DISSERTATION

THE APPLICATION OF NEW METHODOLOGY TO COMPLEX MOLECULE SYNTHESIS: STUDIES TOWARD THE SYNTHESIS OF PORDAMACRINE A AND LIPHAGAL

Submitted by

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ABSTRACT

THE APPLICATION OF NEW METHODOLOGY TO COMPLEX MOLECULE SYNTHESIS: STUDIES TOWARD THE SYNTHESIS OF PORDAMACRINE A AND LIPHAGAL

The coevolution of organic synthesis and methodology has contributed greatly to the growth of both fields. This has been enabled by the invention of new methods during the prosecution of a synthesis in order to solve an unforeseen problem as well as by the novel application of independently developed methods to complex synthetic settings. Our own studies have encompassed both of these strategies, and we present their results herein.

Our initial efforts consisted of synthetic studies towards the complex hexacyclic alkaloid pordamacrine A. This molecule presented many difficulties, and we were forced develop and employ new methods in its synthesis. Ultimately, these studies were stymied by the difficulty of forming the central carbocyclic ring system of this molecule.

Among the methods used in the synthesis of pordamacrine A was a variant of a previously reported boron promoted Ireland-Claisen rearrangement. This rearrangement has been reported in very few papers in the literature, and many details of the reaction were undisclosed at the outset of ourstudies. We report here our investigations of the scope and stereochemical features of this rearrangement.

Finally, methods based on the use of Pt carbenoids have formed a central element in our group's research focus. We apply here the use of this intermediate to the synthesis of liphagal, a complex tetracyclic compound. Our explorations of Pt-catalyzed cycloaddition reactions based on Pt carbenoids in this study have shed valuable light on the scope of this method. Though our studies culminated in a formal synthesis of an epimer of the natural product, we expect that future work towards liphagal will be able to use this methodology to make the correct diastereomer of liphagal, potentially in enantioenriched form.

ACKNOWLEDGEMENTS

Many people have helped me get through these past five years as a PhD student, and without their help and support, I could not have possibly succeeded. It would be criminal not to mention them, so I will try my best to do them justice in the one page I am allowed. If I haven't mentioned you, it is the graduate school's fault.

I owe considerable gratitude to my actual research advisor, Eric Ferreira, for his help and patience with me over the years. I also want to thank the members of my doctoral committee (Drs. Alan Kennan, Eugene Chen, Amy Prieto, and Jeffrey Hansen) for their helpful discussions in preparing this manuscript.

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On the far side of the building, I was stuck with two lost souls whom I could not have been happier to have been stuck with. Cat-like though he is, Paul Allegretti's effectiveness in running experiments was a constant reminder of how to get things done well. Brian "Oily Pete" Knight was a great person to bounce ideas off, and we had a lot of great conversations about C-H activation scaffolds, enolate alkylations, and things that I absolutely will not mention in my dissertation. I owe both of these men a debt of gratitude for putting up with me for these past years.

I must also mention the people who helped prepare me for graduate school well enough that I actually stood a chance. Vladimir Birman, my undergraduate research advisor, taught me what it meant to be a synthetic organic chemist. I am still in awe of his encyclopedic knowledge of organic synthesis, and I can say without equivocation that I would not be the chemist I am today had it not been for him.

Without Srinivas Achanta, I would not be the experimentalist I am today. He taught me how to perform reactions under an inert atmosphere and dry solvents and passed down to me countless other skill that I take for granted now that I use them on a daily basis. His passion for his work shows.

I would also like to thank my family for their unwavering love and support. More than anyone else, my Mom and Dad, and my sister Becky, have taught me to be the person I am today. They have always been willing to listen to what I have to say and help me out when I need it.

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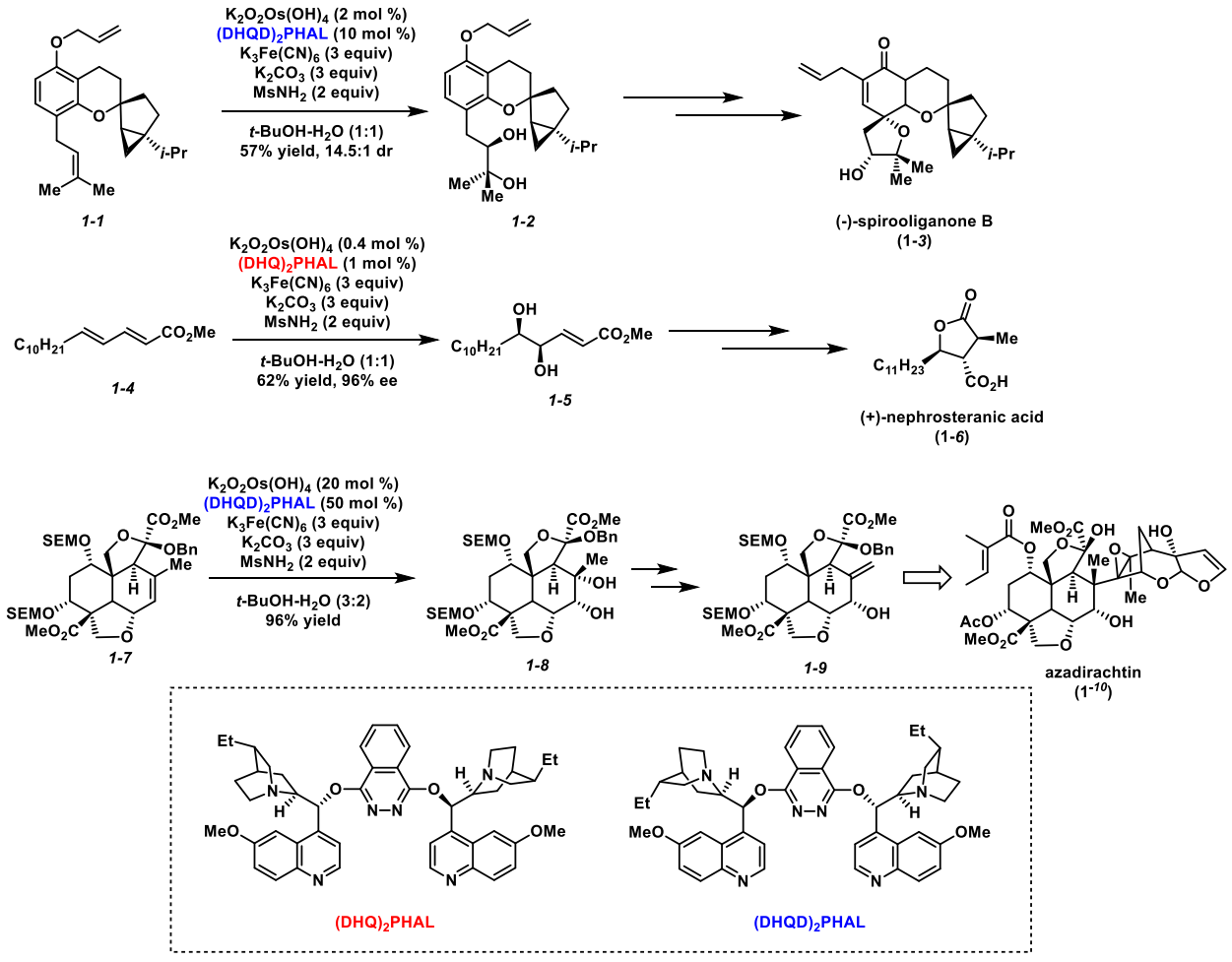
Chapter One: The Coevolution of Synthesis and Methodology

While new methods provide opportunities to study the mechanistic side of unfamiliar reactions and gain a better understanding of molecular predilections, the ultimate test of a method's utility is its applicability to synthetic problems. By this measure, method development has been extremely successful. Ever more powerful methods have allowed the synthesis of ever more complex molecules, and achievements in total synthesis along these lines have made it seem as if no natural product is out of reach. This story, however, has not been one sided. Organic synthesis and methodology have coevolved. While methodology has aided synthesis, feats in organic synthesis have forced workers to deal with weaknesses in existing methods, spurring the development of milder conditions to facilitate reactions and sometimes the creation of new transformations altogether. These two effects form a theme woven throughout the story of the research described herein, but before we begin, it is necessary to introduce this give and take in the work of our forebears and appreciate the achievements that their work has enabled.

We should note before we begin that it would be impossible to detail all, or even a significant portion, of the story of the coevolution of synthesis and methodology in this introduction. We believe that it is a testament to the robustness of the interplay between these two elements that progress in organic chemistry has generated so many examples of it. So rather than attempt any sort of comprehensive treatment of this subject, we briefly introduce here two examples, those of catalytic asymmetric dihydroxylation and macrolide synthesis, to give an idea of the importance of this topic before we show how the interplay has influenced our own work.

Asymmetric dihydroxylation is based largely on the use of chiral, C_2 symmetric ligands with an OsO_4 catalyst or precatalyst.[1] Today, this reaction is seen as an extremely general and reliable way of introducing asymmetry to a synthesis. We owe the reliability of dihydroxylation chemistry to the thorough development of this reaction by K. Barry Sharpless for which (among other things) he shared the Nobel Prize in 2001.[2] In addition to allowing the introduction of asymmetry, the use of $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ ligands, along with a few others, can allow one to overcome substrate bias (or lack thereof) to make diastereomerically enriched products with enantioenriched starting materials. Other workers have taken advantage of both of these abilities of dihydroxylation chemistry in synthetic settings. Xie and coworkers used this methodology to overcome the lack of stereofacial bias present near the prenyl group of spirocycle **1-1** and perform dihydroxylation of this moiety with considerable stereoselectivity. They ultimately carried diol **1-2** forward to accomplish a total synthesis of (-)-spirooliganone (**1-3**).[3] Fernandez used

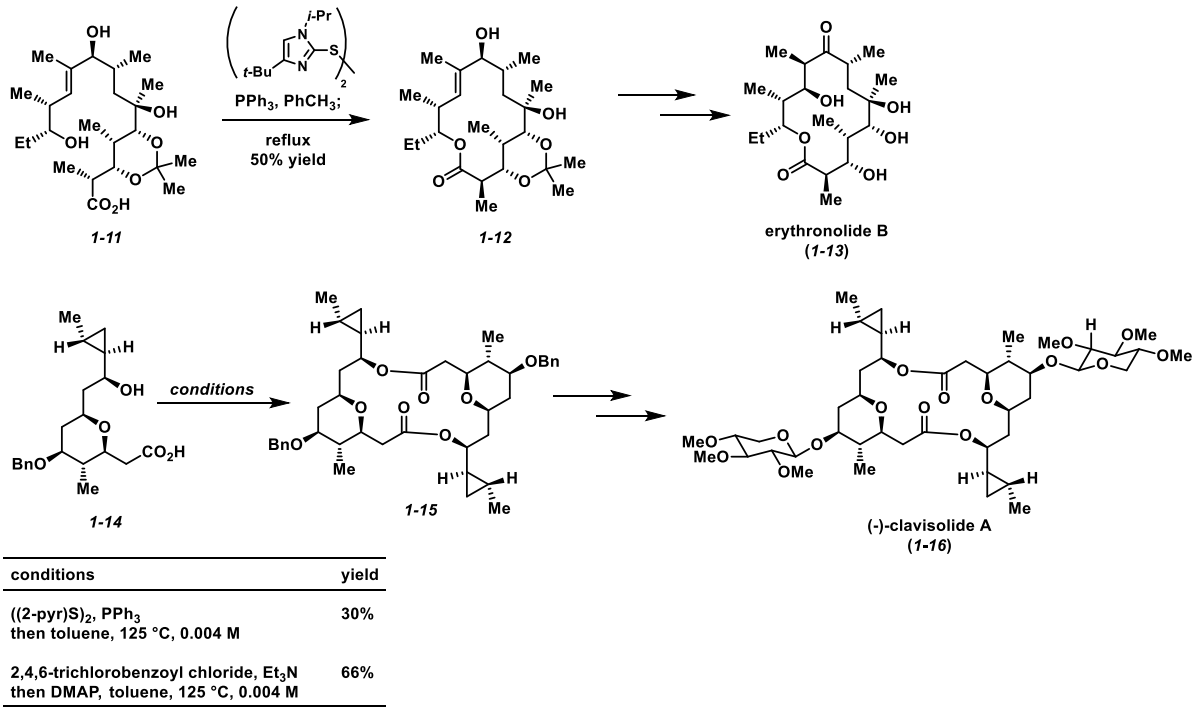
the Sharpless asymmetric dihydroxylation reaction to selectively oxidize the distal olefin of dienoate **1-4** *en route* to enantioenriched (+)-nephrosteranic acid (**1-6**).[4] Finally, Nicolaou and coworkers employed asymmetric dihydroxylation in their studies towards the synthesis of azadirachtin (**1-10**). Using a high catalyst loading, they performed an oxidation of an extremely hindered trisubstituted olefin of tetracycle **1-7** in 96% yield. These examples represent reactions that would have been considerably less efficient, or even impossible, to perform as shown without the prior development of enantioselective dihydroxylation.



Scheme 1.1. Dihydroxylation reactions in complex molecule synthesis.

The synthesis of macrolides represents an example of a situation where the limits of existing methods drove the development of new, more robust ones, and the methods and synthesis progressed hand in hand. This story begins with Corey's synthesis of erythronolide B (**1-13**),[5,6] a 14-membered lactone containing ten stereocenters. While the

medicinal usefulness of macrolide antibiotics was well known prior to Corey's synthesis, the notable dearth of methods of constructing large ring lactones rendered the total synthesis of these compounds very difficult.[7] To efficiently complete his synthesis of erythronolide B, Corey would need to invent a new method to close this large ring. To do this, he used pyridyl or imidazoyl disulfides along with triphenylphosphine to activate the carboxylic acid, which would then undergo intramolecular reaction with the pendant alcohol upon heating to give the macrolactone.[7] This worked very well in practice, and hydroxyacid **1-11** underwent cyclization to give lactone **1-12** in 50% yield, ultimately leading to a synthesis of erythronolide B. In addition, Corey immediately showed the applicability of this method to the synthesis of other large, complex lactones.[8] The synthetic community also recognized the power of this macrocyclization method, and numerous other syntheses utilize this methodology.[9] This has led to the development of other methods for forming macrolactones that could succeed when Corey's did not. After decades of tandem synthesis development-methodology development, the synthetic chemist now has numerous methods from which to choose to form macrolactones.[9] Indeed, groups have exploited this variety to their advantage, such as in the case of Smith's synthesis of clavisolide A (**1-16**).[10] Here, Corey's method was used to prepare diolide **1-15**, but these conditions proved to be inefficient. However, Smith was able to use Yamaguchi's 2,4,6-trichlorobenzoyl chloride activator[11] to perform the cyclization in a much greater yield. For syntheses in the planning stage, a chemist can be relatively certain that there now exist conditions that can be used to form a desired macrolactone, due to the intense trials that each of these methods has been subjected to in the quest for ever more general reactions.



conditions	yield
$((2\text{-pyr})S)_2$, PPh_3 then toluene, 125 °C, 0.004 M	30%
2,4,6-trichlorobenzoyl chloride, Et_3N then DMAP, toluene, 125 °C, 0.004 M	66%

Scheme 1.2. Developing methodology for macrolide synthesis.

In the following three chapters, we describe how the themes we have briefly laid out here have made their way into our own work. Chapter Two details our studies toward the synthesis of pordamacrine A, an alkaloid whose complexity put numerous methods to the test in our attempts to construct it. From these studies was born our work into an Ireland-Claisen variant that uses *boron* ketene acetals rather than the more familiar silicon variants (Chapter Three). Our attempts to utilize the more traditional conditions for this reaction were unsuccessful in our pordamacrine A studies, so we were thus required to further develop relatively unexplored methodology to continue our synthesis. The picture that emerged from our detailed investigations into the Ireland-Claisen rearrangement of boron ketene acetals was one where ostensibly similar intermediates (boron- and silyl ketene acetals) diverge significantly in their behavior in certain situations. We believe that each method has considerable strengths and that boron will indeed find a place beside silicon in promoting this rearrangement in complex synthetic settings.

In the Chapter Four, we discuss our approach to liphagal. Where before our studies were based on the use and development of methods as demand required in our prosecution of a synthesis, here our work centered on the reverse approach. With liphagal, we endeavored to build a synthesis around the use of a Pt carbenoid-based formal cycloaddition reaction. This represented a more complex (and difficult) setting than those in which this methodology had been used before, and as such we discovered some of the strengths of this method as well as the limits of its

usefulness. We expect that the insights gained here will benefit the further development of this methodology and ultimately lead to its increased generality in synthetic settings.

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Chapter 2: A Claisen Rearrangement-Based Approach to Pordamacrine A.

Initially characterized in 2009,[12] pordamacrine A (**2-1**) is a heavily oxygenated, hexacyclic alkaloid found in the leaves of *daphniphyllum macropodum*. Plants of this genus are prolific producers of structurally complex alkaloids, and over 200 have been characterized[13] since initial reports on the structures of daphniphylline[14] (**2-3**) and yuzurimine[15] (**2-6**) in 1966. Because of the number of these alkaloids produced by plants of this genus, they are further subdivided into categories based on structural resemblance. Pordamacrine A belongs to the Yuzurimine class of compounds along with the structurally very similar Yuzurimine C. All of the daphniphyllum alkaloids share the polyene squalene (**2-8**) as a common biogenic ancestor. The route by which nature forms these diterpenes from squalene was suggested by Heathcock,[16–18] who used consideration of this route to complete numerous total syntheses of molecules in this family.[19–32]

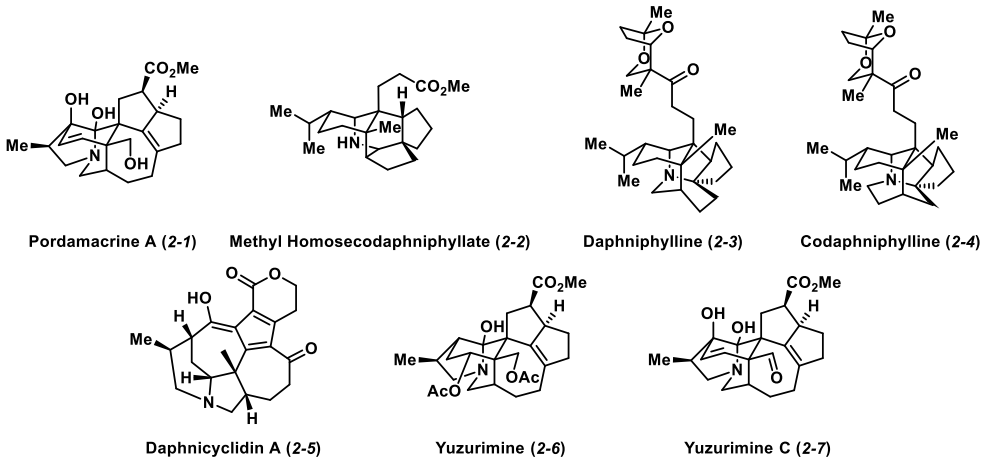
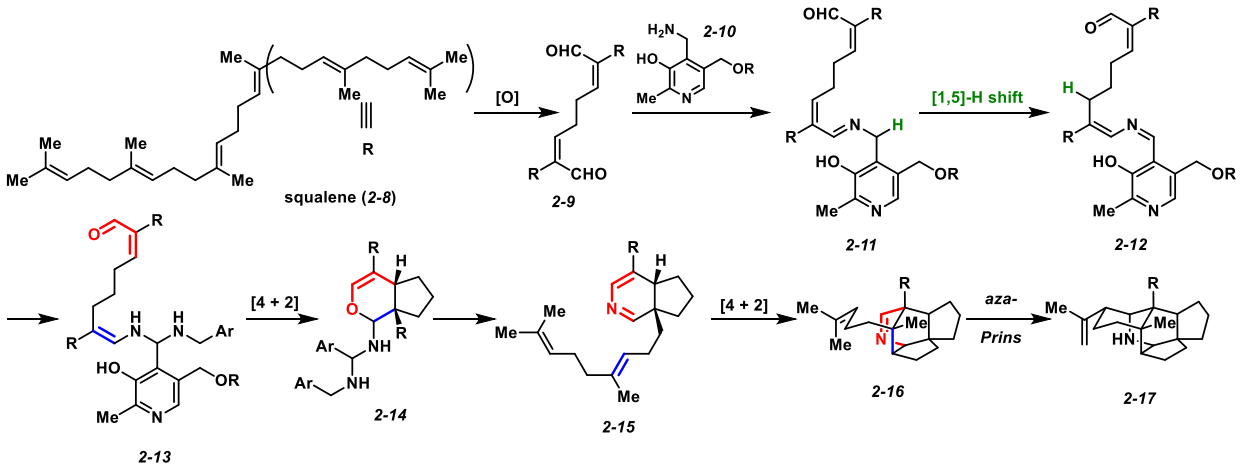


Figure 2.1 Some representative daphniphyllum alkaloids.

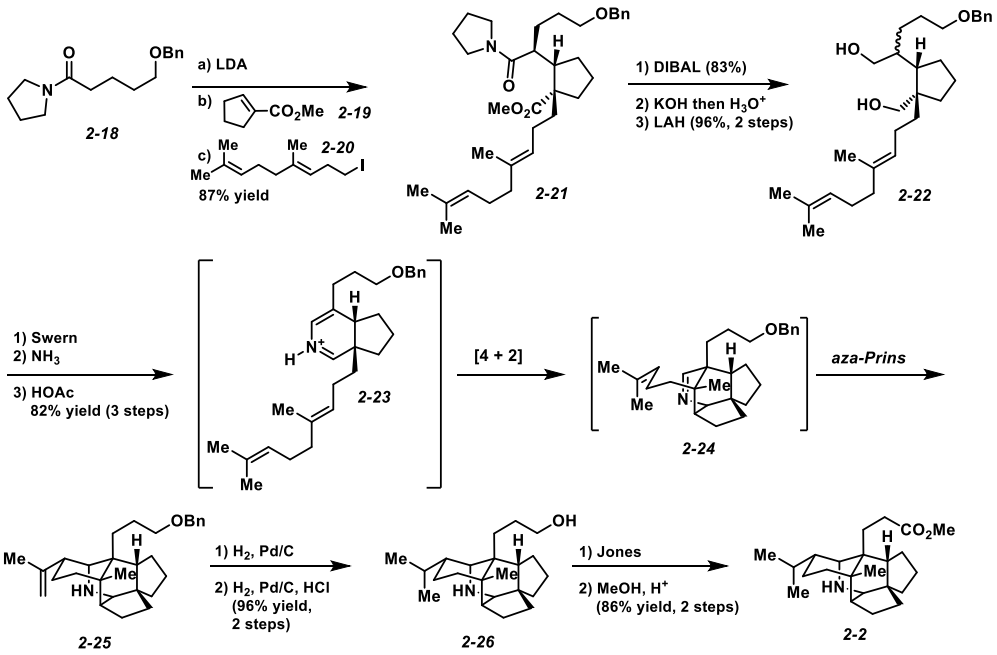
Heathcock formulated a plausible biosynthesis based on the elaboration of squalene as shown in Scheme 2.1.[16] Oxidation of squalene provides dialdehyde **2-9**, which then undergoes condensation with pyridoxamine (**2-10**), a nitrogen carrier in alkaloid biosynthesis. The resulting α,β-unsaturated imine **2-11** would suffer a pericyclic 1,5-hydride shift and condensation with another molecule of pyridoxamine to generate enamine **2-13**. Enamine **2-13** would then undergo a hetero-Diels-Alder cycloaddition, followed by condensation, to generate dihydropyridine **2-15**.

The dihydropyridine moiety would then participate in a Diels-Alder reaction with a pendant dienophile to give tetracycle **2-16**, which would finally undergo an aza-Prins reaction to generate the secodaphnane core (**2-17**).



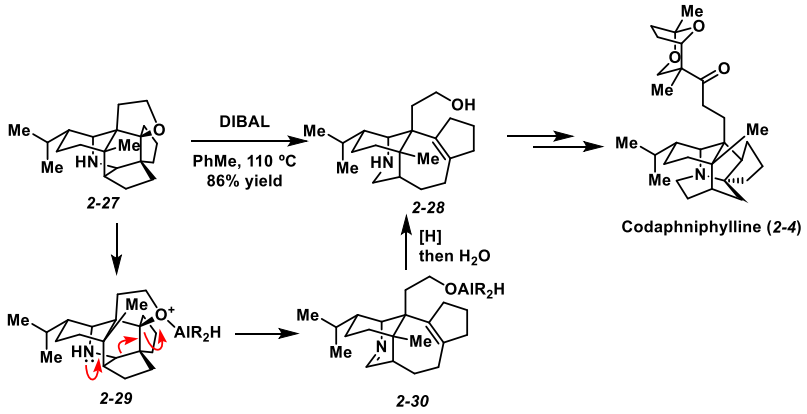
Scheme 2.1. Heathcock's proposal for the synthesis of the secodaphnane skeleton.

Heathcock tested his biosynthetic hypothesis in the synthesis of methyl homosecodaphniphyllate (Scheme 2.2).[21] Here he employed a polycyclization cascade that incorporated an intramolecular Diels-Alder reaction of a dihydropyridinium and a pendant alkene (**2-23**) followed by an aza-Prins reaction, similar to the sequence in his biosynthetic proposal. This reaction generated three news rings and six new stereocenters in a single step. The completion of the synthesis followed a few straightforward functional group manipulations.



Scheme 2.2. Heathcock's biomimetic synthesis of methyl homosecodaphniphyllate.

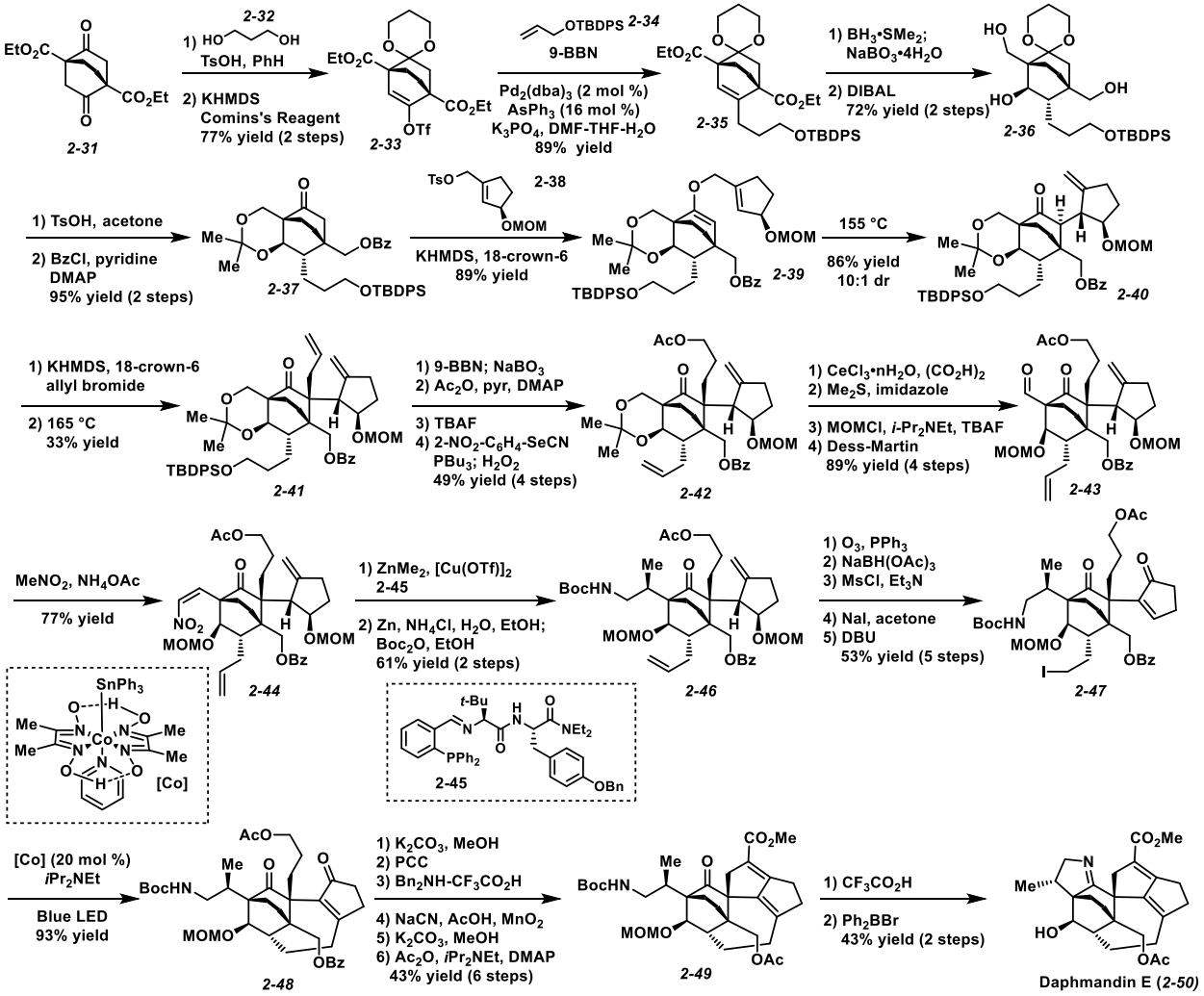
Heathcock also hypothesized that this complex polycyclization cascade was at the heart of the biosynthesis of all daphniphyllum alkaloids and that individual variations in structure were simply due to further biosynthetic manipulations on the secodaphnane skeleton. He illustrated this principle in his synthesis of codaphniphyllane (**2-4**).[22,28] In this synthesis, he utilized a fragmentation-reduction cascade to unveil the tetracyclic core of the Yuzurimine skeleton (**2-28**). This skeleton was taken on to codaphniphyllane through further synthetic manipulations, including an intramolecular hydroamination that further modified the skeleton of this intermediate. The fragmentation reaction in this sequence inspired the centerpiece fragmentation cyclization reaction at the heart of our own synthetic plan.



Scheme 2.3. Fragmentation of the seco-daphnane skeleton to the yuzurimine skeleton *en route* to codaphniphylline.

While Heathcock's strategy was elegant, we thought it would be inappropriate for pordamacrine A. We hypothesized the key polycyclization cascade would fail for more heavily oxygenated molecules of this family, where nature likely conducts cytochrome P450-based oxidations after this process takes place. Since *in vitro* mimics of these oxidations of complex substrates generally fall outside the ability of the synthetic organic chemist,[33] thus we sought an alternative route to our target.

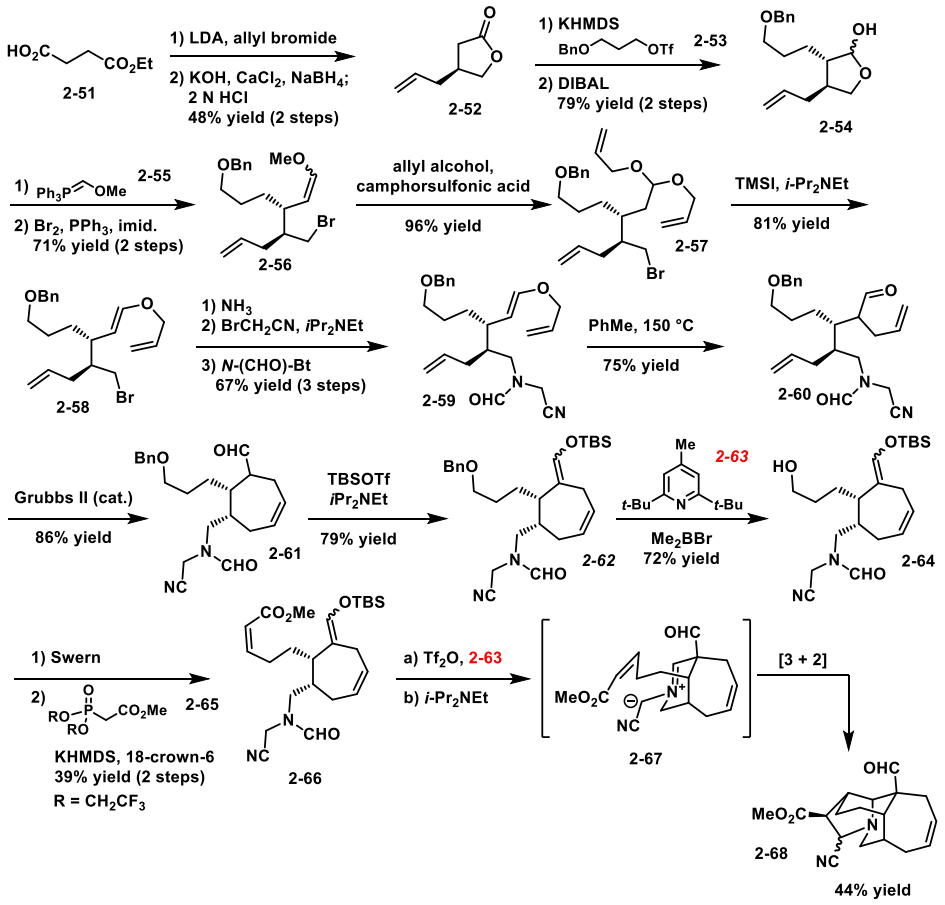
In addition to Heathcock's syntheses of daphniphyllum alkaloids, there has been one other completed synthesis of a compound in this family: Carreira and Weiss's synthesis of Daphmandin E (**2-50**) (Scheme 2.4),[34] with a structure that is architecturally distinct from any of Heathcock's targets. The synthesis centers on a series of two *O*-alkylation-Claisen Rearrangement sequences as well as an "alkyl-Heck" reaction catalyzed by a cobalt complex in the presence of blue light. Overall, the synthesis of this structurally complex, oxygenated alkaloid takes 36 steps, and represents a considerable achievement in total synthesis.



Scheme 2.4. Carreira and Weiss's synthesis of Daphmandin E

Along with these successful syntheses of daphniphyllum alkaloids, there have been numerous attempts and partial syntheses published.[35–40] The one that arguably gets closest to the core of the yuzurimine alkaloids is the approach of Bélanger (Scheme 2.5).[37] The synthesis targets a tetracyclic portion of the core of the molecule including the two nitrogen containing and two carbocyclic rings. The latter is formed first with a ring closing metathesis reaction to give **2-61**, and all the others are constructed in the final step via a Vilsmeier-Haack/azomethine ylide cycloaddition cascade to give **2-68**. Though the last step of this synthetic route is impressive, it suffers from the difficulty of synthesizing the starting material for this cascade reaction, which required 17 steps to access. Moreover, the elaboration of this synthetic route in order to access the yuzurimine type natural products would be an extremely difficult task. These partial syntheses and the fact that none of these groups has later gone on to publish a completed

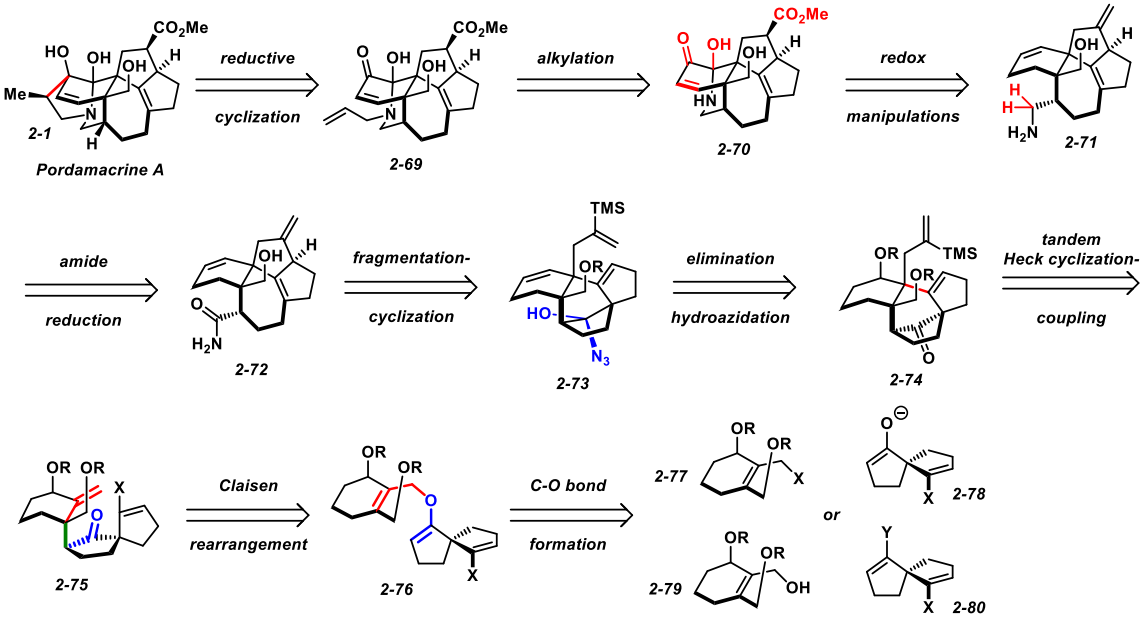
synthesis serve to illustrate the difficulty involved in the synthesis of any of these structurally complex natural products.



Scheme 2.5. Bélanger's synthesis of the core of the yuzurimine alkaloids.

With the difficulty of our forebears in mind and inspired by Heathcock's shining example, we began our series of retrosynthetic simplifications of Pordamacrine A. In our retrosynthesis (Scheme 2.6), we first disconnected the pyrrolidine ring in the natural product via a single-electron reductive cyclization involving the ketone and pendant alkene of ketone **2-69**, imagining that the forward reaction would be performed by a reagent such as SmI_2. The required olefin would be introduced by allylation of secondary amine **2-70**. This compound would be obtained by several straightforward oxidations of its precursor, primary amine **2-71**, as well as a spontaneous hemiaminal formation. This compound (**2-71**) would be formed through a key fragmentation-cyclization reaction, followed by reduction of the resulting amide (**2-72**) to a primary amine (*vide infra*). We expected that the former reaction would

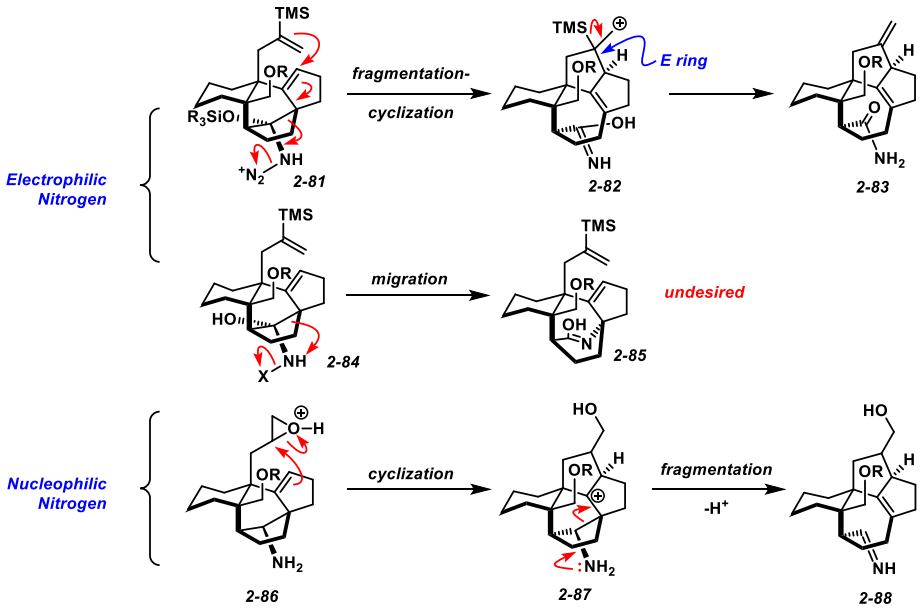
result spontaneously during hydro- or silyl-azidation of ketone **2-74** under the acidic conditions required. We planned to accomplish the synthesis of ketone **2-74** by a tandem Heck cyclization-cross coupling reaction that would both close the seven membered ring of **2-74** and introduce its vinyl-TMS moiety. A Claisen rearrangement of allyl alkenyl ether **2-76** would form the key carbon-carbon bond of vinyl halide **2-75** and position us for the tandem Heck cyclization-coupling reaction. We planned to use a fragment coupling to synthesize ether **2-76** in one of two ways. We could either perform an O-alkylation of ketone enolate **2-78** with allylic (pseudo)halide **2-77** or utilize a C-O cross coupling between the alcohol of **2-79** and the alkenyl-Y moiety of alkenyl halide **2-80** to combine two considerably simpler fragments to synthesize our Claisen precursor, ether **2-76**.



Scheme 2.6. Initial retrosynthesis of pordamacrine A.

Though we had looked to biosynthesis for inspiration in this retrosynthesis, there were no biosynthetic proposals that dealt with the formation of the E-ring of the Yuzurimine skeleton (see compound **2-82** in Scheme 2.7). We saw two possibilities differing in the 'direction of flow' of electrons for effecting closure of this E-ring along with a fragmentation reaction similar to that used by Heathcock. The first ("electrophilic nitrogen") was our favored choice, whereby a hydro- or silyl-azidation reaction would generate a potentially electrophilic nitrogen of compound **2-81**, which would lose N_2 on protonation of the azido nitrogen in concert with breaking of a skeletal C-C bond. The cation would be immediately trapped by a pendant vinylsilane (either in concert with fragmentation or in a stepwise process)

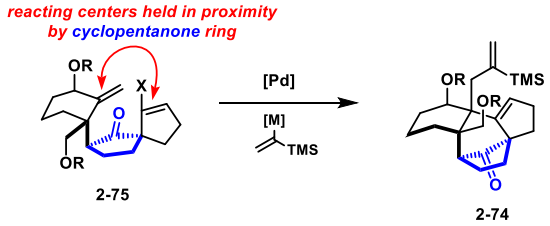
to generate the E-ring of compound **2-82**.[41] Desilylation would generate the exo-methylene moiety of tetracycle **2-83** that would be amenable to further elaboration to the ester group present in the natural product. A potential pitfall in this strategy was the possibility that a migration (**2-84 → 2-85)** might take place instead of a fragmentation, as it does in the Schmidt rearrangement. We were confident, however, that the molecular geometry of this system would favor fragmentation over migration due to the greater strain-producing distortion of the molecular skeleton that would have to occur in the latter process, but we still had a contingency plan. The other option ("nucleophilic nitrogen") would be to initiate the sequence by the cyclization reaction, using an epoxide as an electrophile in compound **2-86**. The resulting cation of pentacycle **2-87** would then initiate a Grob-type fragmentation to give tetracycle **2-88**, accomplishing a similar outcome as before. The resulting primary alcohol of compound **2-88** could also serve as a handle with which to form the ester that would ultimately be in the natural product.



Scheme 2.7. Two electron flow motifs for the fragmentation cyclization reaction.

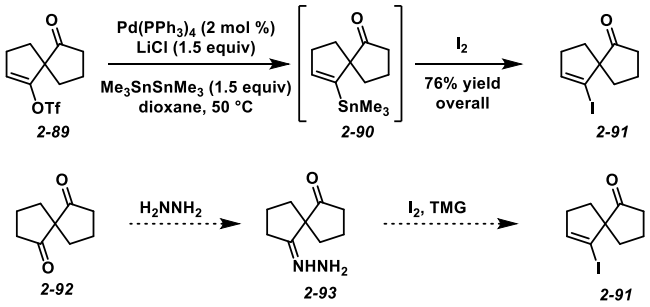
A key feature of the fragmentation cyclization strategy was that it should facilitate our other key step, a cascade Heck cyclization-cross coupling reaction (Scheme 2.8). We anticipated that the cyclopentanone ring that would eventually be broken in spirocycle **2-75** would hold the vinyl halide and alkene in close proximity to facilitate the cyclization step to give compound **2-74**. Though intramolecular Heck reactions to form variously sized carbocylcles are well precedented,[42] we felt that the formation of two vicinal quaternary stereocenters would render

this one quite challenging and that our chances of success would be improved by minimizing the loss of entropy resulting from the cyclization by limiting the conformational freedom of the starting material.



Scheme 2.8. A potential benefit of the fragmentation-cyclization strategy.

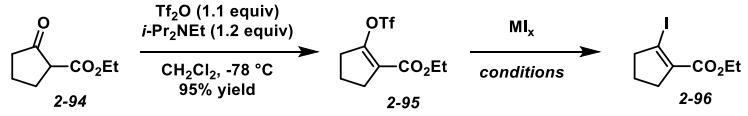
Our first challenge was the synthesis of the required vinyl iodide **2-91** (Scheme 2.9). While we were quickly able to prepare this compound by I_2 oxidation of known trimethylstannane **2-90**,[43] we sought a more scalable synthesis that would obviate the use of toxic and expensive hexamethylditin. The synthesis of acyclic vinyl iodides is normally accomplished from alkyne precursors,[44] but that is not an option in small ring cyclic systems due to the strain inherent in the would-be precursor alkynes. In such cases vinyl iodides are generally derived from ketones, either by treatment of ketone hydrazones with I_2 and tetramethylguanidine (**2-92** → **2-93**)[45,46] or by a stannylation oxidation sequence of enol triflates (*e.g.*, **2-89** → **2-91** via known alkenyl stannane **2-90**).[47]



Scheme 2.9. Alternative possible and realized routes to keto-iodide **2-91**.

We opted instead for an earlier introduction of the vinyl iodide, which would then be transformed into the target compound by a deconjugative alkylation reaction followed by Dieckmann cyclization and decarboxylation. We thought the vinyl iodide could be installed via the vinyl triflate through a straightforward addition-elimination type

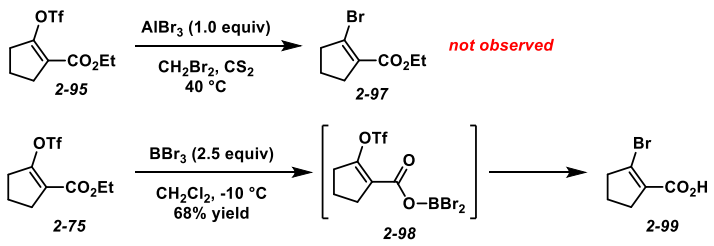
process. We synthesized known vinyl triflate **2-95** from the corresponding β-ketoester (**2-94**) and triflic anhydride, using diisopropylethylamine as a base, in nearly quantitative yield (Scheme 2.10).[48] Sources of iodide with mildly Lewis acidic metal cations did not facilitate transformation of triflate **2-94** to iodide **2-95**, but using the much more strongly acidic AlI_3 gave conversion to the iodide. Upon switching from MeCN to CS_2, a solvent in which AlI_3 is also soluble but would not be expected to attenuate its Lewis acidity as much due to its reduced capacity to act as a Lewis base, we obtained full conversion to the required vinyl iodide in excellent yield. This reaction is known to proceed under the influence of NaI in DMF at high temperatures, albeit in only 35% yield.[49] It is interesting to note here that very little ester cleavage is observed here, even though that is a reaction which AlI_3 is known to promote.[50] Curiously, when we tried to replace CS_2 as the solvent with CH_2Cl_2, the reaction failed to provide any conversion at all. Although AlI_3 is not soluble in pure CH_2Cl_2 to any significant extent, the reaction mixture became homogeneous as soon as substrate was added to a suspension of AlI_3 in this solvent. We suspect that CS_2 plays a role in the partial ionization of AlI_3, increasing its reactivity towards this (pseudo)halide metathesis reaction.



conditions	result
MgI_2	no reaction
ZnI_2	no reaction
AlI_3, MeCN, 80 °C	low conversion
AlI_3, CS_2, CH_2Cl_2, 40 °C	93% yield (10 gram scale)

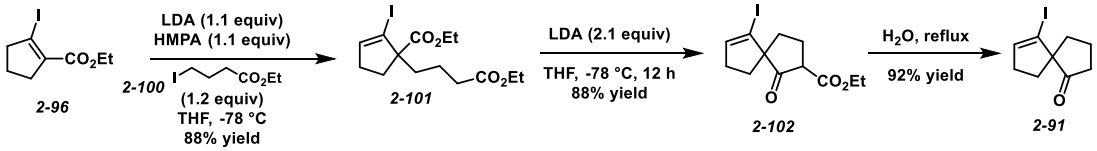
Scheme 2.10. Synthesis of vinyl iodide **2-96**.

We were also curious as to whether or not this method could be extended to making the analogous vinyl bromide (**2-97**) from triflate **2-95** (Scheme 2.11). Interestingly, $AlBr_3$ in CS_2 gave no conversion whatsoever to the **2-97**. However, BBr_3 in CH_2Cl_2 quickly gave conversion to carboxylic acid **2-99**, arising from both substitution of bromide for triflate and ester cleavage, in 68% yield. Our attempts to limit the ester cleavage at low temperature were unsuccessful, and we suspect that a putative acyloxyborane intermediate **2-98** resulting from rate determining ester cleavage possesses enhanced electrophilicity compared to the starting ester. The substitution reaction then in fact occurs quickly from this intermediate to give the final product (**2-99**).



Scheme 2.11. Extending the vinyl halide synthesis to bromide **2-99**.

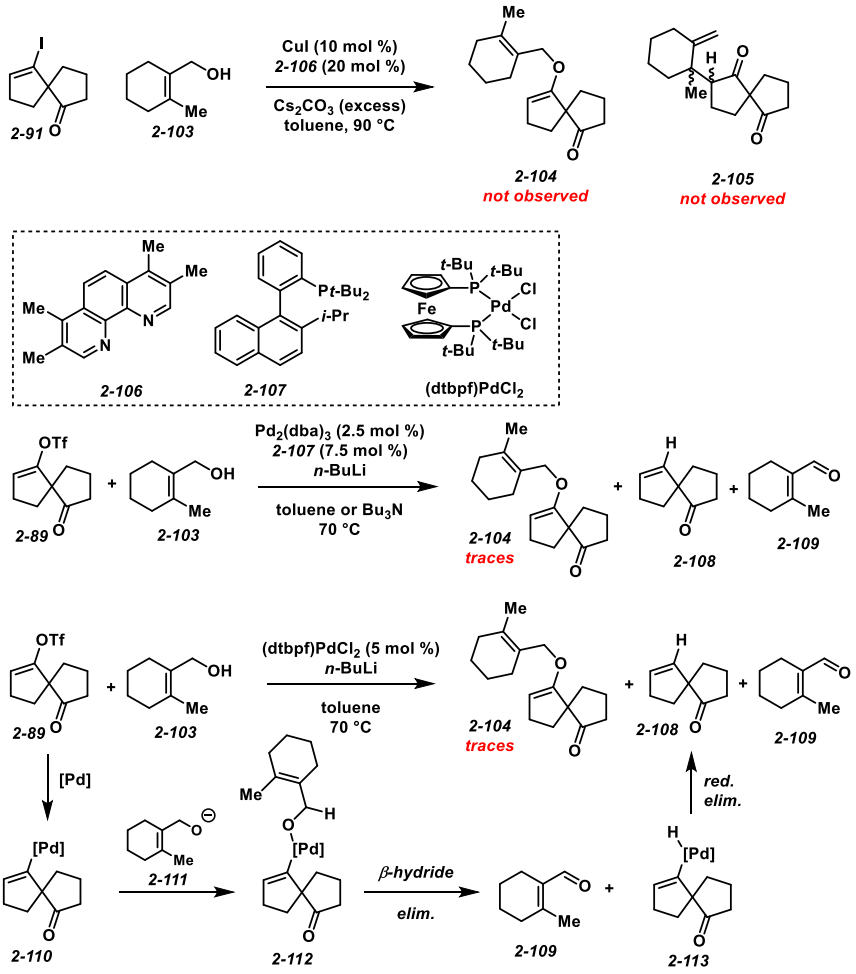
With vinyl iodide **2-96** in hand we completed the synthesis of our target ketone (Scheme 2.12) by performing a deconjugative alkylation reaction promoted by HMPA to give diester **2-101** (88% yield) followed by a Dieckman cyclization promoted by 2.1 equivalents of LDA at -78 °C to give ketoester **2-102** in 88% yield. Finally, ester hydrolysis-decarboxylation by refluxing in water furnished the spirocyclic keto-alkenyl iodide **2.91** in 92% yield. The overall synthesis is extremely efficient, with all steps proceeding in >85% yield, making this a very useful route with which to prepare precursors to test the key reactions in our synthesis.



Scheme 2.12. Synthesis of spirocyclic ketone **2-91**.

From this point, we had secured an intermediate that was amenable to two paths forward to our Claisen precursor: a C-O cross coupling reaction (Scheme 2.13), and an enolate *O*-alkylation (Scheme 2.14). On attempting to apply the closest precedent to our system, a CuI/3,4,7,8-tetramethylphenanthroline (**2-106**) catalytic system to couple vinyl iodide **2-91** to the requisite allylic alcohol (**2-103**),[51] we obtained only decomposition and recovered starting material. When we attempted to apply Pd catalyzed cross coupling conditions using ligand **2-107**[52] and $Pd_2(dba)_3$ we obtained only alkene **2-108** and aldehyde **2-109**, indicating that the allyic alcohol had undergone β-hydride elimination as Pd alkoxide **2-112**, and resulting Pd hydride intermediate **2-113** underwent reductive elimination of R-H to give alkene **2-108**. We suspect that this process is especially favorable for allylic alcohols, which form enals (*e.g.*, **2-109**) stabilized by conjugation after β-hydride elimination, facilitating this unwanted process. With $(dtbpf)PdCl_2$ [53] we observed traces of the desired cross coupled product (**2-104**) in the crude reaction mixture,

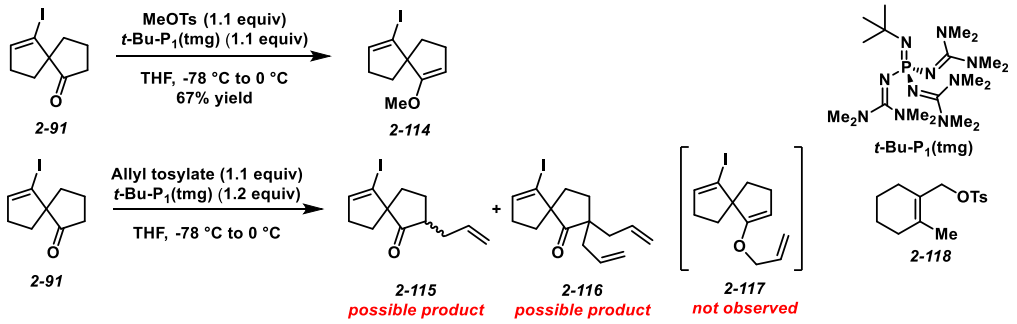
along with β-hydride elimination products **2-108** and **2-109**, but the amount of our desired compound (**2-104**) was too small for the reaction to be synthetically useful. Therefore, we decided to take a slightly different tack, keeping in mind that we could revisit the Pd catalyzed reaction if we were unable to make the Claisen precursor (**2-104**) in a different manner.



Scheme 2.13. Attempted C-O coupling of vinyl iodide **2-91** or vinyl triflate **2-89** and alcohol **2-103**.

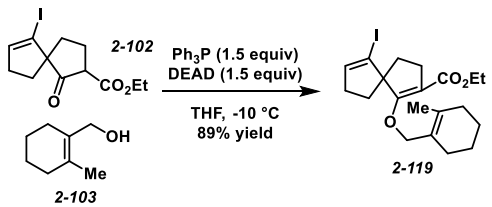
Unfortunately, enolate *O*-alkylation also failed to deliver the Claisen precursor. In the first iteration of our model system, using a base with an extremely non-coordinating counterion, phosphazene *t*-Bu-P$_1$(tmg),[54] along with MeOTs and ketone **2-91**, we obtained only the product of *O*-alkylation, enol ether **2-114**. Indeed, these are conditions that would be expected to greatly favor *O*-alkylation, since this mode of reactivity of the ambident enolate nucleophile is favored by non-coordinating counterions along with sulfonate electrophiles.[55] In the second iteration of our model

system, we replaced MeOTs with allyl tosylate, but this time obtained no detectable products of *O*-alkylation (**2-117**). Because the reaction mixture contained a complex, intractable mixture of compounds, even after purification, we were not able to make a definitive assignment of the major products. However, diagnostic chemical shifts in the ^{13}C NMR spectrum lead us to believe that the reaction formed a mixture of diastereomeric mono-*C*-alkylation products **(2-115**) and di-*C*-alkylation product **2-116**. Because of the difficulty in preparing samples of the more complex tosylate **2-118**, along with the probable *C*-alkylation that our result with allyl tosylate had portended, we sought out another method for making our Claisen precursor.



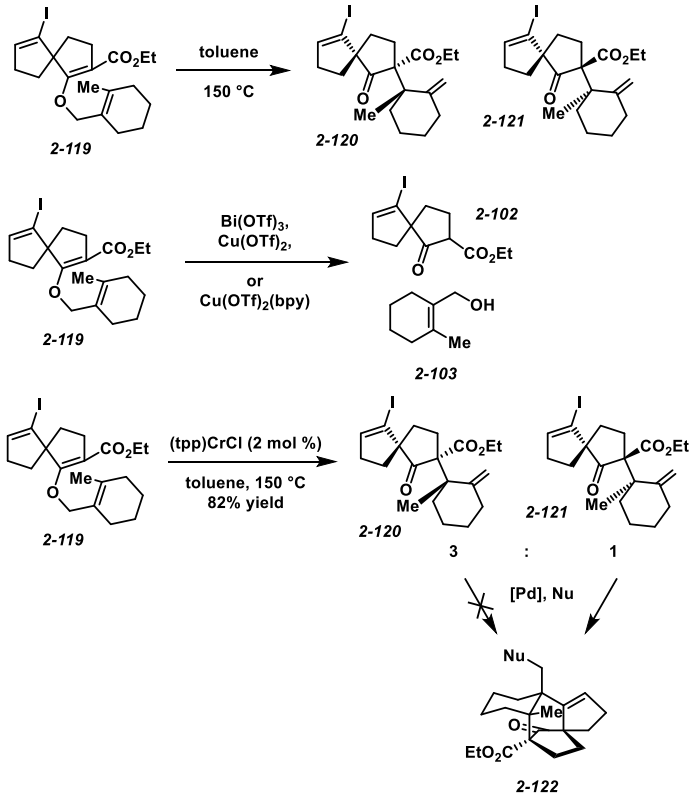
Scheme 2.14. Attempted O-alkylation of ketone **2-91**.

Literature studies have indicated that β-ketoesters can act as *O*-nucleophiles with allylic alcohol partners under Mitsunobu conditions (Scheme 2.15).[56] Although this would furnish a Claisen product with an unwanted ester group (**2-119**), we decided to use this system to test the Claisen reaction and the crucial Heck-cyclization. Gratifyingly, the use of the DEAD/PPh_3 Mitsunobu system along with allylic alcohol **2-103** and β-ketoester **2-102** indeed furnished the desired Claisen precursor (**2-119**) in 89% yield. It is worth noting that the yield here was significantly higher than that obtained using the simpler substrates present in a previous study.[56]



Scheme 2.15. Mitsunobu coupling.

On heating allyl alkenyl ether **2-119** to 190 °C, we were gratified to find that it indeed furnished the desired Claisen product as a 3:1 mixture of diastereomers **2-120** and **2-121** (Scheme 2.16). Because this reaction generated a considerable amount of side products, we tried several catalysts to improve the reaction. $Bi(OTf)_3$, $Cu(OTf)_2$, and $Cu(OTf)_2$(bpy) all gave complete hydrolysis of the vinylogous carbonate **2-119** back to β-keto ester **2-102** and allylic alcohol **2-103**. However, heating **2-119** with 2 mol % (tpp)CrCl[57] in toluene at 160 °C furnished an 82% yield of the mixture of diastereomers (**2-120** and **2-121**). Although we were unable to separate the two compounds by chromatography, careful crystallization of the mixture afforded X-ray quality crystals of major diastereomer. An X-ray crystal structure of this compound revealed that it was the undesired diastereomer (**2-120**), with the vinyl iodide and pendant alkene on different faces of the central cyclopentanone, making the compound unable to undergo the cyclization reaction that would take place next in our synthesis to give (**2-122**). Apparently, the steric bulk of the vinyl iodide moiety of compound **2-119** is enough to slightly bias the diastereofacial preference of the Claisen reaction away from this motif to yield a majority of the undesired diastereomer (**2-120**).



Scheme 2.16. Catalyzed Claisen rearrangement of allyl alkenyl ether **2-119**.

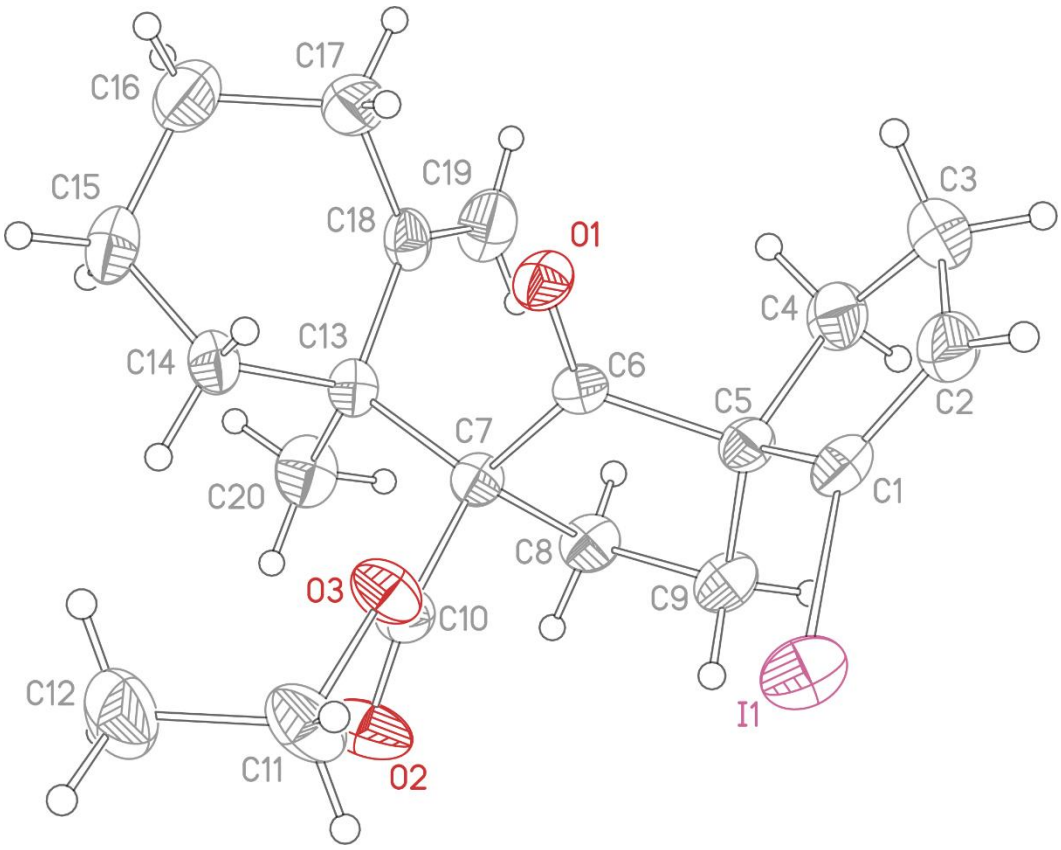
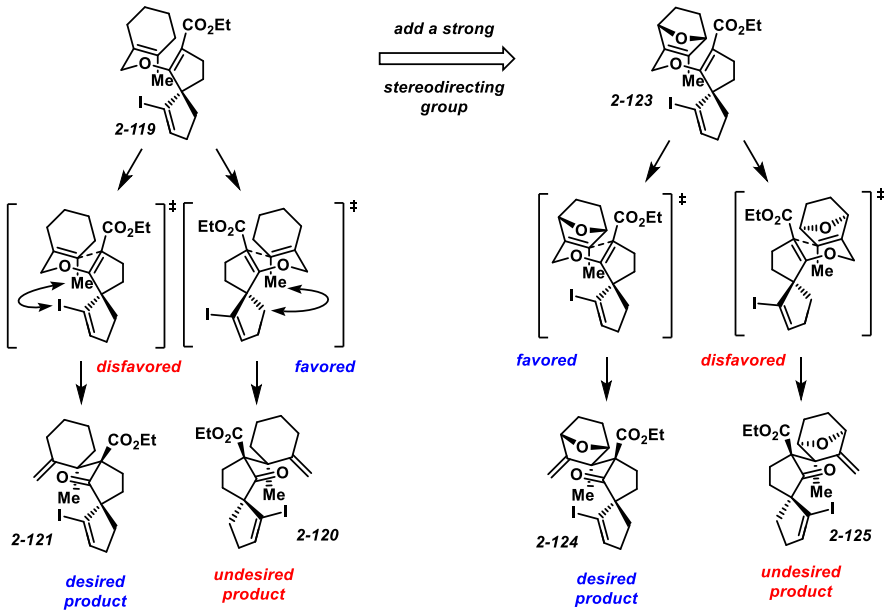


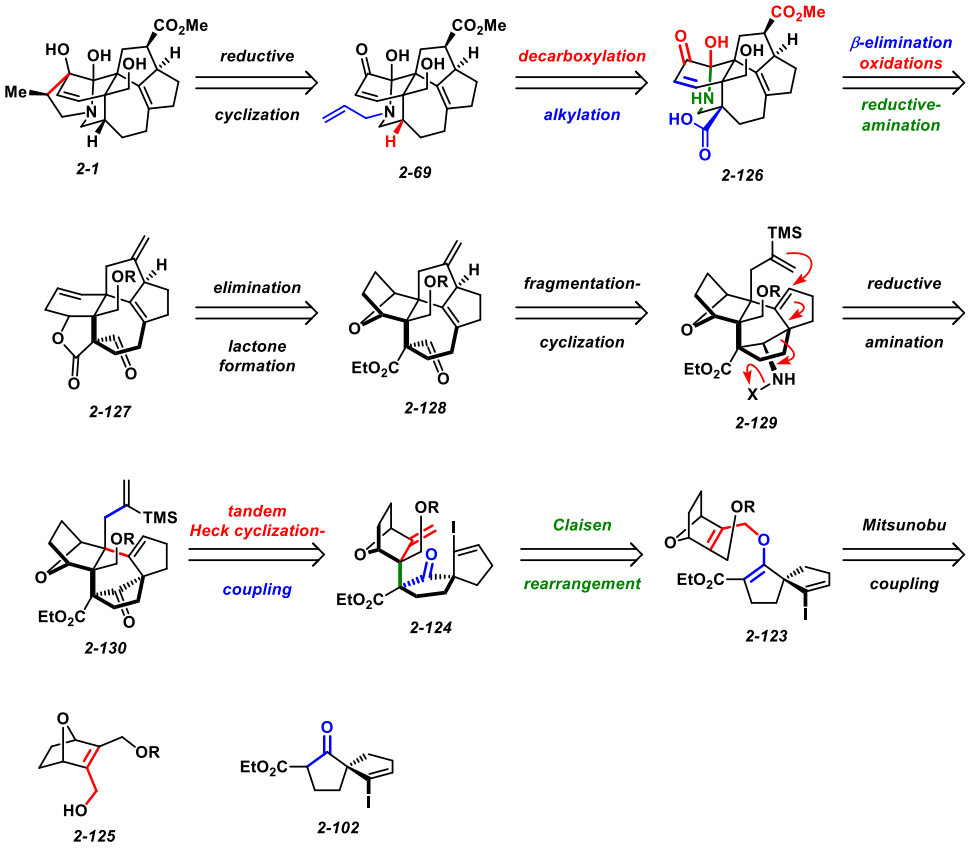
Figure 2.2. X-ray crystal structure of Claisen product **2-120**.

Because of the Claisen rearrangement's known strong preference for occurring through a chairlike transition state,[58] a strong diastereofacial preference with respect to the allyl moiety can direct the sense of diastereoselection on the vinyl ether side as well (Scheme 2.17). Since 7-oxanorbornane systems (*e.g.*, **2-123**) strongly favor reaction on the same face as the oxygen atom,[59–65] we figured that we could exploit this propensity in order to gain access to a larger amount of our desired diastereomer (**2-124**). Due to the fact that we would not be coupling two enantiopure fragments, we were limited to a 1:1 mixture of diastereomers (*vide infra*). We decided, however, that this could increase our odds of obtaining the correct diastereomer enough that the strategy was worth pursuing.



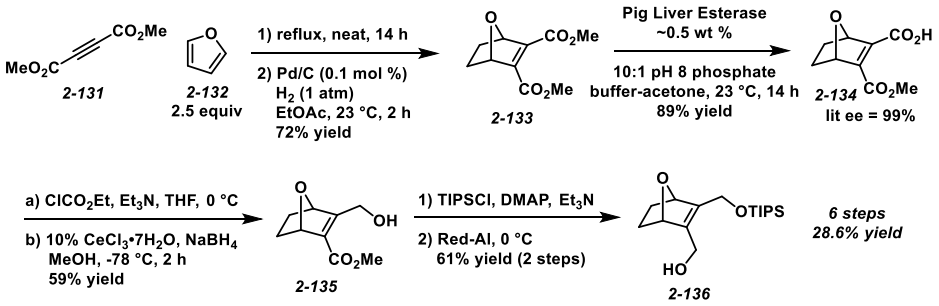
Scheme 2.17. Rationale for a different Claisen approach.

Using this strategy as a backbone, we formulated another retrosynthesis to determine the feasibility of the strategy in the overall context of the synthesis of pordamacrine A (Scheme 2.18). Many of the features of this scheme are similar to those in the previous iteration of our retrosynthesis. The differences lie in the necessary introduction of an ester group in order to join the allyl (**2-125**) and vinyl ether (from **2-102**) fragments prior to the Claisen rearrangement, necessitating its later removal (**2-126** → **2-69**). Our scheme also differed in functionality on the central six-membered ring, allowing us to direct the diastereomeric preference of the Claisen rearrangement (*vide supra*). We decided the ester could be removed late in the synthesis via a metal catalyzed decarboxylation reaction of **2-126** to give **2-69**. An alkene could be installed after the cyclization by a $Et_2Al(tmp)$ promoted elimination of **2-128** to provide **2-127**, where the remaining alcohol group would spontaneously lactonize. This reagent is usually used with epoxides,[66] but we reasoned that the strained nature of the 7-oxanorbornane system of **2-128** would allow it to serve as a substrate for this reaction as well. After oxidation of alkene **2-127** to a dione, we predicted that the β-carboxylate group would eliminate spontaneously to give α,β-unsaturated ketone **2-126**. The rest of the synthesis would follow our previous plan.



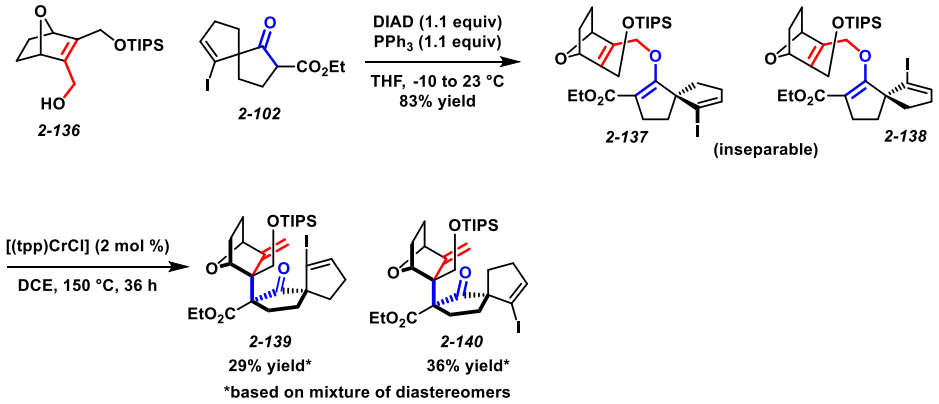
Scheme 2.18. Second generation retrosynthesis of pordamacrine A.

We began by synthesizing the required bicyclic allylic alcohol (**2-136**, Scheme 2.19). A Diels-Alder reaction between furan (**2-132**) and dimethyl acetylenedicarboxylate (**2-131**) furnished bicyclic diester **2-133**. Selective enzymatic hydrolysis of the symmetrical diester with pig liver esterase according to precedent afforded diacid monoester **2-134** in nearly enantiopure form.[67] We were able to perform a selective reduction of the acid moiety by first forming a mixed anhydride using $ClCO_2Et$ and Et_3N and directly reducing this anhydride without purification under Luche type conditions to give primary alcohol **2-135**. Though this reduction reaction was capricious, especially on large scale, the ease of producing large quantities of diacid monoester **2-134** easily made up for this fact. It is also worth noting that although hydroxyester **2-135** contains a carboxyl and hydroxyl group positioned such that a γ-lactone could be formed, a normally very facile and difficult to stop process, this is a side reaction which we did not observe. Protection of the allylic alcohol with TIPSCl/DMAP/Et_3N followed by reduction of the remaining ester with Red-Al furnished allylic alcohol **2-136**. Interestingly, other commonly used reducing agents like $LiAlH_4$ and DIBAL were ineffective for this second reduction, leading only to decomposition.



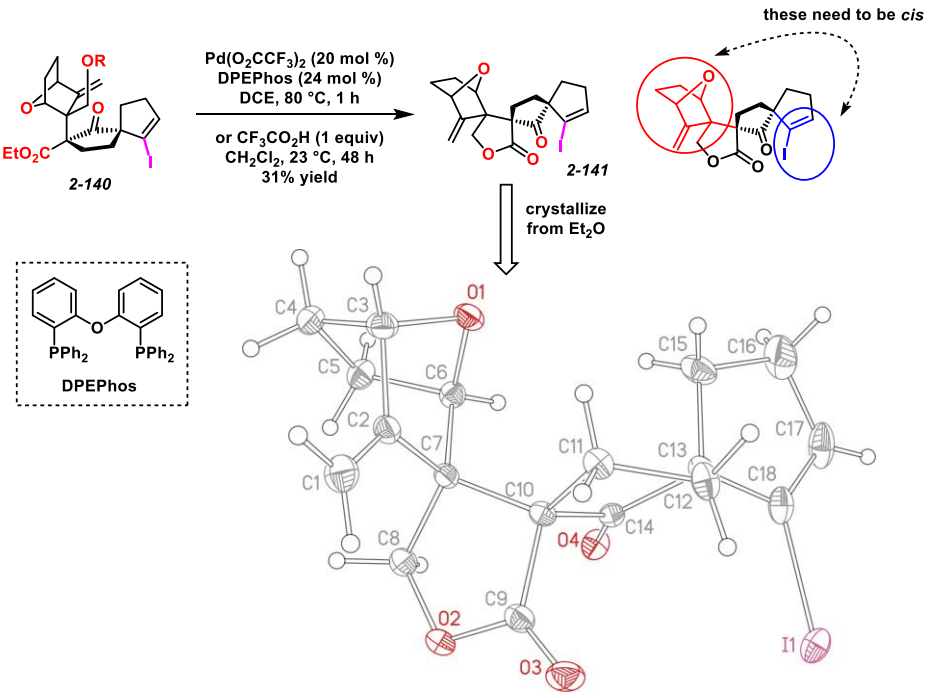
Scheme 2.19. Synthesis of bicyclic alcohol **2-136**.

Mitsunobu conditions again succeeded in joining the allylic alcohol (**2-136**) and β-ketoester (**2-102**) fragments to form allyl vinyl ethers **2-137** and **2-138** in high yield (Scheme 2.20). These two diastereomers, resulting from joining a racemic fragment with an enantioenriched one, were inseparable at this point. Under several of the conditions we first tried to effect the Claisen rearrangement we only obtained hydrolysis of the vinyl ether to reform β-ketoester **2-102**, even when water was rigorously excluded from the reaction mixture. However, using 2 mol % of (tpp)CrCl[57] again facilitated the desired Claisen rearrangement to give a 1:1 mixture of diastereomers (**2-139** and **2-140**). The fact that the reaction only formed two diastereomers rather than the possible four indicated that each of the epimeric starting materials had undergone rearrangement with perfect diastereoselectivity. As an added bonus, diastereomers **2-139** and **2-140** were completely separable by column chromatography.



Scheme 2.20. Mitsunobu coupling and Claisen rearrangement.

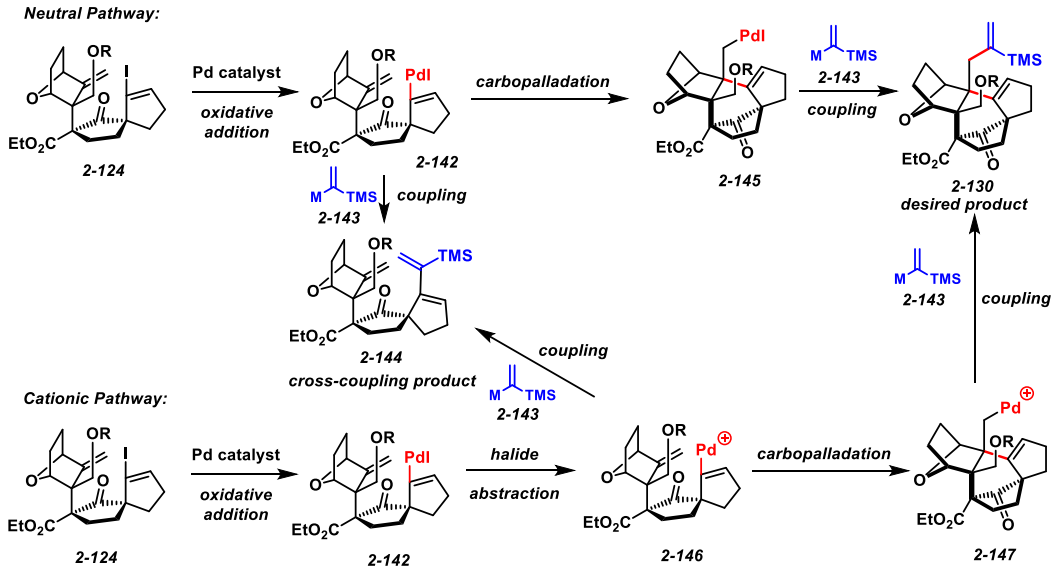
Unfortunately, we could not discern by NMR which diastereomer was our desired product, and both compounds **2-139** and **2-140** were viscous liquids, so we could not obtain an X-ray crystal structure. A solution to this problem came as we tried conditions to effect the cyclization of each diastereomer (Scheme 2.21). Upon treatment of **2-140** with $Pd(O_2CCF_3)_2$ and $(2\text{-fur})_3P$, we observed rapid formation of spirocyclic lactone **2-141** formed by hydrolysis of the TIPS ether and spontaneous cyclization of the alcohol and ester moieties. We suspected that this reaction is actually catalyzed by trifluoroacetic acid generated by the reduction of $Pd(O_2CCF_3)_2$, and we repeated this reaction using CF_3CO_2H to perform the lactonization in 31% yield. This fourfold spirocycle (**2-141**) produced X-ray quality crystals on crystallization purified reaction mixture from Et_2O, allowing us to identify each diastereomer. The lactone we obtained represented the undesired diastereomer, with the vinyl iodide and alkene on opposite sides of the cyclopentenone moiety. As such it was incapable of undergoing cyclization, leaving the other diastereomer as the correct one.



Scheme 2.21. Assignment of stereochemistry of Claisen product **2-140** by X-ray crystallography of lactone **2-141**.

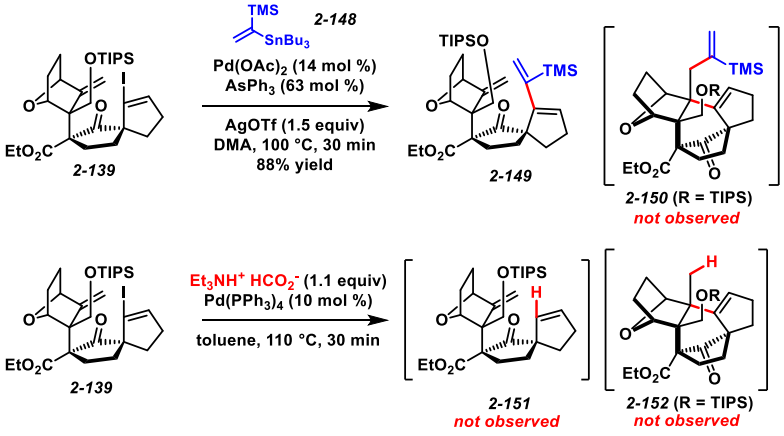
Having thus synthesized and identified the correct diastereomer of our cyclization precursor (**2-139**) we were in a position to more thoroughly consider the mechanistic particulars of our cascade cyclization-coupling reaction (Scheme 2.22). Like all Heck and cross-coupling reactions, this transformation can occur via either a neutral or

cationic pathway, with these two options differing in the number of covalent ligands attached to palladium. Since we were beginning with an alkenyl iodide (**2-139**), the oxidative addition in both pathways would create the same alkenylpalladium iodide (**2-142**). In the neutral pathway, the Pd center of this compound would go on to bind the alkene (not shown) and then undergo carbopalladation, the carbon-carbon bond forming step of the Heck reaction, to create cyclized product **2-145**. Neopentylpalladium compound **2-145** would then undergo coupling with alkenylmetal **2-143** to give the final product (**2-130**). In the cationic pathway, instead of alkenylpalladium iodide **2-142** undergoing direct binding and carbopalladation of its pendant alkene, it would first be subject to halide abstraction by an added silver or thallium salt of a nonbinding anion (*e.g.*, AgOTf). This would create cationic palladium species **2-146**, which would have an additional coordination site available and be much more readily able to bind the pendant alkene, a prerequisite for carbopalladation.[42] This feature of the cationic pathway should facilitate otherwise unfavorable cyclization events in the case that the reaction presents difficulties. The rest of the mechanism of the cationic pathway would follow along similar lines as the neutral one. We should note that both alkenylpalladium iodide **2-142** and alkenylpalladium cation **2-146** have the possibility of undergoing direct coupling with compound **2-143** to give cross-coupling product **2-144**. In theory, we could increase the relative rate of cyclization vs. direct coupling by increasing the dilution of the reaction mixture, thus disfavoring the bimolecular coupling step that would compete with our desired carbopalladation. With a mechanistic plan for this reaction in hand, we were positioned to put our plan into practice.



Scheme 2.22. Cationic and neutral mechanisms for the Pd catalyzed cascade reaction.

While the oxidative addition step of the mechanism appeared to present no problems to us, the crucial cyclization step was difficult. We began our studies of this reaction by exploiting the neutral pathway, but we quickly found that halide abstracting additives like AgOTf proved helpful. Our first isolated products from this work came from a direct Stille reaction to make coupled diene **2-149**,[68] presumably proceeding through cationic palladium intermediates due to the use of AgOTf. This reaction apparently bypassed the key carbopalladation/cyclization step to make our desired pentacycle (**2-150**). In an attempt to further simplify our reaction and test just the cyclization step, we decided to omit the cross coupling step. We could not perform a pure Heck reaction on our substrate, at least in the 7-*exo* sense that we desired, because the neopentylpalladium species (**2-145**, Scheme 2.22) lacks β-hydrogen atoms and thus cannot undergo the β-hydride elimination that frees the catalyst from the substrate. We therefore opted to perform a reductive Heck reaction, a transformation that is much more thoroughly precedented than one that would rely on a cross coupling of a neopentylpalladium species such as compound **2-145** or **2-147**.[42] Under several sets of conditions, this reaction gave neither alkene **2-151**, arising from direct reduction, nor the desired cyclized product (**2-152**). We took these results, along with those from the numerous other conditions we had tried (in excess of 100), to indicate that this cyclization reaction was impractical.



Scheme 2.23. Unsuccessful attempts at cyclization.

In order to move forward with our synthesis, we needed to analyze the reasons for the failure of our cyclization attempts in this system in order to engineer one that would be more likely to allow us to move past this

bottleneck. Our rationale for the failure of this system is based on the relative 'stiffness' of the central cyclopentanone moiety of alkenylpalladium iodide **2-142**, which needs to distort significantly in order to bring the palladium center and pendant olefin into the proximity required for cyclization (Figure 2.3). In addition to increasing torsional strain in the central cyclopentanone ring, these distortions also incur strongly repulsive *syn*-pentane type interactions. Thus we set out to design a system that would not rely on this spirocyclic tether and would hopefully be freer to allow the cyclization to occur.

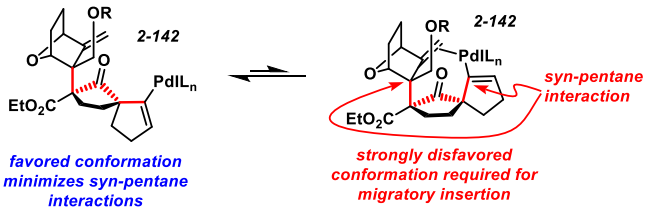
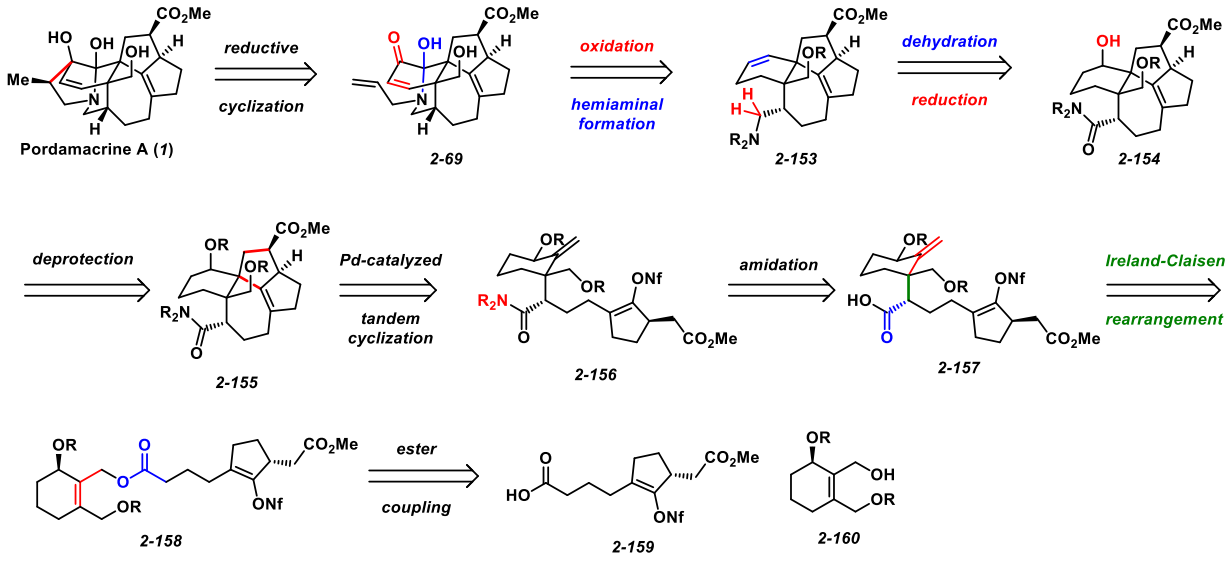


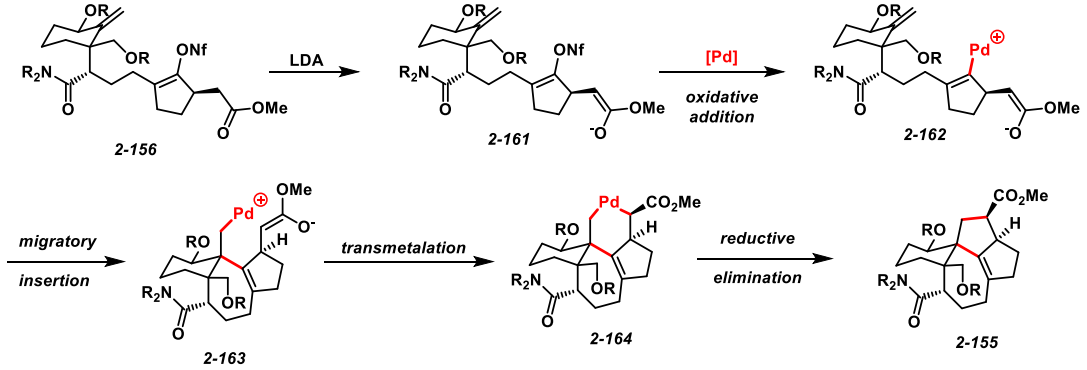
Figure 2.3. Rationale for failure of the cyclization reaction.

To this end, we designed a retrosynthesis that would not include intermediates with this type of spirocyclic tether (Scheme 2.24). The final steps of the synthesis would follow similar lines as before, ending with a reductive carbonyl-alkene cyclization. We would prepare the fully decorated cyclohexane ring of compound **2-69** by oxidations of an alkene containing precursor (**2-153**), along with a spontaneous hemiaminal formation to close the piperidine ring of the natural product. We would in turn install the alkene of compound **2-153** by a dehydration reaction of alcohol **2-154**, positioning us to make the disconnections corresponding to our key double cyclization event (*vide infra*). The precursor to the double cyclization (**2-156**) would be prepared by amidation of a carboxylic acid (**2-157**) that would arise from an Ireland-Claisen rearrangement of allyl ester **2-158**. The Ireland-Claisen precursor (**2-158**) would be straightforwardly be prepared by an ester coupling, bringing together two fragments (**2-159** and **2-160**) of the molecule that would contain all but three of the carbon atoms of the natural product.



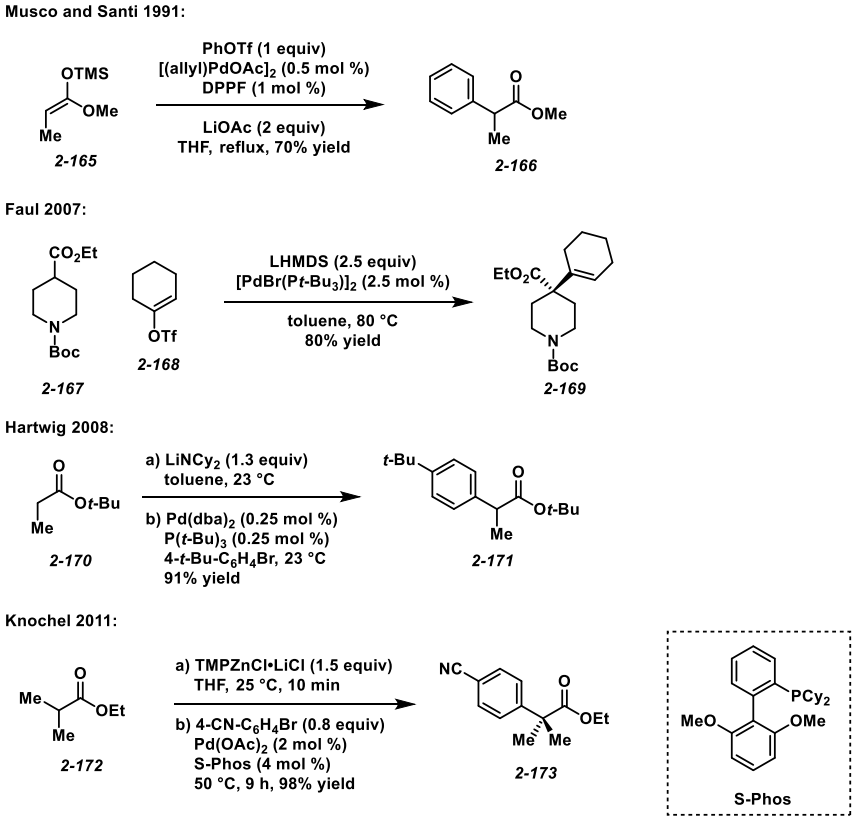
Scheme 2.24. Third generation retrosynthesis of pordamacrine A.

The key step in this synthesis would be a Pd-catalyzed double cyclization event (Scheme 2.25). The sequence would begin with deprotonation of the ester moiety of **2-156** to make enolate **2-161**. The alkenyl nonaflate of **2-161** would then undergo oxidative addition with catalytic Pd to make alkenylpalladium cation **2-162**. This palladium species would then undergo migratory insertion in a 7-*exo* fashion to close the seven-membered ring of **2-163**, similar to our previous retrosyntheses. The captive neopentylpalladium moiety of tricycle **2-163** would then undergo transmetalation with the pendant enolate to give palladacycle **2-164**, which would then reductively eliminate to generate the five-memered ring of the natural product in compound **2-155**.



Scheme 2.25. Mechanistic proposal for our planned key step.

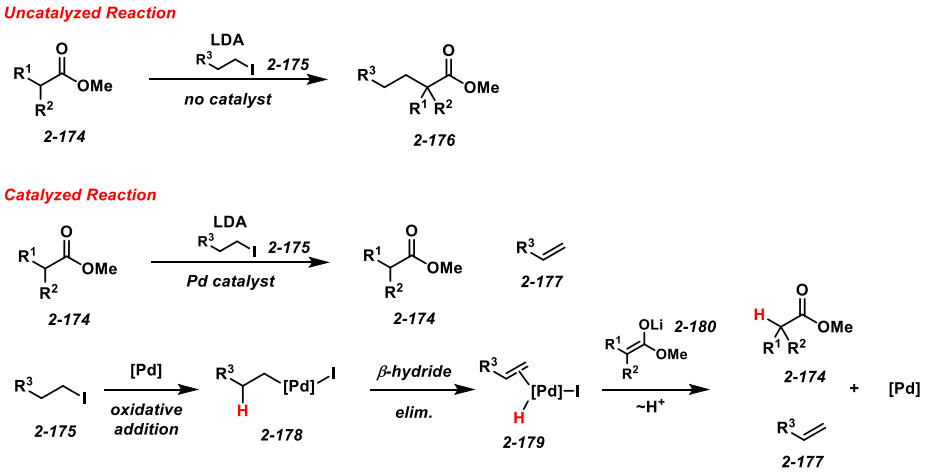
In addition to the solid precedent for the migratory insertion process in this cascade, there is a large body of research on the coupling of enolates to sp^2 electrophiles under the catalytic influence of palladium (Scheme 2.26).[69] The reaction occurs with a wide scope, and, among other examples, silyl ketene acetals have been coupled to aryl triflates (*e.g.*, **2-165 → 2-166**),[70] lithium ester enolates have been coupled to alkenyl triflates (*e.g.*, **2-167 → 2-169**)[71] and aryl halides (*e.g.*, **2-170 → 2-171**),[72] and zinc ester enolates have been coupled to aryl halides (*e.g.*, **2-172 → 2-173**).[73] Moreover, the catalyst system used in Hartwig's example[72] has also been used in Heck reactions,[74,75] demonstrating that this catalyst could be competent in both parts of the cascade sequence.



Scheme 2.26. Examples of Pd-catalyzed ester enolate arylation and vinylation.

However, while the coupling of enolates to sp^2 electrophiles is well precedented, the coupling of an enolate and an sp^3 carbon bound palladium is not.[76] The paucity of examples related to the use of sp^3 carbon electrophiles is likely due to two factors (Scheme 2.27): (1) sp^3 electrophiles are often competent in *un*catalyzed enolate alkylation reactions ("uncatalyzed reaction," **2-174 → 2-175**) and (2) sp^3 carbon bound palladium intermediates that would be

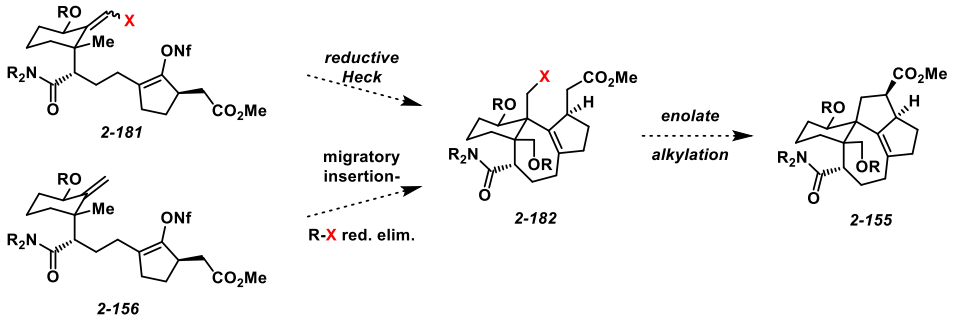
involved in catalyzed enolate coupling reactions could likely undergo β-hydride elimination (**2-178** → **2-179**) as a dominant side reaction, decreasing the efficiency of the coupling or stopping it altogether ("catalyzed reaction").



Scheme 2.27. Sp^3 electrophiles in catalyzed and uncatalyzed enolate alkylation reactions.

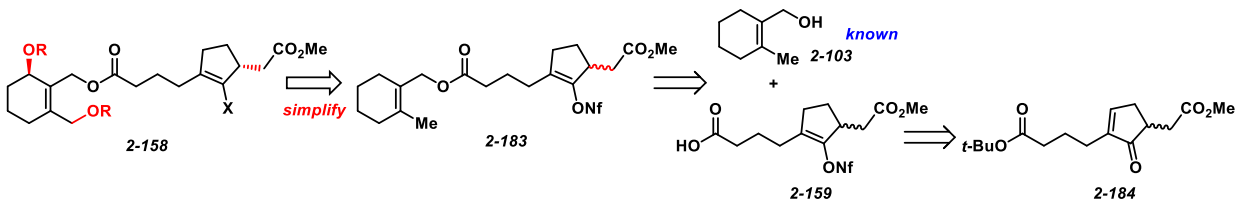
Neither of these two considerations applied to our situation. In our system, the possibility of using a traditional enolate alkylation reaction would be difficult to implement because this would require us to install a leaving group on the carbon to which palladium becomes bound in the migratory insertion step to ultimately give alkyl halide **2-182** (Scheme 2.28). The two methods of accomplishing this would both face significant challenges. One would be the prior installation of a leaving group on the *exo*-methylene moiety that participates in the migratory insertion reaction (compound **2-181**), followed by a reductive Heck reaction to give alkyl halide **2-182**, then an intramolecular enolate alkylation to give the cyclized product (**2-155**) in a separate step. We suspected that a leaving group installed on that carbon would create challenges during the Heck reaction from competitive oxidative addition. The other method would involve the use of a migratory insertion process with a non-halogenated alkene (**2-156**) followed by reductive elimination of R-X to generate the enolate alkylation electrophile (**2-182**). Except in the case of alkyl fluorides, which are not good electrophiles for enolate alkylation, reactions that feature reductive elimination of an alkyl(pseudo)halide from palladium are extremely rare,[77] so this possibility also seemed questionable. Even if one of these methods did succeed, we would face the challenge of conducting an enolate alkylation of a neopentyl electrophile (**2-182** → **2-155**). Though they are primary, neopentyl systems are known to undergo S_N2 reactions at exceptionally slow rates, slower than even *tert*-butyl.[78,79] Thus there would be several roadblocks to implementing this sequence in

a stepwise fashion. It is necessary to note that the neopentyl limitation of enolate alkylation would be overcome in our use of palladium catalysis, since the enolate addition reaction comprising the transmetalation step (**2-163** → **2-164**, Scheme 2.25) would occur at *palladium*, rather than at carbon, and should therefore represent a considerably easier substitution reaction.



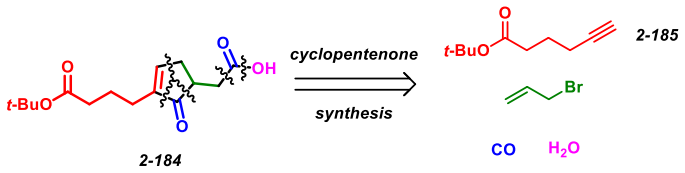
Scheme 2.28. Dubious possibilities for a stepwise version of our planned cascade reaction.

With the broad strokes of our synthetic plan penned, we set out to synthesize a suitable model system on which to test our key step. We decided to employ a system which had a simplified cyclohexene fragment and was also racemic, streamlining synthesis. We chose to use an alkenyl nonaflate, which could be prepared from a ketone and NfF via enolate chemistry, as the future electrophile in our palladium catalyzed cascade reaction. Compound **2-158** could be made by an ester coupling between known allylic alcohol **2-103** and acid **2-159**. This deceptively simple acid, however, would pose a challenge to synthesize. In order to make the tetrasubstituted enol nonaflate of **2-159**, we would need a way of regioselectively generating the required ketone enolate. Because both sides of such a ketone would be similarly substituted methine carbons, it would be unlikely that we could generate this enolate with the desired regiochemistry by simple deprotonation. After some deliberation, we decided upon the use of enone **2-184** as a precursor. The regiospecific generation of ketone enolates by reduction of enones with Li(*s*-Bu)$_3$BH[80] is known to work particularly well with cyclopentenone substrates,[81] where competing 1,2-reduction is suppressed almost entirely. Even using this method, we were wary of the feasibility of this reaction, since the enolate generated by reduction of enone **2-184** would have, in addition to the exogenous sulfonyl fluoride electrophile, two pendant esters that it could react with, both capable of undergoing particularly rapid 5-*exo*-cyclization.



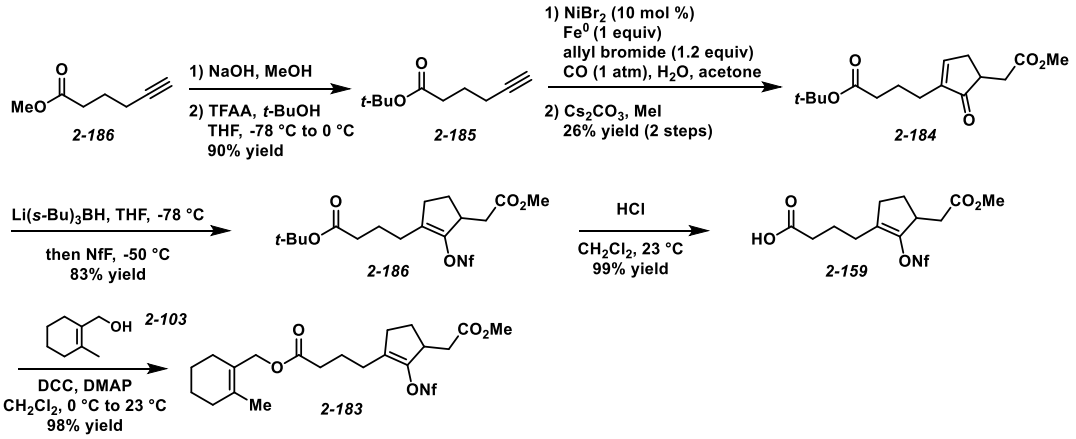
Scheme 2.29. Retrosynthetic simplifications for our model system.

We ultimately dismissed our doubts as overcautious, in no small part due to the simplicity of constructing what initially looks like a fairly elaborate cyclopentenone system via this method. Indeed, the carboxylic acid corresponding to this ester can be made in one step in a nickel and iron catalyzed multi-component coupling reaction of **2-185**, allyl bromide, CO, and H_2O (Scheme 2.30).[82]



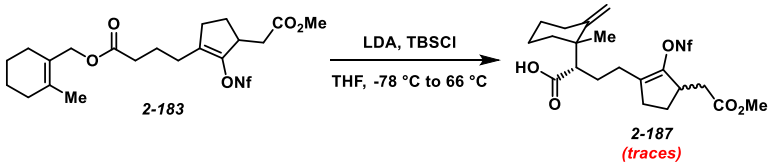
Scheme 2.30. Multicomponent cyclopentenone synthesis.

In the forward sense, the route to our Ireland-Claisen precursor worked just as planned. Straightforward synthesis of *tert*-butyl ester **2-185** from commercially available ynoic acid methyl ester **2-187** proceeded efficiently. The cyclopentenone synthesis, while giving a wide range of yields that seemed to be based both on the quality of the iron used and the speed of stirring, gave acceptable yields of our required diester (**2-184)** after alkylating the carboxylic acid reaction product with MeI and Cs_2CO_3. The reductive nonaflation of enone **2-184** proceeded reliably to give nonaflate **2-186**, and our fears about competing intramolecular reactions proved groundless. The transformation of the *tert*-butyl ester of **2-186** into acid **2-159** surprisingly did not work under the standard reaction conditions for this transformation, using CF_3CO_2H, but did proceed in essentially quantitative yield under the influence of gaseous HCl in CH_2Cl_2. Finally, DCC coupling of acid **2-159** with alcohol **2-103** under the catalytic influence of DMAP provided our desired allylic ester (**2-183**) as the substrate for our planned Ireland-Claisen rearrangement.



Scheme 2.31. Synthesis of the Ireland-Claisen precursor (**2-183**).

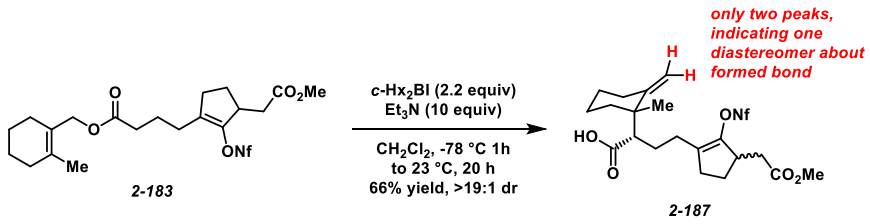
On attempting the proposed Ireland-Claisen rearrangement under the standard conditions (LDA, HMPA, TBSCl, -78 °C to 66 °C), we were disappointed with the results (Scheme 2.32). Only a small amount of our desired product (**2-187**) was formed, along with copious amounts of decomposition products. Because of the failure of the standard conditions, we looked into the use of a boron ketene acetal intermediate, rather than the much more common silyl ketene acetal. Because boron ketene acetals can be formed rapidly at -78 °C without the use of strong base,[83] they can demonstrate orthogonal functional group tolerance to the use of strong base requiring silyl ketene acetals or lithium ester enolates, through which the former are often generated. We were most intrigued by the use of *c*-Hx_2BI as a boron source, because the reported selectivity of enolization was very high and proceeded in nearly quantitative yields.[84]



Scheme 2.32. First attempts at an Ireland-Claisen rearrangement.

