Catalytic Desymmetrization of Cyclohexadienones

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Kyle A. Kalstabakken

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To Amanda.

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Abstract

2,5-Cyclohexadienones are versatile synthetic building blocks that are currently underutilized in natural product synthesis. The desymmetrization of symmetrically substituted cyclohexadienones is a strategy for the asymmetric synthesis of complex frameworks that has been rapidly gaining popularity. Two desymmetrization methodologies developed by our group are described herein.

The first is a phase-transfer catalyzed intramolecular Michael addition of malonate-tethered cyclohexadienones mediated by *Cinchona* alkaloid-derived ammonium salts. Under these conditions, bicyclic lactones are formed in enantiomeric ratios of up to 91:9. For unsymmetrically substituted substrates, the regioselectivity of the reaction is governed by a combination of steric and electronic affects: cyclization occurs away from sterically bulky substituents and towards electron-withdrawing substituents. In the case of brominated substrates, unique tricyclic cyclopropanes are obtained.

The second methodology is a Pd-catalyzed intramolecular enyne reaction of alkyne-tethered cyclohexadienones. This cyclization occurs with enantiomeric ratios of up to 81:19 in the presence of bipyridine-based chiral ligands. Substituents on the cyclohexadienone core were found to have a great influence on the both the selectivity and the efficiency of the reaction, which can likely be attributed to steric effects.

Finally, the use of the phase-transfer catalysis methodology in the total synthesis of the briarane family of natural products was explored. In the pursuit of a key intermediate containing the briarane core, it was discovered that the enolates of the bicyclic lactone products are particularly unstable, and are not amenable to functionalization. Further studies toward this goal are underway.

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List of Abbreviations

Ac	acetyl
ACN	1,1'-azobis(cyclohexanecarbonitrile)
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	generic aryl group
BHT	butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
cat.	catalytic
coe	cyclooctene
conc.	concentrated
Cy	cyclohexyl
D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dig	digonal
DCC	*N*,*N*′-dicyclohexylcarbodiimide

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DET	diethyl tartrate
DIBAL-H	diisobutylaluminum hydride
DIPEN	1,2-diphenyl-1,2-ethylenediamine
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTS	dimethylthexylsilyl
EC_{50}	half maximal effective concentration
ED_{50}	effective dose for 50% of population
equiv	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
GC	gas chromatography
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple-bond correlation

HRMS	high-resolution mass spectrometry
HPLC	high-performance liquid chromatography
i	iso
IBX	2-iodoxybenzoic acid
IR	infrared
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
M	molar (concentration, moles/L)
M	generic metal, usually group 1 or 2, possibly with ligands
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
mol%	molecular percentage
MoOPD	MoO_5•pyridine•DMPU
Ms	mesyl (methanesulfonyl)
n	normal
NaHMDS	sodium hexamethyldisilazide
NF-κB	nuclear factor- κB
NHK	Nozaki–Hiyama–Kishi
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone

NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
Ph	phenyl
Phe	phenylalanine
PIDA	phenyliodine diacetate (bis(acetoxy)iodobenzene)
PIFA	bis(trifluoroacetoxy)iodobenzene
PINDY	pinene-derived bipyridine
Piv	pivaloyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Pro	proline
PTC	phase-transfer catalyst
Py	pyridyl
pybox	pyridyl bisoxazoline
pymox	pyridyl monooxazoline
R	generic substituent
SPRIX	spiro bis(isooxazoline)
t	tertiary
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
taut.	Tautomerization

TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
Tf	triflyl (trifluoromethylsulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMP	tetramethylpiperidide
TMS	trimethylsilyl
Tol	tolyl
Ts	4-tosyl (4-toluenesulfonyl)
X	generic atom, possibly substituted

Chapter 1

Introduction to Cyclohexadienones

Cyclohexadienones are a synthetically versatile class of molecules derived from phenols.[1] These compounds are present in two varieties: 2,4-cyclohexadienones (**1.1**) and 2,5-cyclohexadienones (**1.2**). Both of these motifs can undergo a large array of transformations, a few examples of which are shown in Figure 1.1. Additionally, the products of these transformations often retain a synthetic handle, such as an enone, useful for further elaboration. As a result, these molecules are attractive intermediates for natural product synthesis.[1,2]

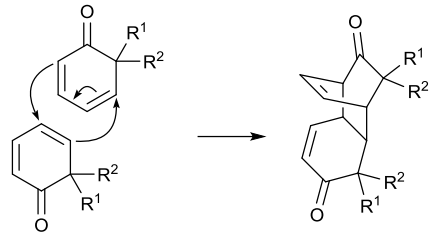
1.1
2,4-cyclohexadienone

1.2
2,5-cyclohexadienone

Figure 1.1. Structure and reactivity of cyclohexadienones.

The greatest practical difference between the two varieties relates to stability. 2,4-Cyclohexadienones have a propensity to dimerize via [4+2] cycloaddition[1] (**1.1**→**1.3**, Scheme 1.1); in many cases, this dimerization is so rapid that the monomeric products cannot be isolated. In contrast, 2,5-cyclohexadienones are usually isolable and generally stable over the time periods required for use as a synthetic intermediate. For this reason, our research has focused on 2,5-cyclohexadienones and all discussion in the remainder of this dissertation pertains to this variety, unless otherwise specified.

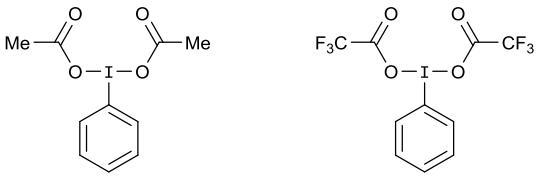
Scheme 1.1. Dimerization of 2,4-cyclohexadienones.



1.1 **1.3**

1.1 Dearomatization of phenols

The most straightforward synthetic route to cyclohexadienones is through the direct oxidative dearomatization of phenols. There are many notable procedures for accomplishing this transformation, including the use of transition-metal complexes,[3–10] singlet-oxygen species,[11–13] or electrochemical systems.[14–16] More recently, the use of hypervalent iodine reagents has become a popular approach.[17–24] The simplicity of the reactions and the commercial availability of reagents such as phenyliodine diacetate (PIDA, **1.4**) and phenyliodine bis(trifluoroacetate) (PIFA, **1.5**) (Figure 1.2) have made hypervalent iodine oxidation the dearomatization method of choice in our group.



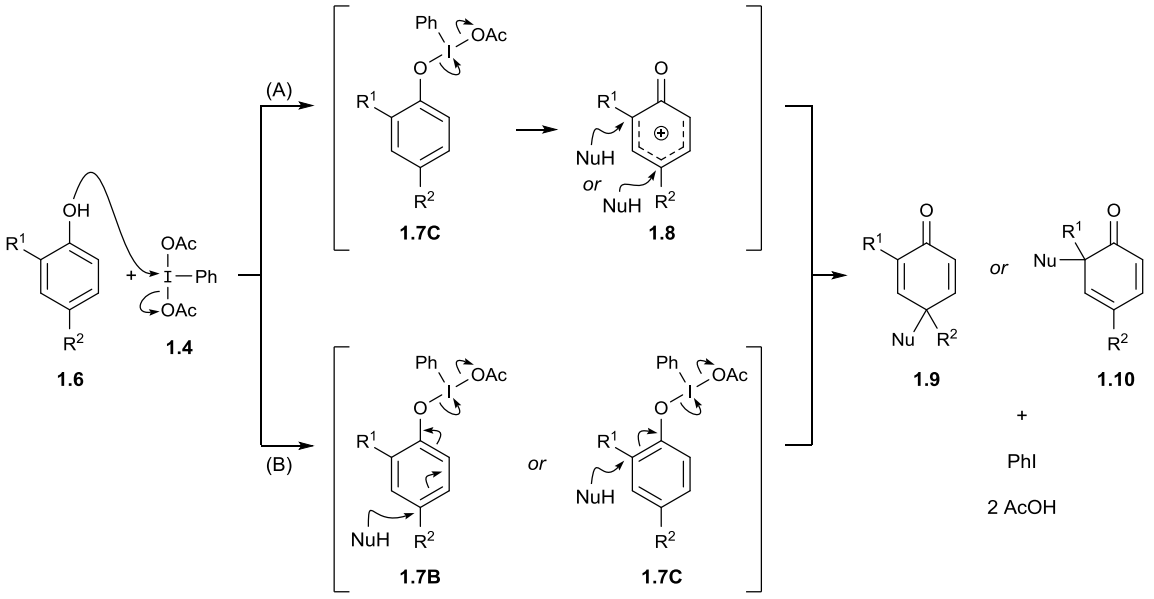
1.4 *PIDA* **1.5** *PIFA*

Figure 1.2. Hypervalent iodine reagents PIDA and PIFA.

The reaction begins with ligand exchange on the iodine center, with the phenolic substrate **1.6** displacing one of the original ligands (e.g., acetate in **1.14**) to provide iodine phenolate **1.7**. At this point, the reaction likely proceeds through a substrate- and solvent-dependent mechanism, the exact nature of which lies somewhere between two extremes.[25] The first (pathway A, Scheme 1.2) is an S_N1-like mechanism in which the aryl iodide dissociates completely (**1.7A**), leaving behind a highly reactive phenoxenium

ion intermediate (**1.8**).[26–28] The nucleophile then adds into the ring, providing the cyclohexadienone product. The second (pathway B) is S_N2'-like: nucleophilic attack and aryl iodide dissociation occur simultaneously (**1.7B** or **1.7C**), directly providing the cyclohexadienone.

Scheme 1.2. Mechanism of hypervalent iodine mediated oxidative dearomatization.

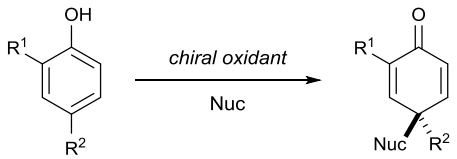


These reactions can produce either 2,5- (**1.9** via para addition) or 2,4-cyclohexadienones (**1.10** via ortho addition). Generally, addition will only occur at a substituted position on the phenol, providing an opportunity for substrate control. Additionally, reagent choice can have a significant influence on regioselectivity: many hypervalent iodine reagents, including PIDA and PIFA, favor para addition. In most cases the nucleophile must either be tethered to the phenol, or be available in solvent quantities.

Most natural product synthetic targets in the literature are chiral and generally exist as a single enantiomer. As a result, the development of synthetic methodologies that provide enantioenriched products is highly desirable. One way to accomplish this goal would be through the investigation of direct enantioselective syntheses of chiral cyclohexadienones. Unfortunately, the enantioselective dearomatization of unsymmetrically substituted phenols has proven to be a very difficult problem However,

some recent advances have been made.[29–34] When successful, this approach affords enantioenriched cyclohexadienones **1.9** directly from phenols **1.6** (Scheme 1.3), providing a framework for the construction of asymmetric complex molecules.

Scheme 1.3. Enantioselective dearomatization of phenols.

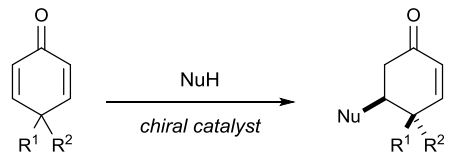


1.6 **1.9**

1.2 Enantioselective desymmetrization of cyclohexadienones

An alternative, and complementary, approach to using these molecules in asymmetric synthesis is the enantioselective desymmetrization of symmetrically substituted cyclohexadienones. Enantioselective desymmetrization[35,36] involves the differentiation of two enantiotopic functional groups (in this case, the two enones) through selective reactivity, thus breaking the symmetry of the molecule. This strategy is extremely versatile, as many of the reactions applicable to cyclohexadienones have the potential provide chiral products through desymmetrization under the appropriate conditions. For example, nucleophilic conjugate addition into cyclohexadienone **1.11** could generate the chiral enone **1.12** in the presence of a chiral catalyst (Scheme 1.4).

Scheme 1.4. Example cyclohexadienone desymmetrization.



1.11 **1.12**

Although the specific challenges of this approach depend on the exact transformation at hand, the general stereochemical considerations are the same. Any reaction that involves the enone double bond has four possible stereochemical outcomes: specifically, the four stereoisomers (**1.12a**–**d**) shown in Figure 1.3. The distribution of

these isomers depends on selective approach to one face of the dienone (**1.13**, diastereoselectivity) and preferential reaction with one of the two olefins (**1.14**, enantioselectivity).

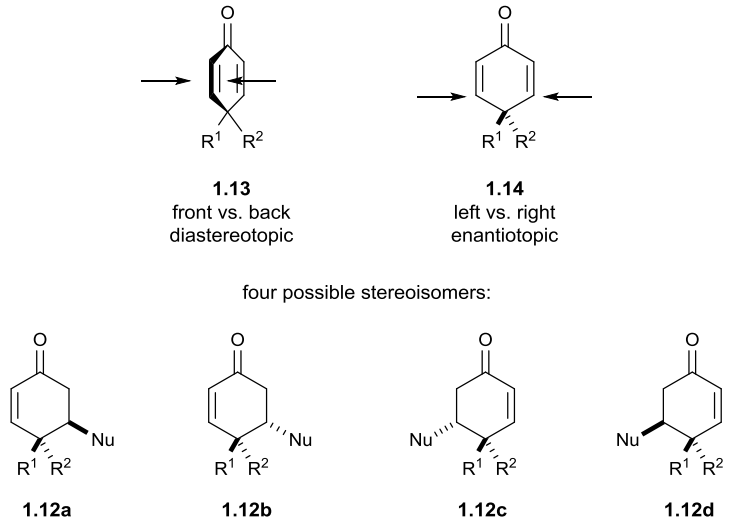
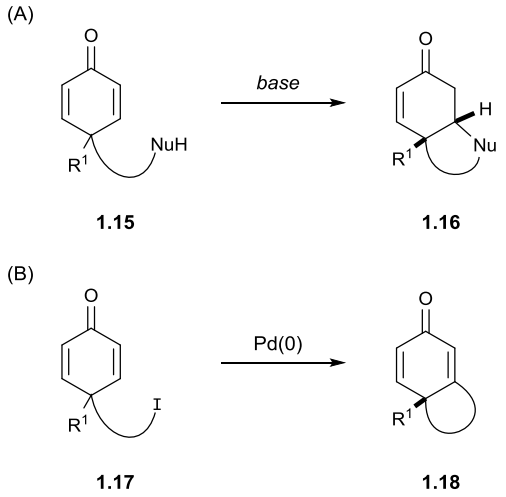


Figure 1.3. Potential stereochemical outcomes of cyclohexadienone desymmetrization.

Designing a catalyst or ligand to control the reaction both diastereoselectively and enantioselectively can be challenging. While many methodologies will necessarily be affected by both issues, there are strategies available to simplify the problem. A common approach is to utilize a reaction with an inherent diastereoselective bias, such as a cyclization reaction that preferentially forms a cis-fused bicyclic system (**1.15→1.16**, Scheme 1.5A). Alternatively, the issue of diastereoselectivity can be avoided completely with transformations that ultimately retain the double bond (e.g., the intramolecular Heck reaction of compound **1.17** to provide bicyclic cyclohexadienone **1.18**, Scheme 1.5B). In both cases, only the enantioselective aspect of the problem remains.

Scheme 1.5. Diastereochemical considerations in the desymmetrization of cyclohexadienones.



No comprehensive review of these desymmetrization reactions has been performed. Recently, Wang and Li reviewed the asymmetric organocatalytic construction of chiral cyclohexenones.[37] Although a section of this review did highlight one class of cyclohexadienone desymmetrization reactions (specifically, organocatalytic Michael additions), a large body of work remains to be covered. The remainder of this chapter aims to address this deficiency by reviewing previous examples of enantioselective cyclohexadienone desymmetrization.

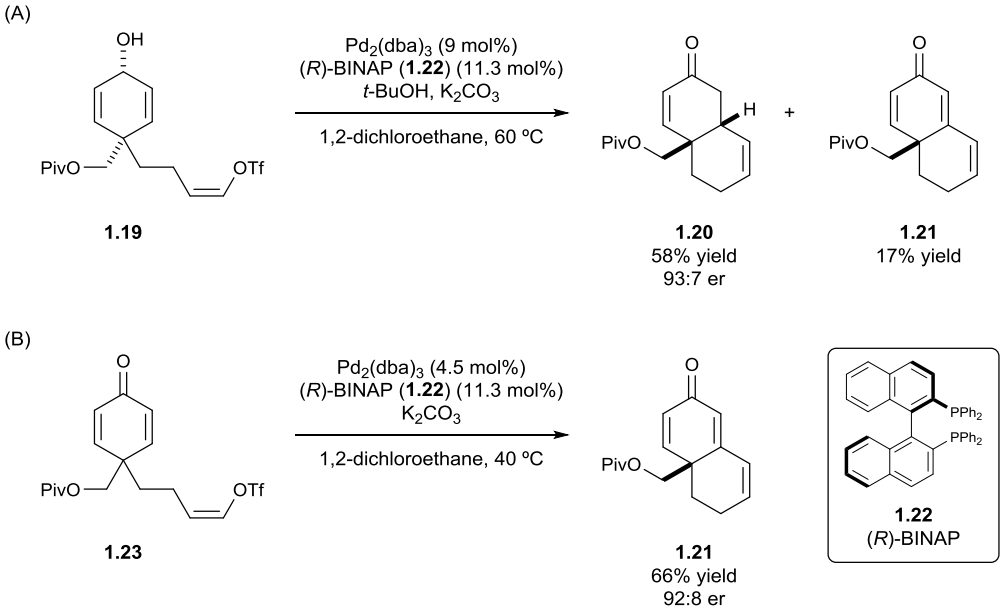
1.3 Transition-metal catalyzed cyclizations

1.3.1 Heck reactions

The first example of enantioselective cyclohexadienone desymmetrization was reported by Shibasaki and coworkers in 1993.[38,39] The authors' primary interest was in the development of an intramolecular Heck reaction of bisallylic alcohol **1.19** to provide cyclohexenone **1.20** in the presence of (*R*)-BINAP (**1.22**) (Scheme 1.6A). Interestingly, cyclohexadienone **1.21** was observed as a side product in significant amounts. The authors postulated that this product might arise from oxidized intermediate **1.23**. To further investigate this observation, **1.23** was subjected to the cyclization conditions. The

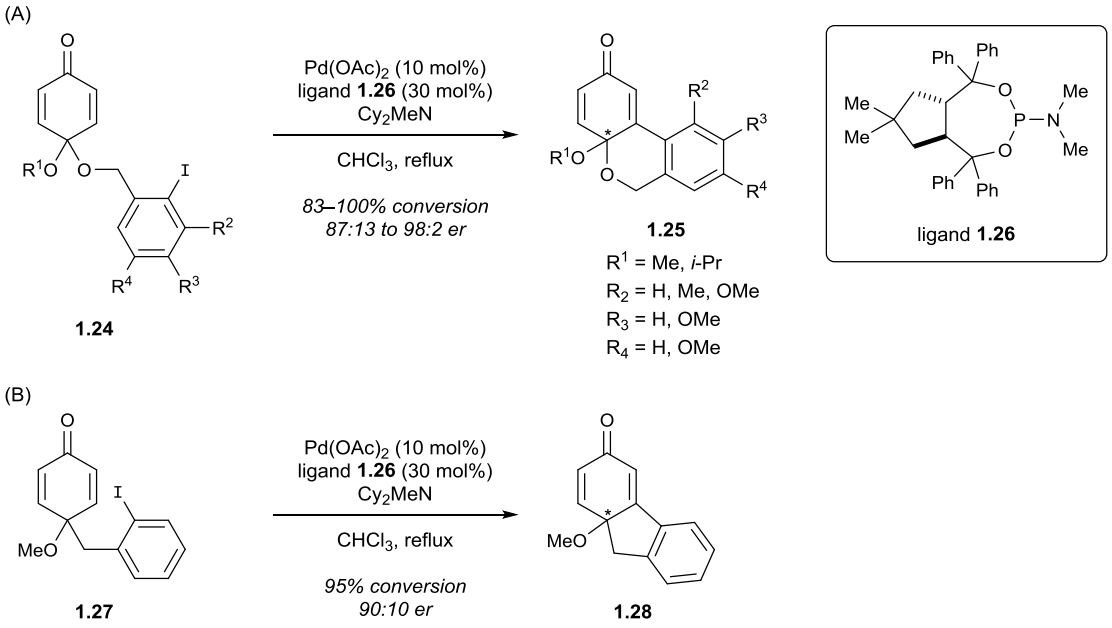
reaction proceeded efficiently, providing the desymmetrized product **1.21** in 66% yield and an enantiomeric ratio of 92:8 (Scheme 1.6B).

Scheme 1.6. Shibasaki's asymmetric Heck cyclization.



Although this result theoretically would serve as a strong preliminary result for developing a cyclohexadienone desymmetrization methodology, the Heck reaction was not investigated in this context again for nearly ten years. In 2002, Feringa reported the Heck cyclization of cyclohexadienone-tethered aryl iodides **1.24** to provide bicyclic dienones **1.26** (Scheme 1.7A).[40,41] A variety of TADDOL-derived monodentate phosphoramidite ligands were screened, with **1.26** providing the highest level of enantioselectivity. Variation of substitution on the substrate had a slight negative effect on both conversion and selective, as the parent substrate (R^1 = Me, R^2,R^3,R^4 = H) provided the best results (100% conversion, 98:2 er). Additionally, carbon-tethered substrate **1.27** successfully underwent cyclization to provide product **1.28** with an enantiomeric ratio of 90:10 (Scheme 1.7B).

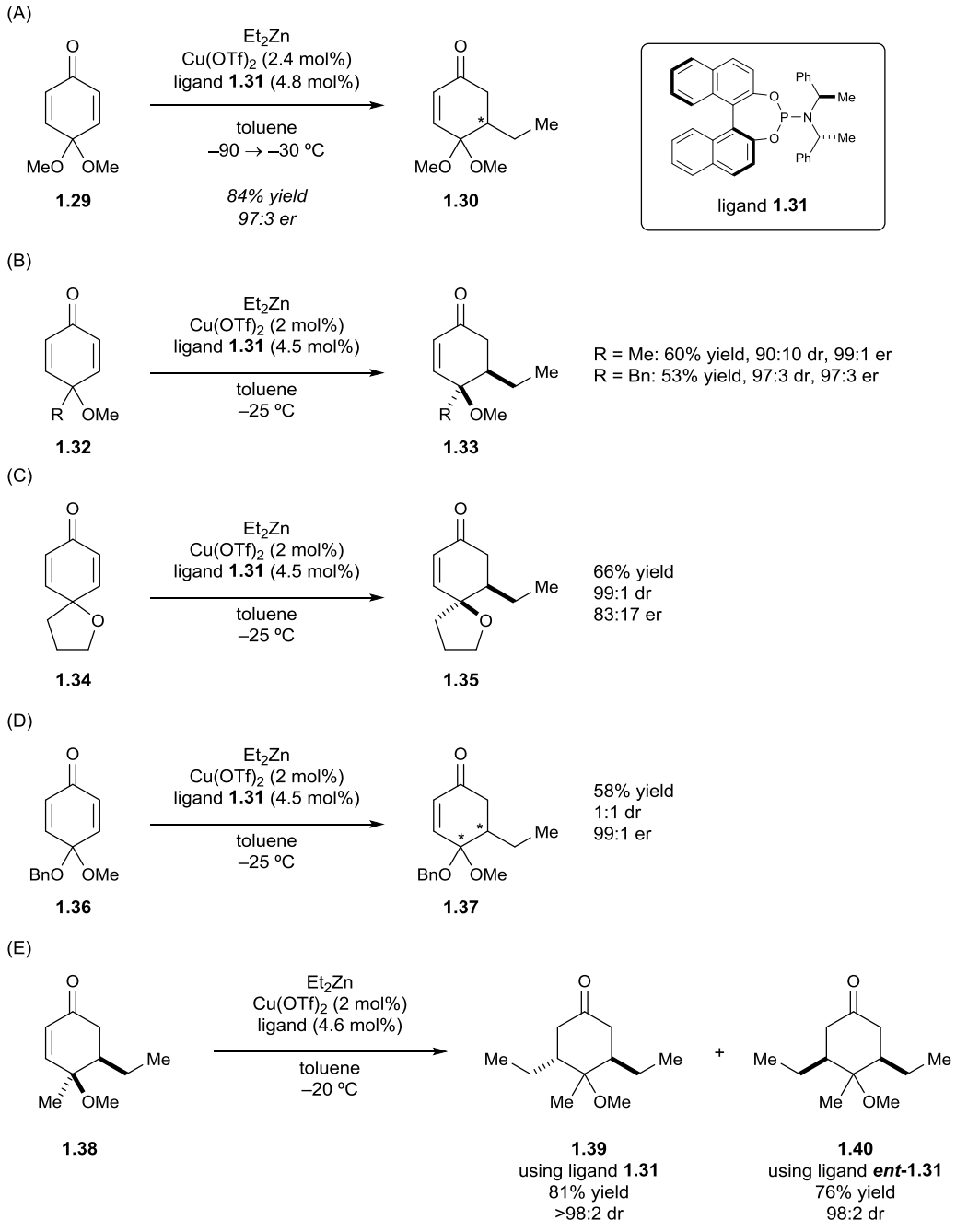
Scheme 1.7. Feringa's asymmetric Heck cyclization.



1.3.2 Conjugate additions

In addition to the Heck cyclization example above, Feringa also performed a serious of studies on the conjugate addition of alkylzinc reagents to cyclohexadienones. A preliminary report in 1997[42] showed the successful Cu-catalyzed addition of Et_2Zn to dienone **1.29** in the presence of phosphoramidite ligand **1.31**, providing enone **1.30** in very good yield and enantiomeric ratio of 97:3 (Scheme 1.8A). This specific example is not a desymmetrization as defined above: because the two substituents at the 4 position of the cyclohexadienone are identical, the two enones are homotopic, not enantiotopic. Feringa and coworkers later expanded on this result, performing conjugate additions into substrates **1.32** to provide desymmetrized enones **1.33** with high levels of enantioselectivity (Scheme 1.8B).[43] Notably, spirocyclic substrate **1.34** exhibited a drastically reduced level of selectivity upon cyclization to **1.35** (Scheme 1.8C).

Scheme 1.8. Feringa's Cu-catalyzed asymmetric conjugate addition.



The authors also found that the diastereoselectivity of the reaction was dictated by a directing effect of alkoxy substitutents in the 4 position, as monoalkoxides **1.32** exhibited excellent stereocontrol, whereas mixed dialkoxide **1.36** was converted to

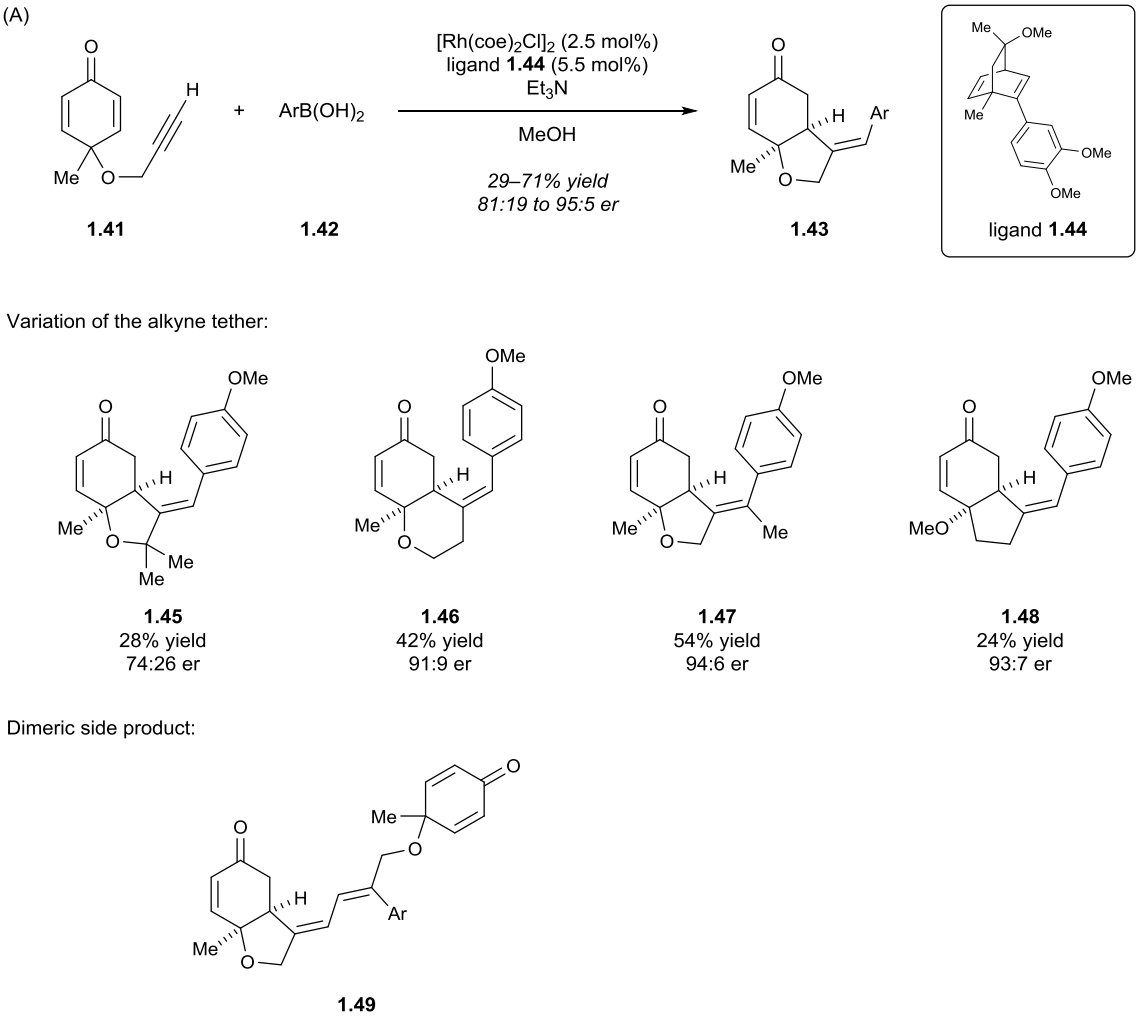
product **1.37** as a 1:1 mixture of diastereomers (Scheme 1.8D). In an additional report,[44] products **1.38** were subjected to a second conjugate addition, providing 3,5-disubstituted cyclohexenones **1.39** and **1.40** (Scheme 1.8E). Interestingly, the authors were able to control the diastereoselectivity of this second addition by utilizing either enantiomer of the phosphoramidite ligand **1.31**, indicating that the selectivity of this addition is completely under catalyst control.

1.3.3 Enyne cyclizations

Recently, a variety of enyne cyclizations of cyclohexadienones have been reported. These reactions are of immediate interest to our group: we reported initial investigations into Pd-catalyzed cyclization in 2009[45] and published the results of our efforts towards an enantioselective version of the reaction in 2013.[46] These findings are discussed in detail in Chapter 3.

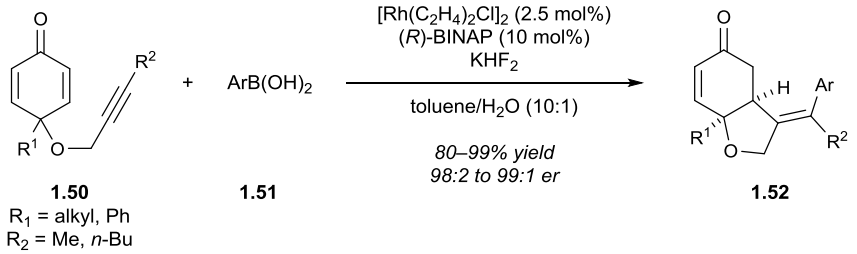
In 2013, Lautens and coworkers developed a Rh-catalyzed cyclization of alkyne-tethered cyclohexadienones.[47] Subjecting substrates **1.41** and aryl boronic acids **1.42** to catalytic $[Rh(coe)_2Cl]_2$ in the presence of diene ligand **1.44** provided bicyclic enones **1.43** in moderate yields with good stereocontrol (Scheme 1.9). The authors found that the stereoselectivity of the reaction was generally insensitive to the nature of the aryl boronic acid, and also to variations of the alkyne tether (products **1.45**–**1.48**). The enantioselectivity of the reaction decreased significantly only when a sterically crowded tether was utilized, providing product **1.45**. Product **1.47** is particularly notable, as it demonstrates that this methodology is also applicable to internal alkynes. The choice of ligand was found to play a large role in both the efficiency and the selectivity of the reaction. Diene ligands were found to be necessary, as phosphine ligands generally lead to decomposition of the starting material. The substitution pattern on the ligand was also found to be very important in suppressing the formation of dimeric side products **1.49**.

Scheme 1.9. Lautens' Rh-catalyzed asymmetric arylative cyclization.



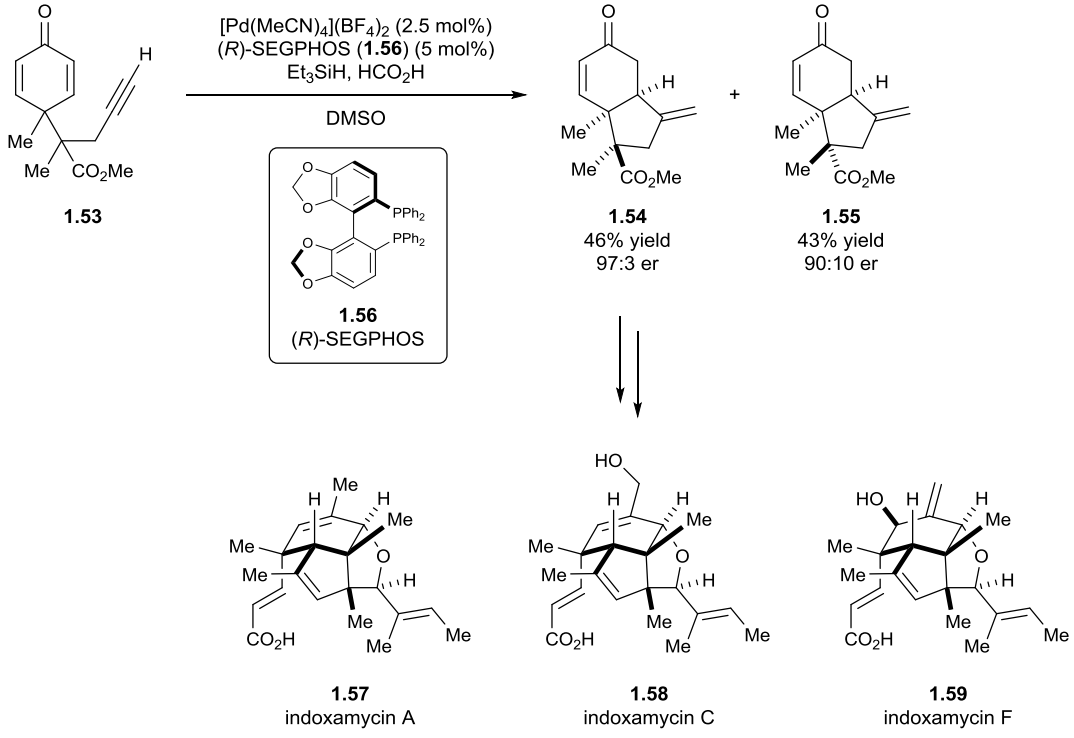
Around the same time as the Lautens report, Tian and Lin published a similar Rh-catalyzed arylative cyclization.[48] In this case, catalytic $[Rh(C_2H_4)_2Cl]_2$ was utilized with (*R*)-BINAP as the chiral ligand to provide products **1.52** from internal alkynes **1.50** and aryl boronic acids **1.51** in excellent yields with high levels of stereocontrol (Scheme 1.10). Once again, the efficiency and selectivity of the reaction were found to be largely insensitive to both substrate substitution and aryl boronic acid identity.

Scheme 1.10. Tian and Lin's Rh-catalyzed asymmetric arylative cyclization.



Recently, Ding and coworkers utilized a Pd-catalyzed reductive enyne cyclization in their synthesis of indoxamycins A, C, and F (**1.57**–**1.59**, Scheme 1.11).[49] Alkyne-tethered cyclohexadienone **1.53** was treated with a cationic Pd catalyst in the presence of (*R*)-SEGPHOS (**1.56**) to provide epimeric products **1.54** and **1.55** with enantiomeric ratios of 97:3 and 90:10, respectively.

Scheme 1.11. Ding's Pd-catalyzed asymmetric cyclization in the synthesis of indoxamycins A, C, and F.



Although this reaction would typically be viewed in terms of diastereoselectivity (and is technically not a desymmetrization reaction as defined above), the stereocenter

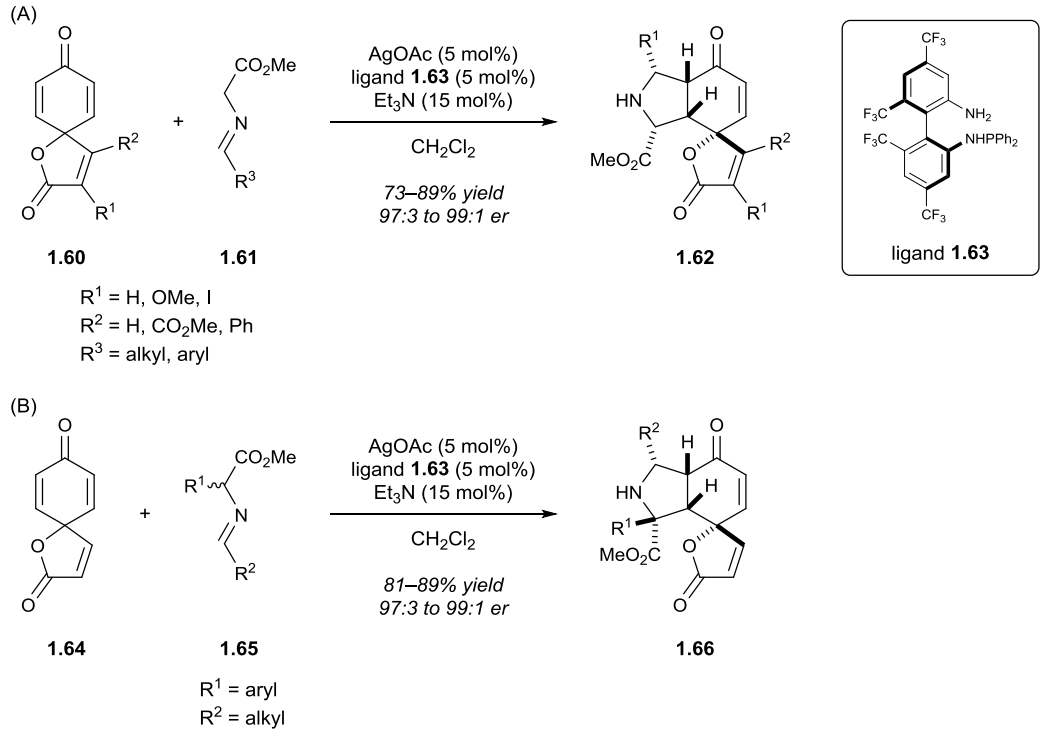
already present in substrate **1.53** appears to have little to no influence on selectivity. As a result, the overall transformation is essentially an enantioselective desymmetrization of the cyclohexadienone core.

Two other asymmetric enyne cyclizations of cyclohexadienone substrates have recently been published.[50,51] The products provided in these reactions are very similar to those provided by our methodology and a discussion of these studies can be found in Chapter 3.

1.3.4 Cycloadditions

Wang and coworkers utilized a Ag-catalyzed [3+2] cycloaddition to provide tricyclic products **1.62** from spiro cyclohexadienones **1.60** and imino esters **1.61** (Scheme 1.12A).[52] These products contain five contiguous stereocenters and are formed with impressive stereocontrol (>20:1 dr, up to 99:1 er) in the presence of TF-BiphamPhos[53] ligand **1.63**. Modifications to the catalyst largely resulted in lower efficiency or selectivity, especially for examples with increased steric bulk near the phosphorus atom. Additional complexity could be incorporated by the use of α-substituted imino esters **1.65**, which yields products **1.66** containing two quaternary stereogenic centers after cyclization with unsubstituted cyclohexadienone substrate **1.64**. These reactions also proceeded in good yields and with high selectivity.

Scheme 1.12. Wang's Ag-catalyzed [3+2] cyclization.



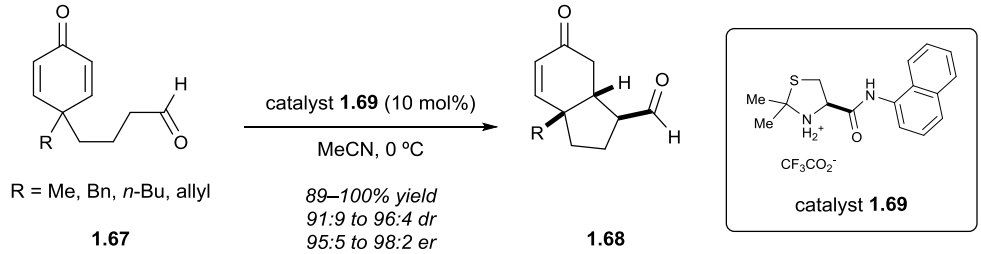
1.4 Organocatalytic reactions

1.4.1 Michael additions

Organocatalytic Michael additions have provided the basis for a large number of desymmetrization methodologies, including our own. This work, published in 2011,[54] will be discussed in Chapter 2.

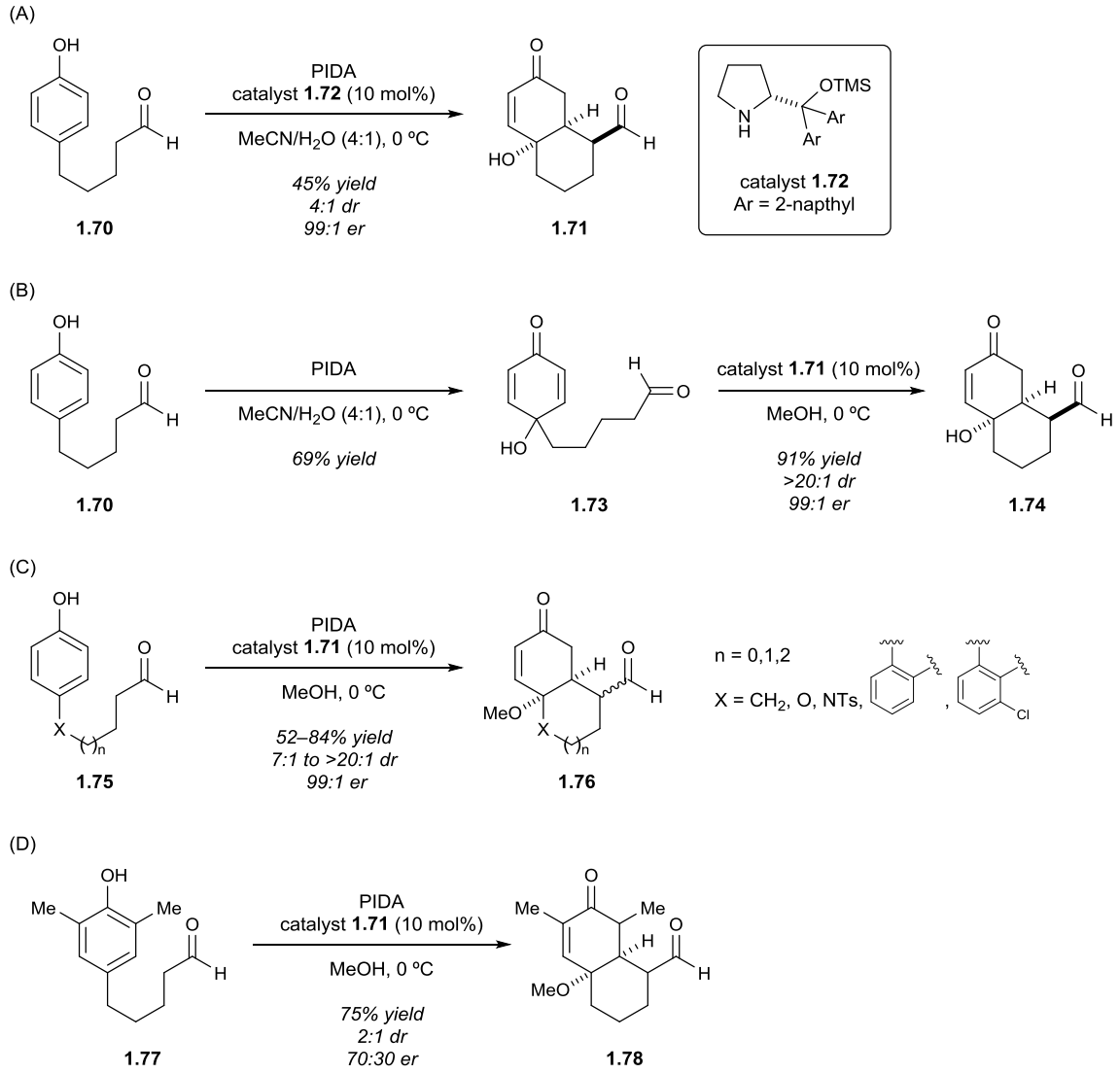
The earliest example of cyclohexadienone desymmetrization through an asymmetric Michael addition was reported by Hayashi in 2005.[55] After a brief catalyst screening, it was found that cysteine-derived catalyst **1.69** promoted the cyclization of aldehydes **1.67**, providing bicyclic products **1.68** with an enantiomeric ratio of up 98:2 (Scheme 1.13). The alkyl substituent at the 4 position of the cyclohexadienone could be varied with very little effect on yield or selectivity. Excellent diastereocontrol was also observed: only cis-ring fusion was observed and the *endo*-aldehyde was observed in only minor amounts.

Scheme 1.13. Hiyashi's organocatalytic asymmetric Michael addition.



In 2007, Gaunt and coworkers demonstrated a one-pot dearomatization/Michael addition sequence.[56] By subjecting aldehyde-tethered phenol **1.70** to PIDA and proline-derived catalyst **1.72**, bicyclic product **1.71** was obtained in modest yield and good selectivity (Scheme 1.14A). The steric bulk of catalyst **1.72** was not only required to obtain high levels of enantioselectivity, but also to protect the amine functional group in the catalyst from oxidation by excess PIDA. To further investigate the diastereoselectivity of the reaction, the authors isolated the intermediate cyclohexadienone **1.73**. When this intermediate was subjected to the Michael addition conditions, the selectivity of the reaction was found to have a strong solvent dependence. Methanol was found to be particularly effective, providing **1.74** in 91% yield and >20:1 dr (Scheme 1.14B). This discovery was then applied to the one-pot reaction, in which enones were produced via intermediate methyl quinols using methanol as the solvent. The cyclization of a variety of aldehyde tethers (**1.75**) was examined, producing enones **1.76** in consistently high yields and enantiomeric ratios (Scheme 1.14C). However, diastereoselectivity was highly substrate dependent, both in the level of selectivity and the identity of the major diastereomer. Finally, α,α-disubstituted substrate **1.77** was cyclized, affording the product **1.78** with poor selectivity, indicating that α substitution is not well tolerated by this reaction (Scheme 1.14D).

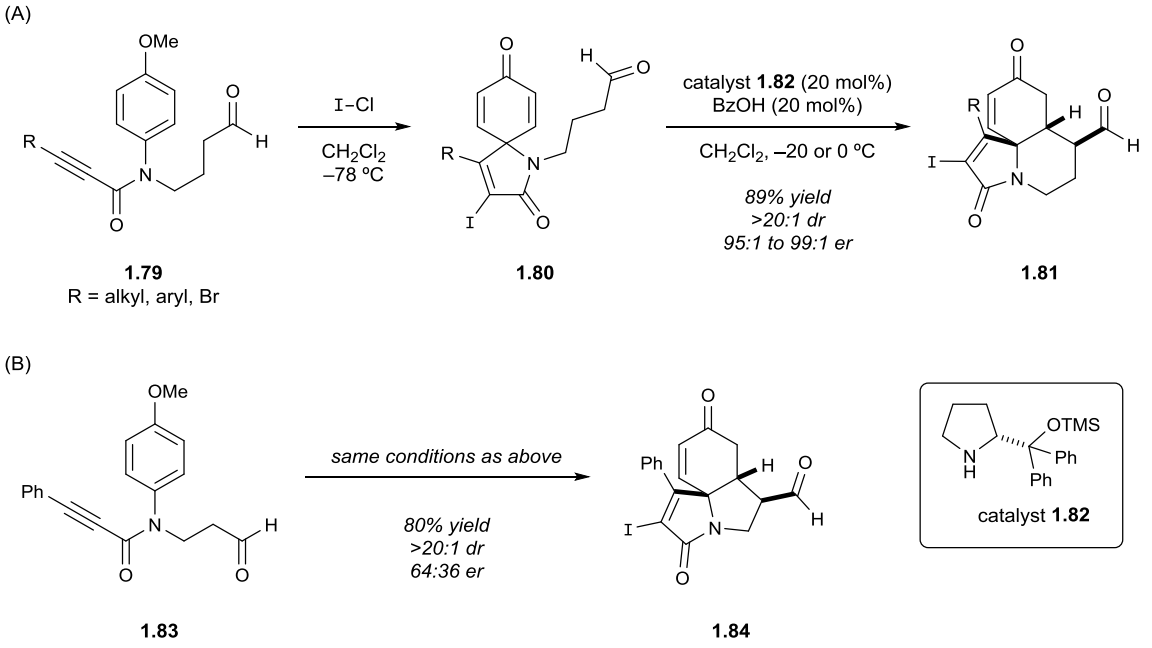
Scheme 1.14. Gaunt's one-pot asymmetric dearomatization/Michael addition sequence.



Gaunt continued to work in the area of dearomatization and desymmetrization, publishing a report of a second conjugate addition methodology in 2011.[57] In this work, alkynamide-tethered cyclohexadienones **1.79** are dearomatized using ICl to provide spirocycles **1.80** (Scheme 1.15A).[58] These intermediates are used without purification in the next step, in which the benzoic acid salt of pyrrolidine catalyst **1.82** promotes the Michael addition of the aldehyde side chain into the dienone core. This reaction provides tricyclic products **1.81**, which contain three contiguous stereocenters and a variety of synthetically useful functional groups. The reaction generally proceeds with high yields

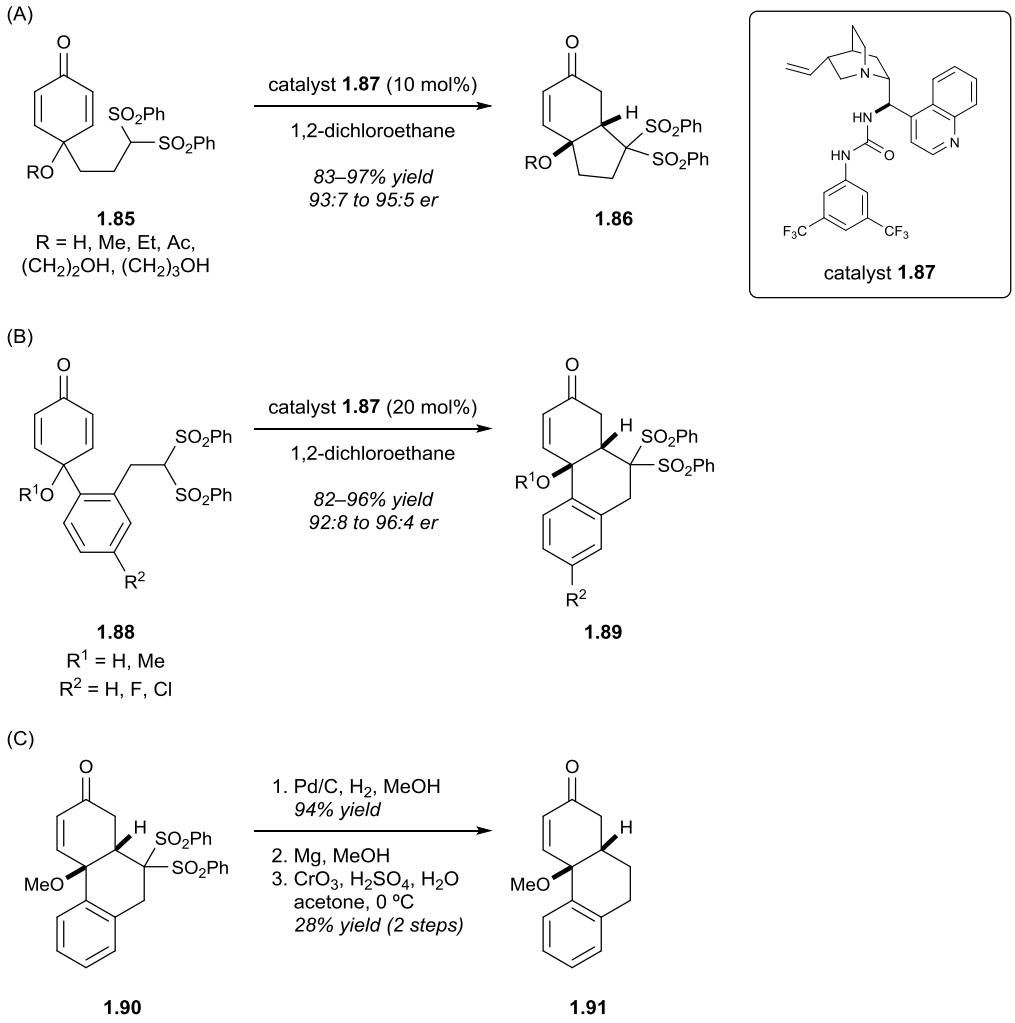
and selectivity – the only notable exception is the cyclization of substrate **1.83**, containing a shortened carbon chain between the amide and aldehyde. In this case, tricyclic lactone **1.84** is obtained as a single diastereomer, but low levels of enantioselectivity are observed (Scheme 1.15B).

Scheme 1.15. Gaunt's asymmetric I-Cl dearomatization/Michael addition sequence.



In 2011, You and coworkers reported an asymmetric bifunctional-urea catalyzed Michael addition.[59] Substrates **1.85** contain a bisphenylsulfonyl methylene group, which is highly activated for use as a Michael donor. Treatment with the *Cinchona* alkaloid-derived catalyst **1.87** provides bicyclic enones **1.86** in high yields with good enantioselectivity (Scheme 1.16A). Substrates with an aryl group internal to the bisphenylsulfonyl tether were also viable in the reaction (**1.88**→**1.89**, Scheme 1.16B). A key feature of these products is the potential to remove the bisphenylsulfonyl groups, which was demonstrated by the conversion bisphenylsulfonyl product **1.90** to the unsubstituted tricyclic enone **1.91** using a three step procedure (Scheme 1.16C).

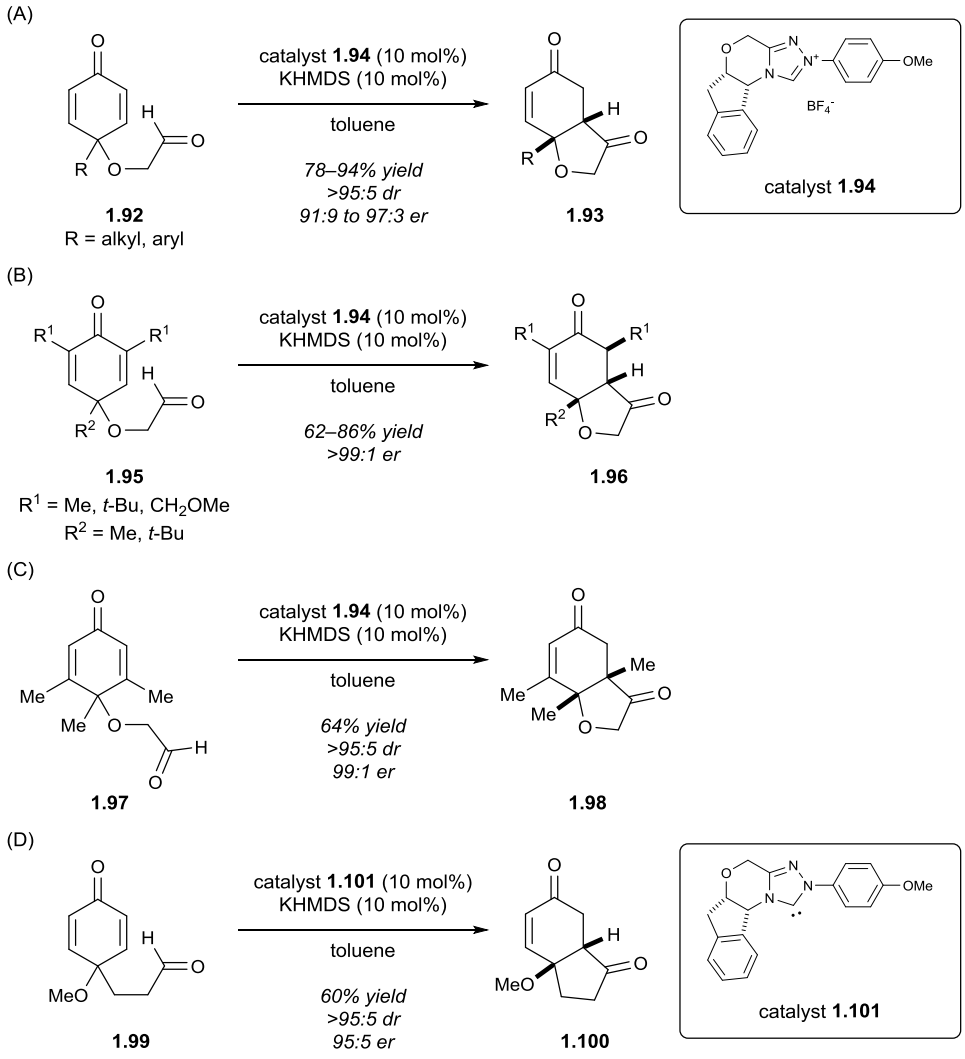
Scheme 1.16. You's asymmetric bifunctional-urea catalyzed Michael addition.



1.4.2 Stetter reactions

In 2006, Rovis and coworkers demonstrated the desymmetrization of cyclohexadienones using an intramolecular Stetter reaction.[60] Aminoindanol-derived triazolium catalyst **1.94** promoted the cyclization of aldehyde substrates **1.92**, providing bicyclic diketones **1.93** in good yield with excellent stereocontrol (Scheme 1.17A).

Scheme 1.17. Rovis' asymmetric intramolecular Stetter reaction.

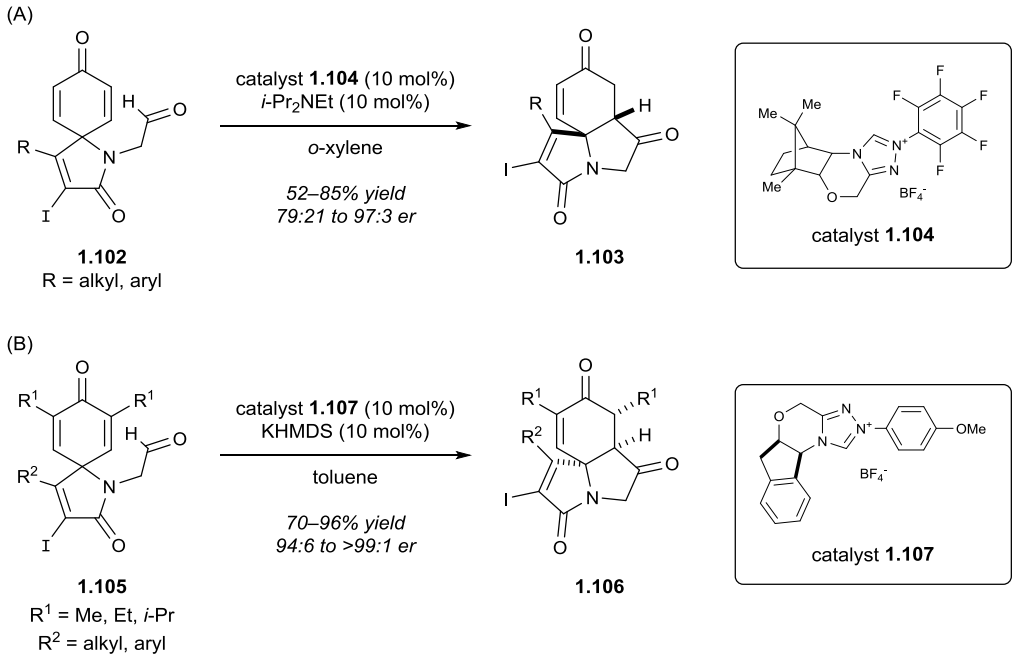


Substitution around the cyclohexadienone ring was well tolerated: α,α-disubstituted substrates **1.95** provided products **1.96** as a single diastereomer (Scheme 1.17B) and β,β-disubstituted substrates **1.97** cyclized efficiently to give products **1.98** containing an additional quaternary stereocenter (Scheme 1.17C). Substrate **1.99** with an all-carbon aldehyde tether also successfully underwent cyclization, providing bicyclic enone **1.100** (Scheme 1.17D), although the use of free carbene catalyst **1.101** was required in this case. Interestingly, the efficiency and selectivity of this reaction were highly dependent on concentration, with dilute conditions (0.008 M) found to be optimal.

The authors suggest that this effect is caused by the increased potential for hydrogen bonding at higher concentrations. In addition to the preliminary report, a detailed account of the development of the methodology, including conditions for gram-scale reactions, has been published.[61]

In 2012, You and coworkers reported the asymmetric intramolecular Stetter reaction of spirocyclic cyclohexadienones.[62] Aldehydes **1.102**, reminiscent of the starting materials used by Gaunt described above, were treated with camphor-derived triazolium catalyst **1.104** to induce cyclization (Scheme 1.18A). Tricyclic products **1.103** were obtained as a single diastereomer in moderate yields with good stereocontrol. In a separate study, the authors extended this methodology to α,α-disubstituted cyclohexadienones.[63] The cyclization of these substrates (**1.105→1.106**) required altered conditions, including the use of aminoindanol-derived triazolium catalyst **1.107**.

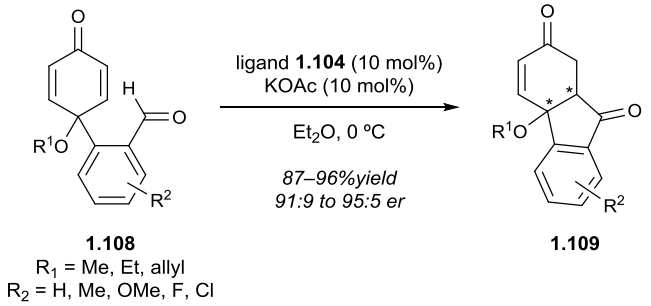
Scheme 1.18. You's asymmetric intramolecular Stetter reaction of spirocyclic cyclohexadienones.



Continuing their investigation of desymmetrizations via Stetter reactions, You and coworkers also developed the cyclization of aryl-substituted cyclohexadienones **1.108**.[64]

Using the camphor-derived catalyst **1.104** from their previous study, products **1.109** were obtained in very good yield with high enantioselectivity.

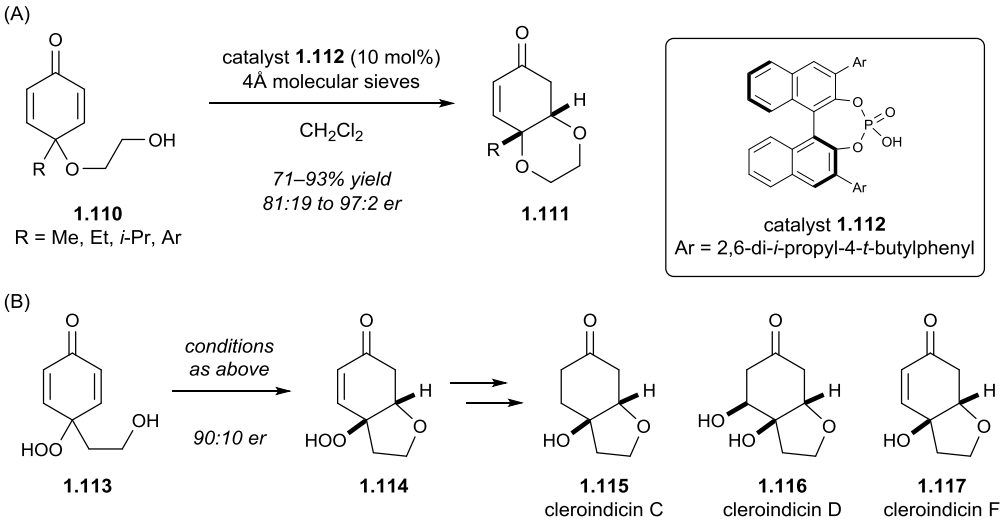
Scheme 1.19. You's asymmetric intramolecular Stetter reaction of 4-aryl substituted cyclohexadienones.



1.4.3 Other conjugate additions

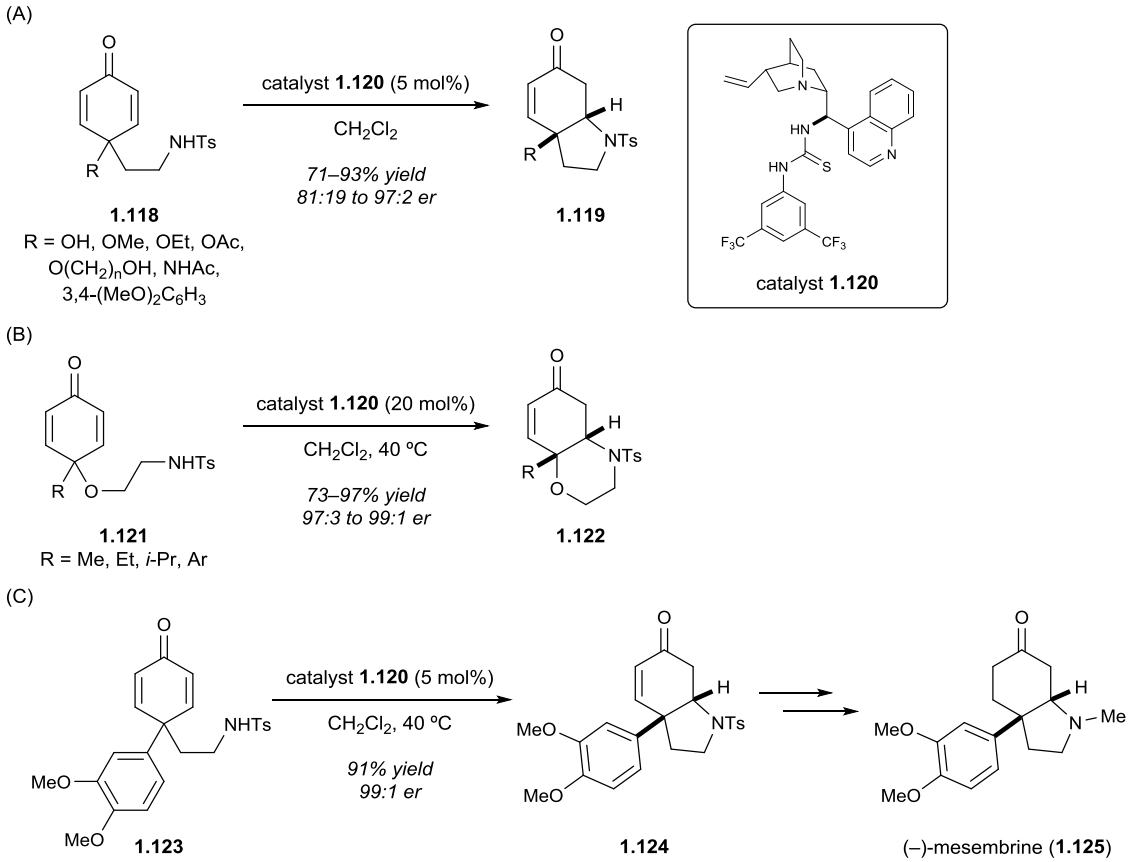
You and coworkers also investigated desymmetrizations involving other conjugate addition reactions. In 2010, they reported the Brønsted acid-catalyzed intramolecular oxo-Michael addition of cyclohexadienones **1.110**.[65] Cyclization to afford bicyclic products **1.111** in the presence of chiral phosphoric acid **1.112** proceeded in good yields with high levels of stereocontrol (Scheme 1.20A). Aryl-substitution at the 4 position of the cyclohexadienone was well tolerated; however, the use of alkyl groups larger than methyl resulted in decreased enantioselectivity. The utility of this methodology was demonstrated in the synthesis of cleroindicins C, D, and F (**1.115**–**1.117**, Scheme 1.20B).

Scheme 1.20. You's asymmetric intramolecular oxo-Michael addition.



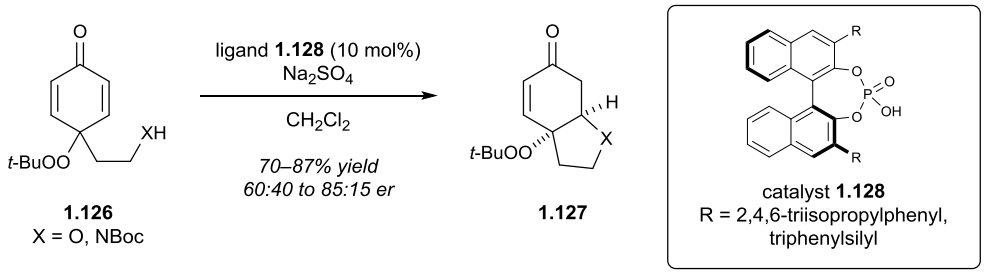
In a separate study, You also described an aza-Michael addition catalyzed by *Cinchona* alkaloid-derived thioureas.[66] Catalyst **1.120** promoted the cyclization of sulfonamide-tethered cyclohexadienones **1.118**, providing bicyclic enones **1.119** (**Scheme 1.21**A) in good yields with high levels of enantioselectivity. Interestingly, substrates capable of undergoing oxo-Michael addition (**1.118**, R = $O(CH_2)_nOH$) preferentially cyclize through sulfonamide addition. The cyclization of oxygen-tethered substrates **1.121** to afford morpholine derivatives **1.122** was also investigated (**Scheme 1.21**B). The efficiency of this reaction followed the same trend as the oxo-Michael addition: high yields and enantiomeric ratios were obtained for most 4-substituted substrates, but isopropyl substitution caused a drop in yield and *t*-butyl substitution shut down the reaction completely. Finally, the authors applied this methodology in the total synthesis of (–)-mesembrine (**1.125**), obtaining key intermediate **1.124** from the cyclization of cyclohexadienone **1.123** (**Scheme 1.21**C).

Scheme 1.21. You's asymmetric intramolecular aza-Michael addition.



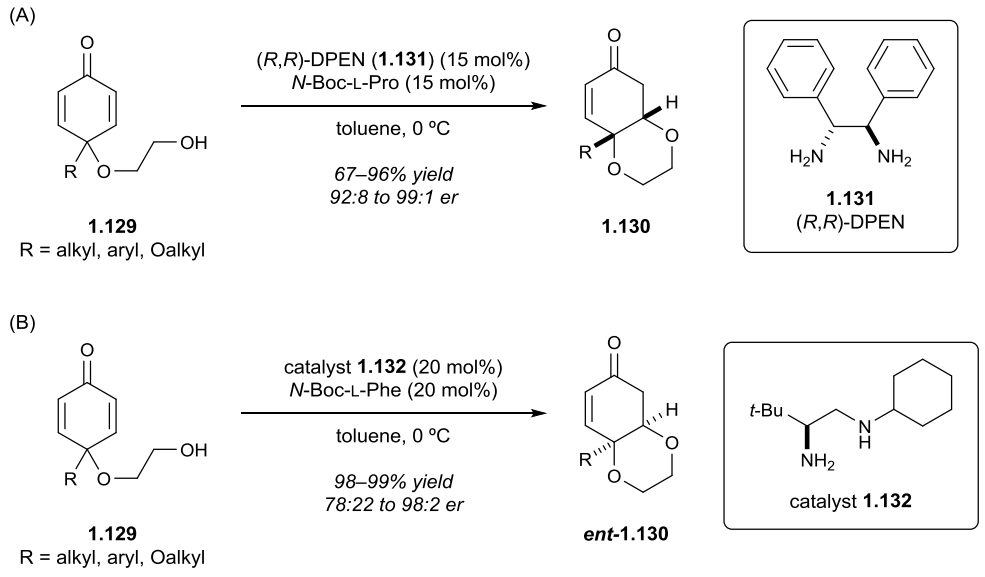
Doyle and coworkers reported a one-pot tandem dearomatization/conjugate addition procedure.[67] While the desired reaction did occur with excellent diastereocontrol, an efficient enantioselective version was elusive. As a part of their investigation, the authors attempted the asymmetric cyclization of cyclohexadienones **1.126** using chiral phosphoric acid catalysts **1.128**. Bicyclic ethers and carbamates **1.127** were afforded in good yields, but with modest enantioselectivity (Scheme 1.22).

Scheme 1.22. Doyle's assymetric intramolecular conjugate additions.



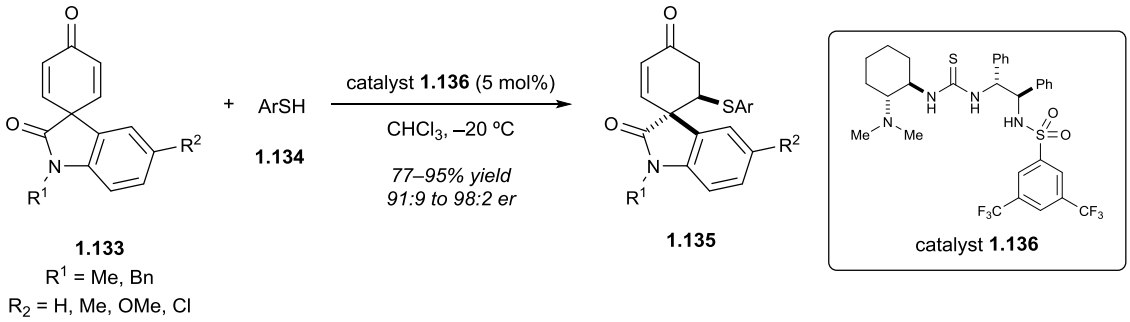
Ye and coworkers developed a chiral diamine-catalyzed version of oxo-Michael addition, published in 2013.[68] (*R*,*R*)-DPEN (**1.131**) mediated cyclization of cyclohexadienones **1.129** provided byclic ethers **1.130** in good yields with very good stereocontrol (Scheme 1.23A). The authors were also able to access the enantiomeric series of products (***ent*-1.130**) through the use of diamine catalyst **1.132** (Scheme 1.23B). In both cases, an amino acid additive was required for the reaction to proceed. Substitution at the 4 position of the cyclohexadienone was well tolerated, as a variety of alkyl-, aryl-, and oxo-substituted substrates cyclized efficiently. However, variation of the alcohol tether length was not well tolerated: both increasing and decreasing the chain length resulted in the formation of nearly racemic products.

Scheme 1.23. Ye's asymmetric intramolecular oxo-Michael addition.



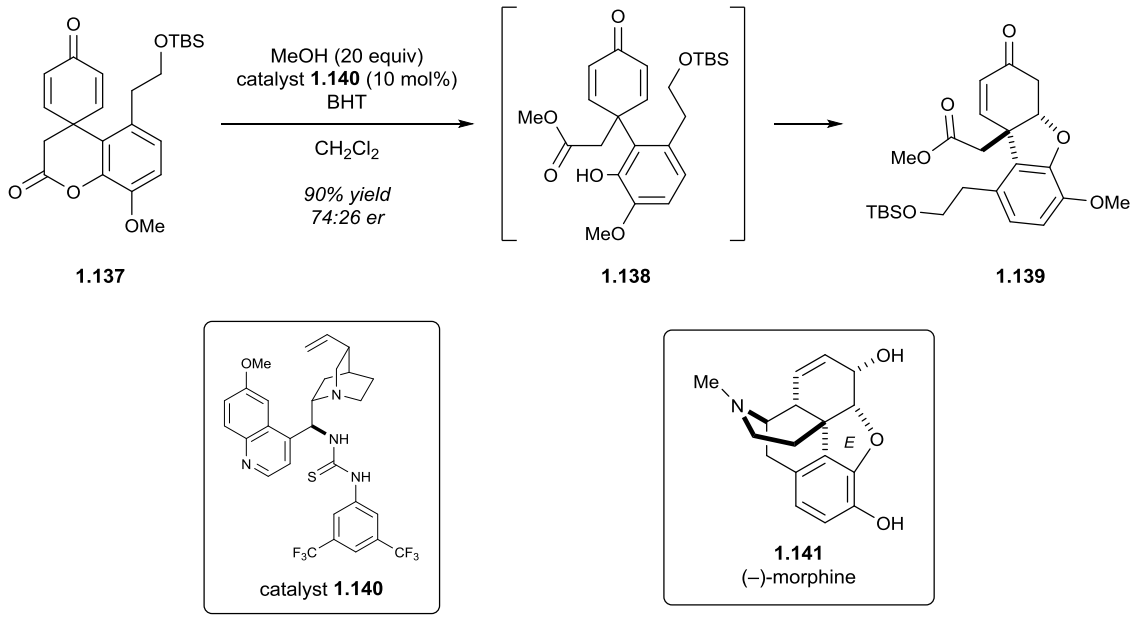
Later in 2013, Wang and coworkers reported the desymmetrization of cyclohexadienones via an asymmetric sulfa-Michael addition.[69] Spirocyclic oxindole substrates **1.133** were treated with aryl sulfides **1.134** in the presence of bifunctional thiourea catalyst **1.136** (Scheme 1.24). Products **1.135** were obtained in high yields and with high levels of enantiocontrol. The reaction is very tolerant of substitution on both the aryl sulfide as well as the arene ring of the oxindole.

Scheme 1.24. Wang's asymmetric intramolecular sulfa-Michael addition.



The potential utility of desymmetrizing conjugate additions was demonstrated by Fan and coworkers in their formal synthesis of (±)-morphine (**1.141**).[70] Although the overall synthesis accesses racemic material, the authors did investigate a potential asymmetric desymmetrization reaction for the formation of the morphine E ring. Specifically, spirolactone **1.137** was treated with various alcohols in the presence of bifunctional thiourea catalyst **1.140** to induce a tandem alcoholysis/oxa-Michael addition. Although the reaction did proceed in good yield, the authors were unable to attain high levels of enantioselectivity despite extensive optimization. The best conditions, shown in **Scheme 1.25**, provided **1.138** through intermediate **1.139** with in an enantiomeric ratio of 74:26.

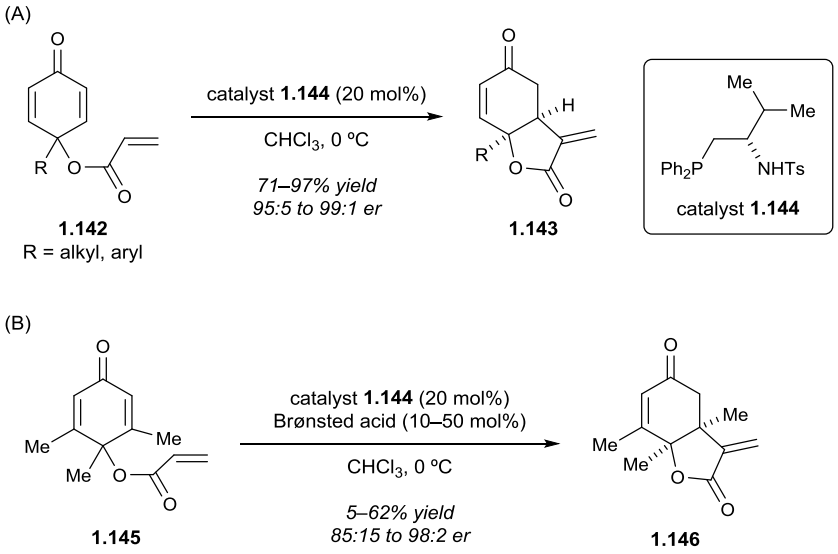
Scheme 1.25. Asymmetric alcoholysis/oxo-Michael addition in Fan's synthetic investigations of morphine.



1.4.4 Rauhut–Currier reactions

In 2012, Sasai and coworkers reported the asymmetric Rauhut–Currier reaction[71] of cyclohexadienones bearing unsaturated esters.[72,73] Substrates **1.142** were efficiently converted to bicyclic lactones **1.143** in good yields and high levels of enantioselectivity (Scheme 1.26A). Lewis basic catalysts (e.g., PPh_3) could be employed in the reaction, but only with an accompanying Brønsted acid catalyst (e.g., phenol). The authors identified bifunctional catalyst **1.144**, which satisfied both catalytic requirements and provided excellent stereocontrol. The cyclization of β,β-disubstituted substrate **1.145** was also investigated (Scheme 1.26B). In this case, the reaction provided lactone **1.146** with a low level of stereoselectivity. The use of a Brønsted acid catalyst in addition to catalyst **1.144** provided higher levels of selectivity, but also lower yields. This inverse relationship was observed with a variety of phenolic Brønsted acids, with the extreme example being the use of phenol (50 mol%) to afford **1.146** in 5% yield and an enantiomeric ratio of 98:2. Unfortunately, the authors were unable to find conditions that provided both high yields and high levels of selectivity.

Scheme 1.26. Sasai's asymmetric intramolecular Rauhut–Currier reaction.

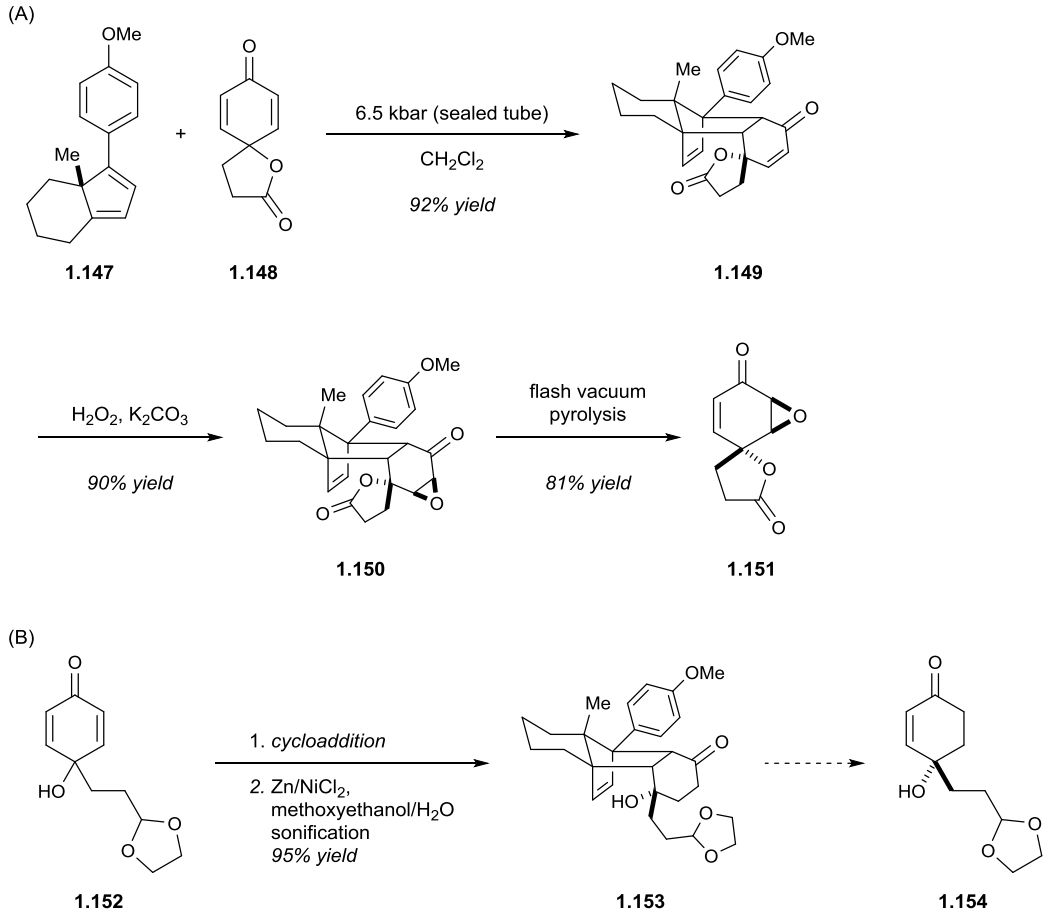


1.5 Desymmetrization using internal asymmetric induction

There have been a few examples of internal asymmetric induction being used to achieve formal enantioselective transformations of cyclohexadienones. These sequences allow the relevant stereocenters to be installed in a diastereoselective manner, greatly simplifying the challenges associated with cyclohexadienone desymmetrization.

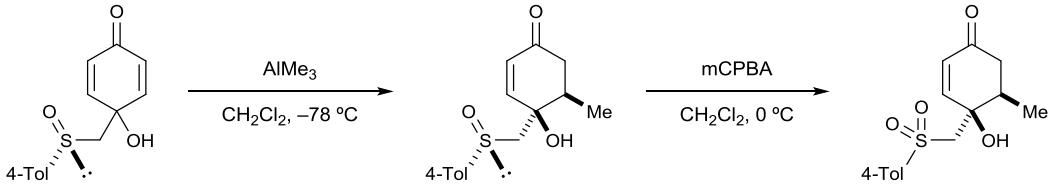
In 1995, Winterfeldt and coworkers reported the formal enantioselective epoxidation of spirolactone **1.148** through the use of a chiral Diels–Alder adduct.[74] The cycloaddition of **1.148** and cyclopentadiene **1.147** provided adduct **1.149**, which underwent diastereoselective epoxidation when treated with H_2O_2 and K_2CO_3 to afford **1.150** (Scheme 1.27A). Release of the enone core was accomplished by flash vacuum pyrolysis, affording the formal desymmetrization product **1.151** after a three step sequence. In a later report, the Winterfeldt group described an in depth investigation of the Diels–Alder reaction.[75] This study also included a cycloaddition/reduction sequence (**1.152→1.153**, Scheme 1.27B) that upon release of enone **1.154** would correspond to a formal enantioselective hydrogenation of a cyclohexadienone; however, the authors did not perform the cycloreversion reaction on this particular substrate.

Scheme 1.27. Winterfeldt's use of a Diels–Alder adduct as a chiral auxiliary.



Also in 1995, Carreño and coworkers reported the synthesis of chiral sulfoxide **1.155**.[76] Shortly thereafter, the group described the diastereoselective addition of $AlMe_3$ into the cyclohexadienone core[77,78] (**1.155→1.156**, Scheme 1.28). Oxidation of the sulfoxide with mCPBA provides sulfone **1.157**, the formal result of an enantioselective $AlMe_3$ conjugate addition. The Carreño group has demonstrated this methodology numerous times in the synthesis of natural products.[79–82]

Scheme 1.28. Carreño's use of a chiral sulfoxide for internal asymmetric induction.



1.155 **1.156** **1.157**

1.6 Summary

Over the past 20 years, there have been numerous advances in techniques for the enantioselective desymmetrization of cyclohexadienones. Although a few of these techniques have been applied in the total synthesis of relatively simple natural products, the widespread use of cyclohexadienone desymmetrization has yet to be realized. Given the rapidly growing interest in this field, this trend is likely to change in the coming years. The remainder of this dissertation describes our contributions in this area, as well as progress towards the application of our methodologies to natural product synthesis.

Chapter 2

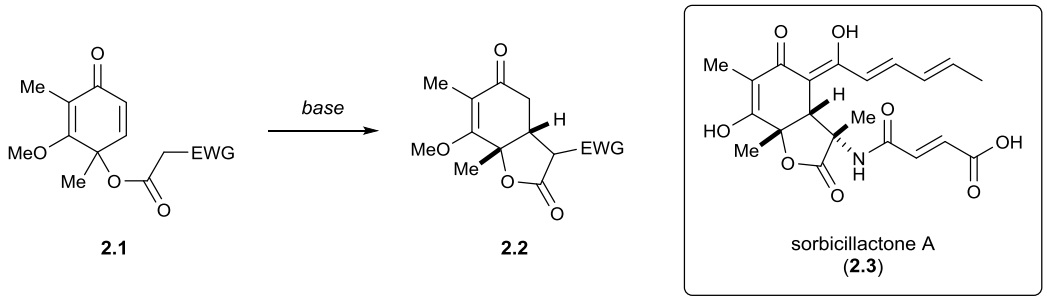
Phase-Transfer Catalyzed Cyclization of Cyclohexadienones Tethered to Active Methylene Groups[†]

2.1 Background

In 2009, our group began work on the total synthesis of sorbicillactone A (**2.3**, Scheme 2.1).[83] This natural product, isolated in 2003, is a member of the sorbicillinoid family[84] and has shown antileukemia, anti-HIV and neuroprotective activity.[85,86] A key sequence in the synthesis involved the cyclization of cyclohexadienone **2.1**. The base sensitivity that cyclohexadienones exhibit necessitated the use of a mild base for the reaction. Therefore, an electron-withdrawing group was required in order to activate the methylene protons in **2.1** for deprotonation. Successful intramolecular Michael addition would provide compound **2.2**, which contains the bicyclic core of sorbicillactone A.

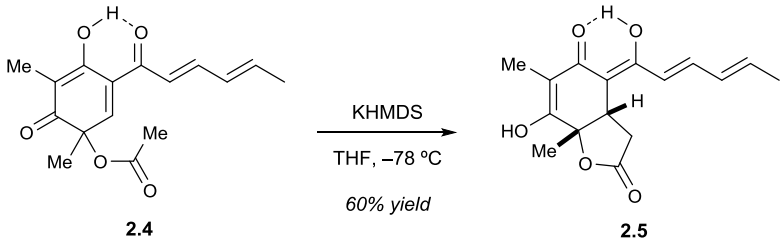
[†] This work was performed in collaboration with Rodolfo Tello-Aburto and Kelly Volp. A significant portion of these results have been published previously.[54] Relevant sections reproduced by permission of The Royal Society of Chemistry (RSC).

Scheme 2.1. Intramolecular Michael addition in the synthesis of sorbicillactone A.



A similar cyclization was achieved by Nicolaou in his synthetic studies of various bisorbicillinoid analogues[87] (**2.6**, Scheme 2.2). In this case, the Michael acceptor was activated by the sorbyl sidechain in **2.4**. This activation allowed for the use of KHMDS to deprotonate the unactivated acetate, providing **2.5** after cyclization. While the use of a strong base was successful in this case, the authors did specify that Lewis acids caused decomposition of the starting material, emphasizing the sensitivity of these substrates.

Scheme 2.2. Nicolaou's intramolecular cyclization of acetate **2.4**.

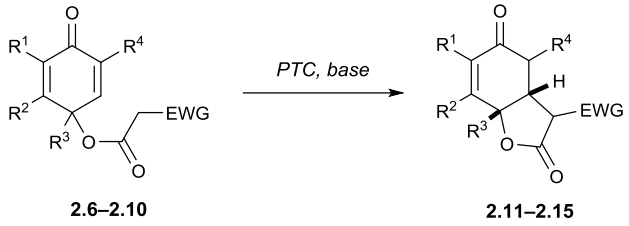


2.2 Objective

While our initial motivation for developing this reaction arose in the context of synthesizing sorbicillactone A, we realized that this methodology could prove to be of general use. Therefore, we sought to investigate the transformation of a wide variety of cyclohexadienones **2.6–2.10** to bicyclic lactones **2.11–2.15** (Scheme 2.3) in order to determine the scope of the reaction, observe any trends in regioselectivity, and ultimately develop conditions for enantioselective cyclization. We hypothesized that selective

desymmetrization could be achieved using a suitable chiral phase-transfer catalyst (PTC)[88–90].

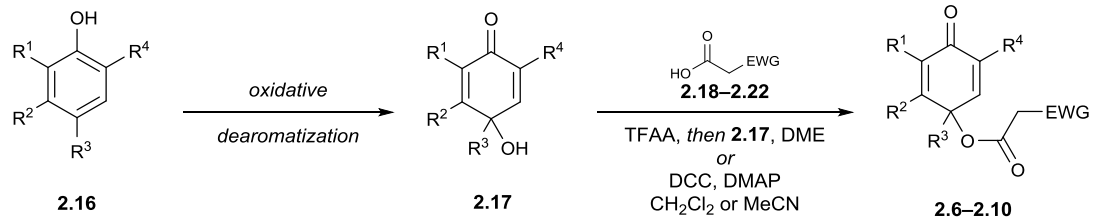
Scheme 2.3. Desymmetrization of cyclohexadienones via phase-transfer catalyzed cyclization.



2.3 Substrate synthesis

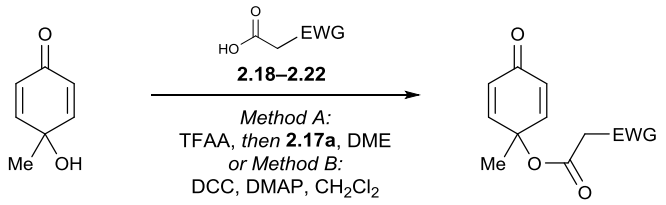
All substrates (**2.6**–**2.10**) used for this study were prepared in two steps from the corresponding phenols **2.16**: oxidative dearomatization was followed by coupling of the resulting quinols **2.17** to malonic acid monoesters **2.18–2.22** or other activated methylene compounds (Scheme 2.4). Coupling was initially accomplished with a trifluoroacetic anhydride-mediated coupling of the tertiary alcohol with the malonic acid mono ester;[91] however, the use of DCC was later found to be more convenient and cost effective, particularly on larger scales.

Scheme 2.4. Synthesis of substrates through dearomatization and ester coupling



These reactions are applicable to a wide range of substrates. Various malonic esters are tolerated (Table 2.1, entries 1, 2, 3), as are other electron-withdrawing groups such as amides (entry 4) and sulfones (entry 5).

Table 2.1. Synthesis of substrates with varied electron-withdrawing groups.

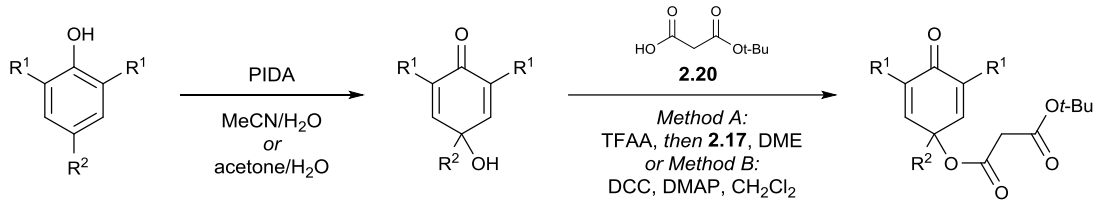


Entry	Ester	Acid	EWG	Method	Yield (%)
1	**2.6**	**2.18**	CO_2allyl	A	66
2	**2.7**	**2.19**	CO_2Bn	A	63
3	**2.8a**	**2.20**	CO_2*t*-Bu	A	43
4	**2.9**	**2.21**	morpholine amide	B	96
5	**2.10**	**2.22**[a]	4-toluenesulfonyl	B	57[b]

[a] Acid **2.22** is the corresponding aryl sulfide. [b] After oxidation of the aryl sulfide to the aryl sulfone.

As discussed below (Section 2.6), the majority of our substrates were derived from mono-*t*-butyl malonate (**2.20**). Two series of substrates were synthesized: the first (Table 2.2) was derived from symmetrically substituted phenols **2.16a–m** for use in our initial studies (Section 2.4) and in our enantioselectivity studies (Section 2.6), while the second (Table 2.3) was derived from unsymmetrically substituted phenols **2.16n–t** and was designed to be utilized in our regioselectivity studies (Section 2.5).

Table 2.2. Synthesis of substrates derived from symmetrically substituted phenols.



2.16a–m **2.17a–m** **2.8a–m**

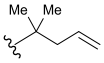
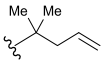
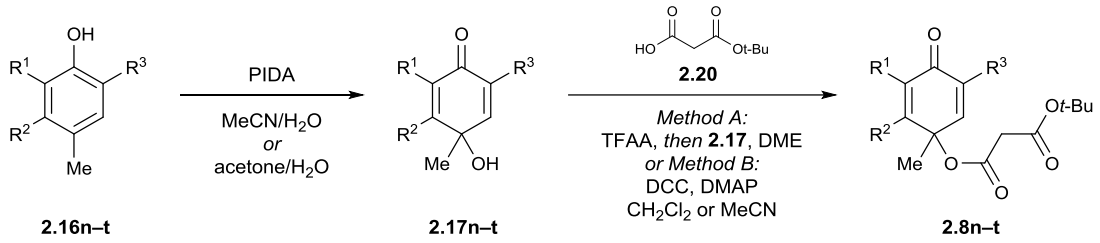
Entry	Quinol	R^1	R^2	Yield (%) of quinol	Ester	Method	Yield (%) of ester
1	**2.17a**	H	Me	known[13]	**2.8a**	A	43
2	**2.17b**	H	Ph	known[92]	**2.8b**	A	36
3	**2.17c**	H	*i*-Pr	73	**2.8c**	A	56
4	**2.17d**	H	CH_2CO_2Me	40	**2.8d**	A	38
5	**2.17e**	H	CH_2t-Bu	31	**2.8e**	B	>99
6	**2.17f**	H	CH_2CH_2OTBS	known[93]	**2.8f**	B	74
7	**2.17g**	H		37	**2.8g**	B	50
8	**2.17h**	Me	Me	78	**2.8h**	B	>99
9	**2.17i**	TMS	Me	67	**2.8i**	B	86
10	**2.17j**	Br	Me	known[21]	**2.8j**	B	>99
11	**2.17k**	Br	*i*-Pr	78	**2.8k**	B	95
12	**2.17l**	Br		74	**2.8l**	B	81
13	**2.17m**	Br	CH_2CH_2OTBS	42	**2.8m**	B	96

Table 2.3. Synthesis of substrates derived from unsymmetrically substituted phenols.

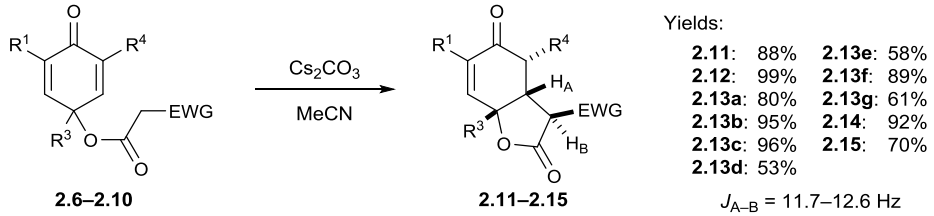


Entry	Quinol	R^1	R^2	R^3	Yield (%) of quinol	Ester	Method	Yield (%) of ester
1	**2.17n**	Me	OMe	H	80	**2.8n**	B	98
2	**2.17o**	Me	H	H	known[13]	**2.8o**	B	95
3	**2.17p**	H	Me	H	48	**2.8p**	B	73
4	**2.17q**	TMS	H	H	51	**2.8q**	B	82
5	**2.17r**	H	H	Br	76	**2.8r**	A	69
6	**2.17s**	H	Me	Br	74	**2.8s**	B	96
7	**2.17t**	Me	OMe	Br	51	**2.8t**	B	55

2.4 Initial studies

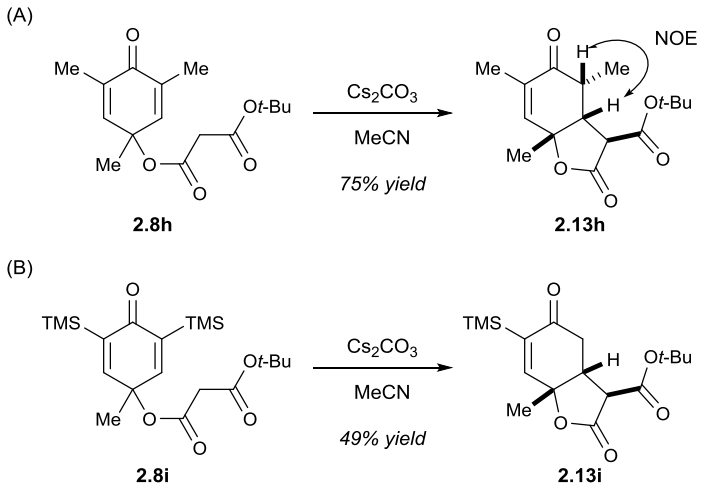
Despite the base sensitivity that cyclohexadienones generally exhibit,[1] the cyclization of dienones **2.6–2.10** proceeded well with Cs_2CO_3 in acetonitrile, providing bicyclic products **2.11–2.15** (Scheme 2.5). Cyclization occurred efficiently even for sterically hindered systems (e.g., **2.8c**, **2.8e**, and **2.8g**). Substrate **2.8d** is also notable, as the potential problem of tertiary carboxylate elimination was not observed. In all cases, the bicyclic lactone product was isolated as a single diastereomer. The cis-fused ring system was confirmed by NOE experiments on **2.11** and **2.13h**, while the configuration of the stereocenter bearing the electron-withdrawing group was assigned through coupling constant analysis. At this time, it is not clear if a second diastereomer also forms during the reaction and then epimerizes under either the reaction or isolation conditions.

Scheme 2.5. Cyclization of symmetric substrates.



α-Disubstituted cyclohexadienones also underwent cyclization successfully, albeit with much longer reaction times (1–4 days). In the case of **2.8h**, the product **2.13h** contains four contiguous stereocenters and was formed as a single diastereomer (Scheme 2.6A). Although disilane **2.8i** did cyclize successfully (Scheme 2.6B), the product (**2.13i**) contained only one trimethylsilyl group, resulting from protodesilylation of the α-silyl ketone.[94–96] The region- and stereochemical features of this reaction are discussed in the following sections (Sections 2.5 and 2.6).

Scheme 2.6. Cyclization of α-substituted symmetric substrates.

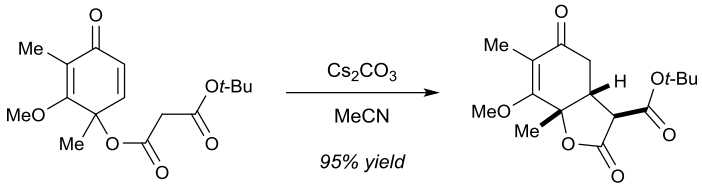


2.5 Regioselectivity studies

We were interested in examining the influence of various substituents on the regioselectivity of these anionic reactions. The cyclization of vinylogous ester substrate **2.8n** (Scheme 2.7) was completely regioselective and afforded **2.13n** (the intermediate

used in our groups synthesis of sorbicillactone A,[83] see Section 2.1) in high yield. This result can most simply be explained by electronic effects, as one olefin of the cyclohexadienone can be considered to be a vinylogous ester and, consequently, less electrophilic.

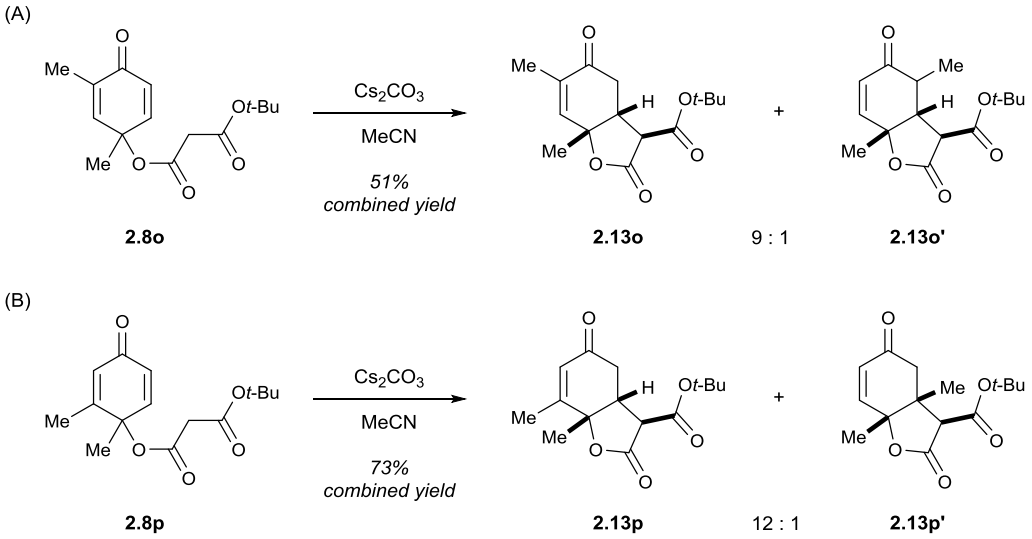
Scheme 2.7. Regioselective cyclization of vinylogous ester substrate **2.8n**.



2.8n **2.13n**

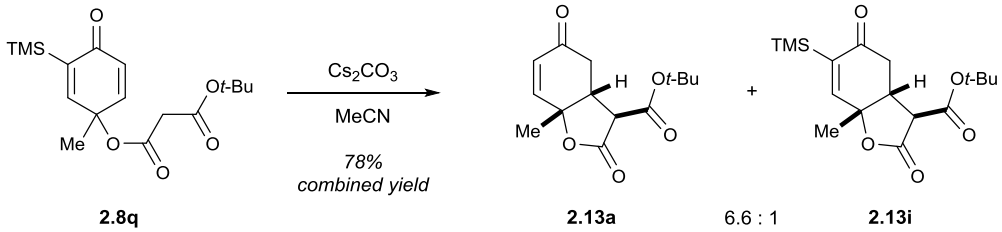
The methylated substrates **2.8o** and **2.8p** cyclized with very good regioselectivity. Compound **2.8o**, with the methyl group in the α position, cyclized with a 9:1 ratio of regioisomers **2.13o** and **2.13o'** (Scheme 2.8A). This result is in agreement with an observation made by Giomi and co-workers concerning the addition of diethyl malonate to a α-methyl substituted dienone.[97] Higher regioselectivity (12:1) was observed in the cyclization of β-methyl substrates **2.8p** to **2.13p** and **2.13p'** (Scheme 2.8B). This dependence could easily be attributed to steric effects; however, an electronic argument involving the weakly electron-donating nature of methyl substituents should not be discounted.

Scheme 2.8. Regioselective cyclizations of methyl-substituted substrates.



Finally, the cyclization of vinyl silane **2.8q** (Scheme 2.9) was investigated. Considering a purely steric model, the increased bulk of the trimethylsilyl group in **2.8q** as compared to the methyl group in **2.8o** should increase selectivity. Similarly, the lower group electronegativity of a TMS group (2.06 eV)[98] relative to a methyl group (~2.3 eV)[99] would also be expected to give rise to higher regioselectivity. In practice, however, the cyclization of **2.8q** afforded **2.13a** as the major product (6.6:1 ratio of **2.13a** and **2.13i**). In this case, compound **2.13a** is the product of conjugate addition onto the silicon-bearing olefin, followed by protodesilylation. This reversal in selectivity can be attributed to silicon's ability to stabilize an adjacent negative charge,[100,101] while the aforementioned electronegativity difference likely explains why complete selectivity is not observed. These findings imply that electronic effects are the major factor that determines the selectivity of these cyclizations.

Scheme 2.9. Regioselective cyclization of trimethylsilyl-substituted substrate **2.8q**.



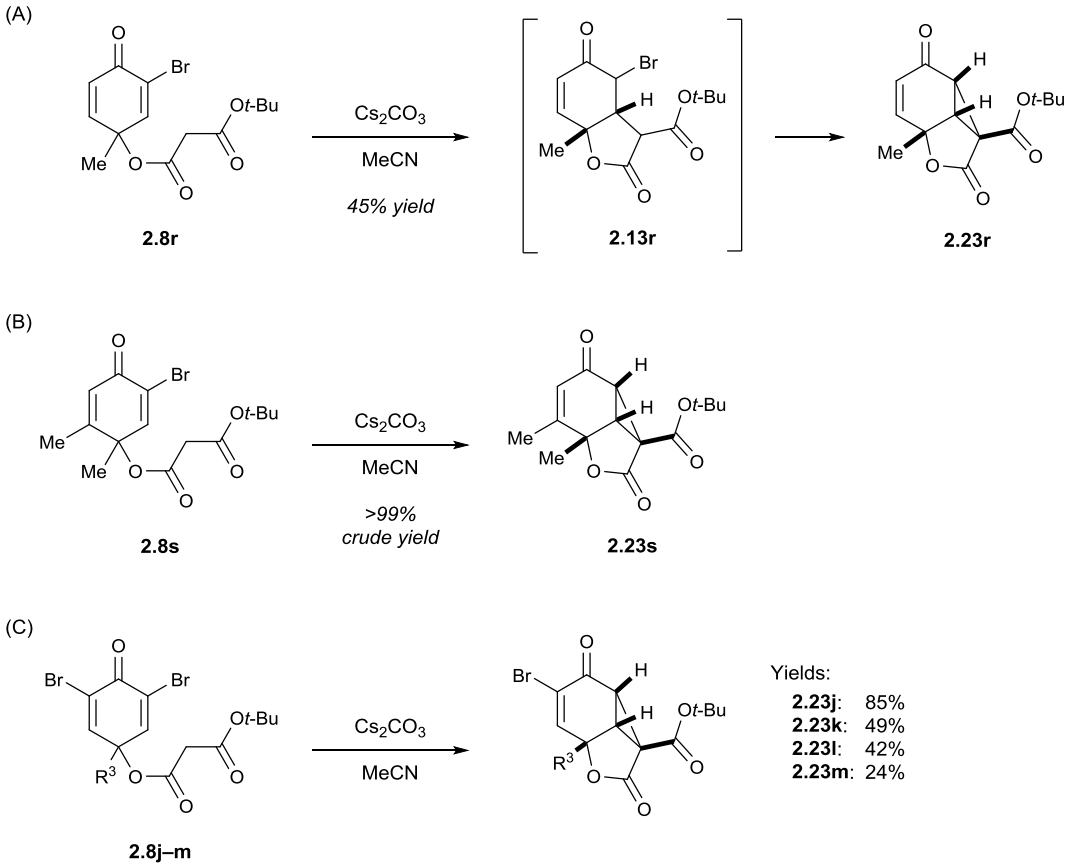
2.8q **2.13a** **2.13i**

2.5.1 Brominated substrates

If the regioselectivity observed during the cyclizations described in the previous section was indeed due primarily to electronic effects, the presence of an electron-withdrawing group on the cyclohexadienone should reverse the observed regioselectivity. In other words, an anionic nucleophile should preferentially attack the olefin bearing the electron-withdrawing group. Bromine is particularly attractive in that it is easily installed, usually has a positive impact in terms of chemical yield on the oxidative dearomatization step, and serves as a useful handle for further synthetic transformations.

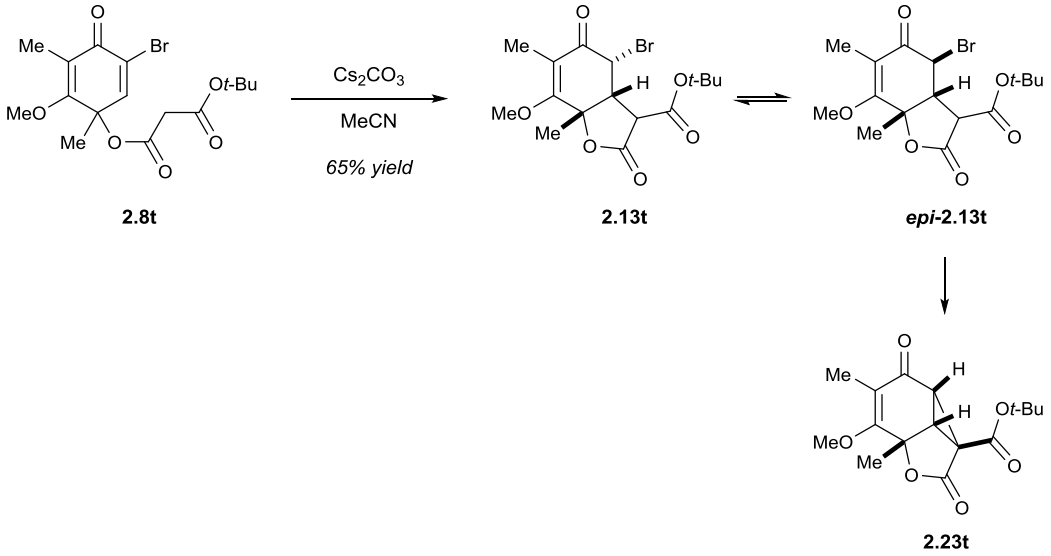
When the bromine-containing substrate **2.8r** was subjected to the cyclization conditions, the tricyclic cyclopropane **2.23r** was obtained (Scheme 2.10A). While this outcome was unexpected, there have been numerous examples in the literature of similar cyclopropanations.[102–105] Importantly, the conjugate addition required to initiate the cyclopropanation pathway occurred with complete regioselectivity: no products arising from addition into the less substituted double bond in **2.8r** were observed. Similarly, substrate **2.8s** cyclized to give cyclopropane **2.13s** exclusively (Scheme 2.10B). This cyclopropanation could also be extended to the symmetric dibromides **2.8j–m** (Scheme 2.10C).

Scheme 2.10. Cyclization of bromine-substituted substrates.



Interestingly, while the cyclization of **2.8t** proceeded well, it was noticeably slower than the reactions of **2.8r** and **2.8s**. If the reaction of **2.8t** was terminated early, bromide **2.13t** could be isolated as a single diastereomer (Scheme 2.11). The configuration of the bromine-bearing stereocenter in **2.13t** does not allow for backside attack by the malonate. By resubjecting bromide **2.13t** to the reaction conditions (or allowing **2.8t** to react overnight), the complete reaction can be realized. Presumably, the reaction proceeds through epimerization of the relevant stereocenter, affording ***epi*-2.13t**, which does have the correct configuration for S_N2 substitution. The slow epimerization of **2.13t** might be related to the pKa difference between the α'-bromoenones (e.g., **2.13r**) formed during the reactions in Scheme 2.10 and the α'-bromovinylogous ester contained in **2.13t**.

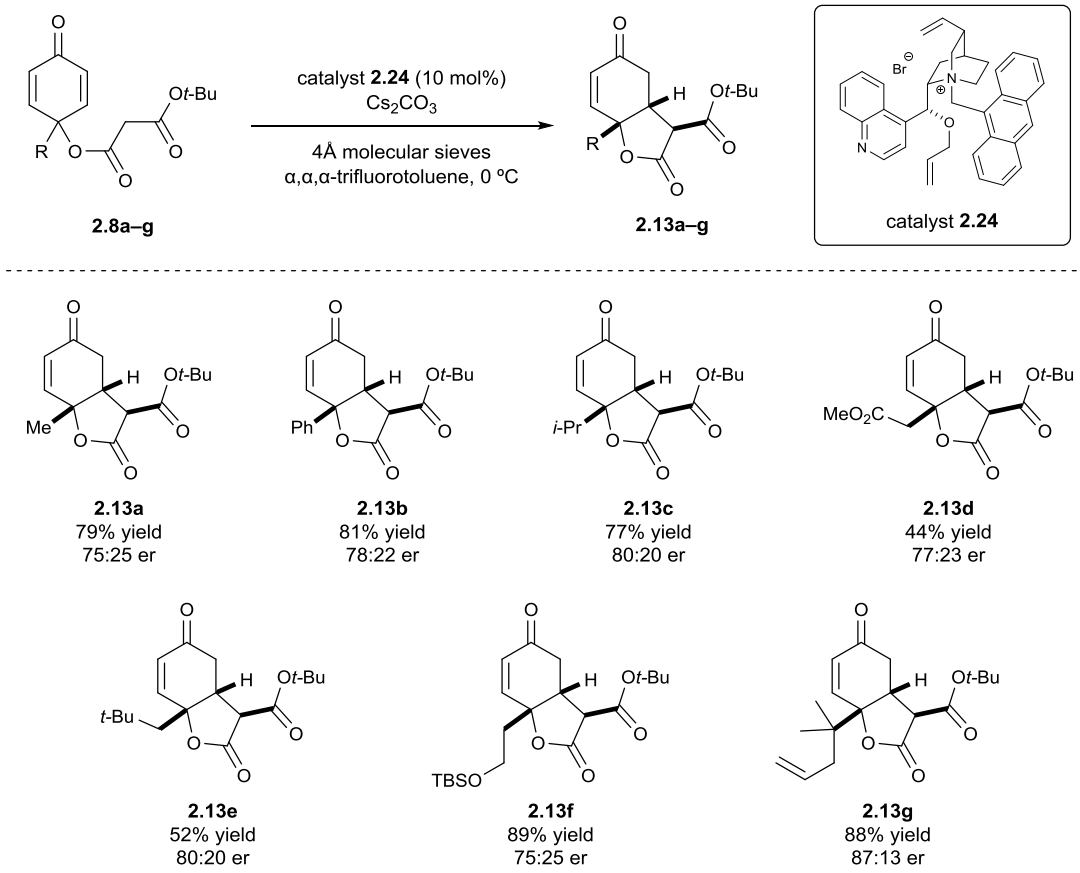
Scheme 2.11. Cyclization of substrate **2.8t**.



2.6 Enantioselectivity studies

Recognizing that the symmetric dienones discussed above contain enantiotopic olefins, we hypothesized that a chiral phase-transfer catalyst might be able to desymmetrize these prochiral compounds. Asymmetric phase-transfer catalysis has proven to be a valuable tool for constructing enantioenriched products.[88–90] However, to the best of our knowledge, there have been no examples of enantioselective phase-transfer catalyzed desymmetrization reactions. While we were confident that the desired cyclization would occur on only one face of the dienone, we expected the discrimination of the two enantiotopic olefins based solely on non-bonding interactions to be a significant challenge.

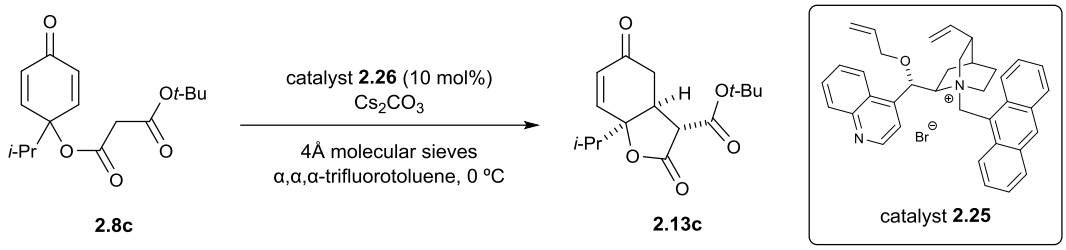
Scheme 2.12. Enantioselective cyclization via phase-transfer catalysis.



Cinchona alkaloid-based phase-transfer catalysts are particularly attractive because of their ready availability and ease of modification. Efforts toward optimization[†] included variation of the electronic and steric properties of the catalyst; modification of the base, temperature, and solvent; and a brief survey of the malonate ester (substrates **2.6–2.8a**). The best catalyst was found to be **2.24**, using the conditions shown in Scheme 2.12. Importantly, when using catalyst **2.25**, the pseudo-enantiomer of catalyst **2.24**, the opposite enantiomer, ***ent*-2.13c** was obtained with similar levels of enantioinduction (Scheme 2.11).

[†] This optimization was performed by Rodolfo Tello-Aburto. Details can be found in the supplementary information for reference [45].

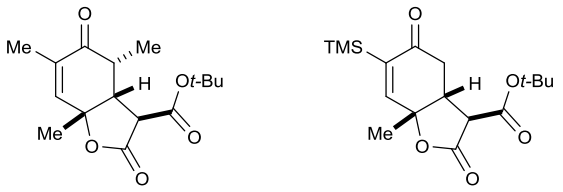
Scheme 2.13. Enantioselective cyclization using catalyst **2.25**.



2.8c **2.13c**

There was concern that the background reaction might be a competing process, which would lead to the diminished selectivity relative to other asymmetric phase-transfer reactions. Importantly, under otherwise identical conditions (1 equiv Cs_2CO_3, CH_2Cl_2, 0 ºC, 4 h), no conversion of **2.8a** to **2.13a** was observed. Another potential problem was that the reaction might be reversible, again leading to lower selectivity. When enantioenriched **2.13a** (71:29 er) was resubmitted to the asymmetric reaction conditions over an extended time (12 h), the product was isolated with an enantiomeric ratio of 67:33. In a separate experiment, substrate **2.8a** was cyclized in the absence of catalyst (1 equiv Cs_2CO_3) to give racemic **2.13a**. Catalyst **2.24** was then added and the reaction continued for another 12 h. In this case, racemic product was isolated. While these experiments do not conclusively rule out the possibility of a reversible reaction, such a process is unlikely to be important with short reaction times (1–3 h).

Interestingly, increased enantioselectivity was observed with substrates bearing more sterically demanding substituents at the γ position of the cyclohexadienone ring (compounds **2.8b** to **2.8g**). We speculated that substituents in the α positions of the cyclohexadienone might offer similar steric benefits; in practice, however, substrates **2.8h** and **2.8i** were poor candidates for this desymmetrization reaction, affording **2.13h** and **2.13i** in enantiomeric ratios of 69:31 and 65:35, respectively (Figure 2.1). These reactions were significantly slower than those performed previously and required 1.5 to 4 days to reach complete conversion. At this point, it is not clear if the decreased enantioselectivity is caused by catalyst decomposition over the prolonged reaction times or to poor interaction with the catalyst.

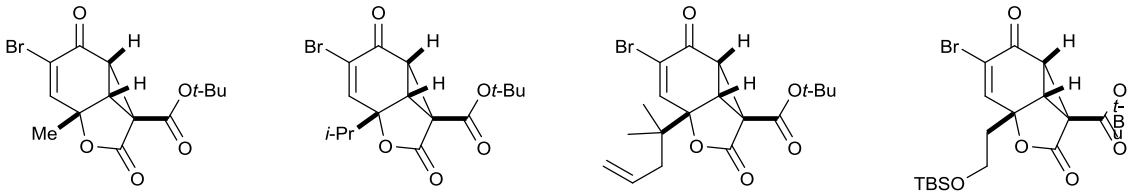


2.13h
67% yield
69:31 er

2.13i
61% yield
65:35 er

Figure 2.1. α-Substituted asymmetric cyclization products.

Gratifyingly, desymmetrization of the dibrominated compounds **2.8j–m** produced enantioenriched cyclopropanes **2.23j–m** (Figure 2.2) with enantioselectivity that was improved relative to their desbromo counterparts, with the exception of **2.23l**, which exhibited reduced enantioselectivity after extended reaction time that was needed for complete conversion. Additionally, the absolute configuration of **2.23k** was determined by X-ray crystallography.[†]



2.23j
56% yield
83:17 er

2.23k
81% yield
91:9 er
X-ray

2.23l
63% yield
72:28 er

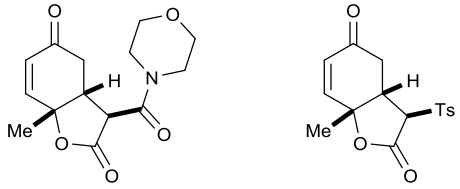
2.23m
35% yield
79:21 er

Figure 2.2. Asymmetric cyclization products from dibrominated substrates.

We also speculated that we might not be achieving optimal selectivity as a result of the capability of the malonate substrates to form two different reactive intermediates (i.e., the enolate could form on the carbonyl of either ester). These two intermediates might have different interactions with the catalyst and therefore lead to different levels of enantioinduction. In an attempt to address this problem, the cyclization of substrates containing electron-withdrawing groups other than esters (compounds **2.9** and **2.10**) was

[†] X-ray analysis was performed by Diane Quern.

performed. By introducing additional electronic differentiation, using amides or sulfones, we had hoped to favor the formation of only one reactive intermediate that could proceed to the cyclization event. Unfortunately, a decreased level of enantioselectivity was observed and products **2.14** and **2.15** (Figure 2.3) were both obtained with a modest enantiomeric ratio of 68:32.



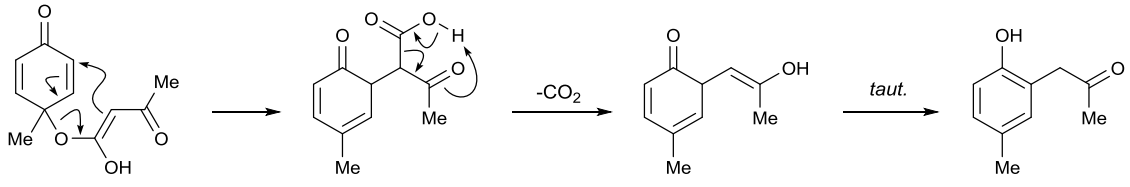
2.14
87% yield
68:32 er

2.15
90% yield
68:32 er

Figure 2.3. Asymmetric cyclization products containing varied electron-withdrawing groups.

To further interrogate this problem, we were also interested in testing cyclohexadienone-tethered β-ketoesters, which would also be useful in the syntheses of natural products. However, we were unable to obtain these compounds as a result of the facile decarboxylation of acetoacetic acid and its derivatives, as well as the propensity of the desired substrates to undergo rearomatization via Carroll rearrangement (Scheme 2.14).[106] In this process, the substrate **2.26** undergoes a Cope rearrangement to give β-ketoacid **2.27**. This intermediate rapidly decarboxylates to enol **2.28**, which provides phenol **2.29** upon tautomerization.

Scheme 2.14. Carroll rearrangement of β-ketoester substrates.

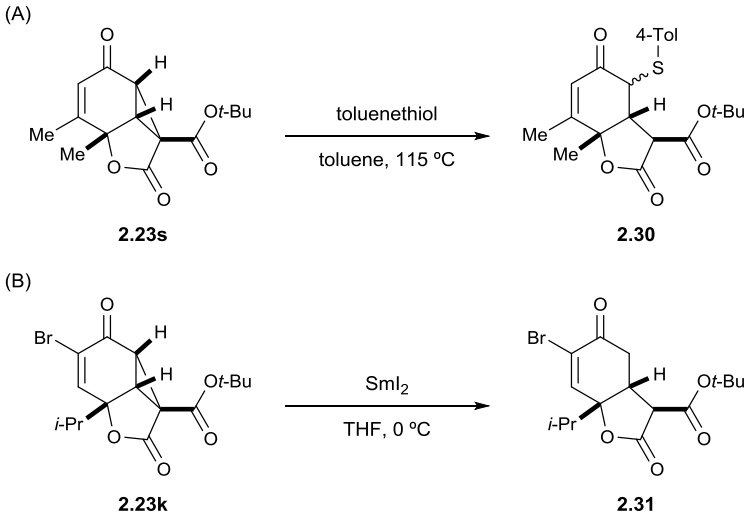


2.26 **2.27** **2.28** **2.29**

2.7 Elaboration of products

We have already begun to explore the utility of these bicyclic lactones as synthetic intermediates (Scheme 2.15). The electron-deficient tricyclic cyclopropanes appear to be unknown in the literature and might prove to be valuable synthetic scaffolds as well.[107] For example, heating cyclopropane **2.23s** with toluenethiol in toluene produced the sulfide **2.30** as a ~2:1 mixture of epimers (Scheme 2.15). Alternatively, the cyclopropane ring of **2.23k** can be reductively cleaved[108–110] with SmI_2 to form **2.31**. Notably, the bromoenone moiety was left intact. Enone **2.31** is interesting in that it is formally the product of an enantioselective dearomatization/conjugate addition sequence. However, the occurrence of such a conjugate addition is at this point hypothetical, as our earlier results have shown that cyclization would occur preferentially on the olefin bearing the bromine (see Section 2.5.1).

Scheme 2.15. Elaboration of cyclopropane products.



2.8 Conclusions

We have shown that intramolecular conjugate additions of cyclohexadienones can proceed regioselectively. The selectivity of these cyclizations appears to be governed largely by electronic factors, although steric effects cannot be completely ruled out in some cases. This result is in contrast to that observed with our previously reported Pd-

catalyzed cyclizations, which were controlled mainly by steric factors. Together, these observations will be important for synthetic planning and might prove to be a useful tool for elucidating the mechanisms of future reactions.

We have also shown that chiral phase-transfer catalysts can be used to desymmetrize prochiral cyclohexadienones. The capability of the *Cinchona* alkaloid catalysts to differentiate the two enantiotopic olefins solely on the basis of non-bonding interactions is remarkable.

2.9 Future work

Further efforts to improve the enantioselectivity of this reaction will require the screening of a larger number of phase-transfer catalysts. While additional variants of the *Cinchona* alkaloid-based catalysts would represent the most straightforward extension of this work, exploration of other catalyst classes, such as those derived from tartaric acid, might prove to be more fruitful.

As discussed in Section 2.7, we believe that the products provided by this methodology have potential use in natural product synthesis. Our preliminary investigations into this utility are presented in Chapter 4.

Chapter 3

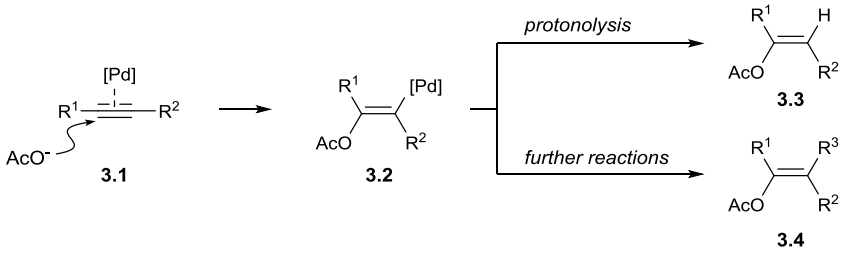
Pd-Catalyzed Cyclization of Alkyne-Tethered Cyclohexadienones†

3.1 Background

3.1.1 Alkyne acetoxypalladation

Alkyne acetoxypalladation (Scheme 3.1) is the addition of an acetoxy ligand to an alkyne (**3.1**) that is coordinated to a Pd complex. This process produces vinyl-Pd intermediate **3.2**, in which the Pd center is situated in a trans relationship to the acetoxy substituent. This intermediate can either undergo protonolysis to provide alkene **3.3**, or proceed through any of a large number of transformations common to Pd-catalysis (e.g., migratory insertion) to provide more complex products (**3.4**).

Scheme 3.1. Alkyne acetoxypalladation.

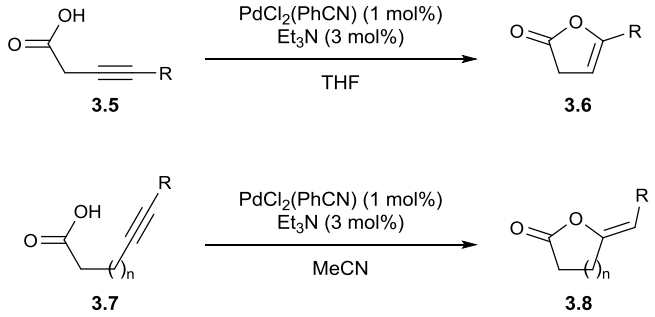


In 1984, Nozaki and coworkers reported the first example of alkyne acetoxypalladation, utilizing the strategy in the cyclization of alkynoic acids to

† This work was performed in collaboration with Rodolfo Tello-Aburto and a significant portion of these results have been published previously.[46] Relevant sections reproduced by permission of The Royal Society of Chemistry (RSC).

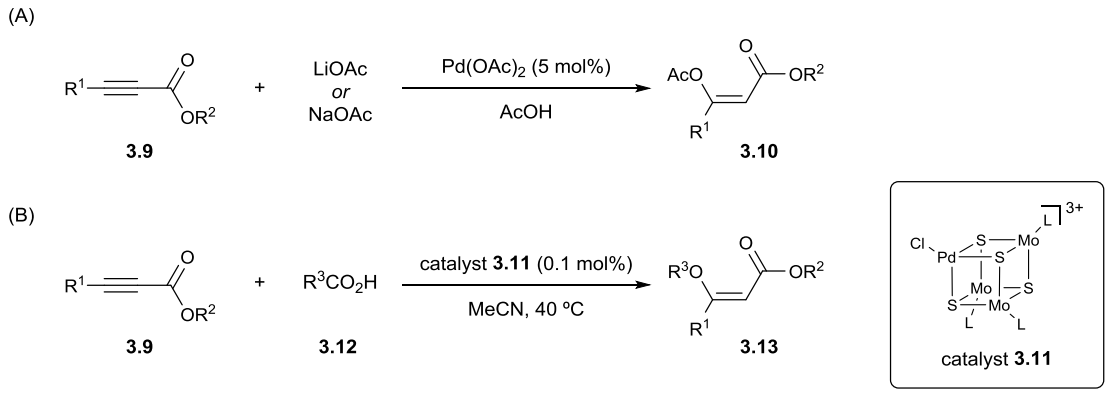
unsaturated lactones (Scheme 3.2).[111] They observed excellent regioselectivity: homopropargylic acids (**3.5**) undergo 5-endo-dig cyclization to afford endocyclic alkenes (**3.6**), while substrates with longer tethers (**3.7**) proceed through a 5-exo-dig reaction to provide exocyclic alkenes (**3.8**).

Scheme 3.2. Pd(II)-catalyzed acetoxylation and cyclization of alkynoic acids.



An intermolecular version of the reaction was demonstrated by Lu in 1992 through the use of acetate salts as external nucleophile in converting alkynoic esters **3.9** to vinyl esters **3.10** (Scheme 3.3A).[112] This report was followed by Hidai's use of a Pd/Mo sulfide cluster complex (**3.11**, Scheme 3.3B) to perform similar transformations with a variety of carboxylic acid nucleophiles (**3.12**), providing a series of substituted products (**3.13**).[113]

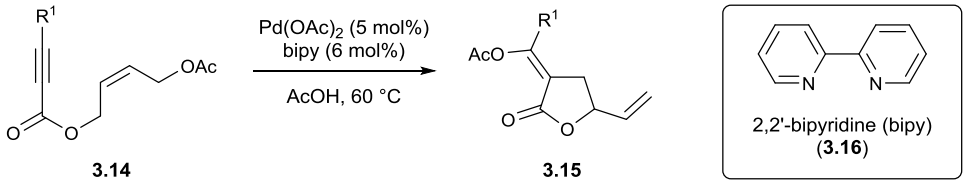
Scheme 3.3. (A) Lu and (B) Hidai's examples of intermolecular acetoxylation.



3.1.2 Enyne coupling triggered by alkyne acetoxypalladation

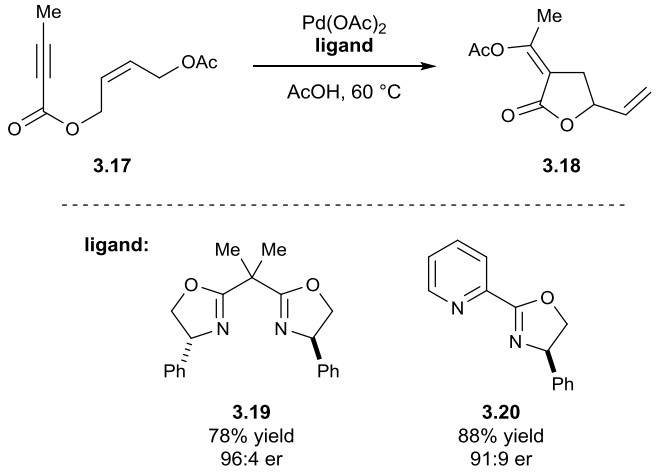
Lu and coworkers continued to investigate the reaction, showing that the vinyl-Pd intermediate that is produced can be used for further reactions. Specifically, they reported an acetoxypalladation initiated cyclization of alkene-tethered alkynoic esters (**3.14**) in which the vinyl-Pd species undergoes syn-migratory insertion across the tethered alkene (Scheme 3.4).[114,115] The final product (**3.15**) results from β-acetoxy elimination. Interestingly, the authors noted that higher yields were obtained when the acetic acid solvent was used as a nucleophile and acetate salts were omitted. A variety of alkyl and aryl alkynes were shown to successfully undergo cyclization; however, terminal alkynes were not suitable substrates for this transformation.

Scheme 3.4. Pd-catalyzed cyclization of alkene-tethered alkynoic esters.



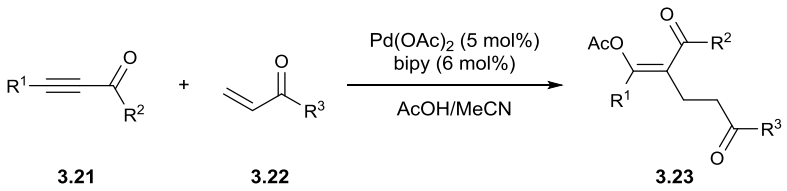
It was found that the bipyridine ligand (bipy, **3.16**) was vital for both initiation of the migratory insertion and suppression of β-hydride elimination. With the goal of developing an enantioselective version of the reaction, a ligand screen was performed. While a variety of pyridine and oxazoline ligands did promote the reaction, phosphine ligands were found to be ineffective, potentially resulting from the formation of a Pd(0) species. Additionally, tridentate amine ligands were similarly unsuitable. A screen of bidentate amines revealed bisoxazoline **3.19** and pymox **3.20** as the best ligands for inducing enantioselectivity in the cyclization of **3.17** to **3.18**, producing enantiomeric ratios of 96:4 and 91:9, respectively (Scheme 3.5).

Scheme 3.5. Asymmetric cyclization of alkene-tethered alkynoic esters.



The presence of the acetate as a leaving group is also crucial to this reaction, as the β-acetoxy elimination step is necessary to regenerate the Pd(II) catalyst (without the acetate, the alkyl-Pd intermediate is quenched by β-hydride elimination, eventually forming Pd(0)). Looking to expand the usefulness of this strategy, the Lu group explored substrates that would allow for protonolysis as to regenerate Pd(II) as the final step in the catalytic cycle. They found success using unsaturated esters and ketones (**3.21**) as partners in an intermolecular reaction with electron-deficient alkynes **3.22** to give the coupled products **3.23** (Scheme 3.6).[116]

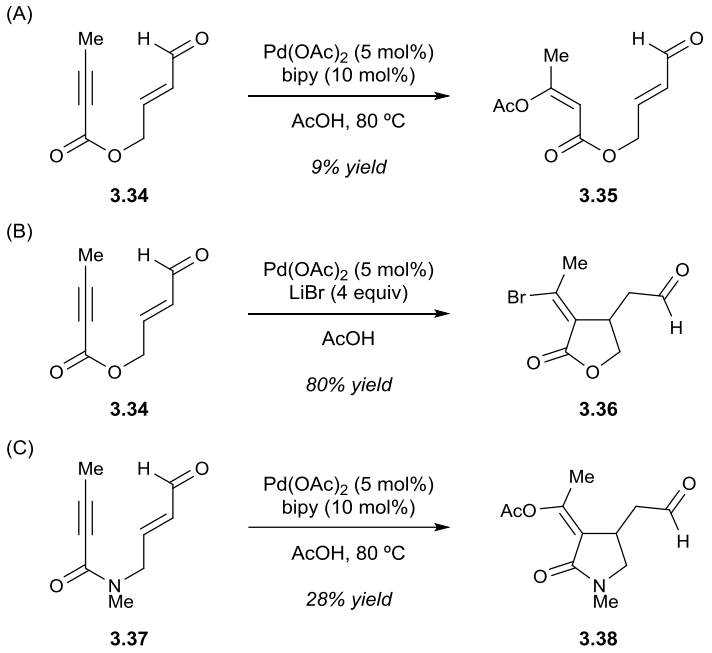
Scheme 3.6. Intermolecular enyne coupling terminated by protonolysis.



When the analogous intramolecular reaction was attempted with enyne **3.34**,[117] only the alkyne hydroacetoxylation product **3.35** was observed (Scheme 3.7A). This outcome was in direct contrast to previous results published by the group,[118,119] in which the use of LiBr as the nucleophile did induce the desired cyclization, providing lactone **3.36** (Scheme 3.7B). The authors attribute this difference to the electron-donating nature

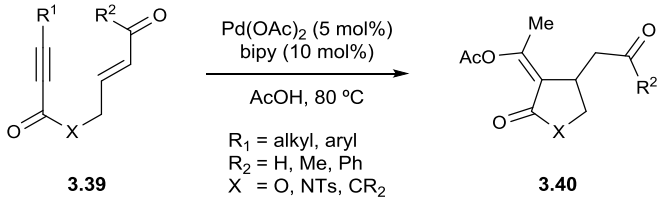
of vinyl acetates versus the electron-withdrawing nature of vinyl halides. They also speculated that the electronic influence of the ester moiety in **3.34** contributes to the propensity for protonolysis. This hypothesis was supported by the successful, albeit low-yielding, cyclization of alkynoic amide **3.37** to lactone **3.38** (Scheme 3.7C).

Scheme 3.7. Attempted intramolecular enyne couplings.



