0.6193	-0.0371	0.046
O1	0.17530(13)	0.4639(3)	0.46868(12)	0.0287(5)
O2	0.1816(2)	0.3805(4)	0.62859(14)	0.0450(6)
O3	0.23622(13)	0.7811(3)	0.25758(12)	0.0310(5)
O4	0.2332(2)	0.4161(3)	0.28016(13)	0.0374(5)

$U_{eq}=1/3[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*cos\gamma+2U_{13}aa^*cc^*cos\beta+2U_{23}bb^*cc^*cos\alpha]$

Table 4-3. Refined Thermal Parameters (U's) for Compound 6122

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.039(2)	0.024(2)	0.030(2)	-0.0022(14)	0.0055(11)	-0.0014(14)
C2	0.037(2)	0.022(2)	0.0273(14)	0.0006(13)	0.0018(11)	-0.0003(13)
C3	0.036(2)	0.023(2)	0.040(2)	-0.0033(14)	0.0098(11)	0.0018(14)
C4	0.0253(13)	0.026(2)	0.040(2)	0.0016(14)	-0.0002(11)	0.0016(13)
C5	0.0279(13)	0.019(2)	0.0270(13)	0.0014(12)	0.0014(10)	-0.0024(12)
C6	0.0255(13)	0.022(2)	0.0269(13)	-0.0007(13)	0.0013(10)	0.0004(13)
C7	0.058(2)	0.032(2)	0.032(2)	-0.0030(14)	-0.0005(13)	-0.005(2)
C8	0.030(2)	0.030(2)	0.047(2)	0.000(2)	-0.0025(12)	0.0041(14)
C9	0.0311(14)	0.026(2)	0.038(2)	-0.0008(14)	0.0006(11)	-0.0050(14)
C10	0.0256(14)	0.025(2)	0.032(2)	-0.0016(14)	-0.0022(10)	-0.0017(13)
C11	0.044(2)	0.028(2)	0.0221(14)	-0.0020(13)	0.0029(11)	0.0017(14)
C12	0.039(2)	0.027(2)	0.0218(13)	0.0015(12)	0.0041(11)	0.0007(13)
C13	0.046(2)	0.040(2)	0.036(2)	-0.006(2)	0.0077(12)	-0.007(2)
C14	0.040(2)	0.060(3)	0.048(2)	-0.009(2)	0.0051(13)	-0.012(2)
C15	0.039(2)	0.058(2)	0.039(2)	0.001(2)	0.0033(13)	0.005(2)
C16	0.052(2)	0.039(2)	0.036(2)	0.003(2)	0.0067(13)	0.010(2)
C17	0.044(2)	0.029(2)	0.031(2)	-0.0030(14)	0.0008(12)	0.000(2)
C18	0.046(2)	0.029(2)	0.032(2)	0.0008(14)	0.0085(12)	-0.0023(14)
C19	0.044(2)	0.031(2)	0.037(2)	0.007(2)	0.0103(12)	0.002(2)
C20	0.034(2)	0.042(2)	0.031(2)	0.010(2)	0.0065(11)	0.003(2)
C21	0.038(2)	0.055(3)	0.046(2)	0.011(2)	0.0025(13)	0.006(2)
C22	0.032(2)	0.071(3)	0.049(2)	0.014(2)	-0.0036(13)	-0.001(2)
C23	0.043(2)	0.064(3)	0.036(2)	0.006(2)	-0.0021(13)	-0.009(2)
C24	0.047(2)	0.043(2)	0.032(2)	0.000(2)	0.0042(13)	0.002(2)
C25	0.033(2)	0.048(2)	0.0235(14)	0.005(2)	0.0020(11)	-0.002(2)
O1	0.0391(10)	0.0173(12)	0.0298(10)	-0.0016(8)	0.0035(7)	-0.0043(9)
O2	0.076(2)	0.0260(13)	0.0336(11)	0.0046(10)	0.0112(10)	-0.0033(11)
O3	0.0426(11)	0.0223(12)	0.0283(10)	-0.0007(9)	0.0071(8)	-0.0005(10)
O4	0.0544(13)	0.0261(13)	0.0319(11)	-0.0042(10)	0.0024(9)	-0.0044(10)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+ 2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$.

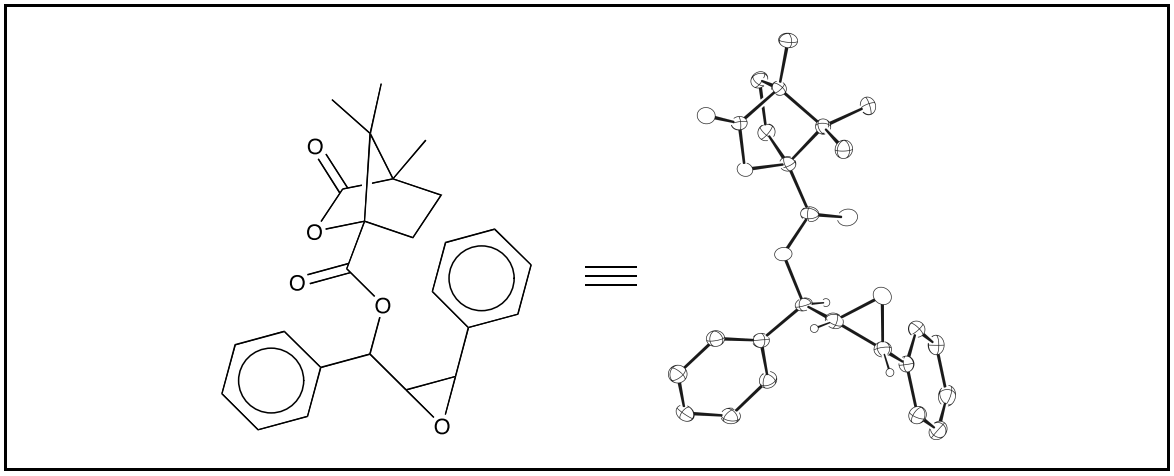
Table 4-4. Bond Distances in Compound 6122, Å