When we applied modified versions of these conditions to our substrate, adding 2.2 equiv of *c*-Hx_2BI (to enolize both esters) to a mixture of compound **2-183** and 10 equiv of Et_3N in CH_2Cl_2 at -78 °C, followed by warming the product to room temperature, we obtained a good yield of our desired Ireland-Claisen product (**2-187**, Scheme

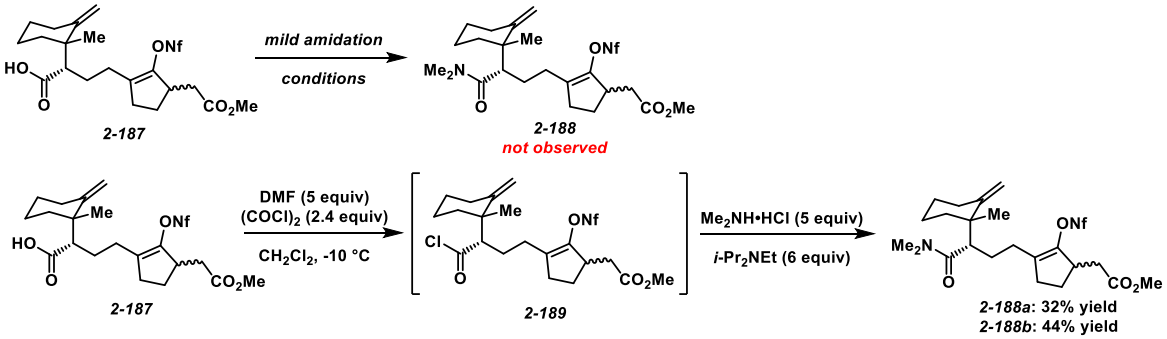
2.33). Importantly, only two diastereomers were formed, differing only in the orientation of their distal methyl acetate moieties, indicating that the rearrangement proceeded with complete diastereoselectivity. That these two products were not in fact epimeric at one of the newly created stereocenters was evident from interpretation of the ^{1}H NMR spectrum, which showed only one set of peaks corresponding to the alkene protons in the product. We would strongly expect that different epimers of the methane center α to the carboxylic acid moiety of the product should exhibit markedly different shifts for these protons in their respective ^{1}H NMR spectra. The configuration of this center was determined from the strong propensity of our enolization reagent, *c*-Hx$_2$BI, to generate (*Z*)-boron ketene acetals from esters bearing *n*-alkyl chain substituents. If the rearrangement proceeded through a chairlike transition state, which should *a priori* be favored based on inspection of 3D molecular models, then the relative stereochemistry about the formed bond would be as drawn. Further support for our stereochemical assignment came from NOESY data of the iodolactone derivative of a related product (Chapter 3).



Scheme 2.33. Boron Ireland-Claisen rearrangement.

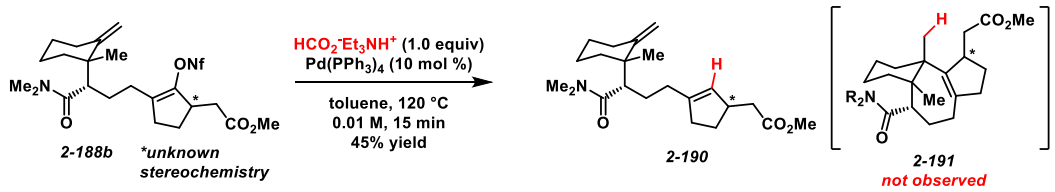
Having thus created the carbon skeleton of our cyclization cascade precursor, all that remained to do was transform the carboxylic acid moiety of **2-187** into an amide (**2-188**), installing a nitrogen atom in order to mimic more closely the system that would ultimately be carried on to the natural product. On our initial attempts at this transformation, we were worried about the possibility of epimerizing our newly created methane stereocenter, so we attempted several sets of amide coupling conditions that are reported to reduce the likelihood of epimerization. Under all of these conditions, however, we only recovered our starting acid, sometimes along with decomposed products. We reasoned that our target carbonyl group was likely unreactive due to the steric bulk surrounding it[85] and that activation of the acid with mild reagents gave intermediates that were inert amidation. However, when we prepared the acyl chloride **2-189** as an intermediate, a species that is very prone to epimerization but is also more reactive, we were indeed able to isolate our target amide (**2-188**) on treatment with this compound with dimethylamine. We were

initially disappointed with the results of this reaction because it gave two readily separable apparently diastereomeric products. We reasoned that this was likely due to extensive epimerization during the amidation step. However, an additional experiment suggested that this was not the case. During diazomethane esterification of this acid to give the methyl ester of carboxylic acid **2-187**, we also observed two separable products with nearly identical ^{1}H NMR spectra. Because this is a reaction that is extremely unlikely to give any α-epimerization, we reasoned that these 1,6-diastereomers were indeed separable, a very unexpected observation. This observation, coupled with the fact that the ^{1}H NMR spectra of the amidation products were nearly identical, suggested that the stereochemistry of this methane center had remained intact.



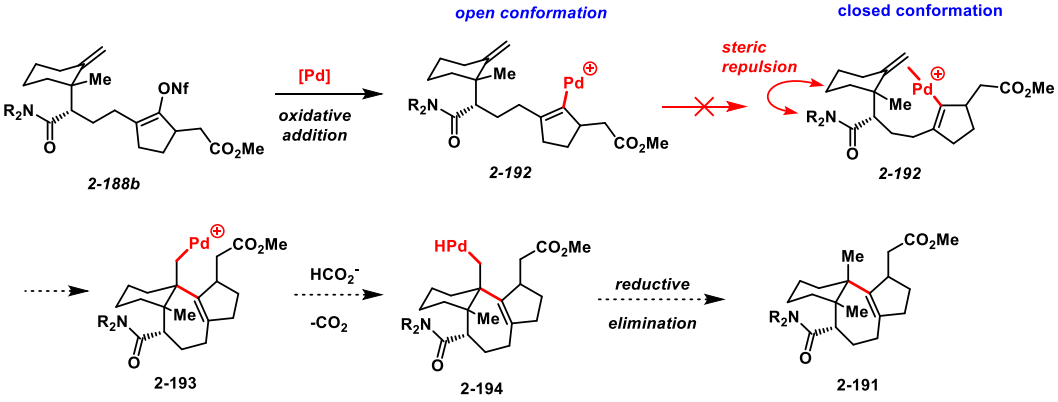
Scheme 2.34. Amidation of acid **2-187**.

With our cyclization precursor in hand, we were in a position to explore our crucial cyclization cascade reaction (Scheme 2.35). We wanted to test only the initial formation of the seven-membered ring at first because the inclusion of the second cyclization event would introduce a number of extra variables into the system, including the metal counterion for the enolate and how to generate it. Thus we attempted a simple reductive Heck reaction, which would serve as an indicator for the viability of the initial cycliziation event. Unfortunately, this system, like our spirocyclic one, gave only the product of simple reduction (**2-190**) and none of the cyclization product (**2-191**). Our attempts to use enolate coupling conditions to affect the overall reaction in spite of this result only returned starting material and products of decomposition.



Scheme 2.35. Simple reduction instead of reductive Heck cyclization.

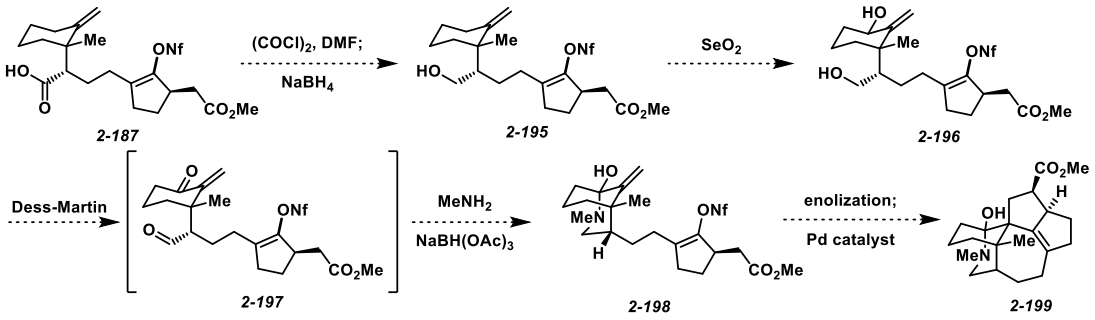
We looked to conformational analysis to justify the lack of desired reactivity in the system. The most likely culprit was a nonbonded interaction between the amide group and the cyclohexyl ring, which needs to be positioned directly over the former in the conformation (**2-192** "closed conformation") required for cyclization to occur. Because the steric bulk of an axial cyclohexyl group is extremely large, we propose a way of removing these severe steric interactions that were presumably to blame for the failure of our cyclization plan, allowing future workers to continue our work toward this crucial cyclization reaction.



Scheme 2.36. Rationale for the lack of cyclization.

The most straightforward way in which to remove this nonbonded interaction would be to tether the nitrogen of the amide to the carbon to which it will ultimately be attached in the natural product. To accomplish this, we would reduce the carboxylic acid of the Ireland-Claisen product (**2-187**) to primary alcohol **2-195**. This compound would then be treated with SeO_2 to give allylic alcohol **2-196**.[86–88] The resulting diol would be oxidized to 1,5-ketoaldehyde **2-197**, which would not be isolated but rather treated with $MeNH_2$ under reductive amination conditions to generate piperidine derivative **2-198**. This compound could no longer suffer repulsive nonbonded interactions as the two

potentially repelling centers would now be joined by a C-N-C linkage. Compound **2-198** would then be subjected to enolization conditions and treated with a Pd catalyst to induce the cascade cyclization reaction to form pentacycle **2-199**. If this reaction were successful, it would generate a compound (**2-199**) with all but one of the rings of the natural product and lack only two hydroxyl groups, essentially completing the model study. From this point, we would be well positioned to attempt the synthesis of the complete natural product by analogous methods.



Scheme 2.37. Future directions – creation of nitrogen tethered cascade cyclization substrate **2-198** and its cyclization.

Here we have described our studies toward the synthesis of Pordamacrine A. These efforts ultimately progressed through three conceptual iterations, all of which were stymied by the difficulty of synthesizing the central seven-membered ring of the natural product. However, we expect that further refinements based on what we have learned about this system in the work we have described could ultimately culminate in a concise synthesis of the natural product along the rough lines that we have drawn here. We have presented one such refinement here that would serve to solve the most likely problem preventing the cyclization in the systems we studied. While we were unable to complete the synthesis, our work did include the development of new methodology such as the AlI_3 promoted (pseudo)halide metathesis reaction as well as the refinement of existing methods such as the boron Ireland-Claisen reaction. We hope that these methods we have described here as well as our insights into this complex system will be of use to future synthetic chemists.

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(75) Contrary to the initial assertion that P*t*-Bu_3 complexes of Pd do not undergo oxidative addition to aryl or alkenyl triflates (ref 74), Faul's work (ref 71) on enolate coupling demonstrates that aryl and alkenyl sulfonates can be competent electrophiles in conjunction with this ligand.

(76) Enolate allylation, which generally proceeds through a different mechanism than would be expected for the coupling of enolates to non-allyl sp^3 electrophiles, presents a notable exception to this.

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Chapter 3. The Scope and Stereochemistry of the Boron Ireland-Claisen Rearrangement

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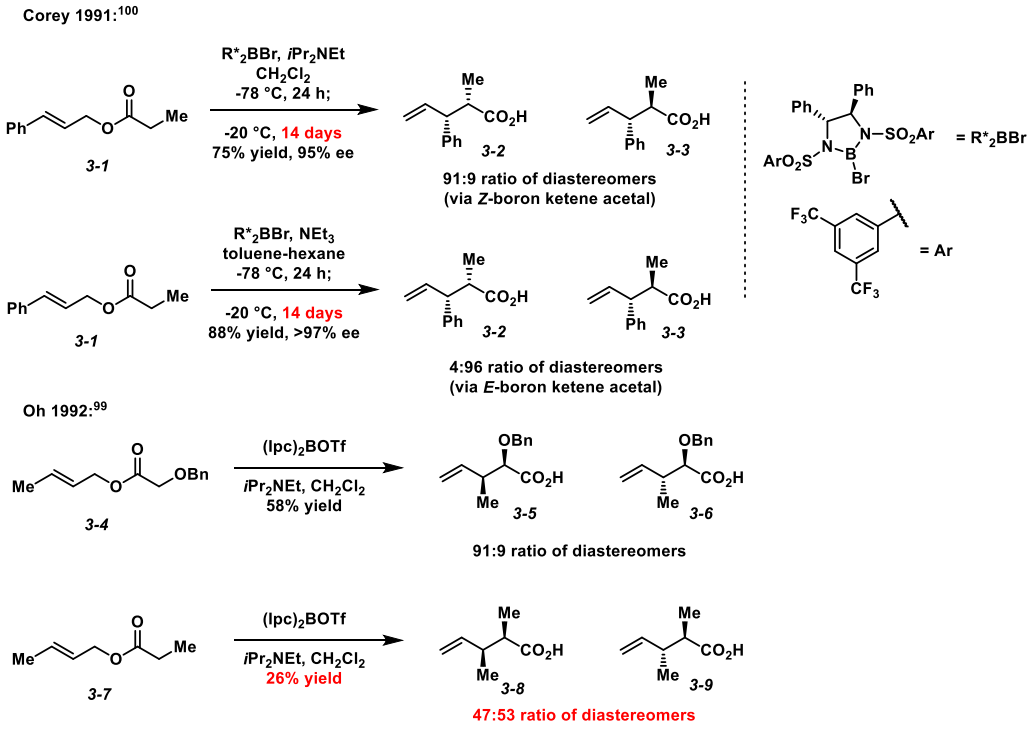
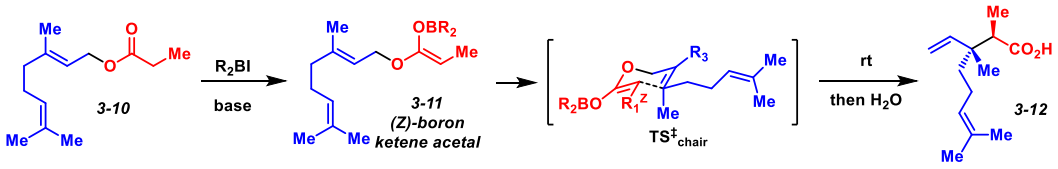
The Ireland–Claisen rearrangement is a transformation of fundamental importance in organic synthesis.[89–92] It has been used in numerous total syntheses, oftentimes as a key step.[93–96] Its power stems both from its generality and its predictable stereoselectivity, a consequence of its preference for proceeding through a chairlike transition state. The initially developed method of conducting the rearrangement involves enolization of the ester substrate with a strong base, such as lithium diisopropylamide (LDA), followed by trapping with a silyl chloride to give a silyl ketene acetal. The latter is then heated without isolation to effect rearrangement. Later efforts have explored alternative methods of generating silyl ketene acetals.[97] Although a limited body of work emerged in the early 1990s demonstrating the viability of phosphorus[98] and boron[99,100] ketene acetals (Scheme 3.1) in this rearrangement, the majority of reports has continued to focus on silicon. Alternative protocols for conducting this rearrangement may have unique attractive attributes, and the low required temperatures and high stereoselectivity observed in the rearrangements using boron especially piqued our interest. With this motivation in mind, we set to further explore the Ireland–Claisen rearrangement of boron ketene acetals. Through our studies, we have found that the soft enolization reagent combination of dicyclohexyliodoborane (Cy_2BI)·Et_3N is effective at promoting this rearrangement, and an array of allylic esters can be converted to γ,δ-unsaturated acids in good yields and excellent diastereoselectivities. We also demonstrate a detailed analysis of the transformation, illustrating important structural considerations that can govern this process.



Scheme 3.1. Previous work using boron reagents to promote the Ireland-Claisen rearrangement.

Although many amine-boron Lewis acid pairs are known to generate boron enolates from ketones, few of these are able to form boron ketene acetals from esters.[101] To undergo enolization, esters require more reactive boron Lewis acids along with a tertiary amine of intermediate steric demand. Too small amines form tight adducts with the boron reagent, while too hindered ones fail presumably due to their inability to deprotonate the borane–ester complex. With the very reactive boron iodides, there is also the possibility of ester cleavage promoted by the nucleophilic iodide counterion.

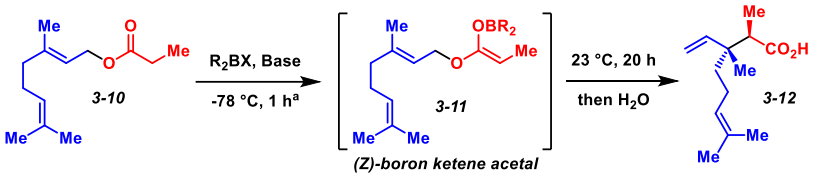
Of the reagent pairs we screened for promoting the rearrangement of geranyl propionate (**3-10**), we found $Cy_2BI \cdot Et_3N$ was the most efficient, producing a 6:1 mixture of diastereomers in 81 % yield (entry 1, Table 3.1). The major diastereomer is consistent with the intermediacy of the expected (*Z*)-boron ketene acetal (Scheme 3.1).[102] The relative inefficiency of $Cy_2BOTf \cdot Et_3N$ and $(c\text{-}C_5H_9)_2BOTf \cdot iPr_2NEt$ came as a surprise, since both pairs have been shown to achieve near quantitative enolization of propionate esters (entries 2 and 3).[103–106] The reagents $n\text{-}Bu_2BOTf$ and $(Ipc)_2BOTf$ (entries 4 and 5) used in Oh's work[99] also gave poor results when applied to geranyl propionate. Here, all reagents gave major products consistent with the rearrangement proceeding through a chairlike transition state from (*Z*)-boron ketene acetal **3-13**.



Scheme 3.2. Stereoselectivity of rearrangement of geranyl propionate.

To further optimize the reaction we evaluated a number of other variables. Using an excess of base proved beneficial to stereoselectivity. Triethylamine and diisopropylethylamine worked equally well when used in excess (entries 6 and 7); with other bases, including the strongly basic pentaisopropylguanidine (entry 8) used successfully by Corey,[109] we observed reduced yields. Methylene chloride proved to be the optimal solvent in terms of yield; less polar solvents, like toluene and CCl_4, gave higher diastereoselectivity but at the cost of considerable overall efficiency. Like in entries 2 and 3, the conditions in entry 11 were less effective, despite their prior use wherein they afforded quantitative yields of enolization products.[104] Finally, room temperature proved to be the optimal temperature at which to conduct the rearrangement, with both higher and lower temperatures giving lower yields. These reactions suffered mainly from lower conversion, suggesting that boron ketene acetals are slowly quenched[110] in competition with rearrangement. These experiments imply that successful rearrangement requires more than efficient formation of the boron ketene acetal intermediate, as several sets of conditions shown to effect ester enolization in >95 % yield fared poorly in our optimization study.

Table 3.1. Optimization Studies

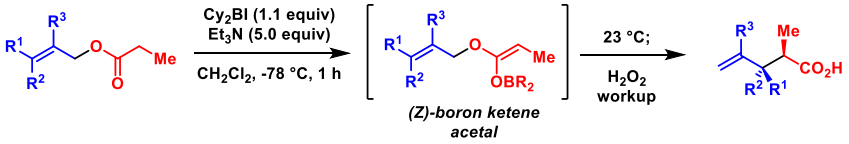


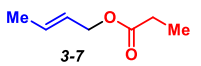
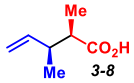
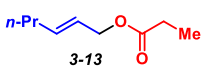
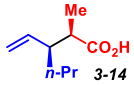
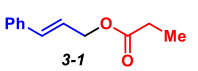
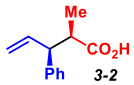
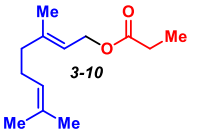
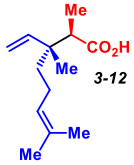
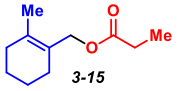
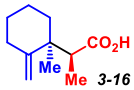
Entry	R_2BX (equiv)	Base (equiv)	Solvent	Yield (%)	dr
1	Cy_2BI (1.1)	Et_3N (1.2)	CH_2Cl_2	81	6.0:1
2	Cy_2BOTf (2.0)	Et_3N (2.5)	CH_2Cl_2	52	5.3:1
3	$(c\text{-}C_5H_9)_2BOTf$ (2.0)	*i*-Pr_2NEt (2.5)	CH_2Cl_2	44	1.9:1
4	*n*-Bu_2BOTf (1.3)	Et_3N (2.0)	CH_2Cl_2	<2	-
5	$(Ipc)_2BOTf$ (1.3)	*i*-Pr_2NEt (2.0)	CH_2Cl_2	19	1.9:1
6	Cy_2BI (1.1)	Et_3N (5.0)	CH_2Cl_2	79	14:1
7	Cy_2BI (1.1)	*i*-Pr_2NEt (5.0)	CH_2Cl_2	80	13:1
8	Cy_2BI (1.1)	PIG[b] (1.2)	CH_2Cl_2	69	17:1
9	Cy_2BI (1.1)	Et_3N (5.0)	toluene	62	23:1
10	Cy_2BI (1.1)	Et_3N (5.0)	Et_2O	51	22:1
11[c]	Cy_2BI (1.1)	Et_3N (1.03)	CCl_4	22	>49:1
12	Cy_2BI (1.1)	Et_3N (5.0)	hexanes	55	20:1
13	Cy_2BI (1.1)	*i*-Pr_2NEt (5.0)	CH_2Cl_2	43[d]	26:1
14	Cy_2BI (1.1)	Et_3N (5.0)	CH_2Cl_2	68[e]	12:1

[a]Borane was added to a solution of **3-10**, base, and 4,4-di-*t*-butylbiphenyl (internal standard) at -78 °C. The resulting solution was stirred 1 h at this temperature then allowed to warm to ambient temperature and stirred 20 h. Yield and d.r. were obtained by ^1H NMR analysis of the crude reaction mixture after aqueous workup (no oxidation). [b]PIG: pentaisopropylguanidine. [c]Compound 1 was added to a solution of base and Cy_2BI at 0 °C according to Brown's procedure.[ref] [d]Rearrangement at -10 °C for 24 h followed by warming to ambient temperature. [e]Rearrangement at 40 °C.

Having found an optimal set of conditions, we examined a range of substrates to probe whether or not the concept of soft enolization could be applied more generally to the Ireland–Claisen rearrangement (Table 3.2). We were particularly curious as to whether easily ionized (or cleaved) allylic esters would be compatible with the strongly Lewis acidic iodoborane. We were pleased to observe that, under our optimized conditions, even those esters that would be expected to form particularly stable carbocations (e.g., **3-1**, **3-10**, and **3-15**) participated efficiently in the rearrangement. We observed high levels of stereoselectivity, particularly with increased substitution on the alkene. The reason for the lower selectivity for the less-substituted alkene esters is not clear, but it likely stems at least partly from a smaller relative preference for a chairlike transition state over a boatlike one engendered by the low steric demand of the allylic fragment (*vide infra*).

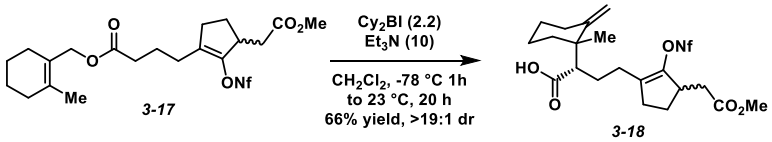
Table 3.2. Rearrangement of propionates via (*Z*)-boron ketene acetals.



Entry	Substrate	Product	Yield (%)[a]	dr[b] (*syn*:*anti*)	time
1	 *3-7*	 *3-8*	(82)[c]	83:17	2 h
2	 *3-13*	 *3-14*	58(60)	83:17	24 h
3	 *3-1*	 *3-2*	78(92)	83:17	2 h
4	 *3-10*	 *3-12*	74(79)	93:7	20 h
5	 *3-15*	 *3-16*	68(92)	>98:2	20 h

[a]Isolated; NMR yields after workup and oxidation of the crude reaction mixture using a suitable internal standard are in parentheses. [b]Diastereoselectivity measured by ^{1}H NMR spectroscopy. [c]Not isolated, assayed as the methyl ester.

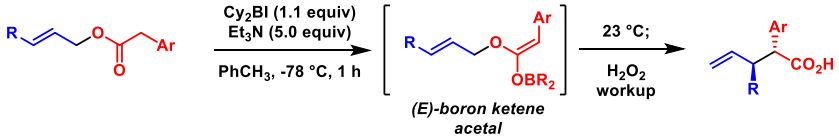
Also notable is the example from our previous synthetic efforts toward pordamacrine A discussed in Chapter 2 that spurred on this research (Scheme 3.2). This substrate (**3-17**) contains a methyl ester that is not involved in the rearrangement and does not appear to interfere with the reaction, as evidenced by the similarity in yields between this example and that of entry 5 in the previous table. It is also notable that the rearrangement proceeds with complete diastereoselectivity to give acid **3-18**.

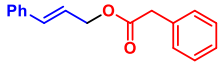
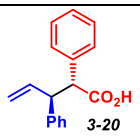
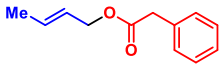
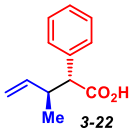
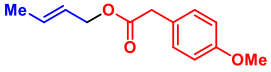
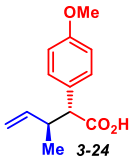
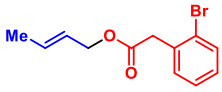
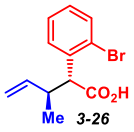
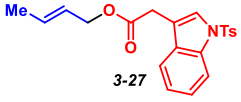
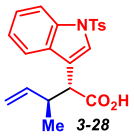


Scheme 3.2. Boron Ireland-Claisen rearrangement of a complex substrate.

Whereas *n*-alkyl esters rearrange via a (*Z*)-boron ketene acetal, arylacetates rearrange via the (*E*)-boron ketene acetal (Table 3.3). Possibly due to the extended conjugation of the phenyl-substituted boron ketene acetal, these rearrangements are overall faster than those of *n*-alkyl esters, with that of cinnamyl phenylacetate (**3-19**) complete within 10 min at room temperature. We found that toluene was a more effective solvent than methylene chloride in these reactions in terms of stereoselectivity. The rearrangement tolerated a variety of aryl groups, including a protected indole moiety (compound **3-27**), and all of the rearrangements of arylacetate esters of (*E*)-disubstituted allylic alcohols gave high diastereoselectivity.

Table 3.3. Rearrangement of arylacetates via (*E*)-boron ketene acetals.

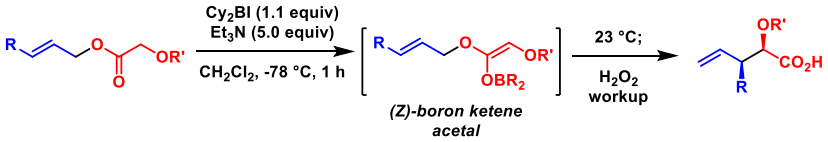


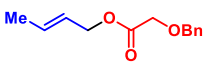
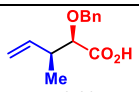
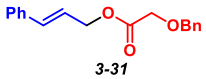
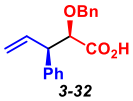
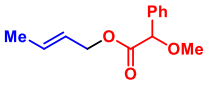
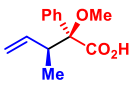
Entry	Substrate	Product	Yield (%)[a]	dr[b] (anti:syn)	time
1	 *3-19*	 *3-20*	83(89)[c]	96:4	10 min
2			(95)[d]	91:9	10 min
3	 *3-21*	 *3-22*	79(80)	97:3	2 h
4	 *3-23*	 *3-24*	80(82)	98:2	30 min
5	 *3-25*	 *3-26*	74	93:7	45 min
6	 *3-27*	 *3-28*	84	94:6	24 h

[a]Isolated; NMR yields after workup and oxidation of the crude reaction mixture using a suitable internal standard are in parentheses. [b]Diastereoselectivity measured by ^{1}H NMR spectroscopy. [c]Isolated as the methyl ester. [d]Reaction performed in CH_2Cl_2.

Having demonstrated the efficacy of the reaction with simple alkyl esters, we were curious if it could be extended to α-alkoxy substituted esters (Table 3.4). Gratifyingly, these gave comparable yields to our previous substrates along with high stereoselectivities. The major diastereomer in these reactions is consistent with a (*Z*)-boron ketene acetal rearranging through a chairlike transition state. The success of these substrates along with those of the arylacetates shows that alkoxy and nonbasic nitrogen substituents are tolerated in this reaction. Based on all of the above observations, the relative stereochemistry presumably originates via a highly preferred chairlike transition state (Scheme 3.3).

Table 3.4. Rearrangement of α-oxygenated esters via (*Z*)-boron ketene acetals.



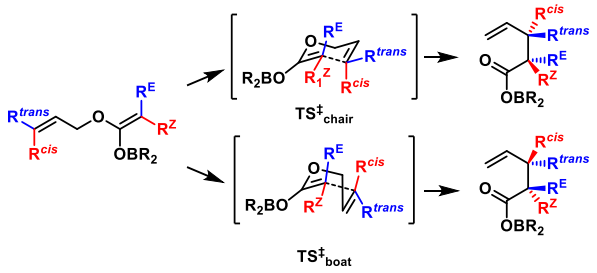
Entry	Substrate	Product	Yield (%)[a]	dr[b] (*syn*:*anti*)	time
1	 *3-29*	 *3-30*	71(79)	>98:2	20 min
2	 *3-31*	 *3-32*	74	98:2	30 min
3	 *3-33*	 *3-34*	55	>98:2	5 min

[a]Isolated; NMR yields after workup and oxidation of the crude reaction mixture using a suitable internal standard are in parentheses. [b]Diastereoselectivity measured by ^{1}H NMR spectroscopy.

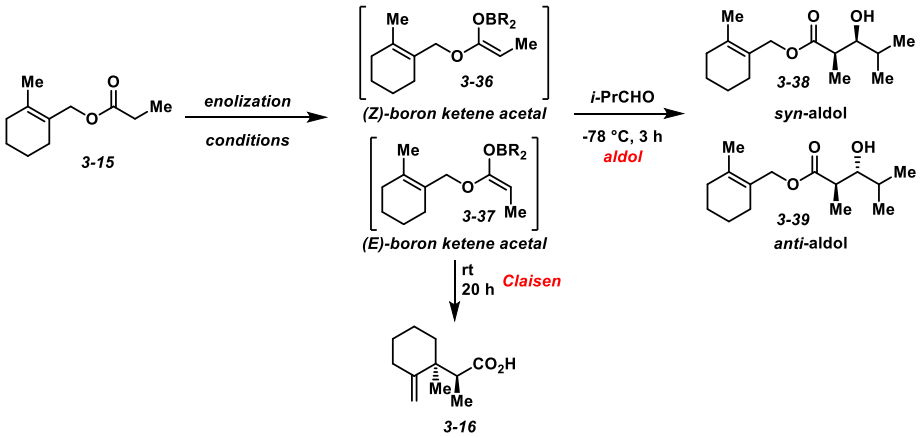
Having examined the scope of this reaction, we turned our attention to a more detailed analysis of this diastereoselectivity. Because of the nearly perfect stereospecificity of the aldol reaction with boron enolates[101] and the difficulty of directly assaying the *Z*/*E* ratio of boron ketene acetals by NMR spectroscopy, the former is the method of choice in determining the geometric purity of these intermediates. When we subjected propionate **3-15** to our standard enolization conditions (CH_2Cl_2, −78 °C, 1 h) and trapped the resulting boron ketene acetal with isobutyraldehyde, we observed a 94:6 mixture of *syn*/*anti* aldol products (**3-38** and **3-39**) in 55 % yield (conditions A),[111] indicating an approximately 94:6 mixture of *Z*/*E* boron ketene acetals (**3-36** and **3-37**, Scheme 3.4). Although

the yield of the aldol reaction is low, it is notable that the crude product did not contain any starting material by ^{1}H NMR spectroscopy, suggesting that enolization was complete within 1 h at −78 °C.

With this result in mind, the rearrangement of propionate **3-19** (Table 3.2, entry 5) is somewhat anomalous. This product forms as a >98:2 mixture of diastereomers,[112] a larger ratio than that of the intermediate boron ketene acetals. There are two possible explanations for this outcome (Scheme 3.5). In Scenario A, the (*Z*)-boron ketene acetal could selectively rearrange through a chairlike transition state and the *(E)-isomer* rearrange selectively through a boatlike transition state, converging to the same diastereomeric acid. This behavior has been observed[113] and can serve to relieve substantial nonbonded interactions present in the competing transition state.[115] In this case, however, a boatlike transition state for the rearrangement of the (*E*)-boron ketene acetal of **3-15** would be significantly hindered due to the fact that it requires the close approach of two methyl groups in an eclipsed butane conformation about the forming bond. This makes it unlikely that preferential rearrangement of the *(E)-isomer* through this alternative transition state topology is the operative process to account for the observed stereoselectivity.

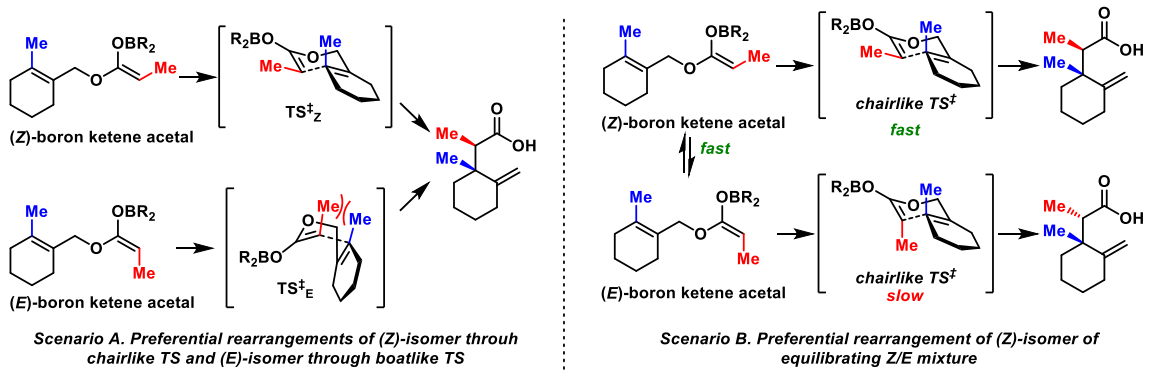


Scheme 3.3. Stereochemistry of the Ireland-Claisen rearrangement of boron ketene acetals.



Enolization conditions	Yield of aldol	*syn*:*anti* of aldol	Claisen Yield	dr of Claisen
A: Cy_2BI (1.1 equiv), Et_3N (5.0 equiv), CH_2Cl_2, -78 °C, 1 h.	55%	96:4	92%	>98:2
B: Cy_2BOTf (1.7 equiv), Et_3N (2.5 equiv), CH_2Cl_2, -78 °C, 1 h.	81%	50:50	80%	97:3

Scheme 3.4. Enolization stereoselectivity via a standard aldol reaction.

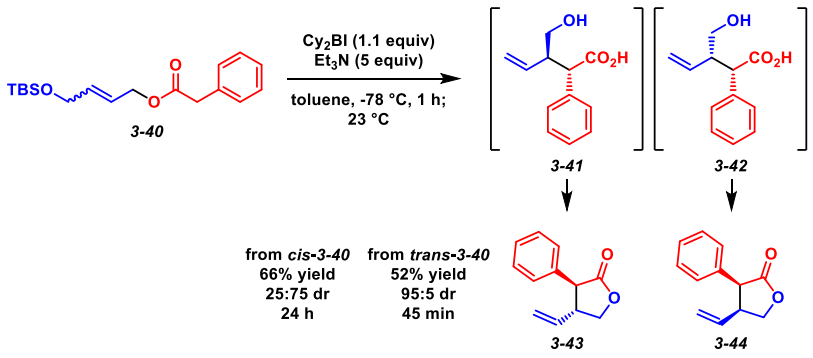


Scheme 3.5. Rationales for the diastereoselectivity of the rearrangement of ester **3-15**.

We favor another explanation. The boron ketene acetal intermediate could undergo *Z*/*E* equilibration at the temperature required for the rearrangement with the (*Z*)-boron ketene acetal rearranging much more quickly than the *(E)-isomer* (Scheme 3.5, Scenario B). In this scenario, the reaction operates under Curtin–Hammett type dynamics,[117] requiring that the intermediate undergo *Z*/*E* isomerization. Although this isomerization is generally not considered to occur with silyl ketene acetals under the conditions used to effect rearrangement,[118] such isomerization has been observed with boron ketene acetals.[120,121] In this case, the product ratio of the reaction is determined by the relative energies of the competing transition states, and the isomeric ratio of the boron ketene acetal intermediate is relatively inconsequential.

To further probe this issue, we performed a second comparison of aldol and Ireland–Claisen diastereoselectivities (Scheme 3.4, conditions B). With appropriate propionate substrates it is known that $Cy_2BOTf{\cdot}Et_3N$ favors the formation of the (*E*)-boron ketene acetal.[123] When we conducted enolization of ester **9** with this reagent pair followed by trapping with isobutyraldehyde under conditions identical to those above, we obtained a 50:50 mixture of *syn*/*anti* diastereomers of the aldol adduct in a combined NMR yield of 81 %. When we allowed the boron ketene acetal formed under these conditions to warm to ambient temperature to effect the rearrangement, we again observed almost complete selectivity for the formation of one diastereomer of acid **3-16**, just as we had with Cy_2BI. This represents an even more dramatic example of funneling diastereomeric intermediates to one diastereomer of a product and implies that both the isomerization and the rearrangement of the (*Z*)-boron ketene acetal must be faster than the rearrangement of the (*E*)-isomer.[124] The results of these experiments underscore the fact that the diastereoselectivity of the rearrangement is not necessarily dependent on the geometric selectivity of the enolization event.

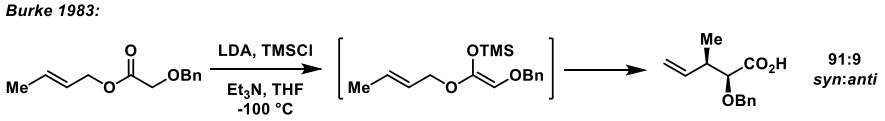
Scheme 3.6 illustrates two rearrangements consistent with this explanation. In this case, the phenylacetate ester initially undergoes an (*E*)-selective enolization.[101] When the allylic fragment contains a *cis* olefin, R^E and R^{cis} (Scheme 3.6) must both be axial in a chairlike transition state. Once again, a boatlike transition state is disfavored due to the close approach of R^1 and R^2 in this topology. This rearrangement should occur more slowly than one in which the two substituents around the forming bond need not both be axial, and we indeed observe this, with the rearrangement of *cis*-**3-40** requiring 24 h at room temperature to reach full conversion and that of *trans*-**3-40** requiring only 45 min. The long reaction time of the former implies that for a *cis* olefin the enolate isomerization is kinetically competitive with the rearrangement. This leads to a significant amount of product being formed through rearrangement of the (*Z*)-boron ketene acetal, which is not initially formed in significant amounts through enolization.



Scheme 3.6. Lactonization of a TBS ether containing substrate.

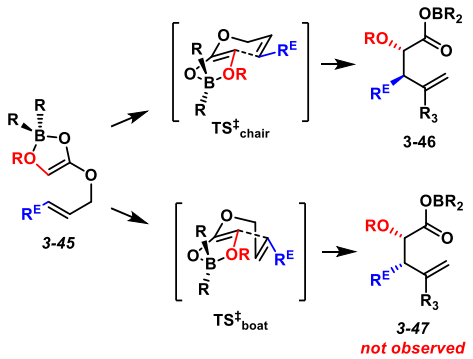
This rationale, however, does not appear to fully explain the fact that propionates rearrange with observed lower stereoselectivity than those with an α-oxygenated group. Both give products with the same relative configuration, but α-oxygenated esters rearrange with approximately tenfold greater selectivity than their α-methyl equivalents. For example, crotyl propionate (**3-7**) rearranges to give an 83:17 mixture of diastereomers (Table 3.2, entry 1), whereas crotyl benzyloxyacetate (**3-29**) rearranges to give a >98:2 mixture (Table 3.4, entry 1). This difference could be due to the lack of boron ketene acetal isomerization because of complexation to the α-ether moiety, but this alone does not guarantee formation of a single product diastereomer because of the potential operation of paths leading through both chair and boat transition states.

Burke has demonstrated that silyl ketene acetals of *O*-benzylglycolates rearrange to give a 91:9 mixture of diastereomers (Scheme 3.7).[125] Since the enolization of these esters is geometrically controlled by chelation, giving exclusively the (*Z*)-isomer, this work suggests that silyl ketene acetals of these substrates prefer to rearrange through chair versus boat transition states in an equivalent ratio of 91:9, respectively. The ratios obtained here should be similar in magnitude to those obtained by Burke if the stereoselectivity is governed by a similar chair/boat preference as it is with silyl ketene acetals.[126]



Scheme 3.7. Benchmark results for differences in the stereoselectivity of the silicon Ireland-Claisen rearrangement between propionates and α-alkoxyacetates.

We attribute the observed difference in stereoselectivity between propionates and glycolates to the formation of a boron chelate (**3-45**) that changes the steric properties of the boron ketene acetal (Scheme 3.8). This rigid structure causes a change in boron's geometry from trigonal planar to tetrahedral, locking its alkyl substituents into positions relatively close to the bond-forming centers. This change would not cause a significant increase in nonbonded interactions in the more extended chair transition state but would result in severe steric repulsions between the boron alkyl groups and R^{trans} of the allylic fragment in the more compact boat transition state, thus disfavoring the latter.



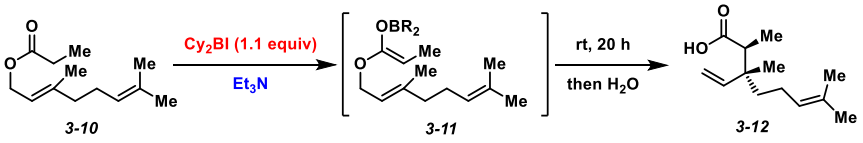
Scheme 3.8. Stereochemistry of the Ireland-Claisen rearrangement of chelate boron ketene acetals.

During the course of our optimization studies, we observed some curious results that, while failing to improve upon our best conditions, shed some additional light on the nature of the soft enolization reaction. Abiko and Masamune's work with Cy_2BOTf revealed a considerable dependence of the order of addition of base, ester, and borane on enolization efficiency.[104] In their case, mixing base and borane prior to addition of the ester substrate led to a time-dependent deactivation of the borane—longer premixing times gave especially poor results. They favored adding borane to a solution of ester and base with Cy_2BOTf and base to borane and ester with Bu_2BOTf. These respective modes of addition gave >95 % yields of boron ketene acetals. These results are in contrast to Ganesan and Brown's experiments using Cy_2BI,[101] where most of the work was conducted by mixing equimolar amounts of borane and triethylamine prior to addition of the ester. Using this procedure, they obtained nearly quantitative yields of boron ketene acetals. Thus, each mode of addition of the three reagents had been used successfully in the past.

In our own work, the three possible modes of addition gave very different results (Table 3.5). Most of the optimization studies (see Table 3.1) were conducted by adding borane last, and this procedure ultimately gave the highest yields (Table 3.5, entry 1). When borane was premixed with excess base in CH_2Cl_2 at 0 °C prior to addition of ester **3-10** at −78 °C, we obtained low conversion and no detectable product (entry 2). When borane and ester **3-10** were mixed at −78 °C prior to addition of base (entry 3), we again saw decreased yields along with apparent decomposition products that we had not observed in our best procedure. To further understand this result, we repeated the process in a separate experiment at −40 °C in $CDCl_3$ to allow us to observe the reaction mixture by ^1H NMR spectroscopy directly. Here, we added Cy_2BI to the solution of ester **3-10** at −40 °C and stirred for 120 s before adding Et_3N, and the ester was consumed almost immediately. Upon warming to ambient temperature, we observed geranyl iodide, which had presumably been formed by iodide cleavage of the ester prior to amine addition. It seems that this

cleavage reaction is suppressed somewhat at −78 °C but is extremely rapid at −40 °C. It is important to note we obtained very clean crude reaction mixtures using our favored mode of addition, with the sum of product and recovered starting material yields almost always 85–90 %, indicating that ester cleavage is not an important side-reaction under these conditions. Apparently, the coexistence of base in the reaction mixture is very important to direct the reaction manifold from cleavage to enolization.

Table 3.5. Effect of mode of reagent addition.



3-10 *3-11* *3-12*

Entry	Order of Addition[a]	Et_3N equiv	Solvent	Conv. (%)	Yield (%)	dr
1[b]	A: ester; base; borane	5.0	CH_2Cl_2	90	79	14:1
2	B: borane; base; ester	20	CH_2Cl_2	17	<2	-
3	C: ester; borane; base	5.0	CH_2Cl_2	74	45	21:1

[a] Order of addition: A: Cy_2BI added to solution of ester **3-10** and Et_3N at -78 °C and stirred 1 h before warming to ambient temperature and stirring 20 h. B: Cy_2BI and Et_3N mixed at 0 °C 5 min before cooling to -78 °C and adding ester **3-10**. The mixture was then stirred 1 h before warming to ambient temperature and stirring 20 h. C: Cy_2BI was added to solution of ester **3-10** at -78 °C and stirred 5 min before adding Et_3N and stirring 1 h. The mixture was then warmed to ambient temperature and stirred 20 h. [b] Identical to Table 3.1 1, entry 6.

Notably, there were a few classes of substrates that failed to give any detectable rearrangement (Figure 3.1). Although *n*-alkylacetates, arylacetates, and α-heteroatom-substituted esters rearranged smoothly, isopropylacetates and *tert*-butylacetates failed to rearrange, instead decomposing slowly at slightly elevated temperatures over long reaction times. We believe this is due to increased steric hindrance around the bond-forming centers. Strangely, acetates also failed to rearrange (*vide infra*). Secondary alcohols appeared to survive the enolization conditions but did not give rearrangement products, even with prolonged heating. These results are noteworthy considering that all of these substrates have been shown to undergo enolization, notwithstanding the anomalous behavior of acetates, and all of these types of silyl ketene acetals do undergo rearrangement.[92]

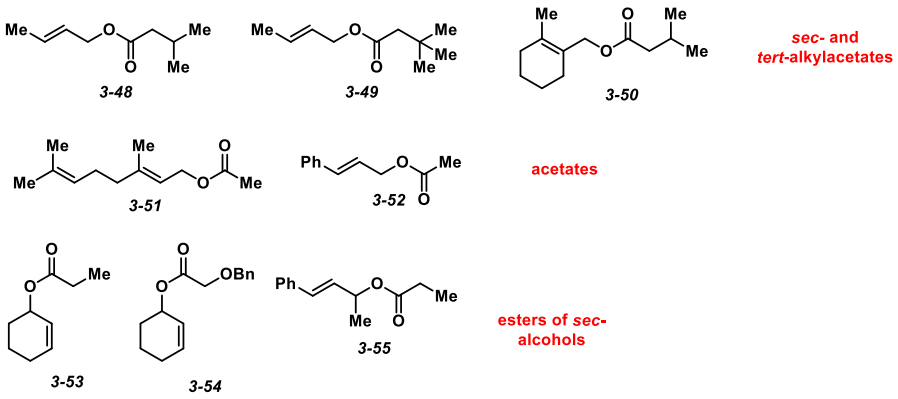
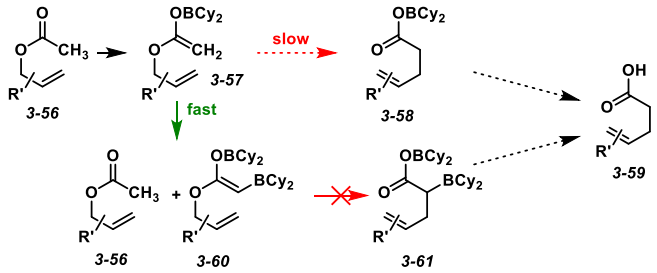


Figure 3.1. Esters that do not undergo rearrangement.

Our rationale for the fact that acetates do not rearrange is based on others' observations in soft enolization in relation to aldol chemistry. Abiko, Masamune, and co-workers have shown that acetates are *C,O*-diborylated under enolization conditions,[128,129] and we hypothesize that the α-boryl substituent plays a similar steric role as that of a branched alkyl group (Scheme 3.9), and thus diborylated ester **3-60** is unable to rearrange to α-borylacyloxyborane **3-61**. The lack of monoborylated ester **3-57** in the reaction mixture can be due to either the second borylation occurring more quickly than the first or an essentially irreversible disproportionation of two molecules of compound **3-57** to diborylated ester **3-60** and starting material (**3-56**). Because there is no obvious reason why monoborylated acetate **3-57** should behave any differently in the rearrangement in the absence of diborylation pathways, we believe that it must not exist in the reaction mixture in any significant concentration at temperatures at which the rearrangement takes place.



Scheme 3.9. Rationale for the unreactivity of acetates.

Overall, our results suggest that the Ireland–Claisen rearrangement of boron ketene acetals holds promise as a synthetically applicable method. The nonbasic nature of the conditions for promoting ketene acetal formation, as well as the generally high levels of observed stereoselectivity, suggest that it should prove to be a viable alternative to existing methods of promoting this useful rearrangement.

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(91) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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(100) Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.

(101) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 2336.

(102) Here we adopt the convention of giving boron the highest priority when assigning the *E/Z* geometry of the enolate.

(103) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

(104) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250.

(105) It should be noted that these systems have been demonstrated to afford the (Z)- and (E)-boron ketene acetals, respectively, implicating that the geometry was not the sole determinant in the relative inefficiency.

(106) It is possible that the Cy_2BI may also be catalyzing the rearrangement itself. However, varying the quantity of the iodoborane did not improve the overall efficacy of the reaction. For select examples of Lewis acid catalyzed Ireland–Claisen rearrangements of silyl ketene acetals, see: refs *16*, *17*.

(107) Koch, G.; Janser, P.; Kottirsch, G.; Romero-Giron, E. *Tetrahedron Lett.* **2002**, *43*, 4837.

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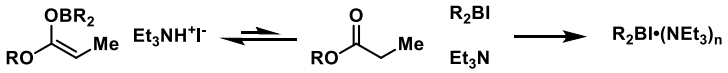
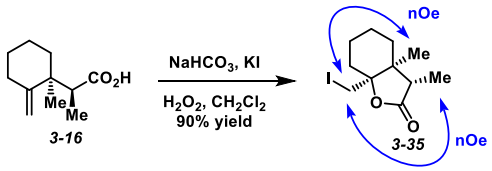
(109) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229.

(110) The slow quenching of the boron ketene acetal was observed in $CDCl_3$ when the 1H NMR spectrum of the reaction mixture was recorded directly. This behavior occurred even when the reaction mixture was rigorously protected from atmospheric oxygen and moisture and was unaffected by changes in scale. We hypothesize that the soft enolization reaction is reversible at ambient temperatures and that Cy_2BI generated by this reverse enolization reaction is trapped by excess Et_3N, deactivating the borane toward re-enolization of the ester.



(111) The aldol reaction promoted by Cy_2BI proceeded in 55 % NMR yield and 38 % isolated yield. Because the crude product was clean by NMR and free of obvious aldol decomposition products, we believe the diastereomer ratio of this reaction is indicative of the Z/E selectivity of the enolization process.

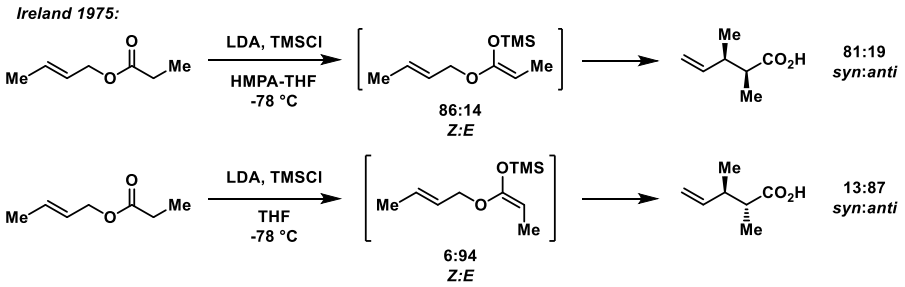
(112) The stereochemistry of this product was established by NOESY NMR of the iodolactonization product **3-35**.



(113) This behavior is most common in the case of esters of cyclic allylic alcohols, see ref 114.

(114) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572.

(115) Analysis of Ireland's experiments with silyl ketene acetals (see refs 90, 91), which are generally (ref *116*) unable to isomerize, suggests that propionates of (E)-allylic alcohols rearrange via an 86:14 mixture of (Z:E)-silyl ketene acetals through both chair and boat transition states in a 93:7 ratio, respectively. Solving the binary eq (1) for c and b with the data from these two examples reveals that both (E)- and (Z)-isomers prefer chair to boat in the same ratio of 93:7.



(1) $(Z)(c) + (E)(b) = syn$

Where Z and E are the fractions of Z and E silyl ketene acetals, respectively, c and b are the fraction of molecules that pass through a chair and boat transition state, respectively, and syn is the fraction of the product with syn stereochemistry

(116) Chen, C.-L.; Namba, K.; Kishi, Y. *Org. Lett.* **2008**, *11*, 409.

(117) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(118) There are exceptions of silyl ketene acetal isomerization, where it has been observed under specific conditions. For discussions, see refs 116, 119.

(119) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451.

(120) Results in the aldol reaction of the boron ketene acetals of phenylacetates are consistent with their isomerization. See ref 122.

(121) The presence of Cy_2BI may also facilitate isomerization of the boron ketene acetal.

(122) Ramachandran, P. V.; Chanda, P. B. *Org. Lett.* **2012**, *14*, 4346.

(123) Although (E)-selectivity is most pronounced in the case of secondary and tertiary propionates, benzyl propionate gives exclusive formation of the (E)-boron ketene acetal at −95 °C with Cy_2BOTf and Et_3N; see ref 104.

(124) It is possible that the conversion of the (E)-boron ketene acetal to the product proceeds first through a rate-limiting isomerization to the (Z)-boron ketene acetal followed by a fast rearrangement of the (Z)-isomer to the product. However, observations of the isomerization occurring at 0 °C taken with the fact that the rearrangement takes 20 h to reach completion at 23 °C suggest that this scenario is unlikely.

(125) Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905.

(126) There are conflicting reports as to the diastereoselectivity of Ireland–Claisen rearrangements of α-oxygenated esters. For one report of higher diastereoselectivity, see ref 127.

(127) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889.

(128) Abiko, A.; Inoue, T.; Furuno, H.; Schwalbe, H.; Fieres, C.; Masamune, S. *J. Am. Chem. Soc.* **2001**, *123*, 4605.

(129) Abiko, A.; Inoue, T.; Masamune, S. *J. Am. Chem. Soc.* **2002**, *124*, 10759.

Chapter Four: A Platinum Catalyzed Tandem Cyclization Approach to Liphagal.

Liphagal (**4-1**) is a tetracyclic terpenoid natural product originally isolated from the marine sponge *Aka coralliphaga* in 2006 by Andersen and coworkers.[130] Their search for this compound was guided by bioassays of the extracts of various marine sources of natural products for human phosphatidylinositol-3-kinase (PI3K) inhibitory activity. The PI3K signaling pathway is an important way that the body regulates such crucial tasks as cell proliferation and survival, among others, so compounds that can modulate this pathway have important therapeutic potential in the treatment of autoimmune disorders, cancer, and cardiovascular diseases.[131,132] Indeed, the PI3K inhibitor Idelalisib (**4-2**)[133] was approved by the FDA on July 25, 2014 for the treatment of leukemia.[134] Other PI3K inhibitors include wortmannin (**4-3**),[135] whose very short half-life *in vivo* limits its potential as a drug candidate but which has served as a template with which to design analogues with more medicinally useful properties. Despite advances in controlling this signaling pathway, much work remains to be done in developing *selective* PI3K inhibitors that may be effective treatments for different types of diseases or have reduced side-effect profiles in human subjects. The synthesis of liphagal, especially in such a way that it enables the synthesis of analogues of this natural product, constitutes a considerable entry into this type of development, a fact attested to by the multiple syntheses[130,136–139] and attempted syntheses[140,141] of this natural product. Ultimately, we expect that our synthesis of liphagal can be of medicinal value, as well as of value in further exploring the synthetic utility of platinum carbenoids, a major focus of our group's research that will be discussed later.

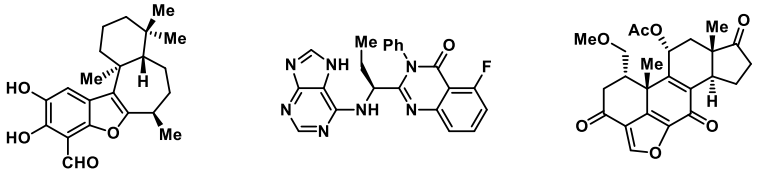
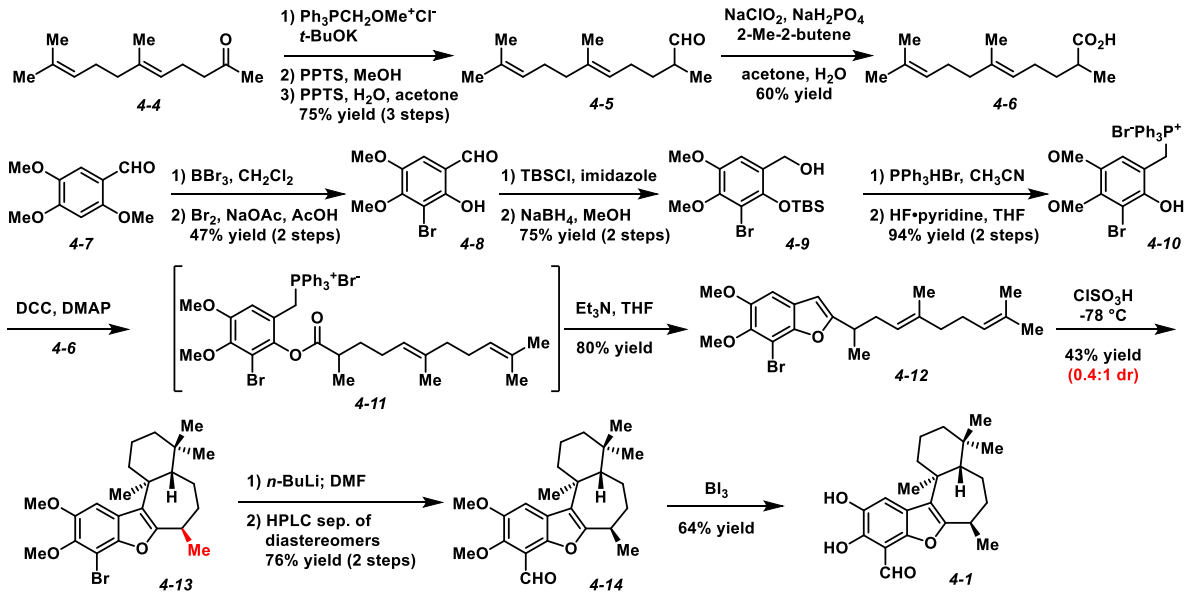


Figure 4.1. Common PI3K inhibitors.

Along with their characterization of liphagal, Andersen and coworkers proposed a biosynthesis for the natural product which they supported with a biomimetic total synthesis (Scheme 4.2). The synthesis centered around a cationic polyene cyclization to generate the bicyclic aliphatic portion of the molecule (**4-12** → **4-13**). Although this

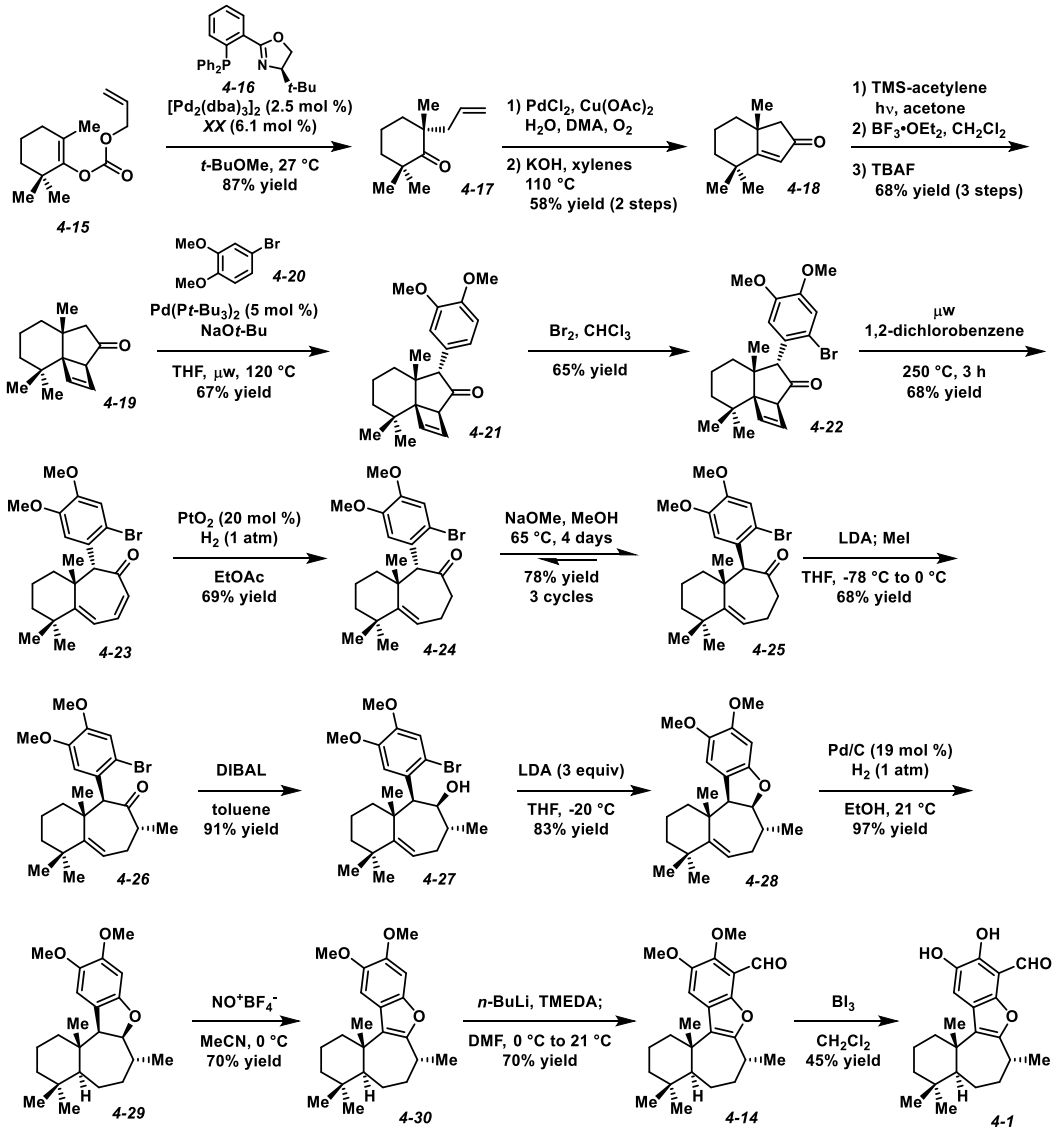
reaction proceeded in fairly modest yield and low diastereoselectivity (with respect to the disposition of the highlighted angular methyl group), it generated a considerable amount of molecular complexity as well as correctly establishing the *trans*-stereochemistry of the 7-6 junction in the natural product, which would later prove to be a stumbling block for other groups' syntheses of liphagal. This racemic synthesis produced liphagal in a relatively expeditious 12 steps if one includes the HPLC separation of diastereomers necessitated by the polyene cyclization among the steps required for completion.



Scheme 4.1. Andersen and coworkers' biomimetic synthesis of liphagal.

In 2011, Stoltz and coworkers completed the first catalytic enantioselective synthesis of liphagal.[138] This synthesis generated enantioenriched 2,2,6,6-tetrasubstituted cyclohexanone derivative **4-17** that would serve as the ultimate source of chirality in the natural product in the first step with a catalytic enantioselective Pd-catalyzed enolate allylation. Other crucial reactions included a photochemical [2 + 2] reaction (**4-18** → **4-19**) followed by ring expansion (**4-22** → **4-23**) to generate the seven membered ring of the natural product, along with a benzyne cyclization to generate the dihydrobenzofuran framework of the natural product (**4-27** → **4-28**). The use of a *dihydro*benzofuran in this synthesis seems to be a crucial feature, since the bowed shape of intermediate **4-28** directs the approach of a Pd catalyst for hydrogenation to the convex face of the olefin to give the correct *trans*-stereochemistry of the 6-7 junction

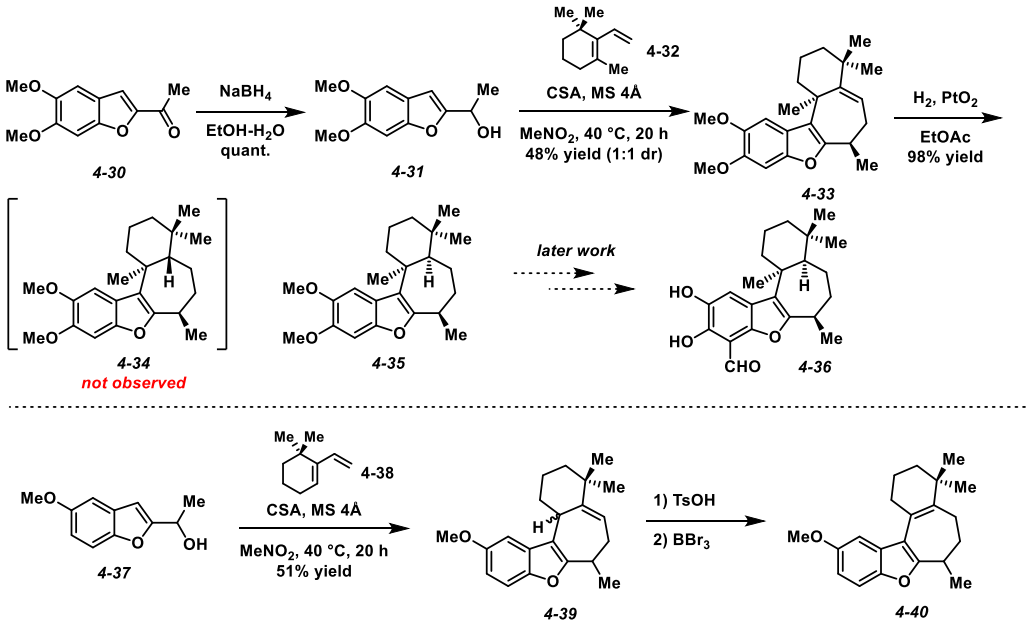
of the natural product. Again, this problem would be a stumbling block that would ultimately stymie multiple would-be syntheses of liphagal.



Scheme 4.2. Stoltz and coworkers' catalytic enantioselective total synthesis of liphagal.

Two synthetic efforts that were unable to overcome the problem of the trans 7-6 ring junction were both based on acid catalyzed [4 + 3][142] approaches to liphagal. The first to appear was that of Li and coworkers (Scheme 4.3), who successfully reported the synthesis of frondosin B (**4-40**), a close structural analogue of liphagal, in the same publication.[140] These syntheses were based upon the notion that an 'allylic' cation derived from alcohol **4-31** could

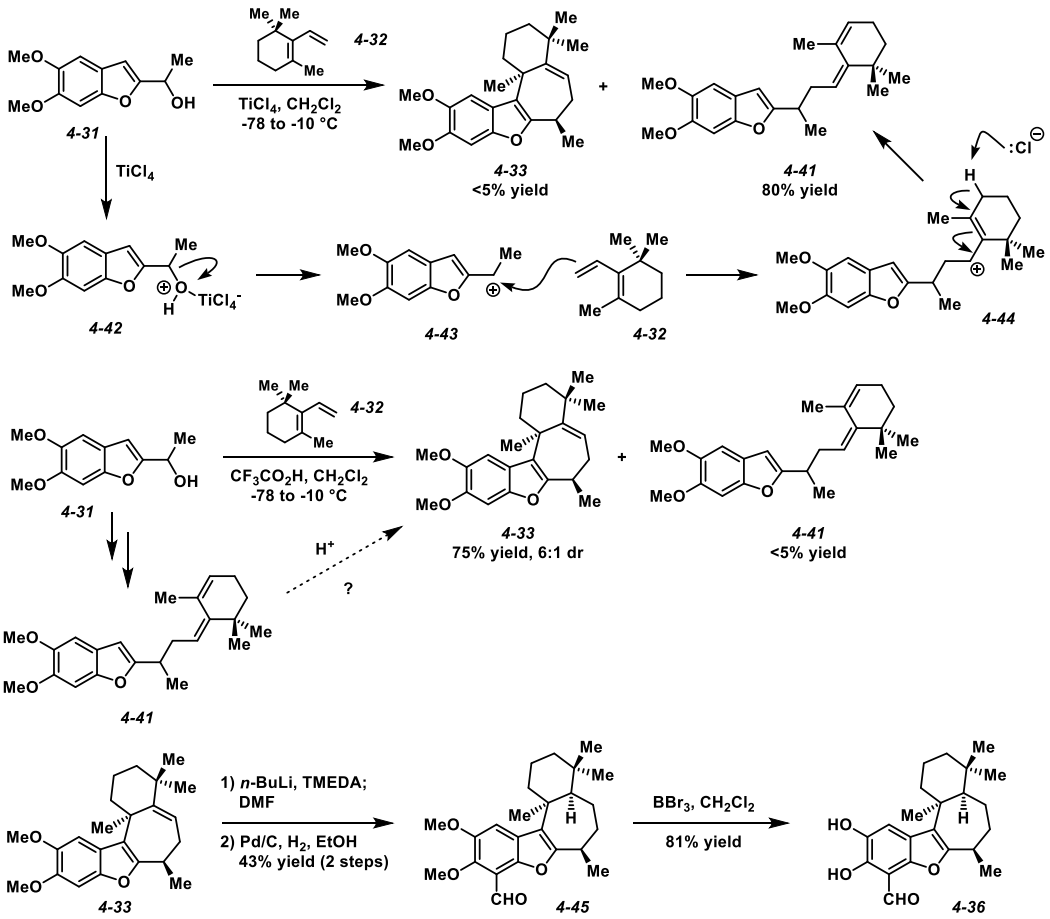
act as a two-electron, three-atom component in a [4 + 3] cycloaddition[140] when combined with a diene (**4-32** or **4-38**). In practice, this cycloaddition, though proceeding in moderate yield and giving a 1:1 mixture of diastereomers, formed the basis for an extremely expeditious synthesis of the liphagal core. The final task remaining to complete a formal synthesis of the natural product was an olefin hydrogenation. Unlike in the case of Stoltz's synthesis, this hydrogenation could not benefit from the concavity of a *dihydro*benzofuran to direct the diastereofacial selectivity of the reaction. Thus, the hydrogenation gave only the incorrect, *cis*-fused 7-6 junction. Though the group attempted to solve this problem through the use of multiple hydrogenation conditions, they could not achieve the synthesis of the correct diastereomer and were thus content to produce an advanced intermediate that could presumably be taken to an epimer of the natural product (**4-36**) by the same methods used in Stoltz's endgame (**4-30** → **4-1**). That these methods could be used to produce *epi*-liphagal would ultimately be confirmed by another group.



Scheme 4.3. Li and coworkers' synthesis of an advanced *epi*-liphagal intermediate.

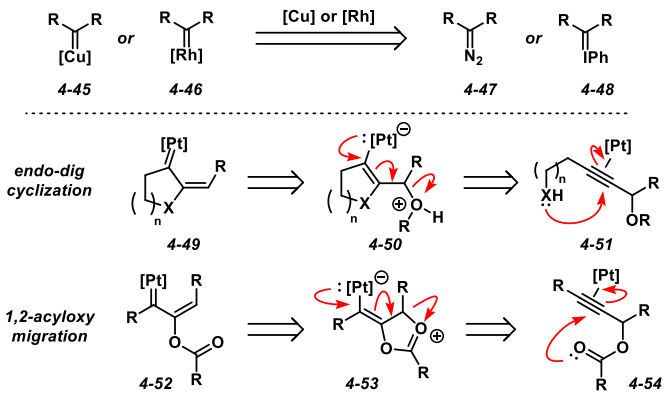
This group was that of Winne and coworkers, who proceeded along the same lines as Li. The publication outlining their work[141] provided a detailed account of their synthetic efforts and disclosed some improvements upon Li's synthesis (Scheme 4.4). Most notably, they both confirmed that Stoltz's methods could be used to produce *epi*-liphagal (**4-36**) from advanced intermediate **4-35** as well as developing conditions for promoting the [4 + 3]

cycloaddition with increased yield and diastereoselectivity. In both Li's and Winne's cases, we initially regarded the implicit assertion that this cycloaddition proceeded in a concerted sense as somewhat dubious, and this suspicion was compounded by Winne's disclosure that Lewis acid based conditions (rather than the Brønsted acid based conditions that they ultimately settled on) gave the product (**4-41**) of an elimination reaction of intermediate carbocation **4-44** that would arise from a stepwise mechanism for this formal cycloaddition. Though we would ultimately be forced to revise our mechanistic hypothesis about the nature of this cycloaddition in light of our own observations, this initial hypothesis nonetheless served to guide our own approach to liphagal. In any event, the supposition that an α,β-unsaturated Pt carbenoid could serve the same purpose as an allylic cation in this reaction was the basis for our own synthetic approach toward liphagal.



Scheme 4.4. Key experiments from Winne's synthesis of *epi*-liphgal.

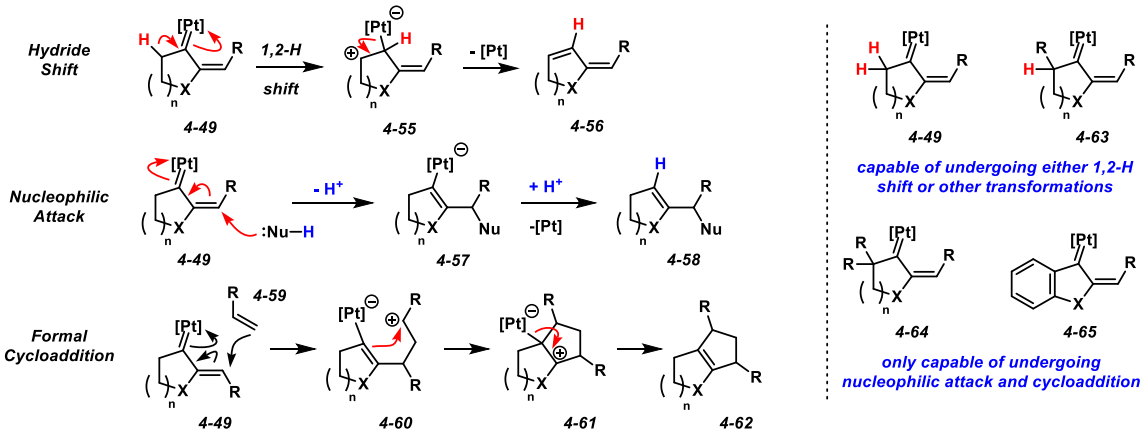
Pt carbenoids, specifically α,β-unsaturated Pt carbenoids, have been a major focus of our group's research efforts over the last six years, due largely to the valuable work of Paul Allegretti.[143–145] In conjunction with these efforts, we planned to exploit the reactivity of Pt carbenoids in our synthesis of liphagal. Like the more common carbenoids of copper and rhodium (**4-45** and **4-46**, Scheme 4.5), Pt carbenoids do not appear to be readily isolable intermediates, but unlike these carbenoids, Pt carbenoids come not from the decomposition of diazo compounds (*e.g.*, **4-47**) or λ^3-iodanes (**4-48**) but from the presence of a weak leaving group positioned α to an anionic vinylplatinum intermediate (*e.g.* **4-50** or **4-53**). These intermediates are in turn accessible by attack of a pendant nucleophile onto the alkyne moiety of a propargylic alcohol or ether (**4-51** → **4-50**) or 1,2-migration of a propargylic acyloxy group (**4-54**→ **4-53**).



Scheme 4.5. Preparation of carbenoid intermediates.

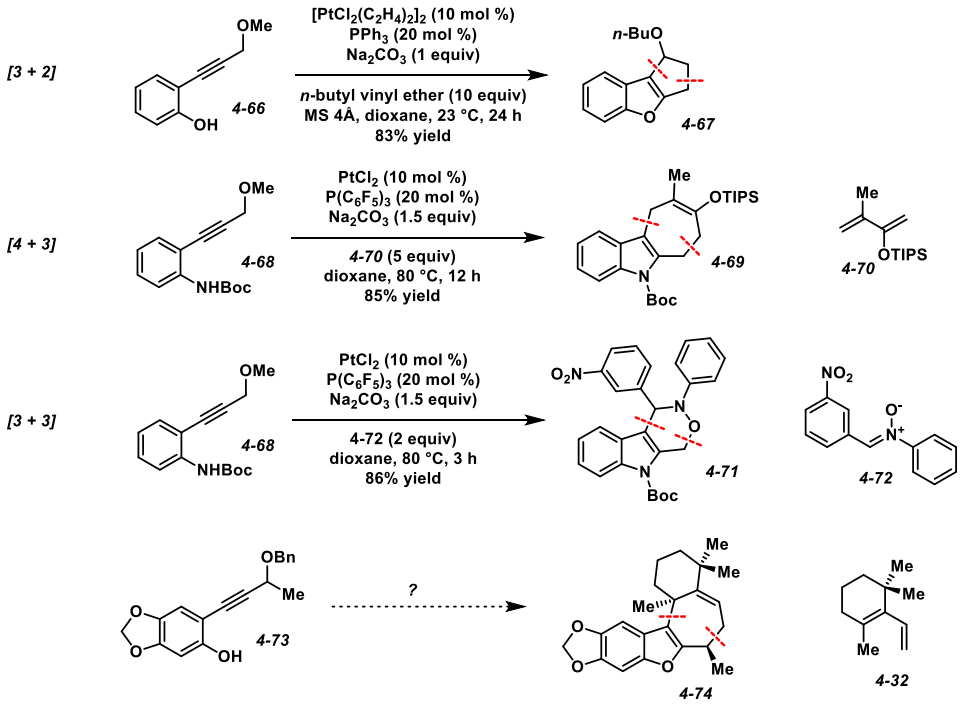
Depending on the conditions used to prepare them, α,β-unsaturated Pt carbenoids can undergo a variety of mechanistic transformations (Scheme 4.6). Instead of taking part in the more common C-H insertion or cyclopropanation reactions,[146] these unsaturated Pt carbenods tend to act as electrophiles, undergoing either 1,2-hydride shifts[147] (**4-49** → **4-55**) or addition of weak nucleophiles to the β-carbon of the unsaturated system (**4-49** → **4-57**).[145] In the former case, Pt acts as an electrofuge to quench the β-carbocation (**4-55** → **4-56**) created by this shift, regenerating Pt for reentry into the catalytic cycle. In the latter case, vinylplatinum species **4-57** resulting from nucleophilic addition undergoes protodemetalation, again regenerating the Pt catalyst as well as giving the final product (**4-58**). An additional option lies at this juncture. When the nucleophile was a C-C double bond, the resulting vinylplatinum species **4-60** can itself act as a nucleophile and intercept the pendant carbocation (*vide infra*). As in the

case of hydride shift, loss of Pt regenerates the catalyst and quenches the carbocationic center, giving the product of a formal cycloaddition (**4-62**).[148] While the 1,2-hydride shift of Pt carbenoids is generally a very facile process, judicious choice of conditions can disfavor this reaction course, even when the requisite α-hydrogen is available (*e.g.* **4-49** and **4-63**). By choosing substrates that do not contain this α-hydrogen atom (*e.g.* **4-64** and **4-65**), the possibility of hydride shift can be completely eliminated, and the use of these two strategies has allowed our group and others to explore the relatively more interesting possibility of using Pt carbenoids in other transformations.



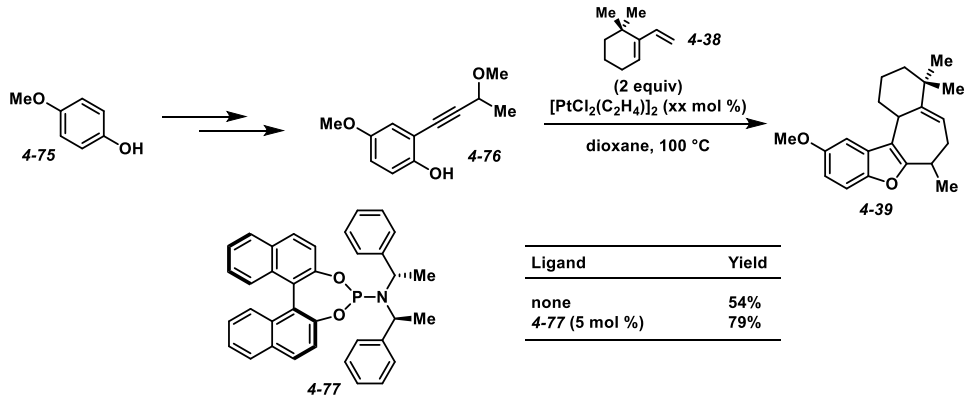
Scheme 4.6. Mechanistic possibilities available to Pt carbenoids.

Among these transformations is the formal cycloaddition type that we planned to use in our synthesis of liphagal (Scheme 4.7). Several examples of this transformation are presented below, including [3 + 2],[149] [4 + 3],[150] and [3 + 3][151] variants. The efficiency of this transformation in these settings led us to ask the question of whether it could be viable as the key step in a total synthesis.



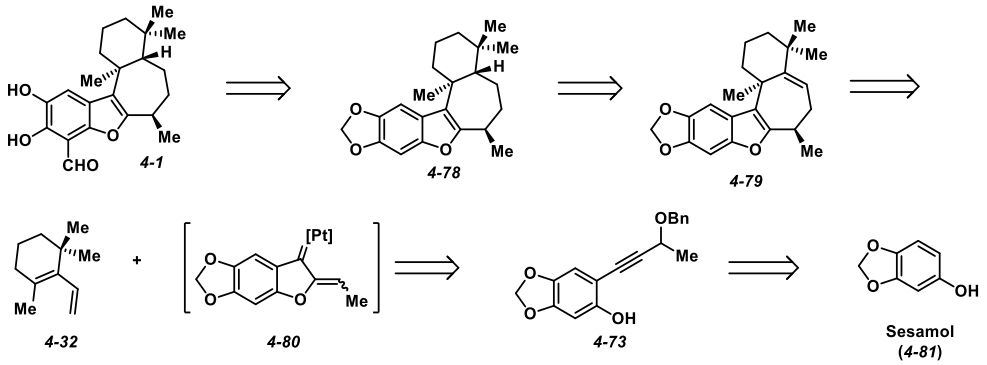
Scheme 4.7. Examples of cycloaddition reactions of α,β-unsaturated Pt carbenoids.

This question was answered in the affirmative by Tarik Ozumerzifon in our group, who used the Pt-catalyzed cycloaddition cascade as the centerpiece of a synthesis of frondosin B (Scheme 4.8, **4-40**).[152] This somewhat simpler system relative to liphagal provided a useful opportunity for testing this methodology in a still fairly complex setting. Ozumerzifon synthesized the precursor to this cycloaddition from hydroquinone monomethyl ether (**4-75**). Upon treatment of alkynyl phenol **4-76** with catalytic Zeise's dimer and 2 equiv diene **4-38**, the cascade reaction took place to smoothly form the skeleton of frondosin B in 54% yield. When ligand **4-77** was included in the reaction, the yield increased significantly to 79%. The preparation of **4-39** represented a formal synthesis of frondosin B, and this advanced intermediate was taken to the natural product in the manner previously described in Li's synthesis. The completion of this formal synthesis served as a model system for our route toward liphagal and provided us with the final impetus necessary to convince us to begin our pursuit of this natural product.



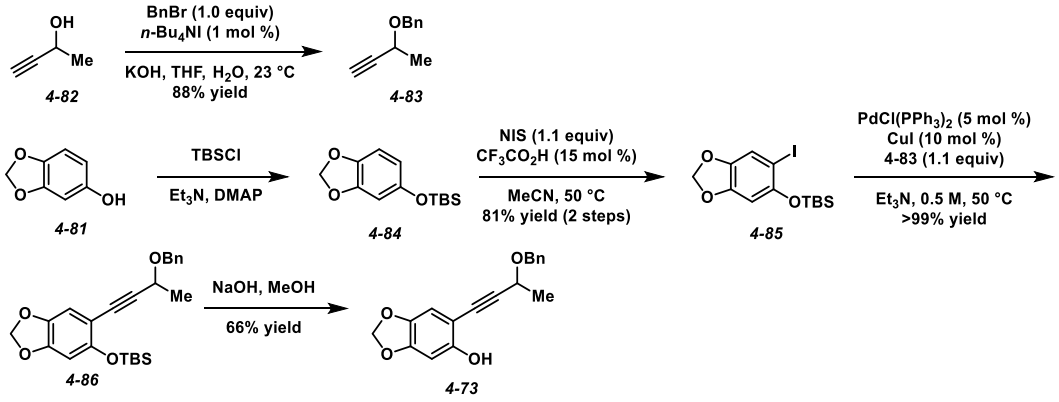
Scheme 4.8. Outline of Ozumerzifon and Ferreira's formal synthesis of Frondosin B.

Our initial retrosynthesis of liphagal was based on a central Pt-catalyzed [4 + 3] cycloaddition reaction that had already been demonstrated in our group's synthesis of frondosin B. The final steps of our synthesis would largely mirror those of previous efforts by completing the substitution pattern of the arene ring. We would accomplish this by a directed *ortho*-lithiation-formylation of benzofuran **4-78** followed by deprotection of the methylenedioxy bridge to reveal the two phenolic hydroxyl groups of the natural product, completing the synthesis. We sought to arrive at the precursor for these transformations by a thermodynamically controlled hydrogenation reaction of a dehydroliphagal precursor (**4-79**), which would hopefully address the stereochemical issues associated with kinetically controlled hydrogenations of similar intermediates in previous synthetic attempts. The key step of our synthesis would generate the central seven membered ring of cycloheptene derivative **4-79** by a platinum catalyzed cycloaddition reaction. Finally, we would arrive at the cycloaddition precursor (**4-73**) by a straightforward series of reactions from readily available sesamol (**4-81**).



Scheme 4.9. Initial retrosynthesis of liphagal.

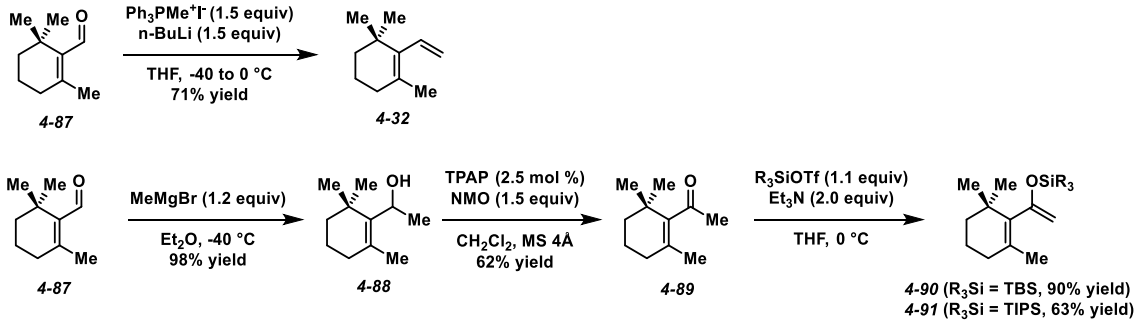
In the forward sense, our sequence began with the TBS protection of sesamol to produce **4-84**, which we then iodinated with NIS catalyzed by CF_3CO_2H to give aryl iodide (**4-85**).[153] Under standard conditions, this compound underwent efficient Sonogashira coupling[154] with propargylic ether **4-83**. We prepared the latter compound by a Williamson ether synthesis of commercially available propargylic alcohol **4-82** with benzyl bromide under Schotten-Baumann type conditions. To our knowledge, Williamson ether syntheses have not been conducted under these conditions previously, and it is noteworthy that less than 5% yield of BnOH arising from basic hydrolysis of BnBr was detected in the crude reaction mixture of this reaction. The TBS group of alkyne **4-86** was removed under basic conditions to avoid potential complications that might arise from the lability of the readily ionized propargylic ether moiety of alkyne **4-86** to acidic conditions, giving us access to sizable quantities to the phenolic precursor of our key step (**4-73**).



Scheme 4.10. Synthesis of phenolic cycloaddition precursor **4-73**.

In addition to this phenol precursor to the cycloaddition, we also prepared three related diene fragments from β-cyclocitral (**4-87**). The first was the simpler hydrocarbon variant **4-32**, which we made through a previously reported Wittig reaction.[140] The second and third were silyloxydienes **4-90** and **4-91**, which we prepared by a three step sequence. First, secondary allylic alcohol **4-88** was prepared by addition of MeMgBr to aldehyde **4-87**. We then oxidized this alcohol to enone **4-89** employing catalytic TPAP with NMO as the stoichiometric oxidant under standard conditions.[155] Finally, we produced silyloxydienes **4-90** and **4-91** by soft enolization of enone **4-89** using TBSOTf or TIPSOTf, respectively. The handling of these potentially hydrolyzable silyl enol ethers did not pose any problems as

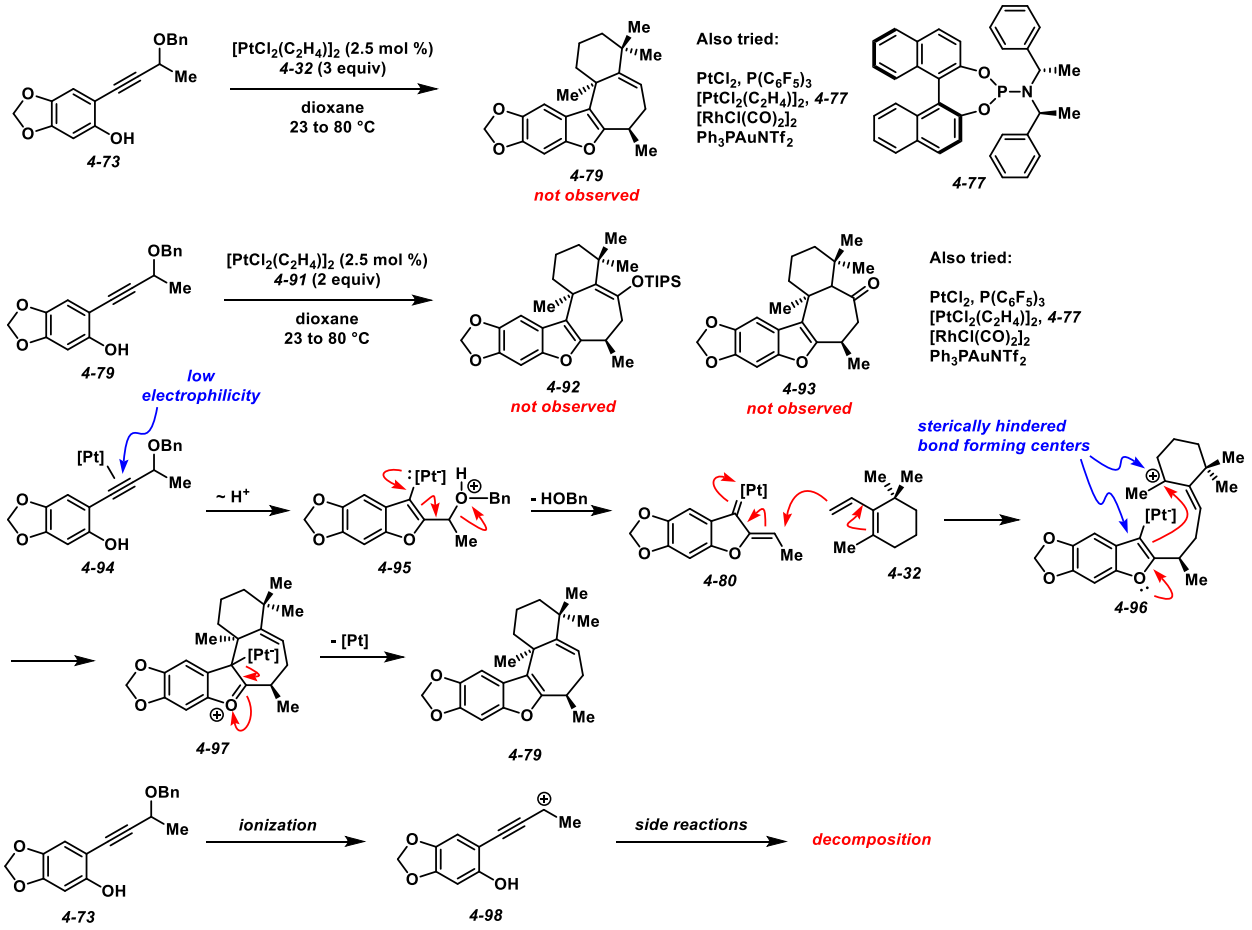
long as contact with acid was avoided, and it could be purified by column chromatography on Et_3N-neutralized silica gel.



Scheme 4.11. Synthesis of two diene variants for the Pt-catalyzed cycloaddition reaction.

In the event, the cycloaddition of phenol **4-73** and diene **4-32** did not proceed under any of the conditions we tried. Similarly, when we replaced hydrocarbon diene **4-32** with the considerably more nucleophilic silyloxydiene **4-91**, we did not observe any cycloaddition products. The failure of this reaction to produce the seven membered ring of liphagal was not wholly unexpected based on precedent. Our analysis of the literature suggested that the generation of a quaternary center by the final cyclization of a carbocation onto the alkenylplatinum moiety of compound **4-97** was especially difficult, likely due to steric repulsion between the two bulky bond forming centers.[150] We did, however, expect to at least observe products of addition of diene **4-32**, or at least silyloxydiene **4-91**, to the putative platinum carbene intermediate based on our group's previous work using very similar substrates in this cycloaddition reaction *en route* to frondosin B. We hypothesized that the lack of formation of the expected products could arise from two effects, possibly acting synergistically. Both would ultimately be due to the generally electron rich nature of the arene ring of alkyne **4-73** as well as the positioning of electron donating groups around the ring. The first of these was that the conjugation of the alkyne to electron donating groups in the aromatic ring of compound **4-73** would inhibit the cyclization. This alkyne must be electrophilic in order for the cyclization to proceed, but electron donation from the arene ring would in fact attenuate this alkyne's electrophilicity, as well as the electrophilicity of Pt-bound alkyne **4-94**.[156] This would ultimately lead to a substantial rate reduction of the initial cyclization reaction and perhaps prevent it from occurring altogether. The second of these effects was that conjugation to the electron rich arene ring of phenol **4-73** would considerably stabilize carbocation **4-98** arising from ionization of the propargylic ether moiety,

conferring considerable lability upon the latter. This effect would likely increase the rate of side reactions originating from this ionization process. Thus, the electron richness of the arene ring would both slow down the desired reaction as well as increase the rate of competing side reactions.



Scheme 4.12. Failure of Pt-catalyzed cycloaddition.

In order to support this diagnosis, we attempted a set of experiments aimed at finding out which of the two partners, alkyne **4-73** or diene **4-32**, was responsible for the failure of the cycloaddition reaction. Because Ozumerzifon's work had produced two components that we knew to be competent in this reaction, we could easily set up a 2x2 set of experiments, partnering each phenol, **4-73** or **4-76**, with each diene, **4-32** or **4-38** (Figure 4.2). We found that both diene **4-32** and alkyne **4-73** were not competent in the cycloaddition, *per se*. However, when alkyne **4-73** was replaced with the less oxygenated analogue **4-76**, our original diene (**4-32**) did in fact couple to the putative Pt carbenoid intermediate, this time forming one bond in an alkenylation reaction to give benzofuran **4-77** in 58% yield rather than forming two bonds in a cycloaddition reaction. In the case of our original alkyne (**4-73**) both dienes

failed to give any recognizable product. Because the largest difference between alkyne **4-73** and **4-76** is the greater amount of oxygenation present on the aryl ring of **4-73**, making this aryl ring more electron rich, the data from these experiments provided support for our hypothesis that the electronic properties of this benzene ring were to blame for the failure of the cycloaddition reaction.

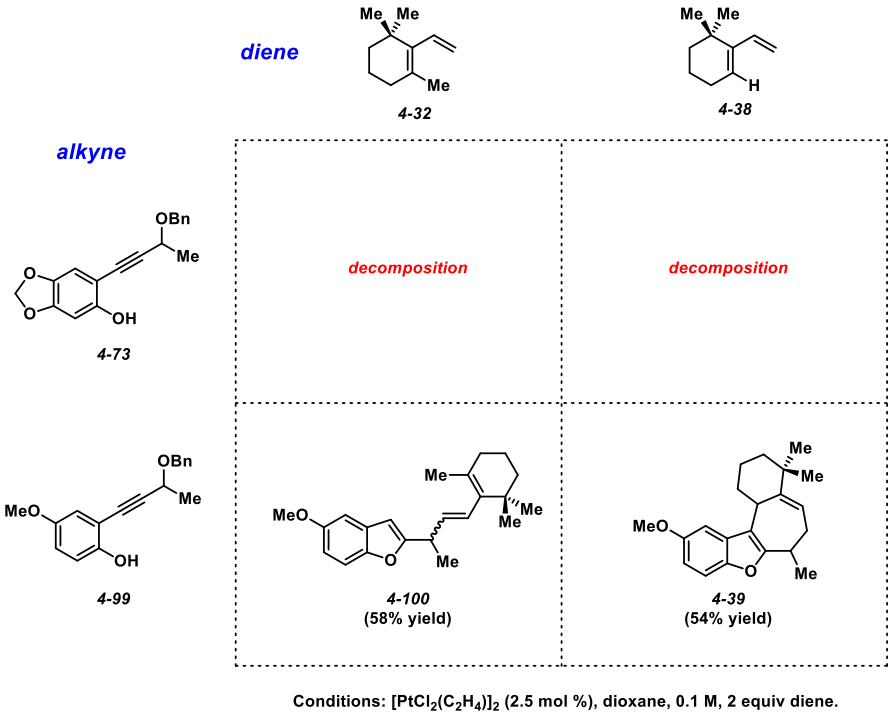
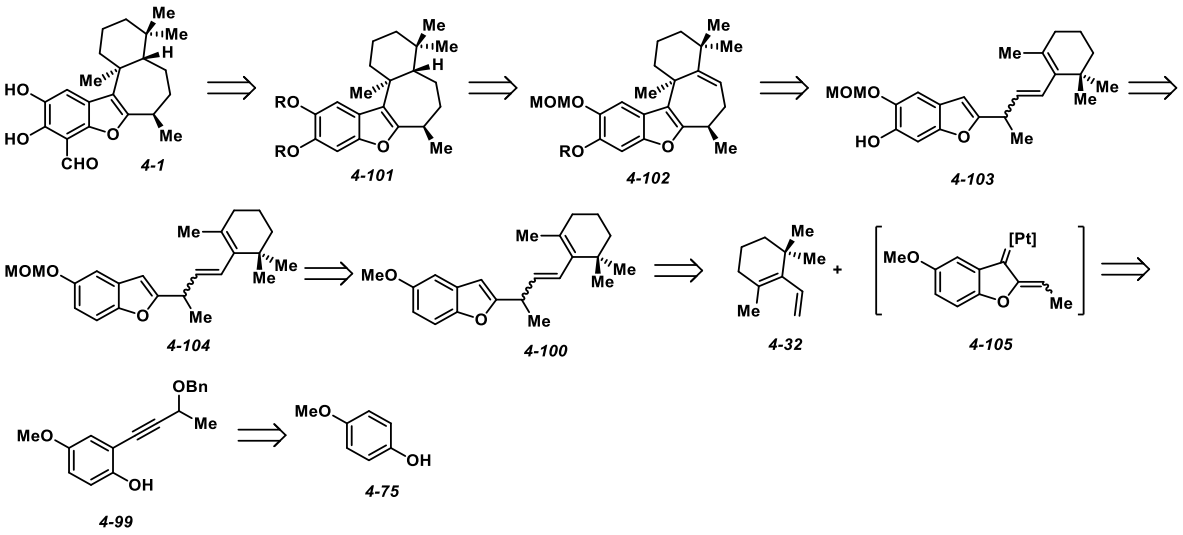


Figure 4.2. Experiments determining the contribution of each coupling component to the success of the Pt-catalyzed cascade cycloaddition reaction.

To continue with our synthesis, we would thus begin with a less substituted and less electron rich arene, planning for its eventual elaboration to the substitution pattern found in liphagal (Scheme 4.13). Our synthesis would end in much the same way as our previous scheme, with a formylation-deprotection of **4-101** giving liphagal. The precursor to this material would again be prepared by hydrogenation of alkene **4-102**. At this stage, however, the route diverges somewhat from our previous. Instead of basing our formation of the seven-membered ring on a cycloaddition reaction, we would form it in two steps. The second of these two steps would be an acid catalyzed cationic cyclization reaction, producing cycloheptene derivative **4-102**. We would at this point introduce the second phenolic hydroxyl group of liphagal, located at the 6-position of the benzofuran ring system, by a standard sequence involving a one-pot lithiation, borylation, oxidation sequence to deliver monoprotected catechol **4-102**. At this stage,

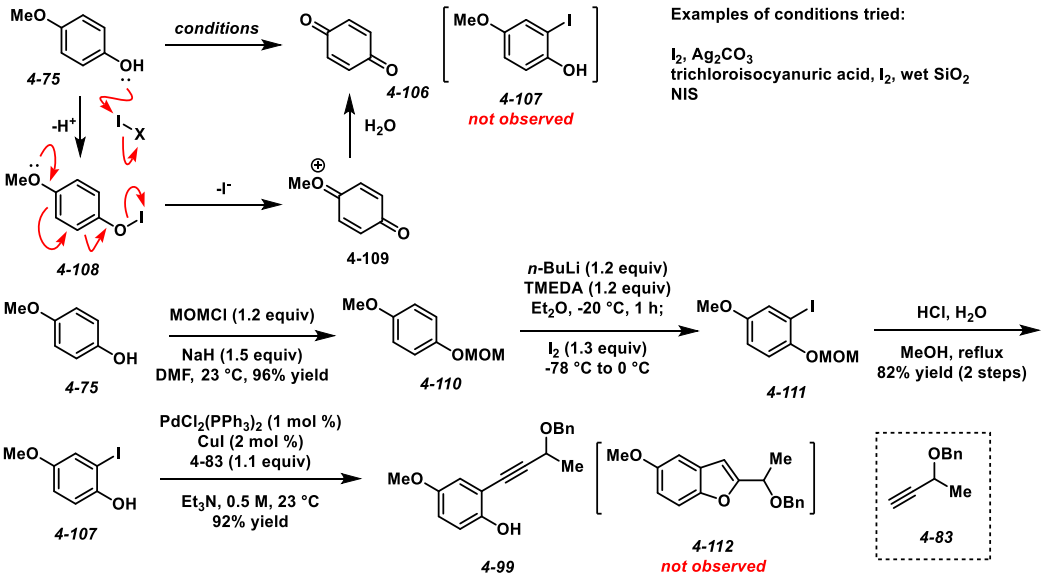
we were not sure if this oxygenation would be a necessary prerequisite to seven-membered ring closure, but because the introduction of this oxygenation and cyclization could easily be reversed in the forward synthesis, we deemed this inconsequential at this stage in the planning. Replacement of the –OMe group of **4-100** with an –OMOM group in **4-104** would allow for the directed lithiation to occur. This would take us back to an alkenylated product (**4-100**) that we had already prepared. We would prepare phenol **4-99** from 4-methoxyphenol (**4-75**) via a four step sequence, leading us back to readily available starting materials.



Scheme 4.13. Retrosynthesis for later stage introduction of an aryl oxygen substituent.