With these results in hand, the authors decided to change the electronic nature of the alkyne by removing the carbonyl functionality and using a variety of oxygen, nitrogen, and carbon based tethers in its place. These new substrates (**3.39**) readily cyclized under the acetoxypalladation conditions to provide tetrahydrofurans, pyrrolidines, and cyclopentanes (**3.40**, Scheme 3.8). Terminal alkynes were again found to be unsuitable substrates.

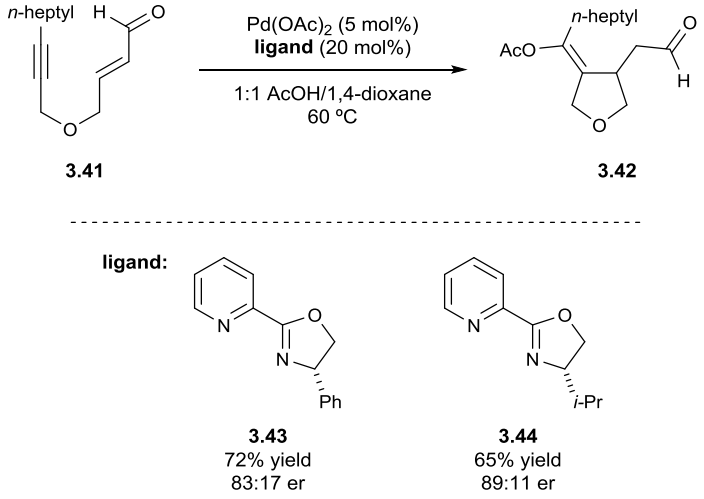
Scheme 3.8. Cyclization of tethered enynes.



3.39 **3.40**

They also sought to perform the reaction enantioselectively. Employing the most successful ligands from their previous work[114,115] (see above), they attempted the cyclization of the ether-tethered enyne **3.41** to tetrahydrofuran **3.42** (Scheme 3.9). Surprisingly, they found that when bisoxazoline ligands were used, the "reaction turned to a disordered reaction," presumably meaning the desired product was not observed. However, phenyl-substituted pymox ligand **3.43** did promote the cyclization with an enantiomeric ratio of 83:17. The highest selectivity observed (89:11) was obtained with isopropyl-substituted ligand **3.44**.

Scheme 3.9. Enantioselective cyclization of tethered enynes.



3.41 **3.42**

3.43
72% yield
83:17 er

3.44
65% yield
89:11 er

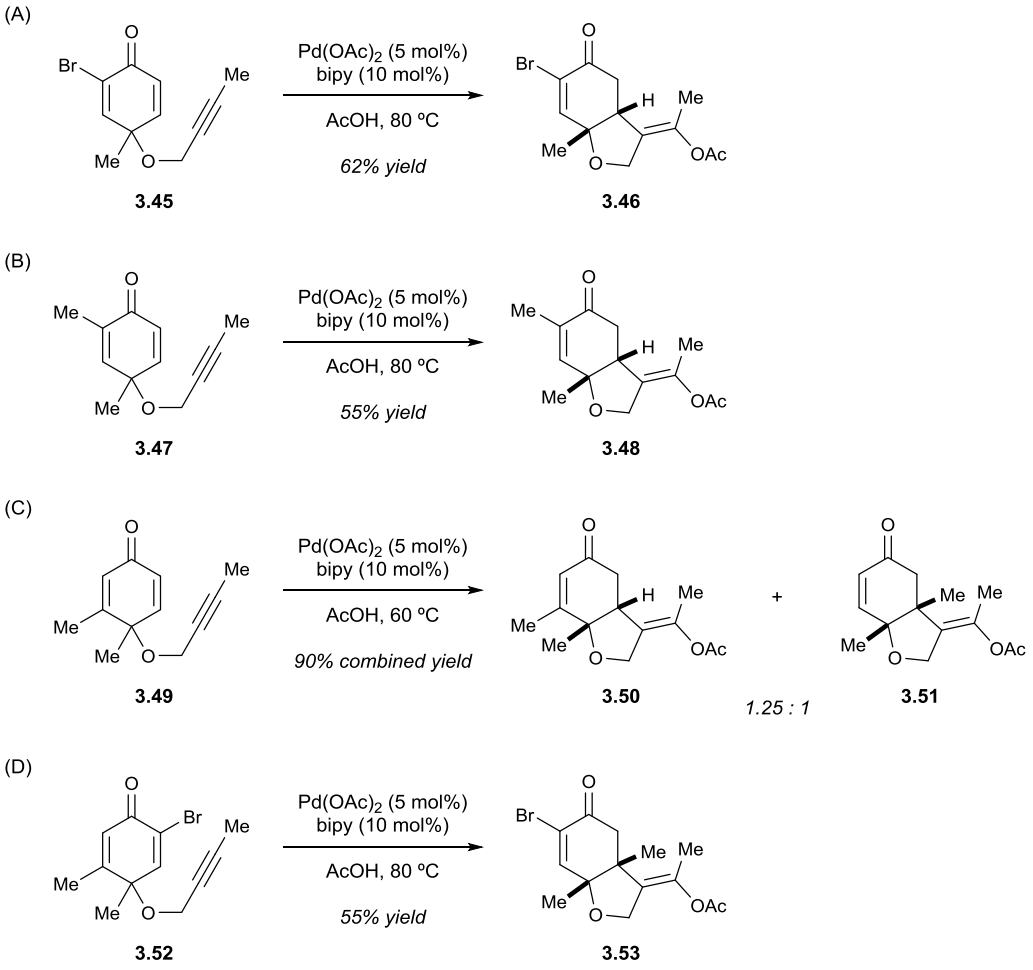
The presence of enones in the substrate scope (**3.39**, R^2 = Me, Ph) piqued our interest. We recognized that performing this cyclization on an alkyne-tethered 2,5-cyclohexadienone would rapidly build molecular complexity. Additionally, the use of

symmetrically substituted substrates would offer an opportunity to generate enantioenrichment through desymmetrization.

3.1.3 Cyclization of alkyne-tethered 2,5-cyclohexadienones

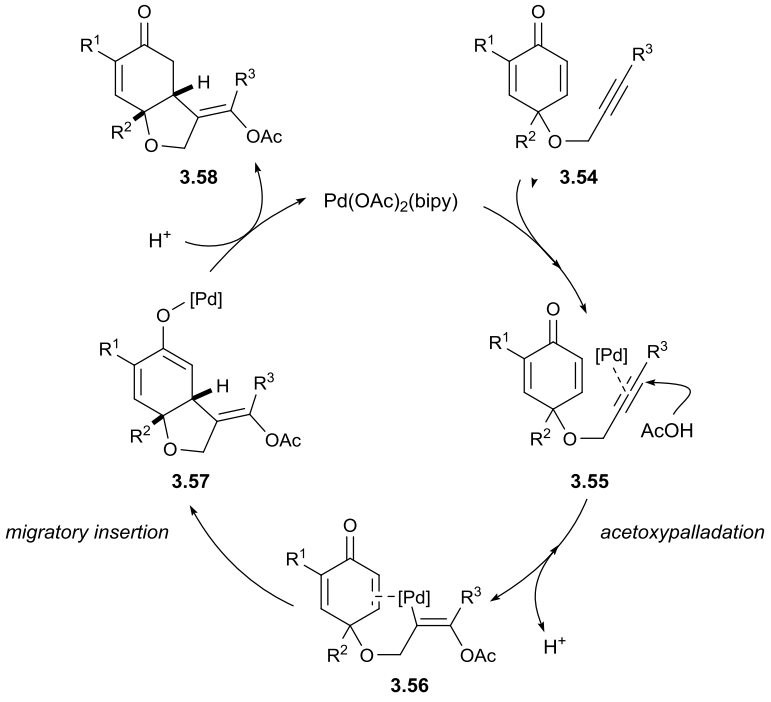
Early efforts by our group[45] confirmed that 2,5-cyclohexadienones are acceptable substrates for enyne coupling, and that the reaction is subject to the same catalyst, ligand, and temperature constraints as described by Lu and coworkers. Additionally, regioselectivity was determined to be primarily governed by a steric model in which cyclization preferentially occurs away from cyclohexadienone substitution. This effect is most notable for α-substituted substrates in which **3.45** and **3.47** cyclized to provide **3.46** and **3.48** as single isomers, respectively (Scheme 3.10A and B). Selectivity is also observable with β substitution, albeit at a much lower level (**3.49** → **3.50** and **3.51**, Scheme 3.10C). The greater influence of α substitution was confirmed by the preferential cyclization of disubstituted substrate **3.52** to give bicyclic enone **3.53** (Scheme 3.10D) as a single regioisomer.

Scheme 3.10. Regioselective cyclization of cyclohexadienone-tethered alkynes.



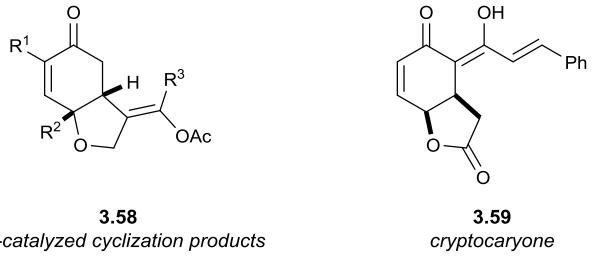
A plausible mechanism for this transformation similar to that previously proposed by Lu (see above) is shown in Scheme 3.11. The Pd catalyst initially coordinates to the alkyne in **3.54**, forming complex **3.55**. This complex undergoes acetoxypalladation to provide vinyl-Pd intermediate **3.56**. Migratory insertion occurs across the less hindered enone, affording Pd-enolate **3.57**. Finally, protonolysis provides the product **3.58** and regenerates the Pd(II) catalyst.

Scheme 3.11. Mechanism for the Pd-catalyzed cyclization of alkyne-tethered cyclohexadienones.



3.1.4 NF-κB inhibition

The products provided by this cyclization reaction are structurally similar to the natural product cryptocaryone[120,121] (**3.59**, Figure 3.1). Cyptocaryone displays a promising level of activity as an inhibitor of NF-κB signaling,[122] a process that is essential in cellular immune response.[123–125] NF-κB inhibitors have potential as anticancer agents,[126] as excessive NF-κB activation has been implicated in a variety of human cancers.[127–131]



3.58
Pd-catalyzed cyclization products

3.59
cryptocaryone

Figure 3.1. Structural similarity between cryptocaryone and Pd-catalyzed cyclization products.

The similarity between the Pd-catalyzed cyclization products and cryptocaryone prompted our group to collaborate with Prof. Daniel Harki in the University of Minnesota Department of Medicinal Chemistry to investigate the cyclization products' potential as NF-κB inhibitors.[132] A series of bicyclic enones were screened using an NF-κB luciferase reporter assay (Figure 3.2). Unfortunately, many of the compounds did not exhibit inhibitory activity; however, at 50 μM concentration, compounds **3.60** and **3.61** did display 38% and 64% NF-κB inhibition, respectively. Interestingly, enantioenriched **3.61** (81:19 er, obtained in preliminary phases of the work described below) exhibited 82% inhibition, representing a twofold increase in potency over the racemic sample.

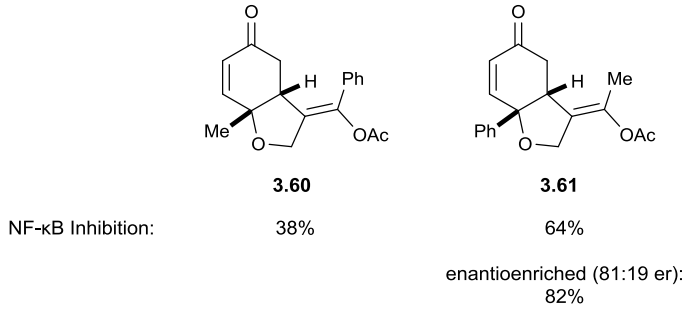
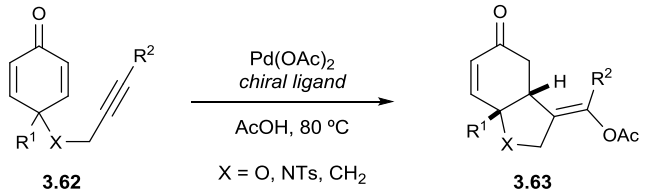


Figure 3.2. NF-κB inhibition levels of Pd-catalyzed cyclization products.

3.2 Objective

Encouraged by the successful application of the enyne coupling to cyclohexadienone systems, and also by the observed potential for the products to act as NF-κB inhibitors, we decided to pursue an enantioselective version of the reaction (Scheme 3.12). Many of the substrates used in our group's previous work were derived from unsymmetrically substituted phenols and were therefore already chiral (and in this case, racemic). For our desymmetrization studies, we required a new series of substrates (**3.62**) derived from symmetrically substituted phenols. These achiral substrates would then be cyclized in the presence of a series of chiral ligands in order to identify optimal conditions for the enantioselective synthesis of bicyclic enones (**3.63**).

Scheme 3.12. Desymmetrization of cyclohexadienones via Pd-catalyzed cyclization.



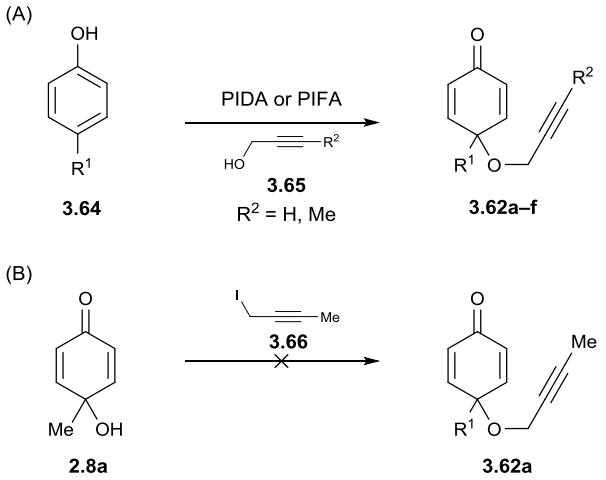
3.3 Substrate synthesis

Three classes of substrates were synthesized based on the composition of the tether between the alkyne and the cyclohexadienone (oxygen, nitrogen, or carbon). Each of these classes presented unique challenges and required a specialized approach.

3.3.1 Oxygen-tethered substrates

Oxygen-tethered substrates were prepared through hypervalent iodine-mediated dearomatization using propargylic alcohols as nucleophiles (Scheme 3.13A). This procedure allowed the variation of substitution around the cyclohexadienone core in **3.62** through the choice of phenol **3.64**, and substitution on the alkyne tether through the choice of nucleophile **3.65**. Unfortunately, this route imposes a significant constraint in that the nucleophile must be present in solvent quantities. As a result, the options were limited to 2-butyn-1-ol and propargyl alcohol itself, as more complex alkynes were either solid at room temperature or prohibitively expensive for use as a solvent. Attachment of the tether was also attempted by alkylation of quinol **2.8a**[13] with propargylic iodide **3.66**; however, these efforts were unsuccessful (Scheme 3.13B).

Scheme 3.13. Synthesis of oxygen-tethered substrates.

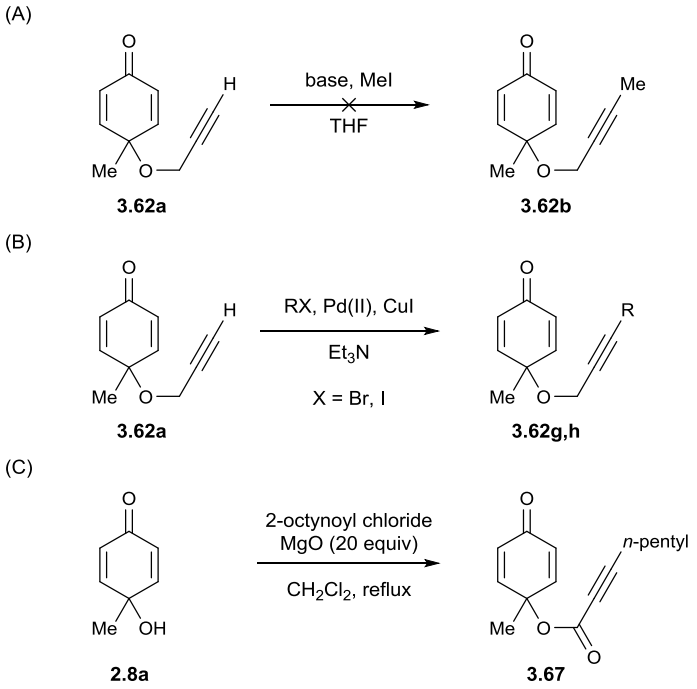


Varied substitution around the cyclohexadienone core was straightforward given the large variety of commercially available phenols. Focusing on variation of the required R^1 substituent, cyclohexadienones were successfully obtained from both alkyl- and arylphenols. 4-Acyl and 4-halophenols, however, were not amenable to dearomatization; we attribute this result to instability of the positive charge necessarily developing in the aromatic ring.

For the alkyne tether, further derivatization of terminal alkyne **3.62a** would in theory provide access to a large variety of substrates. This strategy was applied with mixed results. Attempted alkylation to substrate **3.62b** resulted only in decomposition of the starting material (Scheme 3.14A), which was unsurprising given the general incompatibility of cyclohexadienones with the bases required, such as LDA and NaH.[1] However, Sonogashira coupling with aryl halides to access **3.62g,h** was successful (Scheme 3.14B), providing one method of diversification of the alkyne substituent. Additionally, alkynoate substrate **3.67** was obtained through DCC coupling of 2-octynoic acid and quinol **2.8a** (Scheme 3.14C).[†]

[†] See Section 2.3 for a discussion of coupling techniques.

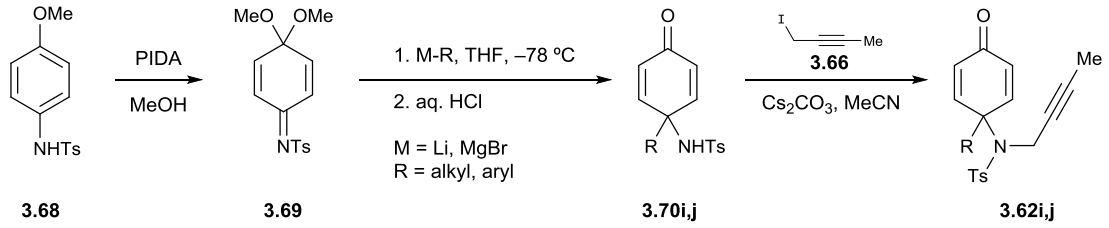
Scheme 3.14. Variation of the alkyne substituent in oxygen-tethered substrates.



3.3.2 Nitrogen-tethered substrates

Nitrogen-tethered substrates were synthesized starting from *N*-tosyl-4-anisidine (**3.68**) via the corresponding quinone imine ketal **3.69** (Scheme 3.15).[133–136] Grignard addition into the imine[137–141] provided tertiary sulfonamides (**3.70**) with variation of the quaternary carbon substituent. Pleasingly, sulfonamide in **3.70** readily alkylated when treated with propargylic iodide **3.66**, providing the desired alkyne tethered substrates **3.62i** and **3.62j**.

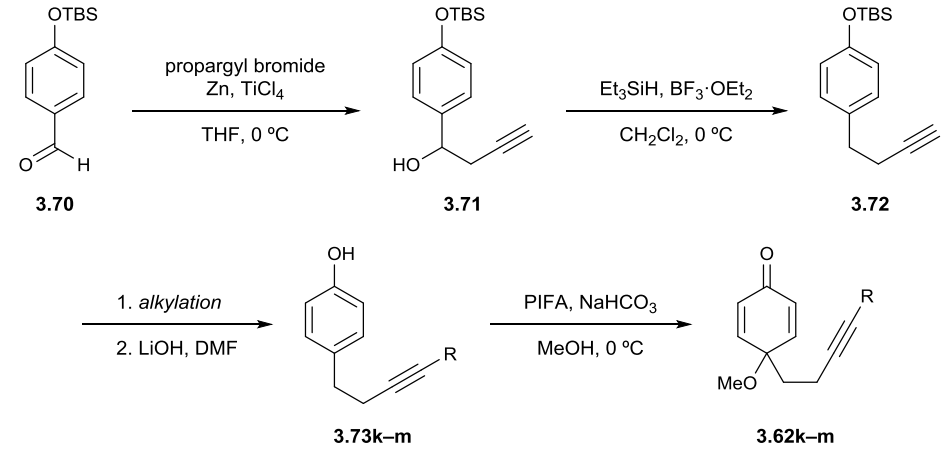
Scheme 3.15. Synthesis of nitrogen-tethered substrates.



3.3.3 Carbon-tethered substrates

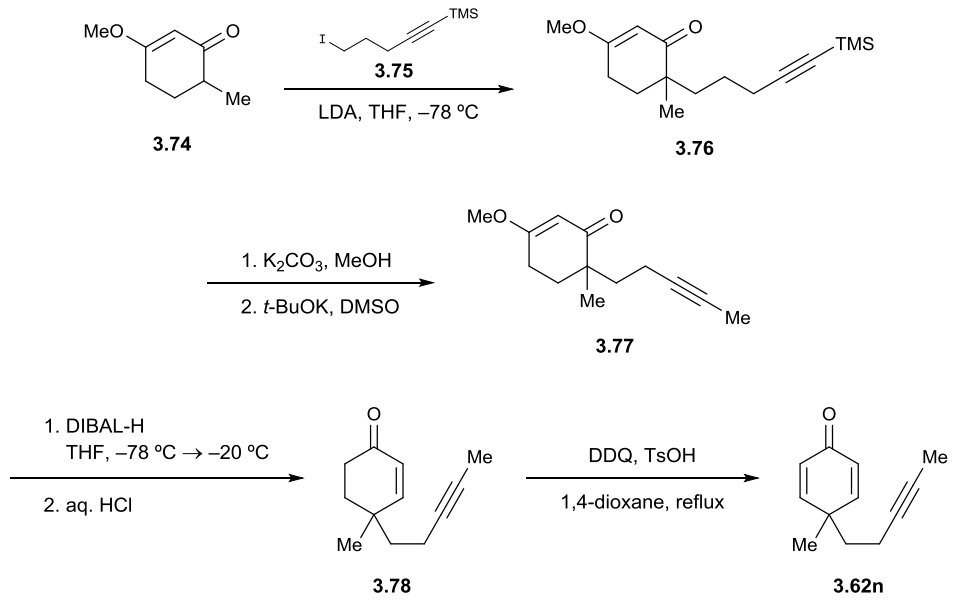
Carbon-tethered substrates were prepared by one of two methods, depending on the identity of the γ substituent on the cyclohexadienone. The first method allowed access to quinol methyl ethers (Scheme 3.16). Propargyl zinc addition into benzaldehyde **3.70** provided alcohol **3.71**, which was deoxygenated with triethylsilane to give alkyne **3.72**. Alkylation of the alkyne and removal of the TBS protecting group furnished phenols **3.73**, with variation at alkyne substituent. Finally, the phenols were subjected to dearomatization conditions in methanol to afford the desired substrates **3.62k–m**.

Scheme 3.16. Synthesis of carbon-tethered substrates: quinol methyl ethers.



Substrates containing a quaternary carbon at the γ position required a different strategy, as examples of carbon-based external nucleophiles in dearomatization reactions have been limited to allyltrimethylsilane.[142] Alkylation of known enone **3.74**[143] with propargylic iodide **3.75**[144] provided alkyne **3.76**. Removal of the TMS protecting group and isomerization with *t*-BuOK afforded the internal alkyne **3.77**. The vinylogous ester was then reduced and converted to enone **3.78** under acidic conditions. Finally, oxidation with DDQ afforded the cyclohexadienone substrate **3.62n**. Because of the length of this procedure and the lack of opportunities for late-stage diversification, variations of **3.62n** were not prepared for the initial studies.

Scheme 3.17. Synthesis of carbon-tethered substrates: quaternary carbon centers.

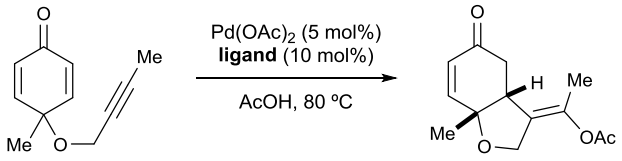


3.4 Enantioselectivity studies

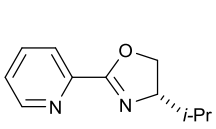
3.4.1 Ligand Screening

In order to pursue the goal of performing the cyclization enantioselectively, a series of nitrogen-based ligands in the cyclization of **3.62b** to **3.63b** (Table 3.1) were tested. Initially, three ligands previously utilized by Lu[114,115,117] (see Section 3.1.2) were screened: pymox **3.79**,[145,146] pybox **3.80**,[147] and bisoxazoline **3.81**.[148] Although the use of **3.79** provided cyclized product **3.63b** in 59% yield and an enantiomeric ratio of 54:46 (entry 1), **3.80** and **3.81** failed to promote the reaction (entries 2 and 3). Gratifyingly, when the pinene-derived bipyridine ligand (−)-*iso*-PINDY[149,150] (**3.82**) was employed, **3.63b** was produced in an improved yield (67%) and improved enantioselectivity (79:21 er) (entry 4).

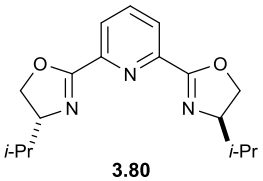
Table 3.1. Initial ligand screening for Pd-catalyzed cyclizations.



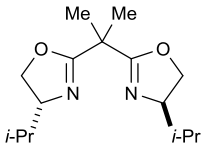
3.62b **3.63b**



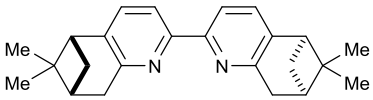
3.79



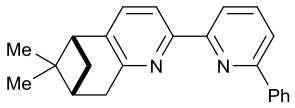
3.80



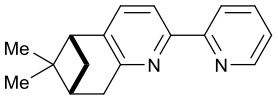
3.81



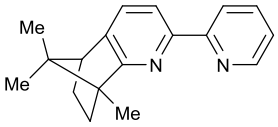
3.82



3.83



3.84



3.85

Entry	Ligand	Yield (%)	er
1	**3.79**	59	54:46
2	**3.80**	–	–
3	**3.81**	trace[a]	–
4	**3.82**	67	79:21
5	**3.83**	–	–
6	**3.84**	85	57:43
7	**3.85**	61	64:36

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

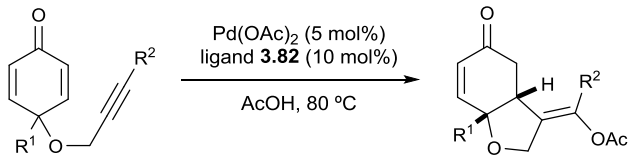
Bipyridine ligands exhibiting C_1 symmetry were also screened; however, the results were discouraging: **3.84**[151] and camphor-derived **3.85**[152,153] induced enantiomeric

ratios of 57:43 and 64:36, respectively (entries 6 and 7), whereas the sterically demanding bipyridine ligand **3.83**[154] failed to promote cyclization (entry 5). Considering these results, ligand **3.82** was utilized in the exploration of substrate influence on enantioselectivity.

3.4.2 Oxygen-tethered substrates

Encouraged by the selectivity afforded with substrate **3.62b**, we sought to investigate the effect of substrate substitution on enantiocontrol. We began by altering the R^1 substituent (Table 3.2). Substrates **3.62c–f** (entries 2–5) behaved similarly to the parent substrate (**3.62b**, entry 1), exhibiting fair yields and moderate enantioselectivity. This outcome indicates that the reaction is not sensitive to changes in R^1 substitution.

Table 3.2. Pd-catalyzed cyclization of oxygen-tethered substrates.



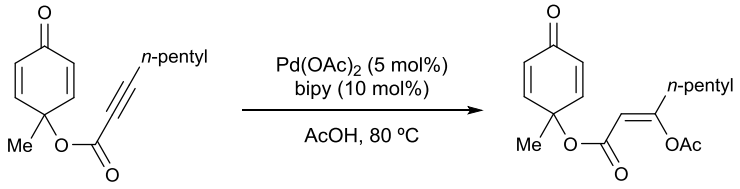
3.62b–h **3.63b–h**

Entry	Alkyne	R^1	R^2	Yield (%)	er
1	**3.62b**	Me	Me	67	79:21
2	**3.62c**	Ph	Me	72	81:19
3	**3.62d**	Et	Me	70	75:25
4	**3.62e**	*i*-Pr	Me	29	75:25
5	**3.62f**	CH_2CO_2Me	Me	59	76:24
6	**3.62g**	Me	Ph	89	52:48
7	**3.62h**	Me	2-Py	–	–

We then turned our attention to the alkyne substituent (R^2). When phenyl-substituted substrate **3.62g** was subjected to the cyclization conditions, essentially no enantioselectivity was observed (entry 6). Additionally, pyridyl-substituted substrate **3.62h** completely failed to undergo cyclization, which can potentially be attributed to

incompatibility of the catalyst with the basic nitrogen atom. Although we expected the alkyne substituent to have some influence on stereoselectivity, we were quite surprised by the magnitude of this effect. We were deterred from further exploration of the influence of the alkyne substituent by the significant drop in selectivity and the difficulties associated with varying the R^2 substituent (see Section 3.3.1). Furthermore, the use of an alkynoate tether was unsuccessful (Scheme 3.18): consistent with earlier observations by Lu[117] (see Section 3.1.2), only the alkyne acetoxylation product **3.86** was obtained from substrate **3.67**.

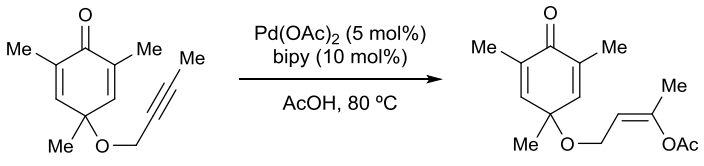
Scheme 3.18. Attempted Pd-catalyzed cyclization of alkynoate-tethered substrate **3.67**.



3.67 **3.86**

We also attempted to probe the effect of enone substituents on the reaction. However, when mesitol-derived cyclohexadienone **3.87** was subjected to the reaction conditions, only acetoxylation of the alkyne (providing alkene **3.88**) was observed (Scheme 3.19). The reluctance of the vinyl-Pd intermediate to cyclize onto either substituted enone fits well with our previous observations of regioselectivity in this reaction (see Section 3.1.3).

Scheme 3.19. Attempted Pd-catalyzed cyclization of mesitol-derived substrate **3.88**.

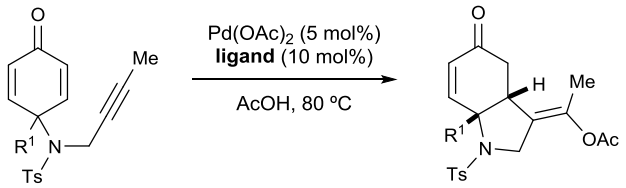


3.87 **3.88**

3.4.3 Nitrogen-tethered substrates

Switching the ether linkage to a sulfonamide had a pronounced influence on the efficiency of these transformations. The cyclizations of substrates **3.62i–j** to bicyclic enones **3.63i–j** were first attempted using the achiral bipy as the ligand (Table 3.3, entries 1 and 5). In both cases, the reaction proceeded smoothly to give the bicyclic product in moderate to good yield. However, in the presence of ligand **3.82**, the cyclizations were very sluggish, requiring extended reaction times to reach even modest levels of conversion (entries 2 and 6). Even after these efforts, the enantioselectivity was quite low (entry 6). Speculating that the increased bulk of the sulfonamide was responsible for this lack of reactivity, we examined the use of modified ligands with decreased steric demands (**3.79**, **3.84**, and **3.85**). While these ligands did improve the overall reactivity, the enantioselectivity remained poor (entries 3–4, 7–9).

Table 3.3. Pd-catalyzed cyclization of nitrogen-tethered substrates.



3.62i,j **3.63i,j**

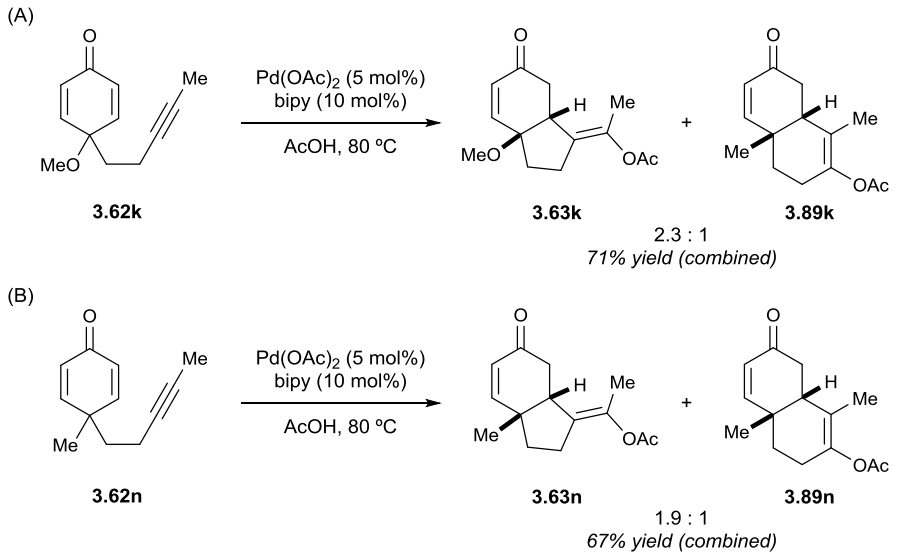
Entry	Alkyne	R^1	Ligand	Yield (%)	er
1	**3.62i**	Me	bipy	49	–
2	**3.62i**	Me	**3.82**	<15[a]	–
3	**3.62i**	Me	**3.84**	39	40:60
4	**3.62i**	Me	**3.85**	52	39:61
5	**3.62j**	Ph	bipy	78	–
6	**3.62j**	Ph	**3.82**	26[b]	62:38
7	**3.62j**	Ph	**3.79**	66	35:65
8	**3.62j**	Ph	**3.84**	85	47:53
9	**3.62j**	Ph	**3.85**	45	58:42

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] After 6 days.

3.5 Regioselectivity studies

In order to continue exploring these ligand effects, the use of an all-carbon tether was investigated. The first such compound to be evaluated was quinol methyl ether **3.62k** (Scheme 3.20A). Cyclization of this substrate using bipy as the ligand resulted in a 2.3:1 mixture of the expected 5,6-fused bicyclic product **3.63k** and new product, determined to be the regioisomeric 6,6-fused bicyclic **3.89k** after extensive NMR analysis. The cyclization of compound **3.62n** (Scheme 3.20B) also produced a mixture of regioisomers, with the 6,6-fused bicyclic product **3.89n** present in an even greater proportion than that observed with substrate **3.62k**. Unfortunately, in both cases the regioisomeric products were inseparable, complicating characterization and precluding our ability to separate the individual enantiomers. This separation is also necessary for conducting enantioselectivity studies on these substrates. As a result, these cyclizations were not attempted in the presence of a chiral ligand.

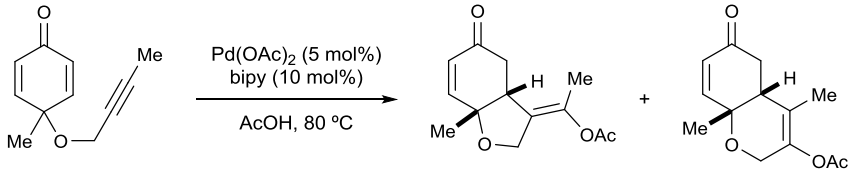
Scheme 3.20. Pd-catalyzed cyclization of carbon-tethered substrates.



The presence of the regioisomeric products **3.63** and **3.89** in these reactions was surprising given the high level of selectivity observed in the cyclizations of oxygen- and

nitrogen-tethered substrates to the 5,6-fused bicyclic products. Indeed, examination of the crude reaction mixture of the cyclization of oxygen-tethered substrate **3.62b** in closer detail revealed that the 6,6-fused bicycle **3.89b** was present in only minor amounts (7.6:1 ratio of **3.63b** and **3.89b**) (Scheme 3.21).

Scheme 3.21. Regioselectivity in the cyclization of oxygen-tethered substrate **3.62b**.



3.62b **3.63b** **3.89b**

7.6 : 1

95% yield (combined)

Considering these results, it is clear that the presence of an electronegative atom (O or N) in or near the alkyne tether has a profound influence on the amount of 6,6-fused bicyclic product formed. This effect can be explained in terms of inductive polarization of the alkyne as illustrated in Figure 3.3. The initial binding of the alkyne and Pd(II) catalyst will make the alkyne more electrophilic and allow the nucleophile (in this case acetic acid) to attack through either path A or path B. This binding will result in the formation of one of two possible vinyl-Pd intermediates (**A** or **B**) that then continue on to perform migratory insertion. We expect that the presence of an electronegative atom polarizes the alkyne in such a way that the distal carbon atom is more electrophilic than the proximal carbon. The magnitude of this effect would depend on the distance between the electronegative atom and the alkyne. If this atom is close, a greater amount of **B** will be formed, leading to the preferential formation of the 5,6-fused bicyclic product. However, if the electronegative atom is positioned farther away, the alkyne polarization becomes less significant and the preference for forming either **A** or **B** is reduced.

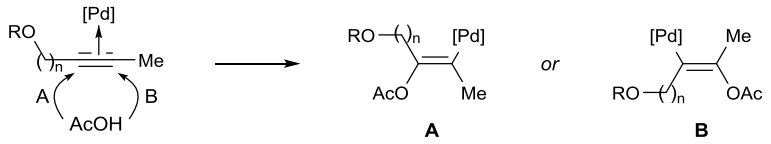
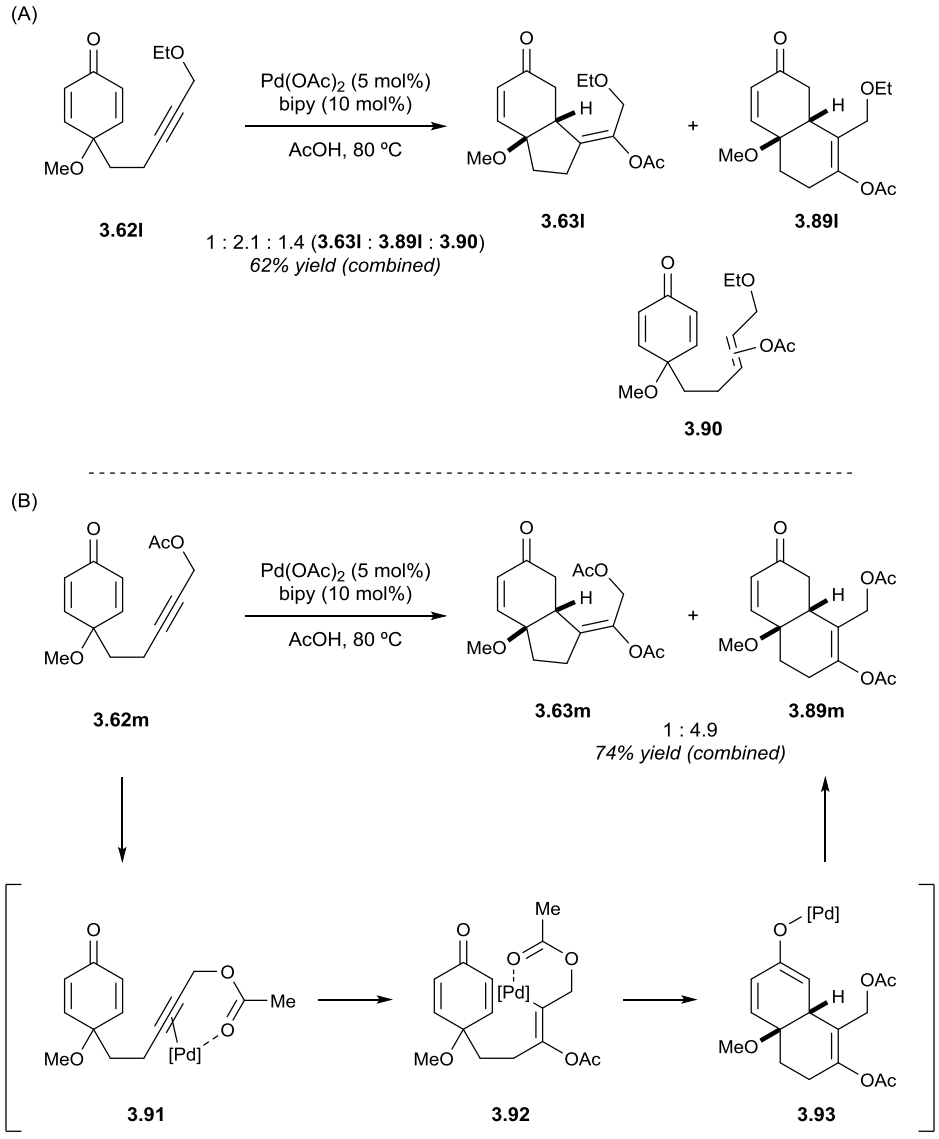


Figure 3.3. Regioselectivity influenced by inductive effects in the acetoxypalladation of alkynes.

This inductive effect appears to be a relatively unexplored phenomenon in the area of Pd-catalyzed acetoxylation reactions. There have been numerous reports on the use of unsymmetrically substituted alkynes; however, the substrate scope has largely been limited to alkynoates, alkynamides, and haloakynes.[114–116,155–162] These compounds are biased by electronic resonance to favor the formation of one regioisomer. We are aware of only three examples by Lu[117,163,164] where the regioselectivity could be attributed to the inductive effect of a nearby electron-withdrawing group.

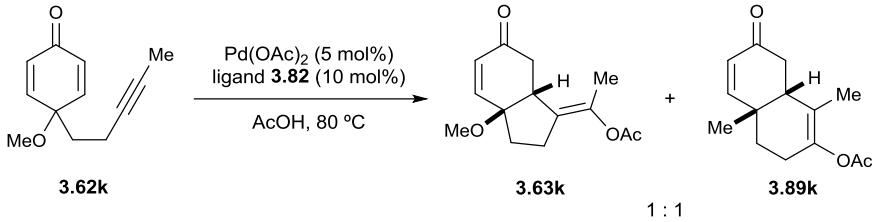
In order to test this hypothesis, we attempted the cyclization of propargylic ether **3.62l** and propargylic acetate **3.62m**, expecting to observe an increase in the relative production of the 6,6-bicyclic products. The cyclization of **3.62l** proceeded to give a complex, inseparable mixture of **3.63l**, **3.89l**, and the unexpected uncyclized alkene **3.90**, with a ratio of 1:2.1 of **3.63l** and **3.89l** (Scheme 3.22A). The cyclization of **3.62m** proceeded much more cleanly, providing **3.63m** and **3.89m** in a 1:4.9 ratio and good yield (Scheme 3.22B). These are the first examples in which the 6,6-fused bicycle is formed as the major product. Although these results are consistent with the presence of the proposed inductive effect, it is plausible that the propargylic acetate in **3.62m** participates in directing the course of the acetoxypalladation event.[165–172] Coordination of the Pd center to both the acetate and the alkyne (**3.91**) would lead preferentially to vinyl-Pd intermediate **3.92** after acetoxypalladation. Finally, Pd enolate **3.93** would undergo protonolysis to provide the 6,6-fused bicycle **3.89m**.

Scheme 3.22. Pd-catalyzed cyclization of oxygen-tethered substrates with propargylic ether substituents.



We also sought to determine the influence of the ligand on the regioselective outcome of the reaction by performing the cyclization of **3.62b** with ligand **3.82** (Scheme 3.23). Products **3.62b** and **3.89b** were obtained in a 1:1 ratio, compared to the 2.3:1 observed when bipy was used as the ligand.

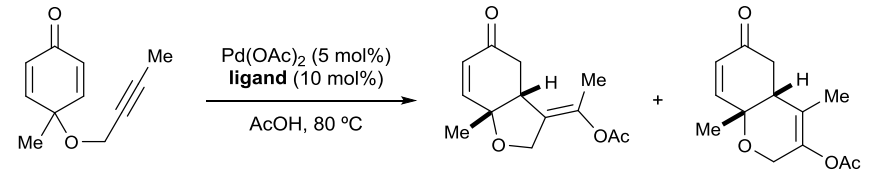
Scheme 3.23. Pd-catalyzed cyclization of substrate **3.62k** with chiral ligand **3.82**.



3.62k **3.63k** 1 : 1 **3.89k**

To further investigate this effect, the crude ^{1}H NMR spectra from our initial ligand screening were examined (see Section 3.4.1). The chiral ligands consistently induced a slight increase in the formation of **3.89b** (Table 3.4).

Table 3.4. Effect of ligand choice on regioselectivity.



3.62b **3.63b** **3.89b**

Entry	Ligand	3.63b : 3.89b
1	bipy	7.6 : 1
2	**3.79**	6.6 : 1
3	**3.82**	6.6 : 1
4	**3.84**	6.9 : 1
5	**3.85**	6.5 : 1

These results cannot be explained by the model proposed above and we believe that, in this case, the steric bulk of the chiral ligands is likely playing a dominant role. As described above in Figure 3.3, vinyl-Pd intermediate **B** is required to form the 5,6-fused bicyclic product. In this configuration, the Pd and its associated ligands are closer to the fully substituted carbon of the cyclohexadienone and, therefore, in a more sterically crowded environment. As the size of the ligand increases, the steric crowding increases as well, disfavoring path B and favoring formation of vinyl-Pd intermediate **A**, directly

competing with the inductive effect discussed above. As all of the chiral ligands are larger than the achiral bipy, the observed decrease in selectivity for the 5,6-fused bicyclic systems is consistent with this model.

This steric rationalization can also be used to explain the lower reaction efficiency observed with larger ligands. For example, ligand **3.83** failed to promote the cyclization of **3.62b** (see Section 3.4.1). This ligand has more localized steric demand that interferes with alkyne-Pd binding, thus disfavoring initial coordination. Similarly, the cyclization of nitrogen-tethered alkynes **3.62i** and **3.62j** exhibited a drastic rate reduction with the used of chiral ligands. The presence of the large sulfonamide moiety in these substrates would compromise the efficiency with which the alkyne binds to a Pd center that is coordinated with a large ligand (e.g., **3.83**), thus requiring ligands with smaller steric demand (e.g., bipy, **3.84** or **3.85**) in order to proceed with high levels of efficiency.

3.6 Conclusions

We have found that the stereoselective Pd-catalyzed cyclization of alkyne-tethered cyclohexadienones is remarkably sensitive to the steric environment of both the ligand and the substrate. We have identified a bipyridine-based ligand [(−)-*iso*-PINDY, **3.82**] capable of inducing selectivity in select substrates, providing a new opportunity for the desymmetrization of cyclohexadienones. Taken as a whole, this work implies that chiral ligands with smaller steric demands are needed in order to realize a desymmetrization reaction that proceeds with high conversion and selectivity.

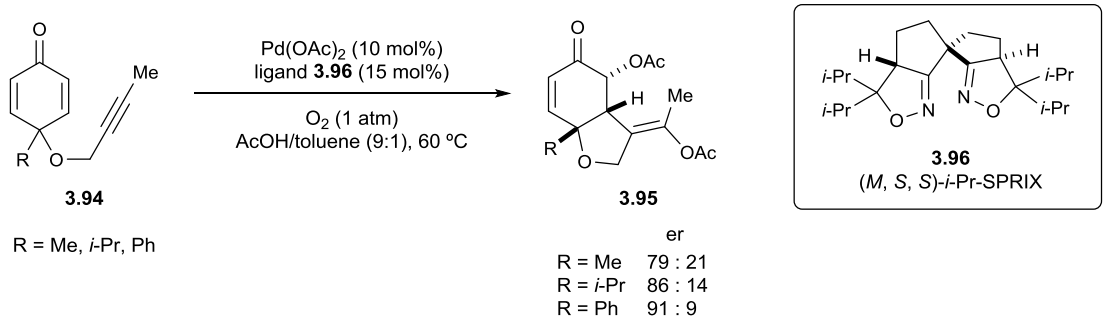
Additionally, we have shown that the regioselectivity of this reaction is greatly influenced by the presence of electronegative atoms proximal to the alkyne. This effect allows for the formation of both 5,6- and 6,6-fused bicyclic products, both of which are common motifs in natural product synthesis.

3.7 Future work

Further studies will be required in order to identify a ligand capable of providing consistently high levels of enantioselectivity. Although there are certainly a large number of bidentate pyridine- and oxazoline-based ligands available, they often require lengthy

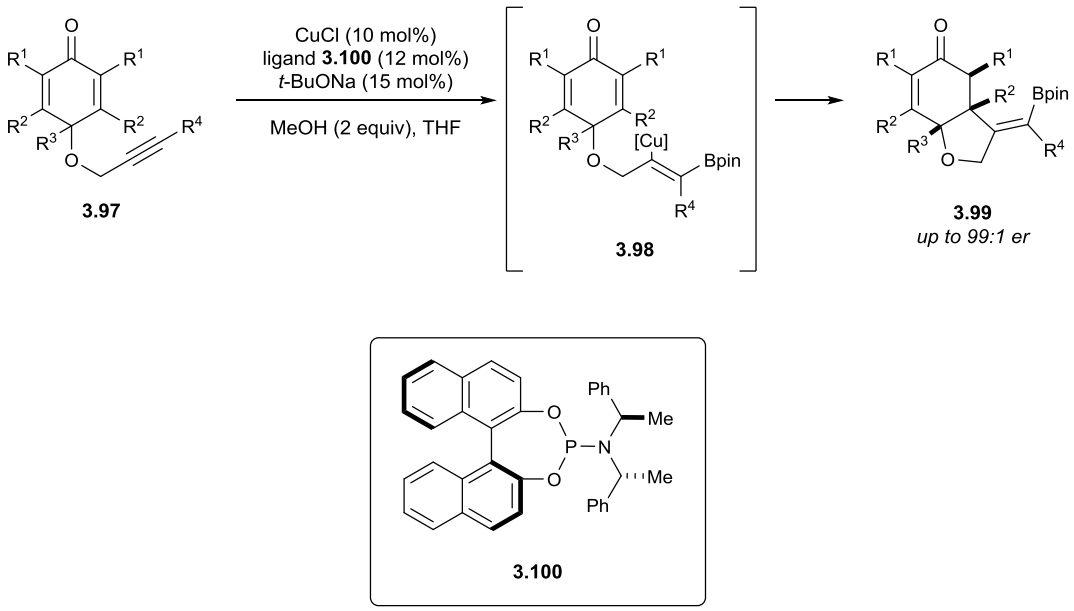
syntheses, making a large-scale screening a very time-consuming process. We are aware of promising preliminary results[51] (Scheme 3.24) obtained by Sasai in an extension of this reaction utilizing the SPRIX ligands (e.g., **3.96**) developed by their group.[173] In this case, alkyne-tethered substrates **3.94** underwent a tandem cyclization/oxidation process to afford products **3.95** in an enantiomeric ratio of up to 91:9.

Scheme 3.24. Sasai's enantioselective cyclative diacetoxylation.



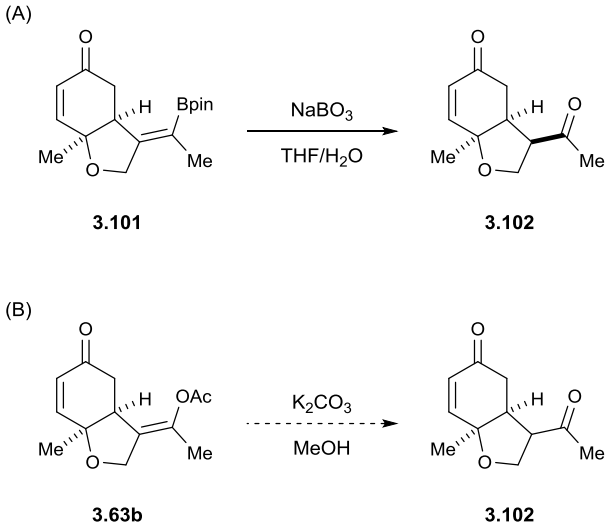
Additionally, Tian and Lin recently published a Cu-catalyzed cyclization that provides very similar bicyclic enone products with up to 99:1 enantioselectivity.[50] Cyclization of the alkyne substrates **3.97** proceeds through cis-borylation to give intermediate alkenyl cuprate **3.98** (Scheme 3.25). This intermediate then undergoes conjugate addition into the cyclohexadienone to generate bicyclic products **3.99**.

Scheme 3.25. Tian and Lin's Cu-catalyzed boralative cyclization.



Notably, $NaBO_3$ oxidation of **3.101** provides ketone **3.102** (Scheme 3.26A), which is identical to the hypothetical hydrolysis product of our byclic enone **3.63b** (Scheme 3.26B).

Scheme 3.26. Elaboration of bicyclic enone products.



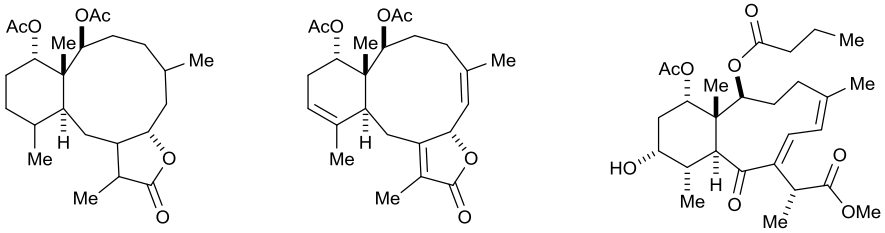
We are also interested in submitting additional compounds for testing as NF-κB inhibitors (see Section 3.1.4). Specifically, our initial screening only included substrates from the oxygen-tethered series – testing of the nitrogen- and carbon-tethered substrates could provide new insights into the structure-activity relationships and mechanism of action of the class of molecules. Prior to undertaking this work, efforts would be required to access a larger variety of nitrogen-tethered products (e.g., different protecting groups on the nitrogen atom) and to successfully separate (or selectively form) the 5,6- and 6,6-fused bicyclic products from the carbon-tethered substrates.

Chapter 4

Applications in Natural Product Synthesis: the Briaranes

4.1 Background

The briaranes are a large family of natural products characterized by a unique bicyclo[8.4.0]tetradecane ring system (**4.1**, Figure 4.1). Many members of the family contain a γ-lactone fused at C7 and C8, and also at least four contiguous stereocenters (C1, C2, C10, and C14). Much of the variety observed in these products arises from various levels of oxidation throughout the briarane core. Over 500 different briaranes have been isolated from various marine organisms around the world.[174–183] Individual family members exhibit a wide range of biological activity,[184,185] including anti-inflammatory, antifouling, antiviral, cytotoxic, and immunomodulatory activity. We are particularly interested in two specific briaranes: brianthein W (**4.2**) and briareolate ester L (**4.3**).



4.1
typical briarane core

4.2
brianthein W

4.3
briareolate ester L

Figure 4.1. The briarane family of natural products.

Brianthein W (**4.2**) was isolated in 1984 from the soft coral *Briareum polyanthes*.[186] Although this compound has been shown to have significant activity

against the P-388 leukemia cell line (ED_{50} of 0.76 μg/mL),[187] our interest lies primarily in the relatively simple structure of the molecule. We intend to use this as an initial target and proof of concept for our synthetic studies towards the briarane family.

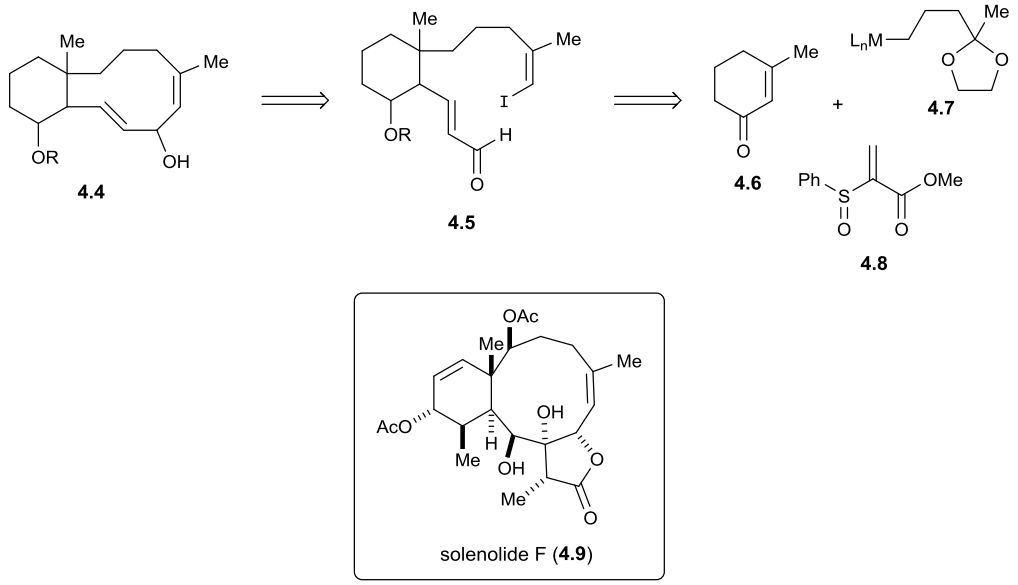
Briareolate ester L (**4.3**) was isolated in 2011 from the gorgonian *Briareum asbestinum*.[188] This briarane contains a characteristic (*E*,*Z*)-diene in the 10-membered ring. Additionally, it contains a C19 methyl ester instead of the γ-lactone, a feature common to the briareolate esters. Briareolate ester L exhibits activity against the BXPC-3 pancreatic cell line (EC_{50} of 9.3 μM), making it a potential lead compound for drug development. It was found that the (*E*,*Z*)-dienone is capable of acting as an extended Michael acceptor, and that the configuration of the double bonds is critical for the observed biological activity.[180]

To our knowledge, no total synthesis of any member of the briarane family has been reported; however, various approaches to the briarane ring system have been described. These reports are discussed below.

4.1.1 Procter's synthesis of the solenolide skeleton

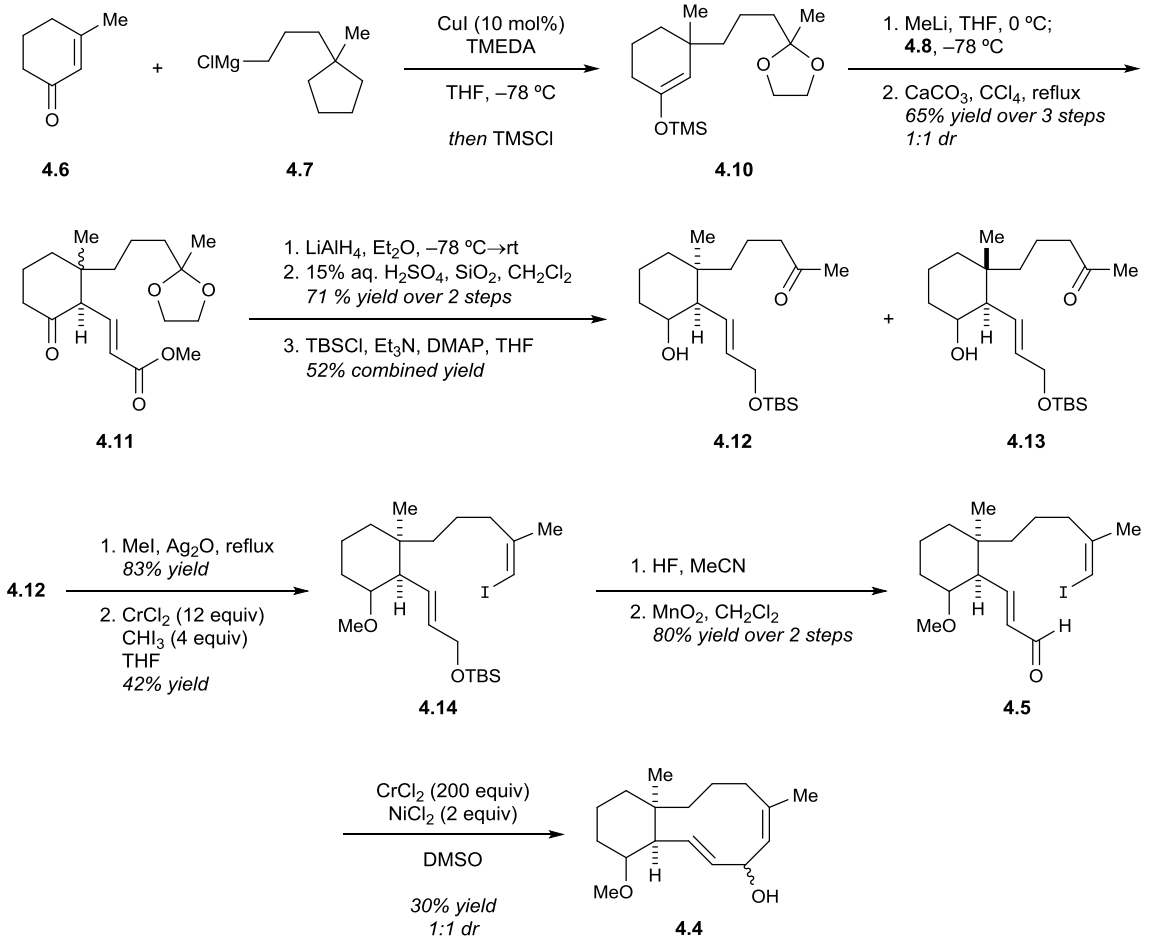
In 1995, Procter and coworkers reported the construction of the 6,10-fused bicyclic structure **4.4** (Scheme 4.1) in their pursuit of solenolide F (**4.9**).[189,190] They intended to form the 10-membered ring via the intramolecular Nozaki–Hiyama–Kishi (NHK) coupling[191,192] of intermediate **4.5**, which would be obtained from the three-component reaction of enone **4.6**, alkyl Grignard reagent **4.7**, and Michael acceptor **4.8**.

Scheme 4.1. Procter's retrosynthetic analysis of the solenolide core.



Conjugate addition of Grignard reagent **4.7** into cyclohexenone **4.6** proceeded efficiently (Scheme 4.2); however, addition of the resulting enolate into Michael acceptor **4.8** did not occur under the reaction conditions. The authors found it necessary to trap the enolate as the silyl enol ether **4.10**, which did successfully add into **4.8** after treatment with MeLi. Finally, elimination of the sulfoxide provided substituted cyclohexanone **4.11** as a 1:1 mixture of diastereomers. Reduction and protecting group manipulation afforded diastereomers **4.12** and **4.13**, which were separable by column chromatography.

Scheme 4.2. Procter's synthesis of the solenolide core.

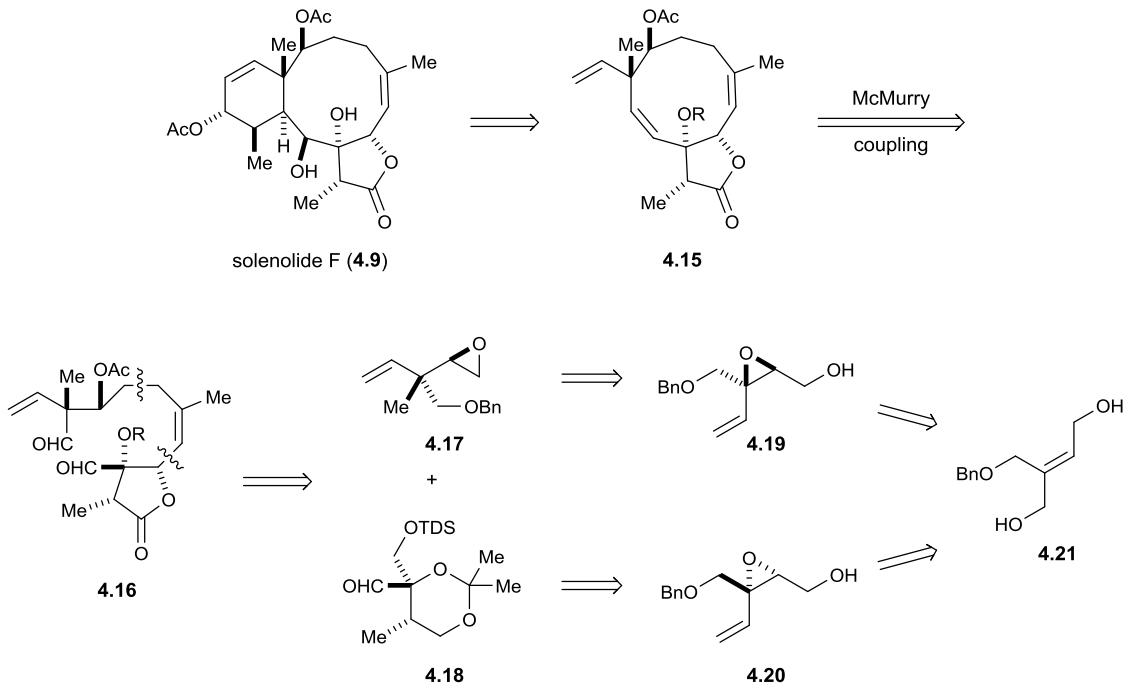


The authors noted that the natural diastereomer **4.13** contained the alkyl sidechains in a trans-axial configuration and postulated that this would cause considerable difficulty in the required ring-closing step. Therefore, the unnatural diastereomer **4.12** was used for the remainder of the study. Protection of the secondary alcohol in **4.12** as a methyl ether followed by Takai olefination[193] of the ketone provided vinyl iodide **4.14**. Removal of the TBS protecting group and oxidation of the primary alcohol afforded aldehyde **4.5**, the required substrate for the NHK coupling reaction. Subjecting **4.5** to the cyclization conditions provided the solenolide skeleton **4.4** as a 1:1 mixture of diastereomers.

4.1.2 Nantz's approach to the solenolide F

In 1997, Nantz and coworkers reported the synthesis of two chiral, quaternary carbon-containing fragments essential to their proposed synthesis of solenolide F (**4.9**, Scheme 4.3).[194] In their proposal, **4.9** would be formed from the elaboration of intermediate **4.15**. They envisioned that the 10-membered ring in **4.15** could be obtained from the intramolecular McMurry coupling[195] of dialdehyde **4.16**, which in turn could be provided by the stepwise alkylation of **4.17** and **4.18**† using a common nucleophile. Fragments **4.17** and **4.18** would be obtained by the regioselective methylation of epoxides **4.19** and **4.20**, respectively, which could both arise from common alkene precursor **4.21**.

Scheme 4.3. Nantz's retrosynthetic analysis of solenolide F.

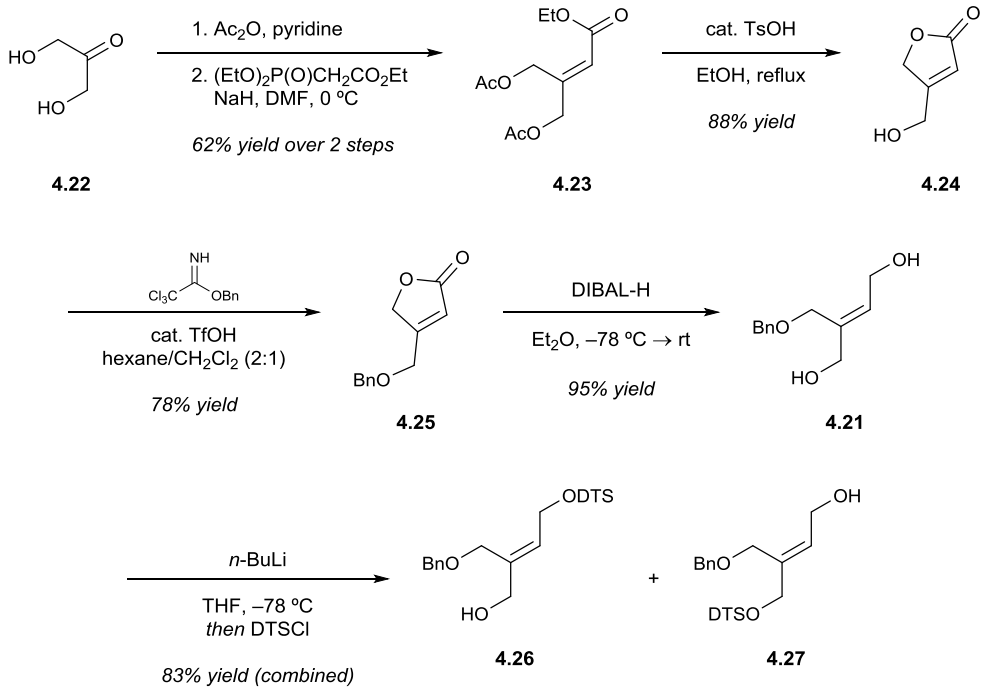


The authors targeted fragments **4.17** and **4.18** for their initial studies. The synthesis of common intermediate **4.21** began with ketone **4.22** (Scheme 4.4). Acetylation of both alcohols followed by Horner–Wadsworth–Emmons olefination[196,197]

† The stereochemical configuration of **4.18** is shown as presented in the original article. The configuration of **4.18** does not match that of retrosynthetic intermediate **4.16** or solenolide F (**4.9**).

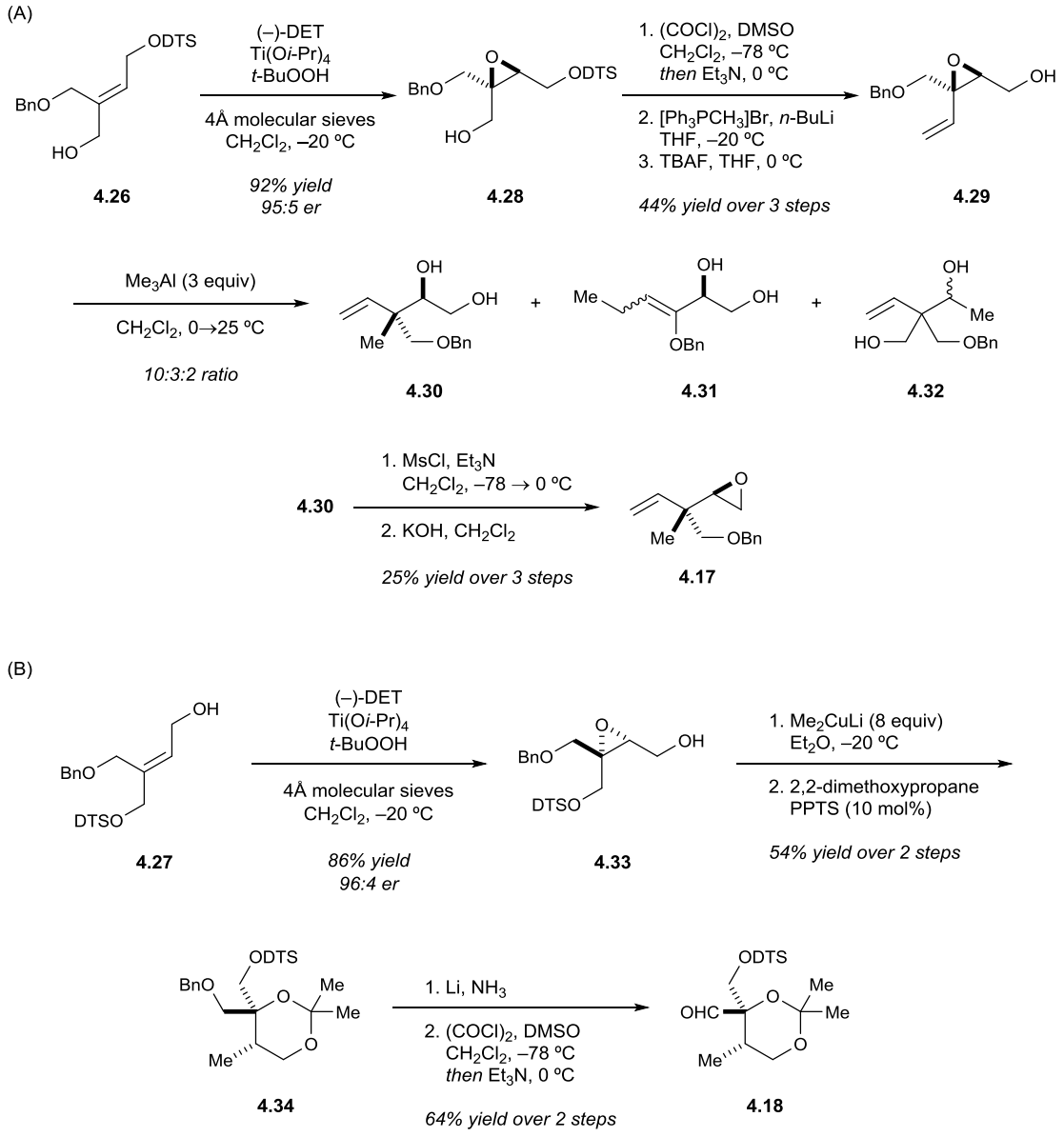
providing unsaturated ester **4.23**. Treatment with TsOH released the free diol, which spontaneously cyclized to afford lactone **4.24**. The remaining alcohol was benzylated to give **4.25**, which provided the desired intermediate **4.21** after reduction. This was then treated with *n*-BuLi and dimethylthexylsilyl chloride (DTSCl) to afford **4.26** and **4.27** as a 1:1 mixture, which were separated and used in the syntheses of **4.17** and **4.18**, respectively.

Scheme 4.4. Synthesis of Nantz's common intermediate **4.21**.



Sharpless epoxidation[198] of compound **4.26** provided epoxide **4.28**, bearing the appropriate configuration for desired fragment **4.17** (Scheme 4.5A). Oxidation of the primary alcohol, Wittig olefination[199] and removal of the DTS protecting group afforded intermediate **4.29**. After an extensive investigation using model substrates, compound **4.29** was treated with trimethylaluminum to effect regioselective ring opening at the more hindered carbon atom. This resulted in a 10:3:2 mixture of desired alcohol **4.30**, regioisomer **4.31**, and alkyl migration product **4.32**. This crude mixture was treated with methanesulfonyl chloride and KOH to provide solenolide fragment **4.17** in 25% yield from **4.29**.

Scheme 4.5. Nantz's synthesis of solenolide fragments **4.17** and **4.18**.

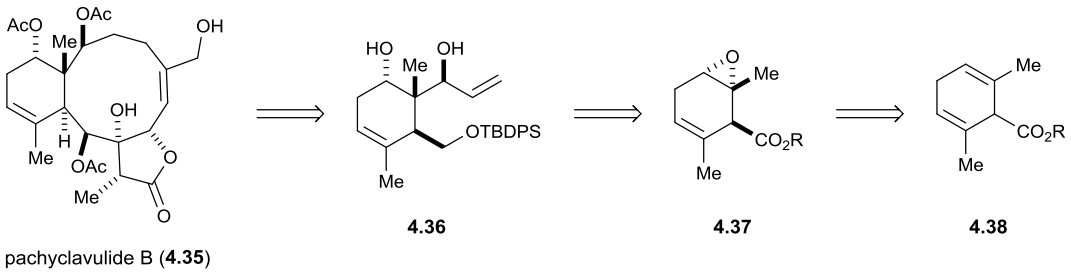


The synthesis of fragment **4.18** began with allylic alcohol **4.27** (**Scheme 4.5**B). Sharpless epoxidation provided epoxide **4.33**. In this case, the epoxide opening was performed with lithium dimethylcuprate and followed by acetonide formation to afford compound **4.34**. Debenzylation and oxidation of the primary alcohol provided the desired solenolide fragment **4.18**.

4.1.3 Iguchi's approach to pachyclavulide B

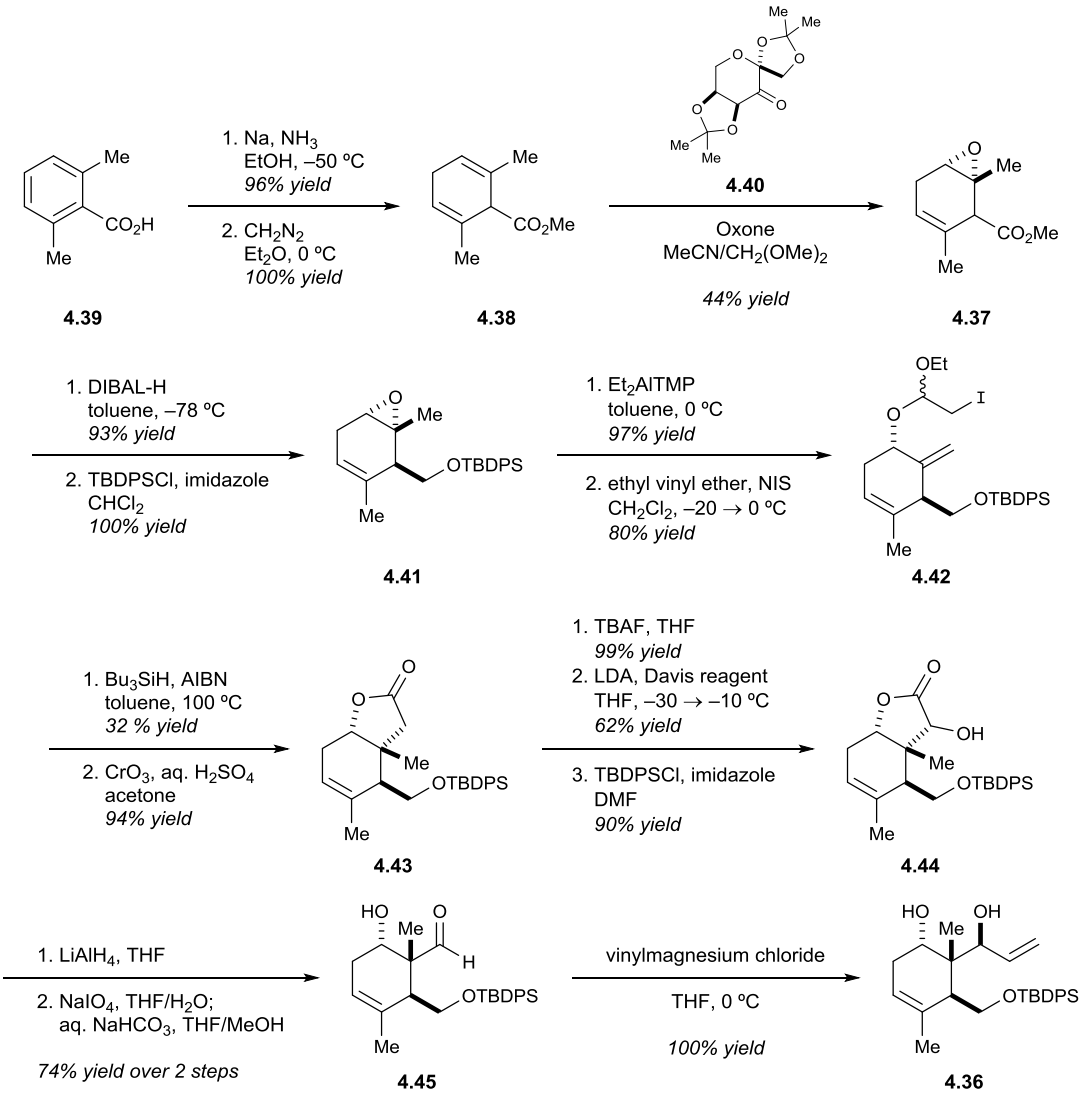
In 2006, Iguchi and coworkers reported the construction of the briarane core as part of their studies towards the total synthesis of pachyclavulide B (**4.35**, Scheme 4.6).[200] For this study, the authors targeted the synthesis of key intermediate **4.36**. This diol could be obtained from epoxide **4.37**, which is the desymmetrization product of cyclohexadiene **4.38**.

Scheme 4.6. Iguchi's retrosynthetic analysis of pachyclavulide B.



Cyclohexadiene **4.38** was obtained from the Birch reduction[201–205] and methylation of benzoic acid **4.39** (Scheme 4.7). Epoxidation with Oxone in the presence of fructose-derived catalyst **4.40** provided compound **4.37**. Reduction of the methyl ether and protection of the resulting alcohol afforded **4.41**. Treatment with Et_2AlTMP induced elimination and opening of the epoxide and the resulting alcohol was converted to acetal **4.42**. Radical cyclization followed by oxidation provided lactone **4.43**, and subsequent oxygenation afforded product **4.44**. The lactone was reduced to the diol, which underwent oxidative cleavage to give aldehyde **4.45**. Finally, nucleophilic addition of vinylmagnesium chloride provided the briarane core **4.36** in 15 overall steps.

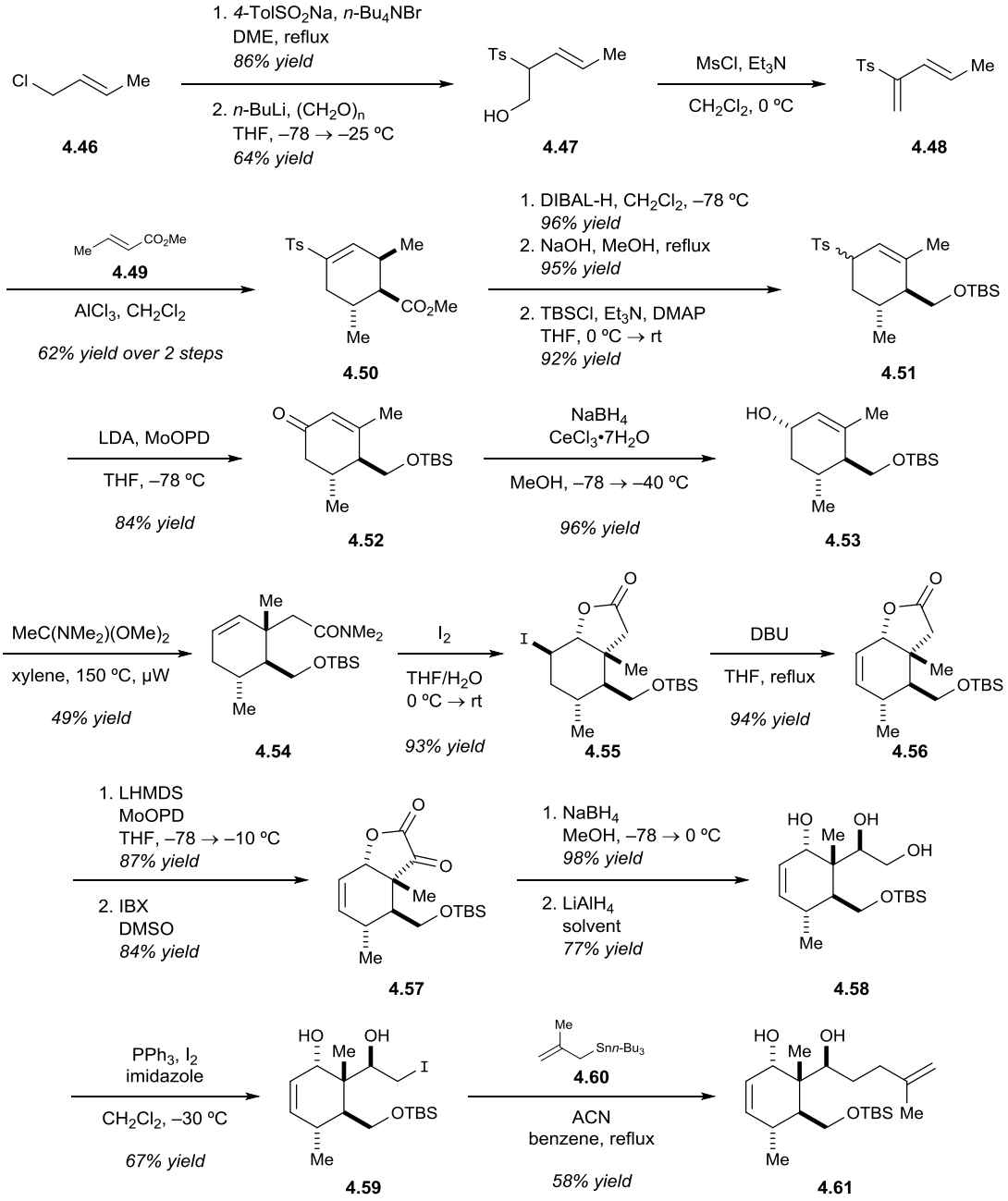
Scheme 4.7. Iguchi's synthesis of the briarane core.



4.1.4 Bates' approach to the briarane core

In 2010, Bates and coworkers reported their own synthesis of the briarane core, highlighted by a diastereoselective Diels–Alder reaction (Scheme 4.8).[206] Starting from crotyl chloride (**4.46**), displacement of the chloride with 4-toluenesulfinate followed by treatment with *n*-BuLi and paraformaldehyde provided alcohol **4.47**.

Scheme 4.8. Bates' synthesis of the briarane core.



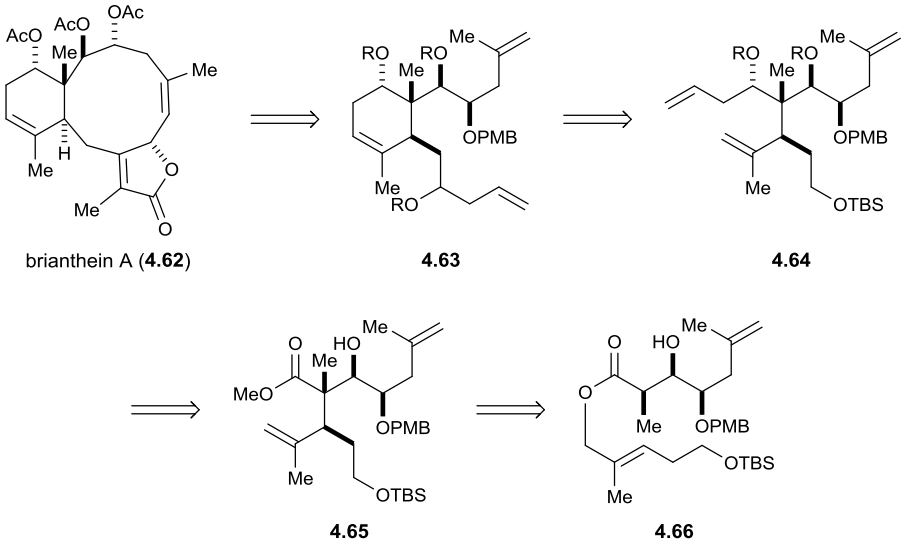
Mesylation and elimination afforded dieone **4.48**, which participated in the Diels–Alder reaction with methyl acrylate (**4.49**), providing cyclohexene **4.50**. Reduction of the methyl ester, isomerization of the alkene, and protection of the primary alcohol afforded product **4.51**. Desulfonation was accomplished via treatment with MoOPD

(MoO_5•pyridine•DMPU)[207] to give enone **4.52**. The ketone was reduced with $NaBH_4$ to provide **4.53**. To install the required quaternary stereocenter, various conditions for [3,3]-sigmatropic rearrangments were investigated. Eventually, Eschenmoser–Claisen conditions[208] provided cyclohexene **4.54** with high diastereoselectivity. Iodolactonization and hydrolysis afforded product **4.55**, and subsequent elimination provided the cyclohexene **4.56**. A two-step oxidation afforded β-ketolactone **4.57**, which was then reduced in a two-step procedure to provide triol **4.58**. Conversion of the primary alcohol to iodide **4.59** followed by radical coupling with allylstannane **4.60** afforded the briarane core **4.61** in 18 overall steps.

4.1.5 Crimmins' approach to brianthein A

In 2014, Crimmins and coworkers reported their use of a dianionic Ireland–Claisen rearrangement to obtain products containing the four contiguous stereocenters found in brianthein A (**4.62**, Scheme 4.9).[209]

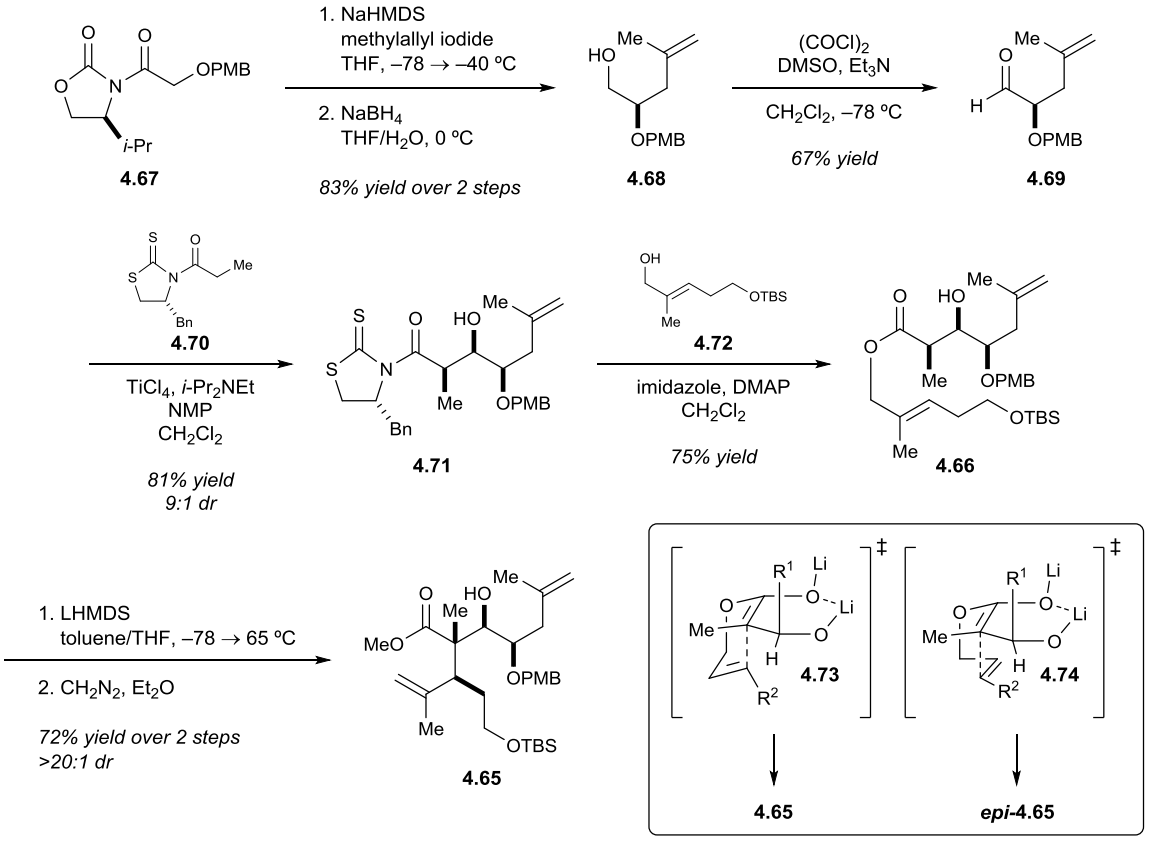
Scheme 4.9. Crimmins' retrosynthetic analysis of brianthein A.



The authors envisioned that the both rings in **4.62** could be formed by ring-closing metathesis, proceeding through intermediates **4.63** and **4.64**. Intermediate **4.64** would arise from methyl ester **4.65**, which is the product of the key Ireland–Claisen rearrangement of ester **4.66**.

The authors began their synthesis with oxazolidinone **4.67** (Scheme 4.10). Alkylation with methallyl iodide followed by reductive cleavage of the auxiliary provided product **4.68**. The primary alcohol was oxidized afford aldehyde **4.69**, which was used in an aldol reaction with thiazolidinone **4.70** to provide intermediate **4.71** with good diastereoselectivity.

Scheme 4.10. Crimmins' approach to brianthein A.



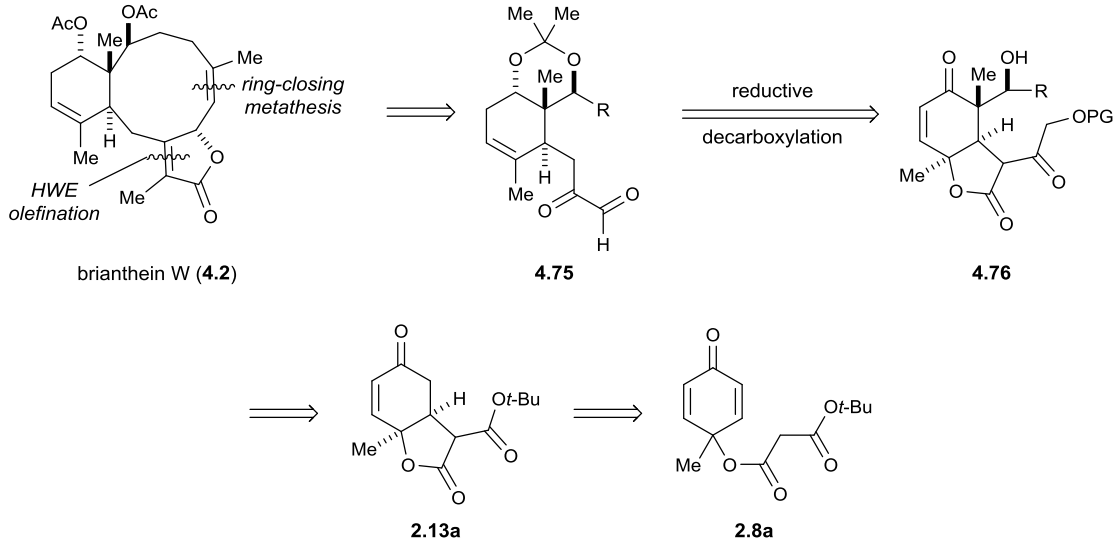
Esterification with alcohol **4.72** provided the Ireland–Claisen substrate **4.66**. Treatment of **4.66** with LHMDS induced the desired rearrangement, which provided brianthein A intermediate **4.65** upon methylation with diazomethane. The proposed rationalization for the observed diastereoselectivity is that chair-like transition state **4.73**, which would lead to **4.65**, is favored over the boat-like transition state **4.74**, which would lead to the undesired ***epi*-4.65**.

4.2 Objective

Although the results discussed above do provide potential access to the briaranes, we feel that a more efficient strategy would be very beneficial for pursuing this goal. The methods above either access the briarane skeleton with very limited remaining functionality, or provide the briarane core in a large number of synthetic steps. The shortest route, developed by Crimmins (Section 4.1.5), accesses a key intermediate in only 7 steps; however, completion of the 6-membered ring and installation of an additional stereocenter are still required to obtain an intermediate similar to those provided by previous methodologies. We recognized that the briarane core could be achieved through the elaboration of our phase-transfer catalysis methodology products (see Chapter 2). We chose to investigate this possibility in the context of the total synthesis of brianthein W (**4.2**).

We envisioned that the 10-membered ring in brianthein W (**4.2**, Scheme 4.11) would be formed by ring-closing metathesis and that the butenolide could be installed via an intramolecular Horner–Wadsworth–Emmons olefination. Given these disconnections, we identified cyclohexene **4.75** as a key intermediate, which could be obtained from the reductive decarboxylation of lactone **4.76**. This intermediate could be obtained through the elaboration of bicyclic enone **2.13a**, which is the product of the cyclization of substrate **2.8a** using our phase-transfer catalysis methodology. For our preliminary investigations of this synthetic route, we targeted the synthesis of intermediate **4.75**, which contains all four of the contiguous stereocenters found in brianthein W.

Scheme 4.11. Retrosynthetic analysis of brianthein W.

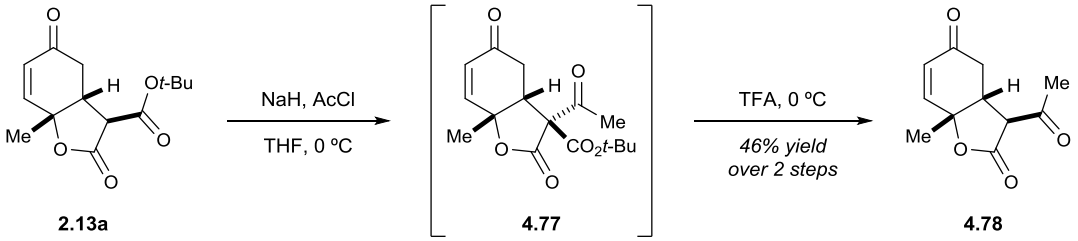


4.3 Elaboration of PTC cyclization products

4.3.1 Conversion of the malonate ester to a ketone

One key difference between PTC cyclization product **2.13a** and the briarane core **4.75** is the presence of a malonic ester in the former and a β-ketoester in the latter. The most straightforward way to address this issue would be the direct use of a β-ketoester in our cyclization reaction; however, the necessary cyclohexadienone substrate is not accessible, as discussed in Section 2.6. Therefore, we sought to convert the *t*-butyl ester in **2.13a** to the required ketone. Gratifyingly, this transformation was achieved by acylation of the malonate to provide triacyl compound **4.77**, followed by acidic hydrolysis to induce decarboxylation of the *t*-butyl ester and provide β-ketoester **4.78** in a one-pot procedure (**Scheme 4.12**).

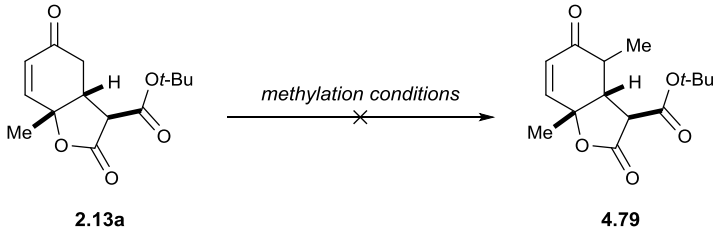
Scheme 4.12. Conversion of malonic ester **2.13a** to β-ketoester **4.78**.



4.3.2 Methylation

Our initial investigation towards installation of the α methyl group in **4.75** began with the attempted direct methylation of PTC cyclization substrate **2.13a** (Scheme 4.13). Unfortunately, the use of a variety of bases (LDA, LHMDS, KHMDS) with methyl iodide did not provide the desired α-methylated product **4.79**. The addition of HMPA or DMPU also did not prove successful. Additionally, attempts at amine catalyzed alkylation only resulted in the formation of rearomatized products.

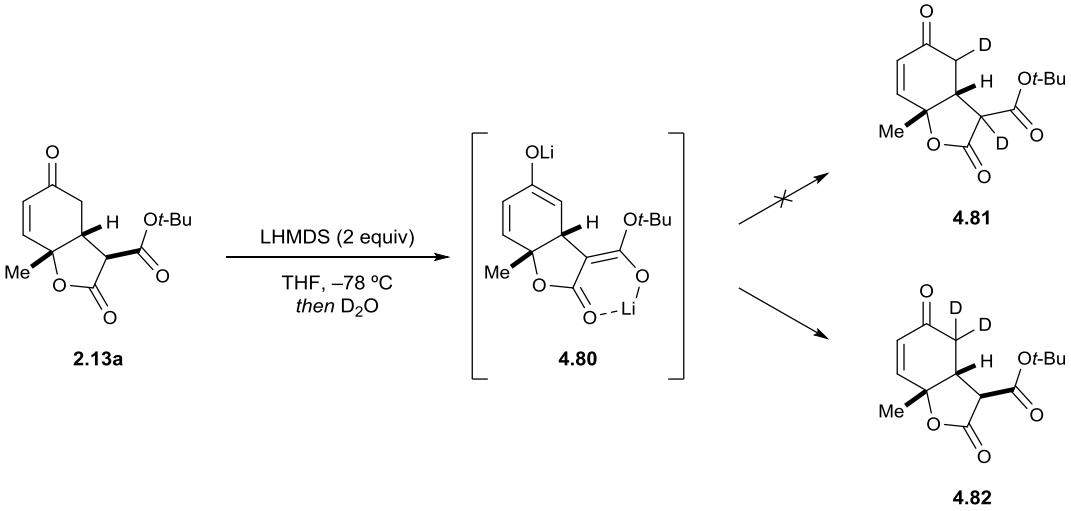
Scheme 4.13. Attempted methylation of bicyclic lactone **2.13a**.



At this point, it was unclear whether the failure of the reaction was a result of problems with enolization of the ketone, or methylation of the resulting enolate. To explore this, **2.13a** was treated with two equivalents of LHMDS to ostensibly provide dianion **4.80** (Scheme 4.14). This was then quenched with D_2O in an attempt to provide the bis-deuterated product **4.81**. Surprisingly, product **4.82** was obtained instead, which contained two deuterium atoms positioned α to the cyclohexadienone ketone. This result has three implications: (1) the desired enolate is successfully being formed, (2) the ketone enolate is more reactive than the malonic ester enolate towards electrophiles, and (3) equilibration occurs between the two enolates after reaction with the first electrophile.

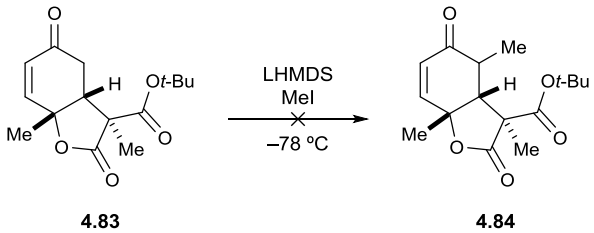
Based on this result, we postulate that methyl iodide is simply an ineffective electrophile under these conditions.

Scheme 4.14. Enolate quenching with D_2O.



We also decided to investigate whether the presence of the second enolate (on the malonic ester) was the source of our alkylation problems. To this end, we attempted the methylation of substrate **4.83**,[210] in which enolization of the malonic ester is prevented by the presence of an additional methyl substituent. Unfortunately, only starting material was recovered and the methylated product **4.84** was not observed (Scheme 4.15).

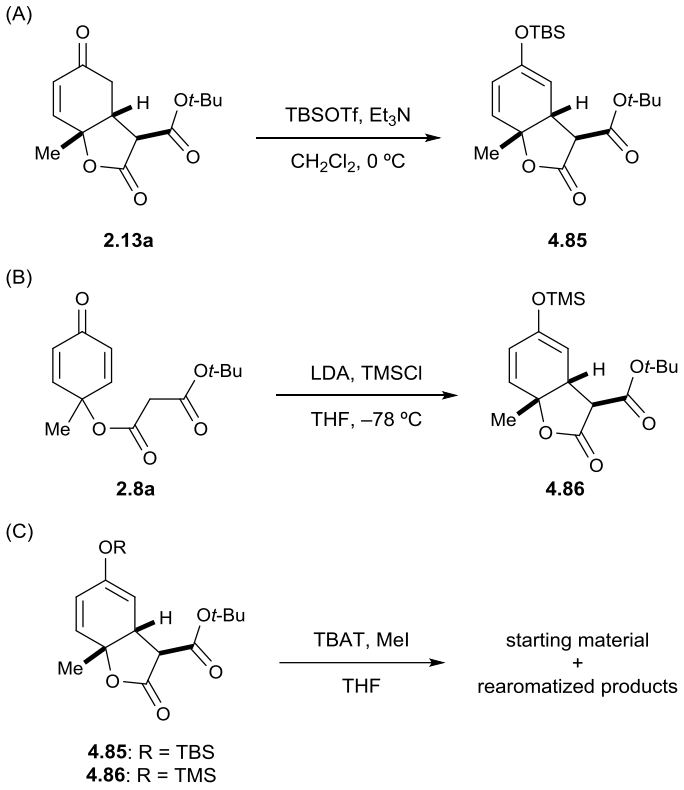
Scheme 4.15. Attempted methylation of substrate **4.83**.



We next investigated the enolate formation via desilylation of silyl enol ethers. To this end, TBS enol ether **4.85** was accessed directly from bicyclic lactone **2.13a** (Scheme 4.16A), whereas the analogous TMS ether **4.86** was provided by performing the cyclization of **2.8a** in the presence of TMSCl (Scheme 4.16B). Unfortunately, in both

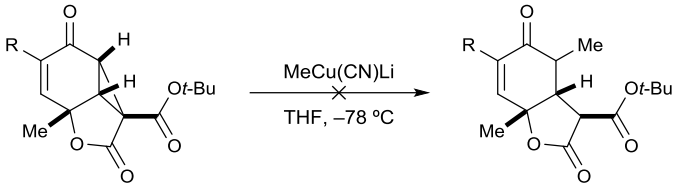
cases, treatment with an anhydrous fluoride source (tetrabutylammonium difluorotriphenylsilicate, TBAT) resulted in no reaction at room temperature and rearomatization upon heating (Scheme 4.16C).

Scheme 4.16. Attempted methylation of silyl enol ethers.



We recognized that they cyclopropane PTC cyclization products (Section 2.5.1) presented an alternative strategy for the synthesis of **4.75**. Hypothetically, addition of an appropriate methyl nucleophile into the cyclopropane in **2.23** would provide the desired methylated product. Because of the potential for competitive nucleophilic addition into the ketone carbonyl, we chose to investigate the use of an alkyl cyanocuprate, a soft nucleophile, as opposed to hard nucleophiles such as alkyllithium or Grignard reagents. Unfortunately, treatment of either **2.23r** or **2.23j** with MeCu(CN)Li did not provide the desired products **4.79** or **4.87** (Scheme 4.17).

Scheme 4.17. Attempted cyclopropane ring opening with methyl cyanocuprate.



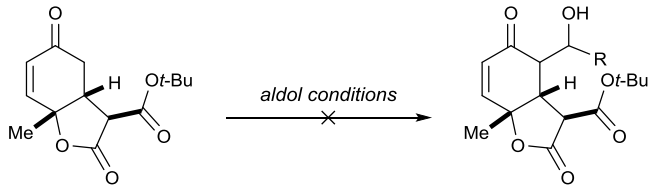
2.23r: R = H
2.23j: R = Br

4.79: R = H
4.87: R = Br

4.3.3 Aldol reactions

We also investigated aldol reactions of **2.13a**, intending to install the sidechain in **4.75** representing a segment of the 10-membered ring in the briarane framework. However, treatment with a strong base and a variety of aldehydes resulted only in the recovery of starting material, with no desired product **4.88** observed (Scheme 4.18). Boron aldol conditions afforded similar results.

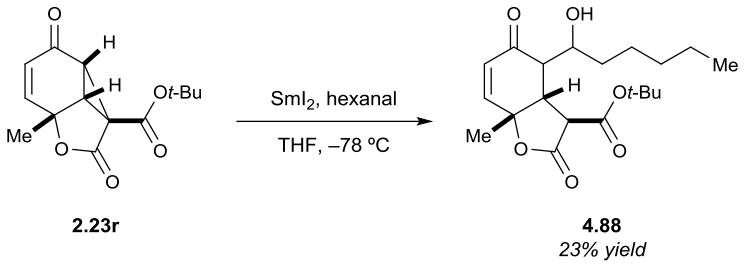
Scheme 4.18. Attempted aldol reactions of bicyclic lactone **2.13a**.



2.13a **4.88**

Turning again to cyclopropane product **2.23r**, we proposed that ring opening with SmI_2 (Section 2.7) would provide a Sm enolate that might be suitable for undergoing an aldol reaction. Treatment of **2.23r** with SmI_2 and hexanal did provide the desired aldol product **4.88**; however, the reaction was low yielding and a large amount of side products were present (Scheme 4.19). Although this result was encouraging, the reaction was found to be generally unreliable and we were unable to optimize the conditions and improve the observed yields.

Scheme 4.19. SmI_2 induced aldol reaction of **2.23r**.

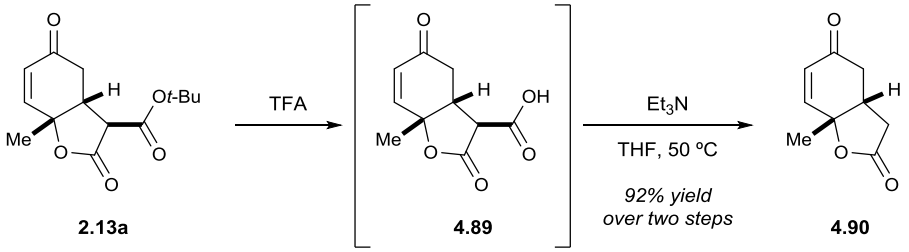


2.23r **4.88**
23% yield

4.4 Elaboration of decarboxylated products

In an attempt to circumvent the issues observed above, we decided to remove the malonic ester from substrate **2.13a**, leaving the cyclohexadienone ketone as the primary site for deprotonation. To accomplish this, **2.13a** was subjected to decarboxylation conditions to remove the malonic ester and provide bicyclic lactone **4.90** through the intermediate β-ketoacid **4.89**.

Scheme 4.20. Synthesis of decarboxylated substrate **4.90**.

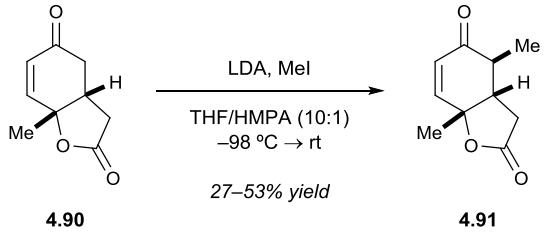


2.13a **4.89** **4.90**

4.4.1 Methylation

Initial attempts at the methylation of substrate **4.90** with strong bases and methyl iodide were unsuccessful; however, in this case the use of LDA with HMPA did prove beneficial and the methylated product **4.91** was obtained as a single diastereomer (Scheme 4.21). Encouraged by this result, optimization of the reaction conditions was attempted. Altering the solvent, temperature, order of addition, and reaction time did not improve conversion. The use of alternate bases, such as LHMDS and KHMDS, resulted in no reaction. Unfortunately, we were unable to identify conditions that provided improved results.

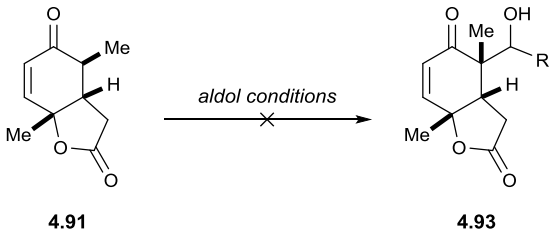
Scheme 4.21. Methylation of decarboxylated substrate **2.13a**.



4.4.2 Aldol reactions

Although the methylation of **4.90** did not proceed efficiently, we were able to obtain enough material to attempt the required aldol reaction of **4.91** under various conditions (Scheme 4.22). Upon treatment with strong base and aldehyde, similar results were obtained as seen for the malonic ester substrate **2.13a** above. In this case, the use of HMPA was avoided, as the additive would have prevented formation of the chelated transition state required to achieve the necessary diastereoselectivity.

Scheme 4.22. Attempted aldol reaction of methylated substrate **4.91**.

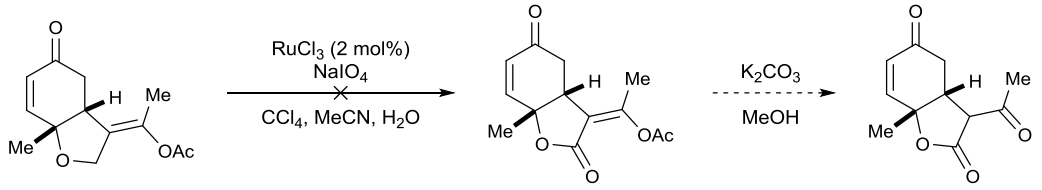


4.5 Elaboration of Pd-catalyzed cyclization products

Given the low yields of the methylation reaction in combination with the lack of reactivity of **4.91** under aldol conditions, we decided to consider other routes to the briarane intermediate **4.75**. Specifically, we identified a strategy for this intermediate from the products of our Pd-catalyzed cyclization methodology. Although the direct cyclization of alkynoate substrates had previously proven unsuccessful (Section 3.4.2), we realized that oxidation of cyclization product **2.63b** would provide bicyclic lactone **4.90** and subsequent hydrolysis of the vinyl acetate (**4.94**) would afford the desired

β-ketoester **4.78**. If successful, this strategy would allow us to attempt the methylation directly on substrate **2.63b**, which would likely display different reactivity than the ester containing substrates **2.13a** and **4.90**. In practice, however, the oxidation conditions provided a complex mixture of unidentifiable products (Scheme 4.23).

Scheme 4.23. Attempted oxidation of Pd-catalyzed cyclization product **2.63b**.



3.63b **4.94** **4.78**

4.6 Conclusions

We have successfully utilized the products of our PTC cyclization methodology in both methylation and aldol reactions towards the synthesis of the briarane core; however, the low efficiency and high variability of these reactions has precluded their use in further synthetic studies. These results can likely be attributed to the instability of the required enolates of substrates **2.13a** and **4.90**, an observation that is corroborated by earlier work on similar systems by Helmchen and coworkers,[211] as well as investigations of a similar acylation reaction in our group's synthesis of sorbicillactone A.[83]

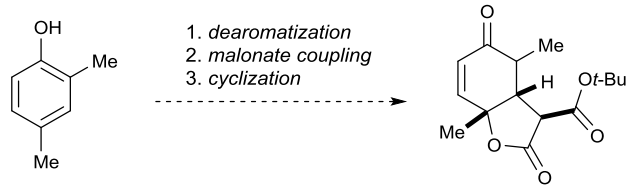
4.7 Future work

Work has continued in our lab in pursuit of the briarane family of natural products.[†] One specific strategy currently under investigation involves transformation of the enone functionality in **2.13a**, potentially altering the reactivity of the substrate to be more amenable to the desired methylation and aldol reaction. Additionally, we are investigating a route starting from 2,4-dimethylphenol (**4.95**), which has the required methyl group already incorporated (Scheme 4.24). Although this route will not take advantage of the enantioselective desymmetrization methodologies discussed here, it will

[†] This work is currently being performed by Nicholas Moon.

potentially demonstrate the utility of the enantioselective dearomatization catalysts currently under development in our group.[32]

Scheme 4.24. Synthetic strategy using 2,4-dimethylphenol.



4.95 **4.79**

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Appendix I

Experimental Procedures and Data

Materials and Methods

Unless otherwise stated, reactions were performed in flame- or oven-dried glassware under an argon or nitrogen atmosphere using anhydrous solvents. Acetic acid was distilled from acetic anhydride with CrO_3 or $KMnO_4$. Acetonitrile, CH_2Cl_2, and toluene were dried by passage through an activated alumina column under argon. Dimethyl sulfoxide (DMSO) was placed over activated alumina overnight, and then distilled from CaH_2 and stored over 4Å molecular sieves. Methanol was dried over 3Å molecular sieves. 1,4-Dioxane and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Powdered 4Å molecular sieves were activated by heating under vacuum and stored at 90 ºC until use. $Pd(OAc)_2$ was purchased from Strem Chemicals. Unless otherwise stated, reactions were monitored using thin-layer chromatography (TLC) using plates precoated with silica gel XHL w/ UV254 (250 μm) and visualized by UV light or $KMnO_4$, phosphomolybdic acid, or anisaldehyde stains, followed by heating. Silica gel (particle size 32–63 μm) was used for flash column chromatography. ^1H and ^{13}C NMR spectra are reported relative to the residual solvent peak (δ 7.26 and δ 77.2 for ^1H and ^{13}C in $CDCl_3$, δ 7.16 and δ 128.0 for ^1H and ^{13}C in C_6D_6, respectively), or tetramethylsilane (δ 0.00 for ^1H) when the residual solvent peak is obscured. Data for ^1H NMR spectra are reported as follows: chemical shift (ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity is described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, bs = broad singlet. IR samples were prepared on NaCl plates either neat or by evaporation from $CHCl_3$ or CH_2Cl_2.

Experimental Details – Chapter 2

General method A: dearomatization of phenols using PIDA

A solution of the corresponding phenol (1 equiv) in 3:1 MeCN/H_2O (0.1 M in substrate) was cooled to 0 ºC and treated with PIDA (1.1 equiv). The reaction mixture was stirred until consumption of the starting material (usually within 1 h), then diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated.

General method B: coupling of phenols using trifluoroacetic anhydride

A procedure by Stork[1] was adapted. Trifluoroacetic anhydride (2 mL per mmol of substrate) was added to a flask containing the mono-alkyl malonate (2.5 equiv). The mixture was stirred for 30 min before it was placed it under high vacuum to remove formed TFA and excess trifluoroacetic anhydride. The flask was back-filled with nitrogen and a solution of the appropriate quinol (1 equiv) in DME (0.05 M in substrate) was added. The solution was stirred until consumption of the starting material (usually between 1 and 3 h), at which point it was quenched by addition of saturated aq. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4, filtered, and concentrated.

General method C: coupling of phenols using DCC

DCC (3 equiv) was added to a solution of the appropriate quinol (1 equiv), the corresponding acid (3 equiv), and DMAP (10 mol%) in CH_2Cl_2 (0.4 M in substrate). The mixture was stirred until consumption of the starting material (usually between 1 and 3 h), then diluted with Et_2O, filtered, and concentrated.

[1] Stork, G.; La Clair, J. J.; Spargo, P.; Nargund, R. P.; Totah, N. *J. Am. Chem. Soc.* **1996**, *118*, 5304–5305.

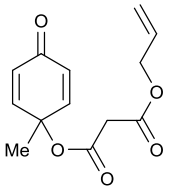
General method D: cyclization using Cs_2CO_3 in MeCN

A solution of the appropriate substrate (1 equiv) in MeCN (0.05 M in substrate) was treated with solid Cs_2CO_3 (2.5 equiv). The reaction mixture was stirred until consumption of the starting material (usually within 30 min for sterically unhindered substrates), then concentrated and purified directly by flash-column chromatography.

General method E: asymmetric cyclization using phase-transfer catalysis

A mixture of the cyclohexadienone substrate (1 equiv), 4Å molecular sieves (100% w/w), and catalyst **2.24** (10 mol%) was suspended in α,α,α-trifluorotoluene (0.05 M in substrate) and cooled to 0 ºC. Cs_2CO_3 (1 equiv) was added and the mixture was stirred until consumption of the starting material. In cases where no conversion was observed after ~4 h, the reaction mixture was allowed to gradually reach rt and stirred until consumption of the starting material. The solvent was then removed under reduced pressure and the products purified directly by flash-column chromatography.

Allyl malonate-tethered cyclohexadienone 2.6



Using general method B, mono-allyl malonate (2.18)[2] was coupled to quinol 2.17a[3] to give 2.6 in 66% yield after flash-column chromatography (3:1 hexanes/EtOAc).
IR (thin film) 2983, 2941, 1736, 1668, 1631, 1329, 1270, 1150, 1053, 992, 858 cm^{-1}

[2] Prepared according to: Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräckow, J.; Barret, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293–10298.

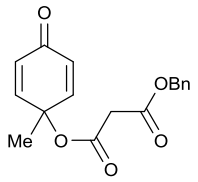
[3] Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 2737–2741.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 10.2 Hz, 2 H), 6.25 (d, J = 10.2 Hz, 2 H), 6.00–5.81 (m, 1 H), 5.35 (ddd, J = 17.2, 2.6, 1.2 Hz, 1 H), 5.28 (ddd, J = 10.4, 2.3, 1.2 Hz, 1 H), 4.65 (d, J = 5.8 Hz, 2 H), 3.40 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.0 (C), 166.0 (C), 165.0 (C), 148.4 (CH × 2), 131.4 (CH), 128.6 (CH × 2), 119.3 (CH_2), 75.5 (C), 66.4 (CH_2), 41.8 (CH_2); 26.3 (CH_3)

HRMS (ESI+) 273.0733 calcd for $C_{13}H_{14}O_5Na$, found 273.0742

Benzyl malonate-tethered cyclohexadienone 2.7



Using general method B, mono-benzyl malonate (**2.19**)[4] was coupled to quinol **2.17a** to give **2.7** in 63% yield after flash-column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 3036, 2983, 2937, 1734, 1666, 1630, 1328, 1266, 1149, 1152, 858 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5 H), 6.78 (d, *J* = 10.2 Hz, 2 H), 6.20 (d, *J* = 10.2 Hz, 2 H), 5.18 (s, 2 H), 3.41 (s, 2 H), 1.49 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.9(C), 166.1(C), 164.9(C), 148.4 (CH × 2), 135.1(C), 128.8 (CH × 4), 128.7 (CH), 128.5 (CH × 2), 75.4(C), 67.5 (CH_2), 41.9 (CH_2), 26.2 (CH_3)

HRMS (ESI+) 323.0890 calcd for $C_{17}H_{16}O_5Na$, found 323.0898

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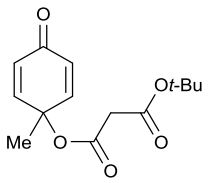
[4] Thetiot-Laurent, S. A.-L.; Nadal, B.; Le Gall, T. *Synthesis* **2010**, 1697–1701.

Malonate-tethered cyclohexadienone 2.8a



Using general method B, mono-*t*-butyl malonate (**2.20**)[5] was coupled to quinol **2.17a** to give **2.8a** in 43% yield after flash-column chromatography (3:1 hexanes/EtOAc).

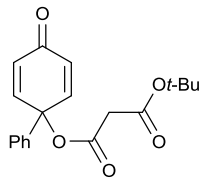
IR (thin film) 2983, 2937, 1755, 1728, 1671, 1629, 1144, 1055, 854 cm^{-1}

^{1}H NMR (300 MHz, C_6D_6) δ 6.35 (d, *J* = 10.2 Hz, 2 H), 6.07 (d, *J* = 10.2 Hz, 2 H), 2.97 (s, 2 H), 1.30 (s, 9 H), 1.04 (s, 3 H)

^{13}C NMR (75 MHz, C_6D_6, DEPT) δ 189.6 (C), 165.4 (C), 165.1 (C), 147.8 (CH × 2), 128.6 (CH × 2), 81.7 (C), 75.0 (C), 43.0 (CH_2), 27.9 (CH_3 × 3), 25.9 (CH_3)

HRMS (ESI+) 289.1046 calcd for $C_{14}H_{18}O_5Na$, found 289.1059

Malonate-tethered cyclohexadienone 2.8b



Using general method B, mono-*t*-butyl malonate was coupled to quinol **2.17b**[6] to give **2.8b** in 36% yield after flash-column chromatography (4:1 hexanes/EtOAc).

IR (thin film) 1729, 1670, 1625, 1325, 1135, 994, 842 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.30 (m, 5 H), 6.97 (d, *J* = 10.1 Hz, 2 H), 6.34 (d, *J* = 10.1 Hz, 2 H), 3.40 (s, 2 H), 1.48 (s, 9 H)

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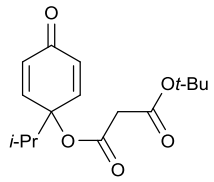
[5] Although this substrate is commercially available, it is also easily obtained by DCC coupling of malonic acid with 1 equiv of *t*-BuOH; see: Shelkov, R.; Nahmany, M.; Melman, A. *J. Org. Chem.* **2002**, *67*, 8975.

[6] Prepared according to: Felpin, F.-X. *Tetrahedron Lett*. **2007**, *48*, 409–412.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.5 (C), 165.3 (C), 165.0 (C), 147.1 (CH × 2), 136.1 (C), 129.2 (CH × 2), 129.0 (CH), 128.4 (CH × 2), 125.4 (CH × 2), 82.7 (C), 78.2 (C), 43.4 (CH_2), 28.1 (CH_3 × 3)

HRMS (ESI+) 351.1203 calcd for $C_{19}H_{20}O_5Na$, found 351.1199

Malonate-tethered cyclohexadienone 2.8c



Using general method B, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17c** to give **2.8c** in 56% yield after flash-column chromatography (5:1 hexanes/EtOAc).

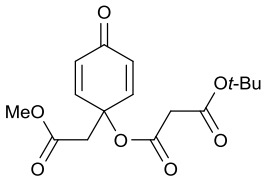
IR (thin film) 2976, 2937, 2880, 1751, 1730, 1670, 1629, 1461, 1333, 1272, 1146, 1005 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, *J* = 10.3 Hz, 2 H), 6.31 (d, *J* = 10.3 Hz, 2 H), 3.27 (s, 2 H), 2.11 (hept, *J* = 6.9 Hz, 1 H), 1.45 (s, 9 H), 0.93 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.3 (C), 165.5 (C), 165.3 (C), 146.8 (CH × 2), 130.1 (CH × 2), 82.5 (C), 80.4 (C), 43.2 (CH_2), 36.5 (CH), 28.0 (CH_3 × 3), 16.9 (CH_3)

HRMS (ESI+) 317.1359 calcd for $C_{16}H_{22}O_5Na$, found 317.1417

Malonate-tethered cyclohexadienone 2.8d



Using general method B, mono-*t*-butyl malonate (**2.20**) was coupled to jacaranone[7] (**1d)** to give **4d** in 38% yield after flash-column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 2980, 1734, 1672, 1633, 1333, 1249, 1154, 1032, 855 cm^{-1}

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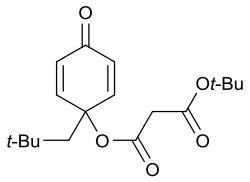
[7] Parker, K. A.; Andrade, J. R. *J. Org. Chem.* **1979**, *44*, 3964–3966.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 10.2 Hz, 2 H), 6.29 (d, J = 10.2 Hz, 2 H), 3.67 (s, 3 H), 3.26 (s, 2 H), 2.82 (s, 2 H), 1.44 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.7 (C), 168.0 (C), 165.2 (C), 165.1 (C), 146.2 (CH × 2), 129.4 (CH), 82.7 (C), 74.5 (C), 52.3 (CH_3), 43.8 (CH_2), 43.0 (CH_2), 28.0 (CH_3 × 3)

HRMS (ESI+) 347.1101 calcd for $C_{16}H_{20}O_7Na$, found 347.1126

Malonate-tethered cyclohexadienone 2.8e



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17e** to give **2.8e** in quantitative yield after flash-column chromatography (5:1 hexanes/EtOAc).

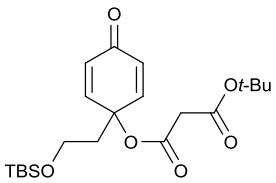
IR (thin film) 2976, 2935, 2870, 1732, 1671, 1630, 1368, 1331, 1143, 1046, 853 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 10.2 Hz, 2 H), 6.22 (d, J = 10.2 Hz, 2 H), 3.24 (s, 2 H), 1.81 (s, 2 H), 1.44 (s, 9 H), 0.99 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.4 (C), 165.4 (C), 165.2 (C), 149.0 (CH × 2), 128.0 (CH × 2), 82.6 (C), 78.5 (C), 53.1 (CH_2), 43.3 (CH_2), 31.8 (C), 31.5 (CH_3 × 3), 28.0 (CH_3 × 3)

HRMS (ESI+) 345.1672 calcd for $C_{18}H_{26}O_5Na$, found 345.1679

Malonate-tethered cyclohexadienone 2.8f



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17f**[8] to give **2.8f** as a white solid in 74% yield after flash-column chromatography (10:1 hexanes/EtOAc).

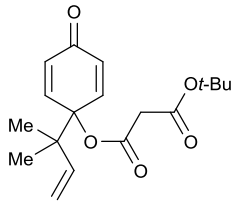
IR (thin film) 2955, 2929, 2857, 1757, 1730, 1674, 1632, 1258, 1148, 1100, 839, 778 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 10.2 Hz, 2 H), 6.24 (d, *J* = 10.2 Hz, 2 H), 3.72 (t, *J* = 6.1 Hz, 2 H), 3.27 (s, 2 H), 2.03 (t, *J* = 6.1 Hz, 2 H), 1.46 (s, 9 H), 0.85 (s, 9 H), 0.00 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.3 (C), 165.4 (C), 165.3 (C), 148.1 ($CH \times 2$), 128.6 ($CH \times 2$), 82.6 (C), 76.8 (C), 57.8 (CH_2), 43.2 (CH_2), 42.9 (CH_2), 28.1 ($CH_3 \times 3$), 25.9 ($CH_3 \times 3$), 18.2 (C), −5.4 ($CH_3 \times 2$)

HRMS (ESI+) 433.2017 calcd for $C_{21}H_{34}O_6SiNa$, found 433.2028

Malonate-tethered cyclohexadienone 2.8g



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17g** to give **2.8g** in 50% yield after flash-column chromatography (3:1 hexanes/Et_2O).

IR (thin film) 2977, 2941, 1759, 1731, 1671, 1629, 1332, 1257, 1143, 1000, 914, cm^{-1}

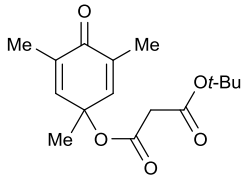
[8] Prepared according to: You, A.; Hoveyda, A. H.; Snapper, M. L. *Ang. Chem. Int. Ed.* **2009**, *48*, 547–550.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 10.3 Hz, 2 H), 6.35 (d, *J* = 10.3 Hz, 2 H), 5.75 (ddt, *J* = 17.3, 10.0, 7.4 Hz, 1 H), 5.07 (d, *J* = 10.3 Hz, 1 H), 5.02 (d, *J* = 17.2 Hz, 1 H) 3.31 (s, 2 H), 2.15 (d, *J* = 7.4 Hz, 2 H), 1.47 (s, 9 H), 0.98 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.0 (C), 165.5 (C), 165.2 (C), 146.9 (CH × 2), 134.0 (CH), 130.4 (CH × 2); 118.6 (CH_2), 82.7 (C), 82.0 (C), 43.3 (C), 43.2 (CH_2), 41.5 (CH_2), 28.1 (CH_3 × 3), 21.9 (CH_3 × 2)

HRMS (ESI+) 357.1672 calcd for $C_{19}H_{26}O_5Na$, found 357.1690

Malonate-tethered cyclohexadienone 2.8h



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17h** to give **2.8h** in quantitative yield after flash-column chromatography (9:1 hexanes/EtOAc).

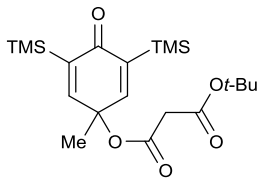
IR (thin film) 2979, 2930, 1731, 1679, 1644, 1370, 1333, 1144, 1048, 971, 847 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 2 H), 3.22 (s, 2 H), 1.87 (s, 6 H), 1.52 (s, 3 H), 1.45 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 186.4 (C), 165.7 (C), 165.5 (C), 143.4 (CH × 2), 134.9 (C × 2), 82.3 (C), 75.9 (C), 43.5 (CH_2), 28.1 (CH_3 × 3), 26.4 (CH_3), 16.0 (CH_3 × 2)

HRMS (ESI+) 317.1359 calcd for $C_{16}H_{22}O_5Na$, found 317.1373

Malonate-tethered cyclohexadienone 2.8i



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17i** to give **2.8i** in 86% yield after flash-column chromatography (19:1 hexanes/EtOAc).

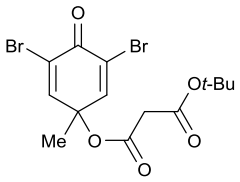
IR (thin film) 2953, 1725, 1630, 1313, 1244, 1157, 1047, 843 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 2 H), 3.26 (s, 2 H), 1.50 (s, 3 H), 1.47 (s, 9 H), 0.16 (s, 18 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 190.7 (C), 165.5(C), 165.3(C), 155.1 (CH × 2), 140.9 (C × 2), 82.2 (C), 75.3 (C), 43.5 (CH_2), 28.1 (CH_3 ×3), 26.6 (CH_3), −1.3 (CH_3 ×6)

HRMS (ESI+) 433.1837 calcd for $C_{20}H_{34}O_5Si_2Na$, found 433.1853

Malonate-tethered cyclohexadienone 2.8j



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17j**[9] to give **2.8j** in quantitative yield after flash-column chromatography (5:1 hexanes/EtOAc).

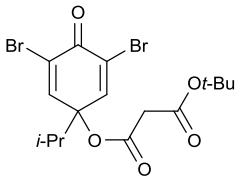
IR (thin film) 3051, 2977, 2927, 1729, 1681, 1600, 1310, 1142, 1052, 698 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 2 H), 3.30 (s, 2 H), 1.63 (s, 3 H), 1.48 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 165.3 (C × 2), 165.1 (C), 148.9 (CH × 2), 82.9 (C), 77.7(C), 42.9 (CH_2), 28.1 (CH_3 × 3), 25.7 (CH_3)

HRMS (ESI+) 444.9257 calcd for $C_{14}H_{16}Br_2O_5Na$, found 444.9250

Malonate-tethered cyclohexadienone 2.8k



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17k** to give **2.8k** in 95% yield after flash-column chromatography (9:1 hexanes/EtOAc).

IR (thin film) 2976, 2934, 1730, 1682, 1599, 1463, 1329, 1255, 1147, 1002, 842 cm^{-1}

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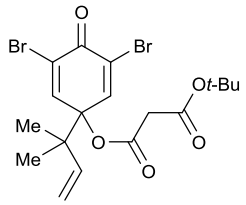
[9] Prepared according to: McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047–2048.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 2 H), 3.35 (s, 2 H), 2.22 (hept, *J* = 6.9 Hz 1 H), 1.49 (s, 9 H), 1.01 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.2 (C), 165.1 (C), 165.0 (C), 147.6 (CH × 2), 122.6 (C), 82.8 (C), 82.6 (C), 42.8 (CH_2), 36.9 (CH), 27.9 (CH_3 × 3), 16.9 (CH_3 × 2)

HRMS (ESI+) 474.9550 calcd for $C_{16}H_{20}{}^{81}Br_2O_5$, found 474.9569

Malonate-tethered cyclohexadienone 2.8l



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17l** to give **2.8l** in 81% yield after flash-column chromatography (19:1 hexanes/EtOAc).

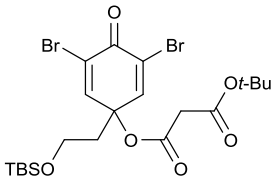
IR (thin film) 2974, 1730, 1682, 1595, 1466, 1313, 1254, 1145, 991, 697 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 2 H), 5.75 (ddt, *J* = 17.3, 10.1, 7.4 Hz, 1 H), 5.12 (dd, *J* = 10.1, 1.8 Hz, 1 H), 5.06 (dd, *J* = 17.3, 1.7 Hz, 1 H), 3.35 (s, 2 H) 2.17 (d, *J* = 7.4 Hz, 2 H), 1.50 (s, 9 H), 1.03 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.1 (C), 165.1 (C), 165.0 (C), 147.8 (CH × 2), 133.2 (CH), 122.7 (C), 119.2 (CH_2), 84.7 (C), 82.9 (C), 44.3 (C), 42.9 (CH_2), 41.8 (CH_2), 28.1 (CH_3 × 3), 22.3 (CH_3 × 2)

HRMS (ESI+) 514.9864 calcd for $C_{19}H_{24}Br_2O_5Na$, found 514.9882

Malonate-tethered cyclohexadienone 2.8m



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17m** to give **2.8m** as a colorless oil in 96% yield after flash-column chromatography (10:1 hexanes/EtOAc).

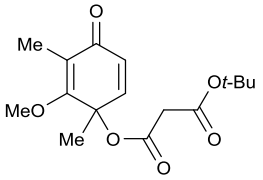
IR (thin film) 2953, 2929, 2856, 1757, 1732, 1682, 1599, 1369, 1257, 1142, 1099, 838, 779 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 2 H), 3.79 (t, 5.5 Hz, 2 H), 3.30 (s, 2 H), 2.08 (t, 5.5 Hz, 2 H), 1.48 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.5 (C), 165.0 (C × 2, overlapped), 148.7 (CH × 2), 121.9 (C × 2), 82.9 (C), 79.5 (C), 57.5 (CH_2), 43.0 (CH_2), 42.7 (CH_2), 28.1 (CH_3 × 3), 26.0 (CH_3 × 3), −5.3 (CH_3 × 2)

HRMS (ESI+) 589.0227 calcd for $C_{21}H_{32}Br_2O_6SiNa$, found 589.0229

Malonate-tethered cyclohexadienone 2.8n



Using a modification of general method C, in which MeCN was used as solvent, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17n** to give **2.8n** in 98% yield (3:1 hexanes/EtOAc).

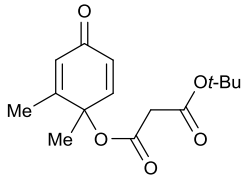
IR (neat) 2987, 2922, 1753, 1730, 1665, 1614, 1321, 1143, 1056 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, J = 10.0 Hz, 1H), 6.22 (d, J = 10.0 Hz, 1 H), 3.91 (s, 3 H), 3.29 (s, 2 H), 1.92 (s, 3 H), 1.56 (s, 3 H), 1.48 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.7, 170.1, 165.40, 165.35, 144.4, 128.0, 118.2, 82.4, 76.6, 61.5, 43.1, 28.1, 25.4, 9.7

HRMS (ESI+) 333.1309 calcd for $C_{16}H_{22}NaO_6$, found 333.1307

Malonate-tethered cyclohexadienone 2.8p



Using a modification of general method C, in which MeCN was used as solvent, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17p** to give **2.8p**, in 73% yield (9:1 hexanes/EtOAc).

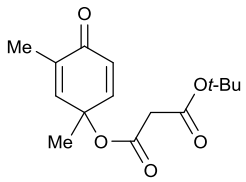
IR (neat) 2979, 2932, 1753, 1729, 1670, 1635, 1142, 1958 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, *J* = 10.1, 1 H), 6.21 (dd, *J* =1.9, 10.0, 1 H), 6.10–6.08 (m, 1 H), 3.29 (s, 2 H), 1.97 (d, *J* = 1.4 Hz, 3 H), 1.51 (s, 3 H), 1.47 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.4 (C), 165.4 (C), 165.1 (C), 158.7 (C), 149.2 (CH), 128.2 (CH), 127.0 (CH), 82.6 (C), 77.3 (C), 43.0 (CH_2), 28.1 (CH_3 × 3), 26.3 (CH_3), 17.9 (CH_3)

HRMS (ESI+) 303.1203 calcd for $C_{15}H_{20}O_5Na$, found 303.1206

Malonate-tethered cyclohexadienone 2.8o



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17o**[3] to give **2.8o**, in 95% yield (9:1 hexanes/EtOAc).

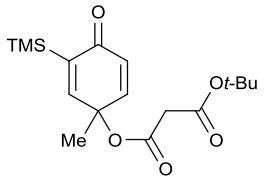
IR (thin film) 2980, 1753, 1730, 1673, 1645, 1369, 1333, 1144, 1051, 969 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 10.1, 3.2 Hz, 1 H), 6.61 (dq, *J* = 3.2, 1.4 Hz, 1 H), 6.15 (d, *J* = 10.1 Hz, 1 H) 3.19 (s, 3 H), 1.82 (d, *J* = 1.4 Hz, 3 H), 1.48 (s, 3 H), 1.40 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.5 (C), 165.4 (C), 165.3 (C), 148.3 (CH), 143.6 (CH), 135.1 (C), 128.1 (CH), 82.2 (C), 75.6 (C), 43.1 (CH_2), 27.9 (CH_3 × 3), 26.2 (CH_3), 15.6 (CH_3)

HRMS (ESI+) 303.1203 calcd for $C_{15}H_{20}O_5Na$, found 303.1196

Malonate-tethered cyclohexadienone 2.8q



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17q** to give **2.8q** in 82% yield after flash-column chromatography (9:1 hexanes/EtOAc).

IR (thin film) 2978, 1754, 1732, 1657, 1628, 1369, 1333, 1248, 1140, 1055, 845 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 3.1 Hz, 1 H), 6.85 (dd, J = 10.0, 3.1 Hz, 1 H), 6.15 (d, J = 10.0 Hz, 1 H), 3.23 (s, 2 H), 1.50 (s, 3 H), 1.43 (s, 9 H), 0.14 (s, 9 H)

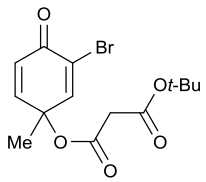
^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 187.8 (C), 165.4 (C), 165.3 (C), 155.6 (CH), 147.6 (CH), 140.4 (C), 129.0 (CH), 82.3 (C), 75.2 (C), 43.3 (CH_2), 28.0 (CH_3 × 3), 26.4 (CH_3), −1.5 (CH_3 × 3)

HRMS (ESI+) 361.1442 calcd for $C_{17}H_{26}O_5SiNa$, found 361.1443

Cyclization of 2.8q

Using general method D, **2.8q** cyclized to give **2.13a** (70% yield) and **2.13i** (8% yield) after flash-column chromatography (3:1 hexanes/EtOAc). Both products were identified by comparison of their spectroscopic data with that previously obtained.

Malonate-tethered cyclohexadienone 2.8r



Using a modification of general method B, in which the concentration was 0.2 M in quinol, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17r** to give **2.8r** as a yellow oil in 69% yield after flash-column chromatography (3:1 hexanes/EtOAc).

