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Development and Applications of (Hetero)cycloisomerization Methodologies to Access Natural Product Scaffolds

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Development and Applications of (Hetero)cycloisomerization Methodologies to Access Natural Product Scaffolds

by

Sidney Malik Wilkerson-Hill

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requirements for the degree of

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In

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of the

University of California, Berkeley

Committee in charge:

Professor Richmond Sarpong, Chair
Professor Matthew B. Francis
Professor Wenjun Zhang

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Abstract

Development and Applications of (Hetero)cycloisomerization Methodologies to Access Natural Product Scaffolds

by

Sidney Malik Wilkerson-Hill

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

The development of new heterocycloisomerization reactions as a tactic to access natural product scaffolds is an active area of research. Chapter 1 describes the development of a new heterocycloisomerization reaction of alkynyl-[4.1.0]-bicycloheptanones using $W(CO)_5$•THF complex to access 4,5-dihydrobenzo[b]-furans and –indoles. Specifically, the methodology developed provides a unique entry into dihydro-benzofurans and –indoles that contain carbon substitution at the C4-position, which is a common motif in many biologically active indole alkaloid natural products (e.g. the ergot alkaloids). The unique reactivity of dihydro-benzofurans and –indoles as it pertains to accessing natural product scaffolds is also described.

Chapter 2 describes a mechanistic investigation of the trace-metal catalyzed cycloisomerization of alkynyl-[4.1.0]-bicycloheptanones to access annulated aminopyrroles by heating the ketone substrates with *p*-toluenesulfonylhydrazide in methanol. From our mechanistic studies, we demonstrate that the cycloisomerization reaction, which was previously thought to have been metal free, is actually catalyzed by trace copper salts at parts-per-million loading. Furthermore, we demonstrate the presence of *E*- and *Z*-hydrazone intermediates and conclusively demonstrate that, the more sterically encumbered *Z*-hydrazone is initially formed in the reaction and is thermodynamically lower in energy than its corresponding *E*- isomer. These studies were carried out in collaboration with the Hein group at the University of California, Merced and the Tantillo Group at the University of California, Davis and are a testament to the importance and power of collaborative research.

Chapter 3 describes our efforts to leverage a Pt(II)-catalyzed carbocycloisomerization reaction as a means for accessing functionalized tetrahydrofluorenes through the use of 2-substituted indene compounds. We were able to synthesize a variety of functionalized tetrahydrofluorenes using a Diels—Alder cycloaddition reaction of 2-vinylindenes and various dienophiles. We also describe our attempts to effect a double Diels—Alder cycloaddition reaction using bisketenes or bisketene equivalents with 2-vinylindenes to

access the dimeric lomaiviticin natural products. Though we were unable to realize the desired double Diels—Alder cycloaddition reactivity, we discovered a new method for generating 3-oxidopyrylium ions from bis(1-cyanovinyl acetate). Furthermore, we were able to access a variety of 2-alkynyl indenes and utilize these substrates to access the carbocyclic core of the diterpenoid euphorbactin using Rh(II)-catalyzed cycloaddition chemistry.

To
Sheila M. Wilkerson, for shaping my past,
Charlotte E. Lewis, for loving and keeping me in the present
and Sonya M. Wilkerson, for a future full of laughter.

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"*We choose to go to the moon. We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win, and the others, too."*
– JFK Moon Speech – Rice Stadium, 09-12-1962

CHAPTER 1: TUNGSTEN-CATALYZED HETEROCYCLOISOMERIZATION OF [4.1.0]-BICYCLES TO ACCESS 4,5-DIHYDROBENZOFURANS AND -INDOLES

(with Dr. Ethan L. Fisher)

Fisher, E. L.; Wilkerson-Hill, S. M.; Sarpong, R.
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Section 1.0. Brief Historical Perspective on Indoles and Benzofurans and their Reactivity

The importance of heterocycles, especially indole and its derivatives, in chemistry is without question. Indeed, the discovery of the heterocyclic compound indigo, an oxindole-based alkaloid, in many ways gave rise to the pharmaceutical industry and, in some respects, to modern day natural products chemistry.[1] During the latter half of the 19th century, chemists developed an interest in natural products. Indigo was an early subject of their investigations as people realized the academic challenge and economic importance of synthesizing this compound.[2] This motivation of making molecules for academic or monetary value still exists to this very day. The first synthetic method for obtaining indigo was accomplished by Adolph von Baeyer in 1882 and purchased by Badische Anilin und Soda Fabrik (BASF) for the equivalent of $100,000. BASF would in turn invest approximately $5,000,000 in Bayer's technology; his process is still used today with only slight modifications.[3] For this contribution to chemistry, Baeyer was awarded the Nobel Prize in 1905.[4] The name "indole" is derived from the word, India, from where indigo was primarily obtained in the 16th century.[1] Indole was first prepared from indigo in 1866 by zinc-dust distillation of oxindole.[5]

Benzo[b]furans (for the rest of this chapter referred to as simply benzofurans) are the oxygen analogues of indole and have been studied much less than their nitrogen counterparts.[6] In fact, to date, no historical perspectives on the parent molecule exist. Benzofuran, however, was isolated by Fittig and Ebert in 1882 by calcining coumarilic acid (from coumarin) with lime.[6b] Eight years later, benzofuran was isolated from coal tar by Kraemer and Spilker.[7] Benzofuran can be synthesized from gas phase dehydrogenation of the 2-ethylphenol.[7] The dearth of information on this parent heterocycle may be due to its infrequent occurrence in nature and/or it's nonselective chemistry with electrophiles (*vide infra).*

Both indole and benzofuran are benzannulated versions of the monocyclic heterocycles pyrrole and furan, respectively. Consequently, the reactivity of the benzannulated heterocycles mirrors that of the monocycles, however benzannulation plays an important role in influencing the types of reactivity modes that are available for these substrates. For example, both indole and pyrrole (and benzofuran and furan) are nucleophilic heterocycles, and react smoothly with a variety of electrophilic reagents. However, because of benzannulation, the position where the electrophilic reagents react on the heterocycle changes. Indoles, for example are well known to be most nucleophilic at the 3-position while pyrroles are most reactive at the 2- and 5-positions. As a first approximation, this reactivity can be explained using valence bond theory and resonance structures (Figure 1, shown for indole). For indole, benzannulation results in

the 3-position becoming the most nucleophilic (as opposed to the 2- position) because this avoids disruption of the aromatic ring, which would lead to a “less important” resonance form. Because pyrrole lacks this benzannulation, the 2- and 5-positons become most nucleophilic. Though rudimentary, this analysis is in accord with quantum theory of atoms in molecules (QTAIM) studies on the protonation of indole.[8] An alternative way of considering the above statement is that electrophilic substitution on indole at the 3-position results in an *increase* in aromaticity in the benzenoid portion of the heterocycle. The index of aromatic stabilization for indole has been computed to be 23.8 kcal/mol for indole by Pople versus 36 kcal/mol for benzene.[8c]

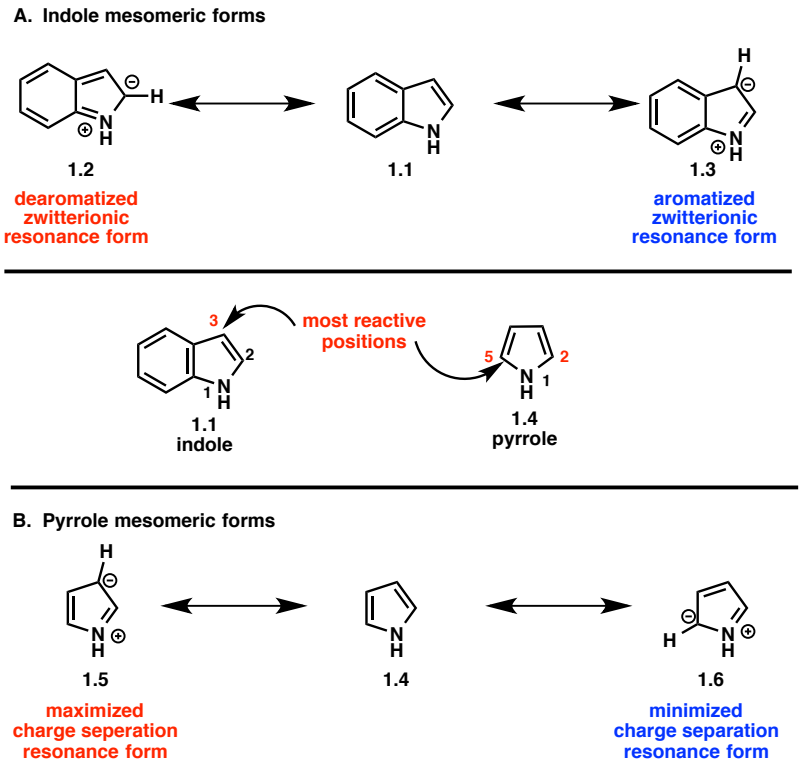


Figure 1: Resonance forms for indole and pyrrole comparing and contrasting reactivity.

In contrast to indole, the electronic properties of benzofuran are much less well understood. Compared to indole, benzofuran typically reacts less selectively or sometimes even with reversal of selectivity. The formylation of benzofuran, for example, produces exclusively the 2-formyl product.[9] One can attribute this difference in reactivity to the decreased ability of oxygen to stabilize cationic intermediates relative to nitrogen because of its higher electronegativity (N = 3.04, O = 3.44, Pauling scale).[10] Considering the condensed Fukui function, an aromatic reactivity index for an atom in a molecule, Martínez and coworkers showed using DFT calculations that indole has a much larger Fukui parameter (f^-_{AK}) at the C3- position whereas for benzofuran, the C2- and C3-positions were about equal, which parallels the reactivity of these positions that is

observed in these heterocycles .[11] The index of aromatic stabilization for benzofuran is computed to be 20.3 kcal/mol .[11]

Given the electronic properties of indoles and benzofurans, achieving functionalization on the benzenoid portion of these compounds is often difficult. The direct functionalization of the benzenoid portion of indoles and benzofurans constitutes an unsolved problem in organic chemistry and was the basis for the investigations in this chapter. Because the chemistry of indoles is better studied, they will be the primary focus of this chapter.

Section 1.1. Importance of C-substituted indole natural products and benzofurans

As of 2014, the indole core was the 9th most common heterocycle in U.S. FDA approved drugs.[12a] Artificial indole pharmaceuticals (i.e., compounds not found in nature), such as Etodolac, Sumatriptan (GSK), Naratriptan (GSK), Rizatriptan (Merck), Almotriptan (Janssen), Frovatriptan (GSK), Eletriptan (Pfizer) and Zolmitriptan (GSK, Astra Zeneca), all have alkyl substitution on the benzenoid portion of the aromatic ring (**1.7 – 1.14**, Figure 2).[12b] Noticeably however, these compounds (except for Etodolac) all contain substitution at the 5-position of the indole, which is inherently a less challenging position to functionalize from the saturated indoline core or from inexpensive 5-bromoindole. The lack of methods to functionalize the 4-, 6- and 7- positions of indoles results in the inability to explore that chemical space during SAR studies of lead compounds. In general, clinically useful indole alkaloids can be divided into three classes a) Ergot alkaloids b) Rauvolfia (Rauwolfia) alkaloids, and c) dimeric alkaloids of *Catharanthus*. The vinca alkaloids were the first plant-derived alkaloids to advance into clinical use by Eli Lilly in the 1960s, however of the three classes, only compounds from the Ergot class contain functionalization (C4) on the indole nucleus and thus their background will be discussed further.

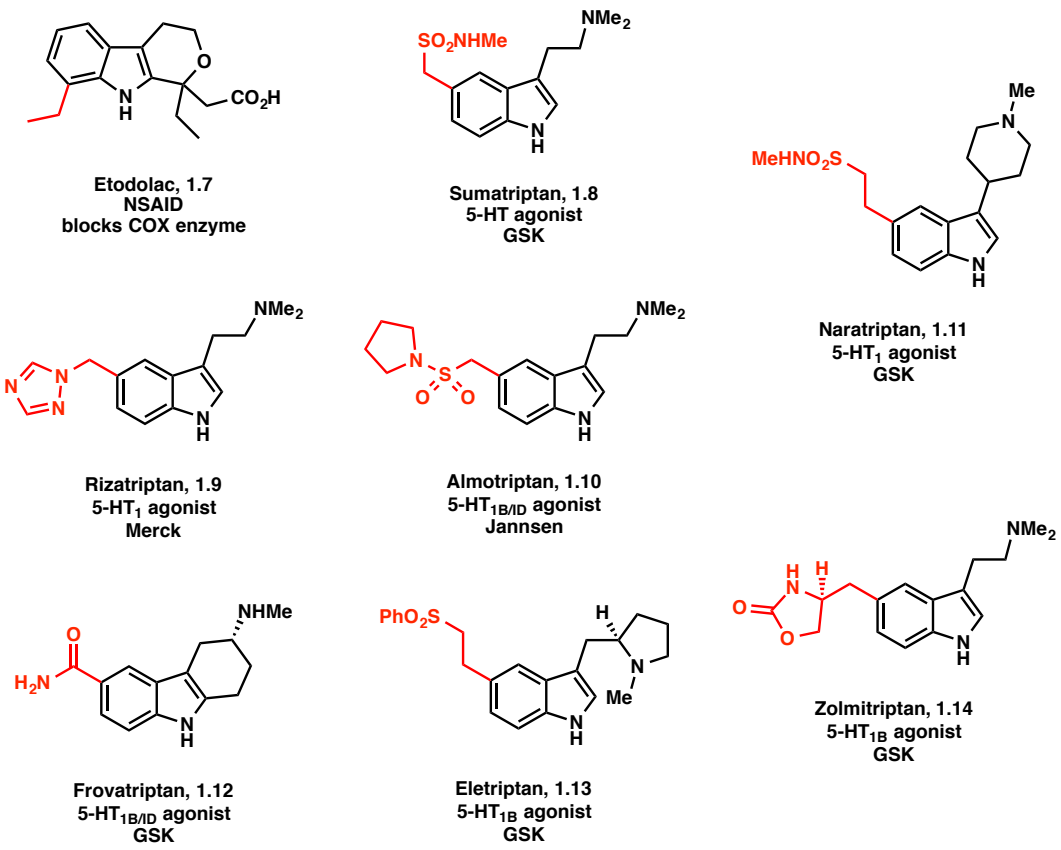


Figure 2: Indole containing pharmacophores with alkyl substitution on the benzenoid protion of the indole ring. Most compounds are 5-HT$_{1B}$ agonists.

Ergot alkaloids are mycotoxins that historically could only be obtained from the fungus *Claviceps purpurea*, which grows on rye. The name *ergot* means 'spur' in French, is a reference to the shape of the fungal sclerotium from which the compounds are obtained. Ergot alkaloids have had unique roles in history and for a long time were dreaded as poisonous contaminants as they had led to the death of tens of thousands of people in Europe in the middle ages due to the consumption of rye contaminated with ergot.[13] These epidemics, termed ergotism, where often characterized by nervous convulsive symptoms of gangrenous manifestations leading to mummification of the extremities. Upon more detailed scientific inspection of ergot, the pharmaceutical relevance of these compounds was realized. The first ergot alkaloid, ergotoxine (**1.15**, Figure 3), was isolated in 1906 by Barger and Carr and its adrenolytic activity (i.e., its ability to inhibit the action of adrenergic nerves) was discovered by Dale in the same year. Ergotoxine was later found to be a mixture of several peptide amides of the ergoline class (*i.e.*, **1.15a -1.15d**). In 1935, the specific oxytocic agent of ergot, ergonovine, was identified and isolated by Dudley and Moir. After this point, extensive investigations of the chemistry of ergot alkaloids were initiated with efforts mainly spurred by Jacobs and Craig in the United States, and Smith and Timmins in England, and Hofmann *et al*. in Switzerland. Jacobs and Craig in 1934, identified the common nucleus of these pharmacologically important alkaloids, which they named lysergic acid

(**1.16**).[14] Thus, the ergoline ring system is defined as the partially hydrogenated indolo[4,3-fg]quinonline (**1.20**) system found in lysergic acid.

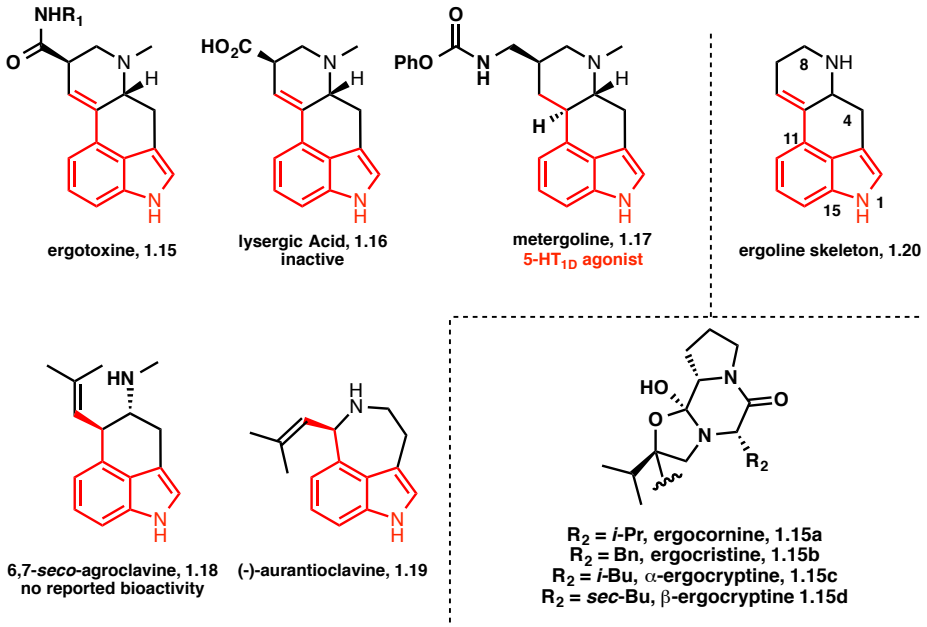


Figure 3: Ergot alkaloids are naturally occurring C4-subsituted indoles. Some family members (*e.g.*, (-)-aurantioclavine contain a modified ergoline skeleton.

For years, the production of ergot alkaloids as pharmaceuticals and for research studies primarily relied on collecting naturally occurring ergot from rye. Bekesy in Hungary and Brack of Switzerland pioneered the first artificial inoculation of rye on an industrial scale for the production of ergot alkaloids.[15] Today, ergot alkaloids are obtained through semi-synthesis of material isolated from strains of the fungus that are grown submerged in tanks. As of 1999, approximately 60% of ergot alkaloid production was based on fermentations while the rest came from field ergot. Although considerable synthetic efforts were expended into producing ergot alkaloids more effectively compared to their isolation from biological sources, a solution to this problem has as yet not been realized.[15]

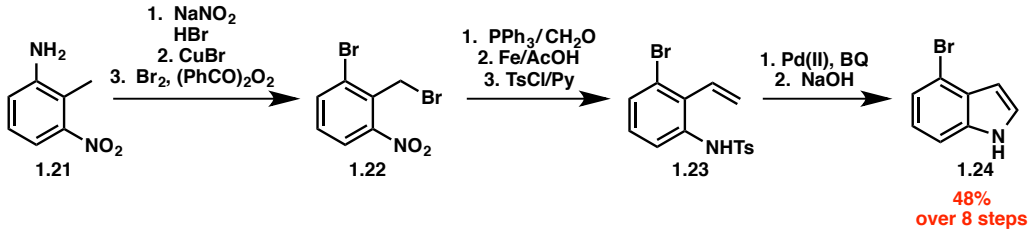
Ergot alkaloids display a wide variety of clinically useful biological activity. They are known to act on 5-HT receptors (*e.g.,* metergoline, **1.17**,[16] dopamine receptors,[17] adrenoceptors,[18] histamine receptors,[19] and to interact with endogenous prostaglandin synthesis.[20] Interestingly, lysergic acid (**1.16**) itself is biologically inactive.[21] Amides of lysergic acid, though, are well known to induce a wide variety of biological responses that are largely dependent upon the stereochemical configuration of the compound.[22] Because of the wide array of biological modes for these compounds, numerous investigators have developed strategies for accessing these compounds, in particular with regard to the development of methods for installing carbon substitution at the 4-position of indoles.

Section 1.2. Known syntheses of 4-substitued indoles and benzofurans

Because there are many synthesis of ergot alkaloids and the ergoline indolo[4,3-fg]quinonline ring system, these works will not be covered.[23] Instead, and perhaps more pertinent to the research presented within, is a background on how researchers approach the synthesis of C4-substitued indoles and benzofurans in order to access natural products such as the ergot alkaloids.

As mentioned previously, due to the electronics of the indole framework, direct Friedel-Crafts type acylation or alkylation of indoles will not occur at the C4-positon (Figure 1). Indeed, it is well known that reacting indole with acetyl chloride in the presence of imidazole, cleanly effects acylation at the indole 3-position.[24] Consequently, to obtain C4-subsitution, this must typically be introduced on the aromatic portion *before* forming the indole. Thus, 4-bromoindole (**1.24**) has historically been a common starting point for the synthesis of C4-substituted indoles because of the plethora of methods for converting an arylbromide bond into an aryl carbon bond.

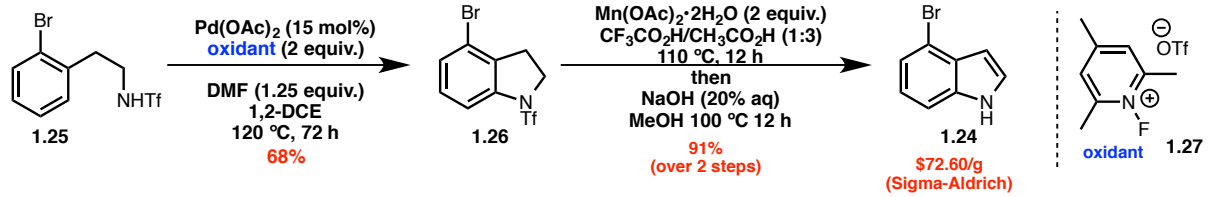
Hegedus and coworkers were among of the earliest researchers to develop a scalable method for obtaining 4-bromoindole.[25] In general, their method is a variant of the Leimgruber-Batcho indole synthesis (Scheme 1).[24] Starting from 2-methyl-3-nitro-aniline the authors effect a Sandmeyer reaction of the aniline and then induce a radical bromination of the benzylic position to give benzylic bromide **1.22**. Compound **1.22** is then taken to *ortho*-tosylamino styrene **1.23** by converting the benzylic bromide to a vinyl group using standard Wittig olefination chemistry, followed by a reduction of the nitro-group with iron and acetic acid, and protection of the resulting aniline with tosyl chloride and pyridine. The authors then effect an intramolecular Heck reaction, to provide 4-bromoindole after removal of the sulfonyl group under basic conditions. Overall this procedure works well and gives 48% yield of the desired indole over the eight-step sequence.



Scheme 1: Hegedus synthesis of 4-bromoindole.

In 2009, the Yu group at the Scripps Research Institute reported a new strategy for synthesizing 4-bromoindole as a part of a broader study of C-H functionalization reactions to access functionalized indoline cores.[26] The Yu strategy utilizes triflamide protected *ortho*-bromoethylamines and effects a C–N bond forming reaction using $Pd(OAc)_2$ and a pyridinium fluoride oxidant. In this reaction, ethylaminotriflamide **1.25** directs a palladation of the bromoarene, and indoline **1.26** is formed following reductive elimination from a Pd(IV) species. With the indoline in hand, this compound is then oxidized to the required indole using $Mn(OAc)_3 \cdot H_2O$ to give the triflate-protected 4-

bromoindole. Overall this procedure gives 65% of the protected indole over the two steps.



Scheme 2: The Yu synthesis of 4-bromoindoline utilizing a C-H functionalization reaction. The protected 4-bromoindoline is then carried forward to 4-bromoindole.

Alternatively, Rapoport and coworkers utilize the Leimgruber-Batcho synthesis to synthesize 4-bromoindole (and 5-7 haloindoles) in excellent yield.[27] This methodology has even been implemented on gram scale in the synthesis of natural products.[28] Production of 4-bromoindole indole derivatives on the industrial scale is less clear. Prices for the compound vary widely from Sigma-Aldrich $55.2/g from Sigma-Aldrich[29] to $5.25/g from Chem Impex.[30] One patent by the Eisai Co. Ltd utilizes procedures by Rapoport to synthesize 4-bromoindole and uses this compound as a starting point for Suzuki cross coupling reactions.[31]

Other methods for accessing C4-substitued indoles rely on processes such as directed thallations of indole-3-carboxaldehyde,[32] directed lithiations of gramine derivatives,[33] and the use of η^6-chromium indole complexes,[34] however these methods have been exploited to a lesser extent in (ergot) indole alkaloid synthesis.

Section 1.3. Research Hypotheses

With the existing precedent in mind, we desired to develop a unified methodology to access both indole and (benzo)furan compounds with *carbon substitution* at the 4-position such as tyrolobibenzyl A and B[35] (**1.28a**, **1.28b**, Figure 4), hibiscone C[36] (**1.29**), verticillantine[37] (**1.30**), pibocin B[38] (**1.31**),and hapalindole J[39] (**1.32**).

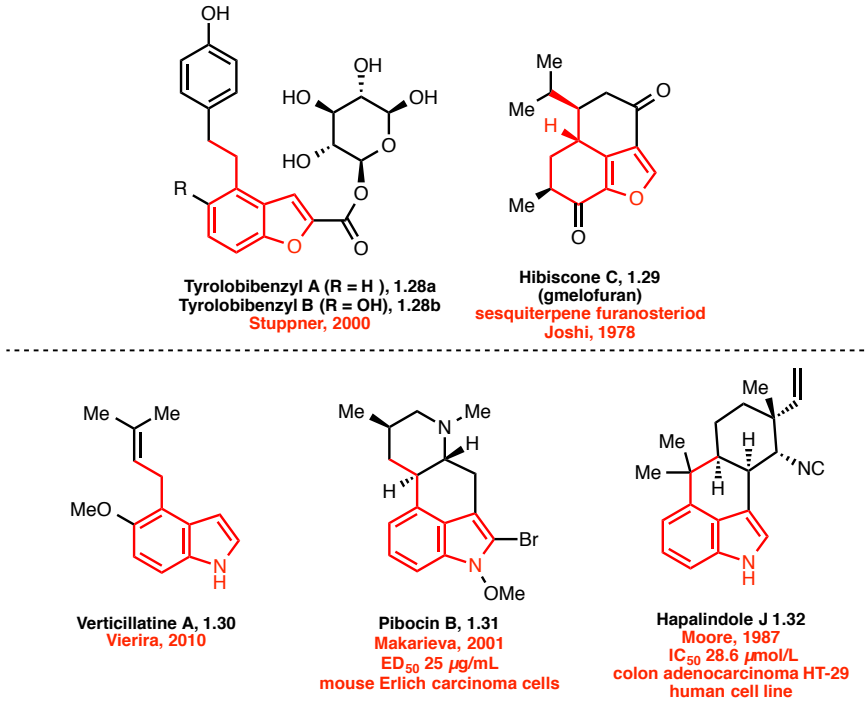
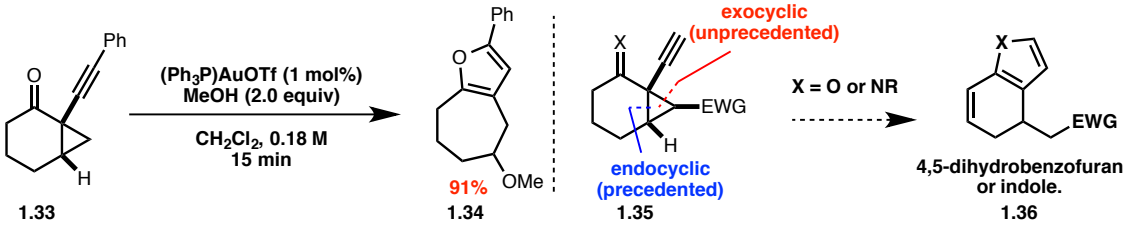


Figure 4: Other C4-subsituted (benzo)furan and indole natural products.

In light of the recent advances in heterocycloisomerization chemistry by our group[40] and others[41] we hypothesized that this would be an ideal approach for accessing these compounds. We were inspired by the work of Schmalz[42] and coworkers who had shown previously that alkynylcyclopropylketone **1.33** undergoes a gold-catalyzed cycloisomerization reaction to afford furan **1.34** annulated with seven membered ring (Scheme 3).



Scheme 3: Schmalz cycloisomerization and proposed extension to new reaction.

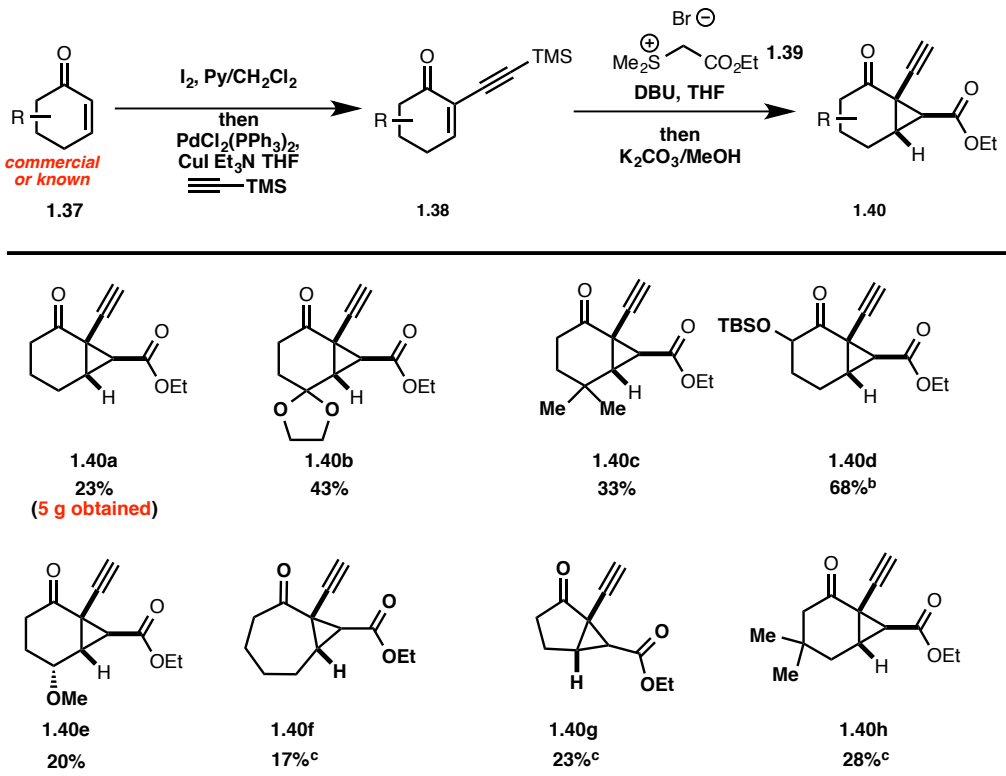
We asked the question as to whether we could effect a cycloisomerization reaction on analogues of ketone **1.33** where instead of fragmenting the endocyclic cyclopropane C–C bond using a nucleophile we would instead fragment the exocyclic cyclopropane C–C bond using an internal electrophile (see **1.35** to **1.36**, Scheme 3). By achieving this, we would then obtain the desired substitution pattern for accessing C4-substituted benzofuran. Furthermore, condensation of these ketones with an amine would give an imine substrate that would analogously give rise to the C4-substituted indole framework.

In light of our hypothesis, we were drawn to a recent report by Bartoli and coworkers that demonstrated the synthesis of ketone **1.40a**, which they used in an approach to lancifodilactone F and micrandilactone B.[43] Ketone **1.40a** was desirable to us because it contained an electron-withdrawing group on the cyclopropane ring. At the same time, we were conscious of work by Ohe and coworkers that demonstrated that alkynylcyclopropanes could undergo a cycloisomerization reaction to afford functionalized phenol.[44] In the Ohe transformation, a 6-*exo*-trig cyclization takes place from a metal vinylidene intermediate, which would not be desirable for our purposes. As such, we began our studies by synthesis of ketone **1.40a** and associated derivatives. We then investigated various catalysts known to effect heterocycloisomerization reactions.

Section 1.4. Synthesis of substrates and Screening of Reactivity

Our synthesis of ketones of the type **1.40** followed Bartoli's report and began with commercial or known cyclohexenones (Table 1). Treating these substrates with I_2 and pyridine effects an iodination at the 2-position. These iodoketones then undergo a Sonogashira cross coupling reaction with various alkynes at room temperature to afford enynes of the type **1.38**.[45] Treating these enynes with a sulfur ylide generated *in situ* by reacting sulfonium salt **1.39** and 1,4-diazabicycloundec-7-ene (DBU) results in the [4.1.0]-bicycle. Removing the silylgroup from the alkyne is then accomplished with K_2CO_3 in MeOH or tetra-*n*-butylamonium fluoride (TBAF) in THF to give ketone **1.40** in 23% yield over the four steps. Of note, this reaction sequence could be performed routinely for **1.40a** on 10 g scale resulting in 5 g of product without diminishing yields. Furthermore, this procedure worked well starting from both cyclopentenones **1.40g**, cycloheptenones **1.40g**, and ketone **1.40h** where *gem*-dimethyl groups are β-to the carbonyl group.

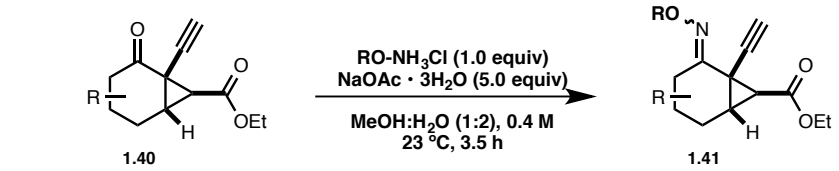
Table 1: Substrate scope for bicyclo-[4.1.0]-heptanone synthesis.



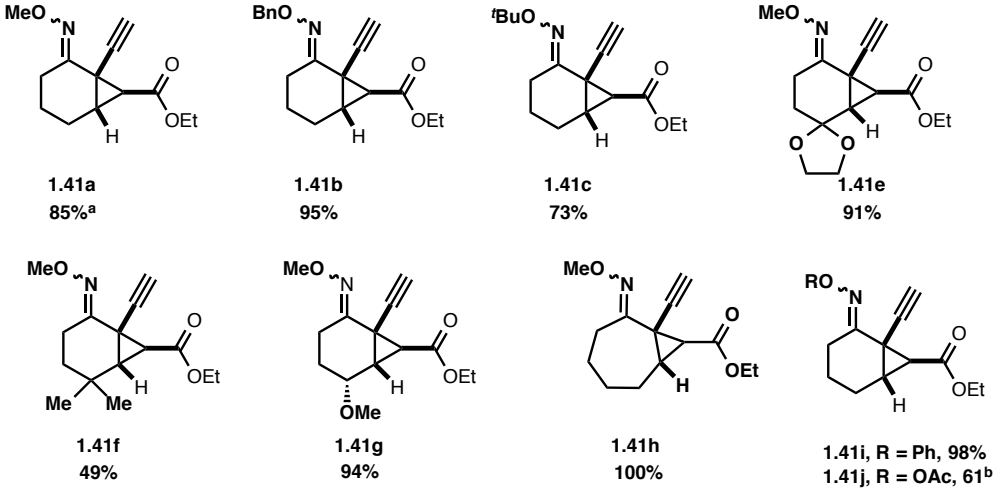
a) Yields given are over four steps unless otherwise stated. b) Yield given for two steps from 1.40a. c) Substrate was made from the bromoenone. TBS = tert-butyldimethylsilyl.

In order to access substituted indoles using our planned cycloisomerization reaction, nitrogen-containing analogues of the above ketones were required. Initially, we explored condensing amines onto ketones **1.40a – 1.40h** in order to make imines. Unfortunately, imines of ketone **1.40** hydrolyzed readily back to ketone **1.40** and so characterization of these compounds proved difficult. We thus turned to synthesizing oxime ethers of ketones **1.40a** – **1.40h** because these compounds are typically less prone to hydrolysis. Gratifyingly, we found that stirring ketones **1.40a** – **1.40h** with different hydroxylamine hydrochloride salts in the presence of sodium acetate, resulted in clean formation of oxime ethers **1.41a** – **1.41j**. Oxime acetate **1.41j** was synthesized by acylation of the corresponding hydroxylamine.

Table 2: Substrate scope for oxime ether formation from bicyclo-[4.1.0]-heptanones.



1.40 → 1.41



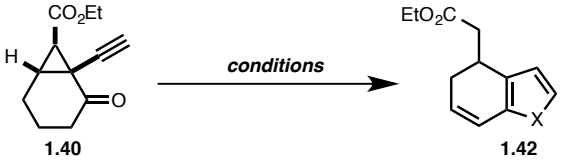
1.41a	1.41b	1.41c	1.41e
85%[a]	95%	73%	91%

1.41f	1.41g	1.41h	1.41i, R = Ph, 98% 1.41j, R = OAc, 61[b]
49%	94%	100%	

a) All oxime ethers were obtained as a mixture of *E*- and *Z*- isomers. b) Yield over two steps, see supporting information for details.

With these substrates in hand, we then explored various conditions to effect our desired cycloisomerization reaction. Various transition metal salts[46a,b] such as Au(I), Ag(I), Cu(I), Pt(II), and recently Rh(I)[47c] are known to effect cycloisomerization reactions (Rautenstrauch manifold). However, ketones **1.40a** – **1.40h** all contained terminal alkynes, so a cycloisomerization reaction that is initiated by an alkyne to metal vinylidene isomerization can also take place.[47] Upon screening a variety of transition metals known to effect alkyne to metal vinylidene conversions, we identified the $W(CO)_5$•THF complex as being efficient in cleanly converting ketone **1.40a** into furan **1.42a** (Table 3). $W(CO)_5$•THF is generated by irradiating a solution of $W(CO)_6$ in THF at 350 nm for 2 hours. Pt(II) salts with added amine bases were also competent for effecting this transformation, but the use of Pt(II) salts was often accompanied by the formation of aldehydes and other inseparable side products (Table 3, entry 7).

Table 3: Screening conditions to effect cycloisomerization reaction on ketone 1.40.



1.40 1.42

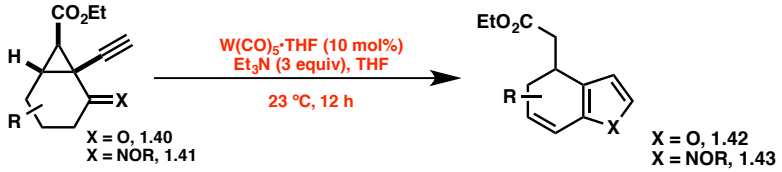
entry	catalyst	additive	result
1	$RuCl_2(PPh)_3$	NH_4PF_6	no reaction
2	$[RuCl_2(p\text{-cymene})]_2$	NH_4PF_6	no reaction
3	$[Rh(OH)COD]_2$	none	no reaction
4	$Rh(PPh_3)_3Cl$	NH_4PF_6	no reaction
5	$[Ru(Cl)COD]_2$	NH_4PF_6	no reaction
6	$PtCl_2$	none	polymerization
7	$PtCl_2$	DABCO	prod+aldehyde
8	WCO_5·THF	Et_3N	95%

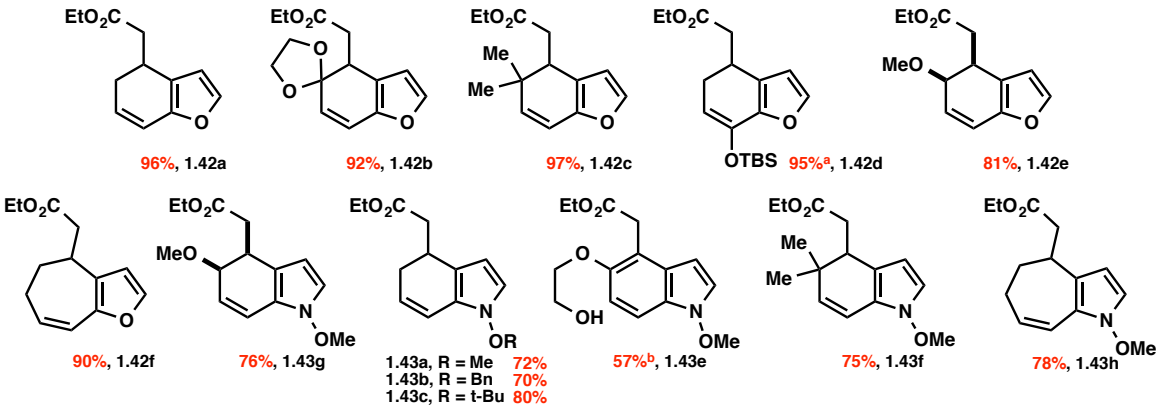
With these conditions in hand we then investigated the scope of the reaction using our synthesized ketones and oxime ethers as substrates.

Section 1.5. Substrate scope, Mechanism, and Product Manipulation

Upon subjecting ketones **1.40a** – **1.40h** and oxime ethers **1.41a** – **1.41j** to the optimized reaction conditions, we were pleased to find that a variety of ketone and oxime ether substrates were converted to the corresponding 4,5-dihydrobenz[b]furans (**1.42**) or *N*-alkoxyindoles (**1.43**) (Table 4).

Table 4: Scope of newly developed cycloisomerization reaction.





a) Reaction conducted using 20 mol% $W(CO)_5$·THF. b) The reported yield of *N*-alkoxyindole 1.43e was obtained upon stirring the crude reaction product with oxalic acid and SiO_2 in wet CH_2Cl_2 for 3 h (see the Supporting information for details)

We found that the reaction was general and proceeded in the presence of a wide array of substituents on the cyclohexane ring. Acetals (**1.42b**), *gem*-dimethyl groups (**1.42c**),

and protected alcohols (**1.42d**, **1.42e**) did not have an adverse effect on reactivity. Larger ring systems (**1.42f**) also participated in this reaction. Cyclopentanone **1.40g**, however did not undergo cycloisomerization. At first glance, this effect may appear to be due to the inherent strain present within a 5-membered ring (5.1 kcal/mol).[38] However, the strain energy of a 7-membered ring is exactly the same (5.1 kcal/mol). Considering that combined strain energies are additive, the strain energy of a [3.1.0]-bicycle should be approximately the same as a [5.1.0]-bicycle. Thus, one would not expect substrate **1.40f** containing a 7-membered ring to undergo the reaction either. Thus, the lack of reactivity of the 5-membered ring substrates may actually be due to the reduced conformational flexibility in these systems. Ketone **1.40h** also did not participate in the reaction, presumably due to the required proton transfer (*vide infra*) needed for the reaction to proceed.

The oxime ether substrates **1.41a** – **1.41h** also reacted fairly smoothly under the reaction conditions. Of note, the yields for these reactions are typically lower than that of the furan substrates (compare furans **1.42a**, **1.42c**, **1.42e** to pyrroles **1.43a**, **1.43f** and **1.43g**). This is presumably due to the π-excessive nature of the vinyl-*N*-alkoxypyrrole products, which makes them susceptible to oxidative degradation and polymerization pathways. We found that it was critically important to minimize the time these substrates were exposed to air, acid, and especially light as these are known to facilitate the decomposition *N*-hydroxyindole products.[49] Oxime ethers **1.43a** – **1.43b** bearing different alkyl groups on the oxime oxygen proceeded smoothly and without event. We found that in contrast to furan **1.42b**, *N*-alkoxypyrrole product **1.43e** was very sensitive to acid and ring opening would take place upon purification by SiO_2-gel chromatography. Thus, the crude cycloisomerization product was stirred in wet CH_2Cl_2 with oxalic acid and SiO_2-gel to promote acetal opening and aromatization to the *N*-alkoxyindole **1.43e**.

Interestingly, oxime substrates **1.41i** and **1.41j** did not undergo cycloisomerization suggesting that alkylsubstitution on the oxime ether was critical. In the case of **1.41i**, even heating the solution to 75 ºC did not facilitate the cycloisomerization reaction. To verify that the catalyst was indeed competent in these reactions, we subjected an equimolar mixture of ketone **1.40a** and oxime **1.41i** to the optimized reaction conditions. We observed that furan **1.42a** is indeed formed while oxime ether **1.41i** remains untouched (Figure 5). Thus, the phenyl group on the oxime ether imparts a deleterious electronic effect that is reflected in the lack of nucleophilicity of the oxime ether nitrogen.

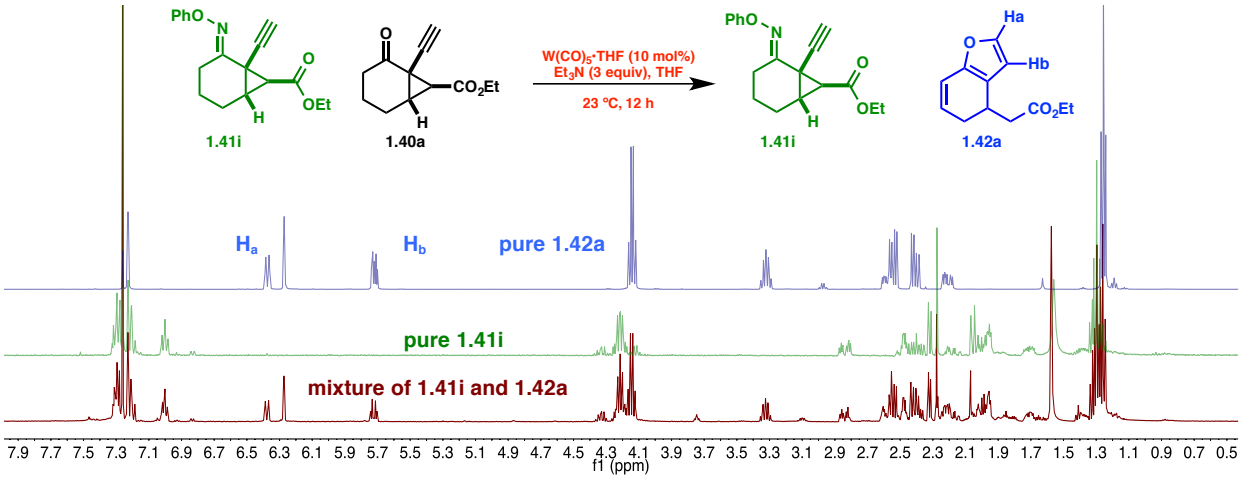
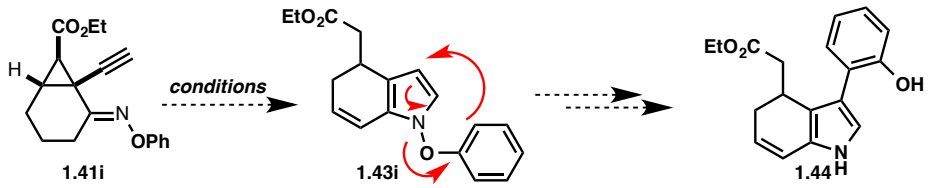


Figure 5: Competition experiment between oxime ether 1.41i and ketone 1.40a.

Ideally, we anticipated performing a cascade cycloisomerization-Claisen rearrangement from the *N*-phenoxypyrrole to arrive at products such as **1.44a**.[49] These arylated pyrroles could then lead to 3-arylindoles, which have gained considerable attention in recent years by the MacMillan, Reisman and Davies groups.[50]

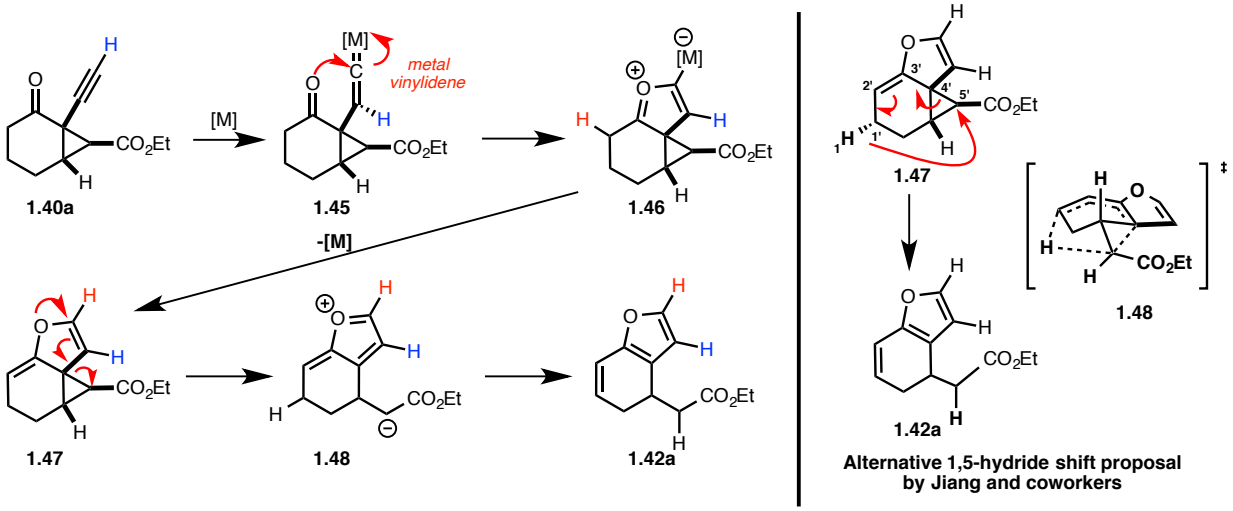


Scheme 4: Proposed cycloisomerization-Claisen rearrangement domino reaction.

1.5.1. Mechanism

Based on the above data and precedent by Ohe and others we propose a mechanism for the transformation depicted in Scheme 5. We hypothesize that the reaction proceeds by an isomerization of alkyne **1.40a** to metal vinylidene **1.45**. The electrophilic metal vinylidene is then engaged by the pendant keto-group. Of note, we observed no products from the participation of the ester moiety. This may be due to a kinetic preference for the 5-*exo*-dig cyclization mode over the 6-*exo*-dig mode. Upon cyclization to zwitterionic intermediate **1.46**, protodemetallation then occurs to give isofuran **1.47**, which is also a donor-acceptor cyclopropane. Thus, the polarized nature of **1.47** and inherent strain promotes another fragmentation to zwitterion **1.48**. This zwitterion then undergoes another proton transfer to afford the product. In accord with our proposed mechanism, ketone **1.40h** bearing a *gem*-dimethyl group β- to the carbonyl group does not undergo our cycloisomerization reaction because the required proton transfer (i.e., **1.48** to **1.42a**) cannot take place. After our work was published, the Liang group at Guangxi University studied the mechanism our reaction using Density Functional Theory (DFT) calculations.[51] The results of this report are in accord with our

proposed mechanism, however the authors propose that the isomerization of **1.47** to **1.42a** takes place through a 1,5-hydride shift and is not mediated by triethylamine.

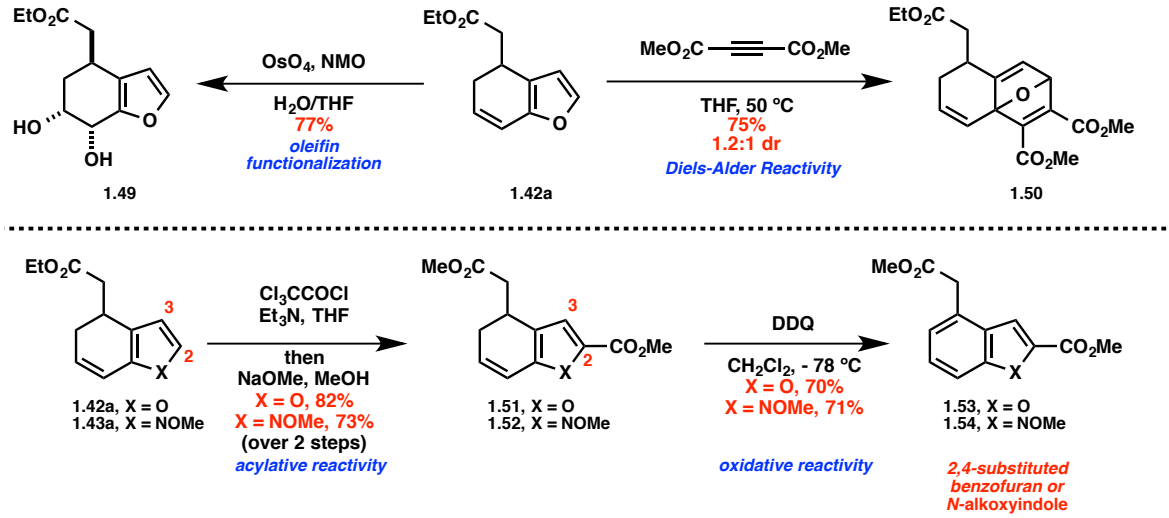


Scheme 5: Proposed mechanism for conversion of ketone 1.40a to furan 1.42a

Interestingly though, the proposed "1,5-hydride shift" utilizes one π-bond and one σ-bond of the bond of the cyclopropane ring (i.e., the Walsh orbitals) as the other 2π electron component instead of two π-bonds.

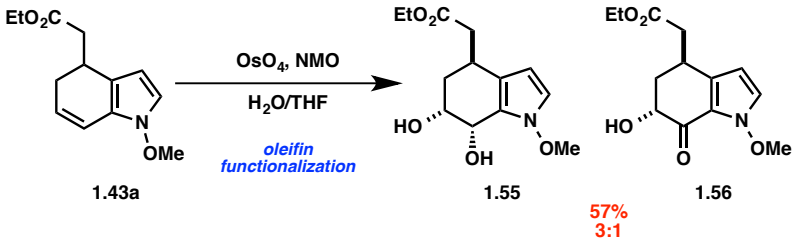
1.5.2. Product Manipulations: Connection to Natural Products

With dihydro-benzofuran **1.42a** – **1.42f** and -indole **1.43a** – **1.43h** in hand, we next investigated transformations of these compounds. Specifically, we were interested in making the connection of these substrates to the ergot alkaloids and (benzo)furan containing natural products. To this end, we investigated four main reactivity modes of these dihydroindole and dihydrobenzofuran substrates: oxidative reactivity, dihydroxylation reactivity, acylation reactivity, and olefin functionalizations (Scheme 6).



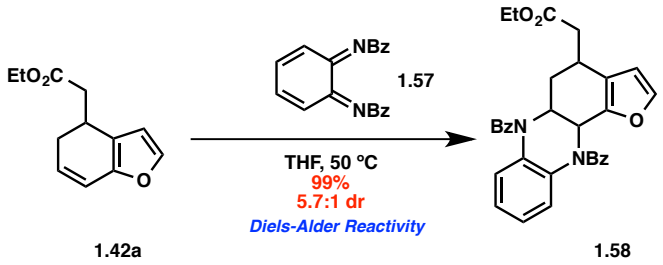
Scheme 6: Different reactivity modes of dihydrobenzofuran and -indole subtrates.

Because these compounds are one oxidation level below the fully aromatic benzofurans or indoles, they undergo various complementary modes of reactivity. Dihydroxylation of furan **1.42a** proceeded readily resulting in the *syn*-diol **1.49** where the hydroxyls are disposed *anti*- relative to the methylenecarboxyethyl group. Performing this reaction on the analogous pyrrole compound **1.43a** was met with extreme difficulty (Scheme 7). In this case, the dihydroxylation at room temperature was often accompanied by over oxidation of the diol to the α-hydroxy ketopyrrole **1.56** (3:1 diol to ketoalcohol) after purification by column chromatography.



Scheme 7: Oxidation of dihydropyrrole substrate.

Furan **1.42a** also undergoes a clean normal-electron demand Diels-Alder cycloaddition reaction with dimethylacetylene dicarboxylate to give functionalized decaline **1.50** as a mixture of diastereomers (Scheme 6). Furthermore, we found that the double bond in furan **1.42a** was also acts as a dienophile in inverse electron demand Diels—Alder cycloaddtion reactions. Thus, furan **1.42a** (obtained directly from the cycloisomerization reaction without isolation) reacts with dienophile **1.57** to afford the Diels-Alder adduct **1.58** in 99% yield as a 5.7:1 mixture of diastereomers.



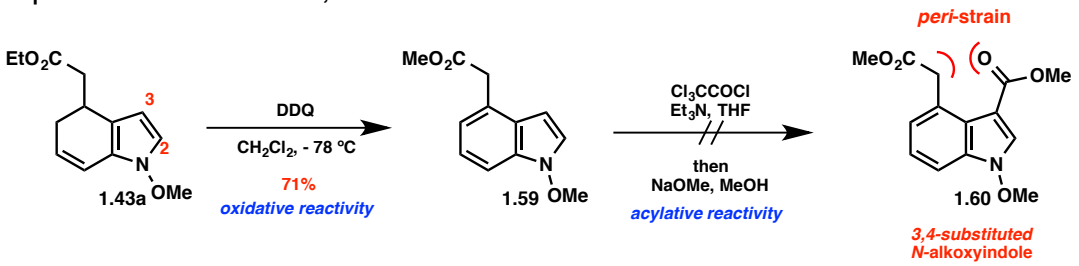
Scheme 8: Inverse electron-demand Diels - Alder cycloaddition reaction

When these cycloaddition reactions were applied to the more electron rich vinylpyrroles, we observed complex mixtures of products that we could not characterize.

We next investigated the acylative reactivity of these compounds. This reaction manifold proved interesting because we anticipated acylation of these partially hydrogenated indole and benzofuran compounds would occur at the 2-position (indole/benzofuran numbering) of these substrates. Thus, this reactivity manifold would be *orthoganol* to that of indoles and benzofurans and would allow us to access substitution patterns that would be otherwise difficult to obtain starting from the fully

aromatic benzofurans or indoles. As such, taking either furan **1.42a** or pyrrole **1.43a** and subjecting them to trichloroacetyl chloride in the presence of triethylamine, resulted in clean acylation of both the furan and pyrrole substrates. Reacting the resulting trichloroacetyl-heterocycles with sodium methoxide gave the methyl esters **1.51** and **1.52** in 82% and 73% yields respectively over the two steps. Upon acylation of the *N*-alkoxylprryole substrate, we observed that this compound was much less susceptible to oxidative decomposition and was much easier to handle.

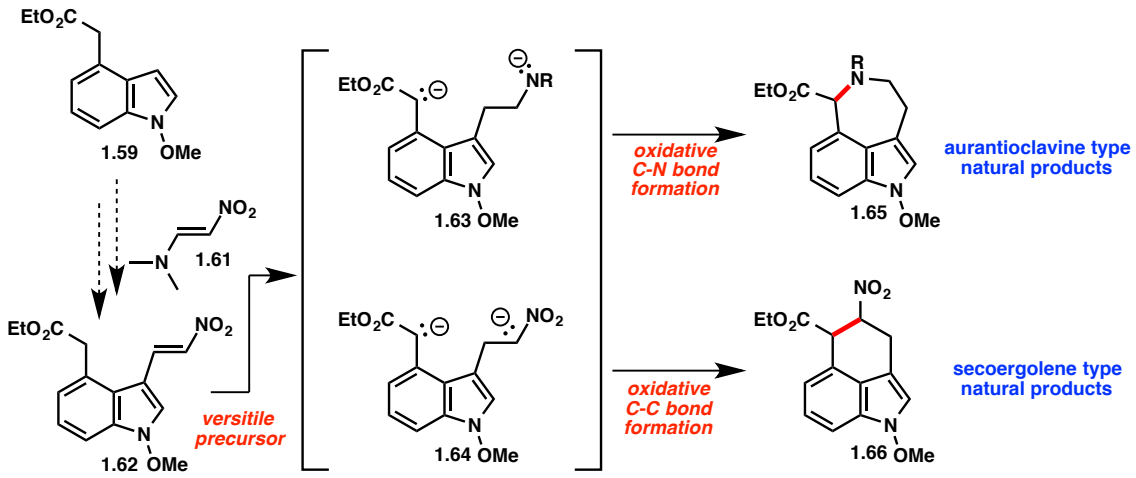
Finally, in order to make the connection between these compounds and ergot alkaloid natural products, we demonstrated that these compounds could be oxidized to the fully aromatic benzofurans and indoles. Thus exposing **1.51** or **1.52** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at – 78 ºC resulted in the oxidation of both acylated compounds **1.53** and **1.54** (Scheme 6) and their nonacylated analogues (e.g., **1.59**) (Scheme 9). For the *N*-alkoxypyrrole substrates, we found that it was critical to perform this reaction at low temperatures in order to isolate significant quantities of the product. Other oxidizing agents such as chloranil were ineffective for this transformation even at room temperature. We then attempted to acylate the resulting *N*-alkoxyindoles at the 3-positon to arrive at 3,4-disubstituted indoles.



Scheme 9: Oxidation of nonacylated *N*-alkoxypyrrole substrate 1.43a and attempted acylation.

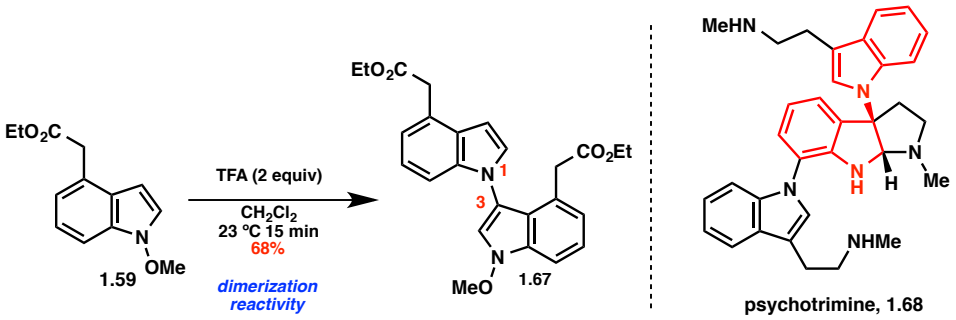
Though *N*-akoxyindoles are known to acylate at the 3-positon, we found that under a wide variety of conditions, acylating reagents (e.g., $ClCH_2COCl$) or brominating reagents (NBS, $PyHBr_3$) were ineffective at functionalizing the 3-position of these compounds. This was a major impediment for accessing ergot alkaloid natural products. We attributed this lack of reactivity to the incipient *peri*-strain present between the 3- and 4-positions in the indole ring reflected in the transition state of these transformations.[52] Thus, the 4-functionalization which served as a platform for these investigations, seemed to become a detriment to accessing natural products.

In addition to the above reactivity, we uncovered very interesting reactivity of *N*-alkoxyindoles while trying to access the ergot alkaloids. In addition to the acylation studies, we aimed to functionalize the 3-postion of the *N*-alkoxyindoles substrates with nitroethylene unit using dimethylaminonitroethylene **1.61**. Then, depending on the oxidation level of the substrate, we envisioned carrying out either an oxidative C–N (**1.63**) or C–C (**1.64**) forming reaction to access the aurantioclavine (**1.65**) or secoergolene skeletons (**1.66**).



Scheme 10: Proposed route to aurantioclavine and secoergolene type natural products.

In this vein, we attempted to react indole **1.59** with dimethylaminonitroethylene in the presence of trifluoroacetic acid (TFA) to arrive at **1.62**. Instead, we observed the clean formation of indole dimer **1.67** within 15 minutes. This structure was confirmed by COSY, NOESY, and LCMS analysis. Removing reagent **1.61** from the reaction, we isolated the same product in 68% yield (Scheme 11). This reactivity was remarkable to us *it demonstrates an electrophilic attack of the indole 3-postion on nitrogen!* Thus, the nitrogen atom of the *N*-alkoxyindole becomes electrophilic upon protonation of the methoxy group with a strong Brønsted acid. Substitution reactions on the sp^2 nitrogen atom of indoles are extremely rare, however this reaction manifold has been well studied by Somei and coworkers and they have demonstrated by (X-ray crystallographic analysis) that these substitution reactions on *N*-hydroxyl and alkoxy indoles can take place because the N—OR bond actually lies 14° out of plane for these substrates.[44] Therefore, nucleophiles can indeed interact with the σ^* of the N-OR bond whereas in substrates where aromaticity is more pronounced, this would be impossible because the σ^* lies in the plan of the molecule. These dimers are furthermore interesting because of their relationship with polymeric indole alkaloids such as psychotrimine **1.68**.[53]



Scheme 11: Indole dimerization reactivity. Relationship of dimer to psychotrimine.

Section 1.6. Conclusions

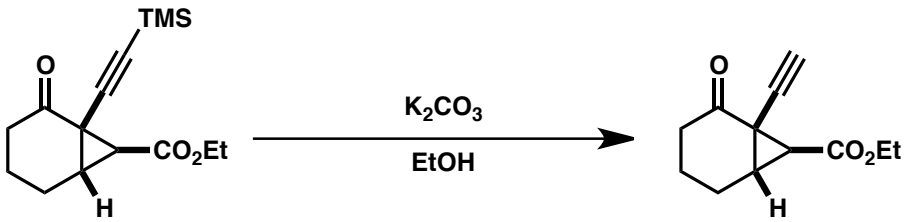
In this chapter, our efforts to develop a concise method to access 4-substituted benzofurans and indoles is described. These studies were pursued because of the prevalence of this motif in natural products such as the ergot alkaloids. We discovered a new cycloisomerization reaction utilizing metal vinylidines to access the 4,5-dihydro-indoles or -benzofuran and used these compounds to access the fully aromatic benzofurans and indoles as well as functionalized pyrroles and furan substrates. We also show that the alkoxyindole indole substrates undergo a dimerization reaction to give 1,3-linked indole dimers. In summary, the developed method can be readily applied to the synthesis of natural product scaffolds.

Section 1.7.1. Supporting Information – General Procedures

All reactions were run in flame-dried round-bottom flasks or vials under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Silicycle Siliaplate™ glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV irradiation and *para*-anisaldehyde or $KMnO_4$ stain. Dry tetrahydrofuran, triethylamine, and methanol were obtained by passing these previously degassed solvents through activated alumina columns. Dichloromethane was distilled over calcium hydride before use. Irradiation of $W(CO)_6$ was performed in a Luzchem photoreactor at 350 nm. Volatile solvents were removed under reduced pressure on a rotary evaporator. All flash chromatography was done using Sorbent Technologies 60 Å, 230x400 mesh silica gel (40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were taken with Bruker AV3--00, AVB-400, AVQ-400, AV-500, and AV-600 MHz (75, 100, 125, and 150 MHz for ^{13}C NMR) spectrometers in $CDCl_3$ or C_6D_6 as noted. Chemical shifts were measured relative to the shift of the residual solvent (^{1}H NMR, $CDCl_3$ δ = 7.26, C_6D_6 δ = 7.16 ppm; ^{13}C NMR $CDCl_3$ δ = 77.00 ppm). NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Splitting is reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, a = apparent, b = broad. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates unless otherwise specified. Spectra are reported in frequency of absorption in cm^{-1}. Only selected resonances are reported. High-resolution mass spectra (HRMS) were performed by the mass spectral facility at the University of California, Berkeley.

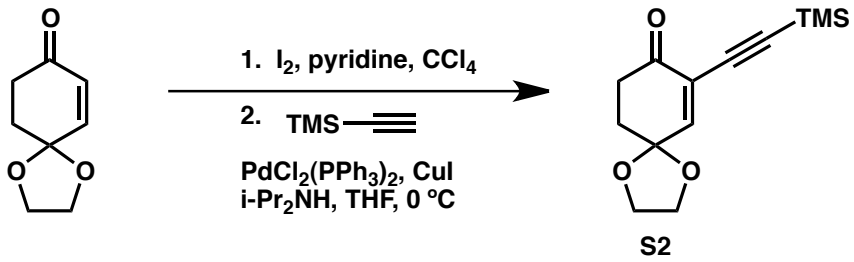
Section 1.7.2 Supporting information – Experimental Procedures

The synthesis of the [4.1.0]-bicycles has been adapted from Chouraqui and Parrain[43] and references within.



S1

The reported trimethylsilyl alkyne (2.0 g, 7.2 mmol) was dissolved in absolute ethanol (36 mL) under an atmosphere of nitrogen. Pulverized K_2CO_3 (4.9 g, 36 mmol) was then added and the suspension was vigorously stirred for 6 hours. The suspension was filtered through Celite and the filtrate concentrated *in vacuo*. The crude residue was purified via silica gel chromatography (10% to 20% EtOAc: hexanes) to afford terminal alkyne **7a** (1.1 g, 5.33 mmol, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.2 Hz, 2H), 2.59 (m, 1H), 2.53 (d, *J* = 6.4 Hz, 1H), 2.41 (dt, *J* = 18.4, 5.2 Hz, 1H), 2.26 (s, 1H), 2.22 (m, 1H), 2.05 (m, 2H), 1.81 (m, 1H), 1.63 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.3, 267.5, 78.2, 71.5, 61.6, 36.4, 32.5, 31.3, 30.9, 20.1, 18.7, 14.2. **IR** (thin film) ν_{max} 3269, 2938, 2124, 1736, 1699, 1262, 1197 cm^{-1}. **HRMS (ESI)** calcd for $C_{12}H_{15}O_3$ $(M+H)^+$ *m/z* 207.1016, found 207.1019.

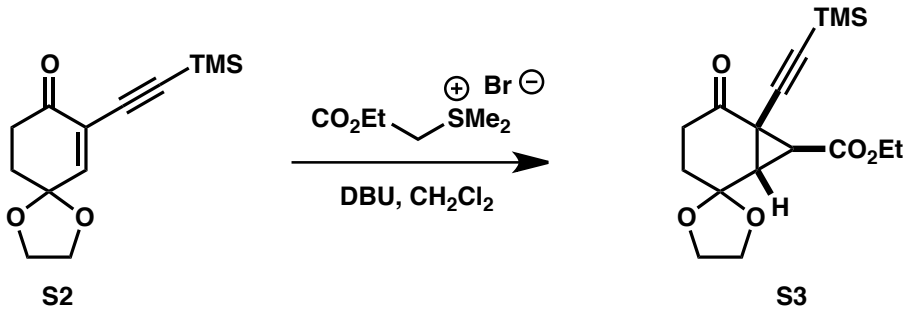


S2

1,4-Dioxaspiro[4.5]dec-6-en-8-one[54] (3 g, 19.5 mmol) was dissolved in a mixture of carbon tetrachloride (15 mL) and pyridine (15 mL) under a nitrogen atmosphere and cooled to 0 °C. A solution of iodine (9.87 g, 38.9 mmol) in carbon tetrachloride (15 mL) and pyridine (15 mL) was added over 10 minutes. The solution was stirred at room temperature for 2 hours and then diluted with diethyl ether. The organic solution was washed with 1 N HCl (2 x 75 mL) and saturated Na_2SO_3 (2 x 75 mL). The organic layer was dried over $MgSO_4$, concentrated, filtered, and used without any further purification.

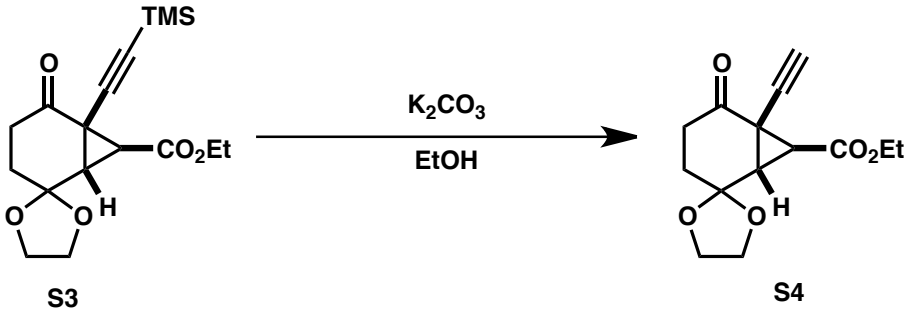
The crude vinyl iodide (19.5 mmol), $PdCl_2(PPh_3)_2$ (684 mg, 0.98 mmol), and CuI (371 mg, 1.95 mmol) were placed in a dry flask under nitrogen and dissolved in THF (150 mL). The yellow suspension was cooled to 0 °C. Trimethylsilylacetylene (5.5 mL, 39 mmol) was added followed by slow addition of diisopropylamine (8.2 mL, 58.5 mmol) over 1 minute. The solution was allowed to stir for 1.5 hours, then diluted with diethyl ether (200 mL) and washed consecutively with 1 N HCl (200 mL) and brine (200 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography of the resulting crude mixture (15% to 25% EtOAc; hexanes) yielded alkyne **S1** (3.4 g, 13.6 mmol, 70% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ

6.85 (s, 1H), 4.02 (m, 4H), 2.65 (t, J = 6.8 Hz, 2H), 2.18 (t, J = 6.8 Hz, 2H), 0.24 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.4, 149.1, 125.7, 103.9, 100.5, 97.8, 65.1, 35.2, 32.8, –0.3. **IR** (thin film) ν_{max} 2962, 2893, 2157, 1708, 1601, 1340, 1254, 1135, 1082 cm^{-1}. **HRMS (EI)** calcd for $C_{13}H_{18}O_3Si$ $(M)^+$ *m/z* 250.1025, found 250.1029.



S2 **S3**

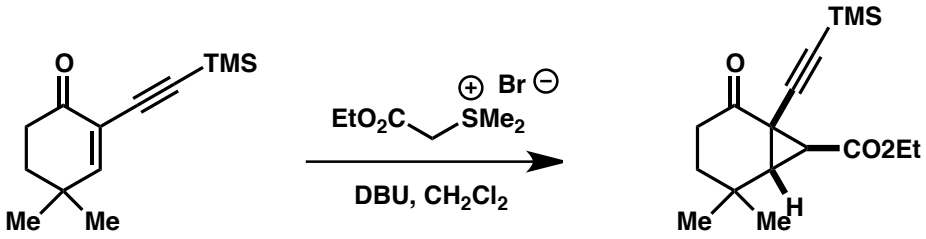
DBU (6.1 mL, 40.8 mmol) was added to a stirring suspension of (Ethoxycarbonylmethyl)dimethylsulfonium bromide (7.79 g, 34 mmol) in DCM (100 mL). After 45 minutes, enyne **S1** (3.4 g, 13.6 mmol) was added and the solution was allowed to stir for 12 hours. The organic solvents were evaporated and then partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with 1 N HCl (100 mL), water (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (30% to 50% EtOAc: hexanes) to yield bicycle **S2** as a single diastereomer (3.4 g, 10.1 mmol, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.23–3.97 (m, 6H), 2.62 (d, J = 6 Hz, 1H), 2.57 (d, J = 6 Hz, 1H), 2.42 (m, 2H), 1.85 (dd, J = 8.4, 5.2, Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.12 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.6, 166.3, 104.9, 98.3, 88.6, 98.3, 88.6, 65.1, 65.0, 61.6, 37.1, 34.3, 34.0, 32.3, 29.3, 14.2, –0.2. **IR** (thin film) ν_{max} 2958, 2889, 2178, 1744, 1712, 1454, 1368, 1348, 1254, 1201, 1168, 1091 cm^{-1}. **HRMS (EI)** calcd for $C_{17}H_{24}O_5Si$ $(M)^+$ *m/z* 336.1393, found 336.1400.



S3 **S4**

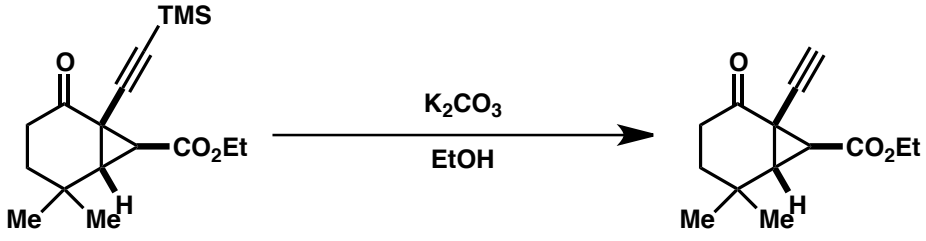
Silyl alkyne **S2** (1.0 g, 2.97 mmol) was dissolved in absolute ethanol (14 mL) under an atmosphere of nitrogen. Pulverized K_2CO_3 (1.2 g, 8.91 mmol) was then added and the suspension was vigorously stirred for 5 hours at 23 °C. The suspension was filtered through Celite and the filtrate concentrated *in vacuo*. The crude residue was purified via silica gel chromatography (25% to 40% EtOAc: hexanes) to afford terminal alkyne **S3** (650 mg, 2.46 mmol, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.22 (q, J = 6.8 Hz, 2H), 4.15–

4.00 (m, 4H), 2.66 (ad, *J* = 6.4 Hz, 1H), 2.62 (ad, *J* = 6.4 Hz, 1H), 2.52 (m, 2H), 2.29 (s, 1H), 1.89 (add, *J* = 9.2, 5.6 Hz, 2H), 1.29 (t, *J* = 6.8 Hz, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.6, 166.6, 104.8, 76.9, 72.2, 65.2, 65.0, 61.9, 37.0, 34.2, 33.3, 31.6, 29.2, 14.2. **IR** (thin film) ν_{max} 3260, 2978, 2893, 2120, 1744, 1716, 1373, 1344, 1275, 1238, 1201 cm^{-1}. **HRMS (EI)** calcd for $C_{14}H_{16}O_5$ $(M)^+$ *m/z* 264.0998, found 264.1005.



S5

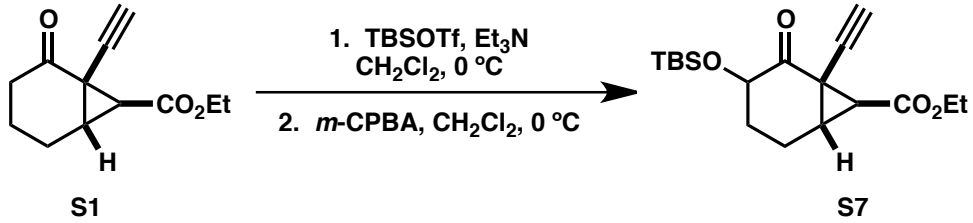
DBU (4.9 mL, 32.7 mmol) was added to a stirring suspension of (Ethoxycarbonylmethyl)dimethylsulfonium bromide (6.24 g, 27.3 mmol) in DCM (100 mL). After 45 minutes, the reported enyne[55] (2.4 g, 10.9 mmol) was added and the solution was allowed to stir for 12 hours. The organic solvents were evaporated and then partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with 1 N HCl (100 mL), water (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (15% to 20% EtOAc: hexanes) to yield bicycle **S4** as a single diastereomer (1.83 g, 5.97 mmol, 55%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.15 (m, 2H), 2.50 (d, *J* = 6.4 Hz, 1H), 2.30 (m, 3H), 1.44 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.11 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.2, 167.1, 99.5, 88.1, 61.4, 42.8, 34.1, 33.0, 31.7, 31.4, 29.2, 28.4, 26.5, 14.2, –0.1. **IR** (thin film) ν_{max} 2954, 2897, 2165, 1736, 1704, 1462, 1368, 1340, 1242, 1205, 1176 cm^{-1}. **HRMS (EI)** calcd for $C_{17}H_{26}O_3Si$ $(M)^+$ *m/z* 306.1651, found 306.1659.



S6

Silyl alkyne **S4** (1.83 g, 5.97 mmol) was dissolved in absolute ethanol (30 mL) under an atmosphere of nitrogen. Pulverized K_2CO_3 (2.48 g, 17.9 mmol) was then added and the suspension was vigorously stirred for 4 hours. The suspension was filtered through Celite and the filtrate concentrated *in vacuo*. The crude residue was purified via silica

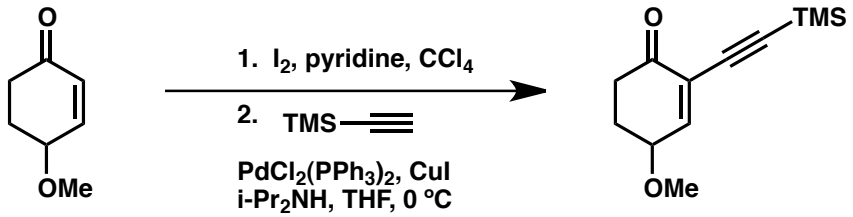
gel chromatography (25% EtOAc: hexanes) to afford terminal alkyne **S5** (1.16 g, 4.95 mmol, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (m, 2H), 2.54 (d, *J* = 6.4 Hz, 1H), 2.35 (m, 3H), 2.27 (s, 1H), 1.49 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 3H), 1.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.2, 167.2, 77.9, 71.6, 61.4, 42.7, 33.2, 32.7, 31.2, 30.7, 29.1, 28.3, 26.4, 14.1. **IR** (thin film) n_{max} 3265, 2962, 2901, 2872, 2120, 1728, 1699, 1471, 1373, 1340, 1291, 1209, 1185 cm^{-1}. **HRMS (EI)** calcd for $C_{14}H_{18}O_3$ $(M)^+$ *m/z* 234.1256, found 234.1261.



S1 **S7**

TBSOTf (778 μL, 3.39 mmol) was added dropwise to a stirring solution of ketone **7a** (500 mg, 2.42 mmol) and triethylamine (540 μL, 3.87 mmol) in dichloromethane (11.5 mL) at 0 °C. After 15 minutes, the solution was washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was then extracted with dichloromethane, dried over $MgSO_4$, filtered, and concentrated.

m-CPBA (recrystallized, 543 mg, 3.15 mmol) was added in a single portion to a solution of crude silyl enol ether in dichloromethane (11.5 mL) at 0 °C. After 1 hour, excess peracid was quenched with saturated Na_2SO_3 (5 mL). The mixture was washed with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated. Silica gel column chromatography of the residue (5% to 10% EtOAc: hexanes) afforded TBS ether **S6** (550 mg, 1.63 mmol, 68% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.2 Hz, 2H), 3.98 (dd, *J* = 8.8, 3.6 Hz, 1H), 2.57 (t, *J* = 6.4 Hz, 1H), 2.36 (m, 1H), 2.26 (s, 1H), 2.24 (d *J* = 6.4 Hz, 1H), 1.89 (m, 1H), 1.82 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.9, 167.4, 77.8, 71.6, 71.3, 61.6, 34.7, 32.2, 31.8, 31.4, 25.6, 18.8, 18.3, 14.2, –4.7, –5.5. **IR** (thin film) v_{max} 3314, 3273, 2954, 2925, 2889, 2851, 2128, 1720, 1479, 1258, 1185 cm^{-1}. **HRMS (ESI)** calcd for $C_{18}H_{28}O_4NaSi$ $(M+Na)^+$ *m/z* 359.1160, found 359.1169.

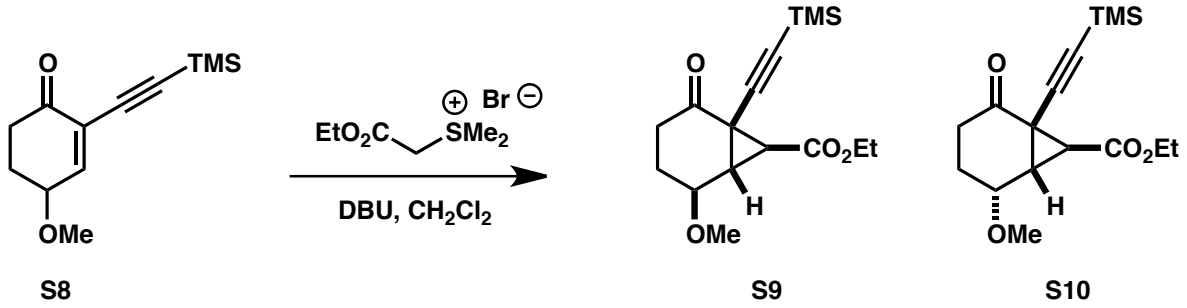


S8

4-Methoxycyclohex-2-en-1-one[56] (800 mg, 6.34 mmol) was dissolved in a mixture of dichloromethane (6.5 mL) and pyridine (6.5 mL) under a nitrogen atmosphere and cooled to 0 °C while stirring. Iodine (3.22 g, 12.7 mmol) was added in portions over 10

minutes. The solution was stirred at room temperature for 1 hour, then diluted with diethyl ether. The organic solution was washed with 1 N HCl (2 x 75 mL) and saturated Na_2SO_3 (2 x 75 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated, and used without any further purification.

The crude vinyl iodide (6.34 mmol), $PdCl_2(PPh_3)_2$ (222 mg, 0.32 mmol), and CuI (120 mg, 1.95 mmol) were placed in a dry flask under nitrogen and dissolved in THF (48 mL). The yellow suspension was cooled to 0 °C. Trimethylsilylacetylene (1.8 mL, 12.7 mmol) was added followed by diisopropylamine (2.7 mL, 19 mmol) over 1 minute. The solution was allowed to stir for 2 hours, then diluted with diethyl ether (100 mL) and washed consecutively with 1 N HCl (100 mL) and brine (100 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography of the resulting crude mixture (15% to 25% EtOAc: hexanes) yielded alkyne **S7** (580 mg, 2.61 mmol, 70% over two steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (m, 1H), 4.08 (ddd, J = 9.6, 4.8, 3.2 Hz, 1H), 3.42 (s, 3H), 2.64 (ddd, J = 18.4, 4.8, 3.6 Hz, 1H), 2.32 (m, 2H), 1.93 (m, 1H), 0.20 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3, 153.6, 125.1, 99.1, 98.2, 74.5, 56.6, 35.1, 28.3, –0.3. **IR** (thin film) ν_{max} 2954, 2901, 2815, 2153, 1691, 1458, 1344, 1242, 1103 cm^{-1}. **HRMS (ESI)** calcd for $C_{12}H_{18}O_2NaSi$ $(M+Na)^+$ *m/z* 245.0968, found 245.0966.

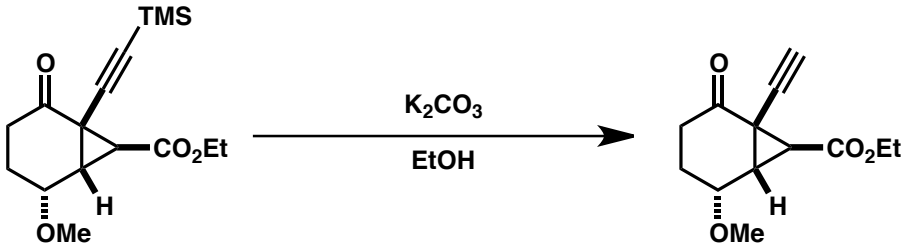


S8 **S9** **S10**

DBU (1.2 mL, 7.83 mmol) was added to a suspension of (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (1.5 g, 6.53 mmol) in DCM (23 mL). After 45 minutes, enyne **S7** (580 mg, 2.61 mmol) was added and the solution was allowed to stir for 12 hours. The organic solvents were evaporated and then partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with 1 N HCl (50 mL), water (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (30% diethyl ether: hexanes) to yield *syn*-bicycle **S8** (318 mg, 1.03 mmol, 39%) and *anti*-bicycle **S9** (425 mg, 1.38 mmol, 53%)

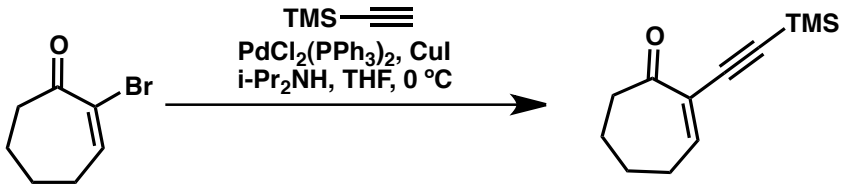
S8: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.19 (m, 2H), 3.87 (m, 1H), 3.45 (s, 3H), 2.83 (m, 1H), 2.48 (m, 1H), 2.45 (d, J = 6.4 Hz, 1H), 2.25 (ddd, J = 18.4, 6.4, 2.8 Hz, 1H), 2.04 (m, 1H), 1.63 (dddd, J = 14.8, 11.6, 6.4, 2.8 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 0.14 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.2, 166.6, 98.9, 88.2, 71.0, 61.5, 56.3, 34.5, 33.1, 32.6, 31.5, 22.9 14.2, –0.2. **IR** (thin film) ν_{max} 2958, 2901, 2815, 2173, 1736, 1699, 1467, 1377, 1246, 1181 cm^{-1}. **HRMS (ESI)** calcd for $C_{16}H_{24}O_4NaSi$ $(M+Na)^+$ *m/z* 331.1336 found 331.1335.

S9: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.18 (m, 2H), 3.96 (dd, *J* = 12, 5.2 Hz, 1H), 3.40 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 1H), 2.67 (d, *J* = 6.8 Hz, 1H), 2.43 (ddd, *J* = 17.2, 8.0, 4.8 Hz, 1H), 2.22 (ddd, *J* = 16.8, 8.4, 5.2 Hz, 1H), 1.99 (m, 1H), 1.74 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.13 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.7, 166.8, 98.9, 88.5, 70.6, 61.6, 56.3, 34.6, 33.4, 33.3, 31.3, 27.1 14.3, –0.2. **IR** (thin film) ν_{max} 2958, 2892, 2819, 2169, 1740, 1704, 1434, 1250, 1193, 1082 cm^{-1}. **HRMS (ESI)** calcd for $C_{16}H_{24}O_4NaSi$ $(M+Na)^+$ *m/z* 331.1336 found 331.1336.



S10 **S11**

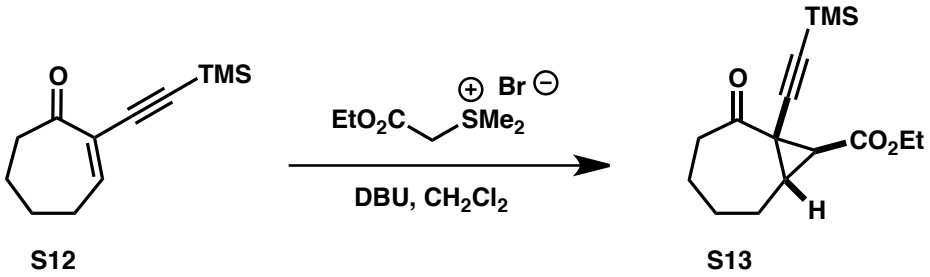
Anti diastereomer **S9** (425 mg, 1.38 mmol) was dissolved in absolute ethanol (6.5 mL) under an atmosphere of nitrogen. Pulverized K_2CO_3 (953 mg, 6.9 mmol) was then added and the suspension was vigorously stirred for 7 hours. The suspension was filtered through Celite and the filtrate concentrated *in vacuo*. The crude residue was purified via silica gel chromatography (25% to 33% EtOAc: hexanes) to afford terminal alkyne **S10** (180 mg, 0.76 mmol, 55%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (m, 2H), 3.91 (aq, 1H), 3.30 (s, 3H), 2.76 (t, *J* = 5.6 Hz, 1H), 2.60 (d, *J* = 6.4 Hz, 1H), 2.36 (ddd, *J* = 17.2, 8.4, 4.8 Hz, 1H), 2.20 (s, 1H), 2.16 (ddd, *J* = 17.2, 8.4, 5.2 Hz, 1H), 1.88 (m, 1H), 1.70 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.7, 166.9, 77.2, 71.8, 70.2, 61.5, 56.1, 34.3, 32.9, 32.4, 30.3, 26.8 14.0. **IR** (thin film) n_{max} 3265, 2987, 2934, 2905, 2827, 2247, 2124, 1736, 1712, 1442, 1373, 1266, 1209 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{16}O_4Na$ $(M+Na)^+$ *m/z* 259.0941 found 259.0939.



S12

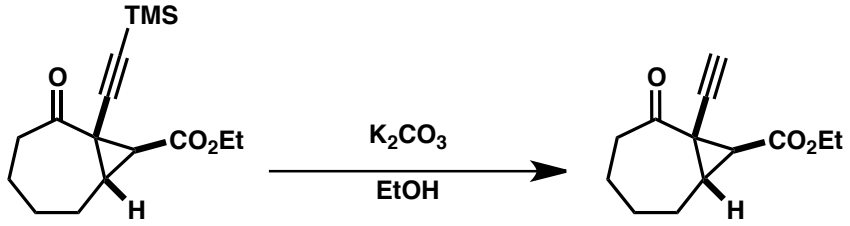
2-Bromocyclohept-2-en-1-one[57] (3 g, 15.9 mmol), $PdCl_2(PPh_3)_2$ (558 mg, 0.8 mmol), and CuI (302 mg, 1.29 mmol) were placed in a dry flask under nitrogen and dissolved in THF (110 mL). The yellow suspension was cooled to 0 °C. Trimethylsilylacetylene (4.5 mL, 31.8 mmol) was added followed by diisopropylamine (6.7 mL, 47.7 mmol) over 1 minute. The solution was allowed to warm to room temperature and stir for 12 hours. The organic solution was diluted with diethyl ether (200 mL) and washed consecutively with 1 N HCl (200 mL) and brine (200 mL), then dried over $MgSO_4$, filtered, and

concentrated *in vacuo*. Silica gel chromatography of the resulting crude mixture (10% to 20% EtOAc: hexanes) yielded alkyne **S11** (1.4 g, 6.8 mmol, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (t, *J* = 6.6 Hz, 1H), 2.64 (t, *J* = 6.3 Hz, 2H), 2.47 (m, 2H), 1.78 (m, 4H), 0.19 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 200.7, 151.9, 128.6, 101.6, 95.1, 42.3, 28.5, 24.8, 21.4, –0.13. **IR** (thin film) ν_{max} 2950, 2860, 2149, 1691, 1462, 1364, 1250 cm^{-1}. **HRMS (EI)** calcd for $C_{12}H_{18}OSi$ $(M)^+$ *m/z* 206.1127, found 206.1127.



S12 **S13**

DBU (1.1 mL, 7.26 mmol) was added to a suspension of (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (1.38 g, 6.05 mmol) in DCM (23 mL). After 45 minutes, enyne **S11** (500 mg, 2.42 mmol) was added and the solution was allowed to stir for 24 hours. The organic solvents were evaporated and then partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with 1 N HCl (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (10% EtOAc: hexanes) to yield bicycle **S12** as a single diastereomer (480 mg, 1.64 mmol, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (m, 2H), 3.00 (td, *J* = 11.2, 4 Hz, 1H), 2.40 (ddd, *J* = 15.6, 6.8, 3.6 Hz, 1H), 2.33 (d, *J* = 6.4 Hz, 1H), 2.28 (m, 1H), 1.96 (ddd, *J* = 11.2, 5.6, 5.6 Hz, 1H), 1.87 (m, 1H), 1.70 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.3, 168.2, 100.1, 88.3, 60.8, 41.2, 37.6, 33.8, 30.1, 28.6, 25.7, 25.4, 14.2, –0.3. **IR** (thin film) ν_{max} 2962, 2934, 2851, 2161, 1740, 1720, 1454, 1246, 1181 cm^{-1}. **HRMS (ESI)** calcd for $C_{16}H_{25}O_3Si$ $(M+H)^+$ *m/z* 293.1567, found 293.1571.

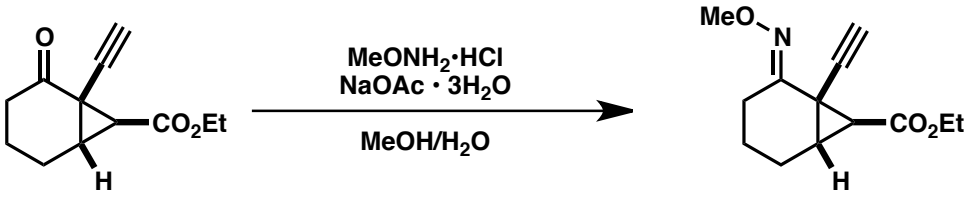


S13 **S14**

Silyl alkyne **S12** (480 mg, 1.64 mmol) was dissolved in absolute ethanol (8 mL) under an atmosphere of nitrogen. Pulverized K_2CO_3 (682 mg, 4.92 mmol) was then added and the suspension was vigorously stirred for 12 hours. The suspension was filtered through Celite and the filtrate concentrated *in vacuo*. The crude residue was purified via silica gel chromatography (15% to 20% EtOAc: hexanes) to afford terminal alkyne **S13** (210

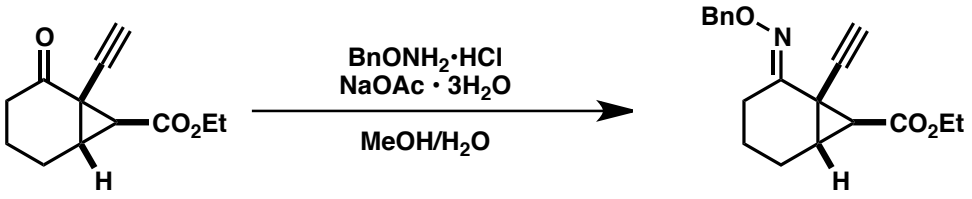
mg, 0.95 mmol, 58%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.2 Hz, 2H), 3.04 (td, *J* = 12, 4.4 Hz, 1H), 2.46 (ddd, *J* = 10.8, 7.2, 3.6 Hz, 1H), 2.40 (d, *J* = 6.4 Hz, 1H), 2.32 (m, 1H), 2.27 (s, 1H), 2.02 (aq, *J* = 5.6 Hz, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.53 (m, 1H), 1.40 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.81(m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.4, 168.6, 78.8, 71.8, 41.2, 36.7, 33.2, 30.3, 28.5, 25.6, 25.5, 14.2. **IR** (thin film) ν_{max} 3269, 2983, 2934, 2860, 2116, 1736, 1720, 1446, 1421, 1323, 1270, 1193 cm^{-1}. **HRMS (EI)** calcd for $C_{13}H_{16}O_3$ $(M)^+$ *m/z* 220.1099, found 220.1103.

Representative Procedure for the Synthesis of Oxime Ethers:



S1 **S15**

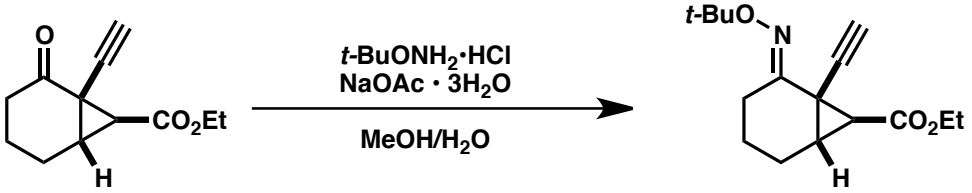
To a flame-dried round bottom flask was added ketone **7a** (2.00 g, 9.70 mmol) in CH_3OH:H_2O (24.2 mL, 1:2). Sodium acetate trihydrate (3.74 g, 45.6 mmol) was then added to the mixture followed by methoxylamine hydrochloride (0.696 g, 8.28 mmol). The solution was stirred for 3.5 hours at room temperature, after which the organic solvent was removed under reduced pressure. The remaining aqueous solvent was extracted with CH_2Cl_2 (24 mL x 3), dried with Na_2SO_4, concentrated, and purified by silica gel chromatography (33% EtOAc: hexanes) to yield oxime **S14** as a crystalline white solid (1.46 g, 8.2 mmol, 85%, mixture of *E* and *Z* diastereomers). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.25 – 4.05 (m, 2H), 3.93 (s, 3H), 2.62 (ad, *J* = 16.2 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.23 – 2.20 (m, 2H), 2.14 – 2.07 (m, 1H), 2.06 – 1.77 (m, 3H), 1.64 – 1.62 (m, 1H), 1.29 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) (major diastereomer reported) δ 168.6, 154.2, 80.8, 69.7, 61.9, 61.2, 30.6, 29.2, 24.3, 21.8, 20.14, 16.5, 14.2. **IR** (thin film) ν_{max} 3276, 2939, 2121, 2819, 1732, 1369, 936 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{18}NO_3$ $(M+H)^+$: *m/z* 236.1281, found 236.1283.



S1 **S16**

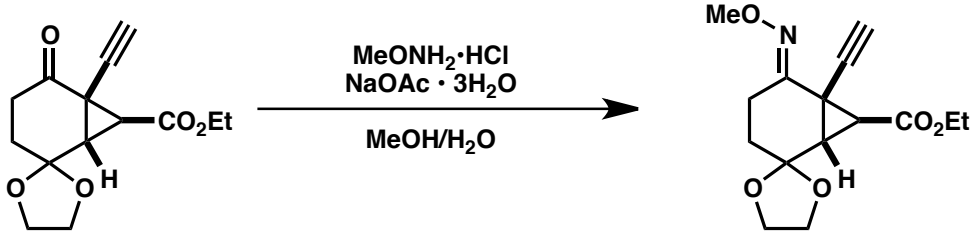
The general procedure for the synthesis of oximes was followed using ketone **7a** (50 mg, 0.24 mmol), *O*-benzylhydroxylamine hydrochloride (33 mg, 0.21 mmol), and sodium acetate trihydrate (93 mg, 1.14 mmol) yielding benzyl oxime **S15** (61 mg, 0.20 mmol, 95%, mixture of *E* and *Z* diastereomers). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 5.18 (dt, *J* = 16.2, 11.4 Hz, 2H), 4.25 – 4.15 (m, 2H), 2.66 (ad, *J* = 18.0 Hz, 1H), 2.39 (ad, *J* = 3.0 Hz, 1H), 2.32 – 2.22 (m, 2H), 2.19 – 2.11 (m, 1H), 2.09 – 1.78 (m, 3H),

1.62 – 1.56 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) (mixture of diastereomers reported) δ 169.0, 168.6, 154.4, 153.5, 138.3, 137.5, 128.3, 128.3, 128.1, 127.8, 127.3, 127.3, 80.7, 80.3, 76.3, 75.7, 69.7, 67.9, 61.2, 61.0, 30.5, 30.3, 29.3, 28.4, 27.1, 24.4, 22.1, 21.0, 20.6, 20.1, 19.4, 16.5, 14.3,14.2. **IR** (thin film) ν_{max} = 3284, 3063, 2039, 2935, 2873, 2120, 1732, 1369, 959 cm^{-1}. **HRMS (ESI)** calcd for $C_{19}H_{22}NO_3$ $(M+H)^+$: *m/z* 312.1594, found 312.1597.



S1 **S17**

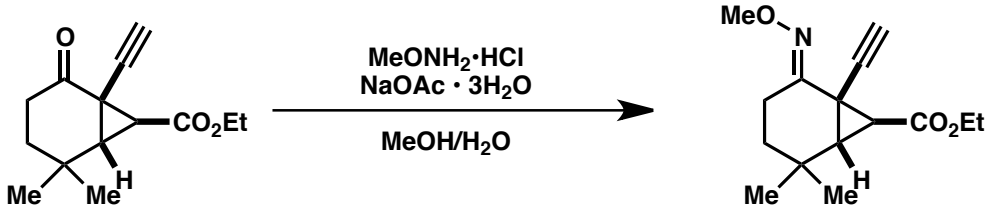
The representative procedure for the synthesis of oximes was followed using ketone **7a** (50 mg, 0.24 mmol), *O-tert*-butylhydroxylamine hydrochloride (26 mg, 0.21 mmol), and sodium acetate trihydrate (93.5 mg, 1.14 mmol), yielding *tert*-butyl oxime **S16** (49 mg, 0.15 mmol, 73%, mixture of *E* and *Z* diastereomers). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.31 – 4.15 (m, 2H), 2.57 (ad, *J* = 18.6 Hz, 1H), 2.36 – 2.32 (m, 1H), 2.19 – 2.16 (m, 1H), 2.10 (ddd, *J* = 18.6, 12.0, 6.6 Hz, 1H), 2.07 – 1.92 (m, 1H), 1.91- 1.75 (m, 2H), 1.62 – 1.60 (m, 1H), 1.31 – 1.22 (m, 12H). **^{13}C NMR** (150 MHz, $CDCl_3$) (major diastereomer reported) δ 169.0, 151.4, 81.2, 78.8, 69.1, 61.1, 30.3, 29.3, 27.6, 25.1, 21.8, 20.3, 16.7, 14.3. **IR** (thin film) ν_{max} = 3287, 2977, 2934, 2123, 1733, 1364, 962 cm^{-1}. **HRMS** (**ESI)** calcd for $C_{16}H_{24}NO_3$ $(M+H)^+$: *m/z* 278.1751, found 278.1752.



S4 **S18**

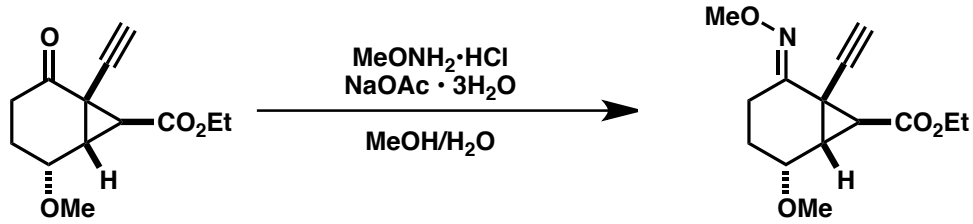
The general procedure for the synthesis of oximes was followed using ketone **S3** (200 mg, 0.78 mmol), methoxylamine hydrochloride (70 mg, 0.84 mmol), and sodium acetate trihydrate (137 mg, 1.66 mmol) affording methyl oxime **S17** (201 mg, 0.71 mmol, 91%, mixture of *E* and *Z* diastereomers). **^{1}H NMR** (600 MHz, CDCl3) δ 4.24 – 4.12 (m, 3H), 4.06 – 4.03 (m, 1H), 4.00 – 3.96 (m 2H), 3.94 (s, 3H), 2.65 (dt, *J* = 18.6, 4.8 Hz, 1H), 2.57 – 2.49 (m, 1H), 2.47 (d, *J* = 6.6 Hz, 1H), 2.26 (d, *J* = 6.6 Hz, 1H), 2.25 (s, 1H), 1.72 – 1.70 (m, 1H), 1.59 – 1.53 (m, 1H), 1.29 (t, *J* = 4.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) (major diastereomer reported) δ 167.6, 152.3, 105.6, 79.4, 70.3, 65.0, 64.9, 62.0, 61.5, 35.1, 31.9, 27.5, 26.5, 20.5, 14.2. **IR** (thin film) ν_{max} = 3280, 2960, 2895, 2123, 1731,

1369, 962 cm^{-1} **HRMS (ESI)** calcd for $C_{15}H_{20}NO_5$ $(M+H)^+$: *m/z* 294.1336, found 294.1331.



S6 **S19**

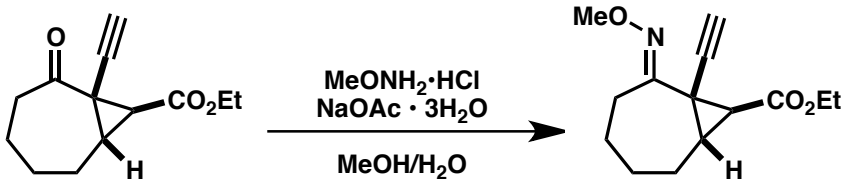
To a solution of ketone **S5** (200 mg, 0.85 mmol) in a mixture of methanol (870 μL) and water (600 μL) was added sodium acetate trihydrate (277 mg, 2.04 mmol) and methoxylamine hydrochloride (85 mg, 1.02 mmol). After stirring for 12 hours, the solution was diluted with water (2 mL), extracted into dichloromethane (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude oxime was purified by silica gel chromatography (15% EtOAc: hexanes) to yield the pure oxime **S18** (112 mg, 0.42 mmol, 49%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.14 (m, 2H), 3.88 (s, 2.4H), 3.85 (s, 0.6H), 2.51 (m, 0.8H), 2.23–2.15 (m, 1.8 H), 2.13–2.05 (m, 1.8H), 1.80 (d, *J* = 6.4 Hz, 0.2H), 1.67 (d, *J* = 6.8 Hz, 0.2H), 1.42 (m, 0.2H), 1.26 (m, 4H), 1.12 (m, 0.2H), 1.07 (s, 3H), 1.01 (s, 2.4 H), 0.97 (s, 0.6H). **^{13}C NMR** (101 MHz, $CDCl_3$) *denotes oxime isomer δ 168.8*, 168.3, 153.3, 152.7*, 80.6, 80.2*, 69.9, 67.6*, 61.8, 61.6*, 61.1, 60.9*, 40.5, 38.8*, 33.3*, 30.5, 30.4*, 29.5, 29.4, 29.38*, 28.4*, 28.1, 27.7*, 26.1, 25.4, 25.1*, 21.3*, 19.1, 14.2*, 14.1. **IR** (thin film) ν_{max} 3276, 2961, 2900, 2810, 2116, 1732, 1462, 1433, 1302, 1204, 1045 cm^{-1}. **HRMS (ESI)** calcd for $C_{15}H_{22}O_3N$ $(M+H)^+$ *m/z* 264.1594, found 264.1593.



S11 **S20**

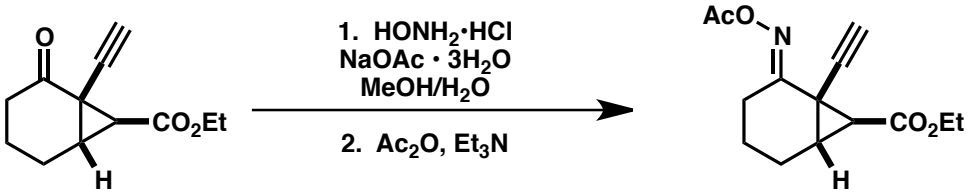
To a solution of ketone **S10** (75 mg, 0.32 mmol) in a mixture of methanol (700 μL) and water (220 μL) was added sodium acetate trihydrate (105 mg, 0.72 mmol) and methoxylamine hydrochloride (32 mg, 0.38 mmol). After stirring for 12 hours, the solution was diluted with water (1 mL), extracted into dichloromethane (3 x 5 mL), washed with saturated $NaHCO_3$ dried over $MgSO_4$, filtered, and concentrated. The resulting oxime (**S19**) was used without any further purification (80 mg, 0.30 mmol,

94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.18 (m, 2H), 3.91 (s, 3H), 3.84 (dt, *J* = 9.2, 4.8 Hz, 1H), 3.37 (s, 3H), 2.64 (t, *J* = 6.0 Hz, 1H), 2.53 (dt, *J* = 18, 5.6 Hz, 1H), 2.33 (d, *J* = 6.4 Hz, 1H), 2.26 (m, 1H), 2.23 (s, 1H), 1.80 (m, 1H), 1.32 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 153.1, 79.9, 71.5, 70.1, 61.9, 61.4, 56.4, 31.8, 29.6, 25.8, 23.8, 19.7, 14.2. **IR** (thin film) ν_{max} 3269, 2929, 2892, 2819, 2120, 1732, 1438, 1295, 1205 cm^{-1}. **HRMS (ESI)** calcd for $C_{14}H_{20}O_4N$ $(M+H)^+$ *m/z* 266.1387, found 266.1383.



S14 **S21**

To a solution of ketone **S13** (80 mg, 0.36 mmol) in a mixture of methanol (800 μL) and water (250 μL) was added sodium acetate trihydrate (117 mg, 0.86 mmol) and methoxylamine hydrochloride (36 mg, 0.43 mmol). After stirring for 12 hours, the solution was diluted with water (1 mL), extracted into dichloromethane (3 x 5 mL), washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The crude oxime was purified by silica gel chromatography (10 % EtOAc: hexanes) to yield the pure oxime **S20** (90 mg, 0.36 mmol, quantitative). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (m, 2H), 3.85 (s, 3H), 2.95 (ddd, *J* = 14, 7.2, 2.8 Hz, 1H), 2.38 (d, *J* = 6.0 Hz, 1H), 2.25 (m, 1H), 2.13 (s, 1H), 1.92 (m, 2H), 1.66 (m, 1H), 1.49 (m, 1H), 1.39 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.73 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 156.1, 81.4, 69.3, 61.7, 60.9, 34.6, 30.3, 28.3, 28.2, 27.5, 25.9, 24.7, 14.2. **IR** (thin film) ν_{max} 3285, 2933, 2851, 2810, 2116, 1736, 1450, 1290, 1184, 1053 cm^{-1}. **HRMS (ESI)** calcd for $C_{14}H_{20}O_3N$ $(M+H)^+$ *m/z* 250.1438 found 250.1436.

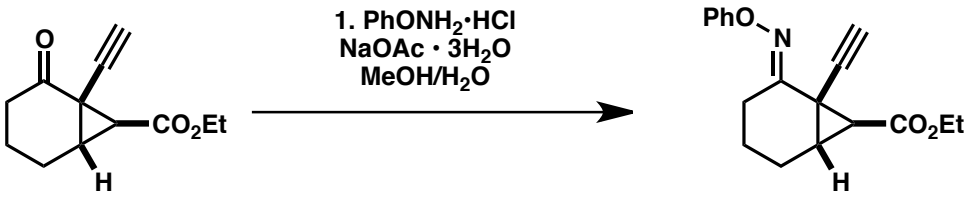


S1 **S22**

To a solution of ketone **S1** (200 mg, 0.970 mmol) in a mixture of methanol (1 mL) and water (700 μL) was added sodium acetate trihydrate (175 mg, 2.13 mmoL) and hydroxylamine hydrochloride (74.0 mg, 1.02 mmol). The heterogenous mixture was allowed to stir overnight upon which it was diluted with deionized H_2O (2 mL), extracted with CH_2Cl_2 (3 x 2 mL) and dried over $MgSO_4$ and concentrated. The crude hydroxylamine was used in the next step without further purification.

To a solution of the crude hydroxylamine (50 mg, 0.23 mmol) in THF (1 mL) was added 4-dimethylaminopyridine (2 mg) followed by acetic anhydride (45 μL, 0.46 mmol) and

then triethylamine (64 μL, 0.46 mmol). The solution was stired for 12 hours upon which it was diluted with ethylacetate (3 mL) then washed with saturated $NaHCO_3$ (3 mL, x3). The organic layer was then dried over $MgSO_4$ and then purified by silica gel chromatography (50% EtOAc:Hex) to afford hydrazone **S22** (40 mg, 66%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 – 3.95 (m, 2H), 2.68 (dt, *J* = 18.6, 4.5 Hz, 1H), 2.45 (dt, *J* = 6.6, 3.3 Hz, 1H), 2.38 – 2.22 (m, 3H), 2.19 (s, 3H) 1.93 (dt, *J* = 8.1, 4.1 Hz, 2H), 1.76 – 1.59 (m, 1H), 1.41 – 1.22 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5, 168.0, 162.7, 79.2, 70.8, 61.4, 30.4, 29.4, 24.3, 23.1, 19.8, 19.7, 16.2, 14.2 ppm **IR** (thin film) ν_{max} cm^{-1}. **HRMS (EI)** calcd for $C_{12}H_{14}O_3$ $(M)^+$ *m/z* 263.1158, found 206.0941.

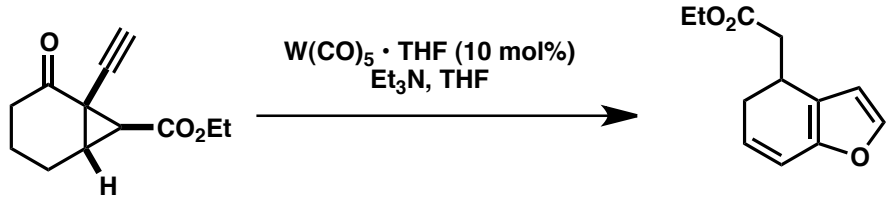


S1 **S23**

To a round bottom flask containing ketone **S1** (500 mg, 2.42 mmol) in MeOH (2 mL) and water (4 mL) was added sodium acetate (1.09 g, 13.3 mmol) and then phenylhydroxylamine hydrochloride (388 mg, 2.66 mmol). The mixture was then concentrated to remove methanol and then diluted with deionized water (6 mL). The mixture was then extracted with CH_2Cl_2 (24 mL, x3) dried over Na_2SO_4, concentrated, and then purified by silica gel chromatography (25% EtOAc in Hexanes) to afford oxime ether **S23** (704 mg, 97%) as an amorphous white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.28 – 7.21 (m, 2H), 7.13 – 6.98 (m, 1H), 4.42 – 4.16 (m, 2H), 2.88 (ddd *J* = 18.6, 5.3, 3.7 Hz, 1H), 2.64 – 2.49 (m, 1H), 2.43 (ddd *J* = 18.5, 11.9, 6.6 Hz, 1H), 2.38 – 2.14 (m, 2H), 2.14 – 1.87 (m, 3H), 1.81 – 1.67 (m, 1H), 1.43 – 1.28 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) 168.8, 168.5, 159.4, 159.2, 157.7, 157.0, 129.3, 129.2, 122.2, 122.1, 114.7, 114.6, 80.2, 79.9, 70.2, 68.2, 21.4, 61.2, 30.6, 30.4, 29.4, 28.4, 26.9, 24.7, 22.5, 20.9, 20.8, 20.1, 19.2, 16.5, 14.6, 14.3; **IR** (ATIR) 3289, 3062, 3038, 2979, 2939, 2872, 1727, 1589, 1486, 1197 cm^{-1}; **HRMS** (ESI) cacld for $C_{18}H_{20}O_3N_1$ $(M+H)^+$ m/z 298.1438, found 298.1436.

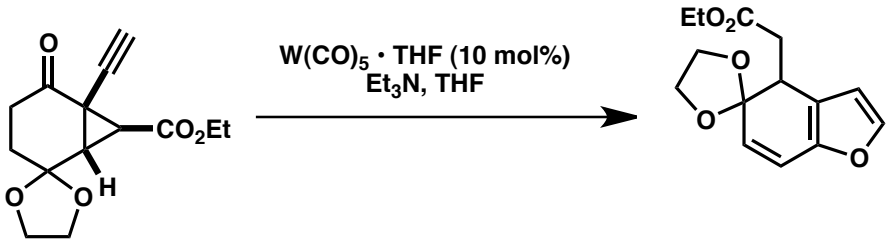
Representative Procedure for Synthesis of 4,5-Dihydrobenzo[b]furans:

A dry sealed vial was charged with $W(CO)_6$ (10 mol %) and a stir bar, then evacuated and placed under a nitrogen atmosphere. Dry THF (4.6 mL/mmol substrate) was added and the solution was irradiated at 350 nm for 2 hours. The vial was removed and a solution of cycloisomerization substrate and Et_3N (3 eq) in THF (4.6 mL/mmol substrate) was added. The yellow solution turned dark orange/red and was allowed to stir for 12 hours. Upon completion, the solvents were removed *in vacuo* and purified via silica gel chromatography as noted.



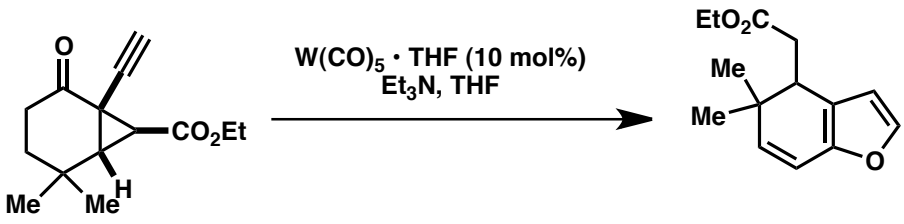
S1 **S24**

Following the general procedure, ketone **S1** (500 mg, 2.42 mmol) was cyclized to dihydrobenzofuran **S24** (490 mg, 2.36 mmol, 98%). Purification was accomplished with 5% EtOAc: hexanes. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.38 (d, *J* = 9.9 Hz, 1H), 6.27 (s, 1H), 5.72 (ddd, *J* = 9.3, 4.2, 4.2 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.33 (ap, *J* = 7.8 Hz, 1H), 2.57 (m, 1H), 2.54 (dd, *J* = 15.3, 6.6 Hz, 1H), 2.40 (dd, *J* = 15.3, 8.1 Hz, 1H), 2.21 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 150.2, 140.6, 123.9, 119.4, 117.8, 109.6, 60.4, 39.0, 30.1, 29.2, 14.2. **IR** (thin film) ν_{max} 2991, 2933, 3872, 1732, 1364, 1266, 1172 cm^{-1}. **HRMS (EI)** calcd for $C_{12}H_{14}O_3$ $(M)^+$ *m/z* 206.0943, found 206.0941.



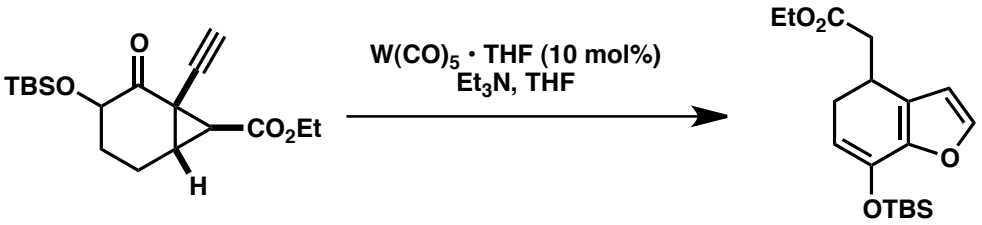
S4 **S25**

Following the general procedure, ketone **S4** (100 mg, 0.38 mmol) was cyclized to dihydrobenzofuran **S25** (92 mg, 0.35 mmol, 92%). Purification was accomplished with 15% to 25% EtOAc: hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 1.6 Hz, 1H), 6.52 (d, *J* = 10 Hz, 1H), 6.9 (d, *J* = 1.6 Hz, 1H), 5.57 (d, *J* = 10 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.08–3.84 (m, 4H), 3.54 (at, *J* = 7.2 Hz, 1H), 2.73 (dd, *J* = 16, 6.8 Hz, 1H), 2.36 (dd, *J* = 16, 8 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5, 147.9, 141.9, 125.2, 120.5, 120.2, 110.5, 108.8, 65.3, 64.2, 60.4, 39.0, 34.2, 14.1. **IR** (thin film) ν_{max} 3146, 2987, 2889, 1936, 1732, 1487, 1372, 1275, 1156, 1103 cm^{-1}. **HRMS (EI)** calcd for $C_{14}H_{16}O_5$ $(M)^+$ *m/z* 264.0998, found 264.1000.



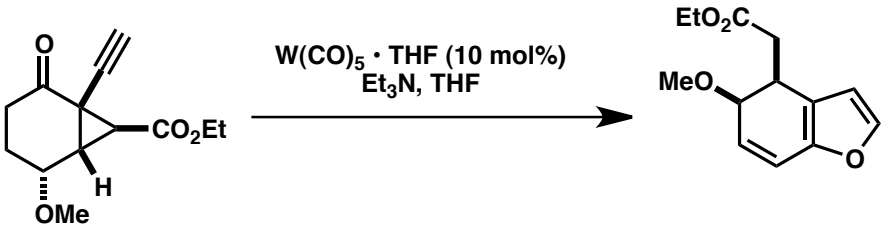
S6 **S26**

Following the general procedure, ketone **S6** (100 mg, 0.43 mmol) was cyclized to dihydrobenzofuran **S27** (97 mg, 0.41 mmol, 97%). Purification was accomplished with 5% EtOAc: hexanes. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.5 Hz, 1H), 6.27 (d, *J* = 10.2 Hz, 1H), 6.23 (s, 1H), 5.42 (d, *J* = 9.9 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.01 (dd, *J* = 10.5, 4.5 Hz, 1H), 2.53 (dd, *J* = 15, 4.5 Hz, 1H), 2.29 (dd, *J* = 14.7, 10.5 Hz, 1H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.11 (s, 3H), 1.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3, 149.1, 140.6, 136.5, 119.5, 115.4, 110.9, 60.4, 40.2, 36.6, 35.2, 27.5, 23.7, 14.1. **IR** (thin film) ν_{max} 2966, 2929, 2872, 1740, 1373, 1287, 1246, 1168 cm^{-1}. **HRMS (EI)** calcd for $C_{14}H_{18}O_3$ $(M)^+$ *m/z* 234.1256, found 234.1255.



S7 **S27**

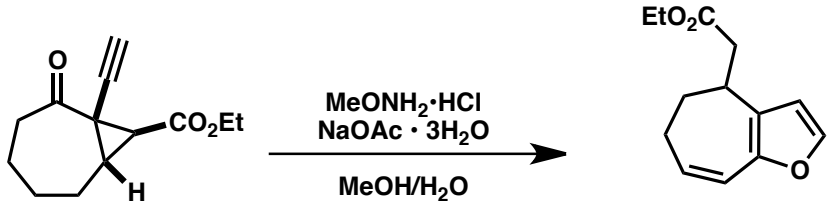
Following the general procedure, ketone **S7** (200 mg, 0.59 mmol) and $W(CO)_6$ (42 mg, 0.12 mmol, 20 mol %) used to afford dihydrobenzofuran **S27** (190 mg, 0.56 mmol, 95%). Purification was accomplished with 10% EtOAc: hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.27 (s, 1H), 4.79 (t, *J* = 4.8 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.24 (p, *J* = 7.6 Hz, 1H), 2.60 (ddd, *J* = 16.4, 7.6, 4 Hz, 1H), 2.54 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.42 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.20 (ddd, *J* = 16.4, 7.6, 5.2 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 9H), 0.17 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 147.3, 142.6, 140.8, 122.5, 109.8, 100.5, 60.3, 38.6, 29.7, 29.5, 25.6, 18.3, 14.2, –4.69, –4.73. **IR** (thin film) ν_{max} 2958, 2929, 2852, 1945, 1736, 1622, 1475, 1446, 1377, 1246, 1201 cm^{-1}. **HRMS (EI)** calcd for $C_{18}H_{28}O_4Si$ $(M)^+$ *m/z* 336.1757, found 336.1757.



S11 **S28**

Following the general procedure, ketone **S11** (50 mg, 0.21 mmol) was cyclized to dihydrobenzofuran **S28** (40 mg, 0.17 mmol, 81%). Purification was accomplished with 25% EtOAc: hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.40 (dd, *J* = 10, 1.2 Hz, 1H), 6.31 (s, 1H), 5.76 (dd, *J* = 10, 3.2 Hz, 1H), 4.26 (ddd, *J* = 7.2, 2.4, 2.4 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.45 (m, 1H), 3.36 (s, 3H), 2.74 (dd, *J* = 16, 6.0 Hz, 1H), 2.42

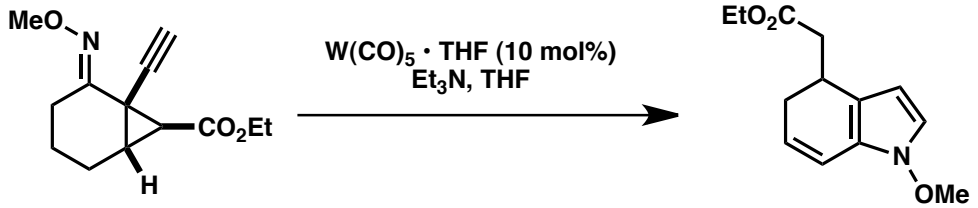
(dd, *J* = 16, 8.8 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.9, 149.3, 141.3, 125.8, 120.0, 118.4, 110.4, 77.6, 60.3, 56.8, 33.1, 31.9, 14.2. **IR** (thin film) ν_{max} 2983, 2929, 2815, 1924, 1732, 1364, 1254, 1168, 1099 cm^{-1}. **HRMS (EI)** calcd for $C_{13}H_{16}O_4$ $(M)^+$ *m/z* 236.1049, found 236.1053.



S14 **S29**

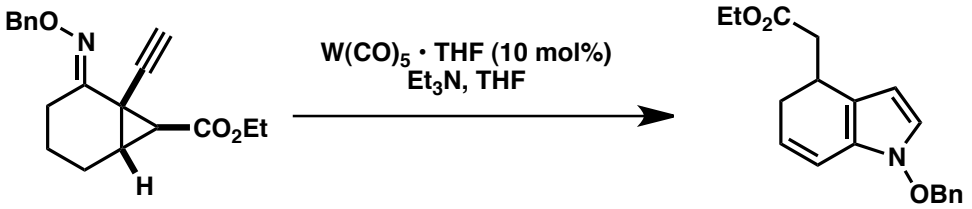
Following the general procedure, ketone **S14** (100 mg, 0.45 mmol) was cyclized to dihydrobenzofuran **S29** (90 mg, 0.41 mmol, 90%). Purification was accomplished with 5% EtOAc: hexanes. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.6 Hz, 1H), 6.33 (d, *J* = 11.6 Hz, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 5.74 (dt, *J* = 10.8, 5.2 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.36 (m, 1H), 2.57 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.40 (m, 3H), 1.90 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4, 149.2, 140.2, 128.6, 125.1, 119.4, 112.4, 60.4, 40.7, 32.6, 28.6, 26.9, 14.2. **IR** (thin film) ν_{max} 2987, 2925, 1928, 1736, 1503, 1373, 1283 1193, 1156 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{17}O_3$ $(M+H)^+$ *m/z* 221.1172, found 221.1181.

Note: The cycloisomerization reaction of oximes were performed and worked up in the dark, and the product N-alkoxydihydroindole was stored in an amber vial at –25 ºC.



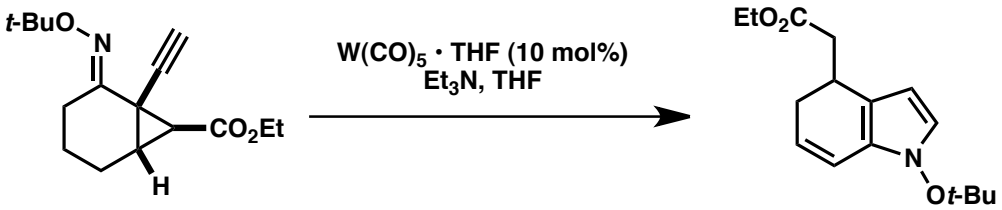
S15 **S30**

Following the general procedure, oxime **S15** (50 mg, 0.21 mmol) was cyclized to dihydroindole **S30** (36 mg, 0.15 mmol, 72%). Purification was accomplished with 5% EtOAc: hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.62 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 5.81 (d, *J* = 3.0 Hz, 1H), 5.69 (dt, *J* = 9.6, 4.8 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 3.269 (apparent p, *J* = 8.4 Hz, 1H), 2.59 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.52 (dddd, *J* = 17.4, 7.8, 4.8, 2.4 Hz, 1H), 2.40 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.15 (dddd, *J* = 16.8, 8.4, 4.2, 1.8 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.7, 123.3, 122.2, 116.06, 115.2, 113.3, 101.4, 67.3, 60.2, 39.4, 30.4, 30.0, 14.2. **IR** (thin film) ν_{max} = 3446.1, 3131.8, 2979.5, 2937.4, 2868.6, 2822.1, 1923.2, 1732.2 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{18}NO_3$ $(M+H)^+$: *m/z* 236.1281, found 236.1282.



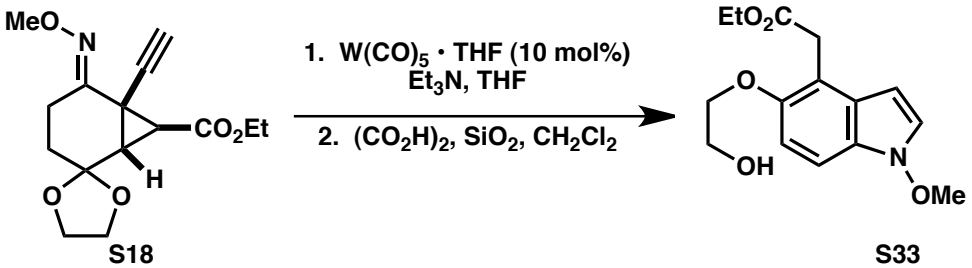
S16 **S31**

Following the general procedure, oxime **S17** (50 mg, 0.16 mmol) was cyclized to afford the desired dihydroindole **S31** (35 mg, 0.11 mmol, 70%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 3H), 7.32 – 7.29 (m, 2H), 6.48 (d, *J* = 3.0 Hz, 1H), 6.24 (d, *J* = 9.6 Hz, 1H), 5.77 (d, *J* = 3.0 Hz, 1H), 5.59 (dt, *J* = 9.6, 4.8 Hz, 1H), 5.03 (d, *J* = 1.8 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.24 (ap, *J* = 7.8 Hz, 1H), 2.55 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.49 (dddd, *J* = 16.8, 7.2, 4.2, 1.8 Hz, 1H), 2.36 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.12 (dddd, *J* = 16.8, 8.4, 4.8, 1.8 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.8, 134.4, 129.5, 129.1, 128.5, 128.1, 127.3, 124.0, 121.8, 115.9, 115.5, 114.3, 101.3, 81.8, 60.2, 39.4, 30.4, 30.1, 14.2. **IR** (thin film) n_{max} = 3420, 2033, 2928, 1732 cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{22}NO_3$ $(M+H)^+$: *m/z* 312.1594, found 312.1591.



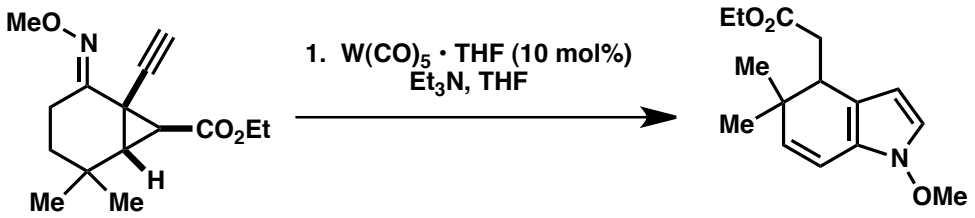
S17 **S32**

Following the general procedure, oxime **S17** (40 mg, 0.14 mmol) was cyclized to dihydroindole **S32** (32 mg, 0.11 mmol, 80%). Purification was accomplished with 5% EtOAc: hexanes. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.53 (d, *J* = 3.0 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 5.79 (d, *J* = 2.4 Hz, 1H), 5.62 (dt, *J* = 14.4, 4.8 Hz, 1H), 4.14 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.26 (ap, *J* = 8.4 Hz, 1H), 2.57 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.50 (dddd, *J* = 16.8, 7.8, 4.2, 2.4 Hz, 1H), 2.38 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.13 (dddd, *J* = 16.8, 8.4, 4.2, 1.8, 1H), 1.31 (s, 9H), 1.25 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.9, 126.2, 121.2, 117.7, 117.0, 115.6, 100.7, 84.7, 60.1, 39.4, 30.3, 30.2, 27.2, 14.2. **IR** (thin film) ν_{max} = 3289, 2980, 2934, 1924, 1733 cm^{-1}. **HRMS (ESI)** calcd for $C_{16}H_{24}NO_3$ $(M+H)^+$: *m/z* 278.1751, found 278.1749.



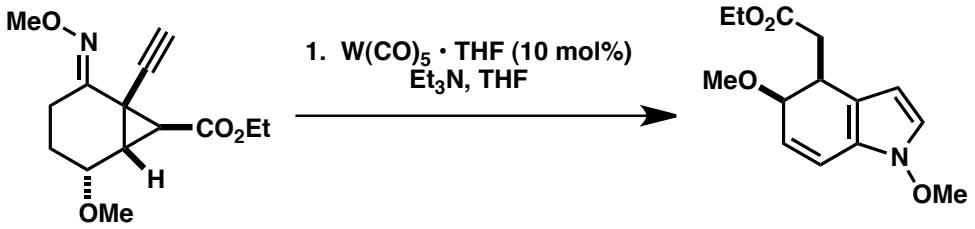
S18 **S33**

A solution of *N*-methoxydihydroindole in DCM (250 μL) (synthesized using oxime **S18** (50 mg, 0.17 mmol, following the representative procedure) was added to a suspension of saturated aqueous oxalic acid (50 μL) and silica gel (100 mg) in dichloromethane (250 μL) that was allowed to premix for 15 minutes. After 1 hour, the reaction was then quenched with saturated $NaHCO_3$ (1 mL), filtered through silica with EtOAc, and purified by silica gel chromatography (33% to 50 % EtOAc: hexanes) to afford the desired indole **S33** (29 mg, 0.1 mmol, 57%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 3.0 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.33 (d, *J* = 3.0 Hz, 1H), 4.18 (t, *J* = 4.2 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 3H), 3.90 (m, 4H), 3.18 (bs, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.5, 150.5, 127.7, 125.1, 124.1, 114.5, 110.4, 107.7, 95.8, 71.8, 65.9, 61.5, 61.0, 32.8, 14.1. **IR** (thin film) ν_{max} = 3447, 3128, 2979, 2938, 1918, 1727 cm^{-1}. **HRMS (ESI)** calcd for $C_{15}H_{18}NO_5Na$ $(M+Na)^+$: *m/z* 316.1155, found 316.1158.



S19 **S34**

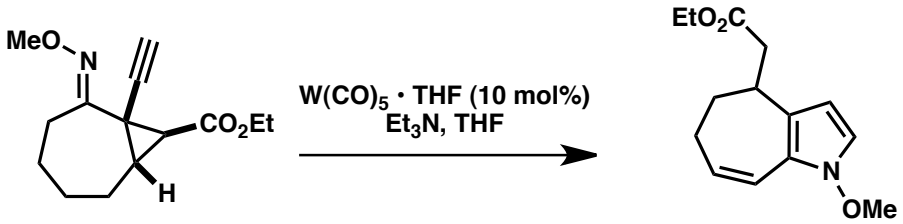
Following the general procedure, oxime **S19** (60 mg, 0.23 mmol) was cyclized to the desired dihydroindole **S34** (45 mg, 0.17 mmol, 75%) after purification by silica gel chromatography (10% EtOAc: hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.57 (d, *J* = 3.2 Hz, 1H), 6.28 (d, *J* = 10 Hz, 1H), 5.74 (d, *J* = 2.8 Hz, 1H), 5.35 (d, *J* = 9.6 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 2.99 (dd, *J* = 10, 4.4 Hz, 1H), 2.51 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.30 (dd, *J* = 14.4, 10 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 134.6, 122.1, 116.2, 113.3, 112.9, 102.8, 67.2, 60.2, 41.0, 36.6, 35.7, 27.8, 23.5, 14.2. **IR** (thin film) ν_{max} 2962, 2934, 1928, 1732, 1446, 1364, 1283, 1168 cm^{-1}. **HRMS (ESI)** calcd for $C_{15}H_{22}O_3N$ $(M+H)^+$ *m/z* 264.1594, found 264.1591.



S20 **S35**

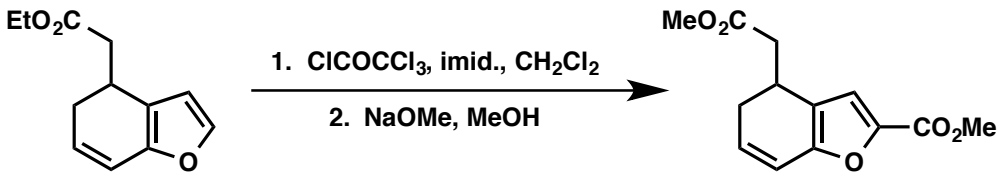
Following the general procedure, oxime **S20** (50 mg, 0.19 mmol) was cyclized to the desired dihydroindole **S35** (38 mg, 0.14 mmol, 76%) after purification by silica gel chromatography (25% EtOAc: hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.59 (d, *J* = 3.2

Hz, 1H), 6.42 (dd, *J* = 10, 1.6 Hz, 1H), 5.84 (d, *J* = 2.8 Hz, 1H), 5.69 (dd, *J* = 10, 3.2 Hz, 1H), 4.22 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 3.42 (m, 1H), 3.36 (s, 3H), 2.70 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.41 (dd, *J* = 15.6, 8.4 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3, 123.9, 122.4, 115.9, 114.2, 102.6, 78.2, 67.4, 60.1, 56.7, 34.1, 32.6, 14.2. **IR** (thin film) ν_{max} 2978, 2934, 2819, 1924, 1724, 1442, 1368, 1156, 1107 cm^{-1}. **HRMS (ESI)** calcd for $C_{14}H_{20}O_4N$ $(M+H)^+$ *m/z* 266.1387, found 266.1384.



S21 **S36**

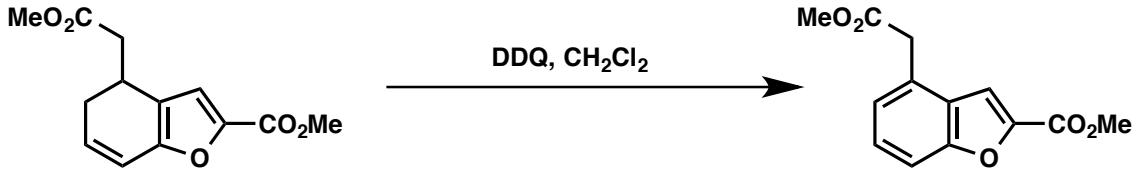
Following the general procedure, oxime **S21** (50 mg, 0.2 mmol) was cyclized to the desired dihydroindole **S36** (39 mg, 0.16 mmol, 78%) after purification by silica gel chromatography (10% EtOAc: hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 12 Hz, 1H), 5.87 (d, *J* = 3.2 Hz, 1H), 5.71 (dt, *J* = 10.4, 2.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 3.44 (m, 1H), 2.65 (dd, *J* = 14.8, 6.4 Hz, 1H), 2.46 (m, 3H), 1.94 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 126.9, 122.9, 121.8, 115.6, 113.4, 103.3, 67.0, 61.2, 40.8, 34.8, 29.1, 28.1, 27.8, 14.2. **IR** (thin film) ν_{max} 2983, 2934, 1924, 1732, 1454, 1373, 1275, 1160 cm^{-1}. **HRMS (ESI)** calcd for $C_{14}H_{20}O_3N$ $(M+H)^+$ *m/z* 250.1438, found 250.1436.



S24 **S37**

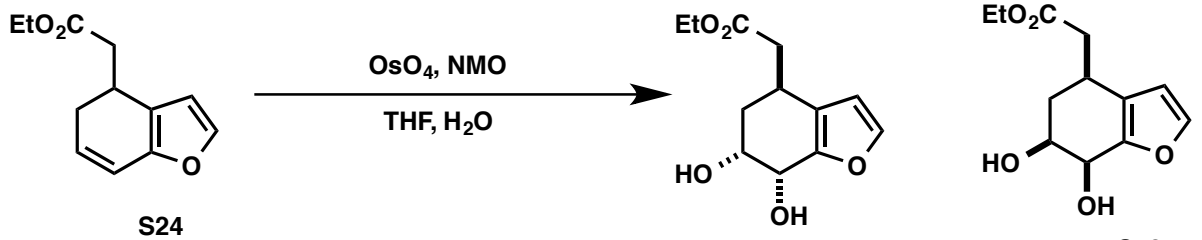
Trichloroacetyl chloride (974 μL, 8.7 mmol) was added dropwise to a solution of dihydrobenzofuran **S24** (1.0 g, 4.85 mmol) and imidazole (660 mg, 9.7 mmol) in dichloromethane (10 mL) at 0 °C. The reaction was allowed to stir at 23 °C for 3 hours. 200 μL more acid chloride was added and the solution was stirred an additional hour. At this time, the solution was washed with saturated $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude ketone was then dissolved in dry MeOH (40 mL) and NaOMe (0.5 M in MeOH, 5 mL, 2.5 mmol) was added over 1 minute. After 5 hours, 5 mL of saturated NH_4Cl was added and the organics were removed. The residue was diluted with water (10 mL), extracted into EtOAc (3 x 20 mL), then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (15 to 33% EtOAc: hexanes) to yield diester **S37** (1.0 g, 4.0 mmol, 82% over 2 steps). **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.43 (d, *J* = 10 Hz, 1H), 5.98 (dt, *J* = 10, 4.4 Hz, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.35 (p, *J* = 7.6 Hz, 1H), 2.61 (m, 1H), 2.56 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.43 (dd, *J* = 16, 7.6 Hz, 1H), 2.25 (dddd, *J* = 14, 7.6, 4.8, 2.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.2, 159.3, 154.0, 142.1, 129.6, 121.4, 117.9, 117.5, 51.7, 51.6, 38.5, 29.4, 28.4. **IR** (thin film) ν_{max} 3003, 2949, 2847, 1736, 1711, 1503, 1433, 1327, 1298, 1192 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{15}O_5$ $(M+H)^+$ *m/z* 251.0914, found 251.0924.



S37 **S38**

DDQ (54 mg, 0.24 mmol) was added to a solution of dihydrobenzofuran **S37** (50 mg, 0.2 mmol) in dichloromethane (2 mL). Over 3 hours, the solution turned from dark green to orange with a precipitate. The suspension was loaded onto a basic alumina column and purified with 15% EtOAc in hexanes to 100% EtOAc. Benzofuran **S38** was isolated as an off-white solid (34 mg, 0.14 mmol, 70%), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 3.98 (s, 3H), 3.87 (s, 2H), 3.70 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1, 159.9, 155.7, 145.3, 128.8, 127.8, 127.0, 124.7, 112.7, 111.5, 52.4, 52.3, 38.8. **IR** (thin film) ν_{max} 2999, 2950, 2831, 1736, 1556, 1434, 1291, 1197, 1176 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{12}O_5Na$ $(M+Na)^+$ *m/z* 271.0577, found 271.0579.