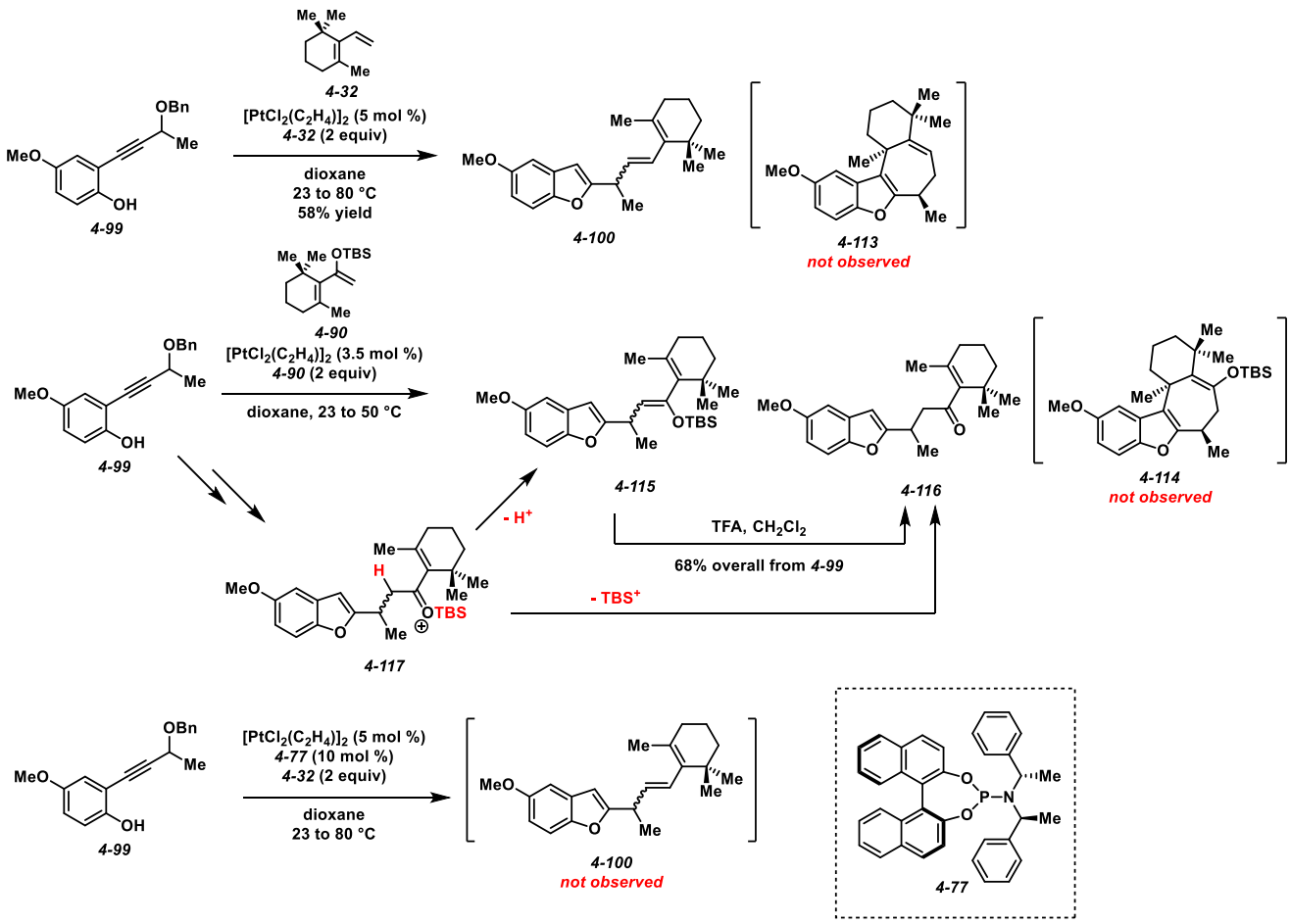
In the forward sense, our synthesis began with the iodination of 4-methoxyphenol (**4-75**, Scheme 4.14). Though there exist numerous published methods to effect this transformation,[157–160] in our hands these reactions invariably gave conversion to benzoquinone, presumably by the mechanism shown in Scheme 4.14, or no conversion whatsoever. Instead, we developed a high yielding three step sequence based on *ortho*-lithiation. First, we treated phenol **4-75** with MOMCl and NaH in DMF to prepare MOM ether **4-110** in nearly quantitative yield. Second, we lithiated this compound *ortho* to the OMOM group with *n*-BuLi in the presence of TMEDA followed by quenching with iodine to give iodide **4-111**, which we deprotected under acidic conditions to give iodophenol **4-107** in 82% yield. We decided to perform this deprotection prior to the Sonogashira reaction in order to avoid side reactions that might occur with a potentially ionizable propargylic ether. Finally, we prepared our Pt-catalyzed cycloaddition precursor (**4-99**) by a Sonogashira reaction with alkyne **4-83** in 92% yield. The careful handling of this reaction mixture was

crucial, since alkynylphenols such as **4-99** have been known to cyclize to benzofurans (e.g. **4-112**) under Pd catalysis. Fortunately, we did not observe this side reaction.



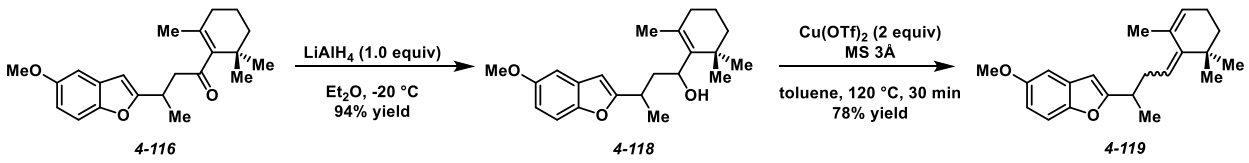
Scheme 4.14. Synthesis of Pt-catalyzed cascade reaction precursor **4-99**.

Reaction of phenol **4-99** and diene **4-32** under Pt catalysis conditions gave alkenylation product **4-100** in 55% yield. Using silyloxydiene **4-90** in place of hydrocarbon diene **4-32** gave the same result, although we observed ketone **4-116** as well as silyl enol ether **4-115** in the reaction mixture. The creation of these two products presumably arises by a bifurcation of the reaction pathway at the silyloxocarbenium (**4-117**) stage. At this point intermediate **4-117** can undergo either deprotonation to give silyl enol ether **4-115** or desilylation to give ketone **4-116**. In order to accurately obtain the overall yield of the reaction, we treated the crude reaction mixture with CF_3CO_2H in order to hydrolyze **4-115** to ketone **4-116**, giving us a 68% yield of the latter from phenol **4-99**. When we employed phosphoramidite ligand **4-77** in conjuction with $[PtCl_2(C_2H_4)]_2$, conditions that improved the yield of the cycloaddition in our group's frondosin B synthesis, we in fact observed no formation of product whatsoever. It is curious that this additive seems to only increase the efficiency of the cycloaddition while decreasing the efficiency of the alkenylation reaction, suggesting that it may alter the mechanistic course of the reaction after the Pt carbenoid stage (**4-49** → **4-62** in Scheme 4.6).



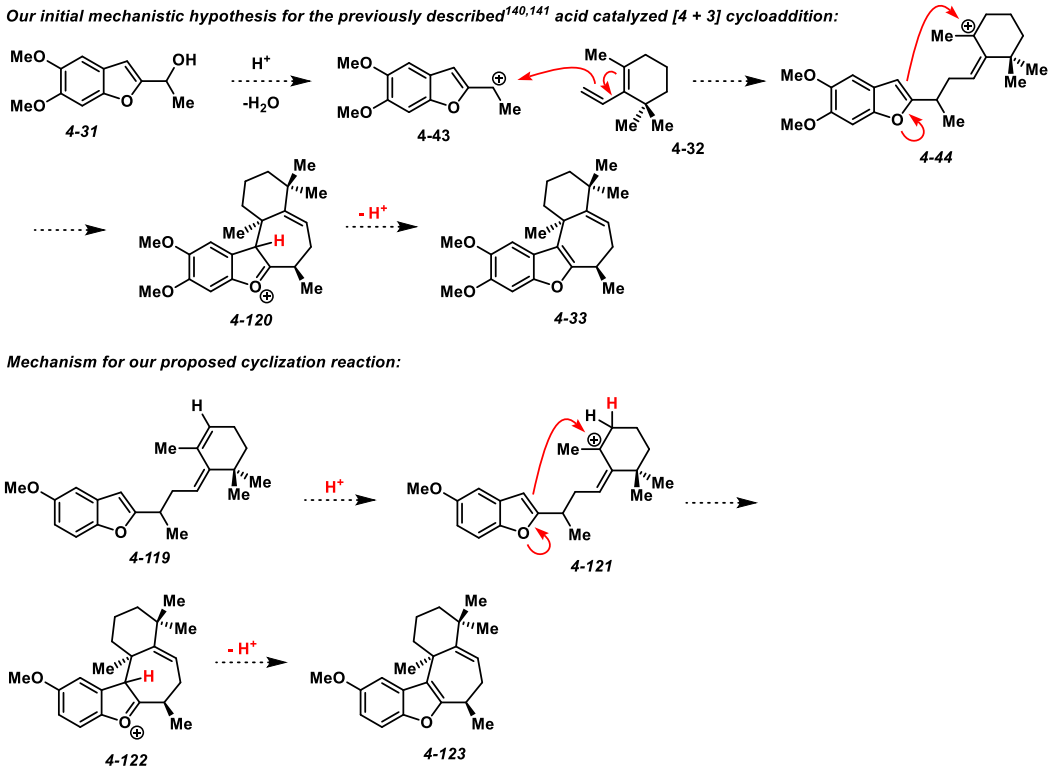
Scheme 4.15. Pt-catalyzed alkenylations.

The use of hydrocarbon diene **4-32** in this alkenylation reaction, however, proved somewhat problematic. As we attempted to scale up the reaction, it consistently failed to give useable amounts of alkenylated product **4-100**. In light of this, we opted for a more efficient way (Scheme 4.16) to produce such a diene. Since we were easily able to secure large amounts of ketone **4-116**, we opted to convert it into an isomer of diene **4-110** by first reducing the ketone with $LiAlH_4$ to give alcohol **4-118** in 94% yield, followed by dehydration of alcohol **4-118** to diene **4-119**.



Scheme 4.16. An alternative diene synthesis.

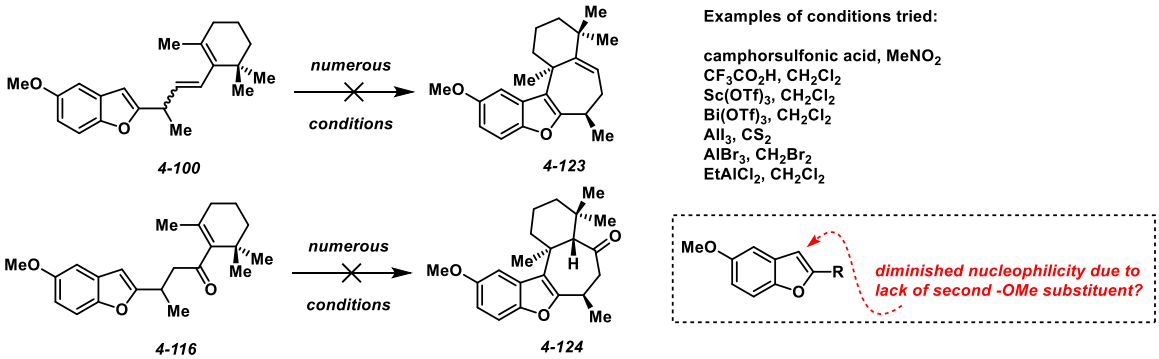
Because diene isomer **4-119** was analogous to one that Winne suggested was involved in the acid catalyzed [4 + 3] cycloaddition reaction, we were poised to consider our own cyclization in more detail. We hypothesized that previous efforts towards liphagal that employed acid catalyzed formal [4 + 3] cycloaddition reactions were in fact stepwise processes (Scheme 4.16), so we hoped that we might generate one of these carbocationic intermediates independently, with it undergoing cyclization to give the [4 + 3] product after two steps instead of one.



Scheme 4.17. Mechanistic comparison between our proposed cyclization reaction and previously described cycloaddition reactions.

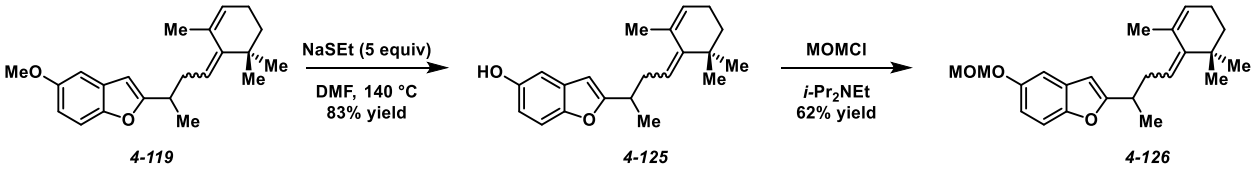
Unfortunately, all of our attempts at effecting this cyclization failed to give any product (Scheme 4.18). The efficacy of this cyclization ultimately not only rests on the ability of carbocation **4-121** produced by protonation of **4-100** to act as an electrophile but also on the ability of the pendant benzofuran ring system to act as a nucleophile. Because the only difference between our system and those that had been demonstrated to undergo successful cycloaddition was the presence of an additional methoxy substituent in the 6-position of the latter (products **4-33** vs.

4-123), we thought the ability of the benzofuran to act as a nucleophile might be compromised. Thus, we hypothesized that introduction of this additional methoxy substituent might be a prerequisite for cyclization of alkene **4-100** or ketone **4-116** to occur.



Scheme 4.18. Failure of cyclization of alkene **4-119** and ketone **4-116**.

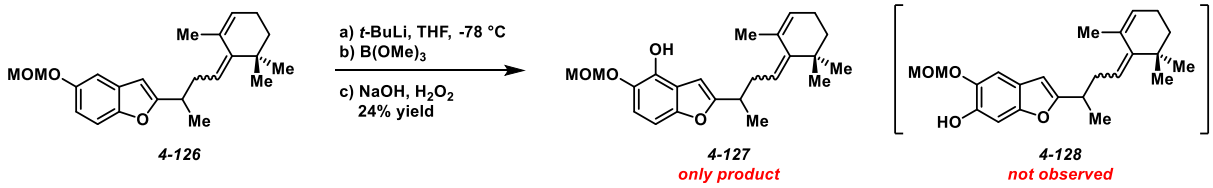
In order to test this theory and ultimately complete the construction of the liphagal ring system, it was therefore incumbent upon us to introduce the 6-methoxy substituent of arene **4-119** (Scheme 4.19). Our strategy for doing so would be to replace the aryl 5–OMe substituent of anisole derivative **4-119** with a better directing group and perform a lithiation, borylation, oxidation sequence to introduce the 6-OH group. To install a directing group, we first removed the OMe group of **4-119** with NaSEt in DMF at 140 °C giving phenol **4-125** in 83% yield. We then introduced the MOM group of ether **4-126** by treating phenol **4-125** with MOMCl and *i*-Pr_2NEt.



Scheme 4.19. Introduction of a directing group.

However, our initial attempts at introducing the -OH substituent gave a majority of hydroxylation in the 4-position of the benzofuran ring system to give phenol **4-127** rather than desired phenol **4-128** (Scheme 4.20). This came as quite a surprise to us since the greater steric bulk of the 4-position, engendered by the presence of the ring

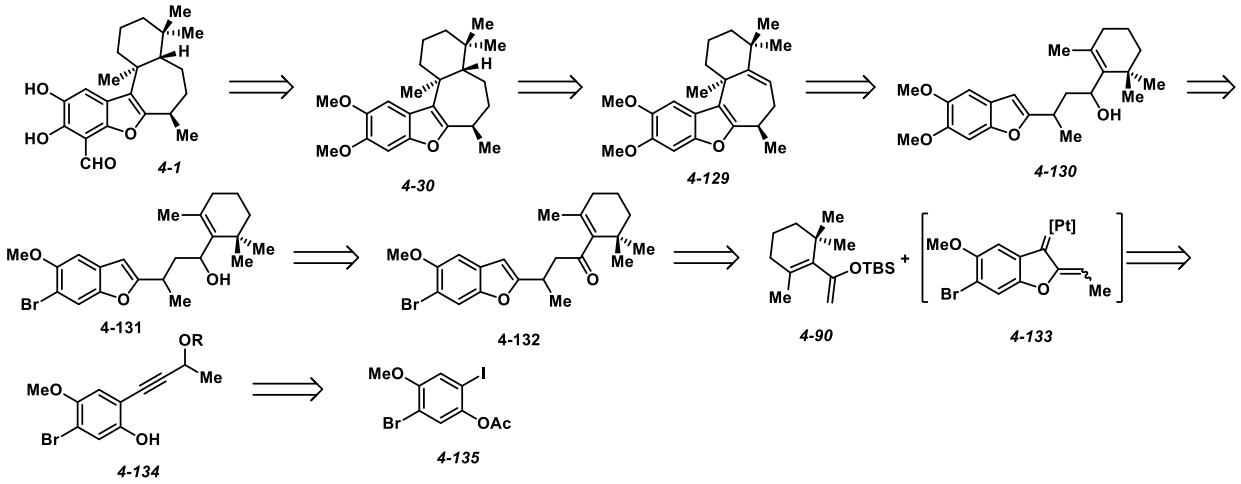
fusion adjacent to that position, would be expected to direct lithiation towards the less hindered 6-position. While we tried alternative methods to introduce the hydroxyl group onto the 6-position of MOM ether **4-126**, these all failed. The use of these different conditions failed to give a synthetically useful mixture of isomers.



Scheme 4.20. Directed *ortho*-metalation-hydroxylation of ether **4-126**.

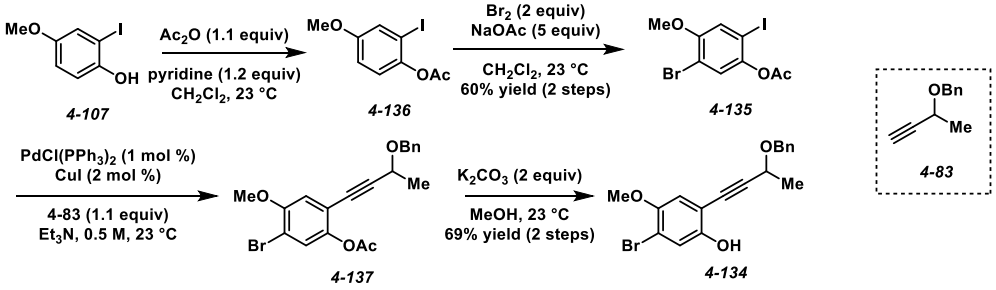
Our solution to this problem ultimately led us to considerably retool the synthesis. Thus far, our construction of the 7-membered ring had seemed to require two incompatible substrate requirements. First, the presence of an oxygen substituent at the 6-position of the benzofuran ring seemed to be necessary for closure of the 7-memered ring, but this substituent also appeared to be incompatible with the Pt-catalyzed cyclization cascade. Second, our solution to the latter problem by removing the oxygen substituent in what would become the 6-position of the benzofuran ring system appeared to be incompatible with cyclization of the 7-membered ring. Furthermore, our attempts to work around this issue by introducing the oxygen substituent after the Pt-catalyzed cyclization reaction gave the incorrect isomer!

We hypothesized that we could begin the synthesis with a -Br substituent (Scheme 4.21) that would be compatible with the Pt-catalyzed cyclization reaction and then regiospecifically substitute this Br with an oxygen substituent in order to effect cyclization. Because it is a mildly electron withdrawing group, this aryl –Br substituent would not lead to either of the possible effects that we hypothesized were at the root of the failure of the Pt-catalyzed cycloaddition (or alkenylation reaction) of sesamol derived phenol **4-73**. Moreover, because of the considerably greater reactivity of aryl iodides over aryl bromides in Pd catalyzed coupling reactions using 'classical' conditions (*e.g.* PPh_3 as a ligand), the aryl bromide moiety should be compatible with this reaction without undergoing its own coupling. As an added benefit, our required aryl dihalide **4-135** was an easily synthesized known compound,[161] and thus we set out to explore this synthetic possibility.



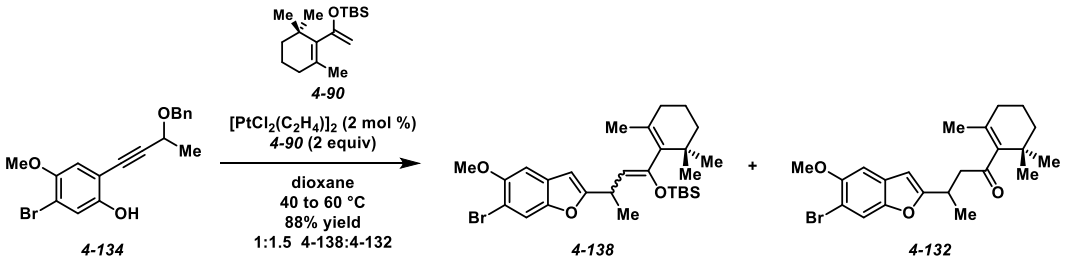
Scheme 4.21. A further revised retrosynthesis of liphagal.

The synthesis began with the preparation of our new Pt-catalyzed cyclization precursor (Scheme 4.22). We constructed the required tetrasubstituted arene by a known method.[161] First, the phenol was changed to aryl acetate **4-134** by acetylation with acetic anhydride and pyridine. Treating acetate **4-136** with 2 equiv Br_2 in the presence of excess sodium acetate to neutralize the formed HBr then furnished the desired arene **4-135** in analogy with precedent. We elected to perform the Sonogashira reaction with alkyne **4-83** prior to removing the acetate group in order to remove the possibility of an undesired benzofuran formation reaction occurring in conjunction with the installation of the alkyne moiety to give arylacetylene **4-137**. Finally we removed the acetate group by stirring acetate **4-137** in MeOH with stoichiometric K_2CO_3 to furnish phenol **4-134** in 69% yield from aryl iodide **4-135**.



Scheme 4.22. Construction of Pt-catalyzed cyclization precursor **4-135**.

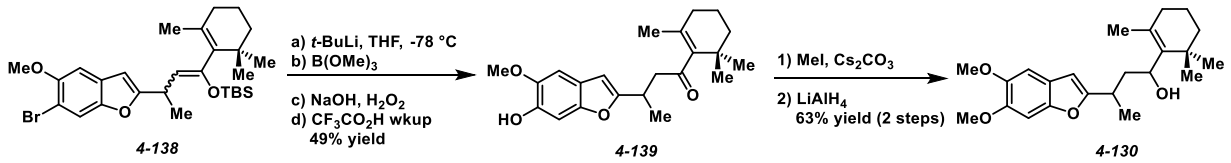
We hoped that the Br substituent of **4-135** would not considerably affect the electronics of the alkyne moiety relative to its desbromo analogue **4-99**, for which we had previously described the Pt-catalyzed cyclization-alkenylation reaction in Scheme 4.15, and that the reaction would follow the same course. We were delighted to find that this was indeed the case (Scheme 4.23), and treatment of alkyne **4-134** with Zeise's dimer and 2 equiv of silyloxydiene **4-90** furnished the desired alkenylation products in an impressive 88% yield, making the reaction even more efficient than in the case of desbromo analogue **4-99**. As before, we obtained the product as a mixture of ketone **4-132** and its silyl enol ether derivative **4-138**, deriving from formal loss of TBS^+ and H^+, respectively. Though we expected that silyloxy diene **4-138** could readily be converted to ketone **4-132** by treatment with catalytic acid, we elected to simply use the two products for different routes to prepare a precursor that we could ultimately use to form the final, seven-membered ring of the natural product.



Scheme 4.23. Pt-catalyzed cyclization-alkenylation of **4-134**.

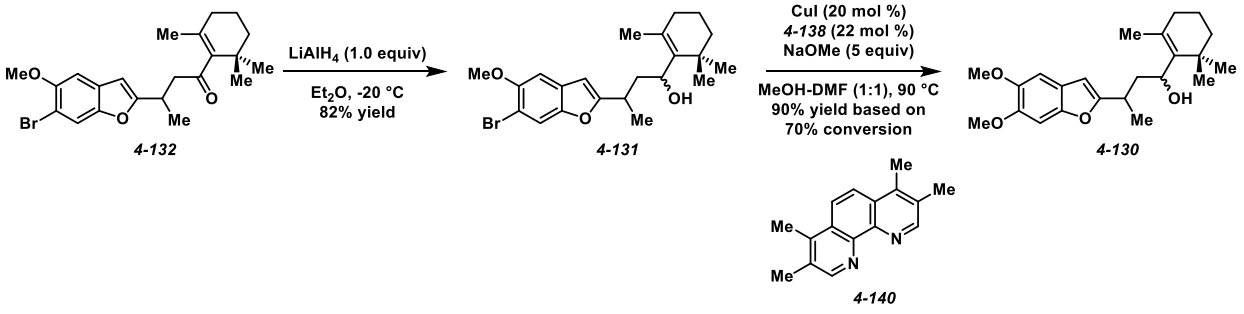
To replace the –Br substituent with an –OMe substituent that we had surmised was necessary for the final required substituent, we utilized a route based on lithium halogen exchange. This sequence was based on our successful (albeit regiochemically incorrect) introduction of a phenolic hydroxyl group in Scheme 4.24. This time, however, the reaction would be regiospecific, since lithium halogen exchange is considerably faster than deprotonation of hydrocarbons. Thus, we treated aryl bromide **4-138** with 2.2 equiv *t*-BuLi to generate the intermediate aryllithium, which we then quenched with $B(OMe)_3$ and oxidized to the phenol with basic H_2O_2. We also elected to hydrolyze the silyl enol ether to its parent ketone at this point, simplifying purification, to give monomethyl catechol derivative **4-139** in a one pot procedure in 49% yield. Finally, we prepared the cyclization precursor (**4-130**) by introduction of a methyl group with MeI and Cs_2CO_3 followed by reduction of the ketone with $LiAlH_4$. We were now in a position to

attempt the cyclization reaction. However, the low yields of this sequence, coupled with the fact that it was performed at a fairly late stage in the sequence led us to seek an alternative way to make our cyclization precursor (**4-130**).



Scheme 4.24. Synthesis of cyclization precursor **4-128** via a lithium-halogen exchange route.

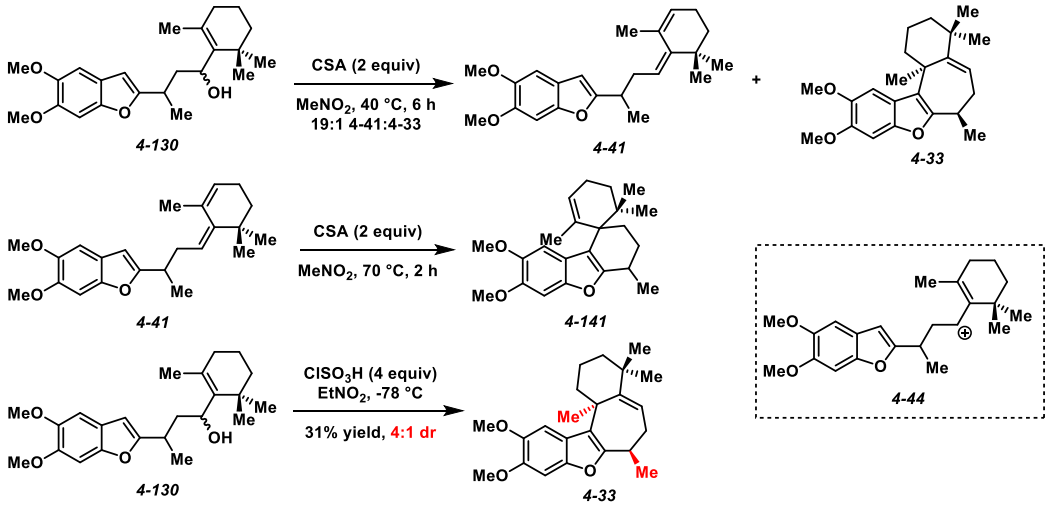
In a quest to obviate this relatively inefficient substitution procedure based on lithium halogen exchange, we devised a route based on a copper catalyzed substitution reaction (Scheme 4.25). We reasoned that ketone **4-132** might be unstable to extended exposure to strong base at relatively high temperatures, so we elected to reduce it to the corresponding allylic alcohol, a moiety that we would require to perform the acid catalyzed seven-membered ring formation anyway. Thus, reduction of the α,β-unsaturated ketone with $LiAlH_4$ gave the desired allylic alcohol **4-131** in 82% yield. The copper catalyzed substitution reaction efficiently provided the desired dimethoxyarene (**4-130**), although it was difficult to achieve complete consumption of starting material. In any event, the crude reaction mixture essentially contained only starting material and product, so the isolation of both **4-130** and **4-131** was relatively simple. Thus, we had finally devised an efficient method to access the precursor to our final cyclization reaction.



Scheme 4.25. Copper catalyzed methoxylation as an alternative route to prepare cyclization precursor **4-130**.

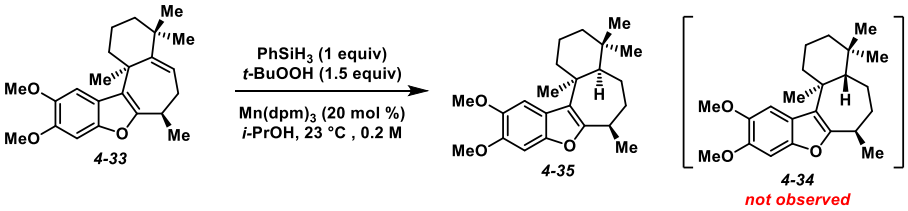
As discussed previously, we had hypothesized that the literature examples of [4 + 3] reactions *en route* to *epi*-liphagal had in fact been stepwise processes, so we had at this point prepared a compound (**4-130**) that would give

us access to what we had assumed was an intermediate in this known reaction (carbocation **4-44**). Unfortunately, conditions that had been previously used to effect this cycloaddition reaction did not work for our substrate (Scheme 4.26), instead giving a vast majority of diene **4-41**, the product of simple dehydration of our substrate (**4-130**). Because the reaction mixture containing this intermediate should have been virtually identical in both our case and the literature example, we took this as evidence that our mechanistic hypothesis for this cycloaddition reaction was in fact incorrect, and thus it was most likely that the reaction did actually occur in a concerted sense. Because the dehydration reaction to produce diene **4-41** was theoretically reversible, both allylic alcohol **4-130** and diene **4-41** should serve as potential precursors to our desired carbocationic intermediate (**4-44**). Thus, we attempted to induce this reverse reaction by simply raising the temperature of the reaction once it had consumed starting material. We were dismayed to find that this strategy did not lead to our product but instead gave one that we have tentatively assigned as spirocycle **4-141**. Though, in principle, diene **4-41** could in fact produce the desired allylic carbocation **4-44** by protonation, it can also produce another allylic carbocation, and both of these species could potentially undergo cyclization at both termini of this resonance stabilized cation. Thus, this diene could serve as the precursor for cyclization to produce anywhere from five- to eight-membered rings. It was clear that in order for the cyclization reaction to proceed as we desired, we had to shift the fate of this carbocation from predominantly undergoing elimination to predominantly undergoing substitution. Unexpectedly, we found that there is a paucity of literature describing factors that affect this partitioning of mechanistic pathways, but we decided that, based on first principles, a lower temperature would tend to favor cyclization. This is because ring formation should require a greater decrease in entropy in the transition state, and the effect of entropy on the free energy of a reaction (and its activation barrier) is positively correlated to absolute temperature. It was also clear that camphorsulfonic acid and nitromethane would not be suitable for this task, since these conditions failed to produce any product at less than 40 °C and nitromethane has the relatively high melting point of -20 °C. Therefore, we switched to a stronger acid ($ClSO_3H$) and a lower melting but similar solvent, $EtNO_2$. Using these conditions we were finally able to induce our desired cyclization reaction, albeit in the low yield of 31%. Attempts to further increase this yield by changing acids (*e.g.*, TfOH and $HBF_4{\bullet}OEt_2$) or further lowering the temperature to -90 °C only decreased the efficiency of the reaction. In addition, these conditions did not completely suppress the formation of spirocycle **4-141**, which presumably forms through the intermediacy of diene **4-41** followed by its further protonation and cyclization in these conditions as well. Nonetheless, we had finally achieved a formal synthesis of *epi*-liphagal.



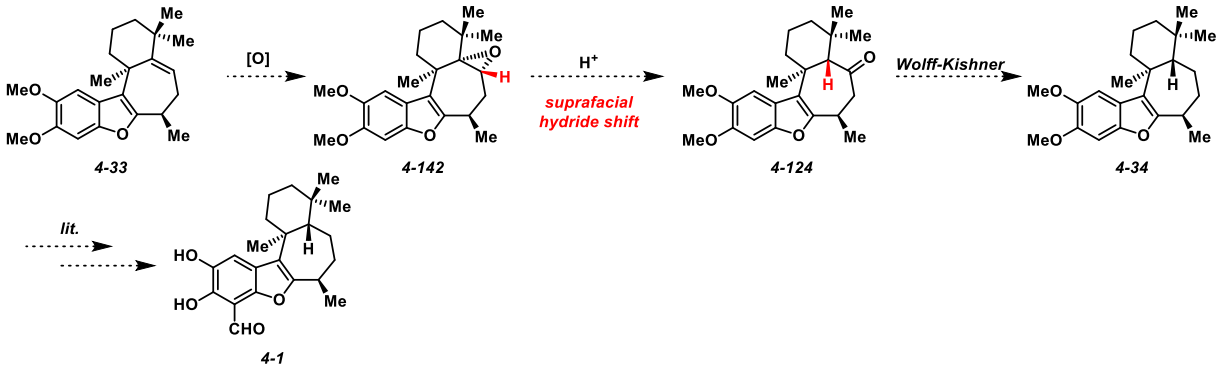
Scheme 4.26. Acid catalyzed cyclization of **4-130**.

Though other groups had failed at achieving hydrogenation of the olefin of **4-33** with the correct diastereoselectivity, we thought it worthwhile to attempt the synthesis of the correct, *trans* isomer of the natural product from this intermediate (Scheme 4.27). The vast majority of conditions for hydrogenation of olefins rely on kinetic control to generate product, so the favored diastereomer is determined based on the easiest sense of approach for the hydrogenation catalyst. We reasoned that all kinetically controlled hydrogenations were likely to give the same result, ultimately producing an intermediate that would be convertible to *epi*-liphagal rather than the natural product. However, since the publication of these previous reports on the synthesis of *epi*-liphagal, the Shenvi group had developed a radical hydrogenation that reliably produced diastereomeric products based on *thermodynamic* control rather than kinetic.[162] Based on first principles, we expected that the trans 7-6 junction would be thermodynamically favored over the *cis* junction, so we also expected that this method of hydrogenation would produce our desired diastereomer. Unfortunately, when we subjected olefin **4-33** to Shenvi's conditions, we obtained a complex mixture of products in which we could only detect the hydrogenation product containing the undesired cis 7-6 ring junction (**4-35**).



Scheme 4.27. Attempted thermodynamically controlled hydrogenation of dihydroliphagal precursor **4-33**.

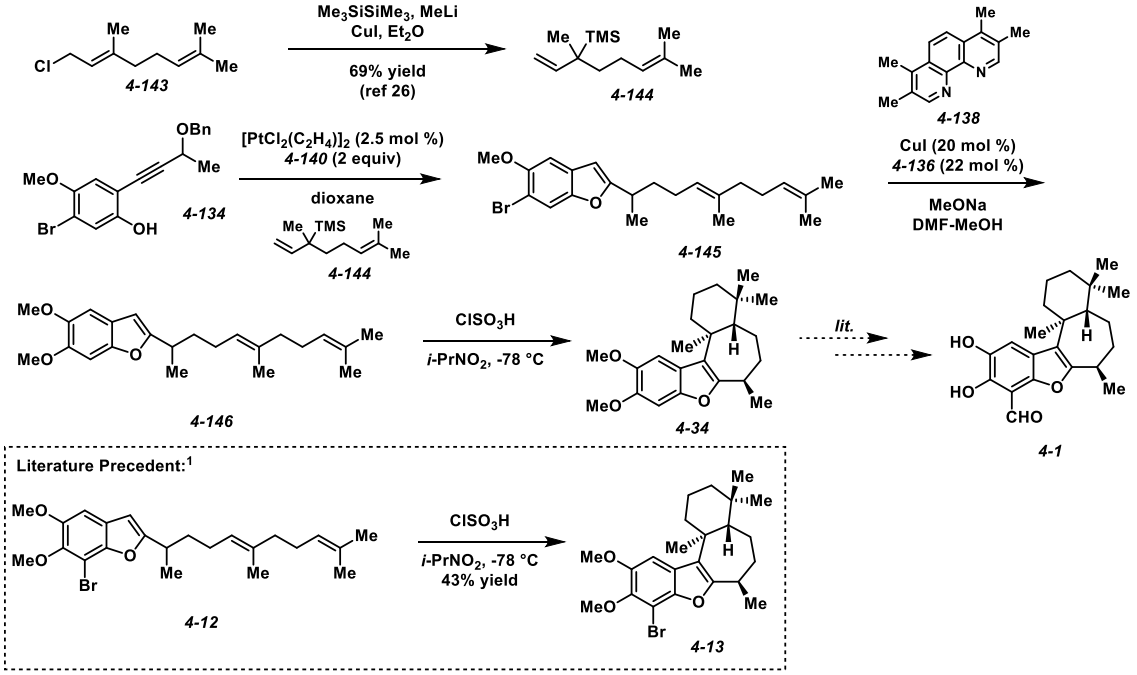
Though we decided to stop at this point, we propose here a plausible method for producing the desired stereochemistry of the natural product (Scheme 4.28). Because kinetically controlled hydrogenation gives a vast majority of the diastereomer arising from hydrogen adding to the α-face of the olefin, epoxidation, which is also a kinetically controlled reaction, should give delivery of oxygen from the same face to give epoxide **4-142**. This epoxide could then be induced to undergo a stereospecific suprafacial hydride shift based isomerization by treatment with either Brønsted or Lewis acid to give ketone **4-124**, which would contain the desired stereochemistry of the 7-6 ring junction. The carbonyl of ketone **4-124** could then be converted to a methylene group by a Wolff-Kishner reaction to achieve a formal synthesis of the correct diastereomer of liphagal (**4-1**).



Scheme 4.28. A possible method of constructing the crucial trans 7-6 junction.

A further alternative method confronts the problem of the trans 6-7 junction by avoiding the need for formal hydrogenation of cycloheptene **4-33** altogether (Scheme 4.29). This synthesis would install a geranyl fragment to the α,β-unsaturated Pt carbenoid generated as before by the addition of allylsilane nucleophile **4-144**. This allylsilane would be prepared from geranyl chloride (**4-143**) by a known cuprate S_N2' substitution.[163] Benzofuran **4-145** would then be subjected to our previous formal S_NAr conditions to install a methoxy group. Dimethoxyaryl polyene **4-146**

would then undergo an acid catalyzed cationic ring closure on treatment with $ClSO_3H$ to give cyclized product **4-34** in direct analogy to a system that only contains an additional bromine atom attached to the aromatic ring (**4-12** → **4-13**). This cyclization would, according to literature precedent,[130] likely give the correct trans 6-7 junction and thus represent a formal synthesis of liphagal.



Scheme 4.29. A possible synthesis of liphagal based on a cationic polyene cyclization analogous to a known example.

We have described above our synthetic efforts directed toward liphagal that ultimately culminated in a formal total synthesis of *epi*-liphagal (**4-36**). Our studies highlight the synthetic utility of α,β-unsaturated Pt carbenoids in complex settings as well as providing some guidelines of tolerated structural features, specifically with respect to the substitution of the aromatic ring. Furthermore, we provide here some ideas for accomplishing a total synthesis of the correct diastereomer of liphagal using many of the methods that we have developed for the synthesis of its epimer. We believe that the efforts we have described herein will contribute meaningfully to the usefulness of Pt carbenoids in a synthetic sense. Further efforts in our group have revealed that chiral ligands can be incorporated into this reaction to induce asymmetry in the product. This work, as well as that which I have described, could potentially be combined to produce a catalytic enantioselective total synthesis of liphagal.

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(156) Another possibility is that resonance donation from one oxygen atom on the aromatic ring decreases the electrophilicity of Pt carbenoid **4-96**. We see this as less likely to operate than the effect on the reactivity of the alkyne because we do not observe any products downstream from the putative hydroalkoxylation event. This observation, however, does not rule out the possibility of effects originating from the electronic properties of Pt carbenoid **4-96** influencing the course of the reaction, and this may in fact work in conjunction with the other effects delineated above.

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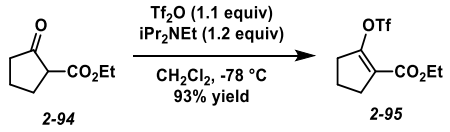
Appendix One: Experimental Section for Chapter Two.

Materials and Methods: Reactions were performed under an argon atmosphere unless otherwise noted. Hexanes, ether, dichloromethane, THF and toluene were purified by passing through activated alumina columns. Triethylamine, diisopropylamine, and diisopropylethylamine were distilled under Ar from CaH_2. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA) or Sigma-Aldrich (St. Louis, MO). Visualization was accomplished with UV light and exposure to $KMnO_4$ solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz) or a Varian 400 MR (at 400 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 101 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.0). ^{19}F NMR spectra were acquired on a Varian 400 MR (at 376 MHz) and are reported in ppm relative to HF (δ 0.0). Infrared spectra were recorded as films on a Nicolet 380 FTIR. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS, low resolution mass spectrometry data were acquired on an Agilent 6100 Single Quad LC/MS.



To a solution of **2-94** (40.3 g, 258 mmol) and *i*-Pr_2NEt (54.0 mL, 310 mmol) in CH_2Cl_2 (250 mL) at -78 °C was added Tf_2O (47.8 mL, 284 mmol) over the course of 20 min. The solution was stirred at -78 °C for 10 min. The reaction mixture was quenched by adding MeOH (10 mL) followed by H_2O (20 mL). The reaction mixture was then concentrated to remove CH_2Cl_2 (ammonium triflate salts are difficult to remove if this step is omitted). The residue was then slurried with Et_2O (125 mL) and petroleum ether (250 mL). This slurry was filtered, rinsing with petroleum ether (300 mL). The resulting solution was washed with sat. aq. NH_4Cl (200 mL) followed by brine (100 mL), dried by sequentially swirling with Na_2SO_4 and $MgSO_4$, filtered, and concentrated. The crude residue was purified by distillation at 0.015 mm Hg from a foil-wrapped flask through a vacuum jacketed, silvered 15 cm Hempel column to

maintain as low a temperature as possible. The fraction distilling at 58.5 - 66 °C was collected to give pure enol triflate **2-95** (69.1 g, 93% yield). The spectroscopic data for **2-95** matched those presented in the literature.[1]

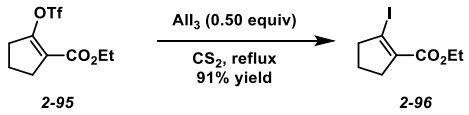
Data for enol triflate 2-95.

Physical State: Clear, yellow liquid.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.23 (q, *J* = 7.0 Hz, 2 H), 2.76 - 2.62 (comp m, 4 H), 1.99 (quin, *J* = 7.6 Hz, 2 H), 1.29 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 162.3, 153.4, 123.4, 118.3 (q, J_{C-F} = 320 Hz), 61.1, 32.7, 29.2, 18.7, 13.9.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -74.6 (s, 3 F).



2-95 *2-96*

A 100 mL Schlenk flask was charged with cut Al foil (405 mg, 15 mmol), I_2 (5.71 g, 22.5 mmol), and a stir bar, fitted with a reflux condenser, and purged quickly with Ar. CS_2 (15 mL) was then added through the top of the reflux condenser, and the resulting purple solution was stirred with brief heating with a heat gun. As soon as the reaction began to take place as evidenced by refluxing without external heat, the reaction mixture was immersed in an ice bath. The initial reaction is very rapid and exothermic, and a dry-ice acetone bath was kept on hand in case the reaction became too vigorous. When reflux began to slow, the ice bath was removed, and external heating was applied to keep the reaction slowly refluxing for an additional 1 h. The resulting solution of AlI_3 in CS_2 was used immediately.

Neat **2-95** (8.47 g, 30.0 mmol) was added through the condenser to the above solution of AlI_3 in CS_2 cooled in a water bath, and an additional portion of CS_2 was used to rinse the condenser. The resulting mixture was heated to a gentle reflux (to minimize foaming) for 8 h. At the end of this period, TLC indicated consumption of **2-95**. The reaction mixture was diluted with CH_2Cl_2 (75 mL) and carefully poured over crushed ice (~200 mL). Rochelle's salt (21.2 g, 75 mmol) was added to the biphase, and the mixture was stirred vigorously overnight. The organic layer was then separated and the aqueous layer extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed

with sat. aq. $Na_2S_2O_3$ (50 mL), dried with Na_2SO_4, and concentrated. The resulting crude residue was purified by flash column chromatography (19:1 pentane-Et_2O) to yield pure iodoenoate **2-96** (7.26 g, 91% yield).

Data for iodoenoate 2-96.

Physical State: Clear yellow liquid.

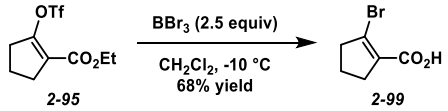
TLC: R_f = 0.53 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.23 (q, *J* = 7.0 Hz, 2H), 2.90 - 2.79 (m, 2H), 2.66 - 2.55 (m, 2H), 1.96 (app quintet, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 164.2, 138.4, 106.1, 60.5, 47.9, 33.2, 23.6, 14.2.

IR (film): ν = 2977, 2902, 2852, 1703, 1249, 1191, 1125, 1111, 1055.

MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_8H_{11}IO_2 + H]^+$: 267.0, found 267.1.



To a solution of alkenyl triflate **2-95** (2.88 g, 10.0 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added BBr_3 (2.37 mL, 25.0 mmol), dropwise. The reaction mixture was stirred 24 h at -10 °C and then cooled to -78 °C. The excess BBr_3 was quenched by adding Et_2O (10 mL) and the solution was then allowed to warm to ambient temperature. The reaction mixture was then poured into 1 M HCl (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and concentrated. The resulting crude residue was purified by recrystallization from heptane to yield pure alkenyl bromide **2-99** (1.28 g, 68% yield).

Data for bromide 2-99.

TLC: R_f = 0.19 (89:10:1 hexanes-EtOAc-AcOH, $KMnO_4$ stain solution).

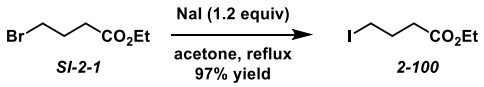
Physical State: Colorless solid.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 9.54 (br. s, 1 H), 2.86 (tt, *J* = 7.8, 2.5 Hz, 2 H), 2.68 (tt, *J* = 7.4, 2.3 Hz, 2 H), 1.99 (quintet, *J* = 7.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 169.1, 135.6, 131.4, 43.5, 32.9, 21.6.

IR (film): ν = 2975, 2900 (br), 2883, 2837, 1666, 1649, 1614, 1427, 1407, 1284, 917.

MS (ESI-): *m/z* calc'd for $(M - H)^-$ $[C_6H_7BrO_2 - H]^-$: 188.9557, found 188.9555.



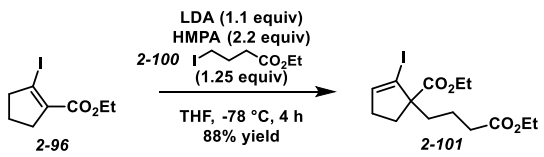
A solution of **SI-2-1** (42.5 g, 218 mmol) and NaI (39.2 g, 262 mmol) in acetone (220 mL) was heated to reflux for 16 h. At this point, ^{1}H NMR of an evaporated aliquot indicated >97% conversion. The reaction mixture was diluted with Et_2O (200 mL) and filtered, rinsing with Et_2O (100 mL). The filtrate was concentrated, redissolved in Et_2O (200 mL), and washed sequentially with H_2O (100 mL mL), sat. aq. Na_2CO_3 (50 mL), sat. aq. $Na_2S_2O_3$ (50 mL), and brine (50 mL). The ether extract was dried with Na_2SO_4 and concentrated to give alkyl iodide **2-100** (51.3 g, 97% yield). The spectroscopic data for **2-100** matched that in the literature.[2]

Data for iodide 2-100.

Physical State: Clear yellow liquid.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.12 (q, *J* = 7.3 Hz, 2 H), 3.22 (t, *J* = 6.8 Hz, 2 H), 2.42 (t, *J* = 7.2 Hz, 2 H), 2.11 (app quintet, *J* = 6.9 Hz, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 172.3, 60.5, 34.8, 28.5, 14.2, 5.5.



To a solution of *i*-Pr_2NH (6.56 mL, 46.4 mmol) in THF (120 mL) at -78 °C was added *n*-BuLi (17.0 mL, 2.5 M in hexanes, 42.6 mmol). The solution was allowed to warm to 0 °C and stirred for 15 min before recooling to -78 °C. HMPA (14.8 mL, 85.1 mmol) was added followed by a solution of **C-1** (10.3 g, 38.7 mmol) in THF (20 mL) at -78 °C. The latter transfer was quantitated with THF (2 x 5 mL). The resulting red solution was stirred at -78 °C for 30 min and then neat **C-16** (12.1 g, 50.0 mmol) was added. The reaction mixture was stirred at -78 °C for 4 h at which point TLC indicated consumption of **C-1**. The reaction mixture was quenched by adding 1 M HCl (20 mL) at -78 °C. The reaction mixture was then concentrated *in vacuo* to remove THF. The resulting residue was partitioned between pentane (100 mL) and 10% aq. HCl (100 mL). The organic layer was collected and the aqueous layer extracted with pentane (2 x 50 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (SiO_2, hexanes → 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc) to afford pure **C-2** (13.0 g, 88% yield) and a mixed fraction (1.66 g, 58 wt % **C-2**, 42 wt % **C-16**, 6.5% yield **C-2**).

Data for diester 2-101.

Physical State: Clear yellow liquid.

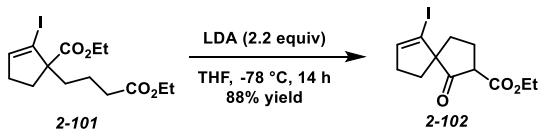
TLC: R_f = 0.27 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.27 (t, *J* = 2.5 Hz, 1 H), 4.14 (app. dq, *J* = 7.0, 1.6, 4 H), 4.11 (q, *J* = 7.0 Hz, 1 H), 2.54 - 2.27 (m, 5 H), 1.99 - 1.78 (m, 2 H), 1.62 - 1.46 (m, 3 H), 1.25 (t, *J* = 7.0 Hz, 6 H), 1.24 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 174.0, 173.3, 143.2, 98.5, 63.1, 61.0, 60.3, 35.6, 34.4, 34.0, 30.9, 19.5, 14.25, 14.19.

IR (film): ν = 2979, 2935, 2872, 2851, 1725, 1232, 1161, 1093, 1023.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{14}H_{21}IO_4 + NH_4]^+$: 398.0823, found 398.0825.



2-101 2-102

To a solution of *i*-Pr_2NH (11.1 mL, 78.4 mmol) in THF (300 mL) at -78 C was added *n*-BuLi (28.6 mL, 2.5 M in hexanes, 71.4 mmol). The solution was allowed to warm to 0 °C and stirred for 15 min before recooling to -78

°C. To this solution was added a solution of **2-101** (10.3 g, 38.7 mmol) in THF (10 mL) at -78 °C. This transfer was quantitated with THF (2 x 5 mL). The resulting solution was aged at -78 °C without stirring for 14 h then warmed to 0 °C and stirred at this temperature for 1 h, at which point TLC indicated consumption of **2-101**. The reaction mixture was quenched by adding sat. aq. NH_4Cl and concentrated to remove THF. The resulting residue was partitioned between Et_2O (100 mL) and sat. aq. NH_4Cl (100 mL). The organic layer was collected and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and concentrated. The crude residue was purified by passing through a plug of SiO_2 rinsing with 9:1 hexanes-EtOAc to afford **2-102** (10.0 g, 88% yield).

Data for ketoester 2-102.

Physical State: Clear red liquid.

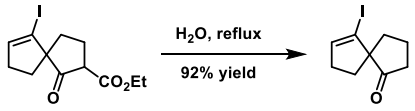
TLC: R_f = 0.36 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 10.19 (br. s, 1 H, enol), 6.34 (t, *J* = 2.3 Hz, 1 H, ketone), 6.20 (t, *J* = 2.5 Hz, 1 H, enol), 4.31 - 4.04 (comp. m, 4 H, both), 3.32 (dd, *J* = 4.3, 8.6 Hz, 1 H, enol), 3.15 (dd, *J* = 11.3, 8.6 Hz, 1 H, ketone), 2.61 - 1.65 (comp. m, 16 H, both), 1.36 - 1.17 (comp. m, 6 H, both).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 212.0, 169.3, 168.0, 144.04, 143.99, 142.0, 101.8, 101.3, 96.8, 67.6, 67.4, 61.5, 61.4, 60.1, 54.8, 53.2, 35.7, 34.5, 34.2, 33.73, 33.65, 33.4, 33.31, 33.27, 24.6, 24.1, 23.8, 14.4, 14.3, 14.2.

IR (film): ν = 2958, 2936, 2865, 1750, 1722, 1243, 1222, 1182, 1139, 1021.

MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{15}IO_3 + H]^+$: 335.0, found 335.0.



2-102 *2-91*

A biphase of ketoester **2-102** (8.16 g, 24.4 mmol) in H_2O (200 mL) was heated to reflux with vigorous stirring for 20 h. The resulting mixture was allowed to cool and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic

extracts were washed with brine (50 mL), dried with Na_2SO_4, and concentrated to give pure ketone **2-91** (5.92 g, 92% yield).

Data for ketone 2-91.

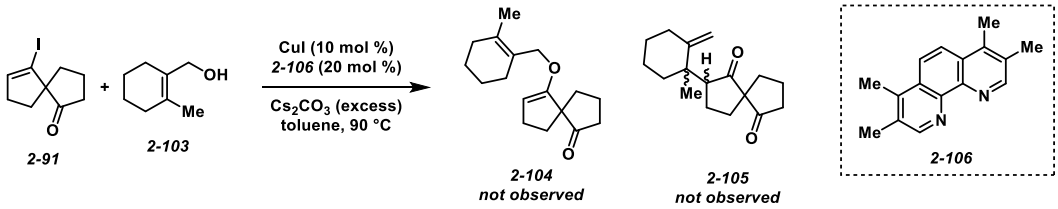
Physical State: Clear yellow liquid.

TLC: R_f = 0.29 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

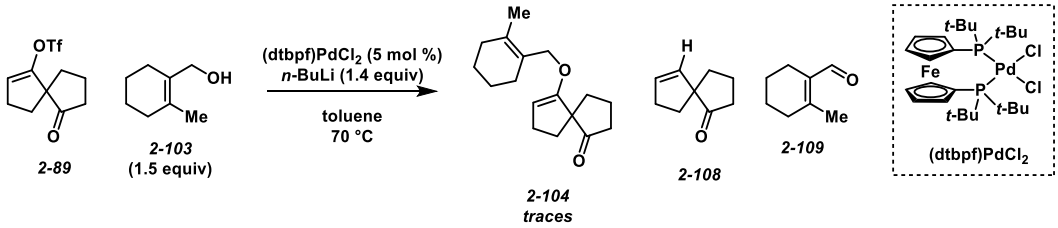
^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.32 (t, *J* = 2.5 Hz, 1 H), 2.49 - 2.25 (m, 4 H), 2.24 - 2.03 (m, 5 H), 1.94 - 1.74 (m, 4 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 219.7, 143.3, 97.8, 66.8, 37.8, 35.6, 34.4, 33.2, 19.7.

IR (film): ν = 2955, 2884, 2847, 1734, 1154, 1032, 851, 815.

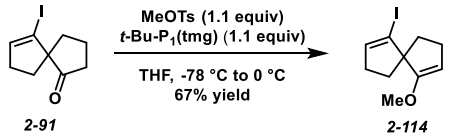


To a solution of vinyl iodide **2-91** (77.4 mg, 0.293 mmol) and allylic alcohol **2-103** (76.0 mg, 0.600 mmol) in toluene (0.150 mL) in an oven dried 2 dram vial was added CuI (11.4 mg, 0.0600 mmol), 3,4,7,8-tetramethylphenanthroline (**2-106**, 28.3 mg, 0.120 mmol), and dry Cs_2CO_3 (240 mg, 0.750 mmol) under an Ar purge. The vial was capped and heated in an Al block to 90 °C with vigorous stirring for 1 h. At this point, the solvent had completely evaporated, so an additional charge of toluene was added (0.100 mL) under an Ar purge after the vial had cooled. The reaction was reheated to 90 °C. This procedure was repeated at 3 h with an additional charge of toluene (0.200 mL), and the reaction was reheated to 90 °C for an additional 12 h. The reaction was then allowed to cool and partitioned between 10% NH_4OH (25 mL) and $CHCl_3$ (25 mL). The organic layer was separated, washed with brine (25 mL), dried with $MgSO_4$, concentrated, and analyzed by ^{1}H NMR.



2-89 *2-103* (1.5 equiv) *2-104* *traces* *2-108* *2-109*

A solution of allylic alcohol **2-103** (45.8 mg, 0.360 mmol) in toluene (0.60 mL) at 0 °C in an oven dried 2 dram vial was treated with *n*-BuLi (0.132 mL, 2.5 M in hexanes, 0.336 mmol). To the resulting solution was added vinyl triflate **2-89**[3] (68.5 mg, 0.240 mmol) and (dtbpf)$PdCl_2$ (7.9 mg, 0.0480 mmol) under an Ar purge. The resulting solution was heated to 70 °C and stirred for 2 h, at which point TLC indicated consumption of triflate **2-89**. The reaction mixture was then allowed to cool, diluted with Et_2O, and filtered through a plug of SiO_2, rinsing with Et_2O. The filtrate was concentrated and analyzed by ^1H NMR. Keto olefin **2-108**[3] and enal **2-109**[4] were identified by their literature spectra. The assignment of unisolated enol ether **2-104** was made by analogy to methyl enol ether **2-114**.



2-91 *2-114*

To a solution of ketone **2-91** (46.4 mg, 0.177 mmol) and MeOTs (35.9 mg, 0.193 mmol) in THF (2.0 mL) at -78 °C was added a solution of *t*-Bu-P_1(tmg)[5] (0.772 mL, 0.25 M in hexanes, 0.193 mmol). The resulting solution was stirred at -78 °C for 2 min the allowed to warm to 0 °C, at which point the reaction was complete. The solution was then poured into a mixture of sat. aq. NH_4Cl (10 mL) and H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 39:1 hexanes-EtOAc) to give **2-114** (32.7 mg, 67% yield).

Data for enol ether 2-114.

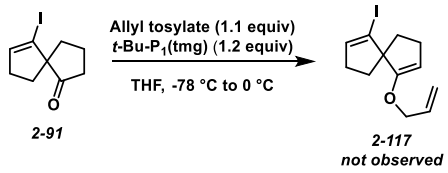
Physical State: Clear yellow liquid.

TLC: R_f = 0.45 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution)

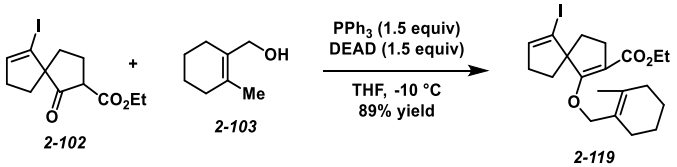
^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.14 (t, *J* = 2.2 Hz, 1 H), 4.63 (t, *J* = 2.2 Hz, 1 H), 3.61 (s, 3 H), 2.47 - 2.15 (comp m, 5 H), 2.02 (ddd, *J* = 13.7, 9.4, 5.5 Hz, 1 H), 1.88 (ddd, *J* = 12.5, 8.0, 4.5 Hz, 1 H), 1.80 (ddd, *J* = 12.9, 8.6, 4.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 161.8, 140.2, 106.2, 95.6, 65.2, 57.2, 35.4, 33.4, 33.2, 26.1.

IR (film): ν = 3438 (br), 2989, 2954, 2915, 1847, 1710, 1438, 1271, 1254, 1222, 1204, 1124, 1099, 1033, 932, 878.



To a solution of ketone **2-91** (44.1 mg, 0.157 mmol) and allyl tosylate (42.5 mg, 0.172 mmol) in THF (1.5 mL) at -78 °C was added a solution of *t*-Bu-P_1(tmg)[5] (0.752 mL, 0.25 M in hexanes, 0.188 mmol). The resulting solution was stirred at -78 °C for 2 min the allowed to warm to 0 °C, at which point the reaction was complete. The solution was then poured into a mixture of sat. aq. NH_4Cl (10 mL) and H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$, and concentrated. The resulting residue was partially purified by flash column chromatography (SiO_2, 39:1 hexanes-EtOAc) to give a colorless liquid (33.3 mg) that contained a complex mixture of compounds. The liquid was analyzed by ^{1}H and ^{13}C NMR and did not contain any of the diagnostic peaks that would be associated with enol ether **2-117**.



To a stirred solution of PPh_3 (1.57 g, 6.00 mmol) in THF (8.0 mL) at -10 °C (ice/brine) was added DEAD (0.944 mL, 6.00 mmol), immediately discharging the color of the latter. To the resulting clear, colorless solution was added **2-103** (631 mg, 5.00 mmol), neat, followed by **2-102** (1.31 g, 3.92 mmol), neat, both via tared syringe. The

reaction mixture was stirred at -10 °C for 1 h, and allowed to warm to ambient temperature with the ice bath at which point TLC indicated consumption of starting materials. The reaction mixture was diluted with pentane (20 mL) and filtered through a pad of celite, rinsing with pentane (50 mL). The filtrate was concentrated and purified by flash column chromatography (SiO_2 neutralized with 99:1 hexanes/Et_3N, 19:1 hexanes/EtOAc) to give enol ether **2-119** (1.55 g, 89% yield).

Data for enol ether 2-119.

Physical State: Clear yellow liquid.

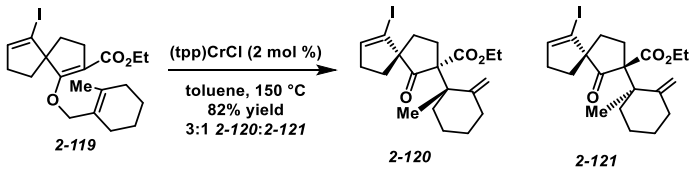
TLC: R_f = 0.53 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.12 (t, *J* = 2.3 Hz, 1 H), 4.91 (d, *J* = 10.6 Hz, 1 H), 4.46 (d, *J* = 11.0 Hz, 1 H), 4.17 (qd, *J* = 7.1, 2.5 Hz, 2 H), 2.71 (ddd, *J* = 14.7, 9.2, 5.9 Hz, 1 H), 2.49 (ddd, *J* = 14.6, 9.3, 4.7 Hz, 1 H), 2.42 - 2.22 (comp m, 3 H), 2.10 - 2.03 (m, 2 H), 1.99 (ddd, *J* = 13.7, 9.0, 4.7 Hz, 1 H), 1.95 (br. s, 2 H), 1.89 - 1.79 (m, 1 H), 1.68 (s, 3 H), 1.68 (ddd, *J* = 13.7, 9.0, 5.5 Hz, 1 H), 1.56 (app dt, *J* = 6.4, 3.3 Hz, 4 H), 1.28 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR ($CDCl_3$, 101MHz): δ = 168.9, 165.5, 141.3, 132.6, 126.7, 106.7, 103.4, 74.0, 68.4, 59.8, 34.5, 33.8, 33.1, 32.0, 28.9, 27.6, 22.94, 22.91, 19.3, 14.4.

IR (film): ν = 2927, 3857, 1701, 1615, 1193, 1072, 1031.

MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{27}IO_3 + H]^+$:443.1, found 443.1.



To a 2 dram vial containing a solution of **2-119** (1.49 g, 3.37 mmol) in toluene (6.7 mL) was added (tpp)CrCl (47.0 mg, 0.0673 mmol). The solution was sparged with Ar for 15 min, sealed and heated in an Al block to 150 °C for 12 h. The solution was then cooled and the reaction mixture directly purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc) to give a 3:1 mixture (by ^{1}H NMR) of **2-120** and **2-121** (1.22 g, 82% yield). An analytical sample was prepared from this mixture by recrystallization from MeOH to give pure **2-121** as x-ray quality crystals.

Data for isolated keto ester 2-120.

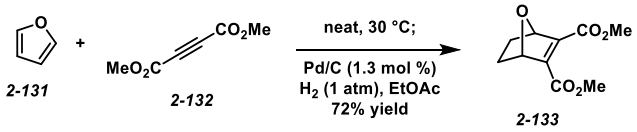
Physical State: Colorless needles (MeOH).

TLC: R_f = 0.46 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.34 (t, *J* = 2.5 Hz, 1 H), 4.94 (s, 1 H), 4.91 (s, 1 H), 4.27 (dq, *J* = 10.6, 7.0 Hz, 1 H), 4.12 (dq, *J* = 11.0, 7.0 Hz, 1 H), 2.62 (ddd, *J* = 12.9, 6.3, 0.8 Hz, 1 H), 2.44 - 2.16 (m, 5 H), 2.04 (ddd, *J* = 12.9, 8.6, 5.5 Hz, 1 H), 1.92 (td, *J* = 13.3, 6.3 Hz, 1 H), 1.75 - 1.34 (m, 6 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.22 (s, 3 H), 1.18 (dt, *J* = 13.3, 3.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 212.6, 169.4, 152.4, 144.0, 113.2, 98.6, 68.8, 67.7, 61.6, 45.0, 34.7, 33.1, 33.0, 31.9, 28.8, 24.3, 23.0, 19.3, 14.2.

IR (film): ν = 2972, 2932, 2866, 1707, 1227, 1199, 1177, 1089, 823.



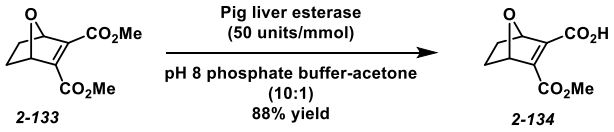
A mixture of **2-131** (7.27 mL, 100 mmol) and **2-132 (**5.68 g, 40.0 mmol) was heated to 30 °C for 36 h (at which time ^{1}H NMR indicated ~90% conversion). The resulting mixture was concentrated *in vacuo* to remove excess **2-131**, and the residue was dissolved in EtOAc (25 mL). To this solution was added a stir bar and Pd/C (10 wt % Pd, 53.2 mg, 0.500 mmol), and the reaction mixture was sparged with H_2 for 2 min and then stirred vigorously under H_2 (balloon pressure) for 3 h. The reaction mixture was filtered through SiO_2, rinsing with 4:1 hexanes-EtOAc (100 mL). The filtrate was concentrated, coevaporated with hexanes, and then held under high vacuum for 1 h. The resulting residue was extracted with boiling hexanes (50 mL then 25 mL) and decanted from viscous insoluble material. The extracts were diluted with toluene (25 mL) and crystallized at -10 °C to give diester **2-133** (6.11 g, 72% yield). The spectroscopic data for diester **2-133** matched those in the literature.[6]

Data for diester 2-133.

Physical State: Colorless prisms.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.23 (dd, *J* = 3.1, 1.6 Hz, 2 H), 3.78 (s, 6 H), 2.00 – 1.89 (m, 2 H), 1.45 (dd, *J* = 11.7, 3.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 162.9, 143.1, 80.5, 52.2, 24.2.



A solution of 0.10 M pH 8 phosphate buffer was prepared by adding NaOH (1.48 g, 37.1 mmol) and NaH_2PO_4 (4.80 g, 40.0 mmol) to H_2O (100 mL) and then diluting with H_2O until the total volume of the solution had reached 200 mL. A solution of **C-19** (4.24 g, 20.0 mmol) in acetone (20 mL) was diluted with pH 8 phosphate buffer (200 mL, 0.10 M) and charged with pig liver esterase (19 units/mg, 58.8 mg, 1000 units) and stirred at ambient temperature for 16 h. The reaction mixture was then acidified with 10% aq. HCl (25 mL), saturated with NaCl, and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. The resulting residue was purified by recrystallization from 3:2 heptane-toluene to give a first crop of **2-134** (2.75 g). The mother liquor was concentrated *in vacuo* and the resulting residue was recrystallized from 3:2 heptane-toluene to give a second crop of **2-134** (750 mg, 88% yield overall).

Data for 2-134.

Physical State: Colorless powdery solid.

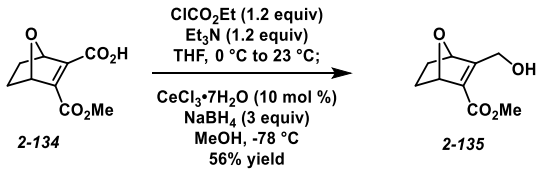
TLC: R_f = 0.38 (1:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.41 (d, *J* = 2.7 Hz, 1 H), 5.34 (d, *J* = 3.1 Hz, 1 H), 3.96 (s, 3 H), 2.06 - 1.98 (m, 2 H), 1.42 (d, *J* = 3.5 Hz, 1 H), 1.39 (d, *J* = 3.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 166.5, 160.6, 151.1, 141.1, 81.0, 79.9, 54.0, 24.2, 23.5.

IR (film): ν = 3028, 2964, 2741, 1729, 1656, 1621, 1443, 1424, 1349, 1315, 1291, 854.

MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_9H_{10}O_5 + H]^+$:199.1, found 199.1.



A solution of **2-134** (2.38 g, 12.0 mmol) and Et_3N (2.01 mL, 14.4 mmol) in THF (24 mL) at 0 °C was treated with $ClCO_2Et$ (1.38 mL, 14.4 mmol) causing a colorless precipitate to form. This solution was then allowed to warm to ambient temperature and allowed to stand for 10 min. The mixed anhydride solution was then diluted with sufficient THF (~36 mL) to make a fluid suspension and then filtered, rinsing the filtrant with THF (50 mL). Meanwhile, a solution of $CeCl_3•7H_2O$ in THF-MeOH was prepared by first dissolving $CeCl_3•7H_2O$ (447 mg, 1.20 mmol) in MeOH (12 mL) and diluting with THF (12 mL). This solution was cooled to -78 °C and treated with $NaBH_4$ (454 mg, 12.0 mmol). The mixed anhydride solution was then added dropwise via dropping funnel at a rate of approximately 3 drops/s. Once a third of the mixed anhydride solution had been added, addition was ceased and an additional portion of $NaBH_4$ (454 mg, 12.0 mmol) was added, and addition was resumed. Once two thirds of the mixed anhydride solution had been added, this procedure was repeated. The solution was stirred at -78 °C for 1 h, at which point TLC indicated consumption of **C-20** (formed by silica gel hydrolysis of the first-formed mixed anhydride). The reaction mixture was warmed to room temperature and carefully quenched with H_2O (5 mL). The mixture was then concentrated to remove THF and MeOH. The resulting residue was suspended in H_2O (100 mL) and treated with 10% HCl until solids disappeared. This aqueous emulsion was then saturated with NaCl and extracted with EtOAc (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried with Na_2SO_4, and concentrated. The resulting crude residue was purified by flash column chromatography (SiO_2, 1:1 hexanes-EtOAc) to give pure hydroxyester **2-135** (1.24 g, 56% yield)

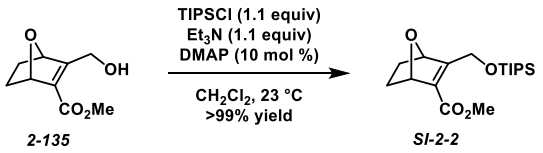
Data for hydroxyester 2-135.

Physical State: Colorless liquid.

TLC: R_f = 0.18 (1:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.20 (d, *J* = 3.5 Hz, 1 H), 5.02 (d, *J* = 4.3 Hz, 1 H), 4.65 (d, *J* = 17.6 Hz, 1 H), 4.54 (d, *J* = 17.6 Hz, 1 H), 3.78 (s, 3 H), 1.97 - 1.83 (m, 2 H), 1.38 (dt, *J* = 17.2, 8.6 Hz, 1 H), 1.34 (dt, *J* = 17.2, 9.05 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 165.0, 162.3, 132.5, 80.7, 79.4, 58.4, 52.0, 25.0, 23.9.



To a solution of **2-135** (3.96 g, 21.3 mmol), Et_3N (3.26 mL, 23.4 mmol) and DMAP (260 mg, 2.13 mmol) in CH_2Cl_2 (21 mL) was added TIPSCl (5.01 mL, 23.4 mmol). The resulting solution was stirred at room temperature for 14 h, at which point TLC indicated consumption of **2-135**. The reaction mixture was poured into NH_4Cl and extracted with $CHCl_3$ (3 x 25 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. The resulting crude residue was purified by passing dissolving in hexanes (25 mL) and passing through a short column of SiO_2, rinsing with 4:1 hexanes-Et_2O (125 mL) to give pure silyl ether **SI-2-2** (7.26 g, >99% yield).

Data for TIPS ether SI-2-2.

Physical State: Colorless liquid.

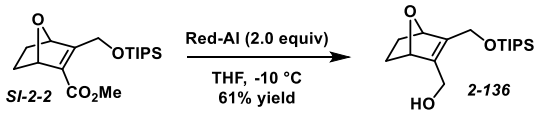
TLC: R_f = 0.27 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.31 (d, *J* = 4.3 Hz, 1 H), 5.19 (d, *J* = 3.9 Hz, 1 H), 4.91 (d, *J* = 16.0 Hz, 1 H), 4.71 (d, *J* = 16.0 Hz, 1 H), 3.73 (s, 3 H), 1.91 (s, 2 H), 1.42 - 1.28 (m, 2 H), 1.18 - 1.00 (m, 21 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 163.8, 161.7, 130.7, 80.5, 79.3, 58.9, 51.3, 24.8, 24.0, 17.9, 11.8.

IR (film): ν =3425 (br), 2934, 2866, 1719, 1463, 1270, 1248, 1104, 1014, 995, 919, 818.

MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{32}O_4Si + H]^+$:341.2143, found 341.2143.



To a solution of **SI-2-2** (8.04 g, 23.5 mmol) in THF (100 mL) at -78 °C was added Red-Al (65% (w/w) in toluene, 13.8 mL, 47.0 mmol) over 10 min. The reaction mixture was stirred at this temperature for 2 h then allowed to warm to 0 °C, at which point TLC indicated consumption of **2-136**. The solution was then quenched carefully with H_2O (2.4 mL) and diluted with Et_2O (200 mL). The resulting solution was then treated with 5.0 M NaOH (2.4 mL) followed by H_2O (7.2 mL) and allowed to warm to room temperature. The reaction mixture formed a copious white precipitate and was stirred for an additional hour before adding $MgSO_4$ (2.0 g). The mixture was stirred an additional 5 min and filtered, rinsing with Et_2O (100 mL). The filtrate was concentrated, and the resulting crude residue was purified by flash column chromatography (SiO_2, 4:1 hexanes-EtOAc) to give pure diol monosilyl ether **2-136** (4.47 g, 61% yield).

Data for diol mono-TIPS ether 2-136.

Physical State: Colorless liquid.

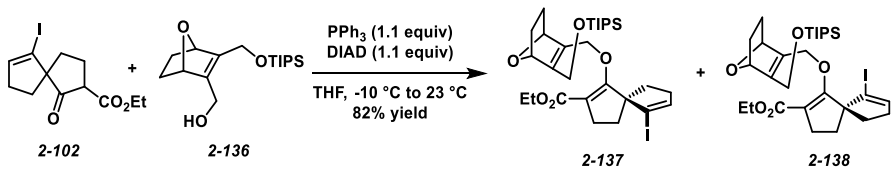
TLC: R_f = 0.11 (4:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.91 (d, *J* = 3.5 Hz, 1 H), 4.88 (d, *J* = 3.1 Hz, 1 H), 4.49 (d, *J* = 14.1 Hz, 1 H), 4.38 (d, *J* = 14.1 Hz, 1 H), 4.30 (td, *J* = 14.1, 1.6 Hz, 1 H), 4.25 (td, *J* = 14.5, 1.2 Hz, 1 H), 2.80 (br. s, 1 H), 1.88 - 1.73 (m, 2 H), 1.31 (dd, *J* = 7.4, 1.6 Hz, 2 H), 1.18 - 0.98 (comp m, 23 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 141.24, 141.17, 80.3, 80.1, 58.5, 56.9, 25.2, 25.1, 17.9, 11.8.

IR (film): ν = 3419 (br), 2943, 2890, 2865, 1462, 1098, 1061, 1012, 880.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{17}H_{32}O_3Si + NH_4]^+$: 330.2459, found 330.2459.



To a stirred solution of PPh_3 (1.15 g, 4.40 mmol) in THF (6.5 mL) at -10 °C was added DIAD (0.872 mL, 4.40 mmol), immediately discharging the color of the latter. This solution was stirred 10 min. To the resulting clear, colorless solution was added a solution of **2-102** (1.25 g, 4.00 mmol) and **2-136** (1.34 g, 4.00 mmol) in THF (3.5 mL) *via* cannula. The transfer was quantitated with THF (2.0 mL). The reaction mixture was stirred at 10 °C for 15 min then warmed to ambient temperature and stirred for 2 h, at which point TLC indicated consumption of starting materials. The reaction mixture was concentrated *in vacuo* and applied directly to a silica gel column topped with a layer of hexanes (10 mL) as a solution in CH_2Cl_2 (2 mL), eluting with 19:1 hexanes-EtOAc to give pure diatereomeric mixture **2-137** and **2-138** (2.07 g, 82% yield).

Data for mixture of diastereomeric enol ethers 2-137 and 2-138.

Physical State: Colorless liquid.

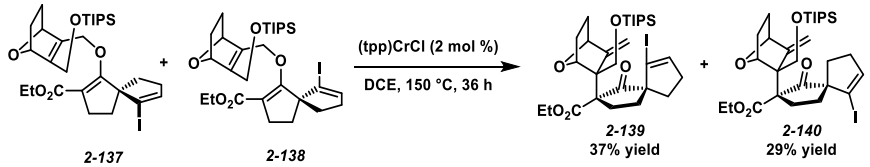
TLC: R_f = 0.29 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.37 (t, *J* = 2.3 Hz, 1 H), 6.15 (app dt, *J* = 8.2, 2.3 Hz, 2 H), 5.22 (d, *J* = 12.9 Hz, 1 H), 5.13 (d, *J* = 12.5 Hz, 1 H), 5.05 (d, *J* = 3.9 Hz, 4 H), 4.67 (d, *J* = 12.1 Hz, 1 H), 4.57 (d, *J* = 12.5 Hz, 1 H), 4.52 - 4.41 (m, 2 H), 4.40 - 4.29 (m, 2 H), 4.27 - 4.11 (m, 7 H), 3.18 (dd, *J* = 8.4, 11.2 Hz, 1 H), 2.75 - 2.64 (m, 2 H), 2.60 - 2.06 (m, 18 H), 2.06 - 1.55 (m, 15 H), 1.38 - 1.21 (m, 15 H), 1.17 - 0.96 (m, 44 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 212.0, 211.9, 169.3, 168.5, 168.4, 165.1, 144.10, 144.05, 144.0, 143.9, 142.1, 141.5, 141.4, 136.8, 136.6, 107.4, 106.8, 103.3, 103.2, 101.3, 80.4, 79.93, 79.88, 79.8, 68.65, 68.56, 67.7, 67.65, 67.61, 61.4, 60.1, 60.0, 59.9, 57.7, 57.6, 54.8, 53.2, 35.7, 34.6, 34.4, 34.25, 34.19, 33.75, 33.71, 33.68, 33.65, 33.5, 33.31, 33.27, 32.8, 32.7, 28.9, 28.8, 25.2, 25.0, 24.9, 24.8, 24.6, 24.1, 18.0, 17.7, 14.3, 14.1, 12.3, 11.9

IR (film): ν = 2941, 2864, 1703, 1196, 1106, 1064, 1028, 880.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{29}H_{45}IO_5Si + NH_4]^+$: 646.2419, found 646.2429.



2-137 *2-138* *2-139* 37% yield *2-140* 29% yield

A stirred solution of diastereomers **2-137** and **2-138** (1.70 g, 2.71 mmol) and (tpp)CrCl (38.0 mg, 0.0540 mmol) in DCE (5.4 mL) in a 2 dram vial was sparged with Ar for 15 min and capped with a PTFE lined cap. The solution was then heated to 150 °C for 36 h, at which point TLC (9:1 hexanes/EtOAc) showed completion by the absence of a UV active spot at the starting material R_f (this R_f still contained a $KMnO_4$ active spot). The reaction mixture was then allowed to cool, diluted with pentane (5 mL), and filtered through a plug of SiO_2, rinsing with 4:1 hexanes-EtOAc. The filtrate was concentrated and applied to a silica gel column eluting with CH_2Cl_2 → 99:1 CH_2Cl_2-Et_2O → 98:2 CH_2Cl_2-Et_2O to afford keto esters **C-8** (629 mg, 37% yield) and **C-9** (493 mg, 29% yield).

Data for keto ester 2-139.

Physical State: Pale brown oil.

TLC: R_f=0.03 (CH_2Cl_2, $KMnO_4$ stain solution)

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.40 (t, *J* = 2.3 Hz, 1 H), 5.28 (d, *J* = 5.1 Hz, 1 H), 5.04 (s, 1 H), 4.71 (s, 1 H), 4.62 (d, *J* = 5.1 Hz, 1 H), 4.28 - 4.06 (comp m, 3 H), 3.97 (d, *J* = 11.0 Hz, 1 H), 2.68 (dd, *J* = 13.3, 5.9 Hz, 1 H), 2.46 - 2.23 (comp m, 3 H), 2.16 (ddd, *J* = 12.6, 8.5, 4.3 Hz, 1 H), 2.08 (ddd, *J* = 12.2, 8.9, 3.5 Hz, 1 H), 1.87 (dt, *J* = 13.3, 5.9 Hz, 1 H), 1.84 - 1.76 (m, 1 H), 1.66 (dd, *J* = 12.5, 2.0 Hz, 1 H), 1.71 - 1.57 (comp m, 3 H), 1.57 - 1.49 (m, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.07 (s, 21 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 212.4, 169.0, 152.1, 144.5, 106.4, 98.4, 82.2, 82.0, 68.5, 65.5, 63.4, 62.1, 57.8, 35.3, 32.9, 32.4, 31.1, 30.3, 25.5, 18.1, 14.0, 12.2.

IR (film): ν = 2942, 2891, 2866, 1723, 1206, 1096, 914, 882.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{29}H_{45}IO_5Si + NH_4]^+$: 629.2429, found 646.2429.

Data for keto ester 2-140.

Physical State: Pale yellow oil.

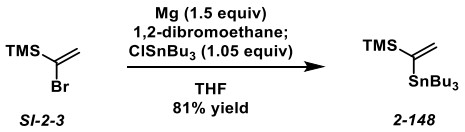
TLC: R_f=0.10 (CH_2Cl_2, $KMnO_4$ stain solution)

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.31 (t, *J* = 2.5 Hz, 1 H), 5.31 (s, 1 H), 5.12 (s, 1 H), 4.89 (d, *J* = 5.5 Hz, 1 H), 4.59 (d, *J* = 5.1 Hz, 1 H), 4.23 - 4.01 (m, 2 H), 3.92 (d, *J* = 1.2 Hz, 2 H), 2.87 - 2.70 (m, 2 H), 2.47 - 2.19 (m, 3 H), 2.09

(ddd, *J* = 13.1, 11.5, 7.4 Hz, 1 H), 1.93 - 1.73 (m, 3 H), 1.71 - 1.59 (m, 2 H), 1.55 - 1.45 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.05 (s, 21 H)

^{13}C NMR ($CDCl_3$, 101MHz): δ = 213.1, 168.0, 153.9, 143.7, 108.3, 99.0, 82.7, 81.8, 77.3, 77.0, 76.7, 68.6, 67.5, 65.4, 61.7, 59.4, 35.5, 33.2, 32.7, 32.2, 28.1, 25.0, 18.2, 18.12, 18.09, 13.9, 12.2

IR (film): ν = 2942, 1891, 1866, 1749, 1723, 1463, 1196, 1094, 1065, 1013, 881, 804.



To a stirred suspension of Mg turnings (362 mg, 15.0 mmol) in THF (20 mL) were added sequentially 1,2-dibromoethane (0.215 mL, 2.50 mmol) and neat **SI-2-3**[7] (1.83 g, 10.2 mmol) in 4 equal portions over 5 min *via* tared syringe. The reaction mixture was heated to reflux for 10 min, then treated with a second portion of 1,2-dibromoethane (0.215 mL, 2.50 mmol) to quench the remaining Mg. The solution was then cooled to 0 °C and treated with $ClSnBu_3$ (2.90 mL, 10.7 mmol). The reaction was stirred at 0 °C for 90 min then diluted with pentane (150 mL) and washed sequentially with 0.5 M aq. HCl (200 mL), 1 M aq. NaOH (100 mL), and brine (50 mL). The organic extracts were then passed through a column of activated Al_2O_3 (6" h x 1.5" d, Brockman I), rinsing with pentane (100 mL). The eluate was then concentrated and then stirred under vacuum (<0.1 mm Hg) for 1.5 h to afford pure **2-148** (3.20 g, 81% yield).

Data for alkenylstannane 2-148.

Physical State: colorless liquid.

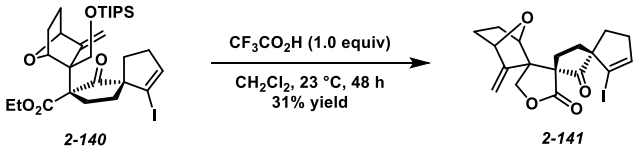
TLC: R_f=0.91 (19:1 hexanes-EtOAc, $KMnO_4$ stain solution)

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.47 (d, *J* = 4.7 Hz, 1 H), 6.20 (d, *J* = 4.7 Hz, 1 H), 1.66 - 1.18 (m, 12 H), 0.98 - 0.76 (m, 15 H), 0.05 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 156.7, 140.5, 29.1, 27.4, 13.6, 9.8, -0.8.

IR (film): ν = 2955, 2924, 1245, 955, 851.

MS (DART): *m/z* calc'd for (M) $^{\bullet+}$ $[C_{17}H_{38}SiSn]^{\bullet+}$: 388.1759, found 388.1300.



2-140 *2-141*

To a solution of **2-140** (69.0 mg, 0.110 mmol) in CH_2Cl_2 (1.1 mL) was added CF_3CO_2H (8.2 μL, 0.110 mmol). The resulting solution was allowed to stand for 48 h, then concentrated and applied to a silica gel column eluting with 9:1 hexanes-EtOAc → 2:1 hexanes-EtOAc to afford lactone **2-141** (13.2 mg, 31% yield). Crystals suitable for X-ray crystallography were grown from a saturated solution of **2-141** in Et_2O cooled to -10 °C.

Data for spirolactone 2-141.

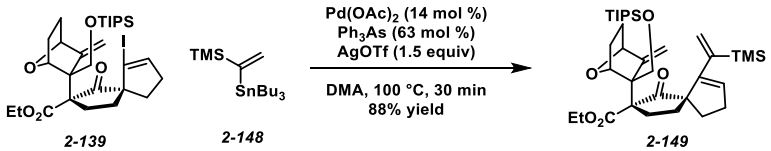
Physical State: Colorless needles.

TLC: R_f=0.05 (9:1 hexanes-EtOAc $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 6.16 (t, *J* = 2.5 Hz, 1 H), 5.08 (s, 1 H), 4.96 (s, 1 H), 4.81 (d, *J* = 4.7 Hz, 1 H), 4.68 (d, *J* = 8.2 Hz, 1 H), 4.48 (d, *J* = 5.5 Hz, 1 H), 4.16 (d, *J* = 8.2 Hz, 1 H), 2.71 (dt, *J* = 12.9, 7.0 Hz, 1 H), 2.44 - 2.37 (comp m, 2 H), 2.35 - 2.24 (comp m, 2 H), 2.16 (dt, *J* = 12.9, 7.0 Hz, 1 H), 2.01 - 1.72 (comp m, 4 H), 1.64 (ddd, *J* = 11.3, 9.4, 3.9 Hz, 1 H), 1.51 - 1.41 (ddd, *J* = 12.5, 8.6, 4.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 213.3, 173.3, 155.6, 135.5, 121.9, 104.6, 81.8, 80.5, 73.0, 67.4, 64.1, 58.4, 34.8, 31.1, 30.9, 30.6, 28.7, 25.2.

IR (film): ν = 3075, 2960, 2868, 1772, 1729, 1228, 1161, 1143, 1120, 1032, 1016, 993, 931, 915.



2-139 *2-148* *2-149*

A solution of alkenyl iodide **2-139** (25.9 mg, 0.0412 mmol) and alkenyl stannane **2-148** (24.1 mg, 0.0618 mmol) in DMA (2.1 mL) was sparged with Ar for 15 min. This solution was then transferred to an Ar flushed vial

charged with $Pd(OAc)_2$ (1.3 mg, 0.00579 mmol), Ph_3As (7.9 mg, 0.0258 mmol), and AgOTf (15.9 mg, 0.0618 mmol) under Ar purge. The solution was heated to 80 °C and stirred for 30 min, at which point TLC indicated consumption of alkenyl iodide **2-139**. The reaction mixture was poured into H_2O (20 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed sequentially with 10% LiCl (10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated. The resulting crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give pure diene **2-149** (21.9 mg, 88% yield).

Data for diene 2-149.

Physical State: colorless liquid.

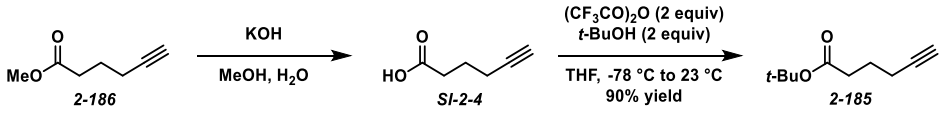
TLC: R_f=0.42 (CH_2Cl_2, $KMnO_4$ stain solution)

^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.68 (t, *J* = 2.3 Hz, 1 H), 5.52 (d, *J* = 2.7 Hz, 1 H), 5.42 (d, *J* = 3.1 Hz, 1 H), 5.31 - 5.27 (m, 1 H), 5.05 (s, 1 H), 4.75 (s, 1 H), 4.62 (d, *J* = 5.1 Hz, 1 H), 4.18 - 4.09 (comp m, 2 H), 4.06 - 3.99 (m, 1 H), 3.92 (d, *J* = 11.0 Hz, 1 H), 2.66 (dd, *J* = 13.3, 5.5 Hz, 1 H), 2.46 - 2.02 (comp m, 6 H), 1.91 - 1.74 (comp m, 3 H), 1.70 - 1.47 (comp m, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.07 (s, 21 H), 0.08 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 214.1, 169.2, 151.7, 146.9, 145.8, 130.6, 127.7, 106.4, 82.4, 82.0, 67.6, 65.5, 63.3, 61.7, 58.1, 38.0, 31.2, 31.1, 30.6, 30.1, 25.5, 18.2, 18.13, 18.09, 13.9, 12.3, 12.2, -1.0.

IR (film): ν = 2944, 2866, 1724, 1246, 1205, 1096, 882, 857, 838.

MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{34}H_{56}O_5Si_2 + H]^+$:601.3739, found 601.3741.



To a solution of **2-186** (15.5 g, 123 mmol) in MeOH (160 mL) and H_2O (40 mL) at ambient temperature was added KOH (85%, 15.5 g, 184 mmol). The solution was stirred for 30 min, at which point TLC indicated consumption of **2-186**. The solution was quenched with sat. aq. NH_4Cl, and the MeOH was removed *in vacuo*. The resulting biphase was diluted with 10% aq. HCl (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, and concentrated to afford **SI-2-4**, which was used directly without further purification.

To a solution of acid **SI-2-4** (13.8 g, 123 mmol) in THF (40 mL) at -78 °C was added TFAA (34.1 mL, 245 mmol) over 2 min. The solution was then allowed to warm to ambient temperature. Once it had reached ambient temperature, the solution was recooled to -78 °C, and a solution of *t*-BuOH (18.2 g, 245 mmol) in THF (10 mL) was added. The reaction mixture was then sealed and stirred 14 h. The reaction mixture was then poured into a well stirred solution of K_2CO_3 (50.9 g, 368 mmol) in H_2O (200 mL) at a rate such that evolution of CO_2 was controlled. The resulting mixture was then extracted with pentane (3 x 50 mL), and the combined organic extracts were washed with H_2O (2 x 200 mL) then dried with $MgSO_4$ and applied directly to a SiO_2 column (3 x 15 cm), eluting with 9:1 pentane-Et_2O. The combined product containing fractions were concentrated to give **2-185** (18.6 g, 90% yield).

Data for ester 2-185.

Physical State: Colorless liquid.

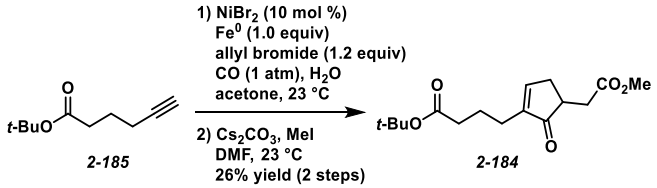
TLC: R_f = 0.36 (19:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 2.33 (t, *J* = 7.4 Hz, 2 H), 2.23 (td, *J* = 6.9, 2.5 Hz, 2 H), 1.94 (t, *J* = 2.5 Hz, 1 H), 1.79 (app quintet, *J* = 7.2 Hz, 2 H), 1.43 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 172.4, 83.5, 80.3, 68.8, 34.2, 28.1, 23.8, 17.8.

IR (film): ν = 3296, 3005, 2975, 2935, 2119, 1723, 1367, 1144.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{10}H_{16}O_2 + NH_4]^+$: 186.1489, found 186.1493.



A 250 mL round bottom flask charged with a large stirbar, $NiBr_2$ (1.09 g, 5.00 mmol), NaI (3.00 g, 20.0 mmol), and Fe powder (10 μm particle size, 2.79 g, 50.0 mmol) was stirred under vacuum for 10 minutes. The flask was then backfilled with CO, fitted with a CO balloon, and charged with acetone (25 mL). The resulting suspension was stirred for 30 minutes, changing the color from dark red to pale green. A portion of water (1.00 mL, 55.5 mmol) was added at the end of this period. Next, a solution of alkyne **2-185** (8.41 g, 50.0 mmol), allyl bromide (5.19 mL,

60.0 mmol), and *i*-Pr_2NEt (0.218 mL, 1.25 mmol) in acetone (10 mL) was added *via* syringe pump at a rate of 8.0 mL/h. The stirring during the addition was extremely vigorous to keep the solution saturated with CO. At the end of the addition, the reaction mixture was stirred for an additional hour. The solvent was then removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (50 mL), and filtered through a plug of celite, rinsing with CH_2Cl_2. The filtrate was washed sequentially with 10% HCl (3 x 50 mL), H_2O (50 mL), and brine (50 mL), dried with $MgSO_4$, and concentrated. The resulting crude product was used in the next step without further purification.

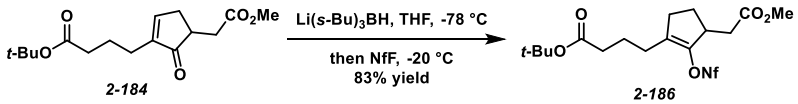
The crude product was dissolved in DMF (50 mL), and treated sequentially with dry Cs_2CO_3 (9.77 g, 30.0 mmol) and MeI (6.24 mL, 100 mmol). The resulting solution was stirred 14 h at ambient temperature then poured into H_2O (100 mL) and extracted with pentane (3 x 50 mL). The pentane extracts were washed with 10% LiCl (50 mL) followed by brine (50 mL), dried with Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc eluent) to give **2-184** (3.79 g, 26% yield).

Data for diester 2-184.

Physical State: Colorless liquid.

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.28 (br s, 1 H), 3.66 (s, 3 H), 2.86 (dddt, *J* = 18.8, 6.7, 3.1, 1.6 Hz, 1 H), 2.82 (dd, *J* = 16.4, 4.3 Hz, 1 H), 2.68 (dddd, *J* = 9.3, 6.7, 3.9, 2.7 Hz, 1 H), 2.40 (dd, *J* = 16.6, 9.2 Hz, 1 H), 2.29 (d quintet, *J* = 18.8, 2.3 Hz, 1 H), 2.21 (t, *J* = 7.4 Hz, 2 H), 2.16 - 2.22 (m, 1 H), 1.76 (quintet, *J* = 7.4 Hz, 2 H), 1.42 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 209.2, 172.6, 172.4, 156.2, 144.7, 80.2, 51.7, 41.6, 35.0, 34.9, 33.6, 28.1, 24.3, 23.0.



To a solution of **2-184** (3.79 g, 12.8 mmol) in THF (20 mL) at -78 °C was added Li(*s*-Bu)$_3$BH (13.4 mL, 1.0 M in THF, 13.4 mmol) over 5 min. The resulting solution was stirred 10 min then treated with NfF (2.98 mL, 16.6 mmol). The resulting biphasic mixture was stirred 60 s then removed from the dry ice bath and allowed to warm 5 min before placing in a -20 °C bath. The reaction mixture became homogeneous in 5 min, and an additional portion

of NfF was added (0.460 mL, 2.56 mmol). The reaction mixture was stirred an additional 30 min and quenched with H_2O (1.0 mL). The resulting solution was cooled to -78 °C and treated slowly (*caution: exothermic!*) with H_2O_2 (30% in H_2O, 5.50 mL, 51.2 mmol). The dry ice bath was removed and the solution heated under its own exotherm to ~40 °C. The quenched reaction mixture was poured into H_2O (150 mL) and 1 M aq. NaOH (50 mL), and the resulting mixture was extracted with pentane (3 x 50 mL). The combined organic extracts were washed sequentially with H_2O (100 mL), 1 M aq. NaOH (50 mL), and brine (50 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc eluent) to give **2-186** (6.19 g, 83% yield).

Data for alkenyl nonaflate 2-186.

Physical State: Colorless liquid.

TLC: R_f = 0.09 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

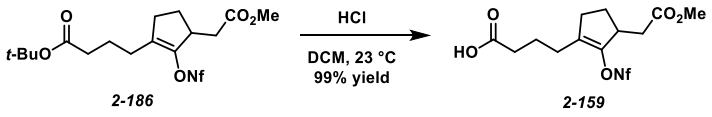
^{1}H NMR ($CDCl_3$, 400MHz): δ = 3.68 (s, 3 H), 3.31 (br. s., 1 H), 2.65 (dd, *J* = 15.7, 3.9 Hz, 1 H), 2.44 - 2.09 (comp m, 8 H), 1.80 - 1.57 (comp m, 3 H), 1.44 (s, 9 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 172.3, 171.9, 143.6, 134.0, 80.4, 51.7, 40.0, 37.1, 34.9, 28.9, 28.0, 26.4, 26.1, 22.2.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -80.7 (t, *J* = 9.5 Hz, 3 F), -110.3 (tq, *J* = 15.0, 2.7 Hz, 2 F), -120.9 (m, 2 F), -125.9 (m, 2 F).

IR (film): ν = 2978, 2955, 2855, 1729, 1238, 1199, 1143, 909.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{20}H_{25}F_9O_7S + NH_4]^+$: 598.1516, found 598.1540.



2-186 *2-159*

An apparatus to generate HCl gas was assembled by charging a 50 mL Schlenk flask with ~50 g NaCl. The flask was capped with a rubber septum and the side arm fitted with PVC tubing connected to a long 18 gauge needle. The needle was immersed in a solution of **2-186** (5.00 g, 9.11 mmol) in CH_2Cl_2 (91 mL) at ambient temperature in a 250 mL round bottom flask fitted with a rubber septum and an outlet needle. The solution was sparged with HCl gas by slowly adding H_2SO_4 (98%, 6.0 mL) to the Schlenk flask containing NaCl at a rate so as to control the evolution

of gas. Near the end of the addition, the HCl gas needle was raised above the level of the solution and the outlet needle was removed to create a slight positive pressure of HCl in the flask. When the addition was complete, the needle was removed altogether and the flask sealed with parafilm and stirred 16 h at ambient temperature. At the end of this time, TLC indicated consumption of **2-186**. The reaction mixture was then poured into H_2O (50 mL), the organic phase separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo* to afford to **2-159** (4.45 g, 99% yield).

Data for acid 2-159.

Physical State: Clear, pale brown liquid.

TLC: R_f = 0.01 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

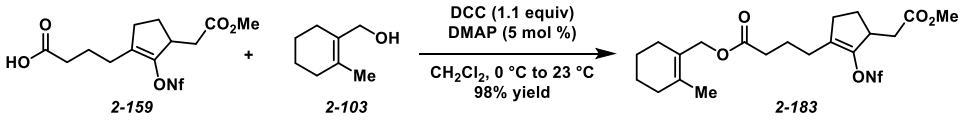
^{1}H NMR ($CDCl_3$, 400MHz): δ = 11.25 (br s., 1 H), 3.67 (s, 3 H), 3.34 - 3.24 (m, 1 H), 2.64 (dd, *J* = 15.7, 3.9 Hz, 1 H), 2.39 - 2.14 (m, 8 H), 1.83 - 1.63 (m, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 178.8, 171.9, 143.8, 133.5, 51.7, 40.0, 36.9, 33.2, 28.9, 26.4, 26.0, 21.7.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -80.7 (t, *J* = 9.5 Hz, 3 F), -110.2 (tq, *J* = 15.0, 2.7 Hz, 2 F), -120.9 (m, 2 F), -125.9 (m, 2 F).

IR (film): ν = 3000 (br), 2957, 1739, 1711, 1419, 1235, 1197, 1141, 1033.

MS (ESI): *m/z* calc'd for $(M + Na)^+$ $[C_{16}H_{17}F_9O_7S + Na]^+$: 547.0443, found 547.0446.



To a solution of alcohol **2-103** (1.21 g, 9.55 mmol), **2-159** (5.15 g, 9.09 mmol), and DMAP (56.0 mg, 0.455 mmol) in CH_2Cl_2 (9.1 mL) at 0 °C was added DCC (2.06 g, 10.0 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring for 12 h. At this point, TLC indicated that alcohol **2-103** remained, so additional charges of alcohol **2-103** (126 mg, 0.909 mmol) and DCC (206 mg, 1.00 mmol) were added. The reaction mixture was stirred an additional 12 h, until TLC showed consumption of acid **2-159**. Then the reaction was diluted with hexanes (20 mL) and filtered, rinsing with

hexanes (20 mL). The filtrate was concentrated, and the crude product further purified by flash column chromatography (SiO_2, 9:1 hexanes/EtOAc eluent) to give ester **2-183** (6.02 g, 98% yield).

Data for ester 2-183.

Physical State: Pale yellow liquid.

TLC: R_f = 0.27 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

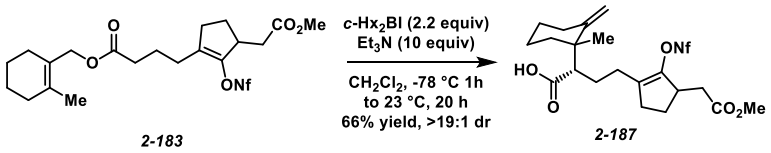
^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.56 (s, 2 H), 3.66 (s, 3 H), 3.34 - 3.22 (m, 1 H), 2.63 (dd, *J* = 15.7, 3.9 Hz, 1 H), 2.38 - 2.11 (comp m, 8 H), 1.97 (d, *J* = 5.1 Hz, 4 H), 1.82 - 1.63 (comp m, 3 H), 1.67 (s, 3 H), 1.58 ppm (app d, *J* = 2.3 Hz, 4 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 173.2, 171.9, 143.7, 133.8, 133.6, 125.0, 64.9, 51.7, 40.0, 37.0, 33.7, 31.9, 28.9, 27.7, 26.4, 26.1, 22.78, 22.75, 22.1, 19.0.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -80.7 (t, *J* = 10.2 Hz, 3 F), -110.3 (t, *J* = 15.0 Hz, 2 F), -120.9 (m, 2 F), -125.9 (m, 2 F).

IR (film): ν = 2933, 2859, 1737, 1419, 1235, 1198, 1142, 1033, 852.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{24}H_{29}F_9O_7S + NH_4]^+$: 650.1829, found 650.1823.



A stirred solution of **2-183** (876 mg, 1.39 mmol) and Et_3N (1.94 mL, 13.9 mmol) in CH_2Cl_2 (14 mL) was cooled to -78 °C. Neat *c*-Hx_2BI (0.698 mL, 3.04 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 20 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with

brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (14 mL) and treated with H_2O_2 (1.39 mL, 30% in H_2O, 13.9 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was analyzed by ^{1}H NMR (d1=10 s) to obtain a dr of the reaction and then purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **2-187** (581 mg, 66% yield).

Data for acid 2-187.

Physical State: Clear, colorless liquid.

TLC: R_f = 0.24 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$).

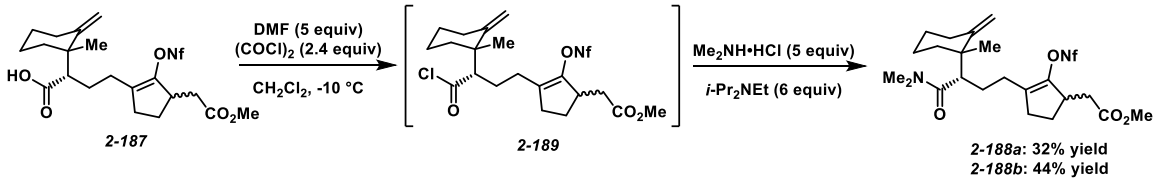
^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.72 (s, 1 H), 4.62 (s, 1 H), 3.71 - 3.64 (s, 3 H), 3.31 (br. s, 1 H), 2.92 - 2.81 (m, 1 H), 2.75 - 2.61 (comp m, 2 H), 2.50 - 2.01 (comp m, 7 H), 1.89 - 1.63 (comp m, 4 H), 1.62 - 1.42 (comp m, 3 H), 1.34 - 1.13 (comp m, 3 H), 1.09 (app d, *J* = 3.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 178.9, 178.8, 172.1, 171.9, 153.6, 153.5, 143.9, 143.4, 134.1, 133.6, 108.4, 108.3, 51.8, 51.7, 49.0, 48.6, 44.6, 41.7, 41.6, 40.1, 40.0, 37.12, 37.05, 37.0, 32.8, 29.24, 29.18, 28.0, 27.9, 26.6, 26.5, 26.2, 25.7, 24.1, 23.9, 21.73, 21.70, 21.6, 21.5, 20.2.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -80.7 (m, 3 F), -110.2 (m, 2 F), -120.9 (m, 2 F), -125.9 (m, 2 F).

