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# The Synthesis of Highly Substituted Aromatics and the Reaction of Alkene Pi Systems with Vinyl Cations

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THE SYNTHESIS OF HIGHLY SUBSTITUTED AROMATICS AND THE  
REACTION OF ALKENE PI SYSTEMS WITH VINYL CATIONS

A Dissertation Presented

by

Nicholas Dodge

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements  
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## ABSTRACT

This dissertation presents work on three distinct projects that are all related to unique pi systems:

Aldol cyclotrimerizations have been used to achieve the rational chemical synthesis of fullerenes, fullerene fragments, and carbon nanotubes in the past. Under certain conditions this reaction produces the corresponding cyclotetramer which has sometimes been regarded as an undesired byproduct. This work details efforts to synthesize and use these cyclotetramers toward a synthesis of a C<sub>240</sub> fullerene fragment. One principal focus in this work is tridecacyclene, a cyclic tetramer of acenaphthylene given its name by our group for its thirteen rings. Relatively low yields for the synthesis of tridecacyclene and its derivatives drove us to investigate the mechanism of its formation and attempt to optimize its production. During this process, novel dione products were isolated from the attempted cyclotetramerization of two dimeric species. Characterization of these products by X-ray crystallography gave valuable insight into the reaction pathway, leading us to a new proposed mechanism of formation for the cyclotetramerization products observed in these aldol reactions.

$\beta$ -Hydroxy- $\alpha$ -diazoketones are suitable progenitors to vinyl cation intermediates whose use in chemical synthesis is relatively unexplored. As part of an extensive project to develop the chemistry of vinyl cations for use in carbon-carbon bond forming reactions to build important molecular scaffolds, a range of  $\beta$ -hydroxy- $\alpha$ -diazoketones containing a pendent nucleophilic alkene were synthesized. Treatment of these compounds with a Lewis acid gave either lactone or cyclopentenone products depending on the substrate used. Proposed herein is a mechanism involving a key acylium intermediate which, depending on the position of the pendent alkene, results in different product outcomes.

In a collaborative effort to further investigate the known anti-cancer properties of fusarochromanone, a fungal metabolite that is isolated from *Fusarium*-infected feed from cold climates, a large-scale synthesis of this natural product was explored. An efficient, scalable synthesis of the previously prohibitively expensive amidochromanone starting material has been achieved and its elaboration to fusarochromanone has been demonstrated.

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My family also has my eternal gratitude. My siblings, Katie, A.J. and Jake, are truly the greatest gifts my parents ever have given me. I would not trade their love and comradery for anything. To my Dad, words could never do justice to thank you properly for the support you showed me during the formative years of my life.

Finally, to the love of my life, Dongmin—many days I felt sorry for putting you through the struggle of dealing with me during the emotional roller coaster ride that I was going through outside of graduate school but crossing the finish line with you smiling at my side made it all worth it.

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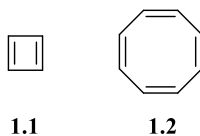
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## CHAPTER 1: SYNTHESIS OF CONTORTED AROMATICS: BACKGROUND

### 1.1 Introduction to Contorted Aromatics

The discovery of benzene by Faraday in 1825 effectively gave birth to an entirely new field of organic chemistry research.<sup>1</sup> The first simple aromatic compounds such as benzene and toluene, so named for their smell<sup>2</sup>, were more stable than predicted based on their given elemental composition and bonds; a theory classifying this stability was developed by Erich Hückel in 1931 on the basis of pi-electron delocalization under a set of parameters now referred to as Hückel's rules for aromaticity.<sup>3-5</sup> The term aromaticity, initially ascribed to these compounds because of their pleasant odors, thus came to refer to this special stability imparted by the electron delocalization found in planar, cyclic systems containing a continuous set of pi-orbitals having  $4n+2$  electrons where  $n$  is an integer.<sup>6</sup> Corresponding rings containing  $4n$  pi-electrons (referred to as antiaromatic) are predicted by this theory to be unstable and have ground states that contain unpaired electrons.

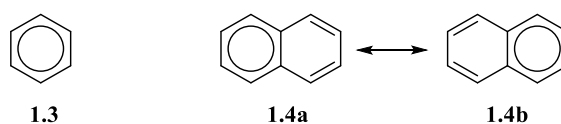


**Figure 1-1: Cyclobutadiene and cyclooctatetraene [COT]**

In reality, such compounds distort to avoid this destabilization. Two of the most well-known examples of this phenomenon are cyclobutadiene, which is believed to adopt a rectangular shape to isolate its pi bonds and thereby prevent delocalization, and

cyclooctatetraene, which, being a larger ring with more flexibility, distorts to a “boat” or “tub” shape (Figure 1-1).<sup>7-9</sup>

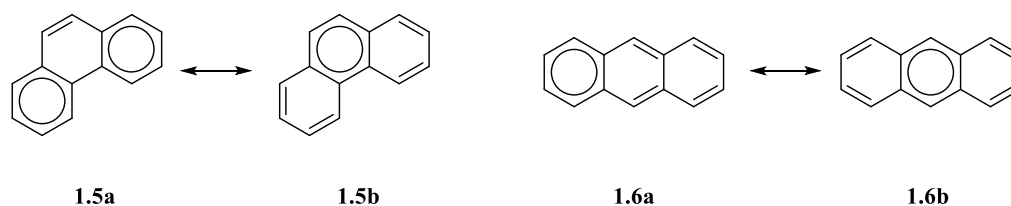
So far, this discussion of aromaticity has focused on monocyclic systems, but the fusion of one or more rings onto benzene often has dramatic, intriguing effects on both the structure and properties of such molecules. A molecule containing multiple fused benzene rings is classified as a polycyclic aromatic hydrocarbon (PAH). Naphthalene, the simplest PAH, contains two fused benzene rings and maintains a planar structure. However, naphthalene is more reactive than benzene toward electrophilic aromatic substitution. These findings highlight not only the complexity of aromaticity but also the inadequacy of relying solely on Hückel’s rules to judge stability; naphthalene, having 10 pi-electrons, satisfies Hückel’s rules and so one might not predict its greater reactivity compared to benzene.<sup>10</sup> A prominent theory explaining this disparity was published by Erich Clar in 1964. This theory posits that for a PAH, the resonance structure containing the largest number of isolated aromatic sextets (or benzene-like rings) will be the most important structure for understanding the properties of that PAH. This is known as Clar’s rule.<sup>11-12</sup>



**Figure 1-2: Aromatic sextet view of benzene and naphthalene**

Applied to our simple example (Figure 1-2), we can see that when drawing resonance structures for naphthalene, we are always left with two alkenes that, while conjugated, are not part of an aromatic sextet. Another intriguing example is a comparison of anthracene

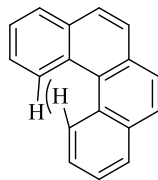
to its constitutional isomer phenanthrene, the former being more reactive. Whereas either resonance structure for anthracene only has one aromatic sextet, phenanthrene has a resonance form containing two aromatic sextets and an isolated pi bond in the middle ring—this resonance form has the strongest contribution to the overall resonance hybrid and, not surprisingly, reactions conducted with phenanthrene usually take place at these positions. Additionally, this resonance form helps to explain phenanthrene's greater stability over anthracene because of the extra aromatic sextet (Figure 1-3).



**Figure 1-3: Resonance forms of phenanthrene and anthracene**

This example shows that the power of this theory lies in its ability to not only help us compare relative stability between different PAH's but also to compare relative stability of the pi bonds within the same PAH. A successful application of Clar's rule by the Whalley group will be highlighted later in this chapter.

All of the compounds discussed above adopt planar conformations, but the fusion of multiple benzene rings together can lead to nonplanar species as seen in the helicene class of PAH's. This distortion from planarity is caused by steric clash between the C-H bonds in the cove region (see [4]helicene in Figure 1-4).<sup>13-14</sup>



1.7

**Figure 1-4: Steric clash leading to twisting in [4]helicene**

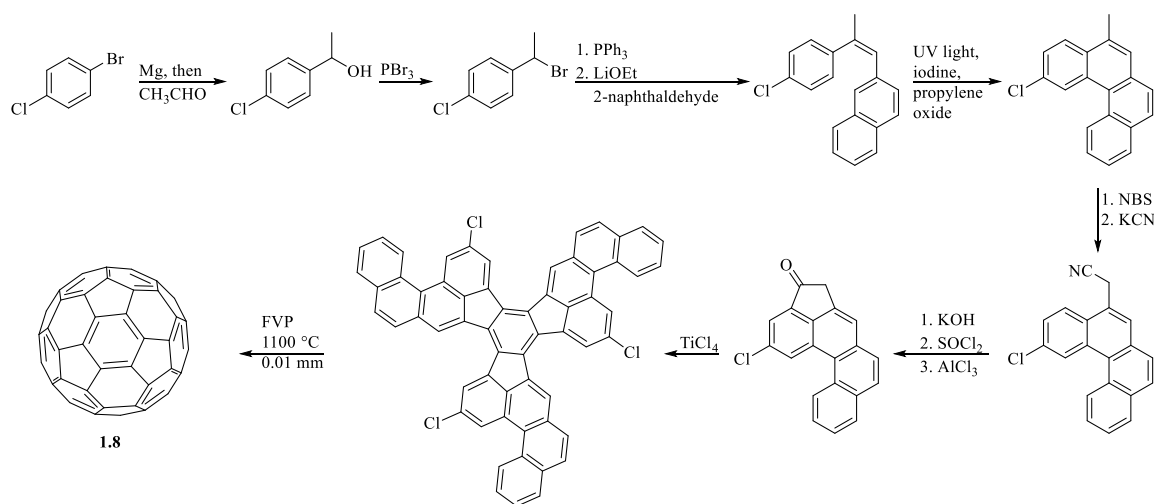
Another way to impart curvature to a PAH is by the incorporation of other ring sizes into the framework.<sup>15</sup> The discovery and synthesis of buckminsterfullerene, also referred to as  $C_{60}$ , by Smalley and coworkers in 1985 demonstrated that this type of curvature in PAH's can be extended to give completely spherical, all-carbon compounds.<sup>16</sup>



**Figure 1-5: Buckminsterfullerene**

The structure of  $C_{60}$ , shown in Figure 1-5, is a truncated icosahedron comprised of 20 hexagonal rings and 12 pentagonal rings. The pentagonal rings do not share a single vertex (the “Isolated Pentagon Rule” or IPR) and are entirely responsible for the molecule's curvature.<sup>17</sup> Additionally,  $C_{60}$  is not the only fullerene; higher-order fullerenes have been isolated, most prominently  $C_{70}$ .<sup>16, 18</sup> As the fullerene gets larger, the number of possible isomers increases exponentially ( $C_{60}$  has only a single isomer) and the molecule can

incorporate larger ring sizes than 5- and 6-membered; it has even been shown that a fullerene containing 240 carbon atoms can incorporate 8-membered rings within its framework.<sup>19</sup> Progress in this area of research has been remarkable—a mere 17 years after the synthesis of buckminsterfullerene from laser irradiation of graphite the Scott group reported a 12-step rational chemical synthesis of C<sub>60</sub> using an aldol cyclotrimerization-flash vacuum pyrolysis sequence as the key steps, demonstrating the fundamental importance of organic synthesis to this field (Scheme 1-6).<sup>20-21</sup>



**Scheme 1-6: A rational chemical synthesis of C<sub>60</sub>**

This synthesis gave C<sub>60</sub> as the exclusive fullerene product—no others were detected despite rigorous analysis. Despite the fact that this rational synthesis of buckminsterfullerene was not a high-yielding process, it stands as a landmark of achievement in the field of synthetic organic chemistry.



As a final introductory aside, since the discovery of this class of compounds (sometimes referred to as buckyballs) a plethora of research has been conducted to investigate their properties and applications. The outer convex surface of  $C_{60}$  is electron deficient, leading to the investigation into its use as an electron acceptor for donor/acceptor based organic photovoltaics (including perovskite solar cells).<sup>22</sup> The potential applications of fullerenes are not just limited to materials chemistry:  $C_{60}$  is even currently being studied for potential use in the treatment of cancer.<sup>23</sup> It is easy to understand why such compounds have generated intense research interest for the last several decades. In fact, several other classes of compounds within this family have also garnered significant attention—one of which being molecules that represent *fragments* of fullerene structures. These compounds will be the focus of the remainder of this chapter.

## 1.2 The Chemical Synthesis of Buckybowls

One can easily imagine a molecule that represents a portion of a fullerene—these are often referred to as fullerene fragments or buckybowls. If such molecules contained ring sizes other than 6 they would be expected to have curvature, the key feature that imparts on  $C_{60}$  its interesting properties, but their syntheses might be more readily achievable given their smaller size. In fact, these open-faced geodesic polyarenes have attracted significant attention from the synthetic community and an impressive number of compounds from this class of molecules have been successfully targeted and synthesized.<sup>24</sup> An assortment (not a comprehensive list) of fragments of  $C_{60}$  whose syntheses have been achieved is pictured in Figure 1-7.

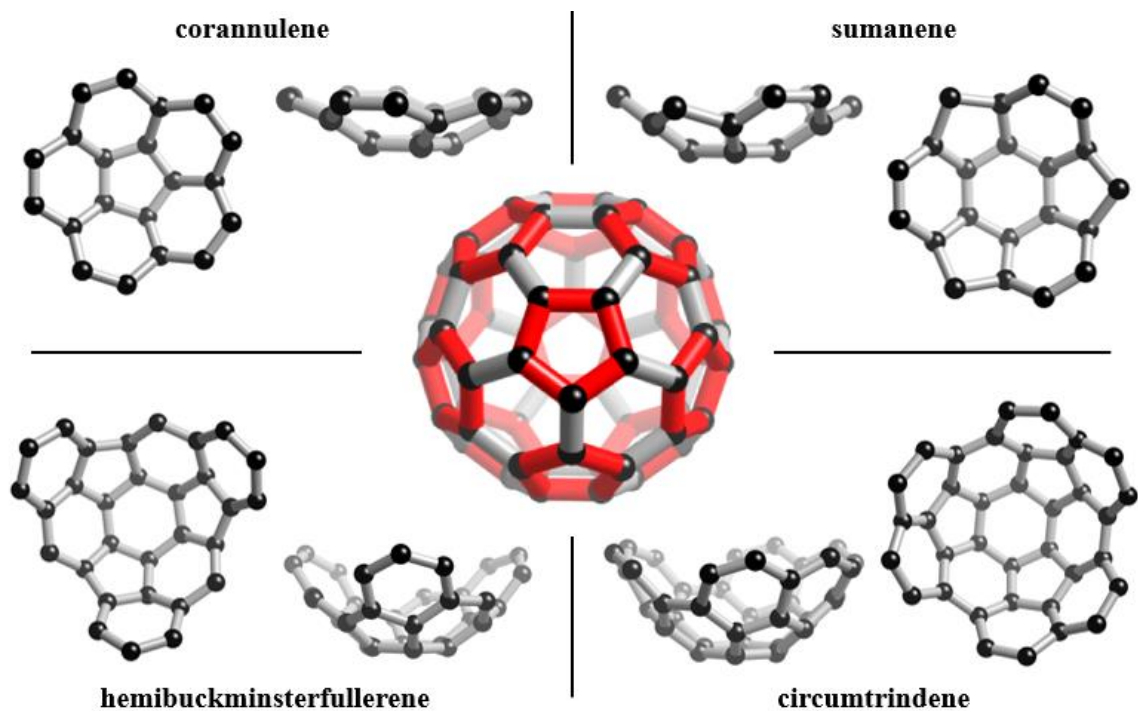
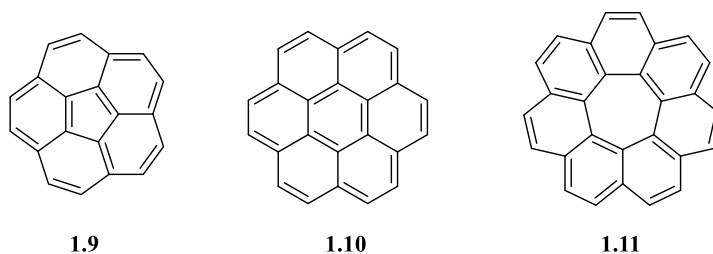


Figure 1-7: Geodesic polyarenes

The following sections will highlight the chemical syntheses of each of these bowl-shaped aromatics pictured above as well as the synthesis of some fragments of higher-order fullerenes.

### 1.2.1 Corannulene and Introduction to [ $n$ ]Circulenes

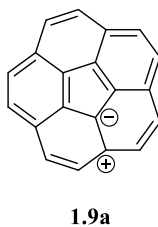
Arguably the most famous buckybowl, whose synthesis and isolation predates that of buckminsterfullerene by nearly 2 decades, is corannulene, also known as [5]circulene. The [ $n$ ]circulenes are a class of macrocyclic arenes containing a central ring completely surrounded by  $n$  fused benzene rings.<sup>25</sup> Though they are classified together, the different [ $n$ ]circulenes adopt vastly different conformations.



**Figure 1-8: [n]Circulenes**

Corannulene (**1.9**) is bowl-shaped and represents a fragment of  $C_{60}$ , hence its inclusion in this section;<sup>26</sup> [6]circulene (coronene) is fully planar; and [7]circulene adopts a saddle-shaped conformation.<sup>27</sup>

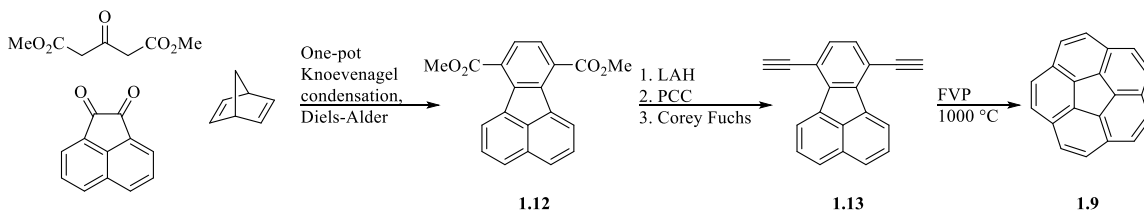
The trivial name corannulene also holds a special meaning—referring to the “annulene within an annulene” model postulated by Barth and Lawton after their remarkable, though low-yielding synthesis in 1966. Barth and Lawton proposed a resonance form of the molecule as a composite of an inner 6-electron aromatic anion and an outer 14-electron aromatic cation.<sup>28</sup>



**Figure 1-9: "Annulene within an annulene" resonance form**

While this theory has not been definitively proven, it explains the nomenclature and is an interesting conceptualization of the compound.

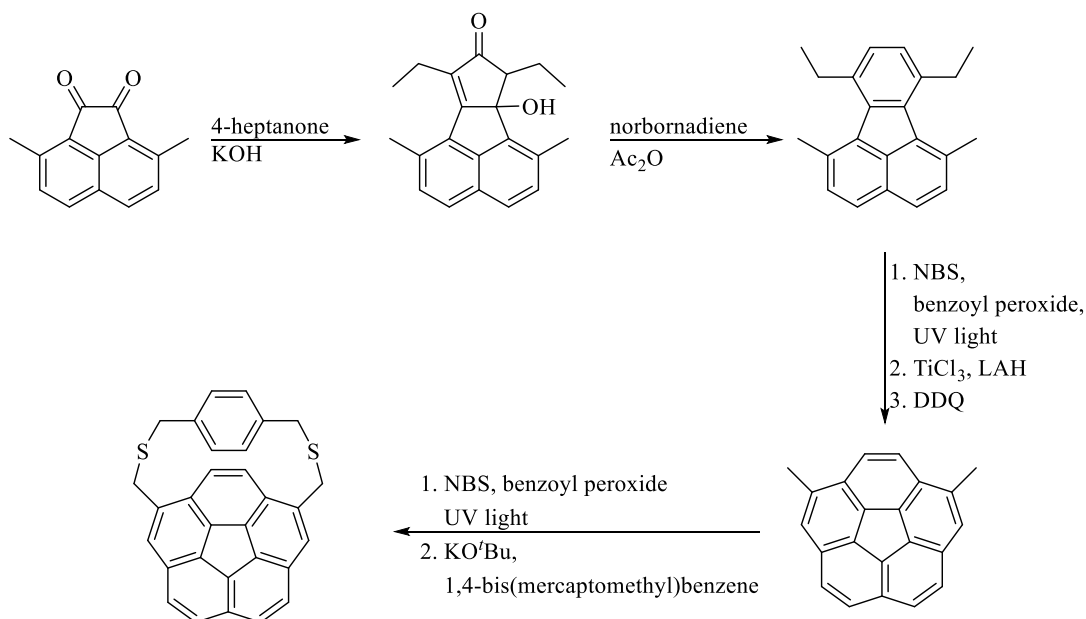
While the original synthesis of corannulene stands as a landmark achievement of organic synthesis, it was too long and too low yielding to efficiently generate large quantities of corannulene for studies of its chemistry. Many years later, in 1991, Scott's group accomplished the synthesis of corannulene using flash vacuum pyrolysis (FVP) as the key step, taking advantage of a report by Brown that terminal acetylenes reversibly rearrange to vinylidenes under these conditions (Scheme 1-10).<sup>29-30</sup> A one-pot double Knoevenagel condensation and Diels-Alder sequence, after loss of carbon monoxide and cyclopentadiene, gave the corresponding diester **1.12**. Conversion of the diester to alkyne **1.13** was accomplished using classic synthetic methods. This alkyne was then converted to corannulene by FVP in low (ca. 10%) yields.



**Scheme 1-10: Synthesis of corannulene, Scott 1991**

This procedure drastically reduced the number of steps required (5 steps compared to the 16 steps in Barth and Lawton's synthesis) for the synthesis and allowed for sufficient preparation of corannulene to begin the investigation of its properties and applications. The following year, the Siegel group published two different routes to corannulene, one employing FVP at 1000 °C and the other accomplished by the extrusion of sulfur dioxide using static vacuum at 400 °C.<sup>31</sup>

Several years later in 1996, a new approach to the corannulene nucleus was reported, again by the Siegel group, in their synthesis of the first corannulene cyclophane (Scheme 1-11).<sup>32</sup>

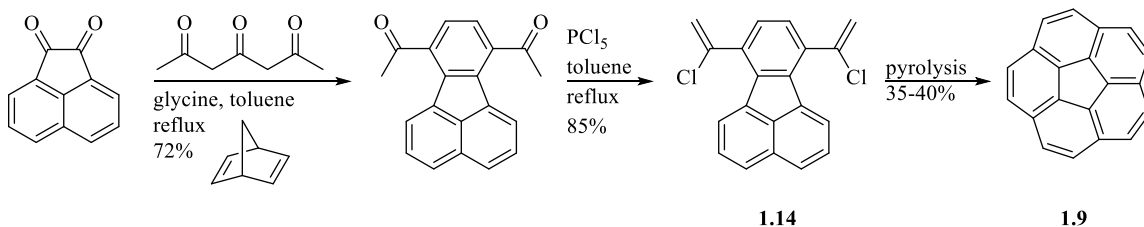


**Scheme 1-11: Synthesis of first corannulene cyclophane by Siegel**

The key step in this approach was a reductive coupling of benzylic bromides using low-valent titanium or vanadium followed by dehydrogenation with DDQ. This represented a milestone in the synthesis of corannulene derivatives as this method avoided the use of FVP which, because of the extreme temperatures employed, results in minimal functional group tolerance.

The Scott group persisted in efforts to further shorten their FVP-mediated synthesis of corannulene, publishing a remarkable high-yielding 3-step procedure the following year in 1997.<sup>33</sup> Building off of their earlier findings that the incorporation of halogens into the

FVP precursors led to higher yields after pyrolysis, their approach hinged on the key vinyl chloride intermediate shown in Scheme 1-12.

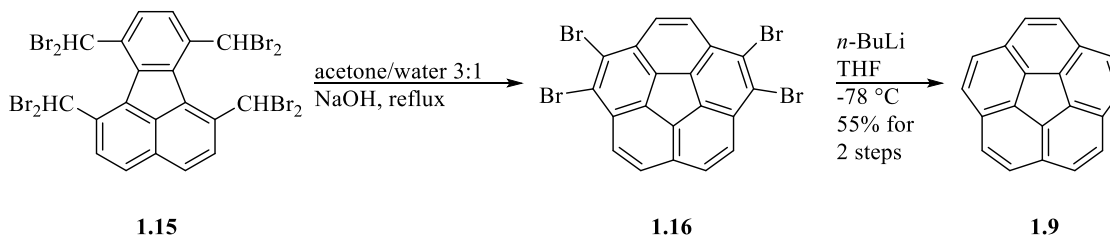


**Scheme 1-12: 3-Step synthesis of corannulene**

The original FVP route used by Scott employing the terminal acetylenes as precursors to vinylidenes was hampered by significant polymerization of the starting material under the reaction conditions due to its extremely low volatility. Employing a vinyl chloride precursor (**1.14**) instead of an ethynyl species drastically increased the yield of corannulene; Scott also mentioned that this process likely still proceeds through the alkyne as an intermediate after elimination of  $\text{HCl}$ —the diyne (**1.13**) was isolated as the only product from a pyrolysis run conducted at a lower temperature. Using this method, the Scott lab was able to turn out corannulene in quantities of hundreds of milligrams per FVP run—a significant advancement from prior efforts.

Researchers were unrelenting in their search for an efficient, high-yielding solution-phase synthesis of corannulene and in 2000 the Rabideau group reported a breakthrough.<sup>34</sup> While attempting to convert the readily available octabromide **1.15** shown in Scheme 1-13 to the corresponding tetraaldehyde under hydrolysis conditions, the

tetrabromocorannulene **1.16** was instead obtained in an optimized 83% yield! Conversion to corannulene could be effected by treatment with *n*-butyllithium.



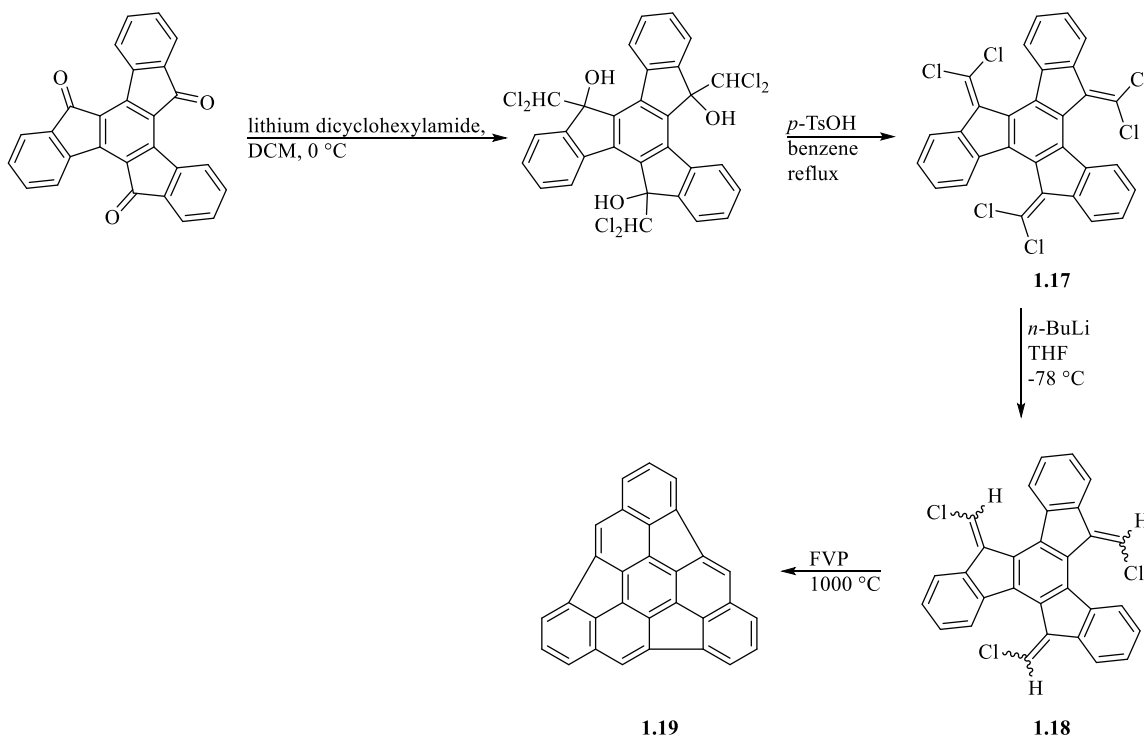
**Scheme 1-13: 2-Step large scale corannulene synthesis**

This serendipitous outcome not only resulted in access to corannulene on very large scales but also to the facile functionalization of corannulene via metal-catalyzed cross coupling reactions via the bromide substituents. Since then, the Siegel group has developed a route to corannulene that can be executed on kilogram scales.<sup>35</sup> The progress achieved by the synthetic community in pursuit of corannulene is truly remarkable, from the pioneering work by Barth and Lawton in 1996 to Siegel's large-scale preparation in 2012. Corannulene is now so widely available that it is commonly used a *starting material* for the synthesis of other carbon-rich molecules including carbon nanotubes.<sup>36</sup>

### 1.2.2 Hemibuckminsterfullerene and Sumanene

Hemibuckminsterfullerene (**1.19**), as the name implies, represents half of  $\text{C}_{60}$ . However, it is not the only fragment that maps to 50% of buckminsterfullerene—this specific fragment was targeted because, of the  $\text{C}_{30}\text{H}_n$  hydrocarbons that represent half of  $\text{C}_{60}$ , it was predicted to be the most stable since it contains fewer strain-inducing five-

membered rings than the rest. Its synthesis, accomplished by the Rabideau group in 1995, is shown in Scheme 1-14.<sup>37</sup>

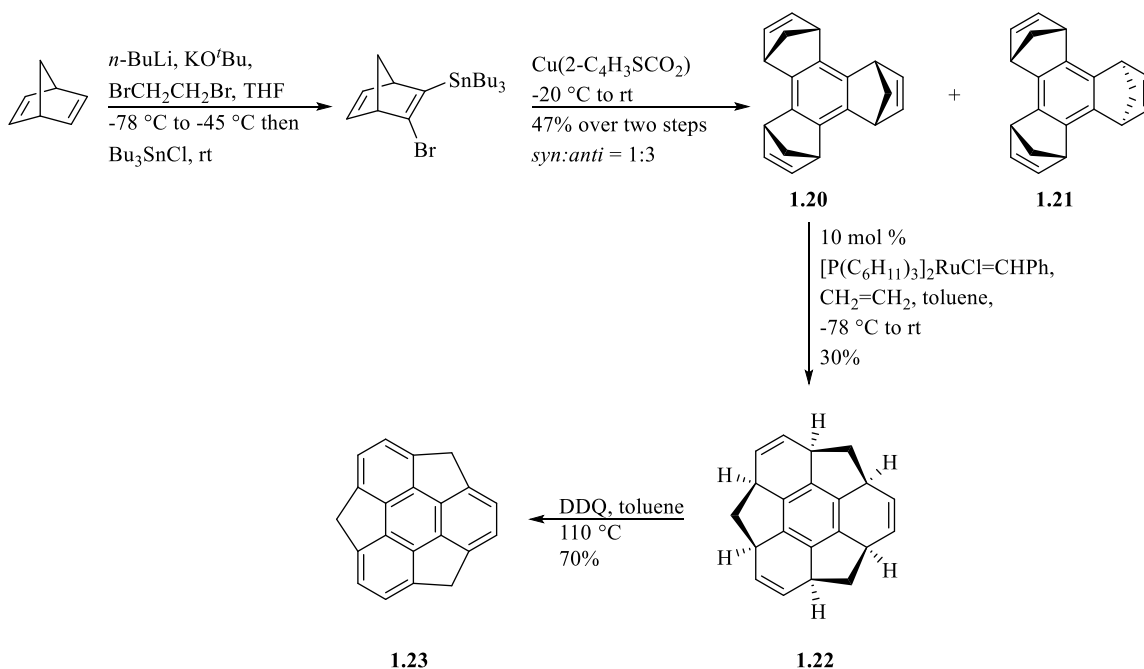


**Scheme 1-14: Hemibuckminsterfullerene synthesis in 1996**

The Rabideau group, like the Scott group, accessed this fullerene fragment using a flash vacuum pyrolysis approach from a vinyl chloride precursor. Notably, FVP on the hexachloro precursor **1.17** gave an intractable mixture of chlorinated products. Desiring to reduce the total amount of chlorine in the FVP chamber, half of the halogens were removed using *n*-butyllithium prior to the pyrolysis. This strategy proved fruitful, leading to the isolation of pure hemibuckminsterfullerene after column chromatography, albeit in low yield (<10%). Nevertheless, this report underscores the importance of developing alternative methods to FVP for the synthesis of buckybowls.



Another enticing fullerene fragment targeted by chemists in the early 2000's is sumanene, which is notable for its three benzylic positions that would theoretically render functionalization of the parent compound more facile than other all-sp<sup>2</sup> frameworks such as corannulene. In 2003, Sakurai and coworkers published a concise synthesis of sumanene using a key trimerization of an organotin norbornadiene (Scheme 1-15).<sup>38</sup>



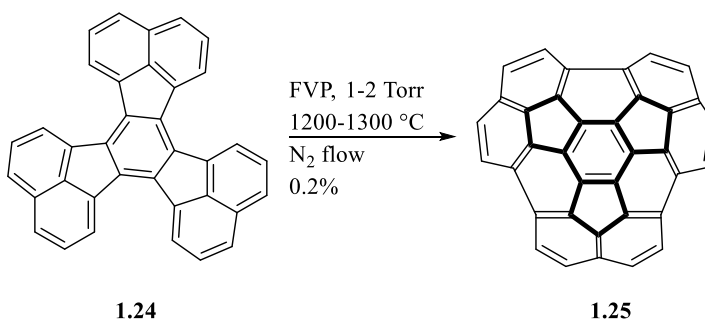
**Scheme 1-15: Synthesis of sumanene in 2003**

This key step gave both *syn*- and *anti*-products in 1:3 ratio, but only the *syn*-product **1.20** was an effective substrate for the tandem ring-opening metathesis (ROM) / ring-closing metathesis (RCM) procedure. Oxidation with DDQ afforded sumanene (**1.23**). Compared to the synthesis of other open geodesic polyarenes, this approach employs relatively mild conditions with no need for extreme temperatures as in FVP. Additionally, the design of this synthesis resulted from impressive ingenuity by the researchers; after reading reports

detailing the failed synthesis of sumanene from planar precursors by FVP (suggesting that strain energy is the limiting factor), Sakurai and coworkers devised this synthesis of sumanene to start with norbornadiene, a compound whose tetrahedral carbons come with strain already built in.

### 1.2.3 Circumtrindene

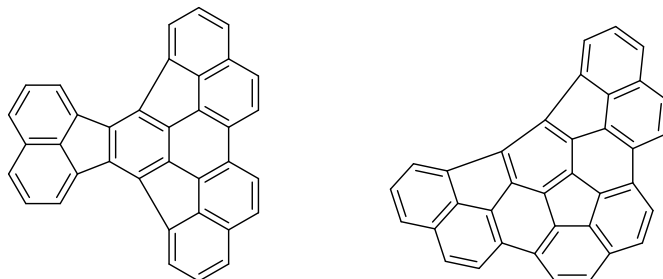
Another compound that had been envisioned as an enticing substrate for FVP due its large commercial availability at the time (it has since been discontinued by the supplier) is decacyclene (**1.24**, named for its 10 rings, Scheme 1-16).<sup>39</sup> This pyrolysis would, in theory, produce a geodesic dome that corresponds to 60% of C<sub>60</sub> (**1.25**). Initial FVP trials by the Scott lab and others were met with disappointment, as the typical FVP conditions proved ineffective, returning decacyclene as the only recoverable product.



**Scheme 1-16: Flash vacuum pyrolysis of decacyclene**

In 1996, Scott's lab published the successful, albeit inefficient, pyrolysis of decacyclene to the corresponding geodesic polyarene in 0.2% yield (10 mg of the buckybowl was isolated starting from 5 g of decacyclene).<sup>40</sup> Higher temperatures (1200-1300 °C) as well as other optimizations to the FVP setup were required to achieve this result. Though the desired

buckybowl could be isolated readily by column chromatography, the products corresponding to a singly-closed and doubly-closed decacyclene were also detected (Figure 1-17).

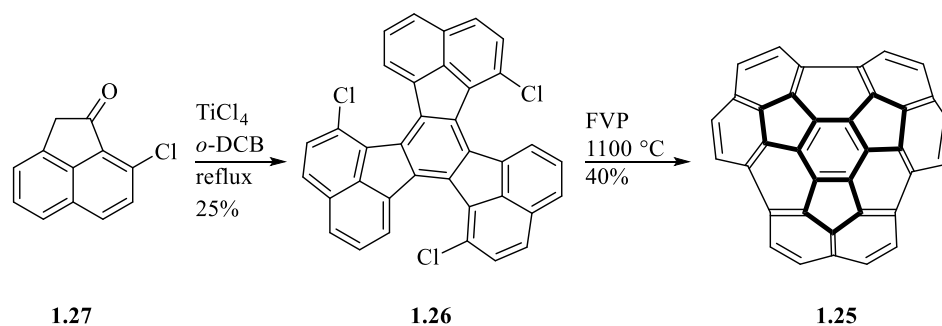


**Figure 1-17: Bond closures of decacyclene induce strain**

The original failed standard FVP conditions at 1100 °C were then repeated and the reaction was more closely examined—it was found that the crude reaction mixture contained decacyclene, singly-closed, and doubly-closed products in a 15:1:6 ratio, respectively. From this it was concluded that pyrolysis at 1100 °C simply does not provide the energy required to perform the 3 strain-inducing cyclodehydrogenations. Though decacyclene is not planar (it is twisted into a propeller shape), these bond closures impart further, remarkable contortion and strain on the molecule that can even be understood by examining the crude 2-dimensional representations of the singly- and doubly-closed products pictured above.

In 2000, Scott's group suggested the trivial name circumtrindene for this buckybowl **1.25** based on the circumtrindene nomenclature discussed previously as it contains a trindene core surrounded completely by fused benzene rings.<sup>41</sup> While circumtrindene had already been synthesized in their group, the FVP yield was abysmal and a rational synthesis, rather than a brute force strategy, was devised. Scott's strategy was to install

functional groups that would be capable of generating radicals at the desired ring-closure sites—halogens were the first choice for such a substituent. However, a new approach to decacyclene would be required—at the time it was prepared by oxidative trimerization of acenaphthylene,<sup>39</sup> a process that would lack regiochemical control if applied to an asymmetrically-substituted acenaphthylene. Instead, Ansems and Scott envisioned constructing the requisite  $C_3$ -symmetric trichloro-decacyclene **1.26** (choosing chlorine over bromine to maximize substrate volatility and minimize potentially detrimental steric effects) by a head-to-tail aldol trimerization. Addition of a dilute solution of 8-chloroacenaphthenone to a boiling solution of  $TiCl_4$  (6 equivalents) in 1,2-dichlorobenzene gave the desired trimer in a 25% yield that was unable to be further optimized (Scheme 1-18). FVP (1100 °C) on this substrate proved challenging due its low volatility, but, of the material that entered the pyrolysis tube, 35-40% was converted to circumtrindene. This pyrolysis not only required lower temperatures than the approach from decacyclene, it also represented a significant improvement in the yield of circumtrindene.

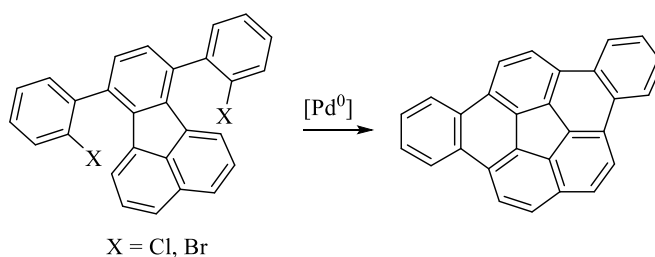


**Scheme 1-18: Rational synthesis of circumtrindene**

As alluded to at the introduction to this section, these geodesic polyarenes that represent fragments of fullerenes are expected to have similar curvature and, hence, properties to the fullerenes they map to. Excitingly, Ansems and Scott found that the carbon atoms at the top of the dome in circumtrindene experience a similar distortion from planarity as those in  $C_{60}$  and the molecule underwent similar cycloaddition reactions to  $C_{60}$  at the bonds nearest the top of the dome.<sup>42</sup> The successful synthesis and study of circumtrindene stands not only as an impressive feat of rational synthesis but also as evidence that fullerene fragments hold promising properties (and are therefore worthwhile of synthetic pursuit) just like their parent fullerenes.

#### 1.2.4 Other Buckybowls and Palladium-Catalyzed Arylation

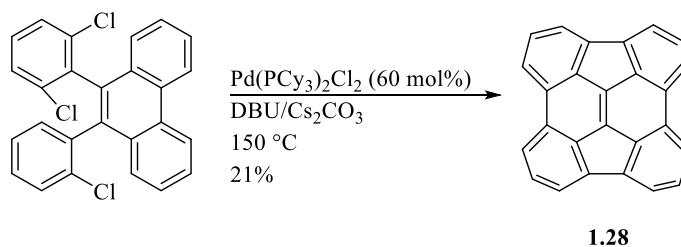
While the examples discussed previously demonstrate the importance of flash vacuum pyrolysis to the field of buckybowl synthesis, this method ultimately limits chemists in their synthetic targets. The extreme conditions of FVP result in minimal functional group tolerance, driving a need for milder, solution-based approaches.<sup>43</sup> One strategy that has emerged as a prominent alternative to FVP is palladium-catalyzed arylation—an example in Scheme 1-19 shows the preparation of a dibenzocorannulene by Scott's group using this method in 2000).<sup>44</sup>



**Scheme 1-19: Palladium-catalyzed arylation as a method for PAH synthesis**

This section will highlight two reports by the Wu group where this transformation was used to construct bowl-shaped fullerene fragments.

In 2010 Wu's group reported the synthesis of diindeno[1,2,3,4-*defg*;1',2',3',4'-*mno*]chrysenes (**1.28**) in 20% yield using palladium-catalyzed arylation on 9,10-diarylphenanthrene precursors (readily prepared by palladium-catalyzed cycloaddition between 2-iodobiphenyl and 2,2',6-trichlorodiphenylethyne). The result shown in Scheme 1-20 was only achieved after significant optimization efforts.<sup>45</sup>

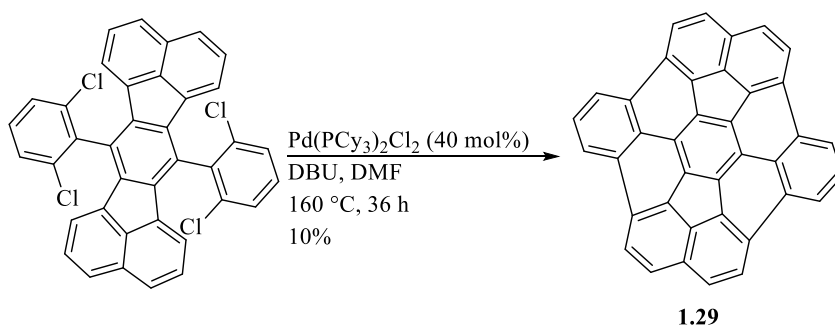


**Scheme 1-20: Wu's strategy for diindeno-chrysenes**

The choice of catalyst was crucial, with  $\text{Pd}(\text{PCy}_3)_2\text{Cl}_2$  being the most effective of those tried, though it required high loading. Increasing the reaction temperature led to full consumption of the starting material but with an increased incidence of reductive dechlorination. Reducing the reaction time increased the overall yield by limiting product decomposition. The choice of base as a combination of cesium carbonate and DBU ultimately led to the most successful outcome. While the yield for the palladium-catalyzed process was lower than the FVP strategy for this molecule (21% vs 37%), isolation of the product from the former set of conditions was more facile. Importantly, in many of the other conditions attempted the product was obtained in trace to no yield! This underscores

the importance of a thorough condition screening if one wishes to use the palladium-catalyzed arylation strategy.

Wu's group continued to employ palladium-catalyzed arylation to achieve the synthesis of bowl-shaped aromatics, reporting one of the first syntheses of a subunit of C<sub>70</sub> (**1.29**). The success of the key arylation step, shown in Scheme 1-21, was ultimately hindered by product loss during chromatography due to low solubility.<sup>46-47</sup>



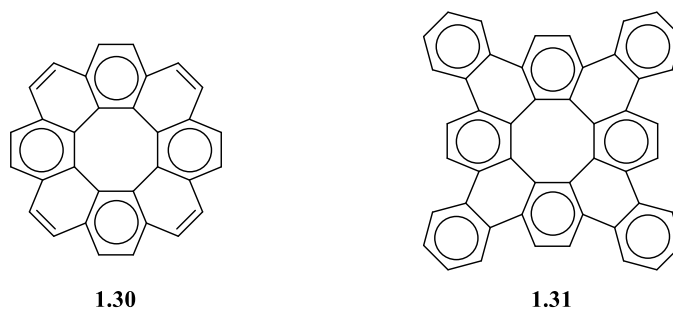
**Scheme 1-21: Synthesis of a fragment of C<sub>70</sub>**

Attempts to synthesize a more soluble *n*-butyl-substituted derivative of **1.29** were unsuccessful. The work accomplished by the Wu group and others demonstrates that FVP is not the only tool available for the synthesis of geodesic polyarenes and that the investigation of other methodologies is certainly worthwhile.

### 1.3 Tetrabenzo[8]circulene and the Scholl Reaction

One of the first synthetic challenges undertaken by the Whalley group was [8]circulene. Prior to this only one report on the preparation of [8]circulenes was present in the literature.<sup>48</sup> The [8]circulene derivatives reported in this paper, however, were not

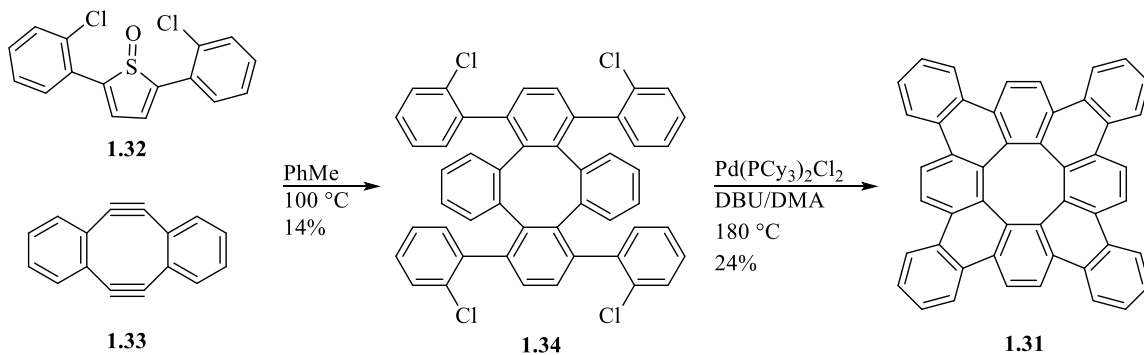
indefinitely stable. The instability of [8]circulene (**1.30**), predicted to have a saddle-shaped structure with higher overall strain than [7]circulene, can also be understood in the context of Clar's rule, Figure 1-22.



**Figure 1-22: Clar's rule and [8]circulene**

When drawing a resonance form maximizing the number of aromatic sextets for [8]circulene, we are left with 4 isolated alkenes that could be rationalized as a source of reactivity and, hence, instability for the compound. However, fusing additional benzene rings to these isolated alkenes, giving tetrabenzo[8]circulene (TB[8]C, **1.31**), would be expected to increase the molecule's stability. In 2013 our group became one of the first to report this molecule; Dr. Rob Miller's successful synthesis of tetrabenzo[8]circulene is shown in Scheme 1-23.<sup>49</sup>

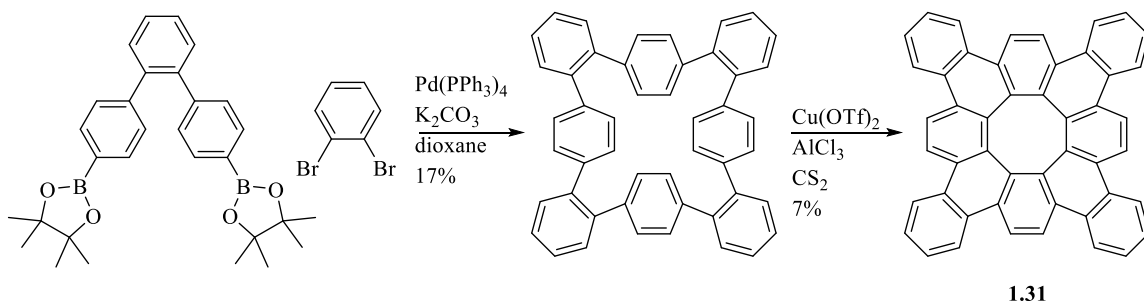




**Scheme 1-23: Synthesis of tetrabenzo[8]circulene using palladium-catalyzed arylation**

This strategy hinged on a double Diels-Alder reaction between dibenzocyclooctadiene (**1.33**) and a 2,5-diarylthiophene oxide diene (**1.32**) to construct the required framework. The product of this Diels-Alder reaction (**1.34**) was notable for its proton NMR spectrum which contained multiple broad peaks—in theory due to the presence of atropisomers caused by hindered rotation of the aryl substituents. Attempts to sharpen the peaks by heating were not successful. Despite the complex NMR spectrum, this compound was successfully converted to tetrabenzo[8]circulene in 24% yield using palladium-catalyzed arylation at an elevated temperature (70% yield per coupling reaction).

Concurrent with publication of these results, Suzuki et al. published a different approach to tetrabenzo[8]circulene that utilized an oxidative cyclodehydrogenation (Scholl) reaction to construct the COT core, shown in Scheme 1-24.<sup>50</sup>

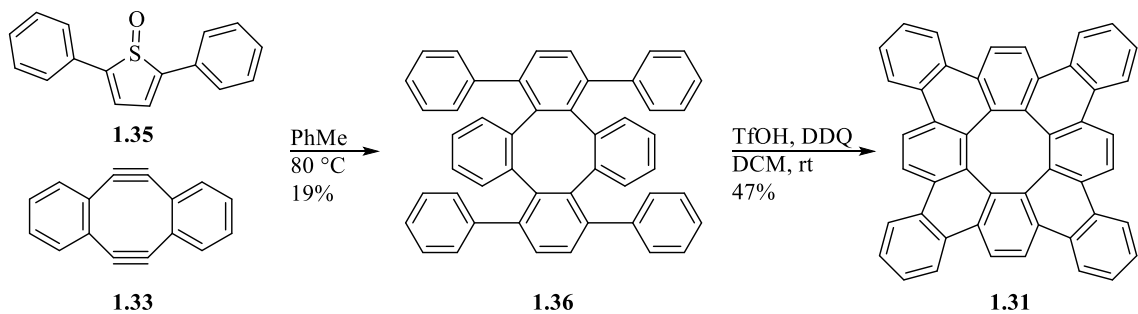


**Scheme 1-24: Synthesis of TB[8]C by Suzuki**

This approach, however, only afforded TB[8]C in a 7% yield from the Scholl reaction with the yield loss being attributed to intermolecular oxidation resulting in dimerization. Installation of methyl groups onto the parent boronic ester compound increased the effectiveness of the Scholl reaction, allowing the preparation of octamethyl-TB[8]C in 35% yield. What is remarkable about this method is the use of oxidative cyclodehydrogenation to form a contorted COT core. This type of transformation had historically been used for the construction of 6-membered rings to form planar PAH's and its ability to form other ring sizes that impart curvature to a molecule was not fully realized until this time period in the early 2010's. In fact, in 2013, Scott reported the synthesis of a warped nanographene that was prepared using a triflic acid and DDQ Scholl strategy to create five new 7-membered rings in one reaction!<sup>51</sup>

In 2015, encouraged by others' success at using the Scholl reaction to form contorted aromatics, our group published an improved synthesis of TB[8]C using this reaction (Scheme 1-25).<sup>52</sup> Of special note is that this strategy both improved the yield of the final product (yield ranges for the Scholl reaction were from 47-72% depending on

substituents) and it allowed for the synthesis of several different derivatives of TB[8]C depending on the functionalization of the aryl rings on thiophene oxide diene **1.35**.<sup>53</sup>

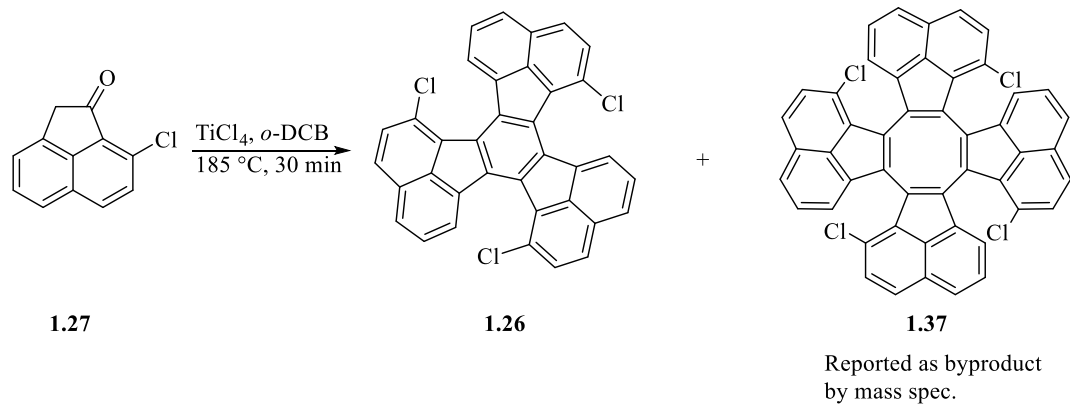


**Scheme 1-25: Improved TB[8]C synthesis using Scholl reaction**

The strategies for the synthesis of contorted aromatics outlined in the sections so far, from FVP to palladium-catalyzed arylation to Scholl oxidative cyclodehydrogenation, set the stage for the main body of work in this dissertation. Before that, however, one facet of the synthesis of circumtrindene deserves a second look.

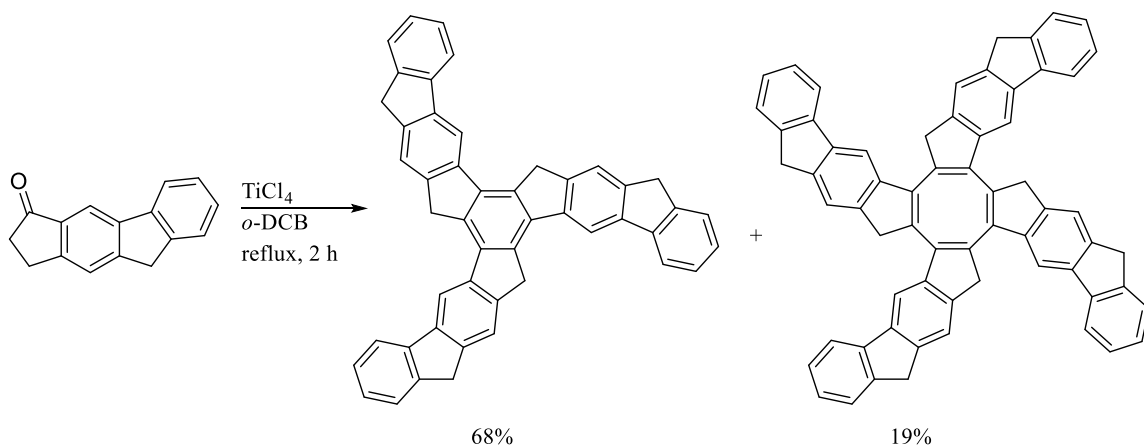
#### 1.4 Cyclotetramers from Aldol Cyclotrimerizations of Aromatic Ketones

The key step in the construction of the carbon framework for the synthesis of circumtrindene reported in 2000 by Ansems and Scott was a head-to-tail aldol cyclotrimerization. In the footnote section of that paper the authors reported detection of the cyclotetramer product by mass spectrometry. That expected product (**1.37**) is pictured in Scheme 1-26.<sup>41</sup>



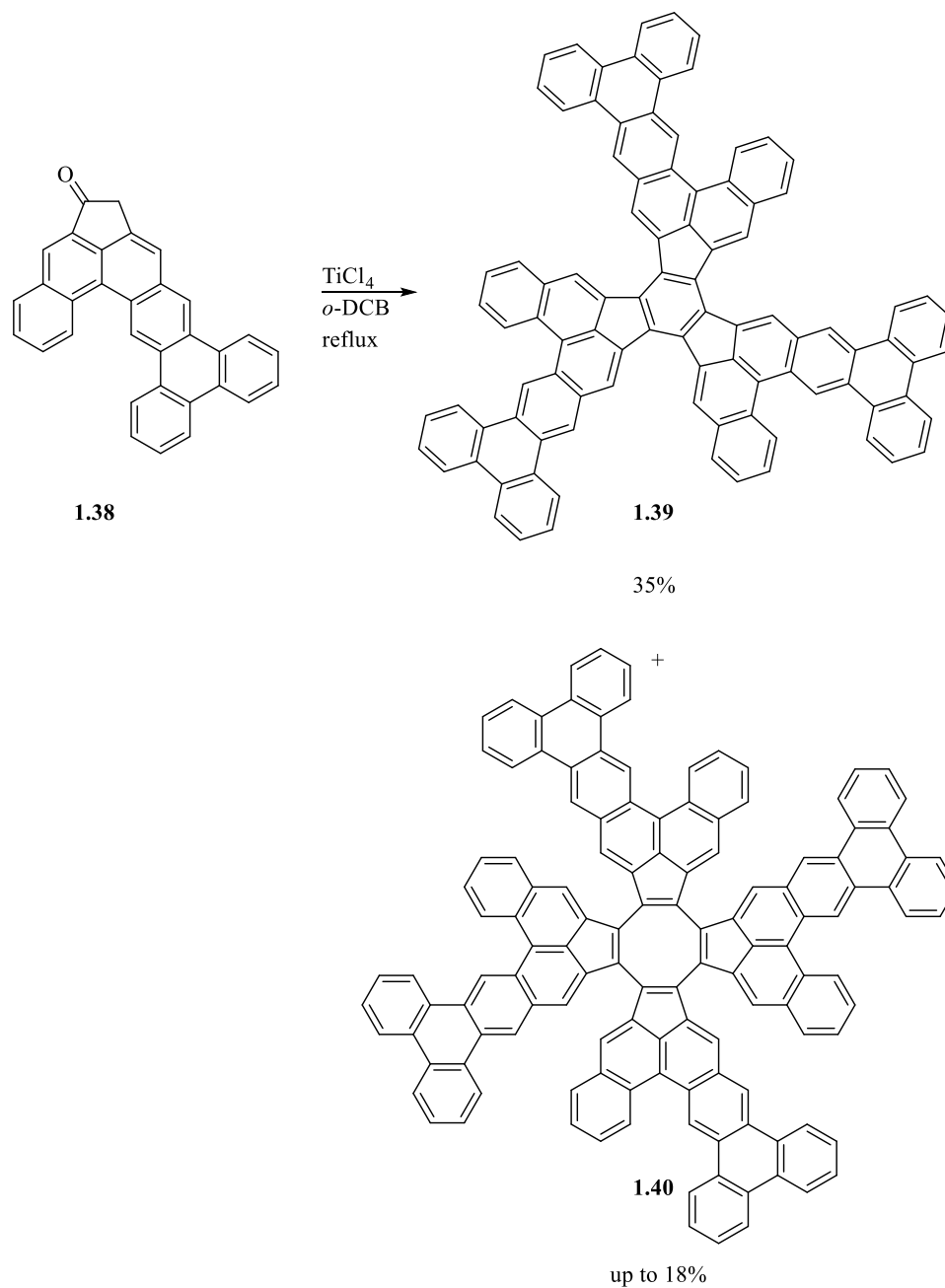
**Scheme 1-26: Tetrameric byproduct from aldol cyclotrimerization**

At the time, this cyclotetramer was considered an undesired byproduct and was not investigated further. Additionally, though never published, Ansems reported several aldol cyclization reactions where the cyclotetramer was the only major isolable product.<sup>54</sup> The nuisance of the cyclotetramer to the Scott group became apparent when they reported a comprehensive optimization of the aldol reaction to limit completely the formation of the cyclotetramer, enabling the preparation of trimers such as decacyclene in high yields using Brønsted acid conditions.<sup>55</sup> It was not until 2005 that the Pei group purified and fully characterized a cyclotetramer minor product during their synthesis of truxene derivatives from the aldol cyclotrimerization of indanones shown in Scheme 1-27. At the time of its isolation this tetramer was the largest fully conjugated COT derivative.<sup>56</sup>



**Scheme 1-27: Isolation of a cyclotetramer from aldol cyclization**

Relatively recently in 2015 the Amsharov group also isolated a pure cyclotetramer product containing a COT core during the synthesis of carbon nanotubes.<sup>57</sup> Several products could be detected by mass spectrometry in the crude reaction mixture obtained by the aldol cyclization of an extended acenaphthenone (**1.38**, Scheme 1-28)—these include not only the major trimer product **1.39** but also the higher homologues: tetramer **1.40**, pentamer, and hexamer. It was further found that the yield of the tetramer could be maximized by increasing the reaction temperature (up to 18% yield on small scales). The utility of these compounds, including the higher homologues produced in the aldol cyclization, became clear as Amsharov demonstrated that they are effective precursors to single-walled carbon nanotubes (SWCNT); in fact, pure SWCNTs were successfully synthesized and purified using the trimer and tetramer as precursors. Progress toward efficient syntheses of SWCNTs from the pentamer and hexamer were also reported, though the extremely low volatility of these precursors presented a formidable challenge.



**Scheme 1-28: Aldol cyclization products used for SWCNT synthesis**

Aiming to expand on the dearth of research concerning these long-ignored cyclic tetramers, our group set off on an ambitious project to use them in the synthesis of a fullerene fragment containing a COT core. The difficulties of adding strain or contortion to a PAH

through synthetic transformations has already been established; however, these cyclotetramers are an attractive starting point for the synthesis of a COT core contorted aromatic as they come with the central 8-membered ring built in. The efforts toward this goal and other assorted pursuits of contorted aromatics are detailed in chapter 2.

## CHAPTER 2: THE CYCLOTETRAMERIZATION OF ACENAPHTHENONES AND SYNTHETIC EFFORTS TOWARD CONTORTED AROMATICS

### 2.1 Progress toward a C<sub>240</sub> Fullerene Fragment

#### 2.1.1 Synthesis of Tridecacyclene

One of the continued interests of the Whalley group has been the synthesis of contorted polycyclic aromatic hydrocarbons, particularly those containing cyclooctatetraene (COT) cores. My studies in this field began in collaboration with Dr. Dan Sumy, working to synthesize a C<sub>240</sub> fullerene fragment **2.1**. Figure 2-1 depicts an image of the fragment highlighted within the fullerene.

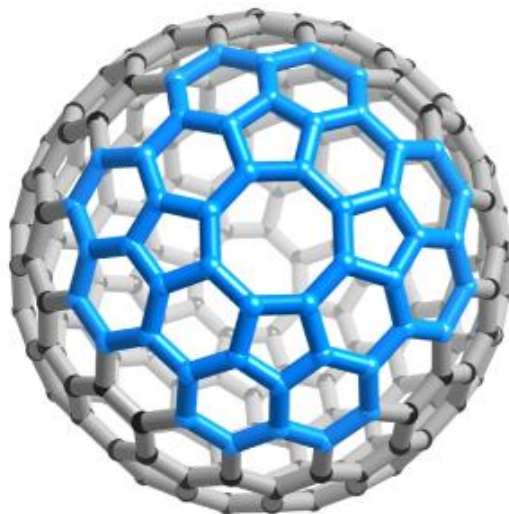
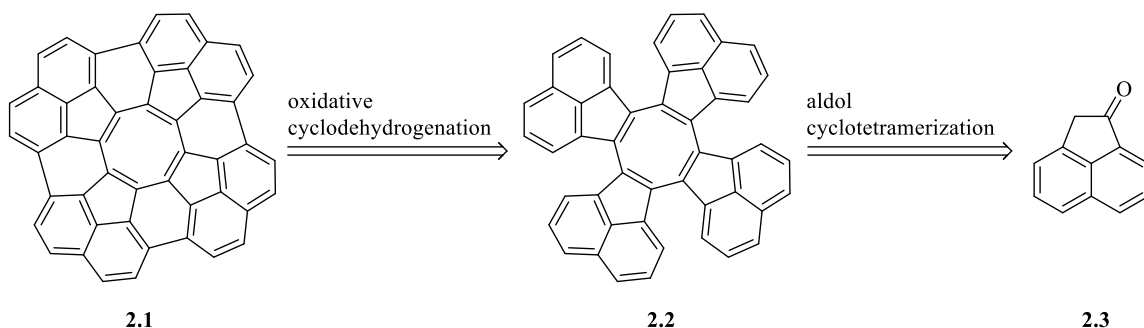


Figure 2-1: Overlay of targeted buckybowl onto C<sub>240</sub> fullerene

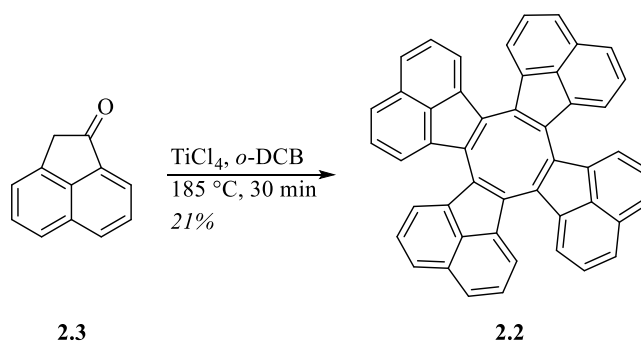
One strategy envisioned to form **2.1** was through oxidative cyclodehydrogenation via a Scholl reaction on the cyclic tetramer of acenaphthenone (**2.2**, Scheme 2-2).





**Scheme 2-2: Retrosynthetic analysis of buckybowl 2.1**

Acenaphthenone (**2.3**), the required monomeric unit provided by Dr. Sumy by means of acenaphthylene oxidation, was subjected to the aldol conditions used by the Scott group to form cyclotrimer **1.26** (Scheme 2-3). Surprisingly, yet fortunately for us, this reaction produced the desired cyclotetramer **2.2** as the major product in 21% yield with minimal evidence of decacyclene (the cyclotrimer) formation. This was in accordance with the dissertation work of Dr. Ronald Ansems, which suggested this was not such an anomalous result—for several substrates he also observed the cyclotetramer as the major or only isolable product.<sup>54</sup> The reason for such wildly different outcomes in the aldol reaction of differing monomeric units is still unclear but will be explored in a later section of this chapter.



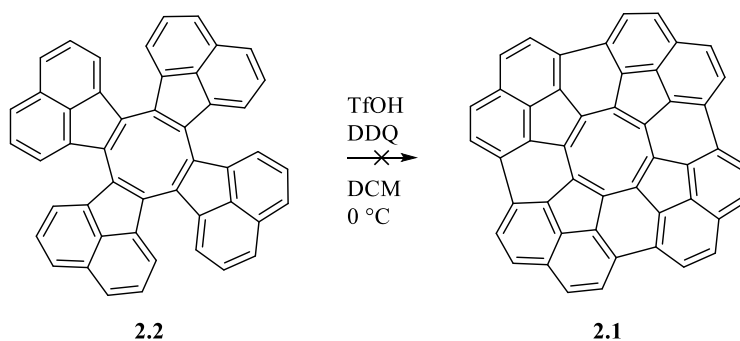
**Scheme 2-3: Synthesis of tridecacyclene**

This cyclotetramer, in addition to being the desired hopeful precursor to fullerene fragment **2.1**, was a previously unreported molecule. It was named tridecacyclene (TDC) by our group for its thirteen rings and, because of its interesting shape and ease of synthesis, its properties were investigated by Dr. Sumy.<sup>58</sup> It showed binding to C<sub>60</sub> in the solid-state crystal structure and could be reduced to both a monoanionic and dianionic species with elemental potassium. Interestingly, the dianion, despite its cyclooctatetraene core having the correct electron count for aromaticity, did not display a planar structure because of steric interactions.<sup>59</sup>

### 2.1.2 Attempted Scholl Reactions of Tridecacyclene

Tridecacyclene was then subjected to a variety of Scholl conditions. Our major efforts focused on a relatively mild room temperature reaction with triflic acid and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).<sup>60</sup> Despite combined efforts with Dr. Sumy, no fullerene fragment product was ever observed, nor was there any indication such a reaction had taken place. In most cases the starting material was recovered unreacted. In fact, one of the only transformations found to have taken place under these conditions was

the multiple chlorination of tridecacyclene using aluminum chloride in carbon disulfide, as determined by LCMS. Additionally, circumtrindene was even detected as a product from these reactions! The trace amount of decacyclene present in certain samples of tridecacyclene underwent oxidative cyclodehydrogenation effectively enough to be detected by proton NMR.