C1-O2	1.201(3)	C1-O1	1.368(3)	C1-C2	1.508(4)
C2-C7	1.512(4)	C2-C3	1.551(4)	C2-C6	1.564(3)
C3-C4	1.548(4)	C4-C5	1.528(3)	C5-O1	1.465(3)
C5-C10	1.504(3)	C5-C6	1.557(3)	C6-C9	1.516(4)
C6-C8	1.540(4)	C10-O4	1.201(3)	C10-O3	1.343(3)
C11-O3	1.466(3)	C11-C18	1.495(4)	C11-C12	1.517(4)
C12-C17	1.382(4)	C12-C13	1.395(4)	C13-C14	1.394(4)
C14-C15	1.381(5)	C15-C16	1.379(4)	C16-C17	1.383(4)
C18-C19	1.333(4)	C19-C20	1.467(4)	C20-C25	1.389(4)
C20-C21	1.402(4)	C21-C22	1.376(5)	C22-C23	1.380(5)
C23-C24	1.381(4)	C24-C25	1.387(4)		

Table 4-5. Bond Angles in Compound 6122, °

O2-C1-O1	121.4(3)	O2-C1-C2	130.9(3)	O1-C1-C2	107.7(2)
C1-C2-C7	115.8(2)	C1-C2-C3	103.3(2)	C7-C2-C3	115.6(2)
C1-C2-C6	99.0(2)	C7-C2-C6	118.4(2)	C3-C2-C6	102.2(2)
C4-C3-C2	104.4(2)	C5-C4-C3	101.0(2)	O1-C5-C10	107.9(2)
O1-C5-C4	105.7(2)	C10-C5-C4	118.3(2)	O1-C5-C6	102.7(2)
C10-C5-C6	116.5(2)	C4-C5-C6	104.2(2)	C9-C6-C8	109.2(2)
C9-C6-C5	115.9(2)	C8-C6-C5	112.6(2)	C9-C6-C2	114.0(2)
C8-C6-C2	113.4(2)	C5-C6-C2	91.0(2)	O4-C10-O3	125.1(2)
O4-C10-C5	126.4(3)	O3-C10-C5	108.5(2)	O3-C11-C18	102.9(2)
O3-C11-C12	110.2(2)	C18-C11-C12	113.1(2)	C17-C12-C13	118.9(3)
C17-C12-C11	121.0(3)	C13-C12-C11	120.1(3)	C14-C13-C12	119.9(3)
C15-C14-C13	120.2(3)	C16-C15-C14	119.9(3)	C15-C16-C17	120.0(3)
C16-C17-C12	121.0(3)	C19-C18-C11	128.1(3)	C18-C19-C20	129.3(3)
C25-C20-C21	117.2(3)	C25-C20-C19	124.1(3)	C21-C20-C19	118.7(3)
C22-C21-C20	121.3(3)	C21-C22-C23	120.5(3)	C22-C23-C24	119.4(3)
C23-C24-C25	120.0(3)	C24-C25-C20	121.5(3)	C1-O1-C5	105.8(2)
C10-O3-C11	117.2(2)				

X-ray Structure Determination of Derivative of 1-20 (#6125)



Compound 6125, $C_{25}H_{26}O_5$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=6.4191(8)Å, b=12.211(2)Å, c=27.390(4)Å, V=2146.9(5)Å^3, Z=4 and d_{calc}=1.258 g/cm^3. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-K_α radiation (λ=0.71069 Å) at a temperature of 143K. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A total of 244 rotation images were collected with a crystal to detector distance of 35 mm, a 2θ swing angle of -12°, rotation widths of 0.5° and exposures of 15 seconds: scan no. 1 was a ϕ-scan from 200° to 322° at ω = 10° and χ = 20°. Rotation images were processed using CrystalClear[I], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the CrystalStructure[II] program package for further processing and structure solution on a Dell Pentium III computer. A total of 6608 reflections were measured over the ranges $5.58 \le 2\theta \le 50.06$ °, $-5 \le h \le 7$, $-14 \le k \le 11$, $-23 \le l \le 32$ yielding 3646 unique reflections (R_{int} = 0.0245). The intensity data were corrected for Lorentz and

polarization effects and for absorption using REQAB[III] (minimum and maximum transmission 0.817, 1.000).

The structure was solved by direct methods (SIR97[IV]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97[V]. All reflections were used during refinement (F^2's that were experimentally negative were replaced by $F^2 = 0$). The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ 0.0479P^2 + 0.6641P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a "riding" model. Refinement converged to R_1=0.0501 and wR_2=0.1049 for 2887 reflections for which $F > 4\sigma(F)$ and R_1=0.0693, wR_2=0.1225 and GOF = 1.119 for all 3646 unique, non-zero reflections and 275 variables.[VI] The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.191 and -0.219 e/Å^3.