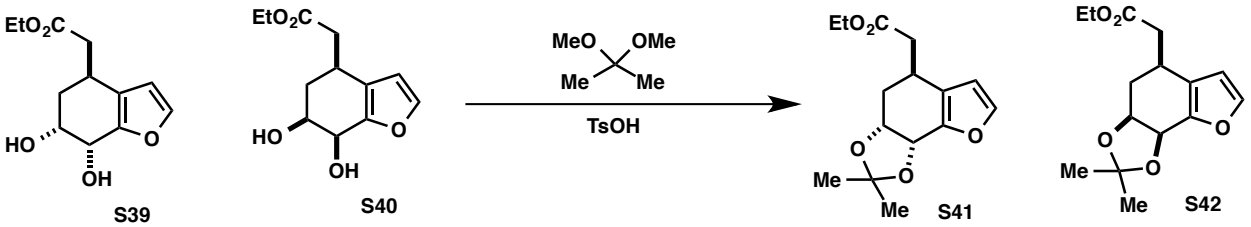


S24 **S39** **S40**

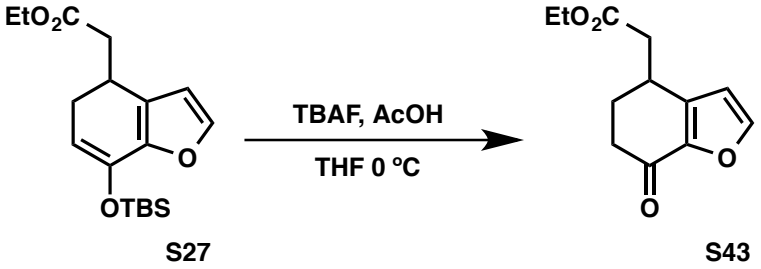
N-Methylmorpholine-*N*-oxide (50 wt % in H_2O, 199 μL, 0.96 mmol), was added to a solution of dihydrobenzofuran **S24** (100 mg, 0.48 mmol) in THF (1.1 mL). Then OsO_4 (2.5 wt % in t-BuOH, 48 μL, 0.0048 mmol) was added and the solution was left to stir for 2.5 hours. $NaHSO_3$ (55 mg) was added and stirred to 10 minutes, then diluted with water (2 mL), and extracted with dichloromethane (3 x 10 mL). The organics were dried over $MgSO_4$, filtered, concentrated, and purified via silica gel plug (50% EtOAc: hexanes) to yield the diols (**S39 and S40**) as a 9:1 mixture of diastereomers (88 mg, 0.37 mol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) major resonance only δ 7.33 (d, *J* = 1.6 Hz, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 4.70 (bs, 1H), 3.31 (m, 1H), 3.06 (bm, 1H), 2.90 (bs, 1H), 2.52 (dd, *J* =

15.2, 6.8 Hz, 1H), 2.40 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.18 (m, 1H), 1.64 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *denotes minor diastereomer δ 172.3*, 172.2, 149.3*, 148.8, 143.7*, 143.4, 123.4*, 122.6*, 109.2, 108.5*, 69.6*, 67.3, 64.4, 63.7*, 60.6, 40.0, 39.7*, 32.9*, 32.8, 28.5*, 27.2, 14.2. **IR** (thin film) ν_{max} 3408, 2987, 2929, 1724, 1704, 1377, 1291, 1254, 1176, 1046 cm^{-1}. **HRMS (ESI)** calcd for $C_{12}H_{16}O_5Na$ $(M+Na)^+$ *m/z* 263.0890, found 263.0895.

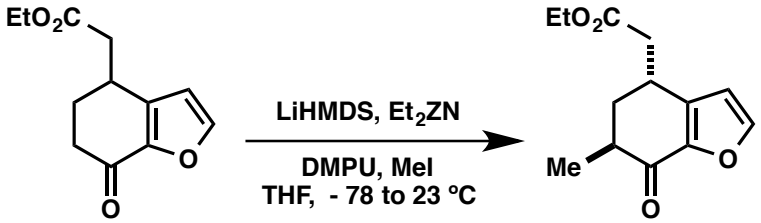


p-Toluenesulfonic acid monohydrate (1 mg) was added to a solution of diol **S39 and S40** (50 mg, 0.21 mmol) in 2,2-dimethoxypropane (440 μL). After 2 hours, the solution was concentrated and purified through a silica plug with 15% EtOAc: hexanes to yield a mixture of diastereomeric acetonides **S41 and S42** (40 mg, 0.14 mmol, 68%). Major diastereomer elucidated from 1D selective nOe experiments. (See accompanying spectra.) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.0 Hz, 0.25H), 7.35 (d, *J* = 2.0 Hz, 0.75H), 6.24 (d, *J* = 2.0 Hz, 0.25H), 6.23 (d, *J* = 2.0 Hz, 0.75H), 5.07 (d, *J* = 5.6 Hz, 0.75H), 5.03 (d, *J* = 6.0 Hz, 0.25H), 4.60 (m, 0.75H), 4.51 (ddd, *J* = 7.6, 6.0, 4.0 Hz, 0.25H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.29 (m, 0.75H), 3.14 (m, 0.25H), 2.63 (m, 1.4H), 2.36 (m, 1.6H), 2.08 (ddd, *J* = 13.7, 5.1, 4.1 Hz, 0.25H), 1.85 (m, 0.25H), 1.61 (ddd, *J* = 14.1, 10, 2.5 Hz, 0.75H), 1.41 (s, 0.75H), 1.40 (s, 2.3H), 1.39 (s, 0.75H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 2.3H). **^{13}C NMR** (101 MHz, $CDCl_3$) * denotes minor diastereomer δ 172.5*, 172.0, 147.8, 143.6*, 143.1, 123.8*, 122.7, 110.2*, 109.5, 108.9*, 108.3, 75.2*, 74.0, 69.4, 68.8*, 60.5, 60.4*, 40.0*, 39.3, 33.1, 32.9*, 28.2*, 27.9*, 27.6, 26.4, 26.2*, 26.1, 14.2. **IR** (thin film) n_{max} 2974, 2934, 1736, 1377, 1238, 1213, 1074, 1025 cm^{-1}. **HRMS (EI)** calcd for $C_{15}H_{20}O_5$ $(M)^+$ *m/z* 280.1311, found 280.1310.



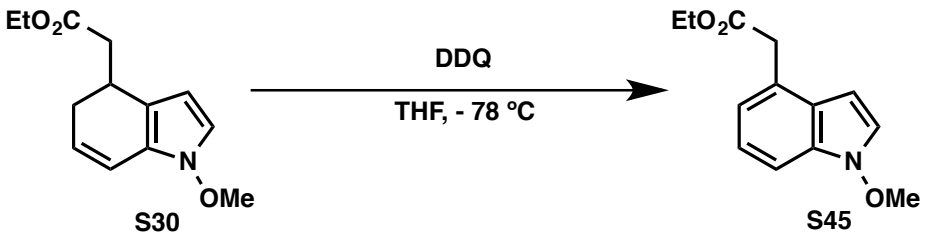
Crude dihydrobenzofuran **S27** (1.34 mmol) from the heterocycloisomerization was dissolved in THF (7 mL) and cooled to 0 °C. AcOH (383 μL, 6.7 mmol) was added followed by TBAF (1 M in THF, 2 mL, 2.0 mmol). After 2.5 hours, the reaction was quenched by the addition of saturated $NaHCO_3$ (2 mL) and then extracted with EtOAc.

The organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (10 to 25% EtOAc: hexanes) to yield ketone **S43** (170 mg, 0.76 mmol, 57% from bicycle **S7**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 4.0 Hz, 1H), 6.41 (d, *J* = 4.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.41 (m, 1H), 2.71 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.55 (m, 3H), 2.29 (m, 1H), 1.91 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 185.5, 171.5, 147.5, 147.0, 141.8, 110.5, 60.8, 38.7, 36.7, 30.7, 30.4, 14.2. **IR** (thin film) ν_{max} 3105, 2978, 2934, 1924, 1724, 1663, 1422, 1299, 1187 cm^{-1}. **HRMS (ESI)** calcd for $C_{12}H_{14}O_4Na$ $(M+Na)^+$ *m/z* 245.0784, found 245.0786.



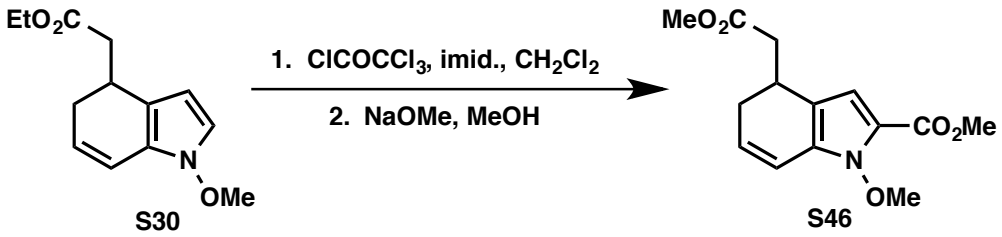
S43 **S44**

Adapted from the literature[58]: LiHMDS (1 M in hexanes, 260 μL, 0.26 mmol) was added dropwise to a solution of ketone **S43** (30 mg, 0.13 mmol) in THF (780 μL) at –78 °C. After 10 minutes, neat $ZnEt_2$ (27 μL, 0.26 mmol) was added and the solution was stirred an additional 5 minutes. Then DMPU (157 μL, 1.3 mmol) and iodomethane (32 μL, 0.52 mmol) was added. The solution was allowed to warm to 23 °C over 5 hours and kept at that temperature for 7 hours. Saturated $NaHCO_3$ was then added and the biphasic mixture was extracted into diethyl ether. The organics were dried over $MgSO_4$, filtered, and concentrated to yield a residue that was purified by silica gel chromatography (15% EtOAc: hexanes) to afford adduct **S44** (24 mg, 0.10 mmol, 78%) as a 7:3 mixture of diastereomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55 (s, 0.7H), 7.54 (s, 0.3H), 6.40 (s, 0.7H), 6.38 (s, 0.3H), 4.17 (m, 2H), 3.47 (m, 1H), 2.68 (m, 2H), 2.57 (dd, *J* = 16.2, 7.8 Hz, 0.7H), 2.45 (dd, *J* = 16.2, 7.8 Hz, 0.3H), 2.1–1.8 (m, 2H), 1.29 (m, 3H), 1.23 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) *denotes minor diastereomer δ 191.1*, 188.6, 171.7, 147.9*, 147.7, 146.5, 146.0*, 140.9, 139.9*, 110.8, 109.9*, 60.8*, 60.7, 45.2*, 43.1*, 39.1, 39.0*, 38.6, 37.5, 28.3, 28.0*, 24.6*, 24.0*, 15.2, 14.2. **IR** (thin film) ν_{max} 3113, 2974, 2934, 1732, 1679, 1418, 1373, 1287, 1185 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{16}O_4Na$ $(M+Na)^+$ *m/z* 259.0941, found 259.0943.

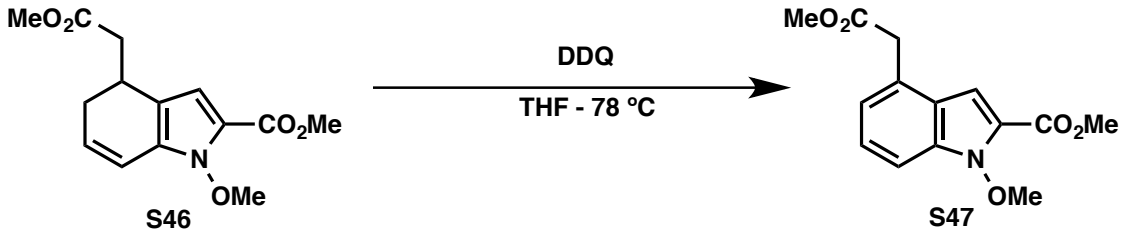


S30 **S45**

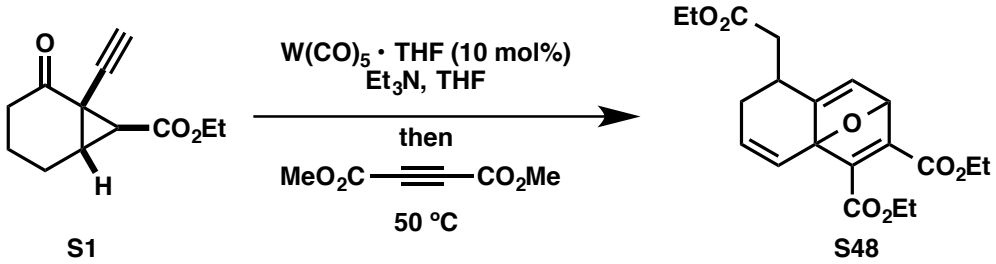
To a flame dried vial under an atmosphere of nitrogen was added 2,3-dichloro-4,5-dicyano-1,6-benzoquinone (DDQ) (19.5 mg, 0.07 mmol) in 200 μL of tetrahydrofuran and cooled to –78 °C. *N*-methoxydihydroindole **S30** (15 mg, 0.064 mmol) in THF (400 μL) was then added dropwise to the solution over one minute. After five minutes the solution was concentrated and then purified by column chromatography using basic alumina (33% EtOAc: hexanes to 100% EtOAc) to afford *N*-methoxyindole **S45** as an orange oil (11 mg, 76%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.6 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.21 (t, *J* = 9 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 3.6 Hz, 1H), 4.15 (q, *J* = 8.5 Hz, 2H), 4.09 (s, 3H), 3.87 (s, 2H), 1.25 (t, *J* = 8.5 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.5, 131.7, 126.6, 123.7, 122.8, 122.4, 120.8, 107.4, 96.4, 65.9, 60.8, 39.0, 14.2. **IR** (thin film) ν_{max} = 3129, 3055, 2981, 2938, 1732 cm^{-1}. **HRMS (ESI)** calcd for $C_{13}H_{16}NO_3$ $(M+H)^+$: *m/z* 234.1125, found 234.1130.



The general procedure for the heterocycloisomerization was followed using oxime **S15** (200 mg, 0.85 mmol). After completion of the heterocycloisomerization, trichloroacetyl chloride (145 μL, 1.27 mmol) was added directly to the solution. After stirring for 2.5 h, the solution was quenched with 12 mL saturated $NaHCO_3$, and the aqueous layer was separated and extracted with dichloromethane (3 x 10 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated to afford the crude acylated product as a brown oil. This product was then dissolved in a solution of NaOMe in MeOH (1.7 mL, 0.5M) and allowed to stir for 12 hours. Excess NaOMe was then quenched 4 mL saturated NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 x 4 mL). The combined organic layers were then dried over Na_2SO_4, concentrated and purified by silica gel chromatography (33% EtOAc: hexanes) to afford the desired pyrrole **S46** as an orange oil (165 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.47 (d, *J* = 10.4 Hz, 1H), 5.97 (dt, 9.6, 4.4 Hz, 1H), 4.06 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 3.28 (ap, *J* = 8.4 Hz, 1H), 2.60 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.42 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.19 (dddd, *J* = 17.2, 8.4, 4.4, 2.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.7, 159.5, 129.8, 128.2, 116.5, 115.9, 114.9, 110.6, 67.1, 51.6, 51.1, 38.9, 30.4, 29.0. **IR** (thin film) ν_{max} = 3446, 2950, 1736, 1708 cm^{-1}. **HRMS (ESI)** calcd for $C_{14}H_{18}NO_5$ $(M+H)^+$: *m/z* 280.1179, found 280.1177.

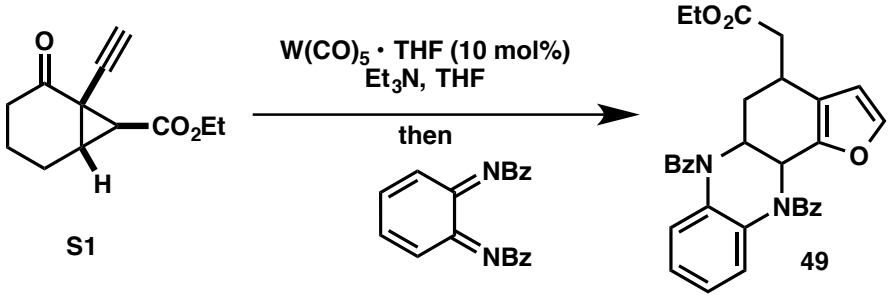


To a flame dried vial under an atmosphere of nitrogen was added DDQ (22 mg, 0.08 mmol) in 200 μL of tetrahydrofuran and cooled to –78 °C. *N*-methoxydihydroindole **S46** (20 mg, 0.07 mmol) in THF (400 μL) was then added dropwise to the solution over one minute. After five minutes the solution was concentrated and then purified by column chromatography using basic alumina (33% EtOAc: hexanes to 100% EtOAc) to afford *N*-methoxyindole **S47** as an orange oil (14 mg, 0.05 mmol, 71%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 1H), 7.34 (at, *J* = 7.4 Hz, 1H), 7.18 (s, 1H), 7.07 (d, *J* = 7.0 Hz, 1H), 4.20 (s, 3H), 3.95 (s, 3H), 3.88 (s, 2H), 3.69 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.5, 160.3, 135.2, 128.1, 126.0, 124.9, 122.2, 121.4, 108.6, 105.4, 66.1, 52.1, 51.8, 38.4. **IR** (thin film) ν_{max} = 2993, 2951, 1724 cm^{-1}. **HRMS (ESI)** calcd for $C_{14}H_{16}NO_5$ $(M+H)^+$: *m/z* 278.1023, found 278.1024.



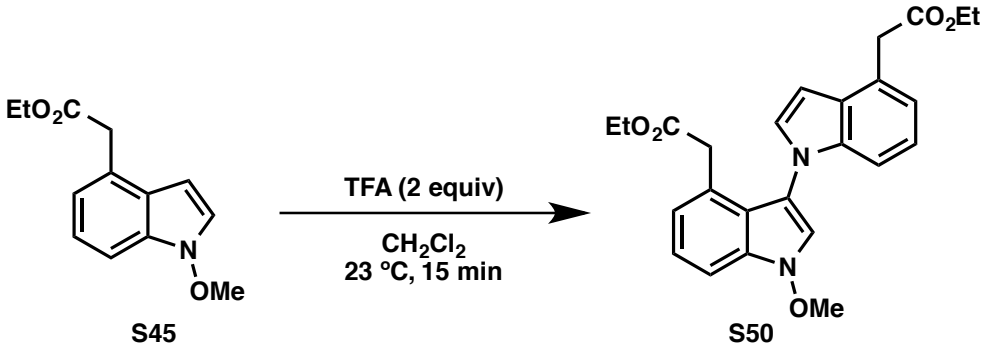
The $W(CO)_5$•THF catalyzed heterocycloisomerization general procedure was followed using cyclization substrate **S1** (50 mg, 0.24 mmol). Upon completion of the cyclization, dimethyl acetylenedicarboxylate (59 μL, 0.48 mmol) was added and the solution was heated to 50 °C for 12 hours. The solution was then concentrated and the residue purified by silica gel chromatography (33% EtOAc: hexanes) to yield cycloadduct **S48** (63 mg, 0.18 mmol, 75%) as a 1.2:1 mixture of diastereomers. **^{1}H NMR** (400 MHz, $CDCl_3$) *denotes minor diastereomer δ 6.73* (s, 1H), 6.60 (s, 1.2H), 6.29 (ddd, *J* = 10, 6.0, 1.6 Hz, 1.2H), 6.22* (ddd, *J* = 10.4, 5.2, 3.2 Hz, 1H), 6.05* (d, *J* = 10 Hz, 1H), 6.00, d, *J* = 10.4 Hz, 1.2H), 5.59 (d, *J* = 2 Hz, 1.2H), 5.51* (d, *J* = 2 Hz, 1H), 4.10 (m, 2.4H), 4.05* (m, 2H), 3.80 (s, 6.6H, mix of diast.), 3.76* (s, 3H), 3.75 (s, 3.6H), 3.39* (m, 1H), 3.04 (m, 1.2H), 2.64 (dd, *J* = 15.6, 5.2 Hz, 1.2H), 2.55* (m, 1H), 2.50* (m, 1H), 2.44 (d, *J* = 7.6 Hz, 2H), 2.37 (dd, *J* = 15.6, 8.8 Hz, 1.2H), 2.24* (m, 1H), 1.99 (dddd, *J* = 16, 11.2, 2.4, 2.4, 1.2H), 1.22 (t, *J* = 7.2 Hz, 3.6H), 1.17* (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) mixture of diastereomers δ 171.7, 171.5, 164.6, 164.0, 162.9, 162.7, 158.5, 156.6, 154.5, 154.0, 152.0, 150.7, 137.2, 135.2, 133.9, 131.2, 121.2, 120.5, 91.8, 89.9, 83.0, 82.7, 60.5, 60.3, 52.22, 52.19, 52.16, 52.12, 37.6, 37.2, 33.0, 31.2, 31.1, 28.8,

14.1, 14.0. **IR** (thin film) ν_{max} 2987, 2950, 2840, 1728, 1646, 1430, 1324, 1266, 1197 cm^{-1}. **HRMS (ESI)** calcd for $C_{18}H_{21}O_7$ $(M+H)^+$ *m/z* 349.1293, found 349.1306.



The $W(CO)_5$•THF catalyzed heterocycloisomerization general procedure was followed using cyclization substrate **S1** (50 mg, 0.24 mmol). Upon completion of the cyclization, *o*-quinonedibenzimide (58) (91 mg, 0.29 mmol) was added and the solution was stirred for 4 hours. The solution was then concentrated and the residue purified by silica gel chromatography (33% EtOAc: hexanes) to yield cycloadduct **S49** (124 mg, 0.24 mmol, 99%) as a 85:15 mixture of diastereomers. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.75 (m, 2H), 7.59 (d, *J* = 6.8 Hz, 2H), 7.04–6.90 (m, 7H), 6.74 (m, 1H), 6.37 (m, 3H), 6.21 (m, 1H), 5.63 (d, *J* = 10 Hz, 1H), 5.39 (dt, *J* = 9.2, 4 Hz, 0.15H), 5.29 (dt, *J* = 8.8, 4.0 Hz, 0.85H), 4.05 (m, 2H), 3.41 (m, 0.15H), 3.00 (m, 1.7H), 2.78 (dd, *J* = 14.8, 3.2 Hz, 0.15H), 2.49 (dd, *J* = 15.6, 10.4 Hz, 0.85H), 2.31 (m, 0.3H), 2.15 (m, 1.85H), 1.03 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) major resonances only δ 172.3, 170.0, 153.8, 134.3, 133.8, 131.4, 130.8, 130.7, 128.8, 128.3, 128.1, 126.7, 126.5, 126.0, 116.8, 105.0, 89.9, 62.8, 60.3, 36.7, 29.1, 27.4, 14.1. **IR** (thin film) n_{max} 3056, 2974, 2934, 2275, 1728, 1675, 1650, 1499, 1389, 1336, 1156 cm^{-1}. **HRMS (ESI)** calcd for $C_{32}H_{29}O_5N_2$ $(M+H)^+$ *m/z* 521.2071, found 521.2075.

Dimerization of *N*-alkoxyindole S45.



To a flame dried 4-mL vial was added ethyl 2-(1-methoxy-1H-indol-4-yl)acetate (**S45**) (50 mg, 0.22 mmol) in CH_2Cl_2 (2.2 mL). Trifluoroacetic acid (33 μL, 0.43 mmol) was then added all at once. The solution was stirred for 15 minutes at room temperature until TLC analysis indicated the reaction was complete. The solution was then diluted with CH_2Cl_2 (1 mL) and washed with deionized water (1 mL). The aqueous layer was then extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4,

concentrated and purified by silica gel chromatography (2:1 hexanes:ethyl acetate) to afford indole dimer (27 mg) **S50** as an oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.49 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.29 (apparent t, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 3.1 Hz, 1H), 7.10 (apparent t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 3.1 Hz, 1H), 4.25– 4.13 (m, 5H), 3.97 (d, *J* = 14.7 Hz, 1H), 3.92, (d, *J* = 14.5 Hz, 1H), 3.85 – 3.73 (m, 1H), 3.60 – 3.51 (m, 1H), 3.24 (d, *J* = 16.7 Hz, 1H), 3.17 (d, *J* = 16.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$) 171.6, 171.2, 139.5, 131.6, 131.0, 127.8, 126.2, 126.1, 123.4, 123.0, 122.3, 121.1, 120.9, 120.3, 111.7, 110.0, 107.8, 100.9, 66.3, 60.7, 60.3, 39.3, 36.8, 14.2, 13.9 ppm. **IR (ATIR)** 3127, 3051, 2979, 2936, 2904, 1730, 1173, 751 cm^{-1}. **HRMS (ESI)** calcd for $C_{25}H_{26}N_2O_5{}^{23}Na$ $(M+H)^+$ *m/z* 457.1734, found 457.1733.

Section 1.8 REFERENCES

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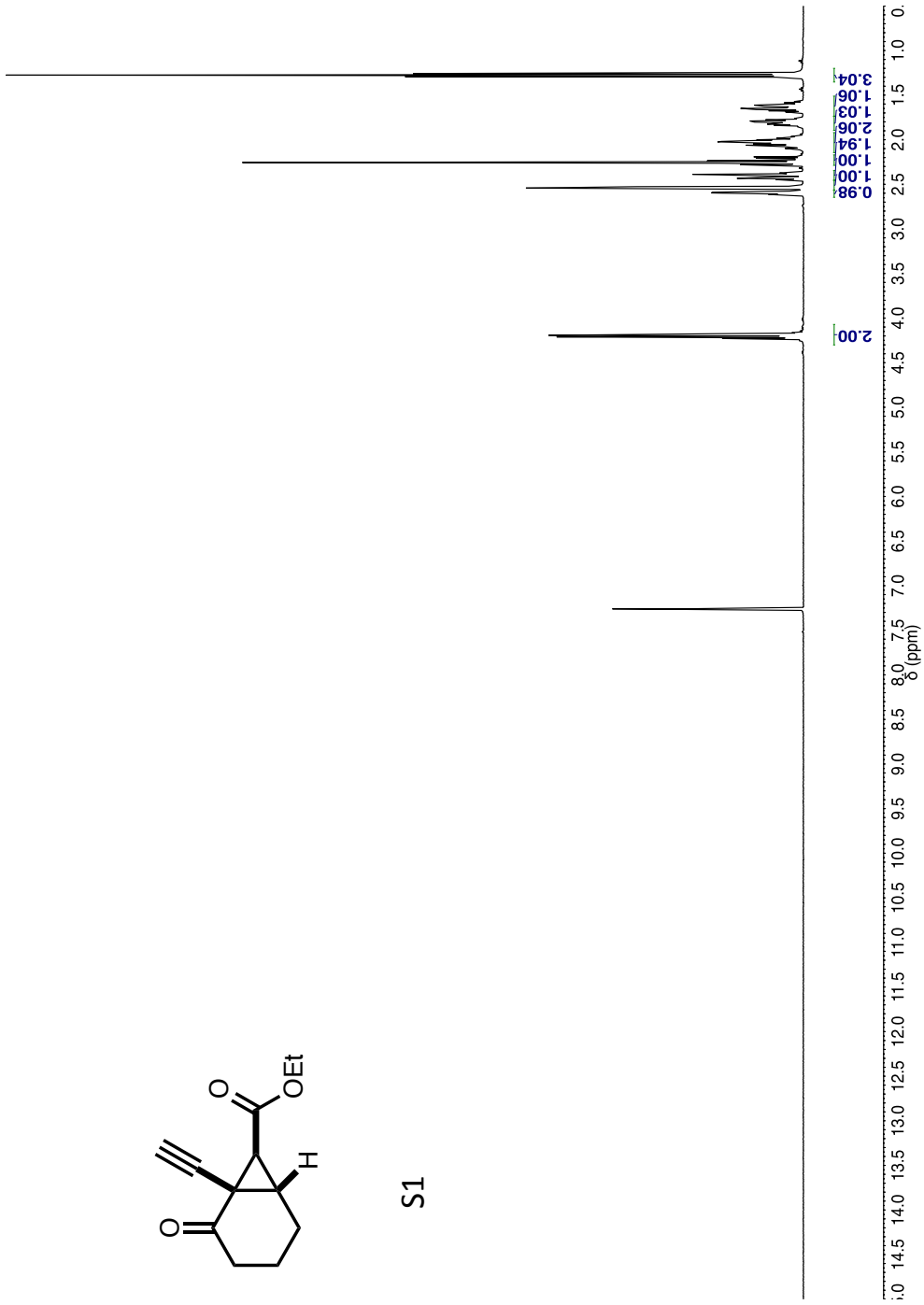
APPENDIX I. SELECTED SPECTRA



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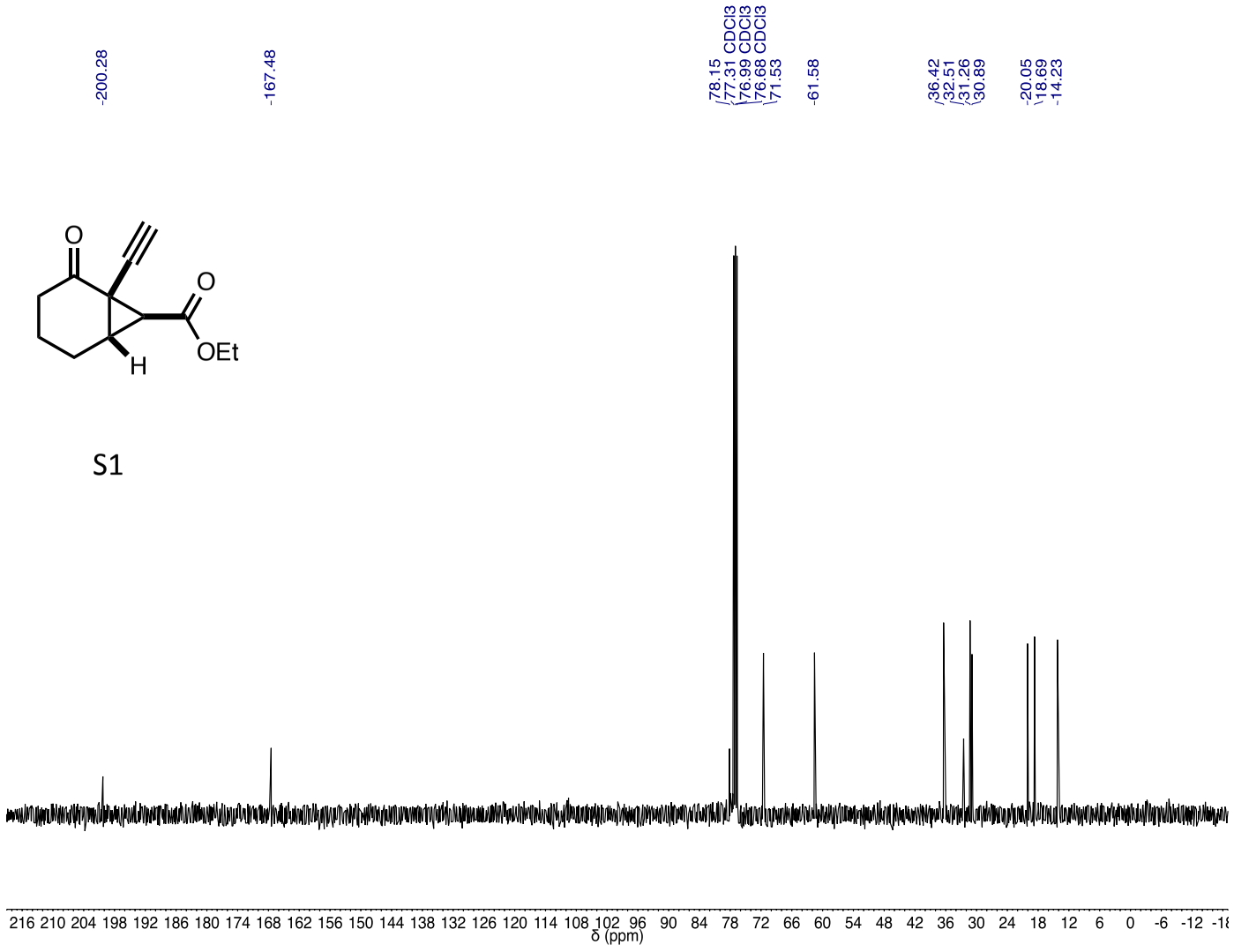
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78.15
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76.99 CDCl3
76.68 CDCl3
71.53
-61.58
36.42
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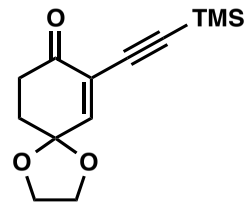
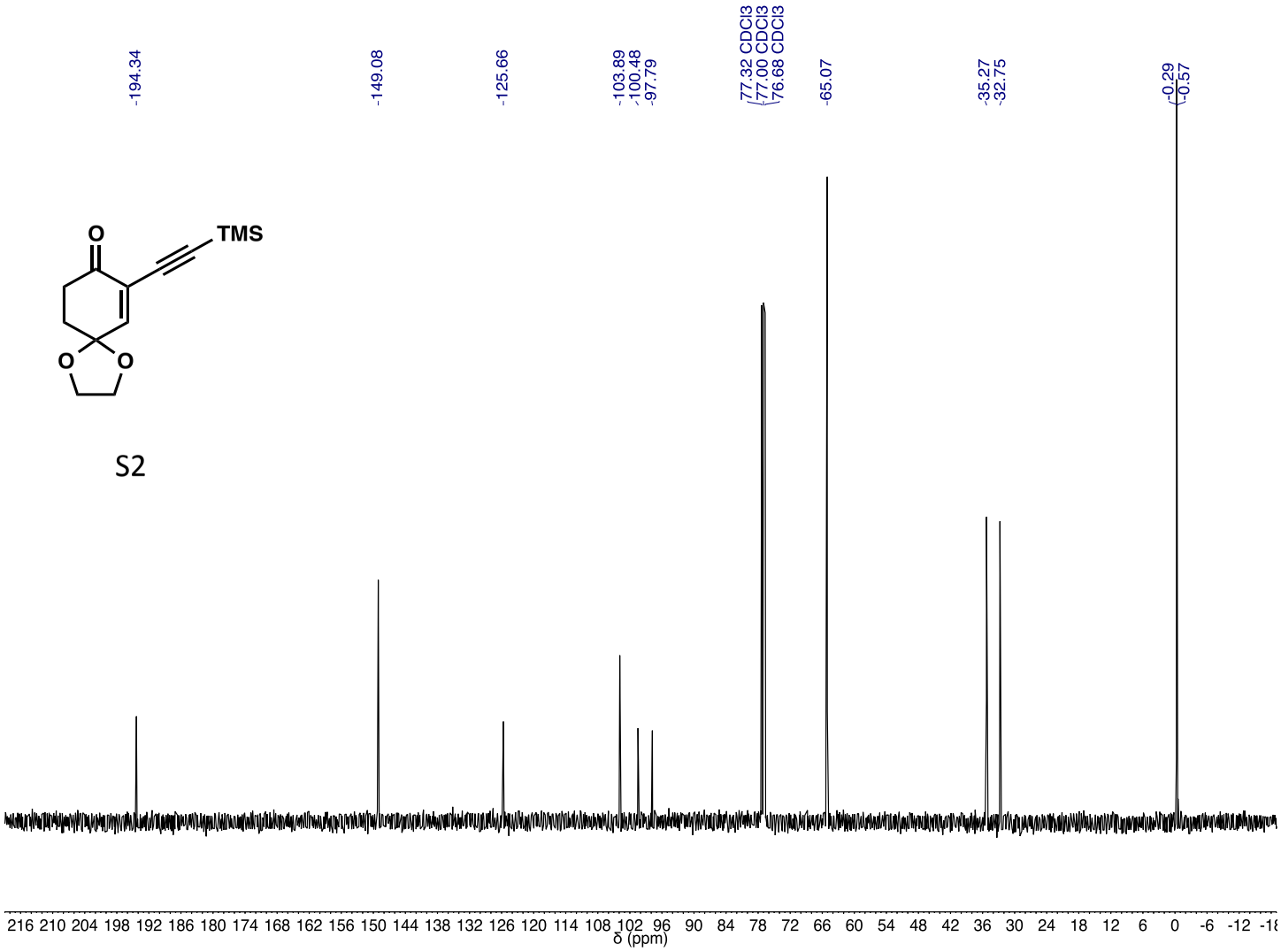
31.26
30.89
-20.05
18.69
-14.23
O
O
OEt
H
δ (ppm)

S1



S2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-100.48
-97.79
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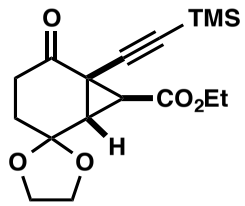
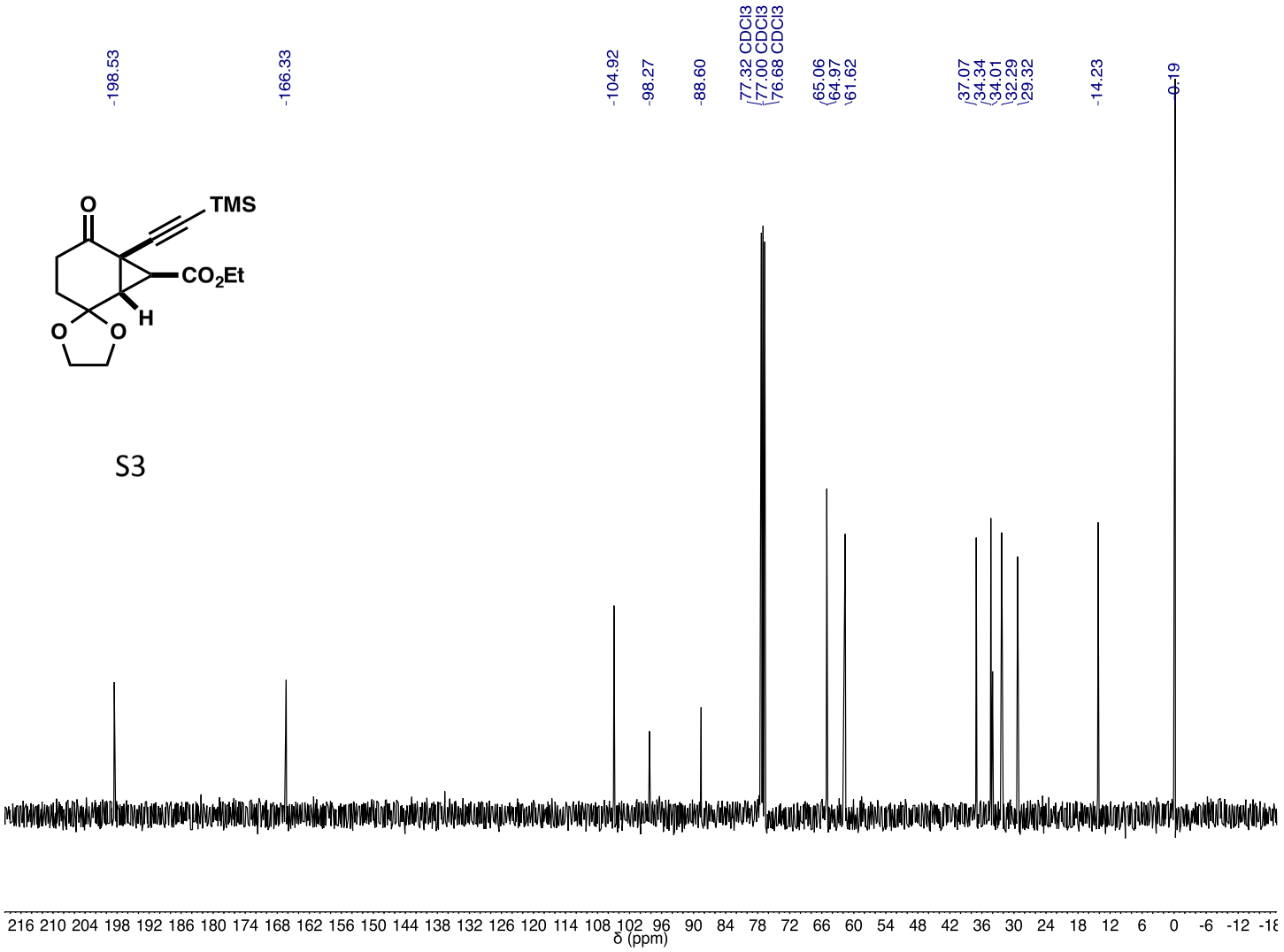
77.00 CDCl3
76.68 CDCl3
-65.07
-35.27
-32.75
-0.29
-0.57
O
TMS
O
O
S2
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)


O
TMS
CO2Et
H
O
O

S3

6.00
0.97
0.95
1.99
1.96
3.00
8.78
16.2 15.6 15.0 14.4 13.8 13.2 12.6 12.0 11.4 10.8 10.2 9.6 9.0 8.4 7.8 7.2 6.6 6.0 5.4 4.8 4.2 3.6 3.0 2.4 1.8 1.2 0.6 0.0 -0.6 -1.2 -1.8 -2.4 -3.0 -3.6 -4
δ (ppm)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76.68 CDCl3
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64.97
61.62
37.07
34.34
34.01
32.29
29.32
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0.19
O
TMS
CO2Et
H
O
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S3
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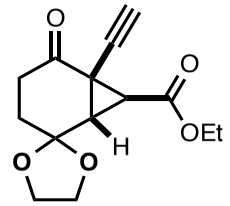
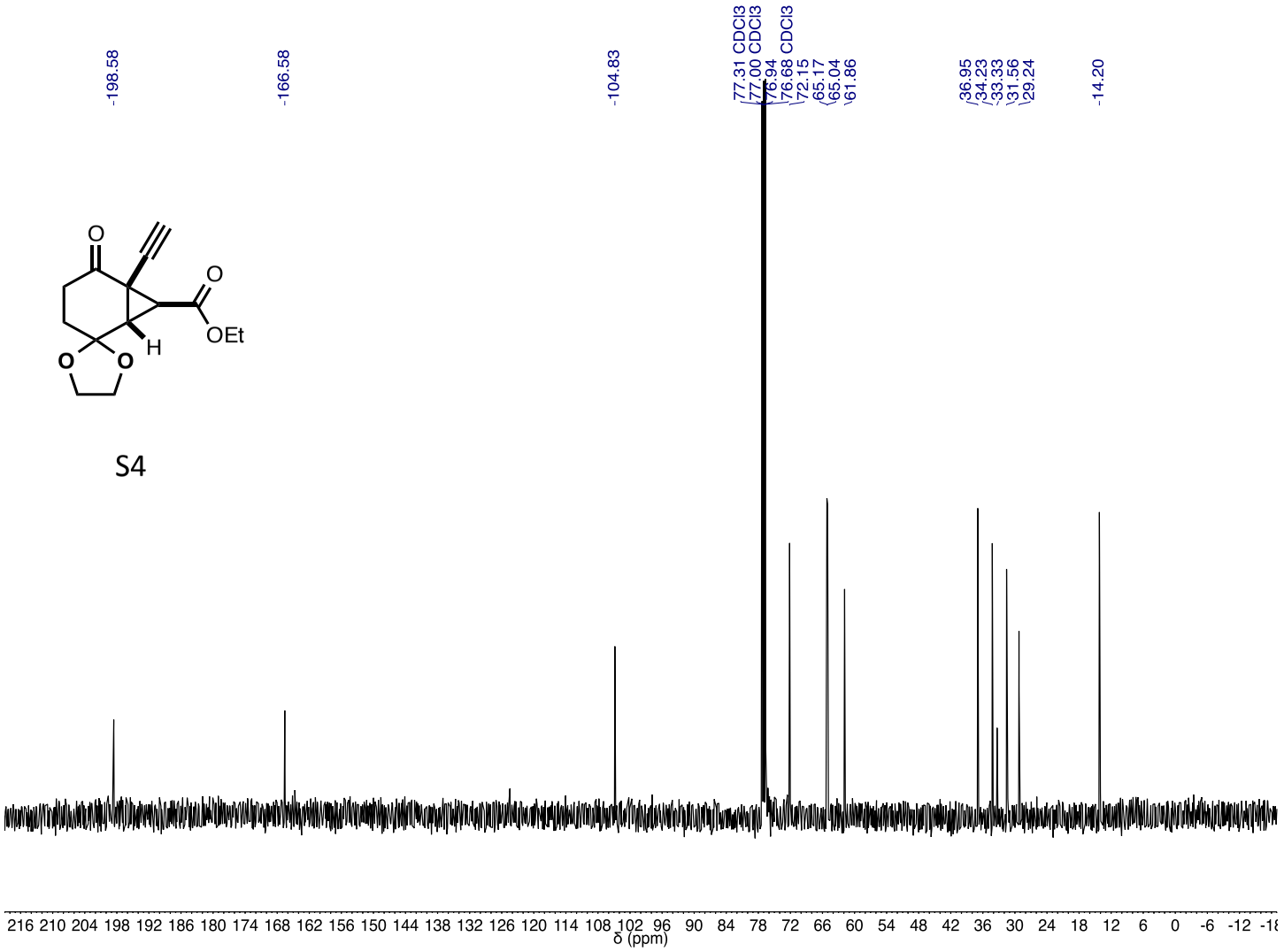
δ (ppm)


O
O
OEt
H
O
O

S4

2.29
4.39
1.06
1.14
1.85
1.00
2.16
3.39
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
δ (ppm)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76.68 CDCl3
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65.17
65.04
61.86
36.95
34.23
33.33
31.56
29.24
-14.20
O
O
OEt
H
O
O
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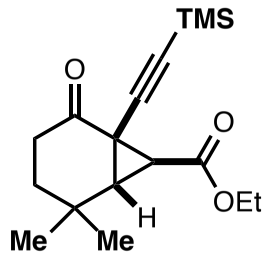
δ (ppm)

S4



S5

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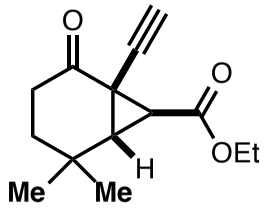
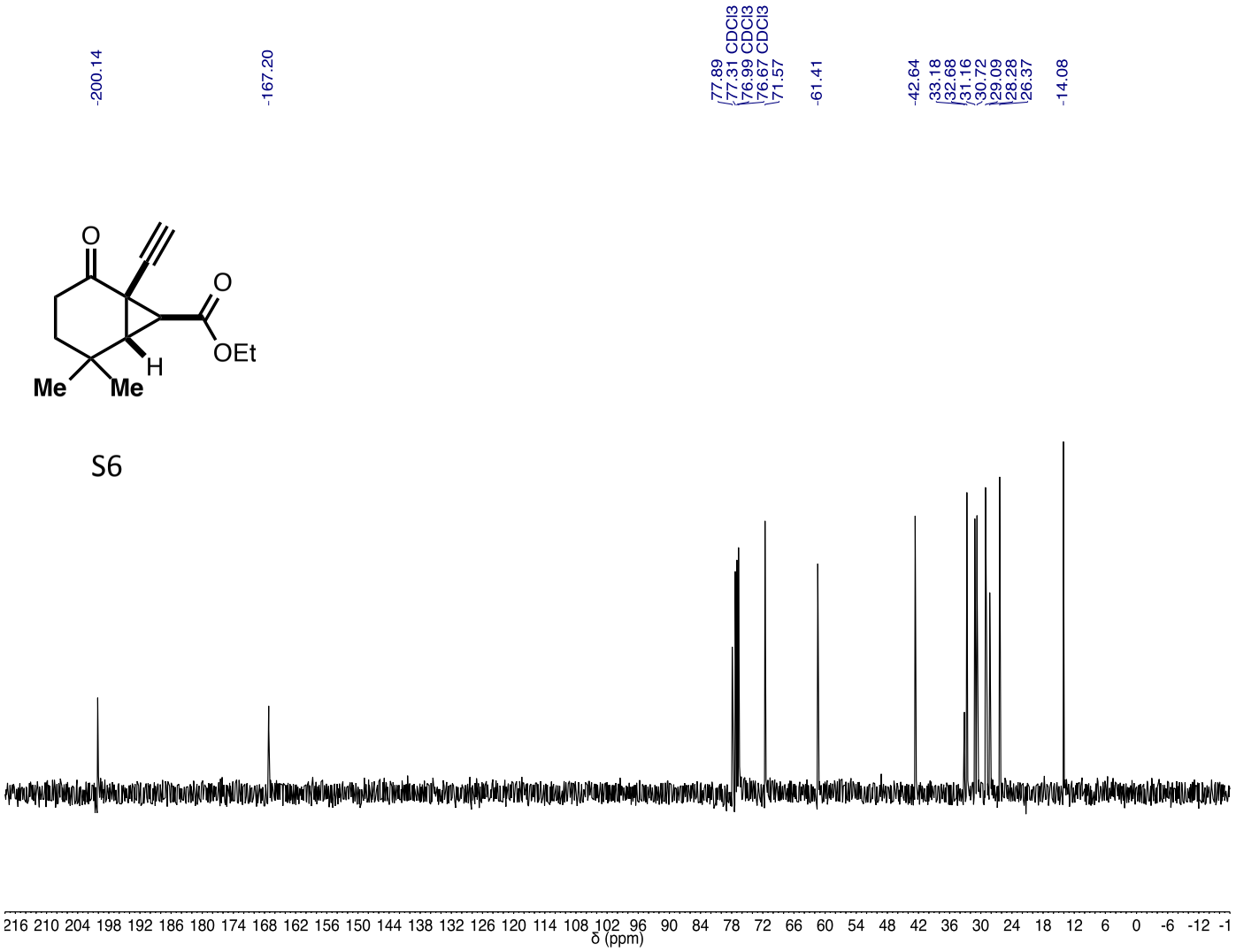
77.00 CDCl3
76.68 CDCl3
-61.35
-42.85
34.87
34.13
32.95
31.67
31.39
29.24
28.41
26.52
-14.24
-0.08
-0.11
δ (ppm)
TMS
O
OEt
H
Me
Me
O

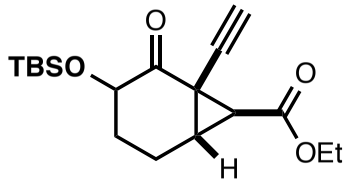
S5


O
O
OEt
H
Me
Me

S6

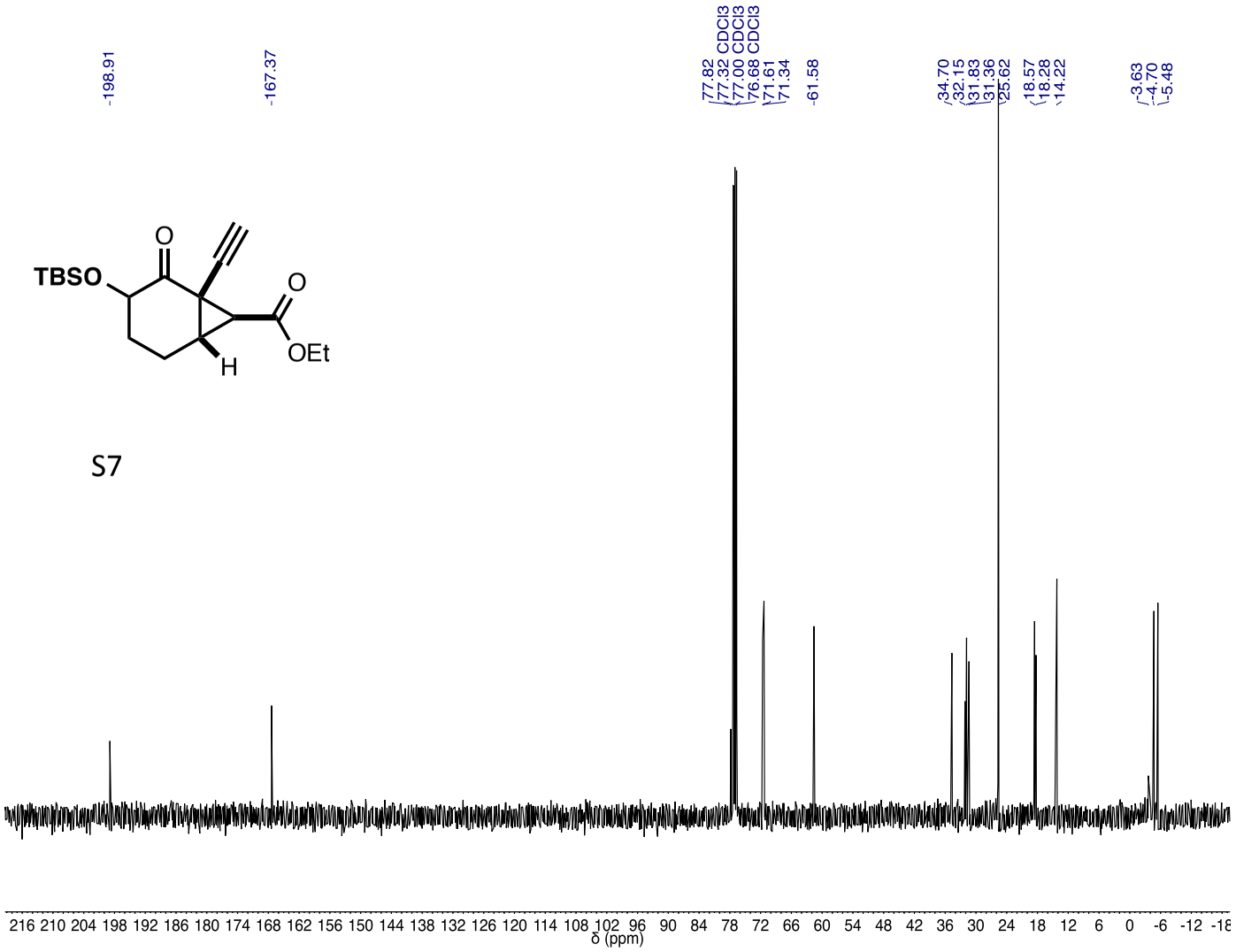
2.00
0.99
2.89
0.94
1.94
3.09
2.96
2.95
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)

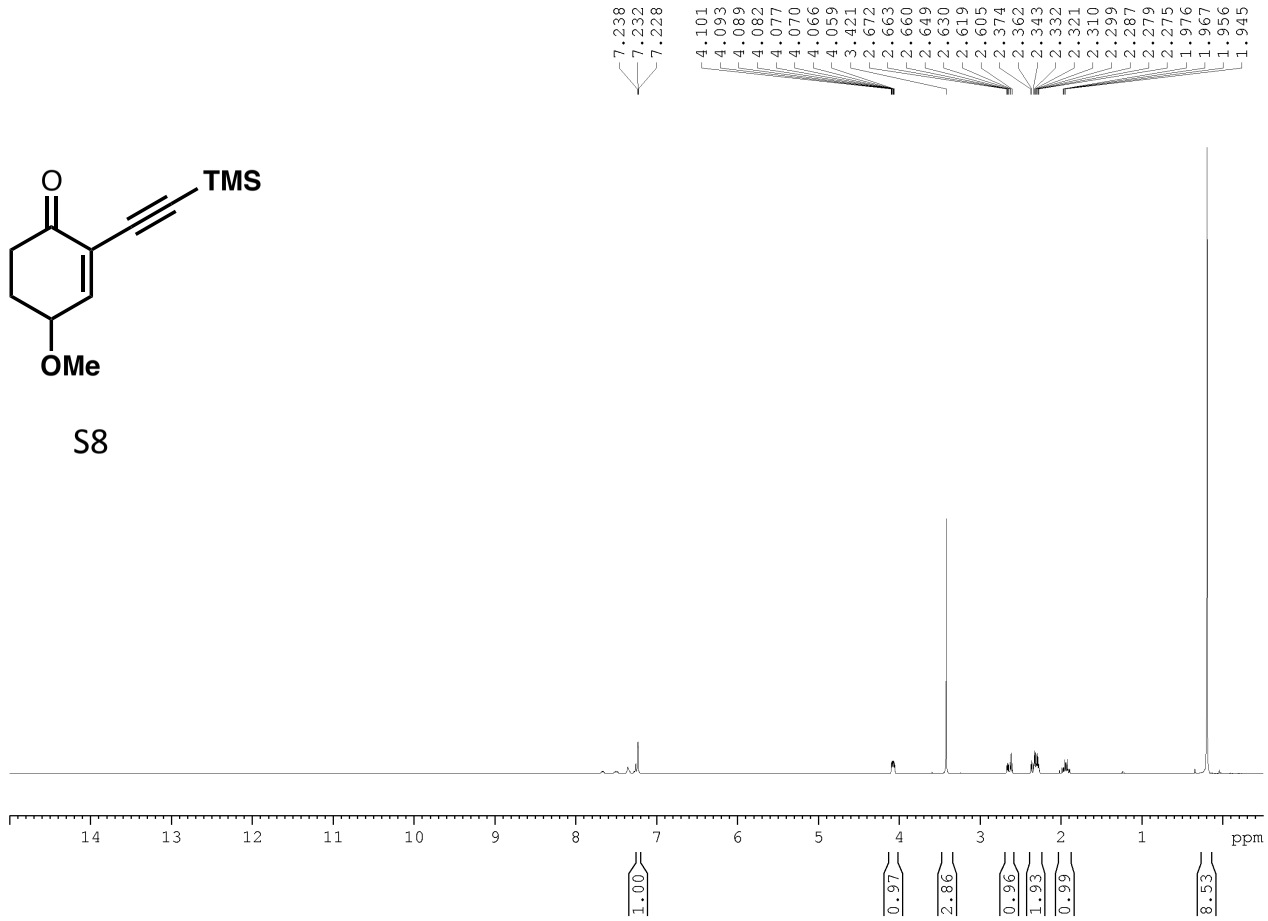

-200.14
-167.20
77.89
77.31 CDCl3
76.99 CDCl3
76.67 CDCl3
71.57
-61.41
-42.64
33.18
32.68
31.16
30.72
29.09
28.28
26.37
-14.08
O
O
OEt
H
Me
Me
S6
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -1
δ (ppm)


TBSO
O
O
OEt
H

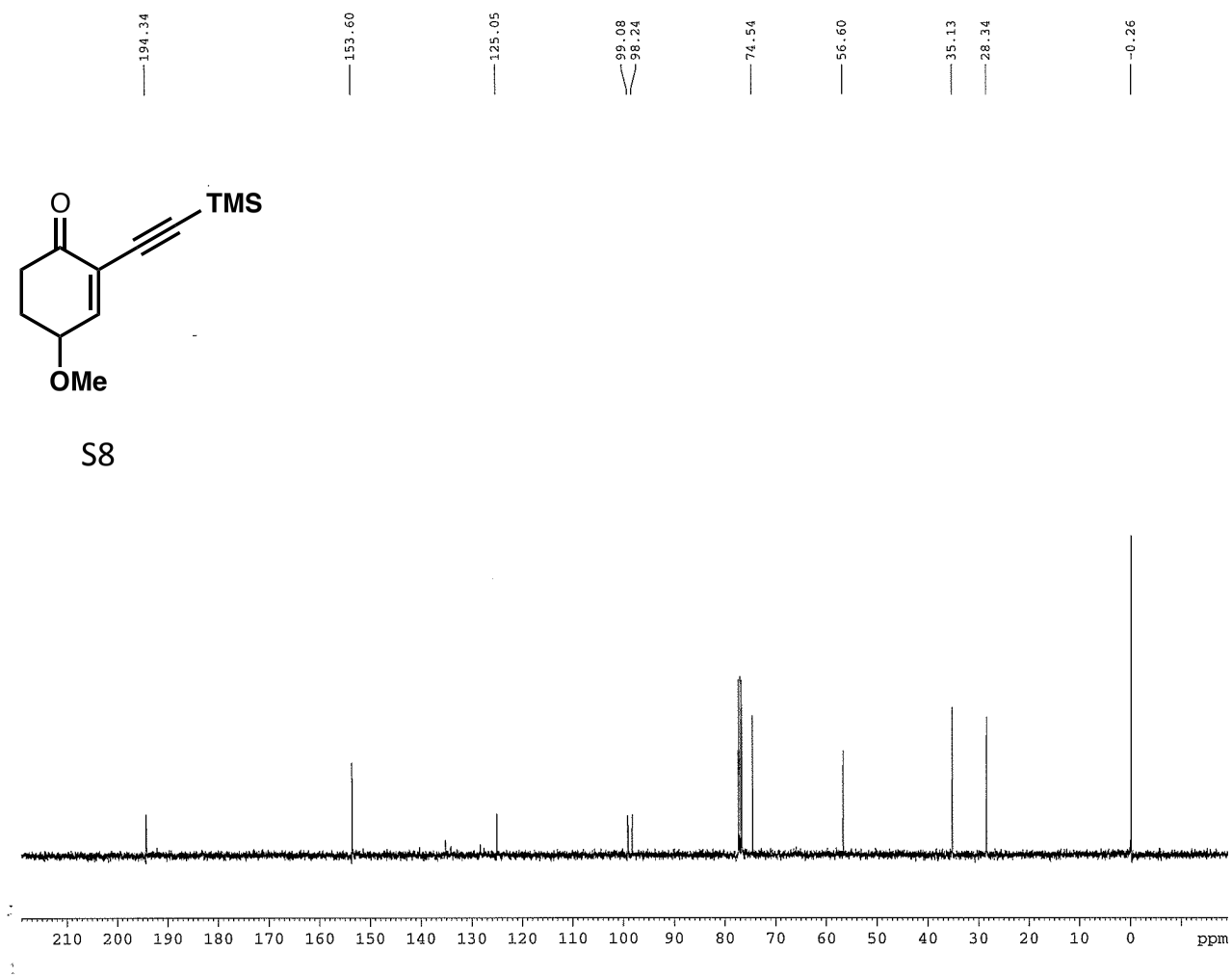
S7

2.00
0.91
0.91
1.02
1.81
2.84
3.01
9.53
3.23
2.85
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
δ (ppm)

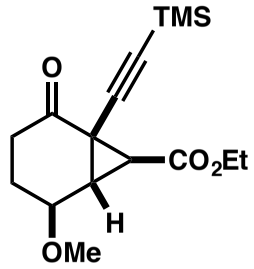

-198.91
-167.37
77.82 CDCl3
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
71.61
71.34
-61.58
34.70
32.15
31.83
31.36
25.62
18.57
18.28
14.22
-3.63
-4.70
-5.48
TBSO
O
O
OEt
H
S7
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


7.238
7.232
7.228
4.101
4.093
4.089
4.082
4.077
4.070
4.066
4.059
3.421
2.672
2.663
2.660
2.649
2.630
2.619
2.605
2.374
2.362
2.343
2.332
2.321
2.310
2.299
2.287
2.279
2.275
1.976
1.967
1.956
1.945
O
TMS
OMe
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.97
2.86
0.96
1.93
0.99
8.53

S8


194.34
153.60
125.05
99.08
98.24
74.54
56.60
35.13
28.34
-0.26
O
TMS
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

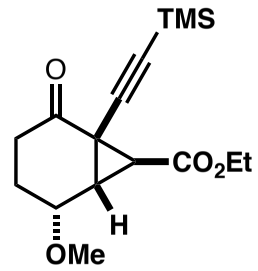
S8



S9

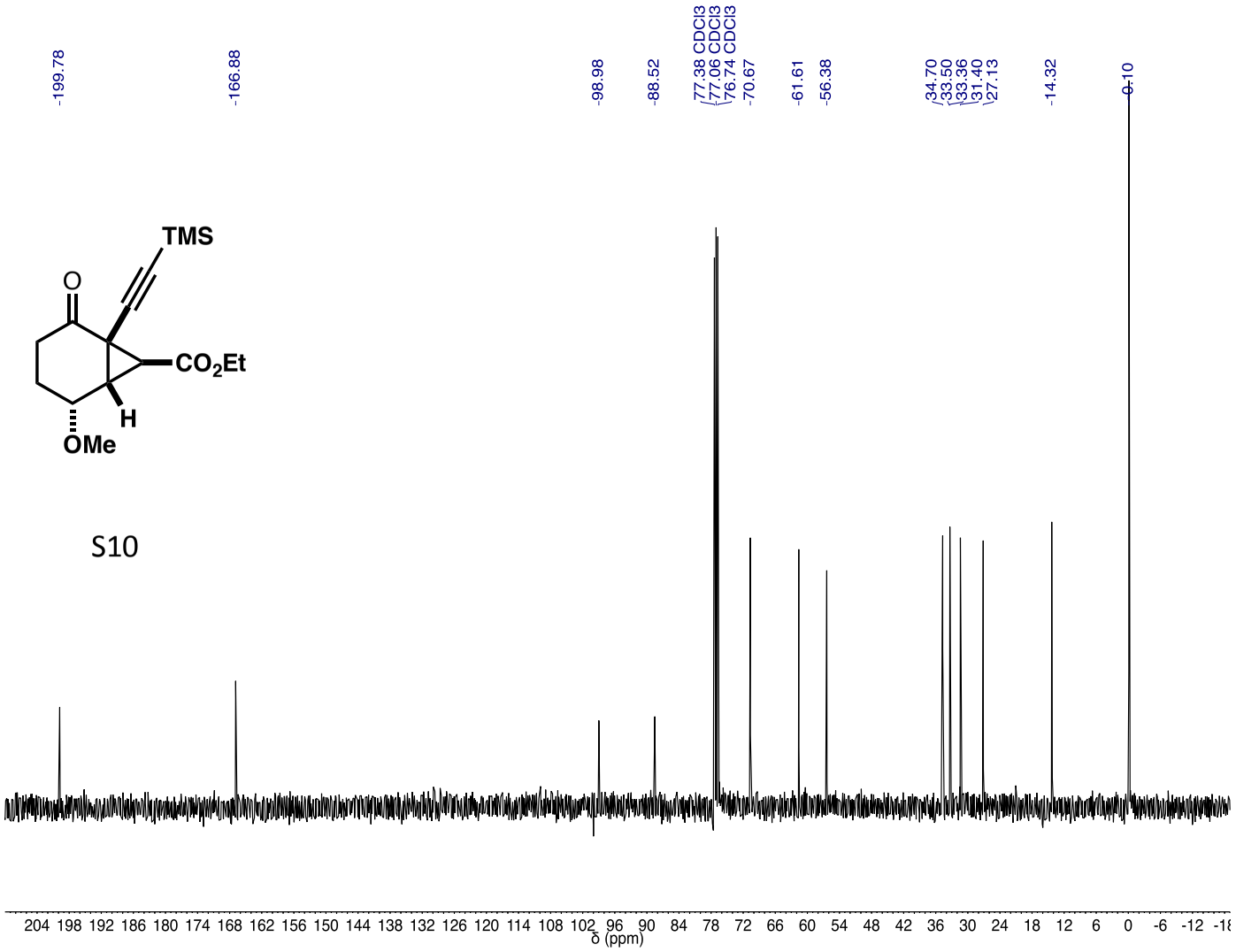
-199.30
-166.68
-99.01
-88.30
77.41 CDCl3
77.09 CDCl3
76.77 CDCl3
71.06
61.62
60.34
56.40
34.55
33.25
32.65
31.56
22.98
21.02
14.31
14.19
0.09
TMS
CO2Et
H
OMe
O
δ (ppm)

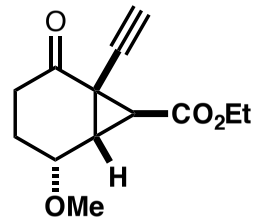
S9


TMS
O
CO2Et
H
OMe

S10

2.28
1.00
3.00
0.98
0.98
0.97
1.04
1.01
1.06
3.46
8.99
δ (ppm)

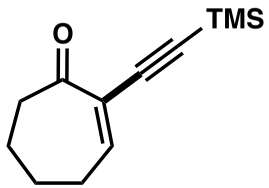

-199.78
-166.88
-98.98
-88.52
77.38 CDCl3
77.06 CDCl3
76.74 CDCl3
-70.67
-61.61
-56.38
34.70
33.50
33.36
31.40
27.13
-14.32
0.10
TMS
O
CO2Et
H
OMe
S10
204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)


O
CO2Et
H
OMe

S11

2.00
1.00
2.96
0.96
0.97
0.98
1.03
0.82
1.07
1.00
3.04
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
δ (ppm)

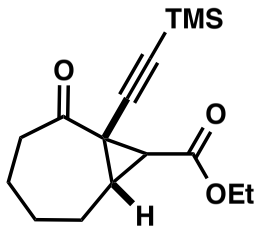
199.79
167.00
77.48 CDCl3
77.38
77.16 CDCl3
76.84 CDCl3
71.91
70.37
61.66
56.27
34.43
33.07
32.59
30.49
26.99
14.15
O
H
OMe
CO2Et
S11
δ (ppm)


O
TMS

S12

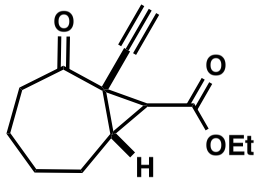
1.00
2.13
2.13
4.23
9.36
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)

-200.76
-151.94
-128.67
-101.67
-95.13
77.36 CDCl3
77.25
77.05 CDCl3
76.73 CDCl3
-42.39
28.53
24.89
21.50
1.96
0.05
TMS
O
S12
δ (ppm)



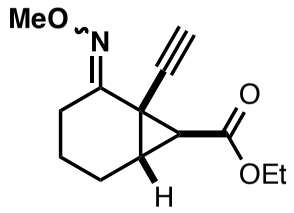
S13

TMS
O
OEt
H
O
S13
δ (ppm)

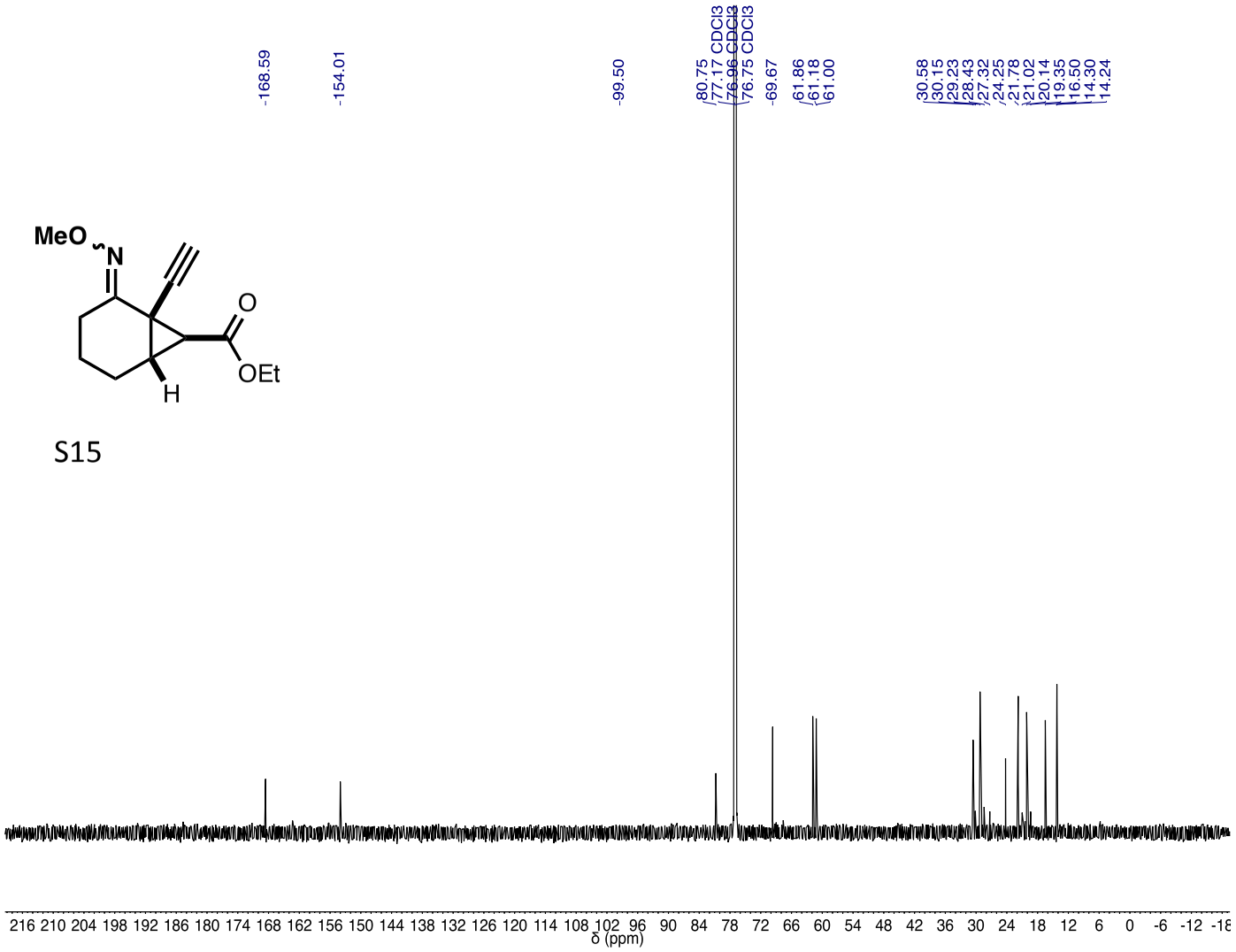


S14

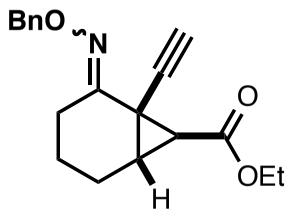
-201.38
-168.56
78.76
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
71.83
-61.11
41.15
36.69
33.21
30.35
28.51
25.64
25.46
-14.22
O
O
OEt
H
S14
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)



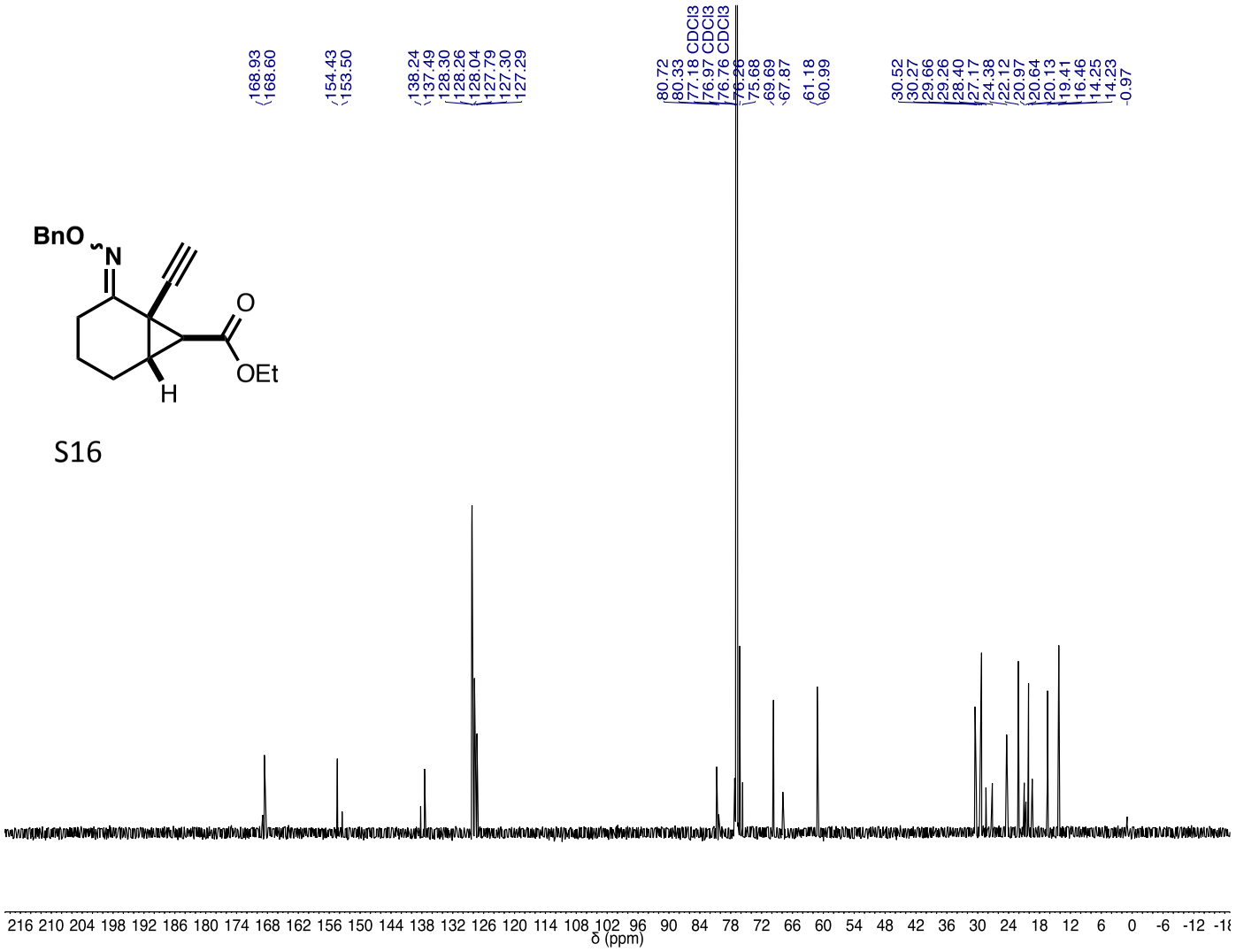
S15

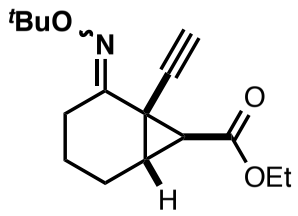

-168.59
-154.01
-99.50
80.75
77.17 CDCl3
76.96 CDCl3
76.75 CDCl3
-69.67
61.86
61.18
61.00
30.58
30.15
29.23
28.43
27.32
24.25
21.78
21.02
20.14
19.35
16.50
14.30
14.24
MeO
N
O
OEt
H
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S15

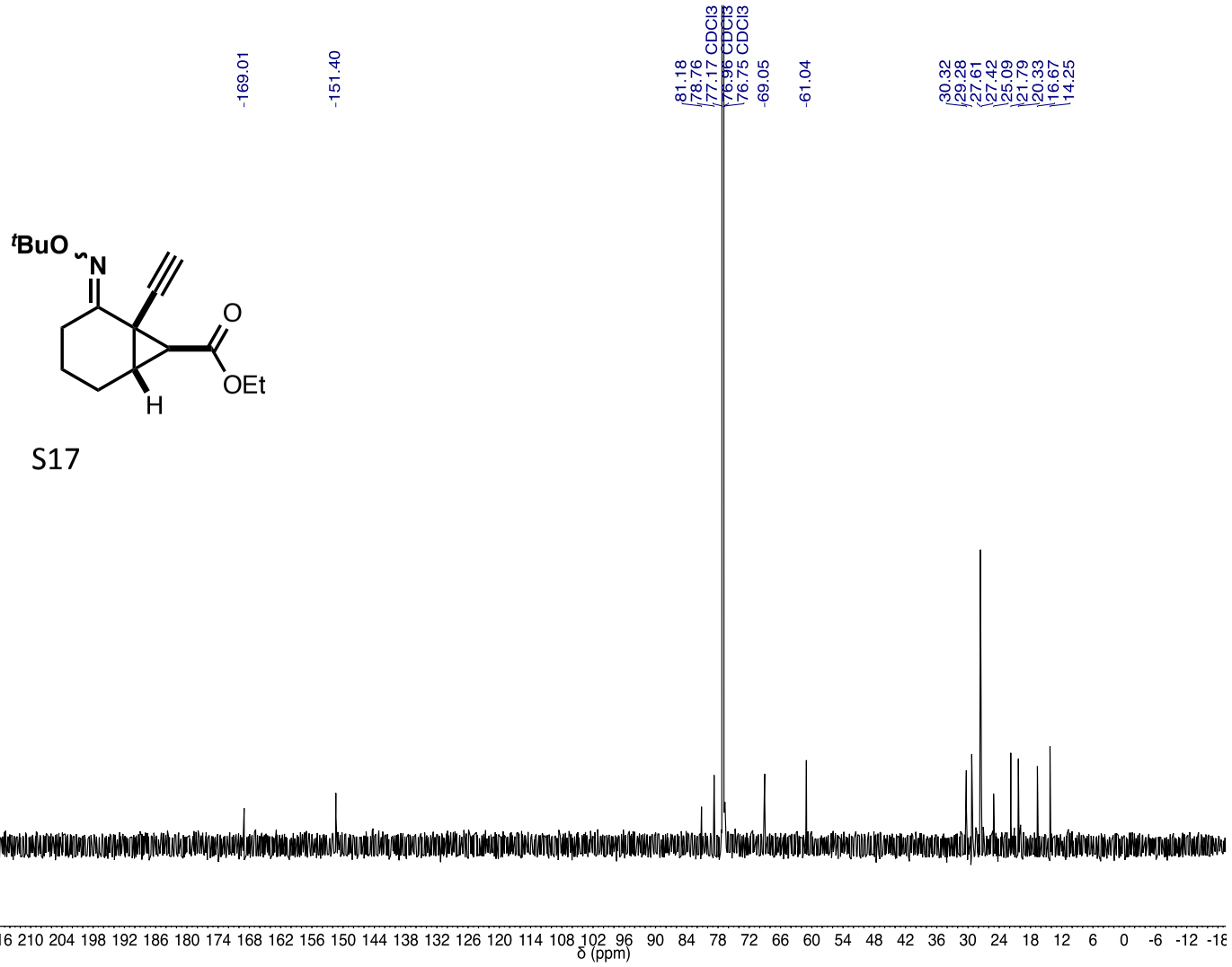


S16

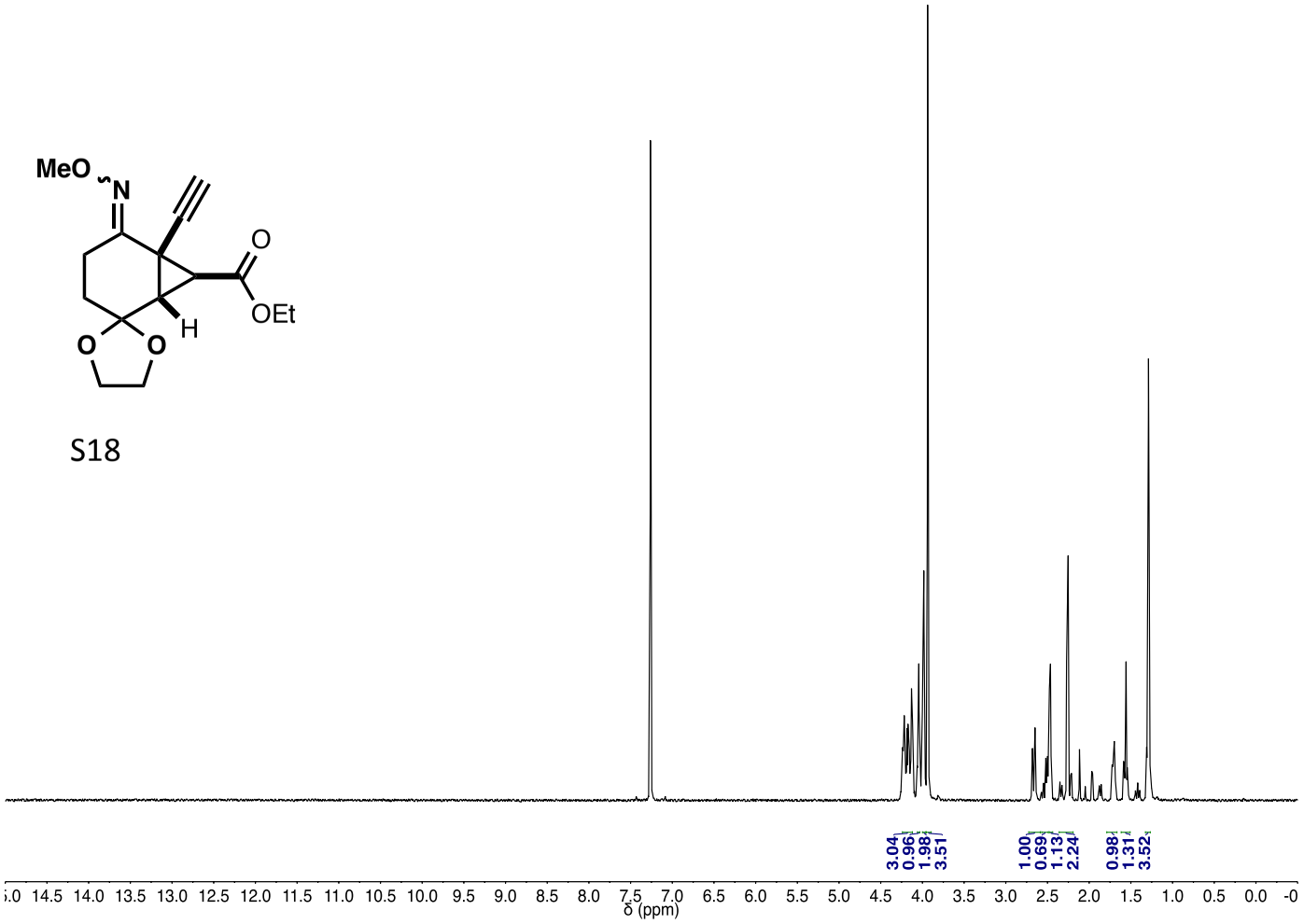

168.93
168.60
154.43
153.50
138.24
137.49
128.30
128.26
128.04
127.79
127.30
127.29
80.72
80.33
77.18 CDCl3
76.97 CDCl3
76.76 CDCl3
76.26
75.68
69.69
67.87
61.18
60.99
30.52
30.27
29.66
29.26
28.40
27.17
24.38
22.12
20.97
20.64
20.13
19.41
16.46
14.25
14.23
-0.97
BnO
N
O
OEt
H
S16
δ (ppm)



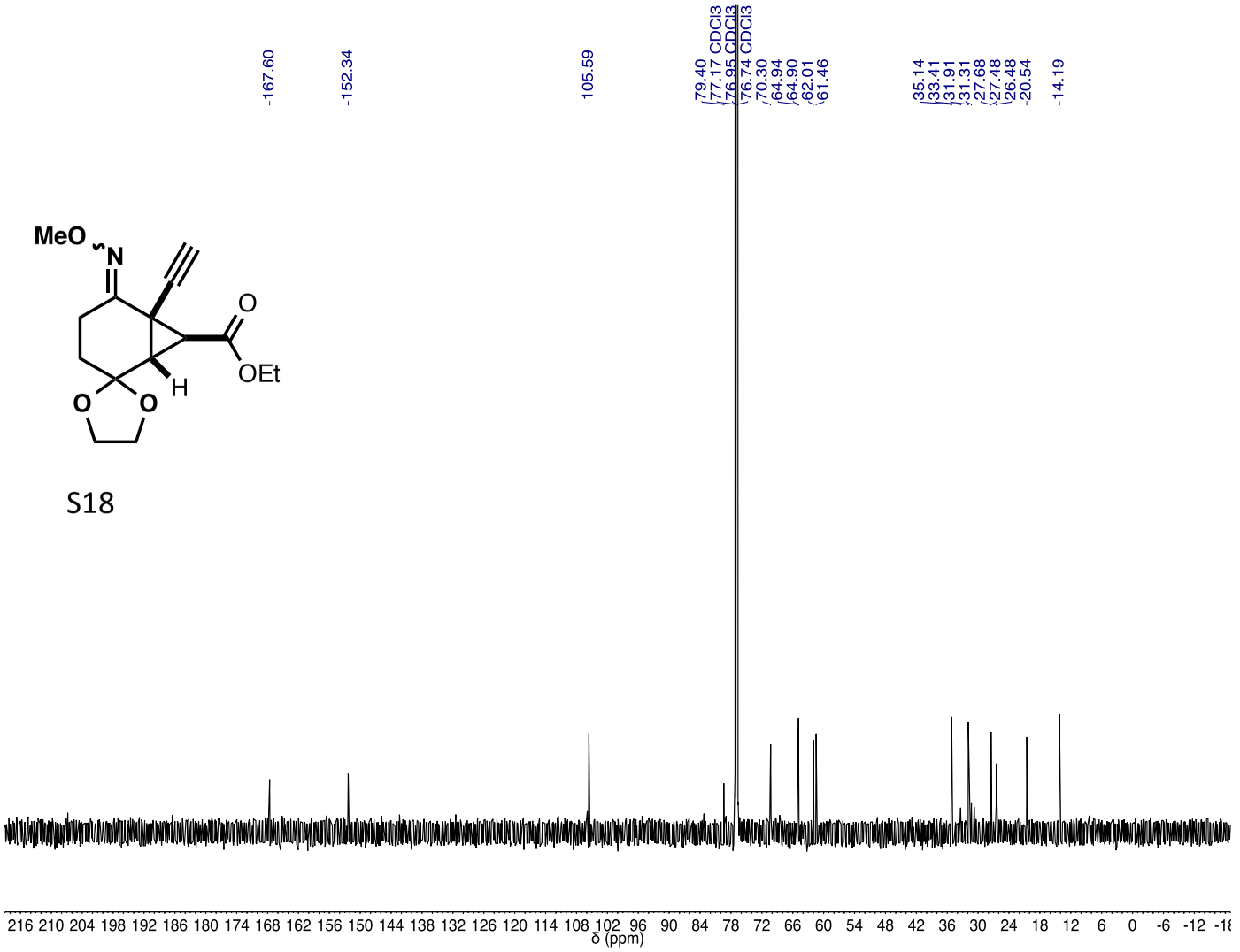
S17


-169.01
-151.40
81.18
78.76
77.17 CDCl3
76.96 CDCl3
76.75 CDCl3
69.05
61.04
30.32
29.28
27.61
27.42
25.09
21.79
20.33
16.67
14.25
tBuO
N
O
OEt
H
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

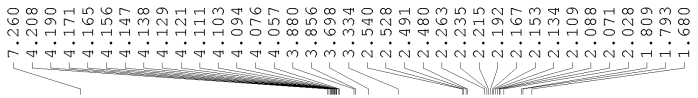
S17

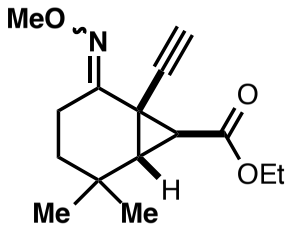


S18

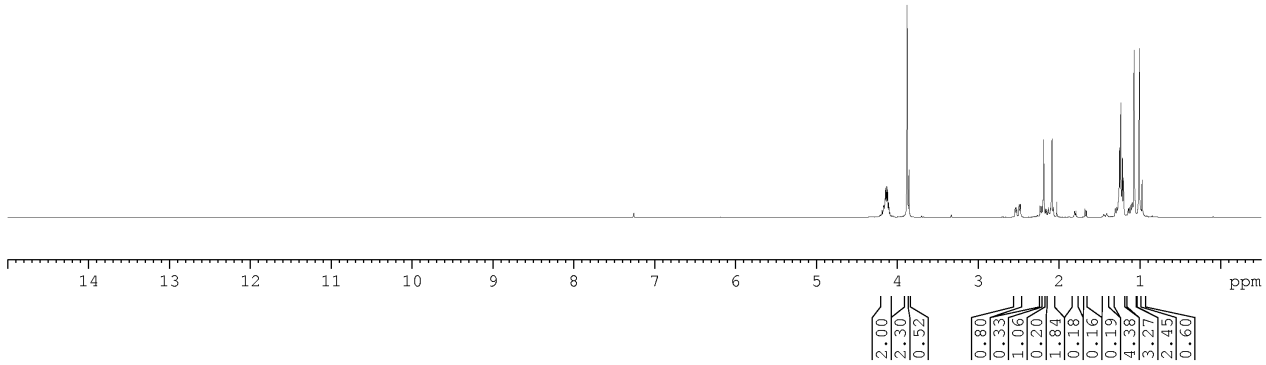

-167.60
-152.34
-105.59
79.40
77.17 CDCl3
76.95 CDCl3
76.74 CDCl3
70.30
64.94
64.90
62.01
61.46
35.14
33.41
31.91
31.31
27.68
27.48
26.48
-20.54
-14.19
MeO
N
O
OEt
H
O
O
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

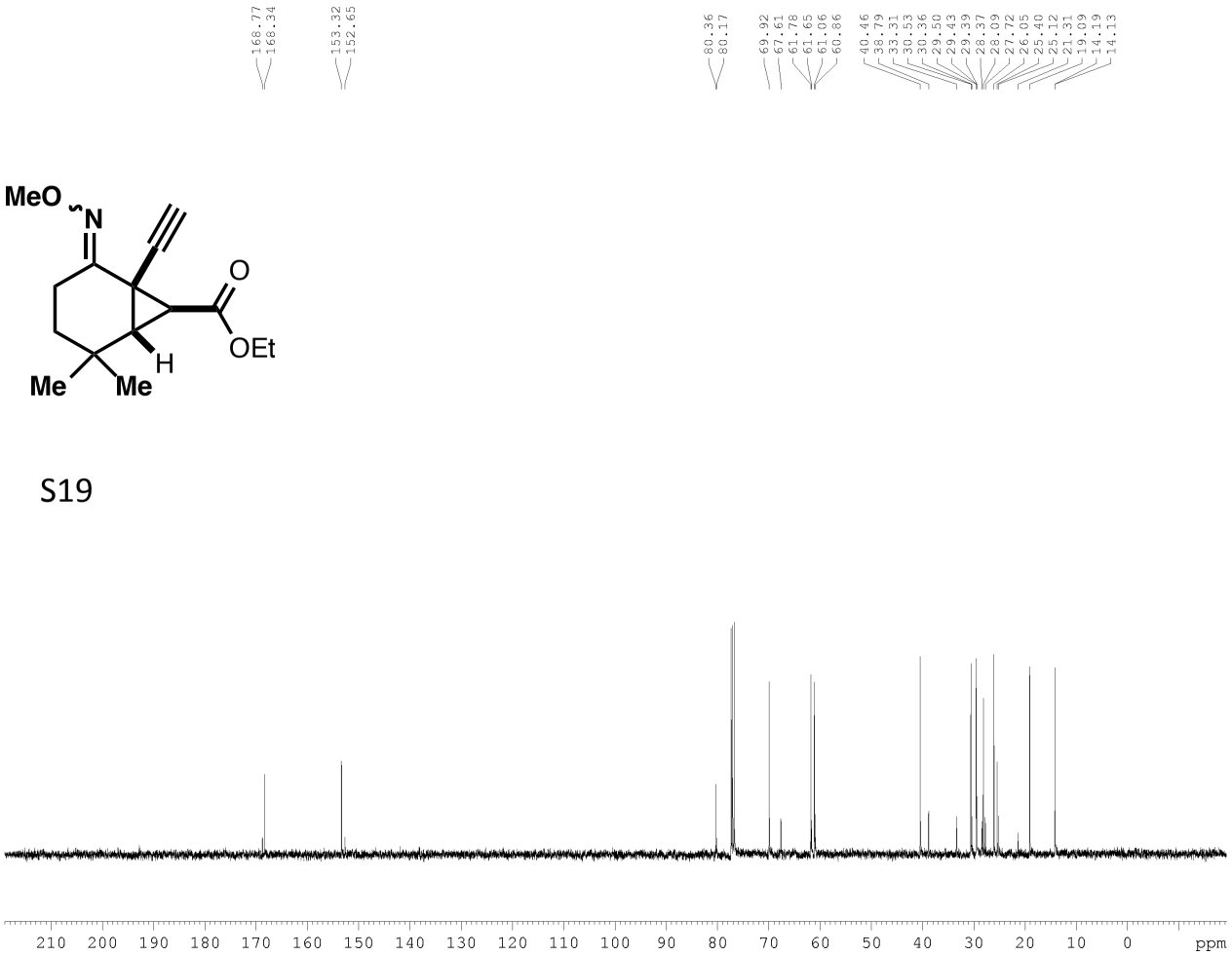
S18


7.260
4.208
4.190
4.171
4.165
4.156
4.147
4.138
4.129
4.121
4.111
4.103
4.094
4.076
4.057
3.880
3.856
3.698
3.334
2.540
2.528
2.491
2.480
2.263
2.235
2.215
2.192
2.167
2.153
2.134
2.109
2.088
2.071
2.028
1.809
1.793
1.680

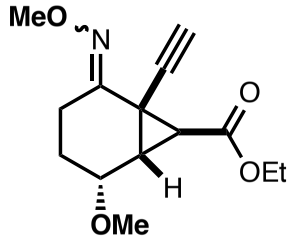

MeO
N
O
OEt
H
Me
Me

S19

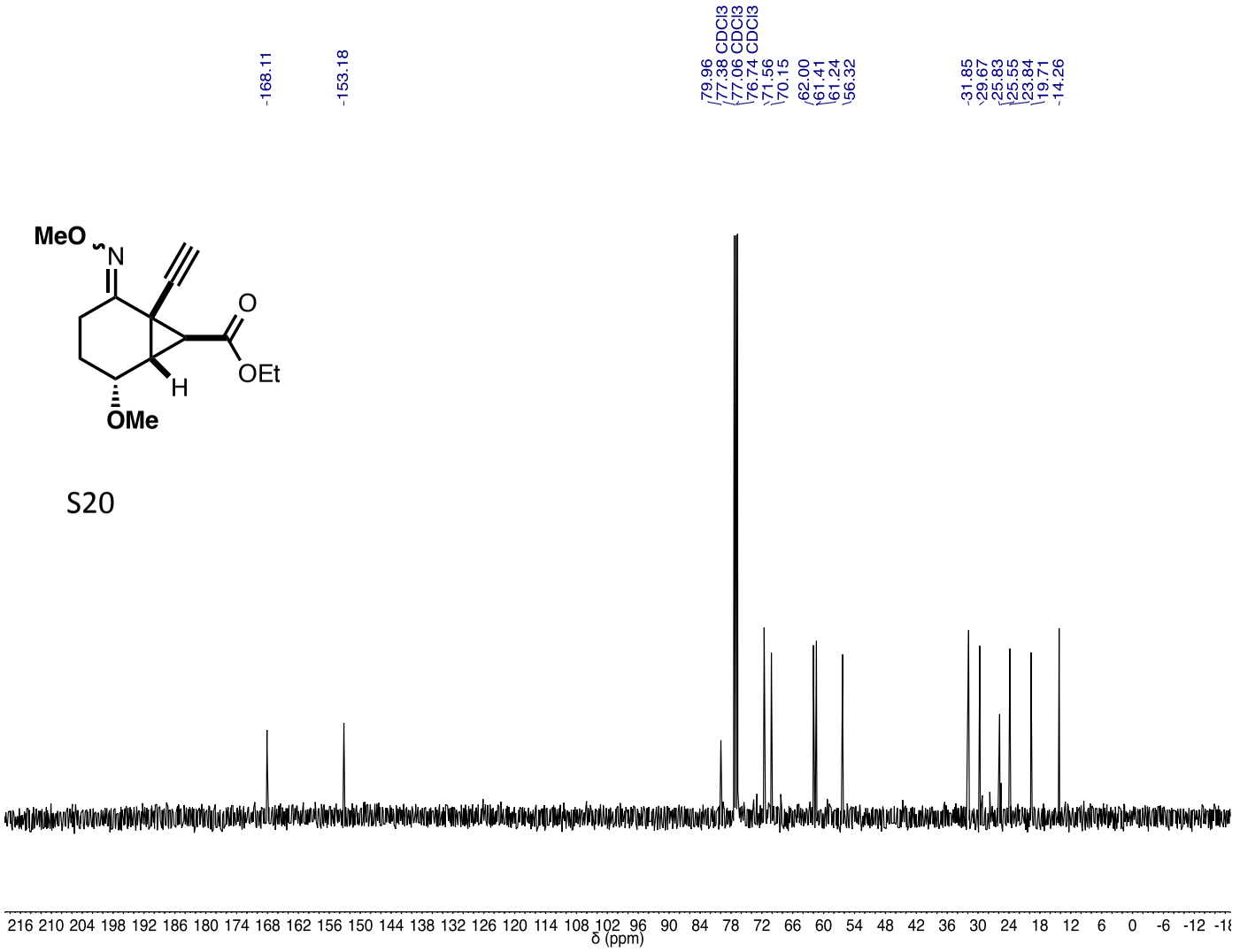

14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.30
0.52
0.80
0.33
1.06
0.20
1.84
0.18
0.16
0.19
4.38
3.27
2.45
0.60

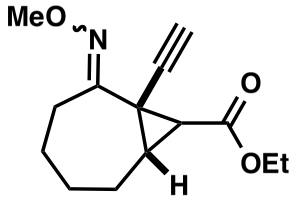

168.77
168.34
153.32
152.65
80.36
80.17
69.92
67.61
61.78
61.65
61.06
60.86
40.46
38.79
33.31
30.53
30.36
29.50
29.43
29.39
28.37
28.09
27.72
26.05
25.40
25.12
21.31
19.09
14.19
14.13
MeO
N
O
OEt
H
Me
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

S19



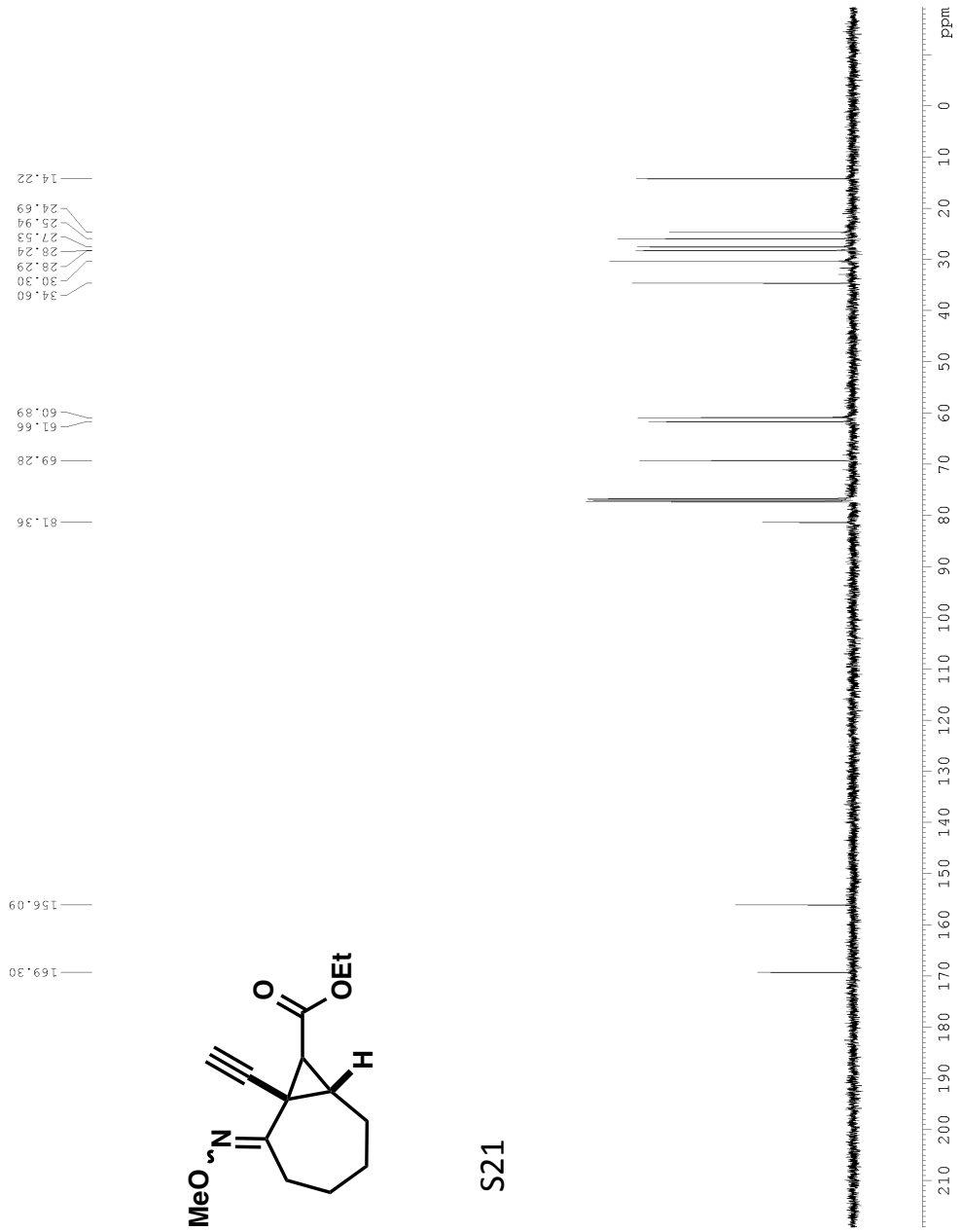
S20


-168.11
-153.18
79.96
77.38 CDCl3
77.06 CDCl3
76.74 CDCl3
71.56
70.15
62.00
61.41
61.24
56.32
31.85
29.67
25.83
25.55
23.84
19.71
-14.26
MeO
N
O
OEt
H
OMe
S20
δ (ppm)

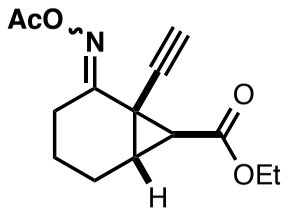

MeO
N
O
OEt
H

S21

2.00
2.81
0.93
0.95
1.91
0.88
1.96
1.08
1.99
3.10
1.00
15.5
14.5
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
-2.5
-3.5
δ (ppm)

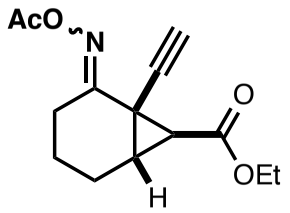

14.22
24.69
25.94
27.53
28.24
28.29
30.30
34.60
60.89
61.66
69.28
81.36
156.09
169.30
MeO
N
O
OEt
H
ppm

S21


AcO
N
O
OEt
H

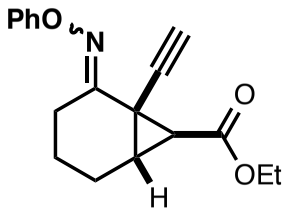
S22

2.01
0.96
0.96
2.90
3.13
1.99
0.98
4.07
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
δ (ppm)

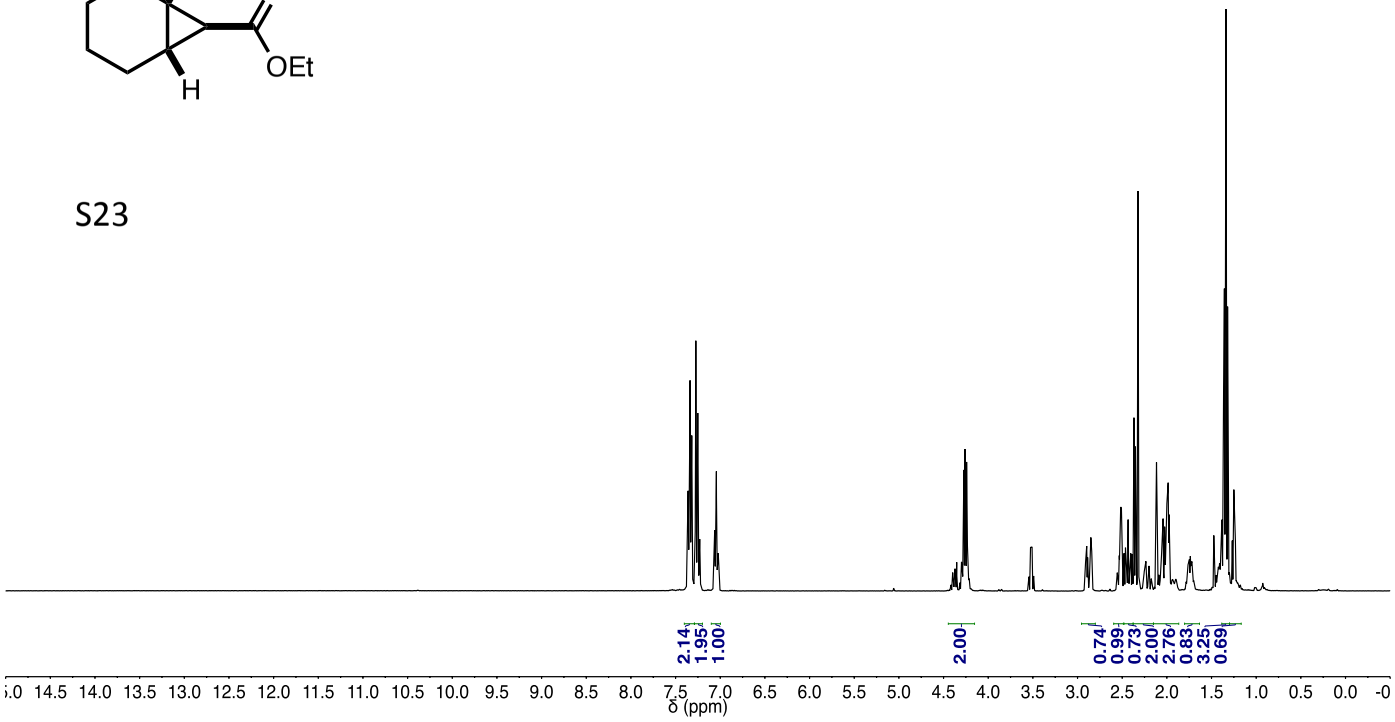

AcO
N
O
OEt
H

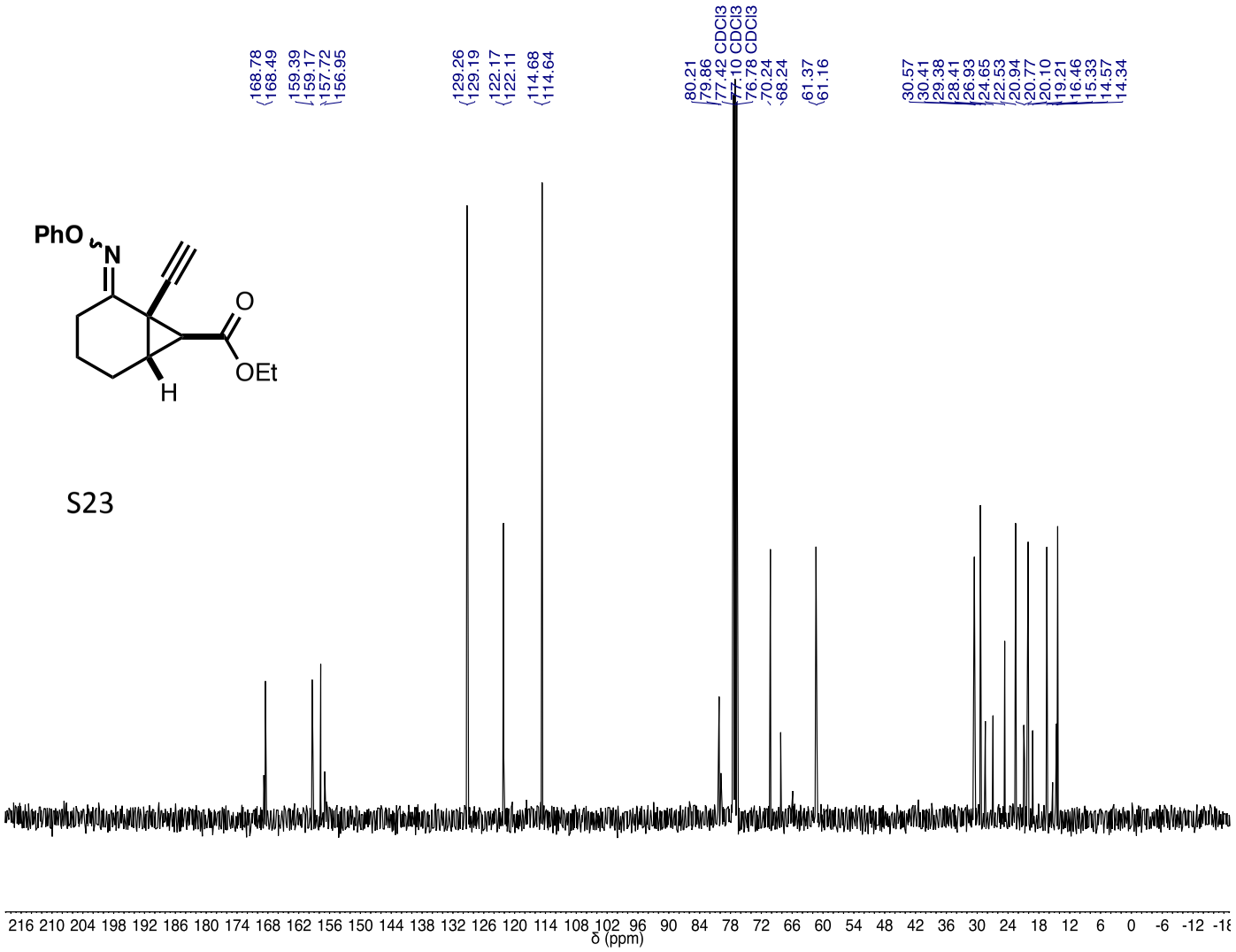
S22

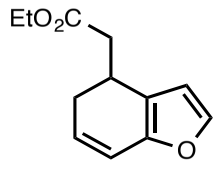
2.01
0.96
0.96
2.90
3.13
1.99
0.98
4.07
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)



S23

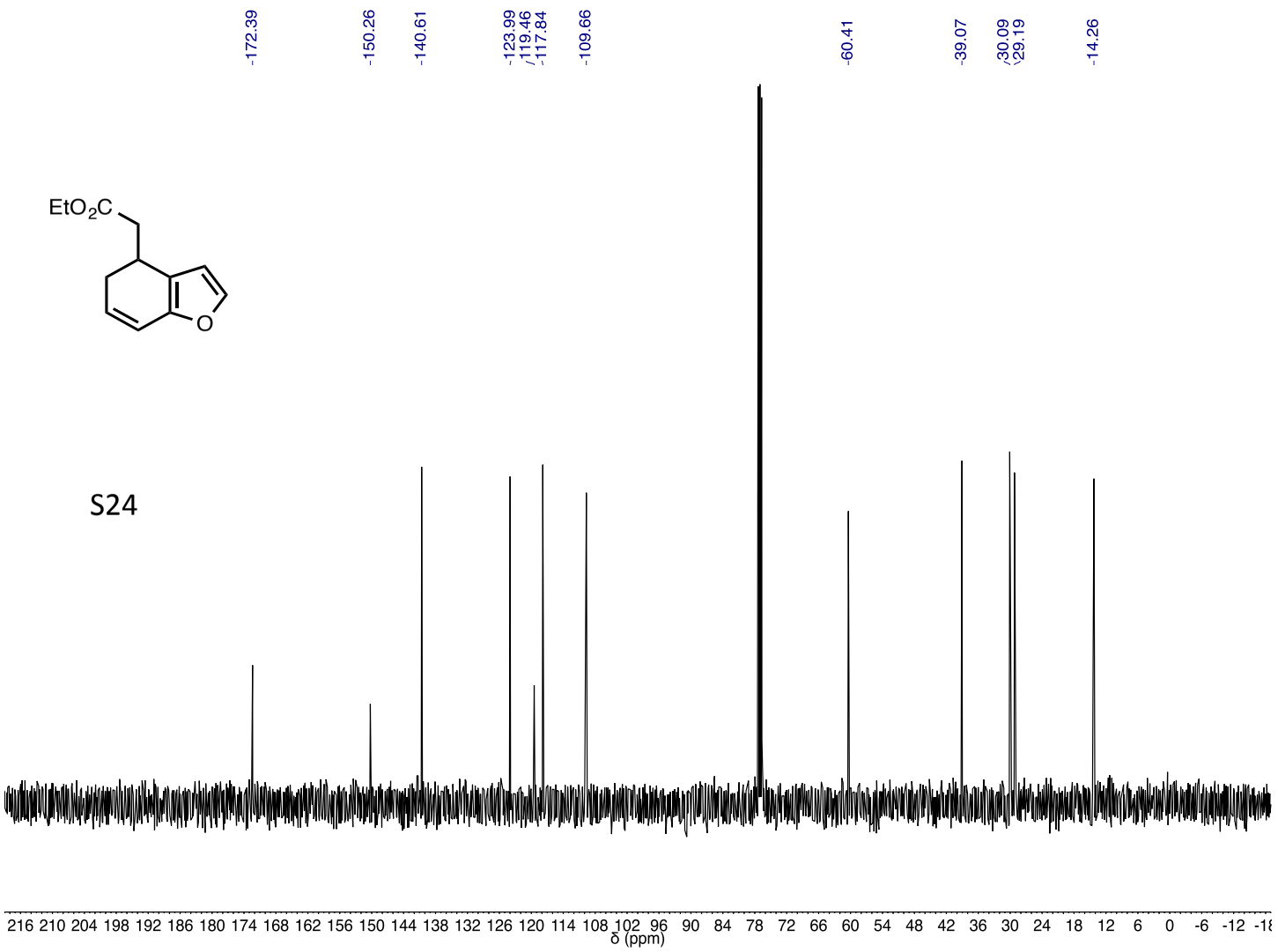


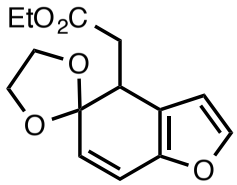

168.78
168.49
159.39
159.17
157.72
156.95
129.26
129.19
122.17
122.11
114.68
114.64
80.21
79.86
77.42 CDCl3
77.10 CDCl3
76.78 CDCl3
70.24
68.24
61.37
61.16
30.57
30.41
29.38
28.41
26.93
24.65
22.53
20.94
20.77
20.10
19.21
16.46
15.33
14.57
14.34
PhO
N
O
OEt
H
S23
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


EtO2C
O

S24

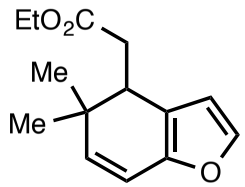
0.79
0.81
0.84
0.88
1.89
0.90
1.98
1.00
0.99
3.00
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)


172.39
150.26
140.61
123.99
119.46
117.84
109.66
60.41
39.07
30.09
29.19
14.26
EtO2C
O
S24
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)



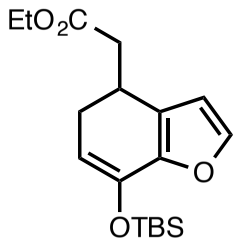
S25

172.45
147.90
141.83
125.20
120.52
120.19
110.46
108.83
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
65.29
64.19
60.41
39.00
34.19
14.15
δ (ppm)
S25
EtO2C
O
O
O



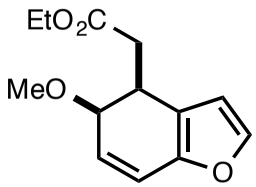
S26

173.25
149.13
140.56
136.46
127.32
119.51
115.40
110.91
77.31 CDCl3
76.99 CDCl3
76.68 CDCl3
60.35
40.17
36.57
35.15
27.47
23.68
14.15
EtO2C
Me
Me
O
S26
δ (ppm)



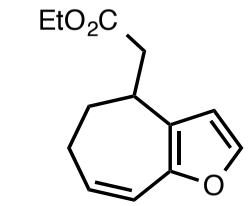
S27

-172.39
-147.24
142.55
-140.82
-122.48
-109.77
-100.46
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
-60.34
-38.57
29.68
29.46
25.64
-18.25
-14.22
-4.68
-4.72
δ (ppm)
EtO2C
OTBS
O
S27



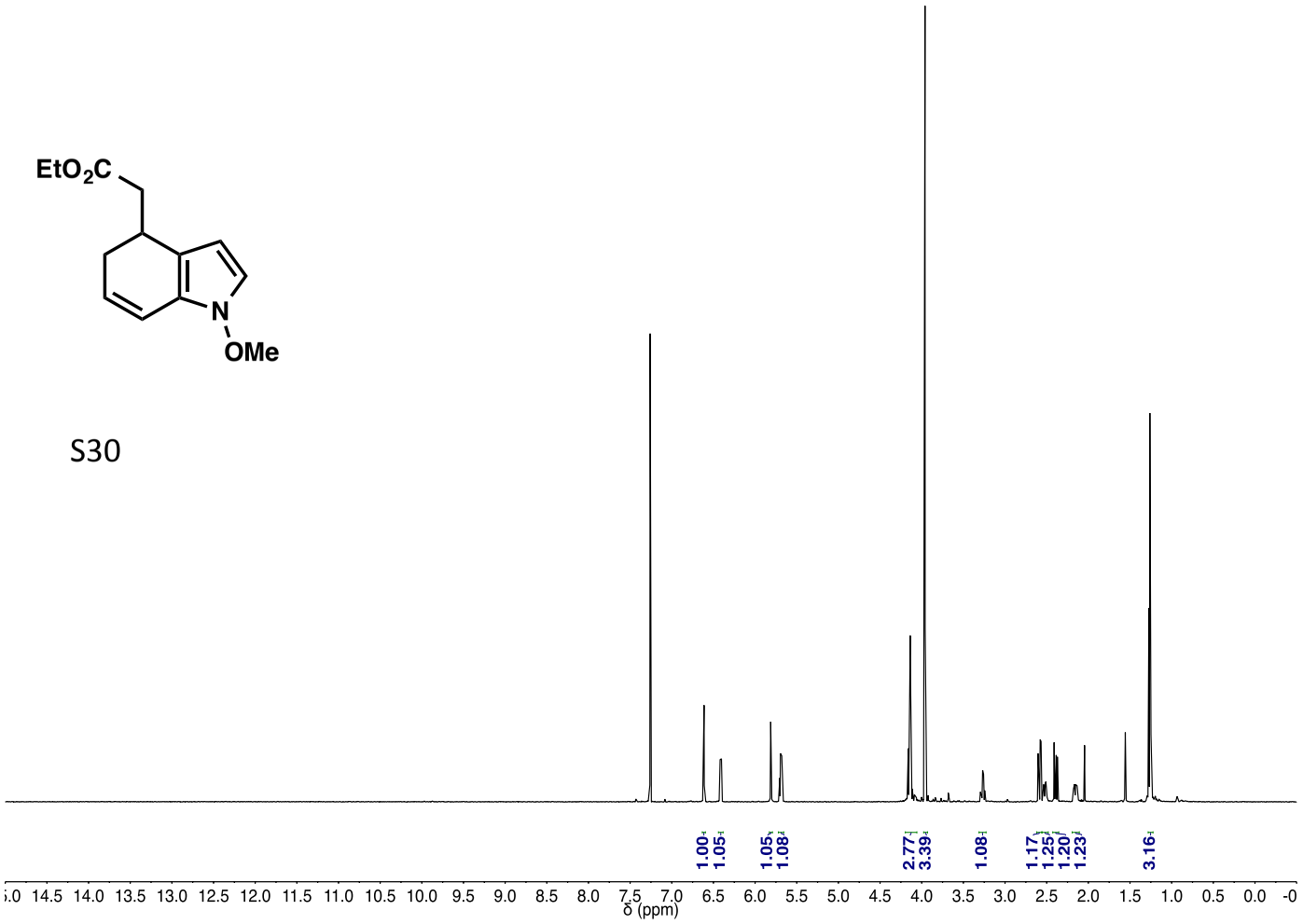
S28

172.97
149.33
141.36
125.86
120.04
118.39
110.46
77.67
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
60.38
56.85
33.17
31.96
14.25
MeO
EtO2C
O
S28
δ (ppm)

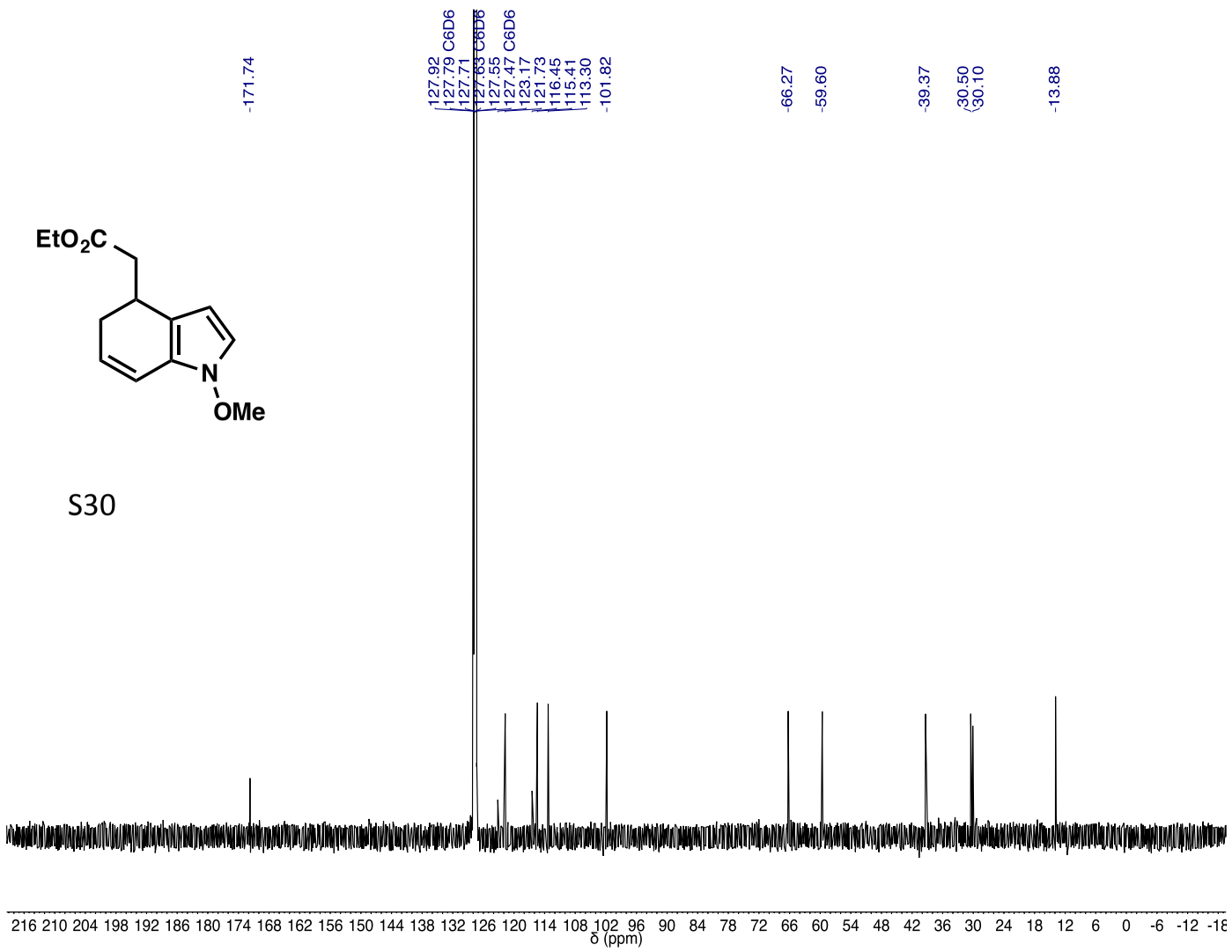


S29

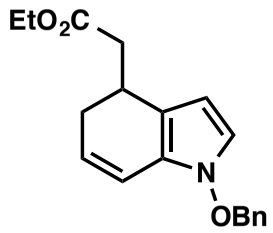
172.36
149.15
140.21
128.57
125.06
119.36
112.43
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
60.38
40.71
32.58
28.61
26.89
14.22
δ (ppm)
EtO2C
O
S29



S30

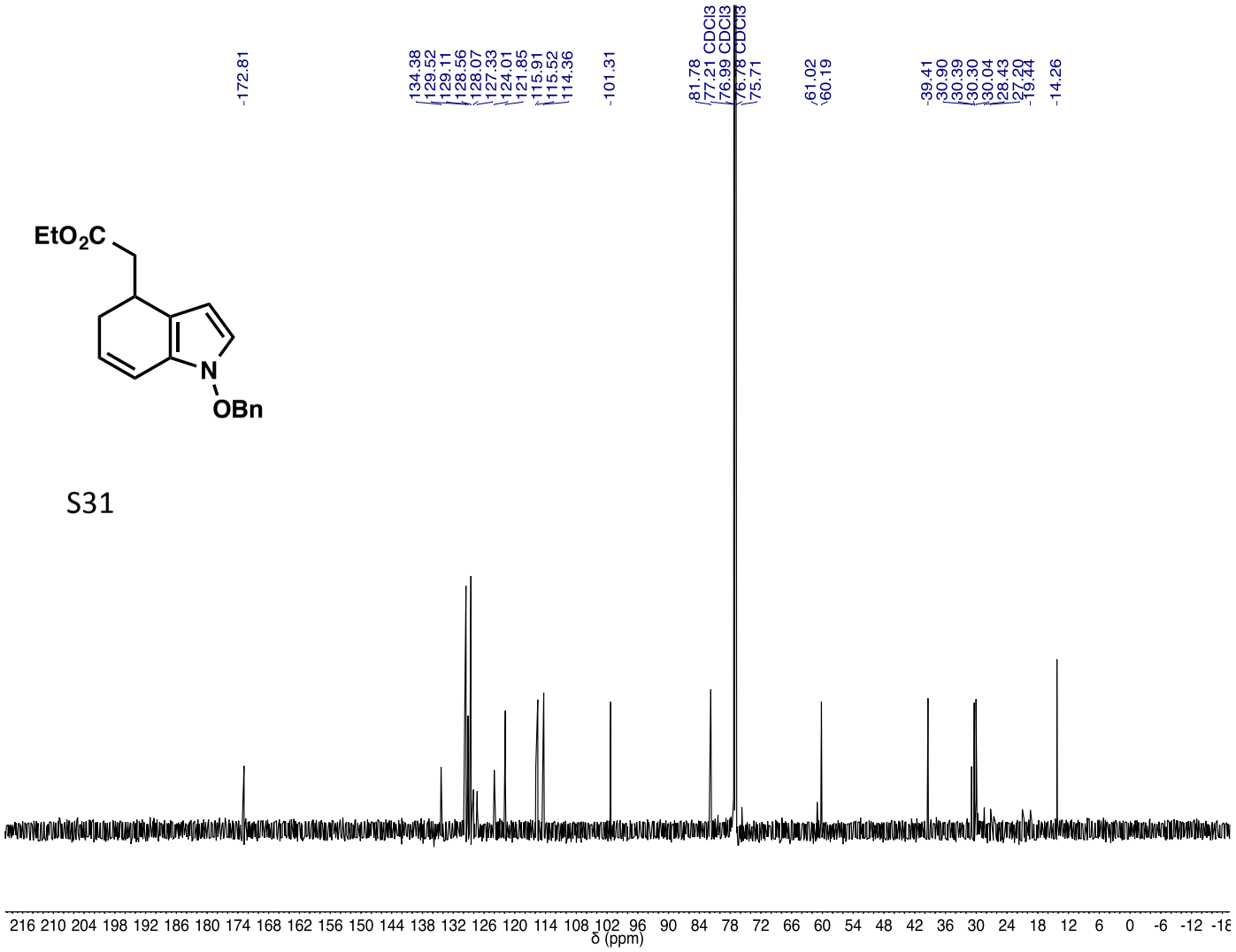

-171.74
127.92
127.79 C6D6
127.71
127.63 C6D6
127.55
127.47 C6D6
123.17
121.73
116.45
115.41
113.30
-101.82
-66.27
-59.60
-39.37
30.50
30.10
-13.88
EtO2C
N
OMe
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S30

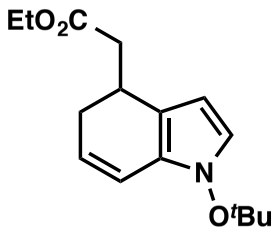

EtO2C
N
OBn

S31

3.58
2.58
1.00
1.07
1.06
1.11
2.46
3.12
1.16
2.63
1.29
2.48
1.60
4.37
δ (ppm)


EtO2C
N
OBn
-172.81
134.38
129.52
129.11
128.56
128.07
127.33
124.01
121.85
115.91
115.52
114.36
-101.31
81.78
77.21 CDCl3
76.99 CDCl3
76.78 CDCl3
75.71
61.02
60.19
39.41
30.90
30.39
30.30
30.04
28.43
27.20
19.44
14.26
δ (ppm)

S31

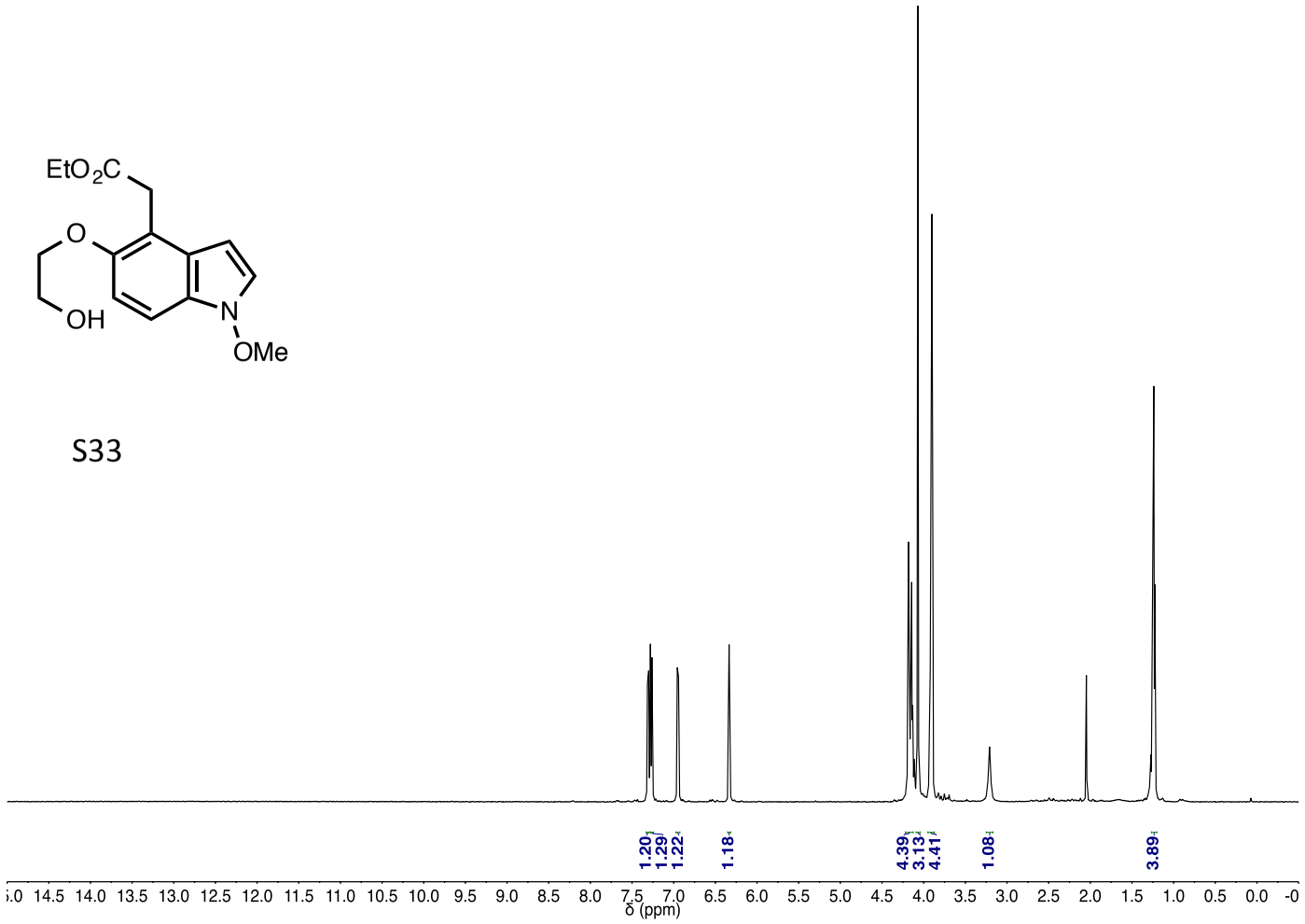

EtO2C
N
OtBu

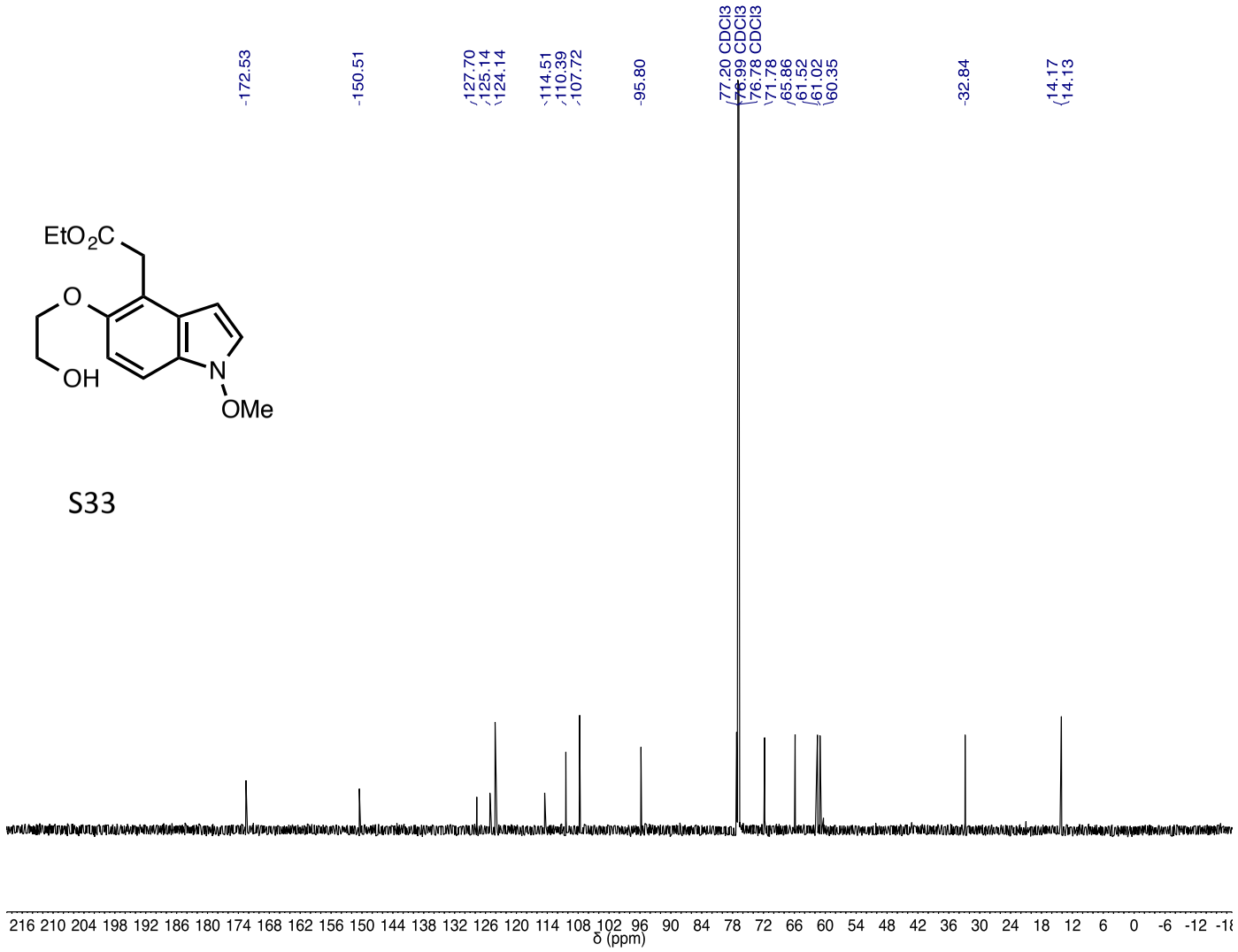
S32

1.00
1.10
1.01
1.04
2.68
1.10
1.22
1.26
1.51
1.08
1.00
0.47
0.56
8.72
2.89
δ (ppm)

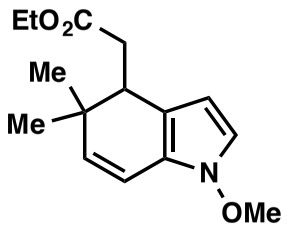
172.86
126.20
121.16
117.66
117.02
115.58
100.70
84.66
78.19
77.17 CDCl3
76.96 CDCl3
76.74 CDCl3
66.95
60.73
60.12
39.39
30.61
30.31
30.16
28.49
27.41
27.23
27.06
21.11
20.92
19.91
14.45
14.22
δ (ppm)
EtO2C
N
OtBu

S32


EtO2C
O
OH
N
OMe
S33
1.20
1.29
1.22
1.18
4.39
3.13
4.41
1.08
3.89
δ (ppm)

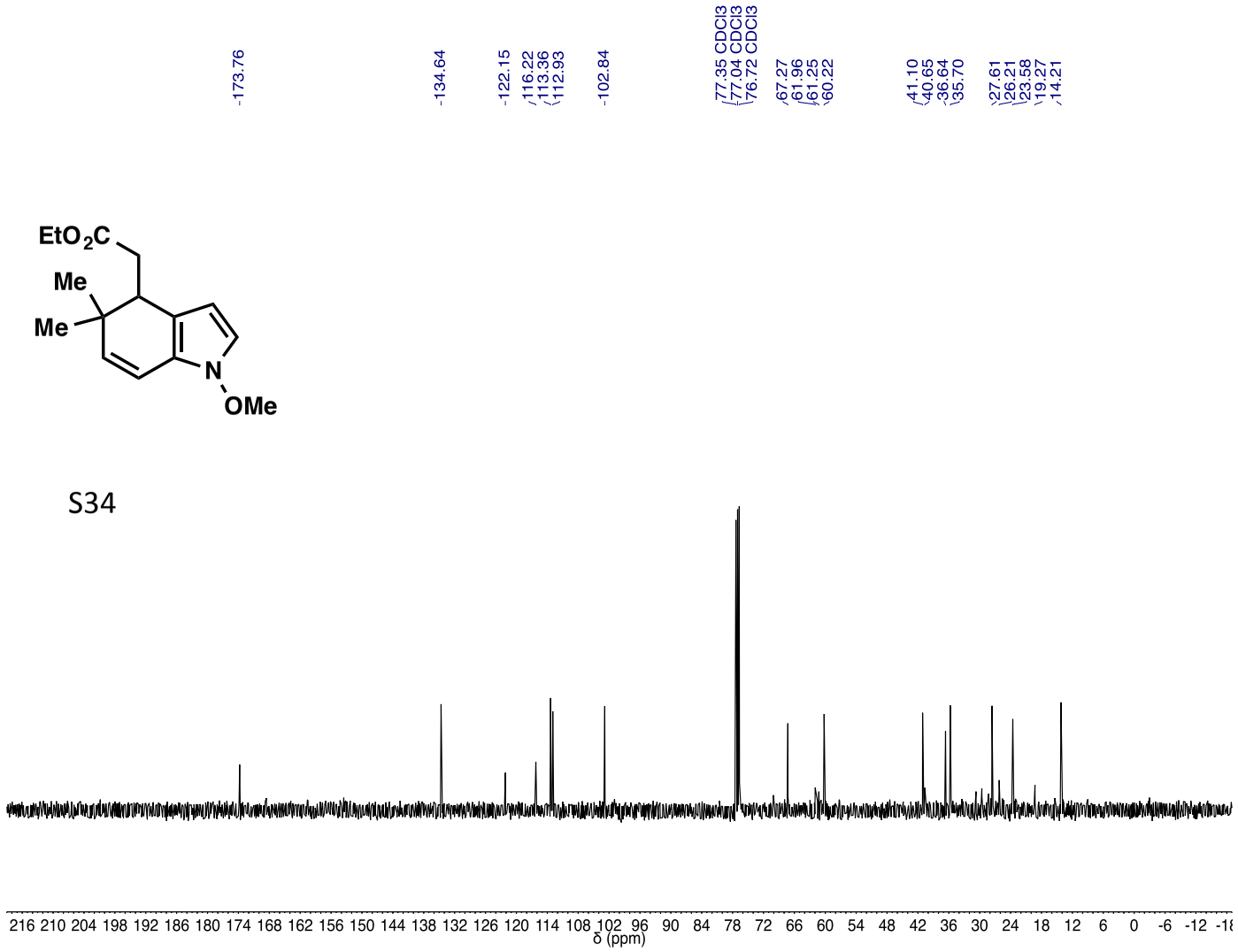

-172.53
-150.51
127.70
125.14
124.14
114.51
110.39
107.72
-95.80
77.20 CDCl3
76.99 CDCl3
76.78 CDCl3
71.78
65.86
61.52
61.02
60.35
-32.84
14.17
14.13
EtO2C
O
OH
N
OMe
δ (ppm)

