Synthesis of Substrates for Cyclization Studies Using Phenylselenium Ion and for Hydrovinylation Reactions

A Senior Honors Thesis

Presented in Partial Fulfillment of the Requirements for graduation *with research distinction* in Chemistry in the undergraduate colleges of The Ohio State University.

by

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Abstract

Development of novel methods for making useful, enantiopure pharmaceutical compounds is an active area of current synthetic organic chemistry research. Many of these compounds contain heterocyclic components, which are ubiquitous in organic chemistry, but not always easy to synthesize. This project is aimed at making substrates for a reaction that utilizes a phenylselenium cation to induce an electrophilic cyclization by a heteroatom, thereby creating a heterocyclic compound. It is anticipated that this work will assist in the syntheses of pyrrolidinoindoline alkaloids such as physostigmine and the kinase inhibitor lyngbyatoxin. The use of the phenylselenium cation is found to have broad applications for the synthesis of diverse heterocycles that contain different leaving groups. Additionally, diverse vinylarene derivatives have been synthesized to explore the scope of the asymmetric hydrovinylation reactions. These include substrates for 2-arylpropionic acids (e. g., ibuprofen and naproxen) and also Frondosin B.

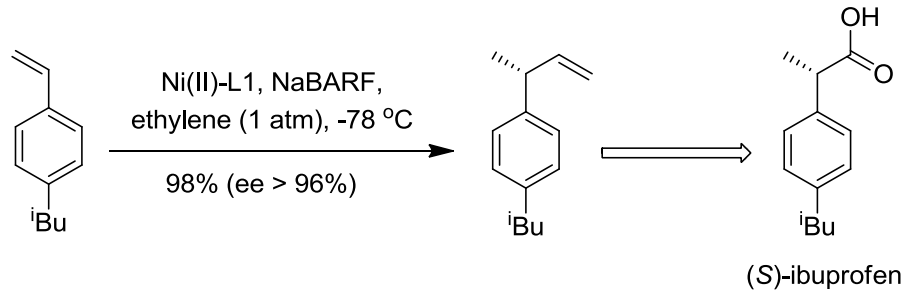
1 Introduction

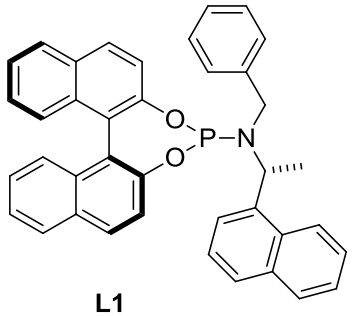
1.1 Background

Stereoselective formation of quaternary carbon centers has historically been a great synthetic challenge to organic chemists. Although classical methods can accomplish the arduous synthetic task, each approach poses unique disadvantages. Asymmetric hydrovinylation (the addition of a vinyl group and a hydrogen atom across a double bond) provides an economical, less-toxic alternative.

During hydrovinylation, a branched alkene product that includes a quaternary carbon chiral center is generated, making regioselective and stereoselective control over this reaction enormously relevant in the realm of drug-like molecule synthesis. The asymmetric hydrovinylation of styrene derivatives leads to 3-arylbutenes and other substituted styrenes, which could be used as intermediates towards the enantioselective synthesis of the commonly used 2-arylpropionic acids such as ibuprofen (Scheme 1) and naproxen. Currently, the pharmaceutical industry markets many of these popular drugs as a racemic mixture, even though only the (*S*)-enantiomer mostly exhibits the desired anti-inflammatory biological response.[1]

Scheme 1 Synthesis of (*S*)-ibuprofen from 4-Isobutylstyrene[1]



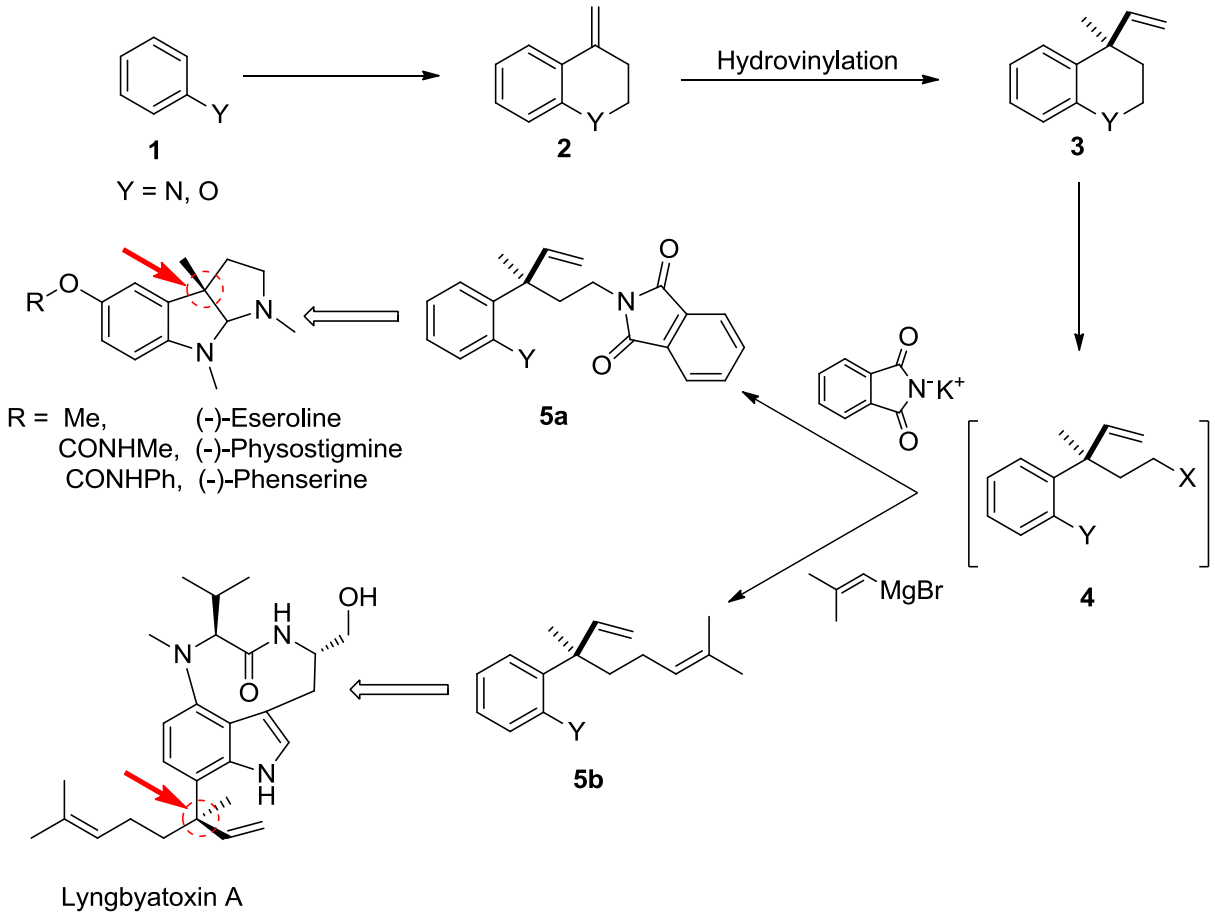


L1

Additionally, asymmetric hydrovinylation of appropriately substituted vinylarenes (e.g. indole, shown in Scheme 2) can be used when planning the enantioselective synthesis of lyngbytoxin A or similar natural products in the telocidin family, where an all-carbon quaternary

center is present at the benzylic position. Similarly, various pyrrolidinoindolines can be built by hydrovinylation of an exo-cyclic methylene intermediate (e.g. **2**) to stereoselectively generate a benzylic quaternary carbon center with a highly versatile vinyl group attached. This latent functionality can easily be differentiated to complete the synthesis of multiple anticholinesterase agents (Scheme 2).[2]

Scheme 2 General Synthesis of Pyrrolidinoindolines and Lynbyatoxin A

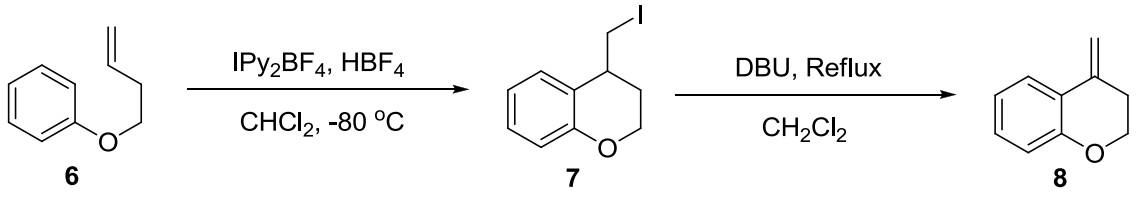


Constructing an exo-methylene compound like **2** with a highly functionalized arene is a challenge, so new methods for syntheses were recently explored. Although previous literature discloses successful syntheses of 4-methylenechroman via the use of Wittig reactions,[3] radical cyclizations,[4] and Heck reactions,[5] these methods generate undesirable products (phosphine oxide), require a stoichiometric amount of hazardous transition metals (3.0 equivalents of Cr), or generate a mixture of heterocyclic products via hydride shift, respectively. Alternatively, Gonzalez published an iodonium ion-triggered cyclization of aryl ethers,[6] which utilizes IPy_2BF_4

as the source of iodonium ion to promote C—C bond forming reactions, affording iodinated chromans. These rings can be easily transformed to give the terminal vinyl group via elimination of the iodine (Scheme 3).

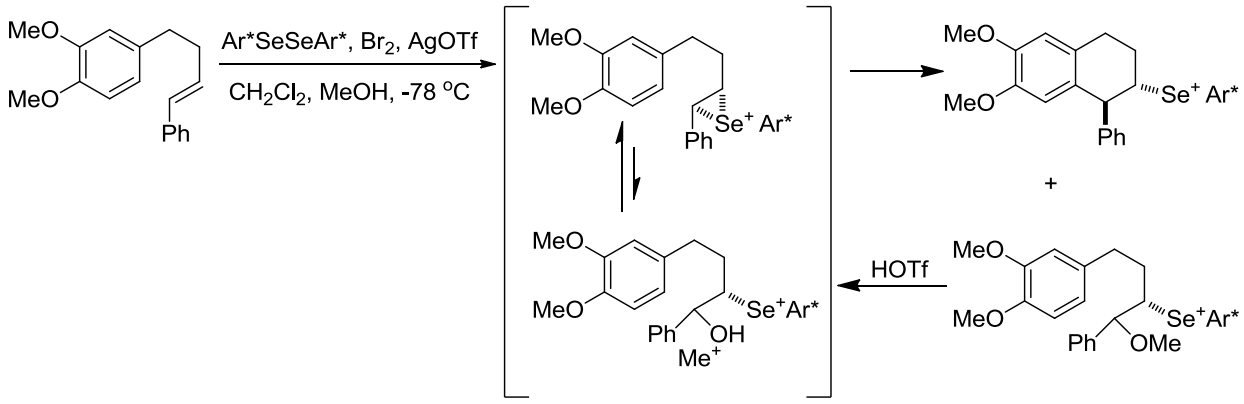
This type of intramolecular electrophilic cyclization produces a Freidel-Crafts alkylation product. Instead of using a traditional Lewis Acid catalyst to generate the reactive carbocation (i.e. $AlCl_3$), the formation of the iodonium ion creates a highly polarized carbon-halogen bond. The positively charged secondary carbon is electrophilic enough for the benzene moiety to donate its π electrons and form a new C—C bond. Consistent with the traditional Freidel-Crafts mechanism, a proton from the cyclohexadienyl cation intermediate is lost to restore aromaticity **(7)**.

Scheme 3 Iodonium Initiated Chroman Synthesis[6]



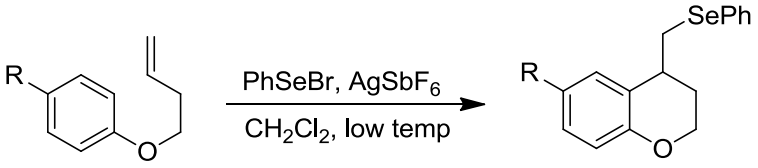
In order to broadly apply this Freidel-Crafts type cyclization to more sensitive, diversely functionalized molecules, milder and commercially available sources of iodonium ion must be found. Prior literature indicates that cationic cyclizations have been initiated by seleniranium ions with a silver triflate counterion,[7] but these methods do not induce the cyclization of 4-aryl-1-butenes (Scheme 4).

Scheme 4 Cationic Phenylselenium Catalyzed Cyclization[7]



Upon analysis of alternative counterions (-OTf, -BF_4, -SbF_6), however, it was found that phenylselenium bromide combined with 3.1 equivalents of $AgSbF_6$ accomplishes the desired Freidel-Crafts intramolecular electrophilic cyclization in good yield[8] (Scheme 5).

Scheme 5 Optimized Cationic Phenylselenium Cyclization[8]

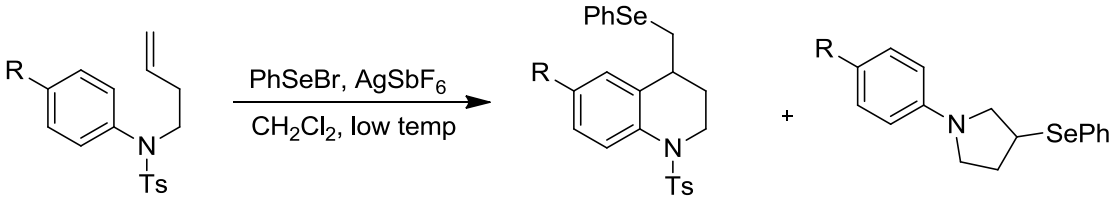


9a R=OMe
9b R=H

10a R = OMe (85%)
10b R = H (97%)

In addition to observing the Freidel-Crafts product, it was found that, when secondary amine tosylates were used as substrates, partial loss of the toluenesulfonyl group occurs (Scheme 6). This appears to be a novel transformation, and after examining electronic factors, it was shown that aryl rings containing electron withdrawing groups (NO_2, CF_3, etc.) proceed exclusively through the detosylative pathway.

Scheme 6 Cyclization Products[8]



11a R = H
11b R = NO_2

12a R = H (55%)
12b R = NO_2 (0%)

13a R = H (30%)
13b R = NO_2 (75%)

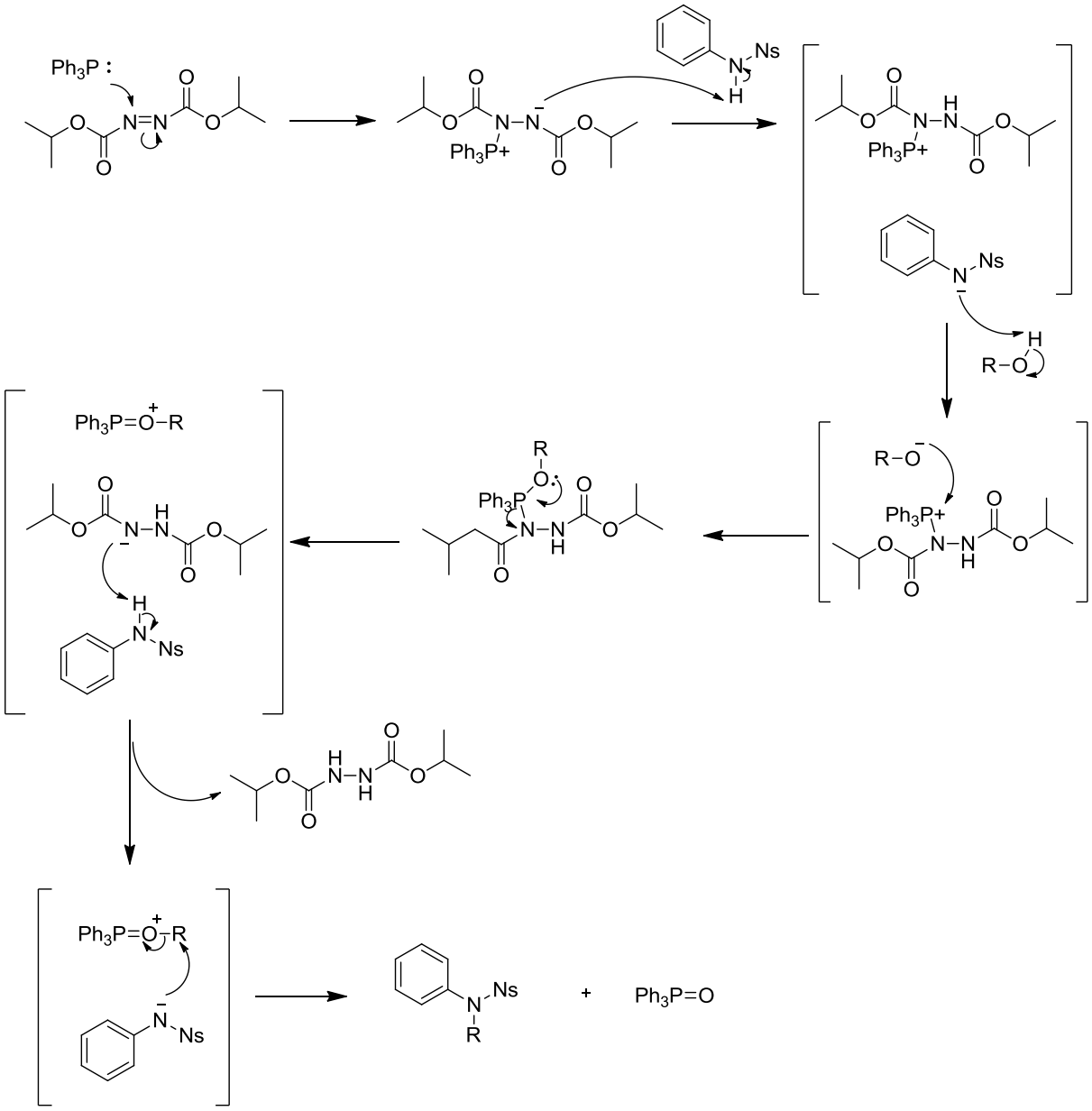
This project was directed at making different substrates to explore the scope and limitations of these novel cyclization methods. The substrates were designed to see under what conditions there will be electrophilic reactions and what conditions would promote heterocycle formation. Different methods were studied for the formation of the terminal alkene, and Mitsunobu reactions gave the best results for the formation of the desired products. Additionally, the Wittig reaction was utilized to make diversely functionalized styrenes to examine the scope of asymmetric hydrovinylation reactions, and steps toward the hydrovinylation step in the total synthesis of (+)-frondosin B were accomplished.