Table 4-6 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 4-7. Anisotropic thermal parameters are in Table 4-8. Table 4-9 and Table 4-10 list bond distances and bond angles. Figure 4-2 is an ORTEP[VII] representation of the molecule with 30% probability thermal ellipsoids displayed.

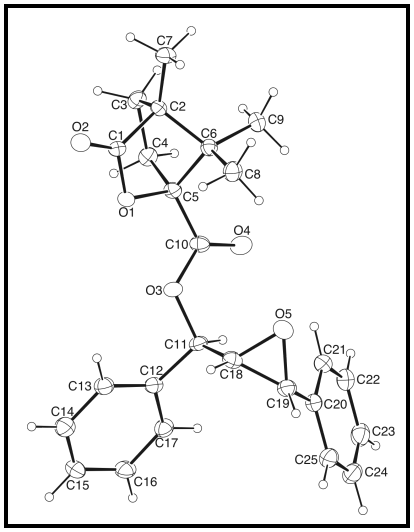


Figure 4-2. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 4-6. Summary of Structure Determination of Compound 6125

Formula:	$C_{25}H_{26}O_5$
Formula weight:	406.46
Crystal class:	orthorhombic
Space group:	$P2_12_12_1$ (#19)
Z	4
Cell constants:	
a	6.4191(8)Å
b	12.211(2)Å
c	27.390(4)Å
V	2146.9(5)Å^3
μ	0.87 cm^{-1}
crystal size, mm	0.32 x 0.26 x 0.05
D_{calc}	1.258 g/cm^3
F(000)	864
Radiation:	Mo-K_α (λ=0.71073Å)
2θ range	5.58 – 50.06 °
hkl collected:	-5≤ h ≤7; -14≤ k ≤11; -23≤ l ≤32
No. reflections measured:	6608
No. unique reflections:	3646 (R_{int}=0.0245)
No. observed reflections	2887 (F>4σ)
No. reflections used in refinement	3646
No. parameters	275
R indices (F>4σ)	R_1=0.0501
	wR_2=0.1049
R indices (all data)	R_1=0.0693
	wR_2=0.1225
GOF:	1.119
Final Difference Peaks, e/Å^3	+0.191, -0.219

Table 4-7. Refined Positional Parameters for Compound 6125

Atom	x	y	z	U_{eq}, Å^2
C1	0.3548(5)	0.8847(2)	0.43251(10)	0.0274(6)
C2	0.1365(4)	0.9165(2)	0.41782(10)	0.0276(6)
C3	0.0035(5)	0.8728(2)	0.46131(11)	0.0334(7)
H3a	0.0597	0.8973	0.4923	0.044
H3b	-0.1401	0.8969	0.4586	0.044
C4	0.0197(5)	0.7473(2)	0.45631(10)	0.0331(7)
H4a	0.0808	0.7144	0.4852	0.044
H4b	-0.1155	0.7144	0.4503	0.044
C5	0.1635(4)	0.7359(2)	0.41193(10)	0.0274(6)
C6	0.0959(4)	0.8302(2)	0.37751(10)	0.0283(6)
C7	0.1101(5)	1.0370(2)	0.40613(13)	0.0434(8)
H7a	0.1519	1.0800	0.4338	0.065
H7b	-0.0333	1.0516	0.3987	0.065
H7c	0.1951	1.0556	0.3785	0.065
C8	0.2388(5)	0.8412(3)	0.33285(11)	0.0391(8)
H8a	0.3809	0.8468	0.3434	0.059
H8b	0.2016	0.9057	0.3148	0.059
H8c	0.2231	0.7780	0.3123	0.059
C9	-0.1310(5)	0.8245(3)	0.36008(11)	0.0397(8)
H9a	-0.1471	0.7640	0.3380	0.060
H9b	-0.1666	0.8914	0.3436	0.060
H9c	-0.2212	0.8145	0.3877	0.060
C10	0.1753(5)	0.6242(2)	0.39000(12)	0.0319(7)
C11	0.3854(5)	0.4676(2)	0.37307(10)	0.0307(7)
H11	0.2483	0.4332	0.3695	0.041
C12	0.5210(5)	0.3985(2)	0.40487(10)	0.0301(7)
C13	0.6914(5)	0.4403(3)	0.42960(12)	0.0369(8)
H13	0.7192	0.5150	0.4281	0.049
C14	0.8207(5)	0.3733(3)	0.45647(13)	0.0443(8)
H14	0.9335	0.4029	0.4732	0.059
C15	0.7819(5)	0.2611(3)	0.45852(12)	0.0440(8)
H15	0.8684	0.2155	0.4766	0.059
C16	0.6140(5)	0.2181(3)	0.43344(12)	0.0404(8)
H16	0.5885	0.1431	0.4344	0.054
C17	0.4839(5)	0.2858(2)	0.40699(11)	0.0357(7)
H17	0.3707	0.2562	0.3904	0.047
C18	0.4836(5)	0.4840(2)	0.32354(11)	0.0342(7)
H18	0.6292	0.5081	0.3239	0.046
C19	0.4218(5)	0.4180(2)	0.28055(11)	0.0366(7)
H19	0.5334	0.4063	0.2567	0.049
C20	0.2601(5)	0.3317(3)	0.28094(10)	0.0336(7)
C21	0.0598(5)	0.3504(3)	0.29777(12)	0.0417(8)
H21	0.0211	0.4205	0.3075	0.056
C22	-0.0831(5)	0.2659(3)	0.30019(12)	0.0446(8)
H22	-0.2160	0.2786	0.3124	0.059
C23	-0.0279(6)	0.1623(3)	0.28436(12)	0.0477(9)
H23	-0.1238	0.1052	0.2857	0.064
C24	0.1698(6)	0.1439(3)	0.26652(12)	0.0466(9)