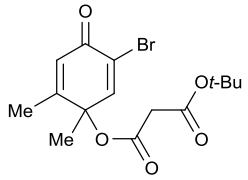
IR (neat) 3050, 2981, 2934, 1759, 1728, 1672, 1640, 1606, 1334, 1146, 1056, 965, 824 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.9 Hz, 1 H), 6.94 (dd, *J* = 10.0, 2.9 Hz, 1 H), 6.37 (d, *J* = 10.0 Hz, 1 H), 3.30 (s, 2 H), 1.62 (s, 3 H), 1.49 (s, 9 H)

^{13}C NMR (MHz, $CDCl_3$, DEPT) δ 177.9 (C), 165.3 (C), 165.2 (C), 148.79 (CH), 148.72 (CH), 126.7 (CH), 124.6 (C), 82.7 (C), 76.7 (C), 43.0 (CH_2), 28.0 (CH_3 × 3), 25.9 (CH_3)

HRMS (ESI+) 367.0152 calcd for $C_{14}H_{17}BrO_5Na$, found 367.0143

Malonate-tethered cyclohexadienone 2.8s



Using general method C, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17s** to give **2.8s** in 96% yield after flash-column chromatography (5:1 hexanes/EtOAc).

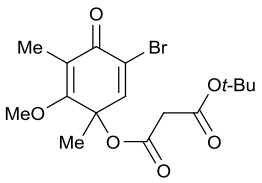
IR (thin film) 2979, 2933, 2859, 1729, 1666, 1332, 1222, 1145 1030 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1 H), 6.20 (q, *J* = 1.3 Hz, 1 H), 3.30 (s, 2 H), 1.99 (d, *J* = 1.3 Hz, 3 H), 1.55 (s, 3 H) 1.47 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 177.9 (C), 165.0 (C), 164.8 (C), 159.3 (C), 149.2 (CH), 124.8 (CH), 124.0 (C), 82.4 (C), 78.4 (C), 42.6 (CH_2), 27.8 (CH_3 × 3), 25.7 (CH_3), 17.5 (CH_3)

HRMS (ESI+) 381.0308 calcd for $C_{15}H_{19}O_5BrNa$, found 381.0337

Malonate-tethered cyclohexadienone 2.8t



Using a modification of general method C, in which MeCN was used as solvent, mono-*t*-butyl malonate (**2.20**) was coupled to quinol **2.17t** to give **2.8t** in 55% yield and 19% of recovered **2.17t** after flash-column chromatography (9:1 hexanes/EtOAc).

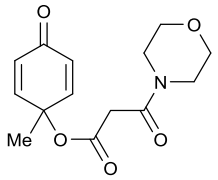
IR (neat) 2979, 2933, 2853, 1754, 1730, 1657, 1651, 1613, 1309, 1214, 1143, 1054 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 1 H), 3.90 (s, 3 H), 3.28 (s, 2 H), 1.95 (s, 3 H), 1.56 (s, 3 H), 1.46 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 180.5 (C), 170.2 (C), 165.3 (C), 165.1 (C), 144.1 (CH), 124.7 (C), 117.0 (C), 82.5 (C), 77.6 (C), 61.7 (CH_3), 42.9 (CH_2), 28.0 (CH_3 × 3), 25.1 (CH_3), 10.6 (CH_3)

HRMS (ESI+) 441.0414 calcd for $C_{16}H_{21}BrO_6Na$, found 411.0432

Morpholine-tethered cyclohexadienone 2.9



Using general method C, mono-morpholine malonic acid (**2.21**)[10] was coupled to quinol **2.17a** to give **2.9** in 96% yield after flash-column chromatography (2:1 hexanes/acetone).

IR (thin film) 3497, 3288, 2925, 2856, 1744, 1657, 1444, 1313, 1230, 1052, 857 cm^{-1}

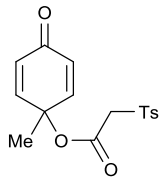
[10] (a) Angelastro, M. R.; Baugh, L. E.; Bey, P.; Burkhart, J. P.; Chen, T.-M.; Durham, S. L.; Hare, C. M.; Huber, E. W.; Janusz, M. J.; Koehl, J. R.; Marquart, A. L.; Mehdi, S.; Peet, N. P. *J. Med. Chem.* **1994**, *37*, 4538–4553. (b) Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 3073–3076.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 10.2 Hz, 2 H), 6.20 (d, *J* = 10.2 Hz, 2 H), 3.69–3.55 (m, 6 H), 3.40 (s, 2 H), 3.43–3.34 (m, 2 H) 1.54 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.9 (C), 166.0 (C), 164.3 (C), 148.6 (CH × 2), 128.4 (CH × 2), 75.3 (C), 66.6 (CH_2), 66.4 (CH_2), 46.6 (CH_2), 42.2 (CH_2), 41.1 (CH_2), 26.3 (CH_3)

HRMS (ESI+) 302.0999 calcd for $C_{14}H_{17}NO_5Na$, found 302.0990

Sulfone-tethered cyclohexadienone 2.10



Sulfide **S13** (89 mg, 0.30 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with 77% mCPBA (207 mg, 0.9 mmol). The mixture was stirred for 2 h before being quenched with saturated aq. $NaHCO_3$ (10 mL). The phases were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give **2.10** (87.3 mg, 88% yield) after flash-column chromatography (2:1→1:1 hexanes/EtOAc).

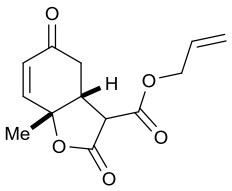
IR (thin film) 3051, 2992, 2937, 1746, 1669, 1632, 1391, 1320, 1280, 1152, 1050, 859 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 6.78 (d, *J* = 10.2 Hz, 2 H), 6.18 (d, *J* = 10.2 Hz, 2 H), 4.07 (s, 2 H), 2.43 (s, 3 H), 1.50 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.7 (C), 160.9 (C), 147.5 (CH × 2), 145.8 (C), 135.7 (C), 130.0 (CH × 2), 128.7 (CH × 2), 128.5 (CH × 2), 76.3 (C), 61.4 (CH_2), 25.9 (CH_3), 21.8 (CH_3)

HRMS (ESI+) 343.0611 calcd for $C_{16}H_{16}O_5SNa$, found 343.0616

Bicyclic lactone 2.11



Using a modification of general method E, in which CH_2Cl_2 was used as solvent, $CsOH{\cdot}H_2O$ was used as a base, and the reaction temperature was −78 °C, **2.6** cyclized to give **2.11** in 75% yield after flash-column chromatography (3:1 hexanes/EtOAc). Chiral-phase HPLC analysis (Chiralcel OD, 3% ethanol in hexanes, 1.5 mL/min, λ= 225 nm) showed 65:35 er (RT_{major} = 22.3 min., RT_{minor} = 23.5 min.). When crude **2.6** (obtained using general method B) was allowed to stand at –15 ºC overnight, racemic **2.11** was obtained in 88% yield after chromatographic purification. The relative stereochemistry of **2.11** was determined by NOE analysis.

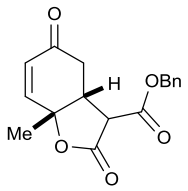
IR (thin film) 2983, 2929, 1785, 1737, 1685, 1381, 1294, 1164, 1093, 998, 781 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 10.3, 2.0 Hz, 1 H), 6.09 (d, *J* = 10.3 Hz, 1 H), 5.90 (dddd, *J* = 16.2, 10.5, 5.8, 5.8 Hz, 1 H), 5.38 (dq, *J* = 17.2, 1.4 Hz, 1 H), 5.28 (dd, *J* = 10.4, 1.1 Hz, 1 H), 4.77–4.62 (m, 2 H), 3.49 (d, *J* = 12.5 Hz, 1 H), 3.38–3.31 (m, 1 H), 2.75 (dd, *J* = 17.8, 5.3 Hz, 1 H), 2.64 (dd, *J* = 17.8, 1.6 Hz, 1 H), 1.72 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.2 (C), 168.7 (C), 166.1 (C), 146.7 (CH), 131.0 (CH), 129.5 (CH), 119.6 (CH_2), 80.6 (C), 67.1 (CH_2), 51.5 (CH), 44.7 (CH), 35.9 (CH_2), 23.9 (CH_3)

HRMS (ESI+) 273.0733 calcd for $C_{13}H_{14}O_5Na$, found 273.0729

Bicyclic lactone 2.12



Using a modification of general method E, in which CH_2Cl_2 was used as solvent and the reaction was started at −78 °C and gradually allowed to warm to rt, **2.7** cyclized to give **2.12** in 99% yield after flash-column chromatography (3:1 hexanes/EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 8% ethanol in hexanes, 1 mL/min, λ= 225 nm) showed ~racemic material (RT_{first} = 20.4 min., RT_{second} = 23.7 min.). Also, using general method D, racemic **2.12** was obtained in 91% yield.

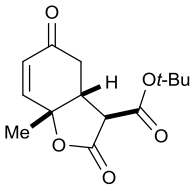
IR (thin film) 3059, 3032, 2910, 1778, 1731, 1679, 1378, 1291, 1158, 1090, 987 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.36 (m, 5 H), 6.68 (dd, *J* = 10.4, 2.0 Hz, 1 H), 6.08 (d, *J* = 10.4 Hz, 1 H) 5.28 (d, *J* = 12.3 Hz, 1 H), 5.22 (d, *J* = 12.3 Hz, 1 H), 3.52 (d, *J* = 12.5 Hz, 1 H), 3.39–3.32 (m, 1 H), 2.74 (dd, *J* = 17.8, 5.3 Hz, 1 H), 2.63 (dd, *J* = 17.9, 2.3 Hz, 1 H), 1.73 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 194.1 (C), 168.6 (C), 166.3 (C), 146.7 (CH), 134.8 (C), 129.5 (CH), 128.9 (CH × 2), 128.8 (CH), 128.4 (CH × 2), 80.6 (C), 68.3 (CH_2), 51.5 (CH), 44.7 (CH), 35.9 (CH_2), 23.9 (CH_3)

HRMS (ESI+) 323.0890 calcd for $C_{17}H_{16}O_5Na$, found 323.0889

Bicyclic lactone 2.13a



Using general method E, **2.8a** cyclized in 2 h to give **2.13a** in 79% yield after flash-column chromatography (5:1 hexanes/EtOAc). Using general method D, racemic **2.13a** was obtained in 80% yield.

IR (thin film) 2983, 2929, 1786, 1728, 1686, 1371, 1295, 1150, 1148, 1089, 983 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 10.3, 1.6 Hz, 1 H), 6.08 (d, *J* = 10.3 Hz, 1 H), 3.35 (d, *J* = 12.3 Hz, 1 H), 3.32–3.29 (m, 1 H), 2.74 (dd, *J* = 17.8, 4.8 Hz, 1 H), 2.63 (d, *J* = 17.8 Hz, 1 H), 1.71 (s, 3 H), 1.49 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.5 (C), 169.2 (C), 165.3 (C), 147.0 (CH), 129.4 (CH), 83.8 (C), 80.3 (C), 52.4 (CH), 44.5 (CH); 36.0 (CH_2), 28.1 (CH_3 × 3), 24.0 (CH_3)

HRMS (ESI+) 289.1046 calcd for $C_{14}H_{18}O_5Na$, found 289.1056

HPLC (CHIRALCEL OJ, 8% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 20.4, 23.7 min

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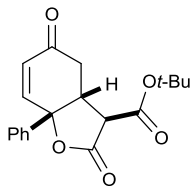
Bicyclic lactone 2.13b



Using general method E, **2.8b** cyclized in 3 h to give **2.13b** in 72% yield after flash-column chromatography (5:1 hexanes/EtOAc). Using general method D, racemic **2.13b** was obtained in 95% yield.

IR (thin film) 2976, 2930, 1786, 1727, 1688, 1370, 1293, 1144, 989, 767, 700 cm^{-1}

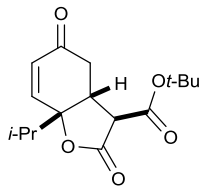
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.44 (m, 5 H), 6.81 (dd, *J* = 10.3 Hz, 1 H), 6.37 (d, *J* = 10.3 Hz, 1 H), 3.47–3.45 (m, 2 H), 2.78–2.71 (m, 1 H), 2.61 (d, *J* = 17.7 Hz, 1 H), 1.50 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.8 (C), 169.4 (C), 165.3 (C), 144.8 (CH), 137.3 (C), 130.9 (CH), 129.5 (CH), 129.4 (CH × 2), 125.2 (CH × 2), 84.0 (C), 83.2 (C), 52.9 (CH), 46.9 (CH), 35.6 (CH_2), 28.1 (CH_3 × 3)

HRMS (ESI+) 351.1203 calcd for $C_{19}H_{20}O_5Na$, found 351.1217

HPLC (CHIRALCEL OD-H, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 9.6, 10.3 min

Bicyclic lactone 2.13c



Using general method E, **2.8c** cyclized in 3 h to give **2.13c** in 77% yield after flash-column chromatography (3:1 hexanes/EtOAc). Using general method D, racemic **2.13c** was obtained in 96% yield.

IR (thin film) 2976, 2937, 2884, 1784, 1730, 1688, 1470, 1369, 1294, 1149, 980 cm^{-1}

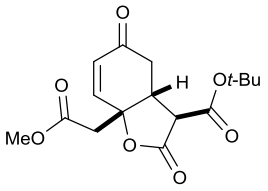
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 10.5, 1.9 Hz, 1 H), 6.21 (d, *J* = 10.5 Hz, 1 H), 3.43 (dddd, *J* = 12.0, 5.5, 1.9, 1.9 Hz, 1 H), 3.33 (d, *J* = 12.1 Hz, 1 H), 2.72 (dd, *J* = 18.3, 5.7, Hz, 1 H), 2.58 (d, *J* = 17.2 Hz, 1 H), 2.25 (hept. *J* = 6.9 Hz, 1 H), 1.49 (s, 9 H), 1.11 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.9 (C), 169.3 (C), 165.6 (C), 145.6 (CH), 131.1 (CH), 84.7 (C), 83.8 (C), 53.6 (CH), 40.1 (CH), 37.4 (CH_2), 36.1 (CH), 28.1 (CH_3 × 3), 17.7 (CH_3), 16.8 (CH_3)

HRMS (ESI+) 317.1359 calcd for $C_{16}H_{22}O_5Na$, found 317.1375

HPLC (CHIRALCEL OD-H, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 7.7, 8.2 min

Bicyclic lactone 2.13d



Using general method E, **2.8d** cyclized in 3 h to give **2.13d** in 44% yield after flash-column chromatography (3:1 hexanes–EtOAc). Using general method D, racemic **2.13d** was obtained in 53% yield.

IR (thin film) 2979, 2926, 2884, 1783, 1724, 1679, 1431, 1364, 1298, 1253, 1131, 979 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, *J* = 10.4, 2.0 Hz, 1 H), 6.17 (d, *J* = 10.4 Hz, 1 H), 3.74 (s, 3 H), 3.58–3.68 (m, 1 H), 3.35(d, *J* = 12.2 Hz, 1 H), 3.05 (d, *J* = 15.5 Hz, 1 H), 2.99 (d, *J* = 15.5 Hz, 1 H), 2.84 (dd, *J* = 18.0, 5.8 Hz, 1 H), 2.62 (d, *J* = 17.0 Hz, 1 H), 1.50 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.5 (C), 168.6 (C), 168.3 (C), 165.0 (C), 144.5 (CH), 130.7 (CH), 84.1 (C), 79.2 (C), 52.6 (CH_3), 52.4 (CH), 42.7 (CH), 42.3 (CH_2) 36.1(CH_2), 28.1 (CH_3 × 3)

HRMS (ESI+) 347.1101 calcd for $C_{16}H_{20}O_7Na$, found 347.1111

HPLC (CHIRALCEL OD-H, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 21.9, 27.4 min

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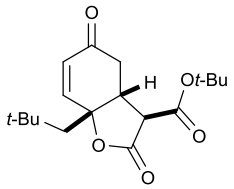
Bicyclic lactone 2.13e



Using general method E, **2.8e** cyclized in 2.5 h to give **2.13e** in 52% yield after flash-column chromatography (9:1→5:1 hexanes/EtOAc). Using general method D, racemic **2.13e** was obtained in 58% yield.

IR (thin film) 2957, 1783, 1731, 1687, 1369, 1295, 1260, 1141, 983, 941 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 10.5 Hz, 1 H), 6.06 (d, *J* = 10.5 Hz, 1 H), 3.29 (s, 2 H), 2.74 (ddd, *J* = 17.9, 3.7, 1.4 Hz, 1 H), 2.61 (d, *J* = 18.2 Hz, 1 H), 2.04 (d, *J* = 15.2 Hz, 1 H), 1.93 (d, *J* = 15.2 Hz, 1 H), 1.49 (s, 9 H), 1.09 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.6 (C), 169.7 (C), 165.6 (C), 146.9 (CH), 128.7 (CH), 83.8 (C), 83.0 (C), 51.36 (CH), 51.30 (CH_2), 45.7 (CH), 35.7(CH_2), 31.5 (C), 31.4 (CH_3 × 3), 28.0 (CH_3 × 3)

HRMS (ESI+) 345.1672 calcd for $C_{18}H_{26}O_5Na$, found 345.1677

HPLC (CHIRALCEL OJ, e% ethanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 8.8, 9.8 min

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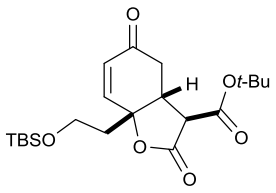
Bicyclic lactone 2.13f



Using general method E, **2.8f** cyclized in 22 h to give **2.13f** in 89% yield after flash-column chromatography (5:1 hexanes/EtOAc). Using general method D, racemic **2.13f** was obtained in 50% yield.

IR (thin film) 2952, 2931, 2857, 1789, 1732, 1689, 1147, 1087, 838, 779 cm^{-1}

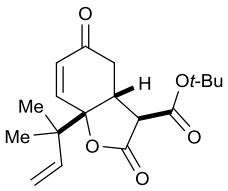
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 10.4, 1.8 Hz, 1 H), 6.10 (d, *J* = 10.4 Hz), 3.91–3.79 (m, 2 H), 3.55 (dddd, *J* = 12.6, 5.6, 2.0, 2.0 Hz, 1 H), 3.34 (d, *J* = 12.4 Hz), 2.87 (dd, *J* = 17.9, 5.6 Hz, 1 H), 2.60 (d, *J* = 17.9 Hz, 1 H), 2.23 (ddd, *J* = 14.8, 7.1, 4.6 Hz, 1 H), 2.13 (ddd, *J* = 14.8, 6.1, 4.4 Hz, 1 H), 1.49 (s, 9 H), 0.88 (s, 9H), 0.07 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 195.1 (C), 169.5 (C), 165.4 (C), 146.7 (CH), 129.6 (CH), 83.6 (C), 82.0 (C), 57.9 (CH_2), 52.4 (CH), 43.0 (CH), 40.4 (CH_2), 36.1 (CH_2), 28.1 (CH_3 × 3), 25.9 (CH_3 × 3), 18.2 (C), −5.4 (CH_3 × 2)

HRMS (ESI+) 433.2028 calcd for $C_{21}H_{34}O_6SiNa$, found 433.1996

HPLC (CHIRALCEL OD-H, 2% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 11.8, 12.9 min

Bicyclic lactone 2.13g



Using general method E, **2.8g** cyclized in 19 h to give **2.13g** in 88% yield after flash-column chromatography (5:1 hexanes/EtOAc). Using general method D, racemic **2.13g** was obtained in 61% yield.

IR (thin film) 2977, 2934, 1784, 1730, 1689, 1369, 1291, 1146, 982, 784 cm^{-1}

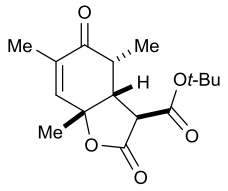
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 10.7, 2.0 Hz, 1 H), 6.24 (d, *J* = 10.6 Hz, 1 H), 5.81 (dddd, *J* = 17.4, 10.2, 7.3, 7.3 Hz, 1 H), 5.13 (d, *J* = 10.2, Hz, 1 H) 5.08 (d, *J* = 17.6 Hz, 1 H), 3.66 (dddd, *J* = 11.8, 6.1, 1.8, 1.8 Hz, 1 H), 3.31 (d, *J* = 11.9 Hz, 1 H), 2.75 (dd, *J* = 18.6, 6.1 Hz, 1 H), 2.57 (d, *J* = 18.1 Hz, 1 H), 2.28 (dd, *J* = 13.9, 7.7 Hz, 1 H), 2.21 (dd, *J* = 13.7, 7.8 Hz), 1.50 (s, 9 H), 1.10 (s, 3 H), 1.09 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.7 (C), 169.2 (C), 165.7 (C), 145.0 (CH), 133.3 (CH), 131.4 (CH), 119.2 (CH_2), 86.5 (C), 83.9 (C), 54.0 (CH), 41.7 (C), 41.5 (CH_2), 38.4 (CH), 37.9 (CH_2), 28.1 (CH_3 × 3), 22.0 (CH_3), 21.8 (CH_3)

HRMS (ESI+) 357.1672 calcd for $C_{19}H_{26}O_5Na$, found 357.1662

HPLC (CHIRALCEL OJ, 3% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 16.1, 19.5 min

Bicyclic lactone 2.13h



Using general method E, **2.8h** cyclized in 36 h to give **2.13h** in 67% yield (isolated as a 12:1 mixture of diastereomers, measured by ^{1}H NMR) after flash-column chromatography (9:1→5:1 hexanes/EtOAc). Using general method D, racemic **2.13h** was

obtained in 74% yield. The relative stereochemistry of **2.13h** was determined by NOE analysis.

IR (thin film) 2991, 2987, 1785, 1736, 1690, 1451, 1371, 1283, 1148, 1078 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$, data for major diastereomer) δ 6.34 (dq, *J* = 1.6, 1.4 Hz, 1 H), 3.32 (ddd, *J* = 12.1, 5.0, 2.0 Hz, 1 H), 3.15 (d, *J* = 12.1 Hz, 1 H), 2.79 (qd, *J* = 6.9, 5.0 Hz, 1 H), 1.79 (d, *J* = 1.5 Hz, 3 H), 1.69 (s, 3 H), 1.46 (s, 9 H), 1.11 (d, *J* = 6.9 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT, data for major diastereomer) δ 197.9 (C), 170.3 (C), 166.7 (C), 141.2 (CH), 136.2 (C), 83.3 (C), 81.8 (C), 51.5 (CH), 51.4 (CH), 40.4 (CH), 27.8 (CH_3 × 3), 24.1 (CH_3), 15.9 (CH_3), 12.9 (CH_3)

HRMS (ESI+) 317.1359 calcd for $C_{16}H_{22}O_5Na$, found 317.1370

HPLC (CHIRALCEL AS, 8% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 5.0 (major diastereomer), 5.9 (minor diastereomer), 6.4 (both diastereomers) min

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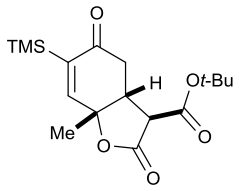
Bicyclic lactone 2.13i



Using general method E, **2.8i** cyclized in 4 d to give **2.13i** in 61% yield after flash-column chromatography (19:1→9:1 hexanes/EtOAc). Using general method D, racemic **2.13i** was obtained in 49% yield.

IR (thin film) 2984, 2927, 1779, 1730, 1655, 1340, 1297, 1248, 1145, 1096, 978, cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, *J* = 1.2 Hz, 1 H), 3.26–3.25 (m, 2 H), 2.71 (ddd, *J* = 17.4, 3.9, 1.5 Hz, 1 H), 2.56 (dd, *J* = 17.5, 1.8 Hz, 1 H), 1.68 (s, 3 H), 1.49 (s, 9 H), 0.15 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.9 (C), 169.6 (C), 165.4 (C), 153.4 (CH), 142.8 (C), 83.8 (C), 80.6 (C), 52.5 (CH), 44.4 (CH), 36.7 (CH_2), 28.1 (CH_3 × 3), 24.1 (CH_3), −1.5 (CH_3 × 3)

HRMS (ESI+) 361.1442 calcd for $C_{17}H_{26}O_5SiNa$, found 361.1437

HPLC (CHIRALCEL OD-H, 8% isopropanol in hexanes, 1 mL/min, $\lambda = 225$ nm) $T_R = 4.7$, 5.1 min

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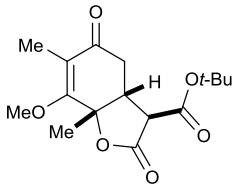
Bicyclic lactone 2.13n



Using a modification of general method D, in which 1.1 equiv of Cs_2CO_3 was used, **2.8n** cyclized to give **2.13n** as a single regioisomer in 95% yield after flash-column chromatography (3:1 hexanes/EtOAc).

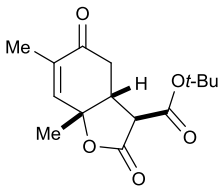
IR (neat) 2978, 2928, 1784, 1732, 648, 1610, 1369, 1311, 1150 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3 H), 3.35 (d, J = 12.4 Hz, 1 H), 3.21 (ddd, J = 12.4, 4.9, 2.9 Hz, 1 H), 2.73–2.59 (m, 2 H), 1.79 (s, 3 H), 1.77 (s, 3 H), 1.48 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 195.1 (C), 169.4 (C), 166.4 (C), 165.4 (C), 121.2 (C), 83.8 (C), 82.6 (C), 61.4 (CH_3), 52.0 (CH), 44.1 (CH), 35.7 (CH_2), 28.0 ($CH_3 \times 3$), 22.9 (CH_3), 9.2 (CH_3)

HRMS (ESI+) 333.1309 calcd for $C_{16}H_{22}O_6Na$, found 333.1308

Bicyclic lactone 2.13o



Using general method D, **2.8o** gave **2.13o** and its regioisomer as a 9:1 inseparable mixture in 74% combined yield after flash-column chromatography (9:1→5:1 hexanes/EtOAc).

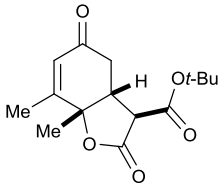
IR (thin film) 2981, 2932, 1785, 1730, 1684, 1369, 1297, 1151, 1078, 983, 916, 840 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$, data for major regioisomer) δ 6.42 (s, 1 H), 3.31 (d, J = 12.3 Hz, 1 H), 3.27–3.20 (m, 1 H), 2.71 (dd, J = 17.7, 4.6 Hz, 1 H), 2.63 (dd, J = 17.6, 2.2 Hz, 1 H), 1.80 (d, J = 1.2 Hz, 3 H), 1.67 (s, 3 H), 1.48 (s, 9 H). Signals at δ 6.58 (dd, J = 10.3, 2.0 Hz) and δ 6.04 (d, J = 10.3 Hz) were ascribed to the minor regioisomer.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT, data for major regioisomer) δ 195.0 (C), 169.6 (C), 169.5 (C), 142.3 (CH), 136.4 (C), 83.6 (C), 81.1 (C), 52.6 (CH), 44.7 (CH), 36.2 (CH_2), 28.0 (CH_3 × 3), 24.2 (CH_3), 15.8 (CH_3)

HRMS (ESI+) 303.1203 calcd for $C_{15}H_{20}O_5Na$, found 303.1213

Bicyclic lactone 2.13p



Using general method D, **2.8p** gave **2.13p** and its regioisomer as a 12:1 inseparable mixture in 73% combined yield (3:1 hexanes/EtOAc).

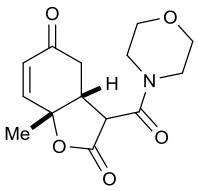
IR (neat) 2986, 2921, 1783, 1732, 1660, 1369, 1304, 1145, 1084 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (dq, J = 1.2, 1.2 Hz, 1 H), 3.36 (d, J = 12.7 Hz, 1 H), 3.27 (ddd, J = 12.7, 5.2, 2.1 Hz, 1 H), 2.71 (dd, J = 18.0, 5.3 Hz, 1 H), 2.59 (ddd, J = 18.0, 2.1, 0.9 Hz, 1 H), 2.02 (d, J = 1.4 Hz, 3 H), 1.72 (s, 3 H), 1.48 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 194.2 (C), 169.4 (C), 165.5 (C), 157.9 (C), 127.9 (CH), 83.7 (C), 82.4 (C), 51.9 (CH), 45.4 (CH), 35.7 (CH_2), 28.0 (CH_3 × 3), 23.0 (CH_3), 18.5 (CH_3)

HRMS (ESI+) 303.1203 calcd for $C_{15}H_{20}O_5Na$, found 303.1204

Bicyclic lactone 2.14



Using general method E, **2.9** cyclized to give **2.14** in 87% yield after flash-column chromatography (2:1 hexanes/EtOAc). Using general method D, racemic **2.14** was obtained in 92% yield.

IR (thin film) 2971, 2859, 1773, 1681, 1645, 1441, 1297, 1242, 1113, 1094, 975 cm^{-1}

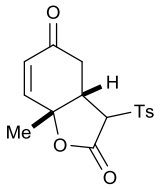
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 10.3, 2.0 Hz, 1 H), 6.06 (d, *J* = 10.3, 1.0 Hz, 1 H), 4.00 (dt, *J* = 13.4, 3.0 Hz, 1 H), 3.82–3.57 (m, 6 H), 3.58 (d, *J* = 11.9 Hz, 1 H), 3.39–3.26 (m, 2 H), 2.72 (dd, *J* = 17.8, 5.5 Hz, 1 H), 2.54 (ddd, *J* = 17.9, 2.0, 1.1 Hz, 1 H), 1.72 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 195.2 (C), 169.9 (C), 162.4 (C), 147.1 (CH), 129.7 (CH), 80.9 (C), 66.9 (CH_2), 66.6 (CH_2), 48.5 (CH), 46.6 (CH_2), 43.7 (CH), 43.2 (CH_2), 36.2 (CH_2), 23.9 (CH_3)

HRMS (ESI+) 302.0999 calcd for $C_{14}H_{17}NO_5Na$, found 302.1016

HPLC (CHIRALCEL OD, 10% ethanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 23.2, 42.5 min

Bicyclic lactone 2.15



Using general method E, **2.10** cyclized to give **2.15** in 90% yield after flash column chromatography (1:1 hexanes/EtOAc). Using general method D, racemic **2.15** was obtained in 70% yield.

IR (thin film) 2923, 1783, 1687, 1595, 1318, 1245, 1149, 1085, 965, 813 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 6.61 (dd, *J* = 10.4, 1.8 Hz, 1 H), 6.06 (dd, *J* = 10.4, 0.9 Hz, 1 H), 3.94 (d, *J* = 11.6 Hz, 1 H), 3.55 (ddt, *J* = 11.6, 5.8, 2.0 Hz, 1 H), 3.18 (ddd, *J* = 17.9, 1.8, 1.1 Hz, 1 H), 2.82 (dd, *J* = 17.9, 5.8 Hz, 1 H), 2.46 (s, 3 H), 1.75 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 193.9 (C), 165.6 (C), 146.5 (CH), 146.4 (C), 134.0 (C), 130.0 (CH × 2), 129.9 (CH × 2), 129.8 (CH), 80.1 (C), 67.1 (CH), 42.7 (CH), 36.7 (CH_2), 23.9 (CH_3), 22.0 (CH_3)

HRMS (ESI+) 343.0611 calcd for $C_{16}H_{16}O_5SNa$, found 343.0604

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 27.9, 32.0 min

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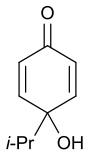
Quinol 2.17c



Using general method A, 4-isopropyl phenol was converted into quinol **2.17c** in 73% yield after flash-column chromatography (3:1 hexanes/EtOAc). This compound has been prepared and characterized before;[11] however, our ^{1}H NMR spectrum differs from the literature data.

IR (thin film) 3343, 2960, 1648, 1641, 1496, 1454, 1367, 1311, 1186, 1028, 968, 865, 774 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 10.2 Hz, 2 H), 6.14 (d, *J* = 10.2 Hz, 2 H), 3.14 (bs, 1 H), 1.96 (hept, *J* = 6.9 Hz, 1 H), 0.91 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 186.3 (C), 151.1 (CH × 2), 128.8 (CH × 2), 72.3 (C), 36.7 (CH), 17.0 (CH_3 × 2)

HRMS (ESI+) 175.0740 calcd for $C_9H_{12}O_2Na$, found 175.0741

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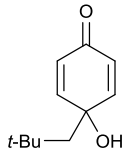
[11] McKinley, J.; Aponick, A.; Raber, J. C.; Fritz, C.; Montgomery, D.; Wigal, C. T. *J. Org. Chem.* **1997**, *62*, 4874–4876.

Quinol 2.17e



Using general method A, phenol **S1** was converted into **2.17e** in 31% yield after flash-column chromatography (3:1 hexanes/EtOAc)

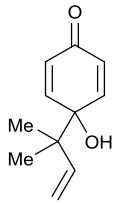
IR (thin film) 3429, 2960, 2873, 1661, 1621, 1470, 1397, 1279, 1074 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 10.1 Hz, 2 H), 6.12 (d, *J* = 10.1 Hz, 2 H), 2.42 (bs, 1 H), 1.85 (s, 2 H), 0.93 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 186.1 (C), 152.7 (CH × 2), 127.2 (CH × 2), 69.6 (C), 53.8 (CH_2), 31.3 (CH_3 × 3), 30.9 (C)

HRMS (ESI+) 203.1043 calcd for $C_{11}H_{16}O_2Na$, found 203.1059

Quinol 2.17g



Using general procedure A, 4-(2-methylpent-4-en-2-yl)phenol[12] was converted into quinol **2.17g** in 37% yield after flash-column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 3398, 2970, 1667, 1620, 1385, 1463, 1173, 1063, 955, 916, 859 cm^{-1}

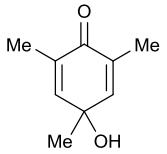
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 10.4 Hz, 2 H), 6.18 (d, *J* = 10.4 Hz, 2 H), 5.80 (ddt, *J* = 17.7, 10.3, 7.4 Hz, 1 H), 5.10–4.97 (m, 2 H), 2.66 (s, 1 H), 2.14 (d, *J* = 7.4 Hz, 1 H), 0.98 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.7 (C), 150.5 (CH × 2), 134.8 (CH), 129.0 (CH × 2), 118.2 (CH_2), 74.1 (C), 41.8 (C, overlapped), 41.8 (CH_2), 21.9 (CH_3 × 2)

HRMS (ESI+) 215.1043 calcd for $C_{12}H_{16}O_2Na$, found 215.1059

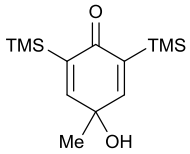
[12] Cella, J. A. *J. Org. Chem.* **1982**, *47*, 2125–2130.

Quinol 2.17h



Using general method A, 2,4,6-trimethylphenol was converted to **2.17h** in 78% yield after flash-column chromatography (4:1→3:1 hexanes–EtOAc). Identity was verified by comparison of ^{1}H NMR spectrum with literature data.[3,13]

Quinol 2.17i



Using a modification of general method A in which 10:1 acetone/H_2O was used as solvent, phenol **S2** was converted to quinol **2.17i** in 67% yield after flash-column chromatography (19:1 hexanes/EtOAc).

IR (thin film) 3464, 1619, 1351, 1246, 1032, 841, 740 cm^{-1}

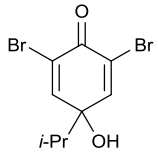
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 2 H), 1.84 (bs, 1 H), 1.42 (s, 3 H), 0.17 (s, 18 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 190.9 (C), 158.7 (CH × 2), 140.2 (C × 2), 66.6 (C), 27.3 (CH_3), −1.3 (CH_3 × 6)

HRMS (ESI+) 291.1207 calcd for $C_{13}H_{24}O_2Si_2Na$, found 291.1209

[13] Ochiai, M.; Miyamoto, K.; Shiro, M.; Ozawa, T. Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 13006–13007.

Quinol 2.17k



Using general method A, phenol **S3** was converted into quinol **2.17k** in 78% yield after flash-column chromatography (5:1 hexanes/EtOAc).

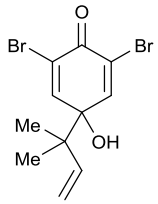
IR (thin film) 3434, 1671, 1596, 1461, 1358, 997, 692 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 2 H), 2.29 (bs, 1 H), 2.06 (hept, *J* = 6.9 Hz, 1 H), 1.01 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.5 (C), 151.0 (CH × 2), 122.2 (C × 2), 77.3 (C), 37.3 (CH), 17.1 (CH_3 × 2)

HRMS (ESI+) 330.8940 calcd for $C_9H_{10}Br_2O_2Na$, found 330.8940

Quinol 2.17l



Using general method A, phenol **S4** was converted into quinol **2.17l** in 74% yield after flash-column chromatography (5:1 hexanes/EtOAc).

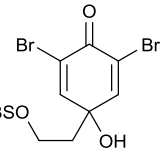
IR (thin film) 3470, 2970, 1677, 1592, 1467, 1312, 988, 918 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 2 H), 5.79 (ddt, *J* = 17.5, 10.1, 7.4 Hz, 1 H), 5.11 (d, *J* = 10.1 Hz, 1 H), 5.07 (d, *J* = 17.5 Hz, 1 H), 3.08 (s, 2 H) 2.17 (d, *J* = 7.4 Hz, 2 H), 1.04 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.5 (C), 151.5 (CH × 2), 134.0 (CH), 121.8 (C × 2), 118.7 (CH_2), 79.0 (C), 43.0 (C), 42.0 (CH_2), 22.2 (CH_3 × 2)

HRMS (ESI+) 370.9253 calcd for $C_{12}H_{14}Br_2O_2Na$, found 370.9264

Quinol 2.17m



Using a modification of general method A, in which 10:1 acetone/H_2O was used as solvent, **S6** gave **2.17m** as a yellow solid in 42% yield after flash-column chromatography (5:1 hexanes/EtOAc).

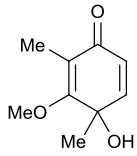
IR (thin film) 3466, 3036, 2926, 2856, 1668, 1592, 1471, 1349, 1093, 992, 840, 770, 701 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 2 H), 4.51 (s, 1 H), 3.96 (t, J = 5.4 Hz, 2 H), 1.99 (t, J = 5.4 Hz, 2 H), 0.91 (s, 9 H), 0.11 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 172.4 (C), 151.7 (CH × 2), 121.0 (C × 2), 74.3 (C), 60.4 (CH_2), 41.0 (CH_2), 25.9 (CH_3 × 3), 18.1 (C), 5.5 (CH_3 × 2)

HRMS (ESI+) 446.9608 calcd for $C_{17}H_{22}Br_2O_3SiNa$, found 446.9600

Quinol 2.17n



A mixture of phenol **S10** (53 mmol, 8.0 g) and hexamethyldisilazane (17 mL) was heated at 125 °C for 10 minutes in a microwave reactor.[14] General method A was then used to convert the resulting TMS phenol to quinol **2.17n** in 80% yield after flash-column chromatography (1:0→1:1 hexanes/EtOAc).

IR (neat) 3391, 2981, 2932, 2851, 1662, 1608, 1456, 1214, 1094 cm^{-1}

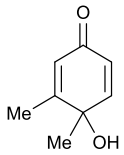
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, J = 9.9 Hz, 1 H), 6.09 (d, J = 9.9 Hz, 1 H), 4.02 (s, 3 H), 2.61 (s, 1 H), 1.87 (s, 3 H), 1.51 (s, 3 H)

[14] Mojtahedi, M. M.; Saidi, M. R.; Bolourtchian, M.; Heravi, M. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 289–292.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 188.5 (C), 171.5 (C), 147.8 (CH), 126.5 (CH), 117.5 (C), 69.8 (C), 61.7 (CH_3), 26.5 (CH_3), 9.2 (CH_3)

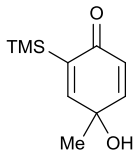
HRMS (ESI+) 191.0679 calcd for $C_9H_{12}NaO_3$, found 191.0674

Quinol 2.17p



A mixture of 3,4-dimethylphenol (8.84 mmol, 1.08 g) and hexamethyldisilazane (2 mL) was heated at 125 °C for 10 min in a microwave reactor.[14] General method A was then used to convert the resulting TMS phenol to quinol **2.17p** in 48% yield (two steps) after flash-column chromatography (1:0→1:1 hexanes/EtOAc). Identity was verified by comparison of the ^{1}H NMR spectrum with literature data.[3]

Quinol 2.17q



Using a modification of general method A in which 10:1 acetone/H_2O was used as solvent, phenol **S11** was converted into quinol **2.17q** in 51% yield after flash-column chromatography (5:1 hexanes/EtOAc).

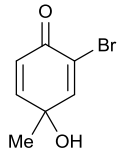
IR (thin film) 3381, 2958, 1649, 1611, 1361, 1242, 1138, 1050, 841 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 3.1 Hz, 1 H), 6.83 (dd, J = 10.0, 3.1 Hz, 1 H), 2.12 (bs, 1 H), 1.44 (s, 3 H), 0.17 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 188.5 (C), 160.0 (CH), 151.7 (CH), 139.0 (C), 127.8 (CH), 66.8 (C), 27.0 (CH_3), −1.4 (CH_3 × 3)

HRMS (ESI+) 219.0812 calcd for $C_{10}H_{16}O_2SiNa$, found 219.0825

Quinol 2.17r



Using a modification of general method A, in which 10:1 acetone/H_2O was used as solvent, 2-bromo-4-methylphenol gave **2.17r** as a yellow/orange solid in 76% yield after flash-column chromatography (3:1 hexanes/EtOAc).

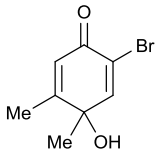
IR (thin film) 3474, 3045, 2980, 2937, 1660, 1594, 1052 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.8 Hz, 1 H), 6.92 (dd, *J* = 10.0, 2.8 Hz, 1 H), 6.27 (d, 10.0 Hz, 1 H), 2.04 (bs, 1 H), 1.53 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 178.6 (C), 152.9 (CH), 152.7 (CH), 125.6 (CH), 123.4 (C), 70.1 (C), 26.5 (CH_3)

HRMS (ESI+) 224.9522 calcd for $C_7H_7BrO_2Na$, found 224.9531

Quinol 2.17s



Using general method A, 2-bromo-4,5-dimethylphenol[15] was converted into quinol **2.17s** in 74% yield after flash-column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 3457, 3038, 2986, 2934, 1648, 1626, 1596, 1363, 1231, 1132, 1041, cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1 H), 5.95 (q, *J* = 1.4 Hz, 1 H), 3.64 (s, 1 H), 2.05 (d, *J* = 1.4 Hz, 3 H), 1.41 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 179.3 (C), 164.1 (C), 154.1 (CH), 123.8 (CH), 122.6 (C), 71.7 (C), 25.9 (CH_3), 18.2 (CH_3)

HRMS (ESI+) 238.9678 calcd for $C_8H_9OBr_2Na$, found 238.9736

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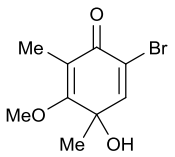
[15] Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Nakamura, H.; Fujikawa, M.; Ube, T. *Bull Chem. Soc. Jpn.* **1987**, *60*, 4187–4189.

Quinol 2.17t



Using general method A, phenol **S12** was converted into quinol **2.17t** in 51% after flash-column chromatography (1:0→1:1 hexanes/EtOAc).

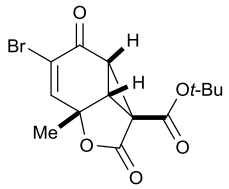
IR (neat) 3397, 2928, 2853, 1640, 1601, 1370, 1299, 1208, 1150, 1062, 868, 762 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1 H), 4.05 (s, 3 H), 1.85 (s, 3 H), 1.51 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 181.6 (C), 171.7 (C), 148.7 (CH), 122.7 (C), 116.8 (C), 71.6 (C), 61.6 (CH_3), 25.8 ($CH_3 \times 3$), 9.9 (CH_3)

HRMS (ESI+) 268.9784 calcd for $C_9H_{11}BrO_3Na$, found 268.9781

Cyclopropane 2.23j



Using general method E, **2.8j** cyclized in 5.5 h to give **2.23j** in 56% yield after flash-column chromatography (4:1 hexanes–EtOAc). Using a modification of general method D, in which CH_2Cl_2 was used as solvent and 10 mol% tetrabutylammonium iodide was added, racemic **2.23j** was obtained in 85%.

IR (thin film) 3055, 2980, 2929, 1786, 1723, 1692, 1602, 1454, 1326, 1154, 1036, 917 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1 H), 3.25 (d, J = 7.5 Hz, 1 H), 3.18 (d, J = 7.5 Hz, 1 H) 1.81 (s, 3 H), 1.51 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 181.6 (C), 165.0 (C), 163.0 (C), 149.3 (CH), 128.5 (C), 84.9 (C), 76.3 (C), 44.8 (C), 42.3 (CH), 35.4 (CH), 28.0 ($CH_3 \times 3$), 25.9 (CH_3)

HRMS (ESI+) 342.0097 calcd for $C_{14}H_{15}BrO_5$, found 341.9251

HPLC (CHIRALCEL OD-H, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 13.1, 16.6 min

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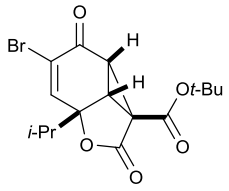
Cyclopropane 2.23k



Using general method E, **2.8k** cyclized in 3.5 h to give **2.23k** in 81% yield after flash-column chromatography (5:1 hexanes/EtOAc). Using general method D, racemic **2.23k** was obtained in 49% yield.

IR (thin film) 3060, 2977, 1788, 1693, 1608, 1465, 1324, 1153, 1080, 955 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1 H), 3.20 (d, *J* = 7.9 Hz, 1 H), 3.17 (d, *J* = 7.7 Hz, 1 H), 2.27 (qq, *J* = 6.8, 6.8 Hz, 1 H), 1.50 (s, 9 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 182.0 (C), 165.4 (C), 163.0 (C), 147.8 (CH), 129.3 (C), 84.7 (C), 81.7 (C), 44.6 (C), 38.5 (CH), 34.6 (CH), 34.3 (CH), 28.0 (CH_3 × 3), 16.1 (CH_3), 15.6 (CH_3)

HRMS (ESI+) 370.0410 calcd for $C_{16}H_{19}BrO_5$, found 370.0141

HPLC (CHIRALCEL OD-H, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 8.3, 11.9 min

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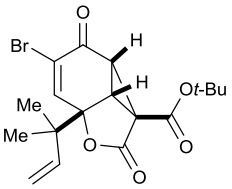
Cyclopropane 2.23l



Using general method E, **2.8l** cyclized in 6.5 d to give **2.23l** in 63% yield after flash-column chromatography (9:1 hexanes/EtOAc). Using general method D, racemic **2.23l** was obtained in 42% yield.

IR (thin film) 2976, 1786, 1728, 1694, 1314, 1261, 1150, 1092, 990, 837 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 1 H), 5.83 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1 H), 5.17 (dd, *J* = 10.1, 1.0 Hz, 1 H), 5.12 (dd, *J* = 17.4, 1.5 Hz, 1 H), 3.31 (d, *J* = 7.7 Hz, 1 H), 3.16 (d, *J* = 7.7 Hz, 1 H), 2.22 (d, *J* = 7.4 Hz, 2 H), 1.51 (s, 9 H), 1.11j (s, 3 H), 1.09 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 181.9 (C), 165.4 (C), 163.0 (C), 146.3 (CH), 132.8 (CH), 129.6 (C), 119.5 (CH_2), 84.8 (C), 83.7 (C), 44.7 (C), 40.7 (CH_2), 39.2 (C), 39.1 (CH), 34.3 (CH), 28.0 (CH_3 × 3), 21.0 (CH_3), 20.6 (CH_3)

HRMS (ESI+) 433.0621 calcd for $C_{19}H_{23}O_5BrNa$, found 433.0556

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 6.5, 10.1 min

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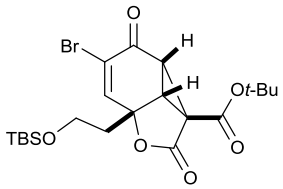
Cyclopropane 2.23m



Using general method E, **2.8m** cyclized in 22 h to give **2.23m** in 35% yield after flash-column chromatography (9:1 hexanes/EtOAc). Using general method D, racemic **2.23m** was obtained in 24% yield.

IR (thin film) 2952, 2930, 2857, 1792, 1726, 1694, 1152, 837 cm^{-1}

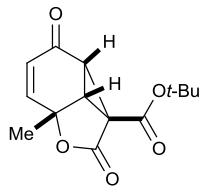
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 3.98–3.89 (m, 2 H), 3.59 (d, 7.5 Hz), 3.18 (d, 7.5 Hz), 2.33–2.18 (m, 2 H), 1.51 (s, 9 H), 0.90 (s, 9 H), 0.084 (s, 3 H), 0.078 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 181.8 (C), 165.2 (C), 163.0 (C), 149.2 (CH), 127.9 (C), 84.7 (C), 78.3 (C), 57.9 (CH_2), 44.4 (C), 41.4 (CH), 40.2 (CH_2), 35.4 (CH), 28.0 (CH_3 × 3), 26.0 (CH_3 × 3), 18.3 (C), −5.4 (CH_3 × 2)

HRMS (ESI+) 509.0965 calcd for $C_{21}H_{31}BrO_6SiNa$, found 509.0965

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 7.4, 8.4 min

Cyclopropane 2.23r



Using a modification of general method D, in which 1.0 equiv of Cs_2CO_3 was used and the concentration was 0.1 M in substrate, **2.8r** cyclized to give **2.23r** in 45% yield after flash-column chromatography (2:1 hexanes/EtOAc).

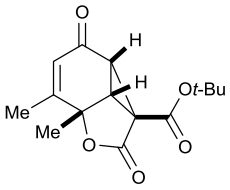
IR (thin film) 2979, 2932, 2856, 1784, 1726, 1685, 1370, 1315, 1137 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, *J* = 9.8 Hz, 1 H), 6.18 (d, *J* = 9.8 Hz, 1 H), 3.18 (d, *J* = 7.5 Hz, 1 H), 3.02 (d, *J* = 7.5 Hz, 1 H), 1.80 (s, 3 H), 1.50 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 188.0 (C), 165.7 (C), 163.6 (C), 149.2 (CH), 131.6 (CH), 84.5 (C), 74.2 (C), 44.3 (C), 42.2 (CH), 35.6 (CH), 28.0 (CH_3 × 3), 25.6 (CH_3)

HRMS (ESI+) 287.0890 calcd for $C_{14}H_{16}O_5Na$, found 287.0880

Cyclopropane 2.23s



Using general method D, **2.8s** cyclized to give **2.23s** in >99% crude yield. Attempts to further purify the crude material by chromatography resulted in decomposition.

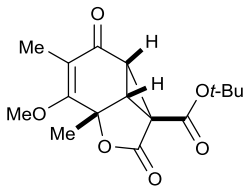
IR (thin film) 2980, 2934, 1782, 1724, 1671, 1370, 1314, 1251, 1161, 1032, 919, cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$,) δ 6.03 (app. t, *J* = 1.3 Hz, 3 H), 3.13 (d, *J* = 7.5 Hz, 1 H), 3.01 (dd, *J* = 7.5, 1.2 Hz, 1 H), 2.06 (d, *J* = 1.5 Hz, 3 H), 1.77 (s, 3 H), 1.51 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 187.9 (C), 165.8 (C), 163.7 (C), 159.2 (C), 129.1 (CH), 84.4 (C), 76.5 (C), 44.0 (C), 42.9 (CH), 36.1 (CH), 28.0 (CH_3 × 3), 23.3 (CH_3), 20.2 (CH_3)

HRMS (ESI+) 301.1046 calcd for $C_{15}H_{18}O_5Na$, found 301.1052

Cyclopropane 2.23t



Using a modification of general method D, in which 1.1 equiv of Cs_2CO_3 was used, **2.8t** cyclized to give **2.23t** as a single regioisomer in 65% yield after flash column chromatography (3:1 hexanes/EtOAc).

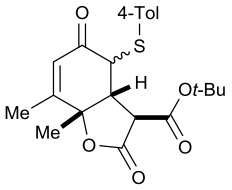
IR (neat) 2980, 2936, 1784, 1723, 1661, 1607, 1370, 1316, 1164, 1034 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 3.08 (d, *J* = 7.7 Hz, 1 H), 3.02 (d, *J* = 7.7 Hz, 1 H), 1.86 (s, 3 H), 1.71 (s, 3 H), 1.49 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 189.3 (C), 170.4 (C), 166.0 (C), 163.4 (C), 120.5 (C), 84.2 (C), 78.3 (C), 61.6 (CH_3), 43.8 (C), 41.6 (CH), 35.4 (CH), 28.0 (CH_3 × 3), 22.1 (CH_3), 9.8 (CH_3)

HRMS (ESI+) 331.1152 calcd for $C_{16}H_{20}O_6Na$, found 331.1158

Sulfide 2.30



A mixture of crude cyclopropane **2.23s** (68 mg, 0.24 mmol) and 4-toluenethiol (30.3 mg, 0.24 mmol) was dissolved in 5 mL toluene. A condenser was attached to the flask and the reaction was heated to 115 ºC for 1 h. The mixture was allowed to cool to rt. The solvent was removed in vacuo and the residue purified by flash-column chromatography to give **2.32** (36.7 mg, 37.2% yield from **2.8s**), as a 2:1 inseparable mixture of diastereomers.

IR (thin film) 2979, 2928, 1787, 1731, 1675, 1370, 1293, 1257, 1153, 1090, 952 cm^{-1}

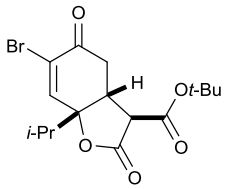
^{1}H NMR (300 MHz, $CDCl_3$, *denotes minor diastereomer) δ *7.39 (d, *J* = 8.2 Hz), 7.34 (d, *J* = 8.2 Hz, 2 H), 7.16 (d, *J* = 7.9 Hz, 2 H), *7.15 (d, *J* = 8.4 Hz), *6.02 (q, *J* = 1.4

Hz), 5.94 (dq, *J* = 1.3, 1.3 Hz, 1 H), *4.16 (d, *J* = 5.0 Hz), 3.74 (dd, *J* = 1.9, 1.2 Hz, 1 H), *3.66 (dd, *J* = 11.9, 5.0 Hz), 3.48 (dd, *J* = 12.5, 2.0 Hz, 1 H), *3.37 (d, *J* = 11.9 Hz), 3.32 (d, *J* = 12.5, Hz, 1 H), 2.34 (s, 3 H) *2.34 (s), 2.06 (d, *J* = 1.4 Hz, 3 H), *2.01 (d, *J* = 1.3 Hz), 1.90 (s, 3 H), *1.66 (s), *1.53 (s), 1.46 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT, mixture of diastereomers) δ 191.2 (C), 190.5 (C), 169.7 (C), 168.5 (C), 166.3 (C), 164.9 (C), 157.1 (C), 156.0 (C), 139.5 (C), 138.5 (C), 133.9 (CH), 132.8 (CH), 130.3 (CH), 130.2 (CH), 129.6 (C), 128.6 (C), 127.0 (CH), 126.0 (CH), 84.0 (C), 83.4 (C), 83.3 (C), 81.9 (C), 56.3 (CH), 52.7 (CH), 51.9 (CH), 51.7 (CH), 51.3 (CH), 50.0 (CH), 28.04 (CH_3), 28.02 (CH_3), 25.5 (CH_3), 22.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 18.6 (CH_3), 18.3 (CH_3)

HRMS (ESI+) 425.1393 calcd for $C_{22}H_{26}O_5SNa$, found 425.1403

Bicyclic lactone 2.31



A solution of SmI_2 in THF (4.5 mL, ~0.16 mmol) was added slowly to cyclopropane **2.23k** (22 mg, 0.059 mmol) at 0 °C. The reaction mixture was stirred for ~5 min before quenching with 0.5 mL of 10% aq. HCl. The cooling bath was removed and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash-column chromatography (5:1 hexanes/EtOAc) to give **2.33** (8.7 mg, 39% yield).

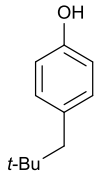
IR (thin film) 2978, 2927, 1785, 1716, 1699, 1371, 1152, 994, 948 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 1.7 Hz, 1 H), 3.47 (dtd, *J* = 11.9, 3.8, 1.7 Hz, 1 H), 3.35 (d, *J* = 12.0 Hz, 1 H), 2.84 (d, *J* = 3.8 Hz, 2 H), 2.27 (hept, *J* = 6.9 Hz, 1 H), 1.50 (s, 9 H), 1.14 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 187.3 (C), 168.8 (C), 165.2 (C), 146.4 (CH), 126.5 (C), 86.5 (C), 84.2 (C), 53.3 (CH), 40.0 (CH), 37.4 (CH_2), 36.1 (CH), 28.1 (CH_3 × 3), 17.7 (CH_3), 16.9 (CH_3)

HRMS (ESI+) 395.0465 calcd for $C_{16}H_{21}BrO_5Na$, found 395.0445

Phenol S1



A solution of 4-hydroxybenzaldehyde (1.0 g, 8.2 mmol) in THF (40 mL) was cooled to 0 ºC and treated with *t*-BuLi (1.28 M in pentane, 14.0 mL, 18.0 mmol). The mixture was stirred for 1 h before being quenched with 10% aq. HCl (1 mL). The mixture was diluted with brine and acidified with 10% aq. HCl until a clear solution was obtained. Extraction with Et_2O followed by drying over $MgSO_4$ and concentration gave a residue that was purified by flash-column chromatography (3:1 hexanes–EtOAc). Further purification was achieved by suspending the obtained solid in chloroform, followed by filtration to give 471 mg of the intermediate benzylic alchohol. This material was dissolved in EtOH (35 mL), treated with 100 mg Pd/C (10% w/w) and 1 drop of conc. HCl. The mixture was stirred under an atmosphere of H_2 (balloon) for 14 h, then filtered through a short plug of Celite. Solvent was removed in vacuo and the residue purified by flash-column chromatography (19:1 hexanes/EtOAc) to give **S1** (387 mg, 24% yield over two steps). Identity was verified by comparison of the ^{1}H NMR spectrum with literature data.[16]

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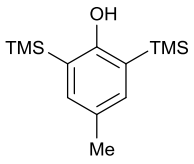
[16] Bates, R. B.; Siahaan, T. J. *J. Org. Chem.* **1986**, *51*, 1432–1434.

Phenol S2



A mixture of 2-bromo-4-methyl-6-(trimethylsilyl)phenol[17] (660 mg, 2.54 mmol), TMSCl (0.64 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol) was dissolved in toluene (20 mL) and refluxed for 12 h. The mixture was then allowed to cool to rt and concentrated. Full conversion of the phenol to the TMS ether was confirmed by ^{1}H NMR analysis. The residue was then dissolved in 20 mL THF and cooled to −100 ºC. *n*-BuLi (2.5 M in hexanes, 1.01 mL, 2.54 mmol) was added and the mixture was allowed to gradually warm to −50 ºC, at which point it was quenched with saturated aq. NH_4Cl (1 mL). The cooling bath was removed and the mixture was diluted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash-column chromatography (100% petroleum ether) afforded phenol **S2** (564.2 mg, 87% yield over two steps).

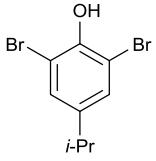
IR (thin film) 3599, 2951, 1572, 1403, 1241, 1169, 832 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 2 H), 4.85 (s, 1 H), 2.29 (s, 3 H), 0.34 (s, 18 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 163.4 (C), 137.3 (CH × 2), 129.2 (C), 124.1 (C × 2), 20.8 (CH_3), −0.3 (CH_3 × 6)

HRMS (ESI–) 251.1282 calcd for $C_{13}H_{23}OSi_2$, found 251.0992

Phenol S3

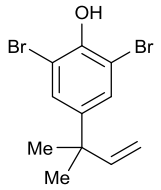


A solution of 4-isopropyl phenol (266 mg, 1.95 mmol) in 15 mL of dry CH_2Cl_2 was treated with 1,3-dibromo-5,5-dimethylhydantoin (614.3 mg, 2.14 mmol) in small

[17] Akai, S.; Ikawa, T.; Takayanagi, S.-i.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada, Y. Kita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 7673–7676.

portions. The mixture was then protected from light and stirred. After 16 h, the mixture was diluted with CH_2Cl_2 and washed with 10% HCl solution, dried over Na_2SO_4, filtered and concentrated. Crude product was purified by flash-column chromatography (39:1 hexanes/EtOAc) to give 285.8 mg of **S3** in 49% yield. Identity was verified by comparison of ^{1}H NMR spectrum with literature data.[18]

Phenol S4



A solution of 4-(2-methylpent-4-en-2-yl)phenol[12] (159.9 mg, 0.90 mmol) in 12 mL of CH_2Cl_2 was treated with 1,3-dibromo-5,5-dimethylhydantoin (259.3 mg, 0.9 mmol). The reaction flask was protected from light and stirred for 16 h. The mixture was then diluted with CH_2Cl_2, washed with 10% aq. HCl and brine, dried over Na_2SO_4, filtered, and concentrated. Flash-column chromatography (20:1 hexanes/Et_2O) provided **S4** (243 mg, 80% yield)

IR (thin film) 3498, 2964, 1555, 1475, 1393, 1285, 1163, 998, 917, 733 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 2 H), 5.74 (s, 1 H), 5.61–5.42 (m, 1 H), 4.99 (s, 1 H), 4.97–4.90 (m, 1 H), 2.28 (d, J = 7.3 Hz, 2 H), 1.24 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 147.2 (C), 144.2 (C), 134.6 (CH), 129.8 (CH × 2), 117.8 (CH_2), 48.7 (CH_2), 37.4 (C), 28.5 (CH_3 × 2)

HRMS (ESI–) 333.9386 calcd for $C_{12}H_{14}Br_2O$, found 333.1305

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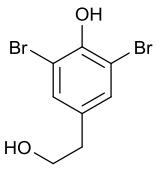
[18] (a) A. Fitton, O.; Rigby, A.; Hurlock, R. J. *J. Chem. Soc. C* **1968**, 1000–1001. (b) Eriksson, J.; Rahm, S.; Green, N.; Bergman, Å.; Jakobsson, E. *Chemosphere* **2004**, *54*, 117–126.

Alcohol S5



To a solution of 2-(4-hydroxyphenyl)ethanol[19] (150 mg, 1.09 mmol) in EtOAc (11 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (312 mg, 1.09 mmol). The solution was protected from light and stirred for 15 h. The reaction was then diluted with EtOAc and quenched with 10% aq. HCl. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash-column chromatography (2:1 hexanes/EtOAc) to give **S5** as a yellow solid (190 mg, 59% yield).

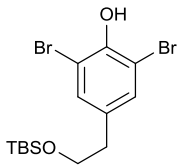
IR (thin film) 3389, 2975, 2952, 2891, 1557, 1475, 1408, 1238, 1012, 997, 736 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 2 H), 5.80 (bs, 1 H), 3.83 (t, J = 6.4 Hz, 2 H), 2.76 (t, J = 6.4 Hz, 2 H), 1.47 (s, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 148.1 (C), 133.5 (C), 132.6 (CH × 2), 109.9 (C × 2), 63.4 (CH_2), 37.7 (CH_2)

HRMS (ESI–) 292.8818 calcd for $C_8H_7Br_2O_2$, found 292.8810

Phenol S6



Imidazole (48 mg, 0.71 mmol) was added to a solution of alcohol **S5** (175 mg, 0.591 mmol) in THF (6 mL). The solution was cooled to 0 °C and TBSCl (107 mg, 0.710 mmol) was added. The mixture was stirred for 7 h, then quenched with saturated aq. $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O and the organic layer was

[19] Although this substrate is commercially available, we chose to prepare it by LAH reduction of the less expensive methyl 4-hydroxyphenylacetate.

washed with water and brine, dried over $MgSO_4$, and concentrated. The crude material, a mixture of alkyl and aryl silyl ethers, was purified by flash-column chromatography (5:1 toluene/petroleum ether) to give **S6** as a yellow oil (65 mg, 27% yield).

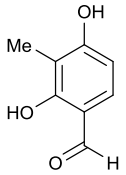
IR (thin film) 3512, 2955, 2928, 2858, 1563, 1472, 1256, 1163, 1100, 836, 778, 738 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 2 H), 5.77 (s, 1 H), 3.74 (t, *J* = 6.4 Hz, 2 H), 2.69 (t, *J* = 6.4 Hz, 2 H), 0.87 (s, 9 H), –0.03 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 147.7 (C), 134.4 (C), 132.8 (CH × 2), 109.5 (C × 2), 63.9 (CH_2), 38.0 (CH_2), 26.0 (CH_3 × 3), 18.4 (C), −5.3 (CH_3 × 2)

HRMS (ESI–) 406.9683 calcd for $C_{14}H_{21}Br_2O_2Si$, found 406.9683

Hydroxybenzaldehyde S7



Phosphorus oxychloride (83 mL, 0.89 mol) was added dropwise to DMF (250 mL) at 0 °C. This was transferred via cannula to a solution of 2-methylresorcinol (50.0 g, 0.40 mol) in DMF (250 mL) at 0 °C. The reaction was stirred for 1.5 h, gradually warming to rt The mixture was then cooled to 0 °C and quenched with 2 M NaOH until pH 6. The product was extracted with EtOAc and concentrated. The resulting residue was recrystallized from hot 10% IPA/H_2O to give **S7** (30.30 g) as beige crystalline needles. A second crop of crystals yielded an additional 6.99 g for a total of 37.29 g (61% yield).

mp 153.0–154.4 °C (uncorrected)

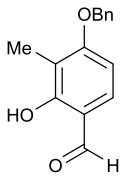
IR (neat)**:** 3276, 2780, 1622,1596, 1493, 1435, 1306, 1251, 1217, 1095 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.67 (s, 1 H), 9.69 (s, 1 H), 7.29 (d, *J* = 8.5 Hz, 1 H), 6.47 (d, *J* = 8.5 Hz, 1 H), 5.62 (s, 1 H), 2.14 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 162.4, 161.2, 133.1, 115.3, 111.2, 108.2, 7.2

HRMS (ESI+) 151.0390 calcd for $C_8H_7O_3$, found 151.0399

Benzyloxybenzaldehyde S8



A literature procedure was adapted.[20] 2,4-Dihydroxy-3-methylbenzaldehyde (**S7**) (30.0 g, 0.197 mol), $NaHCO_3$ (18.88 g, 0.23 mol), and KI (6.54 g, 0.039 mol) were dissolved in MeCN (500 mL). The flask was fitted with a reflux condenser and slowly warmed to 60 °C. At this time, benzyl bromide (28.3 mL, 0.236 mol) was added and the mixture was warmed to 80 °C. After refluxing overnight, $KHCO_3$ (9.86 g, 0.099 mol) was added and the mixture was stirred for an additional 5 h, then cooled to rt and concentrated. The residue was quenched with 10% aq. HCl (100 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. The resulting oil was purified by flash-column chromatography using 100% hexanes until removal of benzyl bromide, then 6:1 hexanes/EtOAc to afford a **S8** as a yellow solid (46.89 g, 98% yield).

IR (thin film) 3030, 2923, 2839, 1641, 1626, 1498, 1289, 1250, 1111 cm^{-1}

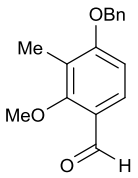
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.47 (s, 1 H), 9.71 (s, 1 H), 7.42–7.34 (m, 6 H), 6.61 (d, J = 8.7, 1H), 5.19 (s, 2 H), 2.17 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 163.5, 161.3, 136.4, 133.3, 128.8, 128.3, 127.2, 115.6, 104.4, 104.2, 70.4, 7.7

HRMS (CI, CH_4) 243.1016 calcd for $C_{15}H_{15}O_3$, found 243.1031

[20] Mendelson, W. L.; Holmes, M.; Dougherty, J. *Synth. Commun.* **1996**, *26*, 593–601.

Methoxybenzaldehyde S9



To a solution of benzaldehyde **S8** (18.5 g, 0.076 mol) in DMF (300 mL) was added K_2CO_3 (31.7 g, 0.229 mol) and MeI (5.14 mL, 0.826 mol). The flask was fitted with a reflux condenser and the solution was heated to 80 °C for 3 hours. The reaction was then cooled to rt, diluted with water and extracted with Et_2O. The combined organic layers were washed with water, 10% aq. NaOH and brine; dried over $MgSO_4$; filtered; and concentrated to obtain **S9** as a yellow solid (19.1 g, 97% yield).

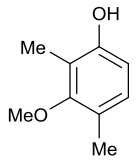
IR (thin film) 2934, 2861, 1678, 1591, 1277, 1256, 1100 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1 H), 7.73 (d, *J* = 8.7 Hz, 1 H), 7.46–7.32 (m, 5 H), 6.81 (d, *J* = 8.7 Hz, 1 H), 5.16 (s, 2 H), 3.87 (s, 3 H), 2.23 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 163.2, 162.8, 136.4, 128.8, 128.3, 128.0, 127.3, 123.1, 120.7, 107.9, 70.4, 63.4, 8.9

HRMS (ESI+) 279.0992 calcd for $C_{16}H_{16}NaO_3$, found 279.0986

Phenol S10



Benzaldehyde **S9** (15.0 g, 58.5 mmol) 10% Pd/C[21] (3 mol%, 3.2 g) were suspended in MeOH (250 mL) and placed under a H_2 atmosphere (balloon). The mixture was stirred for 3 h. After such time, 1 drop of conc. HCl was added and the reaction was stirred overnight. The mixture was then filtered through a pad of Celite and concentrated. The

[21] Pd/C catalyst obtained from Johnson Matthey (56% H_2O, Type 10R39).

crude residue was purified by flash-column chromatography (3:1 hexanes/EtOAc) to give **S10** as a pale yellow crystalline solid (8.6 g, 96% yield).

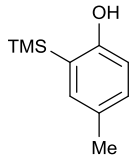
IR (neat) 3388, 2940, 2861, 1603, 1496, 1469, 1411, 1285, 1079, 999 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 8.1 Hz, 1 H), 6.50 (d, *J* = 8.2, 1 H), 4.58 (s, H), 3.71 (s, 3 H), 2.21 (s, 3 H), 2.18 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 153.0, 128.2, 122.9, 117.4, 110.8, 60.1, 15.8, 9.0

HRMS (CI, CH_4) 153.0910 calcd for $C_9H_{13}O_2$, found 153.0930

Phenol S11



A solution of 2-bromo-4-methyl phenol (500 mg, 2.67 mmol) in 1 mL of hexamethyldisilazane was heated at 125 ºC for 20 min in a microwave reactor.[14] After excess hexamethyldisilazane was removed in vacuo, the resulting TMS ether was dissolved in 15 mL of dry THF and cooled to −100 ºC. *n*-BuLi (2.5 M in hexanes, 1.06 mL, 2.65 mmol) was added slowly, then the mixture was allowed to warm to −50 ºC. The reaction was then quenched with saturated aq. NH_4Cl (10 mL). The cooling bath was removed and the mixture was diluted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash-column chromatography (95:5 hexanes/EtOAc) afforded phenol **S11** (343.1 mg, 62% yield over two steps).

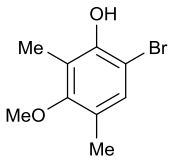
IR (thin film) 3533, 2953, 1599, 1490, 1389, 1244, 1181, 1073, 890, 839 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 8.1, 2.3 Hz, 1 H), 6.59 (d, *J* = 8.1, 1 H), 4.62 (s, 1 H), 2.29 (s, 3 H), 0.31 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 158.3 (C), 135.8 (CH), 131.2 (CH), 129.5 (C), 125.2 (C), 114.5 (CH), 20.7 (CH_3), −0.8 (CH_3 × 3)

HRMS (ESI–) 179.0887 calcd for $C_{10}H_{15}OSi$, found 179.1305

Phenol S12



Phenol **S10** (500 mg, 3.29 mmol) was dissolved in chloroform (30 mL). To this, 1,3-dibromo-5,5-dimethylhydantoin (70 mg, 2.5 mmol) was added portionwise. The reaction mixture was protected from light and stirred overnight before being quenched with 10% aq. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting brown solid was purified by flash-column chromatography (9:1 hexanes/EtOAc) to afford **S12** as a yellow solid (39 mg, 51% yield), which quickly turned brown upon standing (product is suspected to be light sensitive).

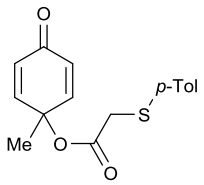
IR (neat) 3511, 2939, 1596, 1470, 1405, 1308, 1235, 1209, 1085, 1003, 778 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 1 H), 5.42 (s, 1 H), 3.69 (s, 3 H), 2.23 (s, 3 H), 2.20 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 157.3 (C), 149.3 (C), 129.8 (CH), 124.3 (C), 119.2 (C), 104.7 (C), 60.1 (CH_3), 15.6 (CH_3), 10.1 (CH_3)

HRMS (ESI+) 229.9937 calcd for $C_9H_{11}BrO_2$, found 229.0151

Sulfide-tethered cyclohexadienone S13



Using general method C, 2-(*p*-tolylthio)acetic acid (**2.22**)[22] was coupled to **2.17a** to give sulfide **S13** in 65% yield after flash-column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 3022, 2779, 2924, 1739, 1668, 1631, 1269, 1134, 1052, 857 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 6.72 (d, *J* = 10.2 Hz, 2 H), 6.17 (d, *J* = 10.2 Hz, 2 H), 3.52 (s, 2 H), 2.31 (s, 3 H), 1.45 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.9 (C), 168.3 (C), 148.5 (CH × 2), 137.8 (C), 131.4 (CH × 2), 130.6 (C), 129.9 (CH × 2), 128.3 (CH × 2), 75.0 (C), 37.5 (CH_2), 26.0 (CH_3), 21.1 (CH_3)

HRMS (ESI+) 311.0712 calcd for $C_{16}H_{16}O_3SNa$, found 311.0708

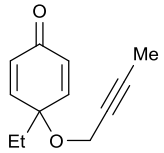
[22] (a) Prepared according to Kenney, W. J.; Walsh, J. A.; Davenport, D. A. *J. Am. Chem. Soc.* **1961**, *83*, 4019–4022. (b) Nagao, Y.; Miyamoto, S.; Miyamoto, M.; Takeshige, H.; Hayashi, K.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y. *J. Am. Chem. Soc.* 2006, **128**, 9722–9729.

Experimental Details – Chapter 3

General method F: Pd-catalyzed cyclization

A mixture of the appropriate cyclohexadienone (1 equiv), $Pd(OAc)_2$ (0.05 equiv.), and ligand (0.1 equiv) was suspended in acetic acid and heated to 80 °C. The reaction mixture was stirred until the starting material was consumed (2–144 h). The solvent was removed under vacuum and the resulting residue was purified by flash column chromatography. Product configuration was determined by analogy to **3.63a**, **3.62i**, or **3.89m**, unless otherwise stated.

Alkyne-tethered cyclohexadienone 3.62d



4-Ethylphenol (107 mg, 0.876 mmol) was dissolved in 2-butyn-1-ol (1 mL) and cooled to 0 ºC. PIFA (377 mg, 0.877 mmol) was added and the mixture and stirred for 1 h. The reaction mixture was diluted with EtOAc; washed with saturated aq. $NaHCO_3$, water, and brine; dried over Na_2SO_4; filtered; and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give cyclohexadienone **3.62d** (60 mg, 36% yield) as a yellow oil.

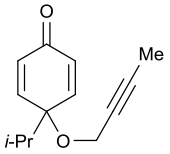
IR (thin film) 2970, 2922, 2858, 1669, 1632, 1515, 1082, 1051, 859 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (d, *J* = 10.3 Hz, 2 H), 6.37 (d, *J* = 10.2 Hz, 2 H), 3.99 (q, *J* = 2.4 Hz, 2 H), 1.84 (t, *J* = 2.4 Hz, 3 H), 1.84 (q, *J* = 7.7 Hz, 2 H), 0.83 (t, *J* = 7.6 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.6 (C), 150.4 (CH × 2), 131.7 (CH × 2), 129.0 (C), 115.2 (C), 75.9 (C), 54.4 (CH_2), 32.4 (CH_2), 8.0 (CH_3), 3.9 (CH_3)

HRMS (ESI+): Calculated for $C_{12}H_{14}O_2Na^+$: 213.0886; Observed: 213.0885

Alkyne-tethered cyclohexadienone 3.62e



4-Isopropylphenol (136 mg, 0.999 mmol) was dissolved in 2-butyn-1-ol (1 mL) and cooled to 0 ºC. PIFA (430 mg, 1.00 mmol) was added and the mixture and stirred for 2 h. The reaction mixture was diluted with EtOAc; washed with saturated aq. $NaHCO_3$, water, and brine; dried over Na_2SO_4; filtered; and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give cyclohexadienone **3.62e** (36 mg, 18% yield) as a yellow oil.

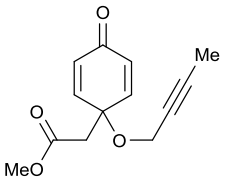
IR (thin film) 2964, 2922, 1669, 1630, 1384, 1048, 855 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, *J* = 10.3 Hz, 2 H), 6.39 (d, *J* = 10.3 Hz, 2 H), 3.96 (q, *J* = 2.4 Hz, 2 H), 2.05 (sept, *J* = 6.9 Hz, 1 H), 1.84 (t, *J* = 2.4 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.7 (C), 149.6 (CH × 2), 132.3 (CH × 2), 83.1 (C), 78.8 (C), 76.1 (C), 54.3 (CH_2), 36.7 (CH), 17.2 (CH_3 × 2), 3.87 (CH_3)

HRMS (ESI+): Calculated for $C_{13}H_{16}O_2Na^+$: 227.1043; Observed: 227.1043

Alkyne-tethered cyclohexadienone 3.62f



Methyl 4'-hydroxyphenylacetate (166 mg, 0.999 mmol) was dissolved in 2-butyn-1-ol (1 mL) and cooled to 0 ºC. PIFA (430 mg, 1.00 mmol) was added and the mixture and stirred for 1 h. The reaction mixture was diluted with EtOAc; washed with saturated aq. $NaHCO_3$, water, and brine; dried over Na_2SO_4; filtered; and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give cyclohexadienone **3.62f** (58 mg, 25% yield) as a yellow oil.

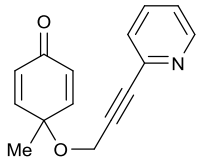
IR (thin film) 2953, 2922, 2856, 1734, 1670, 1634, 1436, 1159, 1051, 860 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 10.3 Hz, 2 H), 6.37 (d, *J* = 10.3 Hz, 2 H), 3.98 (q, *J* = 2.4 Hz, 2 H), 3.66 (s, 3 H), 2.78 (s, 2 H), 1.83 (t, *J* = 2.4 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.0 (C), 168.7 (C), 148.4 (CH × 2), 131.6 (CH × 2), 83.8 (C), 75.5 (C), 73.2 (C), 54.3 (CH_2), 52.2 (CH_3), 44.6 (CH_2), 3.8 (CH_3)

HRMS (ESI+): Calculated for $C_{13}H_{14}O_4Na^+$: 257.0784; Observed: 257.0781

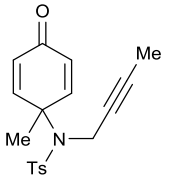
Alkyne-tethered cyclohexadienone 3.62h



Terminal alkyne **3.62a** (155.6 mg, 0.9594 mmol), $Pd(Ph_3P)_2Cl_2$ (6.7 mg, 0.0095 mmol), and CuI (0.9 mg, 0.005 mmol) were suspended in Et_3N (5 mL). 2-Bromopyridine (0.10 mL, 1.0 mmol) was added and the mixture was stirred overnight. The reaction mixture was then diluted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash-column chromatography (1:1 hexanes/EtOAc) to give **3.62h** (103.7 mg, 46% yield), although it still contained significant impurities.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (dt, *J* = 4.9, 0.8 Hz, 1 H), 7.66 (td, J = 7.7, 1.8 Hz, 1 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.28-7.23 (m, 1 H), 6.90 (d, *J* = 10.2 Hz, 3 H), 6.35 (d, *J* = 10.2 Hz, 3 H), 4.25 (s, 2 H), 1.51 (s, 3 H).

Alkyne-tethered cyclohexadienone 3.62i



Dienone **3.70i** (27 mg, 0.099 mmol) and Cs_2CO_3 (49 mg, 0.15 mmol) were added to a solution of 5-iodopent-2-yne[23] (60 mg, 0.33 mmol) in acetonitrile (1 mL). The mixture was stirred for 5 h, at which point it was diluted with CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give alkyne **3.62i** as a white solid (28 mg, 86% yield).

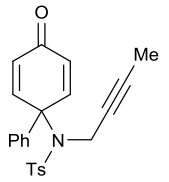
IR (thin film) 2919, 1667, 1628, 1333, 1157, 1090, 889, 861, 810 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.2 Hz, 2 H), 7.03 (d, *J* = 10.2 Hz, 2 H), 6.14 (d, *J* = 10.2 Hz, 2 H), 4.23 (q, *J* = 2.3 Hz, 2 H), 2.43 (s, 3 H), 1.78 (t, *J* = 2.3 Hz, 3 H), 1.60 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 184.7 (C), 151.8 (CH × 2), 143.9 (C), 138.6 (C), 129.5 (CH × 2), 128.0 (CH × 2), 127.7 (CH × 2), 81.9 (C), 75.6 (C), 60.0 (C), 37.0 (CH_2), 26.3 (CH_3), 21.7 (CH_3), 3.6 (CH_3)

HRMS (ESI+): Calculated for $C_{18}H_{19}NO_3SNa^+$: 352.0978; Observed: 352.0975

Alkyne-tethered cyclohexadienone 3.62j



A mixture of **3.70j** (249 mg, 0.734 mmol) and Cs_2CO_3 (357 mg, 1.10 mmol) was treated with a solution of 5-iodopent-2-yne[23] in MeCN (7 mL). The reaction mixture was stirred for 1.5 h, and then concentrated under reduced pressure. The resulting solids were partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with EtOAc and

[23] Hewson A. T.; MacPherson, D. T. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2625–2635.

the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to give alkyne **3.62j** (287 mg, 100% yield) as a white foam.

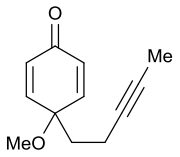
IR (thin film) 3062, 2919, 1668, 1629, 1339, 1159, 1089, 923, 811, 699 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2 H), 7.38–7.30 (m, 7 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.10 (d, *J* = 10.1 Hz, 2 H), 4.08 (q, *J* = 2.3 Hz, 2 H), 2.39 (s, 3 H), 1.75 (t, *J* = 2.3 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 184.7 (C), 147.8 (CH × 2), 144.0 (C), 138.1 (C), 137.2 (C), 129.4 (CH × 2), 129.1, (CH), 129.1 (CH × 2), 128.5 (CH × 2), 127.5 (CH × 2), 126.7 (CH × 2), 81.7 (C) 75.5 (C), 65.1 (C), 37.3 (CH_2), 21.6 (CH_3), 3.7 (CH_3)

HRMS (ESI+): Calculated for $C_{23}H_{21}NO_3SNa^+$: 414.1134; Observed: 414.1132

Alkyne-tethered cyclohexadienone 3.62k



A mixture of phenol **3.73k** (199 mg, 1.24 mmol) and $NaHCO_3$ (521 mg, 6.20 mmol) was suspended in methanol (12 mL) and cooled to 0 ºC. PIFA (587 mg, 1.37 mmol) was added and the mixture and stirred for 20 min. The methanol was then removed under reduced pressure, and the resulting residue was purified by flash column chromatography (9:1 hexanes/EtOAc) to give cyclohexadienone **3.62k** (46 mg, 19% yield).

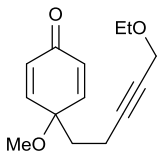
IR (thin film) 3040, 2933, 2827, 1673, 1632, 1075, 861, 703 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (d, *J* = 10.2 Hz, 2 H), 6.34 (d, *J* = 10.2 Hz, 2 H), 3.17 (s, 3 H), 2.12 (tq, *J* = 7.7, 2.5 Hz, 2 H), 1.89 (t, *J* = 7.9 Hz, 2 H), 1.71 (t, *J* = 2.5 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.3 (C), 150.5 (CH × 2), 131.7 (CH × 2), 78.1 (C), 76.7 (C), 75.1 (C), 53.1 (CH_3), 39.0 (CH_2), 13.5 (CH_2), 3.5 (CH_3)

HRMS (ESI+): Calculated for $C_{12}H_{15}O_2^+$: 191.1067; Observed: 191.1053

Alkyne-tethered cyclohexadienone 3.62l



A mixture of phenol **3.73l** (135 mg, 0.661 mmol) and $NaHCO_3$ (277 mg, 3.30 mmol) was suspended in methanol (6 mL) and cooled to 0 ºC. PIFA (312 mg, 0.726 mmol) was added in small portions. The reaction mixture was stirred for 30 min, and then diluted with CH_2Cl_2, filtered through a silica gel plug, and concentrated under reduced pressure. The crude material was a mixture of the desired product and an impurity.[24] The residue was dissolved in acetic acid, heated to 50 ºC, and stirred overnight. The acetic acid was removed under reduced pressure and the resulting residue was purified by flash column chromatography (5:1 hexanes/EtOAc) to give cyclohexadienone **3.62l** (38 mg, 25% yield) as a yellow oil. An additional ~35 mg of product was obtained in fractions containing an unknown impurity.

IR (thin film) 2968, 2929, 1671, 1631, 1078, 859 cm^{-1}

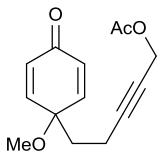
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, *J* = 10.3 Hz, 2 H), 6.36 (d, *J* = 10.3 Hz, 2 H), 4.06–4.05 (m, 2 H), 3.50 (q, *J* = 7.0 Hz, 2 H), 3.19 (s, 3 H), 2.27–2.21 (m, 2 H), 1.95 (t, *J* = 7.7 Hz, 2 H), 1.19 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.0 (C), 150.1 (CH × 2), 131.7 (CH × 2), 85.2 (C), 77.2 (C), 74.8 (C), 65.3 (CH_2), 58.2 (CH_2), 53.0 (CH_3), 38.5 (CH_2), 15.0 (CH_3), 13.5 (CH_2)

HRMS (ESI+): Calculated for $C_{14}H_{18}O_3Na^+$: 257.1148; Observed: 257.1156

[24] This impurity can likely be attributed to product rearrangement to reestablish aromaticity followed by an additional oxidation to form the dimethyl acetal.

Alkyne-tethered cyclohexadienone 3.62m



Phenol **3.73m** (60 mg, 0.27 mmol) and $NaHCO_3$ (116 mg, 1.38 mmol) were suspended in methanol (2.5 mL). PIFA (131 mg, 0.305 mmol) was added in small portions. The reaction mixture was stirred for 20 min, and then diluted with CH_2Cl_2, filtered through a silica gel plug, and concentrated under reduced pressure. The residue was dissolved in acetic acid, heated to 50 ºC, and stirred overnight. The acetic acid was removed under reduced pressure and the resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give cyclohexadienone **3.62m** (35 mg, 52% yield) as a yellow oil.

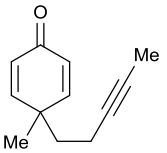
IR (thin film) 2937, 2827, 1745, 1745, 1672, 1633, 1227, 1097, 1076, 1026, 862 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (d, *J* = 10.3 Hz, 2 H), 6.30 (d, *J* = 10.3 Hz, 2 H), 4.54 (t, *J* = 2.1 Hz, 2 H), 3.12 (s, 3 H), 2.19 (tt, *J* = 7.8, 1.9 Hz, 2 H), 2.00 (s, 3 H), 1.88 (t, *J* = 7.8 Hz, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.0 (C), 170.2 (C), 150.1 (CH × 2), 131.8 (CH × 2), 86.1 (C), 75.0 (C), 74.7 (C), 53.0 (CH_3), 52.5 (CH_2), 38.2 (CH_2), 20.7 (CH_3), 13.4 (CH_2)

HRMS (ESI+): Calculated for $C_{14}H_{16}O_4Na^+$: 271.0941; Observed: 271.0946

Alkyne-tethered cyclohexadienone 3.62n[25]



Enone **3.78** (28 mg, 0.16 mmol), DDQ (42 mg, 0.19 mmol), and anhydrous *p*-TsOH (27 mg, 0.16 mmol) were dissolved in 1,4-dioxane (3 mL). The reaction mixture

[25] Procedure adapted from: Chai K.-B.; Sampson, P. *J. Org. Chem.* **1993**, *58*, 6807–6813.

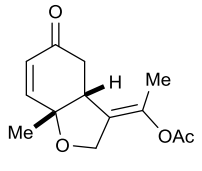
was refluxed for 7 h. It was then diluted with diethyl ether, washed with 10% aq. NaOH and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give cyclohexadienone **3.62n** (15 mg, 54% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 10.2 Hz, 2 H), 6.27 (d, J = 10.2 Hz, 2 H), 1.95–1.82 (m, 4 H), 1.72 (t, J = 2.4 Hz, 3 H), 1.25 (s, 3 H)

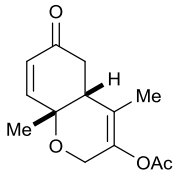
^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 186.2 (C), 154.9 (CH × 2), 129.4 (CH × 2), 78.3 (C), 76.7 (C), 41.9 (C), 40.0 (CH_2), 26.2 (CH_3), 15.0 (CH_2), 3.5 (CH_3)

HRMS (ESI+): Calculated for $C_{12}H_{14}ONa^+$: 197.0937; Observed: 197.0932

Bicyclic enones 3.63b and 3.89b



3.63b



3.89b

Cyclohexadienone **3.62b**[26] was cyclized using general method F to give **3.63b** and **3.89b** after flash column chromatography (5:1 hexanes/EtOAc). Product **3.62b** has been reported previously.[26]

3.89b:

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, J = 10.2 Hz, 1 H), 6.02 (d, J = 10.2 Hz, 1 H), 4.08 (dq, J = 1.9, 1.9 Hz, 2 H), 2.71–2.65 (m, 1 H), 2.64–2.59 (m, 1 H) 2.58–2.53 (m, 1 H), 2.16 (s, 3 H), 1.59 (t, J = 1.9 Hz, 3 H), 1.52 (s, 3 H)

HPLC (CHIRALCEL AS, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 15.7, 23.2 min

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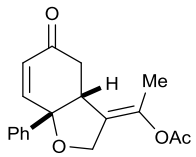
[26] Tello-Aburto, R.; Harned, A. M. *Org. Lett.* **2009**, *11*, 3998–4000.

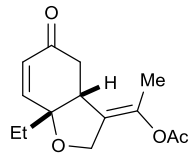
Bicyclic enone 3.63c



Cyclohexadienone **3.62c** was cyclized using general method F to give **3.63c** after flash column chromatography. This product has been reported previously.[27]

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, $\lambda = 225$ nm) $T_R = 13.1$, 17.6 min

Bicyclic enone 3.63d



Cyclohexadienone **3.62d** was cyclized using general method F to give **3.63d** after flash column chromatography (2:1 hexanes/EtOAc).

IR (thin film) 2969, 2924, 2882, 2853, 1754, 1688, 1378, 1256, 1208, 1093, 934 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, J = 10.3 Hz, 2 H), 6.08 (d, J = 10.3 Hz, 2 H), 4.31–4.30 (m, 1 H), 4.23 (ddq, J = 13.2, 2.0, 2.0 Hz, 1 H), 3.13 (app t, J = 6.0 Hz, 1 H), 2.74 (dd, J = 16.4, 6.5 Hz, 1 H), 2.59 (dd, J = 16.4, 5.8 Hz, 1 H), 2.10 (s, 3 H), 1.93 (ddd, J = 1.7, 1.7, 1.7 Hz, 3 H), 1.82–1.74 (m, 2 H), 1.00 (t, J = 7.5 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.5 (C), 168.4 (C), 148.7 (CH), 138.9 (C), 130.6 (CH), 128.3 (C), 82.6 (C), 67.6 (CH_2), 43.0 (CH), 38.4 (CH_2), 29.9 (CH_2), 20.8 (CH_3), 17.2 (CH_3), 8.3 (CH_3)

HRMS (ESI+): Calculated for $C_{14}H_{18}O_4Na^+$: 273.1097; Observed: 273.1094

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, $\lambda = 225$ nm) $T_R = 8.7$, 10.2 min

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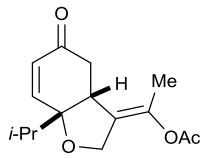
[27] Hexum, J. K.; Tello-Aburto, R.; Struntz, N. B.; Harned, A. M.; Harki, D. A. *ACS Med. Chem. Lett.* **2012**, 459–464

Bicyclic enone 3.63e



Cyclohexadienone **3.62e** was cyclized using general method F to give **3.63d** after flash column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 2964, 1755, 1689, 1370, 1209, 1175, 1013, 938 cm^{-1}

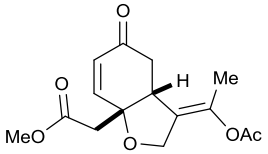
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, *J* = 10.4 Hz, 1 H), 6.15 (d, *J* = 10.4 Hz, 1 H), 4.29–4.25 (m, 1 H), 4.20 (ddq, *J* = 13.1, 2.1, 2.1 Hz, 1 H), 3.22 (app t, *J* = 6.0 Hz, 1 H), 2.71 (dd, *J* = 16.5, 6.3 Hz, 1 H), 2.60 (dd, *J* = 16.5, 6.2 Hz, 1 H), 2.10 (s, 3 H), 2.04 (qq, *J* = 6.9, 6.9 Hz, 1 H), 1.92 (ddd, *J* = 1.6, 1.6, 1.6 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.7 (C), 168.5 (C), 147.2 (CH), 138.7 (C), 131.4 (CH), 129.1 (C), 84.8 (C), 67.2 (CH_2), 41.3 (CH), 39.16 (CH_2), 34.35 (CH), 20.8 (CH_3), 17.6 (CH_3), 17.2 (CH_3), 17.1 (CH_3)

HRMS (ESI+): Calculated for $C_{15}H_{20}O_4Na^+$: 287.1252; Observed: 287.1252

HPLC (CHIRALCEL OJ, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 17.7, 25.7 min

Bicyclic enone 3.63f



Cyclohexadienone **3.62f** was cyclized using general method F to give **3.63f** after flash column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 2991, 2954, 2925, 2843, 1738 (br), 1688, 1437, 1371, 1209, 1146, 1011, 944 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 10.3 Hz, 1 H), 6.10 (d, *J* = 10.3 Hz, 1 H), 4.37–4.33 (m, 1 H), 4.33–4.29 (m, 1 H), 3.70 (s, 3 H), 3.41 (app t, *J* = 6.6 Hz, 1 H), 2.78

(d, *J* = 14.3 Hz, 1 H), 2.75 (d, *J* = 14.1 Hz, 1 H), 2.71 (dd, *J* = 16.2, 7.4 Hz, 1 H), 2.64 (dd, *J* = 16.4, 6.0 Hz, 1 H), 2.11 (s, 3 H), 1.94 (ddd, *J* = 1.1, 1.1, 1.1 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.0 (C), 169.8 (C), 168.3 (C), 146.3 (CH), 139.5 (C), 130.8 (CH), 127.3 (C), 80.0 (C), 67.9 (CH_2), 52.2 (CH_3), 43.8 (CH), 42.3 (CH_2), 38.3 (CH_2), 20.8 (CH_3), 17.3 (CH_3)

HRMS (ESI+): Calculated for $C_{15}H_{18}O_6Na^+$: 317.0996; Observed: 317.1007

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 17.3, 23.2 min

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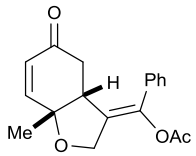
Bicyclic enone 3.63g



Cyclohexadienone **3.62g** was cyclized using general method F to give **3.63g** after flash column chromatography. This product has been reported previously.[26]

HPLC (CHIRALCEL AS, 10% isopropanol in hexanes, 1 mL/min, λ = 254 nm) T_R = 14.0, 23.7 min

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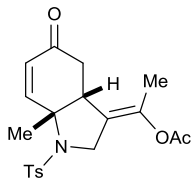
Bicyclic enone 3.63i



Cyclohexadienone **3.62i** was cyclized using general method F to give **3.63i** after flash column chromatography (2:1 hexanes/EtOAc). The configuration of **3.63i** was confirmed by NOE and HMBC NMR experiments.

IR (thin film) 3041, 2967, 2925, 1752, 1687, 1337, 1206, 1158, 1096, 731, 674 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 7.2 Hz, 2 H), 7.17 (d, *J* = 10.3 Hz, 1 H), 6.00 (d, *J* = 10.3 Hz, 1 H), 4.11 (dq, *J* = 14.3, 1.7 Hz, 1 H), 3.95–3.92 (m, 1 H), 2.95 (dd, *J* = 12.4, 5.1 Hz, 1 H), 2.40 (s, 3 H), 2.32 (dd, *J* = 16.2, 5.1 Hz,

1 H), 2.14 (s, 3 H), 2.13 (dd, J = 16.1, 12.6 Hz, 1 H), 1.86 (t, J = 1.8 Hz, 3 H), 1.51 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.2 (C), 168.3 (C), 148.4 (CH), 143.9 (C), 140.8 (C), 137.3 (C), 129.8 (CH × 2), 128.8 (CH), 127.1 (CH × 2), 122.3 (C), 63.7 (C), 49.2 (CH), 48.5 (CH_2), 38.7 (CH_2), 26.1 (CH_3), 21.7 (CH_3), 20.9 (CH_3), 16.8 (CH_3)

HRMS (ESI+): Calculated for $C_{20}H_{23}NO_5SNa^+$: 412.1189; Observed: 412.1181

HPLC (CHIRALCEL OD-H, 5% ethanol in hexanes, 1 mL/min, λ = 225 nm) T_R = 21.5, 22.6 min

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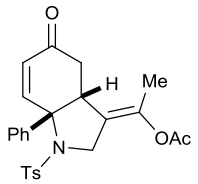
Bicyclic enone 3.63j



Cyclohexadienone **3.62j** was cyclized using general method F to give **3.63j** after flash column chromatography (3:1 hexanes/EtOAc).

IR (thin film) 2960, 2926, 2869, 1755, 1686, 1598, 1339, 1156, 1097, 1066, 762 cm^{-1}

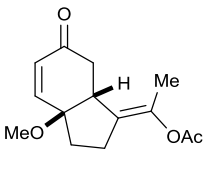
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2 H), 7.39–7.30 (m, 5 H), 7.27–7.24 (m, 3 H), 6.20 (d, J = 10.3 Hz, 1 H), 4.31 (dq, J = 14.3, 1.6 Hz, 1H), 4.13–4.07 (m, 1 H), 3.37 (dd, J = 11.8, 5.0 Hz, 1 H), 2.41 (s, 3 H), 2.32 (dd, J = 16.3, 5.0 Hz, 1 H), 2.12 (s, 3 H), 1.94 (dd, J = 16.2, 11.8 Hz, 1 H), 1.68 (t, J = 1.7 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.0 (C), 168.2 (C), 147.0 (CH), 144.0 (C), 142.3 (C), 140.6 (C), 137.1 (C), 129.8 (CH × 2), 129.2 (CH), 129.0 (CH × 2), 128.2 (CH), 127.0 (CH × 2), 126.1 (CH × 2), 121.5 (C), 70.4 (C), 51.6 (CH), 49.8 (CH_2), 38.8 (CH_2), 21.7 (CH_3), 20.9 (CH_3), 16.7 (CH_3)

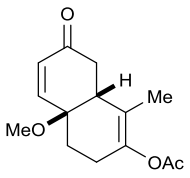
HRMS (ESI+): Calculated for $C_{25}H_{25}NO_5SNa^+$: 474.1346; Observed: 474.1351

HPLC (CHIRALCEL OD, 10% isopropanol in hexanes, 1 mL/min, λ = 254 nm) T_R = 17.6, 24.7 min

Bicyclic enones 3.63k and 3.89k



3.63k

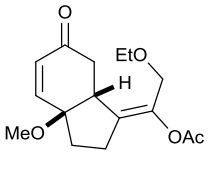


3.89k

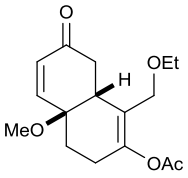
Cyclohexadienone **3.62k** was cyclized using the general method to give a mixture of **3.63k** and **3.90k** after flash column chromatography (5:1 hexanes/EtOAc). Products **3.63k** and **3.90k** were not separable. The ^{1}H NMR data for the mixture of **major** (**3.63k**) and *minor* (**3.90k**) product is listed below. The listed proton count is with respect to the individual molecules. For multiplets that cannot be distinguished, the total proton count (**major** & *minor*) from the spectrum is given.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, *J* = 10.4 Hz, 1 H, **major**), 6.79 (d, *J* = 10.3 Hz, 1 H, *minor*), 6.08 (dd, *J* = 10.3, 0.9 Hz, 1 H, *minor*), 6.05 (dd, *J* = 10.4, 1.0 Hz, 1 H, **major**), 3.34 (dd, *J* = 12.8, 6.1 Hz, 1 H, **major**), 3.25 (s, 3 H, *minor*), 3.23 (s, 3 H, **major**), 2.90–2.79 (m, 2 H, *minor*), 2.67 (ddd, *J* = 16.7, 6.2, 1.0 Hz, 1 H, **major**), 2.57–2.35 (m, 2.1 H total, **major** & *minor*), 2.34 (dd, *J* = 16.6, 12.8 Hz, 1 H, **major**), 2.28 (dd, *J* = 17.5, 13.6 Hz, 1 H, *minor*), 2.14 (s, 3 H, *minor*), 2.11 (s, 3 H, **major**), 2.10–1.85 (m, 5.9 H total, **major** & *minor*)

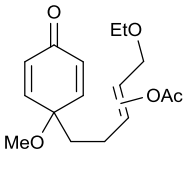
Bicyclic enones 3.63l and 3.89l, and vinyl acetate 3.90



3.63l



3.89l



3.90

Cyclohexadienone **3.62l** was cyclized using the general method to give **3.63l**, **3.89l**, and **3.91** after flash column chromatography (3:1 hexanes/EtOAc). Products **3.89l** and **3.90** were not separable, but the ^{1}H NMR resonances were resolved enough to assign. Product **3.63l** could not be purified enough to obtain a reliable NMR spectrum. The diagnostic peaks are listed below.

3.63l (diagnostic peaks):

^{1}H NMR (300 MHz) δ 6.88 (d, *J* = 10.4 Hz, 1 H), 6.07 (dd, *J* = 10.4, 0.8 Hz, 1 H), 2.28 (ddd, *J* = 16.8, 6.3, 0.8 Hz, 1 H), 2.28 (dd, *J* = 16.7, 13.1 Hz, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H)

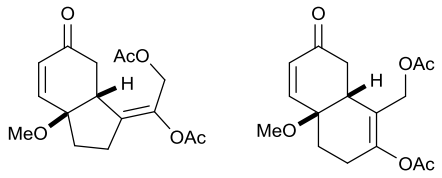
3.89l:

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 10.3 Hz, 1 H), 6.10 (d, *J* = 10.3 Hz, 1 H), 3.98 (d, *J* = 12.0 Hz, 1 H), 3.84 (d, *J* = 12.0 Hz, 1 H), 3.50–3.30 (m, 2 H), 3.25 (s, 3 H), 2.91 (dd, *J* = 16.9, 4.8 Hz, 1 H), 2.57–2.45 (m, 1 H), 2.28 (dd, *J* = 16.9, 13.0 Hz, 1 H), 2.25–2.10 (m, 2 H), 2.16 (s, 3 H), 2.05–1.85 (m, 2 H), 1.17 (t, *J* = 7.0 Hz, 3H)

3.90:

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (d, *J* = 10.3 Hz, 2 H), 6.37 (d, *J* = 10.3 Hz, 2 H), 5.21 (t, *J* = 6.5 Hz, 1 H), 3.87–3.81 (m, 2 H), 3.50–3.30 (m, 2 H), 3.20 (s, 3 H), 2.25–2.10 (m, 2 H), 2.14 (s, 3 H), 2.05–1.85 (m, 2 H), 1.17 (t, *J* = 7.0 Hz, 3 H)

Bicyclic enones 3.63m and 3.89m



3.63m **3.89m**

Cyclohexadienone **3.62m** was cyclized using the general method to give a mixture of **3.63m** and **3.89m** after flash column chromatography (2:1 hexanes/EtOAc). Product **3.63m** was not completely separable from **3.89m**, but the ^{1}H NMR resonances were resolved enough to assign. The resonances listed for **3.63m** were present in the spectrum of the mixture and could be attributed to the minor component. Other resonances were not distinguishable from the baseline or were coincidental with the resonances for **3.89m**. The configuration of **3.89m** was confirmed by NOE and HMBC NMR experiments.

3.63m:

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, *J* = 10.4 Hz, 1 H), 4.82 (d, *J* = 13.1 Hz, 1 H), 3.66 (dd, *J* = 13.0, 6.3 Hz, 1 H), 3.24 (s, 3 H), 2.15 (s, 3 H), 2.06 (s, 3 H)

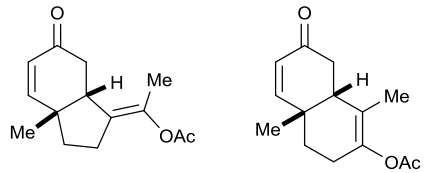
^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 130.9, 110.2, 61.1, 51.4, 44.2, 42.3, 34.9, 29.8, 27.2, 20.8

3.89l:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 10.3 Hz, 1 H), 6.11 (dd, *J* = 10.3, 0.7 Hz, 1 H), 4.57 (d, *J* = 12.5 Hz, 1 H), 4.54 (d, *J* = 12.4 Hz, 1H), 3.25 (s, 3 H), 3.17 (dd, *J* = 12.8, 4.2 Hz, 1 H), 2.88 (ddd, *J* = 16.9, 4.6, 0.7 Hz, 1 H), 2.56–2.49 (m, 1 H), 2.32 (dd, *J* = 16.9, 13.0 Hz, 1 H), 2.26–2.21 (m, 1 H), 2.17 (s, 3 H), 2.04 (s, 3 H), 1.98–1.93 (m, 2 H);

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 197.4 (C), 170.8 (C), 168.9 (C), 154.4 (CH), 148.0 (C), 131.3 (CH), 118.9 (C), 73.9 (C), 59.4 (CH_2), 50.8 (CH_3), 42.0 (CH_2), 37.2 (CH), 27.8 (CH_2), 24.2 (CH_2), 21.0 (CH_3), 20.9 (CH_3)

Bicyclic enones 3.63n and 3.89n

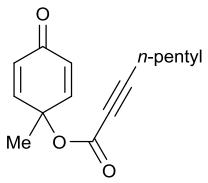


3.63n **3.89n**

Cyclohexadienone **3.62n** was cyclized using general method F to give a mixture of **3.63n** and **3.89n** after flash column chromatography (195:5 hexanes/acetone). Products **3.63n** and **3.89n** were not separable. The ^{1}H NMR data for the mixture of **major** (**3.63n**) and *minor* (**3.89n**) product is listed below. The listed proton count is with respect to the individual molecules. For multiplets that cannot be distinguished the total proton count (**major** & *minor*) from the spectrum is given.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, *J* = 10.2 Hz, 1 H, **major**), 6.61 (d, *J* = 10.1 Hz, 1 H, *minor*), 5.91 (d, *J* = 10.1 Hz, 1 H, *minor*), 5.89 (d, *J* = 10.2 Hz, 1 H, **major**), 2.82 (dd, *J* = 11.0, 6.1 Hz, 1 H, **major**), 2.72–2.23 (m, 6.4 H total, **major** & *minor*), 2.14 (s, 3 H, *minor*), 2.11 (s, 3 H, **major**), 1.95–1.78 (m, 4.5 H total, **major** & *minor*), 1.70–1.60 (m, 2 H, *minor*), 1.60–1.50 (m, 2 H, **major**), 1.20 (s, 3 H, *minor*), 1.16 (s, 3 H, **major**)

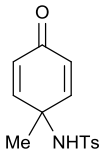
Alkynoate-tethered cyclohexadienone 3.67



2-Octynoic acid (100 μL, 0.686 mmol) and DMF (1 drop) were dissolved in CH_2Cl_2 and cooled to 0 ºC. Oxalyl chloride (59 μL, 0.687 mmol) was added and the solution was stirred for 2 h at rt. MgO (55.3 mg, 1.37 mmol) and quinol **2.17a** (46 mg, 0.37 mmol) were added and the mixture was heated to reflux and stirred overnight. The reaction mixture was concentrated under reduced pressure and the remaining residue was purified by flash-column chromatography (3:1 hexanes/EtOAc) to provide **3.67** (68.4 mg, 75% yield) as a tan solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J = 9.8 Hz, 2 H), 6.25 (d, J = 10.2 Hz, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 1.60 (s, 3 H), 1.59–1.55 (m, 2 H), 1.41–1.29 (m, 4 H), 0.91 (t, J = 6.9 Hz, 3 H)

Cyclohexadienone 3.70i



Quinone imine acetal **3.69**[28] (804 mg, 2.62 mmol) was dissolved in THF and cooled to –78 ºC. MeLi (1.6 M in diethyl ether, 1.96 mL, 3.14 mmol) was added and the solution was stirred for 1.5 h. The reaction was monitored by TLC using alumina plates and, when no starting material remained, 10% aq. HCl (20 mL) was added and the reaction mixture was allowed to warm to rt while stirring overnight. The THF was removed under reduced pressure and the resulting solids were dissolved in diethyl ether; washed with saturated aq. $NaHCO_3$, water, and brine; dried over $MgSO_4$; filtered; and concentrated under

[28] Banfield S. C.; Kerr, M. A. *Can. J. Chem.* **2004**, *82*, 131–138.

reduced pressure. The resulting residue was purified by flash column chromatography (gradient 1:1 hexanes/EtOAc to 100% EtOAc) to give cyclohexadienone **3.70i** (480 mg, 66% yield) as a white powder.

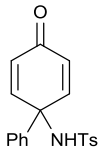
IR (thin film) 3129, 1662, 1617, 1335, 1160, 1094, 1047, 866 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 6.66 (d, *J* = 10.0 Hz, 2 H), 6.02 (d, *J* = 10.1 Hz, 2 H), 5.64–5.61 (m, 1 H), 2.42 (s, 3 H), 1.43 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 150.7 (CH × 2), 144.4 (C), 137.4 (C), 129.8 (CH × 2), 128.2 (CH × 2), 127.9 (CH × 2), 54.6 (C), 27.8 (CH_3), 21.7 (CH_3)

HRMS (ESI+): Calculated for $C_{14}H_{15}NO_3SNa^+$: 300.0665; Observed: 300.0663

Cyclohexadienone 3.70j



Magnesium turnings (139 mg, 5.72 mmol) were activated by flame drying under vacuum. THF (5 mL) was added, followed by bromobenzene (0.49 mL, 4.66 mmol). The mixture was stirred for 30 min, and then transferred via cannula to a solution of quinone imine acetal **3.69**[28] (292 mg, 0.950 mmol) in THF (5 mL) at –78 ºC. The reaction was monitored by TLC using alumina plates and, after 20 min, 10% aq. HCl was added and the reaction mixture was allowed to warm to rt over 1 h. The mixture was then extracted with diethyl ether and EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from hexanes/EtOAc to give cyclohexadienone **3.70j** (250 mg, 78% yield) as a white solid. Alternatively, the crude material was of sufficient purity to use without further purification.

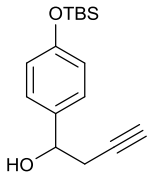
IR (thin film) 3089, 2878, 1657, 1611, 1489, 1399, 1334, 1156, 968, 750 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2 H), 7.45–7.42 (m, 2 H), 7.37–7.33 (m, 3 H), 7.28–7.25 (m, 2 H), 6.78 (d, *J* = 10.2 Hz, 2 H), 6.07 (d, *J* = 10.2 Hz, 2 H), 5.45 (s, 1 H), 2.43 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 185.0 (C), 148.8 (CH × 2), 144.4 (C), 137.9 (C), 137.4 (C), 129.8 (CH × 2), 129.6 (CH × 2), 129.3 (CH), 128.03 (CH × 2), 127.99 (CH × 2), 125.9 (CH × 2), 59.9 (C), 21.8 (CH_3)

HRMS (ESI+): Calculated for $C_{19}H_{17}NO_3SNa^+$: 362.0821; Observed: 362.0823

Benzyl alcohol 3.71



Activated zinc[29] (830 mg, 12.7 mmol) was suspended in THF (20 mL) and cooled to 0 ºC. Propargyl bromide (80% w/w in toluene, 1.88 mL, 12.7 mmol) was added, followed by $TiCl_4$ (1 M in CH_2Cl_2, 0.21 mL, 0.21 mmol). The reaction mixture was stirred for 5 min before a solution of benzaldehyde **3.70**[30] (1.0 g, 4.2 mmol) in THF (20 mL) was added. The mixture was stirred for an additional 1 h before the reaction was quenched with saturated aq. NH_4Cl (20 mL). The reaction mixture was then extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5:1 hexanes/EtOAc) to give benzyl alcohol **3.71** (1.08 g, 93% yield).

IR (thin film) 3386, 3307, 2956, 2933, 2858, 1608, 1511, 1258, 914, 839 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 4.82 (t, *J* = 6.4 Hz, 1 H), 2.63–2.60 (m, 2 H), 2.38 (bs, 1 H), 2.07 (t, *J* = 2.6 Hz, 1 H), 0.98 (s, 9 H), 0.19 (s, 6 H)

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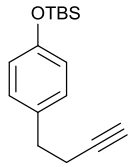
[29] Prepared as described in: Armarego W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, Butterworth Heinemann, Sydney, 2003, p. 497.

[30] Kwong, C. K.-W.; Huang, R.; Zhang, M.; Shi M.; Toy, P. H. *Chem. Eur. J.* **2007**, *13*, 2369–2376.

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 155.6 (C), 135.3 (C), 127.1 (CH × 2), 120.1 (CH × 2), 81.0 (C), 72.2 (CH), 70.9 (CH^{31}), 29.5 (CH_2), 25.8 (CH_3 × 3), 18.3 (C), −4.3 (CH_3 × 2)

HRMS (ESI+): Calculated for $C_{16}H_{24}O_2SiNa^+$: 299.1438; Observed: 299.1426

Alkyne 3.72



A solution of alcohol **3.71** (1.0 g, 3.6 mmol) and Et_3SiH (1.7 mL, 11 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 ºC and $BF_3{\cdot}OEt_2$ (1.4 mL, 11 mmol) was added dropwise. The mixture was stirred for 2 h before the reaction was quenched with saturated aq. $NaHCO_3$ (10 mL). After stirring for an additional 20 min, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered through a plug of silica gel, and concentrated under reduced pressure to give alkyne **3.72** (853 mg, 91% yield).

IR (thin film) 3309, 3027, 2959, 2935, 2858, 1609, 1510, 1510, 1256, 915, 838, 780 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.3 Hz, 2 H), 6.77 (d, *J* = 8.5 Hz, 2 H), 2.78 (t, *J* = 7.6 Hz, 2 H), 2.44 (td, *J* = 7.6, 2.6 Hz, 2 H), 1.97 (t, *J* = 2.6 Hz, 1 H), 0.98 (s, 9 H), 0.19 (s, 5 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.2 (C), 133.3 (C), 129.4 (CH × 2), 120.0 (CH × 2), 84.2 (C), 68.9 (CH^{31}), 34.2 (CH_2), 25.8 (CH_3 × 3), 21.0 (CH_2), 18.3 (C), −4.3 (CH_3 × 2)

HRMS (ESI+): Calculated for $C_{16}H_{24}OSiNa^+$: 283.1489; Observed: 283.1490

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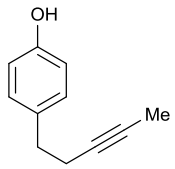
[31] While the size of the ^{13}C peak suggests an attached proton, this peak does not appear in the DEPT spectra. This is expected for a terminal alkyne CH: Simpson, J. H. *Organic Structure Determination Using 2-D NMR Spectroscopy: A Problem-Based Approach,* Academic Press, Boston, 2008, ch. 6, p. 115.

Phenol 3.73k



TBS ether **S14** (400 mg, 1.45 mmol) was dissolved in DMF (14 mL, not anhydrous) and treated with $LiOH \cdot H_2O$ (183 mg, 4.36 mmol). The reaction mixture was stirred overnight and then diluted with EtOAc and washed with brine. The aqueous layer was acidified with 2% aq. HCl and extracted with EtOAc. The combined organic extracted were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5:1 hexanes/EtOAc) to give phenol **3.73k** (200 mg, 86% yield).

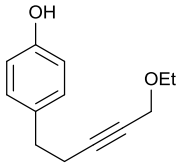
IR (thin film) 3375, 3021, 2919, 2857, 1656, 1612, 1514, 1445, 1235, 825 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 6.22 (s, 1 H), 2.73 (t, *J* = 7.6 Hz, 2 H), 2.39 (tq, *J* = 7.6, 2.5 Hz, 2 H), 1.79 (t, *J* = 2.5 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.0 (C), 133.2 (C), 129.6 (CH × 2), 115.3 (CH × 2), 79.0 (CH), 76.4 (C), 34.7 (CH_2), 21.3 (CH_2), 3.54 (CH_3)

HRMS (ESI-): Calculated for $C_{11}H_{11}O^-$: 159.0815; Observed: 159.0819

Phenol 3.73l



TBS ether **S15** (230 mg, 0.722 mmol) was dissolved in DMF (7 mL, not anhydrous). $LiOH \cdot H_2O$ (91 mg, 2.2 mmol) was added and the mixture was stirred overnight. It was then diluted with EtOAc; washed with water, 10% aq. HCl, and brine; dried over Na_2SO_4; filtered; and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5:1 hexanes/EtOAc) to give phenol **3.73l** (135 mg, 92% yield) as a colorless oil.

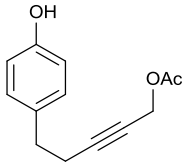
IR (thin film) 3376, 3014, 2974, 2924, 2860, 2222, 1612, 1595, 1514, 1442, 1226, 1065, 1007, 824 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.5 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 5.70–5.67 (m, 1 H), 4.13 (t, *J* = 2.1 Hz, 2 H), 3.55 (q, *J* = 7.0 Hz, 2 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 2.45 (tt, *J* = 7.4, 2.0 Hz, 2 H), 1.22 (t, *J* = 7.0 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.4 (C), 132.6 (C), 129.6 (CH × 2), 115.4 (CH × 2), 86.6 (C), 76.5 (C), 65.5 (CH_2), 58.4 (CH_2), 34.2 (CH_2), 25.7 (CH_2), 21.3 (CH_2), 15.0 (CH_3)

HRMS (ESI+): Calculated for $C_{13}H_{16}O_2Na^+$: 227.1043; Observed: 227.1039

Phenol 3.73m



TBS ether **S17** (108 mg, 0.325 mmol) was dissolved in THF (3 mL) and cooled to 0 ºC. Acetic acid (28 µL, 0.49 mmol) and TBAF (1 M in THF, 0.48 mL, 0.48 mmol) were added and the mixture was stirred for 2 h. The reaction was quenched with saturated aq. $NaHCO_3$ (10 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give phenol **3.73m** (60 mg, 86% yield) as a colorless oil.

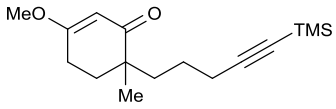
IR (thin film) 3427, 3024, 2937, 2860, 1749, 1719, 1614, 1515, 1223, 1025, 926, 826 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 2 H), 6.77 (d, *J* = 8.5 Hz, 2 H), 5.31 (s, 1 H), 4.66 (t, *J* = 2.1 Hz, 2 H), 2.75 (t, *J* = 7.5 Hz, 2 H), 2.46 (tt, *J* = 7.5, 2.1 Hz, 2 H), 2.10 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 171.4 (C), 154.4 (C), 132.2 (C), 129.5 (CH × 2), 115.3 (CH × 2), 87.2 (C), 74.4 (C), 53.1 (CH_2), 33.8 (CH_2), 21.2 (CH_2), 20.8 (CH_3)

HRMS (ESI+): Calculated for $C_{13}H_{14}O_3Na^+$: 241.0835; Observed: 241.0833

TMS alkyne 3.76



Diisopropyl amine (0.11 mL, 0.78 mmol) was dissolved in THF (2 mL), cooled to 0 ºC, and treated with *n*-BuLi (2.4 M in hexanes, 0.34 mL, 0.82 mmol). The solution was then cooled to –78 ºC and a solution of enone **3.74**[32] (84 mg, 0.60 mmol) in THF (2 mL) was added dropwise. The solution was stirred for 30 min, at which point alkyl iodide **3.75**[33] (334 mg, 1.25 mmol) was added as a solution in THF (2 mL). The reaction mixture was allowed to warm to rt overnight while stirring. The reaction was quenched with saturated aq. NH_4Cl (3 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give alkyne **3.76** (137 mg, 82% yield) as a pale yellow oil.

IR (thin film) 2953, 2172, 1655, 1613, 1373, 1248, 1194, 841, 759 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 1 H), 3.66 (s, 3 H), 2.52–2.32 (m, 2 H), 2.18 (t, *J* = 6.8 Hz, 2 H), 1.90 (dt, *J* = 13.2, 6.4 Hz, 1 H), 1.73 (ddd, *J* = 13.6, 7.8, 5.7 Hz, 1 H), 1.67–1.38 (m, 4 H), 1.07 (s, 3 H), 0.12 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 203.9 (C), 176.5 (C), 107.4 (C), 101.0 (CH), 84.8 (C), 55.7 (CH_3), 43.3 (C), 36.1 (CH_2), 32.3 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 22.3 (CH_3), 20.5 (CH_2), 0.3 (CH_3 × 3)

HRMS (ESI+): Calculated for $C_{16}H_{26}O_2SiNa^+$: 301.1594; Observed: 301.1598

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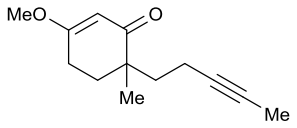
[32] Miyaoka, H.; Kajiwara, Y.; Hara, M.; Suma A.; Yamada, Y. *Tetrahedron: Asymmetry*, **1999**, *10*, 3189–3196.

[33] Baldwin, J. E.; Adlington R. M.; Singh, R. *Tetrahedron*, **1992**, *48*, 3385–3412.

Internal alkyne 3.77[34]



Terminal alkyne **S18** (516 mg, 2.48 mmol) was dissolved in DMSO (16 mL). In a separate flask, *t*-BuOK (834 mg, 7.43 mmol) was also dissolved in DMSO (8 mL). Both solutions were degassed via argon bubbling for 10 min before the *t*-BuOK solution was transferred via syringe to the alkyne solution. The mixture was stirred for 40 min and then cooled to 0 ºC before the reaction was quenched with saturated aq. NH_4Cl (20 mL). The mixture was diluted with brine and extracted with diethyl ether and CH_2Cl_2. The combined organic layers were concentrated under reduced pressure. Residual DMSO was removed by dissolving the residue in CH_2Cl_2 and washing with water and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give internal alkyne **3.77** (434 mg, 84% yield).

IR (thin film) 2918, 2850, 1651, 1611, 1453, 1374, 1194, 1040, 985, 841 cm^{-1}

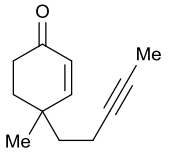
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 1 H), 3.66 (s, 3 H), 2.52–2.32 (m, 2 H), 2.17–1.97 (m, 2 H), 1.91 (dt, *J* = 13.3, 6.5 Hz, 1 H), 1.73 (t, *J* = 2.5 Hz, 3 H), 1.82–1.63 (m, 3 H), 1.06 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 203.2 (C), 176.5 (C), 101.0 (CH), 79.3 (C), 75.7 (C), 55.7 (CH_3), 43.2 (C), 36.4 (CH_2), 32.3 (CH_2), 25.8 (CH_2), 22.1 (CH_3), 14.0 (CH_2), 3.6 (CH_3)

HRMS (ESI+): Calculated for $C_{13}H_{18}O_2Na^+$: 229.1199; Observed: 229.1198

[34] Internal alkyne **3.77** could also be synthesized by sequentially alkylating the methyl enol ether of 1,3-cyclohexadione with methyl iodide and 5-iodopent-2-yne. However, we found this route to be unreliable and low yielding, regardless of the order of alkylation.

Enone 3.78



Vinylogous ester **3.77** (149 mg, 0.715 mmol) was dissolved in toluene (1.5 mL) and cooled to –78 ºC. DIBAL-H (0.14 mL, 0.79 mmol) was added slowly, and then the mixture was allowed to warm to –20 ºC over 1.5 h before the reaction was quenched with methanol (0.5 mL). The reaction mixture was warmed to rt and 10% aq. HCl (0.5 mL) was added. After stirring for 30 min, additional 10% aq. HCl (1 mL) was added. The mixture was stirred for another 2 h, and then diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5:1 hexanes/EtOAc) to give enone **3.78** (125 mg, 99% yield) as a colorless oil.

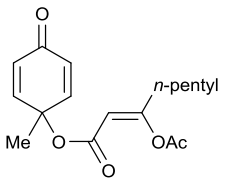
IR (thin film) 3021, 2958, 2933, 2864, 1681, 1451, 1389, 1375, 1239, 1116, 805 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, *J* = 10.2 Hz, 1 H), 5.84 (d, *J* = 10.2 Hz, 1 H), 2.42 (t, *J* = 6.8 Hz, 2 H), 2.18–2.09 (m, 2 H), 1.95 (dt, *J* = 13.8, 7.1 Hz, 1 H), 1.72 (t, *J* = 2.4 Hz, 3 H), 1.76–1.63 (m, 3 H), 1.11 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 199.4 (C), 158.3 (CH), 127.7 (CH), 78.7 (C), 76.2 (C), 40.1 (CH_2), 35.6 (C), 34.1 (CH_2), 33.3 (CH_2), 24.8 (CH_3), 14.1 (CH_2), 3.5 (CH_3)

HRMS (ESI+): Calculated for $C_{12}H_{16}ONa^+$: 199.1093; Observed: 199.1090

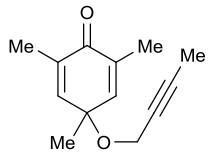
Vinyl acetate 3.86



Cyclohexadienone **3.67** was cyclized using a modification of general method F, where the temperature was 50 ºC, to give **3.86** after flash column chromatography (10:1 hexanes/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 10.2 Hz, 2 H), 6.22 (d, *J* = 10.2 Hz, 2 H), 5.57 (t, *J* = 0.9 Hz), 2.27–2.23 (m, 2 H), 2.20 (s, 3 H), 1.33–1.30 (m, 4 H), 0.91–0.88 (m, 3 H)

Alkyne-tethered cyclohexadienone 3.87



Mesitol (409 mg, 3.00 mmol) was dissolved in 2-butyn-1-ol (3 mL) and cooled to 0 ºC. PIFA (1.54 g, 3.58 mmol) was added in small portions. The mixture was stirred for 30 min, and then diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to give cyclohexadienone **3.87** (436 mg, 71% yield).

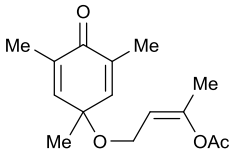
IR (thin film) 2979, 2924, 2858, 2302, 1673, 1644, 1443, 1370, 1073, 1036, 906 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 2 H), 3.86 (q, *J* = 2.4 Hz, 2 H), 1.86 (s, 6 H), 1.79 (t, *J* = 2.4 Hz, 3 H), 1.37 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 186.5 (C), 146.1 (CH × 2), 136.7 (C × 2), 82.8 (C), 75.9 (C), 72.8 (C), 53.7 (CH_2), 26.6 (CH_3), 16.0 (CH_3 × 2), 3.8 (CH_3)

HRMS (ESI+): Calculated for $C_{13}H_{16}O_2Na^+$: 227.1043; Observed: 227.1041

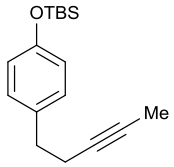
Vinyl acetate 3.88



Cyclohexadienone **3.87** was subjected to the conditions in general method F for 2 days to give a crude product containing **3.88**. Purification was attempted by flash column chromatography (9:1 hexanes/EtOAc); however, while olefin **3.88** was clearly identifiable in the recovered material, it could not be completely separated from impurities.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 2 H), 5.17 (td, *J* = 6.9, 0.9 Hz, 1 H), 3.70 (dd, *J* = 6.9, 0.9 Hz, 2 H), 2.09 (s, 3 H), 1.90 (s, 6 H), 1.89–1.87 (m, 3 H), 1.36 (s, 3 H)

Internal alkyne S14



Alkyne **3.72** (490 mg, 1.88 mmol) was dissolved in THF (18 mL), cooled to –78 ºC, and treated with *n*-BuLi (2.5 M in hexanes, 1.12 mL, 2.82 mmol). The reaction mixture was stirred for 30 min, and then MeI (0.17 mL, 2.7 mmol) was added. The mixture was then allowed to gradually warm to rt and the reaction was monitored by GC.[35] After no starting material remained, the reaction was quenched with saturated aq. NH_4Cl (5 mL) and the mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to give alkyne **S14** (401 mg, 78% yield).

IR (thin film) 2963, 2927, 2858, 1609, 1510, 1257, 916, 837, 781 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.5 Hz, 2 H), 2.73 (t, *J* = 7.7 Hz, 2 H), 2.37 (tq, *J* = 7.7, 2.5 Hz, 2 H), 1.78 (t, *J* = 2.5 Hz, 3 H), 0.98 (s, 9 H), 0.18 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.0 (C), 133.9 (C), 129.4 (CH × 2), 120.9 (CH × 2), 78.9 (CH × 2), 76.2 (C), 34.9 (CH_2), 25.8 (CH_3 × 3), 21.3 (CH_2), 18.3 (C), 3.6 (CH_3), −4.3 (CH_3 × 2)

HRMS (ESI+): Calculated for $C_{17}H_{26}OSiNa^+$: 297.1645; Observed: 297.1639

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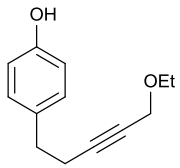
[35] Gas chromatography was performed with a 30 m OPTIMA 5 fused-silica column with a 0.25 µm inner diameter.

Internal alkyne S15



Terminal alkyne **3.72** (265 mg, 1.02 mmol) was dissolved in THF (10 mL), cooled to –78 ºC, and treated with *n*-BuLi (2.4 M in hexanes, 0.46 mL, 1.1 mmol). The reaction mixture was stirred for 30 min, and then chloromethyl ethyl ether (80% purity, 0.14 mL, 1.2 mmol) was added. The mixture was allowed to warm to rt over 2 h, at which point the reaction was quenched with saturated aq. NH_4Cl (10 mL) and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to give ethyl ether **S15** (230 mg, 71% yield) as a colorless oil.

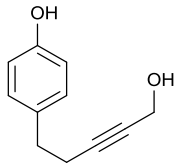
IR (thin film) 3028, 2927, 2855, 1608, 1509, 1471, 1254, 1092, 915, 838, 780 cm^{-1}

^{1}H NMR (300 MHz, CDCl3) δ 7.05 (d, *J* = 8.5 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 4.10 (t, *J* = 2.0 Hz, 2 H), 3.51 (q, *J* = 7.0 Hz, 2 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 2.47 (tt, *J* = 7.6, 2.0 Hz, 2 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 0.97 (s, 9 H), 0.18 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.1 (C), 133.5 (C), 129.4 (CH × 2), 120.0 (CH × 2), 86.1 (C), 76.9 (C), 65.3 (CH_2), 58.4 (CH_2), 34.4 (CH_2), 25.8.3 (CH_3 × 3), 21.3 (CH_2), 18.3 (C), 15.2 (CH_3), −4.29 (CH_3 × 2)

HRMS (ESI+): Calculated for $C_{19}H_{30}O_2SiNa^+$: 341.1907; Observed: 341.1902

Propargylic alcohol S16



Terminal alkyne **3.72** (240 mg, 0.921 mmol) was dissolved in THF (6 mL) and cooled to –78 ºC. *n*-BuLi (2.4 M in hexanes, 0.42 mL, 1.0 mmol) was added, the solution was

stirred for 30 min. Paraformaldehyde (83 mg, 2.8 mmol) was added and the mixture was allowed to warm to rt while stirring overnight. The reaction was then quenched with saturated aq. NH_4Cl (20 mL) and the mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (4:1 hexanes/EtOAc) to give propargylic alcohol **S16** (180 mg, 67% yield) as a colorless oil.

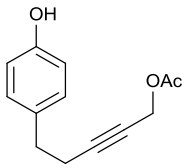
IR (thin film) 3290, 3027, 2855, 1608, 1509, 1470, 1169, 1012, 839, 781 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.5 Hz, 2 H), 6.76 (d, *J* = 8.4 Hz, 2 H), 4.23 (dt, *J* = 6.0, 2.1 Hz, 2 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 2.47 (tt, *J* = 7.6, 2.1 Hz, 2 H), 1.49–1.45 (m, 1 H), 0.98 (s, 9 H), 0.18 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 154.0 (C), 133.3 (C), 129.2 ($CH \times 2$), 119.9 ($CH \times 2$), 85.5 (C), 79.1 (C), 50.9 (CH_2), 34.2 (CH_2), 25.7 ($CH_3 \times 3$), 21.1 (CH_2), 18.1 (C), −4.45 ($CH_3 \times 2$)

HRMS (ESI+): Calculated for $C_{17}H_{26}O_2SiNa^+$: 313.1594; Observed: 313.1586

Propargylic acetate S17



Propargylic alcohol **S16** (99 mg, 0.34 mmol) and triethylamine (0.23 mL, 1.7 mmol) were dissolved in CH_2Cl_2 and cooled to 0 ºC. Acetyl chloride (73 µL, 1.0 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched with saturated aq. $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to give propargylic acetate **S17** (108 mg, 96% yield) as a colorless oil.

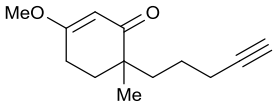
IR (thin film) 3028, 2949, 2930, 2857, 1746, 1608, 1509, 1257, 1024, 915, 837, 781 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.5 Hz, 2 H), 4.65 (t, *J* = 2.2 Hz, 2 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 2.47 (tt, *J* = 7.7, 2.1 Hz, 2 H), 2.09 (s, 3 H), 0.98 (s, 9 H), 0.19 (s, 6 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 170.5 (C), 154.2 (C), 133.3 (C), 129.4 (CH × 2), 120.0 (CH × 2), 87.1 (C), 74.7 (C), 52.9 (CH_2), 34.1 (CH_2), 25.8 (CH_3 × 3), 21.3 (CH_2), 20.9 (CH_3), 18.3 (C), −4.3 (CH_3 × 2)

HRMS (ESI+): Calculated for $C_{19}H_{28}O_3SiNa^+$: 355.1700; Observed: 355.169

Terminal alkyne S18



K_2CO_3 (102 mg, 0.738 mmol) was added to a solution of alkyne **3.76** (137 mg, 0.492 mmol) in methanol (1 mL). The reaction mixture was stirred for 2 h, and then diluted with CH_2Cl_2, filtered through Celite, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3:1 hexanes/EtOAc) to give terminal alkyne **S18** (92 mg, 91% yield) as a colorless oil.

IR (thin film) 3289, 3252, 2937, 2866, 2113, 1650, 1612, 1455, 1377, 1192, 985, 842 cm^{-1}

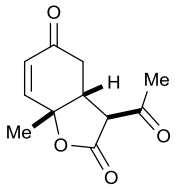
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (s, 1 H), 3.66 (s, 3 H), 2.49–2.32 (m, 2 H), 2.15 (td, *J* = 6.7, 2.6 Hz, 2 H), 1.94–1.86 (m, 2 H), 1.77–1.40 (m, 5 H), 1.07 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 203.8 (C), 176.5 (C), 101.05 (CH), 84.40 (C), 68.5 (CH),[31] 55.7 (CH_3), 43.2 (C), 36.2 (CH_2), 32.2 (CH_2), 25.9 (CH_2), 23.4 (CH_2), 22.4 (CH_3), 19.1 (CH_2)

HRMS (ESI+): Calculated for $C_{13}H_{18}O_2Na^+$: 229.1199; Observed: 229.1190

Experimental Details – Chapter 4

β-Ketoester 4.78



Compound **2.13a** (20 mg, 0.075 mmol) was added to a suspension of NaH (60% in mineral oil, 7.2 mg, 1.8 mmol) in THF (0.75 mL) at 0 °C. After 15 min, acetyl chloride (11 μL, 0.15 mmol) was added. The mixture was allowed to warm to rt and stirred for 16 h, at which point the THF was removed under reduced pressure. The remaining residue[36] was cooled to 0 °C and TFA (2 mL) was added. The solution was allowed to warm to rt and stirred for 4 h. It was then quenched with saturated aq. $NaHCO_3$, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash-column chromatography (3:1 hexanes/EtOAc) to give **4.78** (7.3 mg, 46% yield).

IR (thin film) 2980, 2925, 1769, 1715, 1685, 1372, 1237, 1095, 957 cm^{-1}

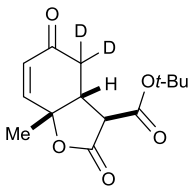
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, *J* = 10.4, 2.1 Hz, 1 H), 6.08 (d, 10.4 Hz, 1 H), 3.52 (d, 12.0 Hz, 1 H), 3.38 (dddd, *J* = 12.0, 5.5, 2.1, 2.1 Hz, 1 H), 2.73 (dd, *J* = 17.7, 5.5 Hz, 1 H), 2.55 (d, *J* = 17.7 Hz, 1 H), 2.46 (s, 3 H), 1.71 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 199.3 (C), 195.0 (C), 169.5 (C), 147.0 (CH), 129.7 (CH), 80.4 (C), 57.8 (CH), 41.9 (CH), 36.3 (CH_2), 30.3 (CH_3), 24.0 (CH_3)

HRMS (ESI–) 207.0663 calcd for $C_{11}H_{11}O_4$, found 207.0684

[36] The crude residue was identified as intermediate **4.77** by ^{1}H NMR.

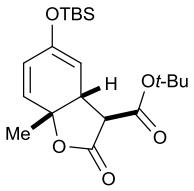
Bis-deuterated enone 4.82



Hexamethydisilazane (34 µL, 0.16 mmol) was dissolved in THF (0.5 mL) and cooled to 0 ºC. *n*-BuLi (2.5 M in hexanes, 66 µL, 0.17 mmol) was added and the solution was stirred for 30 min before being cooled to –78 ºC. In a separate flask, enone **2.13a** (20 mg, 0.075 mmol) was dissolved in THF (0.5 mL) and cooled to –78 ºC. This solution was added to the LHMDS solution and stirred for 30 min. D_2O (0.5 mL) was added and the mixture was allowed to warm to rt. It was then quenched with saturated aq. NH_4Cl, diluted with Et_2O, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was identified by ^{1}H NMR as **4.82**.

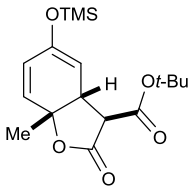
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, J = 10.3, 1.8 Hz, 1 H), 6.09 (d, J = 10.4 Hz, 1 H), 3.35 (d, J = 12.4 Hz, 1 H), 3.32–3.27 (m, 1 H), 1.73 (s, 3 H), 1.50 (s, 9 H)

TBS enol ether 4.85



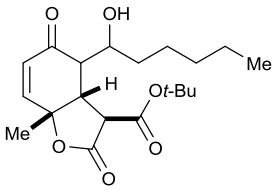
Enone **2.13a** (35 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (0.45 mL) and cooled to 0 ºC. TBSOTf (90 µL, 0.39 mmol) and Et_3N (109 µL, 0.782 mmol) were added and the mixture was stirred until the reaction was complete by TLC (5 h). The mixture was then diluted with CH_2Cl_2, washed with 10% aq. HCl and water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was used immediately.

TMS enol ether 4.86



Diisopropylamide (10.6 μL, 0.075 mmol) was dissolved in THF (0.25 mL) and cooled to 0 ºC. *n*-BuLi (2.5 M in hexanes, 30 μL, 0.075 mmol) was added and the solution was stirred for 30 min before being cooled to –78 ºC. Cyclohexadienone **2.8a** (20 mg, 0.075 mmol) was added as a solution in THF (0.5 mL). The reaction mixture was allowed to warm to rt over 2 h, at which point it was quenched with saturated aq. NH_4Cl. The mixture was diluted with Et_2O, washed with water and brine, and dried over $MgSO_4$. The crude material was used immediately.