2 Synthetic Approaches

2.1 The Mitsunobu Reaction

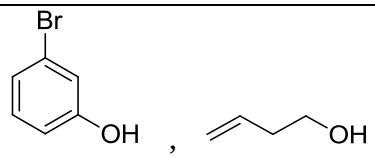
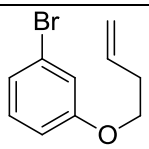
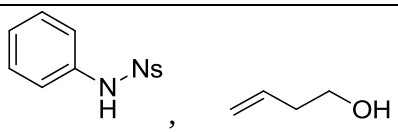
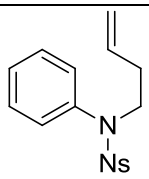
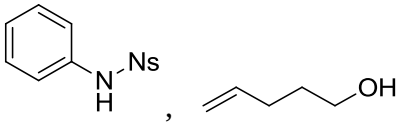
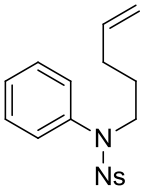
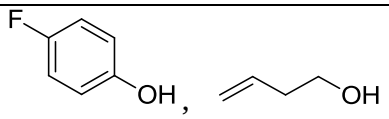
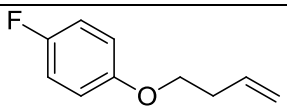
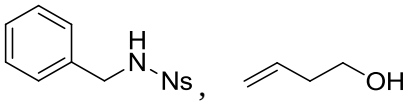
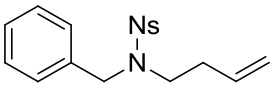
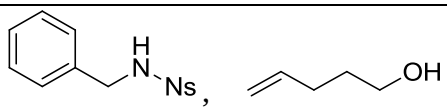
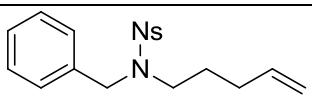
Introduced in 1967, the Mitsunobu reaction involves the condensation reaction of alcohols with various nucleophiles via a redox couple of a triaryl- or trialkylphosphine and a dialkyl azodicarboxylate.[9] Initially, a reactive phosphonium salt is formed from the reaction of alkyl or aryl phosphines with azo compounds. The phosphonium salt then promotes a condensation reaction with compounds having an active hydrogen. The end product, resulting from an alcohol (R—OH) condensing with an acidic compound (H—Nu, pKa <15), takes the form R—Nu, where the triarylphosphine is oxidized to triarylphosphine oxide and the azodicarboxylate is reduced to the corresponding hydrazine (Scheme 7).

Scheme 7 Mitsunobu Reaction Mechanism



In order to further examine the scope of the aforementioned selenium-phenyl catalyzed cyclization (Schemes 5 and 6), the Mitsunobu reaction was utilized to form functionalized ethers and tertiary sulfonamides. In each reaction, nitrogen nucleophiles (secondary sulfonamides, pKa ~12.5) or oxygen nucleophiles (para- or meta- substituted phenols, pKa~10) were reacted with a diisopropyl azodicarboxylate (DIAD)/ triphenylphosphine redox system and a primary alcohol to generate the desired product (Table 1).

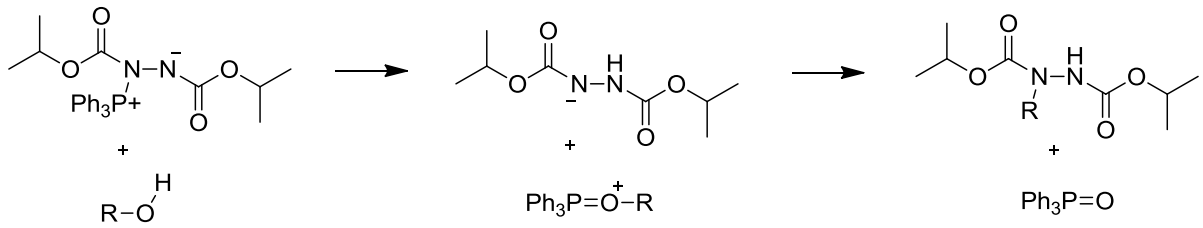
Table 1 Mitsunobu Reaction Results[a]

Entry	Substrate	Product	Yield
14			68%
15			53%
16			67%
17			82%
18			72%
19			67%

[a]Reaction Conditions: See Section 4.2.1, Experimental Procedures.

The success of this reaction relies on substrate balance through each of the three mechanistic steps: (1) adduct formation, (2) alcohol activation, and (3) S_N2 reaction. To construct Products **14**-**19**, a 1:1:1 ratio of triphenylphosphine: DIAD: acidic nucleophile was used. Even though these reactions were all completed at low temperatures (10 ^oC), the poor yields observed in certain reactions where a phenol was used as the nucleophile (**14**, **17**) can be attributed to azaphosphonium adduct decomposition (Scheme 8).[10]

Scheme 8 Azaphosphonium Decomposition



Additionally, work up and purification procedures were rather tedious, also contributing to low yields (**15** especially). It was important to concentrate the reaction mixture to have little excess DIAD, which often formed adverse by-products that would consistently elute with the desired product during column chromatography. To obtain a better separation and prevent running multiple columns, a gradient solvent system was used to successfully isolate substrate **18.**

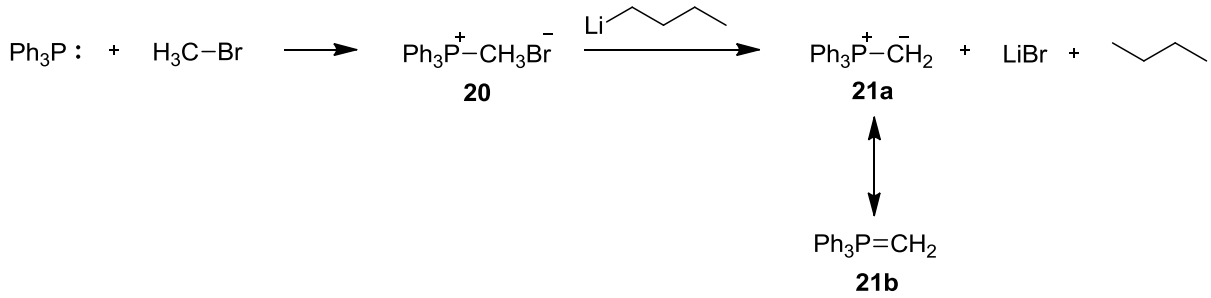
In cases where steric factors were not enough to reduce the nucleophilicity of the conjugate base intermediate, an excess of acid should be initially added to the reaction. This addition would tie up the undesirable early formation of triphenylphosphonium oxide by hydrogen bonding to the conjugate base. Additionally, that conjugate base must efficiently deprotonate the primary alcohol to obtain quantative product yields. This inhibits the use of strong acids because the corresponding conjugate base is too weak to effectively progress the reaction. The use of excess acid, although successfully stabilizing the Mitsunobu intermediate, must be prevented because it solvates the conjugate base, thus decreasing the basicity.[10]

2.2 The Wittig Reaction

The Wittig reaction serves as an alternate route to prepare alkenes as substrates for hydrovinylation. First published in 1953 by Wittig and Geissler, this widely used carbonyl olefination reaction involves the combination of an aldehyde or ketone with a triphenylphosphonium ylide and a strong base.[11] Although other routes of alkene formation are commonly used in synthesis (E1 or E2 reactions from alkyl halides or alcohols, for example), the Wittig reaction is especially attractive because it occurs with total regioselectivity (i.e. the alkene always replaces a carbonyl group). In addition, factors that influence *E*- and *Z*- selectivity are well understood and easily controlled by both the selection of phosphorous reagent and the reaction conditions.

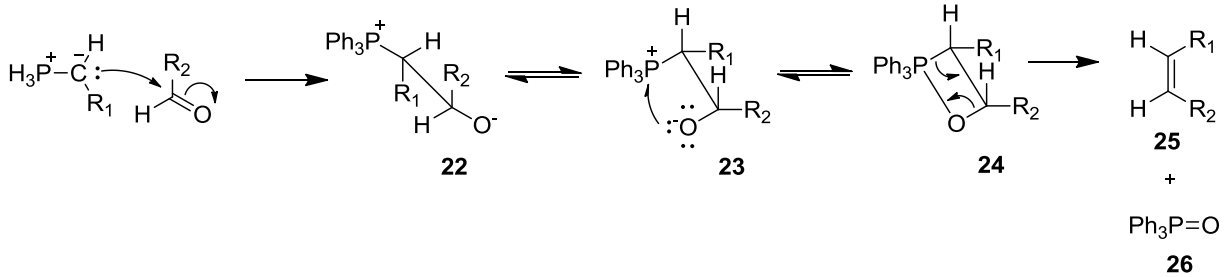
The first step of the reaction involves preparation of the Wittig reagent (ylide **21a**) from a phosphonium salt **20** (Scheme 9). The phosphorous is an electron-withdrawing group, which activates the neighboring carbon atom for deprotonation by a strong base. In each reaction completed (Table 2), n-butyl lithium was required to deprotonate triphenylmethylphosphonium bromide in dry THF. Moisture-free, inert reaction conditions are essential for two reasons: 1) an exceedingly exothermic reaction results from the use of a strong base and water and 2) the ylide produced is very reactive and unstable in the presence of air or water, so it will react before addition of the aldehyde.

Scheme 9 Preparation of the Wittig Reagent



The generated ylide **21a** is strongly nucleophilic, so it readily attacks carbonyl compounds (Scheme 10).

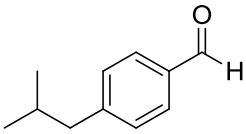
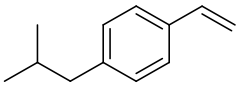
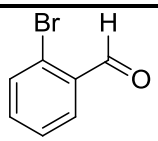
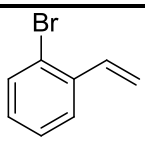
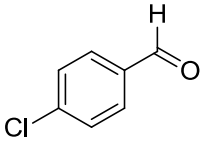
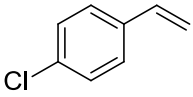
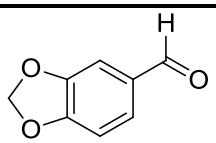
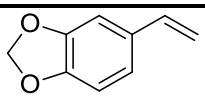
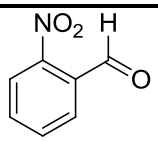
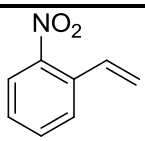
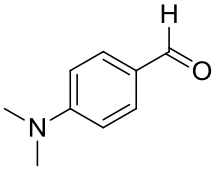
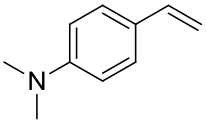
Scheme 10 Classical Wittig Reaction Mechanism



Once the aldehyde is added, the reaction is driven by the formation of the very stable triphenylphosphine oxide **26**, generating a double bond **25** (Table 2).

Although the classical mechanism[12] postulates the formation of the zwitterionic betaine intermediate **23**, recent mechanistic NMR studies are unable to confirm the presence of this ionic structure. Instead, the ylide and carbonyl are hypothesized to react via asynchronous cycloaddition process to form a four-membered cyclic transition state before formation of the oxaphosphetane **.**[13, 14]

Table 2 Wittig Reaction Results[b]

Entry	Substrate	Product	Yield
27			85%
28			37%
29			76%
30			42%
31			63%
32			18%

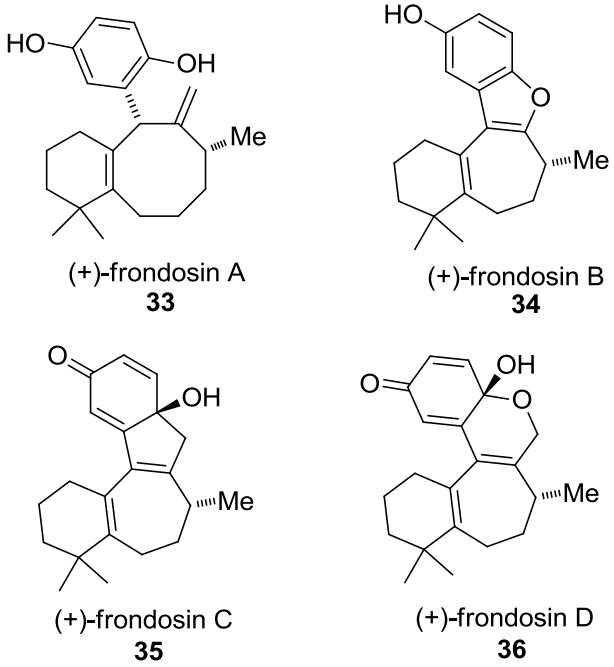
[b]Reaction Conditions: See Section 4.2.2, Experimental Procedures

The poor reaction yields experienced (**30, 32**) can be attributed to the elecrophilicity of the corresponding aldehyde starting material. The reaction with the nitroaromatic is surprisingly good even though aromatic nitrocompounds are known to react with nucleophilic reagents. Substrates that include electron-donating groups ($(CH_3)_2N$-, for example) attached to the arene decrease electrophilicity of the carbonyl carbon, decreasing its affinity for nucleophilic attack, and consequently, the effectiveness of the reaction.

2.3 *En route* to (+)-Frondosin B

A family of terpenoids isolated from the marine sponge *Dysidea frondosa*, the frondosins (Figure 1) have been shown to exhibit HIV-inhibitory properties and to prevent auto-immune disorders such as rheumatoid arthritis by acting as IL-8 receptor antagonists.

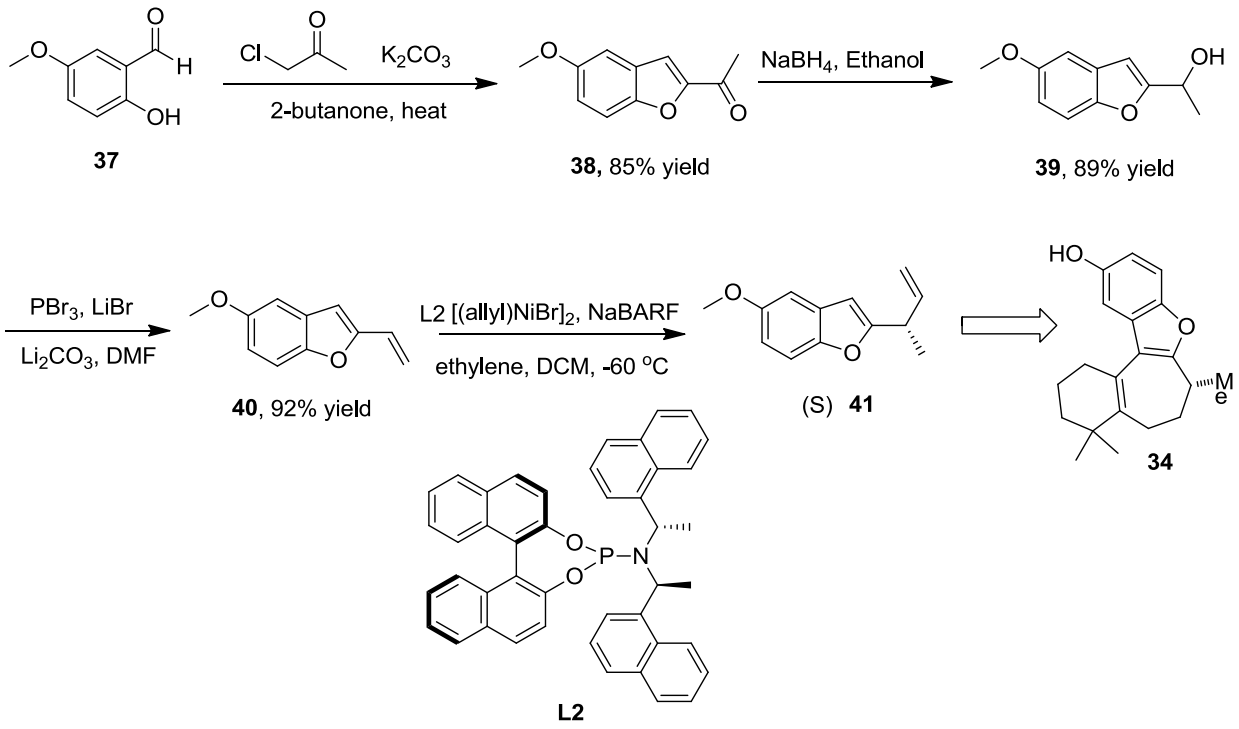
Figure 1 Frondosin Family



Specifically, (+)-frondosin B has attracted much attention because it presents significant synthetic challenges. Although it contains only one stereocenter, to which the absolute configuration was assigned during the first total synthesis by the Danishefsky group,[15] the molecule features an unusual tetracyclic skeleton with a readily isomerized tetrasubstituted alkene and a 2,3-disubstituted benzofuran component.[16]

An alternate synthesis was proposed by the RajanBabu laboratory (Scheme 11), incorporating hydrovinylation as the means by which to construct the stereocenter.