H24	0.2061	0.0746	0.2554	0.062
C25	0.3142(6)	0.2274(3)	0.26508(11)	0.0413(8)
H25	0.4479	0.2139	0.2535	0.055
O1	0.3685(3)	0.7732(2)	0.42886(7)	0.0277(5)
O2	0.4988(3)	0.9392(2)	0.44650(8)	0.0361(5)
O3	0.3627(3)	0.5762(2)	0.39478(7)	0.0319(5)
O4	0.0264(3)	0.5820(2)	0.37091(8)	0.0426(6)
O5	0.3566(3)	0.5313(2)	0.28565(8)	0.0399(5)

$U_{eq}=1/3[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*cos\gamma+2U_{13}aa^*cc^*cos\beta+2U_{23}bb^*cc^*cos\alpha]$

Table 4-8. Refined Thermal Parameters (U's) for Compound 6125

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.028(2)	0.0251(14)	0.0289(14)	-0.0019(13)	0.0031(13)	0.0027(14)
C2	0.0235(14)	0.029(2)	0.0309(14)	-0.0017(13)	-0.0026(12)	0.0032(13)
C3	0.026(2)	0.039(2)	0.035(2)	-0.0091(14)	0.0040(14)	-0.0011(14)
C4	0.030(2)	0.036(2)	0.033(2)	-0.0013(14)	0.0046(13)	-0.0025(14)
C5	0.0184(14)	0.030(2)	0.034(2)	-0.0027(13)	0.0043(12)	-0.0004(13)
C6	0.029(2)	0.029(2)	0.0274(14)	0.0009(13)	0.0000(12)	0.0004(13)
C7	0.047(2)	0.030(2)	0.054(2)	-0.007(2)	-0.009(2)	0.010(2)
C8	0.046(2)	0.042(2)	0.030(2)	0.002(2)	0.0025(14)	0.001(2)
C9	0.036(2)	0.046(2)	0.038(2)	-0.004(2)	-0.0093(14)	0.006(2)
C10	0.024(2)	0.030(2)	0.041(2)	-0.0007(14)	0.0049(14)	0.0011(14)
C11	0.035(2)	0.0221(14)	0.035(2)	-0.0060(13)	0.0014(14)	0.0029(13)
C12	0.034(2)	0.0266(14)	0.0293(14)	0.0009(13)	0.0046(13)	0.0040(13)
C13	0.036(2)	0.031(2)	0.044(2)	-0.004(2)	-0.001(2)	0.0013(14)
C14	0.042(2)	0.040(2)	0.051(2)	-0.006(2)	-0.005(2)	0.002(2)
C15	0.048(2)	0.042(2)	0.043(2)	0.002(2)	-0.006(2)	0.015(2)
C16	0.053(2)	0.026(2)	0.042(2)	0.004(2)	0.001(2)	0.006(2)
C17	0.043(2)	0.028(2)	0.035(2)	-0.0007(13)	0.000(2)	-0.002(2)
C18	0.036(2)	0.031(2)	0.036(2)	0.0054(14)	0.0026(14)	0.0044(14)
C19	0.043(2)	0.035(2)	0.032(2)	-0.001(2)	0.0021(14)	0.009(2)
C20	0.040(2)	0.033(2)	0.0275(14)	-0.0003(14)	-0.0039(14)	0.005(2)
C21	0.039(2)	0.040(2)	0.046(2)	-0.009(2)	-0.011(2)	0.009(2)
C22	0.042(2)	0.048(2)	0.043(2)	-0.006(2)	-0.012(2)	0.001(2)
C23	0.060(2)	0.040(2)	0.043(2)	0.000(2)	-0.013(2)	-0.007(2)
C24	0.065(2)	0.039(2)	0.036(2)	-0.005(2)	-0.005(2)	0.003(2)
C25	0.050(2)	0.041(2)	0.033(2)	-0.002(2)	0.000(2)	0.006(2)
O1	0.0236(10)	0.0251(10)	0.0346(10)	-0.0018(9)	-0.0022(9)	0.0027(9)
O2	0.0252(11)	0.0315(11)	0.0515(13)	-0.0055(10)	-0.0041(10)	-0.0031(9)
O3	0.0313(11)	0.0245(10)	0.0399(11)	-0.0056(9)	-0.0001(9)	0.0037(9)
O4	0.0272(12)	0.0392(12)	0.0615(14)	-0.0131(11)	-0.0002(11)	-0.0023(10)
O5	0.0465(13)	0.0349(11)	0.0384(12)	0.0075(10)	-0.0021(11)	0.0052(11)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+ 2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$.