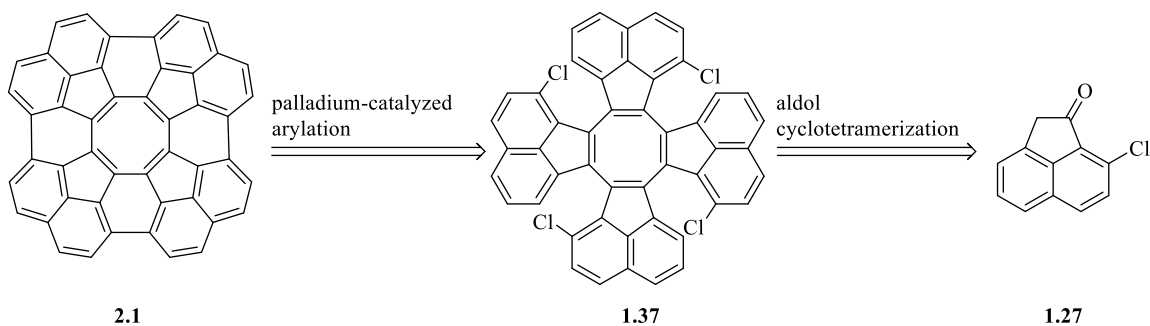


**Scheme 2-4: Attempted Scholl reaction of tridecacyclene**

### 2.1.3 Synthesis of Chlorinated Tridecacyclene and Initial Arylation Attempts

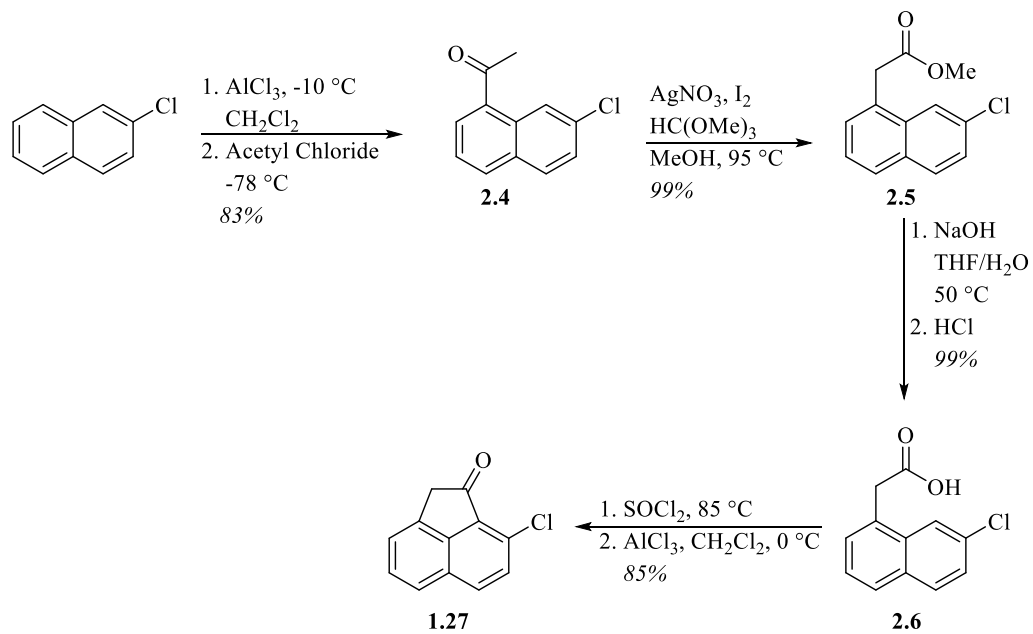
Thus, an alternative strategy was devised, this time aiming to take advantage of palladium-catalyzed arylation chemistry on halogenated aromatics that had already been employed by our group in the synthesis of tetrabenzoo[8]circulene.<sup>49</sup>

As previously mentioned, the tetrachlorinated-TDC derivative **1.37** was already reported to be a byproduct observed in the cyclotrimerization reaction of 8-chloroacenaphthenone (**1.27**) performed by Ansems and Scott in the rational synthesis of circumtrindene.<sup>41</sup> Our aim was to prepare, isolate, and characterize this cyclotetramer and attempt the key bond forming arylation reaction (Scheme 2-5).



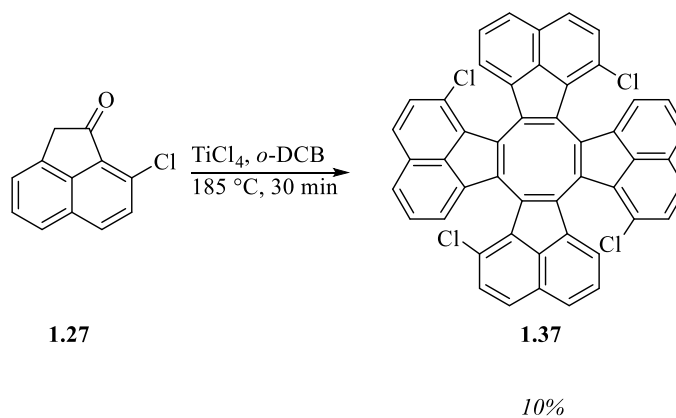
**Scheme 2-5: Revised retrosynthetic analysis of buckyball**

These efforts first required the preparation of 8-chloroacenaphthenone (**1.27**) starting from 2-chloronaphthalene (Scheme 2-6). Treatment of 2-chloronaphthalene with acetyl chloride under Friedel-Crafts acylation conditions gave two products; the major, desired isomer **2.4** was purified by recrystallization and isolated in 80% yield.<sup>41</sup> To circumvent the need to use toxic thallium nitrate as in the reported conditions, a silver nitrate/iodine oxidation with trimethyl orthoformate was employed with great success, giving the desired acetic ester **2.5** in quantitative yield with no purification required.<sup>61</sup> Saponification of the ester, selected over the previously reported acidic hydrolysis, proceeded cleanly to give the free acid **2.6** which, if needed, could be purified by simple trituration with dichloromethane. The acid was then subjected to a one-pot acid chloride formation/intramolecular Friedel-Crafts acylation sequence to give the desired chlorinated acenaphthenone **1.27** in good yields.



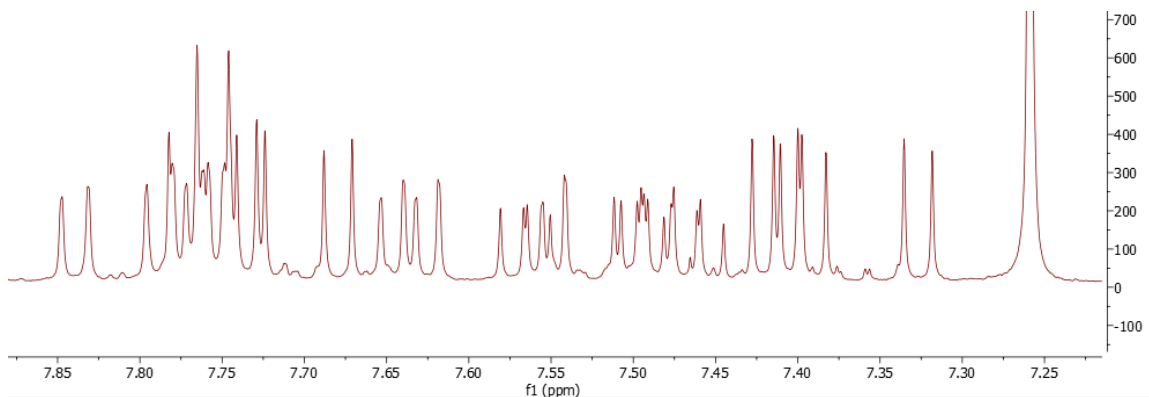
**Scheme 2-6: Synthesis of 8-chloroacenaphthenone**

As previously reported by Scott's group, cyclotetramer **1.37** was indeed a product of the titanium-mediated aldol cyclization reaction.



**Scheme 2-7: Low-yielding aldol cyclotetramerization**

**1.37** could be isolated chromatographically in a low 10% yield from the reaction mixture (Scheme 2-7). Despite mass spectrometry data indicating the success of this purification, the proton NMR spectrum obtained was not interpretable given the expected symmetry of the molecule.



**Figure 2-8: Complex proton NMR spectrum of cyclotetramer 1.37**

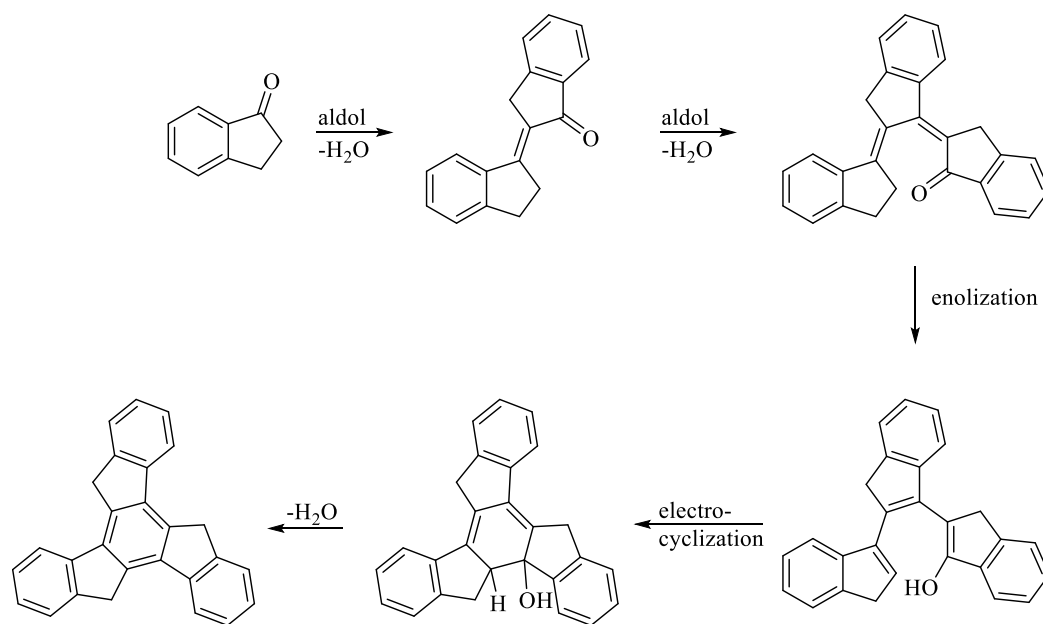
One possibility is that we had obtained the cyclotetramer as a mixture of regioisomers or conformational isomers which could not interconvert. One piece of evidence supporting this, though not definitive, came upon repeated purifications of the sample—after multiple successive column chromatography runs, the proton NMR, while still very messy, had noticeably simplified (Figure 2-8). Interestingly, the total hydrogen count in the aromatic region of this spectrum is 20, which is the total number of hydrogens in a single molecule of **1.37**—this could be consistent with a number of possible outcomes: regioisomerically-pure **1.37** that, for an unknown reason, lacks any symmetry resulting in a unique signal for every hydrogen, a mixture of conformational isomers that could have differing symmetries, or even a mixture of regioisomers. Confident that we had isolated a cyclotetramer product

but wary due to its spectral data, we felt hamstrung in our investigations of this cyclotetramer and its reactivity by a lack of material to work with due to very poor yields in the aldol reaction—especially because 8-chloroacenaphthenone is significantly more expensive than its unsubstituted parent **2.3**. My attention then turned to expanding our understanding of the mechanism of the cyclotetramerization of acenaphthenones with the aim of optimizing the production of these cyclotetramers for use in the construction of contorted aromatics.

## **2.2 Exploring the Cyclotetramerization Pathways of Acenaphthenones**

### **2.2.1 Background and Motivation**

At this point some notable features of the aldol cyclization reaction should be examined; Scheme 2-9 shows the trimerization mechanism proposed by Amick and Scott using indanone as an example.<sup>55</sup> First, the reaction is thought to proceed through a series of head-to-tail aldol condensations mediated by the Lewis acid. Upon successive reaction between three or four units, enolization can occur, setting the stage for an electrocyclization reaction. Upon dehydration to reform aromaticity, the cyclotrimers and cyclotetramers are formed, depending on the length of the acyclic oligomer.

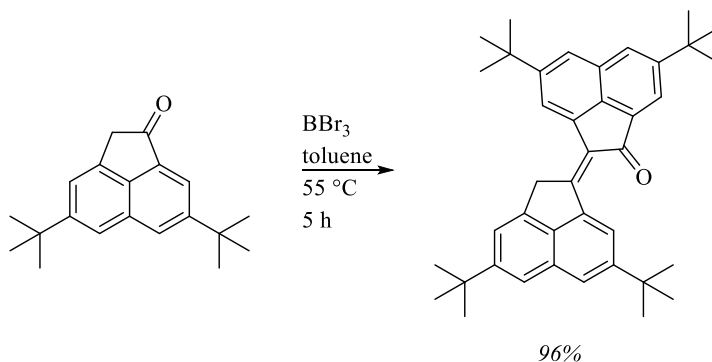


**Scheme 2-9: Proposed mechanism for aldol cyclotrimerization**

Because the aldol reaction is often conducted at elevated temperatures with no explicit control over the outcome, multiple products can result—dimers, trimers, tetramers and higher order oligomers can be detected by mass spectrometry.<sup>54</sup> However, modest selectivity had already been observed in our synthesis of TDC, where only a trace amount of cyclotrimer was detected and the cyclotetramer was the only major isolable product. Amick and Scott in 2007 published an inspirational attempt to understand, probe, and optimize this aldol reaction toward the synthesis of decacyclene.<sup>55</sup> Their efforts highlighted the complexity of this reaction and its dependence on the conditions selected. The following conclusions from that paper should be restated here for emphasis: the solubility of the dimeric species plays a critical role in the success of this reaction; Brønsted acid catalysts were found to work better than Lewis acids for the synthesis of decacyclene; and both the polarity *and* polarizability of the solvent have a dramatic effect on the reaction.

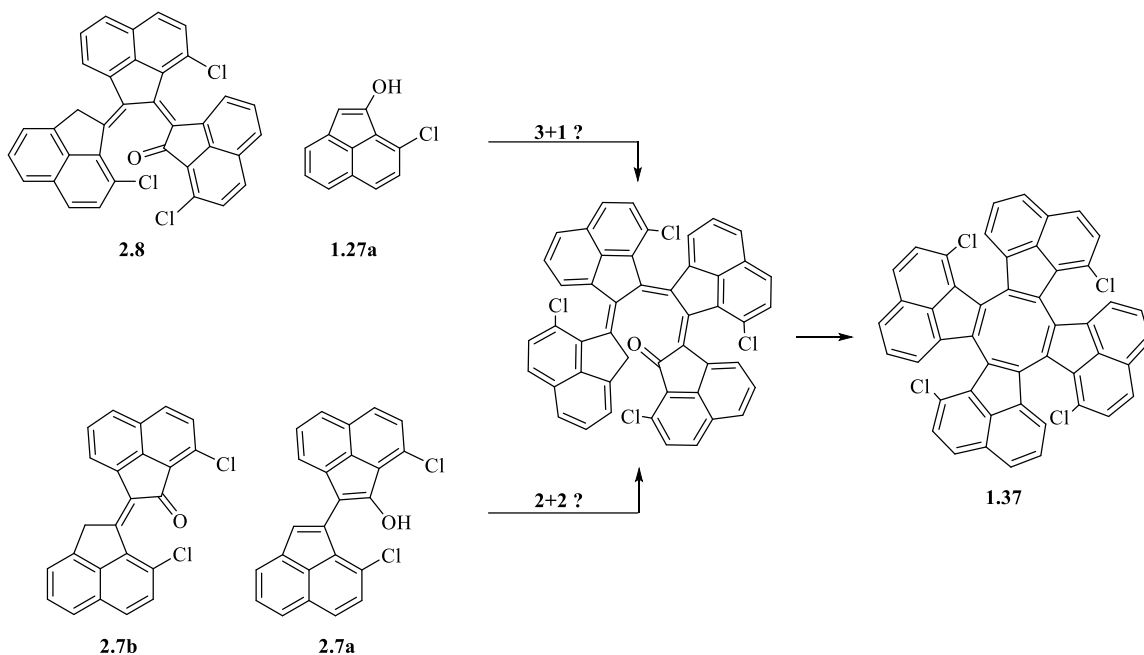


In fact, it was found that using toluene as the solvent at only mildly elevated temperatures produced exclusively the unsaturated dimer (Scheme 2-10).



**Scheme 2-10: Solvent effect investigation by Amick**

Our goal was to investigate whether the cyclotetramer could be formed as the exclusive product from Brønsted or Lewis acid-mediated aldol reactions between two of the corresponding dimers. We envisioned the possibility of the dimers, one as the nucleophilic enol form, combining to form the tetrameric products (Scheme 2-11). It had previously been thought that, because of weak overlap of the pi bonds in enol **2.7a**, it could not function as a nucleophile at the required  $\gamma$ -position, making it unlikely that the cyclotetramer forms as a result of this pathway. However, a computational chemistry-assisted mechanistic study reported in Ansems' dissertation could not explain the predominance of the cyclotetramers as major reaction products. As such, we deemed the question worth investigating.

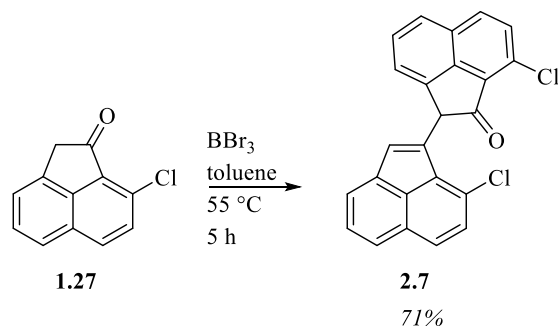


**Scheme 2-11: Possible pathways for cyclotetramer formation**

### 2.2.2 Efforts to Selectively Form Cyclotetramers

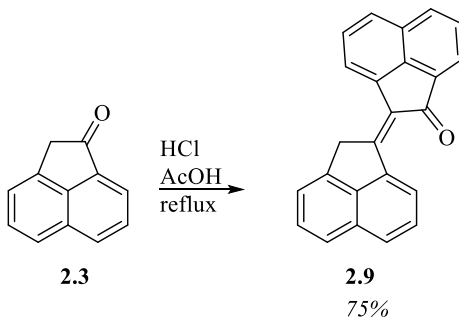
At the outset, 8-chloroacacenaphthenone was treated with excess boron tribromide in toluene for five hours, furnishing a dimeric product as the major product along with trace cyclotrimer. Interestingly, the dimer contained a  $\beta,\gamma$ -unsaturation rather than the  $\alpha,\beta$ -type seen in **2.7b**. A probable explanation for this outcome is the tremendous amount of steric strain that would be expected in the  $\alpha,\beta$ -unsaturated dimer **2.7b** (both E and Z forms) caused by the chlorine atom—it would have a steric clash with the carbonyl oxygen and the C-H fjord region bond in the Z and E dimers, respectively. The failure of certain substrates to undergo aldol cyclotrimerizations was attributed by Amick and Scott to their propensity to form these  $\beta,\gamma$ -unsaturated dimers under the reaction conditions.<sup>41, 55</sup> Here,

the mild temperature and lower polarity solvent were employed to deliberately suppress the cyclotrimerization to give the dimer in a workable yield (Scheme 2-12).



**Scheme 2-12: Selective aldol reaction to unsaturated dimer**

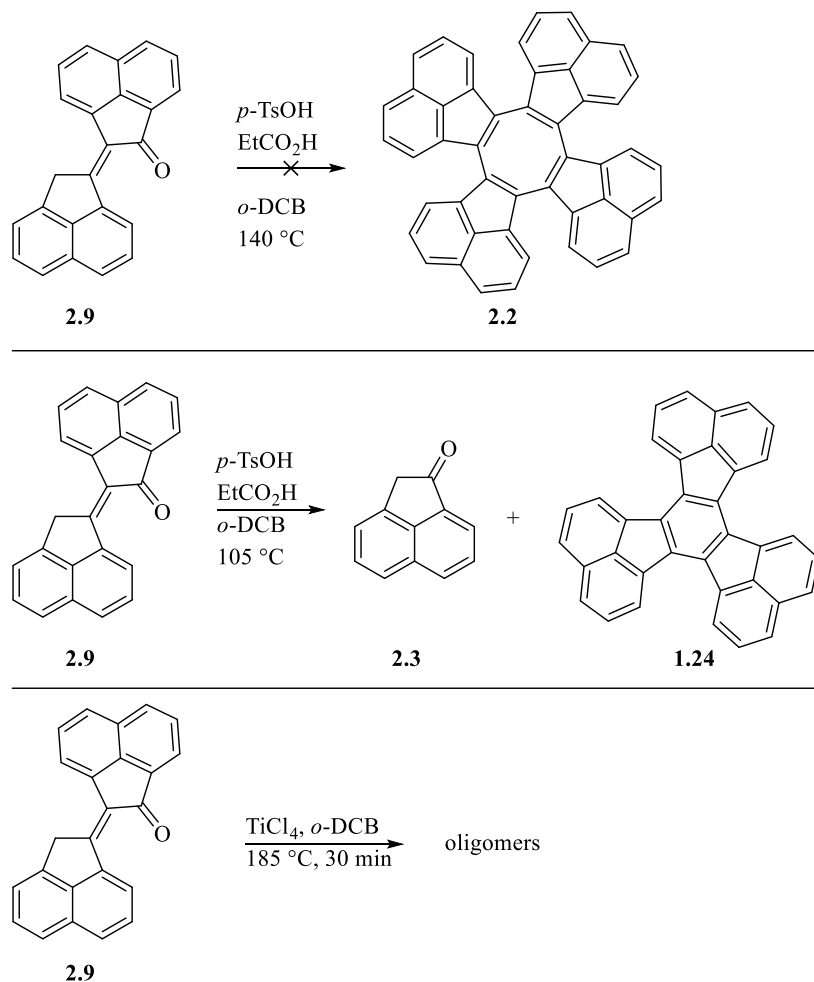
Additionally, the dimer of acenaphthenone (**2.9**, Scheme 2-13) was prepared using the effective method reported by Amick—the dimer's *extremely* low solubility causes it to precipitate from the acetic acid/water mixture and the reaction stops.



**Scheme 2-13: Dimerization of acenaphthenone**

With dimers **2.7** and **2.9** in hand, we began probing these molecules as precursors to the corresponding cyclotetramers (Scheme 2-14). No appreciable quantity of cyclotetramer could be detected from Lewis or Brønsted acid-promoted aldol reactions using either acenaphthenone dimer as the starting material. Treatment of **2.9** with Brønsted

acid conditions simply effected the retro-Aldol reaction to monomer **2.3** and subsequent cyclotrimerization to decacyclene. In trials where the dimers were subjected to titanium chloride in refluxing 1,2-dichlorobenzene, no appreciable amount of product could be isolated and the reaction appeared to simply result in oligomerization.



**Scheme 2-14: Screening dimers as tetramer precursors**

### 2.2.3 Isolation and Characterization of Novel Diones

In one case, however, a most peculiar result was observed: when subjecting chlorinated dimer **2.7** to aldol cyclotrimerization conditions similar to those developed by

Scott to optimize the synthesis of decacyclene (excess hot Brønsted acid in *o*-DCB), two high polarity products, one red, one purple, were observed by TLC and isolated both by preparative TLC and column chromatography in low yields. The NMR spectra for these compounds were unexpectedly clean, showing 10 hydrogen signals and 24 carbon signals, indicating the presence of symmetry in the molecule. Mass spectrometry showed that each compound had the expected molecular weight of the cyclotetramer with two oxygen atoms added on. In 2008 the Scott lab reported a similar high polarity product from an aldol reaction, postulating the structure as an acyclic dione based on mass spectrometry and proton NMR data after isolation by preparative TLC.<sup>62</sup> The possible mechanism of formation for such a product and its definitive characterization was not discussed at the time in that report. Also of note is that Scott's proposed dione structure would not be expected to have symmetry, yet the reported proton NMR indicated a symmetric product.

Seeking to elucidate the structures of these intriguing products, crystals of both the red and purple compounds were grown by Dr. Sumy. The correct structures were then determined by X-ray crystallography in collaboration with Dr. Aaron Finke and are shown in Figure 2-15. These highly colored products were revealed to in fact be oxidized tetrameric species. The red compound **A**) was obtained in higher yield and its structure, having its terminal acenaphthenone units facing in opposite directions, seems to be less strained than its purple counterpart **B**) whose terminal acenaphthenone subunits are aligned in the same direction and thus experience repulsion, causing the compound to distort. An observed experimental consequence of this was that the proton NMR of the purple compound contained several broad peaks that required heating to resolve.

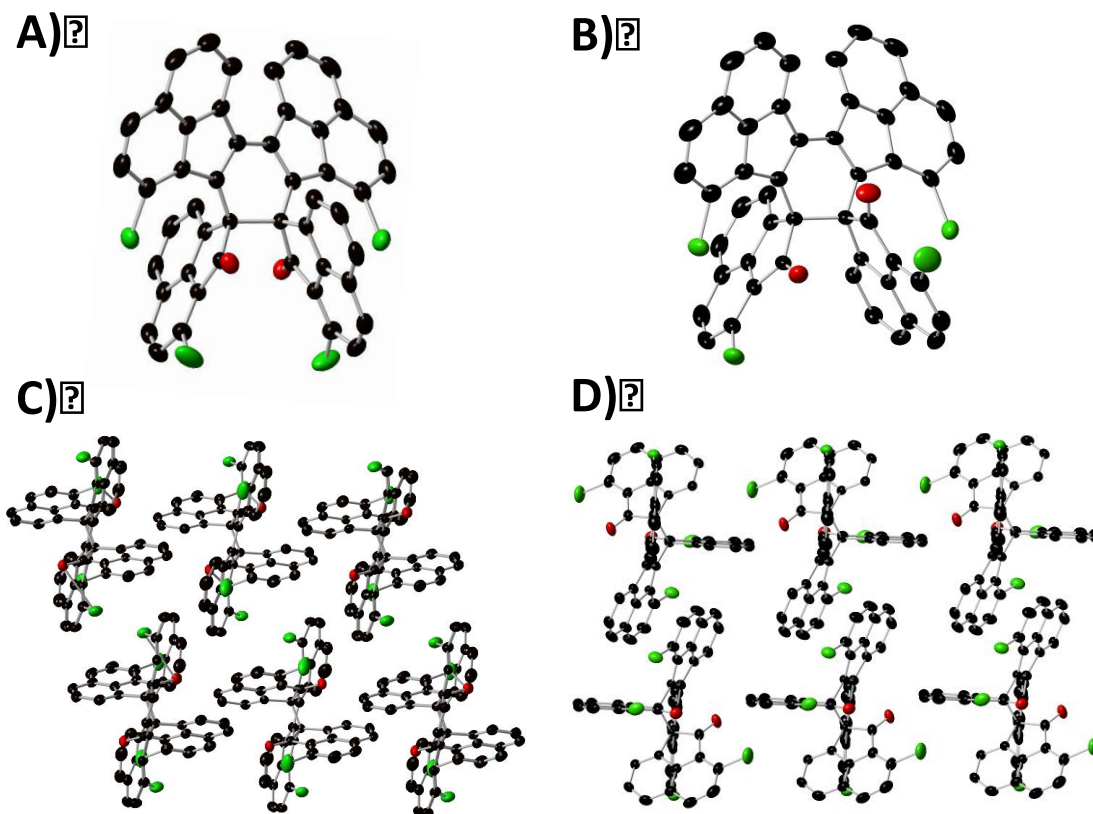
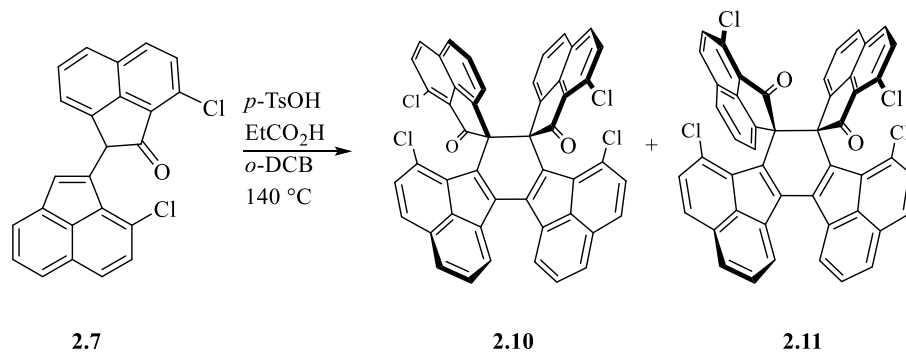


Figure 2-15: X-ray crystallography showed red [2.10, A)], purple [2.11, B)], crystal packing of red [C)], and crystal packing of purple [D)]

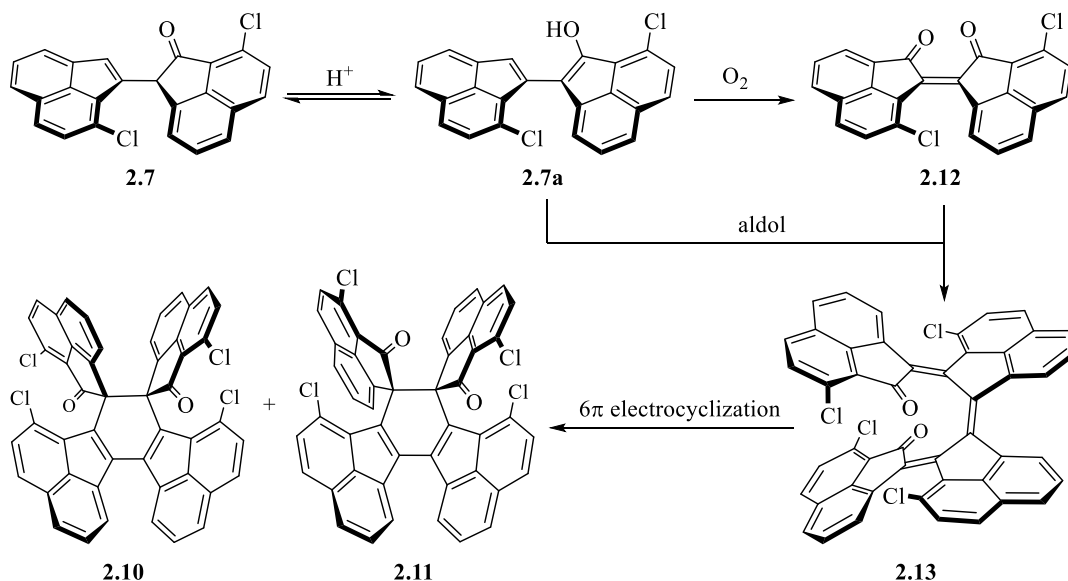
## 2.2.4 Proposed Mechanism of Dione Formation

The red (2.10) and purple (2.11) colored products are diastereomeric diones notable for containing vicinal quaternary carbon centers (Scheme 2-16).



**Scheme 2-16: Synthesis of novel, diastereomeric diones**

Moreover, the formation of these two compounds *cannot* be rationalized using a head-to-tail aldol reaction mechanism—they both contain a tail-to-tail connection between the southern acenaphthylene units. This result both surprised and puzzled us as we struggled to understand this tail-to-tail connection. After an exhaustive search of the literature, we propose the mechanism presented in Scheme 2-17.

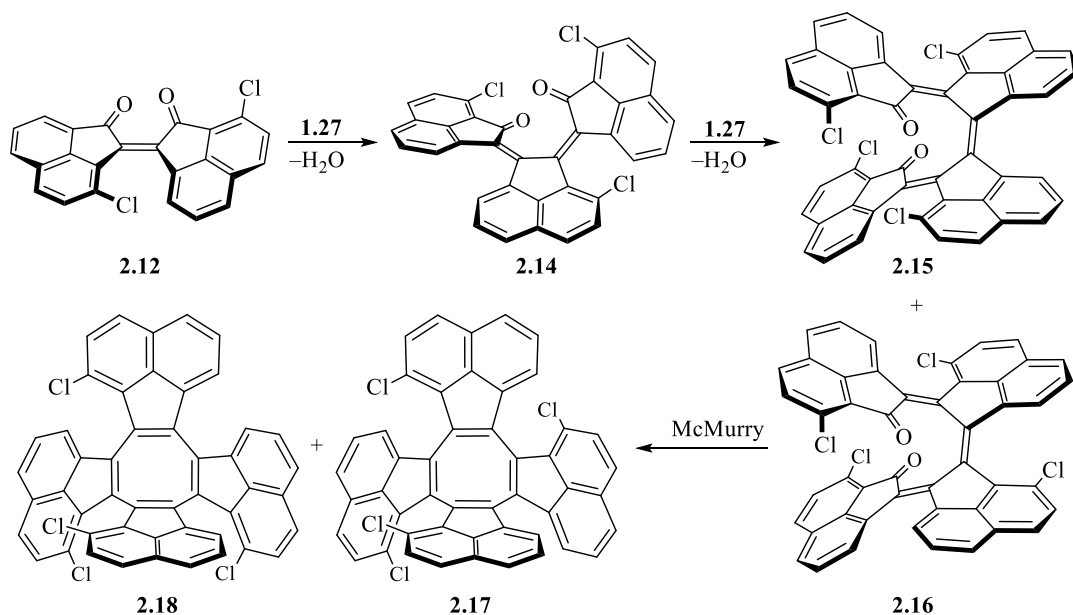


**Scheme 2-17: Proposed mechanism of dione formation**

We hypothesize that the tail-to-tail connection results after an unexpected aerobic  $\gamma$ -oxidation of the extended enol **2.7a**—this reaction has been reported to occur in the presence of peroxides but also simply under an atmosphere of oxygen.<sup>63-64</sup> Indeed, when this reaction was conducted in the absence of oxygen **2.10** and **2.11** were not detected. After this oxidation, enedione **2.12** can undergo aldol condensation at the less hindered carbonyl with the enol **2.7a** to give a helical intermediate **2.13** which furnishes the observed products after  $6\pi$  electrocyclization.

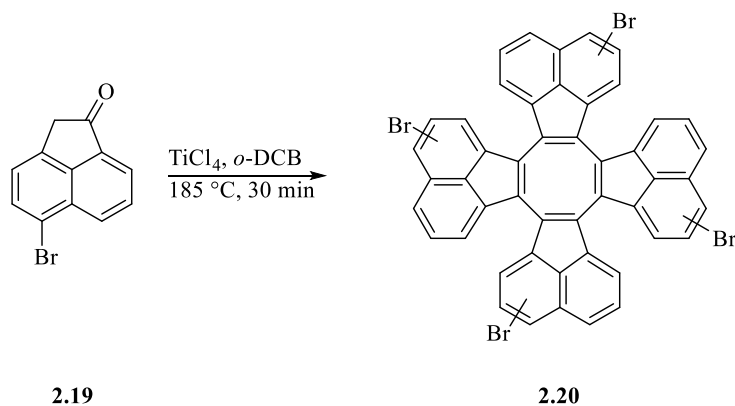
The insight gained from this result can potentially be used to explain our previously mentioned proton NMR for tetrachlorinated-TDC **1.37** (Scheme 2-18). If, after the initial aldol condensation between two 8-chloroacenaphthenone units, the dimer becomes oxidized under these conditions to form **2.12**, it could then react with another monomeric unit (again at the less hindered carbonyl group) leading to acyclic trimer **2.14**. At this point the addition of another monomer would likely be unselective, forming a mixture of products **2.15** and **2.16**. Finally, in the presence of titanium chloride, these acyclic tetramers could proceed to the corresponding cyclotetramers **2.17** and **2.18** by a titanium-mediated McMurry coupling reaction.<sup>65</sup> These proposed unsymmetrical products, if obtained as an inseparable mixture, could potentially be responsible for the intractable proton NMR data.





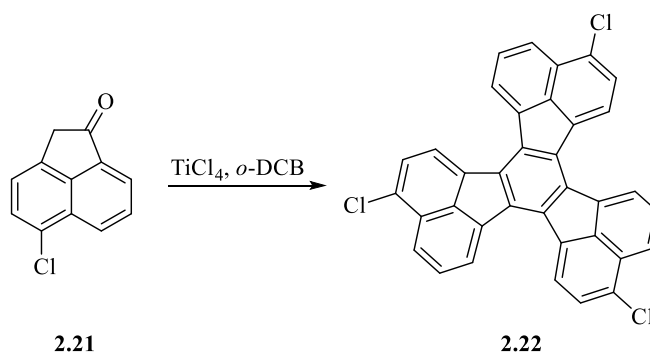
**Scheme 2-18: Proposed mechanism for cyclotetramer formation**

While these investigations were ongoing, Dr. Sumy also observed an unexpectedly complex proton NMR for the cyclotetramer **2.20** (Scheme 2-19) obtained from a synthesis using titanium chloride from acenaphthenone **2.19**, providing further evidence that the cyclotetramerization does not result from a head-to-tail aldol process.



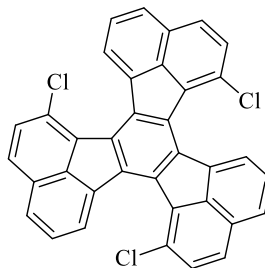
**Scheme 2-19: Tetramer from bromoacenaphthenone gave complex proton NMR**

This mechanistic proposal could also explain some of the wildly differing results between different aldol cyclotrimerizations across acenaphthenones with different substituents. Similar to Dr. Sumy's observations, the cyclotrimer (**2.22**) of acenaphthenone **2.21** isolated by Dr. Ansems (Scheme 2-20) gave an unexpectedly complex proton NMR spectrum—at least ten peaks were observed and, it could be reasonably argued, even more were obscured by solvent peaks.



**Scheme 2-20: Cyclotrimer with complex NMR reported by Ansems**

At the time this was attributed to stacking or aggregation.<sup>54</sup> Now, it seems entirely possible to conclude that the cyclotrimer obtained was in fact a mixture of regioisomers; instead of forming through the aldol-electrocyclization mechanism this could result from a pathway similar to our proposed cyclotetramerization hypothesis. Comparing this result to the clean proton NMR given by the cyclotrimer **1.26** (Figure 2-21) obtained from acenaphthenone **1.27** whose chlorine is in the “fjord region,” it may be that these “fjord” halogens hinder the McMurry coupling that would be required to obtain the non-symmetric regioisomers and instead the head-to-tail aldol process dominates.



1.26

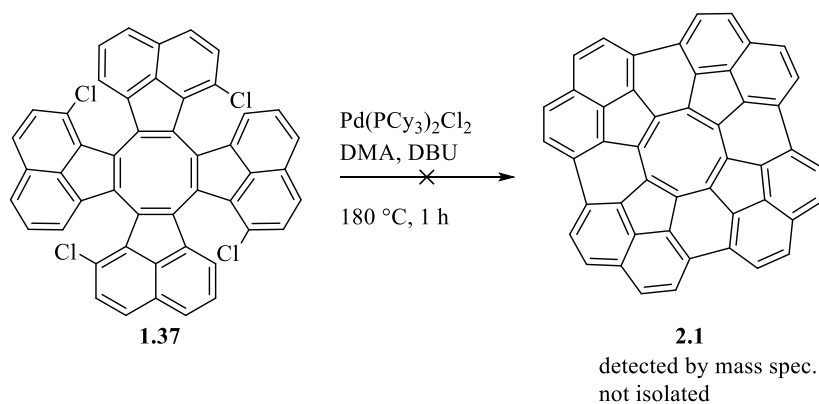
**Figure 2-21: Fjord halogens may impede McMurry coupling**

Importantly, to the best of our knowledge no cyclotetramer has been reported as a byproduct in aldol cyclization reactions conducted with Brønsted acid, supporting our mechanistic proposal that the final step is a McMurry coupling. As Amick mentioned in the published report of Brønsted acid-mediated cyclotrimerizations, one of the major advantages of that method is the cyclotrimer is obtained without contamination of cyclotetramer—often the complete chromatographic separation of these two compounds is nontrivial, at least in our experience.<sup>55</sup>

It is important to emphasize that much of this mechanistic discussion is purely speculation at this point. For one, these aldol reactions usually produce a large amount of oligomeric, high molecular weight material, sometimes making product isolation difficult. Another potential issue is that, since these red and purple compounds were significantly more polar than the desired cyclotrimers and tetramers, products of this type might have gone unnoticed by us and other researchers in previous trials when TLC analysis is primarily used. All the same, the structures of **2.10** and **2.11** themselves stand as a testament to how, despite the significant efforts of ours and other groups, there is much more to be discovered and understood about this class of reactions.

## 2.2.5 Final Attempts at Forming the Buckybowl and Conclusions

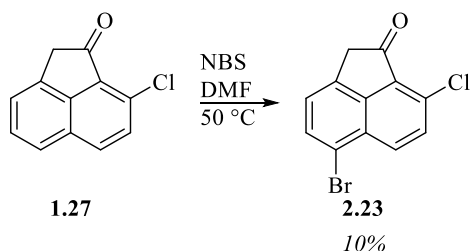
While the investigation of the tetramerization proved highly stimulating, it ultimately did not help us procure greater quantities of cyclotetramer nor did it lead to an alternative method for its synthesis. Pushing forward material by brute force, enough TDC-Cl<sub>4</sub> **1.37** was accumulated to begin a more thorough screening of the palladium-catalyzed arylation reaction. However, none of the arylation conditions employed led to product formation (Scheme 2-22).



**Scheme 2-22: Unsuccessful arylation strategy**

The reaction returned unreacted starting material when conducted at 140 °C. At an elevated temperature of 180 °C conducted in a microwave reactor, the correct molecular ion for the product was detected in the crude reaction mixture by LCMS, yet no appreciable amount of any organic product could be isolated from this effort. Dr. Sumy prepared the corresponding tridecacyclene derivative substituted with “fjord” bromine atoms rather than chlorine to attempt the same reaction. However, subjecting this compound to arylation conditions simply resulted in dehalogenation, producing tridecacyclene. One issue

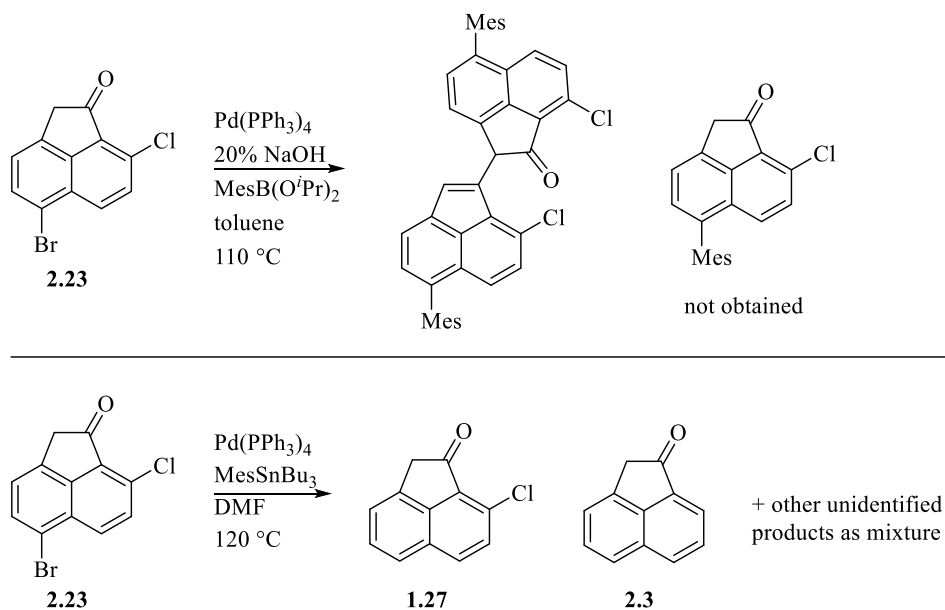
potentially responsible for the failure of this transformation is the stability of the fullerene fragment itself. The COT core, embedded in such a rigid system, might be forced to have a certain degree of planarity, leading to moderate-to-strong antiaromatic character.<sup>66</sup> This could lead to unforeseen electronic properties, a major concern being that the molecule might adopt a diradical or other potentially reactive electronic structure.<sup>67-70</sup> Inspired by Nobusue and coworkers' synthesis of a related PAH containing a COT core, we attempted to synthesize a tridecacyclene group with mesitylene substituents to help stabilize and block any potential reactive radical species formed. 8-chloroacenaphthenone was brominated in low yield using *N*-bromosuccinimide at moderately elevated temperatures (Scheme 2-23). Higher temperatures resulted in bromination of the benzylic site concomitant with the desired aromatic bromination. Running the reaction at room temperature for extended times caused bromination to occur exclusively at the benzylic site. Despite this, enough product was isolated to carry forward for test reactions.



**Scheme 2-23: Further halogenation of 8-chloroacenaphthenone**

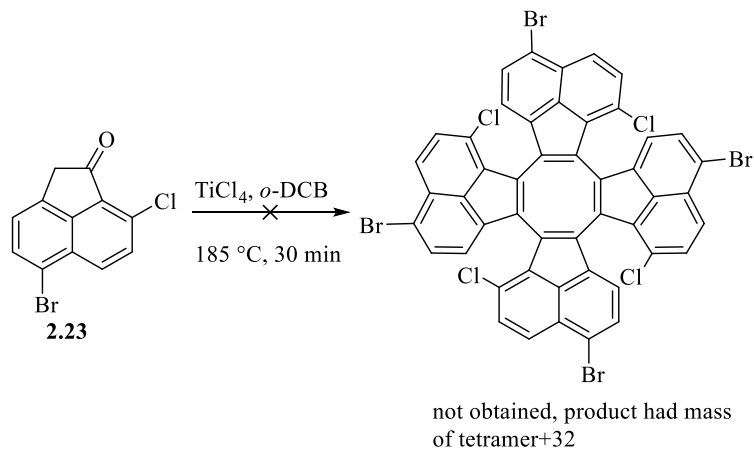
First, Suzuki coupling to install the mesityl group was attempted directly (Scheme 2-24). While the actual coupling reaction appeared successful, it was clear by proton NMR that a dimeric product had formed, likely due to the basic conditions of the Suzuki reaction. We

then tested the Stille coupling as a workaround since no base is required.<sup>71-72</sup> This reaction gave a mixture of dehalogenated products, two of which were identified as acenaphthenone and 8-chloroacenaphthenone.



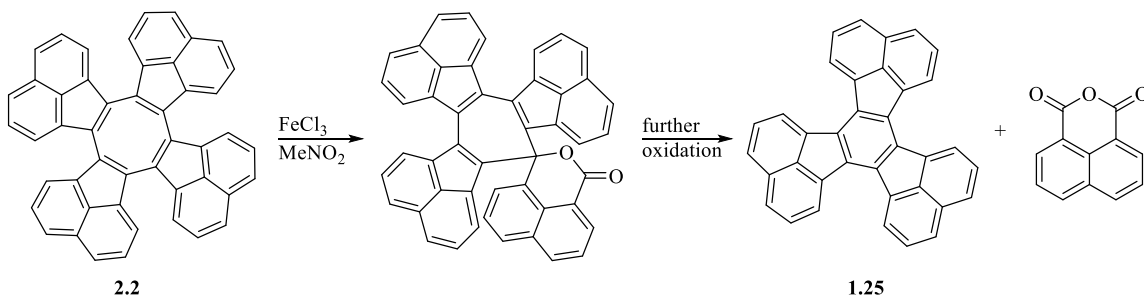
**Scheme 2-24: Attempted mesitylation**

Envisioning instead the installation of the mesityl group after cyclotetramerization, dihalogenated acenaphthenone **2.23** was heated with titanium chloride (Scheme 2-25). A single organic product was isolated and characterized, appearing to have an axis of symmetry; however, it had a mass of 32 units higher than the expected cyclotetramer. This outcome marked the conclusion of these efforts. It is possible that the product of this aldol reaction was a dione similar to the red and purple compounds discussed earlier or some other oxygenated tetrameric species.



**Scheme 2-25: Further observation of oxidized tetrameric species**

Another potential explanation for the high-mass anomalous result of this reaction is a rearrangement reaction of the cyclotetramer product mediated by oxygen; recent research has demonstrated the propensity of tridecacyclene to undergo such reactions. In an unsuccessful effort to form buckybowl **2.1** using oxidative cyclodehydrogenation the researchers instead observed a spiro lactone product, the first of its kind reported to date.<sup>73</sup> Strikingly, further oxidation of the spiro lactone resulted in ejection of a monomeric unit and 40% conversion to decacyclene (Scheme 2-26). Taken together, ours and other groups' results highlight how, despite significant advancements in the field of PAH synthesis, our knowledge concerning their reactivity is far from complete.

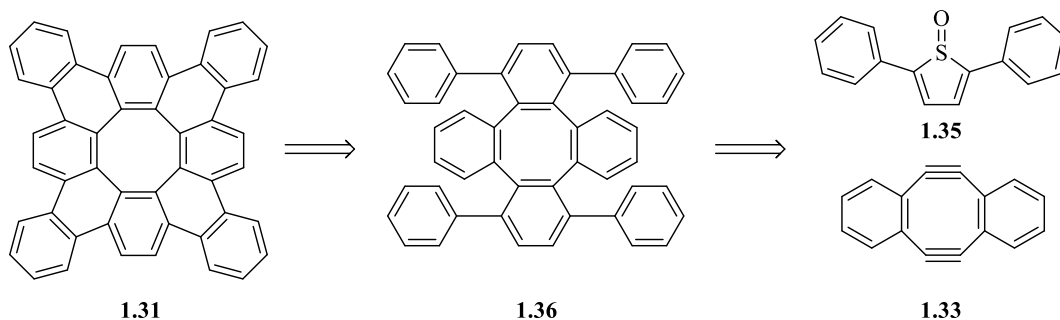


**Scheme 2-26: Conversion of tridecacycene to decacycene observed by Hiroko**

## 2.3 Asymmetric Tetrabenz[8]circulene

### 2.3.1 Synthetic Approach

Previously our group published the synthesis of tetrabenz[8]circulene using a Diels-Alder reaction between dibenzocyclooctadiyne and 2,5-diaryylthiophene oxides followed by bond closure with a Scholl reaction (Scheme 2-27).<sup>52</sup>

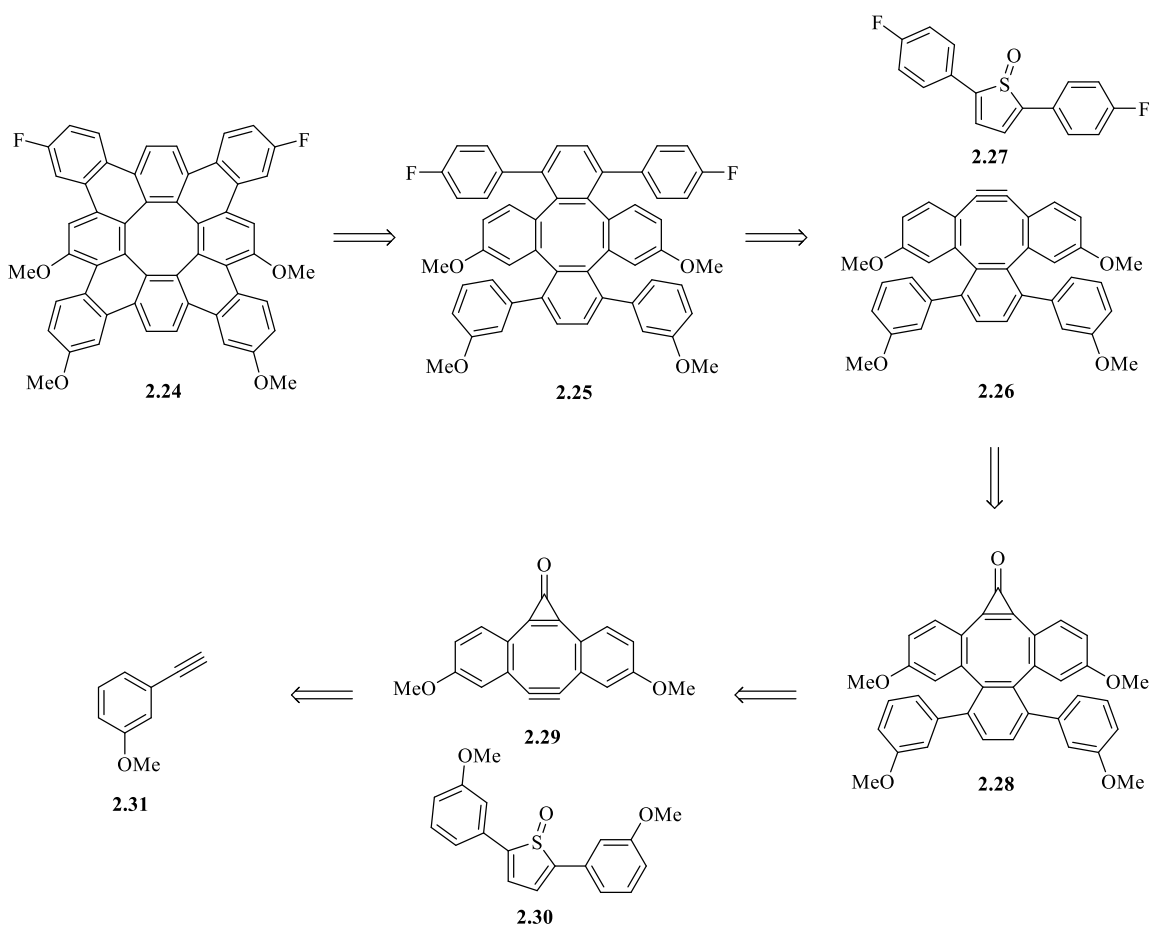


**Scheme 2-27: General retrosynthetic strategy for TB[8]C**

As part of our investigations into [8]circulene we sought ways to make an asymmetric variant, specifically where we might have electron donating groups on one half of the molecule and electron withdrawing groups on the other. This type of push-pull system



might impart interesting and potentially useful electronic properties on the molecule.<sup>74</sup> Envisioning a similar strategy to our group's previous tetrabenzo[8]circulene synthesis (Scheme 2-28), we set out to prepare known cyclooctyne **2.29** which contains a cyclopropenone group that can be unmasked photochemically to give an alkyne.<sup>75</sup> Our main goal was to prepare this compound in large quantities, perform a Diels-Alder reaction on the first alkyne **2.29**, unmask the other alkyne **2.26**,<sup>76</sup> perform a second Diels-Alder reaction, and finally close the final bonds with Scholl conditions to form **2.24**. The substituted 2,5-diphenyl thiophene oxides **2.27** and **2.30** were synthesized as part of a separate project in the group, which will be discussed in section 2.3.3.

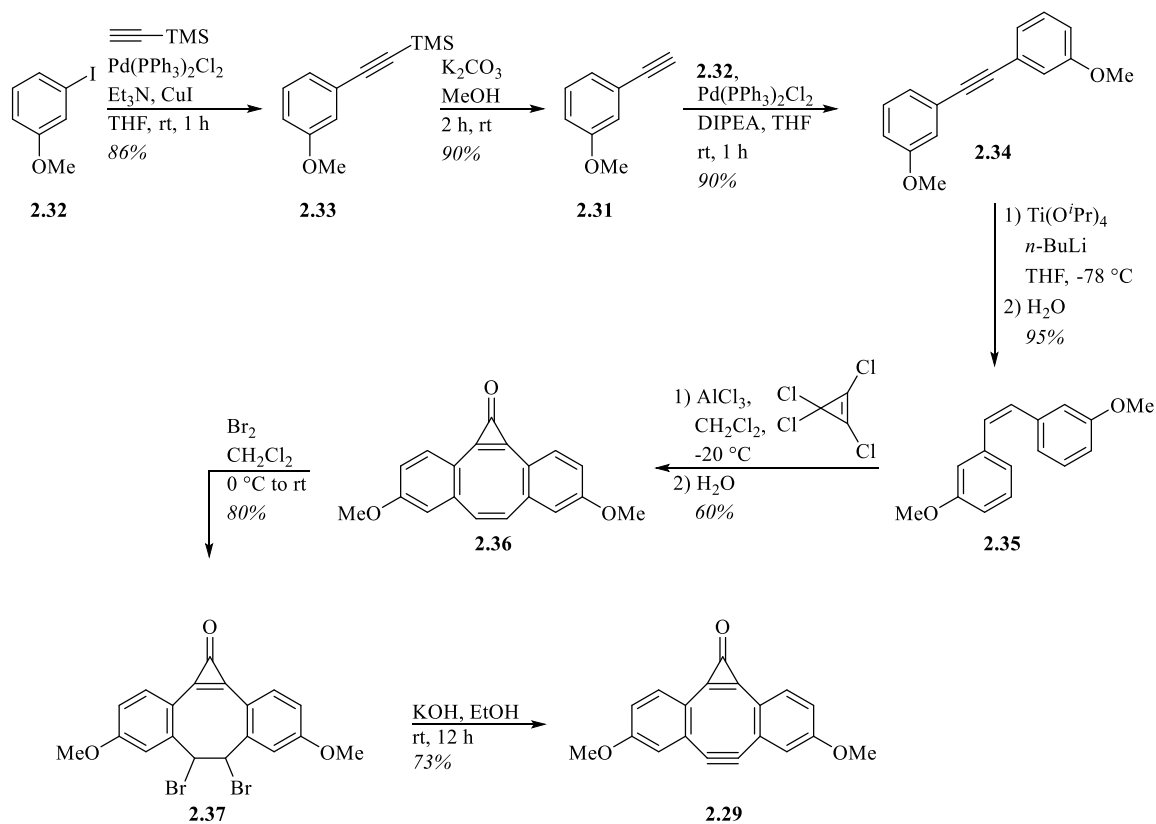


**Scheme 2-28: Asymmetric tetrabenzo[8]circulene retrosynthetic analysis**

### 2.3.2 Synthesis of “Masked Diyne” Dienophile

The reported synthesis of “masked diyne” **2.29** required some optimizations in order for us to procure sufficient quantities for testing the Diels-Alder reaction (Scheme 2-29). Beginning with 3-iodoanisole (**2.32**), Sonogashira coupling with TMS-acetylene was accomplished under significantly more mild conditions than those reported in the literature: full conversion was achieved at room temperature in 10 minutes compared to overnight heating at reflux in THF.<sup>75</sup> Deprotection with potassium carbonate in methanol furnished the terminal alkyne **2.31** which was coupled to another equivalent of 3-iodoanisole by

Sonogashira coupling. It was again found with this Sonogashira reaction that simply stirring at room temperature was enough to effect the transformation—heating the reaction for extended times is both wasteful and unnecessary when using this aryl iodide substrate. At this point reduction to the *cis*-alkene **2.35** was necessary. However, selective reduction with Lindlar catalyst and quinoline gave wildly inconsistent results, sometimes achieving full conversion and other times, inexplicably, stubbornly returning unreacted starting material regardless of catalyst loading. After helpful discussions with Dr. Madalengoitia, it was suggested that the success of the reaction might be highly sensitive to the purity of the starting material and an alternate approach would be desirable. A simple workaround was found in a titanium isopropoxide / *n*-butyllithium reduction that reproducibly gave the *cis*-alkene in high yields.<sup>77-78</sup> The stage was then set for the key Friedel-Crafts reaction with tetrachlorocyclopropene. One important procedural aspect not disclosed in all published descriptions of this method is the need for slow addition of the substrate.<sup>75</sup> As the second step involves an intramolecular cyclization to form an eight-membered ring, the reaction is highly sensitive to concentration and adding the starting material all at once gave high molecular weight insoluble material as the major product. Slow addition gave the desired product **2.36** in modest yield, though some yield is inevitably lost to the undesired regioisomer which can be detected by TLC and NMR. The conversion of the alkene of **2.36** to the desired alkyne **2.29** was achieved following the previously reported bromination/elimination sequence, though no column purification was required for either step—the products can be collected by filtration in both cases.



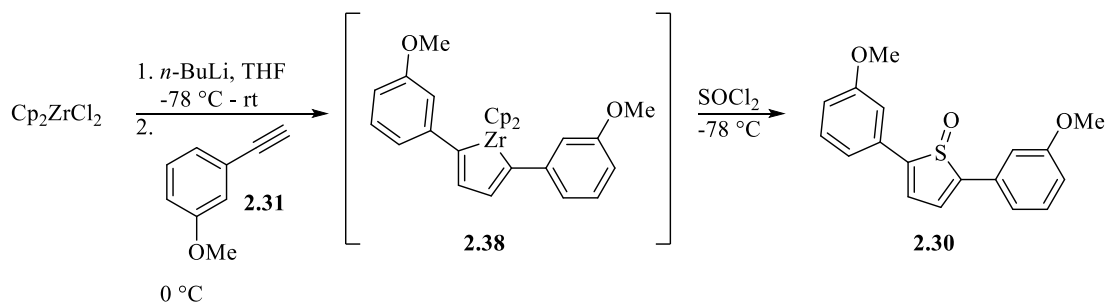
**Scheme 2-29: Synthesis of masked diyne**

### 2.3.3 Synthesis of Thiophene Oxide Dienes

With the requisite dienophile in hand, focus now shifted toward the synthesis of a suitable diene. Typically, thiophene oxides had been employed by our group for the synthesis of tetrabenzoc[8]circulene. These were synthesized by oxidation of the corresponding 2,5-diarylthiophenes using hydrogen peroxide.<sup>49</sup> This method proved problematic however, in that if left running for extended times the thiophene dioxide predominated as the major oxidized product. Additionally, for reasons that are not entirely clear, the reaction fails for certain 2,5-diarylthiophenes depending on the substitution on the aromatic rings. One of these cases is the methoxy-substituted 2,5-diphenylthiophene;

since we were interested in developing a push-pull tetrabenzo[8]circulene, we envisioned installing methoxy groups on one side of the molecule and fluorine substituents on the other—hence, access to methoxy-substituted thiophene oxides was required.

Dr. Rob Miller at the time was spearheading an effort to produce a library of thiophene oxides with varying substitution patterns on the phenyl substituents. As a collaborative group effort, we elaborated on a strategy previously developed by Tilley to synthesize a variety of thiophene oxides from the corresponding arylacetylenes.<sup>53</sup> The reaction details are outlined in Scheme 2-30, showing the synthesis of the specific methoxy-substituted thiophene oxide **2.30** desired for our push-pull system. Generation of “Cp<sub>2</sub>Zr” was accomplished using 2 equivalents of *n*-butyllithium followed by addition of the terminal acetylene to give the corresponding diarylzirconacyclopentadiene intermediate **2.38**.<sup>79-82</sup> Conversion to the thiophene oxide was then accomplished using thionyl chloride at low temperatures.



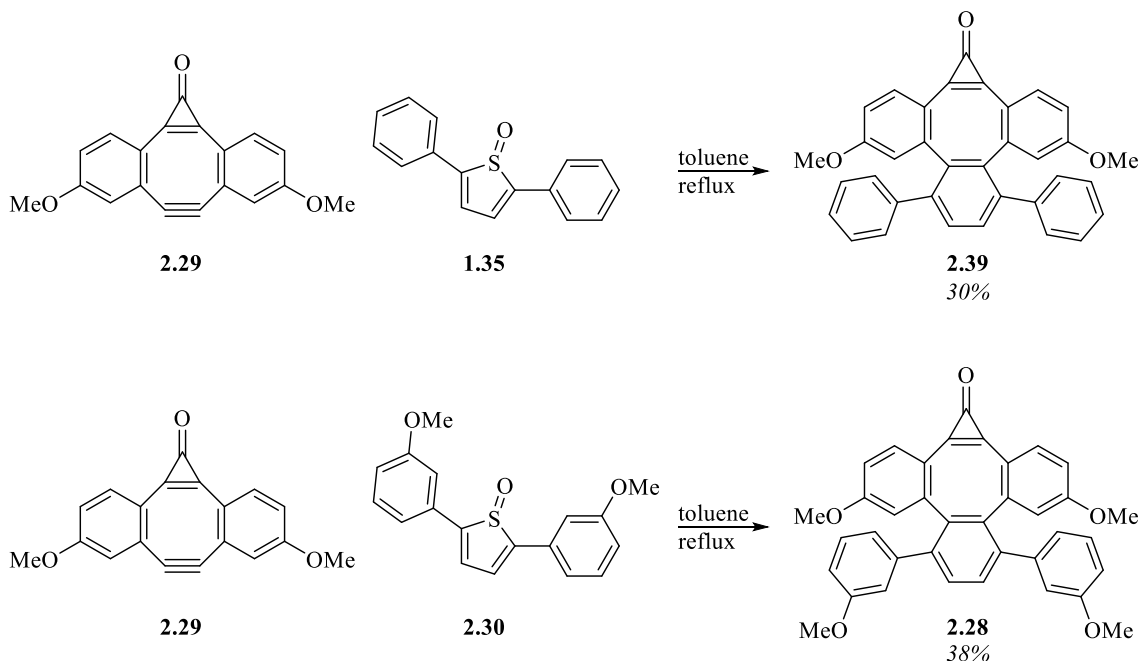
**Scheme 2-30: Strategy for the preparation of 2,5-diarylthiophene-1-oxides from arylacetylenes**

Terminal acetylenes had not been thoroughly investigated for use in this reaction because they had been reported to result in a mixture of regioisomers. We did not observe the

formation of the undesired 2,4-disubstituted thiophene oxide products, though this does not necessarily mean they did not form. The synthesis of these thiophene oxides required careful temperature control at the final step once thionyl chloride had been added. We hypothesized that cyclopentadiene present in the crude mixture from the decomposition of the zirconium species might be capable of reacting with our desired thiophene oxide products in a Diels-Alder reaction. To circumvent this, the crude reaction mixture, while still cold, was immediately purified by column chromatography. Allowing the crude reaction mixture to warm results in greatly diminished product yields. It is possible that both the 2,4- and 2,5-disubstituted regioisomers are formed in this reaction and, due to decreased steric hindrance, the 2,4-disubstituted isomer is reactive enough even at low temperatures to combine with cyclopentadiene. The occurrence of this side reaction, however, was never definitively verified.

#### **2.3.4 Key Diels-Alder Reaction and Photochemical Decarbonylation Attempts**

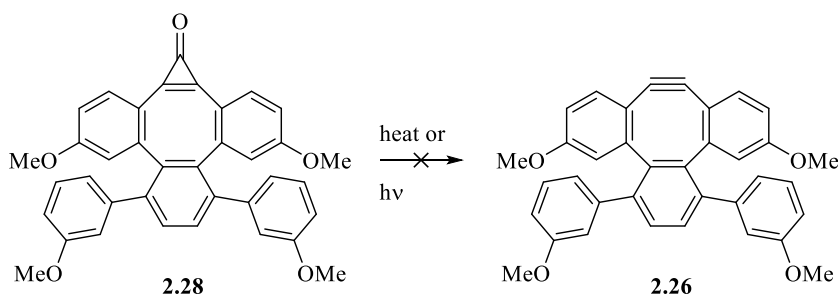
The Diels-Alder reaction between the thiophene oxides (**1.35** and **2.30**) and the masked diyne **2.29** proved successful, with the products **2.39** and **2.28** being obtained in a 30% and 38% yield, respectively (Scheme 2-31). These yields were consistent with Dr. Miller's experiments on similar systems.<sup>49, 52</sup>



**Scheme 2-31: Diels-Alder reaction success**

Interestingly, if the solvent used was not anhydrous, the product was obtained as an inseparable mixture of the title compound and its hydrate (detected by mass spectral analysis and TLC—heating the crude mixture to 200 °C under a high-vacuum was not effective at removing the water). This problem was circumvented simply by using anhydrous solvent. The products of these Diels-Alder reactions, seemingly pure by TLC and mass spectral analysis, gave complex NMR spectra, shown in the Appendix. This result was somewhat anticipated, though, given the previously observed complex spectral data from the Diels-Alder products synthesized by Dr. Rob Miller in the synthesis of tetrabenzo[8]circulene. It is likely that the products exhibit hindered rotation about the aryl substituents that may result in conformational isomers that cannot interconvert.

Several conditions were then investigated to effect the photochemical decarbonylation—none were successful. Irradiation under UV light either returned unreacted starting material or resulted in decomposition (Scheme 2-32).<sup>76, 83</sup>



**Scheme 2-32: Stubborn decarbonylation**

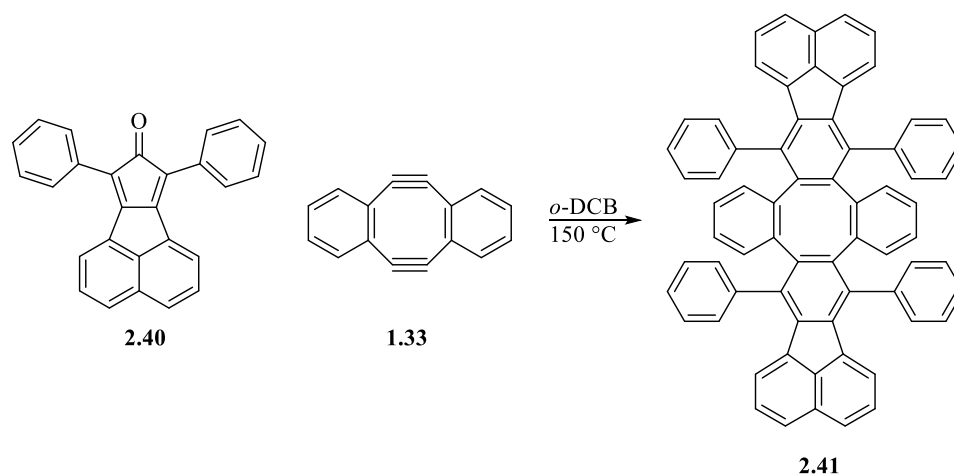
We also explored the possibility of removing the cyclopropenone under thermal conditions and performing the second Diels-Alder reaction in a one-pot process. Even at elevated temperatures, however, the cyclopropenone persisted, with all attempts leading to recovered starting material. The decarbonylation product of **2.28** was observed in LCMS analysis of the starting materials so it appears that the alkyne is a potentially stable compound. It is likely that achieving transformation required a more extensive screening of conditions. However, at this point the focus in our group had turned toward other variants of functionalized [8]circulenes and the project took a backseat to other endeavors.