Scheme 11 Proposed Synthesis of Frondosin B



The transformation from **37** to **38** involves deprotonation of the phenol, followed by a S_N2 reaction to displace the chloride. Next, an intramolecular aldol reaction followed by a dehydration reaction ensues giving the enone. Because the loss of water generates a very stable aromatic product, this reaction is extremely favorable and proceeds in good yield. The ketone **38** is reduced to the alcohol **39** under mild conditions, and purification of the product was unnecessary before use in the next S_N2 reaction and elimination to give **40**.

Use of PBr_3 converts the alcohol **39** into a good leaving group and generates a bromine nucleophile *in situ* that is used to produce a secondary alkyl bromide. Use of dimethylformamide, a polar aprotic solvent, promotes an E2 mechanism to form the terminal alkene **40**, preseumably via an anti- elimination of hydrogen bromide.

3 Conclusions

To summarize the results, three distinct methods were used to construct useful compounds that will act as substrates to examine the scope of both selenium-ion induced cyclizations and hydrovinylation reactions. It is hoped that substrates generated from the Mitsunobu reaction will be used to further differentiate the phenyl-selenium catalyzed Friedel-Crafts pathway from the heterocycle formation pathway (Scheme 6). Alternatively, the Wittig reaction was used to create functionalized vinylarenes, which can be used to explicate the asymmetric hydrovinylation reaction. It is necessary to economically generate styrene compounds because, as demonstrated by the proposed (+)-frondosin B synthesis, they can be directly used to produce biologically interesting natural products.

The total synthesis of frondosin B is currently underway, and hopefully will use substrate **40** in the final successful scheme.

4 Experimental

4.1 General Methods

Air sensitive reactions were performed under nitrogen that had been passed the a Drierite tower. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone ketyl. Dichloromethane was distilled under nitrogen from calcium hydride. All substrates were used as received without further purification. Analytical TLC was performed on E. Merck precoated (0.25 mm) silica gel 60 F254 plates. Flash column chromatography was carried out on silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). NMR spectra (^{1}H, ^{13}C) were recorded on a Bruker AM-250 spectrometer using $CDCl_3$ as the solvent. Chemical shifts were measured in parts per million (δ) relative to $CDCl_3$ (δ = 7.26) for ^{1}H and (δ = 77.16) for ^{13}C. Coupling constants (*J* values) are given in units of Hz.

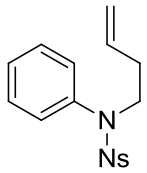
4.2 Experimental Procedures

4.2.1 Mitsunobu Reaction

14

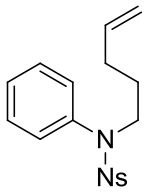
1-bromo-3-(but-3-en-1-yloxy)benzene (14). A flame-dried 50-mL, one-necked round-bottomed flask was equipped with a magnetic stir bar and a drying tube. To the flask was added 3-bromophenol (0.50 g, 2.89 mmol), 3-buten-1-ol (0.208 g, 2.89 mmol), triphenylphosphine (0.758 g, 2.89 mmol) and THF (ca. 20 mL). The flask was cooled with an ice bath and diisopropyl azodicarboxylate (0.59 mL, 2.89 mmol) was added dropwise at a rate to maintain the reaction at 10^{o}C. Upon completion of the addition, the ice bath was removed and the solution was stirred at room temperature overnight (ca. 16h). The reaction progress was monitored by TLC (9:1 hexanes: ethyl acetate) The reaction mixture was diluted with ether (ca. 25 mL), washed with aqueous sodium bicarbonate (1 x 25 mL), 3 M HCl (1 x 25 mL), and brine (1x25mL). The organic layers were combined, dried with sodium sulfate, and concentrated before purification via flash column chromatography (5% Hexanes: ethyl acetate) to yield the desired product. (0.45 g, 68% yield) R_f 0.42 (9:1 hexanes: ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.01-6.92 (m, 3H, Ar), 6.87-6.81 (m, 1H, Ar), 5.96-5.85 (ddt, 1H, *J* = 6.8 Hz, 10.3 Hz, 17.0 Hz, C*H*=CH_2),

5.19 (dd, 1H, *J* = 1.5 Hz, 10.5 Hz, CH=C*H*$_2$ *trans*), 5.12 (dd, 1H, *J* = 1.0 Hz, 5.0 Hz, CH=C*H*$_2$ *cis*), 3.97 (t, 2H, *J* = 6.5 Hz, OC*H*$_2$CH$_2$), 2.54 (q, 2H, *J* = 6.8, OCH$_2$C*H*$_2$).



15

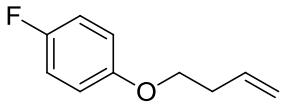
***N*-(but-3-en-1-yl)-4-nitro-*N*-phenylbenzenesulfonamide (15)**. A flame-dried 100-mL, one-necked round-bottomed flask was equipped with a magnetic stir bar and a drying tube. To the flask was added 4-nitro-*N*-phenylbenzenesulfonamide (0.50 g, 1.80 mmol), 3-buten-1-ol (0.13 g, 1.80 mmol), triphenylphosphine (0.47 g, 1.80 mmol) and THF (ca. 40 mL). The flask was cooled with an ice bath and diisopropyl azodicarboxylate (0.36 mL, 1.80 mmol) was added dropwise at a rate to maintain the reaction at 10^{o}C. Upon completion of the addition, the ice bath was removed and the solution was stirred at room temperature overnight (ca. 16h). The reaction progress was monitored by TLC (9:1 hexanes: ethyl acetate) The reaction mixture was diluted with ether (ca. 25 mL). After extraction, the solution was washed with 45 mL of saturated sodium bicarbonate (1 x 25 mL), then 3 M HCl (1 x 25 mL), and finally with brine (1 x 25 mL) and the product was concentrated to get a yellow crystalline solid. The solid was trituated with hexanes, and the solid was purified via flash column chromatography (20% hexanes: ethyl acetate). (1.26g, 53% yield). R_f 0.65 (20% hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.30 (dd, 2H, *J* = 2.2 Hz, 6.8 Hz, Ar), 7.76 (dd, 2H, *J* = 2.0 Hz, 7.0 Hz, Ar), 7.34 (m, 3H, Ar), 7.03 (m, 2H, Ar), 5.75 (ddt, 1H, *J* = 7.0 Hz, 10.5 Hz, 17.3 Hz, C*H*=CH$_2$), 5.06 (dd, 1H, *J* = 3.3 Hz, 8.0 Hz, CH=C*H*$_2$), 5.00 (dd, 1H, *J* = 1.5 Hz, 10.0 Hz, CH=C*H*$_2$), 3.65 (t, 2H, *J* = 7.2 Hz, NC*H*$_2$CH$_2$), 2.21 (q, 2H, *J* = 6.2 Hz, C*H*$_2$CH=CH$_2$).



16

4-nitro-N-(pent-4-en-1-yl)-N-phenylbenzenesulfonamide (16). A flame-dried 100-mL, one-necked round-bottomed flask was equipped with a magnetic stir bar and a drying tube. To the flask was added 4-nitro-*N*-phenylbenzenesulfonamide (0.50 g, 1.80 mmol), 4-penten-1-ol (0.15

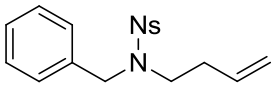
g, 1.80 mmol), triphenylphosphine (0.470 g, 1.80 mmol) and THF (ca. 40 mL). The flask was cooled with an ice bath and diisopropyl azodicarboxylate (0.36 mL, 1.80 mmol) was added dropwise at a rate to maintain the reaction at 10^{o}C. Upon completion of the addition, the ice bath was removed and the solution was stirred at room temperature overnight (ca. 16h). The reaction progress was monitored by TLC (9:1 hexanes: ethyl acetate) The reaction mixture was diluted with ether (ca. 25 mL), washed with aqueous sodium bicarbonate (1 x 25 mL), 3 M HCl (1 x 25 mL), and brine (1x25mL). After workup, the organic layer was concentrated to give a yellow oil that was purified via flash column chromatography using a gradient solvent system to eliminate trace DIAD in the sample (5% hexanes: ethyl acetate, followed by 10% hexanes: ethyl acetate, and finally 20% hexanes : ethyl acetate) to give a white, crystalline product. (1.66 g, 67% yield) R_f 0.43; ^{1}H NMR (250 MHz, $CDCl_3$) δ : 8.27 (dd, 2H, *J* = 5.0 Hz, 5.5 Hz, Ar), 7.77 (dd, 2H, *J* = 2.3 Hz, 5.6 Hz, Ar), 7.35-7.33 (m, 3H, Ar), 7.04-7.01 (m, 2H, Ar), 5.78-5.67 (ddt, 1H, *J* = 7.0 Hz, 10.5 Hz, 17.0 Hz, C*H*=CH_2), 5.01(dd, 1H, *J* = 1.75 Hz, 5.0 Hz, CH=C*H*$_2$), 4.94 (dd, 1H, J = 2.8 Hz, 12.4 Hz, CH=C*H*$_2$), 3.58 (t, 2H, *J* = 7.0 Hz, NC*H*$_2$$CH_2$), 2.14-2.05 (m, 2H, CH_2C*H*$_2$$CH_2$), 1.62-1.54 (m, 2H, CH_2C*H*$_2$CH=CH_2).



17

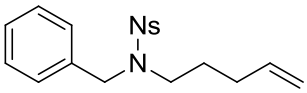
1-(but-3-en-1-yloxy)-4-fluorobenzene (17). A flame-dried 100-mL, one-necked round-bottomed flask was equipped with a magnetic stir bar and a drying tube. To the flask was added 4-fluorophenol (0.50 g, 4.46 mmol), 3-buten-1-ol (0.32 g, 4.46 mmol), triphenylphosphine (1.17 g, 4.46 mmol) and THF (ca. 40 mL). The flask was cooled with an ice bath and diisopropyl azodicarboxylate (0.90 mL, 4.46 mmol) was added dropwise at a rate to maintain the reaction at 10^{o}C. Upon completion of the addition, the ice bath was removed and the solution was stirred at room temperature overnight (ca. 16h). The reaction progress was monitored by TLC (9:1 hexanes: ethyl acetate) The reaction mixture was diluted with ether (ca. 25 mL), washed with aqueous sodium bicarbonate (1 x 25 mL), 3 M HCl (1 x 25 mL), and brine (1x25mL). The organic layers were combined, dried with sodium sulfate, and concentrated before purification via flash column chromatography (5% Hexanes: ethyl acetate) to yield the desired product. (2.43 g, 82% yield). R_f 0.62 (9:1 hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.99-6.91 (m, 2H, Ar), 6.87-6.80 (m, 2H, Ar), 5.955-5.819 (ddt, 1H, *J* = 6.8 Hz, 10.3 Hz, 17.0 Hz, C*H*=CH_2),

5.19 (dd, 1H, *J* = 1.5 Hz, 10.5 Hz, CH=CH_2 *trans*), 5.11 (dd, 1H, *J* = 1.0 Hz, 5.0 Hz, CH=CH_2 *cis*), 3.97 (t, 2H, *J* = 6.5 Hz, OCH_2CH_2), 2.52 (q, 2H, *J* =6.8 Hz, OCH_2CH_2).



18

N-benzyl-N-(but-3-en-1-yl)-4-nitrobenzenesulfonamide (18). A flame-dried 100-mL, one-necked round-bottomed flask was equipped with a magnetic stir bar and a drying tube. To the flask was added *N*-benzyl-4-nitrobenzenesulfonamide (0.50 g, 1.71 mmol), 3-buten-1-ol (0.12 g, 1.71 mmol), triphenylphosphine (0.45 g, 1.71 mmol) and THF (ca. 40 mL). The flask was cooled with an ice bath and diisopropyl azodicarboxylate (0.35g, 1.71 mmol) was added dropwise at a rate to maintain the reaction at 10^{o}C. Upon completion of the addition, the ice bath was removed and the solution was stirred at room temperature overnight (ca. 16h). The reaction progress was monitored by TLC (9:1 hexanes: ethyl acetate) The reaction mixture was diluted with ether (ca. 25 mL), washed with aqueous sodium bicarbonate (1 x 25 mL), 3 M HCl (1 x 25 mL), and brine (1x25mL). The organic layers were combined, dried with sodium sulfate, and concentrated before purification via flash column chromatography (5% Hexanes: ethyl acetate) to yield the desired product. (1.70 g, 72% yield). R_f 0.54 (9:1 hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.34 (d, 2H, *J* = 8.8 Hz, Ar), 7.99 (d, 2H, *J* = 8.8 Hz, Ar), 7.32-7.30 (m, 5H, Ar), 5.59-5.46 (ddt, 1H, *J* = 6.8 Hz, 10.3 Hz, 17.0 Hz, C*H*=CH_2), 4.96 (dd, 1H, *J* = 1.0 Hz, 3.6 Hz, CH=CH_2), 4.90 (dd, 1H, *J* = 1.5 Hz, 16.3 Hz, CH=CH_2), 4.41 (s, 2H, Ar-CH_2N), 3.23 (t, 2H, *J* = 7.3 Hz, NCH_2CH_2), 2.15-2.08 (m, 2H,CH_2CH_2CH=CH_2).

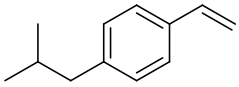


19

N-benzyl-4-nitro-N-(pent-4-en-1-yl)benzenesulfonamide (19). A flame-dried 100-mL, one-necked round-bottomed flask was equipped with a magnetic stir bar and a drying tube. To the flask was added *N*-benzyl-4-nitrobenzenesulfonamide (0.50 g, 1.71 mmol), 4-penten-1-ol (0.15 g, 1.71 mmol), triphenylphosphine (0.45 g, 1.71 mmol) and THF (ca. 40 mL). The flask was cooled with an ice bath and diisopropyl azodicarboxylate (0.35g, 1.71 mmol) was added dropwise at a rate to maintain the reaction at 10^{o}C. Upon completion of the addition, the ice bath was removed and the solution was stirred at room temperature overnight (ca. 16h). The reaction

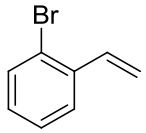
progress was monitored by TLC (9:1 hexanes: ethyl acetate) The reaction mixture was diluted with ether (ca. 25 mL), washed with aqueous sodium bicarbonate (1 x 25 mL), 3 M HCl (1 x 25 mL), and brine (1x25mL). The organic layers were combined, dried with sodium sulfate, and concentrated before purification via flash column chromatography (5% Hexanes: ethyl acetate) to yield the desired product. (1.65 g, 67% yield). R_f 0.64 (5% hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.33 (d, 2H, *J* = 7.0 Hz, Ar), 7.98 (d, 2H, *J* = 7.0 Hz, Ar), 7.32-7.28 (m, 5H, Ar), 5.70-5.51 (m, 1H, C*H*=CH_2), 4.93-4.86 (m, 2H, CH=C*H*$_2$), 4.38 (s, 2H, Ar-C*H*$_2$N), 3.16 (t, 2H, *J* = 7.8 Hz, NC*H*$_2$$CH_2$), 1.89 (q, 2H, *J* = 7.0 Hz, CH_2C*H*$_2$CH), 1.49 (quin, 2H, *J* = 6.5 Hz, CH_2C*H*$_2$$CH_2$).

4.2.2 Wittig Reaction[18]



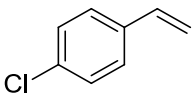
27

1-isobutyl-4-vinylbenzene (27). A 3-necked 100 mL round bottom flask was equipped with 2 glass stoppers, a reflux condenser, gas inlet, and magnetic stir bar. The setup was flame dried and cooled under a stream of nitrogen gas before it was charged with triphenylmethylphosphonium bromide (2.64 g, 7.39 mmol) and THF (50 mL). After the mixture was stirred for 15 min, n-butyl lithium (2.98 mL, 7.39 mmol) was added dropwise with the reaction in an ice/acetone bath. After addition, the ice bath was removed and the mixture was stirred for 1h before 4-isobutylbenzaldehyde (1.00 g, 6.16 mmol) was added. The mixture was heated to reflux for 12 h. The vessel was then cooled to room temperature and the triphenylphosphonium oxide was triturated with pentane. The solution was filtered over Celite/silica in a fritted funnel the solvent was evaporated, and the product was purified via flash column chromatography. (0.85g, 85% yield). R_f 0.75 (pentane); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.36 (d, 2H, *J* = 6.3 Hz, Ar), 7.13 (d, 2H, *J* = 8.3 Hz, Ar), 6.73 (dd, 1H, *J* = 11.0 Hz, 17.6 Hz, C*H*=CH_2), 5.73 (dd, 1H, *J* = 1.0 Hz, 17.8 Hz, CH=C*H*$_2$), 5.21 (dd, 1H, *J* = 1.0 Hz, 10.8 Hz, CH=C*H*$_2$), 2.49 (d, 2H, *J* = 7.3 Hz, C*H*$_2$$CH(CH_3)_2$), 1.88 (n, 1H, *J* = 6.8 Hz, CH_2C*H*$(CH_3)_2$), 0.93 (d, 6H, *J* = 6.5 Hz, CH(C*H*$_3$)$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 141.52, 136.76, 135.05, 129.19, 125.97, 119.80, 45.27, 30.25, 22.35. Literature spectra were consistent with those reported above.[17]