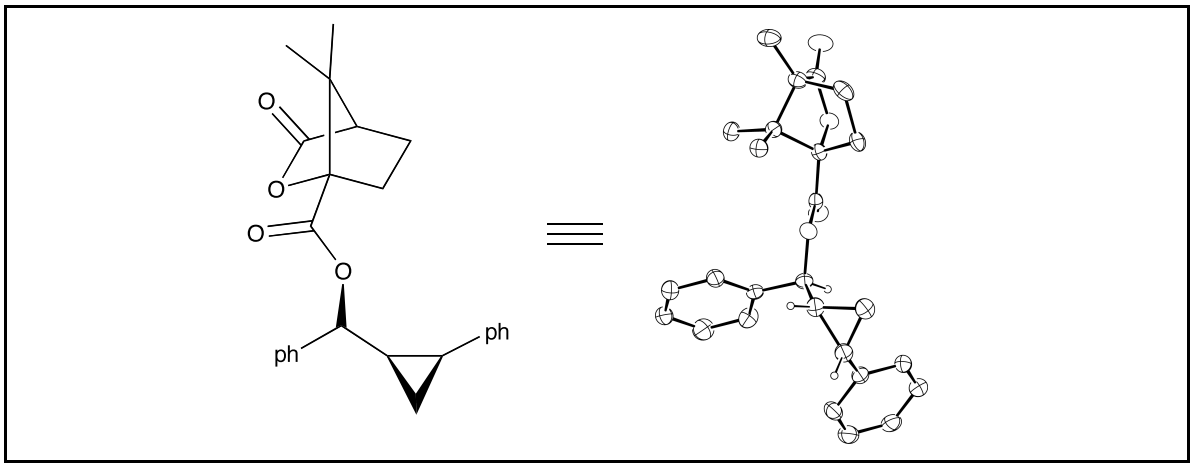
Table 4-9. Bond Distances in Compound 6125, Å

C1-O2	1.202(3)	C1-O1	1.368(3)	C1-C2	1.508(4)
C2-C7	1.514(4)	C2-C6	1.549(4)	C2-C3	1.560(4)
C3-C4	1.543(4)	C4-C5	1.532(4)	C5-O1	1.468(3)
C5-C10	1.492(4)	C5-C6	1.550(4)	C6-C9	1.534(4)
C6-C8	1.535(4)	C10-O4	1.205(4)	C10-O3	1.345(4)
C11-O3	1.460(3)	C11-C12	1.493(4)	C11-C18	1.509(4)
C12-C13	1.384(4)	C12-C17	1.398(4)	C13-C14	1.379(4)
C14-C15	1.393(5)	C15-C16	1.382(5)	C16-C17	1.381(4)
C18-O5	1.440(4)	C18-C19	1.481(4)	C19-O5	1.452(4)
C19-C20	1.479(4)	C20-C21	1.385(4)	C20-C25	1.390(4)
C21-C22	1.383(5)	C22-C23	1.384(5)	C23-C24	1.378(5)
C24-C25	1.378(5)				

Table 4-10. Bond Angles in Compound 6125, °

O2-C1-O1	121.7(3)	O2-C1-C2	131.1(3)	O1-C1-C2	107.2(2)
C1-C2-C7	114.2(2)	C1-C2-C6	99.9(2)	C7-C2-C6	119.4(3)
C1-C2-C3	102.5(2)	C7-C2-C3	115.6(3)	C6-C2-C3	102.7(2)
C4-C3-C2	103.6(2)	C5-C4-C3	101.6(2)	O1-C5-C10	111.4(2)
O1-C5-C4	105.1(2)	C10-C5-C4	115.6(2)	O1-C5-C6	102.2(2)
C10-C5-C6	116.6(2)	C4-C5-C6	104.3(2)	C9-C6-C8	108.9(2)
C9-C6-C2	114.3(2)	C8-C6-C2	114.1(2)	C9-C6-C5	114.9(2)
C8-C6-C5	112.5(2)	C2-C6-C5	91.4(2)	O4-C10-O3	124.5(3)
O4-C10-C5	121.7(3)	O3-C10-C5	113.9(3)	O3-C11-C12	109.5(2)
O3-C11-C18	106.7(2)	C12-C11-C18	110.9(2)	C13-C12-C17	118.5(3)
C13-C12-C11	122.6(3)	C17-C12-C11	118.8(3)	C14-C13-C12	121.2(3)
C13-C14-C15	119.8(3)	C16-C15-C14	119.5(3)	C17-C16-C15	120.3(3)
C16-C17-C12	120.6(3)	O5-C18-C19	59.6(2)	O5-C18-C11	117.7(2)
C19-C18-C11	122.0(3)	O5-C19-C20	118.4(3)	O5-C19-C18	58.8(2)
C20-C19-C18	124.7(3)	C21-C20-C25	119.2(3)	C21-C20-C19	122.4(3)
C25-C20-C19	118.4(3)	C22-C21-C20	120.6(3)	C21-C22-C23	119.9(3)
C24-C23-C22	119.7(3)	C25-C24-C23	120.7(3)	C24-C25-C20	120.0(3)
C1-O1-C5	105.9(2)	C10-O3-C11	116.4(2)	C18-O5-C19	61.6(2)

X-ray Structure Determination of Derivative of 1-28 (#6151)