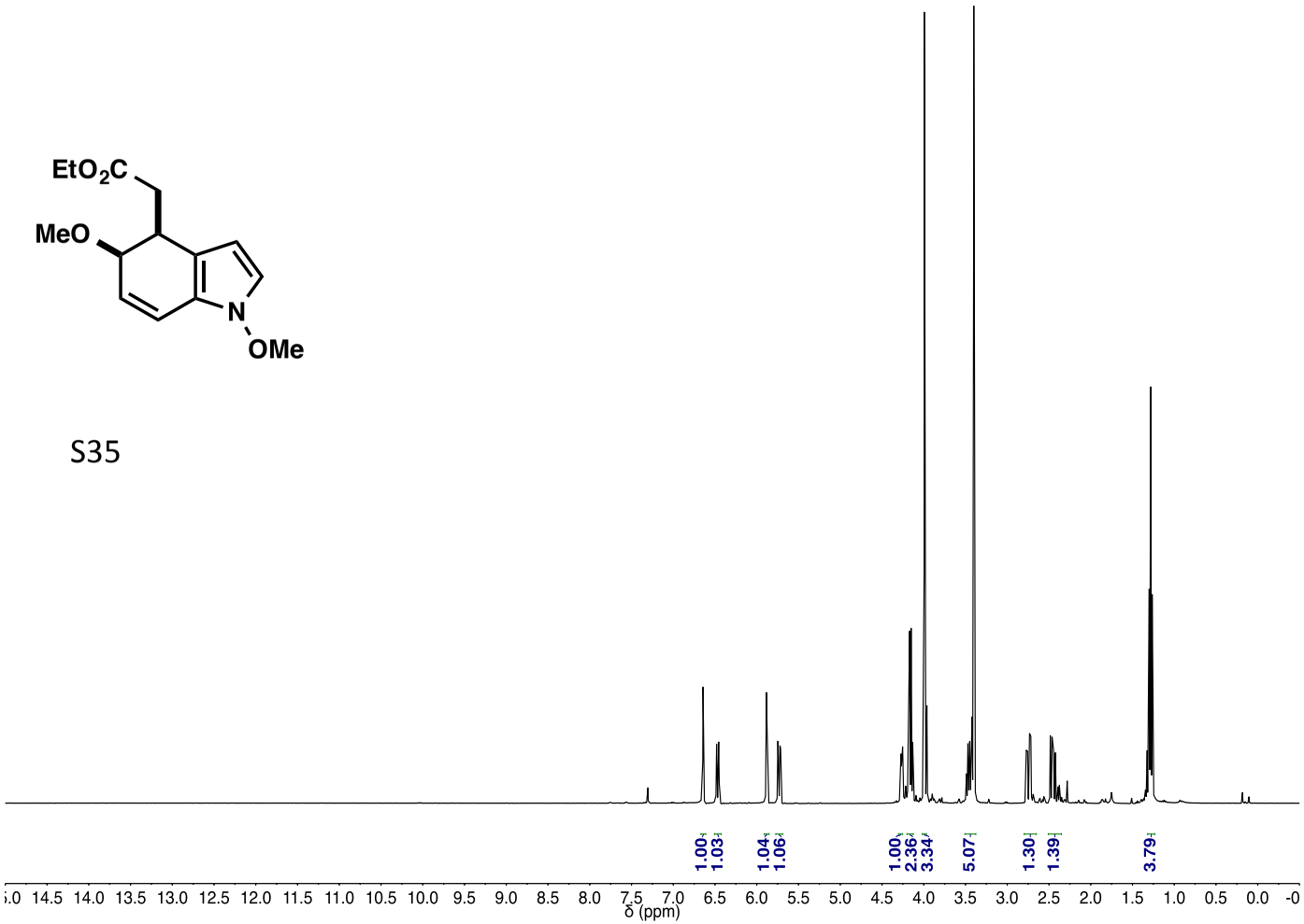
S33


EtO2C
Me
Me
N
OMe

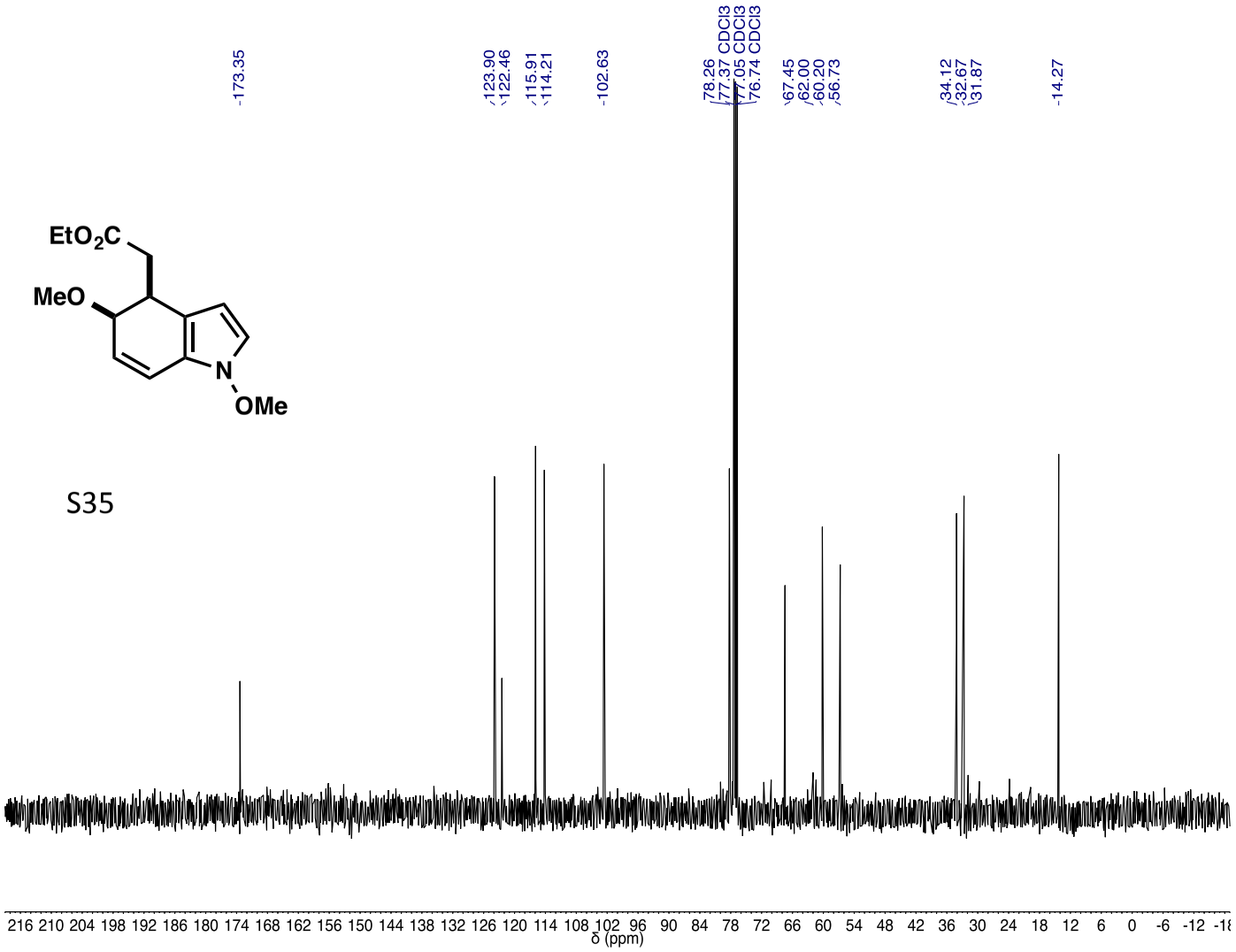
S34

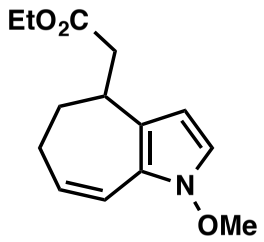
1.00
1.09
1.06
1.13
2.04
3.45
1.19
1.36
1.15
1.28
3.50
3.60
3.58
δ (ppm)


173.76
134.64
122.15
116.22
113.36
112.93
102.84
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
67.27
61.96
61.25
60.22
41.10
40.65
36.64
35.70
27.61
26.21
23.58
19.27
14.21
EtO2C
Me
Me
N
OMe
S34
δ (ppm)

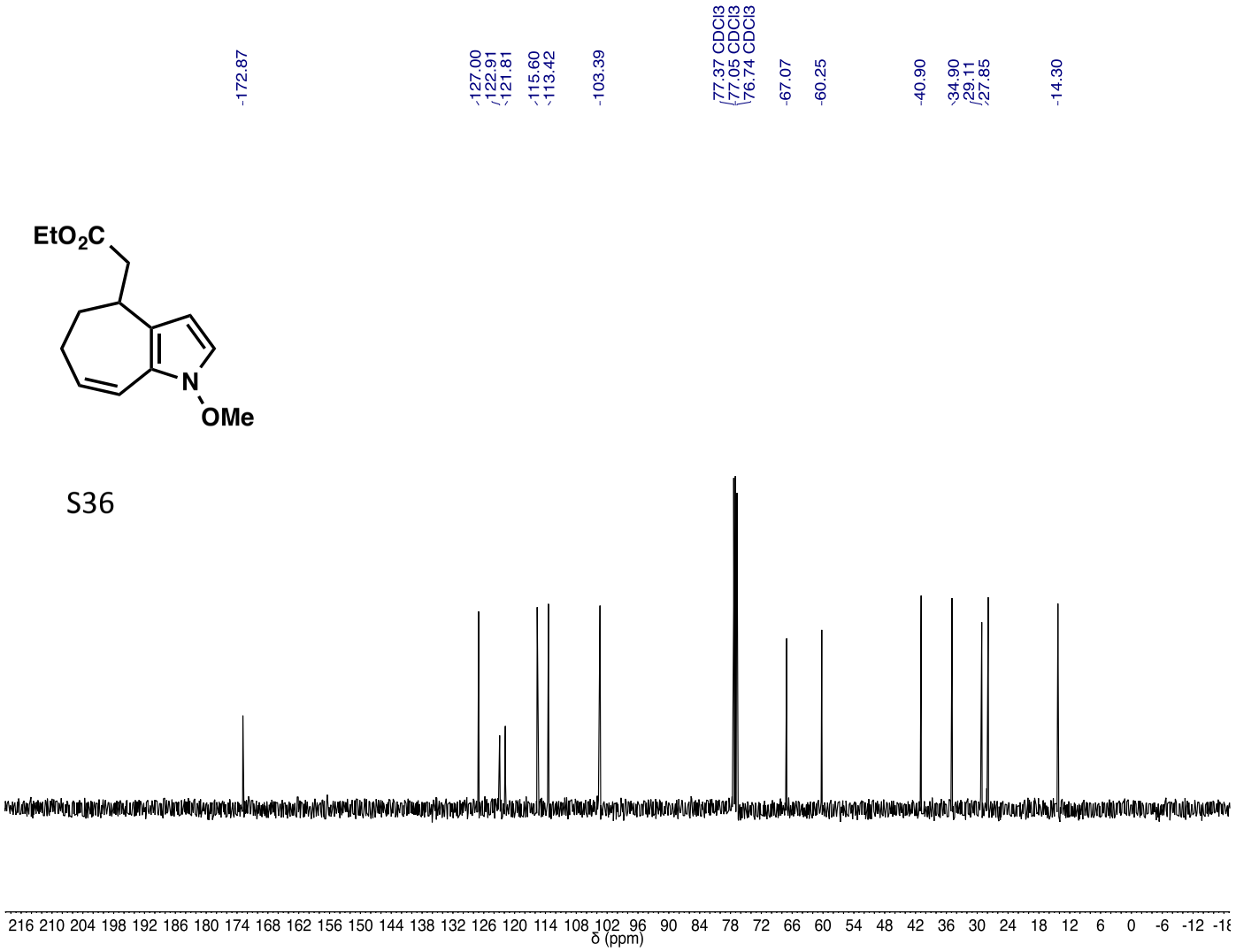


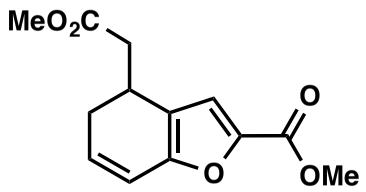
S35


-173.35
123.90
122.46
115.91
114.21
102.63
78.26
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
67.45
62.00
60.20
56.73
34.12
32.67
31.87
14.27
EtO2C
MeO
N
OMe
S35
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

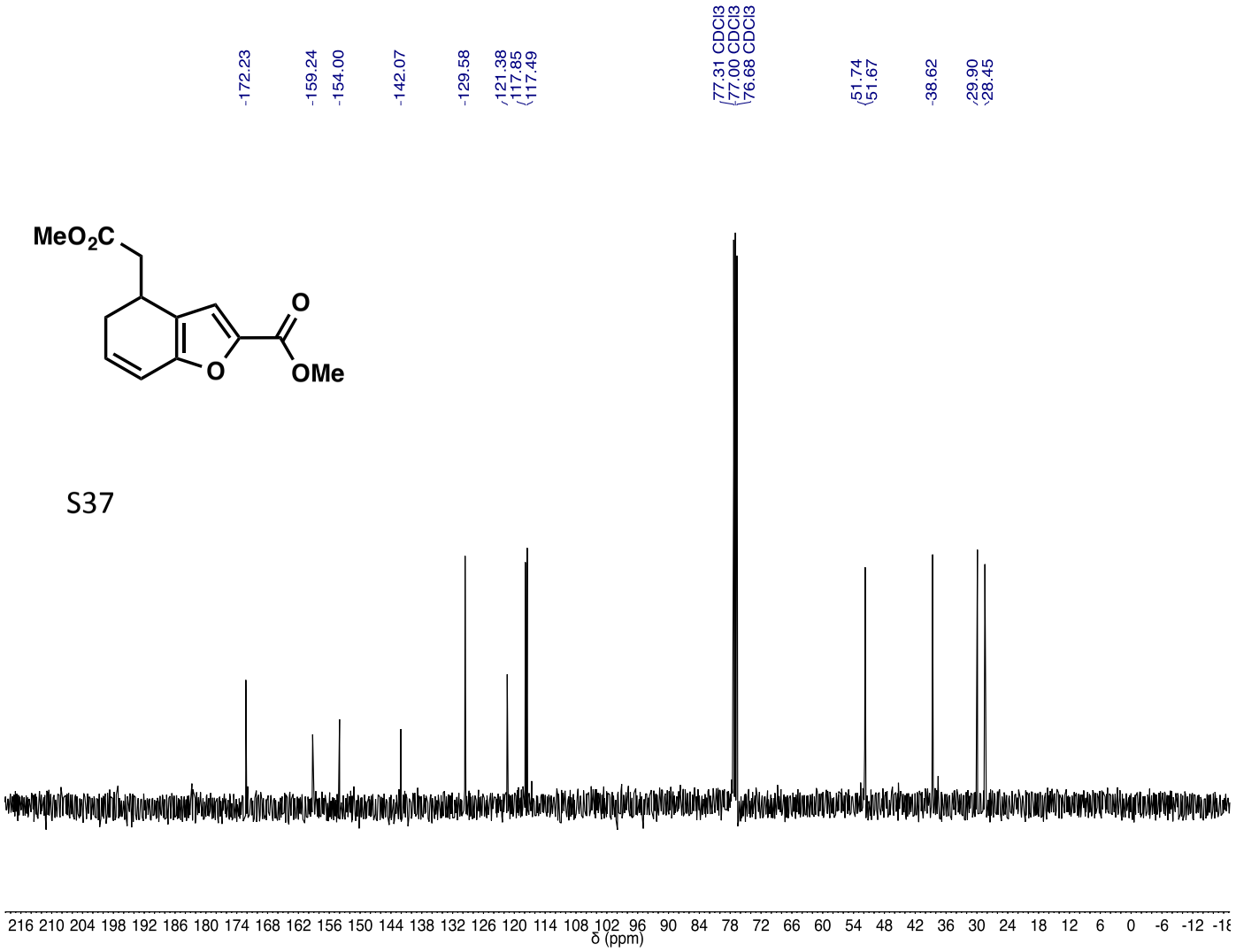


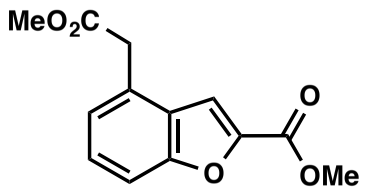
S36


172.87
127.00
122.91
121.81
115.60
113.42
103.39
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
67.07
60.25
40.90
34.90
29.11
27.85
14.30
EtO2C
N
OMe
S36
δ (ppm)

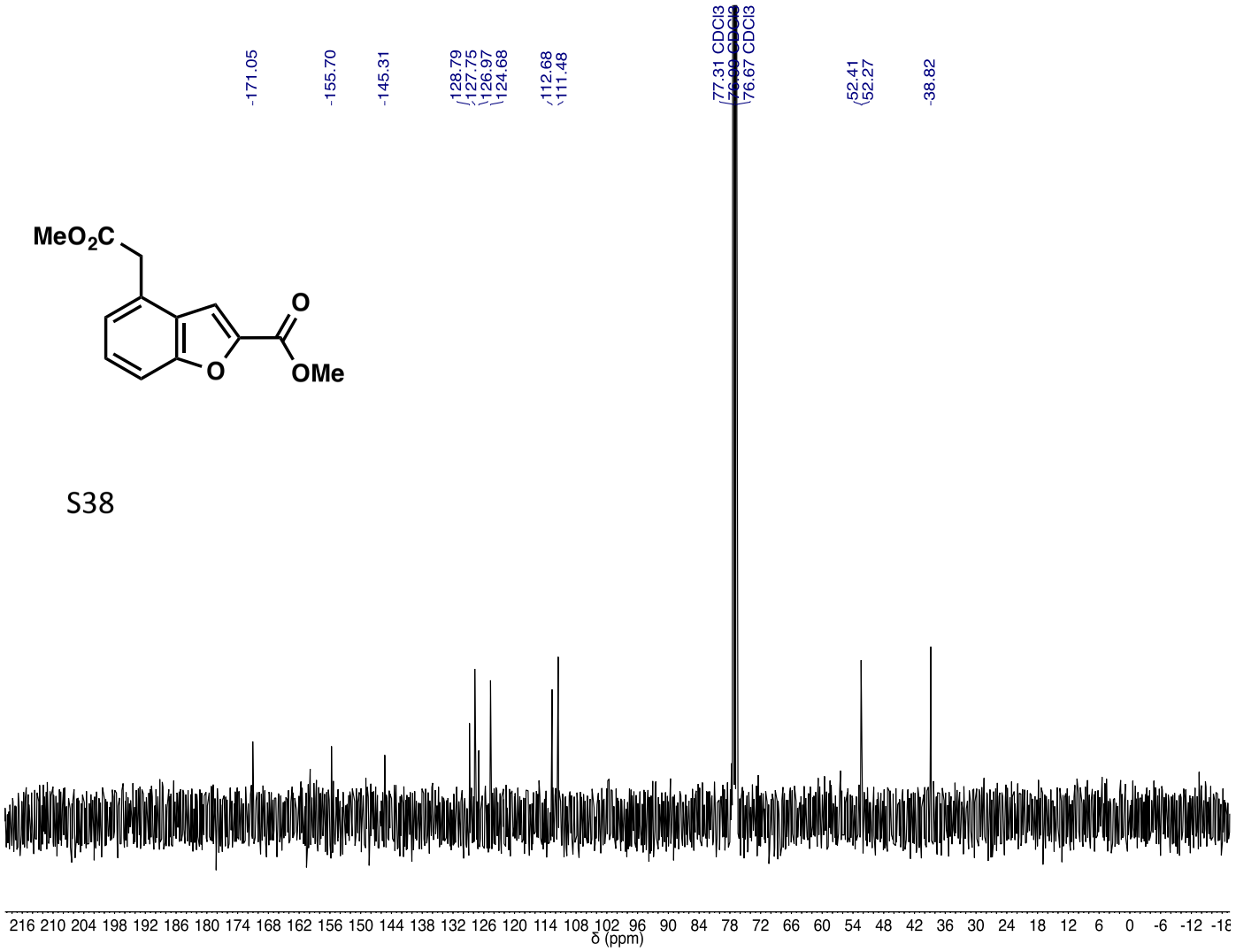


S37

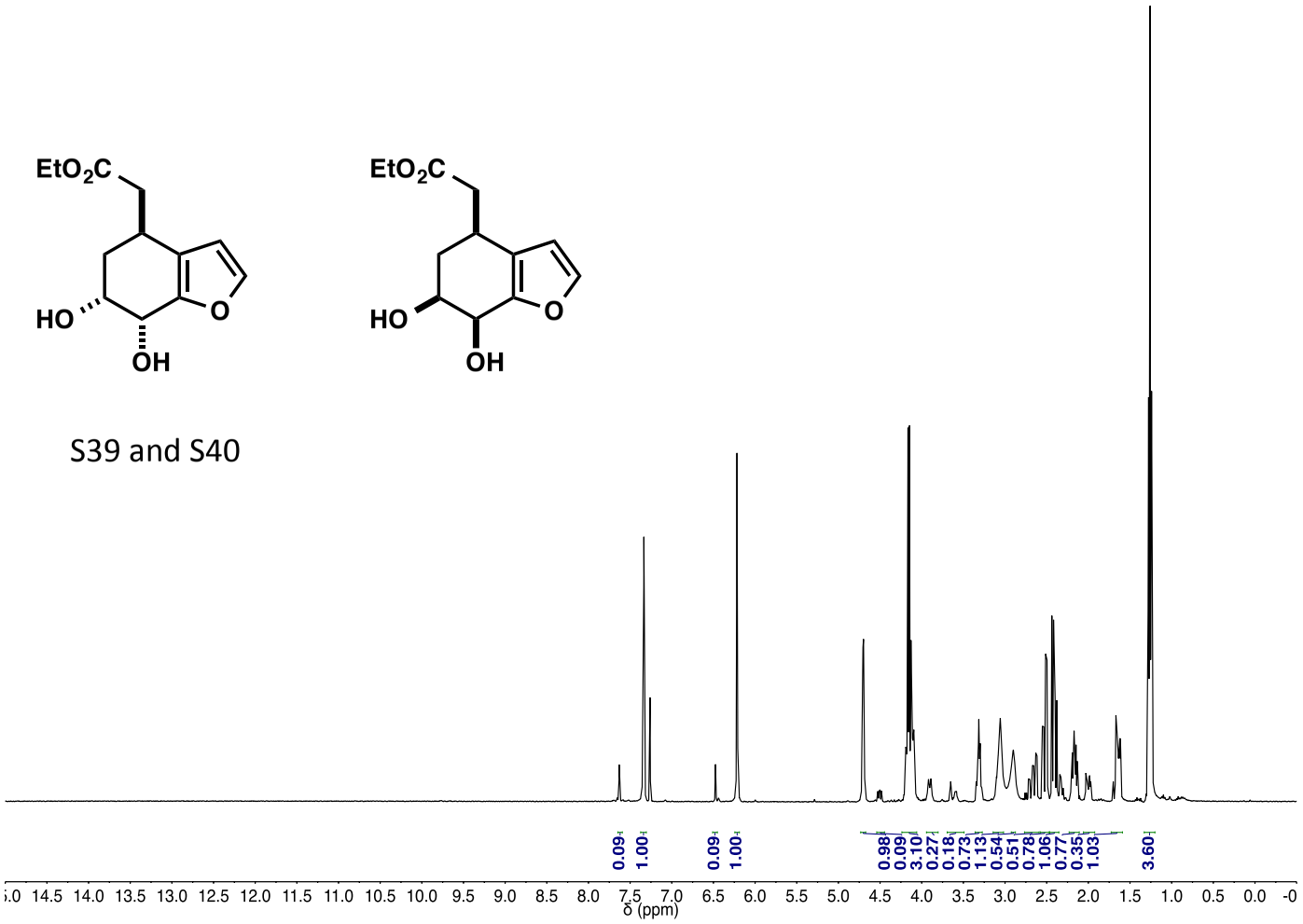

172.23
159.24
154.00
142.07
129.58
121.38
117.85
117.49
77.31 CDCl3
77.00 CDCl3
76.68 CDCl3
51.74
51.67
38.62
29.90
28.45
MeO2C
O
O
OMe
S37
δ (ppm)

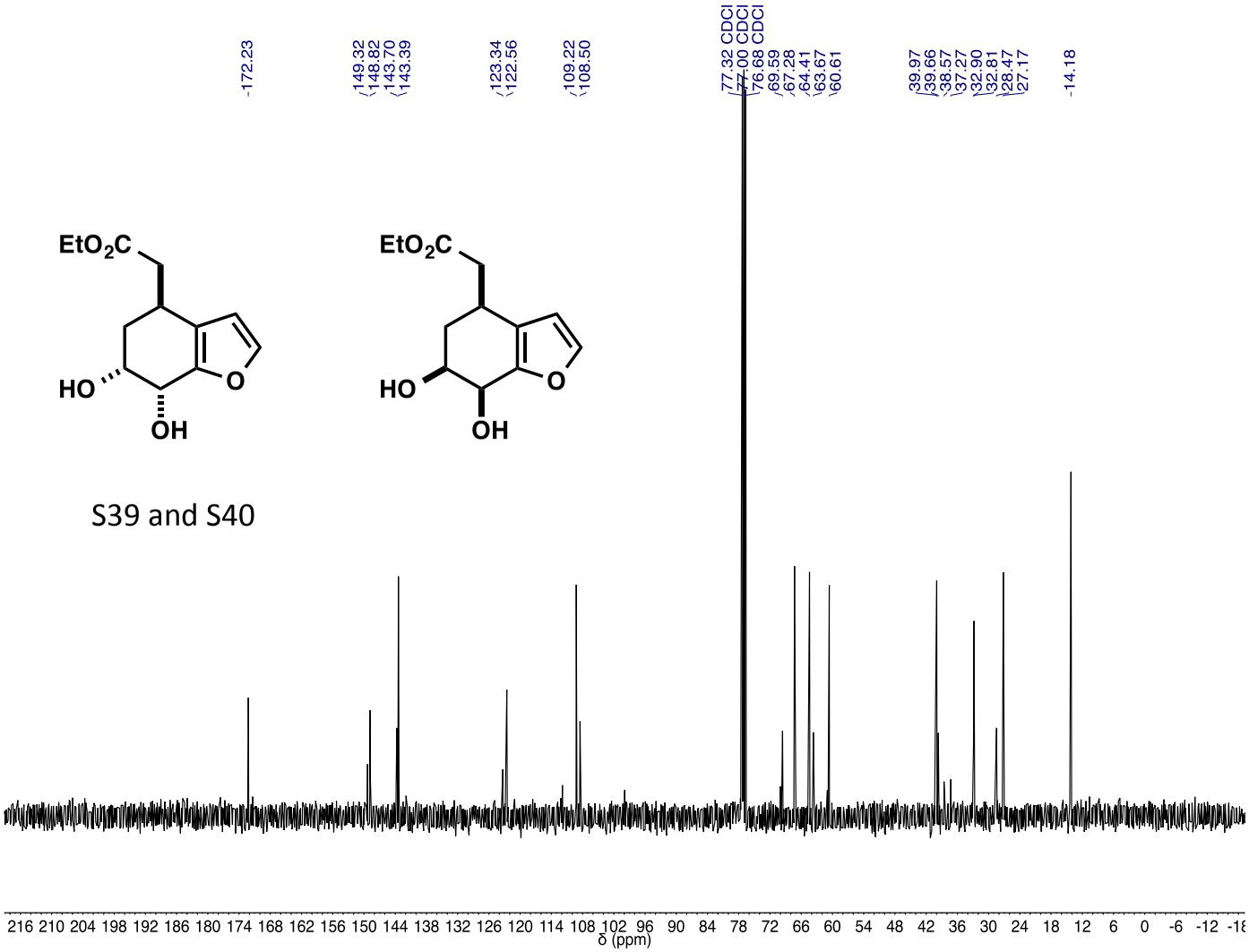


S38

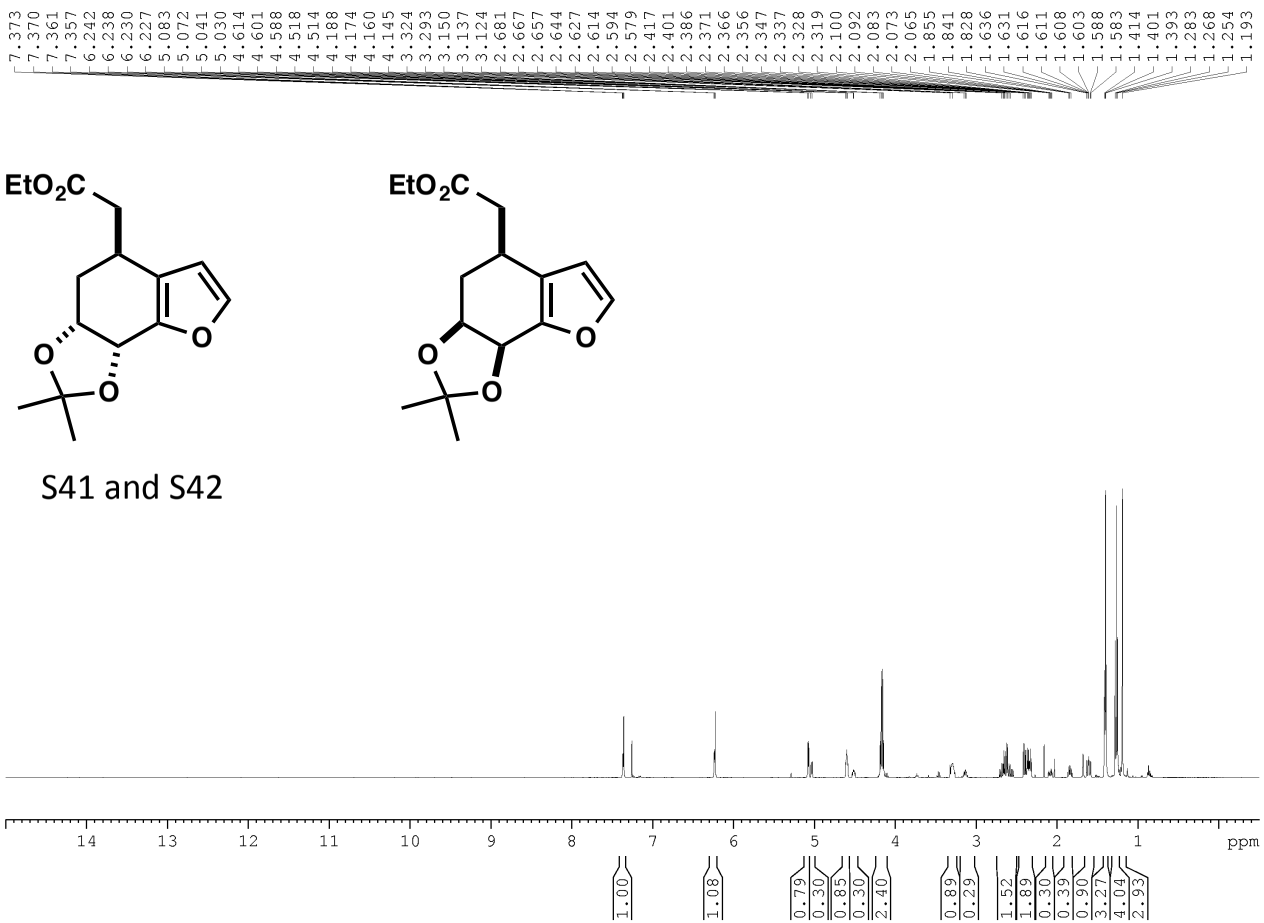

-171.05
-155.70
-145.31
128.79
127.75
126.97
124.68
112.68
111.48
77.31 CDCl3
76.67 CDCl3
52.41
52.27
-38.82
MeO2C
O
O
OMe
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

S38


EtO2C
HO
OH
O
EtO2C
HO
OH
O
S39 and S40
0.09
1.00
0.09
1.00
0.98
0.09
3.10
0.27
0.18
0.73
1.13
0.54
0.51
0.78
1.06
0.77
0.35
1.03
3.60
δ (ppm)


172.23
149.32
148.82
143.70
143.39
123.34
122.56
109.22
108.50
77.32 CDCl
77.00 CDCl
76.68 CDCl
69.59
67.28
64.41
63.67
60.61
39.97
39.66
38.57
37.27
32.90
32.81
28.47
27.17
14.18
EtO2C
HO
OH
O
EtO2C
HO
OH
O
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

S39 and S40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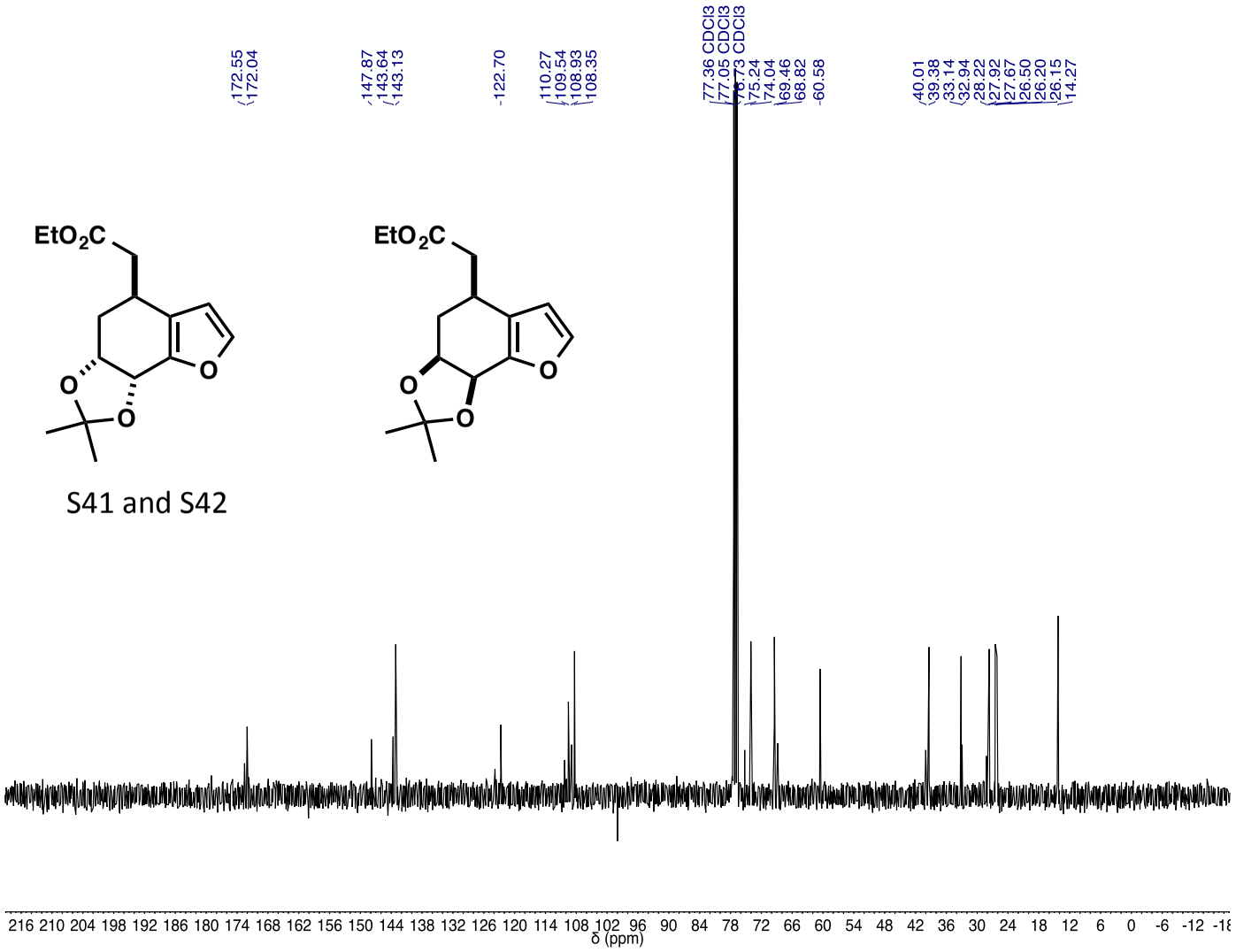
7.370
7.361
7.357
6.242
6.238
6.230
6.227
5.083
5.072
5.041
5.030
4.614
4.601
4.588
4.518
4.514
4.188
4.174
4.160
4.145
3.324
3.293
3.150
3.137
3.124
2.681
2.667
2.657
2.644
2.627
2.614
2.594
2.579
2.417
2.401
2.386
2.371
2.366
2.356
2.347
2.337
2.328
2.319
2.100
2.092
2.083
2.073
2.065
1.855
1.841
1.828
1.636
1.631
1.616
1.611
1.608
1.603
1.588
1.583
1.414
1.401
1.393
1.283
1.268
1.254
1.193
EtO2C
O
O
O
O
EtO2C
O
O
O
O
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.08
0.79
0.30
0.85
0.30
2.40
0.89
0.29
1.52
1.89
0.30
0.39
0.90
3.27
4.04
2.93

S41 and S42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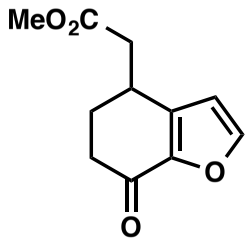
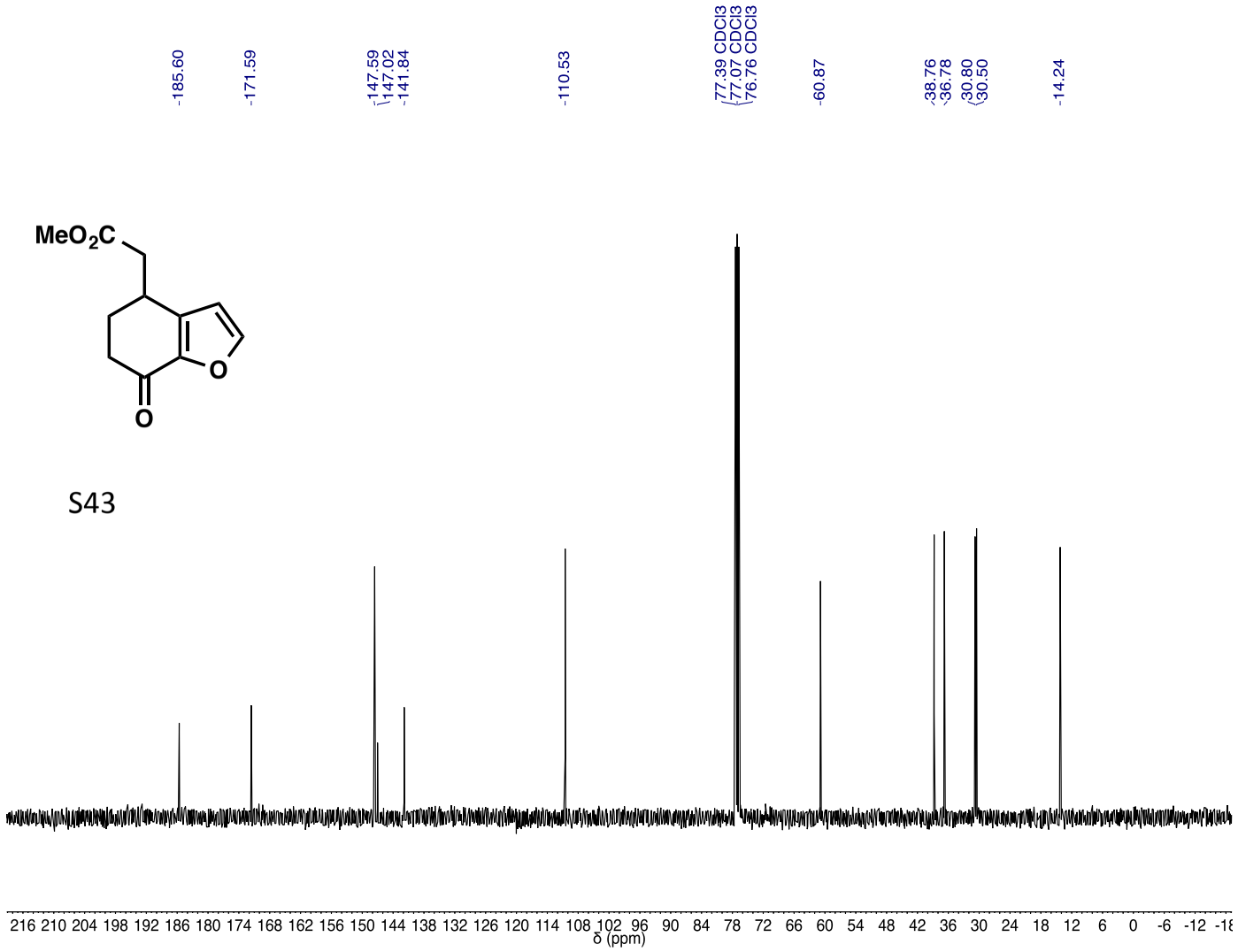
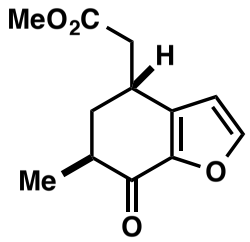
172.04
147.87
143.64
143.13
122.70
110.27
109.54
108.93
108.35
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
75.24
74.04
69.46
68.82
60.58
40.01
39.38
33.14
32.94
28.22
27.92
27.67
26.50
26.20
26.15
14.27
EtO2C
O
O
O
EtO2C
O
O
O
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S41 and S42



S43

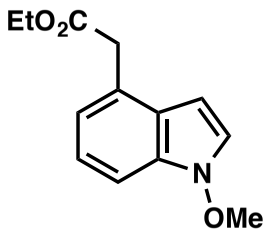

-185.60
-171.59
-147.59
-147.02
-141.84
-110.53
77.39 CDCl3
77.07 CDCl3
76.76 CDCl3
-60.87
-38.76
-36.78
-30.80
-30.50
-14.24
MeO2C
O
O
S43
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)


MeO2C
H
Me
O
O

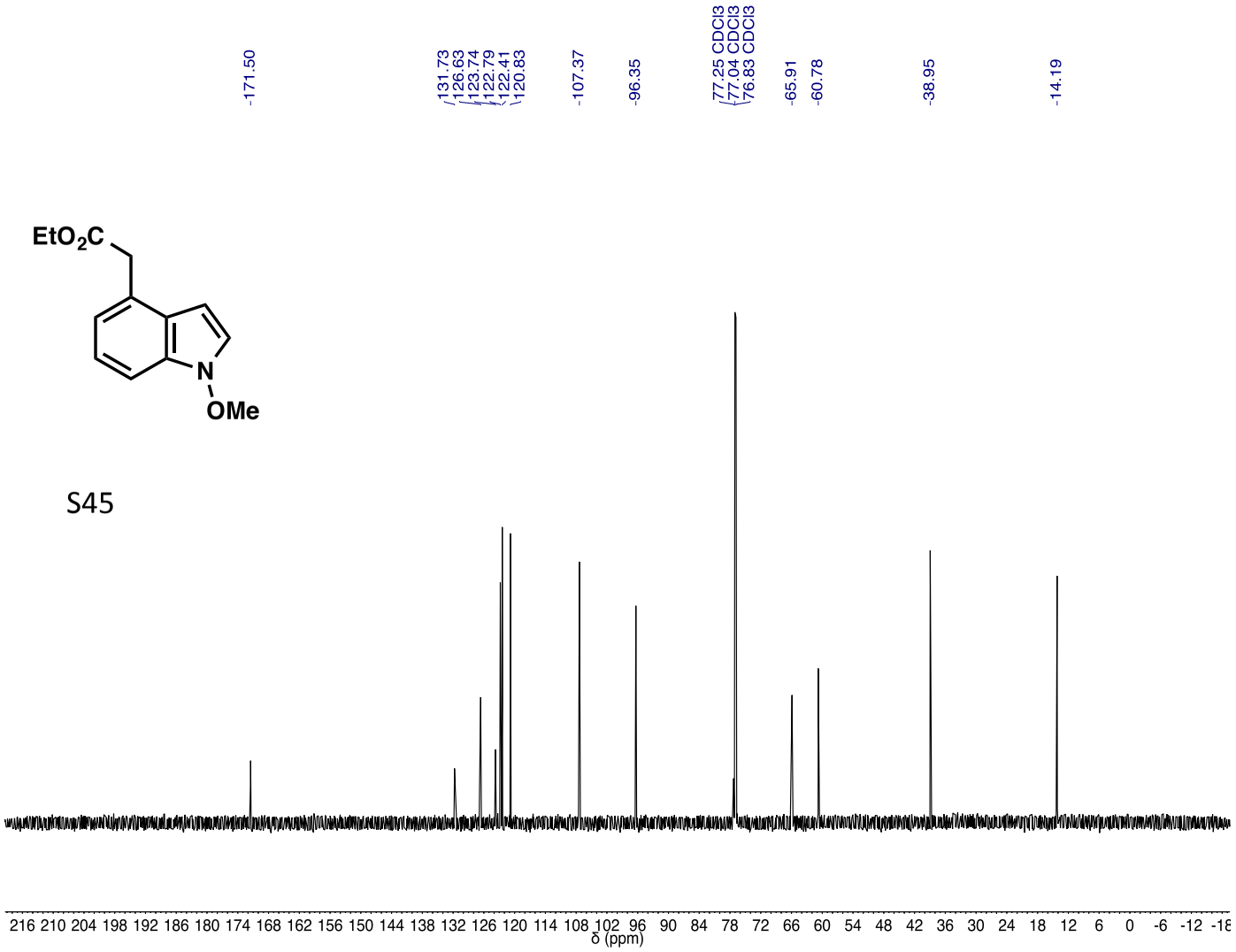
S44

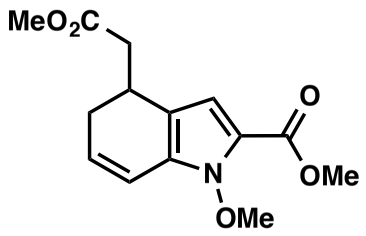
0.96
0.94
2.00
0.92
1.72
0.72
0.72
1.02
6.26
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)

191.11
188.60
171.68
171.64
147.86
147.65
146.45
145.94
140.84
139.92
110.77
109.93
99.92
77.25 CDCl3
77.21
76.99 CDCl3
76.96
76.74 CDCl3
60.79
60.76
45.16
43.05
39.14
39.04
38.63
37.45
37.41
28.27
27.95
24.57
24.03
15.23
14.16
MeO2C
H
O
O
Me
S44
δ (ppm)



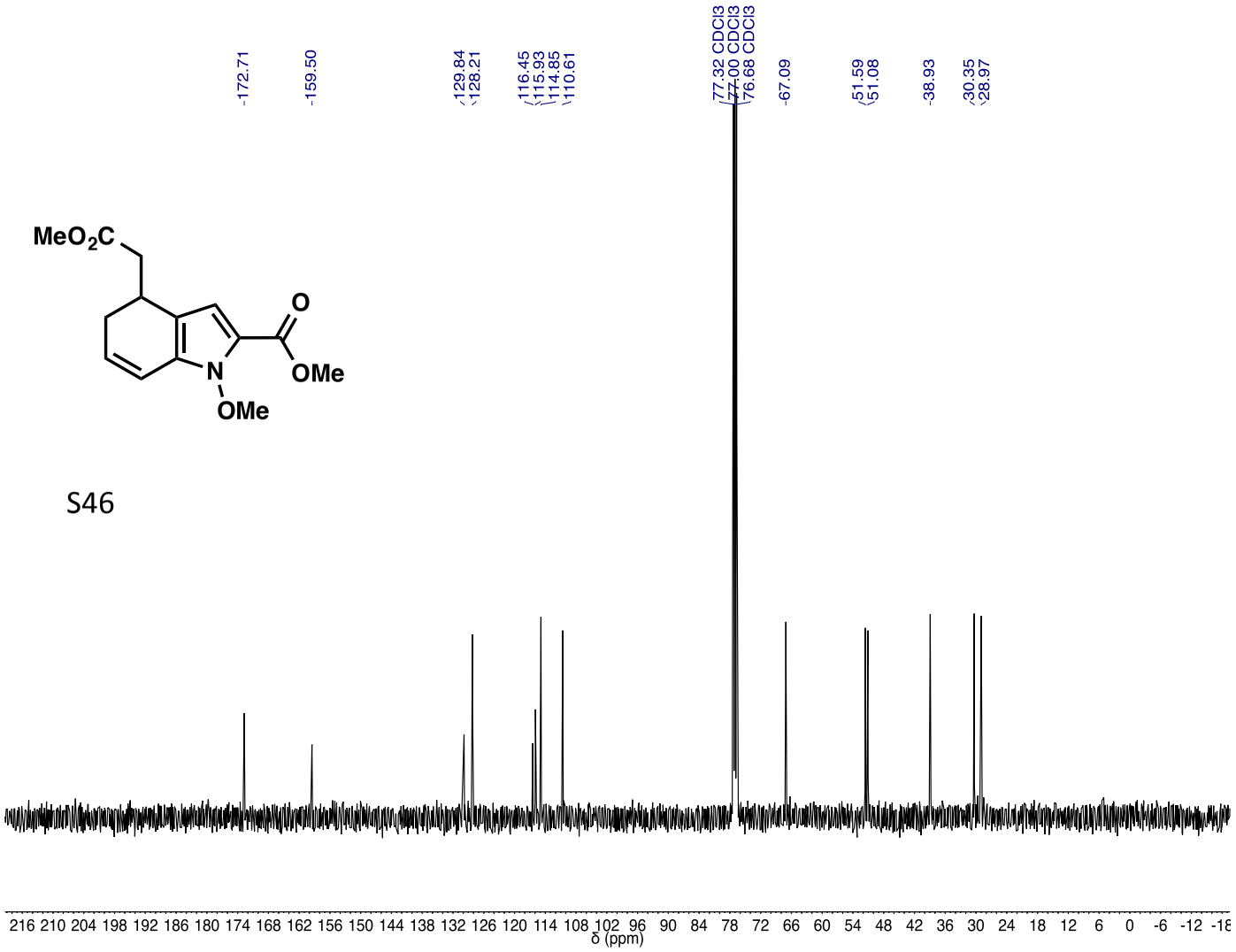
S45

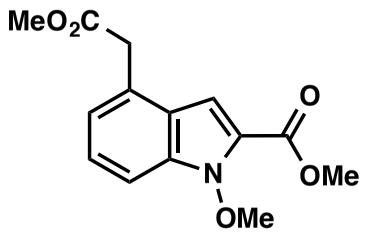

-171.50
131.73
126.63
123.74
122.79
122.41
120.83
-107.37
-96.35
77.25 CDCl3
77.04 CDCl3
76.83 CDCl3
-65.91
-60.78
-38.95
-14.19
EtO2C
N
OMe
S45
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


MeO2C
O
OMe
N
OMe

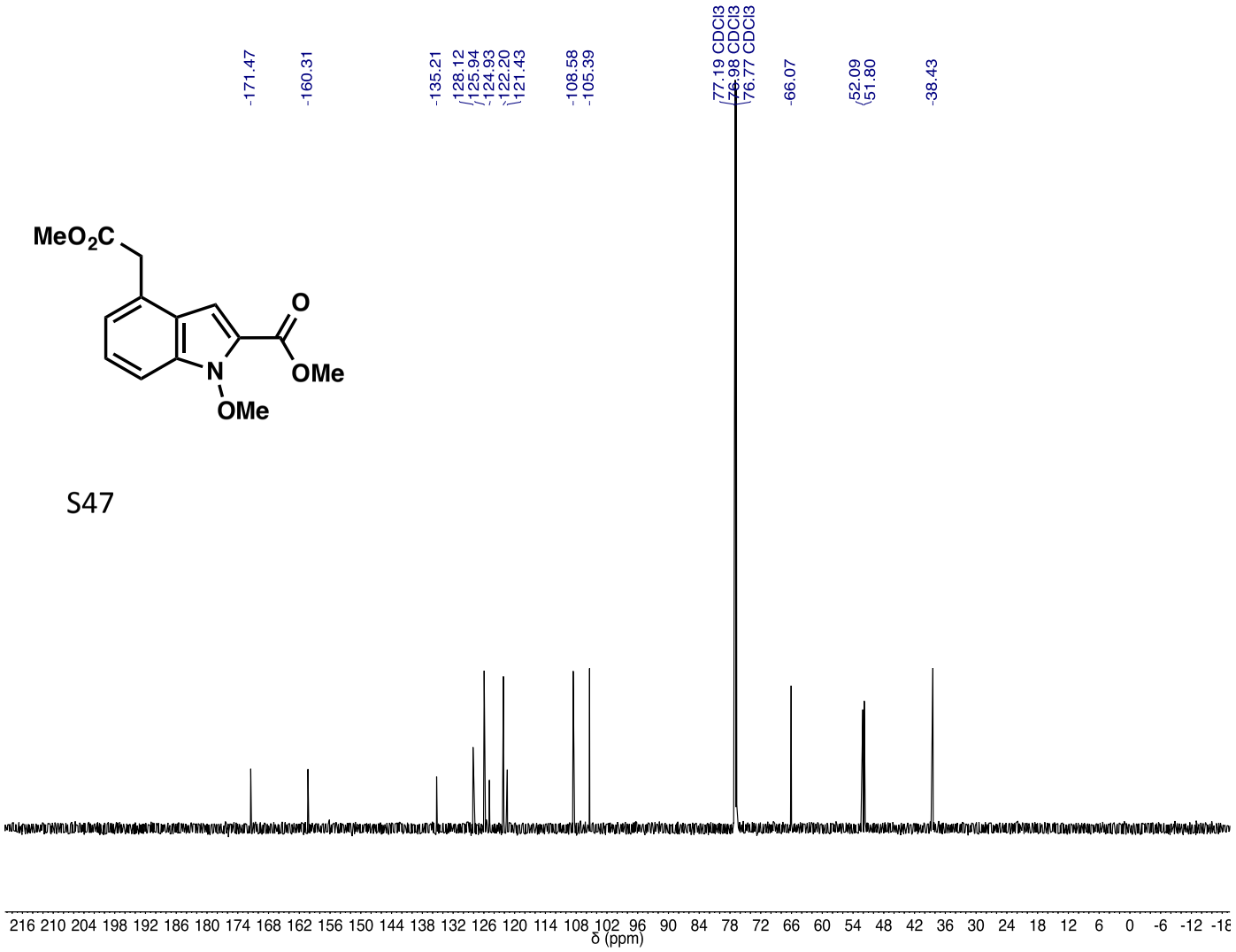
S46

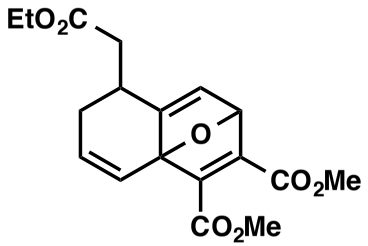
1.00
0.98
0.97
3.02
3.24
3.17
1.11
2.05
1.11
1.10
0.99
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)


-172.71
-159.50
129.84
128.21
116.45
115.93
114.85
110.61
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
-67.09
51.59
51.08
-38.93
30.35
28.97
MeO2C
O
OMe
N
OMe
S46
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)



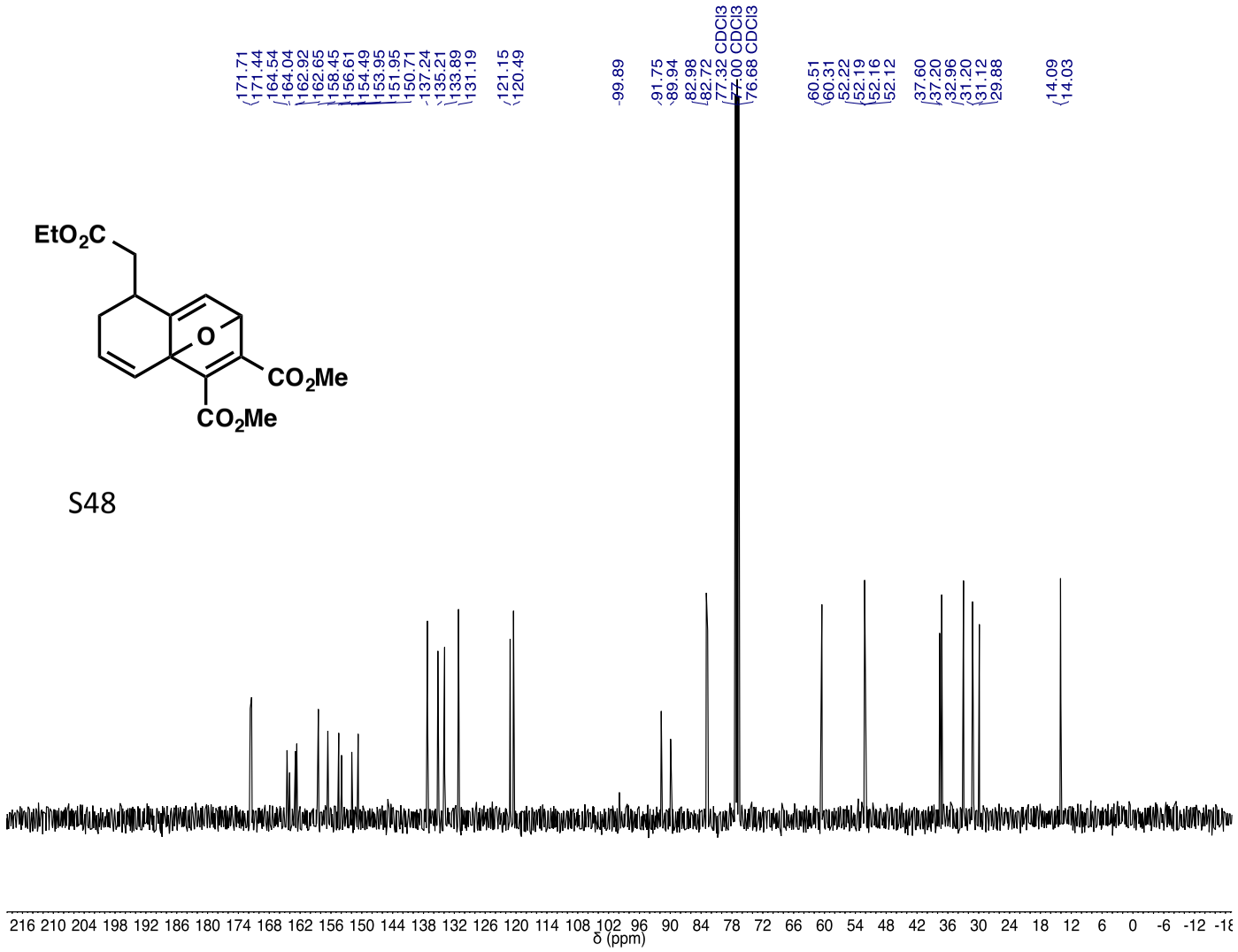
S47

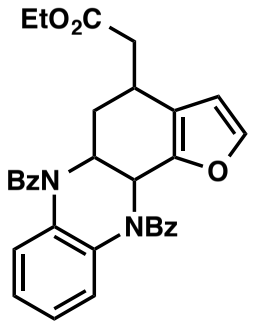

-171.47
-160.31
-135.21
128.12
125.94
124.93
122.20
121.43
-108.58
-105.39
77.19 CDCl3
76.98 CDCl3
76.77 CDCl3
-66.07
52.09
51.80
-38.43
MeO2C
O
OMe
N
OMe
S47
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


EtO2C
O
CO2Me
CO2Me

S48

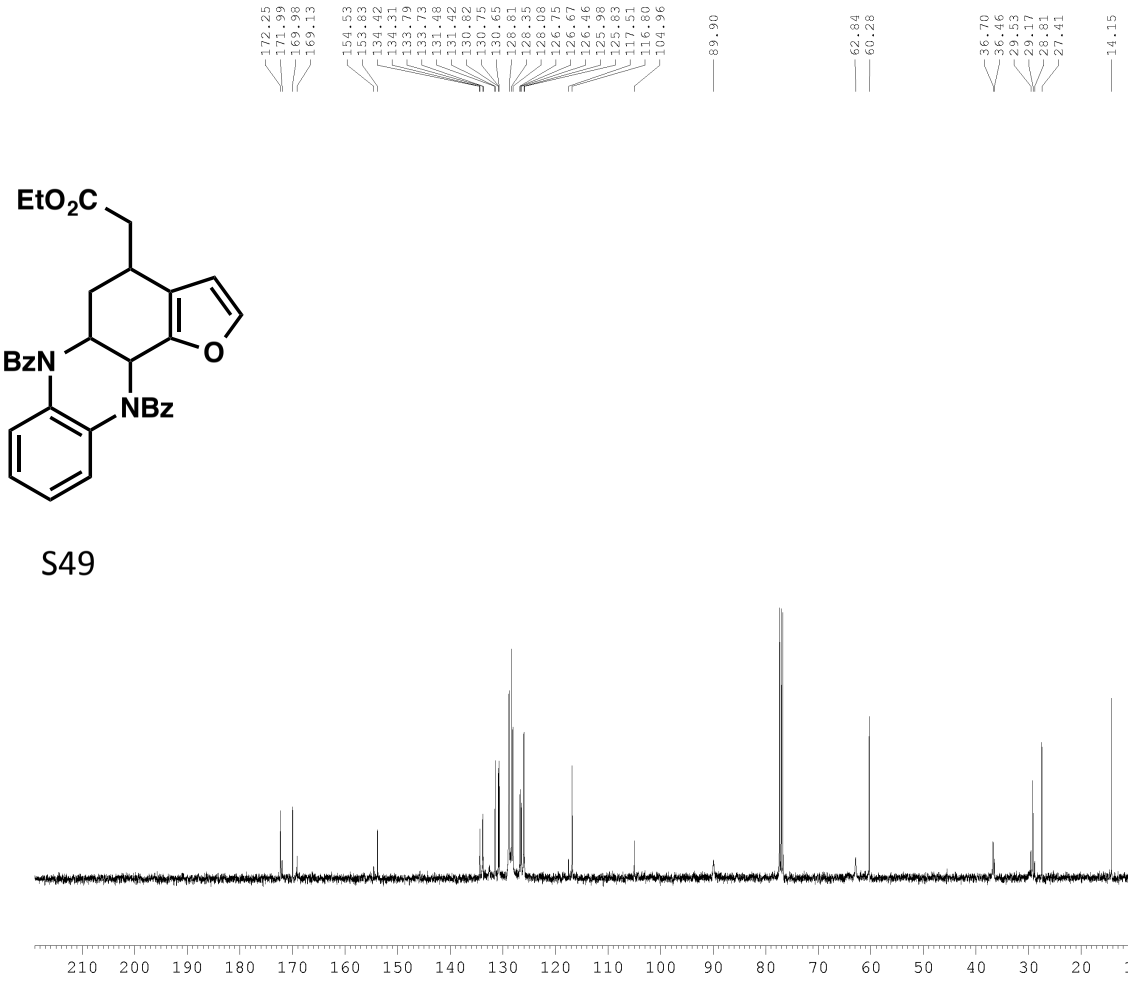
1.00
1.21
2.28
2.22
1.18
0.96
4.65
14.00
1.02
1.23
2.80
1.71
2.50
1.13
1.31
7.72
δ (ppm)


171.71
171.44
164.54
164.04
162.92
162.65
158.45
156.61
154.49
153.95
151.95
150.71
137.24
135.21
133.89
131.19
121.15
120.49
99.89
91.75
89.94
82.98
82.72
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
60.51
60.31
52.22
52.19
52.16
52.12
37.60
37.20
32.96
31.20
31.12
29.88
14.09
14.03
EtO2C
O
CO2Me
CO2Me
S48
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

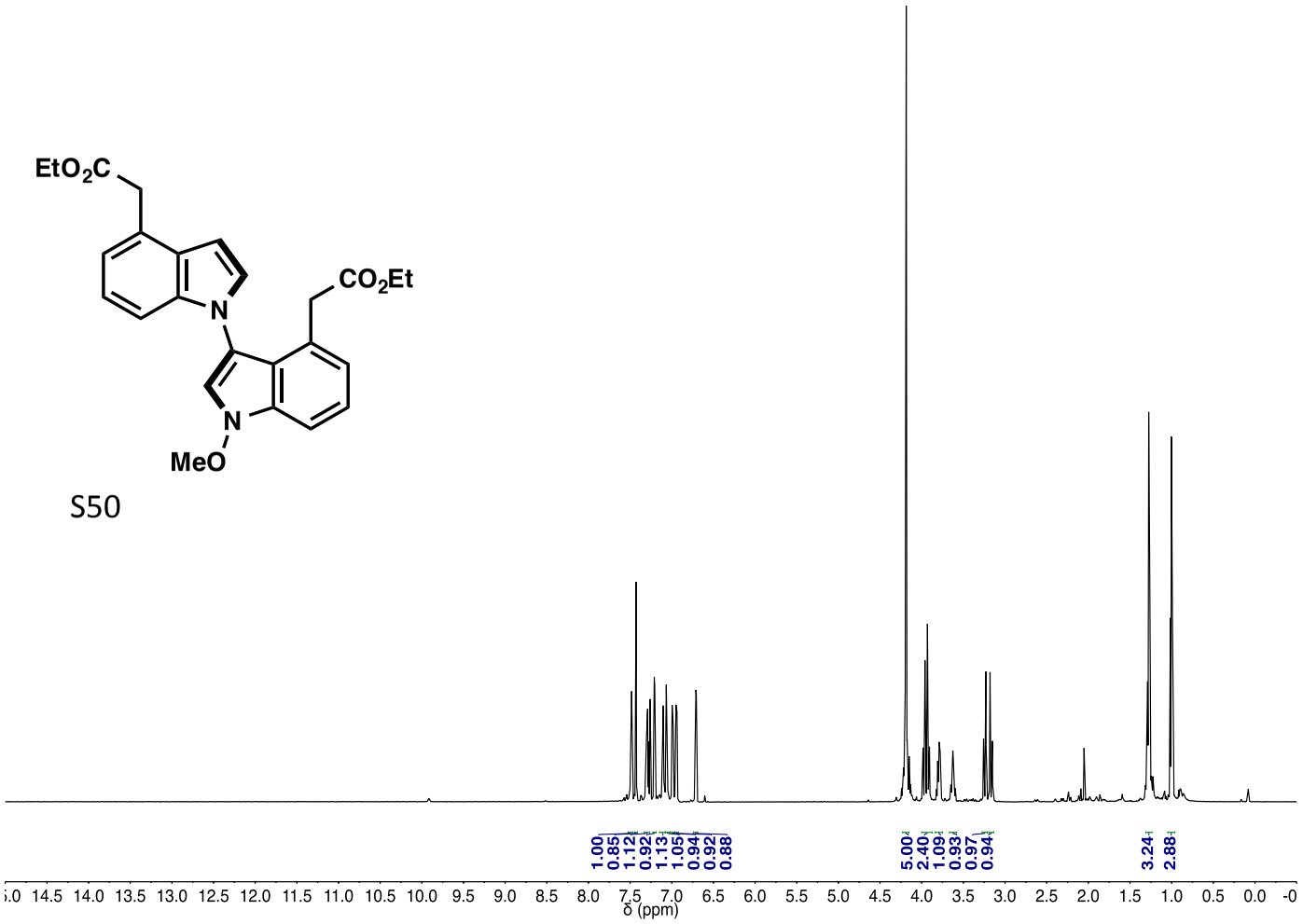

EtO2C
BzN
NBz
O

S49

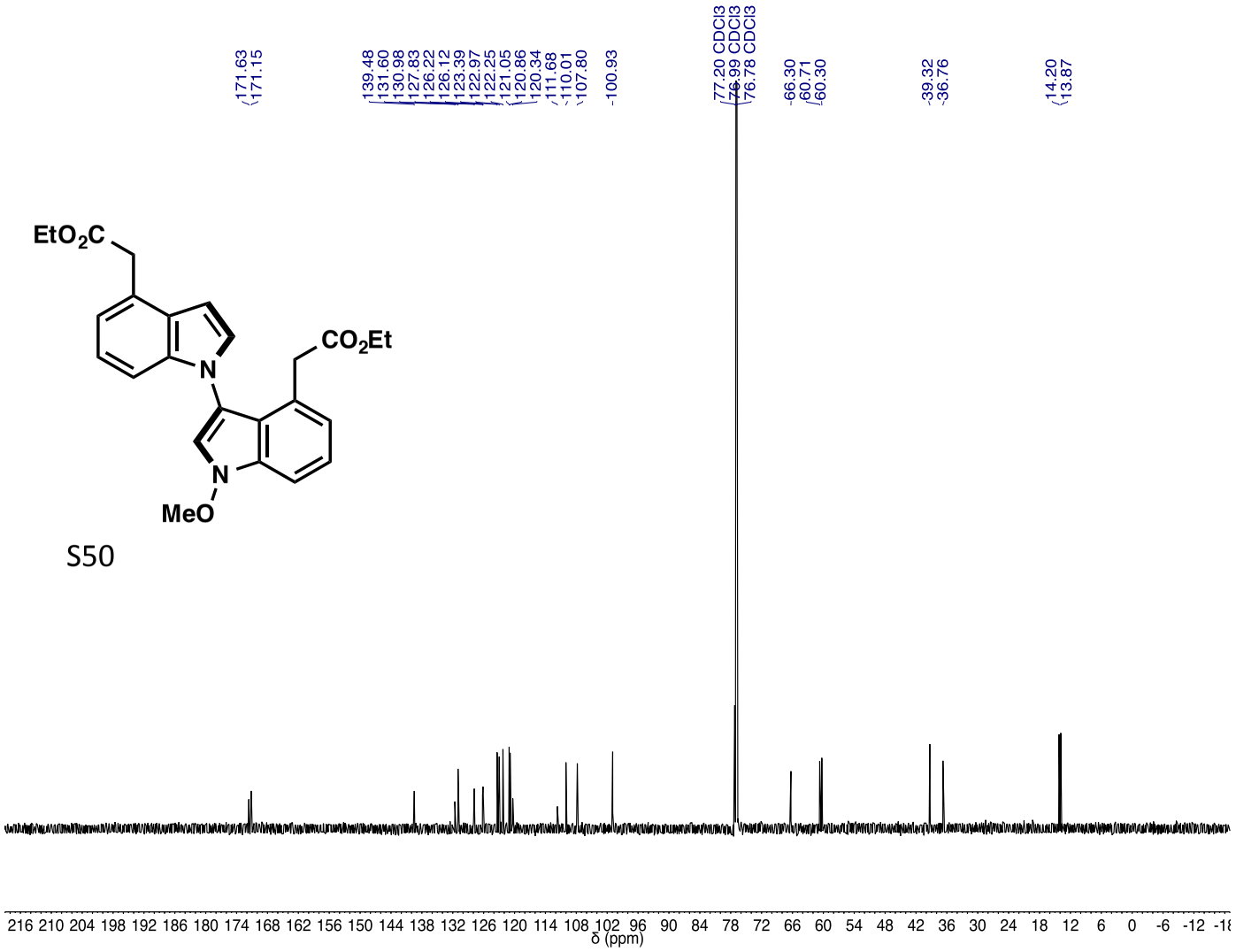
2.00
2.18
7.16
0.64
1.43
0.77
1.05
0.90
2.18
1.64
0.92
1.91
3.47
δ (ppm)


172.25
171.99
169.98
169.13
154.53
153.83
134.42
134.31
133.79
133.73
131.48
131.42
130.82
130.75
130.65
128.81
128.35
128.08
126.75
126.67
126.46
125.98
125.83
117.51
116.80
104.96
89.90
62.84
60.28
36.70
36.46
29.53
29.17
28.81
27.41
14.15
EtO2C
BzN
NBz
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

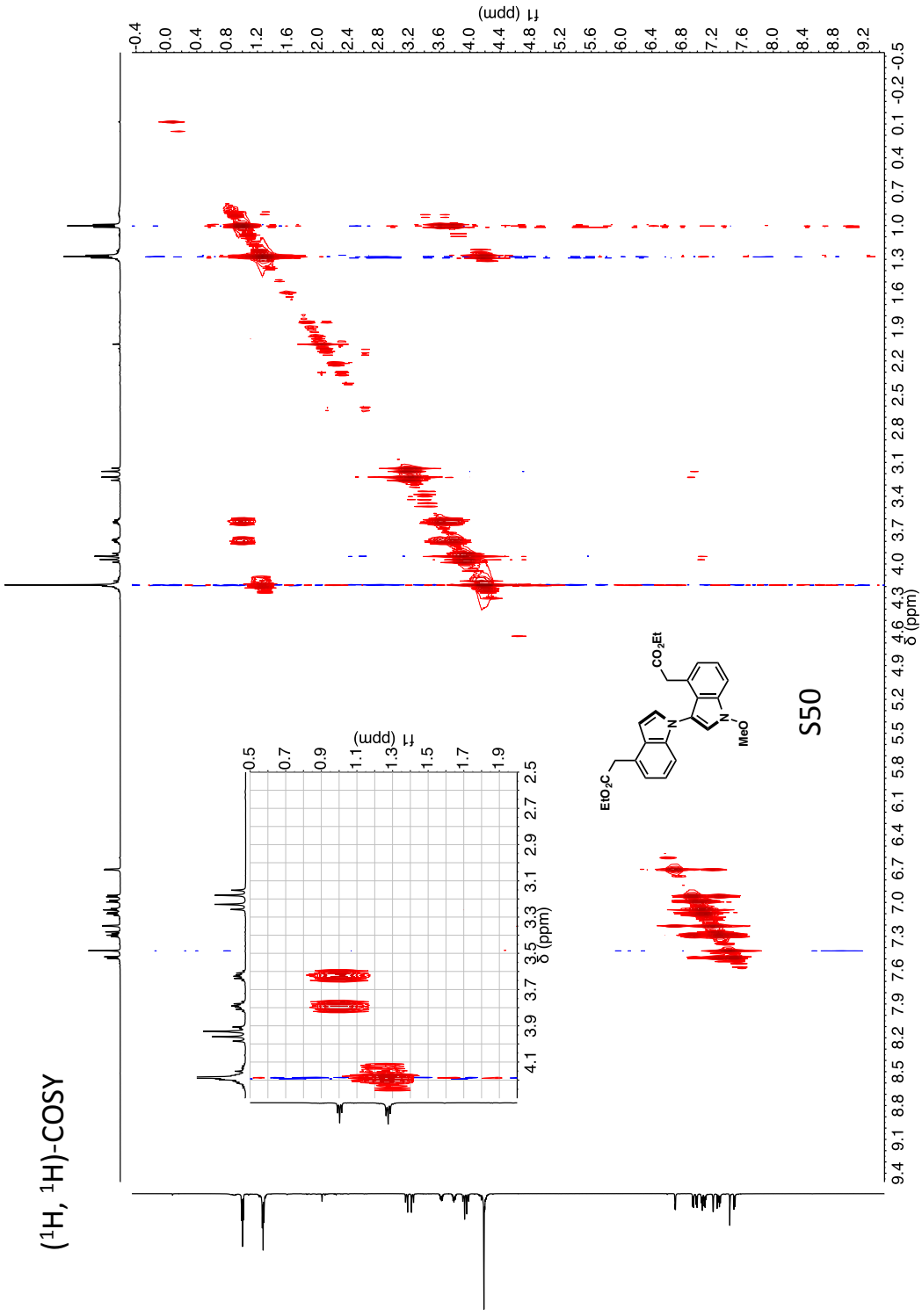
S49

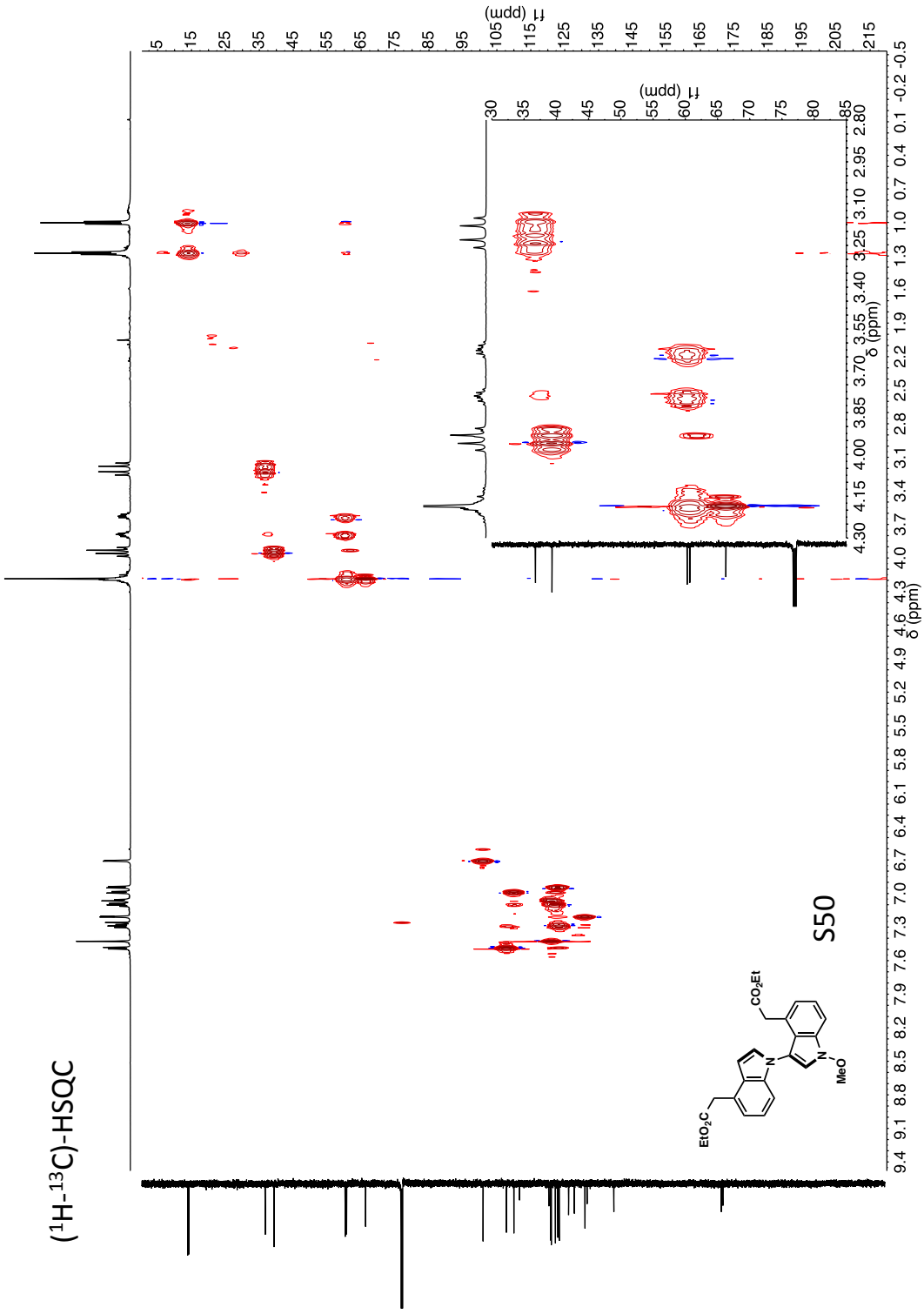

EtO2C
CO2Et
N
N
MeO
1.00
0.85
1.12
0.92
1.13
1.05
0.94
0.92
0.88
5.00
2.40
1.09
0.93
0.97
0.94
3.24
2.88
δ (ppm)

S50


171.63
171.15
139.48
131.60
130.98
127.83
126.22
126.12
123.39
122.97
122.25
121.05
120.86
120.34
111.68
110.01
107.80
100.93
77.20 CDCl3
76.99 CDCl3
76.78 CDCl3
66.30
60.71
60.30
39.32
36.76
14.20
13.87
EtO2C
CO2Et
N
N
MeO
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

S50


(¹H, ¹H)-COSY
δ (ppm)
f1 (ppm)
S50
CO2Et
EtO2C
MeO
N
N


(¹H-¹³C)-HSQC
S50
CO2Et
EtO2C
MeO
δ (ppm)
f1 (ppm)

CHAPTER 2: TRACE COPPER-CATALYZED CYCLOISOMERIZATION REACTION OF ALKYNYLCYCLOPROPYLHYDRAZONES TO FORM ANNULATED AMINOPYRROLES- A COLLABORATIVE STUDY

(with Dr. Ethan Fisher, Prof. Jason Hein, Prof. Dean Tantillo, Diana Yu, and Phil Painter)

Section 2.0. Criticism of metal-free transformations

High turnover catalysis (HTC), defined as catalysis using transition metal complexes at 0.1 mol% or lower loading leading to quantitative conversion of starting materials, has surfaced in recent years as a extremely powerful and environmentally benign type of transition metal catalysis.[1] As one would anticipate, the set of ligands on the metal often dictates whether the metal complex can reach high turnover numbers (TON). Classic studies by the Buchwald group, for example showed that Suzuki couplings of arylhalides could be achieved with palladium catalyst loadings as low as 0.02 – 0.05 mol% when used in conjunction with the now famous (biaryl)dialkyl phosphine ligands that bear his name.[1] Other contributions to ligand design using similar concepts in this field include work by Fu,[2] Hartwig[3] and others[4] who used the sterically demanding phosphine ligands tri-*tert*-butylphosphine and Q-Phos, respectively, for HTC based transformations.

Even with these beneficial contributions, HTC has also beset researchers when trying to develop mechanistic understanding of "transition metal-free" reactions, as these systems may contain very low catalyst loadings and proceed with very high TON. "Transition metal-free" Suzuki cross couplings in water performed by Leadbeater and Marco for example were shown to be catalyzed by trace palladium impurities found in the sodium carbonate used for the reaction.[5a] Though not claimed to be metal-free, classic amination reactions by Carsten Bolm that were thought to be mediated by iron salts, were shown to be in fact catalyzed by trace copper impurities at the parts-per-million level.[5b] Recently potassium *tert*-butoxide catalyzed reactions[5c] have also been question[5d] through the lenses of HTC (*i*.e., are these reactions really catalyzed by potassium *tert*-butoxide or by trace iron salts?). These studies attest to the significant challenge of identifying the true active catalyst in cross-coupling reactions and serve as a starting point for developing a mechanistic understanding metal-free processes.

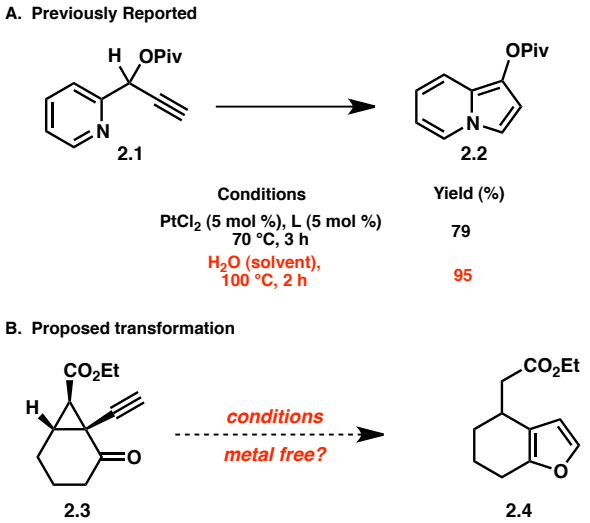
Detailed mechanistic studies of metal-free cycloisomerization reactions have not been performed in the context of HTC catalysis, and so the possibility of trace levels of transition metals facilitating this class of reactions cannot be excluded.

Section 2.1. Development of a Variant of the Schmalz-Zhang Chemistry

Over the last decade, transition metal-catalyzed cycloisomerization reactions involving alkyne substrates that rely on the use of 'soft' π-Lewis acid catalysts have emerged.[6-9] These reactions constitute some of the most powerful complexity building transformations in organic synthesis because, in the ideal scenario, all of the starting material is converted to the product without the formation of byproducts.[10] The underlying tenet for the success of π-Lewis acid metal salts as catalysts in these

reactions is that highly favorable interactions between the alkyne group and metal center serve to initiate the cycloisomerization process. For many of these reactions, substantial rate accelerations are observed compared to the uncatalyzed process, and the course of the reaction is heavily influenced by the choice of metal or ligands on the active catalyst complex.

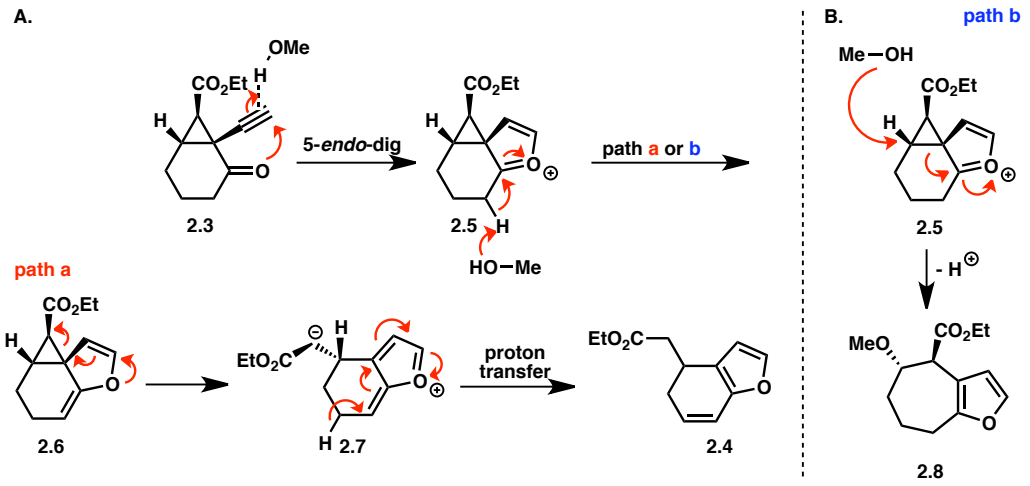
The Sarpong[11] laboratory and others[12] have reported heterocycloisomerization reactions that had been previously conducted using π-phillic transition metal catalysts or electrophilic nonmetal reagents,[13] which can now be effected using hydrogen-bonding networks.[14] For example, in the heterocycloisomerization reaction to form indolizine **2.2** (Scheme 1, A) from **2.1**, several transition metal salts and complexes based on Pt, Cu or Ag had been reported to facilitate this heterocyclization. We have found that the transformation proceeds simply by heating in water (or MeOH) and, importantly, proceeds in an appreciably higher yield (compared to the $PtCl_2$-catalyzed example) (Scheme 1, A). In Chapter 1, the development of a novel cycloisomerization reaction of [4.1.0]-bicyclo-heptanones and their oxime ethers to access dihydro-benzofurans and indoles respectively was discussed. The transformation utilized $W(CO)_5$•THF as a catalyst to electrophilically activate the alkynes present in our starting material through the intermediacy of a metal-vinylidene. However the possibility occurred to us that we could render this reaction metal-free based on the above precedent (Scheme 1, B).



Scheme 1: Metal-free cycloisomerization of 2-pyridylproparglyic alcohol 2.1 and proposed extension of methodology to access alkynylcyclopropylketone 2.4

Our initial mechanistic hypothesis for the formation of furan **2.4** under metal free conditions is outlined below (Scheme 2). We theorized that upon heating ketone **2.3** in a polar protic solvent, such as methanol, we would effect a 5-*endo*-dig cyclization facilitated by the hydrogen bonding network of the solvent resulting in oxocarbenium ion **2.5** which would immediately be deprotonated by the solvent to give tricycle **2.6** (Scheme 2, A). Tricycle **2.6** contains a donor acceptor cyclopropane[15] and thus could undergo fragmentation under elevated temperatures to give zwitterionic intermediate **2.7**. A final proton transfer would restore aromaticity to the furan ring and gives dihydrobenzofuran **2.4**. Alternatively, we were cognizant of the possibility that

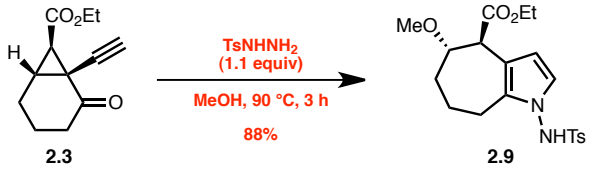
intermediate **2.5** could be trapped by methanol resulting in the ring expanded product **2.8** as originally reported by Schmalz and coworkers (Scheme 2, B).[16]



Scheme 2: a) Hypothesized mechanism for meta-free conversion of ketone 2.3 to furan 2.4. b) Potential side reactivity to afford ring expanded product.

To test this theory, we heated ketone **2.3** in methanol up to 60 ºC but did not observe any of the cycloisomerization products. Instead quantitative conversion of ketone **2.3** to the to the methyl ester was observed. Repeating this reaction in ethanol up to 100 ºC we observed no conversion of ketone **2.3** to furan **2.4**. Interestingly, when ketone **2.3** was heated in the presence of *p*-toluenesulfonyl hydrazide (PTSH) in methanol at 90 ºC for three hours, we detected the formation of annulated aminopyrrole **2.9** and were able to isolate this product in 88% yield. This remarkable transformation appeared to be a metal-free variant of the Schmalz-Zhang reaction.[16] However, further investigations to try and optimize the reaction (Table 1), demonstrated that the newly discovered transformation was very specific to the initial conditions. For example, a screen of other polar protic solvents such as ethanol, isopropanol, and allyl alcohol all returned starting material. Other hydrazines such as Me_2NHNH_2, $BnNHNH_2$, $AcNHNH_2$ and $PhthNHNH_2$ were also ineffective for the cycloisomerization reaction and resulted in the recovery of ketone **2.3**. These data were the first pieces of evidence that the mechanism for the conversion of ketone **2.3** to aminopyrrole **2.9** was not as direct as originally thought, specifically because these observations suggest that tosylhydrazide is important for the reaction, and that the rate of formation of a hydrazone intermediate is much faster than the rate of cyclization of ketone **2.3**.

Table 1: Attempted solvent optimization and extension to other hydrazine reactants.



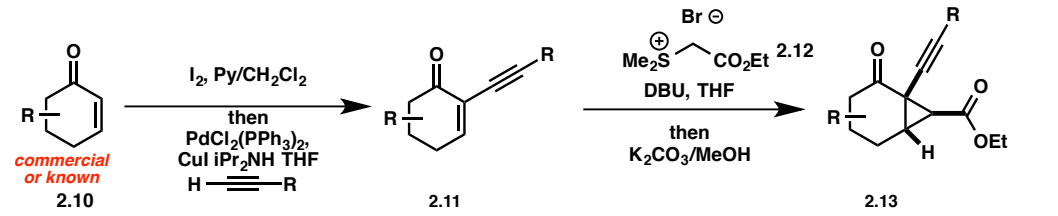
2.3 2.9

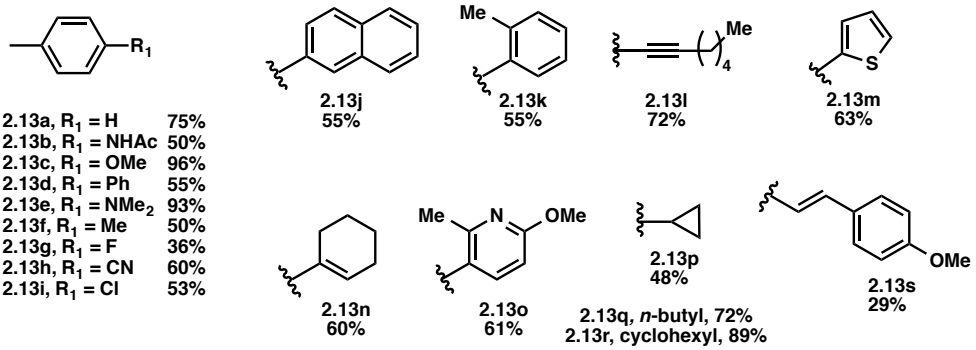
entry	change from original conditions	result
1	EtOH as solvent	complex mixture
2	allyl alcohol	no reaction
3	iPrOH as solvent	complex mixture
4	Me_2NHNH_2	recovered 2.3
5	$BnNHNH_2$	recovered 2.3
6	$AcNHNH_2$	recovered 2.3
7	$BocNHNH_2$	recovered 2.3

Section 2.2. Substrate scope

Undeterred by the above results, we then explored the scope of the newly discovered cycloisomerization reaction. Specifically, using the synthetic strategy outlined in Chapter 1, we were able to rapidly construct a myriad of ketone substrates with substitution on the alkyne. In contrast to the cycloisomerization reaction reported for Chapter 1, the transformation of compound **2.3** to **2.9** does not involve the intermediacy of a metal vinylidene. Consequently, internal alkynes are viable substrates for this reaction and provided a platform for studying electronic effects on reactions yield, diasteroselectivity, and reaction rate (Table 2).

Table 2: Ketones synthesized for metal free cycloisomerization study. Note: Yields given from the cyclopropanation reaction.

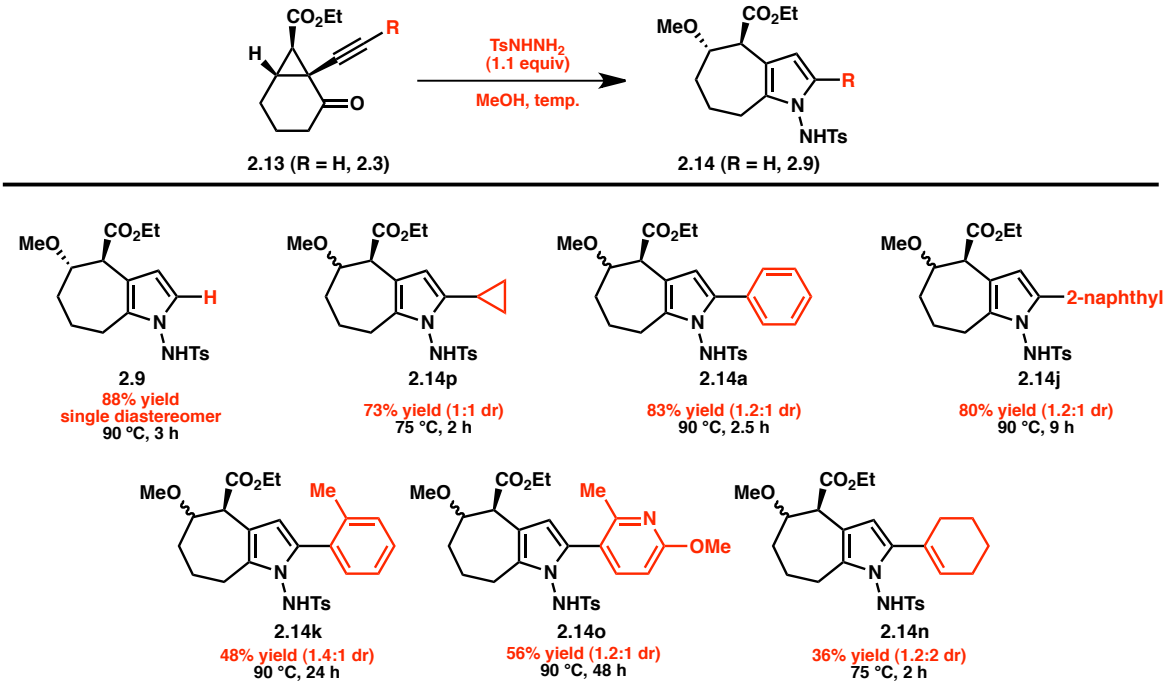




With ketones **2.13a** – **2.13s** in hand we then subjected these substrates to the optimized reaction conditions (90 ºC in MeOH for 3 hours) and found that some of these ketones

were converted into their requisite aminopyrrole products (Table 3). Of note, when several of these ketones were exposed to the optimal reaction conditions for ketone **2.3**, complex mixtures resulted. Thus, some of the ketone substrates were required lower temperatures and times to obtain clean product. From this study several trends became apparent.

Table 3: Scope for the newly discovered heterocycloisomerization reaction.



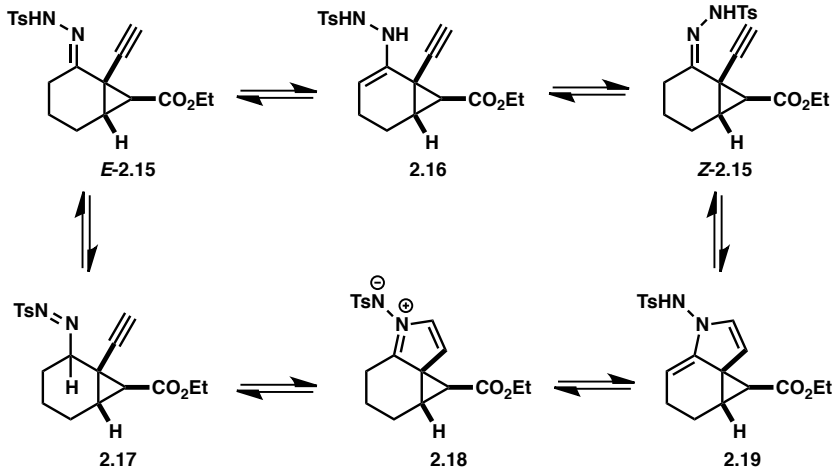
The key difference between the reactivity observed in the terminal alkyne case and the internal alkyne cases is that in the latter, mixtures of diastereomeric products are observed. A cyclopropyl substituent on the alkyne led to the formation of **2.14p** in 73% yield. Importantly, this reaction proceeded at 75 °C as compared to the 90 °C required for terminal alkyne substrate **2.9**. Aryl substitution on the alkyne unit is readily tolerated as evidenced by the formation of products **2.14a**, **2.14j**, **2.14k**. Of note, increasing sterics by *ortho*- substitution on the aryl group (see **2.14k**) leads to a lower yield of the desired product. A cyclohexenyl substituent yielded the corresponding vinyl aminopyrrole product (**2.14n**) in 36% yield. Vinyl pyrroles are known to readily decompose under acidic and aerobic conditions which likely accounts for the low isolated yield of **2.14n**.[17] Perhaps most significantly, none of the desired product was observed for substrates possessing alkyl substitution on the alkyne group (except for compound **2.14p**). In these cases (e.g., R = n-Bu, **2.13q** or cyclohexyl, **2.13r**), none of the desired product was observed and only non-specific decomposition occurred upon prolonged heating. Thus, it would appear that a careful balance of stereoelectronics is important for these transformations. Furthermore the reaction only appears to work for alkynes bearing electron rich R groups (with the exception of substrate **2.9**).

Mechanistically, this suggested to us that the reaction proceeded through some type of cationic intermediate, although the nature of this intermediate is still not apparent to us.

Section 2.3. Mechanistic Investigations and Hypotheses

Section 2.3.1. Computational and deuterium labeling studies (in collaboration with Prof. Dean Tantillo and Phil Painter)

To understand the mechanism for the transformation of ketone **2.3** to aminyopyrrole **2.9** we began with computational studies; however, we quickly realized that myriad intermediates are potentially relevant to the transformation in Table 1. Specifically, after condensation of ketone **2.3** with *p*-toluenesulfonylhydrazide, there are at least six isomeric hydrazone intermediates (Scheme 3)[18] that could possibly be present in the reacting mixture (**2.15** – **2.19**). Furthermore, of these species, hydrazone **2.15**, enhydrazine **2.16**, and alkyldiazine **2.17** could all be viable species for the intramolecular 5-*endo*-dig cyclization. To help elucidate which of these intermediates were potentially viable for DFT analysis, we began with deuterium labeling studies (Figure 1).



Scheme 3: Potential isomers of hydrazone *E*-2.15 present in the reaction.

Upon treatment of ketone **2.3** with $TsNDND_2$ in CD_3OD, deuteration at C(3) (90% D) was observed along with the addition of the CD_3OD group (see Eq. 1, Figure 1) as anticipated. Deuteration at C(2) (97% D) and, surprisingly, at C(8) (99% D) was also observed. At low conversion (*c.a.* 20%), ^1H NMR analysis of the product displayed 88% deuterium incorporation at C(3) and only 42% D at C(2), which increased to 97% over 2 h. These observations support activation of the alkyne by an electrophilic reagent. Deuteration at C(8) however, cannot be explained by the mechanism illustrated in Figure 1, B especially if one considers Eq. 2 (deuterium incorporation at C8 does not occur after product formation). If the mechanism in Scheme 2 were operative (using hydrazone **2.15** instead of ketone **2.3**), deuterium exchange mostly likely would occur after a rate determining cyclization of **2.15** *via* ene-hydrazine **2.19**, which we expect to undergo an irreversible strain promoted fragmentation (analogous to **2.7** to **2.4**).

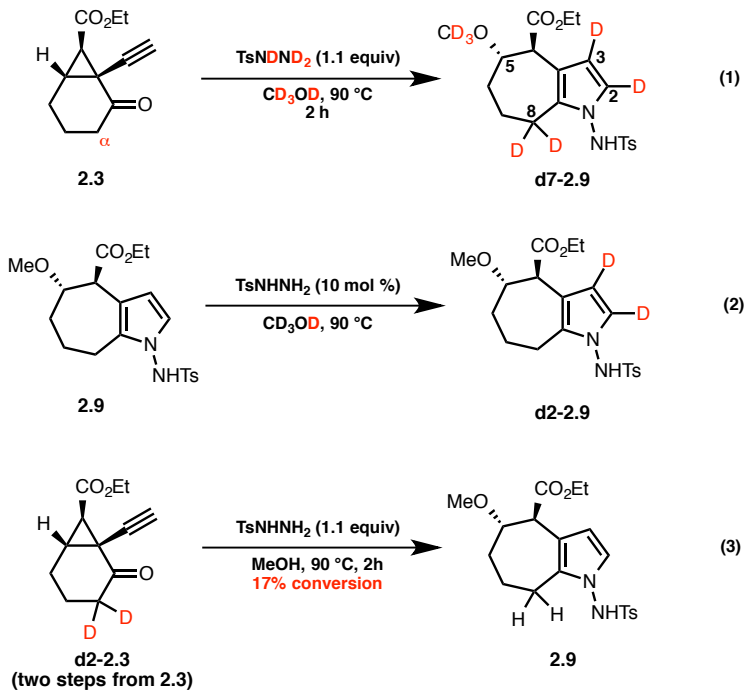
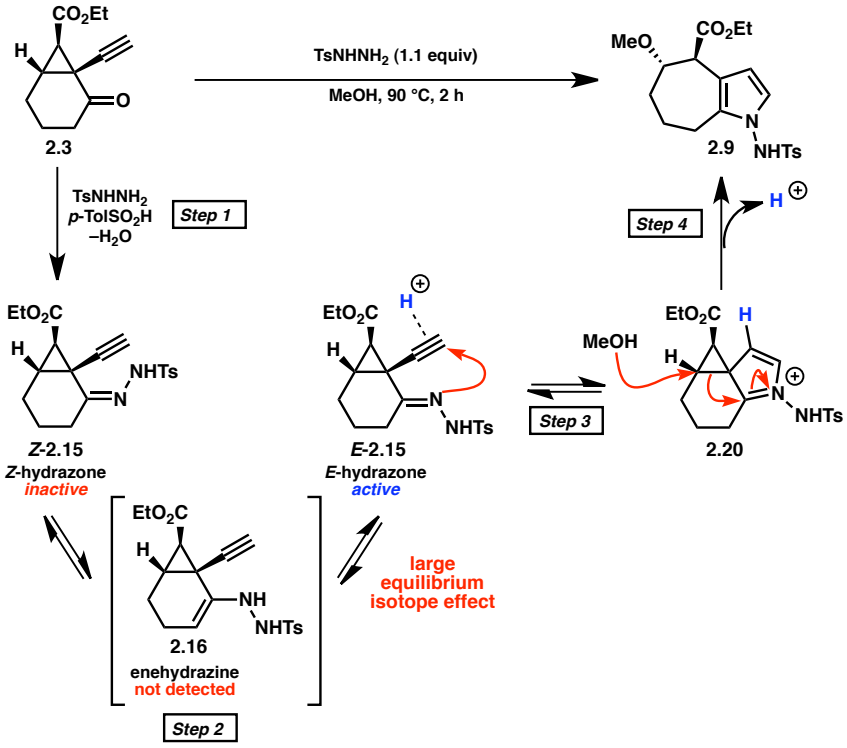


Figure 1: Deuterium labeling studies using ketone 2.3.

The likely explanation for this outcome is that deuteration at C(8) occurs prior to product formation. One possibility is that deuteration of the methylene position that eventually becomes C(8) occurs during the condensation of ketone **2.3** with the hydrazide to form the requisite hydrazone. The ease of exchange of the protons α- to the ketone group of **2.3** under the reaction conditions is convincingly supported by the complete loss of deuterium when **d_2-2.3** (Eq. 3) is subjected to the standard heterocycloisomerization conditions. These observations suggest that hydrazones ***E*-2.15** and ***Z*-2.15** are likely viable intermediates present during the reaction and that deuterium exchange may occur through protonation of enehydrazine **2.16**.[16f,g] Interestingly, we also noticed that the conversion of **d_2-2.3** proceeded very sluggishly, yielding only 17% conversion after 2 hours of heating. Logically, the transformation in Eq 3. suggested some type of primary kinetic isotope effect, however detailed kinetic studies (*vide infra*) measured this kinetic isotope effect to be 24, which was abnormally large and, more importantly, above the theoretical limit for KIE's that do not involve tunneling for proton transfers.[19] Thus, we ascertained there were other factors at play and hypothesized that the effect could possibly be explained by invoking a rate limiting pre-equilibrium of *Z*-hydrazone **2.15** to *E*-hydrazone **2.15** (*i.e.,* the *Z*-hydrazone is formed faster than the *E*-hydrazone and α–deprotonation of the *Z*-hydrazone is required to access the *E*-hydrazone which then undergoes the 5-*exo*-*dig* cyclization, Scheme 4).

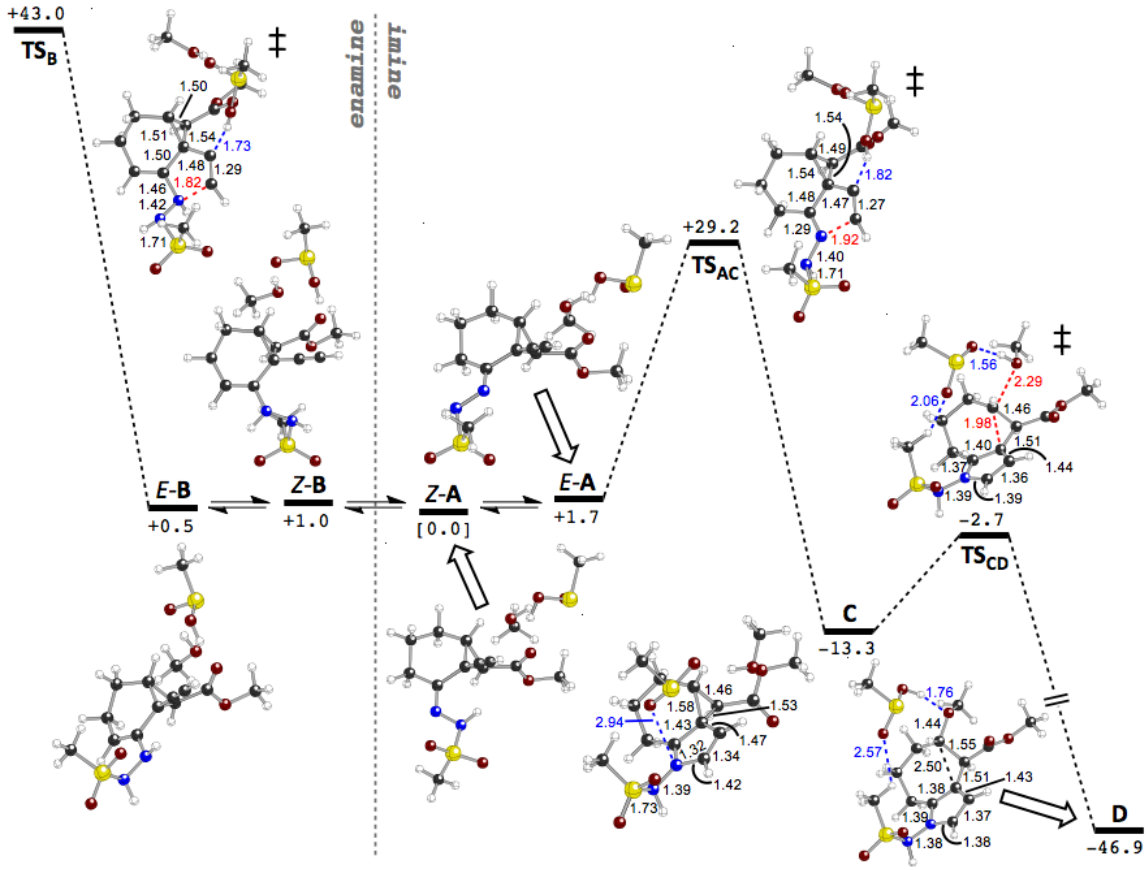


Scheme 4: Initially proposed mechanism for conversion of ketone 2.3 to pyrrole 2.9 invoking large rate-determining equilibrium isotope effect.

Our initial calculations were aimed at finding an energetically viable mechanism that was consistent with the observed isotope effect data. We employed a model system in which the tosyl and ethyl groups of the substrate were truncated to mesyl and methyl groups for computational efficiency, and explicit methanol and CH_3SO_2H molecules were included. The reaction was studied with the M06-2X/6-31+G(d,p) DFT method (20) implemented in GAUSSIAN09 (21), using the SMD continuum solvation model[22] in methanol at 365 K. Frequency analysis was used to assign stationary points as transition state structures or minima, and Intrinsic Reaction Coordinate (IRC) calculations[23] were utilized to connect transition state structures to their associated minima. Structural images were created using *Ball &* Stick.[24] Energies reported are gas phase Gibbs free energies (unless otherwise stated).

Consistent with the experimental results described above, our calculations indeed *predict that the Z-hydrazone (Scheme 5, Z-**A**) is lower in energy than the E-hydrazone (Figure 4, E-**A**)) by almost 2 kcal/mol.* Furthermore, direct interconversion of the two hydrazones through a linear C=N-NR bond is predicted to have a barrier of 27 kcal/mol. Ring closure from the *E*-hydrazone via transition state structure $\mathbf{TS_{AC}}$ is associated with a barrier (versus *Z*-hydrazone) of 29 kcal/mol. Subsequent capture by methanol (via $\mathbf{TS_{CD}}$) is predicted to be facile. These calculations suggest that the ring closure step is rate-determining, yet deuteration of the α-position in such a scenario would result in a secondary inverse isotope effect (supported by DFT predictions; see Supporting Information) (25), as opposed to the observed apparent primary effect. Enamine formation was also considered (Figure 4, left), but ring-closure from an enamine intermediate is predicted to have a prohibitively high barrier (>40 kcal/mol),

due in part to the poor nucleophilicity of the enamine nitrogen associated with loss of conjugation upon attack. These results left us at a loss for understanding the apparent kinetic isotope effect described in Eq. 3 and suggested yet another unanticipated factor was likely operative.

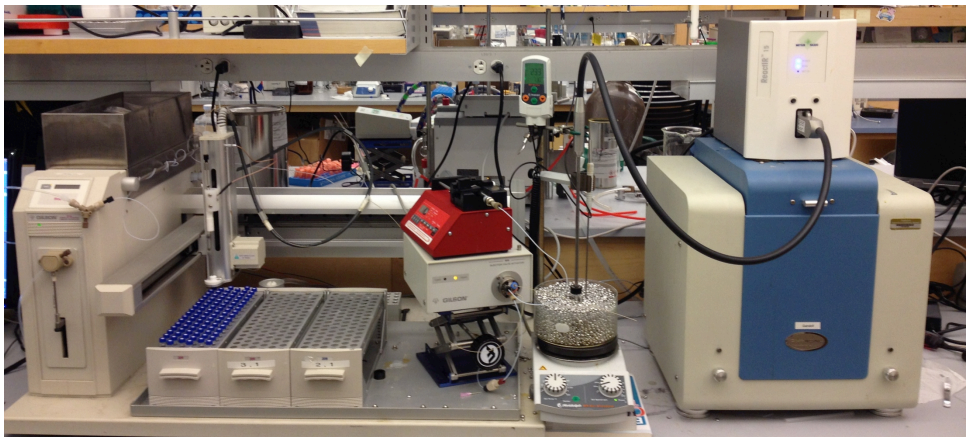


Scheme 5: Optimized structures (M06-2X/6-31+G(d,p)) for metal-free cyclization pathways. Relative free energies are shown in kcal/mol and selected distances are shown in Å.

Section 2.3.2. In situ mechanistic studies (in collaboration with Prof. Jason Hein and Diana Yu)

With the computational model for the reaction developed, we then sought to conclusively exclude the possibility that the large effect of α-deuteration using ketone **d_2-2.3** on the rate of the reaction was not due to a rate determining pre-equilibrium of hydrazone ***Z*-2.15** to ***E*-2.15** (Scheme 4). Furthermore, we sought to rule out the possibility that the sulfinic acid, generated from the thermal decomposition of *p*-$TsNHNH_2$,[26] was the active catalyst for this reaction. As such we turned to monitoring the reaction by React-IR and LCMS to rule out these possibilities. Monitoring this reaction (which proceeds above the boiling point of methanol) was not trivial and required the development of a new apparatus (see Figure 2, A).

A.



B.

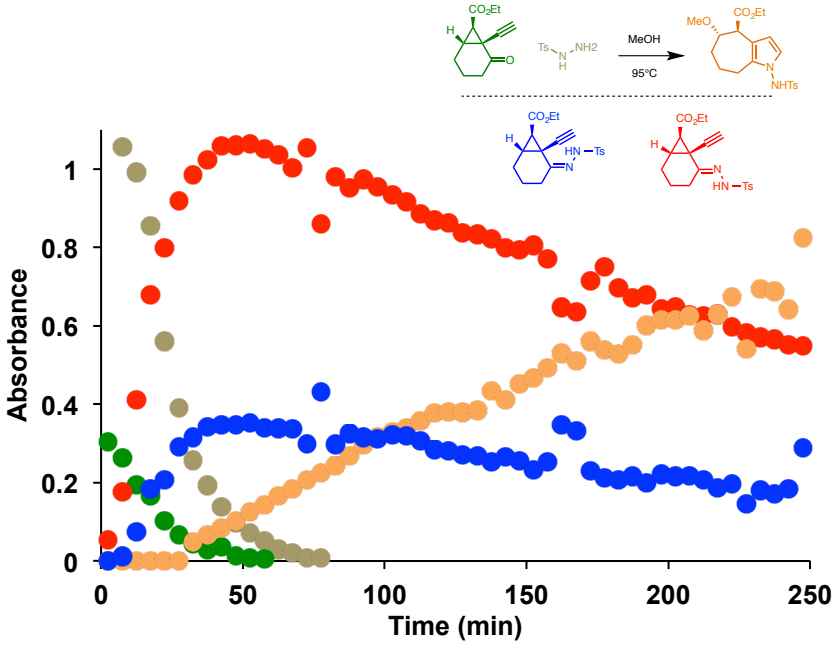


Figure 2: A) Flow chemistry apparatus for monitoring reaction progress. B) Kinetic profile for ketone 2.3 heterocycloisomerization reaction

Reaction progress analysis using the custom-built apparatus shown in Figure 2, A, (see Supporting Information for details) clearly confirms that the cycloisomerization reaction proceeds via first condensation to generate two isomeric hydrazones, which are consumed to give aminopyrrole **2.9** (Figure 2, B). The isomeric hydrazones are initially present in approximately a 3:1 ratio; however, the assignment of their geometry by ^{1}H NMR was complicated by lack of any characteristic nOE signal. Following an empirical relationship developed by Fuchs and coworkers, we used the difference in chemical shifts between the α-carbons of the hydrazone **2.15** and ketone **2.3** to determine the geometry about the imine C-N double bond.[27] In general, Fuchs *et. al.* found that carbons *syn-* to the imine "X" group on a hydrazone (or other imine derivative) are shifted to higher field compared to the same carbon on the keto-substrate (12 – 15 ppm). The carbons *anti-* to the imine "X" moiety only change by 3-6

ppm (Figure 3). Thus, for hydrazone **2.15**, we assigned the carbons of the compound based on ^{13}C DEPT 135 analysis and were able to ascertain that the geometry of the major hydrazone isomer in solution was indeed *syn*- to the alkyne group. This observation was very counterintuitive because it suggests that *the more sterically encumbered hydrazone is thermodynamically favored*. Notably, this was in agreement with the obtained computational results.

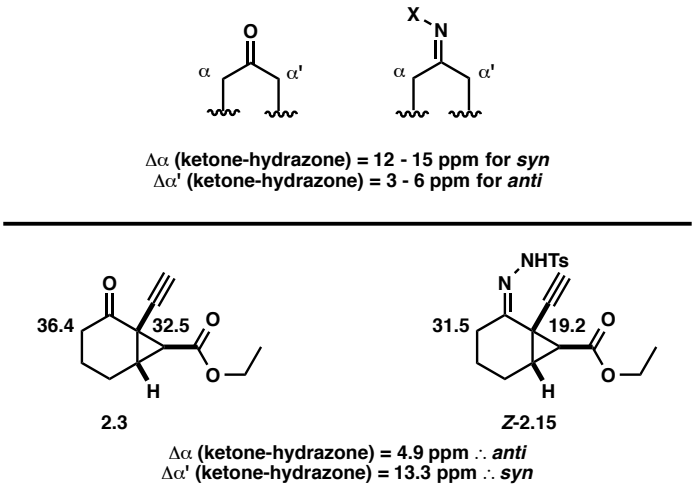


Figure 3: Application of the Fuchs relationship to determine hydrazone geometry in compound 2.15.

As an added measure of certainty, we were able to recrystallize *both Z*-hydrazone **2.15** (from methanol) and *E*-hydrazone **2.15** (from benzene) (Figure 4) thus giving us unambiguous characterization of these intermediates during the course of the reaction. Again contrary to initial intuition, *this result further demonstrates that the Z-hydrazone is the more stable conformation presumably due to intramolecular hydrogen bonding with the alkyne group as predicted by computation.*

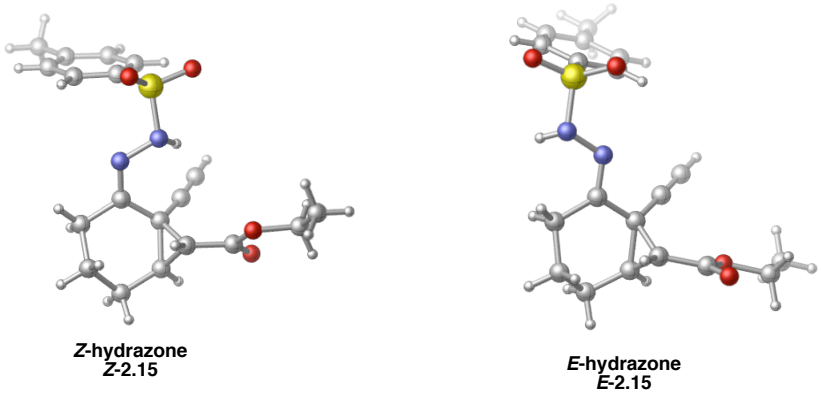


Figure 4: X-ray crystal structures of *E*- and *Z*- hydrazone 2.15.

The relative rates of reaction for the α-proto and α-deutero compounds were next investigated using automated tandem reaction analysis. Preliminary experiments indicated that labeling the α-position had a profound impact on the rate of reaction as suggested in Eq. 3. However, based on our detailed computational results, this could

not be the case. *Thus, after recrystallizing ketone **2.3** from EtOH and subjecting this material and d2-**2.3** to the reaction conditions again, we observed nearly identical rates of product formation*. Moreover, the relative change in concentration for all reaction species are parallel regardless of which ketone is used (Figure 5).

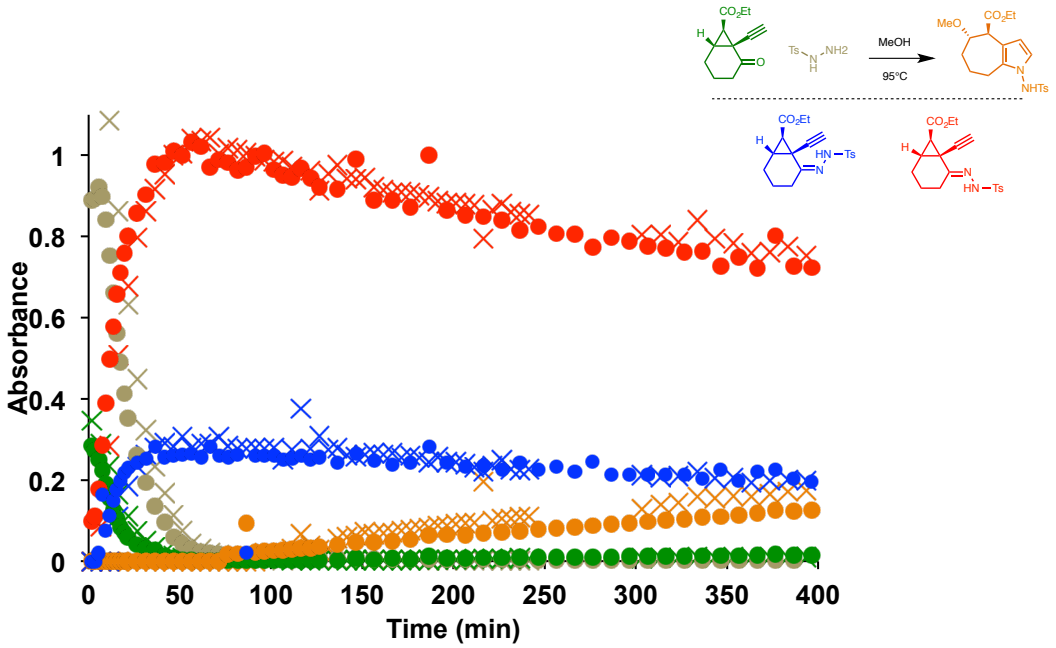


Figure 5: Reactions initiated with either recrystallized ketone 2.3 (trends marked with circle) and d_2-ketone 2.3 (trends marked with cross) show nearly identical kinetic profiles.

Following this observation, we found that the rate of product formation in the cycloisomerization reaction varies with how the ketone is prepared. When material that had been purified by column chromatography was utilized (orange triangles), the rate of aminopyrrole formation was significantly higher than ketone purified by crystallization (orange circles) from EtOH. Furthermore, the accelerated rate of cyclization could be partially restored if an aliquot of the supernatant was returned to the recrystallized ketone (orange squares, Figure 6). Finally, the rate of ketone consumption to form *Z*- and *E*-hydrazones is identical regardless of how the reaction is performed (green line in graph). These results suggest that a trace catalyst exists in the sample that is not effectively removed by column chromatography and specifically accelerates the cyclization from the intermediate hydrazone without impacting the condensation or hydrazone equilibration steps.

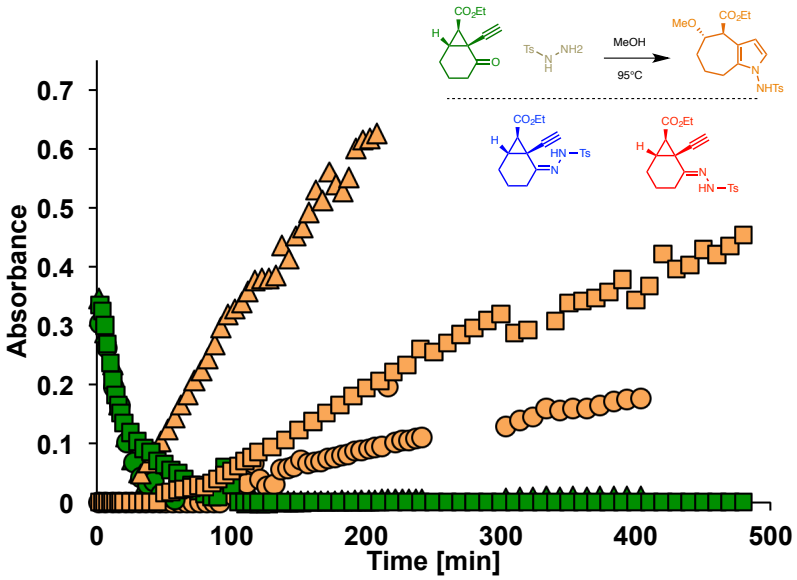


Figure 6: Rate of ketone consumption varies with its preparation. Orange circles signify product formation from recrystallized ketone 2.3. Orange triangles represent product formation from ketone 2.3 directly after column chromatography without recrystallization. Orange squares signify product formation when mother liquor is added to recrystallized ketone.

To identify the nature of the trace catalyst present in the sample, ICP-MS analysis was conducted on both the column-purified and recrystallized ketone, as well as the mother liquor from the crystallization. While many trace metals were present, the key difference between the samples is a depletion of copper upon recrystallization from EtOH (Table 4). In addition, there is a concomitant increase of copper in the mother liquor.

Table 4: Comparison of Cu levels in starting material after purifications.

Entry	Sample	%Cu (mg/mg)	Equiv. Cu
1	Ketone after column	2.76×10^{-2}	9.01×10^{-4}
2	Ketone recrystalized from EtOH	8.40×10^{-3}	2.70×10^{-5}
3	Supernatant	1.17×10^{-1}	3.79×10^{-3}

ICP-MS analysis of the solvent and PTSH show significant elevation in the concentration of copper. Thus, the likely source of this contamination is residual copper from the Sonogashira coupling used to install the alkyne functional group in ketone **2.3**.[28] The remarkable feature of this realization is that a significant quantity of copper remained in the sample even after three synthetic steps, each followed by purification using standard techniques (column chromatography or extraction). Furthermore, this result also indicates the highly efficient nature of copper to facilitate the transformation, as it was quite effective at a loading of less than 3 $x10^{-5}$ mol equiv (TON = 3000). So, while previous experiments had flagged the apparent differences in rate between **2.3** and **d_2-2.3** as having key mechanistic implications, it is likely that the added chemical step of α-deuteration under basic conditions and purification simply removed the trace copper to a level that diminished the rate of cyclization for **d_2-2.3**, and recrystallization of ketone **2.3** also serves a similar purpose.

Finally, we were able to confirm that copper salts were the likely active catalyst by performing a reaction where $Cu(MeCN)_4PF_6$ was employed as a catalyst. In this experiment, recrystallized ketone and hydrazide were incubated in MeOH at 40 °C until all of the ketone substrate was converted to hydrazone. The copper catalyst (0.01 equiv) was then added allowing rapid cyclization to occur, confirming that this metal is operative in the cyclization step (Figure 7).

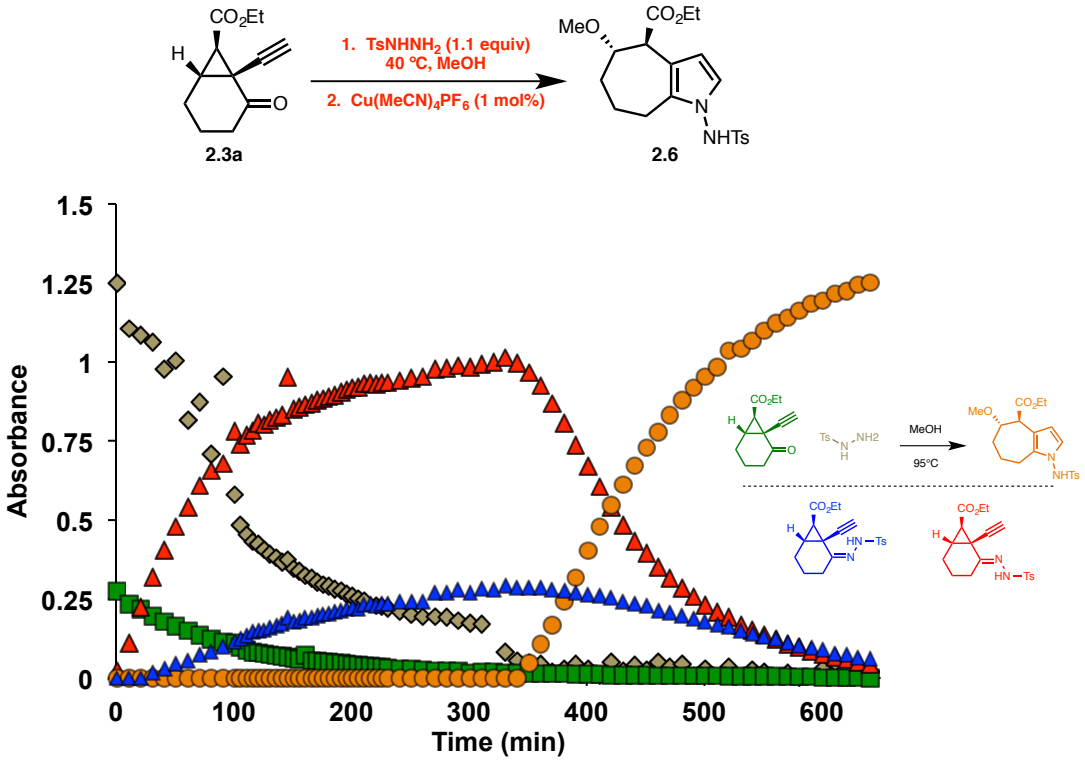


Figure 7: Copper catalyzed cycloisomerization of hydrazone 2.15.

Additional calculations with copper (modeled here as $Cu(CH_3SO_2)$) were performed using the M06-2X/LANL2DZ model chemistry[29] to confirm that Cu(I) does lead to barrier lowering. Our results (Figure 8) indicate that ring-closure from the *E*-hydrazone does indeed have a reduced (by ~6 kcal/mol) barrier when the copper salt complexes to the alkyne π-bond, as expected.

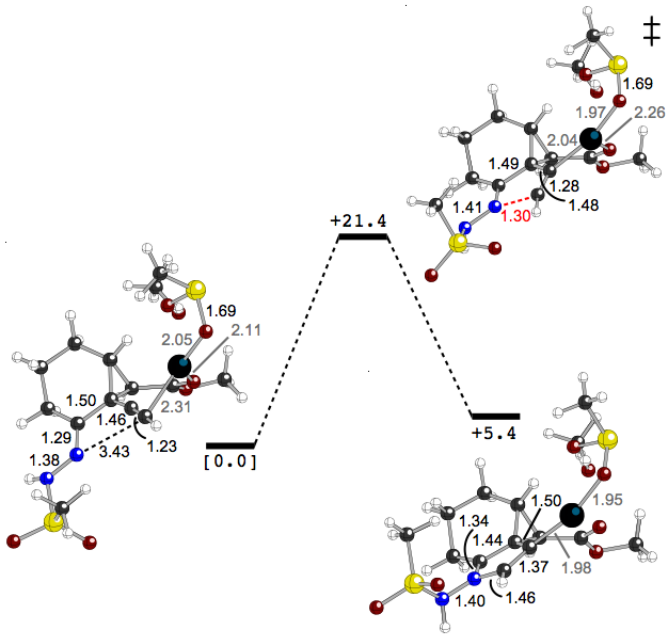


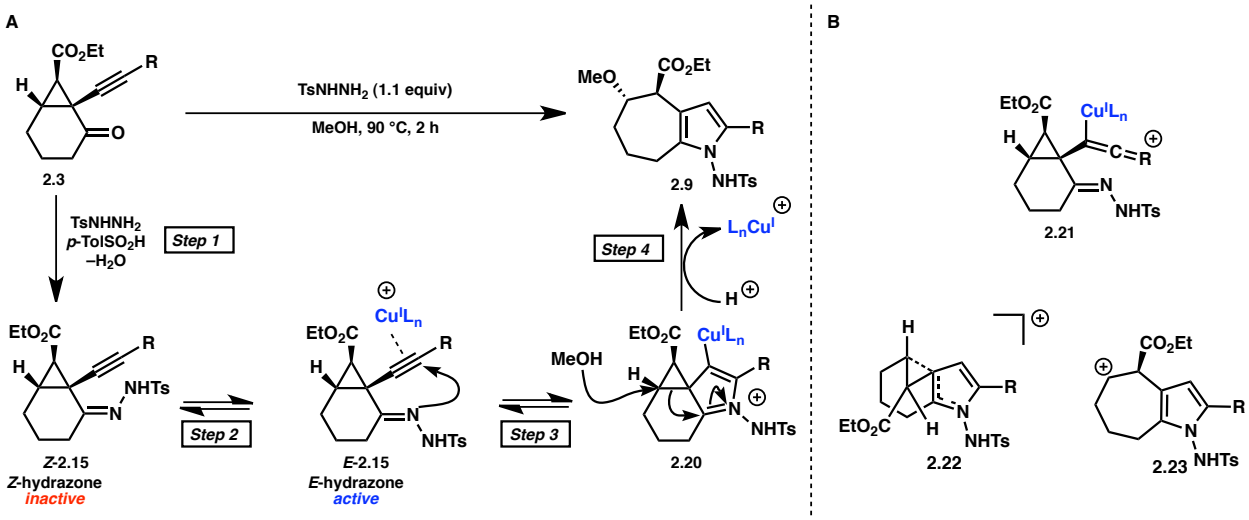
Figure 8: Optimized structures (M06-2X/LANL2DZ) for Cu-promoted cyclization. Relative free energies are shown in kcal/mol and selected distances are shown in Å.

Section 2.3.3. Mechanistic proposal

On the basis of the collection of our observations thus far and insights from the analogous gold-catalyzed transformations described by Schmalz and Zhang,[15] a plausible mechanism for the heterocycloisomerization can be formulated as illustrated in Scheme 6, A. Condensation of ketone **2.3** with $TsNHNH_2$ leads to the formation of hydrazone ***Z*-2.15**. Concurrent thermal decomposition of $TsNHNH_2$ results in the formation of small, but significant, quantities of *p*-$TolSO_2H$, which possibly facilitates the isomerization of *Z*-hydrazone **2.15** to *E*-hydrazone **2.15** through an enehydrazine intermediate (**2.16**) that is undetected in our kinetic studies but implied from our deuterium labeling experiments (see $\mathbf{d_7}$**-2.9**). Activation of the alkyne group with trace copper salts and attack of the hydrazone imine in a 5-*endo*-dig fashion on the activated alkyne group affords iminium ion **2.20**. The addition of methanol to compound **2.20** at this stage may proceed with attendant rupture of the endocyclic cyclopropane C–C bond and aromatization to afford bicyclic aminopyrrole derivative **2.9**.

Finally, changes in the electronic and steric properties of the alkyne substituent impact both the reactivity and diastereoselectivity of the resulting products. This may be explained by the influence of substituents on Step 3 (see Scheme 6, A) of our proposed mechanism. As illustrated in Scheme 6, B, groups that are electron-releasing are likely to stabilize this cumulene intermediates such as **2.21**, which would in turn be reflected in a lower associated barrier for the metal coordination step. Furthermore, intramolecular cyclization by the hydrazone group would be hampered by increased steric interaction with the R group, which is reflected in our observations with, for example, *ortho*-substituted phenyl groups (see **2.14k** and **2.14o**, Table 3). Following attack, iminium ion intermediate **2.20** is formed. The R group (in the cases where it is electron releasing) could enhance stabilization of cationic intermediate **2.22** by the aminopyrrole moiety. As

a result, the methanol addition step would be to a more cationic type intermediate (i.e., **2.23**) as opposed to a more diastereoselective SN2'-like scenario where methanol addition occurs from the β-face of intermediate **2.20**. These observations are fully consistent with the alkyne substituent effects on the stereoselectivity of these hetercycloisomerizations that was observed and rationalized by Schmalz and coworkers using an elegant enantioenriched substrate study.[30]



Scheme 6: Mechanistic proposal and rationalization of diastereoselectivity.

Section 2.4. Conclusion – The importance of collaborative research

In conclusion, we investigated a heterocycloisomerization reaction to form cycloheptane-annulated aminopyrroles and found that the transformation is facilitated by copper at remarkably low catalyst loadings. These reactions are a 'no-metal added' variant of a related gold(I)-catalyzed cycloisomerization developed by Schmalz and Zhang for the corresponding furans. Through computational studies, monitoring reaction kinetics and elemental analysis, we have conclusively established that the active catalyst is a copper complex present in the reaction at trace levels. Furthermore, we have demonstrated that both the *E*- and *Z*- hydrazones exist in this reaction and that, counterintuitively, the *Z*-hydrazone **2.15** is the more thermodynamically stable hydrazone isomer. We also believe that the thermal decomposition of tosylhydrazide generates diimide and sulfinic acid *in situ*, and these components are critical for the success of the reaction, though we have conclusively shown that the rate-determining step in the reaction has no concentration dependence on the amount of tosylhydrazide added. Computational and kinetic results suggest that enehydrazine **2.16** and are plausible intermediates in this reaction; however, they are not the species that undergo cyclization onto the alkyne group and primarily are responsible for isomerizing the hydrazine geometry. With these observations, we are actively investigating the nature of other "metal-free" cycloisomerization reactions such as those described in Figure 1, A to establish whether this reaction involves trace metal catalysis. Finally, these studies attest to the power of unique collaborations between three different chemistry research

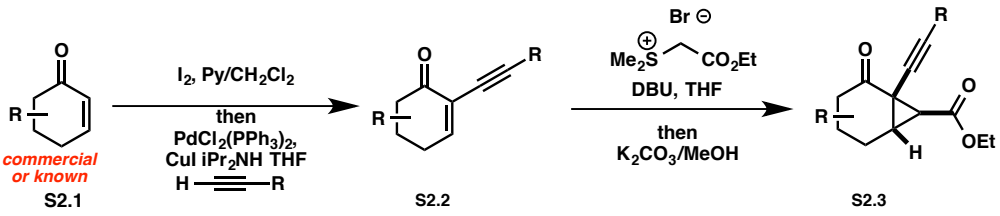
groups. With our combined expertise and results, we were able to gain a more complete picture of a transformation that would have otherwise been classified as "metal-free"

Section 2.5.1. Supporting Information – General Procedures

All reactions were run in flame-dried round-bottom flasks or vials under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Silicycle Siliaplate™ glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV irradiation and *para*-anisaldehyde or $KMnO_4$ stain. Dry tetrahydrofuran, triethylamine, and methanol were obtained by passing these previously degassed solvents through activated alumina columns. Dichloromethane was distilled over calcium hydride before use. Volatile solvents were removed under reduced pressure on a rotary evaporator. All flash chromatography was done using Sorbent Technologies 60 Å, 230 x 400 mesh silica gel (40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were taken with Bruker AV-300, AVB-400, AVQ-400, AV-500, and AV-600 MHz (75, 100, 125, and 150 MHz for ^{13}C NMR) spectrometers in $CDCl_3$ or C_6D_6 as noted. Chemical shifts were measured relative to the shift of the residual solvent (^{1}H NMR, $CDCl_3$ δ = 7.26, C_6D_6 δ = 7.16 ppm; ^{13}C NMR $CDCl_3$ δ = 77.00, C_6D_6 δ = 128.06 ppm). NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Splitting is reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, a = apparent, b = broad. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates unless otherwise specified. Spectra are reported in frequency of absorption in cm^{-1}. Only selected resonances are reported. High-resolution mass spectra (HRMS) were performed by the mass spectral facility at the University of California, Berkeley.

Section 2.5.2. Supporting Information – Experimental Procedures

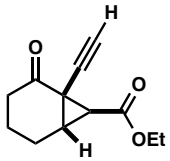
Section 2.5.3. General procedure for the synthesis of alkynylbicyclo[4.1.0]-cycloheptanones



Step 1: 2-iodocyclohex-2-en-1-one (1 equiv) was added to a dry flask under nitrogen to which THF (0.13 M) was added. The solution was cooled to 0 °C with an ice bath and then $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) were added. To the yellow suspension was added the terminal alkyne (1.5 equiv) followed by *N,N*-diisopropylamine (3 equiv) over 10 seconds. The solution was allowed to stir for 2 hours, then diluted with diethyl ether (100 mL/mmol vinyl iodide) and washed consecutively with 1 N HCl (100 mL/mmol vinyl iodide) and brine (100 mL/mmol vinyl iodide), then dried over $MgSO_4$, filtered, and

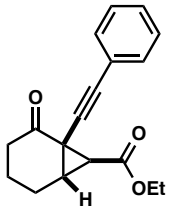
concentrated *in vacuo*. Silica gel chromatography of the resulting crude mixture yielded enyne.

Step 2: DBU (3 equiv) was added to a suspension of (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (2.5 equiv) in DCM (0.11 M). After 45 minutes, the enyne (1 equiv) was added and the solution was allowed to stir until finished as determined by TLC. The organic solvents were evaporated and then partitioned between ethyl acetate (20 mL/mmol enyne) and water (20 mL/mmol enyne). The organic layer was washed with 1 N HCl (20 mL/mmol enyne), water (20 mL/mmol enyne), dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography to yield the desired alkynyl bicyclo[4.1.0]cycloheptanone.



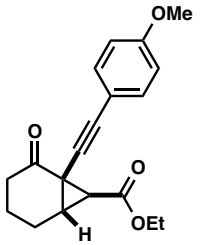
S2.3a

For the preparation of substrate **S2.3a**, see Fisher, E. L.; Wilkerson-Hill, S. M.; Sarpong, R. *J. Am. Chem. Soc.* **2012**, *134*, 9946–9949.



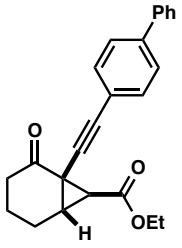
S2.3b

Following step 2 of the general procedure: 2-(phenylethynyl)cyclohex-2-enone[31] (770 mg, 3.92 mmol), DBU (1.77 mL, 11.8 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (2.24 g, 9.8 mmol), and DCM (35 mL) were used to produce substrate **S2.3b** (827 mg, 2.93 mmol, 75% yield) after silica gel chromatography (15 to 25 to 33% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 7.29 – 7.21 (m, 3H), 4.23 – 4.13 (m, 2H), 2.71 – 2.64 (m, 1H), 2.61 (d, *J* = 6. Hz, 1H), 2.42 (dt, *J* = 18, 5 Hz, 1H), 2.25 (ddd, *J* = 17.5, 11, 6 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.05 – 1.97 (m, 1H), 1.88 – 1.75 (m, 1H), 1.72 – 1.59 (m, 1H), 1.25 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.5, 167.5, 131.8, 128.0, 127.9, 122.7, 84.0, 83.0, 61.4, 36.6, 33.3, 31.6, 31.5, 20.2, 18.7, 14.2. **IR** (thin film) ν_{max} = 3052, 2983, 2942, 2227, 1736, 1704, 1491, 1446, 1287, 1185 cm^{-1}. **HRMS** (ESI) calcd for $C_{18}H_{19}O_3^+$ $(M+H)^+$: *m/z* 283.1329, found 283.1329.



S2.3c

Following step 2 of the general procedure: 2-((4-methoxyphenyl)ethynyl)cyclohex-2-enone[31] (900 mg, 4.0 mmol), DBU (1.8 mL, 12 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (2.29 g, 10 mmol), and DCM (35 mL) were used to produce substrate **S2.3c** (1.2 g, 3.84 mmol, 96%) after silica gel chromatography (25 to 33% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 6..77 (d, *J* = 8.5 Hz, 2H), 4.25 – 4.11 (m, 2H), 3.76 (s, 3H) 2.69 – 2.62 (m, 1H), 2.59 (d, *J* = 6.5. Hz, 1H), 2.42 (dt, *J* = 18, 5 Hz, 1H), 2.25 (ddd, *J* = 17.5, 11, 6.5 Hz, 1H), 2.13 – 2.05 (m, 1H), 2.05 – 1.96 (m, 1H), 1.86 – 1.75 (m, 1H), 1.71 – 1.58 (m, 1H), 1.24 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.8, 167.6, 159.3, 133.3, 114.9, 113.6, 82.9, 82.4, 61.4, 55.1, 36.6, 33.4, 31.6, 31.5, 20.2, 18.7, 14.2. **IR** (thin film) ν_{max} = 2925, 2844, 2235, 1736, 1704, 1605, 1516, 1283, 1246, 1189 cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{21}O_3^+$ $(M+H)^+$: *m/z* 313.1434, found 313.1436.

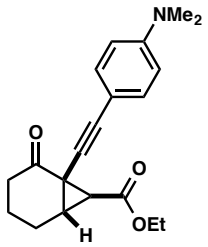


S2.3d

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (1.12 g, 5.05 mmol), THF (40 mL), $PdCl_2(PPh_3)_2$ (177 mg, 0.25 mmol), CuI (97 mg, 0.51 mmol) 4-ethynylbiphenyl[32] (1.35 g, 7.57 mmol), and *N,N*-diisopropylamine (2.1 mL, 15.2 mmol) were used to produce the desired enyne **S2.2d** (1.4 g, 5.0 mmol, 99% yield) after silica gel chromatography (10 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (m, 6H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (m, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 2.49 (dd, *J* = 6, 4.5 Hz, 2H), 2.05 (pent, *J* = 6 Hz, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.5, 154.2, 140.9, 140.1, 132.1, 128.7, 127.5, 126.9, 126.8, 125.5, 121.7, 91.9, 84.4, 38.0, 26.4, 22.3. **IR** (thin film) ν_{max} = 3032, 2950, 2864, 2210, 1691, 1483, 1356, 1156 cm^{-1}. **HRMS** (ESI) calcd for $C_{24}H_{23}O_3^+$ $(M+H)^+$: *m/z* , found .

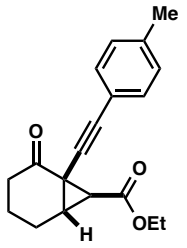
Enyne **S2.2d** (1.4 g, 5.0 mmol), DBU (2.3 mL, 15.3 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (2.97 g, 12.8 mmol), and DCM (46 mL) were used to produce substrate **S2.3d** (1.0 g, 2.79 mmol, 55%) after silica gel chromatography (15 to 25 to 33% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 5 Hz, 2H), 7.55 – 7.47 (m, 4H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7 Hz, 1H), 4.30 – 4.16 (m, 2H), 2.75 – 2.69 (m, 1H), 2.65 (d, *J* = 6.5 Hz, 1H), 2.45 (dt, *J* = 18, 5 Hz, 1H), 2.28 (ddd, *J* = 17.5,

11, 6 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.09 – 2.01 (m, 1H), 1.90 – 1.79 (m, 1H), 1.67 – 1.62 (m, 1H), 1.28 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.6, 167.6, 140.7, 140.3, 132.3, 128.7, 127.5, 126.9, 126.7, 121.7, 84.7, 82.9, 61.5, 36.6, 33.4, 31.7, 31.5, 20.2, 18.7, 14.3. **IR** (thin film) ν_{max} = 3040, 2946, 2255, 1732, 1704, 1487, 1283, 1189 cm^{-1}. **HRMS** (ESI) calcd for $C_{24}H_{23}O_3^+$ $(M+H)^+$: *m/z* 359.1642, found 359.1640.