28

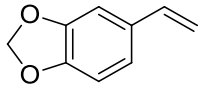
1-bromo-2-vinylbenzene (28). A 3-necked 250 mL round bottom flask was equipped with 2 glass stoppers, a reflux condenser, gas inlet, and magnetic stir bar. The setup was flame dried and cooled under a stream of nitrogen gas before it was charged with triphenylmethylphosphonium bromide (6.95 g, 19.46 mmol) and THF (150 mL). After the mixture was stirred for 15 min, n-butyl lithium (7.85 mL, 19.46 mmol) was added dropwise with the reaction in an ice/acetone bath. After addition, the ice bath was removed and the mixture stirred for 1h before 2-bromobenzaldehyde (3.00 g, 16.21 mmol) was added. The mixture was heated to reflux for 12 h. The vessel was then cooled to room temperature and the triphenylphosphonium oxide was triturated with pentane. The solution was filtered over Celite/silica in a fritted funnel the solvent was evaporated, and the product was purified via flash column chromatography. **(**1.11g, 37% yield). R_f 0.80 (pentane); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.68 (d, 2H, *J* = 1.5 Hz, Ar) 7.441-7.412 (m, 1H, C*H*=CH_2), 7.407-7.147 (m, 2H, Ar), 5.83 (dd, 1H, *J* = 1.0 Hz, 17.5 Hz CH=C*H*$_2$), 5.51 (dd, 1H, *J* = 1.0 Hz, 11.0 Hz, CH=C*H*$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 137.44, 135.78, 132.87, 129.08, 127.48, 126.73, 123.60, 116.71. Literature spectra were consistent with those reported above.[17]



29

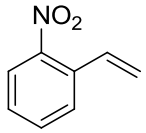
1-chloro-4-vinylbenzene (29). A 3-necked 250 mL round bottom flask was equipped with 2 glass stoppers, a reflux condenser, gas inlet, and magnetic stir bar. The setup was flame dried and cooled under a stream of nitrogen gas before it was charged with triphenylmethylphosphonium bromide (9.15 g, 25.60 mmol) and THF (150 mL). After the mixture was stirred for 15 min, n-butyl lithium (10.30 mL, 25.60 mmol) was added dropwise with the reaction in an ice/acetone bath. After addition, the ice bath was removed and the mixture stirred for 1h before 4-chlorobenzaldehyde (3.00 g, 21.34 mmol) was added. The mixture was heated to reflux for 12 h. The vessel was then cooled to room temperature and the triphenylphosphonium oxide was triturated with pentane. The solution was filtered over

Celite/silica in a fritted funnel the solvent was evaporated, and the product was purified via flash column chromatography. (2.26g, 76% yield). R_f 0.60 (pentane); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.29-7.21 (m, 4H, Ar), 6.63 (dd, 1H, *J* = 11.0 Hz, 17.6 Hz C*H*=CH_2), 5.68 (dd, 1H, *J* = 0.8 Hz, 17.5 Hz, CH=C*H*$_2$), 5.22 (dd, 1H, *J* = 0.8 Hz, 6.4 Hz, CH=C*H*$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 135.65, 133.42, 128.66, 127.42, 114.45, 65.86, 15.28. Literature spectra were consistent with those reported above.[17]



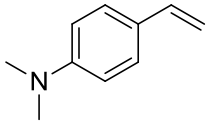
30

5-vinylbenzo[*d*][1,3]dioxole (30). A 3-necked 250 mL round bottom flask was equipped with 2 glass stoppers, a reflux condenser, gas inlet, and magnetic stir bar. The setup was flame dried and cooled under a stream of nitrogen gas before it was charged with triphenylmethylphosphonium bromide (8.63 g, 24.16 mmol) and THF (150 mL). After the mixture was stirred for 15 min, n-butyl lithium (9.74 mL, 24.16 mmol) was added dropwise with the reaction flask in an ice/acetone bath. After addition, the ice bath was removed and the mixture stirred for 1h before benzo[d][1,3]dioxole-5-carbaldehyde (3.00 g, 20.13 mmol) was added. The mixture was heated to reflux for 12 h. The vessel was then cooled to room temperature and the triphenylphosphonium oxide was triturated with pentane. The solution was filtered over Celite/silica in a fritted funnel the solvent was evaporated, and the product was purified via flash column chromatography. The compound was purified via flash column chromatography. (1.23g, 42% yield). R_f 0.21 (pentane), R_f 0.75 (95% hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.97 (d, 1H, *J* = 1.5 Hz, Ar), 6.86-6.74 (m, 2H, Ar), 6.62 (dd, 1H, *J* =11.0 Hz, 10.8 Hz, C*H*=CH_2), 5.95 (s, 2H, OC*H*$_2$O), 5.59 (dd, 1H, *J* = 0.8 Hz, 17.5 Hz, CH=C*H*$_2$), 5.13 (dd, 1H, *J* = 0.5 Hz, 10.8 Hz, CH=C*H*$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 147.35, 136.35, 132.12, 121.01, 111.97, 108.19, 105.38, 101.05. Literature spectra were consistent with those reported above.[17]



31

1-nitro-2-vinylbenzene (31). A 3-necked 250 mL round bottom flask was equipped with 2 glass stoppers, a reflux condenser, gas inlet, and magnetic stir bar. The setup was flame dried and cooled under a stream of nitrogen gas before it was charged with triphenylmethylphosphonium bromide (8,52 g, 23.84 mmol) and THF (150 mL). After the mixture was stirred for 15 min, n-butyl lithium (9.61 mL, 23.84 mmol) was added dropwise while the reaction flask was in an ice/acetone bath. After addition, the ice bath was removed and the mixture stirred for 1h before 2-nitrobenzaldehyde (3.00 g, 19.87 mmol) was added. The mixture was heated to reflux for 12 h. The vessel was then cooled to room temperature and the triphenylphosphonium oxide was triturated with pentane. The solution was filtered over Celite/silica in a fritted funnel the solvent was evaporated, and the product was purified via flash column chromatography. The solvent system used was 1:1 hexanes: THF. (1.87g, 63% yield) R_f 0.43 (pentane, 95% hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.95 (d, 1H, *J* = 7.0 Hz, Ar), 7.62-7.57 (m, 2H, Ar), 7.44-7.40 (m, 1H, Ar), 7.17 (dd, 1H, *J* = 11.0 Hz, 17.3 Hz, C*H*=CH_2), 5.75 (dd, 1H, *J* = 0.8 Hz, 17.4 Hz, CH=C*H*$_2$), 5.48 (dd, 1H, *J* = 0.8 Hz, 11.0 Hz, CH=C*H*$_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 133.12, 132.48, 128.50, 128.34, 124.12, 118.98. Literature spectra were consistent with those reported above.[17]

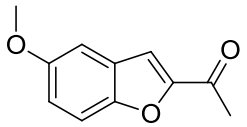


32

***N, N*-dimethyl-4-vinylaniline (32).** A 3-necked 250 mL round bottom flask was equipped with 2 glass stoppers, a reflux condenser, gas inlet, and magnetic stir bar. The setup was flame dried and cooled under a stream of nitrogen gas before it was charged with triphenylmethylphosphonium bromide (8.62 g, 24.13 mmol) and THF (150 mL). After the mixture was stirred for 15 min, n-butyl lithium (9.72 mL, 24.13 mmol) was added dropwise. The mixture stirred for 1h before 4-chlorobenzaldehyde (3.00 g, 20.10 mmol) was added, and the mixture was heated to reflux for 12 h. The vessel was then cooled to room temperature and the triphenylphosphonium oxide was triturated with pentane. The solution was filtered over

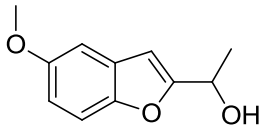
Celite/silica in a fritted funnel the solvent was evaporated, and the product was purified via flash column chromatography. (0.53g, 18% yield). R_f 0.23 (hexanes, 95% hexanes: ethyl acetate); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.33-7.295 (m, 2H, Ar), 6.70-6.68 (m, 2H, Ar), 6.64 (dd, 1H, *J* = 10.8 Hz, 14.5 Hz, C*H*=CH_2), 5.54 (dd, 1H, *J* = 1.0 Hz, 17.6 Hz, CH=CH_2), 5.02 (dd, 1H, *J* = 1.0 Hz, 10.8 Hz, CH=CH_2), 2.96-2.90 (m, 6H, (CH_3)$_2$N). Literature spectra were consistent with those reported above.[17]

4.2.3 Steps Towards the Total Synthesis of (+)-Frondosin B [19, 20]



38

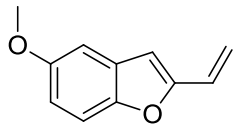
1-(5-methoxybenzofuran-2-yl)ethanone (38). A mixture of 2-hydroxy-5-methoxybenxaldehyde (5 g, 32.9 mmol), chloroacetone (4.56 g, 49.34 mmol) and K_2CO_3 (18.16 g, 131.6 mmol) in 2-butanone (120 mL) was added to a flame dried 3-necked 500-mL round bottom flask equipped with a gas inlet and a reflux condenser. The mixture was stirred at 80 ^{o}C under nitrogen for 17 h. The flask was then cooled to room temperature, added to cool water (120 mL), and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was purified via flash column chromatography (4:1 hexanes: ethyl acetate) to yield 1-(5-methoxybenzofuran-2-yl)ethanone (5.313 g, 85% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.49-7.44 (m, 2H, Ar), 7.12-7.11 (m, 1H, C*H*), 7.09- 7.07 (m, 1H, Ar), 3.86 (s, 3H, CH_3O), 2.60 (s, 3H, COCH_3). Literature spectra were consistent with those reported above.[17]



39

1-(5-methoxybenzofuran-2-yl)ethanol (39). A flame dried 3 necked 500 mL round bottomed flask was equipped with a nitrogen gas inlet, reflux condenser, and magnetic stirbar. To the setup was added 1-(5-methoxybenzofuran-2-yl)ethanone (3.5 g, 18.42 mmol) in ethanol (150 mL). The solution was heated to reflux before sodium borohydride (6.74 g, 178.3 mmol) dissolved in water (55 mL) was added. The mixture was refluxed for 1.5 h, cooled to room temperature and

extracted with cholorform (80 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried (Na_2SO_4), and concentrated to yield 1-(5-methoxybenzofuran-2-yl)ethanol (3.15g, 89% yield) as a white solid, which was used in the next step without purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.32 (d, 1H, *J* = 8.8 Hz, Ar), 6.98 (d, 1H, *J* = 2.5 Hz, Ar), 6.85 (dd, 1H, *J* = 2.8 Hz, 9.0 Hz, Ar), 6.52 (s, 1H, C*H*=C), 4.95 (q, 1H, *J* = 6.5 Hz, C*H*OH), 3.82 (s, 3H, CH_3O), 2.52 (br s, 1H, O*H*), 1.60 (d, 3H, *J* = 6.5 Hz, CHCH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 161.12, 155.85, 149.73, 128.69, 112.71, 111.58, 103.61, 101.92, 64.13, 58.40, 55.89, 21.39, 18.35. Literature spectra were consistent with those reported above.[17]



40

5-methoxy-2-vinylbenzofuran (40). A flame dried 500 mL 3 necked round-bottomed flask was equipped with two glass stoppers, a magnetic stir bar, and a gas inlet. To the setup, a solution of PBr_3 (1.72 mL, 17.9 mmol) in anhydrous $CHCl_2$ (15 mL) was added dropwise to a solution of 1-(5-methoxybenzofuran-2-yl)ethanol (4.1 g, 21.3 mmol) in anhydrous DMF (80 mL) at -10^{o}C under nitrogen. The reaction was stirred at 0^{o}C for 3 h before LiBr (7.94 g, 91.37 mmol) and Li_2CO_3 (4.99 g, 67.52 mmol) were added. The mixture was heated to reflux for 6 h under nitrogen. It was cooled, poured into cold water (100 mL), and extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried (Na_2SO_4) and concentrated to yield the title compound 5-methoxy-2-vinylbenzofuran (3.42g, 92% yield) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.32 (d, 1H, *J* = 9.0 Hz, Ar), 6.97 (d, 1H, *J* = 2.5 Hz, Ar), 6.86 (dd, 1H, *J* = 2.8 Hz, 8.9 Hz, Ar), 6.60 (dd, 1H, *J* = 11.3 Hz 17.50 Hz, C*H*=CH_2), 6.53 (s, 1H, C*H*=C), 5.90 (dd, 1H, *J* = 1.0 Hz, 17.4 Hz, CH=CH_2), 5.35 (dd, 1H, *J* = 1.0 Hz, 11.1 Hz, CH=CH_2), 3.80 (s, 3H, OCH_3). Literature spectra were consistent with those reported above.[17]

5 References

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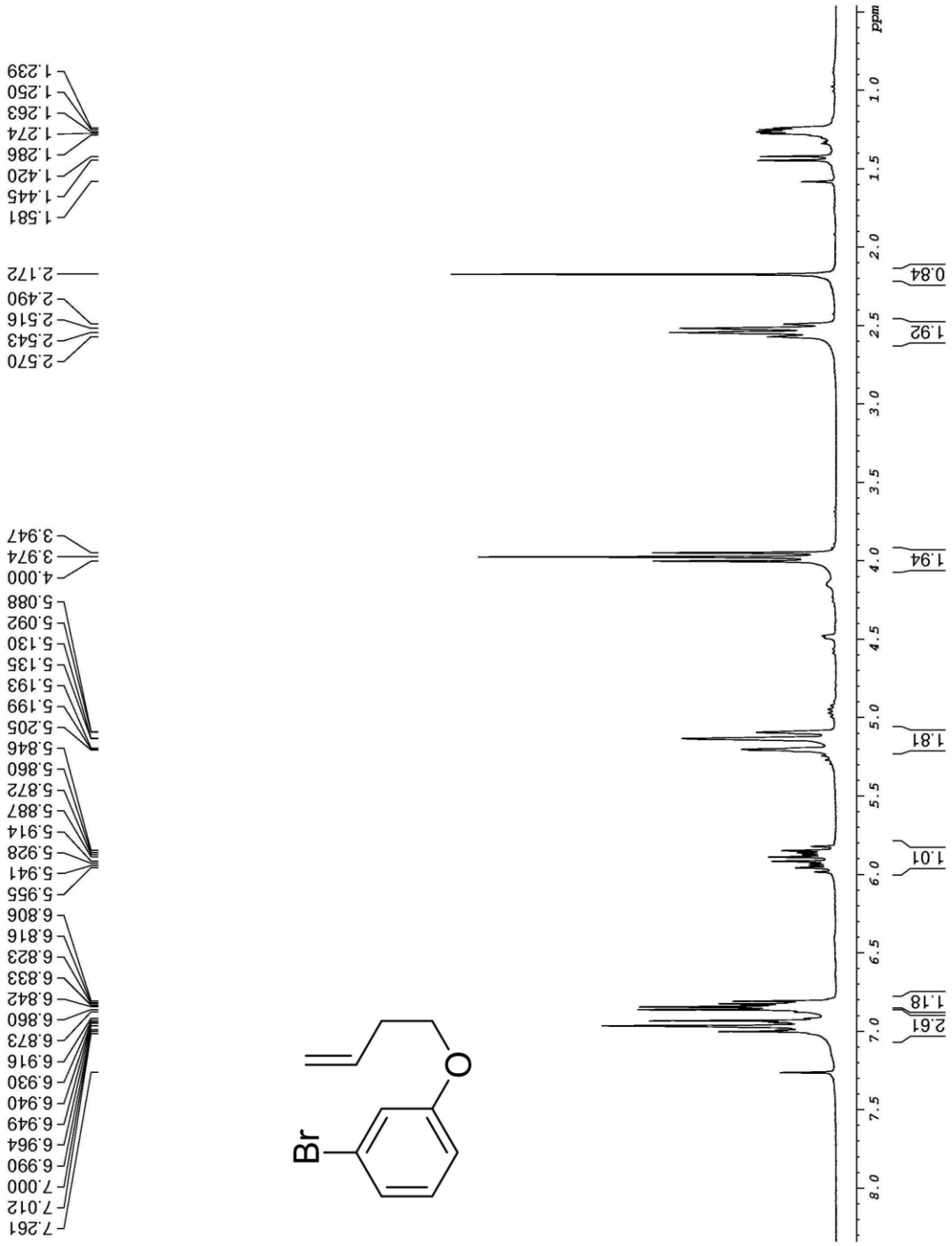
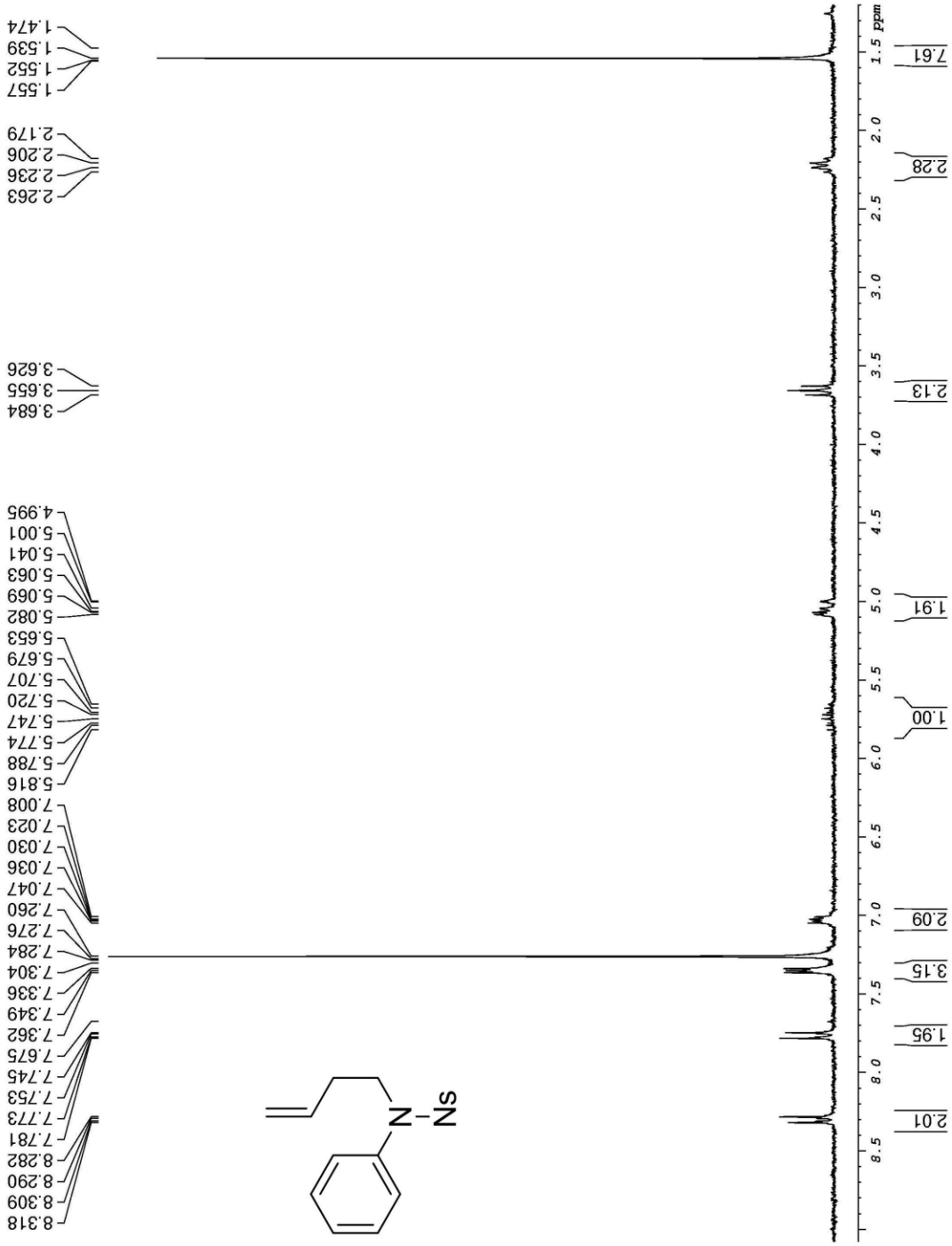
6 Appendix