Compound 6151, $C_{26}H_{28}O_4$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=6.3122(7)Å, b=12.1530(13)Å, c=28.515(3)Å, V=2187.4(4)Å^3, Z=4, and d_{calc}=1.228 g/cm^3 . X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 seconds. A total of 580 rotation images were collected with a crystal to detector distance of 35 mm, a 2θ swing angle of -12°, rotation widths of 0.5° and exposures of 60 seconds:

scan no.	scan type	ω	χ	ϕ
1	ϕ	10.0	20.0	20.0 — 270.0
2	ω	-20.0 — +20.0	-90.0	0.0

Rotation images were processed using CrystalClear,[I] producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the CrystalStructure[II] program package for further processing and structure solution on a Dell Pentium 4 computer. A total of 15440 reflections were measured over the ranges $2.72 \le \theta \le 24.11°$, $-6 \le h \le 7$, $-13 \le k \le 13$, $-32 \le l \le 32$ yielding 3475

unique reflections (Rint = 0.0314). The intensity data were corrected for Lorentz and polarization effects and for absorption using REQAB[III] (minimum and maximum transmission 0.8170, 1.0000). The structure was solved by direct methods (SIR97[IV]). Refinement was by full-matrix least squares based on F^2 using SHELXL-97.[V] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0588P)^2 + 0.2107P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0430 and wR2=0.1030 for 3150 observed reflections for which $F > 4\sigma(F)$ and R1=0.0487 and wR2=0.1081 and GOF =1.112 for all 3475 unique, non-zero reflections and 275 variables.[VI] The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.133 and -0.200 e/Å^3.

Table 4-11 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 4-12 and Table 4-13. Anisotropic thermal parameters are in Table 4-14. Table 4-15 and Table 4-16 list bond distances and bond angles. Figure 4-3 is an ORTEP[VII] representation of the molecule with 30% probability thermal ellipsoids displayed.

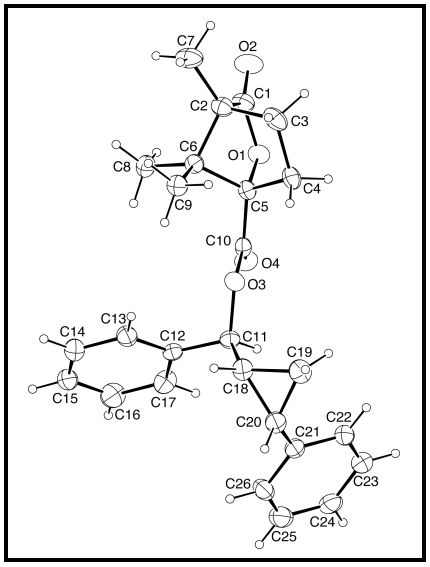


Figure 4-3. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

Table 4-11. Summary of Structure Determination of Compound 6151

Empirical formula	$C_{26}H_{28}O_4$
Formula weight	404.48
Temperature	143(1) K
Wavelength	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Cell constants:	
a	6.3122(7) Å
b	12.1530(13) Å
c	28.515(3) Å
Volume	2187.4(4) $Å^3$
Z	4
Density (calculated)	1.228 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	864
Crystal size	0.34 x 0.10 x 0.10 mm^3
Theta range for data collection	2.72 to 24.11°
Index ranges	$-6 \le h \le 7$, $-13 \le k \le 13$, $-32 \le l \le 32$
Reflections collected	15440
Independent reflections	3475 [R(int) = 0.0314]
Completeness to theta = 24.11°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.8170
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3475 / 0 / 275
Goodness-of-fit on F^2	1.112
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.1030
R indices (all data)	R1 = 0.0487, wR2 = 0.1081
Absolute structure parameter	0.5(11)
Largest diff. peak and hole	0.133 and -0.200 $e.Å^{-3}$

Table 4-12. Refined Positional Parameters for Compound 6151

Atom	x	y	z	U_{eq}, Å^2
C1	0.5103(4)	0.16809(19)	0.24102(8)	0.0452(6)
C2	0.7287(4)	0.15283(18)	0.22142(8)	0.0433(5)
C3	0.8598(4)	0.2405(2)	0.24849(8)	0.0525(6)
C4	0.7762(4)	0.35245(19)	0.22960(7)	0.0444(5)
C5	0.6027(3)	0.31377(17)	0.19606(7)	0.0337(5)
C6	0.6975(3)	0.20916(17)	0.17280(7)	0.0364(5)
C7	0.8101(5)	0.0363(2)	0.22358(9)	0.0592(7)
C8	0.5391(4)	0.14993(18)	0.14128(8)	0.0441(5)
C9	0.9042(4)	0.22689(18)	0.14643(8)	0.0419(5)
C10	0.5015(3)	0.39813(17)	0.16481(7)	0.0342(5)
C11	0.5819(3)	0.53050(16)	0.10550(7)	0.0368(5)
C12	0.4922(3)	0.47868(16)	0.06182(7)	0.0359(5)
C13	0.6068(4)	0.39925(18)	0.03735(8)	0.0471(6)
C14	0.5258(5)	0.3553(2)	-0.00393(9)	0.0574(7)
C15	0.3354(5)	0.3905(2)	-0.02112(8)	0.0569(7)
C16	0.2211(5)	0.4690(2)	0.00285(9)	0.0615(7)
C17	0.3004(4)	0.51316(19)	0.04396(9)	0.0505(6)
C18	0.7750(4)	0.59809(18)	0.09509(7)	0.0437(5)
C19	0.8641(4)	0.67339(19)	0.13131(8)	0.0513(6)
C20	0.7572(4)	0.72265(18)	0.08956(8)	0.0480(6)
C21	0.5519(4)	0.78331(16)	0.09202(7)	0.0447(6)
C22	0.4663(4)	0.82168(18)	0.13393(8)	0.0510(6)
C23	0.2815(5)	0.88348(19)	0.13421(9)	0.0562(6)
C24	0.1793(5)	0.90836(19)	0.09296(9)	0.0553(7)
C25	0.2600(5)	0.8702(2)	0.05113(9)	0.0594(7)
C26	0.4428(5)	0.8087(2)	0.05088(8)	0.0540(6)
O1	0.4354(2)	0.26769(11)	0.22569(5)	0.0405(4)
O2	0.4058(3)	0.11094(14)	0.26717(6)	0.0601(5)
O3	0.6530(2)	0.44534(11)	0.13832(4)	0.0378(4)
O4	0.3159(2)	0.41975(12)	0.16255(5)	0.0423(4)