S2.3e

Following step 2 of the general procedure: 2-((4-(dimethylamino)-phenyl)ethynyl)cyclohex-2-enone[31] (710 mg, 2.97 mmol), DBU (1.3 mL, 8.91 mmol), (Ethoxycarbonylmethyl)dimethylsulfonium bromide (1.7 g, 7.43 mmol), and DCM (26 mL) were used to produce substrate **S2.3e** (900 mg, 2.72 mmol, 93%) after silica gel chromatography (25 to 33% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* = 8.5 Hz, 2H), 4.26 – 4.12 (m, 2H), 2.93 (s, 6H), 2.69 – 2.63 (m, 1H), 2.58 (d, *J* = 6 Hz, 1H), 2.41 (dt, *J* = 18, 5 Hz, 1H), 2.24 (ddd, *J* = 17.5, 11, 6 Hz, 1H), 2.14 – 2.05 (m, 1H), 2.05 – 1.97 (m, 1H), 1.87 – 1.75 (m, 1H), 1.71 – 1.59 (m, 1H), 1.25 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.0, 167.7, 149.9, 132.9, 111.5, 109.6, 83.9, 81.3, 61.3, 40.1, 36.6, 31.6, 31.5, 20.2, 18.8, 14.2. **IR** (thin film) ν_{max} = 2983, 2938, 2803, 2223, 1728, 1704, 1610, 1524, 1442, 1356, 1176 cm^{-1}. **HRMS** (ESI) calcd for $C_{20}H_{24}NO_3^+$ $(M+H)^+$: *m/z* 326.1751 found 326.1751.

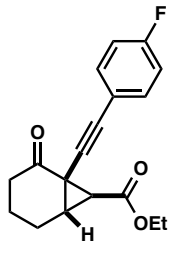


S2.3f

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (2.0 g, 9.0 mmol), THF (70 mL), $PdCl_2(PPh_3)_2$ (315 mg, 0.45 mmol), CuI (171 mg, 0.9 mmol) 4-ethynyltoluene [33] (1.7 mL, 13.5 mmol), and *N,N*-diisopropylamine (3.78 mL, 27 mmol) were used to produce the desired enyne **S2.2f** (900 mg, 4.28 mmol, 48% yield) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.34 (t, *J* = 4.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 2.51 (m, 4H), 2.34 (s, 3H), 2.06 (pent, *J* = 6.5 Hz, 2H).

Enyne **S2.2f** (900 mg, 4.28 mmol), DBU (1.96 mL, 12.8 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (2.45 g, 10.7 mmol), and DCM (36 mL) were used to produce substrate **S2.3f** (640 mg, 2.16 mmol, 50%) after silica gel chromatography (15

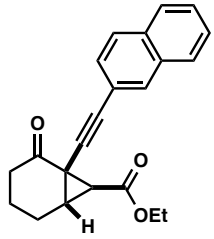
to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8 Hz, 2H), 7.04 (d, *J* = 8 Hz, 2H), 4.26 – 4.12 (m, 2H), 2.70 – 2.64 (m, 1H), 2.59 (d, *J* = 6.5 Hz, 1H), 2.41 (dt, *J* = 18, 5 Hz, 1H), 2.29 (s, 3H), 2.24 (ddd, *J* = 17.5, 11, 6.5 Hz, 1H), 2.15 – 2.06 (m, 1H), 2.06 – 1.97 (m, 1H), 1.87 – 1.76 (m, 1H), 1.71 – 1.58 (m, 1H), 1.24 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.6, 167.6, 138.0, 131.7, 128.7, 119.7, 83.2, 83.1, 61.4, 36.6, 33.3, 31.6, 31.5, 21.4, 20.7, 18.7, 14.2. **IR** (thin film) ν_{max} = 2978, 2946, 2251, 1732, 1699, 1503, 1283, 1242, 1213, 1189 cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{20}O_3Na^+$ $(M+Na)^+$: *m/z* 319.1305 found 319.1304.



S2.3g

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (2.0 g, 9.0 mmol), THF (70 mL), $PdCl_2(PPh_3)_2$ (315 mg, 0.45 mmol), CuI (171 mg, 0.9 mmol) 4-ethynylfluorobenzene[34] (1.55 mL, 13.5 mmol), and *N,N*-diisopropylamine (3.78 mL, 27 mmol) were used to produce the desired enyne **S2.2g** (400 mg, 1.87 mmol, 21% yield) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.35 (t, *J* = 4.5 Hz, 1H), 7.00 (t, *J* = 9 Hz, 2H), 2.52 (m, 4H), 2.04 (pent, *J* = 6.5 Hz, 2H).

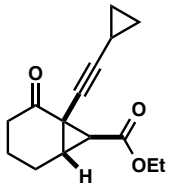
Enyne **S2.2g** (400 mg, 1.87 mmol), DBU (0.84 mL, 5.61 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (1.07 g, 4.68 mmol), and DCM (16 mL) were used to produce substrate **S2.3g** (200 mg, 0.67 mmol, 36%) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (dd, J_{HH} = 8.5 Hz, J_{HF} = 5.5 Hz 2H), 6.90 (t, *J* = 8.5 Hz, 2H), 4.26 – 4.07 (m, 2H), 2.64 – 2.60 (m, 1H), 2.57 (d, *J* = 6.5 Hz, 1H), 2.37 (dt, *J* = 18, 4.5 Hz, 1H), 2.19 (ddd, *J* = 17.5, 11, 6.5 Hz, 1H), 2.09 – 2.01 (m, 1H), 2.01 – 1.92 (m, 1H), 1.82 – 1.71 (m, 1H), 1.67 – 1.54 (m, 1H), 1.19 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.4, 167.4, 162.1 (d, J_{CF} = 248 Hz), 133.5 (d, J_{CF} = 9 Hz), 118.7 (d, J_{CF} = 4 Hz), 115.1 (d, J_{CF} = 21 Hz), 83.7, 81.8, 61.3, 36.4, 33.1, 31.5, 31.3, 20.0, 18.5, 14.1. **IR** (thin film) ν_{max} = 3064, 2946, 2231, 1763, 1708, 1601, 1512, 1368, 1283, 1217, 1187 cm^{-1}. **HRMS** (ESI) calcd for $C_{18}H_{17}O_3FNa^+$ $(M+Na)^+$: *m/z* 323.1054 found 323.1054.



S2.3h

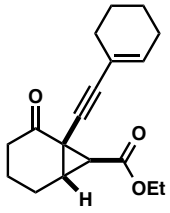
Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (1.36 g, 6.13 mmol), THF (50 mL), $PdCl_2(PPh_3)_2$ (215 mg, 0.31 mmol), CuI (117 mg, 0.61 mmol) 2-ethynylnaphthalene[35] (1.4 g, 9.2 mmol), and *N,N*-diisopropylamine (2.58 mL, 18.4 mmol) were used to produce the desired enyne **S2.2h** (1.12 g, 4.55 mmol, 74% yield) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.03 (s, 1H) 7.79 (m, 3H), 7.54 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.48 (m, 2H), 7.41 (t, *J* = 4.5 Hz, 1H), 2.54 (m, 4H), 2.06 (m, 2H).

Enyne **S2.2h** (1.12 g, 4.55 mmol), DBU (2.0 mL, 13.7 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (2.6 g, 11.4 mmol), and DCM (40 mL) were used to produce substrate **S2.3h** (830 mg, 2.5 mmol, 55%) after silica gel chromatography (15 to 25 to 33% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.81 – 7.75 (m, 2H), 7.75 – 7.71 (m, 1H), 7.51 – 7.43 (m, 3H), 4.30 – 4.16 (m, 2H), 2.78 – 2.71 (m, 1H), 2.66 (d, *J* = 6.5 Hz, 1H), 2.46 (dt, *J* = 18, 5 Hz, 1H), 2.29 (ddd, *J* = 17.5, 11, 6.5 Hz, 1H), 2.19 – 2.10 (m, 1H), 2.09 – 2.01 (m, 1H), 1.91 – 1.80 (m, 1H), 1.75 – 1.62 (m, 1H), 1.27 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.6, 167.6, 132.8, 132.7, 131.7, 128.7, 127.67, 127.66, 127.64, 126.4, 126.3, 120.1, 84.4, 83.5, 61.6, 36.7, 33.4, 31.8, 31.6, 20.3, 18.8, 14.3. **IR** (thin film) ν_{max} = 3060, 2942, 2247, 1740, 1699, 1413, 1283, 1201, 1172 cm^{-1}. **HRMS** (ESI) calcd for $C_{22}H_{20}O_3Na^+$ $(M+Na)^+$: *m/z* 355.1305 found 355.1304.



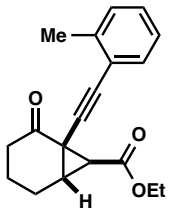
S2.3i

Following step 2 of the general procedure: 2-(cyclopropylethynyl)cyclohex-2-enone (940 mg, 5.87 mmol), DBU (2.64 mL, 17.6 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (3.36 g, 14.7 mmol), and DCM (51 mL) were used to produce substrate **S2.3i** (700 mg, 2.84 mmol, 48%) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.18 – 4.03 (m, 2H), 2.47 – 2.37 (m, 2H), 2.30 (dt, *J* = 18, 5 Hz, 1H), 2.13 (ddd, *J* = 17.5, 11, 6.5 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.94 – 1.86 (m, 1H), 1.78 – 1.67 (m, 1H), 1.62 – 1.51 (m, 1H), 1.21 (t, *J* = 7 Hz, 3H), 1.19 – 1.13 (m, 1H), 0.70 – 0.61 (m, 2H), 0.61 – 0.53 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.2, 167.5, 86.6, 69.2, 61.1, 36.4, 32.9, 31.2, 31.0, 20.0, 18.6, 14.1, 8.2, 8.1, –0.5. **IR** (thin film) ν_{max} = 2983, 2934, 2243, 1736, 1695, 1430, 1381, 1336, 1266, 1213, 1172 cm^{-1}. **HRMS** (ESI) calcd for $C_{15}H_{19}O_3^+$ $(M+H)^+$: *m/z* 247.1329 found 247.1328.



S2.3j

Following step 2 of the general procedure: 2-(cyclohexenylethynyl)cyclohex-2-enone[31] (620 mg, 3.1 mmol), DBU (1.4 mL, 9.3 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (1.78 g, 7.75 mmol), and DCM (27 mL) were used to produce substrate **S2.3j** (534 mg, 1.86 mmol, 60%) after silica gel chromatography (25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.09 – 6.03 (m, 1H), 4.23 – 4.08 (m, 2H), 2.58 – 2.47 (m, 2H), 2.37 (dt, *J* = 18, 5 Hz, 1H), 2.20 (ddd, *J* = 17.5, 11, 6 Hz, 1H), 2.12 – 1.91 (m, 6H), 1.88 – 1.73 (m, 1H), 1.68 – 1.45 (m, 5H), 1.25 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.8, 167.6, 135.2, 120.0, 84.8, 80.9, 61.3, 36.5, 33.3, 31.5, 31.4, 29.0, 25.5, 22.1, 21.4, 20.2, 18.7, 14.2. **IR** (thin film) ν_{max} = 2938, 2856, 2214, 1736, 2704, 1434, 1279, 1217, 1185 cm^{-1}. **HRMS** (ESI) calcd for $C_{18}H_{23}O_3^+$ $(M+H)^+$: *m/z* 287.1642 found 287.1644.

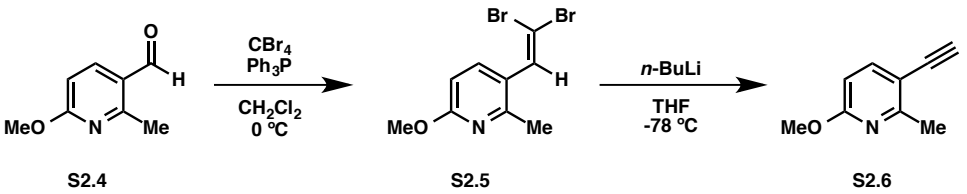


S2.3k

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (871 mg, 3.92 mmol), THF (28 mL), $PdCl_2(PPh_3)_2$ (138 mg, 0.196 mmol), CuI (74.6 mg, 0.392 mmol) 2-ethynyltoluene[36] (501 mg, 4.31 mmol), and *N,N*-diisopropylamine (1.66 mL, 11.8 mmol) were used to produce the desired enyne **S2.2k** (452 mg, 2.14 mmol, 55% yield) after silica gel chromatography (12.5 % EtOAc in hexanes). **^{11}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6, 1H), 7.40 (t, *J* = 4.4 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.22 – 7.15 (m, 1H), 2.59 (t, *J* = 6.7 Hz, 2H), 2.57 – 2.52 (m, 5H), 2.12 (q, *J* = 6.19, 2H). **^{13}C NMR** (125 MHz, CDCl3) δ 195.5, 153.6, 140.4, 131.8, 129.3, 128.3, 125.3, 122.6, 91.0, 87.6, 64.6, 38.1, 26.4, 22.3, 20.6. **IR** (thin film) ν_{max} = 3359, 3021, 2948, 2821, 2196 1688 cm^{-1}. **HRMS (EI)** calcd for $C_{15}H_{14}O^+$ $(M)^+$ *m/z* 210.1045, found 210.1044.

Enyne **S2.2k** (354 mg, 1.68 mmol), DBU (0.755 mL, 5.05 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (964 mg, 4.21 mmol), and DCM (16.8 mL) were used to produce substrate **S2.3k** (493 mg, 1.66 mmol, 98%) after silica gel chromatography (14.3% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.5 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.12 – 7.04 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.72 – 2.66 (m, 1H), 2.63 (d, *J* = 6.4 Hz, 1H), 2.50 – 2.39 (m, 4H), 2.35 – 2.21 (m, 1H), 2.20 –

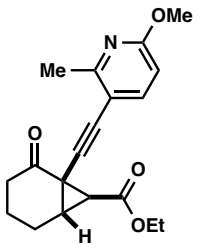
2.00 (m, 1H), 1.75 – 1.60 (m, 1H), 1.26 (q, *J* = 7.1 Hz, 3H) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.5, 167.7, 140.6, 132.3, 129.2, 128.1, 125.3, 122.7, 87.7, 82.3, 61.5, 36.7, 33.7, 31.8, 31.6, 20.7, 20.4, 18.9, 14.2. **IR** (thin film) ν_{max} = 3059, 2980, 2944, 1733, 1705 cm^{-1}. **HRMS (EI)** calcd for $C_{19}H_{20}O_3^+$ $(M)^+$ *m/z* 296.1412, found 296.1410.



S2.4 **S2.5** **S2.6**

To a flame dried round bottom was added carbon tetrabromide (1.73 g, 5.22 mmol). The round bottom was then fitted with a septum and evacuated and backfilled three times with nitrogen. Dichloromethane (3.2 mL) was then added to the vessel, and the solution was cooled to 0 °C. Triphenylphosphine (2.85 g, 10.9 mmol) in dichloromethane (3.2 mL) was then added drop wise to the cooled solution over two minutes and was allowed to stir for 15 minutes at that temperature. 2-Methoxy-6-methylpyridine-3-carboxaldehyde[37] (657 mg, 4.35 mmol) in dichloromethane (6.4 mL) was then added to the solution at 0 °C and allowed to stir for 1 hour. The reaction was then quenched with water (26 mL) and the aqueous layer extracted with dichloromethane (26 mL x3). The combined organic layers were then dried with $MgSO_4$ and concentrated. The crude solids were then purified by chromatography on SiO_2 (10:1 hexanes/EtOAc) to afford compound **S2.5**. **Yield** 1.03 g, 76%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.39 (s, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 3H), 2.40 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.0, 154.2, 138.9, 134.6, 123.3, 107.4, 91.7, 53.5, 22.6. **IR** (thin film) ν_{max} = 3009, 2978, 2952, 2017, 1923, 1600 cm^{-1}. **HRMS (EI)** calcd for $C_9H_9NO^{79}Br_2^+$ $(M)^+$ *m/z* 304.9051, found 304.9038.

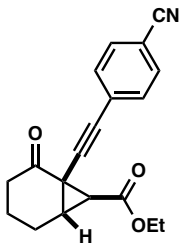
To a flame dried round bottom with dibromide **S2.5** (1.02 g, 3.35 mmol) in tetrahydrofuran (14.6 mL) at -78 °C was added *n*-butyllithium (3.22 mL, 8.05 mmol 2.5 M solution in hexanes) dropwise over 5 minutes. After stirring for one hour at -78 °c, the brown reaction was then quenched with saturated aqueous ammonium chloride (15 mL). The aqueous layer was then extracted with diethyl ether (15 mL x 3) and the combined organics dried over $MgSO_4$ and concentrated to afford compound **S2.6** as a pale yellow oil which was used without further purification. **Yield** 396 mg, 81% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 3H), 3.28 (s, 1H), 2.58 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.8, 159.7, 142.3, 110.2, 107.5, 81.3, 81.1, 53.5, 23.3. **IR** (thin film) ν_{max} = 3265, 2990, 2956, 2859, 2103, 2016, 1937 cm^{-1}. **HRMS (EI)** calcd for $C_9H_9NO^+$ $(M)^+$ *m/z* 147.0684, found 147.0683.



S2.3l

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (545 mg, 2.45 mmol), THF (17.5 mL), $PdCl_2(PPh_3)_2$ (86.0 mg, 0.123 mmol), CuI (46.6 mg, 0.245 mmol) 3-ethynyl-6-methoxypicoline (397 mg, 2.69 mmol), and *N,N*-diisopropylamine (1.04 mL, 7.35 mmol) were used to produce the desired enyne **S2.2l** (364 mg, 1.51 mmol, 61% yiled) after silica gel chromatography (12.5% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.31 (t, *J* = 4.5 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 2.61 (s, 3H), 2.53 (t, *J* = 6.8 Hz, 2H), 2.49 (dt, *J* = 5.9, 5.2 Hz, 2H), 2.06 (q, *J* = 6.35 Hz, 2H). **^{13}C NMR** (125 MHz, CDCl3) δ 195.6, 162.7, 159.3, 141.7, 125.4 111.0, 107.4, 88.6, 87.9, 53.5, 38.1, 26.4, 23.4. **IR** (thin film) ν_{max} = 2943, 2207, 1679 cm^{-1}. **HRMS (ESI)** calcd for $C_{15}H_{16}NO_2^+$ $(M+H)^+$ *m/z* 242.1176, found 242.1174.

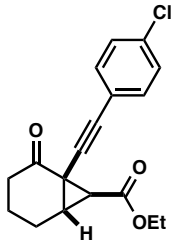
Enyne **S2.2l** (300 mg, 1.24 mmol), DBU (0.557 mL, 3.73 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (712 mg, 3.11 mmol), and DCM (12.4 mL) were used to produce substrate **S2.3l** (354 mg, 1.08 mmol, 87% yield) after silica gel chromatography (16.7% EtOAc in hexanes) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.17 (q, *J* = 4.1 Hz, 2H), 3.88 (s, 3H), 2.70 – 2.64 (m, 1H), 2.62 (d, *J* = 6.4 Hz, 1H), 2.54 (s, 3H), 2.49 – 2.36 (m, 1H), 2.34 – 2.19 (m, 1H), 2.15 – 1.99 (m, 2H), 1.89 – 1.78 (m, 1H), 1.24 (t, *J* = 7.15 Hz, 3H) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.6, 167.6, 162.4, 159.3, 142.1, 111.0, 107.2, 87.8, 80.6, 61.5, 53.4, 36.6, 31.7, 31.5, 23.3, 20.2, 18.8, 14.2. **IR** (thin film) ν_{max} = 3392, 2980, 2867, 1734, 1705 cm^{-1}. **HRMS (ESI)** calcd for $C_{19}H_{22}NO_4^+$ $(M+H)^+$ *m/z* 328.1543, found 328.1542.



S2.3m

Following step 2 of the general procedure: 2-((4-cyanophenyl)ethynyl)cyclohex-2-enone[31] (480 mg, 2.17 mmol), DBU (0.98 mL, 6.51 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (1.24 g, 5.4 mmol), and DCM (19 mL) were used to produce substrate **S2.3m** (400 mg, 1.3 mmol, 60%) after silica gel chromatography (25 to 33%

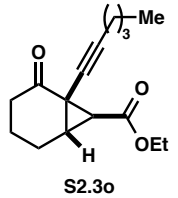
EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 4.20 – 4.11 (m, 2H), 2.69 – 2.60 (m, 1H), 2.66 (d, *J* = 6 Hz, 1H), 2.45 (dt, *J* = 18, 5 Hz, 1H), 2.27 (ddd, *J* = 17.5, 11, 6 Hz, 1H), 2.14 – 1.98 (m, 2H), 1.87 – 1.76 (m, 1H), 1.71 – 1.58 (m, 1H), 1.26 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 167.3, 132.2, 132.1, 127.7, 118.4, 111.2, 89.0, 81.6, 61.5, 36.5, 33.1, 31.9, 31.5, 20.0, 18.5, 14.1. **IR** (thin film) ν_{max} = 2983, 2946, 2227, 1724, 1699, 1601, 1499, 1291, 1246, 1187 cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{18}NO_3^+$ $(M+H)^+$: *m/z* 308.1281 found 308.1279.



S2.3n

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (932 mg, 4.2 mmol), THF (33 mL), $PdCl_2(PPh_3)_2$ (147 mg, 0.21 mmol), CuI (80 mg, 0.42 mmol) 4-ethynylchlorobenzene[38] (900 mg, 6.3 mmol), and *N,N*-diisopropylamine (1.8 mL, 12.6 mmol) were used to produce the desired enyne **S2.2n** (510 mg, 2.21 mmol, 53% yield) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 4.8 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 2.50 (m, 4H), 2.05 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.3, 154.5, 134.2, 132.8, 128.4, 124.9, 121.3, 90.7, 84.7, 38.0, 26.4, 22.2. **IR** (thin film) ν_{max} = 2950, 2880, 2868, 2218, 1691, 1475, 1360, 1225, 1164 cm^{-1}. **HRMS** (ESI) calcd for $C_{14}H_{12}OCl^+$ $(M+H)^+$: *m/z* 231.0571 found 231.0572.

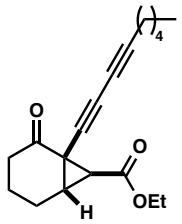
Enyne **S2.2n** (510 mg, 2.21 mmol), DBU (1.0 mL, 6.63 mmol), (Ethoxycarbonylmethyl)-dimethylsulfonium bromide (1.27 g, 5.53 mmol), and DCM (20 mL) were used to produce substrate **S2.3n** (400 mg, 1.26 mmol, 57%) after silica gel chromatography (20 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 4.25 – 4.12 (m, 2H), 2.70 – 2.65 (m, 1H), 2.61 (d, *J* = 6 Hz, 1H), 2.43 (dt, *J* = 18, 5 Hz, 1H), 2.25 (ddd, *J* = 17.5, 11, 6 Hz, 1H), 2.17 – 1.99 (m, 2H), 1.88 – 1.77 (m, 1H), 1.76 – 1.59 (m, 1H), 1.24 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.4, 167.5, 134.0, 133.1, 128.4, 121.3, 85.1, 82.0, 61.5, 36.6, 33.2, 31.7, 31.5, 20.2, 18.7, 14.2. **IR** (thin film) ν_{max} = 2983, 2942, 2230, 1728, 1699, 1483, 1287, 1250, 1189 cm^{-1}. **HRMS** (ESI) calcd for $C_{18}H_{18}O_3Cl^+$ $(M+H)^+$: *m/z* 317.0939 found 317.0942.



S2.3o

Following step 2 of the general procedure: 2-(hex-1-ynyl)cyclohex-2-enone[30] (650 mg, 3.69 mmol), DBU (1.66 mL, 11.1 mmol), (Ethoxycarbonylmethyl)dimethylsulfonium

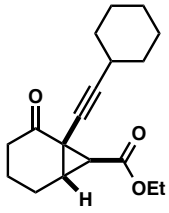
bromide (2.11 g, 9.23 mmol), and DCM (33 mL) were used to produce substrate **S2.3o** (700 mg, 2.67 mmol, 72%) after silica gel chromatography (15% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.22 – 4.09 (m, 2H), 2.53 – 2.48 (m, 1H), 2.46 (d, *J* = 6.5 Hz, 1H), 2.36 (dt, *J* = 18, 5 Hz, 1H), 2.24 – 2.12 (m, 3H), 2.08 – 1.99 (m, 1H), 1.98 – 1.91 (m, 1H), 1.82 – 1.70 (m, 1H), 1.66 – 1.56 (m, 1H), 1.43 (pent, *J* = 6.5 Hz, 2H), 1.36 (pent, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7 Hz, 3H), 0.86 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.4, 167.7, 83.8, 74.0, 61.3, 36.5, 33.1, 31.2, 31.1, 30.7, 21.8, 20.2, 18.8, 18.5, 14.2, 13.5. **IR** (thin film) ν_{max} = 2958, 2929, 2868, 2251, 1732, 1704, 1467, 1426, 1373, 1270, 1205, 1181 cm^{-1}. **HRMS** (ESI) calcd for $C_{16}H_{23}O_3^+$ $(M+H)^+$: *m/z* 263.1642 found 263.1641.



S2.3p

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (1.51 g, 6.8 mmol), THF (54 mL), $PdCl_2(PPh_3)_2$ (238 mg, 0.34 mmol), CuI (130 mg, 0.68 mmol) nona-1,3-diyne[39] (1.22 g, 10.2 mmol), and *N,N*-diisopropylamine (2.86 mL, 20.4 mmol) were used to produce the desired enyne **S2.2p** (1.3 g, 6.07 mmol, 89% yield) after silica gel chromatography (10 to 15% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 4.5 Hz, 1H), 2.50 (m, 4H), 2.27 (t, *J* = 7 Hz, 2H), 1.99 (pent, *J* = 6 Hz, 2H), 1.50 (pent, *J* = 7 Hz, 2H), 1.31 (m, 4H), 0.85 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.3, 156.4, 124.4, 85.0, 77.0, 69.1, 64.8, 37.9, 30.8, 27.7, 26.5, 22.1, 22.0, 19.3, 13.8.

Enyne **S2.2p** (1.3 g, 6.07 mmol), DBU (2.73 mL, 18.2 mmol), (Ethoxycarbonylmethyl)dimethylsulfonium bromide (3.48 g, 15.2 mmol), and DCM (55 mL) were used to produce substrate **S2.3p** (1.1 g, 3.67 mmol, 60%) after silica gel chromatography (10 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.26 – 4.13 (m, 2H), 2.62 – 2.54 (m, 1H), 2.51 (d, *J* = 6.5 Hz, 1H), 2.38 (dt, *J* = 18, 5 Hz, 1H), 2.27 – 2.13 (m, 3H), 2.10 – 1.91 (m, 2H), 1.84 – 1.72 (m, 1H), 1.68 – 1.54 (m, 1H), 1.45 (pent, *J* = 7.5 Hz, 2H), 1.37 – 1.21 (m, 7H), 0.86 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 167.3, 79.9, 70.0, 68.4, 64.9, 61.6, 36.5, 33.2, 31.8, 31.4, 30.8, 27.7, 22.0, 20.1, 19.1, 18.5, 14.1, 13.8. **IR** (thin film) ν_{max} = 2925, 2856, 2251, 2161, 1724, 1708, 1467, 1279, 1221, 1180 cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{25}O_3^+$ $(M+H)^+$: *m/z* 301.1798 found 301.1798.

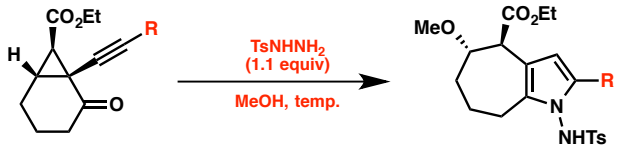


S2.3q

Following step 1 of the general procedure: 2-iodocyclohex-2-en-1-one (2.19 g, 9.87 mmol), THF (78 mL), $PdCl_2(PPh_3)_2$ (346 mg, 0.49 mmol), CuI (188 mg, 0.99 mmol) ethynylcyclohexane[40] (1.6 g, 14.8 mmol), and *N,N*-diisopropylamine (4.2 mL, 29.6 mmol) were used to produce the desired enyne **S2.2q** (1.22 g, 6.03 mmol, 61% yield) after silica gel chromatography (7.5% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 4 Hz, 1H), 2.55 (m, 1H), 2.40 (m, 4H), 1.98 (m, 2H), 1.78 (m, 2H), 1.67 (m, 2H), 1.46 (m, 3H), 1.28 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 196.0, 152.9, 125.4, 97.2, 74.8, 38.0, 32.4, 29.5, 26.2, 25.7, 24.7, 22.4.

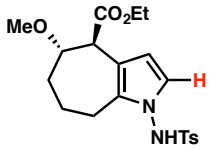
Enyne **S2.2q** (1.22 g, 6.03 mmol), DBU (2.7 mL,18.1 mmol), (Ethoxycarbonylmethyl)dimethylsulfonium bromide (3.46 g, 15.1 mmol), and DCM (55 mL) were used to produce substrate **S2.3q** (930 mg, 3.22 mmol, 53%) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.26 – 4.05 (m, 2H), 2.56 – 2.46 (m, 2H), 2.42 – 2.32 (m, 2H), 2.18 (ddd, *J* = 18, 11, 6 Hz, 1H), 2.11 – 1.90 (m, 2H), 1.86 – 1.52 (m, 6H), 1.50 – 1.33 (m, 3H), 1.33 – 1.16 (m, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 201.2, 167.6, 87.7, 74.1, 61.2, 36.5, 33.0, 32.53, 32.51, 31.3, 29.0, 25.8, 24.6, 20.2, 18.8, 14.2. **IR** (thin film) ν_{max} = 2934, 2844, 2243, 1736, 1712, 1450, 1275, 1205, 1176 cm^{-1}. **HRMS** (ESI) calcd for $C_{18}H_{24}O_3Na^+$ $(M+Na)^+$: *m/z* 311.1618 found 311.1614.

Section 2.5.4 – Supporting Information - General cyclization procedure:



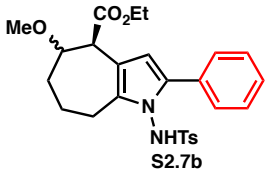
S2.3 S2.7

To a flame-dried 1 dram vial was added alkynyl bicyclo[4.1.0]cycloheptanones (1 equiv), *p*-toluenesulfonhydrazide (1.1 equiv), and anhydrous MeOH (0.4 M). The vial was purged with nitrogen gas for 30 seconds and then sealed with a cap containing a Teflon coated insert. The outside of the vial was sealed with Teflon tape and then submerged in an oil bath at the designated temperature. Upon completion of the reaction, volatiles were evaporated and the crude mixture was purified by silica gel chromatography to yield the cyclized product.



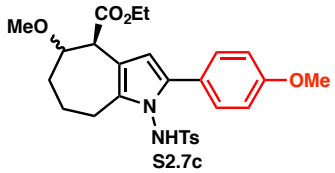
S2.7a

Following the general cyclization procedure, ketone **S2.3a** (50 mg, 0.24 mol) and $TsNHNH_2$ (50 mg, 0.27 mmol) in MeOH (0.6 mL) were stirred at 90 °C for 3 hours to produce pyrrole **S2.7a** (84 mg, 0.21 mmol, 88% yield) as a single diastereomer after silica gel chromatography (25 to 33% EtOAc in hexanes). **^{1}H NMR** (600 MHz, C_6D_6) δ 7.64 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.95 (s, 1H), 6.06 (d, *J* = 3 Hz, 1H), 5.71 (d, *J* = 3 Hz, 1H), 4.22 (m, 2H), 3.72 (d, *J* = 9 Hz, 1H), 3.52 (t, *J* = 9 Hz, 1H), 3.31 (s, 3H), 2.62 (m, 1H), 2.45 (m, 3H), 2.43 (m, 1H), 2.27 (m, 1H), 2.12 (m, 1H), 1.71 (m, 2H), 1.36 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.2, 144.8, 134.0, 132.4, 129.7, 128.4, 118.8, 112.3, 107.1, 80.5, 60.5, 56.5, 51.9, 33.3, 24.3, 22.5, 21.6, 14.2. **IR** (thin film) ν_{max} = 3232, 2925, 1728, 1712, 1597, 1450, 1373, 1344, 1168 cm^{-1}. **HRMS (ESI)** calcd for $C_{20}H_{27}O_5N_2S^+$ $(M+H)^+$ *m/z* 407.1635, found 407.1630.



S2.7b

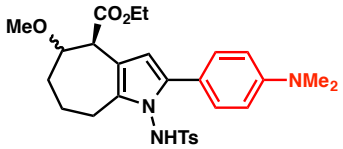
Following the general cyclization procedure, ketone **S2.3b** (50 mg, 0.18 mol) and $TsNHNH_2$ (37 mg, 0.2 mmol) in MeOH (0.45 mL) were stirred at 90 °C for 2.5 hours to produce pyrrole **S2.7b** (71 mg, 0.15 mmol, 83% yield, dr 1.2:1) after silica gel chromatography (25% EtOAc in hexanes). **^{1}H NMR** (600 MHz, C_6D_6) δ 7.88 (s, 0.55H), 7.78 (s, 0.45H), 7.25 (d, *J* = 7.8 Hz, 1.1H), 7.21 (d, *J* = 7.8 Hz, 0.9H), 6.80 (m, 5H), 6.33 (d, *J* = 7.8 Hz, 1.1H), 6.30 (d, *J* = 7.8 Hz, 0.9H), 6.18 (s, 0.45H), 6.13 (s, 0.55H), 4.14 (m, 2.45H), 3.94 (d, *J* = 9 Hz, 0.55H), 3.77 (t, *J* = 9 Hz, 0.55H), 3.69 (t, *J* = 9 Hz, 0.45H), 3.26 (m, 0.55H), 3.19 (s, 1.35H), 3.16 (s, 1.65H), 3.08 (m, 0.45H), 2.96 (m, 0.45H), 2.46 (m, 0.55H), 2.20 (m, 0.55H), 2.12 (m, 0.45H), 1.87 (m, 2H), 1.73 (s, 1.65H), 1.71 (s, 1.35H), 1.53 – 1.41 (m, 0.6H), 1.67 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 1.65H), 1.00 (t, *J* = 7.2 Hz, 1.35H), 0.93 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 172.9, 144.1, 144.0, 134.8, 134.5, 133.4, 133.3, 131.2, 131.1, 131.0, 129.1, 129.0, 127.8, 127.7, 127.1, 127.0, 125.9, 125.8, 113.2, 112.8, 108.5, 108.3, 80.8, 80.1, 60.5, 56.9, 56.8, 52.5, 51.6, 33.8, 33.5, 25.8, 25.6, 23.4, 22.6, 21.5, 14.2, 14.1. **IR** (thin film) ν_{max} = 3236, 2983, 2934, 2276, 1736, 1712, 1593, 1454, 1348, 1164 cm^{-1}. **HRMS (ESI)** calcd for $C_{26}H_{31}O_5N_2S^+$ $(M+H)^+$ *m/z* 483.1948, found 483.1939.



S2.7c

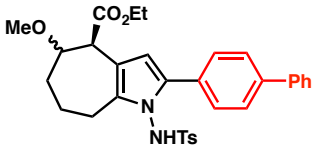
Following the general cyclization procedure, ketone **S2.3c** (50 mg, 0.16 mol) and $TsNHNH_2$ (33 mg, 0.18 mmol) in MeOH (0.40 mL) were stirred at 75 °C for 3 hours to

produce pyrrole **S2.7c** (71 mg, 0.15 mmol, 83% yield, dr 1.2:1). No further purification was needed. **^{1}H NMR** (500 MHz, C_6D_6) δ 8.58 (s, 0.55H), 8.50 (s, 0.45H), 7.31 (m, 2H), 6.93 (d, *J* = 8 Hz, 1.1H), 6.85 (d, *J* = 8 Hz, 0.9H), 6.46 (d, *J* = 8.5 Hz, 2H), 6.41 (m, 2H), 6.16 (s, 0.45H), 6.10 (s, 0.55H), 4.13 (m, 2.45H), 3.92 (d, *J* = 9 Hz, 0.55H), 3.74 (t, *J* = 9 Hz, 0.55H), 3.67 (t, *J* = 9 Hz, 0.45H), 3.31 (m, 4H), 3.19 (s, 1.35H), 3.16 (m, 2.2H), 2.92 (m, 0.45H), 2.48 (m, 0.55H), 2.20 (m, 0.55H), 2.11 (m, 0.45H), 1.83 (m, 3H), 1.66 (m, 1.1H), 1.46 (m, 0.45H), 1.07 (t, *J* = 7.5 Hz, 1.65H), 1.02 (t, *J* = 7.5 Hz, 1.35H), 0.94 (m, 0.45H). **^{13}C NMR** (125 MHz, C_6D_6) δ 173.7, 173.6, 158.9, 158.8, 143.9, 143.8, 135.8, 135.6, 135.1, 134.9, 132.1, 132.0, 129.6, 129.5, 129.49, 128.7, 128.5, 128.3, 125.3, 125.2, 114.1, 113.9, 108.4, 108.1, 81.5, 81.4, 60.9, 57.1, 57.0, 55.1, 53.3, 53.2, 35.2, 34.3, 26.7, 26.4, 24.3, 24.2, 21.5, 14.8, 14.7. **IR** (thin film) ν_{max} = 3244, 2929, 2276, 1736, 1712, 1601, 1540, 1491, 1442, 1348, 1296, 1164 cm^{-1}. **HRMS (ESI)** calcd for $C_{27}H_{32}O_6N_2NaS^+$ $(M+Na)^+$ *m/z* 535.1873, found 535.1865.



S2.7e

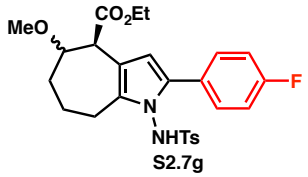
Following the general cyclization procedure, ketone **S2.3e** (50 mg, 0.15 mol) and $TsNHNH_2$ (31 mg, 0.17 mmol) in MeOH (0.375 mL) were stirred at 60 °C for 5 hours to produce pyrrole **S2.7e** (39 mg, 0.08 mmol, 50% yield, dr 1.2:1) after silica gel chromatography (25% EtOAc in hexanes). **^{1}H NMR** (600 MHz, C_6D_6) δ 7.45 (bs, 1H), 7.31 (d, *J* = 7.8 Hz, 1.1H), 7.28 (d, *J* = 7.8 Hz, 0.9H), 6.73 (d, *J* = 8.4 Hz, 1.1H), 6.67 (d, *J* = 8.4 Hz, 0.9 H), 6.38 (d, *J* = 8.4 Hz, 1.1H), 6.35 (d, *J* = 0.9H), 6.19 (m, 2.45H), 6.13 (s, 0.55H), 4.15 (m, 2.45H), 4.03 (d, *J* = 9 Hz, 0.55H), 3.81 (t, *J* = 9 Hz, 0.55H), 3.73 (t, *J* = 9 Hz, 0.45H), 3.23 (m, 1H), 3.20 (s, 1.35H), 3.18 (s, 1.65H), 3.08 (m, 0.55H), 2.95 (m, 0.45H), 2.47 (m, 7H), 2.28 (m, 0.55H), 2.13 (m, 0.55H), 1.99 (m, 2H), 1.77 (m, 4H), 1.64 (m, 1H), 1.48 (m, 0.55H), 1.04 (m, 2.1H), 1.00 (t, *J* = 7.2 Hz, 1.35H) **^{13}C NMR** a spectrum could not be obtained due to the instability of the product. **IR** (thin film) ν_{max} = 3248, 2921, 1732, 1720, 1610, 1593, 1536, 1499, 1450, 1348, 1156 cm^{-1}. **HRMS (ESI)** calcd for $C_{28}H_{36}O_5N_3S^+$ $(M+H)^+$ *m/z* 526.2370, found 526.2363.



S2.7d

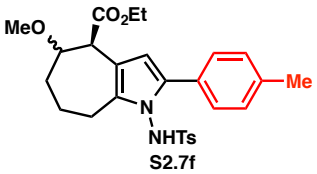
Following the general cyclization procedure, ketone **S2.3d** (50 mg, 0.14 mol) and $TsNHNH_2$ (28 mg, 0.15 mmol) in MeOH (0.35 mL) were stirred at 90 °C for 9 hours to produce pyrrole **S2.7d** (60 mg, 0.11 mmol, 79% yield, dr 1.2:1) after silica gel chromatography (15 to 25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, C_6D_6) δ 8.06 (s, 0.55H), 7.93 (s, 0.45H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.28 (m, 4H), 7.17 (m, 1H), 7.12 (t, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8 Hz, 1.1H), 6.87 (d, *J* = 8 Hz, 0.9H), 6.31 (m, 2H), 6.29 (s,

0.45H), 6.25 (s, 0.55H), 4.18 (m, 2.45H), 3.97 (d, *J* = 6 Hz, 0.55H), 3.75 (m 1H), 3.32 (dt, *J* = 16, 6 Hz, 0.55H), 3.21 (s, 1.35H), 3.18 (m, 1.65H), 3.13 (m, 0.55H), 3.02 (m, 0.45H), 2.51 (m, 0.55H), 2.20 (m, 0.55H), 2.13 (m, 0.45H), 1.97 (m, 0.45H), 1.91 (m, 1.1H), 1.73 (m, 1.45H), 1.66 (m, 3H), 1.50 (s, 0.55H), 1.10 (t, *J* = 7 Hz, 1.65H), 1.04 (t, *J* = 7 Hz, 1.35H). **^{13}C NMR** (125 MHz, C_6D_6) δ 173.2, 143.8, 143.7, 141.1, 138.7, 138.6, 135.9, 135.7, 135.1, 134.9, 131.4, 131.3, 131.1, 131.0, 129.2, 129.1, 128.3, 128.2, 128.0, 129.97, 127.94, 127.5, 127.4, 127.0, 126.9, 126.6, 114.3, 114.2, 109.2, 108.8, 80.94, 80.90, 60.6, 56.8, 56.6, 52.8, 52.7, 34.9, 33.4, 26.4, 26.2, 23.8, 23.7, 21.1, 14.5, 14.4. **IR** (thin film) ν_{max} = 3236, 2925, 1736, 1708, 1597, 1475, 1454, 1340, 1164 cm^{-1}. **HRMS (ESI)** calcd for $C_{32}H_{35}O_5N_2S^+$ $(M+H)^+$ *m/z* 559.2261, found 559.2258.



S2.7g

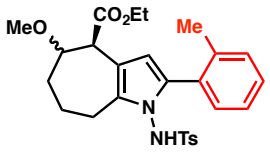
Following the general cyclization procedure, ketone **S2.3g** (50 mg, 0.17 mol) and $TsNHNH_2$ (34 mg, 0.18 mmol) in MeOH (0.42 mL) were stirred at 90 °C for 4.5 hours to produce pyrrole **S2.7g** (38 mg, 0.08 mmol, 50% yield, dr 1:1) after silica gel chromatography (15% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (s, 0.5H), 7.71 (s, 0.5H), 7.19 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 8 Hz, 2H), 6.84 (m, 2H), 6.73 (m, 2H), 5.76 (s, 0.5H), 5.75 (s, 0.5H), 4.26 (m, 2H), 3.82 (d, *J* = 9 Hz, 0.5H), 3.75 (d, *J* = 9 Hz, 0.5H), 3.67 (t, *J* = 6.5 Hz, 0.5H), 3.54 (t, *J* = 6.5 Hz, 0.5H), 3.35 (s, 1.5H), 3.34 (s, 1.5H), 3.00 (m, 0.5H), 2.92 (m, 0.5H), 2.71 (m, 0.5H), 2.58 (m, 0.3H), 2.33 (s, 3H), 2.24 (m, 1H), 1.99 (m, 0.5H), 1.89 (m, 0.5H), 1.79 (m, 1H), 1.68 (m, 1H), 1.55 (m, 1H), 1.30 (m, 3H). **^{13}C NMR** (125 MHz, C_6D_6) δ 173.1, 172.8, 161.4 (d, J_{CF} = 244 Hz), 161.3 (d, J_{CF} = 244 Hz), 144.5, 144.4, 134.6, 134.4, 133.7, 133.6, 130.2, 130.1, 129.2, 129.1, 129.0 (d, J_{CF} = 8 Hz), 128.9 (d, J_{CF} = 8 Hz), 127.9, 127.4 (d, J_{CF} = 3 Hz), 127.3 (d, J_{CF} = 3 Hz), 114.7 (d, J_{CF} = 21 Hz), 114.6 (d, J_{CF} = 21 Hz), 113.4, 113.1, 108.4, 108.2, 80.7, 80.1, 60.6, 56.9, 56.8, 52.4, 51.5, 33.7, 33.4, 25.8, 25.7, 23.3, 22.5, 21.5, 14.3. **IR** (thin film) ν_{max} = 3256, 2921, 1724, 1708, 1593, 1532, 1487, 1446, 1348, 1221, 1160 cm^{-1}. **HRMS (ESI)** calcd for $C_{26}H_{29}O_5N_2FNaS^+$ $(M+Na)^+$ *m/z* 523.1673, found 523.1672.



S2.7f

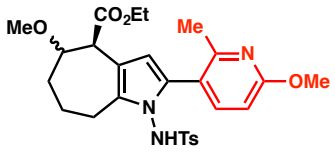
Following the general cyclization procedure, ketone **S2.3f** (50 mg, 0.17 mol) and $TsNHNH_2$ (35 mg, 0.19 mmol) in MeOH (0.43 mL) were stirred at 90 °C for 8.5 hours to produce pyrrole **S2.7f** (48 mg, 0.1 mmol, 59% yield, dr 1:1) after silica gel chromatography (15% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.16 (d, *J* = 8 Hz, 2H), 6.85 (m, 4H), 6.72 (t, *J* = 7.5 Hz, 2H), 5.75 (s, 0.5H), 5.74 (s, 0.5H), 4.21 (m, 2H), 3.81 (d, *J* = 9 Hz, 0.5H), 3.77 (d, *J* = 8.5 Hz, 0.5H), 3.68 (t, *J* = 8.5 Hz, 0.5 H), 3.53 (t, *J* = 8.5 Hz, 0.5H), 3.60 (s, 1.5H), 3.47 (s, 1.5H), 3.02 (m, 1H), 2.70

(m, 0.5H), 2.60 (m, 0.5H), 2.31 (s, 3H), 2.27 (m, 4H), 1.90 (m, 1H), 1.77 (m, 2.5H), 1.55 (m, 0.5H), 1.27 (m, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 172.9, 144.2, 144.1, 135.8, 135.7, 134.4, 134.1, 133.6, 133.5, 131.1, 129.1, 129.0, 128.5, 128.4, 128.3, 127.9, 127.2, 127.1, 113.2, 112.8, 108.2, 107.9, 80.9, 80.2, 60.6, 60.5, 56.9, 56.8, 52.6, 51.6, 33.8, 33.5, 25.8, 25.7, 23.5, 22.6, 21.5, 21.9, 21.0, 14.3. **IR** (thin film) ν_{max} = 3252, 2925, 1736, 1708, 1593, 1536, 1446, 1348, 1168 cm^{-1}. **HRMS (ESI)** calcd for $C_{27}H_{32}O_5N_2NaS^+$ $(M+Na)^+$ *m/z* 519.1924, found 519.1923.



S2.7k

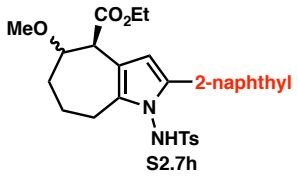
Following the general cyclization procedure, ketone **S2.3k** (59.3 mg, 0.20 mmol) and $TsNHNH_2$ (41.0 mg, 0.22 mmol) in MeOH (500 μL) were stirred at 90 °C for 24 hours to produce pyrrole **S2.7k** (47.8 mg, 48% yield) mixture of diasteromers and rotomers after silica gel chromatography. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.87 (s, 1.3H), 7.83 (s, 0.3 H), 7.77 (s, 1.4 H), 7.24 (apparent d, *J* = 5.0 Hz, 3.4 H), 7.21 (apparent d, *J* = 5.0 Hz, 2.9 H), 6.84 – 6.75 (m, 8.2H), 6.70 (apparent d, *J* = 6.3 Hz, 1.5H), 6.67 (apparent d, *J* = 3.2 Hz, 3.2H), 6.40 – 6.32 (m, 5.9H), 6.11 (s, 1H), 6.07 (s, 0.1 H), 6.05 (s, 1.4H), 5.99 (s, 0.3H), 4.21 – 4.09 (m, 5.2H), 4.09 – 4.00 (m, 1.4H), 3.96 (apparent d, *J* = 9.0 Hz, 0.65H), 3.93 (apparent d, *J* = 9.2 Hz, 1.4H), 3.72 (apparent t, *J* = 9.2 Hz, 1.6H), 3.68 (apparent t, *J* = 8.8 Hz, 1.3 H), 3.50 (s, 0.8H), 2.45 (s, 0.8H), 3.30 – 3.23 (m, 2.2H), 3.23 – 3.12 (m 10.3H), 2.94 – 2.85 (m, 1.4H), 2.50 – 2.39 (m, 1.8H), 2.28 – 2.22 (m, 1.9H), 2.18 – 2.08 (m, 2.1H), 1.94 – 1.86 (m, 10.0H), 1.86 -1.82 (m, 5.1H), 1.80 (s, 9.3H), 1.71 – 1.60 (m, 4.0H), 1.52 – 1.41 (m, 2.0H), 1.41 – 1.22 (m, 2.9H), 1.05 (apparent t, *J* = 6.8 Hz, 4.4H), 1.00 (apparent t, *J* = 6.8 Hz, 3.7H), 0.83 – 0.78 (m, 2.2H). **^{13}C NMR** (250 MHz, $CDCl_3$) δ 173.0, 172.9, 143.2, 143.2, 136.8, 136.7, 135.2, 135.0, 134.0, 133.8, 131.3, 131.2, 130.6, 130.4, 130.18, 130.15, 130.0, 129.9, 129.33, 129.30, 128.5, 128.3, 126.8, 26.7, 125.4, 113.6, 113.4, 110.0, 109.9, 81.1, 80.9, 60.3, 56.7, 56.6, 52.9, 52.8, 52.7, 34.7, 33.9, 26.3, 26.1, 24.0, 23.9, 21.1, 20.92, 20.86, 14.4, 14.3. **IR** (thin film) ν_{max} = 3238, 3090, 3068, 3034, 2978, 2927, 1737, 1598 cm^{-1}. **HRMS (ESI)** calcd for $C_{27}H_{32}O_5N_2SNa^+$ $(M+Na)^+$ *m/z* 519.1924, found 519.1924.



S2.7l

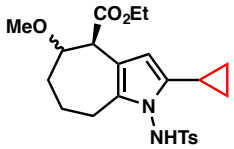
Following the general cyclization procedure, ketone **S2.3l** (65.5 mg, 0.20 mmol) and $TsNHNH_2$ (41.0 mg, 0.22 mmol) in MeOH (500 μL) were stirred at 85 °C for 24 hours to produce pyrrole **S2.7l** (106 mg, 56% yield) mixture of diasteromers and rotomers after silica gel chromatography. Note: Fractional integrations given due to mixture of diastereomers and rotomers. Both major and minor diasteromers and rotomers reported. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.18 – 7.78 (m, 11.1H), 7.36 – 7.24 (m, 6.3H),

7.08 – 6.94 (m, 3.3H), 6.94 – 6.85 (m, 3.6H), 6.85 – 6.66 (m, 6.6H), 6.51 – 6.44 (m, 5.9H), 6.44 – 6.36 (m, 4.6H), 6.28 (apparent d, *J* = 8.2 Hz, 2.7H), 6.07 (s, 1.2H), 6.05 (s, 1.2H), 6.04 (s, 1.0H), 6.02 (s, 1.4H), 4.20 – 4.11 (m, 4.3H), 4.11 – 4.00 (m, 3.3H), 3.95 (apparent t, *J* = 6.8 Hz, 4.0H), 3.93 – 3.88 (m, 4.9H), 3.88 – 3.65 (m, 25.8H), 3.24 – 3.16 (m, 5.7H), 3.14 (s, 4.7H), 3.10 – 3.02 (m, 1.6H), 3.92 – 2.82 (m, 1.8H), 2.58 – 2.51 (m, 1.2H), 2.50 – 2.40 (m, 9.0H), 2.25 – 2.18 (m, 6.5H), 2.18 – 2.06 (m, 6.9H), 1.94 – 1.82 (m, 20.8 H), 1.80 (s, 8.2H), 1.74 – 1.62 (m, 14.1H), 1.62 – 1.52 (m, 4.1H), 1.52 – 1.41 (m, 3.0H), 1.41 – 1.20 (m, 16.4H), 1.20 – 1.11 (m, 5.0H), 1.11 – 0.98 (m, 13.1H), 0.98 – 0.79 (m, 31.1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.0, 172.9, 170.3, 169.0, 163.0, 162.3, 157.4, 154.7, 154.6, 154.3, 143.7, 141.1, 139.4, 136.7, 135.6, 135.4, 134.0, 133.9, 129.7, 129.5, 129.3, 129.1, 128.7, 128.6, 128.5, 128.3, 126.7, 124.8, 119.65, 119.59, 113.8, 113.6, 109.8, 109.6, 107.4, 107.4, 107.2, 80.9, 80.8, 64.1, 60.6, 60.3, 60.1, 56.7, 56.6, 53.1, 53.05, 52.97, 52.7, 35.0, 34.9, 34.7, 33.8, 31.9, 20.9, 30.1, 28.9, 28.7, 26.3, 26.1, 23.81, 23.76, 23.39, 23.38, 23.00, 22.98, 21.15, 21.06, 21.0, 20.5, 19.5, 19.3, 16.5, 14.4, 14.34, 14.27, 14.2, 14.17, 14.16, 13.7. **IR** (thin film) ν_{max} = 3219, 2930, 2280, 1732, 1592, 1570 cm^{-1}. **HRMS (ESI)** calcd for $C_{27}H_{33}O_6N_3S^+$ $(M+H)^+$ *m/z* 528.2163, found 528.2161.



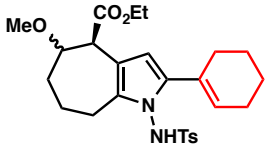
S2.7h

Following the general cyclization procedure, ketone **S2.3h** (50 mg, 0.15 mol) and $TsNHNH_2$ (31 mg, 0.17 mmol) in MeOH (0.38 mL) were stirred at 90 °C for 9 hours to produce pyrrole **S2.7h** (62 mg, 0.12 mmol, 80% yield, dr 1.2:1) after silica gel chromatography (15% EtOAc in hexanes). **^{1}H NMR** (500 MHz, C_6D_6) δ 7.93 (s, 0.55H), 7.79 (s, 0.45H), 7.48 (m, 1H), 7.39 (m, 1H), 7.26 (m, 2H), 7.17 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 0.55H), 6.98 (d, *J* = 8.5 Hz, 0.45H), 6.33 (s, 0.45H), 6.30 (s, 0.55H), 6.00 (d, *J* = 8 Hz, 1.1H), 5.97 (d, *J* = 8 Hz, 0.9H), 4.19 (m, 1.45H), 4.14 (m, 1H), 3.99 (d, *J* = 9 Hz, 0.55H), 3.77 (m, 1H), 3.33 (dt, *J* = 16, 6 Hz, 0.55H), 3.22 (s, 1.35H), 3.18 (s, 1.65H), 3.07 (m, 1H), 2.52 (m, 0.55H), 2.24 (m, 0.55H), 2.15 (m, 0.45H), 2.02 (m, 0.45H), 1.93 (m, 1H), 1.77 (m, 0.55H), 1.70 (m, 0.55H), 1.53 (m, 0.55H), 1.45 (s, 1.35H), 1.44 (s, 1.65H), 1.07 (t, *J* = 7 Hz, 1.65H), 1.02 (t, *J* = 7 Hz, 1.35H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.2m 173.1, 143.7, 143.6, 135.8, 135.7, 135.0, 134.8, 133.73, 133.70, 132.2, 132.1, 131.6, 131.5, 129.5, 129.4, 128.9, 128.4, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4, 126.3, 126.2, 126.17, 126.12, 126.0, 125.9, 125.54, 125.51, 114.4, 114.3, 109.7, 109.3, 81.0, 80.9, 60.6, 56.9, 56.6, 52.7, 34.8, 33.7, 26.4, 23.8, 23.7, 20.92, 20.90, 14.4, 14.3. **IR** (thin film) ν_{max} = 3240, 2934, 1736, 1708, 1597, 1442, 1344, 1164 cm^{-1}. **HRMS (ESI)** calcd for $C_{30}H_{32}O_5N_2KS^+$ $(M+K)^+$ *m/z* 571.1664, found 571.1662.



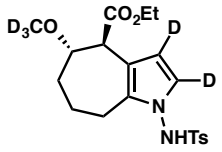
S2.7i

Following the general cyclization procedure, ketone **S2.3i** (49.2 mg, 0.20 mmol) and $TsNHNH_2$ (41.0 mg, 0.22 mmol) in MeOH (500 μL) were stirred at 75 ºC for 2 h hours to produce pyrrole **S2.7k** (64.9 mg, 73% yield) after silica gel chromatography. **Yield** 64.9 mg, 73% mixture of diastereomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.50 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 7.9, 2H), 5.71 (s, 1H), 5.66 (s, 1H), 4.19 – 4.04 (m, 4H), 4.01 (d, *J* = 8.9 Hz, 1H), 3.90 (d, *J* = 8.6 Hz, 1H), 3.68 (dt, *J* 9.0, 2.5 Hz, 1H), 3.60 (dt, *J* = 9.4, 2.3 Hz, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 2.76 (apparent dd, *J* = 15.8, 5.0 Hz, 1H), 2.68 (apparent dd, *J* = 15.2, 8.2 Hz, 1H), 2.38 – 2.19 (m, 2H), 2.15 – 1.99 (m, 2H), 1.83 (s, 3H), 1.81 (s, 3H), 1.70 – 1.51 (m, 5H). 1.49 – 1.39 (m, 1H), 1.32 – 1.10 (m, 4H), 1.08 – 1.00 (m, 6H), 0.49 – 0.39 (m, 5H), 0.33 – 0.25 (m, 2H), 0.23 – 0.13 (m, 2H) **^{13}C NMR** (250 MHz, $CDCl_3$) δ 173.3, 173.0, 144.34, 144.25, 136.5, 136.4, 132.3, 129.9, 128.8, 128.6, 128.4, 112.6, 112.4, 104.02, 103.97, 81.1, 80.7, 60.4, 56.7, 56.6, 52.7, 52.5, 34.2, 34.0, 25.6, 25.7, 23.9, 23.4, 21.2, 14.5, 14.4, 7.5, 7.4, 6.7, 6.61, 6.67, 6.62, 6.60. **IR** (thin film) ν_{max} = 3233, 3088, 2980, 2928, 2278, 1735, 1597 cm^{-1}. **HRMS (ESI)** calcd for $C_{23}H_{31}O_5N_2S^+$ $(M+H)^+$ *m/z* 447.1948, found 447.1947.



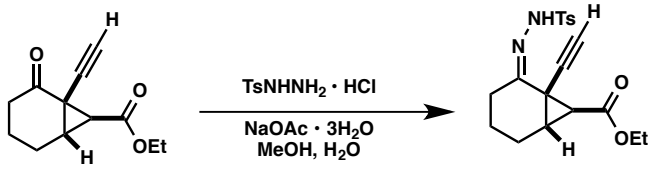
S2.7j

Following the general cyclization procedure, ketone **S2.3j** (57 mg, 0.20 mmol) and $TsNHNH_2$ (41 mg, 0.22 mmol) in MeOH were stirred at 75 ºC for 2 hours to produce pyrrole **S2.7j** (33.4 mg, 36% yield) mixture of diastereomers after silica gel chromatography. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 2.3H), 7.51 (d, *J* = 7.9 Hz, 1.8H), 7.40 (s, 1.1H), 7.38 (s, 1.0H), 6.63 (d, *J* = 8.1 Hz, 2.7H), 6.06 (d, *J* = 8.1 hz, 2.0 H), 6.06 (s, 1.0H), 6.00 (s, 1.2H), 5.34 – 5.29 (m, 1.0), 5.29 – 5.23 (m, 1.0 H), 4.24 – 4.08 (m, 7.0H), 3.97 (d, *J* = 8.8 Hz, 2.0H), 3.89 (apparent q, *J* = 4.5 Hz, 1.5H), 3.75 (apparent t, *J* = 4.1 Hz, 1.3H), 3.67 (apparent t, *J* = 4.0 Hz, 1.4H), 3.19 (s, 3.4H), 3.18 – 3.01 (m, 8.4H), 3.00 – 2.90 (m, 1.2H), 2.82 – 2.73 (m, 1.0H), 2.44 – 2.30 (m, 1.7H), 2.24 – 2.15 (m, 2.1H), 2.15 – 1.98 (m, 5.4H), 1.83 (s, 6.0H), 1.18 (s, 6.5H), 1.77 – 1.66 (m, 8.8H), 1.66 – 1.62 (m, 3.5H), 1.60 – 1.43 (m, 7.4H), 1.43 – 1.19 (m, 22H), 1.19 – 1.10 (m, 5.4H), 1.09 – 0.99 (m, 13.5H), 0.98 – 0.80 (m, 12.1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.0, 172.9, 143.7, 143.6, 136.4, 136.2, 134.8, 134.7, 129.5, 128.6, 128.7, 128.3, 124.0, 123.9, 113.3, 113.1, 107.4, 107.3, 81.0, 80.8, 60.32, 60.30, 56.6, 56.65, 56.57, 52.7, 52.5, 34.6, 33.8, 32.3, 29.8, 27.96, 27.77, 26.0, 25.9 25.5, 23.8, 23.6, 22.70, 22.68, 21.9, 21.3, 21.0, 14.4, 14.34, 14.32, 14.2 . **IR** (thin film) ν_{max} = 3229, 2927, 2856, 1736, 1598 cm^{-1}. **HRMS (ESI)** calcd for $C_{26}H_{35}O_5N_2S^+$ $(M+H)^+$ *m/z* 487.2261, found 487.2260.



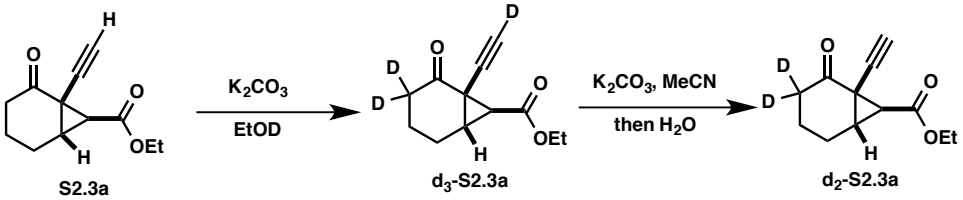
d7-S2.7a

Following the general cyclization procedure, ketone **S2.3a** (50 mg, 0.24 mol) and $TsNDND_2$[41] (51 mg, 0.27 mmol) in CD_3OD (0.6 mL) were stirred at 90 °C for 4.5 hours to produce pyrrole **d_7-S2.7a** (70 mg, 0.17 mmol, 71% yield) as a single diastereomer after silica gel chromatography (25% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.15 (s, 0.9H), 6.03 (s, 0.3H), 5.69 (s, 0.07H), 4.20 (m, 2H), 3.71 (d, *J* = 8.5 Hz, 1H), 3.51 (td, *J* = 9, 2.5 Hz, 1H), 2.45 (s, 3H), 2.12 (m, 1H), 1.70 (m, 2H), 1.31 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.2, 144.9, 134.0, 132.4, 129.8, 128.4, 118.7, 112.3, 107.3, 80.3, 60.6, 51.9, 33.2, 21.6, 14.2. **IR** (thin film) ν_{max} = 3224, 2921, 2063, 1736, 1712, 1589, 1352, 1172 cm^{-1}. **HRMS (ESI)** calcd for $C_{20}H_{20}D_7O_5N_2S^+$ $(M+H)^+$ *m/z* 414.2075, found 414.2076.



S2.3a Z-S2.8

Ketone **S2.3a** (200 mg, 0.97 mmol) and *p*-toluenesulfonhydrazide hydrochloride (260 mg, 1.17 mmol) were dissolved in a mixture of methanol (1.8 mL) and water (0.6 mL). To this solution was added $NaOAc•3H_2O$ (316 mg, 2.32 mmol) and was allowed to stir for 24 hrs. The volatiles were then removed by rotary evaporation and the residue was dissolved in EtOAc and washed with H_2O followed by sat. $NaHCO_3$. The organics were dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (25 to 33% EtOAc in hexanes) of the crude mixture afforded hydrazone ***Z*-S2.8** in quantitative yield (370 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (m, 3H), 7.28 (d, *J* = 6.8 Hz, 2H), 4.17 (m, 2H), 2.41 (s, 3H), 2.35 (m, 2H), 2.33 (m, 1H), 2.24 (d, *J* = 4.8 Hz, 1H), 2.16 (s, 1H), 1.90 (m, 2H), 1.79 (m, 1H), 1.66 (m, 1H), 1.28 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.5, 153.4, 144.0, 135.1, 129.3, 128.3, 80.5, 70.0, 61.2, 29.9, 29.3, 26.8, 23.3, 21.6, 19.5, 16.1, 14.2. **IR** (thin film) ν_{max} = 3277, 3211, 3060, 2983, 2929, 2124, 1732, 1597, 1405, 1344, 1290, 1168 cm^{-1}. **HRMS (ESI)** calcd for $C_{19}H_{23}O_4N_2S^+$ $(M+H)^+$ *m/z* 375.1373, found 375.1370



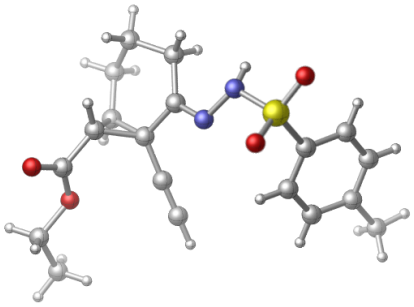
S2.3a d_3-S2.3a d_2-S2.3a

Ketone **S2.3a** (300 mg, 1.45 mmol) and anhydrous K_2CO_3 (50 mg, 0.36 mmol) were stirred in EtOD (6 mL, 99.5 atom % D) for 18 hrs. The suspension was diluted with EtOAc (50 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude trideutero–substrate **d_3-S2.3a**.

To a solution of crude **d_3-S2.3a** in MeCN (6 mL) was added K_2CO_3 (300 mg, 2.18 mmol). After stirring for 50 min, H_2O (1.3 mL) was added and the solution was stirred for an additional 1.5 hrs. DCM (20 mL) was added and the solution was dried over $MgSO_4$, filtered, and concentrated to yield the product **d_2-S2.3a** (226 mg, 1.45 mmol, 75% over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.5 Hz, 2H), 2.55 (m, 1H), 2.51 (d, *J* = 6.5 Hz, 1H), 2.23 (s, 1H), 2.00 (m, 2H), 1.76 (dt, *J* = 14.5, 5 Hz, 1H), 1.61 (m, 1H), 1.24 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.4, 167.4, 78.1, 71.4, 61.5, 32.4, 31.2, 30.8, 19.9, 18.4, 14.1. **IR** (thin film) ν_{max} = 3273, 2683, 2934, 2124, 1736, 1704, 1413, 1348, 1287, 1205, 1181 cm^{-1}. **HRMS (ESI)** calcd for $C_{12}H_{13}D_2O_3^+$ $(M+H)^+$ *m/z* 209.1141, found 209.1141.

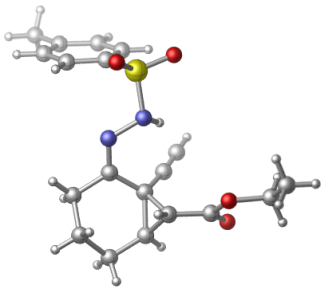
Section 2.5.5. Supporting Information – Isolation of single crystal of hydrazone S2.8 for *E*- and *Z*- isomers.

A single crystal of hydrazone ***E*-S2.8** was obtained using vapor diffusion of hexanes into benzene. Hydrazone **Z-S2.8** was dissolved in benzene (~2 mL) and set in a 4 mL vial. The vial containing the hydrazone solution was then set in a second 20 mL vial containing 10 mL of hexanes and allowed to stand at room temperature. After a period of two weeks clear crystals had formed and we analyzed by X-ray diffraction.



Isolation of single crystal of hydrazone *Z*-S2.8

Hydrazone ***Z*-S2.8** was obtained from a saturated solution in MeOH using slow evaporation. Ketone **S2.3a** was dissolved in MeOH and treated with 1 equiv of $TsNHNH_2$ and allowed to stand in an open 20 mL at room temperature for 12 hours. After this time the solvent had partially evaporated to give large clear crystals which were submitted for X-ray analysis.



For **E-S2.8** Experimental Summary

A yellow plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 100.0% complete to 67.000° in q. A total of 83552 reflections were collected covering the indices, -17<=*h*<=17, -20<=*k*<=25, -25<=*k*<=24. 11014 reflections were found to be symmetry independent, with an R_{int} of 0.0373. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. SQUEEZE was used to treat the disordered solvent contribution to the electron density map and its use has been noted in the CIF file.

Table 1. Crystal data and structure refinement for sarpong81.

X-ray ID	sarpong81	
Sample/notebook ID	SMHVII-020C	
Empirical formula	C34 H33 N O8	
Formula weight	583.61	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 14.4287(4) Å	a= 90°.
	b = 20.8084(6) Å	b= 106.013(2)°.
	c = 20.8192(6) Å	g = 90°.
Volume	6008.2(3) $Å^3$	
Z	8	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	0.757 mm^{-1}	

F(000)	2464
Crystal size	0.050 x 0.040 x 0.020 mm^3
Crystal color/habit	yellow plate
Theta range for data collection	3.064 to 68.733°.
Index ranges	-17<=h<=17, -20<=k<=25, -25<=l<=24
Reflections collected	83552
Independent reflections	11014 [R(int) = 0.0373]
Completeness to theta = 67.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.929 and 0.887
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11014 / 0 / 785
Goodness-of-fit on F^2	1.364
Final R indices [I>2sigma(I)]	R1 = 0.0961, wR2 = 0.2962
R indices (all data)	R1 = 0.1054, wR2 = 0.3104
Extinction coefficient	n/a
Largest diff. peak and hole	1.242 and -0.546 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for sarpong81. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8110(2)	2109(1)	3743(1)	44(1)
C(2)	8844(2)	2583(2)	3586(2)	46(1)
C(3)	8970(2)	3171(2)	4052(2)	50(1)
C(4)	9949(2)	3473(2)	4227(2)	52(1)
C(5)	10676(2)	3256(2)	4006(2)	50(1)
C(6)	11712(3)	3468(2)	4205(2)	60(1)
C(7)	12218(3)	2914(2)	3976(2)	61(1)
C(8)	13209(3)	2851(2)	4063(2)	68(1)
C(9)	13521(3)	2309(2)	3796(2)	75(1)
C(10)	12877(3)	1852(2)	3438(2)	78(1)
C(11)	11880(3)	1918(2)	3340(2)	66(1)
C(12)	11568(2)	2464(2)	3622(2)	53(1)
C(13)	10542(2)	2687(2)	3534(2)	48(1)
C(14)	9796(2)	2212(1)	3648(2)	45(1)
C(15)	10072(2)	1833(1)	4294(1)	44(1)
C(16)	9210(2)	1420(1)	4379(1)	42(1)
C(17)	8750(2)	1032(1)	3743(1)	45(1)
C(18)	7935(2)	1473(1)	3330(1)	44(1)
C(19)	7175(2)	2430(2)	3695(1)	46(1)
C(20)	14785(3)	3281(4)	4551(4)	107(2)
C(21)	11450(5)	954(3)	2703(4)	114(2)
C(22)	8967(2)	612(1)	5177(1)	41(1)
C(23)	9464(2)	212(2)	5770(1)	46(1)
C(24)	7874(2)	1536(2)	2599(1)	44(1)
C(25)	8293(2)	1113(2)	2249(1)	47(1)
C(26)	7992(2)	1304(1)	1543(1)	46(1)
C(27)	8236(3)	1036(2)	1000(2)	55(1)
C(28)	7865(3)	1323(2)	381(2)	60(1)
C(29)	7294(3)	1874(2)	317(2)	56(1)
C(30)	7062(2)	2146(2)	860(2)	49(1)
C(31)	7405(2)	1842(2)	1480(1)	45(1)
C(32)	7271(2)	1999(2)	2145(2)	52(1)
C(33)	9064(5)	207(2)	600(3)	97(2)
C(34)	6443(3)	3116(2)	292(2)	64(1)
C(35)	5611(2)	8500(1)	3257(1)	44(1)

C(36)	6280(2)	8491(1)	2794(1)	45(1)
C(37)	6167(2)	9121(2)	2380(2)	52(1)
C(38)	7100(2)	9389(2)	2299(2)	56(1)
C(39)	7924(2)	9074(2)	2472(2)	51(1)
C(40)	8933(3)	9294(2)	2493(2)	57(1)
C(41)	9566(2)	8774(2)	2873(2)	50(1)
C(42)	10576(2)	8724(2)	3038(2)	56(1)
C(43)	11017(2)	8201(2)	3384(2)	57(1)
C(44)	10499(2)	7718(2)	3584(2)	60(1)
C(45)	9495(2)	7756(2)	3429(2)	54(1)
C(46)	9045(2)	8300(2)	3073(2)	48(1)
C(47)	7984(2)	8411(2)	2787(2)	47(1)
C(48)	7320(2)	8382(1)	3242(1)	43(1)
C(49)	7545(2)	8831(1)	3844(1)	42(1)
C(50)	6735(2)	8833(1)	4206(1)	42(1)
C(51)	6518(2)	8132(1)	4366(2)	47(1)
C(52)	5707(2)	7915(1)	3746(2)	45(1)
C(53)	4598(2)	8589(2)	2866(2)	50(1)
C(54)	12048(3)	9153(2)	2949(3)	87(1)
C(55)	9357(3)	6764(2)	3947(3)	84(1)
C(56)	6291(2)	9383(2)	5105(2)	50(1)
C(57)	6548(3)	9926(2)	5604(2)	59(1)
C(58)	5821(2)	7274(1)	3442(2)	45(1)
C(59)	6527(3)	6786(2)	3747(2)	60(1)
C(60)	6330(2)	6241(2)	3268(2)	55(1)
C(61)	6782(3)	5642(2)	3276(2)	63(1)
C(62)	6405(3)	5214(2)	2768(2)	61(1)
C(63)	5636(2)	5372(2)	2244(2)	52(1)
C(64)	5205(2)	5967(2)	2204(2)	49(1)
C(65)	5563(2)	6397(2)	2732(2)	48(1)
C(66)	5250(2)	7055(2)	2832(2)	51(1)
C(67)	8077(5)	4948(3)	3799(3)	99(2)
C(68)	4115(3)	5752(2)	1138(2)	59(1)
N(1)	6446(2)	2670(2)	3649(1)	55(1)
N(2)	3811(2)	8633(2)	2554(2)	60(1)
O(1)	8482(1)	1891(1)	4421(1)	43(1)
O(2)	13772(2)	3340(2)	4407(2)	86(1)
O(3)	11176(2)	1516(1)	3003(2)	77(1)
O(4)	10836(2)	1837(1)	4714(1)	54(1)
O(5)	9518(2)	1062(1)	4985(1)	53(1)
O(6)	8120(1)	512(1)	4872(1)	48(1)
O(7)	8833(2)	511(1)	1141(1)	73(1)
O(8)	6524(2)	2687(1)	848(1)	63(1)
O(9)	5870(1)	9041(1)	3697(1)	44(1)

O(10)	11036(2)	9231(1)	2833(1)	64(1)
O(11)	8906(2)	7311(1)	3579(1)	60(1)
O(12)	8264(1)	9151(1)	4044(1)	47(1)
O(13)	6930(2)	9280(1)	4733(1)	58(1)
O(14)	5563(2)	9071(1)	5042(1)	56(1)
O(15)	7588(2)	5541(2)	3805(2)	89(1)
O(16)	4464(2)	6178(1)	1693(1)	60(1)

Table 3. Bond lengths [Å] and angles [°] for sarpong81.

C(1)-O(1)	1.438(3)	C(19)-N(1)	1.145(4)
C(1)-C(19)	1.483(4)	C(20)-O(2)	1.413(5)
C(1)-C(2)	1.546(4)	C(20)-H(20A)	0.9800
C(1)-C(18)	1.562(4)	C(20)-H(20B)	0.9800
C(2)-C(3)	1.540(4)	C(20)-H(20C)	0.9800
C(2)-C(14)	1.550(4)	C(21)-O(3)	1.432(5)
C(2)-H(2)	1.0000	C(21)-H(21A)	0.9800
C(3)-C(4)	1.496(4)	C(21)-H(21B)	0.9800
C(3)-H(3A)	0.9900	C(21)-H(21C)	0.9800
C(3)-H(3B)	0.9900	C(22)-O(6)	1.229(3)
C(4)-C(5)	1.335(5)	C(22)-O(5)	1.358(4)
C(4)-H(4)	0.9500	C(22)-C(23)	1.498(4)
C(5)-C(6)	1.503(5)	C(23)-H(23A)	0.9800
C(5)-C(13)	1.516(5)	C(23)-H(23B)	0.9800
C(6)-C(7)	1.510(5)	C(23)-H(23C)	0.9800
C(6)-H(6A)	0.9900	C(24)-C(25)	1.383(4)
C(6)-H(6B)	0.9900	C(24)-C(32)	1.457(4)
C(7)-C(12)	1.385(6)	C(25)-C(26)	1.469(4)
C(7)-C(8)	1.396(5)	C(25)-H(25)	0.9500
C(8)-O(2)	1.375(6)	C(26)-C(31)	1.388(4)
C(8)-C(9)	1.386(7)	C(26)-C(27)	1.391(4)
C(9)-C(10)	1.393(8)	C(27)-O(7)	1.372(4)
C(9)-H(9)	0.9500	C(27)-C(28)	1.386(5)
C(10)-C(11)	1.402(6)	C(28)-C(29)	1.397(6)
C(10)-H(10)	0.9500	C(28)-H(28)	0.9500
C(11)-O(3)	1.352(6)	C(29)-C(30)	1.385(5)
C(11)-C(12)	1.409(5)	C(29)-H(29)	0.9500
C(12)-C(13)	1.514(4)	C(30)-O(8)	1.365(4)
C(13)-C(14)	1.527(4)	C(30)-C(31)	1.398(4)
C(13)-H(13)	1.0000	C(31)-C(32)	1.487(4)
C(14)-C(15)	1.515(4)	C(32)-H(32A)	0.9900
C(14)-H(14)	1.0000	C(32)-H(32B)	0.9900
C(15)-O(4)	1.204(4)	C(33)-O(7)	1.410(5)
C(15)-C(16)	1.562(4)	C(33)-H(33A)	0.9800
C(16)-O(5)	1.426(3)	C(33)-H(33B)	0.9800
C(16)-O(1)	1.457(3)	C(33)-H(33C)	0.9800
C(16)-C(17)	1.537(4)	C(34)-O(8)	1.441(4)
C(17)-C(18)	1.551(4)	C(34)-H(34A)	0.9800
C(17)-H(17A)	0.9900	C(34)-H(34B)	0.9800
C(17)-H(17B)	0.9900	C(34)-H(34C)	0.9800
C(18)-C(24)	1.504(4)	C(35)-O(9)	1.433(3)
C(18)-H(18)	1.0000	C(35)-C(53)	1.476(4)

C(35)-C(36)	1.541(4)	C(53)-N(2)	1.146(4)
C(35)-C(52)	1.569(4)	C(54)-O(10)	1.422(5)
C(36)-C(48)	1.549(4)	C(54)-H(54A)	0.9800
C(36)-C(37)	1.553(4)	C(54)-H(54B)	0.9800
C(36)-H(36)	1.0000	C(54)-H(54C)	0.9800
C(37)-C(38)	1.509(5)	C(55)-O(11)	1.424(4)
C(37)-H(37A)	0.9900	C(55)-H(55A)	0.9800
C(37)-H(37B)	0.9900	C(55)-H(55B)	0.9800
C(38)-C(39)	1.317(5)	C(55)-H(55C)	0.9800
C(38)-H(38)	0.9500	C(56)-O(14)	1.212(4)
C(39)-C(40)	1.515(5)	C(56)-O(13)	1.374(4)
C(39)-C(47)	1.519(4)	C(56)-C(57)	1.510(4)
C(40)-C(41)	1.495(5)	C(57)-H(57A)	0.9800
C(40)-H(40A)	0.9900	C(57)-H(57B)	0.9800
C(40)-H(40B)	0.9900	C(57)-H(57C)	0.9800
C(41)-C(46)	1.374(5)	C(58)-C(66)	1.386(4)
C(41)-C(42)	1.405(5)	C(58)-C(59)	1.455(4)
C(42)-C(43)	1.363(5)	C(59)-C(60)	1.487(5)
C(42)-O(10)	1.376(4)	C(59)-H(59A)	0.9900
C(43)-C(44)	1.382(5)	C(59)-H(59B)	0.9900
C(43)-H(43)	0.9500	C(60)-C(65)	1.376(5)
C(44)-C(45)	1.397(5)	C(60)-C(61)	1.405(5)
C(44)-H(44)	0.9500	C(61)-C(62)	1.376(5)
C(45)-O(11)	1.350(4)	C(61)-O(15)	1.379(4)
C(45)-C(46)	1.410(5)	C(62)-C(63)	1.364(5)
C(46)-C(47)	1.499(4)	C(62)-H(62)	0.9500
C(47)-C(48)	1.523(4)	C(63)-C(64)	1.378(5)
C(47)-H(47)	1.0000	C(63)-H(63)	0.9500
C(48)-C(49)	1.525(4)	C(64)-O(16)	1.357(4)
C(48)-H(48)	1.0000	C(64)-C(65)	1.402(4)
C(49)-O(12)	1.207(4)	C(65)-C(66)	1.474(4)
C(49)-C(50)	1.557(4)	C(66)-H(66)	0.9500
C(50)-O(13)	1.406(4)	C(67)-O(15)	1.423(6)
C(50)-O(9)	1.462(3)	C(67)-H(67A)	0.9800
C(50)-C(51)	1.546(4)	C(67)-H(67B)	0.9800
C(51)-C(52)	1.552(4)	C(67)-H(67C)	0.9800
C(51)-H(51A)	0.9900	C(68)-O(16)	1.434(4)
C(51)-H(51B)	0.9900	C(68)-H(68A)	0.9800
C(52)-C(58)	1.503(4)	C(68)-H(68B)	0.9800
C(52)-H(52)	1.0000	C(68)-H(68C)	0.9800

O(1)-C(1)-C(19)	107.1(2)	O(1)-C(1)-C(18)	103.4(2)
O(1)-C(1)-C(2)	108.5(2)	C(19)-C(1)-C(18)	109.8(2)
C(19)-C(1)-C(2)	111.2(2)	C(2)-C(1)-C(18)	116.1(2)

C(3)-C(2)-C(1)	110.0(2)	C(5)-C(13)-C(14)	112.0(2)
C(3)-C(2)-C(14)	113.3(3)	C(12)-C(13)-H(13)	107.5
C(1)-C(2)-C(14)	108.0(2)	C(5)-C(13)-H(13)	107.5
C(3)-C(2)-H(2)	108.5	C(14)-C(13)-H(13)	107.5
C(1)-C(2)-H(2)	108.5	C(15)-C(14)-C(13)	116.8(3)
C(14)-C(2)-H(2)	108.5	C(15)-C(14)-C(2)	110.0(2)
C(4)-C(3)-C(2)	115.2(3)	C(13)-C(14)-C(2)	108.2(2)
C(4)-C(3)-H(3A)	108.5	C(15)-C(14)-H(14)	107.1
C(2)-C(3)-H(3A)	108.5	C(13)-C(14)-H(14)	107.1
C(4)-C(3)-H(3B)	108.5	C(2)-C(14)-H(14)	107.1
C(2)-C(3)-H(3B)	108.5	O(4)-C(15)-C(14)	127.2(3)
H(3A)-C(3)-H(3B)	107.5	O(4)-C(15)-C(16)	121.3(3)
C(5)-C(4)-C(3)	123.6(3)	C(14)-C(15)-C(16)	111.4(2)
C(5)-C(4)-H(4)	118.2	O(5)-C(16)-O(1)	110.7(2)
C(3)-C(4)-H(4)	118.2	O(5)-C(16)-C(17)	116.4(2)
C(4)-C(5)-C(6)	128.5(3)	O(1)-C(16)-C(17)	104.9(2)
C(4)-C(5)-C(13)	121.0(3)	O(5)-C(16)-C(15)	108.9(2)
C(6)-C(5)-C(13)	110.3(3)	O(1)-C(16)-C(15)	104.3(2)
C(5)-C(6)-C(7)	102.7(3)	C(17)-C(16)-C(15)	111.0(2)
C(5)-C(6)-H(6A)	111.2	C(16)-C(17)-C(18)	104.4(2)
C(7)-C(6)-H(6A)	111.2	C(16)-C(17)-H(17A)	110.9
C(5)-C(6)-H(6B)	111.2	C(18)-C(17)-H(17A)	110.9
C(7)-C(6)-H(6B)	111.2	C(16)-C(17)-H(17B)	110.9
H(6A)-C(6)-H(6B)	109.1	C(18)-C(17)-H(17B)	110.9
C(12)-C(7)-C(8)	121.6(4)	H(17A)-C(17)-H(17B)	108.9
C(12)-C(7)-C(6)	111.6(3)	C(24)-C(18)-C(17)	115.9(2)
C(8)-C(7)-C(6)	126.7(4)	C(24)-C(18)-C(1)	116.0(2)
O(2)-C(8)-C(9)	126.9(4)	C(17)-C(18)-C(1)	102.3(2)
O(2)-C(8)-C(7)	115.8(4)	C(24)-C(18)-H(18)	107.4
C(9)-C(8)-C(7)	117.3(4)	C(17)-C(18)-H(18)	107.4
C(8)-C(9)-C(10)	121.8(4)	C(1)-C(18)-H(18)	107.4
C(8)-C(9)-H(9)	119.1	N(1)-C(19)-C(1)	178.8(4)
C(10)-C(9)-H(9)	119.1	O(2)-C(20)-H(20A)	109.5
C(9)-C(10)-C(11)	121.1(4)	O(2)-C(20)-H(20B)	109.5
C(9)-C(10)-H(10)	119.4	H(20A)-C(20)-H(20B)	109.5
C(11)-C(10)-H(10)	119.4	O(2)-C(20)-H(20C)	109.5
O(3)-C(11)-C(10)	127.5(4)	H(20A)-C(20)-H(20C)	109.5
O(3)-C(11)-C(12)	115.7(3)	H(20B)-C(20)-H(20C)	109.5
C(10)-C(11)-C(12)	116.8(4)	O(3)-C(21)-H(21A)	109.5
C(7)-C(12)-C(11)	121.3(3)	O(3)-C(21)-H(21B)	109.5
C(7)-C(12)-C(13)	110.7(3)	H(21A)-C(21)-H(21B)	109.5
C(11)-C(12)-C(13)	127.7(3)	O(3)-C(21)-H(21C)	109.5
C(12)-C(13)-C(5)	102.5(3)	H(21A)-C(21)-H(21C)	109.5
C(12)-C(13)-C(14)	119.4(2)	H(21B)-C(21)-H(21C)	109.5

O(6)-C(22)-O(5)	123.0(2)	H(33B)-C(33)-H(33C)	109.5
O(6)-C(22)-C(23)	120.9(2)	O(8)-C(34)-H(34A)	109.5
O(5)-C(22)-C(23)	116.1(2)	O(8)-C(34)-H(34B)	109.5
C(22)-C(23)-H(23A)	109.5	H(34A)-C(34)-H(34B)	109.5
C(22)-C(23)-H(23B)	109.5	O(8)-C(34)-H(34C)	109.5
H(23A)-C(23)-H(23B)	109.5	H(34A)-C(34)-H(34C)	109.5
C(22)-C(23)-H(23C)	109.5	H(34B)-C(34)-H(34C)	109.5
H(23A)-C(23)-H(23C)	109.5	O(9)-C(35)-C(53)	107.3(2)
H(23B)-C(23)-H(23C)	109.5	O(9)-C(35)-C(36)	108.2(2)
C(25)-C(24)-C(32)	110.4(2)	C(53)-C(35)-C(36)	110.6(2)
C(25)-C(24)-C(18)	124.3(3)	O(9)-C(35)-C(52)	103.6(2)
C(32)-C(24)-C(18)	124.9(3)	C(53)-C(35)-C(52)	110.6(2)
C(24)-C(25)-C(26)	107.7(3)	C(36)-C(35)-C(52)	116.0(2)
C(24)-C(25)-H(25)	126.1	C(35)-C(36)-C(48)	107.1(2)
C(26)-C(25)-H(25)	126.1	C(35)-C(36)-C(37)	110.4(2)
C(31)-C(26)-C(27)	122.1(3)	C(48)-C(36)-C(37)	113.2(2)
C(31)-C(26)-C(25)	108.5(3)	C(35)-C(36)-H(36)	108.7
C(27)-C(26)-C(25)	129.4(3)	C(48)-C(36)-H(36)	108.7
O(7)-C(27)-C(28)	127.0(3)	C(37)-C(36)-H(36)	108.7
O(7)-C(27)-C(26)	115.4(3)	C(38)-C(37)-C(36)	114.4(3)
C(28)-C(27)-C(26)	117.5(3)	C(38)-C(37)-H(37A)	108.7
C(27)-C(28)-C(29)	120.7(3)	C(36)-C(37)-H(37A)	108.7
C(27)-C(28)-H(28)	119.7	C(38)-C(37)-H(37B)	108.7
C(29)-C(28)-H(28)	119.7	C(36)-C(37)-H(37B)	108.7
C(30)-C(29)-C(28)	121.6(3)	H(37A)-C(37)-H(37B)	107.6
C(30)-C(29)-H(29)	119.2	C(39)-C(38)-C(37)	123.5(3)
C(28)-C(29)-H(29)	119.2	C(39)-C(38)-H(38)	118.3
O(8)-C(30)-C(29)	125.9(3)	C(37)-C(38)-H(38)	118.3
O(8)-C(30)-C(31)	116.4(3)	C(38)-C(39)-C(40)	130.1(3)
C(29)-C(30)-C(31)	117.8(3)	C(38)-C(39)-C(47)	120.6(3)
C(26)-C(31)-C(30)	120.2(3)	C(40)-C(39)-C(47)	108.8(3)
C(26)-C(31)-C(32)	108.7(3)	C(41)-C(40)-C(39)	103.8(3)
C(30)-C(31)-C(32)	131.1(3)	C(41)-C(40)-H(40A)	111.0
C(24)-C(32)-C(31)	104.6(3)	C(39)-C(40)-H(40A)	111.0
C(24)-C(32)-H(32A)	110.8	C(41)-C(40)-H(40B)	111.0
C(31)-C(32)-H(32A)	110.8	C(39)-C(40)-H(40B)	111.0
C(24)-C(32)-H(32B)	110.8	H(40A)-C(40)-H(40B)	109.0
C(31)-C(32)-H(32B)	110.8	C(46)-C(41)-C(42)	119.3(3)
H(32A)-C(32)-H(32B)	108.9	C(46)-C(41)-C(40)	112.0(3)
O(7)-C(33)-H(33A)	109.5	C(42)-C(41)-C(40)	128.7(3)
O(7)-C(33)-H(33B)	109.5	C(43)-C(42)-O(10)	125.6(3)
H(33A)-C(33)-H(33B)	109.5	C(43)-C(42)-C(41)	119.4(3)
O(7)-C(33)-H(33C)	109.5	O(10)-C(42)-C(41)	115.1(3)
H(33A)-C(33)-H(33C)	109.5	C(42)-C(43)-C(44)	121.8(3)

C(42)-C(43)-H(43)	119.1	N(2)-C(53)-C(35)	177.3(3)
C(44)-C(43)-H(43)	119.1	O(10)-C(54)-H(54A)	109.5
C(43)-C(44)-C(45)	120.2(3)	O(10)-C(54)-H(54B)	109.5
C(43)-C(44)-H(44)	119.9	H(54A)-C(54)-H(54B)	109.5
C(45)-C(44)-H(44)	119.9	O(10)-C(54)-H(54C)	109.5
O(11)-C(45)-C(44)	125.9(3)	H(54A)-C(54)-H(54C)	109.5
O(11)-C(45)-C(46)	116.4(3)	H(54B)-C(54)-H(54C)	109.5
C(44)-C(45)-C(46)	117.6(3)	O(11)-C(55)-H(55A)	109.5
C(41)-C(46)-C(45)	121.7(3)	O(11)-C(55)-H(55B)	109.5
C(41)-C(46)-C(47)	110.7(3)	H(55A)-C(55)-H(55B)	109.5
C(45)-C(46)-C(47)	127.2(3)	O(11)-C(55)-H(55C)	109.5
C(46)-C(47)-C(39)	104.0(3)	H(55A)-C(55)-H(55C)	109.5
C(46)-C(47)-C(48)	119.7(2)	H(55B)-C(55)-H(55C)	109.5
C(39)-C(47)-C(48)	109.5(2)	O(14)-C(56)-O(13)	123.5(3)
C(46)-C(47)-H(47)	107.7	O(14)-C(56)-C(57)	121.1(3)
C(39)-C(47)-H(47)	107.7	O(13)-C(56)-C(57)	115.4(3)
C(48)-C(47)-H(47)	107.7	C(56)-C(57)-H(57A)	109.5
C(47)-C(48)-C(49)	117.3(2)	C(56)-C(57)-H(57B)	109.5
C(47)-C(48)-C(36)	106.9(2)	H(57A)-C(57)-H(57B)	109.5
C(49)-C(48)-C(36)	110.9(2)	C(56)-C(57)-H(57C)	109.5
C(47)-C(48)-H(48)	107.1	H(57A)-C(57)-H(57C)	109.5
C(49)-C(48)-H(48)	107.1	H(57B)-C(57)-H(57C)	109.5
C(36)-C(48)-H(48)	107.1	C(66)-C(58)-C(59)	109.7(3)
O(12)-C(49)-C(48)	126.2(3)	C(66)-C(58)-C(52)	124.8(3)
O(12)-C(49)-C(50)	121.4(3)	C(59)-C(58)-C(52)	125.4(3)
C(48)-C(49)-C(50)	112.4(2)	C(58)-C(59)-C(60)	105.0(3)
O(13)-C(50)-O(9)	108.5(2)	C(58)-C(59)-H(59A)	110.8
O(13)-C(50)-C(51)	117.7(2)	C(60)-C(59)-H(59A)	110.8
O(9)-C(50)-C(51)	104.6(2)	C(58)-C(59)-H(59B)	110.8
O(13)-C(50)-C(49)	111.4(2)	C(60)-C(59)-H(59B)	110.8
O(9)-C(50)-C(49)	104.6(2)	H(59A)-C(59)-H(59B)	108.8
C(51)-C(50)-C(49)	109.0(2)	C(65)-C(60)-C(61)	119.1(3)
C(50)-C(51)-C(52)	104.3(2)	C(65)-C(60)-C(59)	109.0(3)
C(50)-C(51)-H(51A)	110.9	C(61)-C(60)-C(59)	131.9(3)
C(52)-C(51)-H(51A)	110.9	C(62)-C(61)-O(15)	125.7(3)
C(50)-C(51)-H(51B)	110.9	C(62)-C(61)-C(60)	118.8(3)
C(52)-C(51)-H(51B)	110.9	O(15)-C(61)-C(60)	115.5(3)
H(51A)-C(51)-H(51B)	108.9	C(63)-C(62)-C(61)	121.4(3)
C(58)-C(52)-C(51)	117.6(2)	C(63)-C(62)-H(62)	119.3
C(58)-C(52)-C(35)	114.6(2)	C(61)-C(62)-H(62)	119.3
C(51)-C(52)-C(35)	102.9(2)	C(62)-C(63)-C(64)	121.3(3)
C(58)-C(52)-H(52)	107.0	C(62)-C(63)-H(63)	119.4
C(51)-C(52)-H(52)	107.0	C(64)-C(63)-H(63)	119.4
C(35)-C(52)-H(52)	107.0	O(16)-C(64)-C(63)	125.7(3)

O(16)-C(64)-C(65)	116.6(3)
C(63)-C(64)-C(65)	117.7(3)
C(60)-C(65)-C(64)	121.6(3)
C(60)-C(65)-C(66)	108.3(3)
C(64)-C(65)-C(66)	130.0(3)
C(58)-C(66)-C(65)	107.9(3)
C(58)-C(66)-H(66)	126.0
C(65)-C(66)-H(66)	126.0
O(15)-C(67)-H(67A)	109.5
O(15)-C(67)-H(67B)	109.5
H(67A)-C(67)-H(67B)	109.5
O(15)-C(67)-H(67C)	109.5
H(67A)-C(67)-H(67C)	109.5
H(67B)-C(67)-H(67C)	109.5
O(16)-C(68)-H(68A)	109.5
O(16)-C(68)-H(68B)	109.5
H(68A)-C(68)-H(68B)	109.5
O(16)-C(68)-H(68C)	109.5
H(68A)-C(68)-H(68C)	109.5
H(68B)-C(68)-H(68C)	109.5
C(1)-O(1)-C(16)	103.54(19)
C(8)-O(2)-C(20)	118.4(4)
C(11)-O(3)-C(21)	118.2(4)
C(22)-O(5)-C(16)	123.7(2)
C(27)-O(7)-C(33)	117.2(3)
C(30)-O(8)-C(34)	116.5(3)
C(35)-O(9)-C(50)	104.5(2)
C(42)-O(10)-C(54)	114.8(3)
C(45)-O(11)-C(55)	116.7(3)
C(56)-O(13)-C(50)	121.5(2)
C(61)-O(15)-C(67)	115.8(4)
C(64)-O(16)-C(68)	117.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sarpong81. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	49(1)	46(2)	39(1)	4(1)	16(1)	5(1)
C(2)	50(2)	42(1)	49(1)	6(1)	18(1)	7(1)
C(3)	53(2)	40(2)	61(2)	3(1)	22(1)	4(1)
C(4)	59(2)	41(2)	60(2)	3(1)	24(1)	3(1)
C(5)	56(2)	43(2)	56(2)	10(1)	21(1)	2(1)
C(6)	57(2)	62(2)	64(2)	8(2)	22(1)	1(2)
C(7)	60(2)	71(2)	58(2)	20(2)	25(1)	10(2)
C(8)	57(2)	82(3)	68(2)	16(2)	24(2)	10(2)
C(9)	60(2)	91(3)	81(2)	33(2)	32(2)	22(2)
C(10)	86(3)	74(3)	91(3)	27(2)	54(2)	32(2)
C(11)	68(2)	58(2)	85(2)	19(2)	45(2)	15(2)
C(12)	55(2)	52(2)	62(2)	17(1)	31(1)	9(1)
C(13)	52(2)	43(2)	55(2)	9(1)	25(1)	7(1)
C(14)	52(2)	39(1)	50(1)	5(1)	24(1)	6(1)
C(15)	48(1)	39(1)	50(1)	3(1)	21(1)	7(1)
C(16)	45(1)	39(1)	45(1)	4(1)	14(1)	5(1)
C(17)	54(2)	40(1)	41(1)	5(1)	14(1)	5(1)
C(18)	49(1)	45(2)	41(1)	6(1)	16(1)	3(1)
C(19)	50(2)	48(2)	42(1)	5(1)	14(1)	3(1)
C(20)	54(2)	135(5)	127(5)	0(4)	15(2)	11(3)
C(21)	128(5)	78(3)	164(6)	-27(4)	85(5)	18(3)
C(22)	43(1)	38(1)	42(1)	-1(1)	14(1)	2(1)
C(23)	46(1)	48(2)	43(1)	4(1)	12(1)	1(1)
C(24)	47(1)	47(2)	41(1)	4(1)	14(1)	0(1)
C(25)	54(2)	44(2)	45(1)	4(1)	15(1)	4(1)
C(26)	53(1)	41(1)	45(1)	4(1)	15(1)	-2(1)
C(27)	72(2)	46(2)	51(2)	-2(1)	22(1)	-2(1)
C(28)	80(2)	56(2)	48(2)	-4(1)	26(2)	-7(2)
C(29)	63(2)	65(2)	40(1)	6(1)	12(1)	-9(2)
C(30)	43(1)	57(2)	47(1)	11(1)	11(1)	3(1)
C(31)	44(1)	49(2)	44(1)	3(1)	13(1)	1(1)
C(32)	64(2)	52(2)	46(1)	6(1)	23(1)	9(1)
C(33)	165(5)	62(2)	81(3)	-5(2)	61(3)	26(3)
C(34)	67(2)	66(2)	59(2)	24(2)	16(2)	8(2)
C(35)	41(1)	39(1)	51(1)	-3(1)	13(1)	1(1)
C(36)	44(1)	40(1)	49(1)	1(1)	12(1)	3(1)

C(37)	50(2)	52(2)	51(2)	8(1)	10(1)	7(1)
C(38)	62(2)	47(2)	61(2)	9(1)	21(1)	3(1)
C(39)	56(2)	47(2)	54(2)	1(1)	23(1)	0(1)
C(40)	59(2)	52(2)	66(2)	4(1)	25(1)	-1(1)
C(41)	53(2)	47(2)	56(2)	-11(1)	23(1)	2(1)
C(42)	55(2)	53(2)	67(2)	-16(1)	29(1)	-9(1)
C(43)	48(2)	55(2)	69(2)	-15(2)	16(1)	5(1)
C(44)	49(2)	55(2)	75(2)	-5(2)	16(1)	7(1)
C(45)	53(2)	47(2)	62(2)	-3(1)	17(1)	8(1)
C(46)	48(2)	50(2)	50(1)	-7(1)	22(1)	1(1)
C(47)	48(1)	44(2)	52(1)	-3(1)	18(1)	2(1)
C(48)	41(1)	41(1)	48(1)	2(1)	14(1)	4(1)
C(49)	38(1)	41(1)	47(1)	7(1)	11(1)	5(1)
C(50)	38(1)	42(1)	46(1)	1(1)	12(1)	2(1)
C(51)	48(1)	43(2)	52(2)	0(1)	18(1)	-2(1)
C(52)	42(1)	41(1)	54(1)	0(1)	17(1)	1(1)
C(53)	46(2)	42(2)	62(2)	-6(1)	15(1)	2(1)
C(54)	66(2)	72(3)	137(4)	-19(3)	50(3)	-12(2)
C(55)	66(2)	62(2)	123(4)	37(2)	23(2)	11(2)
C(56)	50(2)	46(2)	57(2)	-5(1)	22(1)	-2(1)
C(57)	60(2)	65(2)	56(2)	-15(2)	22(1)	-14(2)
C(58)	41(1)	39(1)	57(2)	-1(1)	15(1)	1(1)
C(59)	55(2)	42(2)	76(2)	-5(2)	6(2)	1(1)
C(60)	50(2)	43(2)	67(2)	-4(1)	11(1)	0(1)
C(61)	58(2)	45(2)	77(2)	0(2)	2(2)	4(1)
C(62)	59(2)	41(2)	84(2)	-5(2)	20(2)	3(1)
C(63)	49(1)	43(2)	68(2)	-9(1)	25(1)	-6(1)
C(64)	45(1)	45(2)	62(2)	-6(1)	22(1)	-5(1)
C(65)	43(1)	40(1)	64(2)	-1(1)	20(1)	-1(1)
C(66)	54(2)	39(2)	61(2)	-2(1)	20(1)	4(1)
C(67)	116(4)	84(3)	82(3)	2(2)	2(3)	47(3)
C(68)	64(2)	60(2)	52(2)	-9(1)	16(1)	-1(2)
N(1)	55(1)	62(2)	49(1)	2(1)	13(1)	13(1)
N(2)	45(1)	52(2)	78(2)	-6(1)	8(1)	5(1)
O(1)	47(1)	44(1)	41(1)	4(1)	15(1)	6(1)
O(2)	49(1)	110(3)	96(2)	3(2)	15(1)	6(2)
O(3)	91(2)	54(2)	106(2)	0(1)	61(2)	13(1)
O(4)	47(1)	56(1)	59(1)	12(1)	15(1)	0(1)
O(5)	56(1)	53(1)	50(1)	4(1)	13(1)	1(1)
O(6)	44(1)	50(1)	49(1)	7(1)	9(1)	-3(1)
O(7)	114(2)	54(1)	64(1)	8(1)	44(2)	25(1)
O(8)	61(1)	72(2)	60(1)	25(1)	23(1)	20(1)
O(9)	39(1)	40(1)	52(1)	-3(1)	11(1)	2(1)
O(10)	61(1)	60(1)	82(2)	-7(1)	38(1)	-8(1)

O(11)	53(1)	49(1)	80(2)	12(1)	21(1)	7(1)
O(12)	41(1)	48(1)	53(1)	-2(1)	16(1)	-1(1)
O(13)	56(1)	56(1)	62(1)	-4(1)	18(1)	-3(1)
O(14)	53(1)	53(1)	69(1)	-12(1)	28(1)	-11(1)
O(15)	84(2)	62(2)	97(2)	-8(2)	-16(2)	22(2)
O(16)	64(1)	51(1)	60(1)	-8(1)	11(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for sarpong81.

	x	y	z	U(eq)
H(2)	8587	2733	3115	56
H(3A)	8489	3500	3836	60
H(3B)	8825	3038	4471	60
H(4)	10059	3839	4510	62
H(6A)	11953	3530	4694	72
H(6B)	11797	3872	3976	72
H(9)	14192	2248	3858	90
H(10)	13117	1490	3257	93
H(13)	10295	2856	3069	58
H(14)	9667	1894	3273	55
H(17A)	8484	621	3853	54
H(17B)	9229	939	3494	54
H(18)	7309	1289	3361	53
H(20A)	15088	3690	4726	161
H(20B)	14959	3169	4143	161
H(20C)	15009	2944	4887	161
H(21A)	10870	737	2432	172
H(21B)	11807	662	3054	172
H(21C)	11858	1078	2418	172
H(23A)	10130	361	5949	69
H(23B)	9467	-239	5634	69
H(23C)	9122	251	6114	69
H(25)	8701	762	2433	57
H(28)	8002	1144	-2	72
H(29)	7058	2068	-111	68
H(32A)	7481	2444	2278	63
H(32B)	6587	1951	2141	63
H(33A)	9409	510	388	146
H(33B)	8469	69	273	146
H(33C)	9473	-167	762	146
H(34A)	6126	3514	367	96
H(34B)	6059	2910	-119	96
H(34C)	7087	3214	249	96
H(36)	6095	8120	2479	53
H(37A)	5726	9039	1931	62

H(37B)	5862	9450	2599	62
H(38)	7094	9807	2114	67
H(40A)	9008	9336	2036	69
H(40B)	9083	9712	2725	69
H(43)	11699	8167	3492	69
H(44)	10826	7360	3826	72
H(47)	7742	8093	2418	57
H(48)	7350	7933	3418	51
H(51A)	6298	8112	4775	56
H(51B)	7098	7859	4427	56
H(52)	5097	7895	3885	54
H(54A)	12318	9536	2794	131
H(54B)	12175	8775	2706	131
H(54C)	12349	9094	3429	131
H(55A)	9793	6903	4373	127
H(55B)	9725	6532	3688	127
H(55C)	8863	6479	4032	127
H(57A)	6650	9755	6057	88
H(57B)	6020	10240	5511	88
H(57C)	7139	10136	5567	88
H(59A)	6448	6652	4185	72
H(59B)	7191	6950	3813	72
H(62)	6685	4799	2782	74
H(63)	5393	5066	1900	62
H(66)	4747	7288	2531	61
H(67A)	8226	4898	3371	149
H(67B)	7664	4593	3861	149
H(67C)	8676	4945	4163	149
H(68A)	3594	5962	799	88
H(68B)	3869	5358	1290	88
H(68C)	4642	5644	944	88

For **Z-S2.8** – Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_a radiation (l = 0.71073 Å). A 0.225 x 0.135 x 0.117 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using f and v scans. Crystal-to-detector distance was 35 mm and exposure time was 2 seconds per frame using a scan width of 1.0°. Data collection was 100% complete to 25.00° in *q*. A total of 19309 reflections were collected covering the indices, -10<=h<=12, -30<=k<=30, -13<=l<=9. 4709 reflections were found to be symmetry independent, with a R_{int} of 0.0530. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The

space group was found to be $P2_1/n$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2013). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2013. Crystallographic data are summarized in Table 1.

Table 1. Crystal data and structure refinement for Hein03.

Identification code	DY-hydrazone	
Empirical formula	C19 H22 N2 O4 S	
Molecular formula	C19 H22 N2 O4 S	
Formula weight	374.44	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 9.6878(6) Å	a= 90°.
	b = 23.1088(14) Å	b= 117.3470(18)°.
	c = 9.8408(6) Å	g = 90°.
Volume	1956.9(2) $Å^3$	
Z	4	
Density (calculated)	1.271 Mg/m^3	
Absorption coefficient	0.191 mm^{-1}	
F(000)	792	
Crystal size	0.225 x 0.135 x 0.117 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	1.762 to 28.315°.	
Index ranges	-10<=h<=12, -30<=k<=30, -13<=l<=9	
Reflections collected	19309	
Independent reflections	4709 [R(int) = 0.0530]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.6864	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4709 / 1 / 241	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.0998	
R indices (all data)	R1 = 0.0599, wR2 = 0.1099	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.423 and -0.433 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for Hein03. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	6140(1)	3229(1)	9375(1)	14(1)
O(1)	7615(1)	3443(1)	10476(1)	20(1)
O(2)	5415(1)	2759(1)	9758(1)	20(1)
O(3)	-213(1)	4395(1)	7992(1)	23(1)
O(4)	1728(1)	4437(1)	10399(1)	20(1)
N(1)	5260(2)	4236(1)	8289(2)	14(1)
N(2)	4866(2)	3763(1)	8942(2)	15(1)
C(1)	1269(2)	3539(1)	5998(2)	18(1)
C(2)	1758(2)	4000(1)	6544(2)	14(1)
C(3)	2512(2)	4541(1)	7228(2)	12(1)
C(4)	4169(2)	4592(1)	7503(2)	13(1)
C(5)	4578(2)	5112(1)	6854(2)	17(1)
C(6)	3980(2)	5660(1)	7273(2)	17(1)
C(7)	2212(2)	5649(1)	6601(2)	17(1)
C(8)	1579(2)	5095(1)	6917(2)	14(1)
C(9)	2200(2)	4834(1)	8483(2)	14(1)
C(10)	1091(2)	4536(1)	8894(2)	16(1)
C(11)	750(2)	4125(1)	10916(2)	24(1)
C(12)	1619(3)	4091(1)	12622(2)	42(1)
C(13)	6241(2)	3064(1)	7683(2)	13(1)
C(14)	7274(2)	3367(1)	7330(2)	15(1)
C(15)	7338(2)	3234(1)	5985(2)	18(1)
C(16)	6375(2)	2815(1)	4989(2)	19(1)
C(17)	5327(2)	2531(1)	5355(2)	22(1)
C(18)	5254(2)	2648(1)	6701(2)	19(1)
C(19)	6459(3)	2671(1)	3528(2)	31(1)

Table 3. Bond lengths [Å] and angles [°] for Hein03.

S(1)-O(1)	1.4278(12)	C(16)-C(17)	1.388(3)
S(1)-O(2)	1.4334(12)	C(16)-C(19)	1.514(2)
S(1)-N(2)	1.6559(14)	C(17)-H(17)	0.9500
S(1)-C(13)	1.7547(16)	C(18)-C(17)	1.385(2)
O(3)-C(10)	1.208(2)	C(18)-H(18)	0.9500
O(4)-C(10)	1.337(2)	C(19)-H(19A)	0.9800
O(4)-C(11)	1.455(2)	C(19)-H(19B)	0.9800
N(1)-N(2)	1.4070(19)	C(19)-H(19C)	0.9800
N(1)-C(4)	1.281(2)		
N(2)-H(2)	0.874(15)	O(1)-S(1)-O(2)	120.22(8)
C(1)-H(1)	0.9500	O(1)-S(1)-N(2)	107.78(7)
C(2)-C(1)	1.190(2)	O(1)-S(1)-C(13)	108.77(8)
C(2)-C(3)	1.448(2)	O(2)-S(1)-N(2)	103.59(7)
C(3)-C(4)	1.504(2)	O(2)-S(1)-C(13)	109.43(8)
C(3)-C(9)	1.556(2)	N(2)-S(1)-C(13)	106.09(7)
C(4)-C(5)	1.496(2)	C(10)-O(4)-C(11)	115.35(13)
C(5)-H(5A)	0.9900	C(4)-N(1)-N(2)	116.97(14)
C(5)-H(5B)	0.9900	S(1)-N(2)-H(2)	109.1(13)
C(6)-C(5)	1.527(2)	N(1)-N(2)-S(1)	111.76(11)
C(6)-H(6A)	0.9900	N(1)-N(2)-H(2)	116.7(13)
C(6)-H(6B)	0.9900	C(2)-C(1)-H(1)	180.0
C(6)-C(7)	1.527(2)	C(1)-C(2)-C(3)	173.86(18)
C(7)-H(7A)	0.9900	C(2)-C(3)-C(4)	114.87(14)
C(7)-H(7B)	0.9900	C(2)-C(3)-C(8)	120.54(14)
C(8)-C(3)	1.516(2)	C(2)-C(3)-C(9)	120.28(14)
C(8)-C(7)	1.512(2)	C(4)-C(3)-C(8)	117.27(13)
C(8)-H(8)	1.0000	C(4)-C(3)-C(9)	113.76(13)
C(8)-C(9)	1.500(2)	C(8)-C(3)-C(9)	58.46(10)
C(9)-H(9)	1.0000	N(1)-C(4)-C(3)	125.05(14)
C(10)-C(9)	1.481(2)	N(1)-C(4)-C(5)	117.80(15)
C(11)-H(11A)	0.9900	C(5)-C(4)-C(3)	117.11(14)
C(11)-H(11B)	0.9900	C(4)-C(5)-H(5A)	109.6
C(11)-C(12)	1.495(3)	C(4)-C(5)-H(5B)	109.6
C(12)-H(12A)	0.9800	C(4)-C(5)-C(6)	110.06(13)
C(12)-H(12B)	0.9800	H(5A)-C(5)-H(5B)	108.2
C(12)-H(12C)	0.9800	C(6)-C(5)-H(5A)	109.6
C(13)-C(18)	1.387(2)	C(6)-C(5)-H(5B)	109.6
C(14)-C(13)	1.390(2)	C(5)-C(6)-H(6A)	109.4
C(14)-H(14)	0.9500	C(5)-C(6)-H(6B)	109.4
C(14)-C(15)	1.388(2)	H(6A)-C(6)-H(6B)	108.0
C(15)-H(15)	0.9500	C(7)-C(6)-C(5)	110.98(14)
C(16)-C(15)	1.390(2)	C(7)-C(6)-H(6A)	109.4

C(7)-C(6)-H(6B)	109.4
C(6)-C(7)-H(7A)	108.8
C(6)-C(7)-H(7B)	108.8
H(7A)-C(7)-H(7B)	107.7
C(8)-C(7)-C(6)	113.93(14)
C(8)-C(7)-H(7A)	108.8
C(8)-C(7)-H(7B)	108.8
C(3)-C(8)-H(8)	114.1
C(7)-C(8)-C(3)	119.75(14)
C(7)-C(8)-H(8)	114.1
C(9)-C(8)-C(3)	62.11(11)
C(9)-C(8)-C(7)	122.83(14)
C(9)-C(8)-H(8)	114.1
C(3)-C(9)-H(9)	116.9
C(8)-C(9)-C(3)	59.44(10)
C(8)-C(9)-H(9)	116.9
C(10)-C(9)-C(3)	116.37(13)
C(10)-C(9)-C(8)	117.94(14)
C(10)-C(9)-H(9)	116.9
O(3)-C(10)-O(4)	124.27(16)
O(3)-C(10)-C(9)	124.74(15)
O(4)-C(10)-C(9)	110.99(14)
O(4)-C(11)-H(11A)	110.2
O(4)-C(11)-H(11B)	110.2
O(4)-C(11)-C(12)	107.33(15)
H(11A)-C(11)-H(11B)	108.5
C(12)-C(11)-H(11A)	110.2
C(12)-C(11)-H(11B)	110.2
C(11)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(14)-C(13)-S(1)	119.21(12)
C(18)-C(13)-S(1)	119.34(13)
C(18)-C(13)-C(14)	121.41(16)
C(13)-C(14)-H(14)	120.7
C(15)-C(14)-C(13)	118.63(15)
C(15)-C(14)-H(14)	120.7
C(14)-C(15)-H(15)	119.4
C(14)-C(15)-C(16)	121.14(16)
C(16)-C(15)-H(15)	119.4
C(15)-C(16)-C(19)	120.72(16)
C(17)-C(16)-C(15)	118.74(16)
C(17)-C(16)-C(19)	120.54(16)
C(16)-C(17)-H(17)	119.3
C(18)-C(17)-C(16)	121.43(16)
C(18)-C(17)-H(17)	119.3
C(13)-C(18)-H(18)	120.7
C(17)-C(18)-C(13)	118.61(16)
C(17)-C(18)-H(18)	120.7
C(16)-C(19)-H(19A)	109.5
C(16)-C(19)-H(19B)	109.5
C(16)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Hein03. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	15(1)	13(1)	12(1)	2(1)	6(1)	2(1)
O(1)	16(1)	24(1)	13(1)	-1(1)	2(1)	3(1)
O(2)	26(1)	17(1)	21(1)	7(1)	14(1)	2(1)
O(3)	17(1)	28(1)	22(1)	-1(1)	7(1)	-7(1)
O(4)	21(1)	25(1)	16(1)	-1(1)	11(1)	-7(1)
N(1)	17(1)	11(1)	15(1)	0(1)	8(1)	-1(1)
N(2)	14(1)	13(1)	17(1)	2(1)	7(1)	1(1)
C(1)	20(1)	15(1)	17(1)	-1(1)	7(1)	-1(1)
C(2)	14(1)	15(1)	13(1)	2(1)	5(1)	1(1)
C(3)	14(1)	10(1)	11(1)	0(1)	4(1)	0(1)
C(4)	15(1)	13(1)	11(1)	-3(1)	6(1)	-2(1)
C(5)	18(1)	15(1)	19(1)	2(1)	10(1)	-2(1)
C(6)	19(1)	12(1)	18(1)	1(1)	8(1)	-3(1)
C(7)	19(1)	12(1)	18(1)	2(1)	7(1)	0(1)
C(8)	14(1)	11(1)	14(1)	0(1)	5(1)	0(1)
C(9)	14(1)	13(1)	12(1)	-2(1)	5(1)	-2(1)
C(10)	19(1)	13(1)	17(1)	-2(1)	9(1)	0(1)
C(11)	28(1)	27(1)	25(1)	1(1)	17(1)	-7(1)
C(12)	41(1)	62(2)	27(1)	7(1)	20(1)	-13(1)
C(13)	14(1)	11(1)	12(1)	1(1)	4(1)	2(1)
C(14)	14(1)	13(1)	15(1)	1(1)	4(1)	-1(1)
C(15)	18(1)	17(1)	19(1)	3(1)	10(1)	0(1)
C(16)	23(1)	18(1)	17(1)	0(1)	10(1)	5(1)
C(17)	25(1)	18(1)	20(1)	-8(1)	8(1)	-5(1)
C(18)	19(1)	16(1)	22(1)	-2(1)	10(1)	-4(1)
C(19)	43(1)	30(1)	24(1)	-5(1)	20(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Hein03.

	x	y	z	U(eq)
H(2)	3928(18)	3623(8)	8420(20)	22(5)
H(1)	880	3170	5563	22
H(5A)	4109	5076	5727	20
H(5B)	5720	5135	7262	20
H(6A)	4449	5695	8400	20
H(6B)	4298	6003	6879	20
H(7A)	1880	5978	7026	20
H(7B)	1752	5705	5480	20
H(8)	435	5042	6270	17
H(9)	3097	5036	9328	16
H(11A)	523	3732	10468	29
H(11B)	-246	4332	10597	29
H(12A)	2574	3867	12922	62
H(12B)	969	3901	13013	62
H(12C)	1884	4482	13049	62
H(14)	7923	3660	7997	18
H(15)	8053	3434	5740	21
H(17)	4645	2251	4668	26
H(18)	4543	2447	6947	23
H(19A)	5453	2753	2646	46
H(19B)	6710	2260	3528	46
H(19C)	7267	2907	3463	46

Section 2.5.6 – Supporting information – General Procedure for Reaction Sampling and Kinetic Analysis

All kinetic experiments were conducted with automated sampling with a custom-built apparatus. From the reaction vial, 15 µL samples were automatically taken by a programmable syringe pump at defined time points through a PEEK capillary (1/32" outer diameter, 0.15 mm inner diameter). Samples were rerouted with a Gilson 918 Injection Valve Actuator (rheodyne) to a Gilson 215 automated liquid handler robot, which allowed for the dilution of the samples with 1 mL of methanol directly into LC

vials. The timing and synchronization of the liquid sampling technology was governed by the pump that removed the timed aliquot, triggered the actuation of the rheodyne, and activated the subsequent sample dilution and quenching. These samples were manually transferred to the HPLC-MS for analysis as they were prepared or upon completion of the sampling period.

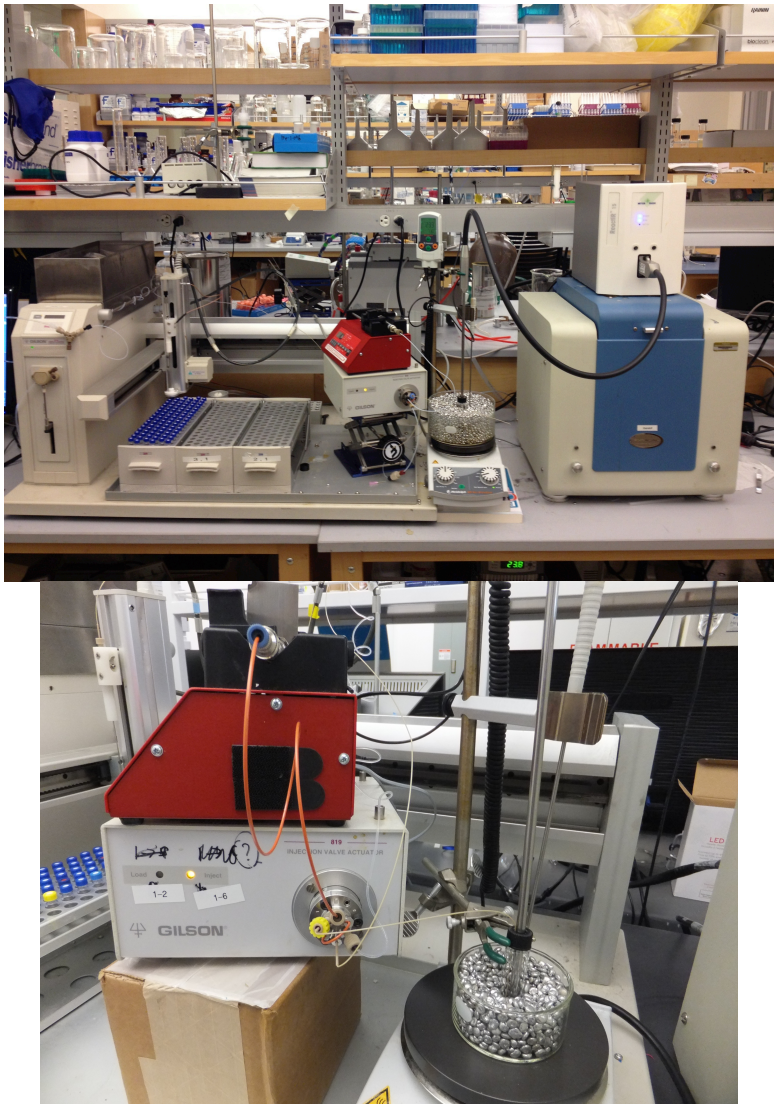


Figure S1: Set up for Tandem reaction progress monitoring. Above: Total Set up showing automatic liquid handling robot coupled to ReacIR; Below: Reactor set-up showing the ReactIR probe for in situ IR analysis and Rheodyne/syringe pump for liquid sampling

The individual aliquots were analyzed by HPLC/MS conducted on an Agilent 1260 Infinity apparatus under the one of the following conditions:

Poroshell 120 SB-C18, 2.1 x 100 mm, 2.7-Micron Column; Temperature = 25 ºC; Solvent A = water, 0.05 % TFA; Solvent B = acetonitrile, 0.05 % TFA; Flow Rate = 0.600 mL/min; Starting Conditions = 70 % A, 30 % B; 3.5 min 33% B; 7.5 min 34% B; 8 min 50%B; 8.5 min 80% B; 10.5 min 80% B.

Procedure for cycloisomerization catalyzed by $Cu(PF_6)$·$MeCN_4$

A solution of ketone X (246 mg, 1.193 mmol) in MeOH (6 mL) was treated with $TsNHNH_2$ (222 mg, 1.193 mmol) and heated to 45°C. The reaction kinetics were monitored continuously using the protocol detailed above. When the concentration of the intermediate hydrazones reached a plateau $Cu(PF_6)$•$MeCN_4$ (0.445 mg, 1.193 μmol, 0.001 equiv) was added in a single portion and reaction monitoring continued.

Section 2.5.7. Computational Methods.

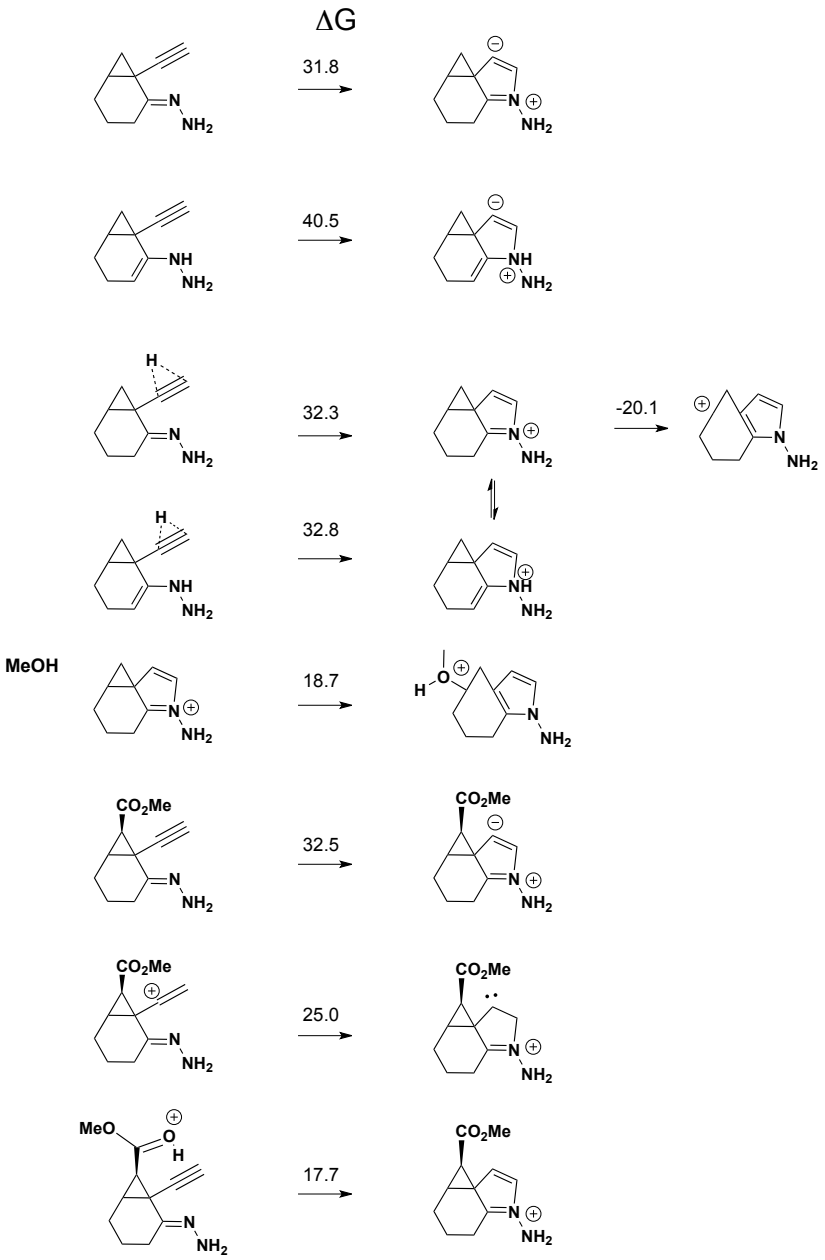
Part 1: Methods
Part 2: SI Table 1. Model systems explored computationally
Part 3: KIE computations
Part 4: Coordinates of stationary points

Computationally, the tosyl and ethyl groups of the substrate were truncated to mesyl and methyl groups for efficiency, and explicit methanol and CH_3SO_2H molecules were included. Stationary points were located using the M06-2X/6-31+G(d,p) DFT method (Zhao, Y.; Truhlar, D. *Theor Chem Account* **2008**, *120*, 215.) implemented in GAUSSIAN09 (Gaussian 09, Revision B.01 Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Wallingford CT, 2009.), in the gas phase. These points were then reoptimized using the SMD continuum solvation model (Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *The Journal of Physical Chemistry B* **2009**, *113*, 6378.) in methanol at 365 K. Frequency analysis was used to assign stationary points as transition state structures or minima, and Intrinsic Reaction Coordinate (IRC) calculations ((a) Gonzalez, C.; Schlegel, H. B. *The Journal of Chemical Physics* **1991**, *95*, 5853. (b) Gonzalez, C.; Schlegel, H. B. *The Journal of Chemical Physics* **1989**, *90*, 2154. (c) C. Lee, C.; Yang, W.; Parr, R. G. *Physical Review B* **1988**, *37*, 785. (d) Fukui, K. *Accounts of Chemical Research* **1981**, *14*, 363.) were utilized to connect transition state structures to their associated minima. Structures containing Copper were studied using the M062X/LanL2DZ model chemistry. (Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270-283.) Structural images were created using *Ball & Stick* (Ball and Stick 4.0a12,

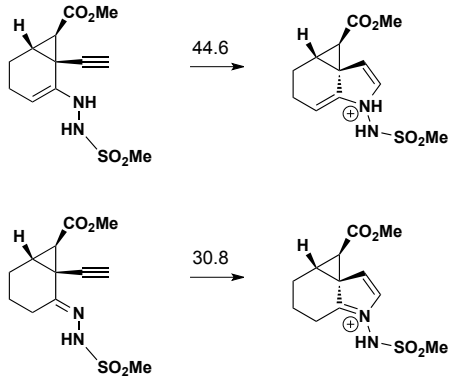
	M062X/6-31+G(d,p)	M062X/6-31+G(d,p) (smd,methanol)	M062X/LanL2DZ
Z-A	0	0	0
E-A	1.7	1.1	2.1
TSAC	30.8	29	29
C	-11.6	-17.8	-21.6
TSCD	-1	-4.9	-15.4
D	-45.3	-44.8	-61.8
Z-B	1	3.1	
E-B	0.5	5.7	
TSB	44.6		
TSZAEA	27.2		22.2
Enamine PR	-5.7		
Cu Reactant			0
Cu TS			21.4
Cu intermediate			5.4

Muller, N.; Faulk, A. *Johannes Kepler University Linz* **2004**.). Energies reported are gas phase Gibbs free energies (unless otherwise stated).
Predicted KIE values were computed using the Bigeleisen and Mayer method, as implemented in *Quiver*. (a) Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, *15*, 261-267. **[Ref. KIE_01]** (b) Saunders, W.; Laidig, K. E.; Wolfsberg, M. *J. Am. Chem. Soc.* **1999**, *111*, 8989-8994. **[Ref. KIE_02]** (c) A modified version of *Quiver* provided by Prof. Daniel Singleton (Texas A&M) was utilized.

Model Systems examined at M062X/6-31+G(d,p)

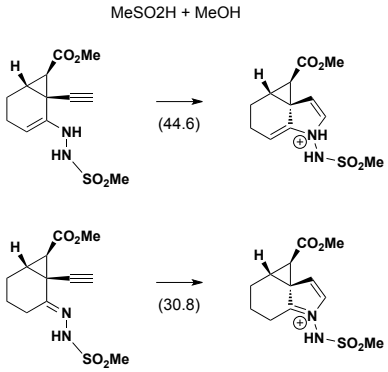


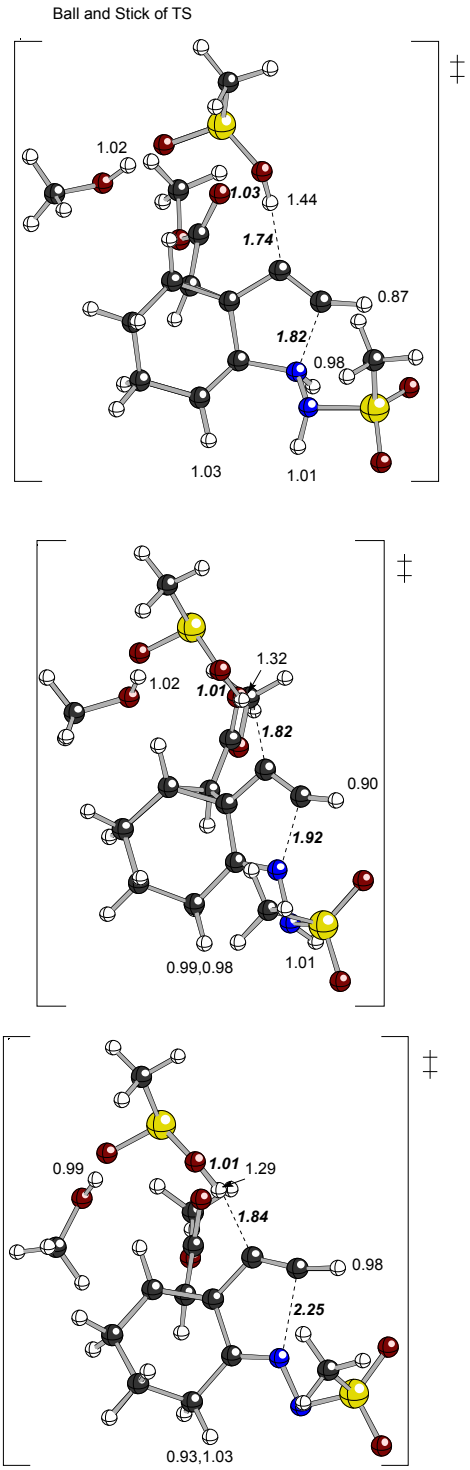
Systems explored with MeSO2H and MeOH as discrete counterions



Scheme 1. Model systems explored computationally using M062X/6-31+G(d,p) in the gas phase. Energies are presented as the uncorrected Gibbs free energy barrier compared to their respective reactants.

KIE Computations





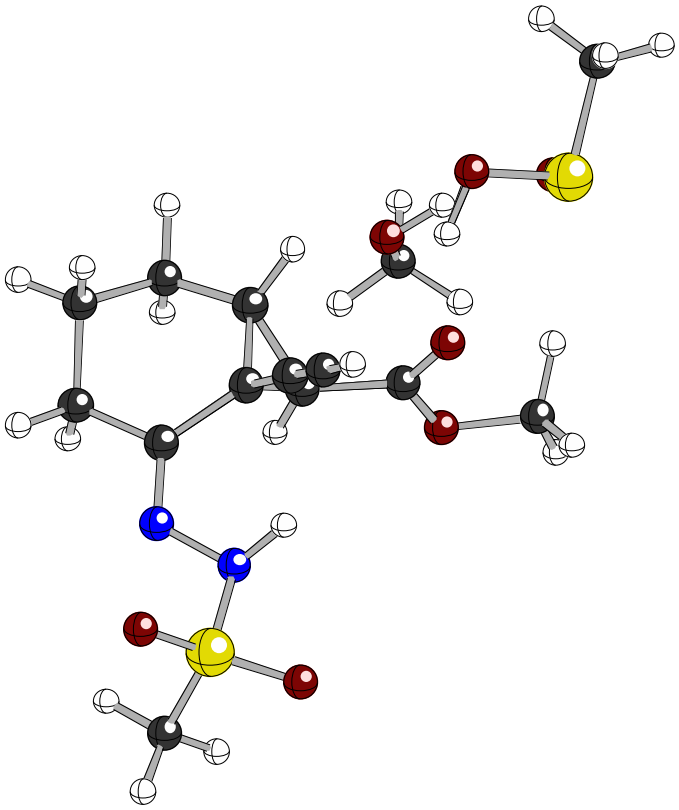
SI Figure 1. KIE computations on select TS structures.