#### 2.4 Synthetic Effort Toward Extended TB[8]C Derivatives

My final pursuit of a variant of [8]circulene is showed in Scheme 2-33. This molecule was pursued because of the readily available starting materials and the increased



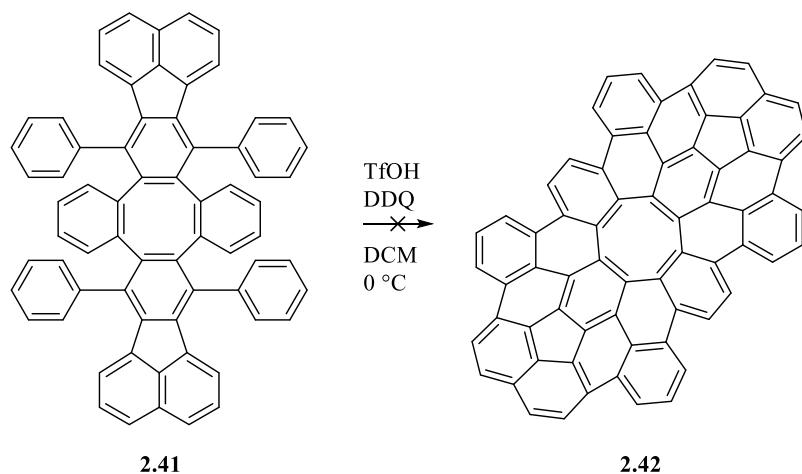
reactivity of cyclopentadienones as dienes. Starting from dibenzocyclooctadiyne, obtained from Dr. Miller, a Diels-Alder reaction between the cyclopentadienone **2.40**, obtained from the high yielding Knoevenaegel condensation between 1,3-diphenyl acetone and acenaphthoquinone,<sup>84</sup> gave the corresponding product **2.41**. Chromatographic separation of this product from leftover cyclopentadienone **2.40** was not achieved. Temperature played a key role in this transformation—at 110 °C full consumption of dibenzocyclooctadiyne was observed by TLC with no indication of product formation. Raising the temperature to 150 °C resulted in the desired reaction taking place.



**Scheme 2-33: Preparation of extended tetrabenzof[8]circulene precursor**

Interestingly, the proton NMR spectrum for **2.41** indicates a high degree of symmetry similar to tridecacyclene—both contain a COT core and it is likely that the COT core of **2.41** also adopts a tub shape that results in a simple NMR spectrum. This compound's crystal-packing structure and properties have yet to be explored but, like tridecacyclene, will surely prove a worthwhile study. We were most interested in trying to form carbon-

carbon bonds between the substituent phenyl rings and the surrounding core structure—this would result in a PAH consisting of tetrabenzo[8]circulene with corannulene units fused at each pole. Several preliminary screenings of oxidative cyclodehydrogenation reactions on this molecule, primarily focusing on the TfOH/DDQ conditions, only returned unreacted pure starting material. One obstacle thought to be at play here is the phenyl substituents. Due to steric constraints, they are not expected to be able to rotate a full 360° (this is corroborated by proton NMR data) and may even be unable to rotate into the required reactive conformation necessary to effect the bond closures at ambient temperatures. It is possible that more forcing conditions including elevated temperature might be required to form these challenging bonds. This effort was, admittedly, a side project at the time and the screening of Scholl reaction conditions was not exhaustive; it is included here in the event that future group members, also intrigued by its structure, wish to pursue it further. Again, as was the case for tridecacyclene, the relatively ease of preparation of **2.41** would facilitate the assuredly worthwhile study of its properties, even if its conversion to the “fully-closed” **2.42** cannot be achieved.



**Scheme 2-34: Attempted Scholl reaction toward extended tetrabenzo[8]circulene**

## 2.5 Conclusions and Future Work

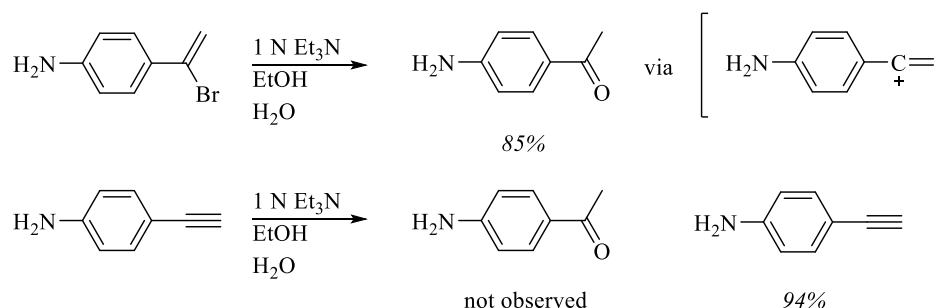
The work and ideas detailed in this chapter represent significant efforts and advancements toward the synthesis of large, contorted polycyclic aromatic hydrocarbons. While the synthesis of the desired  $\text{C}_{240}$  fullerene fragment **2.1** has not yet been achieved by our group (nor others as of this writing),<sup>73</sup> the path to that compound led us to the highly stimulating and equally perplexing cyclotrimerization and cyclotetramerization of acenaphthenones. The fact that even subtle changes to the starting acenaphthenone result in vastly different reaction mixtures is a testament to the complexity of the transformations—this work provides some mechanistic insight as to how these processes occur. Of critical importance is our definitive characterization of the novel diones **2.10** and **2.11** by X-ray crystallography, which proves that reaction pathways leading to products containing “tail-to-tail” connections are prevalent and at times competitive with the pathways leading to “head-to-tail” products as the reaction was originally designed.<sup>41</sup>

Additionally, the progress made toward an asymmetric variant of tetrabenzo[8]circulene leaves the door open for future investigations. The original synthesis of the key “masked diyne” has been streamlined, optimized, and scaled up from the published report, giving access to the starting material in large quantities. The efforts to achieve the photochemical decarbonylation were not exhaustive and it is possible that the failure was largely due to our experimental set up or equipment—our group did not have access to a “Rayonet” photoreactor at the time; most published reports of this photochemical decarbonylation indicate the use of this equipment to accomplish the transformation.<sup>83</sup> Nevertheless, this work proves that the “masked diyne” is a suitable dienophile for the key Diels-Alder reaction and, should there be a pursuit of asymmetrically functionalized [8]circulene derivatives in the future, this project would be a fitting place to continue that work. Finally, the synthesis of compound **2.42** is not an abandoned prospect. The compound’s highly interesting structure, having two corannulene units—one at each end—makes it a worthwhile target and current plans include investigating other oxidative cyclodehydrogenation conditions such as iron trichloride in nitromethane.

## CHAPTER 3: THE REACTION OF VINYL CATIONS WITH PENDENT ALKENES

### 3.1 Background and Motivation

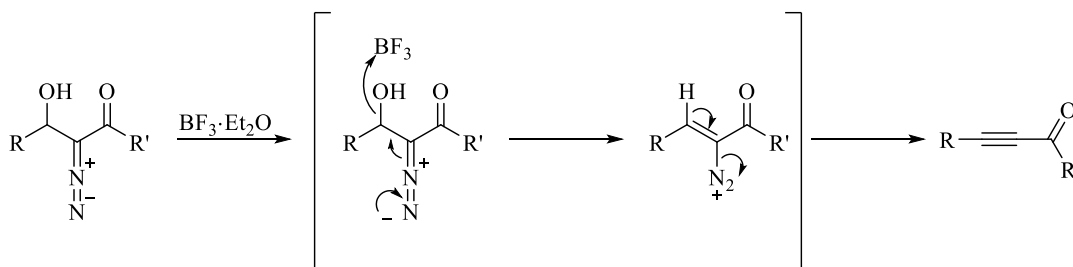
One of the major interests in the Brewer group is fundamental research concerning vinyl cations—their generation, properties, reactivity and utility. Pioneering solvolysis studies by Grob in 1964 involving substituted  $\alpha$ -bromostyrenes helped to establish the validity of vinyl cations as reaction intermediates during a period of skepticism (Scheme 3-1).<sup>85</sup>



**Scheme 3-1: Solvolysis of  $\alpha$ -bromostyrenes**

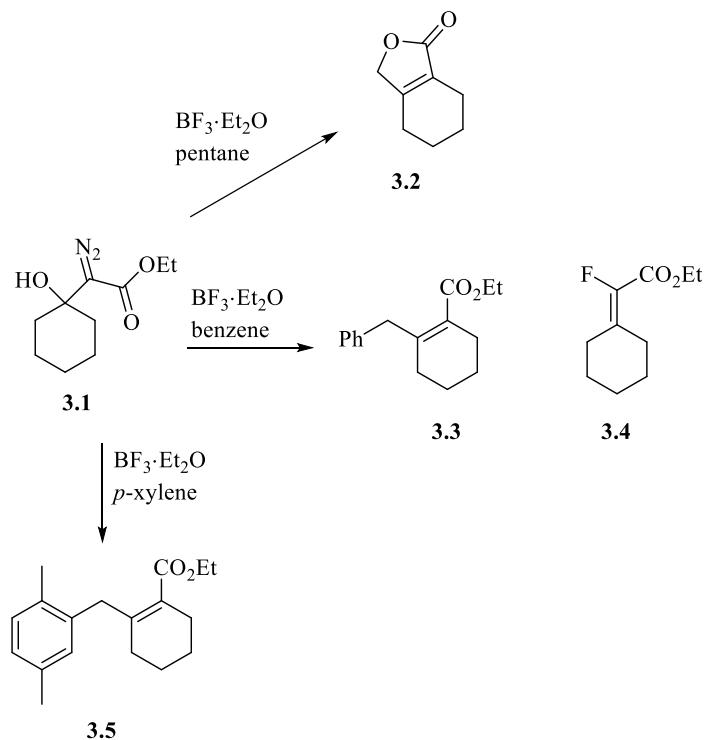
A vinyl cation is an sp-hybridized trivalent alkene carbon that prefers to adopt a linear geometry.<sup>86</sup> Vinyl cations have often been observed as intermediates in solvolysis reactions of vinyl triflates<sup>87</sup> and electrophilic addition to alkynes or allenes.<sup>88-90</sup> While the study of vinyl cations has been quite rich, their use as practical intermediates in organic synthesis is uncommon and our group is interested in harnessing these species for use in carbon-carbon bond forming reactions to build useful, complex molecular scaffolds. The work presented in this chapter was inspired principally by three previous reports.

The first of these reports described a novel and selective way to generate a destabilized vinyl cation. Specifically, in 1996 Pellicciari and Padwa reported that treating  $\beta$ -hydroxy- $\alpha$ -diazo esters with boron trifluoride etherate led to the generation and rearrangement of a destabilized vinyl cation.<sup>91-92</sup> The diazo esters were readily prepared by aldol-type addition of lithio-acyldiazomethanes to either aldehydes or ketones to give the  $\beta$ -hydroxy- $\alpha$ -diazo compounds.<sup>93</sup> It had already been observed that substrates derived from aldehydes, which contain a hydrogen beta to the carbonyl group, react with  $\text{BF}_3$  to give alkyne products by the mechanism shown in Scheme 3-2.<sup>92</sup>



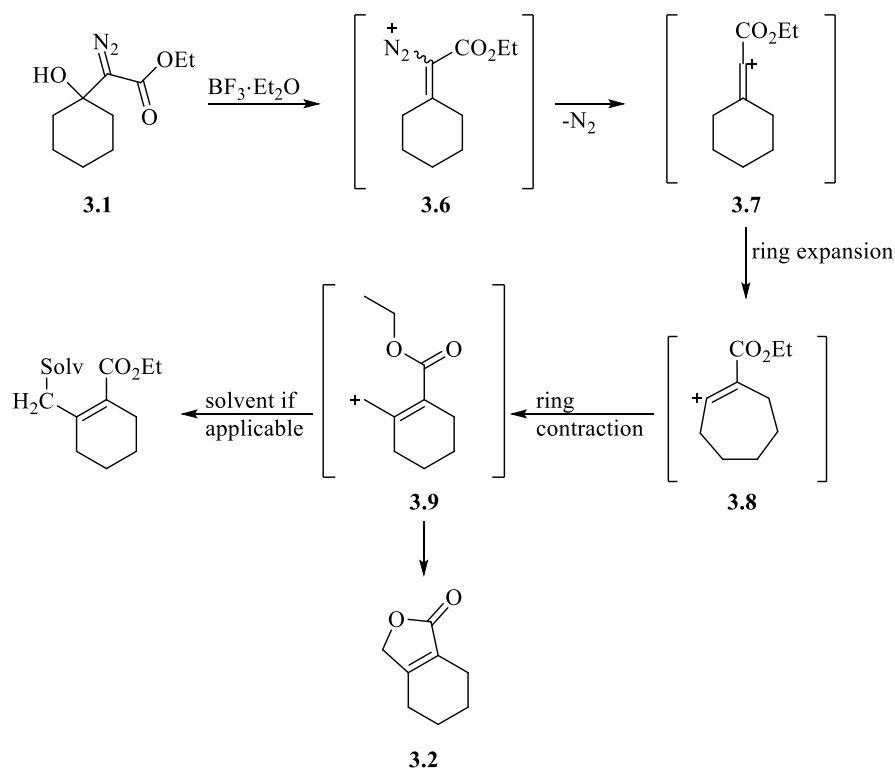
**Scheme 3-2: Elimination across vinyl diazonium**

Pellicciari and Padwa also investigated substrates that were derived from the aldol addition of lithio-diazo esters to ketones (**3.1** for example)—these compounds do not have a hydrogen  $\beta$  to the carbonyl and it was hypothesized that these compounds may lead to the generation of a vinyl cation intermediate. Indeed, treating  $\beta$ -hydroxy- $\alpha$ -diazo esters such as **3.1** (Scheme 3-3) with boron trifluoride etherate gave a variety of interesting products that could be derived from a vinyl cation intermediate.



**Scheme 3-3: Reaction of  $\beta$ -hydroxy- $\alpha$ -diazo esters with boron trifluoride**

For example, when pentane was used as the solvent, lactone **3.2** was formed in 75% yield. In benzene, solvent participation was evident, and **3.3** was formed in 74% yield along with trace amounts of lactone **3.2** and vinyl fluoride **3.4**. Finally, in *p*-xylene a similar solvent trapped product (**3.5**) was obtained in 47% yield. After the completion of an impressive substrate scope, the authors proposed a unifying mechanism for the transformations observed (Scheme 3-4).



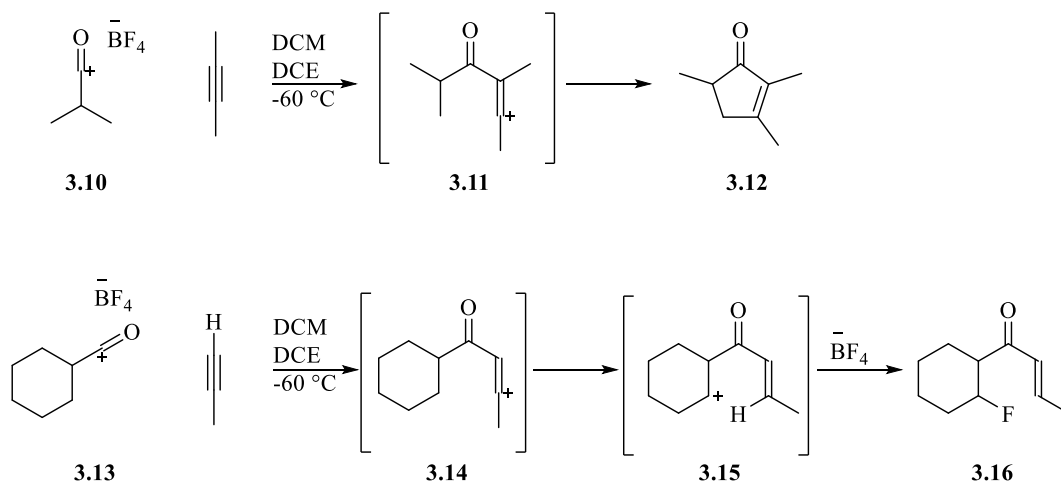
**Scheme 3-4: Vinyl cation intermediate as unifying mechanism**

The proposed mechanism began with Lewis acid-mediated loss of the hydroxyl group to give vinyl diazonium **3.6**. Loss of nitrogen would give a linear vinyl cation **3.7** that is destabilized by the neighboring electron deficient carbonyl group. Ring expansion would result in the more stable cyclic vinyl cation **3.8** that could contract by a 1,2-methylene shift to form allylic cation **3.9**. The allylic cation could then be trapped by the solvent or react intramolecularly with the adjacent ester group to give lactone **3.2**. For us, the most important aspect of this work was the generation of vinyl cations **3.7** and **3.8**.

The second report that was critical to our work came from Schegolev and coworkers who reported the reactivity of a vinyl cation intermediate that was generated by the acylation of alkynes by acylium ions (Scheme 3-5)<sup>94</sup> generated from the parent acid

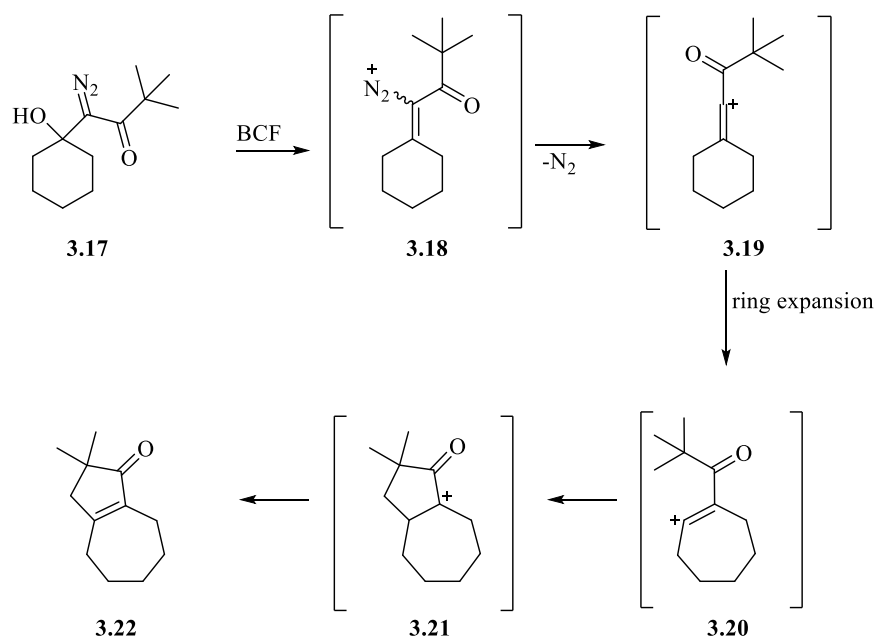


chloride or acid fluoride. Treating the acyl salt **3.10** with 2-butyne gave cyclopentenone **3.12** via a C-H insertion of vinyl cation intermediate **3.11**. The authors also reported that the acylium ion generated from cyclohexanecarbonyl chloride (**3.13**) reacted with 1-propyne to give fluoride **3.16**. This product presumably formed from a 1,5-hydride shift of vinyl cation **3.14** followed by trapping of the secondary carbocation **3.15** with fluoride to give **3.16**.



**Scheme 3-5: 1,5-Hydride shift across vinyl cations**

Cleary, Hensinger and Brewer (our group) took advantage of these two reports to develop a novel synthesis of cyclopentenones via the C-H insertion of vinyl cation intermediates generated from  $\beta$ -hydroxy- $\alpha$ -diazo ketones (see **3.17**). A representative reaction and its proposed mechanism is shown in Scheme 3-6.<sup>95</sup>

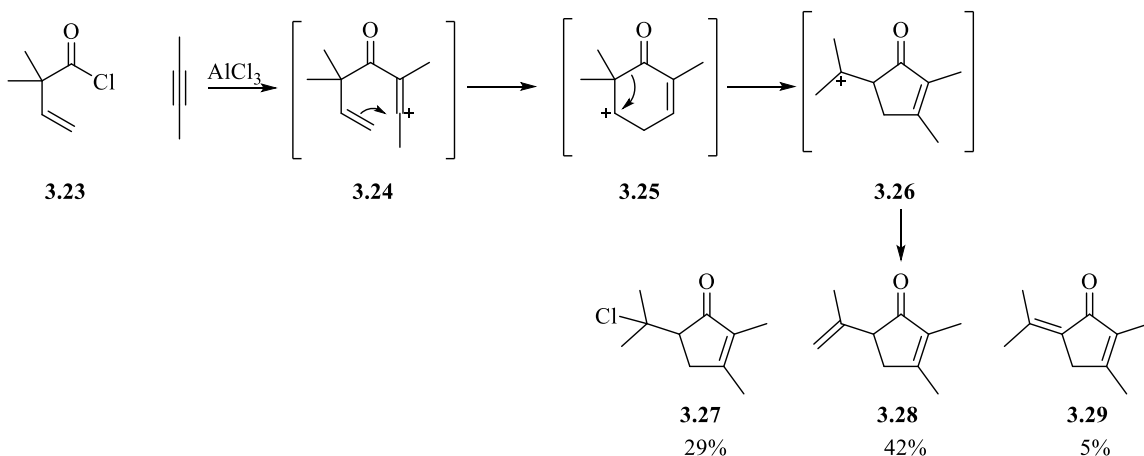


**Scheme 3-6: Remote C-H insertion of vinyl cations**

Loss of the hydroxyl group gives a vinyl diazonium species **3.18** as in Padwa's earlier report. Extrusion of nitrogen results in a destabilized linear vinyl cation that undergoes a ring expansion to the more stable bent vinyl cation. At this point the vinyl cation inserts into one of the methyl groups of the *tert*-butyl ketone. This insertion gives carbocation **3.21** which forms fused bicyclic cyclopentenone **3.22** after elimination. The scope of this reaction was investigated by Dr. Sarah Cleary and Magenta Hensinger, who established that this transformation allows access to a variety of bicyclic fused cyclopentenones. This type of scaffold is present in many natural products and our group has been looking to further develop this insertion methodology and to investigate other potential uses for vinyl cation intermediates.

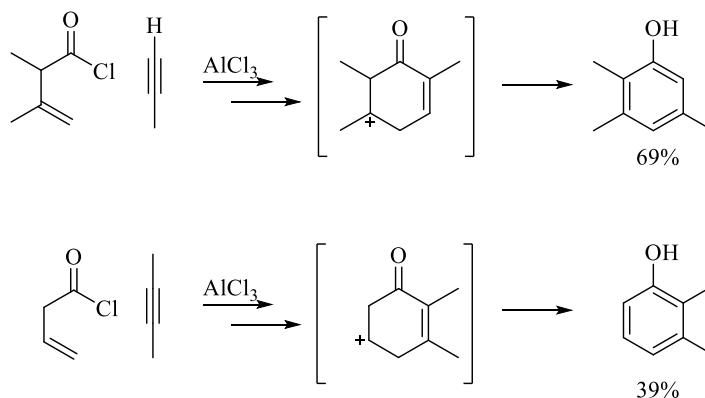
The third important literature report directly influenced my project. In this report Karpf showed that addition of an alkyne to an acyl cation that contained a pendent alkene

also resulted in cyclopentenone products but through a process that does not involve a C-H insertion. A summary of Karpf's key results are shown in Scheme 3-7.<sup>96</sup>



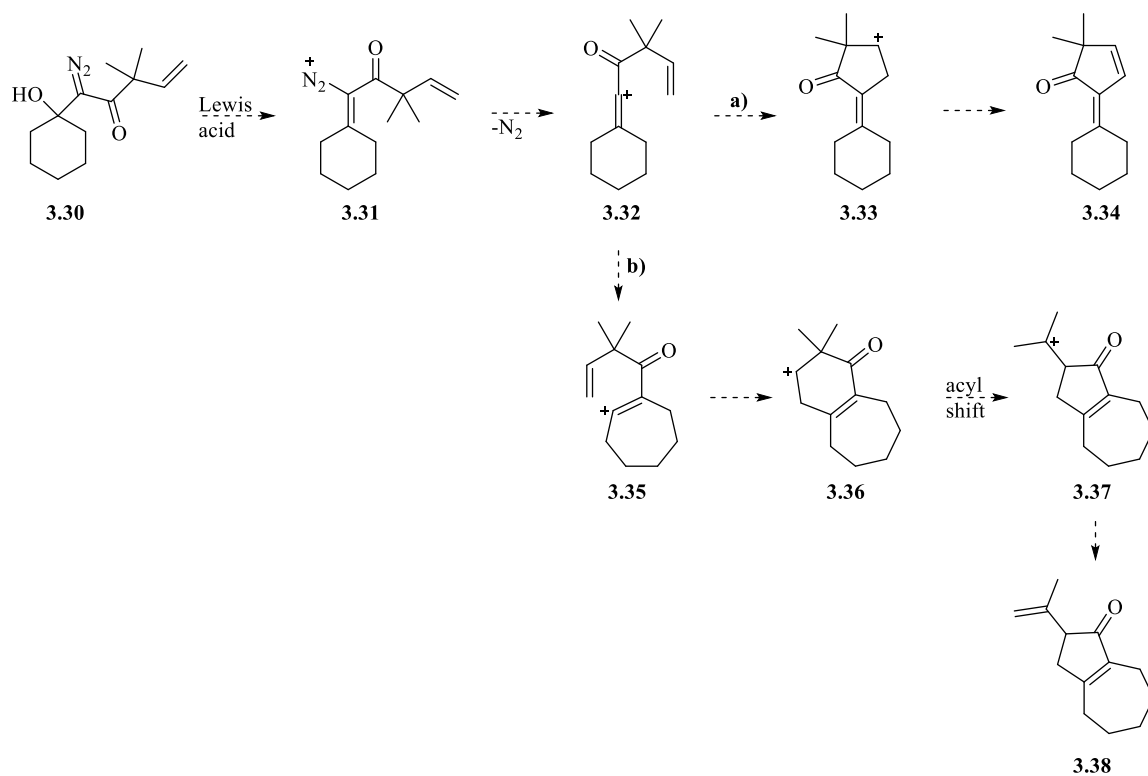
**Scheme 3-7: Reaction of remote alkene with vinyl cation**

Addition of the acyl cation to the alkyne gave a vinyl cation intermediate **3.24** that reacts with the pendent alkene, forming secondary carbocation **3.25**. Karpf then proposed that a ring contraction occurred via an acyl shift, resulting in the more stable tertiary carbocation **3.26** that gave rise to a set of products either by elimination (**3.28**, **3.29**) or chloride addition (**3.27**). When the acyl cation is not vicinal to a gem-dimethyl-substituted carbon the 1,2-acyl shift does not take place. The reaction instead resulted in phenol products by elimination and tautomerization (Scheme 3-8). The scope and utility of vinyl cation intermediates generated by the acylation of alkynes is limited. Multiple addition reactions to the alkyne starting material are possible which would result in potential side products or polymerization. Additionally, the reaction of unsymmetrically-substituted alkynes could produce mixtures of regioisomeric products.



**Scheme 3-8: Phenols from alkyne acylation**

Our aim was to investigate the capture of vinyl cations derived from  $\beta$ -hydroxy- $\alpha$ -diazoketones by pendent alkenes as shown in Figure 3-9. We hypothesized that these systems would react similarly to the systems tested by Karpf, giving cyclopentenones **3.34** and **3.38** as products. In our case, a key question was whether ring expansion of the initially formed vinyl cation would be more rapid than capture of the cation by the alkene (path **a** versus path **b**).



**Figure 3-9: Hypothesized pathways for vinyl cation reaction with remote alkene**

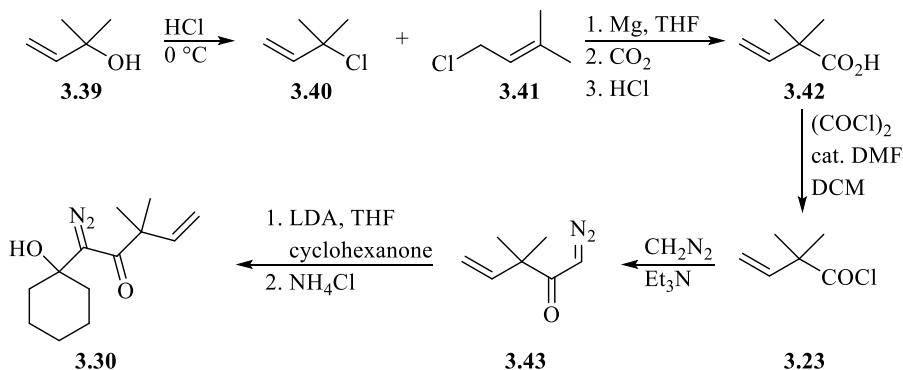
Even if alkene capture outpaced ring expansion, a cyclopentenone product was still anticipated following elimination of a  $\beta$ -hydrogen. The results of our investigations are presented in the following sections.

## 3.2 Initial Investigations

### 3.2.1 Preparation of Requisite $\beta$ -Hydroxy- $\alpha$ -diazoketone

The work began with the synthesis of known diazo ketone **3.43** (Scheme 3-10).<sup>97</sup> Treatment of 2-methyl-3-buten-2-ol with hydrochloric acid gave allylic chlorides **3.40** and **3.41** as an 11:1 mixture on decagram scale.<sup>98</sup> The Grignard reagent generated by treating

this mixture with magnesium turnings was poured onto freshly crushed dry ice to selectively afford carboxylic acid **3.42**. Crushing the dry ice into a fine powder with a hammer before use was sufficient to reproduce literature yields. Initially, thionyl chloride was used to generate acid chloride **3.23**, but this gave poor yields of the pure compound after fractional distillation. Later, it was found that this particular bottle of thionyl chloride had undergone significant decomposition to sulfuryl chloride and sulfur monochloride upon prolonged storage. In any event, oxalyl chloride and a catalytic quantity of DMF gave good yields and the comparatively mild conditions made product isolation simpler. Treatment of the acid chloride with freshly-generated diazomethane furnished the diazo ketone **3.43** in good yield after extraction.



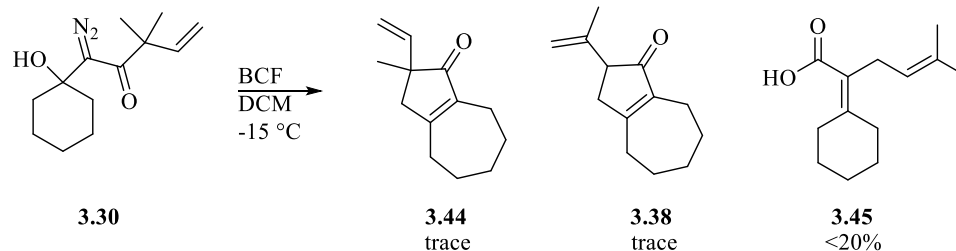
**Scheme 3-10: Synthesis of  $\beta$ -hydroxy- $\alpha$ -diazo ketone with remote alkene**

The final step in the preparation of the desired test substrate was the aldol-type addition of the lithiated diazo ketone to cyclohexanone. Due to acidity differences between the alpha hydrogens of the two starting materials, a solution of lithium diisopropylamide can be added dropwise directly to a cooled solution containing both ketones. The addition product is in equilibrium with the starting materials, and the reaction was found to be quite

sensitive to temperature. The desired addition product (**3.30**) only predominates at low temperature and could be isolated after quenching the reaction with ammonium chloride at low temperature. Although the ammonium chloride solution freezes, slow warming of the heterogeneous mixture to room temperature with *vigorous* mixing gave the protonated alkoxide product. Insufficient mixing during this quench led to recovery of the starting materials; once the solution temperature warms past a certain point the equilibrium shifts from the alkoxide back to the more entropically favored starting materials. After some quenching optimization, the desired  $\beta$ -hydroxy- $\alpha$ -diazo ketone was isolated in 73% yield.<sup>95</sup>

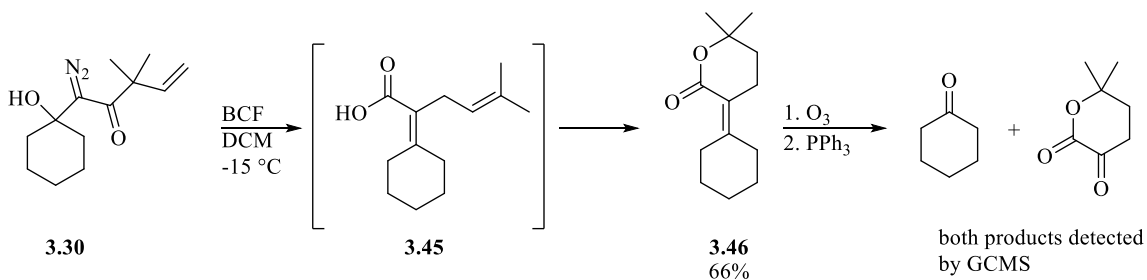
### 3.2.2 Screening and Optimizing Conditions for Vinyl Cation Capture by Alkene

Our first goal was to find effective reaction conditions to generate a vinyl cation intermediate from  $\beta$ -hydroxy- $\alpha$ -diazo ketone **3.30**. This was accomplished by treating **3.30** with BCF in dichloromethane, the preferred conditions for the C-H insertion reaction developed by Dr. Cleary. This reaction, shown in Scheme 3-11, produced three products by TLC analysis. Isolation of the 3 compounds by column chromatography was accomplished, but most of the expected reaction mass was missing. The first two products isolated from this reaction are suspected of being **3.44**, the unexpected C-H insertion product, and **3.38**, the expected alkene capture product, both obtained in trace amounts (<2% yield). The lowest  $R_f$  spot that was collected was more puzzling—by GCMS it was found to contain an extra oxygen and through 2D-NMR experiments it was identified as the  $\gamma,\delta$ -unsaturated carboxylic acid **3.45**.



**Scheme 3-11: Preliminary results with BCF**

Because the typical workup for this reaction involved a sodium bicarbonate wash to remove leftover Lewis acid, the potential to lose the product in the water layer as the carboxylate anion became apparent. Removing this step of the procedure and performing chromatography directly on the crude reaction mixture after solvent removal led to almost full mass recovery across the product mixture. However, under these conditions lactone **3.46** was isolated in 66% yield in place of the carboxylic acid (Scheme 3-12).



**Scheme 3-12: Formation of unexpected lactone product and structure confirmation**

This compound has not been reported previously, and its structure was assigned based on NMR spectroscopy and GCMS analysis of the crude reaction mixture from the subsequent ozonolysis of the internal alkene. It appears that concentrating the mixture under reduced pressure in the presence of the Lewis acid results in the cyclization of the unsaturated



carboxylic acid to the lactone. This type of cyclization isprecedented, though in a similar system the five-membered lactone was formed instead of the six-membered ring. The exocyclic alkene in carboxylic acid **3.45** may be the impetus for the observed result in our case due to the strain it imparts on the system.

Having established the major product of the transformation, a screening of conditions was conducted to investigate possible optimizations or alterations to the reaction pathway (Table 1). A variety of Lewis acids and solvents were explored, with trispentafluorophenyl borane in dichloromethane overall still producing the cleanest product mixtures with the highest yields. Other conditions gave complex mixtures of products from which, even after careful column chromatography, no pure compounds could be procured in high enough yields for complete characterization. In hydrocarbon solvents like pentane, solubility of the Lewis acid appears to become problematic, though starting material cannot be recovered from the reaction. In coordinating solvents like acetonitrile however, the reaction slows considerably and did not go to completion—instead the unreacted starting material simply decomposed during workup. Other Lewis acids were not successful either—using chloride- or triflate-based Lewis acids afforded complex mixtures that contained an appreciable degree of different counterion-trapped products as determined by GCMS analysis. Interestingly, attempts to prevent the formation of lactone **3.46** by the addition of magnesium sulfate (to prevent delivery of a hydroxyl group from the borate formed in the generation of vinyl diazonium **3.31**) resulted in decomposition.

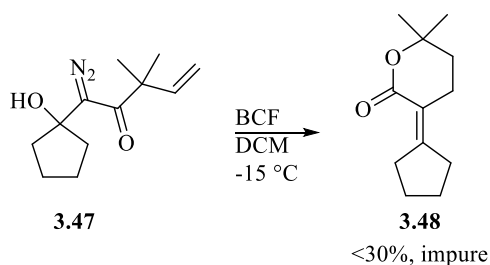
**Table 1: Remote Alkene Capture of Vinyl Cation: Reaction Screening**

Lewis acid	Temperature	Solvent	Additive	Outcome
SnCl <sub>4</sub>	-20 °C	DCM	N/A	Mixture: chloro-trapped and C-H insertion products
Sc(OTf) <sub>3</sub>	rt	DCM	N/A	Decomposition
BF <sub>3</sub> ·Et <sub>2</sub> O	-20 °C - 0 °C	DCM	N/A	Decomposition
In(OTf) <sub>3</sub>	-20 °C	DCM	N/A	Mixture: triflate trapped and C-H insertion products
BCF	-20 °C	pentane	N/A	Complex mixture
BCF	-20 °C - rt	MeCN	N/A	N.R.
BCF	-20 °C	DCM	MgSO <sub>4</sub> (1 equiv.)	Decomposition
BCF	-20 °C	DCM	N/A	<b>3.46</b> , 66% yield

After conclusion of this screening, BCF was identified as the best Lewis acid for this reaction due to its non-nucleophilic pentafluorophenyl groups, which minimizes the occurrence of such trapping products which complicate purification. Additionally, the reaction with BCF does not require low temperatures and can be run at room temperature with no change in yield.

### 3.3 Reaction Scope

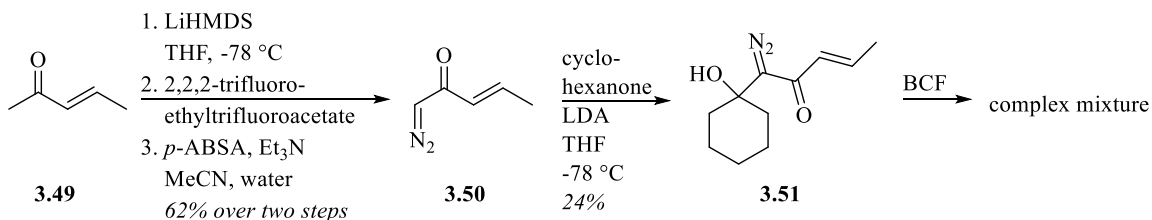
After having identified working reaction conditions, we then set out to test the scope and generalizability of this reaction. It quickly became apparent that the reaction may not be very general. The  $\beta$ -hydroxy compound **3.47** derived from cyclopentanone gave a complex mixture of products (more than 6 spots by TLC) when added to a solution of BCF in dichloromethane (Scheme 3-13). The expected product **3.48** was isolated from this mixture albeit in low (<30%) yield and low purity.



**Scheme 3-13: Unsuccessful cyclopentanone-based substrate**

A more thorough look at the reaction mechanism and potential explanation for this result will be discussed in the following section.

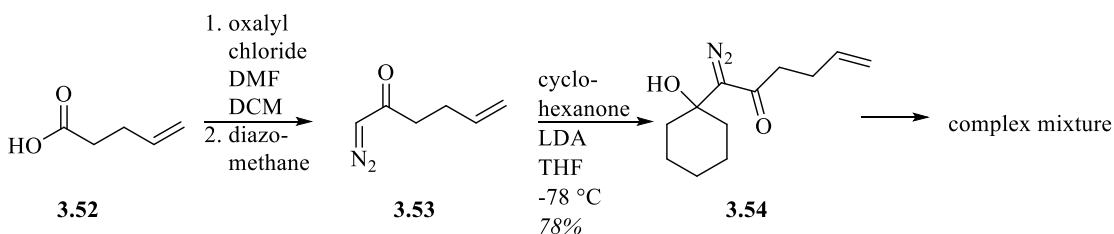
Next, the tether length to the pendent alkene was investigated because variations along this tether could result in the formation of different ring sizes.  $\alpha$ -Diazoketone **3.50** was prepared using a known diazo-transfer reaction, but instead of using the reported conditions employing shock-sensitive tosyl azide, 4-acetamidobenzenesulfonyl azide (*p*-ABSA), which is shelf stable and not shock-sensitive, was successfully used as a substitute (Scheme 3-14).<sup>99</sup>



**Scheme 3-14: Shortening tether to remote alkene**

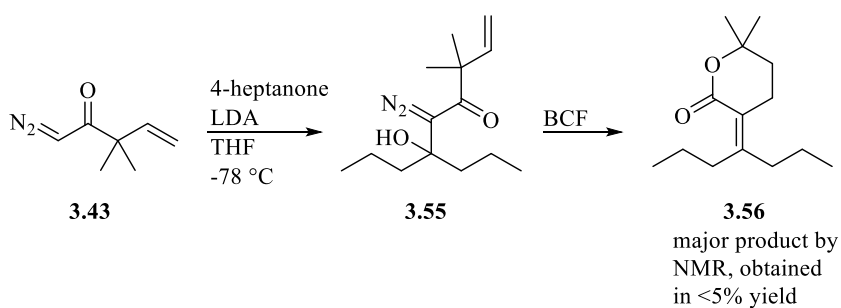
The addition of diazo ketone **3.50** to cyclohexanone proved to be quite challenging, because the unsaturated diazo ketone appears to be unstable to basic conditions. Nevertheless, **3.51** was obtained in a 24% yield. Treating substrate **3.51** with BCF resulted

in a mixture of products that could not be purified and characterized. Investigation of compound **3.54** which contains a longer tether to the pendent alkene compared to the original substrate **3.30** also did not yield promising results (Scheme 3-15).<sup>100</sup>



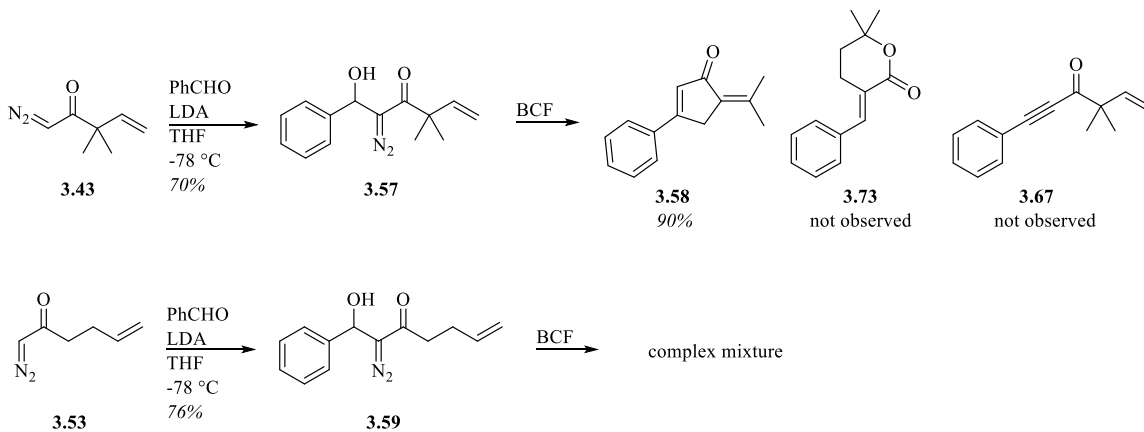
**Scheme 3-15: Increasing tether to remote alkene**

Substrates derived from 4-heptanone were successfully employed by Cleary et al. in 2017 to prepare monocyclic cyclopentenones that could serve as prostaglandin analogues. For this reason,  $\beta$ -hydroxy compound **3.55**, derived from aldol addition to 4-heptanone, was prepared. When **3.55** was subjected to treatment with a Lewis acid, the crude NMR indicated the formation of the expected lactone product **3.56** as the only major product—however, after workup and chromatography minimal product was obtained (Scheme 3-16).



**Scheme 3-16: Investigating an acyclic system**

Finally, to investigate whether styrene-based lactones (**3.73**, Scheme 3-17) could be prepared using this method,  $\beta$ -hydroxy compound **3.57**, derived from the addition of diazo ketone **3.43** to benzaldehyde, was synthesized. Importantly, compound **3.57** does contain a hydrogen beta to the diazo group that could potentially lead to an alkyne product (**3.67**) by elimination after formation of a vinyl diazonium. However, treatment of **3.57** with BCF afforded an entirely unexpected product, giving cyclopentenone **3.58** rather than the expected lactone or elimination products (Scheme 3-17). Increasing the tether length to the pendent alkene in this system also completely shut down this reactivity akin to the aliphatic example shown in Scheme 3-15.

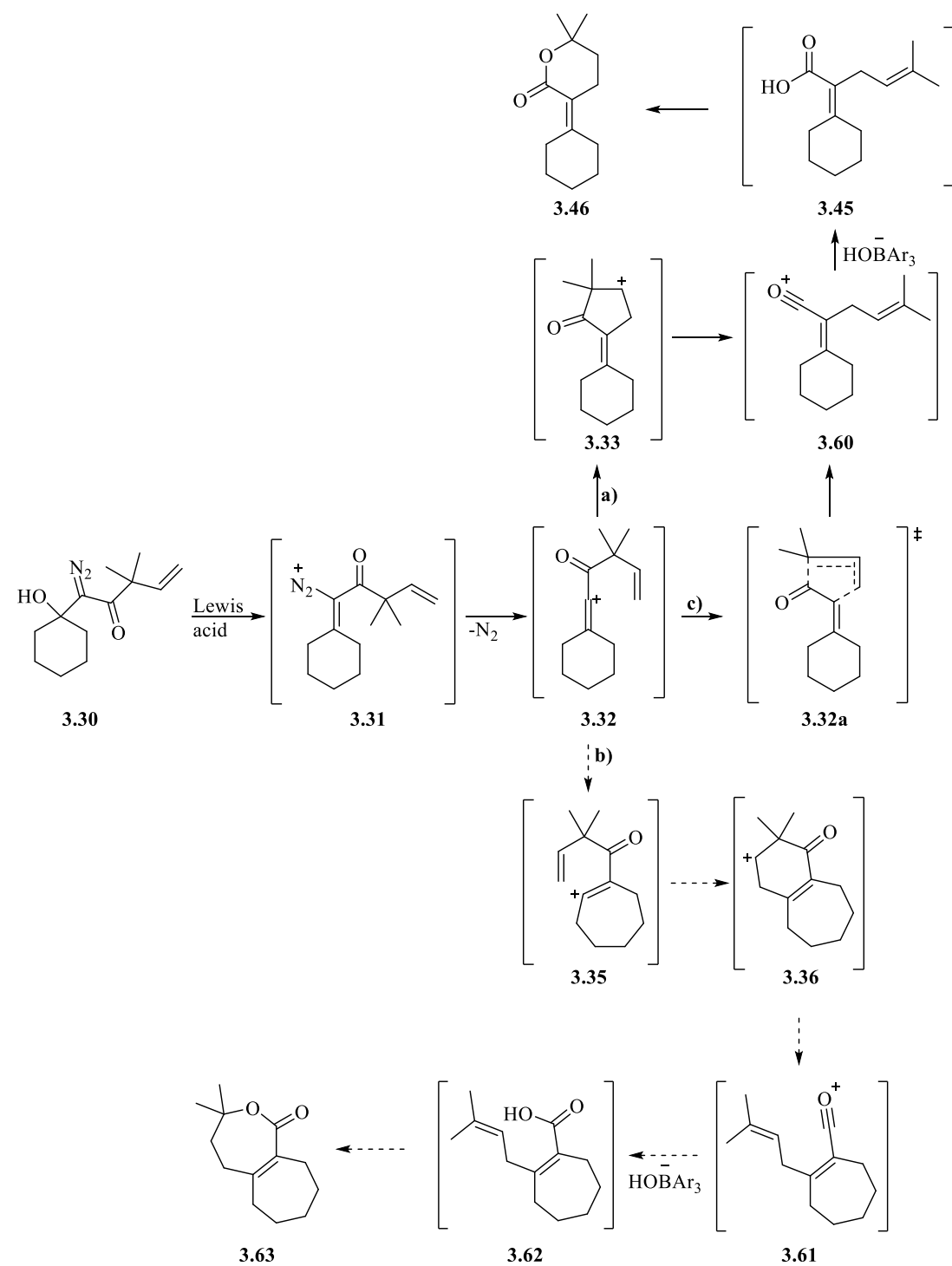


**Scheme 3-17: Cyclopentenone product from aldehyde-derived substrate**

This marked the end of our substrate scope of this reaction. Each of the results presented in this section will be discussed in the next section (**3.4**).

### 3.4 Proposed Mechanisms and Explanations for Vinyl Cation Capture Outcomes

Our investigation of the reaction scope for the capture of vinyl cations by remote alkenes demonstrated that the reaction pathway is very sensitive to changes in the substrate. Each of the substrates will be discussed in detail in this section, beginning with our initial test compound **3.30**, which resulted in lactone **3.46**. A proposed mechanism of formation for product **3.46** along with an illustration of alternate reaction pathways is shown in Figure 79. The formation of lactone **3.46** likely begins by Lewis acid-mediated hydroxyl abstraction to give the vinyl diazonium intermediate **3.31** (Scheme 3-18). Loss of nitrogen gas would result in the formation of the linear vinyl cation **3.32**. This cation is thought to be destabilized by the adjacent electron-deficient carbonyl carbon and is prone to rearrangements to the cyclic vinyl cation **3.35** similar to the example previously discussed in section **3.1**, Scheme 3-6.<sup>91</sup>



**Scheme 3-18: Proposed mechanism for lactone formation**

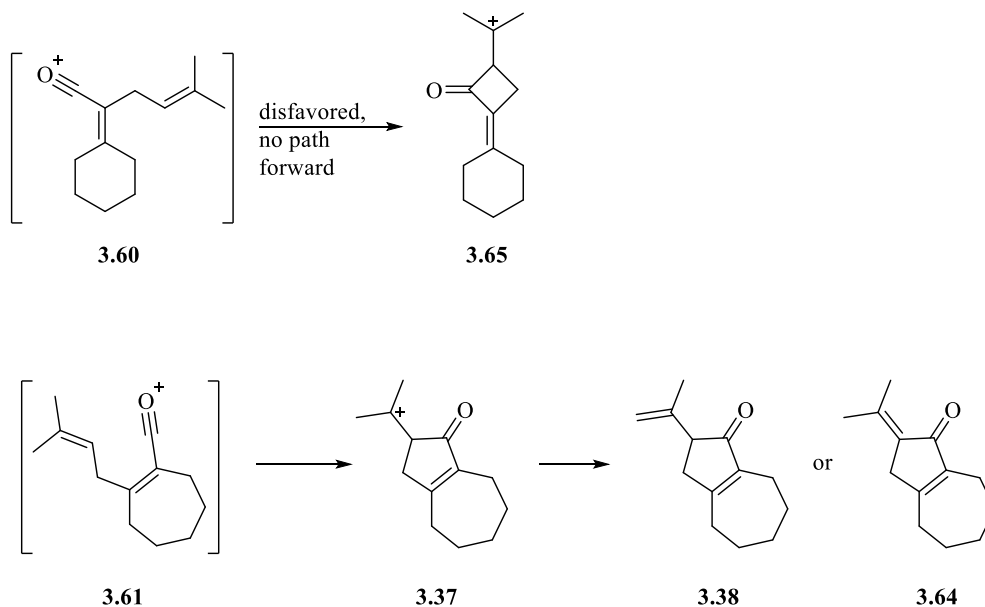
If rearrangement is slower than alkene capture, then the pendent alkene could attack the vinyl cation to give intermediate **3.33** (path **a**), which contains a secondary cation. A 1,2-acyl shift is not expected in this case as it would result in a strained 4-membered ring. Importantly, we have never isolated the alkene product that would result from loss of a  $\beta$ -hydrogen from this cation. However, the observed product could be rationalized as forming by fragmentation of the 5-membered ring facilitated by the carbonyl oxygen lone pair to give an acylium ion **3.60**. However, the orbitals involved in this fragmentation are misaligned in **3.33**. Therefore, it seems more likely that the linear vinyl cation **3.32** fragments directly to acylium **3.60** as the new C-C bond develops (transition state **3.32a**, path **c**). At this point, the borate formed from the first step of the reaction could deliver the hydroxyl group to the acylium to form carboxylic acid **3.45**. It is possible that electrostatic interactions between the negatively charged borate and positively charged acylium enable this process. Finally, as stated previously and with literature precedent, the  $\gamma,\delta$ -unsaturated carboxylic acid could close to give lactone **3.46** during removal of the solvent from the crude mixture.<sup>101</sup>

Alternatively, if ring expansion is fast (path **b**), then the more stable cyclic vinyl cation **3.35** could form. Capture of this cation by the pendent alkene would give a 6,7-fused bicyclic structure (**3.36**). If this structure undergoes fragmentation to the acylium ion followed by hydroxyl delivery, the carboxylic acid **3.62** and subsequent lactone **3.63** could result. To determine which path the reaction had taken and which product had formed we used a combination of 2D NMR spectroscopy and a subsequent ozonolysis reaction. The HMBC spectrum led us to the conclusion that **3.63** is not the product, with



the data being consistent with the proposed structure of **3.46**. Further evidence for this structure was obtained by GCMS analysis of the product mixture from the ozonolysis of **3.46**, which contained peaks for both cyclohexanone and the corresponding 1,2-dicarbonyl fragment (Scheme 3-12).

Further explanation for why lactone **3.63** may not be a plausible product comes from a careful comparison of the acylium ions **3.60** and **3.61** (Scheme 3-19). In ion **3.60**, nucleophilic attack by the alkene of the prenyl group would lead to a highly strained 4-membered ring. In ion **3.61**, a similar nucleophilic attack would lead to a five-membered cyclopentanone intermediate that, upon elimination, would give either products **3.38** or **3.64**.

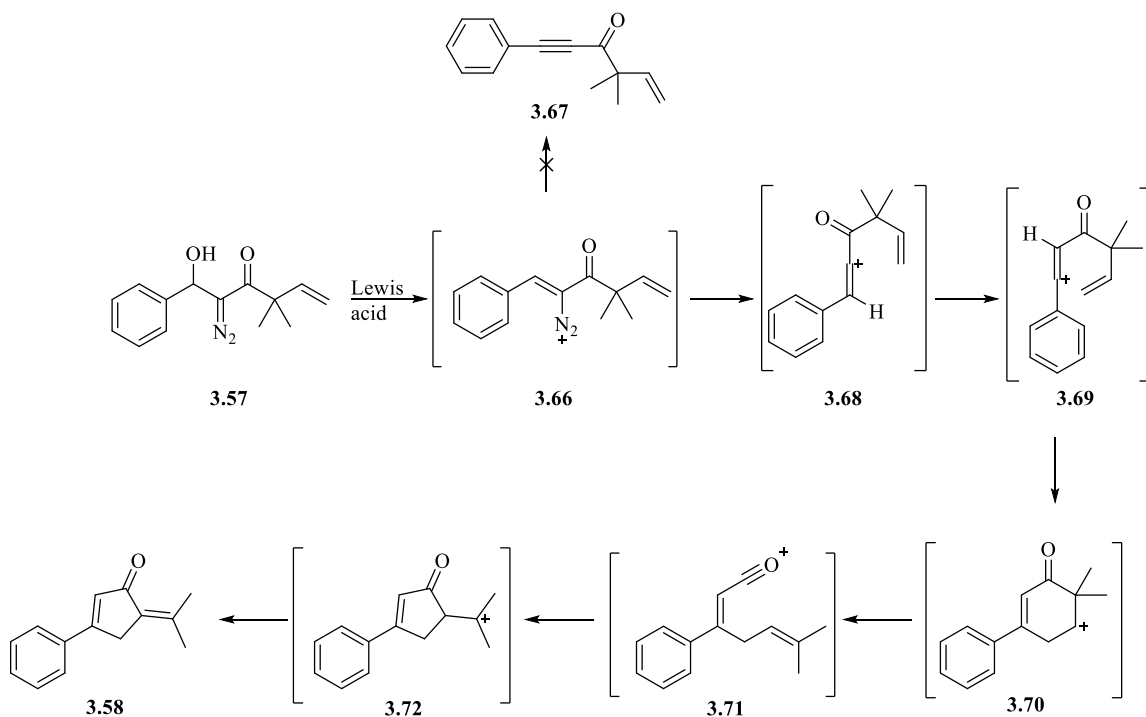


**Scheme 3-19: Mechanistic rationale for acylium ion pathways**

This latter type of reactivity is akin to what Karpf observed (and what we expected to see)—the difference is that he explained the mechanism as a 1,2-acyl shift rather than fragmentation to an acylium ion followed by nucleophilic attack by the alkene; indeed, he had no reason to suspect an acylium intermediate at the time.<sup>96</sup> Our isolation of the lactone product led us to conclude that the fragmentation to the acylium ion is the more likely pathway for this type of cyclization. In summary, if ring expansion of the vinyl cation intermediate was faster than alkene capture, the cyclopentenone products **3.38** or **3.64** would be expected. Based on the experimental outcome, however, it appears that nucleophilic capture of the vinyl cation by the pendent alkene is faster than rearrangement of the vinyl cation species. Because the reaction hits a dead end after formation of acylium **3.60** in terms of intramolecular reactivity, intermolecular delivery of a hydroxyl group to the acylium then results, ultimately leading to the observed lactone product **3.46**. As mentioned previously, attempting to disrupt the hydroxyl delivery process by adding magnesium sulfate to the reaction resulted in decomposition (see Table 1).

A mechanism to explain the outcome of the vinyl cation capture experiment starting from benzaldehyde-derived precursor **3.57** is shown in Scheme 3-20. In this case, a cyclopentenone product (**3.58**) was isolated in high yield as the only major product. Initial hydroxyl abstraction is expected to give vinyl diazonium **3.66**. Based on Pellicciari's earlier report, we expected this species or vinyl cation **3.68**, formed after loss of nitrogen, to be prone to elimination, resulting in alkyne **3.67**. This, however, was not observed. Instead, it appears that a hydride shift occurred, forming the more stable linear vinyl cation **3.69**. Nucleophilic attack by the pendent alkene and fragmentation of the newly formed six-

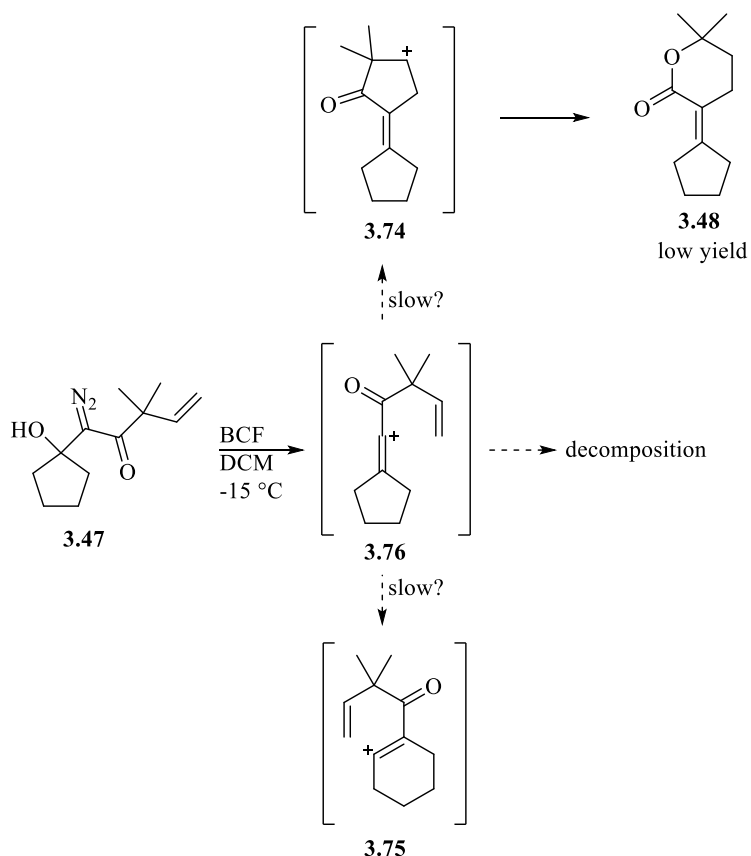
membered ring to an acylium species as described above would give structure **3.71**. At this point, the prenyl group alkene could cyclize onto the acylium to form a cyclopentenone intermediate which, upon elimination of a  $\beta$ -hydrogen, would give the fully conjugated product **3.58**.



**Scheme 3-20: Proposed mechanism for cyclopentenone formation**

The structure of this product was determined by HMBC and DEPT 135 experiments—it has previously been reported in the literature but with no spectroscopic data given.<sup>102</sup> Also of note in this experiment: no trace of lactone products were isolated or detected, which can be rationalized on the basis of this proposed mechanism. The prenyl group alkene should readily cyclize onto the acylium ion in this example, precluding delivery of the hydroxyl group by the borate to form the carboxylic acid and eventual lactone.

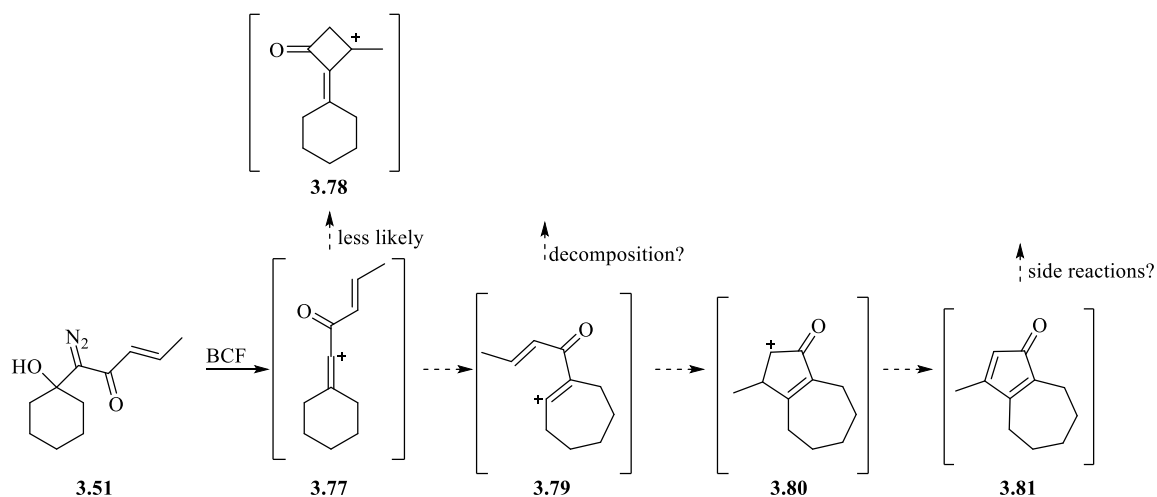
For the substrate derived from cyclopentanone (**3.47**), the observed complex mixture of products may result from a slower rate of attack by the pendent alkene on the linear vinyl cation **3.76** (Scheme 3-21) due to the angle strain of the two alkene-fused cyclopentane rings that would be present in the resulting intermediate (**3.74**). Again, it is likely that secondary cation **3.74** does not represent a valid intermediate and that the fragmentation of linear vinyl cation **3.76** proceeds in a concerted manner. However, the problem of double methylene cyclopentane strain would still apply to the transition state for this concerted process. This would prevent the efficient formation of the observed lactone product **3.48**.



Scheme 3-21: Rationale for failed cyclopentanone-based substrate

Additionally, ring expansion to cyclic vinyl cation **3.75** is expected to be disfavored due to significant ring strain. This may leave vinyl cation **3.76** without any productive pathway, resulting in predominantly decomposition and side products. In the case of the 4-heptanone derivative **3.55**, the NMR of the crude reaction mixture suggested relatively clean formation of the expected lactone product **3.56**, yet this product was only isolated in low yield. Based on Dr. Cleary's successful use of a similar substrate in a C-H insertion reaction, it appears that this result is not due to competing reaction pathways but to challenges in product isolation and purification. Further examination of this particular substrate is warranted.

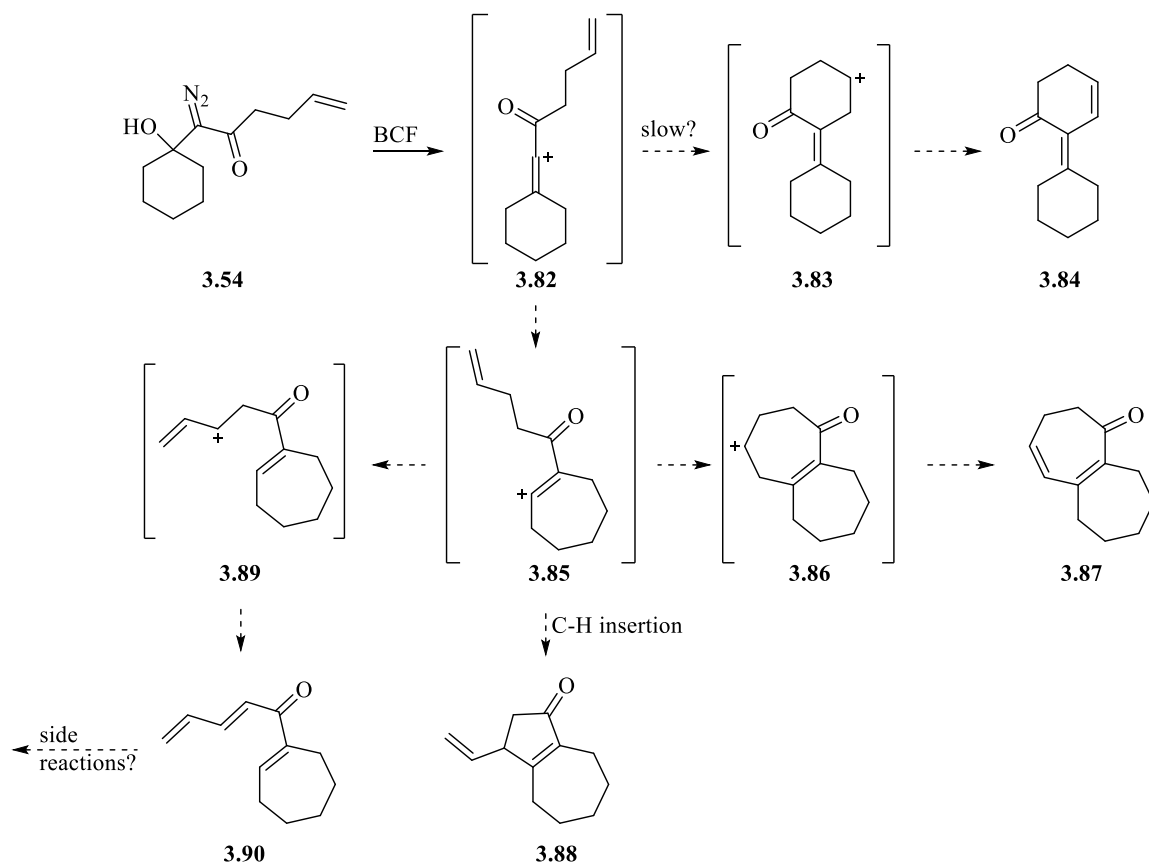
The effect of the tether length to the pendent alkene was explored in the study of substrates **3.51** and **3.54**. First, the linear vinyl cation **3.77** (Scheme 3-22) generated from precursor **3.51** contains a shortened tether to the remote alkene and would be expected to undergo ring expansion to the cyclic vinyl cation **3.79** since nucleophilic attack of the alkene would result in a strained four-membered ring (**3.78**).



**Scheme 3-22: Possible pathways for shortened tether system**

However, it is then possible that conjugation of the pendent alkene with the carbonyl group lessens the nucleophilicity of the alkene, slowing its attack in vinyl cation intermediate **3.79**, leading to other, unidentified side products. It also may be that even if the vinyl cation is captured by the alkene at this stage, the resulting secondary cation **3.80** may lead to side products; removal of a beta hydrogen would give cyclopentadienone **3.81** which could react in [4+2] cycloaddition reactions with other compounds including the starting material **3.51**, as its conjugated alkene could serve as a suitable dienophile for such a process. Unfortunately, no definitive evidence of these hypothesized side reactions was obtained from the complex mixture.

Finally, the vinyl cation derived from precursor **3.54** contains a remote alkene that is tethered further away from the reactive center (Scheme 3-23). In this case nucleophilic attack of the remote alkene could result in a six-membered ring, forming secondary cation **3.83**. This does not seem to be a major reaction pathway, however, as this substrate also gave a complex mixture of products.



**Scheme 3-23: Possible pathways for extended tether system**

Perhaps the gem-dimethyl substituents present in our original test substrate **3.30** are responsible for the efficient alkene cyclization due to the Thorpe-Ingold effect. The lack of such a gem-dimethyl functionality in this case may allow ring expansion to the seven-membered cyclic vinyl cation **3.85** to become a competitive process. The remote alkene could cyclize onto this vinyl cation, forming a bicyclic 7,7-fused skeleton (**3.86**). A more likely pathway for vinyl cation **3.85** would be a C-H insertion to give cyclopentenone **3.88**. This type of C-H insertion at a methylene position is preceded in work reported by Cleary et al., though the yield for this transformation was modest. Yet another possibility

is that instead of a complete C-H insertion reaction, vinyl cation **3.85** could undergo a 1,5-hydride shift to give allylic cation **3.89**. Elimination of a beta hydrogen from this intermediate would give a diene compound (**3.90**) that could participate in side reactions such as cycloadditions.

### 3.5 Conclusions and Future Work

This chapter has showcased some of the reactive pathways of vinyl cation intermediates that contain pendent alkenes. These high-energy intermediates led to both lactone and cyclopentenone products depending on the structure of the precursor compound. In particular, the formation of lactone product **3.46** in good yield gave us a great deal of mechanistic insight into the reaction between remote alkenes and vinyl cations, leading us to propose a fragmentation which results in an acylium ion as the reactive pathway. Also of note is that this type of reactivity is consistent with earlier results observed by Karpf that were attributed to a 1,2-acyl shift in the original report. Additionally, the reaction is very sensitive to the tether length of the pendent alkene, the cyclization pathways available to that alkene, and even the structure of the vinyl cation intermediate. Additionally, the high-yielding formation of a cyclopentenone product from vinyl cation precursors derived from aldehydes holds much promise for future work. These plans include a full substrate scope to investigate different vinyl cation precursors derived from other commercially available aldehydes. The preparation of these precursors should prove more facile than many presented here because they involve aldol addition to aldehydes rather than ketones.