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

Table 4-13. Positional Parameters for Hydrogens in Compound 6151

Atom	x	y	z	U_{iso}, Å^2
H3a	1.0099	0.2323	0.2421	0.070
H3b	0.8365	0.2345	0.2820	0.070
H4a	0.7190	0.3977	0.2546	0.059
H4b	0.8860	0.3930	0.2132	0.059
H7a	0.8029	0.0102	0.2553	0.089
H7b	0.9545	0.0344	0.2130	0.089
H7c	0.7249	-0.0098	0.2038	0.089
H8a	0.5121	0.1938	0.1139	0.066
H8b	0.4091	0.1387	0.1581	0.066
H8c	0.5963	0.0801	0.1320	0.066
H9a	0.9627	0.1569	0.1377	0.063
H9b	1.0027	0.2652	0.1662	0.063
H9c	0.8776	0.2697	0.1188	0.063
H11	0.4740	0.5766	0.1205	0.049
H13	0.7373	0.3756	0.0486	0.063
H14	0.6017	0.3016	-0.0200	0.076
H15	0.2831	0.3615	-0.0490	0.076
H16	0.0907	0.4923	-0.0086	0.082
H17	0.2233	0.5668	0.0598	0.067
H18	0.8799	0.5626	0.0748	0.058
H19a	1.0170	0.6797	0.1333	0.068
H19b	0.7911	0.6778	0.1612	0.068
H20	0.8562	0.7532	0.0665	0.064
H22	0.5339	0.8057	0.1621	0.068
H23	0.2263	0.9083	0.1625	0.075
H24	0.0565	0.9507	0.0933	0.074
H25	0.1909	0.8860	0.0231	0.079
H26	0.4952	0.7832	0.0224	0.072

Table 4-14. Refined Thermal Parameters (U's) for Compound 6151

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0432(14)	0.0493(12)	0.0429(13)	0.0076(11)	0.0045(10)	0.0050(11)
C2	0.0389(13)	0.0488(12)	0.0421(12)	0.0068(10)	0.0025(10)	0.0062(10)
C3	0.0412(14)	0.0778(16)	0.0386(12)	0.0060(12)	-0.0051(10)	0.0073(13)
C4	0.0409(13)	0.0565(12)	0.0358(11)	-0.0069(10)	-0.0079(10)	0.0009(11)
C5	0.0288(11)	0.0405(10)	0.0318(10)	-0.0014(9)	0.0047(9)	-0.0015(9)
C6	0.0345(12)	0.0377(10)	0.0369(10)	0.0002(9)	0.0046(9)	0.0001(9)
C7	0.0560(17)	0.0590(14)	0.0626(15)	0.0182(12)	0.0145(13)	0.0185(12)
C8	0.0444(14)	0.0426(11)	0.0453(12)	-0.0067(10)	0.0029(11)	-0.0053(10)
C9	0.0346(13)	0.0474(11)	0.0438(12)	0.0003(10)	0.0072(10)	0.0019(10)
C10	0.0349(13)	0.0364(10)	0.0313(10)	-0.0062(9)	0.0019(9)	-0.0047(9)
C11	0.0344(12)	0.0363(10)	0.0398(11)	0.0040(9)	0.0002(9)	-0.0008(9)
C12	0.0364(12)	0.0317(9)	0.0396(11)	0.0047(9)	0.0022(9)	-0.0024(8)
C13	0.0509(15)	0.0477(12)	0.0427(12)	-0.0008(11)	-0.0024(11)	0.0108(11)
C14	0.077(2)	0.0493(13)	0.0459(13)	-0.0054(11)	-0.0033(13)	0.0083(13)
C15	0.079(2)	0.0465(13)	0.0450(13)	-0.0003(11)	-0.0168(14)	-0.0086(13)
C16	0.0524(17)	0.0625(15)	0.0697(16)	-0.0011(14)	-0.0226(14)	-0.0021(13)
C17	0.0389(14)	0.0480(12)	0.0645(14)	-0.0055(12)	-0.0060(12)	0.0022(10)
C18	0.0379(13)	0.0484(12)	0.0447(12)	-0.0023(10)	0.0043(10)	-0.0069(10)
C19	0.0421(14)	0.0596(14)	0.0521(13)	-0.0011(12)	-0.0014(11)	-0.0137(12)
C20	0.0531(15)	0.0465(12)	0.0443(12)	0.0006(10)	0.0046(11)	-0.0205(12)
C21	0.0556(15)	0.0362(11)	0.0424(12)	0.0011(10)	0.0006(11)	-0.0195(11)
C22	0.0706(18)	0.0426(12)	0.0397(12)	-0.0003(11)	-0.0050(12)	-0.0094(12)
C23	0.0744(18)	0.0443(12)	0.0497(13)	0.0004(11)	0.0029(13)	-0.0017(13)
C24	0.0662(18)	0.0383(11)	0.0615(15)	0.0068(11)	-0.0022(14)	-0.0096(12)
C25	0.071(2)	0.0530(13)	0.0536(15)	0.0088(12)	-0.0104(14)	-0.0105(14)
C26	0.0683(18)	0.0580(14)	0.0356(12)	0.0038(11)	-0.0014(12)	-0.0126(13)
O1	0.0366(8)	0.0456(8)	0.0392(8)	0.0065(7)	0.0096(7)	0.0045(7)
O2	0.0562(11)	0.0628(10)	0.0613(10)	0.0242(9)	0.0186(9)	0.0081(9)
O3	0.0330(8)	0.0446(7)	0.0358(7)	0.0026(6)	0.0010(7)	0.0001(6)
O4	0.0289(9)	0.0442(8)	0.0537(9)	0.0057(7)	0.0022(7)	-0.0008(6)