Z-A

M062X/6-31+G(d,p)
HF = -1979.669295 hartrees (-1242262.27930545 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.391788 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.341909 hartrees (-1242056.84131659 kcal/mol)

M062X/6-31+G(d,p) scrf=(smd,methanol) temp=365
HF = -1979.7116877 hartrees (-1242288.88114863 kcal/mol)
Sum of electronic and thermal Free Energies =
-1979.410701 hartrees (-1242100.00898451 kcal/mol)
M062X/LanL2DZ HF = -1203.0033033 hartrees (-754896.602853783 kcal/mol)
Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z

1	6	1.033922	3.458486	-1.472457
2	6	2.247106	2.884956	-0.743359
3	6	0.787211	0.730684	-0.616554
4	6	-0.430321	1.625847	-0.606922
5	6	-0.241339	3.130997	-0.692775
6	1	0.964702	3.033110	-2.481285
7	1	1.150287	4.540739	-1.583456
8	1	-0.179801	3.564995	0.312950
9	1	-1.122673	3.565625	-1.170045
10	6	-0.101627	0.859885	0.635069
11	1	0.341293	1.406030	1.462538
12	6	2.136741	1.392941	-0.489548
13	7	3.204671	0.791368	-0.132040
14	7	3.148827	-0.530160	0.241394
15	6	0.748368	-0.459431	-1.439107
16	6	0.781975	-1.438752	-2.144898
17	1	0.802739	-2.305418	-2.768292
18	1	3.177547	3.066447	-1.287949
19	6	-1.018298	-0.233020	1.035217
20	8	-1.546963	-1.020536	0.270804
21	8	-1.204838	-0.270545	2.349078
22	6	-2.209487	-1.194822	2.791986
23	1	-2.292463	-1.039201	3.866111
24	1	-3.155194	-0.979098	2.285117
25	1	-1.899349	-2.218426	2.572229
26	1	2.345774	3.389161	0.228132
27	16	4.654106	-1.306806	0.131602
28	8	4.353757	-2.688434	0.476172
29	6	5.528374	-0.508536	1.457215
30	1	5.526218	0.563040	1.255908
31	1	5.022969	-0.746895	2.392000
32	1	6.543487	-0.906977	1.439267
33	8	5.330228	-0.988340	-1.114512
34	8	-4.788594	-0.500508	0.380574
35	16	-4.398468	-1.559909	-0.607490
36	8	-3.340080	-0.924334	-1.690882
37	1	2.430546	-1.126264	-0.182433
38	1	-2.456665	-0.948805	-1.260512
39	1	-1.277484	1.217247	-1.149810
40	8	-3.033278	1.598360	0.889254
41	1	-3.742392	0.975142	0.649078
42	6	-3.318685	2.161138	2.150864
43	1	-3.475205	1.391850	2.918904
44	1	-2.454995	2.763489	2.445749

45	1	-4.202376	2.810556	2.119509
46	6	-5.741696	-1.567076	-1.803968
47	1	-5.498008	-2.255309	-2.614214
48	1	-6.643253	-1.882626	-1.277649
49	1	-5.845729	-0.544505	-2.171606

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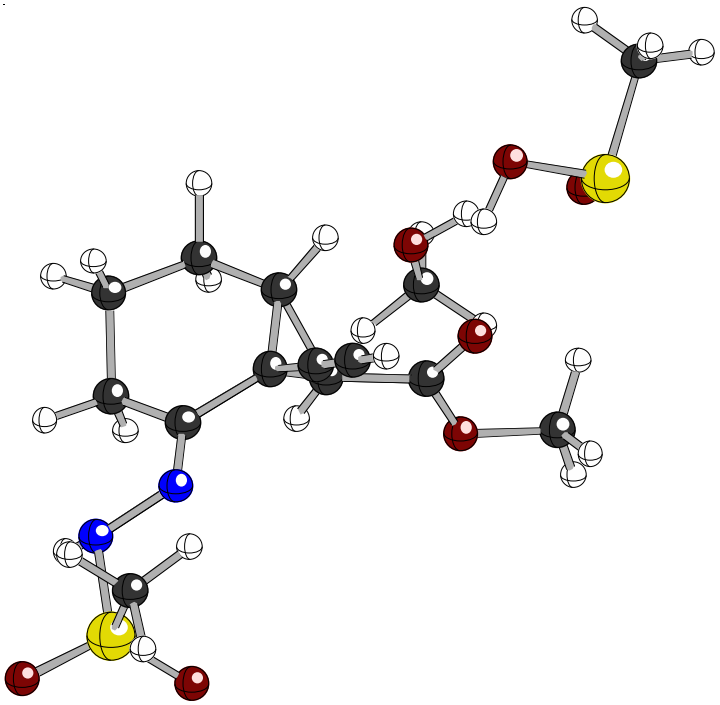
***E*-A**

M062X/6-31+G(d,p)
HF = -1979.6668742 hartrees (-1242260.76022924 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.391907 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.339219 hartrees (-1242055.15331469 kcal/mol)
M062X/6-31+g(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.7150219 hartrees (-1242290.97339247 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.390803 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.409024 hartrees (-1242098.95665024 kcal/mol)
M062X/LanL2DZ HF = -1202.999898 hartrees (-754894.46599398 kcal/mol)
Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	1.217449	2.772244	-1.806670
2	6	2.198269	2.255698	-0.747621
3	6	0.678349	0.166548	-0.648230
4	6	-0.475503	1.088602	-0.986697
5	6	-0.231286	2.534875	-1.388717
6	1	1.418091	2.253142	-2.751616
7	1	1.394133	3.838058	-1.979229
8	1	-0.498579	3.190388	-0.551492
9	1	-0.905840	2.790587	-2.209446
10	6	-0.291651	0.673796	0.436455
11	1	0.116137	1.407977	1.124819
12	6	2.056475	0.762948	-0.558041
13	7	3.010378	-0.054652	-0.340033
14	7	4.298844	0.429938	-0.262657
15	6	0.612776	-1.212831	-1.076372
16	6	0.562230	-2.353378	-1.464793
17	1	0.506984	-3.365473	-1.797667
18	1	3.222897	2.480803	-1.058422
19	6	-1.310178	-0.215747	1.038438
20	8	-1.921646	-1.090014	0.449470

21	8	-1.499130	0.046498	2.326946
22	6	-2.585372	-0.662667	2.939739
23	1	-2.630481	-0.293825	3.962904
24	1	-3.513705	-0.448538	2.400730
25	1	-2.387894	-1.736312	2.924134
26	1	2.025062	2.775852	0.206184
27	16	5.350842	-0.689183	0.473654
28	8	6.634052	-0.001926	0.474768
29	6	5.319770	-1.985451	-0.742747
30	1	4.282735	-2.305074	-0.855436
31	1	5.727347	-1.591269	-1.672583
32	1	5.939429	-2.789932	-0.344633
33	8	4.797812	-1.204873	1.713674
34	8	-5.060657	-0.059336	0.429079
35	16	-4.868508	-1.354358	-0.304246
36	8	-3.743103	-1.144229	-1.480619
37	1	4.439274	1.342637	0.176973
38	1	-2.866683	-1.210004	-1.038344
39	1	-1.303102	0.585237	-1.476861
40	8	-3.033333	1.850299	0.444515
41	1	-3.816770	1.288535	0.308141
42	6	-3.232768	2.628509	1.604607
43	1	-3.540030	2.016338	2.462528
44	1	-2.279125	3.103930	1.852431
45	1	-3.983629	3.412820	1.446531
46	6	-6.218840	-1.396777	-1.491934
47	1	-6.101021	-2.265802	-2.140496
48	1	-7.148953	-1.452323	-0.925208
49	1	-6.168455	-0.467665	-2.062797

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TS_{AC}

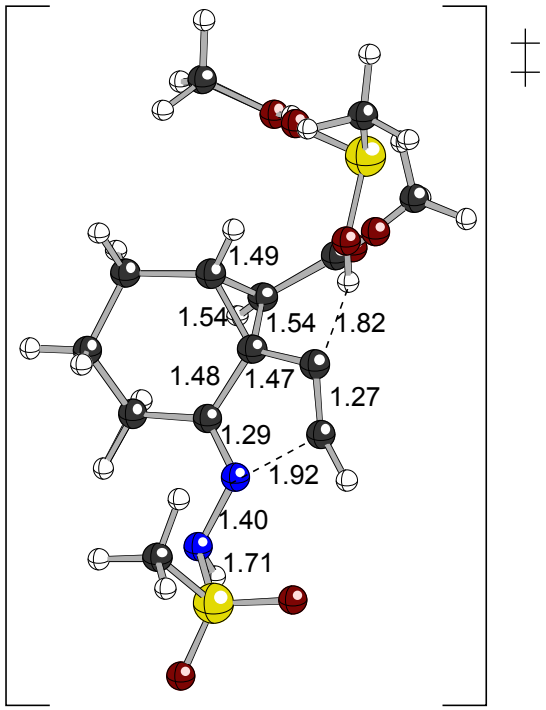
M062X/6-31+G(d,p)
HF = -1979.6231421 hartrees (-1242233.31789917 kcal/mol)
Imaginary Frequencies: 1 (-342.6143 1/cm)
Zero-point correction = 0.391033 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.292761 hartrees (-1242026.00045511 kcal/mol)
M062X/6-31+g(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.6707906 hartrees (-1242263.21780941 kcal/mol)
Imaginary Frequencies: 1 (-364.9102 1/cm)

Zero-point correction = 0.388687 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.364538 hartrees (-1242071.04124038 kcal/mol)
M062X/LanL2DZ HF = -1202.999898 hartrees (-754894.46599398 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-0.978061	-1.884237	-2.364061
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3	6	-0.223798	-0.450976	0.074168
4	6	0.862793	-0.806560	-0.933127
5	6	0.522845	-1.670390	-2.146881
6	1	-1.424172	-0.970072	-2.774730
7	1	-1.143749	-2.679452	-3.096738
8	1	1.019774	-2.641802	-2.033874
9	1	0.949669	-1.202502	-3.038382
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11	1	0.620252	-2.494513	0.472254
12	6	-1.558382	-1.056019	-0.148685

13	7	-2.498389	-0.360305	0.387492
14	7	-3.827429	-0.787844	0.235103
15	6	-0.345999	0.844001	0.761841
16	6	-1.536193	1.141483	1.107288
17	1	-2.280786	1.771398	1.560009
18	1	-2.774762	-2.431923	-1.230889
19	6	1.963439	-1.043148	1.370981
20	8	2.400608	0.076731	1.503439
21	8	2.387240	-2.097170	2.070918
22	6	3.559733	-1.862928	2.858134
23	1	3.771339	-2.808486	3.354402
24	1	4.378176	-1.576344	2.194000
25	1	3.374181	-1.073532	3.589041
26	1	-1.270816	-3.126827	-0.600414
27	16	-4.932824	0.515457	0.286087
28	8	-6.229447	-0.137336	0.316017
29	6	-4.621069	1.247634	-1.303150
30	1	-3.569950	1.542034	-1.338580
31	1	-4.869129	0.517708	-2.072731
32	1	-5.264977	2.125930	-1.365807
33	8	-4.561792	1.477431	1.311866
34	8	3.520932	1.254552	-1.018225
35	16	3.211161	2.328517	-0.004459
36	8	1.615844	2.630676	-0.040245
37	1	-4.105054	-1.438338	0.975471
38	1	1.061586	1.962266	0.484476
39	1	1.597264	-0.015510	-1.076484
40	8	4.050022	-1.378597	-0.357521
41	1	3.933572	-0.409781	-0.426164
42	6	4.277050	-1.866355	-1.659360
43	1	4.315835	-2.957825	-1.606828
44	1	3.470528	-1.577402	-2.349304
45	1	5.226308	-1.504037	-2.074602
46	6	3.607967	3.845524	-0.889518
47	1	3.317940	4.703258	-0.281303
48	1	4.682651	3.843421	-1.076533
49	1	3.051408	3.822165	-1.828077

13-A14-62-06-dicounteriontsguess.log

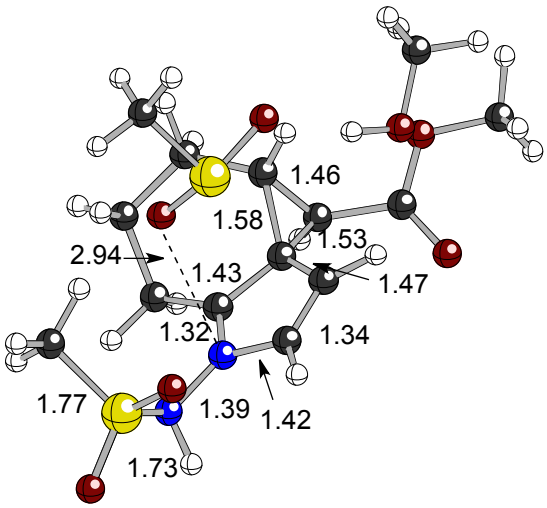
C

M062X/6-31+G(d,p)
HF = -1979.6957487 hartrees (-1242278.87926674 kcal/mol)
Imaginary Frequencies: none found

Zero-point correction = 0.394947 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.360438 hartrees (-1242068.46844938 kcal/mol)
M062X/6-31+G(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.7523254 hartrees (-1242314.38171175 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.393650 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.439125 hartrees (-1242117.84532875 kcal/mol)
M062X/LanL2DZ HF = -1202.9571469 hartrees (-754867.639251219 kcal/mol)
Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
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3	6	-0.747198	-0.993674	0.092214
4	6	-1.554570	-0.270615	1.240080
5	6	-0.977400	-0.251160	2.654166
6	1	1.123515	0.167244	2.540183
7	1	0.682902	-0.948831	3.856429
8	1	-1.616819	-0.888623	3.277912
9	1	-1.074830	0.772728	3.023263
10	6	-2.067560	-1.513912	0.672791

11	1	-1.984442	-2.422370	1.269156
12	6	0.528165	-1.483872	0.525408
13	7	1.361562	-1.347479	-0.491738
14	7	2.698695	-1.707276	-0.402713
15	6	-0.567937	-0.536455	-1.289464
16	6	0.712321	-0.769513	-1.619485
17	1	1.287905	-0.563067	-2.508387
18	1	1.915689	-2.135802	1.991399
19	6	-3.221912	-1.547617	-0.303301
20	8	-3.162063	-2.042453	-1.400315
21	8	-4.321887	-1.029809	0.239624
22	6	-5.442288	-0.960214	-0.651204
23	1	-6.223759	-0.439470	-0.100843
24	1	-5.153592	-0.405649	-1.546708
25	1	-5.764389	-1.965874	-0.929528
26	1	0.263554	-2.757635	2.189403
27	16	3.885631	-0.481759	-0.713243
28	8	5.068439	-1.298709	-0.930098
29	6	3.961655	0.355927	0.842835
30	1	2.979382	0.823298	1.003932
31	1	4.241194	-0.375941	1.600661
32	1	4.739944	1.112953	0.726040
33	8	3.405642	0.423470	-1.739687
34	8	-1.013559	2.467815	-0.007838
35	16	0.512112	2.417330	-0.216352
36	8	1.121968	1.331417	0.690770
37	1	2.913518	-2.485727	-1.028880
38	1	-1.349927	-0.129288	-1.915788
39	1	-1.962753	0.660915	0.863643
40	8	-2.998605	1.251490	-1.179946
41	1	-2.163103	1.709137	-0.893682
42	6	-4.063170	2.032839	-0.677807
43	1	-4.432191	1.632544	0.278791
44	1	-3.750681	3.070819	-0.519993
45	1	-4.888962	2.024604	-1.398012
46	6	0.993835	3.917128	0.685522
47	1	2.083386	3.992425	0.697657
48	1	0.550444	4.784861	0.193725
49	1	0.598074	3.803754	1.698016

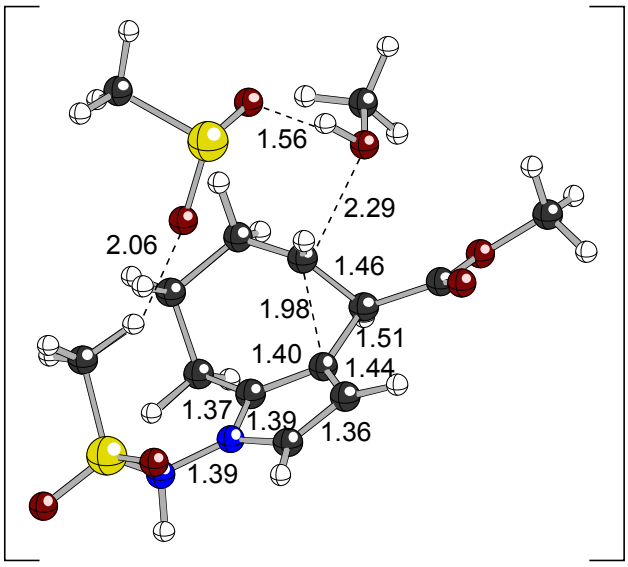
13-A14-63-02-dicounteriontsfopt.log

TS_{CD}

M062X/6-31+G(d,p)
HF = -1979.6790346 hartrees (-1242268.39100185 kcal/mol)
Imaginary Frequencies: 1 (-275.4944 1/cm)
Zero-point correction = 0.394516 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.343484 hartrees (-1242057.82964484 kcal/mol)
M062X/6-31+G(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.7317401 hartrees (-1242301.46423015 kcal/mol)
Imaginary Frequencies: 2 (-378.0906 1/cm) (-14.7231 1/cm)
Zero-point correction = 0.392758 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.418434 hartrees (-1242104.86151934 kcal/mol)
M062X/LanL2DZ HF = -1203.0277814 hartrees (-754911.963106314 kcal/mol)
Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	0.365108	0.524713	2.262059
2	6	0.845948	-0.934156	2.300339
3	6	-0.281661	-1.781150	0.096151
4	6	-1.338502	-0.149331	0.473565
5	6	-1.074308	0.603126	1.737371
6	1	0.992111	1.118347	1.591665

7	1	0.405299	0.967817	3.262145
8	1	-1.764571	0.219273	2.500062
9	1	-1.310148	1.648134	1.505743
10	6	-1.726078	-1.560536	0.495540
11	1	-1.992225	-1.933093	1.485096
12	6	0.811817	-1.484876	0.917561
13	7	1.927137	-1.674874	0.153185
14	7	3.203071	-1.426921	0.635561
15	6	0.225660	-2.127371	-1.205832
16	6	1.581718	-2.085728	-1.130997
17	1	2.351545	-2.265100	-1.865516
18	1	1.863342	-1.001233	2.692183
19	6	-2.784561	-1.883797	-0.534653
20	8	-2.628290	-1.858858	-1.728226
21	8	-3.941660	-2.137801	0.077672
22	6	-5.080859	-2.185309	-0.791769
23	1	-5.931043	-2.403196	-0.148416
24	1	-5.194984	-1.214607	-1.279784
25	1	-4.951209	-2.964972	-1.544030
26	1	0.191530	-1.529501	2.949480
27	16	4.158926	-0.307690	-0.268875
28	8	5.439650	-0.388247	0.412090
29	6	3.333246	1.222163	0.055492
30	1	2.304635	1.201975	-0.328549
31	1	3.374843	1.406429	1.129083
32	1	3.906346	1.976046	-0.488439
33	8	4.064190	-0.608417	-1.688820
34	8	-1.958973	2.833437	-0.330579
35	16	-0.609183	2.994688	-1.075282
36	8	0.424910	2.038695	-0.462991
37	1	3.752629	-2.283721	0.728861
38	1	-0.368704	-2.385187	-2.067318
39	1	-1.175787	0.325176	-0.486115
40	8	-3.393777	0.766177	0.047753
41	1	-2.919947	1.609749	-0.250961
42	6	-4.261491	1.084790	1.113432
43	1	-4.613525	0.147922	1.557916
44	1	-3.754934	1.681090	1.884526
45	1	-5.128767	1.653061	0.756222
46	6	-0.086295	4.583898	-0.374419
47	1	0.911163	4.825429	-0.747183
48	1	-0.806576	5.352592	-0.660126
49	1	-0.075235	4.449658	0.710503

13-A14-71-07-methanolts.log

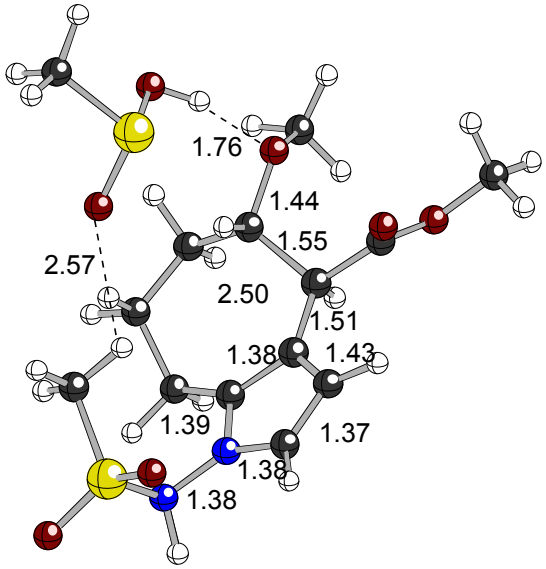
D
M062X/6-31+G(d,p)
HF = -1979.7532585 hartrees (-1242314.96724133 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.398504 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.414025 hartrees (-1242102.09482775 kcal/mol)

M062X/6-31+G(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.7994357 hartrees (-1242343.94389611 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.397003 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.482056 hartrees (-1242144.78496056 kcal/mol)
M062X/LanL2DZ HF = -1203.1017474 hartrees (-754958.377510974 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z

1	6	0.259329	0.574560	2.322134
2	6	1.068520	-0.723972	2.243654
3	6	0.010024	-1.769795	0.094214
4	6	-1.690680	-0.058679	0.746221
5	6	-1.248338	0.398998	2.136974
6	1	0.612516	1.292950	1.575099
7	1	0.423383	1.024332	3.308073
8	1	-1.639587	-0.291125	2.898170
9	1	-1.719482	1.375262	2.306693
10	6	-1.444413	-1.559014	0.439523
11	1	-1.738186	-2.170015	1.302221
12	6	1.056613	-1.353454	0.885865
13	7	2.220127	-1.659710	0.198275
14	7	3.460093	-1.214141	0.616229
15	6	0.560194	-2.339979	-1.097350
16	6	1.922808	-2.252363	-1.012288
17	1	2.708692	-2.497739	-1.709965
18	1	2.107713	-0.529963	2.524347
19	6	-2.353538	-1.919341	-0.721833
20	8	-2.192314	-1.574995	-1.865991
21	8	-3.412629	-2.640572	-0.313140
22	6	-4.372886	-2.933507	-1.331537
23	1	-5.160718	-3.501844	-0.840379
24	1	-4.765770	-2.005114	-1.752332
25	1	-3.912261	-3.519753	-2.129146
26	1	0.673789	-1.439590	2.979440
27	16	4.136864	0.048903	-0.331627
28	8	5.412286	0.307577	0.317373
29	6	2.969384	1.350684	-0.018438
30	1	1.980200	1.054472	-0.377032
31	1	2.967177	1.562814	1.050668
32	1	3.322849	2.213072	-0.585787
33	8	4.092417	-0.280745	-1.748134
34	8	-2.536040	2.943210	0.055004
35	16	-1.259087	2.984459	-0.985792
36	8	0.001529	2.691393	-0.236477
37	1	4.147137	-1.963652	0.704170
38	1	0.005571	-2.731924	-1.936303
39	1	-1.131573	0.498651	-0.011631
40	8	-3.061620	0.301384	0.505141
41	1	-2.866145	2.014859	0.138009
42	6	-4.006239	-0.107448	1.486694
43	1	-3.907584	-1.176139	1.703533
44	1	-3.900155	0.472484	2.409641

45	1	-4.992368	0.075353	1.057195
46	6	-1.314606	4.778333	-1.104688
47	1	-0.464358	5.089948	-1.712437
48	1	-2.256730	5.082009	-1.562350
49	1	-1.226120	5.165627	-0.087791

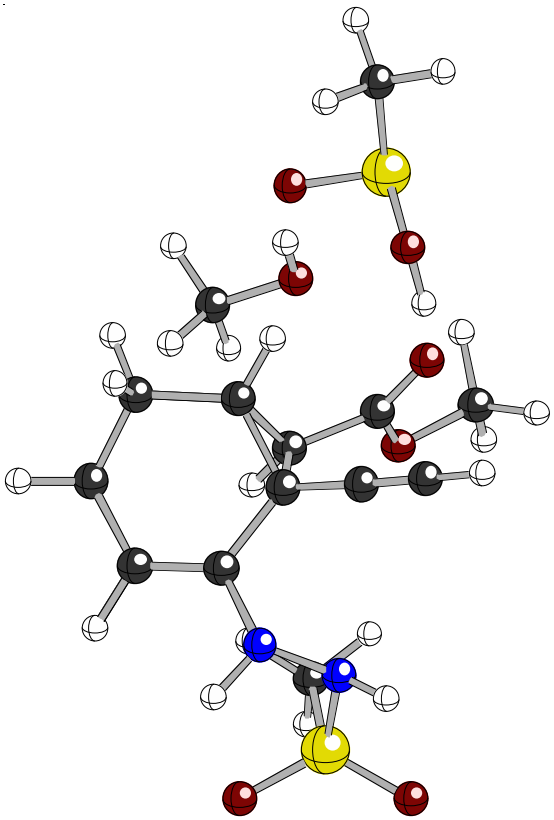
13-A14-72-02-methanolpr.log

***Z*-B**

M062X/6-31+G(d,p)
HF = -1979.6695816 hartrees (-1242262.45914982 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.392632 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.340308 hartrees (-1242055.83667308 kcal/mol)
M062X/6-31+g(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.7108796 hartrees (-1242288.3740578 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.391056 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.405826 hartrees (-1242096.94987326 kcal/mol)
Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-0.700206	-1.398280	2.906330
2	6	-1.854611	-1.619491	1.962795
3	6	-0.475059	-1.052018	-0.026596
4	6	0.749066	-1.010614	0.858133
5	6	0.654107	-1.632661	2.232724
6	1	-0.796544	-2.058402	3.774080
7	1	-0.745633	-0.374675	3.307074
8	1	1.469396	-1.259692	2.861135
9	1	0.813090	-2.710093	2.107668
10	6	0.082226	0.283451	0.513355
11	1	-0.542604	0.757585	1.262695
12	6	-1.745852	-1.499879	0.632390
13	7	-2.809492	-1.801917	-0.250022
14	7	-3.131825	-0.736523	-1.101302
15	6	-0.278590	-1.394383	-1.417726
16	6	-0.079918	-1.695878	-2.569329
17	1	0.098713	-1.967533	-3.585786

18	6	0.736582	1.237653	-0.413508
19	8	1.588026	0.958833	-1.237717
20	8	0.239733	2.465072	-0.272665
21	6	0.944822	3.489744	-0.984236
22	1	0.419362	4.416097	-0.759591
23	1	1.973868	3.523026	-0.619235
24	1	0.930653	3.284602	-2.056010
25	16	-4.291254	0.357738	-0.524939
26	8	-4.862494	0.970875	-1.714704
27	6	-3.301287	1.554798	0.344068
28	1	-2.839349	1.047779	1.192866
29	1	-2.552478	1.953866	-0.340791
30	1	-3.986506	2.332801	0.685306
31	8	-5.129518	-0.323204	0.457835
32	8	3.941413	-0.350958	0.673274
33	16	4.299875	-0.224618	-0.780822
34	8	3.254916	-1.135830	-1.659548
35	1	-3.394293	-1.043683	-2.036167
36	1	2.440653	-0.595294	-1.767770
37	1	1.685234	-1.186919	0.337462
38	8	2.521589	1.936429	1.419855
39	1	3.065473	1.134374	1.301800
40	6	2.001619	1.984861	2.727798
41	1	1.381636	1.105550	2.957730
42	1	2.792209	2.060897	3.484924
43	1	1.370101	2.874737	2.796086
44	6	5.639395	-1.402899	-1.001380
45	1	5.897165	-1.460828	-2.059553
46	1	6.484489	-1.048363	-0.410219
47	1	5.281253	-2.364180	-0.628480
48	1	-2.827614	-1.862939	2.385122
49	1	-3.630075	-2.155706	0.241537

13-A42-01-01-dicounterionenaminereactantZ.log

***E*-B**

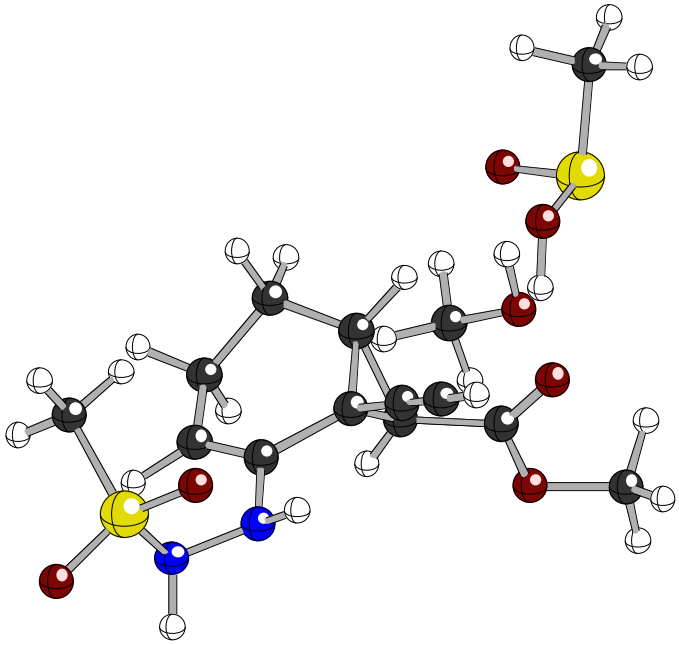
M062X/6-31+G(d,p)
HF = -1979.669916 hartrees (-1242262.66898916 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.392556 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.341175 hartrees (-1242056.38072425 kcal/mol)

M062X/6-31+G(d,p) scrf=(smd,solvent=methanol) temp=365
HF = -1979.709128 hartrees (-1242287.27491128 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.391231 (Hartree/Particle)

Temperature 365.000 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.401566 hartrees (-1242094.27668066 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-0.908984	-1.814907	-2.220326
2	6	-2.003136	-1.504160	-1.231868
3	6	-0.450600	-0.186151	0.196942
4	6	0.597203	-0.279979	-0.882752
5	6	0.162884	-0.724236	-2.260475
6	1	-1.338598	-1.938018	-3.219558
7	1	-0.443455	-2.782013	-1.978258
8	1	1.036740	-1.055980	-2.830562
9	1	-0.236909	0.159453	-2.772607
10	6	0.683377	-1.226863	0.278439
11	1	0.355950	-2.252285	0.146020
12	6	-1.799550	-0.761474	-0.133552

13	7	-2.761732	-0.542797	0.870109
14	7	-4.086297	-0.794501	0.524777
15	6	-0.441468	0.965733	1.071783
16	6	-0.493142	1.936591	1.788045
17	1	-0.529019	2.803022	2.410871
18	6	1.782655	-1.054146	1.259961
19	8	2.314930	0.004876	1.544832
20	8	2.110908	-2.206679	1.829910
21	6	3.286233	-2.170210	2.647914
22	1	3.400588	-3.179482	3.038715
23	1	4.136668	-1.889228	2.022944
24	1	3.159669	-1.451104	3.459101
25	16	-5.011195	0.582145	0.147464
26	8	-6.392590	0.160457	0.323453
27	6	-4.663219	0.817765	-1.580866
28	1	-3.584979	0.937889	-1.696651
29	1	-5.025997	-0.055534	-2.121699
30	1	-5.194499	1.722304	-1.881351
31	8	-4.471849	1.727085	0.871798
32	8	3.610010	0.953354	-1.386013
33	16	3.954517	1.831176	-0.214916
34	8	2.563699	2.448386	0.397973
35	1	-4.583005	-1.311526	1.249642
36	1	2.180255	1.748614	0.973478
37	1	1.337832	0.514728	-0.865275
38	8	3.734686	-1.683038	-0.491381
39	1	3.708578	-0.825452	-0.955910
40	6	3.346213	-2.725587	-1.355304
41	1	2.283766	-2.656203	-1.633338
42	1	3.947057	-2.747767	-2.273062
43	1	3.494949	-3.667892	-0.821938
44	6	4.416987	3.397285	-0.967274
45	1	4.579090	4.139106	-0.184496
46	1	5.328904	3.224295	-1.539831
47	1	3.595234	3.688298	-1.624109
48	1	-2.982987	-1.946946	-1.379770
49	1	-2.633832	0.316173	1.404089

13-A14-66-07-dicounterionenaminereactant.log

TS_B

M062X/6-31+G(d,p)

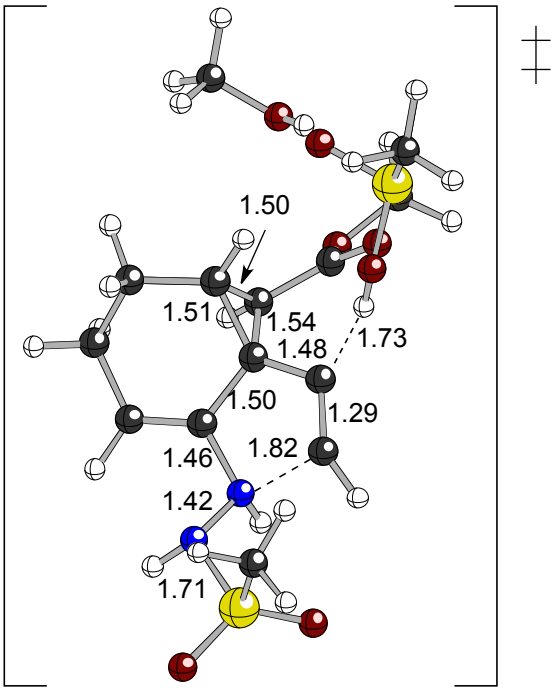
HF = -1979.6010091 hartrees (-1242219.42922034 kcal/mol)

Imaginary Frequencies: 1 (-352.5198 1/cm)

Zero-point correction = 0.390932 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.270853 hartrees (-1242012.25296603 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-0.396354	-2.931456	-1.828035
2	6	-1.590465	-2.429753	-1.054053
3	6	-0.178577	-0.665437	0.040636
4	6	0.932091	-0.933054	-0.939513
5	6	0.608485	-1.807311	-2.133045
6	1	-0.734880	-3.383776	-2.764770
7	1	0.096972	-3.734902	-1.266813
8	1	1.530057	-2.245298	-2.528490
9	1	0.192647	-1.161778	-2.915625
10	6	1.030661	-1.526004	0.432833
11	1	0.837144	-2.586743	0.552943
12	6	-1.453966	-1.405623	-0.214181
13	7	-2.558842	-0.769206	0.496359

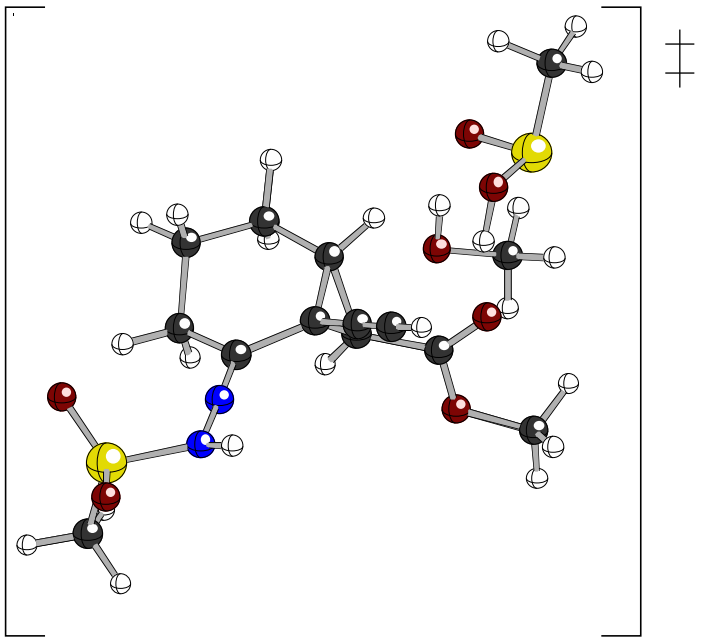
14	7	-3.706995	-0.620209	-0.331196
15	6	-0.463166	0.635910	0.676853
16	6	-1.705640	0.763465	0.998934
17	1	-2.432083	1.341869	1.544459
18	6	2.058172	-0.986134	1.362085
19	8	2.355536	0.180719	1.486229
20	8	2.626906	-1.973776	2.061112
21	6	3.769923	-1.585117	2.829289
22	1	4.102429	-2.489498	3.336423
23	1	4.540085	-1.209980	2.151706
24	1	3.496904	-0.812998	3.551614
25	16	-4.869053	0.510504	0.203386
26	8	-6.112656	-0.010276	-0.335225
27	6	-4.407103	1.975273	-0.688636
28	1	-3.367913	2.214588	-0.459666
29	1	-4.542566	1.767385	-1.749268
30	1	-5.080875	2.764115	-0.349691
31	8	-4.691782	0.731909	1.630593
32	8	3.314593	1.492566	-1.030219
33	16	2.840679	2.524465	-0.035641
34	8	1.225156	2.620064	-0.108692
35	1	-4.201040	-1.503401	-0.475421
36	1	0.733772	1.873328	0.401784
37	1	1.595530	-0.087837	-1.121638
38	8	4.183528	-1.037697	-0.370069
39	1	3.947893	-0.089589	-0.418614
40	6	4.500044	-1.456182	-1.677361
41	1	3.770334	-1.082790	-2.409378
42	1	5.496865	-1.115486	-1.988296
43	1	4.488622	-2.550089	-1.695299
44	6	3.069451	4.072704	-0.929589
45	1	2.652067	4.892504	-0.343307
46	1	4.141026	4.207501	-1.083940
47	1	2.551489	3.966951	-1.884558
48	1	-2.553787	-2.908184	-1.217148
49	1	-2.797441	-1.255260	1.365801

13-A14-65-05-dicounterionenaminetsguess.log

TS*Z-A/E-A*
M062X/6-31+G(d,p)
HF = -1979.6245056 hartrees (-1242234.17350906 kcal/mol)
Imaginary Frequencies: 1 (-364.9841 1/cm)
Zero-point correction = 0.389953 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1979.298554 hartrees (-1242029.63562054 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-1.017568	-0.351320	2.887752
2	6	-1.942155	0.502186	2.013137
3	6	-0.382536	-0.124934	0.055689
4	6	0.744875	-0.161130	1.066381
5	6	0.453626	-0.088362	2.560320
6	1	-1.251382	-1.409035	2.715087
7	1	-1.207583	-0.148367	3.946316
8	1	0.752085	0.900518	2.928706
9	1	1.089184	-0.817504	3.070679
10	6	0.582409	1.064134	0.227762
11	1	0.163857	1.945932	0.701491
12	6	-1.800921	0.107911	0.550987
13	7	-2.769628	-0.064538	-0.215138
14	7	-3.781678	-0.252617	-0.986811
15	6	-0.289655	-0.944567	-1.130558
16	6	-0.245836	-1.643019	-2.115092

17	1	-0.188586	-2.273084	-2.974731
18	1	-2.991378	0.362594	2.288170
19	6	1.571048	1.365528	-0.830199
20	8	2.284425	0.554136	-1.396594
21	8	1.577813	2.660203	-1.144555
22	6	2.481687	3.043349	-2.184385
23	1	2.363675	4.120155	-2.290794
24	1	3.506807	2.791743	-1.906454
25	1	2.224159	2.531427	-3.113923
26	1	-1.696547	1.565755	2.149658
27	16	-5.355972	-0.364430	-0.300407
28	8	-6.160888	-0.939301	-1.368418
29	6	-5.764766	1.355429	-0.078307
30	1	-4.970505	1.809895	0.516362
31	1	-5.845147	1.817688	-1.061270
32	1	-6.713886	1.390168	0.457841
33	8	-5.267264	-0.968256	1.018331
34	8	3.982587	-0.983003	1.058361
35	16	4.307030	-1.405906	-0.345533
36	8	2.962809	-2.052273	-1.026725
37	1	-3.685455	-0.825507	-1.829633
38	1	2.421068	-1.296861	-1.346970
39	1	1.581384	-0.789961	0.776963
40	8	3.222526	1.701900	1.348287
41	1	3.420754	0.749094	1.403248
42	6	4.384346	2.340879	0.869809
43	1	4.735274	1.891784	-0.071553
44	1	4.134623	3.389370	0.684541
45	1	5.204894	2.303309	1.597959
46	6	5.078422	-3.016753	-0.144983
47	1	5.242543	-3.462278	-1.126847
48	1	6.022093	-2.862680	0.379502
49	1	4.396367	-3.621922	0.454981

13-A41-02-02-dicounterionlinearts.log

Enamine Product
M062X/6-31+G(d,p)
HF = -1979.6851701 hartrees (-1242272.24108945 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.394701 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =

-1979.350993 hartrees (-1242062.54161743 kcal/mol)

Comments:

Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	0.063010	-0.860715	2.929139
2	6	0.985710	-1.051511	1.750338
3	6	-0.972019	-0.807074	0.198795
4	6	-1.813765	-0.232121	1.294324
5	6	-1.095957	0.097113	2.588311
6	1	0.631830	-0.451866	3.768056
7	1	-0.323669	-1.830230	3.267306
8	1	-1.811540	0.106793	3.416441
9	1	-0.696331	1.109797	2.468329
10	6	-2.054167	-1.659696	0.877717
11	1	-1.694617	-2.469803	1.503213
12	6	0.448512	-1.046954	0.538784
13	7	1.228079	-1.038743	-0.728567
14	7	2.384614	-0.183872	-0.726659
15	6	-0.964879	-0.436639	-1.237089
16	6	0.253654	-0.585594	-1.746234
17	1	0.656824	-0.404465	-2.731340
18	6	-3.282448	-2.022736	0.121260
19	8	-3.785722	-3.121389	0.123948
20	8	-3.772901	-0.982359	-0.572556
21	6	-4.936050	-1.246180	-1.358761
22	1	-5.155050	-0.311499	-1.873015
23	1	-4.735196	-2.046027	-2.074753
24	1	-5.767029	-1.542629	-0.715043
25	16	3.732745	-1.088534	-0.420168
26	8	4.308415	-0.812321	0.894017
27	6	4.883064	-0.468102	-1.627669
28	1	4.499914	-0.697065	-2.620778
29	1	4.974776	0.608028	-1.476614
30	1	5.836245	-0.963925	-1.440526
31	8	3.399493	-2.491990	-0.748989
32	8	-0.684991	2.419603	0.306215
33	16	0.685160	2.747344	-0.231798
34	8	1.790229	1.979907	0.661930

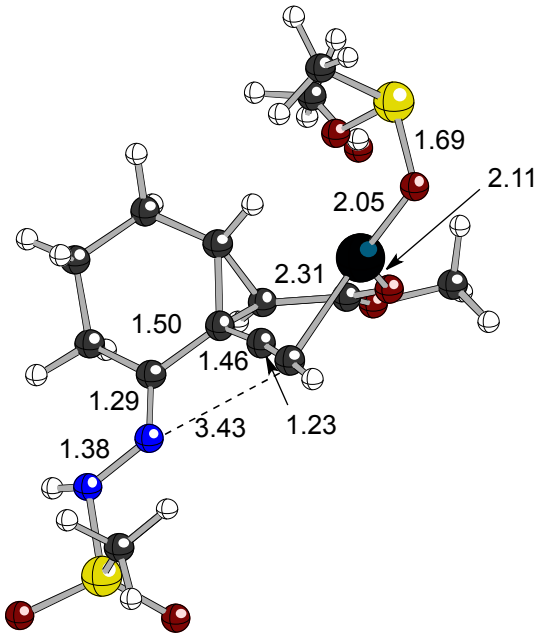
35	1	2.079945	1.125771	0.171018
36	1	-1.837456	-0.070728	-1.765381
37	1	-2.566212	0.478492	0.964780
38	8	-2.861967	1.903277	-1.346237
39	1	-2.092142	2.097961	-0.777783
40	6	-4.040259	2.296327	-0.679388
41	1	-3.920306	3.258396	-0.166590
42	1	-4.830583	2.405872	-1.427545
43	1	-4.364659	1.542948	0.054357
44	6	1.038202	4.364309	0.473881
45	1	2.056442	4.654603	0.212605
46	1	0.310999	5.069521	0.069858
47	1	0.924495	4.265424	1.555345
48	1	2.062637	-1.117633	1.891330
49	1	1.569258	-2.000788	-0.942300

13-A14-67-02-dicounterionenaminereactant.log

Copper Complexed Reactant
HF = -1398.7512058 hartrees (-877730.369151558 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.378518 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1398.438614 hartrees (-877534.21467114 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-1.137264	1.670344	2.923893
2	6	-2.199262	1.846637	1.818367
3	6	-0.635931	0.442743	0.317959
4	6	0.537863	1.060764	1.097932
5	6	0.283154	1.867366	2.370350
6	1	-1.234487	0.664208	3.348886
7	1	-1.324540	2.386817	3.730011
8	1	0.456611	2.931065	2.164633
9	1	1.013115	1.566099	3.127850
10	6	0.158047	1.654476	-0.248539
11	1	-0.359610	2.607316	-0.240267
12	6	-2.033616	0.767924	0.767406
13	7	-2.988251	0.071296	0.245001
14	7	-4.302388	0.285745	0.602655
15	6	-0.475435	-0.884227	-0.257618
16	6	-0.443061	-2.034797	-0.678064
17	1	-0.504430	-3.034916	-1.049793
18	1	-3.196895	1.783321	2.265868
19	6	1.087835	1.517784	-1.395694
20	8	1.627768	0.458517	-1.771046
21	8	1.274353	2.688778	-2.029385
22	6	2.374071	2.736810	-3.000586
23	1	2.373669	3.757318	-3.377240
24	1	3.295587	2.497106	-2.465256
25	1	2.193864	2.017533	-3.802303
26	16	-5.460377	-0.600809	-0.384646
27	8	-6.863633	-0.293858	0.356418
28	6	-4.891514	-2.325734	-0.073752
29	1	-3.843339	-2.362752	-0.368940
30	1	-5.031677	-2.512711	0.989278
31	1	-5.518831	-2.966476	-0.692505
32	8	-5.296748	-0.277411	-1.953477
33	8	3.316835	-0.500493	0.764512
34	16	4.337732	-1.817415	0.446257
35	8	3.335386	-2.691937	-0.600489
36	1	-4.670192	1.161409	0.979064
37	1	1.448390	0.462266	1.093665
38	8	3.364805	1.958736	-0.119347

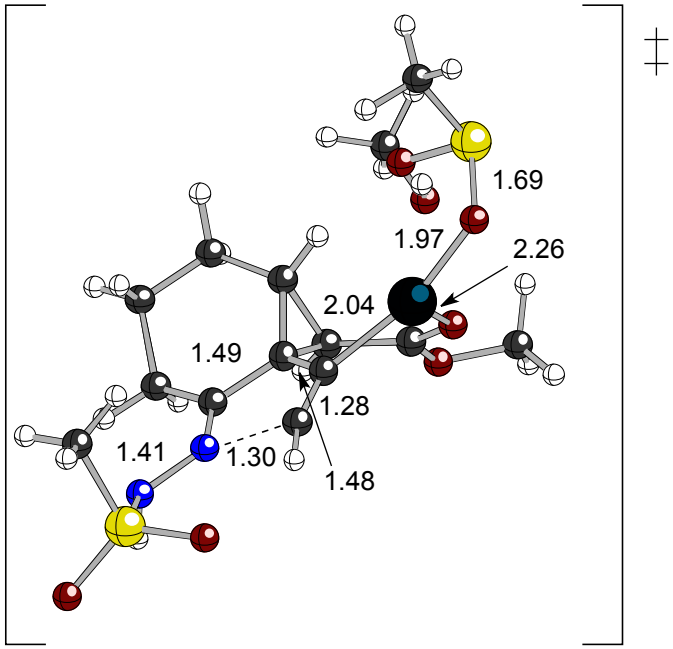
39	1	3.482093	0.996861	0.146436
40	6	3.648597	2.849217	0.975830
41	1	3.325373	3.850069	0.678586
42	1	3.106322	2.558523	1.888109
43	1	4.721300	2.879468	1.207191
44	6	4.070953	-2.786395	2.010038
45	1	4.490953	-3.782529	1.868975
46	1	4.547968	-2.261911	2.838167
47	1	2.988131	-2.831300	2.137608
48	1	-2.105393	2.844573	1.368235
49	29	1.765727	-1.381213	-0.748216

13-A60-02-01-reactant.log

TS_{Copper}
HF = -1398.7194265 hartrees (-877710.427323015 kcal/mol)
Imaginary Frequencies: 1 (-335.6406 1/cm)
Zero-point correction = 0.378377 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1398.404583 hartrees (-877512.85987833 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	-1.268210	2.184865	2.433301
2	6	-2.061798	2.448125	1.124947
3	6	-0.499893	0.723353	0.004070
4	6	0.606622	1.165518	0.984033
5	6	0.246667	2.051755	2.180897
6	1	-1.649902	1.262549	2.888471
7	1	-1.458307	2.999440	3.139188
8	1	0.681492	3.046374	2.021933
9	1	0.721305	1.637621	3.075293
10	6	0.571404	1.778360	-0.394220
11	1	0.240117	2.807520	-0.474570
12	6	-1.871833	1.238426	0.256505
13	7	-2.801177	0.458979	-0.210142
14	7	-4.159235	0.786001	-0.016896
15	6	-0.560776	-0.611043	-0.631926
16	6	-1.702098	-1.084971	-0.965485
17	1	-2.436005	-1.754040	-1.383259
18	1	-3.123724	2.601256	1.336318
19	6	1.635450	1.438746	-1.376630
20	8	2.054944	0.299908	-1.635838
21	8	2.090578	2.551221	-1.997020
22	6	3.339207	2.400733	-2.750358
23	1	3.549400	3.389372	-3.153834
24	1	4.108676	2.072817	-2.047440
25	1	3.208725	1.666556	-3.548572
26	16	-5.218499	-0.639526	-0.220938
27	8	-6.678379	0.021115	-0.419286
28	6	-5.064697	-1.420954	1.439590
29	1	-4.010150	-1.655355	1.587155
30	1	-5.438378	-0.698273	2.162519
31	1	-5.674371	-2.323562	1.407432
32	8	-4.616430	-1.662733	-1.313816
33	8	3.102631	-0.727143	1.099547
34	16	3.853886	-2.128095	0.545293
35	8	2.709632	-2.837709	-0.474330
36	1	-4.527461	1.558120	-0.587551
37	1	1.381500	0.413556	1.138824
38	8	3.685026	1.645616	0.273406
39	1	3.539094	0.674897	0.527001
40	6	4.073635	2.427159	1.416440
41	1	4.098168	3.476917	1.111822

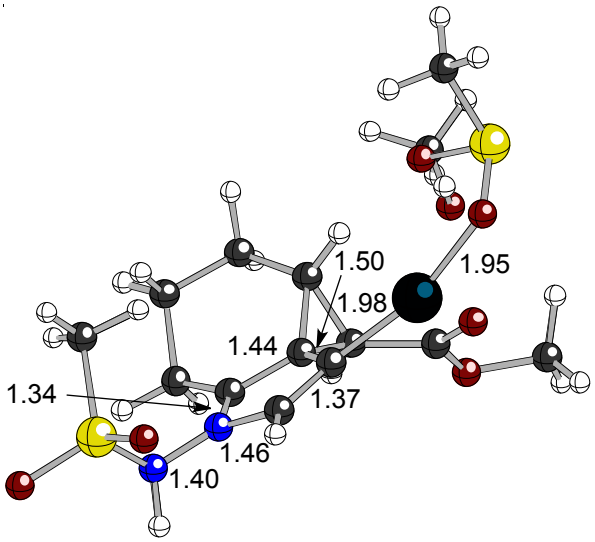
42	1	3.360068	2.318301	2.247759
43	1	5.069948	2.145086	1.783218
44	6	3.600120	-3.203290	2.041126
45	1	3.865346	-4.226664	1.775434
46	1	4.216135	-2.822423	2.855971
47	1	2.537650	-3.119689	2.273874
48	1	-1.676512	3.348861	0.631884
49	29	1.204382	-1.613623	-0.800149

13-A60-01-02-copperts1frozen.log

Copper Complexed Intermediate
HF = -1398.7469728 hartrees (-877727.712901728 kcal/mol)
Imaginary Frequencies: none found
Zero-point correction = 0.380857 (Hartree/Particle)

Temperature 298.150 Kelvin. Pressure 1.00000 Atm.
Sum of electronic and thermal Free Energies =
-1398.429968 hartrees (-877528.78921968 kcal/mol)

Comments:



Coordinates (from last standard orientation):

Center Number	Atomic Number	Coordinates (Angstroms) X	Y	Z
1	6	1.545519	-2.173592	2.103165
2	6	2.184449	-2.488965	0.716325
3	6	0.513463	-0.780863	-0.312040

4	6	-0.495437	-1.145099	0.861547
5	6	0.013288	-2.007478	2.023249
6	1	1.991002	-1.249388	2.493941
7	1	1.795080	-2.976493	2.804126
8	1	-0.455274	-2.995881	1.941265
9	1	-0.342724	-1.563267	2.957234
10	6	-0.688433	-1.788331	-0.456253
11	1	-0.407151	-2.831804	-0.554995
12	6	1.835283	-1.343269	-0.163169
13	7	2.667420	-0.471394	-0.744850
14	7	4.052747	-0.650964	-0.737555
15	6	0.602209	0.555638	-0.982736
16	6	1.939176	0.689393	-1.254057
17	1	2.517836	1.473581	-1.720140
18	1	3.268819	-2.612123	0.786115
19	6	-1.866517	-1.432423	-1.304334
20	8	-2.305839	-0.299415	-1.521248
21	8	-2.412539	-2.562632	-1.821026
22	6	-3.764356	-2.421501	-2.368464
23	1	-4.041647	-3.417801	-2.707013
24	1	-4.411409	-2.069644	-1.560933
25	1	-3.760972	-1.708031	-3.195757
26	16	5.016616	0.648795	0.039946
27	8	6.499452	0.022594	0.119824
28	6	4.203870	0.684416	1.695975
29	1	3.160014	0.966644	1.547219
30	1	4.326594	-0.306517	2.131112
31	1	4.737671	1.444538	2.266783
32	8	4.783460	2.065202	-0.693627
33	8	-2.839938	0.797565	1.275739
34	16	-3.610590	2.141772	0.617039
35	8	-2.539740	2.809080	-0.502447
36	1	4.460692	-0.939068	-1.631920
37	1	-1.163012	-0.309450	1.089220
38	8	-3.584592	-1.591786	0.695921
39	1	-3.365755	-0.613642	0.876227
40	6	-4.061646	-2.250732	1.882326
41	1	-4.230427	-3.302850	1.637783
42	1	-3.332295	-2.194240	2.704810
43	1	-5.007990	-1.818934	2.235873
44	6	-3.310971	3.339260	2.007360
45	1	-3.607041	4.332898	1.671389
46	1	-3.880956	3.016337	2.878754
47	1	-2.237483	3.291504	2.194264

48	1	1.758663	-3.421395	0.324832
49	29	-1.034873	1.671340	-0.980124

13-A60-03-01-intermediate1.log

Section 2.6. References

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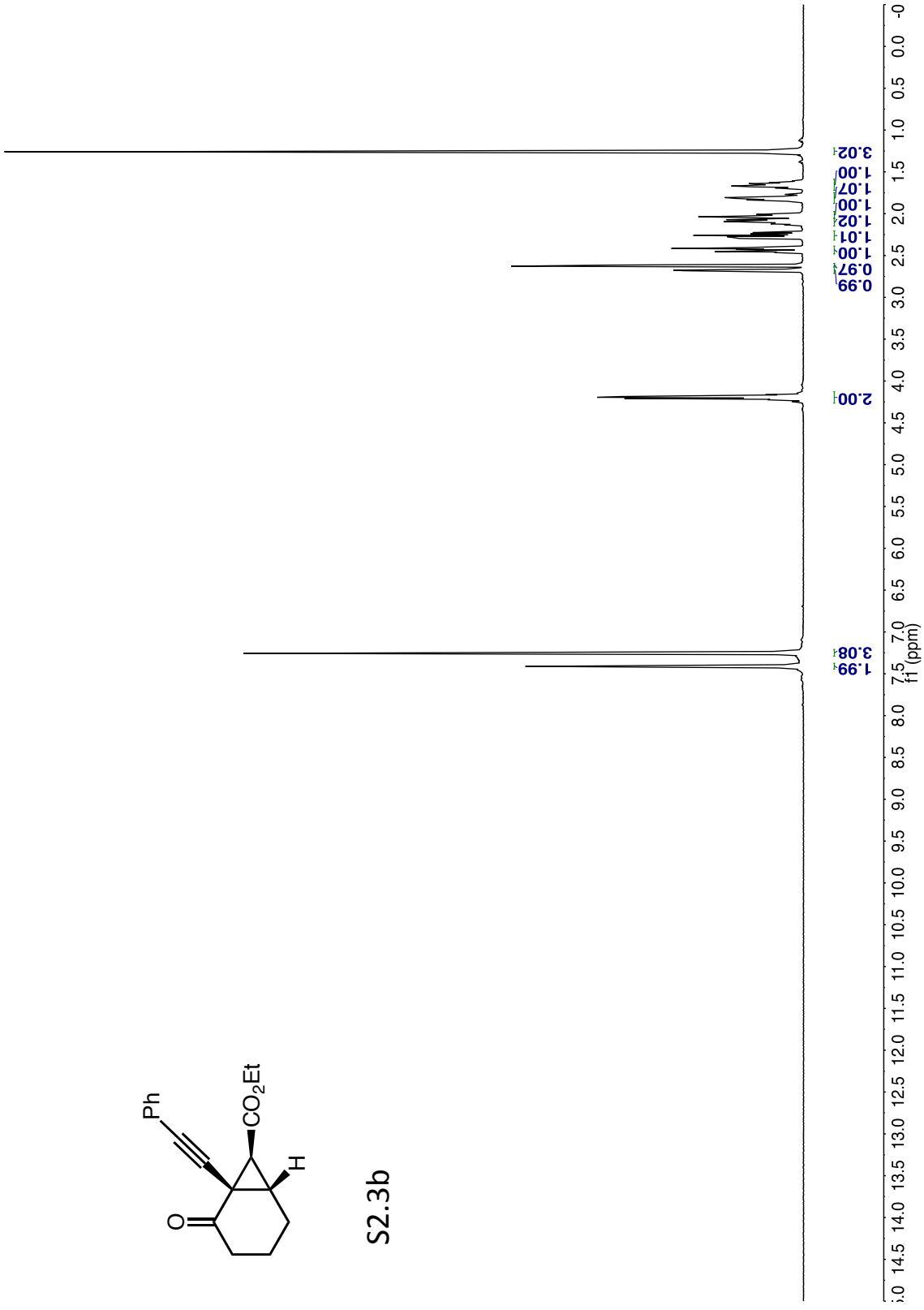
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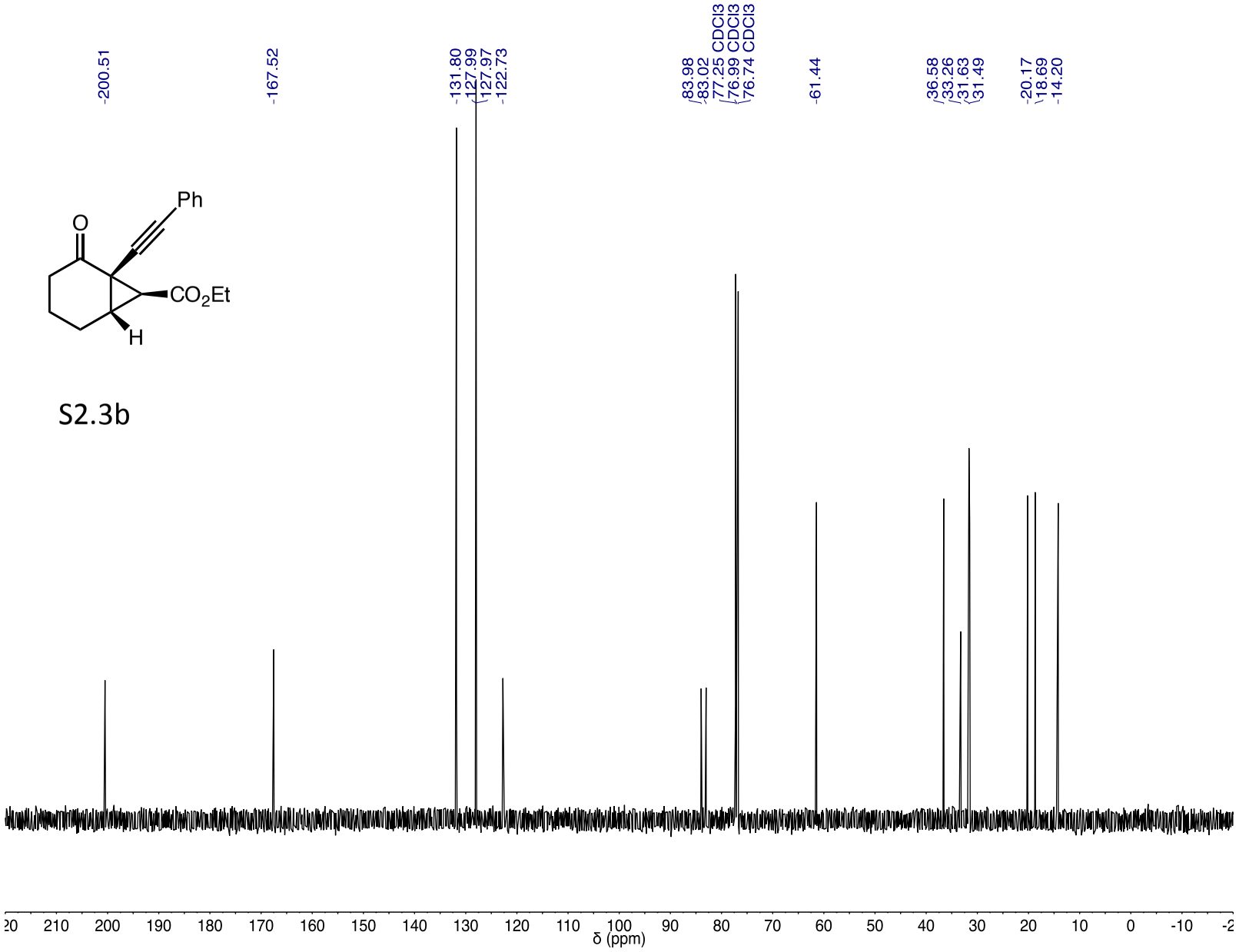
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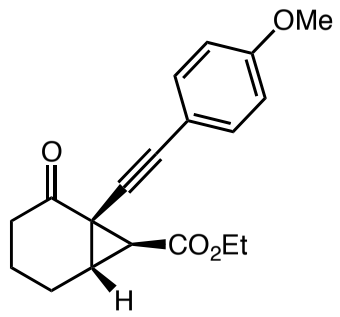
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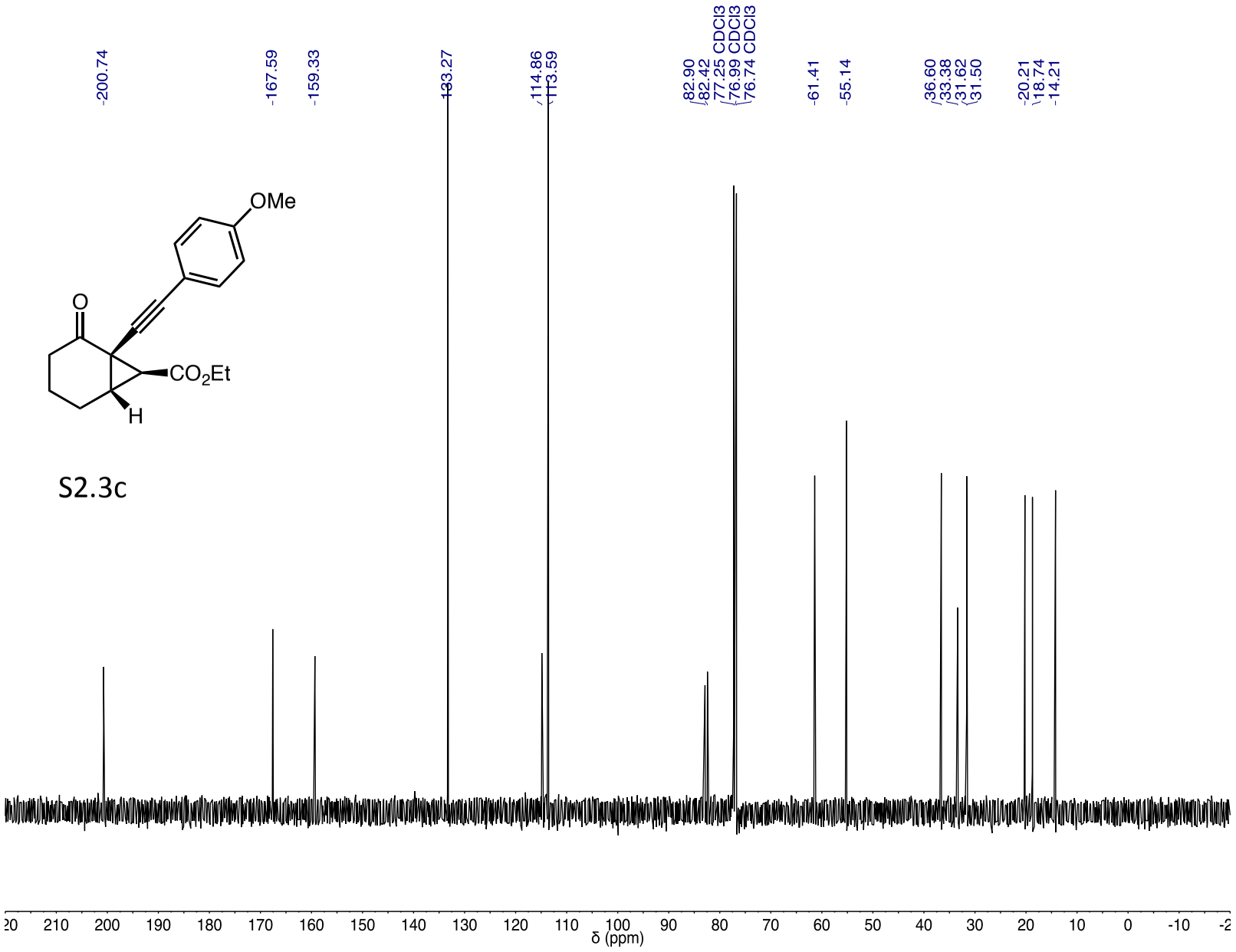
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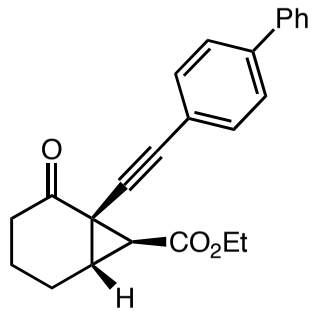
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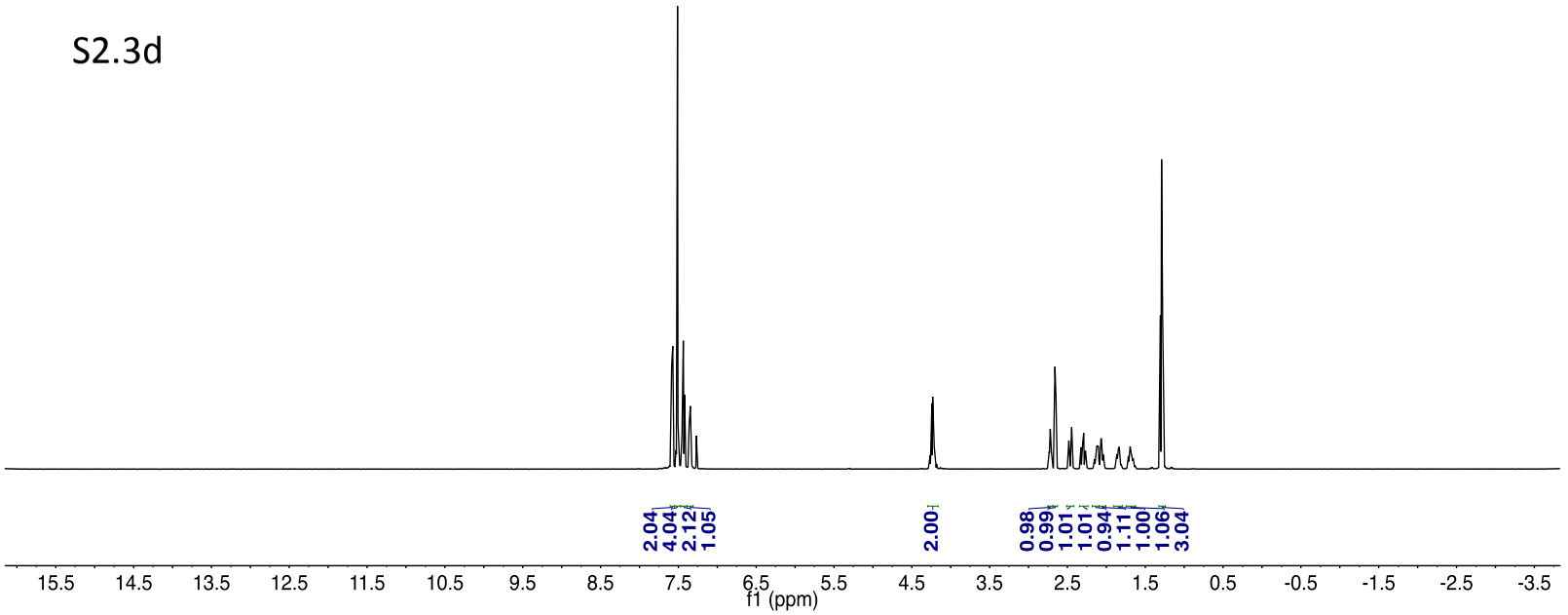
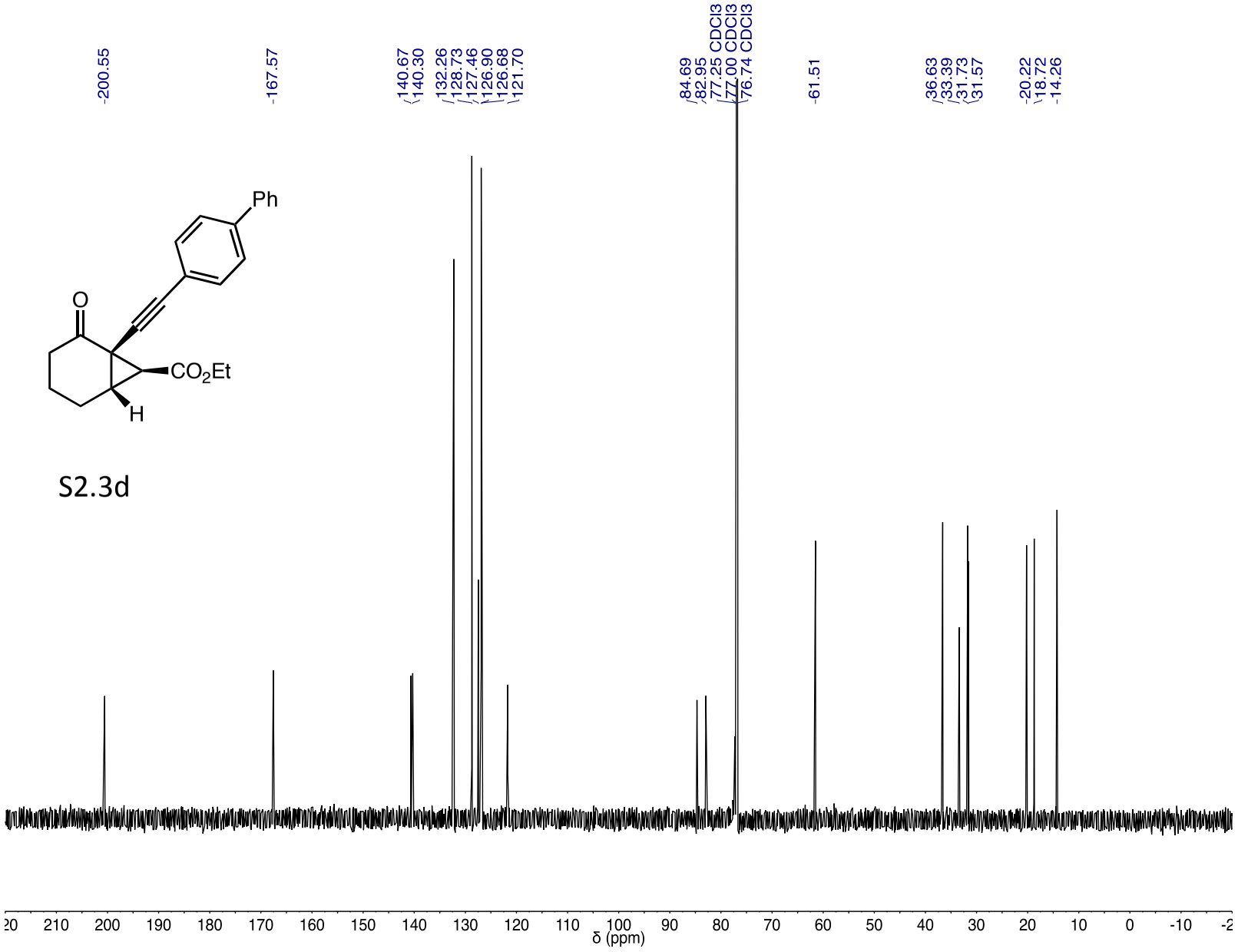
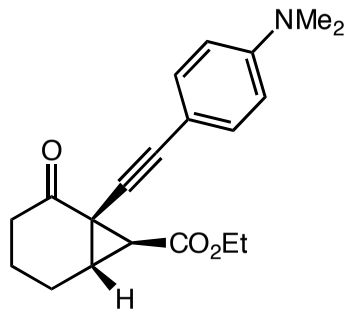
H

S2.3d

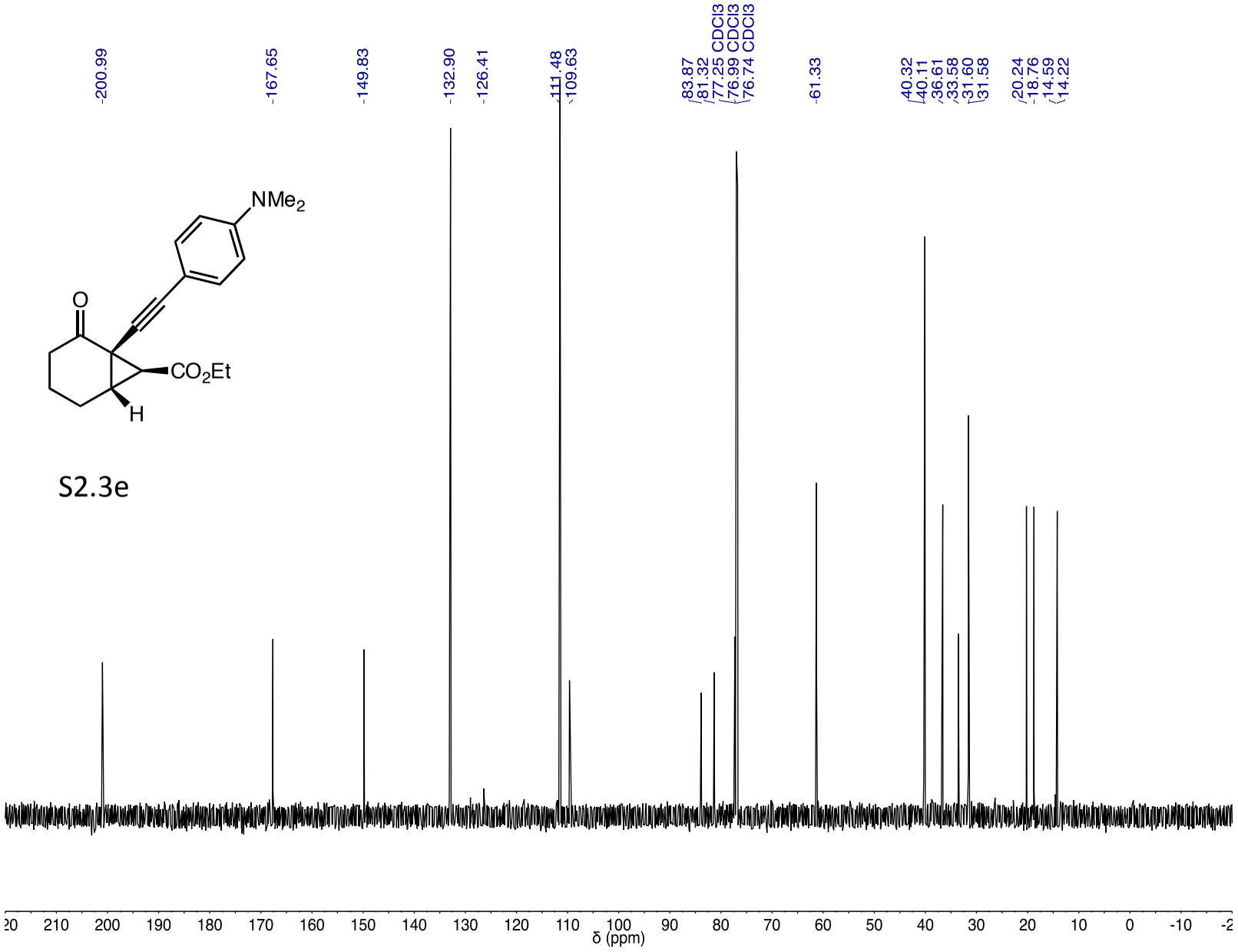

2.04
4.04
2.12
1.05
2.00
0.98
0.99
1.01
1.01
0.94
1.11
1.00
1.06
3.04
15.5
14.5
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
-2.5
-3.5
f1 (ppm)


-200.55
-167.57
140.67
140.30
132.26
128.73
127.46
126.90
126.68
121.70
84.69
82.95
77.25 CDCl3
77.00 CDCl3
76.74 CDCl3
-61.51
36.63
33.39
31.73
31.57
20.22
18.72
14.26
Ph
O
CO2Et
H
S2.3d
δ (ppm)

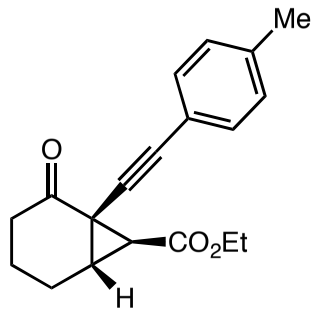

NMe2
O
CO2Et
H

S2.3e

2.15
1.98
2.00
6.46
0.98
1.11
1.09
1.00
1.06
1.09
1.07
0.99
3.01
f1 (ppm)

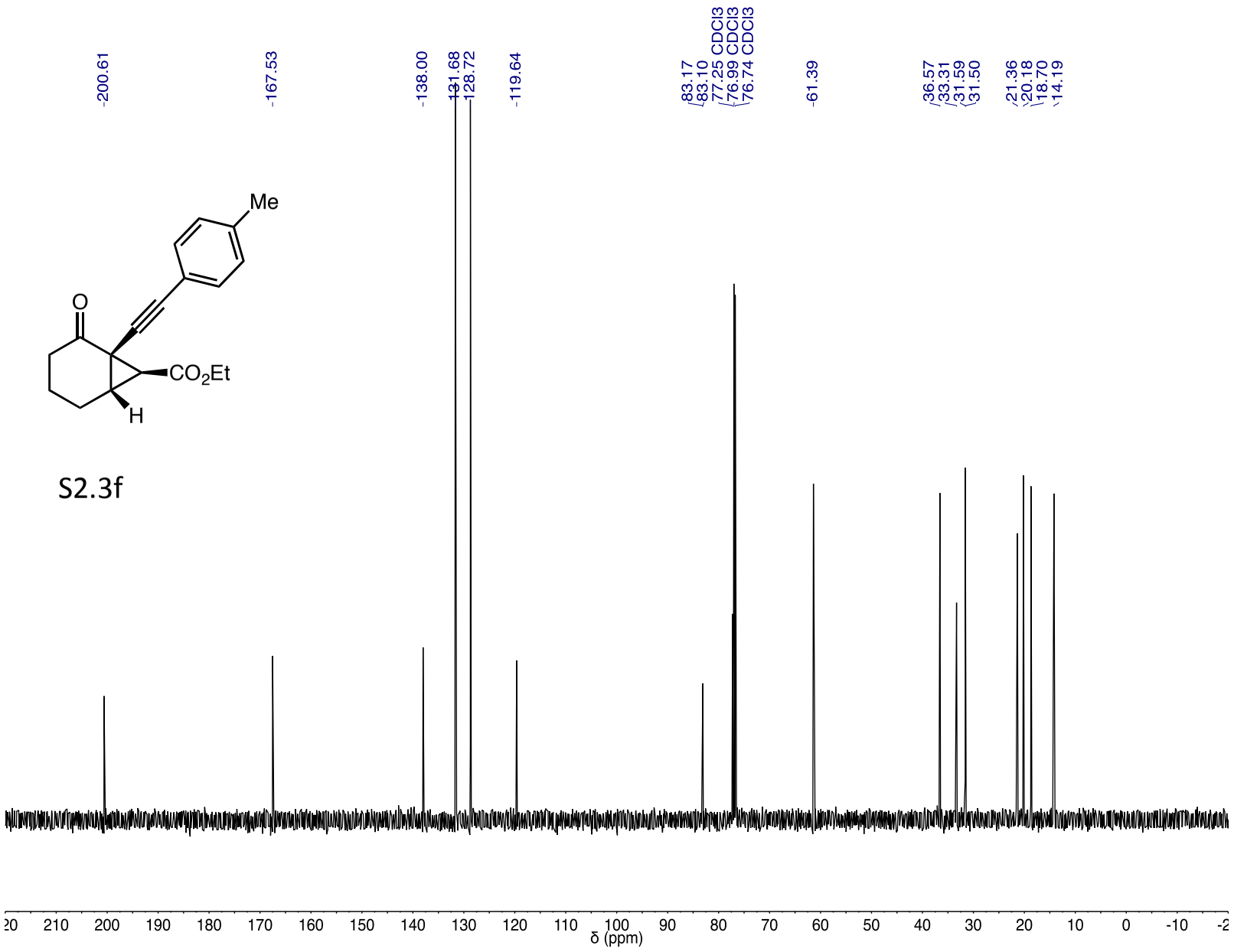

200.99
167.65
149.83
132.90
126.41
111.48
109.63
83.87
81.32
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
61.33
40.32
40.11
36.61
33.58
31.60
31.58
20.24
18.76
14.59
14.22
NMe2
O
CO2Et
H
δ (ppm)

S2.3e

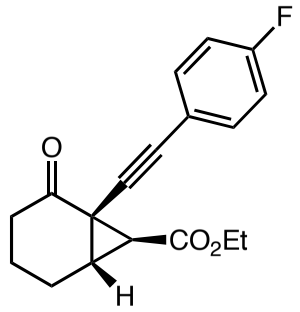

Me
O
CO2Et
H

S2.3f

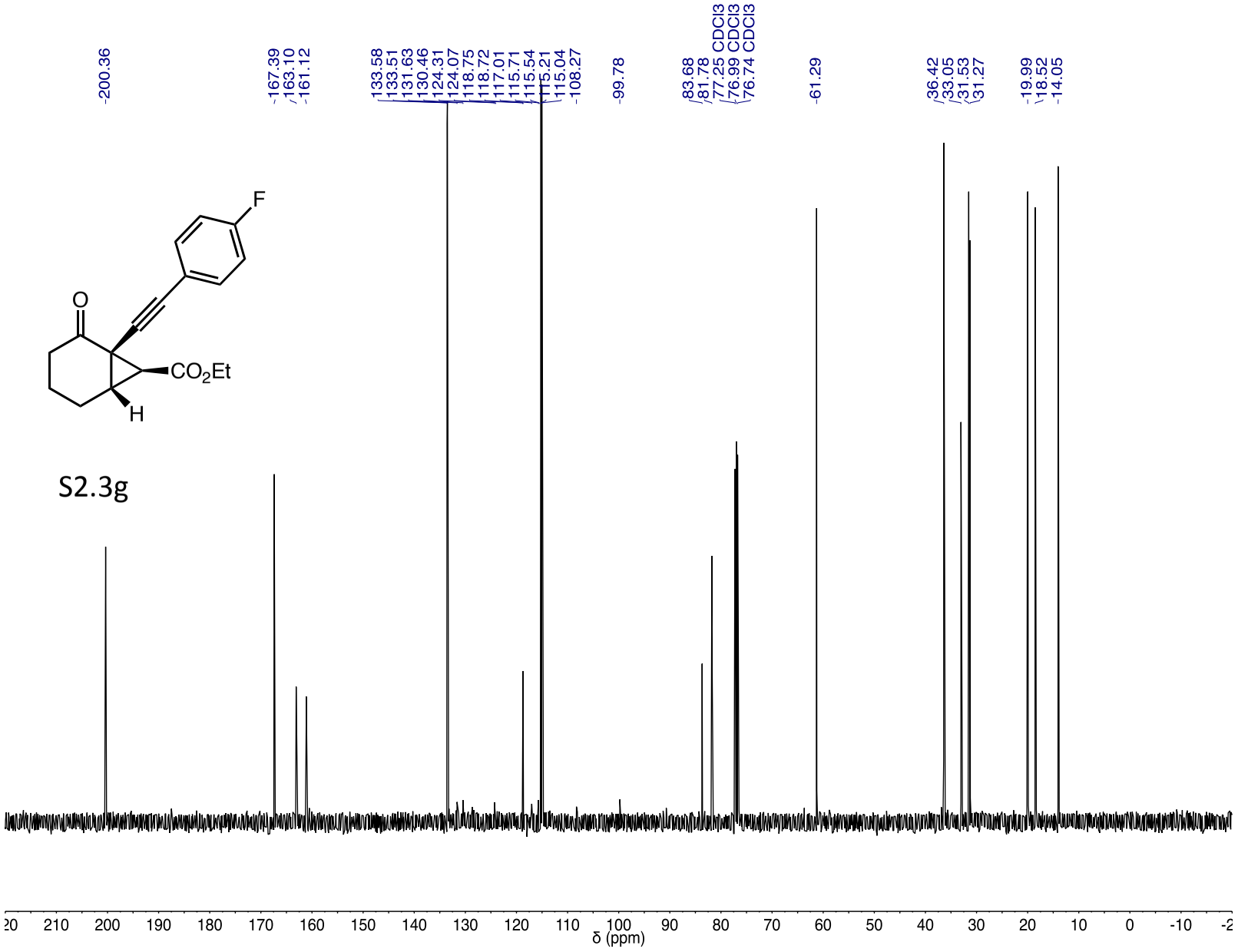
1.90
1.92
2.00
0.97
0.97
1.03
2.86
1.12
0.93
1.11
1.05
1.01
3.15
f1 (ppm)

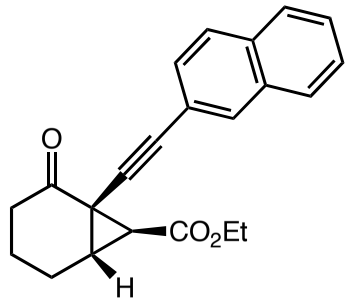

-200.61
-167.53
-138.00
131.68
128.72
-119.64
83.17
83.10
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
-61.39
36.57
33.31
31.59
31.50
21.36
20.18
18.70
14.19
Me
O
CO2Et
H
δ (ppm)

S2.3f



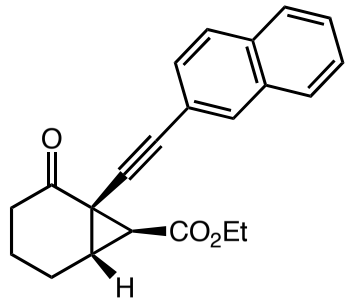
S2.3g


-200.36
-167.39
-163.10
-161.12
-133.58
-133.51
-131.63
-130.46
-124.31
-124.07
-118.75
-118.72
-117.01
-115.71
-115.54
-115.21
-115.04
-108.27
-99.78
-83.68
-81.78
-77.25 CDCl3
-76.99 CDCl3
-76.74 CDCl3
-61.29
-36.42
-33.05
-31.53
-31.27
-19.99
-18.52
-14.05
F
O
CO2Et
H
S2.3g
δ (ppm)


O
CO2Et
H

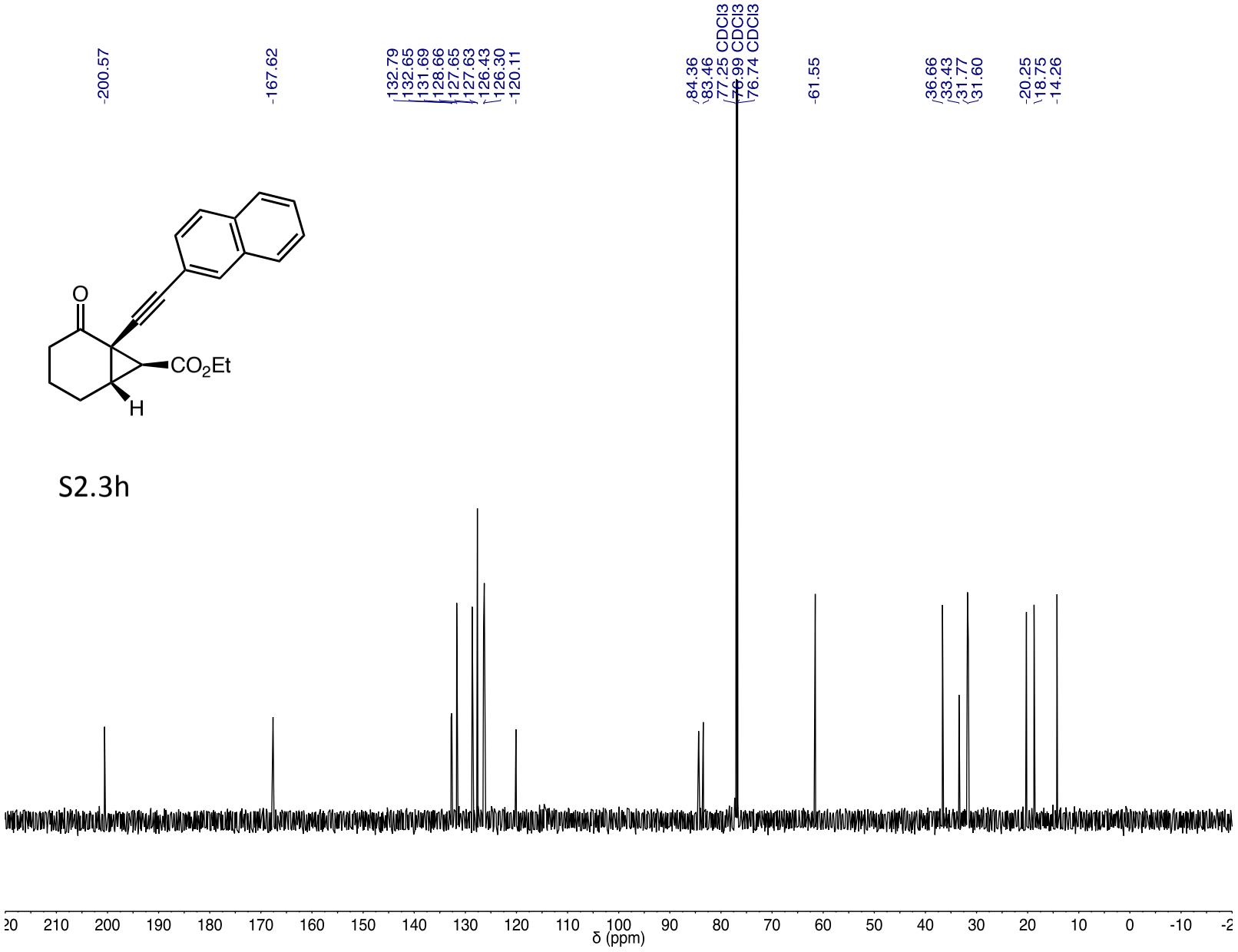
S2.3h

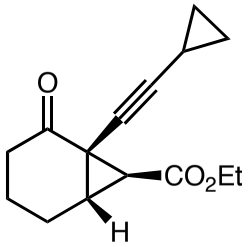
0.95
1.96
1.02
2.95
2.00
0.96
0.96
0.99
0.99
0.99
1.17
0.98
1.07
3.23
f1 (ppm)


O
CO2Et
H

S2.3h

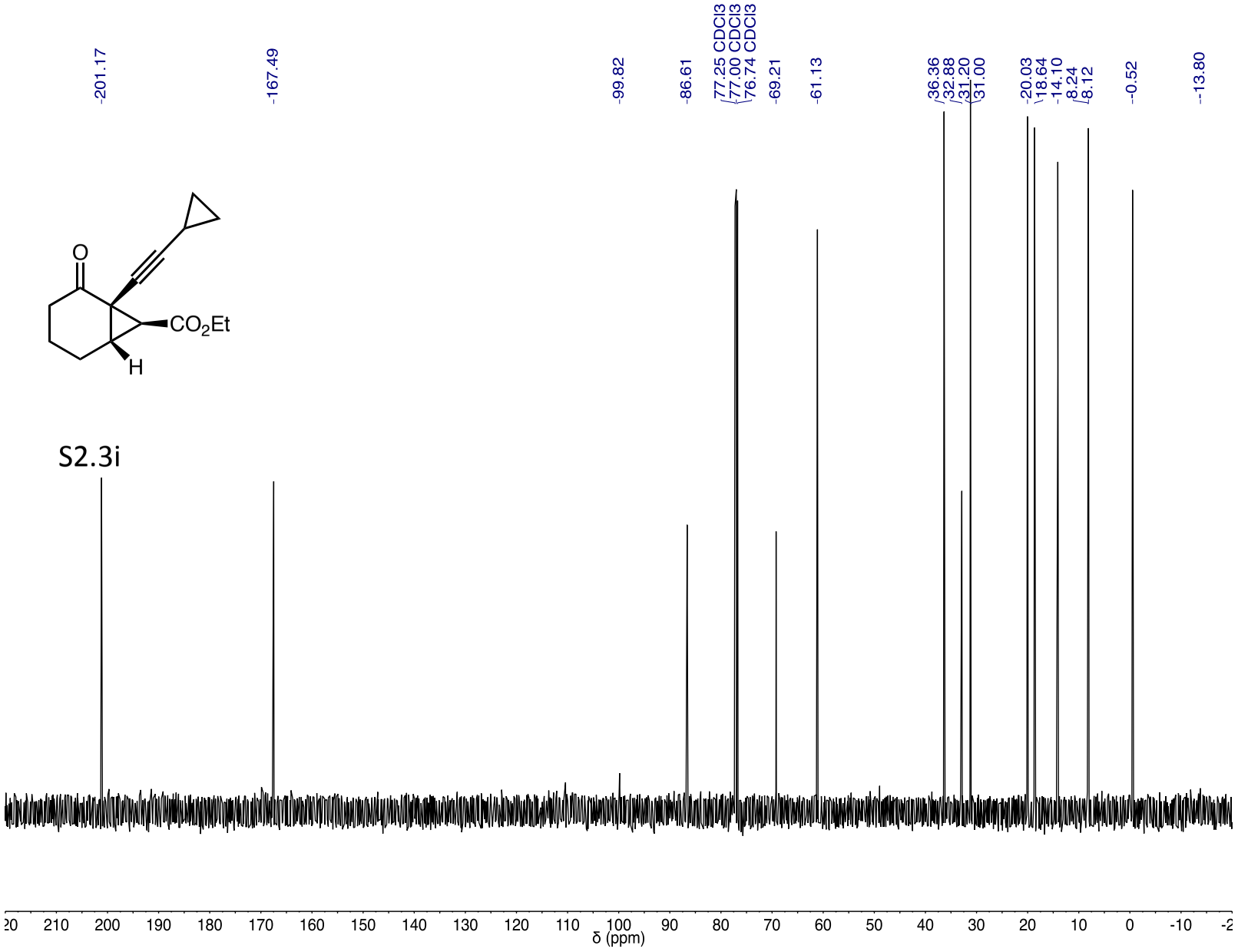
0.95
1.96
1.02
2.95
2.00
0.96
0.96
0.99
0.99
0.99
1.17
0.98
1.07
3.23
f1 (ppm)

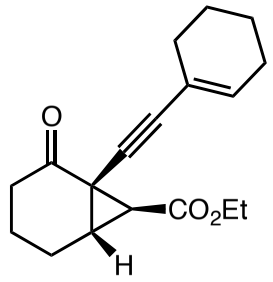

-200.57
-167.62
132.79
132.65
131.69
128.66
127.65
127.63
126.43
126.30
-120.11
84.36
83.46
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
-61.55
36.66
33.43
31.77
31.60
-20.25
18.75
-14.26
O
CO2Et
H
S2.3h
δ (ppm)


O
CO2Et
H

S2.3i

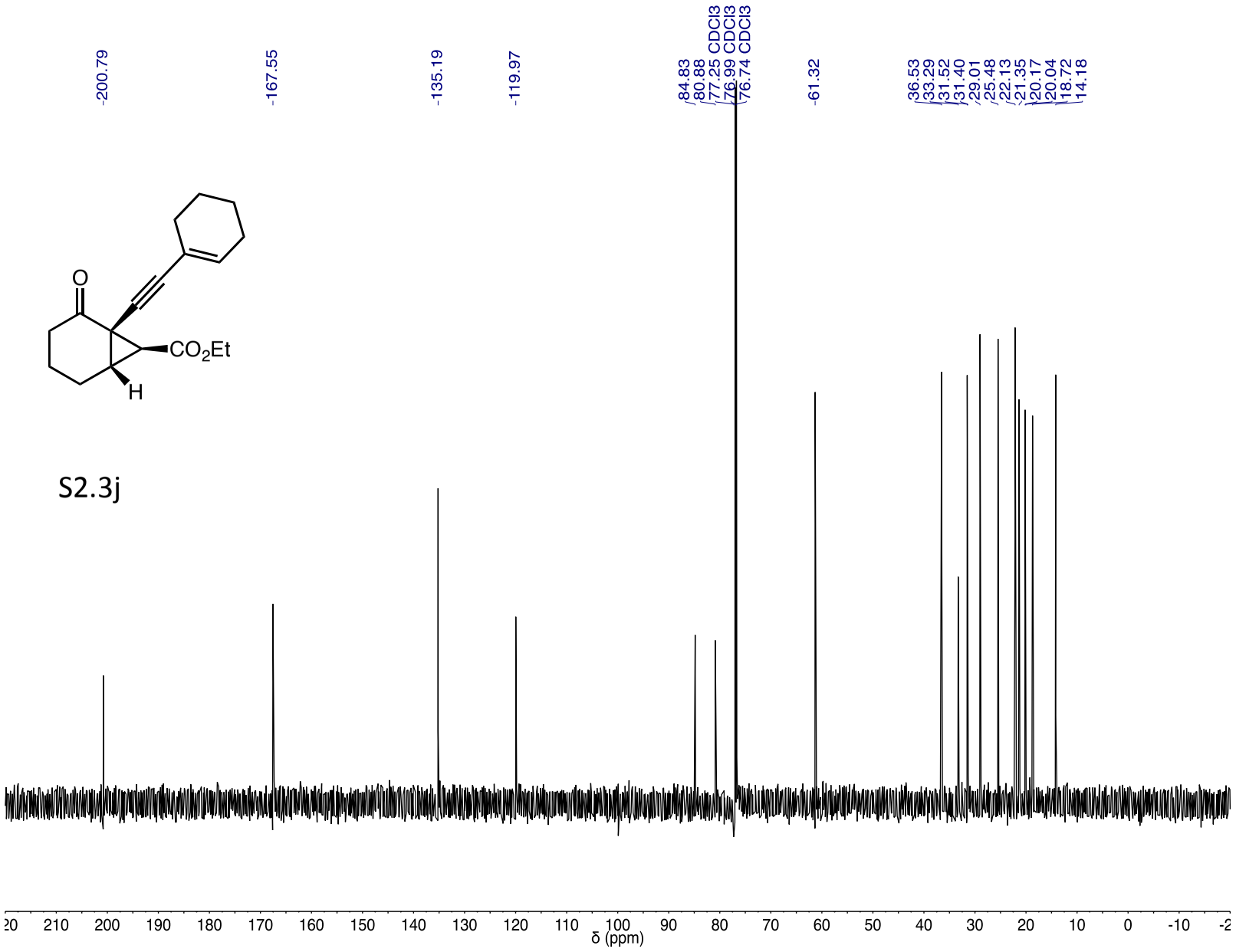
2.00
1.95
1.00
0.99
1.02
1.02
0.99
0.92
3.00
0.97
1.94
1.87
5.0 14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

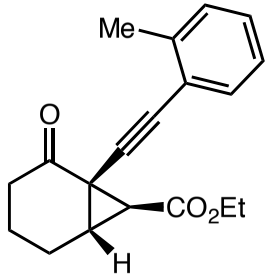

-201.17
-167.49
-99.82
-86.61
77.25 CDCl3
77.00 CDCl3
76.74 CDCl3
-69.21
-61.13
-36.36
-32.88
-31.20
-31.00
-20.03
-18.64
-14.10
-8.24
-8.12
--0.52
--13.80
O
CO2Et
H
S2.3i
δ (ppm)


O
CO2Et
H

S2.3j

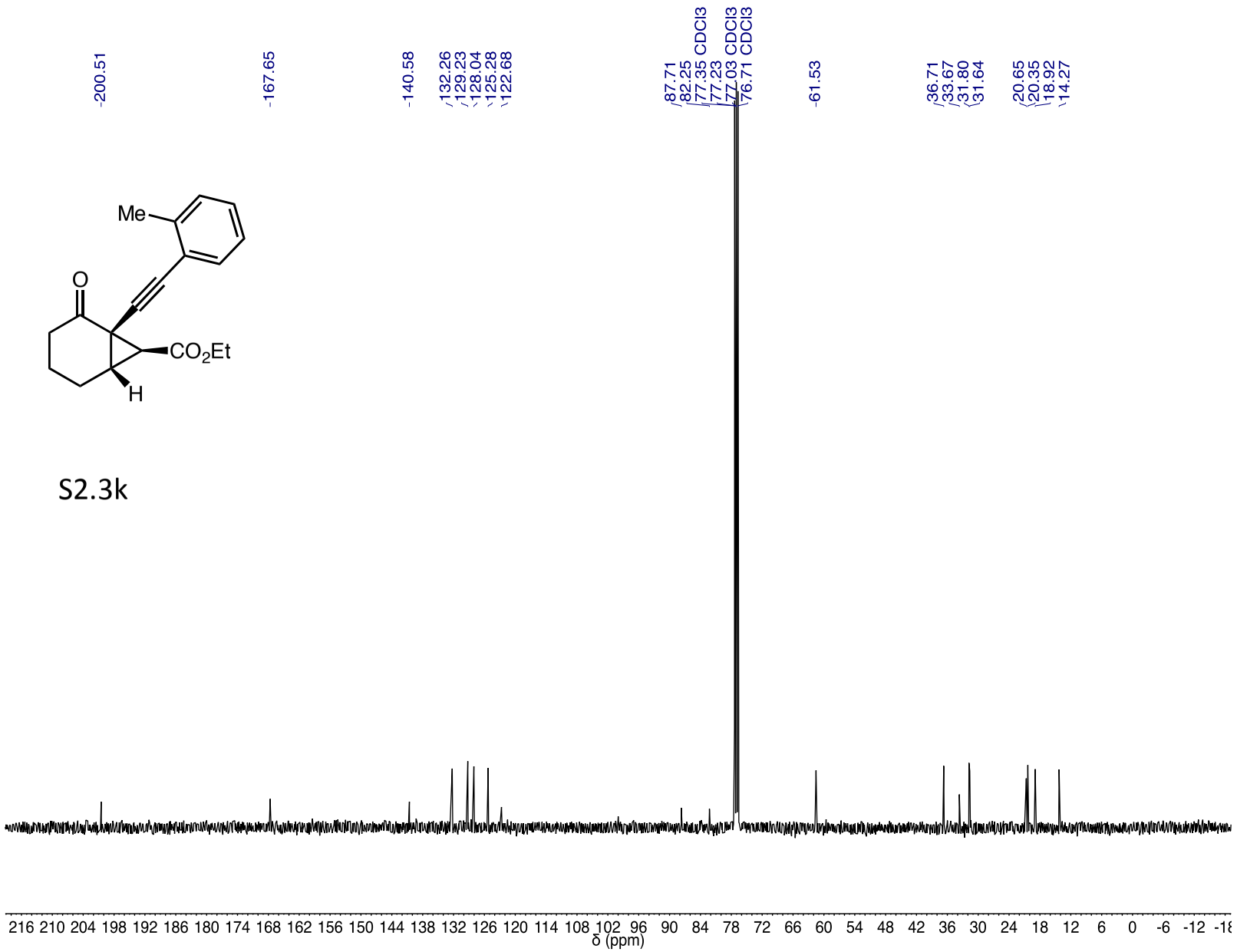
0.78
2.00
1.91
1.09
1.07
5.68
1.32
4.71
3.22
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


-200.79
-167.55
-135.19
-119.97
84.83
80.88
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
-61.32
36.53
33.29
31.52
31.40
29.01
25.48
22.13
21.35
20.17
20.04
18.72
14.18
O
CO2Et
H
S2.3j
δ (ppm)


Me
O
CO2Et
H

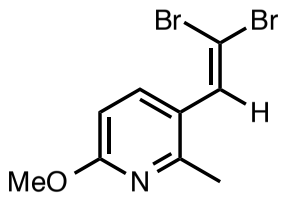
S2.3k

0.85
1.77
0.95
2.00
0.83
0.88
3.42
1.15
2.06
0.98
1.07
3.02
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

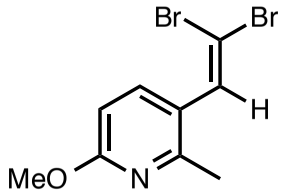

-200.51
-167.65
-140.58
132.26
129.23
128.04
125.28
122.68
87.71
82.25
77.35 CDCl3
77.23
77.03 CDCl3
76.71 CDCl3
-61.53
36.71
33.67
31.80
31.64
20.65
20.35
18.92
14.27
Me
O
CO2Et
H
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S2.3k

S2.5

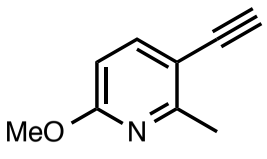


S2.5


Br
Br
H
MeO
N

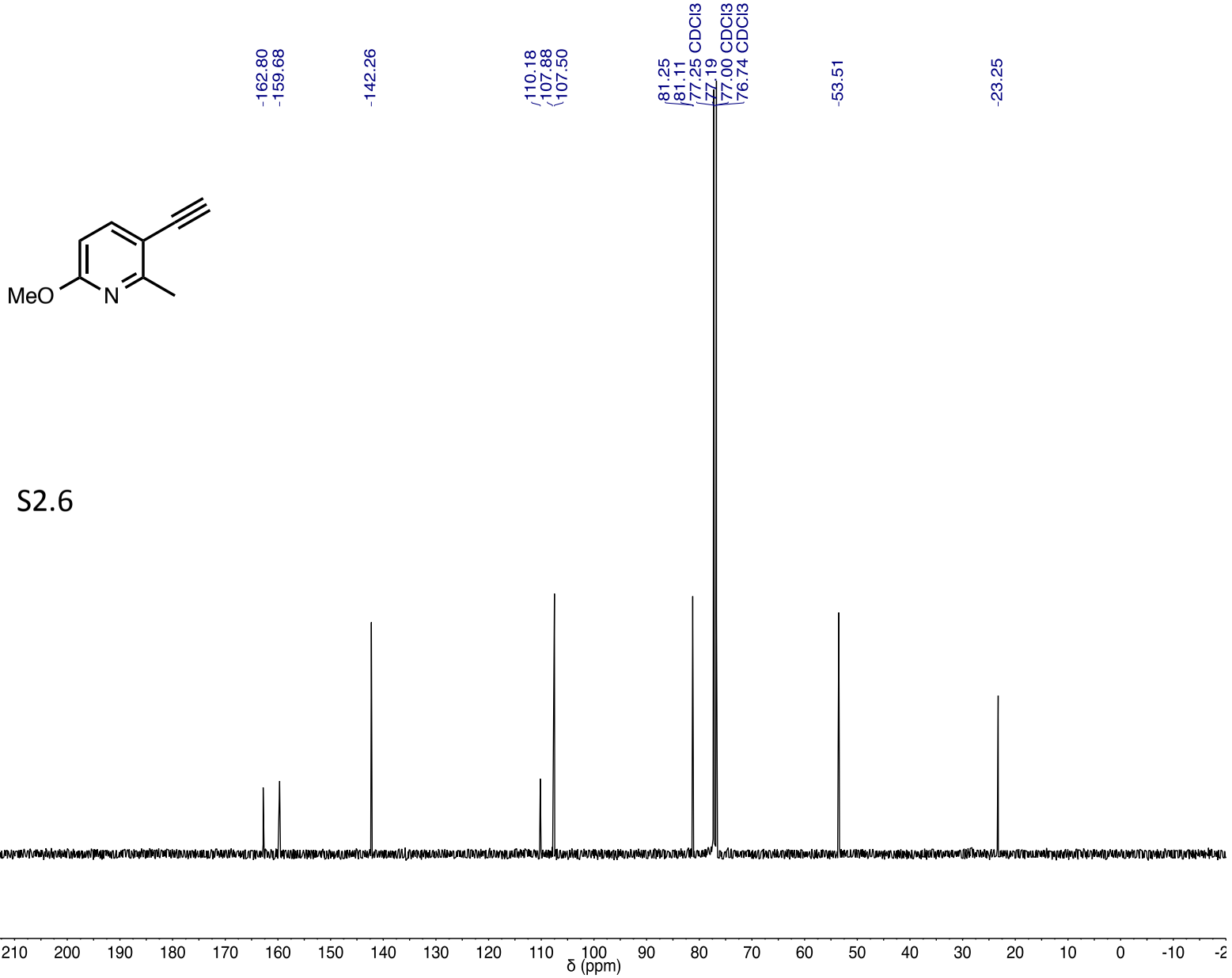
163.00
154.15
138.87
134.57
123.25
107.36
91.68
77.24 CDCl3
77.20
76.99 CDCl3
76.74 CDCl3
53.45
22.60
δ (ppm)

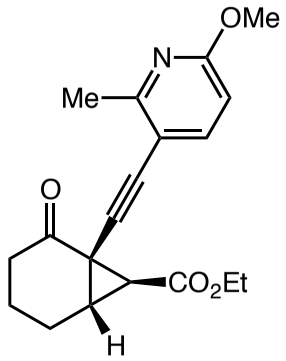
S2.6


MeO
N

1.00
1.00
3.21
0.96
3.08
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

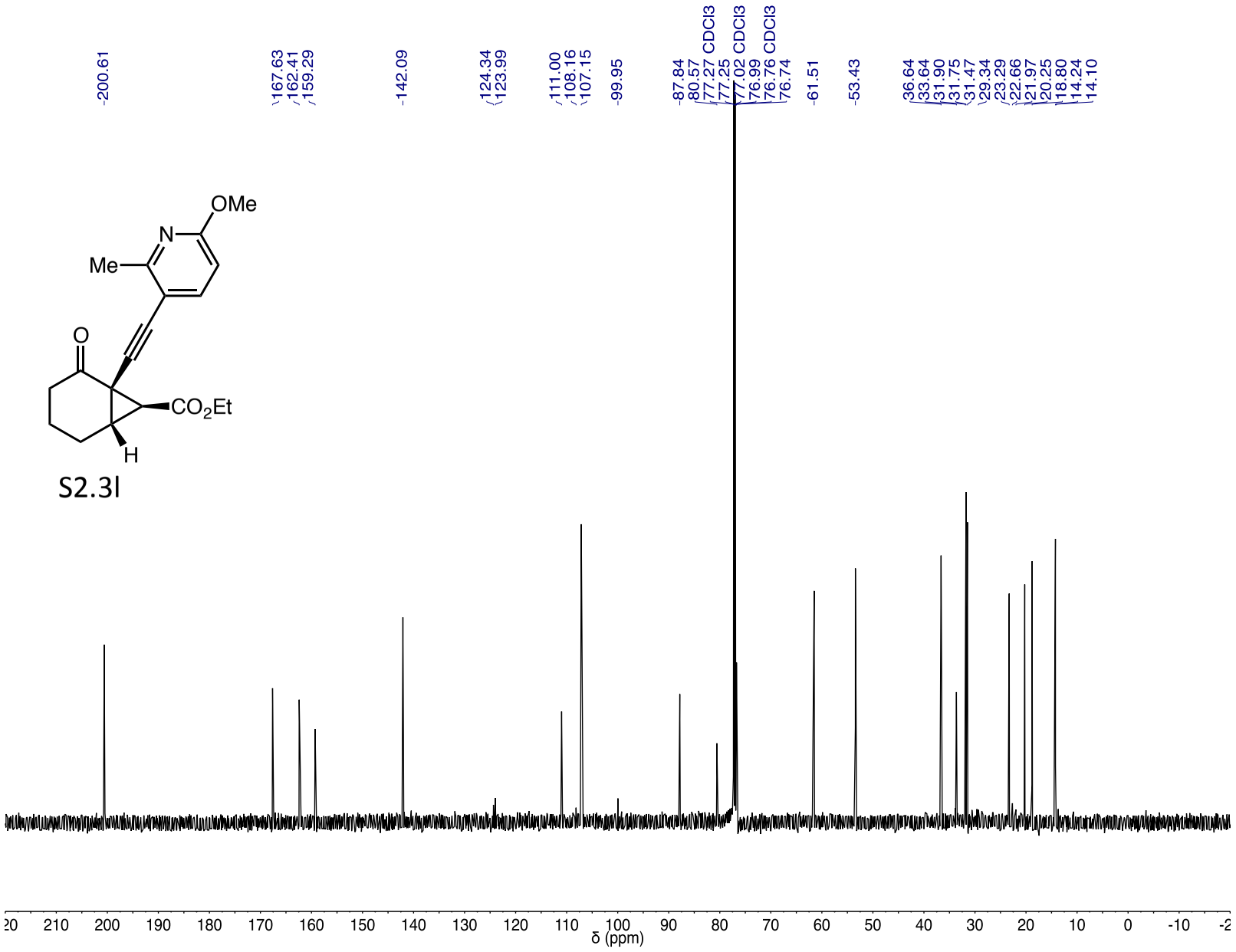
S2.6

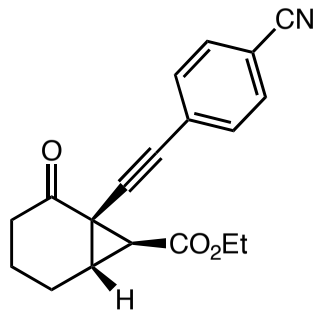

MeO
N
162.80
159.68
142.26
110.18
107.88
107.50
81.25
81.11
77.25 CDCl3
77.19
77.00 CDCl3
76.74 CDCl3
53.51
23.25
δ (ppm)


OMe
N
Me
O
CO2Et
H

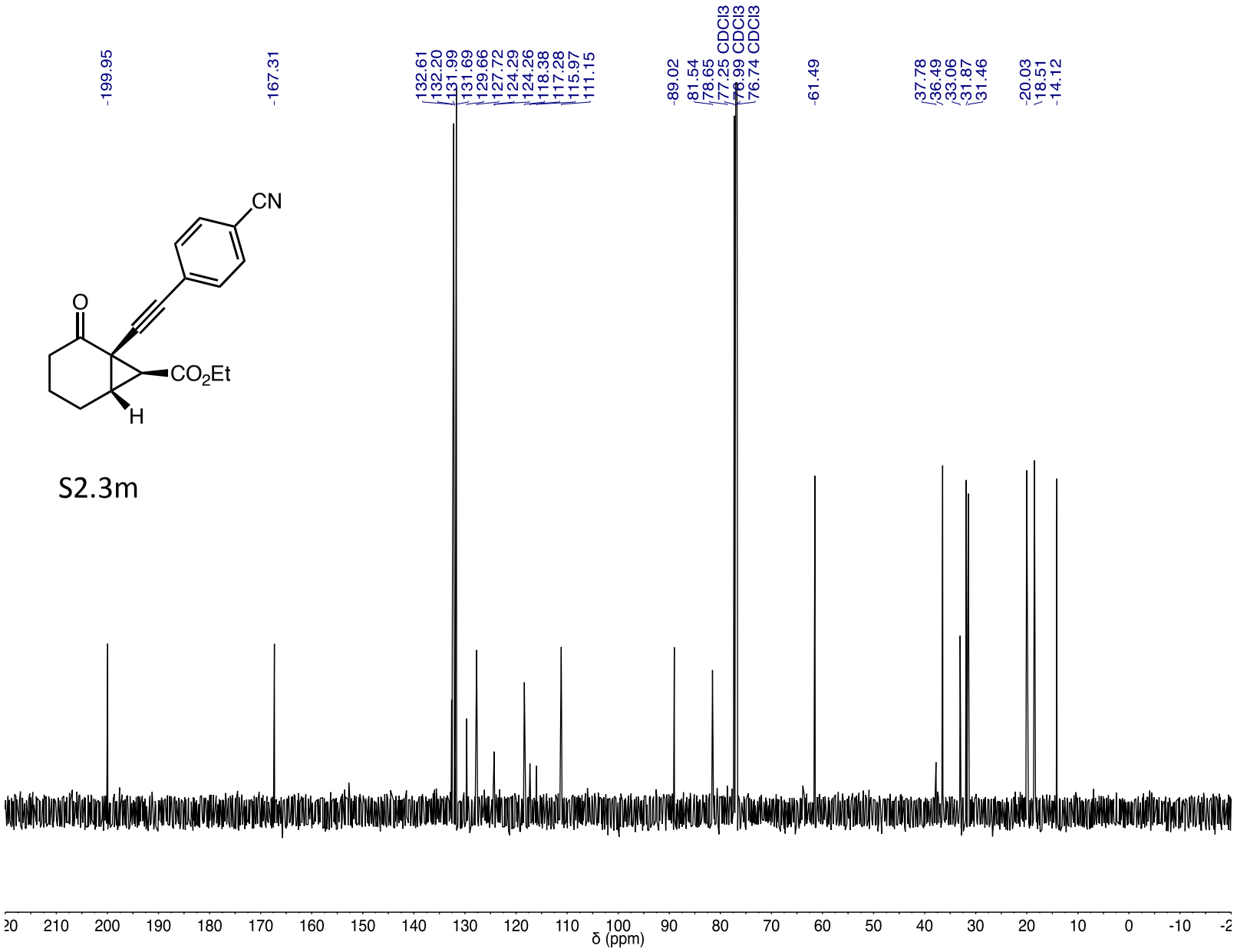
S2.3l

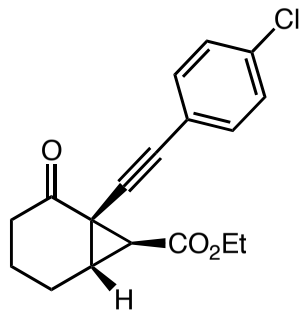
1.05
1.00
2.10
3.19
0.99
1.12
3.15
1.31
1.11
2.49
0.95
1.36
3.95
f1 (ppm)


200.61
167.63
162.41
159.29
142.09
124.34
123.99
111.00
108.16
107.15
99.95
87.84
80.57
77.27 CDCl3
77.25
77.02 CDCl3
76.99
76.76 CDCl3
76.74
61.51
53.43
36.64
33.64
31.90
31.75
31.47
29.34
23.29
22.66
21.97
20.25
18.80
14.24
14.10
OMe
N
Me
O
CO2Et
H
S2.3l
δ (ppm)

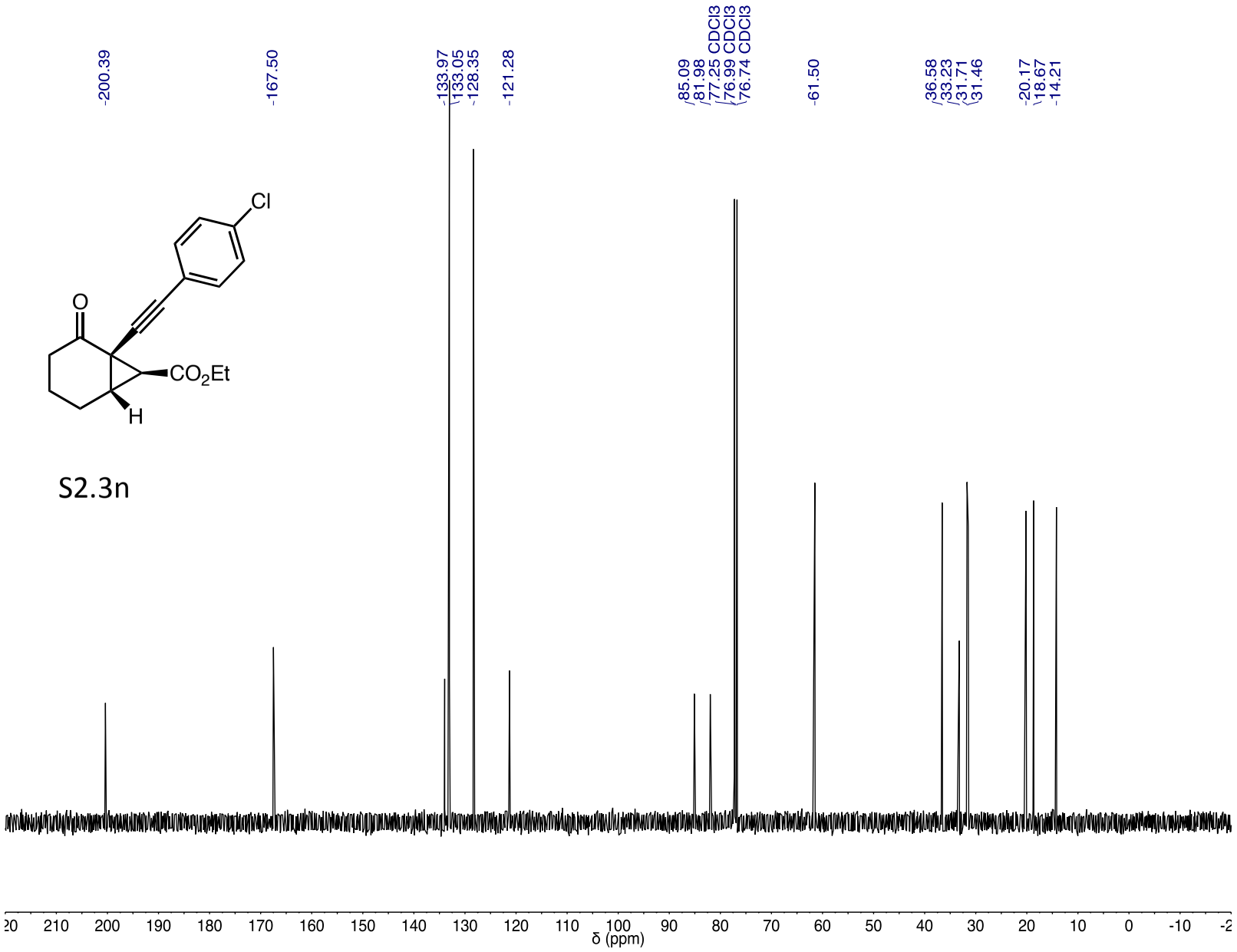


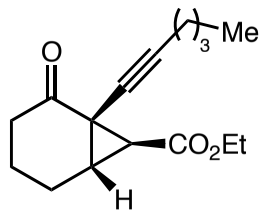
S2.3m


199.95
167.31
132.61
132.20
131.99
131.69
129.66
127.72
124.29
124.26
118.38
117.28
115.97
111.15
89.02
81.54
78.65
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
61.49
37.78
36.49
33.06
31.87
31.46
20.03
18.51
14.12
CN
O
CO2Et
H
S2.3m
δ (ppm)



S2.3n


-200.39
-167.50
-133.97
-133.05
-128.35
-121.28
85.09
81.98
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
-61.50
36.58
33.23
31.71
31.46
-20.17
-18.67
-14.21
Cl
O
CO2Et
H
S2.3n
δ (ppm)


O
Me
3
CO2Et
H

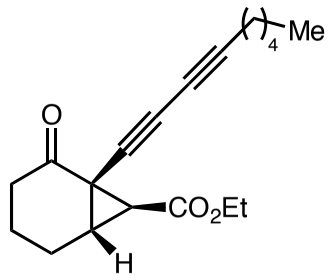
S2.3o

2.00
0.98
0.97
0.99
2.97
1.03
1.02
1.06
0.98
1.90
2.01
3.08
2.92
f1 (ppm)

S2.3o

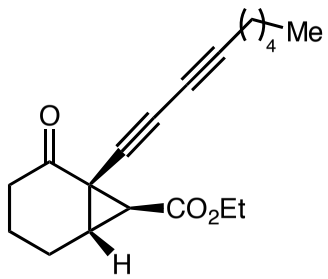

O
Me
3
CO2Et
H

201.38
167.66
83.78
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
73.98
61.26
36.49
33.10
31.18
31.05
30.71
21.79
20.17
18.80
18.50
14.20
13.54
δ (ppm)

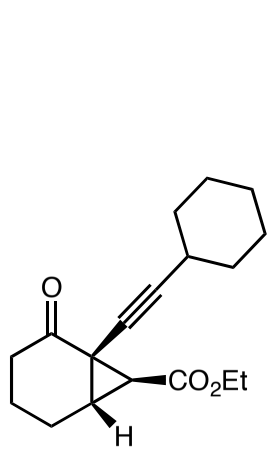


S2.3p

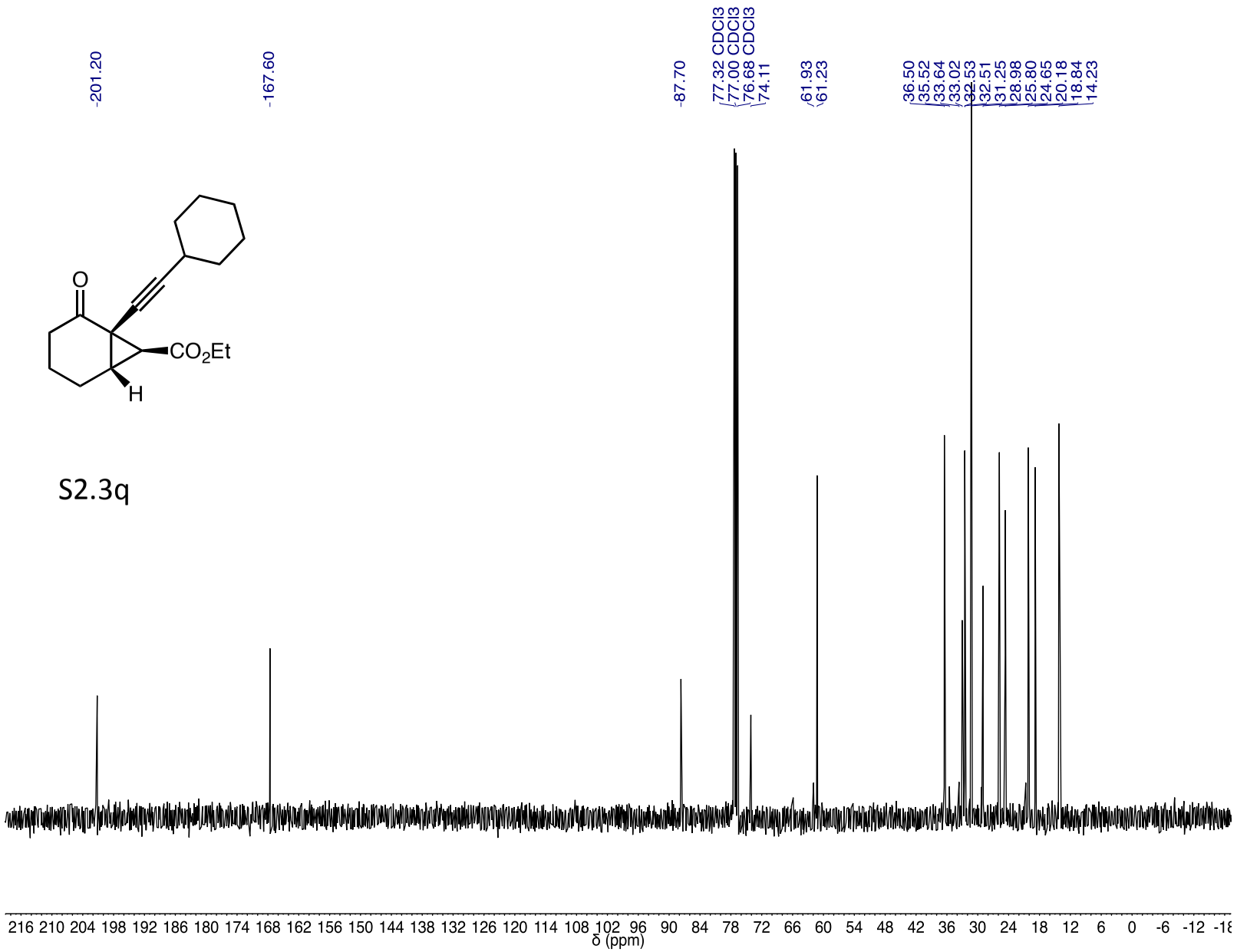
S2.3p

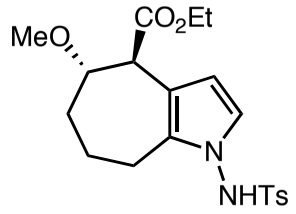

O
CO2Et
H
4
Me

199.96
167.26
79.88
77.25 CDCl3
76.99 CDCl3
76.74 CDCl3
70.04
68.36
64.86
61.93
61.57
36.47
35.53
33.62
33.19
31.86
31.77
31.72
31.35
31.27
30.83
27.72
22.05
20.63
20.07
19.13
18.71
18.54
18.40
14.27
14.13
13.83
δ (ppm)



S2.3q

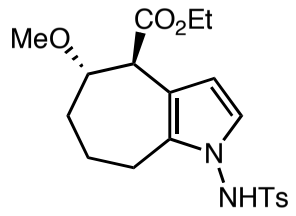

-201.20
-167.60
-87.70
77.32 CDCl3
77.00 CDCl3
76.68 CDCl3
74.11
61.93
61.23
36.50
35.52
33.64
33.02
32.53
32.51
31.25
28.98
25.80
24.65
20.18
18.84
14.23
O
CO2Et
H
S2.3q
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


MeO
CO2Et
N
NHTs

S2.7a

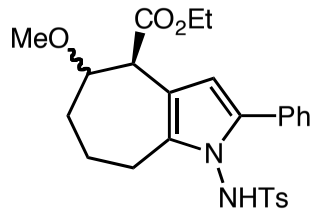
1.98
0.94
2.00
1.89
2.09
1.00
0.97
2.95
1.02
1.09
1.08
3.06
2.22
1.66
3.01
δ (ppm)

S2.7a


MeO
CO2Et
N
NHTs

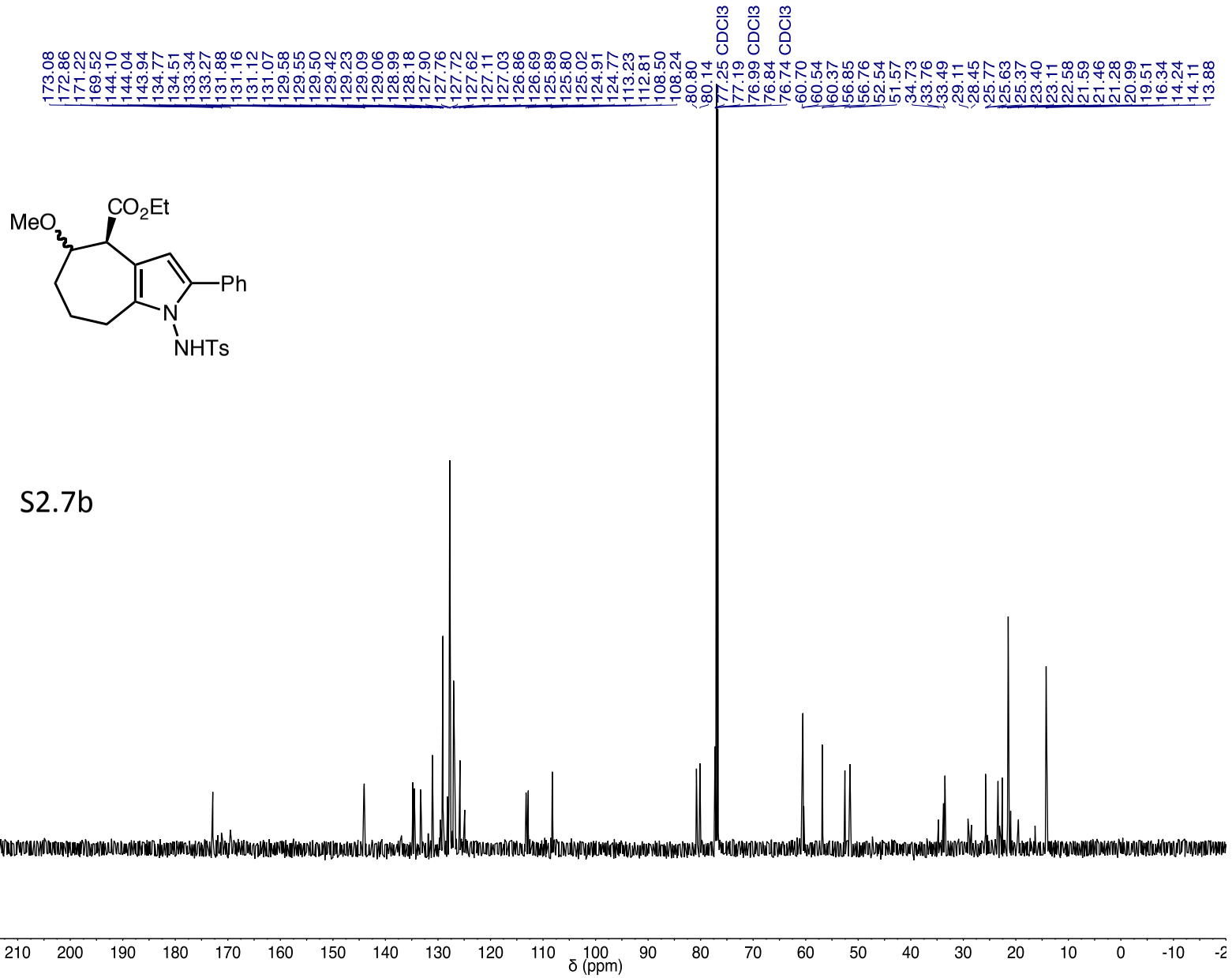
173.22
144.39
135.25
132.94
129.76
128.85
128.30 C6D6
128.18
128.06 C6D6
127.94
127.82 C6D6
118.95
113.30
107.73
80.84
60.45
56.58
52.44
33.94
24.85
23.24
21.19
14.37
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -1
δ (ppm)

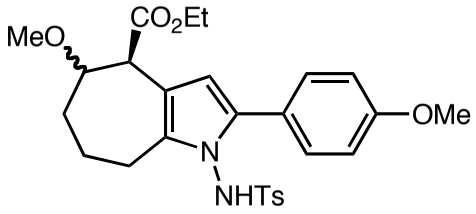
S2.7b


MeO
CO2Et
Ph
N
NHTs

1.06
0.83
3.83
5.89
10.37
3.89
0.82
0.98
4.77
1.32
1.10
0.83
6.78
1.00
0.91
1.10
1.13
0.91
13.34
1.16
9.00
f1 (ppm)

S2.7b

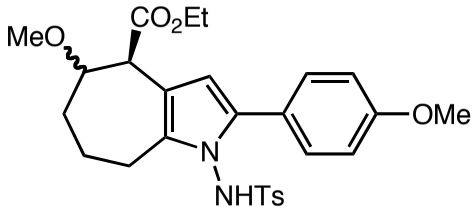

173.08
172.86
171.22
169.52
144.10
144.04
143.94
134.77
134.51
133.34
133.27
131.88
131.16
131.12
131.07
129.58
129.55
129.50
129.42
129.23
129.09
129.06
128.99
128.18
127.90
127.76
127.72
127.62
127.11
127.03
126.86
126.69
125.89
125.80
125.02
124.91
124.77
113.23
112.81
108.50
108.24
80.80
80.14
77.25 CDCl3
77.19
76.99 CDCl3
76.84
76.74 CDCl3
60.70
60.54
60.37
56.85
56.76
52.54
51.57
34.73
33.76
33.49
29.11
28.45
25.77
25.63
25.37
23.40
23.11
22.58
21.59
21.46
21.28
20.99
19.51
16.34
14.24
14.11
13.88
MeO
CO2Et
Ph
N
NHTs
δ (ppm)


MeO
CO2Et
OMe
N
NHTs

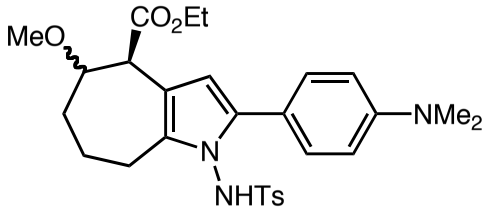
S2.7c

0.85
0.70
3.33
3.06
0.40
4.05
0.86
0.25
0.24
7.31
0.74
0.93
4.87
1.10
1.76
7.71
6.70
0.88
0.99
1.00
1.01
0.36
4.20
1.03
2.10
0.94
6.65
f1 (ppm)

S2.7c

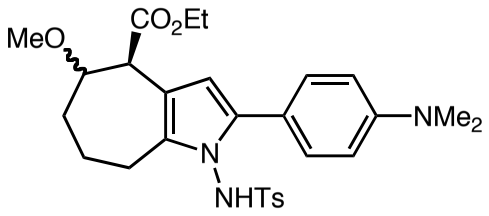

MeO
CO2Et
OMe
N
NHTs

173.71
173.66
158.88
158.85
143.89
143.78
135.83
135.56
135.08
134.90
132.12
131.99
130.57
129.54
129.49
128.67
128.57
128.48
128.38
128.29
128.19
126.05
125.24
125.18
114.92
114.12
113.92
108.37
108.09
81.44
81.39
60.87
57.10
56.95
55.13
55.11
53.29
53.19
35.24
34.31
26.68
26.44
24.34
24.23
21.49
14.77
14.68
δ (ppm)


MeO
CO2Et
NMe2
N
NHTs

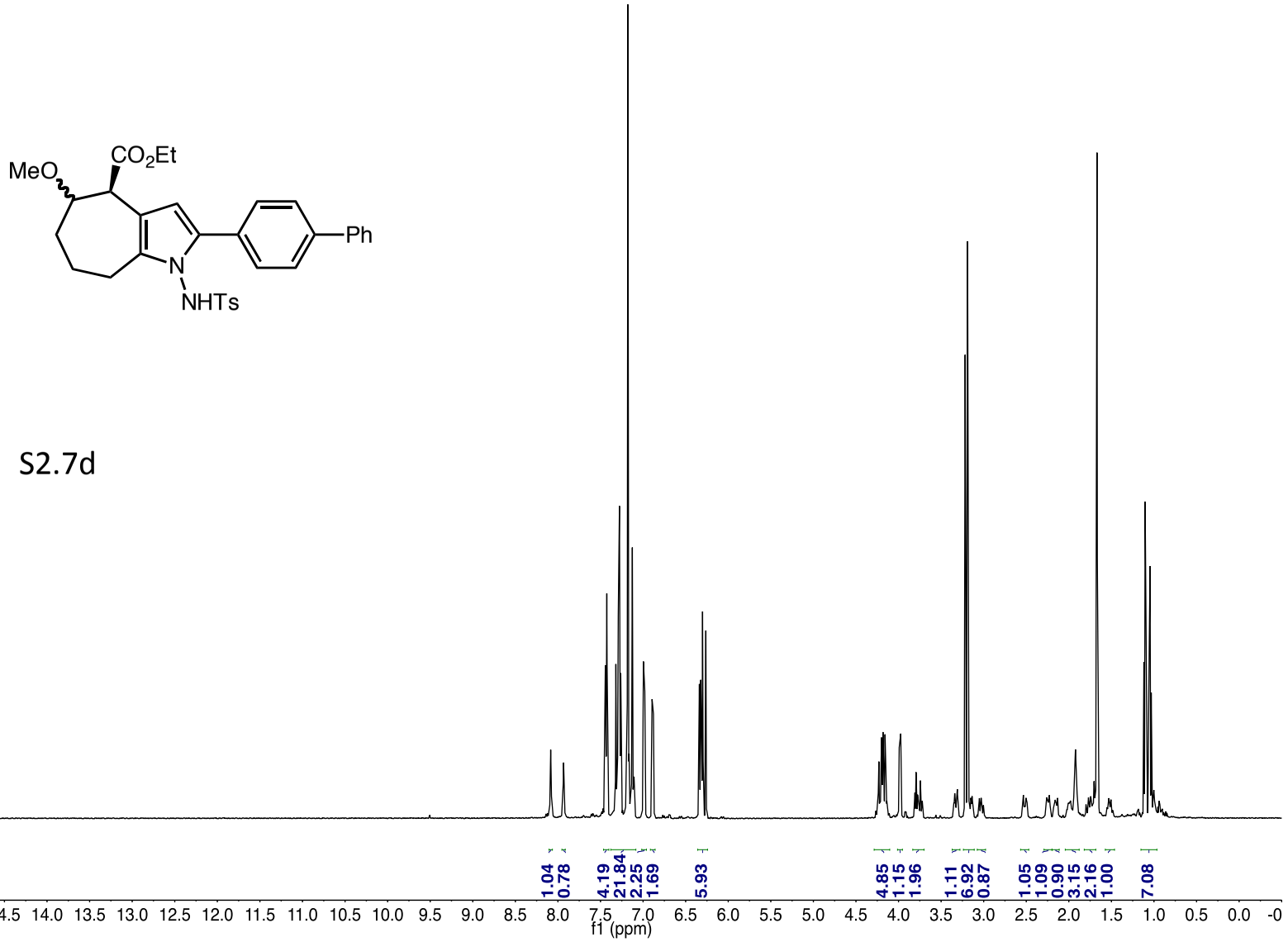
S2.7e

1.01
4.12
29.69
2.60
1.84
3.88
4.59
0.94
5.06
1.15
1.14
0.94
7.11
1.17
13.44
1.43
2.58
8.91
1.82
6.58
f1 (ppm)

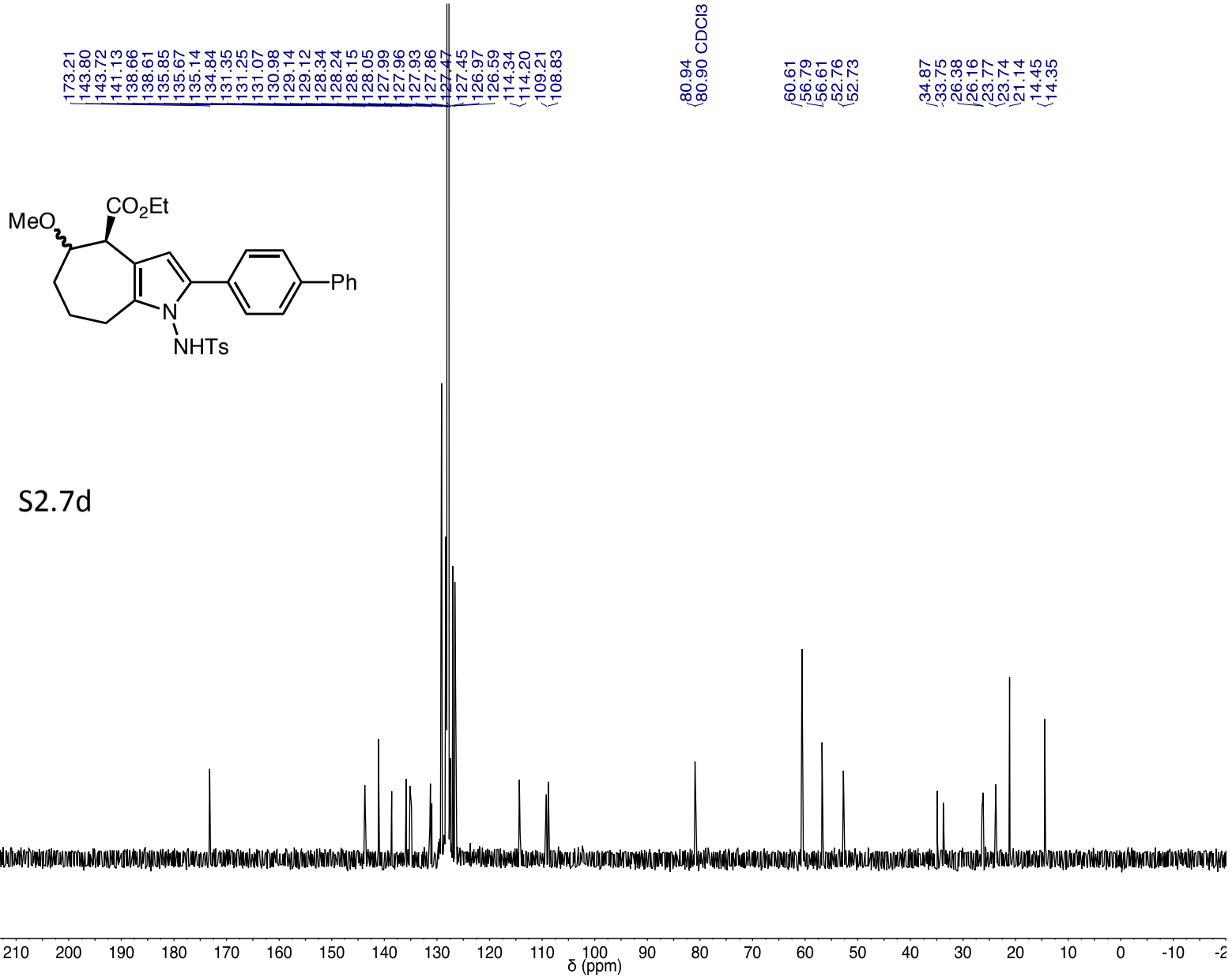


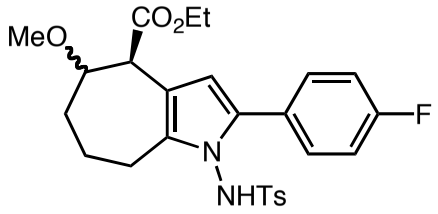
S2.7e

C13 could not be obtained
Because product is too unstable


MeO
CO2Et
Ph
N
NHTs
S2.7d
1.04
0.78
4.19
21.84
2.25
1.69
5.93
4.85
1.15
1.96
1.11
6.92
0.87
1.05
1.09
0.90
3.15
2.16
1.00
7.08
f1 (ppm)

S2.7d

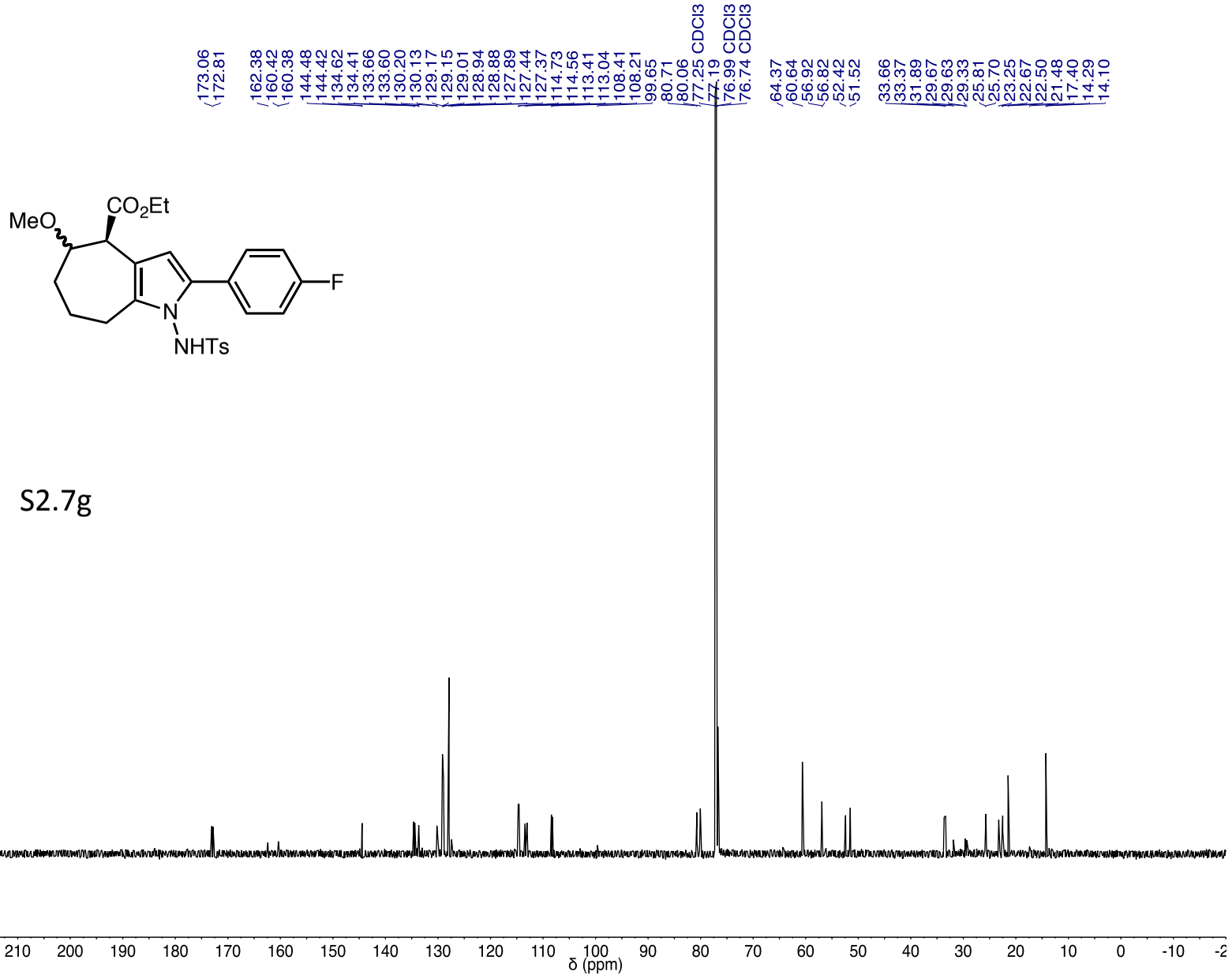

173.21
143.80
143.72
141.13
138.66
138.61
135.85
135.67
135.14
134.84
131.35
131.25
131.07
130.98
129.14
129.12
128.34
128.24
128.15
128.05
127.99
127.96
127.93
127.86
127.47
127.45
126.97
126.59
114.34
114.20
109.21
108.83
80.94
80.90 CDCl3
60.61
56.79
56.61
52.76
52.73
34.87
33.75
26.38
26.16
23.77
23.74
21.14
14.45
14.35
MeO
CO2Et
Ph
N
NHTs
δ (ppm)


MeO
CO2Et
F
N
NHTs

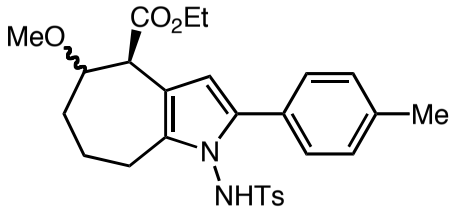
S2.7g

1.94
3.93
3.99
4.24
4.10
1.90
4.25
0.97
1.00
1.02
1.00
5.97
1.96
0.98
1.04
0.43
6.22
2.20
0.57
1.67
5.38
1.82
0.83
11.82
3.76
f1 (ppm)

S2.7g

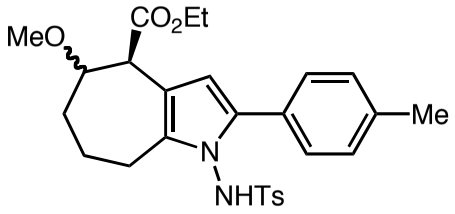

173.06
172.81
162.38
160.42
160.38
144.48
144.42
134.62
134.41
133.66
133.60
130.20
130.13
129.17
129.15
129.01
128.94
128.88
127.89
127.44
127.37
114.73
114.56
113.41
113.04
108.41
108.21
99.65
80.71
80.06
77.25 CDCl3
77.19
76.99 CDCl3
76.74 CDCl3
64.37
60.64
56.92
56.82
52.42
51.52
33.66
33.37
31.89
29.67
29.63
29.33
25.81
25.70
23.25
22.67
22.50
21.48
17.40
14.29
14.10
MeO
CO2Et
F
N
NHTs
δ (ppm)

S2.7f

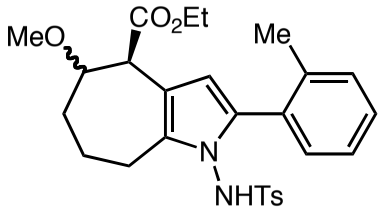

MeO
CO2Et
Me
N
NHTs

2.05
4.29
8.11
4.12
1.90
4.33
2.16
1.02
1.05
6.12
1.98
1.05
1.07
1.57
14.92
0.61
2.03
1.10
3.09
1.51
0.68
10.49
0.48
2.26
f1 (ppm)