## CHAPTER 4: SYNTHESIS OF FUSAROCHROMANONE

### 4.1 Background and Motivation

#### 4.1.1 History of Fusarochromanone and Biological Activity

Fusarochromanone (often abbreviated FC101) is a metabolite produced by the *Fusarium equiseti* fungus which often infects agricultural plants including feedstocks. It was discovered and identified as a mycotoxin after the observation that chickens placed on diets containing *Fusarium*-infected feed led to an increased incidence of bone malformation (specifically, tibial dyschondroplasia or TDP) and a low hatchability of fertile eggs.<sup>103-106</sup> Lee and coworkers screened several isolates of *Fusarium roseum* (collected from overwintered oats from Fairbanks, Alaska) by growing them on rice and identifying which of these cultures reproduced the toxic effects. FC101 was isolated from the rice culture that resulted in TDP and reduced egg hatchability when used as chicken feed. The purified toxin also reproduced these effects. The structure of FC101 was then determined by NMR spectroscopy, mass spectroscopy and X-ray crystallography and is shown in Figure 4-1.<sup>105, 107</sup>

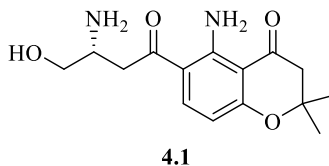


Figure 4-1: Structure of fusarochromanone

Some unique features of this natural product that distinguish it from other chromanones include the geminal methyl groups at C2, the placement of its side chain and its  $\beta$ -keto-amine functionality.

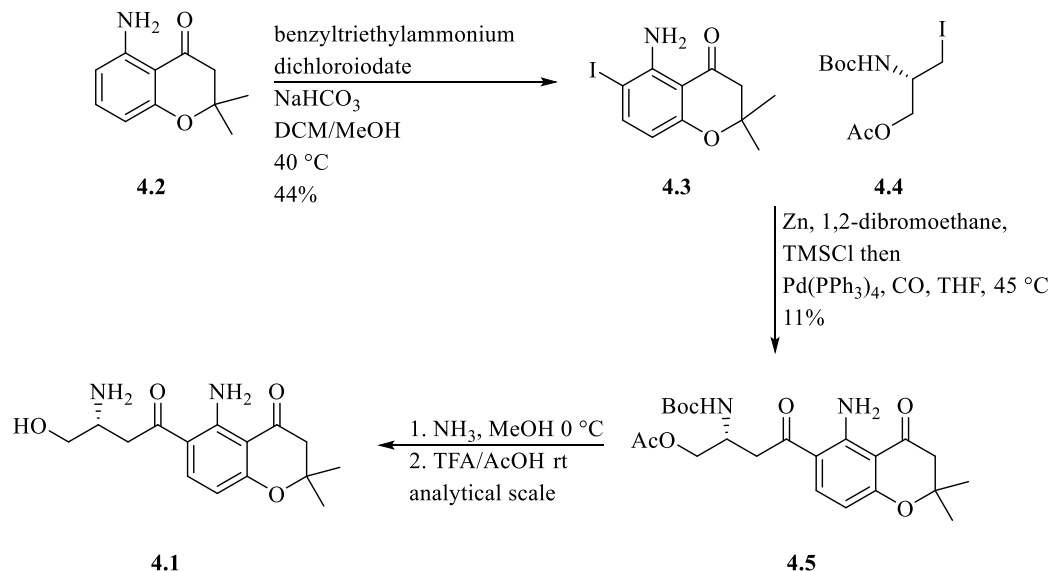
It was found that in addition to FC101 having anti-angiogenic properties in chickens, it also exhibited such activity in human cell lines. The bulk of the investigation into its biological activity has been focused on FC101's promise as an anticancer agent.<sup>108-</sup><sup>112</sup> *In vitro* experiments revealed FC101's potent anticancer activity, due to its suppression of both angiogenesis and tumorigenesis. Additionally, these studies demonstrated that the compound has a strong selectivity for cancer cells over normal cells—cancer cell growth was inhibited without concurrent negative impacts on normal tissues. FC101 was also found to be a candidate for use in the treatment of MDR (multi-drug resistant) cancers. It demonstrated a potent effect against the MCF-7/Dox cell line (MDR cells). These cells overexpress the enzyme glucosylceramide synthase (GCS), which deactivates ceramide by converting it to glucosylceramide. Ceramide-induced apoptosis plays a key role in the effectiveness of traditional chemotherapies; this pathway is shutdown when GCS is overexpressed—higher GCS levels are indeed observed in MDR breast, ovarian, cervical, and colorectal cell lines. The search for an effective, *in vivo* inhibitor of GCS is a fundamental challenge to the medical field and the treatment of cancer; fusarochromanone represents a possible lead for the design of a therapeutic compound for this purpose.

While the *in vitro* studies are impressive, the compound's *in vivo* effects were found to be less promising—treating skin cancer in mice with FC101 resulted in a 30% reduction in tumor size relative to controls, but this required a relatively high dosage (8 mg/kg/day).

However, the treatment was tolerated well and no toxic effects were observed on the animal. The study authors attribute these suboptimal *in vivo* effects to the fact that fusarochromanone likely strongly binds to serum albumin (the most abundant protein in human blood), inhibiting its action on the desired biological targets—it had already been demonstrated that FC101 binds bovine serum albumin by the Wuthier lab.<sup>108</sup> A potential workaround for this problem would be either the encapsulation of FC101 in a nanoparticle designed for drug delivery or the synthesis of a fusarochromanone derivative or analogue with more *in vivo* promise. Nevertheless, fusarochromanone represents a worthwhile target for chemical synthesis and, being a relatively small molecule could ideally be prepared on a large scale for further biological evaluation.

#### 4.1.2 Previous Syntheses

Despite the promising biological activity of fusarochromanone (and its inefficient isolation from natural sources), only two synthetic studies have been reported.<sup>113-114</sup> The first reported synthesis came in a patent from 2004 and the route is shown in Scheme 4-2. This synthesis involved preparation of an amino-iodo-chromanone (**4.3**) by a low-yielding non-regioselective iodination (the undesired regioisomer was formed in a 33% yield). This compound was then coupled to a suitable sidechain precursor (**4.4**) using an organozinc cross coupling reaction that proceeded in very low yields (11% isolated, 21% based on recovered starting material). Removal of the protecting groups was only ever accomplished on an analytical scale and fusarochromanone was detected in the crude mixture by high resolution mass spectrometry.

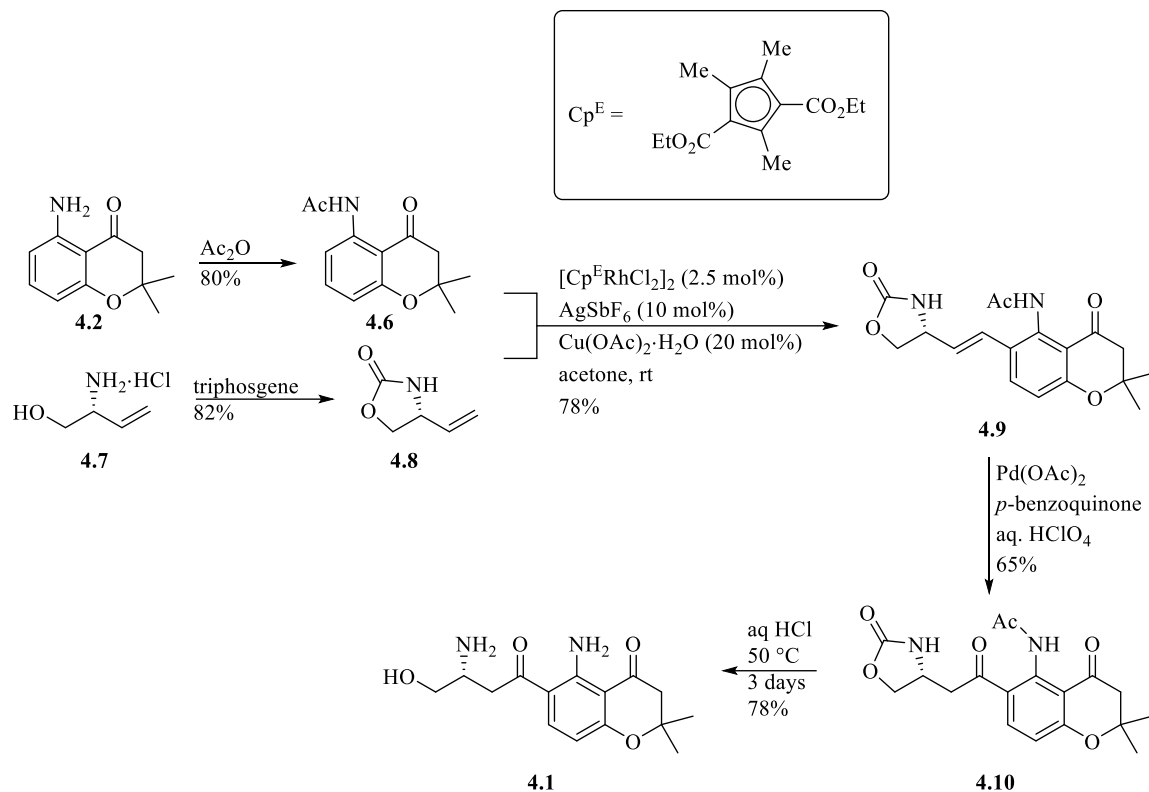


**Scheme 4-2: Patented synthesis of FC101**

An alternative to the low-yielding organozinc coupling (a Mizoroki-Heck reaction that proceeded in 30% yield) was presented in the patent but this route was never fully elaborated to the natural product. This patent highlights that, despite its seemingly simple structure, the substitution pattern on the aromatic ring of fusarochromanone presents a formidable challenge to synthetic chemists as significant effort was required to construct this tetrasubstituted aromatic scaffold.

More than a decade later, Tanaka et al. reported a concise new approach to fusarochromanone where the troublesome regioselective pre-functionalization of the aminochromanone was circumvented by installing the side chain directly using an oxidative olefination.<sup>113</sup> The overall scheme is presented below in Scheme 4-3. Coupling a vinyloxazolidinone (**4.8**) to the N-acetylaminochromanone (**4.6**) using a cationic rhodium(III) catalyst under mild conditions proceeded in 78% yield without formation of

any undesired regioisomers. A subsequent Wacker oxidation was achieved in modest yield followed by protecting group removal to give the natural product.



**Scheme 4-3: Tanaka's 2017 synthesis**

Using this route, fusarochromanone was synthesized on milligram scales from, as asserted by the authors, commercially available starting materials **4.2** and **4.7**. However, we were unable to find a *practical* commercial source for either starting material—all potential vendors listed prices in excess of \$300 per gram.

### 4.1.3 Initial Plan and Strategy

As part of a collaboration seeking to explore fusarochromanone as a potential anticancer agent or as a promising lead for the development of other such medicines, we

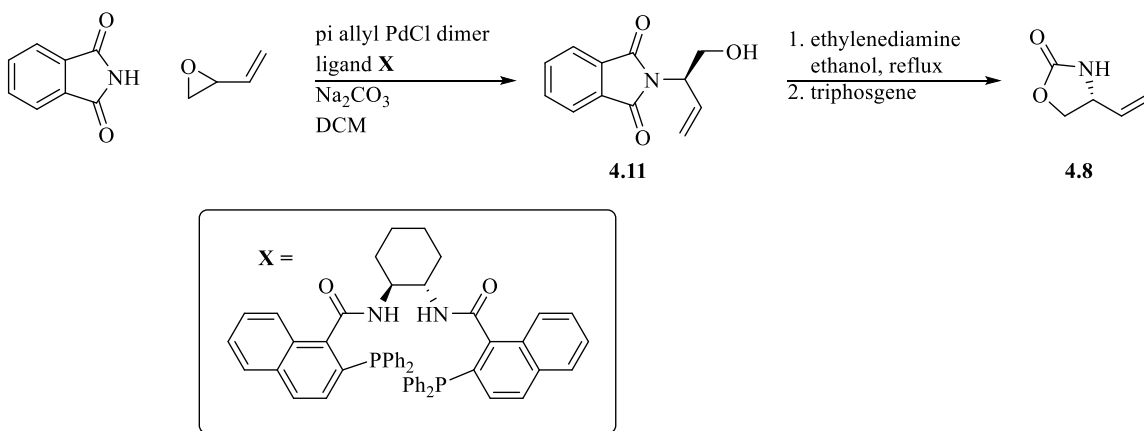
set out to synthesize this natural product. One of our primary goals for this project was to be able to access the compound in large quantities to facilitate both further testing of its biological activities and its derivatization. In terms of the synthesis, two potential strategies emerged: first, to find ways to access the starting materials used for the known route published by Tanaka in a cheap, scalable fashion since they are both prohibitively expensive; second, to develop a new synthetic route to fusarochromanone by exploring other ways to form the key carbon-carbon bond between the aromatic group and the sidechain. Desiring to procure a sizable sample of fusarochromanone in a timely manner, we first focused on the former strategy, seeking ways to access both of the required starting materials using scalable procedures.

## 4.2 Synthesis of Starting Materials

### 4.2.1 Synthesis of Chiral Oxazolidinone

Despite the lack of commercial availability of the vinyloxazolidinone **4.8**, its synthesis is known and reported in the literature as effective at large scales (Scheme 4-4). This preparation involves a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) using a chiral Trost ligand for the ring opening of butadiene monoxide by phthalimide.<sup>115-116</sup> From there, removal of the phthalimide gives the aminoalcohol which can then be protected with triphosgene to give oxazolidinone **4.8**. Despite the apparent ease of this route, significant struggle was met with the DYKAT reaction. Working with Dr. Ramya Srinivasan, many attempts to repeat the published results failed. The complete failure of a reaction that had been reported in the literature at

near quantitative yields suggested there was a major problem with one of our reagents and that our catalyst system was being shut down entirely—being more careful with the reaction set up had little to no effect on the reaction success. Recrystallization of phthalimide before use, using newer palladium catalysts and new bottles of ligand, or using anhydrous dichloromethane from other research groups did not fix the problem.



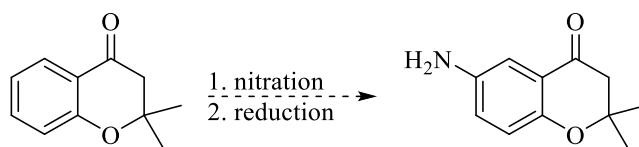
**Scheme 4-4: Synthesis of chiral oxazolidinone**

Upon consulting with Dr. Barry Trost, whose group was responsible for developing this reaction, it was quickly identified that commercial samples of butadiene monoxide from TCI Chemicals and Alfa Aesar were contaminated with significant amounts of peroxide, likely leftover from the synthesis of butadiene monoxide from 1,3-butadiene. A bottle of the epoxide purchased from Sigma Aldrich was free of peroxide contaminants and, not surprisingly, the reaction began working as published in the literature. Many thanks are due to Dr. Trost for his swift and extremely helpful aid in troubleshooting this matter.

Cleavage of the phthalimide group was accomplished by heating **4.11** in an ethanolic solution with ethylene diamine to reflux. Purification of this compound at the smaller scales we were working with proved problematic—it was difficult to separate the product from leftover ethylene diamine. However, simply taking the crude material after filtration on to the next step worked effectively to give oxazolidinone **4.8** after column chromatography.

#### 4.2.2 Development of Route to *N*-Pivaloylaminochromanone

The synthesis design of the other required starting material, aminochromanone **4.2**, began with the challenge of achieving the desired substitution on the aromatic ring. When considering the amination of the chromanone scaffold by a two-step sequence of nitration-reduction the problem of regioselectivity becomes clear.

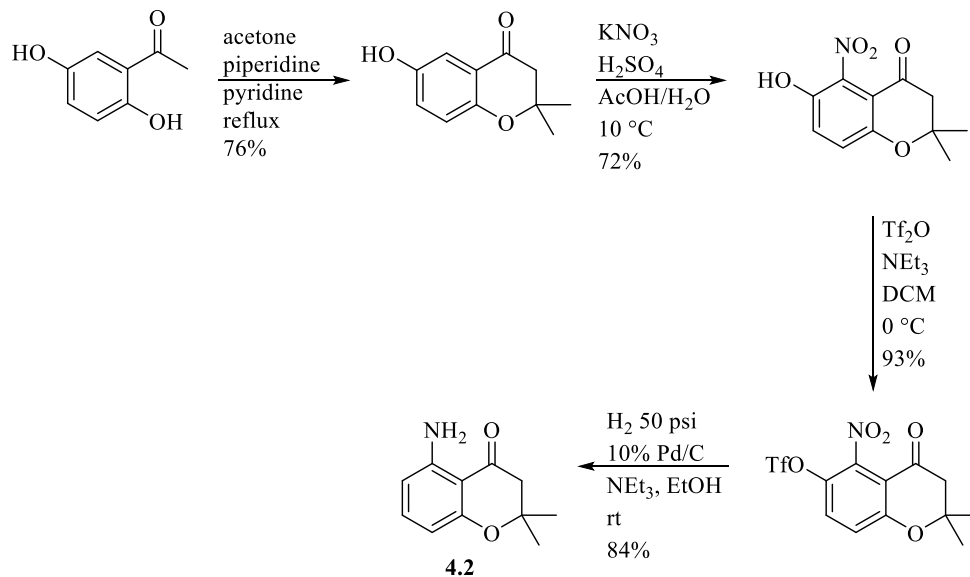


**Figure 4-5: Regioselectivity barrier to chromanone scaffold**

Electrophilic substitution on the aromatic ring in Figure 4-5 would be expected to occur at either the ortho or para positions relative to the ether group, with the para position being the more likely site for substitution due to steric effects. The desired amination could in theory be achieved by using a blocking group, but this would add two extra steps for the installation and removal of such a group.

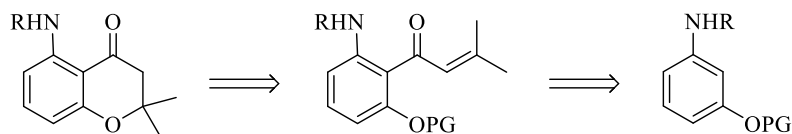


The patent from 2004 did report a detailed synthesis of the desired aminochromanone starting from 2,5-dihydroxyacetophenone (Scheme 4-6). This involved first formation of the chromanone ring followed by regioselective nitration, conversion of the alcohol to the corresponding triflate, and catalytic hydrogenation.



**Scheme 4-6: Patented method for aminochromanone synthesis**

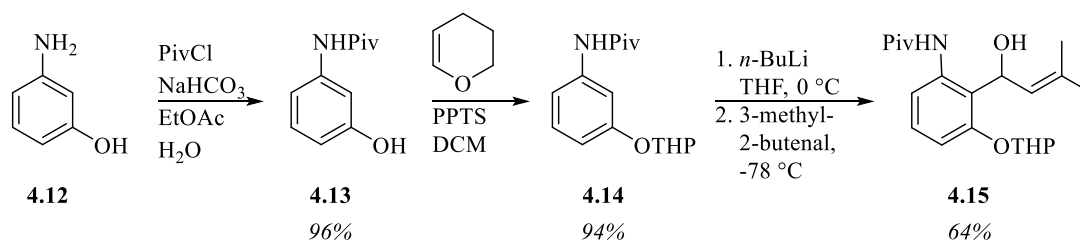
Despite this route seeming plausible, we sought an alternative strategy for two reasons: first, 2,5-dihydroxyacetophenone costs 5\$ per gram from Sigma Aldrich at the time of this writing and we were confident that we could find a more cost-effective starting point; second, the sequence above requires two chromatographic purifications which would be a hindrance in large scale preparations; After considering several options we devised the retrosynthesis shown in Figure 4-7, which circumvents the amination challenge by beginning with the nitrogen atom preinstalled.



**Figure 4-7: Retrosynthetic analysis of amidochromanone**

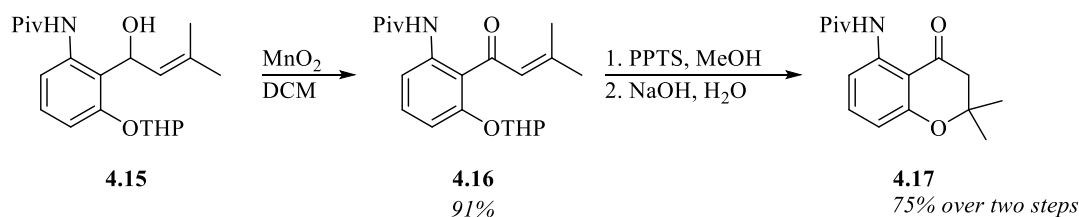
The chromanone would be formed by intramolecular conjugate addition of a phenol oxygen onto the  $\beta$ -carbon of the enone skeleton. We envisioned forming the carbon skeleton using directed ortho metalation (DoM)<sup>117</sup> on bis-protected 3-aminophenol that is readily available from 3-aminophenol, which is commercially available and very inexpensive (\$0.20/gram).

Installation of the protecting groups proceeded cleanly in high yields without incident or need for purification on decagram scales (Scheme 4-8).<sup>118</sup> The pivaloyl and tetrahydropyranyl protecting groups were chosen because of their established efficacy in DoM reactions. The directed ortho metalation was accomplished using *n*-butyllithium at 0 °C—at lower temperatures no reaction took place. Treating the lithiated species with 3-methyl-2-butenal gave the desired alcohol (**4.15**) as an inseparable mixture of diastereomers that was carried on to the next reaction as is.



**Scheme 4-8: Directed ortho metalation strategy**

Oxidation of the alcohol was achieved with manganese dioxide that had been oven dried overnight (Scheme 4-9). This reaction required a large excess of the oxidizing agent, which is consistent with literature reports for this transformation. Attempts to install the desired acyl group directly by quenching the lithiated species derived from **4.14** with either an acid chloride or ester were not successful and generally returned unreacted starting material with additional unidentified products. Removal of the tetrahydropyranyl group was complete within one hour after stirring at room temperature with catalytic pyridinium *p*-toluenesulfonate in methanol. We discovered that removing the methanol by rotary evaporation and then adding of a sodium hydroxide solution gave the desired *N*-pivaloylamidochromanone **4.17** in one pot, in pure form after a simple filtration. This one-pot sequence proceeded in greater yields than when performed as a two-step sequence. If desired, the pivaloyl group can be removed at this stage by heating in hydrochloric acid to give the corresponding aminochromanone.<sup>119</sup>



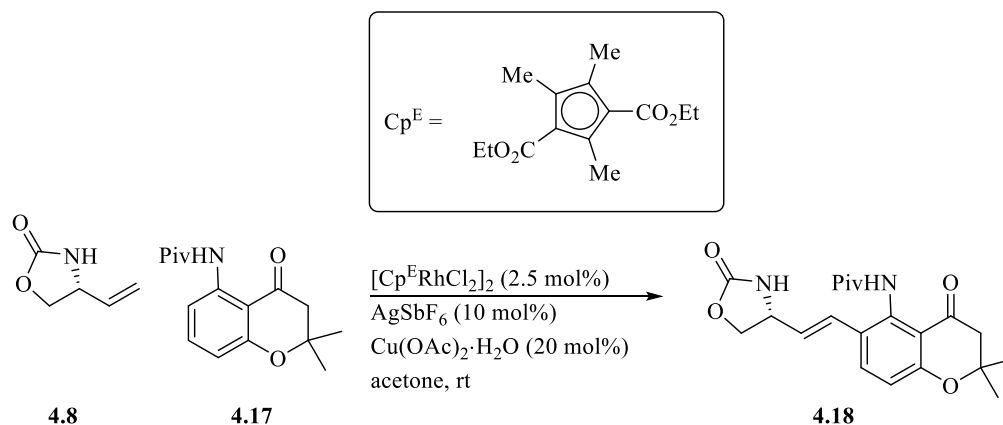
**Scheme 4-9: Completion of chromanone ring**

This overall reaction sequence represented a significant advancement in the scalability of the synthesis of fusarochromanone—pivaloyl-protected aminochromanone **4.17** can be accessed in multi-gram quantities through simple transformations from readily available 3-aminophenol, with the only chromatographic purification being after the directed ortho-

metalation step—though we have found that simply passing the crude reaction mixture through silica suffices without the need for a full scale purification.

### 4.3 Completion of Fusarochromanone Synthesis

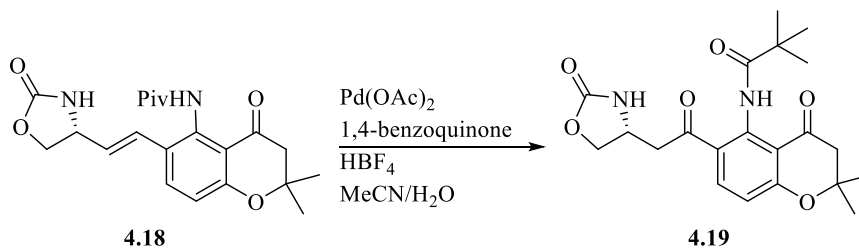
For the completion of our synthesis we based our strategy on Tanaka's work, constructing the key carbon-carbon bond using a rhodium catalyst, kindly prepared by Dr. Cleary.<sup>120</sup> We imagined the oxidative coupling reaction used by Tanaka on the *N*-acetyl version of **4.17** could be generalized to our pivaloyl-protected variant. Indeed, after stirring with the catalyst system in acetone under an open atmosphere for 16 hours, the desired product **4.18** was isolated in 70% yield after column chromatography (Scheme 4-10).



**Scheme 4-10: Rhodium(III) oxidative coupling**

The next step of Tanaka's synthetic route involved a Wacker oxidation that used perchloric acid. This presented a problem because working with this compound requires specially-equipped fume hoods. Desiring to circumvent the use of perchloric acid, a brief screening of alternate protocols was performed. Literature precedent shows that oxidation of internal

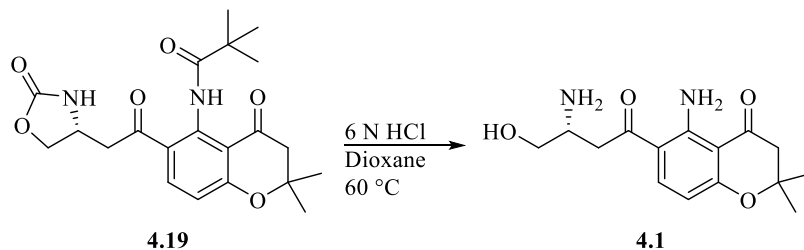
alkenes can be challenging and often requires a mineral acid additive to work effectively. Gratifyingly, replacing the perchloric acid with fluoroboric acid gave the ketone **4.19** with no loss in yield (64%, Scheme 4-11).<sup>121</sup>



**Scheme 4-11: Wacker oxidation**

The final step of the synthesis is to remove the pivaloyl and the oxazolidinone carbonyl protecting groups. Repeating the protocol published by Tanaka (heating the substrate at 50 °C for 3 days) gave promising results. The desired product was detected by LCMS and several key peaks were identified by proton NMR. Not surprisingly, the majority of the fusarochromanone from this reaction was obtained as the hydrochloride salt which, being insoluble in common organic solvents, was not present in the proton NMR of the crude reaction mixture. However, it was isolated from the crude material after trituration with dioxane and column chromatography. Additionally, it was found by LCMS that the reaction mixture contained a significant amount of both unreacted starting material and material where the pivaloyl group remained intact. Pivaloyl amides are known to be resistant to hydrolysis, with reported conditions for this transformation usually involving heating the substrate in concentrated hydrochloric acid.<sup>119</sup> Unfortunately, heating our starting material at reflux in concentrated HCl resulted in decomposition. Eventually, we discovered that heating **4.19** at 60 °C in 6 N HCl/dioxane overnight gave

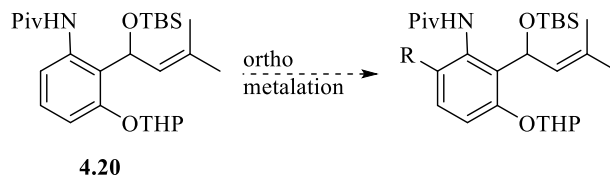
fusarochromanone in 30% yield (Scheme 4-12). Efforts to optimize this hydrolysis step are underway—there appears to be a tenuous balance between effective protecting group removal and product decomposition. The spectroscopic data obtained from the synthetic sample of fusarochromanone matched the reported data from the literature.



**Scheme 4-12: Completion of fusarochromanone**

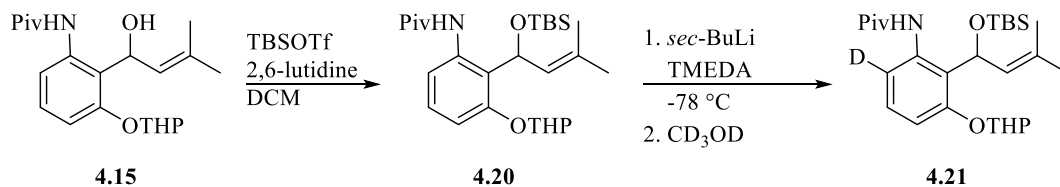
#### 4.4 Alternative Strategies and Methodology Pursued

Concurrent with our efforts to obtain samples of fusarochromanone for collaborator use, we attempted to develop a new synthetic approach to the natural product. Our first thought was to exploit directed ortho metalation for a second time in the synthesis (Figure 4-13)



**Figure 4-13: Double-DoM strategy to construct FC101 skeleton**

Because we anticipated problems with the metalation of ketone **4.16** due to possible alpha carbon reactions, we instead went to our supply of alcohol **4.15**, again used as a mixture of diastereomers, and carried out the facile TBS protection (Scheme 4-14). The product of this reaction was also obtained as an inseparable mixture of diastereomers and was used as such. Directed ortho metalation was attempted under a variety of conditions, mostly using freshly filtered *sec*-butyllithium in diethyl ether<sup>122</sup> (significant solvent polymerization was observed using the standard THF conditions) followed by quenching with deuterated methanol. Deuterium was chosen as the electrophile in order to judge the success of the lithiation step. Additionally, the use of deuterated methanol simplified the interpretation of the reaction success, which was judged by the disappearance of the proton NMR signal at 7.8 ppm, corresponding to the lithiated site.



**Scheme 4-14: Ortho metalation trial reaction**

NMR of the crude reaction mixture seemed promising—the aforementioned peak was almost completely absent by proton NMR after treating **4.20** with *sec*-butyllithium/TMEDA in diethyl ether at -78 °C followed by addition of deuterated methanol. However, after column chromatography, the desired deuterated product was only recovered in 10% yield, with a significant portion of the yield being lost to an aniline

product, indicating that under the ortho metalation conditions the pivaloyl group proved labile.

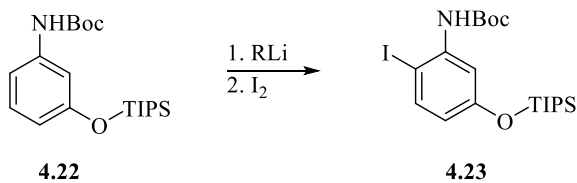
#### 4.5 Conclusions and Future Work

The work presented here demonstrates a new, scalable approach to the uniquely substituted aromatic ring of fusarochromanone that was successfully elaborated to the natural product. Directed ortho metalation emerged as a powerful tool for the construction of the chromanone carbon skeleton, and it allowed us to begin the synthesis with the challenging nitrogen atom preinstalled. This synthetic sequence requires no chromatographic purification and all steps can be carried out on multigram scales. Importantly, the *N*-pivaloylaminochromanone is obtained in high purity from the final 2-step, one-pot procedure after simple filtration. This compound can be effectively used, analogous to the *N*-acetyl derivative employed by Tanaka, in the key oxidative olefination reaction. The Wacker oxidation has also been optimized to not require special working conditions.

Despite this progress, our laboratory's efforts toward the large-scale synthesis of fusarochromanone are far from complete. First, the final deprotection step should be optimized—removing the pivaloyl group is feasible, but the conditions must be finely tuned so as not to cause the thermal decomposition of the natural product. We are also pursuing an *N*-Boc-protected aminochromanone as an alternative to the *N*-pivaloyl variant as this should simplify protecting group removal. Additionally, other routes to fusarochromanone are currently being pursued—of particular interest to us is a report that



directed ortho metalation of compound **4.22** proceeds to give substitution at a site analogous to the position of the side chain of fusarochromanone (Figure 4-15).



**Figure 4-15: Promising alternate method for key C-C bond formation**

This chapter has highlighted the promise of fusarochromanone and made the case that it is worthy of synthetic study. Its seemingly simple structure presents an intriguing challenge to synthetic chemists while also holding great promise for large-scale synthesis. Work in our laboratory will continue toward this goal so that fusarochromanone's anticancer potential can be realized at the clinical level.

## CONCLUDING REMARKS

The fundamental importance of aromatic compounds cannot be overstated—they are of near universal utility in human society, from materials science and device fabrication to pharmaceutical and medicinal applications. The work presented here highlights some of the synthetic strategies used by chemists to construct uniquely substituted aromatic compounds, specifically buckybowls and chromanone natural products. The discovery and study of tridecacyclene, a novel polycyclic aromatic hydrocarbon which contains a cyclooctatetraene core has been reported and it is currently being studied for use in materials chemistry applications. The study of the mechanism of formation of tridecacyclene was both challenging and enlightening, revealing unique reactivity of acenaphthenone dimers that has not previously been reported.

A separate yet equally interesting aromatic compound, the natural product fusarochromanone, was synthesized by means of a novel route to the aminochromanone scaffold. Fusarochromanone represents a promising synthetic target due to its established anticancer activity, though its *in vivo* effects are less potent. Continued efforts by chemists toward the synthesis of this fungal metabolite, such as those presented here, will aid the biomedical community in designing and evaluating new fusarochromanone analogues for the potential treatment of various cancers.

Finally, in addition to these synthetic pursuits of aromatic compounds, the reaction of other interesting pi-based systems was explored—namely, the reaction of vinyl cations with alkenes. The work presented in this chapter showcases the variable reactivity of vinyl cations and that small changes in the substrate precursor used to generate the vinyl

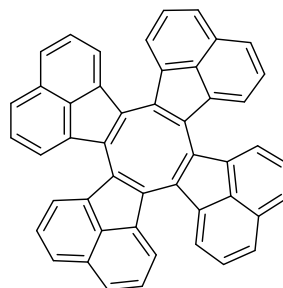
cation can have large implications for the reaction pathways. The development of this type of reactivity into useful methodology in the future will require careful substrate design. Additionally, these findings add to the existing knowledge of the reactivity of vinyl cation intermediates, an area of chemistry that is still underdeveloped.

Overall, this work has focused on the synthesis and reactivity of unique pi systems: contorted polycyclic aromatic hydrocarbons, an aromatic fungal metabolite with promising biological uses, and the reaction of vinyl cations with remote alkenes. The findings that have been described in this dissertation, as in most scientific pursuits, raise just as many questions as they provide answers. As such, these results can provide a worthy starting point for future endeavors.

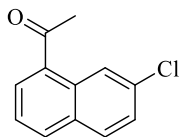
## EXPERIMENTAL

All reactions were performed under an atmosphere of nitrogen in flame-dried glassware. Solvents were removed in vacuo using a rotary evaporator attached to a dry vacuum pump, and further dried under reduced pressure on a high vacuum line. Tetrahydrofuran (THF) and dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) were dried via a solvent-dispensing system. Diisopropylamine was freshly distilled from  $\text{CaH}_2$  prior to use. All other commercially available reagents were used without further purification. Flash column chromatography was performed on silica gel (230-400 mesh) as well as on a CombiFlash® Rf 150 system using RediSep® Rf Gold silica columns. TLC analysis was carried out using silica on glass plates. Visualization of TLC plates was achieved using ultraviolet light, ceric ammonium molybdate, or potassium permanganate.  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were collected at room temperature on a 500 MHz spectrometer (Bruker or Varian) and a 125 MHz spectrometer (Bruker) respectively in  $\text{CDCl}_3$ .  $^1\text{H}$  NMR chemical shifts are reported in ppm ( $\delta$  units) downfield from tetramethylsilane, and  $^{13}\text{C}$  NMR spectra are referenced to the  $\text{CDCl}_3$  signal at 77.0 ppm. IR data were collected on a Shimadzu IR Affinity-1 FTIR and the values are reported in wavenumbers. Exact mass analysis was performed on a Waters Xevo G2-XS LCMS-QTOF operated in positive ESI mode. **Acknowledgement:** the experimental work presented here was supported in part by NIH grants S10-OD018126 and P30-GM118228 and NSF Grant # CHE-1665113.

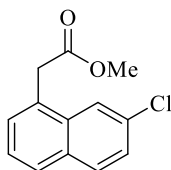
## Chapter 2 Experimental



**Tridecacyclene (2.2):**  $\text{TiCl}_4$  (0.82 mL, 7.5 mmol) was added to *o*-dichlorobenzene (10 mL) in a flame-dried, 100 mL 3-neck flask under a nitrogen atmosphere. The solution was heated to reflux followed by addition of a solution of 1-acenaphthenone (0.210 g, 1.25 mmol) in *o*-dichlorobenzene (10 mL). After stirring at reflux for 15 minutes, the reaction was poured into an Erlenmeyer flask containing 10 mL of concentrated HCl in ice. The mixture was extracted with dichloromethane and the organic layer was dried over magnesium sulfate. Removal of the solvent under reduced pressure followed by column chromatography (25% dichloromethane in cyclohexane) gave 40 mg (21% yield) of tridecacyclene (**2.2**) as a brown solid.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (d, 1H,  $J = 8.0$  Hz), 7.67 (d, 1H,  $J = 6.9$  Hz), 7.56 (t, 1H,  $J = 7.5$  Hz)  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  140.6, 137.7, 129.9, 128.2, 127.7, 127.4, 125.0 HRMS ESI  $[\text{M}+1]$  Calcd for  $\text{C}_{48}\text{H}_{25}$  601.1956  $m/z$ ; Found 601.1951. Full spectroscopic and X-ray crystallography data can be found in Dr. Sumy's dissertation.<sup>123</sup>

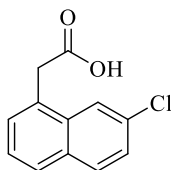


**1-(7-chloronaphthalen-1-yl)ethanone (2.4):** In a flame-dried 250 mL round-bottom flask, 10.0 g (61.5 mmol) of 2-chloronaphthalene was dissolved in 100 mL of anhydrous dichloromethane under a nitrogen atmosphere. The solution was cooled to 0 °C and 25 g (190 mmol) of aluminum chloride was added. When the mixture became dark green, it was cooled to -78 °C followed by addition of 9.1 mL (127 mmol) of acetyl chloride via syringe. The reaction was kept at -78 °C for 5 h before being allowed to warm up to room temperature overnight. The reaction was quenched slowly with a 10% HCl solution on ice before being transferred to a separatory funnel. The products were extracted with dichloromethane and the organic layer was dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a crude tan solid that was purified either by recrystallization with methanol or column chromatography (30% dichloromethane in hexanes) to give 10.0 g (80% yield) of the desired isomer **2.4** as a white solid. Spectral data for this compound matched the reported values from the literature.<sup>41</sup>

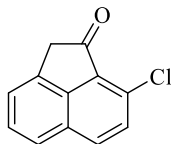


**Methyl 2-(7-chloronaphthalen-1-yl)acetate (2.5):** In a flame-dried 3-neck 500 mL round-bottom flask fitted with a reflux condenser, 6.6 g (32.35 mmol) of 1-(7-chloro-1-naphthalenyl)ethanone and 11.0 g (169.87 mmol) of silver nitrate were dissolved in a

mixture of methanol (145 mL) and trimethylorthoformate (49 mL) under a nitrogen atmosphere. Iodine (8.2 g, 32.35 mmol) was then added and the reaction was heated to reflux for 5 h until full conversion of the starting material was observed by TLC. The silver salts were removed by filtration and the filtrate was washed with 250 mL of water. After extraction with dichloromethane and drying over magnesium sulfate, the solvent was removed under reduced pressure to give 7.4 g (97.4% yield) of ester **2.5** as a yellow oil that slowly crystallized. Spectral data for this compound matched the reported values from the literature.<sup>41</sup>

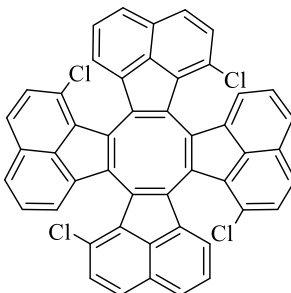


**2-(7-chloronaphthalen-1-yl)acetic acid (2.6):** In a 250 mL round-bottom flask fitted with a condenser, 7.4 g (31.5 mmol) of methyl 2-(7-chloronaphthalen-1-yl)acetate was dissolved in 95 mL of tetrahydrofuran and 95 mL of a 1 M sodium hydroxide solution was added. The reaction was heated to 50 °C for 16 h. The reaction was then poured into concentrated HCl and extracted with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave 6.95 g (quantitative yield) of carboxylic acid **2.6** as an off-white solid. Spectral data for this compound matched the reported values from the literature.<sup>41</sup>



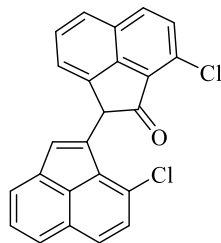
**8-Chloroacenaphthylen-1(2H)-one (1.27):** In a flame-dried 3-neck 1000 mL round-bottom flask fitted with a reflux condenser, 3.0 g (13.6 mmol) of 2-(7-chloronaphthalen-1-yl)acetic acid was dissolved in 50 mL of thionyl chloride. The brown solution was heated to reflux under nitrogen for 1 h. The reflux condenser was then exchanged for a distillation apparatus and the thionyl chloride was removed by distillation under a nitrogen atmosphere. Dichloromethane (750 mL) was then added and the reaction was cooled to 0 °C. Aluminum chloride (3.7 g, 28 mmol) was added and the green solution was kept at 0 °C for 1 h. The mixture was then heated to reflux for 30 minutes before being cooled to room temperature followed by addition of a solution of KF (2.5 g, 43 mmol) in 10% HCl (110 mL). This mixture was transferred to a separatory funnel and extracted with dichloromethane and the red-brown organic layer was dried over magnesium sulfate. Removal of the solvent under reduced pressure and purification of the residue by column chromatography (50% dichloromethane in hexanes) gave 2.4 g (85% yield) of the title compound **1.27** as a white solid. Spectral data for this compound matched the reported values from the literature.<sup>41</sup>



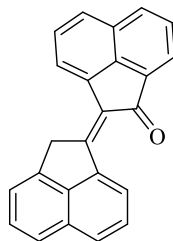


**3,9,15,21-Tetrachlorocycloocta[1,2-*a*:3,4-*a'*:5,6-*a''*:7,8-*a'''*]*tetraacenaphthylene***

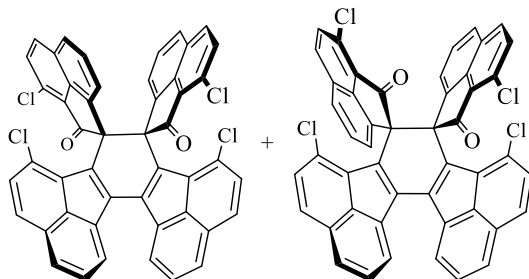
**(1.37):**  $\text{TiCl}_4$  (0.66 mL, 6 mmol) was added to 8 mL of *o*-dichlorobenzene in a flame-dried 3-neck round-bottom flask fitted with a condenser under an atmosphere of nitrogen. The yellow solution was heated to 180 °C and a solution of 8-chloroacenaphthylen-1(2H)-one (200 mg, 0.98 mmol) in *o*-dichlorobenzene (8 mL) was added all at once. The reaction was stirred at 180 °C for another 30 minutes before being cooled to room temperature and poured onto a mixture of concentrated HCl and ice (20 mL). The mixture was transferred to a separatory funnel and extracted with dichloromethane and the organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure to give a black residue that was purified by column chromatography (25% dichloromethane in hexanes) to give the cyclotetramer product **1.37** (19.8 mg, 11% yield) as a red solid. Interpretable NMR data for **1.37** was unable to be obtained due to the presence of other regioisomers or potential atropisomers. HRMS ESI  $[\text{M}+1]$  Calcd for  $\text{C}_{48}\text{H}_{20}\text{Cl}_4$  737.0397  $m/z$ ; Found 737.0400  $m/z$ .



**3,8'-Dichloro-[1,1'-biacenaphthylen]-2(1H)-one (2.7):** 8-chloroacenaphthylen-1(2H)-one (150 mg, 0.74 mmol) was dissolved in anhydrous toluene (6 mL) in a flame-dried 2-neck 50 mL round-bottom flask under an atmosphere of nitrogen. The mixture was heated to 55 °C and BBr<sub>3</sub> (0.75 mL, 8.14 mmol) was added via syringe all at once. The reaction was stirred at 55 °C for 16 h and then cooled to room temperature. The reaction was quenched with 10% HCl and after allowing the red reaction to stir in acid at room temperature for several hours, a yellow solution was obtained. The product was extracted with dichloromethane and the organic layer was dried over magnesium sulfate. Removal of the solvent under reduced pressure followed by column chromatography (50% dichloromethane in hexanes) gave 100 mg (70% yield) of the dimeric product **2.7** as a yellow wax. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.85 (m, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 3H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.46 (m, 2H), 6.52 (s, 1H), 5.97 (s, 1H) <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 198.8, 142.8, 139.1, 137.7, 137.6, 135.1, 132.7, 131.6, 130.4, 130.2, 130.0, 129.9, 129.5, 129.3, 128.8, 128.7, 127.8, 127.4, 127.0, 126.7, 124.8, 124.4, 122.6, 52.0 HRMS ESI [M+1] Calcd for C<sub>24</sub>H<sub>12</sub>Cl<sub>2</sub>O 387.0343 *m/z*; Found 387.0338 *m/z*.



**(Z)-2H,2'H-[1,1'-biacenaphthylenylidene]-2-one (2.9):** 1-acenaphthenone (1.7 g, 10.11 mmol) was dissolved in acetic acid (7.5 mL) and hydrochloric acid (3.75 mL) and heated at reflux for 16 hours. The product was collected as a yellow solid (**2.9**) after filtration (1.2 g, 75% yield) and washing with water. Spectral data for this compound matched the reported values from the literature.<sup>55</sup>

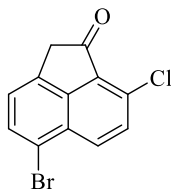


**Colored Compounds Red 2.10 (left) and Purple 2.11 (right):** A mixture of *p*-toluenesulfonic acid monohydrate (0.22 g, 1.16 mmol) and propionic acid (0.09 mL, 1.16 mmol) in 1 mL of *o*-dichlorobenzene was heated to 140 °C in a 2-neck 50 mL round-bottom flask equipped with a reflux condenser under nitrogen. Dimer **2.7** (90 mg, 0.23 mmol) dissolved in 3 mL of *o*-dichlorobenzene was added to the hot reaction mixture by syringe. The black solution was heated for 12 hours and was then quenched with 5 M NaOH. The reaction was extracted with dichloromethane and the organic fractions were dried over magnesium sulfate and the solvent was removed. The crude material was

purified by column chromatography (3:2 dichloromethane:hexanes) to give **2.10** as a red solid (38 mg, 42% yield) and **2.11** as a purple solid (5.3 mg, 5.9% yield).

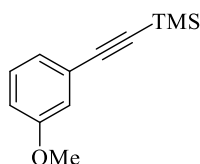
**2.10:** Red solid,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.46 (d,  $J = 7$  Hz, 1H), 7.90 (d,  $J = 8.05$  Hz, 1H), 7.83 (d,  $J = 8.6$  Hz, 1H), 7.76 (dd,  $J = 8.15, 7.1$  Hz, 1H), 7.64 (dd,  $J = 8.5, 2.6$  Hz, 2H), 7.46 (d,  $J = 6.95$  Hz, 1H), 7.42 (d,  $J = 8.6$  Hz, 1H), 7.33 (dd,  $J = 8.3, 7.1$  Hz, 1H), 7.12 (d,  $J = 8.5$  Hz, 1H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  197.1, 142.9, 137.4, 136.1, 134.9, 134.4, 134.1, 132.3, 131.1, 131.0, 130.6, 130.5, 129.6, 129.2, 129.1, 128.8, 128.3, 128.2, 127.3, 127.0, 126.1, 125.1, 123.9, 64.8 HRMS ESI [ $\text{M}+1$ ] Calcd for  $\text{C}_{48}\text{H}_{20}\text{Cl}_4\text{O}_2$  769.0296  $m/z$ ; Found 769.0305  $m/z$ .

**2.11:** Purple solid,  $^1\text{H}$  NMR ( $\text{d}_6\text{-DMSO}$ , 500 MHz, 65 °C)  $\delta$  8.57 (d,  $J = 7.05$  Hz, 1H), 8.12 (d,  $J = 8.2$  Hz, 1H), 8.09 (d,  $J = 8.65$  Hz, 1H), 7.93 (m, 2H), 7.82 (d,  $J = 8.25$  Hz, 1H), 7.54 (d,  $J = 8.6$  Hz, 1H), 7.25 (d,  $J = 8.5$  Hz, 1H), 7.13 (t,  $J = 15.45, 7.25$  Hz, 1H), 6.57 (d,  $J = 6.95$  Hz, 1H)  $^{13}\text{C}$  NMR ( $\text{d}_6\text{-DMSO}$ , 125 MHz, 65 °C)  $\delta$  197.0, 142.4, 137.5, 135.6, 133.6, 133.3, 133.2, 132.5, 130.3, 130.0, 129.7, 129.4, 129.2, 128.9, 128.5, 128.4, 127.9, 127.8, 127.4, 126.7, 126.6, 125.5, 122.4, 63.9 HRMS ESI [ $\text{M}+1$ ] Calcd for  $\text{C}_{48}\text{H}_{20}\text{Cl}_4\text{O}_2$  769.0296  $m/z$ ; Found 769.0308  $m/z$ . Full spectroscopic and X-ray crystallography data can be found in Dr. Sumy's dissertation.<sup>123</sup>



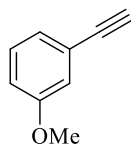
**5-Bromo-8-chloroacenaphthylen-1(2H)-one (2.23):** 8-chloroacenaphthylen-1(2H)-one (100 mg, 0.49 mmol) and *N*-bromosuccinimide (89.5 mg, 0.50 mmol) were dissolved in

0.7 mL of anhydrous DMF in a 10 mL round-bottom flask under nitrogen. The reaction was heated to 50 °C overnight. The mixture was then poured into water and extracted with dichloromethane. Removal of the solvent under reduced pressure and column chromatography (1:1 dichloromethane:hexanes) gave the title compound **2.23** as a pink solid (13.8 mg, 10% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.20 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 9 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 2H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 198.9, 144.3, 133.5, 132.2, 131.6, 131.4, 130.5, 130.1, 129.1, 122.9, 118.8, 42.0 HRMS ESI [M+1] Calcd for C<sub>12</sub>H<sub>6</sub>BrClO 280.9369 *m/z*; Found 280.9367 *m/z*.

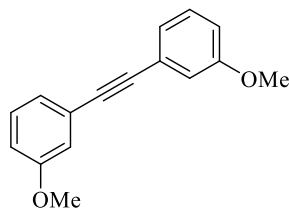


**((3-methoxyphenyl)ethynyl)Trimethylsilane (2.33):** In a flame-dried 100 mL round-bottom flask fitted with a condenser and flushed with nitrogen, 150 mg (0.213 mmol) of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, 2.5 g (10.68 mmol) of 3-iodoanisole, 101 mg (0.534 mmol) of copper iodide and 6 mL (43 mmol) of degassed triethylamine were dissolved in 18 mL of anhydrous, degassed tetrahydrofuran. TMS-acetylene (1.67 mL, 11.75 mmol) was then added via syringe all at once. The reaction mixture turned black and began to reflux on its own without any added heat source. After 1 hour, TLC indicated consumption of the starting material. The reaction was diluted with water and extracted with ethyl acetate. The organic extracts were dried with magnesium sulfate and the solvent was removed. Column chromatography (20% dichloromethane in hexanes) gave 2.05 g (94% yield) of the

coupling product **2.33** as a colorless oil. Spectral data for this compound matched the reported values from the literature.<sup>124</sup>

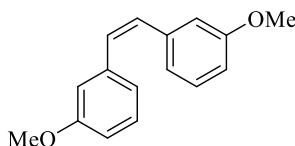


**1-Ethynyl-3-methoxybenzene (2.31):** 2.06 g (10.06 mmol) of **2.33** was dissolved in 40 mL of methanol with potassium carbonate (139 mg, 1 mmol). The reaction was stirred at room temperature under nitrogen and monitored by TLC. After full consumption of the starting material was observed after 2 hours, the reaction was quenched with a saturated ammonium chloride solution and extracted with ethyl acetate. Drying the organic layer with magnesium sulfate and removing the solvent under reduced pressure gave 1.2 g (90% yield) of alkyne **2.31** as a volatile, colorless oil. Spectral data for this compound matched the reported values from the literature.<sup>124</sup>

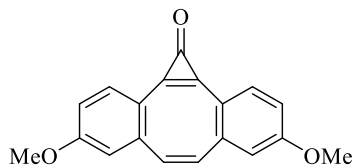


**1,2-Bis(3-methoxyphenyl)ethyne (2.34):** In a flame-dried 3-neck 100 mL round-bottom flask that had been purged with nitrogen, 3-ethynylanisole (1.77 g, 13.44 mmol), 3-iodoanisole (2.99 g, 12.80 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (472 mg, 0.67 mmol), and copper iodide (256 mg, 1.34 mmol) were dissolved in 50 mL of anhydrous, degassed THF. Diisopropylethylamine (7.0 mL, 40.31 mmol) was added by syringe and the reaction was

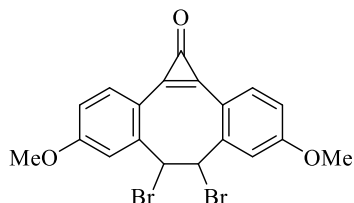
stirred at room temperature under nitrogen. After 10 minutes of stirring at room temperature the reaction was quenched with a saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was removed to give a crude residue that was purified by column chromatography (8:1 hexanes:ethyl acetate) to give 2.95 g (97% yield) of the product **2.34** as a white solid. Spectral data for this compound matched the reported values from the literature.<sup>75</sup>



**(Z)-3,3'-dimethoxystilbene (2.35):** In a flame-dried 2-neck 50 mL round-bottom flask fitted with a condenser, alkyne **2.34** (672 mg, 2.82 mmol) was dissolved in 12 mL of anhydrous THF. The solution was cooled to -78 °C and Ti(O<sup>*i*</sup>Pr)<sub>4</sub> (1.67 mL, 5.64 mmol) was added via syringe. *n*-butyllithium (11.28 mmol) was added dropwise to the yellow mixture causing a color change to red-brown. The reaction was then warmed to 50 °C and the color of the solution became a deep red-black. After 15 minutes of stirring at this temperature, complete consumption of the starting material was observed by TLC (10% ethyl acetate in hexanes). The reaction was cooled to 0 °C and 10 mL of a saturated aqueous ammonium chloride solution was added followed by addition of 10 mL of ethyl acetate. The mixture was extracted with ethyl acetate (3 x 20 mL) and the organic layer was washed with brine, dried over magnesium sulfate and the solvent was removed to give pure product (**2.35**) as an orange oil (650 mg, quantitative yield). Spectral data for this compound matched the reported values from the literature.<sup>75</sup>



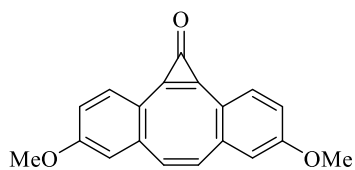
**(Z)-4,9-Dimethoxy-1H-dibenzo[a,e]cyclopropa[c][8]annulen-1-one (2.36):** Aluminum chloride (3.08 g, 23.0 mmol) and tetrachlorocyclopropene (1.45 mL, 9.24 mmol) were dissolved in anhydrous DCM (100 mL) in a flame-dried 3-neck 500 mL round-bottom flask under nitrogen and the mixture was stirred at room temperature for 20 minutes. The mixture was cooled to -78 °C and (Z)-3,3'-dimethoxystilbene (1.85 g, 7.70 mmol) in 40 mL of DCM was added over 1.5 h by syringe pump and the reaction became dark green. The reaction was stirred at -78 °C for 1 h and then it was allowed to warm to room temperature over 1 h. 100 mL of water was then added to the red/brown solution. Immediately upon addition of water a yellow precipitate was formed that was collected by filtration to afford the cyclopropenone product **2.36** as a yellow solid (1.34 g, 60% yield). Note: to maximize the yield, the filtrate was concentrated and filtered again. Spectral data for this compound matched the reported values from the literature.<sup>75</sup>



**6,7-Dibromo-4,9-dimethoxy-6,7-dihydro-1H-dibenzo[a,e]cyclopropa[c][8]annulen-1-one (2.37):** 1.12 g (3.86 mmol) of alkene **2.36** was dissolved in 60 mL of anhydrous DCM in a flame-dried 2-neck 500 mL round-bottom flask under nitrogen. The reaction was

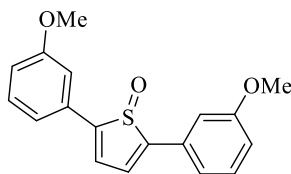


cooled to 0 °C and Br<sub>2</sub> (0.30 mL, 5.79 mmol) dissolved in DCM (20 mL) was added dropwise by syringe. The orange mixture was stirred at room temperature for 2 hours and quenched with 60 mL of saturated aqueous sodium thiosulfate. The product precipitated from the solution and was collected by filtration. Additional product was collected by extracting the filtrate with dichloromethane, removing the solvent and purifying the residue by column chromatography (1% methanol in dichloromethane). The product (**2.37**) was isolated as a white solid (1.25 g, 72% yield). Spectral data for this compound matched the reported values from the literature.<sup>75</sup>

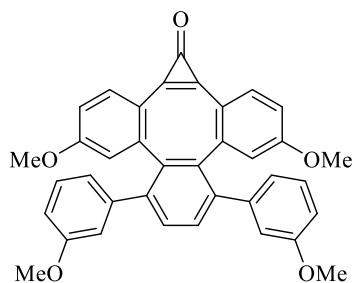


**4,9-Dimethoxy-6,7-didehydro-1H-dibenzo[*a,e*]cyclopropa[*c*]cycloocten-1-one (2.29):**

In a 50 mL round-bottom flask, dibromide **2.37** (150 mg, 0.33 mmol) was dissolved in 10 mL of ethanol and a solution of potassium hydroxide (200 mg, 3.56 mmol) in 10 mL of ethanol was added. The reaction was stirred overnight at room temperature. The reaction was quenched with 10% HCl until the pH was ~6, then extracted with dichloromethane. The dichloromethane extracts were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate and the solvent was removed to give alkyne **2.29** as a yellow solid (70 mg, 73% yield). Spectral data for this compound matched the reported values from the literature.<sup>75</sup>

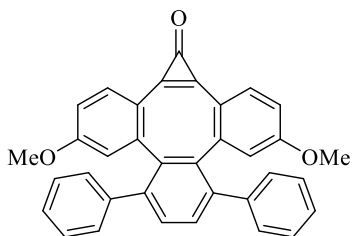


**2,5-Bis(3-methoxyphenyl)thiophene 1-oxide (2.30):** In a flame-dried 2-neck 100 mL round-bottom flask under nitrogen,  $\text{Cp}_2\text{ZrCl}_2$  (1.26 g, 4.31 mmol) was dissolved in anhydrous THF (20 mL) and cooled to  $-78\text{ }^\circ\text{C}$ . *n*-Butyllithium (8.62 mmol) was added dropwise and the yellow reaction was then warmed to room temperature over an hour. The dark red solution was next cooled to  $0\text{ }^\circ\text{C}$  and 3-ethynylanisole (1.14 g, 8.62 mmol) was added by syringe. The mixture was stirred at room temperature for 90 minutes and then cooled to  $-78\text{ }^\circ\text{C}$ .  $\text{SOCl}_2$  (0.31 mL, 4.31 mmol) was added dropwise and the black mixture became bright yellow. While still under nitrogen, silica for column chromatography was added directly to the reaction at  $-78\text{ }^\circ\text{C}$  and the nitrogen inlet was replaced with a vacuum line fitted with a liquid nitrogen trap and the THF was removed under reduced pressure. The product was then eluted from the silica using first dichloromethane as the eluent then switching to 40% ethyl acetate in hexanes. After isolation of the product spots, a filtration through a short plug of silica (ethyl acetate) gave thiophene oxide **2.30** as a bright yellow solid (200 mg, 18% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-7.32 (m, 4H), 7.26 (m, 2H), 6.94 (m, 4H), 3.86 (s, 6H)  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  160.1, 152.1, 132.0, 130.2, 123.9, 119.3, 115.3, 111.8, 55.4 HRMS ESI  $[\text{M}+1]$  calcd for  $\text{C}_{18}\text{H}_{17}\text{O}_3\text{S}$  313.0898; Found 313.0904.



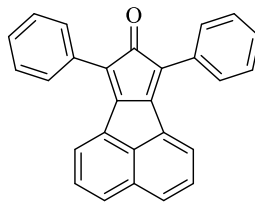
**4,11-Dimethoxy-6,9-bis(3-methoxyphenyl)-1H-**

**tribenzo[*a,c,e*]cyclopropa[*g*][8]annulen-1-one (2.28):** Thiophene oxide **2.30** (180 mg, 0.713 mmol) and alkyne **2.29** (171 mg, 0.594 mmol) were dissolved in 8 mL of anhydrous toluene in a 50 mL flame-dried round-bottom flask fitted with a condenser under nitrogen. The solution was heated to reflux for 16 h. The toluene was removed under reduced pressure and the product was purified by column chromatography (6% methanol in dichloromethane) to give the cycloaddition product **2.28** as a brown solid (125 mg, 38% yield). The proton NMR spectrum for this compound is shown in the Appendix.

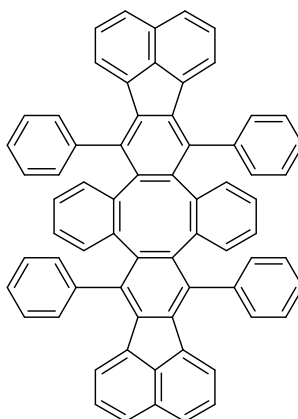


**4,11-Dimethoxy-6,9-diphenyl-1H-tribenzo[*a,c,e*]cyclopropa[*g*][8]annulen-1-one**

**(2.39):** 2,5-diphenyl thiophene oxide (**1.35**) was reacted with alkyne **2.29** in an analogous fashion to the preparation of compound **2.28** to give the title compound (**2.39**) in a 30% yield. The proton NMR spectrum for this compound is shown in the Appendix.



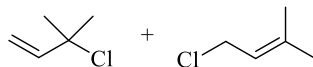
**7,9-Diphenyl-8H-cyclopenta[a]acenaphthylene-8-one (2.40):** 1,3-diphenyl acetone (2.0 g, 9.5 mmol) and acenaphthoquinone (1.73 g, 9.5 mmol) were dissolved in ethanol (10 mL) and toluene (1 mL) and a solution of potassium hydroxide (9.5 mmol) in ethanol (3 mL) was added. After stirring for 5 minutes, the product was collected by filtration as a dark purple solid in quantitative yield. Spectral data for this compound matched the reported values from the literature.<sup>84</sup>



**7,12,19,24-Tetraphenyldiacenaphtho[1,2-*b*:1',2'-*n*]tetraphenylene (2.41):** Cyclopentadienone **2.40** (196 mg, 0.55 mmol) and dibenzocyclooctadiyne (50 mg, 0.25 mmol) were dissolved in 5 mL of *o*-dichlorobenzene in a 50 mL round-bottom flask fitted with a condenser under nitrogen. The mixture was heated to 150 °C for 14 h and the solvent was removed under reduced pressure. The residue was purified by column chromatography (30% dichloromethane in hexanes) to give a mixture of the product and

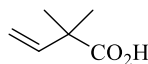
leftover cyclopentadienone **2.40**. Pure cycloaddition product **2.41** was isolated by recollecting it from several failed cyclodehydrogenation attempts.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.62 (m, 2H), 7.41 (t,  $J = 7.5$  Hz, 1H), 7.35 (t,  $J = 7.5$  Hz, 1H), 7.21 (t,  $J = 8$  Hz, 1H), 7.14 (t,  $J = 7$  Hz, 1H), 7.06 (d,  $J = 7.5$  Hz, 1H), 6.81 (dd,  $J = 3$  Hz, 5.5 Hz, 1H), 6.69 (dd,  $J = 3.5$  Hz, 6 Hz, 1H), 6.40 (d,  $J = 7.5$  Hz, 1H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  140.5, 140.0, 139.1, 137.4, 136.6, 136.0, 133.2, 131.4, 131.3, 131.0, 129.5, 128.2, 127.8, 127.5, 127.1, 126.4, 125.1, 123.2 HRMS ESI  $[\text{M}+1]$  Calcd for  $\text{C}_{68}\text{H}_{40}$  857.3208  $m/z$ ; Found 857.3184  $m/z$ .

## Chapter 3 Experimental



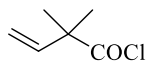
### **3-Chloro-3-methylbut-1-ene (3.40 left) and 1-Chloro-3-methylbut-2-ene (3.41 right):**

Cold (-5 °C) HCl (56 mL) was poured into 20 mL (182 mmol) of cold (-5 °C) 2-methyl-3-buten-2-ol. The reaction was stirred at 0 °C for 90 minutes after which time the mixture was transferred to a separatory funnel and the aqueous layer removed. The organic layer was washed with water (10 mL), brine (10 mL) and dried over sodium sulfate. The product was obtained as a clear oil (15.5 g, 82% yield) consisting of an 11:1 mixture of the two allylic chlorides (**3.40** and **3.41**). Spectral data for this compound matched the reported values from the literature.<sup>98</sup>

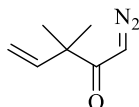


**2,2-dimethyl-3-butenoic acid (3.42):** In a flame-dried, 3-neck 250 mL round-bottom flask fitted with a condenser under nitrogen, magnesium turnings (4.36 g, 179 mmol) were suspended in 40 mL of anhydrous THF and stirred *vigorously*. The allyl chloride mixture (5.0 g, 48 mmol, **3.40** and **3.41**) in dry THF (12 mL) was added dropwise over 15 minutes with continued vigorous stirring. During this time the reaction became quite foamy and heated itself to reflux. After stirring for 30 minutes and allowing the reaction to cool to room temperature on its own, the dark gray solution was poured into a 500 mL beaker filled with finely crushed (by hammer) dry ice. The excess dry ice was allowed to sublime over 6 hours. The gel-like residue was acidified with 40 mL of 4 M HCl and extracted with

diethyl ether (2 x 50 mL). The organics were dried with sodium sulfate, and the solvent was removed *in vacuo* to give 3.2 g (58% yield) of carboxylic acid **3.42** as a pale-yellow oil. Spectral data for this compound matched the reported values from the literature.<sup>98</sup>

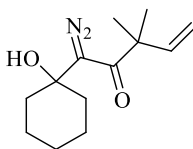


**2,2-dimethyl-3-butenoyl chloride (3.23):** Carboxylic acid **3.42** (3.23 g, 28.3 mmol) was dissolved in 40 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> and 5 drops of DMF were added. The solution was cooled to 0 °C and oxalyl chloride (34 mmol) was added dropwise. The cold bath was removed and the reaction was stirred at room temperature for 3 hours. The solvent was then removed under reduced pressure and the residue was purified by fractional distillation to give 2.00 g (53% yield) of 2,2-dimethyl-3-butenoyl chloride as a colorless oil. Spectral data for this compound matched the reported values from the literature.<sup>97</sup>



**1-Diazo-3,3-dimethylpent-4-en-2-one (3.43):** 2,2-dimethyl-3-butenoyl chloride (780 mg, 5.88 mmol) was added by syringe to a 250 mL round-bottom flask containing triethylamine (0.82 mL, 5.88 mmol) and freshly distilled diazomethane (prepared by treating Diazald® [1.76 g, 8.24 mmol] with a solution of potassium hydroxide [508 mg, 9.06 mmol] in diethyl ether [20 mL], water [1 mL], and 2-(2-ethoxyethoxy)ethanol [3 mL]) in diethyl ether (40 mL) at -78 °C. The solution was allowed to warm to room temperature overnight under a nitrogen atmosphere. The triethylamine hydrochloride salts were removed by filtration and

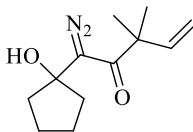
the salts were washed with hexanes. Removal of the solvent under reduced pressure afforded 700 mg (86% yield) of the diazoketone **3.43** as a yellow oil. Spectral data for this compound matched the reported values from the literature.<sup>97</sup>



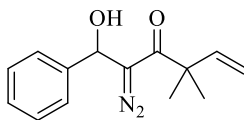
**Representative procedure for the generation of  $\beta$ -hydroxy- $\alpha$ -diazo ketones. 1-diazo-1-(1-hydroxycyclohexyl)-3,3-dimethylpent-4-en-2-one (**3.30**):** Cyclohexanone (0.15 mL, 1.45 mmol) and diazo ketone **3.43** (300 mg, 2.17 mmol) were dissolved in 6 mL of anhydrous THF in a flame-dried flask under nitrogen and the mixture was cooled to -78 °C. Freshly prepared lithium diisopropylamide (2.17 mmol in 6 mL of dry THF at -78 °C) was added dropwise and the yellow solution became red. The mixture was maintained at this temperature for 1 hour at which point 20 mL of saturated aqueous ammonium chloride was added. The cold bath was removed and the reaction was vigorously stirred as it warmed to room temperature to ensure proper mixing of the layers. During this period of warming and mixing the reaction became bright yellow. Extraction with diethyl ether, drying the organic layer over sodium sulfate, and removal of the solvent under reduced pressure gave an orange oil that was purified by column chromatography (10% ethyl acetate in hexanes) to afford 249 mg (73% yield) of addition product **3.30** as a bright yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  5.90 (dd,  $J$  = 10.5, 17.5 Hz, 1H), 5.21 (d,  $J$  = 10.5 Hz, 1H), 5.10 (d,  $J$  = 18 Hz, 1H), 4.49 (s, 1H), 1.94-1.87 (m, 2H), 1.80-1.70 (m, 2H), 1.60-1.50 (m, 3H), 1.47-1.4 (m, 2H), 1.3-1.27 (m, 1H), 1.28 (s, 6H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$



199.2, 141.0, 115.1, 71.7, 50.5, 36.0, 25.4, 24.2, 21.9 IR (film) 2067  $\text{cm}^{-1}$  HRMS ESI [Na adduct] Calcd for  $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$  259.1422  $m/z$ ; Found 259.1430  $m/z$ .