6.1 ^{1}H and ^{13}C NMR Spectra

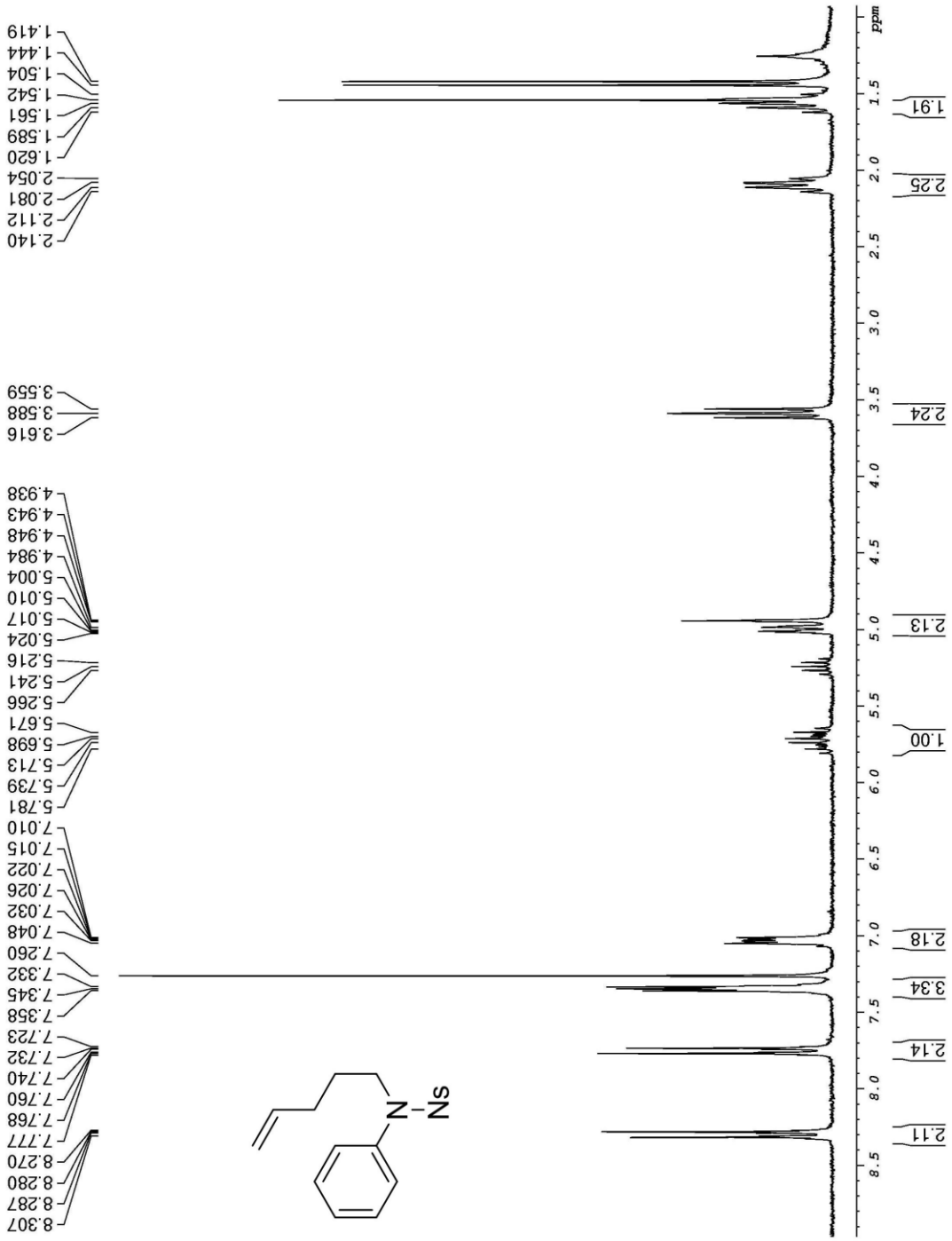
Alkene **14** ^{1}H NMR, 250 MHz, $CDCl_3$



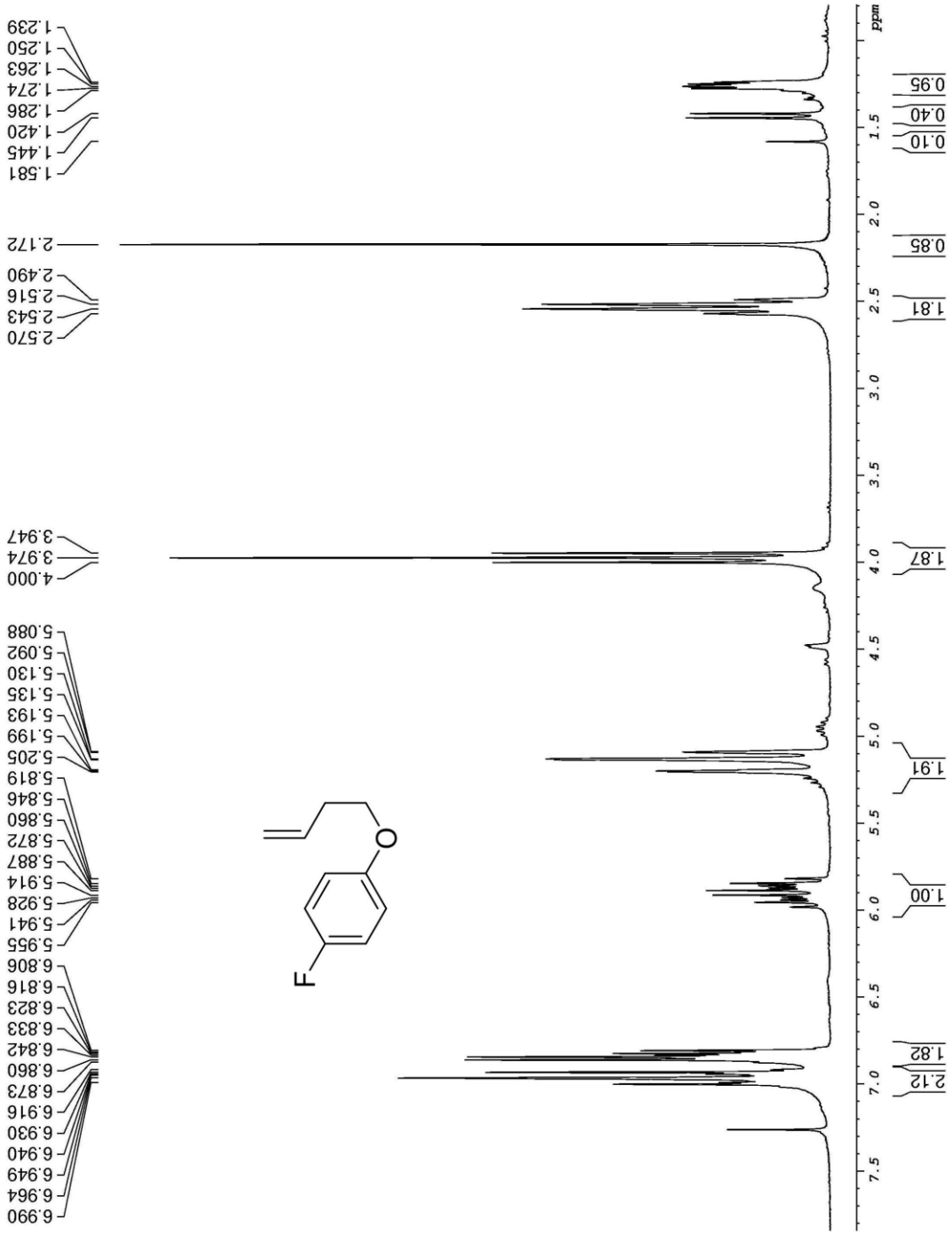
Alkene **15** ^{1}H NMR, 250 MHz, $CDCl_3$



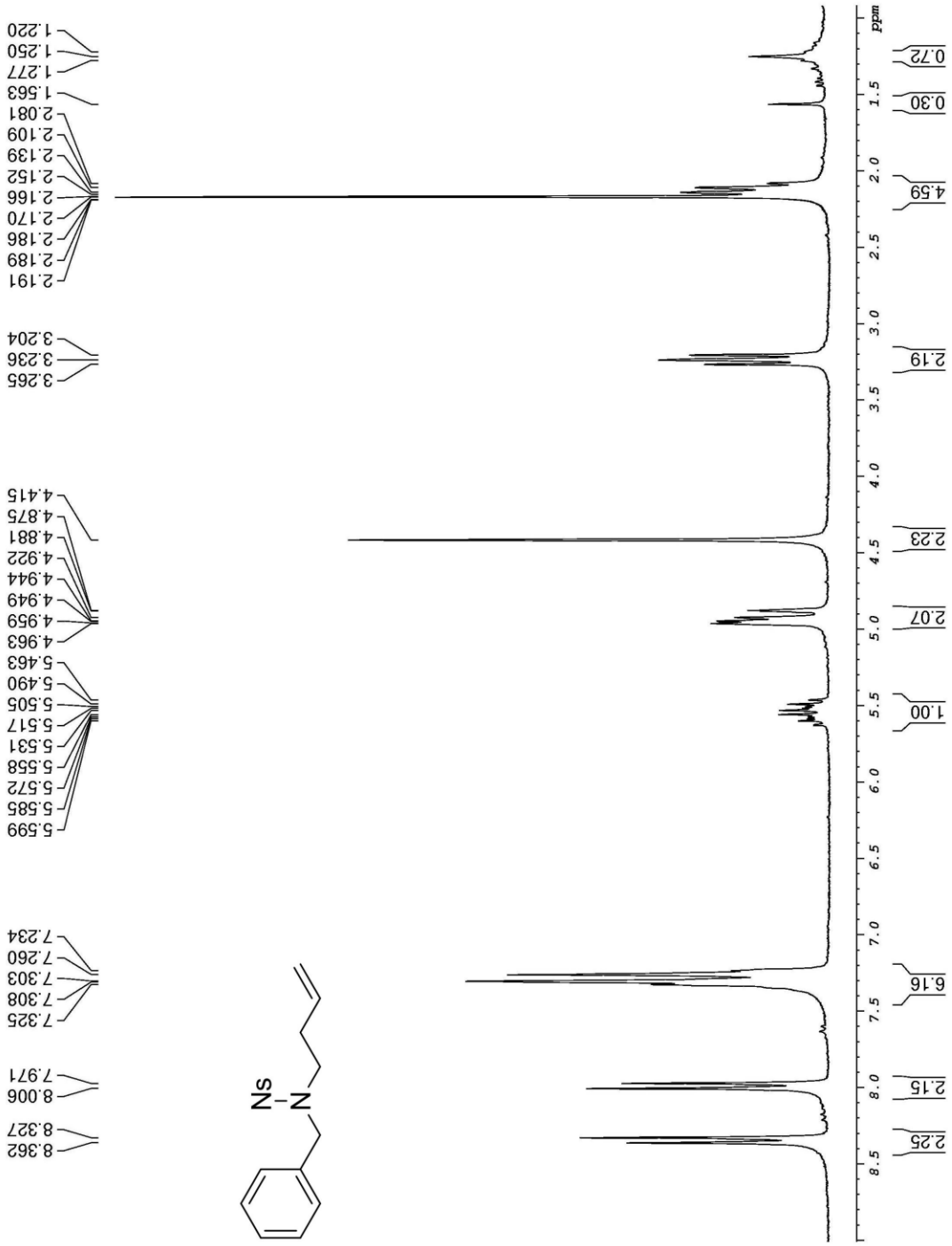
Alkene **16** ^{1}H NMR, 250 MHz, $CDCl_3$



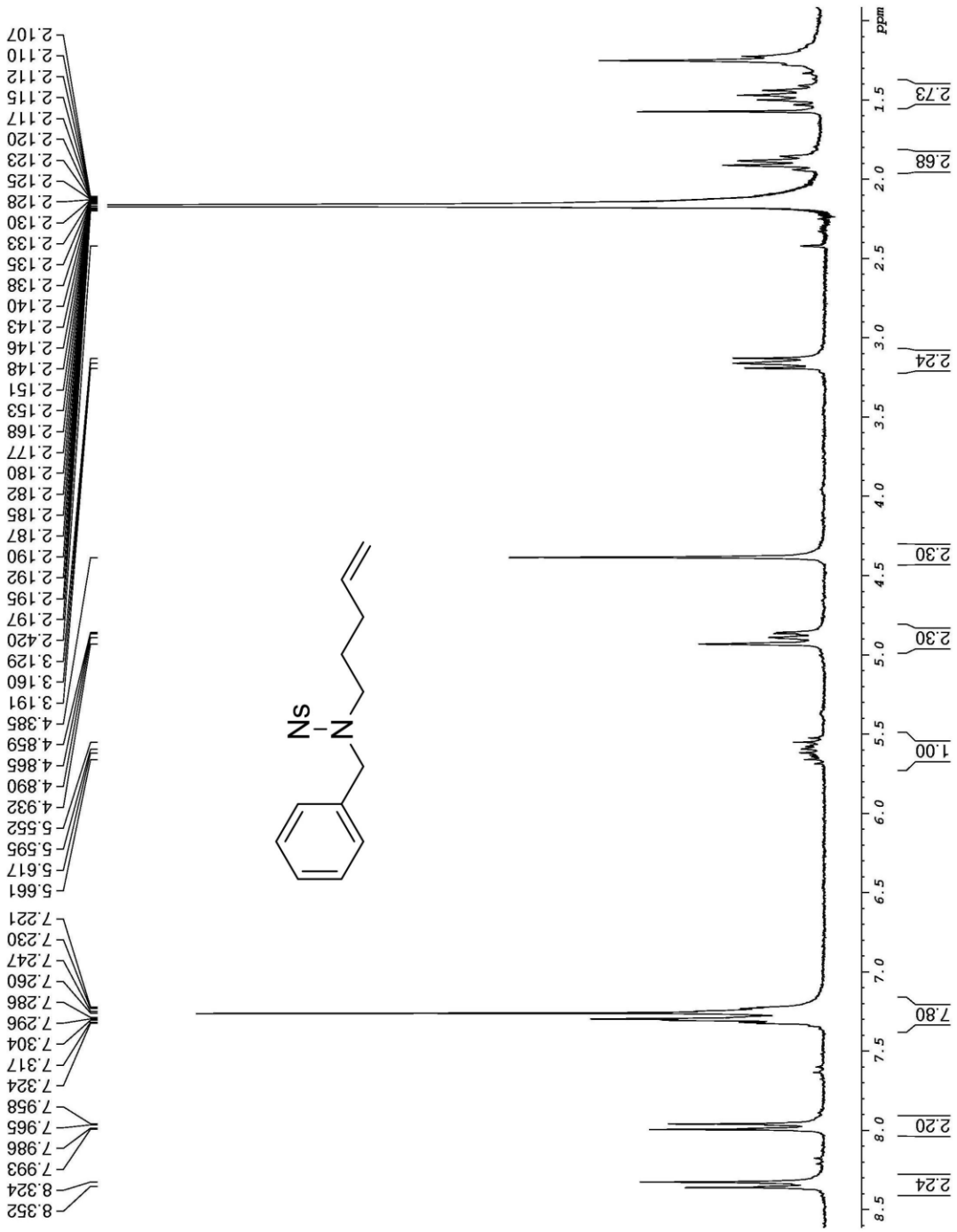
Alkene **17** ^{1}H NMR, 250 MHz, $CDCl_3$