S2.7f

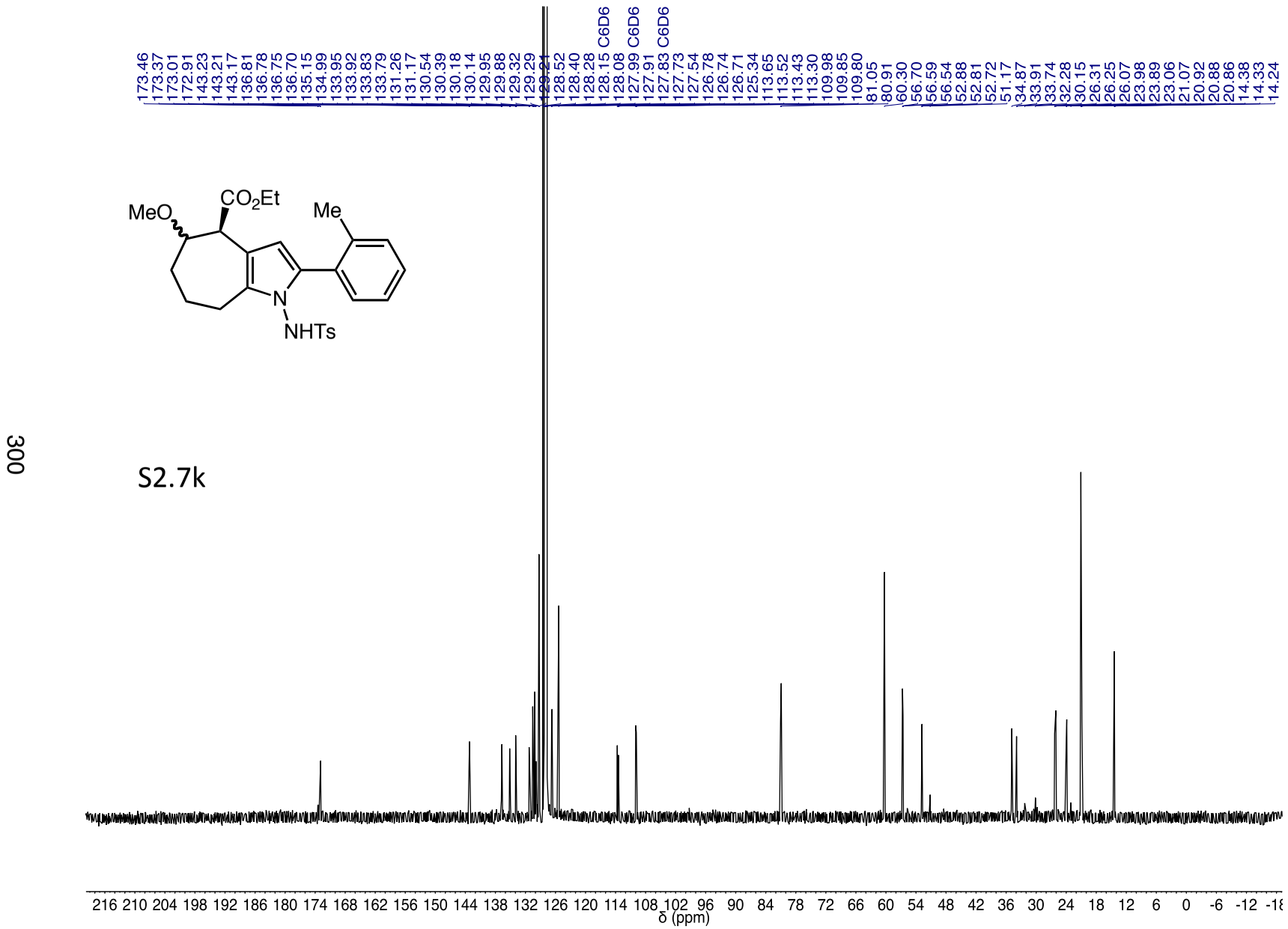

MeO
CO2Et
Me
N
NHTs

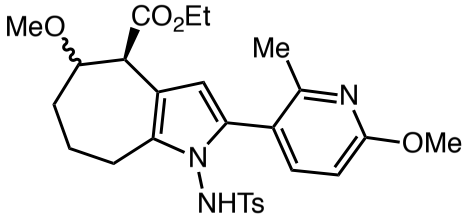
173.08
172.88
144.18
144.12
135.83
135.73
134.36
134.09
133.54
133.50
131.74
131.08
129.04
129.02
128.48
128.36
128.32
127.90
127.18
127.11
113.19
112.75
108.15
107.88
99.62
80.90
80.15
77.25 CDCl3
77.21
76.99 CDCl3
76.74 CDCl3
60.54
56.92
56.81
52.61
51.58
33.75
33.51
31.89
29.33
25.80
25.67
23.46
22.66
22.60
21.54
21.06
14.28
14.10
δ (ppm)


MeO
CO2Et
Me
N
NHTs

S2.7k

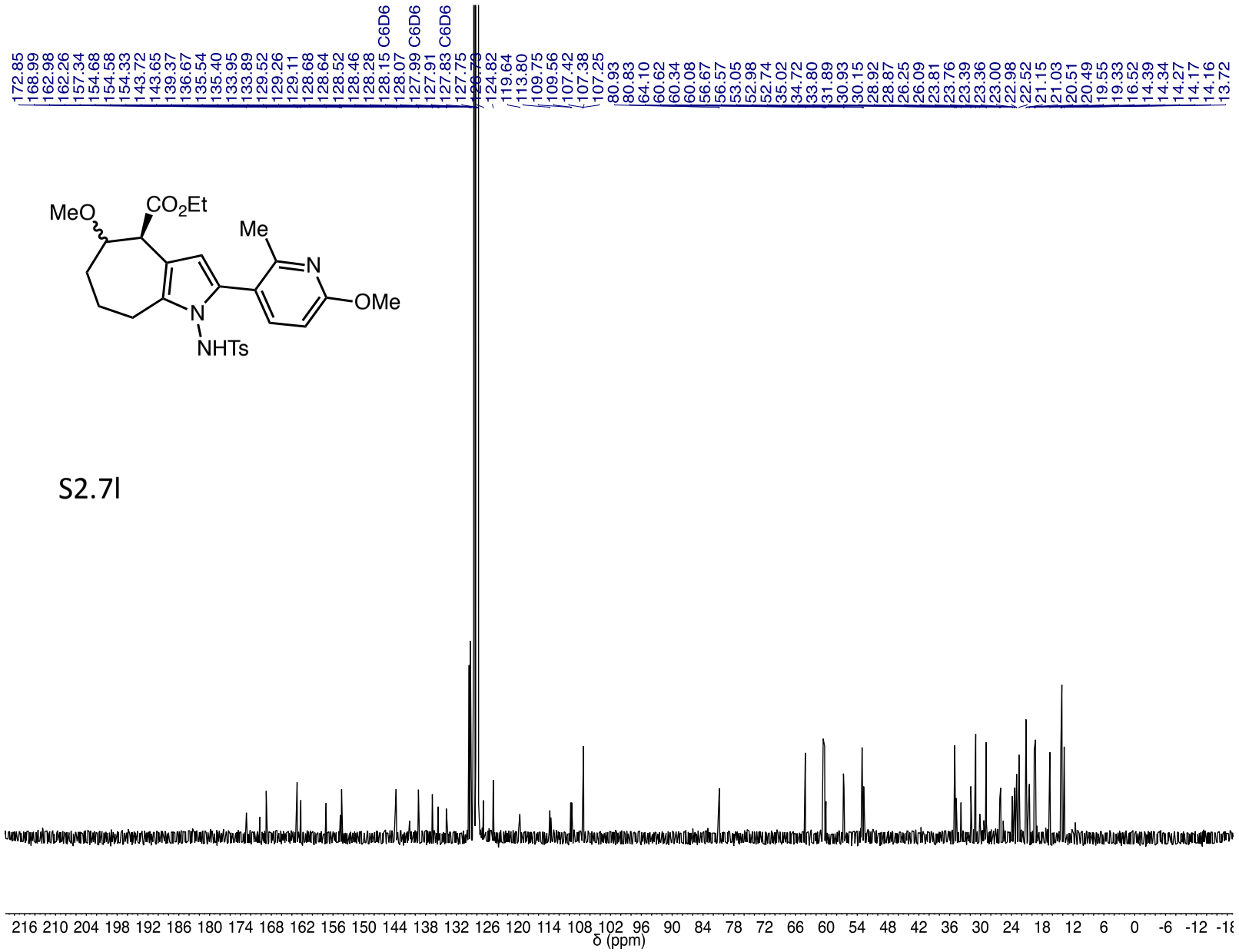
1.30
0.31
1.29
3.40
2.92
8.23
1.45
3.18
5.88
1.00
0.10
1.45
0.27
5.22
1.40
0.55
1.36
1.58
1.33
0.83
0.75
2.17
10.26
1.39
1.82
1.94
2.14
10.09
5.10
9.33
4.02
2.00
4.35
3.68
2.20
f1 (ppm)


173.46
173.37
173.01
172.91
143.23
143.21
143.17
136.81
136.78
136.75
136.70
135.15
134.99
133.95
133.92
133.83
133.79
131.26
131.17
130.54
130.39
130.18
130.14
129.95
129.88
129.32
129.29
129.21
128.52
128.40
128.28
128.15 C6D6
128.08 C6D6
127.99 C6D6
127.91
127.83 C6D6
127.73
127.54
126.78
126.74
126.71
125.34
113.65
113.52
113.43
113.30
109.98
109.85
109.80
81.05
80.91
60.30
56.70
56.59
56.54
52.88
52.81
52.72
51.17
34.87
33.91
33.74
32.28
30.15
26.31
26.25
26.07
23.98
23.89
23.06
21.07
20.92
20.88
20.86
14.38
14.33
14.24
MeO
CO2Et
Me
N
NHTs
S2.7k
300
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

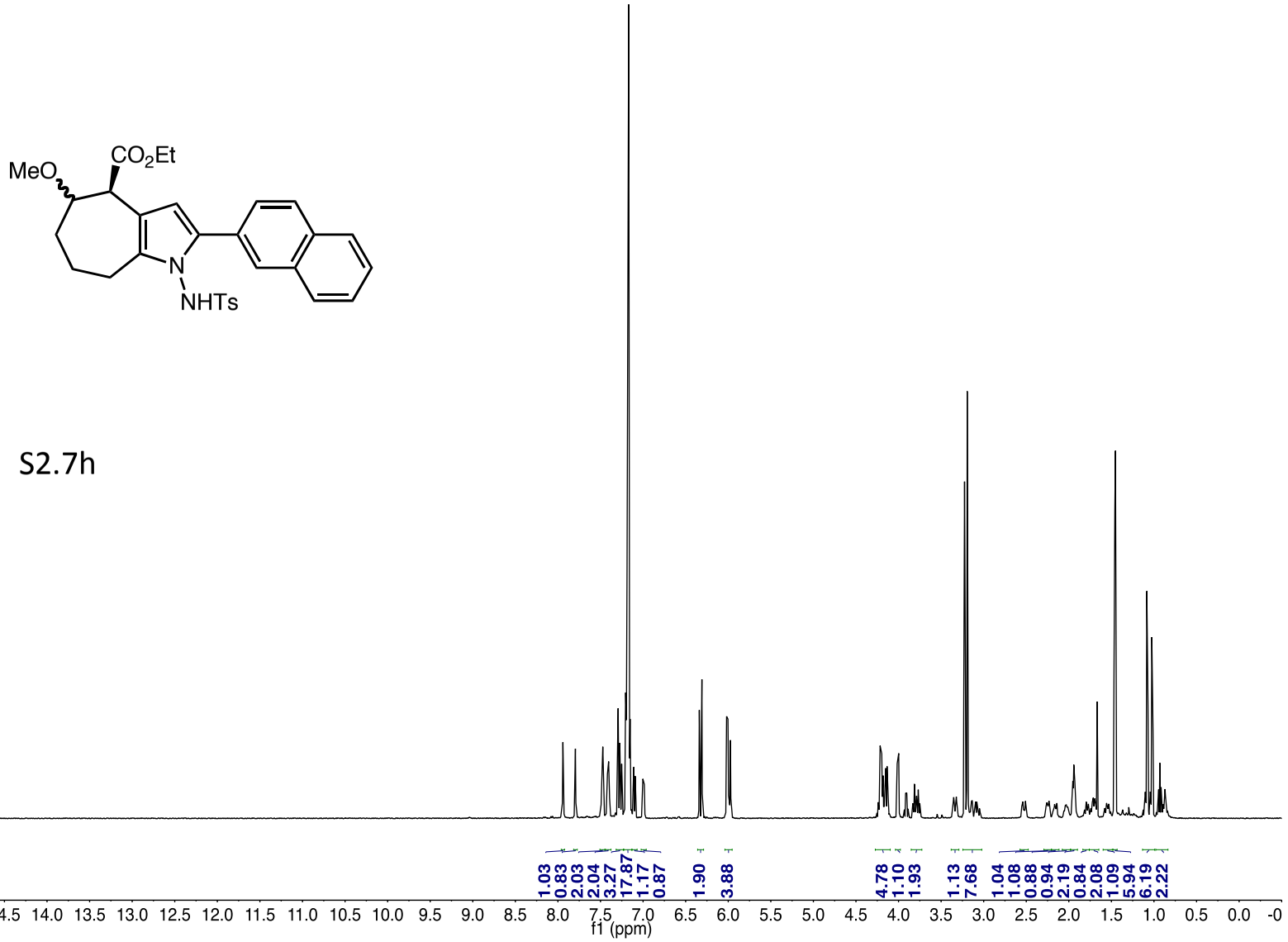

MeO
CO2Et
Me
N
OMe
N
NHTs

S2.7l

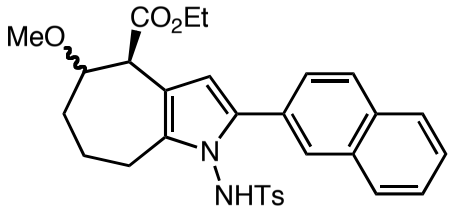
11.16
6.30
3.32
3.60
6.58
5.93
4.59
2.68
1.20
1.18
1.00
1.38
4.27
3.30
4.10
4.93
25.78
5.74
4.71
1.59
1.75
1.20
8.95
6.54
6.87
20.08
8.23
14.07
4.09
2.97
16.35
5.01
13.05
31.12
f1 (ppm)


172.85
168.99
162.98
162.26
157.34
154.68
154.58
154.33
143.72
143.65
139.37
136.67
135.54
135.40
133.95
133.89
129.52
129.26
129.11
128.68
128.64
128.52
128.46
128.28
128.15 C6D6
128.07
127.99 C6D6
127.91
127.83 C6D6
127.75
124.82
119.64
113.80
109.75
109.56
107.42
107.38
107.25
80.93
80.83
64.10
60.62
60.34
60.08
56.67
56.57
53.05
52.98
52.74
35.02
34.72
33.80
31.89
30.93
30.15
28.92
28.87
26.25
26.09
23.81
23.76
23.39
23.36
23.00
22.98
22.52
21.15
21.03
20.51
20.49
19.55
19.33
16.52
14.39
14.34
14.27
14.17
14.16
13.72
MeO
CO2Et
Me
N
OMe
N
NHTs
S2.7l
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S2.7h


MeO
CO2Et
N
NHTs
1.03
0.83
2.03
2.04
3.27
17.87
1.17
0.87
1.90
3.88
4.78
1.10
1.93
1.13
7.68
1.04
1.08
0.88
0.94
2.19
0.84
2.08
1.09
5.94
6.19
2.22
f1 (ppm)

S2.7h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N
NHTs

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126.11
125.95
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125.50
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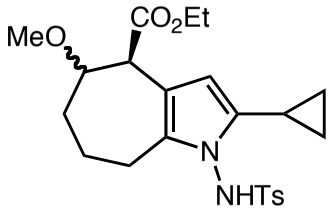
δ (ppm)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NHTs

S2.7i

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1.25
1.05
1.05
3.19
3.26
1.06
1.06
2.27
2.43
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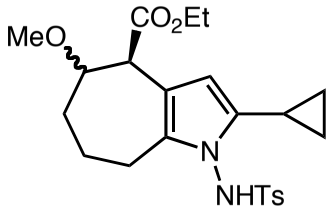
f1 (ppm)

S2.7i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N
NHTs

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128.25 C6D6
128.09 C6D6
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14.42
7.45
7.39
6.72
6.67
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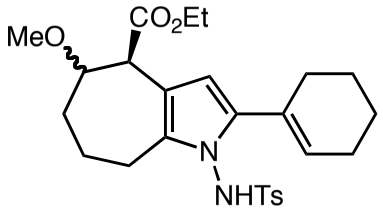
δ (ppm)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CO2Et
N
NHTs

S2.7j

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1.99
1.00
1.18
0.94
0.85
6.92
2.07
1.49
1.28
1.42
3.40
8.37
1.21
1.04
1.66
2.13
5.39
5.73
6.53
8.40
3.53
7.40
22.19
5.44
13.45
12.14
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
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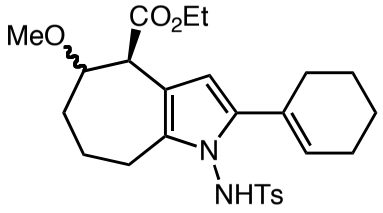
S2.7j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NHTs

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123.98
123.91
107.38
107.31
80.98 CDCl3
80.79
60.30
56.64
56.57
52.69
52.47
34.60
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27.79
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25.88
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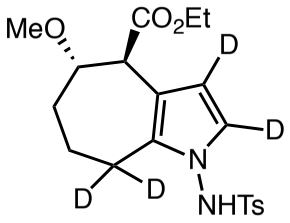
δ (ppm)


MeO
CO2Et
D
D
N
NHTs
D
D

d7-S2.7a

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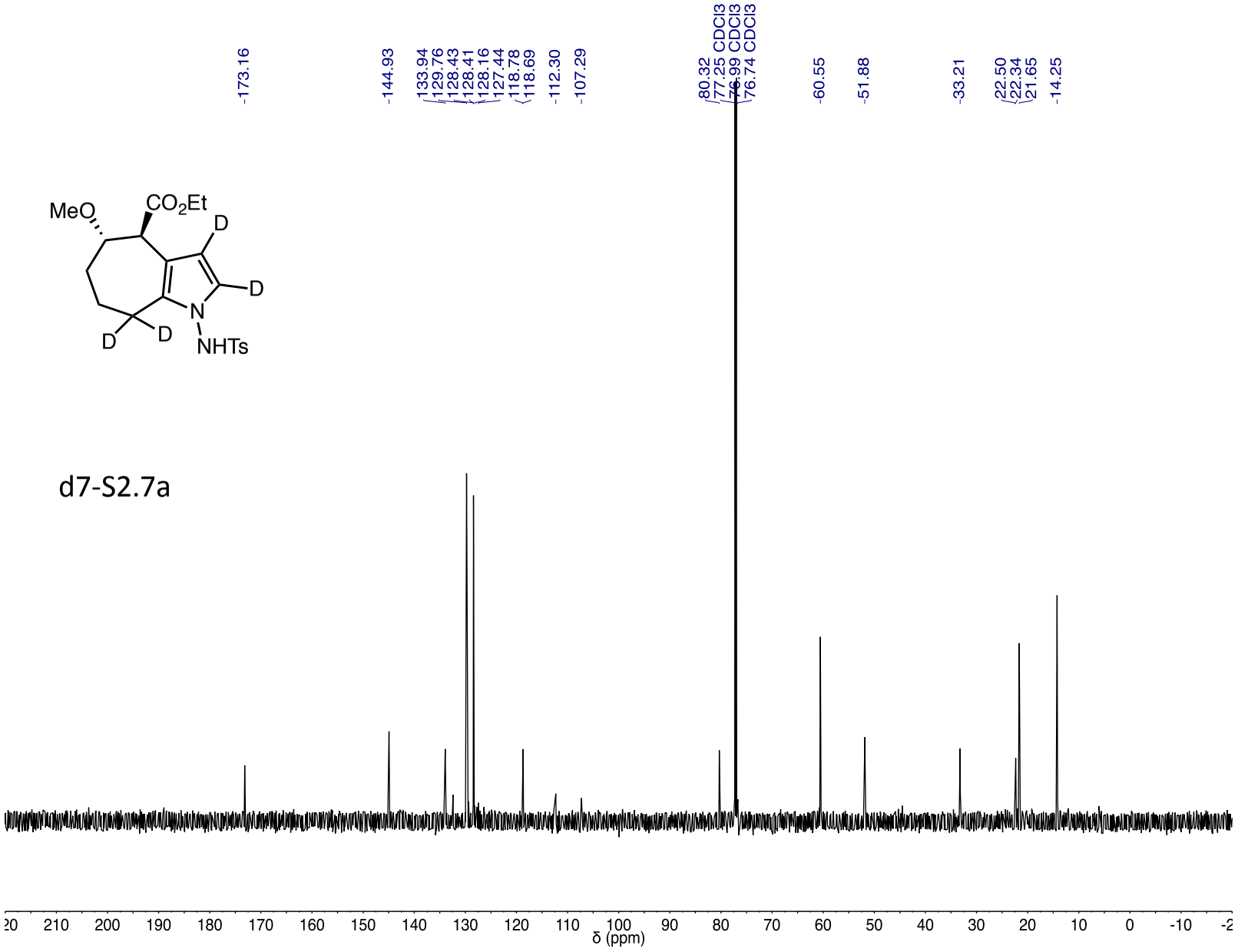
0.20
1.80
0.81
0.81
2.57
0.90
1.04
2.13
3.29
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)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77.25 CDCl3
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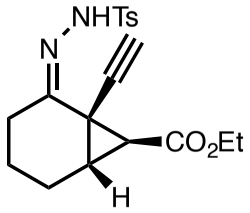
CO2Et
D
D
D
D
N
NHTs
d7-S2.7a
δ (ppm)


NHTs
N
CO2Et
H

Z-S2.8

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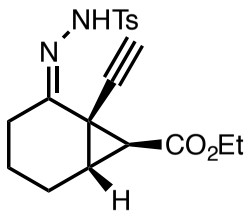
1.27
3.03
δ (ppm)

Z-S2.8


NHTs
N
CO2Et
H

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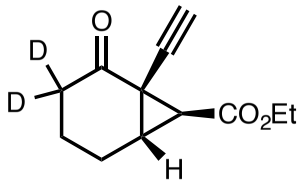
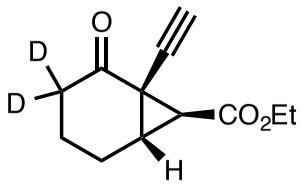
δ (ppm)



d2-S2.3a

d2-S2.3a


O
D
D
CO2Et
H

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76.99 CDCl3
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71.43
-61.47
35.64
32.40
31.24
31.19
31.10
30.87
30.79
30.64
19.91
19.88
18.54
18.40
14.13
δ (ppm)

CHAPTER 3: LEVERAGING Pt(II)-CATALYZED CYCLOISOMERIZATION REACTIONS OF PROPARGYLC ESTERS TO ACCESS ANNULATED INDENE DERIVATIVES

Section 3.0. Indene Background

This chapter describes efforts to leverage the power of Pt(II)-catalyzed cycloisomerization reactions to access 2-substituted indenes in order to showcase their utility in natural product synthesis. Indenes are bicyclic aromatic compounds that are isoelectronic with indole when deprotonated (see Chapter 1). The pKa of 1-*H*-indene is 20.13 and the effect of substitution around the ring on the pKa has been systematically investigated.[1] The name indene (and indane for the fully saturated carbocycle) stems from the world "indole" and signifies an all carbon framework of the compound.[2]

Indenes may be synthesized through several common methods (Figure 1). Classically, indenes are accessed through an intramolecular Friedel-Crafts acylation followed by reduction of the resulting indanone with a reducing agent (or 1,2-addition with a Grignard reagent) and subsequent elimination of the tertiary alcohol.[3] Alternatively, researchers have explored Nazarov cyclizations to obtain these compounds and have exploited this reactivity in the synthesis of complex biologically active natural products (e.g., the aglycon of tetrapetalone).[4] C–H insertion reactions of tethered diazocarbonyl compounds have also served as a practical method for accessing indenes and indanones.[5]

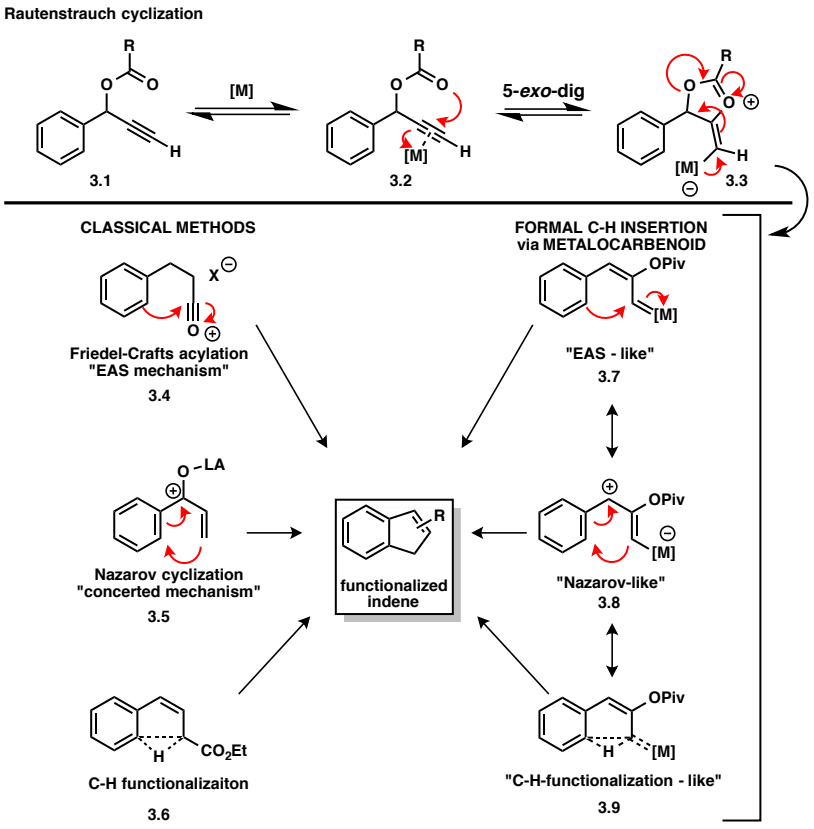


Figure 1: Classical methods for accessing indene substrates and relationship to Rautenstrauch reaction.

Recently, carbocycloisomerization reactions have become one of the premier ways to access the indene moiety. These reactions occur through the electrophilic activation of alkyne compounds using a π-philic Lewis acid. Work in the Sarpong group[6] and by others[7] have shown that aromatic propargylic esters (e.g., Figure 1, **3.1**) can be transformed to indenes using π-Lewis acid catalysis through the Rautenstrauch reaction manifold.[8] Considering the mechanism for this transformation, it is apparent that it echoes features of the Friedel-Crafts acylation, Nazarov cyclization, and C–H insertion reactions (Figure 1). Unlike the traditional methods (see Figure 1, **3.4** – **3.6**) however, carbocycloisomerization reactions using π-Lewis acid catalysis allow for the reaction to take place under mild conditions depending on the choice of metal and ligand and furthermore allow the opportunity for domino reactions.

Because of the novel strategies available to synthesize indenes, we sought to leverage these carbocycles in natural product synthesis, specifically to access tetrahydrofluorenes and their seven-membered analogues. We envisioned cycloisomerization reactions through the Rautenstrauch pathway as being particularly useful because of the ability to access 2-substituted indenes.

Section 3.1. A Novel Approach to tetrahydrofluorenes

Functionalized tetrahydrofluorenes are important scaffolds found in a variety of biologically active natural products with anti-cancer activity such as the kinamycins[9] (e.g., **3.10**, Figure 2), and taiwaniaquinoids,[10] (e.g., **3.12**) as well as lead pharmaceutical compounds that serve as selective estrogen β-agonists (e.g., **3.11**).[11] The tetrahydrofluorene moiety has also been used as a strategic structural motif to access the C19 gibberillin phytohormones (e.g. **3.13**), which contain a partially reduced 9H-fluorene core (**3.14**).[12] Because of the wide variety of biological activities in these molecules, methods for accessing these structural frameworks containing diverse substitution patterns are of high value.

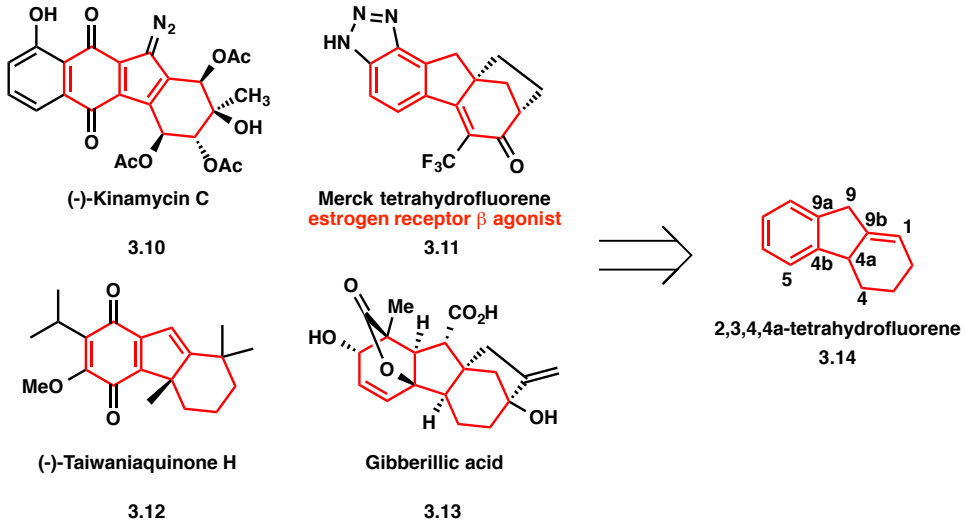
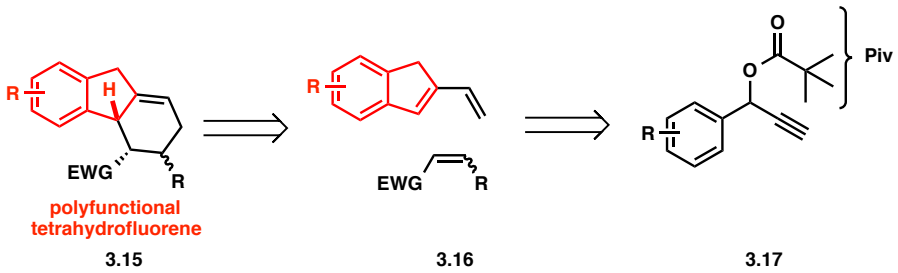


Figure 2: Biologically active molecules containing substituted tetrahydrofluorenes.

Several tactics exist to construct the tetrahydrofluorene core. Commonly, Friedel-Crafts alkylations[13] are employed to access these scaffolds, either by constructing the C4a-C4b bond or the C9-C9a bond. Nazarov reactions have also been extensively investigated to forge the C4a-C4b bond of these compounds.[14] One can also obtain these scaffolds through the stepwise Birch reduction of 9H-fluorenes using lithium metal in ammonia, but this methodology has not been extensively explored.[15] Though the above methods allow access to substituted tetrahydrofluorenes, they all require Lewis or protic acids to mediate the transformations, which are incompatible with acid sensitive functional groups. Furthermore, these methods lack modularity for functionalizing both the A- and C- rings of these compounds.

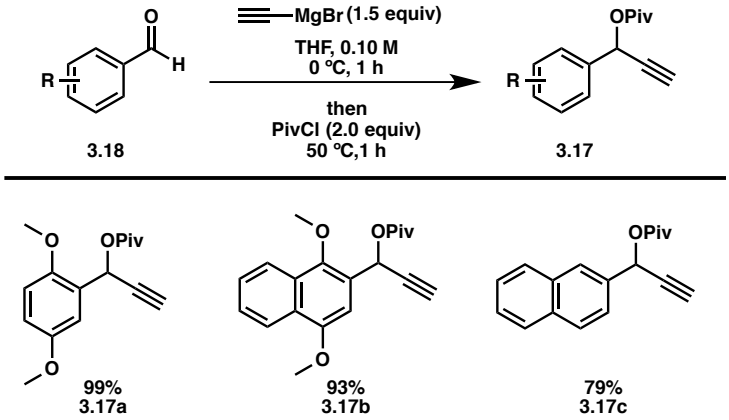
To address these limitations, we hypothesized that we could construct the tetrahydrofluorene core using a Diels–Alder cycloaddition reaction of a 2-vinylindene[16] with a functionalized dienophile (Scheme 1). This strategy is advantageous because it allows for the introduction of functional patterns on tetrahydrofluorenes that are otherwise difficult to access.[17] Interestingly upon inspection of the literature, we found only a single report of 2-vinylindene participating in Diels–Alder cycloaddition reactions (by Adam and deLucci).[18] We surmise that this lack of investigation may have arisen in part due to the lack of methods for accessing 2-substituted indenes at the time. However, using cycloisomerization technology pioneered by our group and others in the past decade for construction of indenes,[19] we predicted that functionalized 2-vinylindenes[20] could be readily accessed through the requisite propargylic esters.



Scheme 1: Strategy for obtaining polysubstituted tetrahydrofluorenes.

Section 3.2. Cycloisomerization scope and elaboration to vinyl-containing systems

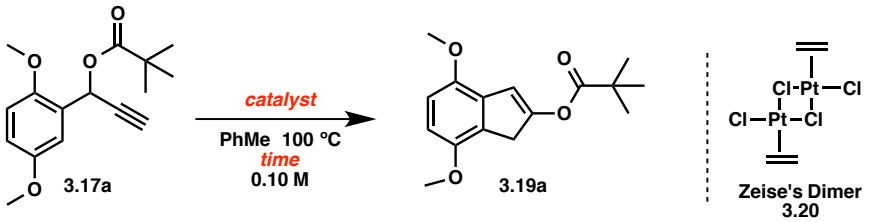
Our studies began with the synthesis of 2-vinylindene from indene in three steps using literature procedures.[21] For indenes with substitution at the 4- and 7- positions, the requisite propargylic esters were readily synthesized on gram scale in excellent yields by the addition of ethynylmagnesium bromide into commercially available 2,5-dimethoxybenzaldehyde, naphthaldehyde, and known 1,4-dimethoxy-2-naphthaldehyde[22] and trapping the resulting alkoxide anions with pivaloyl chloride at 50 ºC to give substrates **3.17a** – **3.17c** (Scheme 2).



Scheme 2: Propargylic ester synthesis

The resulting propargylic esters were then subjected to platinum(II)-catalyzed cycloisomerization conditions. After a short screening campaign (Table 1) we found that modified conditions by Sato and coworkers, afforded optimal yields of the desired indenes (Table 1, Entry 8).[19a] Gold(I) salts were not investigated for this cycloisomerization reaction due to the fact they are typically utilized with internal alkyne substrates and tend to result in a mixture of indene isomers.[7d] Furthermore, these gold(I)-catalyzed cycloisomerization reactions to give indenes typically require propargylic acetate esters as opposed to propargylic pivalate esters.

Table 1: Cycloisomerization reaction optimization table.

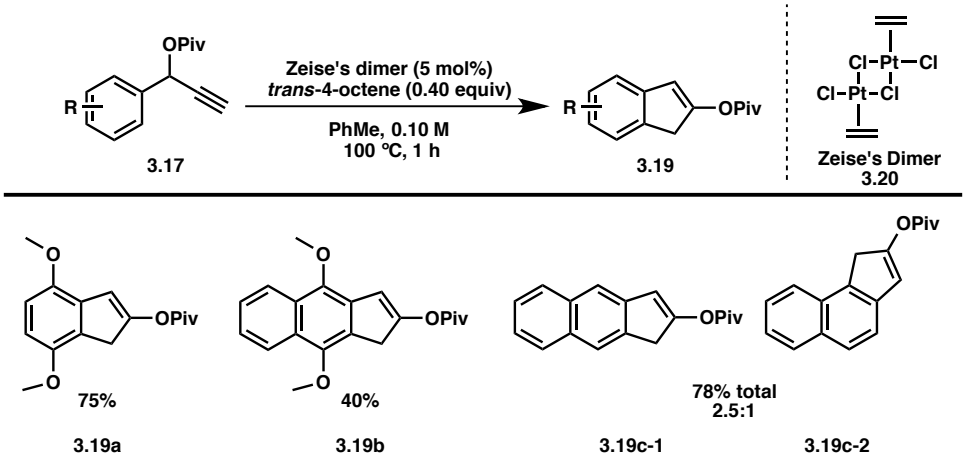


Entry	Catalyst	Catalyst Loading (mol%)	Additive (40 mol%)	Time (h)	Yield (%)
1	$PtCl_2$	10	none	6	36
2	$PtCl_2$	10	trans-4-octene	2.2	47
3	$PtCl_2$	10	norbornene	2.2	47
4	$PtCl_2$	10	K_2CO_3	6	38
5	$PtCl_2$	10	trans-4-octene	1	58
6 [a]	$PtCl_2$	10	trans-4-octene	1	0
7	$PtCl_2$	10	trans-4-octene and CsOPiv	1	0
8 [b]	Zeise's Dimer	5	trans-4-octene	1	75
9 [c]	Zeise's Dimer	5	trans-4-octene	1	74
10	Zeise's Dimer	5	trans-4-octene	1	68

a conducted in MeCN, *b* conducted in PhH, *c* conducted in cyclohexane with Z.D. from Acros
Note: 8 and 9 Zeise's Dimer from Strem

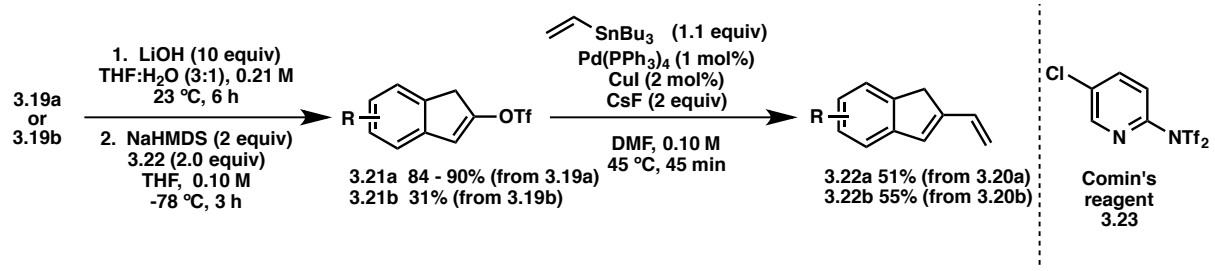
The use of Zeise's dimer and *trans*-4-octene were both critical to the success of this reaction. We surmise that alkene ligands are important 1) for maintaining solubility of the platinum salts in the reaction and 2) increasing the electrophilicity of the Pt(II)-center due to π-backbonding.[23] Interestingly, we found that propargylic ester **3.17b** performed poorly in the cycloisomerization reaction to give benz[b]indene **3.19b** (Scheme 3). We attribute this poor reactivity to a weakening of the C—H bond in the

naphthalene system due to diminished aromatic stabilization of the fused electron rich arene.[24] Propargylic ester **3.17c** gave an inseparable mixture of linear and angular benz[b]indenes **3.19c-1** and **3.19c-2** in a 2.5:1 ratio, reflecting incipient *peri*-strain in the transition state for the C–H insertion step.[25] Using $PtCl_2$ as the catalyst resulted in better selectivity between the two isomers (4.5:1). The effect of the Pt- catalyst on the reaction may suggest that cycloisomerization using $PtCl_2$ occurs through a later transition state where steric *peri*- strain effects would be more pronounced. The inseparable mixture of **3.19c-1** and **3.19c-2** were not carried forward to the vinylation sequence.



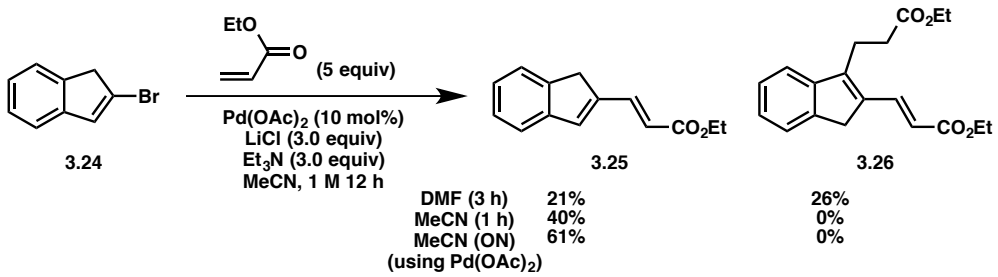
Scheme 3: Cycloisomerization reaction substrate scope. a) For 3.19c-1 and 3.19c-2 using Table 2 conditions 5 gave 4.5:1 ratio of products.

With these propargylic esters in hand, we desired to effect a cross-coupling reaction of the vinyl pivalate groups, based on precedent for C–O bond activation by the Shi and Garg groups.[26] Unfortunately we were unable to realize the desired cross-couplings reactions, presumably because the increased electron density of the arenes inhibits oxidative addition into the C–O bonds. To address this challenge, the 2-indenyl pivalates **3.19a** and **3.19b** were hydrolyzed using $LiOH{\bullet}H_2O$ and then converted to the corresponding 2-indenyl triflates **3.21a** and **3.21b** using sodium hexamethyldisilazane (NaHMDS) and Comin's reagent.[27] With triflates **3.21a** and **3.21b** in hand, a Stille cross-coupling reaction afforded our desired substituted 2-vinylindenes **3.22a** and **3.22b** in moderate yields.



Scheme 4: Conversion of indenyl-2-pivalates to 2-vinylindenes.

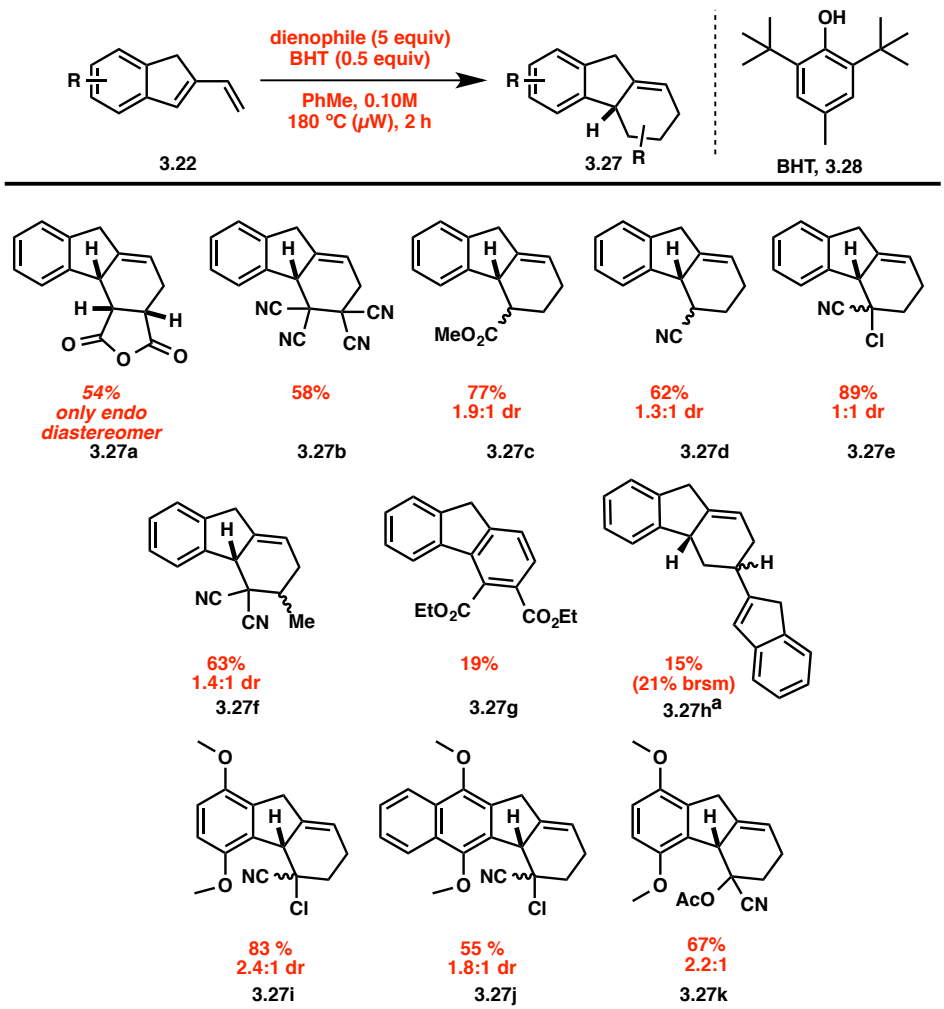
Finally, we also investigated Heck olefination reactions on 2-bromoindene to access electron deficient 2-vinylindenes. To this end, reacting 2-bromoindene with ethylacrylate (Scheme 5) provided the desired indene in low yield. It appears the immediate Heck product undergoes a subsequent conjugate addition[28] into a second equivalent of ethyl acrylate. This undesired pathway can be disfavored by performing the reaction in acetonitrile. Unfortunately, extending the Heck conditions to the corresponding 2-indenyltriflate was not successful and thus this chemistry was not investigated on compounds **3.25** and **3.26**.



Scheme 5: Heck reactivity of 2-bromoindene gives Heck olefination product 3.25 as well as conjugate addition product 3.26.

Section 3.3. The Diels—Alder cycloaddition of 2-vinyl indenes

With vinylindenes **3.22a** and **3.22b** in hand we then began to explore the Diels–Alder cycloaddition reaction with various dienophiles. We were delighted to find that 2-vinylindene participated in a normal electron demand Diels-Alder reaction with various dienophiles (Scheme 6). Reactive dienophiles such as maleic anhydride and tetracyanoethylene gave substituted tetrahydrofluorenes **3.27a** and **3.27b** at room temperature in 54% and 58% yields respectively after recrystallization. Tetrahydrofluorene **3.27a** was obtained as a single diastereomer. Less activated dienophiles such as methyl acrylate, acrylonitrile, and chloroacrylonitrile participated in the cycloaddition reaction but required microwave heating at 180 ºC for 2 hours to afford tetrahydrofluorenes **3.27c**, **3.27d**, and **3.27e**, in 77% (1.9:1 dr), 62% (1.3:1 dr) and 89% (1.0:1 dr) yields, respectively, although with poor diastereoselectivity. Adding 0.5 equivalents of 2,6-di-*tert*-butyl-4-methylphenol (BHT) was critical to obtain satisfactory yields of the Diels–Alder adducts by preventing polymerization of the dienophiles at high temperatures.[29] In each of these cases, a significant portion of the mass balance was accounted for by the isolation of 2-vinylindene dimer **3.27h**. Indeed, a control experiment whereby 2-vinylindene was heated in the absence of dienophile, afforded **3.27h** in 15% yield (21% based on recovered starting material). Alkynes were not generally tolerated in this reaction, however dimethylacetylene dicarboxylate (DMAD) did give the fully aromatic fluorene **3.27g** in 19% after spontaneous oxidation *in situ*.



Scheme 6: Scope for the Diels-Alder cycloaddition reaction of 2-vinylindenes. a) Performed with 4-month old 2-vinylindene.

Dienes such as ethylvinyl ether, cyanovinyl acetate, vinyl acetate, (*E*)-methyl butenoate, and isopropylidene malononitrile did not react with 2-vinylindene. In these cases, only indene dimer **3.27h** was formed. We attribute this to a raising of the LUMO energy levels of the dienophiles due to the presences of the oxygen or methyl substituents on the alkene. Sterically demanding alkenes such as 2-ethylidenemalononitrile however, participated in the reaction giving adduct **3.27f** in 63% yield. Thus, the electron-donating effect of pendent methyl groups on the dienophile is mitigated by incorporating another electron withdrawing group (in this case a cyano group) on the alkene.

We found 4,7-dimethoxy-2-vinylindenes **3.22a** and **3.22b** also participate in the Diels–Alder cycloaddition reaction, giving substituted tetrahydrofluorene **3.27i** in 83% yield (2.4:1 dr) and benz[b]tetrahydrofluorene **3.27j** in 55% yield (1.8:1 dr) when reacted with 2-chloroacrylonitrile under the standard conditions. The slight increase in diastereoselectivity in these cases compared to substrates **3.27c** – **3.27e** can be readily explained on the basis of *peri*-strain arguments. Interestingly, benzannulation has a significant effect on both the yield and the diastereoselectivity of the reaction (compare

3.27i and **3.27j**). This may be due to a stabilization of radical or polar intermediates during the course of the reaction because of extended delocalization into the fused aromatic system (Figure 3, A). Being more electron rich, vinylindene **3.22a** also participates in the Diels–Alder cycloaddition reaction with 1-cyanovinylacetate to give adduct **3.27k** in 67% yield (2.1:1 dr). Notably, adduct **3.27j** provides most of the carbon framework for kinamycin C (**3.10**).

With our substrate scope demonstrated, we then set to rationalize the regioselectivity of the reaction. We were initially intrigued by applying the bent bond model and antiperiplanar hypothesis, first pioneered by Linus Pauling and recently revitalized by Pierre and Ghislain Deslongchamps, to the systems to rationalize the observed regioselectivity in our cycloaddition reactions.[30] Considering both the diene and dienophiles as diradicals in the transition state for the cycloadditions,[31] we predict that the C2-C3 bond would be formed to a lesser extent due to radical stabilization in the transition state from the electron-withdrawing group (for the dienophiles) and aromatic substituents (for the dienes) (Figure 3, A).

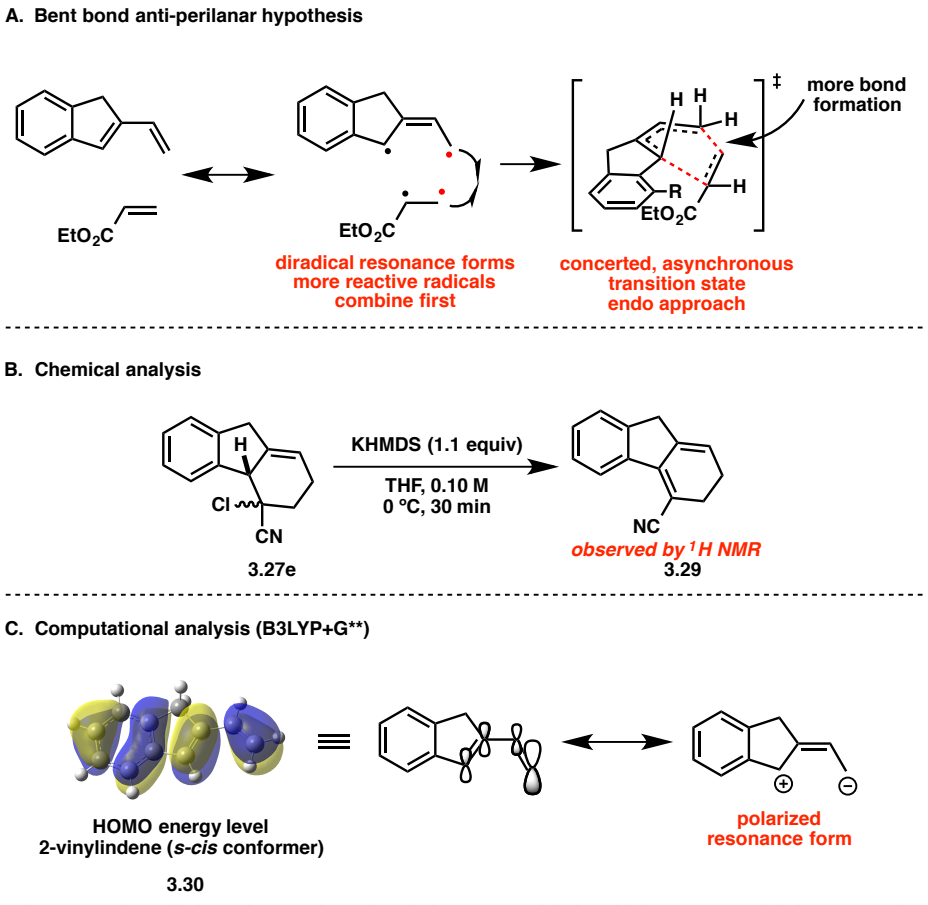


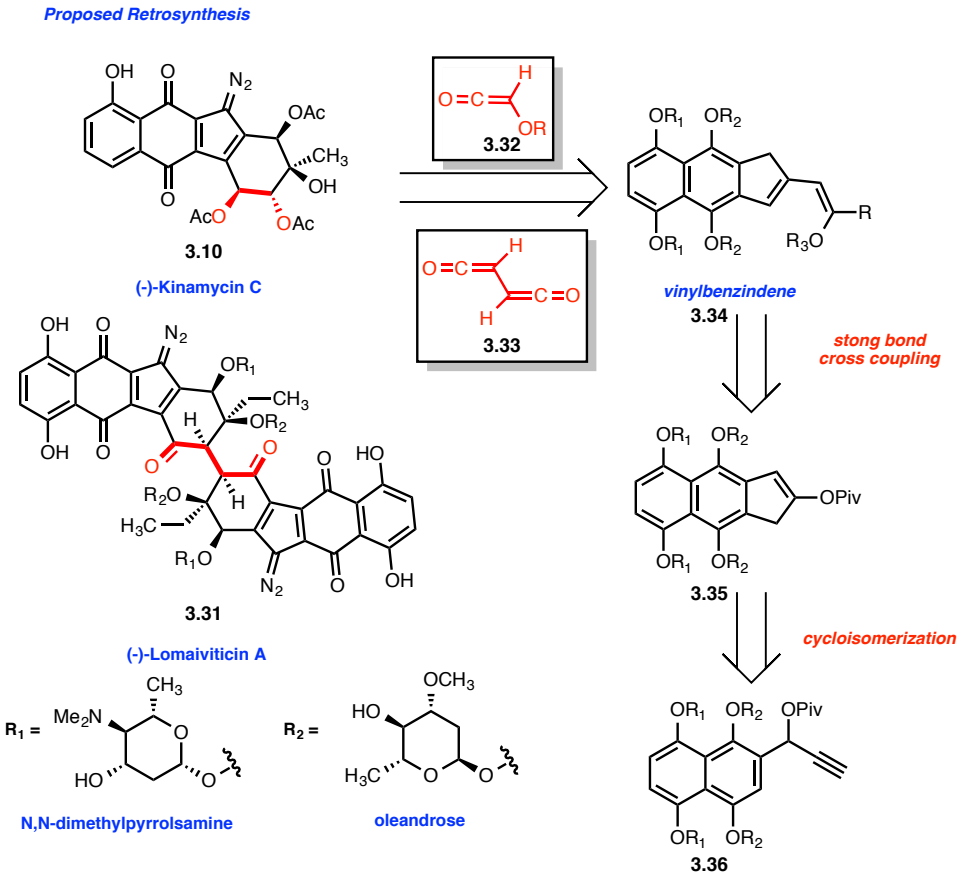
Figure 3: Methods for rationalizing the regioselectivity of the Diels–Alder cycloaddition reactions with 2-vinylendnes.

We also investigated chemical means for determining the regioselectivity for these reactions. Treating adduct **3.27e** with potassium hexamethyldisilazide (KHMDS), we effected an elimination of the chloride and observed the exclusive formation of **3.29** by

analysis of the crude ^{1}H NMR spectrum. We were unable to isolate this compound because it was prone to facile disproportionation reactions (Figure 3, B). We used the single vinyl signal in the ^{1}H NMR spectrum as a diagnostic signal for compound **3.29**. Provided the other regioisomer was formed, elimination of the chloride with NaHMDS would result in a dihydrofluorene with two characteristic vinyl signals by ^{1}H NMR. We turned to computational methods for identifying the HOMO of the 2-vinylindenes in these reactions. Using DFT calculations at the B3LYP+G** level of theory,[32] we found that 2-vinylindene is indeed polarized as predicted when modeled in the *s-cis* conformation (Figure 3, C).

Section 3.4. Extension to a double Diels—Alder cycloaddition reaction

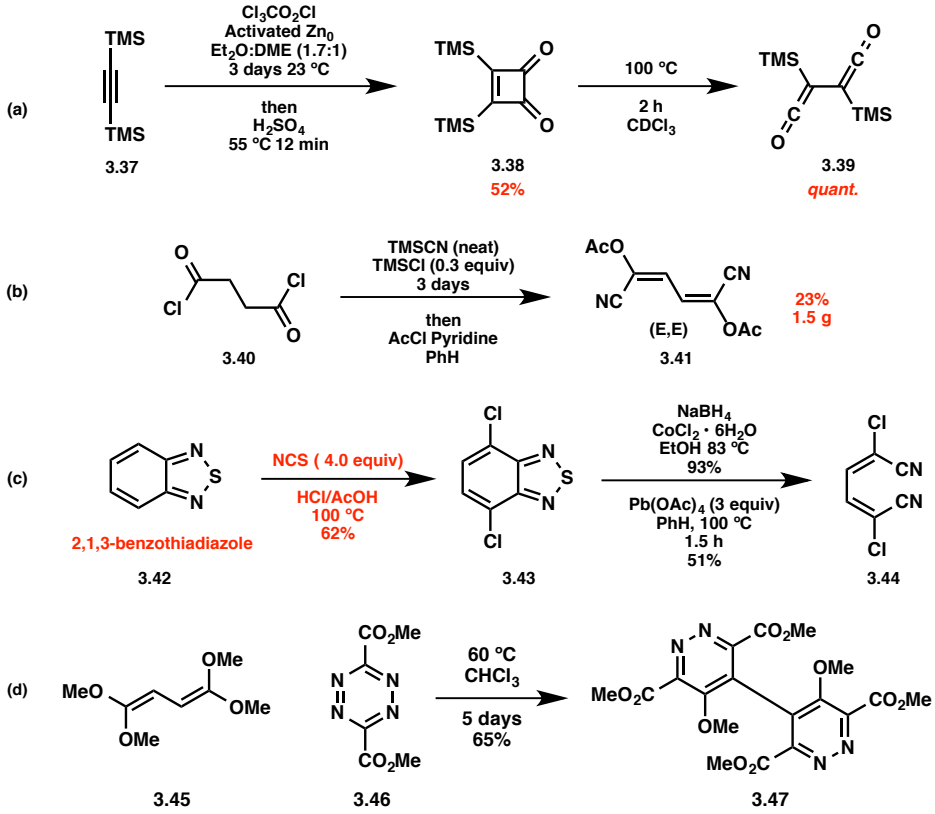
Having explored the scope of a mono Diels–Alder cycloaddition reaction, we were intrigued at the possibility of extending this to a double Diels–Alder cycloaddition reaction to establish a novel method for accessing lomaiviticin natural products **3.31** because of their interesting anticancer bioactivity.[9a] In general we envisioned a unified approach to these compound that rested on a formal double Diels–Alder cycloaddition reaction with a bisketene (**3.33**) or bisketene equivalent (Scheme 7).



Scheme 7: Proposed retrosynthetic analysis of (-)-Kinamycin C and (-)-Lomaiviticin A.

To date, there has only been one completed synthesis of the dimeric natural products by Herzon and coworkers[9a,33] and several approaches that have secured the core framework.[34]

Interestingly, there are a number of bisketene and bisketene equivalents known in the literature. Tidwell and coworkers have conducted extensive studies on persistent bisketenes (**3.39**), and found that these compounds can be accessed by an electrocyclic ring opening of substituted cyclobutenediones (Scheme 8, A).[35] Computational studies have shown that the ring opening of cyclobutenedione is approximately 6.9 kcal/mol uphill in energy, however the incorporation of silyl groups on the cyclobutenedione imparts both kinetic and thermodynamic stability to the bisketene allowing it to be persistent for up to 45 days in the absence of light and oxygen.[35] Bis(1-cyanovinylacetate)[36] and bis(chloroacrylonitrile)[37] are also known (Scheme 8, B and C), however they have not been used extensively in synthesis as bisketene equivalents. To our knowledge, there is only one example of a double Diels-Alder cycloaddition reaction using a bisketene equivalent (1,1,4,4-tetramethoxy-1,3-butadiene) by Boger and coworkers,[38] and this reaction operates under the inverse electron demand Diels–Alder reaction regime (Shceme 8, D). The Boger cycloaddition is furthermore unique in that the productive reaction is driven by the irreversible loss of N_2 gas.

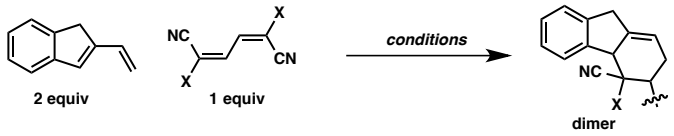


Scheme 8: Known methods to access bisketene and bisketene equivalents and their use in synthesis.

To this end, we synthesized compounds **3.39**, **3.41** and **3.44** to explore their double Diels–Alder reactivity. To access compound **3.44** we modified a previously reported literature procedure to chlorinate 2,1,3-benzothiadiazole by generating chlorine

gas *in situ* using the reaction of *N*-chlorosuccinamide with concentrated hydrochloric acid.[39] Unfortunately, under a wide variety of conditions (Table 2) we were unable to isolate any Diels–Alder cycloadducts. In general, vinylindene dimer **3.27** was isolated when the reaction was conducted thermally. When Lewis or protic acids were employed, decomposition of the vinylindene was observed when reacted with either diene **3.41** or **3.44**. Typically, diene **3.44** could be re-isolated quantitatively even after subjecting the reaction mixtures to high temperatures. Various transition metal-catalyzed procedures were also ineffective (e.g., Table 2, Entry 18 - 20).

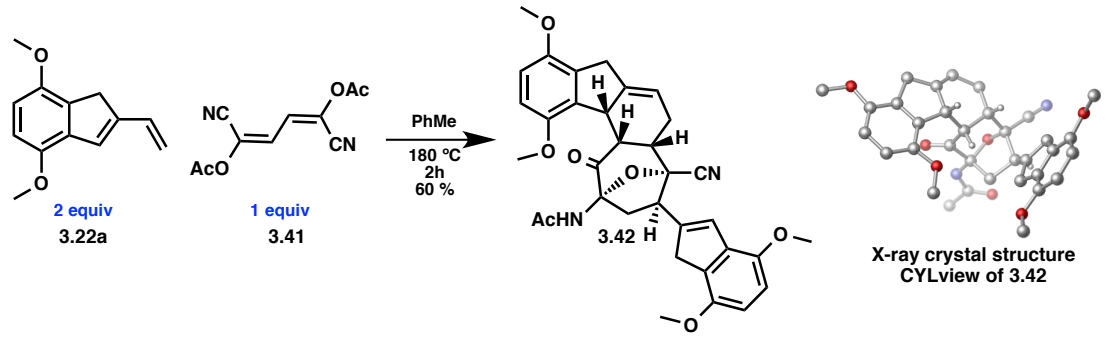
Table 2: Some conditions explored to achieve double Diels--Alder cycloaddition reaction with bisketene equivalents.



2 equiv 1 equiv dimer

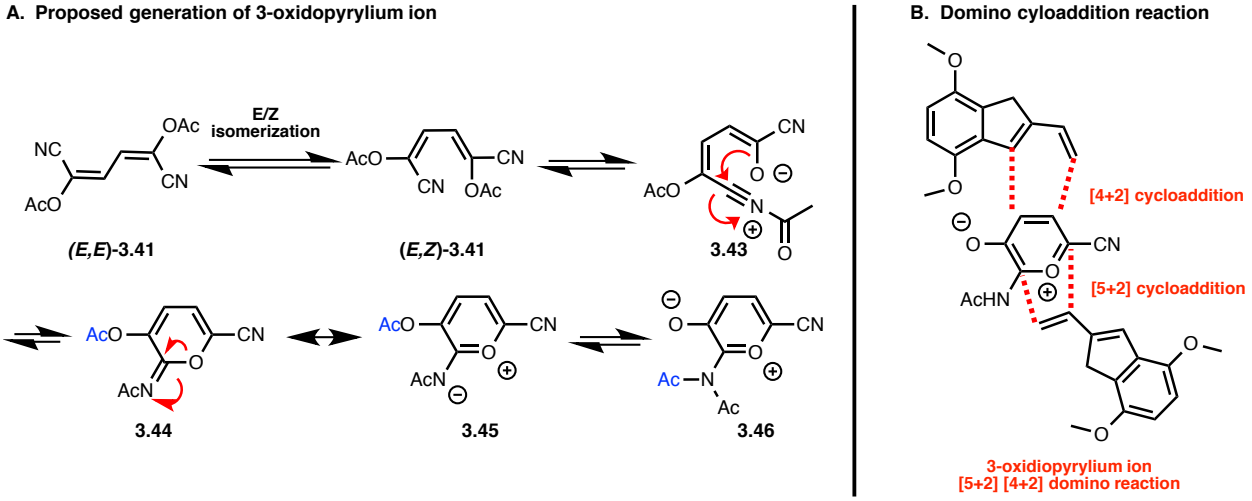
ENTRY	X	CONDITIONS	RESULT	PRECEDENT
1	Cl	BHT (0.10 equv), 180 ºC, PhMe, 2h	indene dimer	optimized conditions
2	Cl	$(MeCN)_4CuPF_6$, Tol 23º - 100 ºC	indene dimer	ref 40
3	Cl	$Cu(OTf)_2$ + hydroquinone, Tol	Diene consumed	ref 40
4	Cl	$Cu(OTf)_2$, Tol	Both consumed	ref 40
5	Cl	$(pBr\text{-}C_6H_4)_3N^{\bullet+}\ PF_6^-$ CH_2Cl_2 0 ºC	Both consumed	ref 41
6	Cl	$AlCl_3$, PhMe - 78 ºC - 23 ºC	Diene consumed	LA catalyzed DA
7	Cl	5M $LiClO_4$, Et_2O	Both consumed.	ref 42
8	Cl	Sonication 23 - 40ºC	NRXN	ref 43
9	Cl	$BF_3{\cdot}OEt_2$ -78 ºC - 45 ºC	Diene decomp	LA catalyzed DA
10	Cl	MPM cyclohexane CH_2Cl_2 1h	NRXN	ref 36
11	Cl	MPM + Acetophenone Cyclohexane CH_2Cl_2	BisCAN consumed some diene left mostly decomp	ref 36
12	OAc	PhMe 180 ªC 2 h	indne dimer	standard conditons
13	OAc	$Cu(OTf)_2$ PhH rt	diene conmsumed	ref 40
14	OAc	CuCl 80 ª THF	mostly SM	ref 40
15	OAc	H_2O	bisketene consumed	ref 44
16	OAc	7000 psi PhME	NRXN	ref 45
17	OAc	BHT PhMe 180 ªC 2h	indene dimer	optimized conditions
18	OAc	PhH Zeise's Dimer, rt	both consumed	ref 46
19	OAc	Gaffar-Parkins, rt	diene consumed	ref 46
20	OAc	$Pt(PEt_3)Cl$, rt - 100 ªC	NRXN then consumes bisketene	ref 46
21	OAc	$CDCl_3$ MPM	slow decompostion over time	ref 36
22	OAc	Acetone MPM	slow decompostion over time	ref 36
23	OAc	Acetone sunlight	slow decompostion over time	ref 36
24	OAc	$Ru(Bipy)_3(PF_6)_2$	both decomposed	ref 47
25	OAc	$LiClO_4$	sm consumed, no obvious product	ref 42
26	H	BHT 180 ºC PhMe 2 h	indene dimer	optimized conditions

Interestingly, when bis(1-cyanovinylacetate) **3.41** was reacted with diene **3.22** we isolated adduct **3.42** as the major product (Scheme 9), and this structure was confirmed by X-ray analysis. We hypothesize that compound **3.42** arises from an unprecedented 3-oxidopyrylium ion [5+2]-[4+2] domino cycloaddition reaction. Oxidopyrylium ion (**3.46**, Scheme 10) in turn arises from an intramolecular cyclization of bis(1-cyanovinylacetate) **3.41** at high temperatures. Attempts to extend this reaction to other dienes have not yet proved fruitful, however we envision that once optimized this methodology will provide a new way to rapidly access sp^3-rich polycyclic scaffolds.



Scheme 9: Newly discovered reactivity of biscyanovinyl acetate 3.41 to tive poly cycle 3.42 and CYL view of 3.42. Hydrogen atoms omitted for clairity.

We hypothesize that the oxidopyrylium ion **3.46** is generated from bis-cyanovinylacetate from the mechanism depicted in Scheme 10. First diene (***E,E*-3.41**) undergoes a *E*- to *Z*- double bond isomerization to give (***E,Z*-3.41**) followed by an intramolecular acyl transfer to give zwitterion **3.43**. Compound **3.43** then undergoes cyclization to give intermediate **3.44** followed by another acyl transfer to give oxidopyrylium ion **3.45**. We surmise that one of the acyl groups is lost during the course of the reaction.



Scheme 10: Mechanistic proposal for the generation of polycycle 3.41.

Considering these results, we proposed that changing the vinylindene to a more reactive diene could possibility facilitate a double Diels–Alder cycloaddition reaction. We envisioned two possibilities for increasing the reactivity of the diene (Figure 4). First, we considered a furan variant (**3.47**) of diene **3.22**. We hypothesized furan **3.47** would be a better dienophile than vinylindene 3.22 because the diene portion is locked in the *s-cis* conformation, which is a requisite for the cycloaddition to proceed. Furan **3.47** would also be more electron-rich, allowing for a smaller HOMO-LUMO gap with dienophiles **3.39**, **3.41**, and **3.44**. Furthermore, furan **3.47** is considerably more strained than diene **3.22** and Amos Smith III and coworkers have shown in their synthesis of (+)-jatropholones A and B that strained furans analogous to **3.47** readily undergo

cycloadditions under high pressures.[48] Finally, the furans would allow for functionalization of the 5-position which is critical for installing the alkyl group (ethyl group) present in the lomaiviticins, and would allow for rapid synthesis of analogues for structure activity relationship (SAR) studies. For these reasons, we set out to synthesize a compound such as **3.47**. Because allenes **3.51** arise from indenyne precursors, their synthesis will be discussed in Section 3.7.

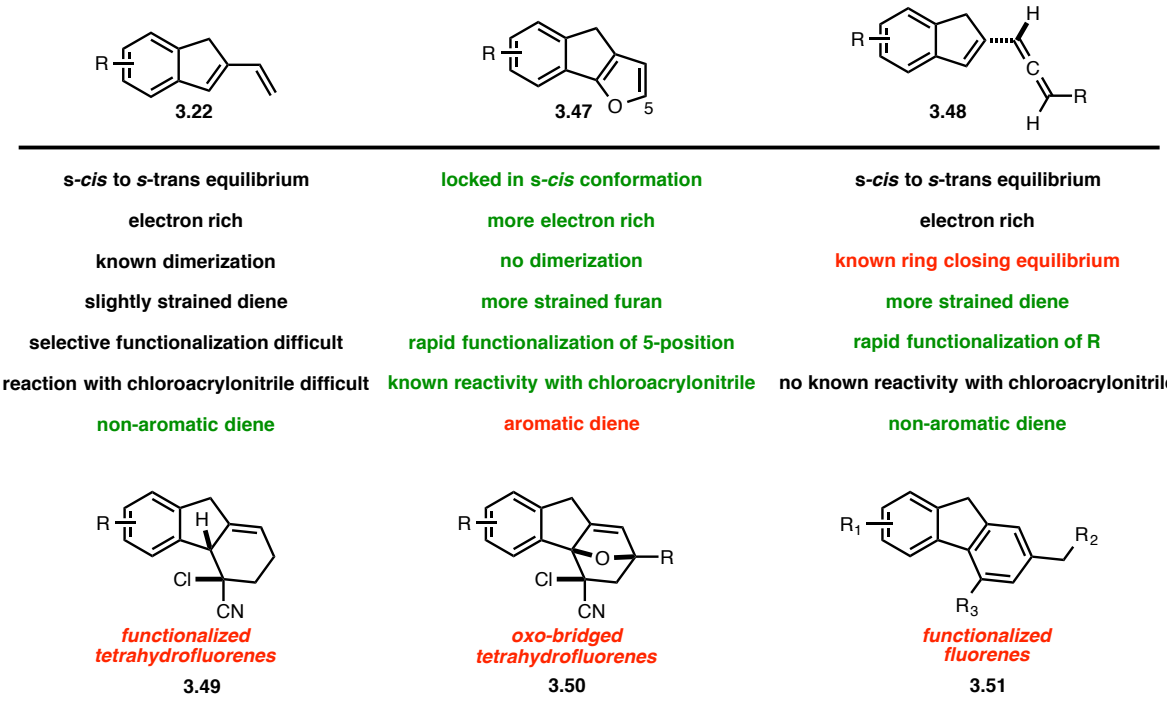


Figure 4: Comparison of other diene partners in Diels-Alder cycloaddition reaction.

Section 3.5. Attempted Synthesis of furans such as 3.47

To access furans such as **3.47** we envisioned a tandem cycloisomerization-dehydration reaction (Figure 5, A).[49] In this regard, accessing diols such as **3.52** through an acetylide addition into a 2-indanone would provide a modular way for installing alkyl and other substituents at the 5-position of the furan and thus into the lomaiviticin skeleton. We were furthermore encouraged by a recent report by Hong and coworkers who utilized this approach in the synthesis of (+/-)-cafestol (**3.58**), which contains an annulated furan moiety (Figure 5, B).[50] Of critical importance, in order for the cycloisomerization reaction to proceed on cyclic diols, the alcohol groups must be *anti*-disposed so that one alcohol can engage the alkyne (Figure 5, C). Therefore, the installation of the alkyne group needed to be stereoselective.

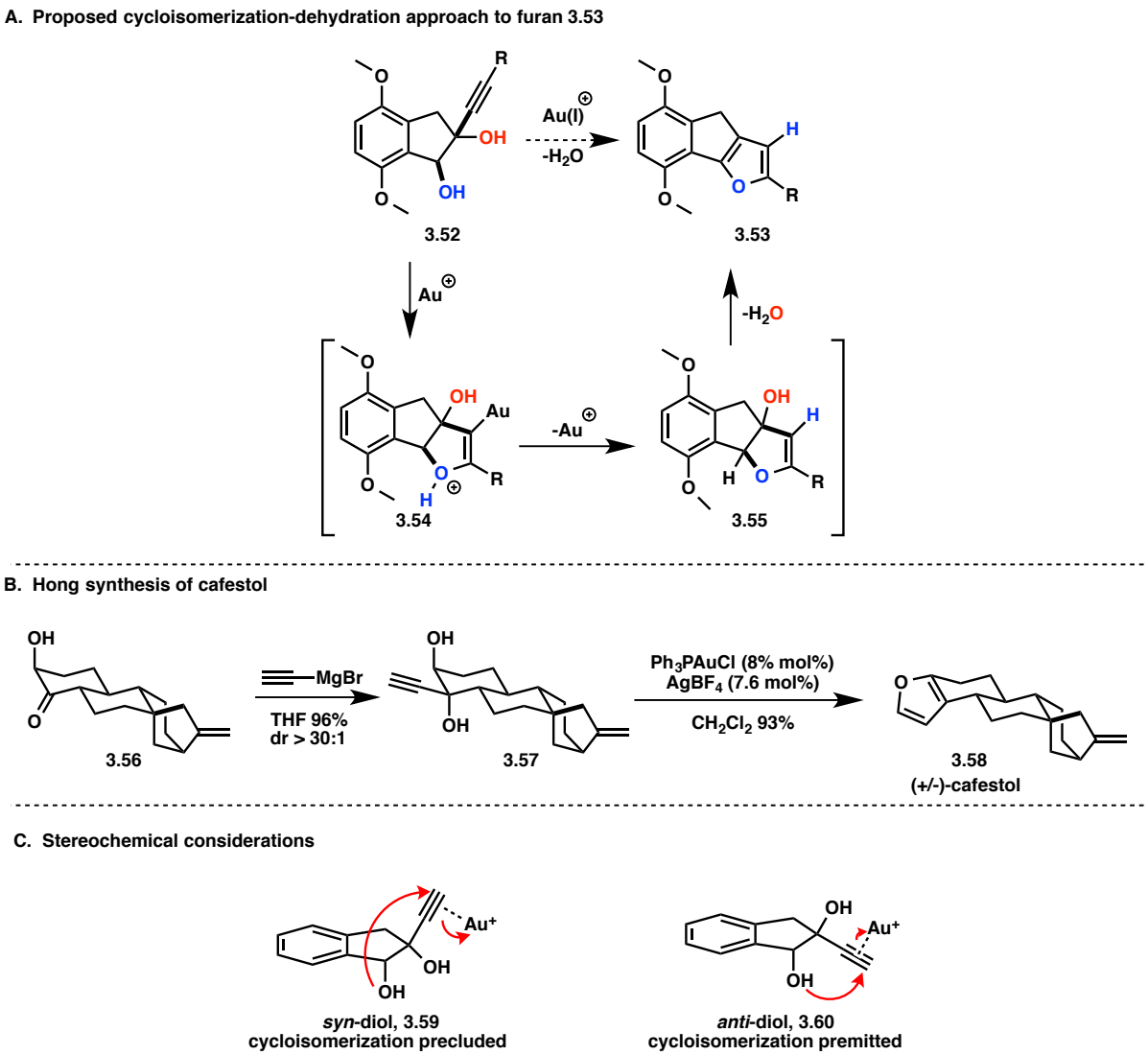
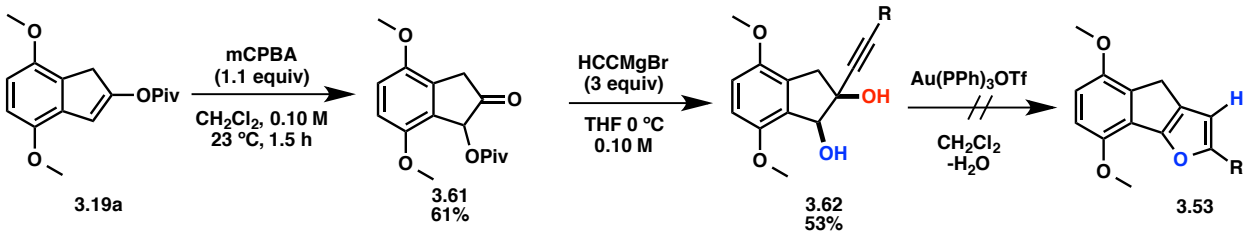


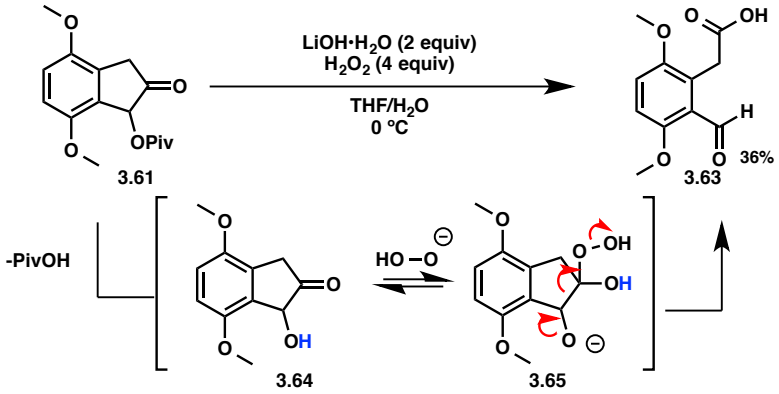
Figure 5: Theoretical considerations for accessing furan 3.53.

To this end we began our investigations into synthesizing furan **3.53** by performing a Rubottom oxidation[51] of indenylpivalate **3.19a** to access 2-indanone **3.61** in 61% yield. Treating this compound with excess ethynylmagnesium bromide effects a 1,2-addition into the carbonyl group with simultaneous removal of the pivaloyl group to give diol **3.62** in 53% yield with the formation of inseparable byproducts. Unfortunately, upon subjecting this diol to gold(I)-catalyzed cycloisomerization conditions, we observed no conversion to the desired furan even at elevated temperatures. We hypothesize that this is because the acetylide addition resulted in *anti*-addition relative to the pivaloyl group resulting in a *syn*-diol. Thus, we sought methods to remove the pivaloyl group so that we could perform a directed addition from the α-hydroxy-2-indanone.



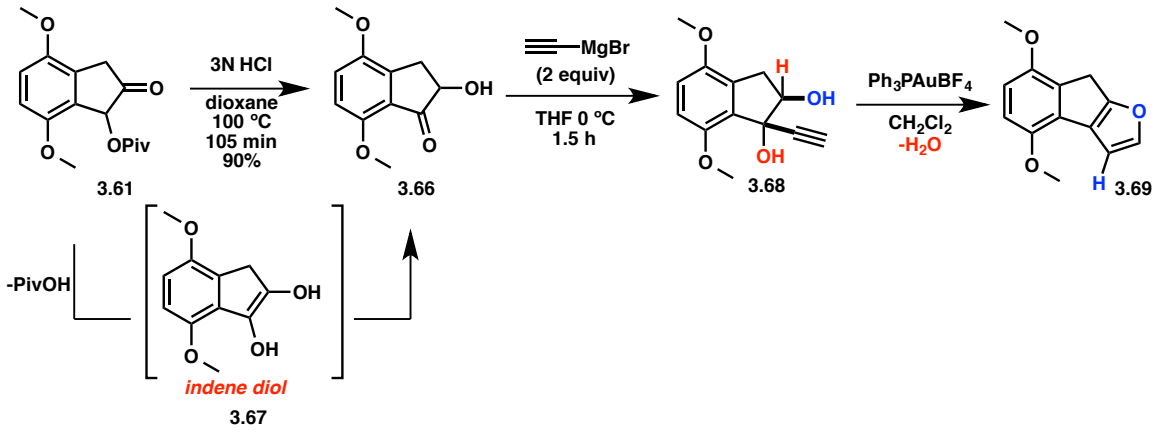
Scheme 11: Acetylide addition into 2-indanone 3.61 results in *syn*-diol.

Revealing the hydroxyl group in indanone **3.61** proved to be rather difficult. Under standard basic hydrolysis conditions (excess LiOH in THF/H_2O), we observed non-specific decomposition. Using lithium hydrogen peroxide,[52] which is considerably less basic than LiOH, we isolated carboxylic acid **3.63** in 36% yield. Presumably this compound arises from a fragmentation of intermediate **3.65**, or alternatively from the hydrolysis of an intermediate lactone.



Scheme 12: C-C bond cleavage reaction of 2-indanone 3.61.

Using acidic conditions to remove the pivaloyl group were also unsuccessful. Treating 2-indanone **3.61** with 3N HCl in dioxane and heating to 100 ºC for 3 hours resulted in the removal of the pivaloyl group with concomitant isomerization of the resulting 1-hydroxy-2-indanone to the more stable 2-hydroxy-1-indanone **3.66** (Scheme 13). Presumably this reaction takes place through the intermediate indene diol **3.67**.[53] Interestingly, we were able to add ethynyl magnesium bromide into indanone **3.66**, followed by treatment with cationic gold(I) to afford furan **3.69** in 5% unoptomized yield. This result suggests that compound **3.68** is an *anti*-diol, and the Grignard addition into ketone **3.66** is directed by the α-hydroxy group.

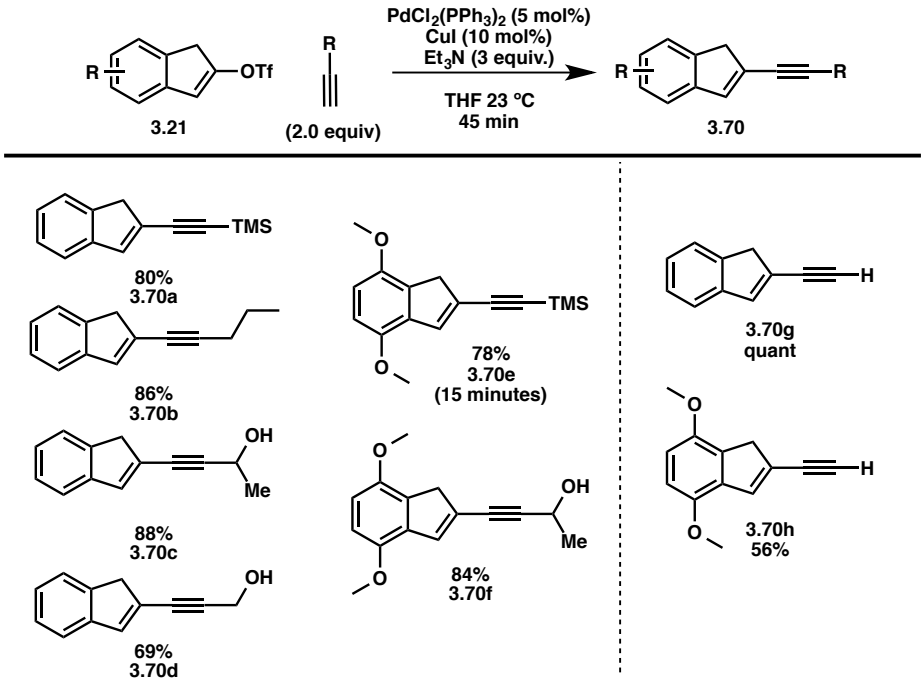


Scheme 13: Synthesis of isomeric furan 3.69.

Because of the lack of success in accessing the requisite diol precursors, we abandoned attempts to synthesize furan **3.53** and turned our attention to preparing indenynes using triflates **3.21a** and **3.21b** in order to access allenes such as **3.48** for cycloaddition studies.

Section 3.6. Synthesis of 2-alkynyl and 2-allenylindenes

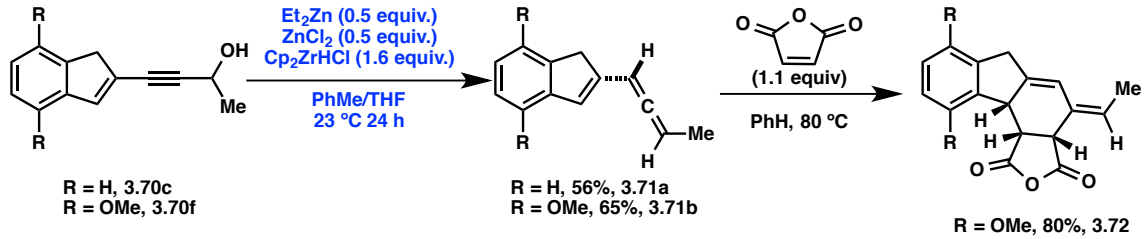
In line with our hypothesis of changing the vinylindene partner to increase its reactivity for the double Diels-Alder cycloaddition reaction, we set out to construct unprecedented 2-allenylindenes compounds. We started by exploring the scope of the Sonogashira cross-coupling of indenyl-2-triflates to afford 2-alkynylindenes (indenynes), which are precursors to 2-allenylindenes. As anticipated, we could effect a cross-coupling reaction using indenyltriflates **3.21a** or **3.21b**, and various alkynes to afford our desired indenynes (**3.70a** – **3.70h**) in good yields. For alkynes **3.70a** and **3.70e** the silyl group could be removed by stirring the compounds in MeOH with K_2CO_3 overnight.



Scheme 14: Sonogashira cross coupling to of indenyl triflates to access indenynes.

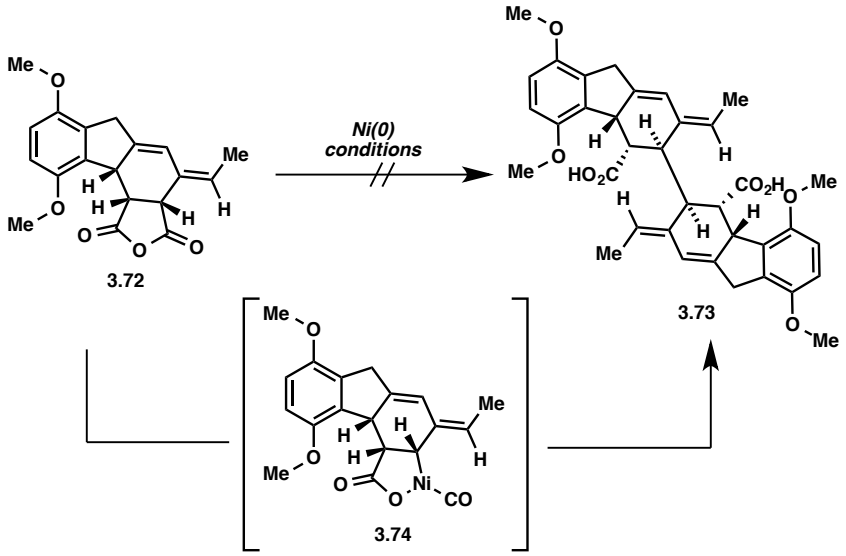
Indenynes **3.70c**, **3.70d** and **3.70f**, could all be converted to their requisite allenes using chemistry developed by Ready and coworkers.[54a] Standard procedures for synthesizing allenes from propargylic esters developed by Myers[54b] and coworkers were ineffective and gave low isolated yields (Scheme 15). Surprisingly, allene **3.71a** was isolated as a white solid and remained unchanged by ^{1}H NMR upon prolonged storage at –20 °C under nitrogen. The terminal allene derived from propargylic alcohol **3.70d** was isolated as an inseparable mixture of products and will not be discussed, as it was not advanced.

Before investigating conditions to effect a double Diels–Alder cycloaddition, we were interested in the mono Diels–Alder cycloaddition reactivity of these substrates. Reacting allenes **3.71a** and **3.71b** with ynoate dienophiles initially proved promising, however the isolation of the resulting fluorene products was hampered by the presence of unidentifiable side products. Furthermore, these reactions tended to be irreproducible. Maleic anhydride, however, did serve as a competent dienophile and Diels-Alder adduct **3.72** derived from dimethoxyallenylindene **3.71b** was isolated consistently in 80% yield.



Scheme 15: Synthesis of 2-allenylindenes and their Diels-Alder reactivity with maleic anhydride.

We envisioned that this compound could provide a route to the dimeric core of the lomaiviticins through a dimerization of the anhydride intermediates. Based on precedent by Rovis, Wiex and Semmelhack, we hypothesized that we could use stoichiomertic Ni(0) complexes to affect an oxidative addition into the anhydride C–O bond and in the absence of a suitable cross coupling partner, promote an unprecedented dimerization of anhydride **3.72** through nickel carbonyl intermediate **3.74**.[55] Unfortunately, this route was not successful.



Scheme 16: Proposed Ni(0)-mediated dimerization of anhydride 3.72.

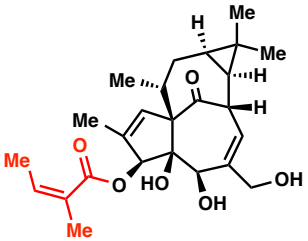
Attempts to react allenes **3.71a** and **3.71b** with bisketenes **3.39**, **3.41**, and **3.44** typically resulted in no reaction at lower temperatures and decomposition of the allene component at elevated temperatures. Also, several metal-catalyzed transformations of allenes that give formal [4+2] adducts with vinylidenes and ketenes were also explored but were not fruitful.

At this point, because we were unable to access furan **3.53** or effect any type of useful Diels-Alder cycloaddition with allenes **3.71a** and **3.71b**, we stopped pursuing the synthesis the lomaiviticin molecules.

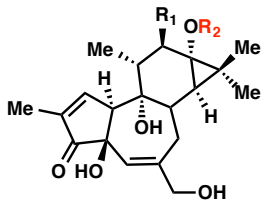
Section 3.7. A new target, euphorbactin

Seeking other applications of the indenynes, we became interested in the synthesis of euphorbactin (**3.77**) because it contains an indene core with an annulated seven-membered ring instead of a six-membered ring. Euphorbactin[56] is a novel diterpenoid that was isolated in 2014 by Shi and coworkers from the roots of *Euphorbia micractina*, and has activity against HIV-1 replication with an IC_{50} of 28.6 μM. Species of the genus *Euphoriba* (Euphorbiaceae)[57] are well known for their biological activity and have been used in traditional folk medicines for some time. Ingenol mebutate (**3.74**) is isolated from the sap of *E. peplus,* and is perhaps one of the most well known compounds of this family[58], and has recently been approved as a topical treatment in the United States, countries in the European Union, Australia, and Brazil for the

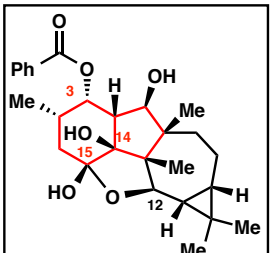
treatment of actinic keratosis.[59] The compound prostratin (**3.76**) is particularly interesting because of its ability to both block HIV-1 entry and induce HIV expression in latently infected HIV cell lines.[60] Thus, studying compounds isolated from this genus of plant holds high promise for developing unique HIV-1 treatments that operate by fundamentally different mechanisms than current Highly Active Antiretroviral Therapy (HAART) treatments. A synthesis of euphorbactin would set the stage for researchers to study the effects of acylation on the biological activity of this molecule, as the acylation pattern of compound **3.74** – **3.76** have been shown to beneficially modulate their biological activity.



ingenol mebutate, 3.74
actinic keratosis
acylation modulates activity

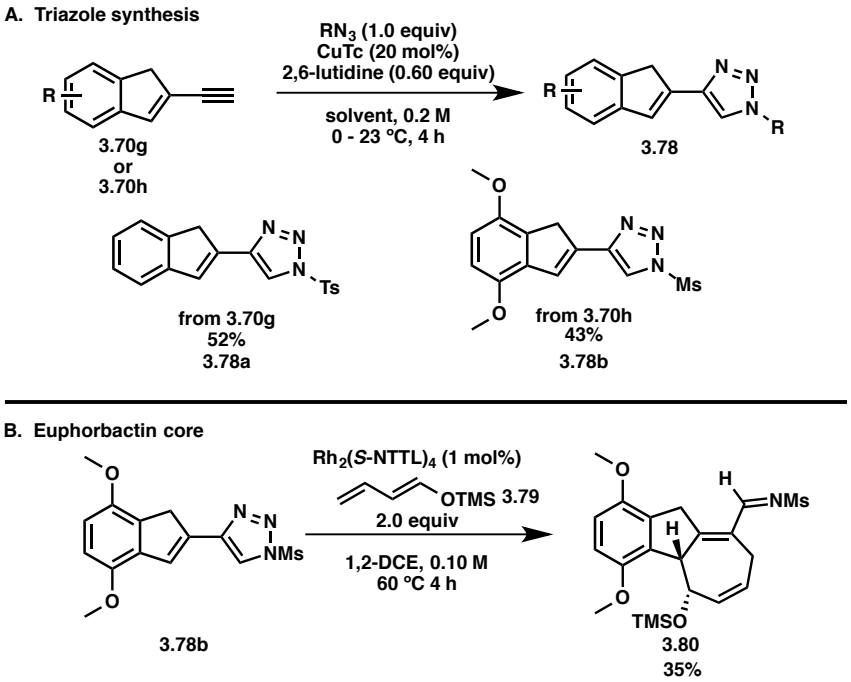


R_1 = OH, R_2 = H phorbol, 3.75
R_1 = H, R_2 = Ac, prostratin, 3.76
activates latent cells
infected with HIV
acylation modulates activity



euphorbactin, 3.77
IC_{50} 23.6 μM
anti-HIV replication
affects of acylation
not known

To this end, we were able to take enynes **3.70g** and **3.70h** and react them with TsN_3 or MsN_3 to affect an Huisgen cycloaddition reaction to obtain triazoles **3.78a** and **3.78b** in 52% and 43% yields, respectively. From these substrates, cycloadditions developed by Davies and coworkers to annulate the seven-membered ring were investigated.[61] Tosyltriazole **3.78a** was a poor substrate for the planned cycloaddition reaction. However using mesyl triazole **3.78b** resulted in the formation of the desired product **3.80** in an unoptimized 35% yield when reacted with diene **3.79**. This initial productive outcome now sets the stage for further elaboration to the natural product and synthesis of derivatives.



Scheme 17: Synthesis of indenyltriazoles and the euphorbactin carbocyclic 6,5,7-framework.

Section 3.8. Conclusion

This chapter describes a novel strategy for obtaining functionalized tetrahydrofluorene scaffolds using 2-vinylindene precursors. Specifically, we utilized a Pt(II)-catalyzed cycloisomerization as a strategy to obtain functionalized indenyl-2-pivalates. These indene compounds were then converted to 2-vinylindenes in good yields over three steps. The 2-vinylindenes participate in normal electron demand Diels-Alder cycloaddition reactions with various dienophiles. DFT calculations were used to help rationalize and understand the regioselectivity for these reactions.

We also investigated a double, normal electron-demand Diels–Alder cycloaddition to access the dimeric lomaiviticin molecules. Under a wide variety of conditions, we were unable to realize the desired reactivity. However, we discovered that diene **3.41** could be used to access 3-oxidopyrylium ions at high temperatures, which in turn undergoes a tandem [5+2], [4+2] double cycloaddition.

To overcome the aforementioned challenges, two strategies using functionalized dienes were explored. In the first strategy, we attempted to synthesize a 2-vinylindene that was embedded within a furan. Unfortunately, the correct constitutional isomer needed to test the double Diels–Alder reaction does not form due to the tendency for 2-indanone **3.67** to undergo an isomerization to the more thermodynamically stable 1-indanone. In a second strategy, we investigated the reactivity of 2-alkynyl and 2-allenyl indenes, however these partners also proved ineffective as dienophiles.

Finally, we demonstrated that terminal indenynes can be converted to their corresponding triazoles and that these compounds will undergo a rhodium-catalyzed [4+3] cycloaddition to give indenes annulated with seven-membered rings. When performed on dimethoxyindene compound **3.78b**, compound **3.80** is generated, which

provides a starting point for accessing the newly isolated anti-HIV compound euphorbactin **3.77**.

Section 3.9. Supporting Information

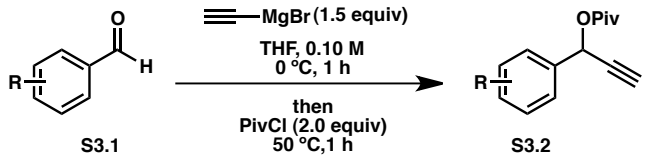
Section 3.9.1. General Procedures

All reactions were run in flame-dried round-bottom flasks or vials under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Silicycle Siliaplate™ glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV irradiation and *para*-anisaldehyde or $KMnO_4$ stain. Dry tetrahydrofuran, triethylamine, and methanol were obtained by passing these previously degassed solvents through activated alumina columns. Dichloromethane was distilled over calcium hydride before use. Volatile solvents were removed under reduced pressure on a rotary evaporator. All flash chromatography was done using Sorbent Technologies 60 Å, 230x400 mesh silica gel (40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were taken with Bruker AV-300, AVB-400, AVQ-400, AV-500, and AV-600 MHz (75, 100, 125, and 150 MHz for ^{13}C NMR) spectrometers in $CDCl_3$ or C_6D_6 as noted. Chemical shifts were measured relative to the shift of the residual solvent (^{1}H NMR, $CDCl_3$ δ = 7.26, C_6D_6 δ = 7.16 ppm; ^{13}C NMR $CDCl_3$ δ = 77.00, C_6D_6 δ = 128.06 ppm). NMR data are reported as follows: chemical shift (multiplicity, coupling constant, integration). Splitting is reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, a = apparent, b = broad. IR spectra were taken on a Bruker ALPHA FT-IR spectrometer. Spectra are reported in frequency of absorption in cm^{-1}. Only selected resonances are reported. High-resolution mass spectra (HRMS) were performed by the mass spectral facility at the University of California, Berkeley. Microwave-assisted reactions were performed using a Biotage Initiator 2.5 reactor on low absorbance irradiation setting with the fix-hold-time feature set to off.

2-vinylindene,[21] bis(1-cyanovinylacetate),[36] and bis(chloroacrylonitrile),[37] were synthesized according to literature procedures.

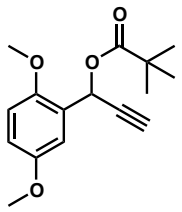
Section 3.9.2 General synthetic procedures

General Propargylic Ester Synthesis



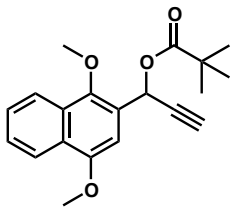
To a flame dried round bottom flask fitted with a rubber septum was added solid aldehyde **S3.1** (5.00 g, 30.0 mmol). The flask was then evacuated and backfilled with nitrogen gas (x 3). THF (300 mL) was then added, and the homogenous solution was

then cooled to 0 ºC using an ice brine bath. Ethynylmagnesium bromide (0.5 M in THF) (66.3 mL, 33.2) was added dropwise over 5 minutes, and the solution was then stirred at 0 ºC for 1 h upon which pivalolyl chloride (7.25 g, 60.1 mmol, 7.4 mL) was added. The solution was then heated to 50 ºC with stirring for 1 h. The solution was then cooled to room temperature (~ 23 ºC) and diluted with ether (600 mL). The solution was then quenched with saturated aqueous $NaHCO_3$ (300 mL). The biphasic mixture was then shaken and the aqueous layer separated. The aqueous layer was then extracted with ether (300 mL x 3). The combined organic layers were then washed with brine (300 mL x3), dried over Na_2SO_4 concentrated and purified by column chromatography to afford the desired propargylic esters.



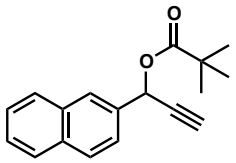
S3.2a

column chromatography (20% diethyl ether in hexanes) to give a yellow oil. **Yield** 99%. **^{1}H NMR $CDCl_3$** (600 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.86 (apparent d, *J* = 8.9 Hz, 1H), 6.82 (apparent d, *J* = 8.9 Hz, 1H), 6.70 (s, 1H), 3.78 – 3.81 (m, 6H), 2.56 (s, 1H), 1.22 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.1, 153.7, 151.0, 126.2, 114.8, 114.4, 112.1, 80.6, 74.5, 60.3, 56.3, 56.0, 38.9, 27.2; **IR (**ATIR**)** 3284, 2971, 2936, 2909, 2874, 2836, 1732; cm^{-1}. **HRMS(ESI)** cald for $C_{16}H_{20}O_4Na$ $(M+Na)^+$ m/z 299.1254, found 299.1253.



S3.2b

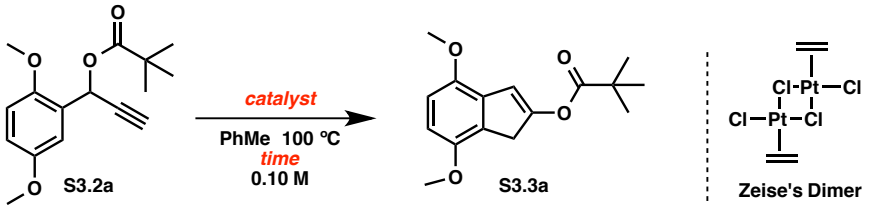
Recrystalized from cold (-20 ºC) solution of hexanes and CH_2Cl_2 overnight. The filtrate was then concentrated and purified by **column chromatography** (9:1 hexanes:diethyl) ether to give a brown crystalline solid. **Yield** 93%; **MP** = 100 – 102 ºC; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.25(d, *J* = 8.2 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 8.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.01 – 6.93 (m, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 2.61 (s, 1H), 1.25 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 177.0,. 152.6, 147.2, 128.5, 127.2, 127.1, 126.4, 125.2, 122.7, 122.6, 102.1, 81.3, 74.8, 63.2, 60.4, 55.9, 39.0, 27.2 cm^{-1}; **IR (**ATIR**)** 3263, 2963, 2938, 2870, 2847, 3123, 1730, 1594, 1366 cm^{-1}; **HRMS(EI)** calcd for $C_{20}H_{22}O_4$ $(M)^{\bullet+}$ m/z 326.1518, found 326.1524.



S3.2c

column chromatography 10:1 hexanes:ethyl acetate to give a white amorphous solid. **Yield** 79%; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.89 – 7.82 (m, 2H), 7.59 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.59 (dt, *J* – 6.2, 3.4 Hz, 2H), 6.59 (d, *J* = 2.2 Hz, 1H), 2.68 (d, *J* = 2.3 Hz, 1H), 1.23 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.4, 134.2, 133.6, 133.2, 128.8, 128.5, 127.9, 127.0, 126.3, 126.6, 124.9, 80.6, 75.6, 65.4, 39.0, 27.2; **IR** (ATIR) 3273, 3061, 2972, 2933, 2907, 2871, 2124, 1729, 1125 cm^{-1}; **HRMS** (EI) calcd for $C_{18}H_{18}O_2$ $(M)^{\bullet+}$ m/z 266.1307 found 266.1309.

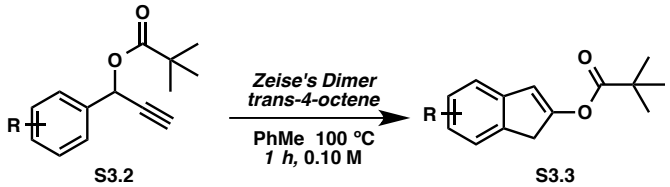
Cycloisomerization optimization table



Entry	Catalyst	Catalyst Loading (mol%)	Additive (40 mol%)	Time (h)	Yield (%)
1	$PtCl_2$	10	none	6	36
2	$PtCl_2$	10	trans-4-octene	2.2	47
3	$PtCl_2$	10	norbornene	2.2	47
4	$PtCl_2$	10	K_2CO_3	6	38
5	$PtCl_2$	10	trans-4-octene	1	58
6 [a]	$PtCl_2$	10	trans-4-octene	1	0
7	$PtCl_2$	10	trans-4-octene and CsOPiv	1	0
8 [b]	Zeise's Dimer	5	trans-4-octene	1	75
9 [c]	Zeise's Dimer	5	trans-4-octene	1	74
10	Zeise's Dimer	5	trans-4-octene	1	68

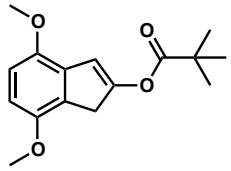
a **conducted in MeCN,** ***b*** **conducted in PhH,** ***c*** **conducted in cyclohexane with Z.D. from Acros**
Note: 8 and 9 Zeise's Dimer from Strem

General procedure for 2-indenyl pivalate synthesis



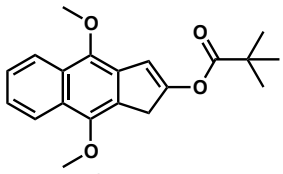
To a flame dried Schlenk flask was added properglic ester **S3.2** (2.76 g, 1.00 mmol). The flask was then brought into a glove box and di-μ-chloro-dichlorobis(ethylene)-diplatinum(II) (Zeise's Dimer) (294 mg, 0.500 mmol) was added. The flask was then brought outside of the glove box and toluene (100 mL) was then added followed by *trans*-4-octene (448 mg, 627 μL, 4.00 mmol) under nitrogen. The flask was then sealed and heated to 100 °C for exactly 1 h. The flask was then immediately cooled in a room

temperature water bath. The solution was then concentrated under reduced pressure and the residue purified by column chromatography to give the desired indene. Note: toluene can be substituted with benzene in this reaction without a significant decrease in reaction yields for **S3.3a.**



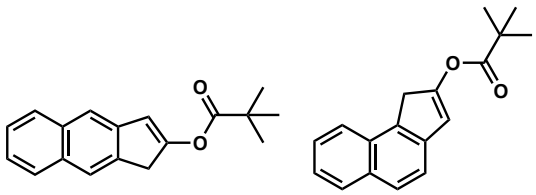
S3.3a

column chromatography (7:1 hexanes:ethyl acetate) to give a yellow oil/low melting amorphous yellow solid. **Yield** 99%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.8 Hz, 1H), 6.67 (s, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.53 (s, 2H), 1.31 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 155.4, 149.8, 148.1, 133.1, 125.9, 111.4, 110.4, 107.6, 56.5, 55.9, 39.5, 36.0, 27.3; **IR (**ATIR**)** 2976, 2941, 2908, 2973, 2835, 1741, 1495 cm^{-1} **HRMS(EI)** calcd for $C_{16}H_{20}O_4$ $(M)^{\bullet+}$ m/z 276.1362 found 276.1366



S3.3b

column chromatography (9:1 hexanes:diethyl ether) to give amorphous orange solid. **Yield** 93%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.21 – 8.04 (m, 2H), 7.47 (dddd, *J* = 22.8, 8.1, 6.8, 1.4 Hz*,* 2H), 6.89 (t, *J* = 1.6 Hz, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.81 (d, *J* =1.5 Hz*,* 1H*),* 1.36 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.0, 155.5, 147.2, 144.7, 128.9, 127.2, 125.7, 124.9, 124.1, 122.3, 122.0, 111.7, 62.4, 60.6, 39.6, 35.7, 27.3; **IR** (ATIR) 3069, 2973, 2934, 1751, 1584, 1352 cm^{-1}; **HRMS** (EI) calcd for $C_{20}H_{22}O_4$ $(M)^{\bullet+}$ m/z 326.1518 found 326.1517.

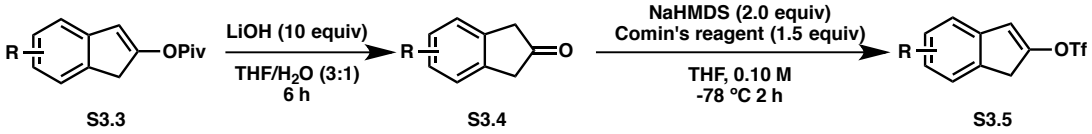


S3.3c-1 **S3.3c-2**

column chromatography (20% CH_2Cl_2 in hexanes to 40% CH_2Cl_2 in hexanes) to give colorless oil. **Yield** 78%; (2.5:1 ratio of isomers using optimized conditions, 4.5:1 ratio of isomers using conditions 5 in Table 1) mixuture of isomers reported. **^{1}H NMR** (600 MHz,

$CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2.5 H), 7.90 (d, *J* = 7.9 Hz, 2.5 H), 7.88 – 7.75 (m, 2.5H), 7.69 (d, *J* = 8.1 Hz, 3H), 7.58 – 7.34 (m, 10H), 7.24 (s, 2.5 H), 6.74 (s, 1H), 3.91 (s, 2H), 3.76 (s, 5H), 1.41(m, 32H); **^{13}C NMR** (150 MHz, $CDCl_3$**)** δ 176.0, 156.7, 156.1, 140.6, 139.4, 134.0, 132.8, 131.5, 129.8, 129.1, 128.6, 127.9, 127.5, 126.4, 125.6, 125.1, 124.5, 124.3, 123.9, 123.0, 122.1, 120.6, 115.1, 112.4, 39.5 (39.5 shoulder) 39.1, 37.1, 27.3; **IR** (ATIR) 3053, 2972, 2933, 2906, 2872, 1745, 1097 cm^{-1}; **HRMS** (EI) cacld for $C_{18}H_{18}O_2$ $(M)^{\bullet+}$ m/z 366.1307 found 366.1310.

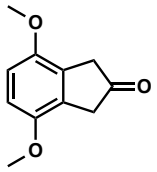
General indenyl-2-triflate Synthesis



S3.3 S3.4 S3.5

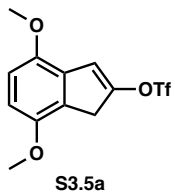
INDANONE SYNTHESIS

To round bottom flask was added 2-indenylpivalate **S3.3** (600 mg, 2.17 mmol) and lithium hydroxide monohydrate (991 mg, 21.7 mmol). The flask was evacuated and backfilled with nitrogen (x3). THF then water (7.5 mL and 2.5 mL respectively) were added and the solution was stirred at room temperature for 6 hours. The solution was then diluted with diethyl ether (30 mL) and washed with brine (30 mL, x3). The organic layer was then dried with sodium sulfate and concentrated to give the crude 2-inandone which was used without further purification.



S3.4a

An analytical sample was obtained by purifying the solids using **column chromatography** (5:1 hexanes:ethylaceate) to give amorphous tan solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.72 (s, 2H), 6.19 (s, 6H), 3.46 (s, 4H). **^{13}C NMR** (150 MHz, $CDCl_3$) 215.4, 150.2, 127.5, 109.3, 55.8, 41.8; **IR** (ATIR) 2961, 2913, 2837, 1737, 1498, 1261 cm^{-1}; **HRMS** (EI) calcd for $C_{11}H_{12}O_3$ $(M)^{\bullet+}$ m/z 192.0786 found 192.0786.

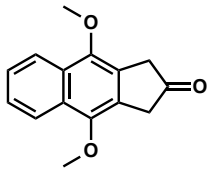


S3.5a

TRIFLATE SYNTHESIS[27]

The crude 2-indanone (19.2 mg, 0.10 mmol) was added to a flame dried round bottom. The flask was then evacuated and backfilled with N_2 (x 3). THF (1.0 mL) was then added and the solution was cooled to -78 ºC. To the cooled solution was added NaHMDS (0.10 mL, 2M in THF) dropwise over one minute and the solution was allowed to stir at -78 ºC for one hour. Solid Comin's reagent (157 mg, 0.40 mmol) was then added all at once at -78 ºC by quickly removing and replacing the fitted septa. The homogenous solution was then allowed to stir two hours at -78 ºC. The solution was then diluted with ether (5 mL), and deionized water (1 mL) was added at -78 ºC). The solution was then warmed to room temperature added to a separatory funnel and shaken. The aqueous layer was then removed and the organic layer was washed with 1 N NaOH (2 mL x2). The organic layers were then dried over sodium sulfate, filtered concentrated and the crude oil purified by column chromatography to give the desired indenyl-2-triflate.

column chromatography (5:1 hexanes:toluene to 2:1 hexanes:toluene) to give a colorless oil. **Yield** 90% (over two steps) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 4H), 3.83 (s, 4H), 3.62 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 152.1, 149.5, 148.5, 130.1, 126.0, 118.9 (q, $J_{C\text{-}F}$ 321.2 Hz), 116.6, 110.4, 109.3, 56.2, 55.8, 36.1; **IR** (ATIR) 3004.5, 2946, 2910, 2838, 1498, 1423, 1204 cm^{-1}; **HRMS** (EI) calcd for $C_{12}H_{11}O_5F_3S$ (M) $^{\bullet+}$ m/z 324.0279 found 324.0285.

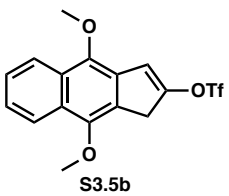


S3.4b

The general procedure for the indenyl-2-triflate was followed for the benzannulated derivative using a two-hour stir time for the indanone formation step.

INDANONE

column chromatography (5:1 hexanes:ethyl acetate to 2:1 hexanes:ethyl acetate) to give an amorphous yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.12 (apparent s, 2H), 7.52 (apparent s, 2H), 3.94 (s, 6H), 3.74 (s, 4H).; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.9, 148.2, 128.6, 126.1, 125.9, 122.2, 60.9, 41.6; **IR** (ATIR) 3072, 2936, 2901, 2838, 1745, 1356 cm^{-1}. **HRMS(EI)** calcd for $C_{15}H_{24}O_3$ (M) $^{\bullet+}$ m/z 242.0943 found 242.0942.

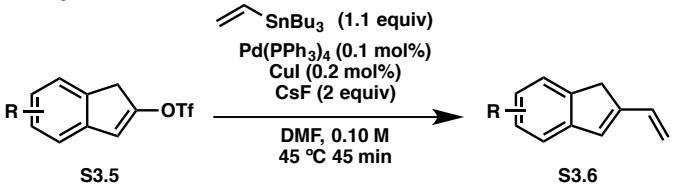


S3.5b

The purified 2-indanone was used for the triflation step. Using the crude 2-indanone results in poor yields. **Column chromatography** (2:1 hexanes:toluene); **Yield** 31% (over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 – 7.83 (m, 2H), 7.70 – 7.33 (m, 2H),

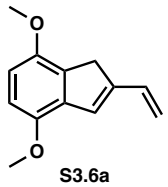
6.95 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.88 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.4, 147.4, 146.2, 128.7, 128.6, 128.0, 126.3, 126.0, 123.1 118.8 (q $^1J_{CF}$ = 312 Hz) 122.6,120.6, 117.5, 115.0) 122.4, 122.3, 116.6, 62.9, 60.7, 35.4; I**R** (ATIR) 3070,2993, 2936, 2843, 1598, 1425, 1355, 1212, 1138 cm^{-1}; **HRMS** (ESI) calcd for $C_{16}H_{12}O_5F_3{}^{32}S$ $(M+H)^+$ 373.0363 found 373.0359.

General 2-Vinylindene Synthesis



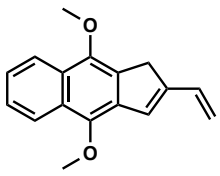
S3.5 S3.6

To a flame dried round bottom flask inside a glove box was added $Pd(PPh_3)_4$ (105 mg, 0.091 mmol), CuI (35.0 mg, 0.181 mmol), and CsF (275 mg, 1.81 mmol). The flask was then brought outside of the glove box and dimethylformamide (9.1 mL) was then added. The indenyl-2-triflate (294 mg, 0.906 mmol) and tri-*n*-butylvinylstanane (0.291 mL, 0.997 mmol) were added as a solution in dimethylformamide all at once, and the solution was headed to 45 ºC for 45 minutes. The solution was then filtered over a pad of Celite® washing with ether. The heterogeneous solution was then diluted with water (90 mL) and extracted with ether (20 mL x3). The organic layers were then combined, dried over sodium sulfate, concentrated and purified by column chromatography.



S3.6a

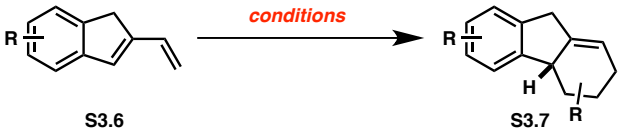
column chromatography (3:1 hexanes:toluene to 2:1 hexanes:toluene) to give an morphous white solid. **Yield:** 51% **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.76 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.44 (d, *J* = 17.5 Hz, 1H), 5.16 (d, *J* = 10.7 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.53 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 150.0, 148.1, 145.7, 135.3, 133.2, 131.3, 127.2, 114.4, 109.8, 108.4, 56.2, 55.8, 35.2; **IR** (ATIR) 3085, 3047, 2997, 2939, 2903, 2831, 1796, 1618, 1491, 1251 cm^{-1}; **HRMS** (EI) calcd for $C_{13}H_{14}O_2$ $(M)^{\bullet+}$ m/z 202.0994 found 202.0998.



S3.6b

column chromatography (2:1 hexanes:toluene to 1:1 hexanes:toluene) to give an amorphous white solid. **Yield** 55%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.18 -8.10 (m, 2H), 7.53 – 7.44 (m, 2H), 7.00 (s, 1H), 6.83 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.51 (d, *J* = 17.4 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.76 (s, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 146.9, 146.0, 144.8, 133.9, 132.9, 128.7, 128.6, 126.7, 127.3, 125.4, 125.1, 122.1, 122.0, 115.9, 62.4, 60.4, 34.4; **IR** (ATIR) 3066, 3002, 2961, 2936, 2902, 2840, 1606, 1454, 1352 cm^{-1}; **HRMS** (EI) calcd for $C_{17}H_{16}O_2$ (M) $^{\bullet+}$ m/z 252.1150 found 252.1154

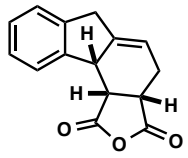
General Tetrahydroflourene Synthesis



S3.6 S3.7

Room temperature Diels-Alder (for compounds **S3.7a** and **S3.7b**)
To a flame dried 20 mL dram was added solid vinyl indene (50 mg, 1 equiv) in benzene (M = 0.10M) under N_2. The solid dienophile (1.1 equiv) was then added and the reaction stirred until complete by TLC (times indicated below). The solvent was then removed under reduced pressure and the Diels-Alder cycloaddition adducts were recrystallized from the indicated solvents.

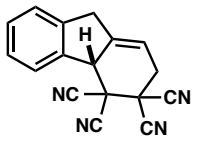
Elevated temperature Diels-Alder (for compounds **S3.7c** – **S3.7k**)
Solid vinylindene (50 mg, 1 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol (0.5 equiv.) were combined in a flamed dried microwave vial. The vial was then sealed and evacuated and refilled with nitrogen three times. Toluene (M = 0.1 M) and dienophile (5 equiv.) were then added to the vial. The homogenous solution was then microwaved at 180 ºC for 2 hours. The solution was then concentrated at room temperature and purified by column chromatography to afford the corresponding adducts.



S3.7a

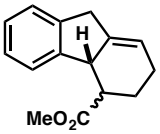
Triturate in diethyl ether to give white amorphous solid as single diastereomer. **Yield** 54%; **^{1}H NMR (**600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.1 Hz, 1H), 7.37 – 7.26 (m, 2H), 5.98 (s, 1H), 3.90 (d, *J* = 8.0 Hz, 1H), 3.98 – 3.90 (m, 2H), 3.70 (s, 2H), 3.56 – 3.41 (m, 1H), 2.90 (dd, *J* = 15.4, 7.2 Hz, 1H), 2.41 – 2.30 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.4, 170.3, 145.1, 141.9, 139.6, 128.0, 126.9, 125.5, 125.3, 118.8, 45.5, 44.2, 40.8, 36.4, 26.0; **^{1}H NMR** ((CD_3)$_2$CO, 600 MHz) δ 7.51 (d, *J* = 7.1 Hz, 1H), 7.50 – 6.61 (m, 2H), 6.02 – 5.96 (m, 1H), 4.24 (t, *J* = 8.4 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.77 – 3.70 (m, 1H), 3.70 – 3.60 (m, 2H), 2.76 (dd, *J* = 15.2, 7.1 Hz, 1H), 2.43 – 2.33 (m, 1H); **NOESY (CD_3)$_2$CO** δ (4.23, 4.02), (4.23, 3.74) (4.00, 4.25) (3.73, 4.25) **IR** (ATIR) – 3024 2959,

2902, 2853, 1846, 1775 cm^{-1}; **HRMS** (EI) calcd for $C_{15}H_{12}O_3$ $(M)^{\bullet+}$ m/z 240.0786 found 240.0787



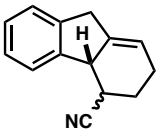
S3.7b

Triturate in cold methanol to give white amorphous solid. **Yield** 58% **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 6.3 Hz, 1H), 7.46 – 7.29 (m, 3H), 5.83 (s, 1H), 4.63 (s, 1H), 3.80 (d, *J* = 18.9 Hz, 1H), 3.68 (d, *J* = 19.1 Hz, 1H), 3.31 (d, 18.0 Hz, 1H), 3.21 (d, *J* = 17.2 Hz, 1H).; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 138.2, 134.9, 130.3, 128.5, 125.6, 123.7, 114.2, 111.7, 111.3, 111.0, 108.4, 48.5, 41.7, 39.1, 37.7, 33.6; **IR** (ATIR) 2967.1, 2952, 1475, 1462, 1438, 1258, 746 cm^{-1}; **HRMS** (EI) calcd for $C_{17}H_{10}N_4$ $(M)^{\bullet+}$ m/z 270.0905 found 270.0901.



S3.7c

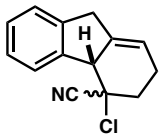
column chromatography 10% Et_2O in hexane to give a colorless oil that turns yellow over upon standing at room temperature. **Yield** 77% (1.9:1 dr); Spectra of major diastereomer reported. HRMS is of diastereomeric mixture. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 1H), 7.20 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 5.64 (apparent s, 1H), 3.90 – 3.82 (m, 1H), 3.75 – 3.63 (m, 1H), 3.60 – 3.54 (1 H), 3.51 – 3.45 (m, 1H), 3.44 (s, 3H), 2.34 – 2.14 (m, 3H), 2.07 – 1.95 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.2, 143.7, 141.6, 139.0, 126.7, 126.3, 124.6, 123.2, 118.7, 51.1, 46.2, 39.9, 38.0, 25.3, 22.5 cm^{-1}; **IR** (ATIR) 3040, 2925, 2837, 1738, 1725, 1156.; **HRMS** (EI) calcd for $C_{15}H_{16}O_2$ $(M)^{\bullet+}$ m/z 228.1150 found 228.1154.



S3.7d

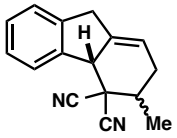
column chromatography (9:1 hexanes:diethyl ether) to give an amorphous white solid. **Yield** 62% total (1.3:1 dr). **R_f =** 0.34 **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 1H), 7.28 – 7.22 (m, 3H), 5.63 (apparent s, 1H), 3.81 (d, *J* = 10.1 Hz, 1H), 3.66 (d, *J* = 18.4 Hz, 1H), 3.46 (d, *J* = 18.5 Hz), 2.49 (t, *J* = 11.7 Hz), 2.37 – 2.24 (m, 2H), 2.24 – 2.12 (m, 1H), 2.14 – 1.84 (m, 1H).; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.4, 141.8, 139.7, 127.8, 127.1, 124.6, 124.0, 122.9, 119.1, 46.3, 38.0, 30.1, 27.3, 24.1; **IR** (ATIR) 3067, 3023, 2917, 2344, 2102, 1748, 1209.; **HRMS** (EI) calcd for $C_{14}H_{13}N$ $(M)^{\bullet+}$ m/z 195.1048 found

195.1051.; **R_f =** 0.14 colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 – 7.12 (m, 4H), 5.72 (apparent s, 1H), 3.82 (apparent s, 1H), 3.67 (dd, *J* = 19.1, 3.3 Hz, 1H), 3.60 (dt, *J* = 5.3, 3.4 Hz, 1H), 3.55 (d, *J* 18.7 Hz, 1H), 2.54 – 2.38 (m, 1H), 2.34 – 2.16 (m, 2H), 2.07 – 1.93 (m, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.0, 141.3, 138.4, 127.9, 127.0, 124.9, 123.4, 119.6, 119.5, 46.1, 38.1, 28.7, 25.2, 21.9.; **IR** (ATIR) 3067, 3043, 2930, 2840, 2237 cm^{-1}; **HRMS** (EI) calcd for $C_{14}H_{13}N$ $(M)^{\bullet+}$ m/z 195.1048 found 195.1051.



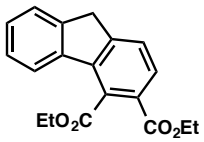
S3.7e

column chromatography (9:1 hexanes:diethyl ether) to give a colorless oil, decomposes to yellow oil over time at -20 ºC. **Yield** 89% (1:1 dr) Mixture of diastereomers reported. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.94 – 7.73 (m, 1H), 7.37 – 7.24 (m, 3H), 5.79 – 5.64 (m, 1H), 4.30 – 4.16 (m, 1H), 3.72 – 3.49 (m, 2H), 2.67 – 2.30 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.8, 141.6, 139.4, 139.0, 138.0, 135.1, 128.6, 128.5, 128.4, 127.2, 127.1, 125.2, 124.8, 124.6, 120.5, 119.6, 118.9, 117.0, 59.2, 55.7, 55.5, 52.6, 38.7, 37.8, 37.5, 35.5, 24.9, 21.4.; **IR** (ATIR) 3634, 3068, 3043, 2956, 2914, 1478, 1460, 1430, 746 cm^{-1}; **HRMS** (EI) calcd for $C_{14}H_{12}N^{35}Cl$ $(M)^{\bullet+}$ m/z 229.0658 found 229.0659



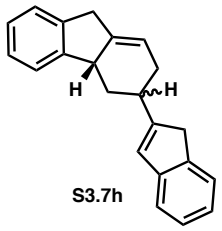
S3.7f

column chromatography (9:1 hexanes:diethyl ether) to give a yellow oil. **Yield** 63% (1.4:1 dr) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 1.4 H), 7.75 – 7.67 (m, 1H), 7.40 – 7.27 (m, 7.2H), 5.78 (s, 1.4H), 5.72 (s, 1H), 4.24 – 4.13 (m , 1.4H), 4.09 (s, 1H), 3.74 – 3.62 (m, 2.4H), 3.61 – 3.45 (m, 2.4H), 2.86 – 2.63 (m, 2H), 2.59 – 2.33 (m, 3H), 2.29 – 1.95 (m, 2.4H), 1.45 (d, J = 6.3 Hz, 4.2H), 1.40 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) 141.6, 141.5, 138.0, 137.9, 136.2, 135.2, 128.8, 128.6, 127.4, 127.4, 124.9, 124.9, 123.7, 123.5, 120.2, 118.3, 116.3, 116.3, 113.9, 111.9, 51.6, 44.8, 41.4, 39.0, 37.5, 37.2, 37.2, 35.3, 30.8, 28.8, 17.7,16.4.; **IR** (ATIR) 3063, 3044, 3025, 2971, 2932, 2879, 2835, 1476, 1459 cm^{-1}; **HRMS** (EI) calcd for $C_{16}H_{14}N_2$ $(M)^{\bullet+}$ m/z 234.1157 found 234.1158.



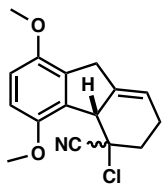
S3.7g

column chromatography (10:1 hexanes:ethyl acetate) to give a colorless oil (fluorescent blue 254 nm by TLC) **Yield** 19%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 5.5 Hz, 1H), 7.42 – 7.31 (m, 1H), 4.59 (q, *J* = 7.1 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.5, 166.0, 149.0, 143.6, 139.1, 138.5, 129.5, 128.7, 127.9, 127.3, 126.7, 125.6, 125.2, 122.2, 62.0, 61.6, 37.1, 14.4, 14.2; **IR** (ATIR) 2982, 2930, 2904, 1726, 1264 cm^{-1}; **HRMS(EI)** calcd for $C_{19}H_{18}O_4$ $(M)^{\bullet+}$ m/z 310.1205 found 310.1207.



S3.7h

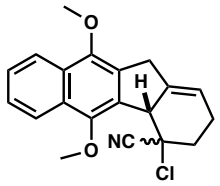
Obtained as the side product from all reactions above room temperature. Can be obtained pure by heating 2-vinylindene in toluene (0.10 M) at 180 ºC (microwave) for 2 hours, concentrating and then purification by **column chromatography** (100% petroleum ether). Obtained as a colorless oil. **Yield** 15% (3.6:1 dr) (21% based on recovered starting material) **^{1}H NMR** (600 MHz, $CDCl_3$) major diastereomer δ 7.25 – 7.19 (m, 2H), 7.14 – 6.95 (m, 6H), 6.74 (s, 1H). 6.24 (s, 1H), 5.65 (s, 1H), 4.06 (s, 1H), 3.89 – 3.35 (m, 5H), 3.15 (d, *J* = 22.5 Hz, 1H), 3.05 (d, *J* = 22.5 Hz, 1H), 2.81 – 2.00 (m, 5H).; **minor** 7.48 (d, *J* = 7.2 Hz, 0.3H), 7.38 (d, *J* = 7.4 Hz, 0.30H), 7.31 (t, *J* = 7.3 Hz, 0.30H), 6.74 (s, 0.30H), 5.65 (m, 1H), 2.81 – 2.52 (m, 0.30H), 1.99 – 1.92 (m, 0.30 H), 1.91 – 1.77 (m, 0.3H).; **^{13}C NMR** (150 MHz, $CDCl_3$) major diastereomer δ 149.7, 145.3, 144.2, 143.0, 141.3, 140.0, 128.6, 126.3, 126.3, 125.9, 124.3, 123.9, 123.3, 123.0, 119.9, 119.2, 48.0, 41.5, 37.8, 35.8, 29.0, 22.2; minor diastereomer 145.3, 145.1, 143.0, 142.1, 141.4, 127.0, 126.5, 126.4, 126.2, 124.4, 124.1, 123.8, 123.7, 120.3, 118.8, 48.2, 41.8, 38.6, 38.1, 32.1, 30.3, 25.7.;**^{13}C NMR DEPT 135º** (600 MHz, $CDCl_3$) major diastereomer; phased up 128.6, 126.3, 126.3, 125.9, 124.3, 123.9, 123.3, 123.0, 119.9, 119.2, 48.0, 35.8. phased down 41.5, 37.8, 29.0, 22.2. null signal 149.7, 145.3, 144.2, 143.0, 141.3, 140.0.; **IR (**ATIR) 3066, 3041, 3017, 2917, 2882, 1460, 741 cm^{-1}; **HRMS** (EI) calcd for $C_{22}H_{20}$ $(M)^{\bullet+}$ m/z 284.1565 found 284.1568.



S3.7i

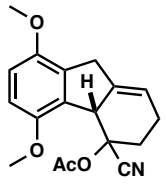
column chromatography (9:1 hexanes:diethyl ether) to give an amorphous white solid. Stable indefinitely at -20 ºC under nitrogen. **Yield** 83% (2.4:1 dr); **^{1}H NMR** (600 MHz,

$CDCl_3$) δ 6.91 – 6.48 (m, 2H), 5.87 – 5.54 (m, 1H), 4.39 – 4.00 (m, 1H), 3.97 – 3.58 (m, 6H), 2.78 – 2.51 (m, 1H), 2.51 – 2.37 (m, 2H) 2.33 – 2.21 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 151.1, 151.0, 149.8, 149.8, 138.1, 135.2, 132.0, 131.5, 128.5, 128.3, 121.5, 119.6, 119.1, 117.4, 111.0, 110.9, 110.6, 109.6, 55.9, 56.6, 55.8, 55.8, 55.8, 55.6, 54.8, 52.6, 39.9, 37.1, 35.1, 35.0, 24.1, 21.2 ppm; **IR (ATIR)** 2997, 2935, 2906, 2834, 1496, 1256 cm^{-1}; **HRMS** (EI) calcd for $C_{12}H_{16}NO_2{}^{35}Cl$ $(M)^+$ m/z 289.0870 found 289.0869



S3.7j

column chromatography (9:1 hexanes:diethyl ether) to give product as a dark yellow oil. **Yield** 55% (1.8:1 dr) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.31 – 8.02 (m, 1H), 8.13 – 8.02 (m, 1H), 7.68 – 7.40 (m, 2H), 5.91 – 5.76 (m, 1H), 4.56 – 4.36 (m, 1H), 4.17 – 4.02 (m, 2H), 4.01 – 3.63 (m, 6H), 3.83 – 3.63 (m, 2H), 2.57 – 2.39 (m, 1H), 2.40 – 2.25 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) (all peaks reported) δ 149.6, 149.1, 149.0, 148.3, 147.7, 147.5, 147.43, 147.1, 146.3, 144.8, 144.6, 143.6, 143.3, 142.8, 138.7, 137.2, 134.5, 133.4, 133.0, 130.1, 129.9, 129.4, 129.4, 129.0, 128.9, 128.7, 128.6, 128.6, 128.53, 128.4, 128.3, 128.3, 128.0, 127.8, 127.7, 127.4, 126.60, 126.4, 126.3, 126.1, 125.5, 125.5, 125.5, 125.2, 125.2, 125.2, 125.1, 124.9, 124.3, 124.2, 123.3, 122.9, 122.2, 122.1, 122.1, 122.1, 122.0, 121.8, 121.8, 121.7, 121.6, 121.3, 120.2, 120.0, 119.3, 119.0, 117.9, 117.0, 114.6, 114.1, 77.2, 77.0, 76.8, 62.5, 62.3, 61.8, 61.4, 60.9, 60.8, 60.8, 60.5, 60.4, 60.39, 60.0, 58.2, 58.0, 57.1, 56.0, 55.2, 55.1, 52.3, 51.5, 48.3, 47.2, 39.9, 38.7, 37.4, 37.2, 37.1, 36.2, 36.1, 35.7, 35.4, 34.9, 34.8, 34.7, 34.6, 34.5, 32.1, 31.5, 30.3, 29.7, 28.0, 26.9, 25.3, 23.9, 22.6, 22.2, 22.1, 21.3, 20.8, 20.7, 14.1; **IR (ATIR)** 3069, 2993, 2934, 2842, 1356 cm^{-1}. **HRMS(EI)** calcd for $C_{20}H_{18}NO_2{}^{35}Cl$ $(M)^{\bullet+}$ m/z 339.1026 found 339.1024.

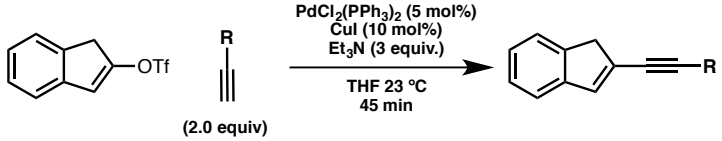


S3.7k

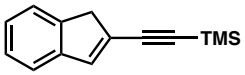
column chromatography: 8:2 hexanes:diethyl ether to give **S3.7** as an amorphous white solid. **Yield** 67% (2.2:1 dr) contains unidentified copolar impurity. **^{1}H NMR** (600 MHz, $CDCl_3$) (mixture of diastereomers reported) δ 6.83 – 6.36 (m, 2H), 5.90 – 5.58 (m, 1H). 4.41 – 4.06 (m, 1H), 3.84 (dd, J = 4.0, 2.1 Hz, 2H), 3.82 – 3.75 (m, 6H), 3.60 – 3.3 (m, 3H), 2.59 – 2.45 (m 1H), 2.21 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.0, 168.7, 150.7, 150.6, 149.8, 149.7, 136.6. 136.2, (8) 132.1, 131.4, 128.4, 128.2, 128.1, 128.3, 126.3, 119.6, 118.7, 110.5, 110.4, 110.0, 109.5, 73.6, 69.1, 56.1, 55.6, 54.8, 52.5, 52.0,

34.9, 34.8, 31.5, 31.4, 23.4, 21.5, 20.7, 20.5. **IR** (ATIR) 2995, 2937, 2910, 2835, 1749, 1495, 1257 cm^{-1}; **HRMS** (ESI) cacld for $C_{18}H_{19}O_4N^{23}Na$ m/z 336.1206 found 336.1204.

General procedure for 2-alkynylindene synthesis

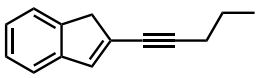


To a flame dried round bottom under nitrogen was added the indenyl-2-triflates **S3.5a** (1.00 g, 3.08 mmol) and but-3-yne-2-ol (0.484 mL, 6.16 mmol) in tetrahydrofuran (31 mL). $PdCl_2(PPh_3)_2$ (0.108 g, 0.15 mmol) and CuI (58.6 mg, 0.308 mmol) were then added simultaneously as solids under N_2. Triethylamine (1.28 mL, 0.935 mmol) was then added dropwise (over approximately one minute) and the solution was stirred at room temperature for 45 minutes. The solution was then diluted with ether (60 mL) and washed twice with 1 N HCl (30 mL). The aqueous layers were then extracted with ether (30 mL, x3) and the combined organics were dried over sodium sulfate. The mixture was then filtered, concentrated and purified by column chromatography to give the desired enynes.



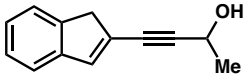
S3.8a

column chromatography (100% hexanes) to give a colorless oil. **Yield** 80%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.12 (s, 1H), 3.55 (s, 2H), 0.27 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.0, 143.0, 138.5, 127.3, 126.9, 126.1, 123.7, 121.7, 102.3, 99.6, 42.9, 0.20.; **IR** (ATIR) 3069, 3023, 2958, 2898, 2140, 1249, 837 cm^{-1}; **HRMS** (EI) calcd for $C_{14}H_{16}Si$ $(M)^{\bullet+}$ m/z 212.1021 found 212.1025.



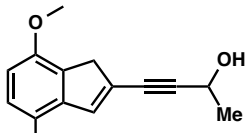
S3.8b

column chromatography (10:1 hexanes:ethyl acetate) to give orange oil. **Yield** 86%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 3.49 (s, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.63 (h, *J* = 7.2 Hz, 2H), (t, *J* = 7.4 Hz, 3H).; **^{13}C NMR** (150 MHz $CDCl_3$) δ 144.6, 142.8, 135.9, 128.5, 128.8, 125.4, 123.6, 121.2, 95.5, 78.0, 43.1, 22.4, 22.0, 13.8. **IR** (ATIR) 3067, 2961, 2931, 2889, 2870, 1703, 1458 750 cm^{-1}; **HRMS** (EI) calcd for $C_{14}H_{14}$ $(M)^{\bullet+}$ m/z 182.1096 found 182.1098.



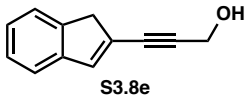
S3.8c

column chromatography (9:1 hexanes:ethyl aceate) to give a pale yellow amorphous solid. **Yield** 88%; **^{1}H NMR** (600 MHz $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.29 (apparent t, *J* = 7.4 Hz, 1H), 7.23 (apparent t, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 4.78 (q, *J* = 6.2 Hz, 1H), 3.52 (s, 1H), 2.17 (s, 1H), 1.56 (d, 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.0, 143.0, 137.7, 126.9, 126.7, 125.9, 123.7, 121.6, 95.8, 81.3, 59.2, 42.8, 24.5. **IR** (ATIR) 3359, 2979, 2935, 2903, 2833, 2211, 1494, 1251 cm^{-1}; **HRMS** (EI) calcd for $C_{13}H_{12}O$ $(M)^{\bullet+}$ m/z 184.0888 found 184.0890.



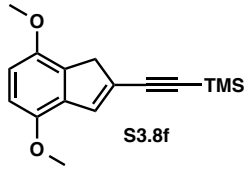
S3.8d

column chromatography (5:1 hexanes:ethyl acetate) to give a pale yellow amorphous solid. **Yield** 84% **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.16 (t, *J* = 1.7 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 4.75 (q, *J* = 6.6 Hz, 1H), 3.87 – 3.74 (m, 6H), 3.48 – 3.45 (m, 2H), 2.62 (s, 1H), 1.53 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 149.6, 147.9, 134.2, 133.9, 131.5, 125.4, 110.0, 109.0, 95.2, 81.3, 59.0, 56.0, 55.7, 40.7, 24.4; cm^{-1}; **IR** (ATIR) 3359, 2979, 2935, 2903, 2833, 2211, 1494, 1250, 1077. **HRMS** (ESI) calcd for $C_{15}H_{17}O_5$ m/z 245.1172 found 245.1171.



S3.8e

column chromatography (6:1 hexanes: ethyl acetate to 3:1 hexanes:ethyl acetate) to give a brown amorphous solid. **Yield** 69%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.51 (s, 1H), 3.52 (s, 2H); **^{13}C NMR (**150 MHz, $CDCl_3$) δ 143.8, 142.8, 137.8, 126.8, 126.5, 125.9, 123.6, 121.5, 91.9, 82.9, 51.9, 42.6.; **IR** (ATIR) 3249, 2919, 2898, 2215, 1458, 1015 cm^1.; **HRMS** (EI) calcd for $C_{12}H_{10}O$ $(M)^{\bullet+}$ m/z 170.0732 found 170.0731.



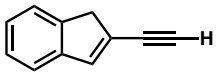
S3.8f

Note: Complete within 15 minutes. **column chromatography** (1:3 CH_2Cl_2:hexanes) to give an amorphous white solid. **Yield** 78%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 3.85 – 3.81 (m, 6H), 3.49 (s, 3H), 0.24 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.8, 148.2, 135.0, 134.4, 131.7, 126.0, 109.9,

109.3, 102.5, 98.2, 56.3, 55.9, 41.0, 0.21; **IR** (ATIR) 3001, 2951, 2898, 2833, 2142, 1495 cm^{-1}; **HRMS** (EI) calcd for $C_{16}H_{20}O_2Si$ $(M)^{\bullet+}$ m/z 272.1233 found 272.1240.

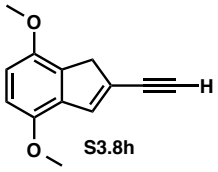
General Enyne Desilylation Procedure.

2-(trimethylsilylethynyl)indene **S3.8a** was dissolved in MeOH (0.10 M). K_2CO_3 (10 equiv) was then added and the heterogeneous mixture was allowed to stir overnight (12 h). The solution was then concentrated and the purple residue dissolved in Et_2O then washed with 1 N HCl (20 mL, x3). The organic layer was then dried over $MgSO_4$ and concentrated and the red oil obtained was then purified by column chromatography.



S3.8g

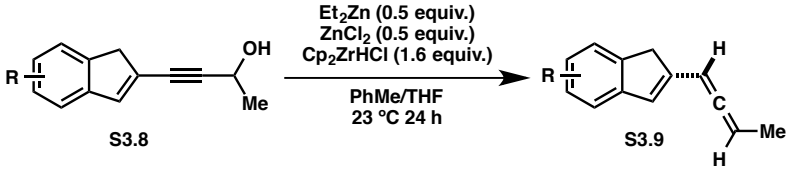
column chromatography (100% hexanes, load from CH_2Cl_2) to give a yellow oil. **Yield** quantitative; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 6.9 Hz, 1H), 7.19 (s, 1H), 3.58 (s, 1H), 3.34 (s, 1H).**^{13}C NMR** (125 MHz, $CDCl_3$) 143.6, 142.8, 138.9, 126.8, 126.1, 126.1, 123.6, 121.6, 81.9, 81.0, 42.6; **IR** (ATIR) 3284, 3067, 3021, 2821, 2897,1719, 1704, 1459, 1391, 867, 753 cm^{-1}; **HRMS** (EI) calcd for $(M)^{\bullet+}$ $C_{11}H_8$ m/z 140.0626 found 140.0623.