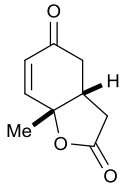
Aldol product 4.88



Cyclopropane **2.23r** (20.2 mg, 0.0764 mmol) and hexanal (9.5 μL, 0.077 mmol) were dissolved in THF (0.75 mL) and cooled to –78 ºC. SmI_2 (0.035 M in THF, 4.5 mL, 0.16 mmol) was added dropwise. The solution was stirred for 2 h at –78 ºC and 2 h at 0 ºC. The mixture was quenched with 10% aq. HCl, extracted with CH_2Cl_2, washed with saturated aq. Na_2SO_3 and water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash-column chromatography (5:1→3:1 hexanes/EtOAc) to provide **4.88** (6.4 mg, 23% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, J = 10.3, 1.8 Hz, 1 H), 6.11 (d, J = 10.4 Hz, 1 H), 3.89–3.84 (m, 1 H), 3.37 (d, J = 11.6 Hz, 1 H), 3.28 (ddd, J = 11.6, 1.9, 1.9 Hz, 1 H), 2.51 (dd, J = 5.9, 2.0 Hz, 1 H), 2.03 (d, J = 4.7 Hz, 1 H), 1.78 (s, 3 H), 1.78–1.72 (m, 2 H), 1.64–1.60 (m, 2 H), 1.51 (s, 9 H), 1.34–1.30 (m, 4 H), 0.92–0.89 (m, 3 H)

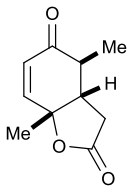
Decarboxylated bicyclic lactone 4.90



Enone **2.13a** (496 mg, 1.86 mmol) was dissolved in TFA (5 mL). The reaction mixture was stirred for 2 h and then the TFA was removed under reduced pressure. The remaining residue was dissolved in THF (5 mL). Et_3N (0.26 mL, 1.9 mmol) was added and the mixture was heated to 50 ºC. After 2 h the reaction mixture was concentrated under reduced pressure. The remaining residue was dissolved in EtOAc; washed with saturated aq. NH_4Cl, water, and brine; and dried over Na_2SO_4 to give **4.90** (284.6 mg, 92% yield) as a tan solid. The crude material was of sufficient purity for use without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, J = 10.3, 1.8 Hz, 1 H), 6.10 (d, J = 10.3, 1 H), 2.99–2.89 (m, 1 H), 2.73 (dd, J = 17.5, 8.1 Hz, 1 H), 2.73–2.64 (m, 2 H), 2.43 (dd, J = 17.5, 11.8 Hz), 1.69 (s, 3 H)

Methylated bicyclic lactone 4.91



Enone **4.90** (284 mg, 1.71 mmol) was dissolved in 10:1 THF/HMPA (17 mL) and cooled to –98 ºC. LDA (1 M in THF, 1.9 mL, 1.9 mmol) was added and the reaction mixture was stirred for 30 min. MeI (0.32 μL, 5.1 mmol) was added and the mixture was allowed to warm to rt overnight. The mixture was quenched with saturated aq. NH_4Cl and concentrated under reduced pressure. The remaining material was diluted with EtOAc, washed with water and brine, and dried over Na_2SO_4. The crude material was purified by

flash-column chromatography (2:1 hexanes/EtOAc) to provide **4.91** (85.8 mg, 28% yield).

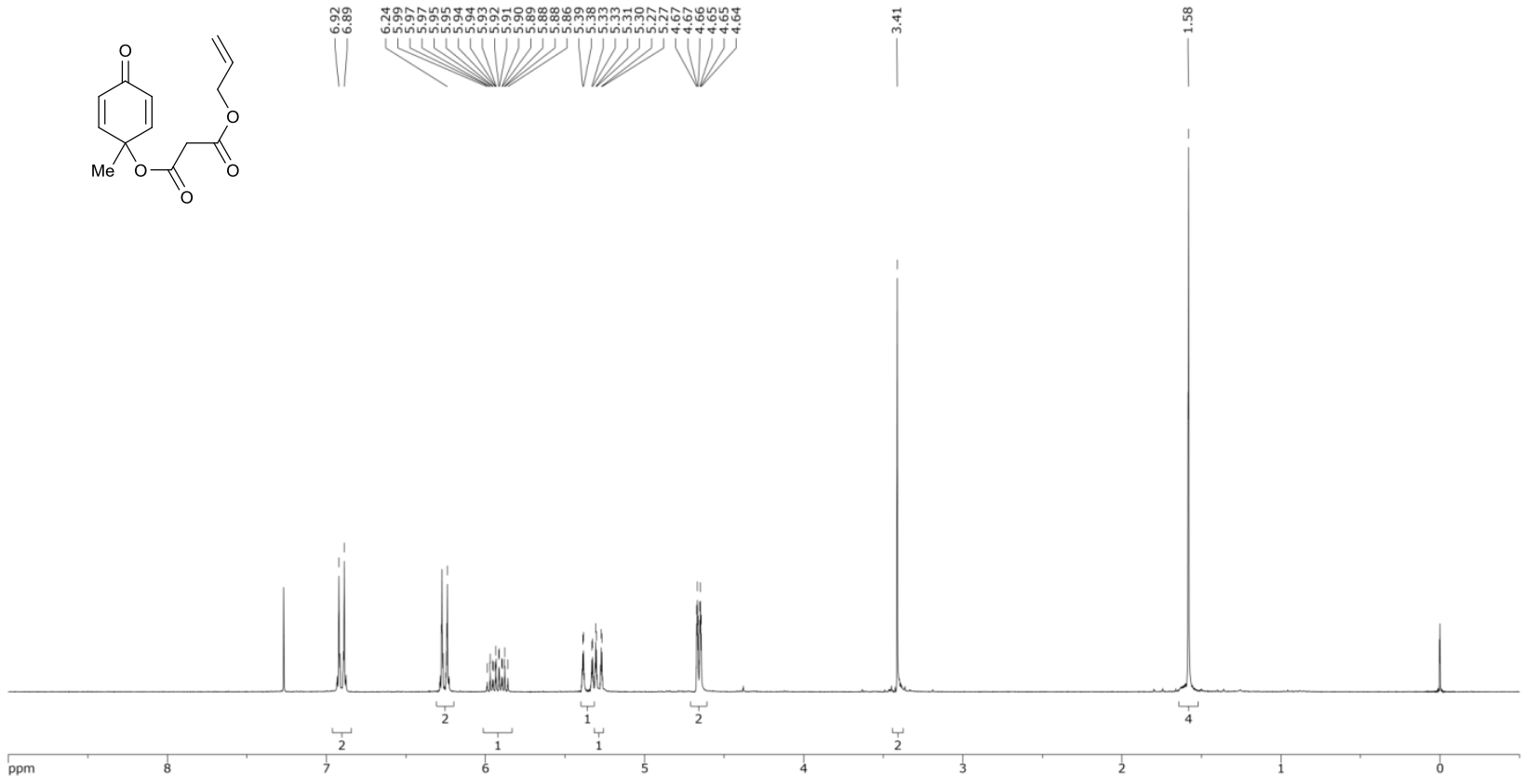
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 10.2 Hz, 1 H), 6.09 (d, *J* = 10.3 Hz, 1 H), 2.93 (dd, *J* = 17.3, 7.4 Hz, 1 H), 2.57–2.46 (m, 3 H), 1.64 (s, 3 H), 1.24 (d, *J* = 6.5 Hz, 3 H)

Appendix II

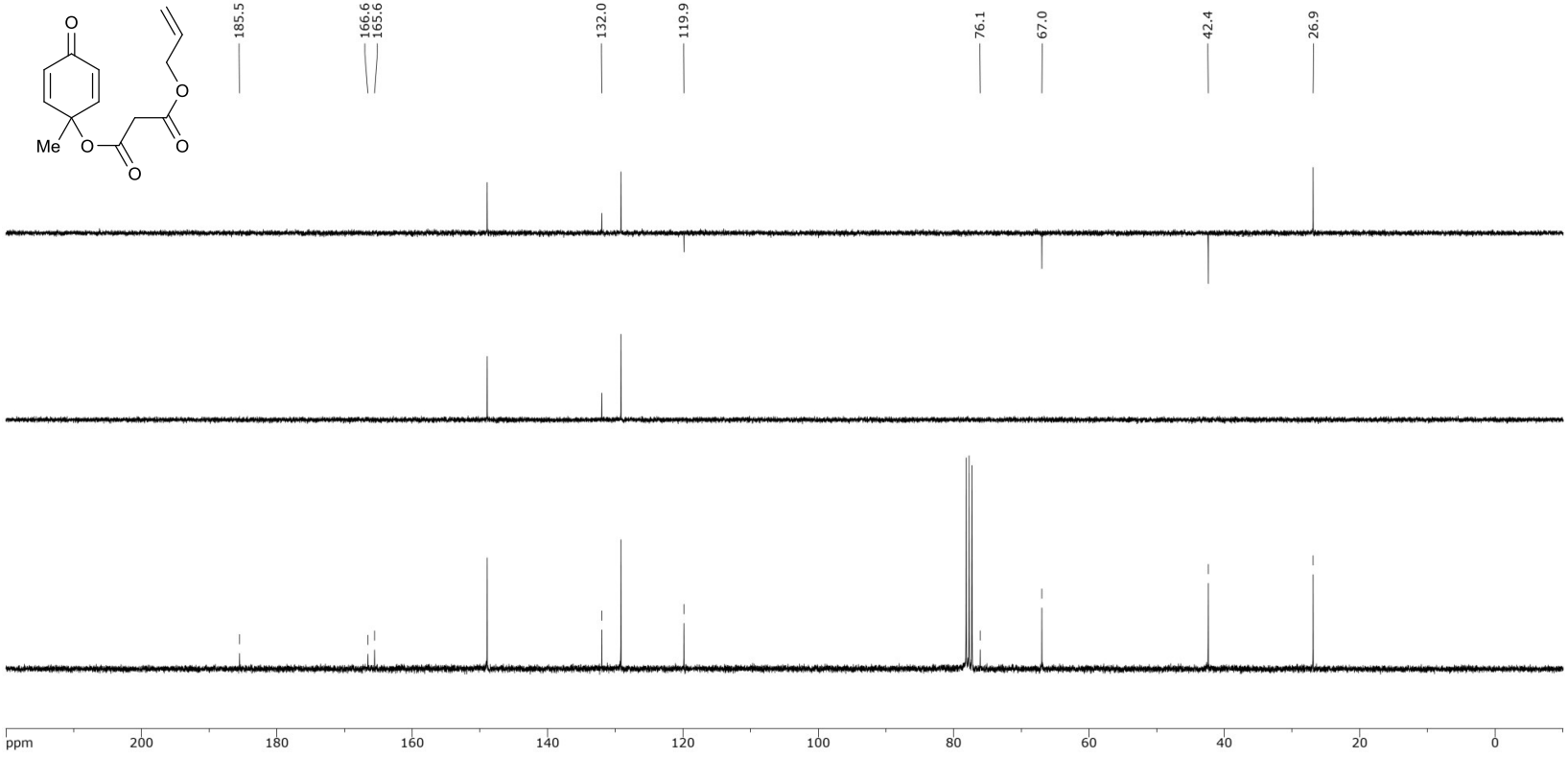
NMR Spectra

NMR Spectra – Chapter 2

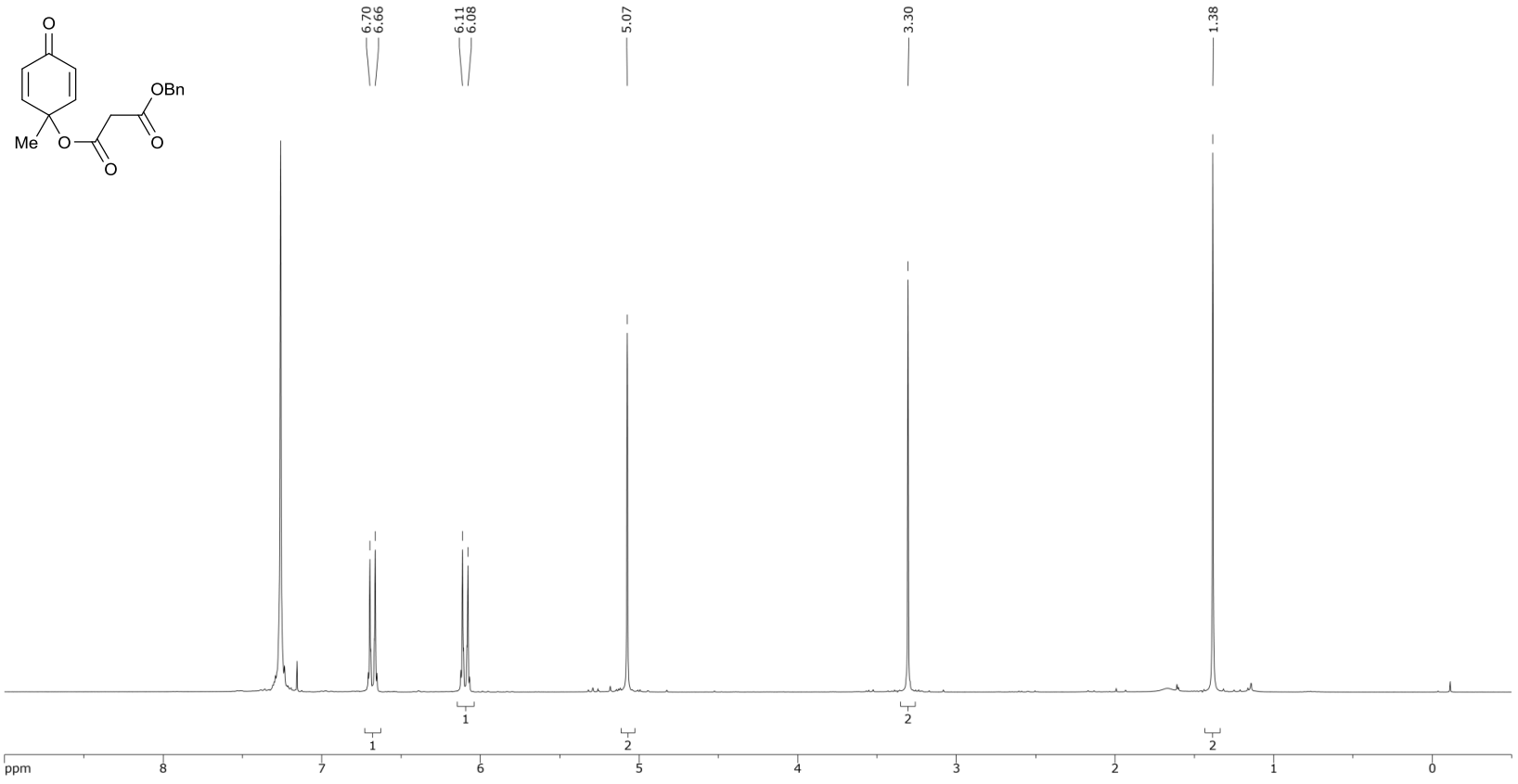
Allyl malonate-tethered cyclohexadienone 2.6 – ^{1}H NMR



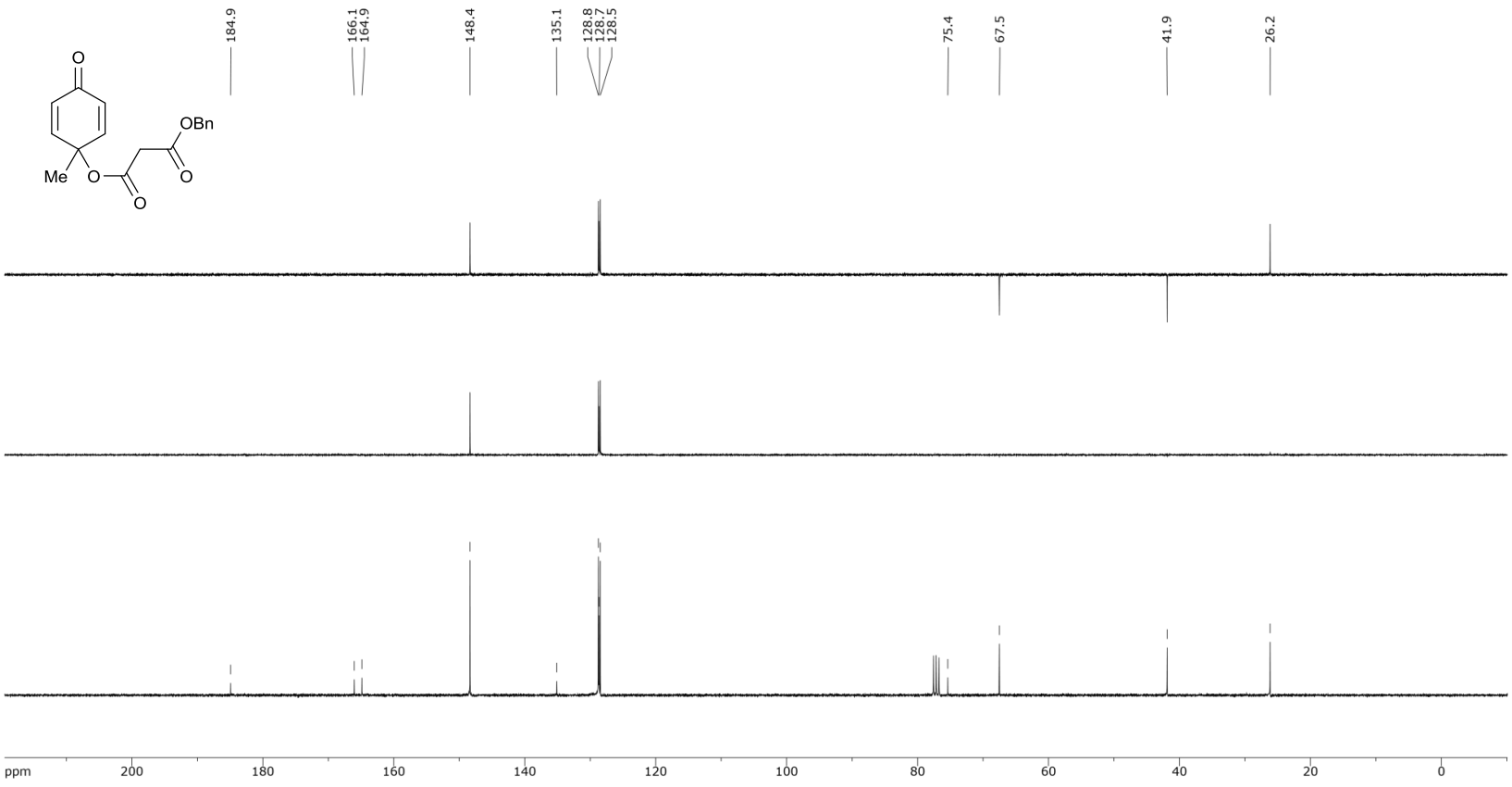
Allyl malonate-tethered cyclohexadienone 2.6 – ^{13}C NMR



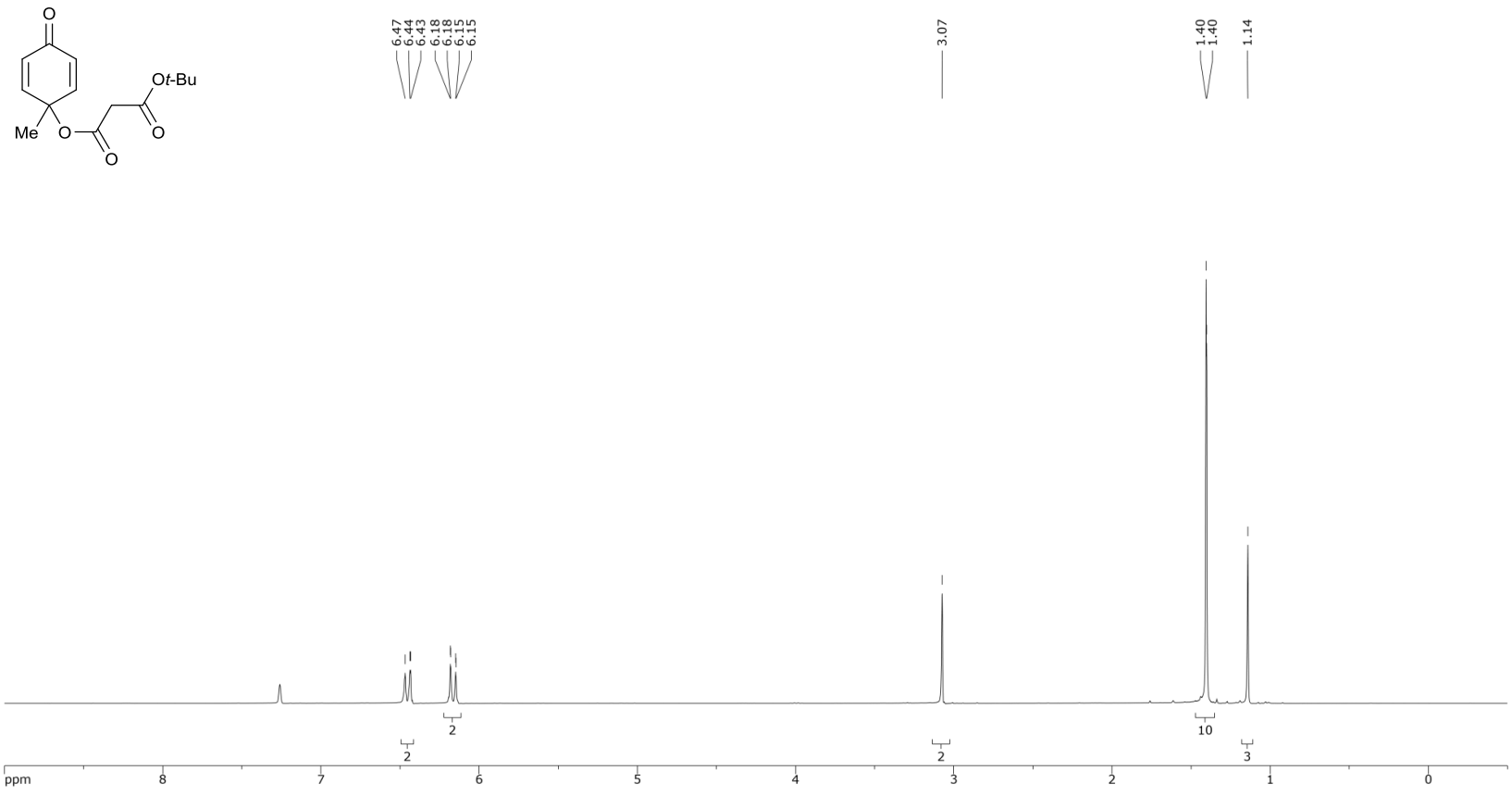
Benzyl malonate-tethered cyclohexadienone 2.7 – ^{1}H NMR



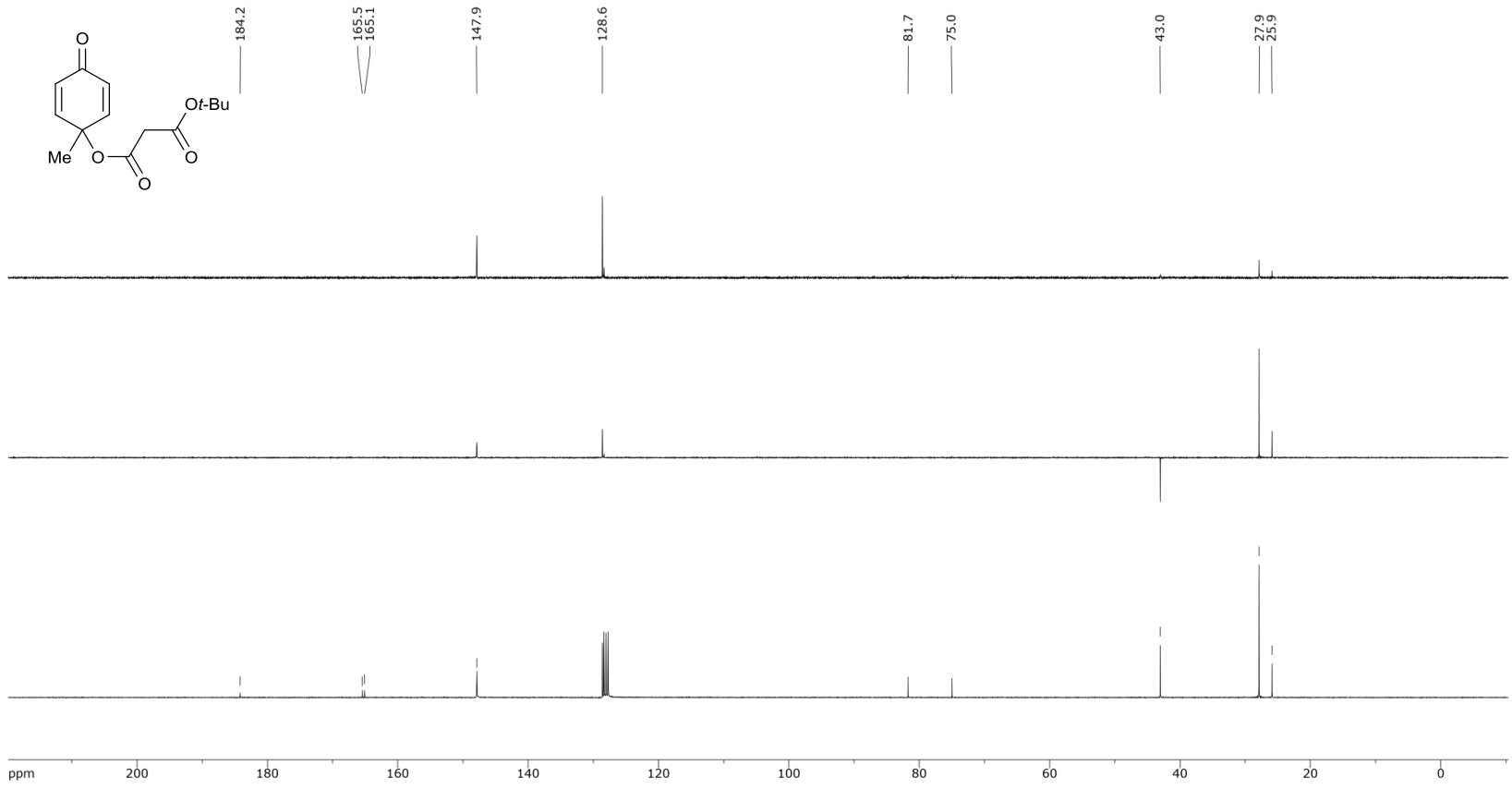
Benzyl malonate-tethered cyclohexadienone 2.7 – ^{13}C NMR



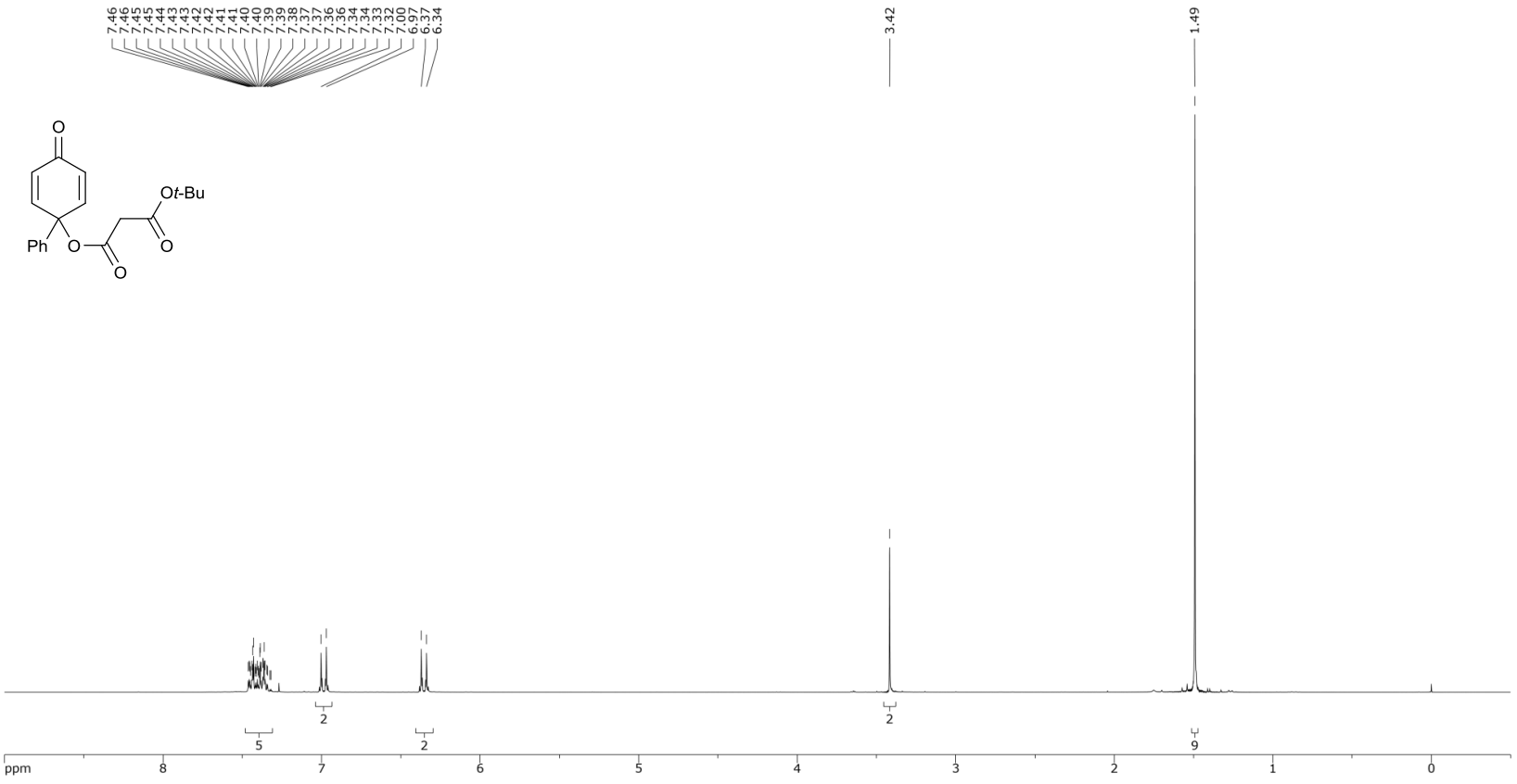
Malonate-tethered cyclohexadienone 2.8a – ^{1}H NMR



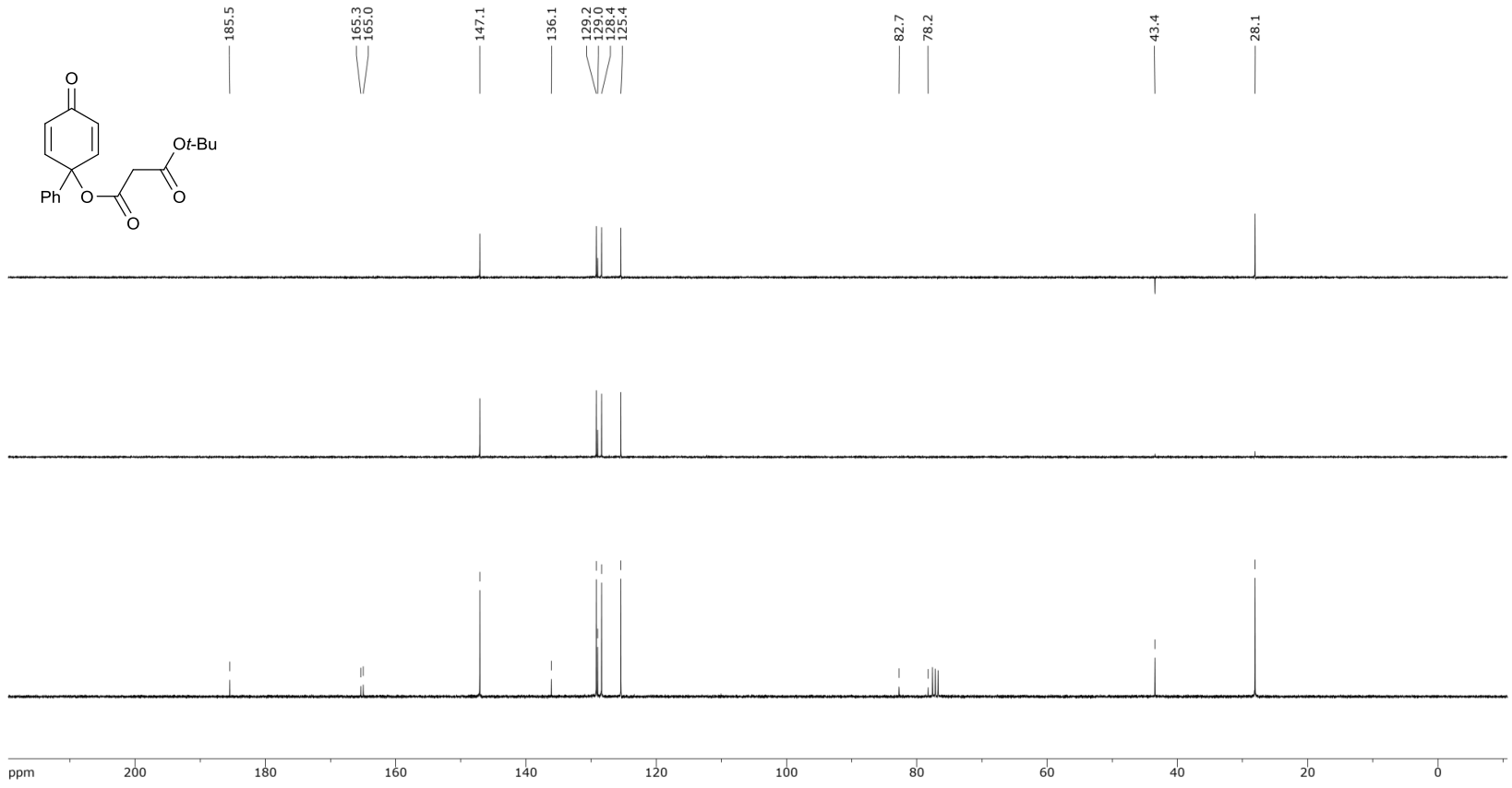
Malonate-tethered cyclohexadienone 2.8a – ^{13}C NMR



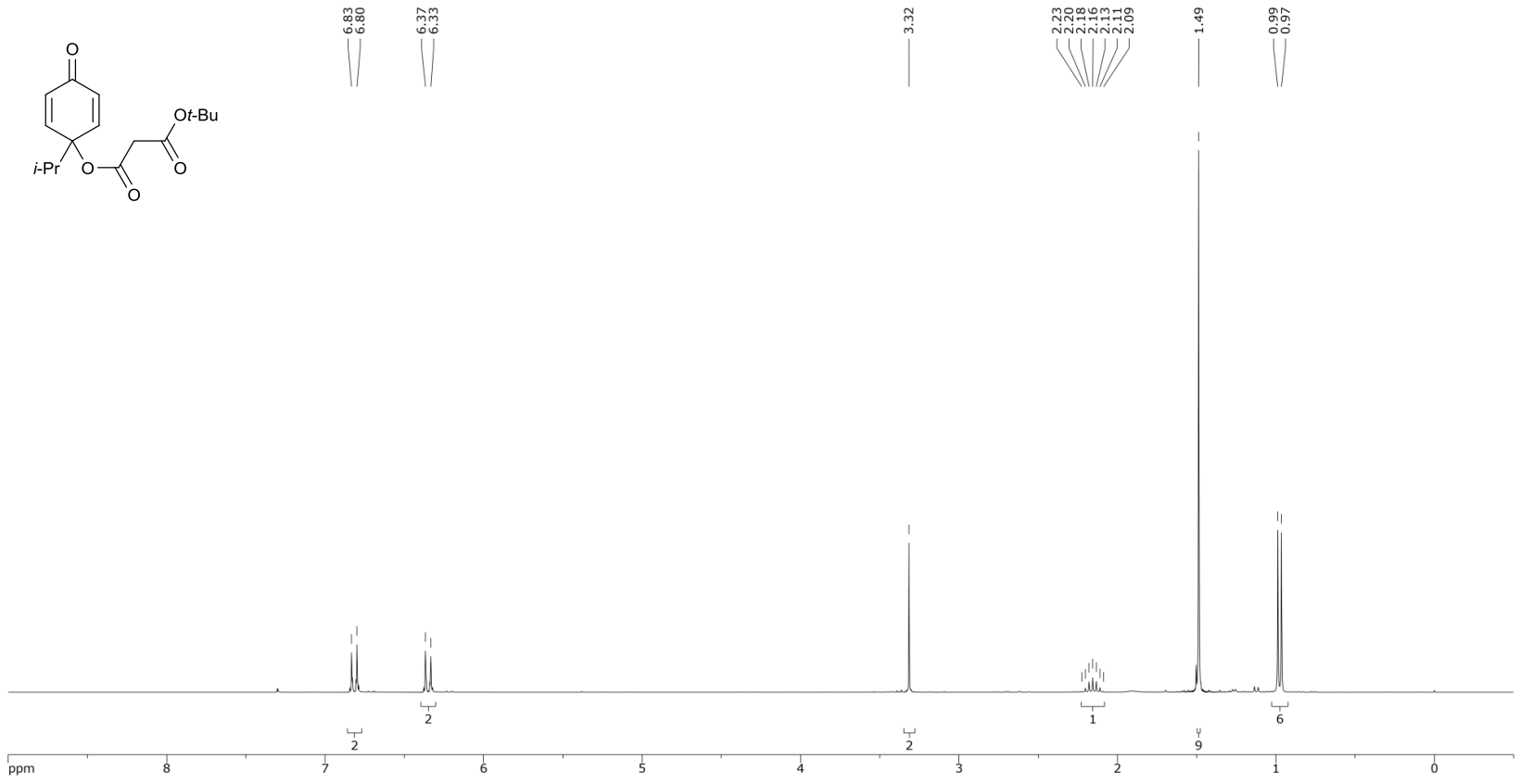
Malonate-tethered cyclohexadienone 2.8b – ^{1}H NMR



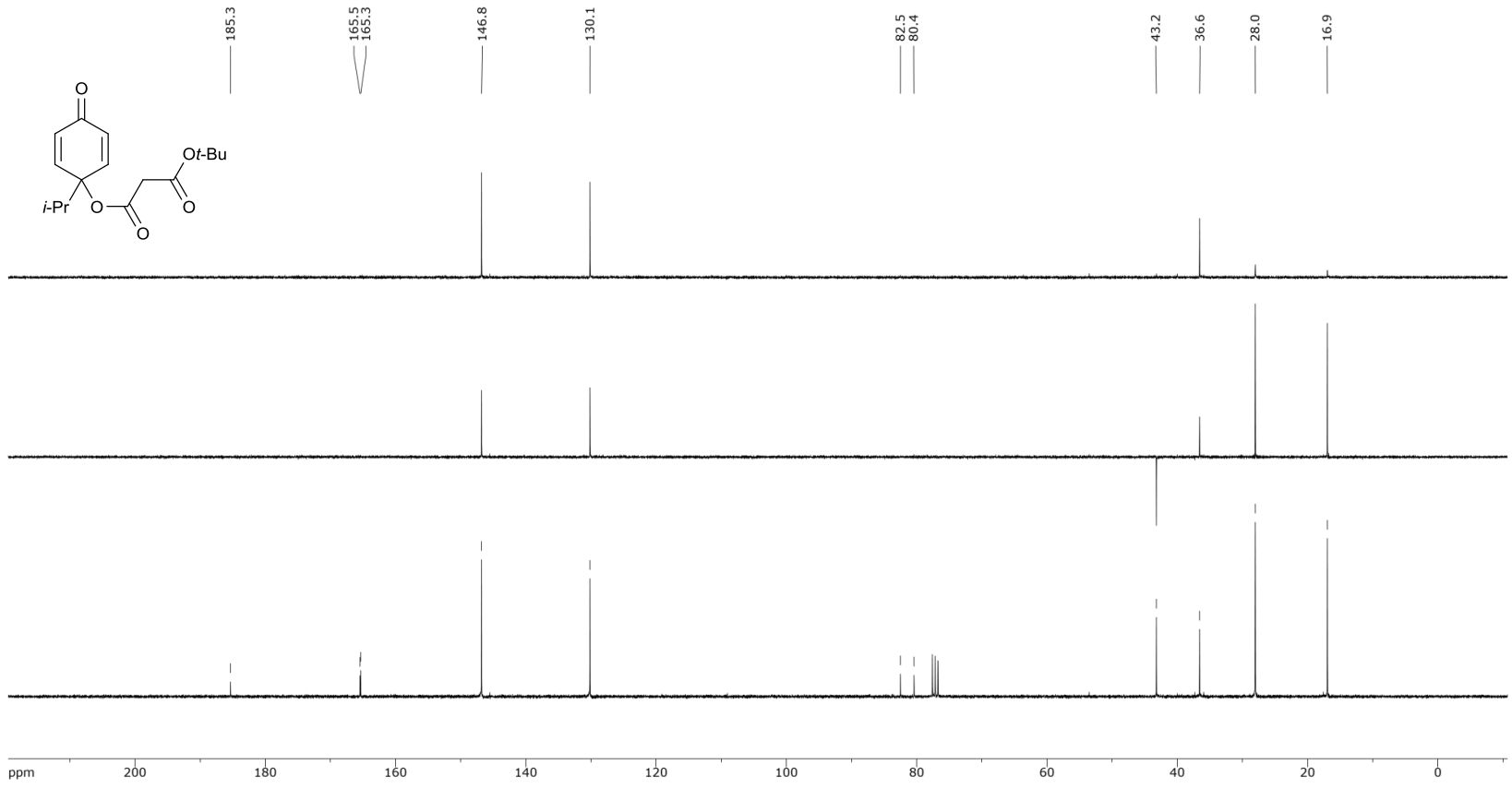
Malonate-tethered cyclohexadienone 2.8b – ^{13}C NMR



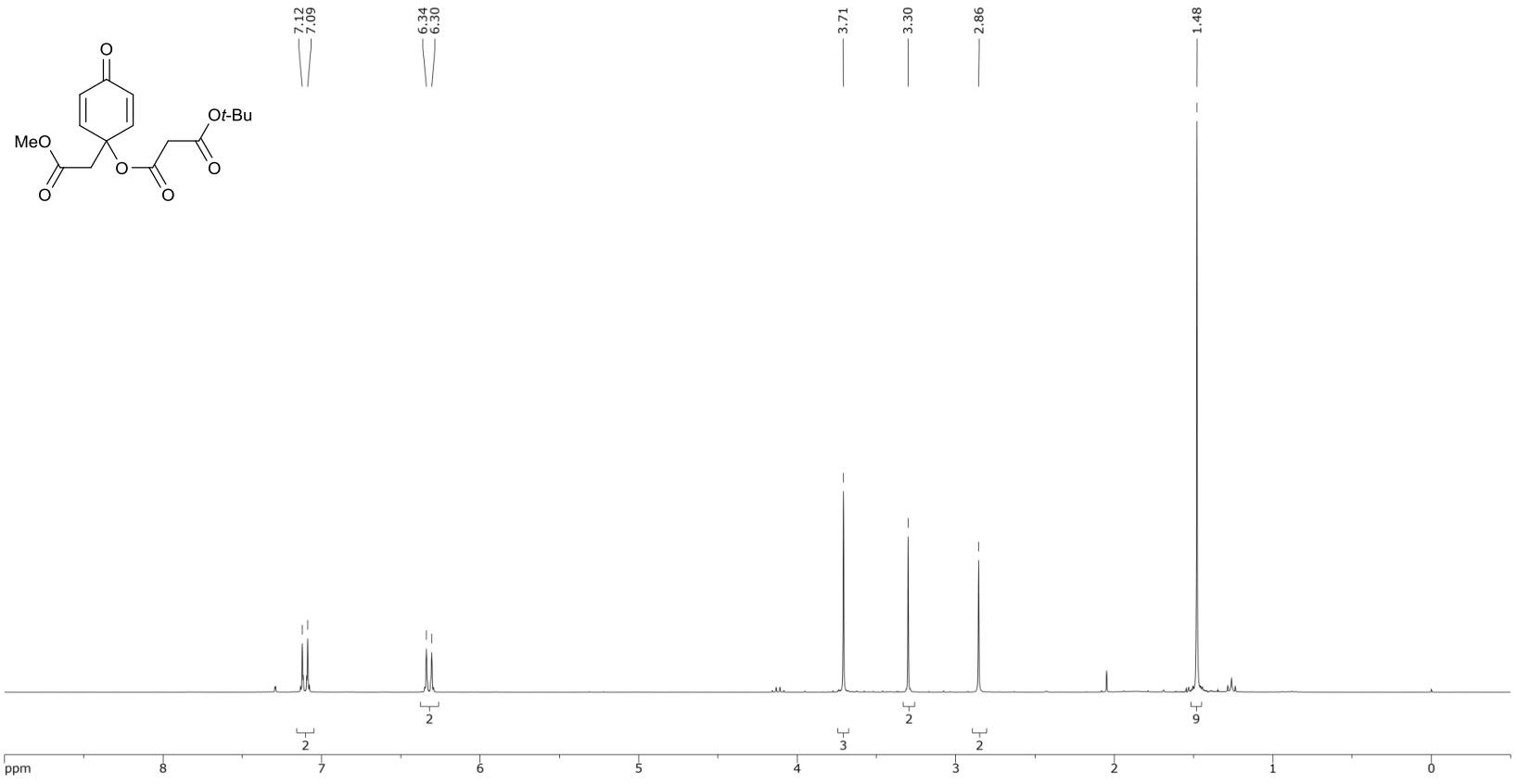
Malonate-tethered cyclohexadienone 2.8c – ^{1}H NMR



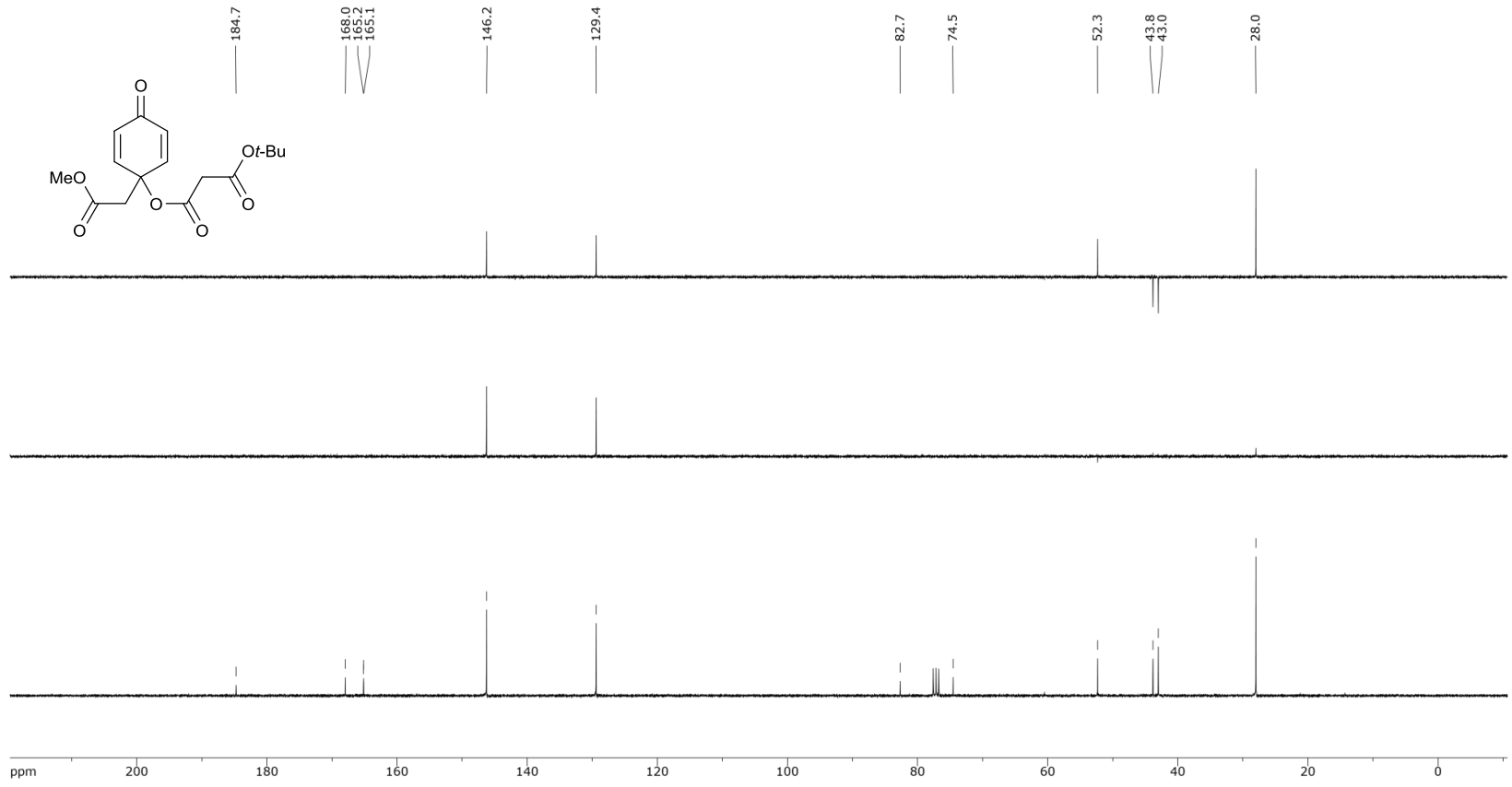
Malonate-tethered cyclohexadienone 2.8c – ^{13}C NMR



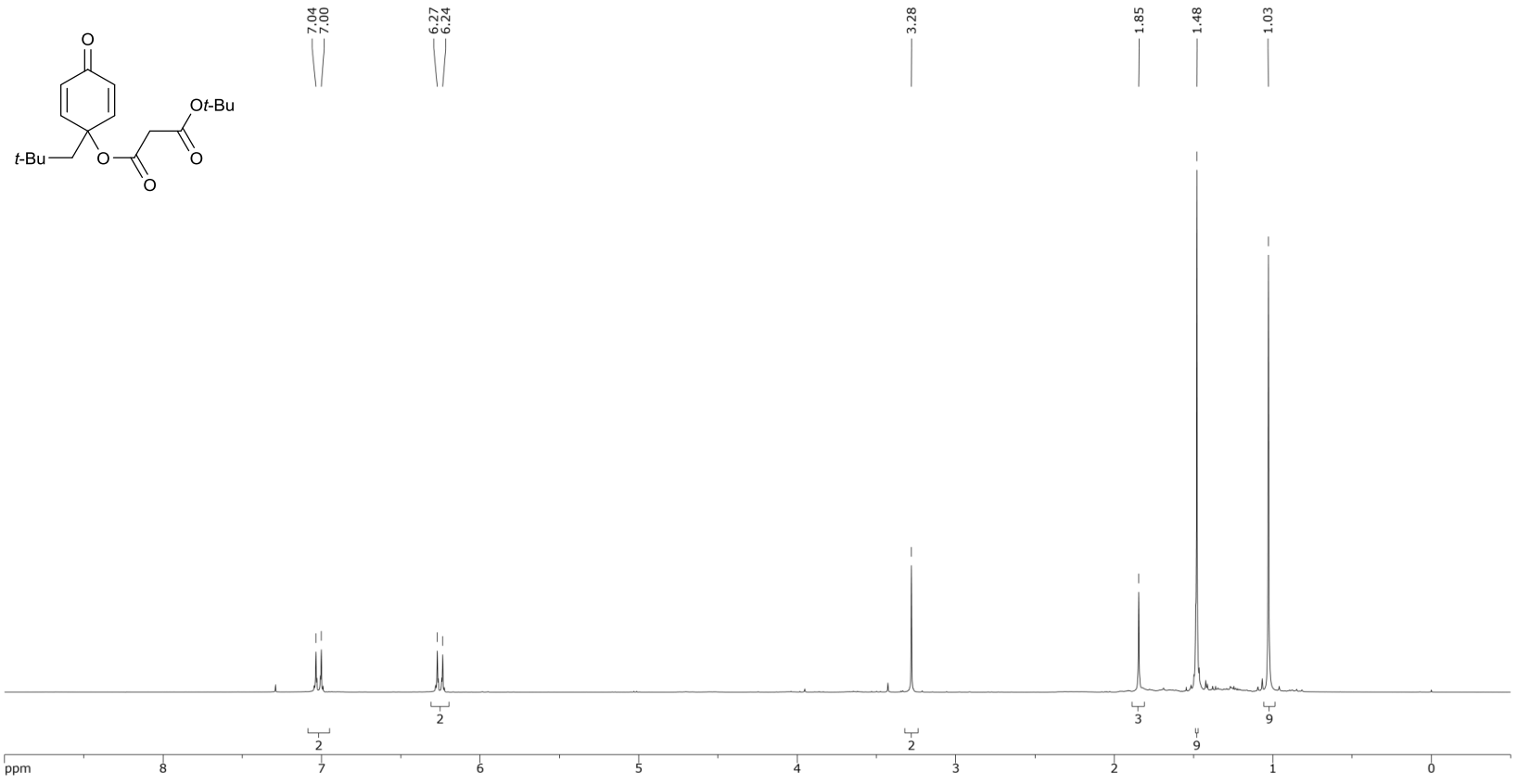
Malonate-tethered cyclohexadienone 2.8d – ^{1}H NMR



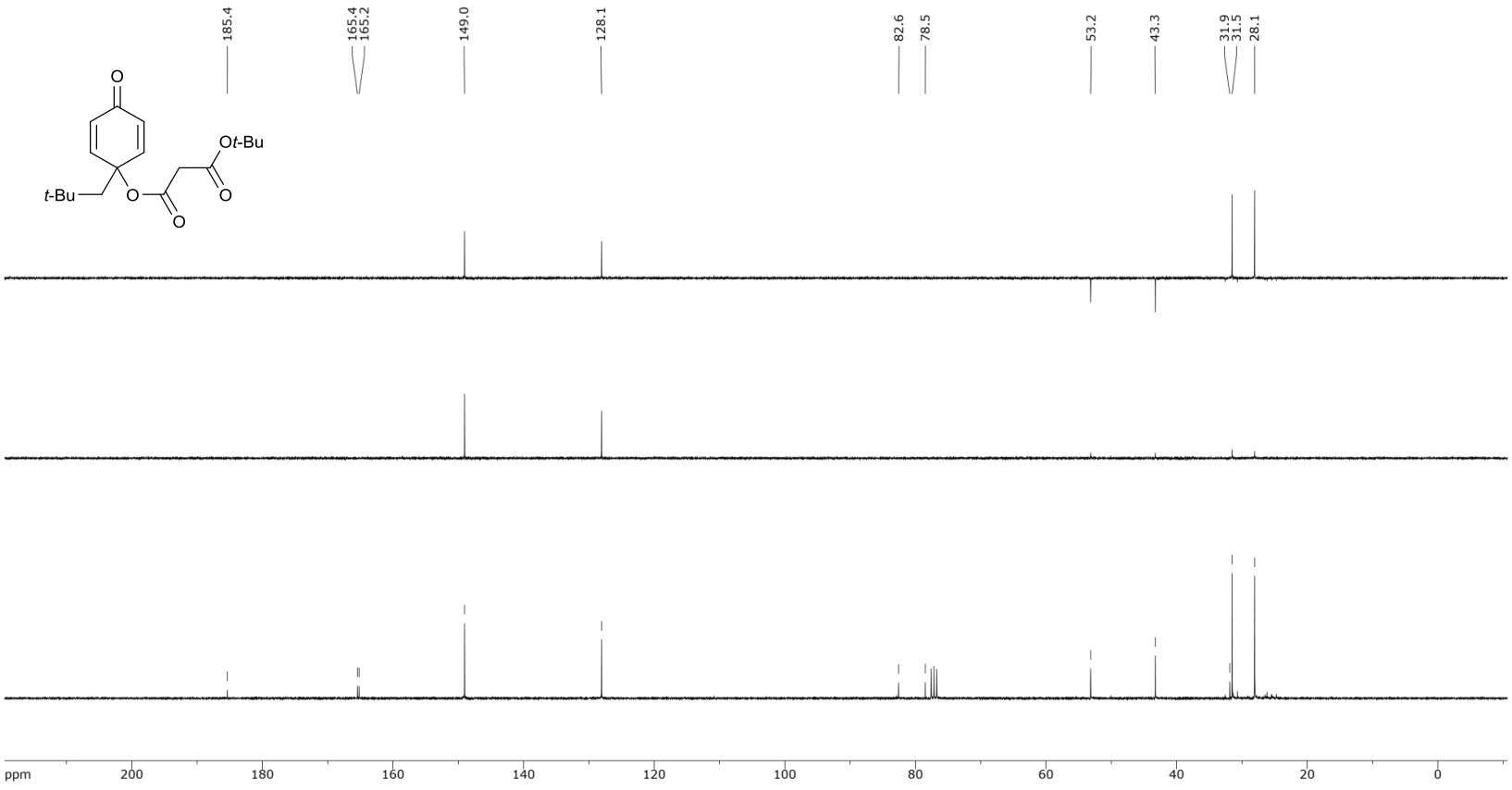
Malonate-tethered cyclohexadienone 2.8d –^{13}C NMR



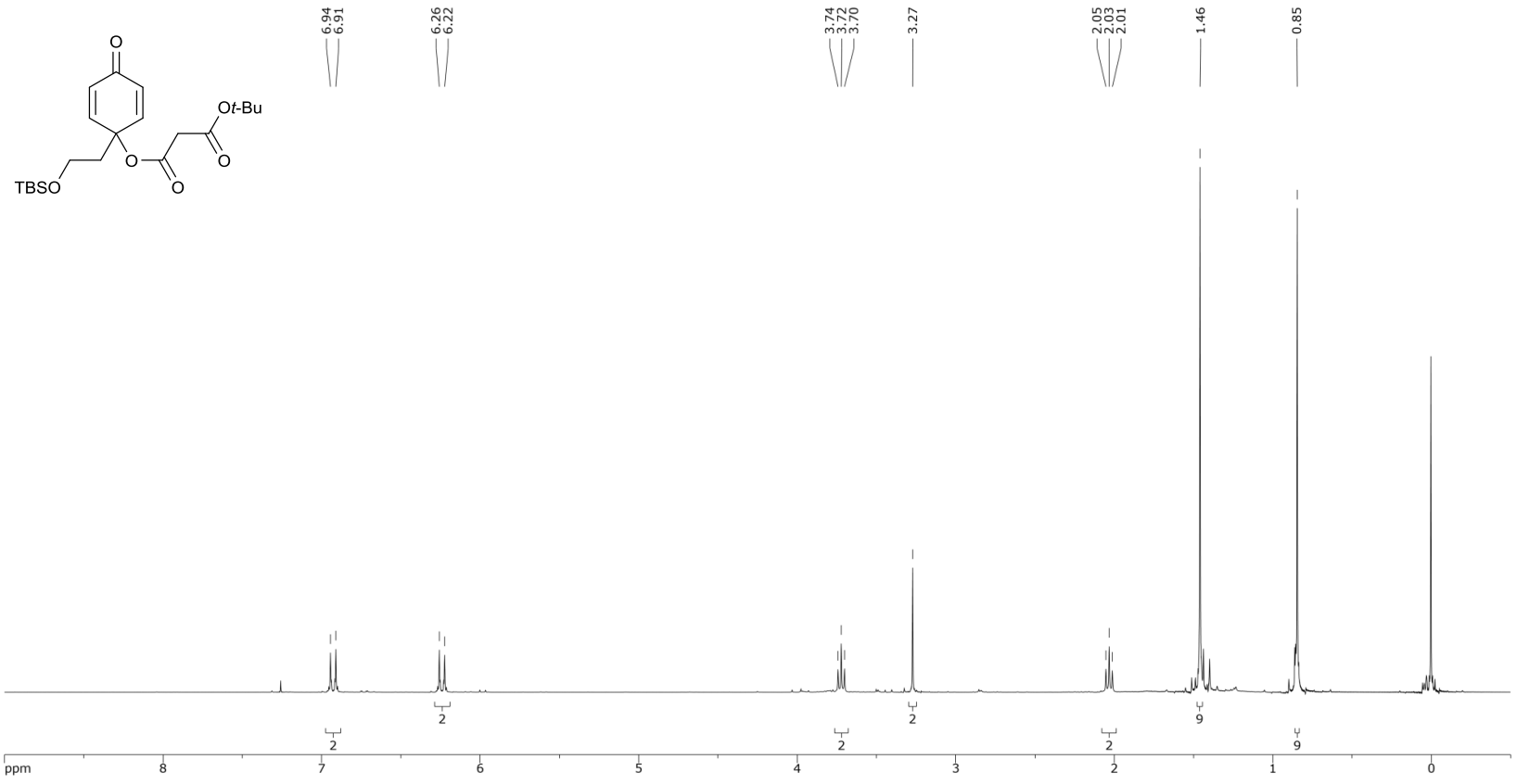
Malonate-tethered cyclohexadienone 2.8e – ^{1}H NMR



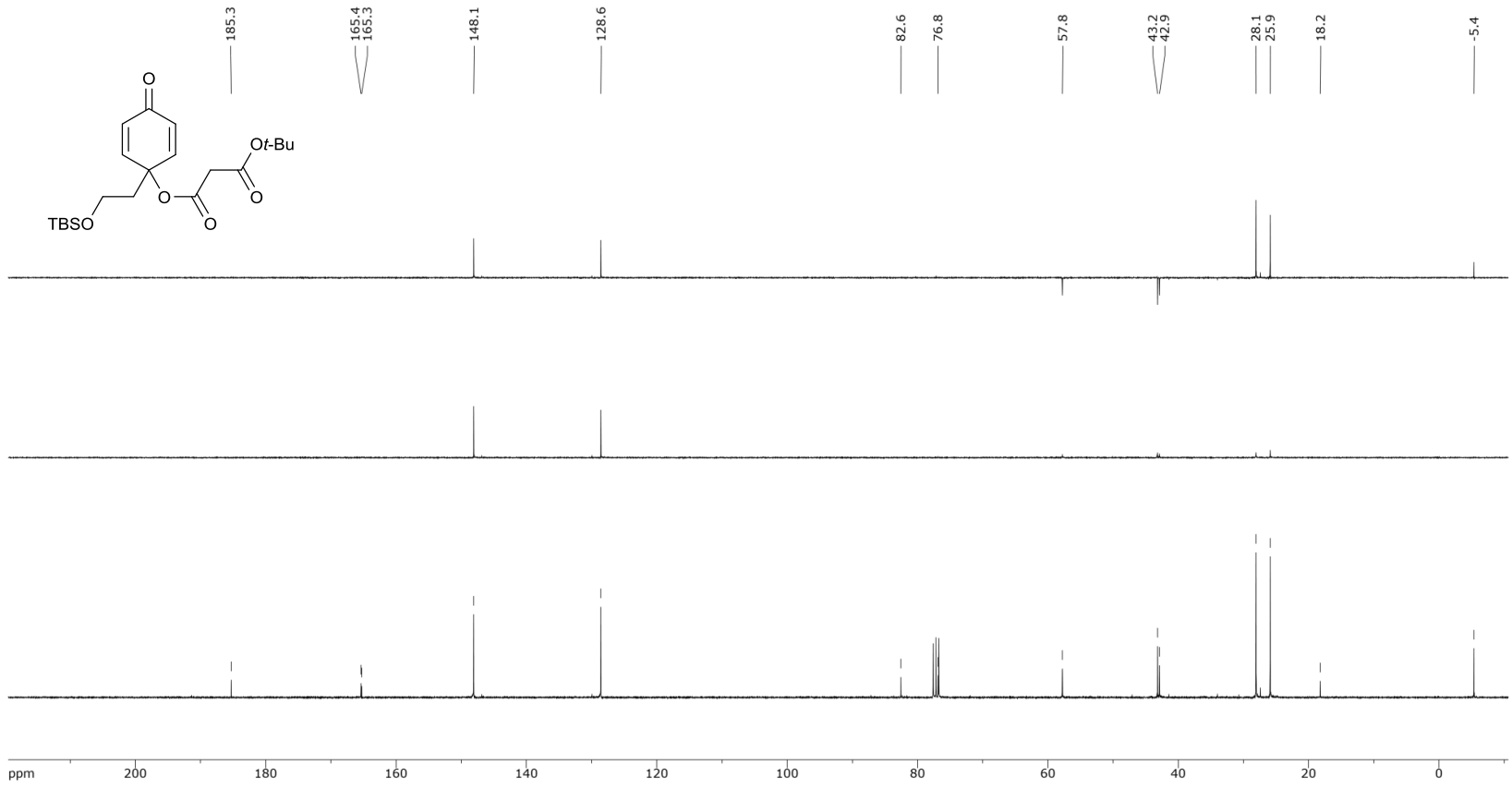
Malonate-tethered cyclohexadienone 2.8e – ^{13}C NMR



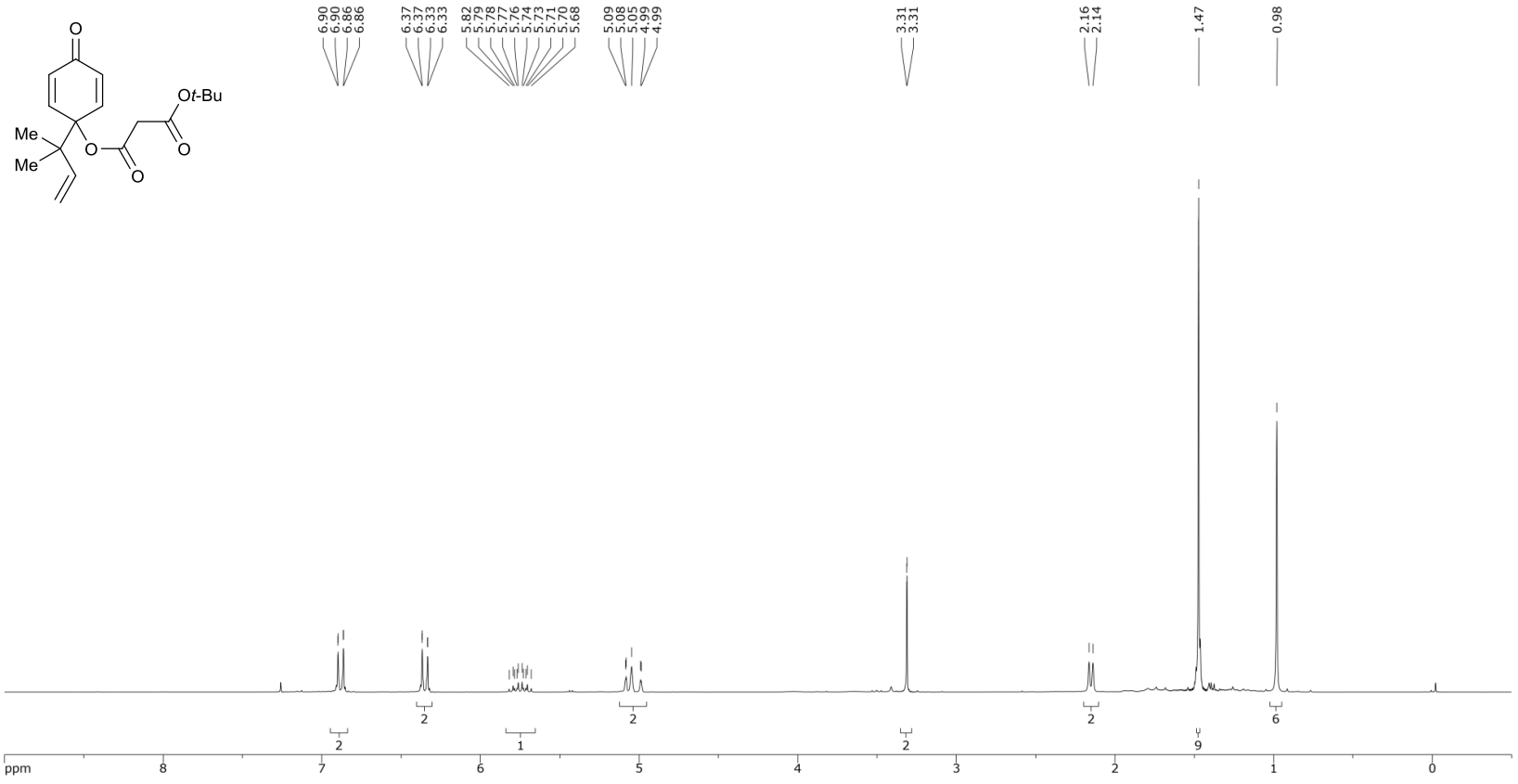
Malonate-tethered cyclohexadienone 2.8f – ^{1}H NMR



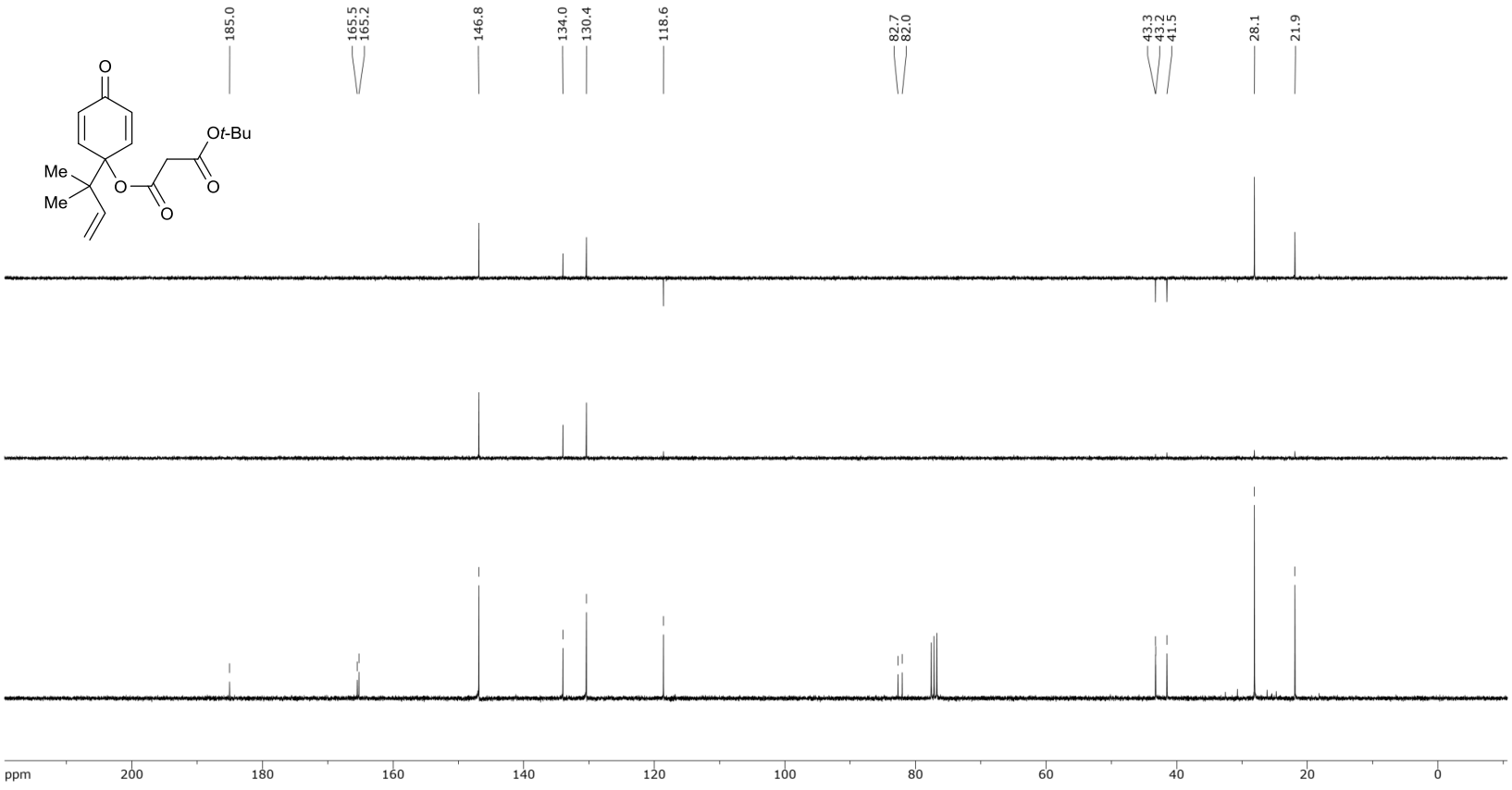
Malonate-tethered cyclohexadienone 2.8f – ^{13}C NMR



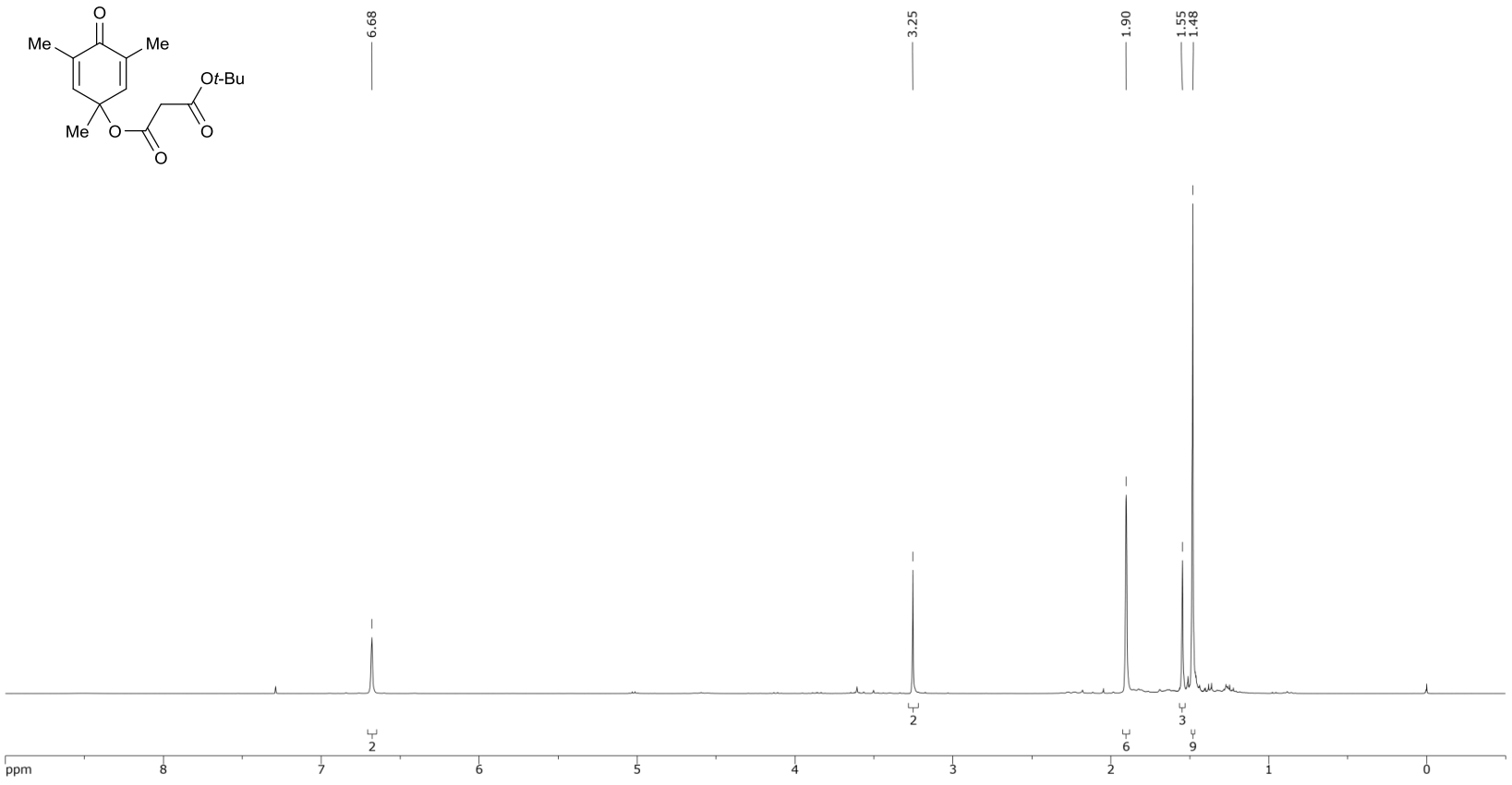
Malonate-tethered cyclohexadienone 2.8g – ^{1}H NMR



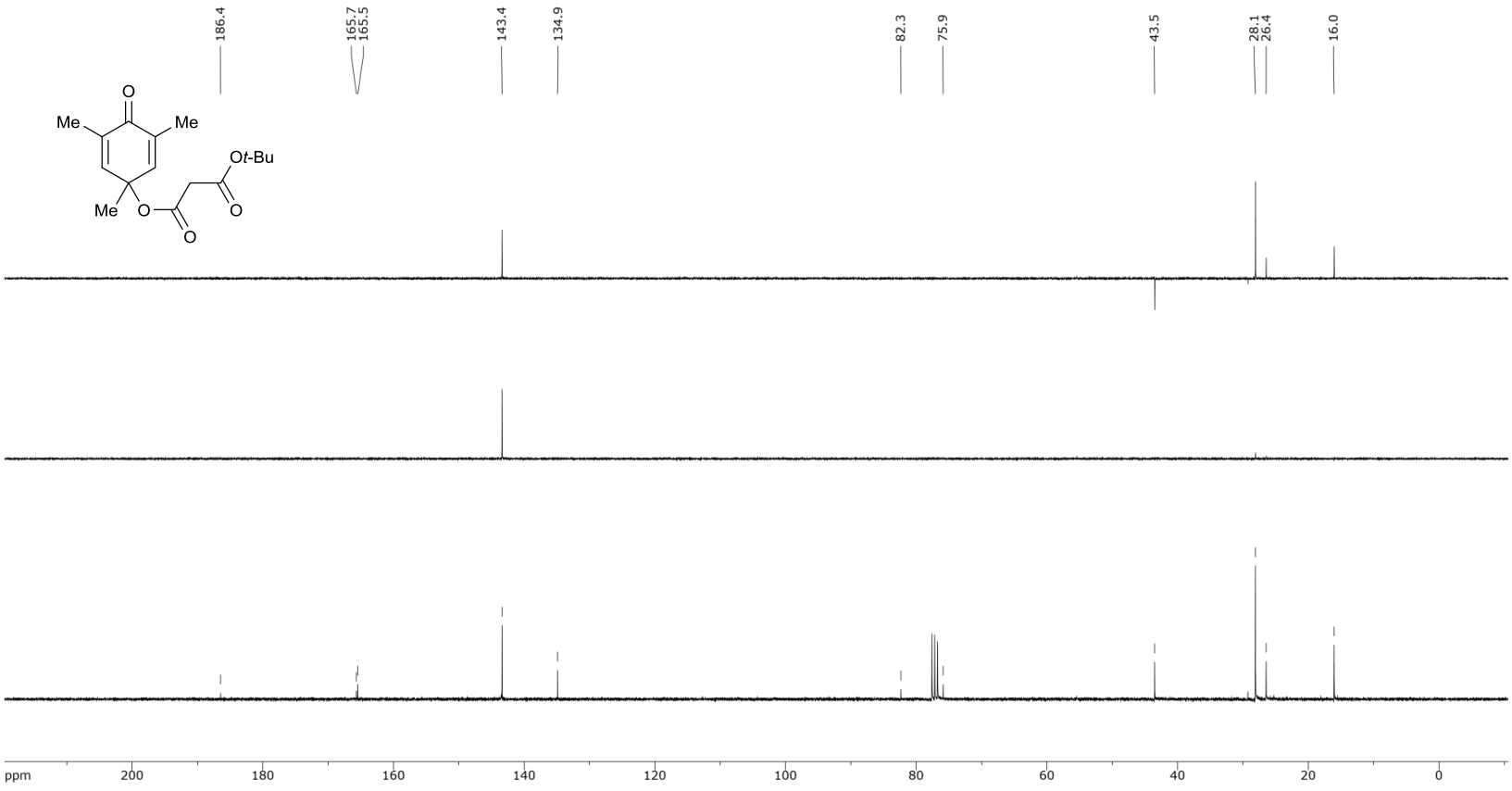
Malonate-tethered cyclohexadienone 2.8g – ^{13}C NMR



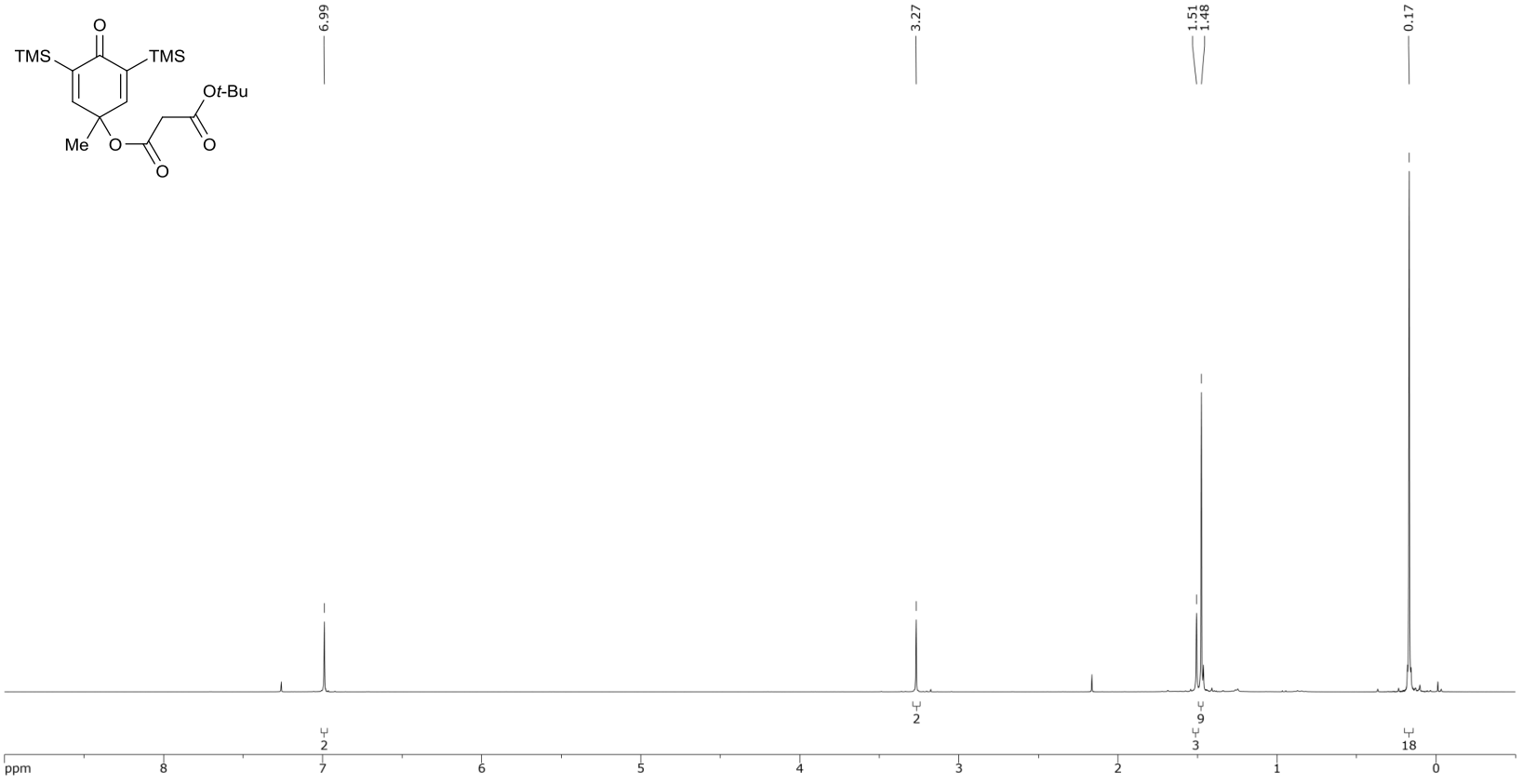
Malonate-tethered cyclohexadienone 2.8h – ^{1}H NMR



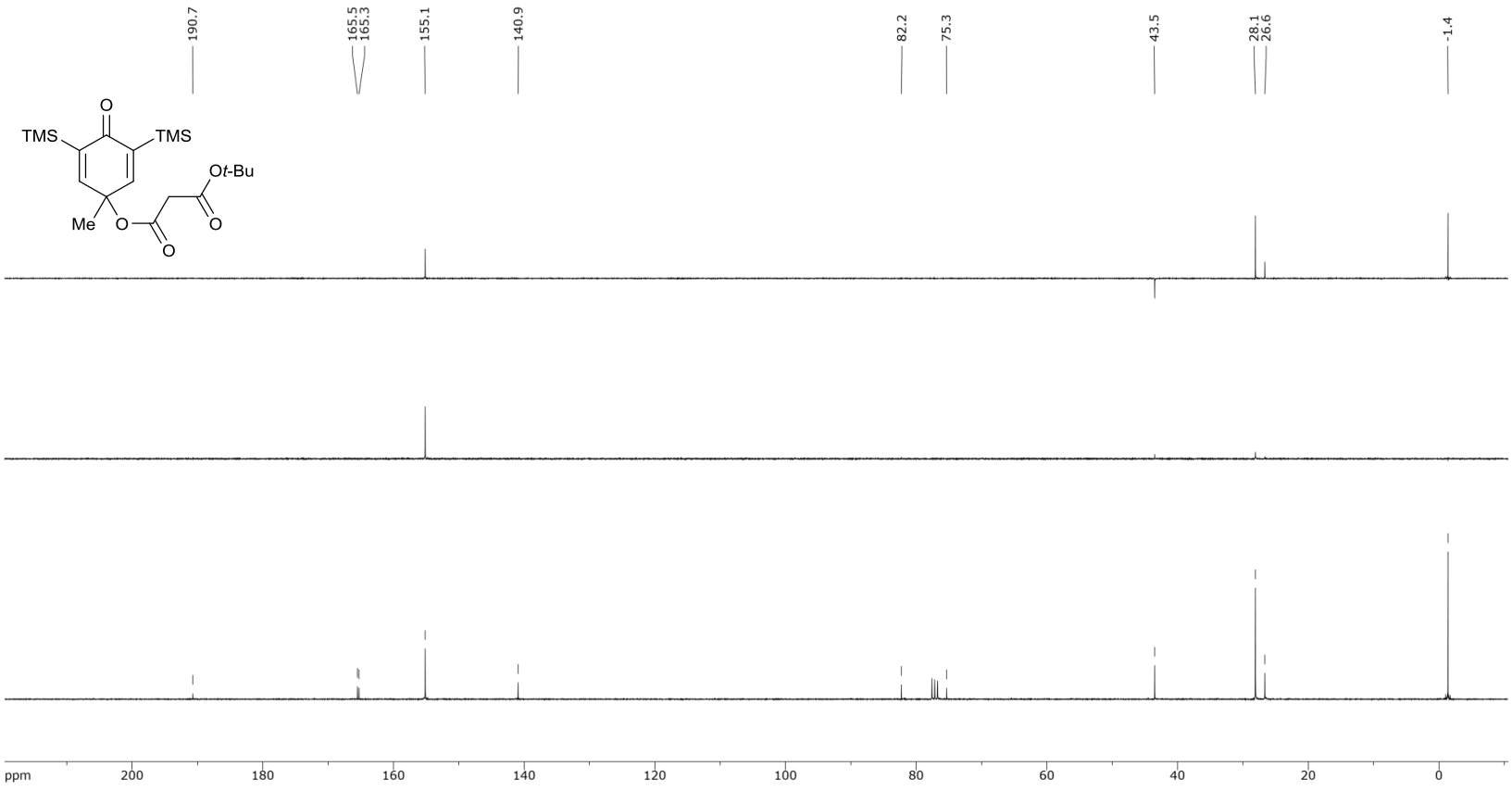
Malonate-tethered cyclohexadienone 2.8h – ^{13}C NMR



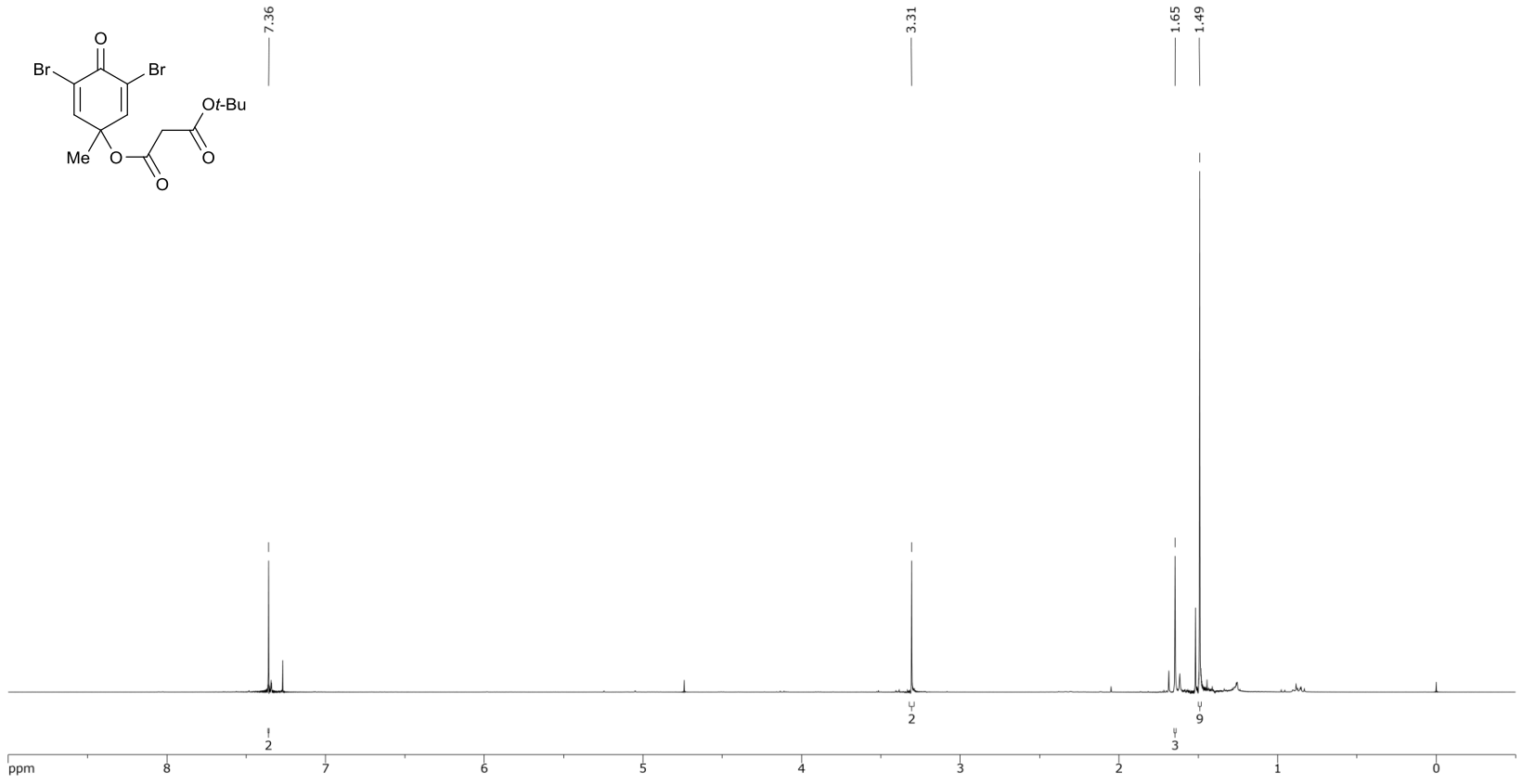
Malonate-tethered cyclohexadienone 2.8i – ^{1}H NMR



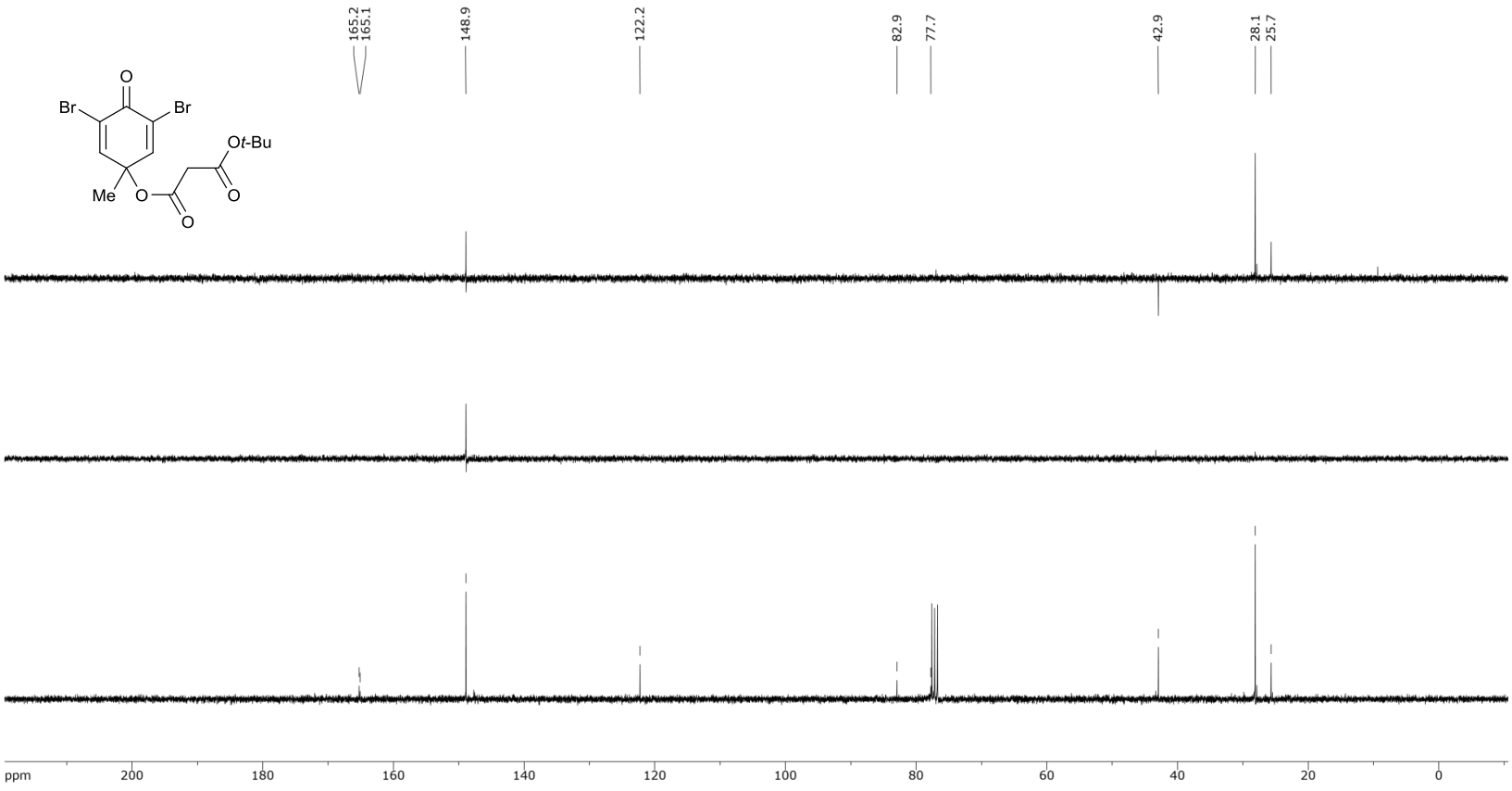
Malonate-tethered cyclohexadienone 2.8i – ^{13}C NMR



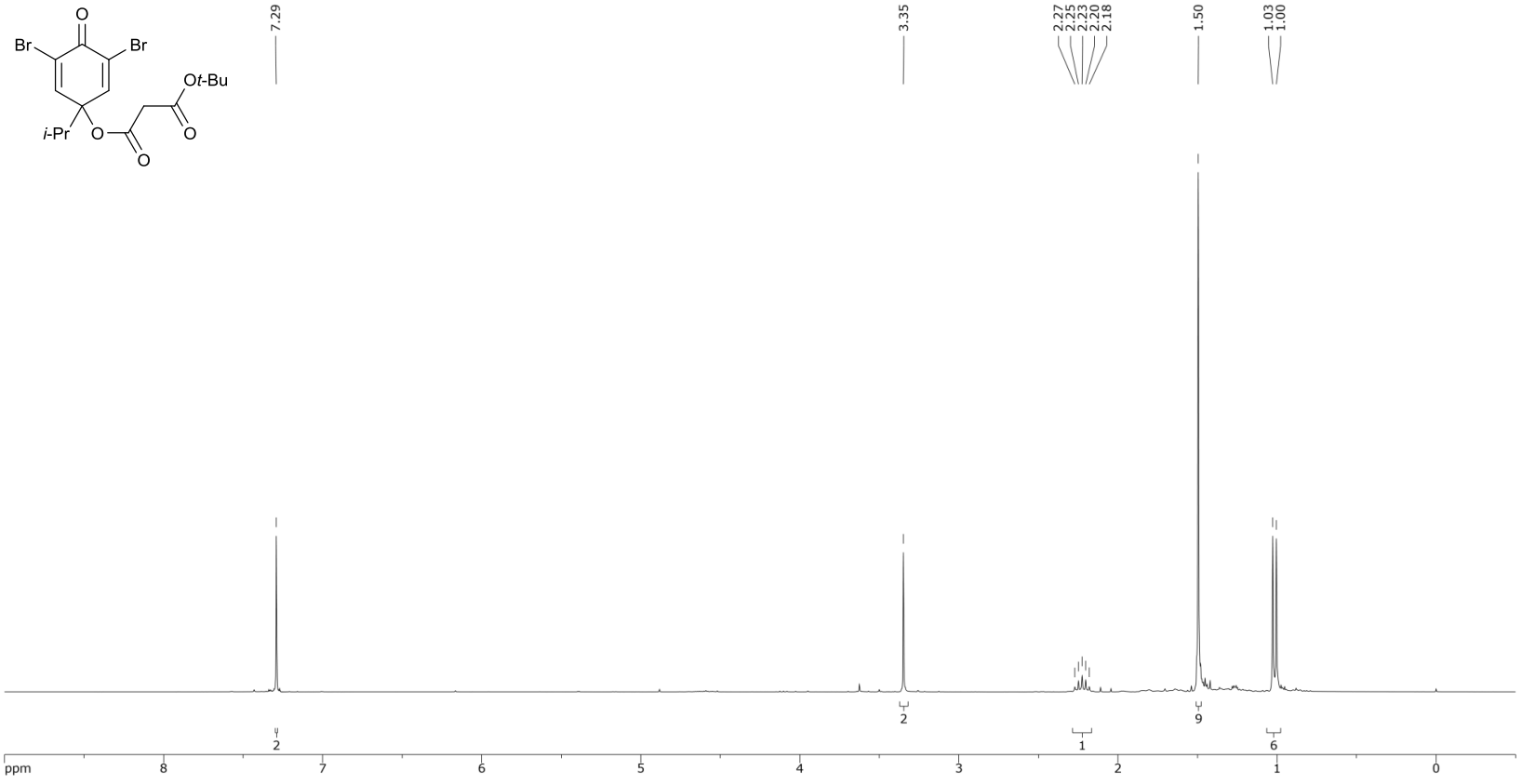
Malonate-tethered cyclohexadienone 2.8j – ^{1}H NMR



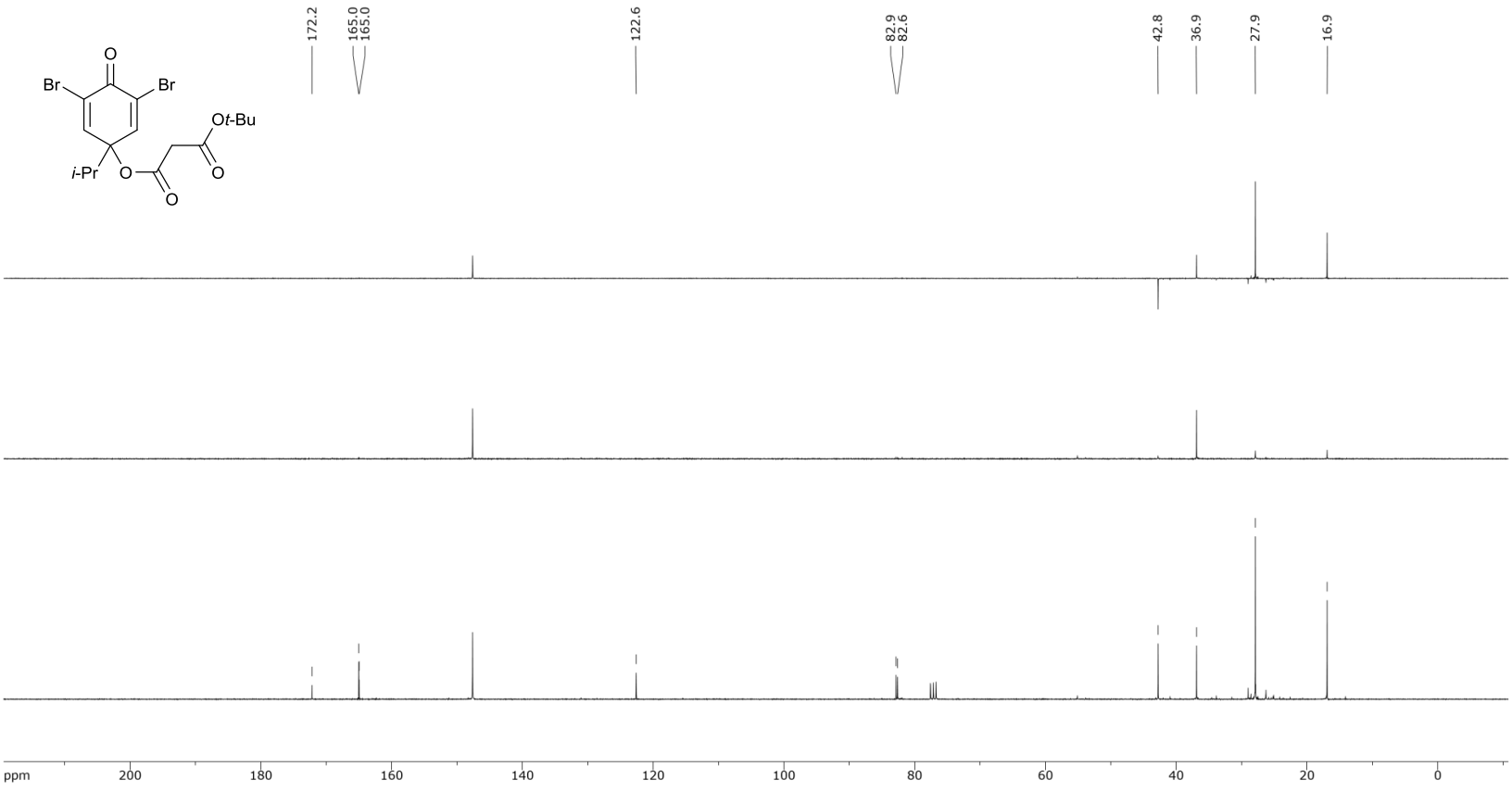
Malonate-tethered cyclohexadienone 2.8j – ^{13}C NMR



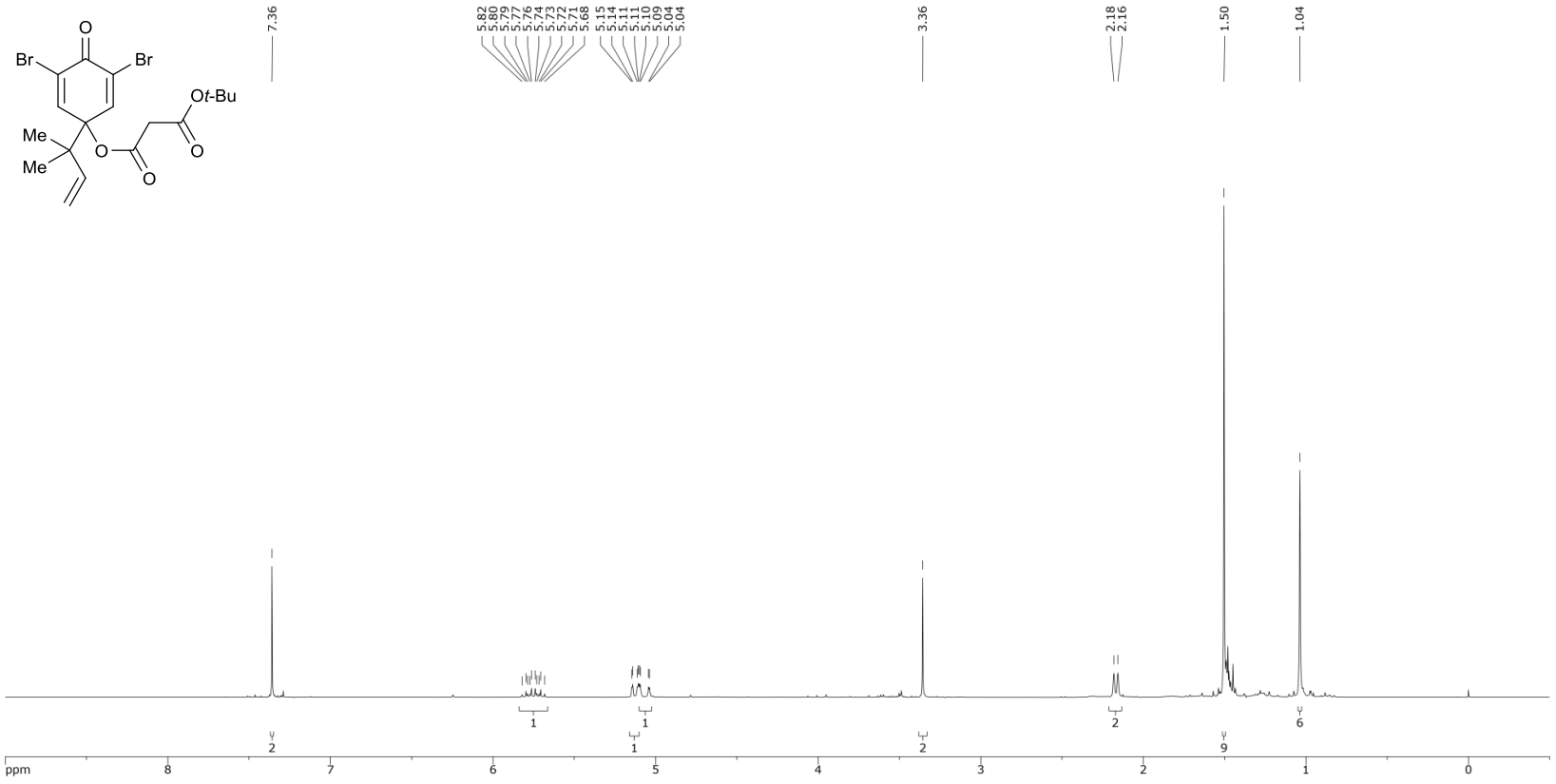
Malonate-tethered cyclohexadienone 2.8k – ^{1}H NMR



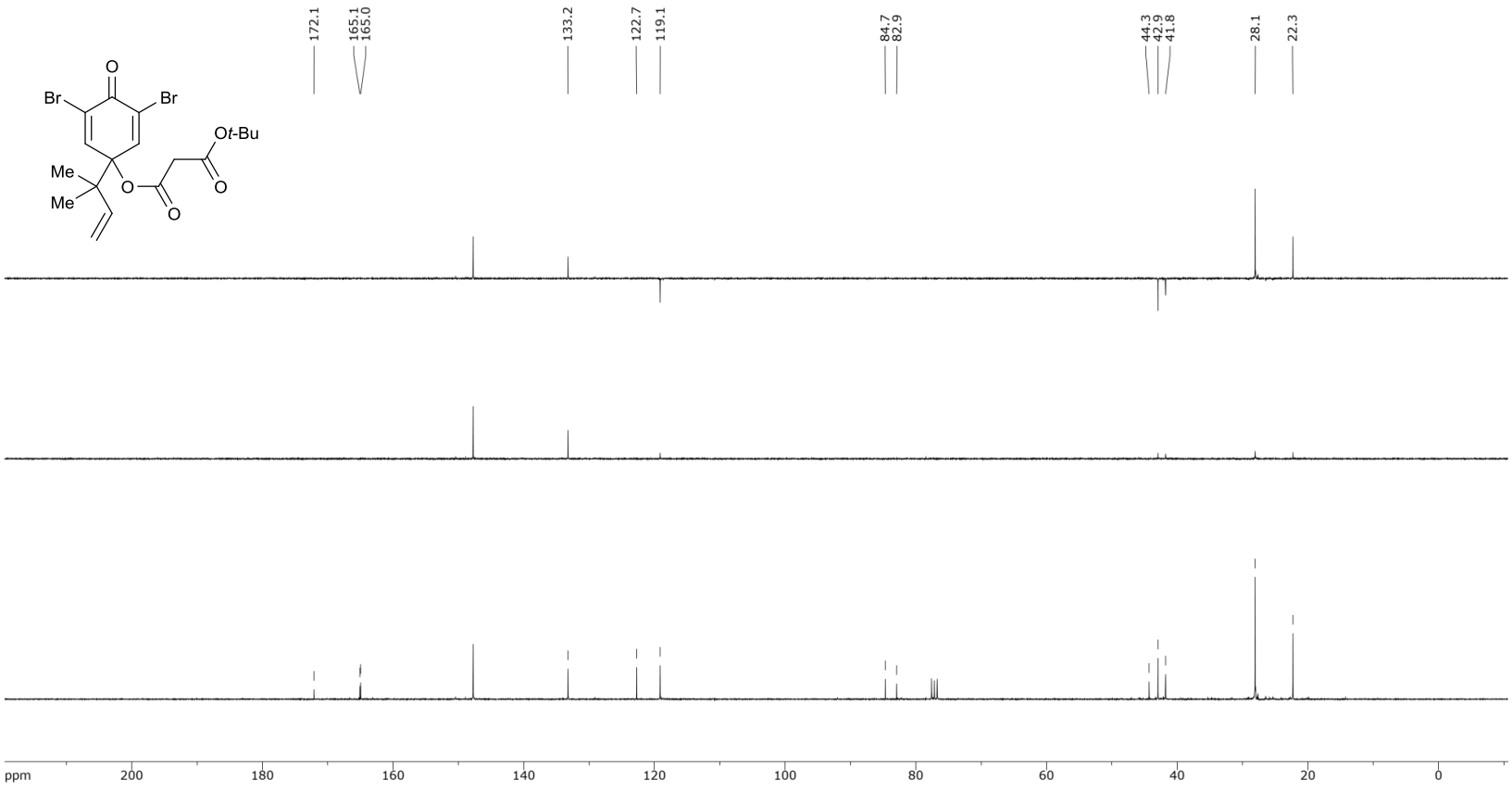
Malonate-tethered cyclohexadienone 2.8k – ^{13}C NMR



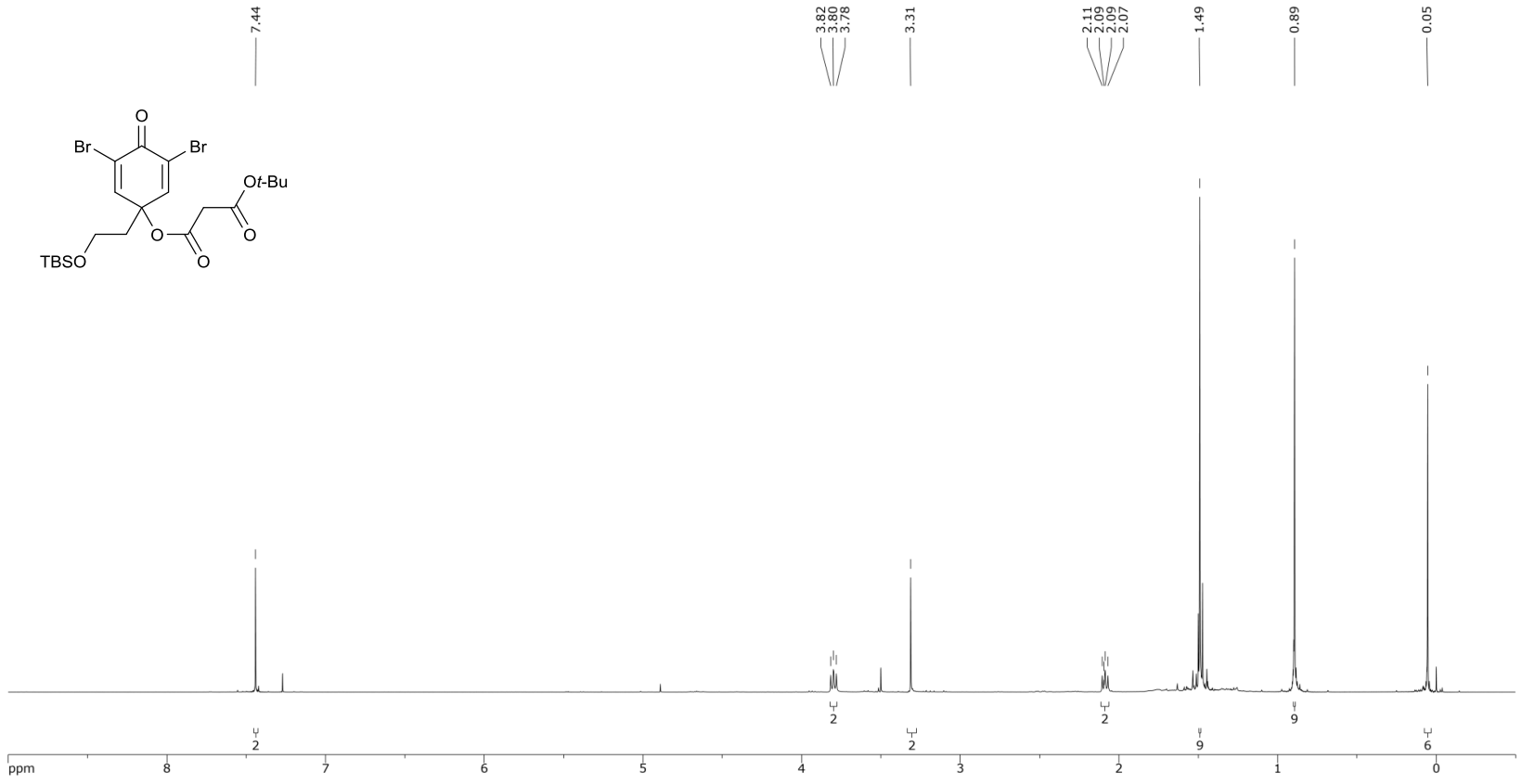
Malonate-tethered cyclohexadienone 2.8l – ^{1}H NMR



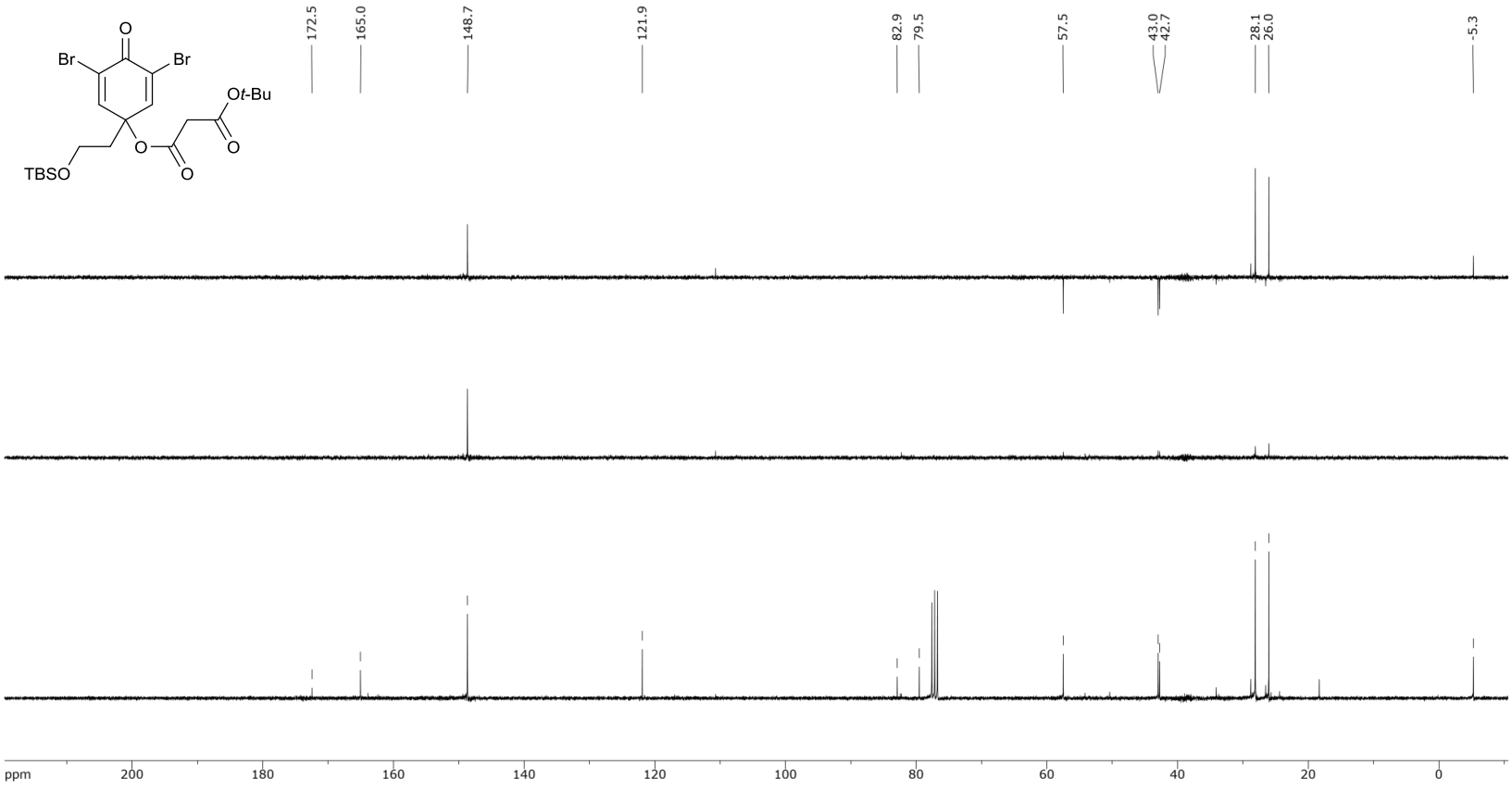
Malonate-tethered cyclohexadienone 2.8l – ^{13}C NMR



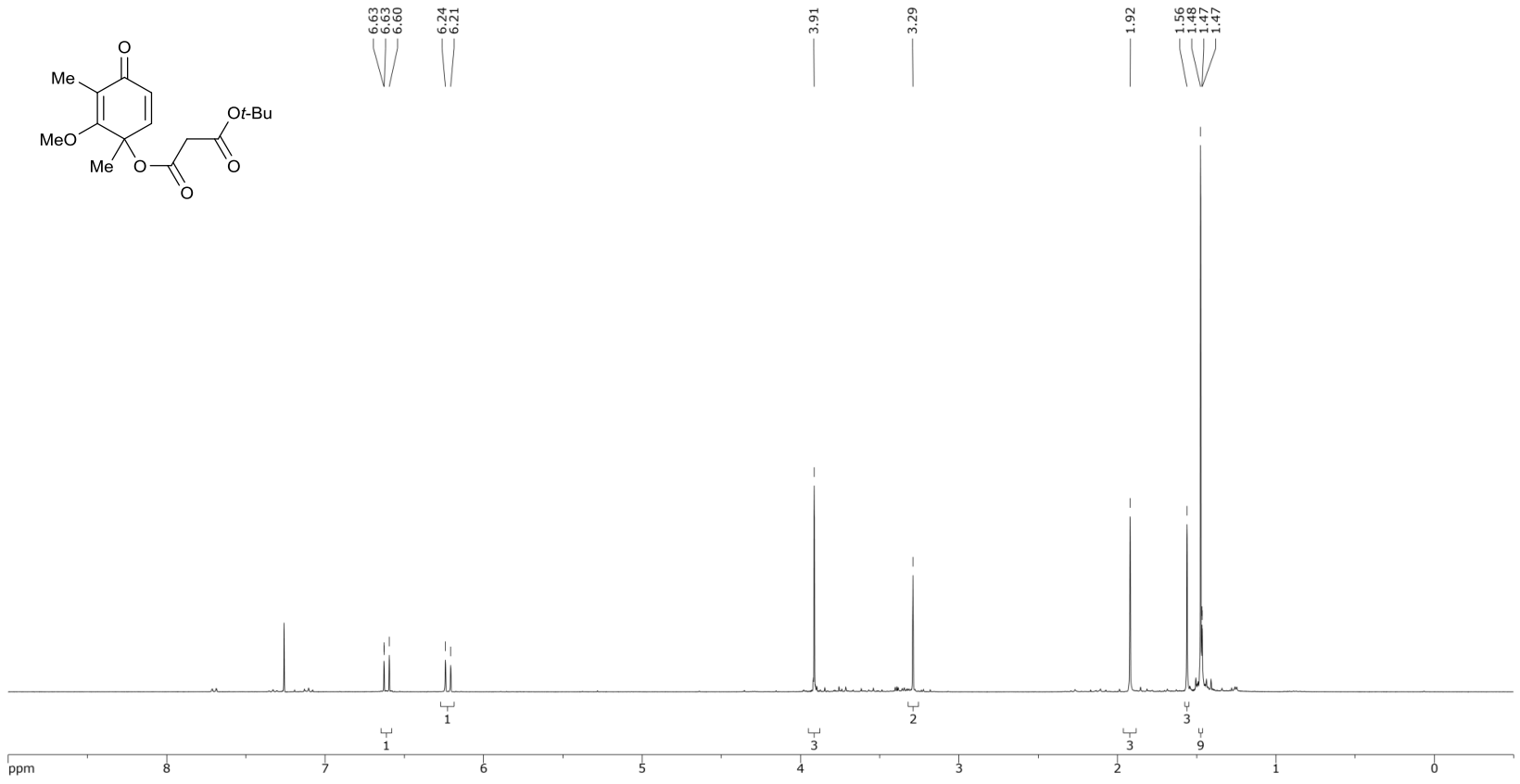
Malonate-tethered cyclohexadienone 2.8m – ^{1}H NMR



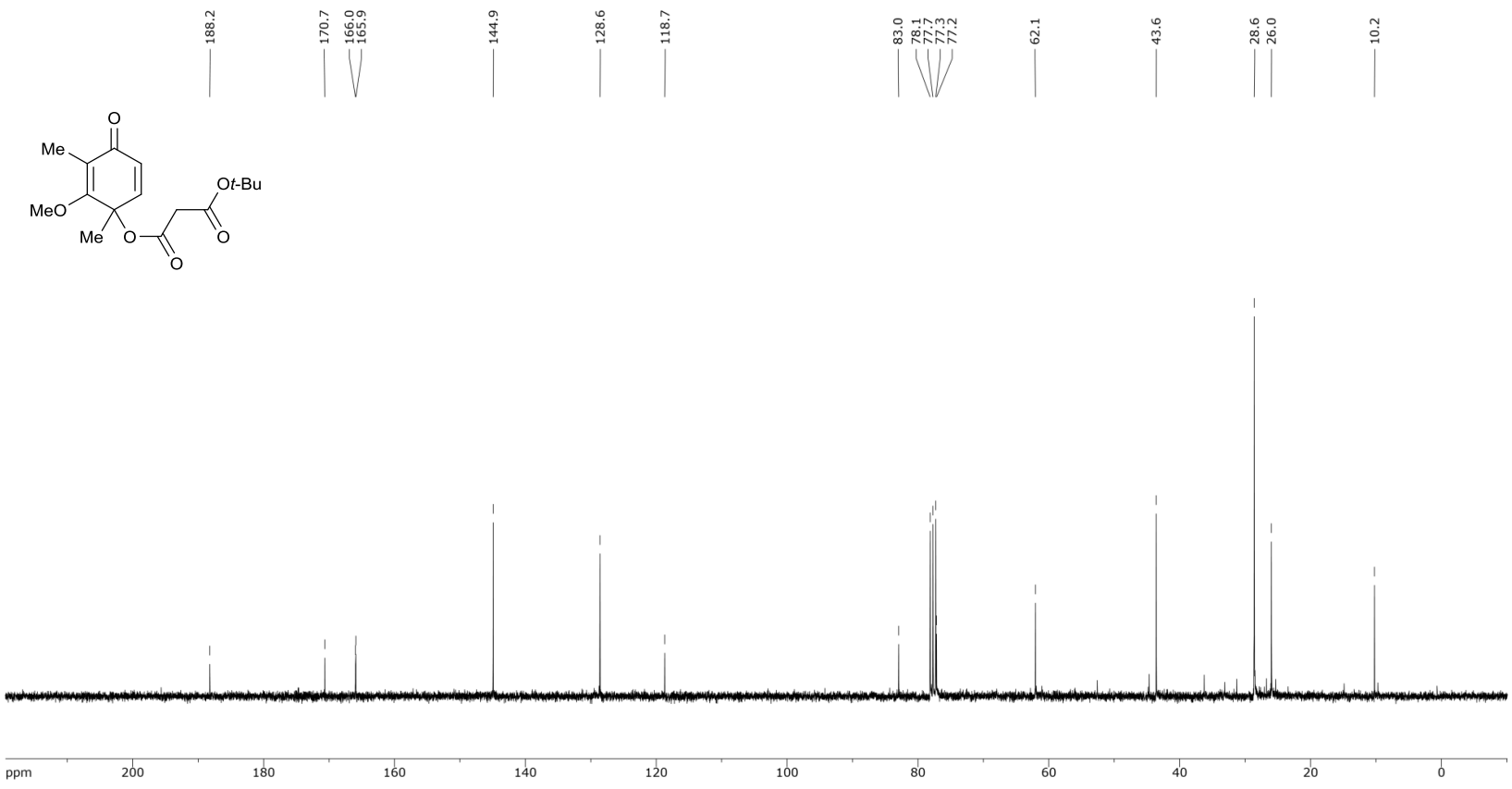
Malonate-tethered cyclohexadienone 2.8m – ^{13}C NMR



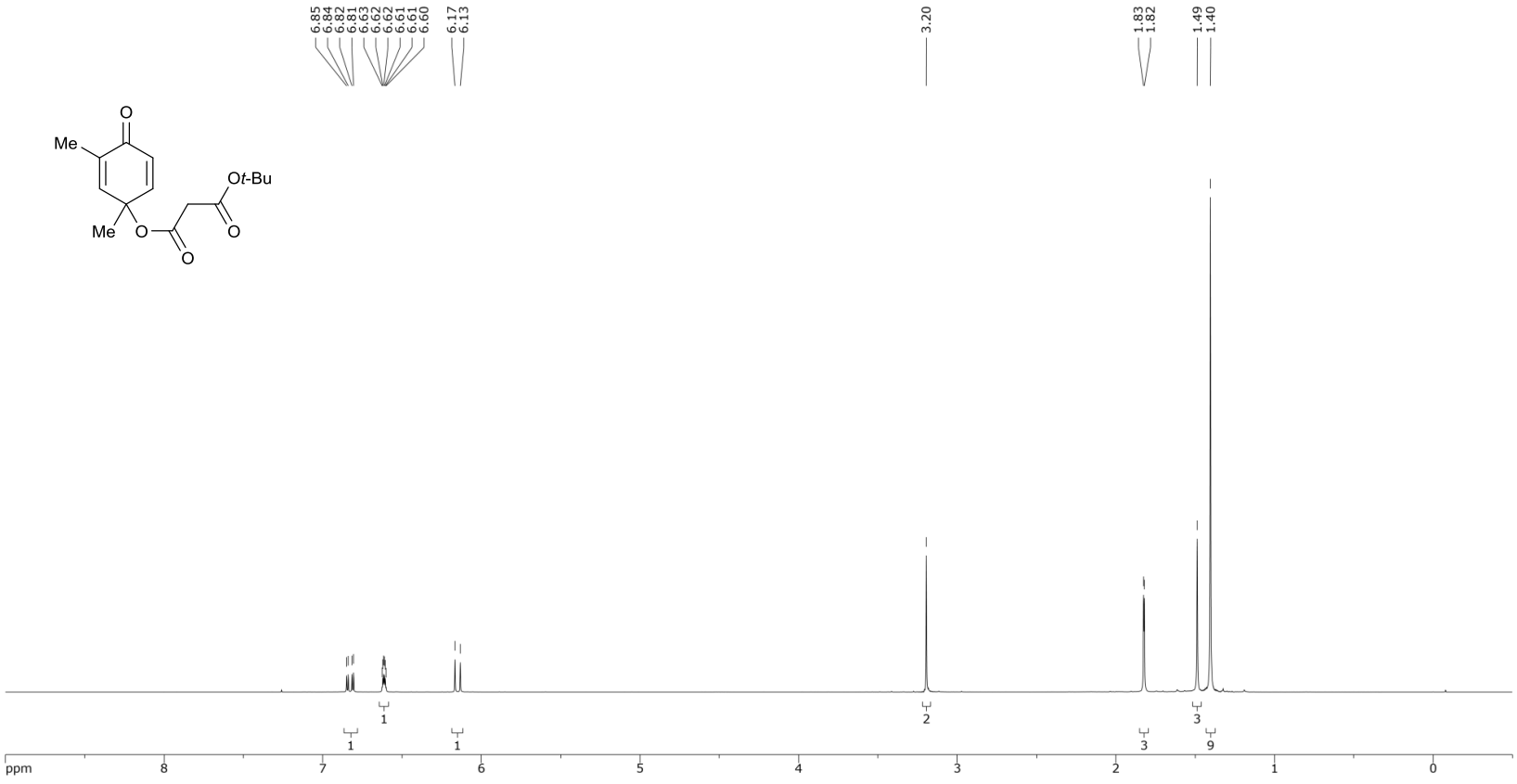
Malonate-tethered cyclohexadienone 2.8n – ^{1}H NMR



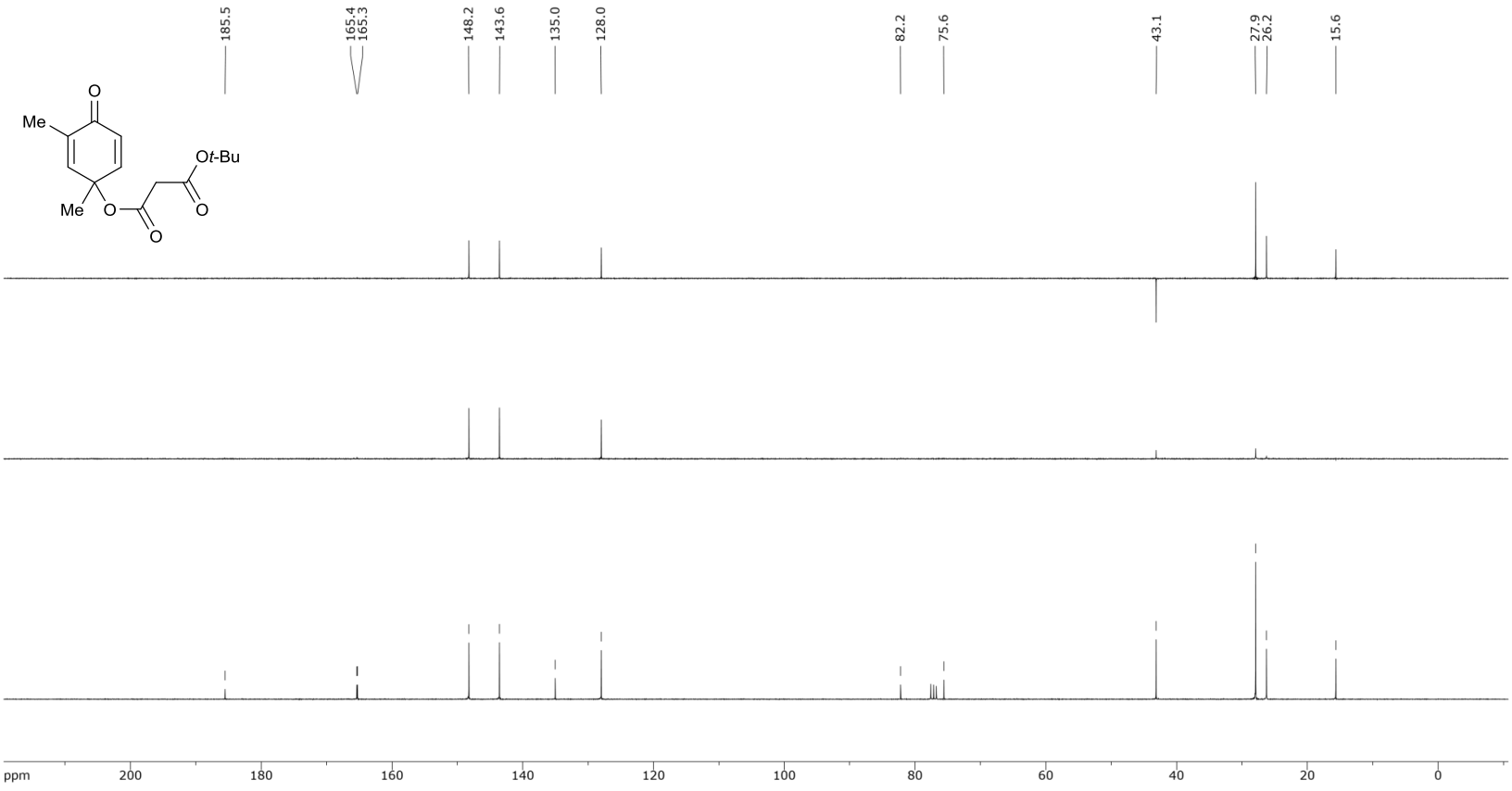
Malonate-tethered cyclohexadienone 2.8n – ^{13}C NMR



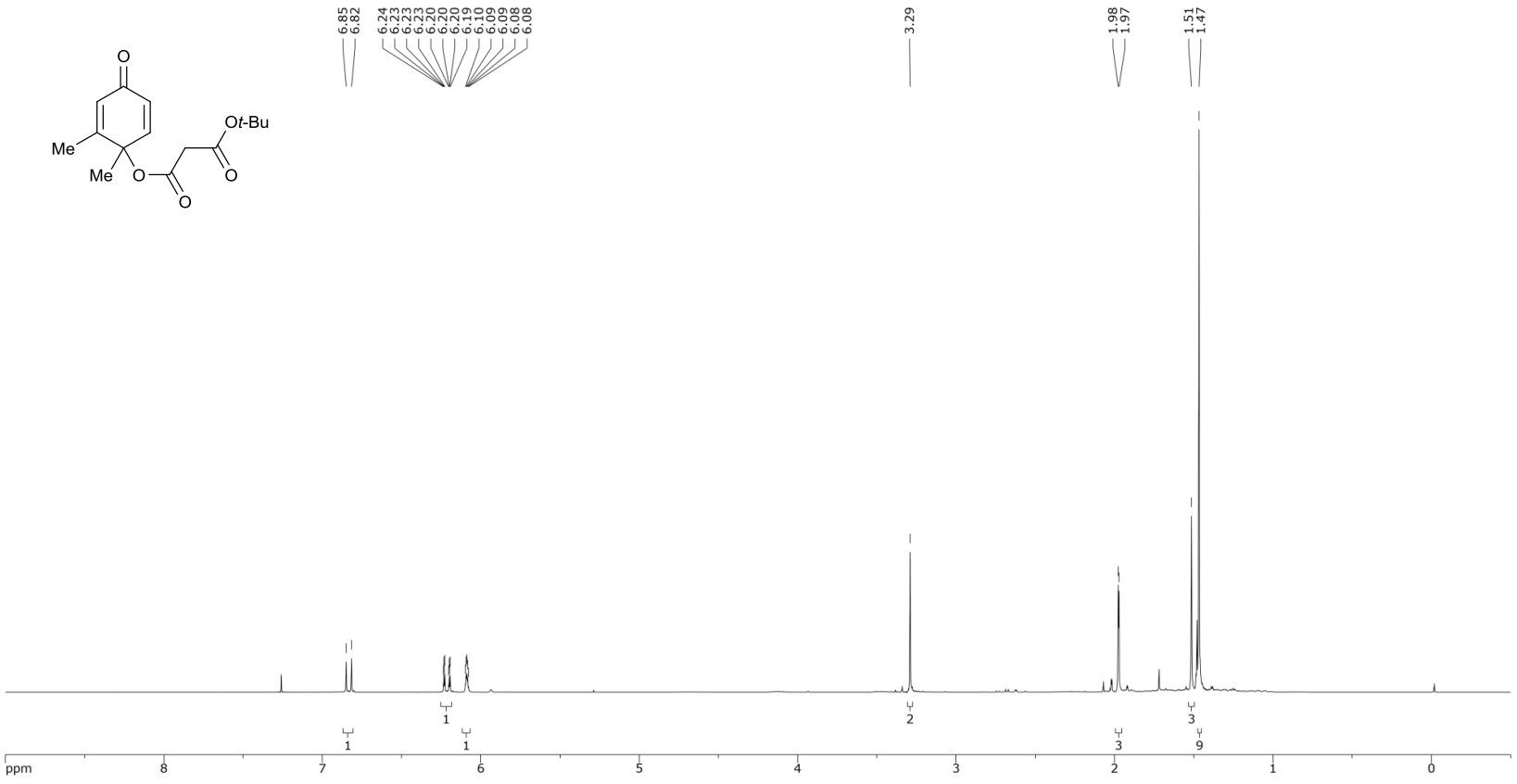
Malonate-tethered cyclohexadienone 2.8o – ^{1}H NMR



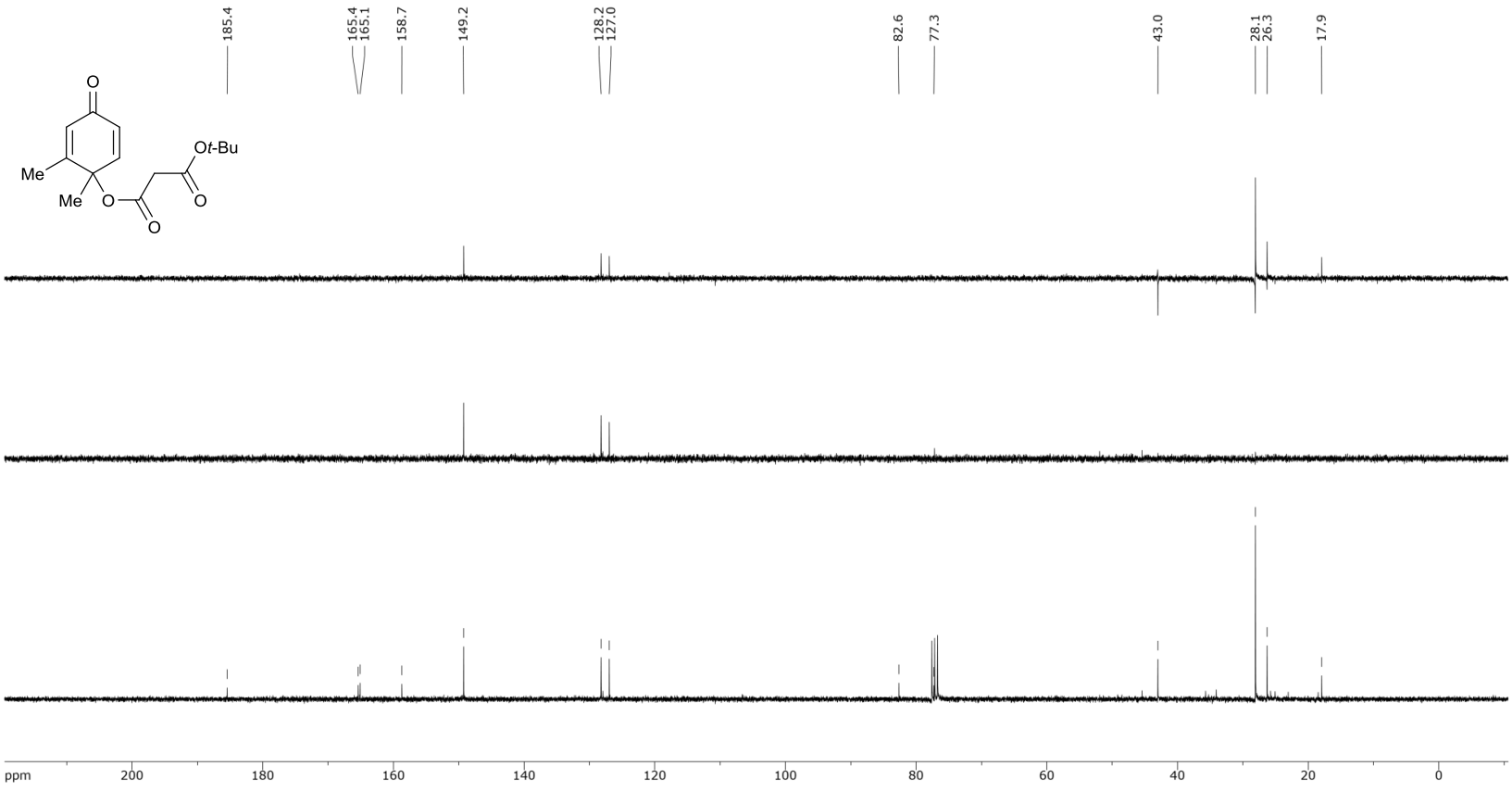
Malonate-tethered cyclohexadienone 2.8o – ^{13}C NMR