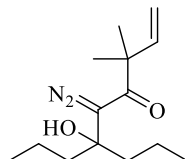


**1-Diazo-1-(1-hydroxycyclopentyl)-3,3-dimethylpent-4-en-2-one (3.47):** A mixture of cyclopentanone (0.13 mL, 1.45 mmol) and diazo ketone **3.43** (300 mg, 2.17 mmol) in THF (6 mL) was treated with a solution of LDA (0.36 M in THF, 2.17 mmol) according to the general procedure for the preparation of **3.30** to give addition product **3.47** in 40% yield (129 mg, 0.58 mmol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  5.91 (dd,  $J = 10.5, 17.5$  Hz, 1H), 5.22 (d,  $J = 10.5$  Hz, 1H), 5.11 (d,  $J = 17.5$  Hz, 1H), 4.14 (s, 1H), 2.10-2.04 (m, 2H), 1.92-1.85 (m, 2H), 1.71-1.62 (m, 4H), 1.29 (s, 6H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  199.0, 141.0, 115.2, 80.3, 50.4, 39.0, 24.1, 22.9 IR (film) 2067  $\text{cm}^{-1}$  HRMS ESI [Na adduct] Calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$  245.1266  $m/z$ ; Found 245.1267  $m/z$ .

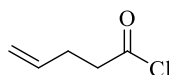


**2-Diazo-1-hydroxy-4,4-dimethyl-1-phenylhex-5-en-3-one (3.57):** A mixture of benzaldehyde (154 mg, 1.45 mmol) and diazo ketone **3.43** (300 mg, 2.17 mmol) in 6 mL of THF was treated with a solution of LDA in THF (2.17 mmol) according to the general procedure for the preparation of **3.30** to give addition product **3.57** in a 70% yield (248 mg, 1.02 mmol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.37 (d,  $J = 4$  Hz, 4H), 7.34-7.29 (m, 1H), 6.04

(d,  $J = 3$  Hz 1H), 5.92 (dd,  $J = 10.5, 17.5$  Hz, 1H), 5.21 (d,  $J = 10.5$  Hz, 1H), 5.12 (d,  $J = 17.5$  Hz, 1H), 3.29 (s, 1H), 1.31 (d,  $J = 8.5$  Hz, 6H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  196.5, 141.0, 138.5, 128.7, 128.3, 125.9, 115.4, 69.7, 50.2, 24.2 IR (film) 2083  $\text{cm}^{-1}$  HRMS ESI [Na adduct] Calcd for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2\text{Na}$  267.1109  $m/z$ ; Found 267.1105  $m/z$ .

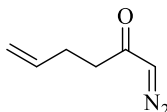


**5-Diazo-6-hydroxy-3,3-dimethyl-6-propylnon-1-en-4-one (3.55):** A mixture of 4-heptanone (165 mg, 1.45 mmol) and diazo ketone **3.43** (300 mg, 2.17 mmol) in 6 mL of THF was treated with a solution of LDA in THF (2.17 mmol) according to the general procedure for the preparation of **3.30** to give the addition product **3.55** in a 35% yield (128 mg, 0.51 mmol).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  5.91 (dd,  $J = 11, 17.5$  Hz, 1H), 5.23 (d,  $J = 11$  Hz, 1H), 5.11 (d,  $J = 17.5$  Hz, 1H), 4.90 (s, 1H), 1.7-1.58 (m, 4H), 1.45-1.30 (m, 4H), 1.28 (s, 6H), 0.92 (t,  $J = 7$  Hz, 6H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  199.3, 141.1, 115.2, 75.0, 69.1, 50.7, 41.3, 24.2, 17.1, 14.3 IR (film) 2075  $\text{cm}^{-1}$  HRMS ESI [Na adduct] Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}$  275.1735  $m/z$ ; Found 275.1732  $m/z$ .

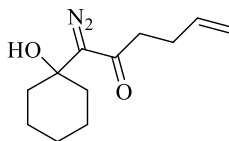


**4-Pentenoyl chloride:** 4-pentenoic acid (2.94 g, 29.4 mmol) was dissolved in 30 mL of dry  $\text{CH}_2\text{Cl}_2$  along with 3 drops of dry DMF. The solution was cooled to 0  $^\circ\text{C}$  and a 2 M solution of oxalyl chloride in  $\text{CH}_2\text{Cl}_2$  (35.3 mmol) was added dropwise. The reaction was

stirred at room temperature for 3 hours and the solvent was then removed. The resulting orange oil was purified by distillation to give 1.67 g (48% yield) of 4-pentenoyl chloride as a colorless oil. Spectral data for this compound matched the reported values from the literature.<sup>100</sup>

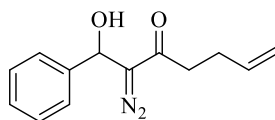


**1-Diazo-5-en-2-one (3.53):** 4-pentenoyl chloride (1.67 g, 14.1 mmol) was added to a 250 mL round-bottom flask containing a solution of freshly distilled diazomethane (19.7 mmol, see procedure for compound **3.43** for generation of diazomethane) and triethylamine (2 mL, 14.1 mmol) in diethyl ether (100 mL) at -78 °C. The reaction was allowed to warm to room temperature with stirring overnight. The salts were removed by filtration and the solid was washed with ether. The filtrate was transferred to a separatory funnel and washed with water (50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and the solvent was removed to give a yellow oily residue that was purified by column chromatography (5:1 petroleum ether:diethyl ether) to give the product **3.53** as a yellow oil. Spectral data for this compound matched the reported values from the literature.<sup>100</sup>

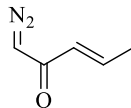


**1-Diazo-1-(1-hydroxycyclohexyl)hex-5-en-2-one (3.54):** A mixture of cyclohexanone (0.17 mL, 1.61 mmol) and diazo ketone **3.53** (300 mg, 2.42 mmol) in 6 mL of THF was

treated with a solution of LDA in THF (2.42 mmol) according to the general procedure for the preparation of **3.30** to give the addition product **3.54** in a 78% yield (279 mg, 1.26 mmol). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 5.86-5.77 (m, 1H), 5.05 (d, *J* = 17 Hz, 1H), 5.02 (d, *J* = 10 Hz, 1H), 4.26 (s, 1H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.40 (dd, *J* = 7.5, 14 Hz, 2H), 1.96-1.90 (m, 2H), 1.80-1.71 (m, 2H), 1.62-1.55 (m, 2H), 1.50-1.43 (m, 2H), 1.34-1.26 (m, 1H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 195.9, 136.4, 115.9, 71.0, 37.9, 36.2, 28.5, 25.3, 21.8 IR (film) 2067 cm<sup>-1</sup> HRMS ESI [Na adduct] Calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>Na 245.1266 *m/z*; Found 245.1270 *m/z*.

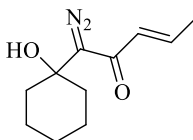


**2-Diazo-1-hydroxy-1-phenylhept-6-en-3-one (3.59):** A mixture of benzaldehyde (171 mg, 1.61 mmol) and diazo ketone **3.53** (300 mg, 2.42 mmol) in 6 mL of THF was treated with a solution of LDA in THF (2.42 mmol) according to the general procedure given for the preparation of **3.30** to give the addition product **3.59** in a 76% yield (283 mg, 1.23 mmol). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 7.42-7.31 (m, 5H), 6.03 (s, 1H), 5.87-5.79 (m, 1H), 5.05 (m, 2H), 3.24 (s, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.43 (dd, *J* = 7, 14 Hz, 2H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 193.4, 128.8, 128.5, 125.8, 115.9, 68.4, 37.6, 28.5 IR (film) 2083 cm<sup>-1</sup> <sup>1</sup> HRMS ESI [Na adduct] Calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Na 253.0953 *m/z*; Found 253.0951 *m/z*.

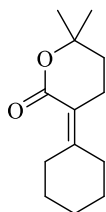


**(E)-1-Diazopent-3-en-2-one (3.50):** THF (7 mL) was added to a 1 M solution of LiHMDS (13 mmol) in THF in a flame-dried flask that was cooled to -78 °C. 3-penten-2-one (1.08 g, 11.89 mmol) was added dropwise to this yellow solution over five minutes. The mixture was stirred for 30 minutes at -78 °C followed by the addition of 2,2,2-trifluoroethyltrifluoroacetate (1.75 mL, 13.08 mmol). After stirring for 30 minutes at -78 °C, the reaction was transferred to a separatory funnel containing 50 mL of diethyl ether and 40 ml of 5% HCl. The yellow organic layer was removed and the aqueous layer was extracted with 25 mL of Et<sub>2</sub>O. The organic layers were combined and washed with brine (50 mL) and dried over MgSO<sub>4</sub>. The solvent was removed to give a brown oil that was immediately dissolved in 10 mL of dry MeCN and 0.2 mL of water. Triethylamine (2.5 mL, 17.9 mmol) was then added dropwise carefully (heating and smoking were observed). 4-acetamidobenzenesulfonyl azide (4.28 g, 17.8 mmol) in 20 mL of MeCN was then added dropwise over 15 minutes. After stirring at room temperature for 30 minutes, the reaction was complete as indicated by TLC. The mixture was poured into a separatory funnel containing 50 mL Et<sub>2</sub>O and 30 mL of 5% NaOH. The layers were separated and the aqueous layer extracted with 50 mL Et<sub>2</sub>O. The organic layers were combined and then washed with 5% NaOH (3 x 30 mL); during these washes the aqueous layers were noticeably orange and the organic layer became progressively more bright yellow. The organic layer was washed with 50 mL of water followed by 50 mL of brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The dark yellow oil

was purified by column chromatography (10% ether in hexanes) to give 811 mg (62% yield over two steps) of the diazo product **3.50** as a bright yellow oil. NOTE: the product is relatively volatile (some codistillation with hexanes was observed) and is presumed, being a diazo compound, to be toxic. Appropriate safety precautions should be taken and the use of a pentane/diethyl ether eluent is recommended for future purifications. Spectral data for this compound matched the reported values from the literature.<sup>99</sup>



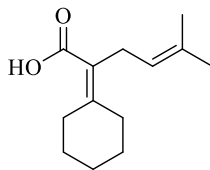
**(E)-1-Diazo-1-(1-hydroxycyclohexyl)pent-3-en-2-one (3.51):** A mixture of cyclohexanone (118 mg, 1.21 mmol) and diazo ketone **3.50** (200 mg, 1.82 mmol) in 6 mL of dry THF was treated with a solution of LDA in THF (1.82 mmol) according to the general procedure for the preparation of **3.30** to give the addition product **3.51** in a 24% yield (60 mg, 0.29 mmol). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 6.95 (m, 1H), 6.30 (dd, *J* = 1 Hz, 15 Hz 1H), 4.56 (s, 1H), 2.0-1.94 (m, 2H), 1.91 (dd, *J* = 2 Hz, 7 Hz, 3H), 1.82-1.72 (m, 2H), 1.64-1.56 (m, 3H), 1.50-1.44 (m, 2H), 1.35-1.25 (m, 1H).



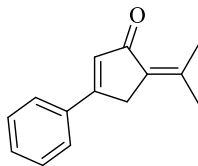
**3-Cyclohexylidene-6,6-dimethyltetrahydro-2H-pyran-2-one (3.46):**

Tris(pentafluorophenyl)borane (224 mg, 0.437 mmol) was dissolved in 6 mL of anhydrous

CH<sub>2</sub>Cl<sub>2</sub> in a flame dried flask and the solution was cooled to -20 °C. A solution of diazo ketone **3.30** (103.3 mg, 0.437 mmol) in 4 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added via syringe all at once. Immediately upon this addition gas evolution was observed and the yellow solution became clear. After 15 minutes of stirring at -20 °C, the cold bath was removed and the reaction was allowed to warm to room temperature. The solvent was removed *in vacuo*. Purification of the residue by column chromatography (15% diethyl ether in hexanes) gave 60 mg (0.29 mmol, 66% yield) of the lactone product **3.46** as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.79 (t, *J* = 6 Hz, 2H), 2.55 (t, *J* = 7 Hz, 2H), 2.34 (t, *J* = 6 Hz, 2H), 1.83 (t, *J* = 7 Hz, 2H), 1.74-1.67 (m, 2H), 1.66-1.60 (m, 2H), 1.60-1.54 (m, 2H), 1.08 (s, 6H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 177.9, 175.2, 112.1, 89.2, 77.2, 34.9, 33.8, 32.7, 29.1, 28.9, 26.2, 25.8, 22.0 HRMS ESI [M+1] Calcd for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub> 209.1542 *m/z*; Found 209.1541 *m/z*.



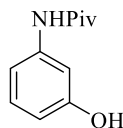
**2-Cyclohexylidene-5-methylhex-4-enoic acid (3.45):** Carboxylic acid **3.45** was isolated as a minor product from the synthesis of compound **3.46** listed above and its spectral data is as follows. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 5.05 (t, *J* = 6.5 Hz, 1H), 3.03 (d, *J* = 6.5 Hz, 2H), 2.56 (m, 2H), 2.27 (m, 2H), 1.67 (d, *J* = 13 Hz, 6H), 1.64-1.57 (m, 6H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 152.0, 132.3, 123.2, 122.2, 32.8, 32.0, 28.4, 28.4, 28.2, 26.5, 25.7, 17.8.



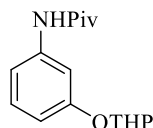
**3-Phenyl-5-(propan-2-ylidene)cyclopent-2-enone (3.58):** BCF (197 mg, 0.385 mmol) was dissolved in 6 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  in a flame-dried flask and the solution was cooled to  $-20\text{ }^\circ\text{C}$ . A solution of diazo ketone **3.57** (94 mg, 0.385 mmol) in 6 mL of dry  $\text{CH}_2\text{Cl}_2$  was added via syringe all at once. Immediately after this addition gas evolution was observed and the bright yellow solution became pale yellow. After 30 minutes of stirring at  $-20\text{ }^\circ\text{C}$ , the cold bath was removed and the reaction was allowed to warm to room temperature. The solvent was removed *in vacuo*. Purification of the residue by column chromatography (10% ethyl acetate in hexanes) gave 70 mg (0.35 mmol, 91% yield) of the cyclopentenone product **3.58** as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.62-7.58 (m, 3H), 7.51 (m, 2H), 6.99 (s, 1H), 3.78 (s, 2H), 2.49 (s, 3H), 2.27 (s, 3H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  197.8, 177.5, 164.9, 134.6, 131.6, 129.9, 129.8, 128.4, 124.9, 35.7, 26.6, 22.4 HRMS ESI  $[\text{M}+1]$  Calcd for  $\text{C}_{14}\text{H}_{14}\text{O}$  199.1123  $m/z$ ; Found 199.1121  $m/z$ .



## Chapter 4 Experimental

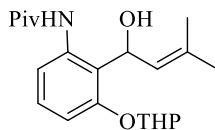


***N*-(3-hydroxyphenyl)pivalamide (4.13):** Pivaloyl chloride (6 mL, 48.6 mmol) was added to a mixture of 3-aminophenol (5 g, 45.8 mmol) and sodium bicarbonate (11.5 g, 137 mmol) in ethyl acetate (150 mL) and water (200 mL) and the reaction was stirred at room temperature for 1 hour. The reaction was transferred to a separatory funnel and the aqueous layer removed. The organic layer was washed with 2 M HCl, water, brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give the anilide **4.13** (8.47 g, 96% yield) as a white solid. Spectral data for this compound matched the reported values from the literature.<sup>118</sup>



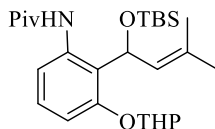
***N*-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)pivalamide (4.14):** Anilide **4.13** (1.77 g, 9.16 mmol) and pyridinium *p*-toluenesulfonate (50 mg, 0.198 mmol) were dissolved in a mixture of anhydrous CH<sub>2</sub>Cl<sub>2</sub> (60 mL) and 3,4-dihydro-2*H*-pyran (2.5 mL, 27.4 mmol). The solution was capped with a septum and stirred at room temperature overnight. After 16 hours of stirring, the reaction was transferred to a separatory funnel and washed with 50 mL of 1 M NaOH, brine (50 mL), and the organic layer was dried over MgSO<sub>4</sub>. The solvent

was removed under reduced pressure to give **4.14** (2.4 g, 94% yield) as a white solid. Spectral data for this compound matched the reported values from the literature.<sup>118</sup>

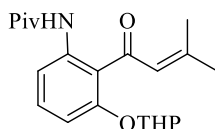


***N*-(2-(1-hydroxy-3-methylbut-2-en-1-yl)-3-((tetrahydro-2*H*-pyran-2-**

**yl)oxy)phenyl)Pivalamide (4.15):** Ether **4.14** (1.8 g, 6.49 mmol) was dissolved in 50 mL of dry THF in a flame-dried flask under nitrogen atmosphere and the solution was cooled to 0 °C. *n*-Butyllithium (14.3 mmol) was added dropwise and the resulting dark yellow solution was stirred at 0 °C for 1 hour before being cooled to -78 °C. 3-methyl-2-butenal (0.75 mL, 7.79 mmol) was added dropwise, immediately causing a color change to pale yellow. The reaction was allowed to warm to room temperature over 2 hours at which point 50 mL of water was added. The layers were separated, the aqueous layer was extracted with Et<sub>2</sub>O (2 x 30 mL) and the organic layers were combined and washed with brine and dried over MgSO<sub>4</sub>. After removal of the solvent and purification by column chromatography (15% ethyl acetate in hexanes), the yellow solid product was isolated as a mixture of diastereomers **4.15** (1.5 g, 64% yield). NMR spectra are shown in the Appendix. HRMS ESI [Na adduct] Calcd for C<sub>21</sub>H<sub>31</sub>NO<sub>4</sub>Na 384.2151 *m/z*; Found 384.2153 *m/z*.

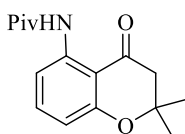


***N*-(2-(1-((*tert*-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)Pivalamide (4.20):** Alcohol **4.15** (382 mg, 1.05 mmol) was dissolved in 25 mL of dry CH<sub>2</sub>Cl<sub>2</sub> in a flame-dried flask under nitrogen atmosphere. The solution was cooled to 0 °C and 2,6-lutidine (0.26 mL, 2.24 mmol) was added by syringe followed by TBSOTf (0.50 mL, 2.11 mmol). The light orange solution was allowed to warm to room temperature with stirring overnight (16 h). 50 mL of water was then added and the layers were separated. The organic layer was dried over MgSO<sub>4</sub> and the solvent was removed *in vacuo*. Purification of the residue by column chromatography (10% ethyl acetate in hexanes) gave the product **4.20** as a colorless oil that was a mixture of diastereomers (409 mg, 82% yield). NMR spectra are shown in the Appendix. HRMS ESI [Na adduct] Calcd for C<sub>27</sub>H<sub>45</sub>NO<sub>4</sub>SiNa 498.3016 *m/z*; Found 498.3029 *m/z*.

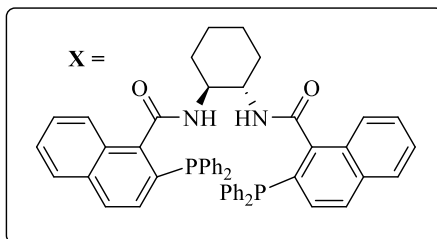
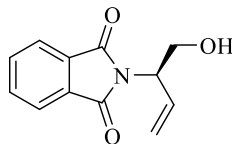


***N*-(2-(3-methylbut-2-enoyl)-3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)Pivalamide (4.16):** Alcohol **4.15** (300 mg, 0.83 mmol) and manganese dioxide (3 g, 10x weight of starting material) was dissolved in 15 mL of CH<sub>2</sub>Cl<sub>2</sub>. The reaction was sealed with a septum and stirred at room temperature overnight (16 h). The mixture was filtered through a short pad of celite followed by a pad of silica gel using ethyl acetate as the eluent. The solvent was removed under reduced pressure to give 270 mg (91% yield) of ketone **4.16** as

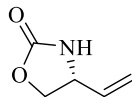
a colorless wax.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  10.04 (s, 1H), 8.04 (d,  $J = 8.5$  Hz, 1H), 7.32 (t,  $J = 8.5$  Hz, 1H), 6.92 (d,  $J = 8.5$  Hz, 1H), 6.55 (s, 1H), 3.84 (m, 1H), 3.66 (m, 1H), 2.23 (s, 3H), 1.95 (s, 3H), 1.90-1.60 (m, 6H), 1.29 (s, 9H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  195.4, 177.3, 156.0, 154.3, 138.6, 132.4, 127.8, 119.9, 115.0, 110.0, 96.9, 61.9, 40.0, 30.2, 27.9, 27.6, 25.1, 21.2, 18.3 HRMS ESI [Na adduct] Calcd for  $\text{C}_{21}\text{H}_{29}\text{NO}_4\text{Na}$  382.1994  $m/z$ ; Found 382.1996  $m/z$ .



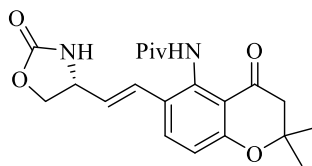
***N*-(2,2-dimethyl-4-oxochroman-5-yl)Pivalamide (4.17):** Ketone **4.16** (975 mg, 2.71 mmol) was dissolved in 100 mL of methanol in a 250 mL round-bottom flask and pyridinium *p*-toluenesulfonate (50 mg, 0.2 mmol) was added. The reaction was stirred under a nitrogen atmosphere for 2 hours and the solvent was removed under reduced pressure. An aqueous sodium hydroxide solution (0.4 M, 130 mL) was added and the reaction was stirred for 1 hour at room temperature. The chromanone product was collected by filtration and washing with water and was obtained as a white solid **4.17** (560 mg, 75% yield over two steps).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  11.99 (s, 1H), 8.31 (dd,  $J = 1$  Hz, 8.5 Hz 1H), 7.43 (t,  $J = 8.5$  Hz, 1H), 6.59 (dd,  $J = 1$  Hz, 8 Hz, 1H), 2.75 (s, 2H), 1.46 (s, 6H), 1.35 (s, 9H)  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  196.8, 178.6, 160.7, 141.7, 137.7, 112.1, 111.6, 107.8, 78.3, 49.6, 40.4, 27.6, 26.4 HRMS ESI [Na adduct] Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{Na}$  298.1419  $m/z$ ; Found 298.1422  $m/z$ .



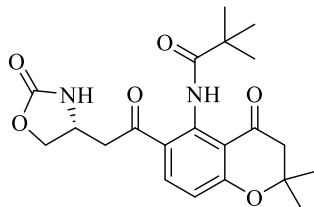
**(R)-2-(1-hydroxybut-3-en-2-yl)isoindoline-1,3-dione (4.11):** To a flame-dried 3-neck 100 mL round-bottom flask under nitrogen was added 5 mg (0.0136 mmol) of  $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ , 34.0 mg of ligand **X** (0.043 mmol), 18.0 mg (0.17 mmol) of sodium carbonate, and 500 mg (3.4 mmol) of phthalimide. The reaction flask was evacuated and backfilled with nitrogen after the addition of each solid. The flask was then degassed with nitrogen for 1 hour. Anhydrous  $\text{CH}_2\text{Cl}_2$  (28 mL) was then added and the solution was stirred for 10 minutes at room temperature during which time it took on a bright yellow color. Butadiene monoxide (0.27 mL, 3.4 mmol) of was added via syringe and the reaction was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure and the residue was purified by column chromatography (30% ethyl acetate in hexanes) to give the DYKAT product **4.11** as a white solid (730 mg, 99% yield). Spectral data for this compound matched the reported values from the literature<sup>115</sup>.



**(R)-4-Vinyloxazolidin-2-one (4.8):** Oxazolidinone **4.8** was prepared from phthalimide **4.11** according to known procedures. Spectral data for this compound matched the reported values from the literature.<sup>116</sup>

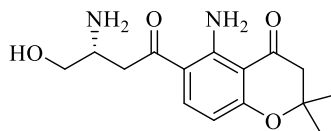


**(R,E)-N-(2,2-dimethyl-4-oxo-6-(2-(2-oxooxazolidin-4-yl)vinyl)chroman-5-yl)Pivalamide (4.18):** Chromanone **4.17** (104.7 mg, 0.38 mmol), rhodium catalyst (8.1 mg, 0.0096 mmol), AgSbF<sub>6</sub> (13 mg, 0.038 mmol), and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (15.2 mg, 0.076 mmol) were dissolved in 3 mL of acetone. Oxazolidinone **4.8** (43 mg, 0.38 mmol) was added as a solution in 2 mL of acetone and the reaction was capped with a septum and stirred for 16 hours at room temperature. The solvent was removed and the residue was purified by column chromatography (24:1 chloroform:methanol) to give the coupling product **4.18** (100 mg, 68% yield) as a brown solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 10.47 (s, 1H), 7.63 (d, *J* = 9 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.30 (d, *J* = 15.5 Hz, 1H), 5.96 (dd, *J* = 7.5, 15.5 Hz, 1H), 5.12 (s, 1H), 4.58 (t, *J* = 8.5 Hz, 1H), 4.48 (dd, *J* = 7.5 Hz, 15 Hz, 1H), 4.15 (dd, *J* = 7 Hz, 8.5 Hz, 1H), 2.73 (s, 2H), 1.46 (s, 6H), 1.36 (s, 9H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 195.7, 177.9, 160.8, 159.0, 136.8, 134.2, 130.8, 124.4, 123.4, 115.5, 111.9, 79.1, 70.5, 55.3, 49.7, 40.0, 27.5, 26.5, 26.4 HRMS ESI [Na adduct] Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>Na 409.1739 *m/z*; Found 409.1748 *m/z*.



**(R)-N-(2,2-dimethyl-4-oxo-6-(2-(2-oxooxazolidin-4-yl)acetyl)chroman-5-**

**yl)Pivalamide (4.19):** Alkene **4.18** (60 mg, 0.155 mmol), Pd(OAc)<sub>2</sub> (14 mg, 0.062 mmol), and 1,4-benzoquinone (25 mg, 0.232 mmol) were added to a 10 mL flask under nitrogen. Degassed acetonitrile (1 mL) was added followed by HBF<sub>4</sub> (50% solution in water, 0.05 mL) and degassed water (0.5 mL). The solution was stirred at room temperature for 16 hours and then transferred to a separatory funnel. The mixture was diluted with water (10 mL) and DCM (10 mL). The layers were separated and the organic layer was dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20:1 chloroform:methanol) to give 40 mg (64% yield) of the oxidation product **4.19** as a brown solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 11.62 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 6.74 (d, *J* = 9 Hz, 1H), 5.85 (s, 1H), 4.61 (t, *J* = 8.5 Hz, 1H), 4.50 (m, 1H), 4.12 (dd, *J* = 6.5, 9 Hz, 1H), 3.18-3.06 (m, 2H), 2.78 (s, 2H), 1.48 (s, 6H), 1.30 (s, 9H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 197.6, 196.0, 178.0, 162.3, 159.0, 136.5, 136.3, 134.3, 125.5, 113.4, 110.1, 79.4, 69.6, 49.5, 49.0, 45.6, 39.7, 26.9, 26.4, 26.3 HRMS ESI [M+1] Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub> 403.1869 *m/z*; Found 403.1874 *m/z*.



**Fusarochromanone (4.1):** Ketone **4.19** (25 mg, 0.062 mmol) was dissolved in 1,4-dioxane (0.27 mL) and 6 N HCl (0.27) in a 5 mL flask fitted with a condenser. The reaction was capped and heated to 60 °C for 16 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (70:10:1 chloroform:methanol:NH<sub>4</sub>OH) to give 5 mg (unoptimized 28% yield) of fusarochromanone **4.1** as a brown solid. Spectral data for this compound matched the reported values from the literature.<sup>113</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 9.57 (s, 1H), 9.40 (s, 1H), 7.84 (d, *J* = 9 Hz, 1H), 6.07 (d, *J* = 9 Hz, 1H), 3.68-3.63 (m, 1H), 3.52-3.48 (m, 2H), 3.06-3.00 (m, 1H), 2.94-2.88 (m, 1H), 2.70 (s, 2H), 1.46 (s, 6H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 198.9, 193.8, 166.1, 154.8, 140.2, 111.8, 104.5, 104.1, 79.4, 66.7, 49.7, 49.0, 43.1, 26.5



## REFERENCES

1. Faraday, M., On new compounds of carbon and hydrogen, and on certain other products obtained during the decomposition of oil by heat. *Philosophical Transactions of the Royal Society of London* **1825**, 115, 440-466.
2. Hofmann, A. W., On insolinic acid. *Proceedings of the Royal Society of London* **1857**, 8, 1-3.
3. Hückel, E., Quantentheoretische Beiträge zum Problem der aromatischen und ungesättigten Verbindungen. III. *Zeitschrift für Physik* **1932**, 76 (9), 628-648.
4. Hückel, E., Quantentheoretische Beiträge zum Benzolproblem. *Zeitschrift für Physik* **1931**, 72 (5), 310-337.
5. Hückel, E., Quantentheoretische Beiträge zum Benzolproblem. *Zeitschrift für Physik* **1931**, 70 (3), 204-286.
6. von E. Doering, W.; Detert, F. L., CYCLOHEPTATRIENYLIUM OXIDE. *Journal of the American Chemical Society* **1951**, 73 (2), 876-877.
7. Cram, D. J.; Tanner, M. E.; Thomas, R., The Taming of Cyclobutadiene. *Angewandte Chemie International Edition in English* **1991**, 30 (8), 1024-1027.
8. Kaufman, H. S.; Fankuchen, I.; Mark, H., Structure of Cyclo-octatetraene. *Nature* **1948**, 161, 165.
9. Kollmar, H.; Staemmler, V., A theoretical study of the structure of cyclobutadiene. *Journal of the American Chemical Society* **1977**, 99 (11), 3583-3587.
10. Cruickshank, D. W. J.; Sparks, R. A., Experimental and theoretical determinations of bond lengths in naphthalene, anthracene and other hydrocarbons. *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* **1960**, 258 (1293), 270-285.
11. Clar, E., *The aromatic sextet*. J. Wiley: London, New York, 1972; p 128.
12. Clar, E., *Polycyclic hydrocarbons*. Academic Press: London, New York, 1964.

13. Martin, R. H., The Helicenes. *Angewandte Chemie International Edition in English* **1974**, *13* (10), 649-660.
14. Newman, M. S.; Lednicer, D., The Synthesis and Resolution of Hexahelicene1. *Journal of the American Chemical Society* **1956**, *78* (18), 4765-4770.
15. Schultz, H. P., Topological Organic Chemistry. Polyhedranes and Prismanes. *The Journal of Organic Chemistry* **1965**, *30* (5), 1361-1364.
16. Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E., C<sub>60</sub>: Buckminsterfullerene. *Nature* **1985**, *318*, 162.
17. Kroto, H. W., The stability of the fullerenes C<sub>n</sub>, with n = 24, 28, 32, 36, 50, 60 and 70. *Nature* **1987**, *329*, 529.
18. Rao, C. N. R.; Seshadri, R.; Govindaraj, A.; Sen, R., Fullerenes, nanotubes, onions and related carbon structures. *Materials Science and Engineering: R: Reports* **1995**, *15* (6), 209-262.
19. Heggie, M. I.; Terrones, M.; Eggen, B. R.; Jungnickel, G.; Jones, R.; Latham, C. D.; Briddon, P. R.; Terrones, H., Quantitative density-functional study of nested fullerenes. *Physical Review B* **1998**, *57* (21), 13339-13342.
20. Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A., A Rational Chemical Synthesis of C<sub>60</sub>. *Science* **2002**, *295* (5559), 1500-1503.
21. Boorum, M. M.; Vasil'ev, Y. V.; Drewello, T.; Scott, L. T., Groundwork for a Rational Synthesis of C<sub>60</sub>: Cyclodehydrogenation of a C<sub>60</sub>H<sub>30</sub> Polyarene. *Science* **2001**, *294* (5543), 828-831.
22. Gatti, T.; Menna, E.; Meneghetti, M.; Maggini, M.; Petrozza, A.; Lamberti, F., The Renaissance of fullerenes with perovskite solar cells. *Nano Energy* **2017**, *41*, 84-100.
23. Prylutska, S.; Panchuk, R.; Gołuński, G.; Skivka, L.; Prylutsky, Y.; Hurmach, V.; Skorohyd, N.; Borowik, A.; Woziwodzka, A.; Piosik, J.; Kyzyma, O.; Garamus, V.; Bulavin, L.; Evstigneev, M.; Buchelnikov, A.; Stoika, R.; Berger, W.; Ritter, U.; Scharff, P., C<sub>60</sub> fullerene enhances cisplatin anticancer activity and overcomes tumor cell drug resistance. *Nano Research* **2017**, *10* (2), 652-671.
24. Li, X.; Kang, F.; Inagaki, M., Buckybowls: Corannulene and Its Derivatives. *Small* **2016**, *12* (24), 3206-3223.

25. Dopfer, J. H.; Wynberg, H., Heterocirculenes a new class of polycyclic aromatic hydrocarbons. *Tetrahedron Letters* **1972**, *13* (9), 763-766.
26. Nestoros, E.; Stuparu, M. C., Corannulene: a molecular bowl of carbon with multifaceted properties and diverse applications. *Chemical Communications* **2018**, *54* (50), 6503-6519.
27. Yamamoto, K.; Sonobe, H.; Matsubara, H.; Sato, M.; Okamoto, S.; Kitaura, K., Convenient New Synthesis of [7]Circulene. *Angewandte Chemie International Edition in English* **1996**, *35* (1), 69-70.
28. Barth, W. E.; Lawton, R. G., Dibenzo[ghi,mno]fluoranthene. *Journal of the American Chemical Society* **1966**, *88* (2), 380-381.
29. Scott, L. T.; Hashemi, M. M.; Meyer, D. T.; Warren, H. B., Corannulene. A convenient new synthesis. *Journal of the American Chemical Society* **1991**, *113* (18), 7082-7084.
30. Brown, R. F. C., Thermal rearrangements of alkynes under FVP conditions. the acetylene-methylenecarbene rearrangement. *Recueil des Travaux Chimiques des Pays-Bas* **1988**, *107* (12), 655-661.
31. Borchardt, A.; Fuchicello, A.; Kilway, K. V.; Baldrige, K. K.; Siegel, J. S., Synthesis and dynamics of the corannulene nucleus. *Journal of the American Chemical Society* **1992**, *114* (5), 1921-1923.
32. Seiders, T. J.; Baldrige, K. K.; Siegel, J. S., Synthesis and Characterization of the First Corannulene Cyclophane. *Journal of the American Chemical Society* **1996**, *118* (11), 2754-2755.
33. Scott, L. T.; Cheng, P.-C.; Hashemi, M. M.; Bratcher, M. S.; Meyer, D. T.; Warren, H. B., Corannulene. A Three-Step Synthesis. *Journal of the American Chemical Society* **1997**, *119* (45), 10963-10968.
34. Sygula, A.; Rabideau, P. W., A Practical, Large Scale Synthesis of the Corannulene System. *Journal of the American Chemical Society* **2000**, *122* (26), 6323-6324.
35. Butterfield, A. M.; Gilomen, B.; Siegel, J. S., Kilogram-Scale Production of Corannulene. *Organic Process Research & Development* **2012**, *16* (4), 664-676.
36. Jackson, E. A.; Steinberg, B. D.; Bancu, M.; Wakamiya, A.; Scott, L. T., Pentaindenocorannulene and Tetraindenocorannulene: New Aromatic Hydrocarbon  $\pi$

Systems with Curvatures Surpassing That of C<sub>60</sub>. *Journal of the American Chemical Society* **2007**, *129* (3), 484-485.

37. Abdourazak, A. H.; Marcinow, Z.; Sygula, A.; Sygula, R.; Rabideau, P. W., Buckybowls 2. Toward the Total Synthesis of Buckminsterfullerene (C<sub>60</sub>): Benz[5,6]-as-indaceno[3,2,1,8,7-mnopqr]indeno[4,3,2,1-cdef]chrysene. *Journal of the American Chemical Society* **1995**, *117* (23), 6410-6411.

38. Sakurai, H.; Daiko, T.; Hirao, T., A Synthesis of Sumanene, a Fullerene Fragment. *Science* **2003**, *301* (5641), 1878-1878.

39. Dziewoński, K., Ueber Dekacyclen (Trinaphtylenbenzol), einen neuen hochmolekularen aromatischen Kohlenwasserstoff, und über Dinaphtylenthiofen, einen rothen Thiokörper. *Berichte der deutschen chemischen Gesellschaft* **1903**, *36* (1), 962-971.

40. Scott, L. T.; Bratcher, M. S.; Hagen, S., Synthesis and Characterization of a C<sub>36</sub>H<sub>12</sub> Fullerene Subunit. *Journal of the American Chemical Society* **1996**, *118* (36), 8743-8744.

41. Ansems, R. B. M.; Scott, L. T., Circumtrindene: A Geodesic Dome of Molecular Dimensions. Rational Synthesis of 60% of C<sub>60</sub>. *Journal of the American Chemical Society* **2000**, *122* (12), 2719-2724.

42. Forkey, D. M.; Attar, S.; Noll, B. C.; Koerner, R.; Olmstead, M. M.; Balch, A. L., Crystallographic Characterization of the Molecular Structure and Solid State Packing of the Fullerene-Shaped Hydrocarbon C<sub>36</sub>H<sub>12</sub>. *Journal of the American Chemical Society* **1997**, *119* (24), 5766-5767.

43. Tsefrikas, V. M.; Scott, L. T., Geodesic Polyarenes by Flash Vacuum Pyrolysis. *Chemical Reviews* **2006**, *106* (12), 4868-4884.

44. Reisch, H. A.; Bratcher, M. S.; Scott, L. T., Imposing Curvature on a Polyarene by Intramolecular Palladium-Catalyzed Arylation Reactions: A Simple Synthesis of Dibenzo[a,g]corannulene. *Organic Letters* **2000**, *2* (10), 1427-1430.

45. Chang, H.-I.; Huang, H.-T.; Huang, C.-H.; Kuo, M.-Y.; Wu, Y.-T., Diindeno[1,2,3,4-defg;1[prime or minute],2[prime or minute],3[prime or minute],4[prime or minute]-mnop]chrysenes: solution-phase synthesis and the bowl-to-bowl inversion barrier. *Chemical Communications* **2010**, *46* (38), 7241-7243.

46. Wu, T.-C.; Chen, M.-K.; Lee, Y.-W.; Kuo, M.-Y., Wu, Y.-T., Bowl-Shaped Fragments of C<sub>70</sub> or Higher Fullerenes: Synthesis, Structural Analysis, and Inversion Dynamics. *Angewandte Chemie International Edition* **2013**, *52* (4), 1289-1293.

47. Chen, M.-K.; Hsin, H.-J.; Wu, T.-C.; Kang, B.-Y.; Lee, Y.-W.; Kuo, M.-Y.; Wu, Y.-T., Highly Curved Bowl-Shaped Fragments of Fullerenes: Synthesis, Structural Analysis, and Physical Properties. *Chemistry – A European Journal* **2014**, *20* (2), 598-608.
48. Feng, C.-N.; Kuo, M.-Y.; Wu, Y.-T., Synthesis, Structural Analysis, and Properties of [8]Circulenes. *Angewandte Chemie International Edition* **2013**, *52* (30), 7791-7794.
49. Miller, R. W.; Duncan, A. K.; Schneebeli, S. T.; Gray, D. L.; Whalley, A. C., Synthesis and Structural Data of Tetrabenzo[8]circulene. *Chemistry – A European Journal* **2014**, *20* (13), 3705-3711.
50. Sakamoto, Y.; Suzuki, T., Tetrabenzo[8]circulene: Aromatic Saddles from Negatively Curved Graphene. *Journal of the American Chemical Society* **2013**, *135* (38), 14074-14077.
51. Kawasumi, K.; Zhang, Q.; Segawa, Y.; Scott, L. T.; Itami, K., A grossly warped nanographene and the consequences of multiple odd-membered-ring defects. *Nature Chemistry* **2013**, *5*, 739.
52. Miller, R. W.; Averill, S. E.; Van Wyck, S. J.; Whalley, A. C., General Method for the Synthesis of Functionalized Tetrabenzo[8]circulenes. *The Journal of Organic Chemistry* **2016**, *81* (23), 12001-12005.
53. Miller, R. W.; Dodge, N. J.; Dyer, A. M.; Fortner-Buczala, E. M.; Whalley, A. C., A one-pot method for the preparation of 2,5-diarylthiophene-1-oxides from arylacetylenes. *Tetrahedron Letters* **2016**, *57* (17), 1860-1862.
54. Ansems, R. B. M. Ph.D. Dissertation. Boston College, Chestnut Hill, 2004.
55. Amick, A. W.; Scott, L. T., Trisannulated benzene derivatives by Acid catalyzed aldol cyclotrimerizations of cyclic ketones. Methodology development and mechanistic insight. *J Org Chem* **2007**, *72* (9), 3412-8.
56. Zhang, W.; Cao, X.-Y.; Zi, H.; Pei, J., Single-Molecule Nanosized Polycyclic Aromatics with Alternant Five- and Six-Membered Rings: Synthesis and Optical Properties. *Organic Letters* **2005**, *7* (6), 959-962.
57. Mueller, A.; Amsharov, K. Y., Synthesis of Robust Precursors for the Controlled Fabrication of (6,6), (8,8), (10,10), and (12,12) Armchair Single-Walled Carbon Nanotubes. *European Journal of Organic Chemistry* **2015**, *2015* (14), 3053-3056.

58. Sumy, D. P.; Dodge, N. J.; Harrison, C. M.; Finke, A. D.; Whalley, A. C., Tridecacyclene: A Cyclic Tetramer of Acenaphthylene. *Chemistry – A European Journal* **2016**, *22* (14), 4709-12.
59. Sumy, D. P.; Finke, A. D.; Whalley, A. C., The reductive aromatization of tridecacyclene. *Chem Commun* **2016**, *52* (83), 12368-12371.
60. Zhai, L.; Shukla, R.; Rathore, R., Oxidative C–C Bond Formation (Scholl Reaction) with DDQ as an Efficient and Easily Recyclable Oxidant. *Organic Letters* **2009**, *11* (15), 3474-3477.
61. Higgins, S. D.; Thomas, C. B., Conversion of aromatic ketones into  $\pi$ -arylalkanoic acids. Oxidation by thallium(III) and by halogens. *Journal of the Chemical Society, Perkin Transactions 1* **1982**, (0), 235-242.
62. Hill, T. J.; Hughes, R. K.; Scott, L. T., Steps toward the synthesis of a geodesic C<sub>60</sub>H<sub>12</sub> end cap for a C<sub>3v</sub> carbon [6,6]nanotube. *Tetrahedron* **2008**, *64* (50), 11360-11369.
63. Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J., Total Synthesis of (–)-Himalensine A. *Journal of the American Chemical Society* **2017**, *139* (49), 17755-17758.
64. Yu, J.-Q.; Corey, E. J., A Mild, Catalytic, and Highly Selective Method for the Oxidation of  $\alpha,\beta$ -Enones to 1,4-Enediones. *Journal of the American Chemical Society* **2003**, *125* (11), 3232-3233.
65. McMurry, J. E.; Fleming, M. P., New method for the reductive coupling of carbonyls to olefins. Synthesis of  $\beta$ -carotene. *Journal of the American Chemical Society* **1974**, *96* (14), 4708-4709.
66. Baryshnikov, G. V.; Karaush, N. N.; Valiev, R. R.; Minaev, B. F., Aromaticity of the completely annelated tetraphenylenes: NICS and GIMIC characterization. *Journal of Molecular Modeling* **2015**, *21* (6), 136.
67. Nobusue, S.; Fujita, K.; Tobe, Y., Skeletal Rearrangement of Twisted Polycyclic Aromatic Hydrocarbons under Scholl Reaction Conditions. *Organic Letters* **2017**, *19* (12), 3227-3230.
68. Nobusue, S.; Tobe, Y., Twisted Polycyclic Aromatic Hydrocarbon with a Cyclooctatetraene Core via Formal [4+4] Dimerization of Indenofluorene. *Synlett* **2016**, *27* (14), 2140-2144.

69. Nobusue, S.; Miyoshi, H.; Shimizu, A.; Hisaki, I.; Fukuda, K.; Nakano, M.; Tobe, Y., Tetracyclopenta[def,jkl,pqr,vwx]tetraphenylene: A Potential Tetraradicaloid Hydrocarbon. *Angewandte Chemie International Edition* **2015**, *54* (7), 2090-2094.
70. Hellwinkel, D.; Reiff, G., Cyclooctatetraene Systems Flattened by Steric Constraints. *Angewandte Chemie International Edition in English* **1970**, *9* (7), 527-528.
71. Miyaura, N.; Yamada, K.; Suzuki, A., A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Letters* **1979**, *20* (36), 3437-3440.
72. Milstein, D.; Stille, J. K., A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *Journal of the American Chemical Society* **1978**, *100* (11), 3636-3638.
73. Tamoto, A.; Aratani, N.; Yamada, H., Contraction of  $\pi$ -Conjugated Rings upon Oxidation from Cyclooctatetraene to Benzene via the Tropylium Cation. *Chemistry – A European Journal* **2017**, *23* (64), 16388-16392.
74. Roncali, J., Molecular Bulk Heterojunctions: An Emerging Approach to Organic Solar Cells. *Accounts of Chemical Research* **2009**, *42* (11), 1719-1730.
75. Friscourt, F.; Fahrni, C. J.; Boons, G.-J., A Fluorogenic Probe for the Catalyst-Free Detection of Azide-Tagged Molecules. *Journal of the American Chemical Society* **2012**, *134* (45), 18809-18815.
76. Arnold, R. M.; McNitt, C. D.; Popik, V. V.; Locklin, J., Direct grafting of poly(pentafluorophenyl acrylate) onto oxides: versatile substrates for reactive microcapillary printing and self-sorting modification. *Chemical Communications* **2014**, *50* (40), 5307-5309.
77. Lara-Ochoa, F.; Espinosa-Pérez, G., A new synthesis of combretastatins A-4 and AVE-8062A. *Tetrahedron Letters* **2007**, *48* (39), 7007-7010.
78. Obora, Y.; Moriya, H.; Tokunaga, M.; Tsuji, Y., Cross-coupling reaction of thermally stable titanium(II)-alkyne complexes with aryl halides catalysed by a nickel complex. *Chemical Communications* **2003**, (22), 2820-2821.
79. Zirngast, M.; Marschner, C.; Baumgartner, J., Group 4 Metallocene Complexes of Tris(trimethylsilyl)silylacetylene and Related Alkynes. *Organometallics* **2008**, *27* (11), 2570-2583.
80. Suh, M. C.; Jiang, B.; Tilley, T. D., An Efficient, Modular Synthetic Route to Oligomers Based on Zirconocene Coupling: Properties for Phenylene–Thiophene-1-

- Oxide and Phenylene–Thiophene-1,1-Dioxide Chains. *Angewandte Chemie* **2000**, *112* (16), 2992-2995.
81. Jiang, B.; Tilley, T. D., General, Efficient Route to Thiophene-1-Oxides and Well-Defined, Mixed Thiophene-Thiophene-1-Oxide Oligomers. *Journal of the American Chemical Society* **1999**, *121* (41), 9744-9745.
82. Fagan, P. J.; Nugent, W. A., Synthesis of main group heterocycles by metallacycle transfer from zirconium. *Journal of the American Chemical Society* **1988**, *110* (7), 2310-2312.
83. Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Flanagan-Steet, H. R.; Wolfert, M. A.; Steet, R.; Boons, G.-J., Polar Dibenzocyclooctynes for Selective Labeling of Extracellular Glycoconjugates of Living Cells. *Journal of the American Chemical Society* **2012**, *134* (11), 5381-5389.
84. Clevenger, R. G.; Kumar, B.; Menuey, E. M.; Lee, G.-H.; Patterson, D.; Kilway, K. V., A Superior Synthesis of Longitudinally Twisted Acenes. *Chemistry – A European Journal* **2018**, *24* (1), 243-250.
85. Grob, C. A.; Cseh, G., Die Solvolyse von  $\alpha$ -Bromstyrolen Substitution am ungesättigten trigonalen Kohlenstoffatom. *Helvetica Chimica Acta* **1964**, *47* (1), 194-203.
86. Schleyer, P. v. R.; Pfeifer, W. D.; Bahn, C. A.; Bocher, S.; Harding, C. E.; Hummel, K.; Hanack, M.; Stang, P. J., Behavior of bent vinyl cations generated by solvolysis of cyclic trifluoromethanesulfonates. *Journal of the American Chemical Society* **1971**, *93* (6), 1513-1516.
87. Stang, P. J.; Hanack, M.; Subramanian, L. R., Perfluoroalkanesulfonic Esters: Methods of Preparation and Applications in Organic Chemistry. *Synthesis* **1982**, *1982* (02), 85-126.
88. Pasto, D. J.; Miles, M. F.; Chou, S.-K., Analysis of reactivity of alkenylidenecyclopropanes with electrophilic reagents. *The Journal of Organic Chemistry* **1977**, *42* (18), 3098-3101.
89. Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D., The mechanism of the Meyer-Schuster rearrangement. *The Journal of Organic Chemistry* **1977**, *42* (21), 3403-3408.
90. Marcuzzi, F.; Melloni, G., Electrophilic additions to acetylenes. V. Stereochemistry of the electrophilic addition of alkyl halides and hydrogen halides to phenyl-substituted acetylenes. *Journal of the American Chemical Society* **1976**, *98* (11), 3295-3300.



91. Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A., The Reaction of  $\alpha$ -Diazo- $\beta$ -hydroxy Esters with Boron Trifluoride Etherate: Generation and Rearrangement of Destabilized Vinyl Cations. A Detailed Experimental and Theoretical Study. *Journal of the American Chemical Society* **1996**, *118* (1), 1-12.
92. Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Rosato, G. C.; Ursini, A., The reaction of  $\alpha$ -diazo- $\beta$ -hydroxy esters with boron trifluoride. *Journal of the Chemical Society, Chemical Communications* **1993**, (24), 1798-1800.
93. Hoppe, D.; Schöllkopf, U., Ethyl 2-Oxazoline-5-carboxylate from Ethyl Isocyanoacetate and Carbonyl Compounds. *Angewandte Chemie International Edition in English* **1970**, *9* (4), 300-301.
94. Kanishchev, M. I.; Shegolev, A. A.; Smit, W. A.; Caple, R.; Kelner, M. J., 1,5-Hydride shifts in vinyl cation intermediates produced upon the acylation of acetylenes. *Journal of the American Chemical Society* **1979**, *101* (19), 5660-5671.
95. Cleary, S. E.; Hensinger, M. J.; Brewer, M., Remote C-H insertion of vinyl cations leading to cyclopentenones. *Chemical Science* **2017**, *8* (10), 6810-6814.
96. Karpf, M., Die Acylierung von Acetylenen mit  $\beta$ ,  $\gamma$ -ungesättigten Säurechloriden. Eine neue Synthese von 5-Cyclopentenonen. *Helvetica Chimica Acta* **1984**, *67* (1), 73-85.
97. Smith, A. B.; Toder, B. H.; Branca, S. J., Vinylogous Wolff rearrangement. 4. General reaction of  $\beta,\gamma$ -unsaturated  $\alpha'$ -diazo ketones. *Journal of the American Chemical Society* **1984**, *106* (14), 3995-4001.
98. Fekner, T.; Muller-Bunz, H.; Guiry, P. J., Synthesis and application of quinazoline-oxazoline-containing (quinazox) ligands. *Org Lett* **2006**, *8* (22), 5109-12.
99. Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J., Rearrangement of ammonium ylides produced by intramolecular reaction of catalytically generated metal carbenoids. Part 1. Synthesis of cyclic amines. *Journal of the Chemical Society, Perkin Transactions 1* **2001**, (24), 3312-3324.
100. Dang, H.-S.; Roberts, B. P., Radical addition to carbenoids. Chain reactions of  $\alpha$ -diazo carbonyl compounds with triorganotin hydrides, tris(trimethylsilyl)silane and allyltributylstannane. *Journal of the Chemical Society, Perkin Transactions 1* **1996**, (8), 769-775.

101. Yang, C.-H.; Fan, W.-W.; Liu, G.-Q.; Duan, L.; Li, L.; Li, Y.-M., On the understanding of BF<sub>3</sub>·Et<sub>2</sub>O-promoted intra- and intermolecular amination and oxygenation of unfunctionalized olefins. *RSC Advances* **2015**, *5* (75), 61081-61093.
102. Murakami, M.; Itami, K.; Ito, Y., Synthesis of (Vinylallene)rhodium(III) Complex of Planar Structure: Perfect  $\pi \rightarrow \sigma$  Conversion of 1,3-Diene System. *Journal of the American Chemical Society* **1996**, *118* (46), 11672-11673.
103. Wu, W.; Cook, M. E.; Chu, Q.; Smalley, E. B., Tibial dyschondroplasia of chickens induced by Fusarochromanone, a mycotoxin. *Avian Dis* **1993**, *37* (2), 302-9.
104. Wright, G. C., Jr.; Marasas, W. F.; Sokoloff, L., Effect of fusarochromanone and T-2 toxin on articular chondrocytes in monolayer culture. *Fundam Appl Toxicol* **1987**, *9* (3), 595-7.
105. Pathre, S. V.; Gleason, W. B.; Lee, Y.-W.; Mirocha, C. J., The structure of fusarochromanone: new mycotoxin from *Fusarium roseum*, "Graminearum". *Canadian Journal of Chemistry* **1986**, *64* (7), 1258-1261.
106. Lee, Y. W.; Mirocha, C. J.; Shroeder, D. J.; Walser, M. M., TDP-1, a toxic component causing tibial dyschondroplasia in broiler chickens, and trichothecenes from *Fusarium roseum* 'Graminearum'. *Appl Environ Microbiol* **1985**, *50* (1), 102-7.
107. Pawlosky, R. J.; Mirocha, C. J., Mass spectral analysis and fragment ion structure of fusarochromanone. *Biol Mass Spectrom* **1991**, *20* (11), 743-9.
108. Mahdavian, E.; Palyok, P.; Adelmund, S.; Williams-Hart, T.; Furmanski, B. D.; Kim, Y. J.; Gu, Y.; Barzegar, M.; Wu, Y.; Bhinge, K. N.; Kolluru, G. K.; Quick, Q.; Liu, Y. Y.; Kevil, C. G.; Salvatore, B. A.; Huang, S.; Clifford, J. L., Biological activities of fusarochromanone: a potent anti-cancer agent. *BMC Res Notes* **2014**, *7*, 601.
109. Mahdavian, E.; Marshall, M.; Martin, P. M.; Cagle, P.; Salvatore, B. A.; Quick, Q. A., Caspase-dependent signaling underlies glioblastoma cell death in response to the fungal metabolite, fusarochromanone. *Int J Mol Med* **2014**, *34* (3), 880-5.
110. Gu, Y.; Chen, X.; Shang, C.; Singh, K.; Barzegar, M.; Mahdavian, E.; Salvatore, B. A.; Jiang, S.; Huang, S., Fusarochromanone induces G1 cell cycle arrest and apoptosis in COS7 and HEK293 cells. *PLoS One* **2014**, *9* (11), e112641.
111. Furmanski, B. D.; Dreau, D.; Wuthier, R. E.; Fuseler, J. W., Differential uptake and selective permeability of fusarochromanone (FC101), a novel membrane permeable anticancer naturally fluorescent compound in tumor and normal cells. *Microsc Microanal* **2009**, *15* (6), 545-57.

112. Dreau, D.; Foster, M.; Hogg, M.; Culberson, C.; Nunes, P.; Wuthier, R. E., Inhibitory effects of fusarochromanone on melanoma growth. *Anticancer Drugs* **2007**, *18* (8), 897-904.
113. Takahama, Y.; Shibata, Y.; Tanaka, K., Concise Synthesis of Fungal Metabolite (+)-Fusarochromanone via Rhodium(III)-catalyzed Oxidative sp<sup>2</sup> C-H Bond Olefination. *Chem Lett* **2016**, *45* (10), 1177-1179.
114. Salvatore, B. A.; Solis, F. C., Synthesis of Chromanones. US Patent No. WO2004/103985, **2004**.
115. Gahalawat, S.; Pandey, S. K., Enantioselective total synthesis of (+)-serinolamide A. *RSC Advances* **2015**, *5* (51), 41013-41016.
116. Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L., Dynamic Kinetic Asymmetric Transformation of Diene Monoepoxides: A Practical Asymmetric Synthesis of Vinylglycinol, Vigabatrin, and Ethambutol. *Journal of the American Chemical Society* **2000**, *122* (25), 5968-5976.
117. Soll, R. M.; Guinasso, C.; Asselin, A., Multigram preparation of 1,8-diethyl-7-hydroxy-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, a phenolic metabolite of the analgesic and antiinflammatory agent etodolac. *The Journal of Organic Chemistry* **1988**, *53* (12), 2844-2847.
118. Abram, T. S.; Norman, P.; Warren, B. T., 5-Substituted chromones and thiochromones. European Patent No. 0163227, **1985**.
119. Park, J.; Lee, J.; Chang, S., Iterative C-H Functionalization Leading to Multiple Amidations of Anilides. *Angewandte Chemie International Edition* **2017**, *56* (15), 4256-4260.
120. Takahama, Y.; Shibata, Y.; Tanaka, K., Oxidative Olefination of Anilides with Unactivated Alkenes Catalyzed by an (Electron-Deficient  $\eta^5$ -Cyclopentadienyl)Rhodium(III) Complex Under Ambient Conditions. *Chemistry – A European Journal* **2015**, *21* (25), 9053-9056.
121. Miller, D. G.; Wayner, D. D. M., Improved method for the Wacker oxidation of cyclic and internal olefins. *The Journal of Organic Chemistry* **1990**, *55* (9), 2924-2927.
122. Kancherla, S.; Lorentzen, M.; Snieckus, V.; Jørgensen, K. B., Directed ortho-Metalation and Anionic ortho-Fries Rearrangement of Polycyclic Aromatic O-Carbamates: Regioselective Synthesis of Substituted Chrysenes. *The Journal of Organic Chemistry* **2018**, *83* (7), 3590-3598.

123. Sumy, D. P. Ph.D. Dissertation. The University of Vermont, Burlington, 2017.
124. Zheng, G.; Zhao, J.; Li, Z.; Zhang, Q.; Sun, J.; Sun, H.; Zhang, Q., Highly Regio- and Stereoselective Intermolecular Seleno- and Thioamination of Alkynes. *Chemistry – A European Journal* **2016**, 22 (10), 3513-3518.

## COMPREHENSIVE BIBLIOGRAPHY

- Abdourazak, A. H.; Marcinow, Z.; Sygula, A.; Sygula, R.; Rabideau, P. W., Buckybowls 2. Toward the Total Synthesis of Buckminsterfullerene ( $C_{60}$ ): Benz[5,6]-as-indaceno[3,2,1,8,7-mnopqr]indeno[4,3,2,1-cdef]chrysene. *Journal of the American Chemical Society* **1995**, *117* (23), 6410-6411.
- Abram, T. S.; Norman, P.; Warren, B. T., 5-Substituted chromones and thiochromones. European Patent No. 0163227, **1985**.
- Amick, A. W.; Scott, L. T., Trisannulated benzene derivatives by Acid catalyzed aldol cyclotrimerizations of cyclic ketones. Methodology development and mechanistic insight. *J Org Chem* **2007**, *72* (9), 3412-8.
- Ansems, R. B. M. Ph.D. Dissertation. Boston College, Chestnut Hill, 2004.
- Ansems, R. B. M.; Scott, L. T., Circumtrindene: A Geodesic Dome of Molecular Dimensions. Rational Synthesis of 60% of  $C_{60}$ . *Journal of the American Chemical Society* **2000**, *122* (12), 2719-2724.
- Arnold, R. M.; McNitt, C. D.; Popik, V. V.; Locklin, J., Direct grafting of poly(pentafluorophenyl acrylate) onto oxides: versatile substrates for reactive microcapillary printing and self-sorting modification. *Chemical Communications* **2014**, *50* (40), 5307-5309.
- Barth, W. E.; Lawton, R. G., Dibenzo[ghi,mno]fluoranthene. *Journal of the American Chemical Society* **1966**, *88* (2), 380-381.
- Baryshnikov, G. V.; Karaush, N. N.; Valiev, R. R.; Minaev, B. F., Aromaticity of the completely annelated tetraphenylenes: NICS and GIMIC characterization. *Journal of Molecular Modeling* **2015**, *21* (6), 136.
- Boorum, M. M.; Vasil'ev, Y. V.; Drewello, T.; Scott, L. T., Groundwork for a Rational Synthesis of  $C_{60}$ : Cyclodehydrogenation of a  $C_{60}H_{30}$  Polyarene. *Science* **2001**, *294* (5543), 828-831.
- Borchardt, A.; Fuchicello, A.; Kilway, K. V.; Baldrige, K. K.; Siegel, J. S., Synthesis and dynamics of the corannulene nucleus. *Journal of the American Chemical Society* **1992**, *114* (5), 1921-1923.
- Brown, R. F. C., Thermal rearrangements of alkynes under FVP conditions. the acetylene-methylenecarbene rearrangement. *Recueil des Travaux Chimiques des Pays-Bas* **1988**, *107* (12), 655-661.

- Butterfield, A. M.; Gilomen, B.; Siegel, J. S., Kilogram-Scale Production of Corannulene. *Organic Process Research & Development* **2012**, *16* (4), 664-676.
- Chang, H.-I.; Huang, H.-T.; Huang, C.-H.; Kuo, M.-Y.; Wu, Y.-T., Diindeno[1,2,3,4-defg;1[prime or minute],2[prime or minute],3[prime or minute],4[prime or minute]-mnop]chrysenes: solution-phase synthesis and the bowl-to-bowl inversion barrier. *Chemical Communications* **2010**, *46* (38), 7241-7243.
- Chen, M.-K.; Hsin, H.-J.; Wu, T.-C.; Kang, B.-Y.; Lee, Y.-W.; Kuo, M.-Y.; Wu, Y.-T., Highly Curved Bowl-Shaped Fragments of Fullerenes: Synthesis, Structural Analysis, and Physical Properties. *Chemistry – A European Journal* **2014**, *20* (2), 598-608.
- Clar, E., *Polycyclic hydrocarbons*. Academic Press: London, New York,, 1964.
- Clar, E., *The aromatic sextet*. J. Wiley: London, New York,, 1972; p 128.
- Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Street, L. J., Rearrangement of ammonium ylides produced by intramolecular reaction of catalytically generated metal carbenoids. Part 1. Synthesis of cyclic amines. *Journal of the Chemical Society, Perkin Transactions 1* **2001**, (24), 3312-3324.
- Cleary, S. E.; Hensinger, M. J.; Brewer, M., Remote C-H insertion of vinyl cations leading to cyclopentenones. *Chemical Science* **2017**, *8* (10), 6810-6814.
- Clevenger, R. G.; Kumar, B.; Menuey, E. M.; Lee, G.-H.; Patterson, D.; Kilway, K. V., A Superior Synthesis of Longitudinally Twisted Acenes. *Chemistry – A European Journal* **2018**, *24* (1), 243-250.
- Cram, D. J.; Tanner, M. E.; Thomas, R., The Taming of Cyclobutadiene. *Angewandte Chemie International Edition in English* **1991**, *30* (8), 1024-1027.
- Cruickshank, D. W. J.; Sparks, R. A., Experimental and theoretical determinations of bond lengths in naphthalene, anthracene and other hydrocarbons. *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* **1960**, *258* (1293), 270-285.
- Dang, H.-S.; Roberts, B. P., Radical addition to carbenoids. Chain reactions of  $\alpha$ -diazo carbonyl compounds with triorganotin hydrides, tris(trimethylsilyl)silane and allyltributylstannane. *Journal of the Chemical Society, Perkin Transactions 1* **1996**, (8), 769-775.

- Dopper, J. H.; Wynberg, H., Heterocirculenes a new class of polycyclic aromatic hydrocarbons. *Tetrahedron Letters* **1972**, *13* (9), 763-766.
- Dreau, D.; Foster, M.; Hogg, M.; Culberson, C.; Nunes, P.; Wuthier, R. E., Inhibitory effects of fusarochromanone on melanoma growth. *Anticancer Drugs* **2007**, *18* (8), 897-904.
- Dziewoński, K., Ueber Dekacyclen (Trinaphtylenbenzol), einen neuen hochmolekularen aromatischen Kohlenwasserstoff, und über Dinaphtylenthiofen, einen rothen Thiokörper. *Berichte der deutschen chemischen Gesellschaft* **1903**, *36* (1), 962-971.
- Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D., The mechanism of the Meyer-Schuster rearrangement. *The Journal of Organic Chemistry* **1977**, *42* (21), 3403-3408.
- Fagan, P. J.; Nugent, W. A., Synthesis of main group heterocycles by metallacycle transfer from zirconium. *Journal of the American Chemical Society* **1988**, *110* (7), 2310-2312.
- Faraday, M., On new compounds of carbon and hydrogen, and on certain other products obtained during the decomposition of oil by heat. *Philosophical Transactions of the Royal Society of London* **1825**, *115*, 440-466.
- Fekner, T.; Muller-Bunz, H.; Guiry, P. J., Synthesis and application of quinazoline-oxazoline-containing (quinazox) ligands. *Org Lett* **2006**, *8* (22), 5109-12.
- Feng, C.-N.; Kuo, M.-Y.; Wu, Y.-T., Synthesis, Structural Analysis, and Properties of [8]Circulenes. *Angewandte Chemie International Edition* **2013**, *52* (30), 7791-7794.
- Forkey, D. M.; Attar, S.; Noll, B. C.; Koerner, R.; Olmstead, M. M.; Balch, A. L., Crystallographic Characterization of the Molecular Structure and Solid State Packing of the Fullerene-Shaped Hydrocarbon C<sub>36</sub>H<sub>12</sub>. *Journal of the American Chemical Society* **1997**, *119* (24), 5766-5767.
- Friscourt, F.; Fahrni, C. J.; Boons, G.-J., A Fluorogenic Probe for the Catalyst-Free Detection of Azide-Tagged Molecules. *Journal of the American Chemical Society* **2012**, *134* (45), 18809-18815.
- Friscourt, F.; Ledin, P. A.; Mbua, N. E.; Flanagan-Steet, H. R.; Wolfert, M. A.; Steet, R.; Boons, G.-J., Polar Dibenzocyclooctynes for Selective Labeling of Extracellular Glycoconjugates of Living Cells. *Journal of the American Chemical Society* **2012**, *134* (11), 5381-5389.

- Furmanski, B. D.; Dreau, D.; Wuthier, R. E.; Fuseler, J. W., Differential uptake and selective permeability of fusarochromanone (FC101), a novel membrane permeable anticancer naturally fluorescent compound in tumor and normal cells. *Microsc Microanal* **2009**, *15* (6), 545-57.
- Gahalawat, S.; Pandey, S. K., Enantioselective total synthesis of (+)-serinolamide A. *RSC Advances* **2015**, *5* (51), 41013-41016.
- Gatti, T.; Menna, E.; Meneghetti, M.; Maggini, M.; Petrozza, A.; Lamberti, F., The Renaissance of fullerenes with perovskite solar cells. *Nano Energy* **2017**, *41*, 84-100.
- Grob, C. A.; Cseh, G., Die Solvolyse von  $\alpha$ -Bromstyrolen Substitution am ungesättigten trigonalen Kohlenstoffatom. *Helvetica Chimica Acta* **1964**, *47* (1), 194-203.
- Gu, Y.; Chen, X.; Shang, C.; Singh, K.; Barzegar, M.; Mahdavian, E.; Salvatore, B. A.; Jiang, S.; Huang, S., Fusarochromanone induces G1 cell cycle arrest and apoptosis in COS7 and HEK293 cells. *PLoS One* **2014**, *9* (11), e112641.
- Heggie, M. I.; Terrones, M.; Eggen, B. R.; Jungnickel, G.; Jones, R.; Latham, C. D.; Bridson, P. R.; Terrones, H., Quantitative density-functional study of nested fullerenes. *Physical Review B* **1998**, *57* (21), 13339-13342.
- Hellwinkel, D.; Reiff, G., Cyclooctatetraene Systems Flattened by Steric Constraints. *Angewandte Chemie International Edition in English* **1970**, *9* (7), 527-528.
- Higgins, S. D.; Thomas, C. B., Conversion of aromatic ketones into  $\pi$ -arylalkanoic acids. Oxidation by thallium(III) and by halogens. *Journal of the Chemical Society, Perkin Transactions 1* **1982**, (0), 235-242.
- Hill, T. J.; Hughes, R. K.; Scott, L. T., Steps toward the synthesis of a geodesic C<sub>60</sub>H<sub>12</sub> end cap for a C<sub>3v</sub> carbon [6,6]nanotube. *Tetrahedron* **2008**, *64* (50), 11360-11369.
- Hofmann, A. W., On insolonic acid. *Proceedings of the Royal Society of London* **1857**, *8*, 1-3.
- Hoppe, D.; Schöllkopf, U., Ethyl 2-Oxazoline-5-carboxylate from Ethyl Isocyanacetate and Carbonyl Compounds. *Angewandte Chemie International Edition in English* **1970**, *9* (4), 300-301.
- Hückel, E., Quantentheoretische Beiträge zum Benzolproblem. *Zeitschrift für Physik* **1931**, *72* (5), 310-337.