S3.8h

Yield 56%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 3.90 – 3.81 (m, 6H), 3.51 (s, 2H), 3.28 (s, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 149.8, 148.2, 135.4, 134.1, 131.7, 124.9, 109.9, 109.4, 81.4, 81.3, 56.2, 55.9, 40.9.; **IR** (ATIR) 3280, 3103, 3085, 3067, 2951, 2938, 2904, 2830, 1490, 1070 cm^{-1}; **HRMS** (EI) calcd for $C_{13}H_2O_2$ $(M)^{\bullet+}$ m/z 200.0837 found 200.0835.

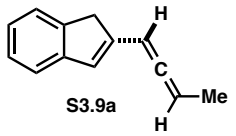
General 2-allenylindene synthesis[54]



S3.8 **S3.9**

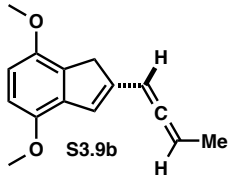
Diethylzinc (2.11 mL, 1 M) was added to a flame dried 2-neck (one neck connected to N_2 and the other stoppered with a rubber septum) round bottom flask containing dry $ZnCl_2$ (287 mg, 2.11 mmol) obtained from a glove box. THF (0.700 mL) was then added and the solution was stirred at room temperature for 30 minutes upon which the reaction became homogenous. Toluene (7.03 mL) was then added, and the solution was then

cooled to 0 ºC. As solution of propargylic alcohol (776 mg, 4.21 mmol) in toluene (14.0 mL) was then added drop wise to the solution by cannula (over ~2 minutes). After 20 minutes, Cp_2ZrHCl (Schwartz's reagent) (1.74 g, 6.74 mmol) was then added as a solid all at once by quickly removing the septum under a high stream of nitrogen (note: Schwartz's reagent is flocculent). The mixture was then warmed to room temperature and stirred vigorously for 24 h upon which the solution turns from yellow and homogenous to black and heterogeneous. Saturated $NaHCO_3$ (50 mL) was then added to the reaction, and the heterogeneous mixture was extracted 5 times with Et_2O (100 mL). The combined organic fractions were then dried over Na_2SO_4, filtered over a short pad of Celite® (1 inch), concentrated and then purified by column chromatography to give the desired allenes.



S3.9a

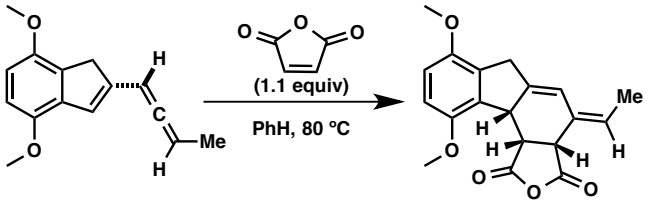
column chromatography (100% hexanes) to give amorphous white solid that yellows upon standing at room temperature. Can be stored in glove box freezer without any apparent changes measured ^{1}H NMR. **Yield** 56%; **^{1}H NMR $CDCl_3$** (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.11 (apparent t, *J* = 7.4 Hz, 1H), 6.65 (s, 1H), 6.20 (apparent s, 1H), 5.46 (p, *J* = 6.6 Hz, 1H), 3.49 – 3.31 (m, 2H), 1.76 (d, *J* = 7.0 Hz, 3H).; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.9, 145.7, 143.5, 143.2, 128.3, 126.5, 124.5, 123.6, 120.5, 91.2, 88.5, 39.0, 14.4; **IR** (ATIR) 3067, 3041, 2921, 2863, 1937, 1604, 1459 cm^{-1}; **HRMS** (EI) calcd for $C_{13}H_{12}$ $(M)^{\bullet+}$ m/z 168.0939 found 168.0939.



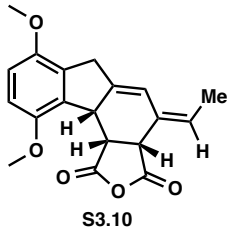
S3.9b

column chromatography (8:2 hexanes:CH_2Cl_2) to give a yellow oil that decomposes at –20 ºC over the course of 1 – 2 months when stored neat. Lifetime can be prolonged by storing as dilute solution in benzene below the freezing point of the solution. **Yield** 65%. **^{1}H NMR** (600 MHz, C_6D_6) δ 7.05 (s, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 6.46 (d, *J* = 8.7, 1H), 6.17 (d, *J* = 6.3, 1H), 5.18 (p, *J* = 6.9 Hz, 1H), 3.65 (d, *J* = 22.8 Hz, 1H), 3.59 (d, 22.8 Hz, *J* = 1H), 3.48 (s, 6H), 3.46 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, C_6D_6) 207.7, 150.1, 147.9, 142.1, 136.1, 131.7, 125.0, 109.6, 107.7, 91.3, 88.1, 55.2, 54.9, 37.2, 13.8; **IR** (ATIR) 3070, 2990, 2940, 2902, 2830, 1493, 1256, 1086 cm^{-1}; **HRMS** (EI) calcd for $C_{15}H_{16}O_2$ $(M)^{\bullet+}$ m/z 228.1150 found 228.1150.

Allene Diels – Alder cycloaddition with maleic anhydride.

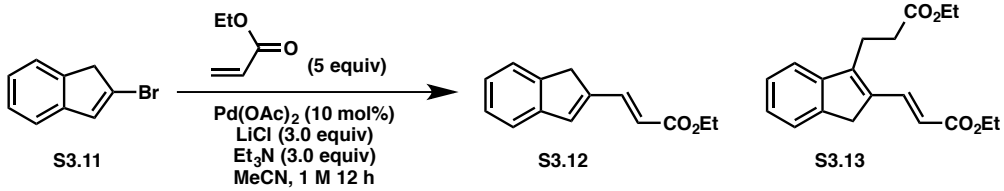


To a flame dried round bottom flask containing allene **S3.9b** (193 mg, 0.849 mmmol) in benzene was added maleic anhydride (91.0 mg, 0.928 mmol) at room temperature. The flask was then sealed and heated to 80 ºC for 2 hours, upon which the contents were then cooled to room temperature, concentrated and purified by column chromatography to afford adduct **S3.10** as a yellow amorphous solid.



column chromatography (7:3 hexanes:diethyl ether) to give product as a yellow amorphous solid. **Yield** 80%. **^{1}H NMR** (600 MHz, C_6D_6**)** δ 6.52 (d, *J* = 8.6 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 5.93 (s, 1H), 5.64 (q, *J* = 7.0 Hz, 1H), 3.98 – 3.84 (m, 2H), 3.69 (d, *J* = 22.2 Hz, 1H), 3.62 – 3.55 (m, 2H), 3.48 (s, 3H), 3.40 (s, 3H), 3.12 (d, *J* = 8.7 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (150 MHz $CDCl_3$) δ 171.4, 170.1, 151.0, 150.4, 144.3, 130.5, 130.0, 126.2, 125.4, 109.3, 108.9, 59.7, 54.9, 54.7, 46.4, 43.2, 42.6, 34.6, 13.4.; **IR** (ATIR) 2932, 2909, 2833, 1776, 1751, 1493, 1248, 1070 cm^{-1}; **HRMS** (EI) calcd for $C_{19}H_{18}O_5$ (M) $^{\bullet+}$ m/z 326.1154 found 326.1156.

General Heck Olefination Procedure



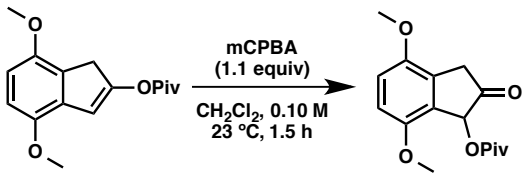
A stir bar and lithium chloride (304 mg, 3.00 mmol) was added to a 20 mL reaction tube and flamed dried under high vacuum. 2-bromoindene (195 mg, 1.00 mmol) and $Pd(OAc)_2$ (22.5 mg, 0.100 mmol) were then quickly added to the vessel. The solids were then dissolved in acetonitrile (1.00 mL) under N_2, and ethyl acrylate (160 μL, 1.50 mmol) was added to the heterogeneous mixture. The mixture was then heated to reflux

(100 ºC bath temperature) for 15 hours. The black mixture was then cooled to room temperature, diluted with 20 mL Et_2O and washed water (10 mL, x2). The organic layers were then dried over $MgSO_4$, filtered over a plug of Celite ® rinsing with Et_2O, concentrated and purified by flash chromatography.

column chromatography (9:1 hexanes:diethyl ether) to give **S3.12** product as an orange solid. **Yield** 61%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 15.7 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.20 m, 2H), 7.09 (s, 1H), 6.07 (d, *J* = 15.7 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.3, 144.2, 143.7, 143.6, 138.3, 127.0, 126.7, 124.1, 122.2, 118.5, 60.5, 37.3, 14.5; **IR** (ATIR) 3054, 2979, 2932, 2903, 1703, 1619; **HRMS** (EI) calcd for $C_{14}H_{14}O_2$ (M) $^{\bullet+}$ m/z 214.0994 found 214.0996.

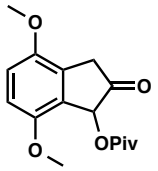
To obtain compound **S3.13** perform reaction in DMF. Aqueous work up dilute with water (x10 volume of DMF) extract into ether. Dry with $MgSO_4$ concentrate and purify as above to give **S3.13** as an orange oil. **Yield** 26%; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 15.6 Hz, 1H), 7.42 (dd, *J* = 13.3, 7.2 Hz, 2H), 7.35 – 7.17 (m, 2H), 6.08 (d, *J* = 15.6 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.53 (s, 2H), 3.08 (t, *J* = 7.9 Hz, 2H), 2.59 (t, *J* = 7.9 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 167.4, 147.6, 144.6, 143.1, 137.8, 137.0, 127.0, 126.8, 124.1, 120.2, 118.1, 60.7, 60.4, 37.3, 33.9, 21.1, 14.5, 14.3. **IR** (ATIR) 3063, 2978, 2933, 2904, 1730, 1701, 1613, 1148 cm^{-1}. **HRMS** (ESI) calcd for $C_{19}H_{22}O_4{}^{23}Na$ $(M+Na)^+$ m/z 337.1410 found 337.1408.

Rubottom Oxidation Procedure



S3.3 S3.14

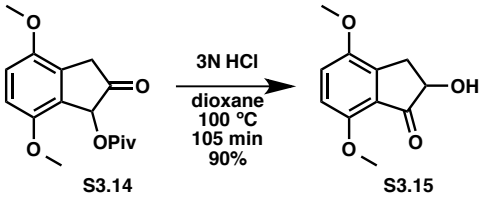
To flame dried round bottom flask was added solid indenylpivalate **S3.3** (27.6 mg, 0.10 mmol) in CH_2Cl_2 (1 mL, 0.10 M). *meta*-Chloroperoxybenzoic acid (*m*-CPBA) (33.6 mg, 0.15 mmol) was then added all at once at room temperature and the solution as allowed to stir for 1 hour. Upon completion, the reaction was diluted with dichloromethane and carefully quenched (evolution of CO_2) with 1 M sodium bisulfite (2 mL). The biphasic mixture was then carefully shaken and the organic layer removed. The aqueous layer was then extracted with CH_2Cl_2 (3 mL, x3). The combined organic layers were then dried over Na_2SO_4, concentrated and the crude solids purified by chromatography to afford the desired α-acyloxy-2-indanone.



S3.14

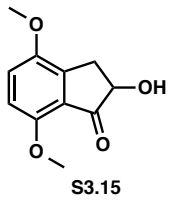
column chromatography (5:1 hexanes:EtOAc) off-white amorphous solid. **Yield** 61%. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 5.97 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.63 (d, *J* = 22.6 Hz, 1H), 3.42 (d, *J* = 22.6 Hz), 1.22 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.6, 177.2, 151.0, 149.7, 127.6, 125.7, 111.3, 109.6, 55.6, 55.4, 38.7, 38.6, 21.0; **IR** (ATIR) 2990, 2960, 2934, 2872, 2838, 1759, 1721, 810 cm^{-1}; **HRMS** (ESI) cald for $C_{16}H_{20}O_5Na$ ($M+Na^+$) m/z 315.1203, found 315.1202.

Pivaloyl deprotection using 3N HCl



S3.14 S3.15

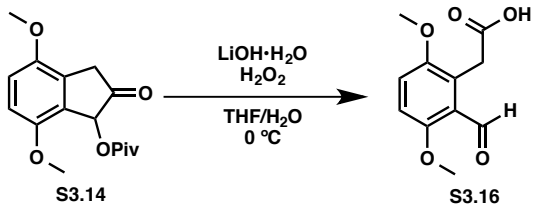
Indanone **S3.14** was dissolved in a biphasic dioxane:3N HCl mixture and heated to 100 °C for 3 hours. The solution as then quenched with saturated bicarbonate, extracted with diethyl ether and then dried over magnesium sulfate. The crude residue was then purified by flash chromatography to afford indanone **S3.15**.



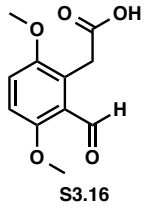
S3.15

column chromatography (2:1 hexanes:ethyl acetate) to give product as an amorphous orange soild. Note: The product is fluorescent blue by TLC under 254 nm light. **Yield** 43% **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.43 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.51 (dd, *J* = 17.0, 7.9 Hz, 1H), 3.04 (s, 1H), 2.78 (dd, *J* = 17.0, 4.8 Hz, 1H); **^{13}C NMR** (150 Mhz, $CDCl_3$) δ 204.1, 151.8, 150.3, 140.9, 123.0, 118.0, 110.0, 74.2, 55.0, 55.9, 31.3, 27.1; **IR** (ATIR) 3450, 2998, 2944, 2913, 2838, 1708, 1596, 1497, 1266 cm^{-1}; **HRMS** (ESI) calcd for $C_{11}H_{13}O_4$ ($M+H)^+$ 209.0808 found 209.0808.

Oxidative opening of 1-pivaloxy-2-indanone using lithium hydrogen peroxide[52]

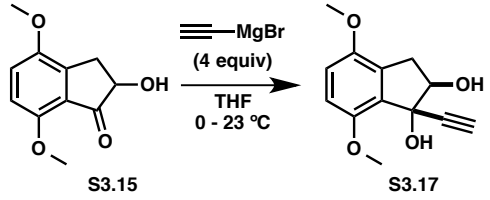


$LiOH{\bullet}H_2O$ (8.34 mg, 0.20 mmol) was added to a biphasic solution of THF:H_2O (3.3:1, 0.05M) and then cooled to 0 ºC upon which hydrogen peroxide (45 μL, 0.40 mmol 30% w/w aqueous) was added and the solution was stirred for 30 minutes at that temperature. Indanone **S3.14** was then added at 0 ºC as a solid in one portion and the solution was stirred for one hour at that temperature. Sodium sulfite (4.4 mmol) was then added and the solution was then washed with saturated $NaHCO_3$ and the aqueous layers were extracted with ethyl acetate. The aqueous layers were then acidified with 1N HCl (pH = 3, litmus paper) and then extracted into ethyl acetate. The organic layers were then dried with Na_2SO_4, concentrated and purified by column chromatography (2:1 hexanes:ethyl acetate) to give acid **S3.16**.



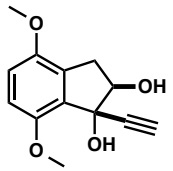
column chromatography (2:1 hexanes:ethyl aceate) to give product as a white solid. **Yield**: 36% **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.11(d, *J* = 9.1 Hz, 1H), 6.92 (d, *J* = 9,1 Hz, 1H), 4.12 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) 192.9, 175.9, 157.2, 141.9, 124.5, 123.9, 117.8, 111.3, 56.7, 56.2, 31.4; **IR** (ATIR) 2997, 2925, 2851, 1707, 1680, 1265 cm^{-1}. **HRMS** (ESI) calcd for $C_{10}H_6N_7{}^{23}Na$ m/z 247.0577 found 247.0576.

Grignard addition into 1-indanone **S3.15**.



To a flame dried round bottom flask was added indanone **S3.15** (30 mg, 0.15 mmol) in THF (1.46 mL) and cooled to 0 ºC. Ethynylmagnesium bromide (0.58 mL, 0.5 M in THF) was then added dropwise to the cooled homogenous solution at 0 ºC. The solution was allowed to stir for 40 minutes and was then warmed to room temperature. Upon stirring

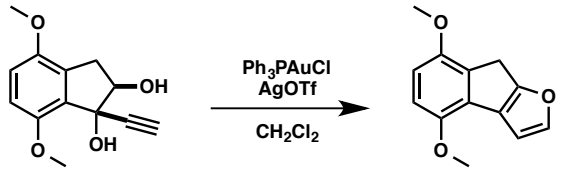
at this temperature for 45 minutes, TLC indicated the presence of the starting indanone and another 0.58 mL of ethynylmagnesium bromide was added. After 15 minutes the saturated ammonium chloride (2 mL) was then carefully added to the solution. The mixture was then extracted with diethyl ether (5 mL) and then ethyl acetate (5 mL) dried over $MgSO_4$ concentrated and purified by column chromatography (1:1 hexanes:diethyl ether to 1:2 hexanes:diethyl ether) to give diol **S3.17** as a white amorphous solid.



S3.17

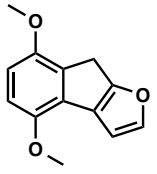
column chromatography (1:1 hexanes:diethyl ether to 1:2 hexanes:diethyl ether) to give product as an amorphous white low melting solid. **Yield** 65%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.79 – 6.60 (m, 2H), 4.47 (q, *J* = 7.6 Hz, 1H), 3.98 (s, 1H), 3.87 (s, 2H), 3.77 (s, 3H), 3.29 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.79 (s, 1H), 2.71 – 2.54 (m, 2H); **^{13}C NMR (**150 Hz**)** 150.2, 149.8, 130.7, 127.7, 111.2, 110.0, 81.5, 81.1, 79.4, 55.9, 55.7 34.2, 30.3; **IR** (ATIR) 3435, 3276, 2946, 2917, 2836, 1499, 1460, 1440, 1259 cm^{-1}; **HMRS** (ESI) calcd for $C_{13}H_{14}O_4{}^{23}Na$ $(M+Na)^+$ m/z 257.0784 found 257.0784.

Cycloisomerization of indanone **S3.17**.



S3.17 **S3.18**

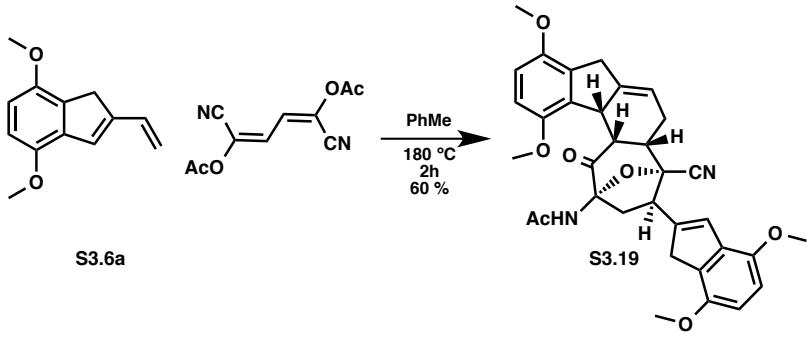
To a flame dried vial was added $Au(PPh_3)Cl$ (0.01 mmol) and silver triflate (0.01 mmol) in CH_2Cl_2 (500 μL). The solution was then stirred for 30 minutes in the dark upon which it became heterogeneous. The solution was then diluted with CH_2Cl_2 and filtered over Celite®. Diol **S3.17** was then dissolved in CH_2Cl_2 (1 mL) and 100 μL of the gold solution was then added and stirred until complete by TLC (~1 h). The solution was then concentrated and purified by column chromatography to give furan **S3.18** as a low melting pale yellow solid.



S3.18

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.82 (d, *J* = 9.4 Hz, 1H), 6.72 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.60 (s, 1H).

Oxidopyrylium ion adduct



Following the general conditions for the microwave Diels–Alder reaction of 2-vinylindenes with dienophiles. Used 20.2 mg diene **S3.6a**, 11 mg bis-cyanovinylacetate in toluene (0.10 M). **column chromatography** (95:5 hexanes: hexanes:ethyl acetate to 100% ethyl acetate) **Yield** 60% **^{1}H NMR (**600 MHz, $CDCl_3$**)** δ 7.17 (s, 1H), 6.83 – 6.75 (m, 2H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 5.57 (s, 1H), 4.57 – 4.50 (m, 1H), 4.43 (dd, *J* = 11.2, 7.5 Hz, 1H), 3.87 (s, 3H), 3.87 – 3.82 (m, 7H), 3.81 – 3.77 (m, 4H), 3.66 – 3.37 (m, 4H), 2.81 (q, *J* = 8.3 Hz, 1H), 2.70 – 2.56 (m, 1H), 2.35 – 2.44 (m, 1H), 2.39 (dd, *J* = 13.3 Hz, 7.0 Hz, 1H), 1.97 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 199.3, 169.8, 150.4, 150.1, 149.9, 147.7, 141.1, 139.4, 133.7, 133.8, 131.8, 130.6, 128.3, 117.4, 116.9, 109.6, 108.8, 108.6, 108.3, 91.4, 79.1, 55.8, 55.6, 55.5, 55.5, 49.3, 44.9, 43.5, 40.8, 39.7, 34.9, 31.9, 25.5, 24.3; **IR** (ATIR) 3375, 2951, 2912, 2852, 1743, 1696, 1495, 1461, 1254 cm^{-1}; **HRMS** (EI) calcd for $C_{34}H_{35}O_7N_2$ ($M+H^+$) 583.2439 found 583.2440.

X-ray quality crystals obtained by slow cooling from a solution of hot ethanol.

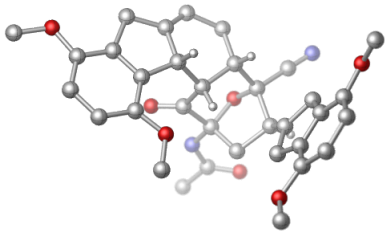
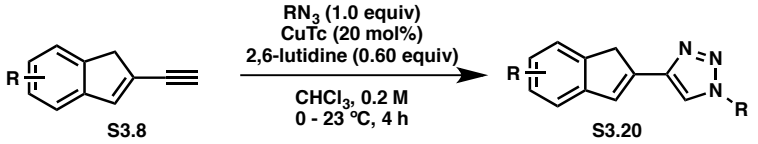


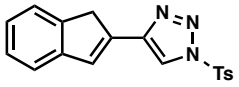
Figure 6: S3.19 CYlview of S3.19

General Huisgen Cycloaddition Procedure



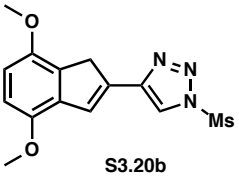
S3.8 S3.20

To a flamed dried round bottom flask was added enyne **S3.8h** (46 mg, 0.30 mmol) in dry toluene (0.74 mL). Copper(thiophene-2-carboxylate) (9.7 mg, 0.059 mmol) was then added in one portion as a solid. Mesyl azide (40 mg, 0.33 mmol) was then added as a solution in toluene (0.74 mL) and then 2,6-lutidine (20.8 μL, 0.18 mmol) was added dropwise to the mixture. The solution was then stirred vigorously for 4 hours upon which the solution was diluted with 20 mL CH_2Cl_2 and washed with saturated NH_4Cl (aq (20 mL). The aqueous layer was then extracted with 40 ml CH_2Cl_2 and the combined organic layers dried over $MgSO_4$ concentrated and then purified by column chromatography (2:1 hexanes:ethyl acetate) to afford triazole **S3.20b** as a tan amorphous solid.



S3.20a

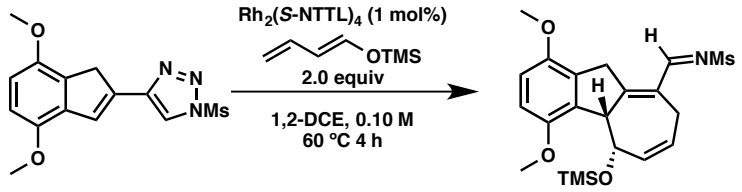
column chromatography (1:1 hexanes:CH_2Cl_2 to 1:2 hexanes:CH_2Cl_2) to give product as an amorphous white solid. **Yield** 51.3 mg**,** 52%. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 3.78 (s, 2H), 2.45 (s, 3H).; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.5, 144.6, 144.4, 142.9, 134.5, 133.2, 130.6, 130.2 128.6, 127.0, 125.7, 124.0, 121.8, 119.0, 39.3, 22.0.; **IR** (ATIR) 3144, 3065, 1594, 1393, 1194, 983 cm^{-1}; **HRMS** (EI) calcd for $C_{18}H_{15}N_3O_2S$ m/z 337.0885 found 337.0884.



S3.20b

column chromatography (2:1 hexanes/ethyl acetate) to give product as an amorphous tan solid. **Yield** 41.3 mg, 43%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.56 (s, 1H), 6.77 (d *J* = 8.7 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 3.88 (s, 6H), 3.79 (s, 2H), 3.55 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) 149.9, 148.3, 144.6, 134.5, 132.7, 121.4, 126.8, 118.5, 110.0, 109.0, 56.1, 55.7, 42.6, 37.2; **IR** (ATIR) 3147, 2940, 2906, 2890, 2832, 1490, 1354, 1250, 1169 cm^{-1}; **HRMS** (EI) calcd for $C_{14}H_{15}N_3O_4S$ $(M)^{\cdot+}$ m/z 321.0783 found 321.0779.

<u>Rhodium catalyzed cycloaddition to triazole **S3.20b**</u>



S3.20b S3.21

To a flame dried 4-mL dram vial was added triazole **S3.20b** (6.3 mg, 0.016 mmol) and Rh_2(*S*-NTTL)$_4$ (0.22 mg, 0.158 μmol). (*E*)-(buta-1,3-dien-1-yloxy)trimethylsilane[62] (4.5 mg, 0.032 mmol) dissolved in 1,2-dichloroethane (158 μL) was then added to the solids under nitrogen. The solution was then capped and heated to 65 ºC until complete by TLC analysis (3 hours). The solution was then concentrated and purified by column chromatography (3:1 hexanes:ethyl acetate to 3:2 hexanes:ethyl acetate) to afford tricycle **S3.21** as a yellow oil.

Yield 35%; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.96 (s, 1H), 6.72 (d, *J* = 8.9 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 1H), 6.06 – 5.83 (m, 1H), 5.83 – 5.55 (m, 1H), 4.81– 4.72 (m, 1H), 4.62 (s, 1H), 4.08 (d, *J* = 22.5 Hz, 1H), 3.95 – 3.70 (m, 7H), 3.72 – 3.52 (m, 1H), 3.07 (s, 3H), 3.04 – 2.92 (m, 1H), -0.25 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.3, 168.5, 150.2, 150.1, 131.7, 131.2, 131.1, 130.0, 128.4, 110.1, 109.1, 67.3, 56.0, 55.7, 55.3, 40.6, 35.3, 24.8, -0.22; **IR** (ATIR) 3500, 3012, 2951, 2929, 2903, 2835, 1565, 1498, 1257 cm^{-1}**; HRMS** (ESI) calcd for $C_{21}H_{29}NO_5{}^{23}Na^{32}S^{28}Si$ m/z 458.1428 found 458.1428.

Section 3.9.3. Crystal structure data

A yellow plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 100.0% complete to 67.000° in q. A total of 83552 reflections were collected covering the indices, -17<=*h*<=17, -20<=*k*<=25, -25<=*l*<=24. 11014 reflections were found to be symmetry independent, with an R_{int} of 0.0373. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. SQUEEZE was used to treat the disordered solvent contribution to the electron density map and its use has been noted in the CIF file.

Table 1. Crystal data and structure refinement for sarpong81.

X-ray ID	sarpong81	
Sample/notebook ID	SMHVII-020C	
Empirical formula	C34 H34 N2 O7	
Formula weight	582.63	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 14.4287(4) Å	a= 90°.
	b = 20.8084(6) Å	b= 106.013(2)°.
	c = 20.8192(6) Å	g = 90°.
Volume	6008.2(3) $Å^3$	
Z	8	
Density (calculated)	1.288 Mg/m^3	
Absorption coefficient	0.739 mm^{-1}	
F(000)	2464	
Crystal size	0.050 x 0.040 x 0.020 mm^3	
Crystal color/habit	yellow plate	
Theta range for data collection	3.064 to 68.733°.	
Index ranges	-17<=h<=17, -20<=k<=25, -25<=l<=24	
Reflections collected	83552	
Independent reflections	11014 [R(int) = 0.0373]	
Completeness to theta = 67.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.887	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11014 / 0 / 785	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0896, wR2 = 0.2587	
R indices (all data)	R1 = 0.0990, wR2 = 0.2705	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.093 and -0.603 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for sarpong81. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8111(2)	2109(2)	3744(1)	46(1)
C(2)	8847(2)	2583(2)	3588(2)	48(1)
C(3)	8973(2)	3172(2)	4052(2)	52(1)
C(4)	9948(3)	3471(2)	4227(2)	54(1)
C(5)	10678(2)	3255(2)	4006(2)	52(1)
C(6)	11716(3)	3467(2)	4208(2)	63(1)
C(7)	12221(3)	2912(2)	3978(2)	63(1)
C(8)	13209(3)	2848(2)	4064(2)	71(1)
C(9)	13521(3)	2310(2)	3797(2)	78(1)
C(10)	12876(4)	1853(2)	3438(3)	82(1)
C(11)	11882(3)	1919(2)	3339(2)	68(1)
C(12)	11570(3)	2463(2)	3622(2)	56(1)
C(13)	10546(2)	2686(2)	3536(2)	50(1)
C(14)	9797(2)	2214(2)	3648(2)	47(1)
C(15)	10070(2)	1832(1)	4295(2)	46(1)
C(16)	9212(2)	1421(1)	4379(2)	44(1)
C(17)	8747(2)	1033(2)	3743(1)	46(1)
C(18)	7936(2)	1474(2)	3331(1)	46(1)
C(19)	7178(2)	2430(2)	3696(2)	48(1)
C(20)	14788(4)	3272(4)	4550(4)	117(2)
C(21)	11443(5)	957(3)	2698(4)	121(2)
C(22)	8965(2)	611(1)	5177(1)	43(1)
C(23)	9461(2)	212(2)	5767(2)	48(1)
C(24)	7874(2)	1536(2)	2601(1)	46(1)
C(25)	8294(2)	1114(2)	2249(2)	49(1)
C(26)	7992(2)	1305(2)	1544(2)	48(1)
C(27)	8238(3)	1037(2)	999(2)	58(1)
C(28)	7866(3)	1325(2)	384(2)	63(1)
C(29)	7294(3)	1875(2)	318(2)	58(1)
C(30)	7063(2)	2147(2)	862(2)	51(1)
C(31)	7404(2)	1843(2)	1480(2)	47(1)
C(32)	7273(3)	2000(2)	2146(2)	54(1)
C(33)	9072(5)	210(2)	600(3)	103(2)
C(34)	6441(3)	3117(2)	295(2)	67(1)
C(35)	5612(2)	8501(1)	3258(2)	46(1)
C(36)	6281(2)	8493(2)	2794(2)	46(1)

C(37)	6168(2)	9121(2)	2379(2)	54(1)
C(38)	7097(3)	9386(2)	2295(2)	58(1)
C(39)	7922(2)	9076(2)	2469(2)	53(1)
C(40)	8932(3)	9294(2)	2489(2)	61(1)
C(41)	9566(2)	8776(2)	2871(2)	53(1)
C(42)	10577(3)	8723(2)	3036(2)	59(1)
C(43)	11012(2)	8201(2)	3383(2)	60(1)
C(44)	10496(3)	7721(2)	3580(2)	62(1)
C(45)	9496(2)	7759(2)	3429(2)	56(1)
C(46)	9045(2)	8301(2)	3070(2)	50(1)
C(47)	7985(2)	8414(2)	2786(2)	49(1)
C(48)	7320(2)	8384(1)	3240(2)	44(1)
C(49)	7545(2)	8832(1)	3842(1)	44(1)
C(50)	6734(2)	8833(2)	4203(2)	44(1)
C(51)	6518(2)	8133(2)	4364(2)	48(1)
C(52)	5708(2)	7917(2)	3746(2)	47(1)
C(53)	4600(2)	8590(2)	2865(2)	52(1)
C(54)	12047(3)	9156(2)	2949(3)	92(2)
C(55)	9360(3)	6765(2)	3946(3)	89(2)
C(56)	6290(2)	9384(2)	5106(2)	51(1)
C(57)	6552(3)	9924(2)	5605(2)	62(1)
C(58)	5823(2)	7275(2)	3441(2)	47(1)
C(59)	6524(3)	6786(2)	3747(2)	62(1)
C(60)	6329(2)	6243(2)	3270(2)	56(1)
C(61)	6778(3)	5643(2)	3277(2)	67(1)
C(62)	6405(3)	5215(2)	2773(2)	64(1)
C(63)	5635(2)	5373(2)	2247(2)	53(1)
C(64)	5206(2)	5967(2)	2204(2)	50(1)
C(65)	5564(2)	6398(2)	2732(2)	49(1)
C(66)	5251(2)	7055(2)	2834(2)	52(1)
C(67)	8075(5)	4946(3)	3803(3)	108(2)
C(68)	4114(3)	5752(2)	1140(2)	61(1)
N(1)	6452(2)	2672(2)	3650(1)	58(1)
N(2)	9513(2)	1062(1)	4983(1)	43(1)
N(3)	3811(2)	8635(2)	2556(2)	63(1)
N(4)	6924(2)	9279(1)	4731(1)	47(1)
O(1)	8482(2)	1890(1)	4420(1)	45(1)
O(2)	13774(2)	3335(2)	4406(2)	93(1)
O(3)	11173(2)	1516(1)	3002(2)	80(1)
O(4)	10837(2)	1836(1)	4714(1)	56(1)
O(5)	8121(2)	513(1)	4871(1)	50(1)
O(6)	8837(2)	513(1)	1141(1)	76(1)
O(7)	6528(2)	2688(1)	851(1)	65(1)
O(8)	5869(1)	9042(1)	3696(1)	46(1)

O(9)	11035(2)	9231(1)	2830(2)	68(1)
O(10)	8905(2)	7313(1)	3578(1)	62(1)
O(11)	8262(2)	9152(1)	4042(1)	49(1)
O(12)	5562(2)	9071(1)	5041(1)	59(1)
O(13)	7583(3)	5542(2)	3810(2)	97(1)
O(14)	4464(2)	6178(1)	1693(1)	62(1)

Table 3. Bond lengths [Å] and angles [°] for sarpong81.

C(1)-O(1)	1.435(3)	C(19)-N(1)	1.142(4)
C(1)-C(19)	1.481(4)	C(20)-O(2)	1.416(6)
C(1)-C(2)	1.548(4)	C(20)-H(20A)	0.9800
C(1)-C(18)	1.560(4)	C(20)-H(20B)	0.9800
C(2)-C(3)	1.540(4)	C(20)-H(20C)	0.9800
C(2)-C(14)	1.547(4)	C(21)-O(3)	1.429(5)
C(2)-H(2)	1.0000	C(21)-H(21A)	0.9800
C(3)-C(4)	1.489(5)	C(21)-H(21B)	0.9800
C(3)-H(3A)	0.9900	C(21)-H(21C)	0.9800
C(3)-H(3B)	0.9900	C(22)-O(5)	1.227(4)
C(4)-C(5)	1.338(5)	C(22)-N(2)	1.358(4)
C(4)-H(4)	0.9500	C(22)-C(23)	1.491(4)
C(5)-C(6)	1.505(5)	C(23)-H(23A)	0.9800
C(5)-C(13)	1.514(5)	C(23)-H(23B)	0.9800
C(6)-C(7)	1.510(6)	C(23)-H(23C)	0.9800
C(6)-H(6A)	0.9900	C(24)-C(25)	1.385(4)
C(6)-H(6B)	0.9900	C(24)-C(32)	1.457(4)
C(7)-C(12)	1.386(6)	C(25)-C(26)	1.466(4)
C(7)-C(8)	1.394(5)	C(25)-H(25)	0.9500
C(8)-O(2)	1.371(6)	C(26)-C(31)	1.389(5)
C(8)-C(9)	1.379(7)	C(26)-C(27)	1.395(5)
C(9)-C(10)	1.395(8)	C(27)-O(6)	1.371(5)
C(9)-H(9)	0.9500	C(27)-C(28)	1.381(5)
C(10)-C(11)	1.399(6)	C(28)-C(29)	1.395(6)
C(10)-H(10)	0.9500	C(28)-H(28)	0.9500
C(11)-O(3)	1.358(6)	C(29)-C(30)	1.387(5)
C(11)-C(12)	1.406(5)	C(29)-H(29)	0.9500
C(12)-C(13)	1.511(4)	C(30)-O(7)	1.362(4)
C(13)-C(14)	1.525(4)	C(30)-C(31)	1.395(4)
C(13)-H(13)	1.0000	C(31)-C(32)	1.488(4)
C(14)-C(15)	1.520(4)	C(32)-H(32A)	0.9900
C(14)-H(14)	1.0000	C(32)-H(32B)	0.9900
C(15)-O(4)	1.205(4)	C(33)-O(6)	1.411(5)
C(15)-C(16)	1.554(4)	C(33)-H(33A)	0.9800
C(16)-N(2)	1.425(4)	C(33)-H(33B)	0.9800
C(16)-O(1)	1.455(3)	C(33)-H(33C)	0.9800
C(16)-C(17)	1.539(4)	C(34)-O(7)	1.439(4)
C(17)-C(18)	1.547(4)	C(34)-H(34A)	0.9800
C(17)-H(17A)	0.9900	C(34)-H(34B)	0.9800
C(17)-H(17B)	0.9900	C(34)-H(34C)	0.9800
C(18)-C(24)	1.503(4)	C(35)-O(8)	1.432(4)
C(18)-H(18)	1.0000	C(35)-C(53)	1.475(4)

C(35)-C(36)	1.542(4)	C(54)-O(9)	1.420(5)
C(35)-C(52)	1.566(4)	C(54)-H(54A)	0.9800
C(36)-C(48)	1.548(4)	C(54)-H(54B)	0.9800
C(36)-C(37)	1.551(4)	C(54)-H(54C)	0.9800
C(36)-H(36)	1.0000	C(55)-O(10)	1.428(5)
C(37)-C(38)	1.503(5)	C(55)-H(55A)	0.9800
C(37)-H(37A)	0.9900	C(55)-H(55B)	0.9800
C(37)-H(37B)	0.9900	C(55)-H(55C)	0.9800
C(38)-C(39)	1.314(5)	C(56)-O(12)	1.212(4)
C(38)-H(38)	0.9500	C(56)-N(4)	1.374(4)
C(39)-C(40)	1.516(5)	C(56)-C(57)	1.507(5)
C(39)-C(47)	1.520(5)	C(57)-H(57A)	0.9800
C(40)-C(41)	1.493(5)	C(57)-H(57B)	0.9800
C(40)-H(40A)	0.9900	C(57)-H(57C)	0.9800
C(40)-H(40B)	0.9900	C(58)-C(66)	1.382(5)
C(41)-C(46)	1.373(5)	C(58)-C(59)	1.452(5)
C(41)-C(42)	1.408(5)	C(59)-C(60)	1.481(5)
C(42)-C(43)	1.360(6)	C(59)-H(59A)	0.9900
C(42)-O(9)	1.375(4)	C(59)-H(59B)	0.9900
C(43)-C(44)	1.375(6)	C(60)-C(65)	1.377(5)
C(43)-H(43)	0.9500	C(60)-C(61)	1.405(5)
C(44)-C(45)	1.392(5)	C(61)-C(62)	1.368(5)
C(44)-H(44)	0.9500	C(61)-O(13)	1.382(5)
C(45)-O(10)	1.353(4)	C(62)-C(63)	1.367(5)
C(45)-C(46)	1.410(5)	C(62)-H(62)	0.9500
C(46)-C(47)	1.497(4)	C(63)-C(64)	1.375(5)
C(47)-C(48)	1.523(4)	C(63)-H(63)	0.9500
C(47)-H(47)	1.0000	C(64)-O(14)	1.357(4)
C(48)-C(49)	1.523(4)	C(64)-C(65)	1.402(5)
C(48)-H(48)	1.0000	C(65)-C(66)	1.472(4)
C(49)-O(11)	1.205(4)	C(66)-H(66)	0.9500
C(49)-C(50)	1.555(4)	C(67)-O(13)	1.431(6)
C(50)-N(4)	1.406(4)	C(67)-H(67A)	0.9800
C(50)-O(8)	1.462(3)	C(67)-H(67B)	0.9800
C(50)-C(51)	1.545(4)	C(67)-H(67C)	0.9800
C(51)-C(52)	1.548(4)	C(68)-O(14)	1.430(4)
C(51)-H(51A)	0.9900	C(68)-H(68A)	0.9800
C(51)-H(51B)	0.9900	C(68)-H(68B)	0.9800
C(52)-C(58)	1.508(4)	C(68)-H(68C)	0.9800
C(52)-H(52)	1.0000	N(2)-H(2A)	0.8800
C(53)-N(3)	1.146(4)	N(4)-H(4A)	0.8800

O(1)-C(1)-C(19)	107.2(2)	C(19)-C(1)-C(2)	111.3(3)
O(1)-C(1)-C(2)	108.4(2)	O(1)-C(1)-C(18)	103.4(2)

C(19)-C(1)-C(18)	109.8(3)	C(12)-C(13)-C(5)	102.6(3)
C(2)-C(1)-C(18)	116.1(2)	C(12)-C(13)-C(14)	119.7(3)
C(3)-C(2)-C(14)	113.3(3)	C(5)-C(13)-C(14)	112.0(3)
C(3)-C(2)-C(1)	110.1(2)	C(12)-C(13)-H(13)	107.3
C(14)-C(2)-C(1)	108.1(2)	C(5)-C(13)-H(13)	107.3
C(3)-C(2)-H(2)	108.4	C(14)-C(13)-H(13)	107.3
C(14)-C(2)-H(2)	108.4	C(15)-C(14)-C(13)	116.8(3)
C(1)-C(2)-H(2)	108.4	C(15)-C(14)-C(2)	109.8(2)
C(4)-C(3)-C(2)	115.3(3)	C(13)-C(14)-C(2)	108.5(2)
C(4)-C(3)-H(3A)	108.5	C(15)-C(14)-H(14)	107.1
C(2)-C(3)-H(3A)	108.5	C(13)-C(14)-H(14)	107.1
C(4)-C(3)-H(3B)	108.5	C(2)-C(14)-H(14)	107.1
C(2)-C(3)-H(3B)	108.5	O(4)-C(15)-C(14)	126.8(3)
H(3A)-C(3)-H(3B)	107.5	O(4)-C(15)-C(16)	121.6(3)
C(5)-C(4)-C(3)	123.8(3)	C(14)-C(15)-C(16)	111.6(3)
C(5)-C(4)-H(4)	118.1	N(2)-C(16)-O(1)	110.4(2)
C(3)-C(4)-H(4)	118.1	N(2)-C(16)-C(17)	116.0(2)
C(4)-C(5)-C(6)	128.5(3)	O(1)-C(16)-C(17)	104.6(2)
C(4)-C(5)-C(13)	120.9(3)	N(2)-C(16)-C(15)	109.2(2)
C(6)-C(5)-C(13)	110.3(3)	O(1)-C(16)-C(15)	104.5(2)
C(5)-C(6)-C(7)	102.6(3)	C(17)-C(16)-C(15)	111.4(2)
C(5)-C(6)-H(6A)	111.3	C(16)-C(17)-C(18)	104.4(2)
C(7)-C(6)-H(6A)	111.3	C(16)-C(17)-H(17A)	110.9
C(5)-C(6)-H(6B)	111.3	C(18)-C(17)-H(17A)	110.9
C(7)-C(6)-H(6B)	111.3	C(16)-C(17)-H(17B)	110.9
H(6A)-C(6)-H(6B)	109.2	C(18)-C(17)-H(17B)	110.9
C(12)-C(7)-C(8)	121.4(4)	H(17A)-C(17)-H(17B)	108.9
C(12)-C(7)-C(6)	111.7(3)	C(24)-C(18)-C(17)	115.9(3)
C(8)-C(7)-C(6)	126.8(4)	C(24)-C(18)-C(1)	116.1(2)
O(2)-C(8)-C(9)	126.6(4)	C(17)-C(18)-C(1)	102.4(2)
O(2)-C(8)-C(7)	115.8(4)	C(24)-C(18)-H(18)	107.3
C(9)-C(8)-C(7)	117.6(4)	C(17)-C(18)-H(18)	107.3
C(8)-C(9)-C(10)	121.7(4)	C(1)-C(18)-H(18)	107.3
C(8)-C(9)-H(9)	119.2	N(1)-C(19)-C(1)	178.9(4)
C(10)-C(9)-H(9)	119.2	O(2)-C(20)-H(20A)	109.5
C(9)-C(10)-C(11)	121.2(4)	O(2)-C(20)-H(20B)	109.5
C(9)-C(10)-H(10)	119.4	H(20A)-C(20)-H(20B)	109.5
C(11)-C(10)-H(10)	119.4	O(2)-C(20)-H(20C)	109.5
O(3)-C(11)-C(10)	127.6(4)	H(20A)-C(20)-H(20C)	109.5
O(3)-C(11)-C(12)	115.6(3)	H(20B)-C(20)-H(20C)	109.5
C(10)-C(11)-C(12)	116.8(4)	O(3)-C(21)-H(21A)	109.5
C(7)-C(12)-C(11)	121.3(3)	O(3)-C(21)-H(21B)	109.5
C(7)-C(12)-C(13)	110.6(3)	H(21A)-C(21)-H(21B)	109.5
C(11)-C(12)-C(13)	127.8(4)	O(3)-C(21)-H(21C)	109.5

H(21A)-C(21)-H(21C)	109.5	O(6)-C(33)-H(33C)	109.5
H(21B)-C(21)-H(21C)	109.5	H(33A)-C(33)-H(33C)	109.5
O(5)-C(22)-N(2)	122.5(3)	H(33B)-C(33)-H(33C)	109.5
O(5)-C(22)-C(23)	121.1(3)	O(7)-C(34)-H(34A)	109.5
N(2)-C(22)-C(23)	116.3(2)	O(7)-C(34)-H(34B)	109.5
C(22)-C(23)-H(23A)	109.5	H(34A)-C(34)-H(34B)	109.5
C(22)-C(23)-H(23B)	109.5	O(7)-C(34)-H(34C)	109.5
H(23A)-C(23)-H(23B)	109.5	H(34A)-C(34)-H(34C)	109.5
C(22)-C(23)-H(23C)	109.5	H(34B)-C(34)-H(34C)	109.5
H(23A)-C(23)-H(23C)	109.5	O(8)-C(35)-C(53)	107.3(2)
H(23B)-C(23)-H(23C)	109.5	O(8)-C(35)-C(36)	108.0(2)
C(25)-C(24)-C(32)	110.2(3)	C(53)-C(35)-C(36)	110.4(3)
C(25)-C(24)-C(18)	124.5(3)	O(8)-C(35)-C(52)	103.7(2)
C(32)-C(24)-C(18)	124.9(3)	C(53)-C(35)-C(52)	110.7(3)
C(24)-C(25)-C(26)	107.7(3)	C(36)-C(35)-C(52)	116.0(2)
C(24)-C(25)-H(25)	126.1	C(35)-C(36)-C(48)	107.2(2)
C(26)-C(25)-H(25)	126.1	C(35)-C(36)-C(37)	110.6(2)
C(31)-C(26)-C(27)	121.9(3)	C(48)-C(36)-C(37)	113.2(3)
C(31)-C(26)-C(25)	108.7(3)	C(35)-C(36)-H(36)	108.6
C(27)-C(26)-C(25)	129.4(3)	C(48)-C(36)-H(36)	108.6
O(6)-C(27)-C(28)	127.2(3)	C(37)-C(36)-H(36)	108.6
O(6)-C(27)-C(26)	115.4(3)	C(38)-C(37)-C(36)	114.5(3)
C(28)-C(27)-C(26)	117.4(3)	C(38)-C(37)-H(37A)	108.6
C(27)-C(28)-C(29)	121.0(3)	C(36)-C(37)-H(37A)	108.6
C(27)-C(28)-H(28)	119.5	C(38)-C(37)-H(37B)	108.6
C(29)-C(28)-H(28)	119.5	C(36)-C(37)-H(37B)	108.6
C(30)-C(29)-C(28)	121.5(3)	H(37A)-C(37)-H(37B)	107.6
C(30)-C(29)-H(29)	119.2	C(39)-C(38)-C(37)	123.8(3)
C(28)-C(29)-H(29)	119.2	C(39)-C(38)-H(38)	118.1
O(7)-C(30)-C(29)	125.9(3)	C(37)-C(38)-H(38)	118.1
O(7)-C(30)-C(31)	116.5(3)	C(38)-C(39)-C(40)	130.7(3)
C(29)-C(30)-C(31)	117.7(3)	C(38)-C(39)-C(47)	120.4(3)
C(26)-C(31)-C(30)	120.4(3)	C(40)-C(39)-C(47)	108.5(3)
C(26)-C(31)-C(32)	108.6(3)	C(41)-C(40)-C(39)	104.0(3)
C(30)-C(31)-C(32)	131.0(3)	C(41)-C(40)-H(40A)	111.0
C(24)-C(32)-C(31)	104.7(3)	C(39)-C(40)-H(40A)	111.0
C(24)-C(32)-H(32A)	110.8	C(41)-C(40)-H(40B)	111.0
C(31)-C(32)-H(32A)	110.8	C(39)-C(40)-H(40B)	111.0
C(24)-C(32)-H(32B)	110.8	H(40A)-C(40)-H(40B)	109.0
C(31)-C(32)-H(32B)	110.8	C(46)-C(41)-C(42)	119.2(3)
H(32A)-C(32)-H(32B)	108.9	C(46)-C(41)-C(40)	112.0(3)
O(6)-C(33)-H(33A)	109.5	C(42)-C(41)-C(40)	128.8(3)
O(6)-C(33)-H(33B)	109.5	C(43)-C(42)-O(9)	126.1(3)
H(33A)-C(33)-H(33B)	109.5	C(43)-C(42)-C(41)	119.2(3)

O(9)-C(42)-C(41)	114.8(3)	C(51)-C(52)-H(52)	107.0
C(42)-C(43)-C(44)	122.1(3)	C(35)-C(52)-H(52)	107.0
C(42)-C(43)-H(43)	119.0	N(3)-C(53)-C(35)	177.4(3)
C(44)-C(43)-H(43)	119.0	O(9)-C(54)-H(54A)	109.5
C(43)-C(44)-C(45)	120.3(4)	O(9)-C(54)-H(54B)	109.5
C(43)-C(44)-H(44)	119.8	H(54A)-C(54)-H(54B)	109.5
C(45)-C(44)-H(44)	119.8	O(9)-C(54)-H(54C)	109.5
O(10)-C(45)-C(44)	126.1(3)	H(54A)-C(54)-H(54C)	109.5
O(10)-C(45)-C(46)	116.3(3)	H(54B)-C(54)-H(54C)	109.5
C(44)-C(45)-C(46)	117.6(3)	O(10)-C(55)-H(55A)	109.5
C(41)-C(46)-C(45)	121.6(3)	O(10)-C(55)-H(55B)	109.5
C(41)-C(46)-C(47)	110.6(3)	H(55A)-C(55)-H(55B)	109.5
C(45)-C(46)-C(47)	127.3(3)	O(10)-C(55)-H(55C)	109.5
C(46)-C(47)-C(39)	104.2(3)	H(55A)-C(55)-H(55C)	109.5
C(46)-C(47)-C(48)	119.8(3)	H(55B)-C(55)-H(55C)	109.5
C(39)-C(47)-C(48)	109.6(3)	O(12)-C(56)-N(4)	123.0(3)
C(46)-C(47)-H(47)	107.5	O(12)-C(56)-C(57)	121.5(3)
C(39)-C(47)-H(47)	107.5	N(4)-C(56)-C(57)	115.5(3)
C(48)-C(47)-H(47)	107.5	C(56)-C(57)-H(57A)	109.5
C(47)-C(48)-C(49)	117.2(3)	C(56)-C(57)-H(57B)	109.5
C(47)-C(48)-C(36)	107.1(2)	H(57A)-C(57)-H(57B)	109.5
C(49)-C(48)-C(36)	110.8(2)	C(56)-C(57)-H(57C)	109.5
C(47)-C(48)-H(48)	107.1	H(57A)-C(57)-H(57C)	109.5
C(49)-C(48)-H(48)	107.1	H(57B)-C(57)-H(57C)	109.5
C(36)-C(48)-H(48)	107.1	C(66)-C(58)-C(59)	109.7(3)
O(11)-C(49)-C(48)	126.2(3)	C(66)-C(58)-C(52)	124.8(3)
O(11)-C(49)-C(50)	121.4(3)	C(59)-C(58)-C(52)	125.4(3)
C(48)-C(49)-C(50)	112.4(2)	C(58)-C(59)-C(60)	105.1(3)
N(4)-C(50)-O(8)	108.2(2)	C(58)-C(59)-H(59A)	110.7
N(4)-C(50)-C(51)	117.4(3)	C(60)-C(59)-H(59A)	110.7
O(8)-C(50)-C(51)	104.7(2)	C(58)-C(59)-H(59B)	110.7
N(4)-C(50)-C(49)	111.6(2)	C(60)-C(59)-H(59B)	110.7
O(8)-C(50)-C(49)	104.9(2)	H(59A)-C(59)-H(59B)	108.8
C(51)-C(50)-C(49)	109.1(2)	C(65)-C(60)-C(61)	118.9(3)
C(50)-C(51)-C(52)	104.2(2)	C(65)-C(60)-C(59)	109.1(3)
C(50)-C(51)-H(51A)	110.9	C(61)-C(60)-C(59)	132.0(3)
C(52)-C(51)-H(51A)	110.9	C(62)-C(61)-O(13)	125.6(3)
C(50)-C(51)-H(51B)	110.9	C(62)-C(61)-C(60)	119.1(3)
C(52)-C(51)-H(51B)	110.9	O(13)-C(61)-C(60)	115.3(3)
H(51A)-C(51)-H(51B)	108.9	C(63)-C(62)-C(61)	121.3(3)
C(58)-C(52)-C(51)	117.5(3)	C(63)-C(62)-H(62)	119.3
C(58)-C(52)-C(35)	114.5(3)	C(61)-C(62)-H(62)	119.3
C(51)-C(52)-C(35)	103.0(2)	C(62)-C(63)-C(64)	121.3(3)
C(58)-C(52)-H(52)	107.0	C(62)-C(63)-H(63)	119.4

C(64)-C(63)-H(63)	119.4
O(14)-C(64)-C(63)	125.8(3)
O(14)-C(64)-C(65)	116.6(3)
C(63)-C(64)-C(65)	117.6(3)
C(60)-C(65)-C(64)	121.7(3)
C(60)-C(65)-C(66)	108.1(3)
C(64)-C(65)-C(66)	130.2(3)
C(58)-C(66)-C(65)	108.0(3)
C(58)-C(66)-H(66)	126.0
C(65)-C(66)-H(66)	126.0
O(13)-C(67)-H(67A)	109.5
O(13)-C(67)-H(67B)	109.5
H(67A)-C(67)-H(67B)	109.5
O(13)-C(67)-H(67C)	109.5
H(67A)-C(67)-H(67C)	109.5
H(67B)-C(67)-H(67C)	109.5
O(14)-C(68)-H(68A)	109.5
O(14)-C(68)-H(68B)	109.5
H(68A)-C(68)-H(68B)	109.5
O(14)-C(68)-H(68C)	109.5
H(68A)-C(68)-H(68C)	109.5
H(68B)-C(68)-H(68C)	109.5
C(22)-N(2)-C(16)	124.4(2)
C(22)-N(2)-H(2A)	117.8
C(16)-N(2)-H(2A)	117.8
C(56)-N(4)-C(50)	122.1(3)
C(56)-N(4)-H(4A)	118.9
C(50)-N(4)-H(4A)	118.9
C(1)-O(1)-C(16)	103.6(2)
C(8)-O(2)-C(20)	118.2(5)
C(11)-O(3)-C(21)	118.2(4)
C(27)-O(6)-C(33)	117.4(3)
C(30)-O(7)-C(34)	116.8(3)
C(35)-O(8)-C(50)	104.2(2)
C(42)-O(9)-C(54)	114.8(3)
C(45)-O(10)-C(55)	116.4(3)
C(61)-O(13)-C(67)	115.7(4)
C(64)-O(14)-C(68)	117.3(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sarpong81. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	52(2)	48(2)	41(1)	5(1)	17(1)	5(1)
C(2)	53(2)	45(2)	49(2)	6(1)	17(1)	8(1)
C(3)	55(2)	43(2)	64(2)	3(1)	24(1)	5(1)
C(4)	63(2)	42(2)	61(2)	3(1)	24(2)	4(1)
C(5)	59(2)	45(2)	57(2)	11(1)	22(1)	2(1)
C(6)	61(2)	65(2)	65(2)	7(2)	22(2)	1(2)
C(7)	60(2)	74(2)	62(2)	21(2)	26(2)	9(2)
C(8)	61(2)	84(3)	72(2)	16(2)	24(2)	11(2)
C(9)	61(2)	93(3)	87(3)	36(2)	34(2)	22(2)
C(10)	90(3)	77(3)	98(3)	29(2)	57(3)	34(2)
C(11)	70(2)	61(2)	88(3)	20(2)	46(2)	15(2)
C(12)	60(2)	53(2)	66(2)	19(2)	34(2)	10(2)
C(13)	55(2)	46(2)	56(2)	9(1)	26(1)	7(1)
C(14)	54(2)	42(2)	51(2)	4(1)	24(1)	5(1)
C(15)	51(2)	41(2)	50(2)	3(1)	20(1)	7(1)
C(16)	48(2)	40(1)	46(1)	4(1)	15(1)	5(1)
C(17)	55(2)	43(2)	41(1)	5(1)	14(1)	5(1)
C(18)	51(2)	46(2)	43(2)	6(1)	16(1)	2(1)
C(19)	53(2)	50(2)	42(1)	5(1)	14(1)	3(1)
C(20)	57(3)	148(6)	143(5)	-1(4)	19(3)	13(3)
C(21)	138(5)	80(3)	174(6)	-27(4)	90(5)	22(3)
C(22)	44(1)	40(1)	44(1)	-2(1)	14(1)	2(1)
C(23)	48(2)	49(2)	46(2)	4(1)	13(1)	1(1)
C(24)	47(2)	50(2)	43(1)	4(1)	14(1)	1(1)
C(25)	55(2)	44(2)	48(2)	4(1)	14(1)	4(1)
C(26)	56(2)	43(2)	46(2)	3(1)	16(1)	-3(1)
C(27)	77(2)	48(2)	52(2)	-2(1)	23(2)	-2(2)
C(28)	85(2)	59(2)	49(2)	-4(2)	26(2)	-7(2)
C(29)	65(2)	68(2)	41(2)	7(1)	12(1)	-8(2)
C(30)	44(2)	59(2)	49(2)	12(1)	12(1)	3(1)
C(31)	45(2)	51(2)	46(2)	4(1)	14(1)	1(1)
C(32)	64(2)	55(2)	48(2)	8(1)	24(1)	9(2)
C(33)	178(6)	63(3)	84(3)	-5(2)	66(4)	27(3)
C(34)	70(2)	68(2)	61(2)	26(2)	17(2)	9(2)
C(35)	43(1)	41(2)	53(2)	-4(1)	13(1)	1(1)
C(36)	46(2)	42(2)	50(2)	0(1)	12(1)	3(1)
C(37)	52(2)	56(2)	54(2)	8(1)	10(1)	8(1)

C(38)	66(2)	49(2)	62(2)	10(2)	22(2)	4(2)
C(39)	57(2)	50(2)	56(2)	0(1)	23(1)	0(1)
C(40)	64(2)	55(2)	68(2)	3(2)	28(2)	-3(2)
C(41)	55(2)	48(2)	60(2)	-12(1)	24(1)	2(1)
C(42)	61(2)	53(2)	71(2)	-18(2)	32(2)	-12(2)
C(43)	49(2)	56(2)	72(2)	-16(2)	15(2)	6(2)
C(44)	51(2)	57(2)	77(2)	-6(2)	16(2)	7(2)
C(45)	55(2)	48(2)	65(2)	-4(1)	17(2)	8(1)
C(46)	50(2)	53(2)	52(2)	-9(1)	23(1)	-1(1)
C(47)	50(2)	46(2)	54(2)	-3(1)	18(1)	2(1)
C(48)	42(1)	42(2)	51(2)	3(1)	16(1)	4(1)
C(49)	39(1)	43(2)	48(2)	7(1)	11(1)	6(1)
C(50)	39(1)	45(2)	48(2)	1(1)	12(1)	2(1)
C(51)	49(2)	45(2)	53(2)	-1(1)	18(1)	-1(1)
C(52)	44(2)	43(2)	55(2)	-1(1)	17(1)	0(1)
C(53)	49(2)	43(2)	64(2)	-7(1)	16(1)	2(1)
C(54)	71(3)	73(3)	147(5)	-19(3)	56(3)	-13(2)
C(55)	66(2)	65(3)	134(4)	40(3)	25(3)	13(2)
C(56)	51(2)	48(2)	58(2)	-4(1)	21(1)	-3(1)
C(57)	63(2)	68(2)	59(2)	-15(2)	24(2)	-13(2)
C(58)	43(1)	40(2)	61(2)	-1(1)	17(1)	0(1)
C(59)	57(2)	45(2)	78(2)	-3(2)	8(2)	-1(1)
C(60)	52(2)	44(2)	69(2)	-4(2)	11(2)	-1(1)
C(61)	62(2)	47(2)	81(2)	1(2)	2(2)	5(2)
C(62)	61(2)	42(2)	88(3)	-6(2)	19(2)	2(1)
C(63)	50(2)	44(2)	71(2)	-9(1)	26(2)	-6(1)
C(64)	45(2)	46(2)	63(2)	-6(1)	23(1)	-6(1)
C(65)	44(2)	42(2)	67(2)	2(1)	22(1)	0(1)
C(66)	54(2)	41(2)	63(2)	-2(1)	20(1)	4(1)
C(67)	128(5)	92(4)	89(3)	4(3)	4(3)	55(3)
C(68)	67(2)	63(2)	53(2)	-9(2)	18(2)	-2(2)
N(1)	58(2)	66(2)	51(1)	3(1)	15(1)	14(1)
N(2)	44(1)	43(1)	40(1)	3(1)	10(1)	0(1)
N(3)	47(2)	54(2)	81(2)	-6(1)	8(1)	5(1)
N(4)	43(1)	46(1)	52(1)	-4(1)	15(1)	-5(1)
O(1)	49(1)	45(1)	42(1)	5(1)	16(1)	7(1)
O(2)	50(2)	123(3)	102(2)	4(2)	16(2)	7(2)
O(3)	94(2)	55(2)	112(2)	-1(2)	64(2)	13(1)
O(4)	49(1)	58(1)	61(1)	12(1)	15(1)	0(1)
O(5)	47(1)	51(1)	50(1)	6(1)	9(1)	-3(1)
O(6)	117(2)	56(2)	68(2)	8(1)	46(2)	26(2)
O(7)	63(1)	75(2)	62(1)	26(1)	24(1)	20(1)
O(8)	42(1)	41(1)	54(1)	-4(1)	13(1)	2(1)
O(9)	65(2)	64(2)	89(2)	-9(1)	43(1)	-9(1)

O(10)	56(1)	51(1)	83(2)	12(1)	23(1)	6(1)
O(11)	42(1)	50(1)	56(1)	-2(1)	16(1)	-2(1)
O(12)	56(1)	56(1)	71(1)	-12(1)	29(1)	-11(1)
O(13)	95(2)	63(2)	103(2)	-10(2)	-21(2)	25(2)
O(14)	66(1)	53(1)	62(1)	-9(1)	11(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3})
for sarpong81.

	x	y	z	U(eq)
H(2)	8589	2733	3116	58
H(3A)	8493	3501	3836	63
H(3B)	8828	3040	4471	63
H(4)	10058	3837	4511	65
H(6A)	11955	3528	4697	75
H(6B)	11802	3871	3980	75
H(9)	14193	2249	3860	93
H(10)	13117	1491	3258	99
H(13)	10300	2856	3071	60
H(14)	9668	1897	3273	56
H(17A)	8479	623	3854	56
H(17B)	9224	937	3493	56
H(18)	7309	1291	3363	55
H(20A)	15097	3669	4755	176
H(20B)	14963	3190	4135	176
H(20C)	15004	2912	4859	176
H(21A)	10864	751	2413	182
H(21B)	11779	656	3047	182
H(21C)	11872	1080	2427	182
H(23A)	10126	363	5947	71
H(23B)	9465	-238	5631	71
H(23C)	9118	251	6112	71
H(25)	8704	764	2432	59
H(28)	8001	1145	0	75
H(29)	7058	2068	-110	70
H(32A)	7487	2445	2278	65
H(32B)	6589	1955	2143	65
H(33A)	9407	515	384	154
H(33B)	8480	62	276	154
H(33C)	9492	-159	765	154
H(34A)	6098	3507	362	100
H(34B)	6080	2904	-119	100
H(34C)	7084	3232	262	100
H(36)	6096	8122	2480	55
H(37A)	5725	9039	1931	65

H(37B)	5866	9451	2598	65
H(38)	7087	9802	2106	70
H(40A)	9008	9334	2033	73
H(40B)	9083	9713	2720	73
H(43)	11695	8166	3492	72
H(44)	10824	7362	3821	74
H(47)	7743	8096	2418	59
H(48)	7350	7935	3416	53
H(51A)	6298	8114	4774	58
H(51B)	7097	7859	4426	58
H(52)	5098	7897	3885	56
H(54A)	12317	9543	2803	138
H(54B)	12177	8784	2698	138
H(54C)	12344	9088	3427	138
H(55A)	9808	6906	4367	134
H(55B)	9715	6529	3682	134
H(55C)	8869	6484	4042	134
H(57A)	6683	9750	6059	93
H(57B)	6016	10230	5528	93
H(57C)	7128	10145	5554	93
H(59A)	6441	6652	4184	74
H(59B)	7189	6949	3815	74
H(62)	6686	4801	2789	77
H(63)	5392	5065	1905	64
H(66)	4746	7287	2535	62
H(67A)	8286	4918	3395	163
H(67B)	7638	4588	3815	163
H(67C)	8637	4923	4195	163
H(68A)	3576	5956	810	91
H(68B)	3892	5352	1297	91
H(68C)	4634	5657	935	91
H(2A)	10092	1137	5249	51
H(4A)	7467	9498	4824	56

Section 3.9.4. Computational information

The reaction was studied with the B3LYP/6-31+G(d,p) DFT method[63] implemented in GAUSSIAN09[64], Frequency analysis was used to assign stationary points to confirm global minima due to the absence of imaginary frequencies. The calculation was carried out in the gas phase at standard temperature and pressure. Structural images were created using Ball & Stick.[65] Energies reported are gas phase Gibbs free energies in Hatree/particle.

Zero-point correction= 0.173000 (Hartree/Particle)
Thermal correction to Energy= 0.181085
Thermal correction to Enthalpy= 0.182029
Thermal correction to Gibbs Free Energy= 0.140125
Sum of electronic and zero-point Energies= -425.023236
Sum of electronic and thermal Energies= -425.015150
Sum of electronic and thermal Enthalpies= -425.014206
Sum of electronic and thermal Free Energies= -425.05611

coordinates

C	-0.69597100	-0.74947600	0.00000000
C	-0.53494700	0.65612400	0.00000000
C	-1.65380700	1.49735800	0.00000000
C	-2.92769100	0.92033400	0.00000000
C	-3.08455900	-0.47198900	0.00000000
C	-1.96430100	-1.31691800	0.00000000
C	0.67136600	-1.38686000	0.00000000
C	1.61802700	-0.19654600	0.00000000
C	0.89147600	0.95543000	0.00000000
H	-1.53814300	2.57789200	0.00000000
H	-3.80693200	1.55841500	0.00000000
H	-4.08244100	-0.90084800	0.00000000
H	-2.09423500	-2.39640600	0.00000000
H	0.83220700	-2.02541700	-0.88034100
H	1.29836200	1.96118700	0.00000000
C	3.06583600	-0.37775400	0.00000000
H	3.40179800	-1.41481300	0.00000100
C	4.00502500	0.58501200	0.00000000
H	3.75363700	1.64216300	-0.00000100
H	5.06081900	0.33495300	0.00000000
H	0.83220700	-2.02541700	0.88034100

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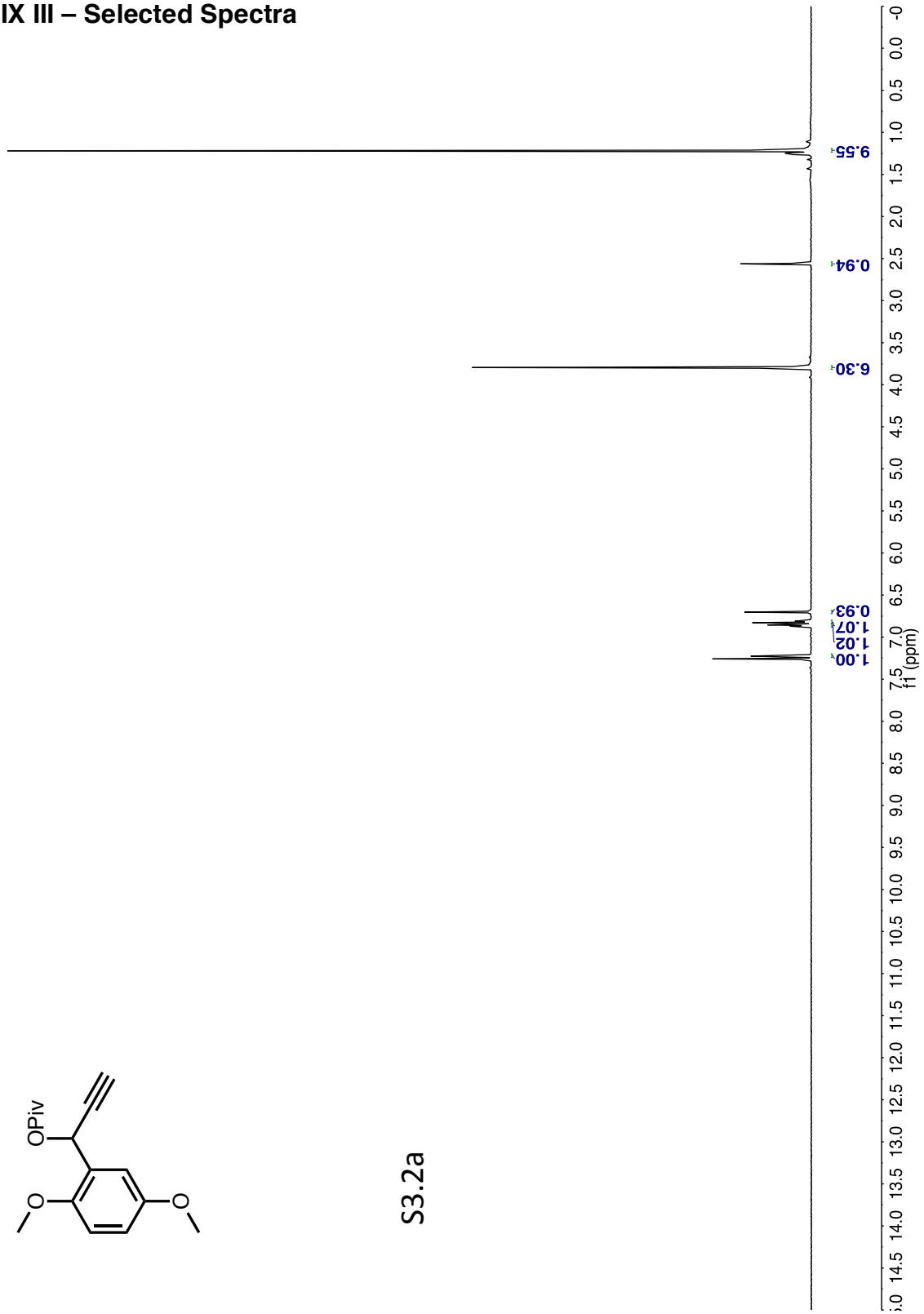
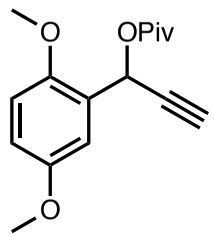
APPENDIX III – Selected Spectra

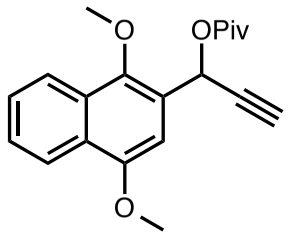


S3.2a

S3.2a

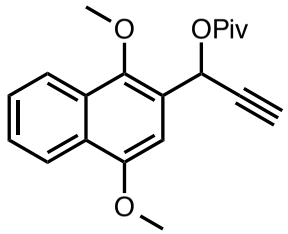

O
OPiv
O

177.10
153.72
151.04
126.22
114.81
114.41
112.06
80.63
77.41
74.54
60.30
56.33
55.95
38.91
27.22
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
f1 (ppm)

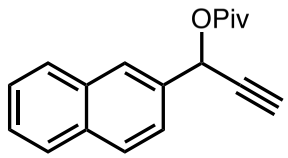


S3.2b

S3.2b


O
OPiv
O

176.97
152.57
147.17
128.45
127.21
127.06
126.40
125.21
122.65
122.61
102.11
81.25
77.41
74.82
63.15
60.44
55.88
38.96
27.23
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
f1 (ppm)



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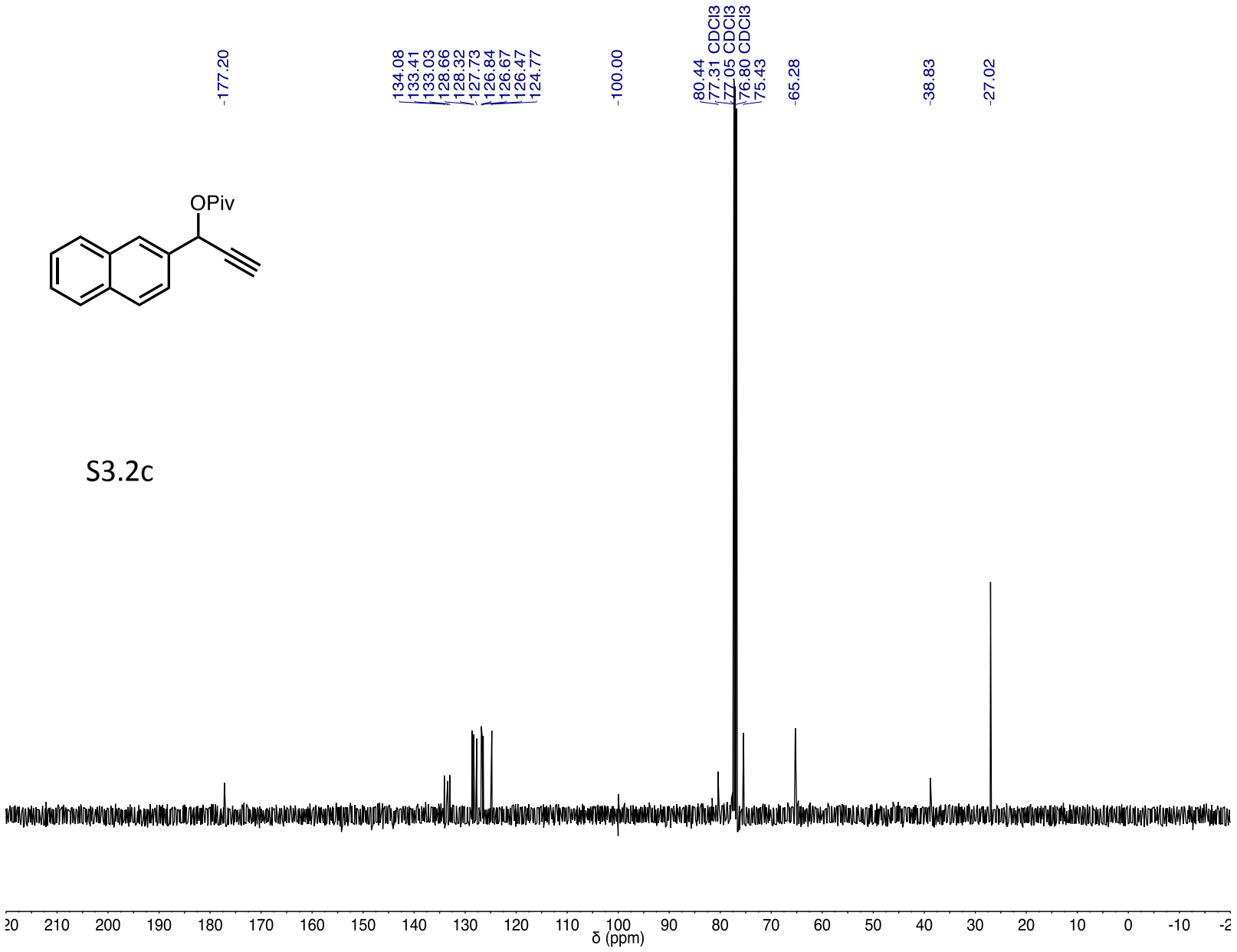
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134.08
133.41
133.03
128.66
128.32
127.73
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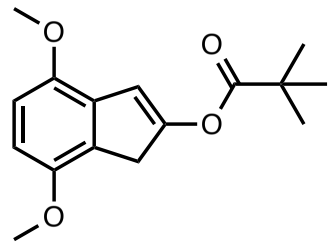
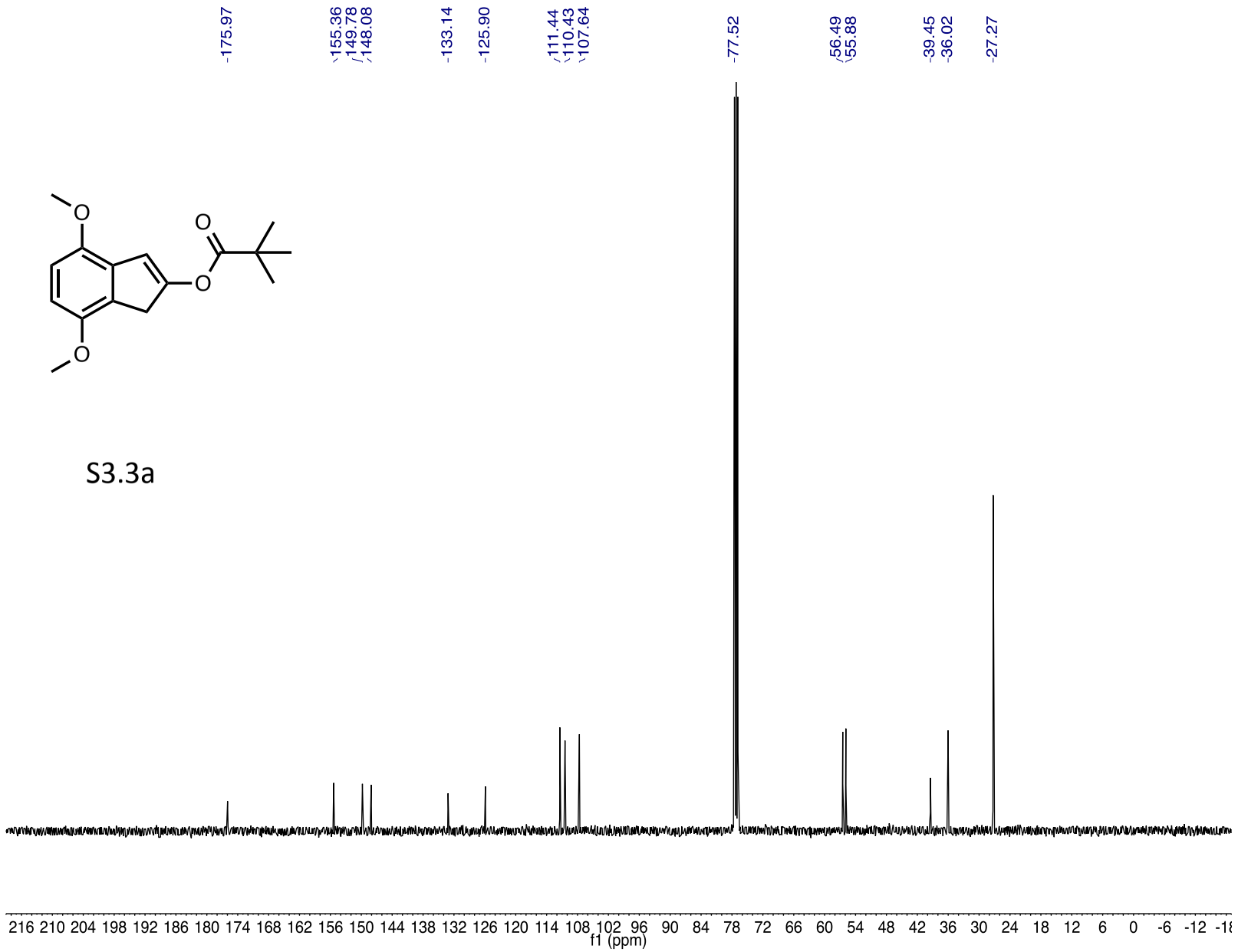
126.67
126.47
124.77
-100.00
80.44
77.31 CDCl3
77.05 CDCl3
76.80 CDCl3
75.43
-65.28
-38.83
-27.02
OPiv
δ (ppm)

S3.2c


O
O
O
O

S3.3a

1.00
0.89
1.00
2.79
2.84
1.84
8.69
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)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155.36
149.78
148.08
133.14
125.90
111.44
110.43
107.64
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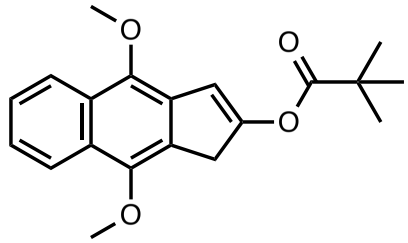
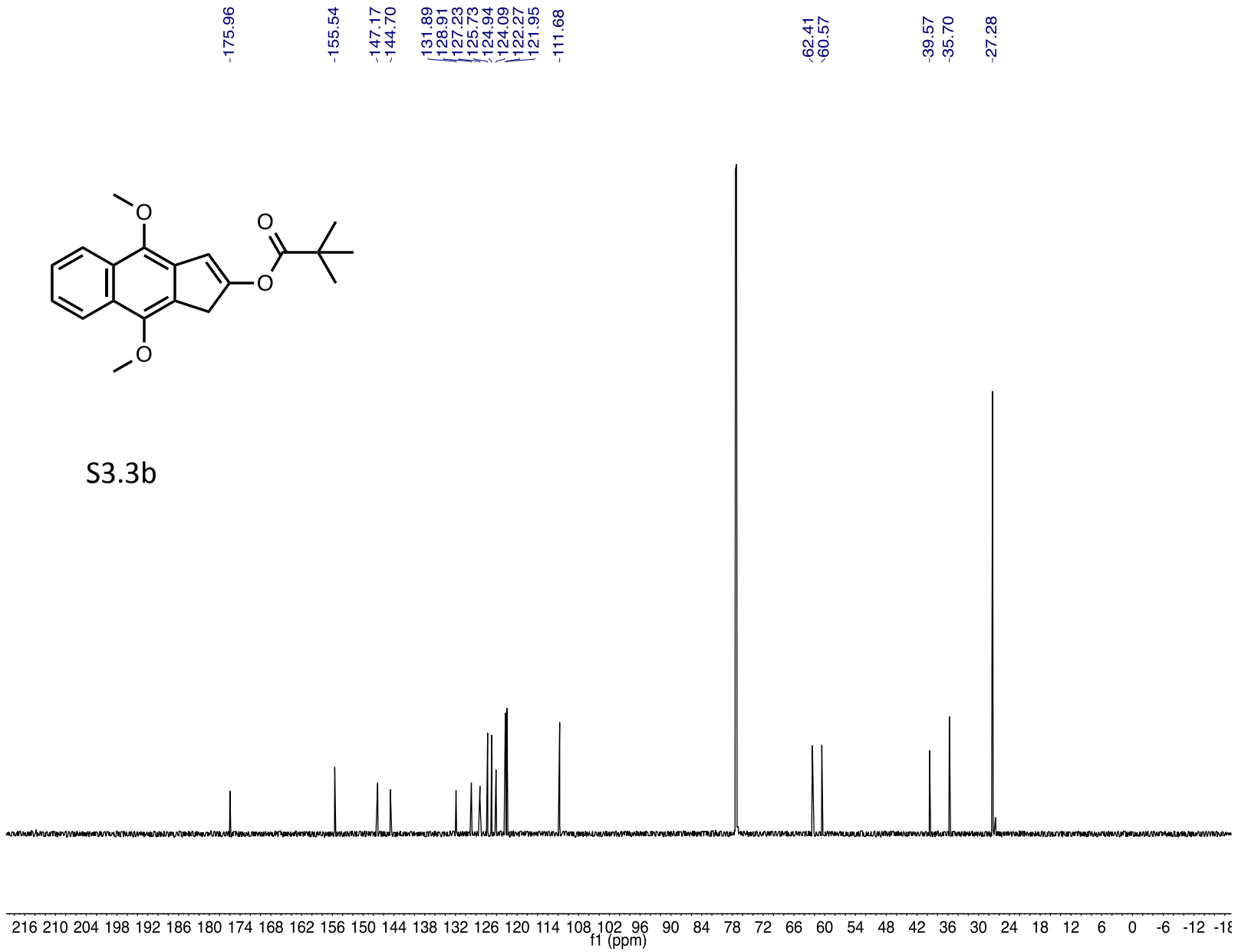
55.88
39.45
36.02
27.27
O
O
O
O
f1 (ppm)

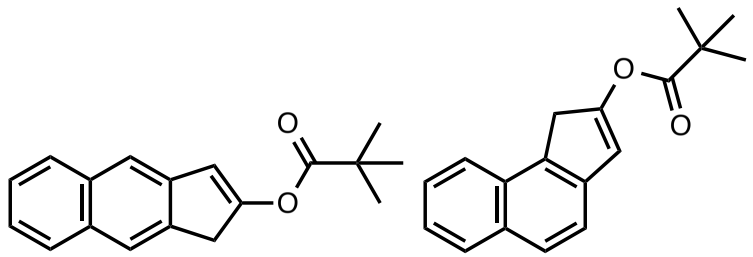
S3.3a


O
O
O
O

S3.3b

2.11
2.25
1.00
3.27
3.24
2.23
9.73
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)


175.96
155.54
147.17
144.70
131.89
128.91
127.23
125.73
124.94
124.09
122.27
121.95
111.68
62.41
60.57
39.57
35.70
27.28
O
O
O
O
S3.3b
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
f1 (ppm)



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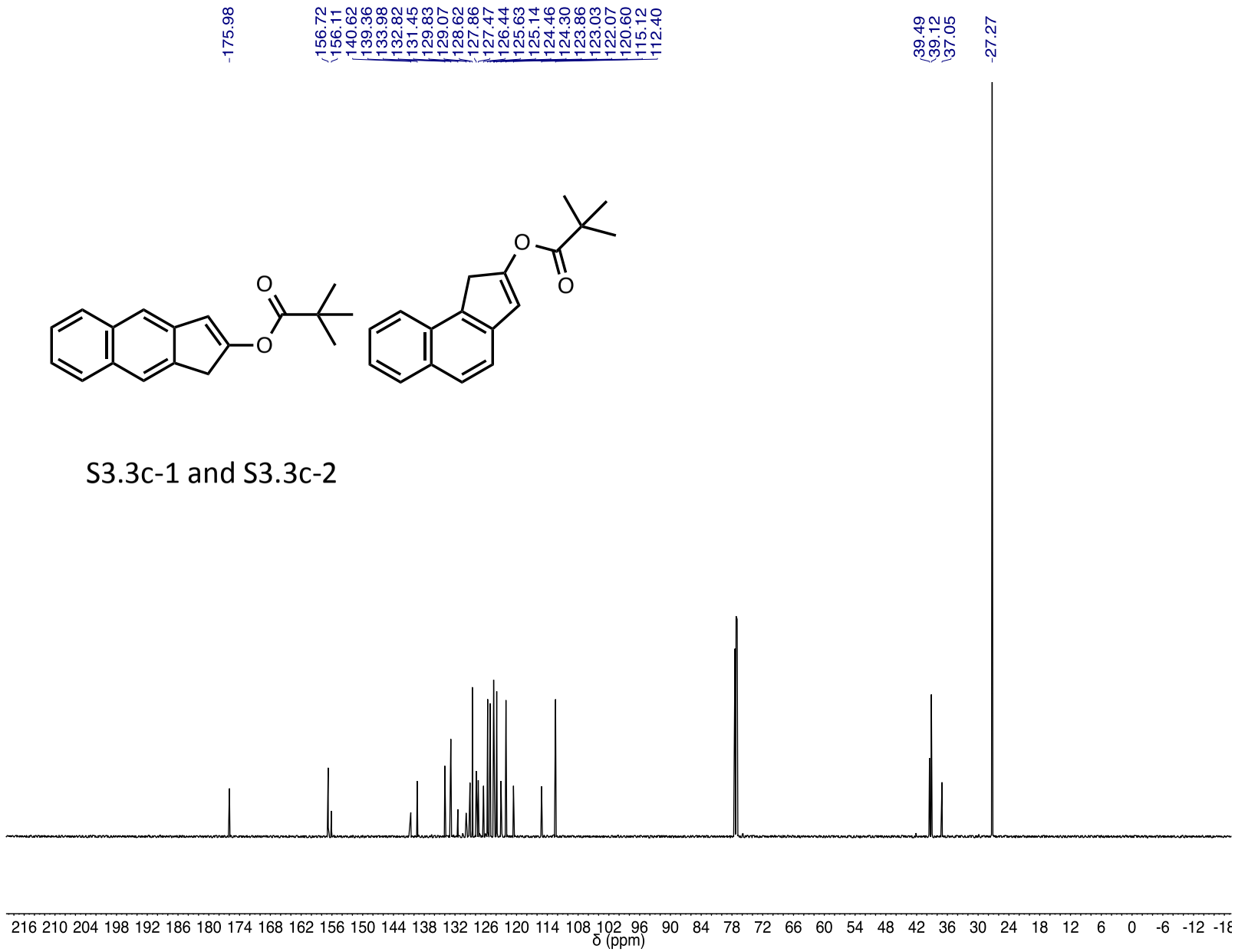
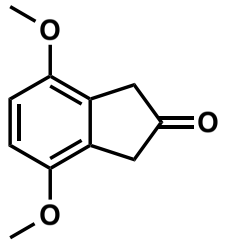
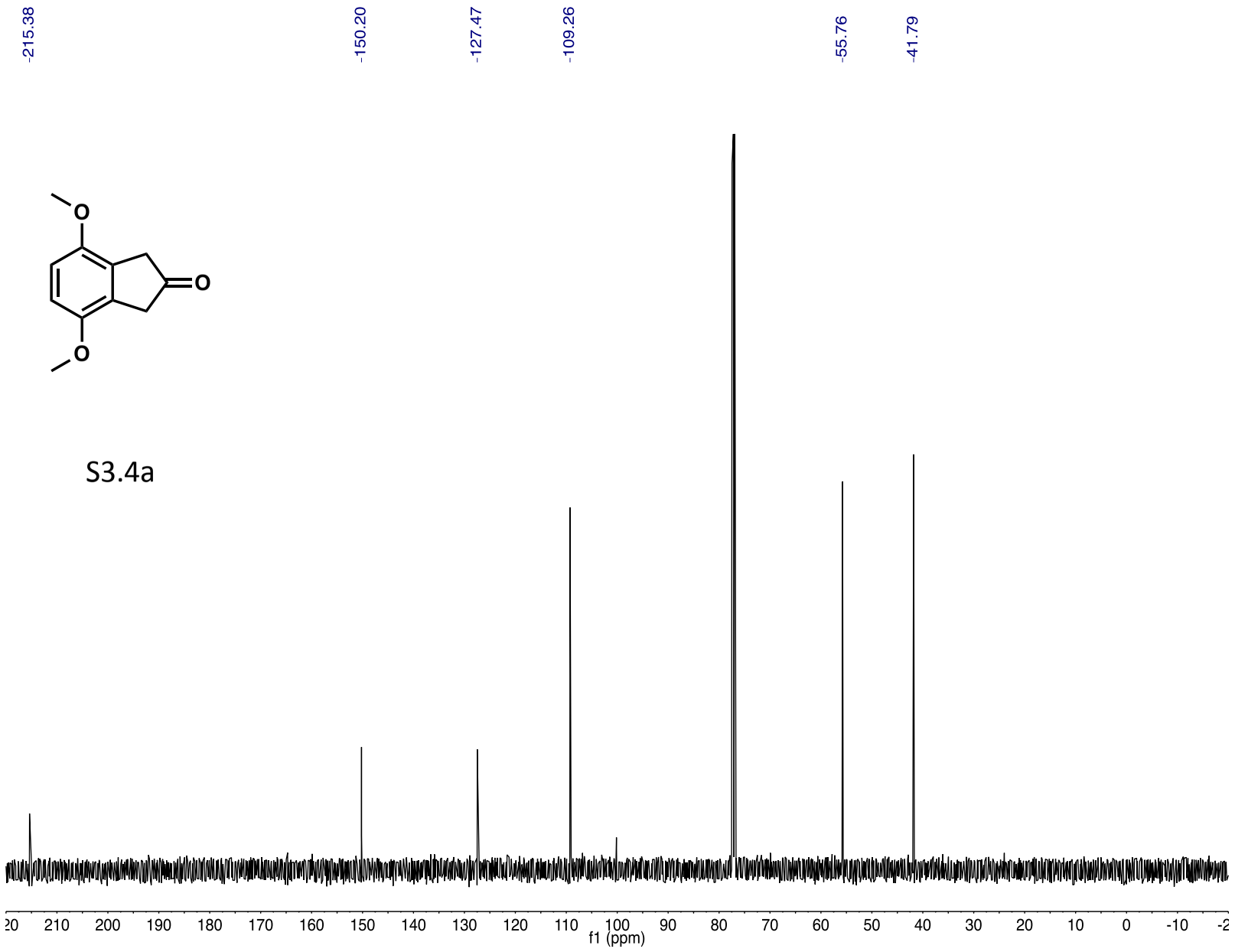


S3.3c-1 and S3.3c-2



S3.4a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-127.47
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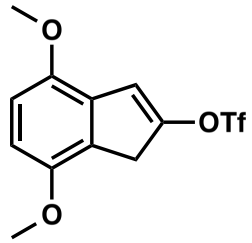
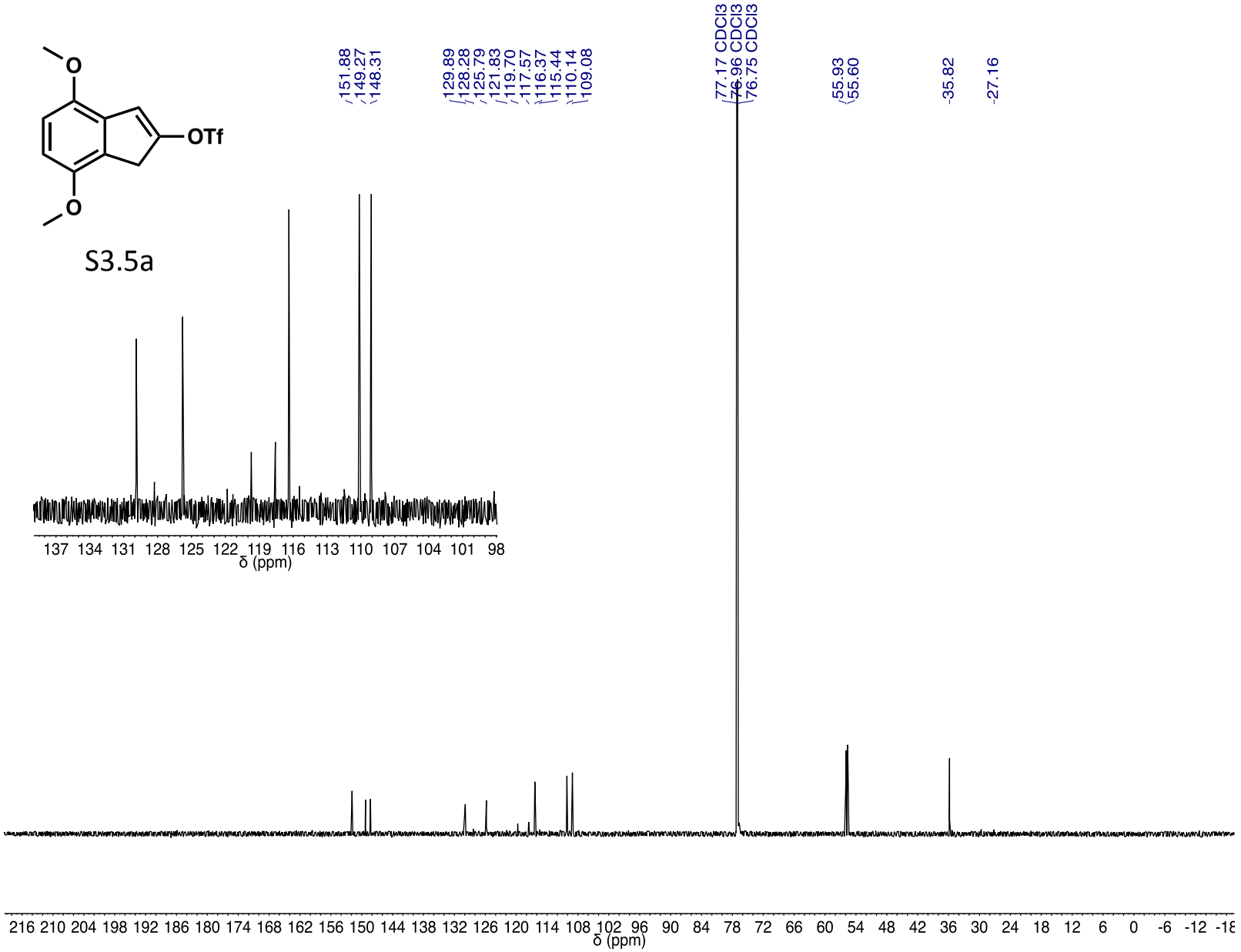
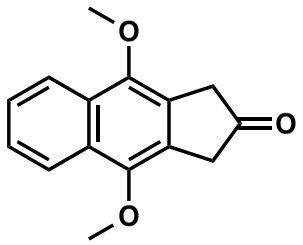
-55.76
-41.79
O
O
O
S3.4a
f1 (ppm)


O
OTf
O

S3.5a

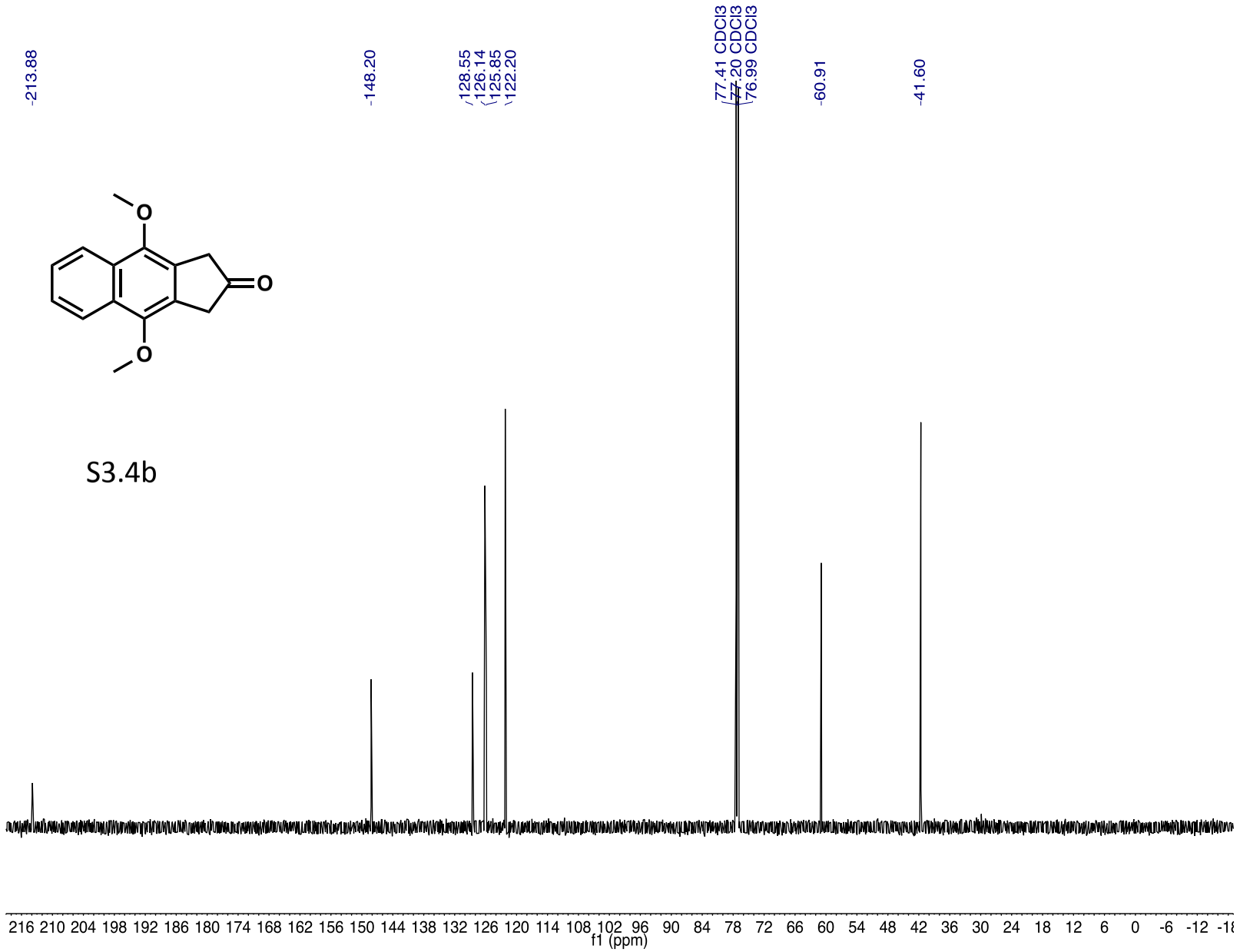
1.00
2.28
6.29
2.32
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)

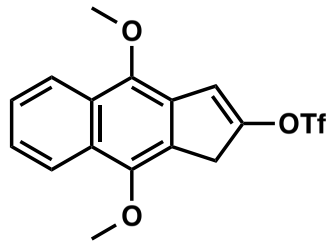

O
OTf
O
S3.5a
151.88
149.27
148.31
129.89
128.28
125.79
121.83
119.70
117.57
116.37
115.44
110.14
109.08
77.17 CDCl3
76.96 CDCl3
76.75 CDCl3
55.93
55.60
35.82
27.16
137 134 131 128 125 122 119 116 113 110 107 104 101 98
δ (ppm)
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


O
O
O

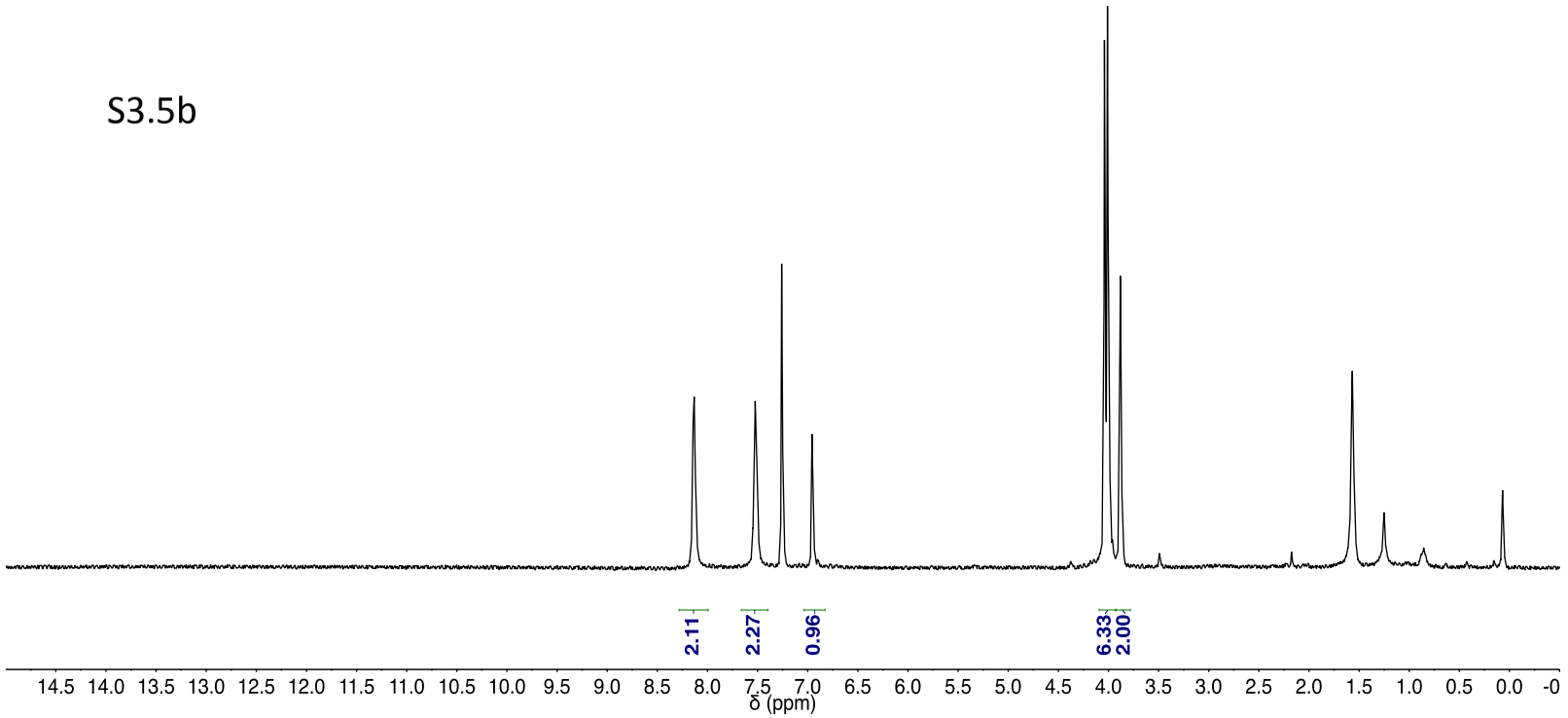
S3.4b

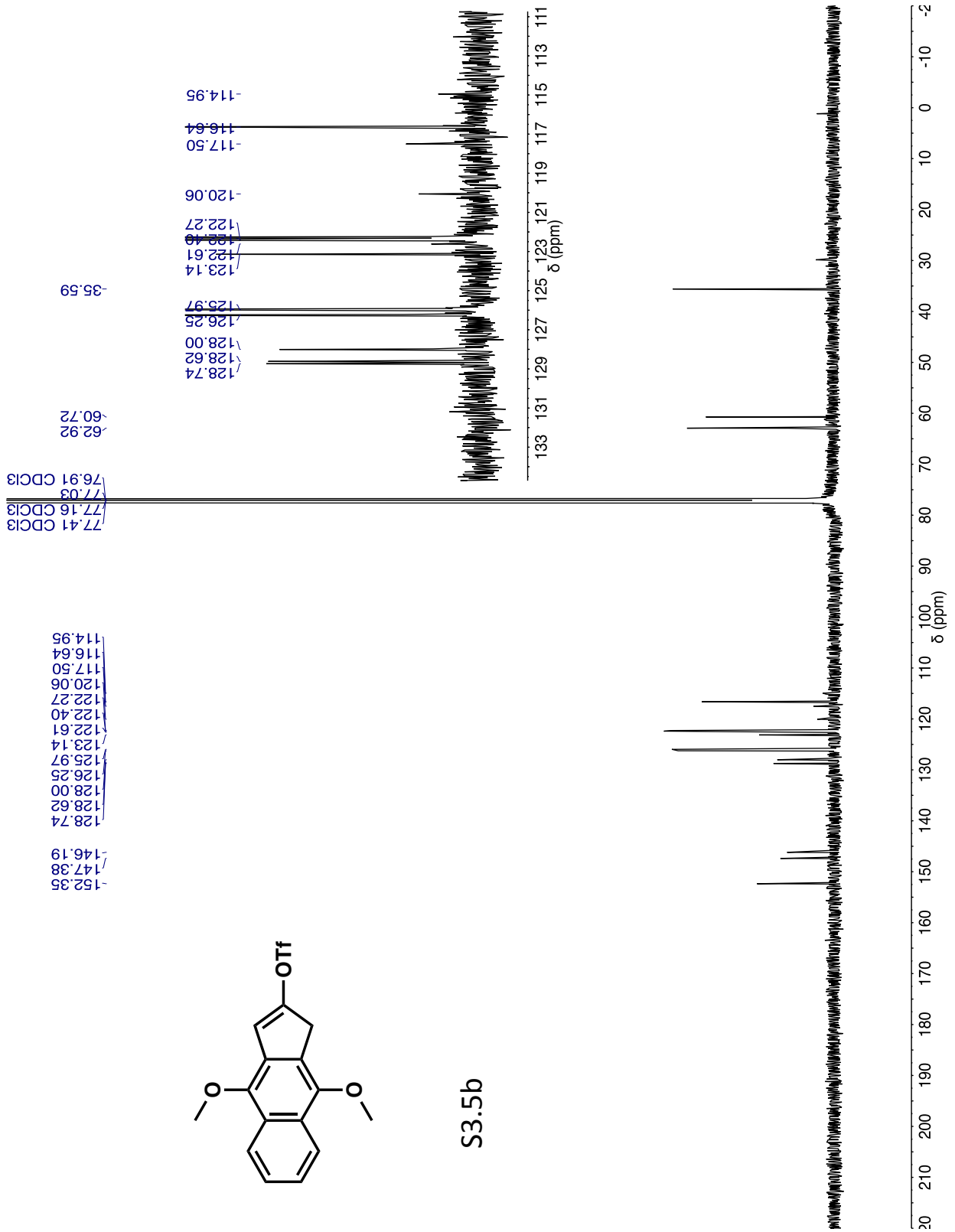
2.00
2.05
5.99
4.16
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

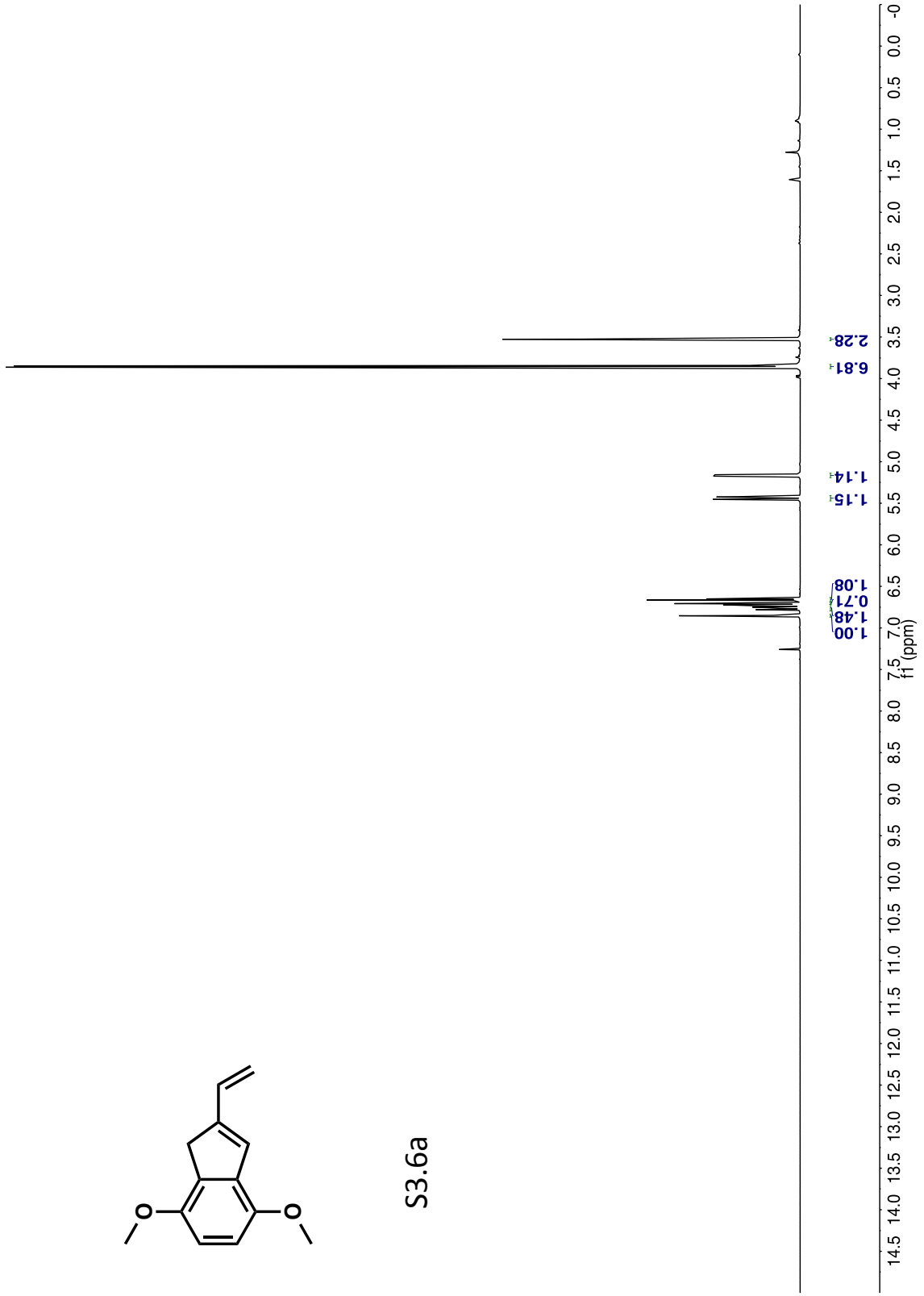

-213.88
-148.20
128.55
126.14
125.85
122.20
77.41 CDCl3
77.20 CDCl3
76.99 CDCl3
-60.91
-41.60
O
O
O
S3.4b
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
f1 (ppm)


O
OTf
O

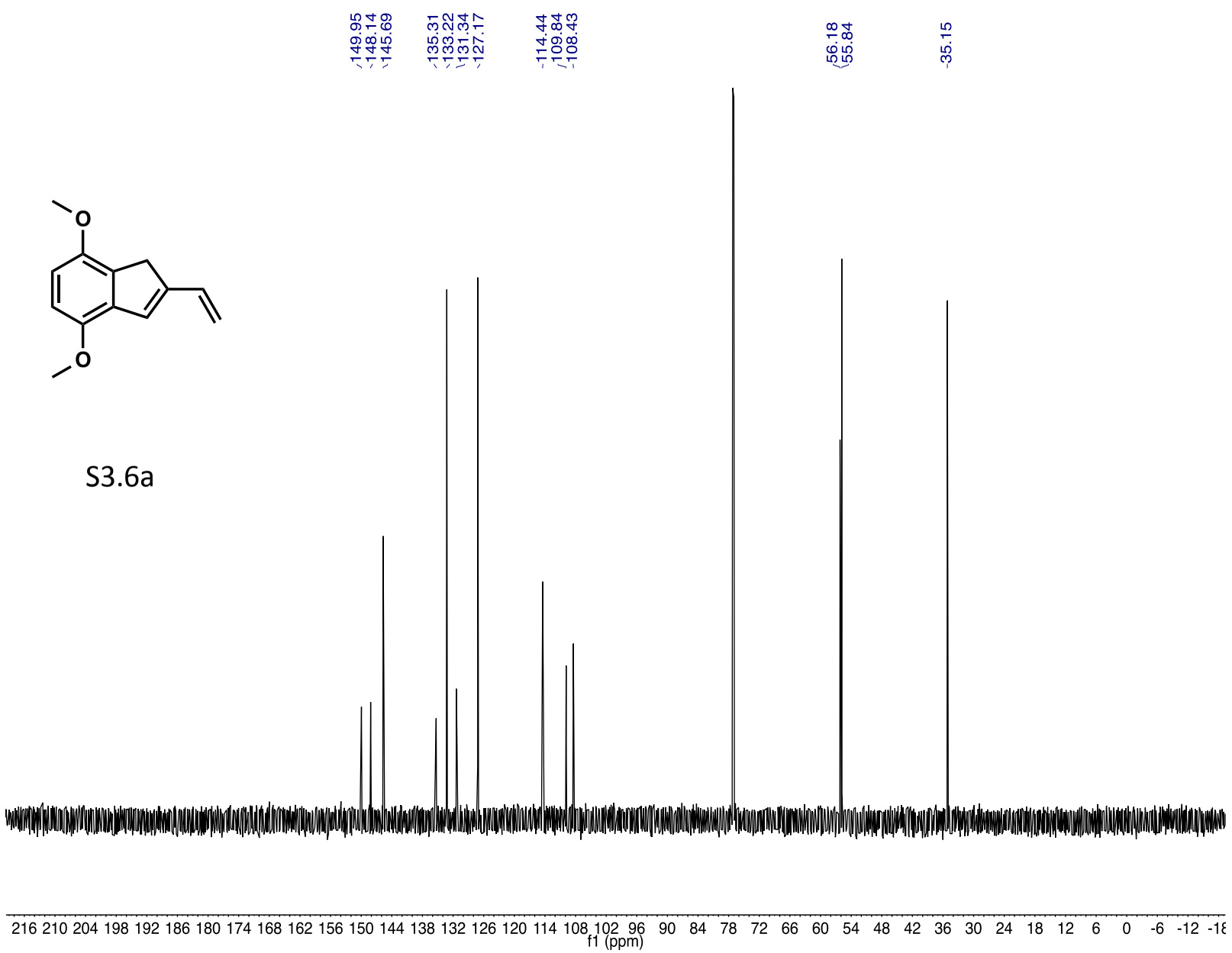
S3.5b

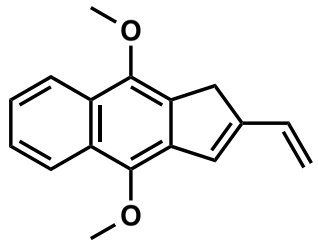

2.11
2.27
0.96
6.33
2.00
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)


OTf
O
O
S3.5b
δ (ppm)
δ (ppm)
152.35
147.38
146.19
128.74
128.62
128.00
126.25
125.97
123.14
122.61
122.40
122.27
120.06
117.50
116.64
114.95
77.41 CDCl3
77.16 CDCl3
77.03
76.91 CDCl3
62.92
60.72
35.59



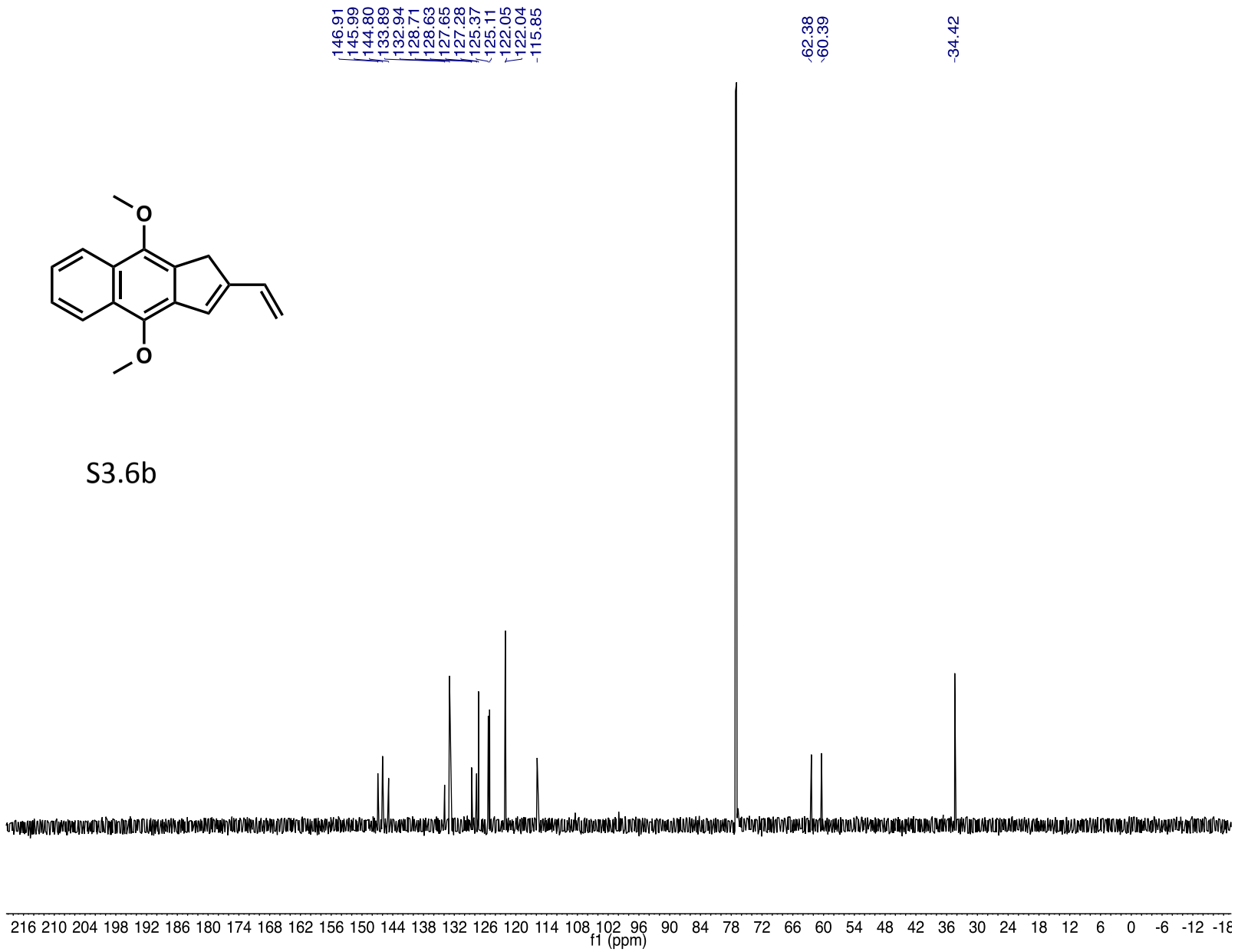
S3.6a

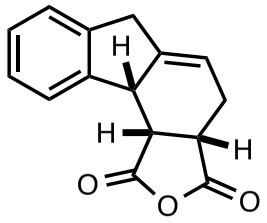

149.95
148.14
145.69
135.31
133.22
131.34
127.17
114.44
109.84
108.43
56.18
55.84
35.15
O
O
S3.6a
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)



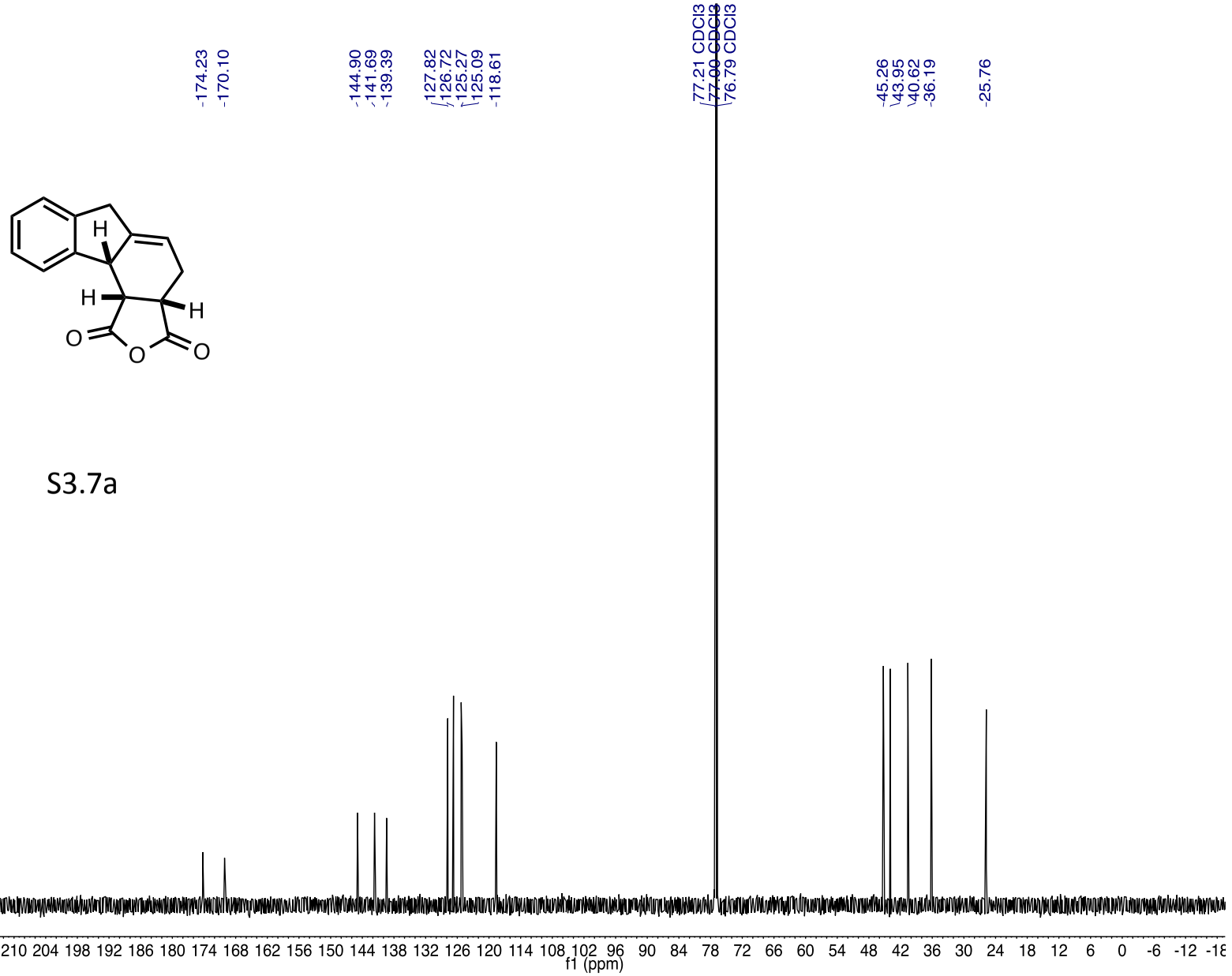
S3.6b

2.04
2.11
1.00
1.04
1.11
1.10
3.14
3.16
2.20
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

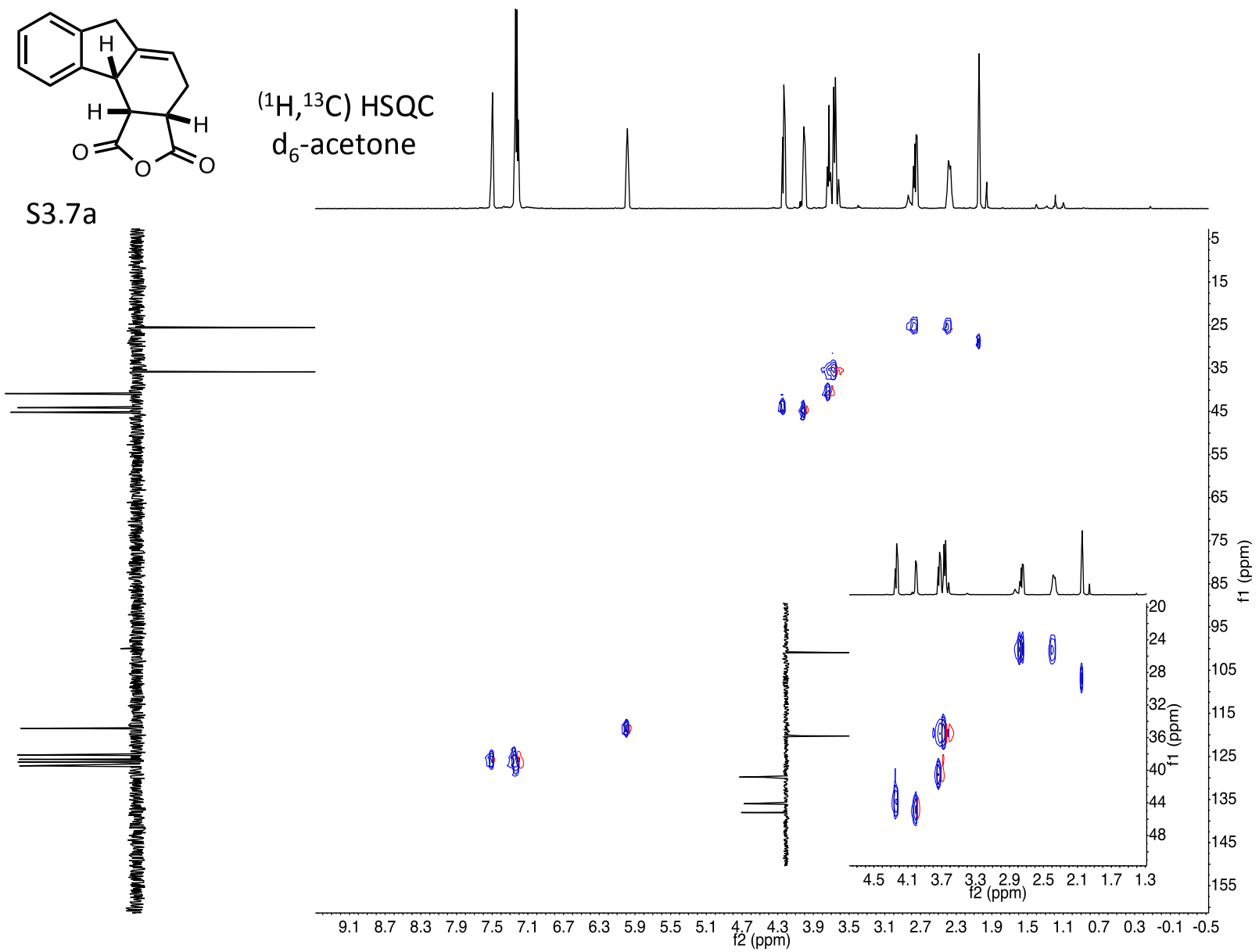

146.91
145.99
144.80
133.89
132.94
128.71
128.63
127.65
127.28
125.37
125.11
122.05
122.04
115.85
62.38
60.39
34.42
O
O
S3.6b
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)

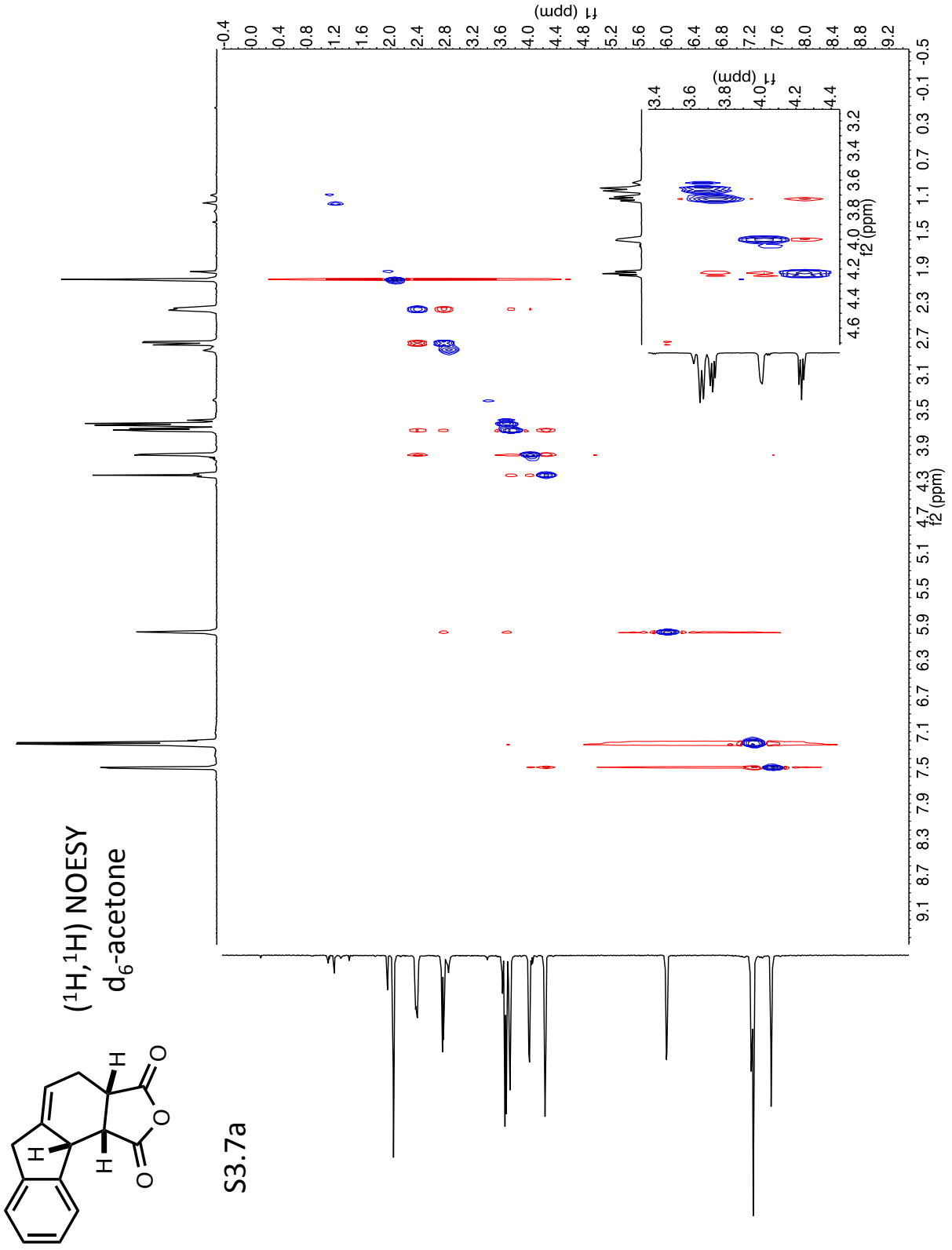


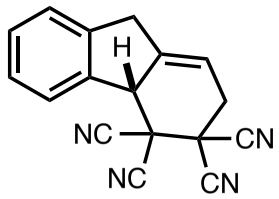
S3.7a


-174.23
-170.10
-144.90
-141.69
-139.39
-127.82
-126.72
-125.27
-125.09
-118.61
-77.21 CDCl3
-77.00 CDCl3
-76.79 CDCl3
-45.26
-43.95
-40.62
-36.19
-25.76
H
H
H
O
O
O
f1 (ppm)

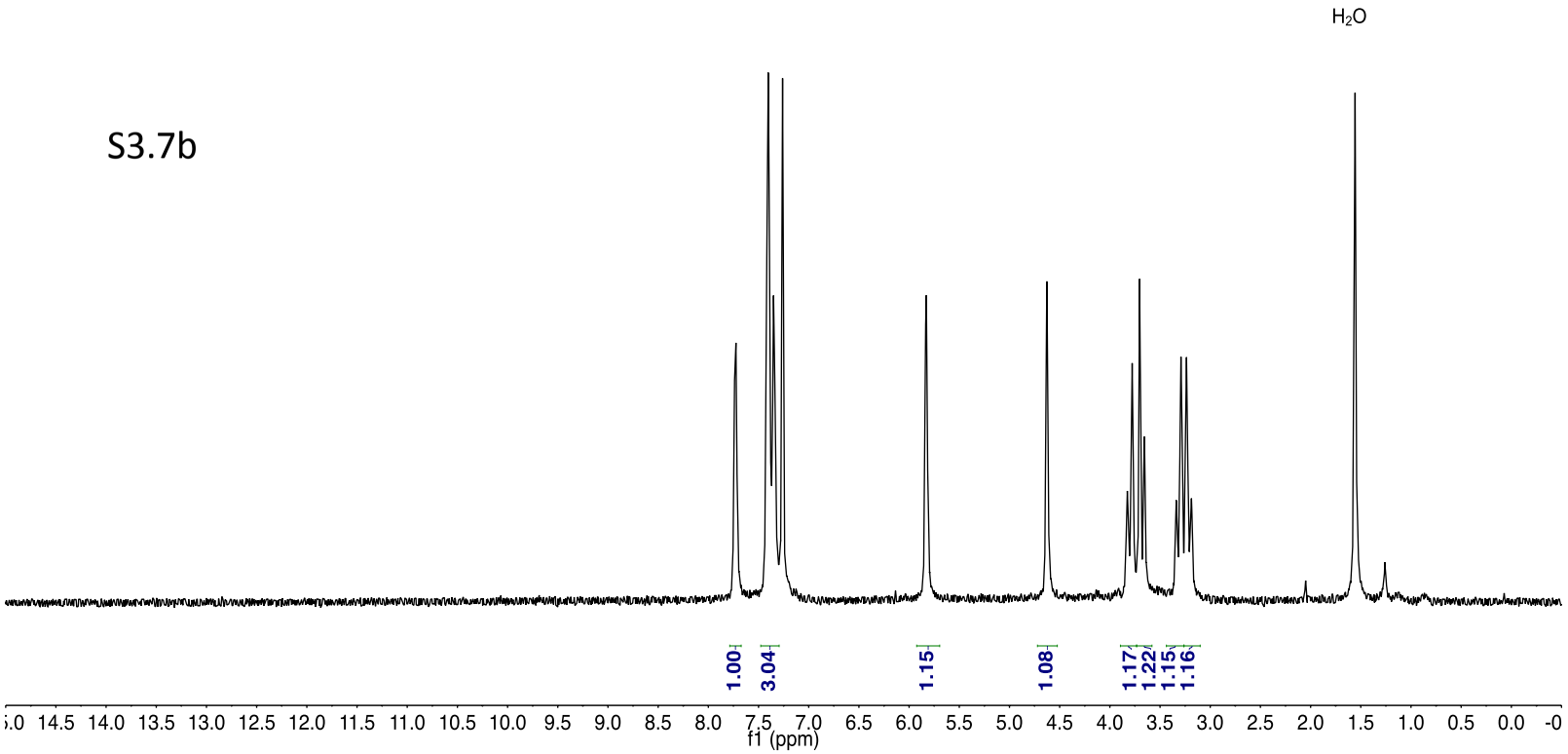
S3.7a

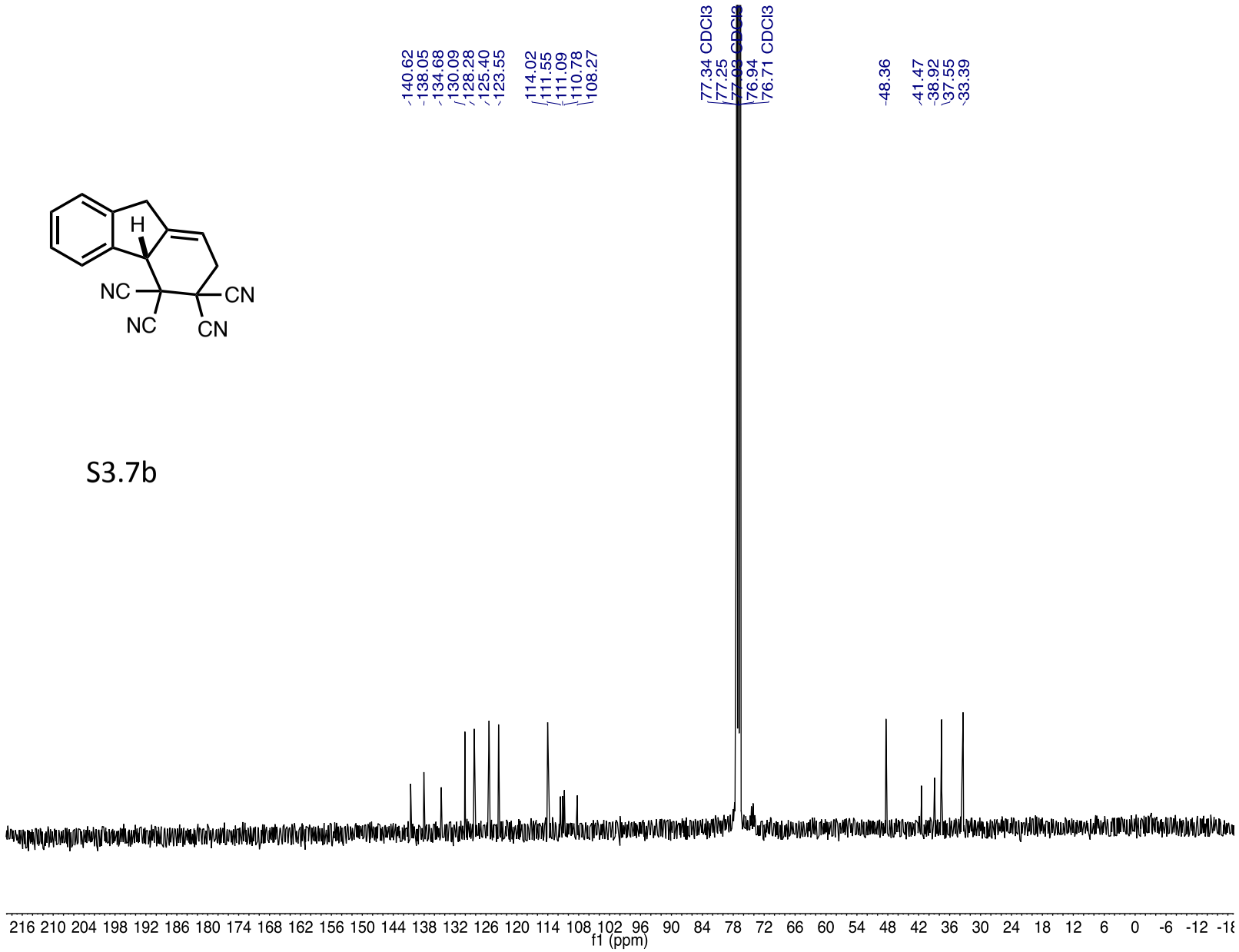

H
H
H
O
O
O
S3.7a
(1H,13C) HSQC
d6-acetone
f2 (ppm)
f1 (ppm)


(1H,1H) NOESY
d6-acetone
S3.7a
f1 (ppm)
f2 (ppm)

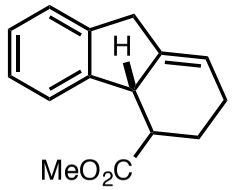


S3.7b



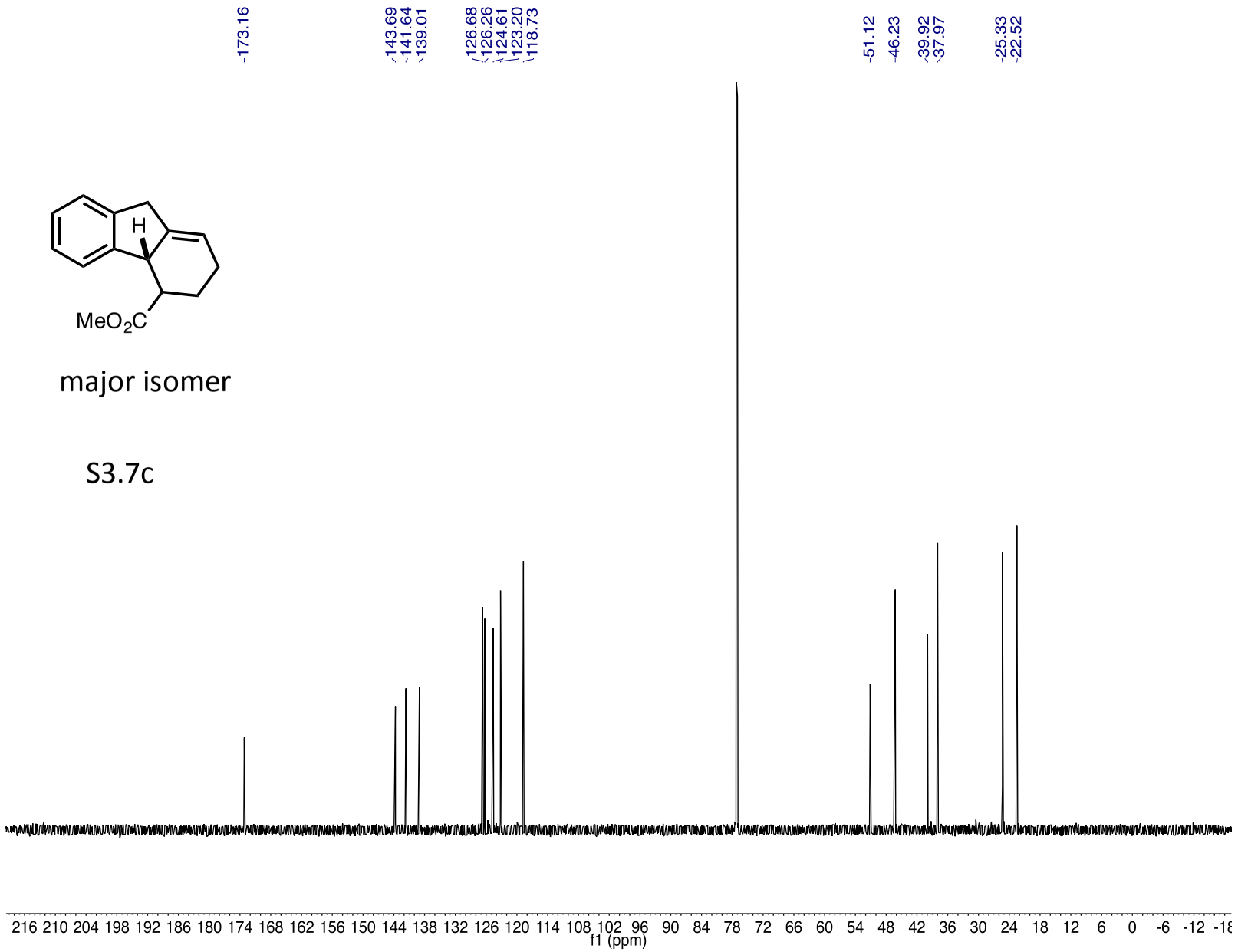

140.62
138.05
134.68
130.09
128.28
125.40
123.55
114.02
111.55
111.09
110.78
108.27
77.34 CDCl3
77.25
77.09 CDCl3
76.94
76.71 CDCl3
48.36
41.47
38.92
37.55
33.39
H
NC
CN
NC
CN
f1 (ppm)