IR (film): ν = 3000 br, 2937, 2859, 1736, 1704, 1421, 1238, 1200, 1144, 907.

MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{24}H_{29}F_9O_7S + H]^+$: 633.2, found 633.2.



To a solution of **2-187** (2.20 mg, 3.26 mmol) in CH_2Cl_2 (13 mL) was added DMF (1.26 mL, 16.3 mmol) followed by $(COCl)_2$ (0.651 mL, 7.69 mmol). Towards the end of this addition, a colorless crystalline precipitate formed. The reaction mixture was stirred 5 min at -10 °C, then Me_2NH•HCl (1.33 g, 16.3 mmol) was added in one portion, followed by *i*-Pr_2NEt (3.41 mL, 19.6 mmol) over 30 s. The solution became clear yellow and was stirred 30

min at -10 °C before being allowed to warm to ambient temperature. The reaction mixture was then diluted with hexanes (50 mL) and Et_2O (50 mL). The resulting solution was washed sequentially with 1M aq. HCl (50 mL), H_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 4:1 hexanes/EtOAc → 2:1 hexanes/EtOAc eluent) to give amides **2-188a** (739 mg, 32% yield) and **2-188b** (1.00 g, 44% yield).

Data for amide 2-188a.

Physical State: Pale yellow liquid.

TLC: R_f=0.14 (4:1 hexanes/EtOAc, $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.73 (s, 1 H), 4.62 (d, *J* = 1.2 Hz, 1 H), 3.68 (s, 3 H), 3.36 - 3.24 (m, 1 H), 3.03 (s, 3 H), 2.90 (s, 3 H), 2.65 (dd, *J* = 15.7, 3.9 Hz, 1 H), 2.50 - 2.39 (m, 1 H), 2.36 - 2.11 (comp m, 6 H), 2.03 - 1.88 (comp m, 4 H), 1.83 - 1.22 (comp m, 19 H), 1.14 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ =173.9, 171.8, 162.7, 162.0, 153.3, 143.6, 134.5, 108.2, 75.0, 51.7, 43.9, 42.1, 40.0, 38.1, 37.1, 37.0, 35.8, 35.6, 33.9, 33.6, 31.3, 28.9, 27.7, 26.5, 25.5, 25.1, 23.6, 23.3, 21.7.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -80.6 (m, 3 F), -110.3 (m, 2 F), -120.9 (m, 2 F), -125.9 (m, 2 F).

IR (film): ν = 2938, 2861, 1737, 1666, 1635, 1418, 1236, 1199, 1143, 1121, 1009.

MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{34}NO_6F_9S + H]^+$: 660.2036, found 660.2039.

Data for amide 2-188b.

Physical State: Pale yellow liquid.

TLC: R_f=0.07 (4:1 hexanes/EtOAc, $KMnO_4$).

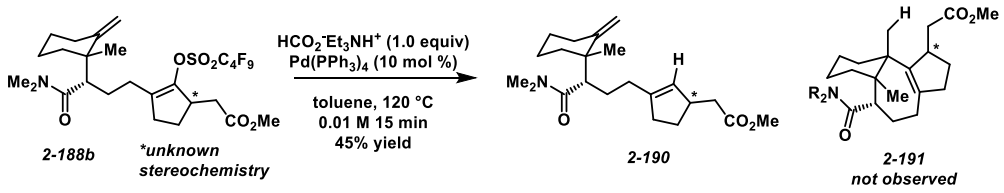
^{1}H NMR ($CDCl_3$, 400MHz): δ = 4.73 (s, 1 H), 4.64 (s, 1 H), 3.68 (s, 3 H), 3.27 (br. s., 1 H), 3.17 (dd, *J* = 11.2, 2.5 Hz, 1 H), 3.07 (s, 3 H), 2.90 (s, 3 H), 2.63 (dd, *J* = 15.7, 3.9 Hz, 1 H), 2.46 - 2.17 (m, 6 H), 2.16 - 2.05 (m, 1 H), 2.03 - 1.83 (m, 2 H), 1.78 - 1.36 (m, 8 H), 1.14 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 174.2, 153.1, 142.8, 134.8, 108.3, 51.7, 44.4, 42.2, 39.9, 38.2, 37.1, 36.0, 35.6, 33.6, 28.8, 27.8, 26.6, 25.9, 25.8, 23.1, 21.6.

^{19}F NMR ($CDCl_3$, 376MHz): δ = -80.6 (m, 3 F), -110.3 (m, 2 F), -120.9 (m, 2 F), -125.8 (m, 2 F).

IR (film): ν = 2933, 2859, 1739, 1418, 1236, 1198, 1142, 1032, 1010.

MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{26}H_{34}NO_6F_9S + H]^+$: 660.2036, found 660.2040



A solution of **2-188b** (33.6 mg, 0.0509 mmol) in toluene (5.1 mL) was sparged with Ar for 15 min. This solution was transferred to an Ar flushed vial charged with a stirbar and $Pd(PPh_3)_4$ (5.9 mg, 0.00509 mmol). To this solution was added $HCO_2^-Et_3NH^+$ (7.6 mg, 0.0509 mmol), and the solution was immediately heated to 120 °C in a preheated oil bath. The reaction mixture was stirred for 15 min at this temperature and then allowed to cool to ambient temperature. The solution was then passed through a short pad of SiO_2, rinsing with Et_2O (10 mL). The filtrate was concentrated and purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc → 2:1 hexanes-EtOAc) to give pure alkene **2-190** (8.5 mg, 45% yield).

Data for alkene 2-190.

Physical State: Pale yellow liquid.

TLC: R_f=0.33 (2:1 hexanes-EtOAc, $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400MHz): δ = 5.29 (br. s, 1 H), 4.71 (s, 1 H), 4.63 (s, 1 H), 3.67 (s, 3 H), 3.13 (d, *J* = 8.6 Hz, 1 H), 3.04 (s, 3 H), 2.99 (d, *J* = 10.2 Hz, 1 H), 2.90 (s, 3 H), 2.31 (dd, *J* = 7.4, 14.5 Hz, 1 H), 2.39 - 2.08 (m, 6 H), 2.04 - 1.85 (m, 3 H), 1.80 - 1.71 (m, 1 H), 1.70 - 1.33 (m, 7 H), 1.15 (s, 3 H)

^{13}C NMR ($CDCl_3$, 101MHz): δ = 174.7, 173.4, 153.5, 145.4, 127.0, 108.2, 51.4, 43.4, 42.2, 42.0, 40.4, 38.3, 36.1, 35.6, 34.3, 33.7, 30.3, 29.7, 27.8, 26.3, 23.2, 21.9

IR (film): ν = 2929, 1736, 1634, 1438, 1394, 1254, 1165, 1132.

MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{35}NO_3 + H]^+$: 362.2690, found 362.2682.

Appendix Two: Experimental Section for Chapter Three.

Materials and Methods: Reactions were performed under an argon atmosphere unless otherwise noted. Hexanes, ether, dichloromethane, THF and toluene were purified by passing through activated alumina columns. Triethylamine and diisopropylethylamine were distilled under Ar from CaH_2. Tributylamine and dicyclohexylmethylamine were distilled from CaH_2 under vacuum. Dicyclohexyl boron triflate[1] and dicyclopentyl boron triflate[2] were prepared according to literature procedures. A solution of (+)-diisopinocampheyl boron triflate was prepared immediately prior to use by treating a 1.0 M solution of diisopinocampheylchloroborane in hexanes with triflic acid at 0 °C for 10 min. Triflic acid was fractionally distilled under Ar from ~10% (v/v) triflic anhydride and stored in a stoppered Schlenk flask under Ar. Isobutyraldehyde was fractionally distilled through a 50 cm Vigreux column from $CaSO_4$ under Ar. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA) or Sigma-Aldrich (St. Louis, MO). Visualization was accomplished with UV light and exposure to $KMnO_4$ solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^{1}H NMR spectra were acquired on either a Varian Mercury 300 (at 300 MHz) or a Varian 400 MR (at 400 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 101 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.0). IR Spectra were recorded as films on a Nicolet 380 FTIR. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS.

Notes on handling Cy_2BI. Dicyclohexyliodoborane, the borane reagent used for most of this work, is a very water and oxygen sensitive compound that must at all times be handled and stored under an inert atmosphere. The pure reagent is a clear, colorless liquid at room temperature. Material kept in septum-capped bottles, either neat or in solution, discolors on the order of days to weeks, and strongly colored reagent gives inferior results. After carfeul experimentation, we found the following protocol to be useful: after synthesis of the reagent by the method of Brown,[3] the crude material was distilled into a Schlenk flask. On completion of the distillation, the product containing flask was stoppered under an Ar purge and immediately evacuated. The flask was taken into a N_2 atmosphere glove box,

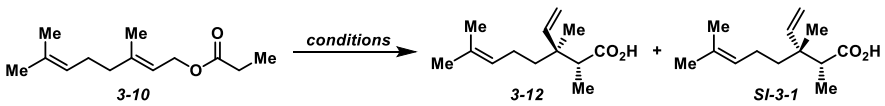
[1]T. Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250–5256.
[2]Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
[3]Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 2336–2340.

transferred to a brown glass bottle, and stored at room temperature. Material stored in this way showed no evidence of decomposition after several months had elapsed. The reagent was removed from the glove box in a syringe as needed and added to a reaction mixture or diluted with hexanes to make a stock solution that was used immediately.

Notes on workup and removal of boron-containing products. Once the crude reaction mixture is exposed to water, which immediately hydrolyzes the acyloxyborane product, the free carboxylic acid is generally sensitive to iodolactonization, which can occur readily when the iodide-containing reaction mixture is exposed to air. Therefore it is important to quench the reaction mixture with a solution capable of reducing any free I_2 to I^-. We favored acidic Na_2SO_3 for this purpose because the more commonly used $Na_2S_2O_3$ decomposes to insoluble S_8 under the acidic conditions necessary for carboxylic acid products to partition into the organic layer.

The removal of boron-containing impurities requires oxidation of the crude reaction mixture with H_2O_2. A neutral medium such as MeOH at ambient temperature is sufficient for this purpose. The oxidation of the boron containing byproducts generates 2 equiv cyclohexanol (b.p. 160-161 °C) and an equivalent of boric acid. Boric acid is easily removed by washing with aqueous acid or by directly applying the concentrated reaction product to a silica gel column. The latter method can also be used to remove cyclohexanol, which can also be removed by heating gently under high vacuum (<0.1 torr) for a few minutes. If the oxidation step is not conducted, the borinic acid side products decompose during chromatography to give boron containing impurities that tend to co-elute with the desired product.

Methylation of the crude acid product with CH_2N_2 requires prior workup and oxidation, along with a final aqueous wash to remove boric acid. The omission of any of these steps gives rise to situations where even a large excess of CH_2N_2 fails to effect methylation to any significant extent. This being said, methylation is not required for efficient purification of these products provided that a small amount of acetic acid is added to the eluent during chromatography.

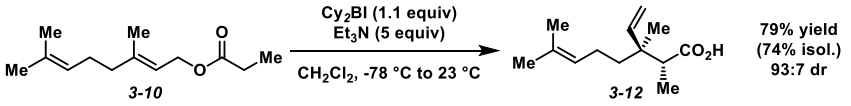


Example procedure for optimization experiments using Cy_2BI. A solution of geranyl propionate (**3-10**, 52.6 mg, 0.250 mmol), an internal standard of 4,4'-di-*tert*-butylbiphenyl (8.3 mg, 0.0313 mmol), and the appropriate base in the appropriate solvent was cooled to -78 °C. To this solution was added Cy_2BI (63.1 µL, 0.275 mmol) dropwise. The solution was stirred at -78 °C for 1 h, allowed to warm to room temperature, and stirred an additional 20 h. The reaction was quenched by pouring into 4:1 sat. aq. NH_4Cl/1 M Na_2SO_3 (25 mL) then acidified to pH 1 with 2 M aq. HCl. This mixture was extracted with Et_2O (3x10 mL). The combined organic extracts were washed with brine (25 mL), dried with $MgSO_4$, and concentrated. The resulting material was dissolved in 3.0 mL $CDCl_3$ and analyzed by ^1H NMR (300 MHz, 10 s relaxation delay). The NMR spectrum was phase and baseline corrected. The diastereoselectivity of the reaction was determined by the ratio of the integrals of the peak centered at δ 5.87 (dd, *J* = 17.4, 10.8 Hz, 1H, diastereomer **3-12**), and δ 5.68 ppm (dd, *J* = 11.0, 17.5 Hz, 1H, diastereomer **SI-3-1**). The yield of the reaction was determined by the ratio of the sum of the integrals of these two peaks to the integral of the aromatic protons of 4,4'-di-*tert*-butylbiphenyl at δ = 7.52 (ddd, *J* = 8.5, 2.2, 1.9 Hz, 4H) and 7.44 (ddd, *J* = 8.5, 2.5, 1.7 Hz, 4H) ppm.

General procedure A: rearrangement in CH_2Cl_2. To a stirred solution of the starting ester in CH_2Cl_2 (0.10 M) was added Et_3N (5 equiv), and the solution was cooled to -78 °C. Neat Cy_2BI (1.1 equiv) was added dropwise, giving a cloudy colorless or pale yellow solution. This solution was stirred at -78 °C for 1 h and then allowed to warm to ambient temperature. The reaction was stirred at room temperature until the starting ester was completely consumed by TLC (eluent typically 19:1 hexanes/ethyl acetate, $KMnO_4$ stain solution) or until the reaction had ceased to progress further, as judged qualitatively by TLC, to a maximum reaction time of 24 h. The reaction was then quenched by pouring into 4:1 sat. NH_4Cl/1.0 M Na_2SO_3, and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with 3 portions of Et_2O or EtOAc. The combined organic extracts were then washed with brine, dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (0.1 M) and treated with 30% aq. H_2O_2 (10 equiv). This mixture was allowed to stand 1 h at room temp, then diluted with EtOH and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was purified by flash column

chromatography (usually 19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give the pure product free from cyclohexanol and boron-containing impurities.

General procedure B: rearrangement in toluene. To a stirred solution of the starting ester in toluene (0.10 M) was added Et_3N (5 equiv), and the solution was cooled to -78 °C. Neat Cy_2BI was diluted with sufficient hexanes to make a 1.0 M solution, and this solution (1.1 equiv) added dropwise giving a cloudy colorless or pale yellow solution. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to ambient temperature, during which time a white solid precipitated, then stirred at room temperature until the starting ester was completely consumed by TLC (eluent typically 19:1 hexanes/ethyl acetate, $KMnO_4$ stain solution) or until the reaction had ceased to progress further, as judged qualitatively by TLC, to a maximum reaction time of 24 h. The reaction was then quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3, and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with 3 portions of Et_2O or EtOAc. The combined organic extracts were then washed with brine, dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (0.1 M) and treated with 30% aq. H_2O_2 (10 equiv). This mixture was allowed to stand 1 h at room temp, then diluted with EtOH and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was purified by flash column chromatography (usually 19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give the pure product free from cyclohexanol and boron-containing impurities.



According to general procedure A, a stirred solution of ester **3-10** (93.7 mg, 0.446) and Et_3N (0.311 mL, 2.23 mmol) in CH_2Cl_2 (4.5 mL) was cooled to -78 °C. Neat Cy_2BI (0.112 mL, 0.490 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min.. The solution was stirred at this temperature 20 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into

4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (4.5 mL) and treated with H_2O_2 (0.45 mL, 30% in H_2O, 4.5 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 4,4'-di-*tert*-butylbiphenyl was added (14.9 mg, 0.0558 mmol) and analyzed by ^{1}H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-12** (69.6 mg, 74% yield).

Data for acid 3-12.

Physical State: Clear, colorless liquid.

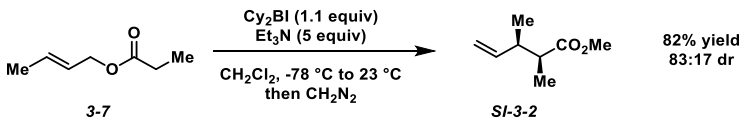
TLC: R_f = 0.24 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.09 (d, *J* = 11.0 Hz, 1H), 5.06 (t, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 2.43 (q, *J* = 7.0 Hz, 1H), 2.00–1.76 (m, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.47 (td, *J* = 12.7, 5.5 Hz, 1H), 1.33 (td, *J* = 12.6, 4.9 Hz, 1H), 1.28 (s, 1H), 1.25-1.21 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.4, 131.4, 124.5, 113.7, 98.7, 48.2, 41.6, 38.8, 25.6, 22.7, 18.9, 17.6, 12.4.

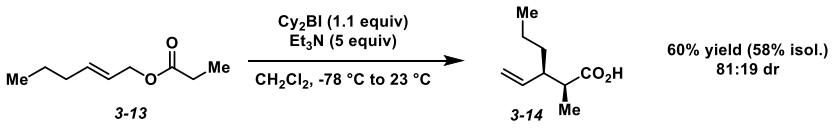
IR (film): ν = 3675, 3050 (br), 2972, 2922, 1703, 1413, 1393, 1379, 1066, 913.

The spectroscopic data for this compound matched those in the literature.[4]



[4]Temmem, O.; Uguen, D.; De Cian, A.; Gruber, N. *Tetrahedron Lett.* **2002**, *43*, 3169–3173.

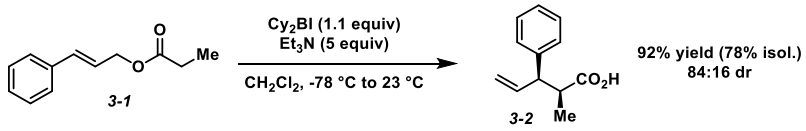
According to general procedure A, a stirred solution of ester **3**-7 (0.126 g, 0.980 mmol) and Et_3N (0.683 mL, 4.90 mmol) in CH_2Cl_2 (9.8 mL) was cooled to -78 °C. Neat Cy_2BI (0.247 mL, 1.08 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 2 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (9.8 mL) and treated with H_2O_2 (0.98 mL, 30% in H_2O, 10.3 mmol). This mixture was allowed to stand 1 h at ambient temperature, then partitioned between 1.0 M HCl (10 mL) and Et_2O (20 mL). The organic layer was separated and treated with CH_2N_2 (7.5 mL, ~0.2 M in Et_2O, ~1.5 mmol) until a pale yellow color persisted. After standing 5 min, excess CH_2N_2 was quenched with AcOH (50 µL). The resulting ether solution was washed with sat. Na_2CO_3 (1x10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (19.3 µL, 0.245 mmol) and analyzed by ^1H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. An analytical sample was obtained by flash column chromatography (19:1 pentane/Et_2O eluent) to give a diastereomeric mixture of ester **SI-3-2** (21.6 mg, 16% yield) as a colorless liquid. The spectroscopic data for **SI-3-2** matched those in the literature.[5]



According to general procedure A, a stirred solution of ester **3-13** (85.7 mg, 0.549 mmol) and Et_3N (0.383 mL, 2.75 mmol) in CH_2Cl_2 (5.5 mL) was cooled to -78 °C. Neat Cy_2BI (0.138 mL, 0.603 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature

[5]Metz, P. *Tetrahedron* **1993**, *49*, 6367–6374.

24 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (5.5 mL) and treated with H_2O_2 (0.55 mL, 30% in H_2O, 5.5 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 4,4'-di-*tert*-butylbiphenyl was added (19.1 mg, 0.0717 mmol) and analyzed by ^1H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (24:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-14** (50.1 mg, 58% yield) as a colorless liquid. The spectroscopic data for **6** matched those in the literature.[5]



According to general procedure A, a stirred solution of ester **3-1** (93.8 mg, 0.493) and Et_3N (0.344 mL, 2.47 mmol) in CH_2Cl_2 (4.9 mL) was cooled to -78 °C. Neat Cy_2BI (0.125 mL, 0.542 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 2 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (4.9 mL) and treated with H_2O_2 (0.49 mL, 30% in H_2O, 4.9 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol.

The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (19.4 μL, 0.247 mmol) and analyzed by ^1H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-2** (73.6 mg, 78% yield). An analytical sample (28.3 mg) of the major diastereomer was obtained after slow crystallization from hexanes (5.0 mL) at -10 °C.

Data for acid 3-2.

Physical State: Colorless, crystalline solid.

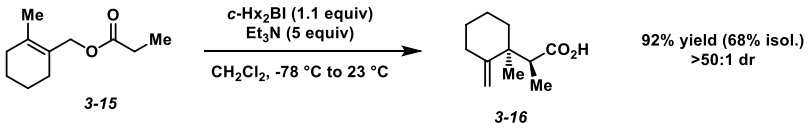
TLC: R_f = 0.19 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (comp m, 2H), 7.25-7.15 (comp m, 3H), 6.03 (ddd, *J* = 17.1, 10.2, 8.2 Hz, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 3.46 (dd, *J* = 9.6, 8.8 Hz, 1H), 2.83 (dq, *J* = 10.4, 7.0 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.8, 140.9, 139.3, 128.7, 128.1, 126.8, 115.8, 53.3, 45.0, 15.8.

IR (film): ν = 3023, 3000 (br), 2979, 1693, 1212, 911.

HRMS (ESI-) *m/z* calc'd for $(M - H)^-$ $[C_{12}H_{14}O_2 - H]^-$: 189.0921, found 189.0921.



According to general procedure A, a stirred solution of ester **3-15** (187 mg, 1.03 mmol) and Et_3N (0.710 mL, 5.13 mmol) in CH_2Cl_2 (10.3 mL) was cooled to -78 °C. Neat Cy_2BI (0.260 mL, 1.13 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 20 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic

extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (10 mL) and treated with H_2O_2 (1.03 mL, 30% in H_2O, 10 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (20.2 μL, 0.256 mmol) and analyzed by ^{1}H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-16** (127 mg, 68% yield).

Data for acid 3-16.

Physical State: Waxy, colorless solid.

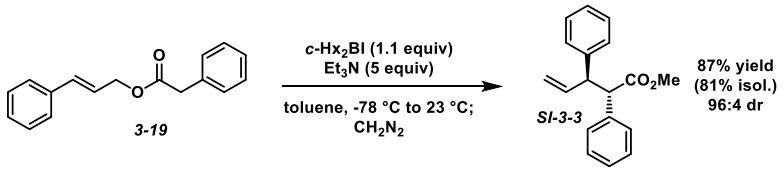
TLC: R_f = 0.32 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (s, 1H), 4.63 (s, 1H), 3.02 (q, *J* = 7.0 Hz, 1H), 2.39 (td, *J* = 14.1, 3.9 Hz, 1H), 2.17 (dt, *J* = 14.1, 2.4 Hz, 1H), 1.77 (d, *J* = 13.7 Hz, 2H), 1.55-1.40 (m, 2H), 1.37–1.22 (m, 1H), 1.20-1.11 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.5, 153.8, 108.2, 42.3, 41.3, 37.0, 32.8, 28.1, 21.6, 21.1, 11.2.

IR (film): ν = 2967, 2943, 2916, 1733, 1213, 1155, 1027, 963.

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{18}O_2 + H]^+$: 183.1380, found 183.1385.



According to general procedure B, a stirred solution of ester **3-19** (76.0 mg, 0.301 mmol) and Et_3N (0.210 mL, 1.51 mmol) in toluene (3.0 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.77 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.331 mL, 1.0 M, 0.331 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this

time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 2 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (3.0 mL) and treated with 30% aq. H_2O_2 (0.30 mL, 3.0 mmol) and Et_2O (20 mL). The organic layer was separated and treated with CH_2N_2 (~0.2 M in Et_2O, 2.5 mL, 0.5 mmol) until a pale yellow color persisted. After standing 5 min, excess CH_2N_2 was quenched with AcOH (50 μL). The resulting ether solution was washed with sat Na_2CO_3 (10 mL) and brine (10 mL), dried with $MgSO_4$ and concentrated. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,3,5-trimethoxybenzene was added (16.2 mg, 0.100 mmol) and analyzed by ^{1}H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The $CDCl_3$ solution was concentrated, and the residue was purified by flash column chromatography (97:3 hexanes/EtOAc eluent) to give ester **SI-3-3** (63.5 mg, 81% yield). An analytical sample of the major diastereomer was obtained by slow crystallization from a hexane solution (5.0 mL) of the product.

Data for methyl ester SI-3-3.

Physical State: Colorless, crystalline solid.

TLC: R_f = 0.32 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

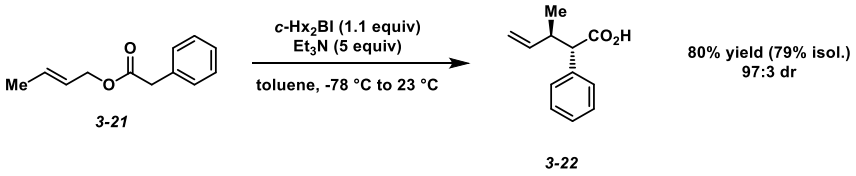
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.40 (comp m, 2H), 7.37-7.18 (comp m, 8H), 5.71 (ddd, *J* = 17.2, 10.0, 7.6 Hz, 1H), 4.84 (d, *J* = 10.2 Hz, 1H), 4.74 (d, *J* = 16.8 Hz, 1H), 4.06 (dd, *J* = 11.7, 7.8 Hz, 1H), 3.96 (d, *J* = 11.7 Hz, 1H), 3.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 141.6, 138.5, 137.0, 128.8, 128.6, 128.5, 128.0, 127.5, 126.8, 116.7, 57.3, 53.1, 51.7.

IR (film): ν = 3058, 3027, 2956, 1724, 1274, 1159, 916.

These spectroscopic data match those reported in the literature[6]

[6]Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026–4028.



According to general procedure B, a stirred solution of ester **3-21** (102 mg, 0.537 mmol) and Et_3N (0.375 mL, 2.69 mmol) in toluene (5.4 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.77 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.590 mL, 1.0 M, 0.590 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 2 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (5.4 mL) and treated with 30% aq. H_2O_2 (0.54 mL, 5.4 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (10.6 μL, 0.134 mmol) and analyzed by ^1H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The $CDCl_3$ solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-22** (80.9 mg, 79% yield).

Data for acid 3-22.

Physical State: Colorless solid.

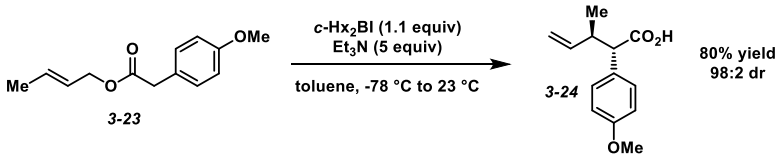
TLC: R_f = 0.26 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^1H NMR (400 MHz, $CDCl_3$): δ 10.50 (br s, 1H), 7.43–7.17 (m, 5H), 5.48 (ddd, *J* = 17.4, 10.0, 7.8 Hz, 1H), 4.89 (d, *J* = 17.6 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 2H), 3.35 (d, *J* = 10.6 Hz, 1H), 2.94 (ddd, *J* = 16.8, 13.7, 7.0 Hz, 1H), 1.17 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.7, 140.1, 137.0, 128.8, 128.4, 127.5, 115.2, 56.2, 40.5, 16.7.

IR (film): ν = 3071, 3029, 3000 (br), 2965, 2930, 1679, 1680, 1413, 1282, 1213, 1188, 945, 917.

HRMS (ESI-) *m/z* calc'd for $(M - H)^-$ $[C_{12}H_{14}O_2 - H]^-$: 189.0921, found 189.0917.



According to general procedure B, a stirred solution of ester **3-23** (108 mg, 0.489 mmol) and Et_3N (0.341 mL, 2.45 mmol) in toluene (4.9 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.77 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.538 mL, 1.0 M, 0.538 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 30 min. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (4.9 mL) and treated with 30% aq. H_2O_2 (0.49 mL, 4.9 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 4,4'-di-*tert*-butylbiphenyl was added (16.3 mg, 0.0611 mmol) and analyzed by ^{1}H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The $CDCl_3$ solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-24** (85.8 mg, 80% yield).

Data for acid 3-24.

Physical State: Colorless, crystalline solid.

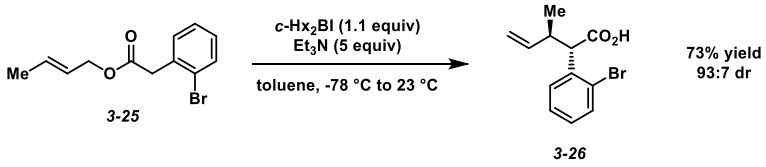
TLC: R_f = 0.14 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.47 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H), 4.86 (d, *J* = 18.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 3.76 (s, 3H), 3.28 (d, *J* = 10.2 Hz, 1H), 2.88 (dt, *J* = 10.2, 6.8 Hz, 1H), 1.14 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.7, 158.9, 140.2, 129.8, 129.0, 115.1, 113.8, 57.2, 55.2, 40.4, 18.7.

IR (film): ν = 2960, 2950 (br), 2985, 2836, 1699, 1511, 1257, 1178, 1027, 827

HRMS (ESI-) *m/z* calc'd for $(M - H)^-$ $[C_{13}H_{16}O_3 - H]^-$: 219.1027, found 219.1026.



According to general procedure B, a stirred solution of **3-25** (133 mg, 0.493 mmol) and Et_3N (0.344 mL, 2.47 mmol) in toluene (4.9 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.77 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.543 mL, 1.0 M, 0.543 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 45 min. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (4.9 mL) and treated with 30% aq. H_2O_2 (0.49 mL, 4.9 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (9.7 μL, 0.123 mmol) and analyzed by ^{1}H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The

$CDCl_3$ solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-26** (96.3 mg, 73% yield).

Data for acid 3-26.

Physical State: Colorless solid.

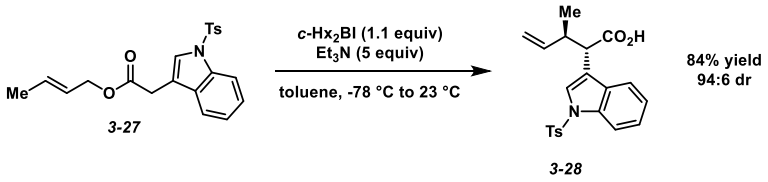
TLC: R_f = 0.23 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 5.53 (ddd, *J* = 16.4, 9.8, 9.0 Hz, 1H), 4.84 (d, *J* = 16.4 Hz, 1H), 4.81 (d, *J* = 9.8 Hz, 1H), 4.16 (d, *J* = 10.2 Hz, 1H), 2.91 (ddq, *J* = 9.8, 8.1, 6.3 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.6, 139.5, 136.6, 132.8, 129.6, 128.8, 127.5, 125.6, 115.6, 55.1, 41.4, 18.8.

IR (film): ν = 3000 (br), 2970, 1702, 1277, 1021, 915

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{13}BrO_2 + H]^+$: 271.0151, found 271.0156.



According to general procedure B, a stirred solution of ester **3-27** (0.196 g, 0.562 mmol) and Et_3N (0.356 mL, 2.56 mmol) in toluene (5.1 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.77 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.562 mL, 1.0 M, 0.562 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 24 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with EtOAc (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (5.1 mL) and treated with 30% aq. H_2O_2 (0.51 mL, 5.1 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically

remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (10.1 μL, 0.128 mmol) and analyzed by NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The $CDCl_3$ solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-28** (165 mg, 84% yield).

Data for acid 3-28.

Physical State: Colorless solid.

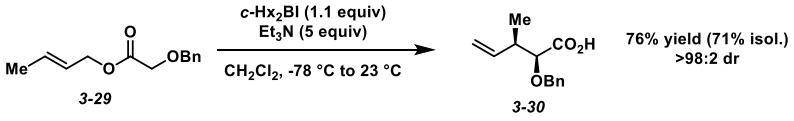
TLC: R_f = 0.05 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.59-7.54 (m, 2H), 7.31-7.17 (m, 3H), 7.14 (d, *J* = 8.2 Hz, 2H), 5.51 (ddd, *J* = 16.8, 10.6, 8.2 Hz, 1H), 4.86 (d, *J* = 17.2 Hz, 1H), 4.76 (d, *J* = 10.2 Hz, 1H), 3.64 (d, *J* = 9.8 Hz, 1H), 2.98 (ddq, *J* = 9.5, 8.2, 6.7 Hz, 3H), 2.28 (s, 3H), 1.14 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.0, 144.9, 139.9, 135.0, 134.9, 130.3, 129.7, 126.7, 125.3, 124.7, 123.2, 119.9, 118.3, 115.4, 113.7, 48.6, 40.2, 21.5, 18.5.

IR (film): ν = 3000 (br), 2964, 2930, 2859, 1706, 1446, 1366, 1187, 1171, 1120, 973

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{21}H_{21}NO_4S + H]^+$: 384.1264, found 384.1274.



According to general procedure A, a stirred solution of **3-29** (85.6 mg, 0.389 mmol) and Et_3N (0.272 mL, 1.95 mmol) in CH_2Cl_2 (3.9 mL) was cooled to -78 °C. Neat Cy_2BI (98.0 μL, 0.427 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 10 min. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL), and the mixture was acidified

(pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (3.9 mL) and treated with H_2O_2 (0.39 mL, 30% in H_2O, 3.9 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL), an internal standard of 1,2-dichloroethane was added (15.3 μL, 0.195 mmol) and analyzed by ^{1}H NMR (d1=10 s) to obtain a crude yield and dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-30** (127 mg, 68% yield).

Data for acid 3-30.

Physical State: Clear, colorless liquid.

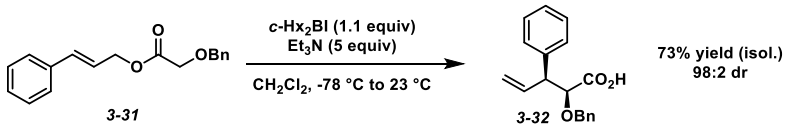
TLC: R_f = 0.10 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.26 (comp m, 5H), 5.82 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.3 Hz, 1H), 3.90 (d, *J* = 5.1 Hz, 1H), 2.71 (ddd, *J* = 13.7, 12.5, 7.0 Hz, 1H), 1.15-1.06 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8, 139.0, 136.9, 128.5, 128.1, 128.0, 115.8, 81.6, 73.1, 40.8, 14.7.

IR (film): ν = 3066, 3050 (br), 2977, 2934, 2875, 1712, 1679, 1641, 1207, 1120, 1028, 916.

The spectroscopic data for this compound matched those in the literature.[7]



According to general procedure A, a stirred solution of **3-31** (0.164 g, 0.582 mmol) and Et_3N (0.406 mL, 2.91 mmol) in CH_2Cl_2 (5.8 mL) was cooled to -78 °C. Neat Cy_2BI (0.147 mL, 0.640 mmol) was added dropwise to

[7]Enders, D.; Bartsch, M.; Runsink, J. *Synthesis* **1999**, 243–248.

the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 15 min. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL) and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (5.8 mL) and treated with H_2O_2 (0.582 mL, 30% in H_2O, 5.82 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 minutes to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL) and analyzed by NMR (d1=10 s) to obtain the dr of the reaction. The chloroform solution was concentrated and purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH) to give acid **3-32** (121 mg, 73% yield).

Data for acid 3-32.

Physical State: Clear, colorless liquid.

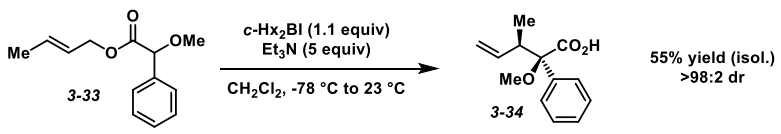
TLC: R_f = 0.07 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.20 (m, 8H), 7.19-7.09 (m, 2H), 6.08 (ddd, *J* = 16.8, 10.4, 8.4 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 2H), 5.13 (d, *J* = 10.2 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.22 (d, *J* = 6.7 Hz, 1H), 3.79 (t, *J* = 7.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9, 139.0, 136.8, 136.7, 128.7, 128.4, 128.3, 128.0, 127.9, 127.0, 117.4, 81.5, 73.1, 53.0.

IR (film): ν = 3675, 2987, 2950 (br), 2900, 1716, 1453, 1249, 1076, 919

HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{18}H_{18}O_3 + Na]^+$: 305.1148, found 305.1148.



According to general procedure A, a stirred solution of ester **3-33** (0.139 g, 0.632 mmol) and Et_3N (0.440 mL, 3.16 mmol) in CH_2Cl_2 (6.3 mL) was cooled to -78 °C. Neat Cy_2BI (0.160 mL, 0.695 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 5 min. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), rinsing the flask with Et_2O (10 mL) and the mixture was acidified (pH 1) with 2 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (6.3 mL) and treated with H_2O_2 (0.63 mL, 30% in H_2O, 6.3 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL) and analyzed by ^1H NMR (d1=10 s) to obtain the dr of the reaction. The chloroform solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give acid **3-34** (76.7 mg, 55% yield).

Data for acid 3-34.

Physical State: Colorless solid.

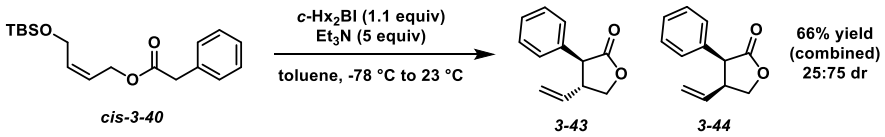
TLC: R_f = 0.11 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.41–7.27 (m, 3H), 5.88 (ddd, *J* = 17.3, 10.3, 7.2 Hz, 1H), 5.12 (d, *J* = 10.6 Hz, 1H), 5.11 (d, *J* = 17.2 Hz, 1H), 3.25 (s, 3H), 3.32 (quintet, *J* = 6.8 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5, 138.0, 135.5, 128.2, 128.1, 128.0, 116.7, 87.9, 53.7, 44.3, 14.5.

IR (film): ν = 3064, 2980, 2964, 2929, 2900 (br), 2827, 2685, 2526, 1708, 1447, 1403, 1270, 1068, 940, 929

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{16}O_3 + H]^+$: 221.1172, found 221.1177.



According to general procedure B, a stirred solution of ***cis*-3-40** (140 mg, 0.438 mmol) and Et_3N (0.305 mL, 2.19 mmol) in toluene (4.4 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.771 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.482 mL, 1.0 M, 0.482 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 2 h. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (4.4 mL) and treated with H_2O_2 (0.44 mL, 30% in H_2O, 4.4 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL) and analyzed by ^{1}H NMR (d1=10 s) to obtain the dr of the reaction. The $CDCl_3$ solution was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give lactones **3-43** and **3-44** (54.7 mg, 66% yield) as an inseparable mixture of diastereomers whose configurations were assigned on the basis of 2D ROESY data of **3-43** prepared by the rearrangement of ***trans*-3-40**.

Data for lactones 3-43 and 3-44.

Physical State: Colorless liquid.

TLC: R_f = 0.12 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

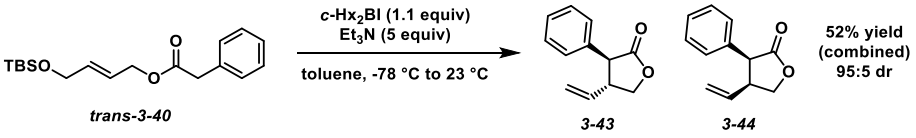
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.17 (comp m, 10H, both diastereomers), 5.76 (ddd, *J* = 17.3, 10.1, 7.8 Hz, 1H, *trans* diastereomer), 5.30 (ddd, *J* = 17.2, 9.5, 9.0 Hz, 1H, *cis* diastereomer), 5.15 (d, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 17.2 Hz, 1H, *trans* diastereomer), 5.06 (d, *J* = 16.8 Hz, 1H, *cis* diastereomer), 5.01 (d, *J* = 10.2 Hz, 1H, *cis* diastereomer), 4.51 (t, *J* = 8.2 Hz, 1H, *trans* diastereomer), 4.47 (dd, *J* = 9.0, 7.0 Hz, 1H, *cis* diastereomer), 4.22 (dd, *J* = 9.0, 6.7 Hz,

1H, *cis* diastereomer), 4.06 (t, *J* = 9.6 Hz, 1H, *trans* diastereomer), 3.98 (d, *J* = 8.6 Hz, 1H, *cis* diastereomer), 3.55 (d, *J* = 11.3 Hz, 1H, *trans* diastereomer), 3.45 (ddt, *J* = 9.0, 8.6, 6.7 Hz, 1H, *cis* diastereomer), 3.28 (ddd, *J* = 18.4, 10.6, 7.8 Hz, 1H, *trans* diastereomer).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.9 (both diastereomers), 135.0 (*trans* diastereomer), 134.0 (*trans* diastereomer), 133.3 (*cis* diastereomer), 133.2 (*cis* diastereomer), 129.1 (*cis* diastereomer), 128.8 (*trans* diastereomer), 128.7 (*cis* diastereomer), 128.5 (*trans* diastereomer), 127.8 (*trans* diastereomer), 127.6 (*cis* diastereomer), 119.2 (*trans* diastereomer), 118.6 (*cis* diastereomer), 70.4 (*cis* diastereomer), 69.9 (*trans* diastereomer), 52.0 (*trans* diastereomer), 50.5 (*cis* diastereomer), 49.4 (*trans* diastereomer), 45.6 (*cis* diastereomer).

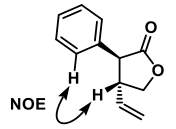
IR (film): ν = 3030, 2984, 2905, 1766, 1147, 1014, 921.

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{12}O_2 + H]^+$: 189.0910, found 189.0916.



According to general procedure B, a stirred solution of ***trans*-3-40** (0.118 g, 0.369 mmol) and Et_3N (0.257 mL, 1.85 mmol) in toluene (3.7 mL) was cooled to -78 °C. Neat Cy_2BI (0.229 mL, 1.00 mmol) was diluted with hexanes (0.771 mL) to make a 1.0 M solution. A portion of this Cy_2BI solution (0.406 mL, 1.0 M, 0.406 mmol) was added dropwise to the reaction mixture at -78 °C, and the latter was stirred at this temperature for 60 min. At this time, the reaction mixture was allowed to warm to ambient temperature over approx. 15 min. The solution was stirred at this temperature 45 min. At this time, TLC indicated consumption of starting material, and the reaction mixture was quenched by pouring into 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (rinsing the flask with a small amount of Et_2O), and the mixture was acidified (pH 1) with 2.0 M aq. HCl. The biphasic mixture was then extracted with Et_2O (3x10 mL). The combined organic extracts were then washed with brine (10 mL), dried with Na_2SO_4 and concentrated. The resulting residue was dissolved in MeOH (3.7 mL) and treated with H_2O_2 (0.37 mL, 30% in H_2O, 3.7 mmol). This mixture was allowed to stand 1 h at ambient temperature, then diluted with EtOH (25 mL) and concentrated to azeotropically remove H_2O. The residue was then gently heated with a heat gun under high vacuum (<0.1 torr) for 1-2 min to remove most of the cyclohexanol. The crude product was dissolved in $CDCl_3$ (4.0 mL) and analyzed by ^{1}H NMR (d1=10 s) to obtain the dr of the reaction. The $CDCl_3$ solution was concentrated, and the residue was purified

by flash column chromatography (19:1 hexanes/EtOAc → 89:10:1 hexanes/EtOAc/AcOH eluent) to give lactone **3-43** (61.8 mg, 52% yield). The relative stereochemistry of **3-43** was assigned on the basis of 2D ROESY data and the correlations shown below.



2D ROESY Correlation of *3-43*

Data for lactone 3-43.

Physical State: Colorless liquid.

TLC: R_f = 0.12 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

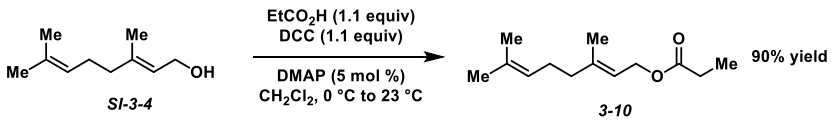
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 5.76 (ddd, *J* = 16.8, 10.2, 7.8 Hz, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 4.51 (t, *J* = 8.4 Hz, 1H), 4.06 (t, *J* = 9.8 Hz, 1H), 3.55 (d, *J* = 11.3 Hz, 1H), 3.28 (ddd, *J* = 18.8, 10.6, 8.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 135.0, 134.0, 128.9, 128.5, 127.8, 119.2, 69.9, 52.0, 49.4.

IR (film): ν = 2975, 2898, 1759, 1021, 1008, 908.

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{12}H_{12}O_2 + H]^+$: 189.0910, found 189.0916.

Starting Material Synthesis.



To a solution of geraniol (**SI-3-4,** 4.06 g, 26.3 mmol), propionic acid (2.21 mL, 29.6 mmol), and DMAP (164 mg, 1.35 mmol) in CH_2Cl_2 (26.3 mL) at 0 °C was added DCC (6.11 g, 29.6 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of geraniol. Then the reaction was diluted with pentane (30 mL) and filtered

through a short column of silica, rinsing with 9:1 hexanes/EtOAc (100 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-10** (4.97 g, 90% yield).

Data for geranyl propionate (3-10).

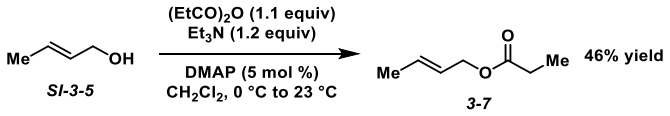
Physical State: Clear, colorless liquid.

TLC: R_f = 0.37 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (td, *J* = 7.1, 1.0 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 2.31 (q, *J* = 7.4 Hz, 2H), 2.13–1.99 (comp m, 4H), 1.68 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.12 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5, 142.0, 131.8, 123.7, 118.4, 61.2, 39.5, 27.6, 26.3, 25.6, 17.6, 16.4, 9.1.

IR (film): ν = 2978, 2926, 2858, 1736, 1378, 1175, 1080, 1011, 939



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5,** 1.09 g, 15.1 mmol), Et_3N (2.52 mL, 18.1 mmol), and DMAP (91.6 mg, 0.750 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added propionic anhydride (2.13 mL, 16.6 mmol). The solution was stirred at 0 °C for 30 min and warmed to ambient temperature, stirring until TLC indicated consumption of **SI-3-5**. The reaction was then poured into 1 M aq. HCl (25 mL), and the resulting biphasic mixture extracted with pentane (3x20 mL). The combined organic extracts were washed sequentially with 1.5 M aq. K_2CO_3 (10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by distillation at atmospheric pressure, collecting the fraction boiling at 145-146 °C to give ester **3-7** (0.887 g, 46% yield).

Data for (*E*)-crotyl propionate (3-7).

[8] Commercial crotyl alcohol is a ~19:1 mixture of E/Z isomers. The method of Denmark was used to prepare geometrically pure (*E*)-crotyl alcohol: Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031–4042.

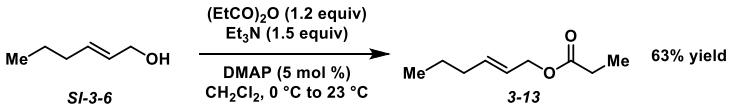
Physical State: Clear, colorless liquid.

TLC: R_f = 0.37 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (dq, *J* = 14.9, 6.7 Hz, 1H), 5.57 (dtq, *J* = 15.3, 6.3, 0.8 Hz, 1H), 4.48 (d, *J* = 6.7 Hz, 2H), 2.31 (q, *J* = 7.4 Hz, 2H), 1.70 (d, *J* = 6.3 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2, 131.2, 125.2, 65.0, 27.6, 17.7, 9.1.

The spectroscopic data for this compound matched those in the literature.[8]



To a solution of 2-hexen-1-ol (**SI-3-6**, 1.93 g, 19.3 mmol), Et_3N (4.03 mL, 28.9 mmol), and DMAP (118 mg, 0.963 mmol) in CH_2Cl_2 (19 mL) at 0 °C was added propionic anhydride (2.97 mL, 23.1 mmol). The solution was stirred at 0 °C for 30 min and warmed to ambient temperature, stirring until TLC indicated consumption of **SI-3-6**. The reaction was then poured into 1 M aq. HCl (50 mL), and the resulting biphasic mixture extracted with Et_2O (3x20 mL). The combined organic extracts were washed sequentially with sat. aq. Na_2CO_3 (50 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (9:1 hexanes/Et_2O eluent) to give ester **5** (1.91 g, 63% yield).

Data for allylic propionate 3-13.

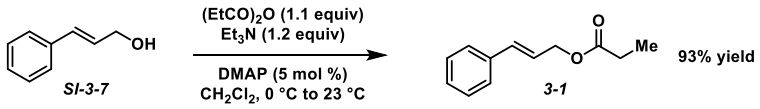
Physical State: Clear, colorless liquid.

TLC: R_f = 0.37 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (dtt, *J* = 15.3, 6.8, 1.0 Hz, 1H), 5.54 (dtt, *J* = 15.3, 6.7, 1.2 Hz, 1H), 4.50 (d, *J* = 6.7 Hz, 2H), 2.31 (q, *J* = 7.7 Hz, 2H), 2.01 (q, *J* = 7.3 Hz, 2H), 1.39 (app. sextet, *J* = 7.4 Hz, 2H), 1.12 (t, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 136.2, 124.0, 65.1, 34.3, 27.6, 22.0, 13.6, 9.1.

The spectroscopic data for this compound matched those in the literature. [9]



To a solution of cinnamyl alcohol (**SI-3-7**, 1.89 g, 14.1 mmol), Et_3N (2.35 mL, 16.9 mmol), and DMAP (86.0 mg, 0.704 mmol) in CH_2Cl_2 (28 mL) at 0 °C was added propionic anhydride (1.99 mL, 15.5 mmol). The solution was stirred at 0 °C for 30 min and warmed to ambient temperature, stirring until TLC indicated consumption of **SI-3-7**. The reaction was then poured into 1 M aq. HCl (50 mL), and the resulting biphasic mixture extracted with Et_2O (3x20 mL). The combined organic extracts were washed sequentially with sat. aq. Na_2CO_3 (50 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give ester **3-1** (2.50 g, 93% yield).

Data for cinnamyl propionate (3-1).

Physical State: Clear, colorless liquid.

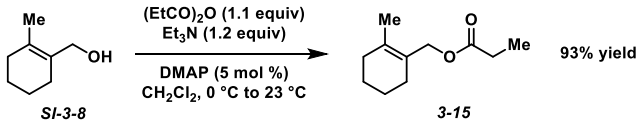
TLC: R_f = 0.32 (9:1 hexanes/EtOAc, $KMnO_4$ stain solution, UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.73 (d, *J* = 6.7 Hz, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 1.16 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2, 136.2, 134.0, 128.6, 128.0, 126.6, 123.3, 64.9, 27.6, 9.1.

The spectroscopic data for this compound matched those in the literature.[10]

[9] Metz, P.; Mues, C. *Tetrahedron* **1988**, *44*, 6841–6853.
[10] Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771–1774.



To a solution of alcohol **SI-3-8**[11] (3.30 g, 26.1 mmol), Et_3N (4.37 mL, 31.3 mmol), and DMAP (160 mg, 1.31 mmol) in CH_2Cl_2 (26.1 mL) at 0 °C was added propionic anhydride (3.68 mL, 28.7 mmol). The solution was stirred at 0 °C for 30 min and warmed to ambient temperature, stirring until TLC indicated consumption of **SI-3-8**. The reaction was then poured into 1.0 M aq. K_2CO_3 (50 mL). The organic layer was separated and washed sequentially with 1.0 M aq. HCl (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give ester **3-15** (4.42 g, 93% yield).

Data for allylic propionate 3-15.

Physical State: Clear, colorless liquid.

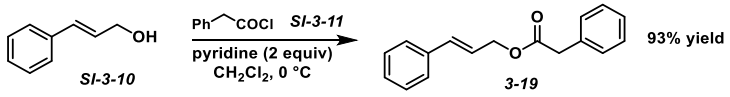
TLC: R_f = 0.42 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 2H), 2.31 (q, *J* = 7.7 Hz, 2H), 2.07-1.90 (m, 4H), 1.67 (s, 3H), 1.63-1.51 (m, 5H), 1.12 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7, 133.3, 125.2, 64.8, 31.9, 27.64, 27.58, 22.81, 22.79, 19.0, 9.2.

IR (film): ν = 2929, 1730, 1462, 1380, 1358, 1339, 1274, 1181, 1081, 1013, 933.

HRMS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{11}H_{18}O_2 + NH_4]^+$: 200.1651, found 200.1644.



To a solution of cinnamyl alcohol (**SI-3-10,** 2.37 g, 17.7 mmol) and pyridine (2.84 mL, 35.4 mmol) in CH_2Cl_2 (35.4 mL) at 0 °C was added phenylacetyl chloride (**SI-3-11**, 2.58 mL, 19.5 mmol). The solution was stirred at 0 °C for 30 min at which time TLC indicated consumption of **SI-3-10**. The reaction was then poured into 1.0 M aq. K_2CO_3

[11]Chow, Ken; Gil, Daniel, W.; Fang, Wenkui K.; Garst, Michael, U.S. Patent 6,534,542, March 18, 2003

(50 mL). The organic layer was separated and washed sequentially with 1.0 M aq. HCl (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-19** (4.14 g, 93% yield).

Data for cinnamyl phenylacetate (3-19).

Physical State: Clear, colorless liquid.

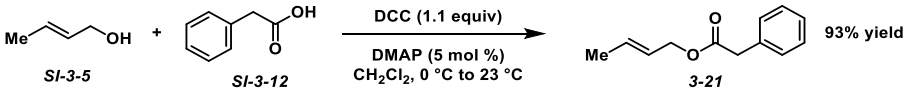
TLC: R_f = 0.27 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.19 (comp m, 10H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 15.7, 6.4 Hz, 1H), 4.75 (d, *J* = 6.3 Hz, 2H), 3.67 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 136.2, 134.1, 134.0 129.3, 128.6, 128.0, 127.1, 126.6, 123.0, 65.3, 41.4.

IR (film): ν = 3060, 3028, 1729, 1494, 1252, 1144, 1073, 965.

The spectroscopic data for this compound matched those in the literature. [12]



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.362 g, 5.02 mmol), phenylacetic acid (**SI-3-12**, 0.751 g, 5.52 mmol), and DMAP (30.7 mg, 0.251 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DCC (1.13 g, 5.52 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then diluted with pentane (10 mL) and filtered through a short plug of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-21** (0.886 g. 93% yield).

Data for (*E*)-crotyl phenylacetate (3-21).

[12] Ishihara, K.; Niwa, M.; Kosugi, Y. *Org. Lett.* **2008**, *10*, 2187–2190.

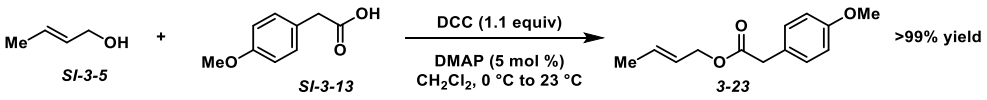
Physical State: Clear, colorless liquid.

TLC: R_f = 0.24 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.20 (m, 5H), 5.76 (dqt, *J* = 15.3, 6.3, 1.2 Hz, 1H), 5.57 (dtq, *J* = 15.3, 6.7, 1.6 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 2H), 3.62 (s, 2H), 1.70 (dd, *J* = 6.5, 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 134.0, 131.4, 129.2, 128.5, 127.0, 124.9, 65.6, 41.3, 17.7.

The spectroscopic data for this compound matched those in the literature.[9]



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.177 g, 2.45 mmol), *p*-methoxyphenylacetic acid (**SI-3-13**, 0.372 g, 2.24 mmol), and DMAP (13.6 mg, 0.111 mmol) in CH_2Cl_2 (4.4 mL) at 0 °C was added DCC (0.506 g, 2.45 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then diluted with pentane (10 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-23** (499 mg, >99% yield).

Data for (*E*)-crotyl *p*-methoxyphenylacetate (3-23).

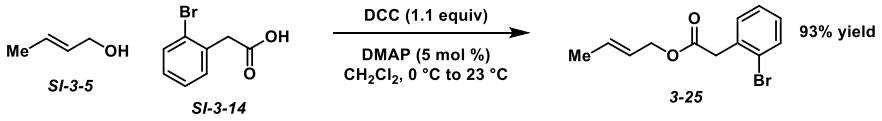
Physical State: Clear, colorless liquid.

TLC: R_f = 0.26 (9:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (ddd, *J* = 9.8, 3.1, 2.0 Hz, 2H), 6.84 (ddd, *J* = 9.8, 3.1, 2.0 Hz, 2H), 5.75 (dqt, *J* = 14.9, 6.7, 1.2 Hz, 1H), 5.56 (dtq, *J* = 15.3, 6.7, 1.6 Hz, 1H), 4.50 (d, *J* = 6.3 Hz, 2H), 3.77 (s, 3H), 3.55 (s, 2H), 1.70 (dd, *J* = 6.5, 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 158.6, 131.4, 130.3, 126.1, 125.0, 113.9, 65.5, 55.2, 40.4, 17.7.

HRMS (APCI) *m/z* calc'd for $(M + H)^+$ $[C_{13}H_{16}O_3 + H]^+$: 221.1172, found 221.1172.



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.194 g, 2.69 mmol), *o*-bromophenylacetic acid (**SI-3-14**, 0.527 mg, 2.45 mmol), and DMAP (15.0 mg, 0.123 mmol) in CH_2Cl_2 (4.9 mL) at 0 °C was added DCC (0.555 g, 2.69 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then diluted with pentane (5 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (10 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-25** (0.615 g, 93% yield).

Data for (*E*)-crotyl *o*-bromophenylacetate (3-25).

Physical State: Clear, colorless liquid.

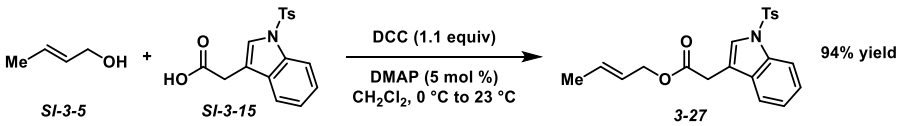
TLC: R_f = 0.30 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.33-7.19 (comp m, 2H), 7.13 (t, *J* = 7.0 Hz, 1H), 5.77 (dq, *J* = 14.9, 6.3 Hz, 6H), 5.58 (dt, *J* = 15.1, 6.3 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 2H), 3.78 (s, 2H), 1.70 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 134.2, 132.8, 131.5, 131.4, 128.8, 127.5, 125.0, 124.8, 65.7, 41.6, 17.8.

IR (film): ν = 3025, 2968, 2943, 2919, 1731, 1159, 956, 905.

HRMS (APCI) *m/z* calc'd for $(M + NH_4)^+$ $[C_{12}H_{13}BrO_2 + NH_4]^+$: 286.0437, found 286.0433.



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 95.2 mg, 1.32 mmol), 2-(*N*-tosyl-3-indole)acetic acid[13] (**SI-3-15**, 0.395 g, 1.20 mmol), and DMAP (7.3 mg, 0.0600 mmol) in CH_2Cl_2 (4.8 mL) at 0 °C was added DCC (0.272 mg, 1.32 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then diluted with pentane (10 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give ester **3-27** (0.432 g, 94% yield).

Data for (*E*)-crotyl 2-(*N*-tosyl-3-indole)acetate (3-27).

Physical State: Pale yellow liquid.

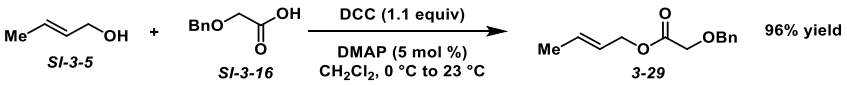
TLC: R_f = 0.06 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution, UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.56 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.25-7.21 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.76 (dq, *J* = 14.9, 6.7 Hz, 1H), 5.56 (dtt, *J* = 15.1, 6.6, 1.6 Hz, 1H), 4.53 (d, *J* = 6.7 Hz, 2H), 3.68 (s, 2H), 2.31 (s, 3H), 1.70 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 144.8, 135.3, 135.0, 131.8, 130.4, 129.8, 126.8, 124.8, 124.74, 124.69, 123.2, 119.5, 115.0, 113.6, 65.8, 31.0, 21.5, 17.8.

IR (film): ν = 2930, 2853, 2118, 1739, 1362, 1171, 1154, 1108, 1091, 973, 948, 806.

HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{21}H_{21}NO_4S + Na]^+$: 406.1083, found 406.1082.



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.359 g, 4.98 mmol), benzyloxyacetic acid (**SI-3-16**, 0.914 g, 5.48 mmol), and DMAP (30.4 mg, 0.249 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C was added DCC (1.13 g, 5.48 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then

[13]Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521–535.

diluted with pentane (10 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc → 9:1 hexanes/EtOAc eluent) to give ester **3-29** (1.05 g, 96% yield). This compound has been reported previously.[14]

Data for (*E*)-crotyl benzyloxyacetate (3-29).

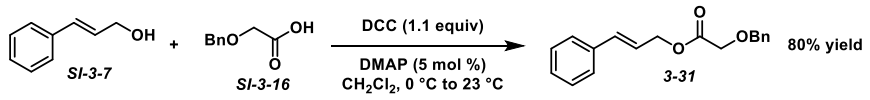
Physical State: Clear, colorless liquid.

TLC: R_f = 0.17 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.23 (comp m, 5H), 5.80 (dq, *J* = 14.9, 6.7 Hz, 1H), 5.58 (dtq, *J* = 14.9, 6.7, 1.2 Hz, 1H), 4.62 (s, 2H), 4.58 (d, *J* = 6.7 Hz, 2H), 4.08 (s, 2H), 1.71 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 137.1, 132.1, 128.4, 128.05, 127.97, 124.6, 73.3, 67.2, 65.5, 17.7.

IR (film): ν = 3030, 2943, 2916, 2884, 1751, 1730, 1190, 1121, 964.



To a solution of cinnamyl alcohol (**SI-3-7**, 5.00 g, 37.2 mmol), benzyloxyacetic acid (**SI-3-16**, 5.62 g, 33.9 mmol), and DMAP (0.207 g, 1.69 mmol) in CH_2Cl_2 (68 mL) at 0 °C was added DCC (7.68 g, 37.2 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of cinnamyl alcohol. The reaction was then diluted with pentane (10 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc → 9:1 hexanes/EtOAc eluent) to give ester **3-31** (7.63 g, 80% yield). This compound has been reported previously.[14]

Data for cinnamyl benzyloxyacetate (3-31).

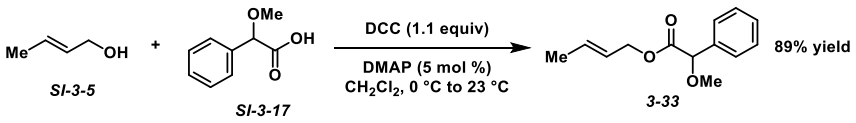
[14] Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889–3901.

Physical State: Clear, colorless liquid.

TLC: R_f = 0.10 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.22 (m, 10H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.27 (dt, *J* = 15.7, 6.6 Hz, 1H), 4.81 (dd, *J* = 6.7, 1.2 Hz, 2H), 4.64 (s, 2H), 4.13 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 137.0, 136.0, 134.8, 128.6, 128.5, 128.2, 128.1, 128.0, 126.6, 122.5, 73.4, 67.2, 65.4.



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.138 g, 1.91 mmol), (±)-α-methoxyphenylacetic acid (**SI-3-17**, 0.288 g, 1.73 mmol), and DMAP (10.6 mg, 0.0865 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C was added DCC (0.394, 1.91 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of **SI-3-17**. The reaction was then diluted with pentane (5.0 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-33** (0.338 mg, 89% yield). This compound has been reported previously.[15]

Data for allylic ester 3-33.

Physical State: Clear, colorless liquid.

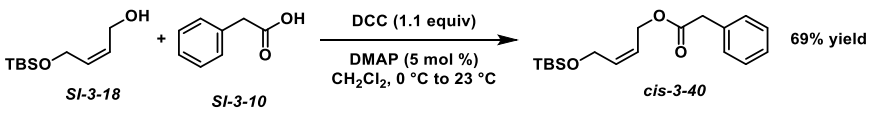
TLC: R_f = 0.18 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.34 (comp m, 3H), 5.70 (dqt, *J* = 15.3, 6.7, 1.2 Hz, 1H), 5.51 (dtq, *J* = 15.3, 6.3, 1.6 Hz, 1H), 4.75 (s, 1H), 4.57 (ddt, *J* = 12.5, 6.7, 1.2 Hz, 1H), 4.48 (ddt, *J* = 12.1, 6.3, 1.2 Hz, 1H), 3.39 (s, 3H), 1.66 (dd, *J* = 6.3, 1.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 136.2, 131.8, 128.7, 128.6, 127.2, 124.5, 82.6, 65.8, 57.3, 17.7.

[15] Oh, T.; Wrobel, Z.; Devine, P. N. *Synlett* **1992**, 81–83.

IR (film): ν = 2936, 2884, 2827, 2117, 1745, 1730, 1198, 1170, 1105, 965.



To a solution of alcohol **SI-3-18**[16] (0.211 g, 1.05 mmol), phenylacetic acid (**SI-3-10**, 0.156 g, 1.15 mmol), and DMAP (6.4 mg, 0.0520 mmol) in CH_2Cl_2 (2.1 mL) at 0 °C was added DCC (0.237 g, 1.15 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of alcohol **SI-3-18**. The reaction was then diluted with pentane (5 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the crude product further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester ***cis*-3-40** (0.232 g, 69% yield).

Data for allylic phenylacetate *cis*-3-40.

Physical State: Clear, colorless liquid.

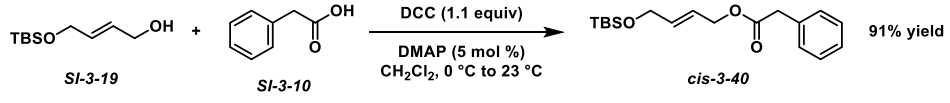
TLC: R_f = 0.32 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.19 (m, 5H), 5.71 (dtt, *J* = 11.3, 5.9, 1.2 Hz, 1H), 5.54 (dtt, *J* = 11.3, 6.7, 1.6 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 2H), 4.23 (dt, *J*=5.9, 0.8 Hz, 2H), 3.61 (s, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 134.2, 133.9, 129.2, 128.5, 127.1, 123.9, 60.8, 59.5, 41.3, 25.9, 18.3, -5.3.

IR (film): ν = 2954, 2929, 2856, 1736, 1251, 1085, 834.

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{28}O_3Si + H]^+$: 321.1880, found 321.1885.



[16] Kondo, Y.; Suzuki, N.; Takahashi, M.; Kumamoto, T.; Masu, H.; Ishikawa, T. *J. Org. Chem.* **2012**, *77*, 7988–7999.

To a solution of alcohol **SI-3-19**[17] (0.116 g, 0.573 mmol), phenylacetic acid (**SI-3-10**, 85.8 mg, 0.630 mmol), and DMAP (3.5 mg, 0.0287 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added DCC (0.130 g, 0.630 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of alcohol **S15**. The reaction was then diluted with pentane (5 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the crude product further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester ***trans*-3-40** (0.167 g, 91% yield).

Data for allylic phenylacetate *trans*-3-40.

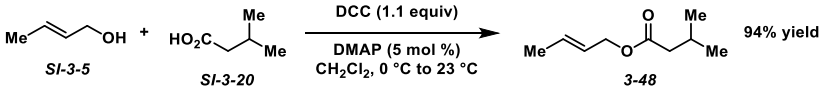
Physical State: Clear, colorless liquid.

TLC: R_f = 0.21 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 5.81 (dd, *J* = 15.7, 3.5 Hz, 1H), 5.76 (dd, *J* = 15.7, 4.7 Hz, 1H), 4.59 (d, *J* = 4.3 Hz, 2H), 4.16 (s, 2H), 3.62 (s, 2H), 0.90 (s, 9H), 0.08-0.00 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 134.1, 134.0, 129.2, 128.5, 127.0, 123.4, 64.8, 62.8, 41.3, 25.9, 18.4, -5.3.

HRMS (ESI+) *m/z* calc'd for $(M + H)^+$ $[C_{18}H_{28}O_3Si + NH_4]^+$: 338.2146, found 338.2152.



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.692 g, 9.59 mmol), isopropylacetic acid (**SI-3-20**, 1.16 mL, 10.6 mmol), and DMAP (58.6 mg, 0.480 mmol) in CH_2Cl_2 (9.6 mL) at 0 °C was added DCC (2.18 g, 10.6 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then diluted with pentane (25 mL) and filtered through a short column of silica, rinsing with 4:1 pentane/Et_2O (20 mL). The filtrate

[17] Nelson, B.; Hiller, W.; Pollex, A.; Hiersemann, M. *Org. Lett.* **2011**, *13*, 4438–4441.

was concentrated, and the residue was further purified by flash column chromatography (4:1 pentane/Et_2O eluent) to give ester **3-48** (1.40 g, 94% yield).

Data for (*E*)-crotyl isopropylacetate (3-48).

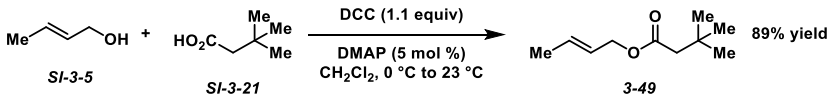
Physical State: Clear, colorless liquid.

TLC: R_f = 0.24 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (dqt, *J* = 15.1, 6.2, 1.2 Hz, 1H), 5.56 (dtq, *J* = 15.1, 6.6, 1.6 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 2H), 2.18-2.13 (m, 2H), 2.07 (septet d, *J* = 6.6, 0.8 Hz, 1H), 1.69 (dd, *J* = 6.6, 1.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 7H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 131.2, 125.2, 64.9, 43.4, 25.7, 22.4, 17.7.

HRMS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_9H_{16}O_2 + NH_4]^+$: 174.1489, found 174.1487.



To a solution of (*E*)-crotyl alcohol[8] (**SI-3-5**, 0.680 g, 9.42 mmol), *tert*-butylacetic acid (**SI-3-21**, 1.32 mL, 10.0 mmol), and DMAP (57.5 mg, 0.471 mmol) in CH_2Cl_2 (9.4 mL) at 0 °C was added DCC (2.06 g, 10.0 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of crotyl alcohol. The reaction was then diluted with pentane (25 mL) and filtered through a short column of silica, rinsing with 4:1 pentane/Et_2O (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (4:1 pentane/Et_2O eluent) to give ester **3-49** (1.43 g, 89% yield).

Data for (*E*)-crotyl *tert*-butylacetate (3-49).

Physical State: Clear, colorless liquid.

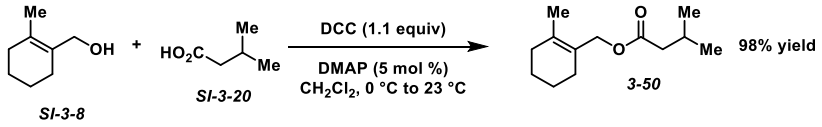
TLC: R_f = 0.28 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (dqt, *J* = 15.3, 6.6, 0.8 Hz, 1H), 5.56 (dtq, *J* = 15.2, 6.6, 0.8 Hz, 1H), 4.46 (dd, *J* = 6.6, 0.8 Hz, 2H), 2.17 (s, 2H), 1.69 (dq, *J* = 6.6, 0.8 Hz, 3H), 1.00 (d, *J* = 0.8 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 131.1, 125.3, 64.7, 47.9, 30.7, 29.6, 17.7.

IR (film): ν = 2956, 1732, 1367, 1322, 1225, 1126, 965.

HRMS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{10}H_{18}O_2 + H]^+$: 171.1380, found 171.1378.



To a solution of allylic alcohol **SI-3-8**[11] (0.716 g, 5.67 mmol), isopropylacetic acid (**SI-3-20**, 0.689 mL, 6.24 mmol), and DMAP (34.7 mg, 0.284 mmol) in CH_2Cl_2 (5.7 mL) at 0 °C was added DCC (1.29 g, 6.24 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of **SI-3-8**. The reaction was then diluted with pentane (15 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-50** (1.17 g, 98% yield).

Data for allylic isopropylacetate (3-50).

Physical State: Clear, colorless liquid.

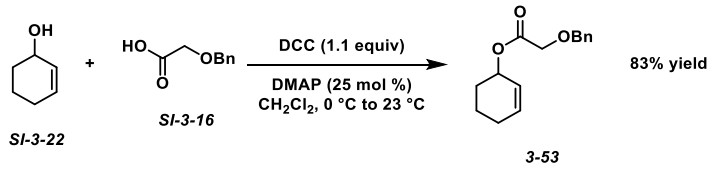
TLC: R_f = 0.24 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (s, 2H), 2.16 (dd, *J* = 7.4, 0.8 Hz, 2H), 2.07 (septet d, *J* = 6.6, 1.2 Hz, 1H), 2.02-1.91 (m, 4H), 1.67 (s, 3H), 1.61-1.52 (m, 4H), 0.92 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 133.4, 125.2, 64.6, 43.5, 31.9, 27.7, 25.7, 22.8, 22.8, 22.4, 19.0.

IR (film): ν = 2958, 2928, 2871, 2832, 1731, 1292, 1183, 1166, 1117, 1093, 976.

HRMS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{13}H_{22}O_2 + NH_4]^+$: 228,1964, found 228.1956.



To a solution of cyclohex-2-en-1-ol (**SI-3-22**, 0.422 g, 4.30 mmol), benzyloxyacetic acid (**SI3-16**, 0.785 g, 4.73 mmol), and DMAP (0.131 g, 1.07 mmol) in CH_2Cl_2 (4.3 mL) at 0 °C was added DCC (0.976 g, 4.73 mmol) in one portion. A precipitate began to form almost immediately. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature, stirring until TLC showed consumption of **SI-3-22**. The reaction was then diluted with pentane (10 mL) and filtered through a short column of silica, rinsing with 9:1 hexanes/EtOAc (20 mL). The filtrate was concentrated, and the residue was further purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to give ester **3-53** (0.883 g, 83% yield).

Data for allylic benzyloxyacetate (3-53).

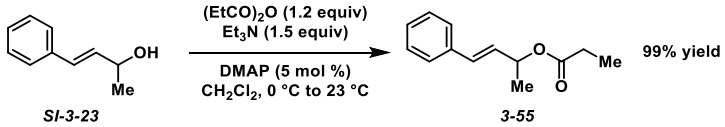
Physical State: Clear, colorless liquid.

TLC: R_f = 0.12 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 5.95 (dtd, *J* = 10.1, 3.8, 1.2 Hz, 1H), 5.70 (ddt, *J* = 10.0, 3.8, 2.2 Hz, 1H), 5.35 (dtd, *J* = 6.7, 3.5, 1.6 Hz, 1H), 4.62 (s, 2H), 4.06 (s, 2H), 2.13–1.81 (m, 4H), 1.78–1.56 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 137.2, 133.1, 128.4, 128.1, 127.9, 125.2, 73.3, 68.7, 67.4, 28.2, 24.8, 18.7.

HRMS (ESI+) *m/z* calc'd for $(M + Na)^+$ $[C_{15}H_{18}O_3 + Na]^+$: 269.1148, found 269.1153.



To a solution of allylic alcohol **SI-3-23**[18] (0.433 g, 2.92 mmol), Et_3N (0.610 mL, 4.38 mmol), and DMAP (17.8 mg, 0.146 mmol) in CH_2Cl_2 (5.8 mL) at 0 °C was added propionic anhydride (0.451 mL, 3.51 mmol). The solution was stirred at 0 °C for 30 min and warmed to ambient temperature, stirring until TLC indicated consumption of **SI-3-23**. The reaction was then poured into 1 M aq. HCl (50 mL), and the resulting biphasic mixture extracted with Et_2O (3x20 mL). The combined organic extracts were washed sequentially with sat. aq. Na_2CO_3 (50 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give ester **3-55** (0.588 g, 99% yield).

Data for allylic propionate (3-55).

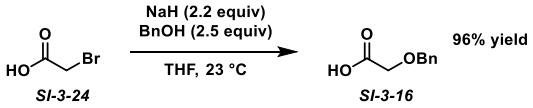
Physical State: Clear, colorless liquid.

TLC: R_f = 0.22 (19:1 hexanes/EtOAc, $KMnO_4$ stain solution, UV).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 7.32-7.26 (m, 2H), 7.25-7.20 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.6 Hz, 1H), 5.52 (dq, *J* = 6.6, 6.2 Hz, 1H), 2.33 (q, *J* = 7.5 Hz, 2H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.13 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 136.4, 131.4, 128.9, 128.5, 127.8, 126.5, 70.7, 27.9, 20.4, 9.1.

These spectroscopic data matched those reported in the literature.[19]



To a suspension of NaH (13.2 g, 60% dispersion in mineral oil, 330 mmol) in THF (100 mL) was added benzyl alcohol (38.8 mL, 375 mmol) over 10 min at such a rate as to control the evolution of H_2. After the gas evolution ceased, the solution was cooled to 0 °C in an ice bath. A solution of bromoacetic acid (**SI-3-24**, 20.9 g, 150 mmol) in THF (50 mL) was added over 10 min with cooling. Upon completion, the ice bath was removed and the solution was stirred 12 h at ambient temperature. At this point, the reaction mixture had almost completely solidified

[18] Li, Z.; Parr, B. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 10942–10946.
[19] Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445–3447.

and was digested by swirling/stirring in a mixture of H_2O (150 mL) and hexanes (100 mL). Once the solid was completely dissolved in this biphasic mixture, the aqueous layer was separated and washed with Et_2O (2x100 mL). It was then acidified with conc. HCl (40 mL, 12 M in H_2O) and extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$ and concentrated to give acid **SI-3-16** (24.0 g, 96% yield) free from benzyl alcohol and mineral oil and used without further purification.

Data for benzyloxyacetic acid (SI-3-16).

Physical State: Pale yellow liquid.

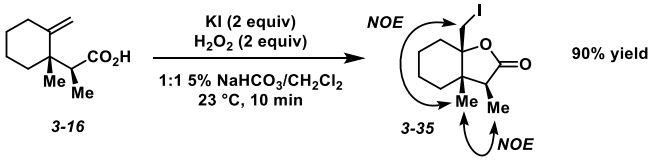
TLC: R_f = 0.05 (89:10:1 hexanes/EtOAc/AcOH, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 7.41-7.32 (comp m, 5H), 4.67 (s, 2H), 4.17 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 136.5, 128.6, 128.2, 128.1, 73.5, 66.5.

IR (film): ν = 3075 (br), 3064, 3032, 2907, 1725, 1205, 1110, 908.

Determination of the stereochemistry of 3-16.



To a solution of **3-16** (57.9 mg, 0.318 mmol) and KI (106 mg, 0.636 mmol) in a biphasic mixture of 5% aq. $NaHCO_3$ (1.00 mL) and CH_2Cl_2 (1.00 mL) under air was added H_2O_2 (63.6 μL, 30 % in H_2O, 0.636 mmol) dropwise. The solution was stirred for 5 min at ambient temperature, at which time TLC indicated consumption of **3-16**. The reaction was then partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was separated and washed with brine (10 mL), dried with Na_2SO_4 and concentrated to afford lactone **3-35** (88.4 mg, 90% yield), which did not require purification. The stereochemistry of lactone **3-35** was assigned on the basis of 1D NOE data with the correlations shown above.

Data for iodolactone 3-35.

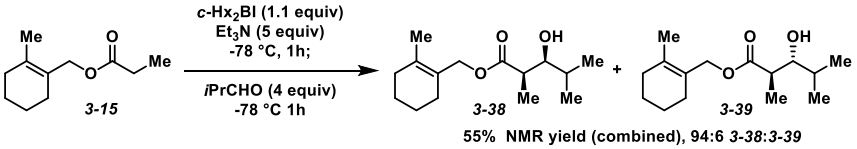
Physical State: Colorless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (d, *J* = 11.0 Hz, 1H), 3.44 (d, *J* = 11.3 Hz, 1H), 3.01 (q, *J* = 7.0 Hz, 1H), 2.52 (br d, *J* = 14.1 Hz, 1H), 1.76-1.08 (comp m, 7H), 1.05 (d, *J* = 7.4 Hz, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 83.5, 44.3, 42.0, 34.6, 32.2, 22.4, 21.0, 19.4, 9.2, 8.7.

IR (film): ν = 3357 (br), 2952, 2923, 2854, 1760, 1175, 1118, 1049, 1023, 974, 931.

Determination of boron ketene acetal geometry by aldolization.



To a solution of propionate **3-15** (91.1 mg, 0.500 mmol), 4,4'-di-*tert*-butylbiphenyl (16.7 mg, 0.0625 mmol), and Et_3N (0.348 mL, 2.50 mmol) in CH_2Cl_2 (5.0 mL) at -78 °C was added neat Cy_2BI (0.126 mL, 0.550 mmol) dropwise. The solution was stirred at -78 °C 1 h then treated dropwise with isobutyraldehyde (0.182 mL, 2.0 mmol). This reaction mixture was stirred 1 h at -78 °C then allowed to warm to ambient temperature. The reaction was quenched by pouring into Et_2O (25 mL) and 4:1 sat. aq. NH_4Cl/1.0 M Na_2SO_3 (25 mL), and the mixture was acidified (pH 1) with 2 M aq. HCl. The organic phase was separated and the aqueous extracted with Et_2O (1x25 mL). The combined organic extracts were washed with brine (25 mL), dried with Na_2SO_4, and concentrated. The resulting residue was dissolved in MeOH (5.0 mL) and treated with 30% aq. H_2O_2 (0.50 mL, 5.0 mmol). This mixture was allowed to stand 12 h then diluted with abs. EtOH (25 mL) and concentrated. The resulting residue was warmed in a water bath to 40 °C under vacuum for 5 min to remove cyclohexanol. The crude product was then dissolved in $CDCl_3$ (4.0 mL) and analyzed by ^{1}H NMR (d1 = 10 s) to obtain a crude yield and dr of the reaction. This material was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give **3-38** (47.9 mg, 38% yield).

Data for *syn*-aldol 3-38.

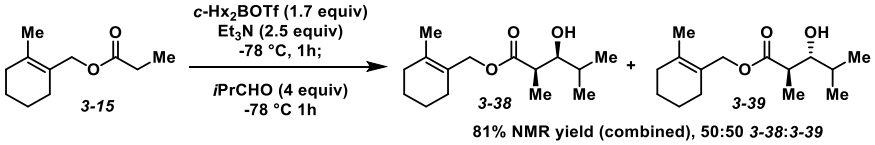
Physical State: Colorless oil

TLC: r_f = 0.21 (9:1 hexanes/EtOAc eluent, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57 (s, 2 H), 3.52 (dt, *J*=7.7, 3.8 Hz, 1 H), 2.64 (qd, *J*=7.1, 3.5 Hz, 1 H), 2.56 (d, *J*=3.9 Hz, 1 H), 2.02 – 1.91 (m, 4 H), 1.67 (s, 3 H), 1.64 (septet, *J*=7.0 Hz, 1 H), 1.60 – 1.54 (m, 4 H), 1.15 (d, *J*=7.4 Hz, 3 H), 0.98 (d, *J*=6.6 Hz, 3 H), 0.84 (d, *J*=7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.9, 133.8, 124.9, 76.7, 65.1, 41.8, 31.9, 30.5, 27.7, 22.78, 22.75, 19.0, 18.6, 10.4.

HRMS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{15}H_{26}O_3 + Na]^+$: 277.1774, found 277.1779.



A stock solution of Cy_2BOTf was prepared by dissolving Cy_2BOTf (0.555 g, 1.70 mmol) in CH_2Cl_2 (1.20 mL) at room temperature for a final volume of 1.7 mL. This solution was used immediately. To a solution of propionate **3-15** (91.1 mg, 0.500 mmol) and 4,4'-di-*tert*-butylbiphenyl (16.7 mg, 0.0625 mmol) in CH_2Cl_2 (5.0 mL) at -78 °C was added a 1.0 M solution of Cy_2BOTf in CH_2Cl_2 (0.850 mL, 0.850 mmol) followed immediately by Et_3N (0.174 mL, 1.25 mmol). The solution was stirred at -78 °C 1 h then treated dropwise with isobutyraldehyde (0.182 mL, 2.0 mmol). This reaction mixture was stirred 1 h at -78 °C then allowed to warm to ambient temperature. The solution was diluted with MeOH (5.0 mL), cooled to 0 C, and treated with 30% aq. H_2O_2 (0.50 mL, 5.0 mmol) dropwise. The reaction mixture was then allowed to reach ambient temperature and stirred 2h. The oxidized reaction mixture was further diluted with abs. EtOH (25 mL) and concentrated. The resulting residue was dissolved in Et_2O (25 mL), poured into sat. NH_4Cl (25 mL), and acidified to pH 1 with 2 M HCl. The organic layer was separated and the aqueous extracted with Et_2O (1x25 mL). The combined organic extracts were washed with brine (25 mL), dried with $MgSO_4$, and concentrated. The resulting residue was warmed in a water bath to 40 °C under vacuum for 5 min to remove cyclohexanol. The crude product was then dissolved in $CDCl_3$ (4.0 mL) and analyzed by ^{1}H NMR (d1 = 10 s) to obtain a crude yield and dr of the reaction. This material was purified by flash column chromatography (19:1 hexanes/EtOAc eluent) to give **3-38** (43.2 mg, 34% yield) and **3-39** (47.0 mg, 37% yield).

Data for *anti*-aldol 3-39.

Physical State: Colorless oil

TLC: r_f = 0.26 (9:1 hexanes/EtOAc eluent, $KMnO_4$ stain solution).

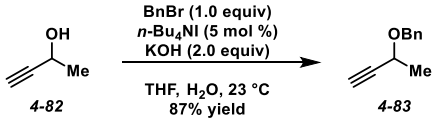
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (s, 2 H), 3.32 (dt, *J*=7.7, 5.9 Hz, 1 H), 2.61 (d, *J*=7.8 Hz, 1 H), 2.64 (qd, *J*=7.0, 6.2 Hz, 1 H), 2.03 – 1.93 (m, 4 H), 1.67 (s, 3 H), 1.69 (septet, *J*=6.6 Hz, 1 H), 1.59 - 1.54 (m, 4 H), 1.19 (d, *J*=7.4 Hz, 3 H), 0.93 (d, *J*=7.0 Hz, 3 H), 0.90 (d, *J*=6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 133.9, 124.8, 78.3, 65.1, 42.5, 31.9, 31.3, 27.7, 22.80, 22.75, 19.7, 19.0, 16.6, 14.9.

HRMS (ESI+): *m*/*z* calc'd for $(M + Na)^+$ $[C_{15}H_{26}O_3 + Na]^+$: 277.1774, found 277.1777.

Appendix Three: Experimental Section for Chapter Four.

Materials and Methods: Reactions were performed under an argon atmosphere unless otherwise noted. Hexanes, ether, dichloromethane, THF and toluene were purified by passing through activated alumina columns. Triethylamine and diisopropylethylamine were distilled under Ar from CaH_2. All other reagents were used as received unless otherwise noted. Commercially available chemicals were purchased from Alfa Aesar (Ward Hill, MA) or Sigma-Aldrich (St. Louis, MO). Visualization was accomplished with UV light and exposure to $KMnO_4$ solutions followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H NMR spectra were acquired on a Varian 400 MR (at 400 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian 400 MR (at 101 MHz) and are reported in ppm relative to $SiMe_4$ (δ 0.0). Infrared spectra were recorded as films on a Nicolet 380 FTIR. High resolution mass spectrometry data were acquired by the Colorado State University Central Instrument Facility on an Agilent 6210 TOF LC/MS, low resolution mass spectrometry data were acquired on an Agilent 6100 Single Quad LC/MS.



To alcohol **4-82** (55% w/w in H_2O, 13.5 g, 106 mmol) was added KOH (85%, 14.0 g, 212 mmol). The solution was stirred until it partially solidified, at which point THF (20 mL) was added, followed by *n*-Bu_4NI (1.96 g, 5.30 mmol). A thermometer was placed directly into the reaction mixture and BnBr (12.6 mL, 106 mmol) was added with vigorous stirring. When the reaction mixture reached 40 °C, the flask was submerged in an ice bath until the internal temperature reached 23 °C. The reaction was stirred an additional 1 h, then partitioned between pentane (150 mL) and H_2O (100 mL). The organic layer was washed sequentially with HCl (1 M in H_2O, 50 mL), H_2O (50 mL), and brine (50 mL). The organic extract was dried with Na_2SO_4 and concentrated. The resulting pale yellow residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc) to give ether **4-83** (14.7 g, 87% yield)

Data for benzyl ether 4-83.

Physical form: Colorless liquid.

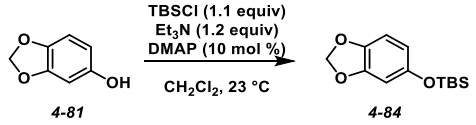
TLC: R_f = 0.36 (19:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 - 7.26 (m, 5 H), 4.80 (d, *J* = 11.7 Hz, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.22 (dq, *J* = 6.7, 2.0 Hz, 1 H), 2.47 (d, *J* = 2.0 Hz, 1 H), 1.49 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.8, 128.4, 128.0, 127.7, 83.7, 73.1, 70.5, 64.2, 22.0.

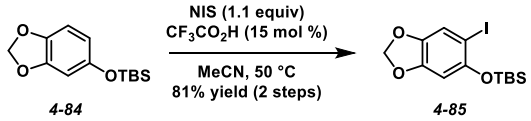
IR (film): ν = 3291, 3031, 2987, 2936, 2867, 1453, 1327, 1097, 1064, 1027.

MS (ESI): *m/z* calc'd for $(M + H)^+$ $[C_{11}H_{12}O + H]^+$ 161.0961, found 161.0966.



4-81 *4-84*

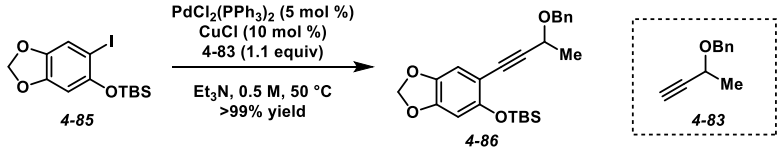
To a solution of sesamol (**4-81**, 10.0g, 72.5 mmol) in CH_2Cl_2 (145 mL) were added sequentially Et_3N (12.1 mL, 87.0 mL), DMAP (886 mg, 7.25 mmol), and TBSCl (12.0g, 79.7 mmol). The reaction mixture was stirred at 23 °C for 16 h then diluted with hexanes (200 mL). The resulting solution was washed sequentially with H_2O (100 mL), 2 M aq. NaH_2PO_4 (100 mL) and brine (100 mL). The organic extract was dried with Na_2SO_4 and concentrated to yield TBS ether **4-84** as a dark brown oil (19.0 g), which was carried directly to the next reaction



4-84 *4-85*

To a solution of TBS ether **4-84** prepared above in dry MeCN (150 mL) was added NIS (17.9 g, 79.7 mmol) followed by CF_3CO_2H (0.810 mL). The resulting solution was heated to 50 °C in an oil bath and protected from light by placing an inverted cardboard box over the entire apparatus. After 2 h, the reaction was quenched with 1 M aw. $NaHCO_3$ (50 mL) and concentrated *in vacuo* to remove MeCN. The resulting residue was partially dissolved in 1 M

aq. $NaHCO_3$ (200 mL), hexanes (200 mL), and Et_2O (50 mL). The organic phase was separated and washed sequentially with 1 M aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic extract was dried with Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give aryl iodide **4-85** as a red liquid that crystallized to a low melting solid at ambient temperature (22.2 g, 81% yield over 2 steps). Spectroscopic data for iodide **4-85** matched those presented in the literature.[1]



A mixture of iodide **4-85** (947 mg, 2.50 mmol), $PdCl_2(PPh_3)_2$ (87.7 mg, 0.125 mmol), and CuCl (24.8 mg, 0.250 mmol) was stirred under Ar for 5 min until a fine powder resulted. The powder was suspended in freshly distilled Et_3N (5.00 mL, 35.9 mmol), and **4-83** (481 mg, 3.00 mmol) was added neat via tared syringe. The reaction quickly turned brick red then dark green over approx. 30 min during which time it was stirred at 23 °C. The reaction mixture was then heated to 50 °C for 3 h, then triturated with hexanes (20 mL) and filtered through celite, rinsing with hexanes (20 mL). The filtrate was washed sequentially with 10% aq. (w/w) NH_3 (25 mL), 10% aq. HCl (25 mL), and brine (25 mL). The organic extract was applied directly to a SiO_2 column, and purified by flash column chromatography eluting with 19:1 hexanes-EtOAc to give alkyne **4-86** (1.04 g, >99% yield).

Data for alkyne 4-86.

Physical Form: Yellow liquid

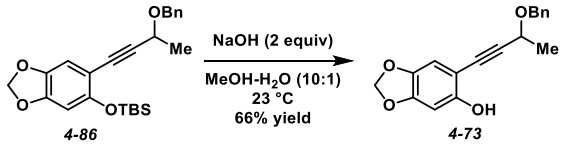
TLC: R_f = 0.48 (9:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 - 7.25 (m, 5 H), 6.81 (s, 1 H), 6.38 (s, 1 H), 5.93 (s, 2 H), 4.85 (d, *J* = 11.7 Hz, 1 H), 4.55 (d, *J* = 11.7 Hz, 1 H), 4.44 (q, *J* = 6.4 Hz, 1 H), 1.54 (d, *J* = 6.7 Hz, 3 H), 1.02 (s, 9 H), 0.24 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.4, 148.5, 141.5, 138.2, 128.3, 128.0, 127.6, 111.8, 106.7, 101.8, 101.5, 91.1, 70.5, 65.2, 25.7, 22.3, 18.2, -4.3.

IR (film): ν = 2954, 2930, 2886, 2857, 1479, 1174, 1037, 837.

MS (ESI+): *m/z* calc'd for $(M + Na)^+$ $[C_{24}H_{30}O_4Si + Na]^+$: 411.1774, found 433.1788.



To a solution of TBS ether **4-86** in MeOH (10 mL) was added NaOH (1.00 mL, 5 M in H_2O, 5.00 mmol). The reaction mixture was stirred at 23 °C for 30 min and quenched with H_3PO_4 (2.00 mL, 2 M in H_2O, 4.00 mmol) and concentrated *in vacuo*. The resulting residue was partitioned between Et_2O (20 mL) and 1 M aq. HCl (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent) to give phenol **4-73** (488 mg, 66% yield).

Data for phenol 4-73.

Physical Form: Pale yellow liquid

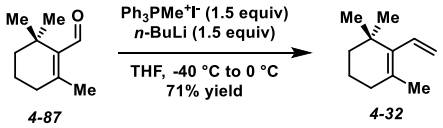
TLC: R_f = 0.17 (9:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 - 7.22 (m, 5 H), 6.75 (s, 1 H), 6.50 (s, 1 H), 5.92 (s, 2 H), 5.65 (s, 1 H), 4.82 (d, *J* = 11.7 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.48 (d, *J* = 6.7 Hz, 1 H), 1.58 (d, *J* = 6.7 Hz, 3 H).

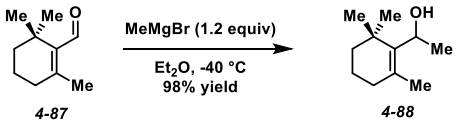
^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.4, 149.5, 141.1, 137.7, 128.5, 128.0, 127.8, 109.7, 101.5, 97.1, 95.3, 79.6, 70.8, 65.0, 22.4.

IR (film): ν = 3495 (br), 3063, 3030, 2983, 2933, 2890, 1478, 1223, 1176, 1076, 1035, 934, 858.

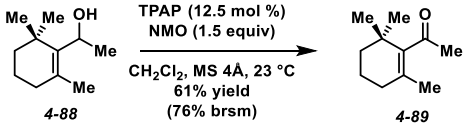
MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{18}H_6O_4 + NH_4]^+$: 314.1387, found 314.1391.



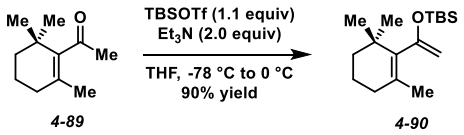
To a well stirred suspension of $Ph_3PCH_3^+I^-$ (24.3 g, 60.0 mmol) in THF (120 mL) at -40 °C was added *n*-BuLi (23.7 mL, 2.53 M in hexanes, 60.0 mmol) over 2 min. The solution became orange and was allowed to warm to ambient temperature and stir for 30 min. The resulting solution was then recooled to -40 °C, and aldehyde **4-87** (6.46 mL, 40.0 mmol) was added over 5 min. The reaction mixture was stirred at -40 °C for 10 min then allowed to warm to ambient temperature and stirred an additional 30 min at which point TLC (4:1 hexanes-EtOAc, $KMnO_4$ stain solution) indicated consumption of aldehyde **4-87**. The reaction mixture was quenched by adding 20 mL sat. aq. NH_4Cl, and most of the THF was removed *in vacuo*. The resulting residue was diluted with 100 mL H_2O and 100 mL pentane and filtered, rinsing with pentane. The organic layer was separated and washed with brine (50 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (SiO_2, pentane eluent) to give diene **4-32** (4.28 g, 71% yield) as a clear colorless liquid. The spectroscopic data for diene **4-32** matched those presented in the literature.[2]



To a solution of aldehyde **4-87** (8.07 mL, 50.0 mmol) in Et_2O (100 mL) at -40 °C was added MeMgBr (20.0 mL, 3.0 M in Et_2O, 60 mmol) over 2 min. The reaction mixture was stirred at -40 °C for 30 min then allowed to warm to ambient temperature, at which point it was poured carefully into a mixture of 1M HCl (60 mL) and sat. aq. NH_4Cl (60 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and concentrated to give alcohol **4-88** as a colorless solid (8.21 g, 98% yield), which was used without further purification. The spectroscopic data for alcohol **4-88** matched those presented in the literature.[3]

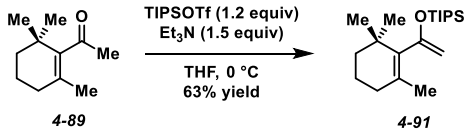


To a solution of alcohol **4-88** (6.55 g, 38.9 mmol), MS 4Å (15.0 g), and TPAP (137 mg, 0.389 mmol) in CH_2Cl_2 (80 mL) was added NMO (6.09 g, 52.0 mmol). The reaction mixture was stirred for 2 h at ambient temperature, at which another portion of TPAP (273 mg, 0.738 mmol) was added. After another 2 h, a further portion of TPAP (273 mg, 0.738 mmol) was added. The reaction mixture was stirred an additional 20 h, at which point it was diluted with pentane (80 mL) and filtered through a pad of SiO_2, rinsing with 9:1 hexanes-EtOAc. The filtrate was washed sequentially with 1 M aq. HCl (60 mL), sat. aq. $NaHCO_3$ (60 mL), and brine (60 mL) then dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent) to give enone **4-89** as a colorless liquid (3.94 g, 61% yield) as well as recovered alcohol **4-88** (1.33 g, 20% yield). The spectroscopic data for enone **4-89** matched those presented in the literature.[3]



4-89 *4-90*

To a solution of enone **4-89** (3.83 g, 23.0 mmol) and Et_3N (6.41 mL, 46.0 mmol) in THF (23 mL) at -78 °C was added TBSOTf (5.81 mL, 25.3 mmol) over 60 s. The reaction mixture was stirred 10 min at this temperature then allowed to warm to 0 °C and stirred an additional 30 min, at which point TLC indicated consumption of enone **4-89**. The reaction mixture was poured into pentane (150 mL) and washed sequentially with sat $NaHCO_3$ (100 mL), H_2O (3 x 100 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 treated with 99:1 hexanes-Et_3N, 99:1 hexanes-Et_3N eluent) to give TBS enol ether **4-90** as a colorless liquid (5.83 g, 90% yield). The spectroscopic data for **4-90** matched those presented in the literature.[3]



To a solution of enone **4-89** (356 mg, 2.14 mmol) and Et_3N (0.447 mL, 3.21 mmol) in THF (2.14 mL) at 0 °C was added TIPSOTf (0.692 mL, 2.57 mmol) over 60 s. The reaction mixture was stirred 10 min at this temperature then aged in a refrigerator at -10 °C an additional 2 h, at which point TLC indicated consumption of enone **4-89**. The reaction mixture was poured into pentane (50 mL) and washed sequentially with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried with K_2CO_3 and concentrated. The resulting residue was purified by flash column chromatography (SiO_2 treated with 99:1 hexanes-Et_3N, 99:1 hexanes-Et_3N eluent) to give TIPS enol ether **4-91** (481 g, 63% yield).

Data for silyl enol ether 4-91.

Physical Form: Colorless liquid.

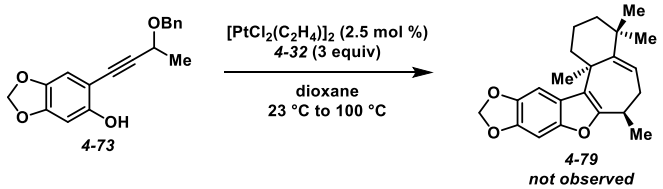
TLC: R_f = 0.75 (hexanes, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (s, 1 H), 3.87 (s, 1 H), 1.95 (t, *J* = 6.5 Hz, 2 H), 1.70 (s, 3 H), 1.62 (tdd, *J* = 3.1, 6.3, 12.1 Hz, 2 H), 1.46 - 1.38 (m, 2 H), 1.31 - 1.16 (comp. m, 3 H), 1.14 - 1.11 (m, 10 H), 1.11 (s, 8 H), 1.07 (s, 6 H).

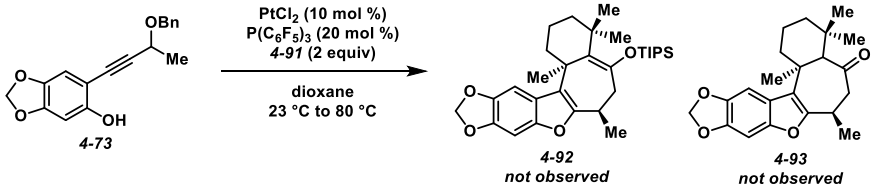
^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.7, 138.9, 129.6, 92.6, 39.6, 33.2, 31.7, 29.2, 21.6, 19.1, 18.2, 12.9.

IR (film): ν = 2943, 2866, 1606, 1463, 1250, 1064, 882, 816.

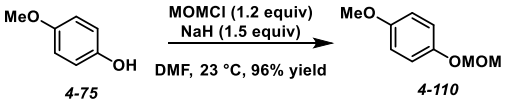
MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{20}H_{38}OSi + H]^+$: 323.2765, found 323.2776.



To a solution of alkyne **4-73** (38.1 mg, 0.129 mmol) and diene **4-32** (58.0 mg, 0.386 mmol) in dioxane (1.29 mL) at ambient temperature was added $[PtCl_2(C_2H_4)]_2$ (1.9 mg, 0.00323 mmol). The resulting solution was stirred for 10 min and then heated to 100 °C in a preheated aluminum block. The reaction mixture was stirred at this temperature for 3 h, at which point TLC indicated consumption of alkyne **4-73**. The reaction mixture was cooled, diluted with hexanes (5 mL), and filtered through a plug of SiO_2, rinsing with 9:1 hexanes-EtOAc. The filtrate was concentrated and analyzed by ^1H NMR.

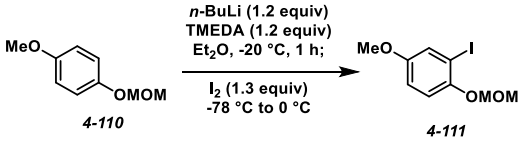


To a solution of alkyne **4-73** (29.6 mg, 0.129 mmol) and silyloxydiene **4-91** (72.1 mg, 0.201 mmol) in dioxane (1.00 mL) at ambient temperature was added $PtCl_2$ (2.7 mg, 0.0100 mmol) and $P(C_6F_5)_3$ (10.6 mg, 0.0200 mmol). The resulting solution was stirred for 10 min and then heated to 80 °C in a preheated aluminum block. The reaction mixture was stirred at this temperature for 3 h, at which point TLC indicated consumption of alkyne **4-73**. The reaction mixture was cooled, diluted with hexanes (5 mL), and filtered through a plug of SiO_2, rinsing with 9:1 hexanes-EtOAc. The filtrate was concentrated and analyzed by ^1H NMR.