- Hückel, E., Quantentheoretische Beiträge zum Benzolproblem. *Zeitschrift für Physik* **1931**, 70 (3), 204-286.
- Hückel, E., Quantentheoretische Beiträge zum Problem der aromatischen und ungesättigten Verbindungen. III. *Zeitschrift für Physik* **1932**, 76 (9), 628-648.
- Jackson, E. A.; Steinberg, B. D.; Bancu, M.; Wakamiya, A.; Scott, L. T., Pentaindenocorannulene and Tetraindenocorannulene: New Aromatic Hydrocarbon  $\pi$  Systems with Curvatures Surpassing That of  $C_{60}$ . *Journal of the American Chemical Society* **2007**, 129 (3), 484-485.
- Jiang, B.; Tilley, T. D., General, Efficient Route to Thiophene-1-Oxides and Well-Defined, Mixed Thiophene-Thiophene-1-Oxide Oligomers. *Journal of the American Chemical Society* **1999**, 121 (41), 9744-9745.
- Kancherla, S.; Lorentzen, M.; Snieckus, V.; Jørgensen, K. B., Directed ortho-Metalation and Anionic ortho-Fries Rearrangement of Polycyclic Aromatic O-Carbamates: Regioselective Synthesis of Substituted Chrysenes. *The Journal of Organic Chemistry* **2018**, 83 (7), 3590-3598.
- Kanishchev, M. I.; Shegolev, A. A.; Smit, W. A.; Caple, R.; Kelner, M. J., 1,5-Hydride shifts in vinyl cation intermediates produced upon the acylation of acetylenes. *Journal of the American Chemical Society* **1979**, 101 (19), 5660-5671.
- Karpf, M., Die Acylierung von Acetylenen mit  $\beta$ ,  $\gamma$ -ungesättigten Säurechloriden. Eine neue Synthese von 5-Cyclopentenonen. *Helvetica Chimica Acta* **1984**, 67 (1), 73-85.
- Kaufman, H. S.; Fankuchen, I.; Mark, H., Structure of Cyclo-octatetraene. *Nature* **1948**, 161, 165.
- Kawasumi, K.; Zhang, Q.; Segawa, Y.; Scott, L. T.; Itami, K., A grossly warped nanographene and the consequences of multiple odd-membered-ring defects. *Nature Chemistry* **2013**, 5, 739.
- Kollmar, H.; Staemmler, V., A theoretical study of the structure of cyclobutadiene. *Journal of the American Chemical Society* **1977**, 99 (11), 3583-3587.
- Kroto, H. W., The stability of the fullerenes  $C_n$ , with  $n = 24, 28, 32, 36, 50, 60$  and  $70$ . *Nature* **1987**, 329, 529.
- Kroto, H. W.; Heath, J. R.; O'Brien, S. C.; Curl, R. F.; Smalley, R. E.,  $C_{60}$ : Buckminsterfullerene. *Nature* **1985**, 318, 162.

- Lara-Ochoa, F.; Espinosa-Pérez, G., A new synthesis of combretastatins A-4 and AVE-8062A. *Tetrahedron Letters* **2007**, *48* (39), 7007-7010.
- Lee, Y. W.; Mirocha, C. J.; Shroeder, D. J.; Walser, M. M., TDP-1, a toxic component causing tibial dyschondroplasia in broiler chickens, and trichothecenes from *Fusarium roseum* 'Graminearum'. *Appl Environ Microbiol* **1985**, *50* (1), 102-7.
- Li, X.; Kang, F.; Inagaki, M., Buckybowls: Corannulene and Its Derivatives. *Small* **2016**, *12* (24), 3206-3223.
- Mahdavian, E.; Marshall, M.; Martin, P. M.; Cagle, P.; Salvatore, B. A.; Quick, Q. A., Caspase-dependent signaling underlies glioblastoma cell death in response to the fungal metabolite, fusarochromanone. *Int J Mol Med* **2014**, *34* (3), 880-5.
- Mahdavian, E.; Palyok, P.; Adelmund, S.; Williams-Hart, T.; Furmanski, B. D.; Kim, Y. J.; Gu, Y.; Barzegar, M.; Wu, Y.; Bhinge, K. N.; Kolluru, G. K.; Quick, Q.; Liu, Y. Y.; Kevil, C. G.; Salvatore, B. A.; Huang, S.; Clifford, J. L., Biological activities of fusarochromanone: a potent anti-cancer agent. *BMC Res Notes* **2014**, *7*, 601.
- Marcuzzi, F.; Melloni, G., Electrophilic additions to acetylenes. V. Stereochemistry of the electrophilic addition of alkyl halides and hydrogen halides to phenyl-substituted acetylenes. *Journal of the American Chemical Society* **1976**, *98* (11), 3295-3300.
- Martin, R. H., The Helicenes. *Angewandte Chemie International Edition in English* **1974**, *13* (10), 649-660.
- McMurry, J. E.; Fleming, M. P., New method for the reductive coupling of carbonyls to olefins. Synthesis of  $\beta$ -carotene. *Journal of the American Chemical Society* **1974**, *96* (14), 4708-4709.
- Miller, D. G.; Wayner, D. D. M., Improved method for the Wacker oxidation of cyclic and internal olefins. *The Journal of Organic Chemistry* **1990**, *55* (9), 2924-2927.
- Miller, R. W.; Averill, S. E.; Van Wyck, S. J.; Whalley, A. C., General Method for the Synthesis of Functionalized Tetrabenzo[8]circulenes. *The Journal of Organic Chemistry* **2016**, *81* (23), 12001-12005.
- Miller, R. W.; Dodge, N. J.; Dyer, A. M.; Fortner-Buczala, E. M.; Whalley, A. C., A one-pot method for the preparation of 2,5-diarylthiophene-1-oxides from arylacetylenes. *Tetrahedron Letters* **2016**, *57* (17), 1860-1862.

- Miller, R. W.; Duncan, A. K.; Schneebeli, S. T.; Gray, D. L.; Whalley, A. C., Synthesis and Structural Data of Tetrabenzo[8]circulene. *Chemistry – A European Journal* **2014**, *20* (13), 3705-3711.
- Milstein, D.; Stille, J. K., A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium. *Journal of the American Chemical Society* **1978**, *100* (11), 3636-3638.
- Miyaura, N.; Yamada, K.; Suzuki, A., A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Letters* **1979**, *20* (36), 3437-3440.
- Mueller, A.; Amsharov, K. Y., Synthesis of Robust Precursors for the Controlled Fabrication of (6,6), (8,8), (10,10), and (12,12) Armchair Single-Walled Carbon Nanotubes. *European Journal of Organic Chemistry* **2015**, *2015* (14), 3053-3056.
- Murakami, M.; Itami, K.; Ito, Y., Synthesis of (Vinylallene)rhodium(III) Complex of Planar Structure: Perfect  $\pi \rightarrow \sigma$  Conversion of 1,3-Diene System. *Journal of the American Chemical Society* **1996**, *118* (46), 11672-11673.
- Nestoros, E.; Stuparu, M. C., Corannulene: a molecular bowl of carbon with multifaceted properties and diverse applications. *Chemical Communications* **2018**, *54* (50), 6503-6519.
- Newman, M. S.; Lednicer, D., The Synthesis and Resolution of Hexahelicene<sup>1</sup>. *Journal of the American Chemical Society* **1956**, *78* (18), 4765-4770.
- Nobusue, S.; Fujita, K.; Tobe, Y., Skeletal Rearrangement of Twisted Polycyclic Aromatic Hydrocarbons under Scholl Reaction Conditions. *Organic Letters* **2017**, *19* (12), 3227-3230.
- Nobusue, S.; Miyoshi, H.; Shimizu, A.; Hisaki, I.; Fukuda, K.; Nakano, M.; Tobe, Y., Tetracyclopenta[def,jkl,pqr,vwx]tetraphenylene: A Potential Tetraradicaloid Hydrocarbon. *Angewandte Chemie International Edition* **2015**, *54* (7), 2090-2094.
- Nobusue, S.; Tobe, Y., Twisted Polycyclic Aromatic Hydrocarbon with a Cyclooctatetraene Core via Formal [4+4] Dimerization of Indenofluorene. *Synlett* **2016**, *27* (14), 2140-2144.
- Obora, Y.; Moriya, H.; Tokunaga, M.; Tsuji, Y., Cross-coupling reaction of thermally stable titanium(II)-alkyne complexes with aryl halides catalysed by a nickel complex. *Chemical Communications* **2003**, (22), 2820-2821.

- Park, J.; Lee, J.; Chang, S., Iterative C–H Functionalization Leading to Multiple Amidations of Anilides. *Angewandte Chemie International Edition* **2017**, *56* (15), 4256-4260.
- Pasto, D. J.; Miles, M. F.; Chou, S.-K., Analysis of reactivity of alkenylidenecyclopropanes with electrophilic reagents. *The Journal of Organic Chemistry* **1977**, *42* (18), 3098-3101.
- Pathre, S. V.; Gleason, W. B.; Lee, Y.-W.; Mirocha, C. J., The structure of fusarochromanone: new mycotoxin from *Fusarium roseum*, "Graminearum". *Canadian Journal of Chemistry* **1986**, *64* (7), 1258-1261.
- Pawlosky, R. J.; Mirocha, C. J., Mass spectral analysis and fragment ion structure of fusarochromanone. *Biol Mass Spectrom* **1991**, *20* (11), 743-9.
- Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A., The Reaction of  $\alpha$ -Diazo- $\beta$ -hydroxy Esters with Boron Trifluoride Etherate: Generation and Rearrangement of Destabilized Vinyl Cations. A Detailed Experimental and Theoretical Study. *Journal of the American Chemical Society* **1996**, *118* (1), 1-12.
- Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Rosato, G. C.; Ursini, A., The reaction of  $\alpha$ -diazo- $\beta$ -hydroxy esters with boron trifluoride. *Journal of the Chemical Society, Chemical Communications* **1993**, (24), 1798-1800.
- Prylutska, S.; Panchuk, R.; Gołuński, G.; Skivka, L.; Prylutsky, Y.; Hurmach, V.; Skorohyd, N.; Borowik, A.; Woziwodzka, A.; Piosik, J.; Kyzyma, O.; Garamus, V.; Bulavin, L.; Evstigneev, M.; Buchelnikov, A.; Stoika, R.; Berger, W.; Ritter, U.; Scharff, P., C<sub>60</sub> fullerene enhances cisplatin anticancer activity and overcomes tumor cell drug resistance. *Nano Research* **2017**, *10* (2), 652-671.
- Rao, C. N. R.; Seshadri, R.; Govindaraj, A.; Sen, R., Fullerenes, nanotubes, onions and related carbon structures. *Materials Science and Engineering: R: Reports* **1995**, *15* (6), 209-262.
- Reisch, H. A.; Bratcher, M. S.; Scott, L. T., Imposing Curvature on a Polyarene by Intramolecular Palladium-Catalyzed Arylation Reactions: A Simple Synthesis of Dibenzo[a,g]corannulene. *Organic Letters* **2000**, *2* (10), 1427-1430.
- Roncali, J., Molecular Bulk Heterojunctions: An Emerging Approach to Organic Solar Cells. *Accounts of Chemical Research* **2009**, *42* (11), 1719-1730.

- Sakamoto, Y.; Suzuki, T., Tetrabenzo[8]circulene: Aromatic Saddles from Negatively Curved Graphene. *Journal of the American Chemical Society* **2013**, *135* (38), 14074-14077.
- Sakurai, H.; Daiko, T.; Hirao, T., A Synthesis of Sumanene, a Fullerene Fragment. *Science* **2003**, *301* (5641), 1878-1878.
- Salvatore, B. A.; Solis, F. C., Synthesis of Chromanones. US Patent No. WO2004/103985, **2004**.
- Schleyer, P. v. R.; Pfeifer, W. D.; Bahn, C. A.; Bocher, S.; Harding, C. E.; Hummel, K.; Hanack, M.; Stang, P. J., Behavior of bent vinyl cations generated by solvolysis of cyclic trifluoromethanesulfonates. *Journal of the American Chemical Society* **1971**, *93* (6), 1513-1516.
- Schultz, H. P., Topological Organic Chemistry. Polyhedranes and Prismanes. *The Journal of Organic Chemistry* **1965**, *30* (5), 1361-1364.
- Scott, L. T.; Boorum, M. M.; McMahon, B. J.; Hagen, S.; Mack, J.; Blank, J.; Wegner, H.; de Meijere, A., A Rational Chemical Synthesis of C<sub>60</sub>. *Science* **2002**, *295* (5559), 1500-1503.
- Scott, L. T.; Bratcher, M. S.; Hagen, S., Synthesis and Characterization of a C<sub>36</sub>H<sub>12</sub> Fullerene Subunit. *Journal of the American Chemical Society* **1996**, *118* (36), 8743-8744.
- Scott, L. T.; Cheng, P.-C.; Hashemi, M. M.; Bratcher, M. S.; Meyer, D. T.; Warren, H. B., Corannulene. A Three-Step Synthesis. *Journal of the American Chemical Society* **1997**, *119* (45), 10963-10968.
- Scott, L. T.; Hashemi, M. M.; Meyer, D. T.; Warren, H. B., Corannulene. A convenient new synthesis. *Journal of the American Chemical Society* **1991**, *113* (18), 7082-7084.
- Seiders, T. J.; Baldrige, K. K.; Siegel, J. S., Synthesis and Characterization of the First Corannulene Cyclophane. *Journal of the American Chemical Society* **1996**, *118* (11), 2754-2755.
- Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J., Total Synthesis of (-)-Himalensine A. *Journal of the American Chemical Society* **2017**, *139* (49), 17755-17758.

- Smith, A. B.; Toder, B. H.; Branca, S. J., Vinylogous Wolff rearrangement. 4. General reaction of  $\beta,\gamma$ -unsaturated  $\alpha'$ -diazo ketones. *Journal of the American Chemical Society* **1984**, *106* (14), 3995-4001.
- Soll, R. M.; Guinasso, C.; Asselin, A., Multigram preparation of 1,8-diethyl-7-hydroxy-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, a phenolic metabolite of the analgesic and antiinflammatory agent etodolac. *The Journal of Organic Chemistry* **1988**, *53* (12), 2844-2847.
- Stang, P. J.; Hanack, M.; Subramanian, L. R., Perfluoroalkanesulfonic Esters: Methods of Preparation and Applications in Organic Chemistry. *Synthesis* **1982**, 1982 (02), 85-126.
- Suh, M. C.; Jiang, B.; Tilley, T. D., An Efficient, Modular Synthetic Route to Oligomers Based on Zirconocene Coupling: Properties for Phenylene–Thiophene-1-Oxide and Phenylene–Thiophene-1,1-Dioxide Chains. *Angewandte Chemie* **2000**, *112* (16), 2992-2995.
- Sumy, D. P. Ph.D. Dissertation. The University of Vermont, Burlington, 2017.
- Sumy, D. P.; Dodge, N. J.; Harrison, C. M.; Finke, A. D.; Whalley, A. C., Tridecacyclene: A Cyclic Tetramer of Acenaphthylene. *Chemistry – A European Journal* **2016**, *22* (14), 4709-12.
- Sumy, D. P.; Finke, A. D.; Whalley, A. C., The reductive aromatization of tridecacyclene. *Chem Commun* **2016**, 52 (83), 12368-12371.
- Sygula, A.; Rabideau, P. W., A Practical, Large Scale Synthesis of the Corannulene System. *Journal of the American Chemical Society* **2000**, *122* (26), 6323-6324.
- Takahama, Y.; Shibata, Y.; Tanaka, K., Concise Synthesis of Fungal Metabolite (+)-Fusarochromanone via Rhodium(III)-catalyzed Oxidative  $sp^2$  C-H Bond Olefination. *Chem Lett* **2016**, *45* (10), 1177-1179.
- Takahama, Y.; Shibata, Y.; Tanaka, K., Oxidative Olefination of Anilides with Unactivated Alkenes Catalyzed by an (Electron-Deficient  $\eta^5$ -Cyclopentadienyl)Rhodium(III) Complex Under Ambient Conditions. *Chemistry – A European Journal* **2015**, *21* (25), 9053-9056.
- Tamoto, A.; Aratani, N.; Yamada, H., Contraction of  $\pi$ -Conjugated Rings upon Oxidation from Cyclooctatetraene to Benzene via the Tropylium Cation. *Chemistry – A European Journal* **2017**, *23* (64), 16388-16392.

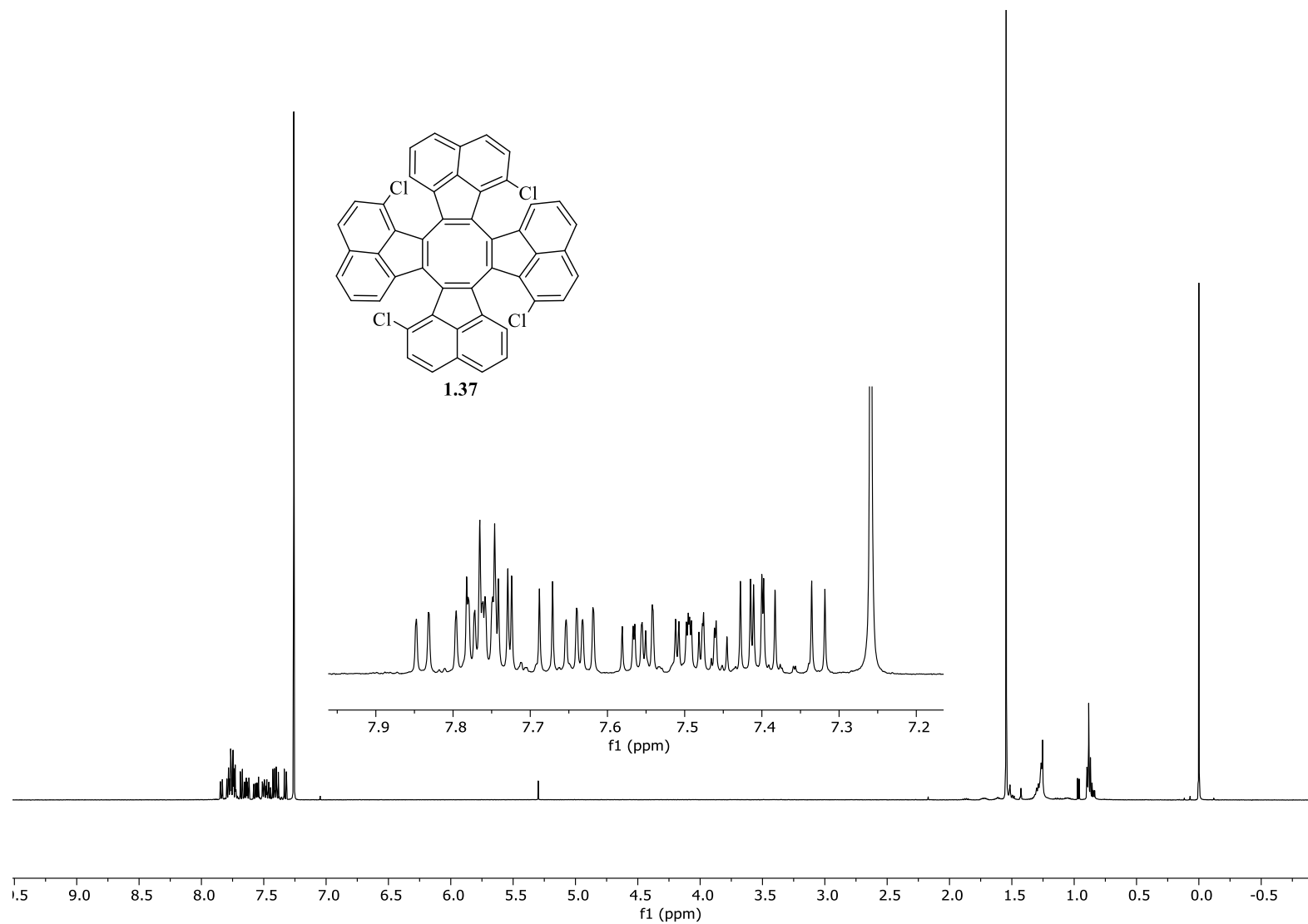
- Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L., Dynamic Kinetic Asymmetric Transformation of Diene Monoepoxides: A Practical Asymmetric Synthesis of Vinylglycinol, Vigabatrin, and Ethambutol. *Journal of the American Chemical Society* **2000**, *122* (25), 5968-5976.
- Tsefrikas, V. M.; Scott, L. T., Geodesic Polyarenes by Flash Vacuum Pyrolysis. *Chemical Reviews* **2006**, *106* (12), 4868-4884.
- von E. Doering, W.; Detert, F. L., CYCLOHEPTATRIENYLIUM OXIDE. *Journal of the American Chemical Society* **1951**, *73* (2), 876-877.
- Wright, G. C., Jr.; Marasas, W. F.; Sokoloff, L., Effect of fusarochromanone and T-2 toxin on articular chondrocytes in monolayer culture. *Fundam Appl Toxicol* **1987**, *9* (3), 595-7.
- Wu, T.-C.; Chen, M.-K.; Lee, Y.-W.; Kuo, M.-Y., Wu, Y.-T., Bowl-Shaped Fragments of C<sub>70</sub> or Higher Fullerenes: Synthesis, Structural Analysis, and Inversion Dynamics. *Angewandte Chemie International Edition* **2013**, *52* (4), 1289-1293.
- Wu, W.; Cook, M. E.; Chu, Q.; Smalley, E. B., Tibial dyschondroplasia of chickens induced by Fusarochromanone, a mycotoxin. *Avian Dis* **1993**, *37* (2), 302-9.
- Yamamoto, K.; Sonobe, H.; Matsubara, H.; Sato, M.; Okamoto, S.; Kitaura, K., Convenient New Synthesis of [7]Circulene. *Angewandte Chemie International Edition in English* **1996**, *35* (1), 69-70.
- Yang, C.-H.; Fan, W.-W.; Liu, G.-Q.; Duan, L.; Li, L.; Li, Y.-M., On the understanding of BF<sub>3</sub>·Et<sub>2</sub>O-promoted intra- and intermolecular amination and oxygenation of unfunctionalized olefins. *RSC Advances* **2015**, *5* (75), 61081-61093.
- Yu, J.-Q.; Corey, E. J., A Mild, Catalytic, and Highly Selective Method for the Oxidation of  $\alpha,\beta$ -Enones to 1,4-Enediones. *Journal of the American Chemical Society* **2003**, *125* (11), 3232-3233.
- Zhai, L.; Shukla, R.; Rathore, R., Oxidative C–C Bond Formation (Scholl Reaction) with DDQ as an Efficient and Easily Recyclable Oxidant. *Organic Letters* **2009**, *11* (15), 3474-3477.
- Zhang, W.; Cao, X.-Y.; Zi, H.; Pei, J., Single-Molecule Nanosized Polycyclic Aromatics with Alternant Five- and Six-Membered Rings: Synthesis and Optical Properties. *Organic Letters* **2005**, *7* (6), 959-962.

Zheng, G.; Zhao, J.; Li, Z.; Zhang, Q.; Sun, J.; Sun, H.; Zhang, Q., Highly Regio- and Stereoselective Intermolecular Seleno- and Thioamination of Alkynes. *Chemistry – A European Journal* **2016**, 22 (10), 3513-3518.

Zirngast, M.; Marschner, C.; Baumgartner, J., Group 4 Metallocene Complexes of Tris(trimethylsilyl)silylacetylene and Related Alkynes. *Organometallics* **2008**, 27 (11), 2570-2583.



## APPENDIX: NMR SPECTROSCOPIC DATA



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Figure A1:  $^1\text{H}$  NMR of **1.37** in  $\text{CDCl}_3$

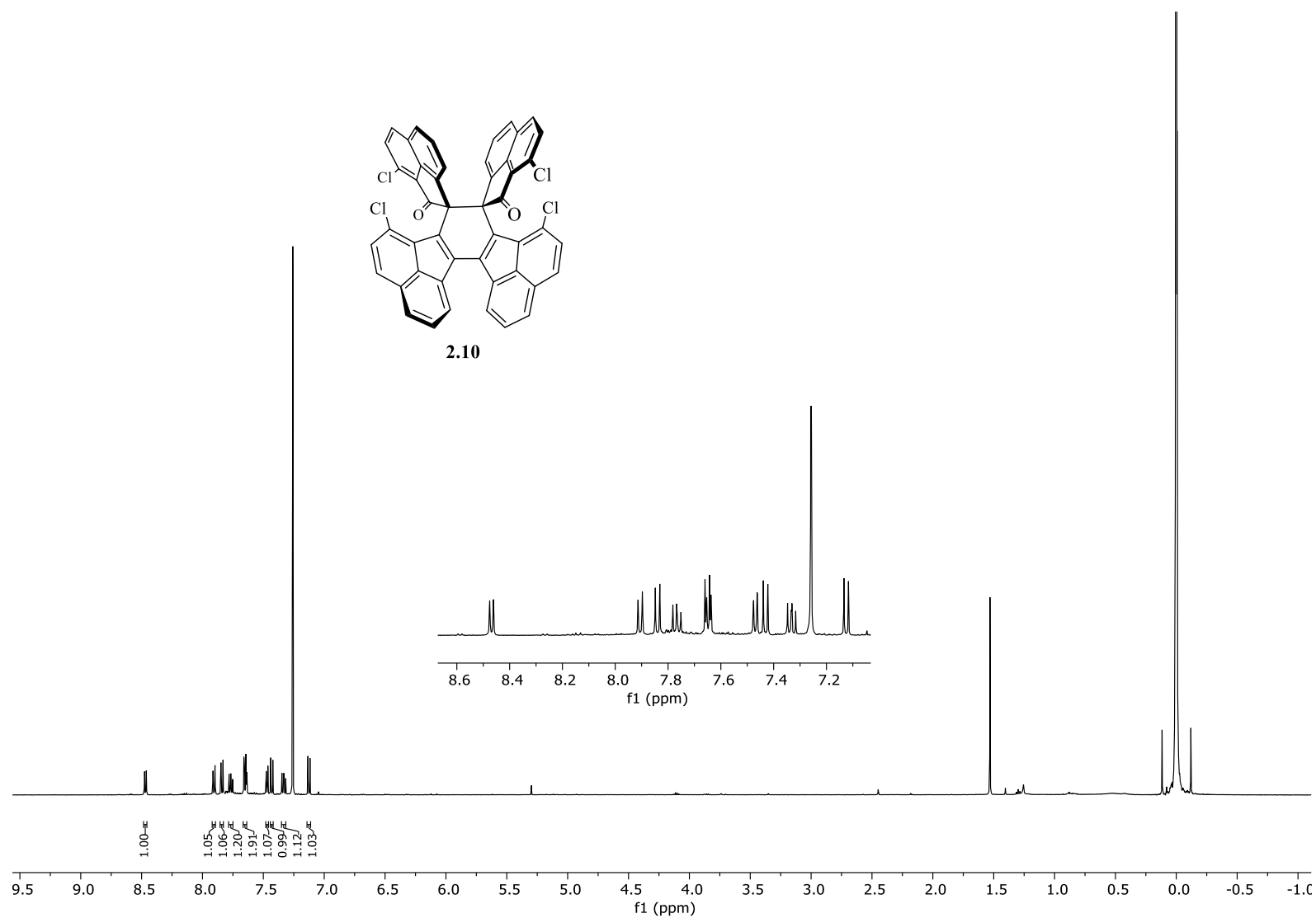


Figure A2:  $^1\text{H}$  NMR of **2.10** in  $\text{CDCl}_3$

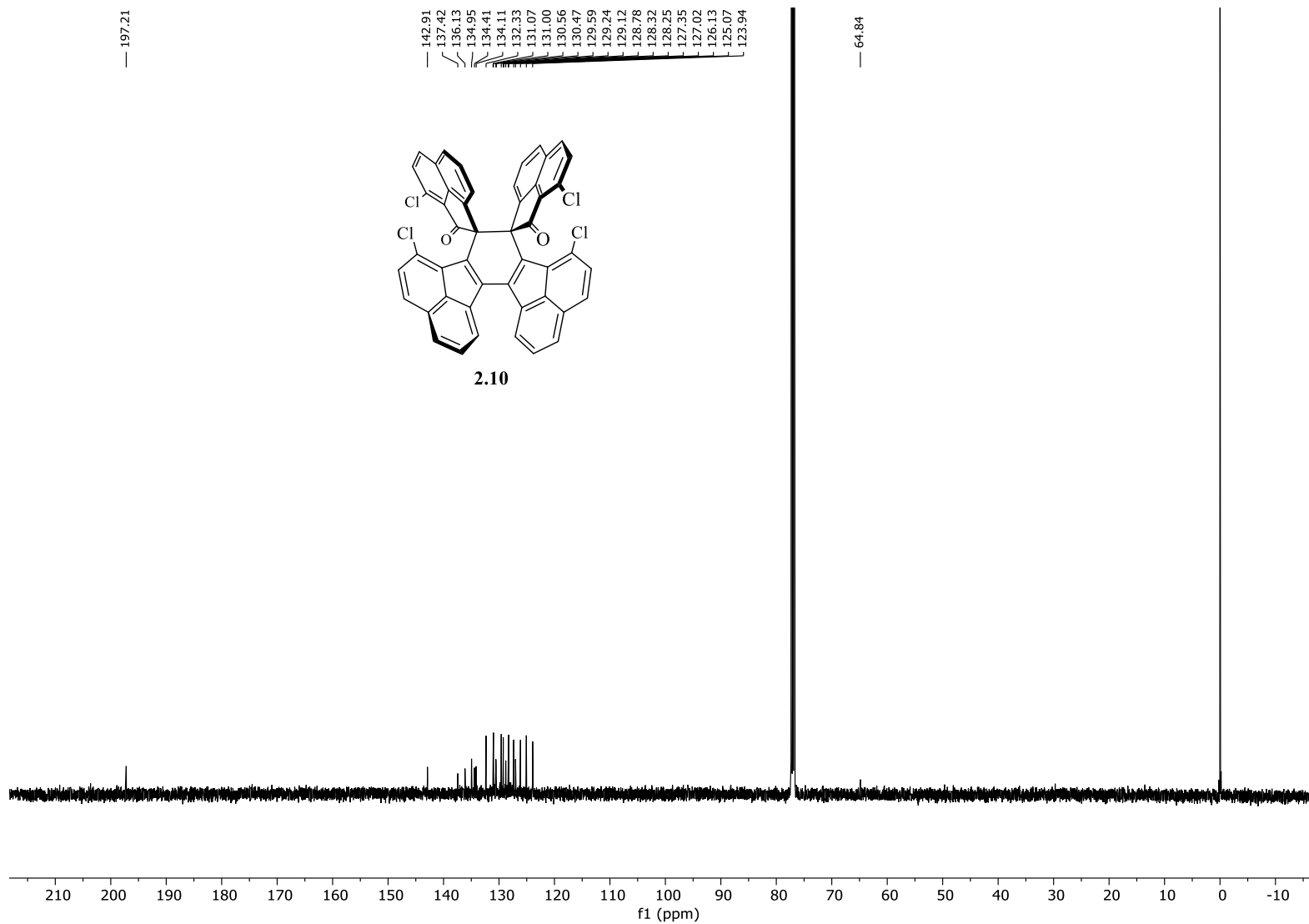


Figure A3: <sup>13</sup>C NMR of **2.10** in CDCl<sub>3</sub>

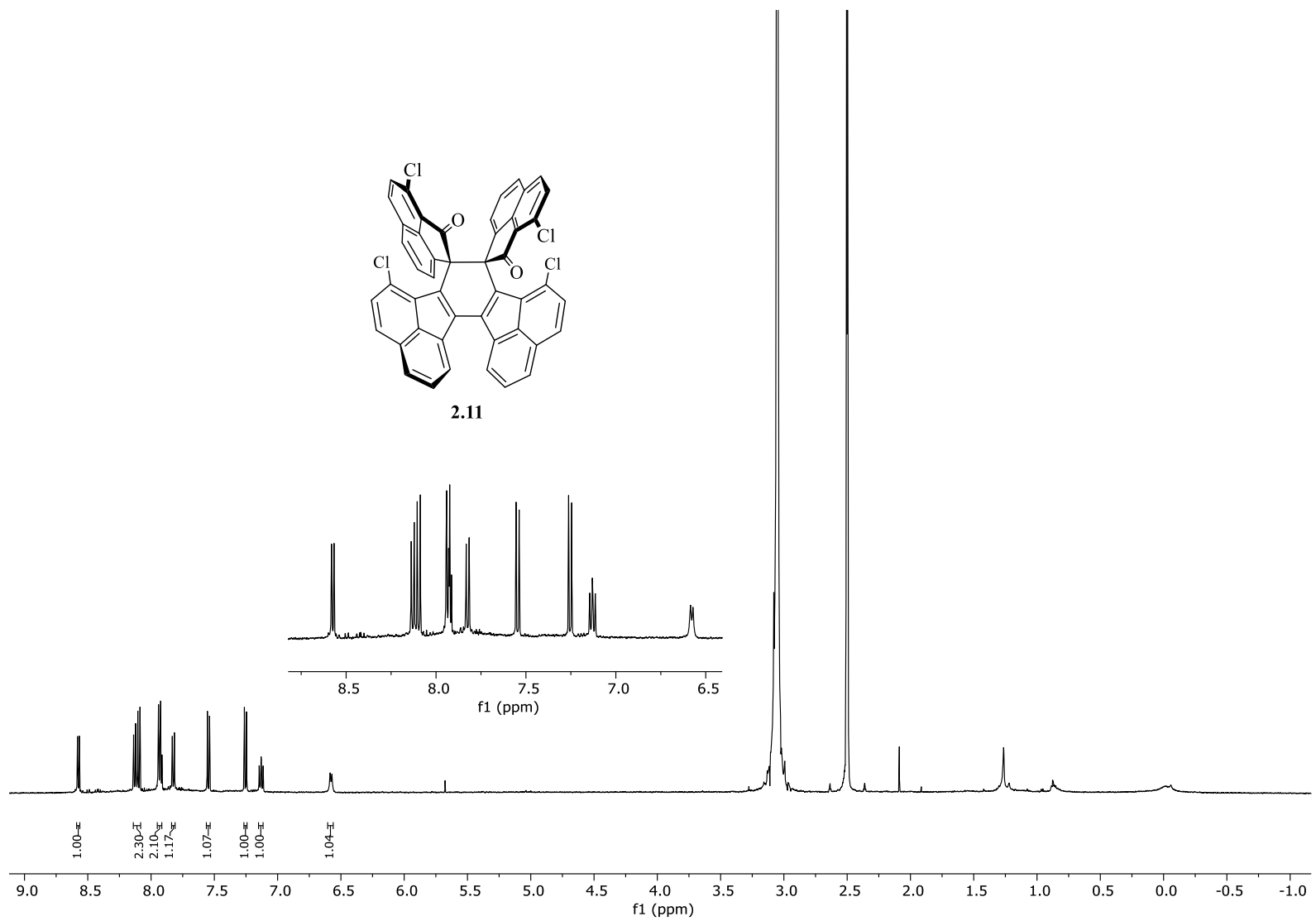


Figure A4: <sup>1</sup>H NMR of 2.11 in d<sub>6</sub>-DMSO at 65 °C

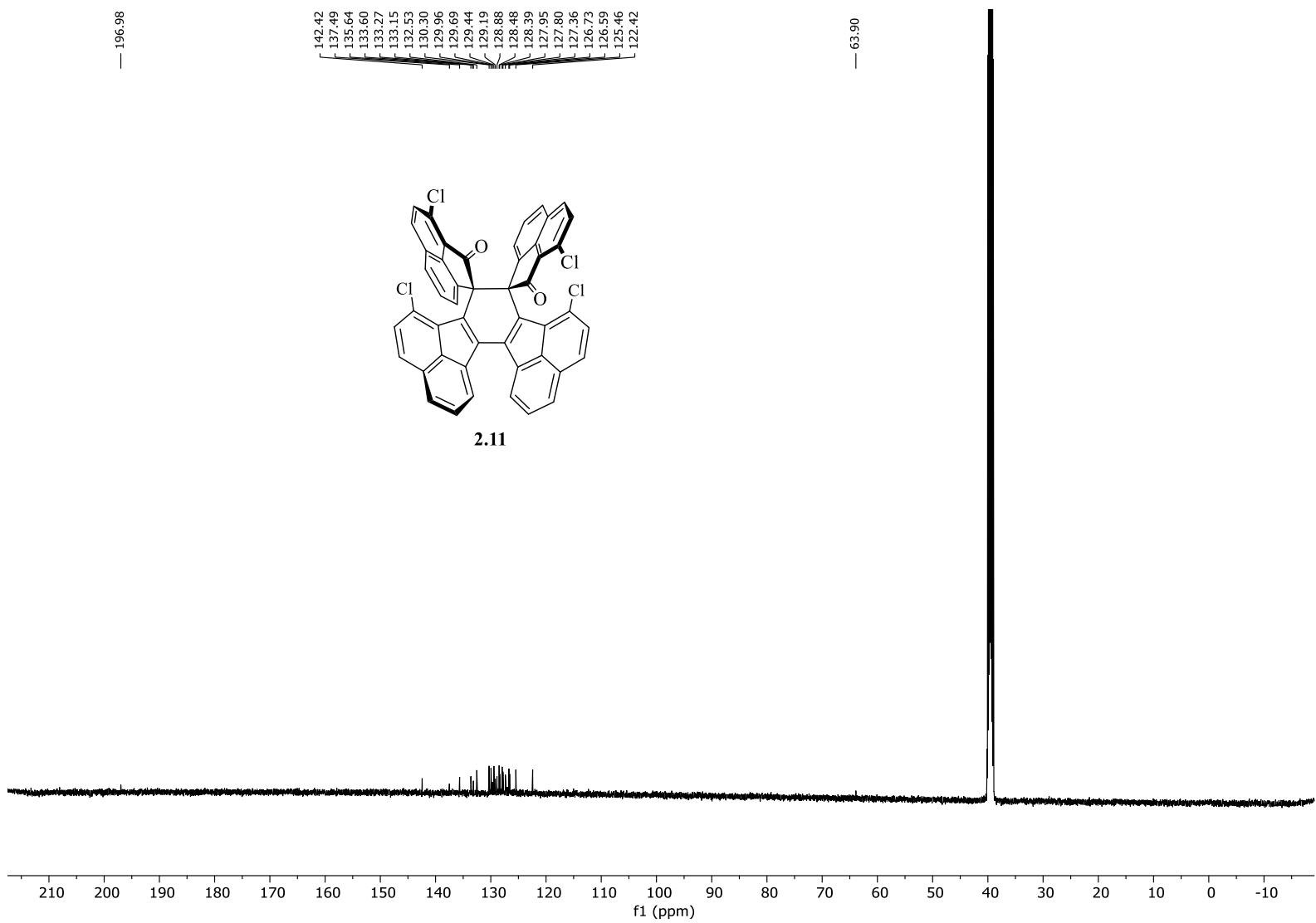


Figure A5:  $^{13}\text{C}$  NMR of 2.11 in  $\text{d}_6\text{-DMSO}$  at  $65^\circ\text{C}$

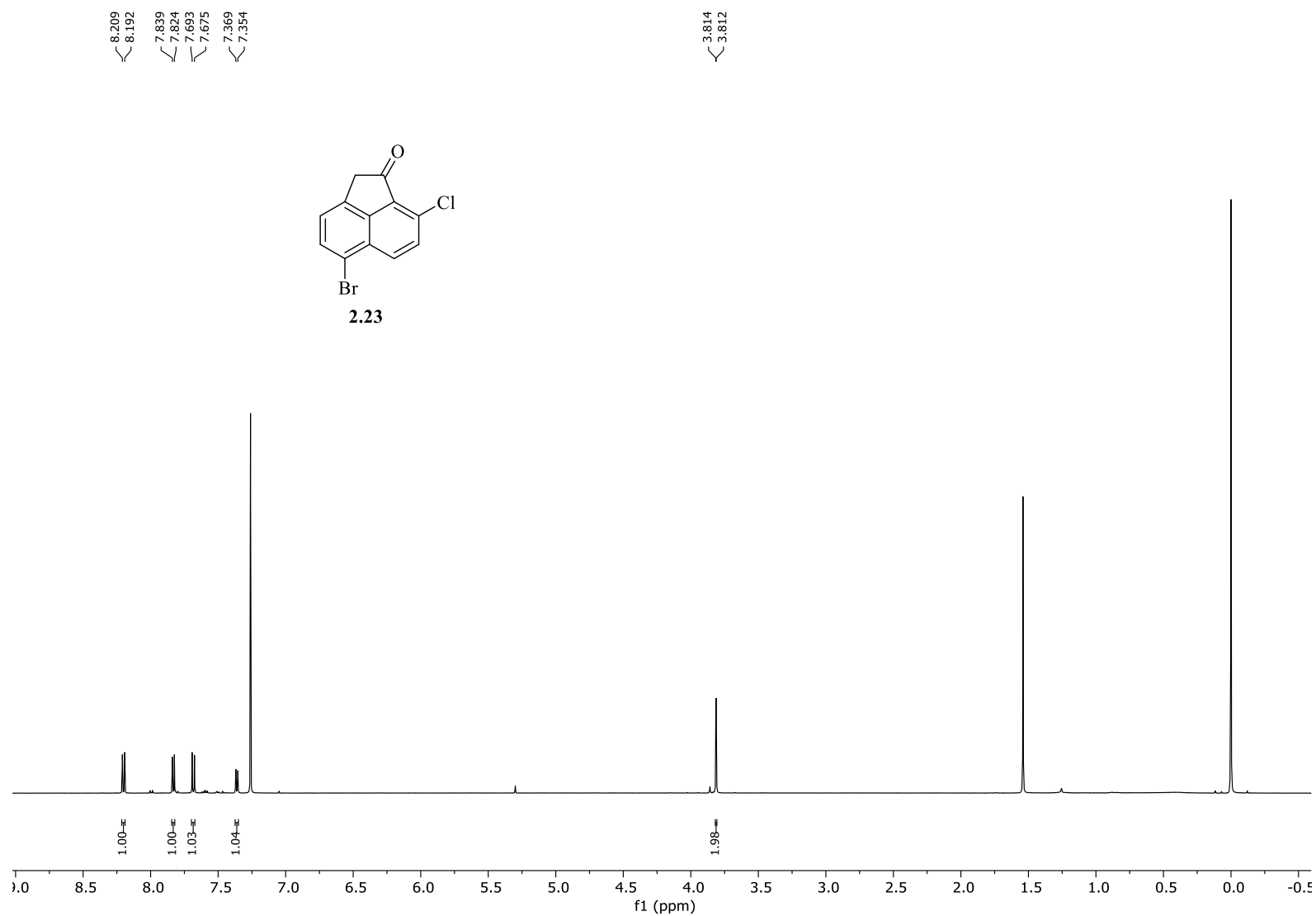


Figure A6:  $^1\text{H}$  NMR of **2.23** in  $\text{CDCl}_3$

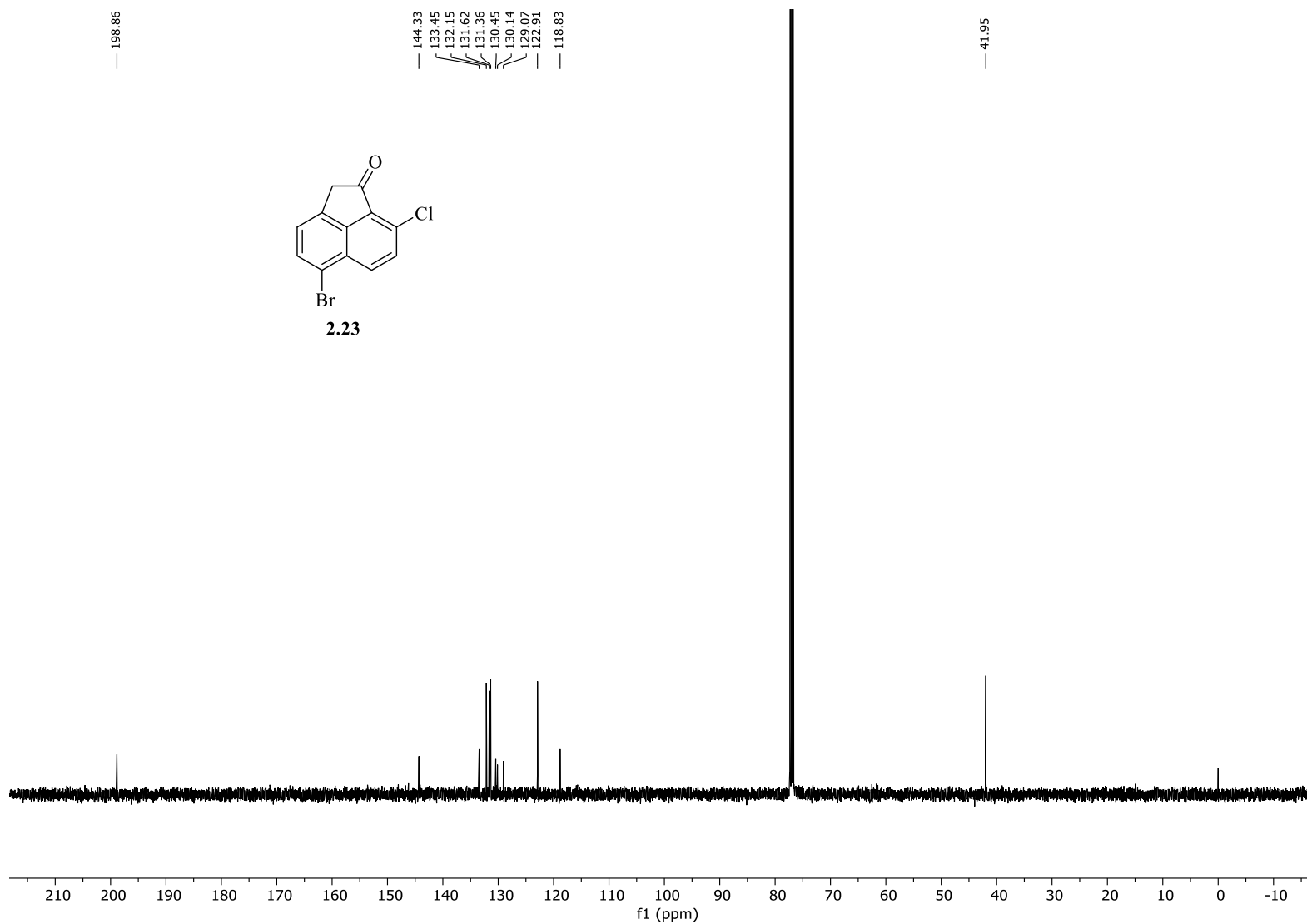


Figure A7:  $^{13}\text{C}$  NMR of **2.23** in  $\text{CDCl}_3$



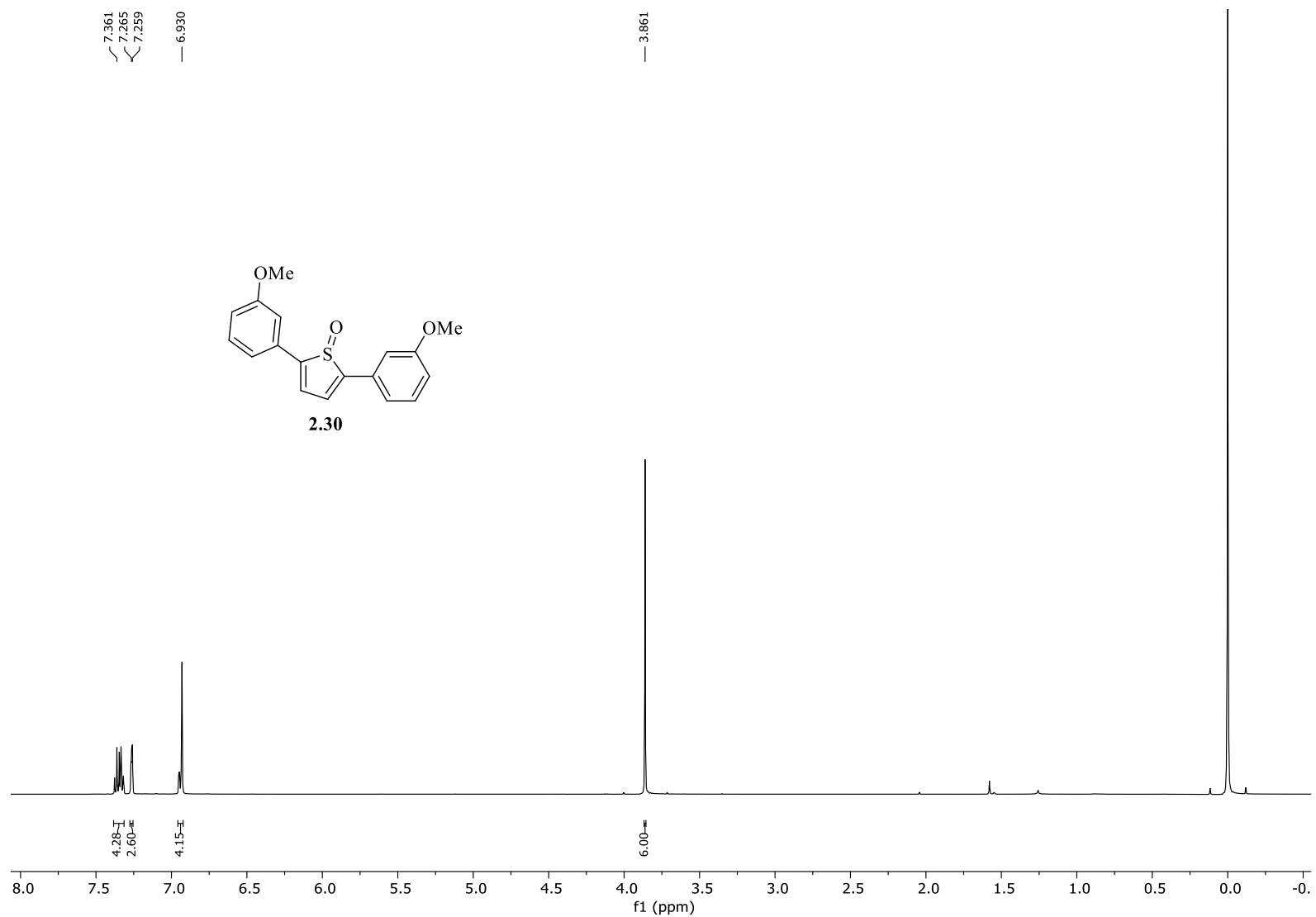


Figure A8: <sup>1</sup>H NMR of 2.30 in CDCl<sub>3</sub>

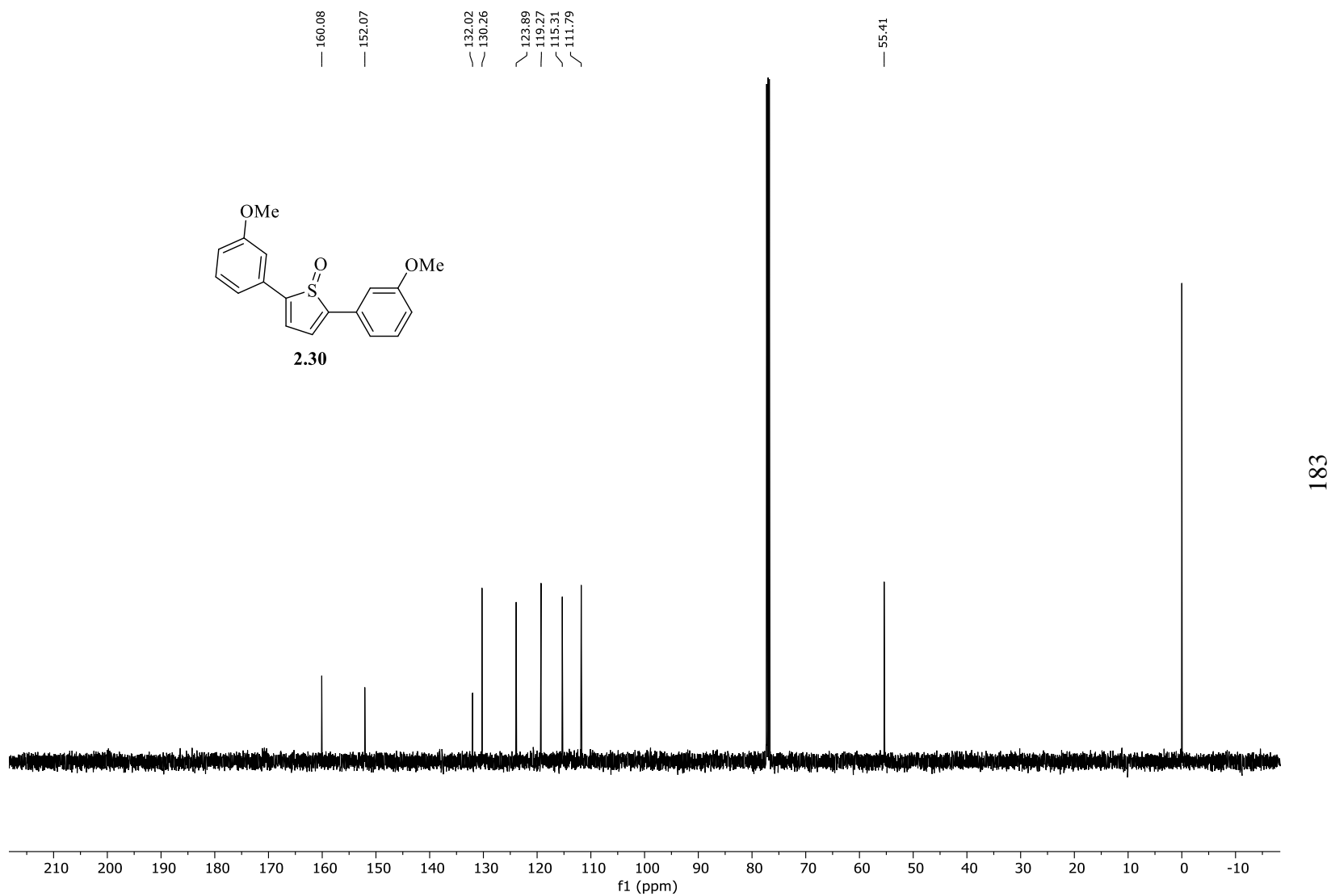


Figure A9: <sup>13</sup>C NMR of **2.30** in CDCl<sub>3</sub>

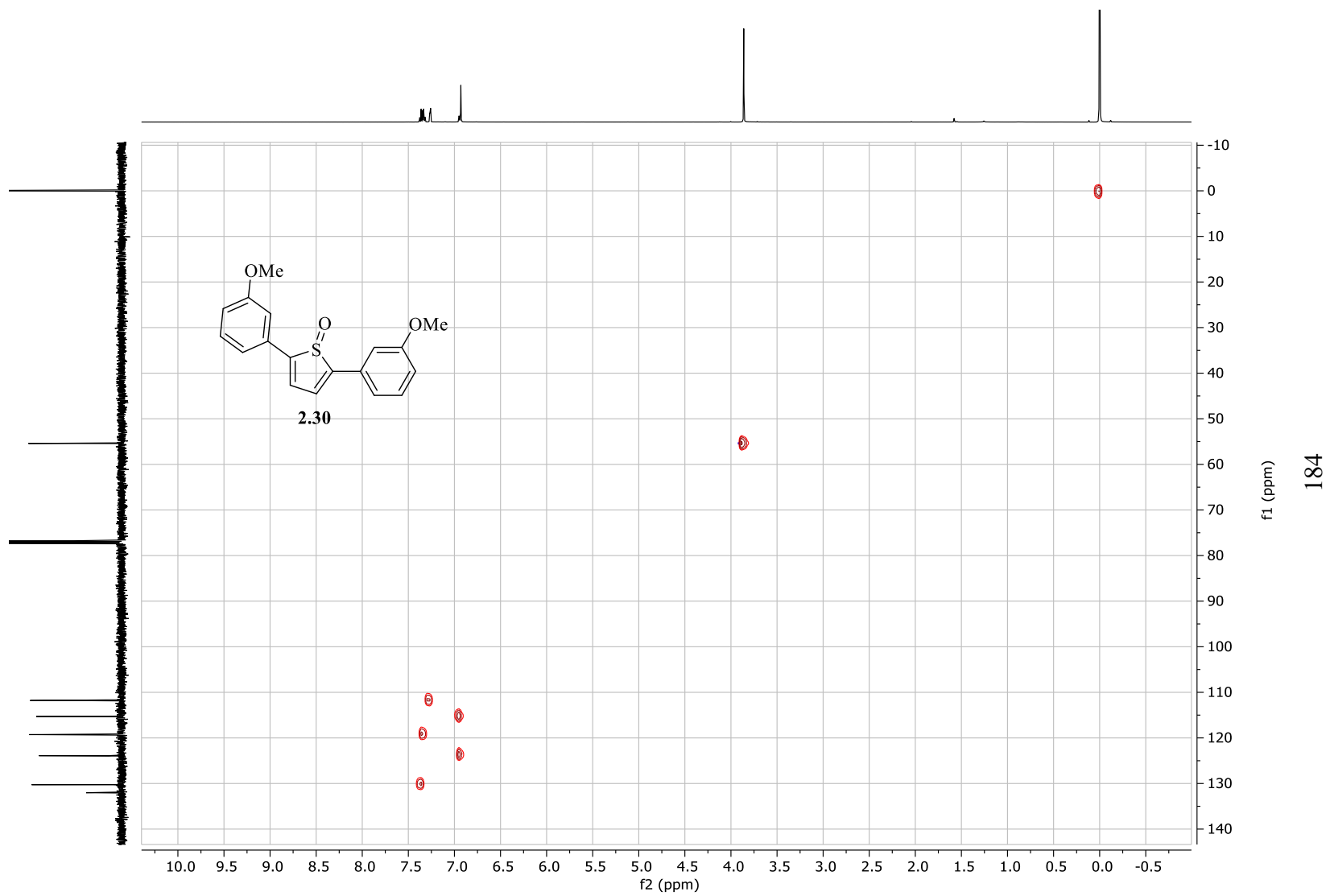


Figure A10: HSQC of **2.30** in CDCl<sub>3</sub>

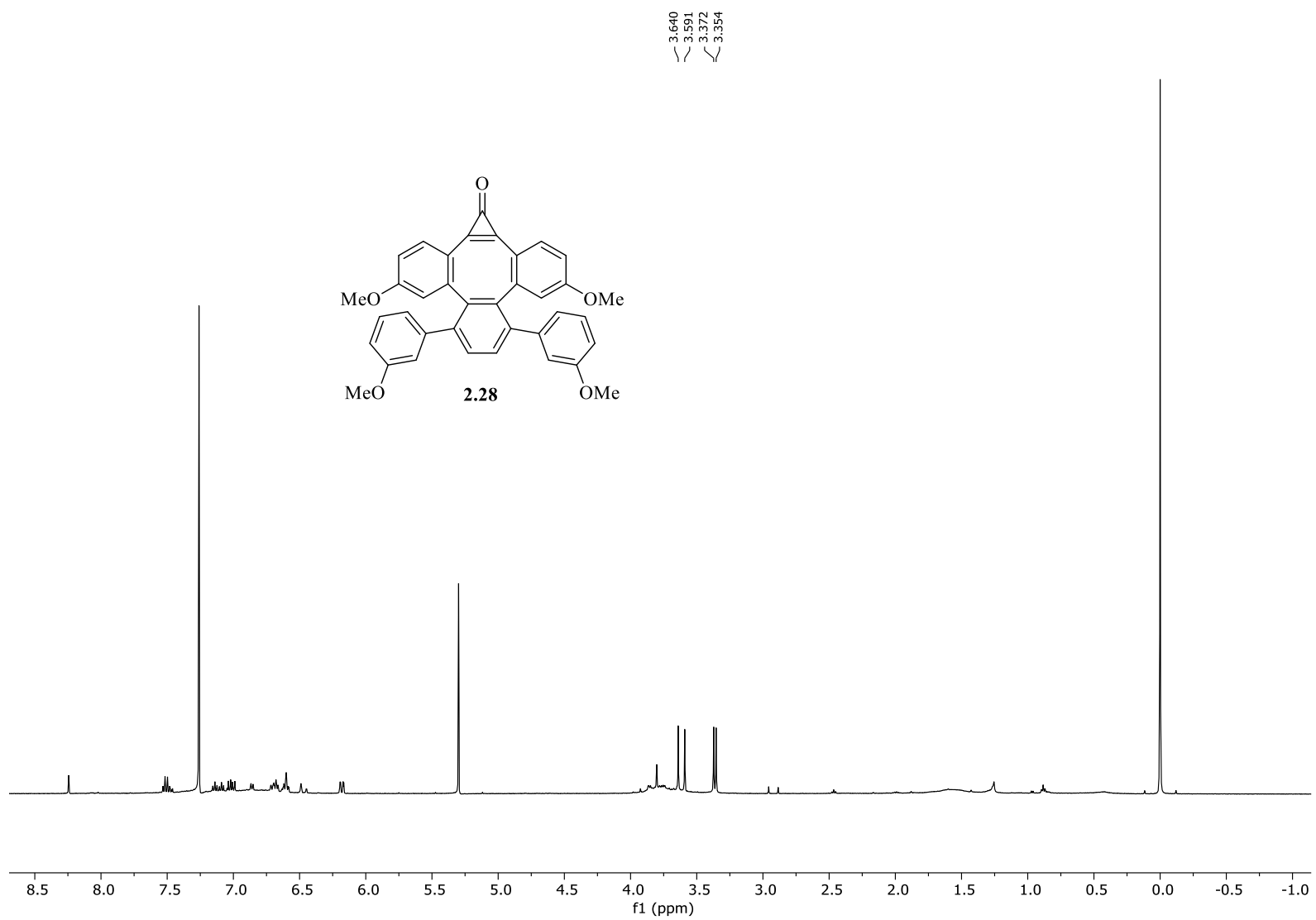
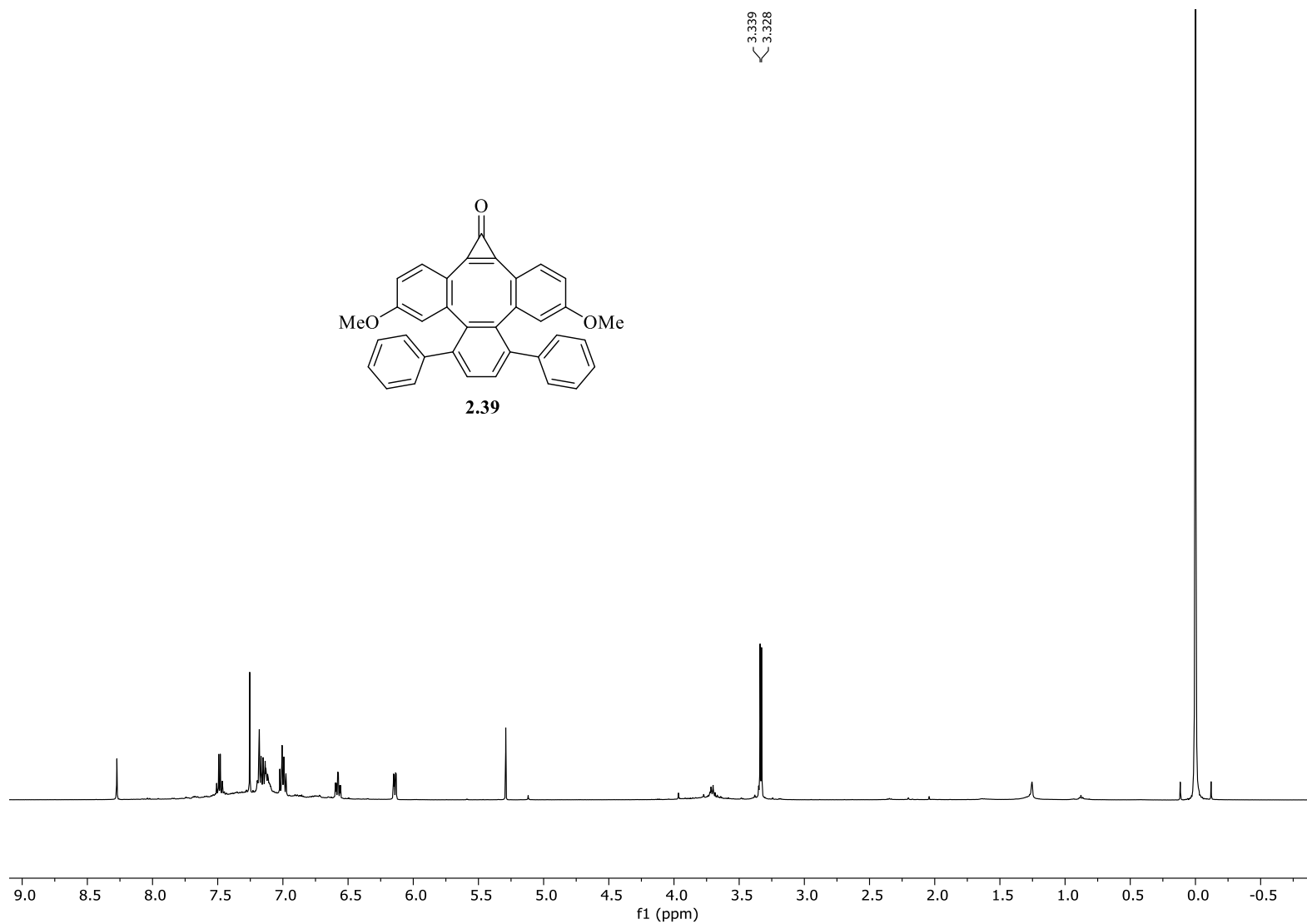
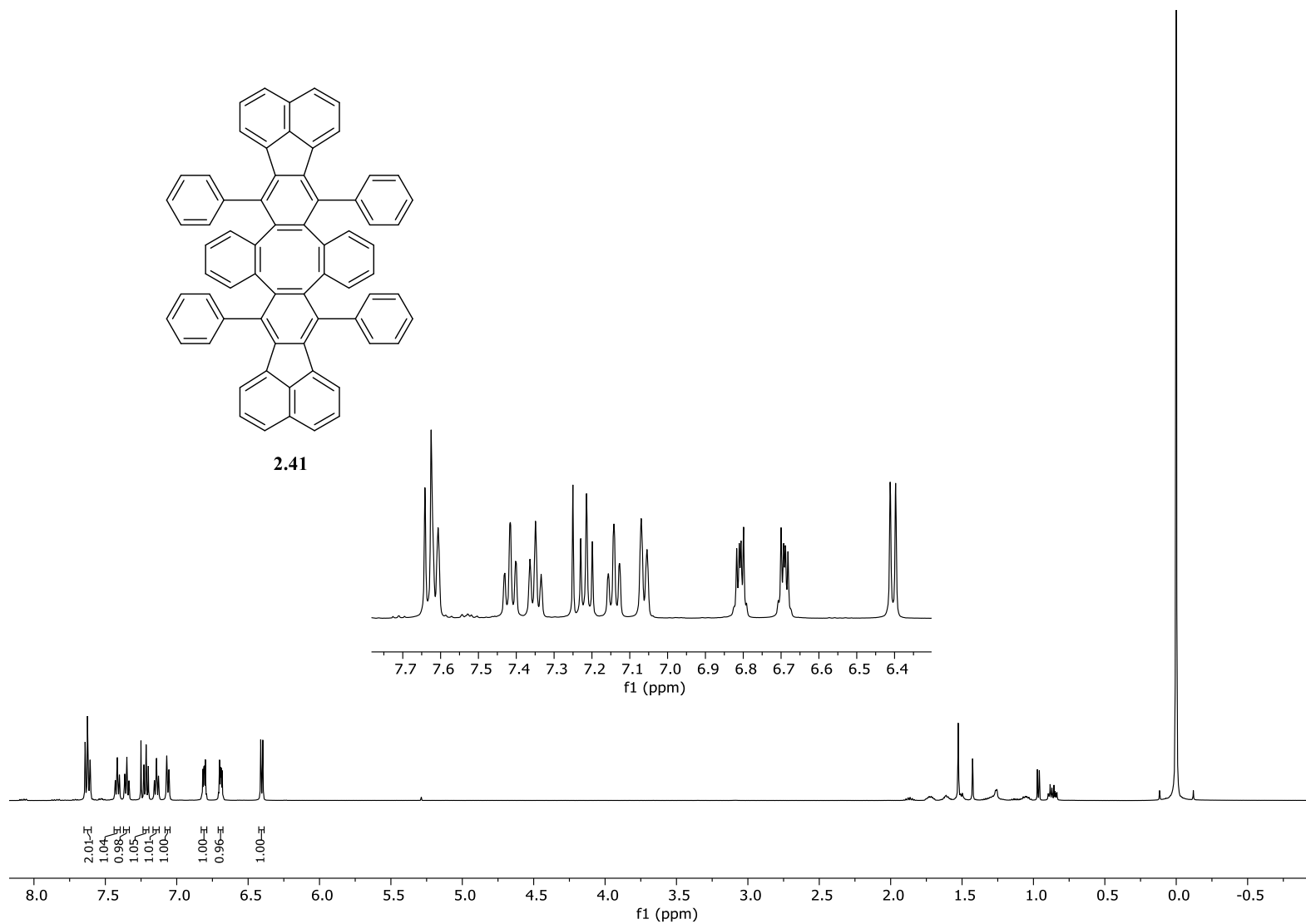