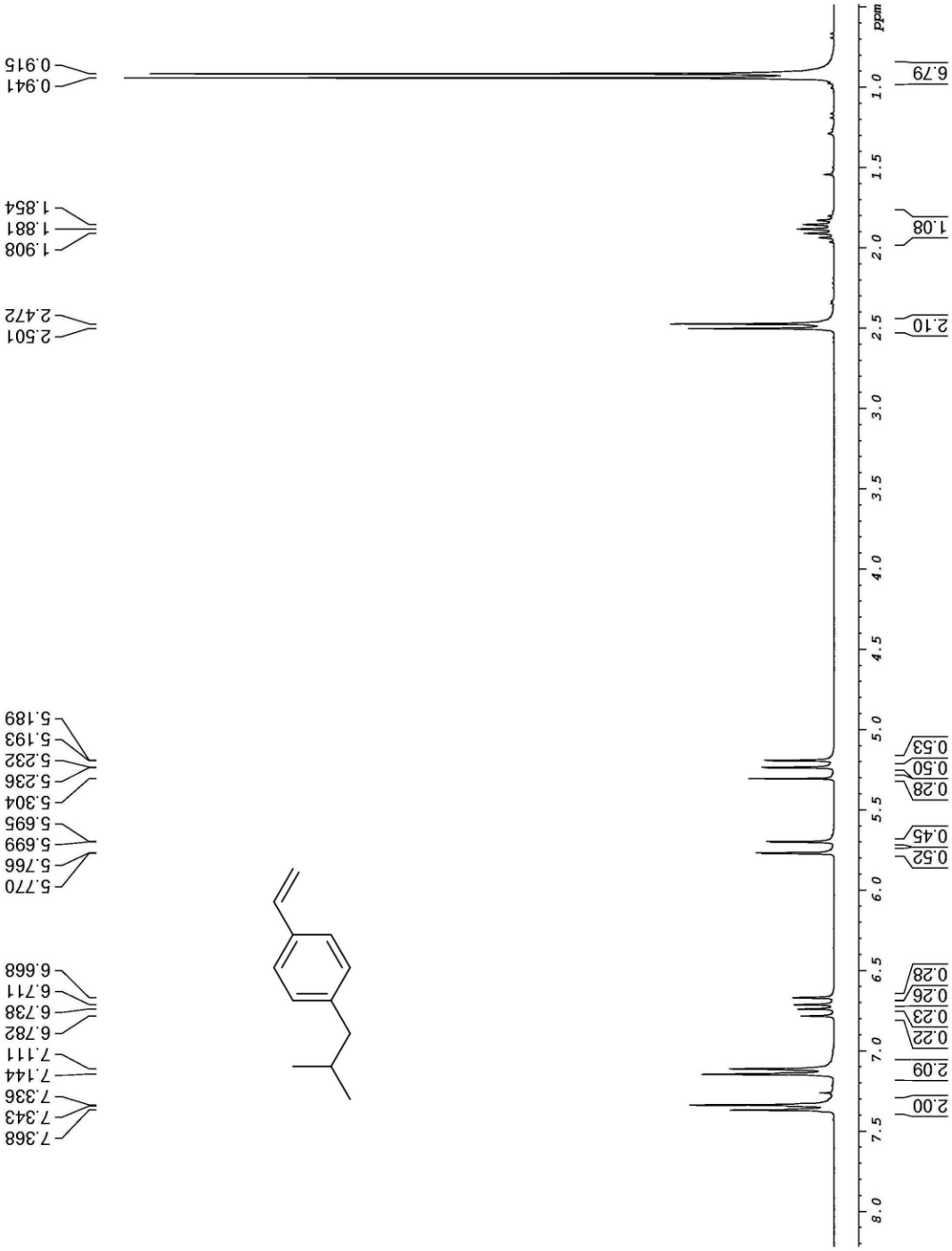
Alkene **18** ^{1}H NMR, 250 MHz, $CDCl_3$



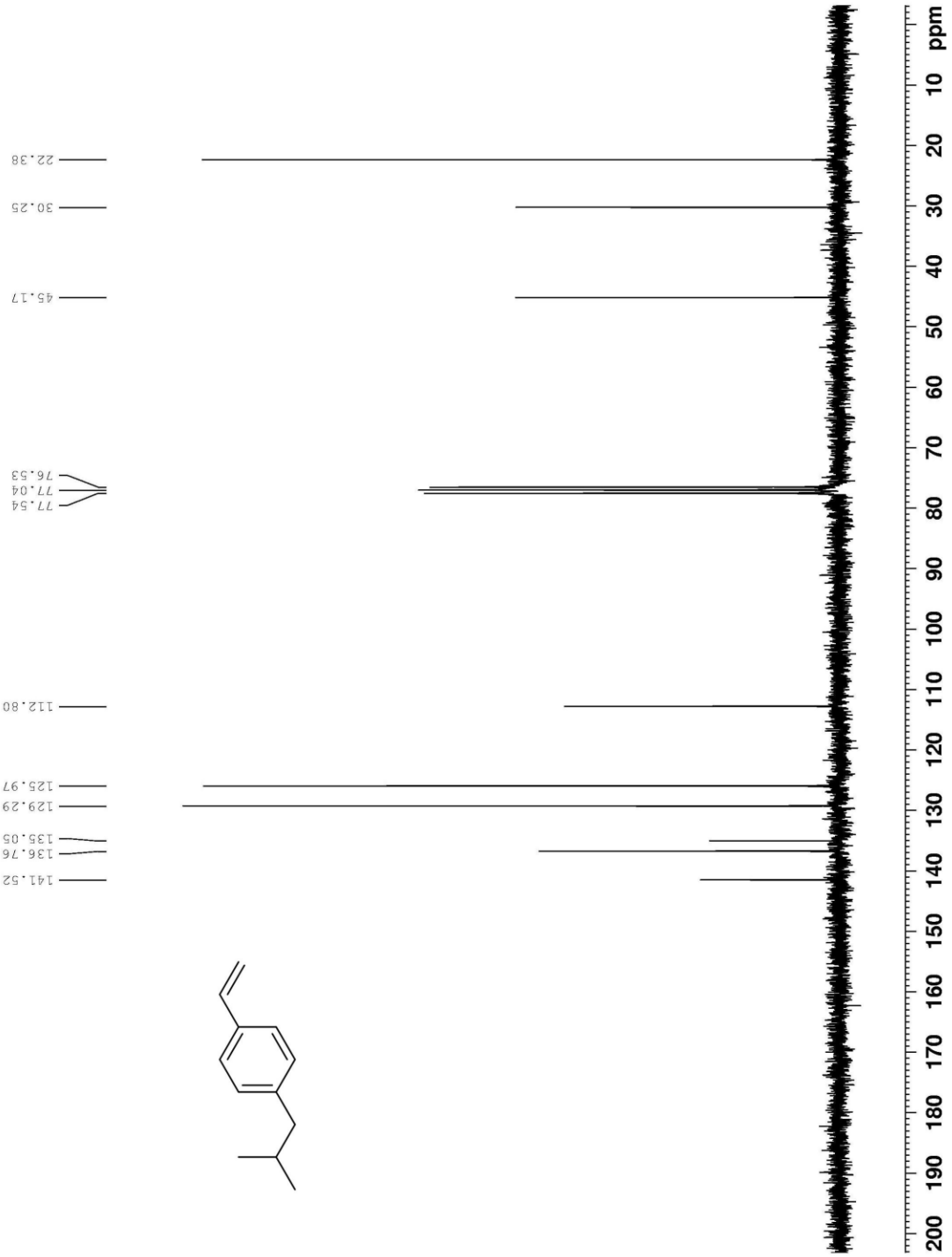
Alkene **19** ^{1}H NMR, 250 MHz, $CDCl_3$



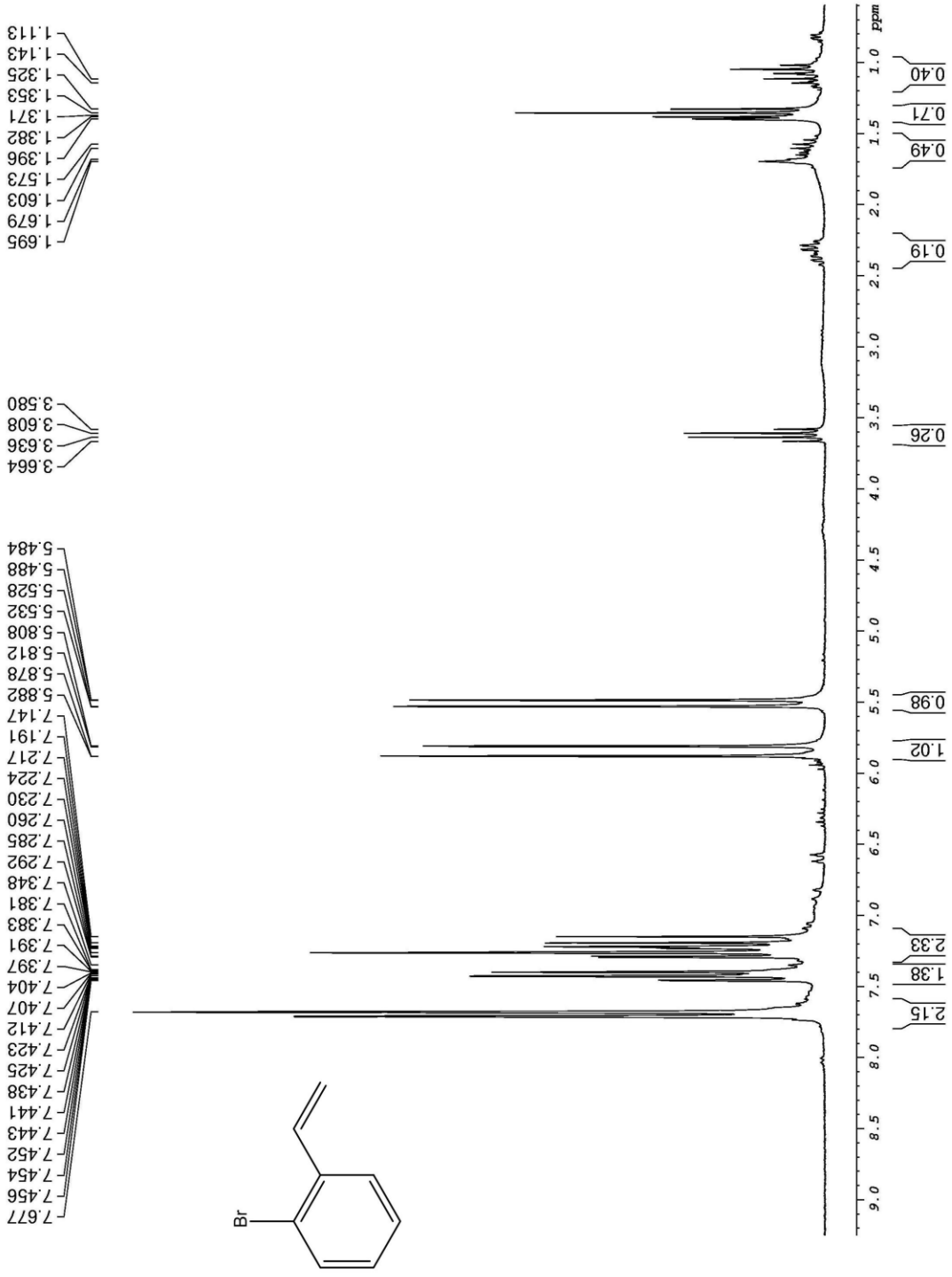
Alkene **27** ^{1}H NMR, 250 MHz, $CDCl_3$



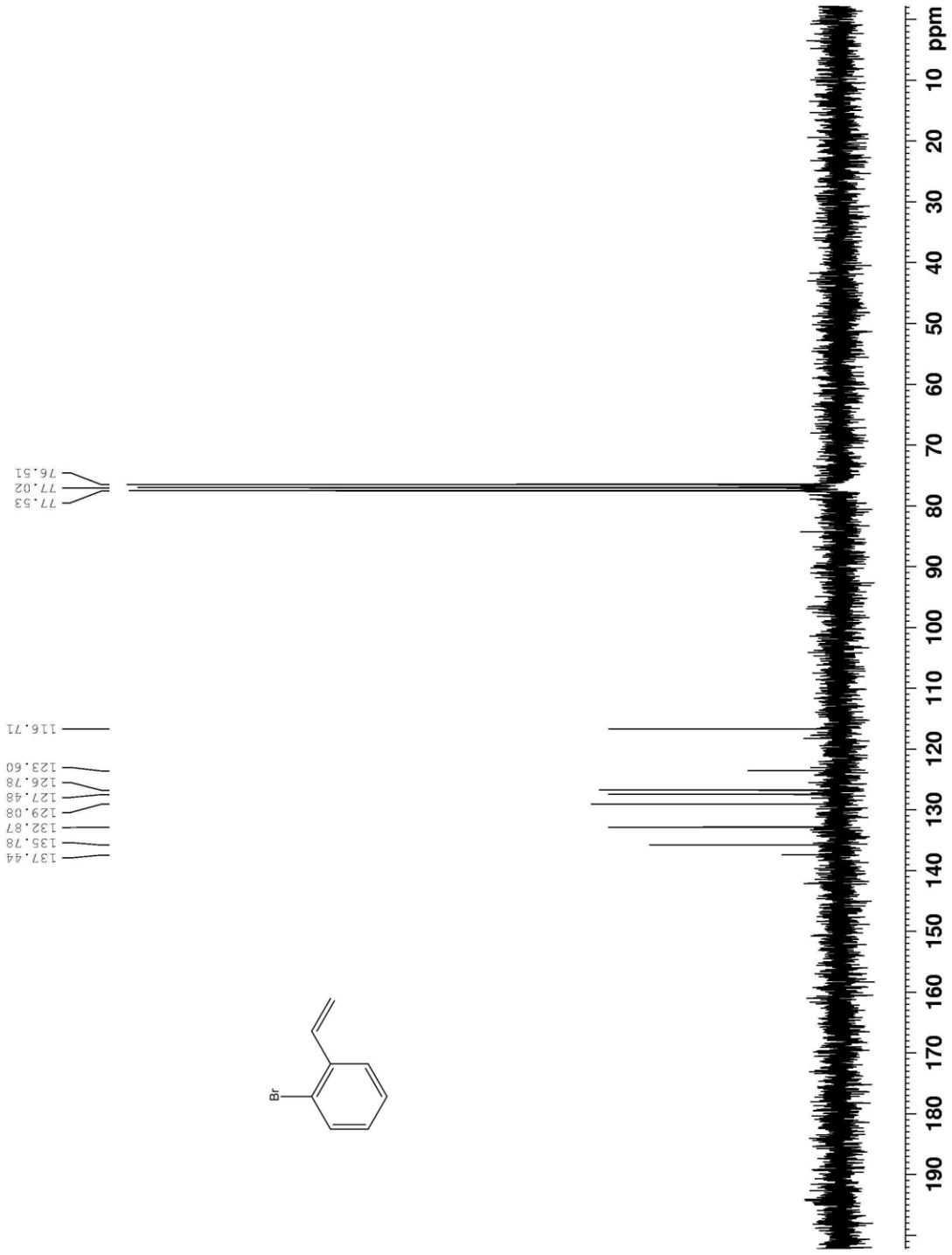
Alkene **27** ^{13}C NMR, 62.9 MHz, $CDCl_3$



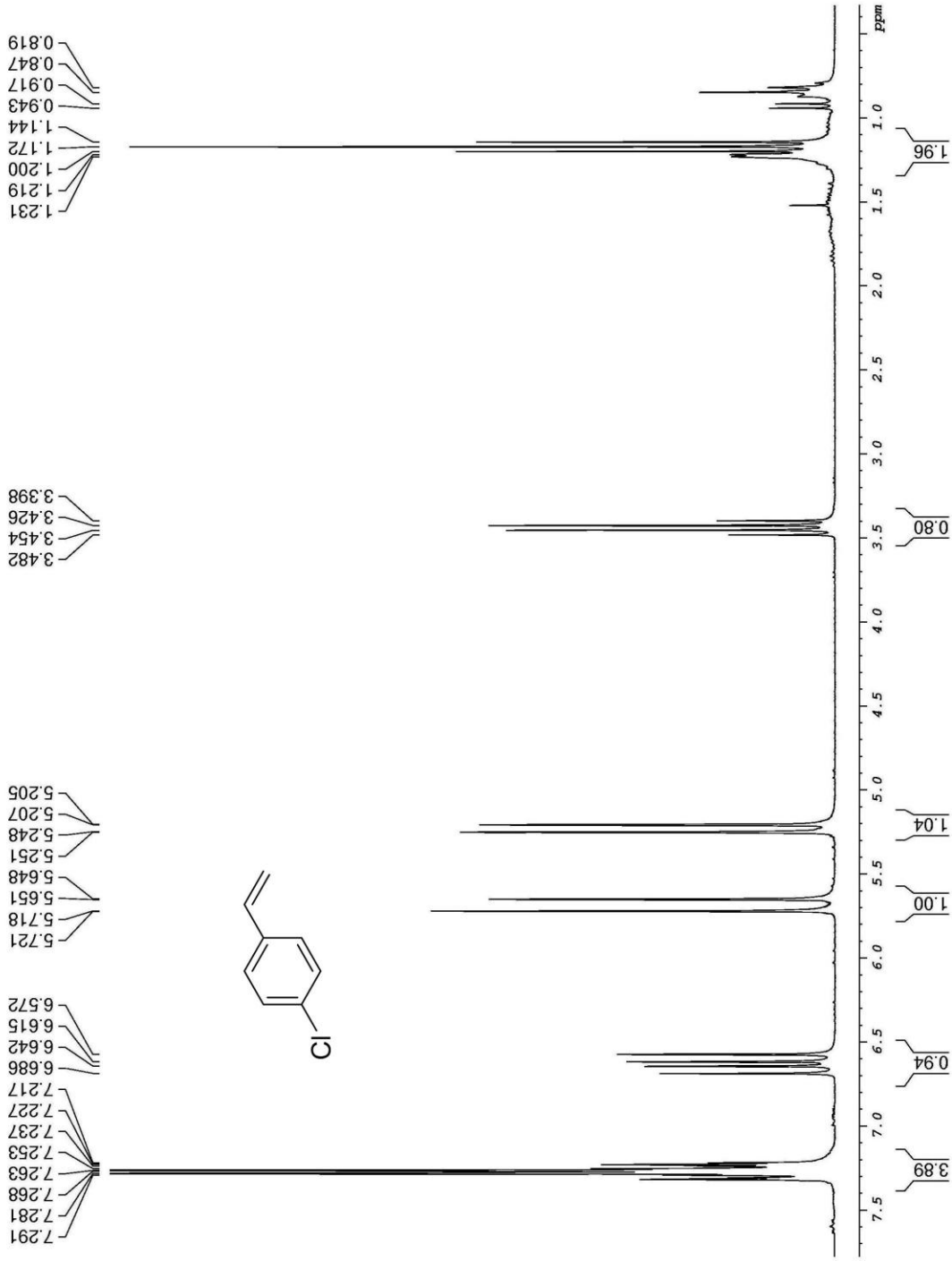
Alkene **28** ^{1}H NMR, 250 MHz, $CDCl_3$