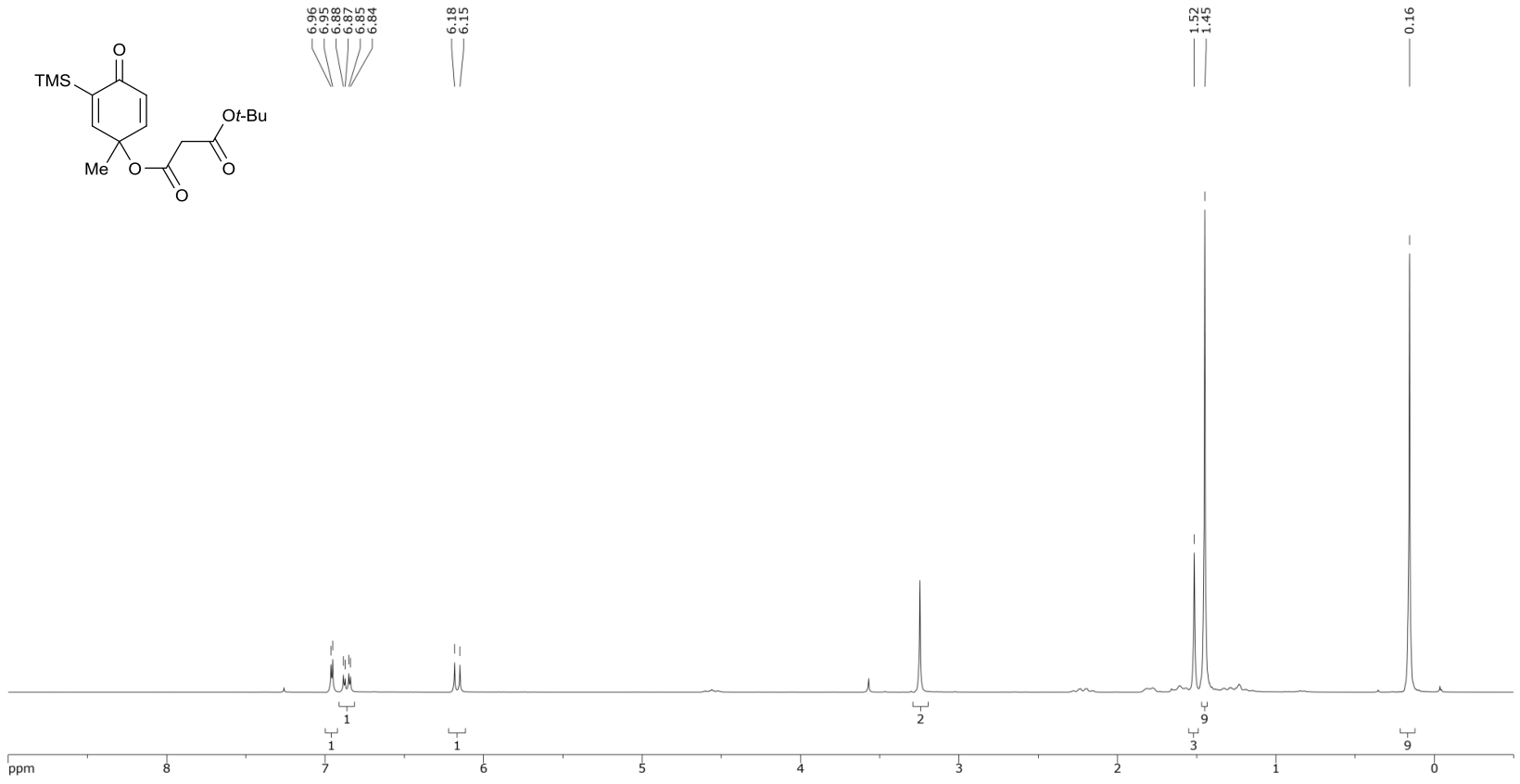
Malonate-tethered cyclohexadienone 2.8p – ^{1}H NMR



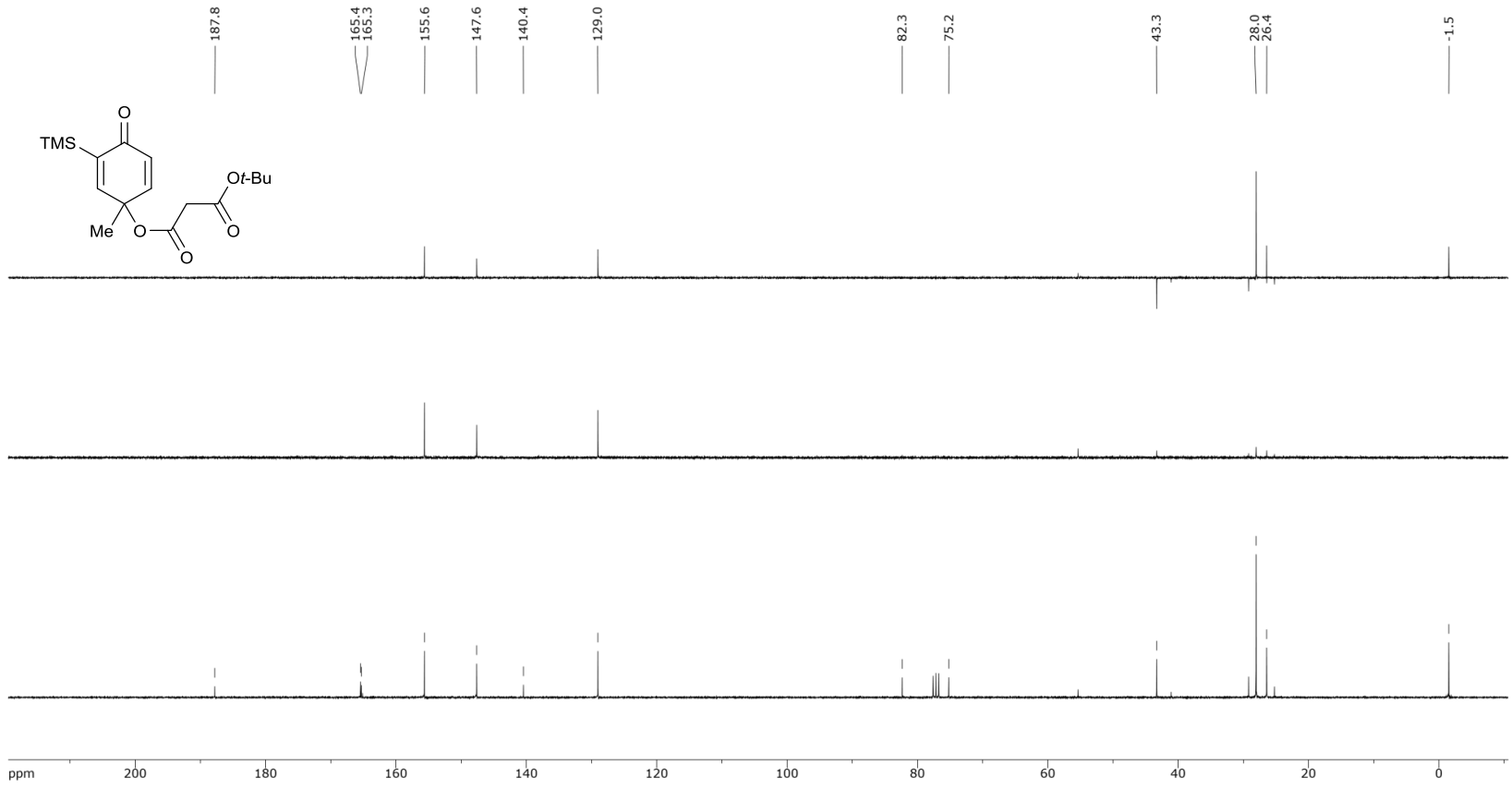
Malonate-tethered cyclohexadienone 2.8p – ^{13}C NMR



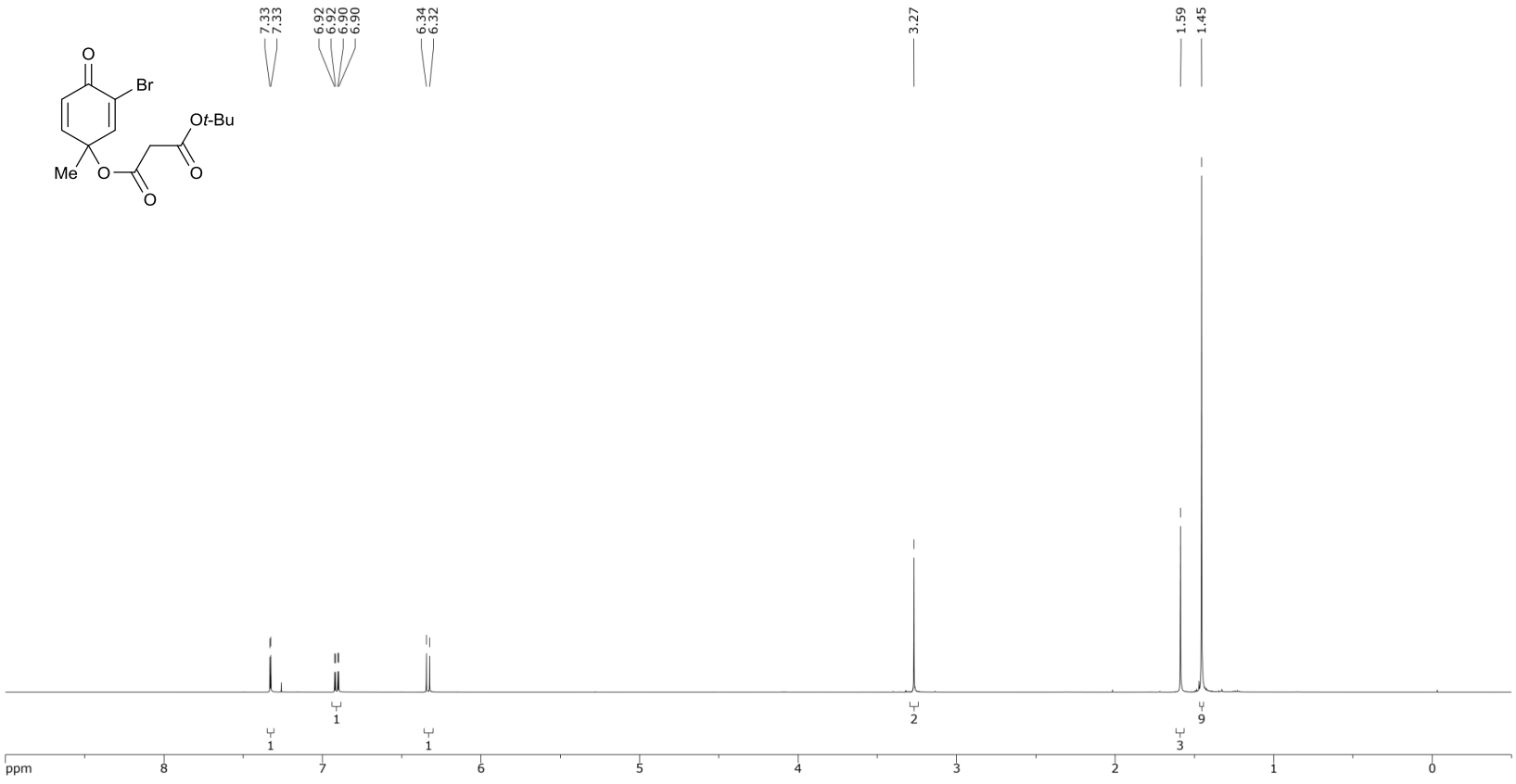
Malonate-tethered cyclohexadienone 2.8q – ^{1}H NMR



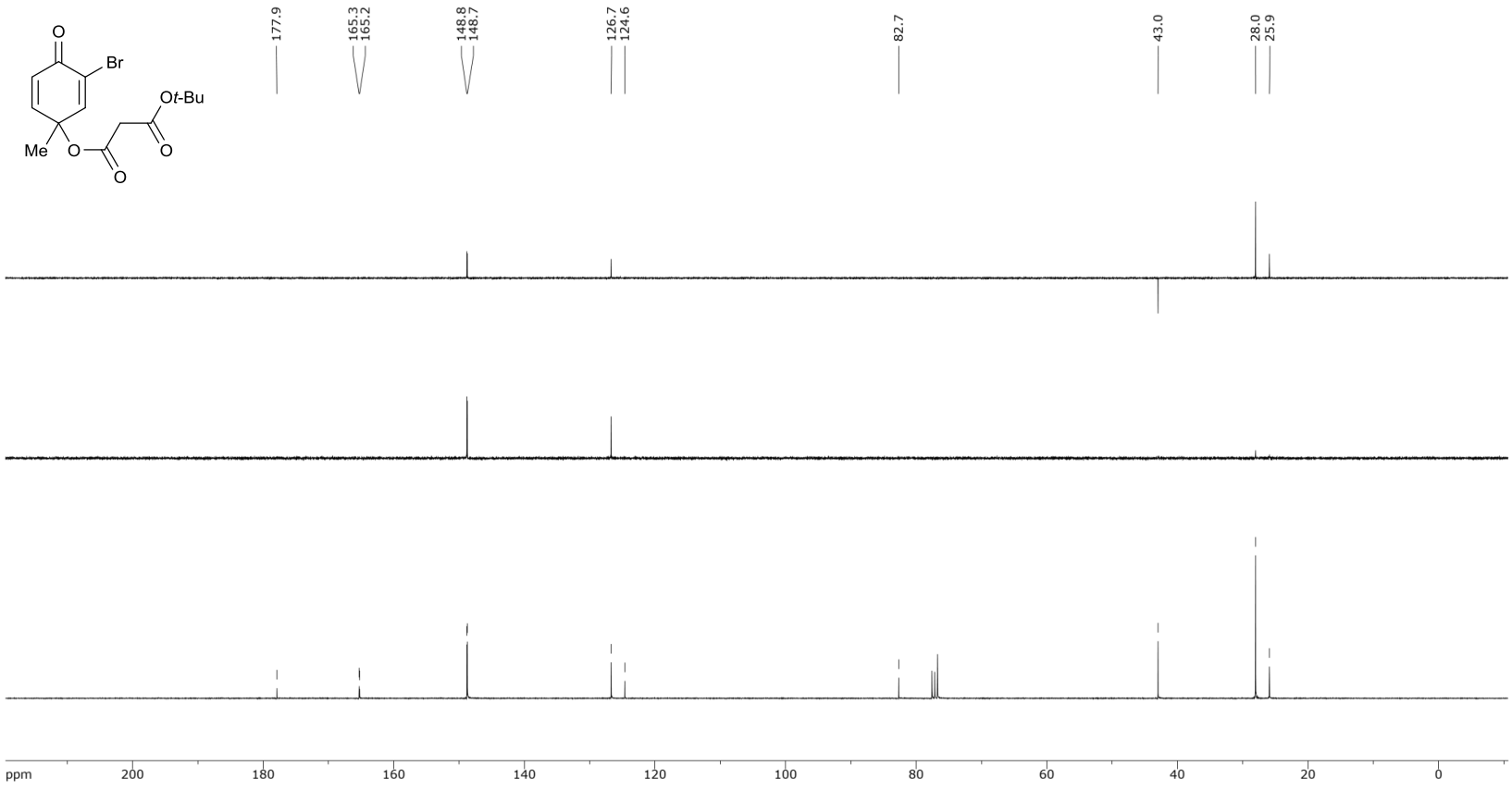
Malonate-tethered cyclohexadienone 2.8q – ^{13}C NMR



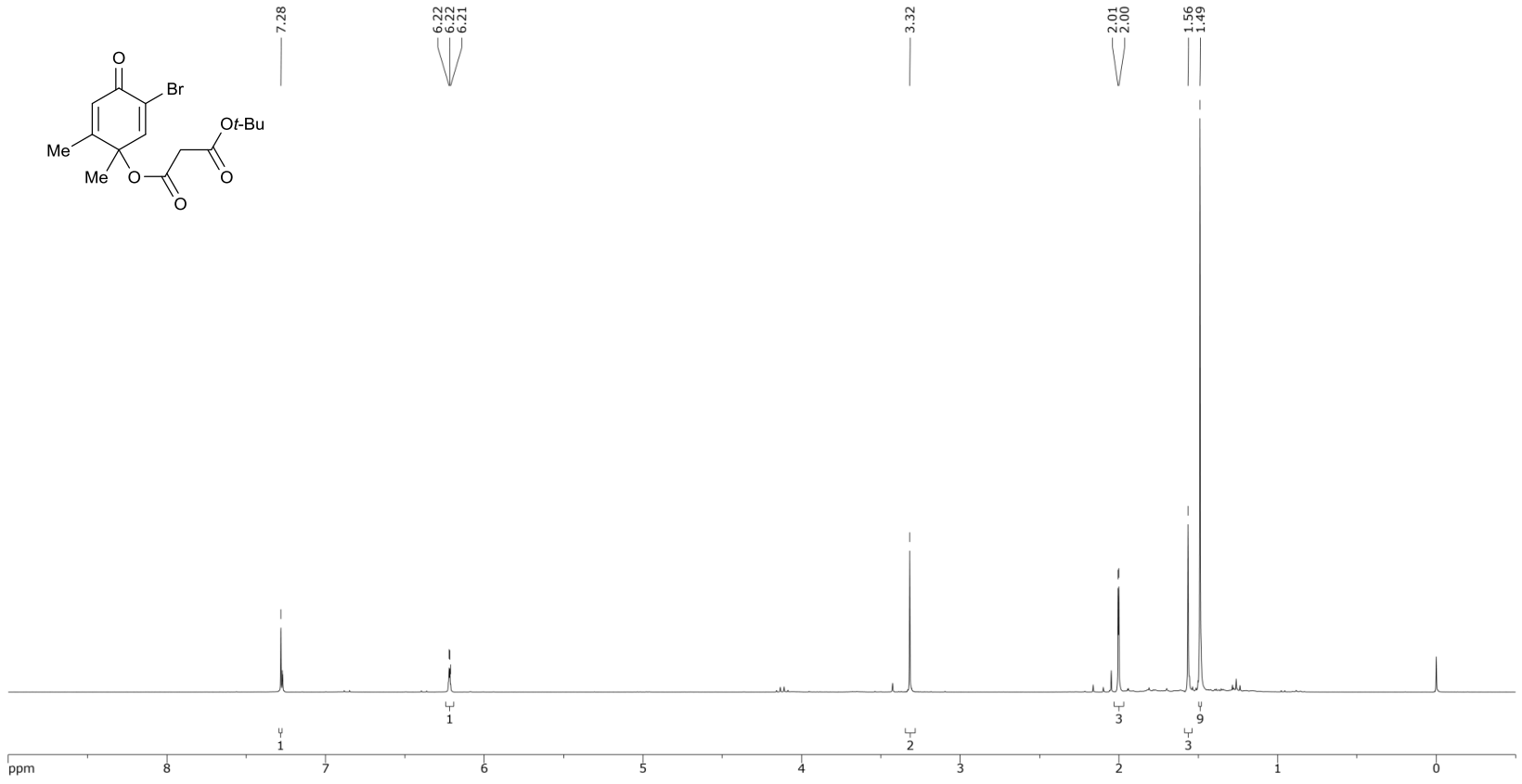
Malonate-tethered cyclohexadienone 2.8r – ^{1}H NMR



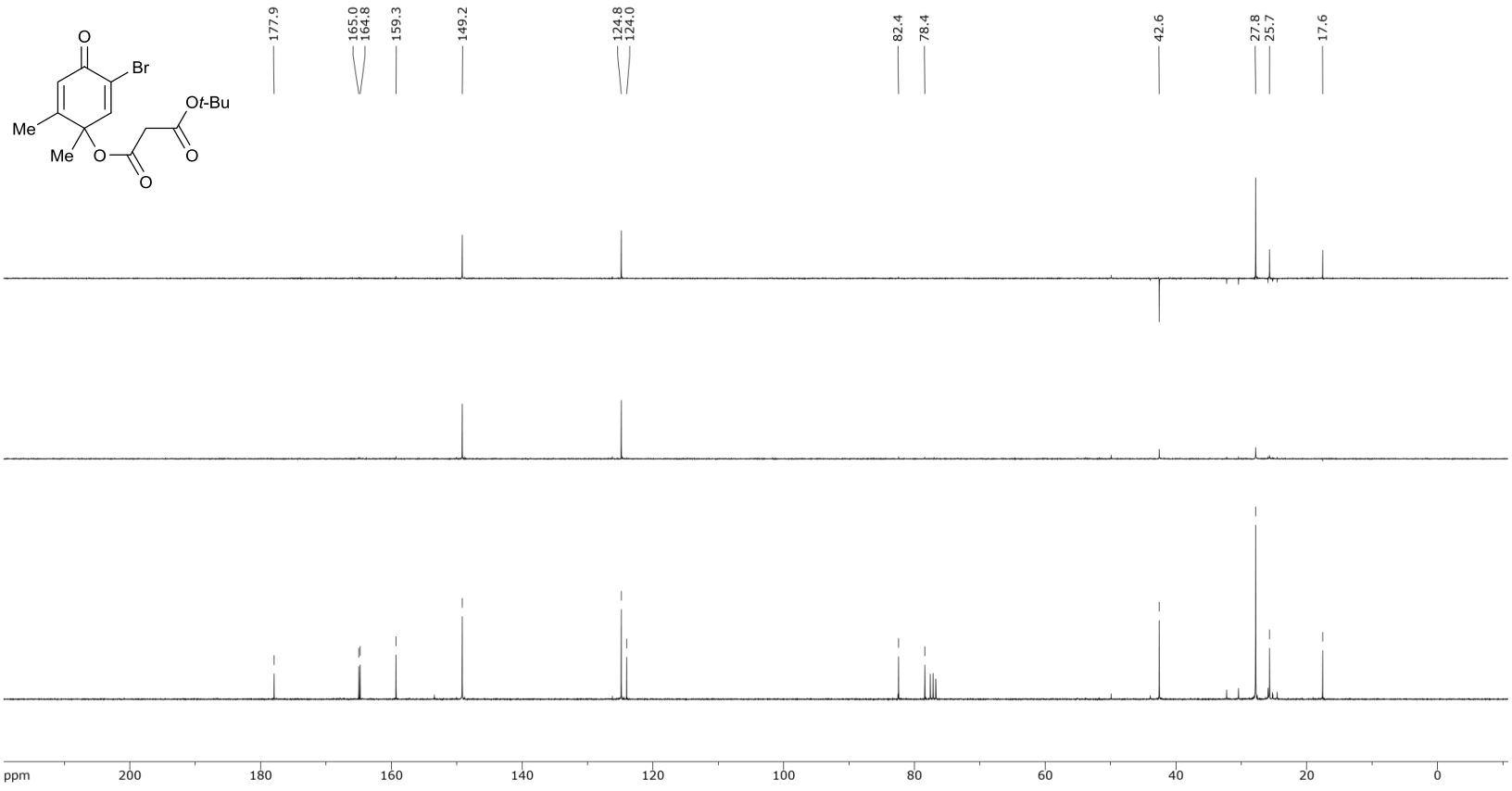
Malonate-tethered cyclohexadienone 2.8r – ^{13}C NMR



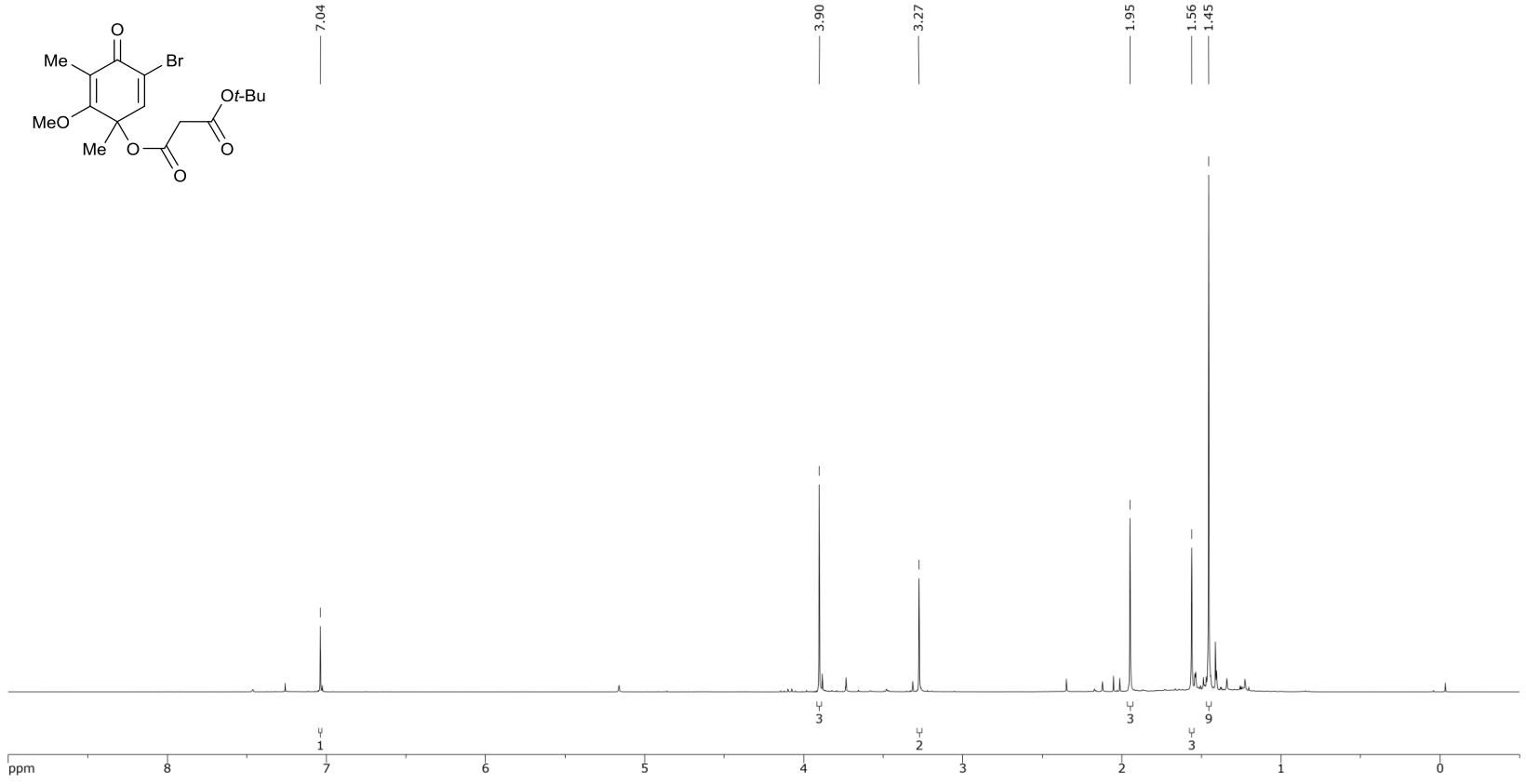
Malonate-tethered cyclohexadienone 2.8s – ^{1}H NMR



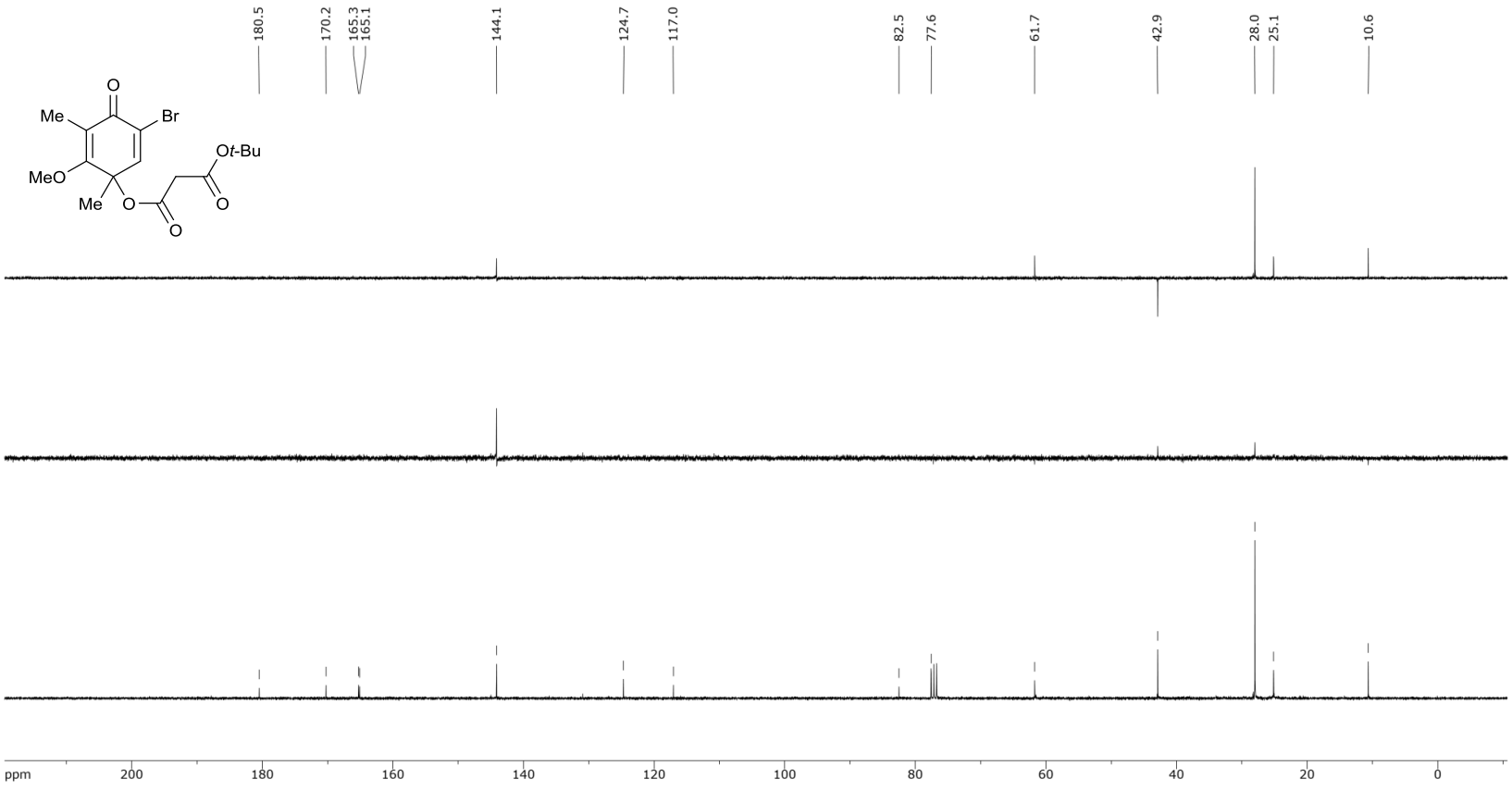
Malonate-tethered cyclohexadienone 2.8s – ^{13}C NMR



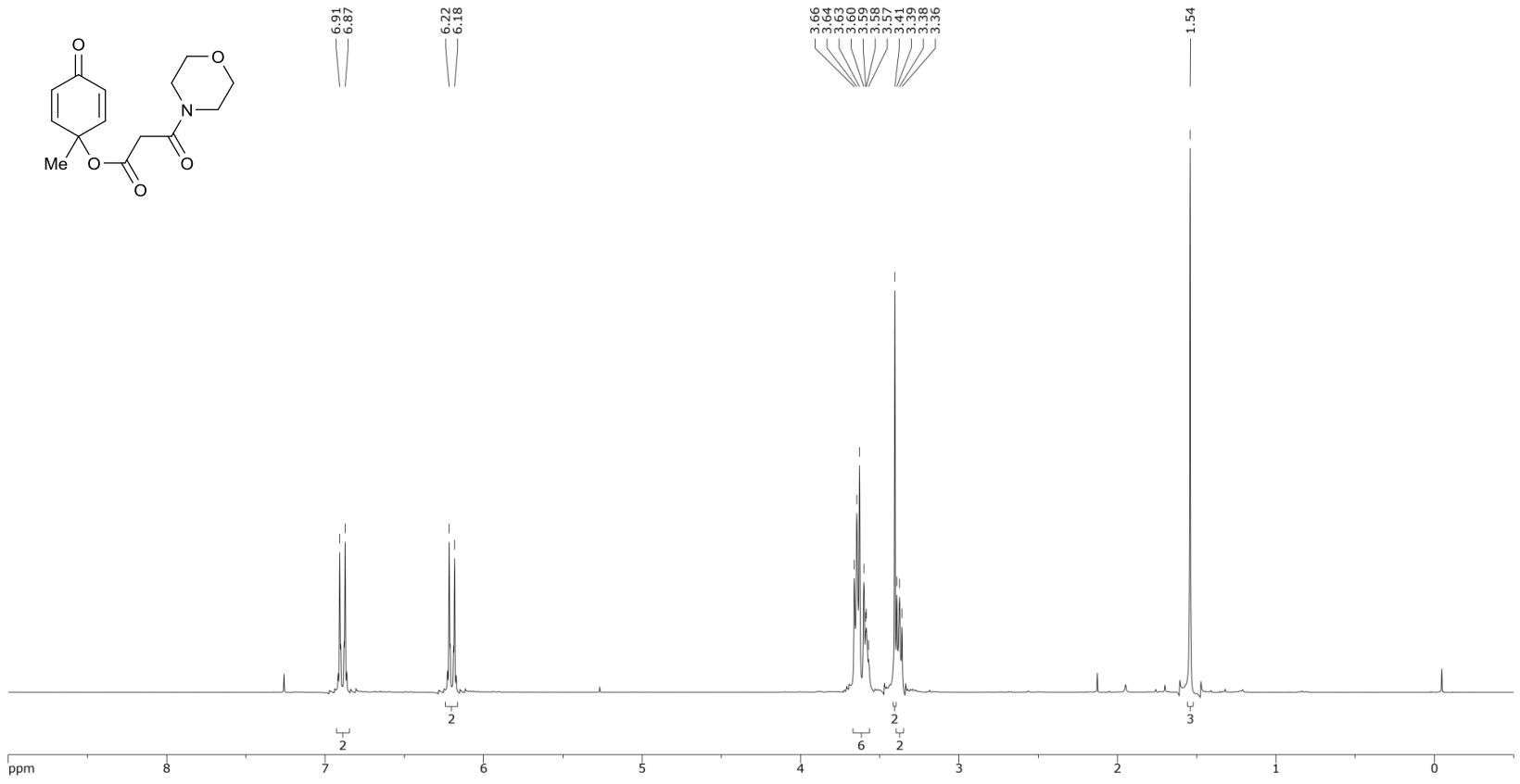
Malonate-tethered cyclohexadienone 2.8t – ^{1}H NMR



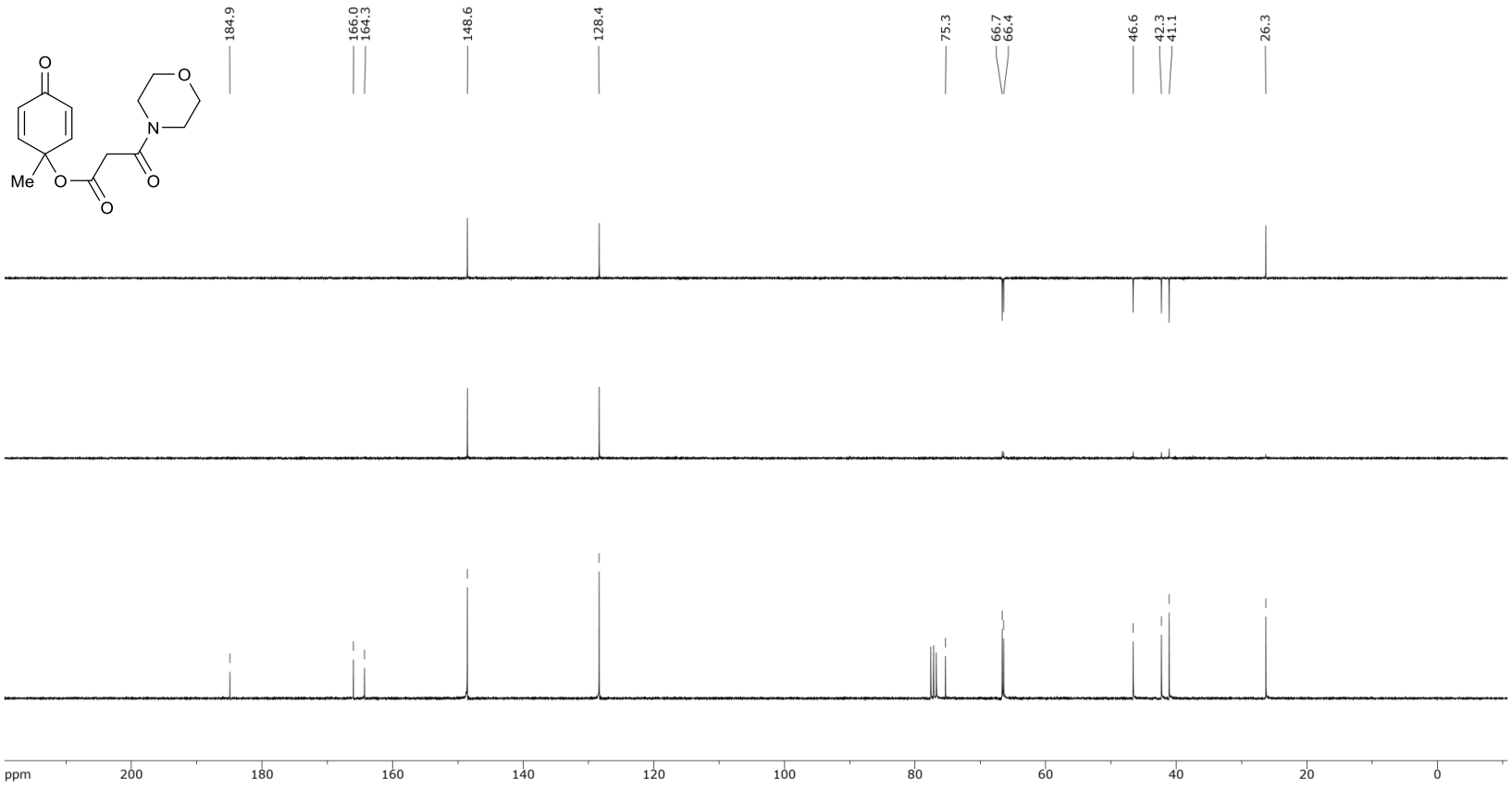
Malonate-tethered cyclohexadienone 2.8t – ^{13}C NMR



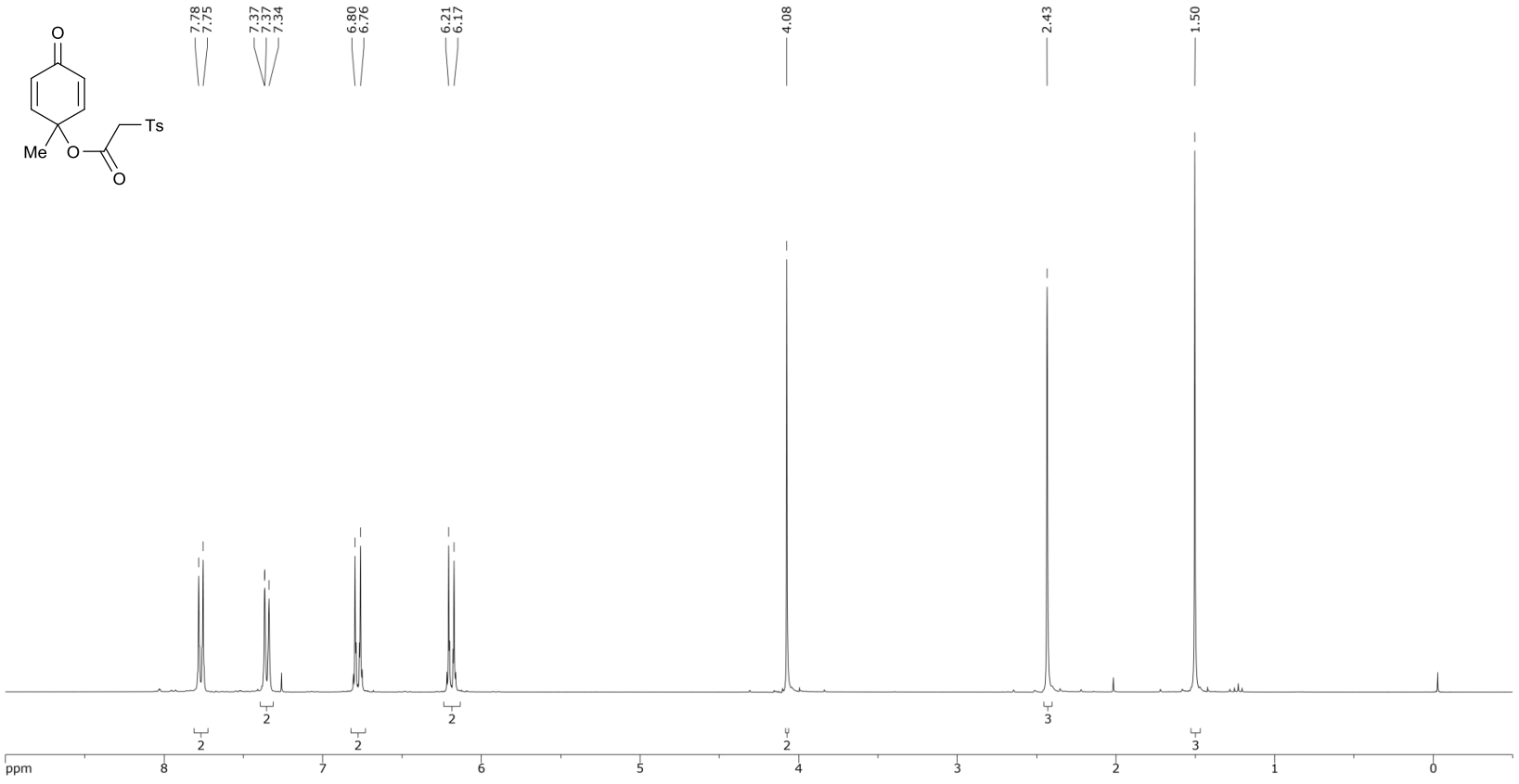
Morpholine-tethered cyclohexadienone 2.9 – ^{1}H NMR



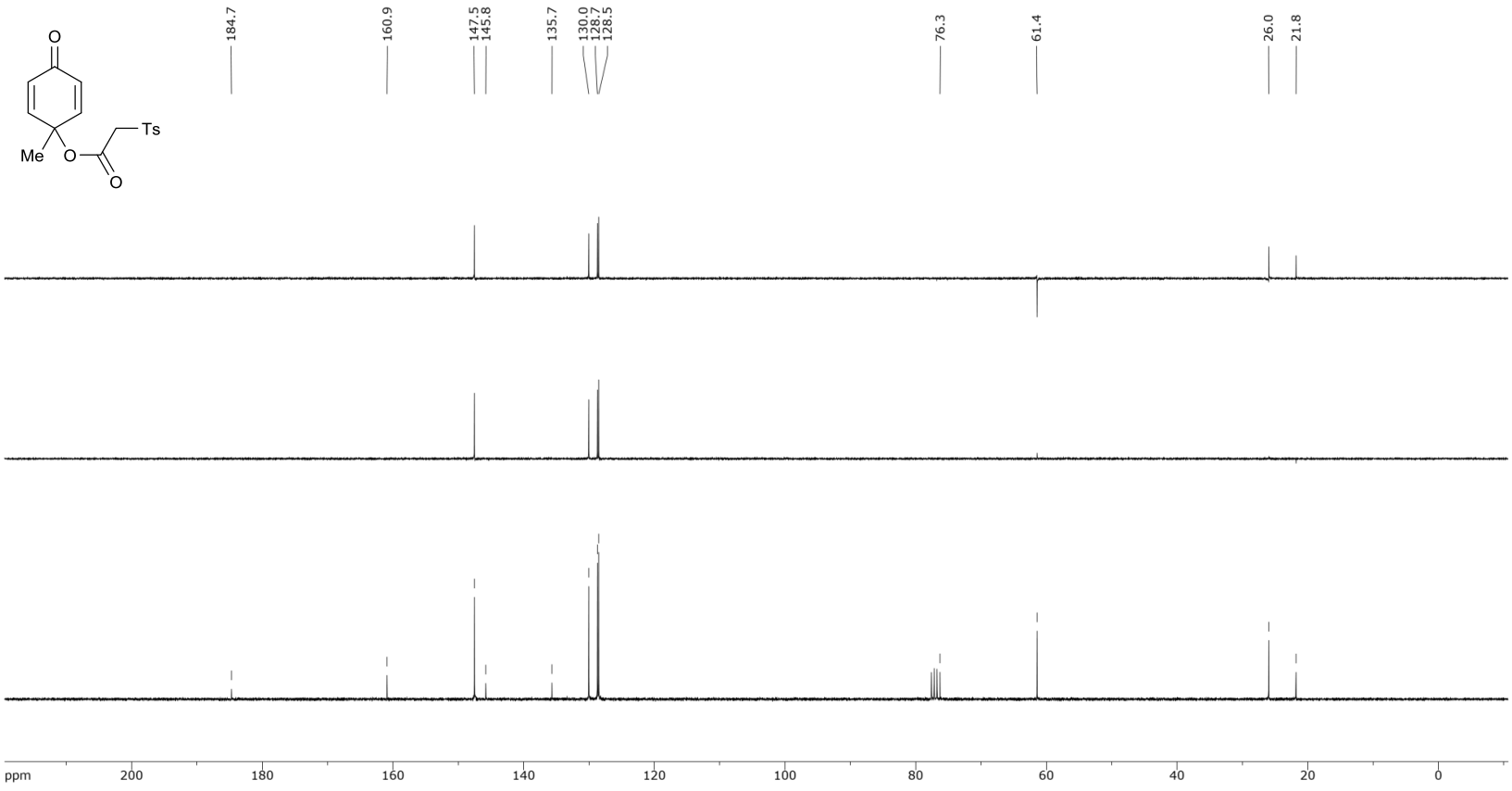
Morpholine-tethered cyclohexadienone 2.9 – ^{13}C NMR



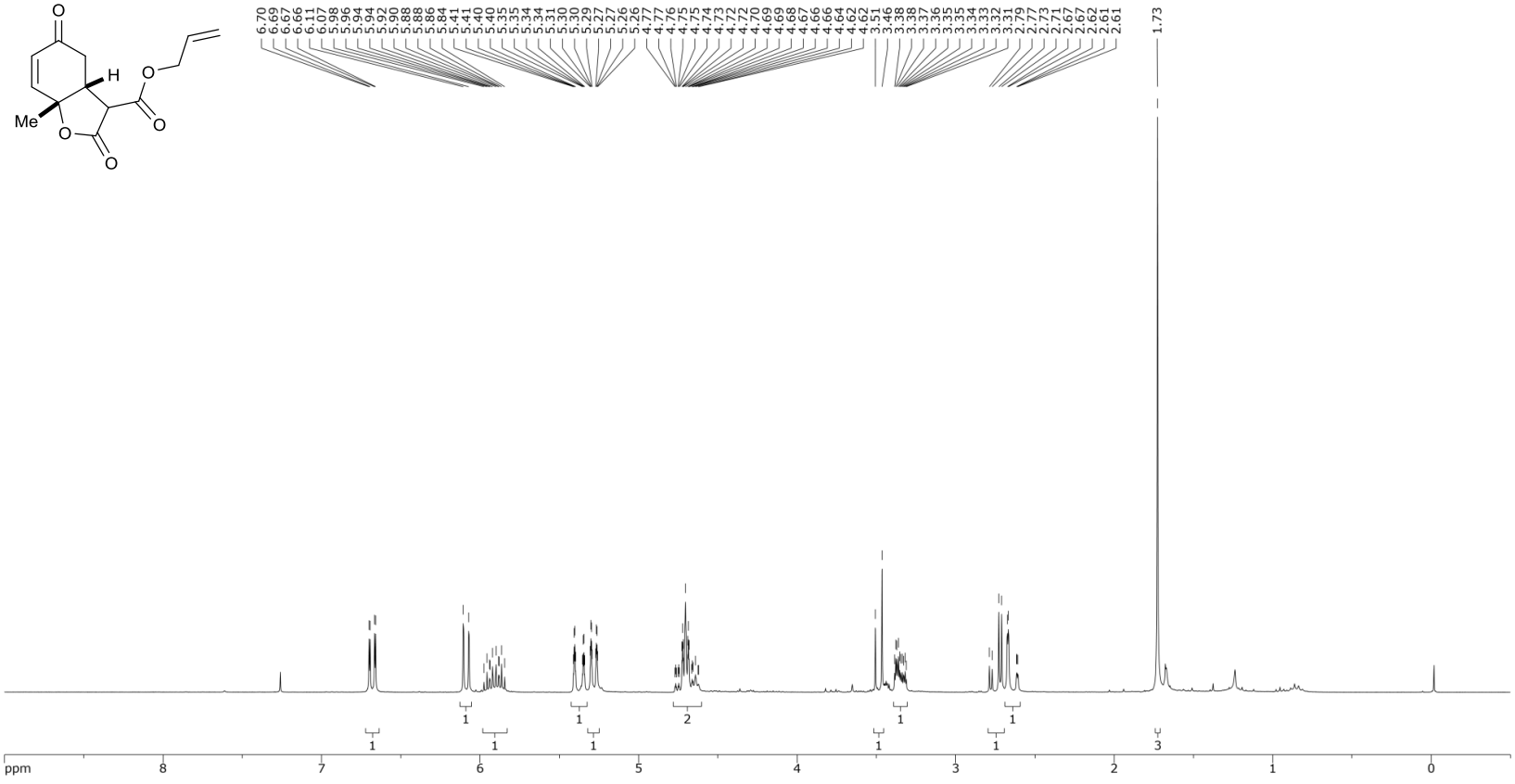
Sulfone-tethered cyclohexadienone 2.10 – ^{1}H NMR



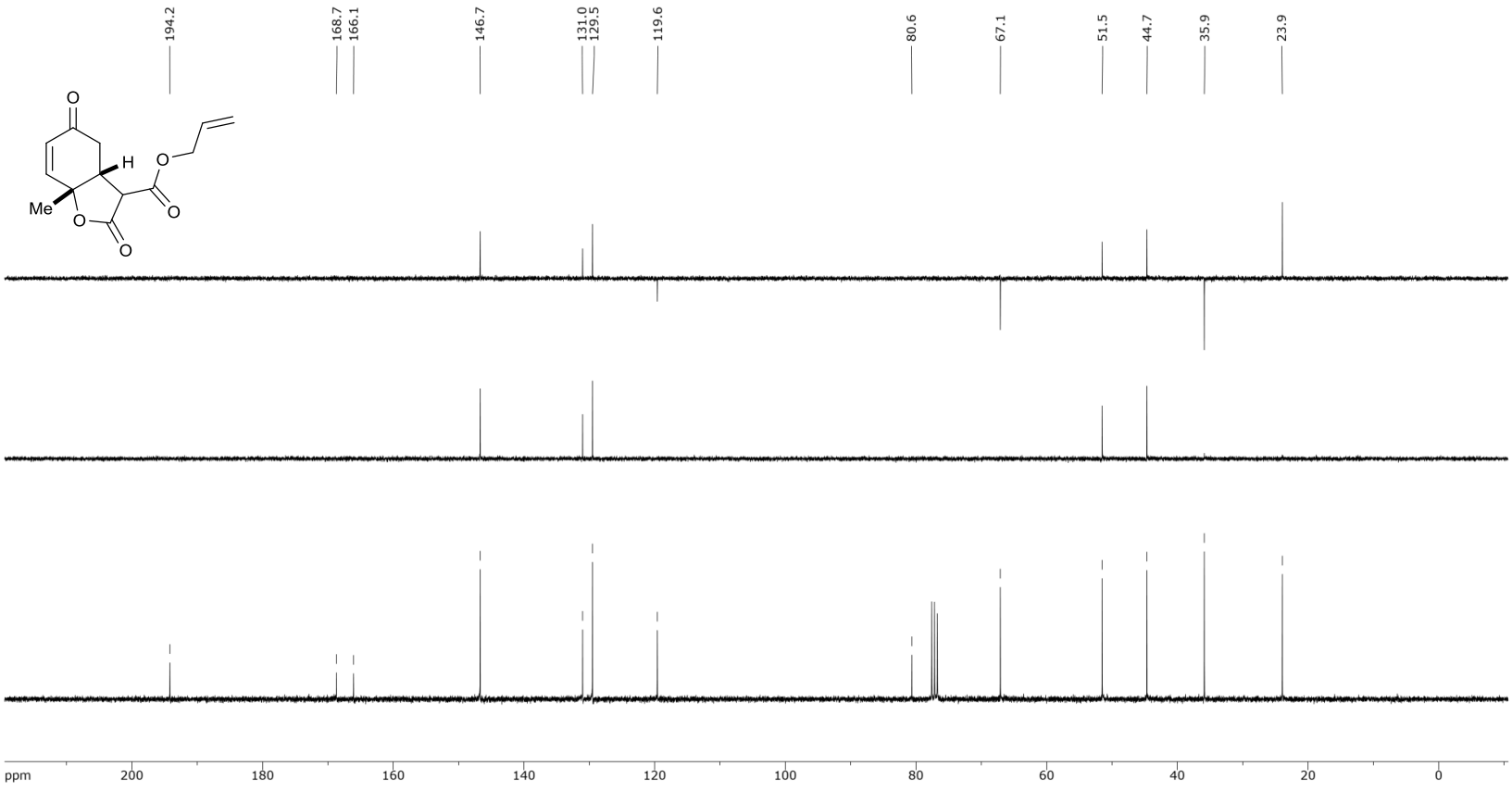
Sulfone-tethered cyclohexadienone 2.10 – ^{13}C NMR