Figure A11:  $^1\text{H NMR}$  of **2.28** in  $\text{CDCl}_3$



**Figure A12:** <sup>1</sup>H NMR of **2.39** in CDCl<sub>3</sub>



**Figure A13:** <sup>1</sup>H NMR of **2.41** in CDCl<sub>3</sub>

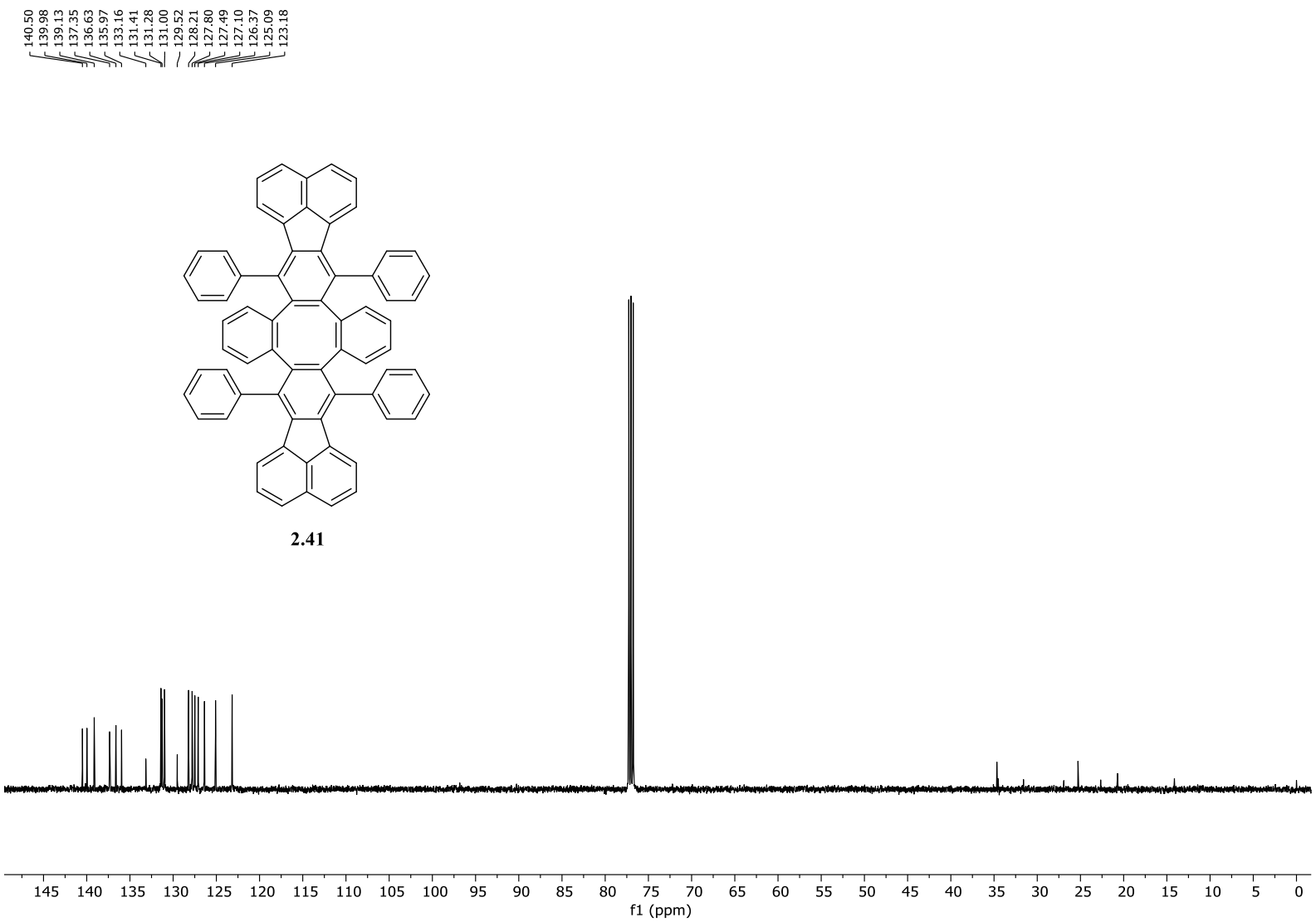


Figure A14:  $^{13}\text{C}$  NMR of **2.41** in  $\text{CDCl}_3$

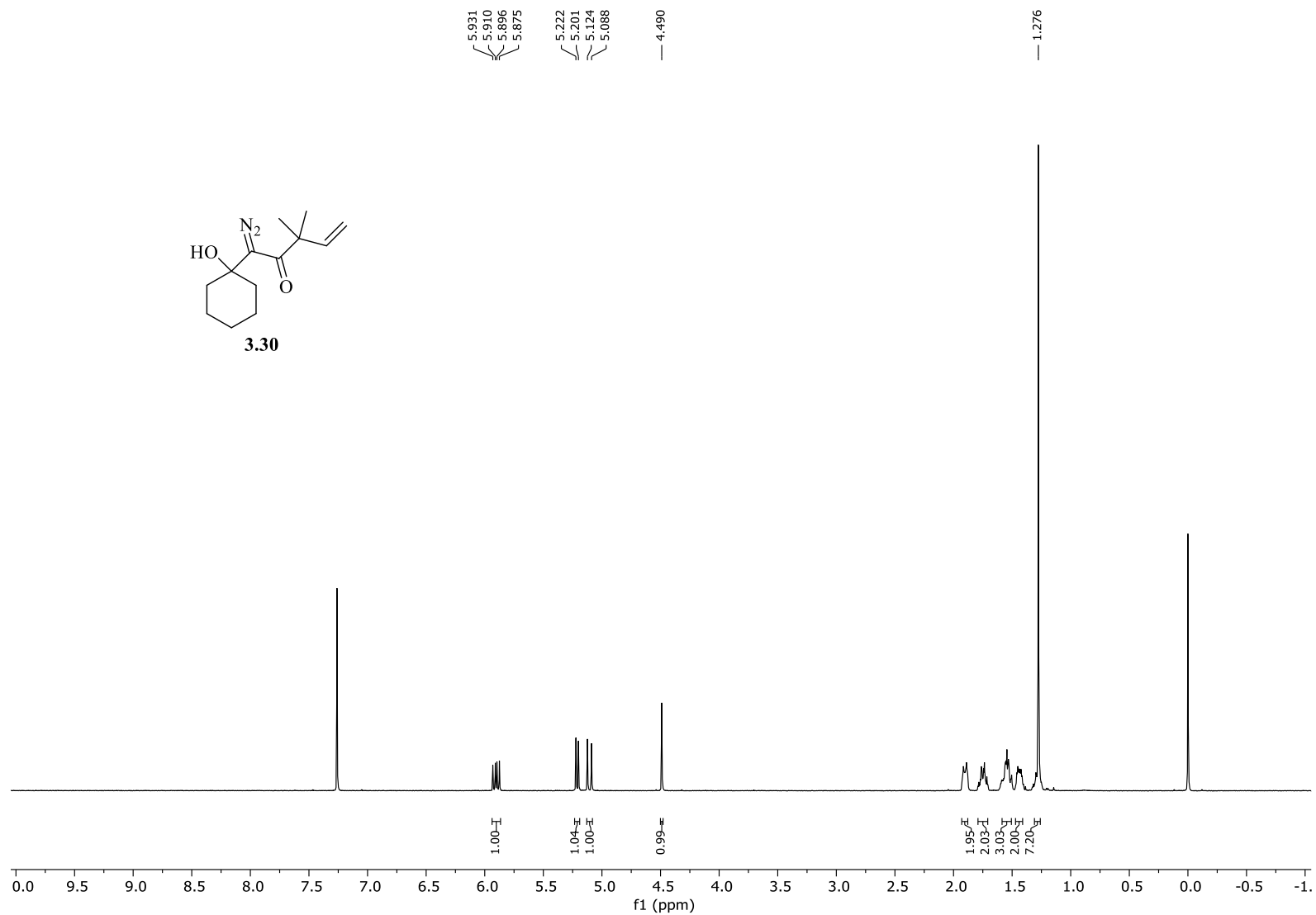


Figure A15: <sup>1</sup>H NMR of **3.30** in CDCl<sub>3</sub>



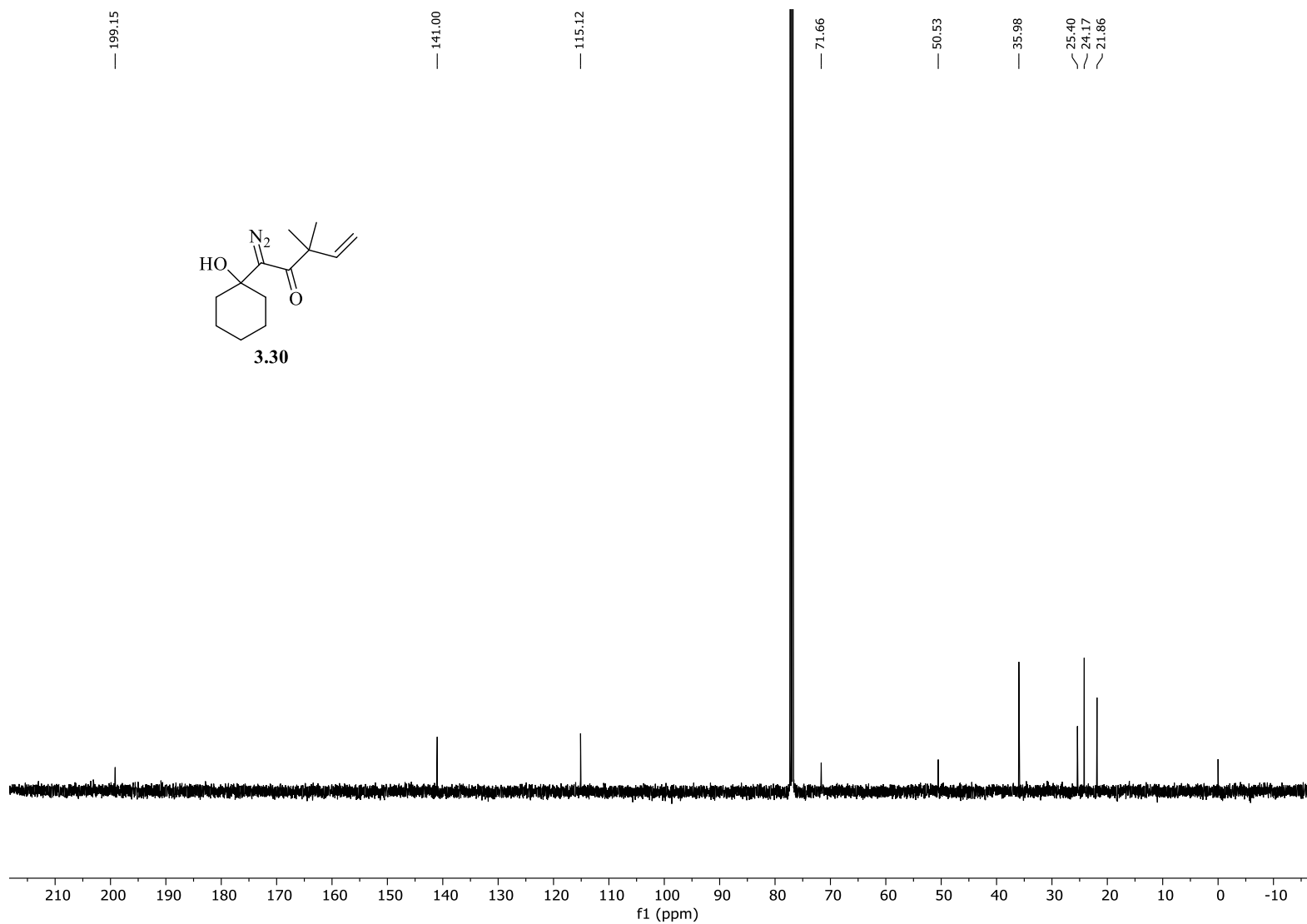


Figure A16:  $^{13}\text{C}$  NMR of **3.30** in  $\text{CDCl}_3$

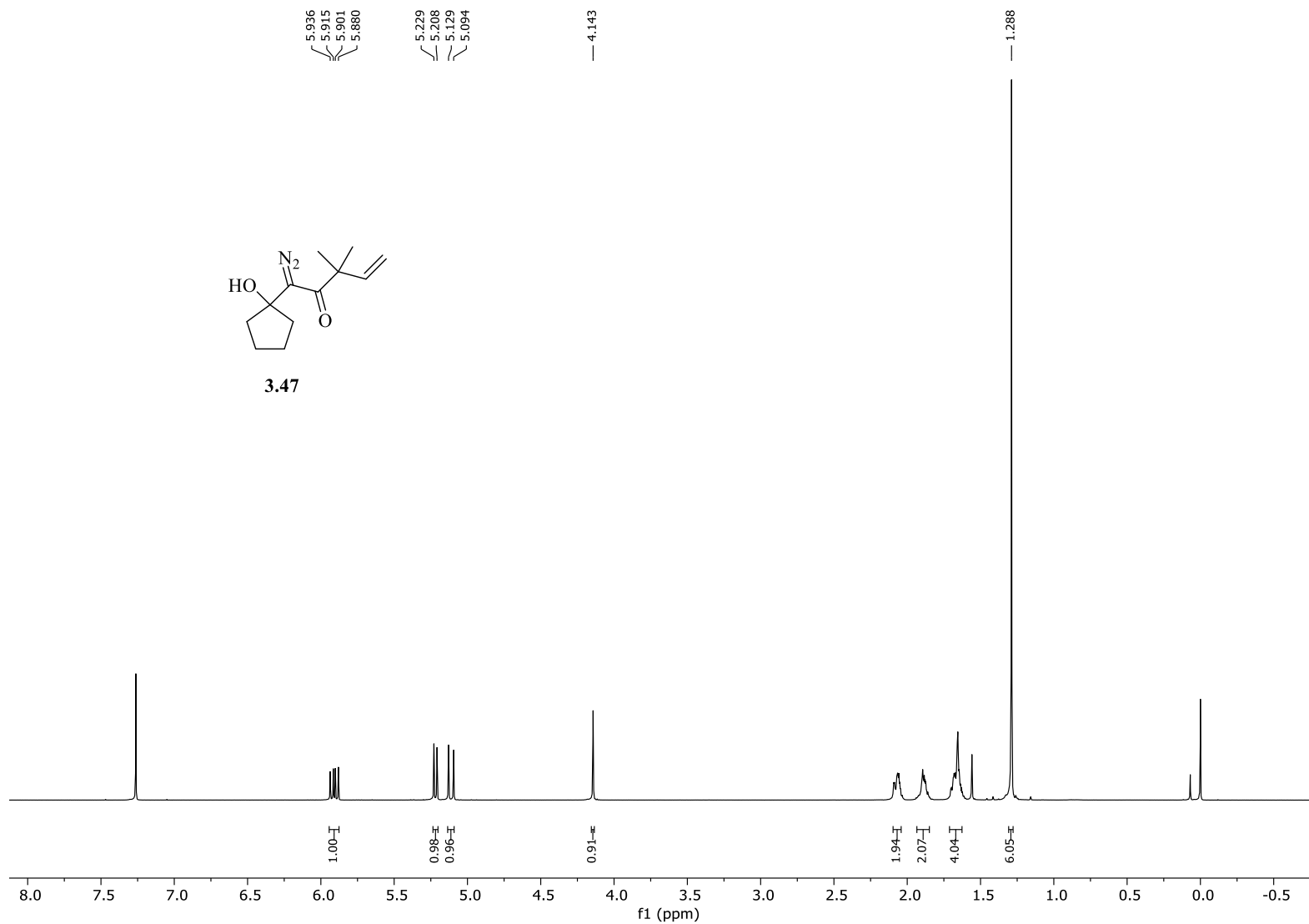


Figure A17:  $^1\text{H}$  NMR of **3.47** in  $\text{CDCl}_3$

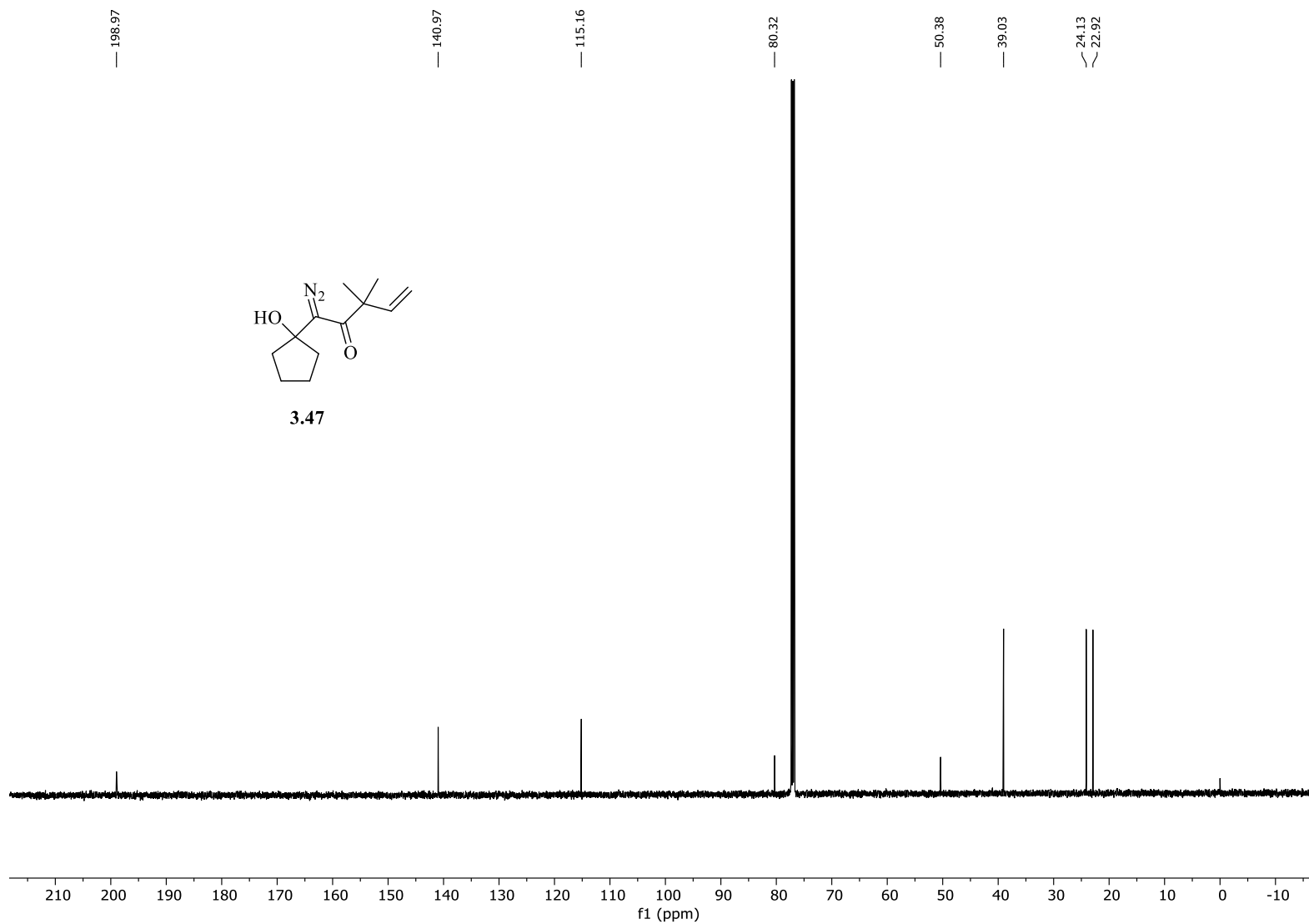
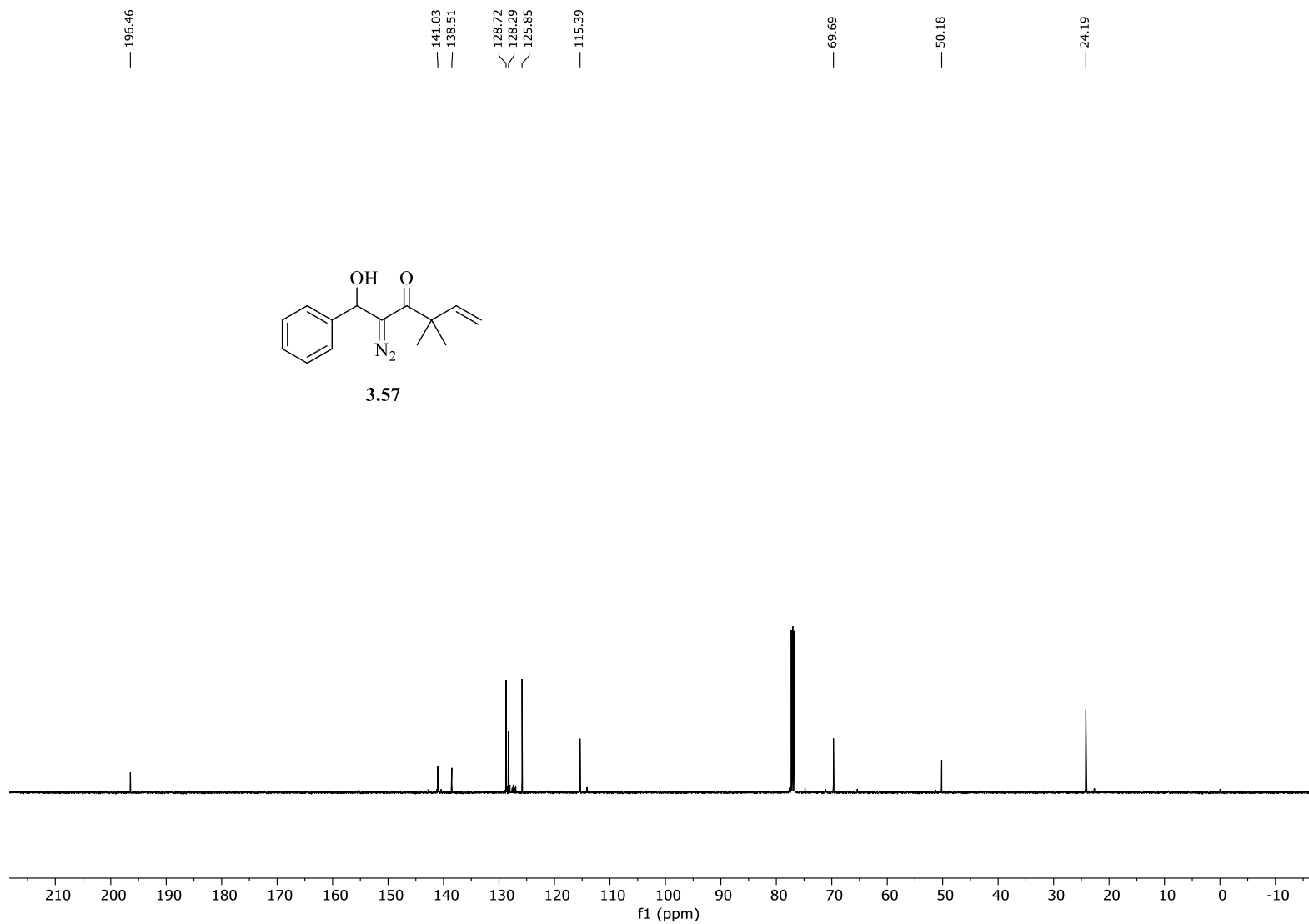




Figure A19:  $^1\text{H}$  NMR of **3.57** in  $\text{CDCl}_3$



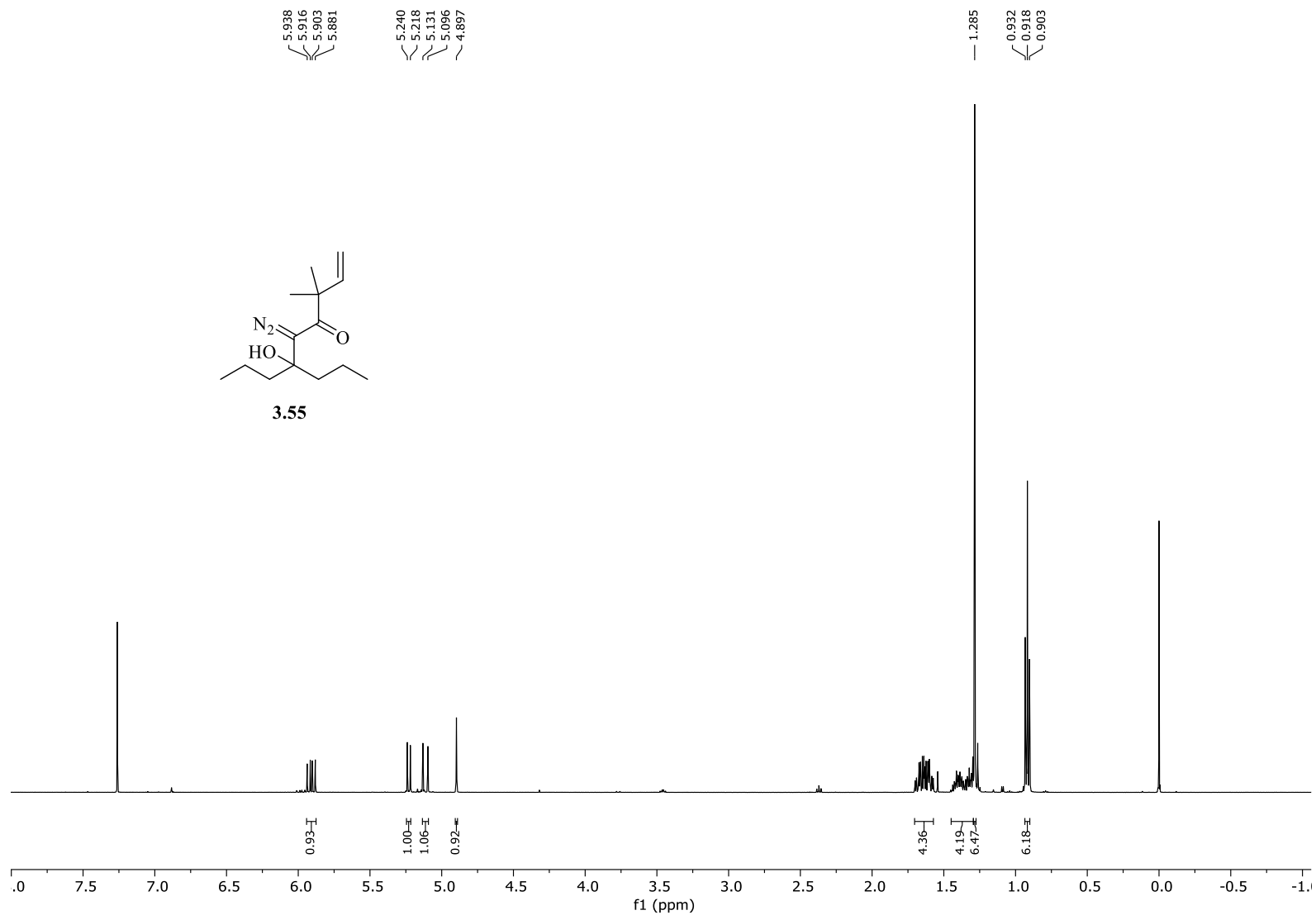


Figure A21: <sup>1</sup>H NMR of **3.55** in CDCl<sub>3</sub>

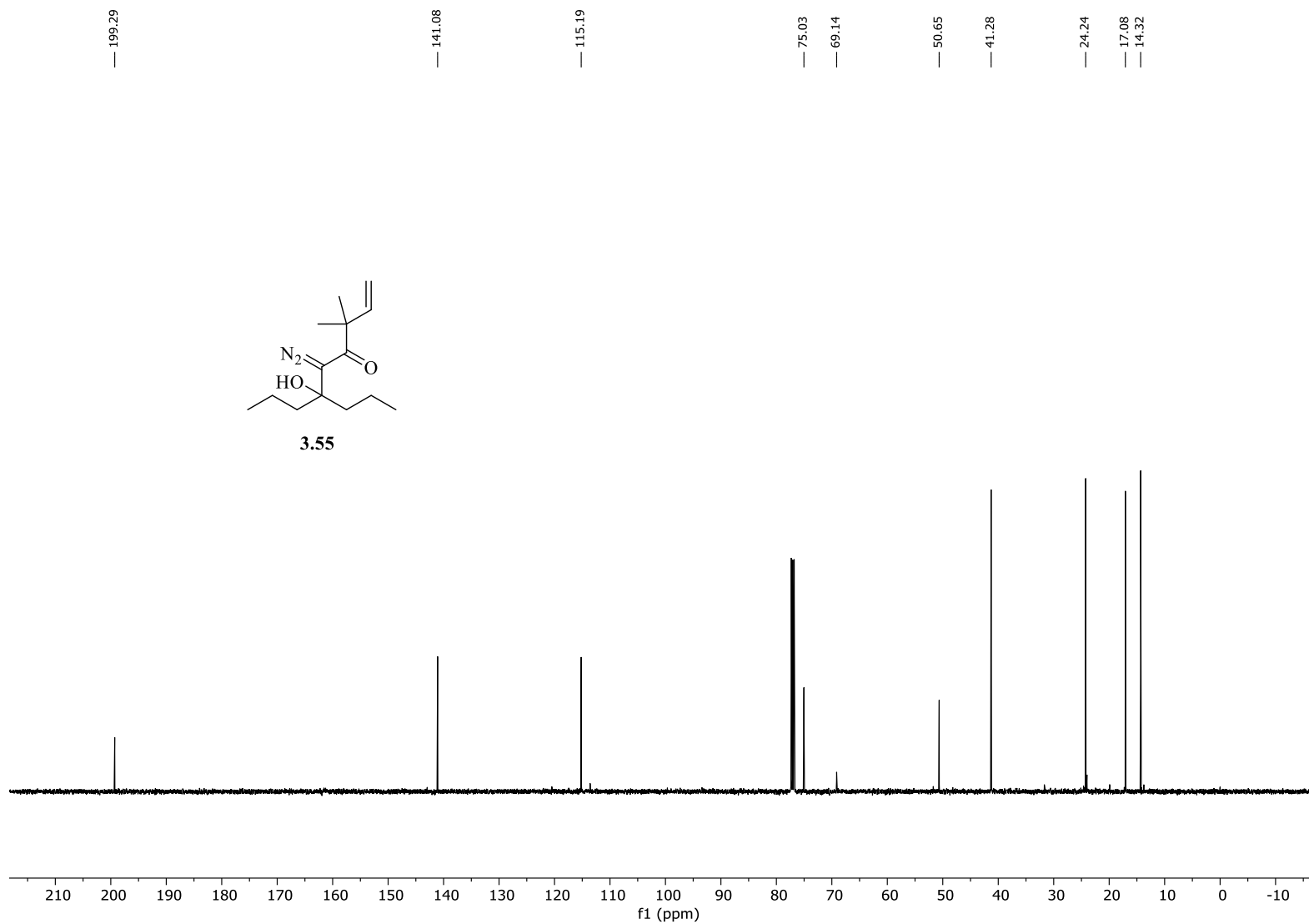


Figure A22: <sup>13</sup>C NMR of 3.55 in CDCl<sub>3</sub>

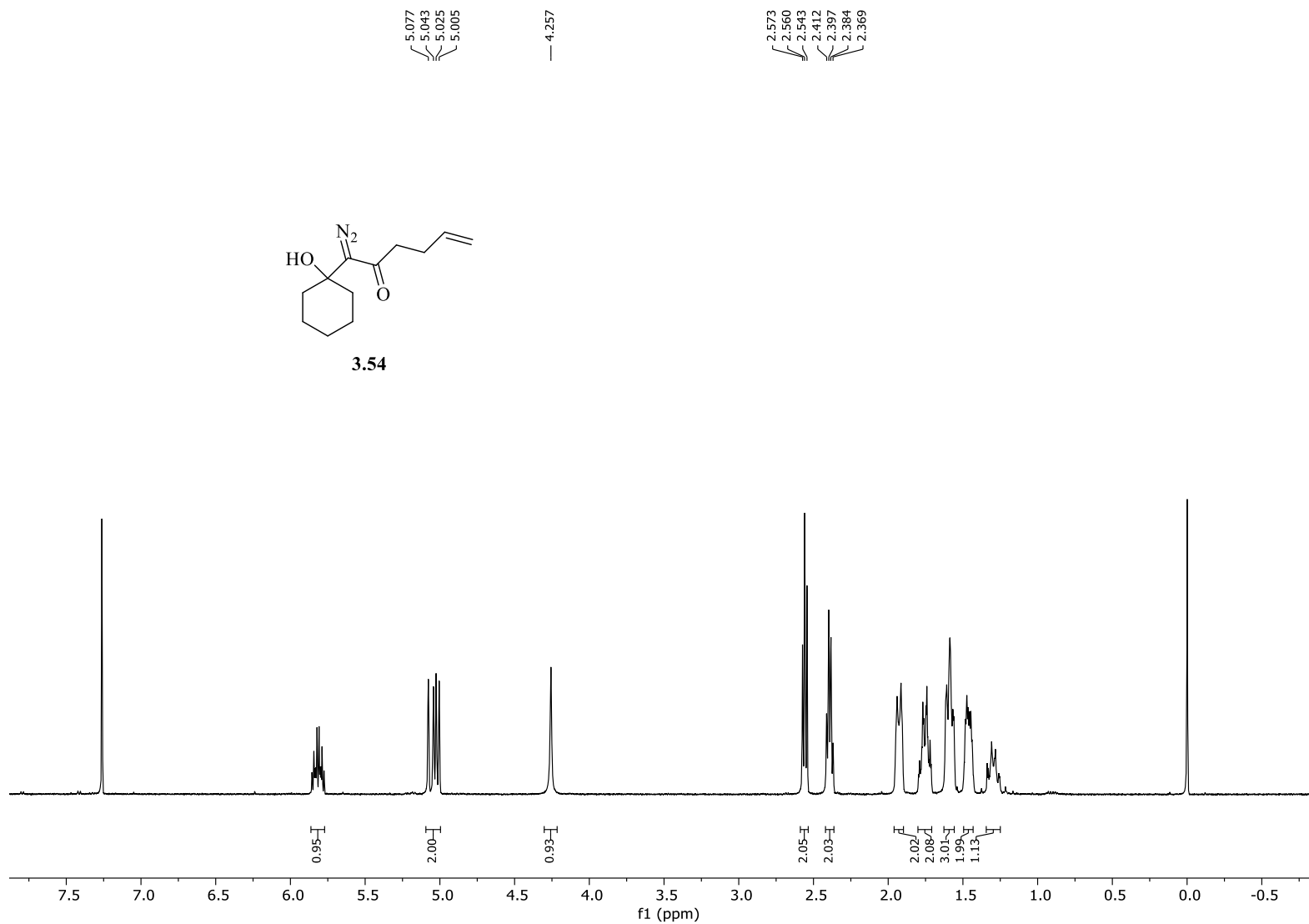
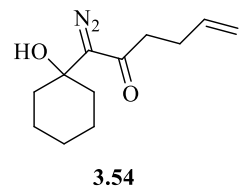


Figure A23: <sup>1</sup>H NMR of 3.54 in CDCl<sub>3</sub>



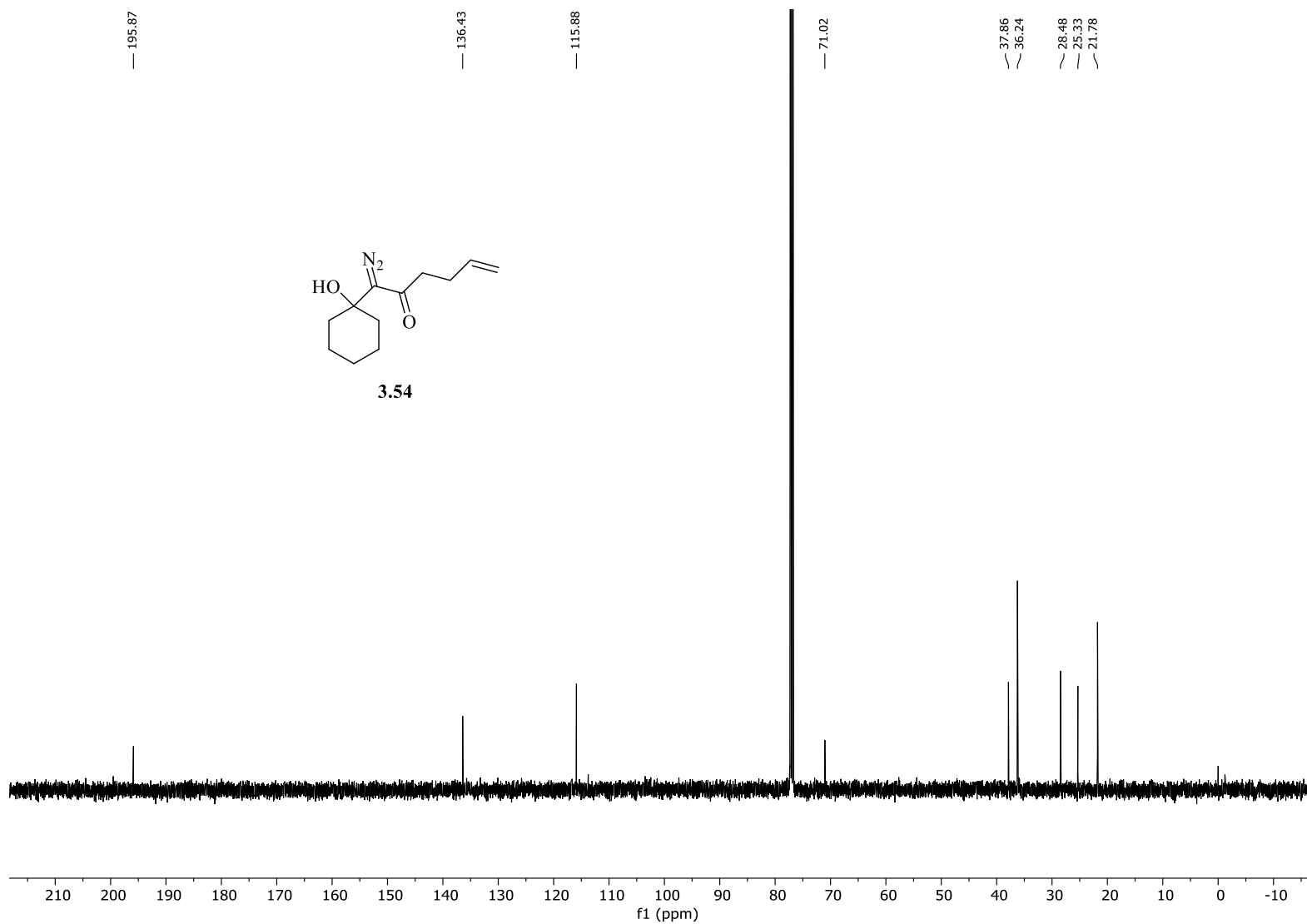


Figure A24:  $^{13}\text{C}$  NMR of 3.54 in  $\text{CDCl}_3$

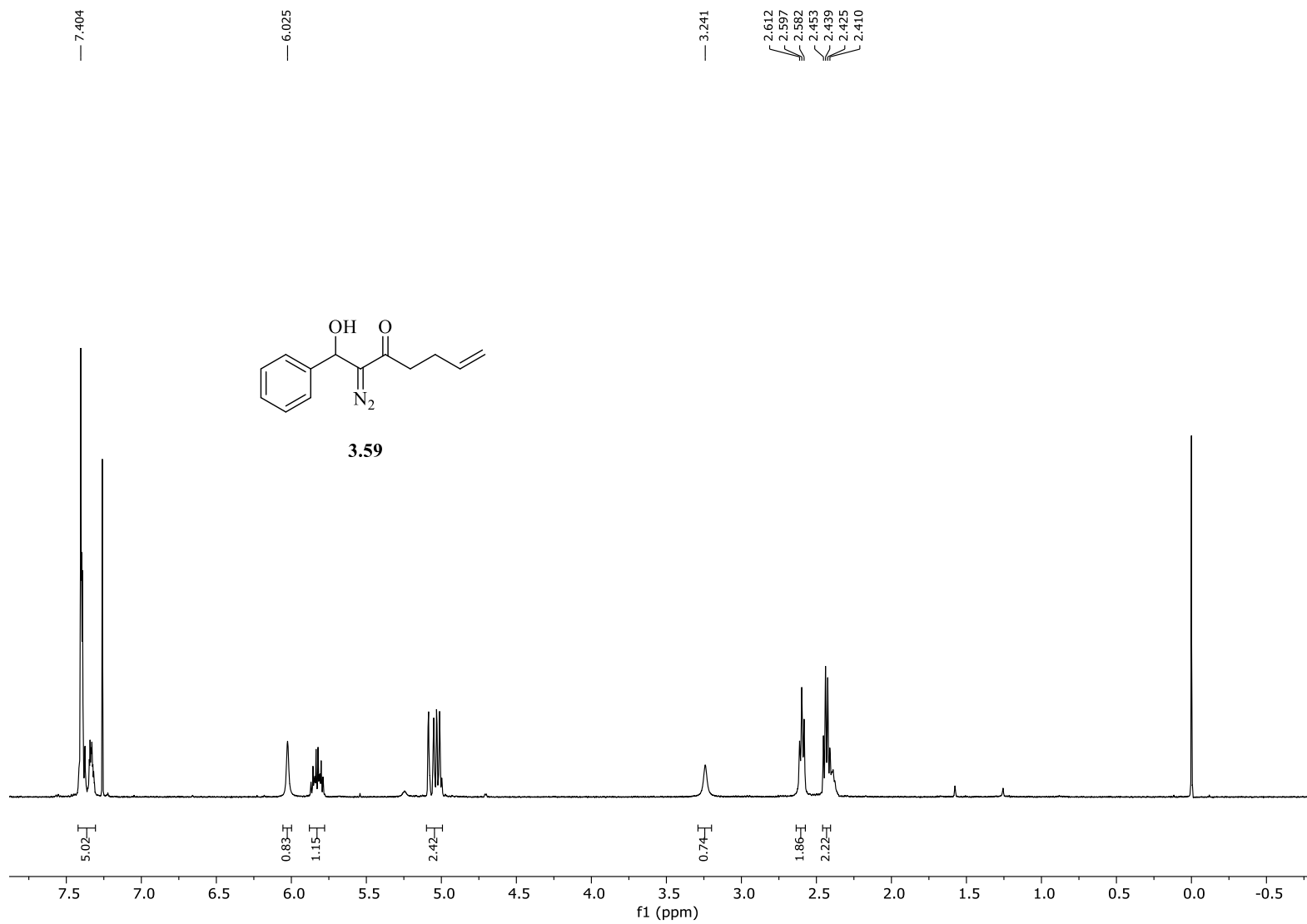


Figure A25:  $^1\text{H}$  NMR of **3.59** in  $\text{CDCl}_3$

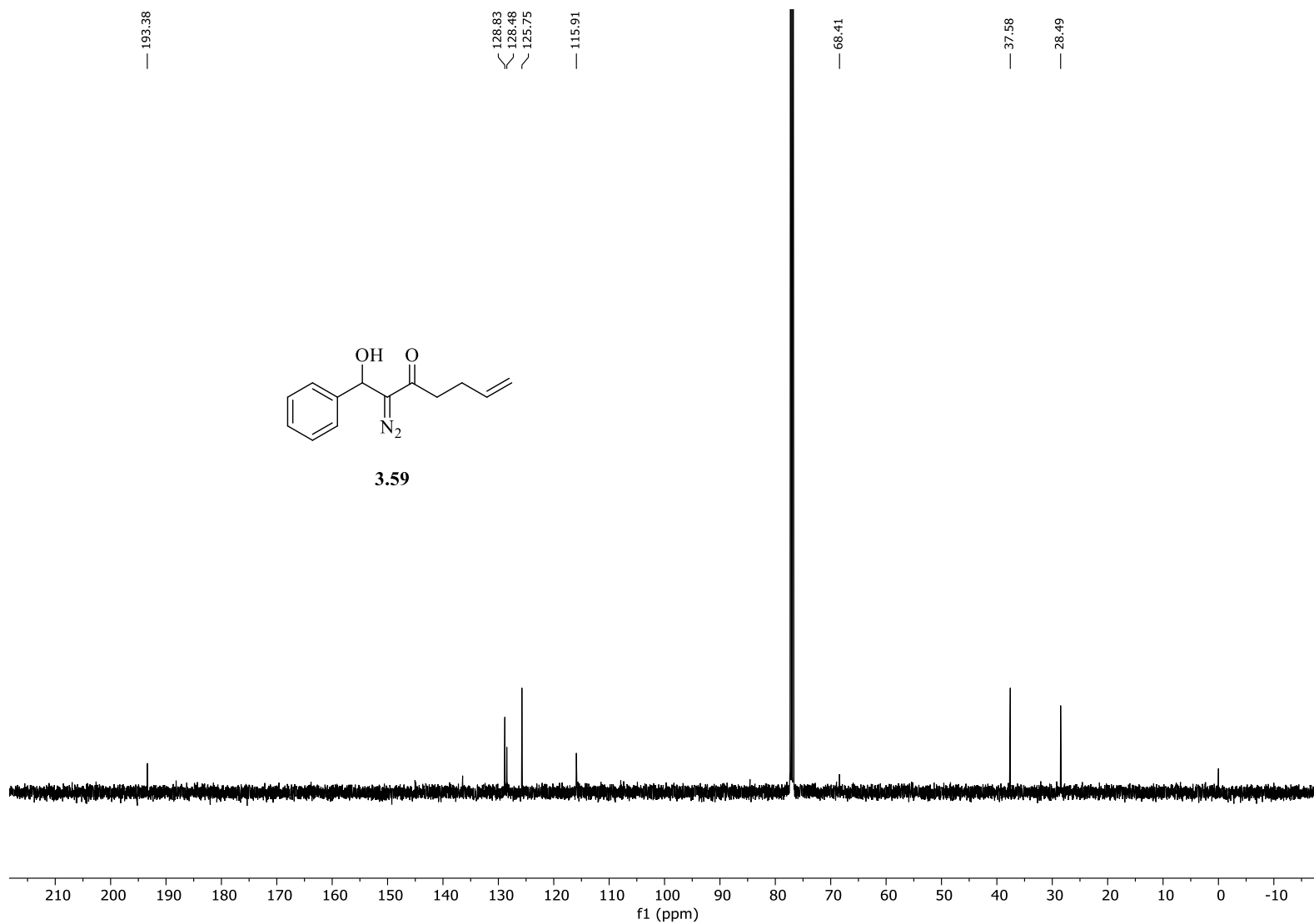


Figure A26:  $^{13}\text{C}$  NMR of **3.59** in  $\text{CDCl}_3$

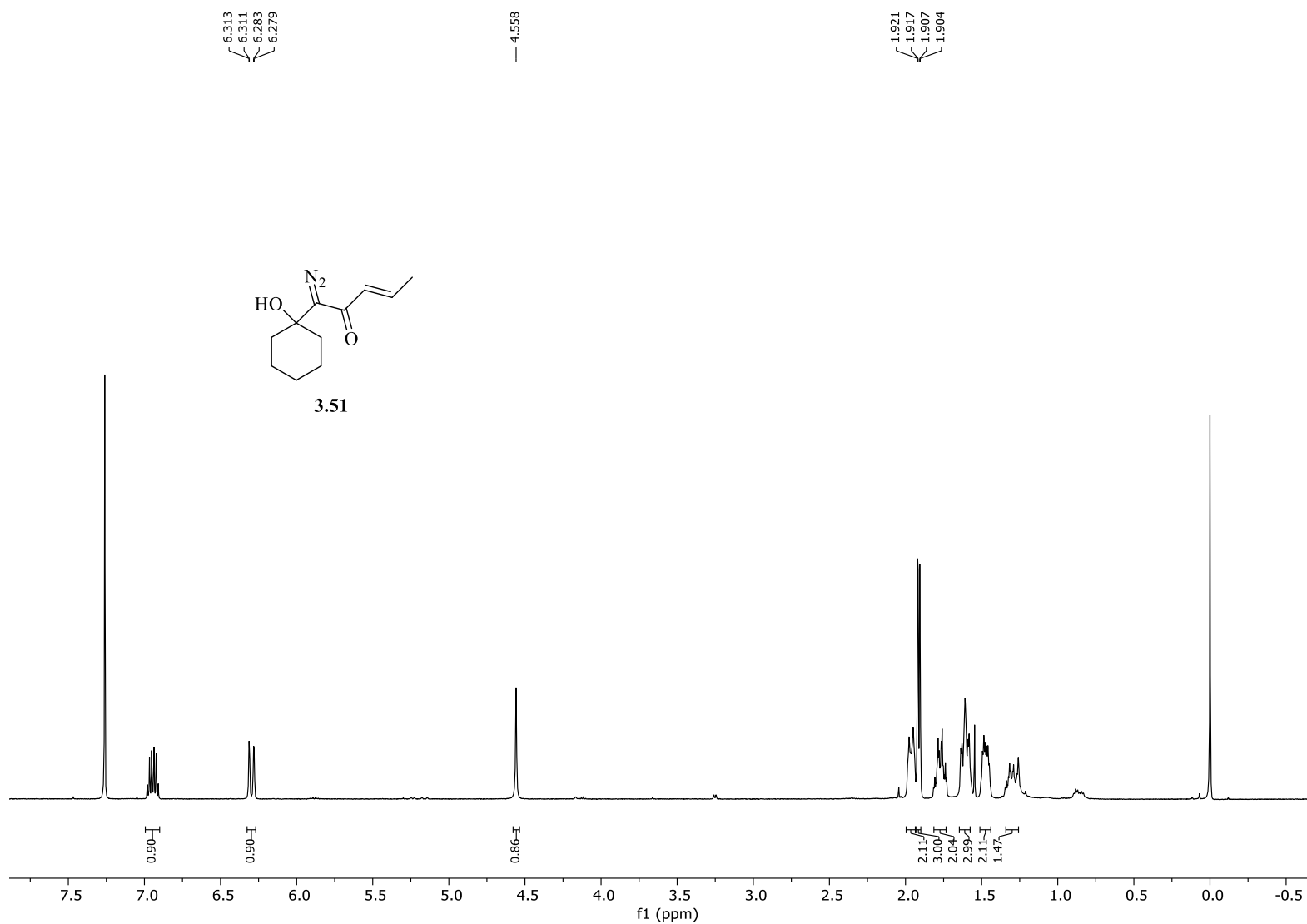


Figure A27: <sup>1</sup>H NMR of **3.51** in CDCl<sub>3</sub>

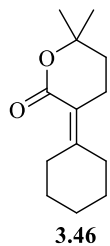
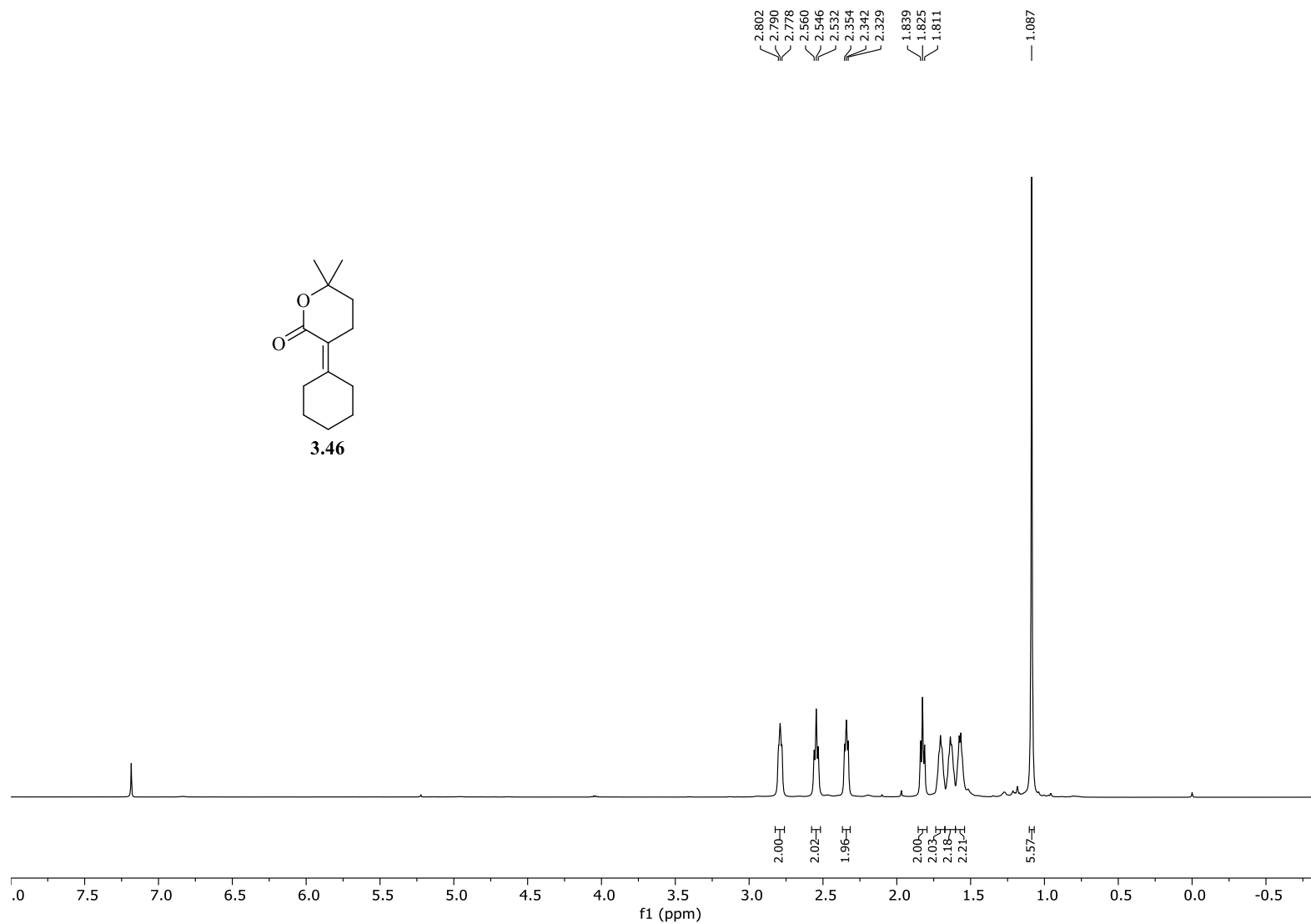