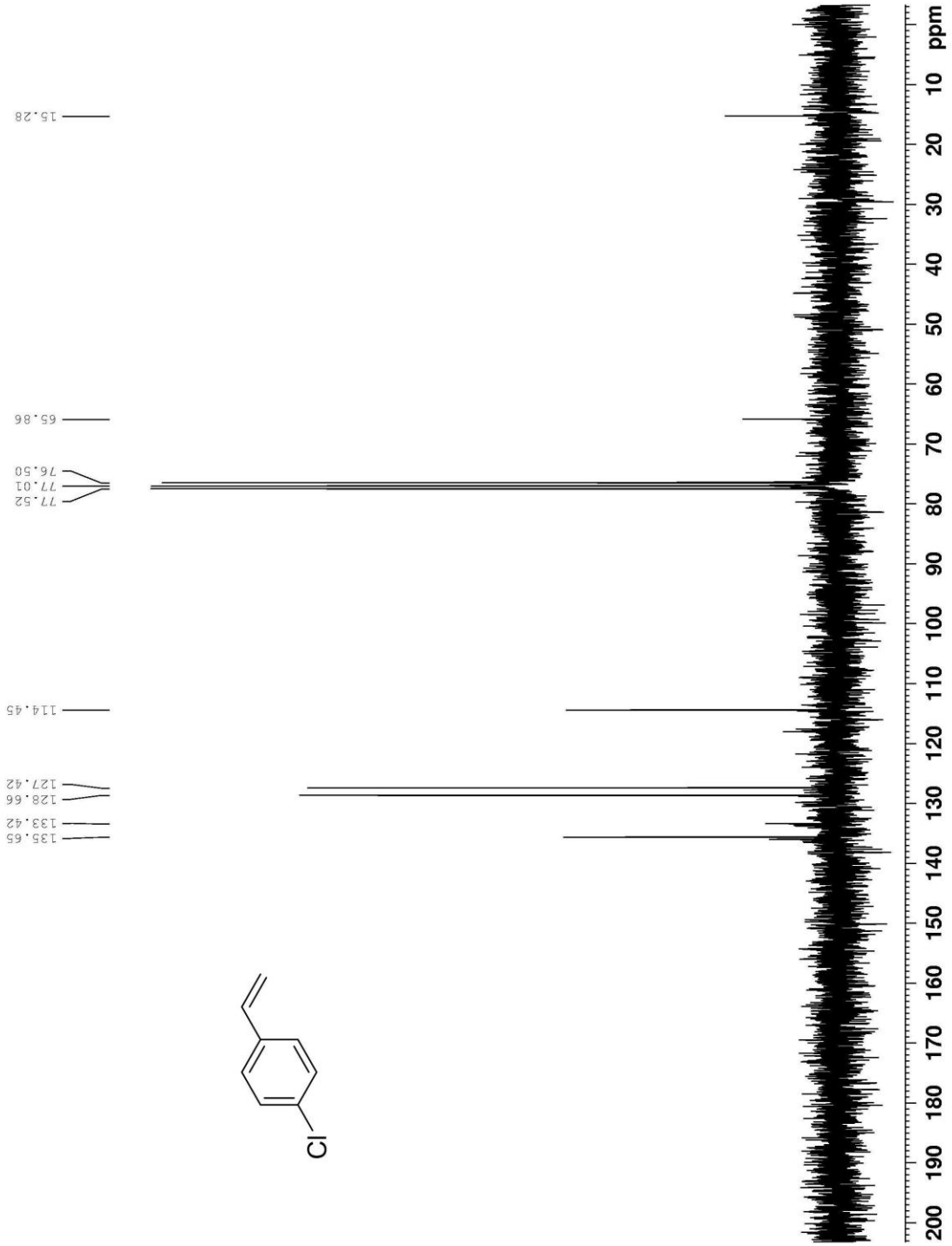
Alkene **28** ^{13}C NMR, 62.9 MHz, $CDCl_3$



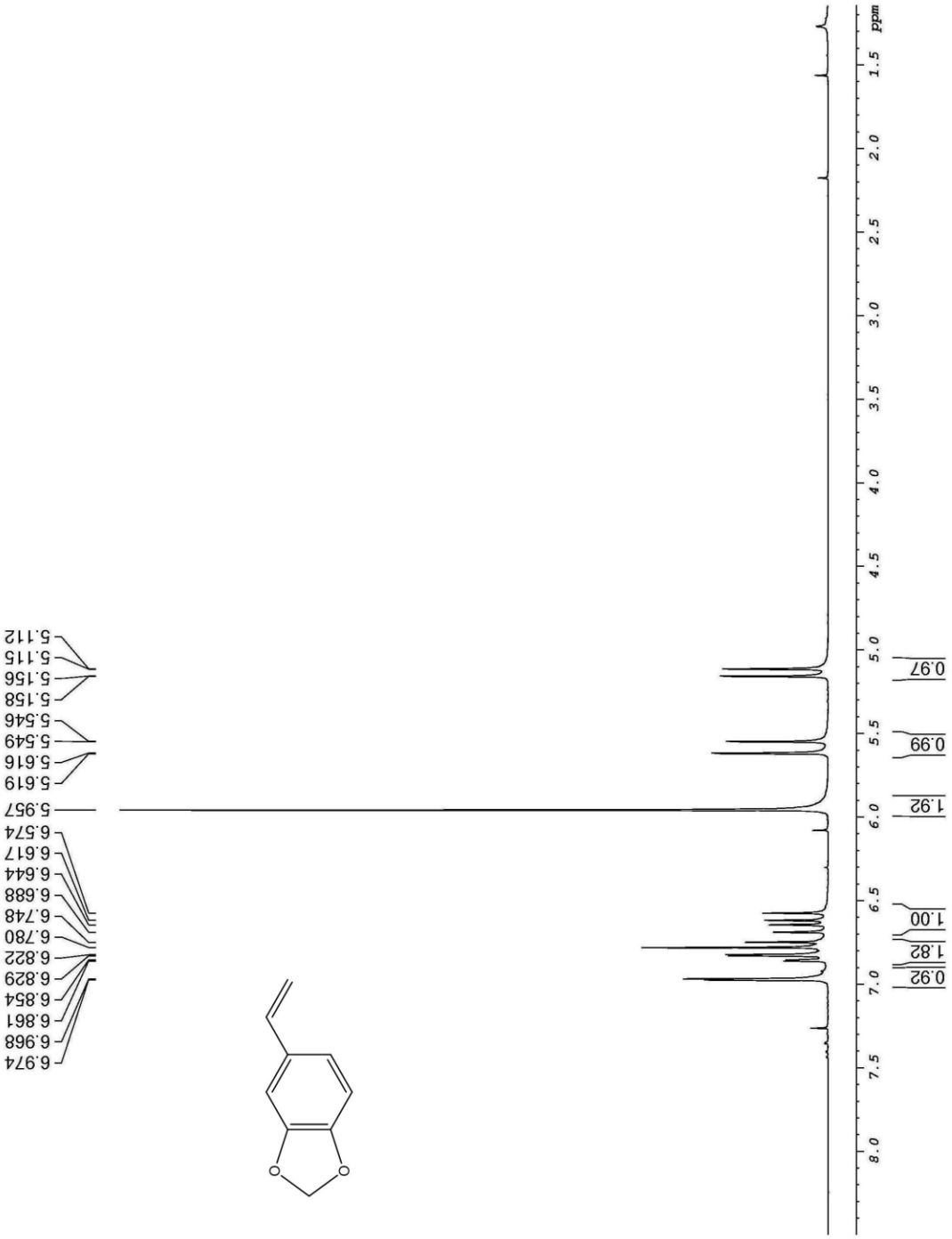
Alkene **29** ^{1}H NMR, 250 MHz, $CDCl_3$



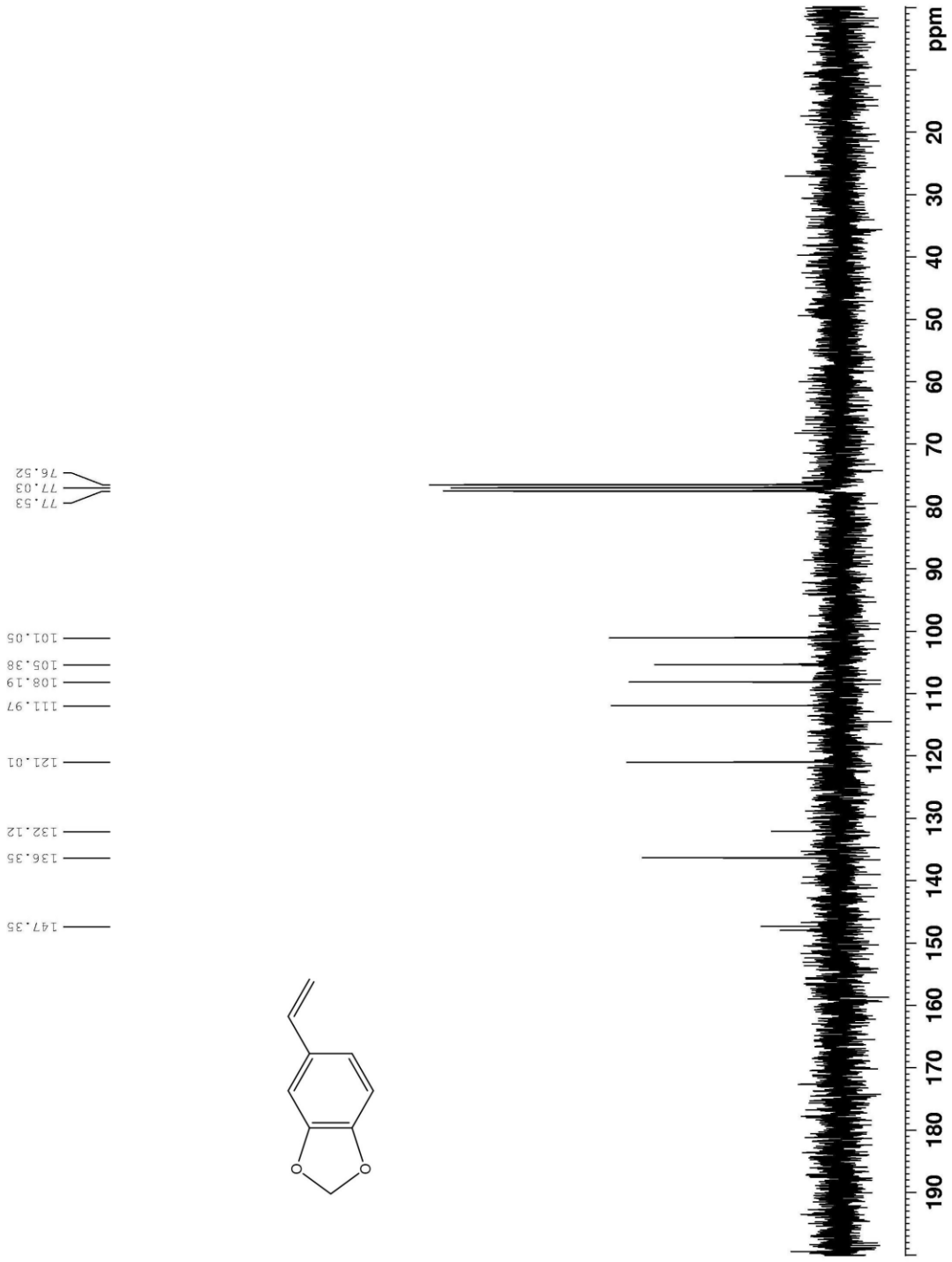
Alkene **29** ^{13}C NMR, 62.9 MHz, $CDCl_3$



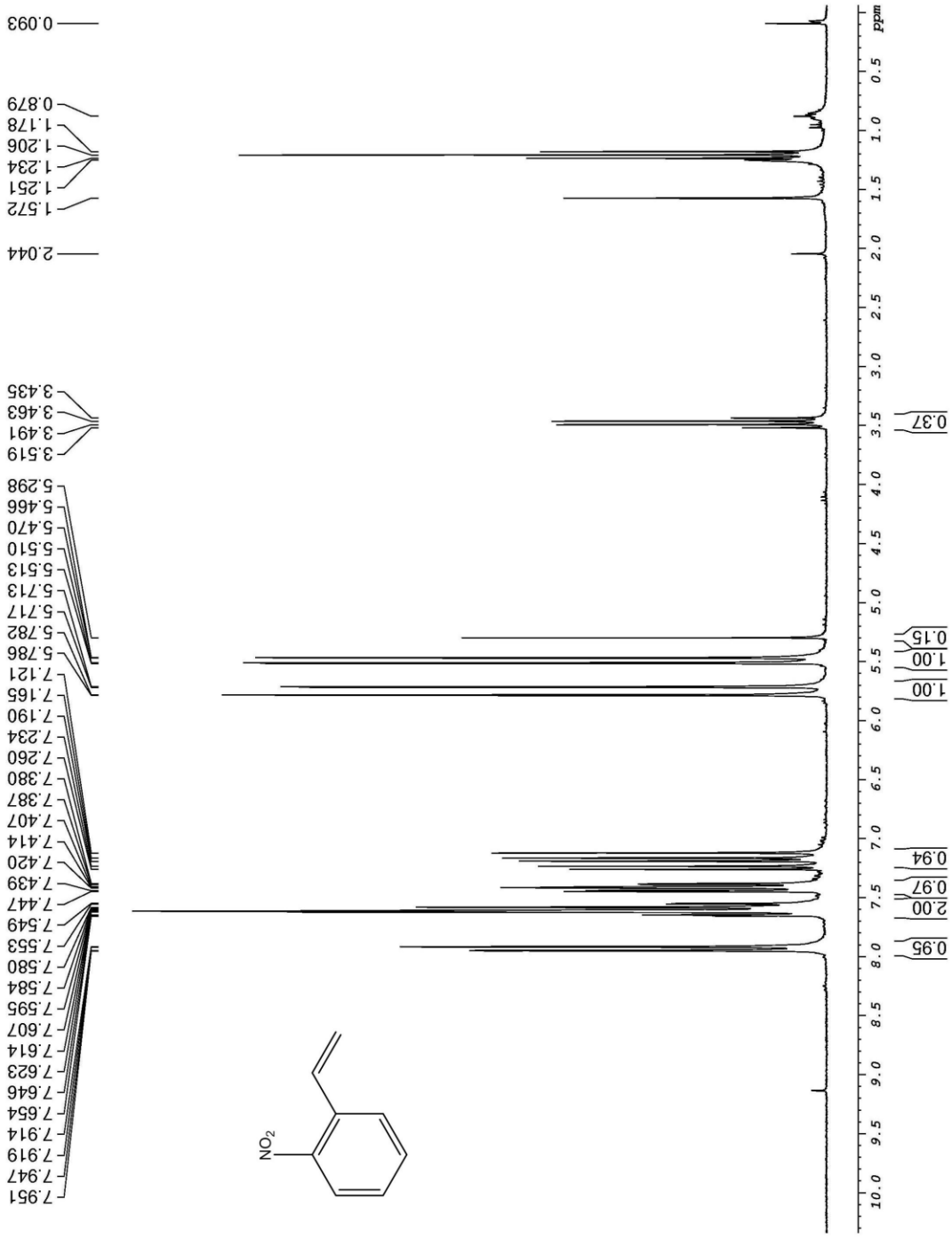
Alkene **30** ^{1}H NMR, 250 MHz, $CDCl_3$