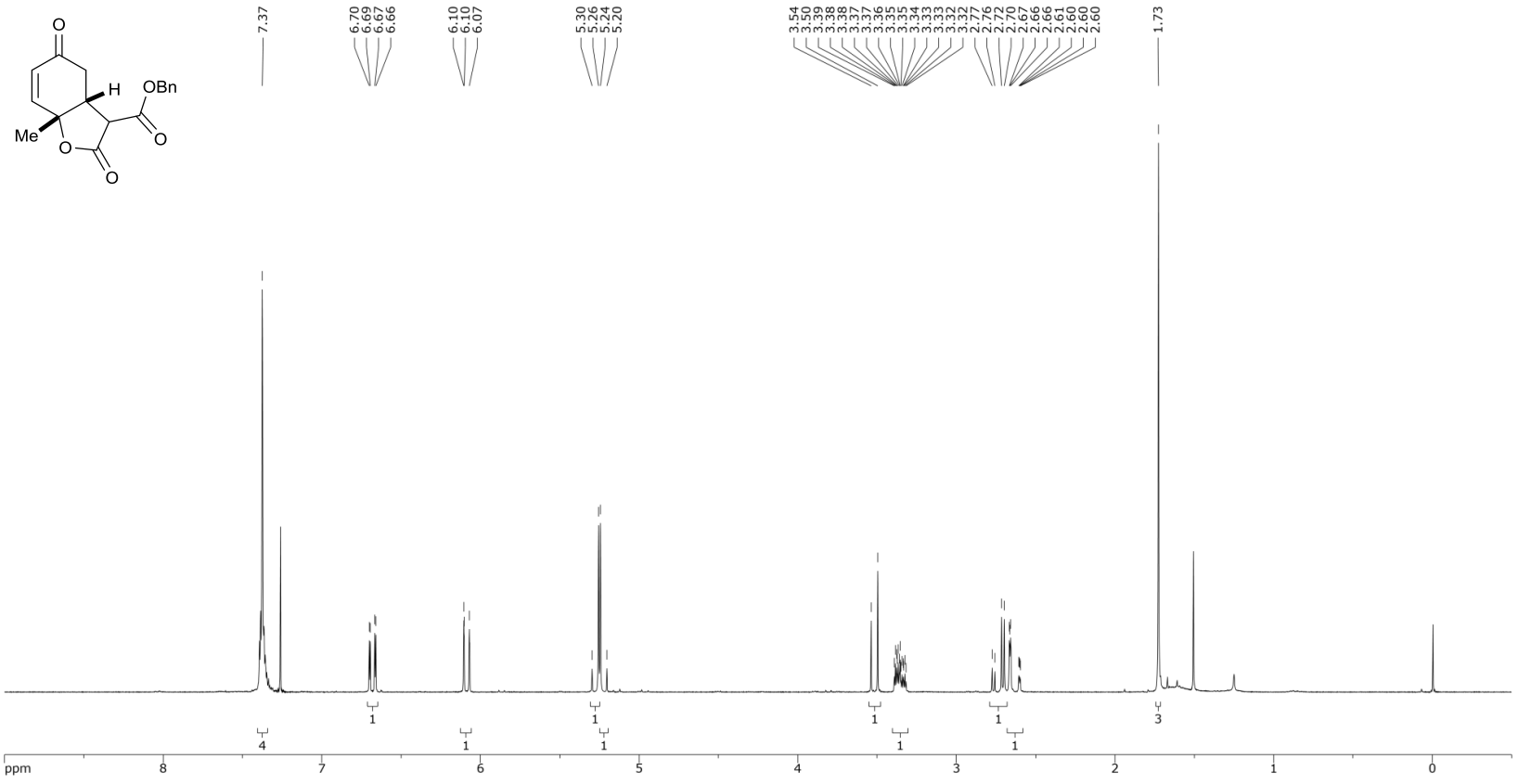
Bicyclic lactone 2.11 – ^{1}H NMR



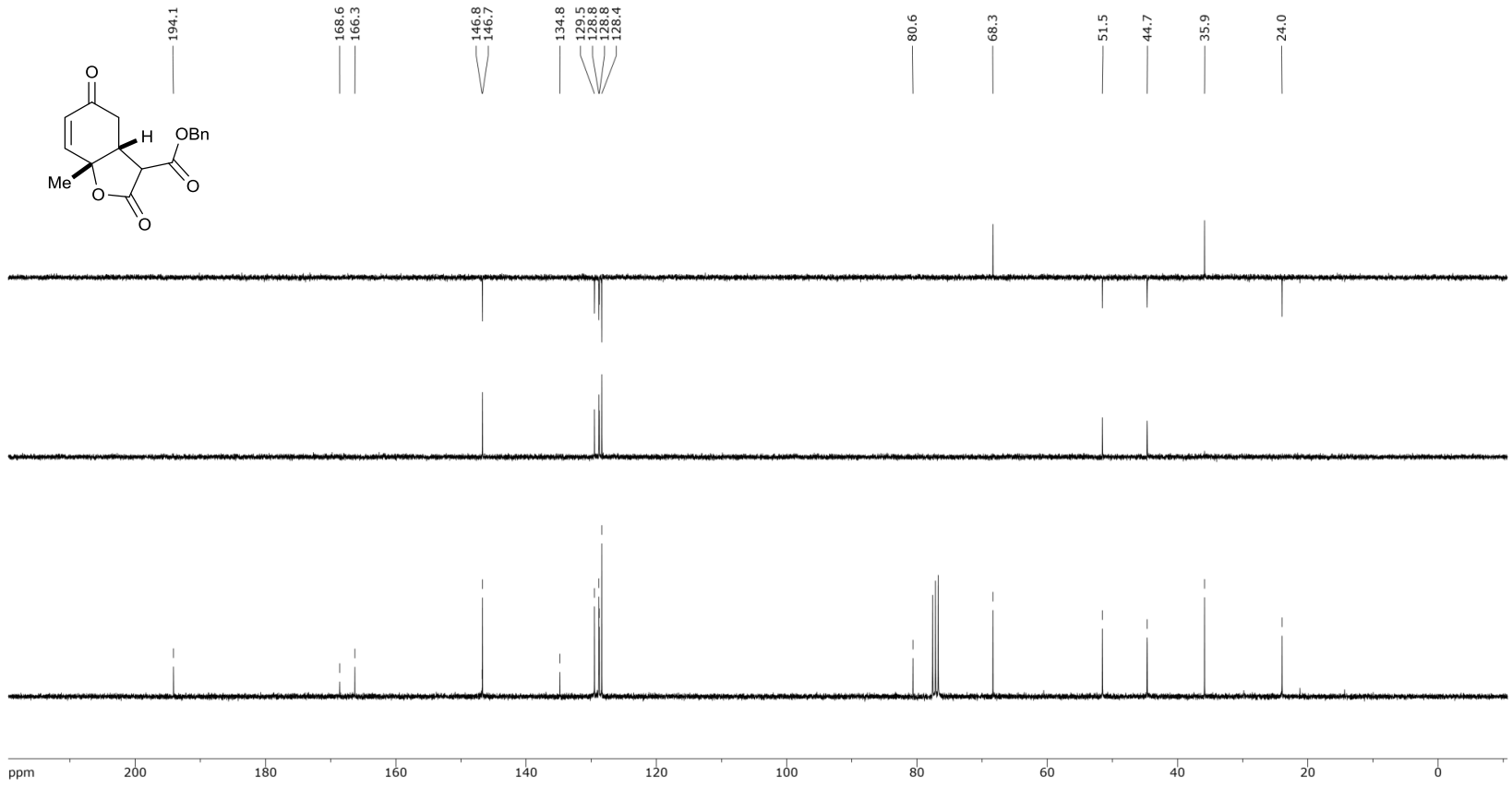
Bicyclic lactone 2.11 – ^{13}C NMR



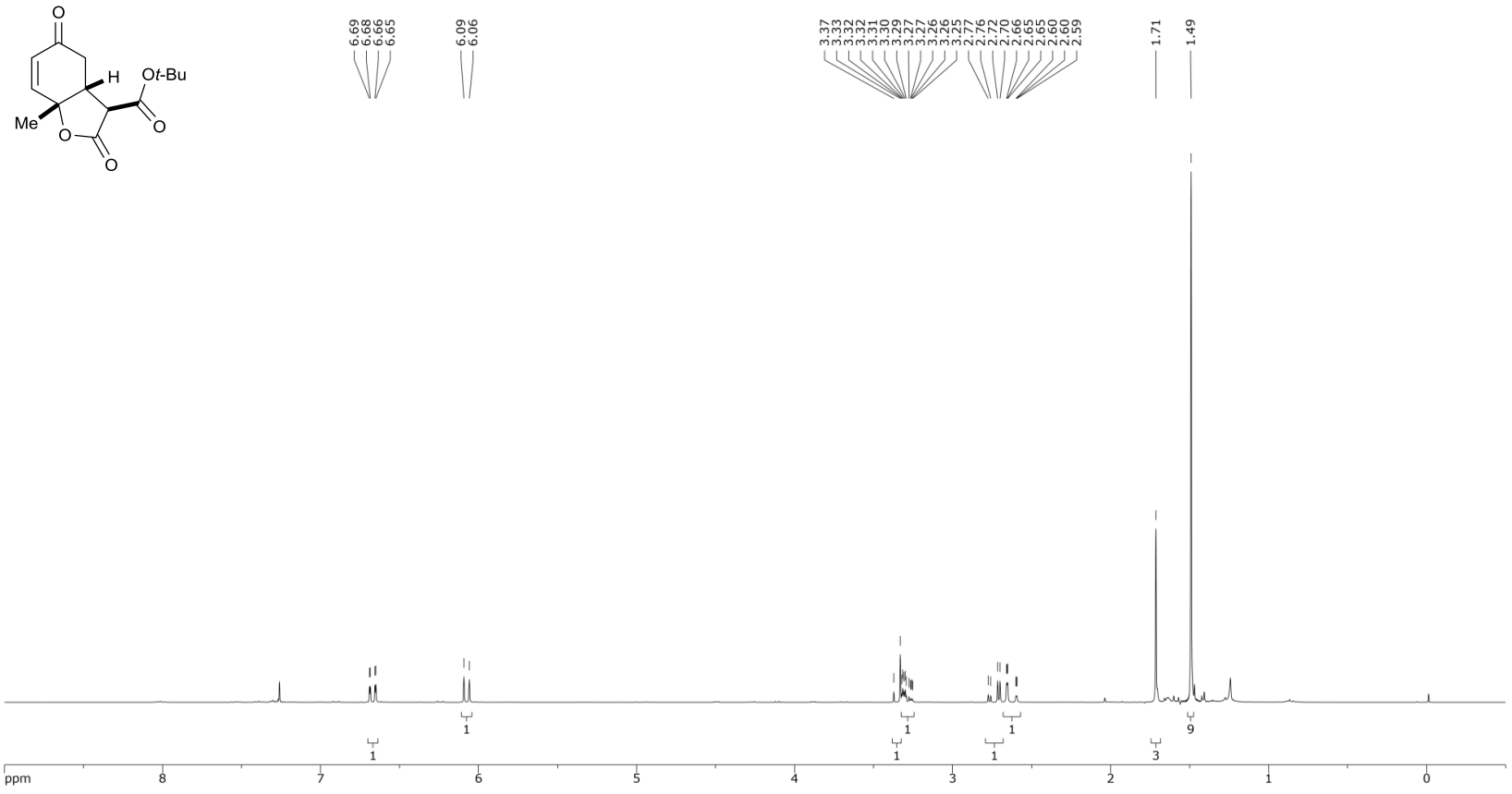
Bicyclic lactone 2.12 – ^{1}H NMR



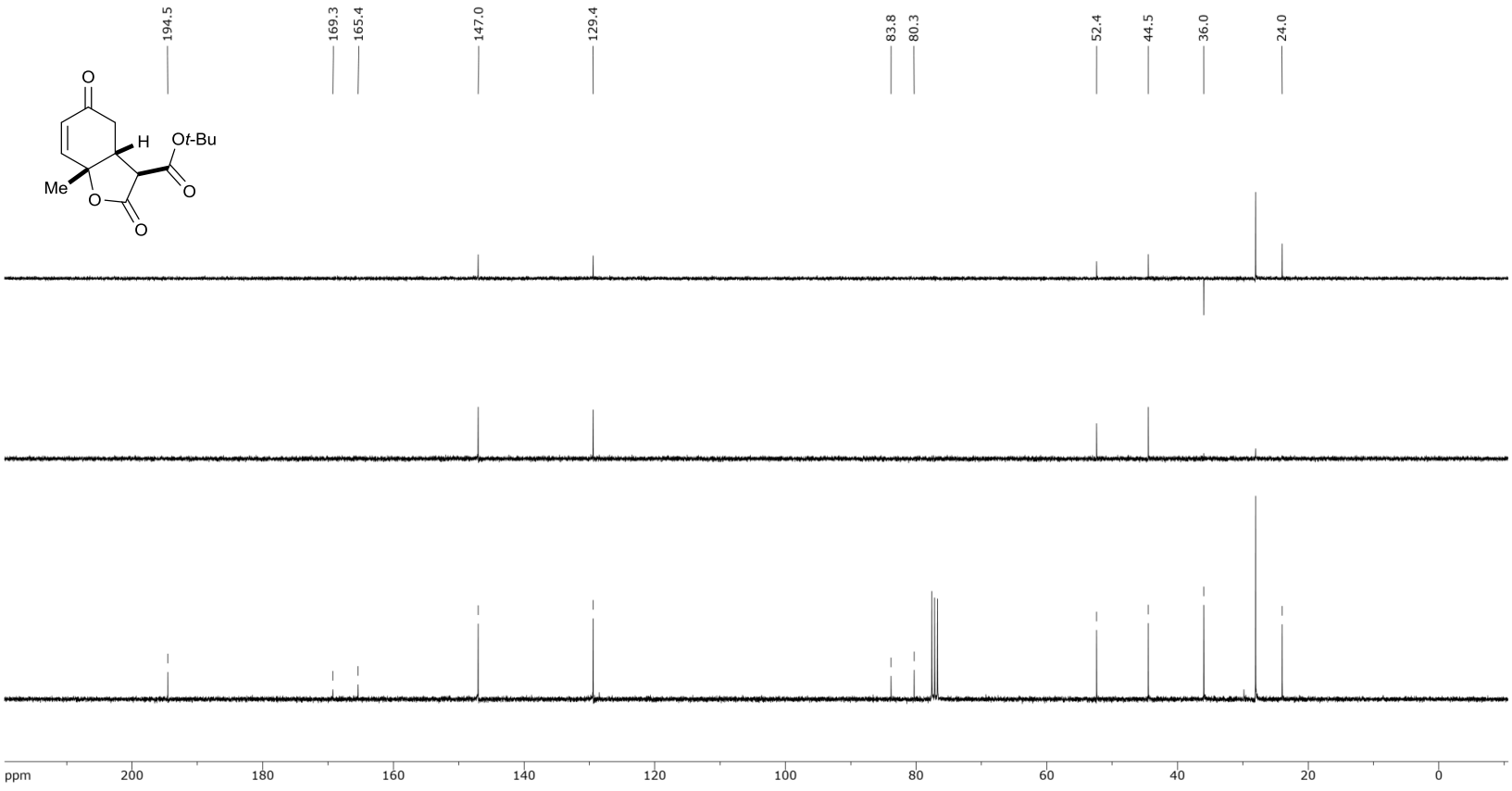
Bicyclic lactone 2.12 – ^{13}C NMR



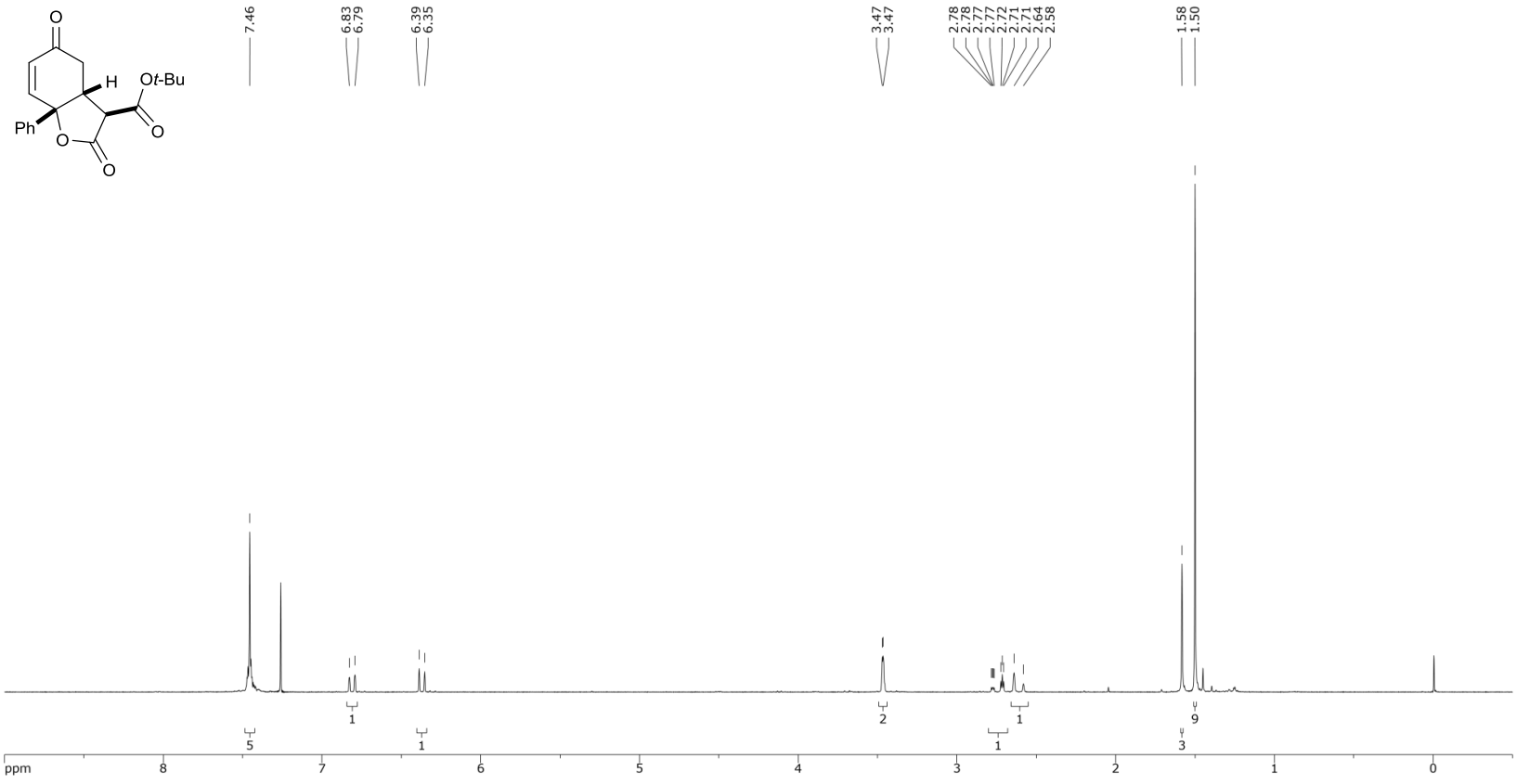
Bicyclic lactone 2.13a – ^{1}H NMR



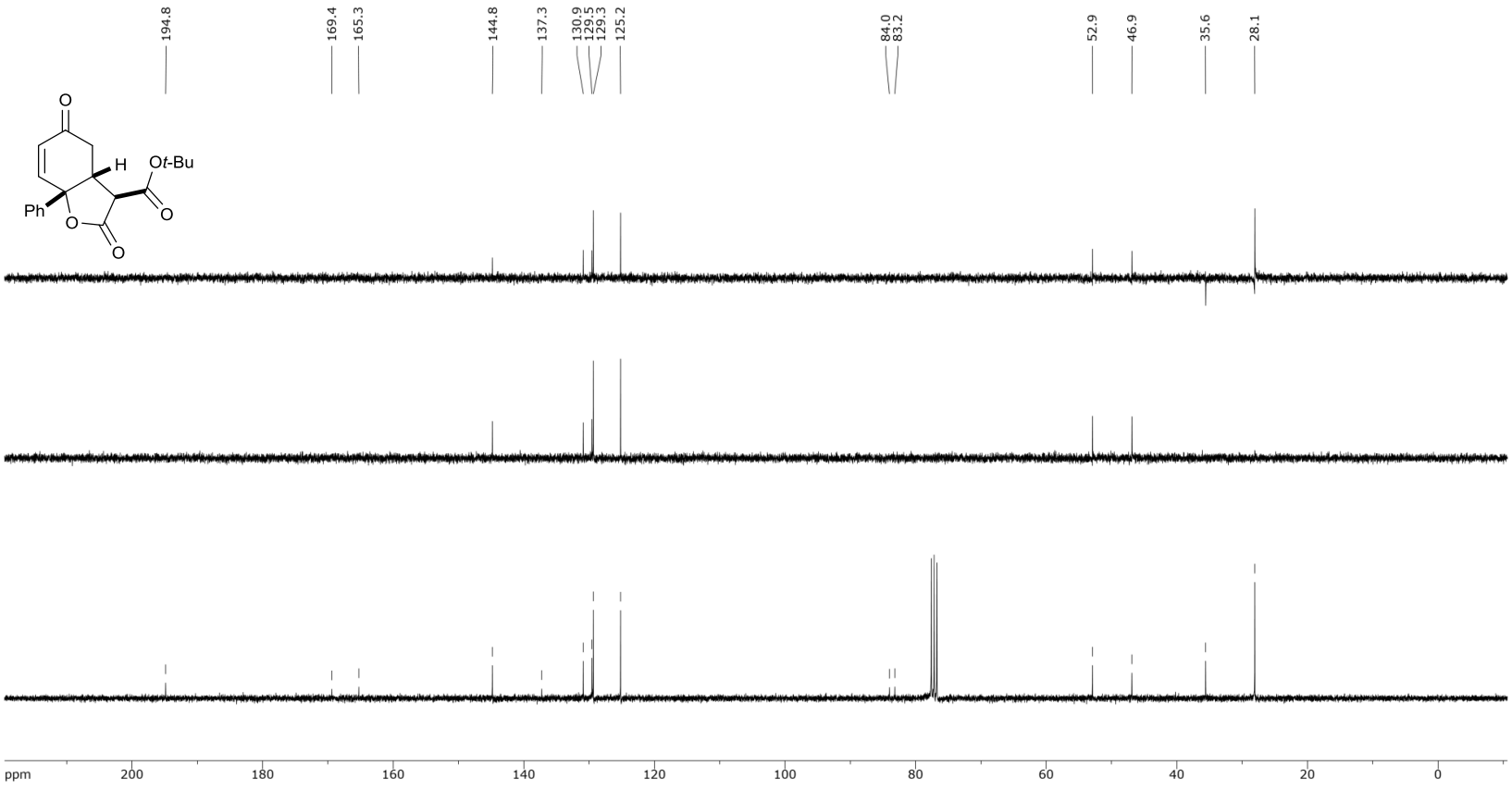
Bicyclic lactone 2.13a – ^{13}C NMR



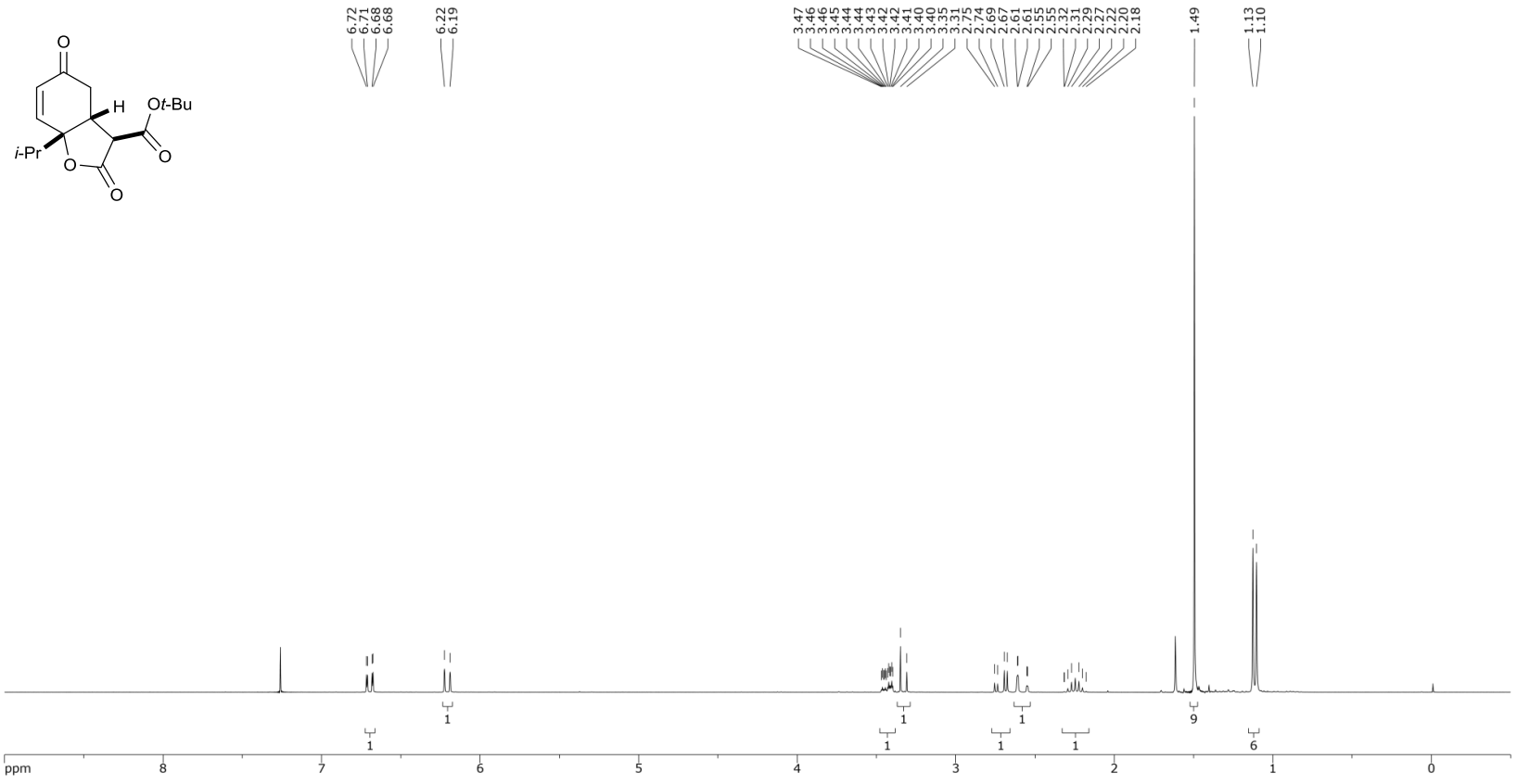
Bicyclic lactone 2.13b – ^{1}H NMR



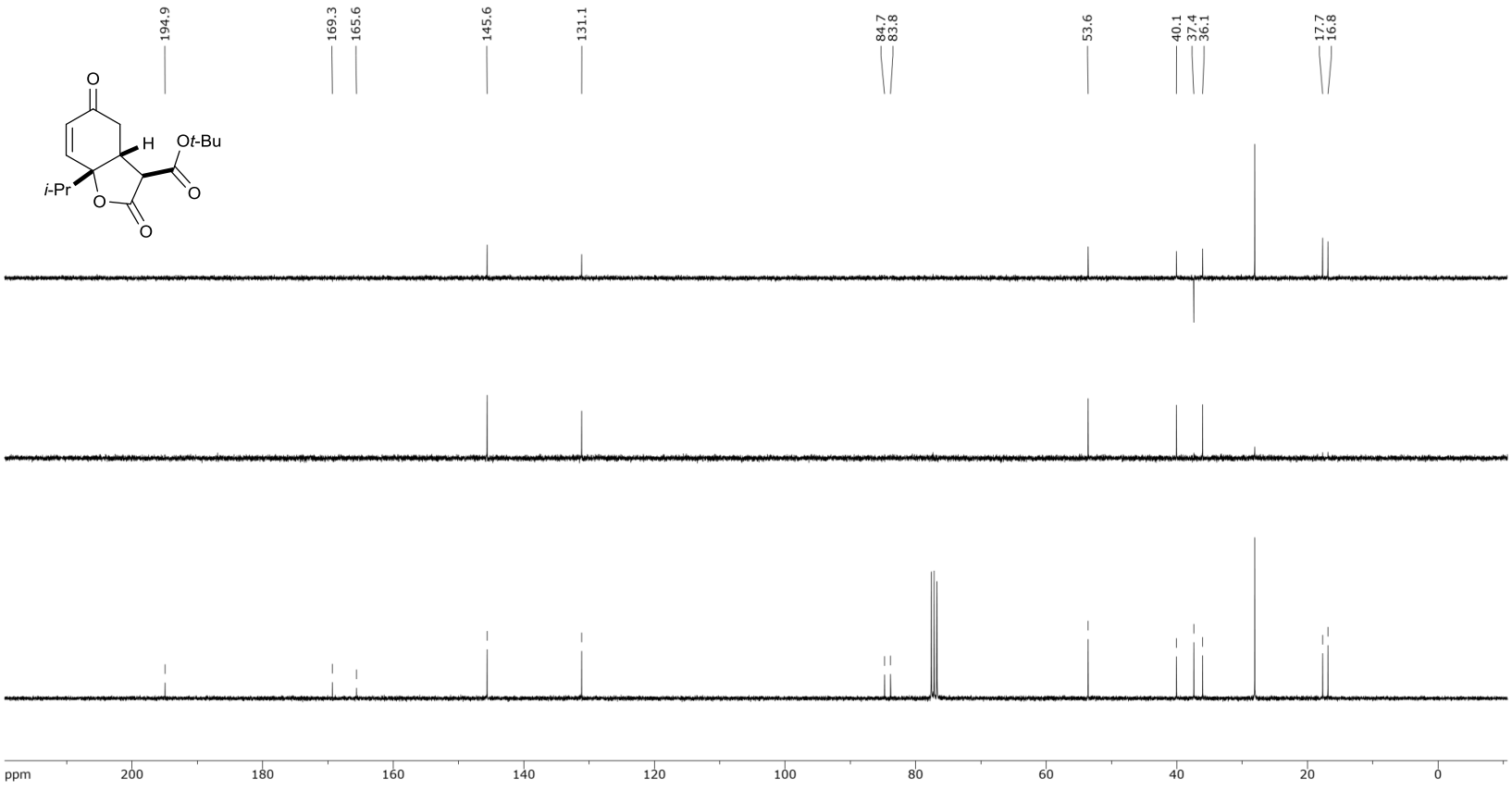
Bicyclic lactone 2.13b – ^{13}C NMR



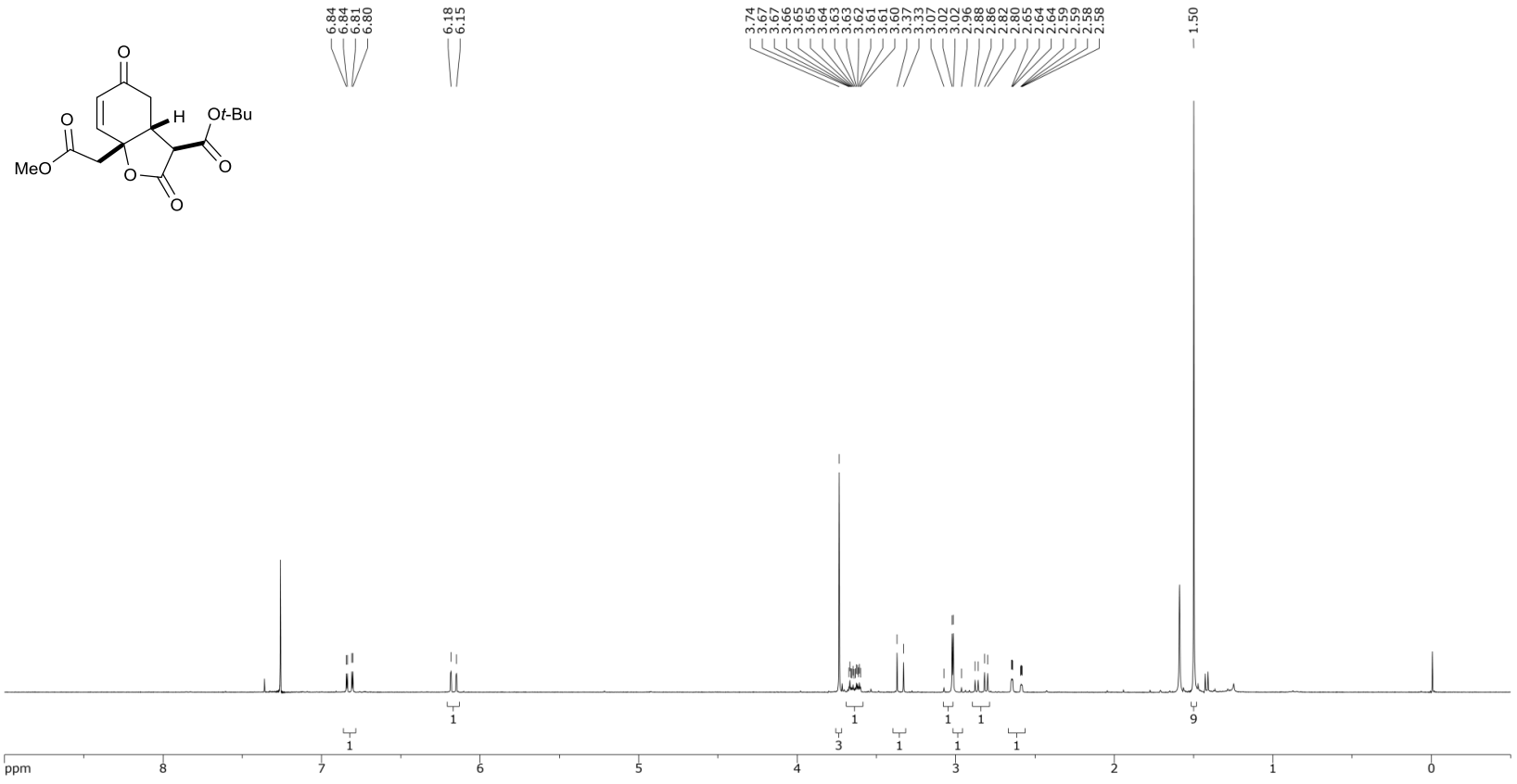
Bicyclic lactone 2.13c – ^{1}H NMR



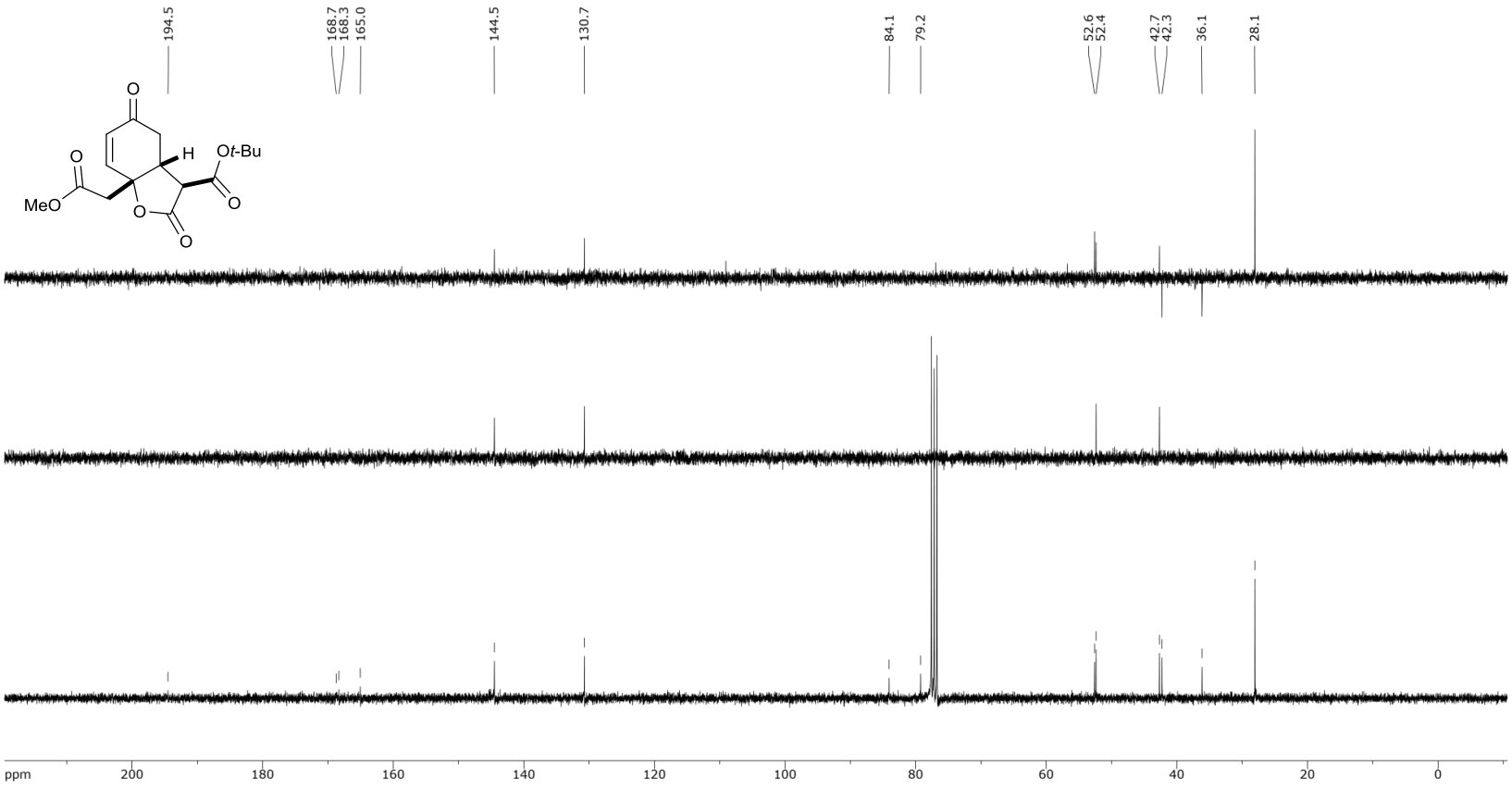
Bicyclic lactone 2.13c – ^{13}C NMR



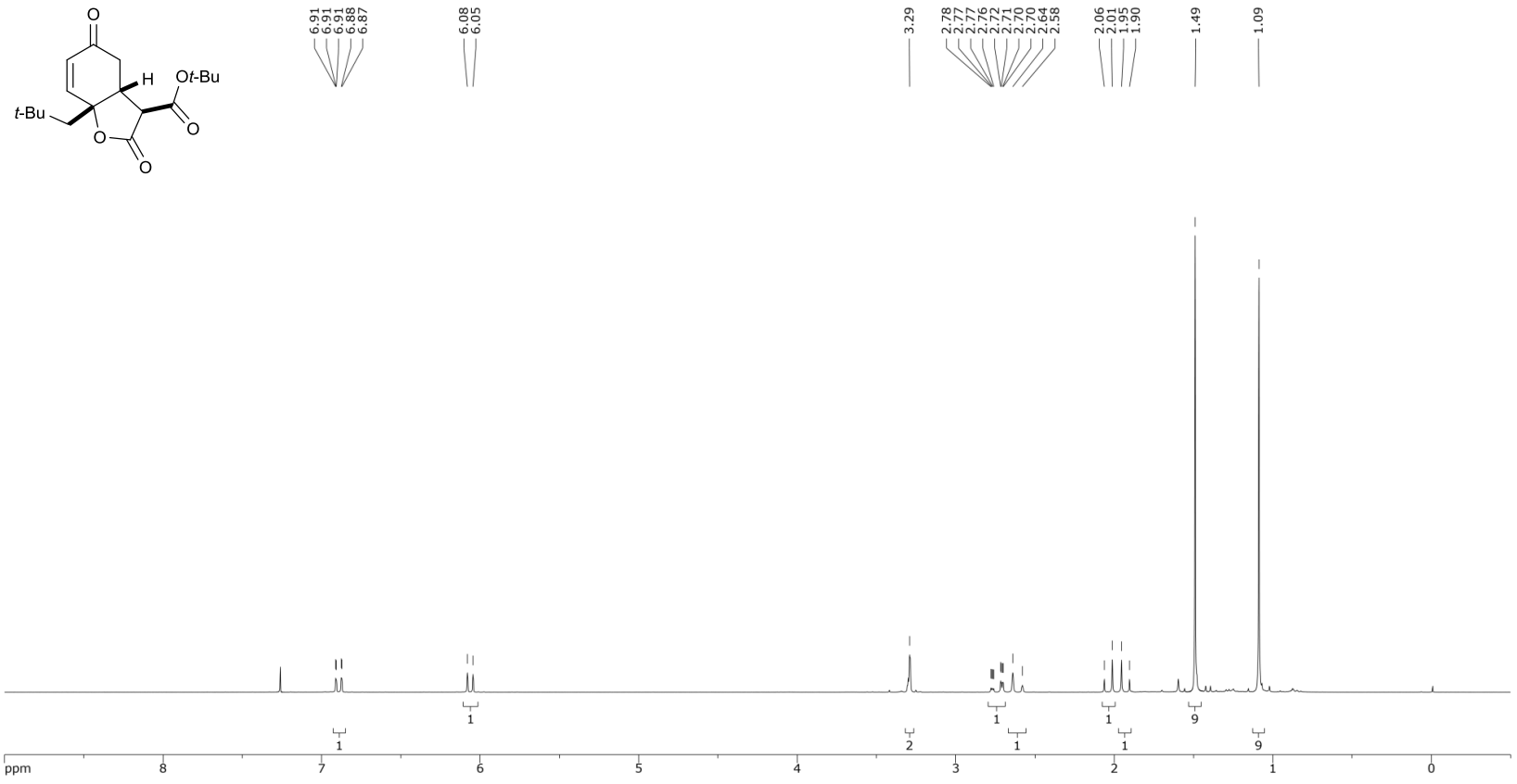
Bicyclic lactone 2.13d – ^{1}H NMR



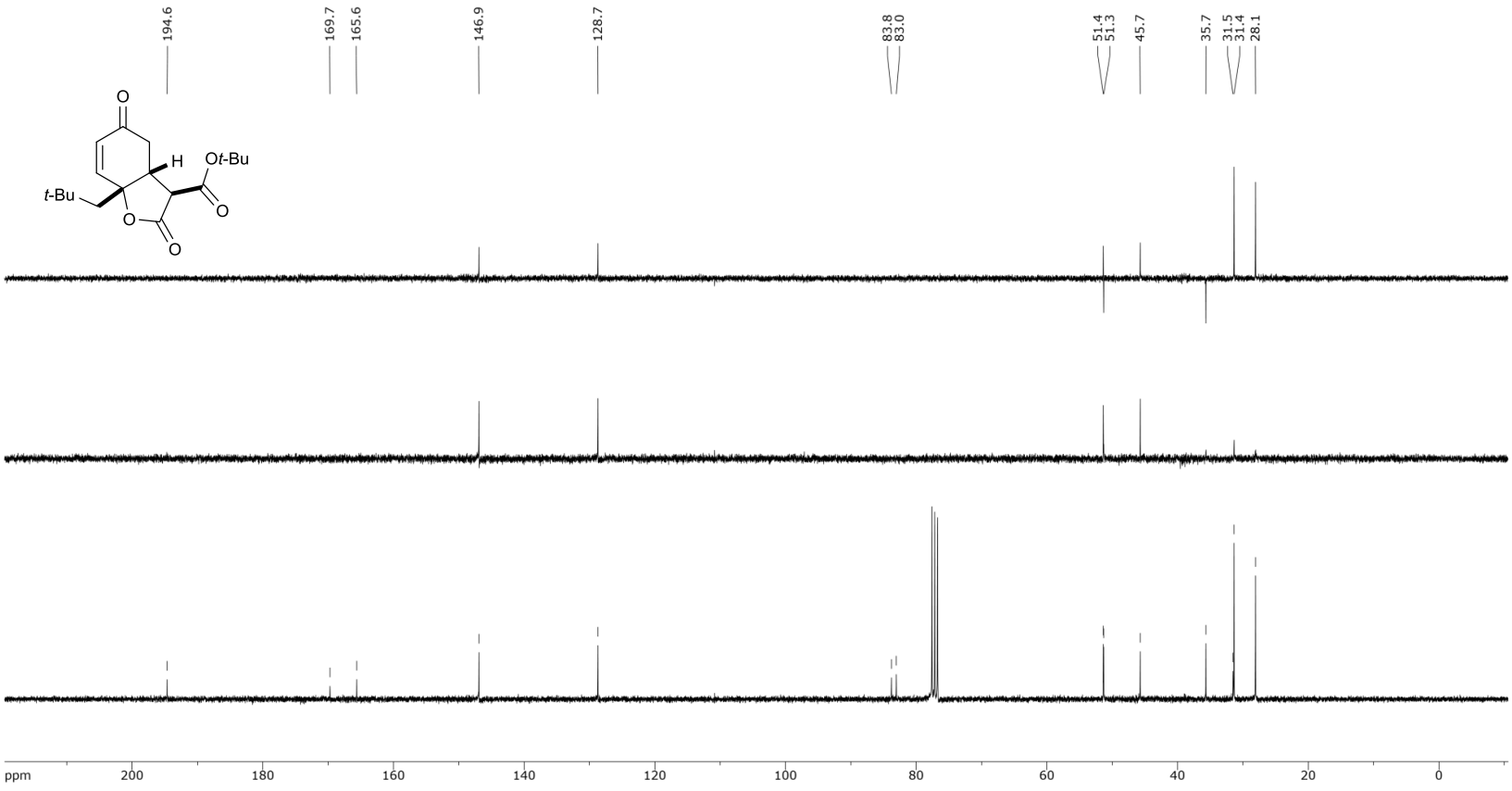
Bicyclic lactone 2.13d – ^{13}C NMR



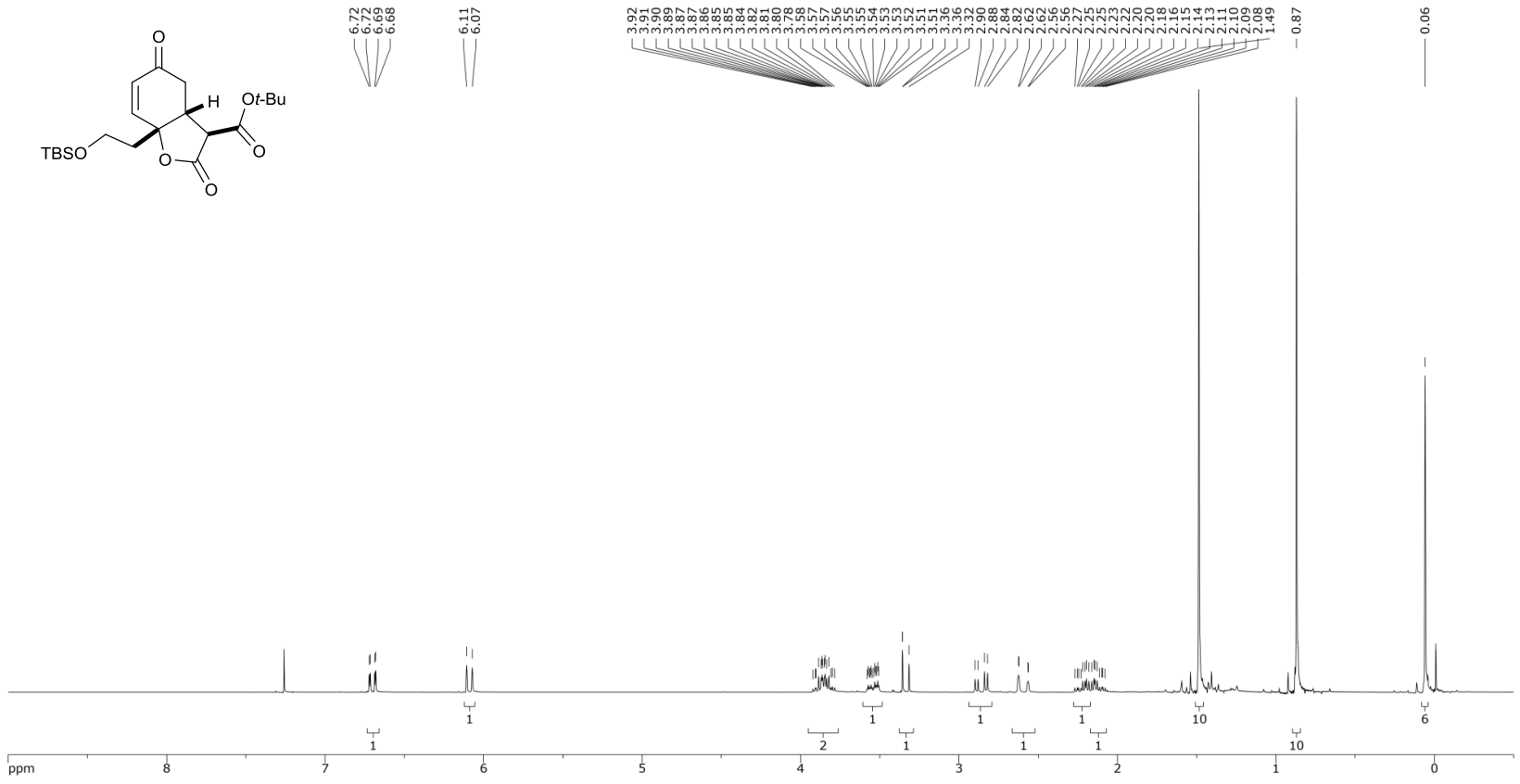
Bicyclic lactone 2.13e – ^{1}H NMR



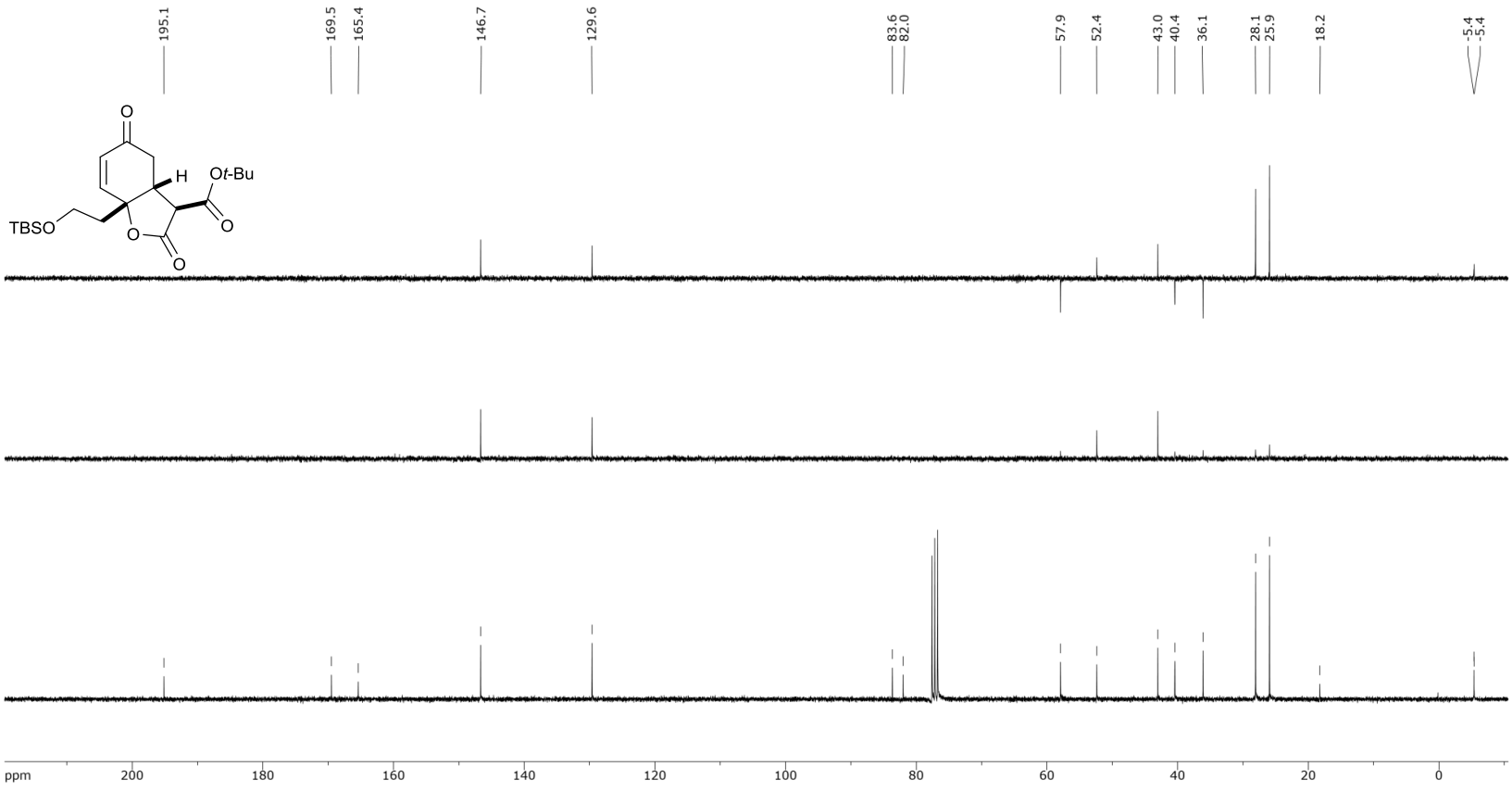
Bicyclic lactone 2.13e – ^{13}C NMR



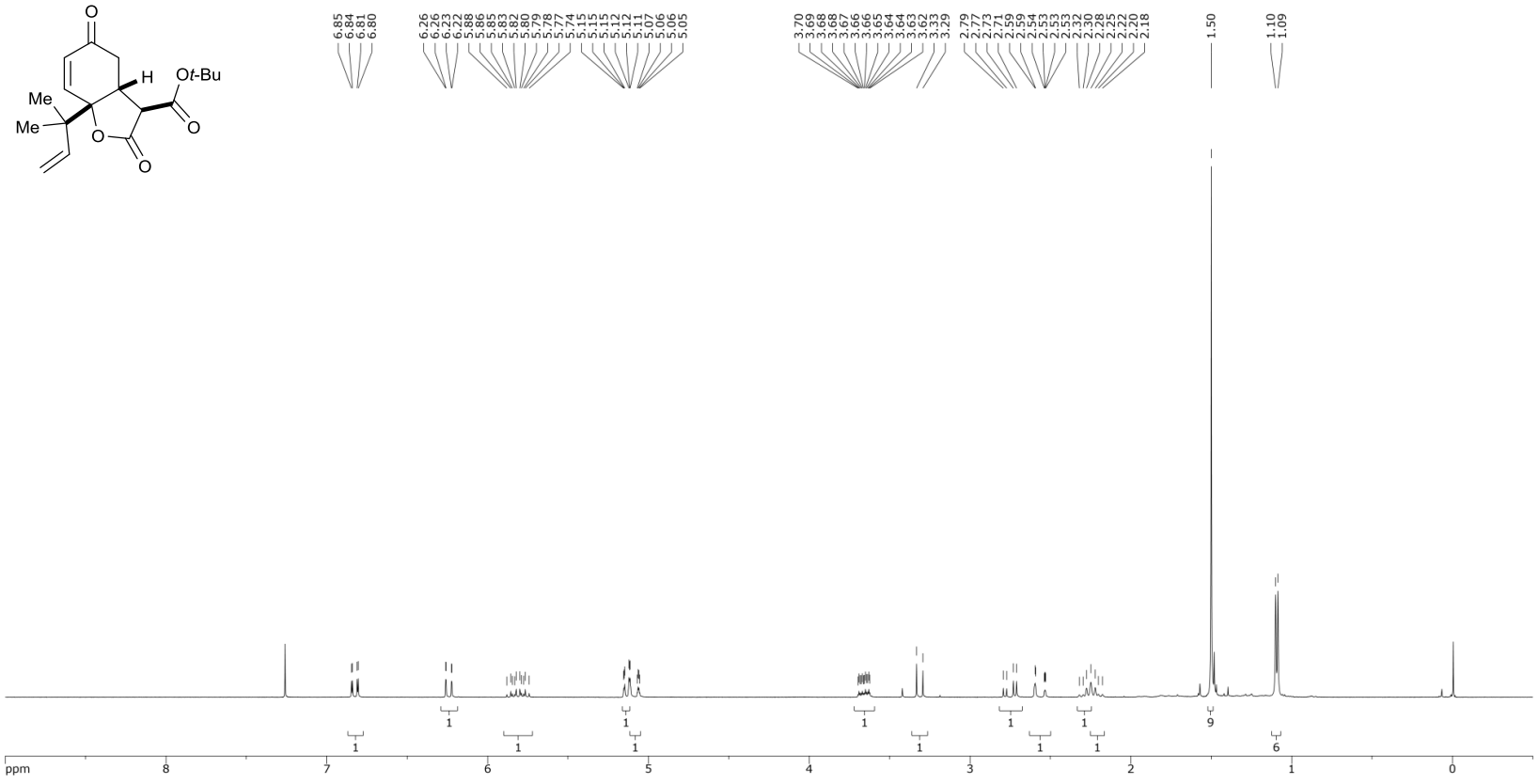
Bicyclic lactone 2.13f – ^{1}H NMR



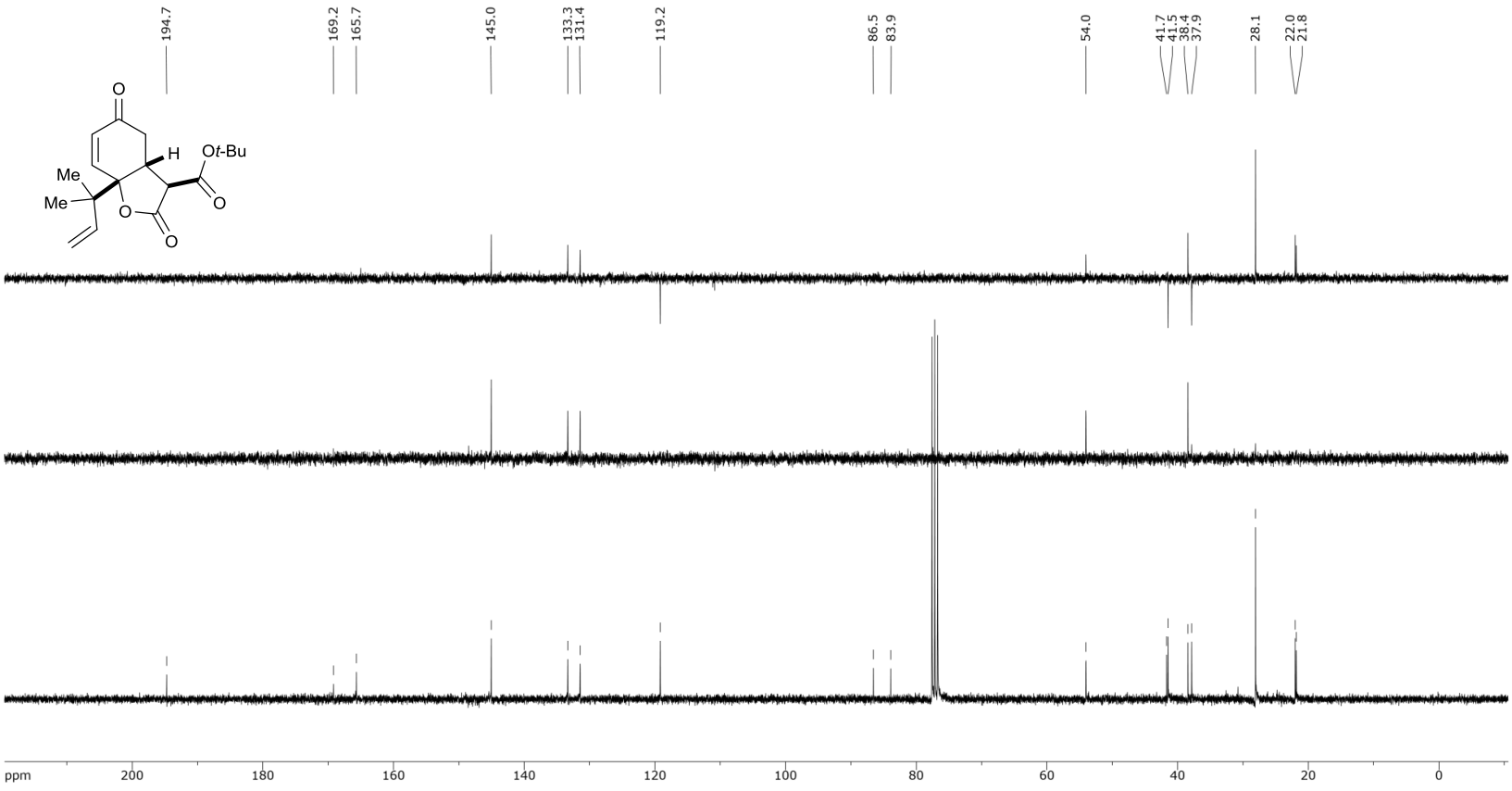
Bicyclic lactone 2.13f – ^{13}C NMR



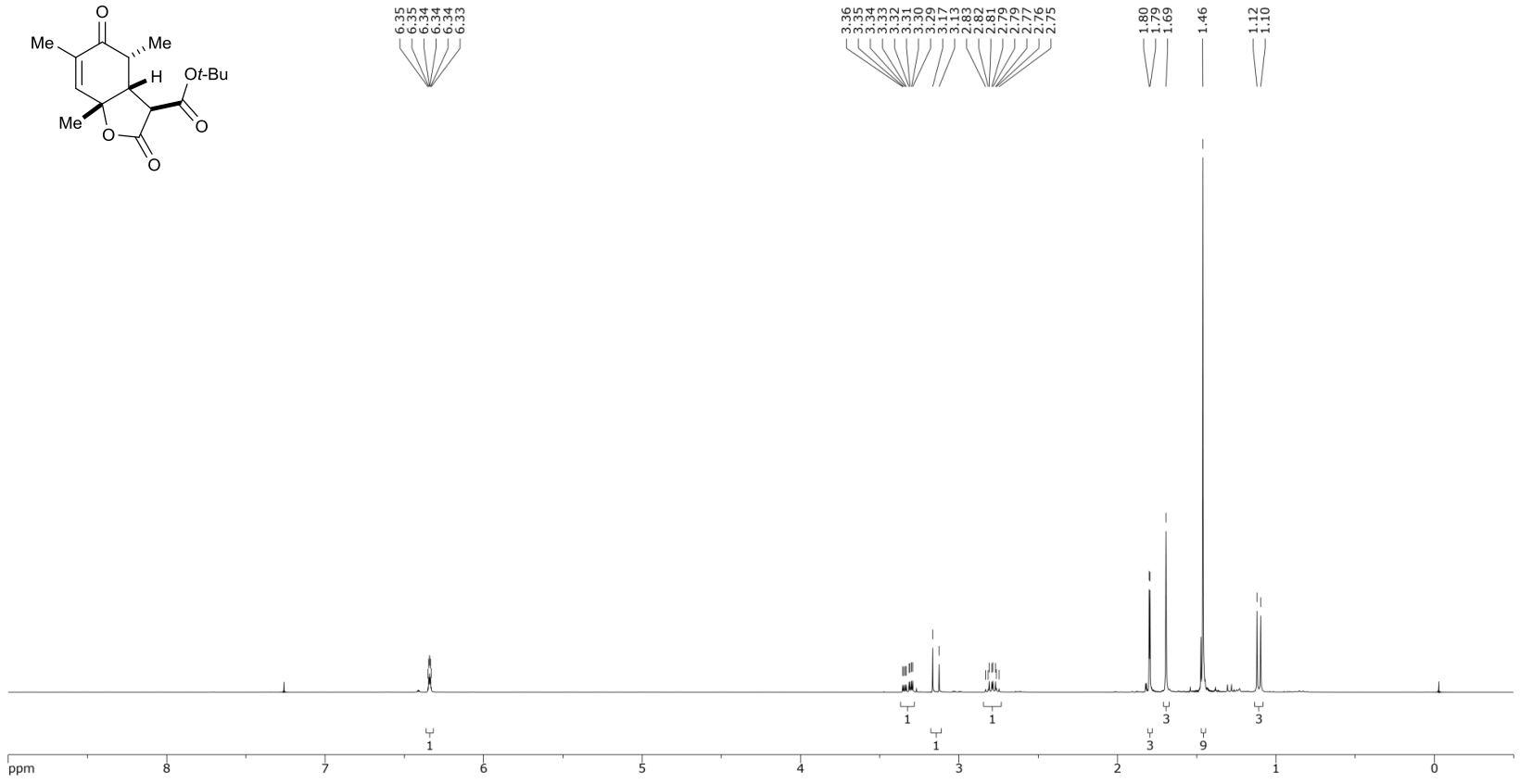
Bicyclic lactone 2.13g – ^{1}H NMR



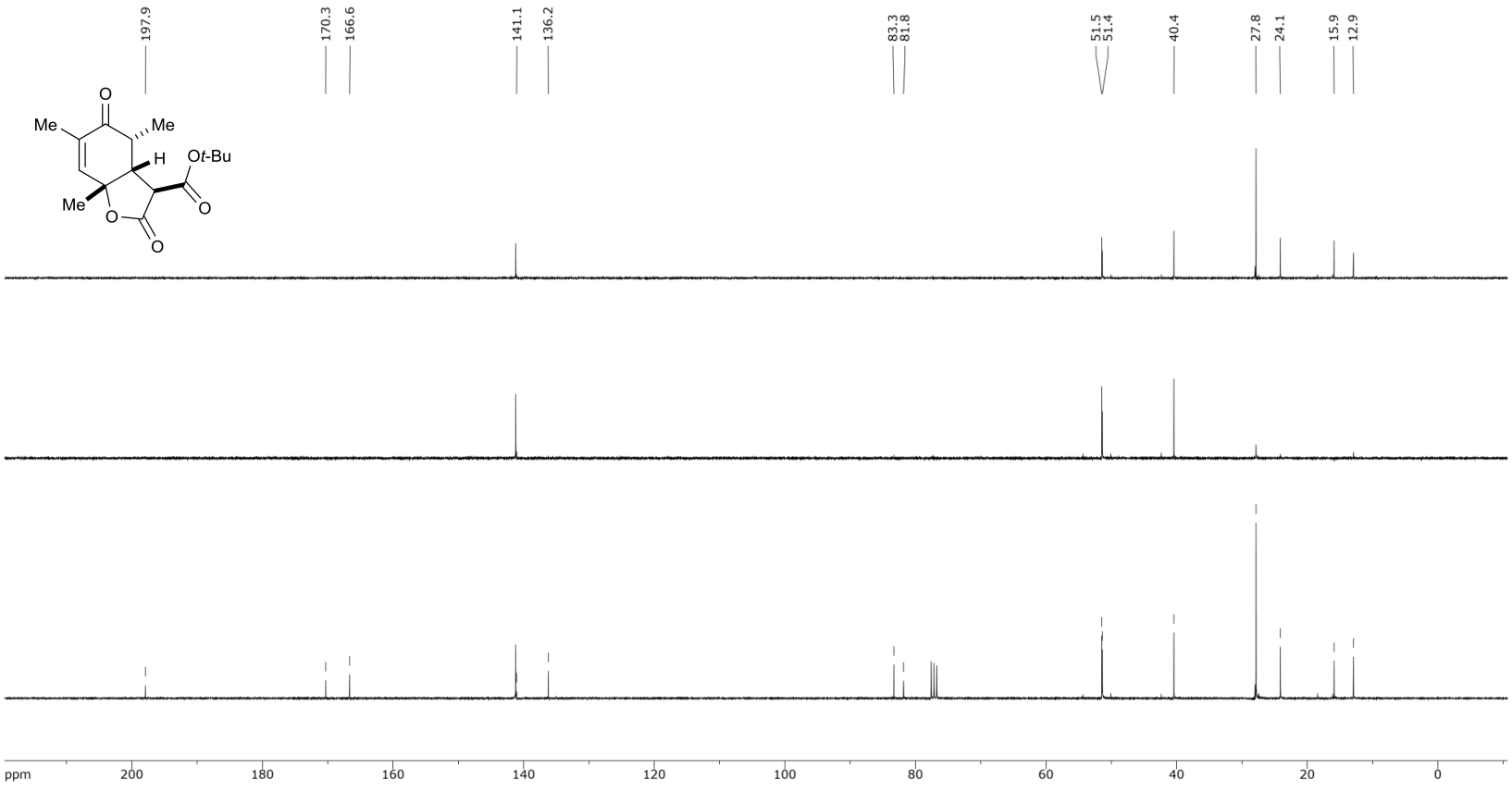
Bicyclic lactone 2.13g – ^{13}C NMR



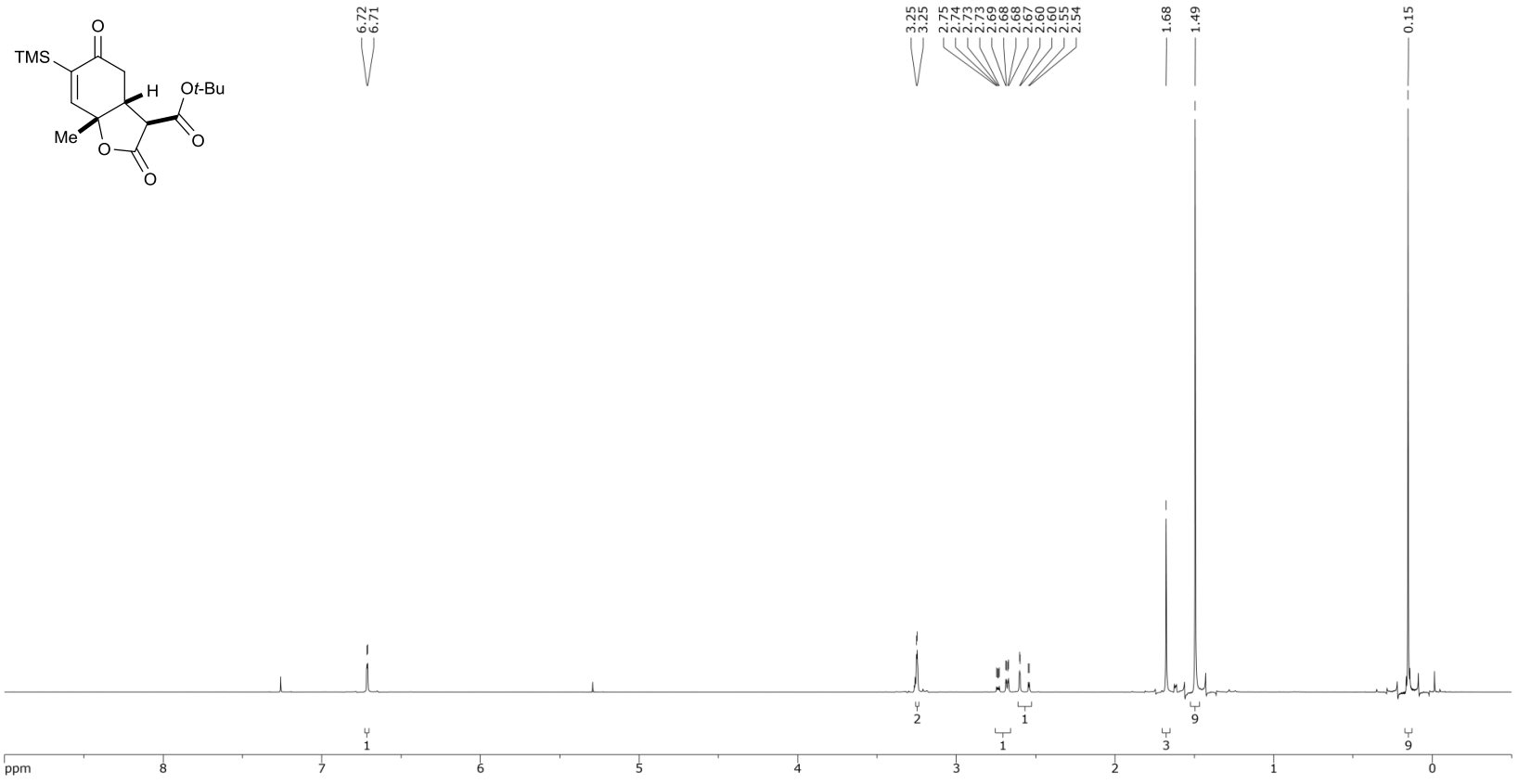
Bicyclic lactone 2.13h – ^{1}H NMR



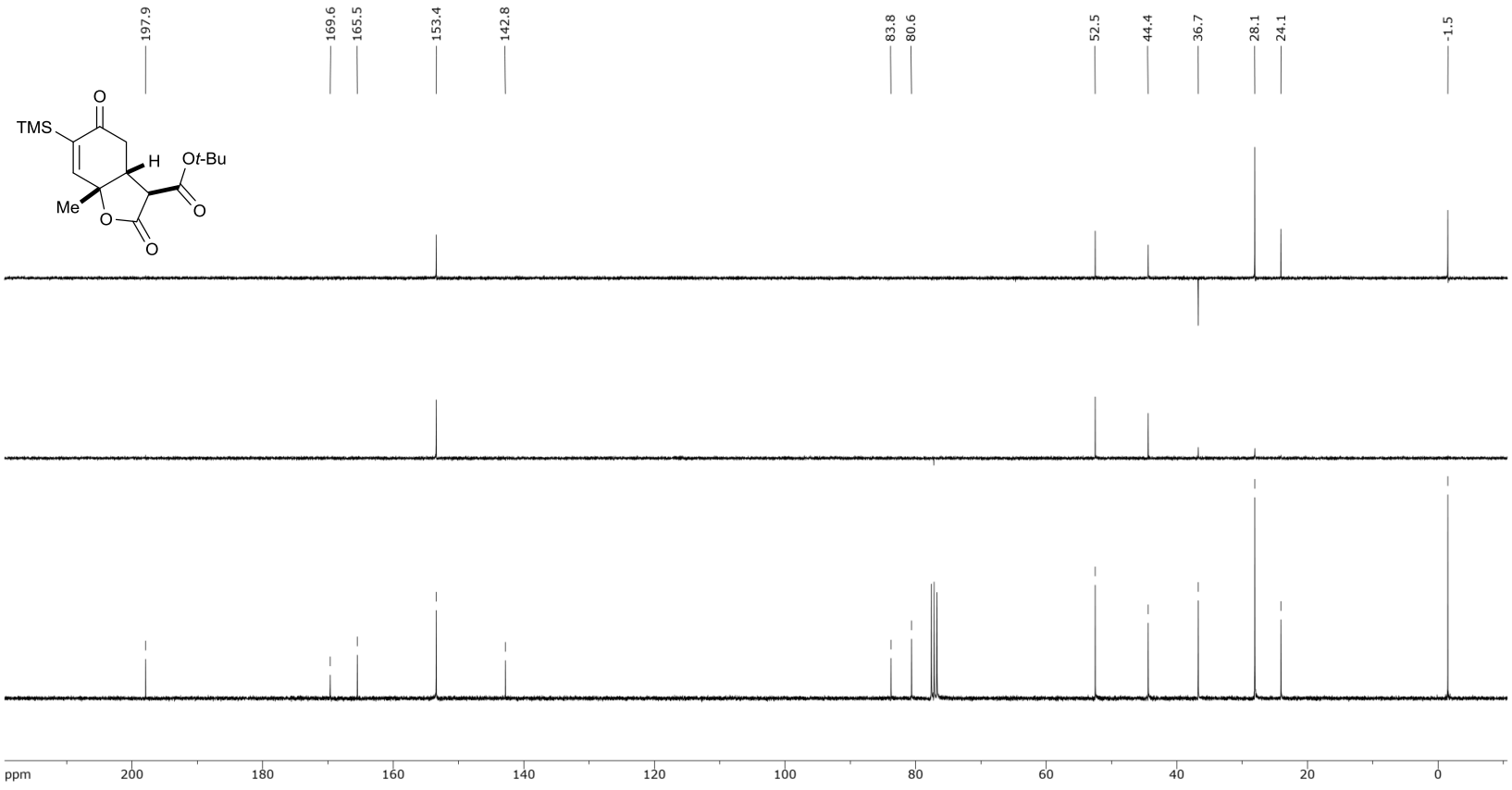
Bicyclic lactone 2.13h – ^{13}C NMR



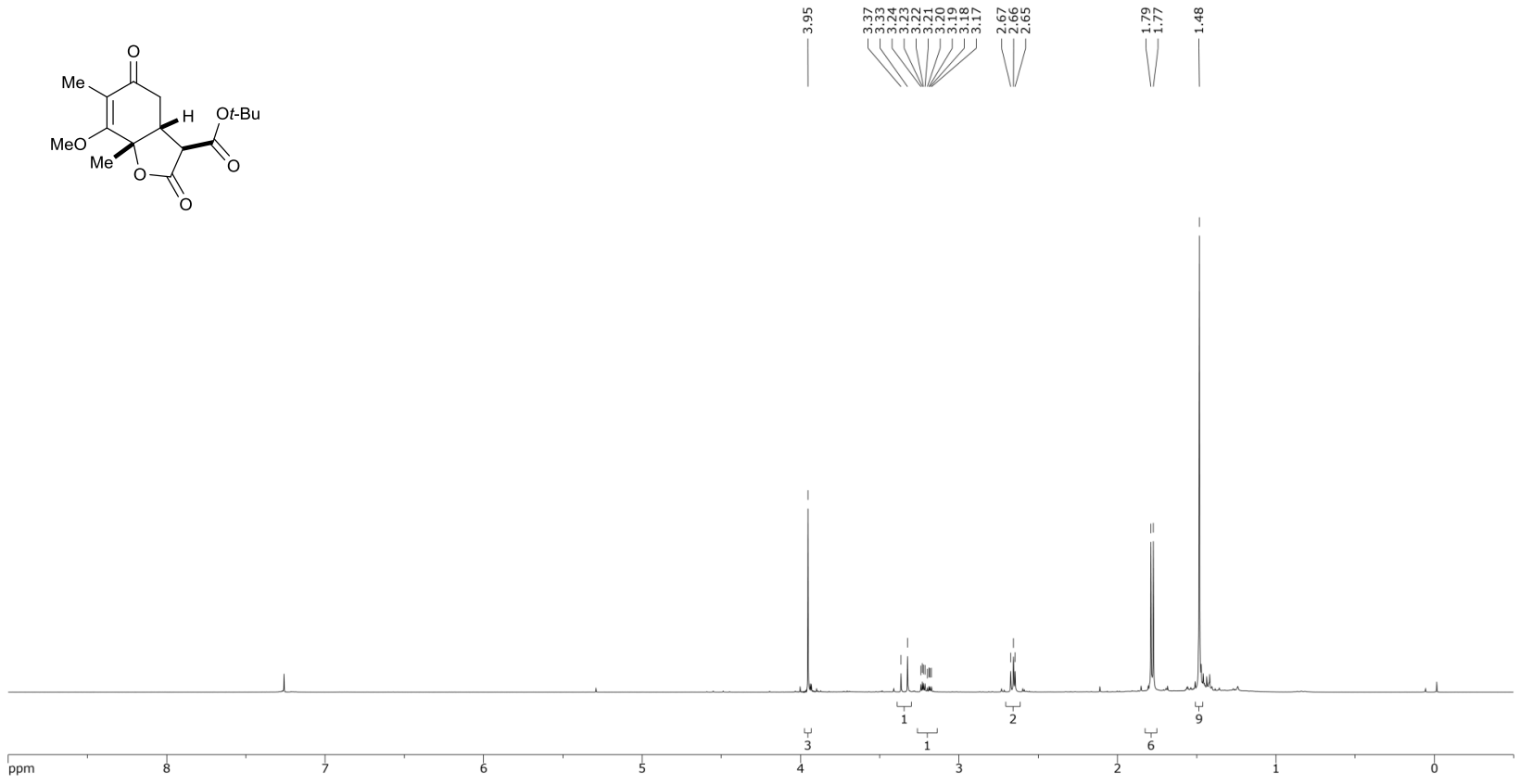
Bicyclic lactone 2.13i – ^{1}H NMR



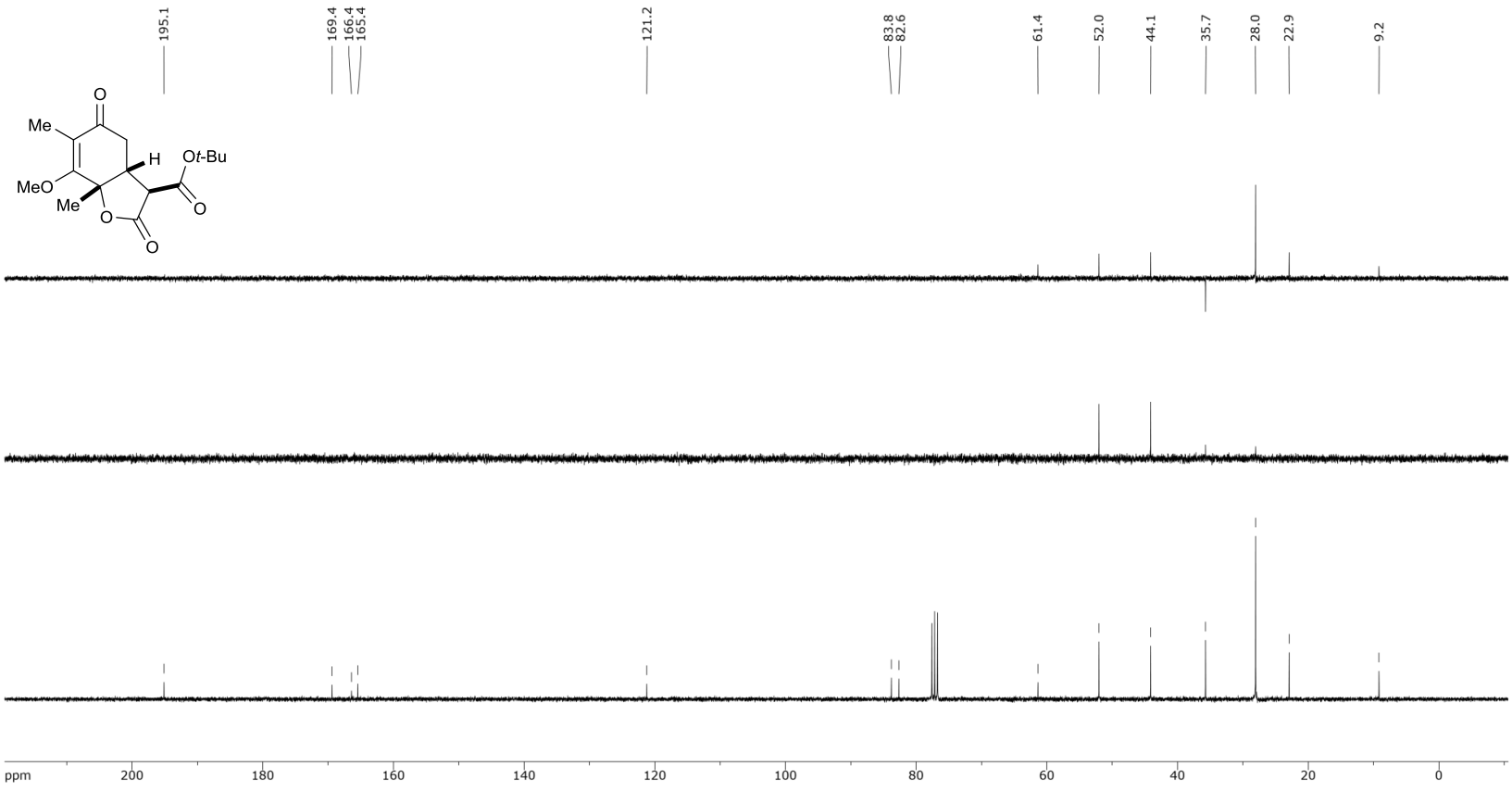
Bicyclic lactone 2.13i – ^{13}C NMR



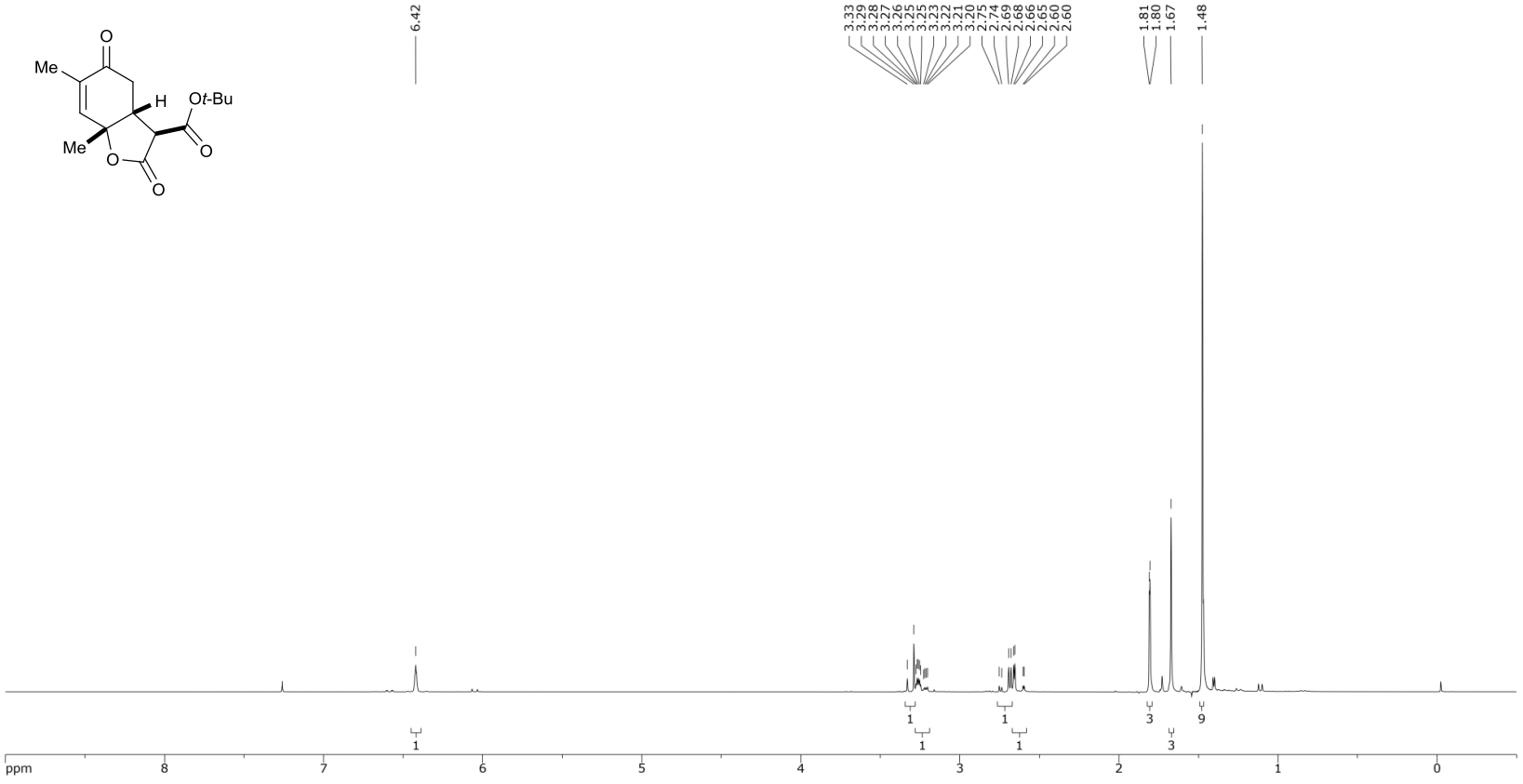
Bicyclic lactone 2.13n – ^{1}H NMR



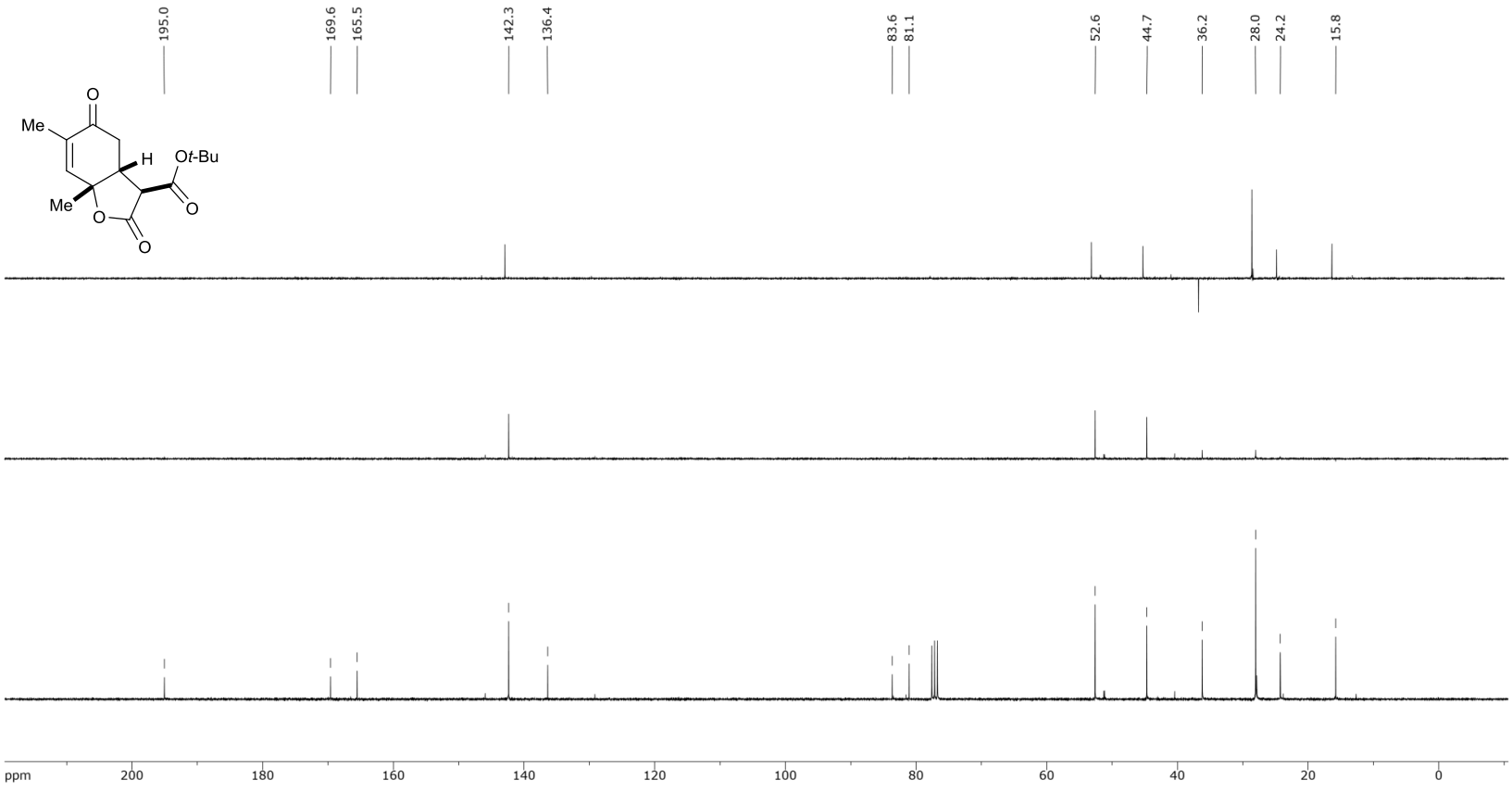
Bicyclic lactone 2.13n – ^{13}C NMR



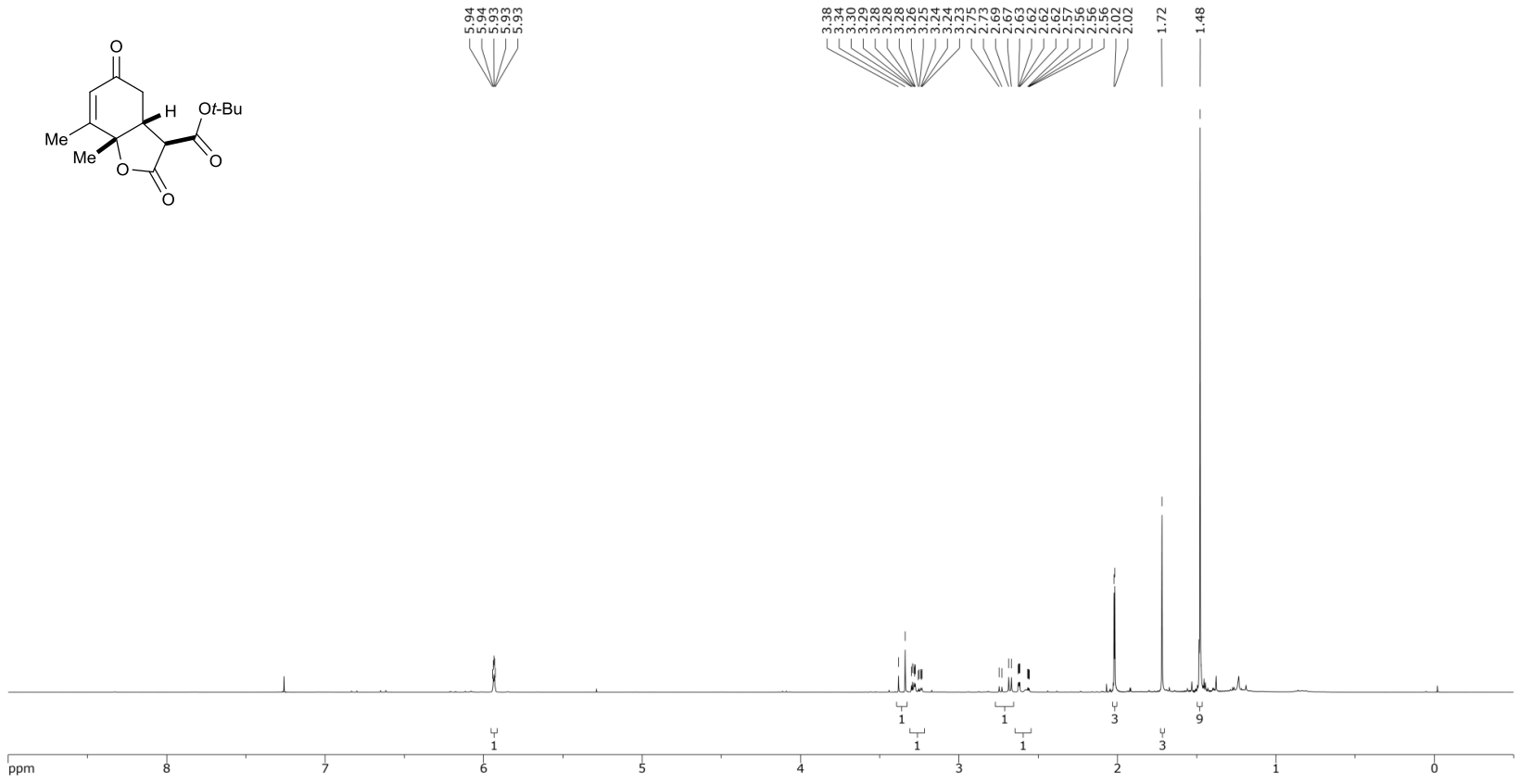
Bicyclic lactone 2.13o – ^{1}H NMR



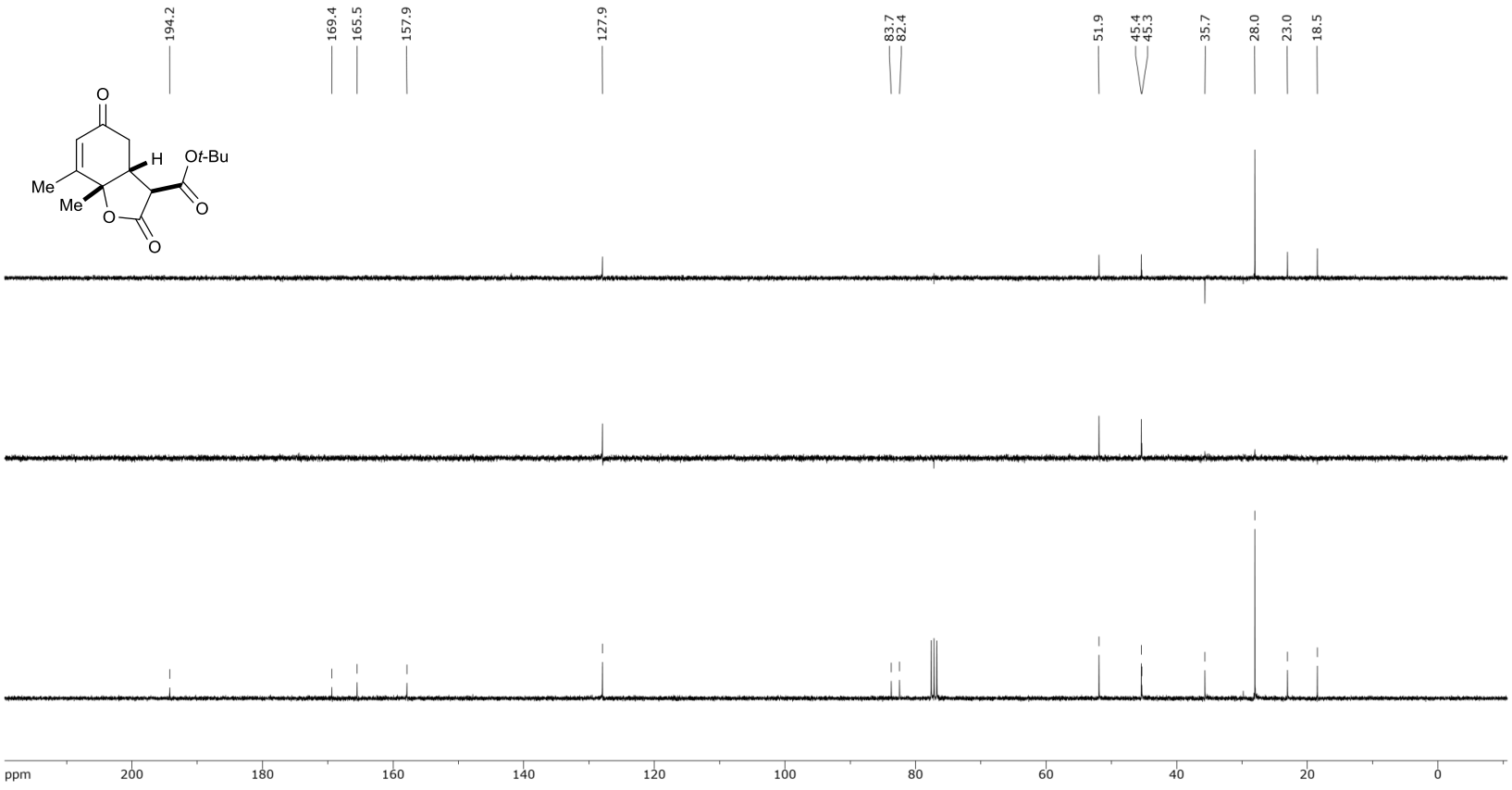
Bicyclic lactone 2.13o – ^{13}C NMR



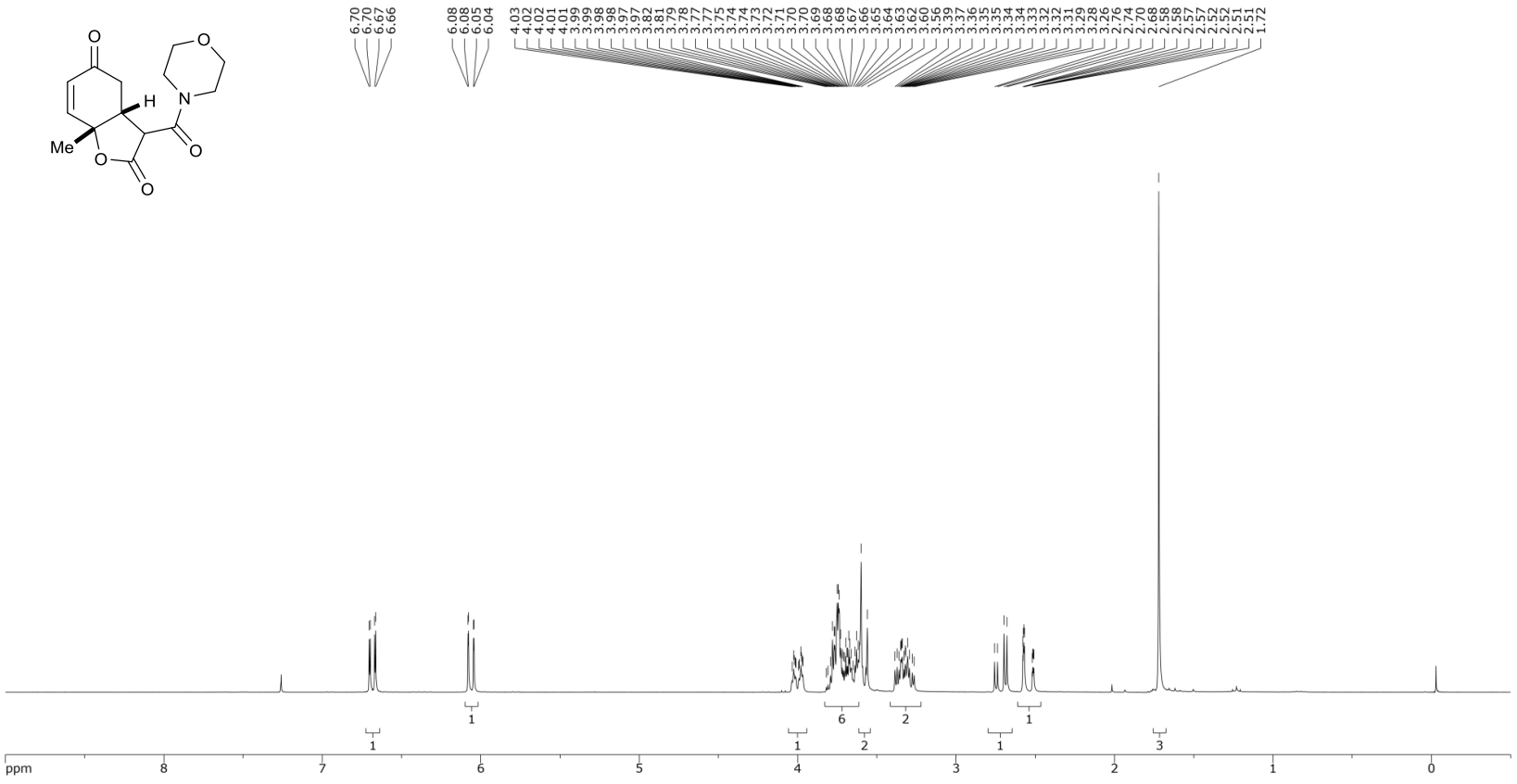
Bicyclic lactone 2.13p – ^{1}H NMR



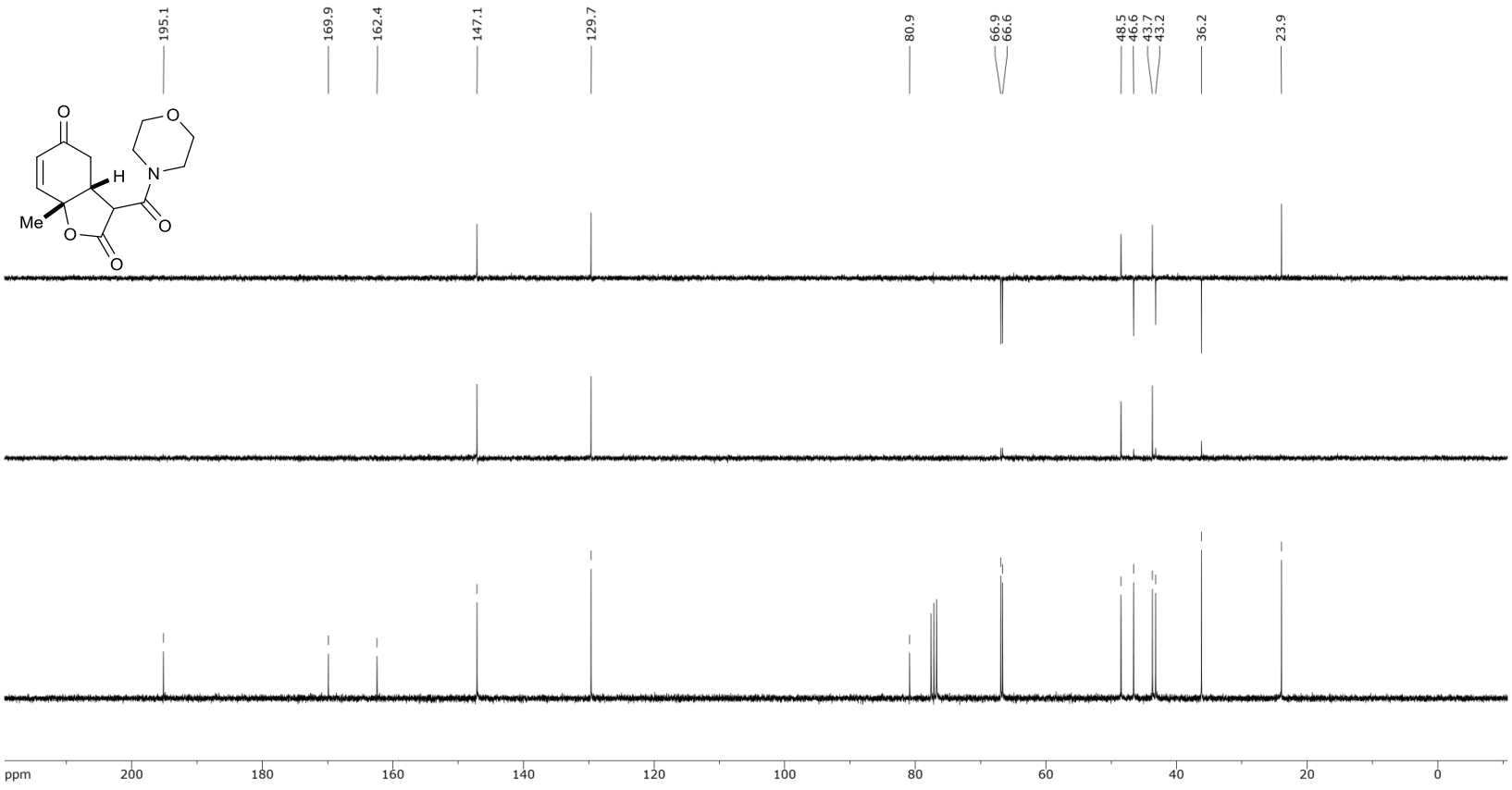
Bicyclic lactone 2.13p – ^{13}C NMR



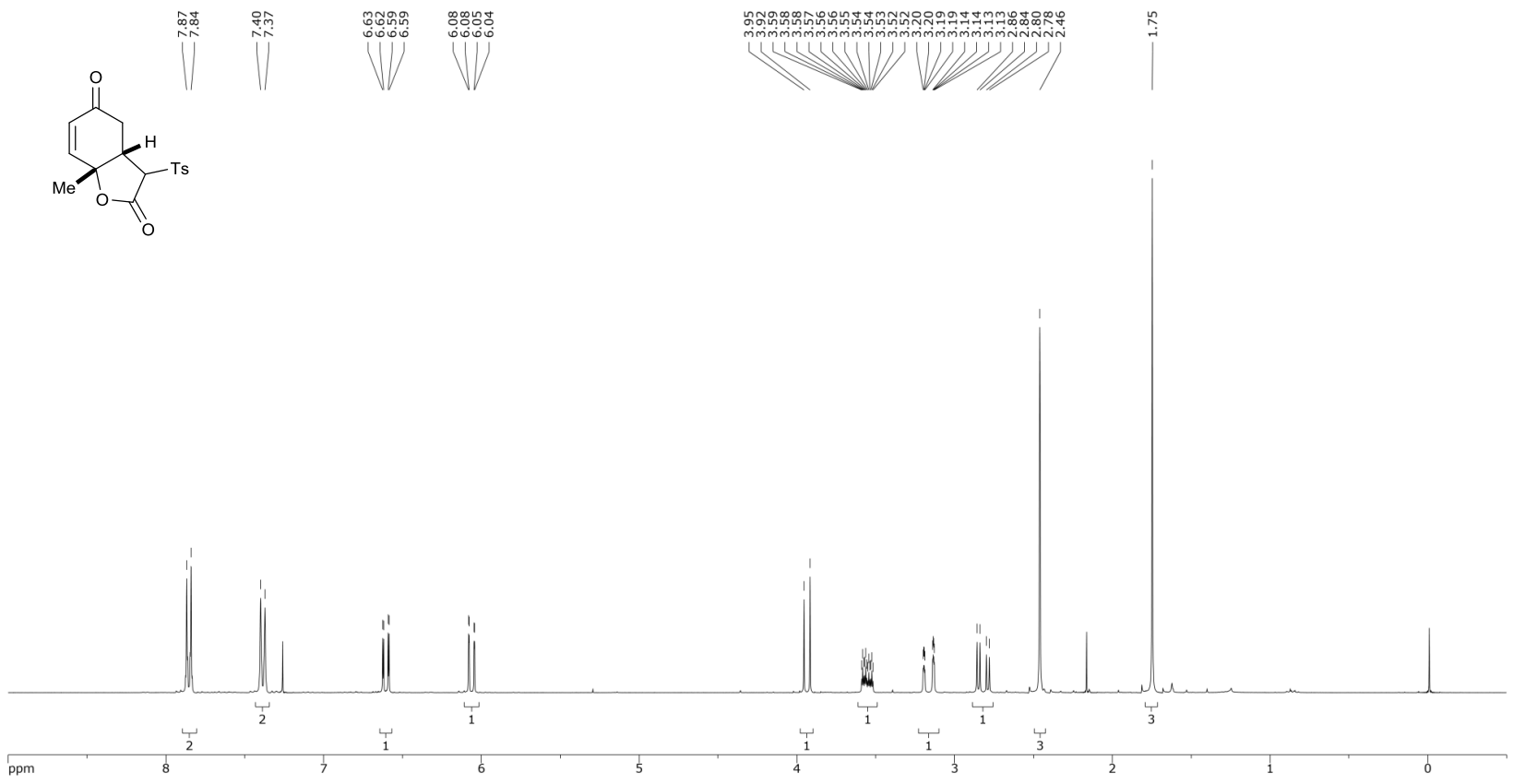
Bicyclic lactone 2.14 – ^{1}H NMR



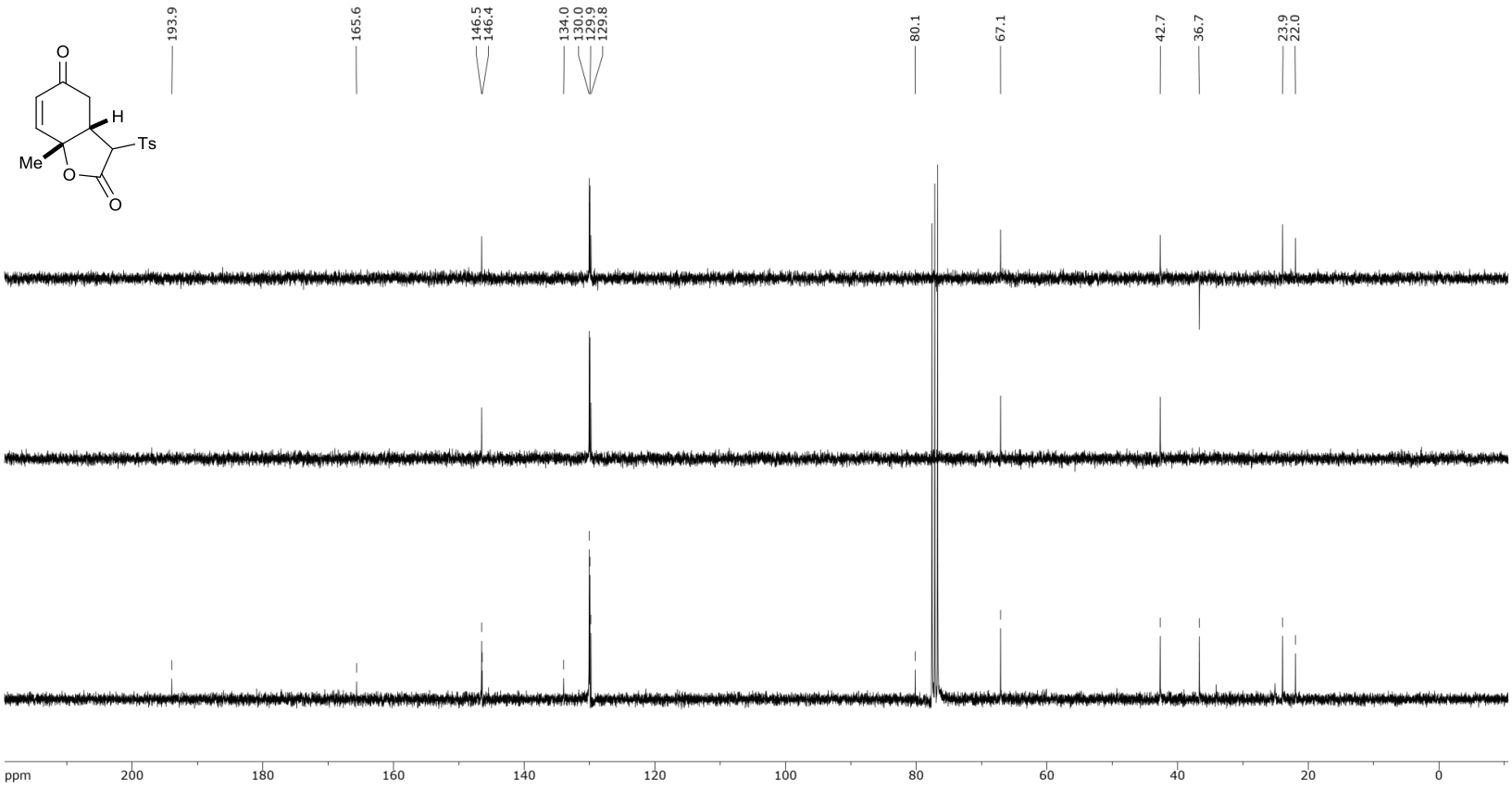
Bicyclic lactone 2.14 – ^{13}C NMR



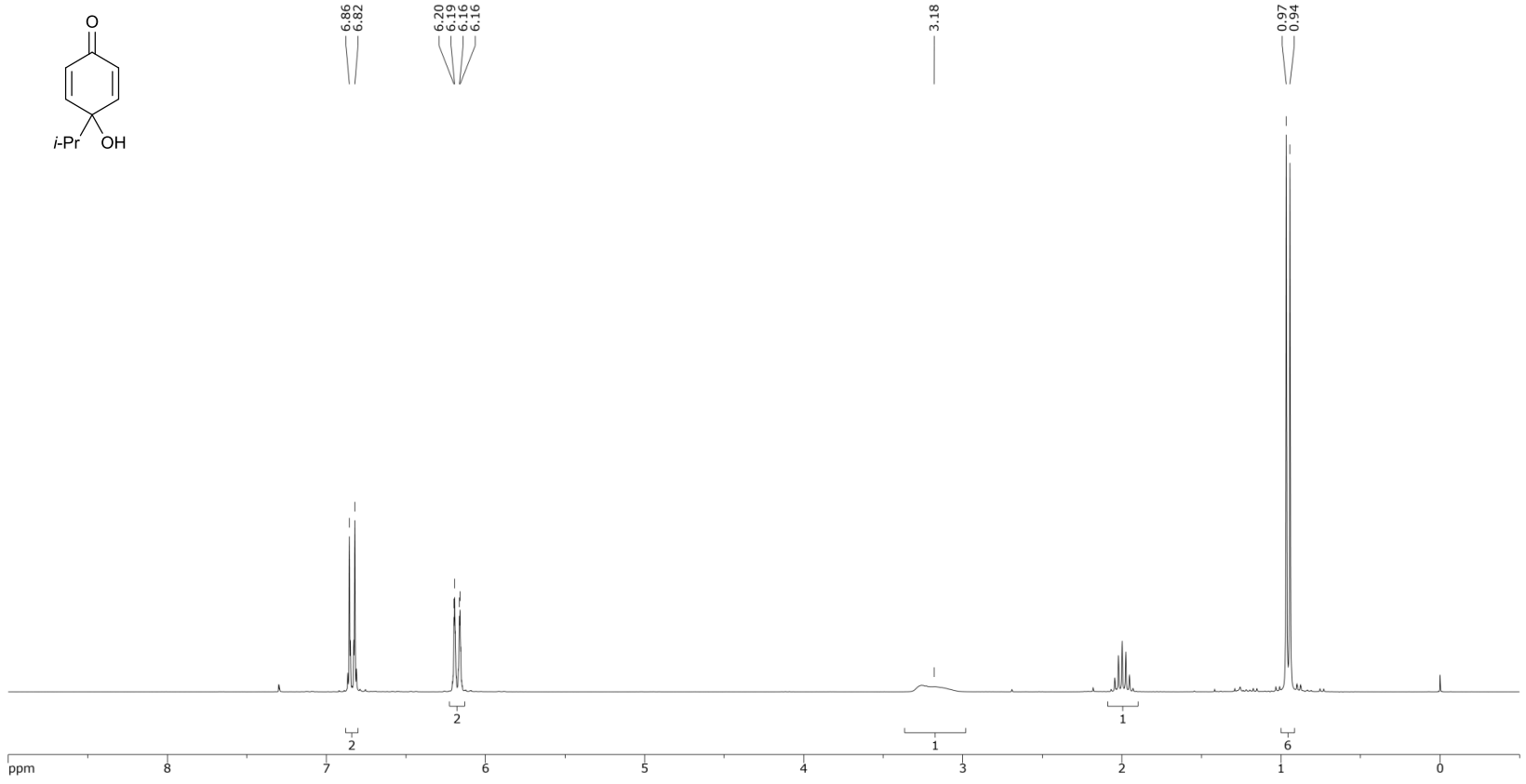
Bicyclic lactone 2.15 – ^{1}H NMR



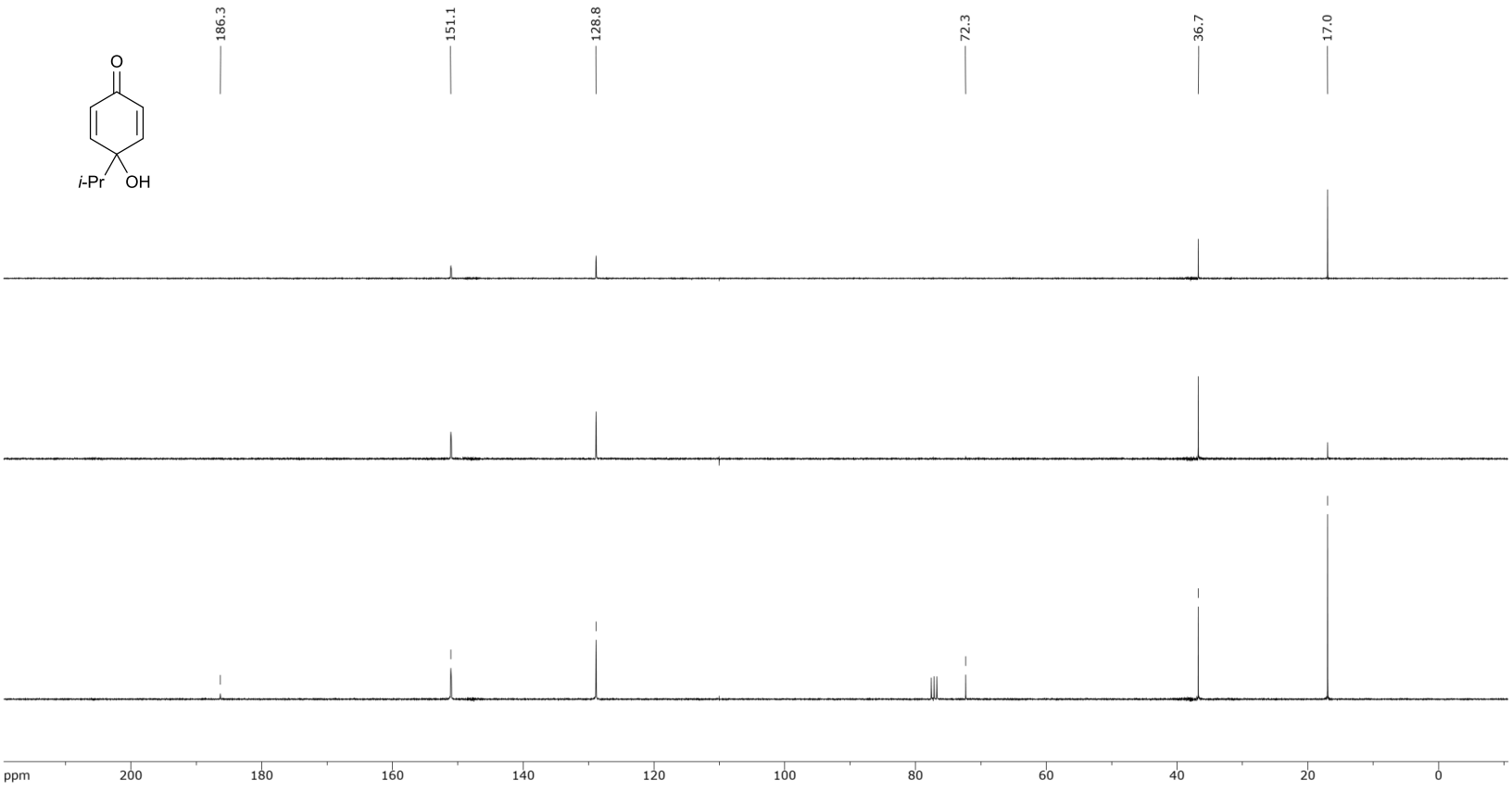
Bicyclic lactone 2.15 – ^{13}C NMR



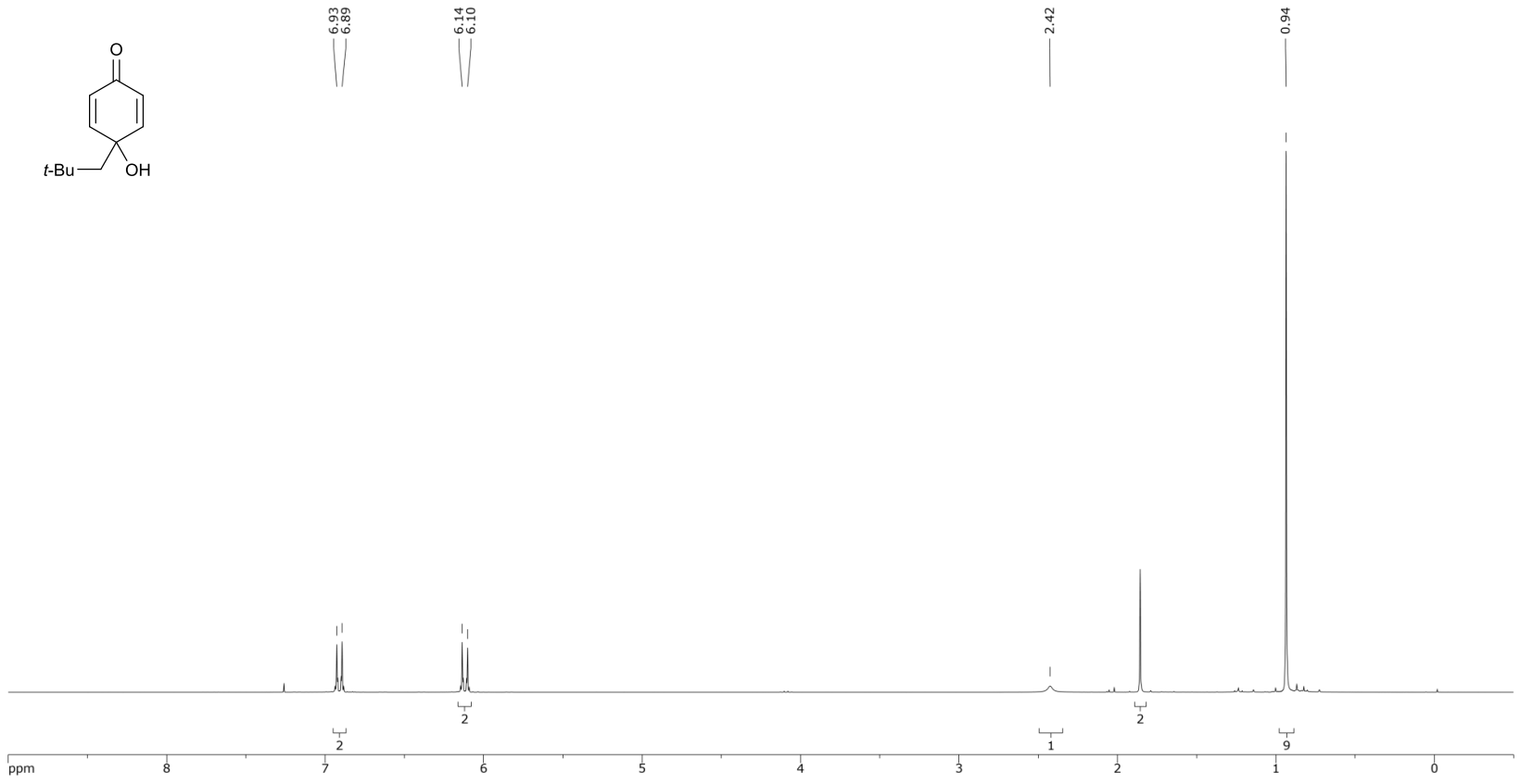
Quinol 2.17c – ^{1}H NMR



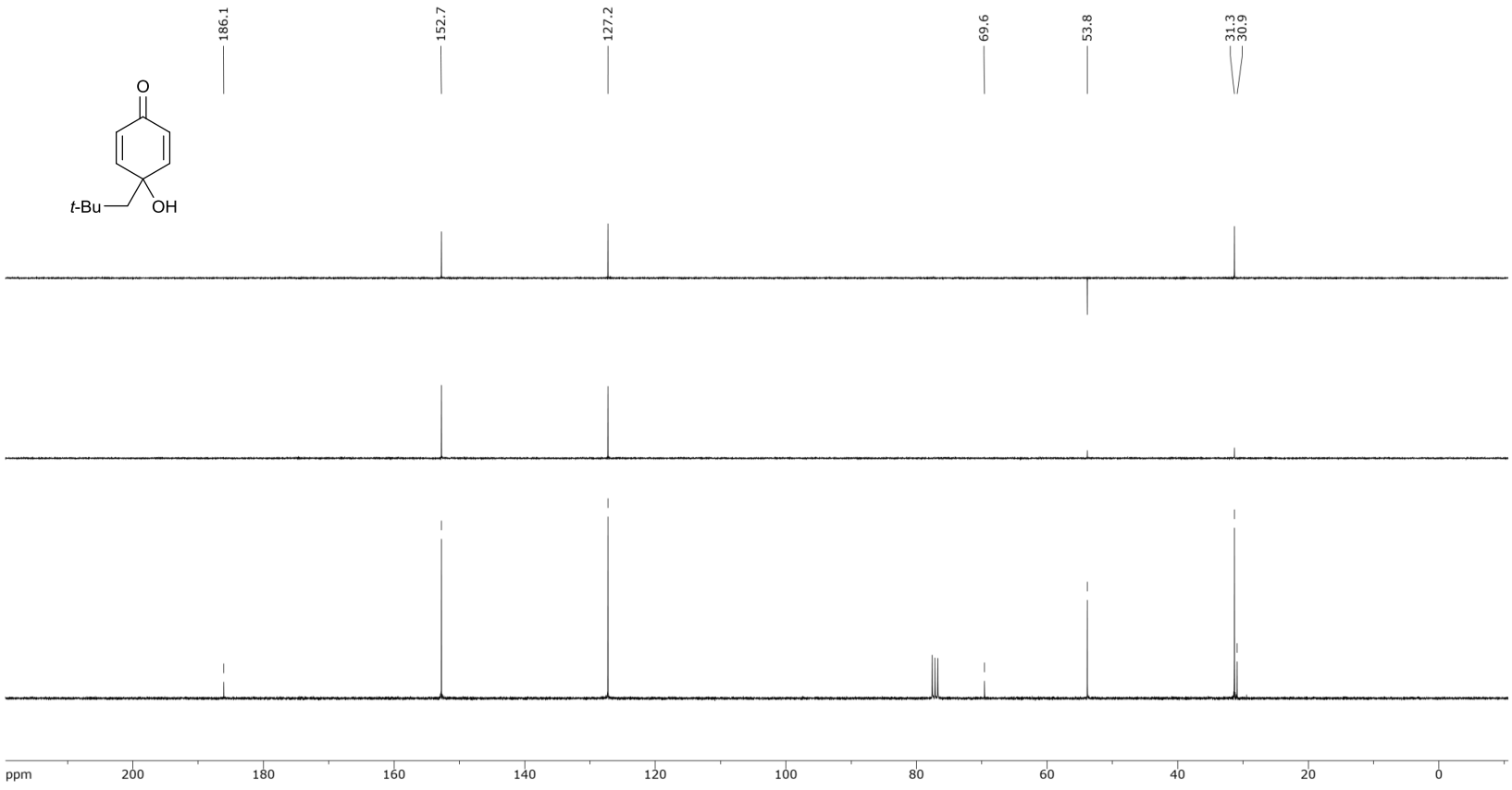
Quinol 2.17c – ^{13}C NMR



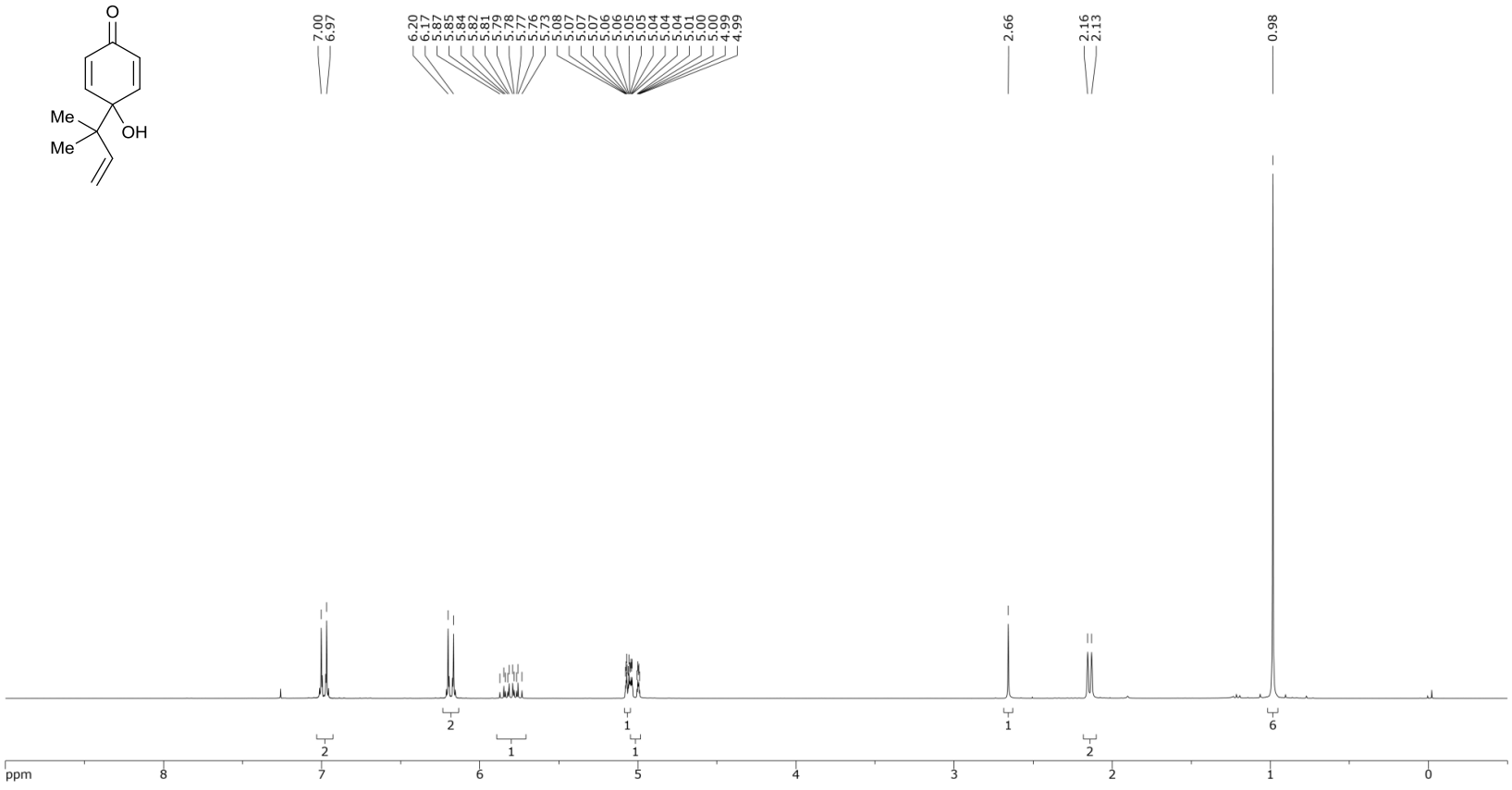
Quinol 2.17e – ^{1}H NMR



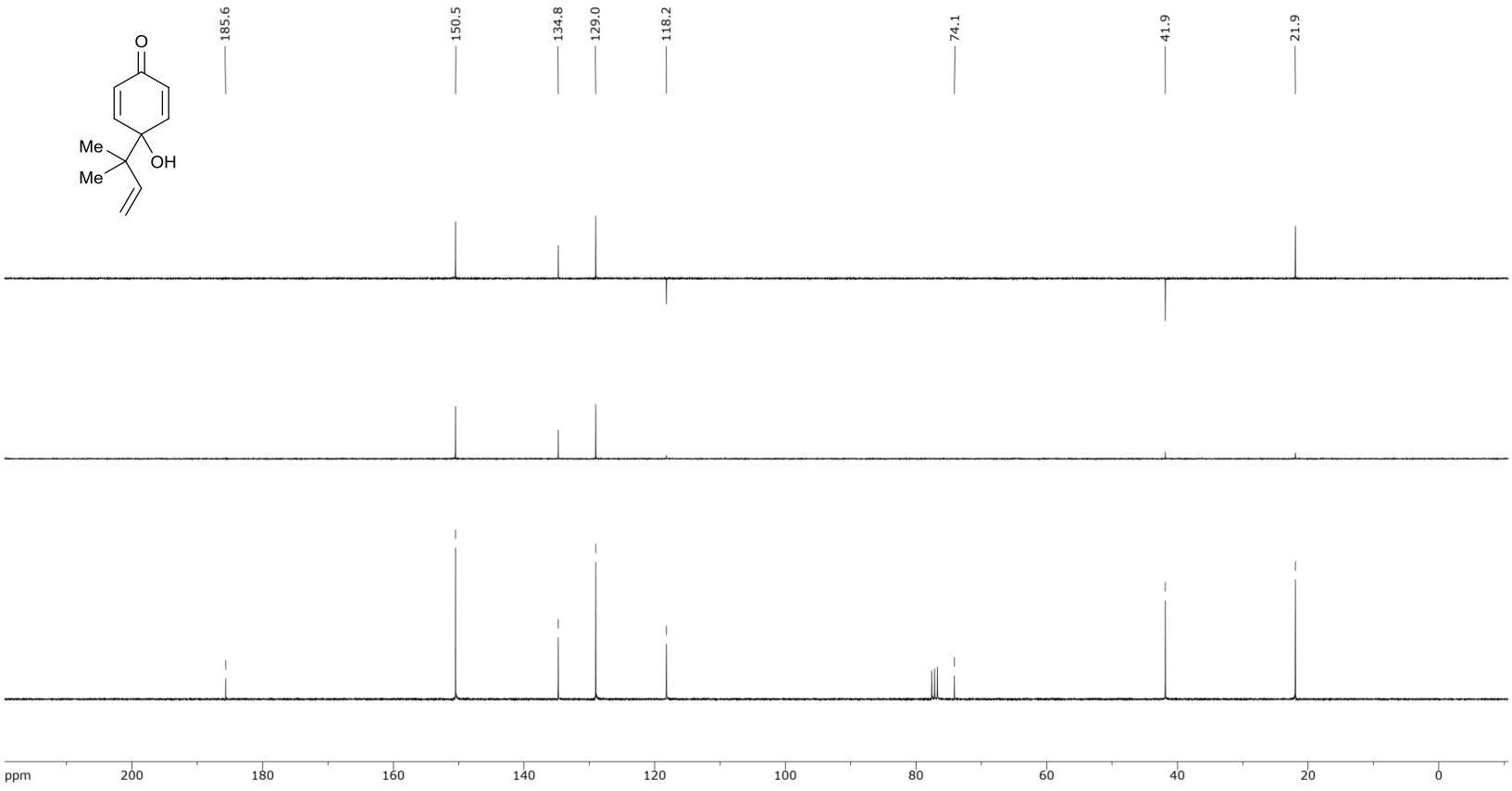
Quinol 2.17e – ^{13}C NMR



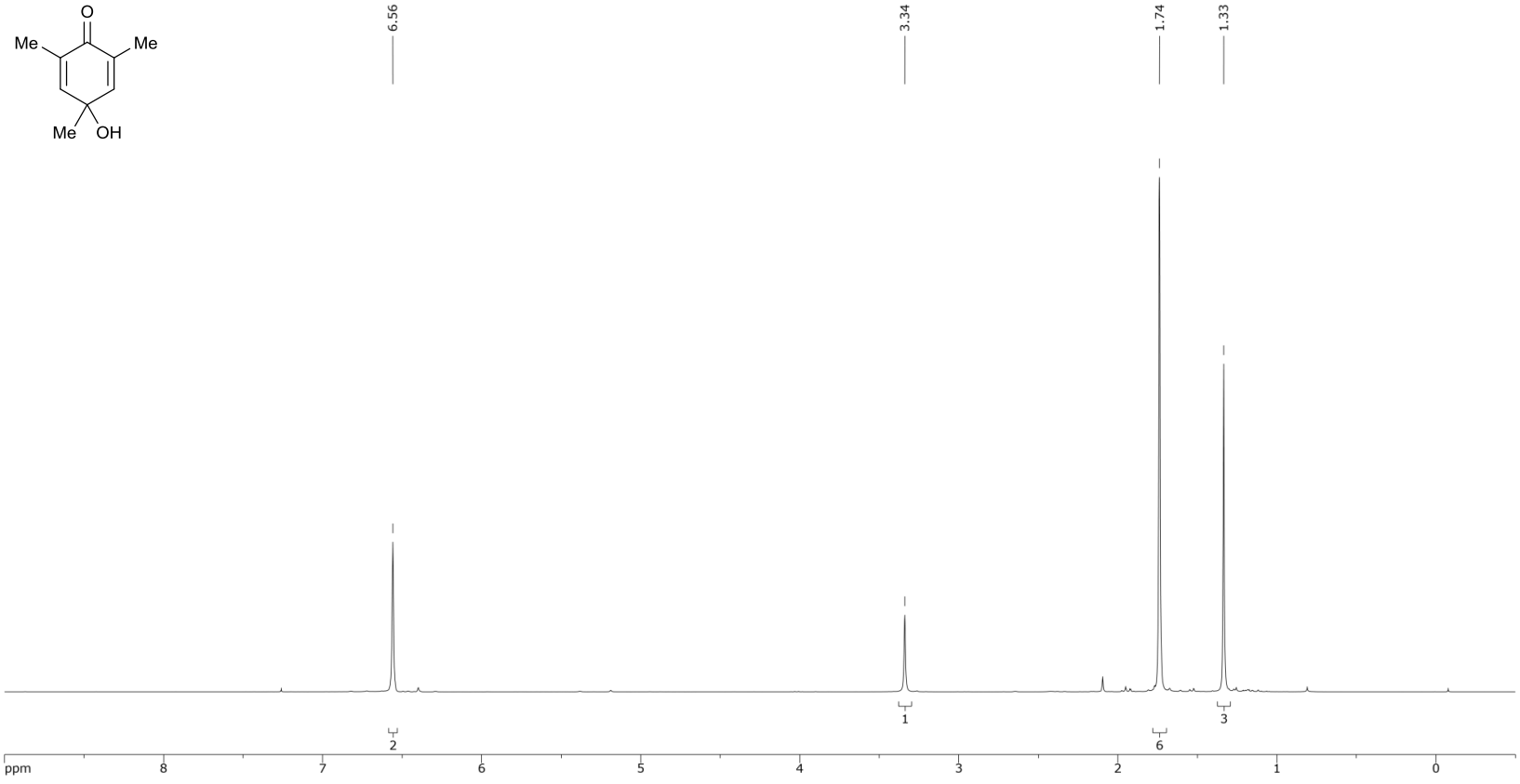
Quinol 2.17g – ^{1}H NMR



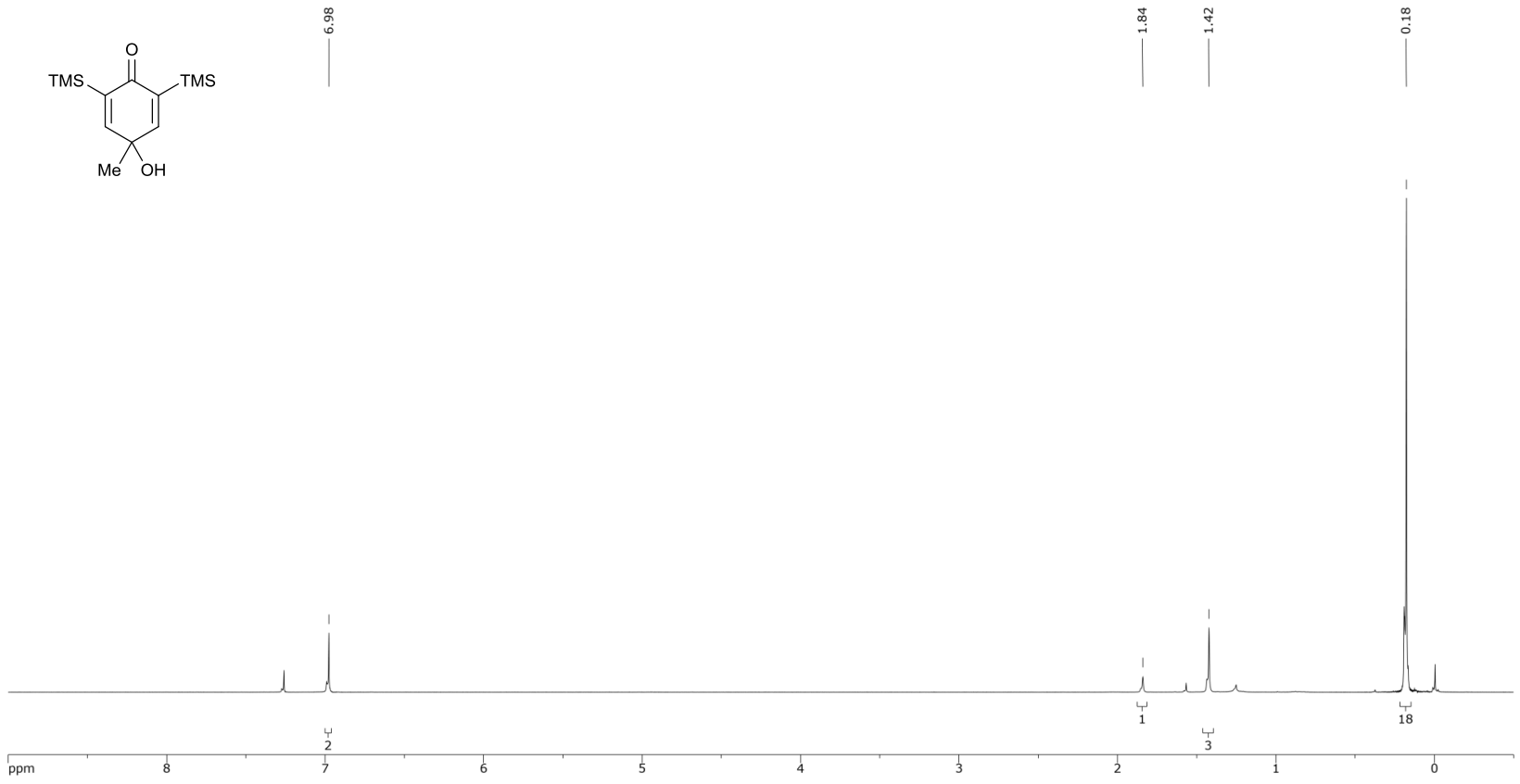
Quinol 2.17g – ^{13}C NMR



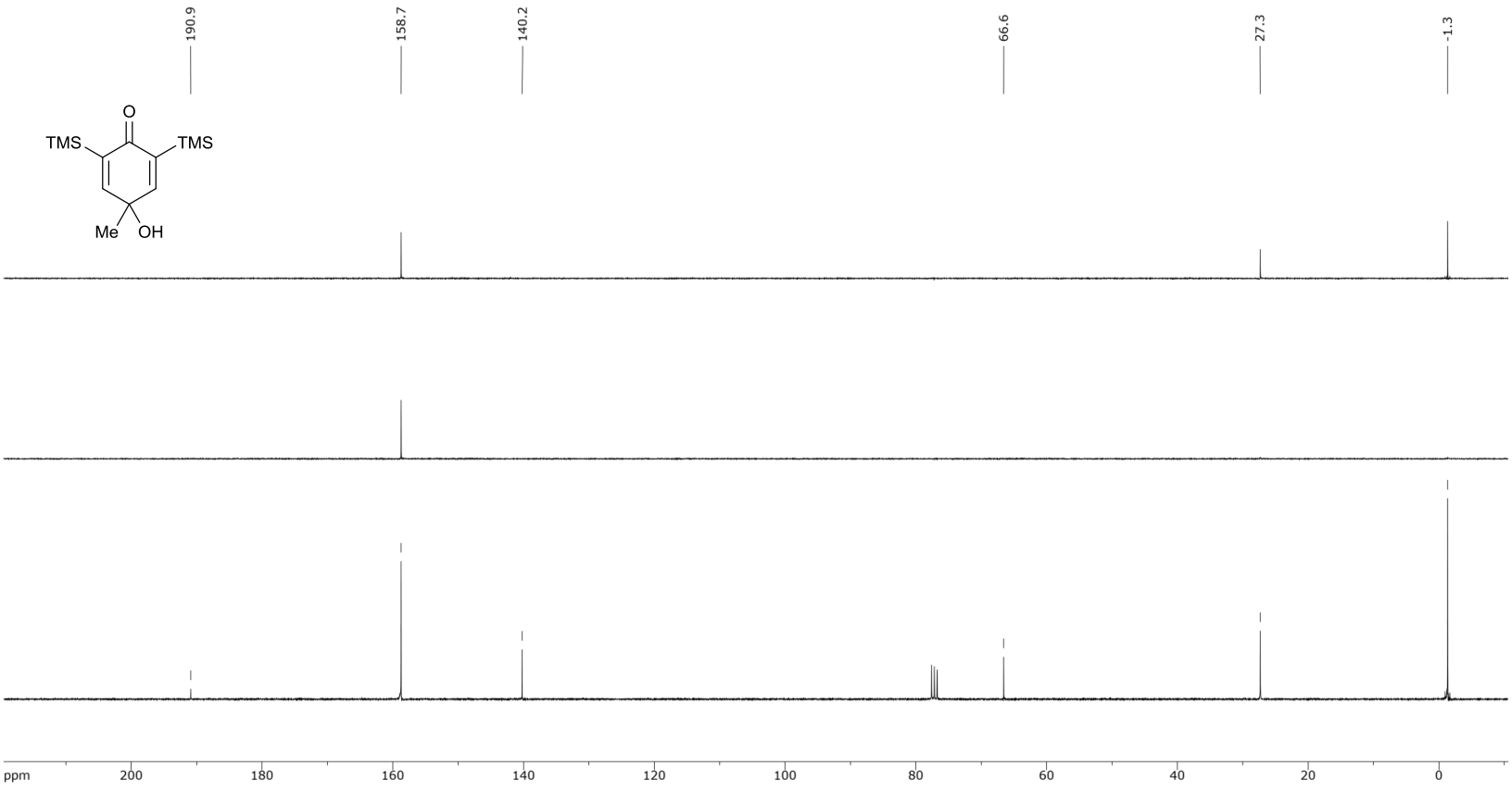
Quinol 2.17h – ^{1}H NMR



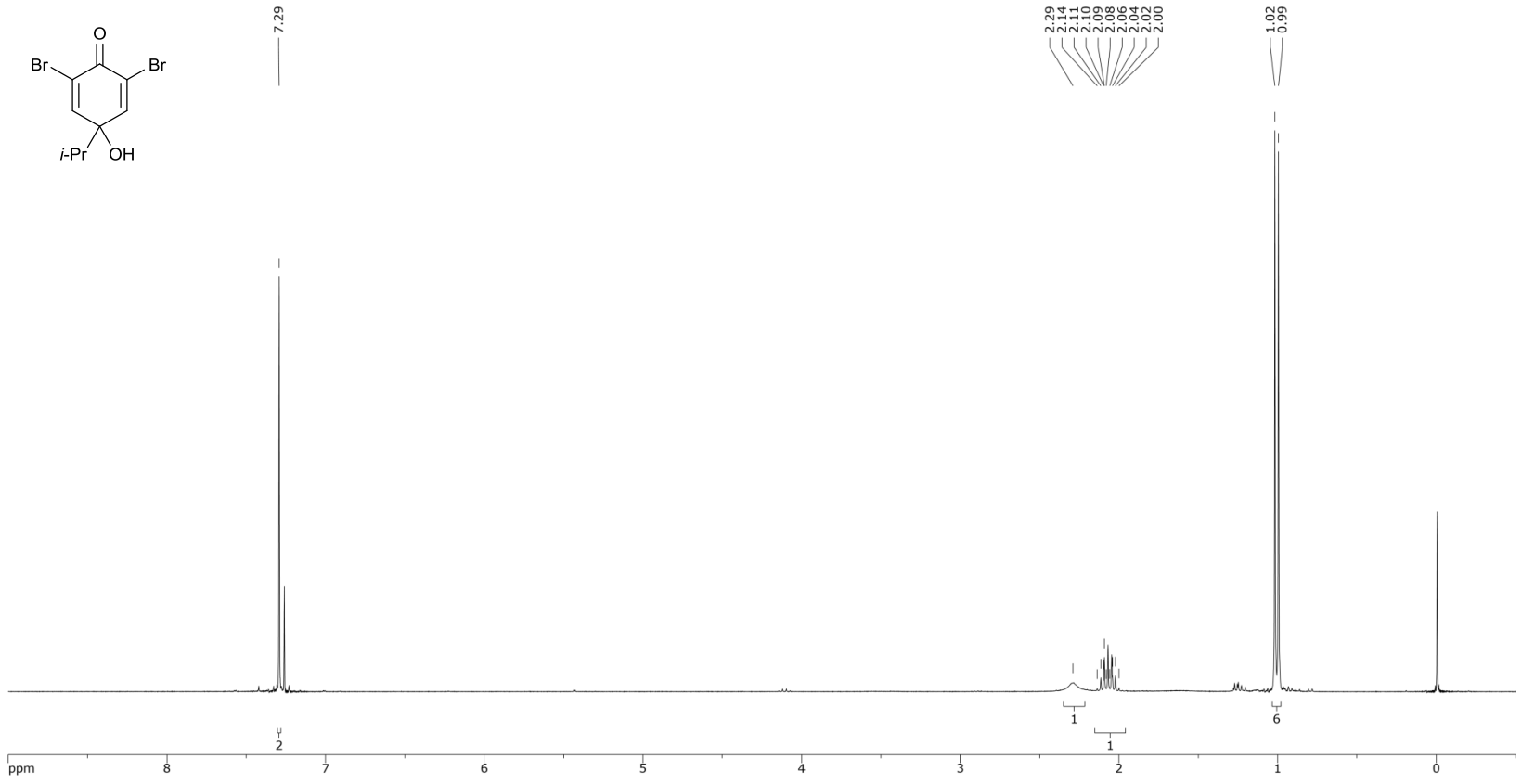
Quinol 2.17i – ^{1}H NMR



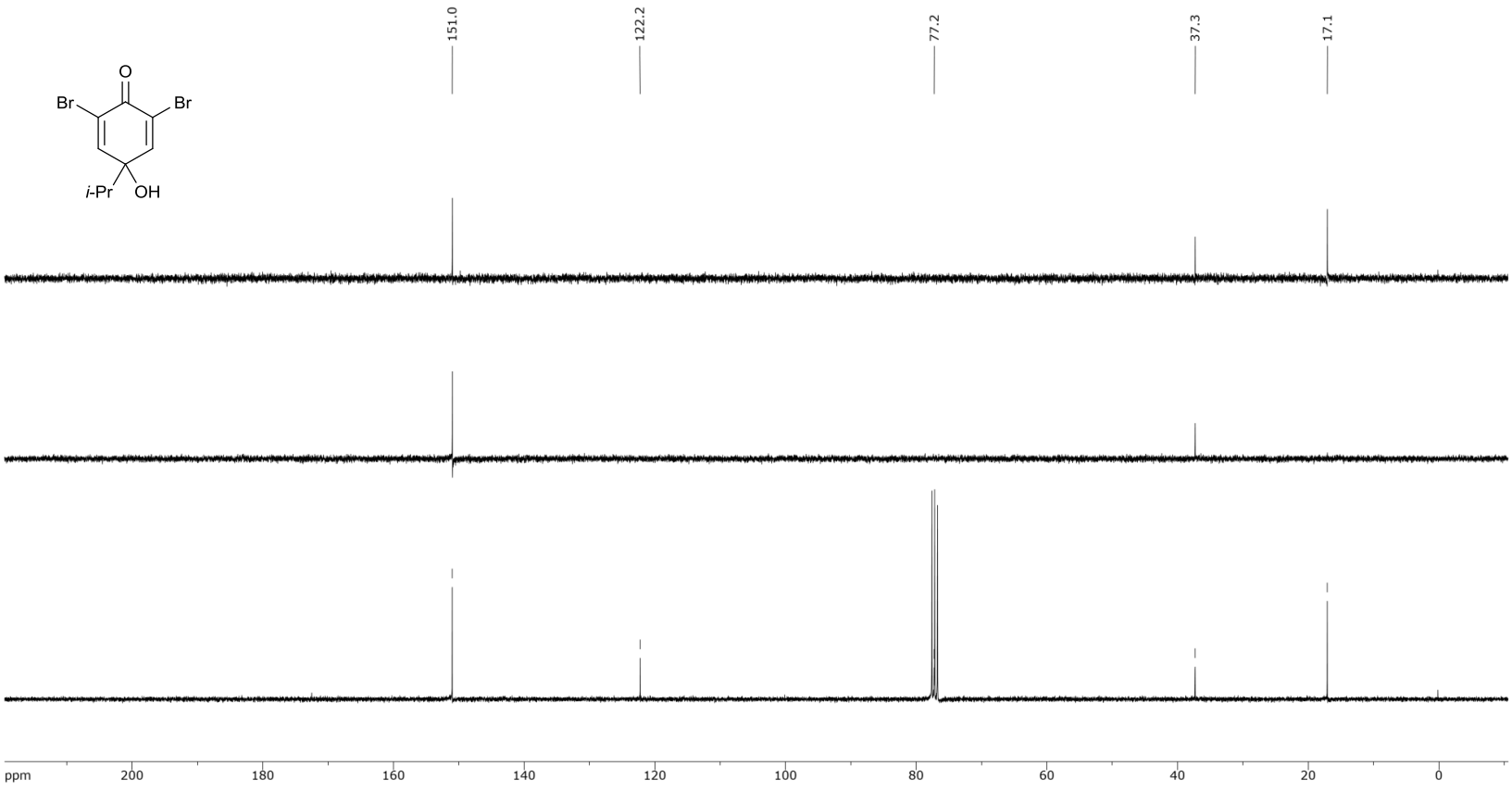
Quinol 2.17i – ^{13}C NMR



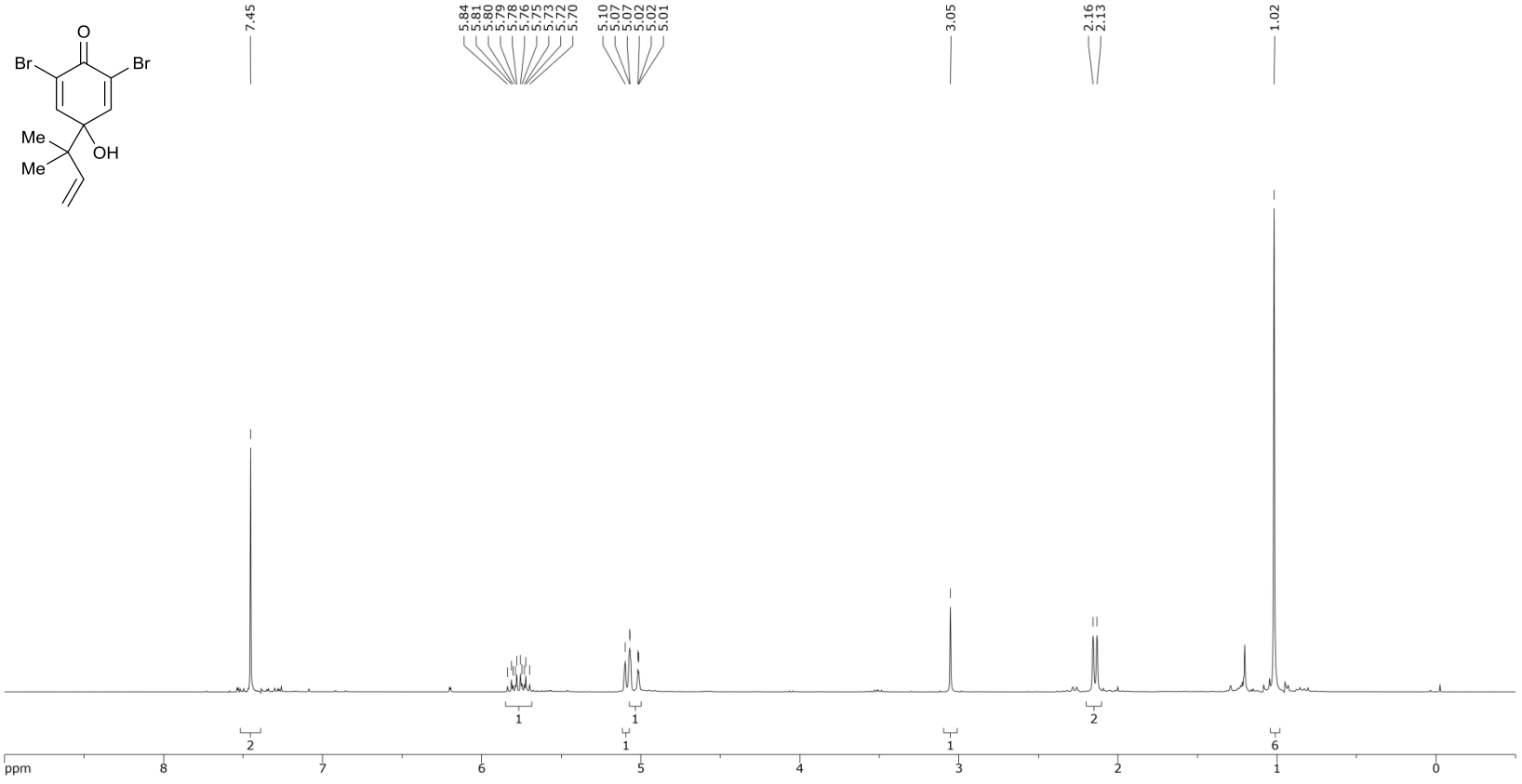
Quinol 2.17k – ^{1}H NMR



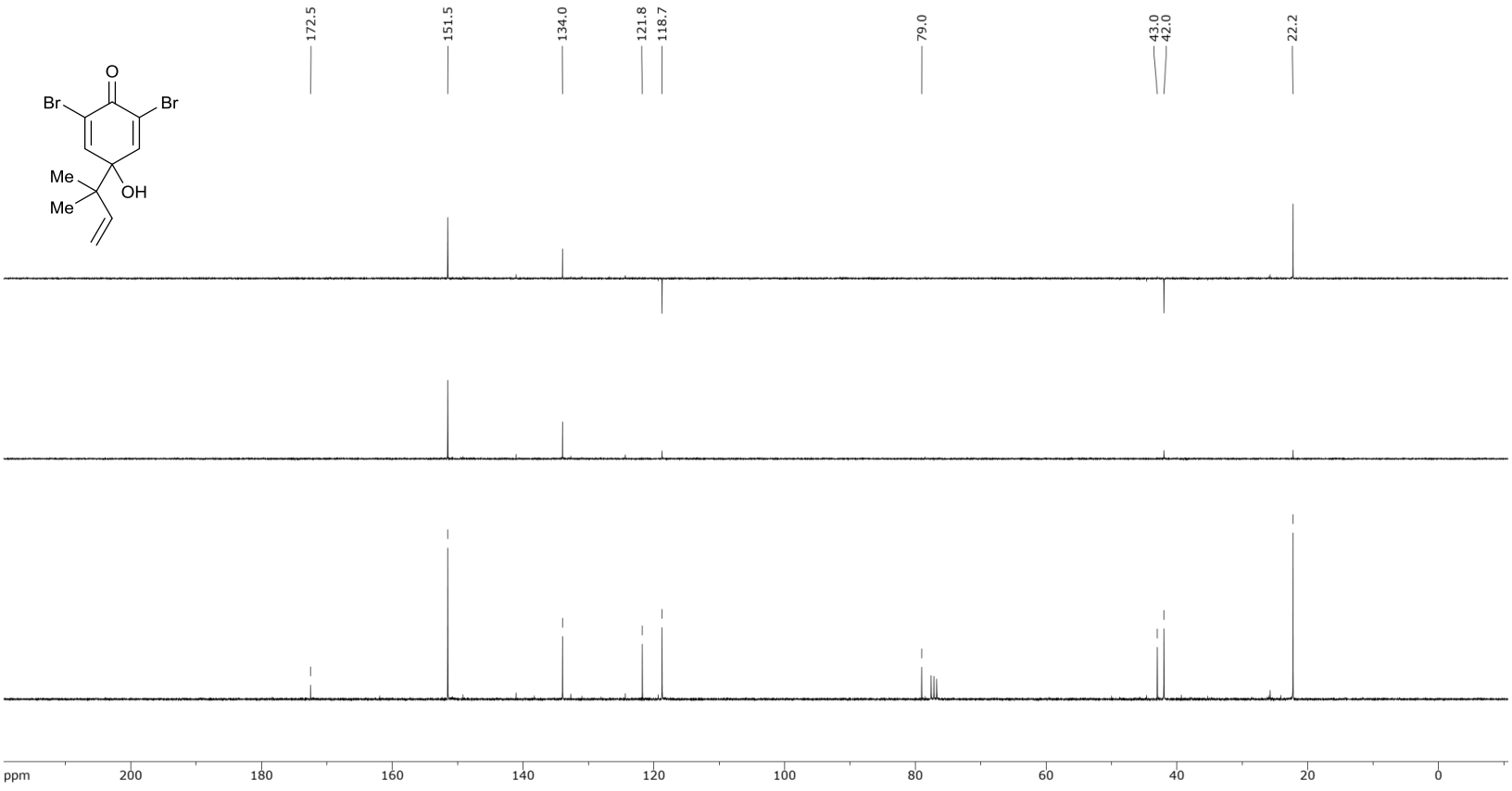
Quinol 2.17k – ^{13}C NMR



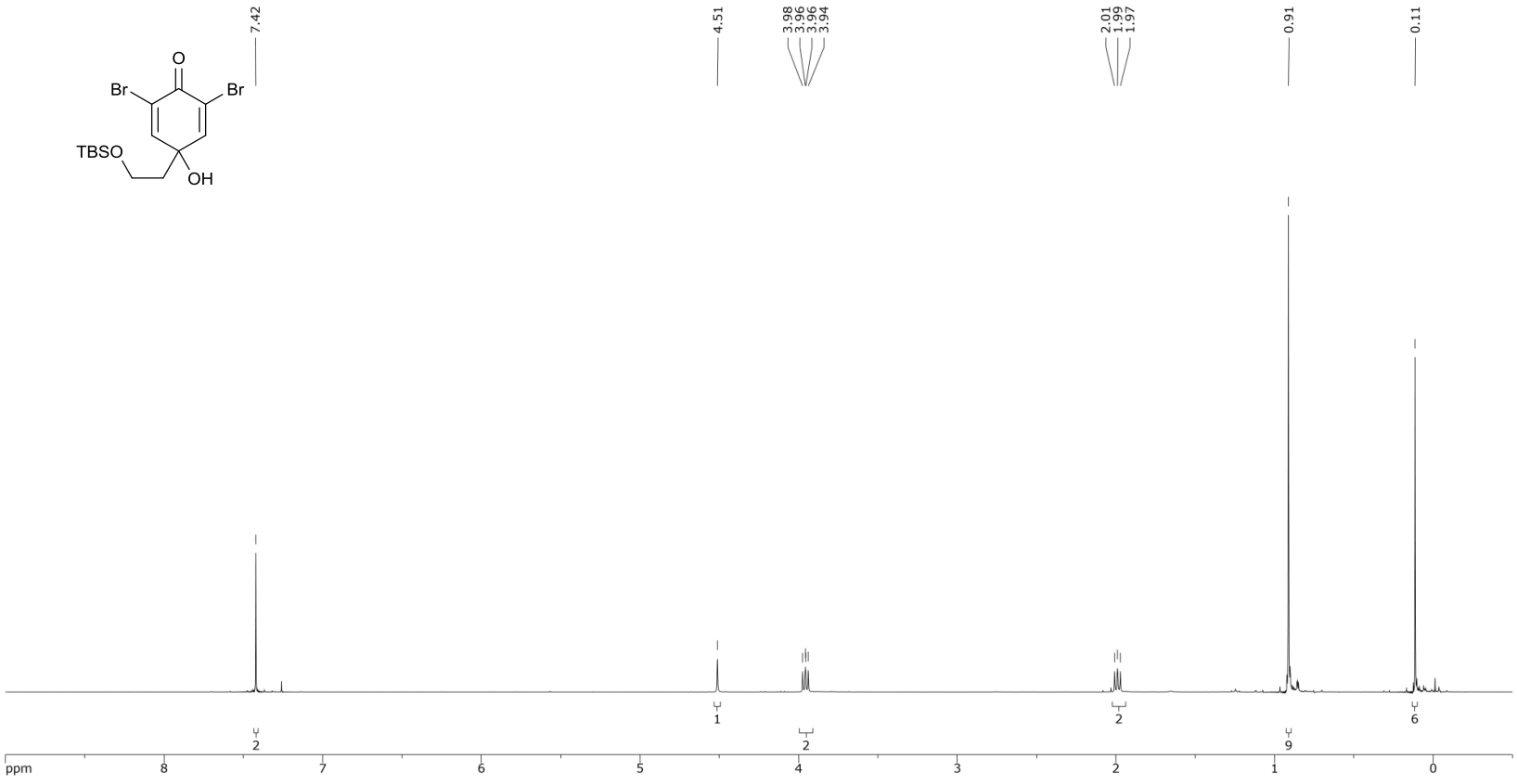
Quinol 2.17l – ^{1}H NMR



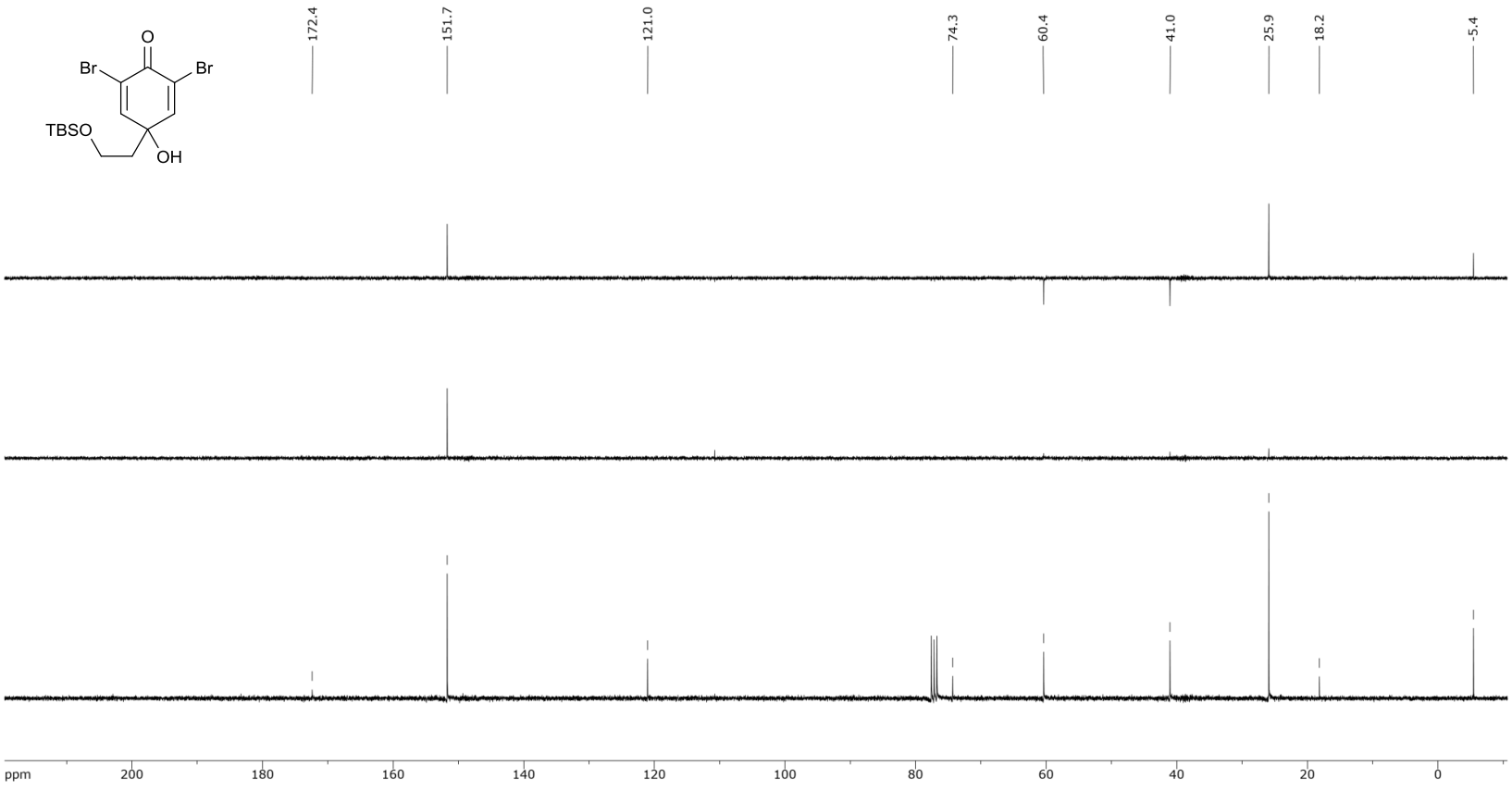
Quinol 2.17l – ^{13}C NMR



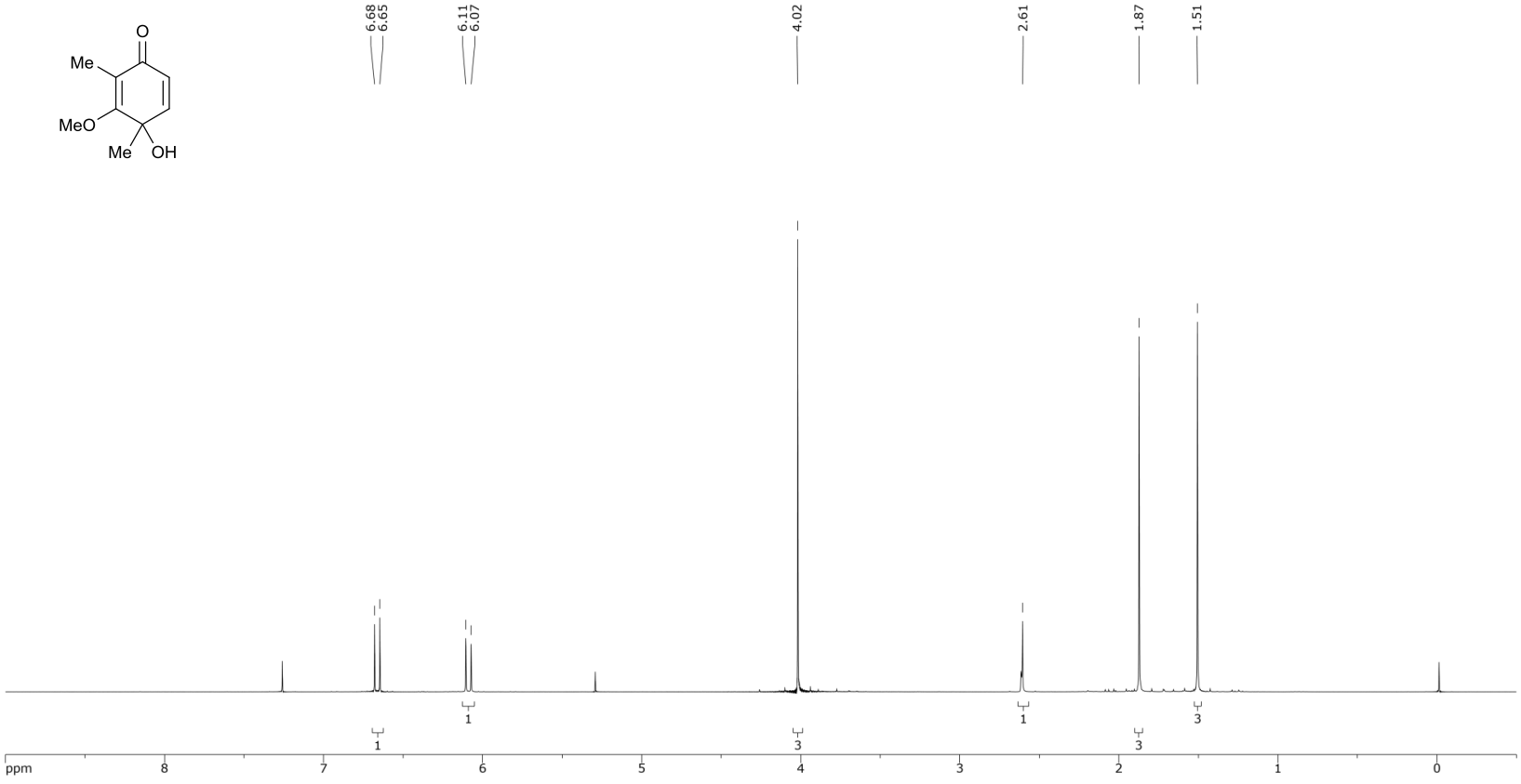
Quinol 2.17m – ^{1}H NMR



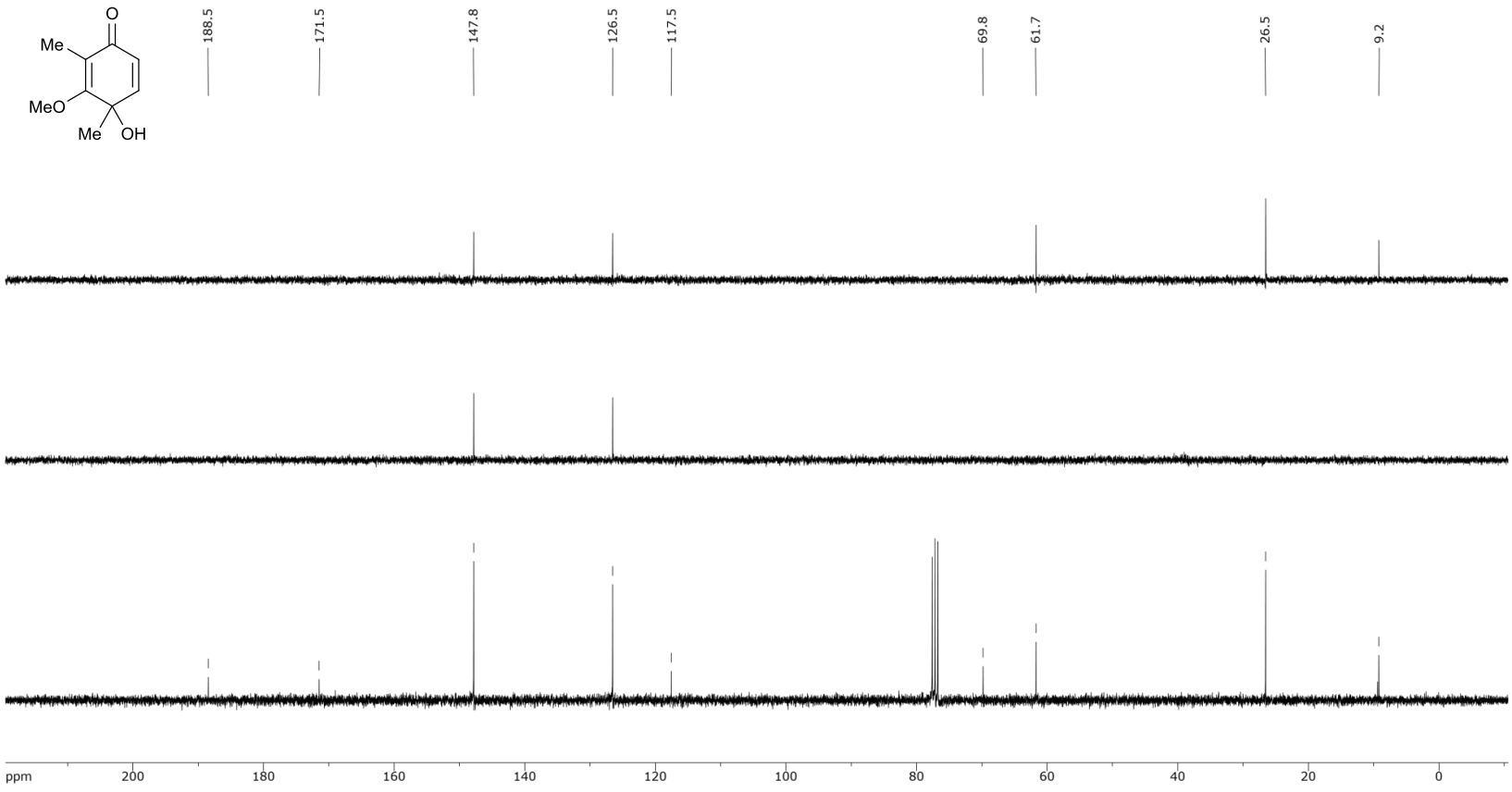
Quinol 2.17m – ^{13}C NMR



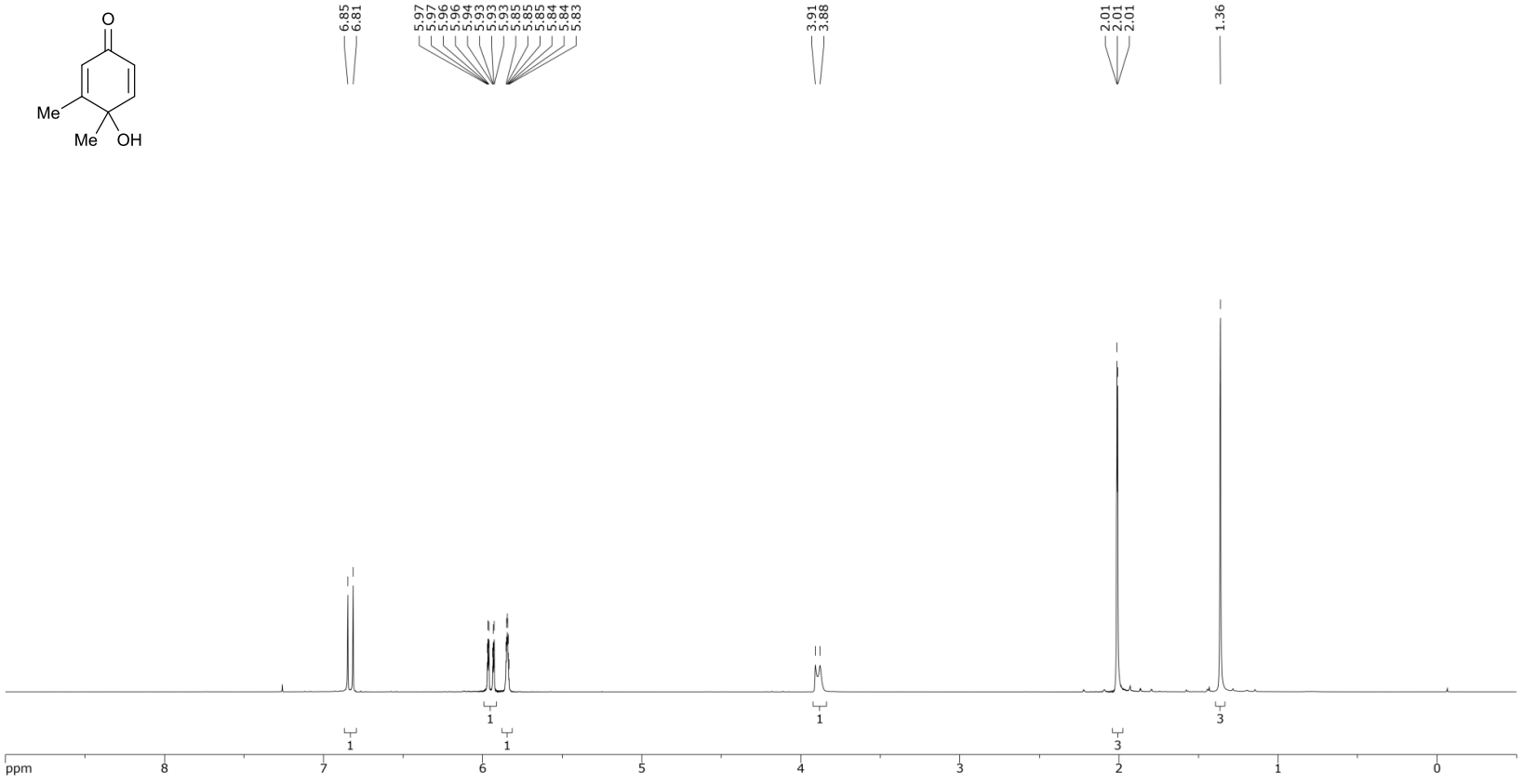
Quinol 2.17n – ^{1}H NMR



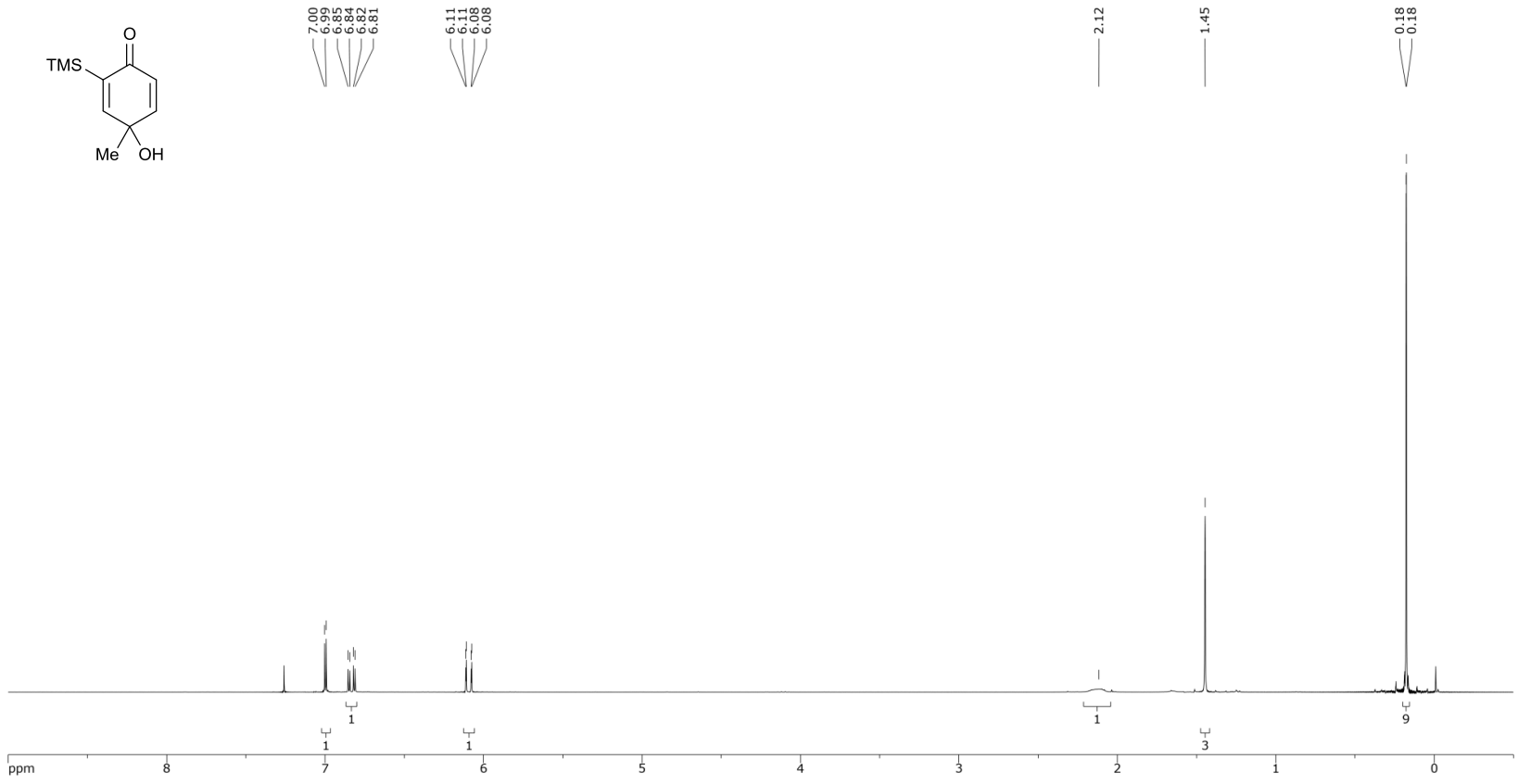
Quinol 2.17n – ^{13}C NMR