Figure A28: <sup>1</sup>H NMR of 3.46 in CDCl<sub>3</sub>

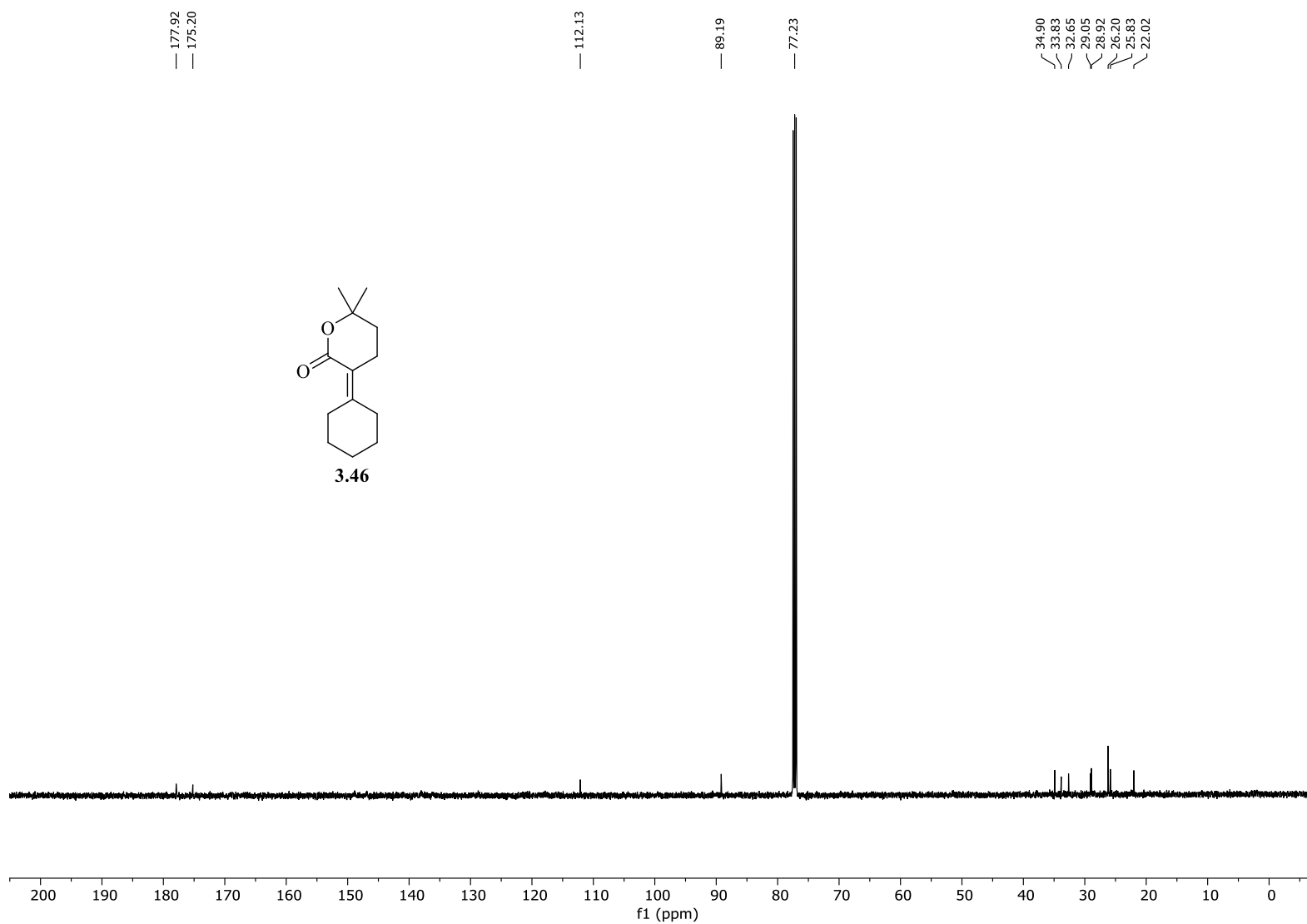


Figure A29:  $^{13}\text{C}$  NMR of 3.46 in  $\text{CDCl}_3$

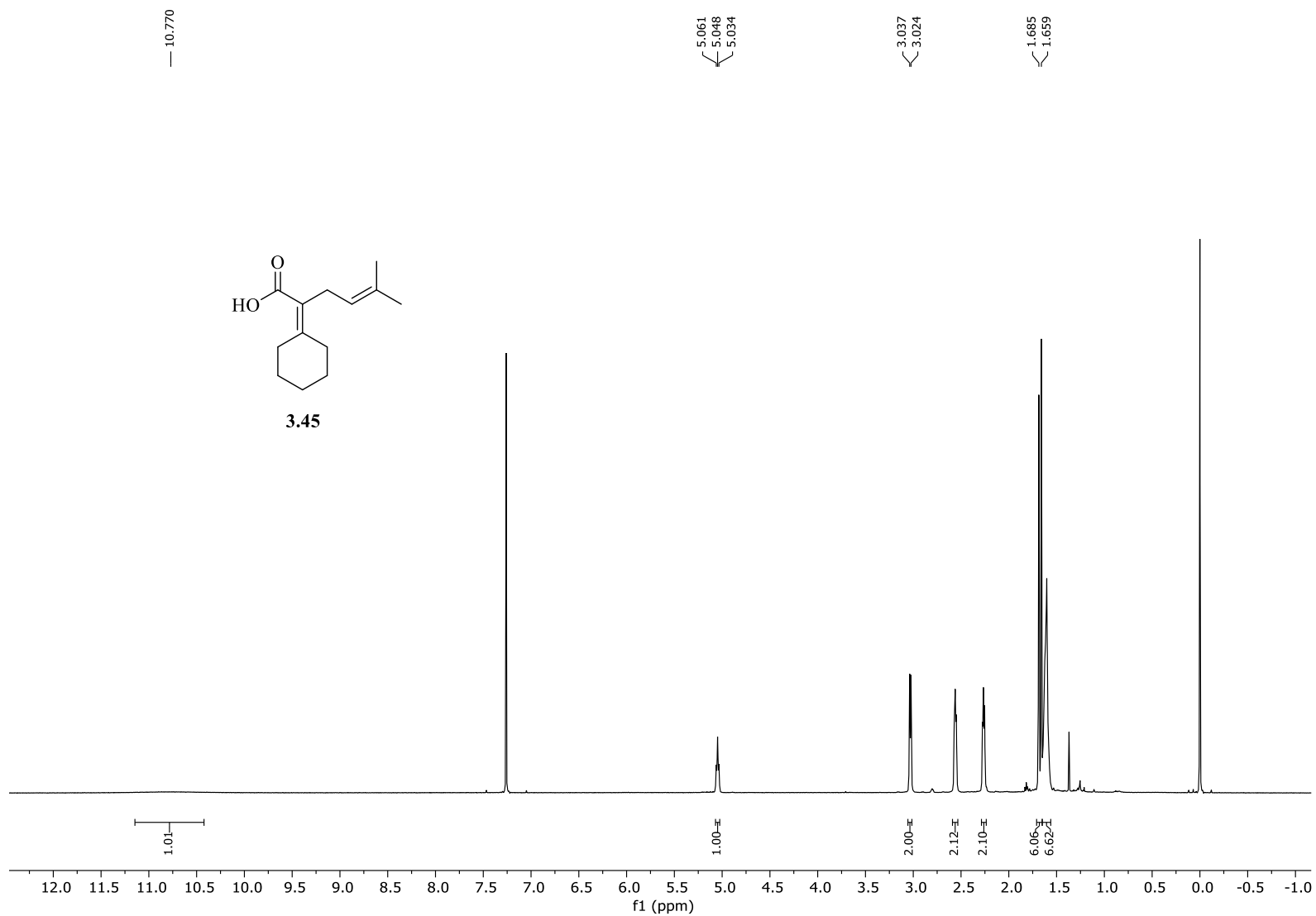


Figure A30:  $^1\text{H}$  NMR of 3.45 in  $\text{CDCl}_3$

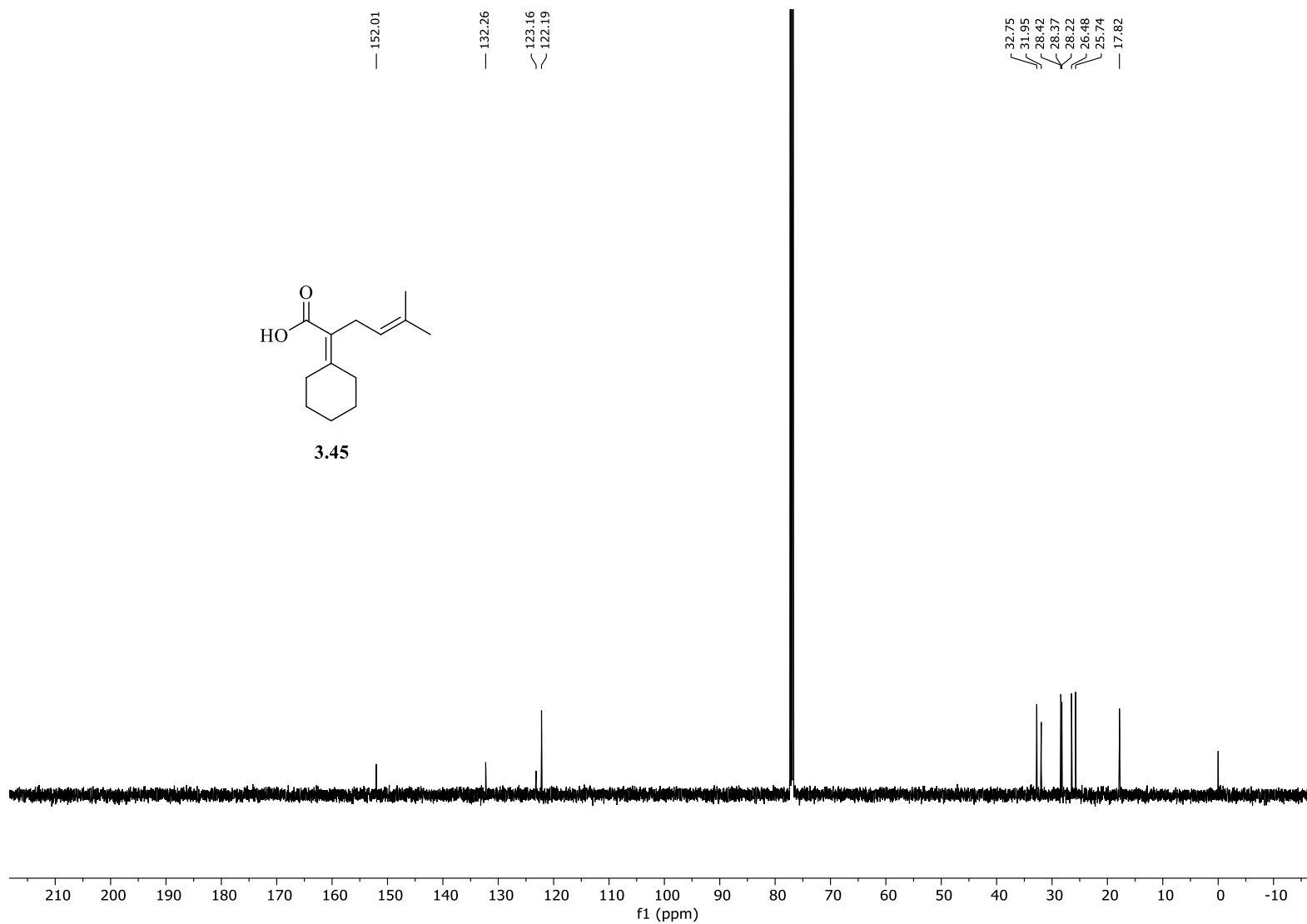


Figure A31:  $^{13}\text{C}$  NMR of 3.45 in  $\text{CDCl}_3$



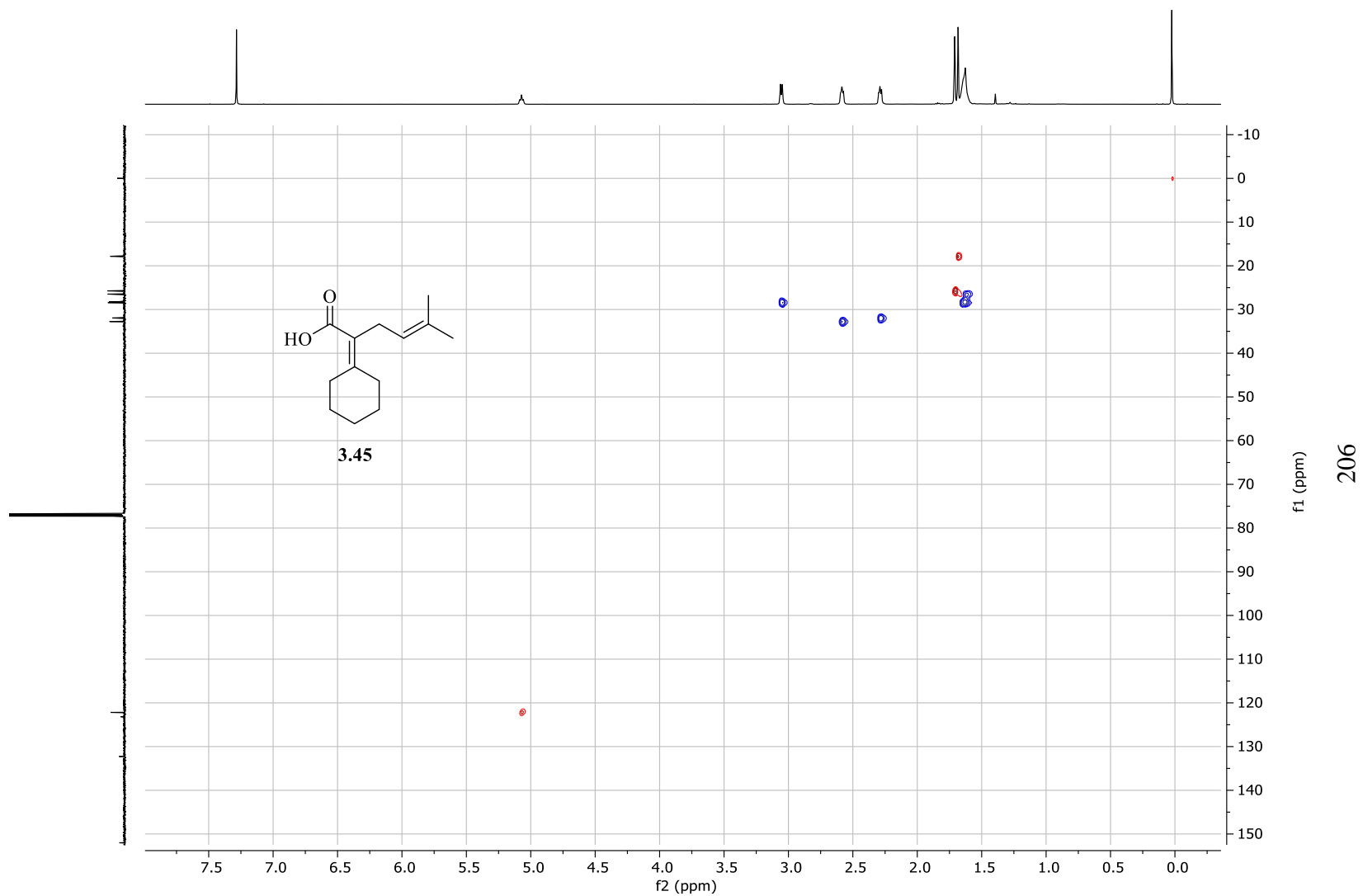


Figure A32: HSQC of 3.45 in  $\text{CDCl}_3$

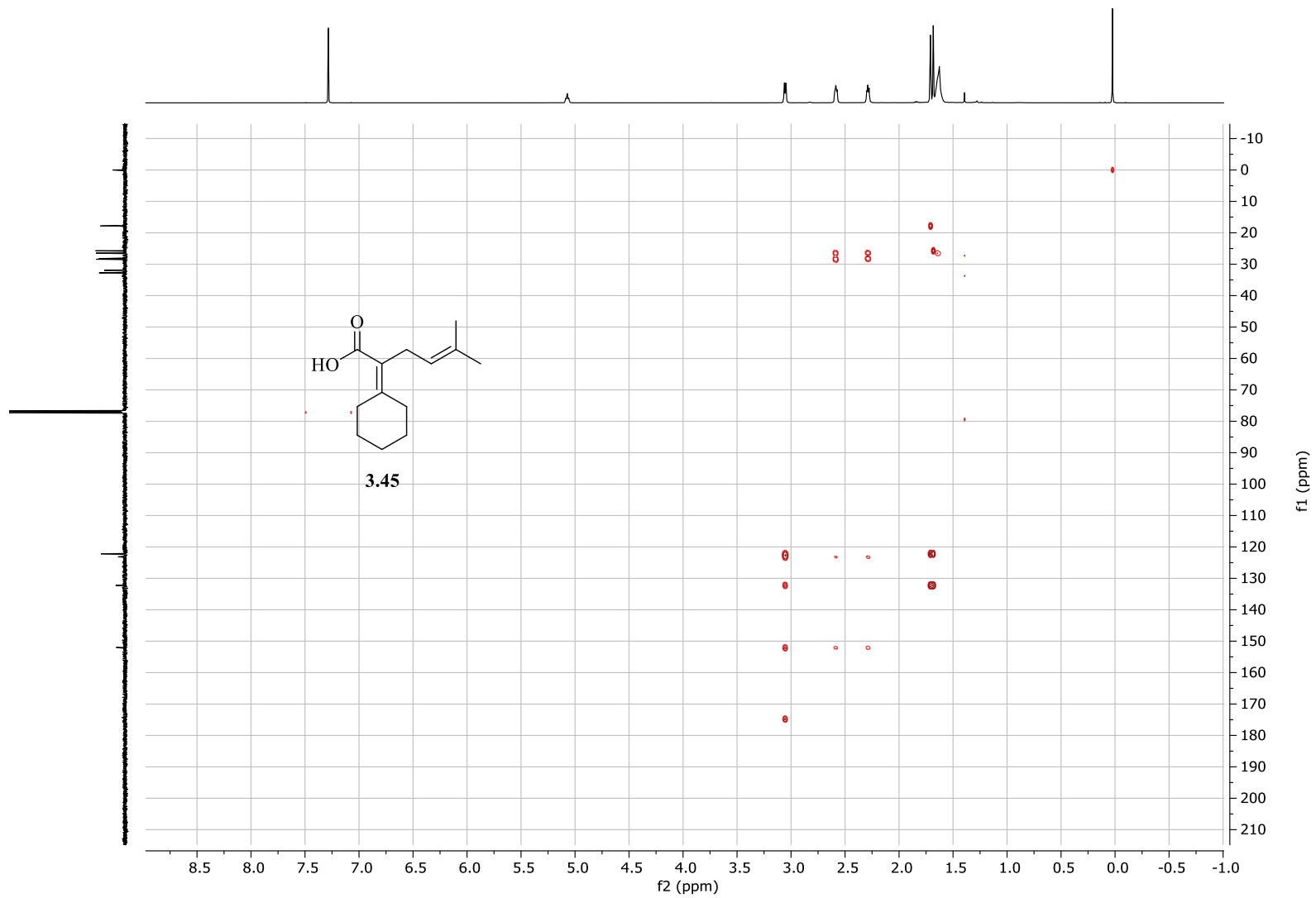


Figure A33: HMBC of 3.45 in CDCl<sub>3</sub>

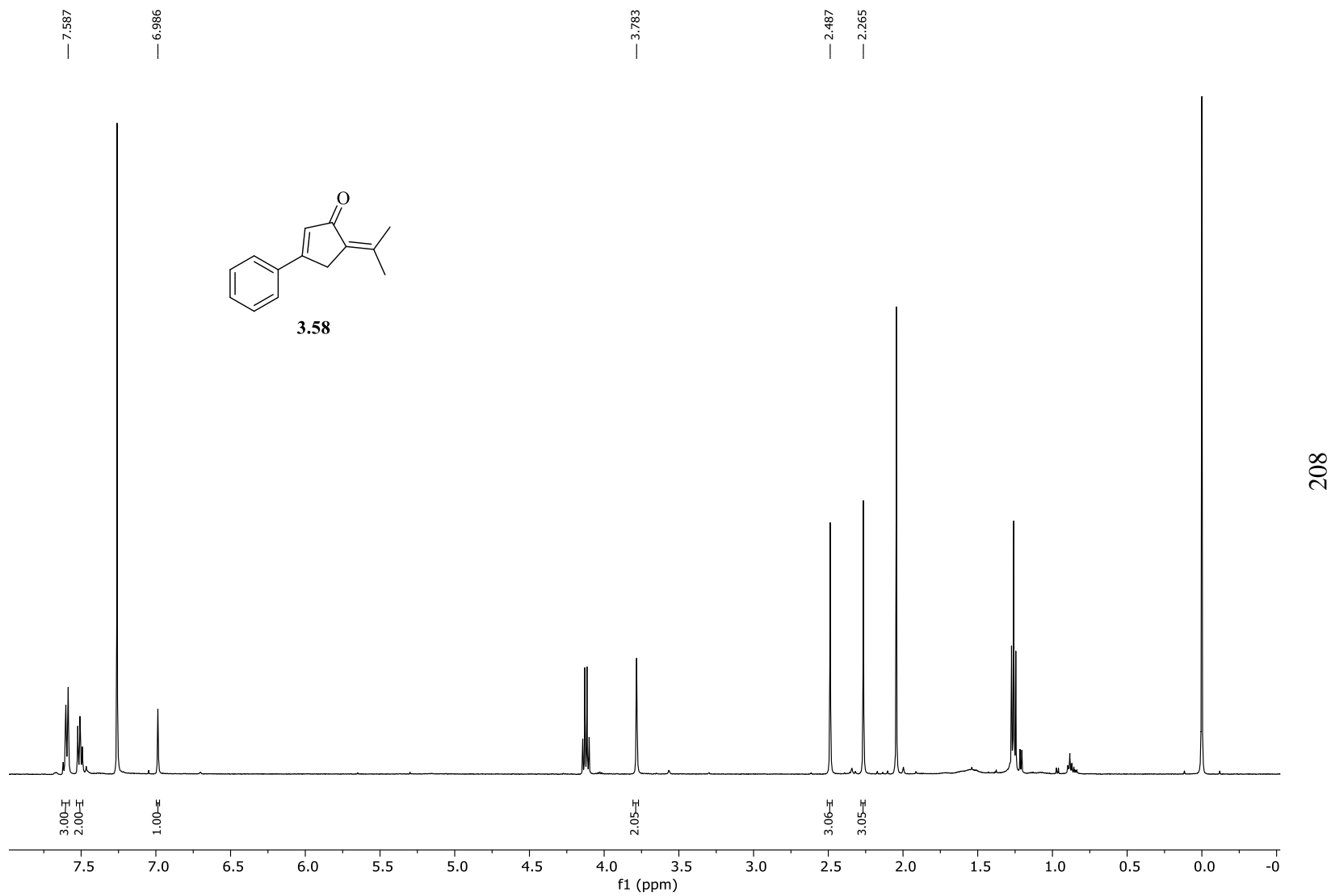


Figure A34:  $^1\text{H}$  NMR of **3.58** in  $\text{CDCl}_3$

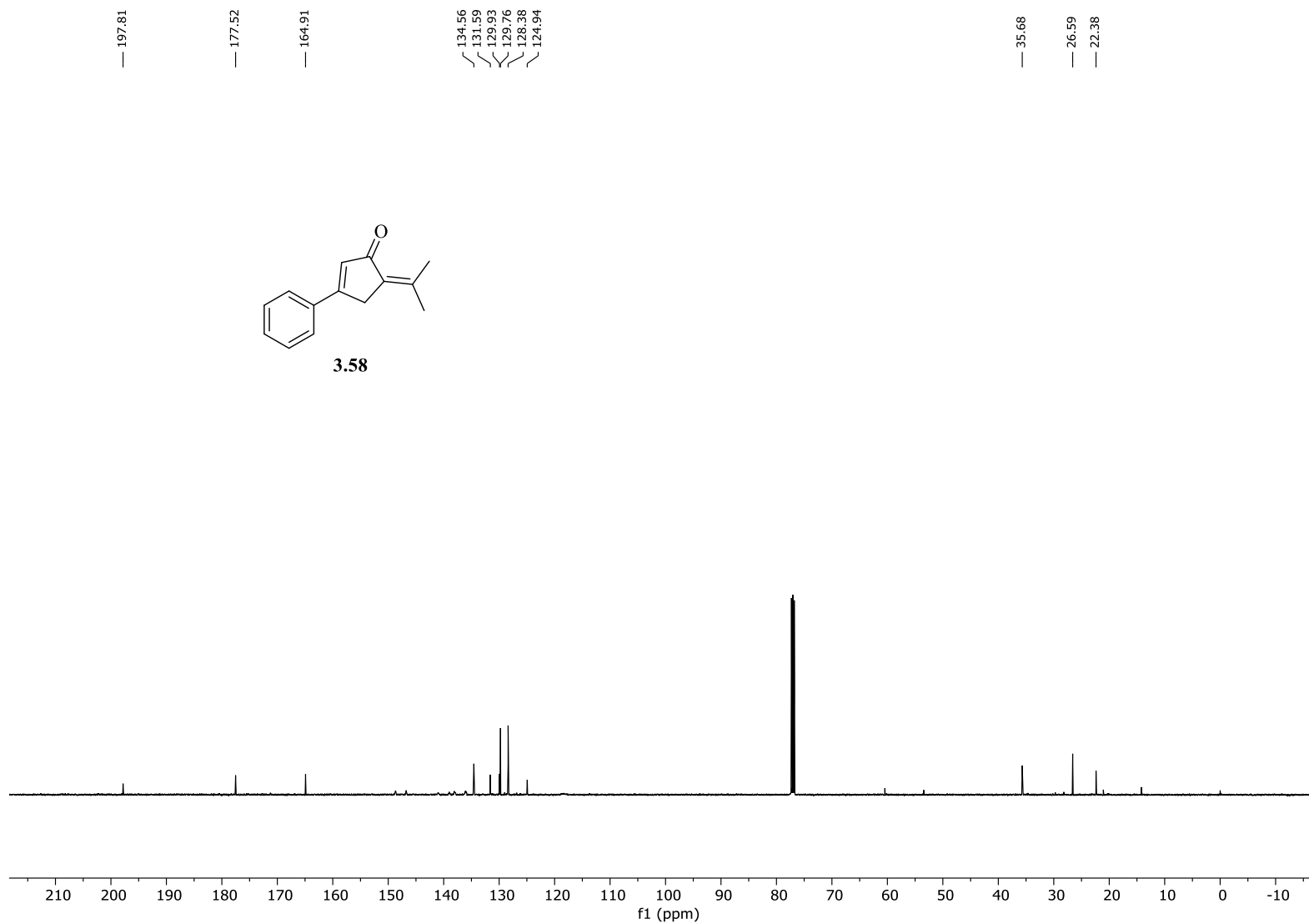




Figure A36: DEPT-135 of 3.58 in CDCl<sub>3</sub>

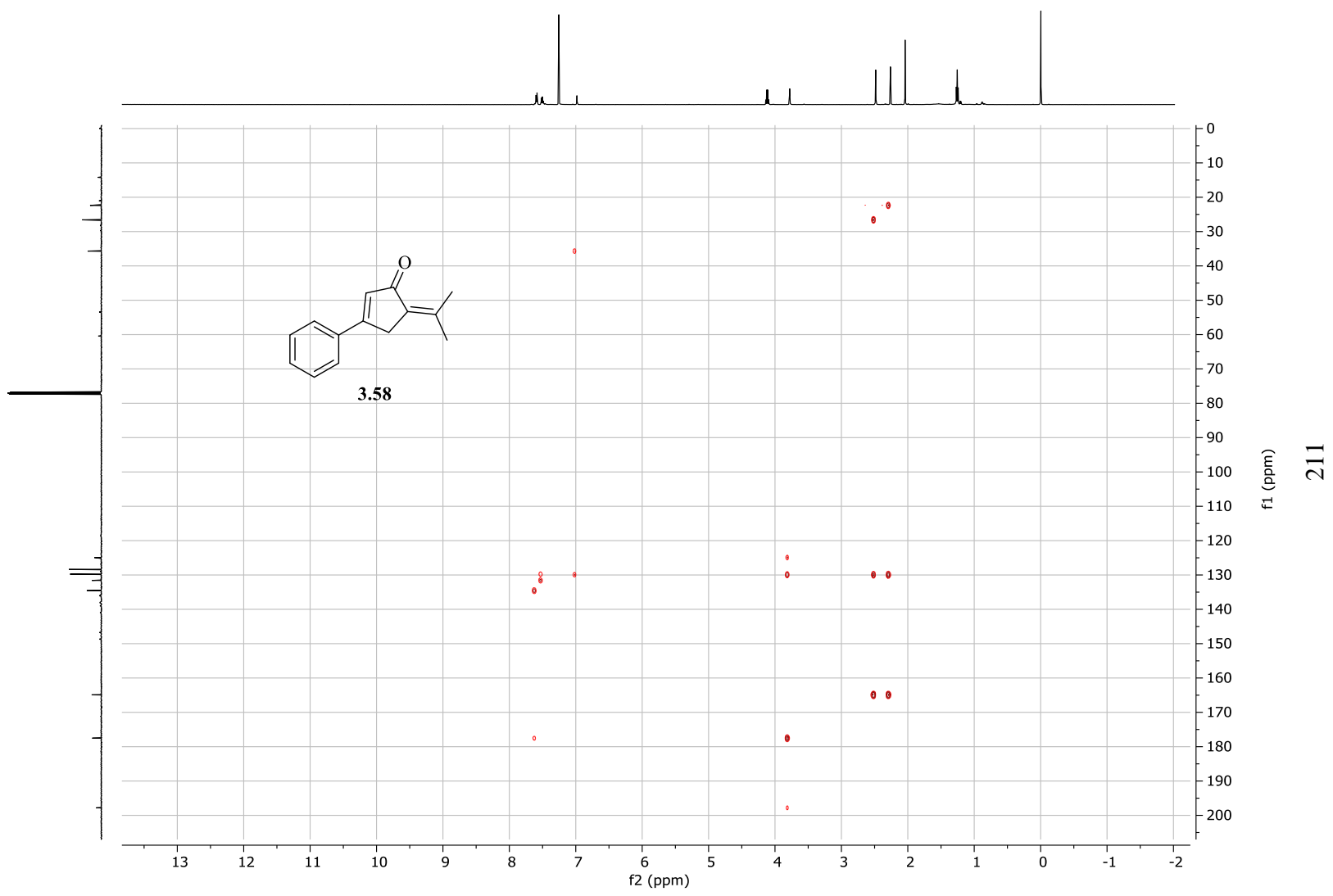
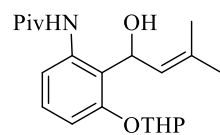


Figure A37: HMBC of 3.58 in CDCl<sub>3</sub>



4.15

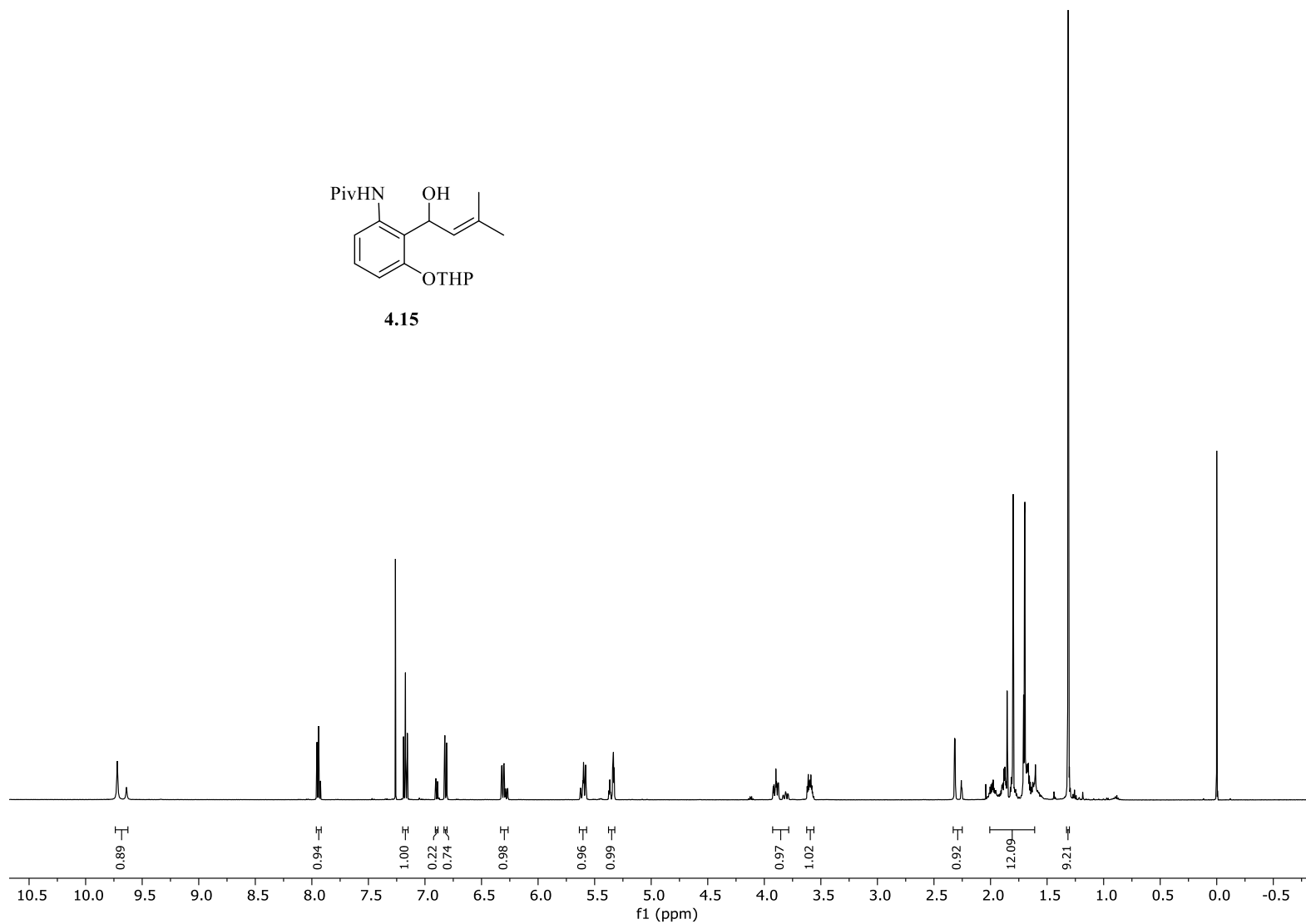
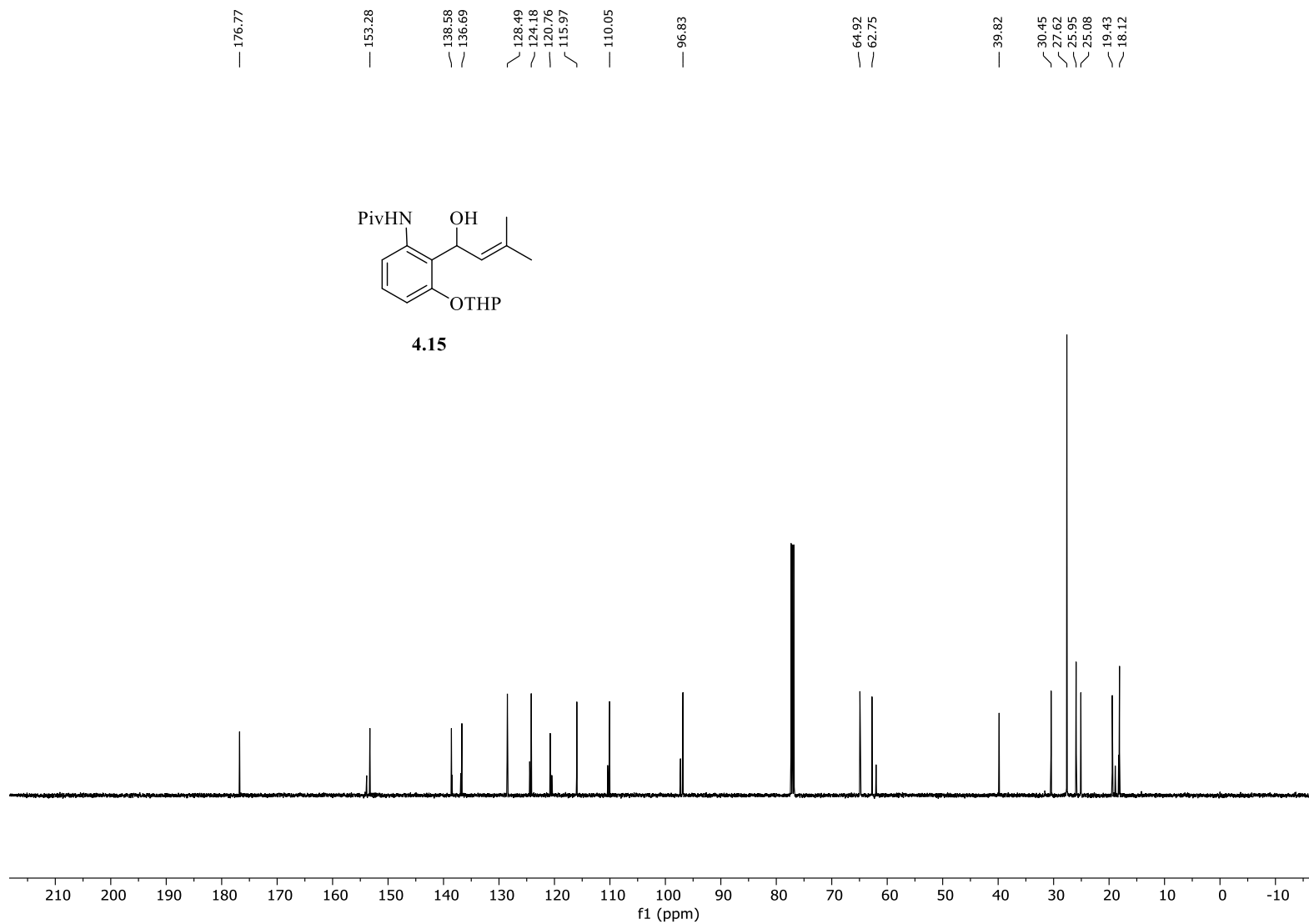


Figure A38: <sup>1</sup>H NMR of 4.15 in CDCl<sub>3</sub>



**Figure A39:**  $^{13}\text{C}$  NMR of **4.15** (major diastereomer peaks picked) in  $\text{CDCl}_3$



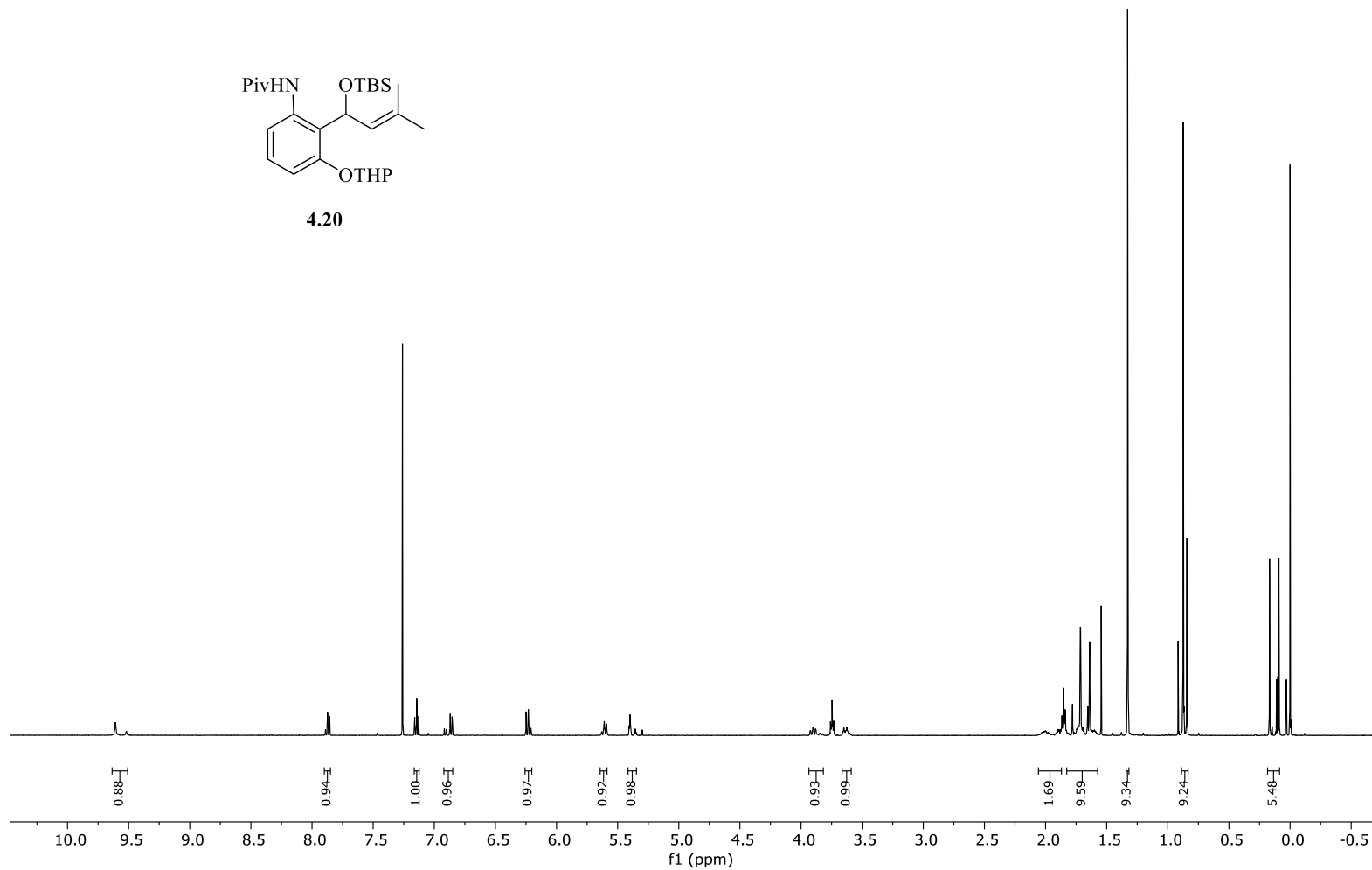
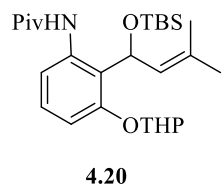
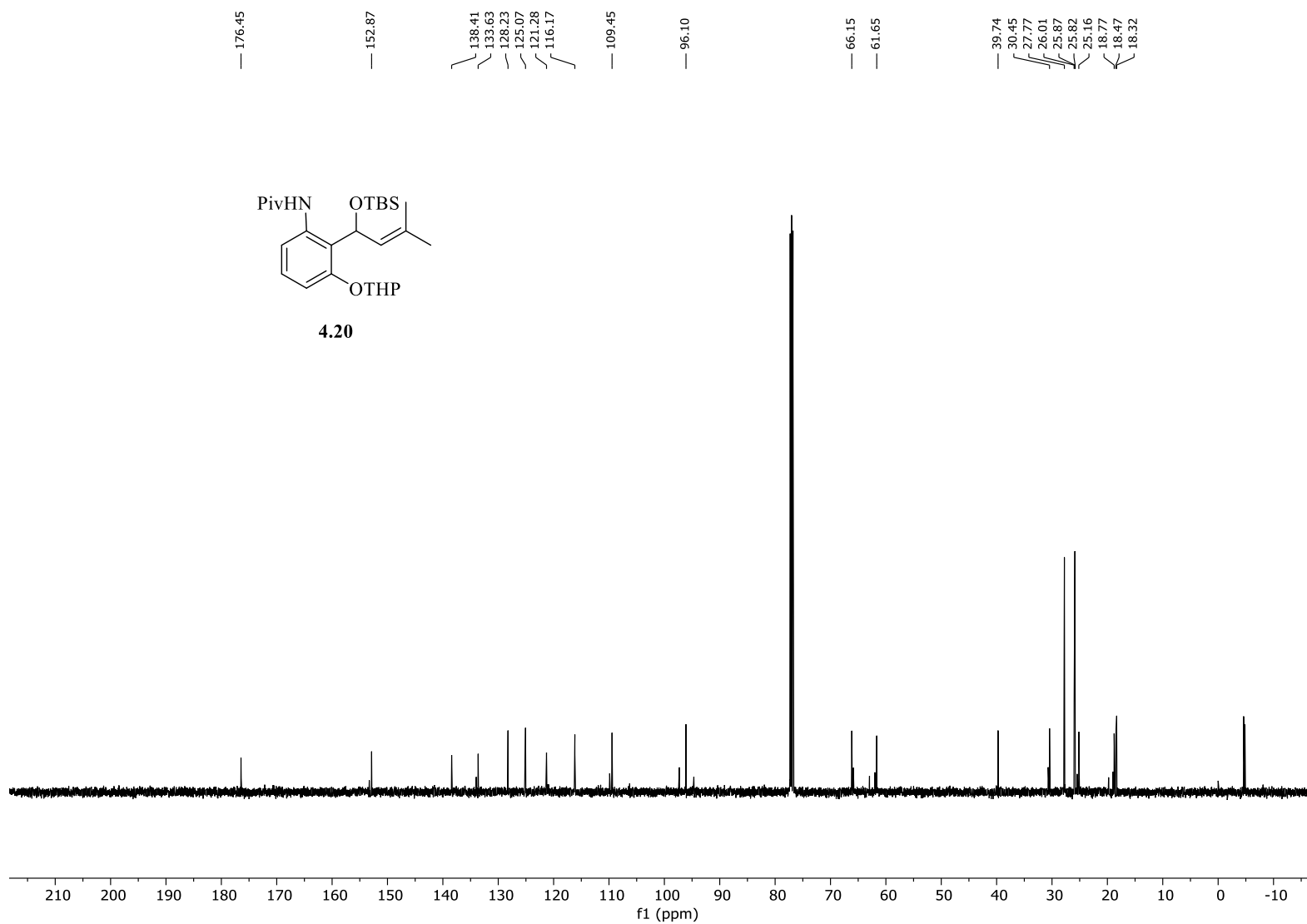


Figure A40: <sup>1</sup>H NMR of 4.20 in CDCl<sub>3</sub>



**Figure A41:**  $^{13}\text{C}$  NMR of **4.20** (major diastereomer peaks picked) in  $\text{CDCl}_3$

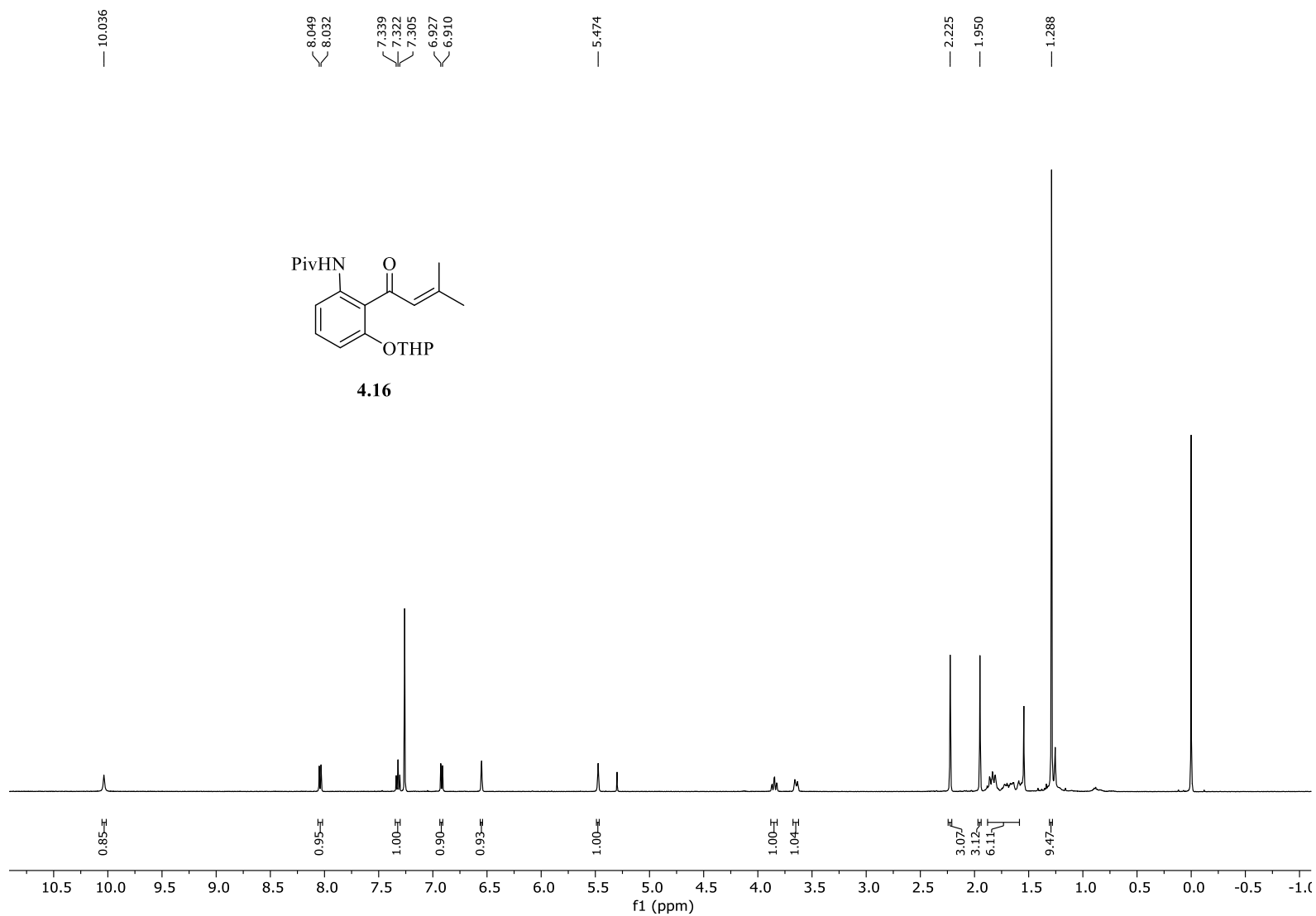


Figure A42: <sup>1</sup>H NMR of **4.16** in CDCl<sub>3</sub>

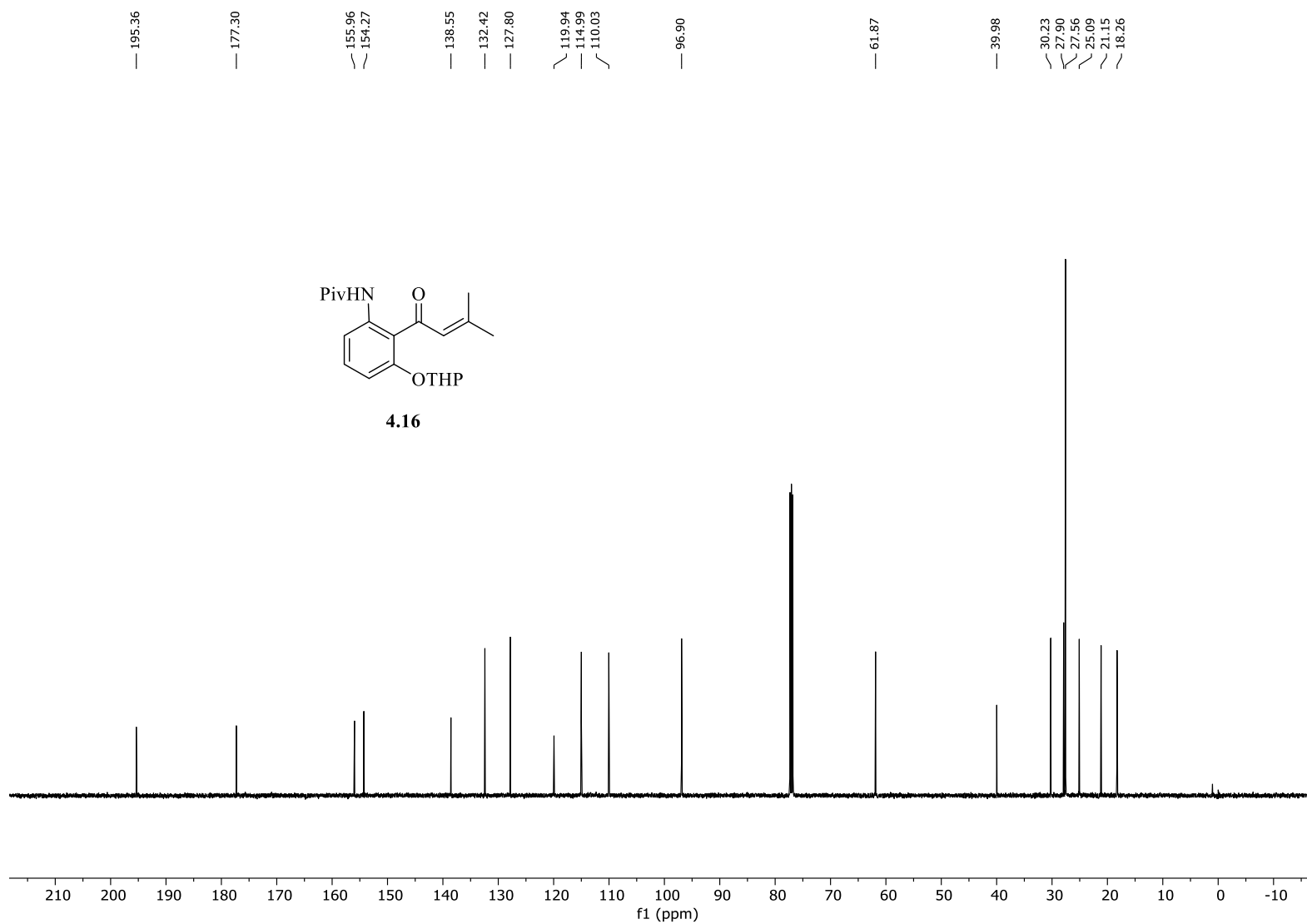
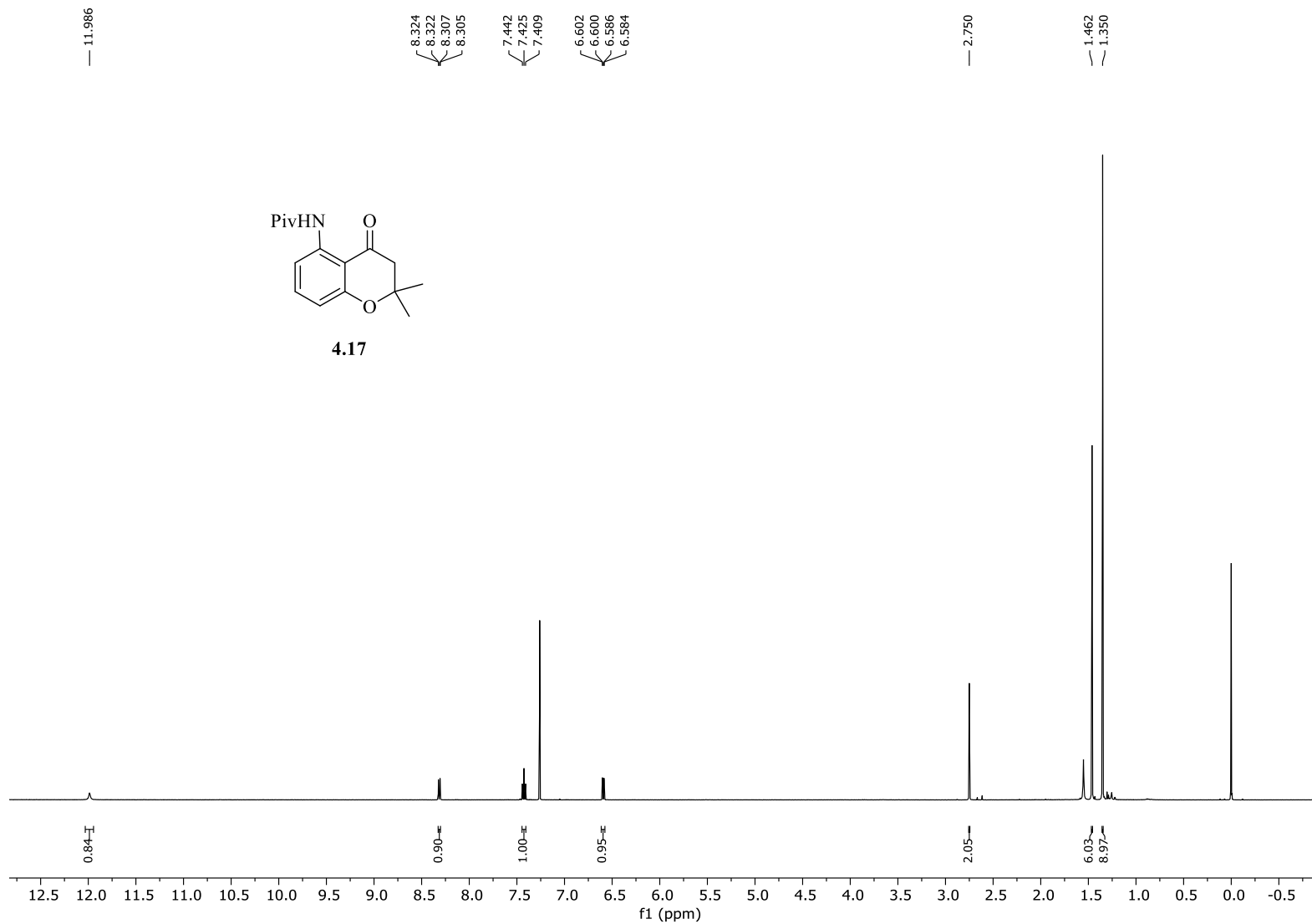


Figure A43:  $^{13}\text{C}$  NMR of **4.16** in  $\text{CDCl}_3$



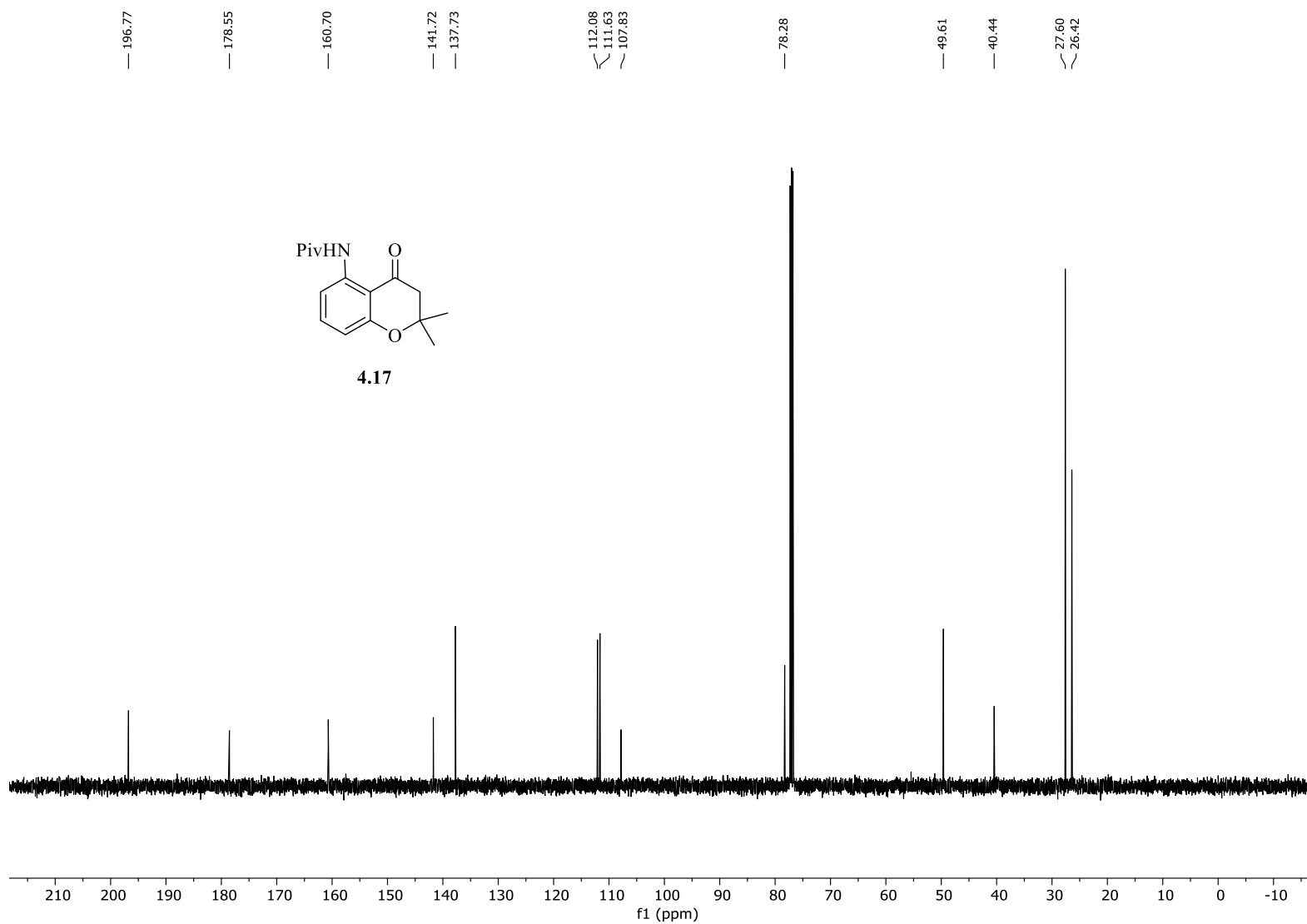


Figure A45:  $^{13}\text{C}$  NMR of **4.17** in  $\text{CDCl}_3$

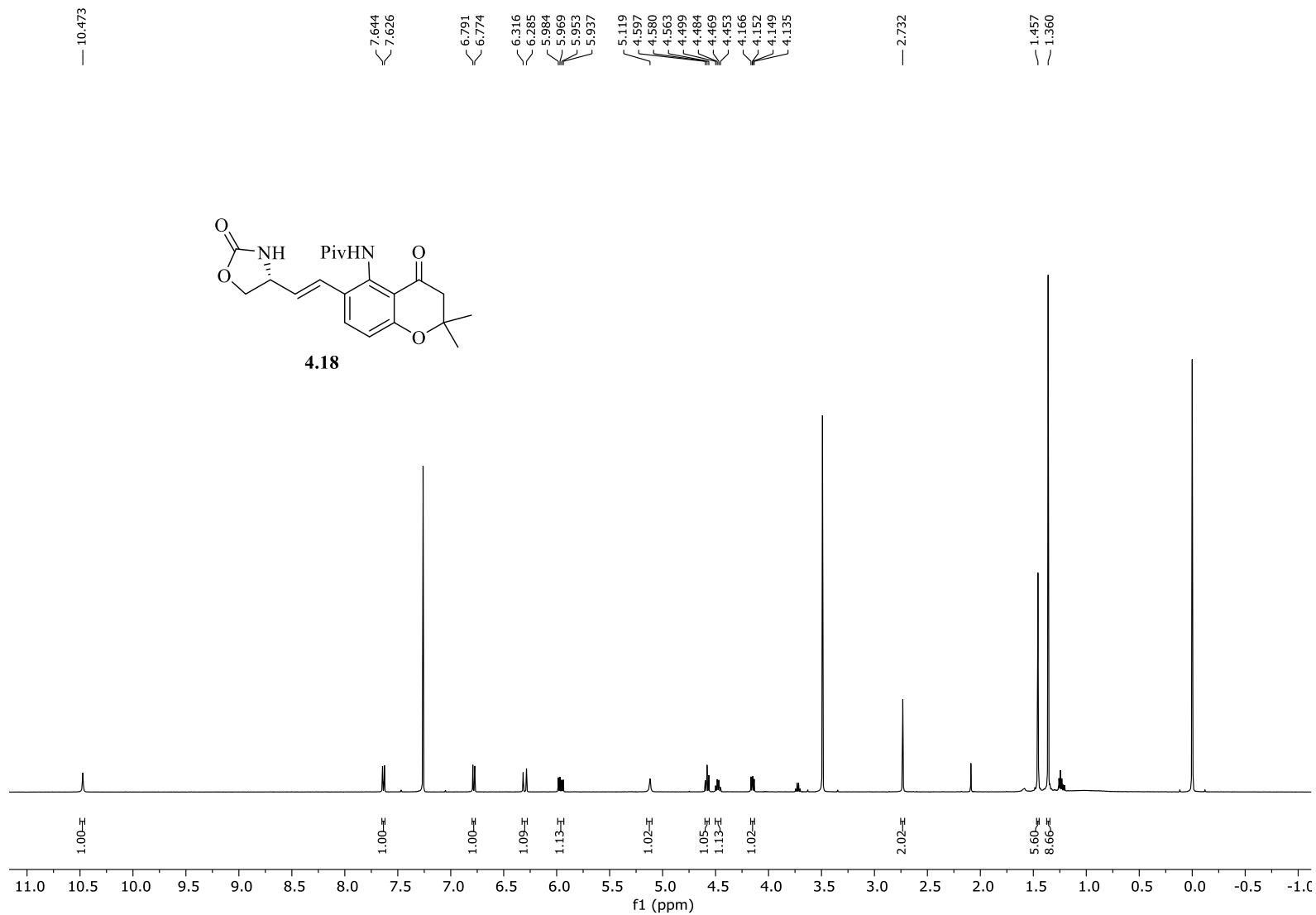


Figure A46:  $^1\text{H}$  NMR of **4.18** in  $\text{CDCl}_3$

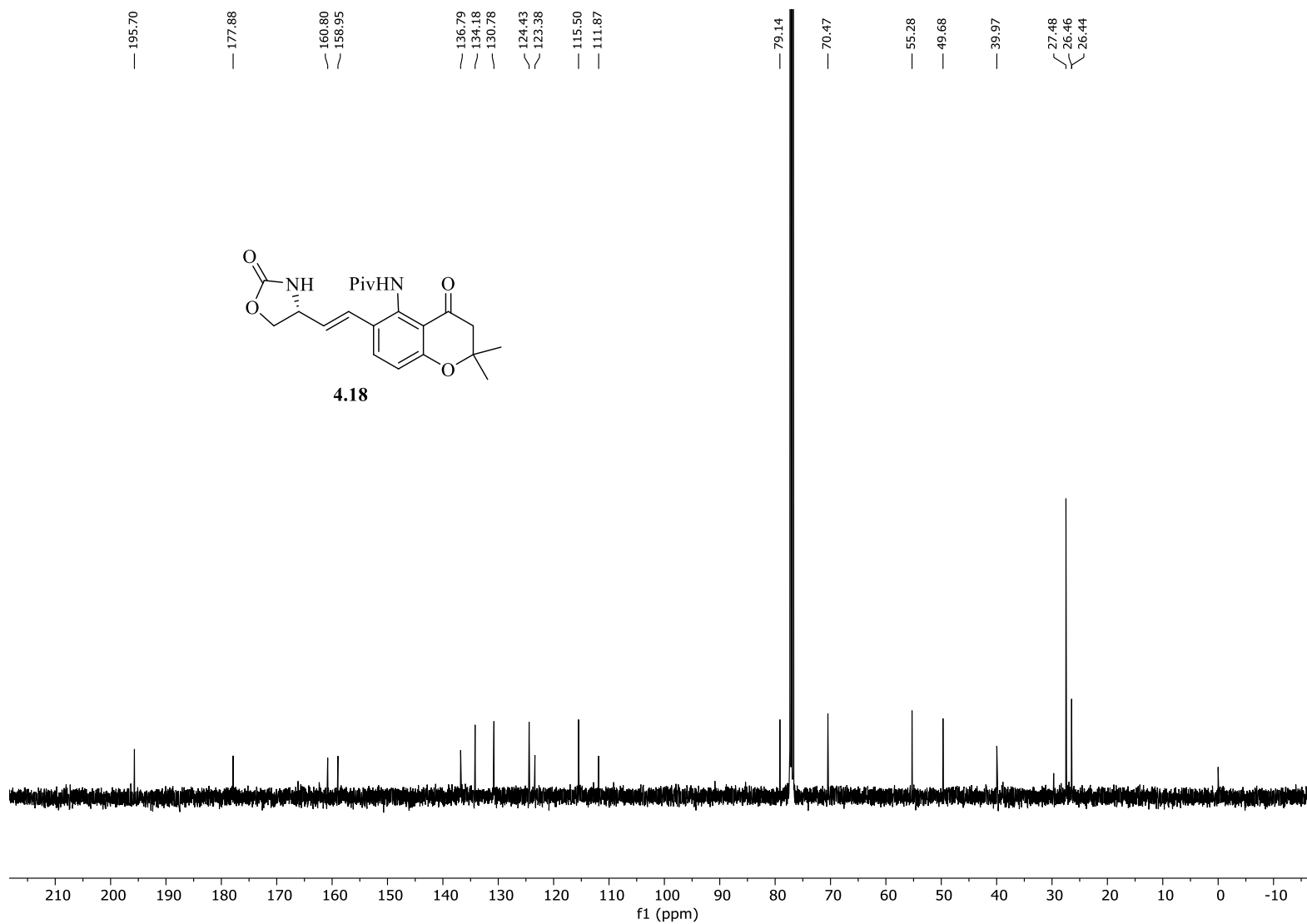
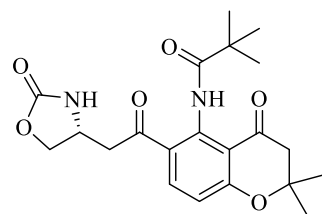


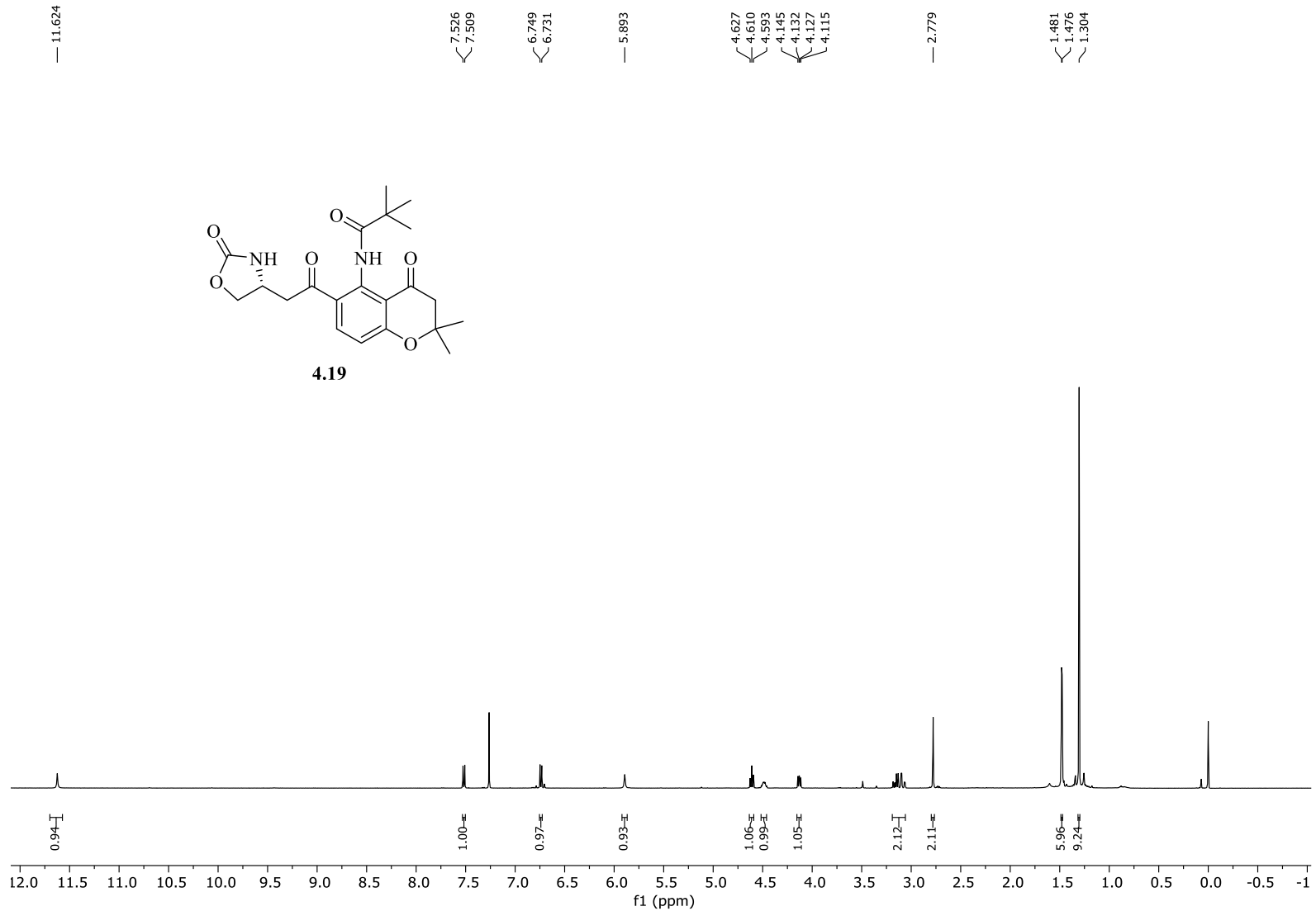
Figure A47:  $^{13}\text{C}$  NMR of **4.18** in  $\text{CDCl}_3$



— 11.624



**4.19**



**Figure A48:**  $^1\text{H}$  NMR of **4.19** in  $\text{CDCl}_3$

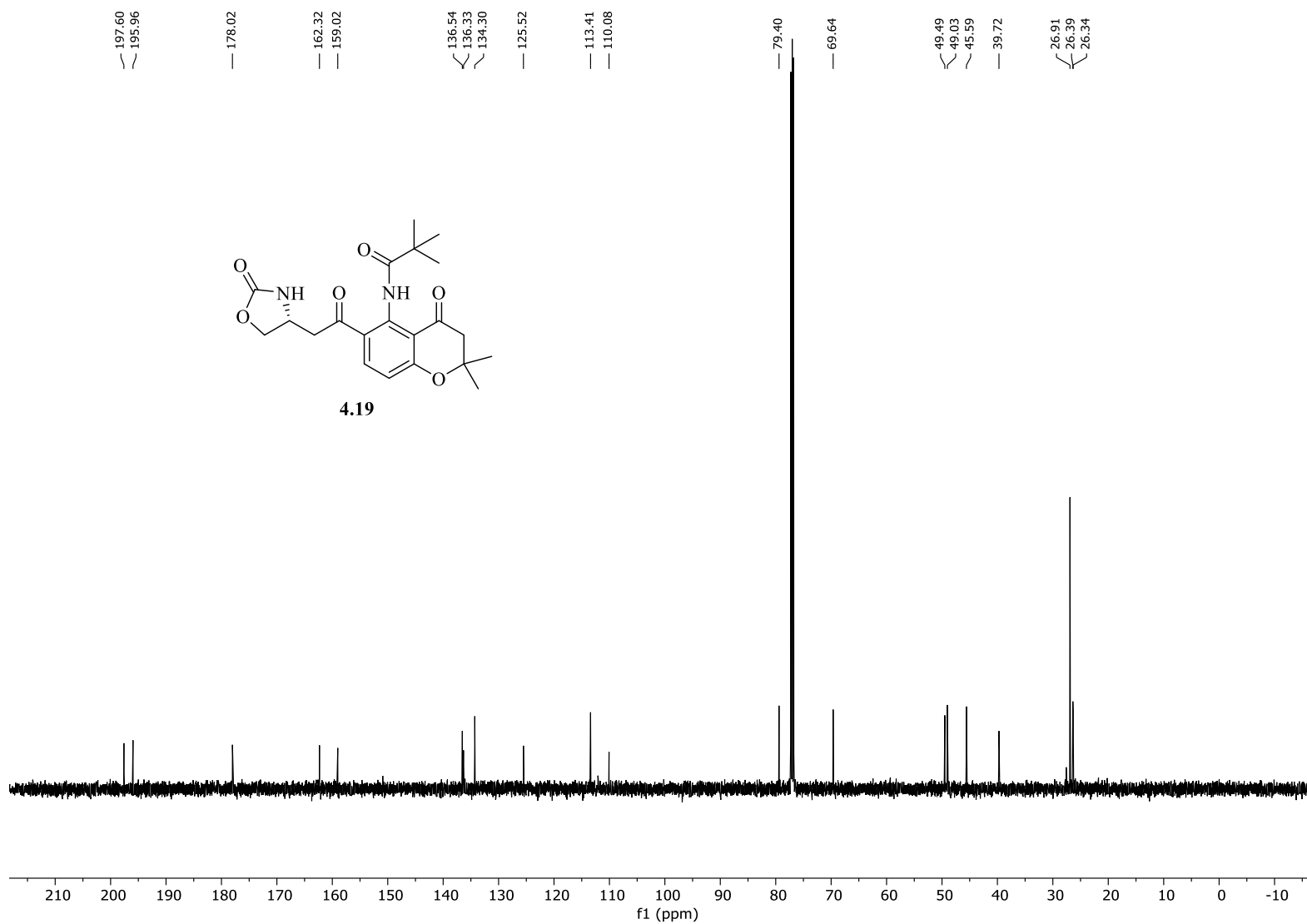


Figure A49: <sup>13</sup>C NMR of **4.19** in CDCl<sub>3</sub>

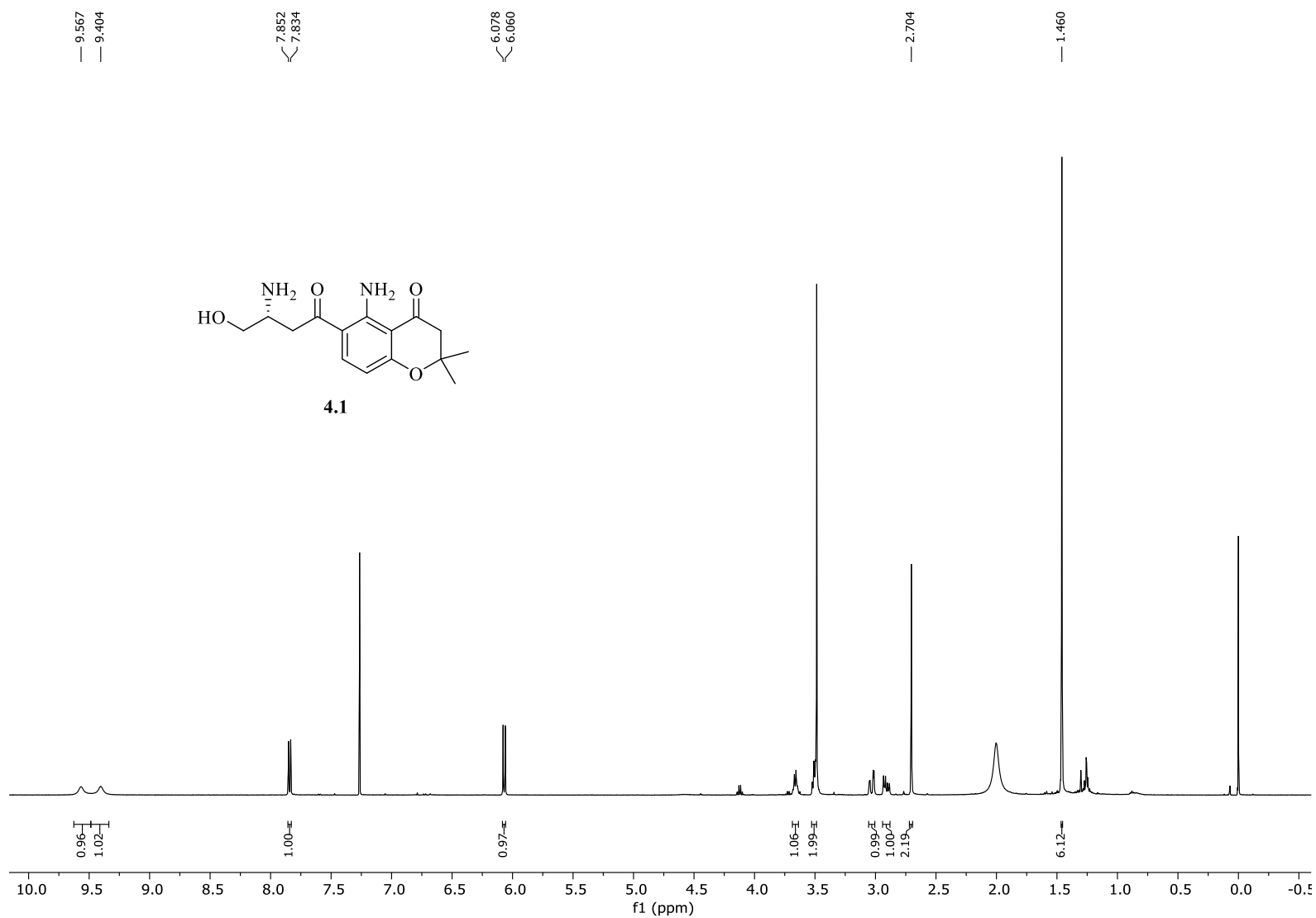


Figure A50:  $^1\text{H}$  NMR of **4.1** in  $\text{CDCl}_3$

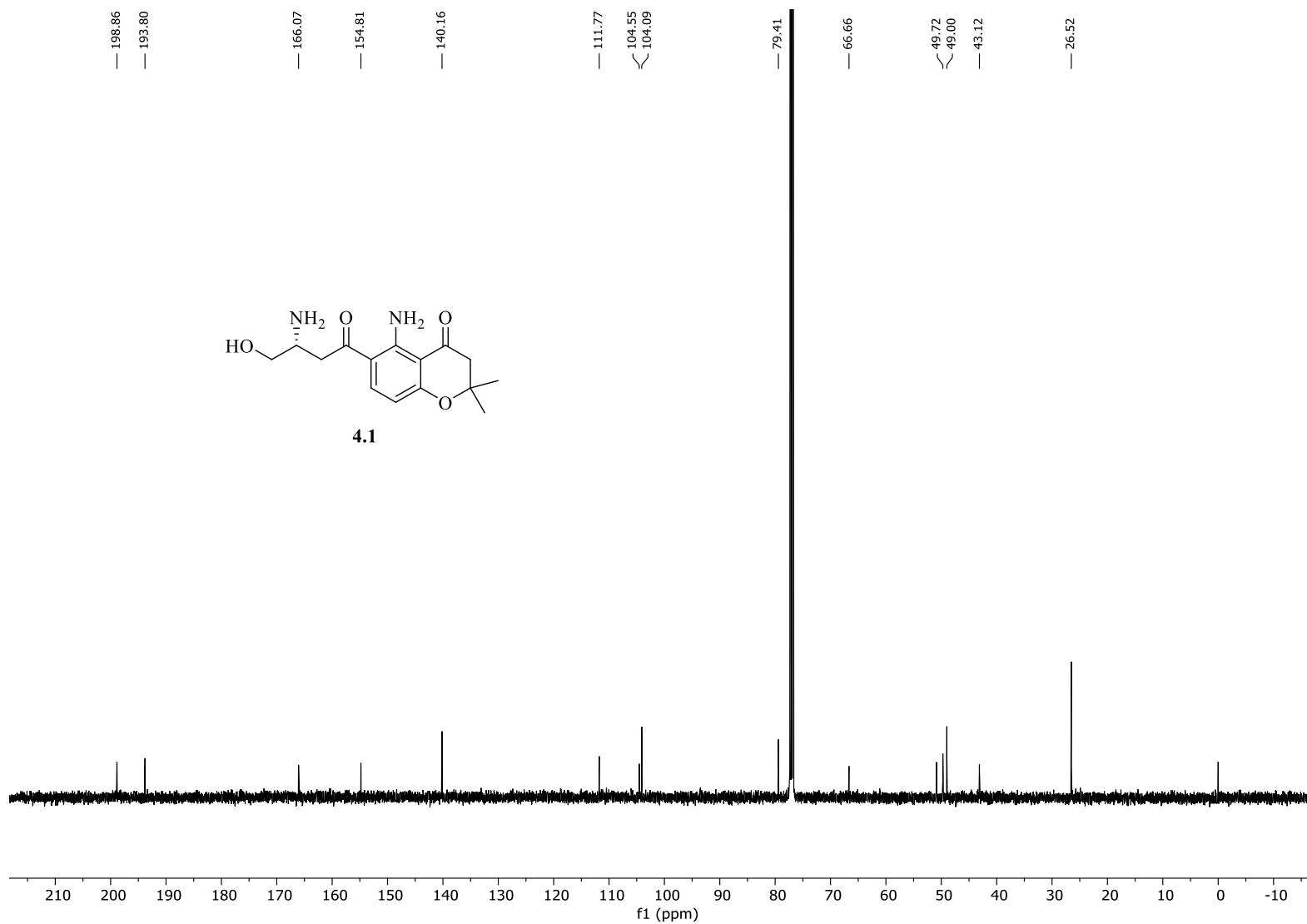


Figure A51:  $^{13}\text{C}$  NMR of **4.1** in  $\text{CDCl}_3$