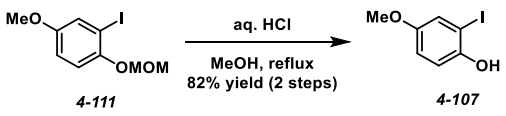


To a solution of 4-methoxyphenol (**4-75**, 12.4 g, 100 mmol) in DMF (100 mL) was added NaH (60% dispersion in mineral oil, 6.00 g, 150 mmol) portionwise at such a rate as to control H_2 evolution with external cooling of the reaction mixture with a 23 °C water bath. Once the addition was complete, MOMCl (9.11 mL, 120 mL) via additional funnel at a rate of 1 drop/s, taking a total of approx. 10 min. Once the addition was complete, the reaction

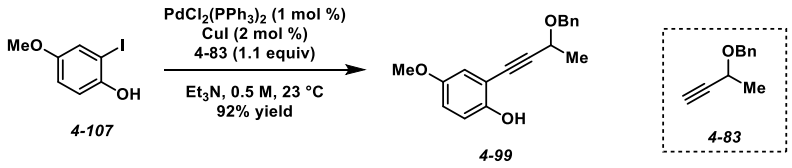
mixture was stirred an additional 1 h, at which point TLC indicated consumption of starting material. The reaction mixture was then poured into H_2O (300 mL) and extracted with pentane (3 x 75 mL). The combined organic extracts were washed sequentially with H_2O (100 mL) and brine (100 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatography (SiO_2, hexanes → 4:1 hexanes-Et_2O eluent) to give MOM ether **4-110** as a colorless liquid (16.1 g, 96% yield). The spectroscopic data for MOM ether **4-110** matched those presented in the literature.[4]



To a 500 mL round bottom flask charged with a large stir bar and a solution of MOM ether **4-110** (16.8 g, 100 mmol) and TMEDA (18.0 mL, 120 mmol) in Et_2O (100 mL) at -78 °C was added *n*-BuLi (48.0 mL, 2.5 M in hexanes, 120 mmol) over 60 s. The reaction mixture was stirred at this temperature for 5 min and then allowed to warm to -20 °C and stir for an additional 30 min. The reaction mixture was then cooled to -78 °C and a solution of I_2 (33.0 g, 130 mmol) in Et_2O (200 mL) was added via cannula over 10 minutes. During this addition, the reaction mixture became a thick slurry, and manual swirling was necessary because of the impossibility of magnetic stirring. When the addition was complete, the reaction mixture was swirled an additional 5 min at -78 °C and then allowed to warm to ambient temperature with occasional swirling. Once the reaction mixture had reached ambient temperature, it was poured into a mixture of 1 M $NaHCO_3$ (100 mL) and sat. $Na_2S_2O_3$ (100 mL). The organic layer was separated and washed sequentially with 1 M HCl (100 mL), 1 M NaOH (100 mL) and brine (100 mL). The organic extract was dried with $MgSO_4$ and concentrated to give aryl iodide **4-111** as a yellow oil that was used immediately without further purification.



To a solution of the previously prepared aryl iodide **4-111** in MeOH (100 mL) was added 10% HCl (30 mL, 100 mmol). The reaction mixture was heated to reflux for 20 minutes at which TLC indicated consumption of iodide **4-111**. The reaction mixture was allowed to warm to ambient temperature and was then concentrated to remove MeOH. The resulting residue was partitioned between EtOAc (100 mL) and brine (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give phenol **4-107** as a colorless solid (20.4 g, 82% yield over 2 steps). The spectroscopic data for phenol **4-107** matched those presented in the literature.[5]



A mixture of aryl iodide **4-107** (5.01 g, 20.0 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 0.200 mmol), and CuI (76.2 mg, 0.400 mmol) were stirred dry under vacuum until a fine powder resulted. The resulting powder was suspended/dissolved in Et_3N (40 mL) and alkyne **4-83** (3.54 g, 22.0 mmol) was added neat via tared syringe. The reaction mixture became black and was stirred for 3 h at ambient temperature, at which point TLC indicated consumption of iodide **4-107**. Then H_2O (20 mL) was added and Et_3N was removed *in vacuo*. The resulting residue was suspended in 1 M HCl (100 mL) and extracted with Et_2O (3 x 50 mL). The organic extracts were then stirred with 0.2 M Na_3EDTA (100 mL) for 30 minutes, separated, washed with brine (100 mL), dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc eluent) and concentrated. This product was then allowed to stand 16 h at -10 C to further precipitate Pd residue. This material was dissolved in Et_2O (20 mL) and filtered through a plug of SiO_2, rinsing with Et_2O (100 mL) to give alkyne **4-99** (5.22 g, 92% yield).

Data for alkyne 4-99.

Physical form: Orange oil.

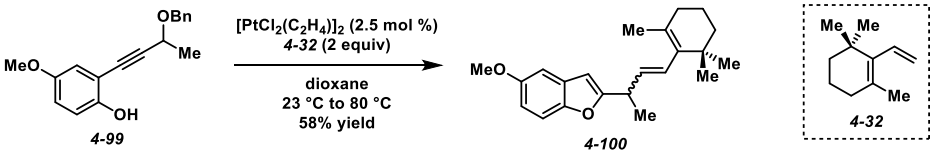
TLC: R_f = 0.18 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 - 7.28 (comp m, 5 H), 6.92 - 6.78 (comp m, 3 H), 5.47 (br. s, 1 H), 4.84 (d, *J* = 11.7 Hz, 1 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.51 (q, *J* = 6.7 Hz, 1 H), 3.76 (s, 3 H), 1.60 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.0, 151.1, 137.7, 128.5, 128.0, 127.9, 117.6, 115.6, 115.6, 109.0, 96.1, 79.6, 70.9, 65.0, 55.8, 22.3.

IR (film): ν = 3383 (br), 2985, 2935, 2865, 2834, 1494, 1275, 1204, 1167, 1090, 1035, 814.

MS (DART): *m/z* calc'd for $(M + NH_4)^+$ $[C_{18}H_{18}O_3 + NH_4]^+$: 300.1594, found 300.1605.



To a solution of alkyne **4-99** (142 mg, 0.504 mmol) and diene **4-32** (152 mg, 1.01 mmol) in dioxane (5.0 mL) at ambient temperature was added $[PtCl_2(C_2H_4)]_2$ (7.4 mg, 0.0126 mmol). The resulting solution was stirred for 10 min and then heated to 80 °C in a preheated aluminum block. The reaction mixture was stirred at this temperature for 1 h, then cooled to ambient temperature and charged with an additional portion of $[PtCl_2(C_2H_4)]_2$ (7.4 mg, 0.0126 mmol). The reaction mixture was reheated to 80 °C and stirred for 30 min, at which point TLC indicated consumption of alkyne **4-99**. The reaction mixture was cooled, diluted with hexanes (10 mL), and filtered through a plug of SiO_2, rinsing with 19:1 hexanes-EtOAc. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography (SiO_2, 1:1 toluene-pentane eluent) to give benzofuran **4-100** (114 mg, 58% yield).

Data for benzofuran 4-100.

Physical form: Colorless liquid.

TLC: R_f = 0.26 (19:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

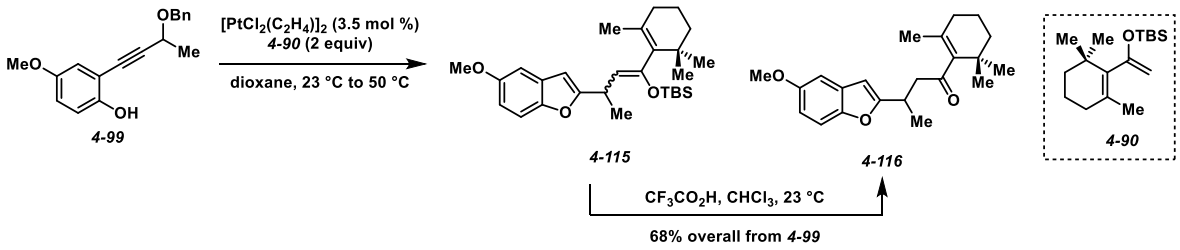
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 9.0 Hz, 1 H), 6.97 (d, *J* = 2.3 Hz, 1 H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.34 (s, 1 H), 6.01 (d, *J* = 16.0 Hz, 1 H), 5.53 (dd, *J* = 15.8, 7.6 Hz, 1 H), 3.83 (s, 3 H), 3.74 - 3.62 (m, 1 H), 1.97 (t, *J*

= 6.3 Hz, 2 H), 1.68 (s, 3 H), 1.64 - 1.57 (comp m, 2 H), 1.54 (s, 3 H), 1.49 - 1.42 (comp m, 4 H), 0.999 (s, 3 H), 0.996 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.4, 155.7, 149.7, 137.1, 134.7, 129.4, 128.42, 128.37, 111.5, 111.1, 103.3, 101.1, 55.9, 39.4, 37.5, 34.0, 32.6, 28.7, 21.4, 19.3, 19.2.

IR (film): ν = 2961, 2927, 2864, 2832, 1478, 1450, 1205, 1179, 1033, 836.

MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{28}O_2 + H]^+$: 325.2162, found 325.2155.



To a solution of alkyne **4-99** (1.42 g, 5.02 mmol) and silyloxydiene **4-90** (2.81 g, 10.0 mmol) in dioxane (25 mL) at ambient temperature was added $[PtCl_2(C_2H_4)]_2$ (73.7 mg, 0.125 mmol). The resulting solution was stirred for 10 minutes and then heated to 50 °C in a preheated oil bath. The reaction mixture was stirred at this temperature for 45 min, then charged with an additional portion of $[PtCl_2(C_2H_4)]_2$ (29.4 mg, 0.0502 mmol). The reaction mixture was reheated to 50 °C and stirred for 30 min, at which point TLC indicated consumption of alkyne **4-99**. The reaction mixture was cooled, quenched with Et_3N (1.00 mL) and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 99:1 hexanes-Et_3N → 97:3 hexanes-EtOAc eluent) to give recovered silyloxydiene **4-115** (1.57 g, 56% recovery) and a mixture of silyl enol ether **4-115** and ketone **4-116** (1.70 g).

The latter mixture was dissolved in $CHCl_3$ (10 mL) at ambient temperature and treated with CF_3CO_2H (0.371 mL, 5.00 mmol) and allowed to stand 5 h, at which point TLC indicated consumption of silyl enol ether **4-115**. The reaction mixture was poured carefully into sat. aq. $NaHCO_3$ (50 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give pure ketone **4-116** (1.15 g, 68% yield).

Data for ketone 4-116.

Physical form: Colorless liquid.

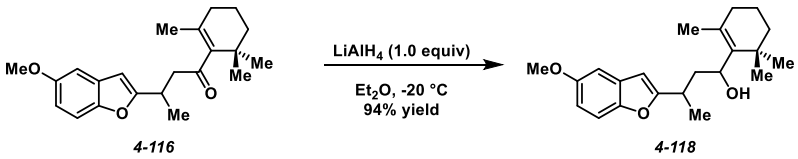
TLC: R_f = 0.46 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.6 Hz, 1 H), 6.95 (d, *J* = 2.3 Hz, 1 H), 6.80 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.36 (s, 1 H), 3.82 (s, 3 H), 3.70 - 3.56 (m, 1 H), 3.09 (dd, *J* = 18.8, 5.1 Hz, 1 H), 2.79 (dd, *J* = 18.8, 8.2 Hz, 1 H), 1.93 (t, *J* = 6.5 Hz, 2 H), 1.69 - 1.60 (comp m, 2 H), 1.51 (s, 3 H), 1.45 - 1.40 (comp m, 2 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.07 (s, 3 H), 1.04 (s, 3 H).

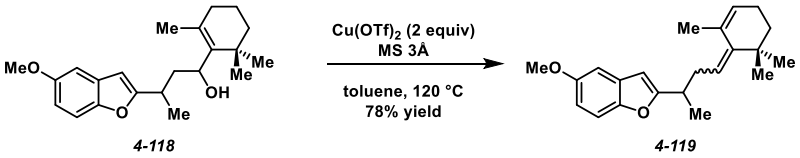
^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.0, 163.4, 155.7, 149.5, 142.9, 129.4, 129.3, 111.6, 111.1, 103.3, 101.3, 55.9, 51.0, 38.9, 33.3, 31.2, 28.7, 28.6, 28.5, 20.6, 18.9, 18.8.

IR (film): ν = 2964, 2935, 2909, 2870, 2831, 1691, 1477, 1449, 1205.

MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{28}O_3 + H]^+$: 341.2111, found 341.2106.



To a solution of ketone **4-116** (124 mg, 0.363 mmol) in Et_2O (3.6 mL) at -20 °C was added $LiAlH_4$ (13.8 mg, 0.363 mmol) in one portion. The reaction mixture was stirred for 30 min at this temperature, at which point TLC indicated consumption of ketone **4-116**. The reaction mixture was quenched by adding H_2O (0.04 mL) and 5 M NaOH (0.04 mL) at -20 °C and stirring 10 min before warming to ambient temperature and adding an additional portion of H_2O (0.04 mL). The resulting mixture was then stirred 1 h at ambient temperature, dried with $MgSO_4$, and filtered through a pad of celite, rinsing with Et_2O. The filtrate was concentrated to give pure alcohol **4-118** as a colorless liquid that was used directly without further purification (117 mg, 94% yield).



To a solution of allylic alcohol **4-118** (57.1 mg, 0.167 mmol) in toluene (1.7 mL) was added $Cu(OTf)_2$ (121 mg, 0.333 mmol) and crushed MS 3Å (333 mg). The resulting solution heated to 120 °C with vigorous stirring for 30 min then cooled to ambient temperature and applied directly to a SiO_2 column, eluting with 9:1 hexanes-EtOAc to give diene **4-119** (42.4 mg, 78% yield).

Data for diene 4-119.

Physical form: Yellow liquid.

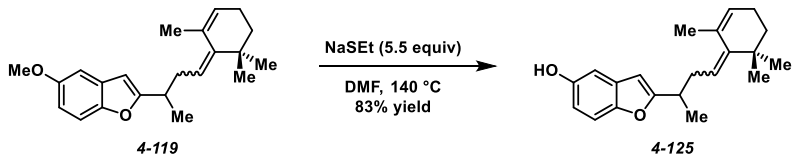
TLC: R_f = 0.48 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9.0 Hz, 1 H), 6.98 (d, *J* = 2.7 Hz, 1 H), 6.82 (dd, *J* = 9.0, 2.7 Hz, 1 H), 6.35 (s, 1 H), 5.63 (t, *J* = 3.5 Hz, 1 H), 5.38 (t, *J* = 6.8 Hz, 1 H), 5.29 (s, 1 H), 3.84 (s, 3 H), 3.09 - 2.96 (m, 1 H), 2.91 - 2.79 (m, 1 H), 2.73 - 2.62 (m, 1 H), 2.07 (d, *J* = 4.7 Hz, 2 H), 1.77 (d, *J* = 1.2 Hz, 3 H), 1.48 (t, *J* = 6.1 Hz, 2 H), 1.38 (d, *J* = 7.0 Hz, 3 H), 1.23 (s, 3 H), 1.21 (s, 3 H)

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2, 155.7, 149.6, 144.2, 133.5, 129.4, 125.7, 123.3, 111.4, 111.1, 103.3, 101.1, 55.9, 40.3, 35.6, 34.9, 34.7, 28.2, 28.0, 22.9, 21.9, 18.6

IR (film): ν = 2962, 2913, 2833, 1475, 1448, 1203, 1179, 1031, 835

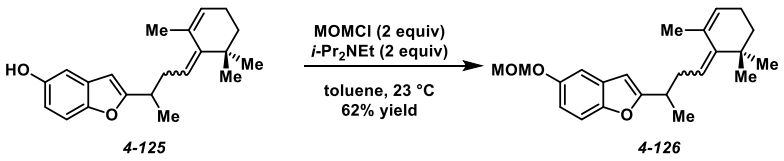
MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{28}O_2 + H]^+$: 325.2, found 325.2.



A ~1.1 M stock solution of NaSEt in DMF was prepared as follows: A 100 mL round bottom flask fitted with a rubber septum was charged with a large stir bar and NaH (60% dispersion in mineral oil, 1.00 g, 25.0 mmol) and

flushed with Ar. The mineral oil was removed by stirring with hexanes (3 x 10 mL), allowing to settle, and decanting the supernatant with a syringe. The NaH was then suspended in DMF (20 mL), and the flask was fitted with an outlet needle and cooled in an ice bath. Neat EtSH (2.04 mL, 27.5 mmol) was then added at such a rate as to control the rate of H_2 evolution. Once the addition was complete, the reaction mixture was stirred until bubbling subsided completely then used immediately.

To a 2 dram vial charged with a stir bar and methyl ether **4-119** (337 mg, 1.04 mmol) under an Ar purge was added a portion of the above NaSEt solution (5.00 mL, 1.1 M in DMF, 5.50 mmol). The vial was capped with a PTFE lined cap under an Ar purge and heated in an oil bath to 140 C and stirred at this temperature for 6 h. The reaction mixture was then allowed to cool to ambient temperature and poured into 1 M aq. NaH_2PO_4 (50 mL), extracting with Et_2O (2 x 25 mL). The organic extracts were then washed sequentially with 10% LiCl (50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give **4-125** (269 mg, 83% yield) as a pale yellow liquid. This material was used immediately in the next step.



4-125 *4-126*

To a solution of phenol **4-125** (252 mg, 0.811 mmol) and *i*-Pr_2NEt (0.282 mL, 1.62 mmol) in toluene (4.1 mL) at ambient temperature was added MOMCl (0.123 mL, 1.62 mmol) in one portion. The reaction mixture was stirred for 48 h, diluted with Et_2O (40 mL), and washed sequentially with 5% $NaHCO_3$ (2 x 20 mL), 2 M NaH_2PO_4 (20 mL), and brine (20 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give MOM ether **4-126** (178 mg, 62% yield, 74% brsm) as well as recovered **4-125** (41.9 mg, 17% recovery).

Data for MOM ether 4-126.

Physical form: Colorless liquid.

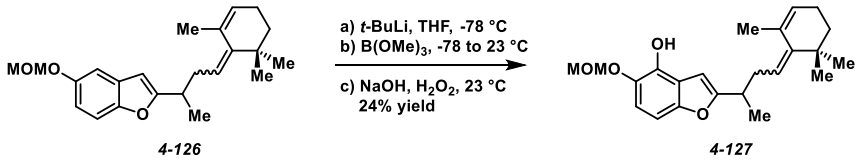
TLC: R_f = 0.47 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.0 Hz, 1 H), 7.08 (d, *J* = 2.3 Hz, 1 H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.25 (s, 1 H), 5.53 (t, *J* = 4.1 Hz, 1 H), 5.28 (t, *J* = 6.8 Hz, 1 H), 5.09 (s, 2 H), 3.42 (s, 3 H), 2.99 - 2.88 (m, 1 H), 2.74 (td, *J* = 15.9, 6.5 Hz, 1 H), 2.63 - 2.50 (m, 1 H), 1.97 (d, *J* = 5.1 Hz, 2 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 1.38 (t, *J* = 6.3 Hz, 2 H), 1.28 (d, *J* = 7.0 Hz, 3 H), 1.13 (s, 3 H), 1.11 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3, 153.1, 150.3, 144.2, 133.4, 125.6, 123.2, 113.3, 110.9, 107.1, 101.1, 95.5, 55.8, 40.2, 35.5, 34.8, 34.6, 28.1, 27.9, 22.8, 21.8, 18.5.

IR (film): ν = 2960, 2916, 1468, 1450, 1214, 1183, 1150, 1071, 1008, 935, 921, 856.

MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{30}O_3 + H]^+$: 355.2273, found 355.2268.



4-126 *4-127*

To a solution of MOM ether **4-126** (87.2 mg, 0.246 mmol) in THF (1.5 mL) was added *t*-BuLi (0.217 mL, 1.7 M in pentane, 0.369 mmol) dropwise. The resulting solution was stirred 1 h and $B(OMe)_3$ (0.274 mL, 2.46 mmol) was added in one portion, discharging the orange-brown color of the reaction mixture to colorless. The reaction mixture was then allowed to warm to ambient temperature and stir 1 h. The reaction was then treated sequentially with H_2O_2 (30% in H_2O, 0.253 mL, 2.46 mmol) and 1 M aq. NaOH (0.246 mL, 0.246 mmol) and stirred an additional hour. The reaction mixture was then poured into a mixture of sat. aq. $NaHCO_3$ (10 mL), H_2O (5 mL), and sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent) to give phenol **4-127** (21.8 mg, 24% yield) as well as recovered MOM ether **4-126**.

Data for phenol 4-127.

Physical form: Pink liquid.

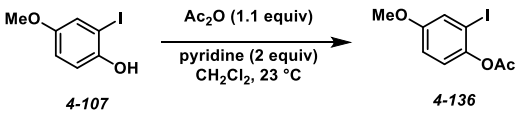
TLC: R_f = 0.14 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 - 6.93 (m, 1 H), 6.92 - 6.85 (m, 1 H), 6.63 (s, 1 H), 6.50 (s, 1 H), 5.61 (t, *J* = 3.5 Hz, 1 H), 5.37 (t, *J* = 6.8 Hz, 1 H), 5.14 (s, 2 H), 3.57 (s, 3 H), 3.06 - 2.94 (m, 1 H), 2.89 - 2.78 (m, 1 H), 2.71 - 2.58 (m, 1 H), 2.05 (d, *J* = 5.5 Hz, 2 H), 1.76 (d, *J* = 1.2 Hz, 3 H), 1.46 (t, *J* = 6.3 Hz, 2 H), 1.36 (d, *J* = 6.7 Hz, 3 H), 1.21 (s, 3 H), 1.20 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.1, 152.1, 144.3, 139.4, 133.5, 125.7, 123.2, 118.2, 113.9, 102.2, 98.4, 98.2, 56.5, 40.2, 35.5, 34.8, 34.7, 28.2, 27.9, 22.8, 21.9, 18.6.

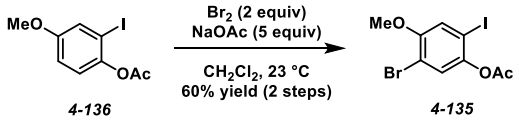
IR (film): ν = 3407 (br), 2962, 2916, 2844, 1494, 1451, 1277, 1226, 1153, 1057, 1009.

MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{30}O_4 + H]^+$: 371.2, found 371.1.



4-107 *4-136*

To a solution of phenol **4-107** (8.70 g, 34.8 mmol) and pyridine (5.63 mL, 69.6 mmol) in CH_2Cl_2 (35 mL) was added Ac_2O (3.72 mL, 38.3 mmol). The solution was stirred at ambient temperature for 1 h, then poured into 10% aq. HCl (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with 2 M aq. K_2CO_3 (50 mL), dried with Na_2SO_4, and concentrated. The resulting crude acetate **4-136** was used in the next step without further purification.



4-136 *4-135*

To a vigorously stirred slurry of the previously prepared aryl acetate **4-136** and NaOAc (14.3 g, 174 mmol) in CH_2Cl_2 (35 mL) was added Br_2 (3.56 mL, 69.6 mmol) over 5 min. The reaction mixture was then stirred 48 h at ambient temperature and then quenched by pouring carefully into a stirred solution of 1 M aq. Na_2SO_3 (200 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the organic extract was dried with Na_2SO_4 and concentrated. The

resulting crude residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent). This product was further purified by recrystallization from heptane (100 mL) to give pure aryl bromide **4-133** (7.78 g, 60% yield).

Data for aryl bromide 4-135.

Physical form: Colorless plates.

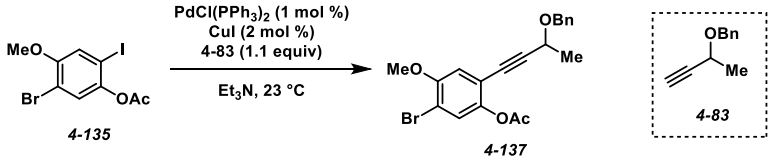
TLC: R_f = 0.28 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (s, 1 H), 7.26 (s, 1 H), 3.88 (s, 3 H), 2.34 (s, 3 H).

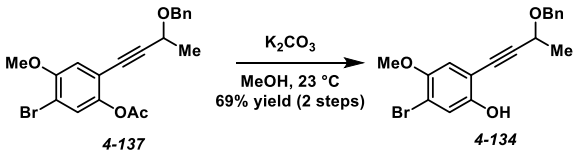
^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7, 154.4, 145.2, 127.0, 121.4, 111.9, 88.7, 56.8, 21.0.

IR (film): ν = 3094, 2971, 2941, 2840, 2766, 1479, 1434, 1354, 1206, 1197, 1060, 1011, 931, 784.

MS (ESI+): *m/z* calc'd for $(M + NH_4)^+$ $[C_9H_8BrIO_3 + NH_4]^+$: 387.9040, found 387.9041.



A mixture of aryl iodide **4-135** (1.99 g, 5.35 mmol), $PdCl_2(PPh_3)_2$ (37.6 mg, 0.0.535 mmol), and CuI (20.4 mg, 0.107 mmol) were stirred dry under vacuum until a fine powder resulted. The resulting powder was suspended/dissolved in Et_3N (10.7 mL) and alkyne **4-83** (943 mg, 5.89 mmol) was added neat via tared syringe. The reaction mixture became black and was stirred for 3 h at ambient temperature, at which point TLC indicated consumption of aryl iodide **4-135**. Then H_2O (20 mL) was added and Et_3N was removed *in vacuo*. The resulting residue was suspended in 1 M HCl (100 mL) and extracted with Et_2O (3 x 50 mL). The organic extracts were then stirred with 0.2 M Na_3EDTA (100 mL) for 30 minutes, separated, washed with brine (100 mL), dried with $MgSO_4$, and concentrated. The crude, yellow residue was used directly in the next step.



To a solution of the previously prepared **4-137** in MeOH (29 mL) was added finely ground K_2CO_3 (1.48 g, 10.7 mmol). The resulting suspension was stirred vigorously for 3 h at ambient temperature. Then the reaction mixture was treated with AcOH (1.00 mL), and MeOH was removed *in vacuo*. The resulting residue was partitioned between 0.1 M aq. HCl (50 mL) and Et_2O (50 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent) to give pure **4-134** (1.34 g, 69% yield).

Data for phenol 4-134.

Physical form: Orange liquid.

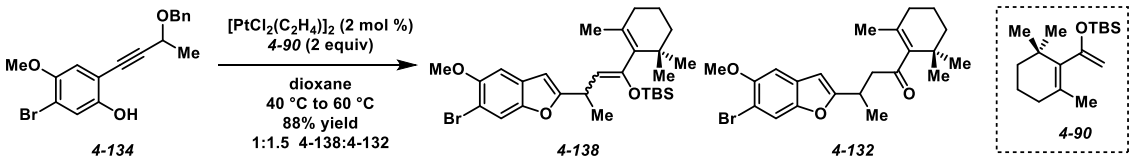
TLC: R_f = 0.16 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.42 - 7.28 (m, 5 H), 7.19 (s, 1 H), 6.84 (s, 1 H), 5.44 (br. s., 1 H), 4.82 (d, *J* = 11.7 Hz, 1 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.49 (q, *J* = 6.7 Hz, 1 H), 3.84 (s, 3 H), 1.59 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 151.2, 149.7, 137.6, 128.5, 127.9, 119.9, 114.3, 114.0, 108.1, 97.0, 78.9, 71.0, 65.0, 56.8, 22.2.

IR (film): ν = 3511, 3406 (br), 3011, 2987, 2938, 1484, 1207, 1092, 1046, 866.

MS (ESI+): *m/z* calc'd for $(M + NH_4)^+$ $[C_{18}H_{17}BrO_3 + NH_4]^+$: 378.0699, 380.0679, found 378.0699, 380.0681.



To a solution of alkyne **4-134** (2.08 g, 5.15 mmol) and silyloxydiene **4-90** (2.89 g, 10.3 mmol) in dioxane (25 mL) at ambient temperature was added $[PtCl_2(C_2H_4)]_2$ (30.3 mg, 0.0515 mmol). The resulting solution was stirred for 10 min and then heated to 40 °C in a preheated oil bath. The reaction mixture was stirred at this temperature for 30 min, then cooled to ambient temperature and charged with an additional portion of $[PtCl_2(C_2H_4)]_2$ (30.3 mg, 0.0515 mmol). The reaction mixture was reheated to 60 °C and stirred for 30 min, at which point TLC indicated consumption of alkyne **4-134**. The reaction mixture was cooled, quenched with Et_3N (0.10 mL) and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 99:1 hexanes-Et_3N → 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent) to give recovered silyloxydiene **4-90**, silyl enol ether **4-138** (1.01 g, 37% yield) and ketone **4-132** (1.11 g, 51% yield).

Data for silyl enol ether 4-138.

Physical form: Clear, colorless oil.

TLC: R_f = 0.60 (9:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 2.7 Hz, 1 H), 7.36 - 7.29 (m, 2 H), 6.99 (s, 1 H), 6.30 (d, *J* = 4.7 Hz, 1 H), 4.75 (s, 1 H), 4.51 (d, *J* = 9.4 Hz, 1 H), 4.44 (d, *J* = 9.4 Hz, 1 H), 4.31 - 4.25 (m, 1 H), 3.90 (s, 3 H), 1.95 (t, *J* = 6.3 Hz, 2 H), 1.73 (d, *J* = 2.0 Hz, 3 H), 1.69 - 1.27 (comp m, 10 H), 1.21 (s, 3 H), 1.10 (s, 3 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 9 H), 0.93 (s, 9 H), 0.10 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2, 165.0, 151.9, 149.4, 149.3, 148.2, 148.1, 141.4, 138.22, 138.15, 134.2, 130.6, 129.5, 128.9, 128.8, 128.2, 126.8, 126.0, 115.3, 115.2, 113.7, 113.4, 106.85, 106.75, 102.60, 102.58, 100.44, 100.36, 67.8, 64.9, 56.8, 39.3, 38.9, 33.8, 33.6, 31.7, 30.6, 30.4, 30.1, 29.63, 29.59, 29.3, 29.2, 29.0, 28.5, 25.9, 25.8, 25.63, 25.56, 24.0, 23.0, 22.1, 22.0, 21.8, 19.9, 19.4, 19.0, 18.4, 18.32, 18.29, 14.0, 11.1, -3.7, -3.9, -4.0, -5.3.

IR (film): ν = 2956, 2929, 2904, 2857, 1463, 1446, 1252, 1196, 1179, 1058, 1042, 1028, 835.

MS (DART): *m/z* calc'd for $(M - TBS + 2H)^+$ $[C_{22}H_{27}BrO_3 + H]^+$: 419.1216, found 419.1227.

Data for ketone 4-132.

Physical form: Pale yellow liquid.

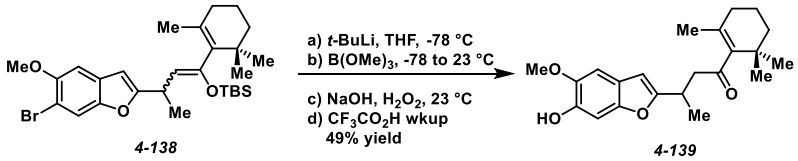
TLC: R_f = 0.28 (9:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 6.96 (s, 1 H), 6.36 (s, 1 H), 3.89 (s, 3 H), 3.66 - 3.54 (m, 1 H), 3.08 (dd, *J* = 18.8, 5.5 Hz, 1 H), 2.78 (dd, *J* = 19.0, 7.6 Hz, 1 H), 1.93 (t, *J* = 6.5 Hz, 2 H), 1.64 (dtd, *J* = 9.4, 6.3, 3.5 Hz, 2 H), 1.49 (s, 3 H), 1.44 - 1.39 (m, 2 H), 1.38 (d, *J* = 7.0 Hz, 3 H), 1.09 - 1.08 (m, 1 H), 1.05 (s, 3 H), 1.03 (s, 3 H).

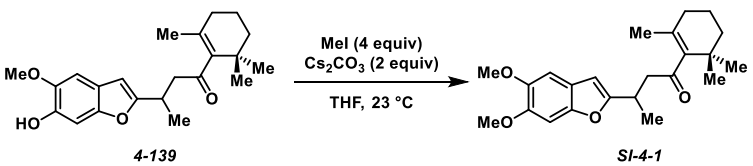
^{13}C NMR (101 MHz, $CDCl_3$): δ = 208.9, 163.8, 152.0, 149.1, 142.8, 129.5, 128.6, 115.3, 107.2, 102.6, 101.4, 77.3, 77.0, 76.7, 56.8, 50.8, 38.9, 33.3, 31.2, 28.7, 28.6, 28.5, 20.6, 18.8.

IR (film): ν = 2964, 2935, 2909, 2868, 2845, 1689, 1462, 1445, 1232, 1196, 1178, 1040, 937, 848.

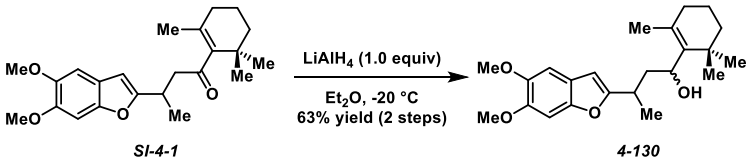
MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{22}H_{27}BrO_3 + H]^+$: 419.1, 421.1, found 419.1, 421.1.



To a solution of silyl enol ether **4-138** (271 mg, 0.508 mmol) in THF (2.5 mL) was added *t*-BuLi (0.598 mL, 1.7 M in pentane, 1.02 mmol) dropwise. The resulting solution was stirred 5 min and $B(OMe)_3$ (0.227 mL, 2.03 mmol) was added in one portion, discharging the orange-brown color of the reaction mixture to colorless. The reaction mixture was then allowed to warm to ambient temperature and stir 1 h. The reaction was cooled to -20 °C then treated sequentially with H_2O_2 (30% in H_2O, 0.253 mL, 2.46 mmol) and 1 M NaOH (0.246 mL, 0.246 mmol), allowed to warm to ambient temperature, and stirred an additional hour. The reaction mixture was then poured into a mixture of $NaHCO_3$ (10 mL), H_2O (5 mL) and sat $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and treated with CF_3CO_2H (38 μL, 0.508 mmol). This mixture was allowed to stand 1h then concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc → 9:1 hexanes-EtOAc eluent) to give ketone **4-139** (82.5 mg, 49% yield) as a pale yellow liquid.



To a solution of phenol **4-139** (105 mg, 0.319 mmol) in THF (0.64 mL) was added Cs_2CO_3 (208 mg, 0.638 mmol) followed by MeI (0.080 mL, 1.28 mmol). The resulting solution was stirred 24 h at ambient temperature then filtered. The filtrate was concentrated to give dimethoxyarene **SI-4-1**, which was used immediately without further purification.



To a solution of the previously prepared ketone **SI-4-1** in Et_2O (3.2 mL) at -20 °C was added $LiAlH_4$ (12.1 mg, 0.319 mmol) in one portion. The reaction mixture was stirred for 30 min at this temperature, at which point TLC indicated consumption of **SI-4-1**. The reaction mixture was quenched by adding H_2O (0.04 mL) and 5 M aq. NaOH (0.04 mL) at -20 °C and stirring 10 min before warming to ambient temperature and adding an additional portion of H_2O (0.04 mL). The resulting mixture was then stirred 1 h at ambient temperature, dried with $MgSO_4$, and filtered through a pad of celite, rinsing with Et_2O. The filtrate was concentrated to give pure alcohol **4-130** (117 mg, 63% yield).

Data for allylic alcohol 4-130.

Physical form: Colorless solid.

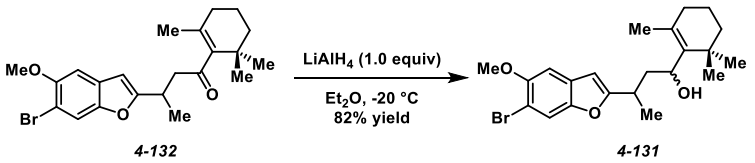
TLC: R_f = 0.25 (4:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1 H), 6.92 (s, 1 H), 6.30 (s, 1 H), 3.88 (s, 3 H), 3.88 (s, 3 H), 3.59 (ddd, *J* = 14.5, 12.7, 7.2 Hz, 2 H), 3.06 (dd, *J* = 18.8, 5.1 Hz, 1 H), 2.77 (dd, *J* = 18.8, 8.2 Hz, 1 H), 1.92 (t, *J* = 6.5 Hz, 2 H), 1.69 - 1.60 (m, 2 H), 1.50 (s, 3 H), 1.44 - 1.39 (m, 2 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 1.06 (s, 3 H), 1.03 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.1, 161.5, 149.0, 147.1, 146.2, 142.9, 129.4, 120.4, 102.2, 101.0, 95.3, 56.4, 56.2, 51.1, 38.9, 33.2, 31.2, 28.7, 28.6, 28.4, 20.6, 18.9, 18.8.

IR (film): ν = 2930, 2868, 2832, 1486, 1208, 1193, 1115, 906.

MS (DART): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{30}O_3 + H]^+$: 355.2268, found 355.2268.



To a solution of ketone **4-132** (1.68 g, 4.00 mmol) in Et_2O (40 mL) at -20 °C was added $LiAlH_4$ (152 mg, 4.00 mmol) in one portion. The reaction mixture was stirred for 30 min at this temperature, at which point TLC indicated consumption of ketone **4-132**. The reaction mixture was quenched by carefully adding H_2O (0.15 mL) followed by 5 M NaOH (0.15 mL) at -20 °C and stirring 10 min before warming to ambient temperature and adding an additional portion of H_2O (0.45 mL). The resulting mixture was then stirred 1 h at ambient temperature, dried with $MgSO_4$, and filtered through a pad of celite, rinsing with Et_2O. The filtrate was concentrated, and the resulting residue purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc → 4:1 hexanes-EtOAc eluent) to give alcohol **4-131** (1.38 g, 82% yield). Analytical samples were obtained for the separated diastereomers (**4-131a** and **4-131b**).

Data for allylic alcohol 4-131a.

Physical form: Colorless solid.

TLC: R_f = 0.13 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.61 (s, 1 H), 6.98 (s, 1 H), 6.35 (s, 1 H), 4.47 (dd, *J* = 11.0, 2.3 Hz, 1 H), 3.95 - 3.87 (m, 3 H), 3.24 (ddd, *J* = 10.1, 6.7, 3.9 Hz, 1 H), 2.46 (ddd, *J* = 14.7, 10.8, 4.3 Hz, 1 H), 1.93 (q, *J* = 5.7 Hz, 2 H), 1.85 (s, 3 H), 1.66 (ddd, *J* = 14.2, 9.9, 2.5 Hz, 1 H), 1.60 - 1.51 (m, 3 H), 1.44 - 1.38 (m, 2 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.11 (s, 3 H), 0.96 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101MHz): δ = 165.6, 152.0, 149.2, 140.5, 131.6, 128.7, 115.4, 107.1, 102.6, 100.5, 68.2, 56.8, 41.6, 39.9, 34.8, 34.0, 30.9, 28.6, 28.2, 21.2, 19.2, 17.6.

IR (film): ν = 3576, 2963, 2931, 2868, 2844, 1463, 1445, 1232, 1196, 1178, 1041, 939, 851, 832.

MS (ESI+): *m/z* calc'd for $(M - H_2O + H)^+$ $[C_{22}H_{29}BrO_3 + H]^+$: 403.1267, 405.1247, found 403.1284, 405.1249.

Data for allylic alcohol 4-131b.

Physical form: Colorless liquid.

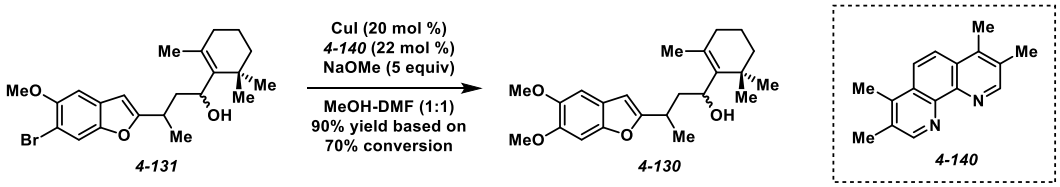
TLC: R_f = 0.06 (9:1 hexanes-EtOAc, $KMnO_4$ stain solution).

^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.60 (s, 1 H), 7.00 (s, 1 H), 6.40 (s, 1 H), 4.15 (dd, *J* = 11.0, 2.0 Hz, 1 H), 3.91 (s, 3 H), 3.26 (dt, *J* = 7.1, 3.3 Hz, 1 H), 2.20 (ddd, *J* = 14.7, 11.0, 4.1 Hz, 1 H), 1.96 - 1.88 (m, 2 H), 1.83 (s, 3 H), 1.58 - 1.45 (comp m, 2 H), 1.42 - 1.31 (m, 1 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 0.91 (s, 3 H), 0.72 (s, 3 H).

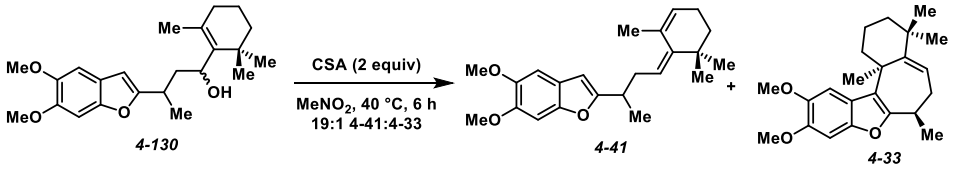
^{13}C NMR ($CDCl_3$, 101MHz): δ = 164.2, 152.0, 149.2, 140.6, 131.2, 128.6, 115.3, 107.1, 102.6, 101.9, 69.0, 56.8, 42.5, 39.8, 34.6, 34.0, 31.5, 28.1, 28.1, 21.1, 20.4, 19.2.

IR (film): ν = 2962, 2930, 2867, 1463, 1445, 1197, 1039, 907, 854, 834.

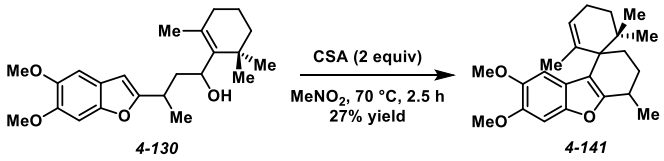
MS (ESI-): *m/z* calc'd for $(M - H)^-$ $[C_{22}H_{29}BrO_3 - H]^-$: 419.1230, 421.1210, found 419.1226, 421.1210.



A 60 mL pressure tube under an Ar purge was charged with a stirbar, Na metal (230 mg, 10.0 mmol), and dry MeOH (10 mL). When the Na had disappeared, aryl bromide **4-131** (843 mg, 2.00 mmol), 3,4,7,8-tetramethylphenanthroline (**4-140**, 93.4 mg, 0.440 mmol), CuI (76.2 mg, 0.400 mmol), and DMF (10 mL) were added. The resulting solution was sparged with Ar for 5 min then capped under an Ar purge and heated to 90 °C in an oil bath. The reaction mixture was stirred 48 h at 90 °C then allowed to cool to ambient temperature. The contents of the pressure tube were poured into sat NH_4Cl aq. (100 mL) and extracted with 2:1 hexanes-Et_2O (3 x 50 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated. The resulting residue was analyzed by ^{1}H NMR, indicating 70% conversion, and purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc → 4:1 hexanes-EtOAc eluent) to give **4-130** (470 mg, 63% yield, 90% based on 70% conversion).



To a solution of allylic alcohol **4-130** (34.5 mg, 0.0926 mmol) in $MeNO_2$ (1.85 mL) was added camphorsulfonic acid (43.0 mg, 0.185 mmol). The reaction mixture was then heated to 40 °C for 6 h, at which point TLC indicated consumption of alcohol **4-130**. The reaction mixture was partitioned between sat. aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, dried with Na_2SO_4, concentrated, and analyzed by ^1H NMR showing that it was nearly pure diene **4-41**. The spectroscopic data for diene **4-41** matched those presented in the literature.[6]



To a solution of allylic alcohol **4-130** (84.0 mg, 0.227 mmol) in $MeNO_2$ (2.3 mL) was added camphorsulfonic acid (105 mg, 0.453 mmol). The reaction mixture was then heated to 70 °C for 2.5 h, at which point TLC indicated consumption of alcohol **4-130**. The reaction mixture was partitioned between sat $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 9:1 hexanes-EtOAc) to give pure spirocycle **4-141** (21.9 mg, 27% yield)

Data for spirocycle 4-141.

Physical form: Colorless liquid.

TLC: R_f = 0.23 (19:1 hexanes-EtOAc, UV, $KMnO_4$ stain solution).

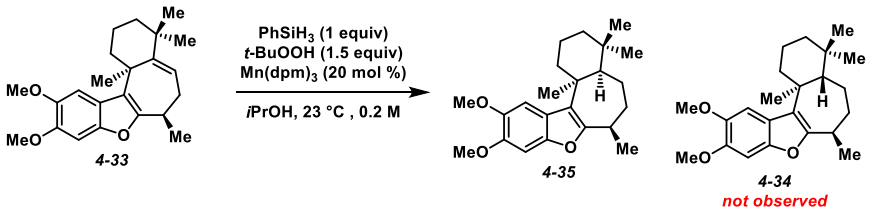
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (s, 1 H), 6.96 (s, 1 H), 3.89 (s, 4 H), 3.84 (s, 3 H), 2.97 - 2.83 (m, 1 H), 2.28 - 2.07 (comp m, 4 H), 2.04 - 1.54 (comp m, 9 H), 1.49 (d, *J* = 1.2 Hz, 3 H), 1.41 (s, 3 H), 1.36 (d, *J* = 6.7 Hz, 3 H), 1.30 (d, *J* = 7.0 Hz, 3 H), 0.99 (s, 3 H), 0.82 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.0, 148.7, 145.1, 138.3, 138.1, 123.1, 122.1, 121.4, 114.5, 104.8, 104.6, 95.0, 94.9, 94.8, 56.5, 56.1, 46.2, 45.9, 38.2, 34.6, 31.6, 30.4, 29.2, 28.9, 28.7, 27.2, 23.1, 23.0, 21.0, 19.0, 18.8.

IR (film): ν = 2930, 2872, 2836, 1486, 1464, 1439, 1208, 1195, 1145, 915.

MS (ESI+): *m/z* calc'd for $(M + H)^+$ $[C_{23}H_{30}O_3 + H]^+$: 355.2268, found 355.2260.

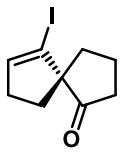
To a solution of allylic alcohol **4-130** (86.1 mg, 0.231 mmol) in dry $EtNO_2$ (2.3 mL) at -78 °C was added $ClSO_3H$ (62 μL, 0.924 mmol) dropwise. The reaction mixture was stirred 10 min then quenched by adding Et_3N (0.279 mL, 2.00 mmol) dropwise. The solution was allowed to warm to ambient temperature and partitioned between sat. aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, dried with Na_2SO_4 and concentrated. The resulting residue was and purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give cycloheptene derivative **4-33** (25.8 mg, 31% yield) as a 4:1 mixture of diastereomers as indicated by integration of ^{1}H NMR peaks. The spectroscopic data for compound **4-33** matched those presented in the literature.[2]



A solution of $PhSiH_3$ (0.123 mL, 1.00 mmol) and *t*-BuOOH (0.273 mL, 5.5 M in decane, 1.50 mmol) in *i*-PrOH (5.0 mL) was degassed by sparging with Ar for 10 min. A portion of this solution (0.62 mL) was added to an Ar purged vial containing alkene **4-33** (40.6 mg, 0.114 mmol), $Mn(dpm)_3$ (13.9 mg, 0.0229 mmol), and a stirbar. The resulting solution was stirred for 2 h, at which point it was concentrated to remove *i*-PrOH. The resulting

residue was partially purified by flash column chromatography (SiO_2, 19:1 hexanes-EtOAc eluent) to give a complex mixture containing only *cis*-fused **4-35** as judged by ^{1}H NMR analysis and comparison with literature spectroscopic data for *cis*-fused **4-35**[6] and *trans*-fused **4-34**.[2]

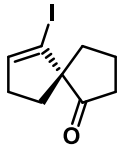
Appendix Four: Spectra Relevant to Chapter Two.



2-91

^{1}H NMR

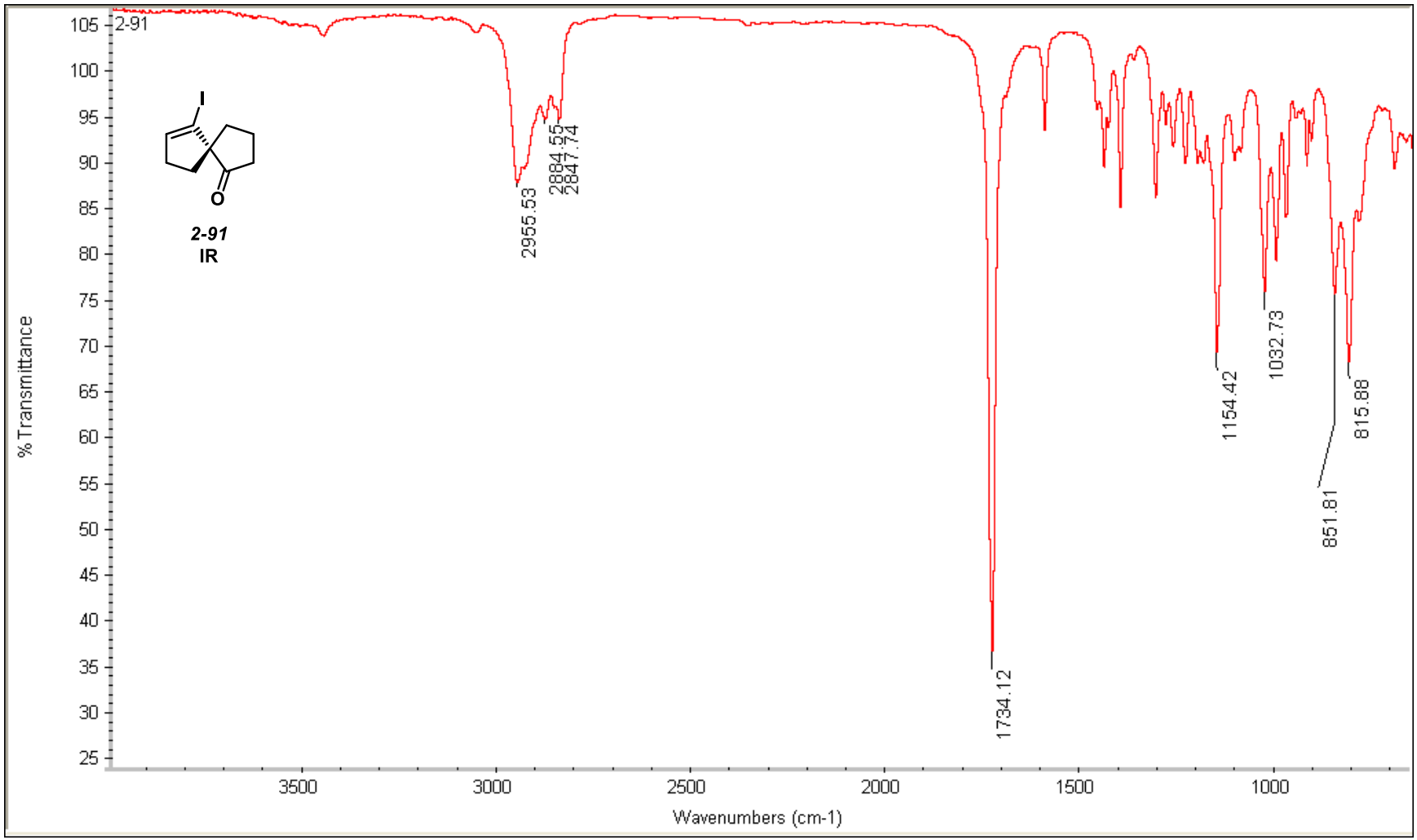
(400 MHz, $CDCl_3$)

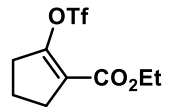


2-91

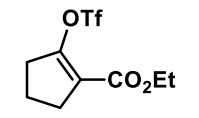
^{13}C NMR

(101 MHz, $CDCl_3$)


2-91
I
O
2-91
IR
% Transmittance
Wavenumbers (cm-1)
2955.53
2884.55
2847.74
1734.12
1154.42
1032.73
851.81
815.88



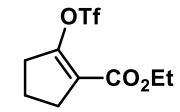
2-95
^{1}H NMR
(400 MHz, $CDCl_3$)



2-95

^{13}C NMR

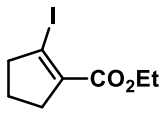
(101 MHz, $CDCl_3$)



2-95

^{19}F NMR

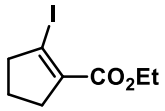
(376 MHz, $CDCl_3$)



2-96

^{1}H NMR

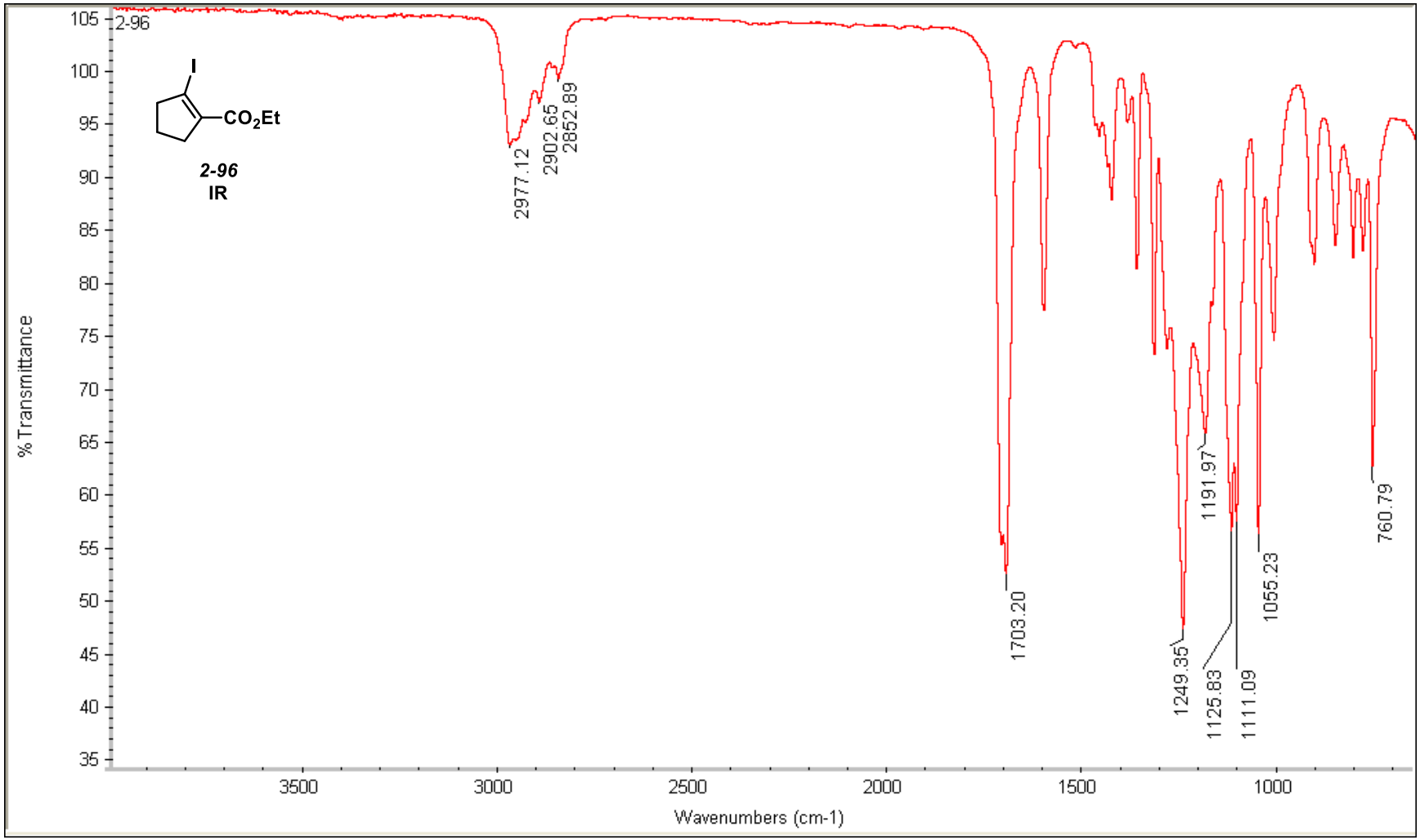
(400 MHz, $CDCl_3$)

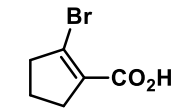


2-96

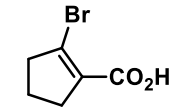
^{13}C NMR

(101 MHz, $CDCl_3$)

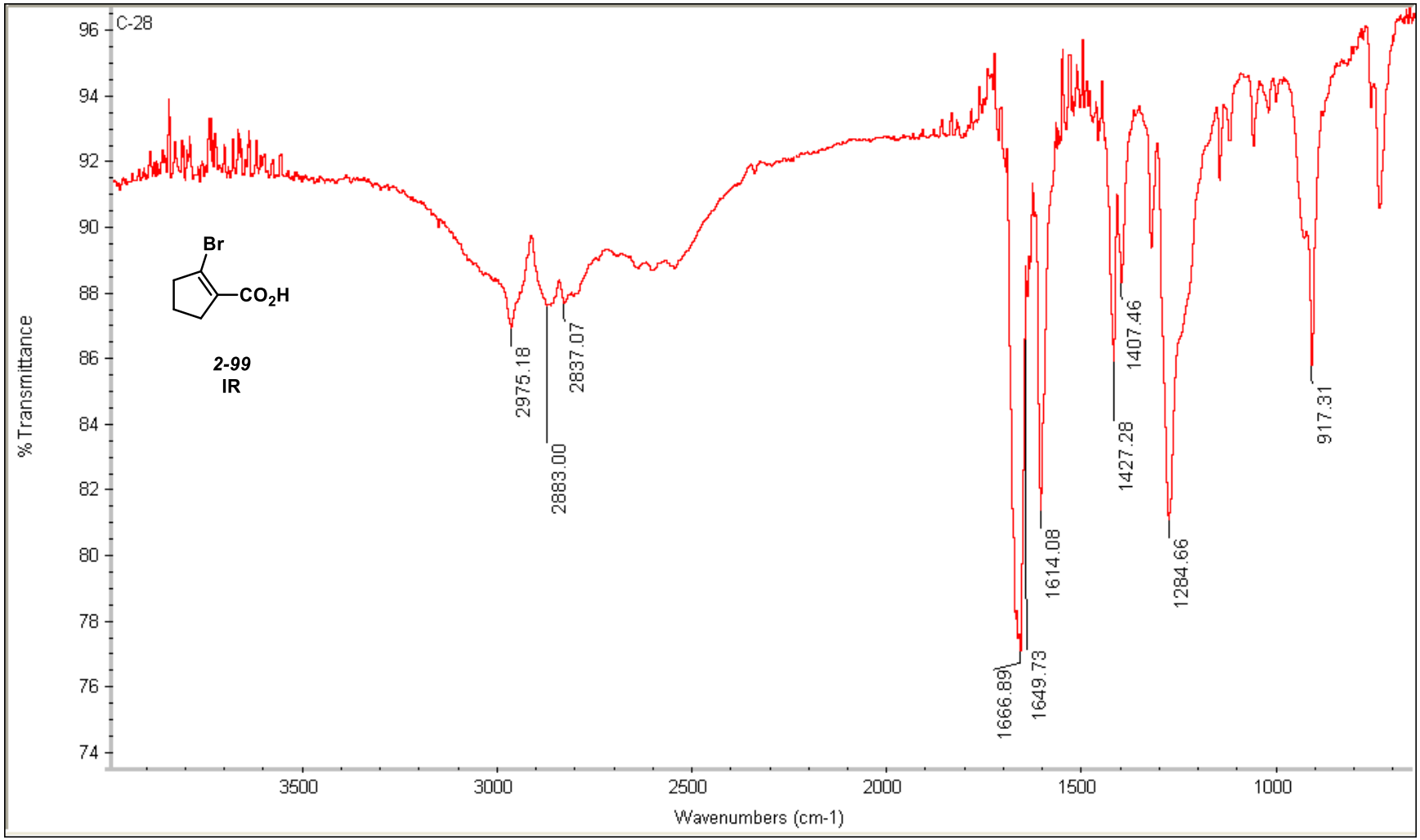

2-96
I
CO2Et
2-96
IR
% Transmittance
Wavenumbers (cm-1)
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
3500
3000
2500
2000
1500
1000
2977.12
2902.65
2852.89
1703.20
1249.35
1191.97
1125.83
1111.09
1055.23
760.79

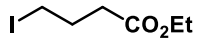


2-99
^{1}H NMR
($CDCl_3$, 400 MHz)



2-99
^{13}C NMR
($CDCl_3$, 101 MHz)

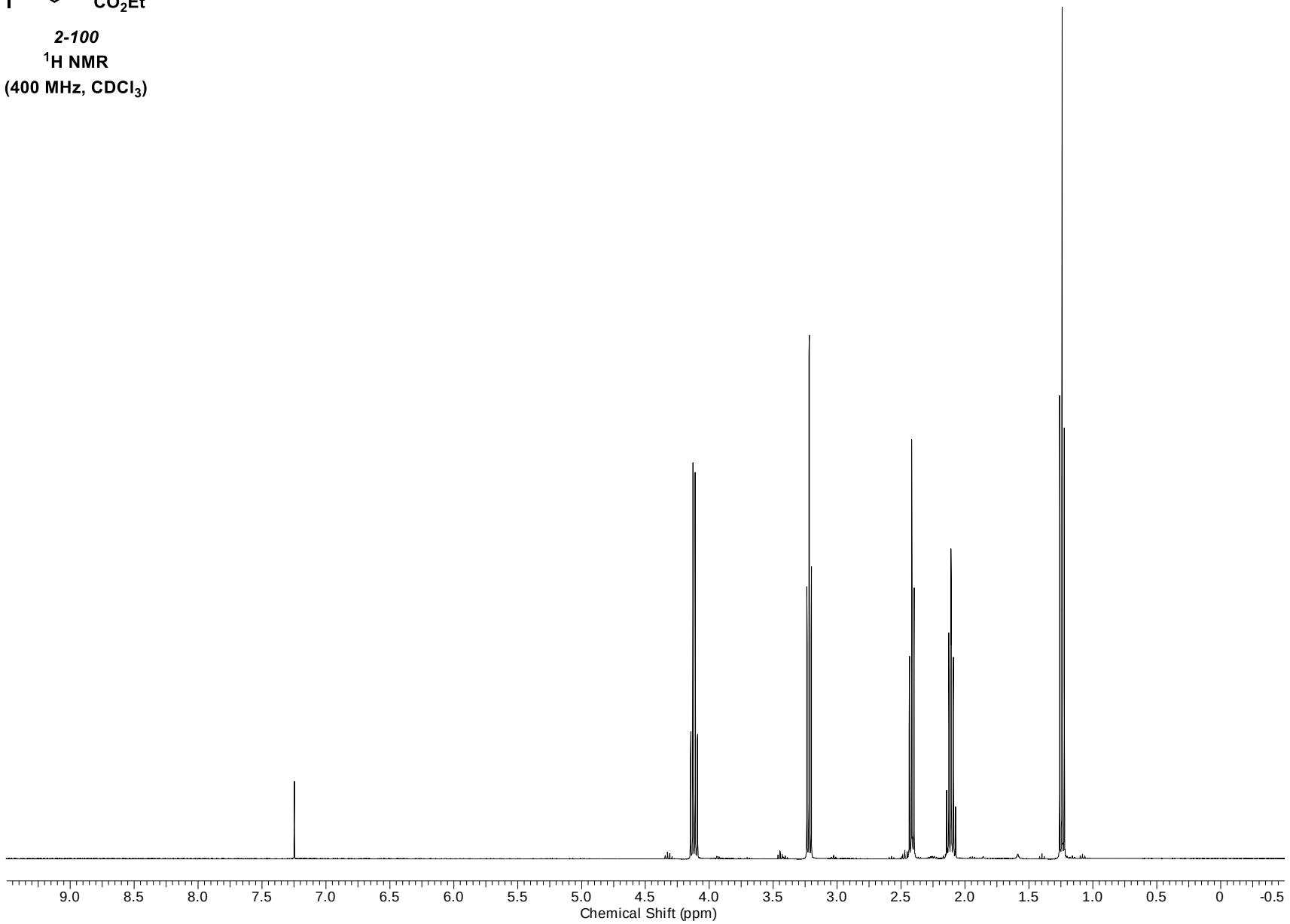

C-28
Br
CO2H
2-99
IR
% Transmittance
Wavenumbers (cm-1)
2975.18
2883.00
2837.07
1666.89
1649.73
1614.08
1427.28
1407.46
1284.66
917.31

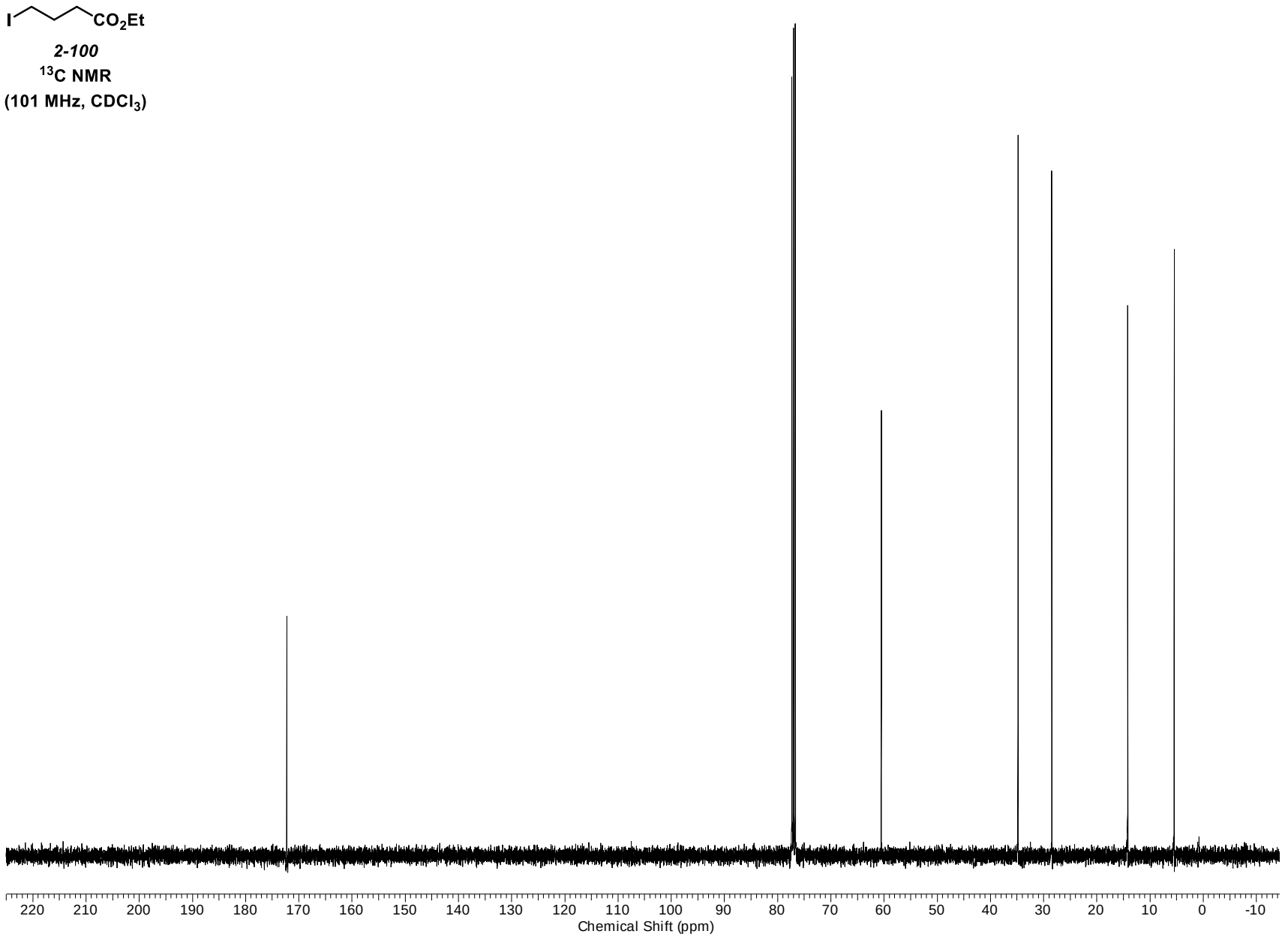


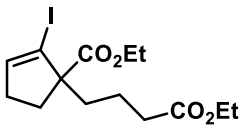
2-100

^{1}H NMR

(400 MHz, $CDCl_3$)



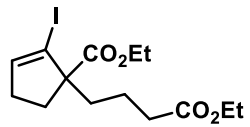

I
CO2Et
2-100
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)



2-101

^{1}H NMR

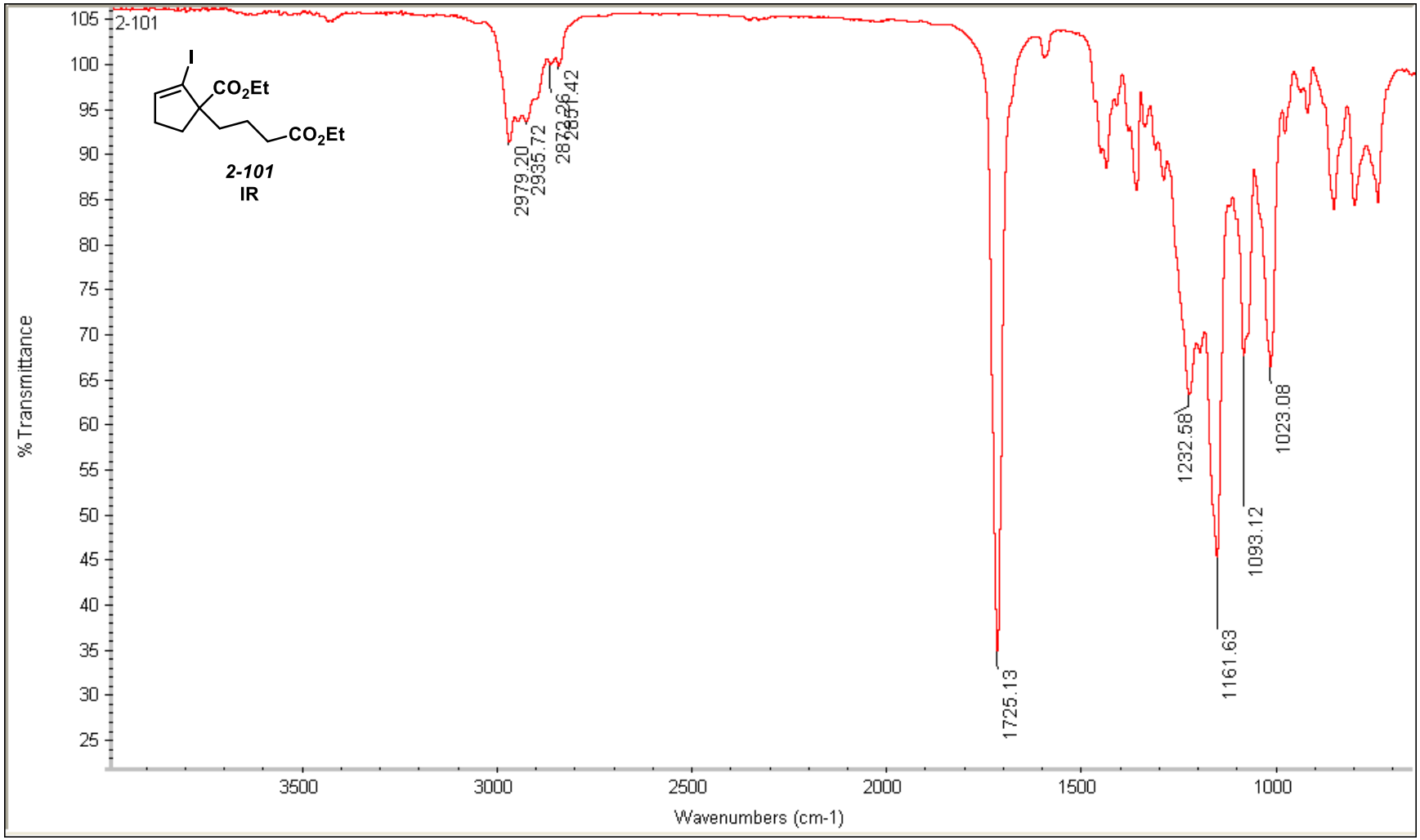
(400 MHz, $CDCl_3$)

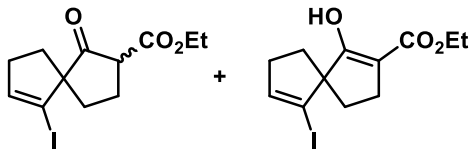


2-101

^{13}C NMR

(101 MHz, $CDCl_3$)

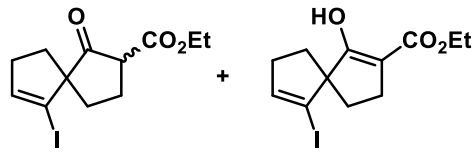

2-101
I
CO2Et
CO2Et
2-101
IR
% Transmittance
Wavenumbers (cm-1)
2979.20
2935.72
2872.26
2857.42
1725.13
1232.58
1161.63
1093.12
1023.08



2-102

^{1}H NMR

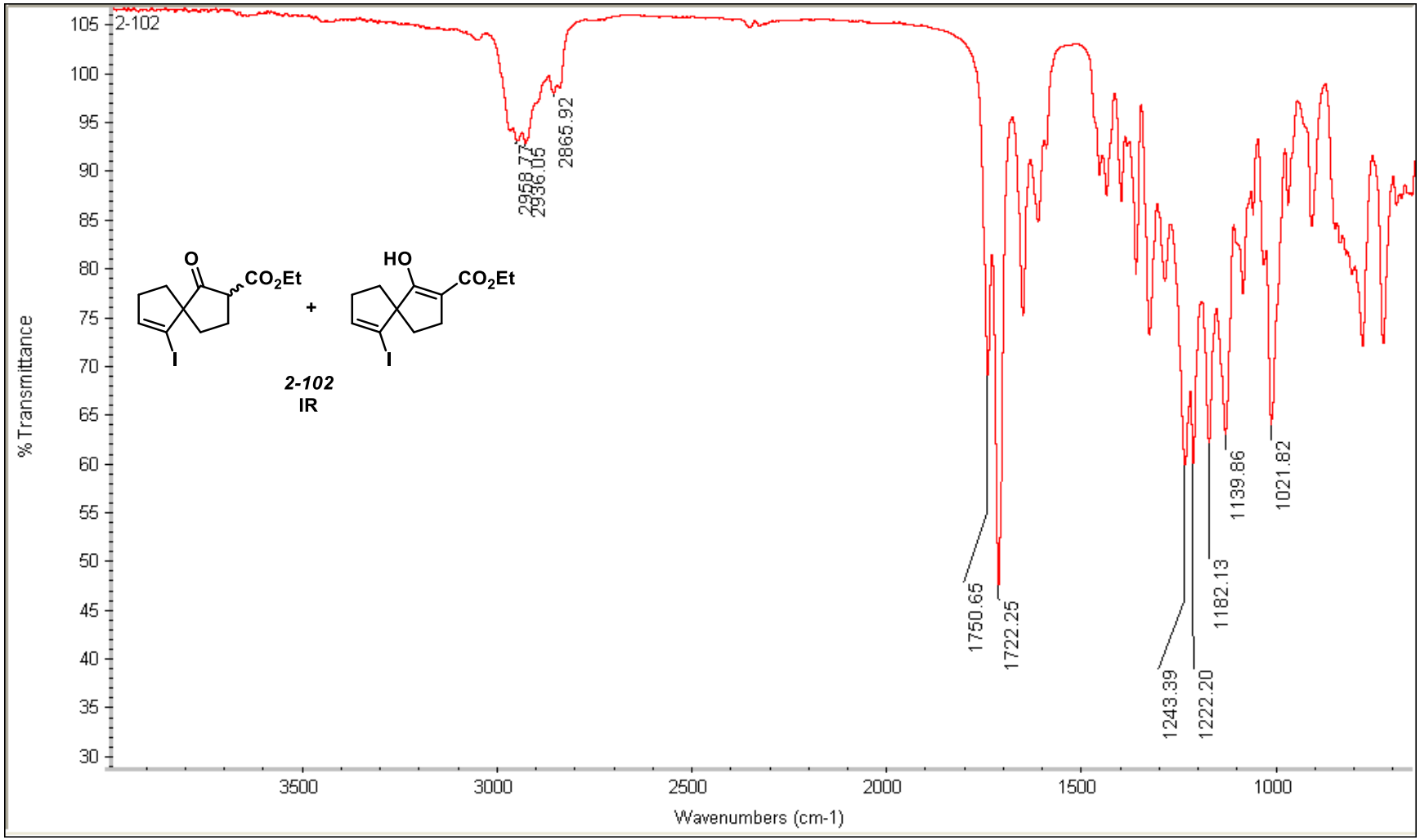
(400 MHz, $CDCl_3$)

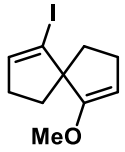


2-102

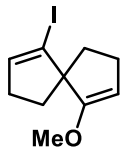
^{13}C NMR

(101 MHz, $CDCl_3$)

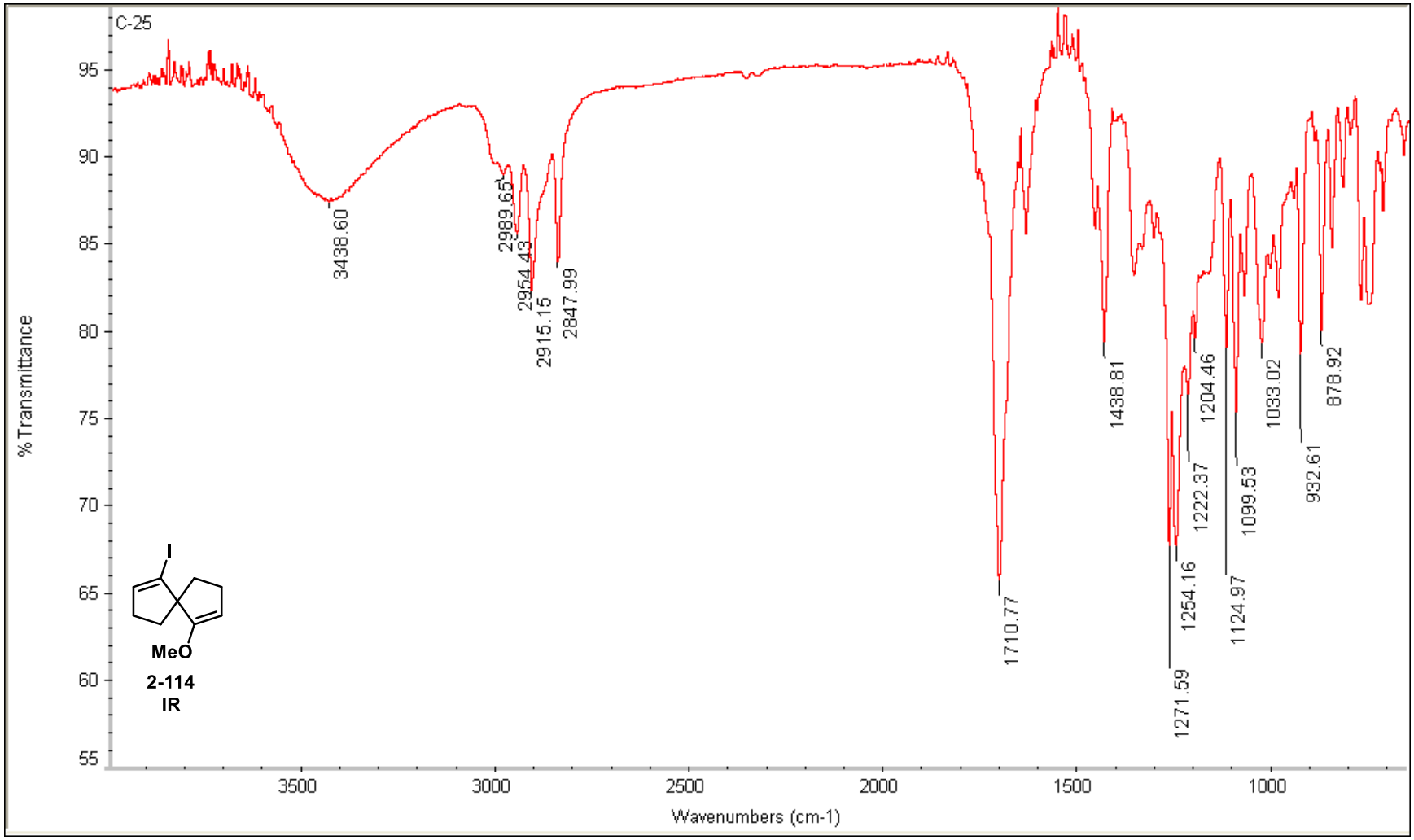

2-102
% Transmittance
Wavenumbers (cm-1)
2958.77
2936.05
2865.92
1750.65
1722.25
1243.39
1222.20
1182.13
1139.86
1021.82
O
CO2Et
I
+
HO
CO2Et
I
2-102
IR

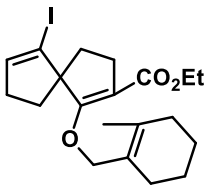


2-114
^{1}H NMR
($CDCl_3$, 400 MHz)



2-114
^{13}C NMR
($CDCl_3$, 101 MHz)

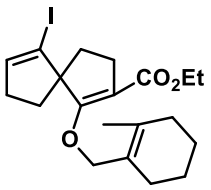

C-25
% Transmittance
Wavenumbers (cm-1)
3438.60
2989.65
2954.43
2915.15
2847.99
1710.77
1438.81
1271.59
1254.16
1222.37
1204.46
1124.97
1099.53
1033.02
932.61
878.92
I
MeO
2-114
IR



2-119

^{1}H NMR

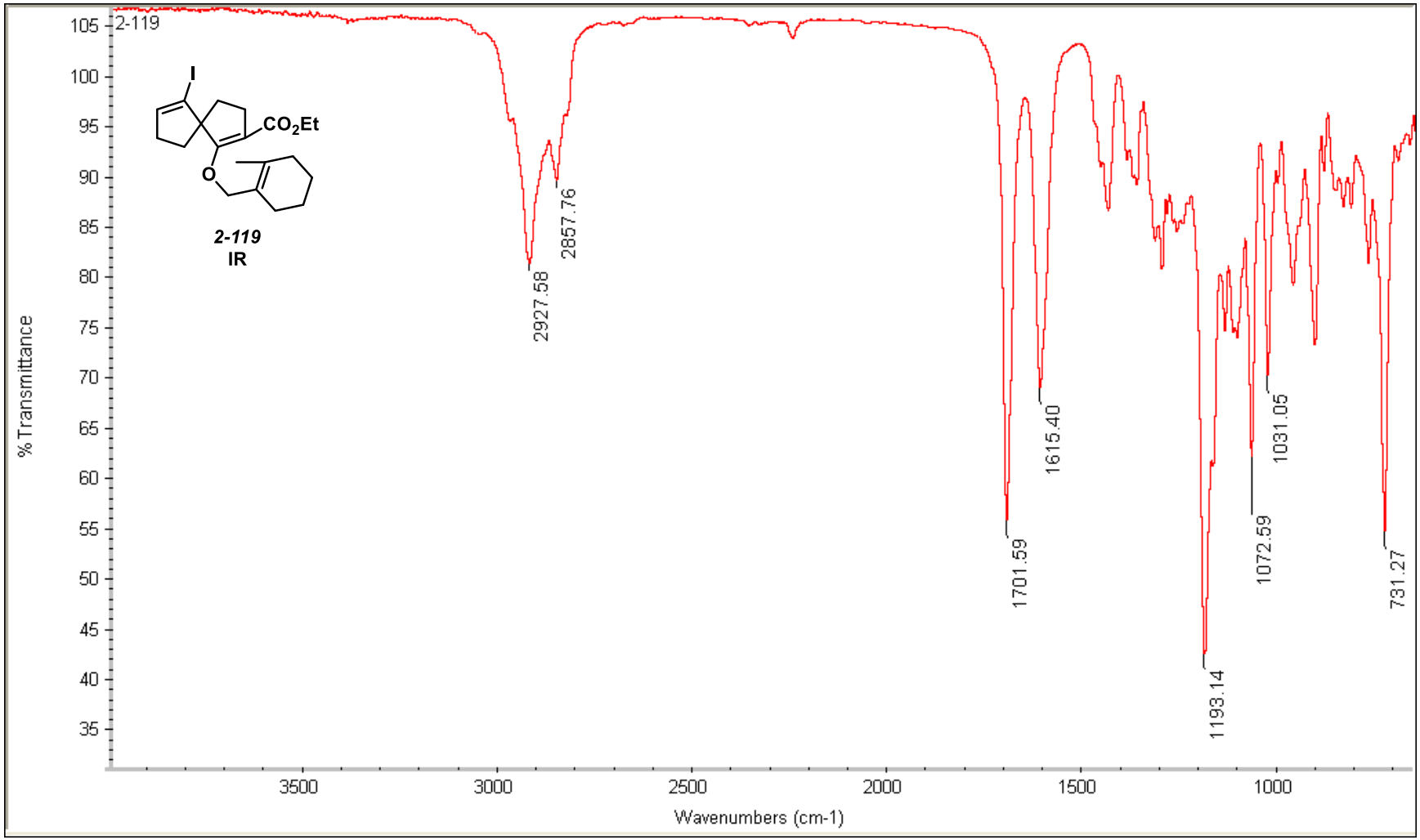
(400 MHz, $CDCl_3$)

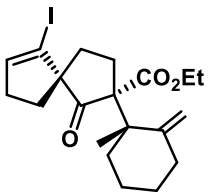


2-119

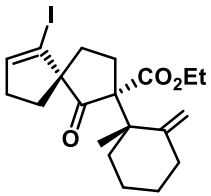
^{13}C NMR

(101 MHz, $CDCl_3$)

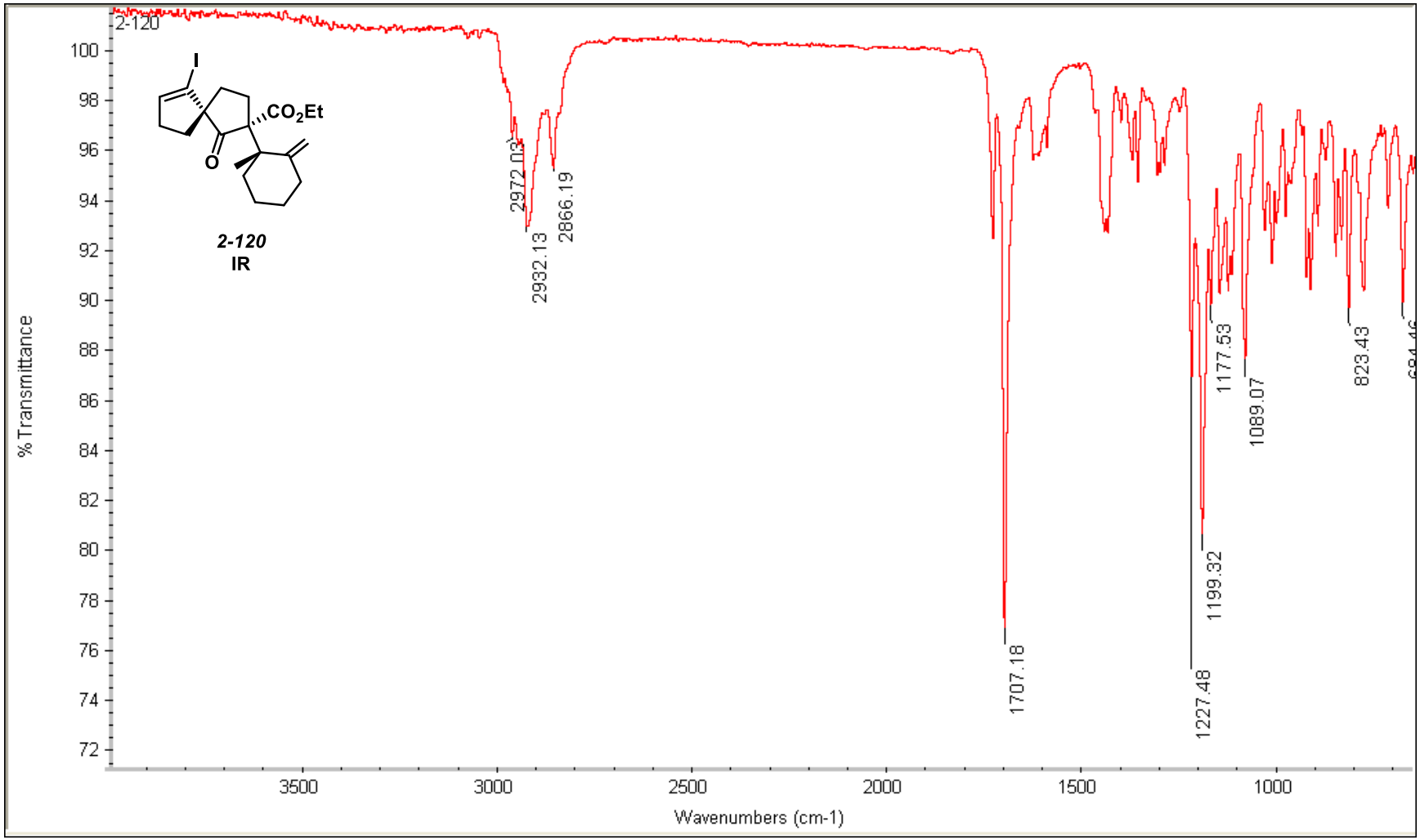

2-119
I
CO2Et
O
2-119
IR
% Transmittance
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
2927.58
2857.76
1701.59
1615.40
1193.14
1072.59
1031.05
731.27
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

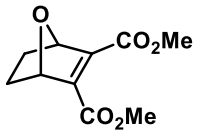


2-120
^{1}H NMR
(400 MHz, $CDCl_3$)

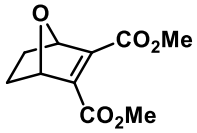


2-120
^{13}C NMR
(101 MHz, $CDCl_3$)

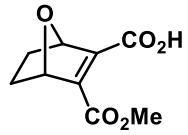

2-120
I
CO2Et
O
2-120
IR
% Transmittance
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
2972.03
2932.13
2866.19
1707.18
1227.48
1199.32
1177.53
1089.07
823.43
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



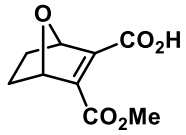
2-133
^{1}H NMR
(400 MHz, $CDCl_3$)



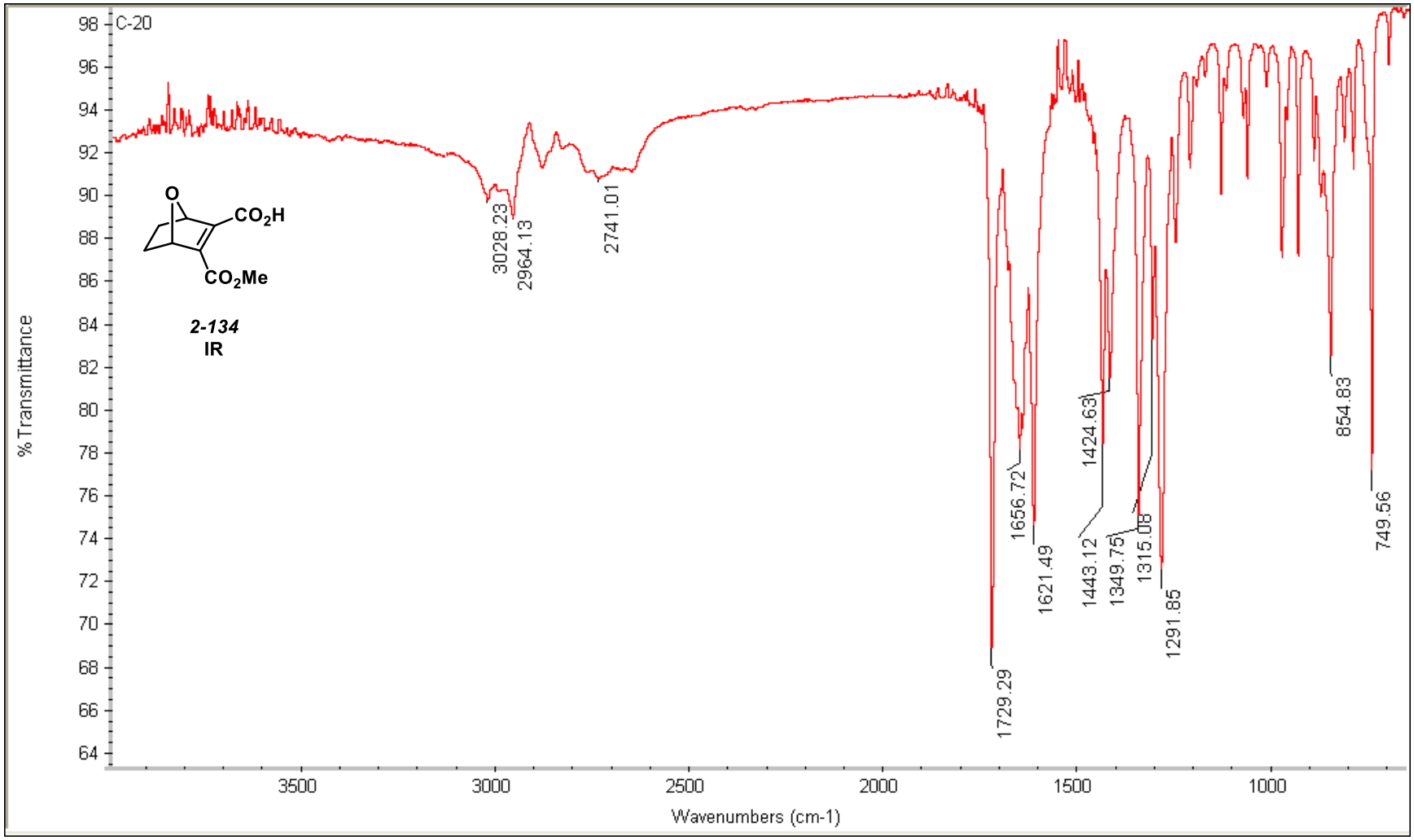
2-133
^{13}C NMR
(101 MHz, $CDCl_3$)

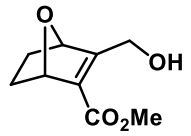


2-134
^{1}H NMR
(400 MHz, $CDCl_3$)

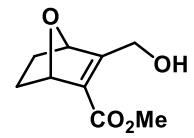


2-134
^{13}C NMR
(101 MHz, $CDCl_3$)

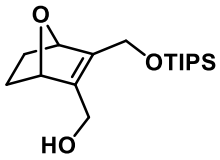

C-20
% Transmittance
Wavenumbers (cm-1)
3028.23
2964.13
2741.01
1729.29
1656.72
1621.49
1443.12
1424.63
1349.75
1315.08
1291.85
854.83
749.56
CO2H
CO2Me
2-134
IR



2-135
^{1}H NMR
(400 MHz, $CDCl_3$)



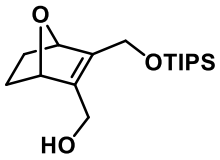
2-135
^{13}C NMR
(101 MHz, $CDCl_3$)



2-136

^{1}H NMR

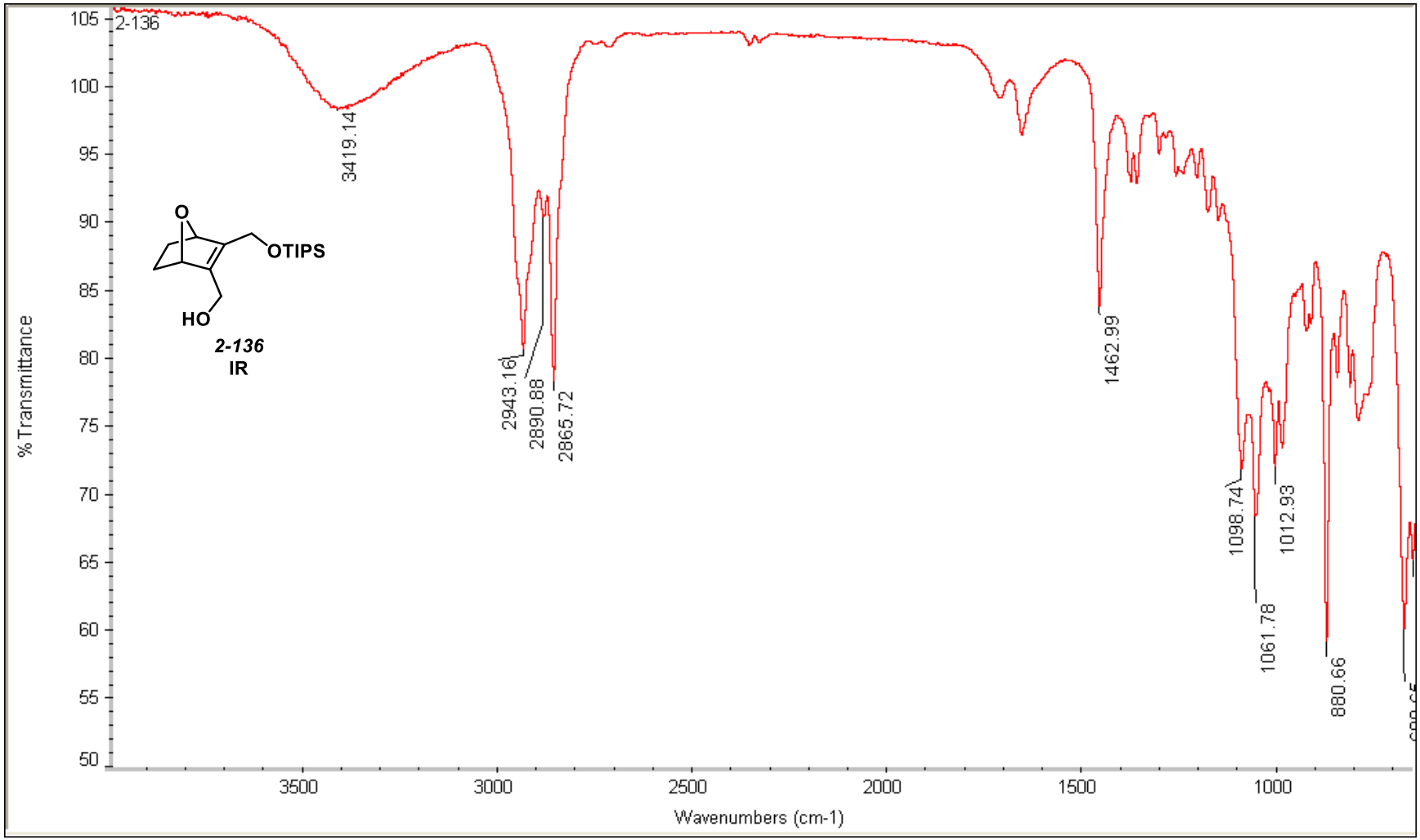
(400 MHz, $CDCl_3$)

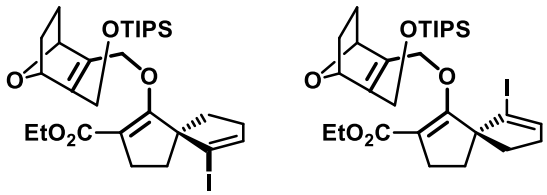


2-136

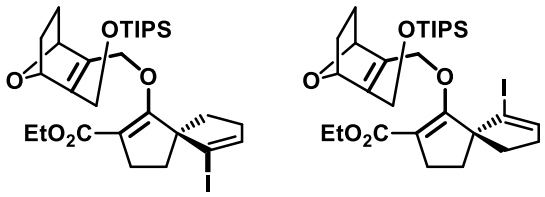
^{13}C NMR

(101 MHz, $CDCl_3$)

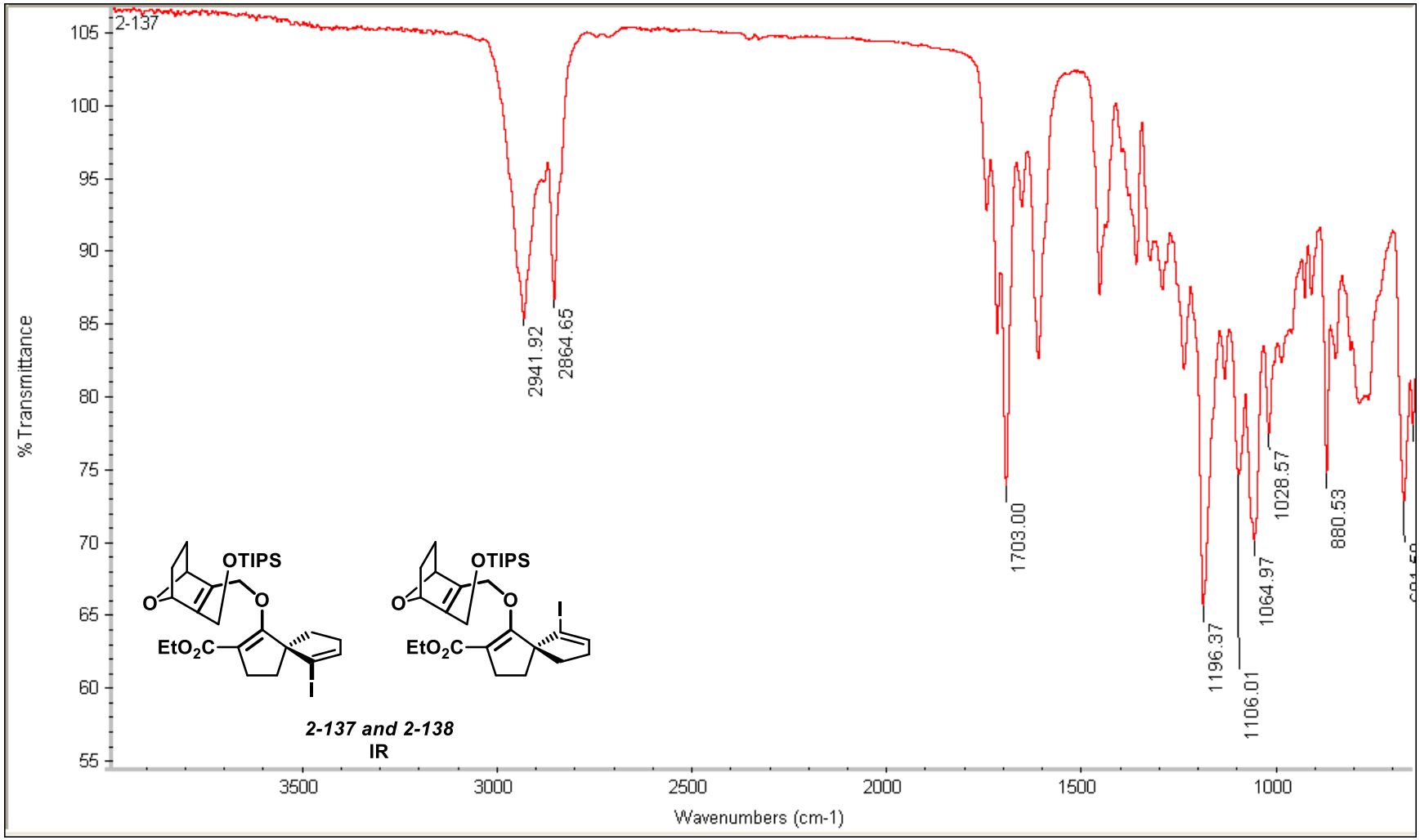

2-136
3419.14
2943.16
2890.88
2865.72
1462.99
1098.74
1061.78
1012.93
880.66
O
OTIPS
HO
2-136
IR
% Transmittance
Wavenumbers (cm-1)
105
100
95
90
85
80
75
70
65
60
55
50
3500
3000
2500
2000
1500
1000

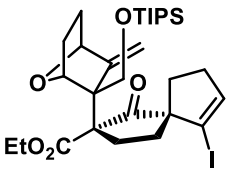


2-137 and 2-138
^{1}H NMR
($CDCl_3$, 400 MHz)



2-137 and 2-138
^{13}C NMR
($CDCl_3$, 101 MHz)

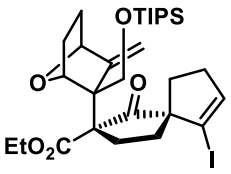

2-137
% Transmittance
Wavenumbers (cm-1)
2941.92
2864.65
1703.00
1196.37
1106.01
1064.97
1028.57
880.53
OTIPS
EtO2C
OTIPS
EtO2C
2-137 and 2-138
IR



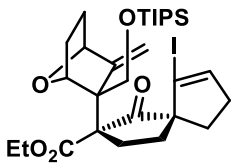
2-139

^{1}H NMR

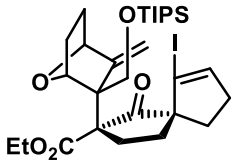
(400 MHz, $CDCl_3$)