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

Table 4-15. Bond Distances in Compound 6151, Å

C1-O2	1.214(3)	C1-O1	1.371(3)	C1-C2	1.499(3)
C2-C7	1.507(3)	C2-C3	1.554(3)	C2-C6	1.559(3)
C3-C4	1.555(3)	C4-C5	1.528(3)	C5-O1	1.464(2)
C5-C10	1.501(3)	C5-C6	1.554(3)	C6-C9	1.521(3)
C6-C8	1.525(3)	C10-O4	1.202(2)	C10-O3	1.347(2)
C11-O3	1.465(2)	C11-C18	1.499(3)	C11-C12	1.506(3)
C12-C17	1.379(3)	C12-C13	1.394(3)	C13-C14	1.390(3)
C14-C15	1.366(4)	C15-C16	1.378(4)	C16-C17	1.383(3)
C18-C19	1.490(3)	C18-C20	1.526(3)	C19-C20	1.494(3)
C20-C21	1.493(4)	C21-C22	1.392(3)	C21-C26	1.395(3)
C22-C23	1.388(4)	C23-C24	1.375(4)	C24-C25	1.377(4)
C25-C26	1.375(4)				

Table 4-16. Bond Angles in Compound 6151, °

O2-C1-O1	120.9(2)	O2-C1-C2	131.1(2)	O1-C1-C2	107.92(18)
C1-C2-C7	114.5(2)	C1-C2-C3	102.67(18)	C7-C2-C3	116.3(2)
C1-C2-C6	99.26(17)	C7-C2-C6	119.47(18)	C3-C2-C6	101.99(17)
C2-C3-C4	104.32(17)	C5-C4-C3	101.01(17)	O1-C5-C10	107.28(16)
O1-C5-C4	105.87(15)	C10-C5-C4	117.79(17)	O1-C5-C6	102.20(15)
C10-C5-C6	117.99(16)	C4-C5-C6	104.05(17)	C9-C6-C8	109.76(17)
C9-C6-C5	115.18(17)	C8-C6-C5	112.64(18)	C9-C6-C2	113.17(18)
C8-C6-C2	113.56(17)	C5-C6-C2	91.62(15)	O4-C10-O3	124.64(19)
O4-C10-C5	126.56(19)	O3-C10-C5	108.79(17)	O3-C11-C18	105.35(17)
O3-C11-C12	110.35(15)	C18-C11-C12	111.77(17)	C17-C12-C13	118.8(2)
C17-C12-C11	120.6(2)	C13-C12-C11	120.6(2)	C14-C13-C12	119.9(2)
C15-C14-C13	120.5(2)	C14-C15-C16	120.0(2)	C15-C16-C17	120.0(2)
C12-C17-C16	120.9(2)	C19-C18-C11	120.39(19)	C19-C18-C20	59.35(15)
C11-C18-C20	120.3(2)	C18-C19-C20	61.52(15)	C21-C20-C19	123.6(2)
C21-C20-C18	123.3(2)	C19-C20-C18	59.13(15)	C22-C21-C26	117.2(2)
C22-C21-C20	122.9(2)	C26-C21-C20	119.9(2)	C23-C22-C21	120.8(2)
C24-C23-C22	120.6(3)	C23-C24-C25	119.5(3)	C26-C25-C24	119.9(2)
C25-C26-C21	122.0(2)	C1-O1-C5	105.84(16)	C10-O3-C11	116.22(16)

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[vi]. $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$

$wR_2 = \{ \sum w (F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2 \}^{1/2}$

$GOF = \{ \sum w (F_o^2 - F_c^2)^2 / (n - p) \}^{1/2}$

where n = the number of reflections and p = the number of parameters refined.

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