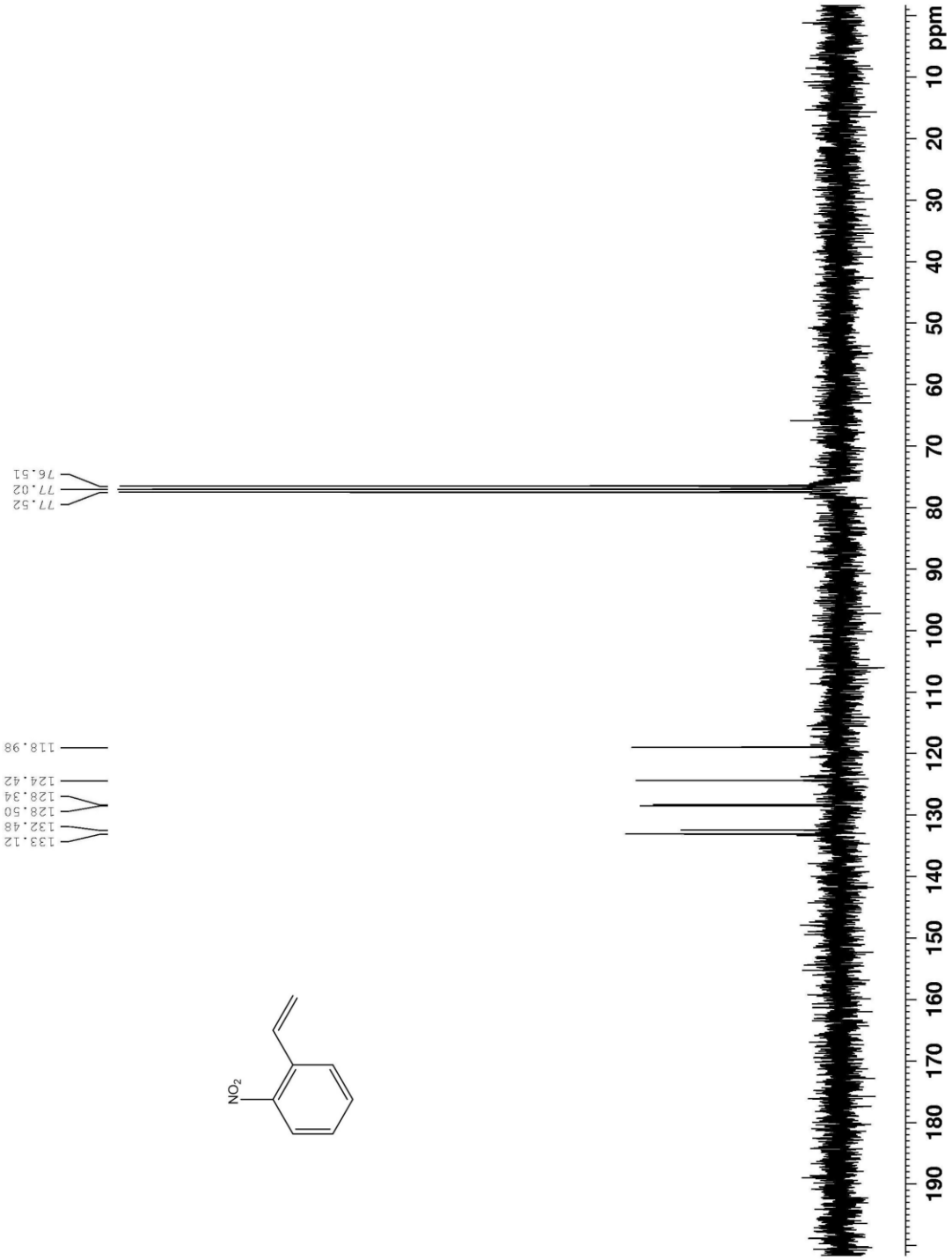
Alkene **30** ^{13}C NMR, 62.9 MHz, $CDCl_3$



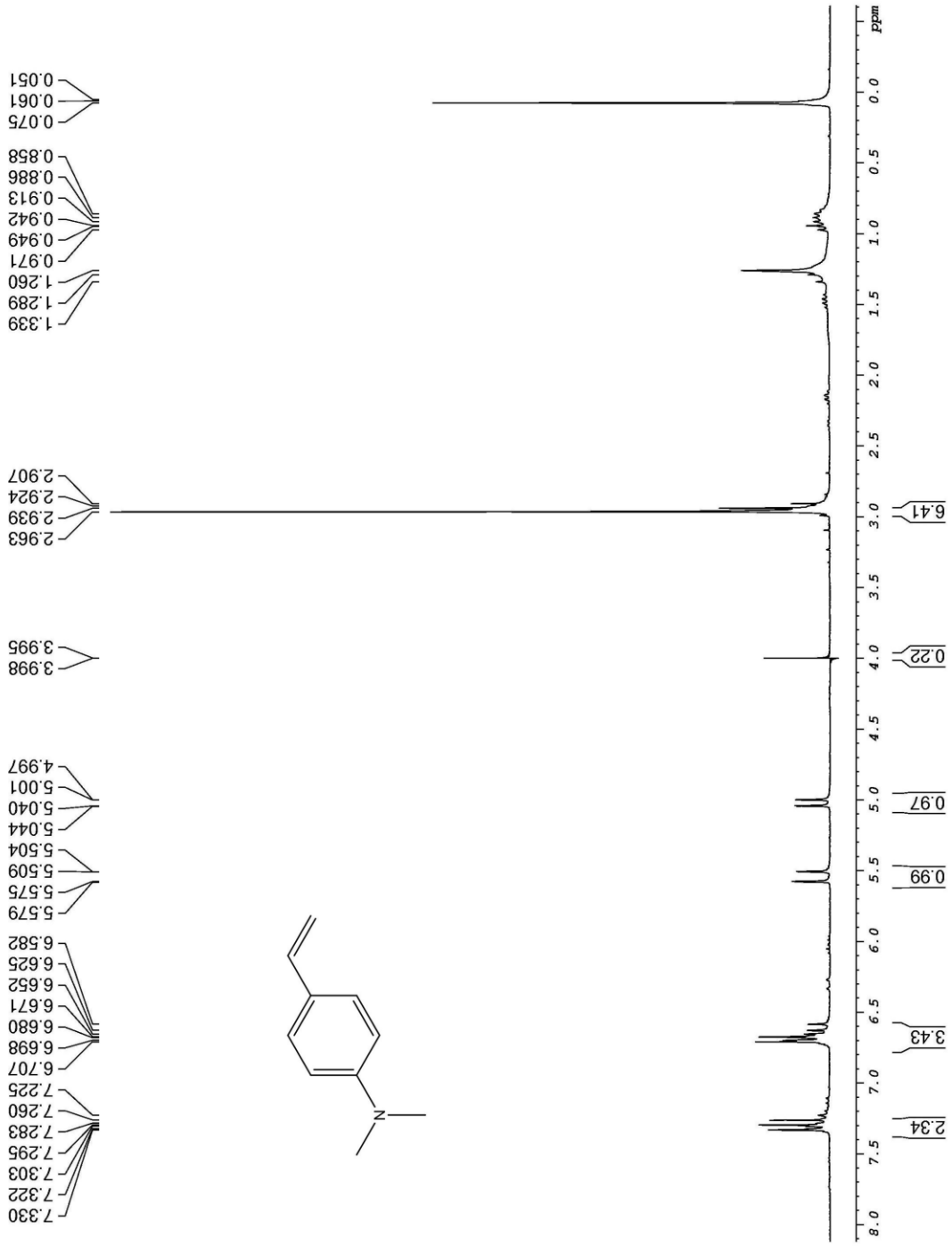
Alkene **31** ^{1}H NMR, 250 MHz, $CDCl_3$



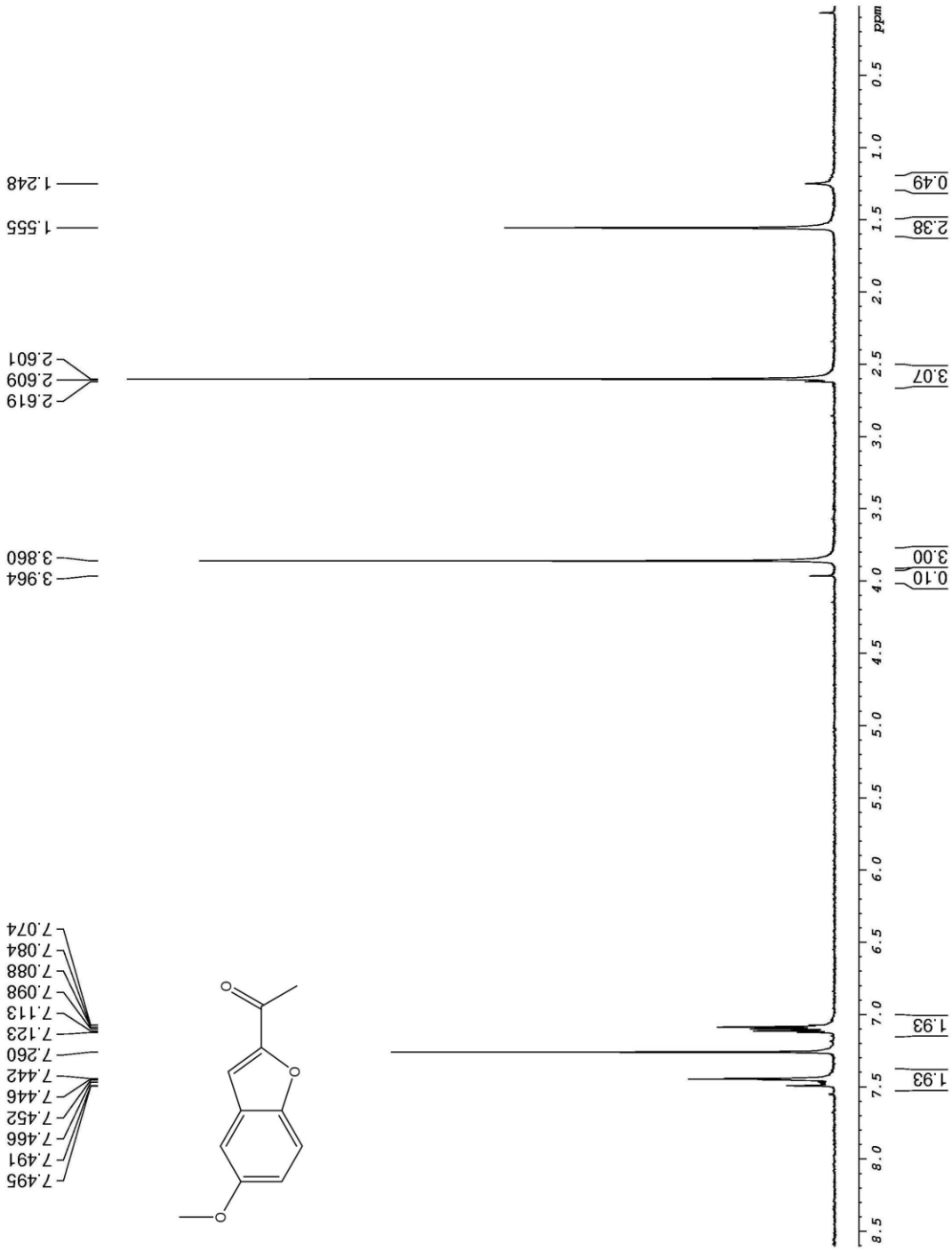
Alkene **31** ^{13}C NMR, 62.9 MHz, $CDCl_3$



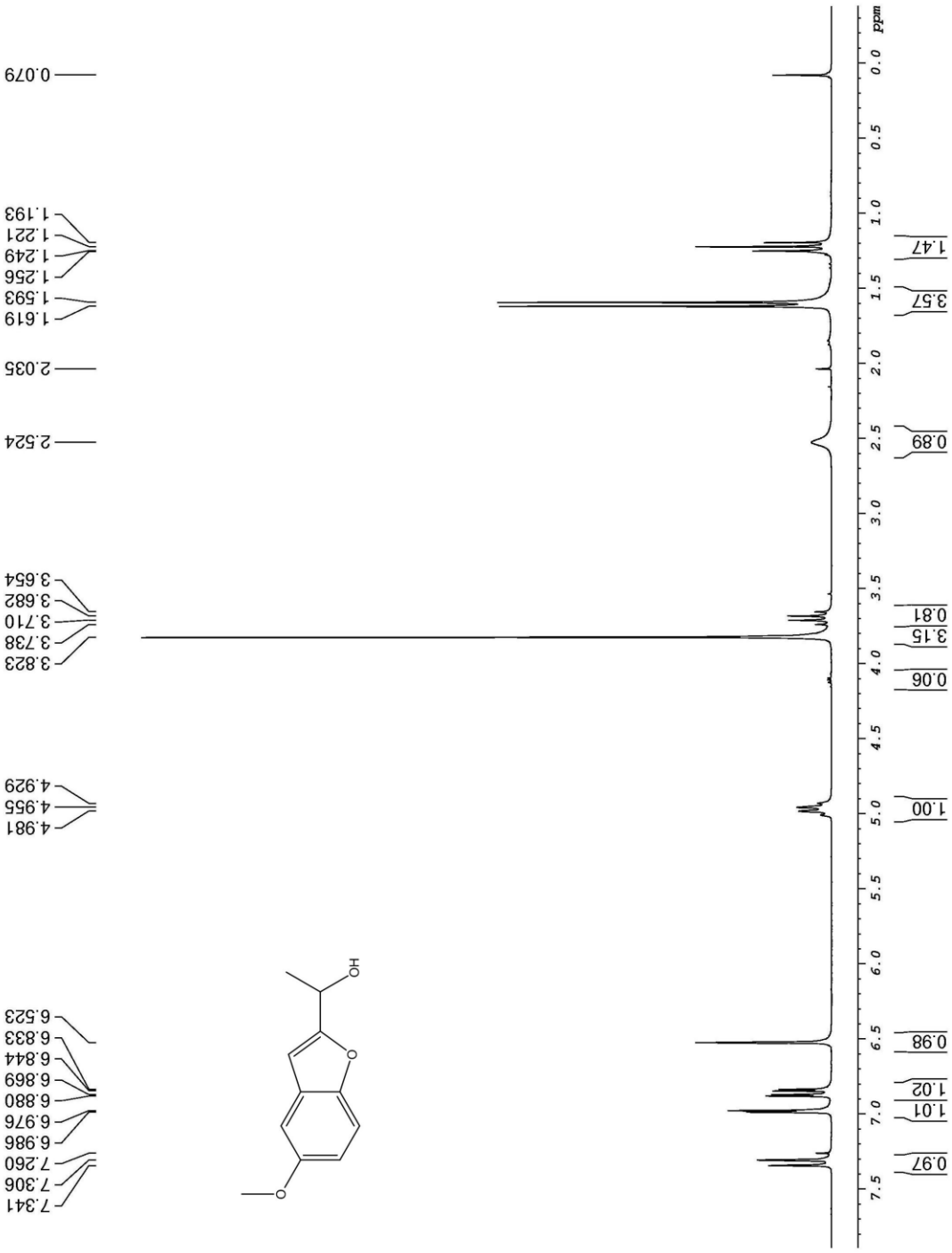
Alkene **32** ^{1}H NMR, 250 MHz, $CDCl_3$



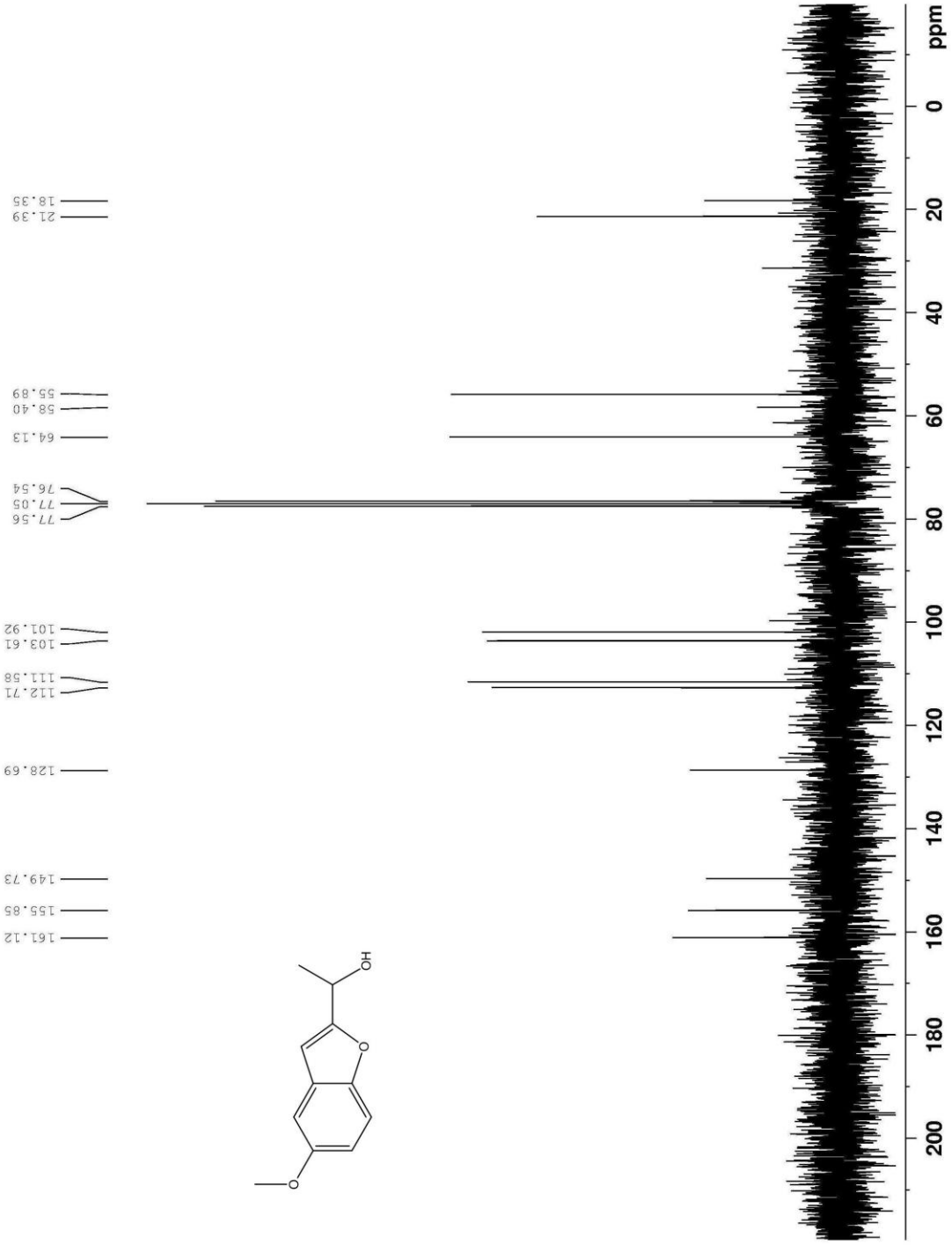
Ketone **44** ^{1}H NMR, 250 MHz, $CDCl_3$



Alcohol **45** ^{1}H NMR, 250 MHz, $CDCl_3$



Alcohol **45** ^{13}C NMR, 62.9 MHz, $CDCl_3$



Alkene **46** ^{1}H NMR, 250 MHz, $CDCl_3$