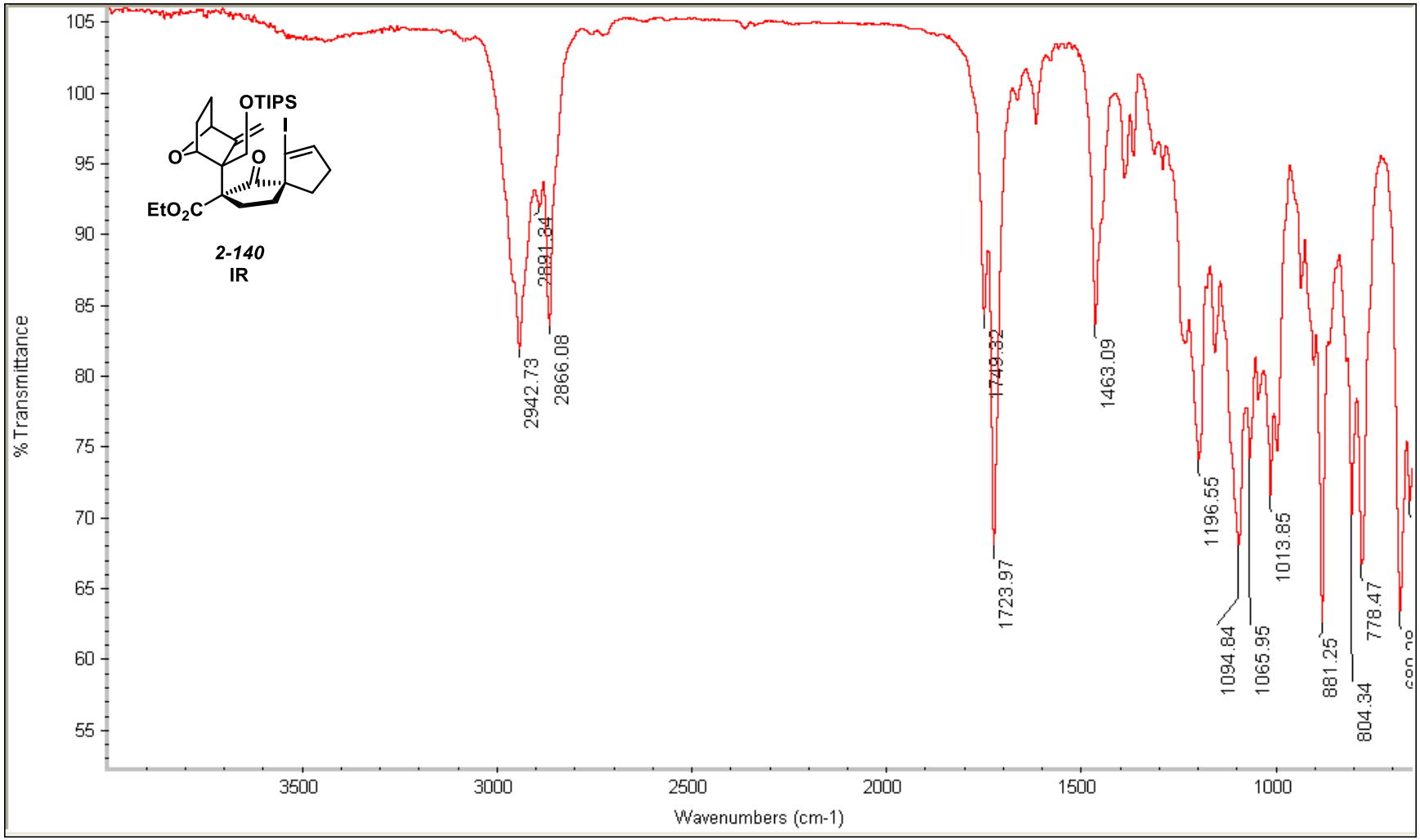
2-139
^{13}C NMR
(101 MHz, $CDCl_3$)

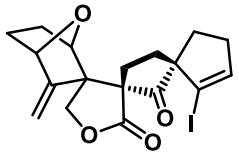


2-140
^{1}H NMR
($CDCl_3$, 400 MHz)

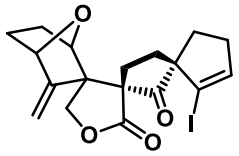


2-140
^{13}C NMR
($CDCl_3$, 101 MHz)

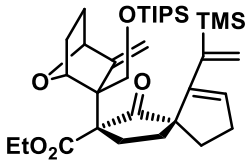

OTIPS
O
O
EtO2C
2-140
IR
% Transmittance
105
100
95
90
85
80
75
70
65
60
55
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
2942.73
2891.34
2866.08
1749.32
1723.97
1463.09
1196.55
1094.84
1065.95
1013.85
881.25
804.34
778.47



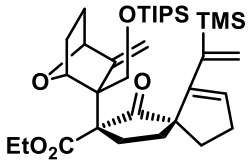
2-141
^{1}H NMR
($CDCl_3$, 400 MHz)



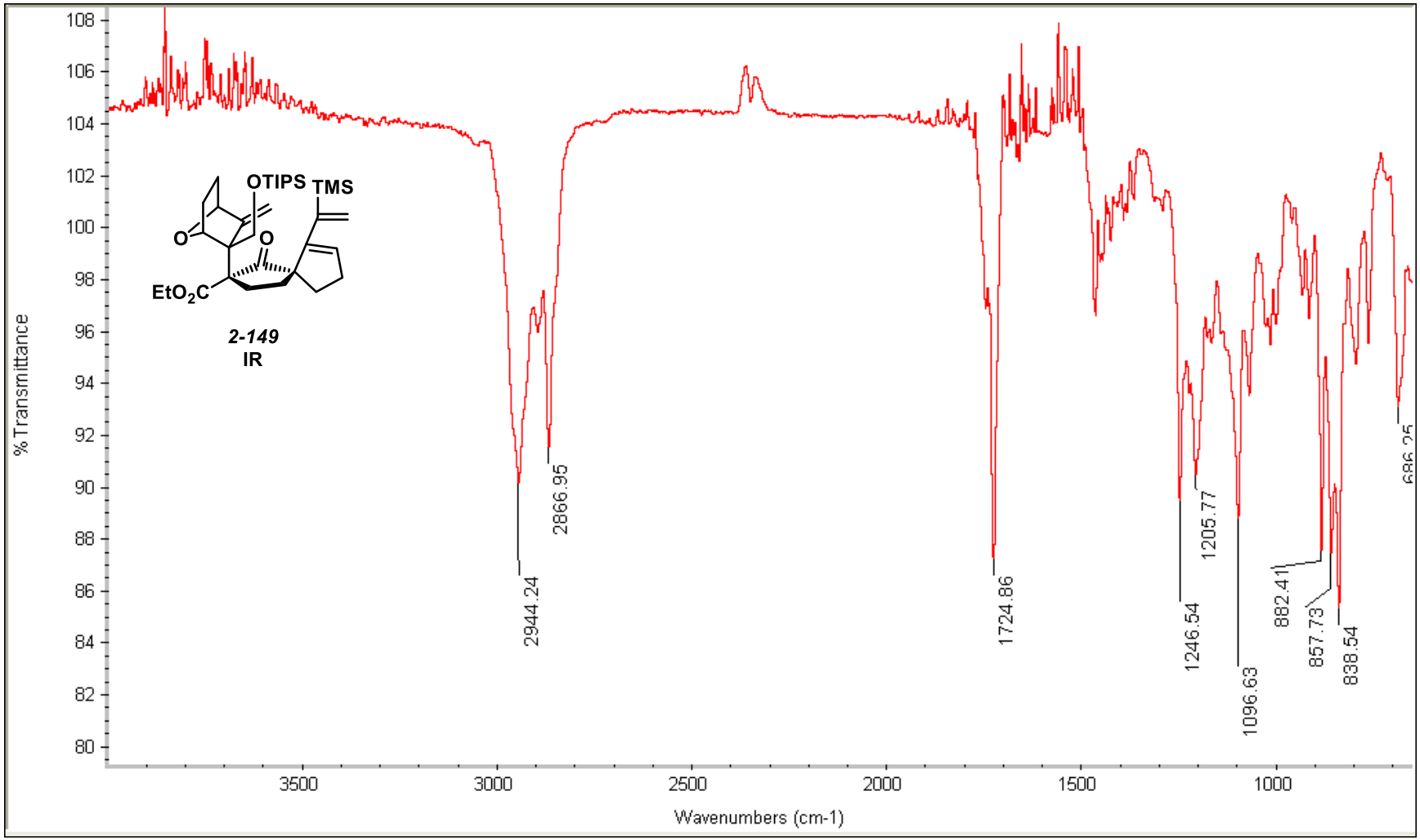
2-141
^{13}C NMR
($CDCl_3$, 101 MHz)

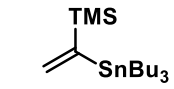


2-149
^{1}H NMR
($CDCl_3$, 400 MHz)



2-149
^{13}C NMR
($CDCl_3$, 101 MHz)

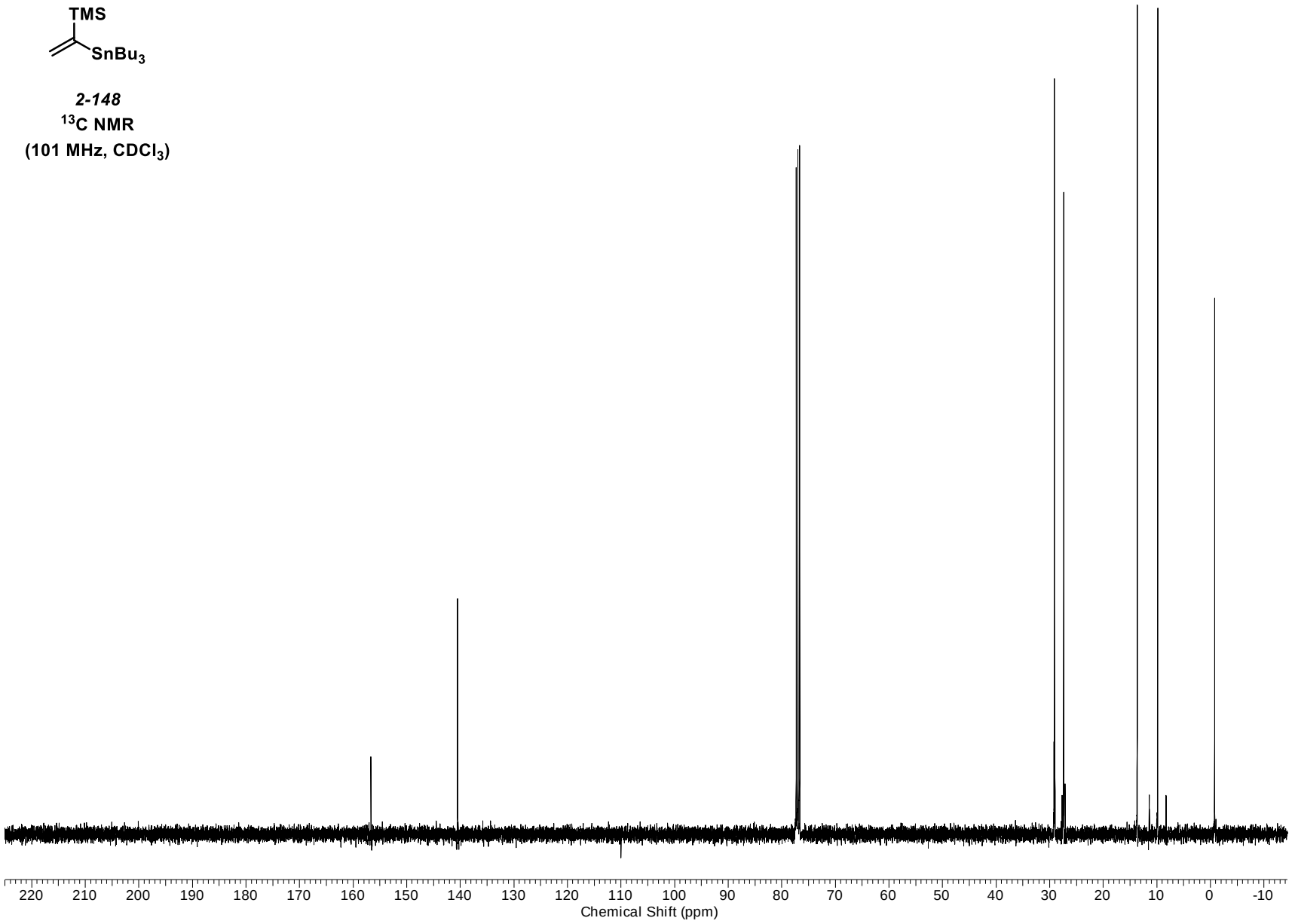

OTIPS
TMS
O
O
EtO2C
2-149
IR
% Transmittance
Wavenumbers (cm-1)
2944.24
2866.95
1724.86
1246.54
1205.77
1096.63
882.41
857.73
838.54

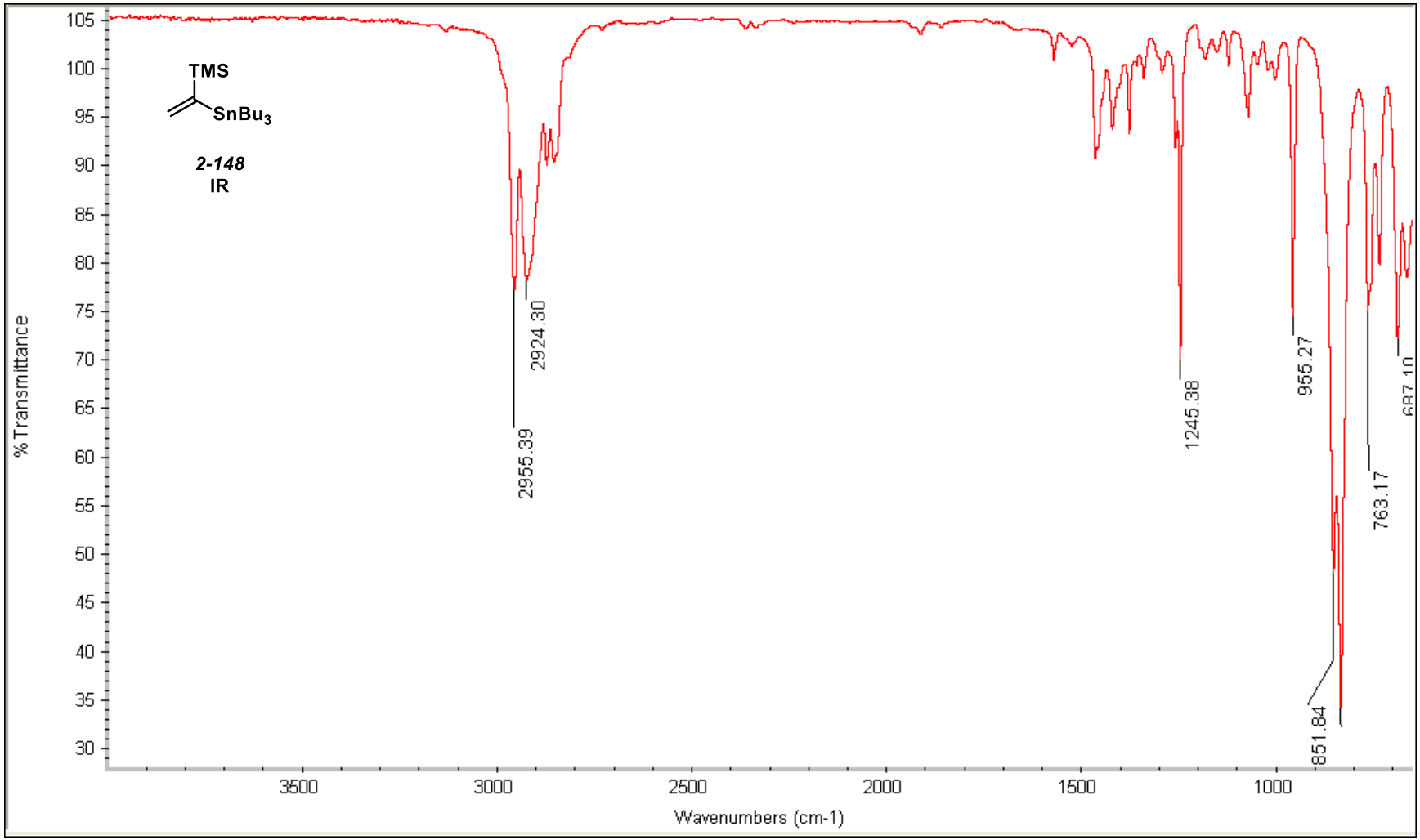


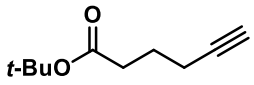
2-148

^{1}H NMR

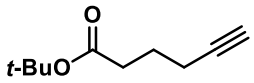
(400 MHz, $CDCl_3$)


TMS
SnBu3
2-148
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

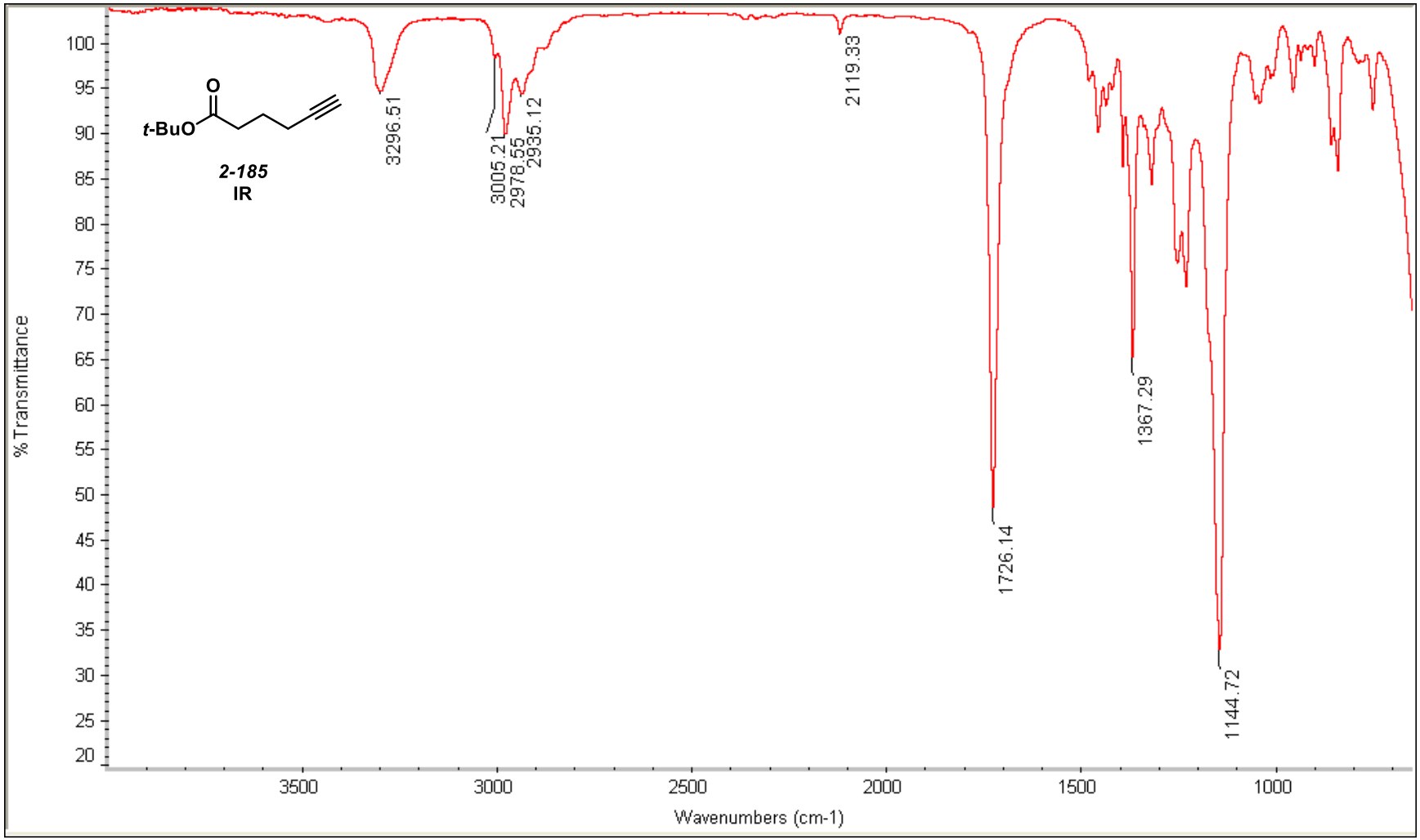

TMS
SnBu3
2-148
IR
% Transmittance
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
2955.39
2924.30
1245.38
955.27
851.84
763.17

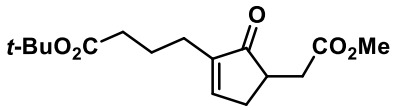


2-185
^{1}H NMR
($CDCl_3$, 400 MHz)

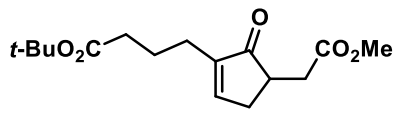


2-185
^{13}C NMR
($CDCl_3$, 101 MHz)

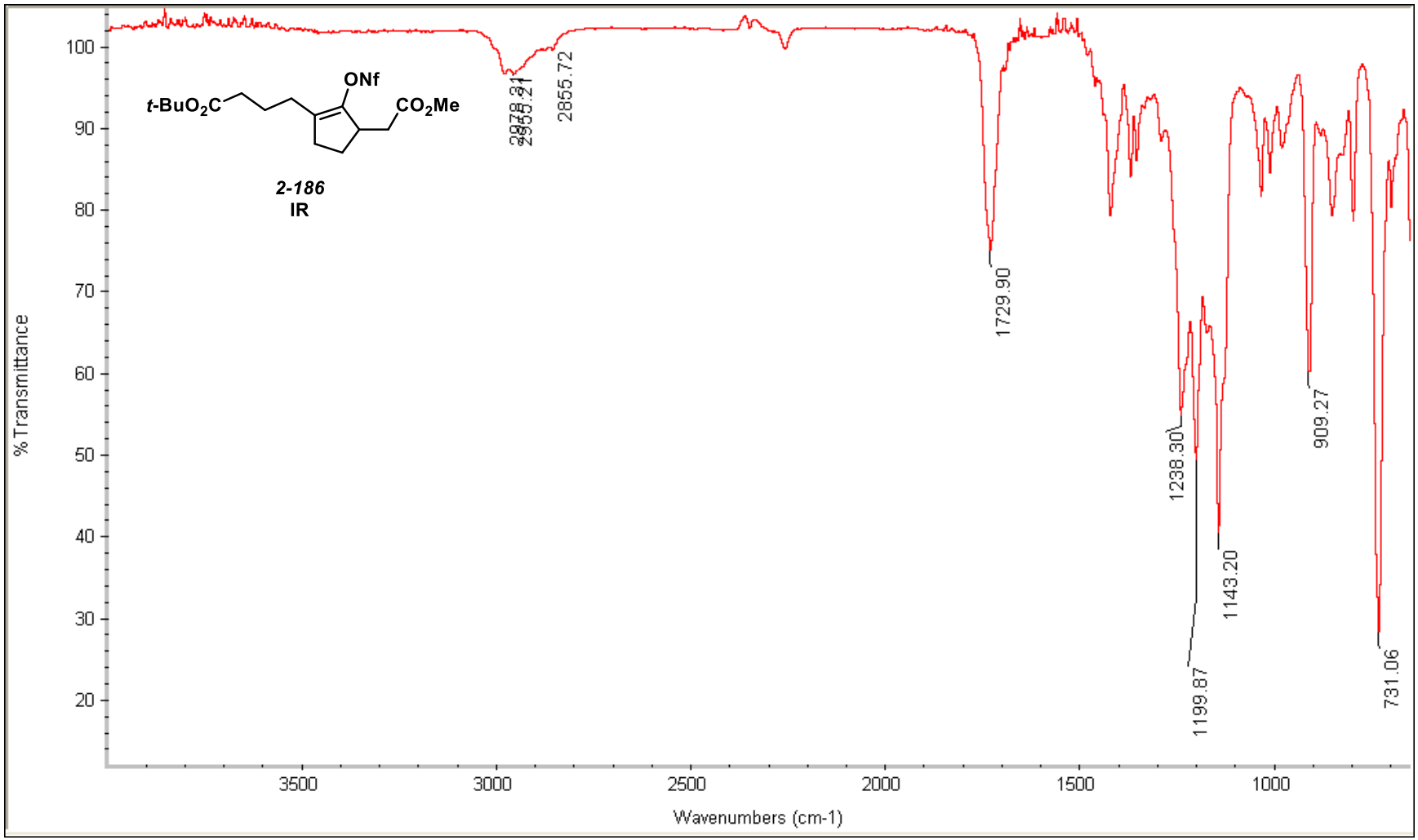

t-BuO
O
2-185
IR
3296.51
3005.21
2978.55
2935.12
2119.33
1726.14
1367.29
1144.72
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
3500
3000
2500
2000
1500
1000

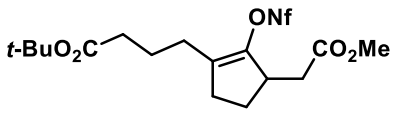


2-184
^{1}H NMR
($CDCl_3$, 400 MHz)

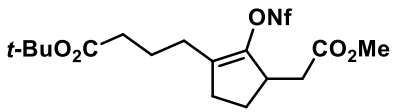


2-184
^{13}C NMR
($CDCl_3$, 101 MHz)

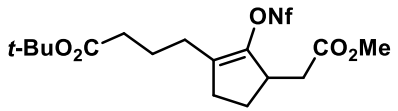

ONf
t-BuO2C
CO2Me
2-186
IR
2978.31
2955.21
2855.72
1729.90
1238.30
1199.87
1143.20
909.27
731.06
% Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
3500
3000
2500
2000
1500
1000



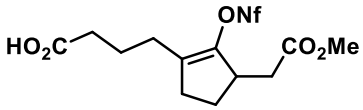
2-186
^{1}H NMR
($CDCl_3$, 400 MHz)



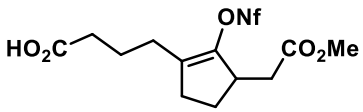
2-186
^{13}C NMR
($CDCl_3$, 101 MHz)



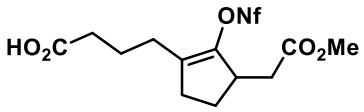
2-186
^{19}F NMR
($CDCl_3$, 376 MHz)



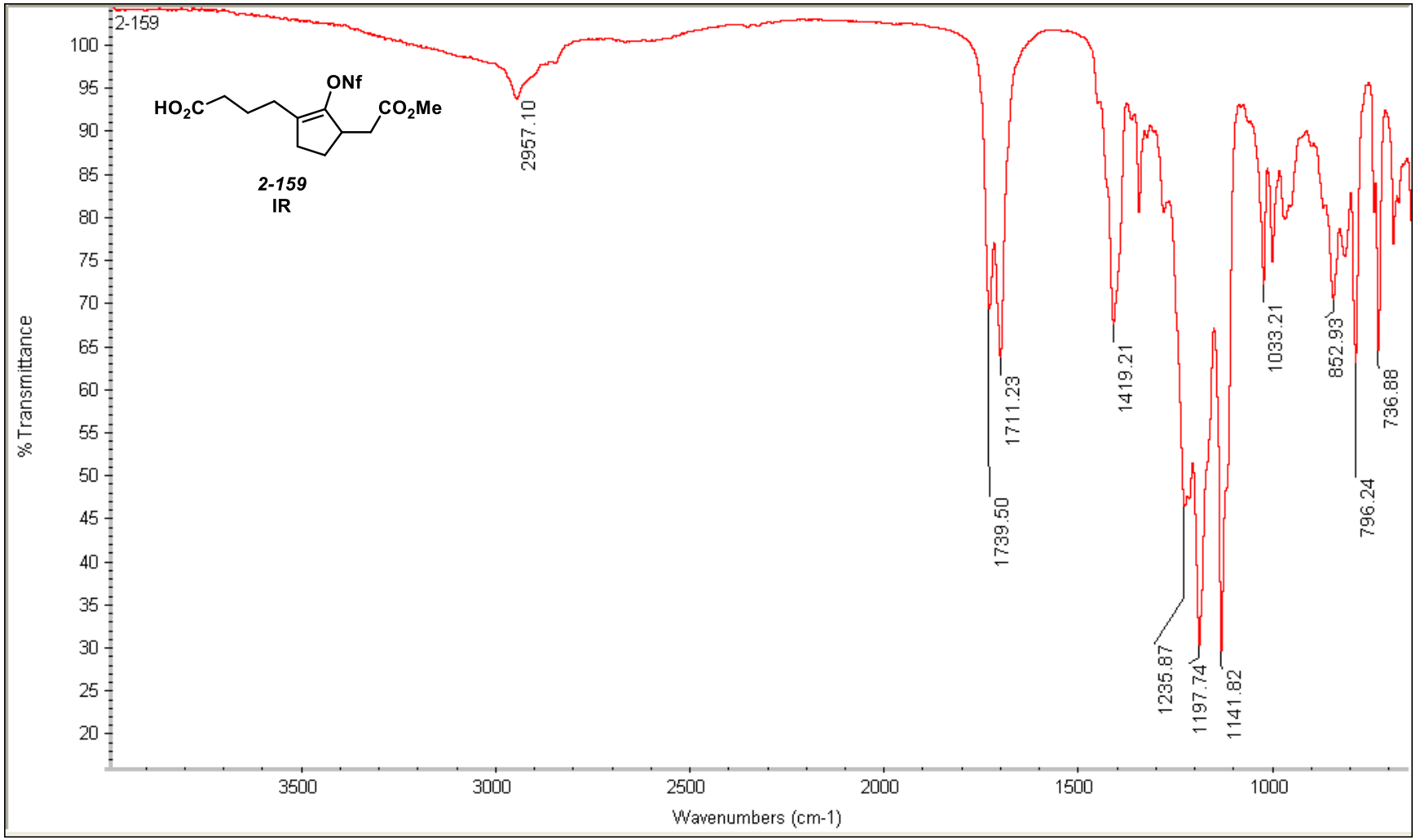
2-159
^{1}H NMR
($CDCl_3$, 400 MHz)

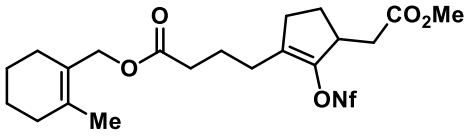


2-159
^{13}C NMR
($CDCl_3$, 101 MHz)

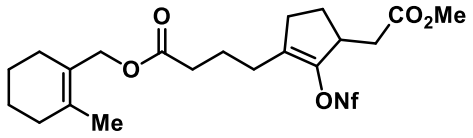


2-159
^{19}F NMR
($CDCl_3$, 376 MHz)

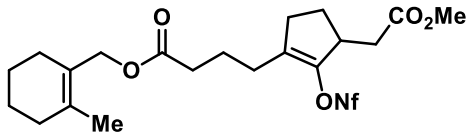

2-159
ONf
HO2C
CO2Me
2-159
IR
% Transmittance
Wavenumbers (cm-1)
2957.10
1739.50
1711.23
1419.21
1235.87
1197.74
1141.82
1033.21
852.93
796.24
736.88



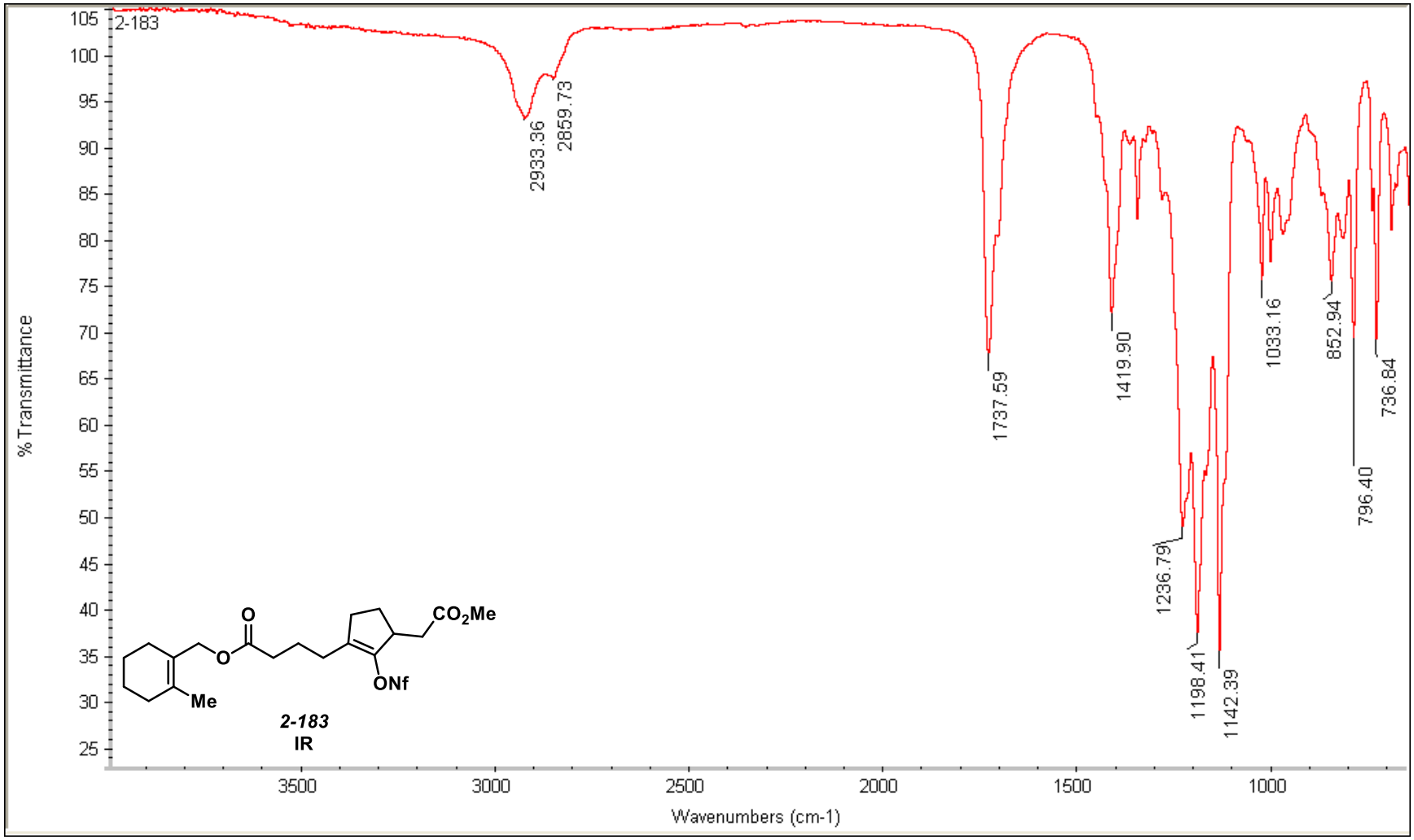
2-183
^{1}H NMR
($CDCl_3$, 400 MHz)

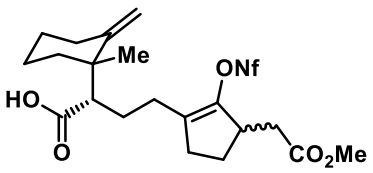


2-183
^{13}C NMR
($CDCl_3$, 101 MHz)

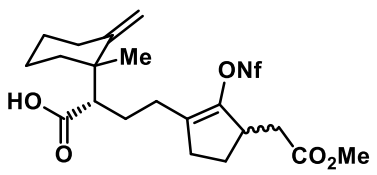


2-183
^{19}F NMR
($CDCl_3$, 376 MHz)

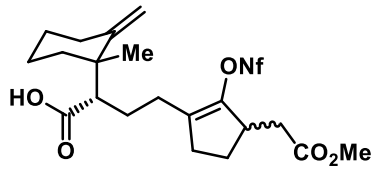

2-183
% Transmittance
Wavenumbers (cm-1)
2933.36
2859.73
1737.59
1419.90
1236.79
1198.41
1142.39
1033.16
852.94
796.40
736.84
O
O
CO2Me
ONf
Me
2-183
IR



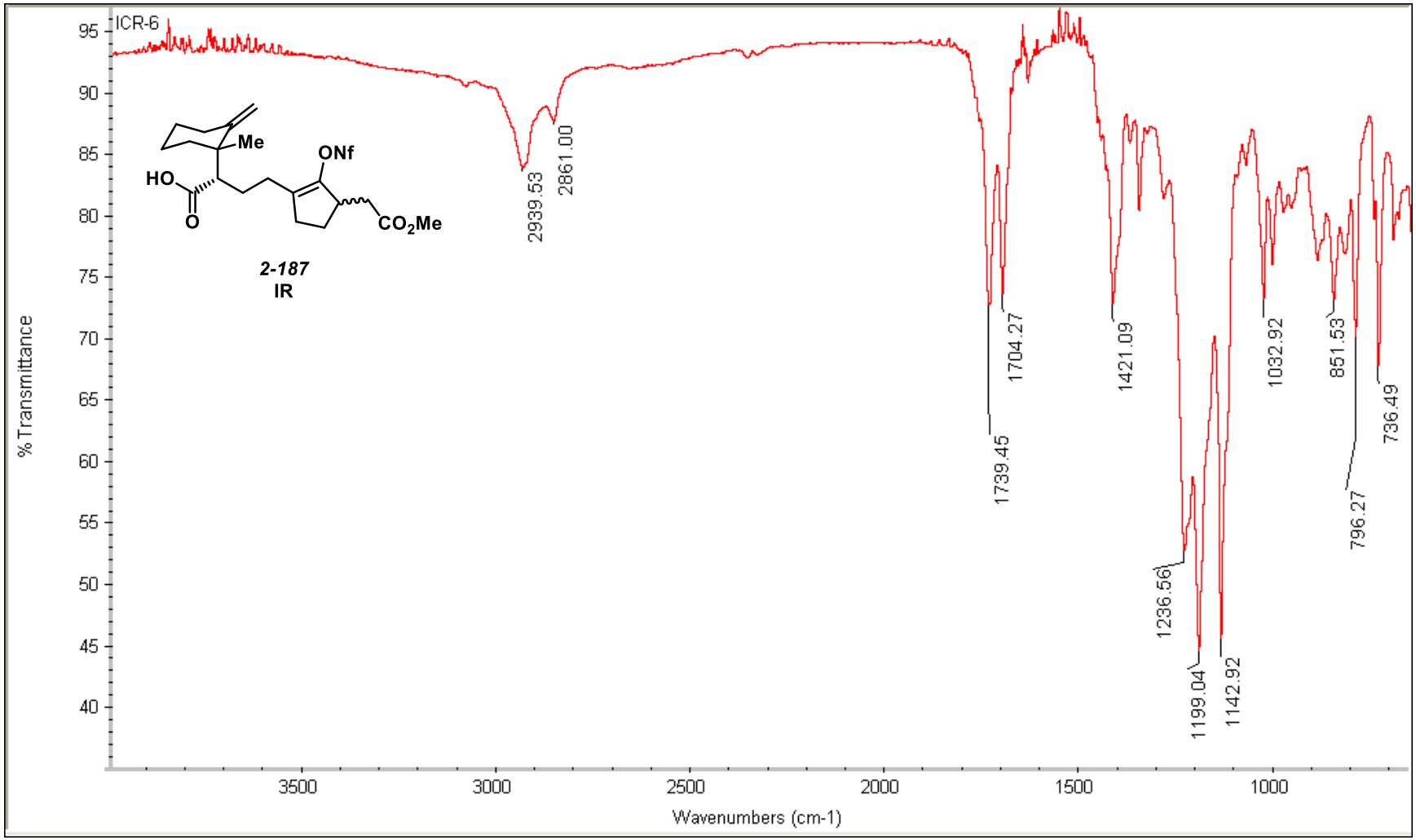
2-187
^{1}H NMR
($CDCl_3$, 400 MHz)

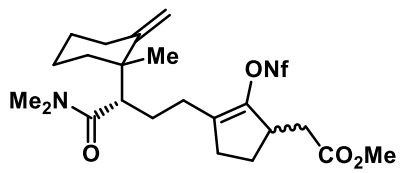


2-187
^{13}C NMR
($CDCl_3$, 101 MHz)

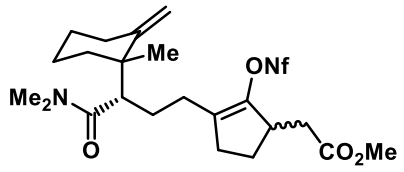


2-187
^{19}F NMR
($CDCl_3$, 376 MHz)

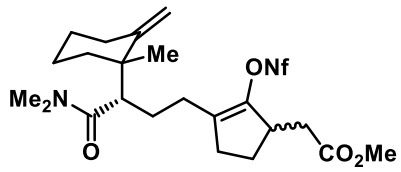

ICR-6
Me
ONf
HO
O
CO2Me
2-187
IR
% Transmittance
Wavenumbers (cm-1)
2939.53
2861.00
1739.45
1704.27
1421.09
1236.56
1199.04
1142.92
1032.92
851.53
796.27
736.49



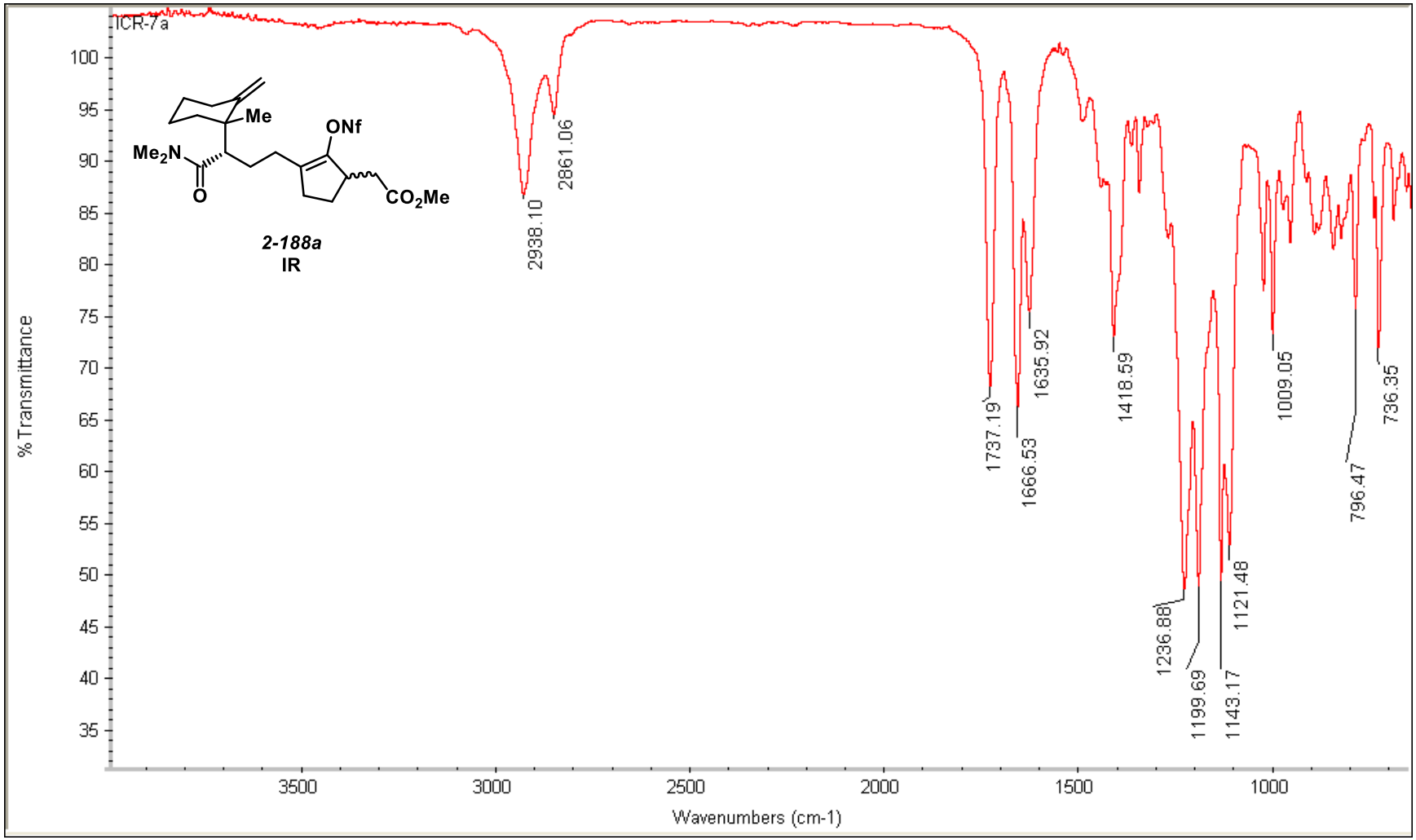
2-188a
^{1}H NMR
($CDCl_3$, 400 MHz)

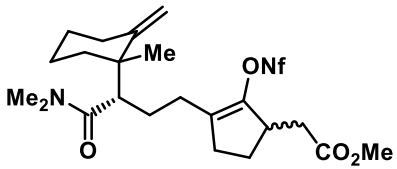


2-188a
^{13}C NMR
($CDCl_3$, 101 MHz)

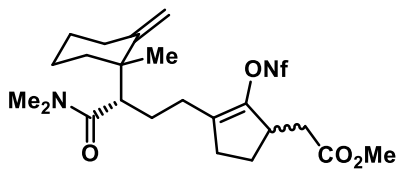


2-188a
^{19}F NMR
($CDCl_3$, 376 MHz)

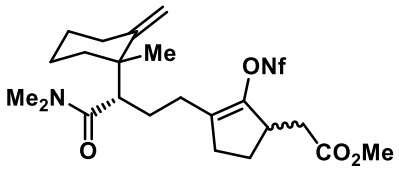

ICR-7a
Me
ONf
Me2N
O
CO2Me
2-188a
IR
2938.10
2861.06
1737.19
1666.53
1635.92
1418.59
1236.88
1199.69
1143.17
1121.48
1009.05
796.47
736.35
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
3500
3000
2500
2000
1500
1000



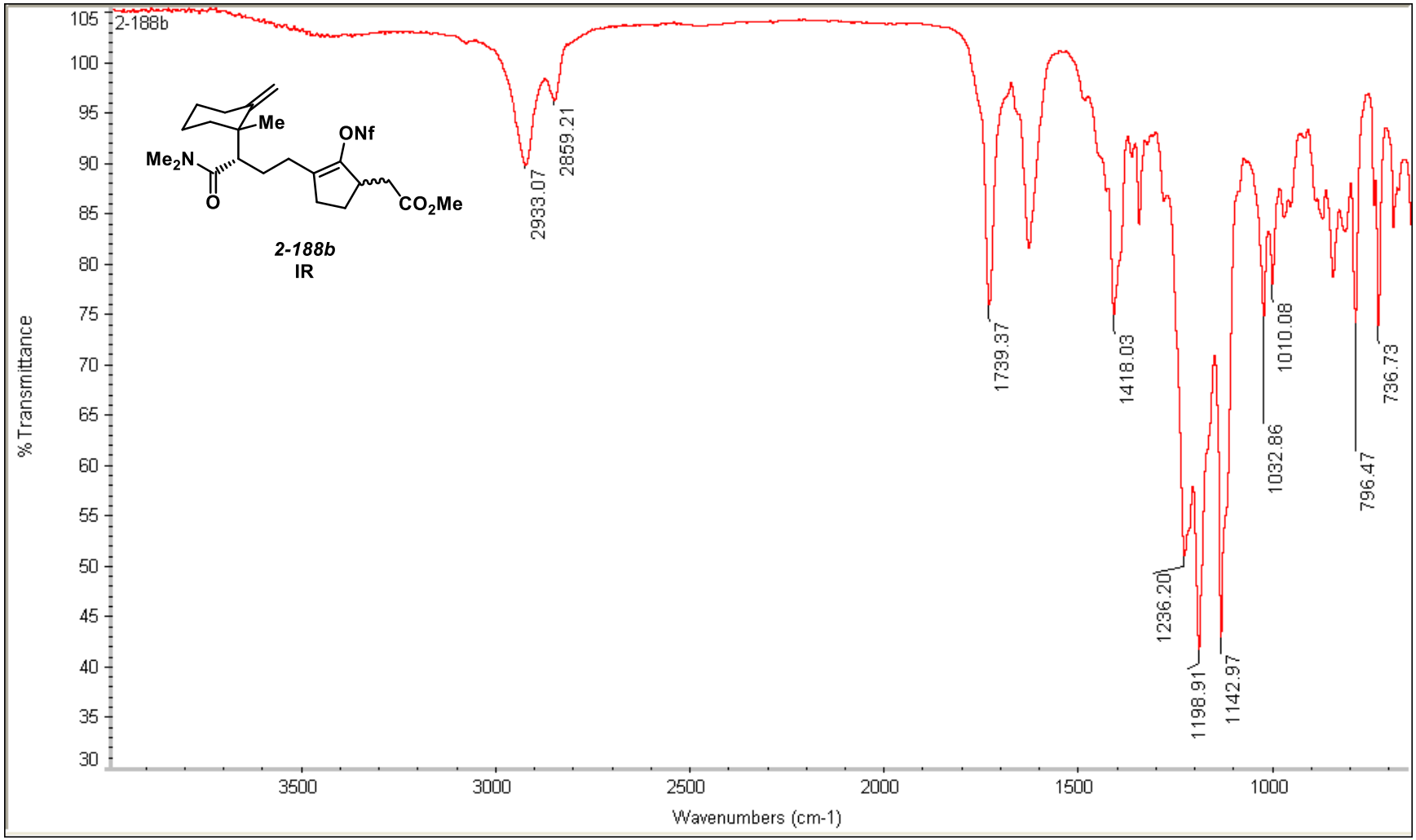
2-188b
^{1}H NMR
($CDCl_3$, 400 MHz)

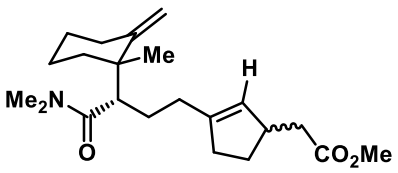


2-188b
^{13}C NMR
($CDCl_3$, 101 MHz)

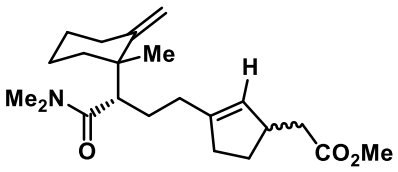


2-188b
^{19}F NMR
($CDCl_3$, 376 MHz)

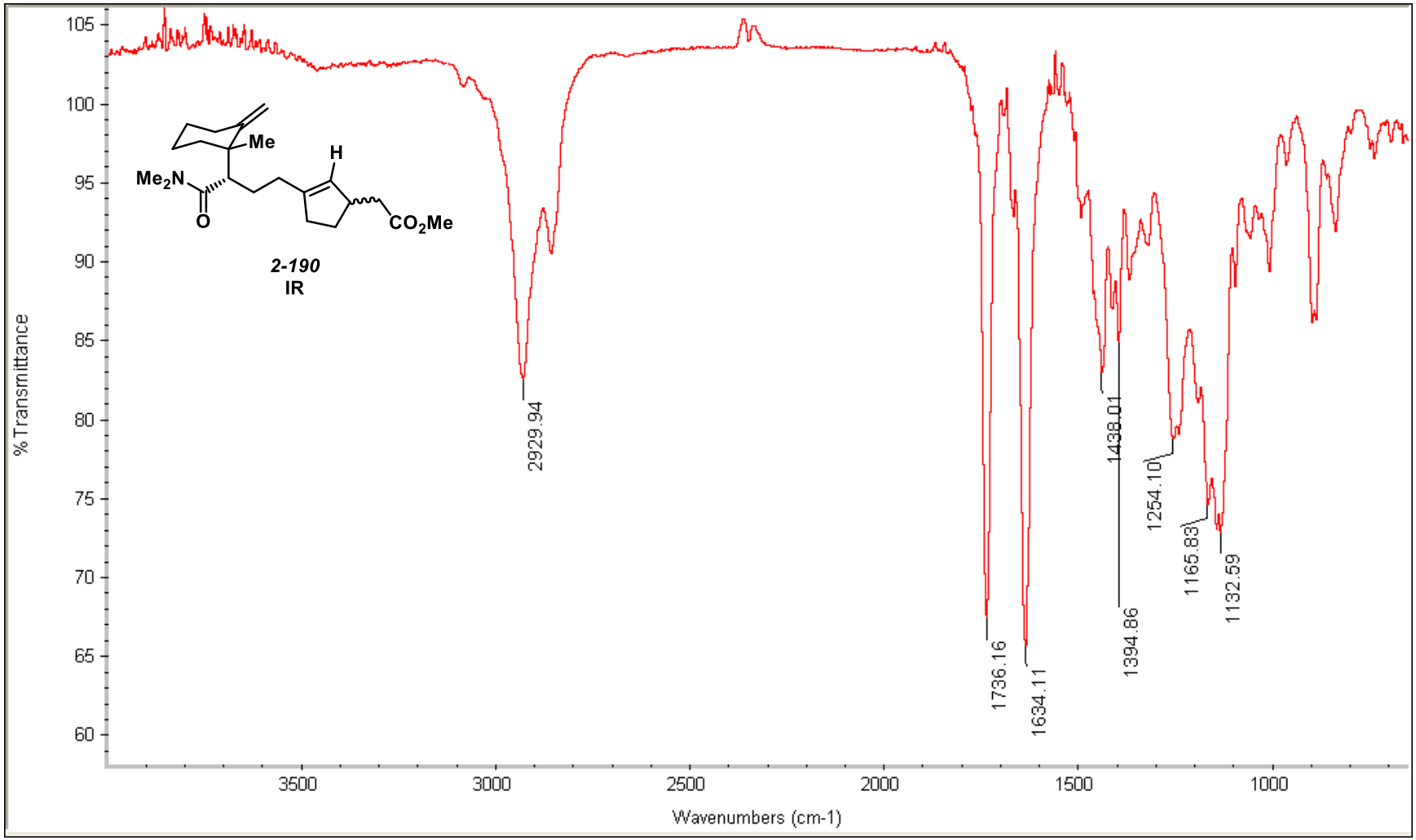

2-188b
Me
ONf
Me2N
O
CO2Me
2-188b
IR
2933.07
2859.21
1739.37
1418.03
1236.20
1198.91
1142.97
1032.86
1010.08
796.47
736.73
% Transmittance
Wavenumbers (cm-1)
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
3500
3000
2500
2000
1500
1000

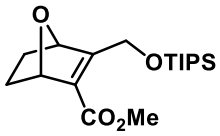


2-190
^{1}H NMR
($CDCl_3$, 400 MHz)

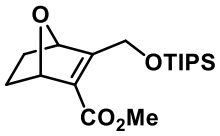


2-190
^{13}C NMR
($CDCl_3$, 101 MHz)

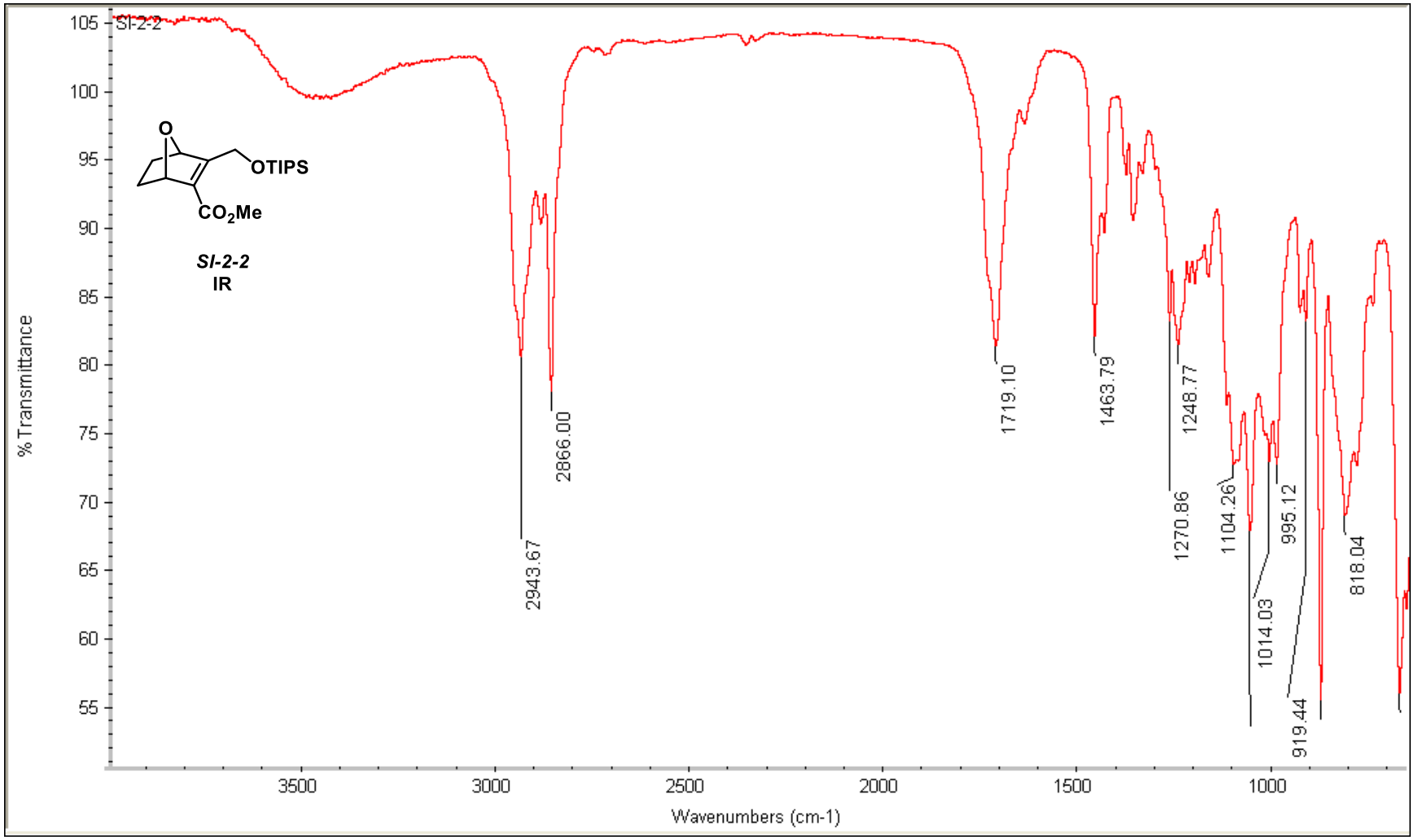

Me
H
Me2N
O
CO2Me
2-190
IR
% Transmittance
105
100
95
90
85
80
75
70
65
60
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
2929.94
1736.16
1634.11
1438.01
1394.86
1254.10
1165.83
1132.59



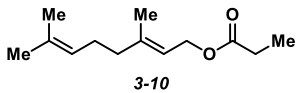
SI-2-2
^{1}H NMR
(400 MHz, $CDCl_3$)



SI-2-2
^{13}C NMR
(101 MHz, $CDCl_3$)


SI-2-2
O
OTIPS
CO2Me
SI-2-2
IR
% Transmittance
Wavenumbers (cm-1)
2943.67
2866.00
1719.10
1463.79
1270.86
1248.77
1104.26
1014.03
995.12
919.44
818.04

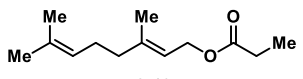
Appendix Five: Spectra Relevant to Chapter Three.



3-10

^{1}H NMR

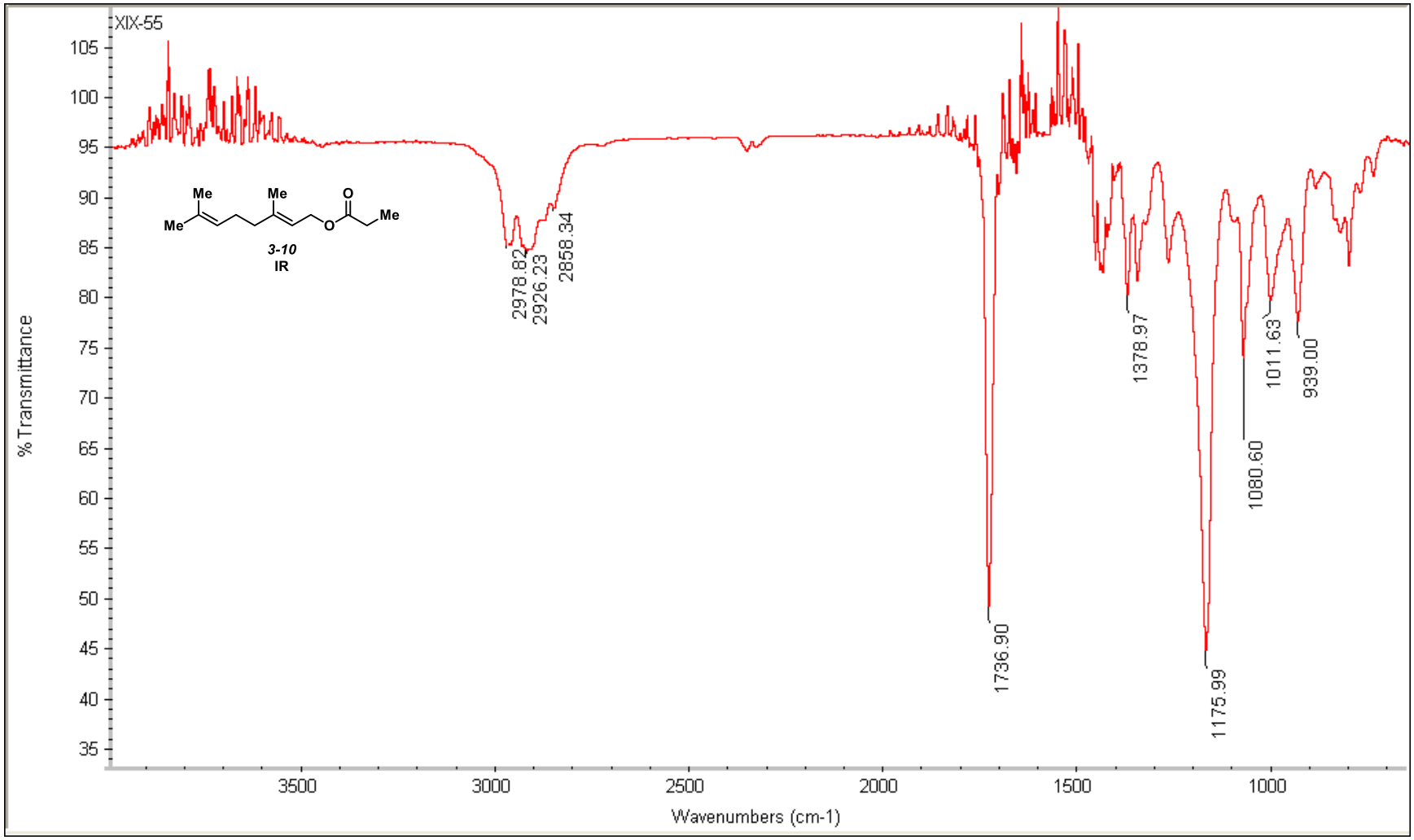
(400 MHz, $CDCl_3$)

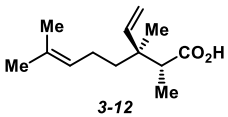


3-10

^{13}C NMR

(101 MHz, $CDCl_3$)

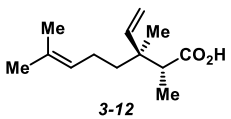

XIX-55
% Transmittance
Wavenumbers (cm-1)
3-10
IR
2978.82
2926.23
2858.34
1736.90
1378.97
1175.99
1080.60
1011.63
939.00



3-12

^{1}H NMR

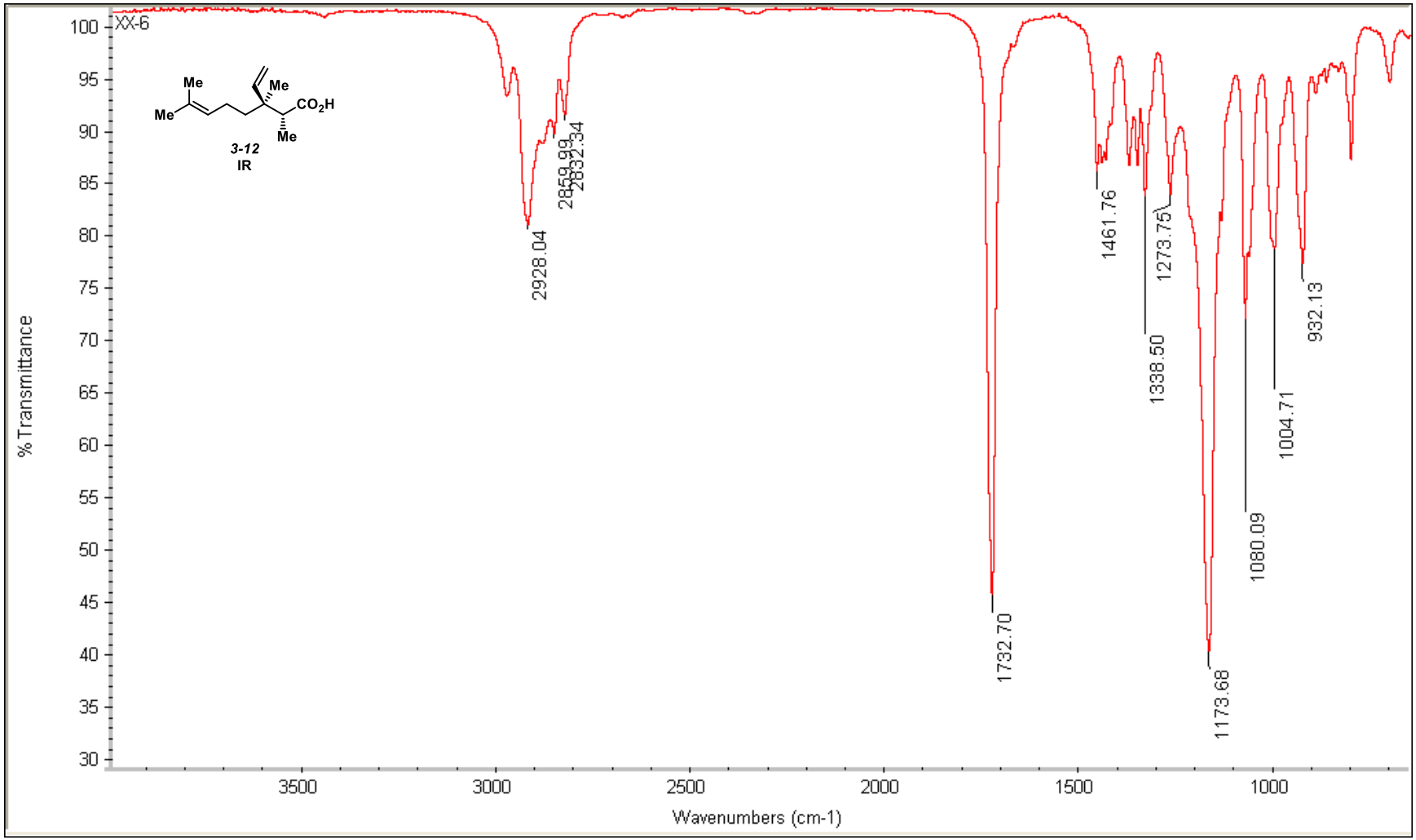
(400 MHz, $CDCl_3$)

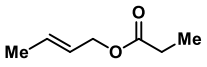


3-12

^{13}C NMR

(101 MHz, $CDCl_3$)

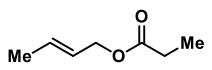

XX-6
Me
Me
Me
CO2H
Me
3-12
IR
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
2928.04
2859.99
2832.34
1732.70
1461.76
1338.50
1273.75
1173.68
1080.09
1004.71
932.13
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



3-7

^{1}H NMR

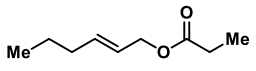
(400 MHz, $CDCl_3$)



3-7

^{13}C NMR

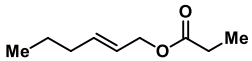
(101 MHz, $CDCl_3$)



3-13

^{1}H NMR

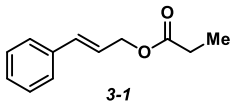
(400 MHz, $CDCl_3$)



3-13

^{13}C NMR

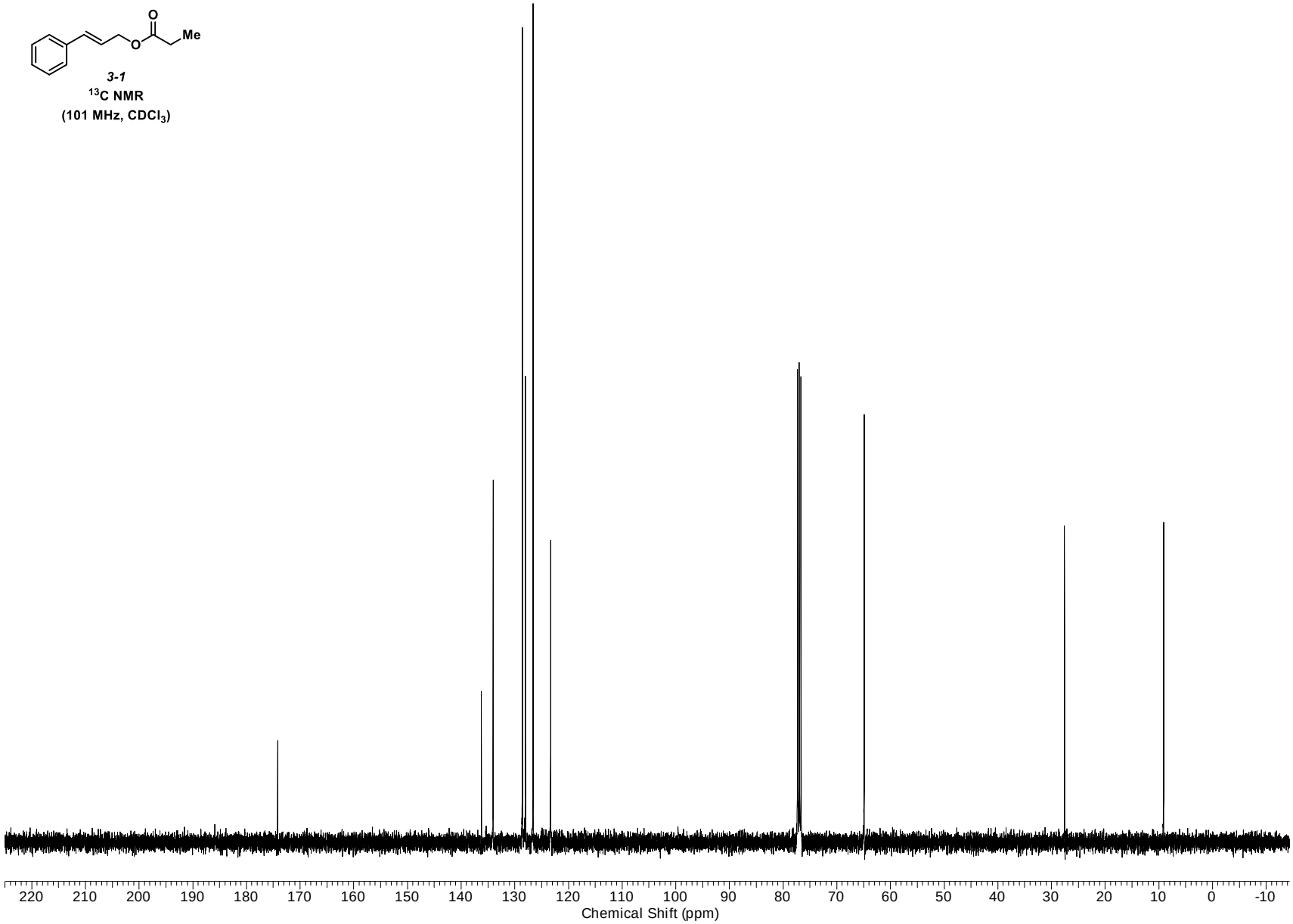
(101 MHz, $CDCl_3$)

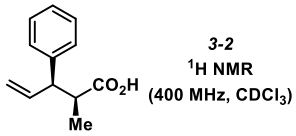


3-1

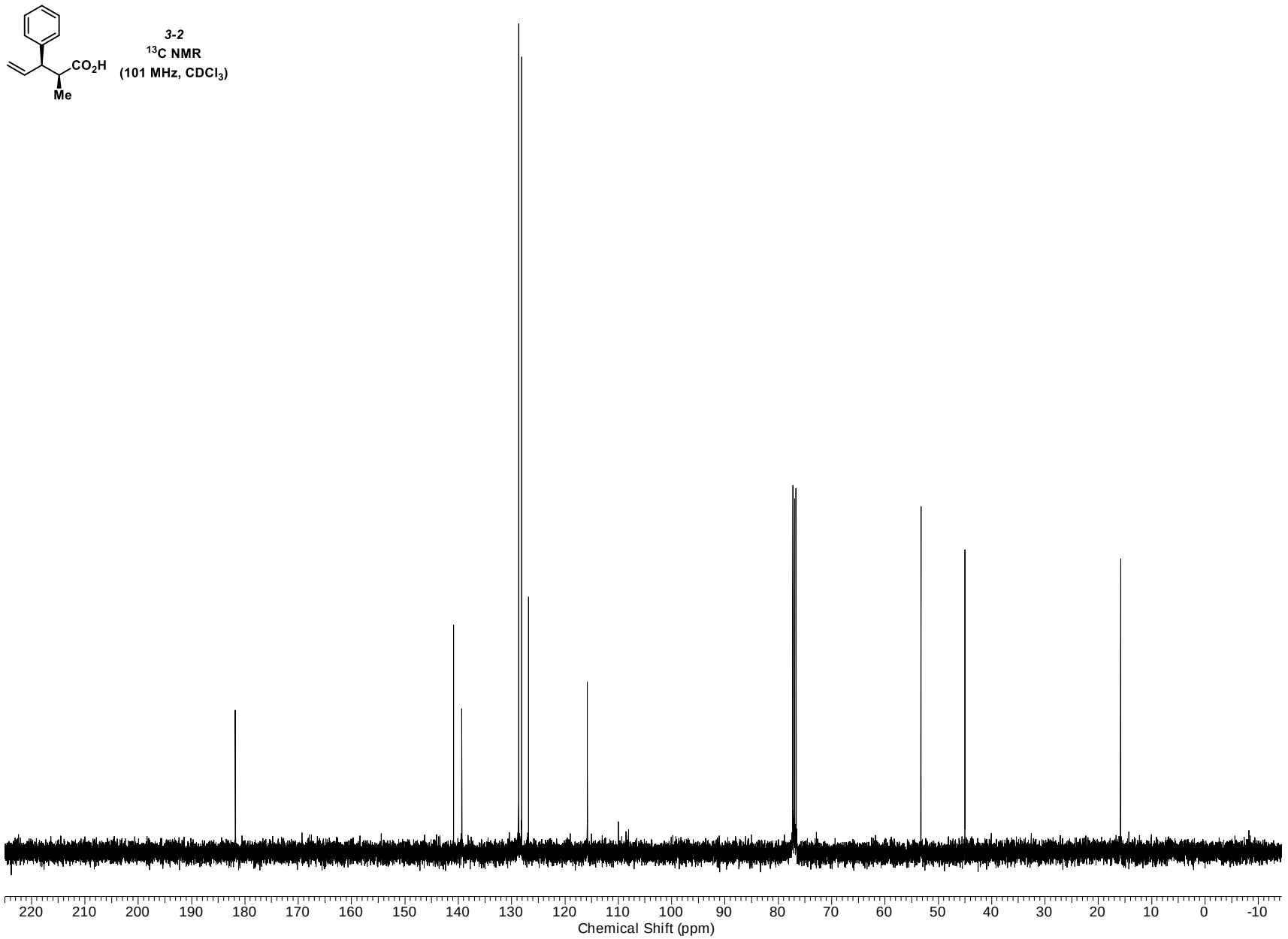
^{1}H NMR

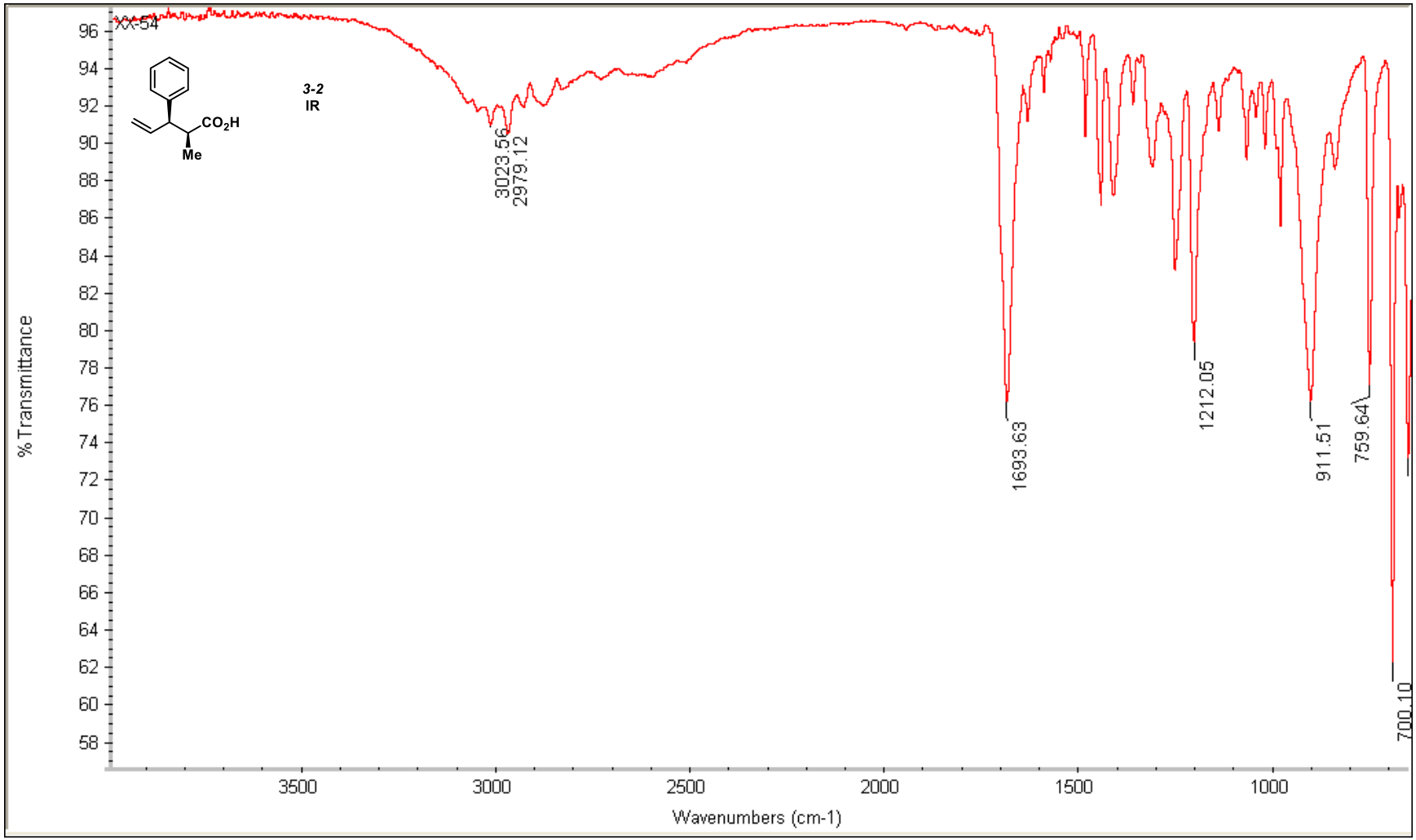
(400 MHz, $CDCl_3$)

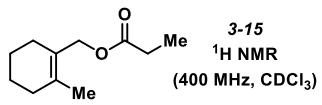

O
O
Me
3-1
13C NMR
(101 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



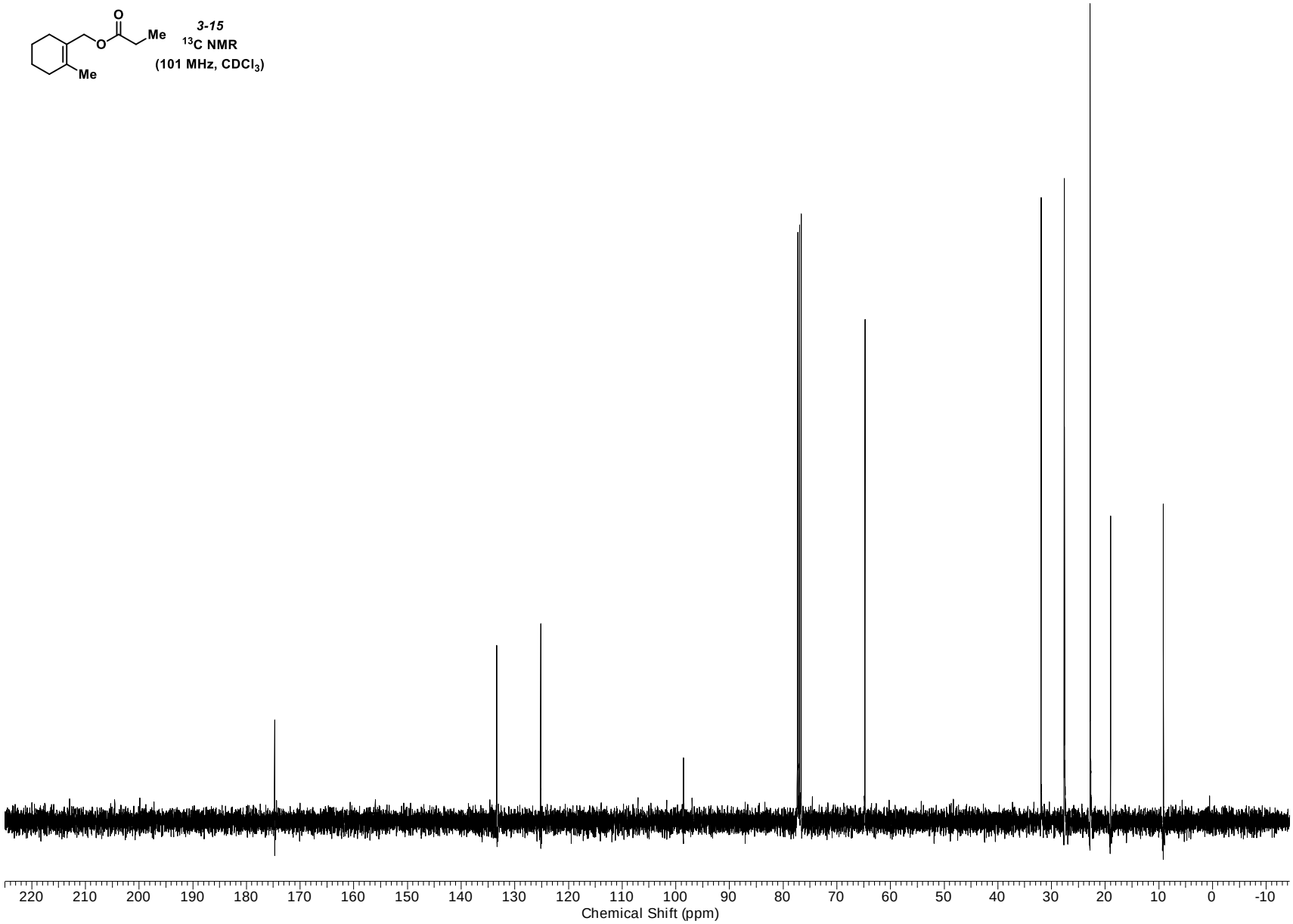
3-2
^{1}H NMR
(400 MHz, $CDCl_3$)

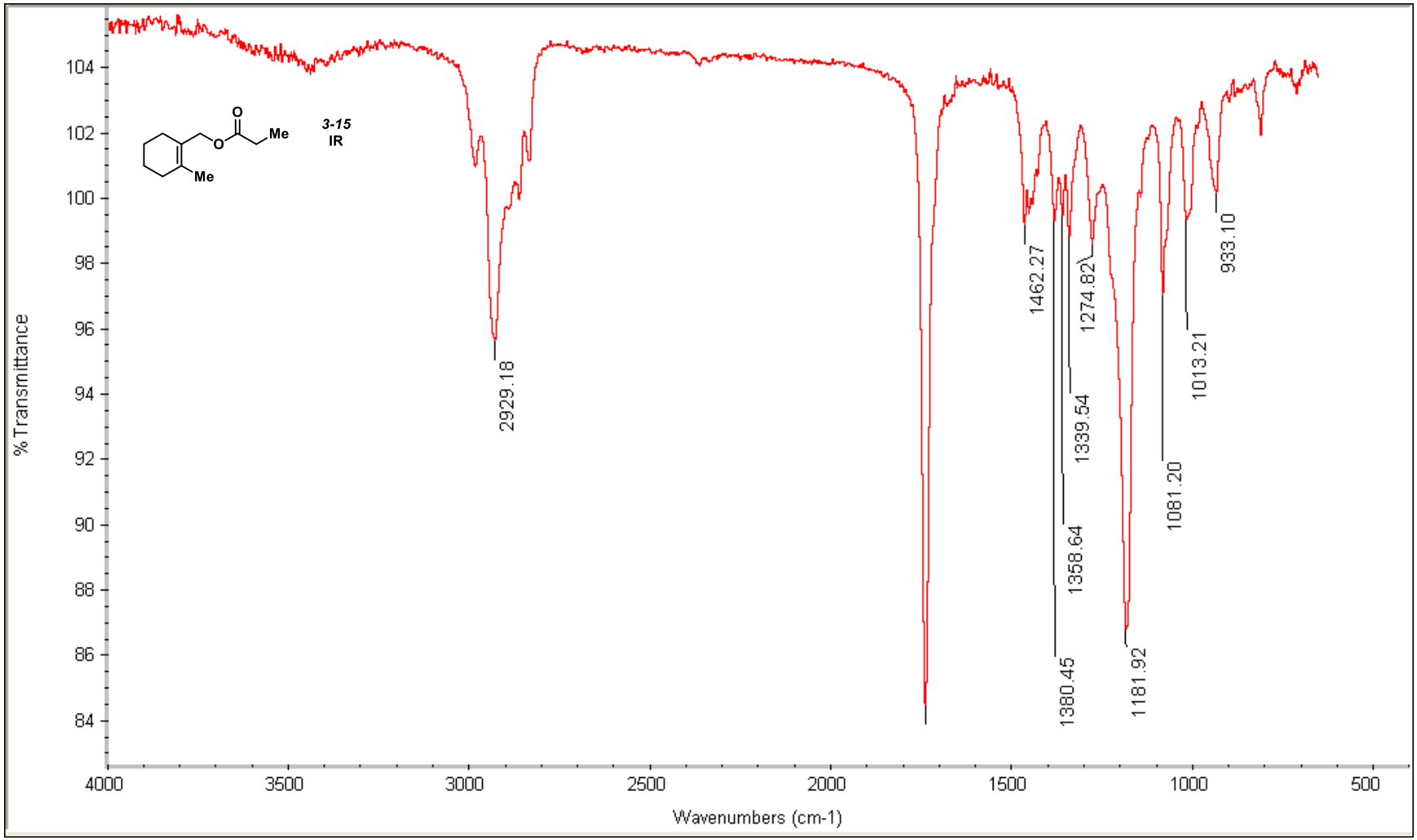

CO2H
Me
3-2
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

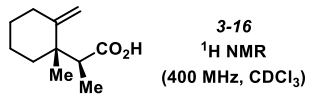

XX-54
3-2
IR
CO2H
Me
% Transmittance
Wavenumbers (cm-1)
3023.56
2979.12
1693.63
1212.05
911.51
759.64
700.10



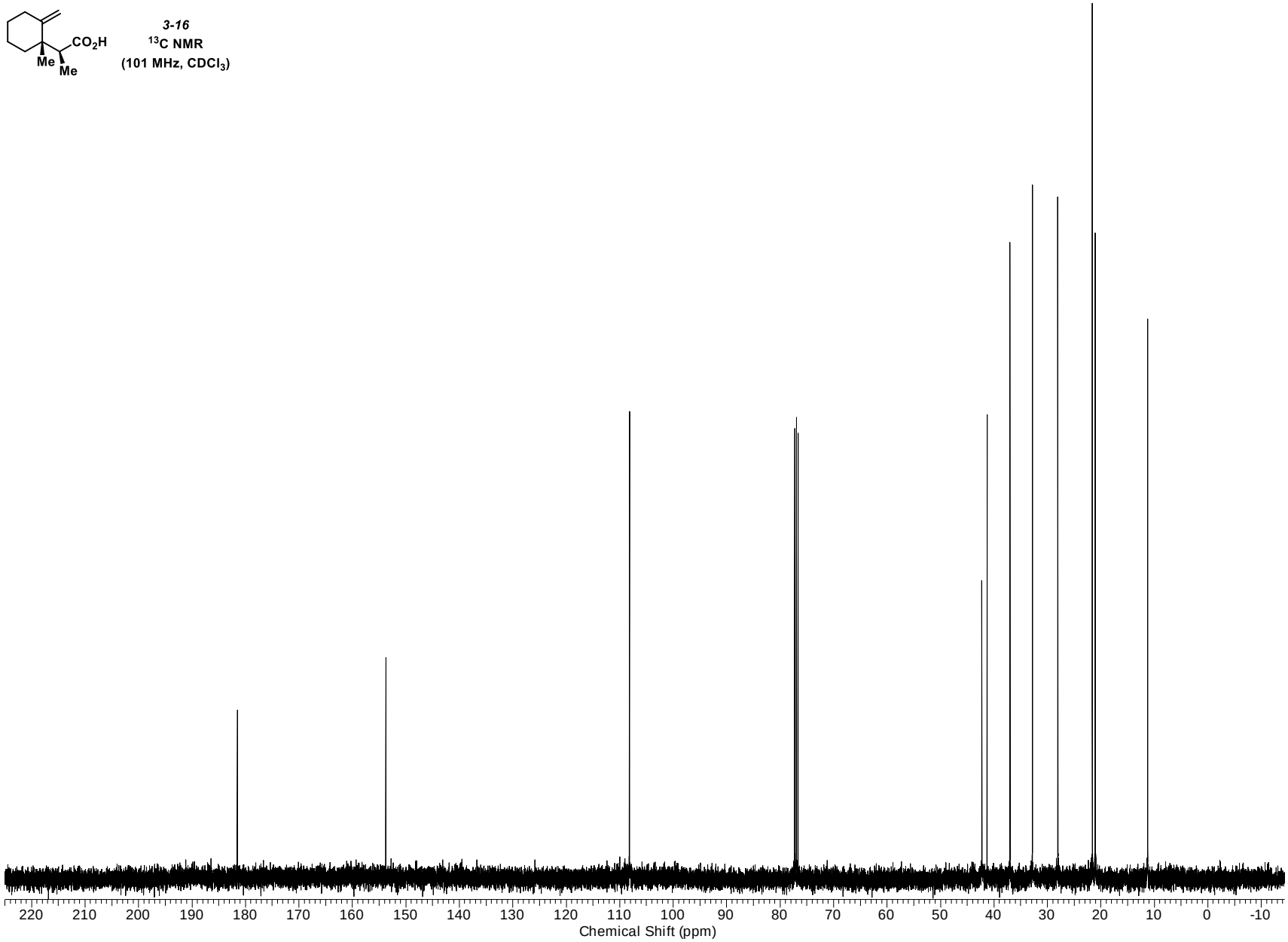
3-15
^{1}H NMR
(400 MHz, $CDCl_3$)

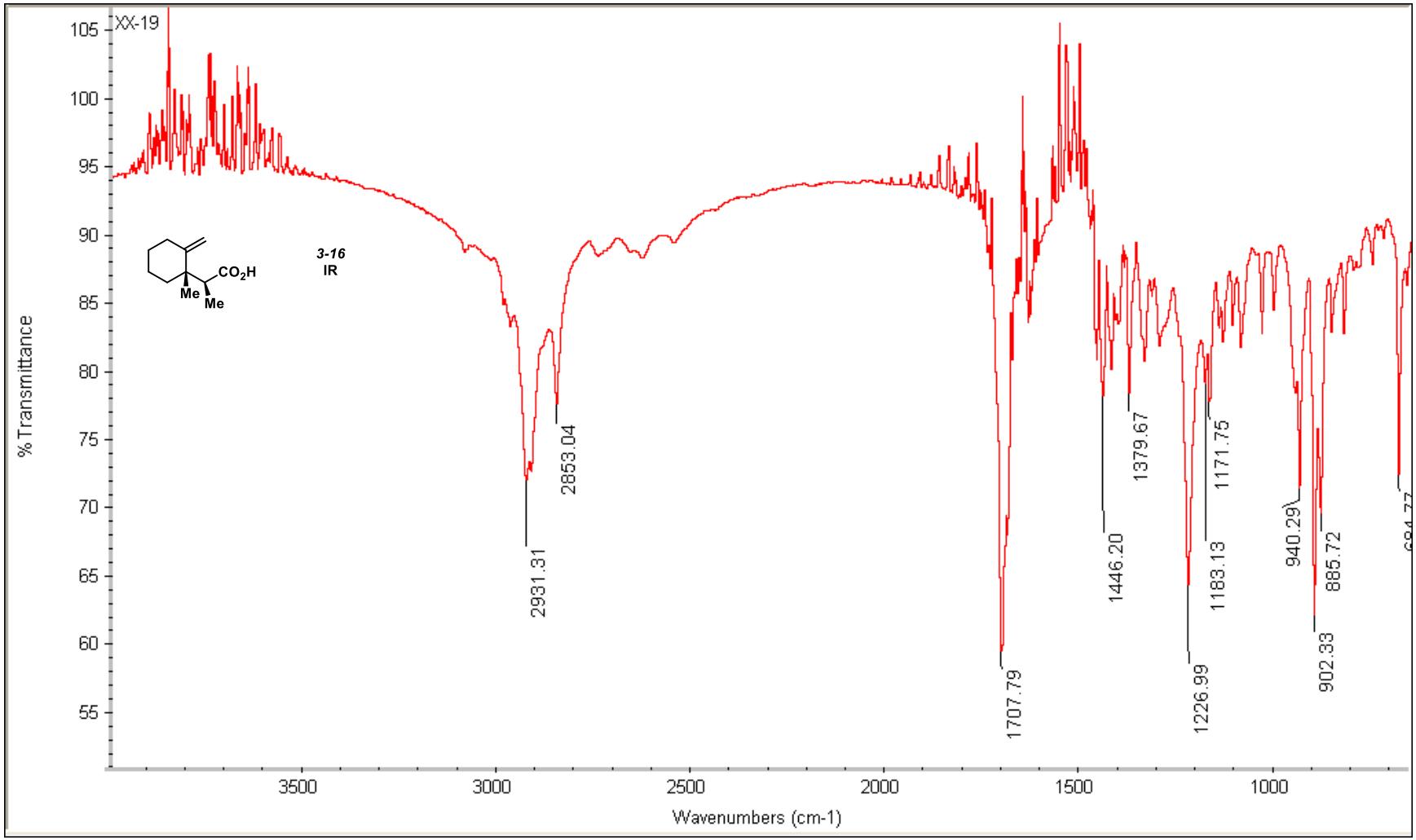

O
Me
O
Me
3-15
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

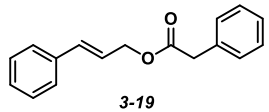

3-15
IR
Me
Me
O
O
% Transmittance
104
102
100
98
96
94
92
90
88
86
84
2929.18
1462.27
1380.45
1358.64
1339.54
1274.82
1181.92
1081.20
1013.21
933.10
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)



3-16
^{1}H NMR
(400 MHz, $CDCl_3$)


CO2H
Me
Me
3-16
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

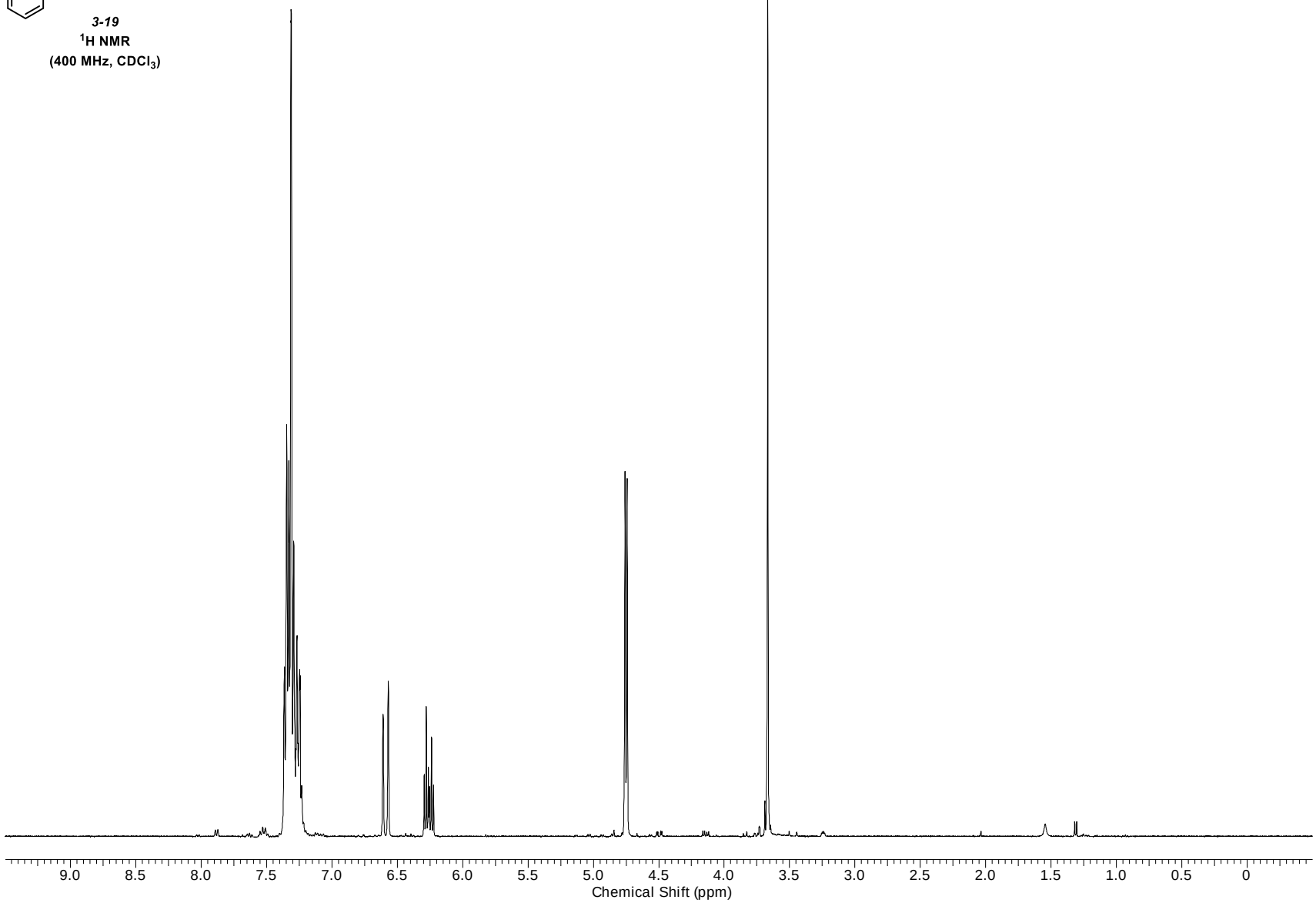

XX-19
3-16
IR
CO2H
Me
Me
% Transmittance
105
100
95
90
85
80
75
70
65
60
55
2931.31
2853.04
1707.79
1446.20
1379.67
1226.99
1183.13
1171.75
940.29
902.33
885.72
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

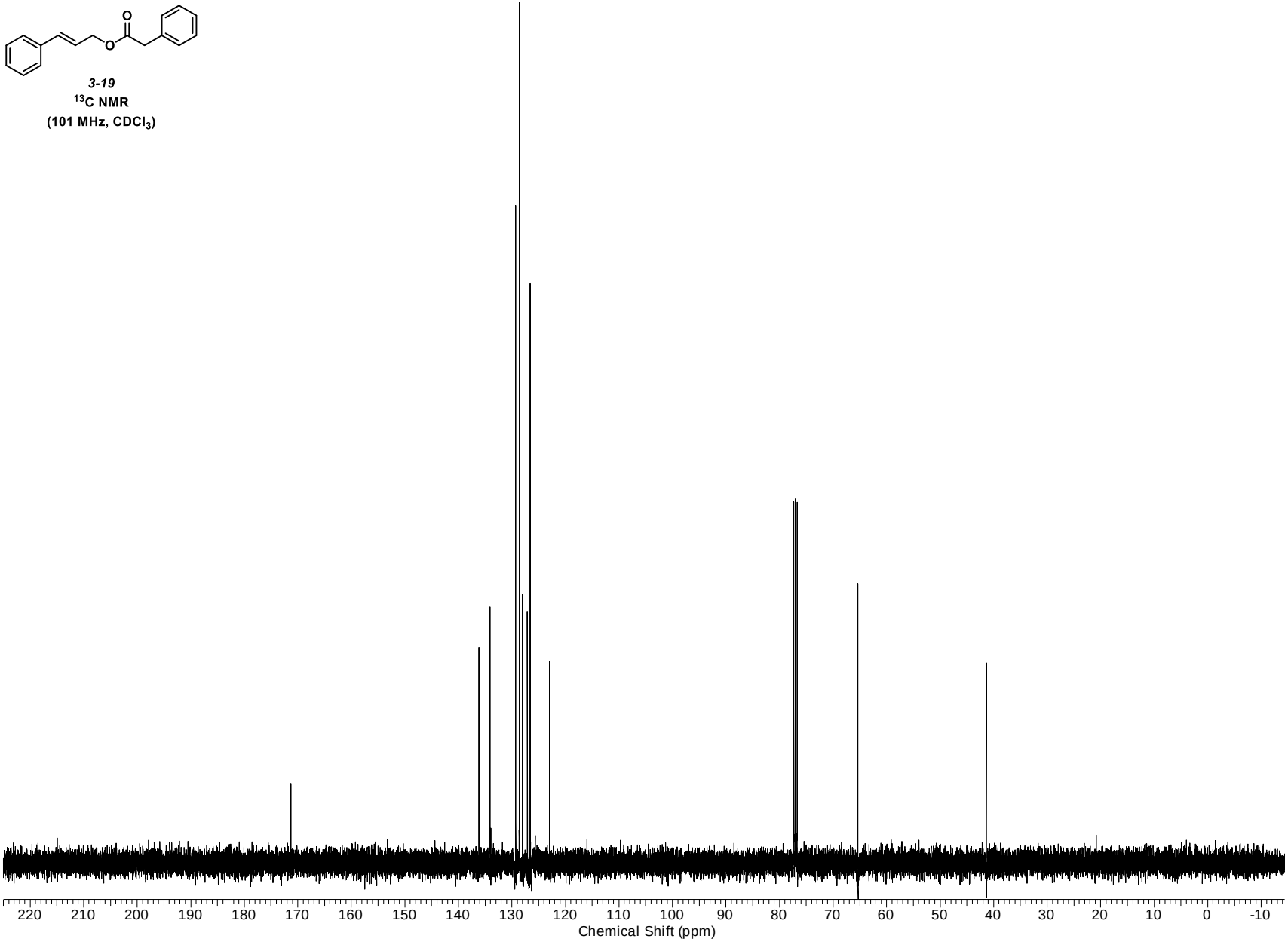


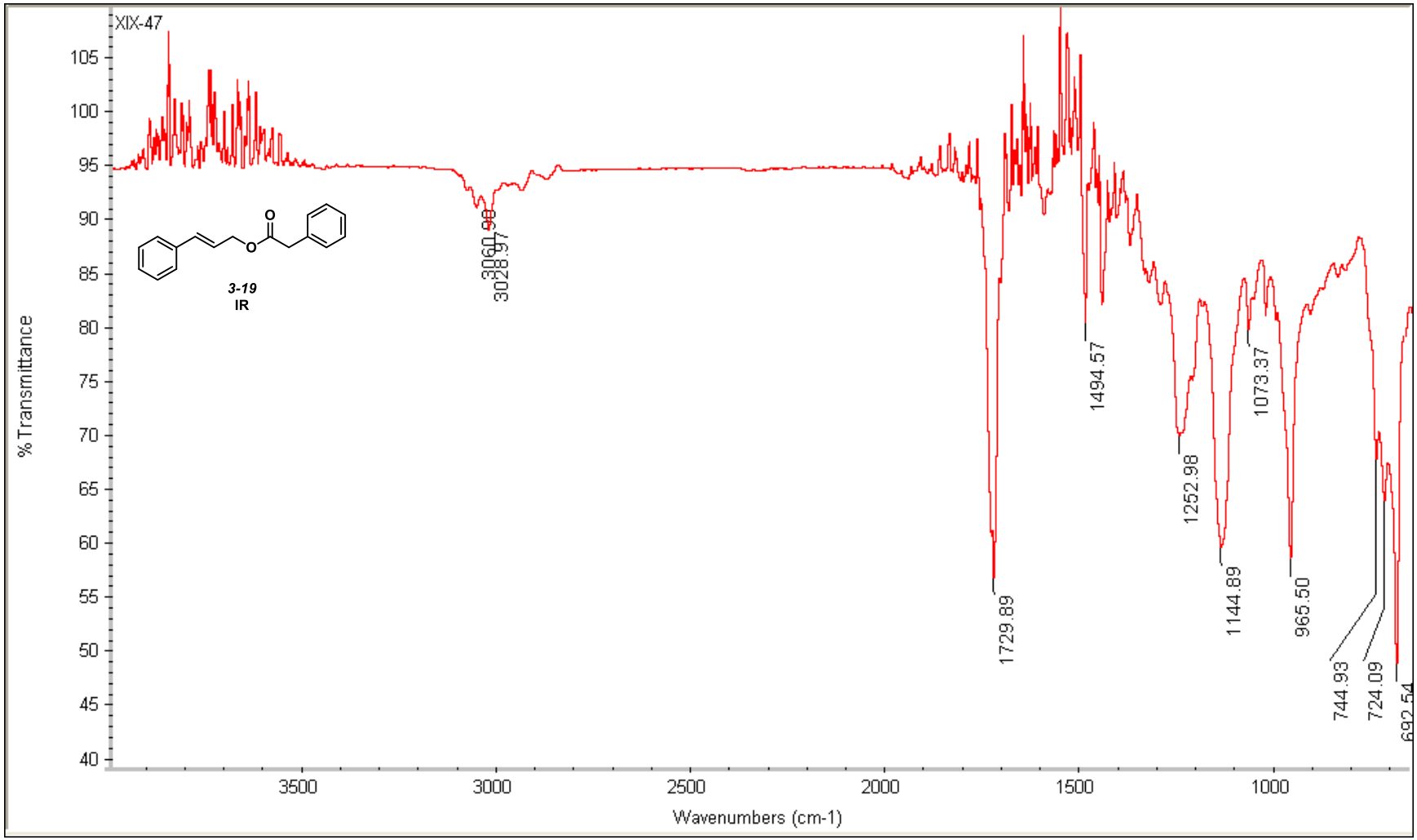
3-19

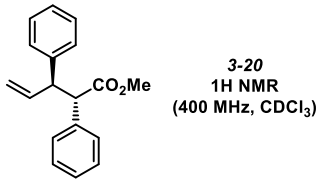
^{1}H NMR

(400 MHz, $CDCl_3$)