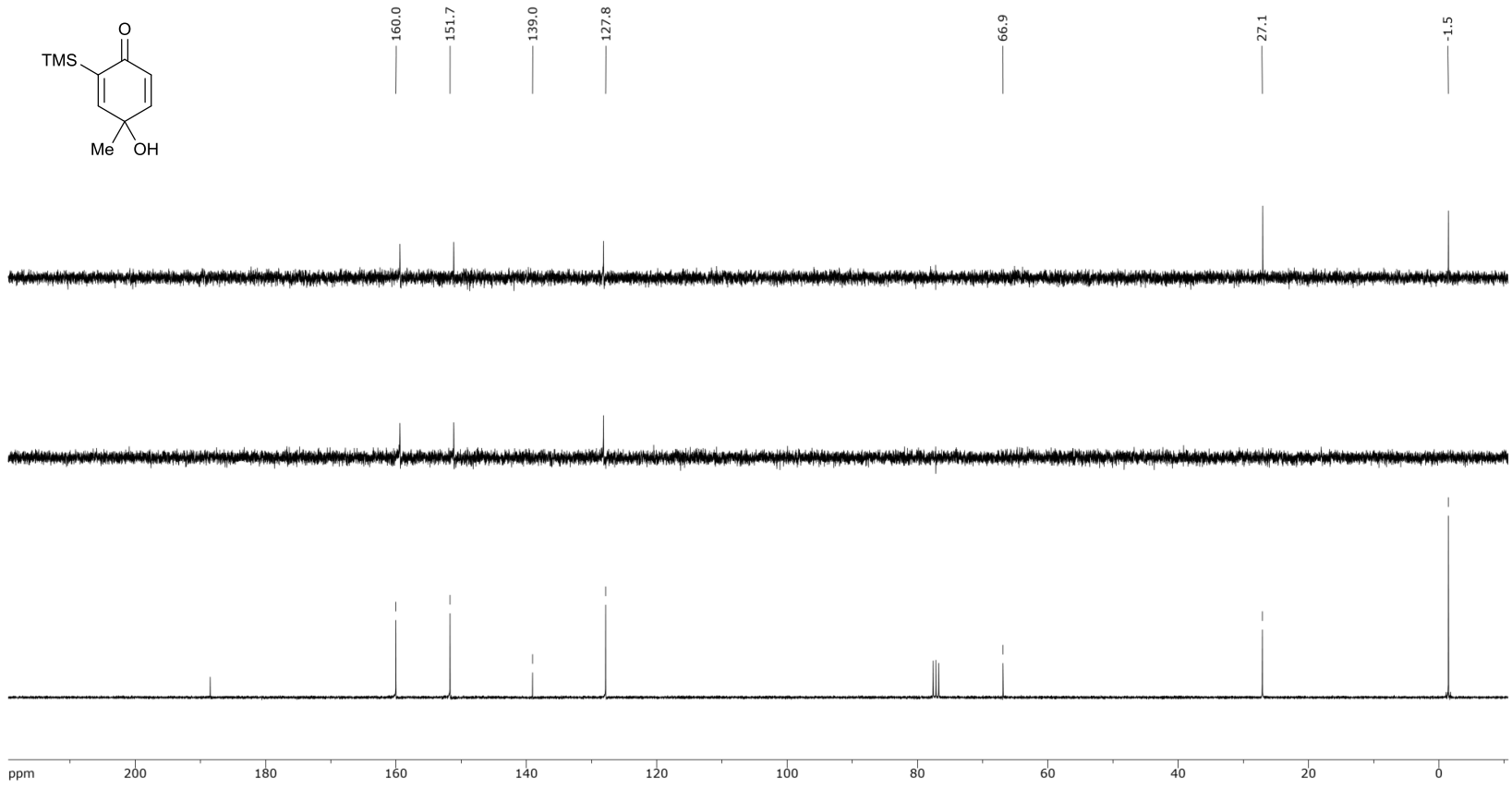
Quinol 2.17p – ^{1}H NMR



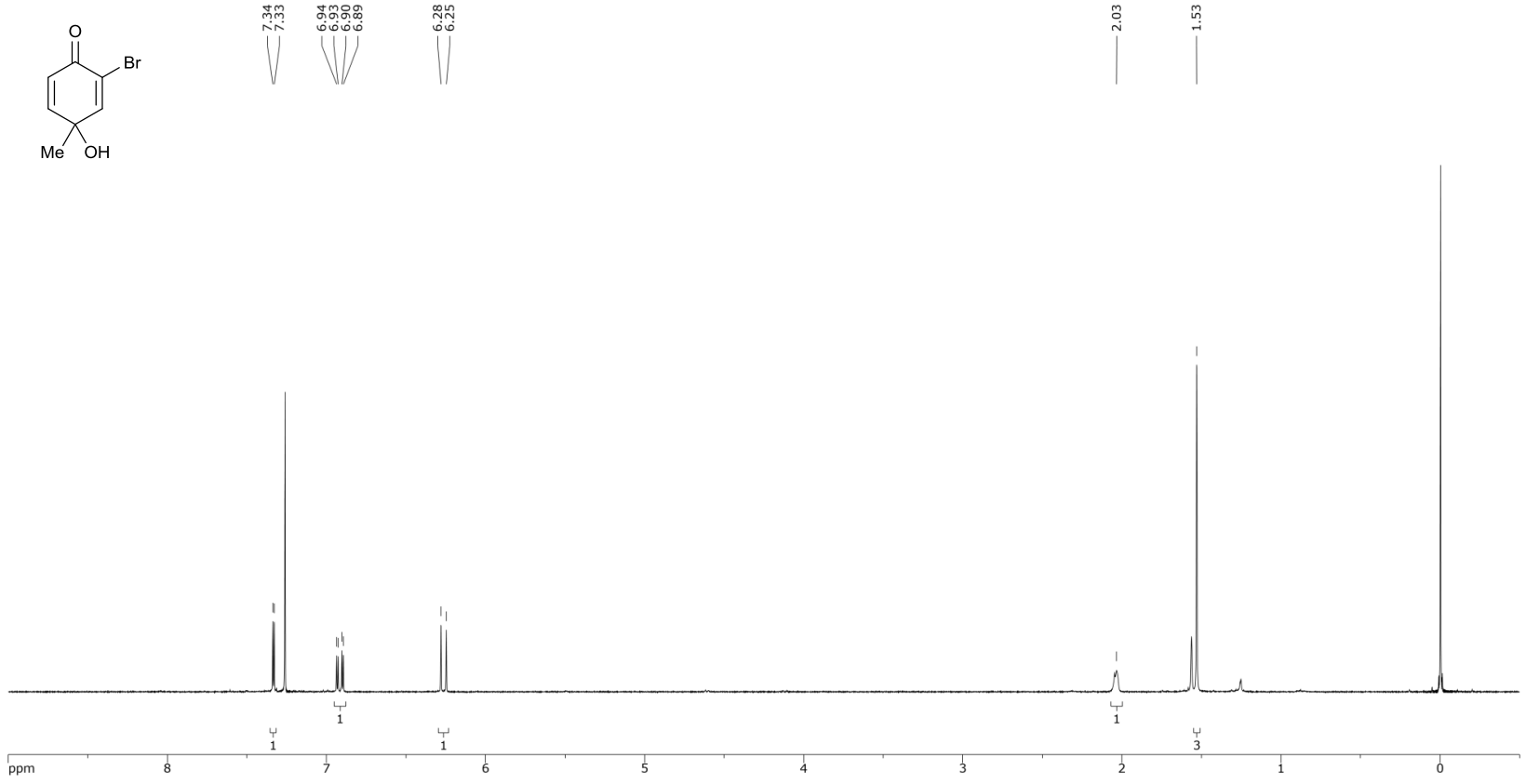
Quinol 2.17q – ^{1}H NMR



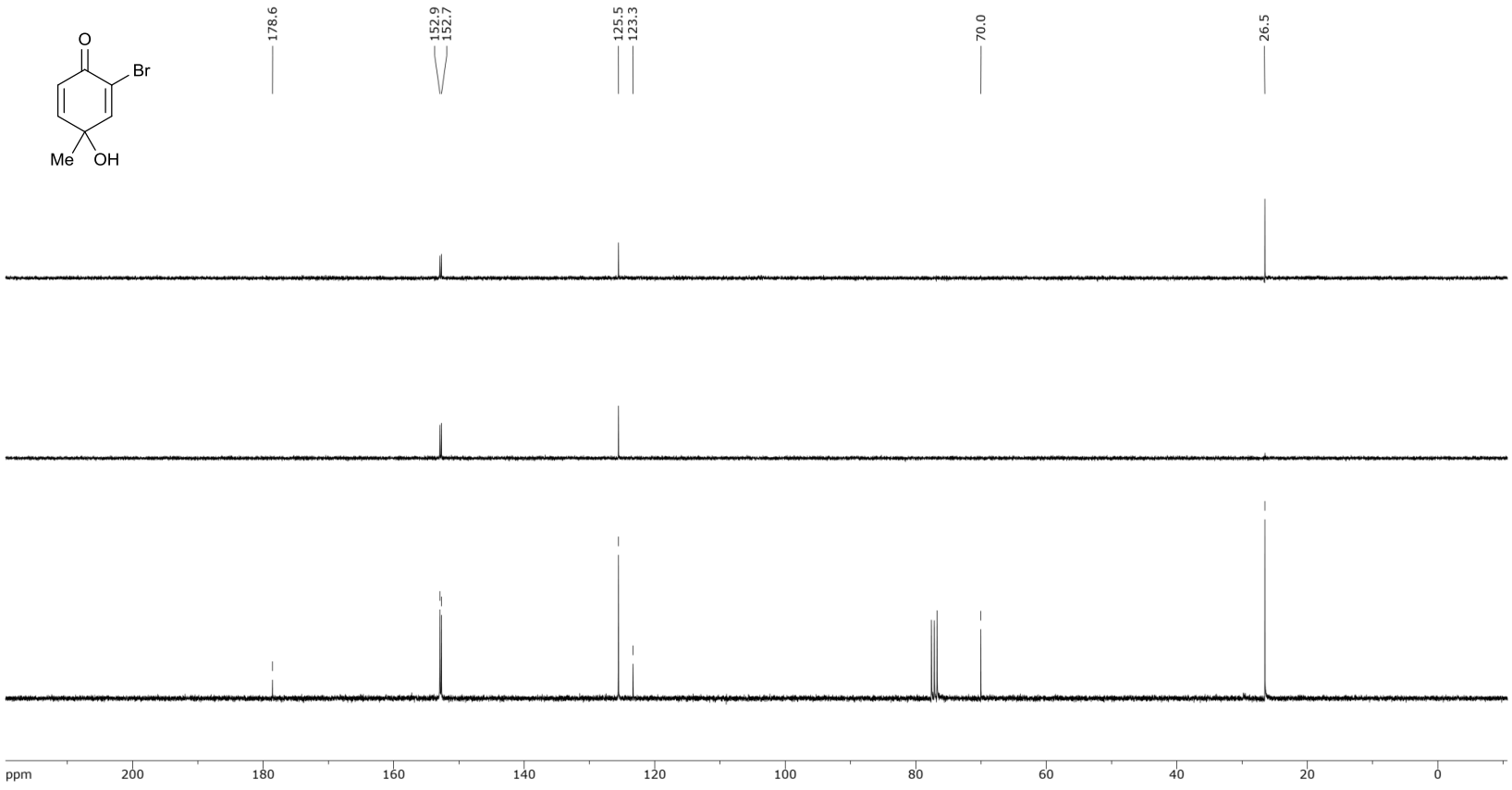
Quinol 2.17q – ^{13}C NMR



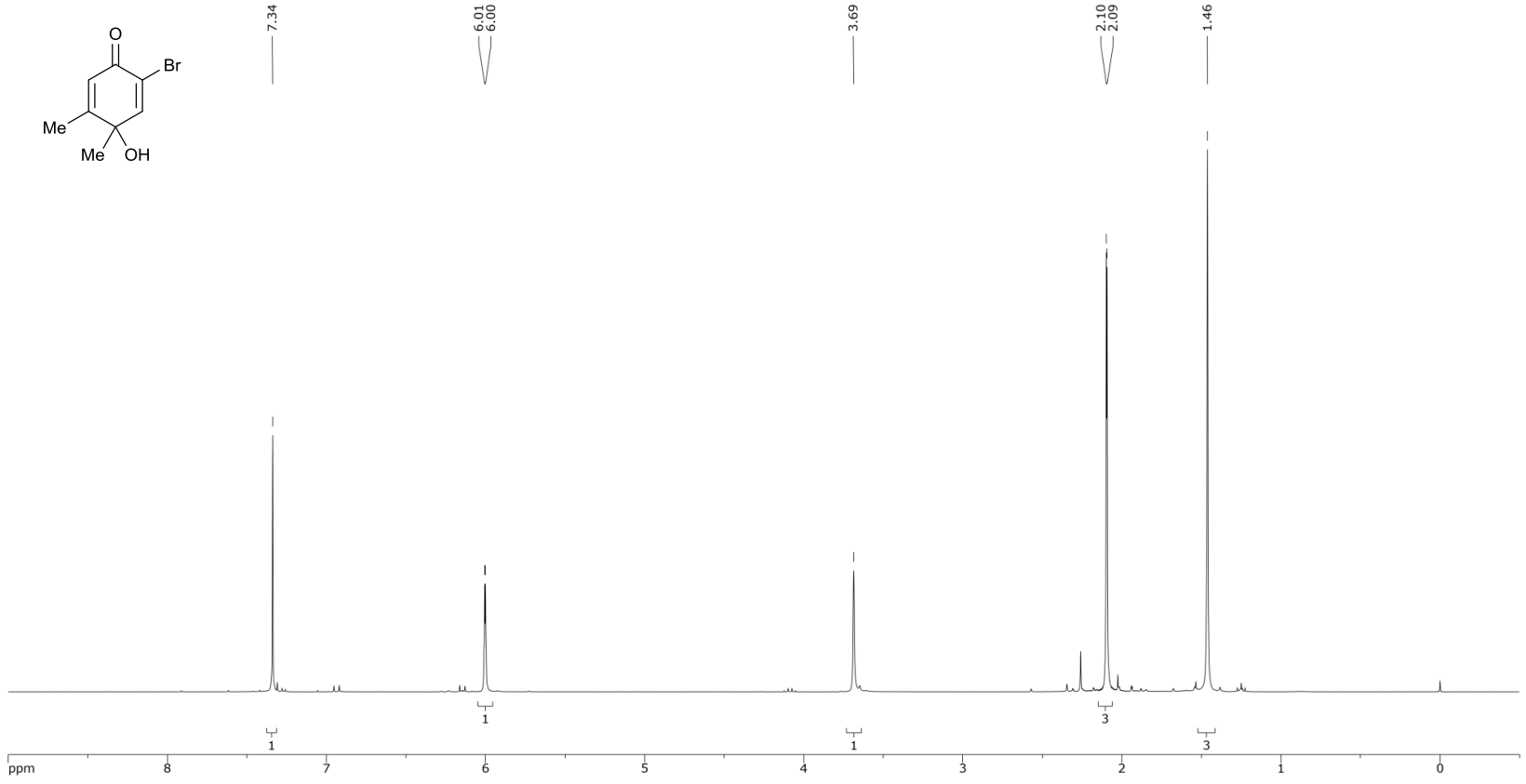
Quinol 2.17r – ^{1}H NMR



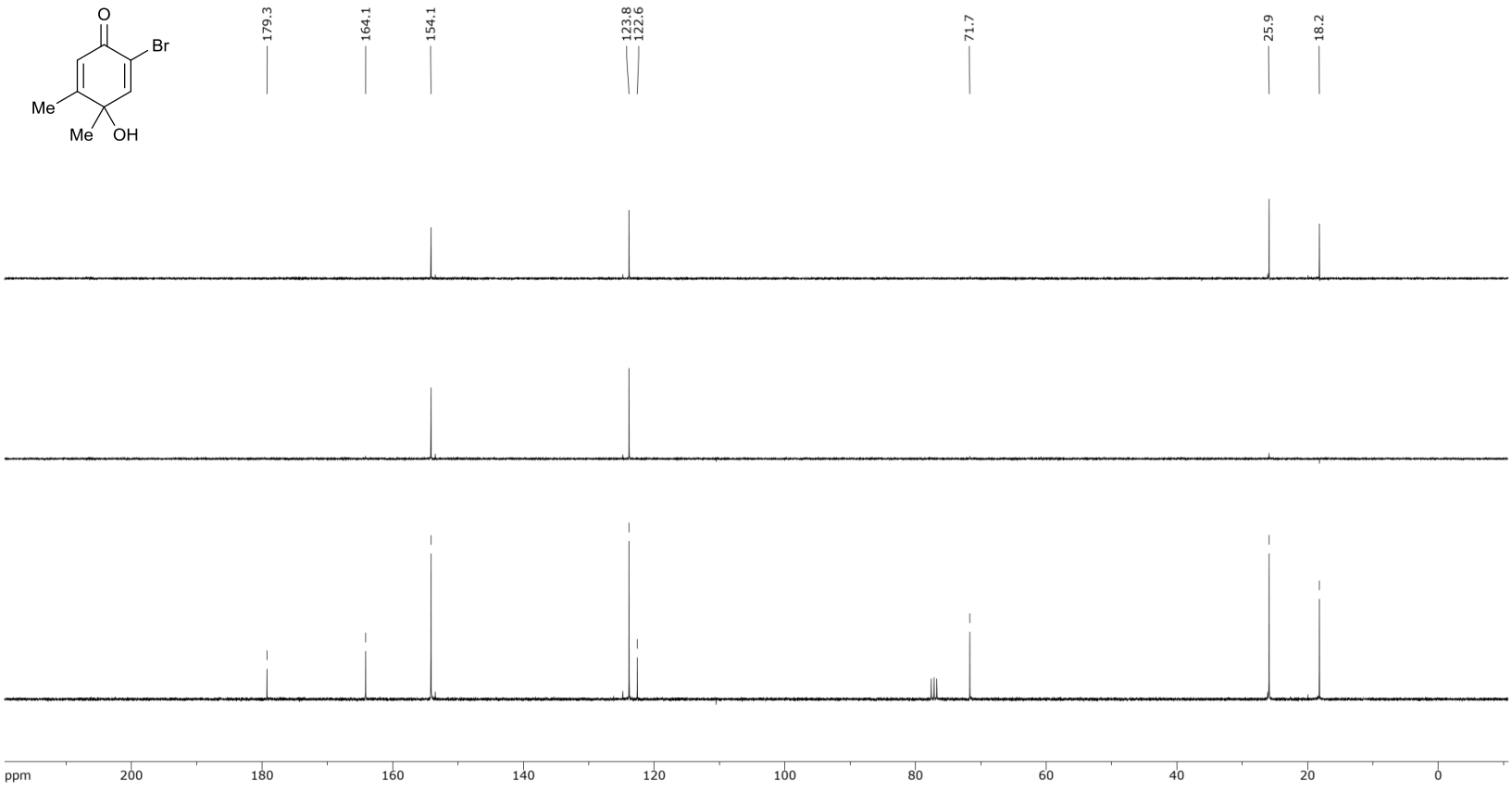
Quinol 2.17r – ^{13}C NMR



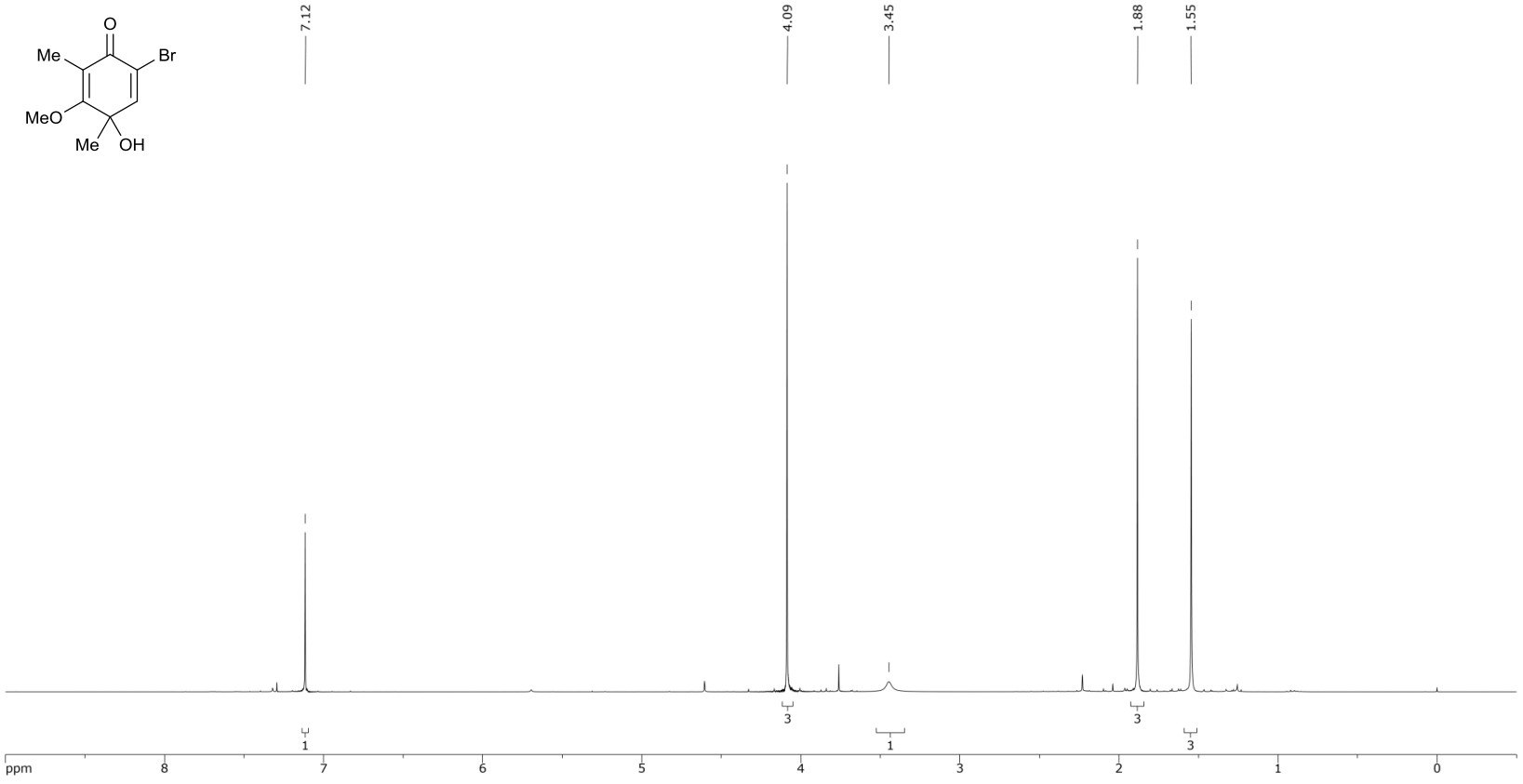
Quinol 2.17s – ^{1}H NMR



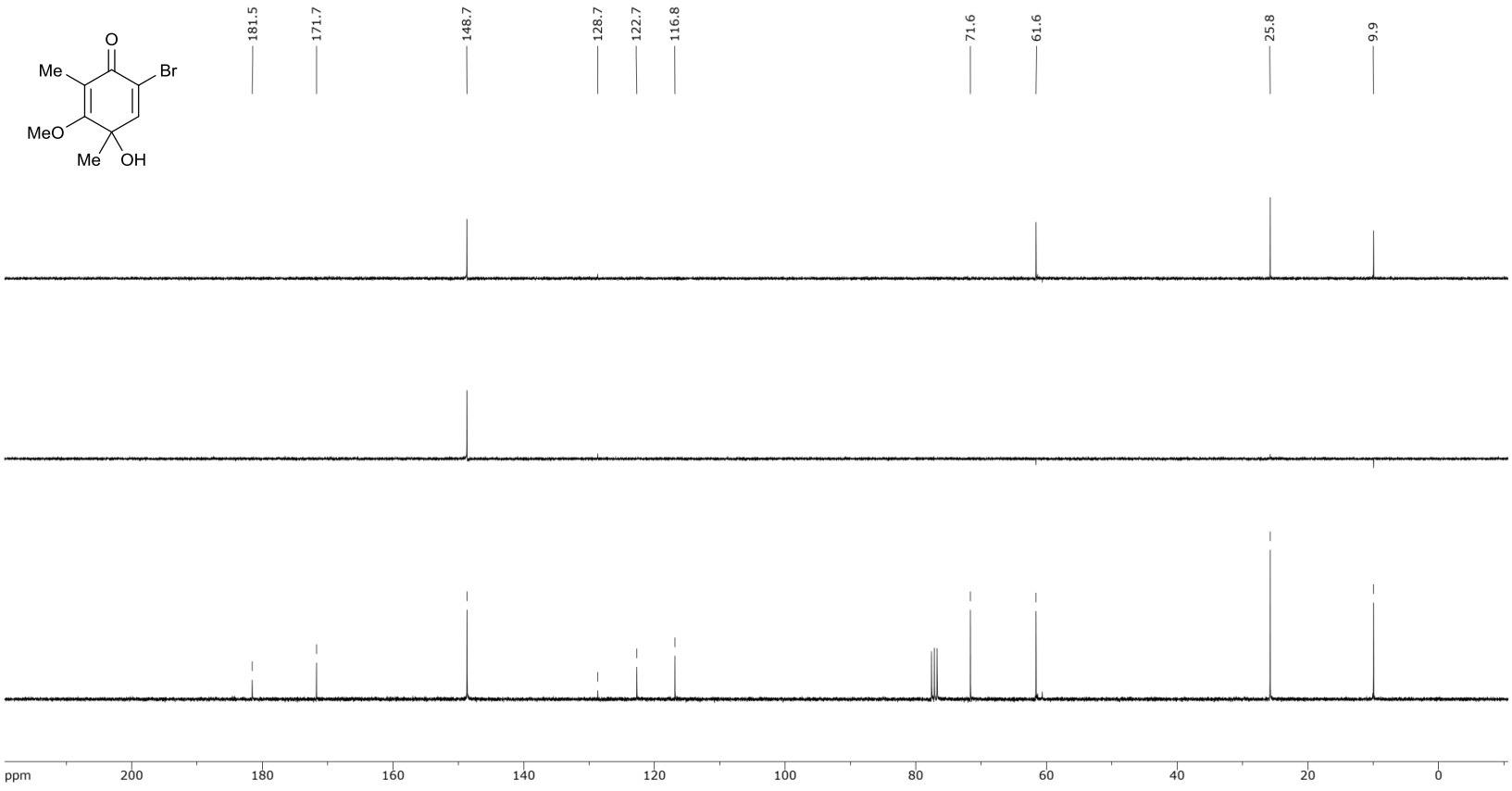
Quinol 2.17s – ^{13}C NMR



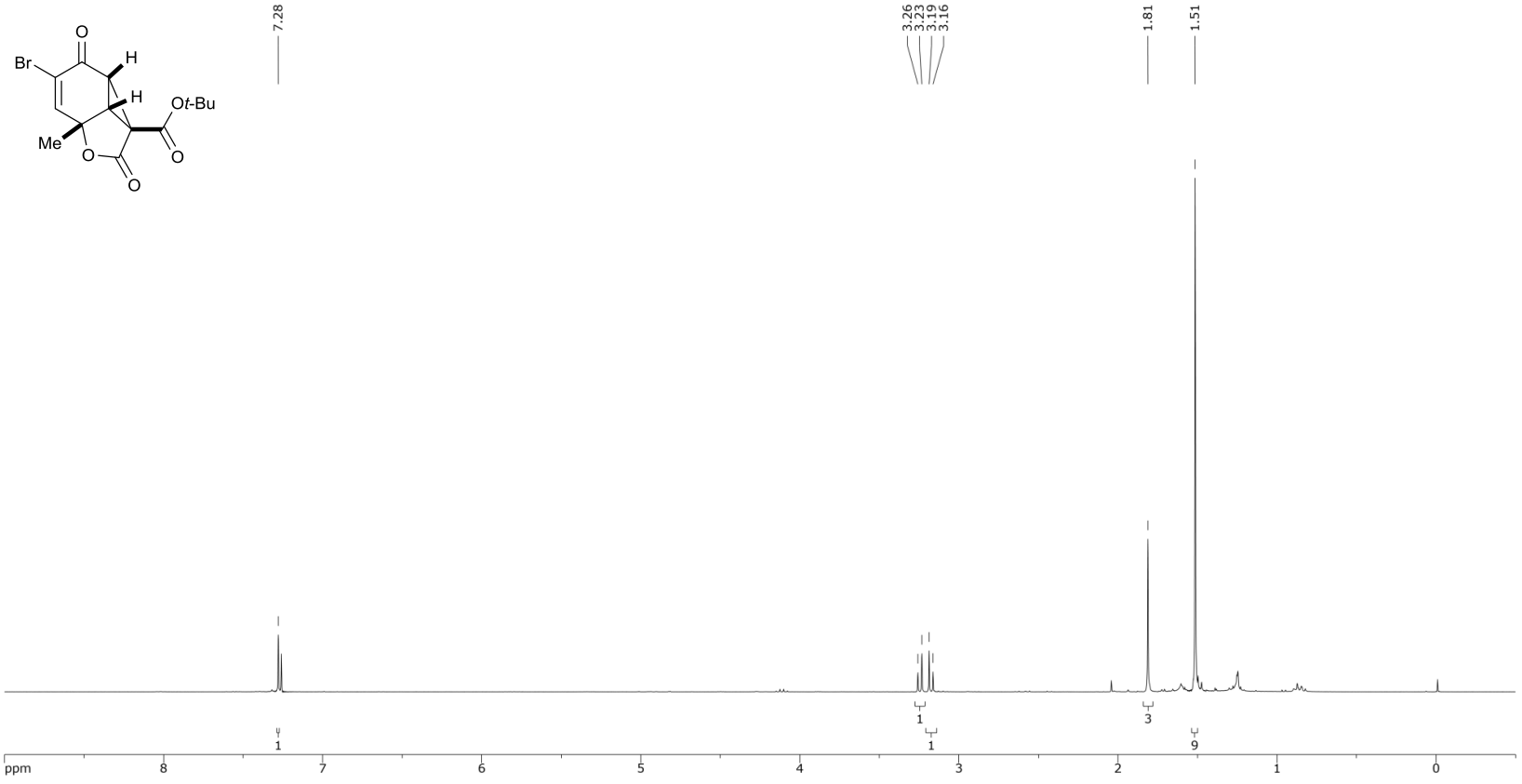
Quinol 2.17t – ^{1}H NMR



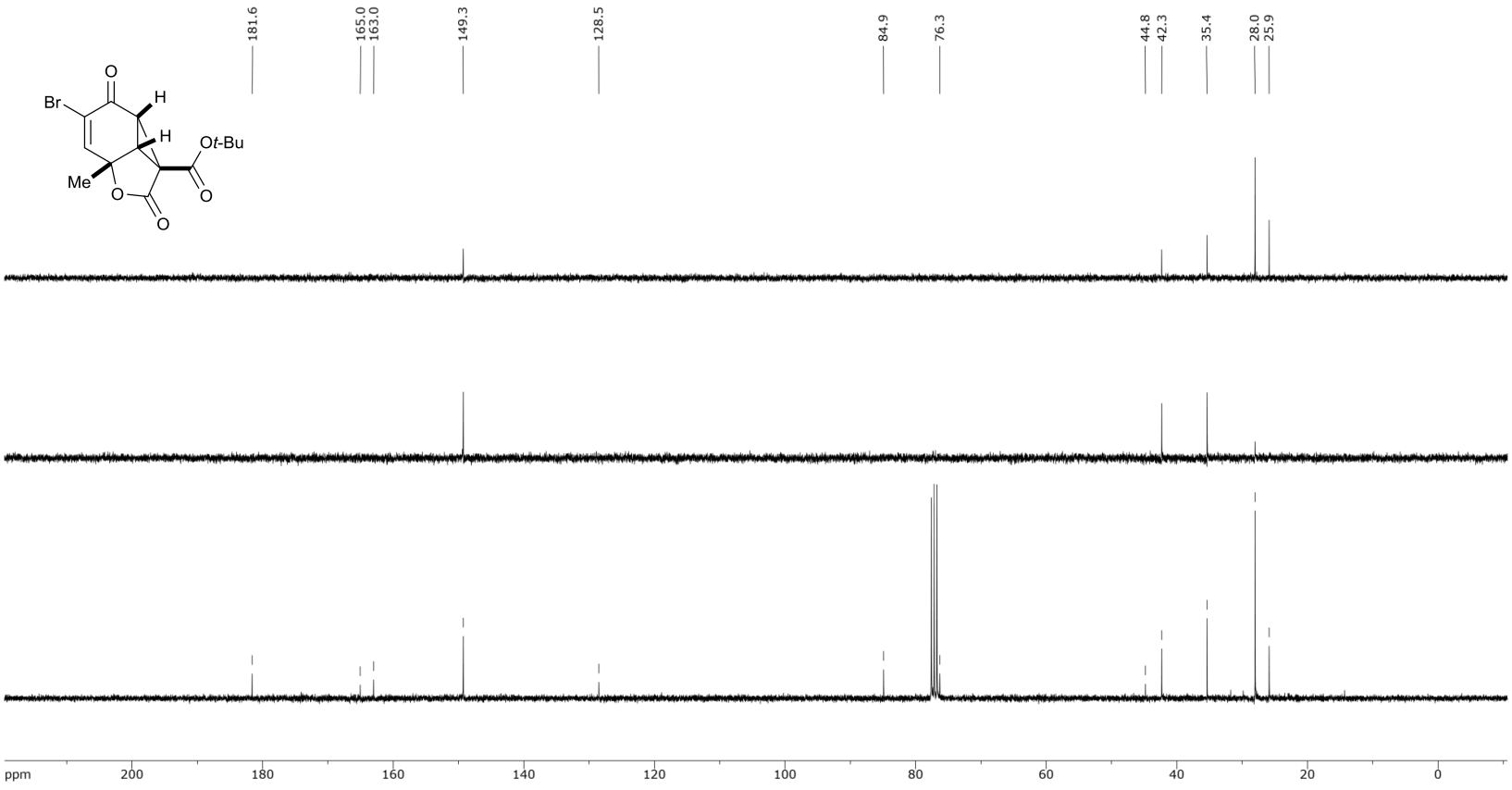
Quinol 2.17t – ^{13}C NMR



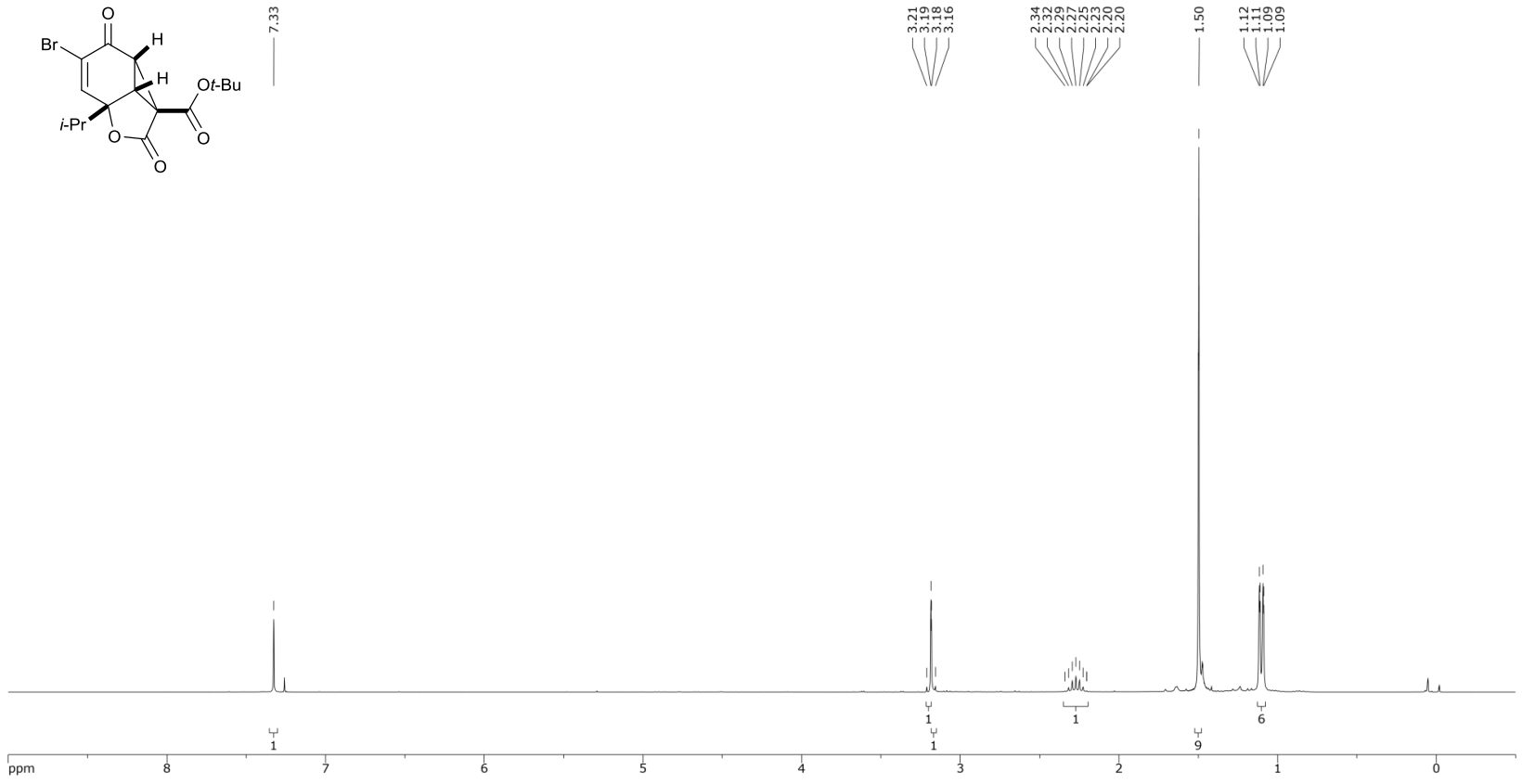
Cyclopropane 2.23j – ^{1}H NMR



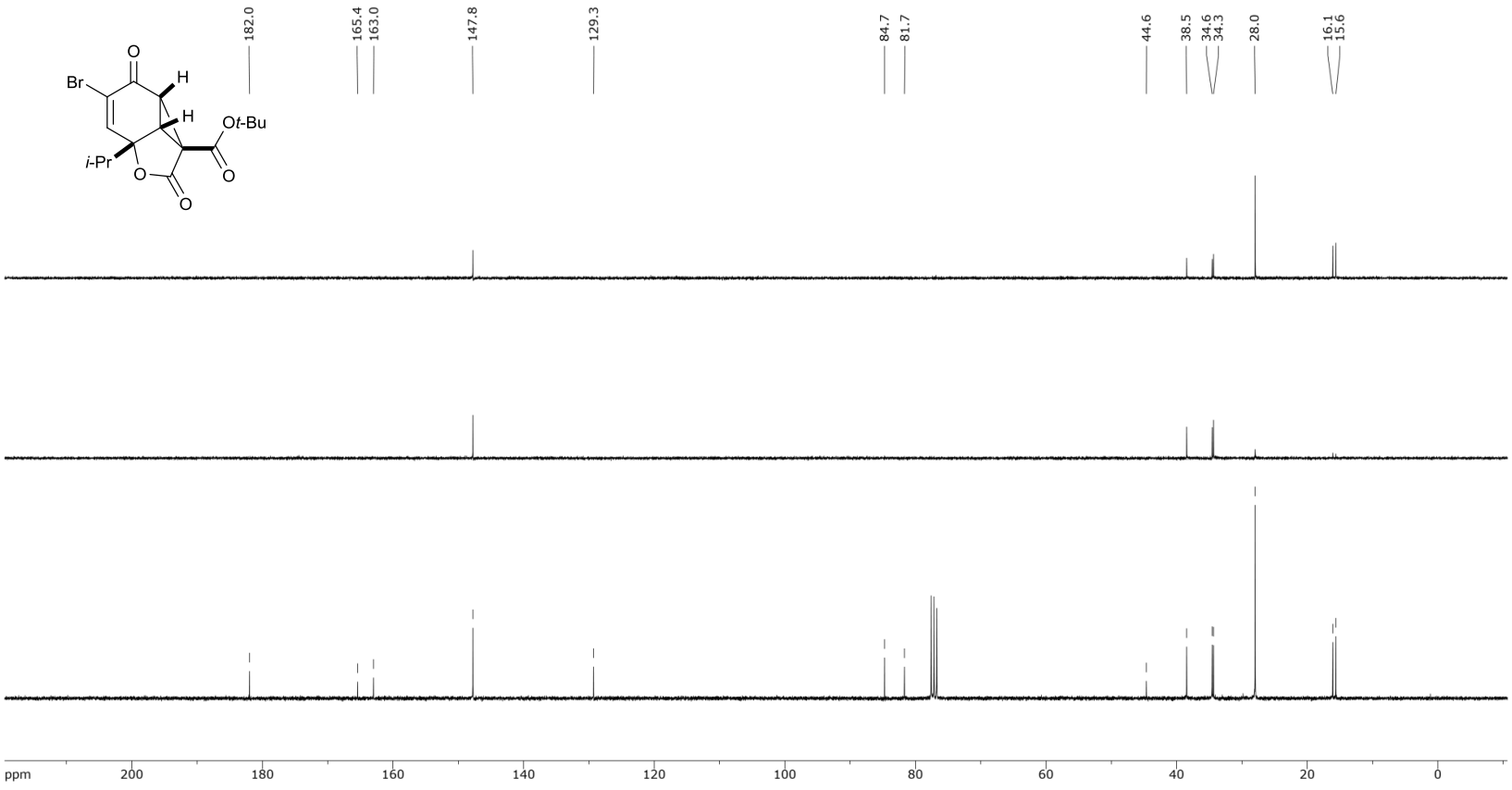
Cyclopropane 2.23j – ^{13}C NMR



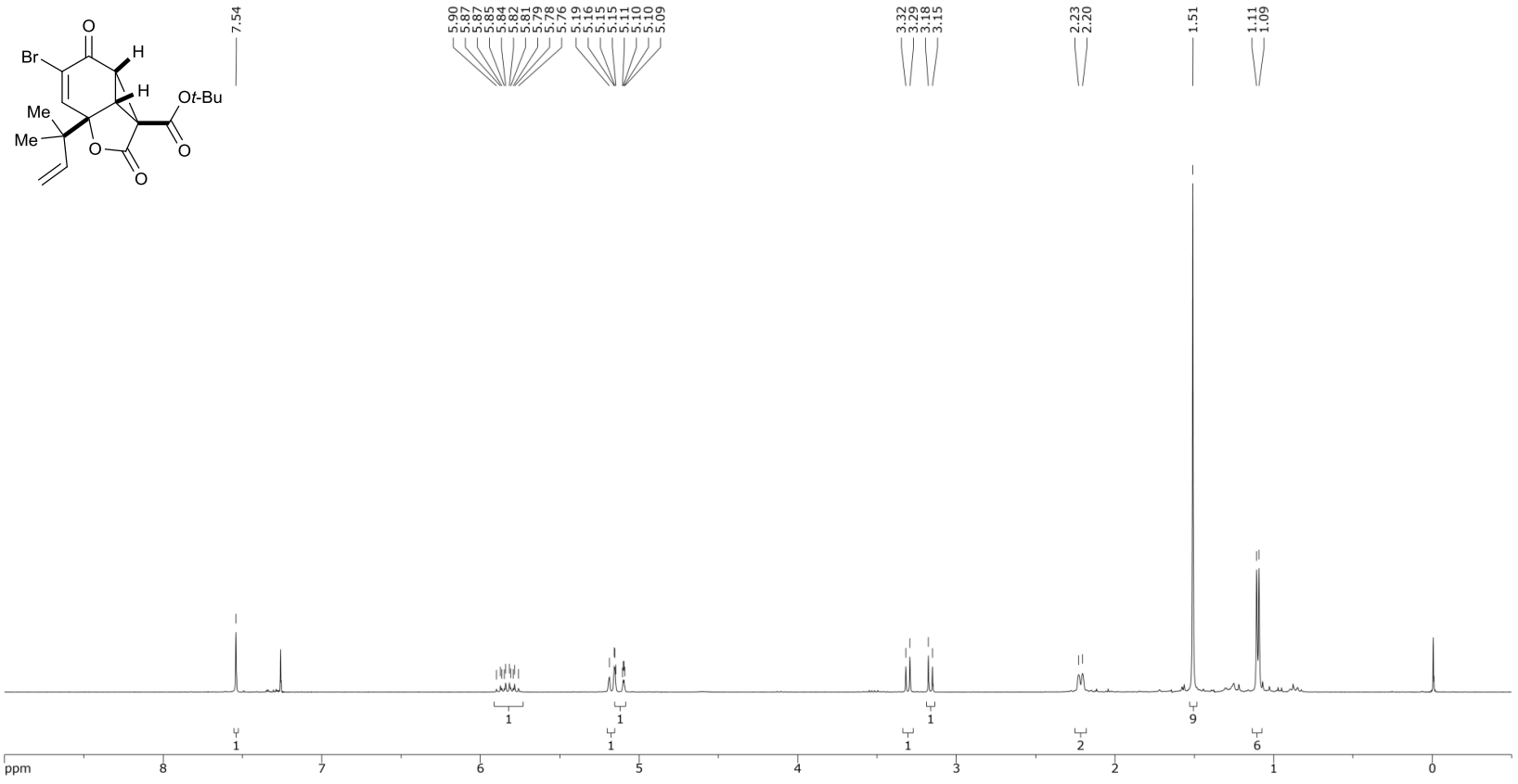
Cyclopropane 2.23k – ^{1}H NMR



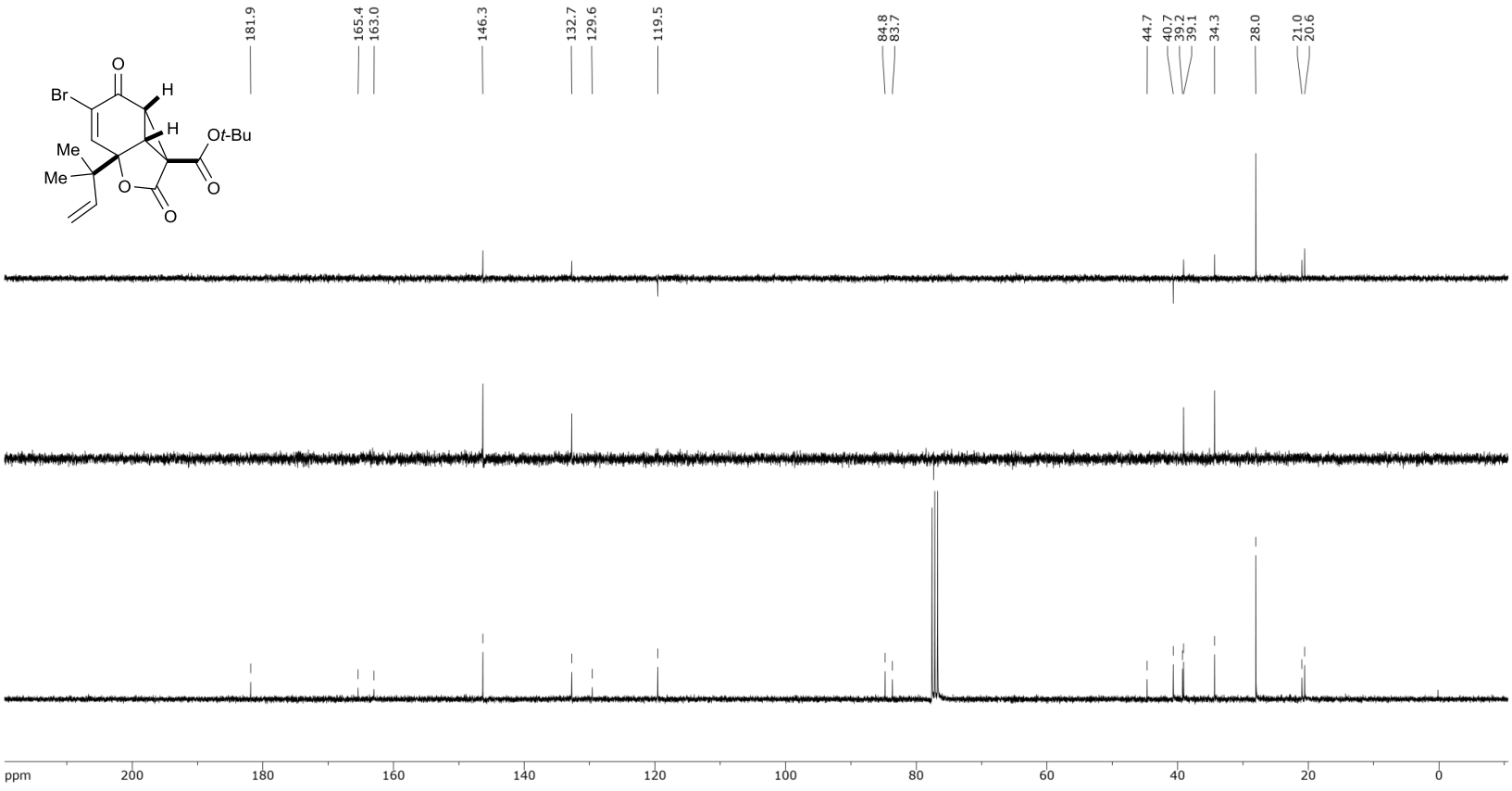
Cyclopropane 2.23k – ^{13}C NMR



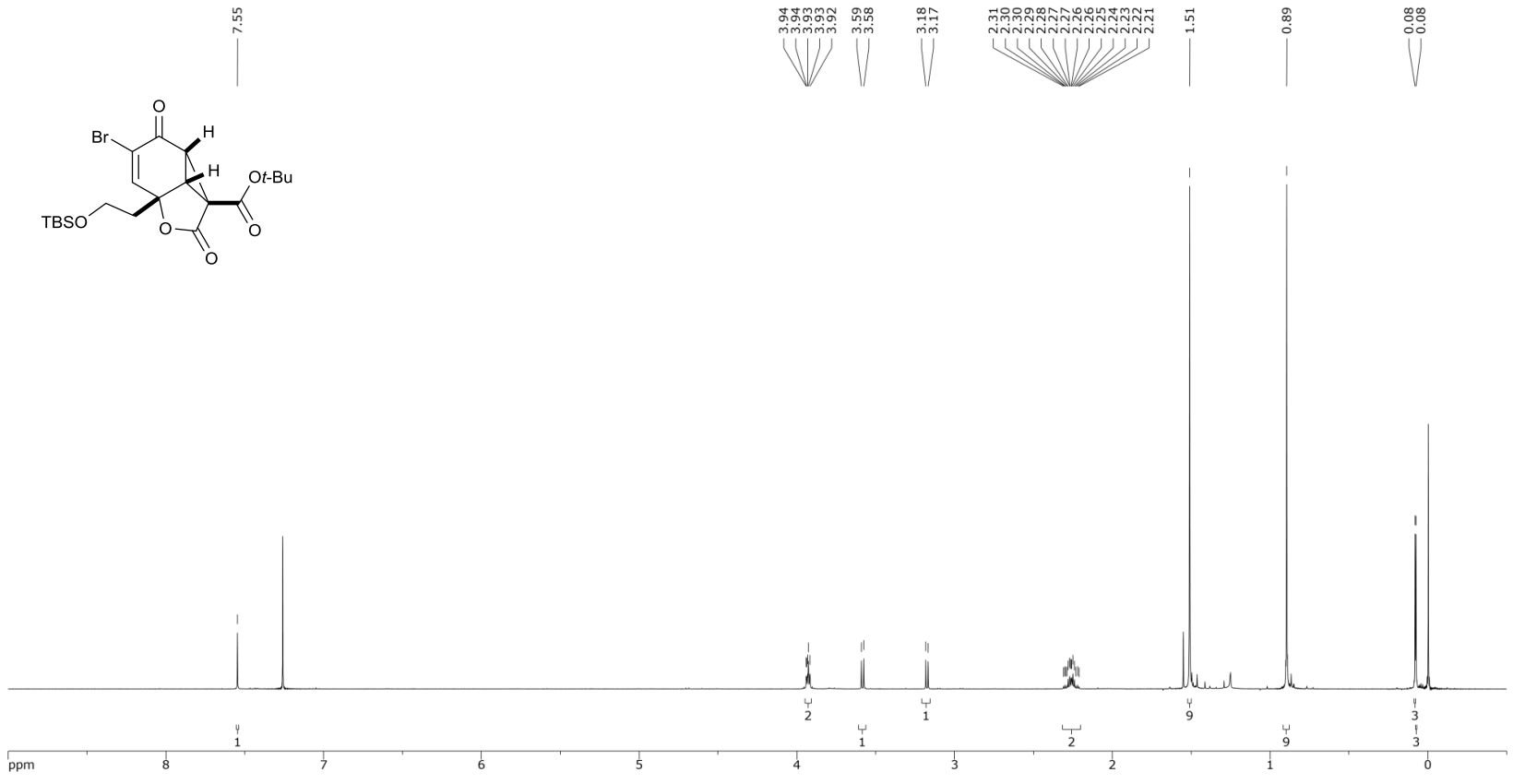
Cyclopropane 2.23l – ^{1}H NMR



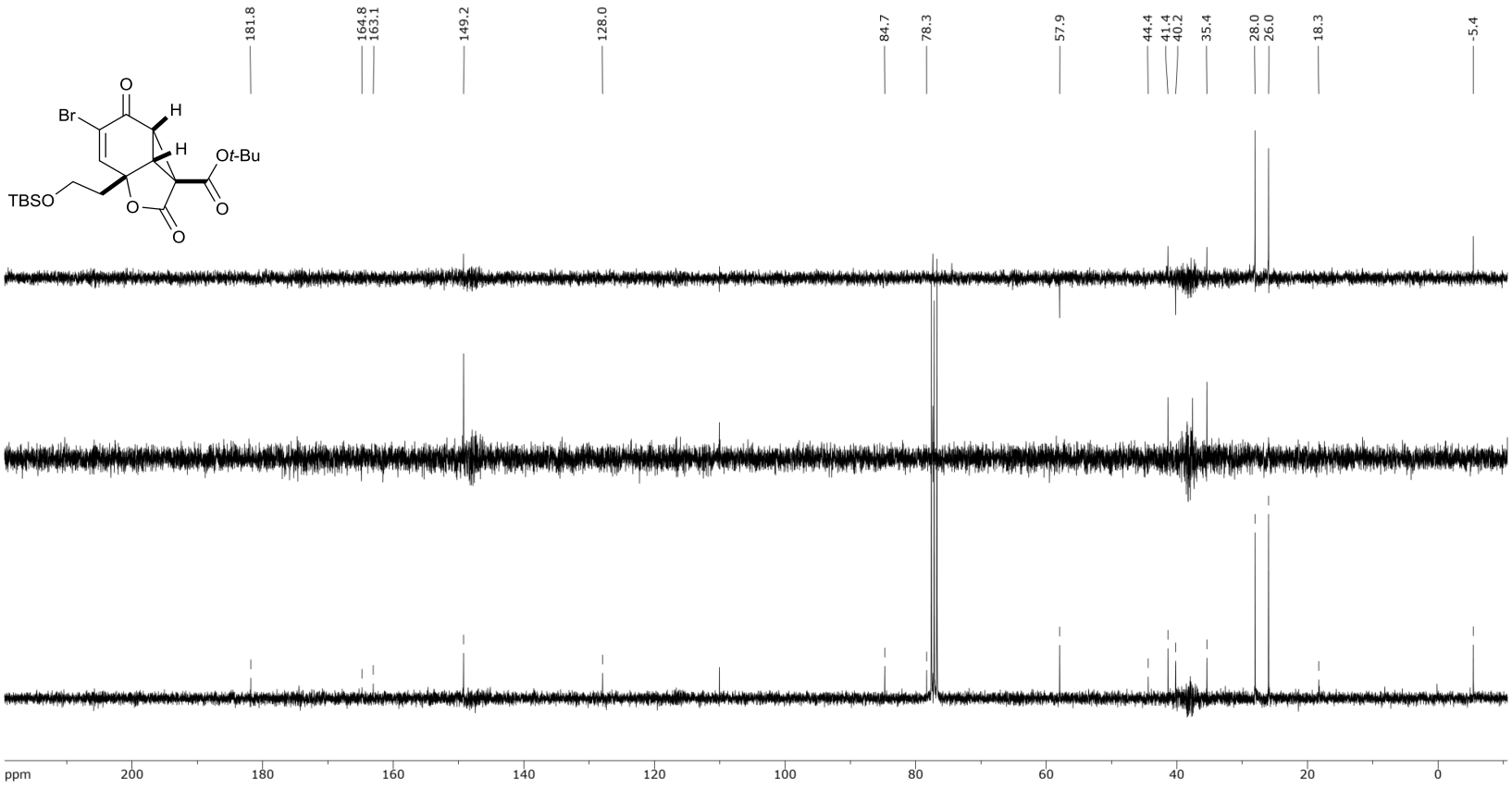
Cyclopropane 2.23l – ^{13}C NMR



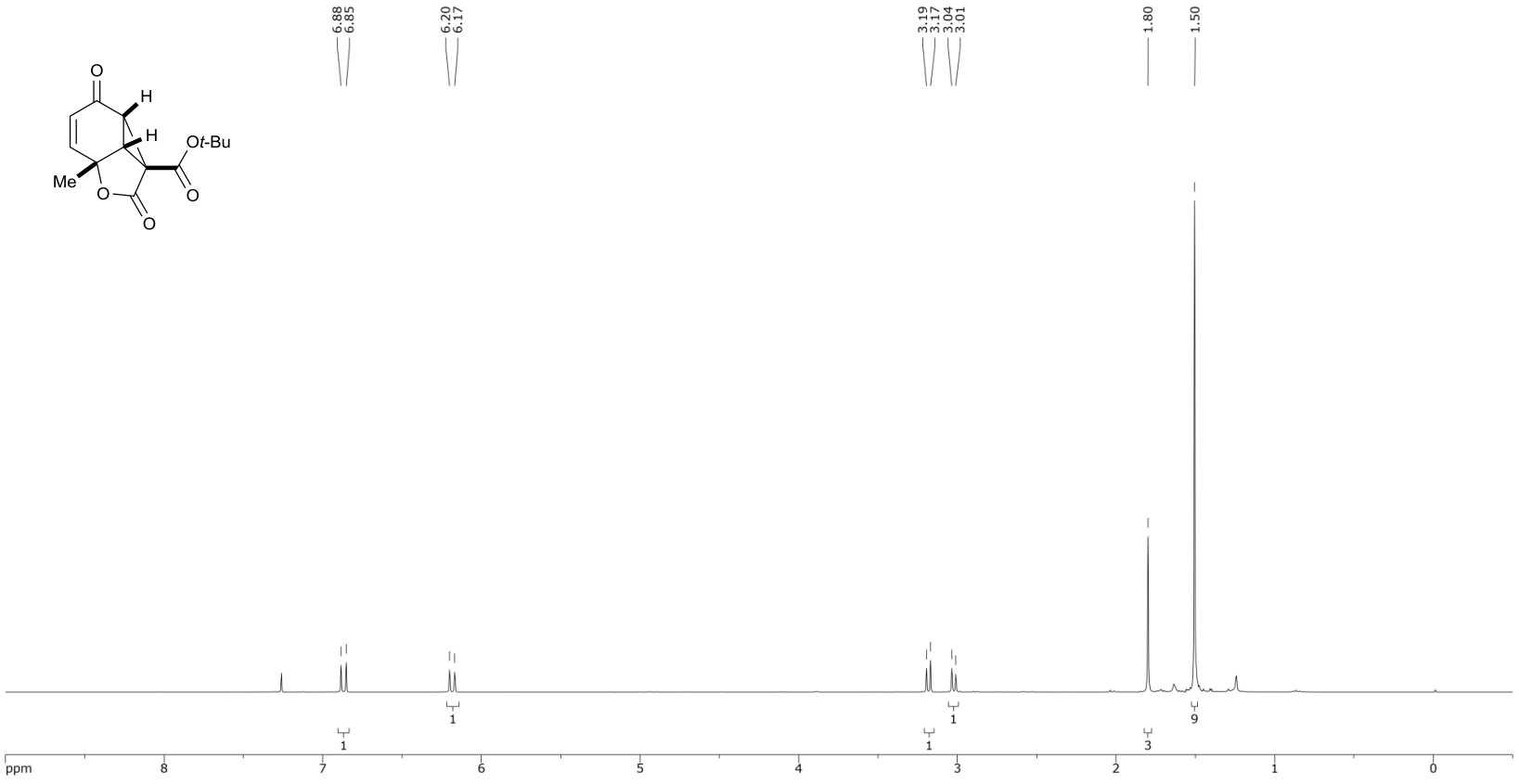
Cyclopropane 2.23m – ^{1}H NMR



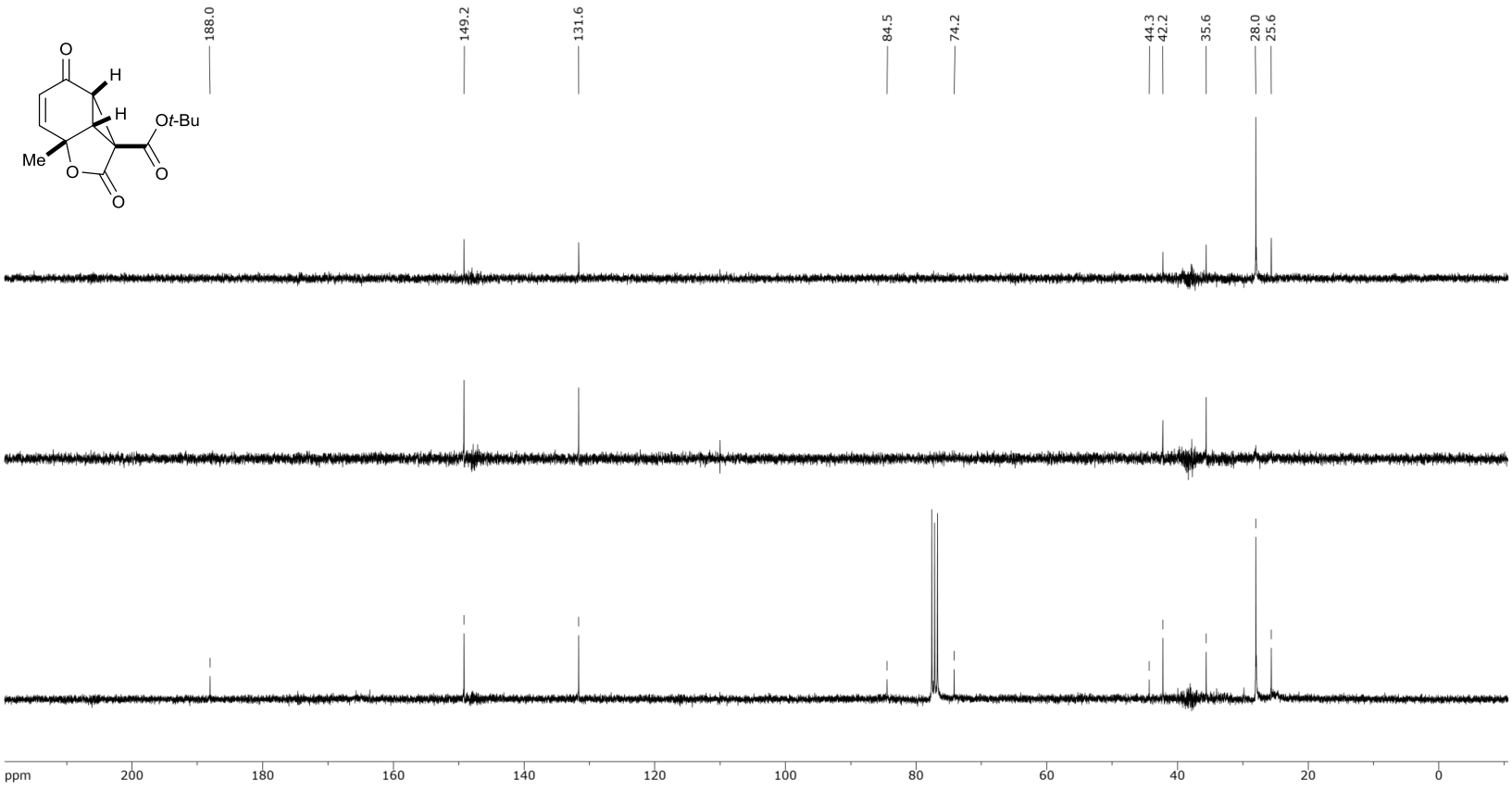
Cyclopropane 2.23m – ^{13}C NMR



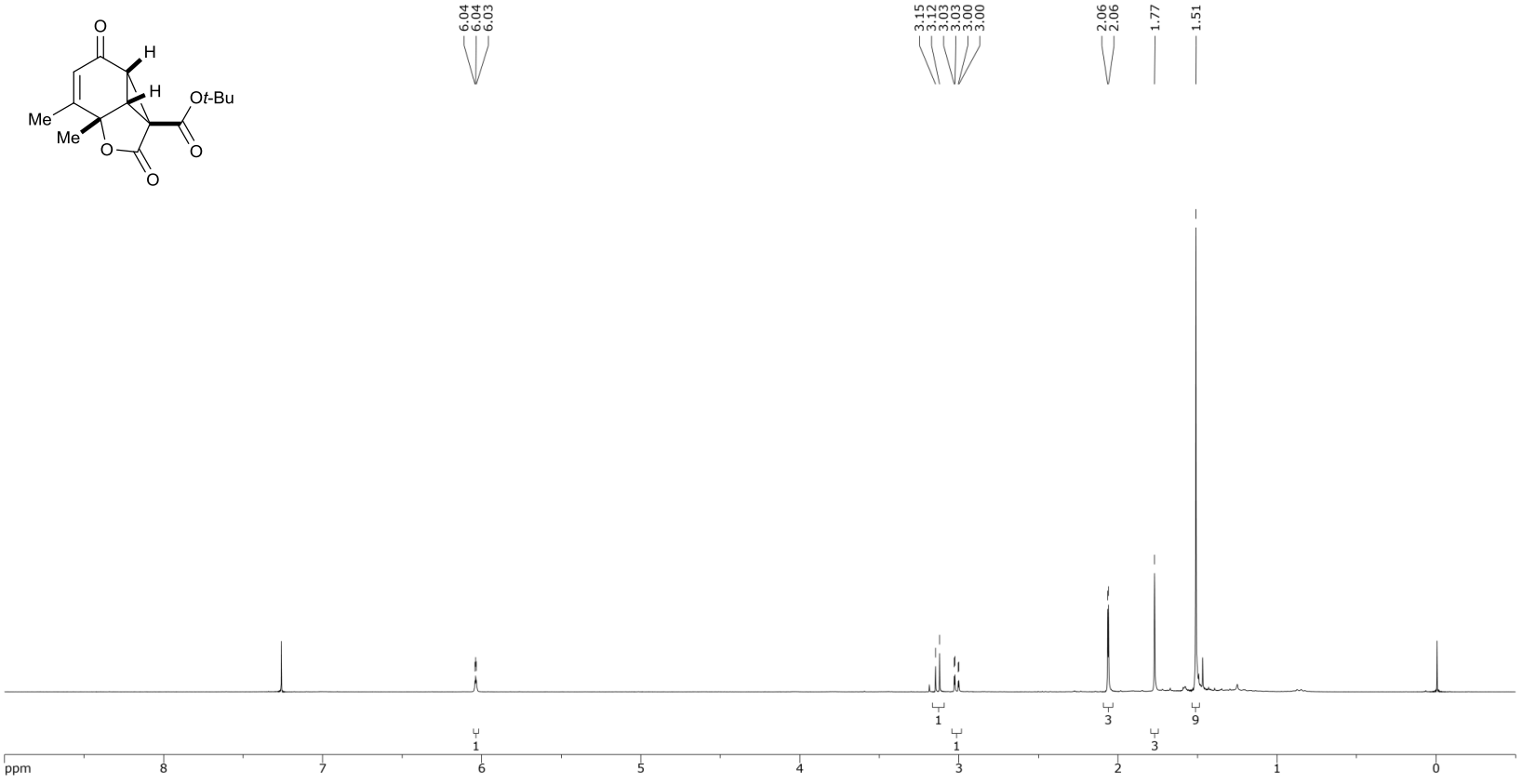
Cyclopropane 2.23r – ^{1}H NMR



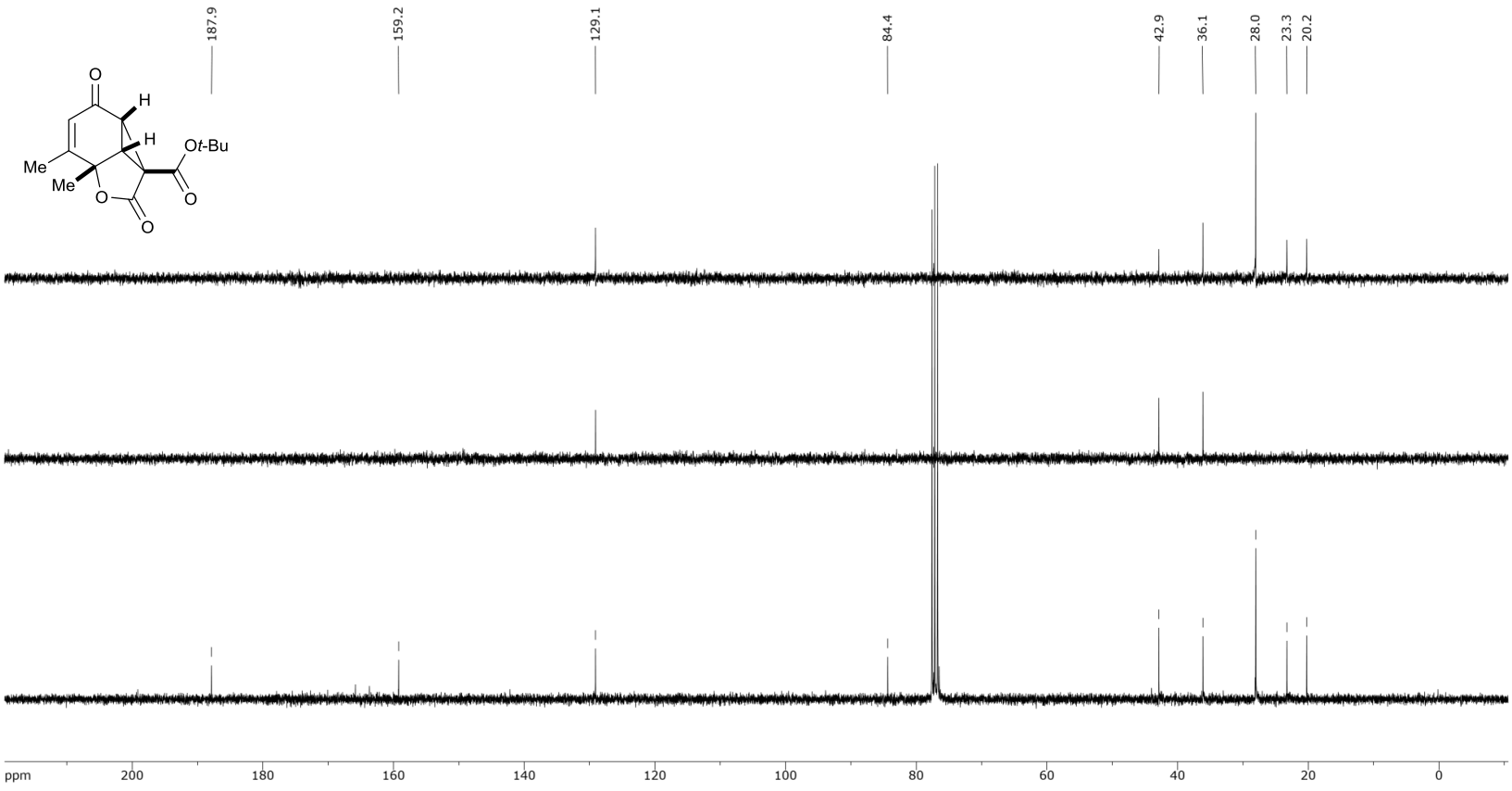
Cyclopropane 2.23r – ^{13}C NMR



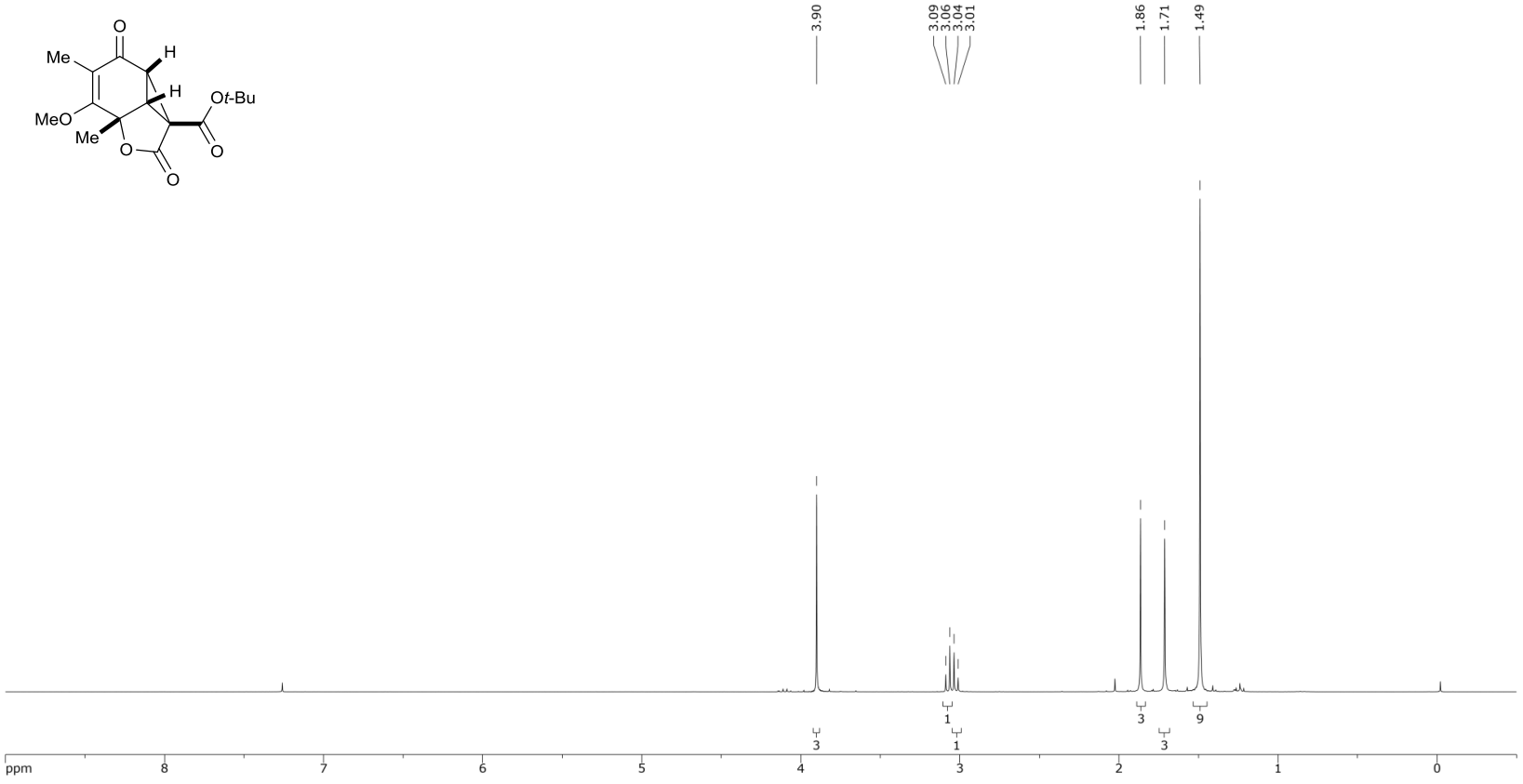
Cyclopropane 2.23s – ^{1}H NMR



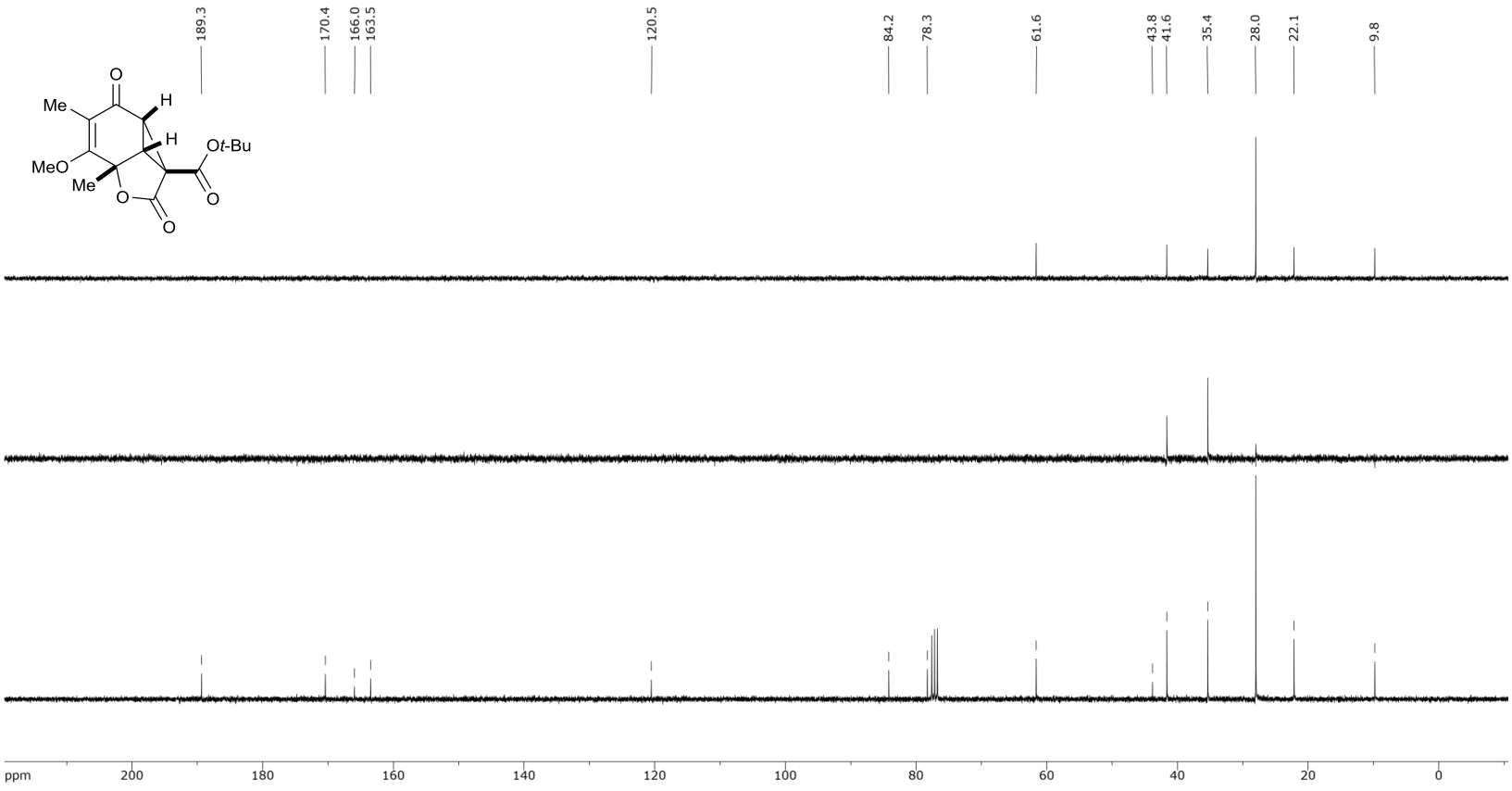
Cyclopropane 2.23s – ^{13}C NMR



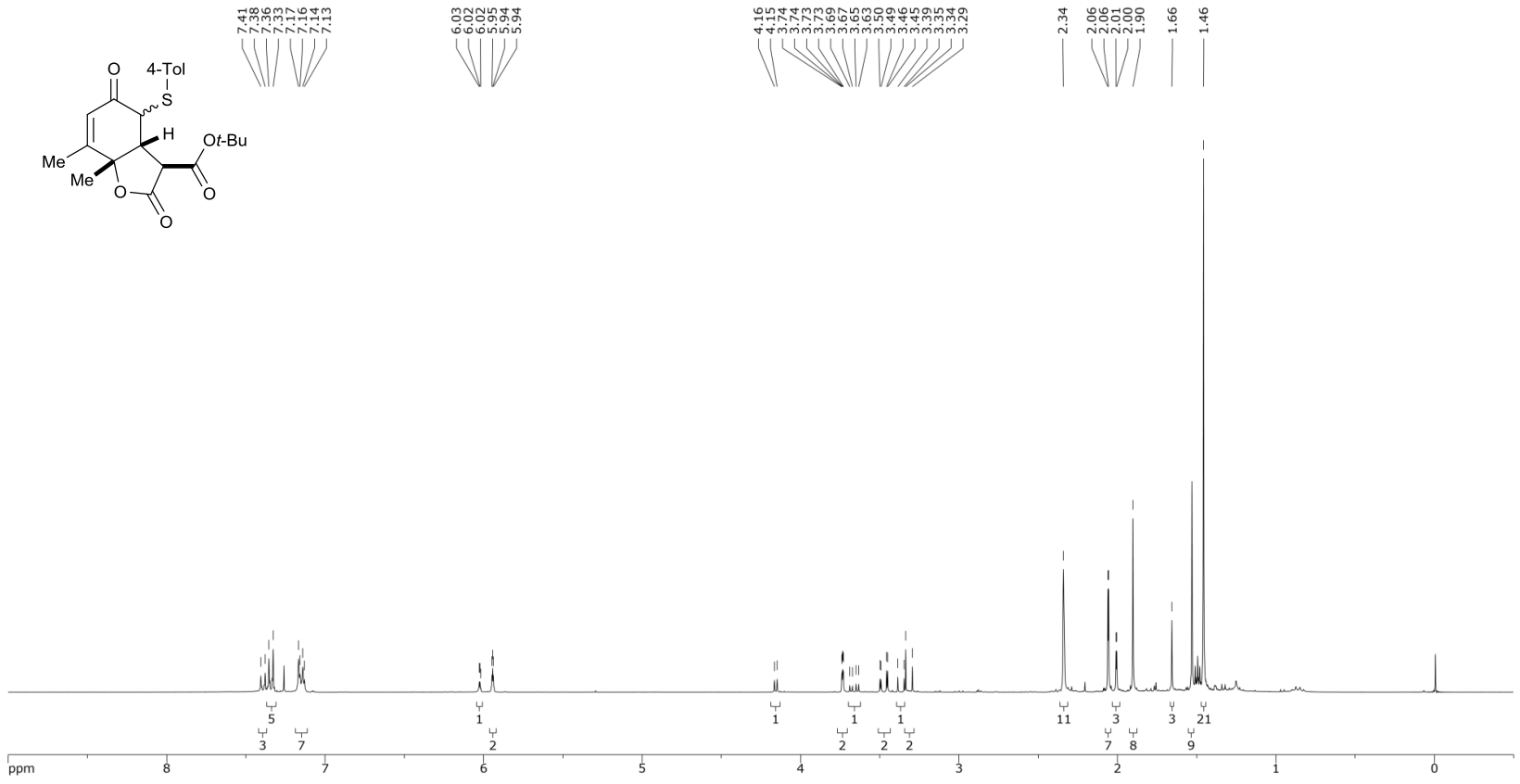
Cyclopropane 2.23t – ^{1}H NMR



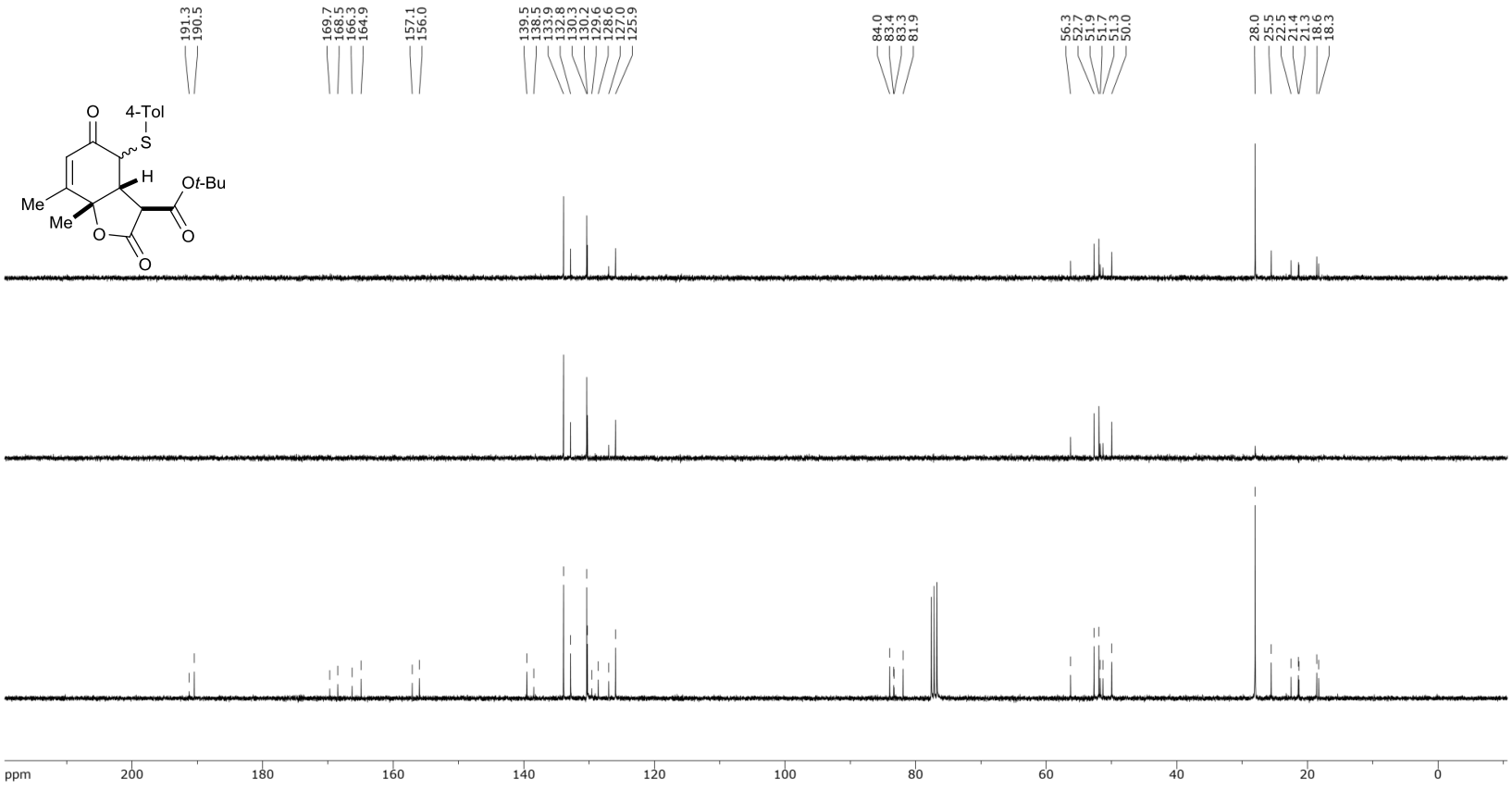
Cyclopropane 2.23t – ^{13}C NMR



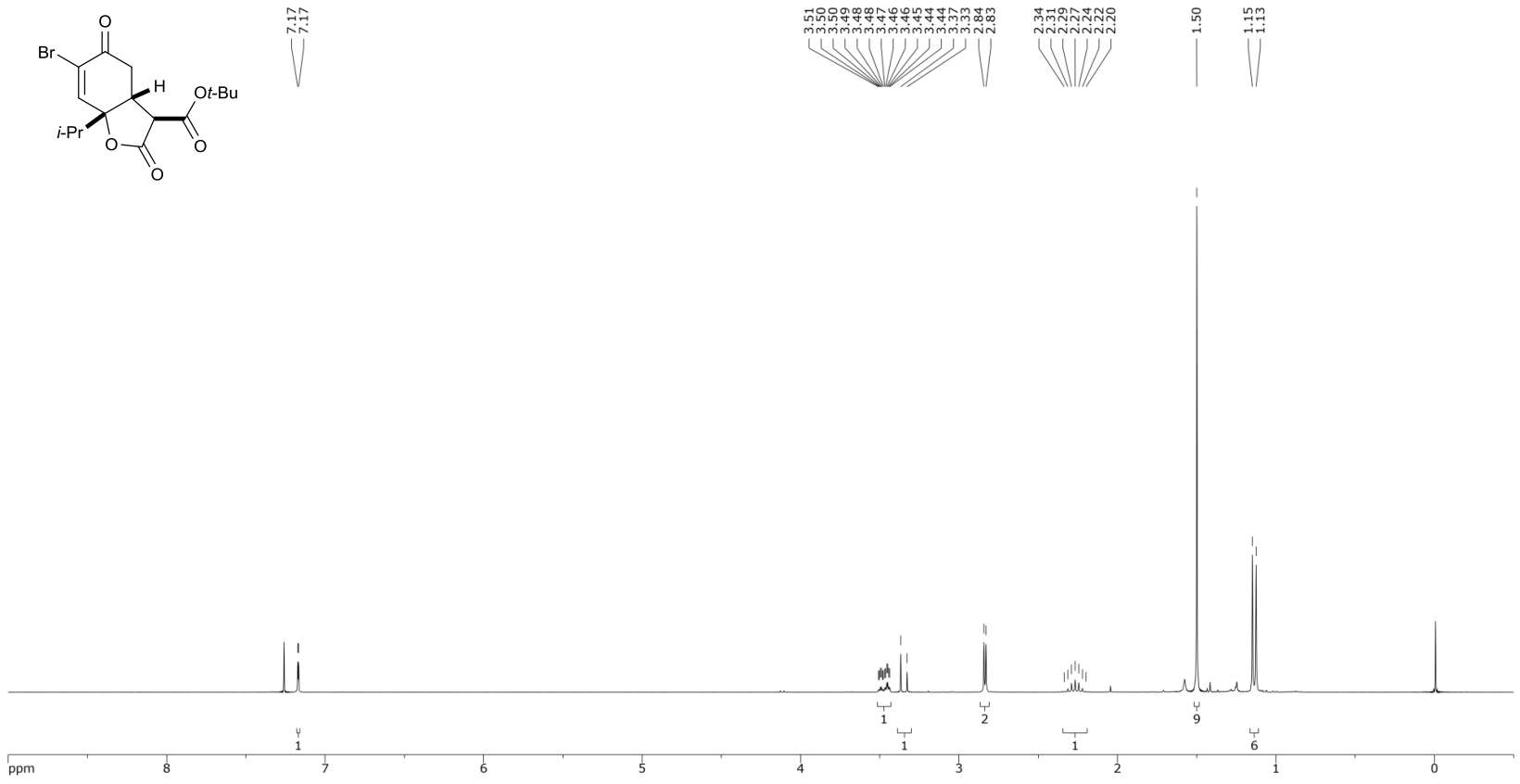
Sulfide 2.30 – ^{1}H NMR



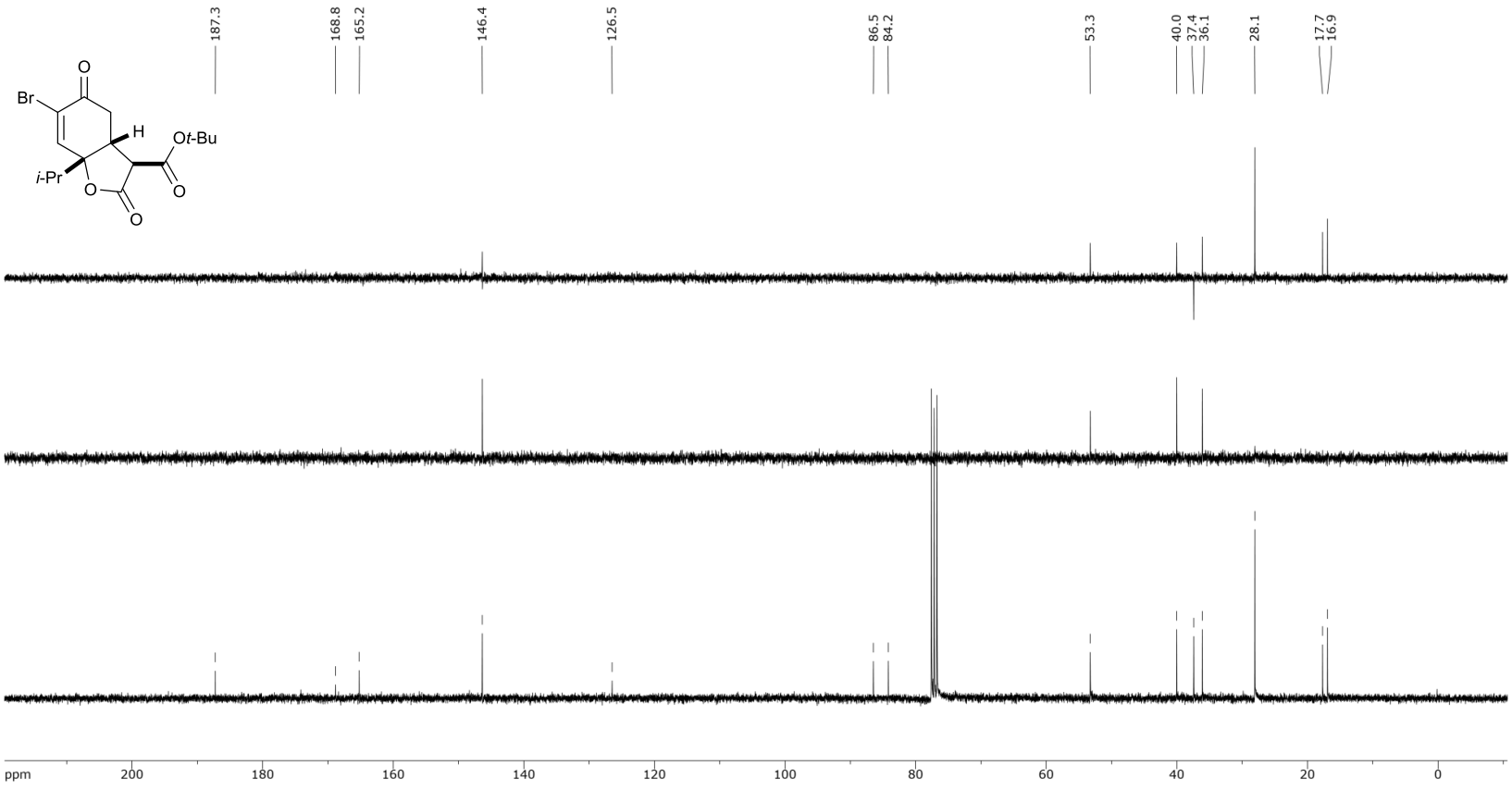
Sulfide 2.30 – ^{13}C NMR



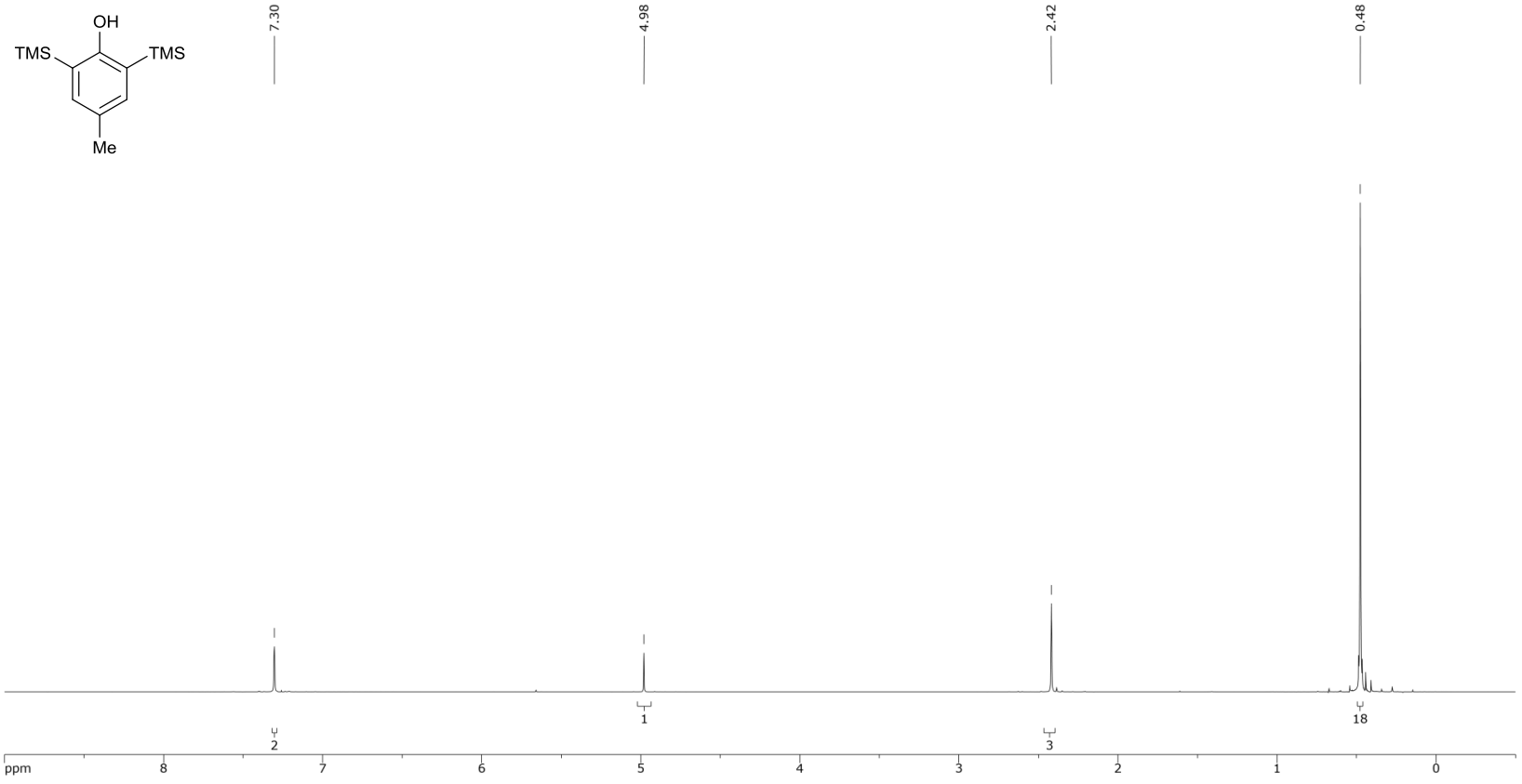
Bicyclic lactone 2.31 – ^{1}H NMR



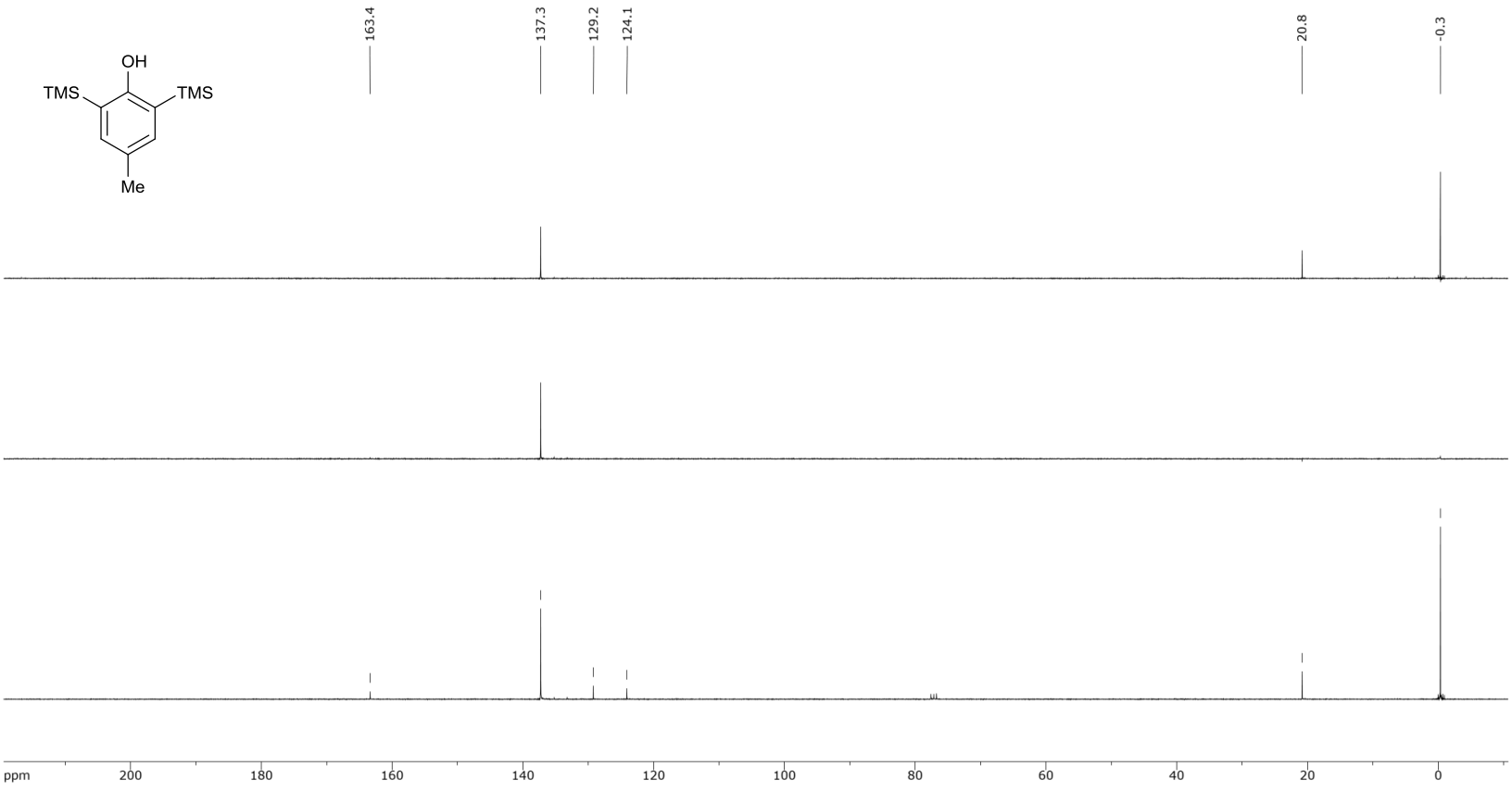
Bicyclic lactone 2.31 – ^{13}C NMR



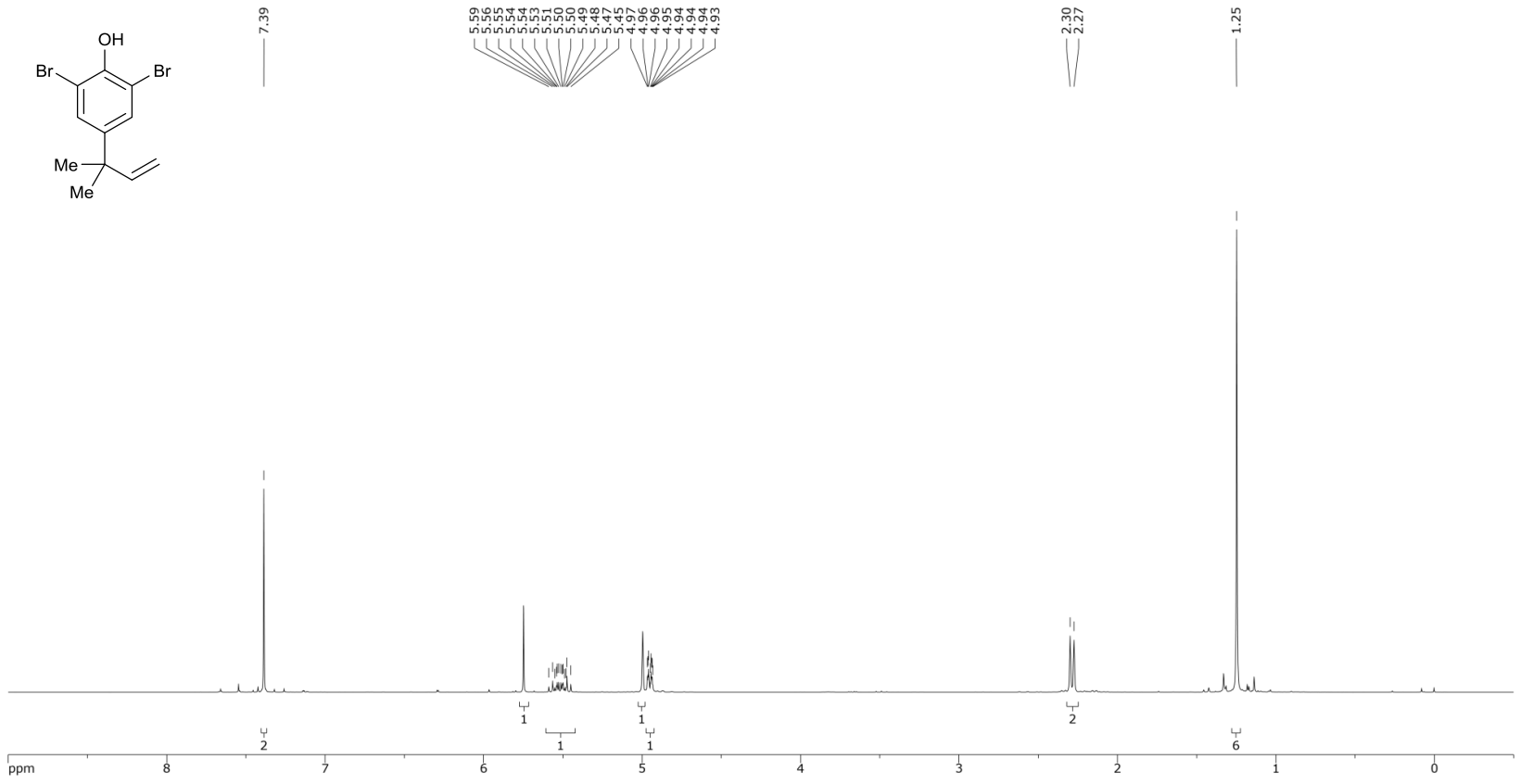
Phenol S2 – ^{1}H NMR



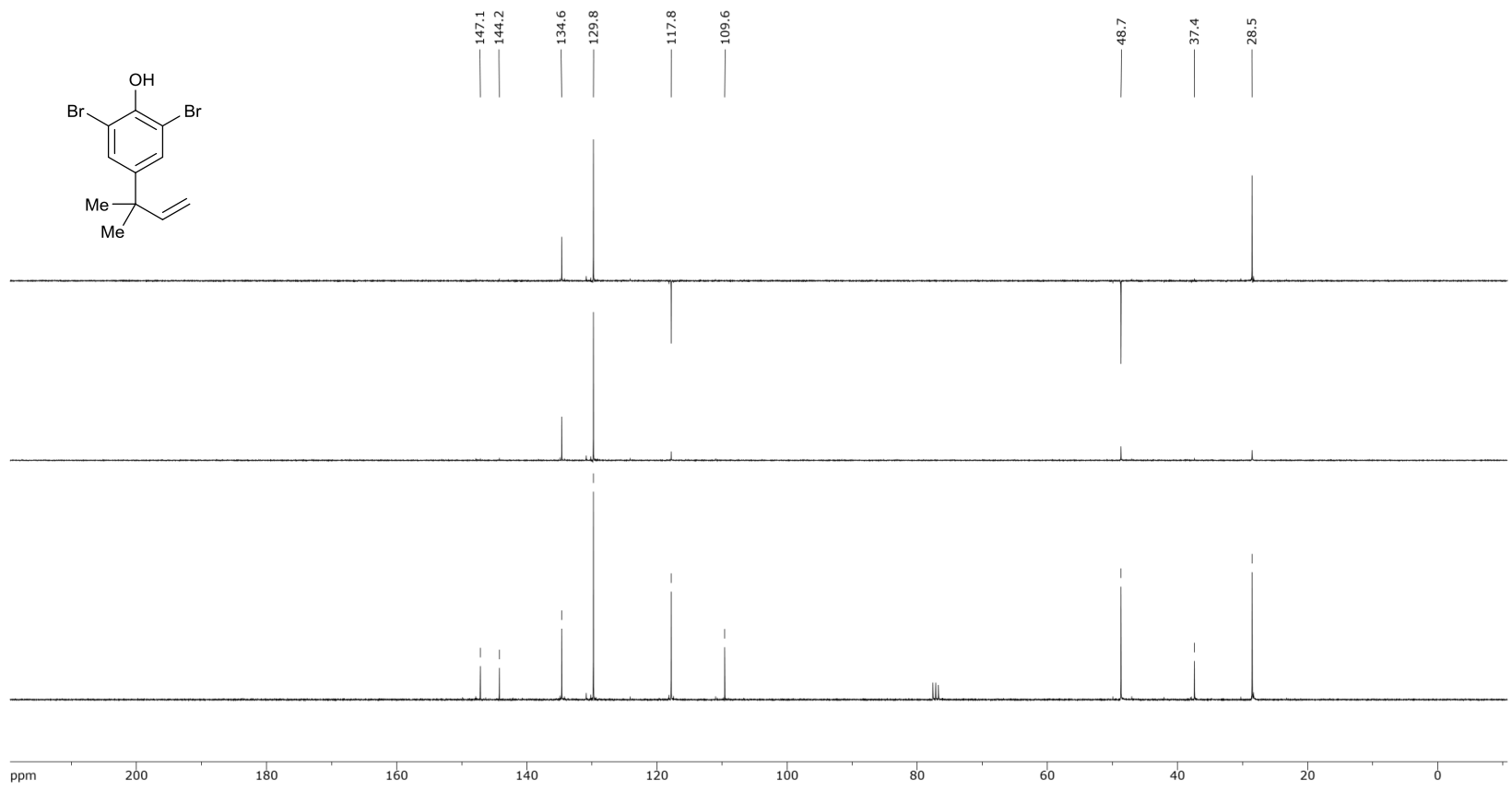
Phenol S2 – ^{13}C NMR



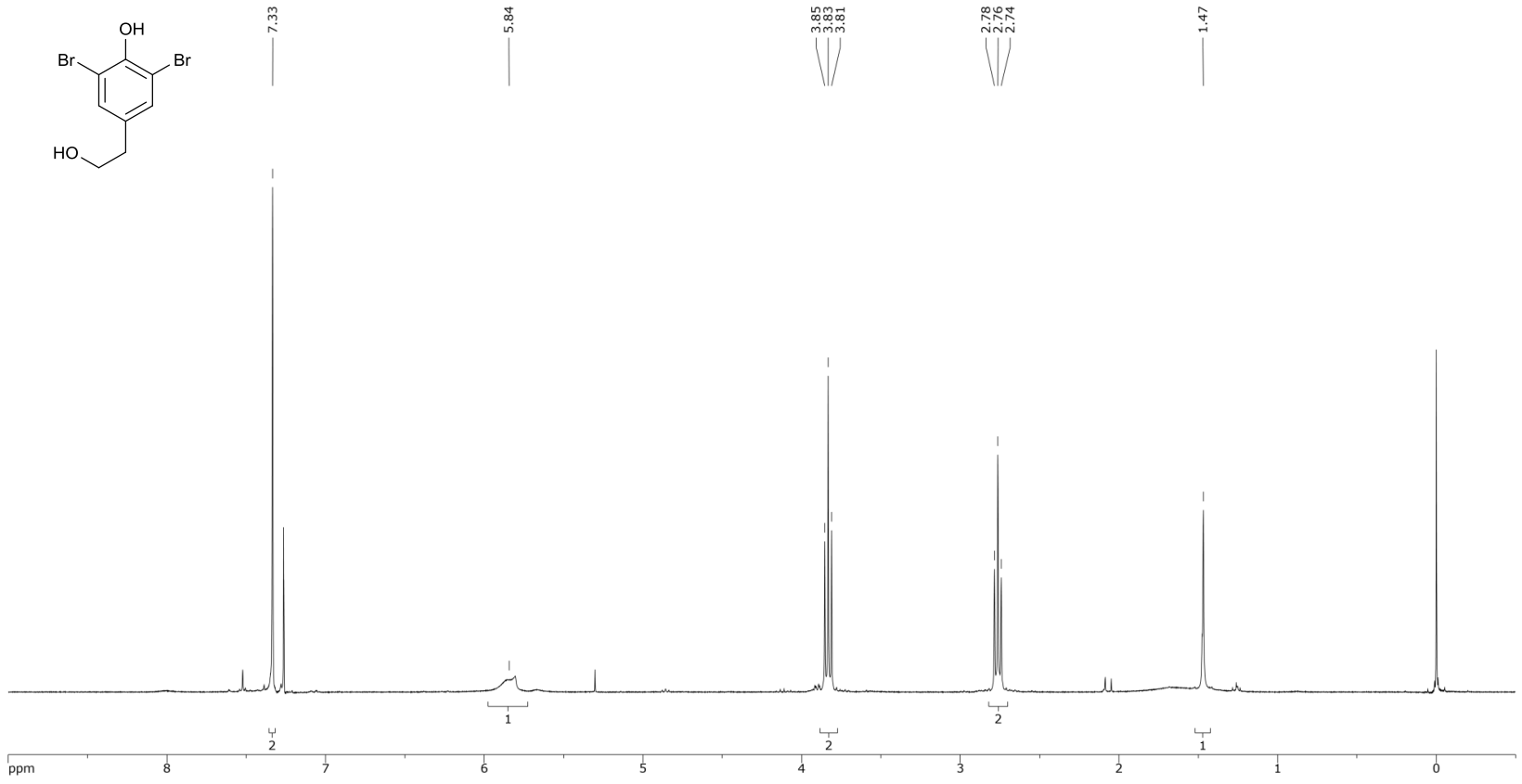
Phenol S4 – ^{1}H NMR



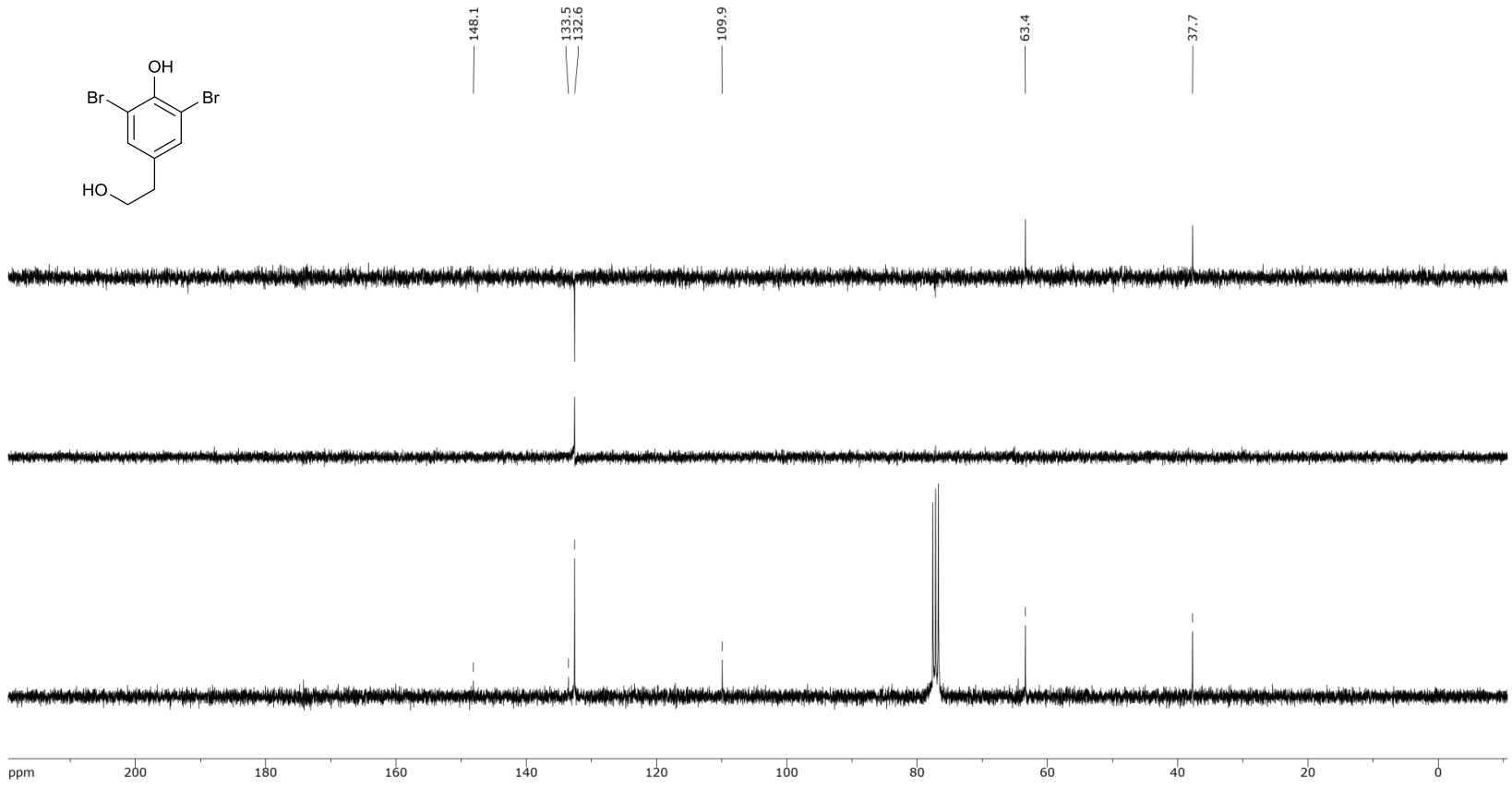
Phenol S4 – ^{13}C NMR



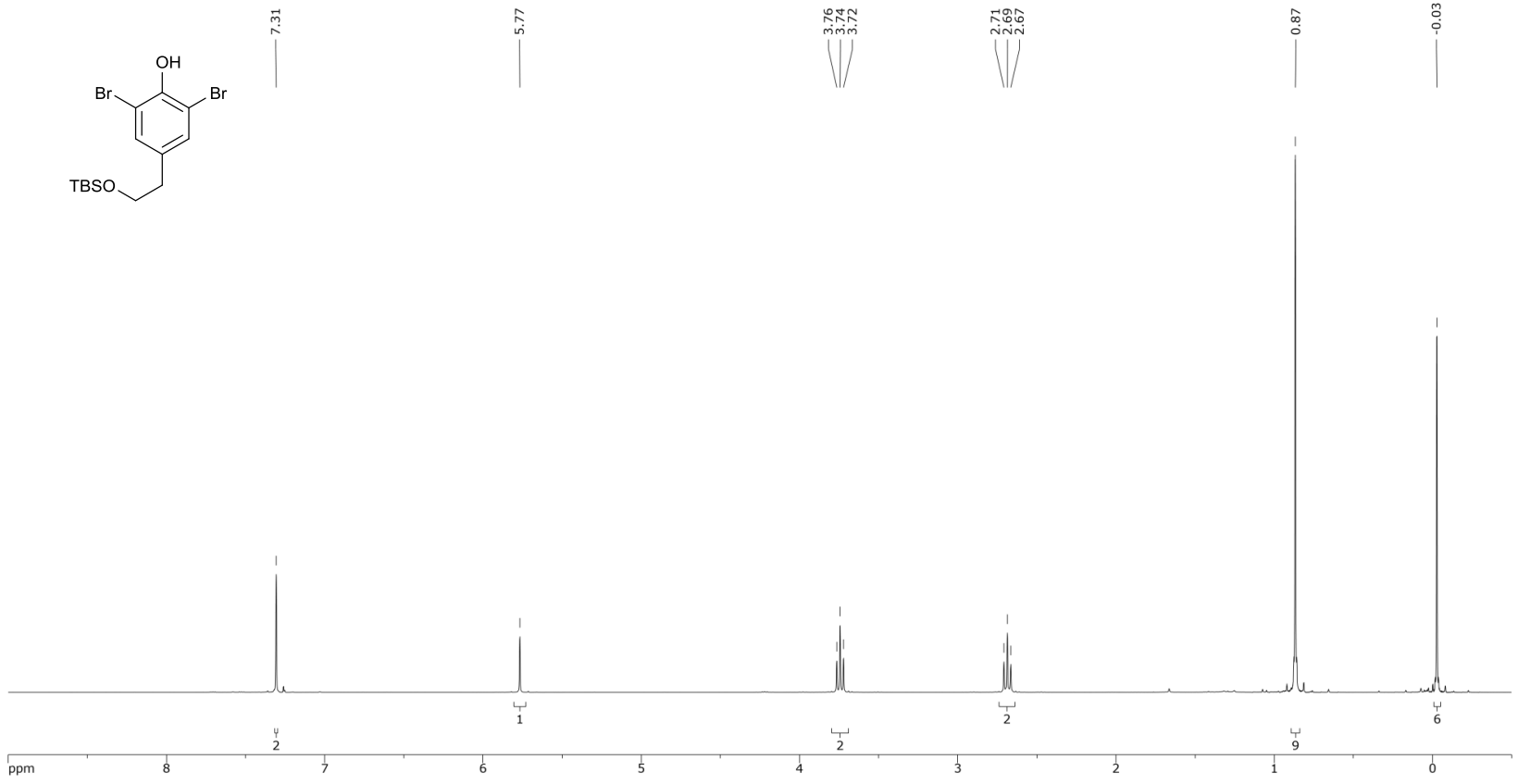
Alcohol S5 – ^{1}H NMR



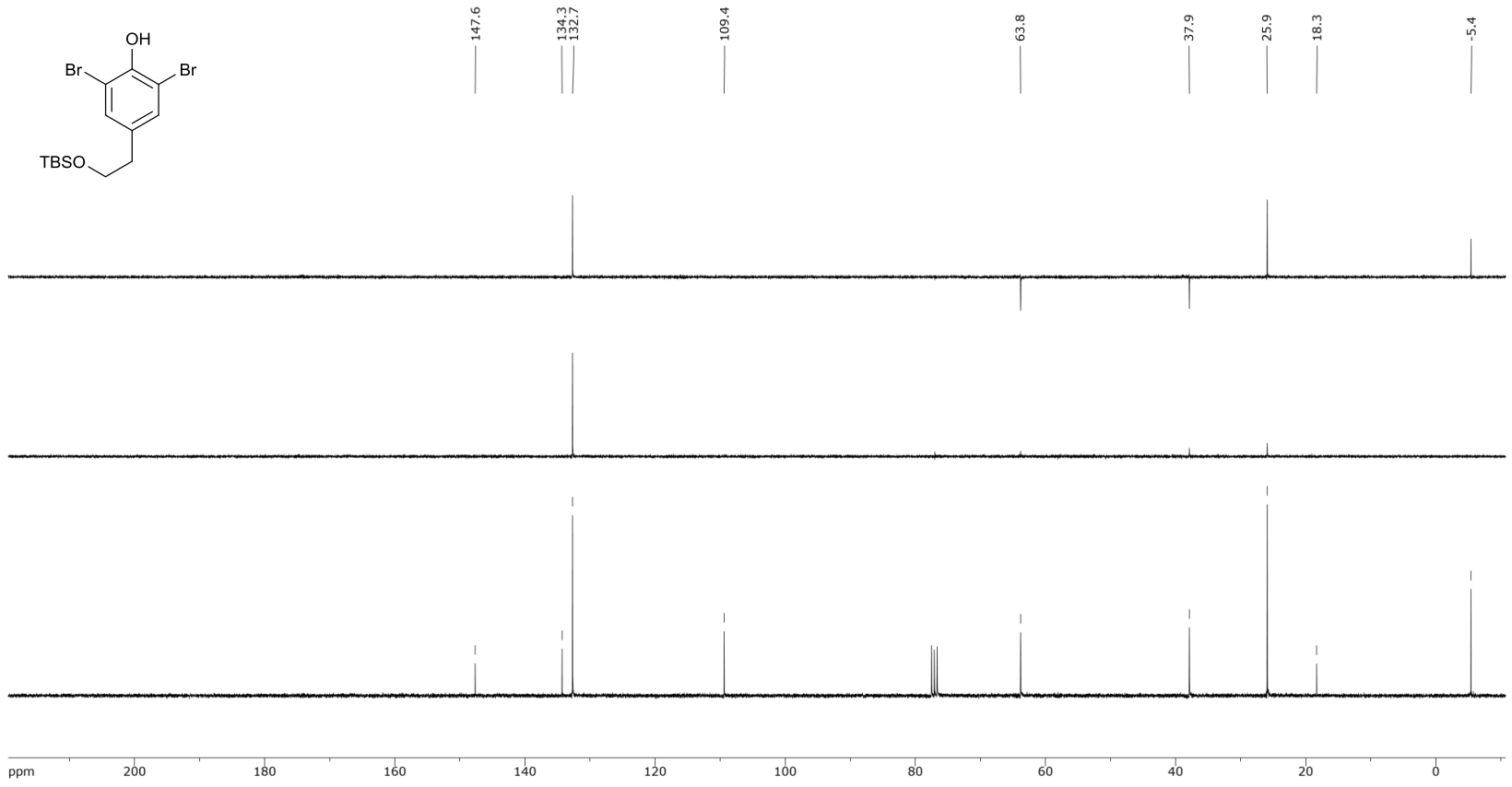
Alcohol S5 – ^{13}C NMR



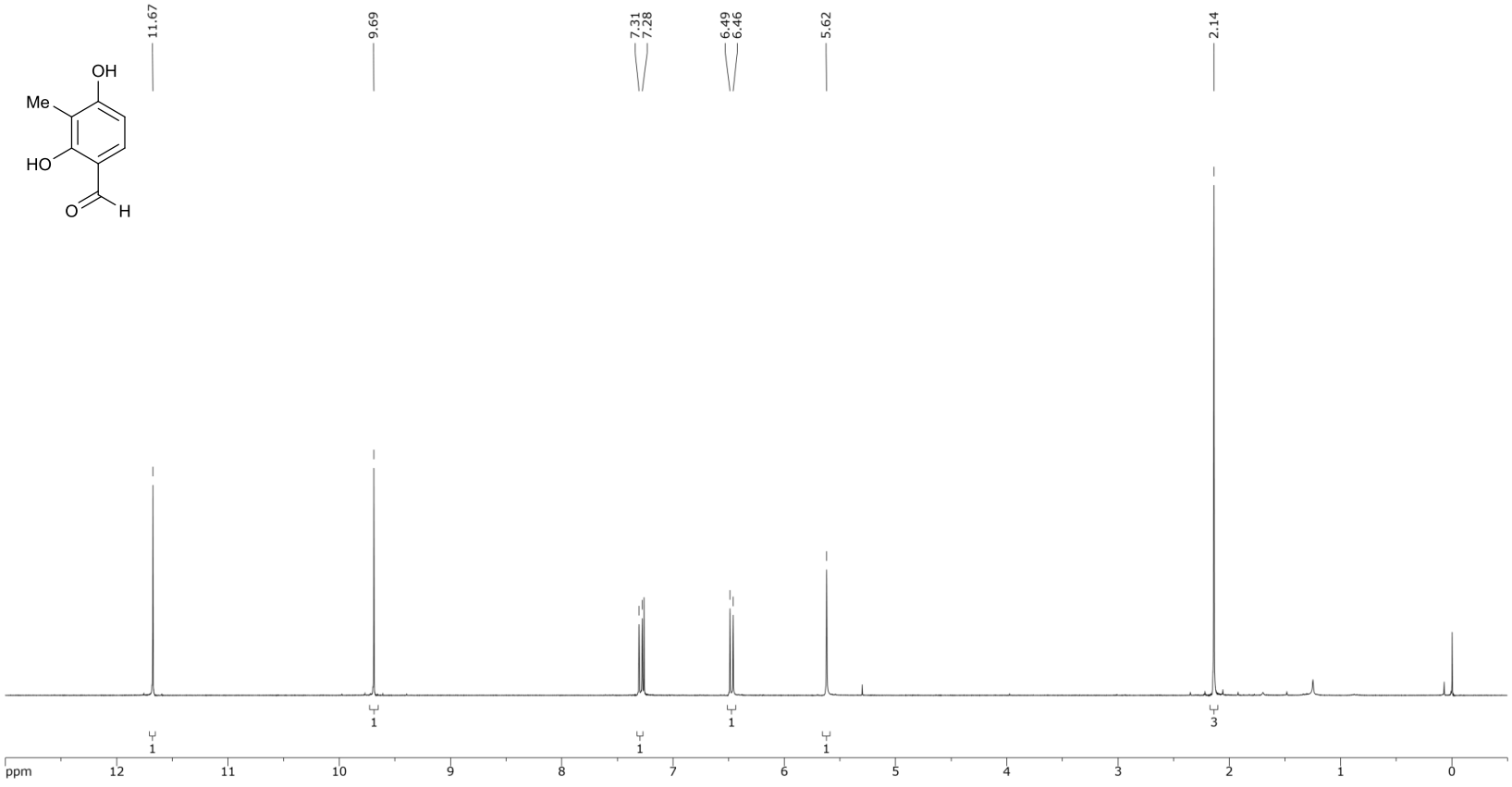
Phenol S6 – ^{1}H NMR



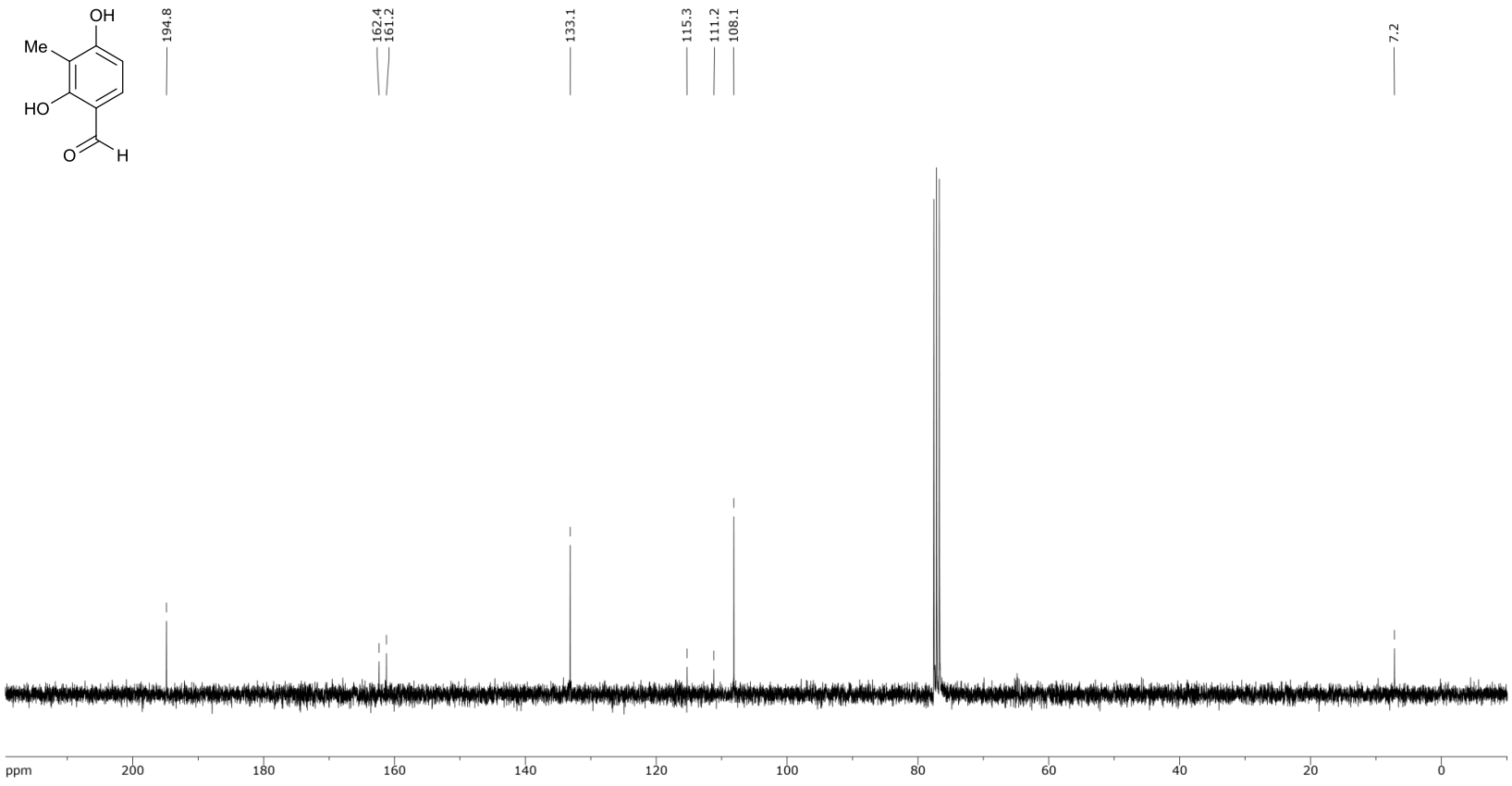
Phenol S6 – ^{13}C NMR



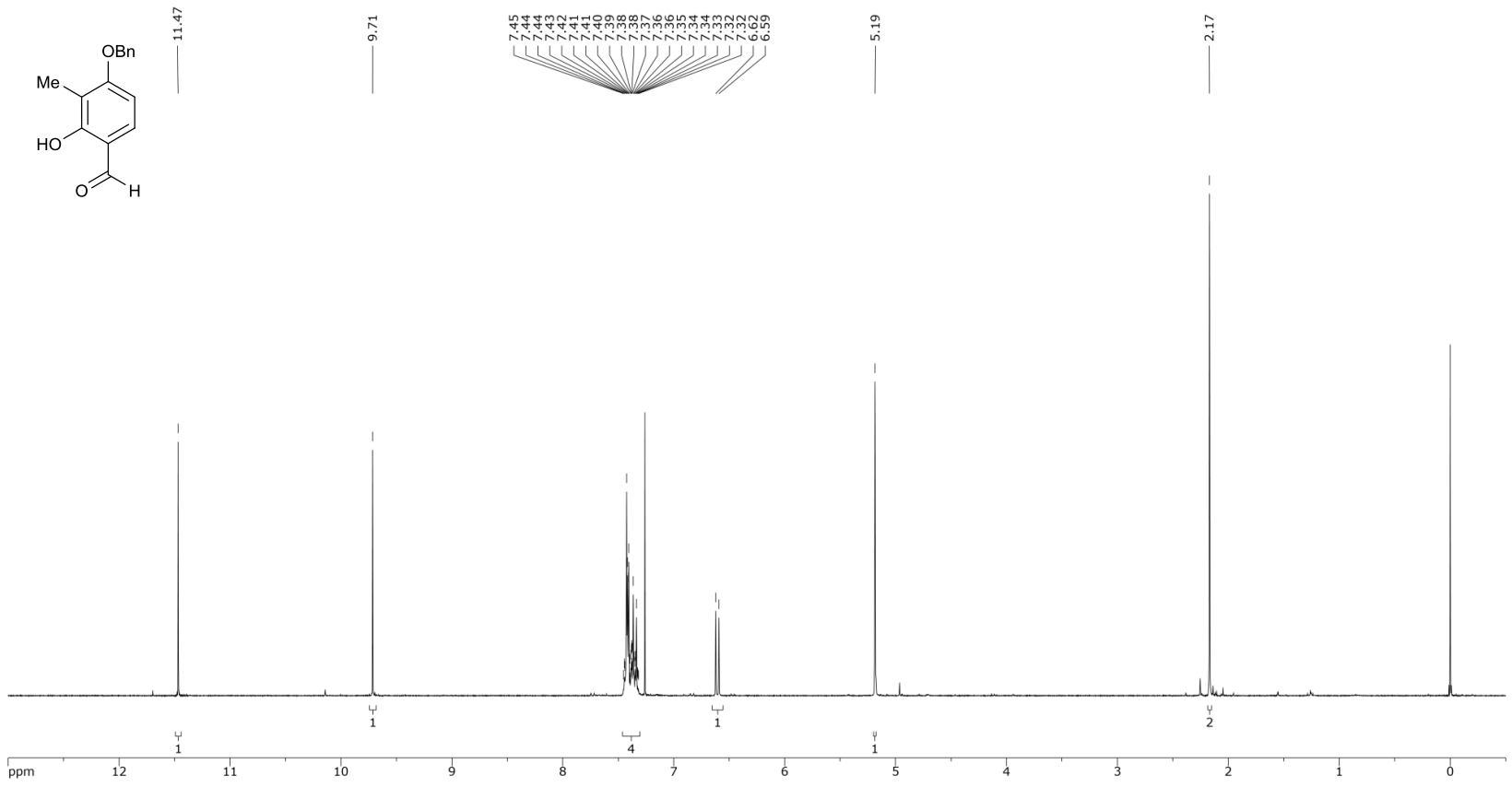
Hydroxybenzaldehyde S7 – ^{1}H NMR



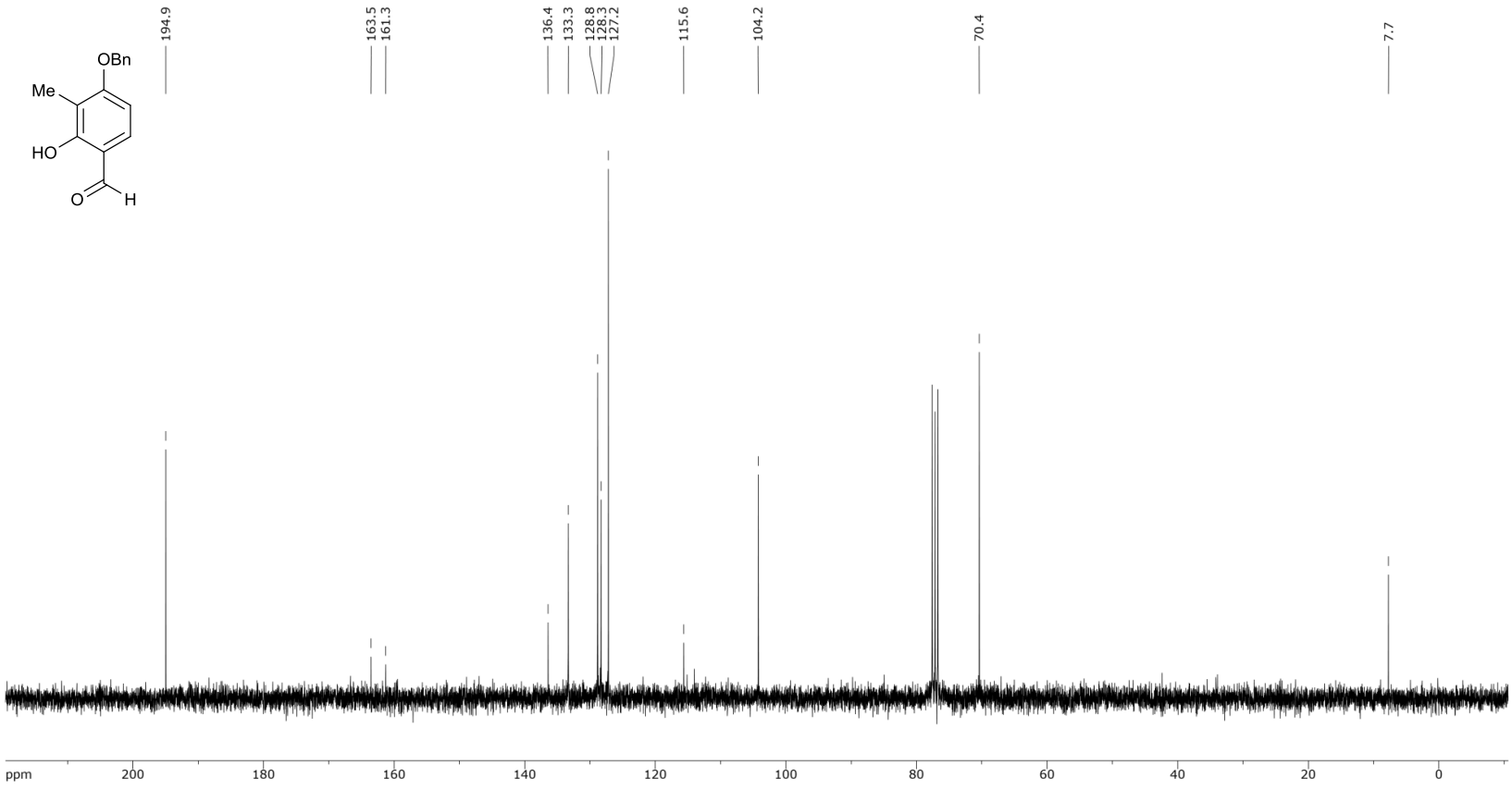
Hydroxybenzaldehyde S7 – ^{13}C NMR



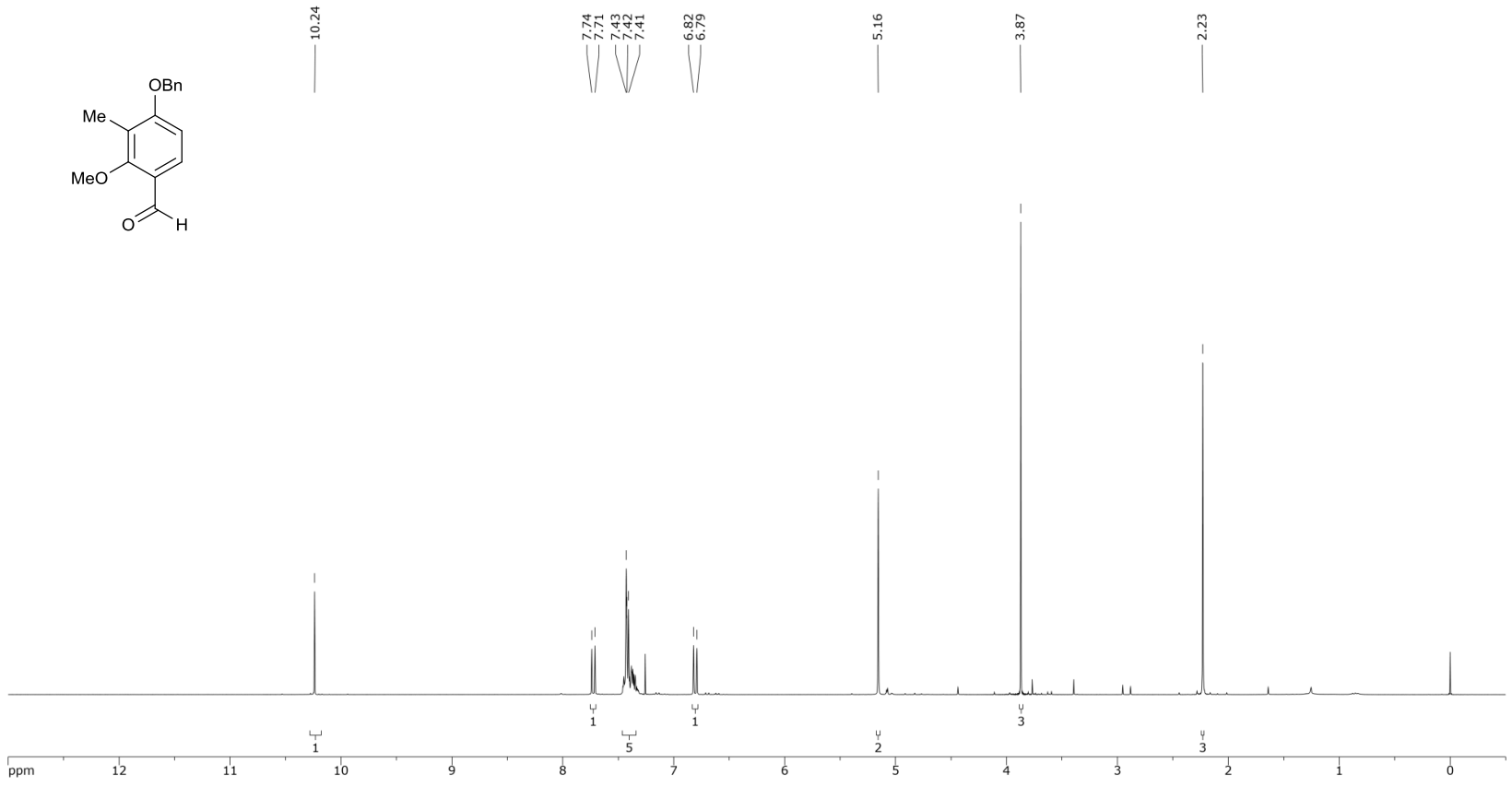
Benzyloxybenzaldehyde S8 – ^{1}H NMR



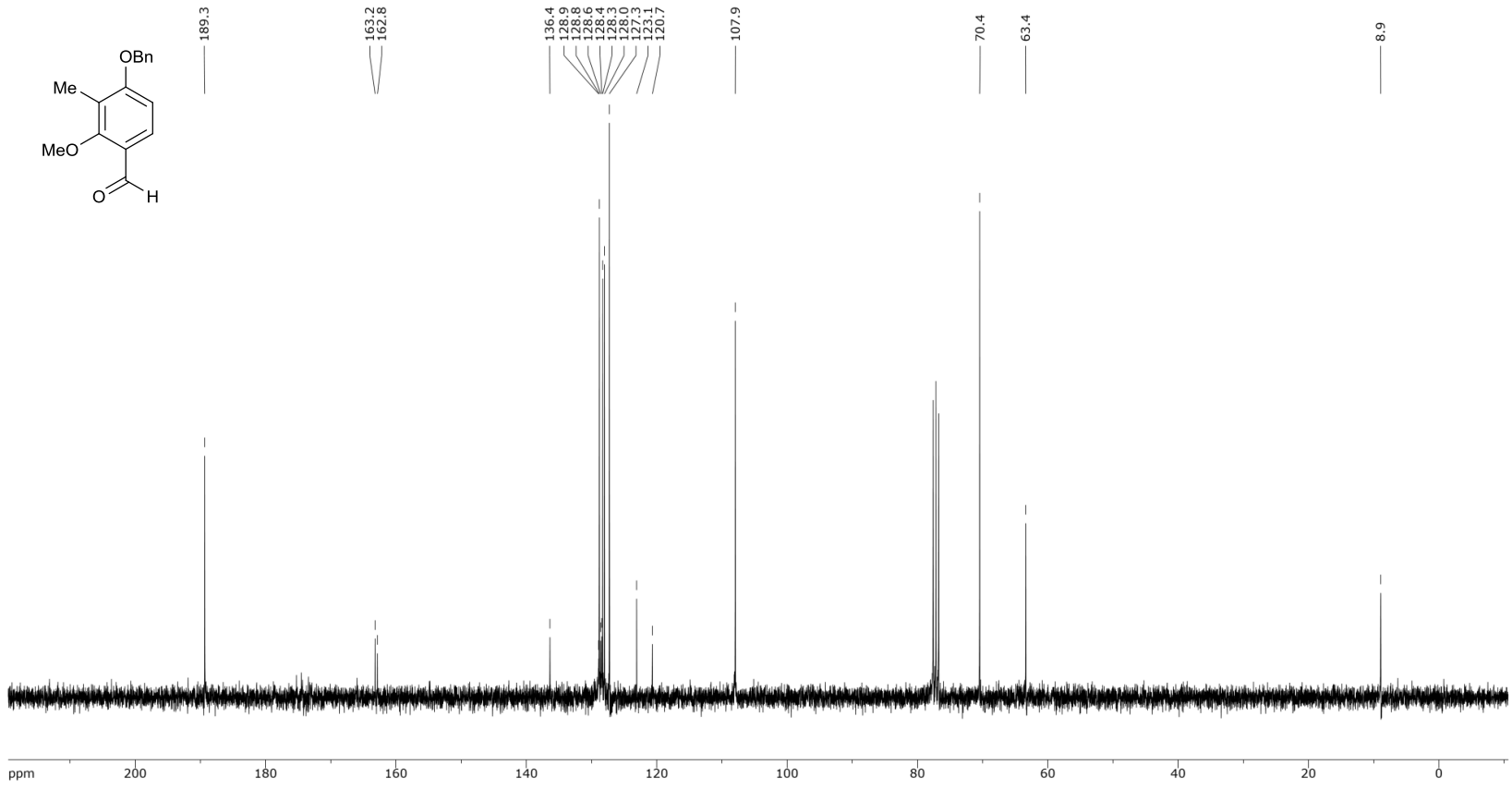
Benzyloxybenzaldehyde S8 – ^{13}C NMR



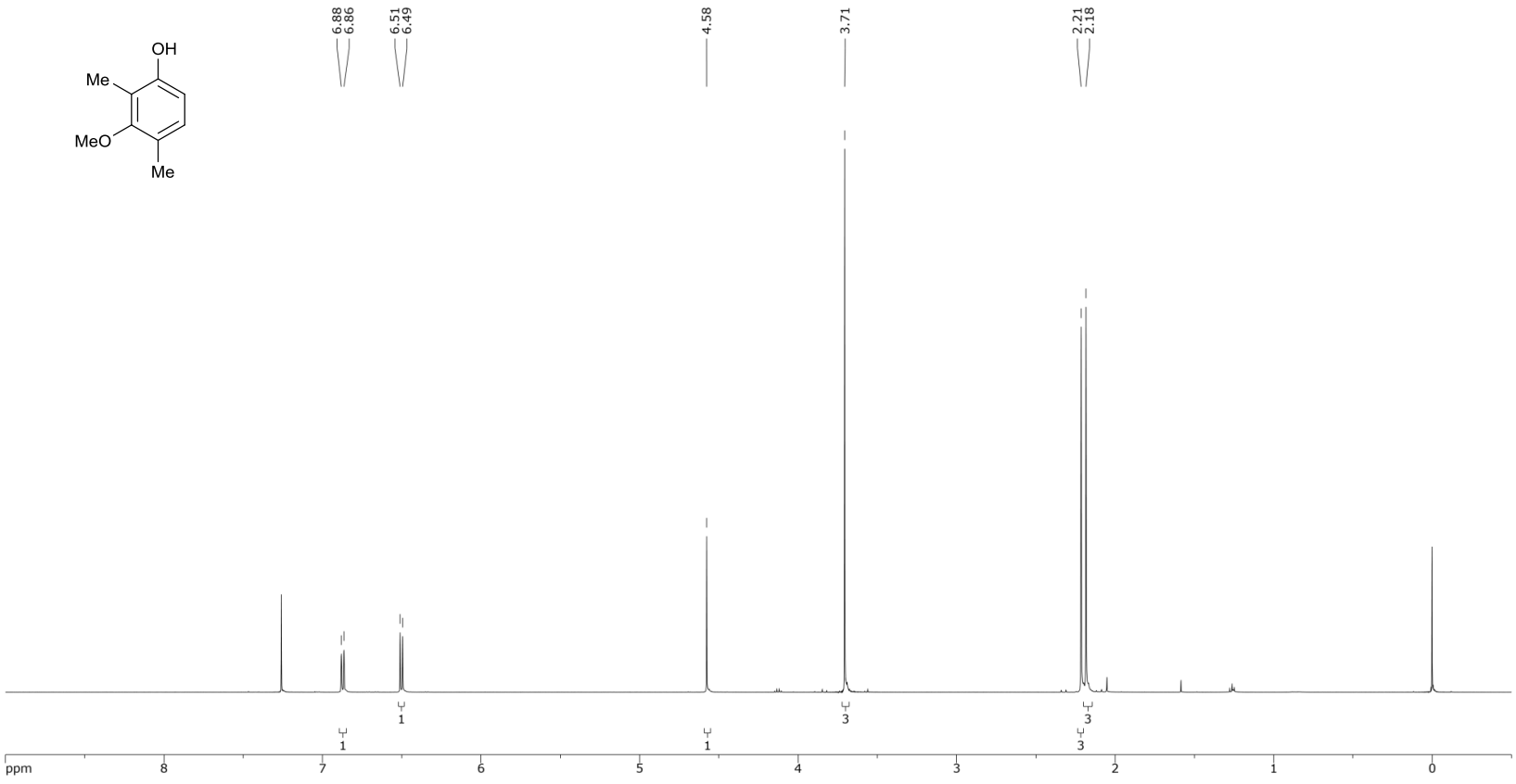
Methoxybenzaldehyde S9 – ^{1}H NMR



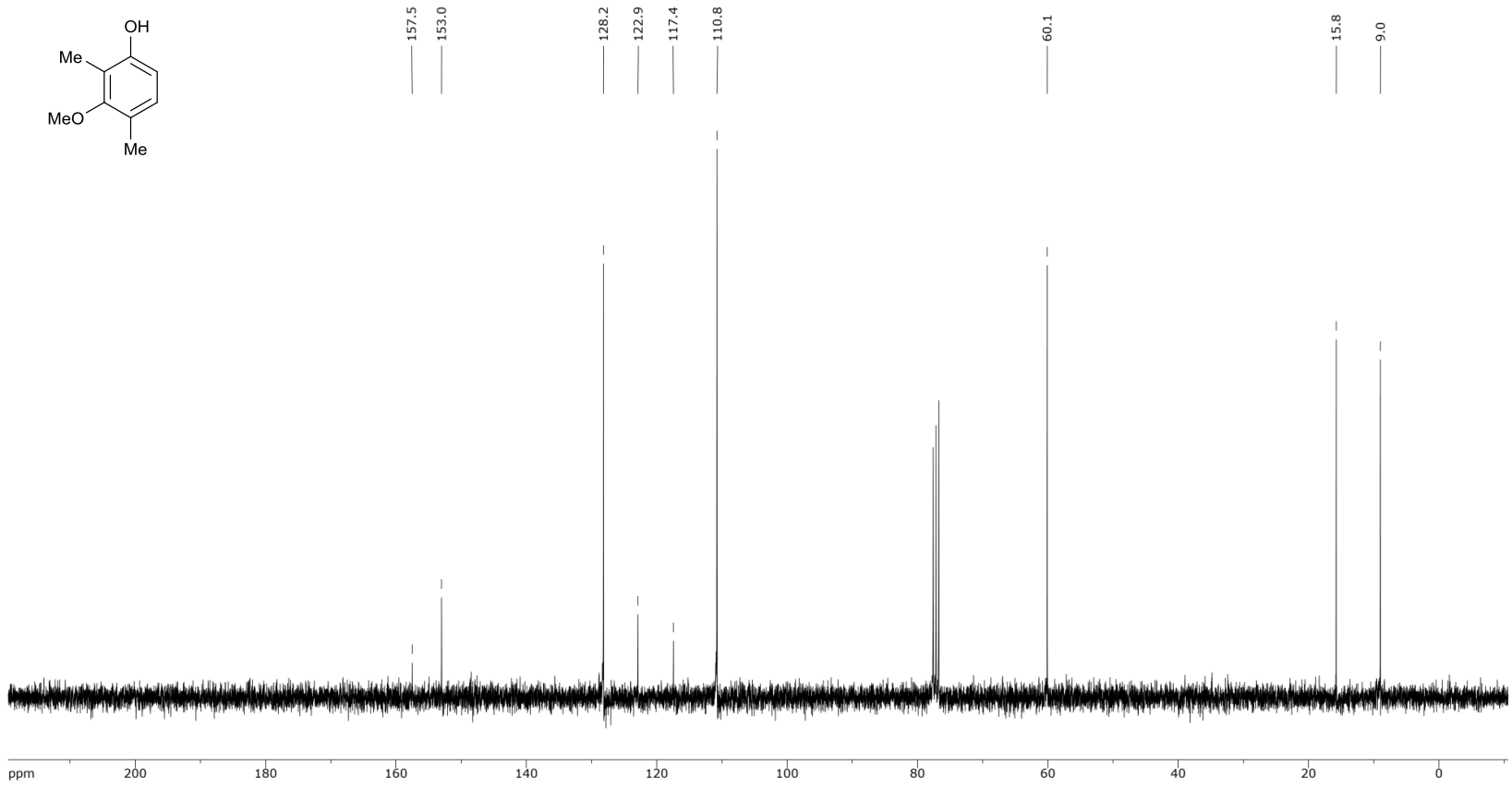
Methoxybenzaldehyde S9 – ^{13}C NMR



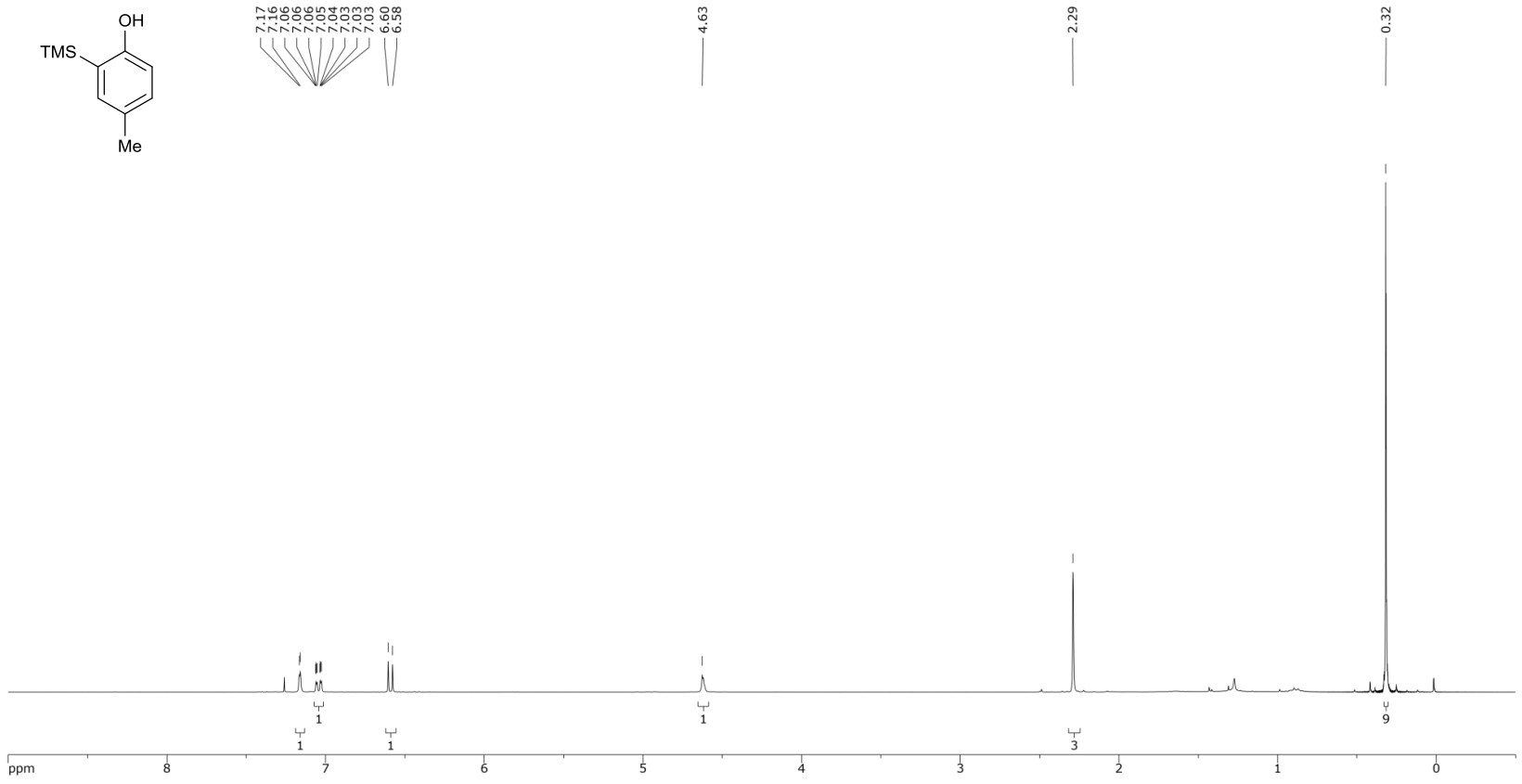
Phenol S10 – ^{1}H NMR



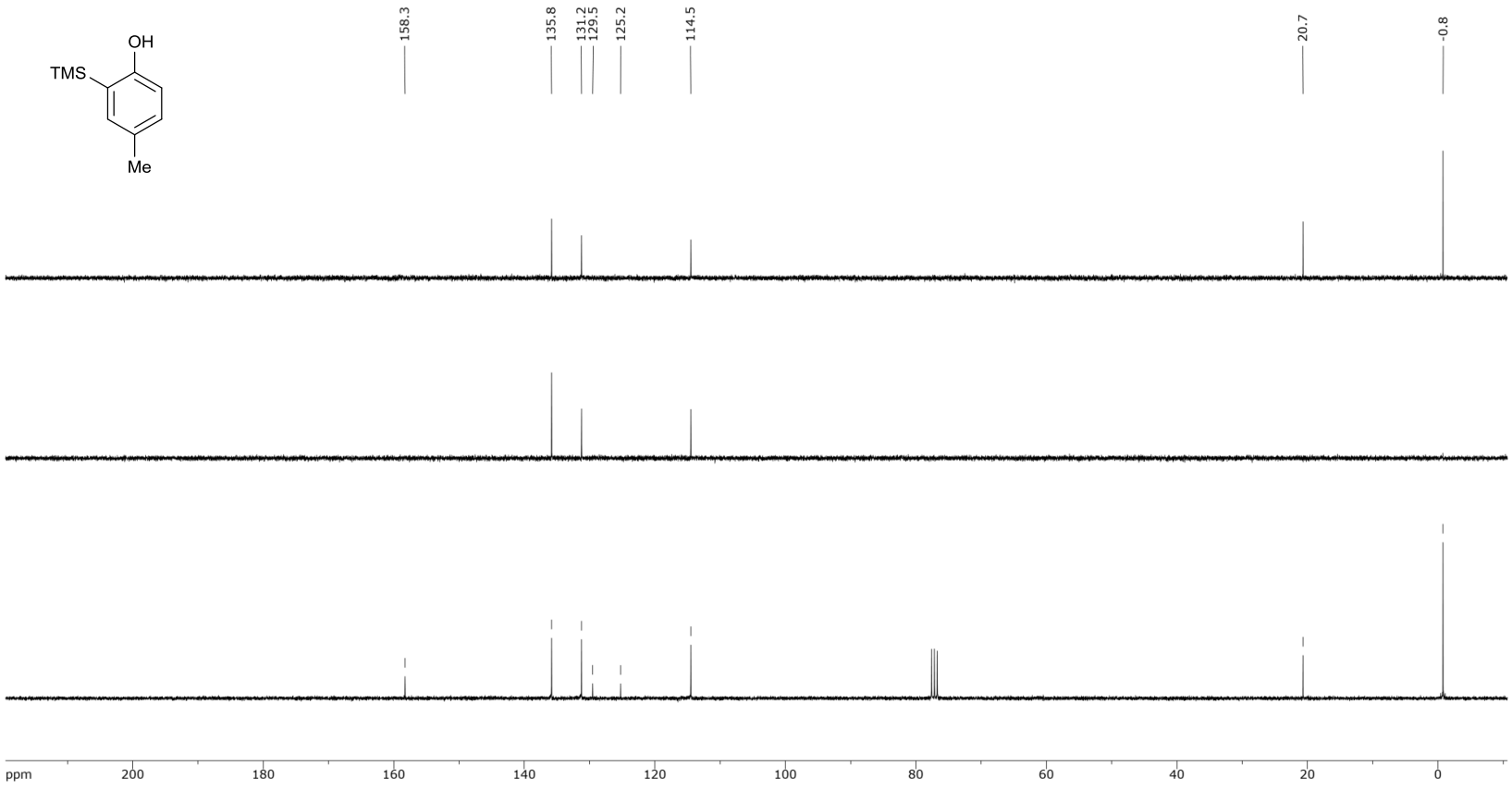
Phenol S10 – ^{13}C NMR



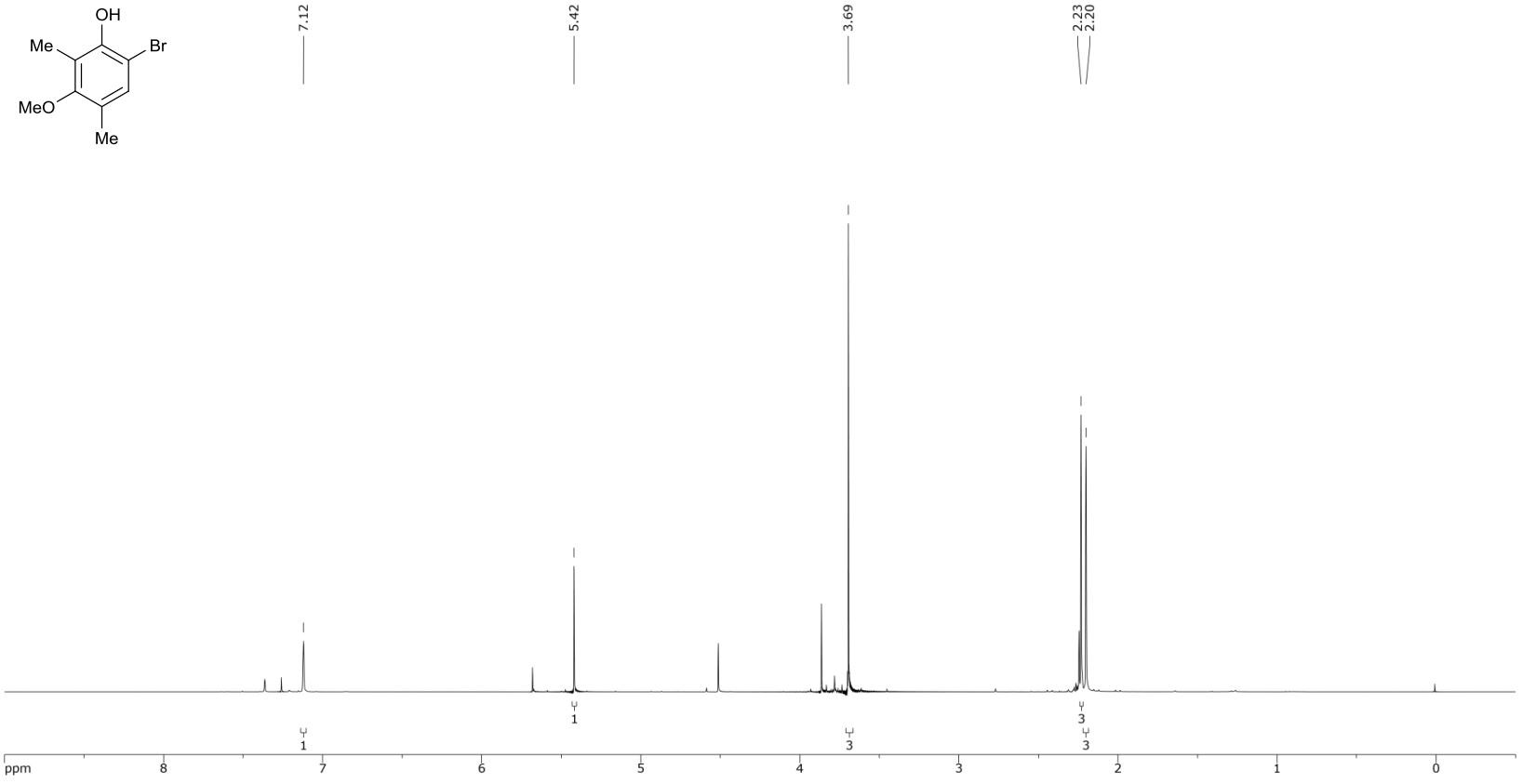
Phenol S11 – ^{1}H NMR



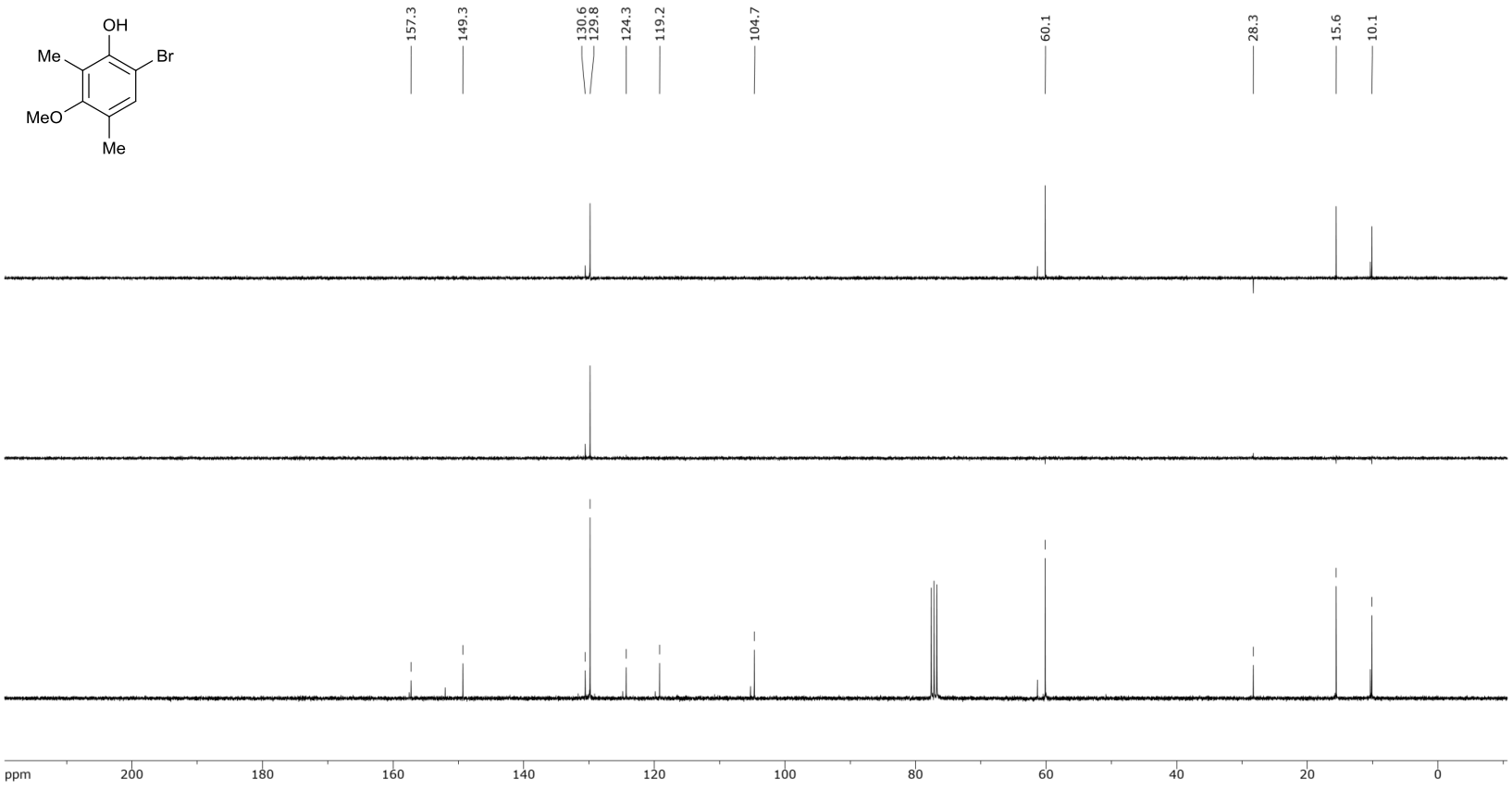
Phenol S11 – ^{13}C NMR



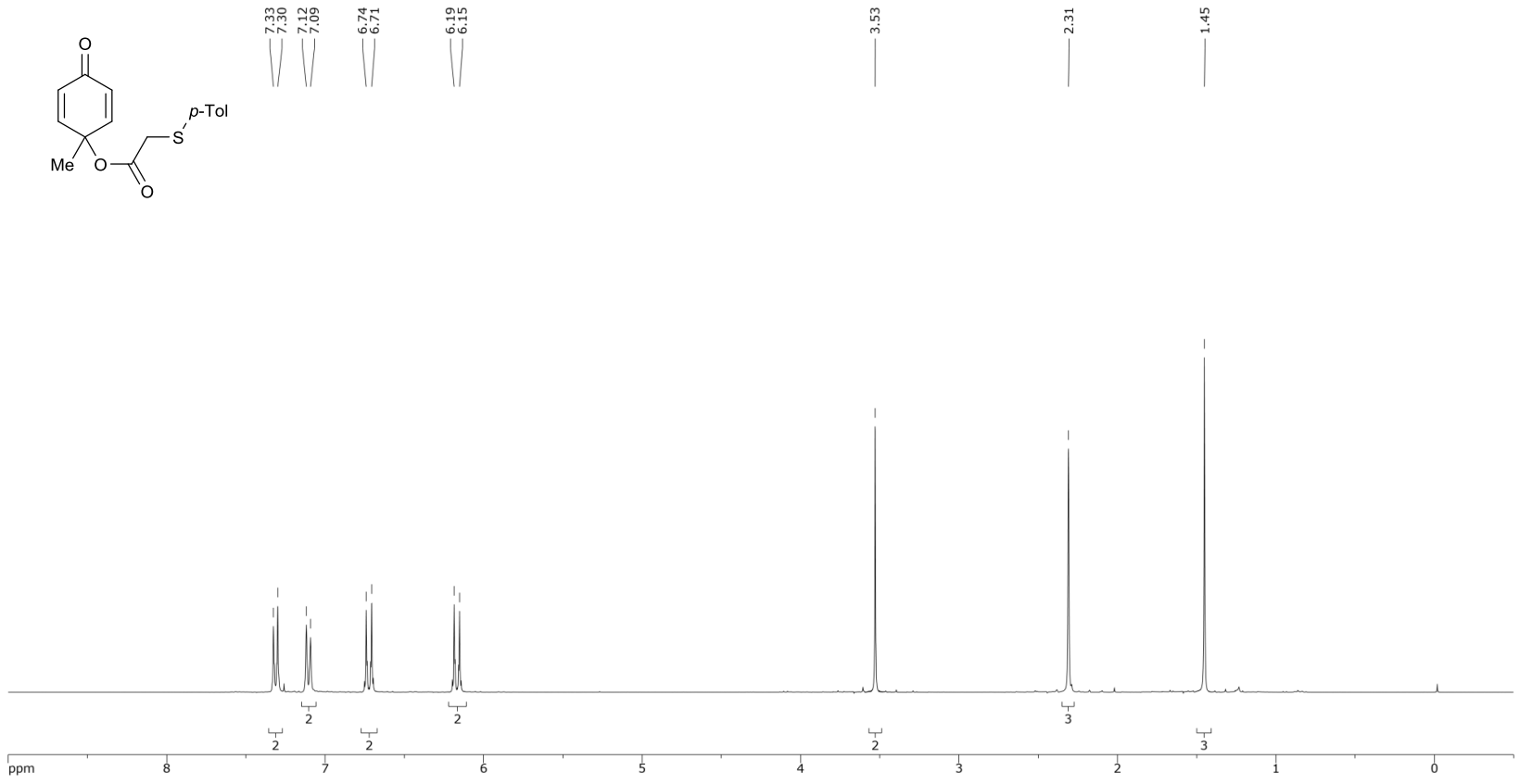
Phenol S12 – ^{1}H NMR



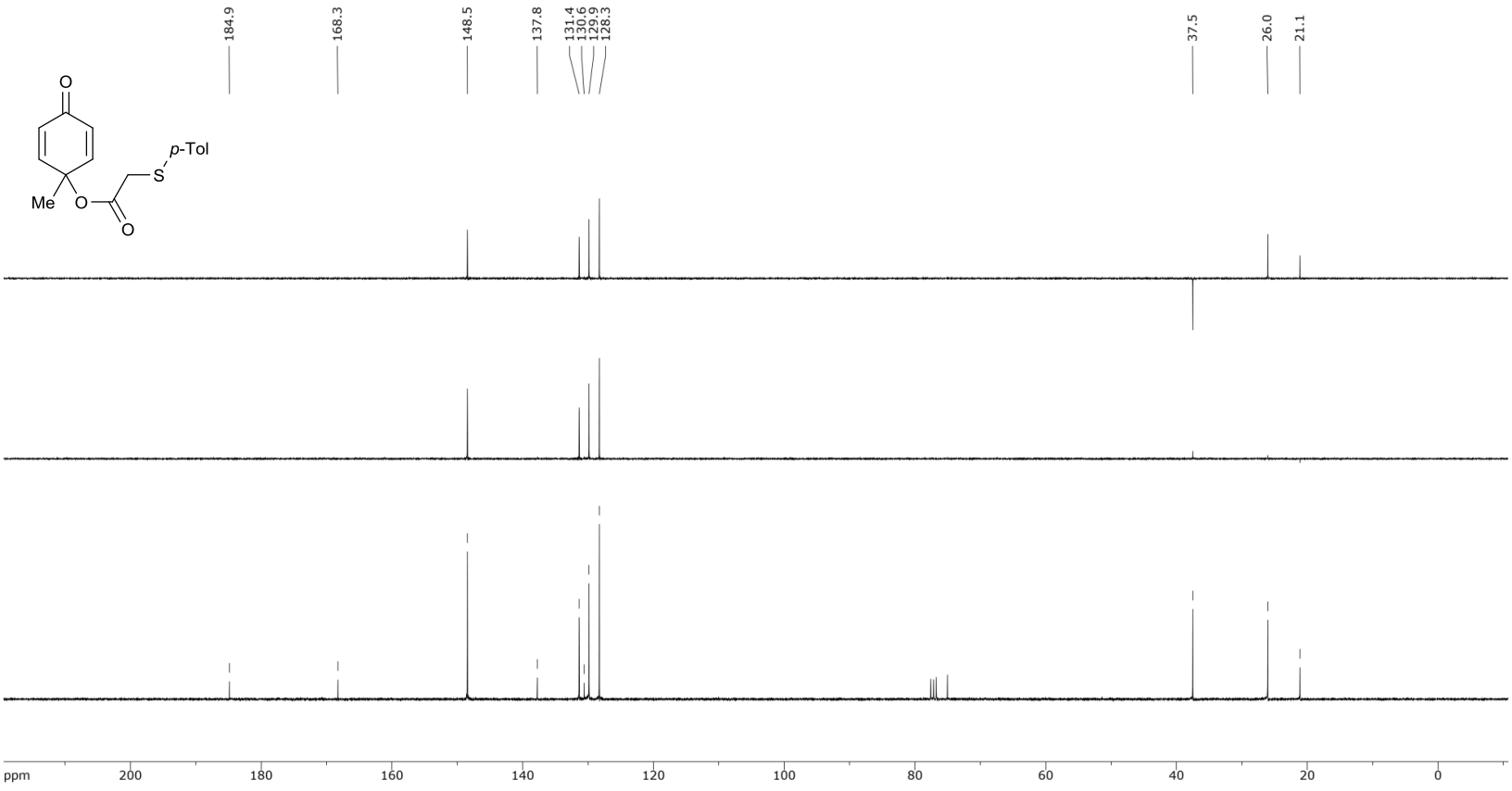
Phenol S12 – ^{13}C NMR



Sulfide-tethered cyclohexadienone S13 – ^{1}H NMR

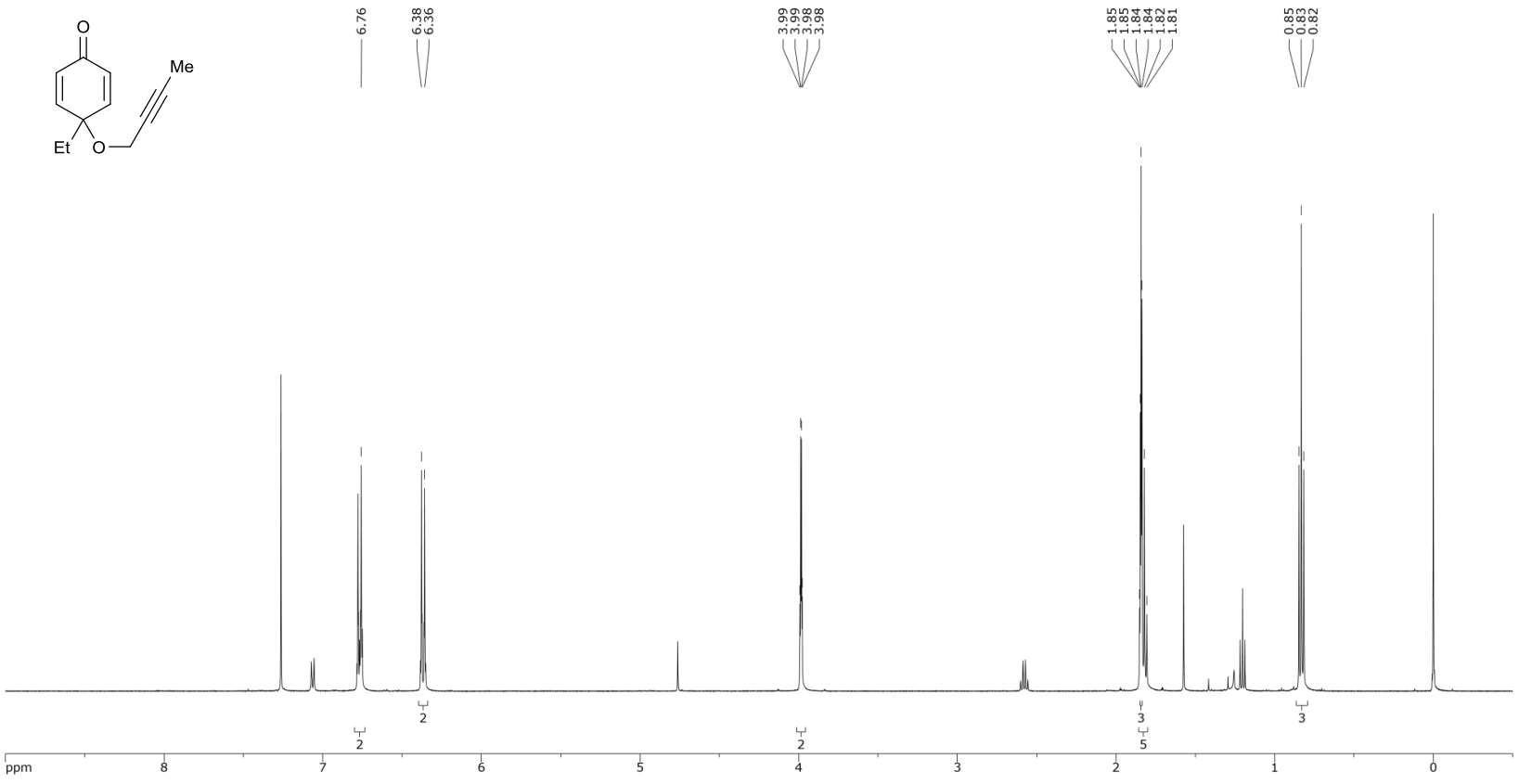


Sulfide-tethered cyclohexadienone S13 – ^{13}C NMR

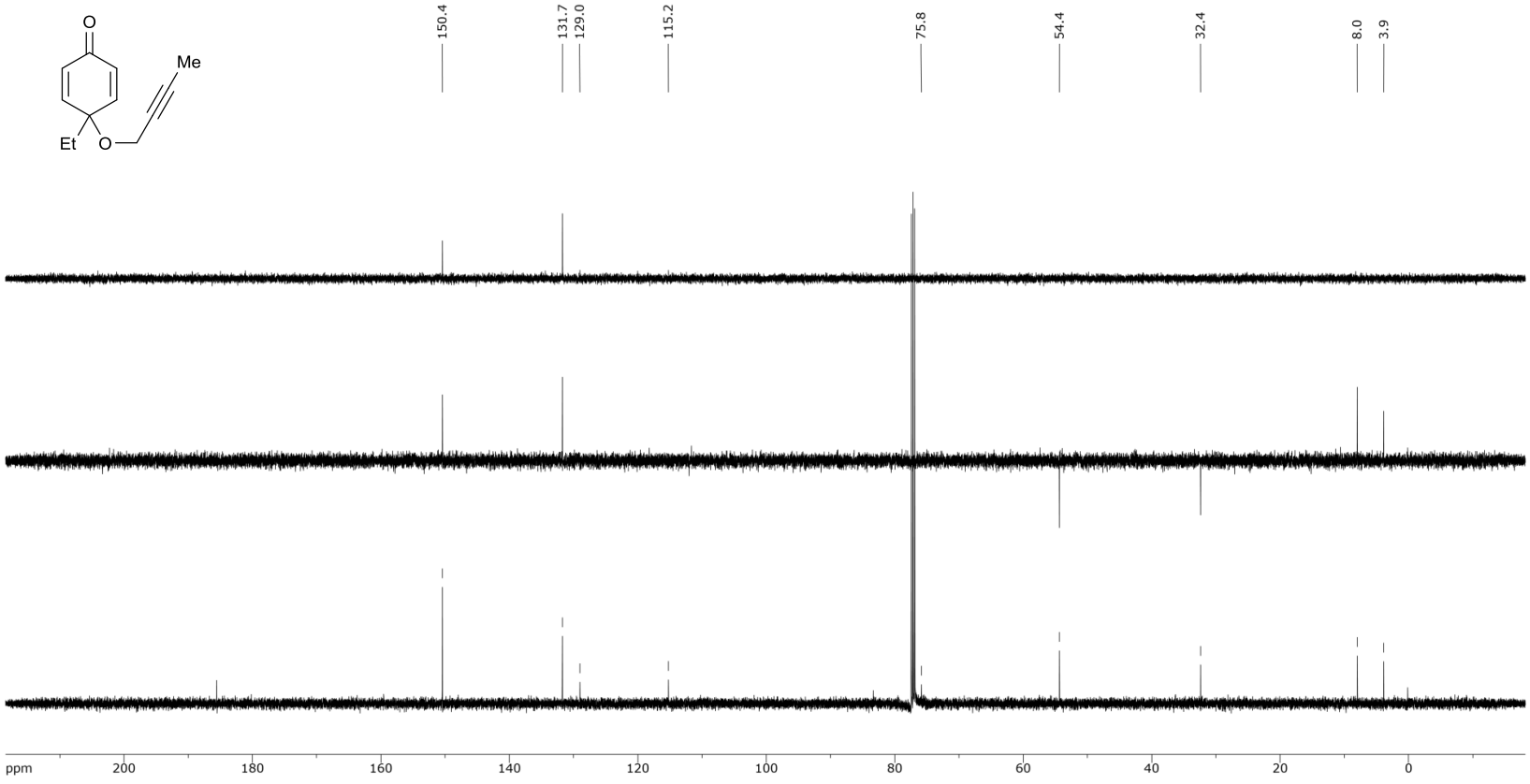


NMR Spectra – Chapter 3

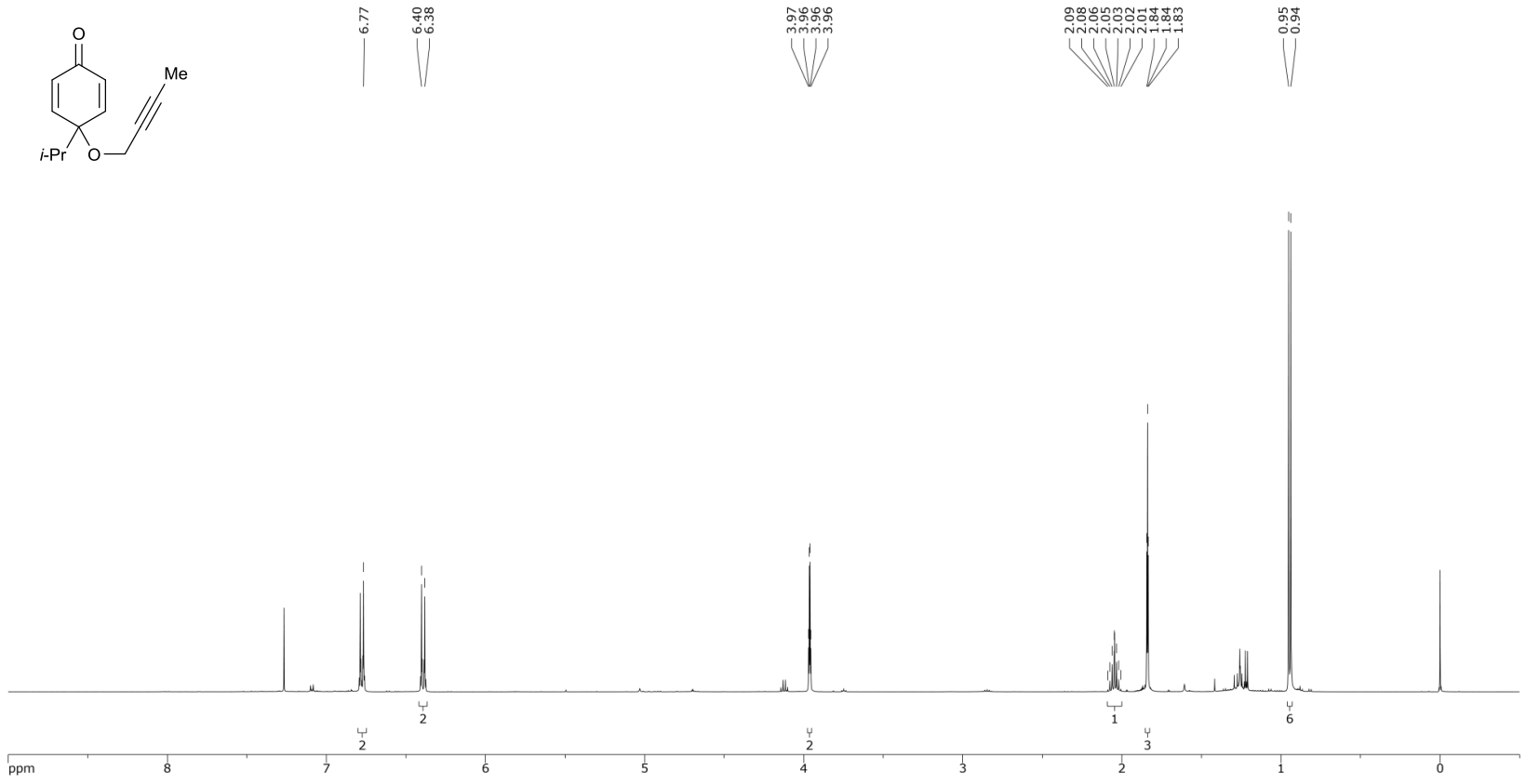
Alkyne-tethered cyclohexadienone 3.62d – ^{1}H NMR