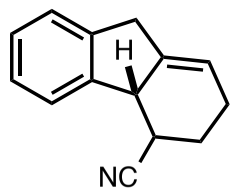
S3.7b



major isomer

S3.7c

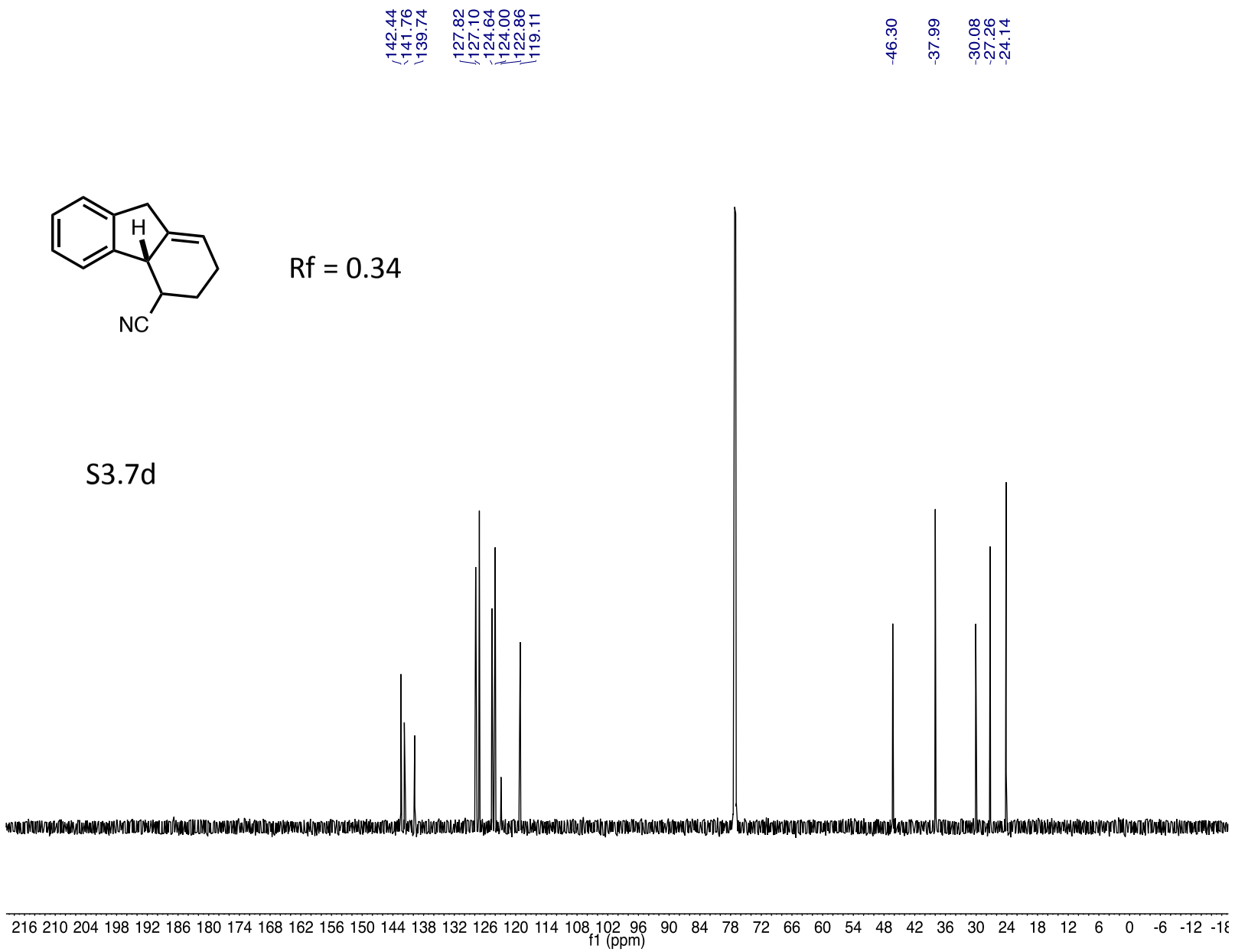

173.16
143.69
141.64
139.01
126.68
126.26
124.61
123.20
118.73
51.12
46.23
39.92
37.97
25.33
22.52
H
MeO2C
major isomer
S3.7c
f1 (ppm)

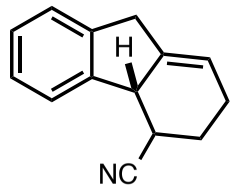

H
NC

Rf = 0.34

S3.7d

1.00
3.26
1.00
1.05
1.19
1.22
1.07
2.21
1.30
1.18
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

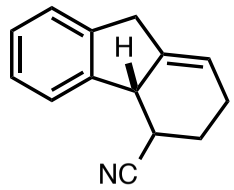

142.44
141.76
139.74
127.82
127.10
124.64
124.00
122.86
119.11
-46.30
-37.99
-30.08
-27.26
-24.14
H
NC
Rf = 0.34
S3.7d
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)


H
NC

Rf = 0.14

S3.7d

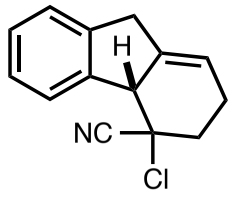
4.35
1.00
1.01
1.11
1.06
1.08
1.15
2.20
1.10
0.33
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


H
NC

Rf = 0.14

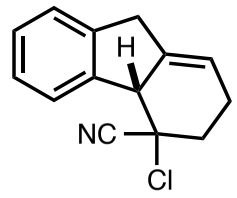
S3.7d

141.98
141.32
138.38
127.88
127.00
124.92
123.37
119.64
119.52
46.11
38.11
28.68
25.16
21.93
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)

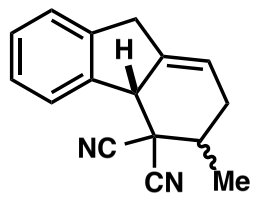


S3.7e

S3.7e

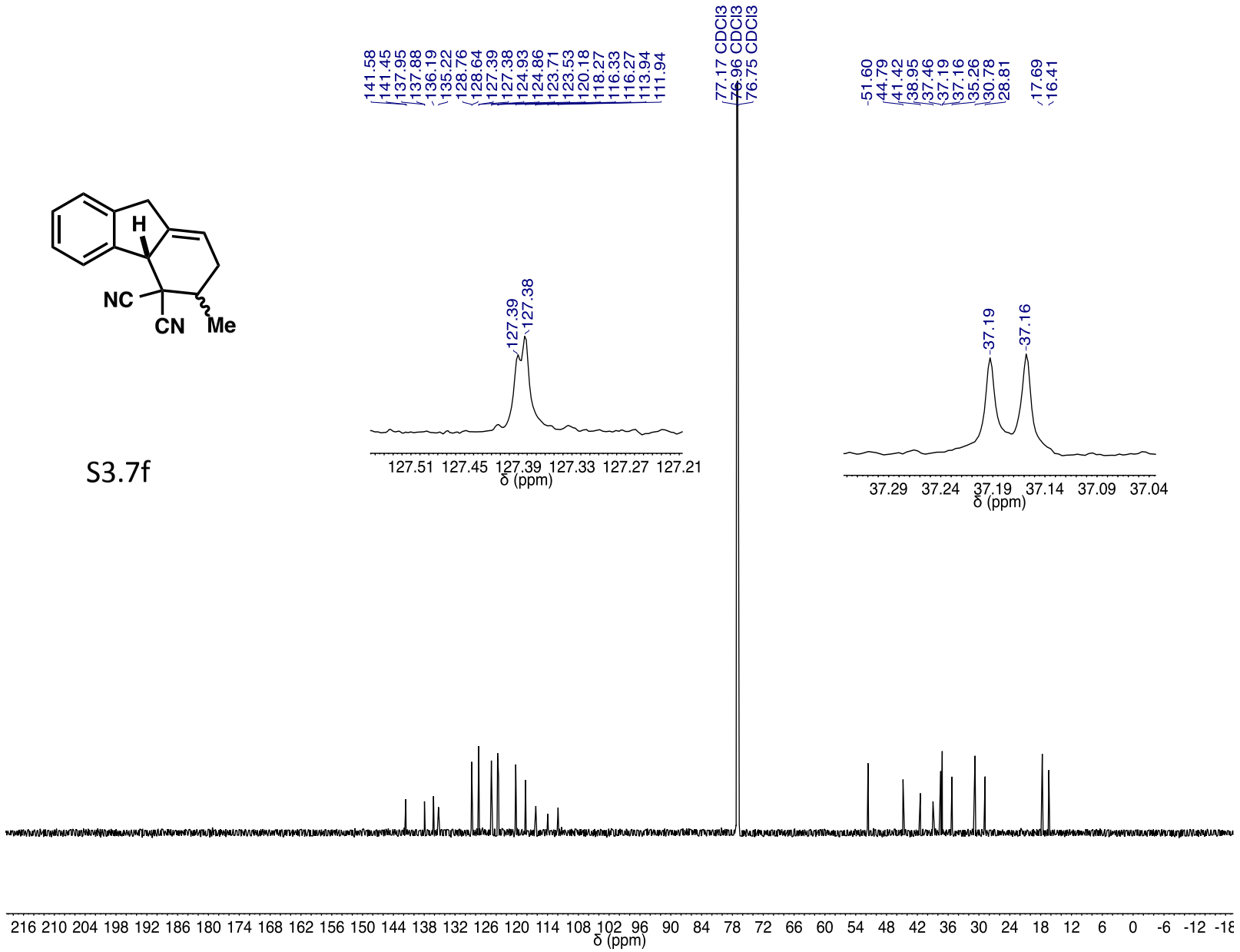

H
NC
Cl

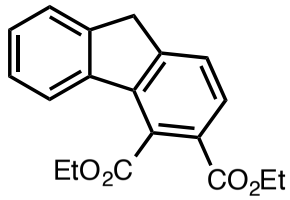
141.53
141.40
139.18
138.77
137.78
134.91
128.36
128.29
128.17
126.95
126.90
125.01
124.58
124.37
120.26
119.41
118.62
116.76
77.18 CDCl3
76.97 CDCl3
76.76 CDCl3
59.01
55.48
55.30
52.37
38.42
37.61
37.23
35.26
24.68
21.22
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)


H
NC
CN
Me

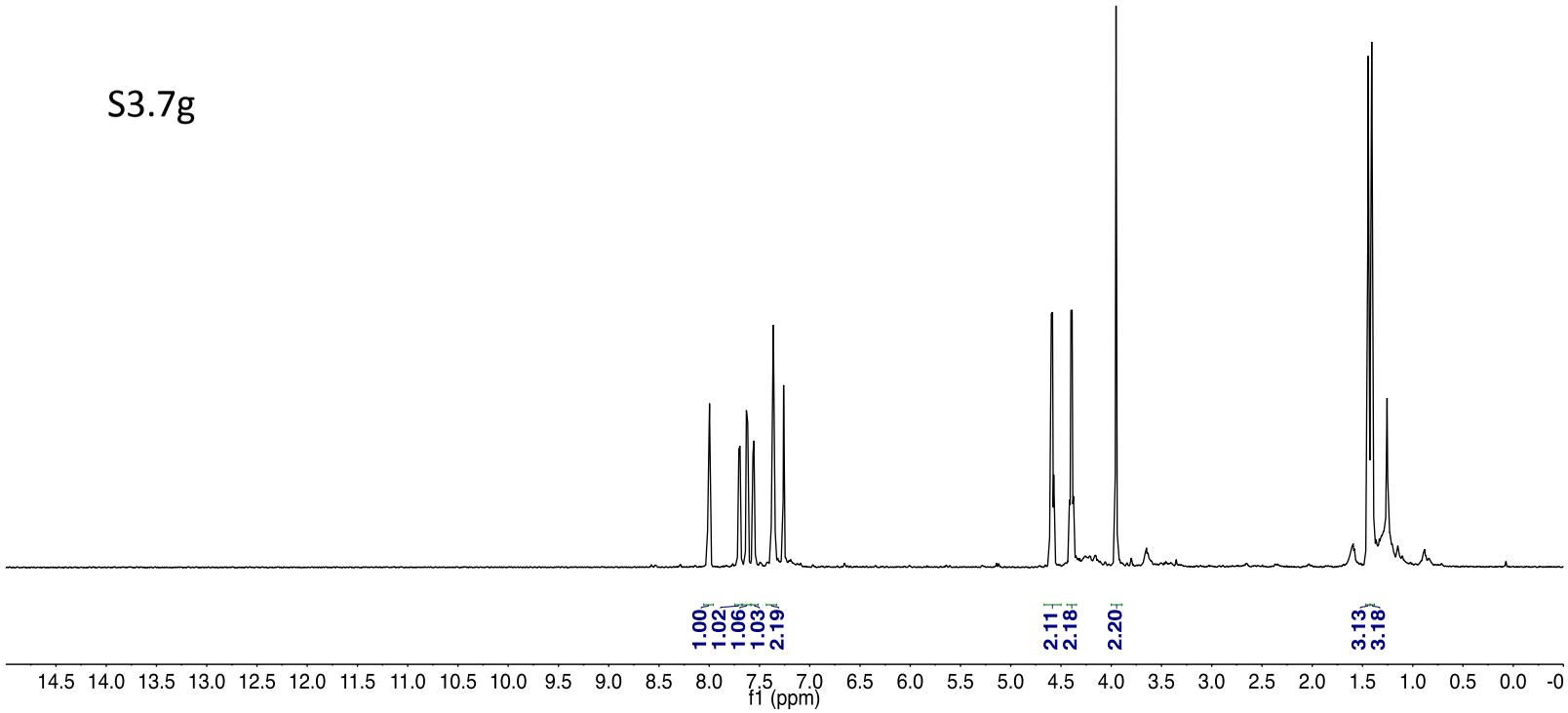
S3.7f

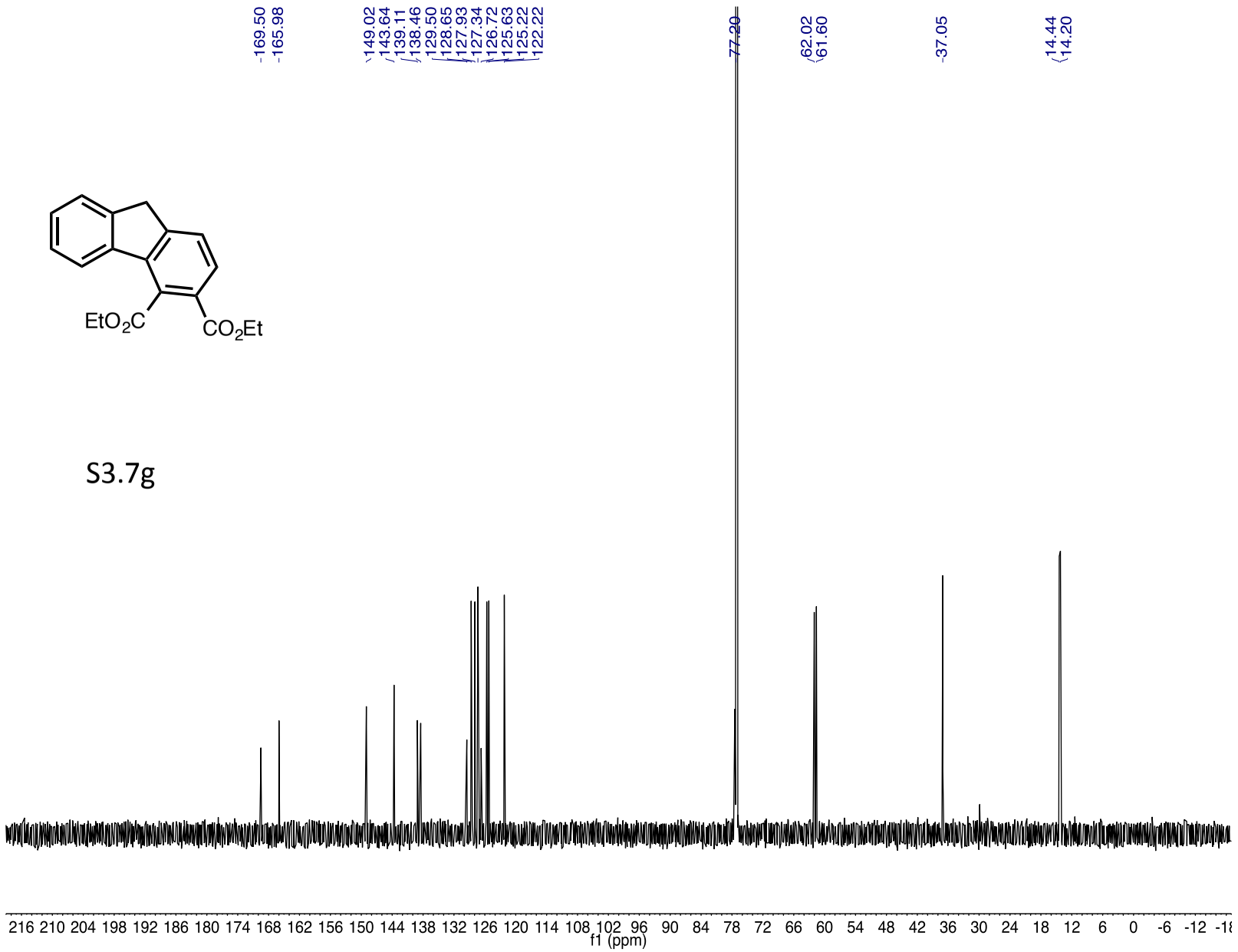
1.41
1.09
7.46
1.42
1.00
1.27
1.02
2.80
2.85
2.18
2.99
2.62
4.22
3.26
δ (ppm)


S3.7f
H
NC
CN
Me
141.58
141.45
137.95
137.88
136.19
135.22
128.76
128.64
127.39
127.38
124.93
124.86
123.71
123.53
120.18
118.27
116.33
116.27
113.94
111.94
77.17 CDCl3
76.96 CDCl3
76.75 CDCl3
51.60
44.79
41.42
38.95
37.46
37.19
37.16
35.26
30.78
28.81
17.69
16.41
127.39
127.38
127.51 127.45 127.39 127.33 127.27 127.21
δ (ppm)
37.19
37.16
37.29 37.24 37.19 37.14 37.09 37.04
δ (ppm)
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

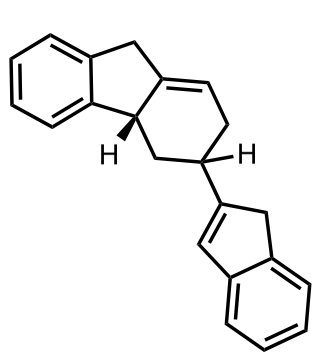

EtO2C
CO2Et

S3.7g


1.00
1.02
1.06
1.03
2.19
2.11
2.18
2.20
3.13
3.18
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

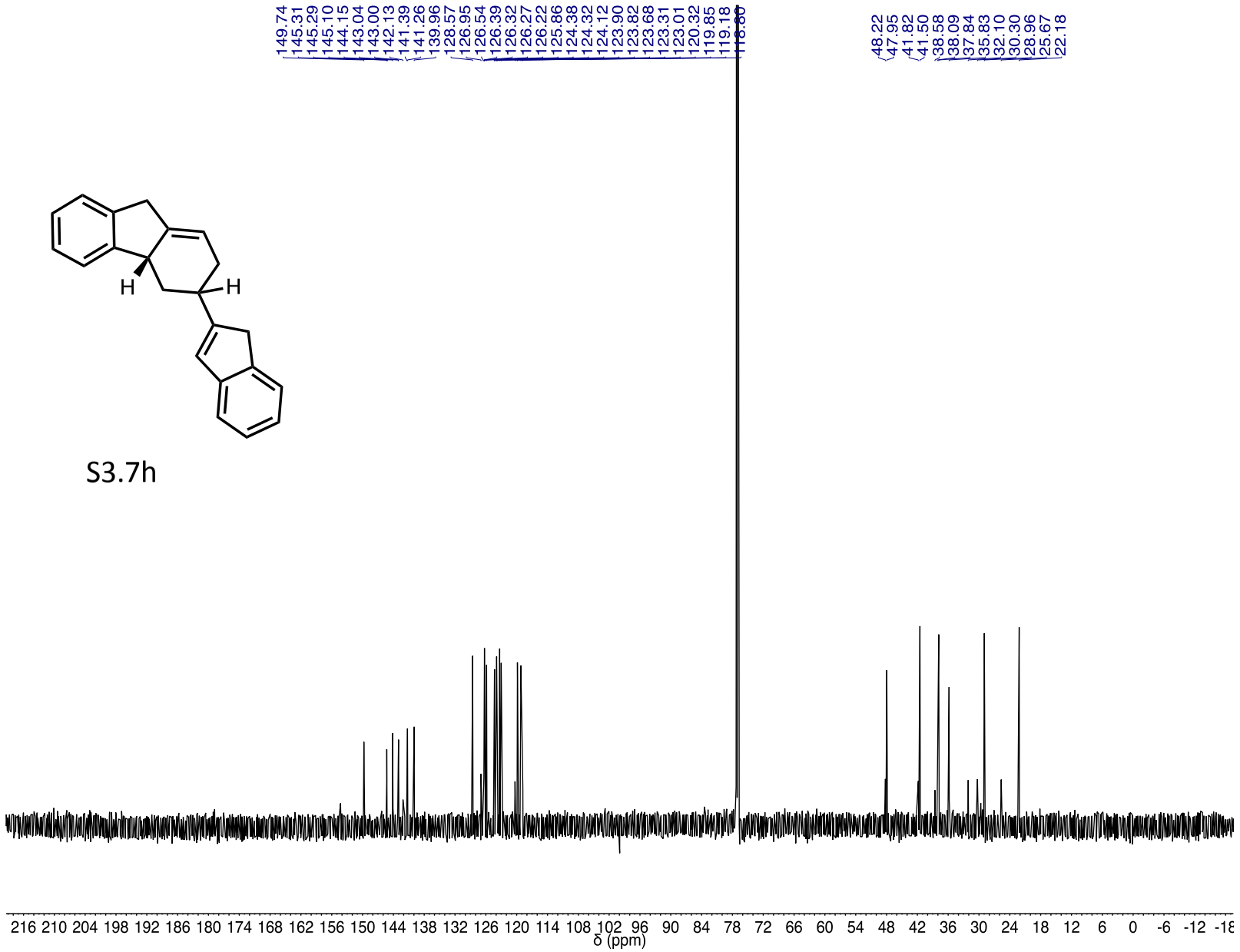

-169.50
-165.98
149.02
143.64
139.11
138.46
129.50
128.65
127.93
127.34
126.72
125.63
125.22
122.22
77.20
62.02
61.60
37.05
14.44
14.20
EtO2C
CO2Et
f1 (ppm)

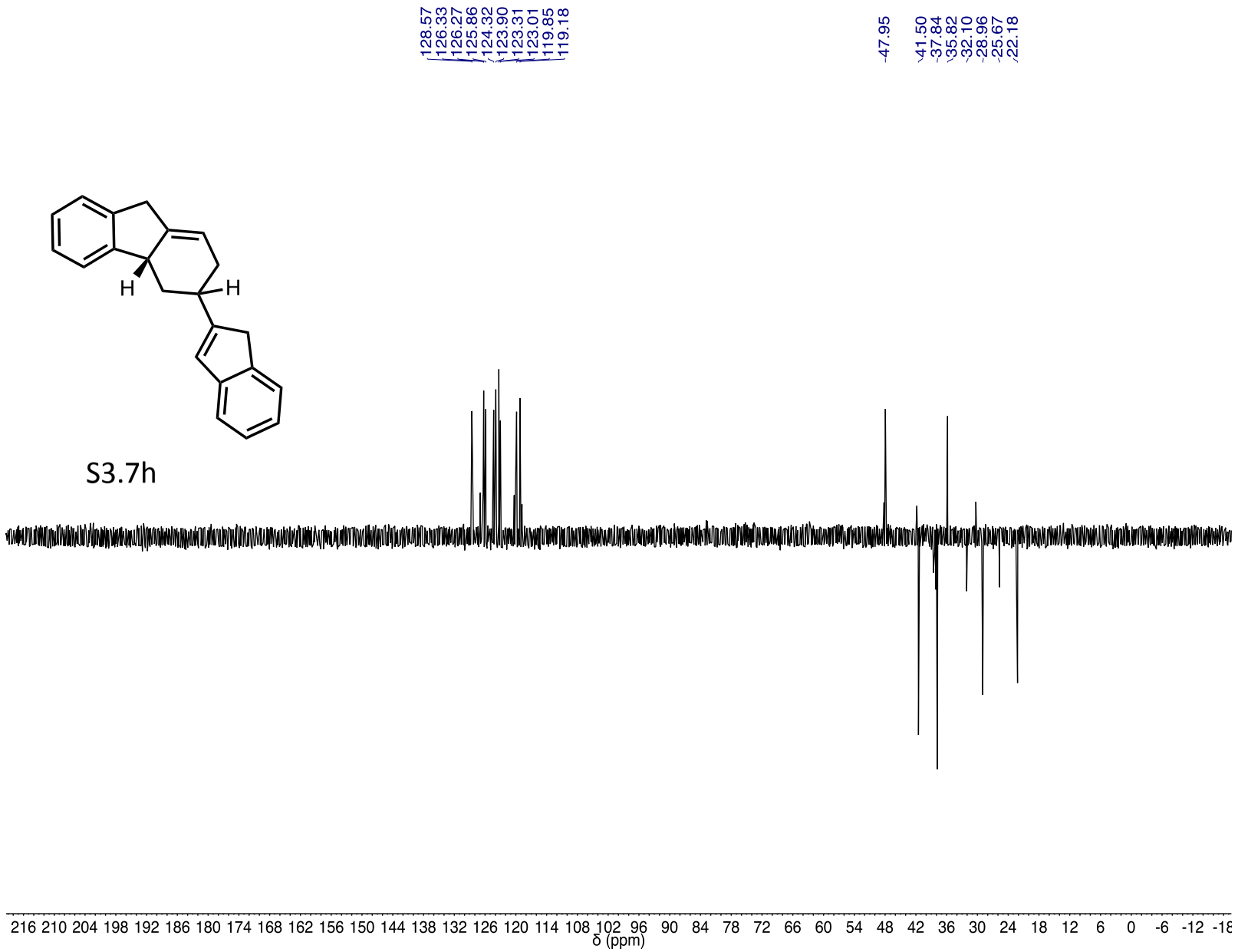
S3.7g

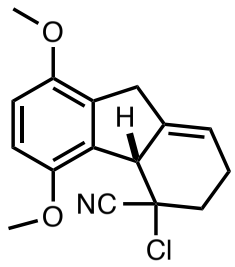

H
H

S3.7h

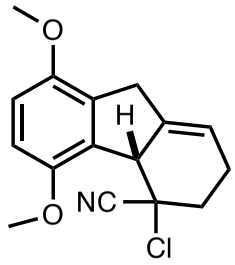
0.28
0.33
0.38
2.40
0.54
7.27
0.28
1.00
1.30
1.01
2.71
2.18
1.09
1.14
0.25
0.68
4.56
0.39
0.34
15.5
14.5
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
-2.5
δ (ppm)


149.74
145.31
145.29
145.10
144.15
143.04
143.00
142.13
141.39
141.26
139.96
128.57
126.95
126.54
126.39
126.32
126.27
126.22
125.86
124.38
124.32
124.12
123.90
123.82
123.68
123.31
123.01
120.32
119.85
119.18
48.22
47.95
41.82
41.50
38.58
38.09
37.84
35.83
32.10
30.30
28.96
25.67
22.18
H
H
S3.7h
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


128.57
126.33
126.27
125.86
124.32
123.90
123.31
123.01
119.85
119.18
47.95
41.50
37.84
35.82
32.10
28.96
25.67
22.18
H
H
S3.7h
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

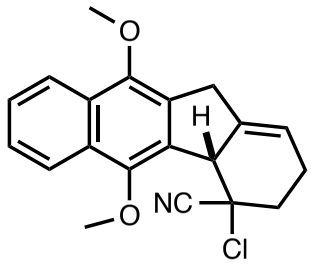


S3.7i


O
H
NC
O
Cl

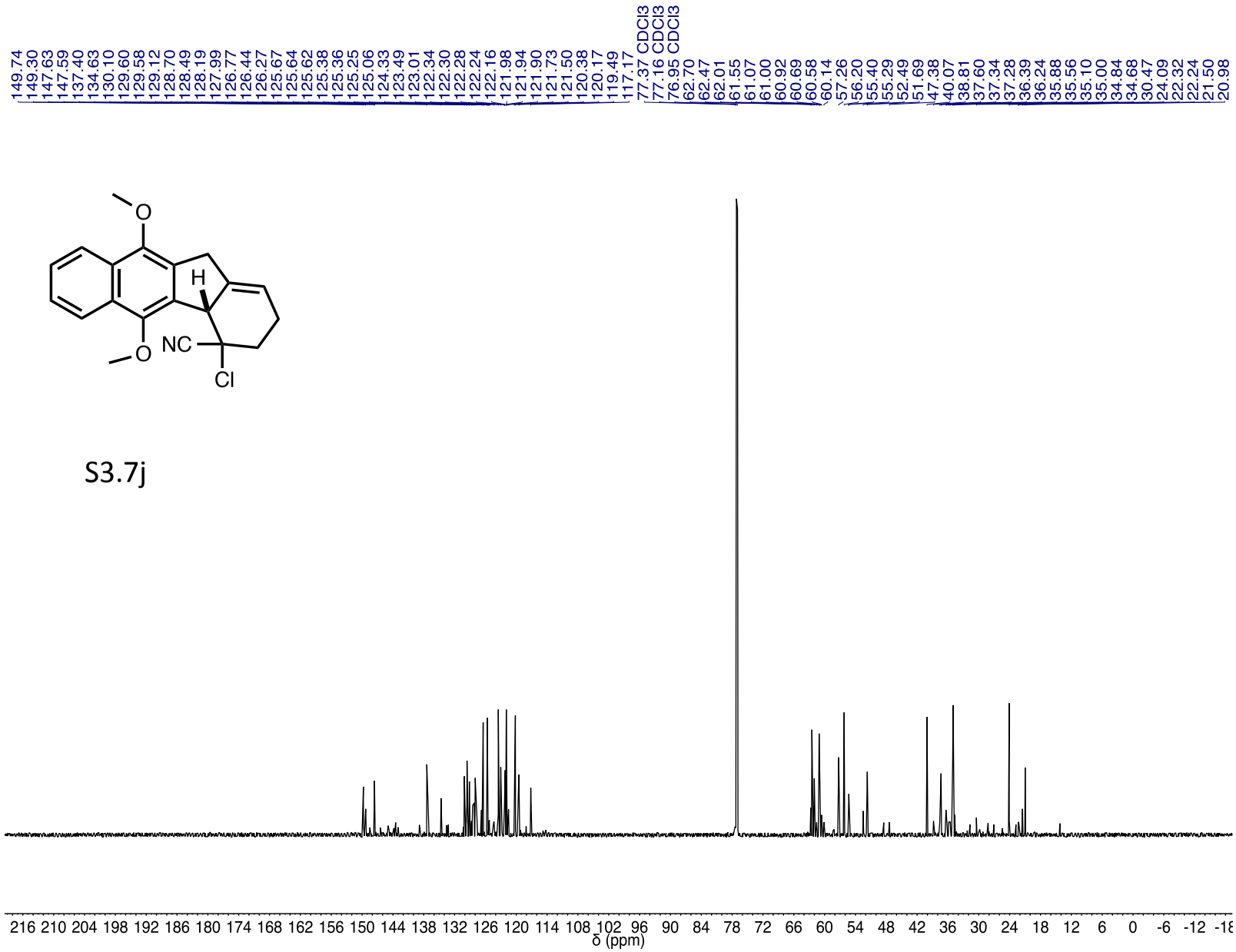
S3.7i

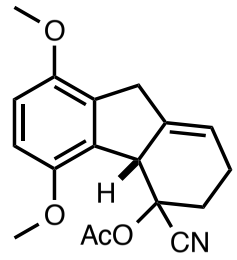
151.06
150.99
149.81
149.78
138.13
135.15
131.99
131.50
128.48
128.33
121.52
119.62
119.09
117.42
110.97
110.92
110.62
109.62
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
56.89
56.59
55.83
55.81
55.77
55.66
54.84
52.58
39.88
37.11
35.11
35.03
24.14
21.16
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


O
H
NC
O
Cl

S3.7j

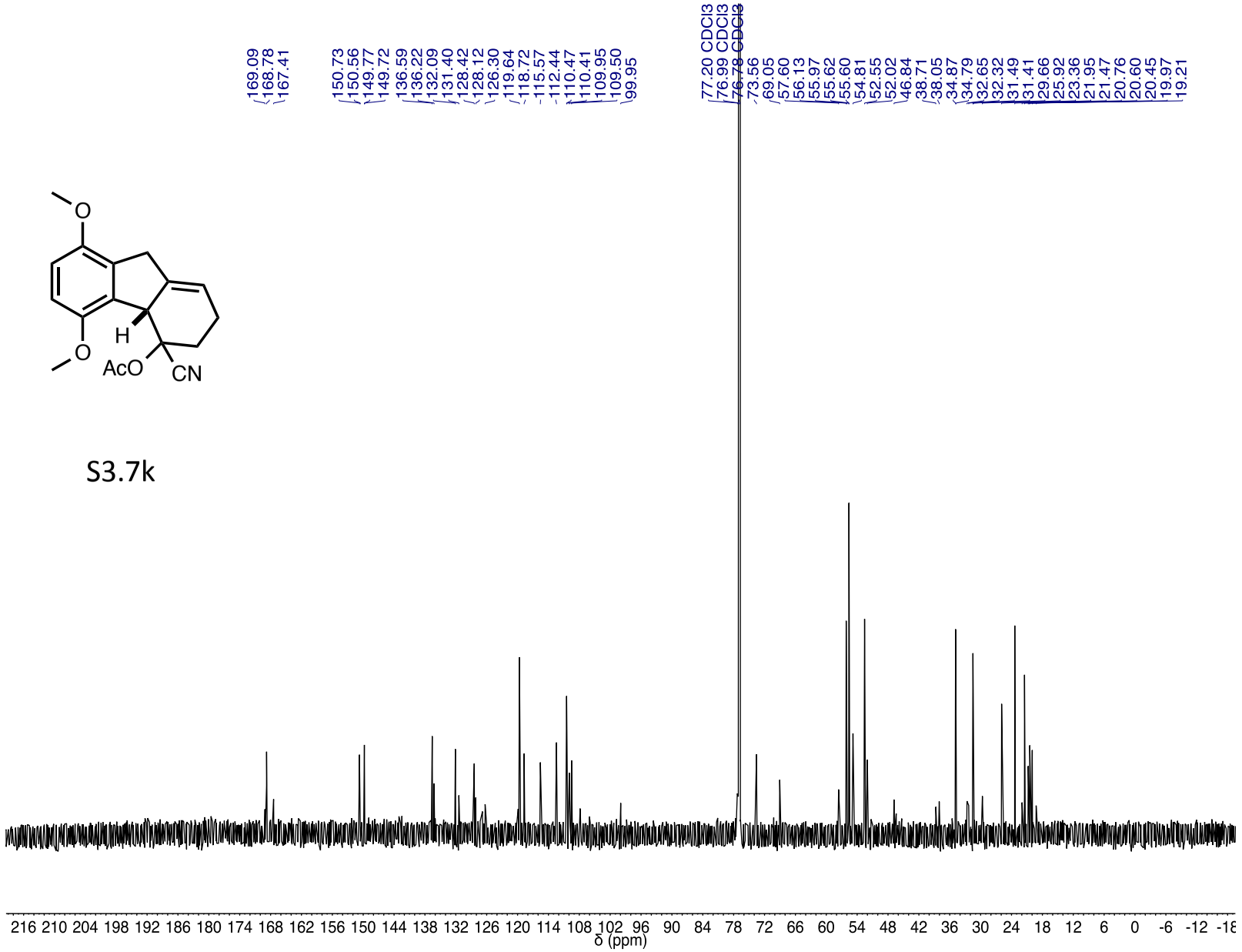
2.56
0.24
2.52
0.35
0.11
0.07
0.07
1.00
0.07
1.00
0.09
2.40
2.31
3.26
0.73
2.49
0.19
0.27
0.83
0.59
2.53
1.09
0.36
δ (ppm)

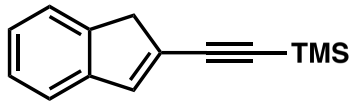

149.74
149.30
147.63
147.59
137.40
134.63
130.10
129.60
129.58
129.12
128.70
128.49
128.19
127.99
126.77
126.44
126.27
125.67
125.64
125.62
125.38
125.36
125.25
125.06
124.33
123.49
123.01
122.34
122.30
122.28
122.24
122.16
121.98
121.94
121.90
121.73
121.50
120.38
120.17
119.49
117.17
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
62.70
62.47
62.01
61.55
61.07
61.00
60.92
60.69
60.58
60.14
57.26
56.20
55.40
55.29
52.49
51.69
47.38
40.07
38.81
37.60
37.34
37.28
36.39
36.24
35.88
35.56
35.10
35.00
34.84
34.68
30.47
24.09
22.32
22.24
21.50
20.98
O
H
NC
O
Cl
S3.7j
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


O
H
O
AcO
CN

S3.7k

0.28
2.25
0.29
1.00
1.07
7.91
2.64
0.30
0.77
0.99
1.46
3.71
2.34
1.09
1.33
δ (ppm)

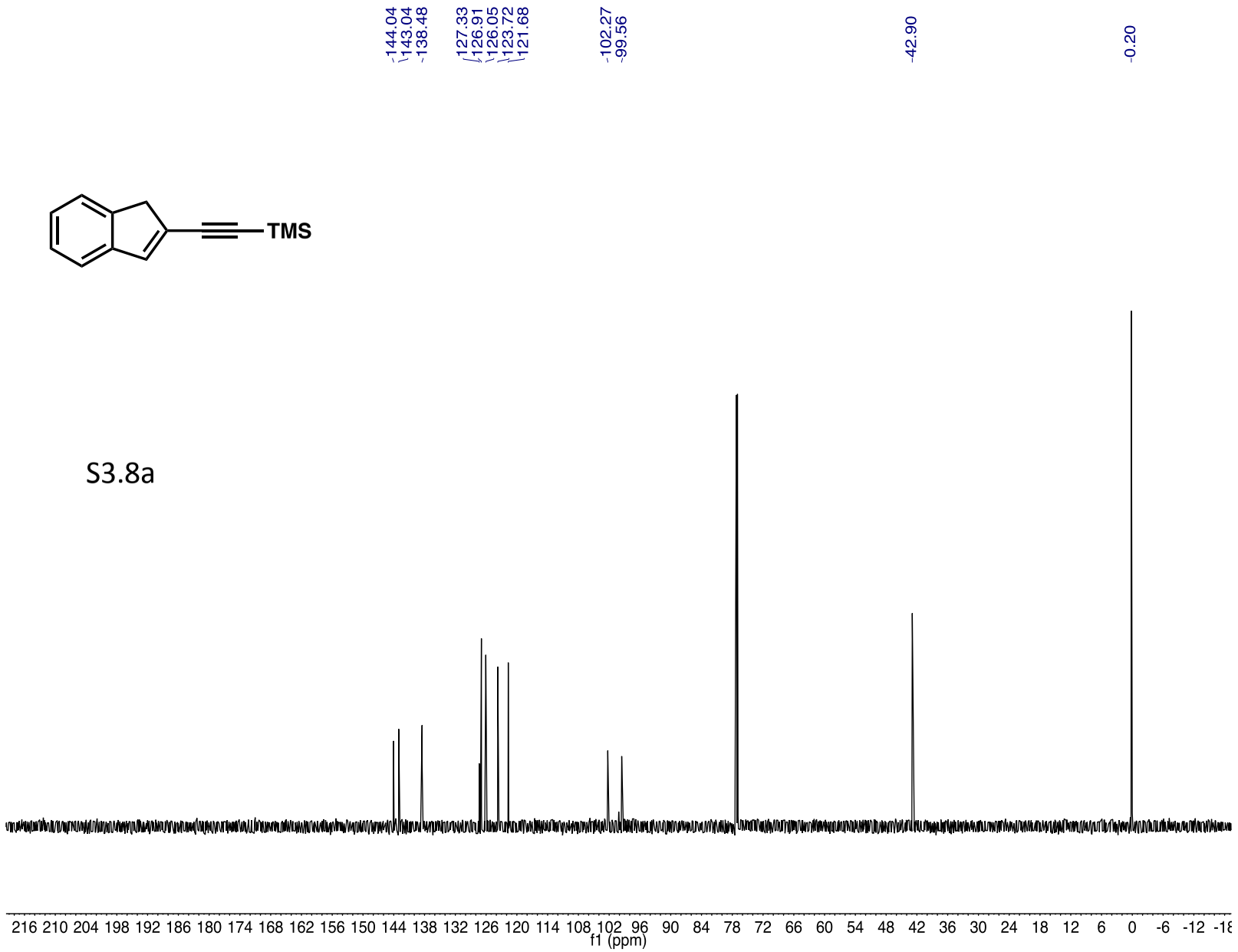

169.09
168.78
167.41
150.73
150.56
149.77
149.72
136.59
136.22
132.09
131.40
128.42
128.12
126.30
119.64
118.72
115.57
112.44
110.47
110.41
109.95
109.50
99.95
77.20 CDCl3
76.99 CDCl3
76.78 CDCl3
73.56
69.05
57.60
56.13
55.97
55.62
55.60
54.81
52.55
52.02
46.84
38.71
38.05
34.87
34.79
32.65
32.32
31.49
31.41
29.66
25.92
23.36
21.95
21.47
20.76
20.60
20.45
19.97
19.21
O
O
H
AcO
CN
S3.7k
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


TMS

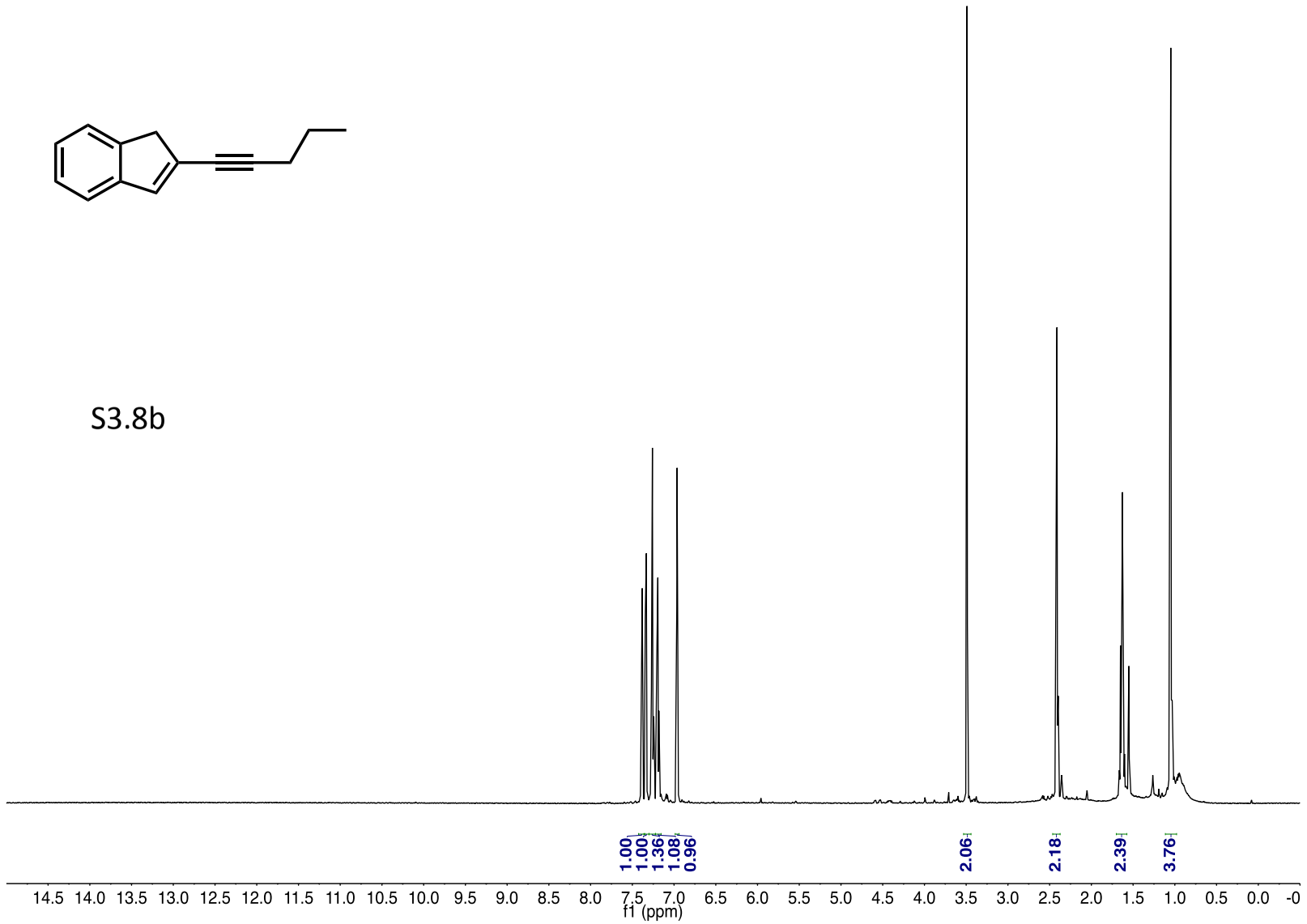
S3.8a

1.00
1.02
1.00
1.13
0.97
2.12
9.32
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

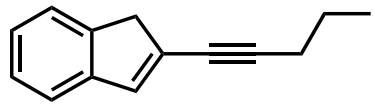
S3.8a


144.04
143.04
138.48
127.33
126.91
126.05
123.72
121.68
102.27
99.56
42.90
0.20
TMS
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)

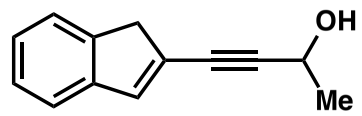
S3.8b


1.00
1.00
1.36
1.08
0.96
2.06
2.18
2.39
3.76
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0 -0
f1 (ppm)

S3.8b



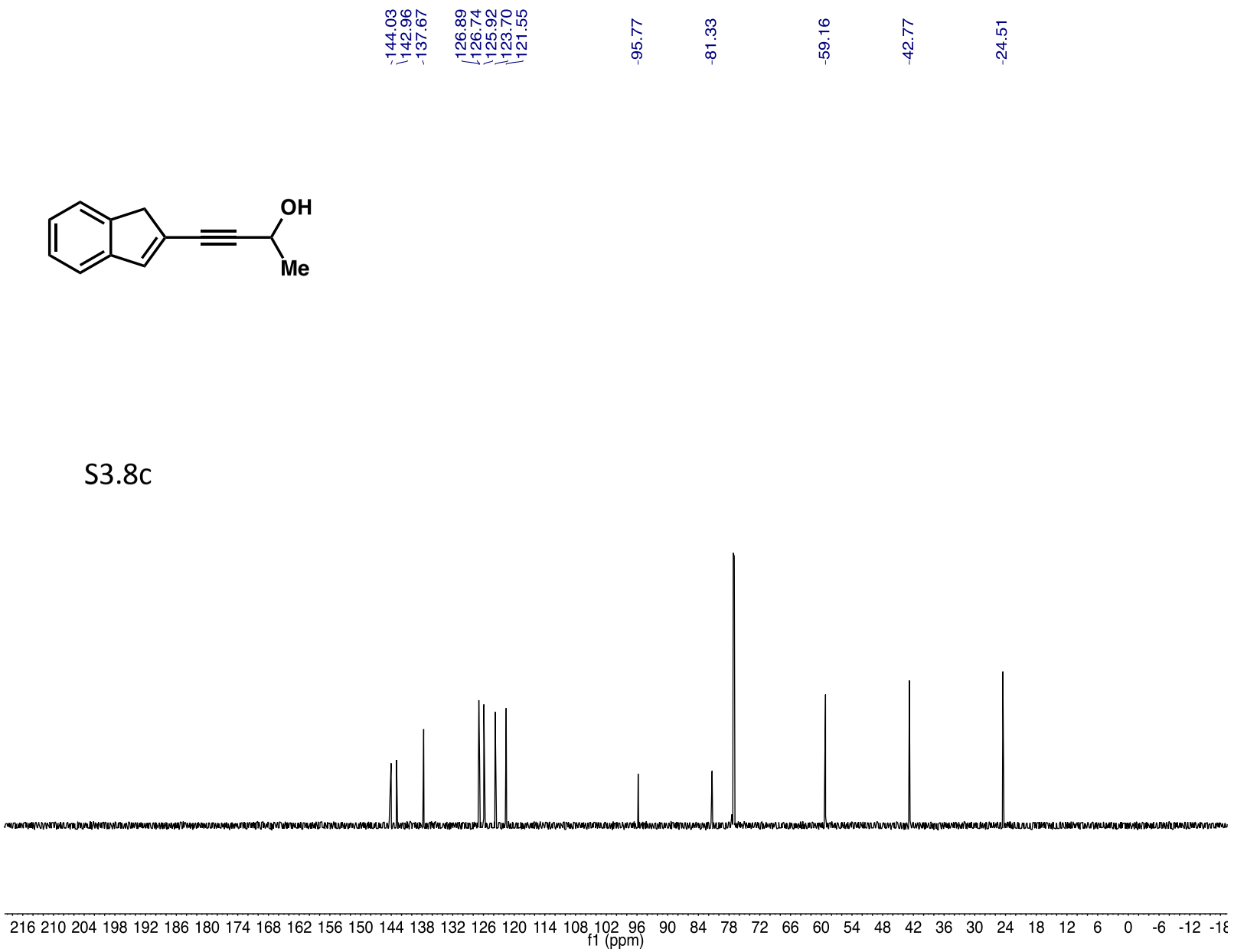
144.57
142.83
135.87
128.49
126.79
125.42
123.60
121.19
95.51
78.03
43.12
22.42
21.98
13.75
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)

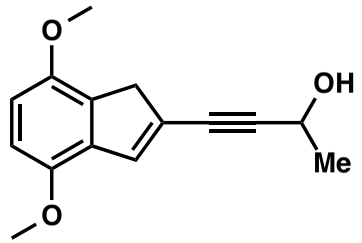

OH
Me

S3.8c

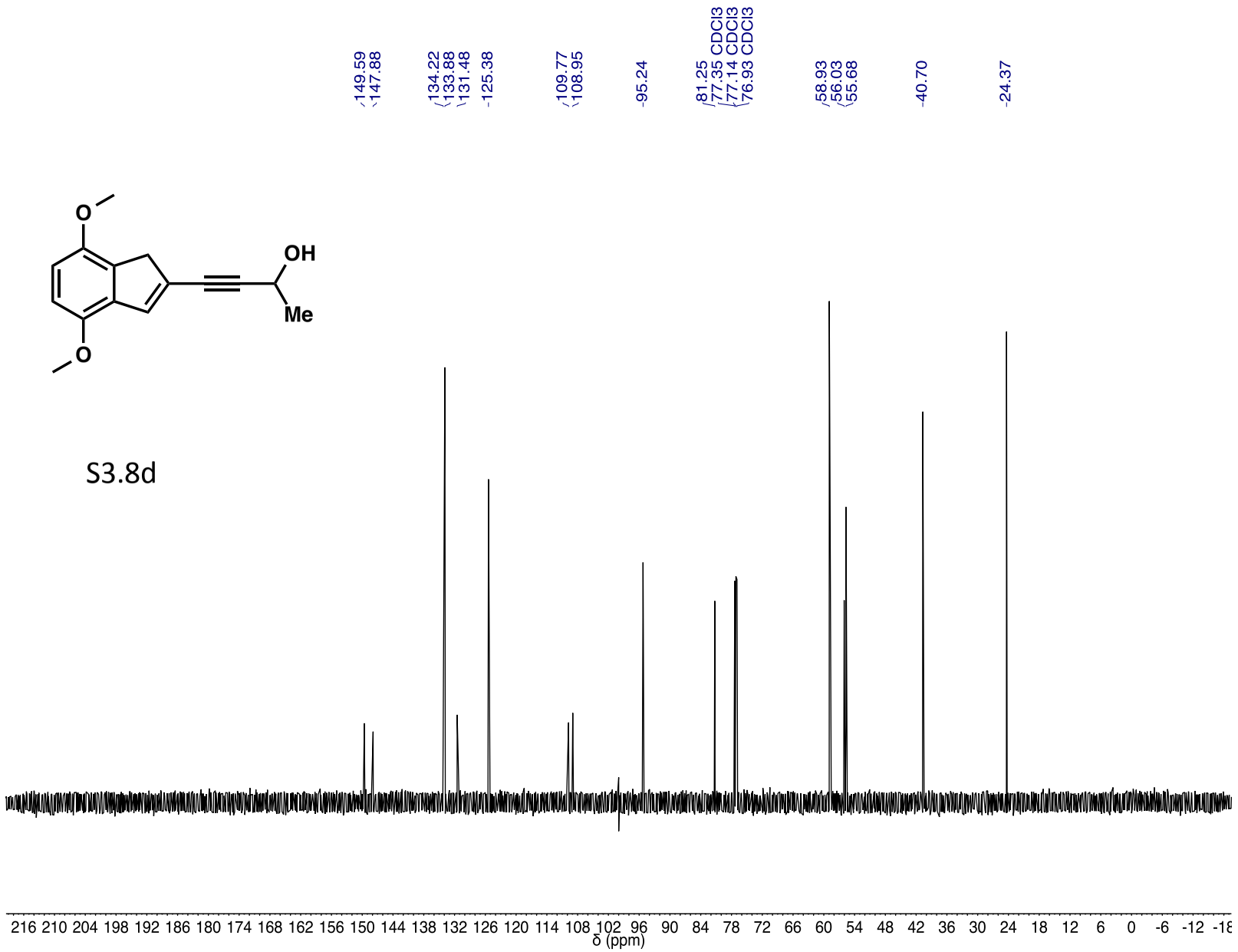
1.00
1.00
0.95
0.94
0.88
0.92
2.03
0.86
3.07
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

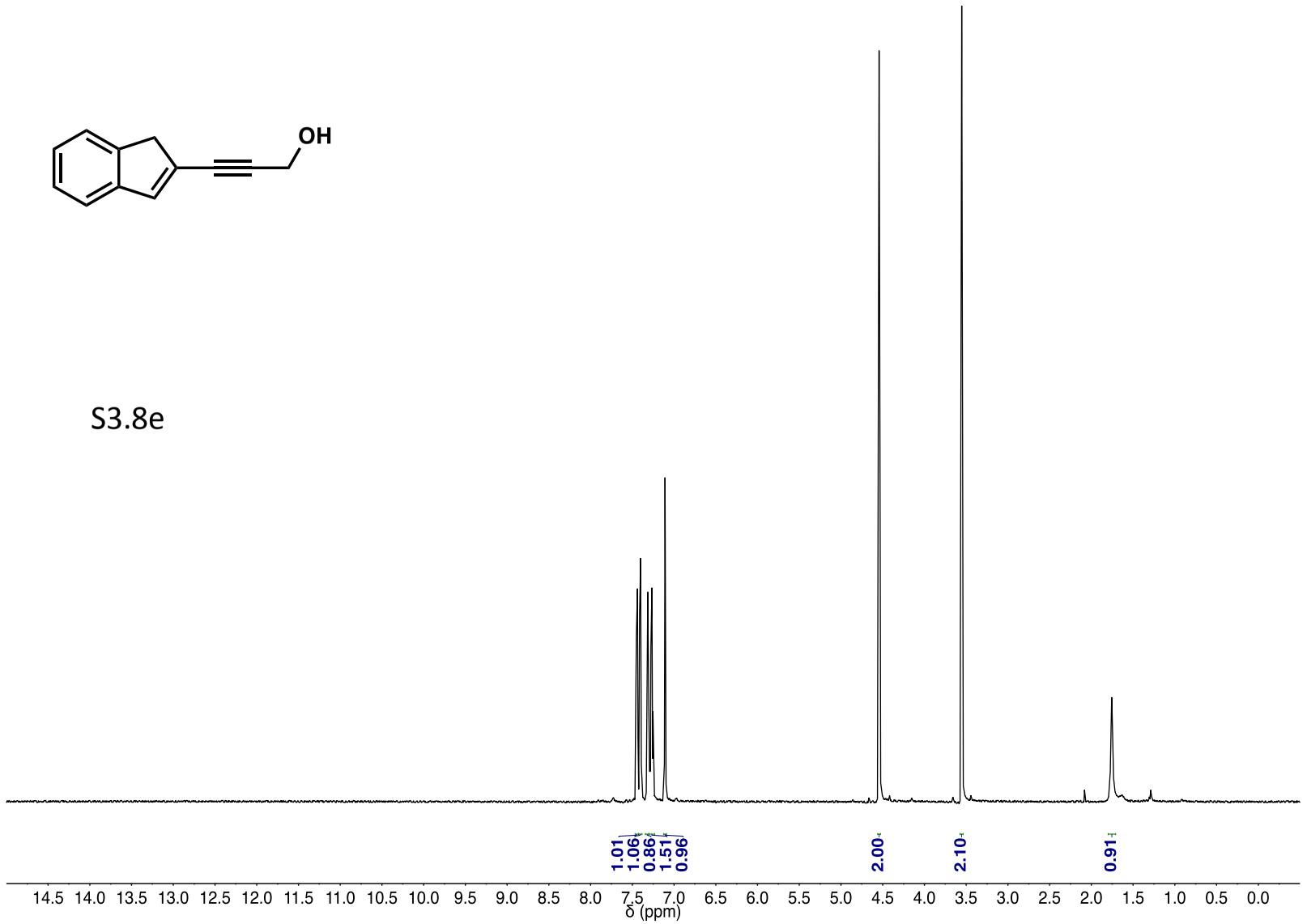
S3.8c


144.03
142.96
137.67
126.89
126.74
125.92
123.70
121.55
95.77
81.33
59.16
42.77
24.51
OH
Me
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
f1 (ppm)

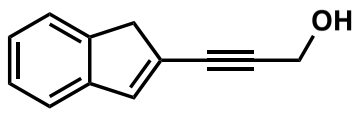


S3.8d

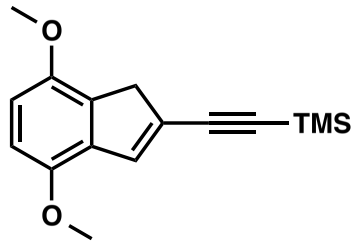

149.59
147.88
134.22
133.88
131.48
125.38
109.77
108.95
95.24
81.25
77.35 CDCl3
77.14 CDCl3
76.93 CDCl3
58.93
56.03
55.68
40.70
24.37
O
OH
Me
O
S3.8d
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


OH
S3.8e
1.01
1.06
0.86
1.51
0.96
2.00
2.10
0.91
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0
δ (ppm)

S3.8e

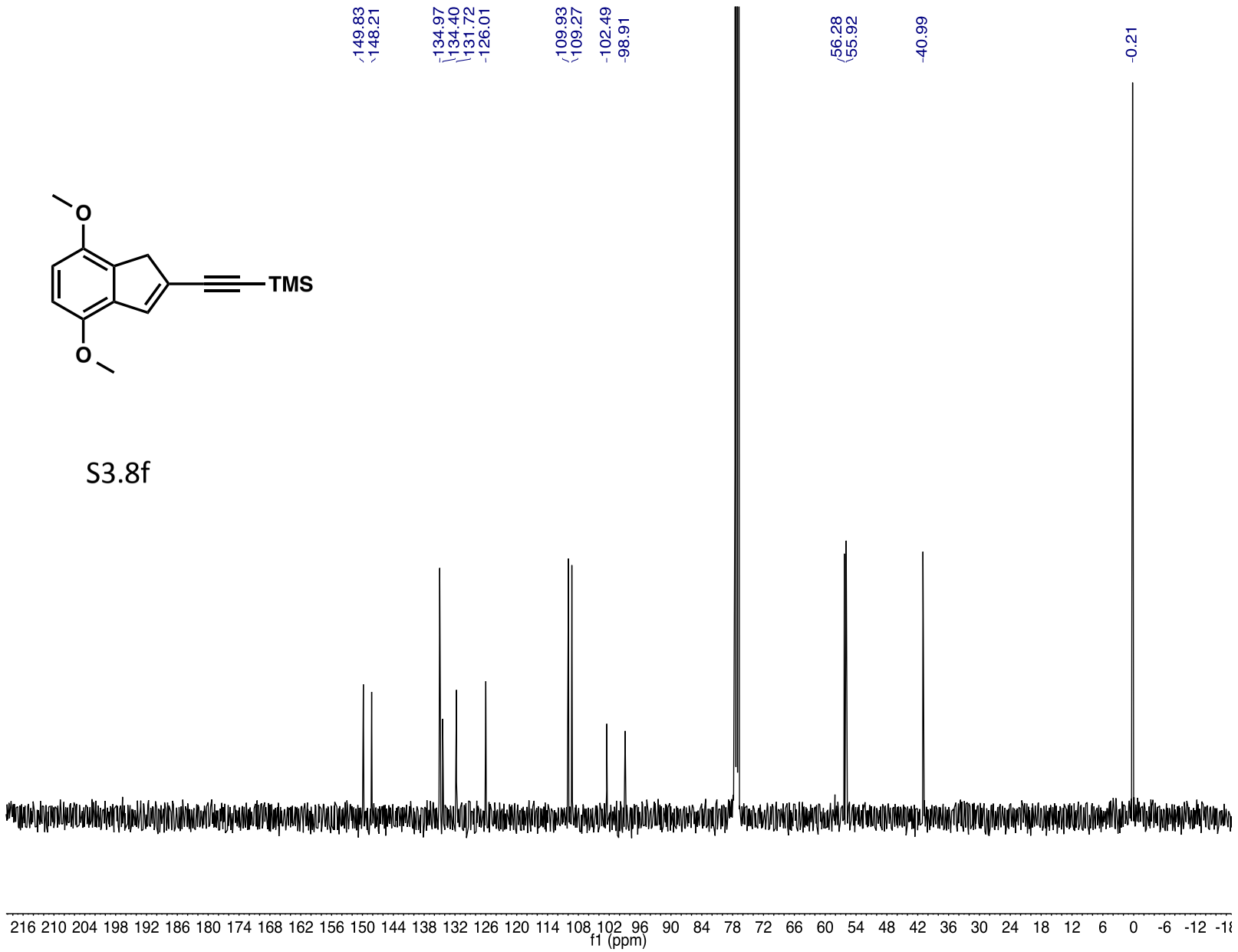

OH

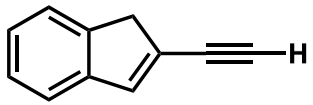
143.84
142.84
137.77
126.79
126.52
125.87
123.60
121.48
91.85
82.93
77.25 CDCl3
77.03 CDCl3
76.82 CDCl3
51.87
42.60
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


O
TMS
O

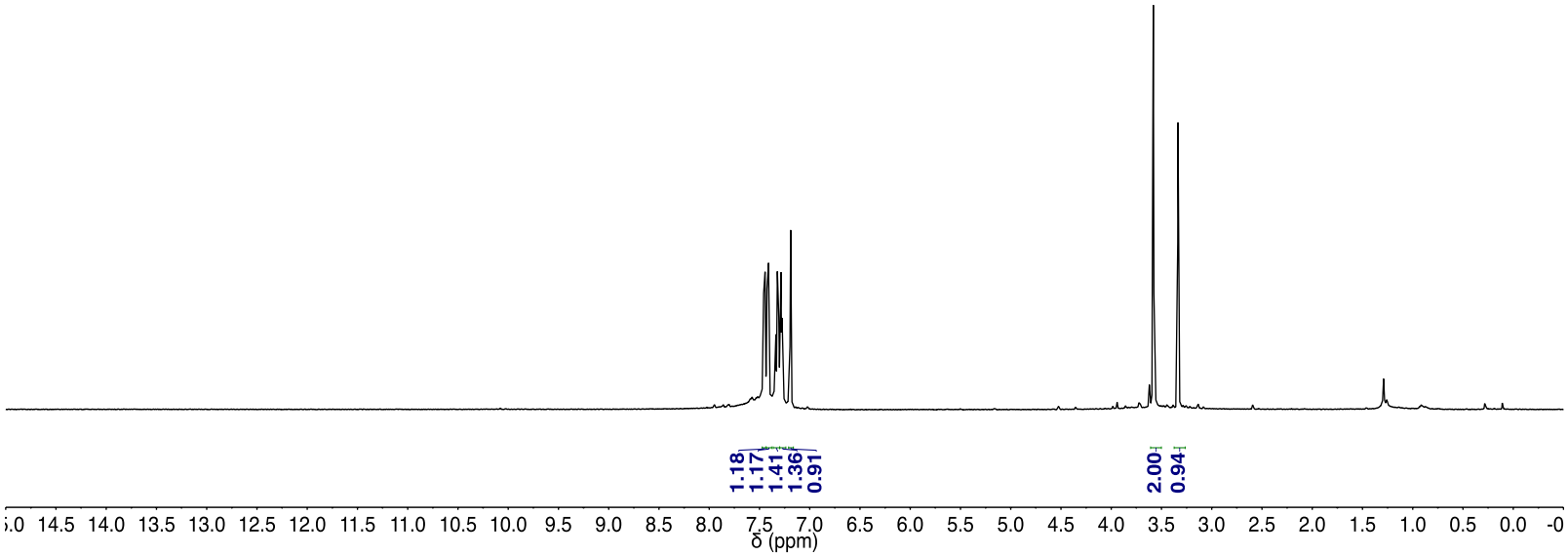
S3.8f

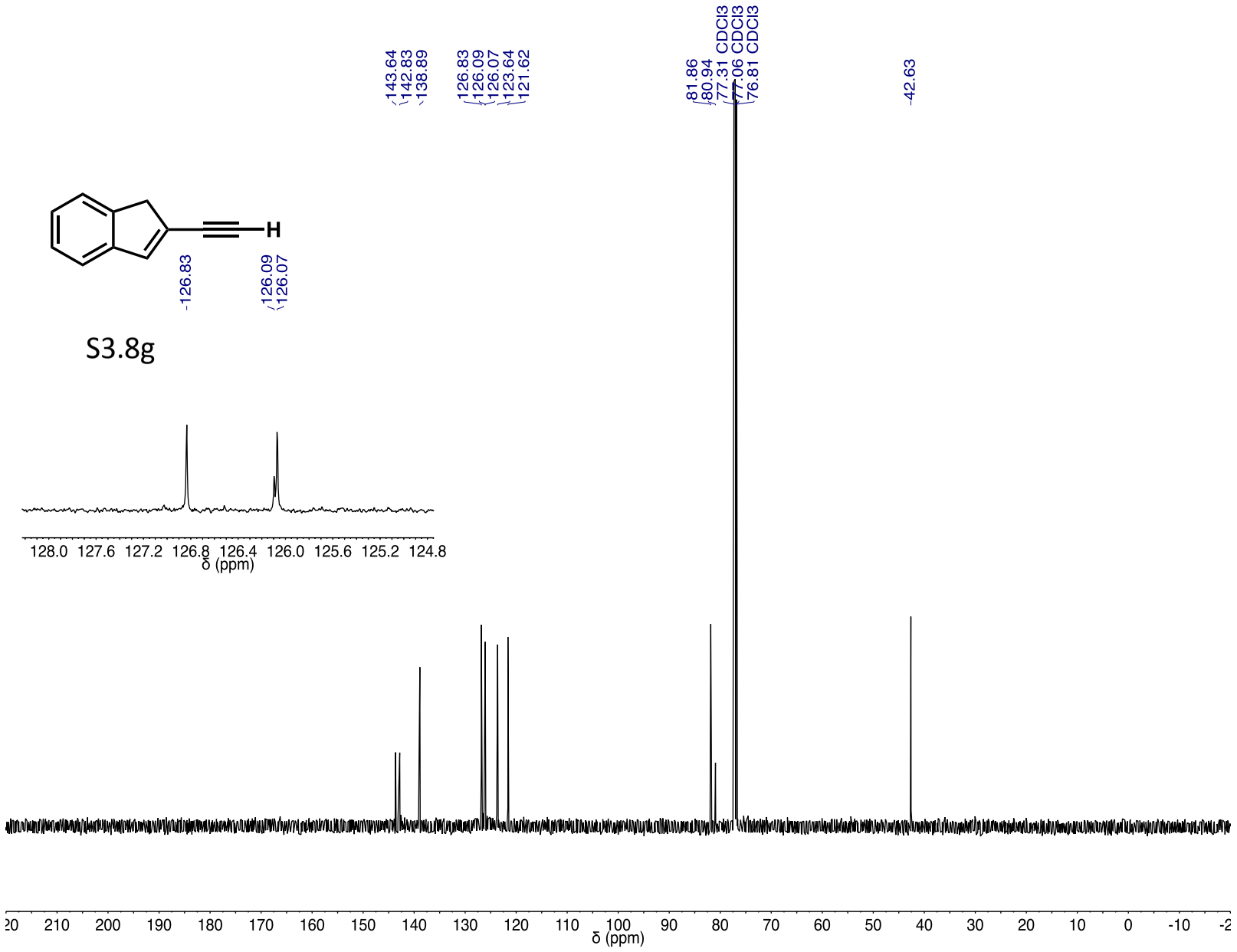
1.00
1.23
0.88
3.37
3.02
2.09
9.43
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

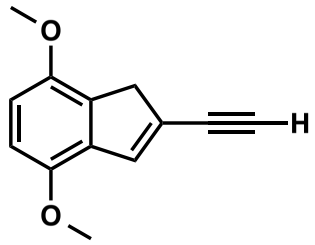

149.83
148.21
134.97
134.40
131.72
126.01
109.93
109.27
102.49
98.91
56.28
55.92
40.99
0.21
O
O
TMS
S3.8f
f1 (ppm)



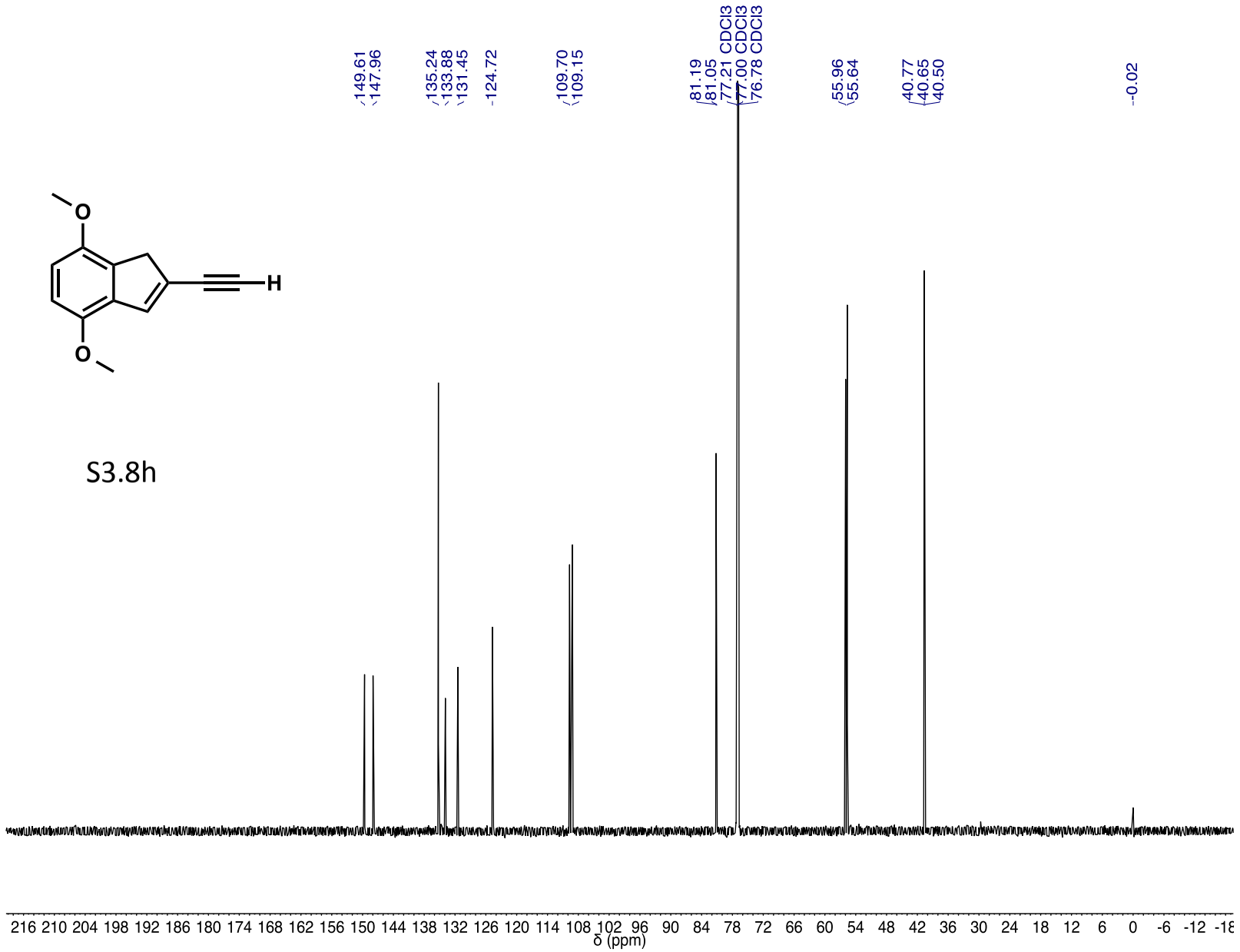
S3.8g

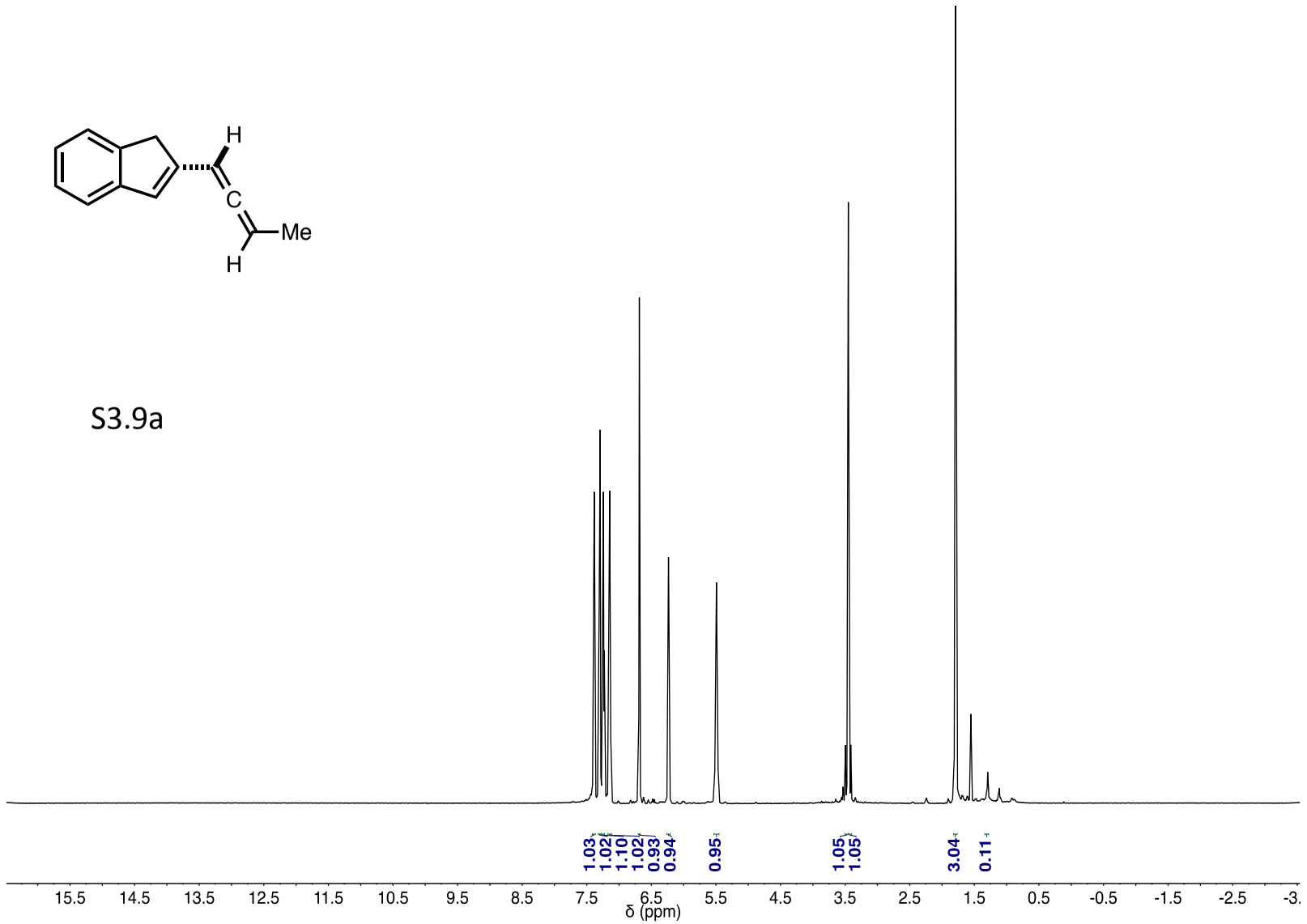



143.64
142.83
138.89
126.83
126.09
126.07
123.64
121.62
81.86
80.94
77.31 CDCl3
77.06 CDCl3
76.81 CDCl3
42.63
H
126.83
126.09
126.07
S3.8g
128.0 127.6 127.2 126.8 126.4 126.0 125.6 125.2 124.8
δ (ppm)
δ (ppm)

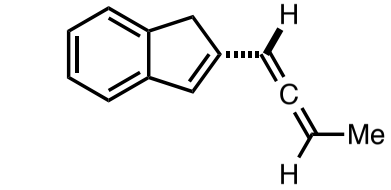


S3.8h

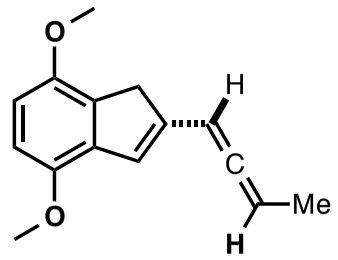

149.61
147.96
135.24
133.88
131.45
124.72
109.70
109.15
81.19
81.05
77.21 CDCl3
77.00 CDCl3
76.78 CDCl3
55.96
55.64
40.77
40.65
40.50
-0.02
O
O
H
S3.8h
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


H
C
Me
H
S3.9a
1.03
1.02
1.10
1.02
0.93
0.94
0.95
1.05
1.05
3.04
0.11
15.5
14.5
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
-2.5
δ (ppm)

S3.9a

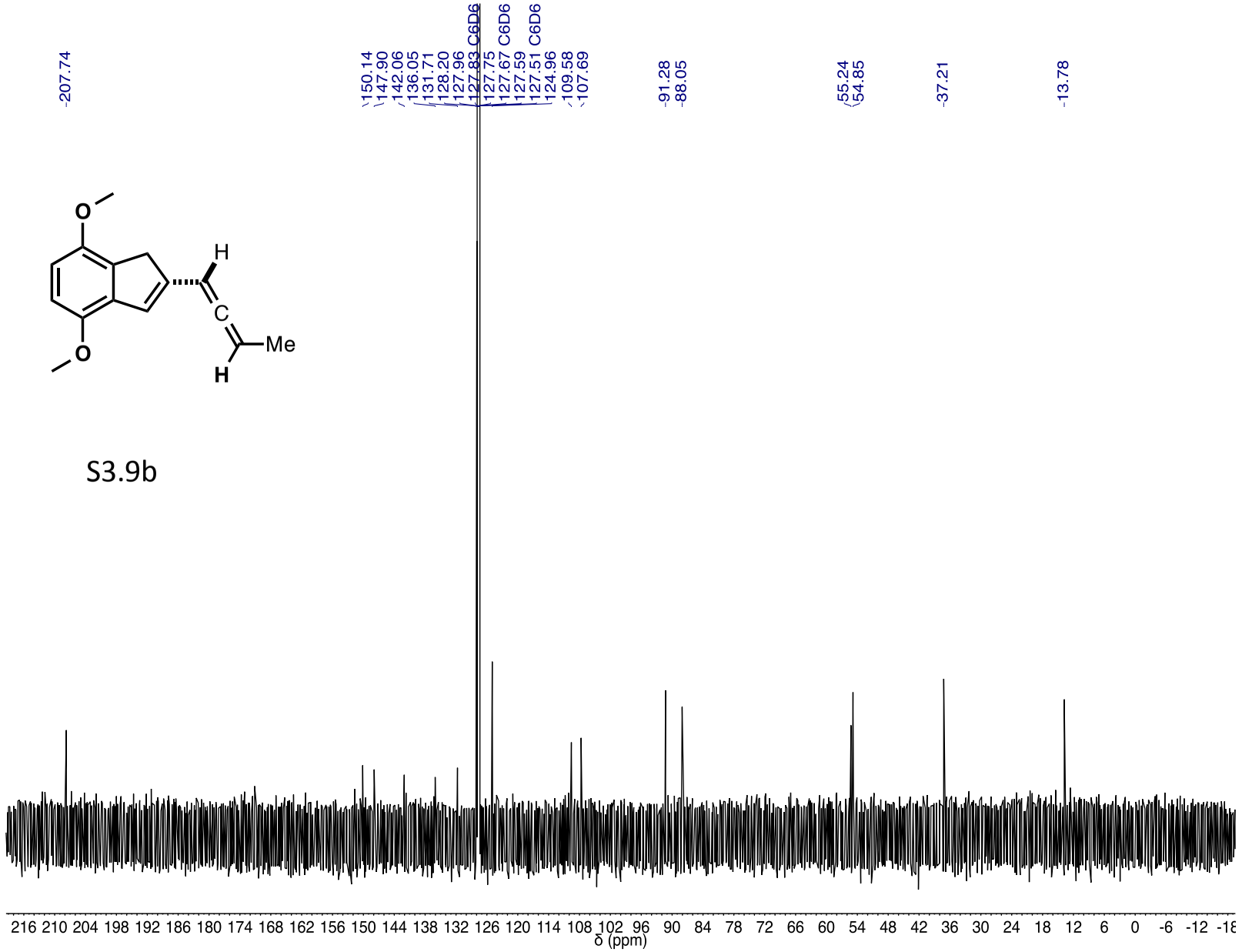

H
C
Me
H

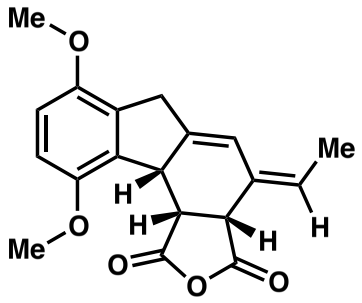
207.71
145.53
143.30
143.06
128.08
126.34
124.32
123.47
120.32
91.01
88.33
77.24 CDCl3
77.03 CDCl3
76.82 CDCl3
38.87
14.28
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


O
H
C
Me
O
H

S3.9b

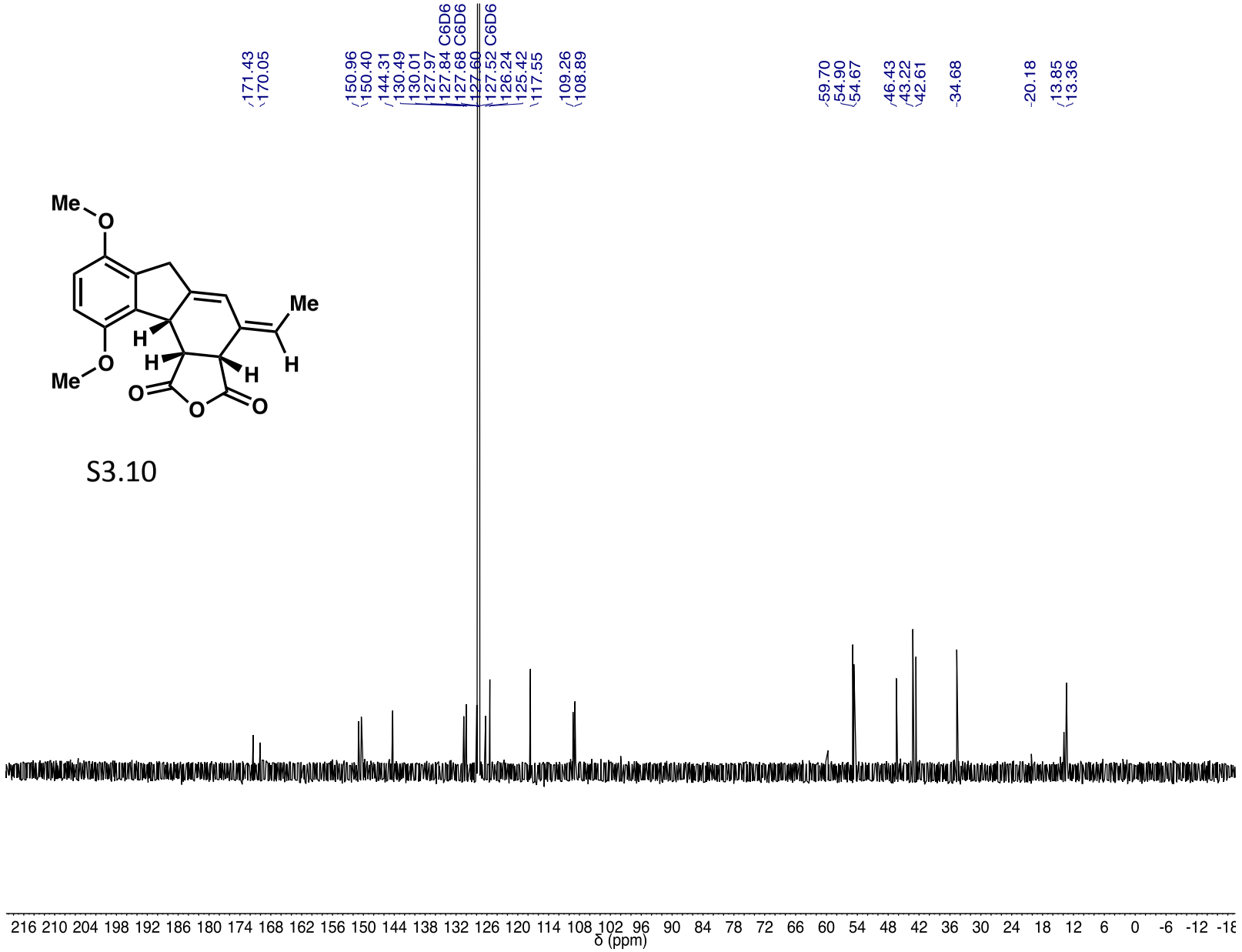
0.40 HDO
0.39 HDO
1.01
1.05
1.07
1.01
0.99
1.17
1.15
3.43
3.30
3.28
δ (ppm)


207.74
150.14
147.90
142.06
136.05
131.71
128.20
127.96
127.83 C6D6
127.75
127.67 C6D6
127.59
127.51 C6D6
124.96
109.58
107.69
91.28
88.05
55.24
54.85
37.21
13.78
O
H
C
Me
O
H
S3.9b
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

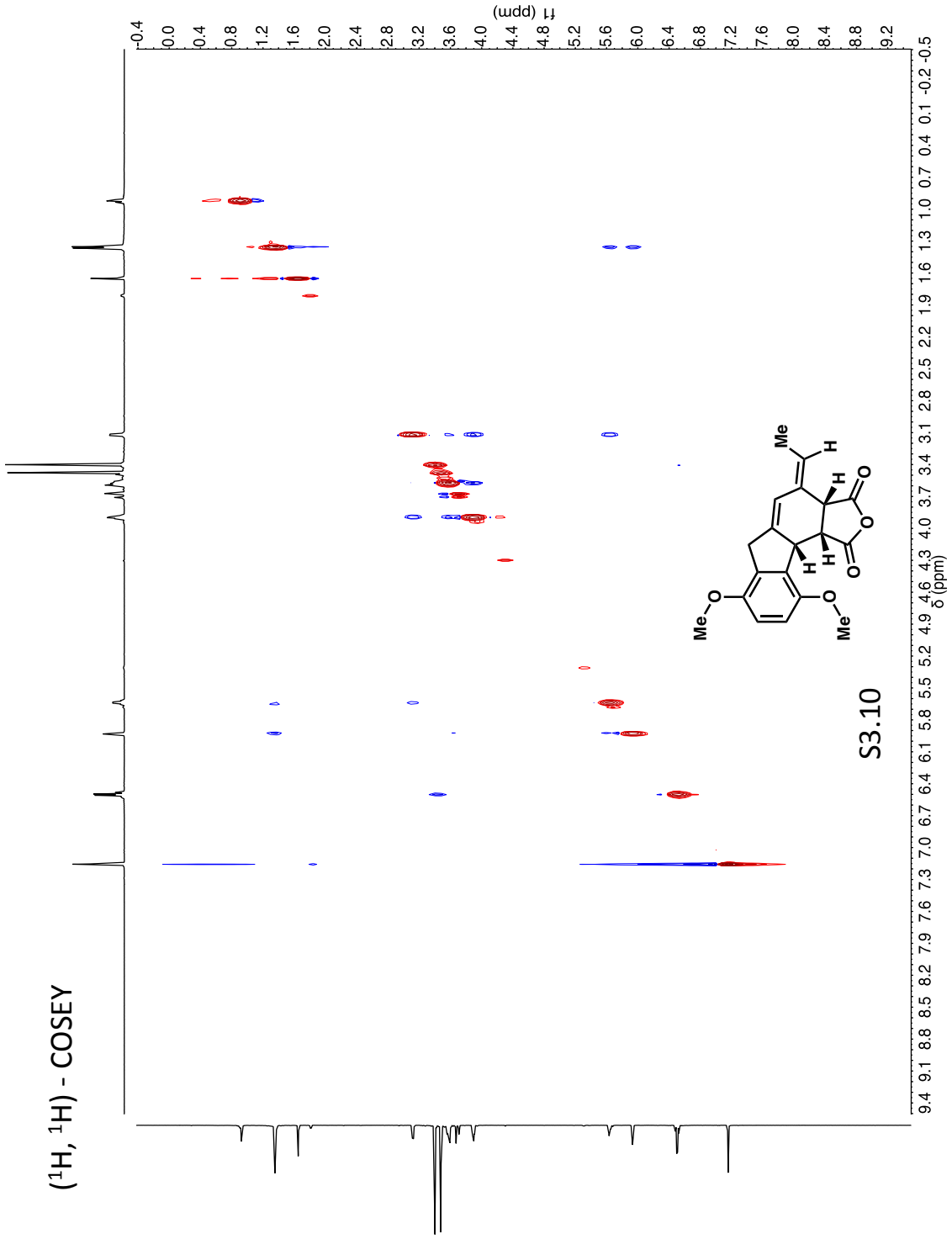

Me
O
Me
H
H
H
H
Me
O
O
O
O

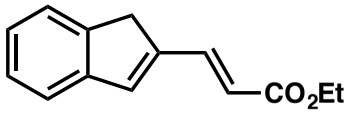
S3.10

1.13
1.11
1.00
1.01
1.58
1.11
2.29
3.16
3.62
1.03
3.35
14.5 14.0 13.5 13.0 12.5 12.0 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 0.0
δ (ppm)

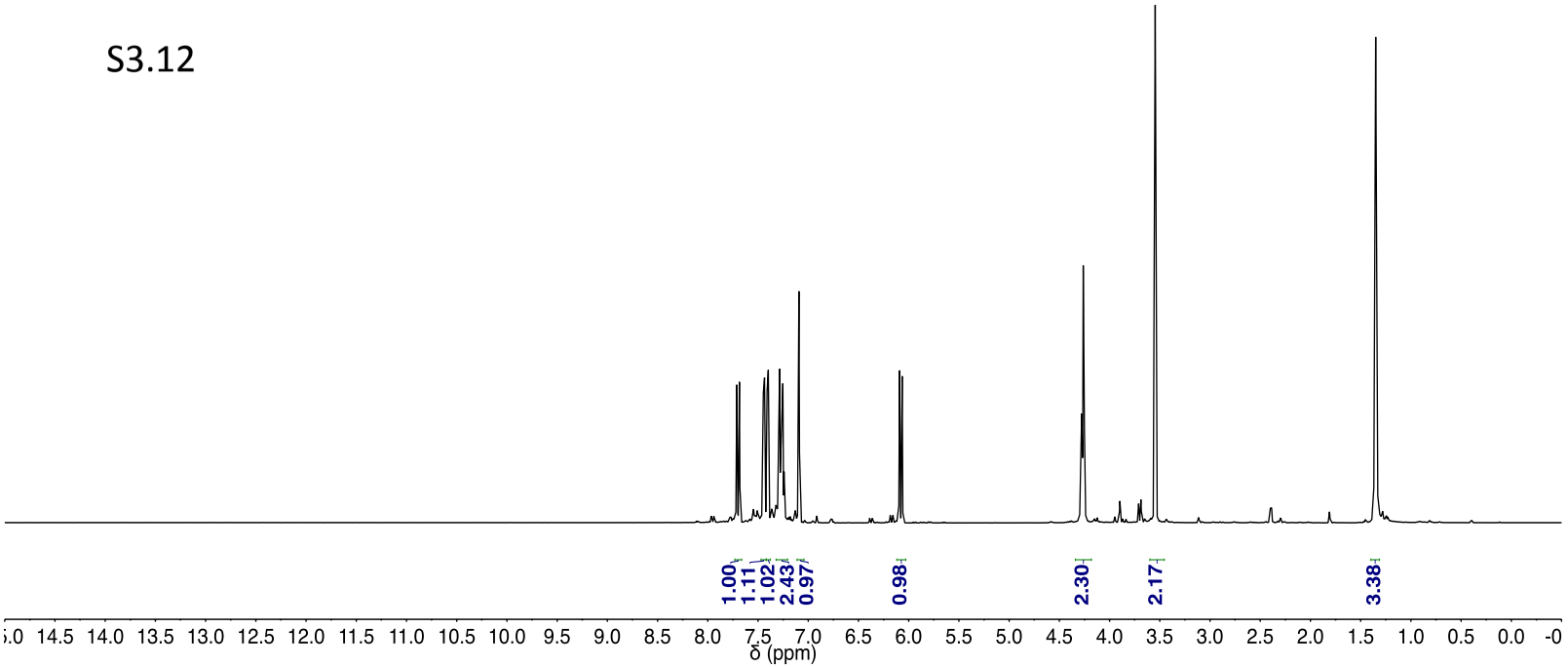

171.43
170.05
150.96
150.40
144.31
130.49
130.01
127.97
127.84 C6D6
127.68 C6D6
127.60
127.52 C6D6
126.24
125.42
117.55
109.26
108.89
59.70
54.90
54.67
46.43
43.22
42.61
34.68
20.18
13.85
13.36
Me
O
Me
H
H
H
H
O
O
O
Me
O
O
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S3.10

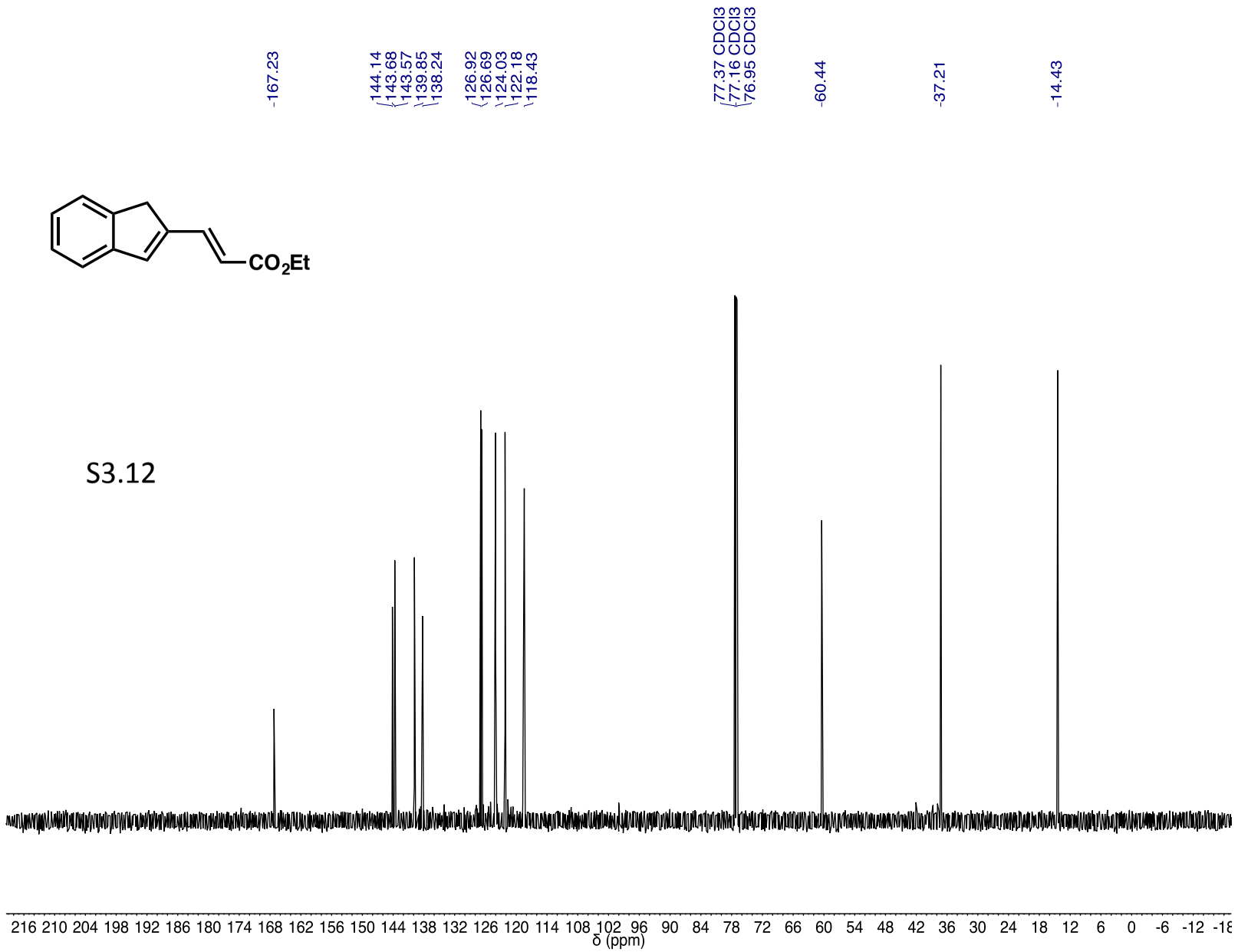

(1H, 1H) - COSEY
f1 (ppm)
δ (ppm)
S3.10
Me
H
H
H
O
O
O
O
Me
Me

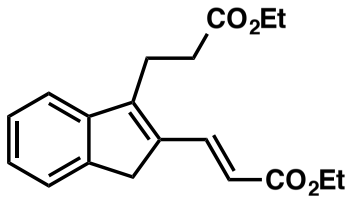


S3.12

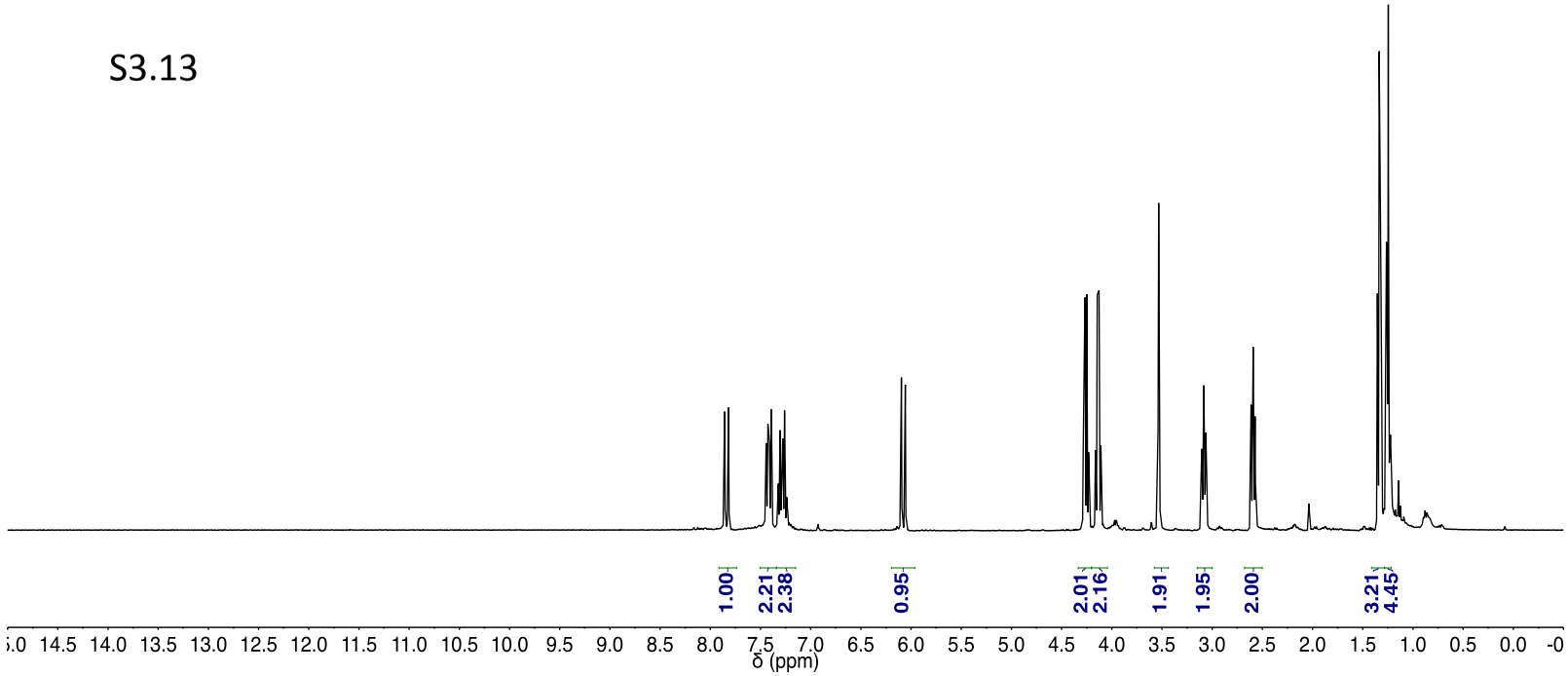


S3.12

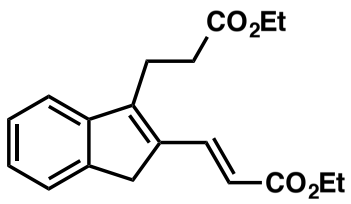

167.23
144.14
143.68
143.57
139.85
138.24
126.92
126.69
124.03
122.18
118.43
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
60.44
37.21
14.43
CO2Et
δ (ppm)



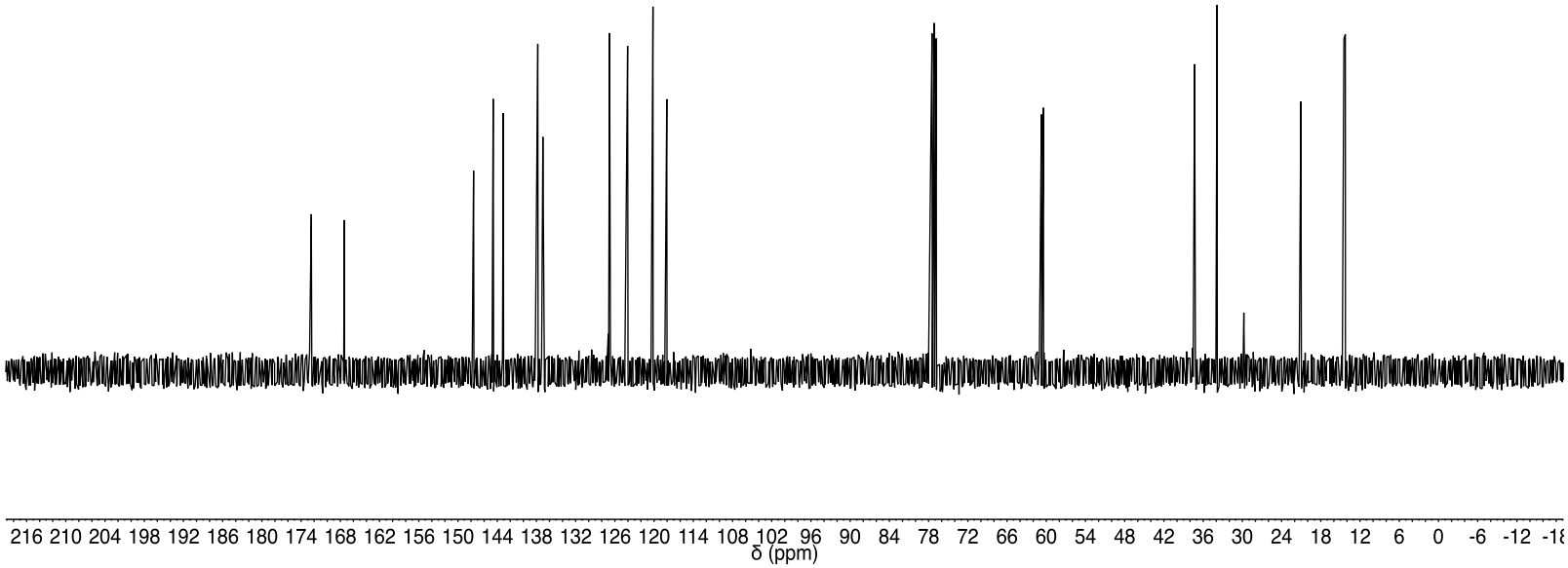
S3.13

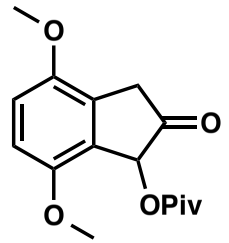


S3.13

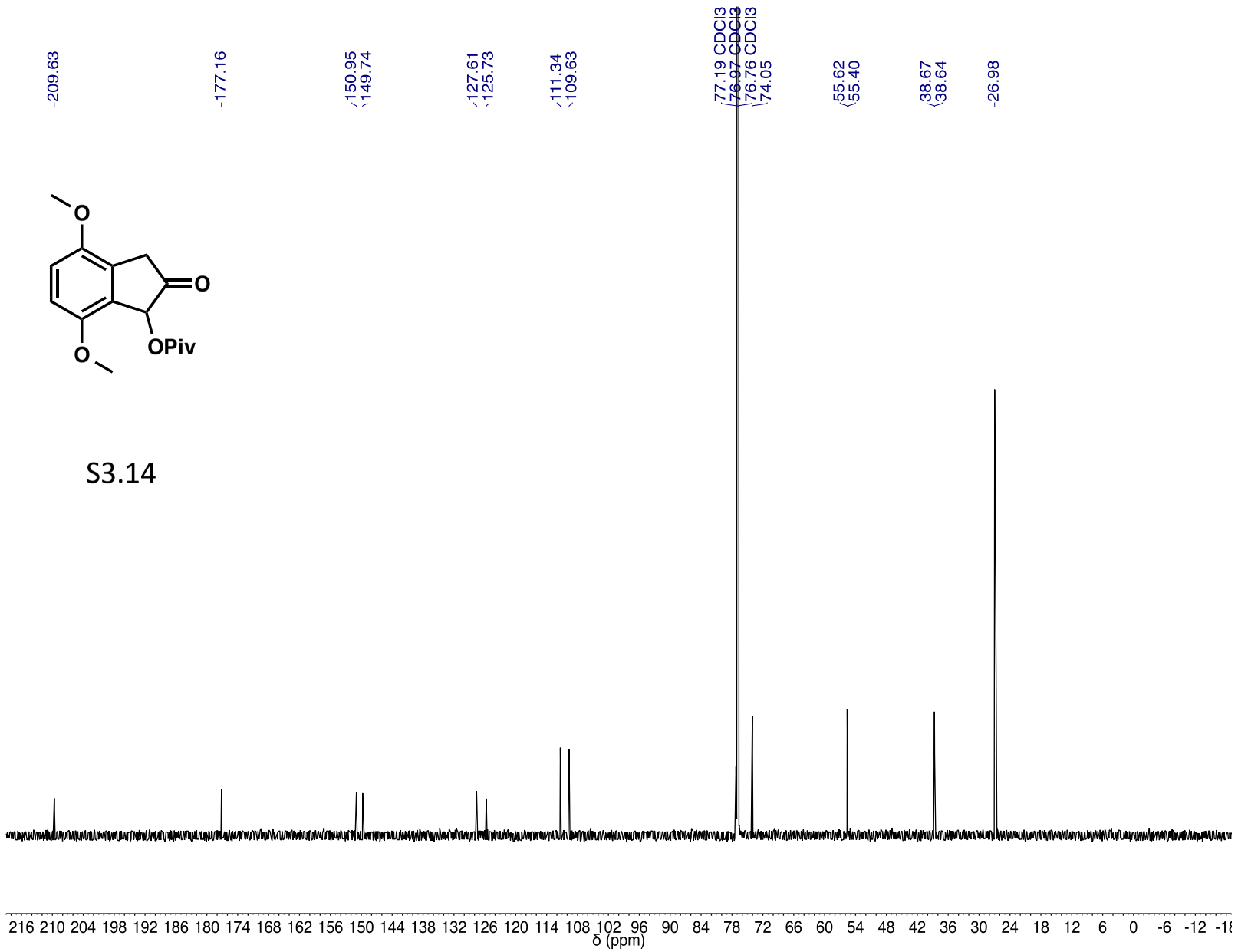


172.44
167.40
147.61
144.62
143.07
137.79
137.01
126.99
126.81
124.05
120.17
118.05
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
60.74
60.43
37.31
33.87
29.77
21.05
14.46
14.25
14.16

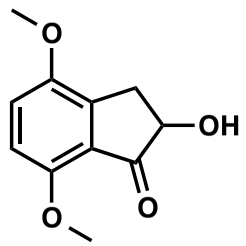




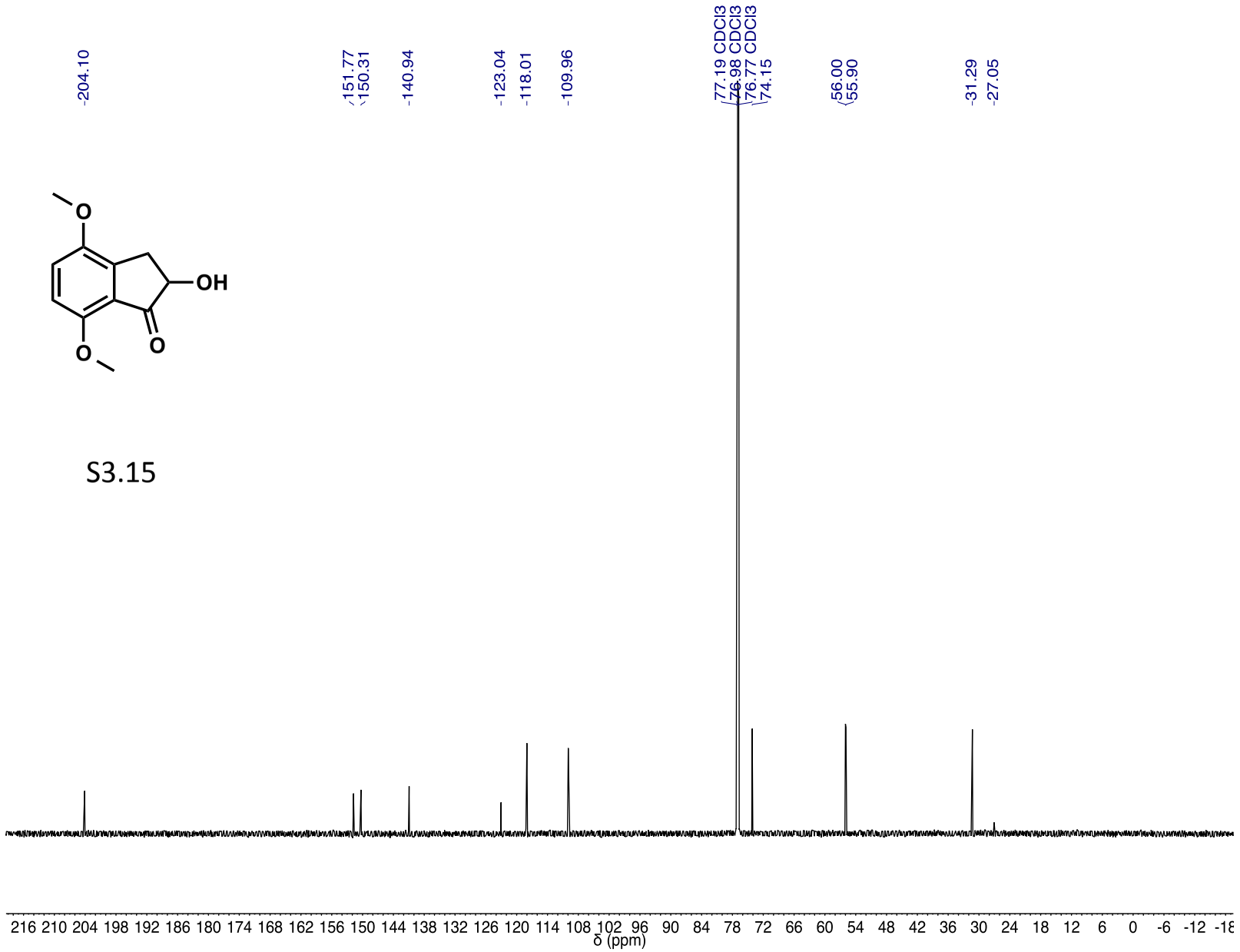
S3.14


209.63
177.16
150.95
149.74
127.61
125.73
111.34
109.63
77.19 CDCl3
76.97 CDCl3
76.76 CDCl3
74.05
55.62
55.40
38.67
38.64
26.98
O
O
O
OPiv
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

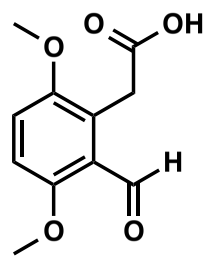
S3.14



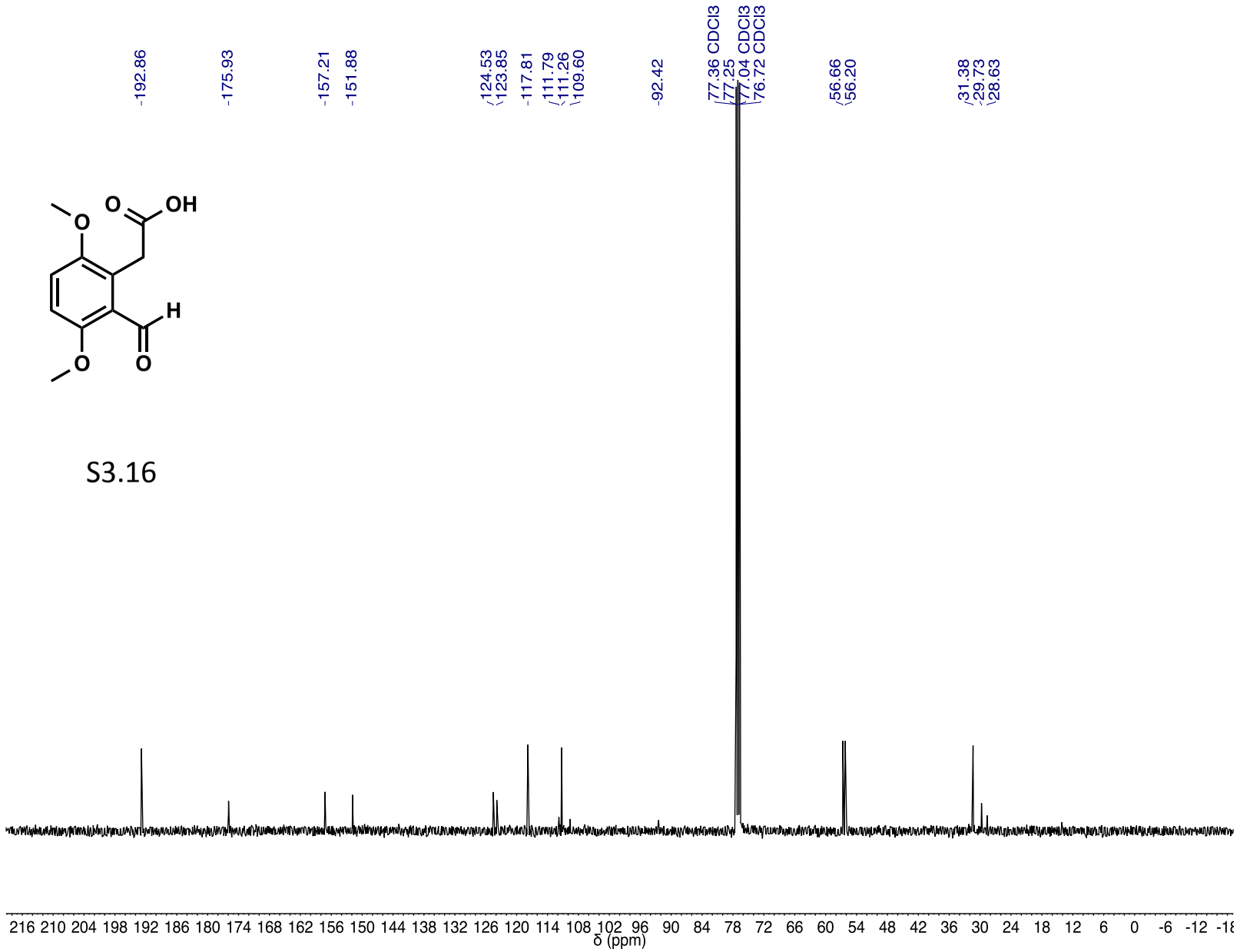
S3.15


204.10
151.77
150.31
140.94
123.04
118.01
109.96
77.19 CDCl3
76.98 CDCl3
76.77 CDCl3
74.15
56.00
55.90
31.29
27.05
O
OH
O
O
δ (ppm)

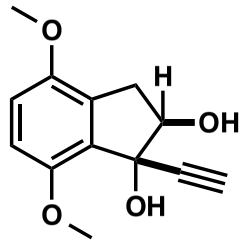
S3.15



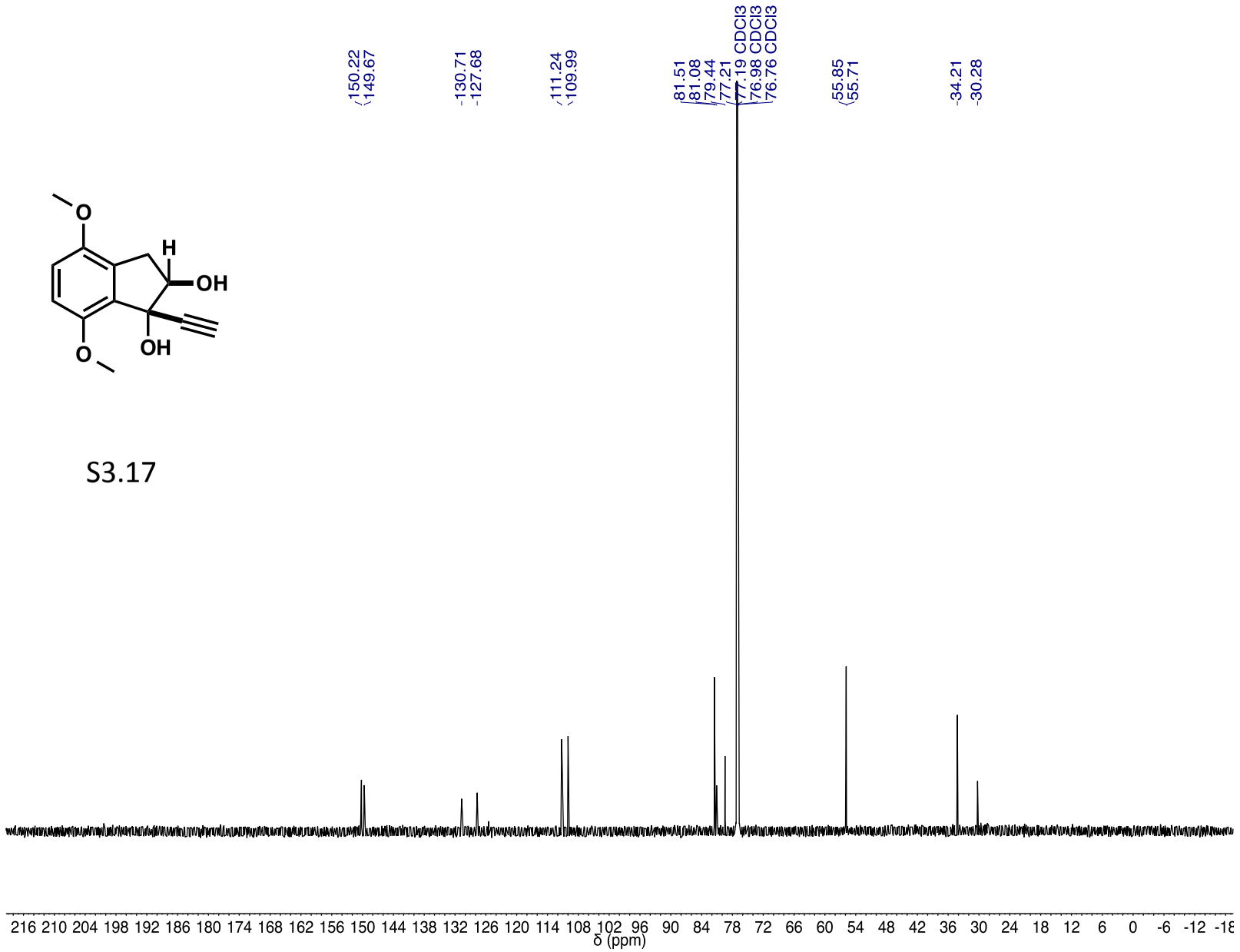
S3.16


192.86
175.93
157.21
151.88
124.53
123.85
117.81
111.79
111.26
109.60
92.42
77.36 CDCl3
77.25
77.04 CDCl3
76.72 CDCl3
56.66
56.20
31.38
29.73
28.63
O
OH
O
H
O
O
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)

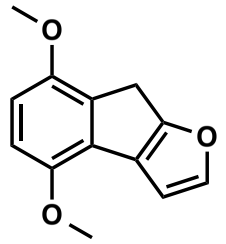
S3.16



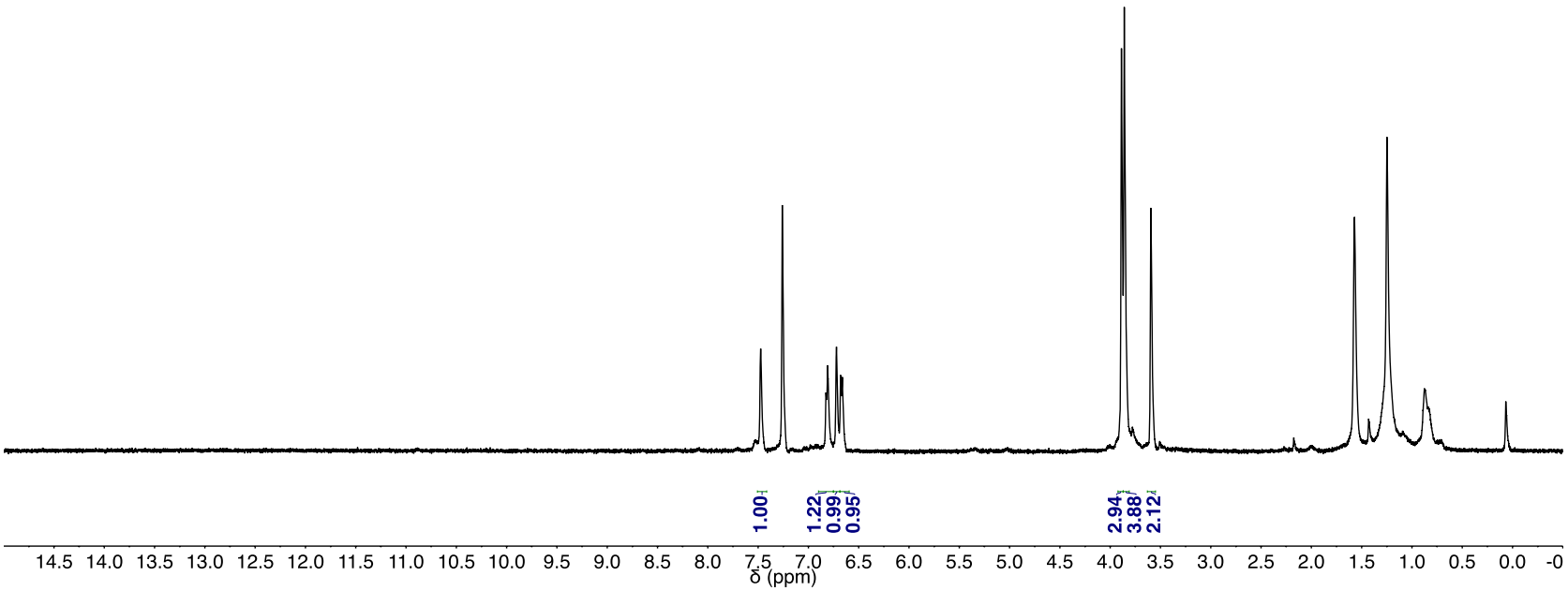
S3.17

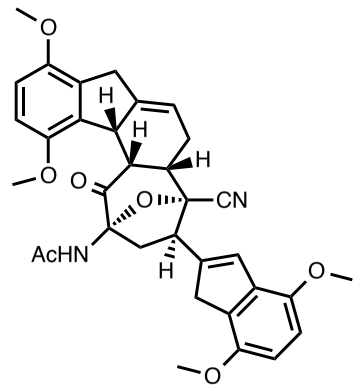

150.22
149.67
130.71
127.68
111.24
109.99
81.51
81.08
79.44
77.21
77.19 CDCl3
76.98 CDCl3
76.76 CDCl3
55.85
55.71
34.21
30.28
O
H
OH
OH
O
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)

S3.17



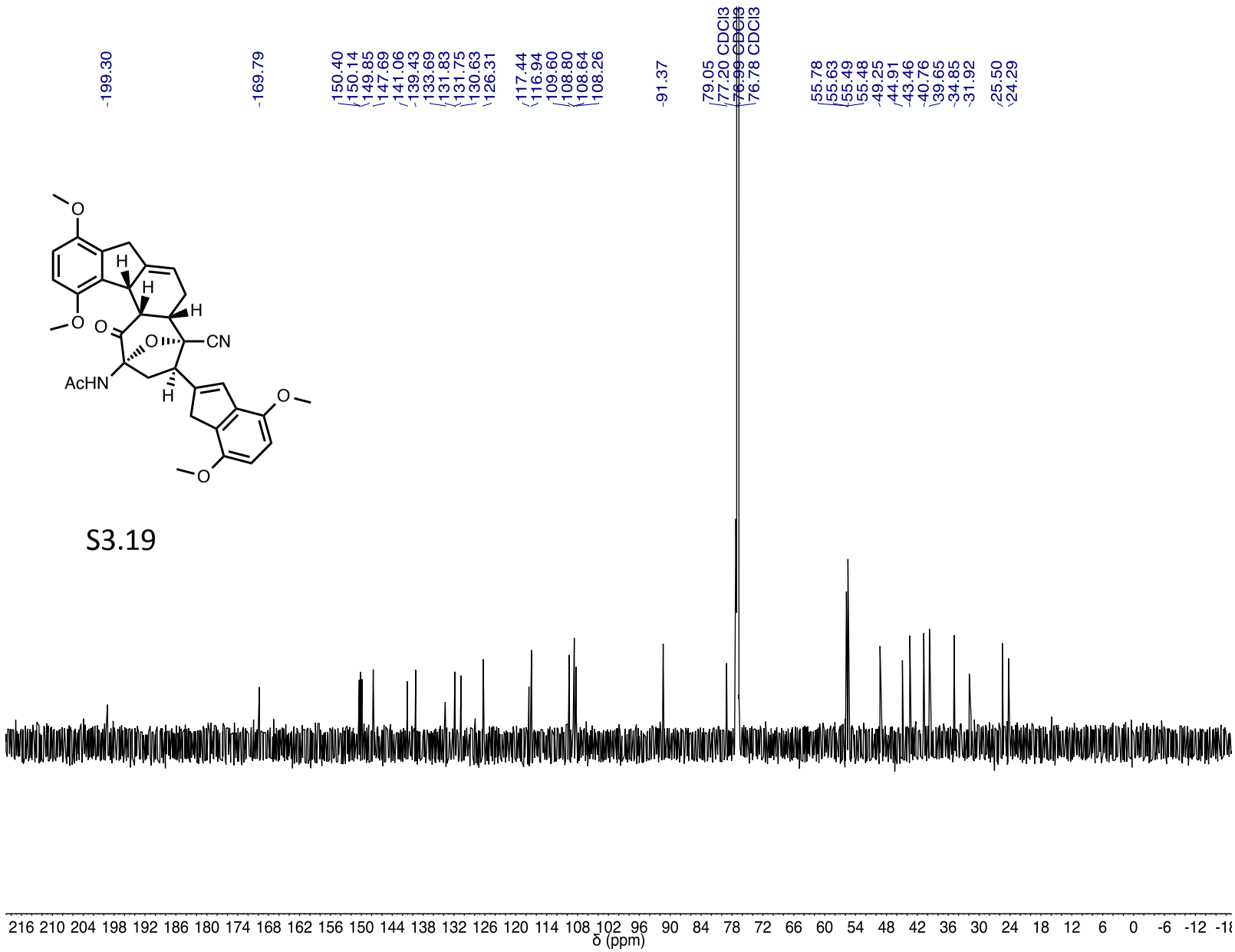
S3.18

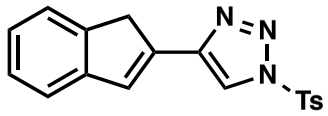

1.00
1.22
0.99
0.95
2.94
3.88
2.12
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
δ (ppm)


O
H
H
H
O
O
O
CN
AcHN
H
O
O

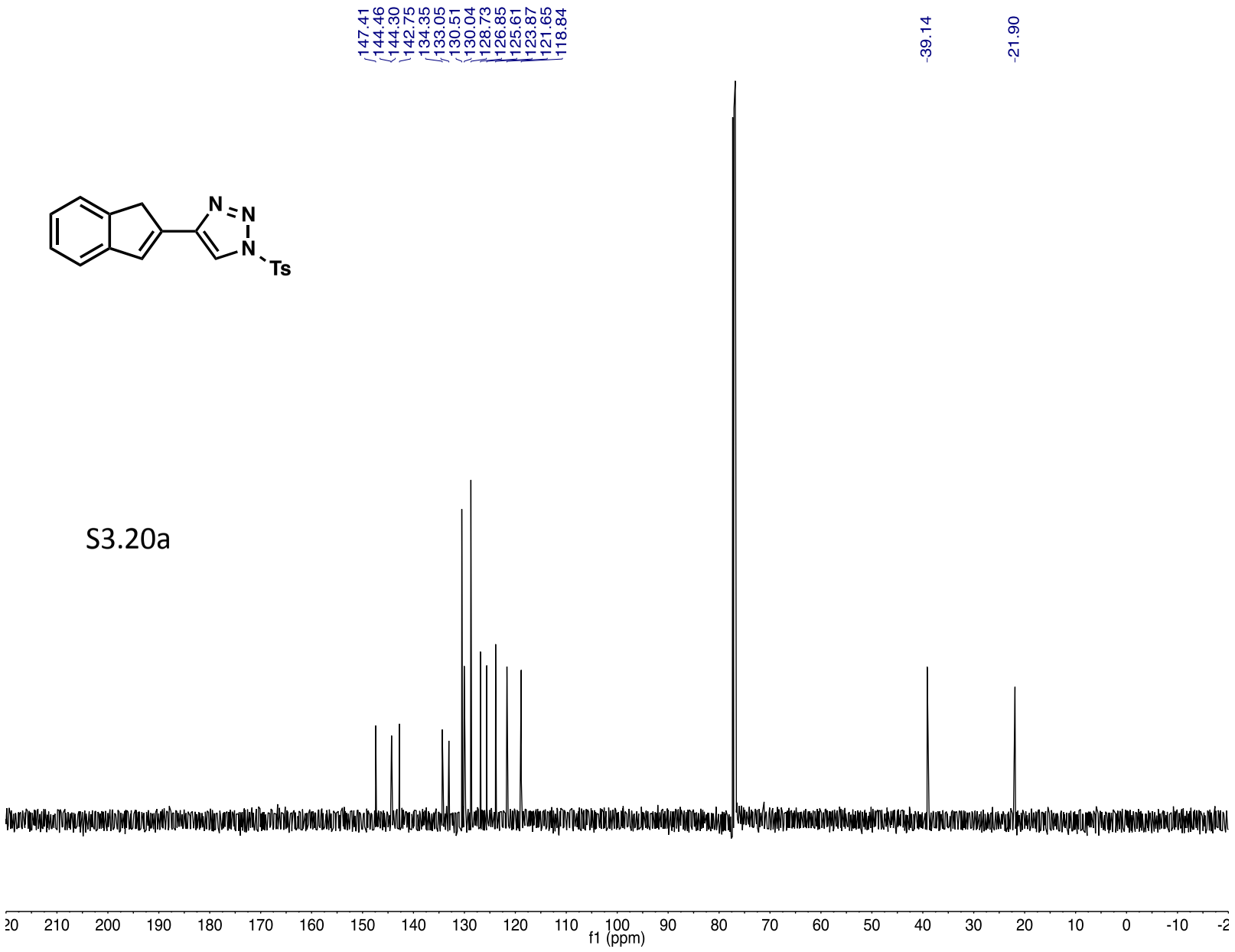
S3.19

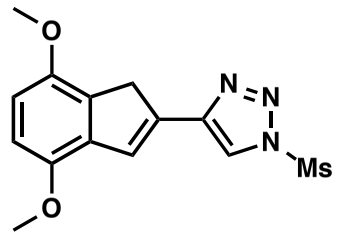
0.86
1.88
1.09
1.01
0.90
0.94
0.95
0.92
2.71
6.15
4.18
4.17
0.92
1.11
1.05
2.68
δ (ppm)


-199.30
-169.79
150.40
150.14
149.85
147.69
141.06
139.43
133.69
131.83
131.75
130.63
126.31
117.44
116.94
109.60
108.80
108.64
108.26
-91.37
79.05
77.20 CDCl3
76.99 CDCl3
76.78 CDCl3
55.78
55.63
55.49
55.48
49.25
44.91
43.46
40.76
39.65
34.85
31.92
25.50
24.29
O
H
H
H
O
O
O
CN
AcHN
H
O
O
S3.19
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12
δ (ppm)



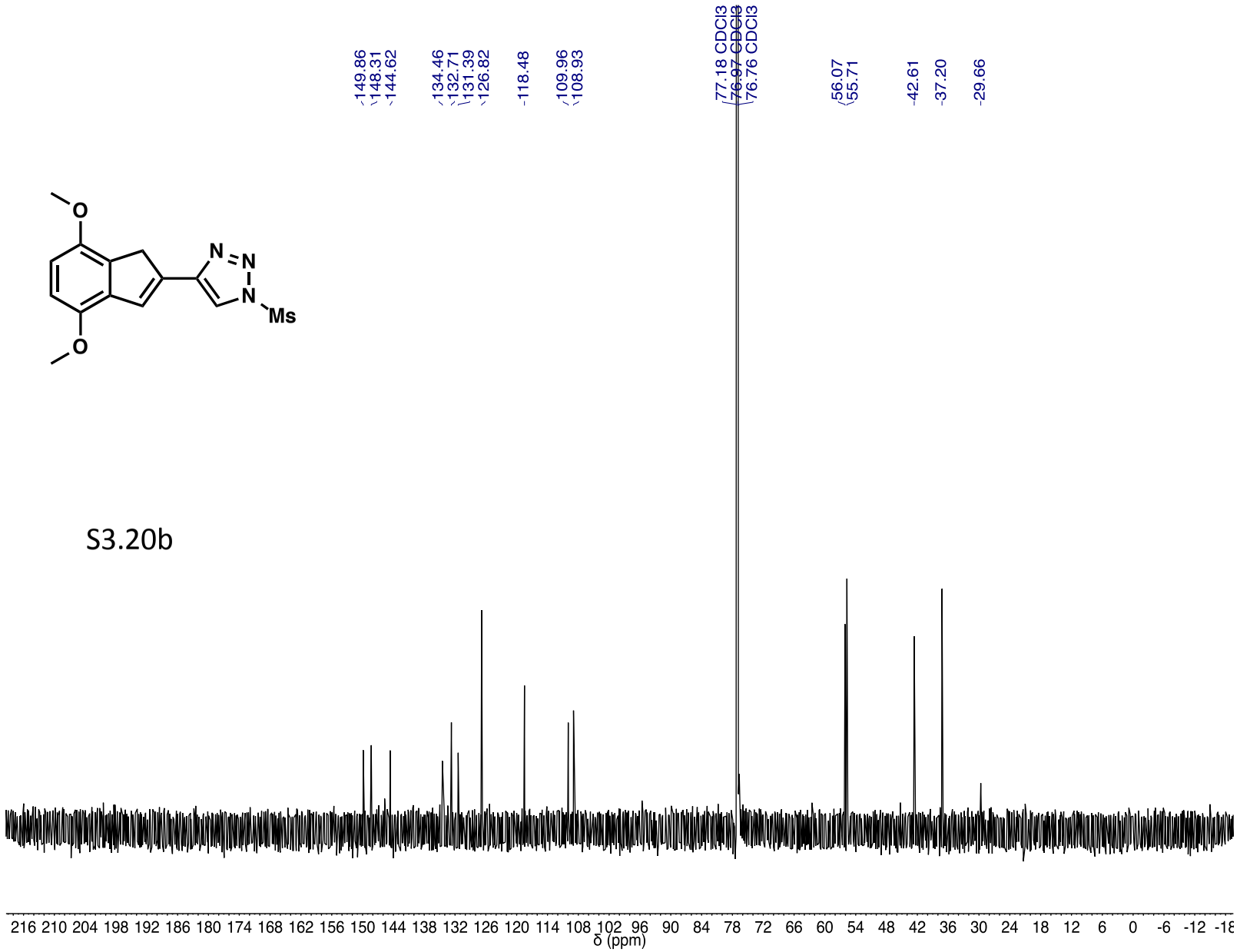
S3.20a

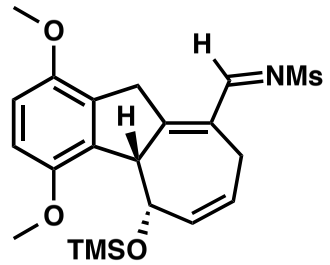

147.41
144.46
144.30
142.75
134.35
133.05
130.51
130.04
128.73
126.85
125.61
123.87
121.65
118.84
-39.14
-21.90
N
N
N
Ts
S3.20a
f1 (ppm)



S3.20b

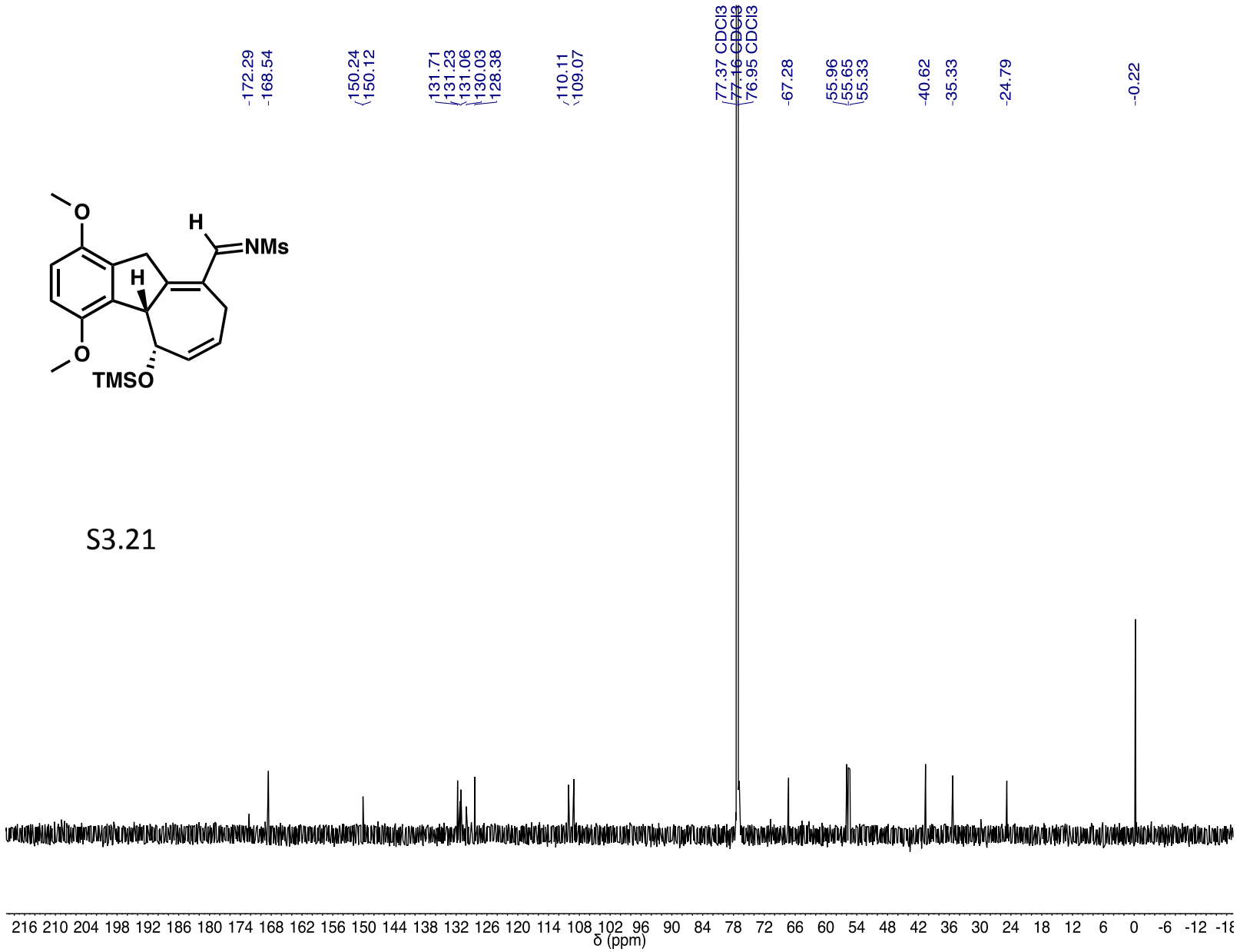
S3.20b


149.86
148.31
144.62
134.46
132.71
131.39
126.82
118.48
109.96
108.93
77.18 CDCl3
76.97 CDCl3
76.76 CDCl3
56.07
55.71
42.61
37.20
29.66
O
O
N
N
N
Ms
216 210 204 198 192 186 180 174 168 162 156 150 144 138 132 126 120 114 108 102 96 90 84 78 72 66 60 54 48 42 36 30 24 18 12 6 0 -6 -12 -18
δ (ppm)


O
H
NMs
H
O
TMSO

S3.21

1.00
1.35
1.25
1.18
1.12
1.08
1.08
1.12
10.12
4.10
3.39
1.59
9.18
δ (ppm)


172.29
168.54
150.24
150.12
131.71
131.23
131.06
130.03
128.38
110.11
109.07
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
67.28
55.96
55.65
55.33
40.62
35.33
24.79
0.22
O
H
NMs
H
O
TMSO
δ (ppm)

S3.21