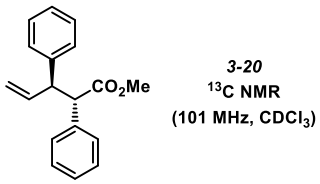



O
O
3-19
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

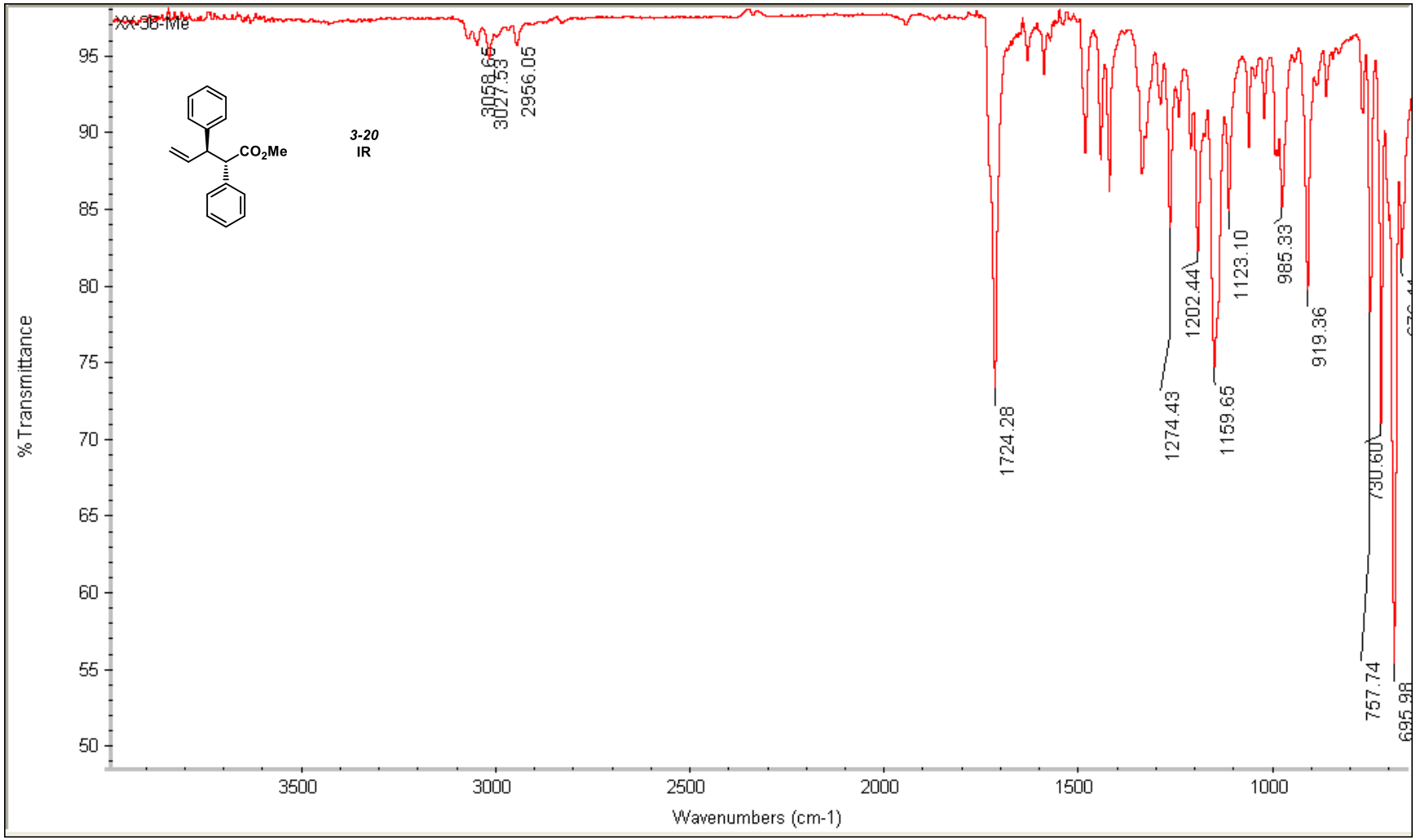

XIX-47
3-19
IR
% Transmittance
Wavenumbers (cm-1)
3060.98
3028.97
1729.89
1494.57
1252.98
1144.89
1073.37
965.50
744.93
724.09
692.54

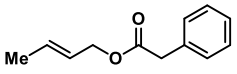


3-20
1H NMR
(400 MHz, $CDCl_3$)



3-20
^{13}C NMR
(101 MHz, $CDCl_3$)

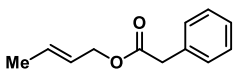

xx-38-Me
3-20
IR
CO2Me
3058.66
3027.53
2956.05
1724.28
1274.43
1202.44
1159.65
1123.10
985.33
919.36
757.74
730.60
695.98
% Transmittance
Wavenumbers (cm-1)
95
90
85
80
75
70
65
60
55
50
3500
3000
2500
2000
1500
1000



3-21

^{1}H NMR

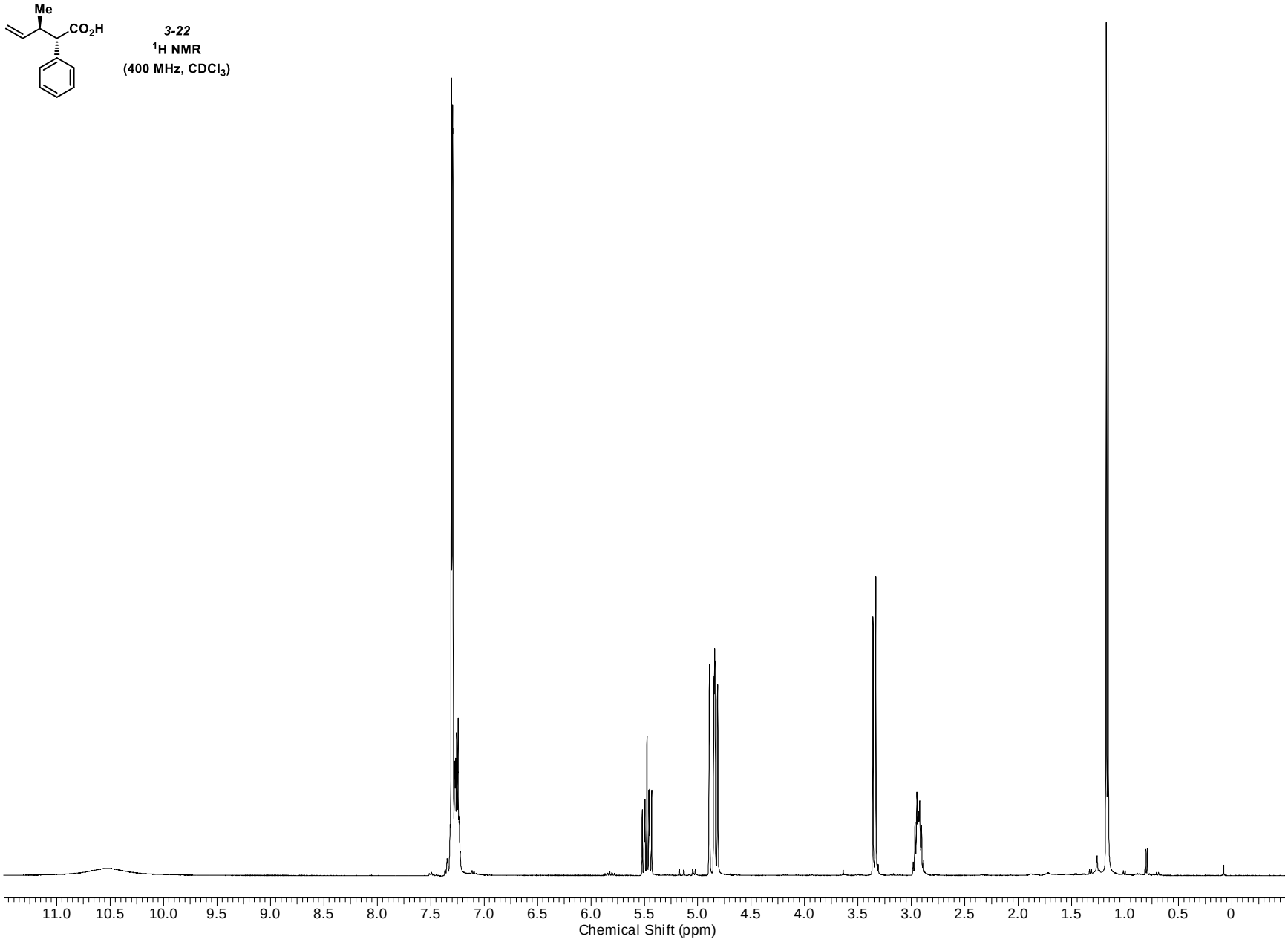
(400 MHz, $CDCl_3$)

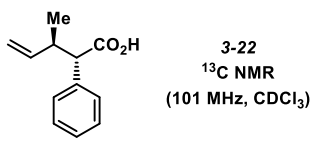


3-21

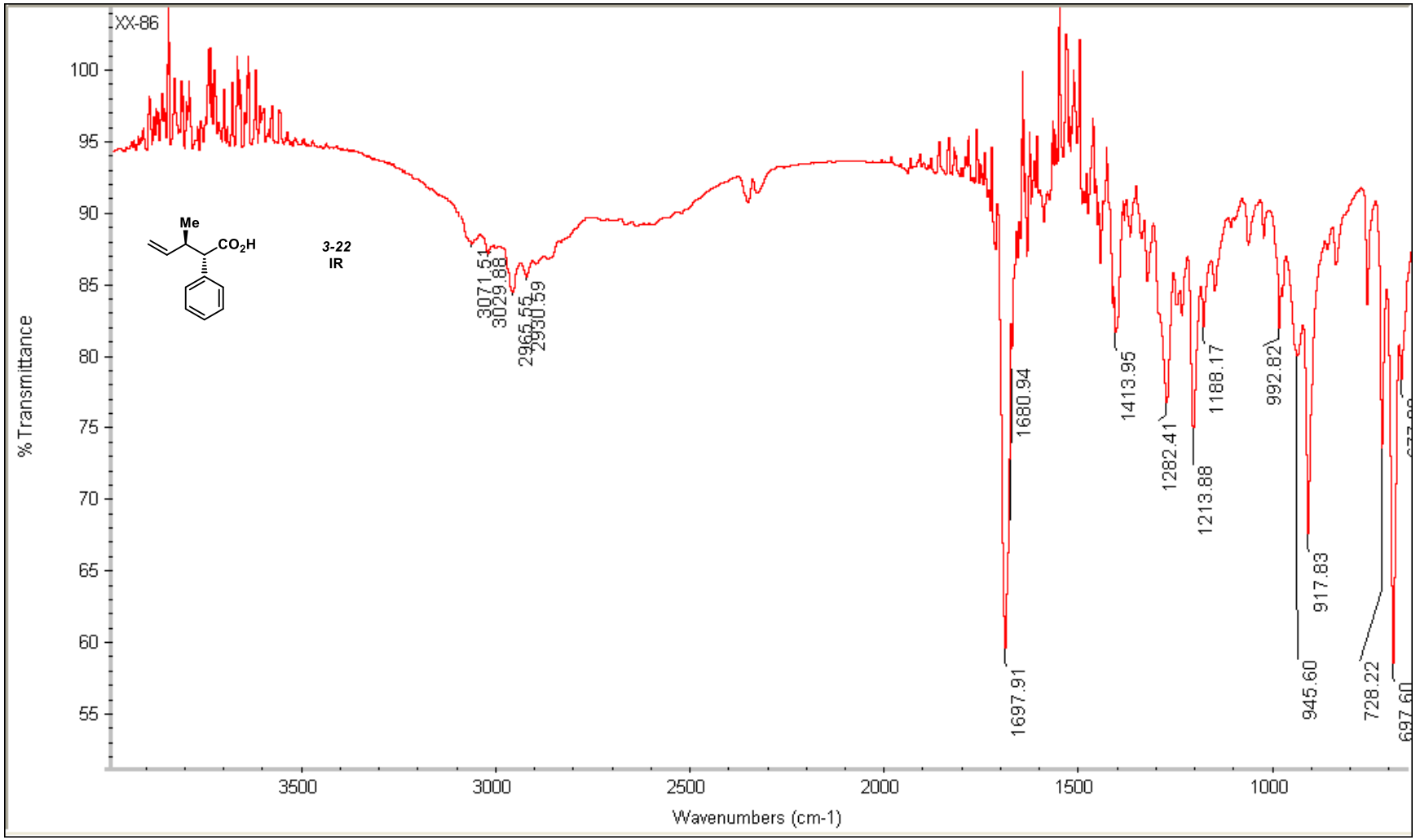
^{13}C NMR

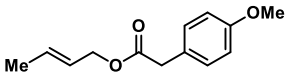
(101 MHz, $CDCl_3$)


Me
CO2H
3-22
1H NMR
(400 MHz, CDCl3)
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)



3-22
^{13}C NMR
(101 MHz, $CDCl_3$)

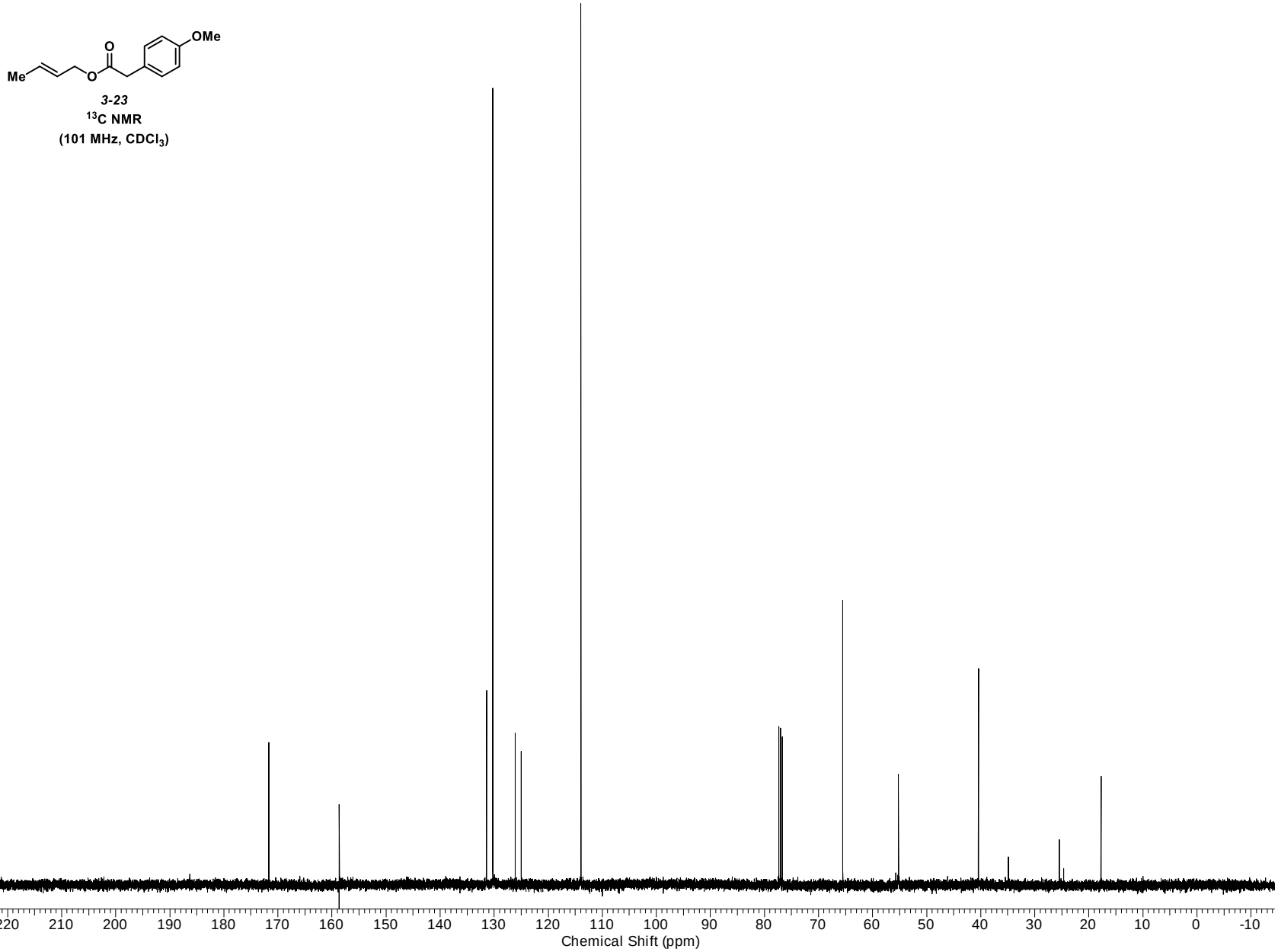

XX-86
Me
CO2H
3-22
IR
% Transmittance
Wavenumbers (cm-1)
3071.51
3029.88
2965.55
2930.59
1697.91
1680.94
1413.95
1282.41
1213.88
1188.17
992.82
945.60
917.83
728.22
697.60

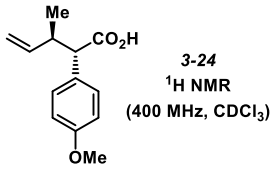


3-23

^{1}H NMR

(400 MHz, $CDCl_3$)

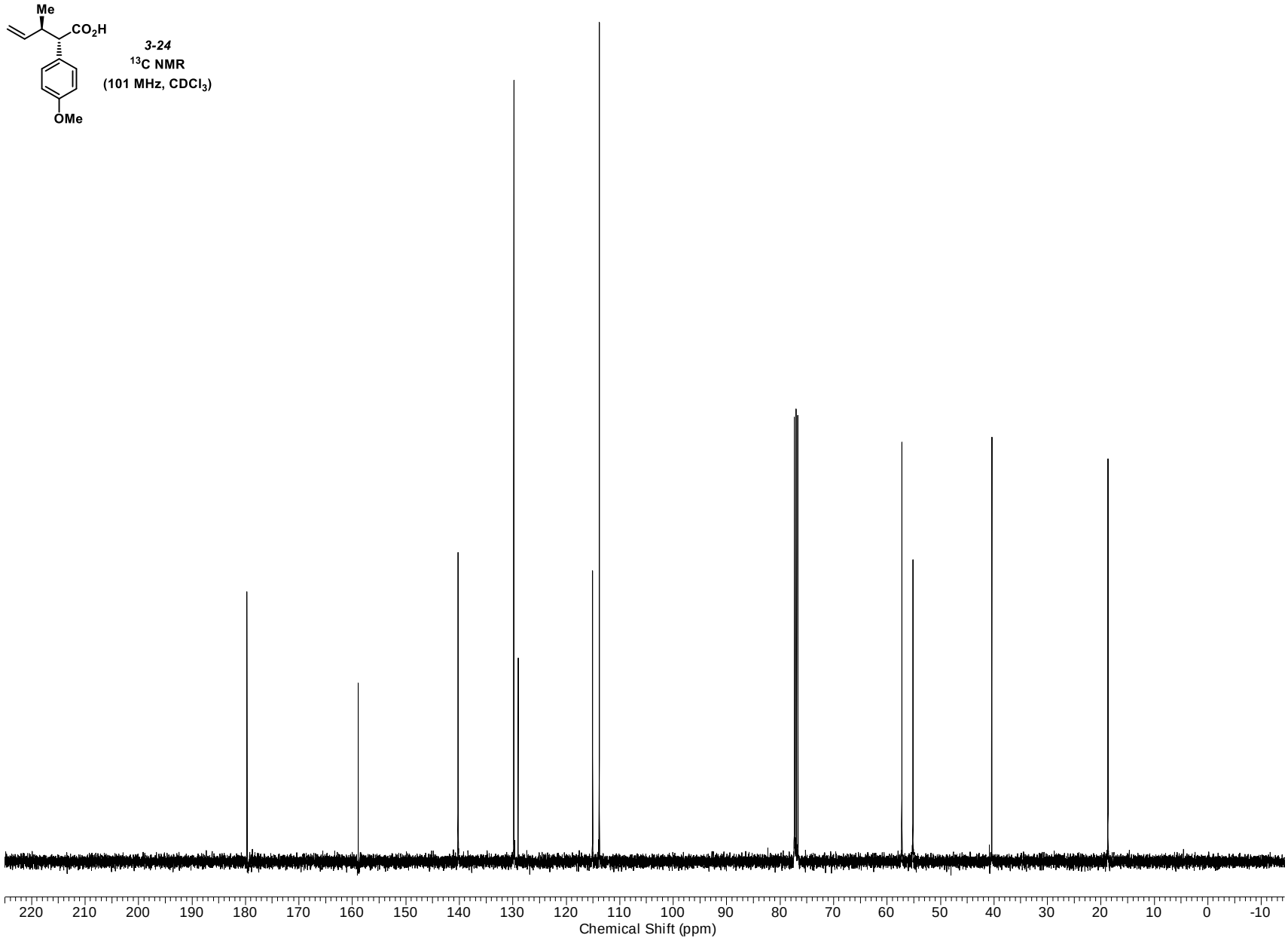

OMe
O
Me
O
3-23
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

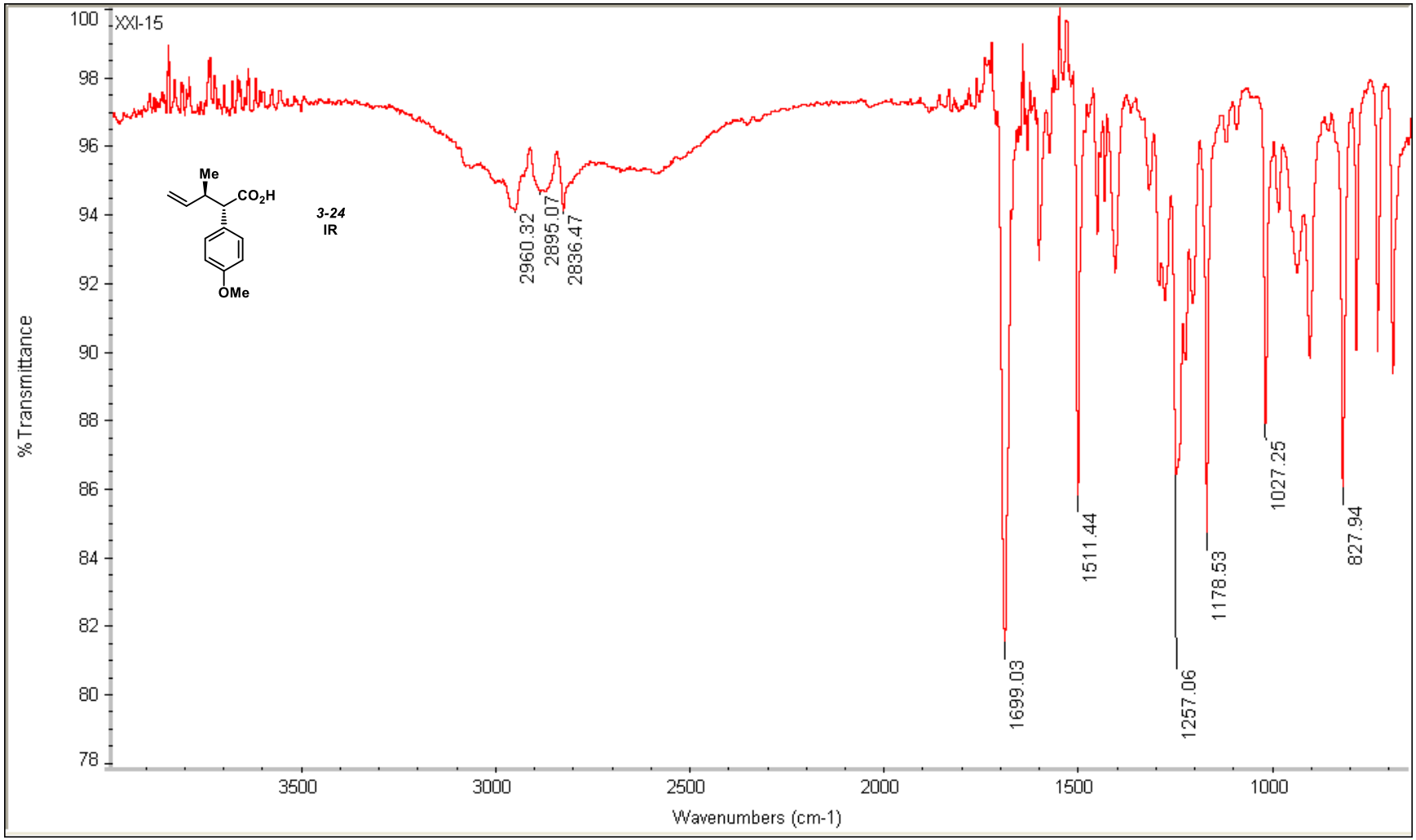


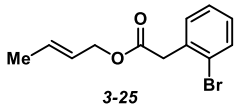
3-24

^{1}H NMR

(400 MHz, $CDCl_3$)


Me
CO2H
OMe
3-24
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

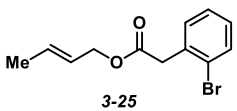

XXI-15
Me
CO2H
OMe
3-24
IR
2960.32
2895.07
2836.47
1699.03
1511.44
1257.06
1178.53
1027.25
827.94
% Transmittance
Wavenumbers (cm-1)
100
98
96
94
92
90
88
86
84
82
80
78
3500
3000
2500
2000
1500
1000



3-25

^{1}H NMR

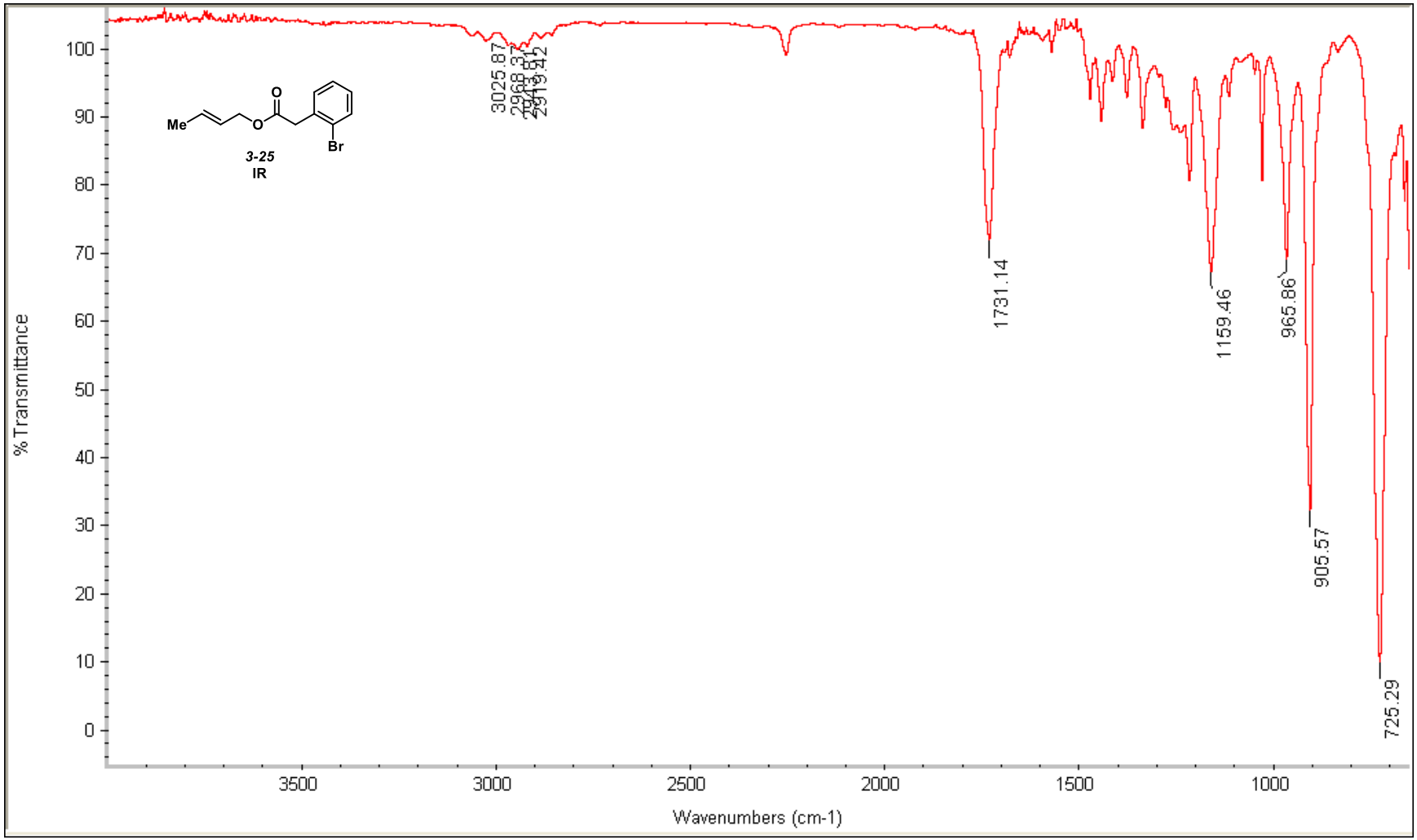
(400 MHz, $CDCl_3$)

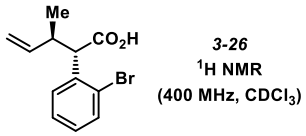


3-25

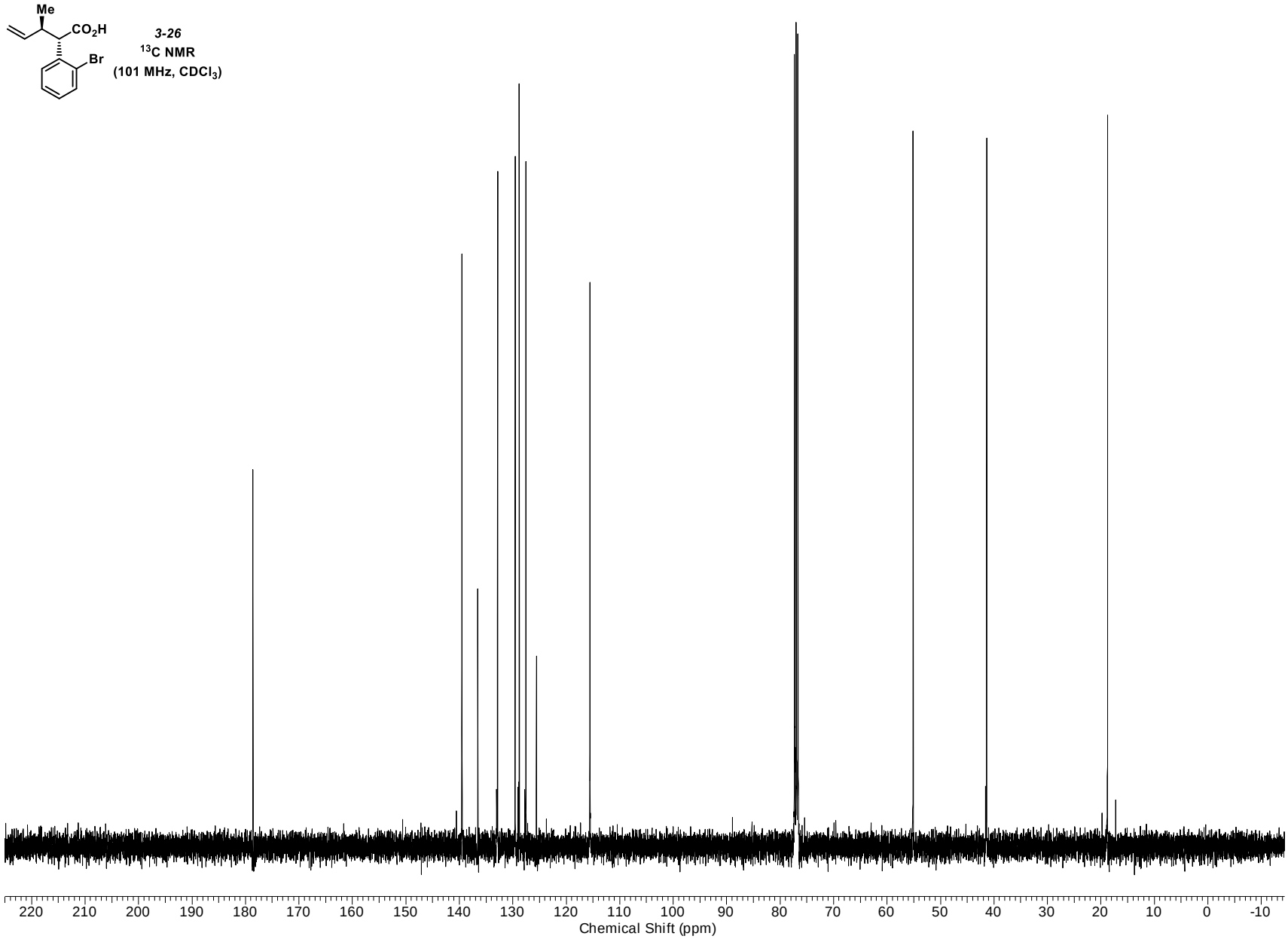
^{13}C NMR

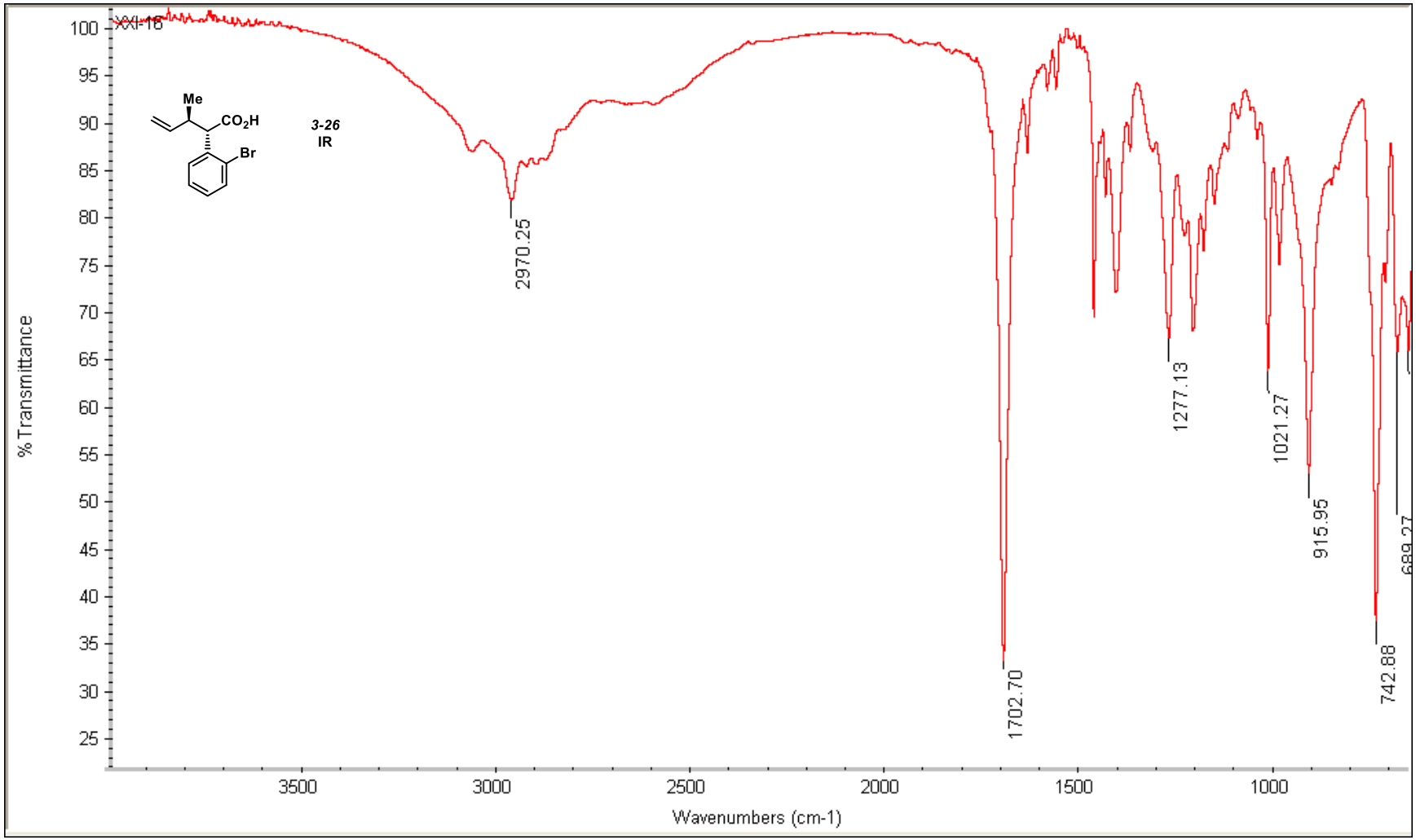
(101 MHz, $CDCl_3$)

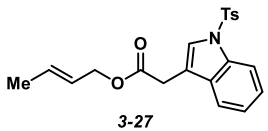

3-25
IR
Me
O
O
Br
% Transmittance
100
90
80
70
60
50
40
30
20
10
0
3025.87
2968.37
2919.42
1731.14
1159.46
965.86
905.57
725.29
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



3-26
^{1}H NMR
(400 MHz, $CDCl_3$)


Me
CO2H
Br
3-26
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

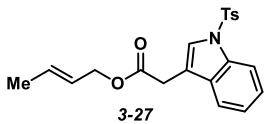

XXI-16
Me
CO2H
Br
3-26
IR
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
2970.25
1702.70
1277.13
1021.27
915.95
742.88
689.27
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



3-27

^{1}H NMR

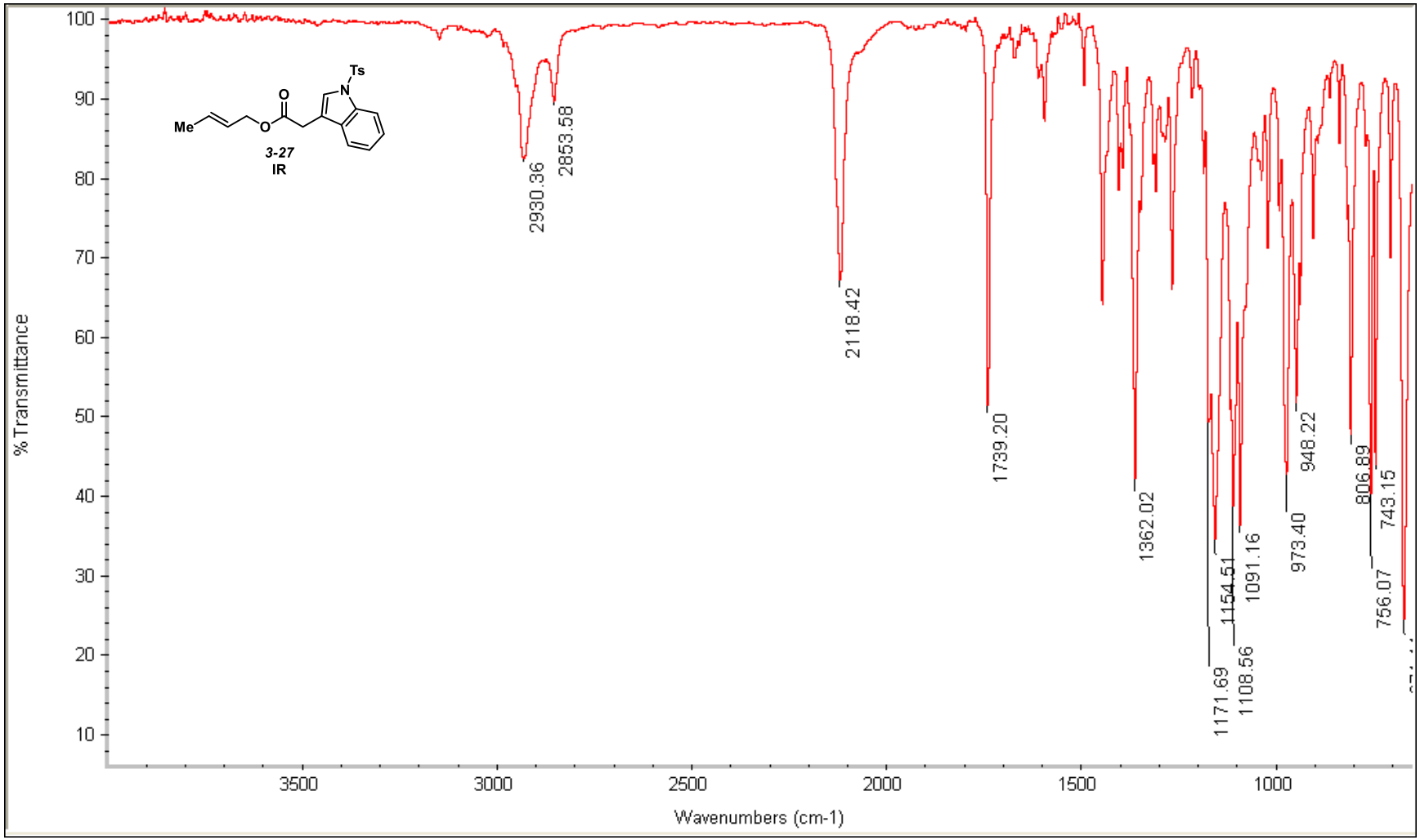
(400 MHz, $CDCl_3$)

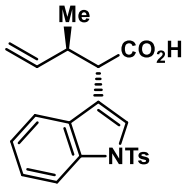


3-27

^{13}C NMR

(101 MHz, $CDCl_3$)

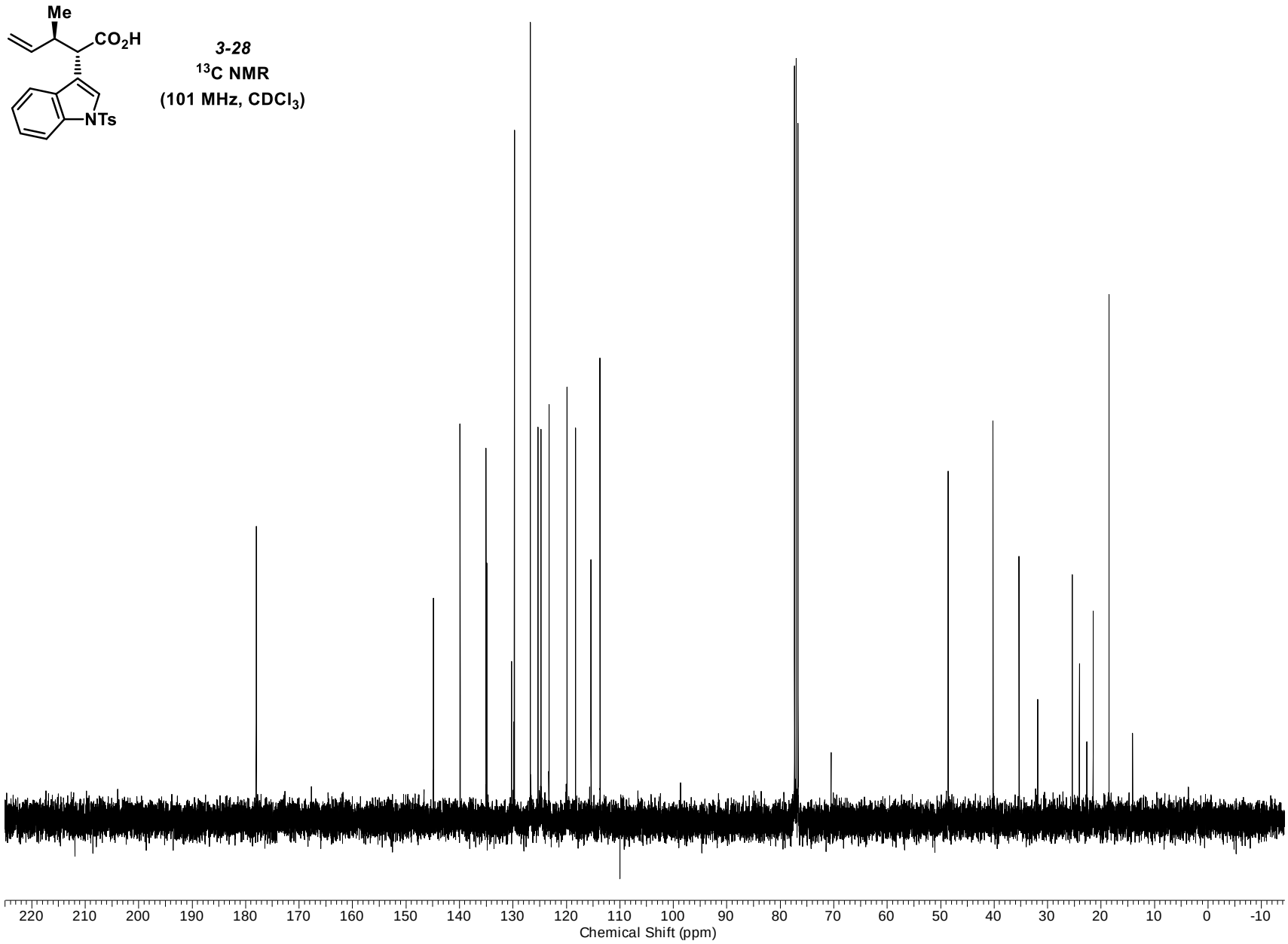

Ts
N
O
Me
O
3-27
IR
2930.36
2853.58
2118.42
1739.20
1362.02
1171.69
1154.51
1108.56
1091.16
973.40
948.22
806.89
756.07
743.15
% Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
3500
3000
2500
2000
1500
1000

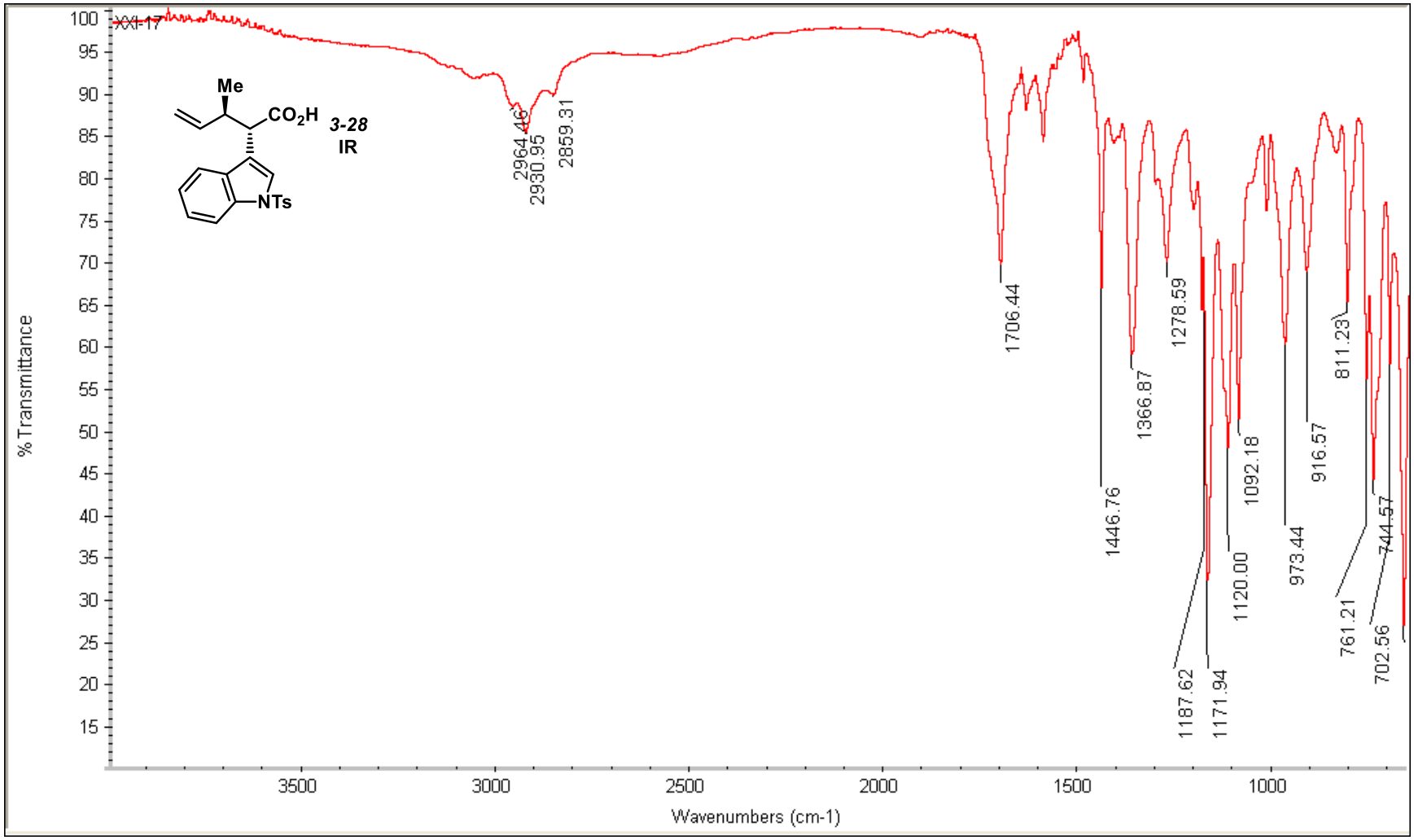


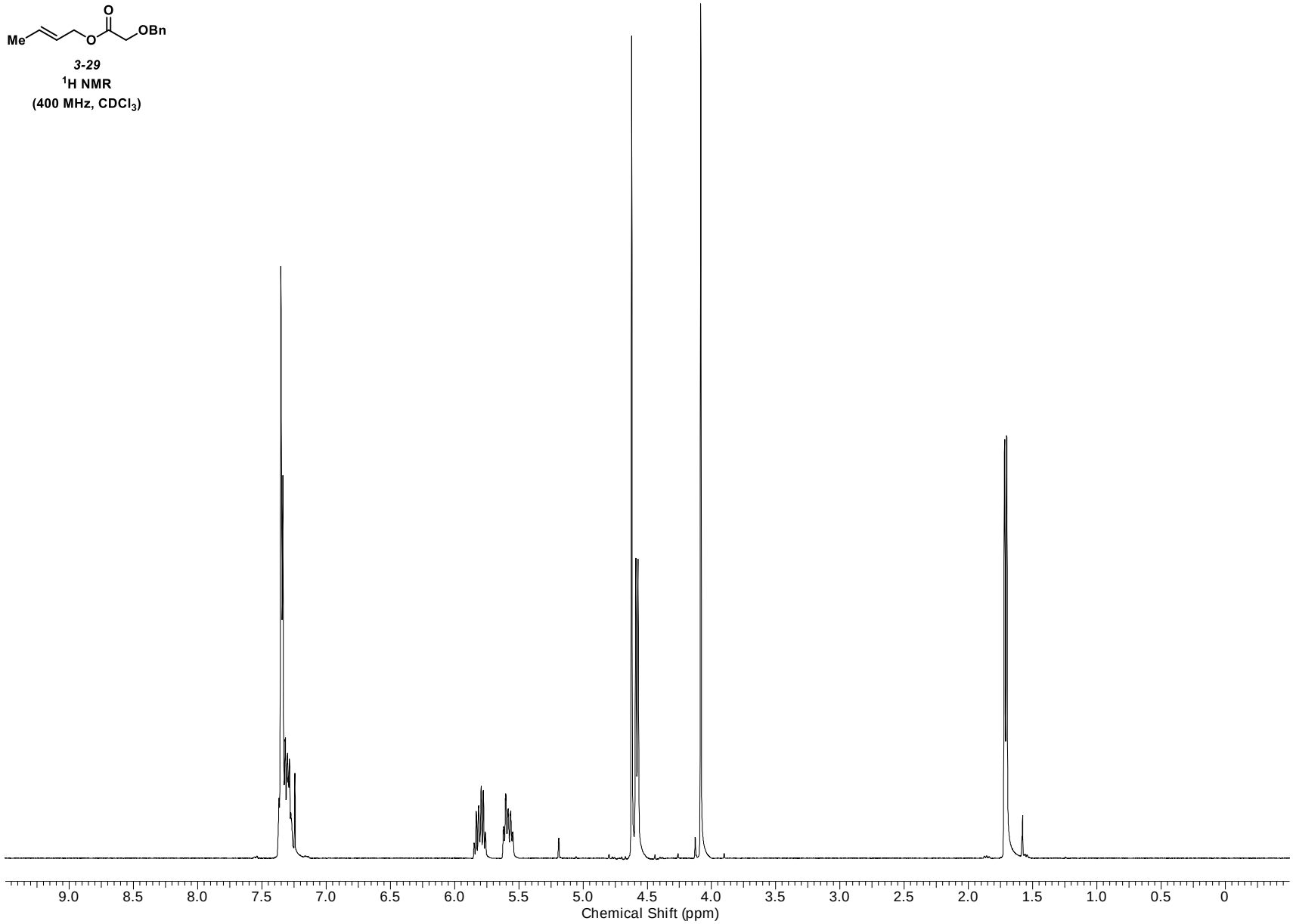
3-28

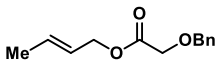
^{1}H NMR

(400 MHz, $CDCl_3$)


Me
CO2H
NTs
3-28
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


XXI-17
Me
CO2H
NTs
3-28
IR
2964.46
2930.95
2859.31
1706.44
1446.76
1366.87
1278.59
1187.62
1171.94
1120.00
1092.18
973.44
916.57
811.23
761.21
744.57
702.56
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
3500
3000
2500
2000
1500
1000

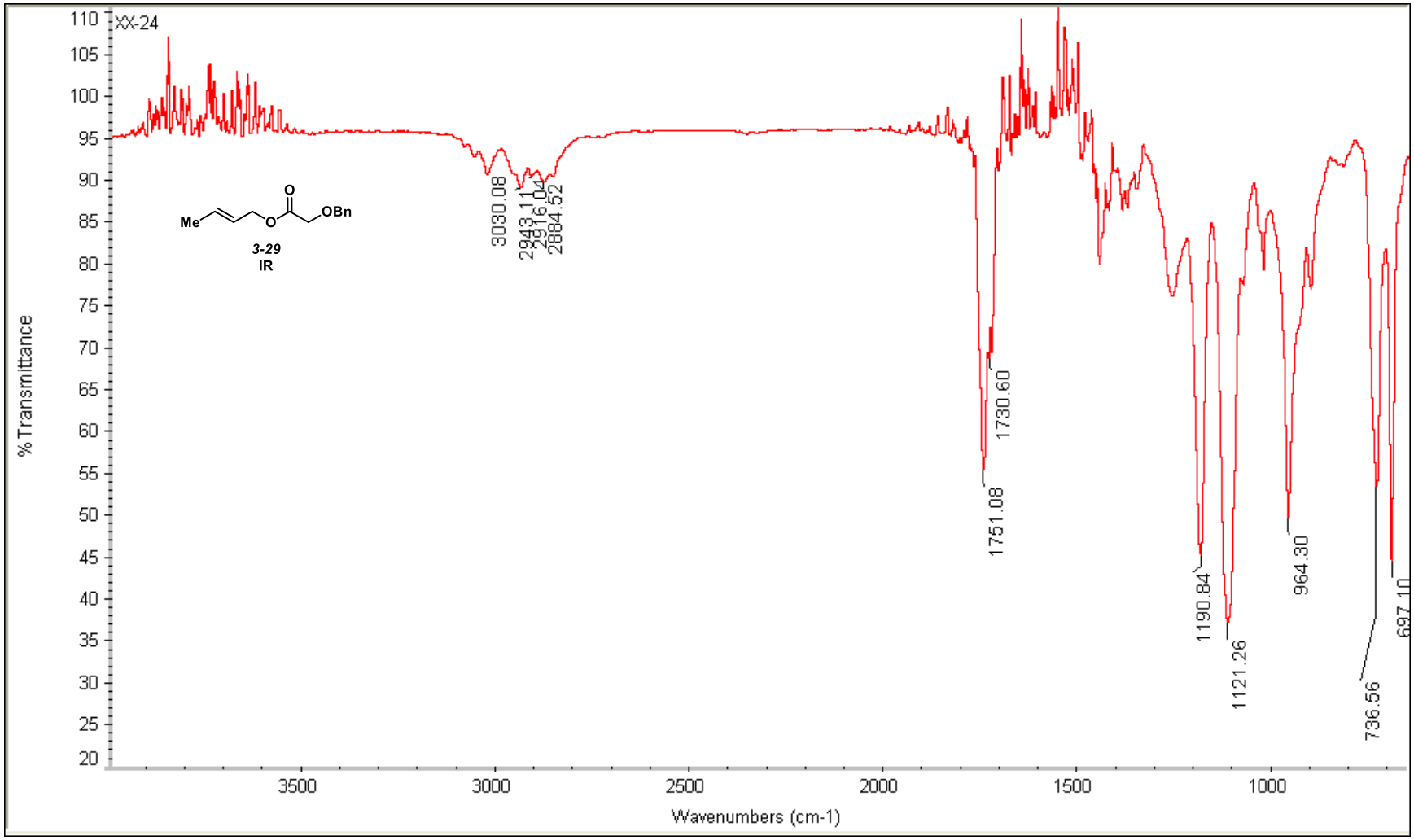

Me
O
O
OBn
3-29
1H NMR
(400 MHz, CDCl3)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

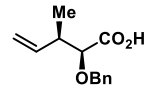


3-29

^{13}C NMR

(101 MHz, $CDCl_3$)

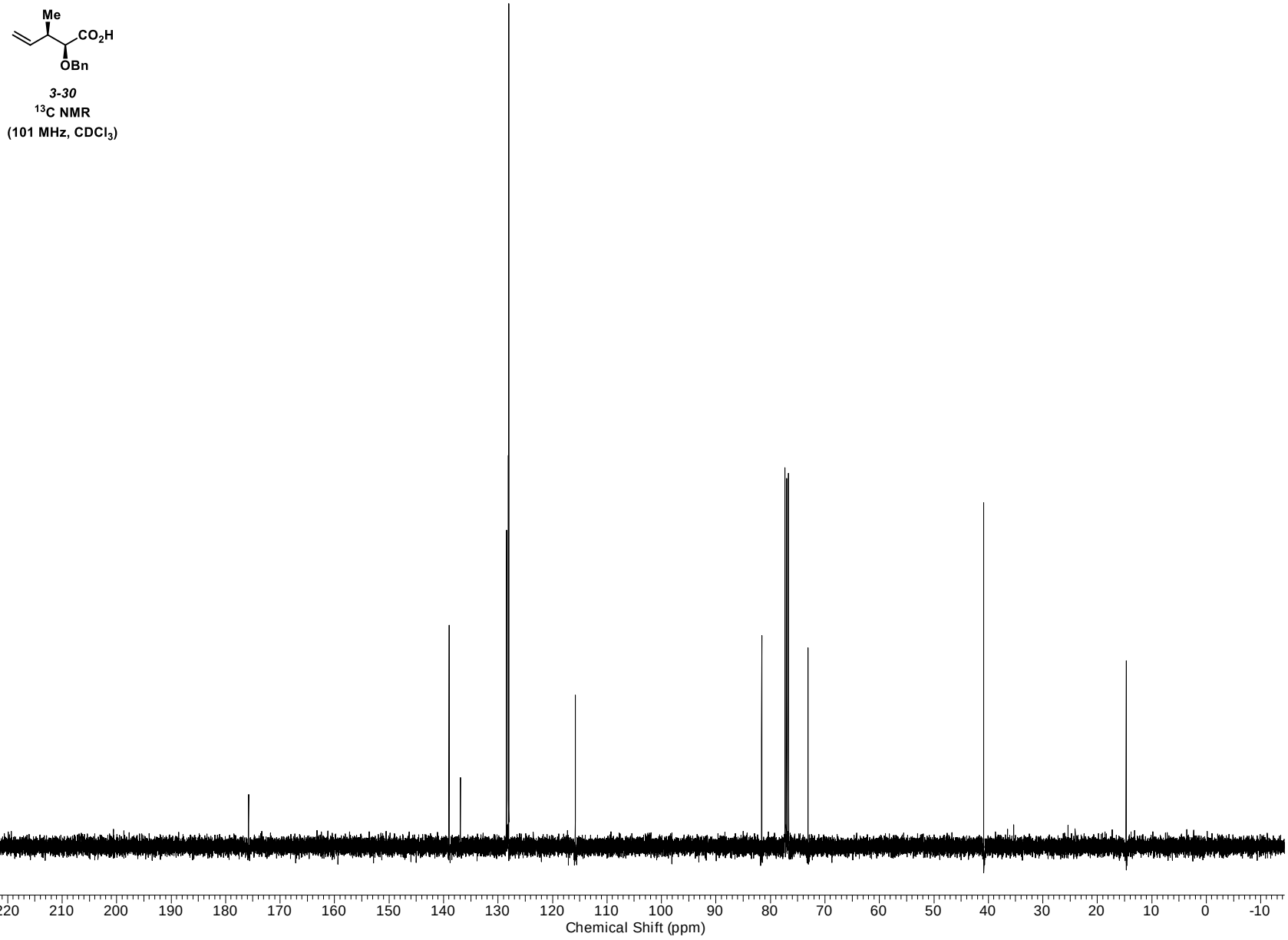

XX-24
3-29
IR
Me
O
OBn
3030.08
2943.11
2916.04
2884.52
1751.08
1730.60
1190.84
1121.26
964.30
736.56
697.10
% Transmittance
Wavenumbers (cm-1)
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
3500
3000
2500
2000
1500
1000

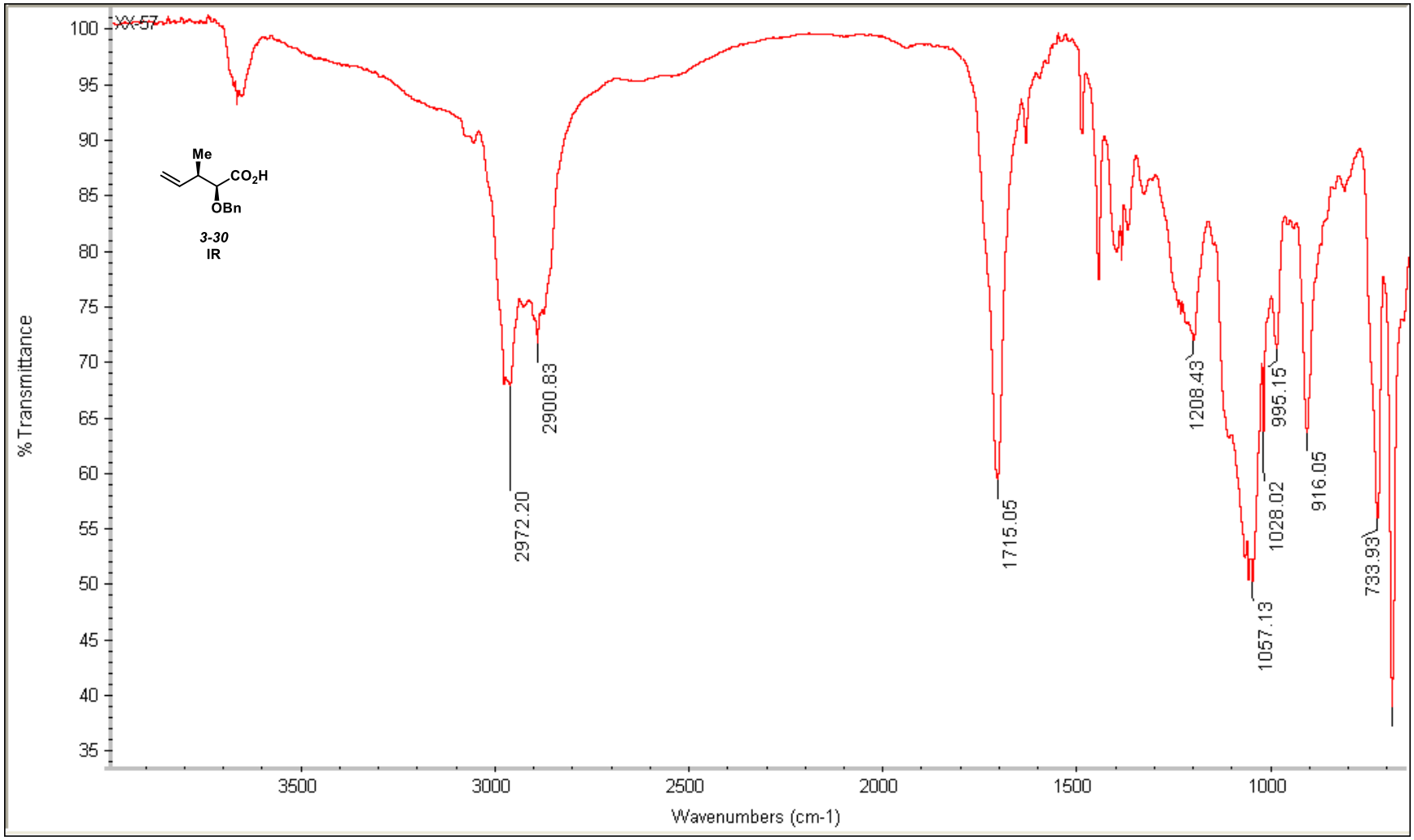


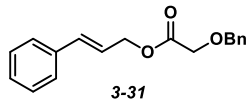
3-30

^{1}H NMR

(400 MHz, $CDCl_3$)


Me
CO2H
OBn
3-30
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

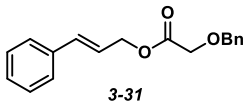

XX-57
Me
CO2H
OBn
3-30
IR
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
2972.20
2900.83
1715.05
1208.43
1057.13
1028.02
995.15
916.05
733.93
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)



3-31

^{1}H NMR

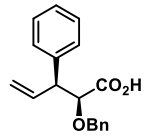
(400 MHz, $CDCl_3$)



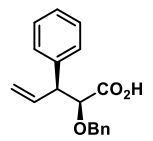
3-31

^{13}C NMR

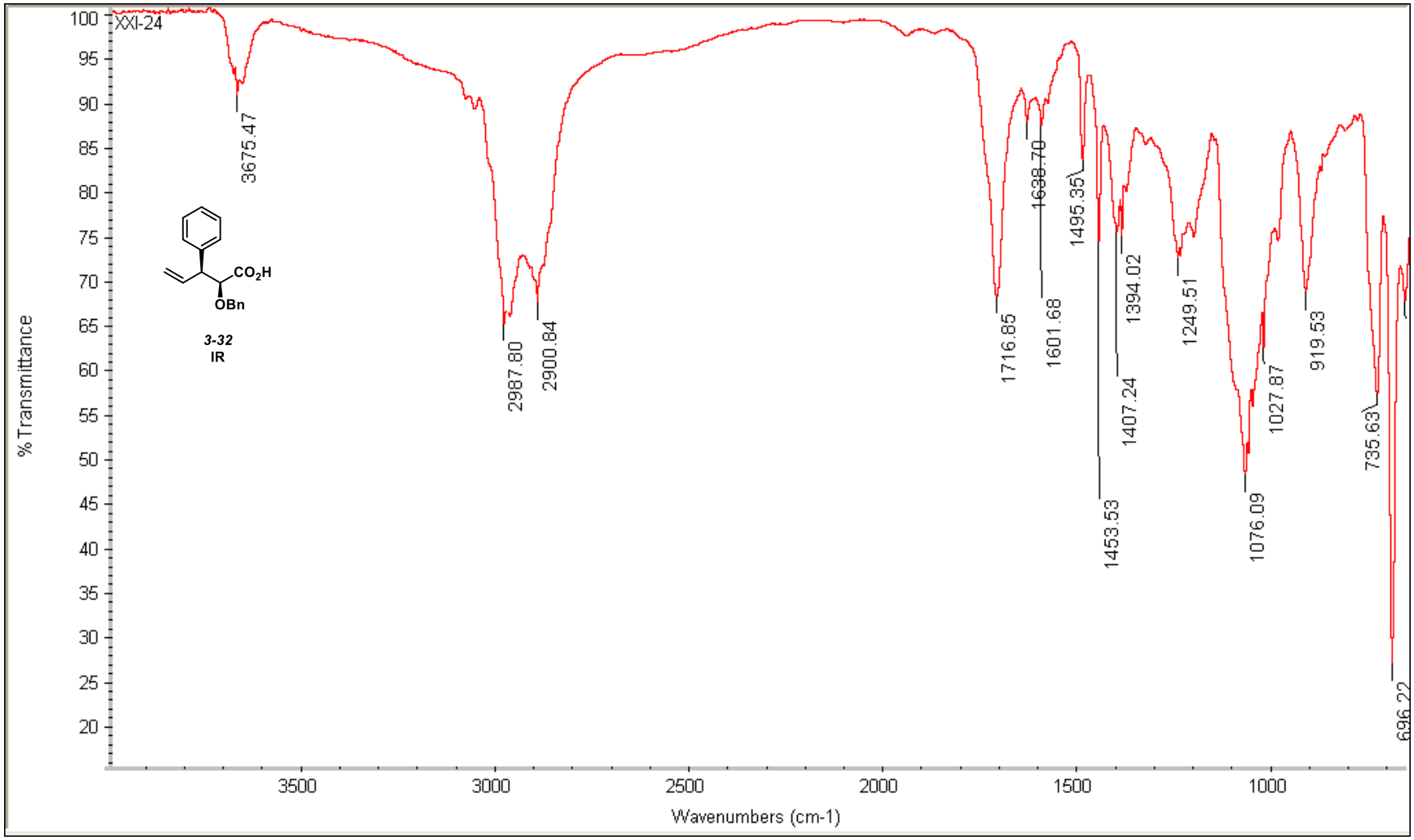
(101 MHz, $CDCl_3$)

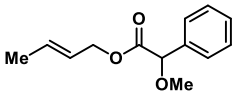


3-32
^{1}H NMR
(400 MHz, $CDCl_3$)

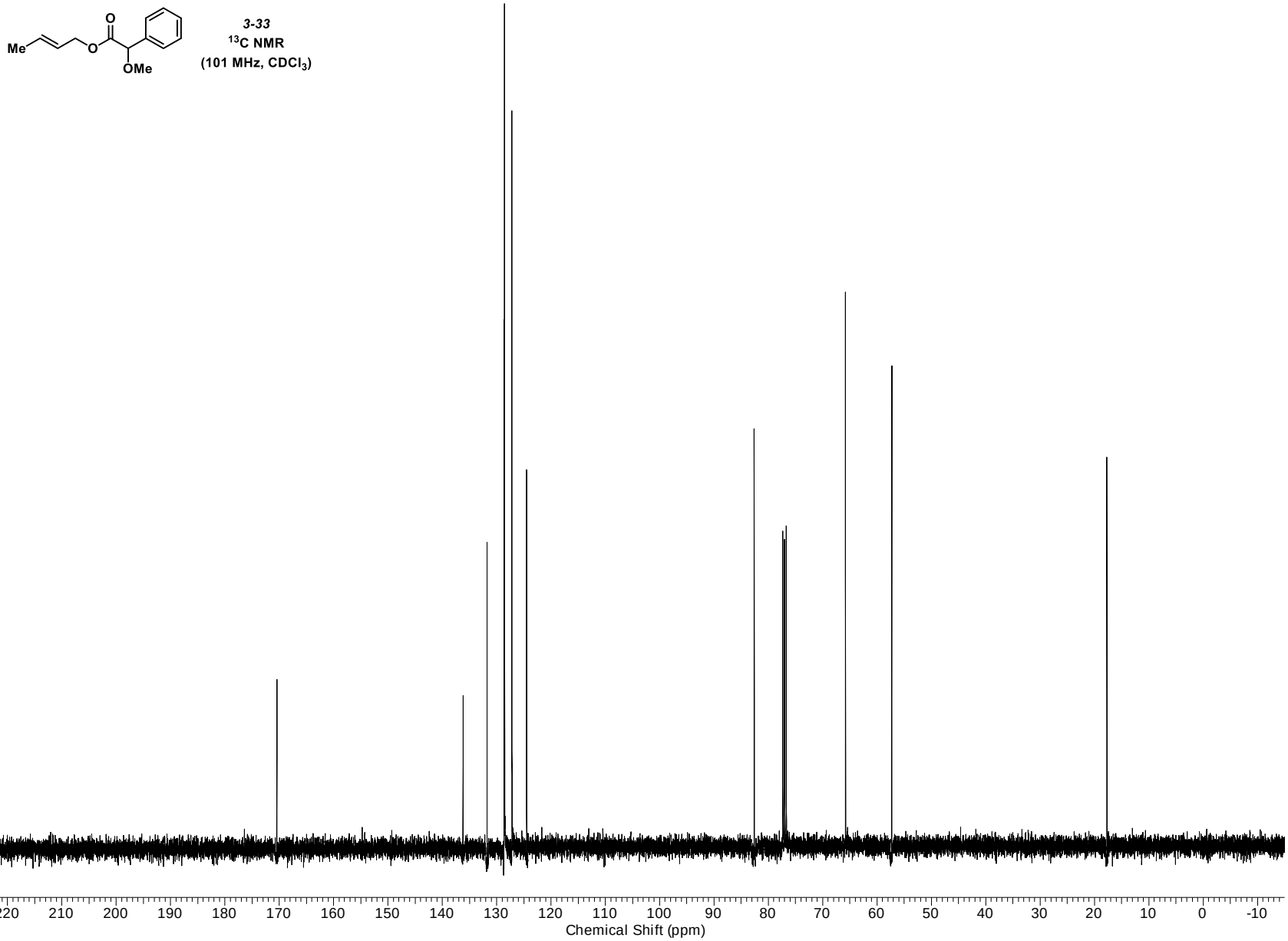


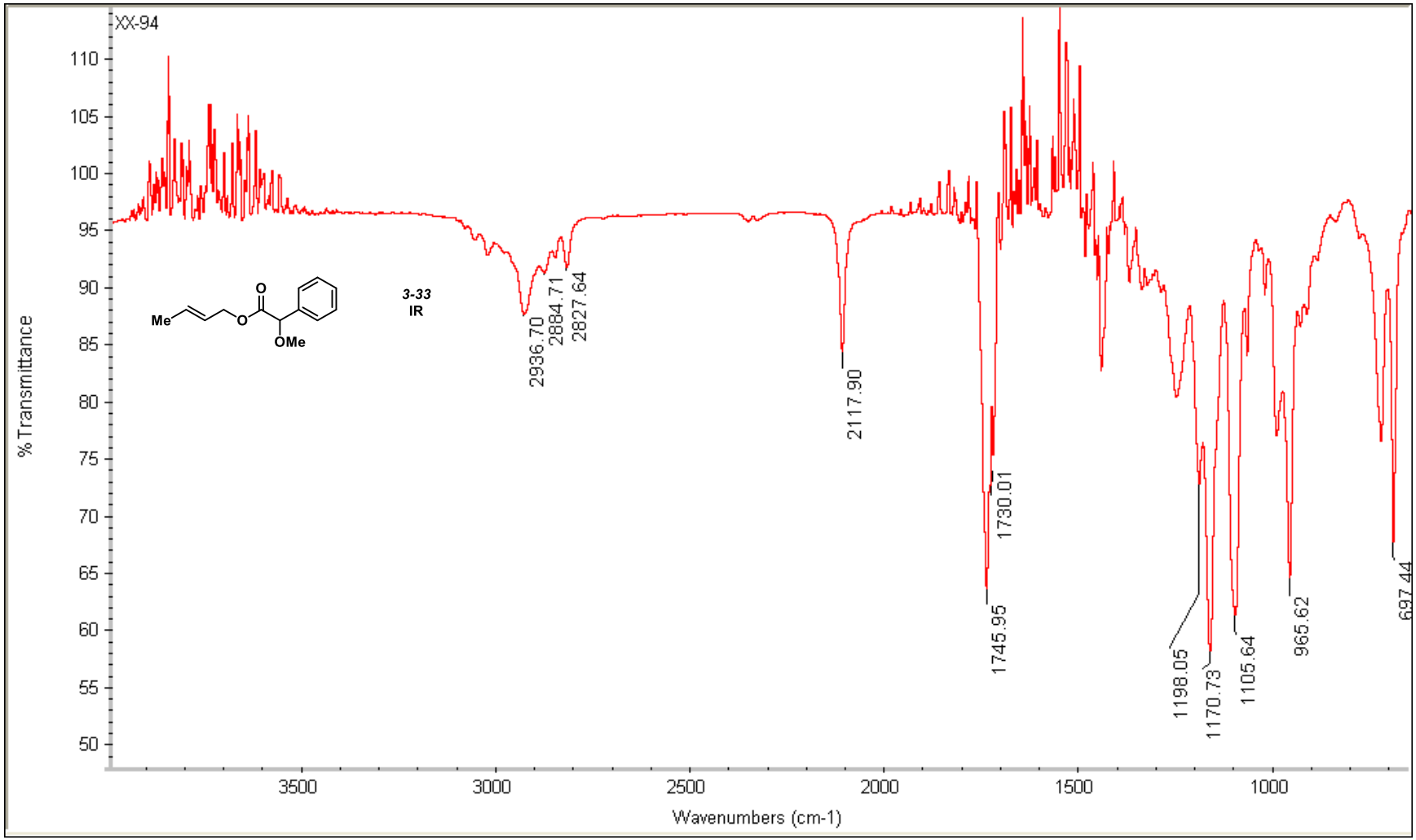
3-32
^{13}C NMR
(101 MHz, $CDCl_3$)

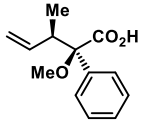

XXI-24
3675.47
2987.80
2900.84
1716.85
1638.70
1601.68
1495.35
1453.53
1407.24
1394.02
1249.51
1076.09
1027.87
919.53
735.63
696.22
CO2H
OBn
3-32
IR
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
3500
3000
2500
2000
1500
1000



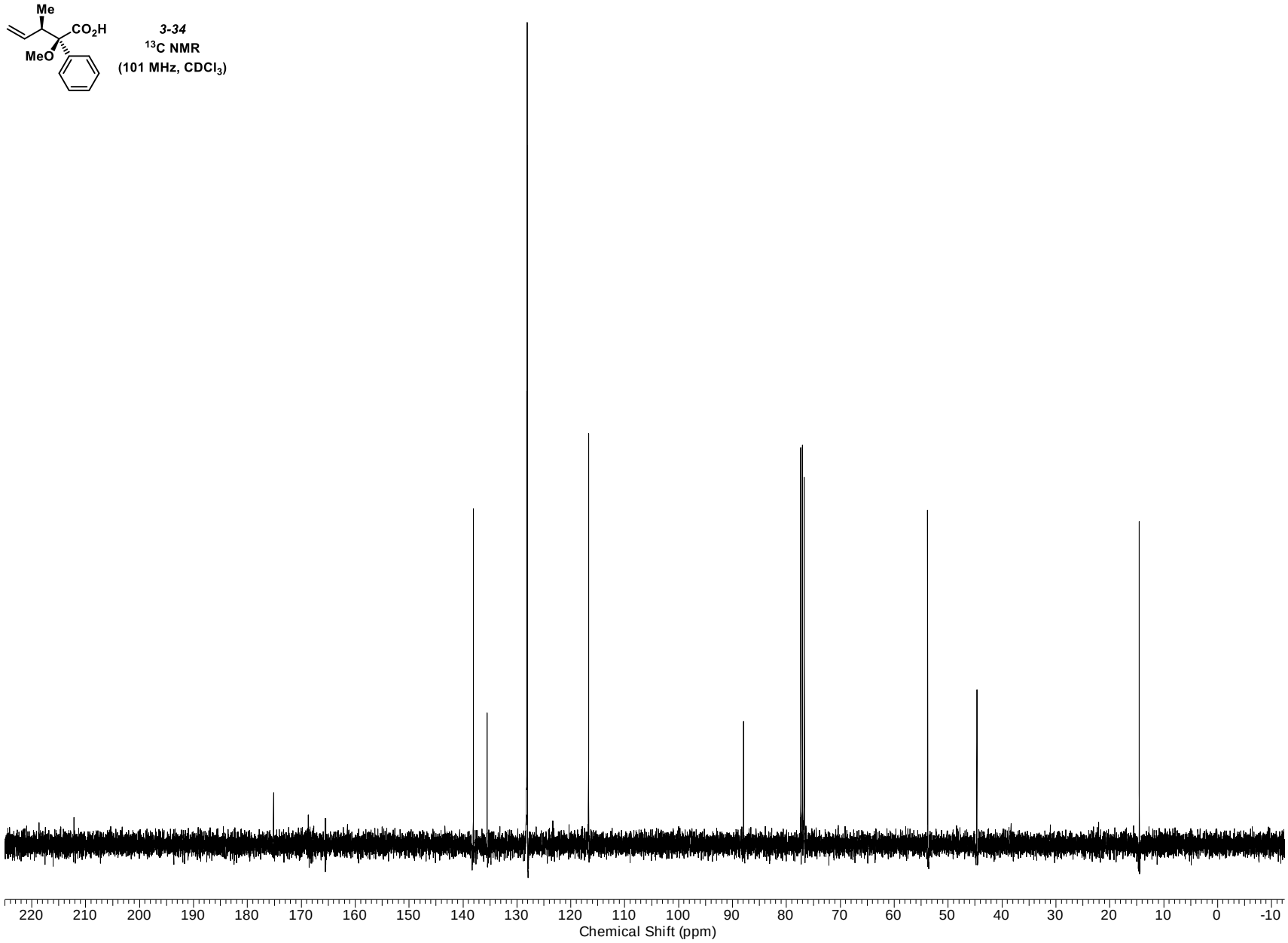
3-33
^{1}H NMR
(400 MHz, $CDCl_3$)

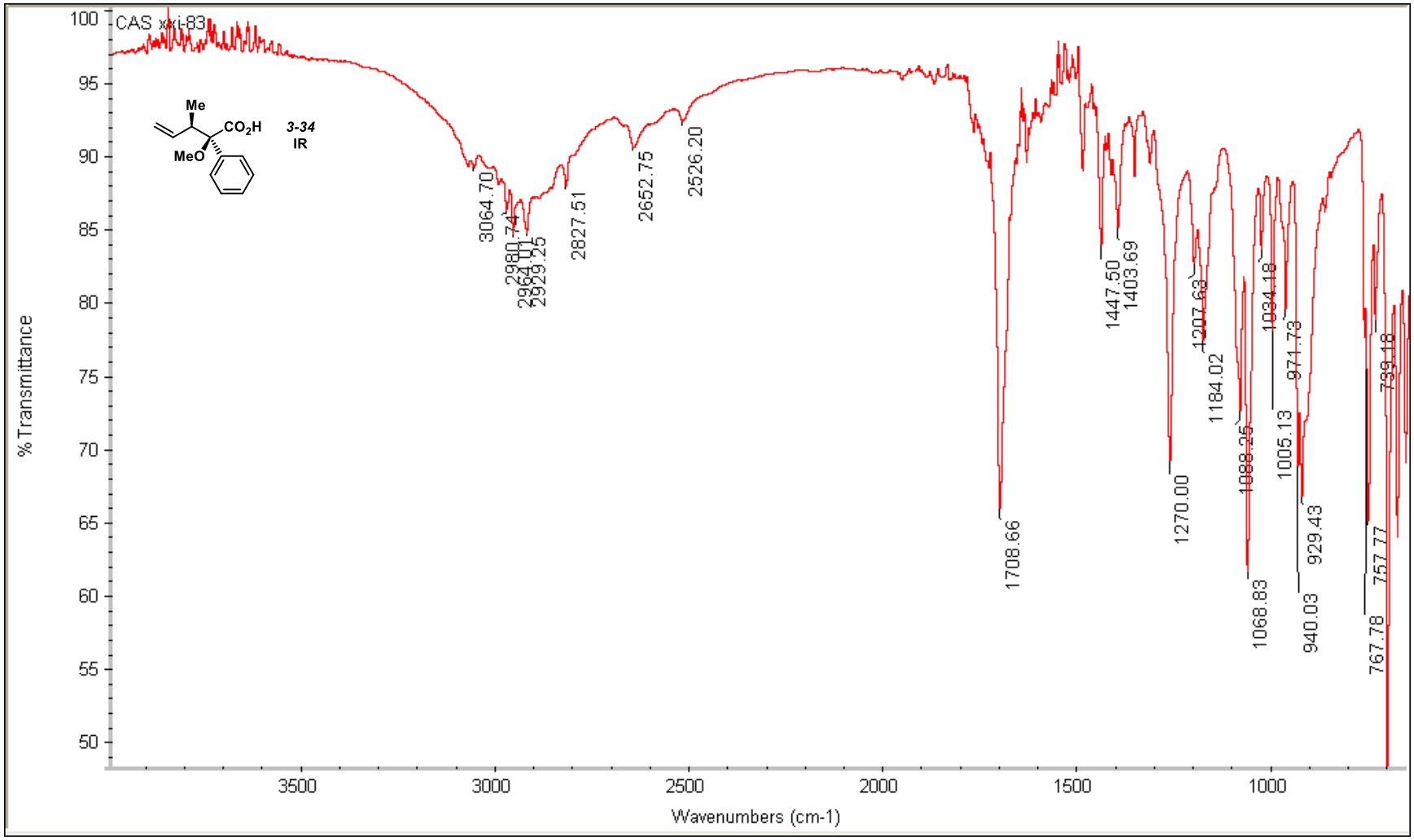

Me
O
O
OMe
3-33
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

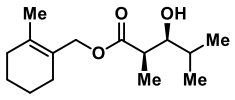

XX-94
3-33
IR
Me
O
O
OMe
% Transmittance
Wavenumbers (cm-1)
2936.70
2884.71
2827.64
2117.90
1745.95
1730.01
1198.05
1170.73
1105.64
965.62
697.44



3-34
^{1}H NMR
(400 MHz, $CDCl_3$)


Me
CO2H
MeO
3-34
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

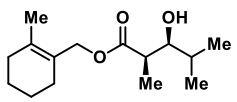

CAS xxi-83
Me
CO2H
MeO
3-34
IR
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
3500
3000
2500
2000
1500
1000
3064.70
2980.74
2964.01
2929.25
2827.51
2652.75
2526.20
1708.66
1447.50
1403.69
1270.00
1207.63
1184.02
1088.25
1068.83
1034.18
1005.13
971.73
940.03
929.43
767.78
757.77
739.18



3-38

^{1}H NMR

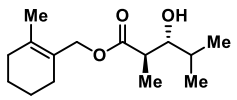
(400 MHz, $CDCl_3$)



3-38

^{13}C NMR

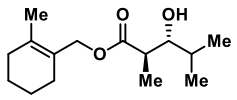
(101 MHz, $CDCl_3$)



3-39

^{1}H NMR

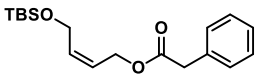
(400 MHz, $CDCl_3$)



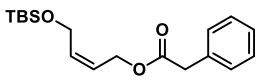
3-39

^{13}C NMR

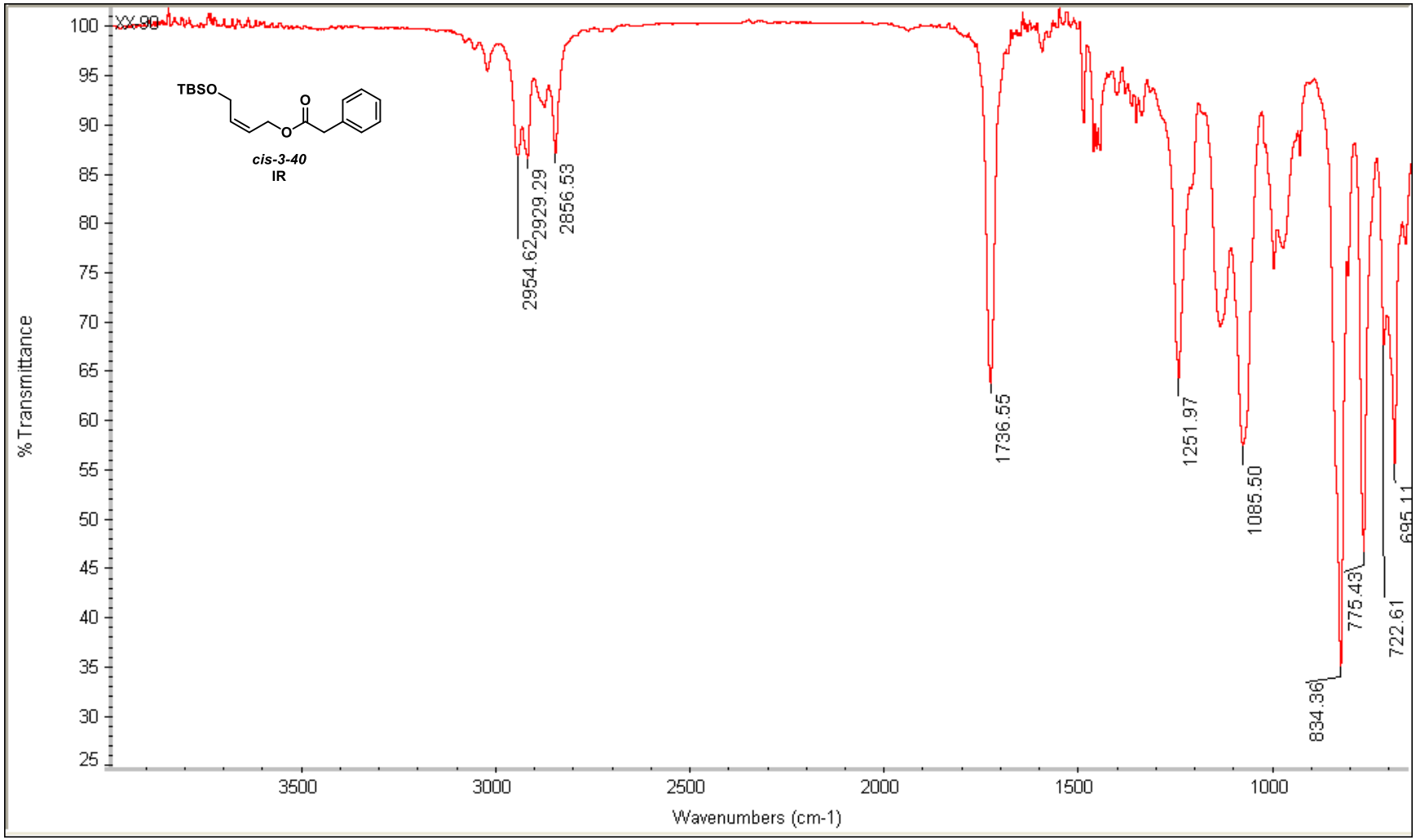
(101 MHz, $CDCl_3$)

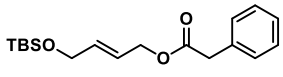


cis-3-40
^{1}H NMR
(400 MHz, $CDCl_3$)

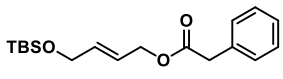


cis-3-40
^{13}C NMR
(101 MHz, $CDCl_3$)

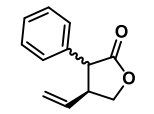

TBSO
O
O
cis-3-40
IR
% Transmittance
Wavenumbers (cm-1)
2954.62
2929.29
2856.53
1736.55
1251.97
1085.50
834.36
775.43
722.61
695.11



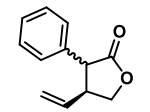
trans-3-40
^{1}H NMR
(400 MHz, $CDCl_3$)



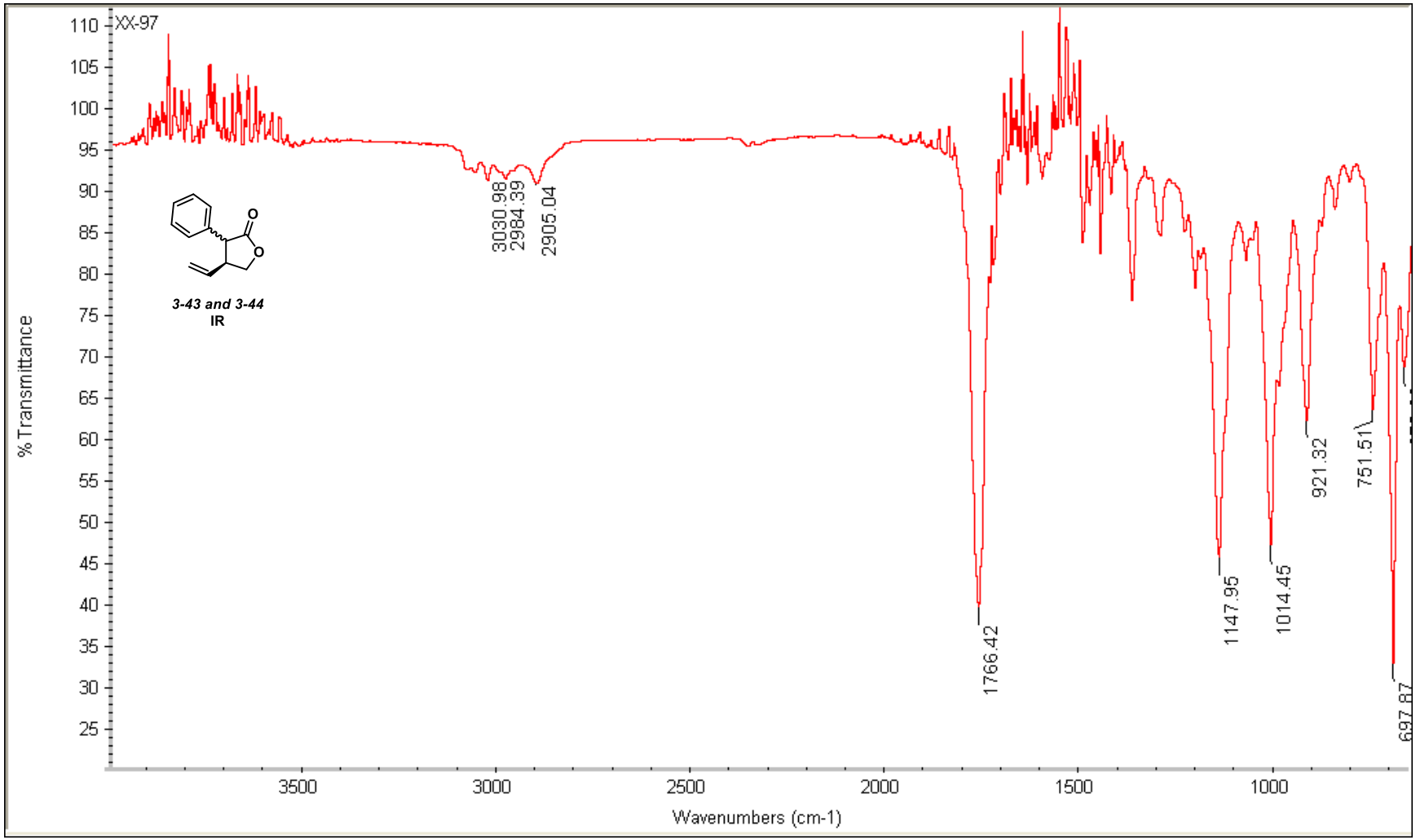
trans-3-40
^{13}C NMR
(101 MHz, $CDCl_3$)

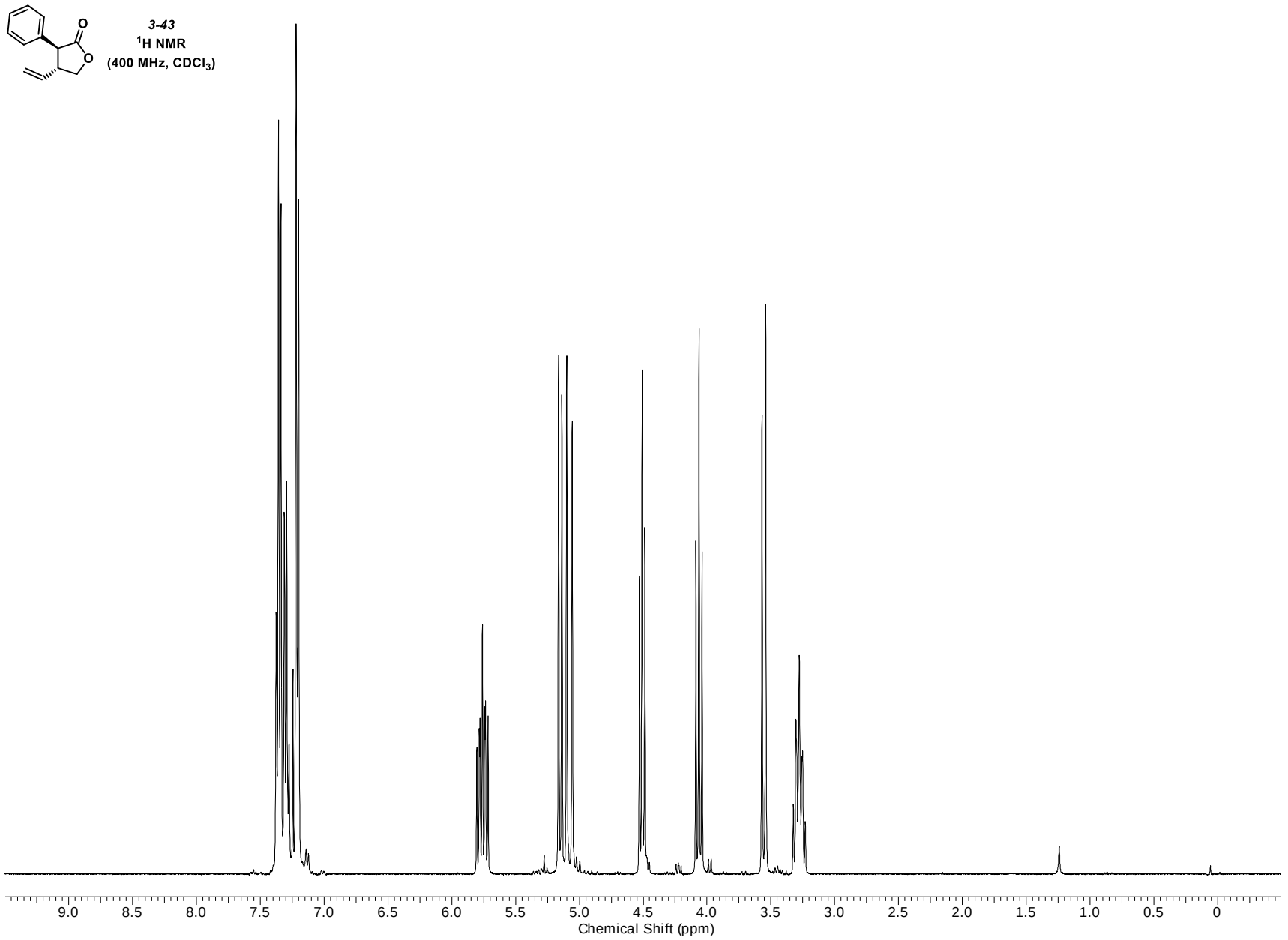


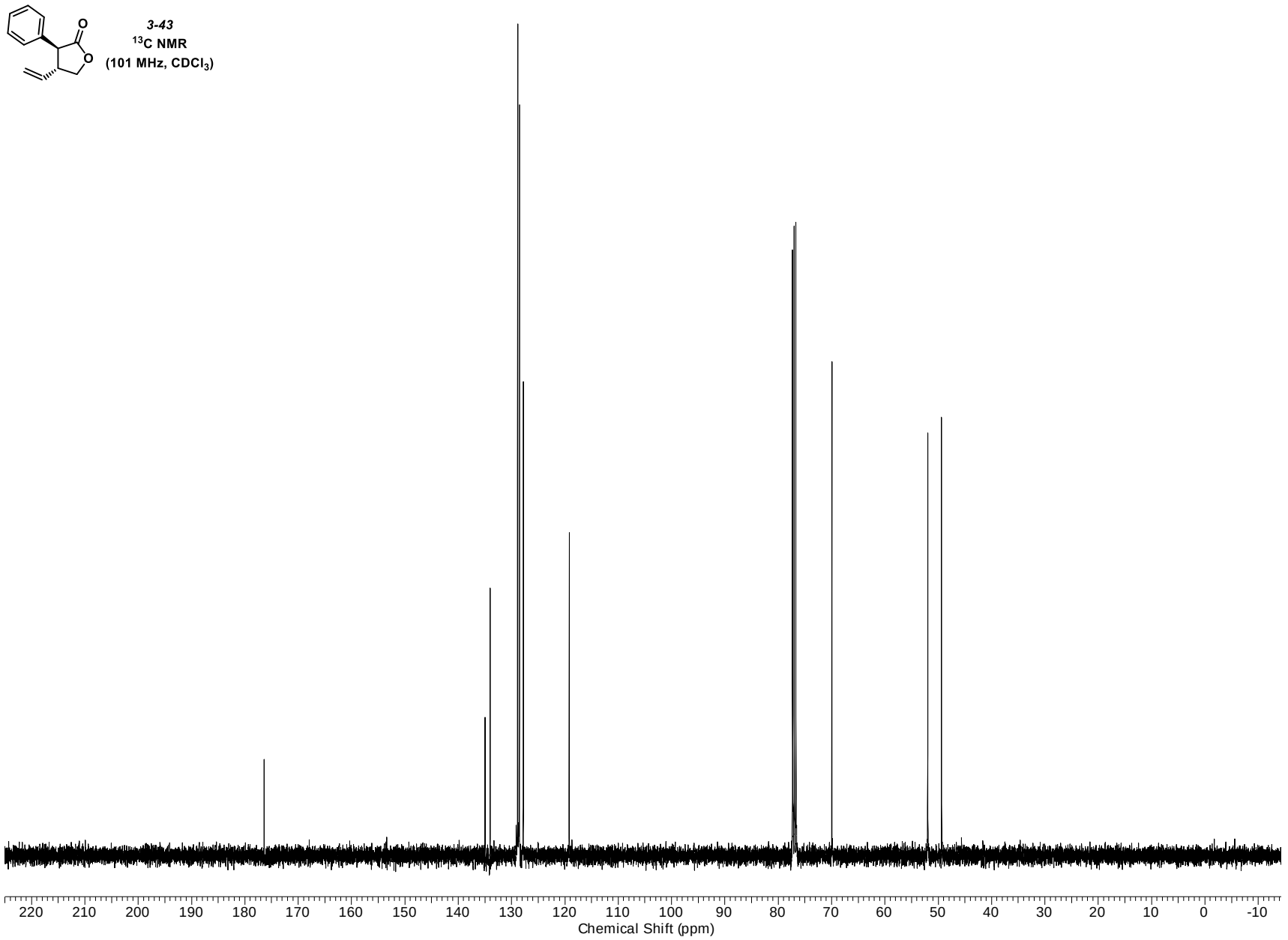
3-43 and 3-44
^{1}H NMR
(400 MHz, $CDCl_3$)

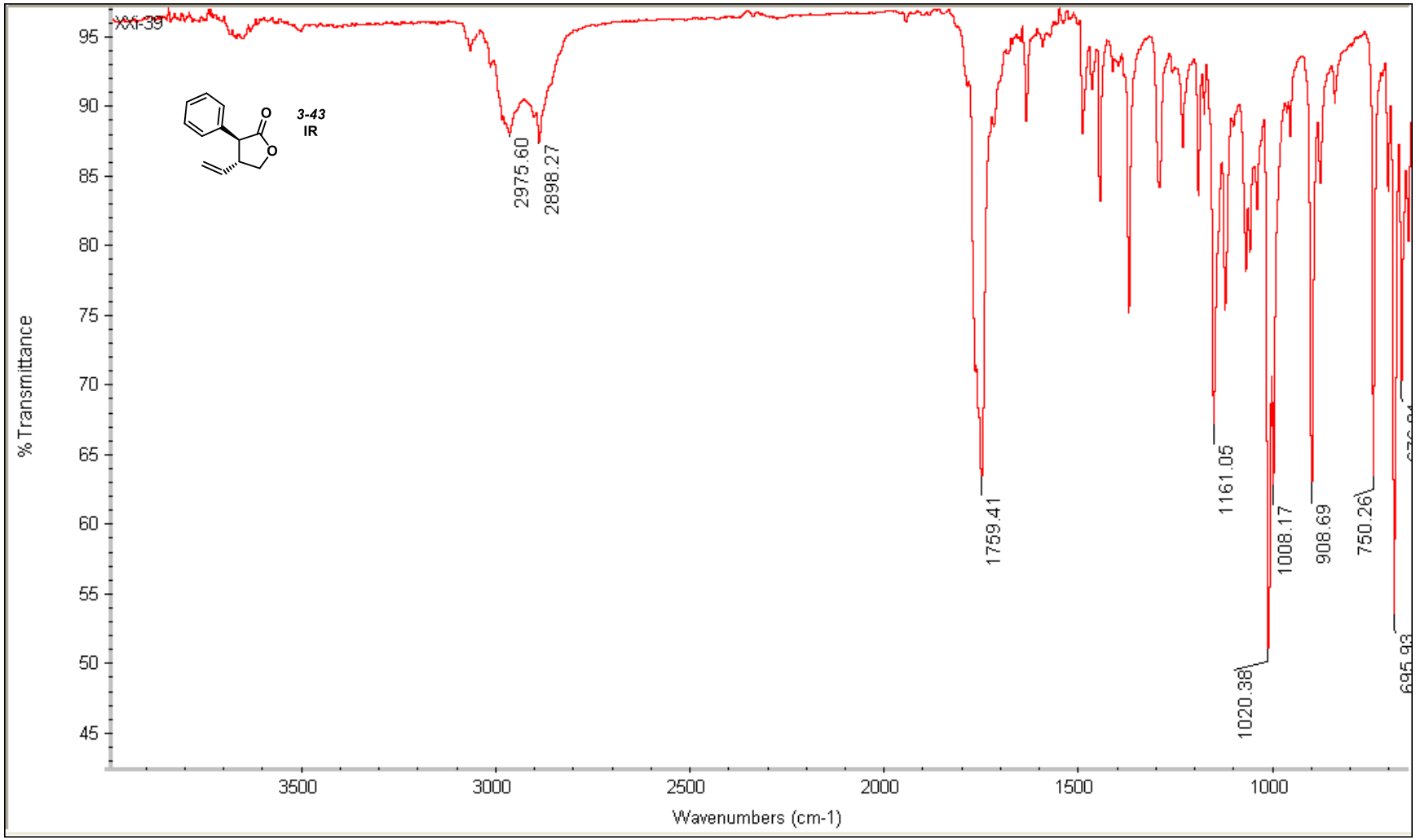


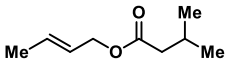
3-43 and 3-44
^{13}C NMR
(101 MHz, $CDCl_3$)


XX-97
3-43 and 3-44
IR
% Transmittance
Wavenumbers (cm-1)
3030.98
2984.39
2905.04
1766.42
1147.95
1014.45
921.32
751.51
697.87


3-43
1H NMR
(400 MHz, CDCl3)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
O
3-43
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

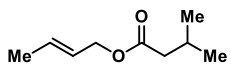

XXI-39
3-43
IR
2975.60
2898.27
1759.41
1161.05
1020.38
1008.17
908.69
750.26
695.93
% Transmittance
Wavenumbers (cm-1)
95
90
85
80
75
70
65
60
55
50
45
3500
3000
2500
2000
1500
1000



3-48

^{1}H NMR

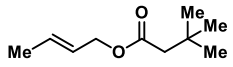
(400 MHz, $CDCl_3$)



3-48

^{13}C NMR

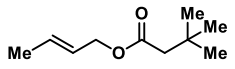
(101 MHz, $CDCl_3$)



3-49

^{1}H NMR

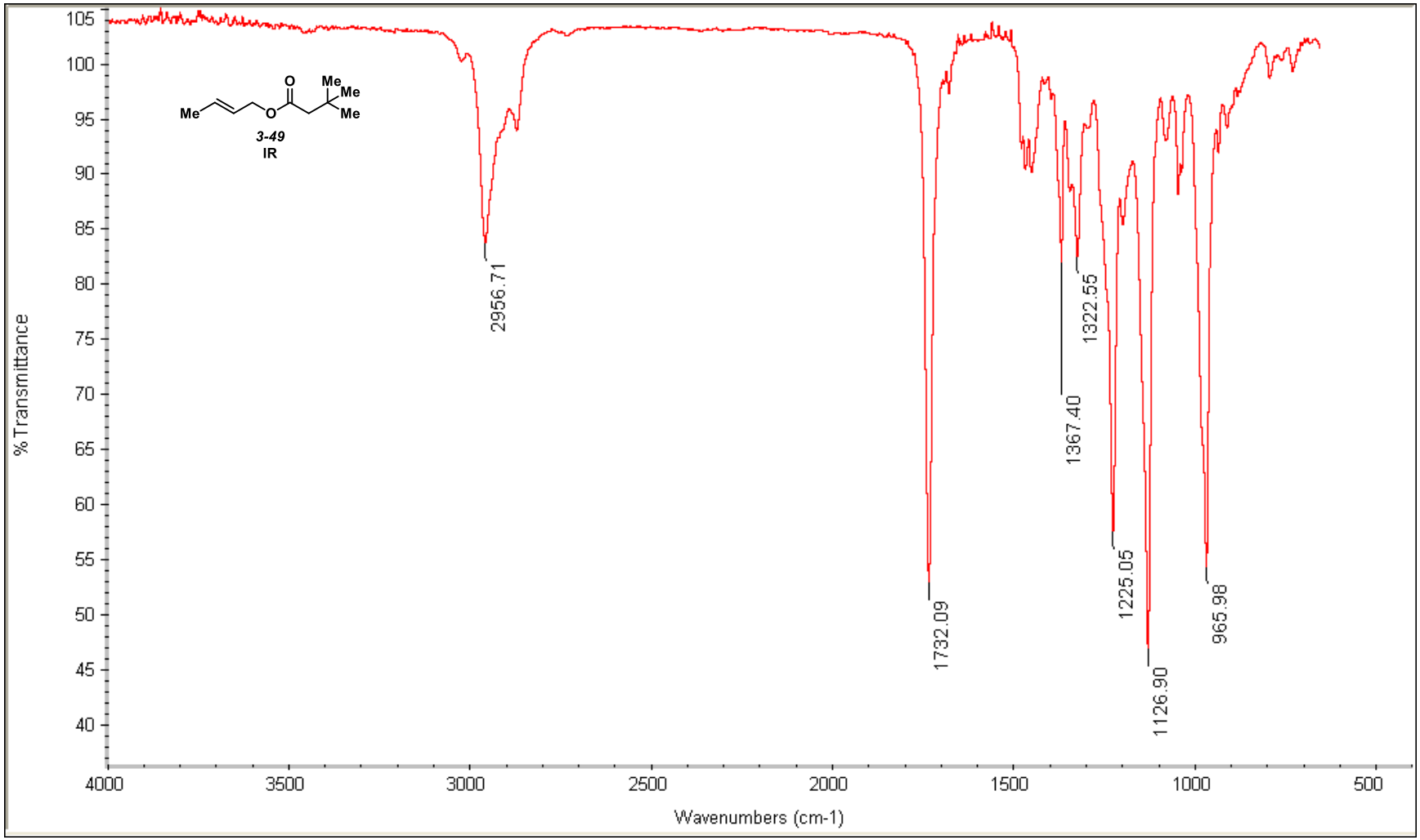
(400 MHz, $CDCl_3$)

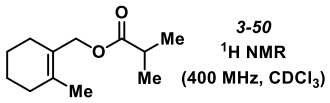


3-49

^{13}C NMR

(101 MHz, $CDCl_3$)

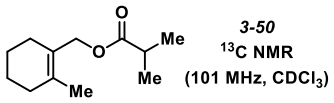

3-49
IR
% Transmittance
Wavenumbers (cm-1)
2956.71
1732.09
1367.40
1322.55
1225.05
1126.90
965.98



3-50

^{1}H NMR

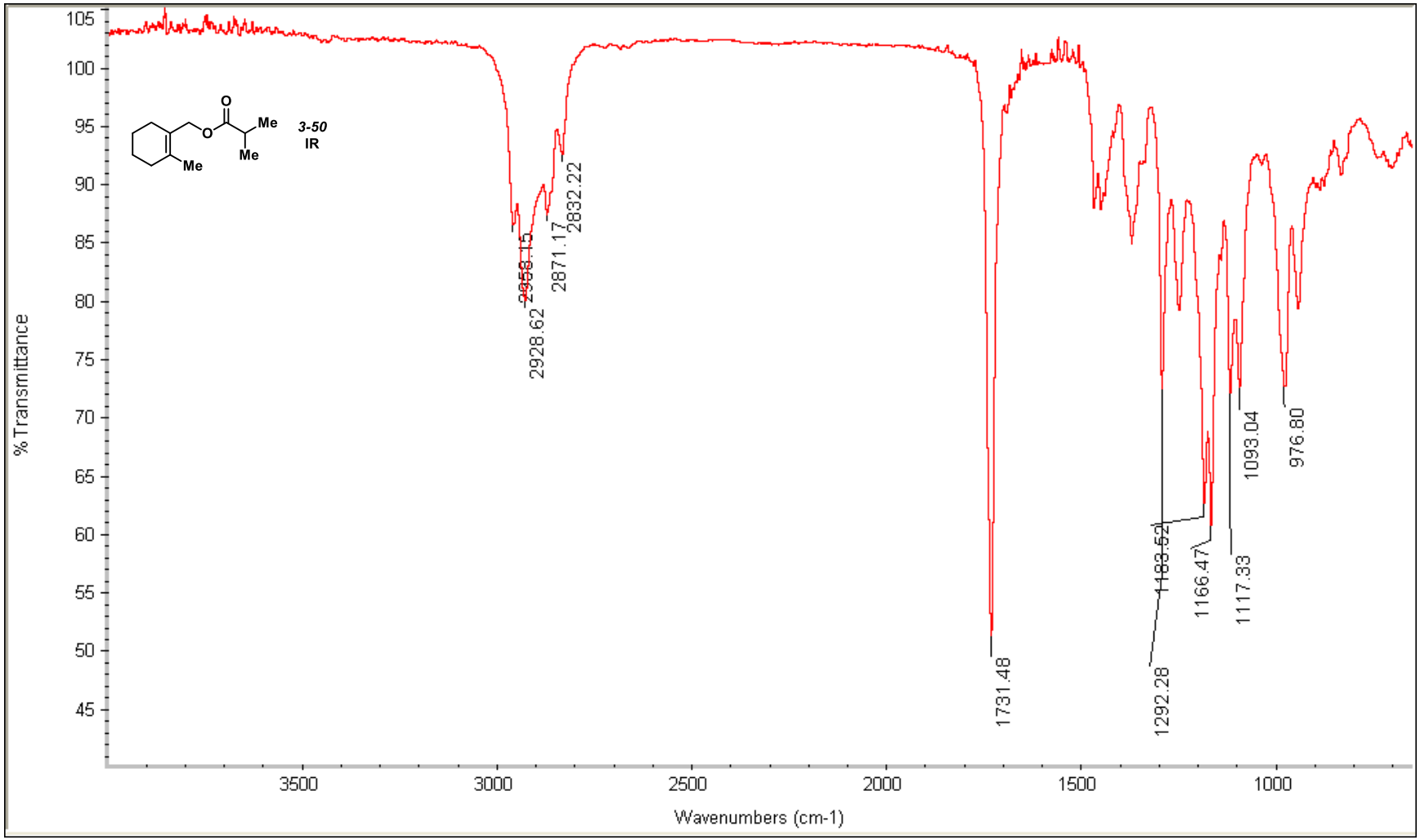
(400 MHz, $CDCl_3$)

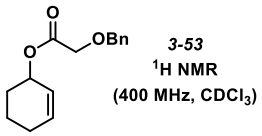


3-50

^{13}C NMR

(101 MHz, $CDCl_3$)

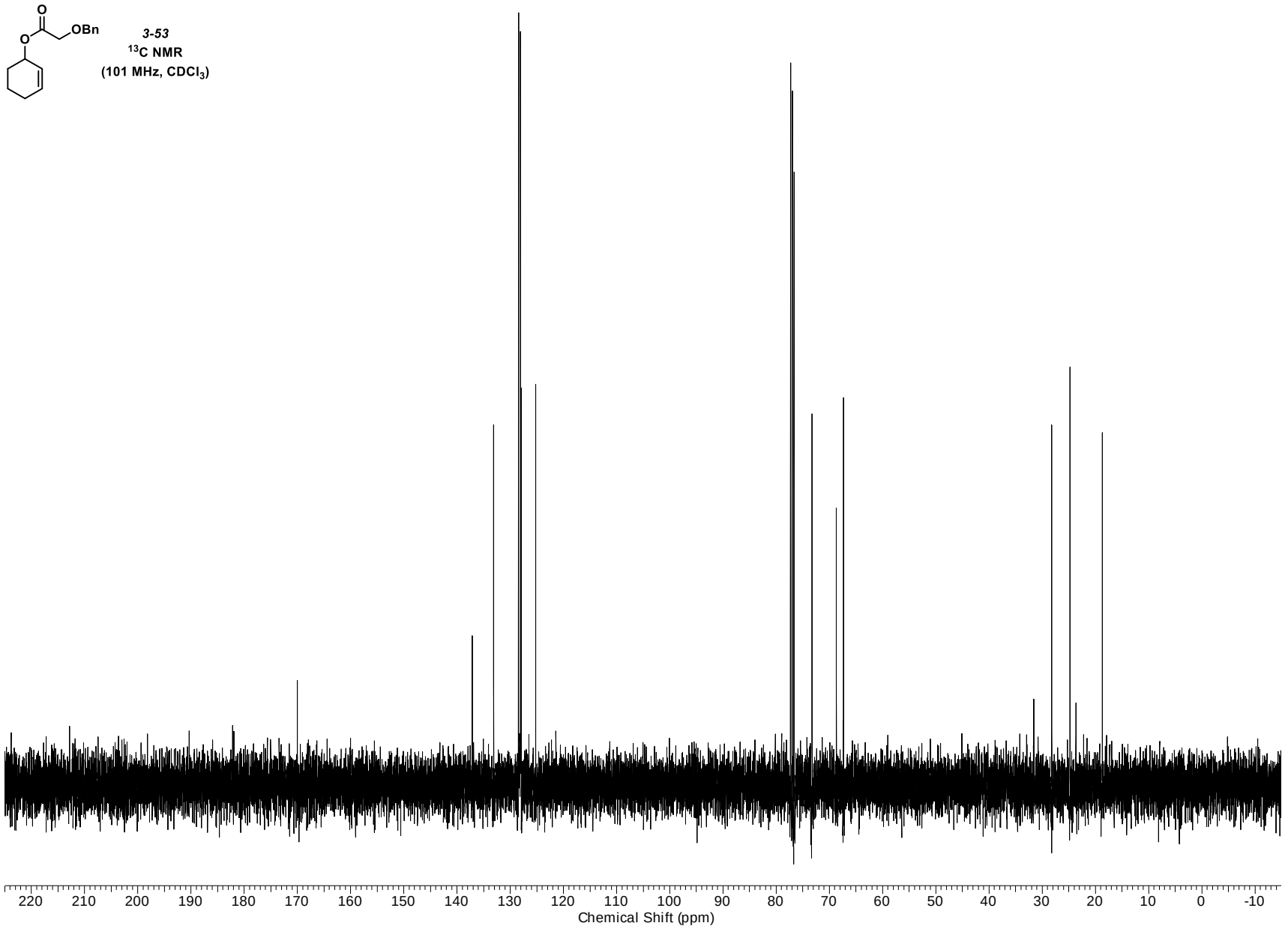

3-50
IR
% Transmittance
Wavenumbers (cm-1)
2928.62
2871.17
2832.22
1731.48
1292.28
1166.47
1117.33
1093.04
976.80

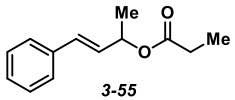


3-53

^{1}H NMR

(400 MHz, $CDCl_3$)

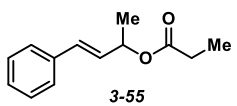

O
O
OBn
3-53
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)



3-55

^{1}H NMR

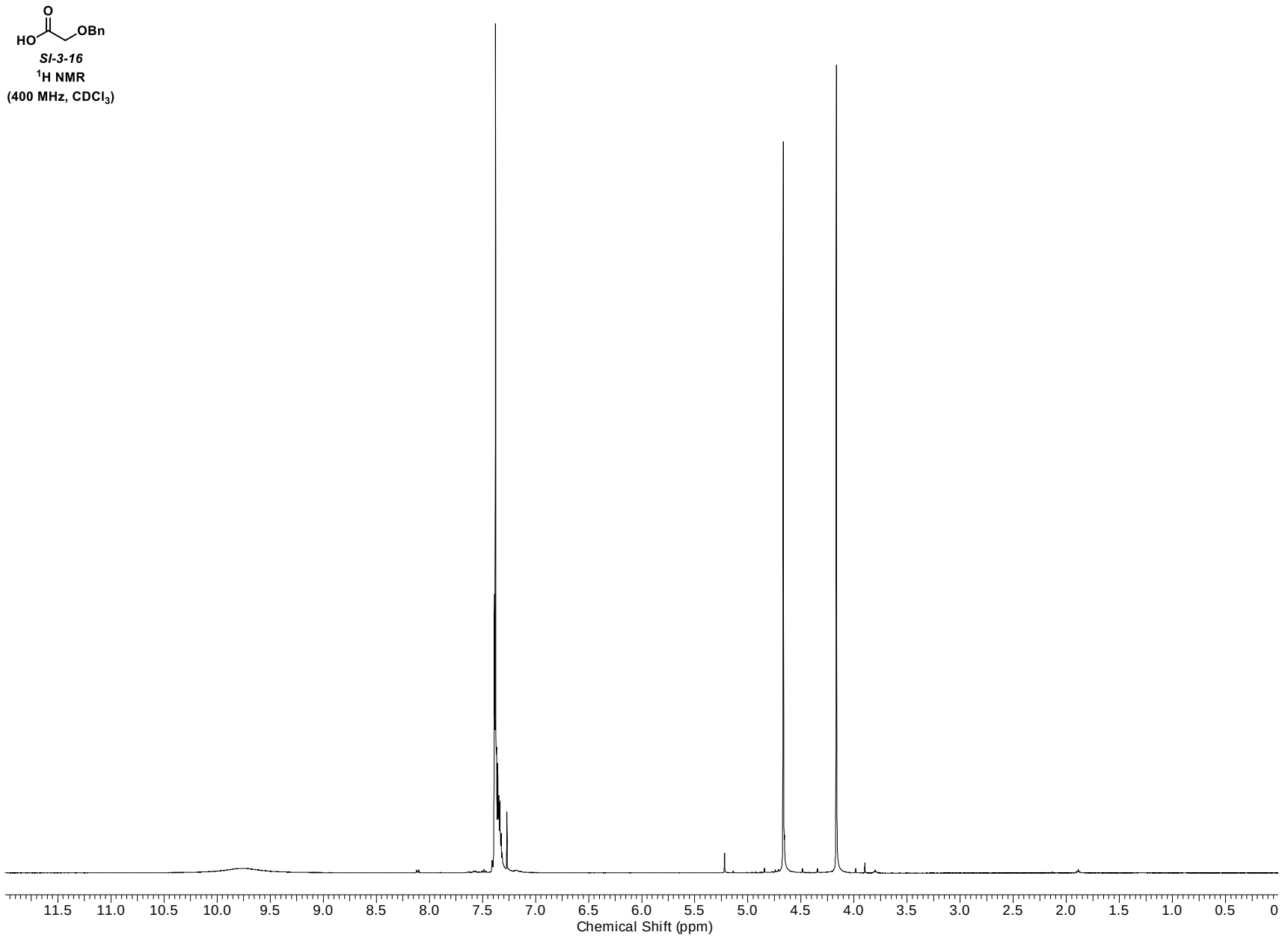
(400 MHz, $CDCl_3$)

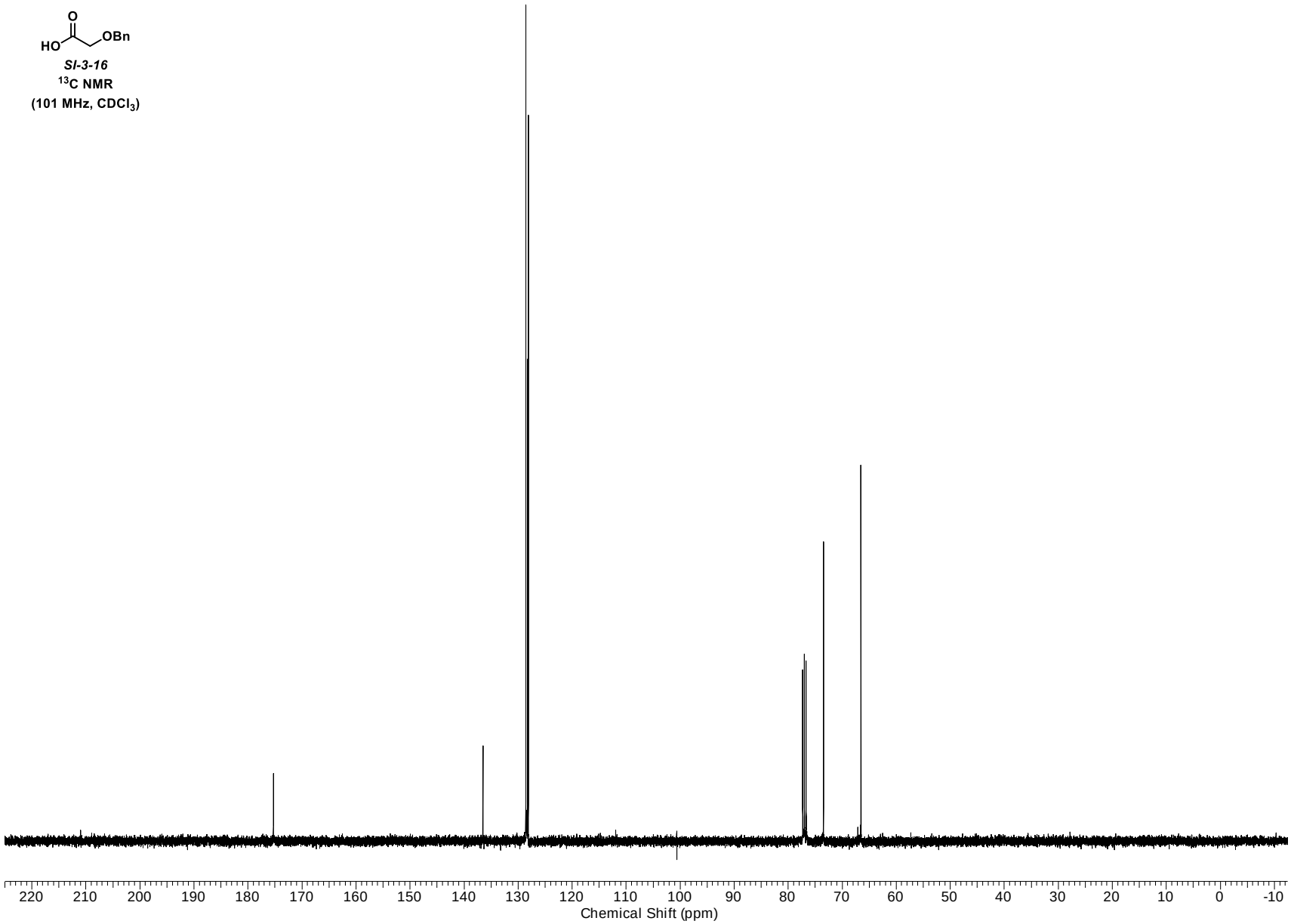


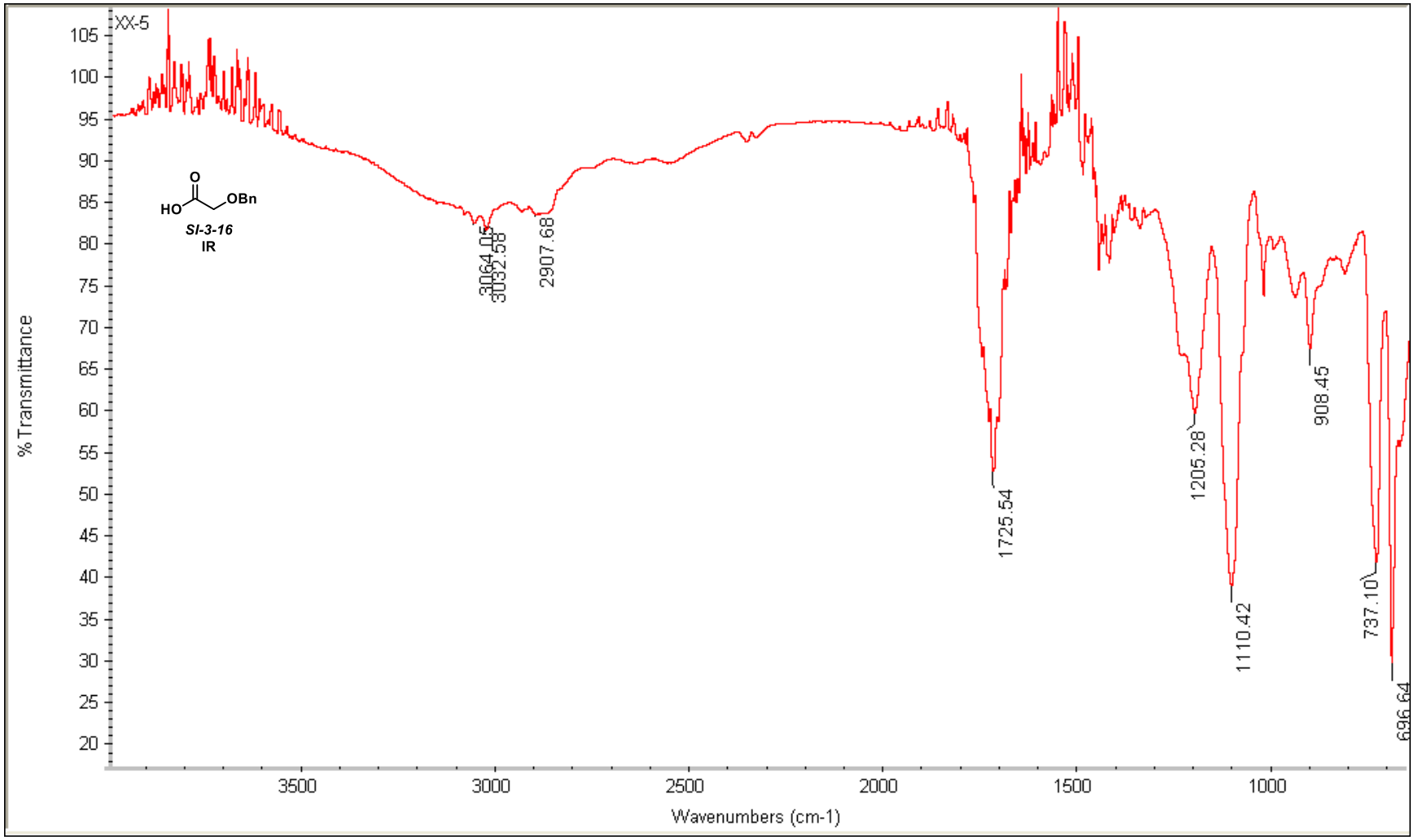
3-55

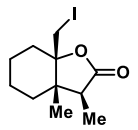
^{13}C NMR

(101 MHz, $CDCl_3$)


O
HO
OBn
SI-3-16
1H NMR
(400 MHz, CDCl3)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


O
HO
OBn
SI-3-16
13C NMR
(101 MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

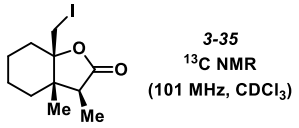

XX-5
SI-3-16
IR
HO
O
OBn
% Transmittance
Wavenumbers (cm-1)
3064.05
3032.58
2907.68
1725.54
1205.28
1110.42
908.45
737.10
696.64



3-35

^{1}H NMR

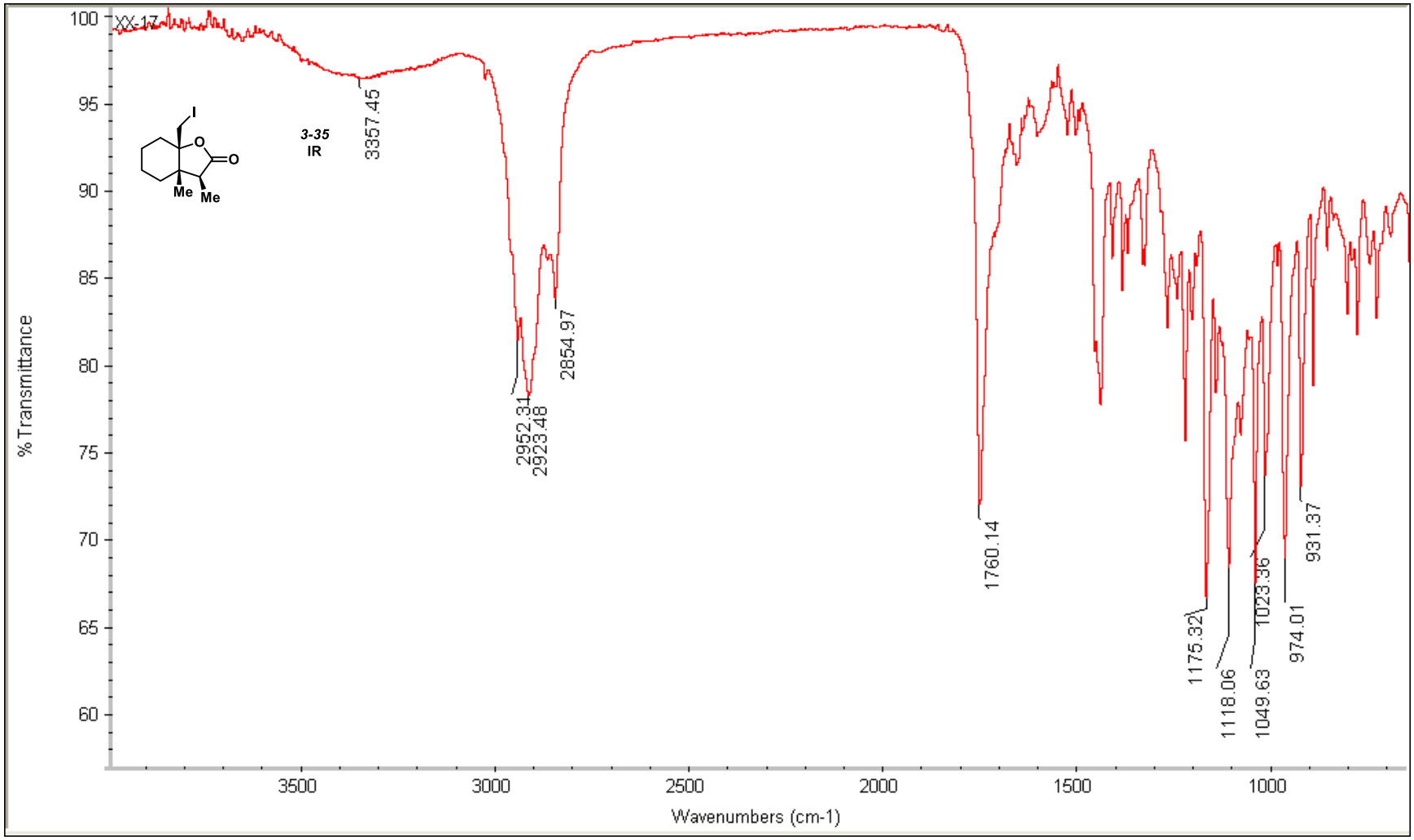
(400 MHz, $CDCl_3$)



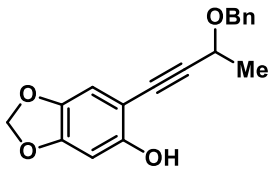
3-35

^{13}C NMR

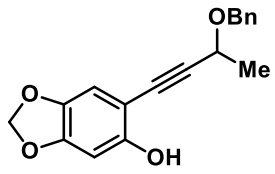
(101 MHz, $CDCl_3$)


XX-17
3-35
IR
I
O
O
Me
Me
% Transmittance
100
95
90
85
80
75
70
65
60
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
3357.45
2952.31
2923.48
2854.97
1760.14
1175.32
1118.06
1049.63
1023.36
974.01
931.37

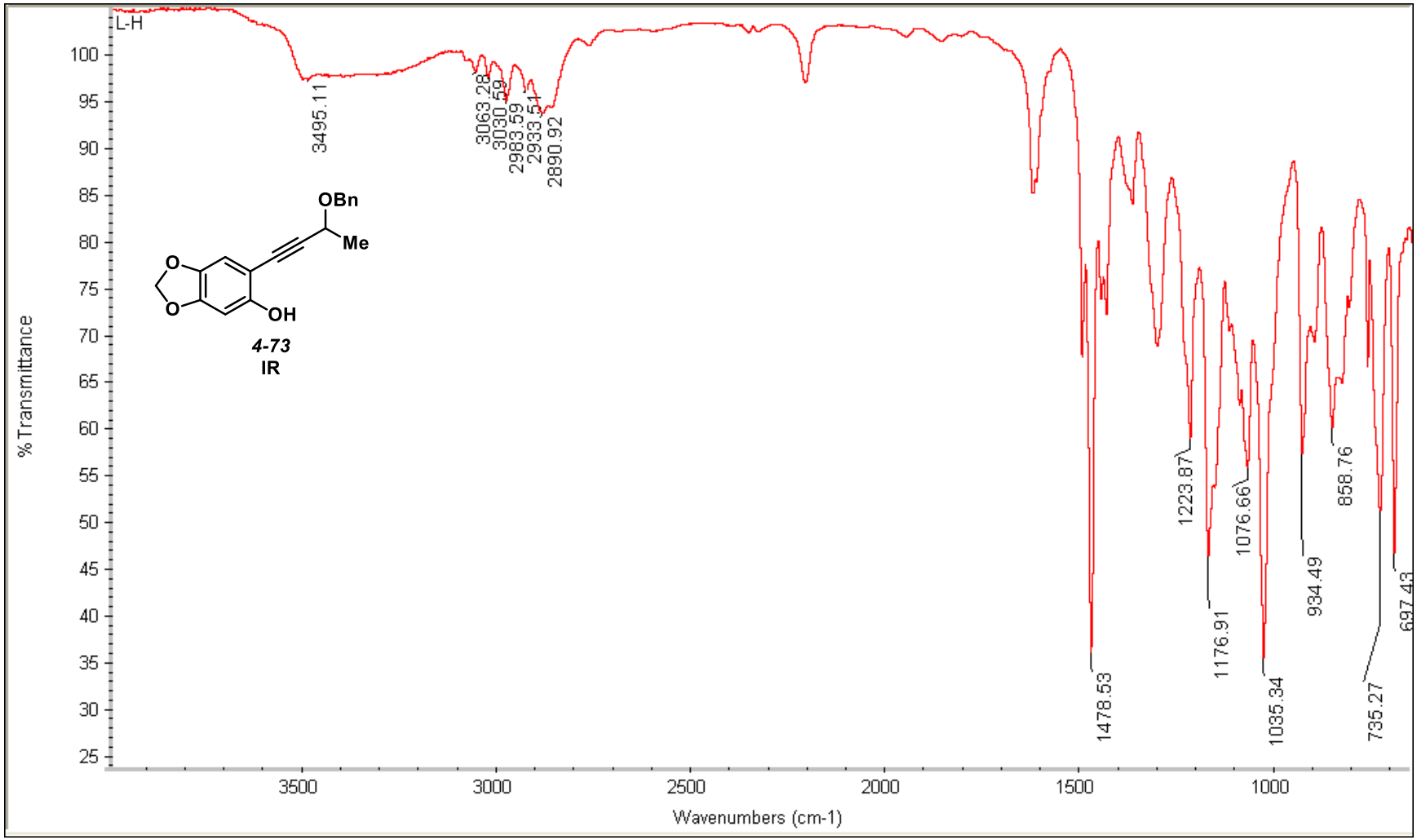
Appendix Six: Spectra Relevant to Chapter Four.

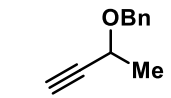


4-73
^{1}H NMR
($CDCl_3$, 400 MHz)

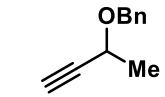


4-73
^{13}C NMR
($CDCl_3$, 101 MHz)

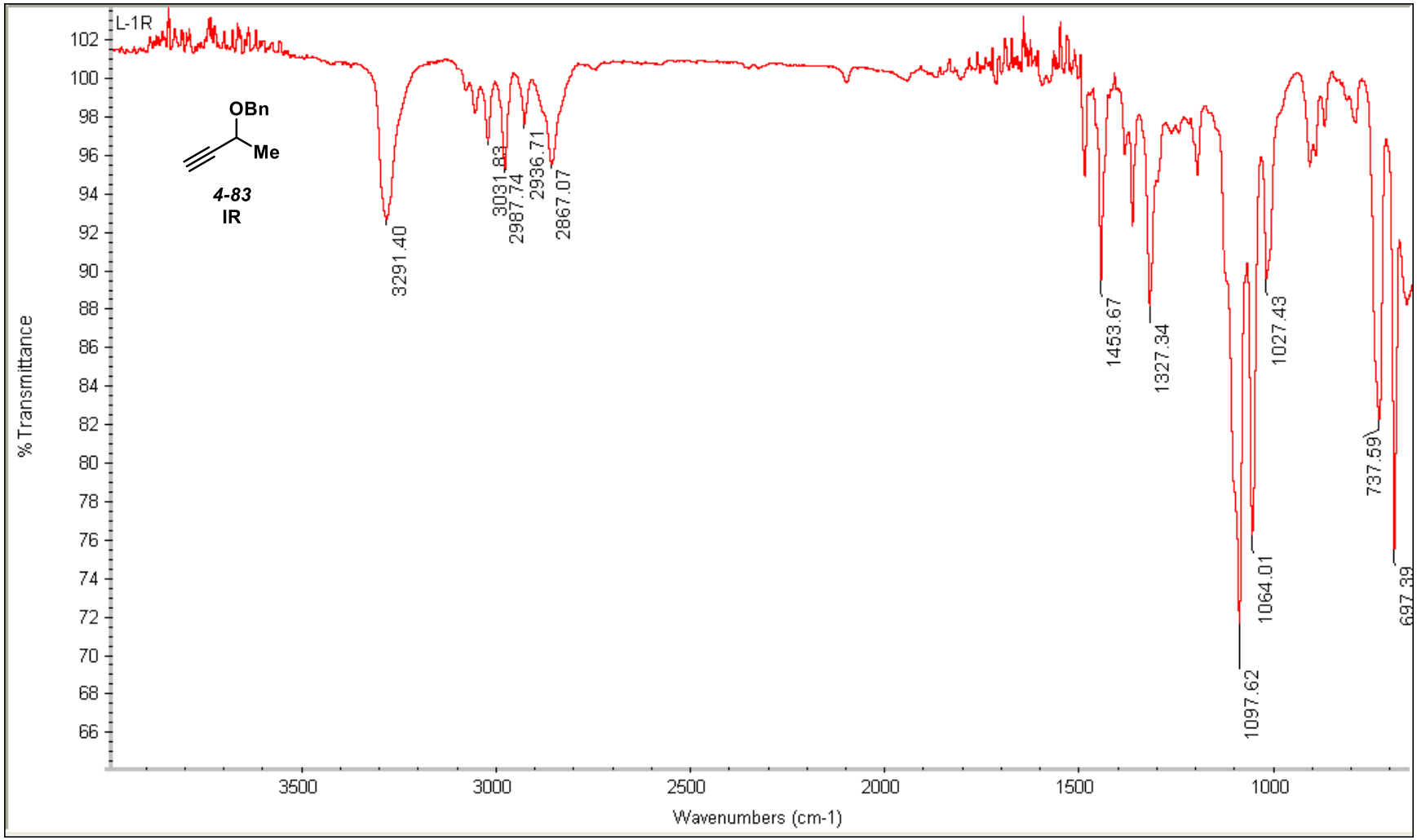

L-H
% Transmittance
Wavenumbers (cm-1)
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
3495.11
3063.28
3030.59
2983.59
2933.54
2890.92
1478.53
1223.87
1176.91
1076.66
1035.34
934.49
858.76
735.27
697.43
OBn
Me
O
O
OH
4-73
IR

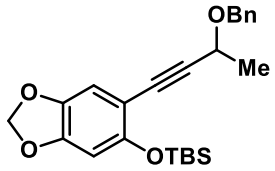


4-83
^{1}H NMR
($CDCl_3$, 400 MHz)

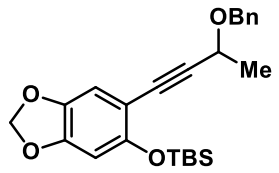


4-83
^{13}C NMR
($CDCl_3$, 101 MHz)

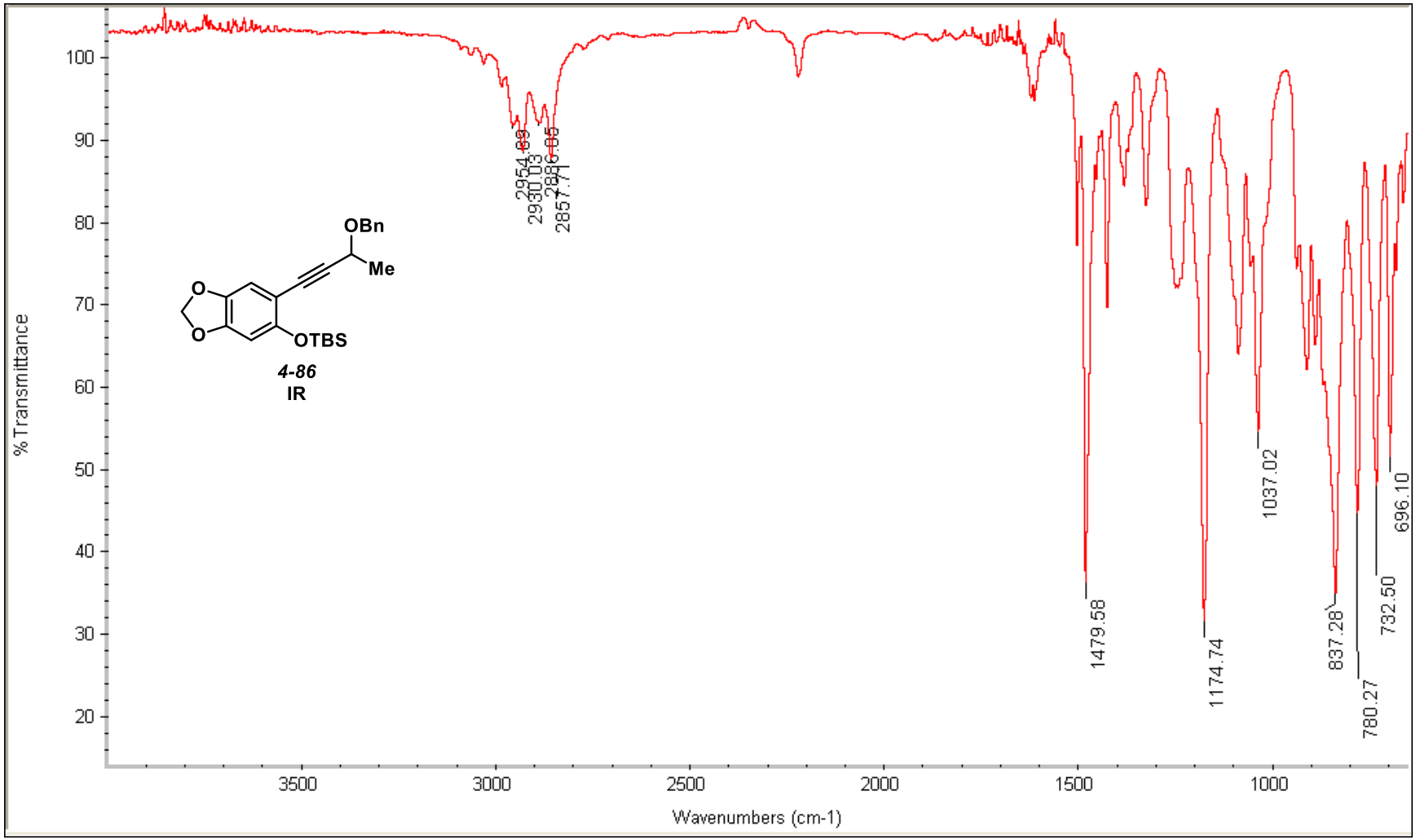

L-1R
OBn
Me
4-83
IR
3291.40
3031.83
2987.74
2936.71
2867.07
1453.67
1327.34
1097.62
1064.01
1027.43
737.59
697.39
% Transmittance
Wavenumbers (cm-1)

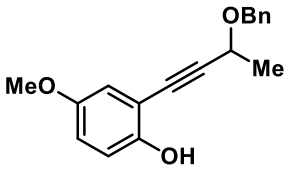


4-86
^{1}H NMR
($CDCl_3$, 400 MHz)

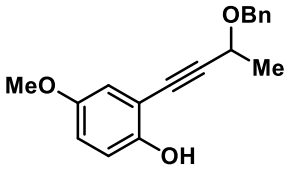


4-86
^{13}C NMR
($CDCl_3$, 101 MHz)

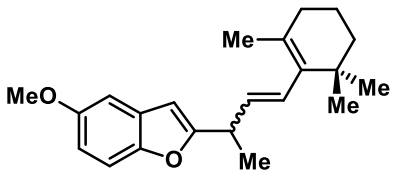

OBn
Me
O
O
OTBS
4-86
IR
% Transmittance
100
90
80
70
60
50
40
30
20
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)
2954.69
2930.03
2886.85
2857.71
1479.58
1174.74
1037.02
837.28
780.27
732.50
696.10



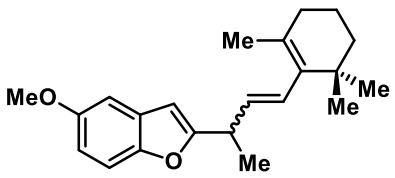
4-99
^{1}H NMR
($CDCl_3$, 400 MHz)



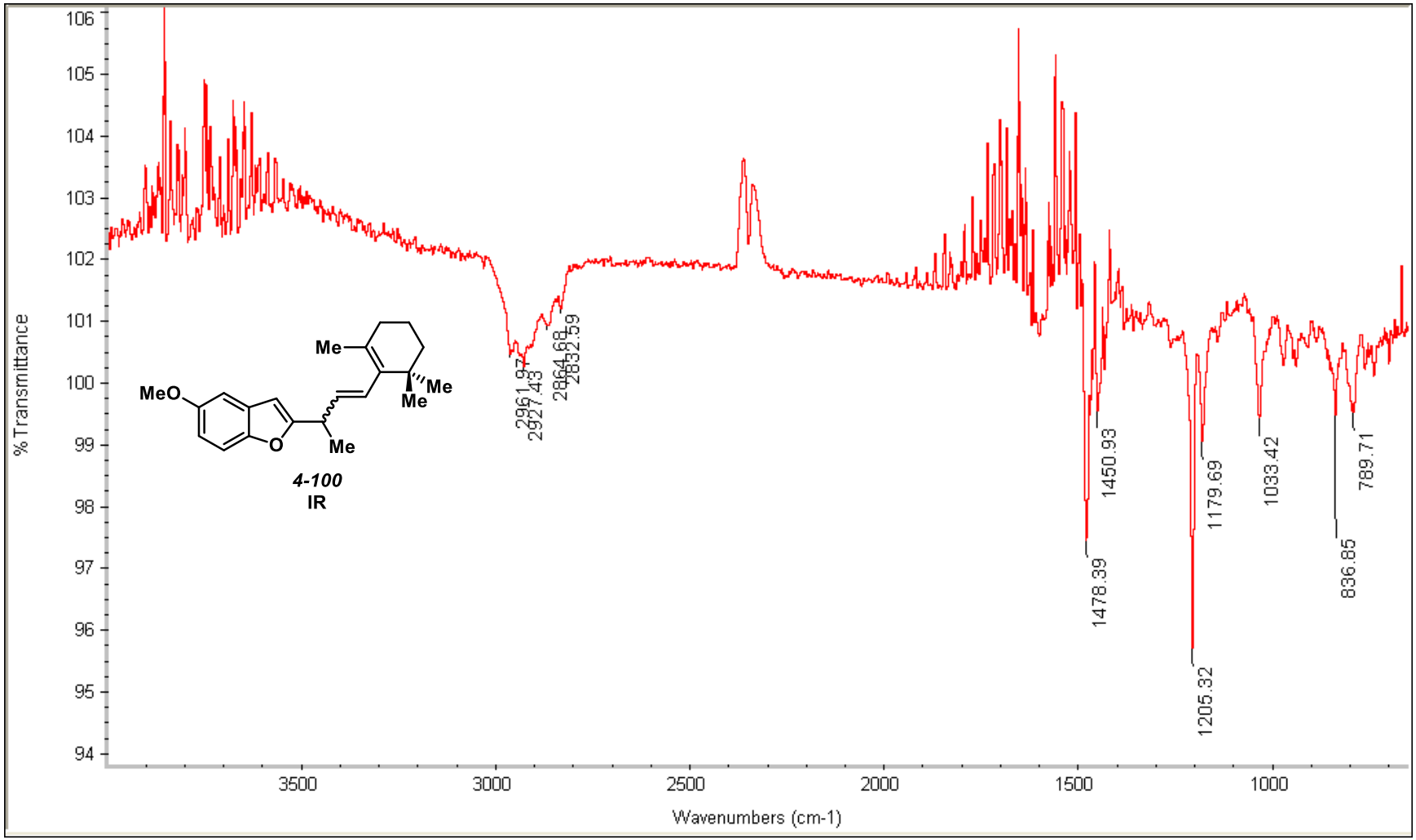
4-99
^{13}C NMR
($CDCl_3$, 101 MHz)

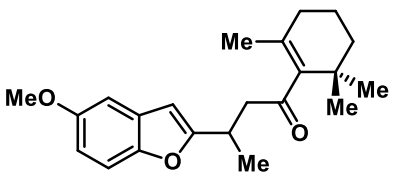


4-100
^{1}H NMR
($CDCl_3$, 400 MHz)

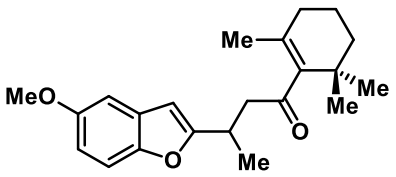


4-100
^{13}C NMR
($CDCl_3$, 101 MHz)

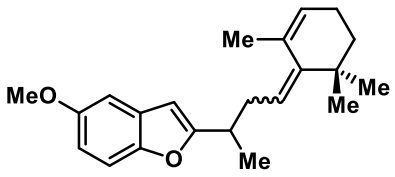

% Transmittance
Wavenumbers (cm-1)
MeO
Me
Me
Me
Me
O
4-100
IR
2961.97
2927.43
2864.68
2832.59
1478.39
1450.93
1205.32
1179.69
1033.42
836.85
789.71



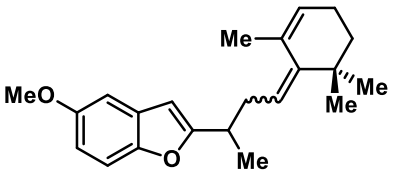
4-116
^{1}H NMR
($CDCl_3$, 400 MHz)



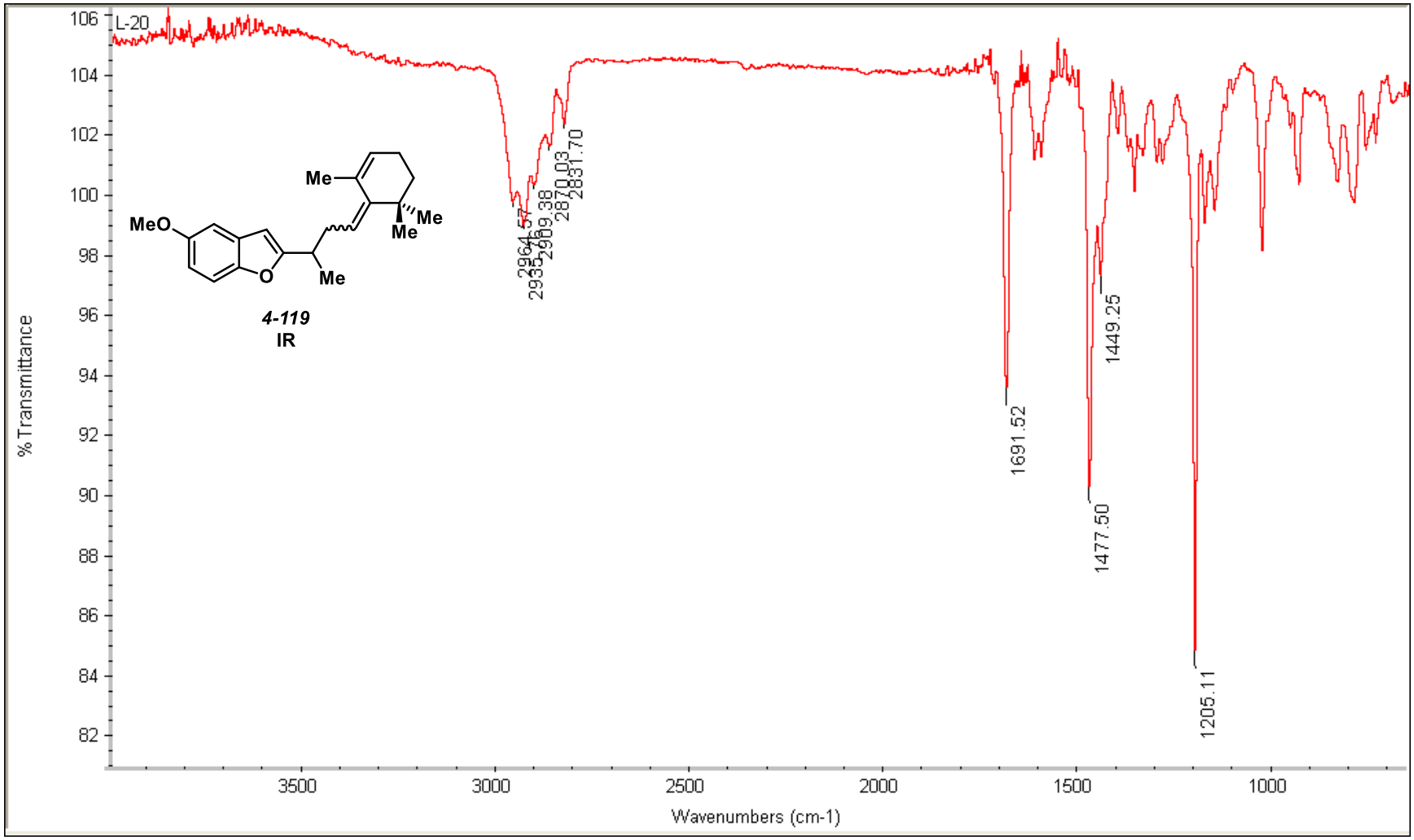
4-116
^{13}C NMR
($CDCl_3$, 101 MHz)

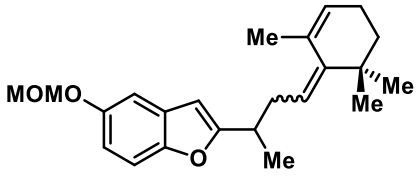


4-119
^{1}H NMR
($CDCl_3$, 400 MHz)

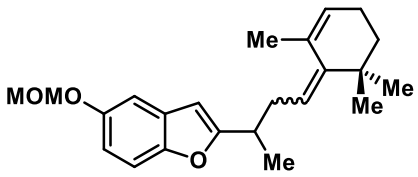


4-119
^{13}C NMR
($CDCl_3$, 101 MHz)

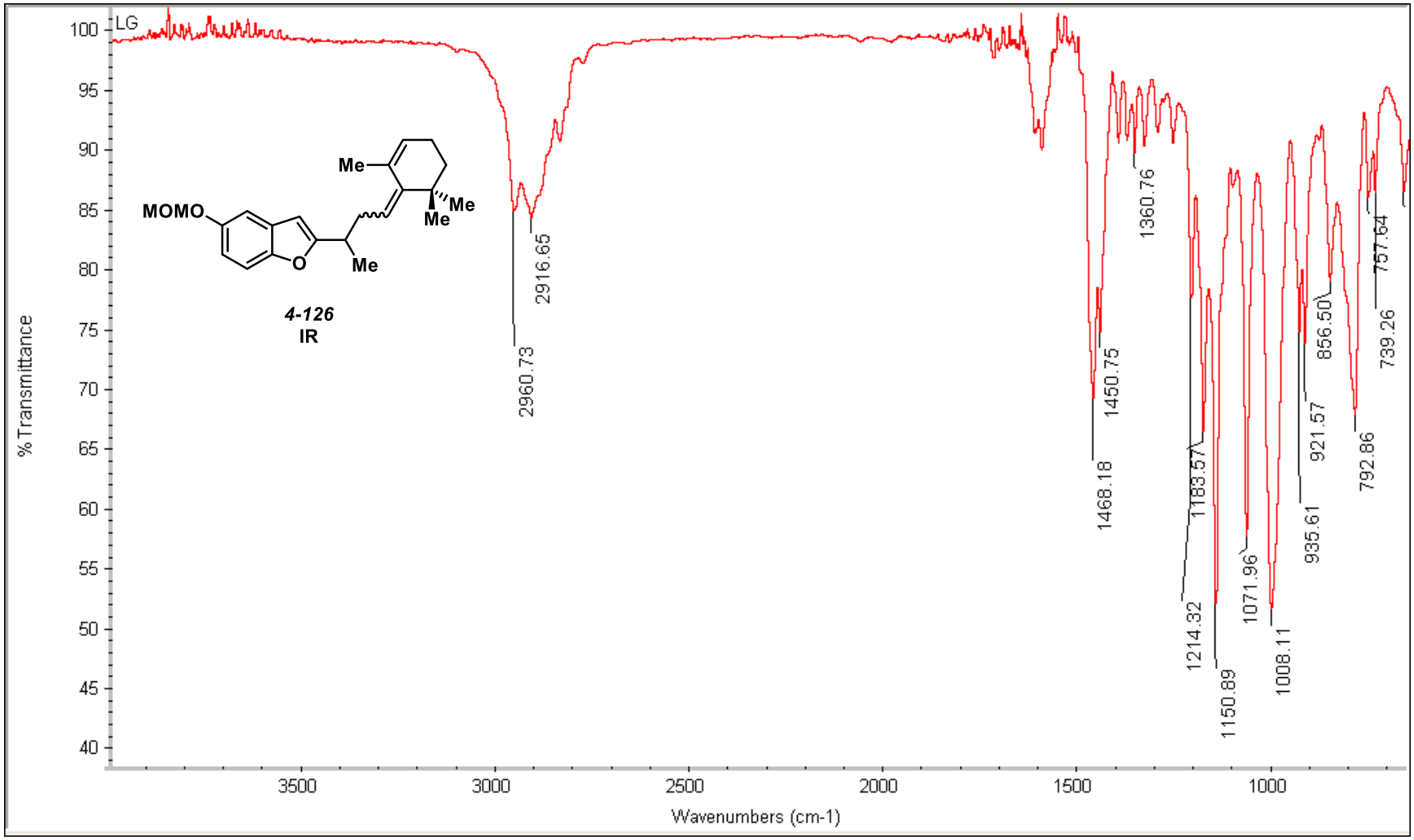

L-20
MeO
Me
Me
Me
Me
4-119
IR
% Transmittance
Wavenumbers (cm-1)
2964.57
2935.76
2909.38
2870.03
2831.70
1691.52
1477.50
1449.25
1205.11

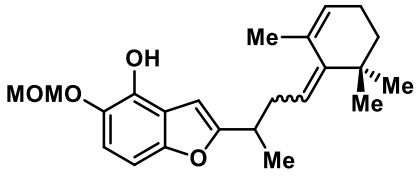


4-126
^{1}H NMR
($CDCl_3$, 400 MHz)

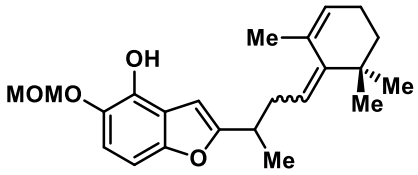


4-126
^{13}C NMR
($CDCl_3$, 101 MHz)

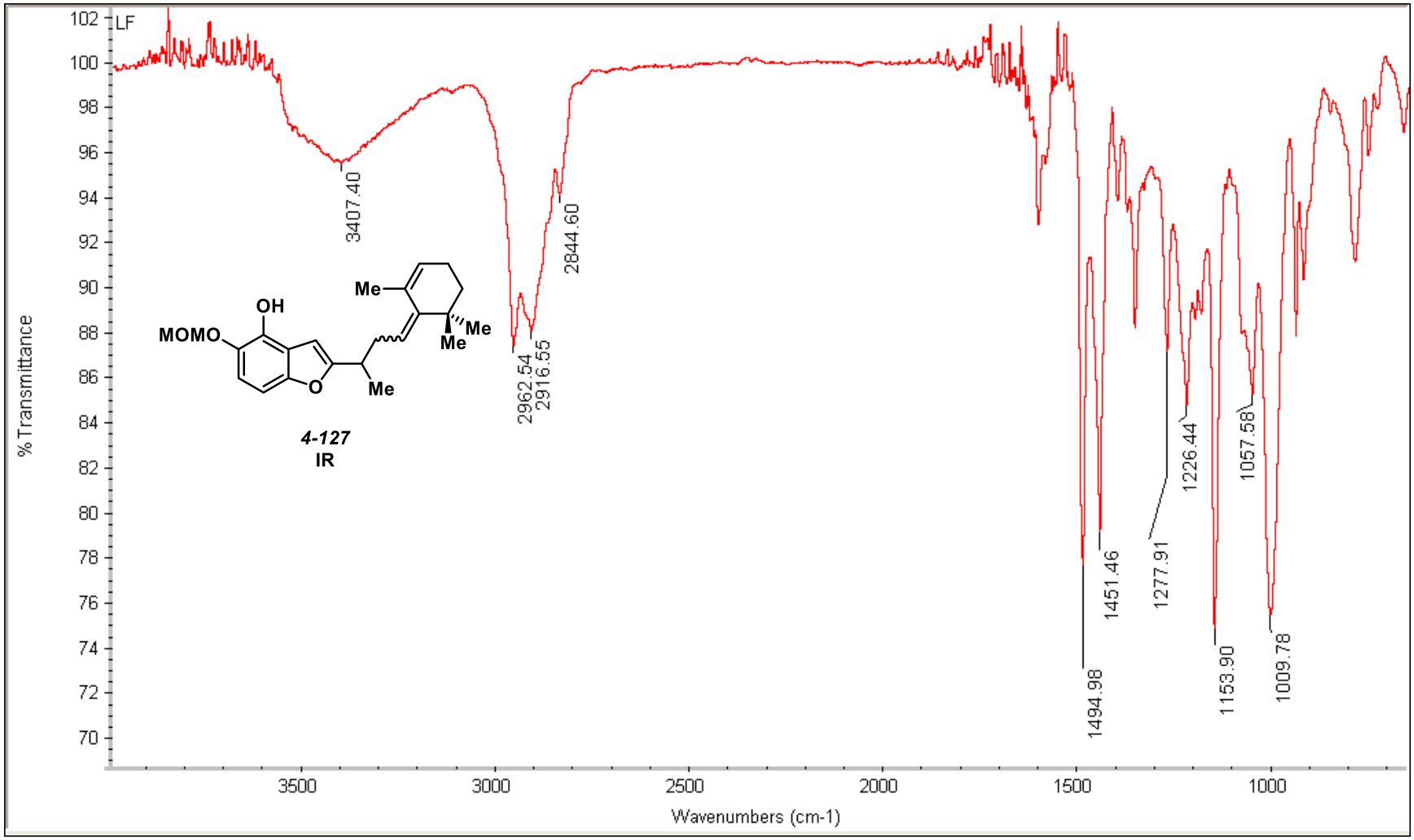

LG
MOMO
Me
Me
Me
O
Me
4-126
IR
% Transmittance
Wavenumbers (cm-1)
2960.73
2916.65
1468.18
1450.75
1360.76
1214.32
1183.57
1150.89
1071.96
1008.11
935.61
921.57
856.50
792.86
757.64
739.26

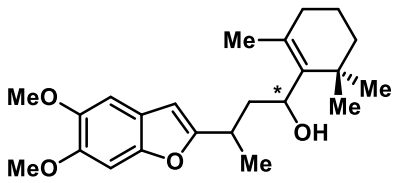


4-127
^{1}H NMR
($CDCl_3$, 400 MHz)

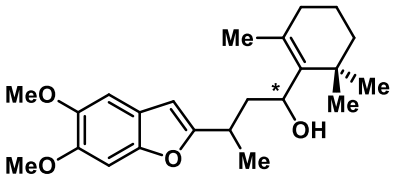


4-127
^{13}C NMR
($CDCl_3$, 101 MHz)

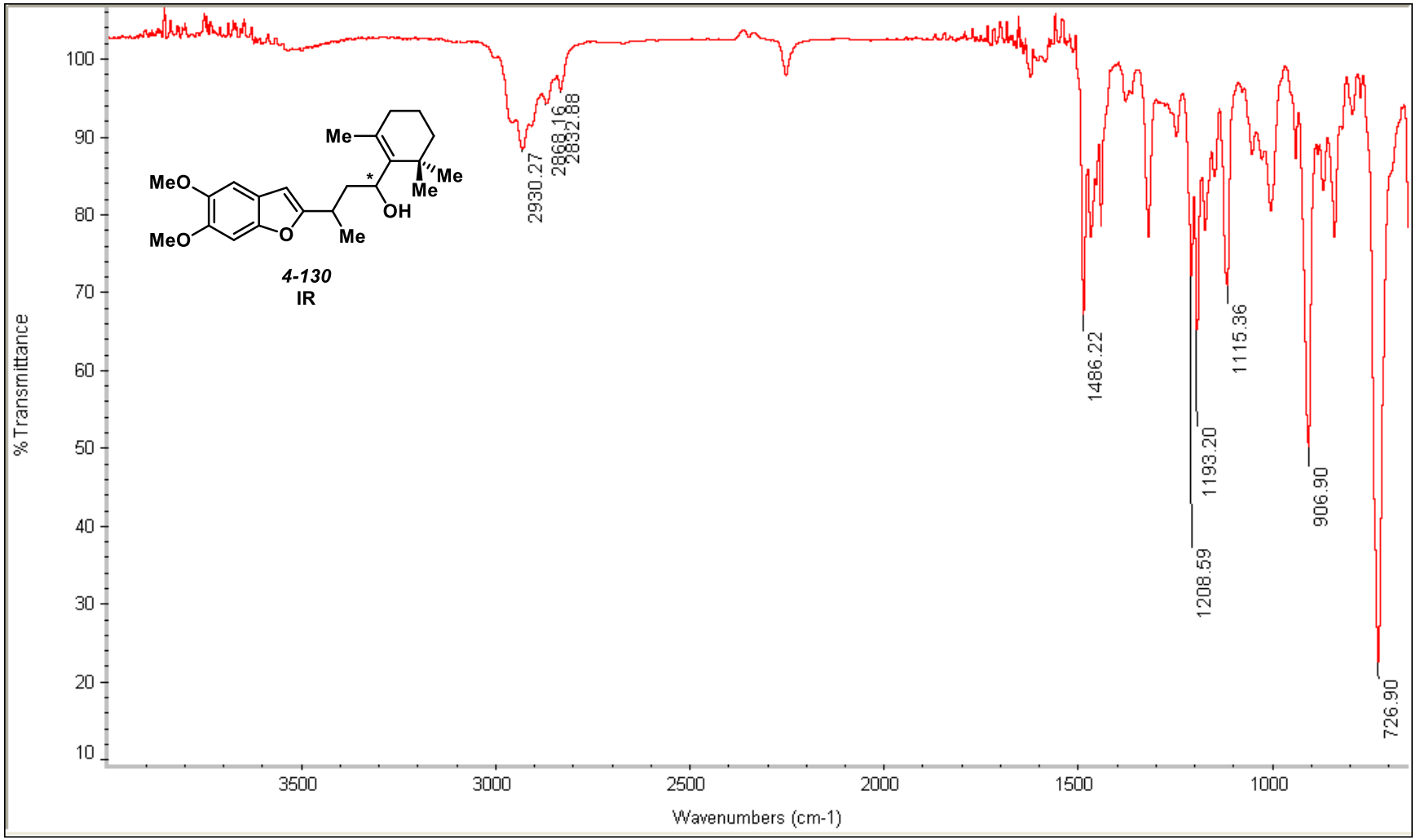

LF
% Transmittance
Wavenumbers (cm-1)
3407.40
2962.54
2916.55
2844.60
1494.98
1451.46
1277.91
1226.44
1153.90
1057.58
1009.78
OH
MOMO
Me
Me
Me
Me
O
4-127
IR

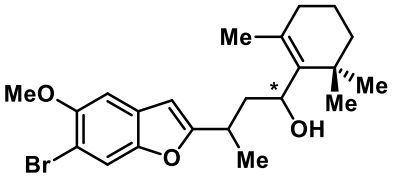


4-130
^{1}H NMR
($CDCl_3$, 400 MHz)

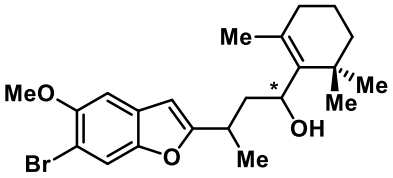


4-130
^{13}C NMR
($CDCl_3$, 101 MHz)

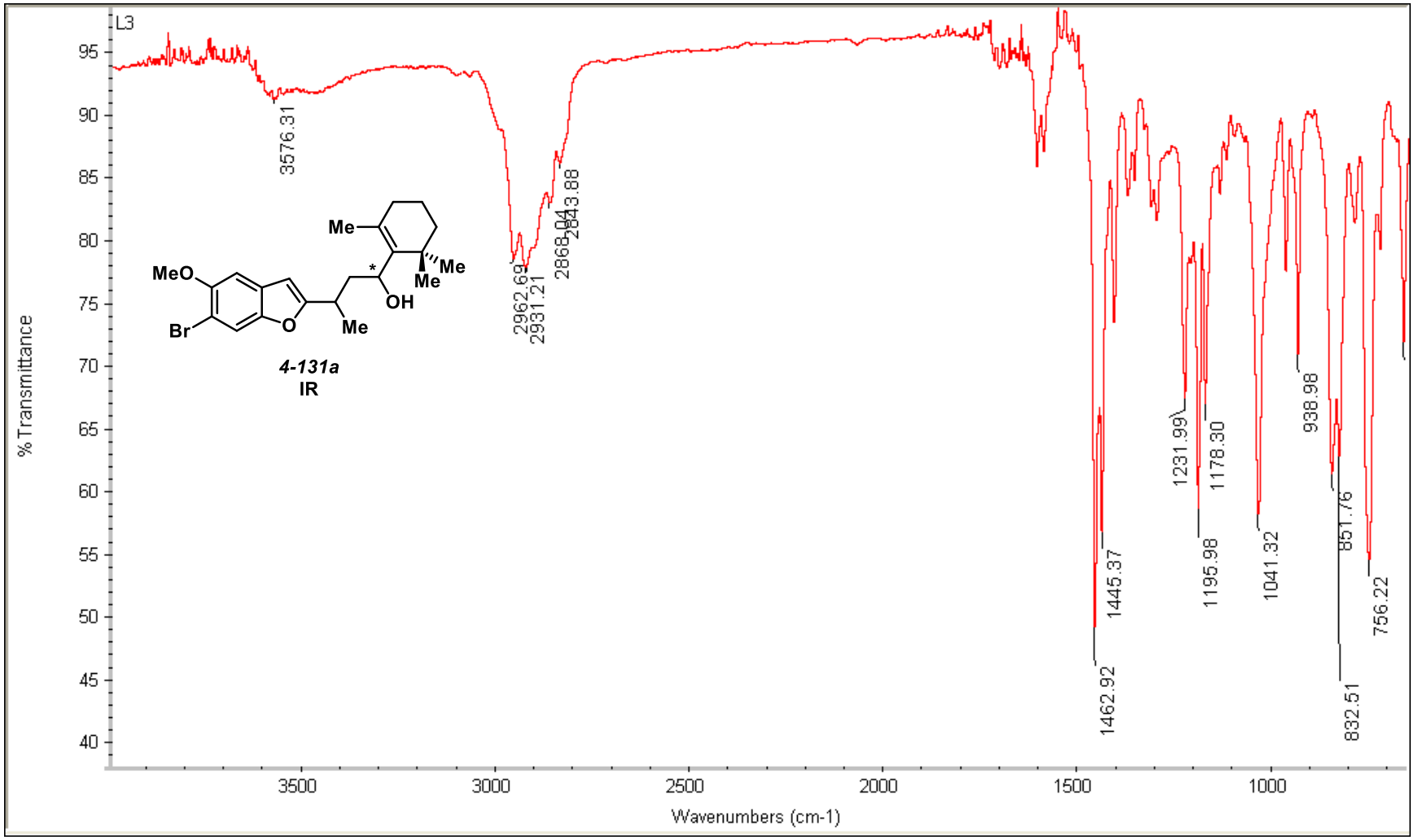

4-130
IR
% Transmittance
Wavenumbers (cm-1)
2930.27
2868.16
2832.88
1486.22
1208.59
1193.20
1115.36
906.90
726.90

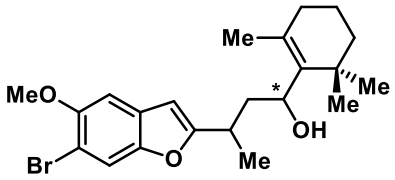


4-131a
^{1}H NMR
($CDCl_3$, 400 MHz)

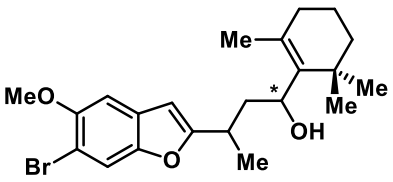


4-131a
^{13}C NMR
($CDCl_3$, 101 MHz)

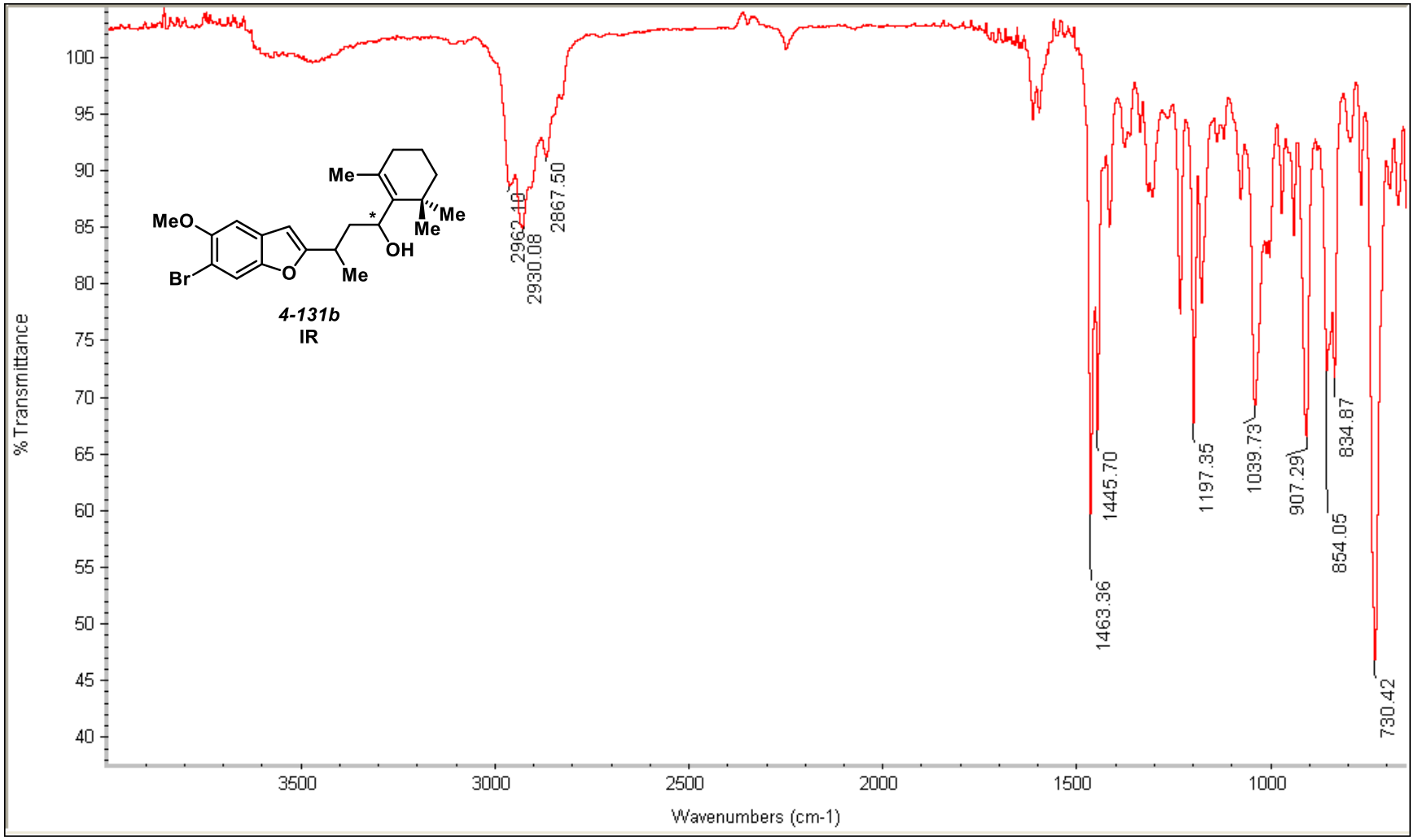

L3
% Transmittance
Wavenumbers (cm-1)
3576.31
2962.69
2931.21
2868.04
2843.88
1462.92
1445.37
1231.99
1195.98
1178.30
1041.32
938.98
851.76
832.51
756.22
MeO
Br
O
Me
OH
Me
Me
Me
*
4-131a
IR

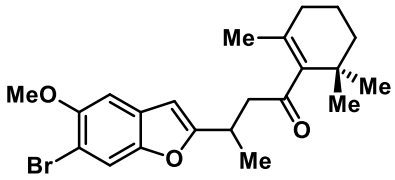


4-131b
^{1}H NMR
($CDCl_3$, 400 MHz)

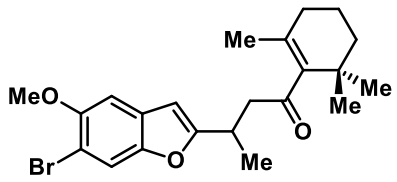


4-131b
^{13}C NMR
($CDCl_3$, 101 MHz)

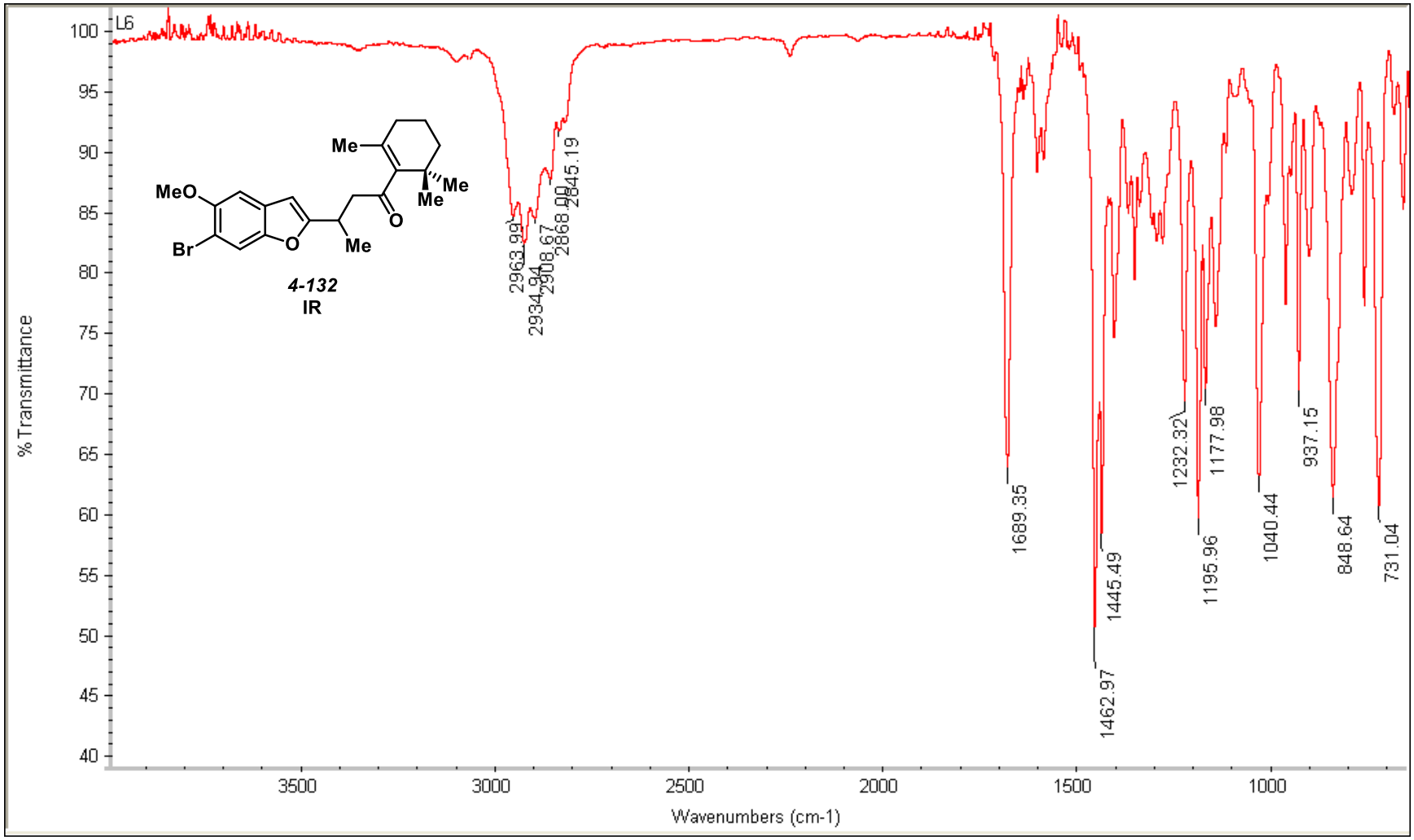

MeO
Br
O
Me
OH
Me
Me
Me
*
4-131b
IR
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
3500
3000
2500
2000
1500
1000
2962.10
2930.08
2867.50
1463.36
1445.70
1197.35
1039.73
907.29
854.05
834.87
730.42

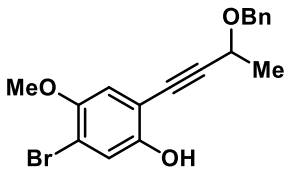


4-132
^{1}H NMR
($CDCl_3$, 400 MHz)

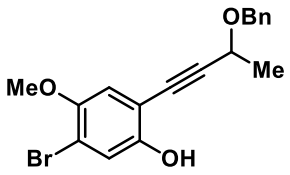


4-132
^{13}C NMR
($CDCl_3$, 101 MHz)

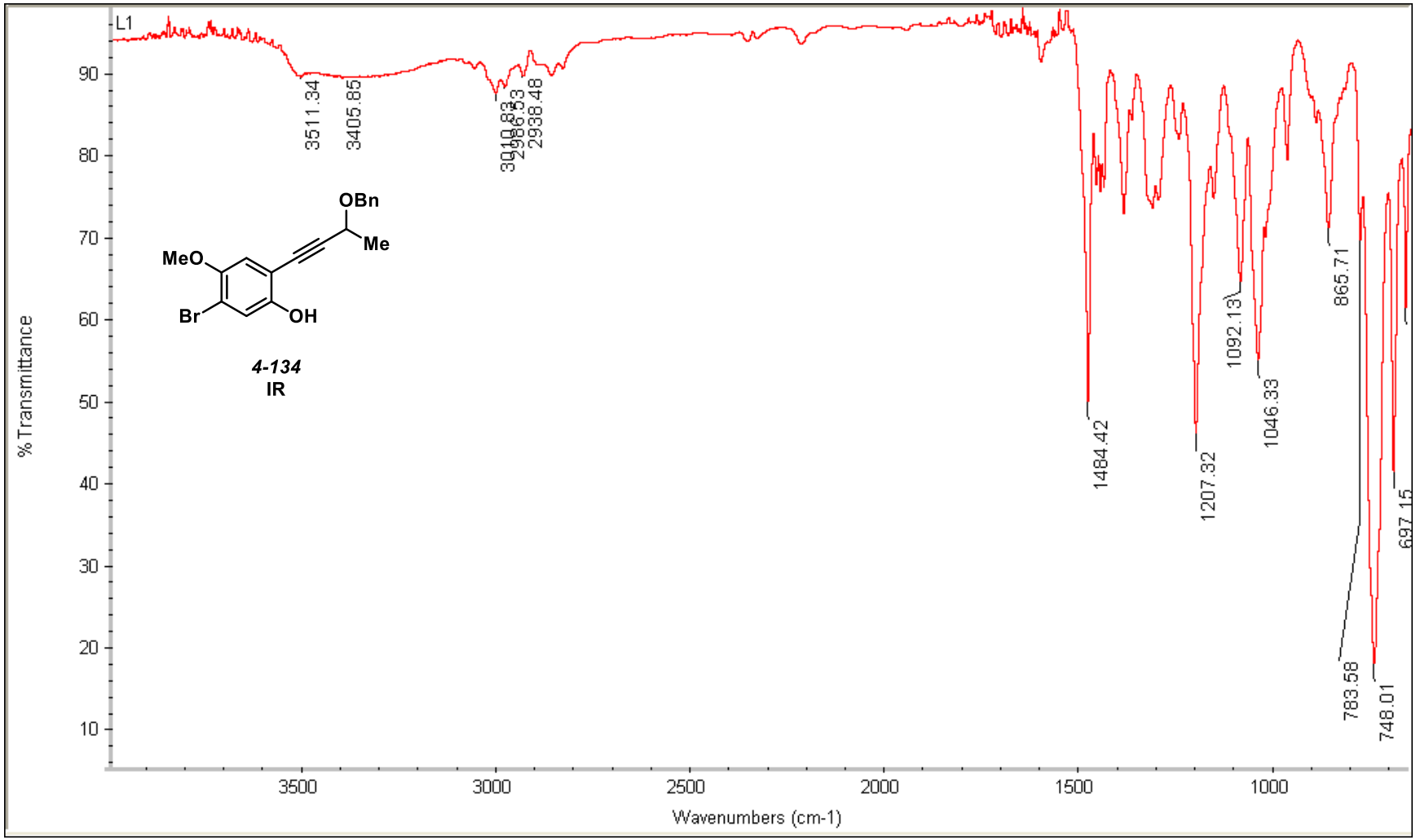

L6
MeO
Br
O
Me
Me
Me
Me
O
4-132
IR
% Transmittance
Wavenumbers (cm-1)
2963.99
2934.94
2908.67
2868.00
2845.19
1689.35
1462.97
1445.49
1232.32
1195.96
1177.98
1040.44
937.15
848.64
731.04

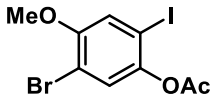


4-134
^{1}H NMR
($CDCl_3$, 400 MHz)

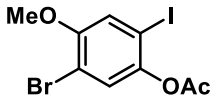


4-134
^{13}C NMR
($CDCl_3$, 101 MHz)

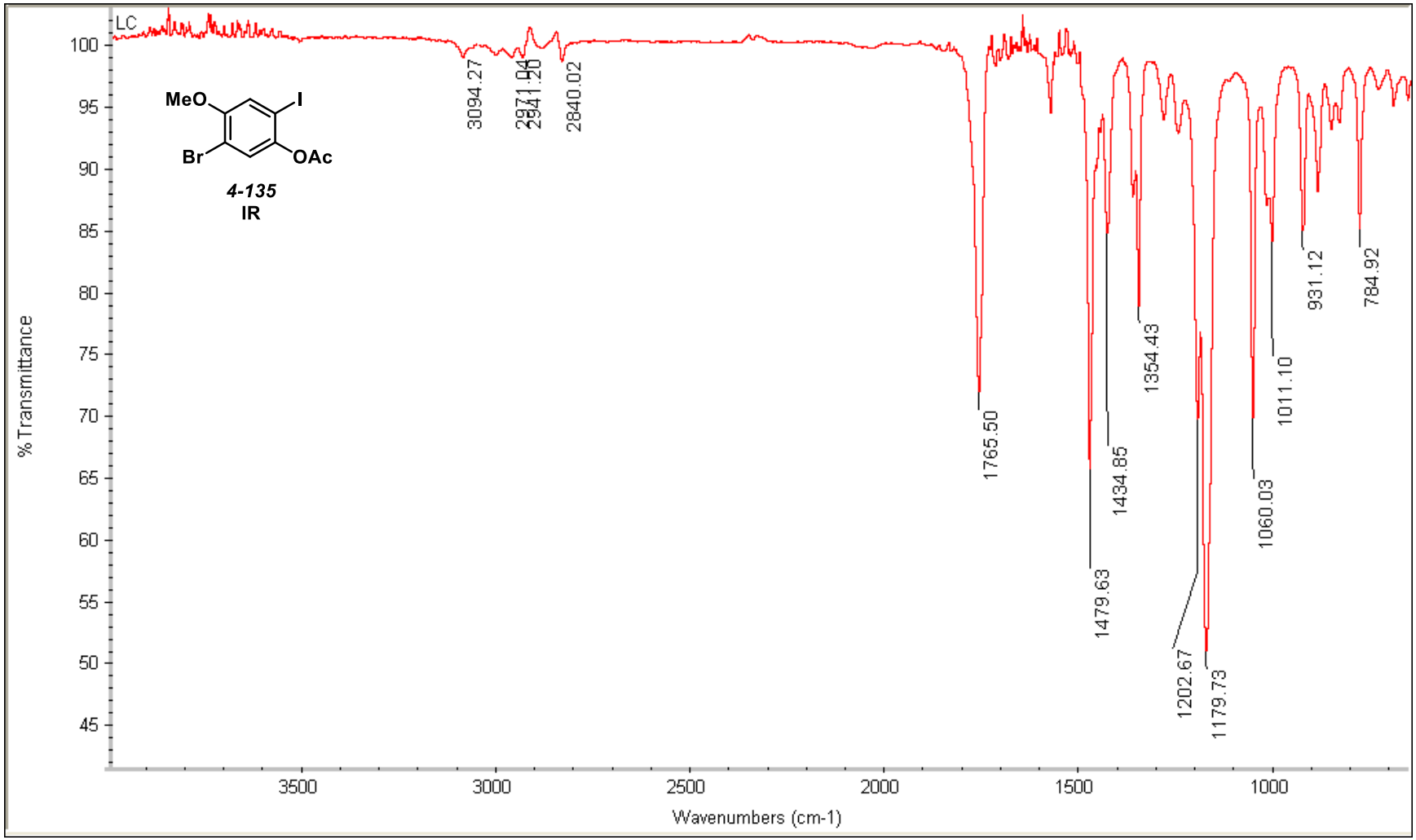

L1
3511.34
3405.85
3010.83
2986.63
2938.48
1484.42
1207.32
1092.13
1046.33
865.71
783.58
748.01
697.15
% Transmittance
Wavenumbers (cm-1)
OBn
Me
MeO
Br
OH
4-134
IR

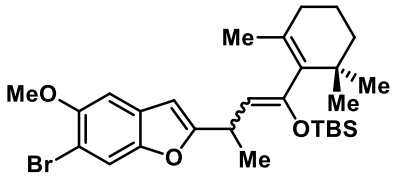


4-135
^{1}H NMR
($CDCl_3$, 400 MHz)

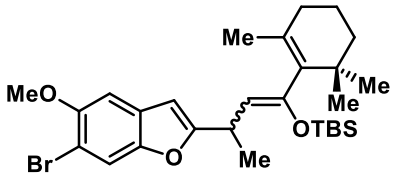


4-135
^{13}C NMR
($CDCl_3$, 101 MHz)

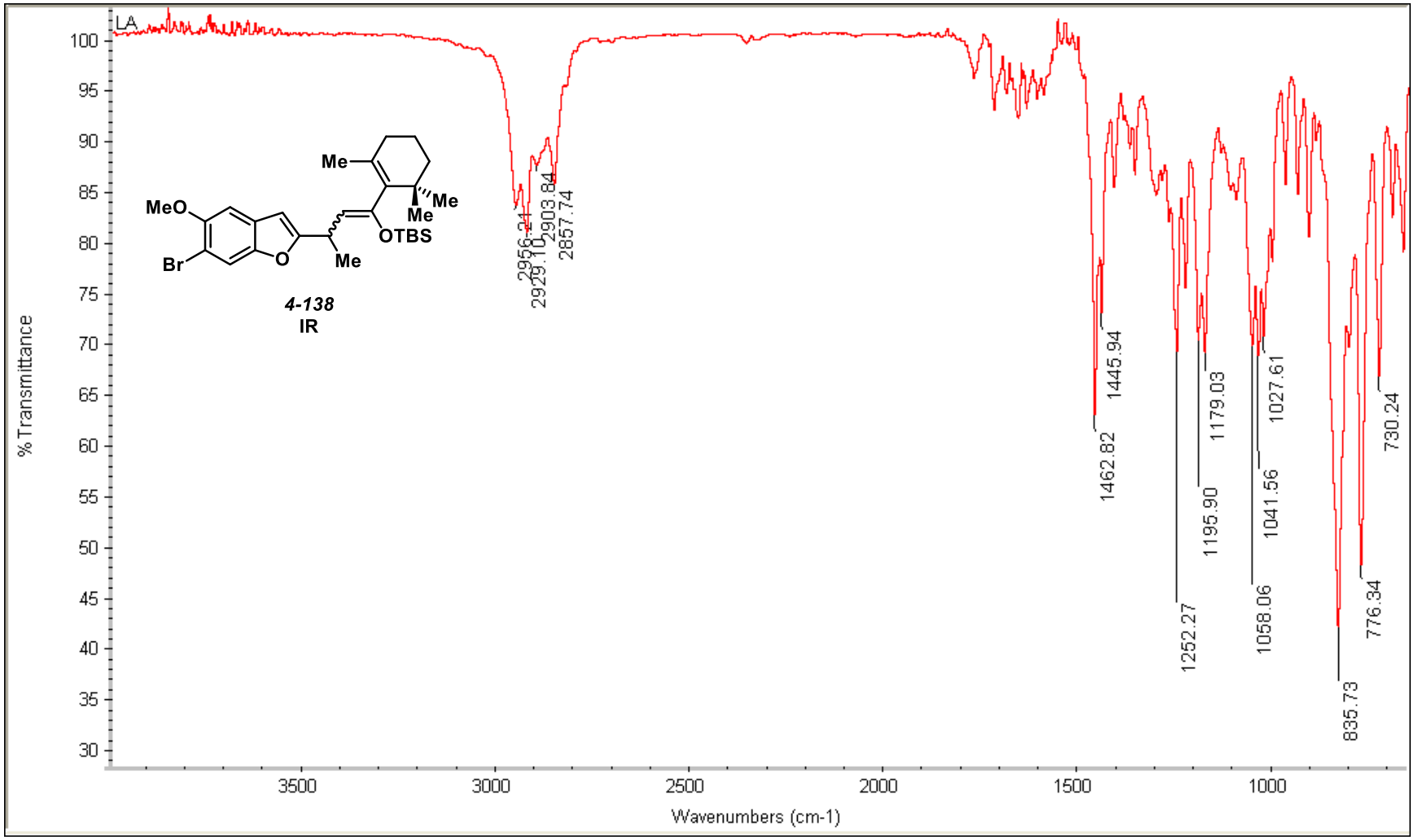

LC
MeO
I
Br
OAc
4-135
IR
3094.27
2971.94
2941.20
2840.02
1765.50
1479.63
1434.85
1354.43
1202.67
1179.73
1060.03
1011.10
931.12
784.92
% Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
3500
3000
2500
2000
1500
1000
Wavenumbers (cm-1)

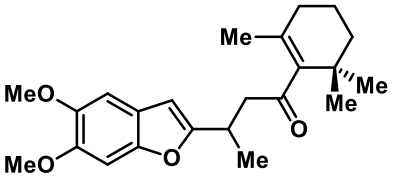


4-138
^{1}H NMR
($CDCl_3$, 400 MHz)

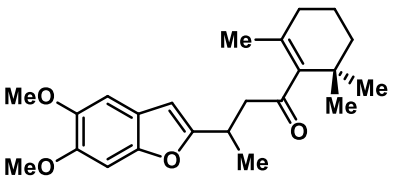


4-138
^{13}C NMR
($CDCl_3$, 101 MHz)

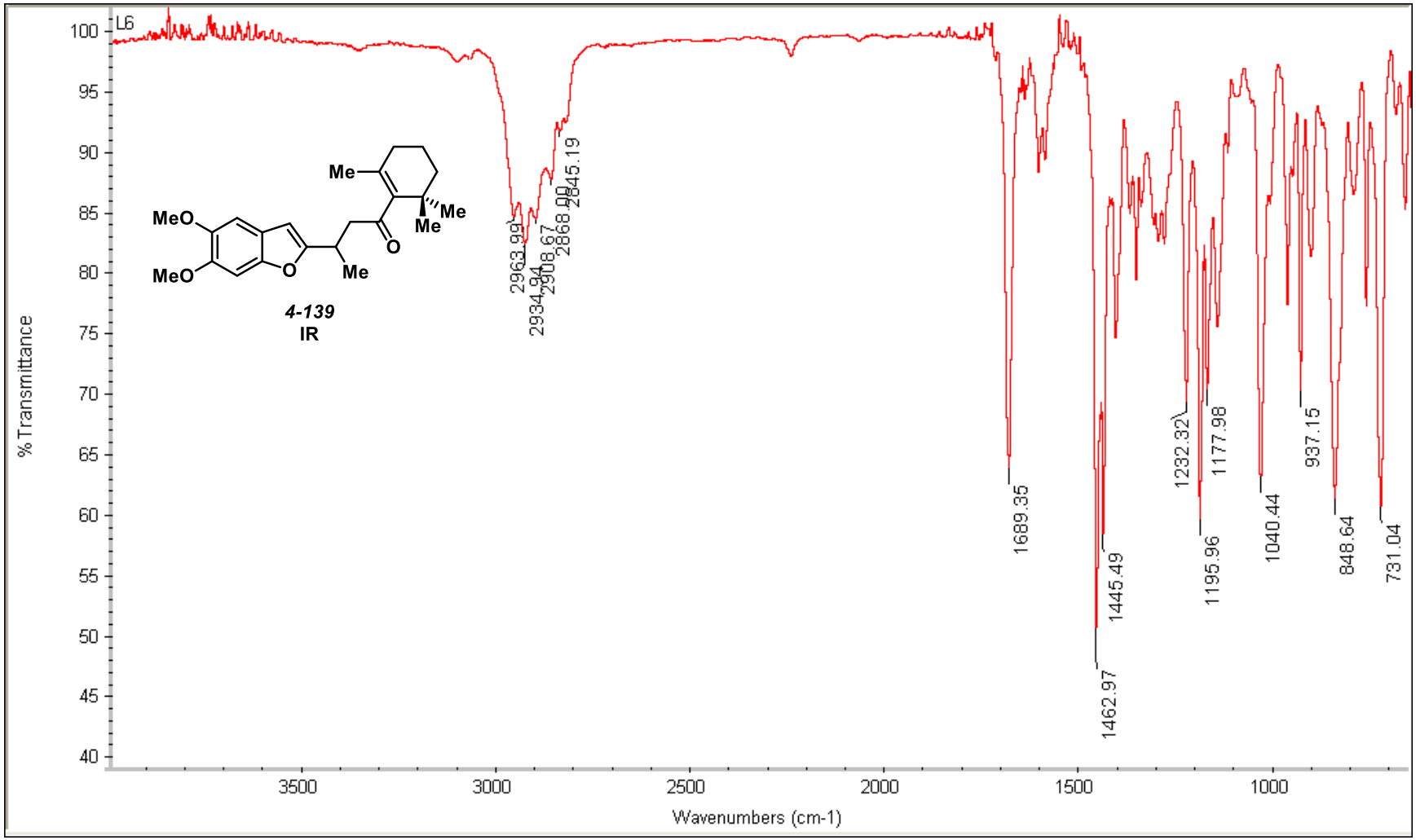

LA
% Transmittance
Wavenumbers (cm-1)
MeO
Br
O
Me
OTBS
Me
Me
Me
4-138
IR
2956.24
2929.10
2903.84
2857.74
1462.82
1445.94
1252.27
1195.90
1179.03
1058.06
1041.56
1027.61
835.73
776.34
730.24

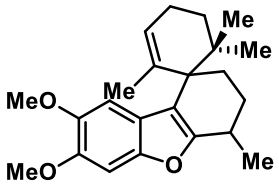


4-139
^{1}H NMR
($CDCl_3$, 400 MHz)

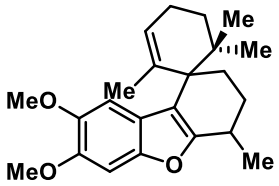


4-139
^{13}C NMR
($CDCl_3$, 101 MHz)

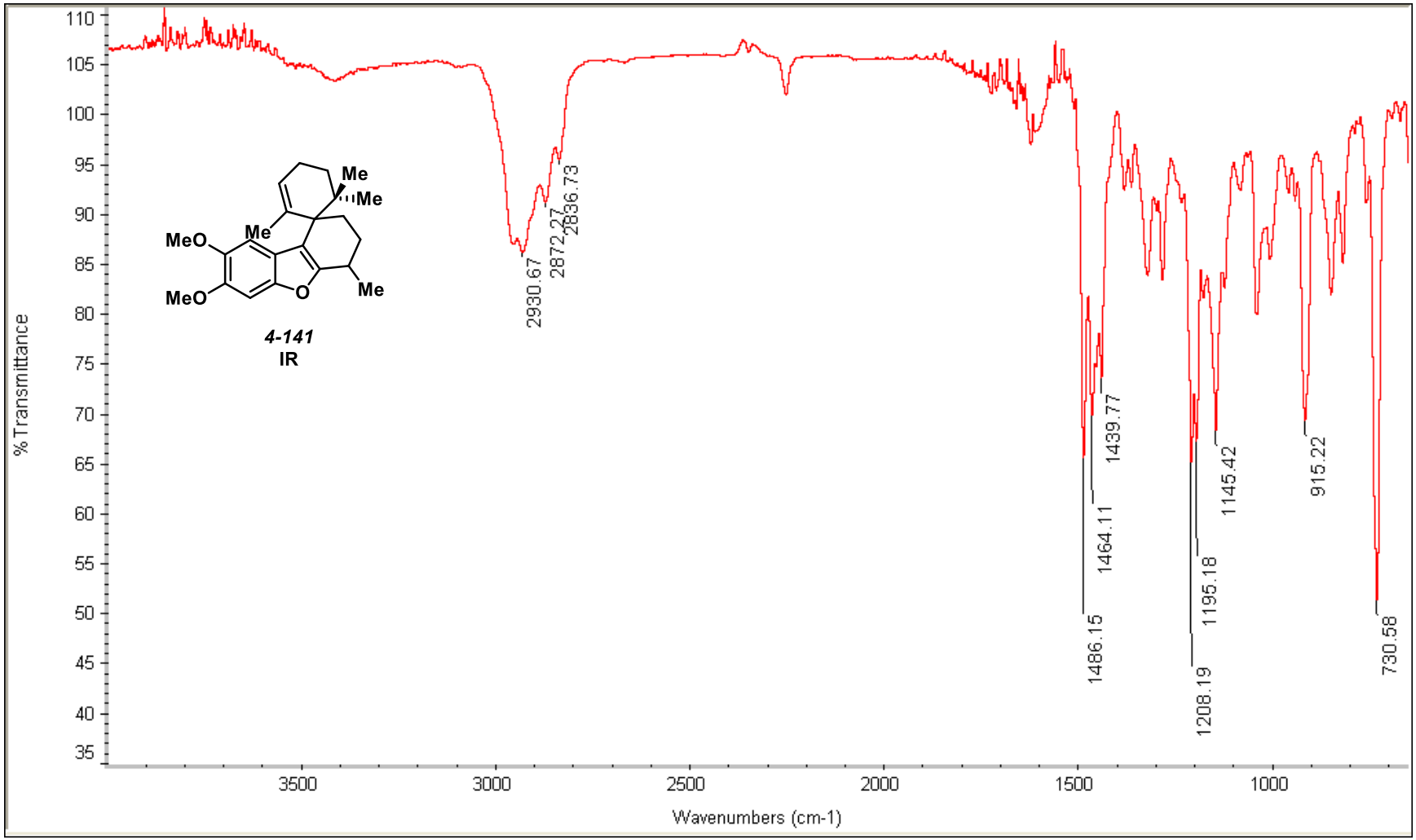

L6
% Transmittance
Wavenumbers (cm-1)
100
95
90
85
80
75
70
65
60
55
50
45
40
3500
3000
2500
2000
1500
1000
2963.99
2934.94
2908.67
2868.00
2845.19
1689.35
1462.97
1445.49
1232.32
1195.96
1177.98
1040.44
937.15
848.64
731.04
MeO
MeO
O
Me
Me
Me
Me
O
4-139
IR



4-141
^{1}H NMR
($CDCl_3$, 400 MHz)



4-141
^{13}C NMR
($CDCl_3$, 101 MHz)


% Transmittance
Wavenumbers (cm-1)
2930.67
2872.27
2836.73
1486.15
1464.11
1439.77
1208.19
1195.18
1145.42
915.22
730.58
MeO
MeO
Me
Me
Me
Me
O
4-141
IR