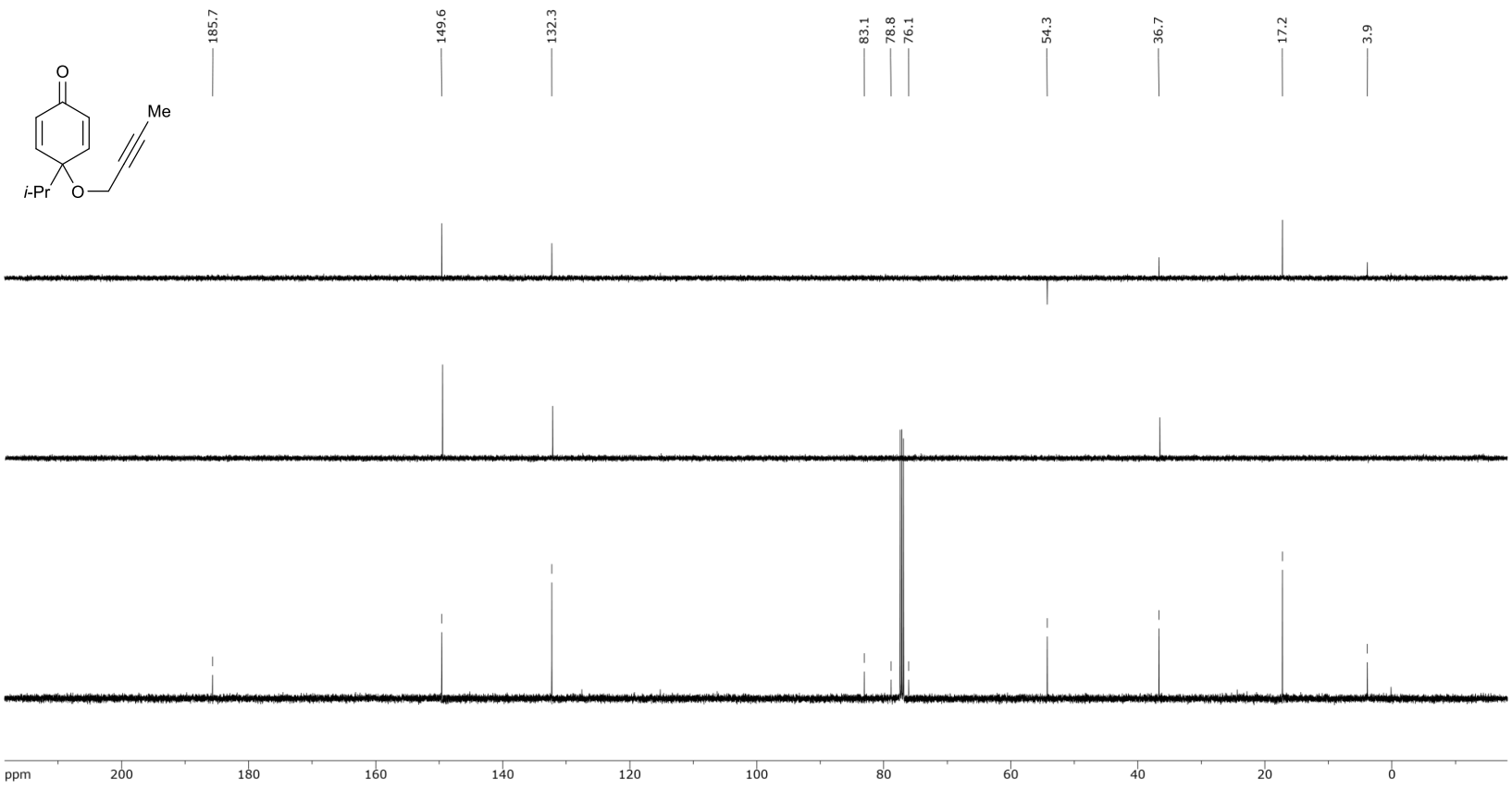
Alkyne-tethered cyclohexadienone 3.62d – ^{13}C NMR



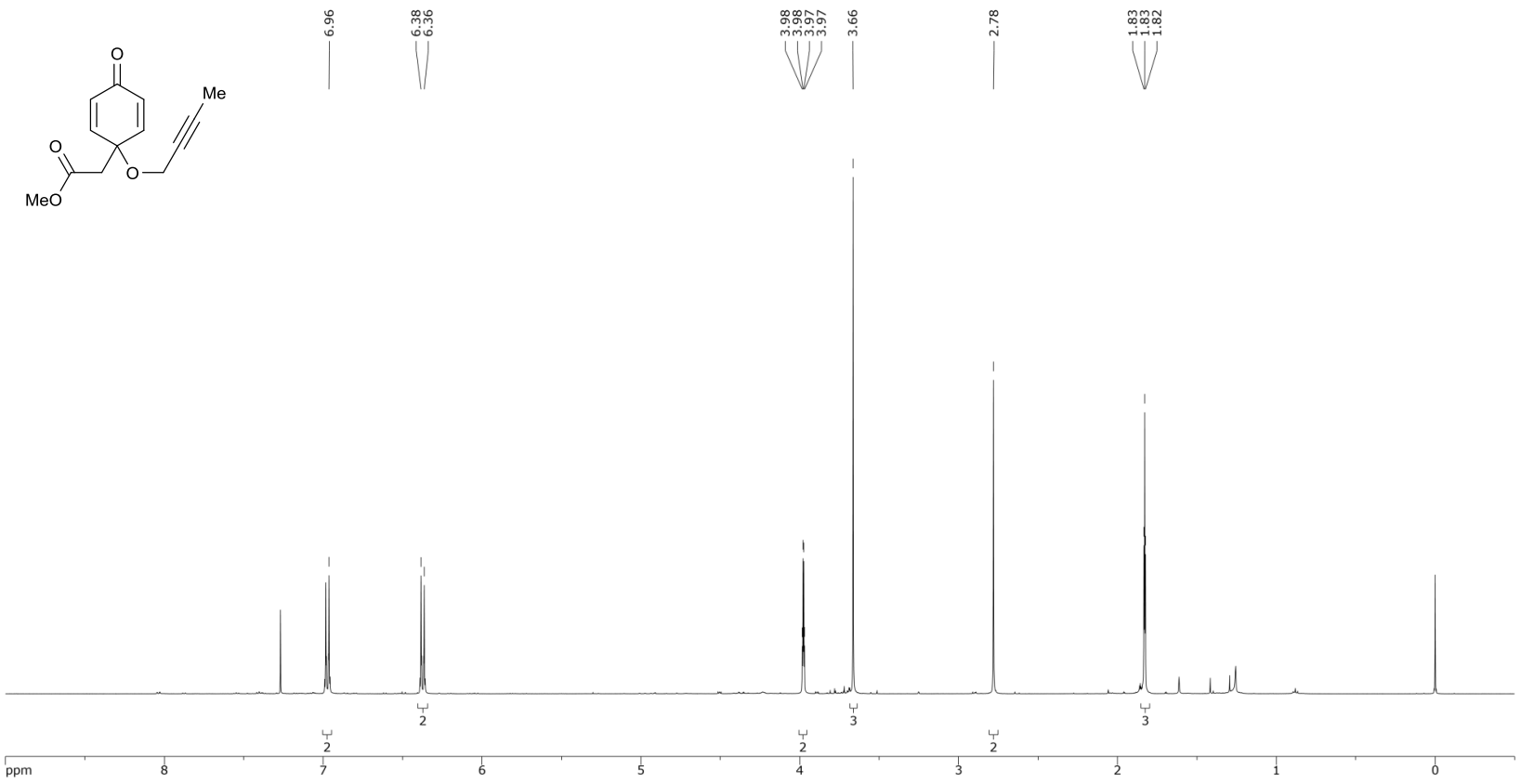
Alkyne-tethered cyclohexadienone 3.62e – ^{1}H NMR



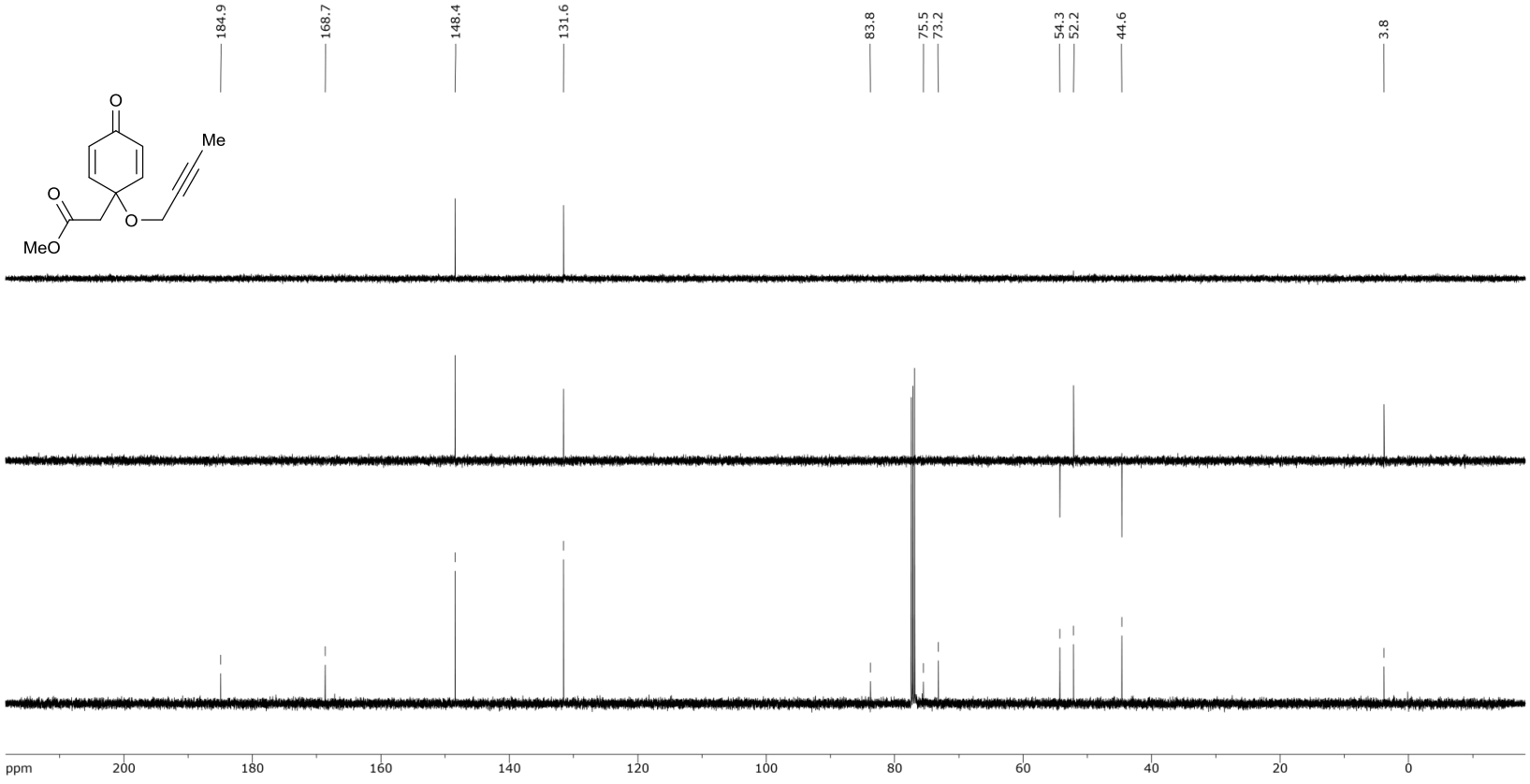
Alkyne-tethered cyclohexadienone 3.62e – ^{13}C NMR



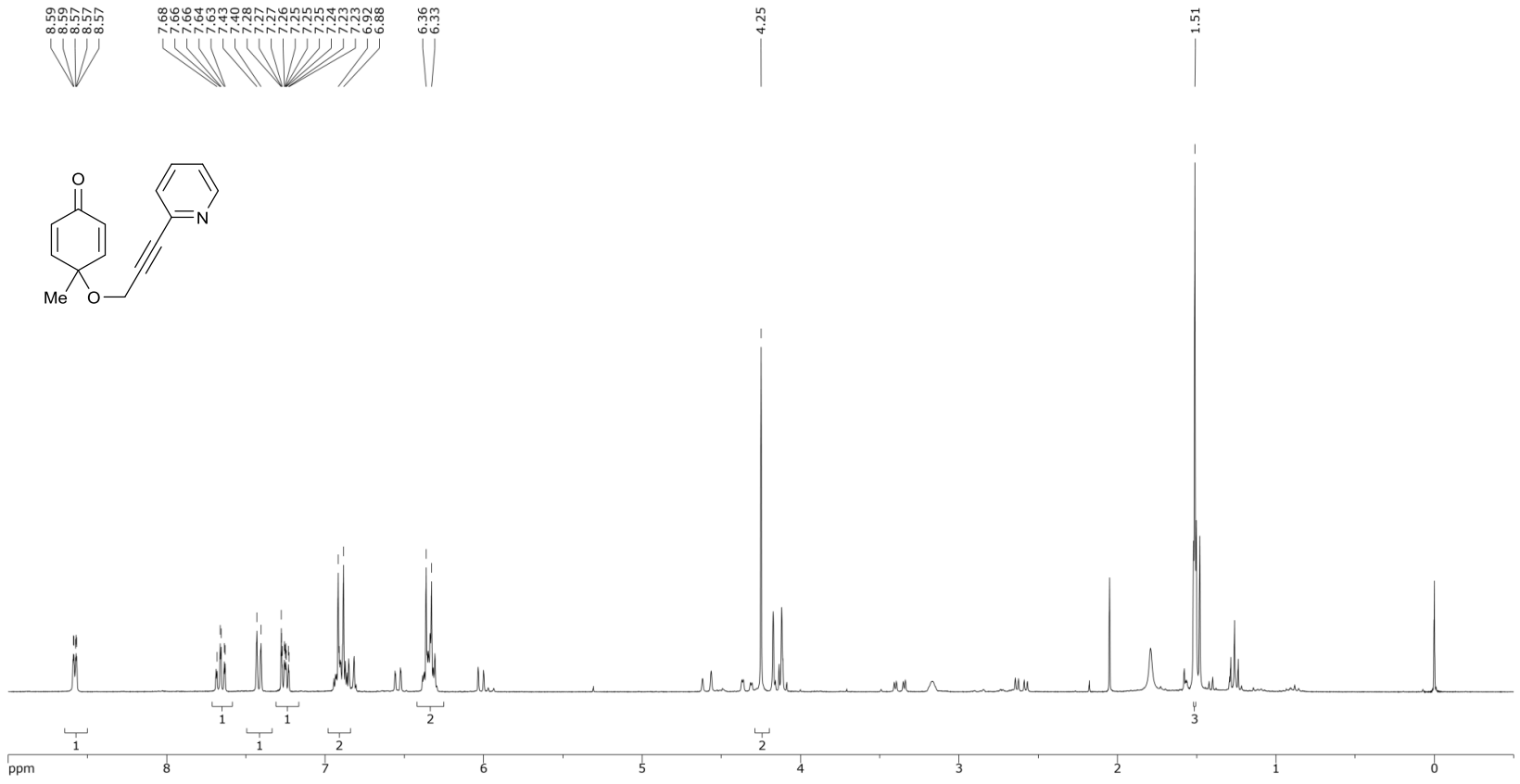
Alkyne-tethered cyclohexadienone 3.62f – ^{1}H NMR



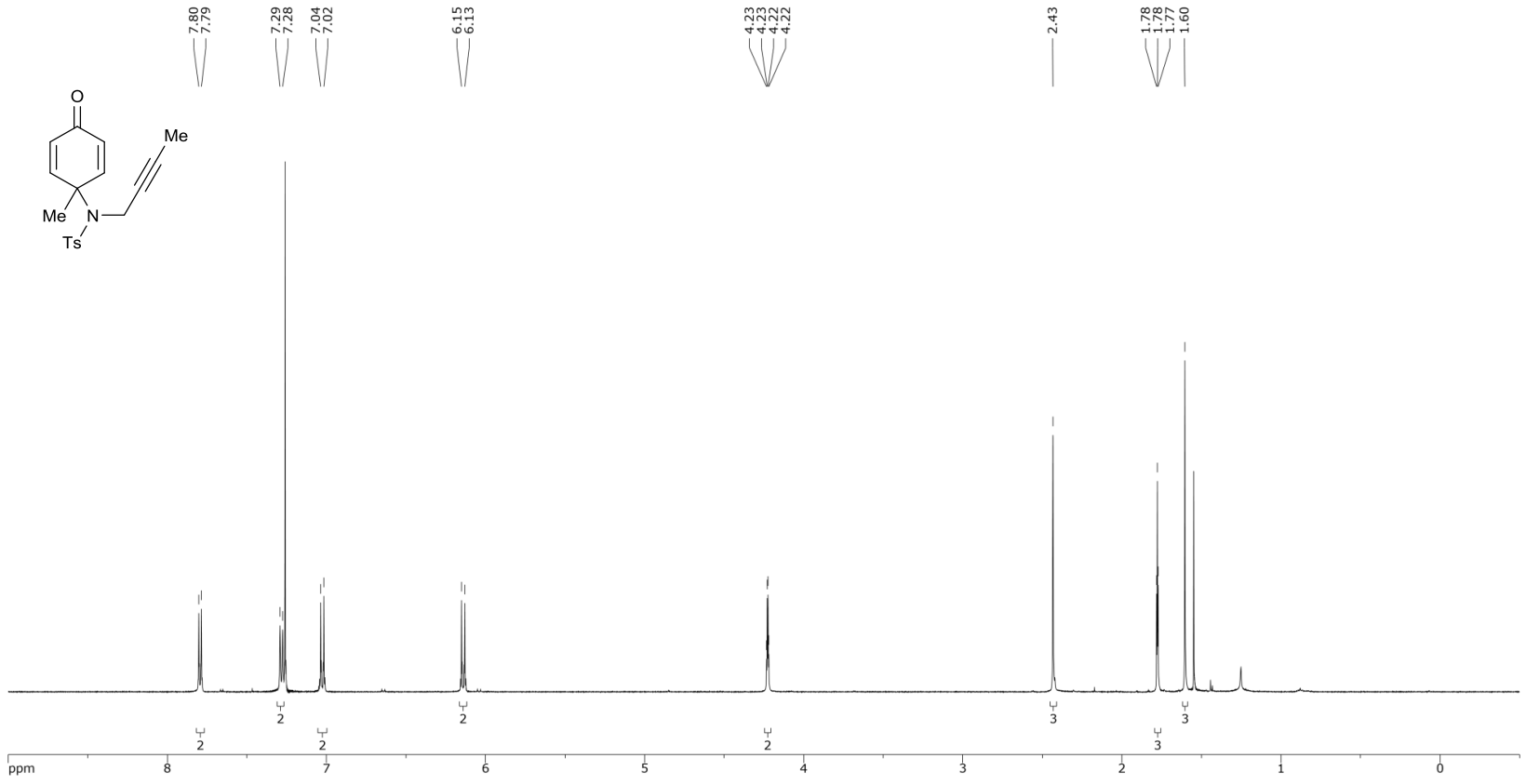
Alkyne-tethered cyclohexadienone 3.62f – ^{13}C NMR



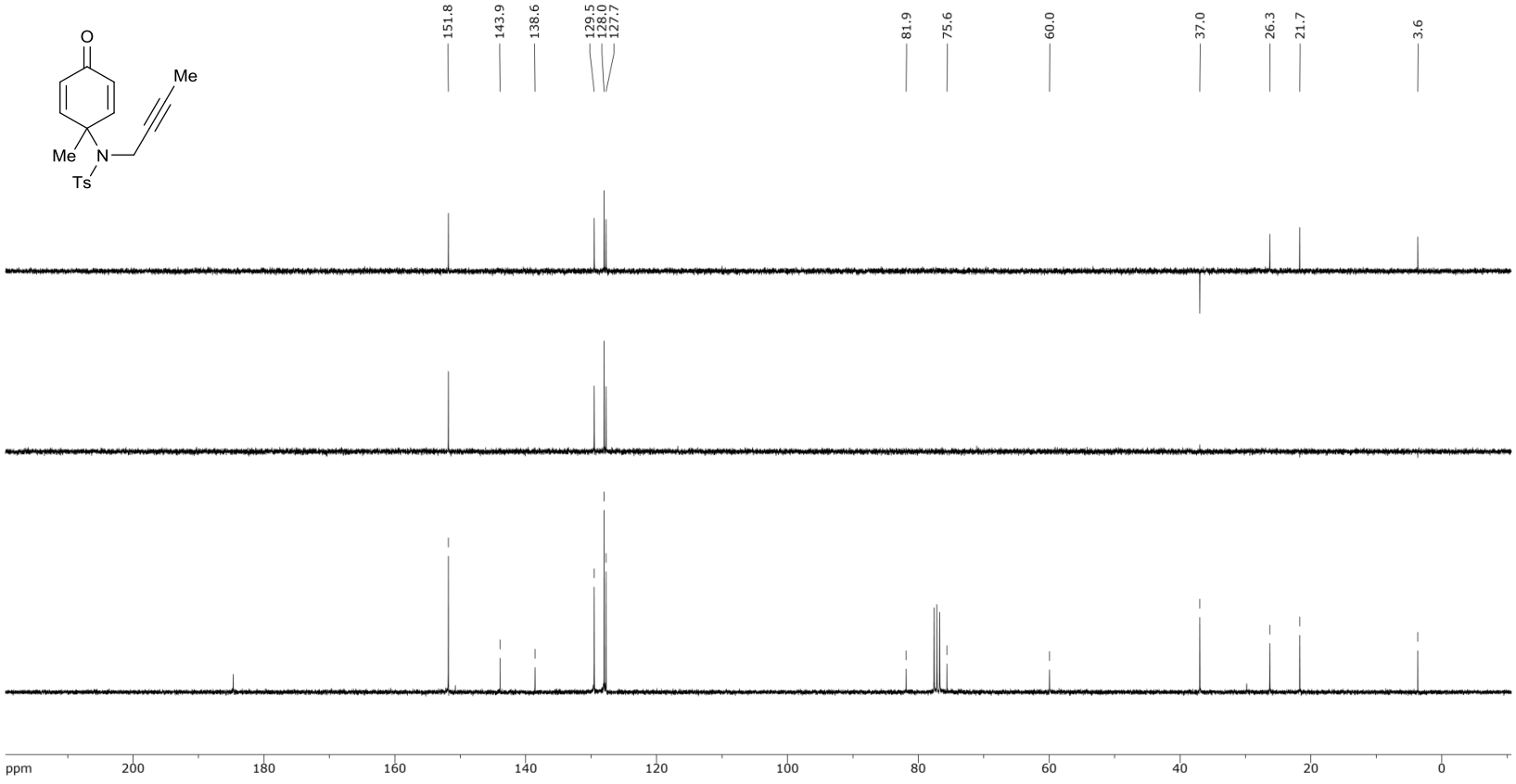
Alkyne-tethered cyclohexadienone 3.62h – ^{1}H NMR



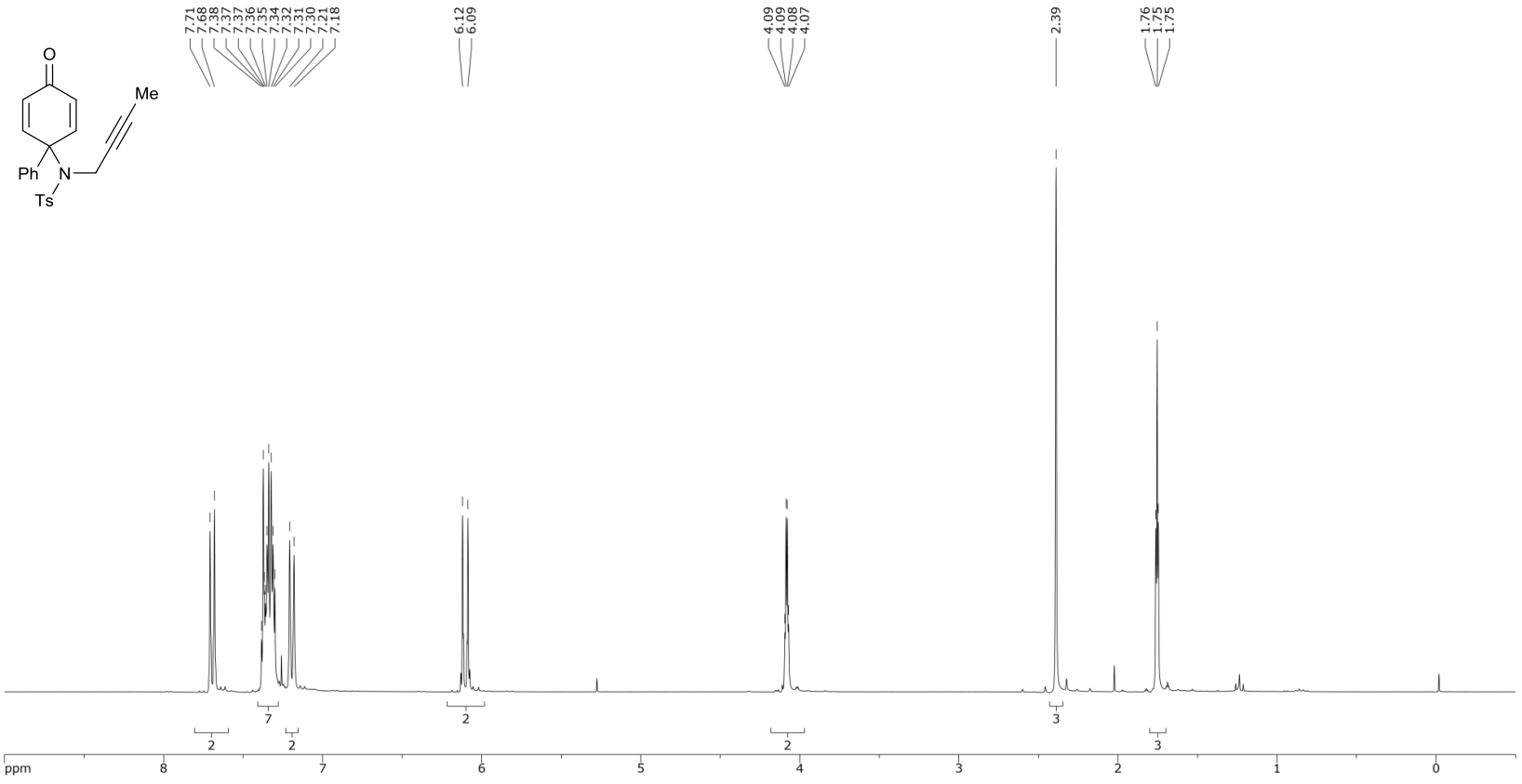
Alkyne-tethered cyclohexadienone 3.62i – ^{1}H NMR



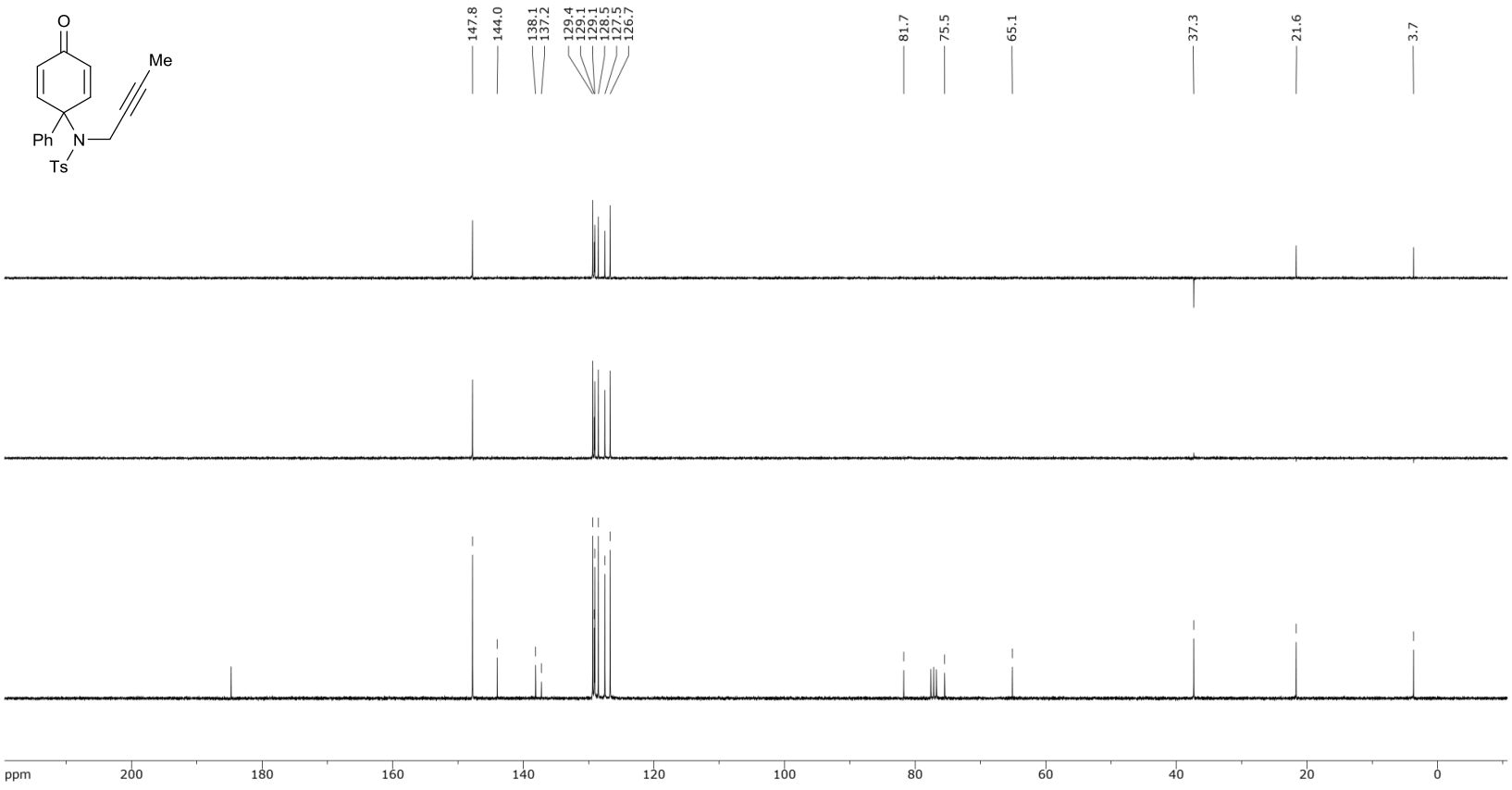
Alkyne-tethered cyclohexadienone 3.62i – ^{13}C NMR



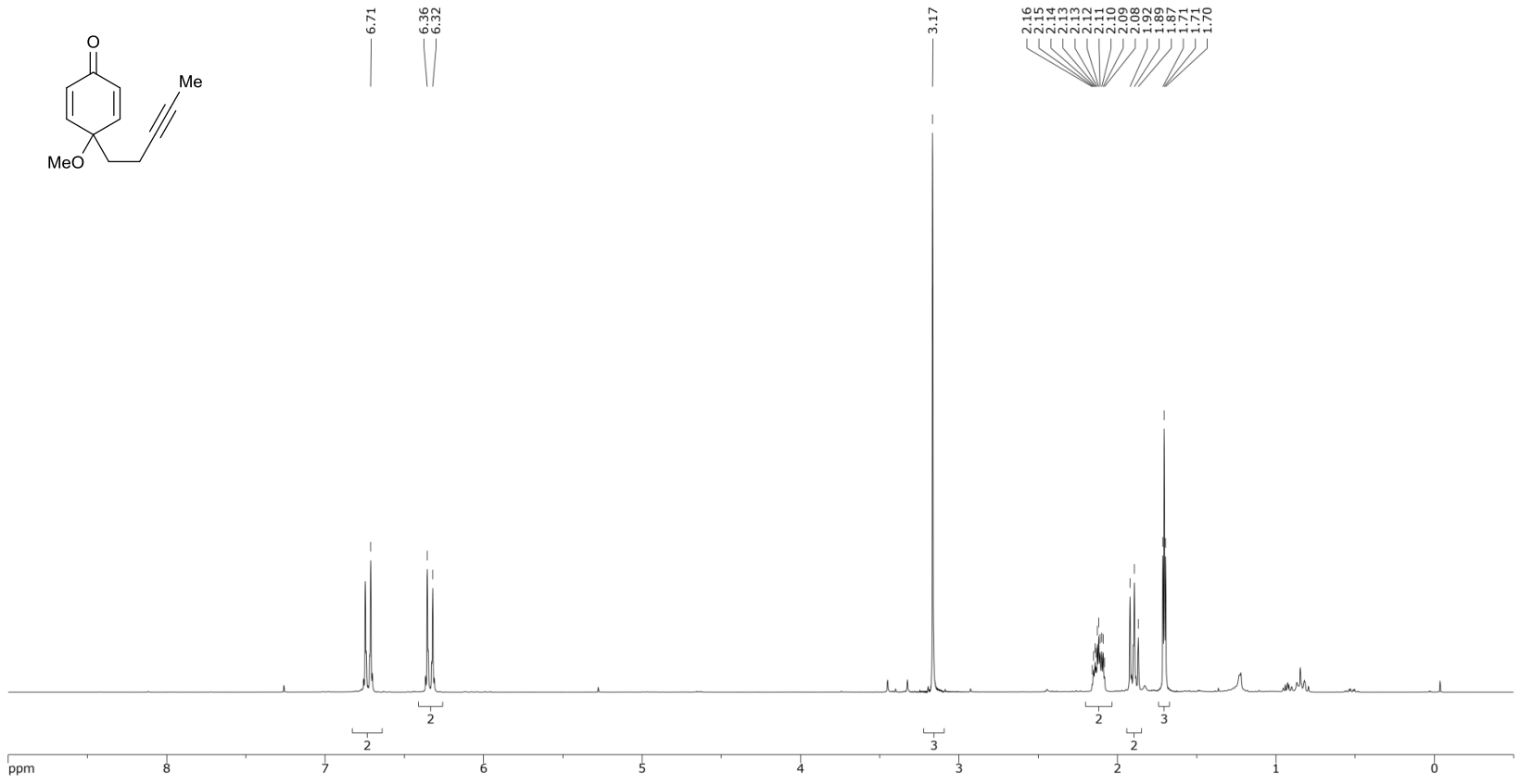
Alkyne-tethered cyclohexadienone 3.62j – ^{1}H NMR



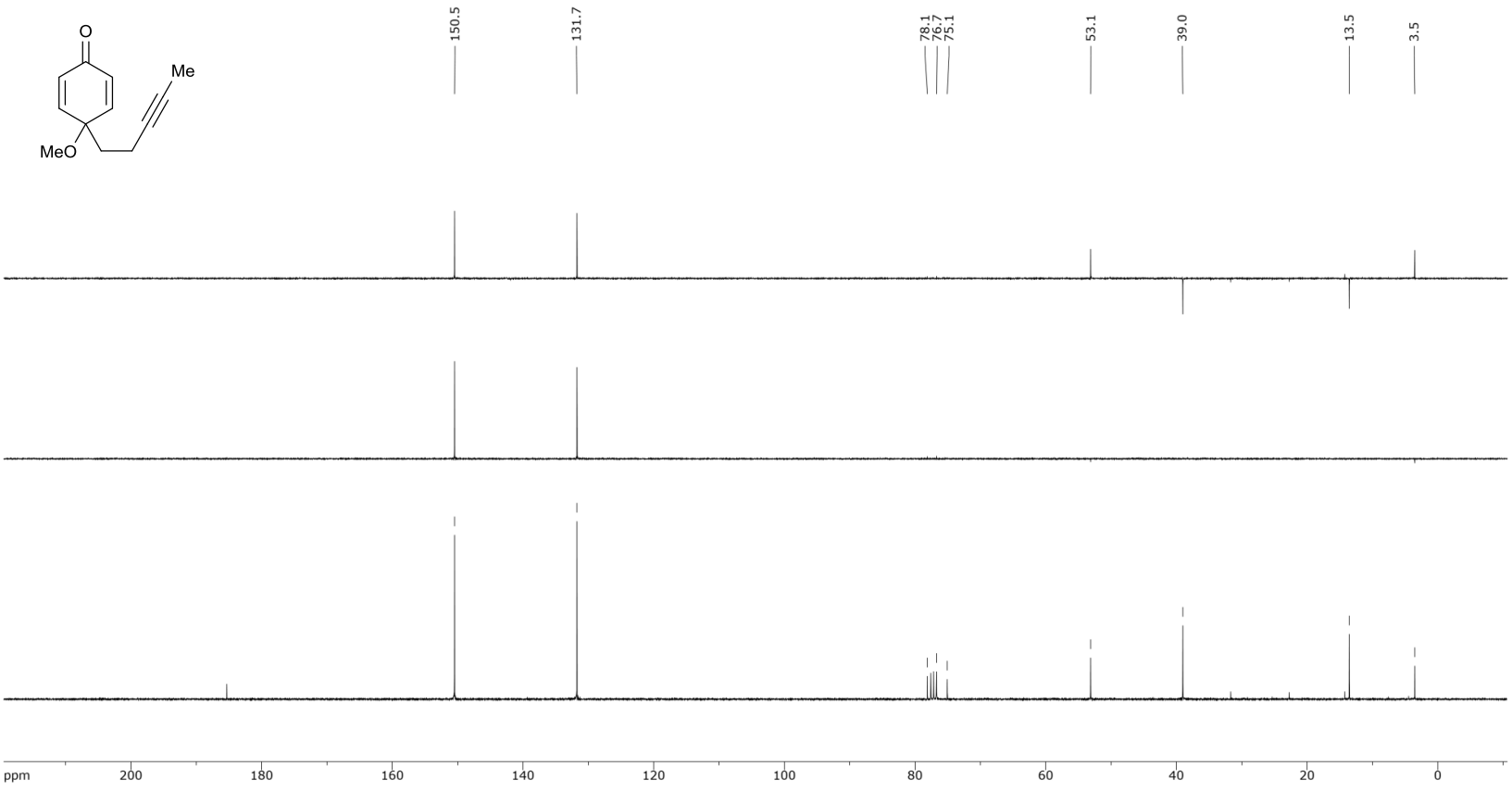
Alkyne-tethered cyclohexadienone 3.62j – ^{13}C NMR



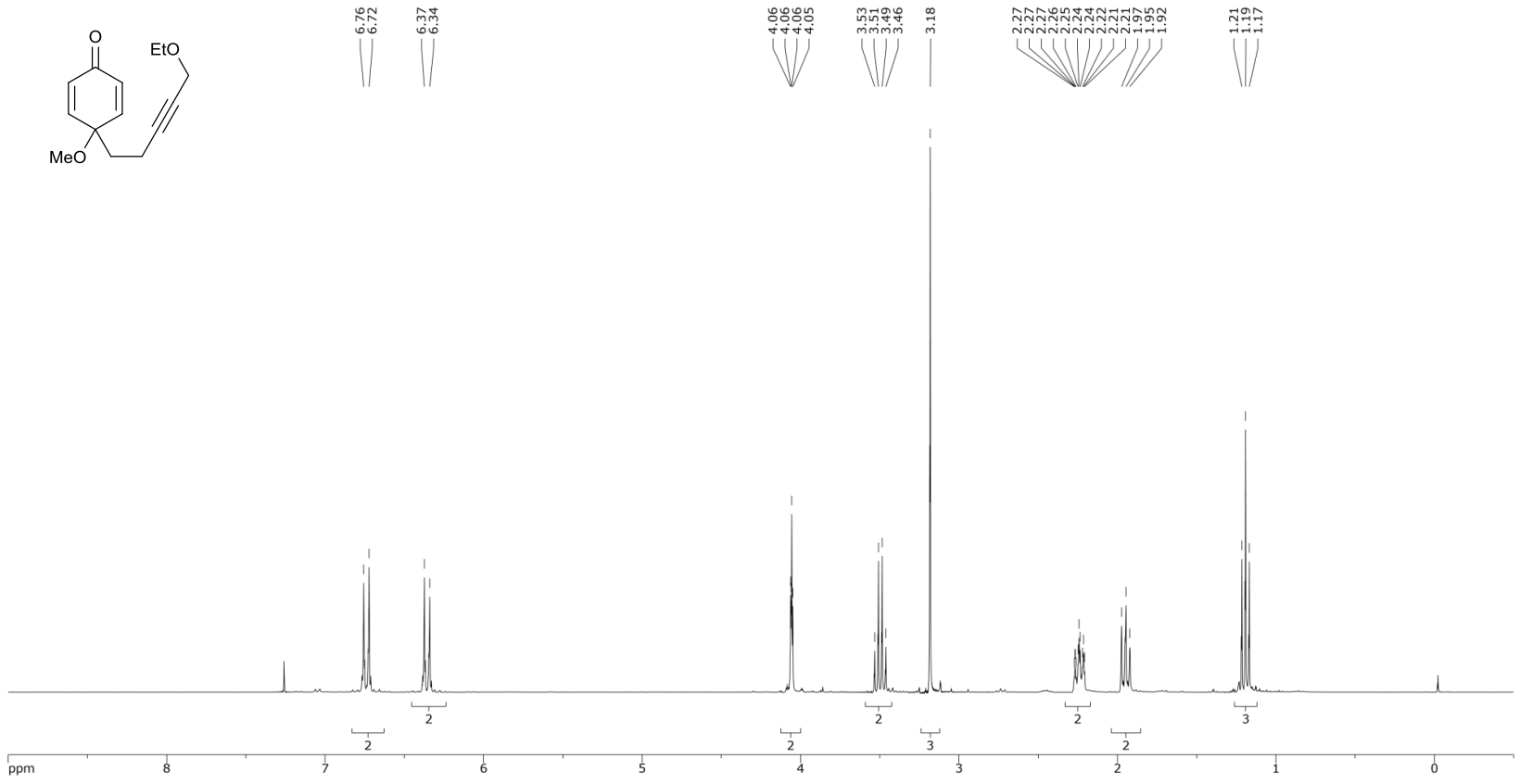
Alkyne-tethered cyclohexadienone 3.62k – ^{1}H NMR



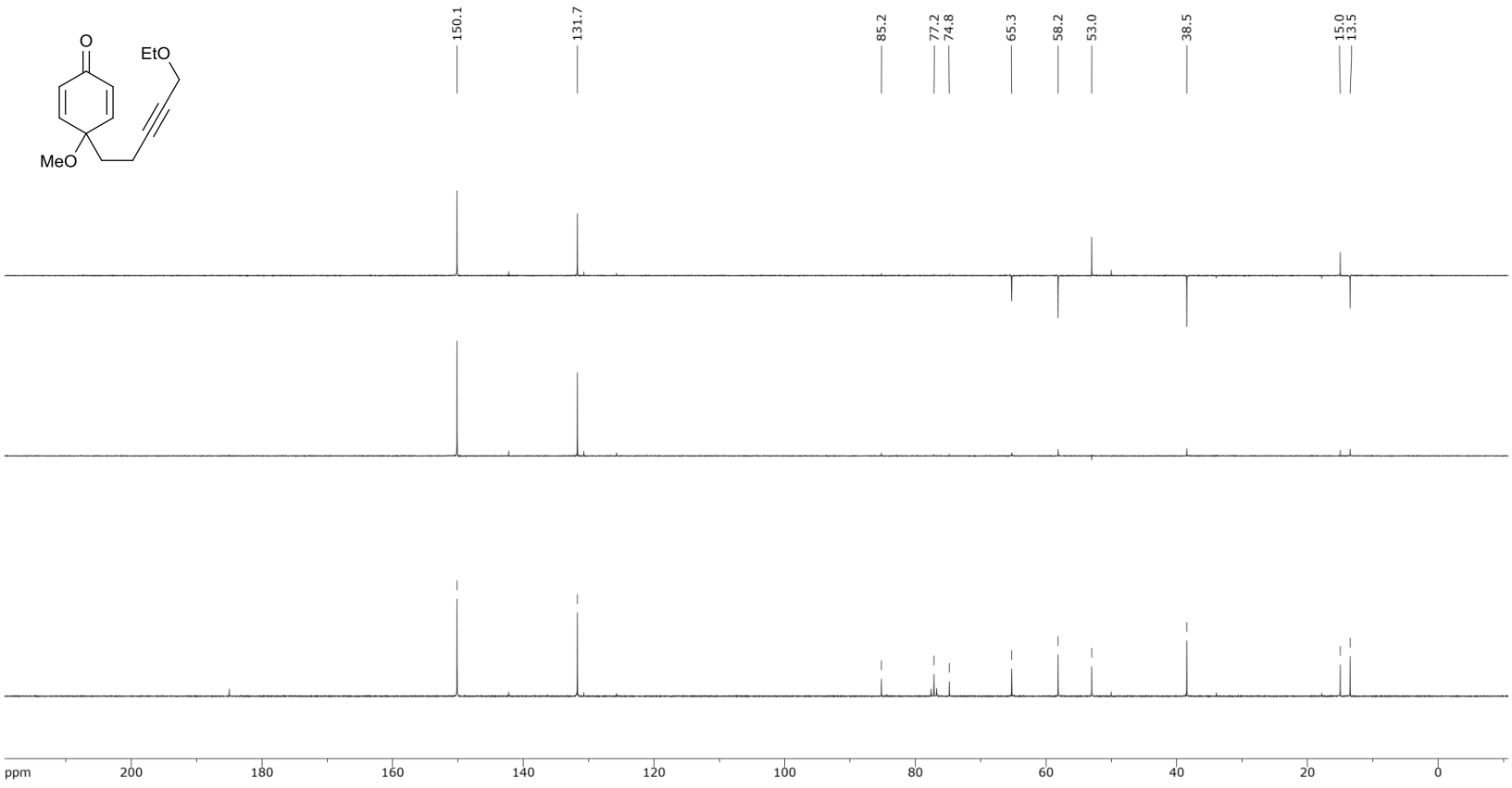
Alkyne-tethered cyclohexadienone 3.62k – ^{13}C NMR



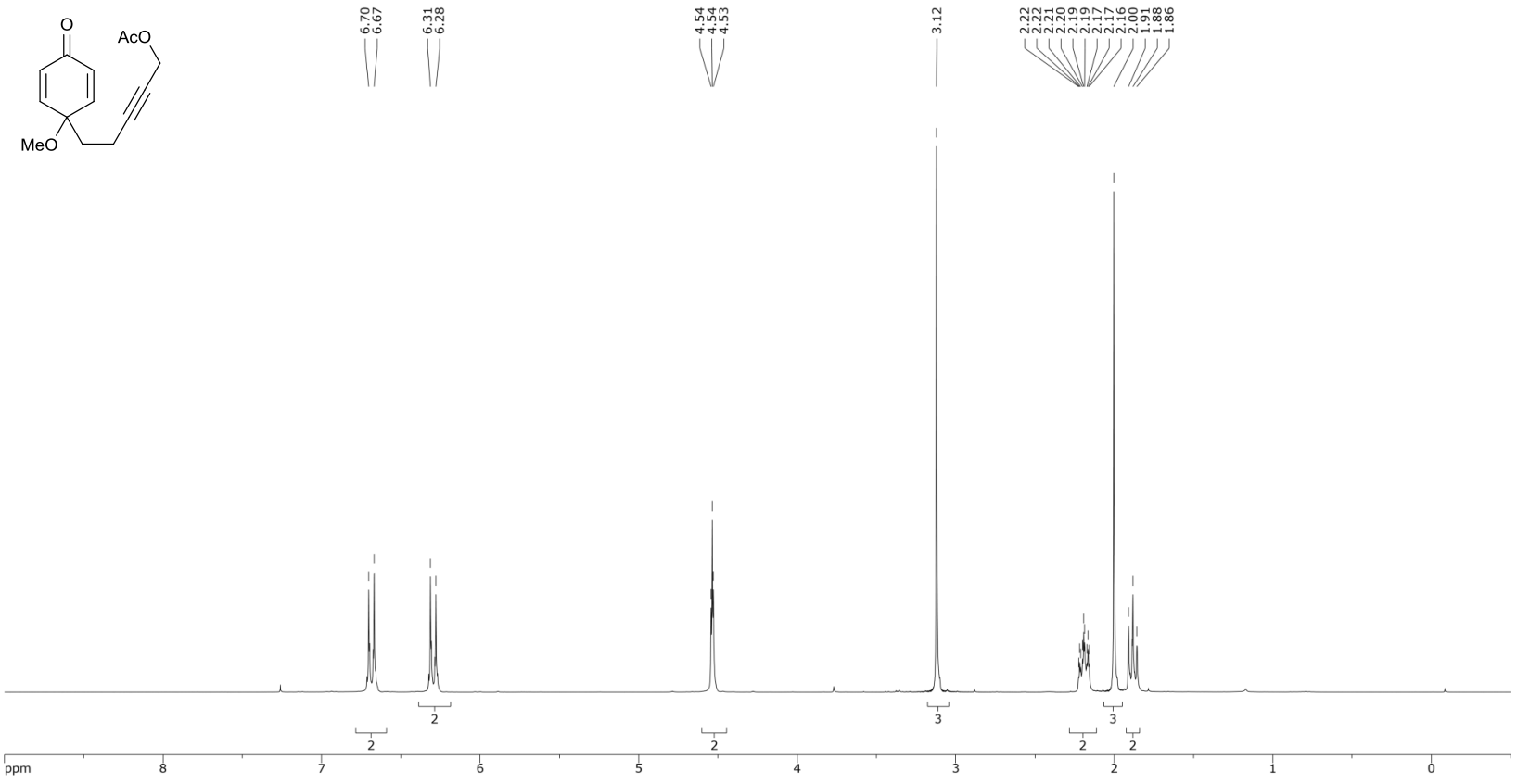
Alkyne-tethered cyclohexadienone 3.62l – ^{1}H NMR



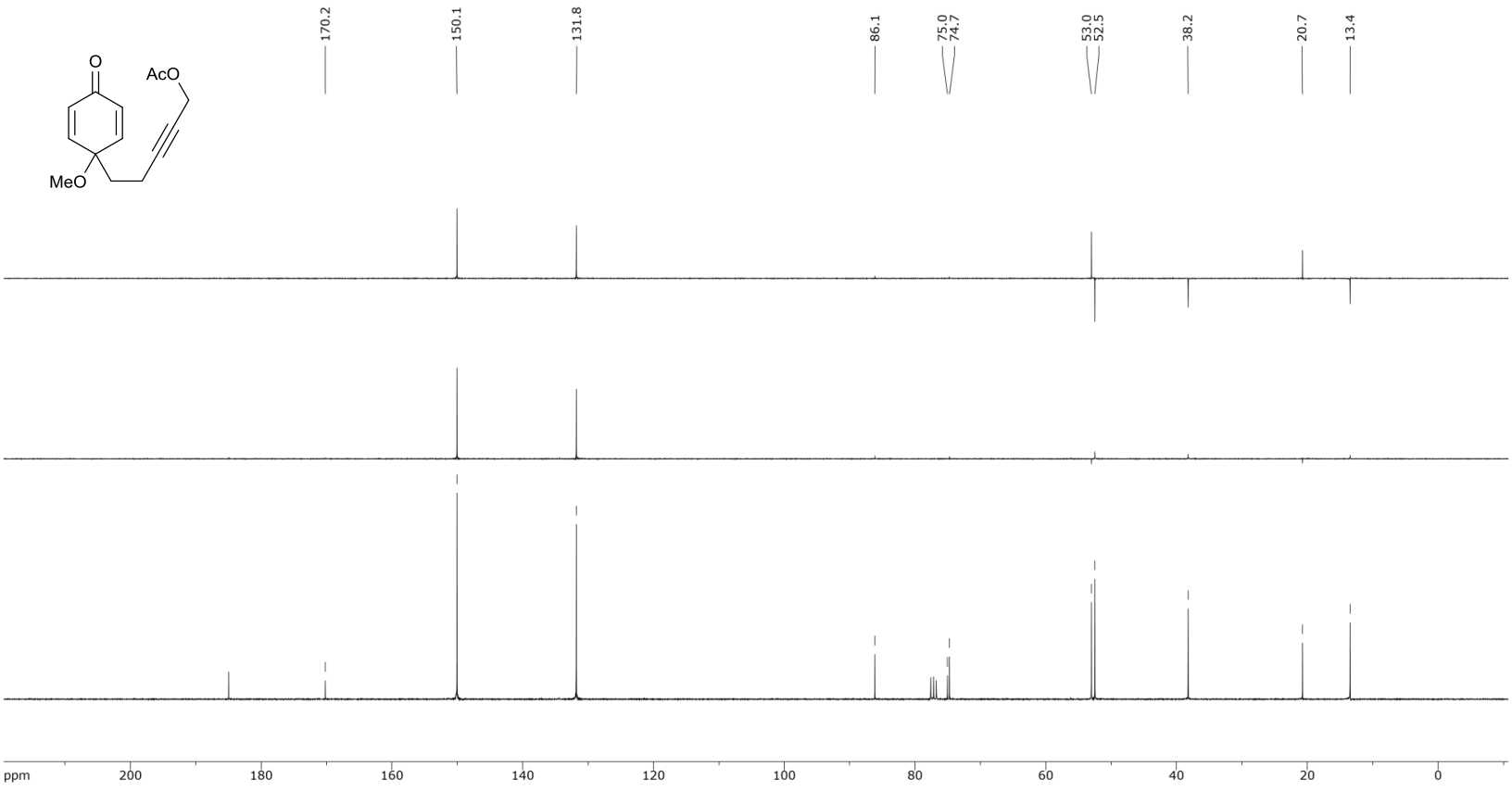
Alkyne-tethered cyclohexadienone 3.62l – ^{13}C NMR



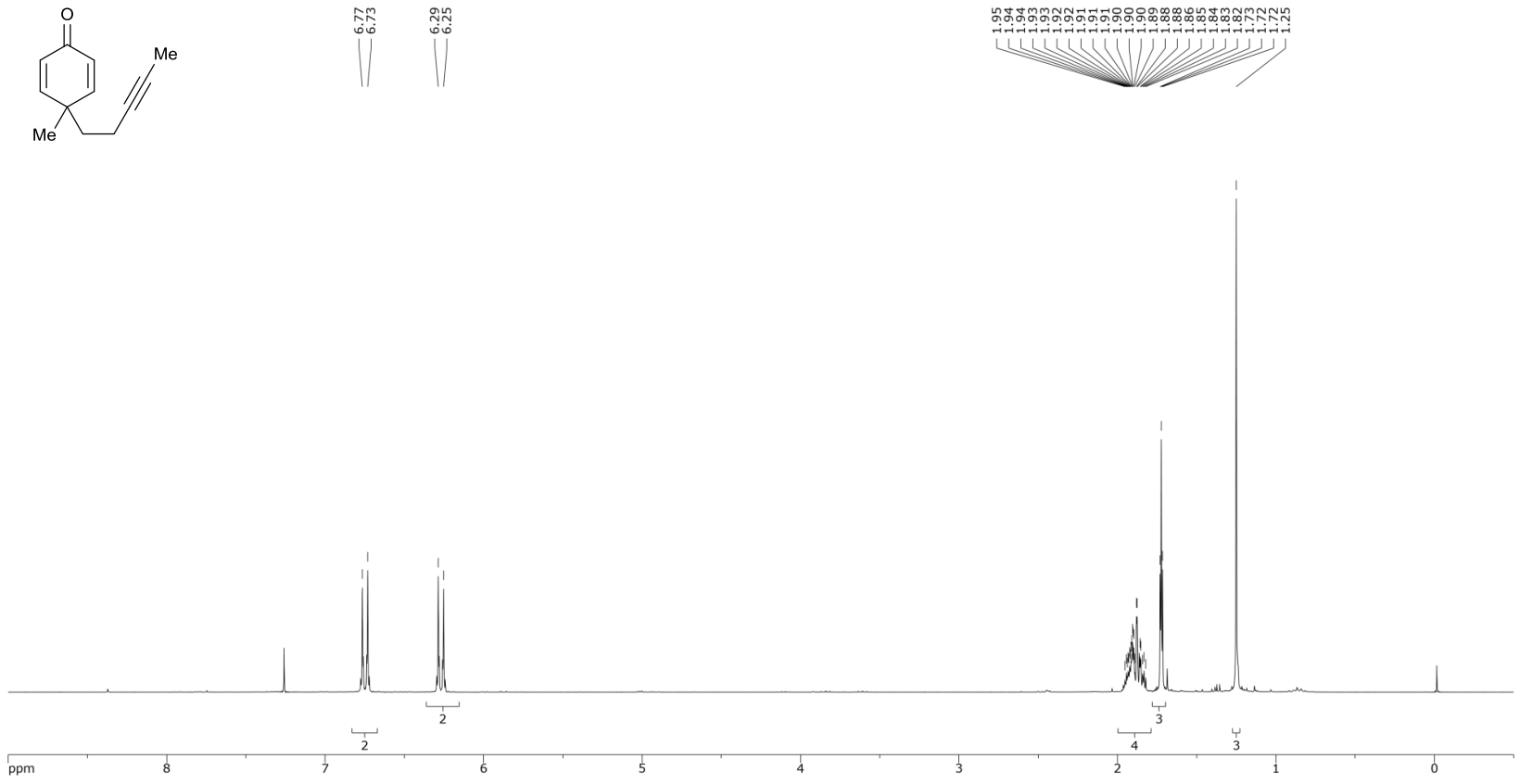
Alkyne-tethered cyclohexadienone 3.62m – ^{1}H NMR



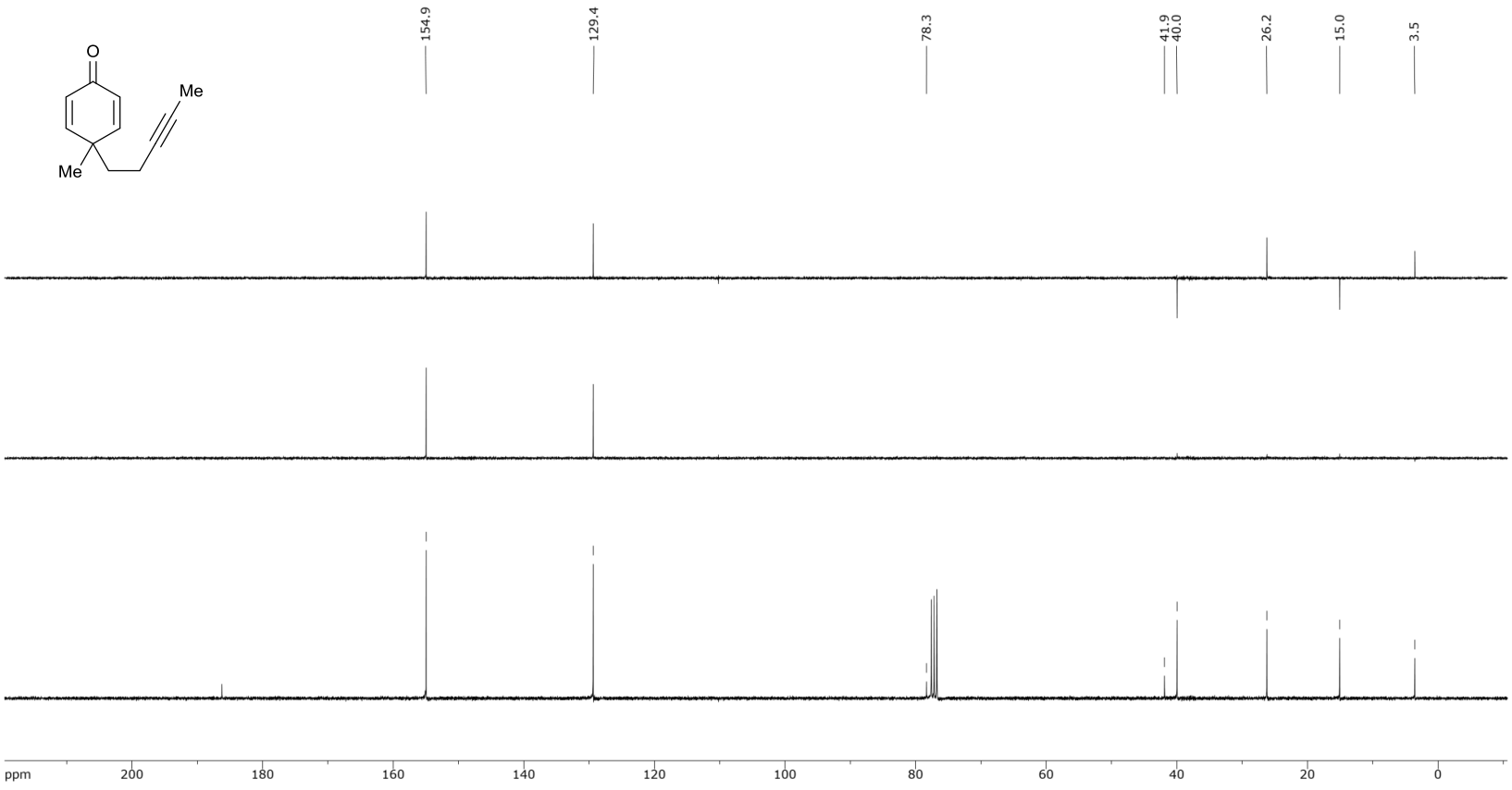
Alkyne-tethered cyclohexadienone 3.62m – ^{13}C NMR



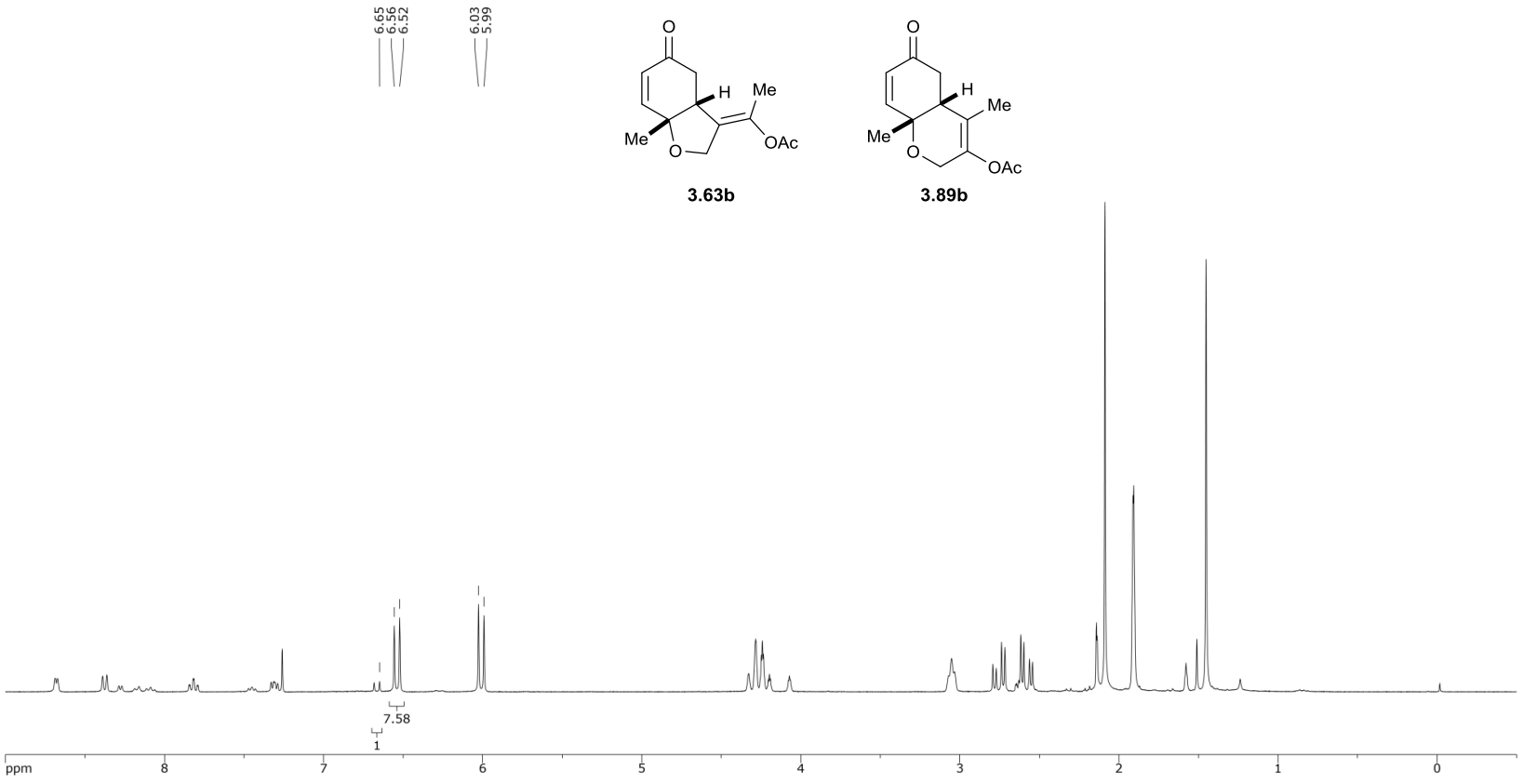
Alkyne-tethered cyclohexadienone 3.62n – ^{1}H NMR



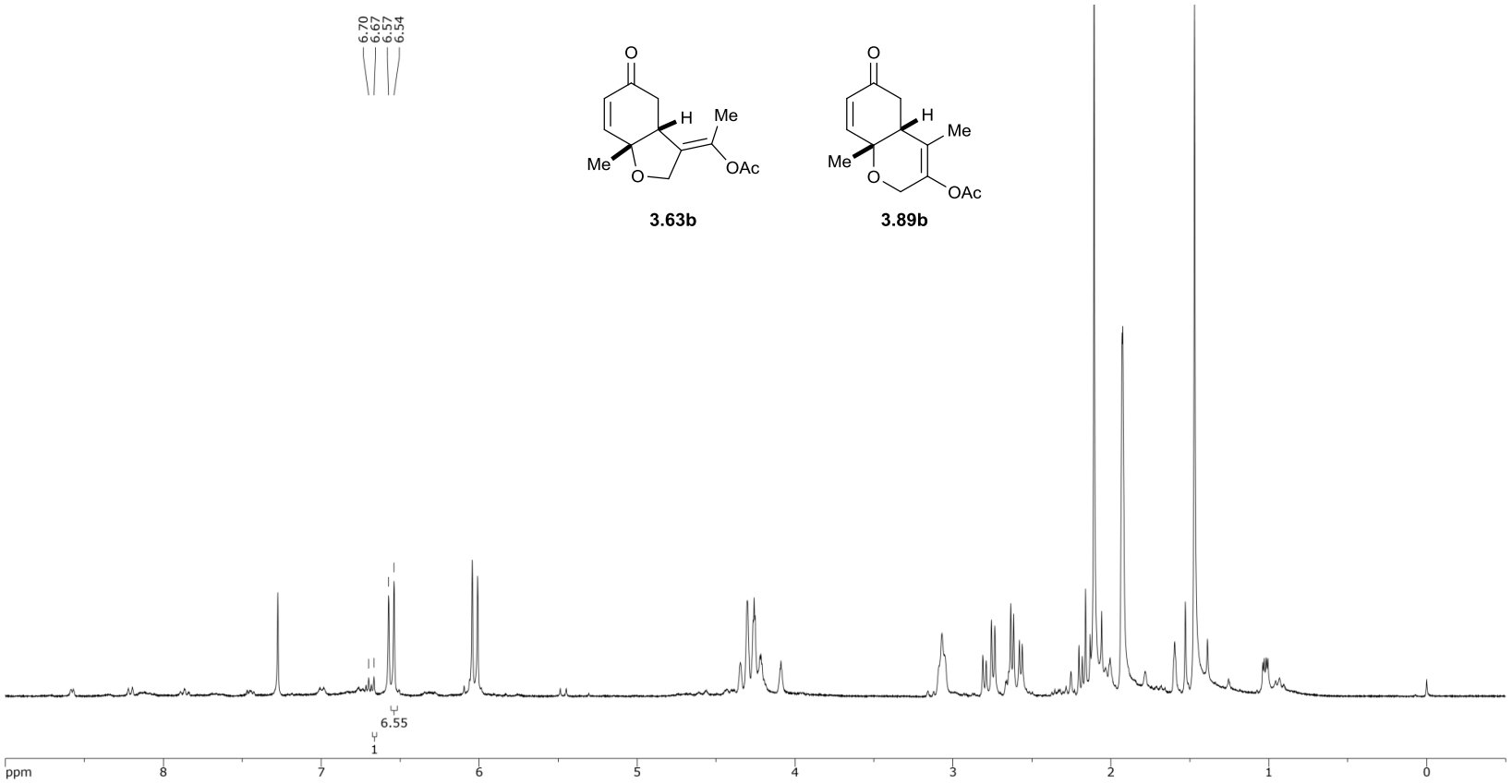
Alkyne-tethered cyclohexadienone 3.62n – ^{13}C NMR



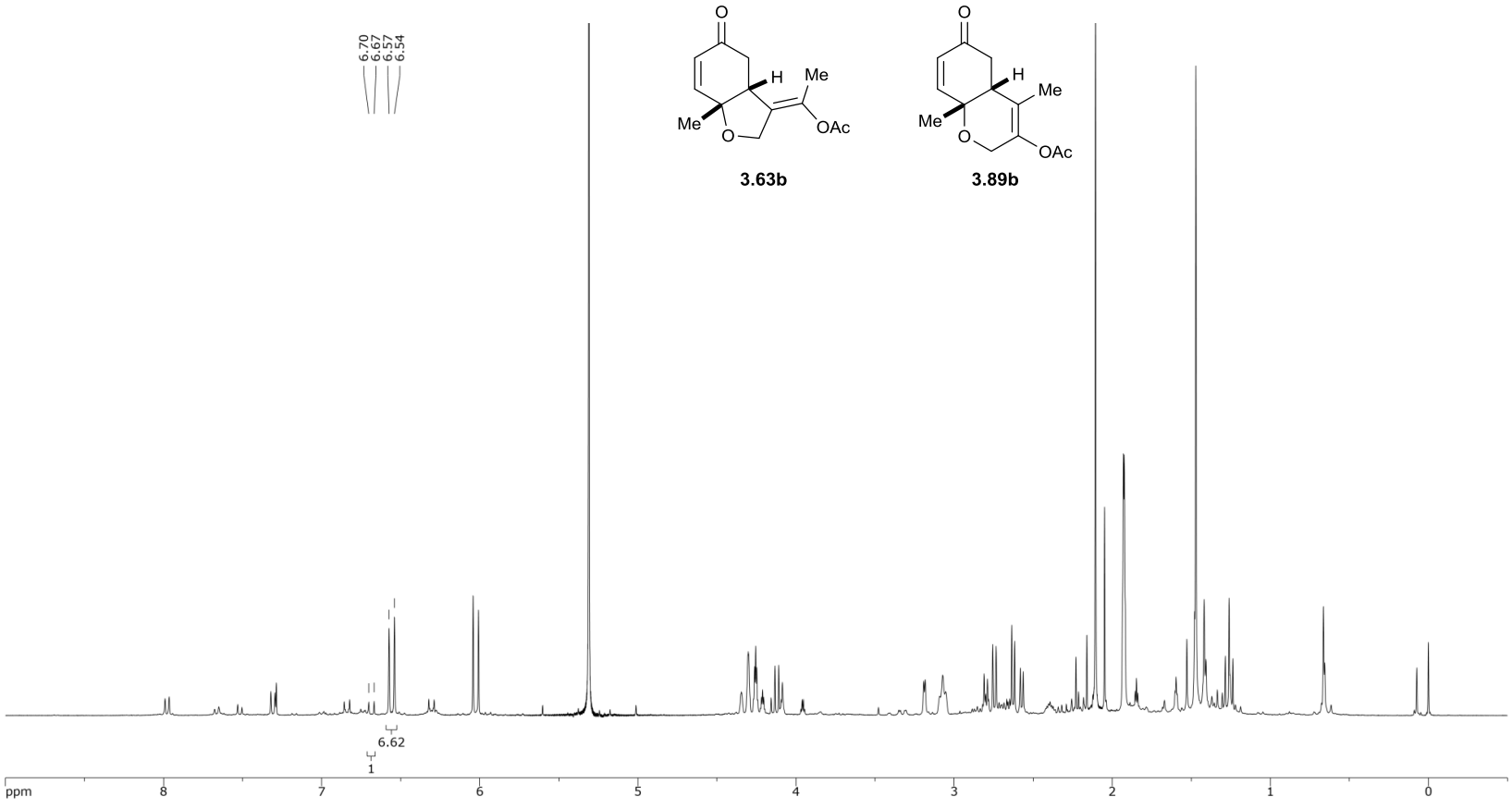
Bicyclic enones 3.63b and 3.89b – bipy – ^{1}H NMR



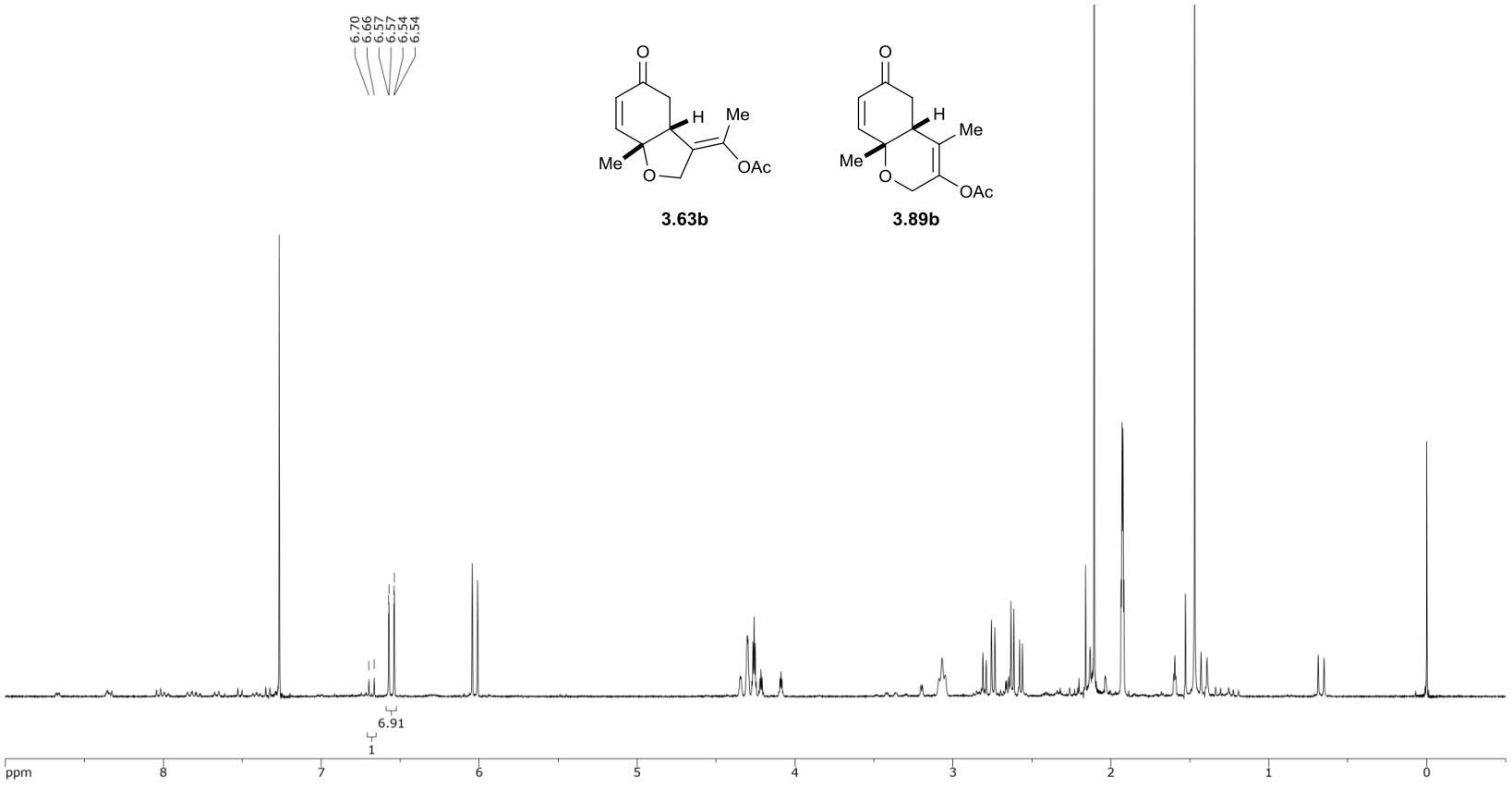
Bicyclic enones 3.63b and 3.89b – ligand 3.79 – ^{1}H NMR



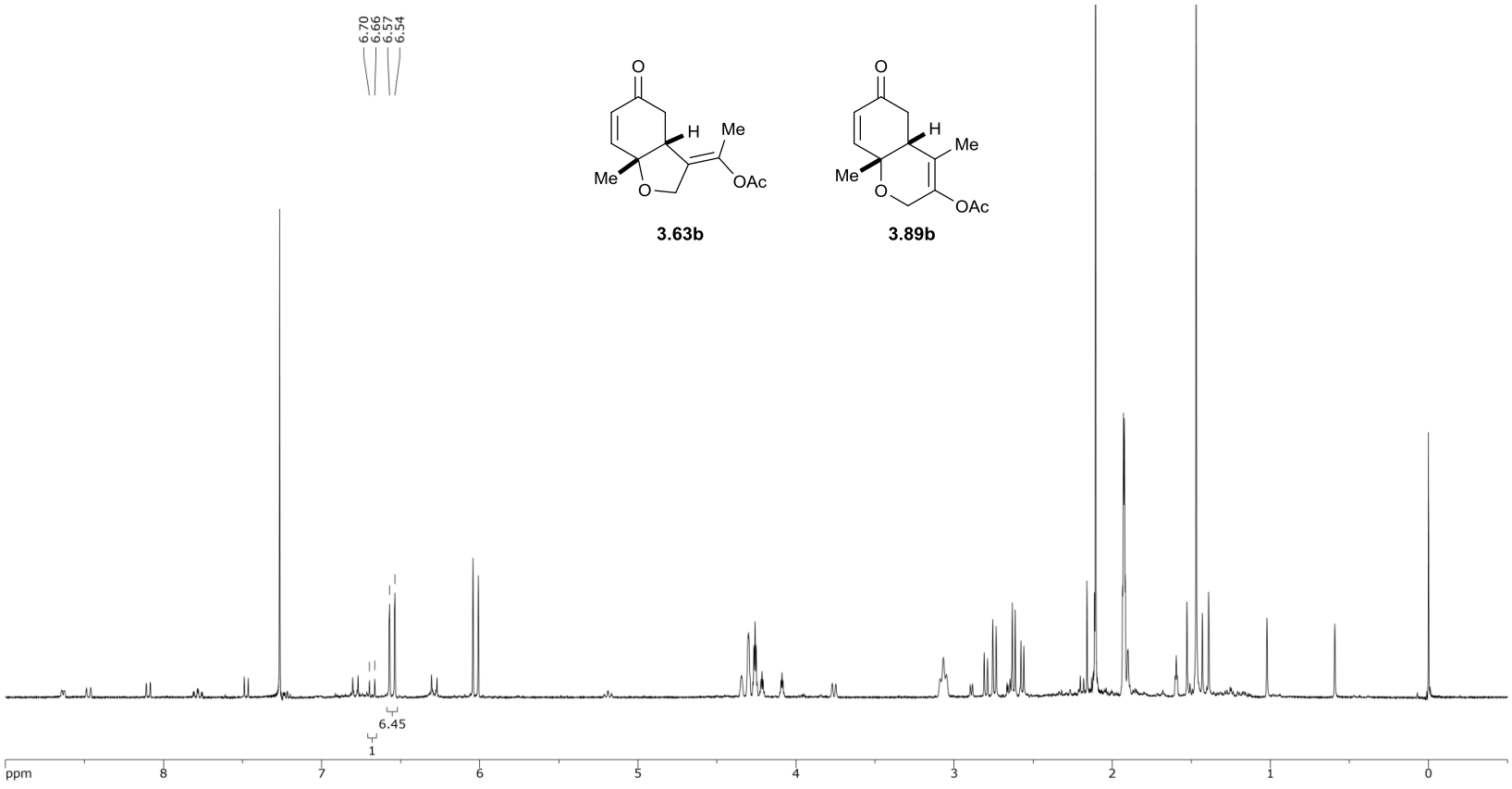
Bicyclic enones 3.63b and 3.89b – ligand 3.82 – ^{1}H NMR



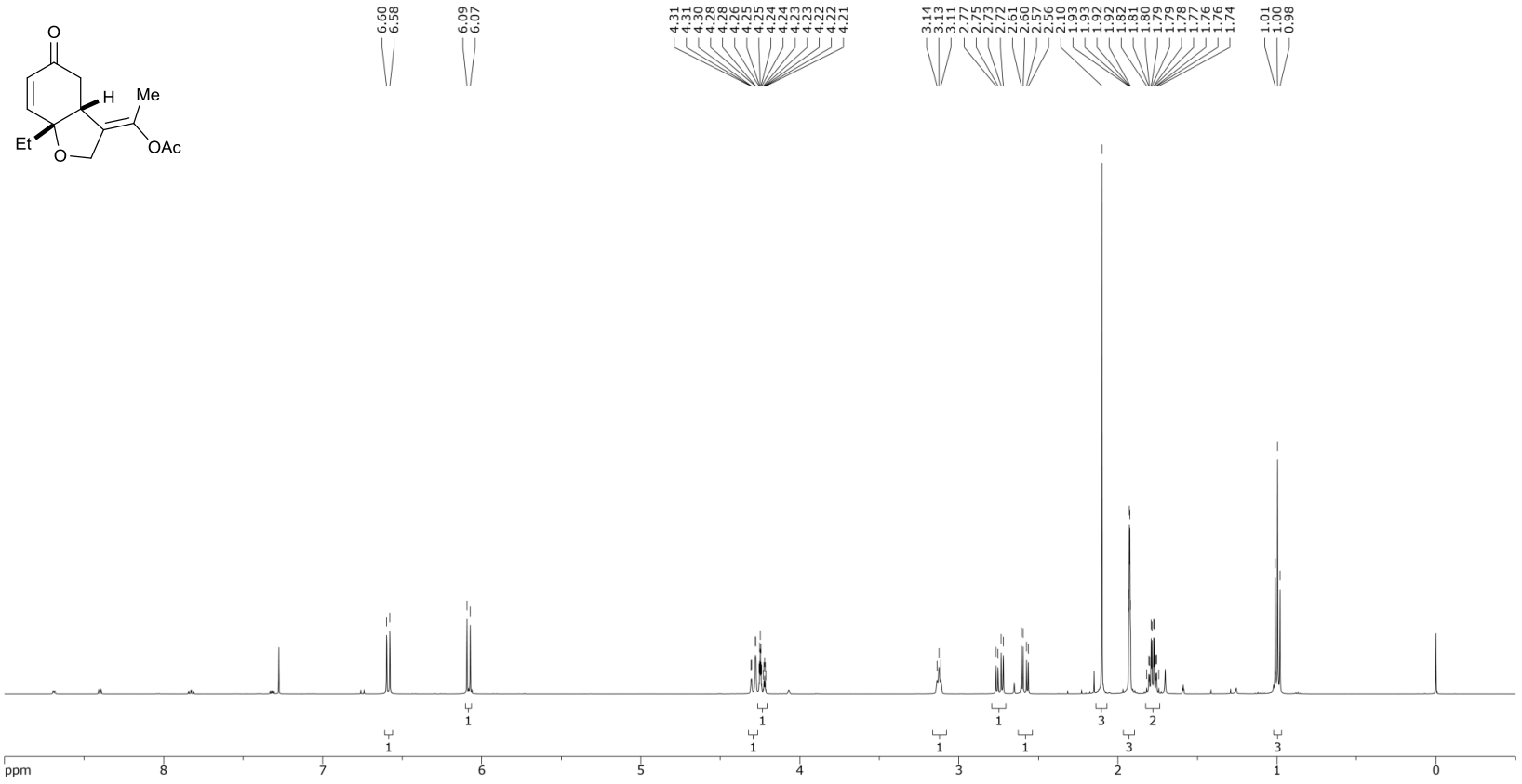
Bicyclic enones 3.63b and 3.89b – ligand 3.84 – ^{1}H NMR



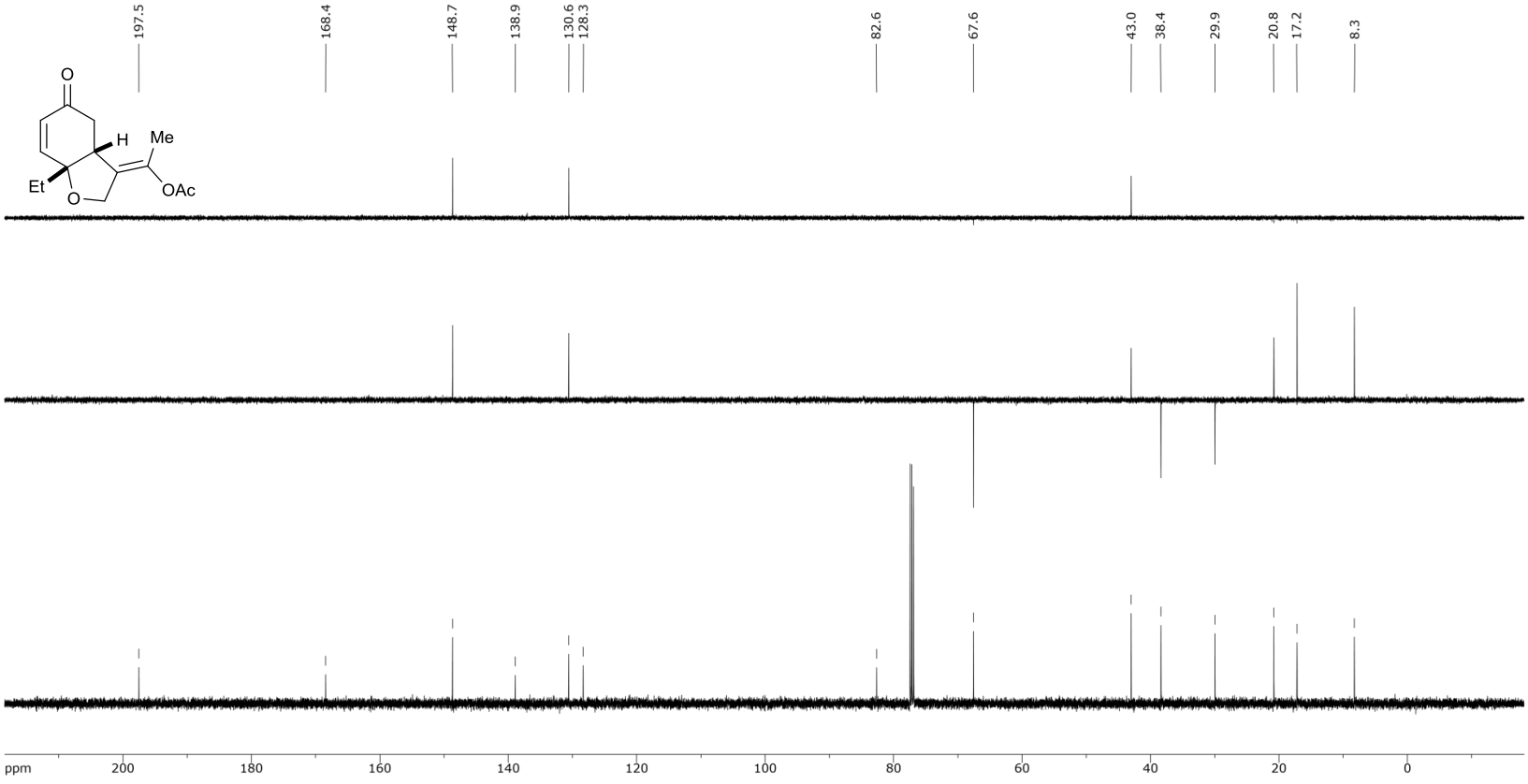
Bicyclic enones 3.63b and 3.89b – ligand 3.85 – ^{1}H NMR



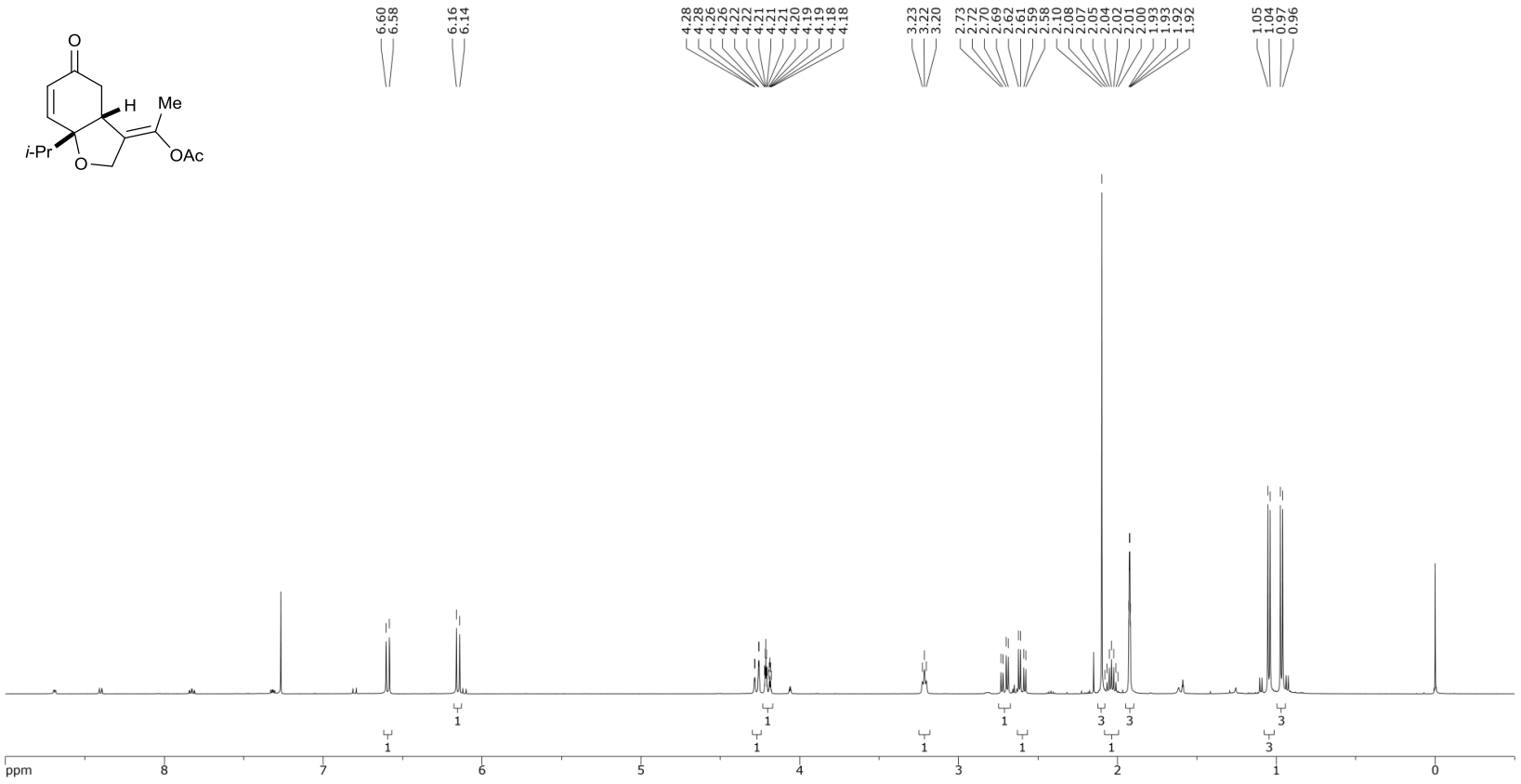
Bicyclic enone 3.63d – ^{1}H NMR



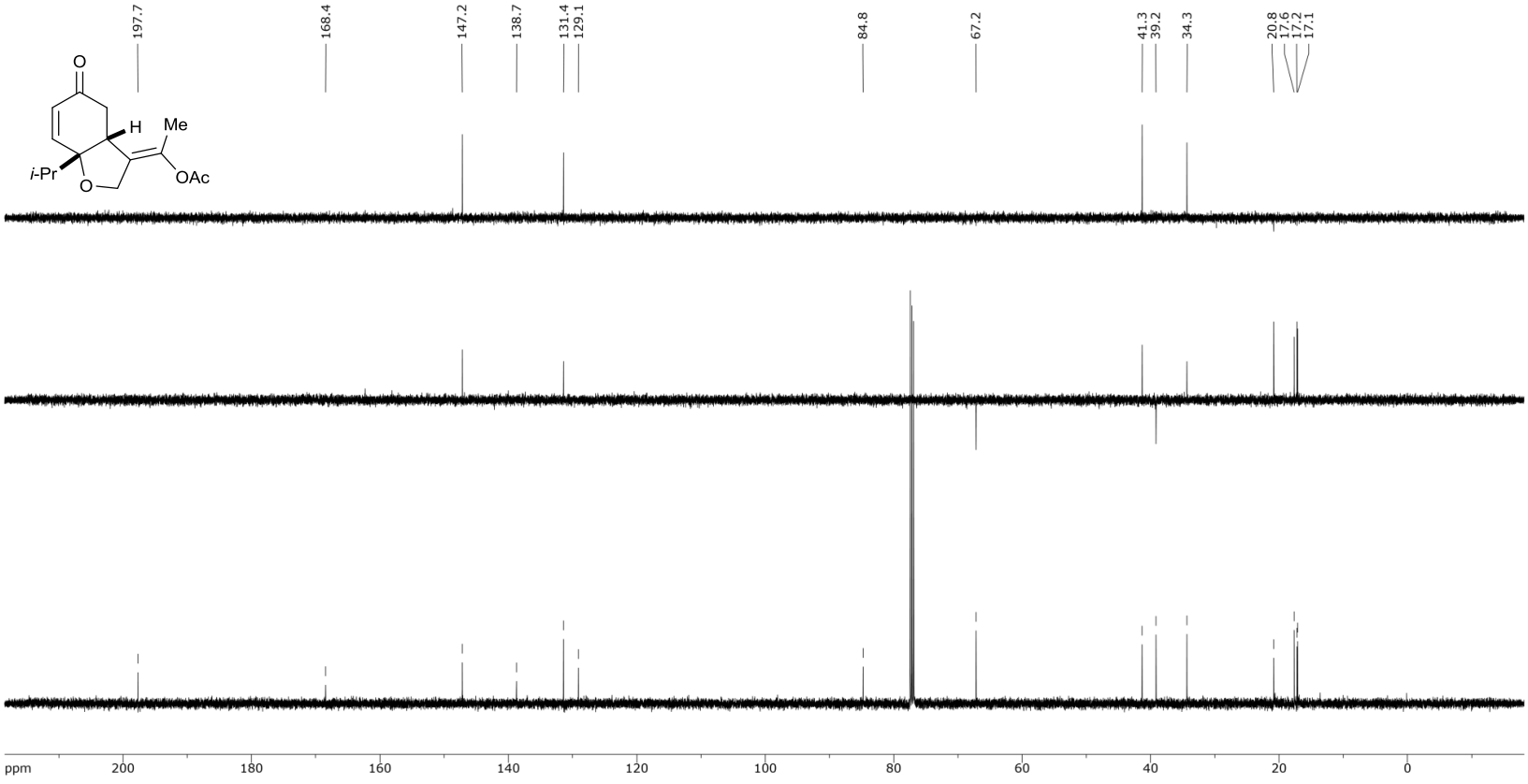
Bicyclic enone 3.63d – ^{13}C NMR



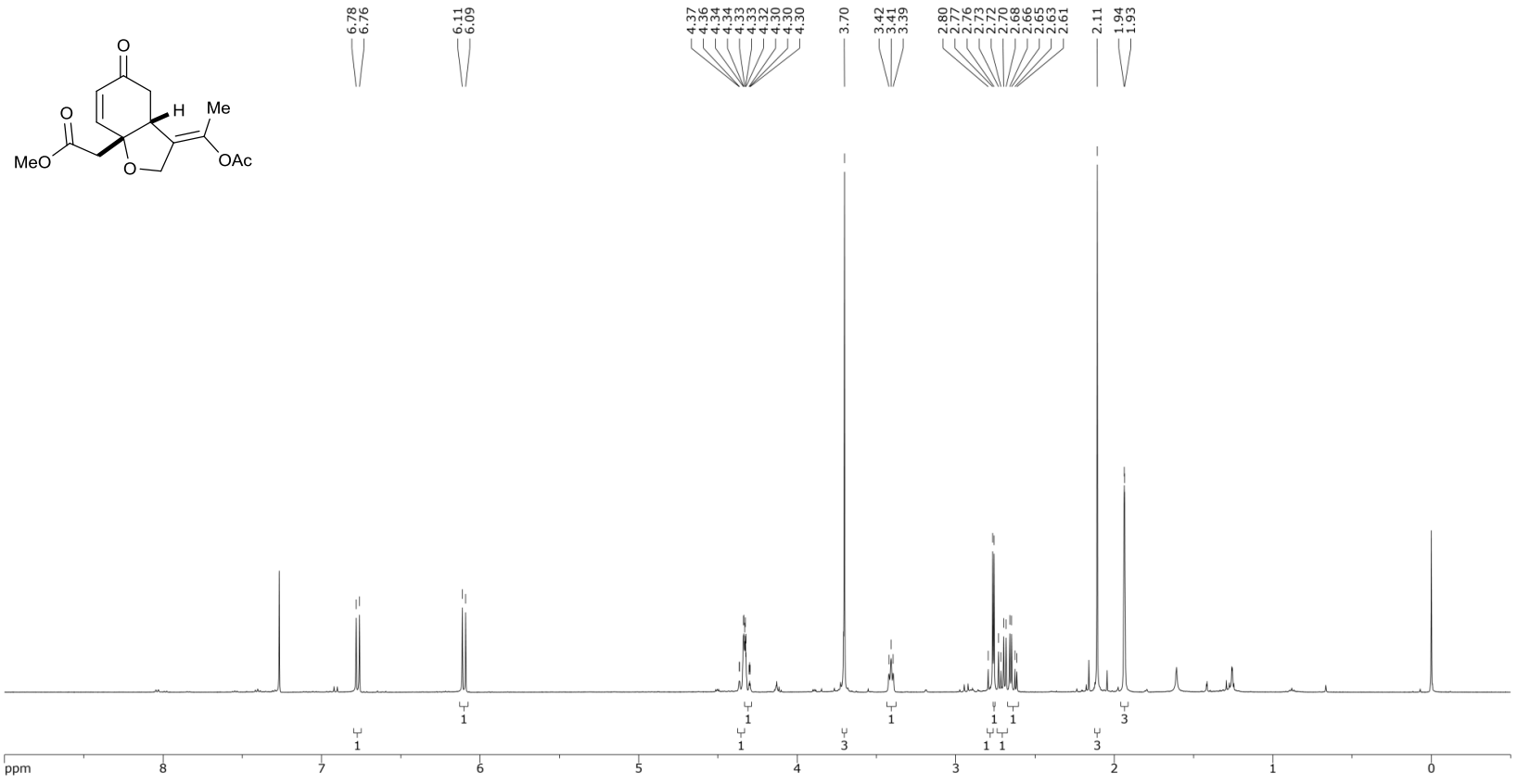
Bicyclic enone 3.63e – ^{1}H NMR



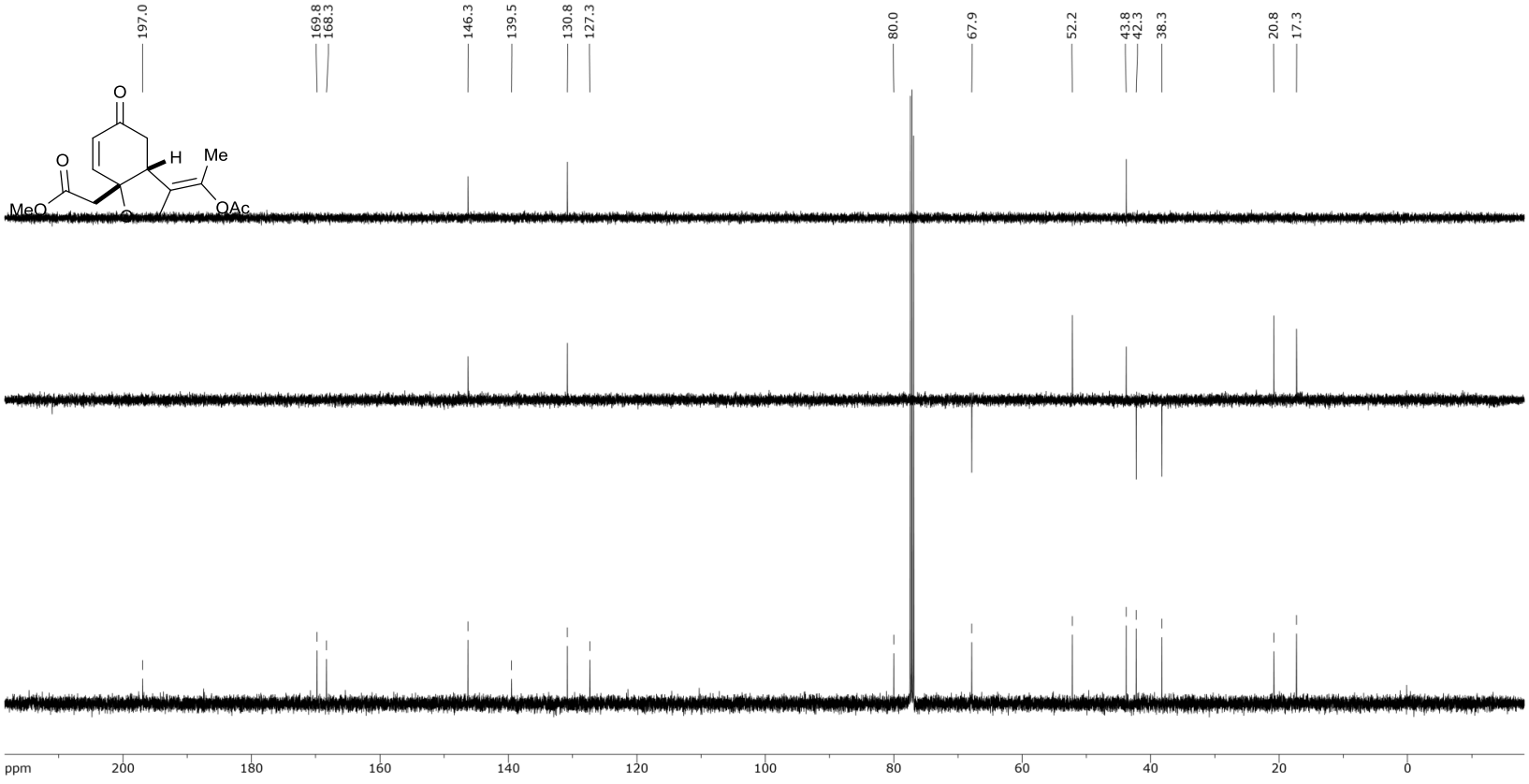
Bicyclic enone 3.63e – ^{13}C NMR



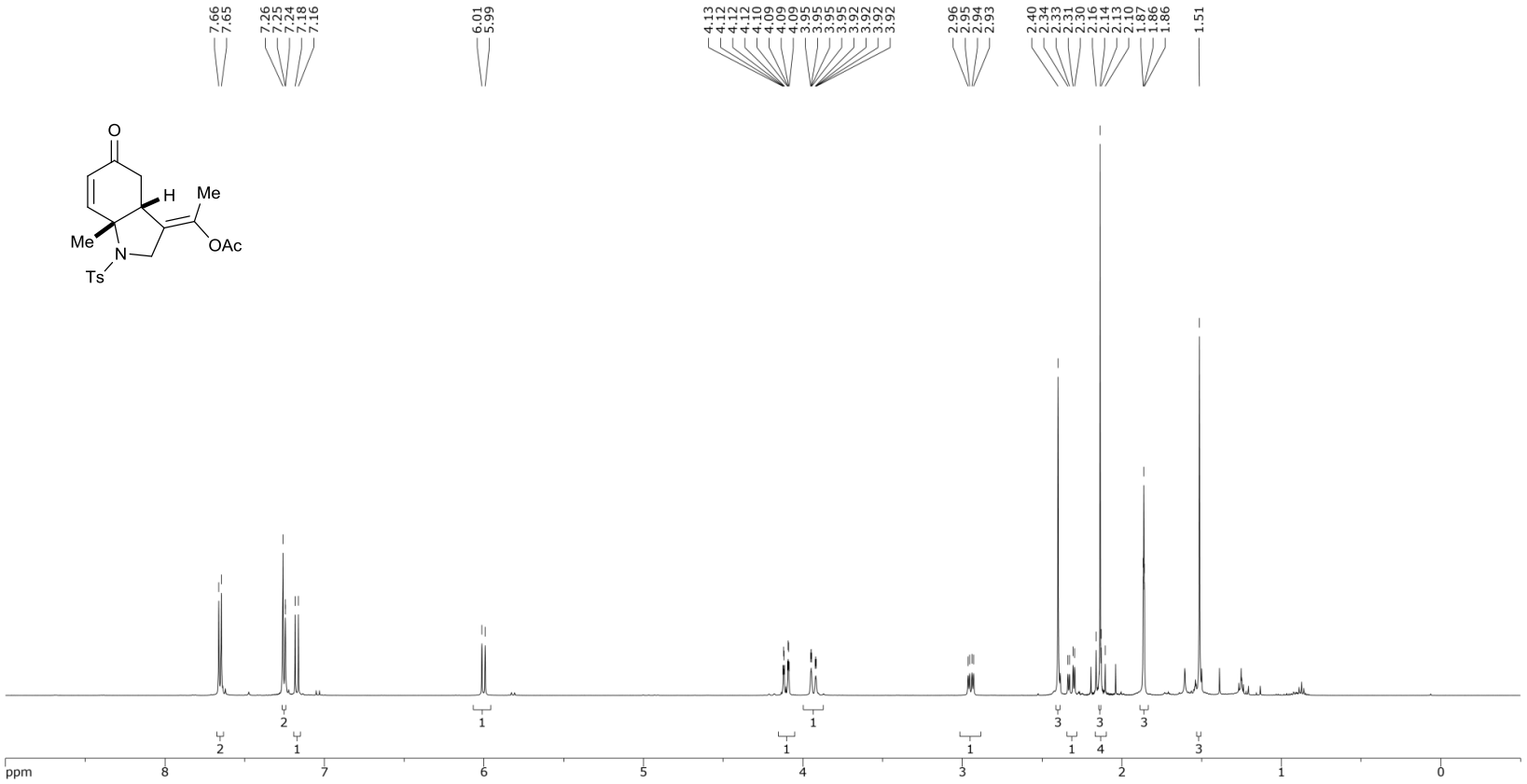
Bicyclic enone 3.63f – ^{1}H NMR



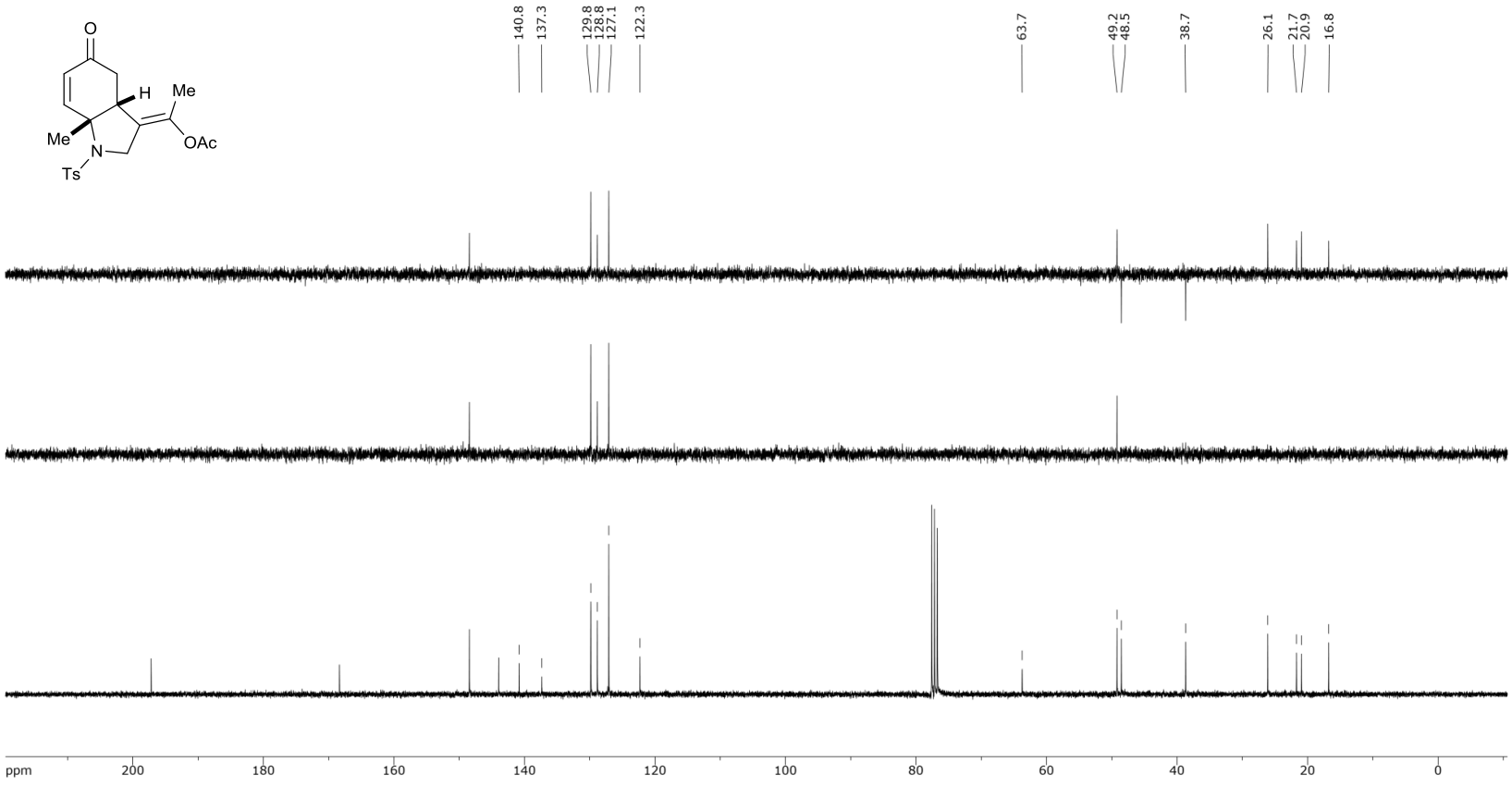
Bicyclic enone 3.63f – ^{13}C NMR



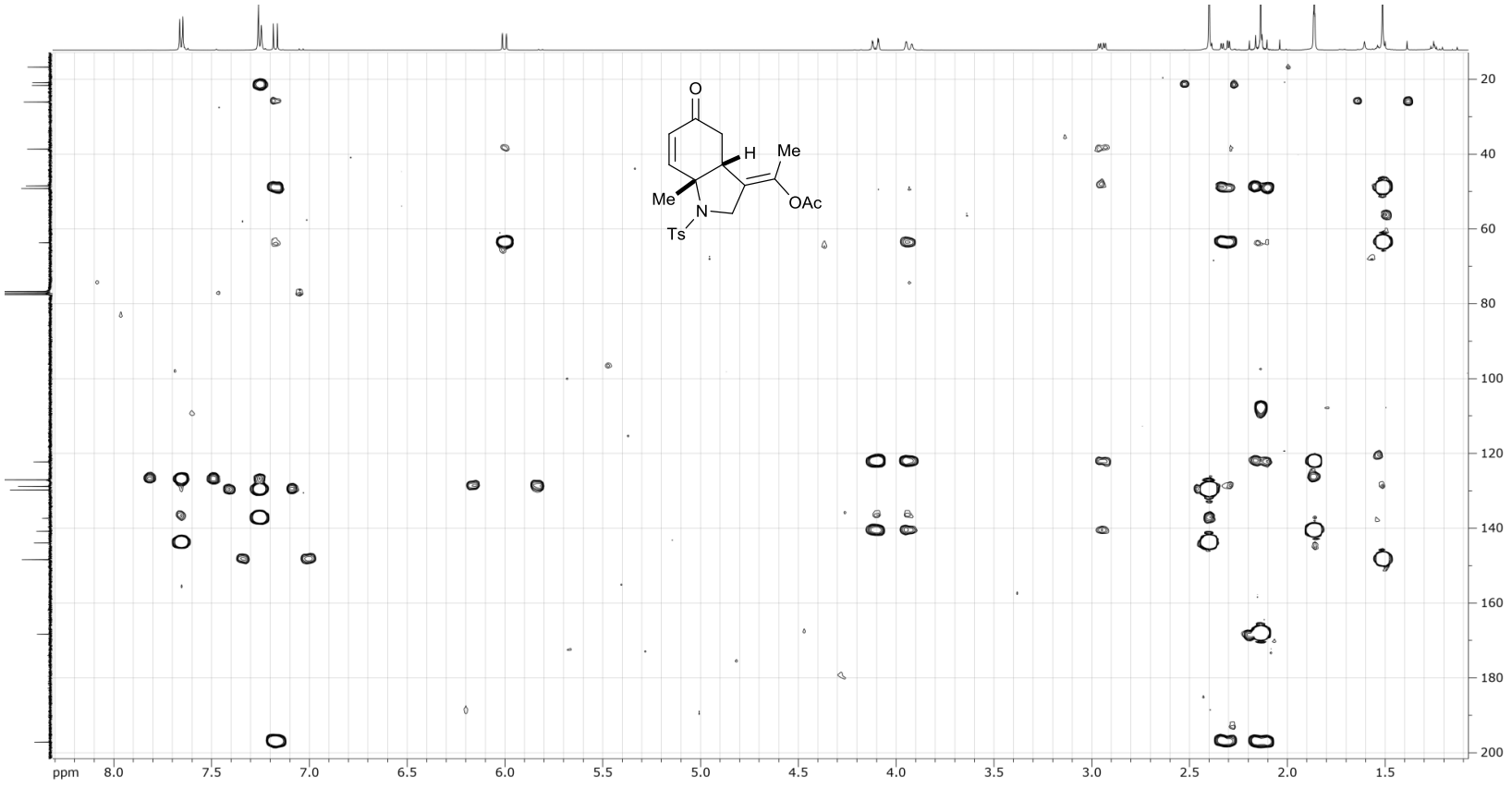
Bicyclic enone 3.63i – ^{1}H NMR



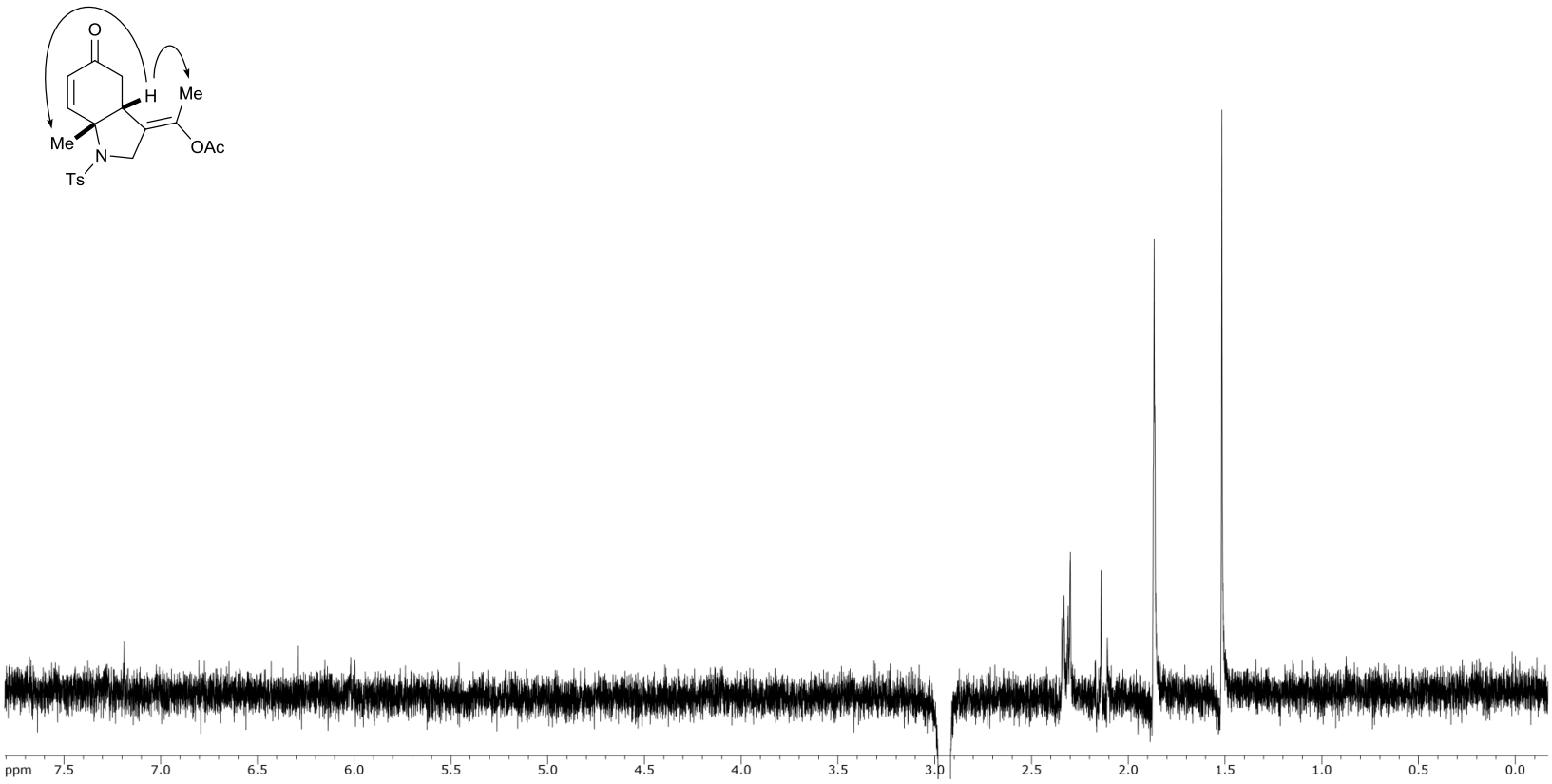
Bicyclic enone 3.63i – ^{13}C NMR



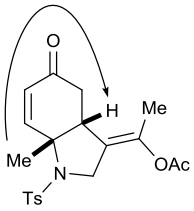
Bicyclic enone 3.63i – HMBC

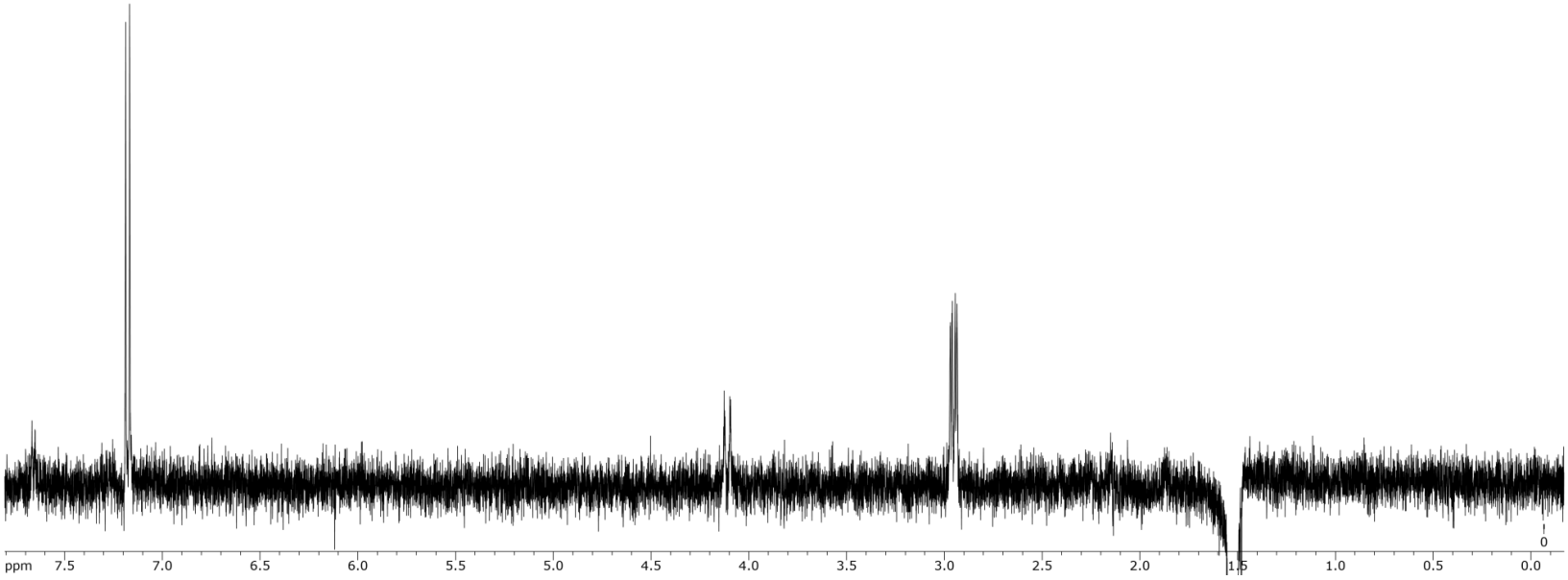


Bicyclic enone 3.63i – NOE

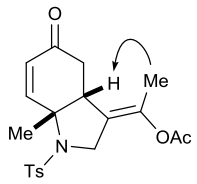


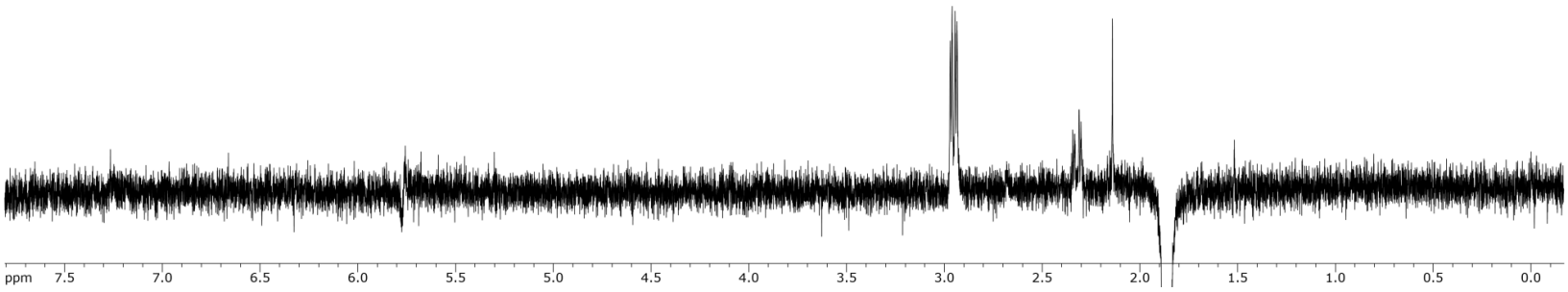
Bicyclic enone 3.63i – NOE



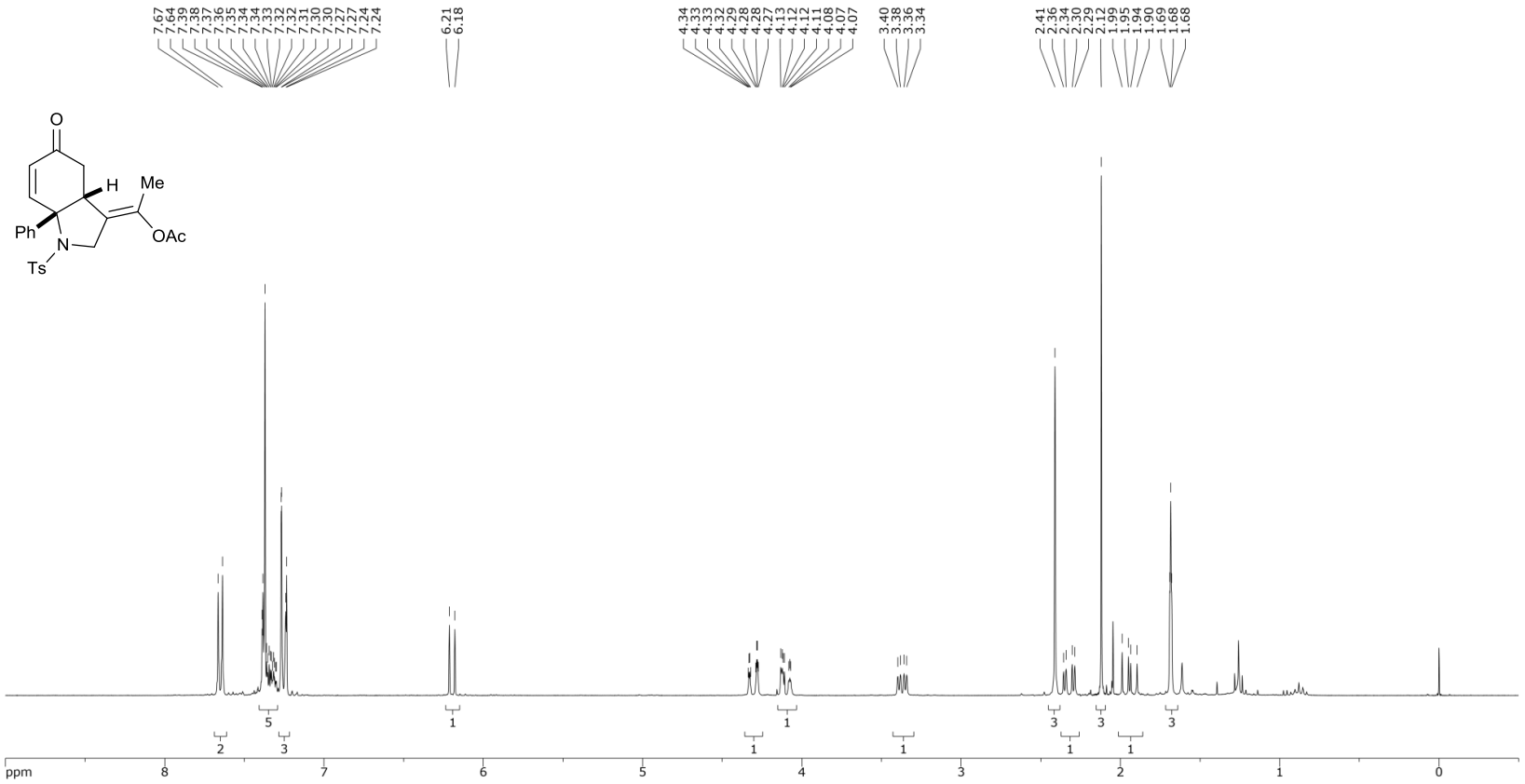


Bicyclic enone 3.63i – NOE

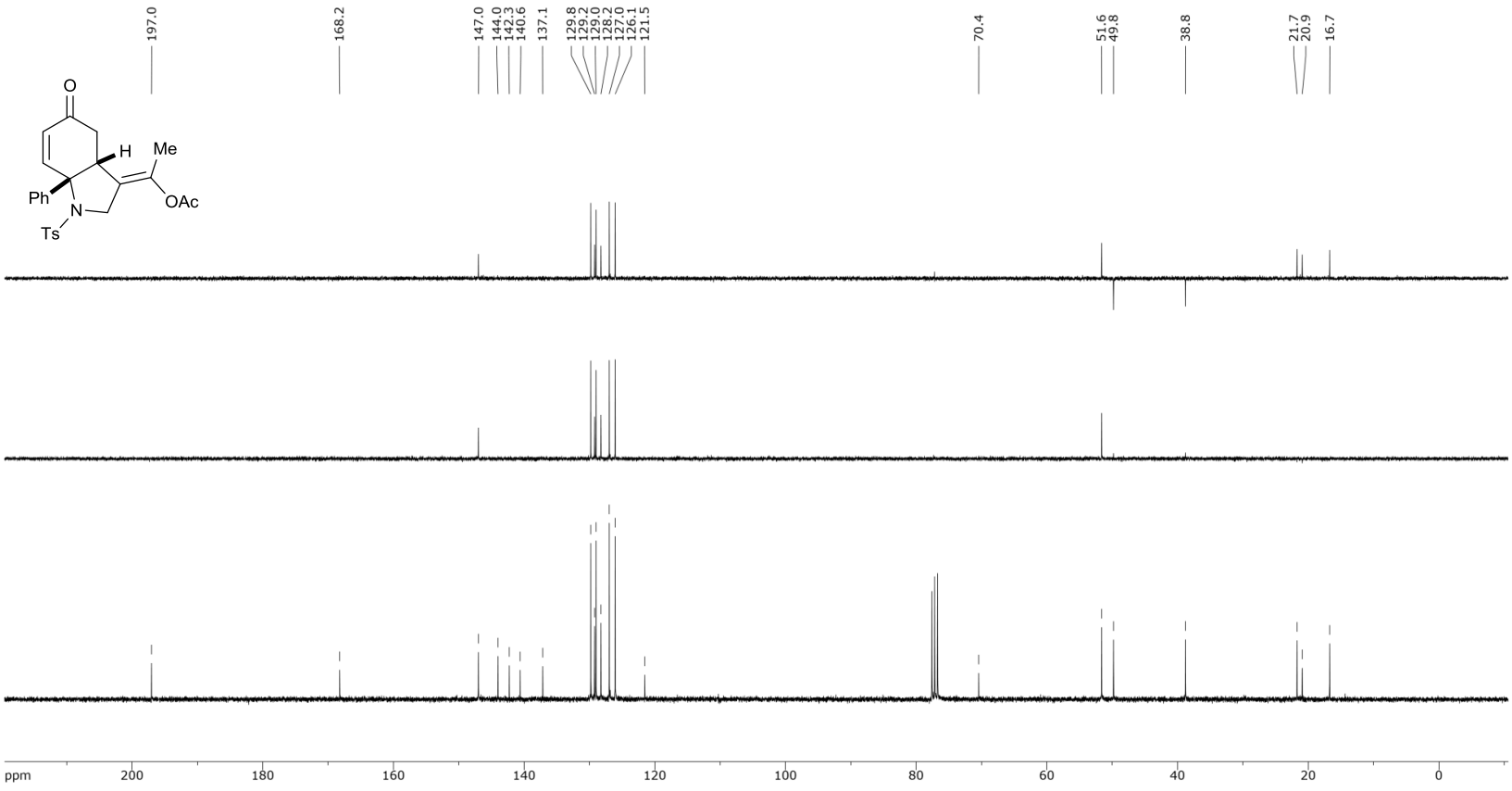




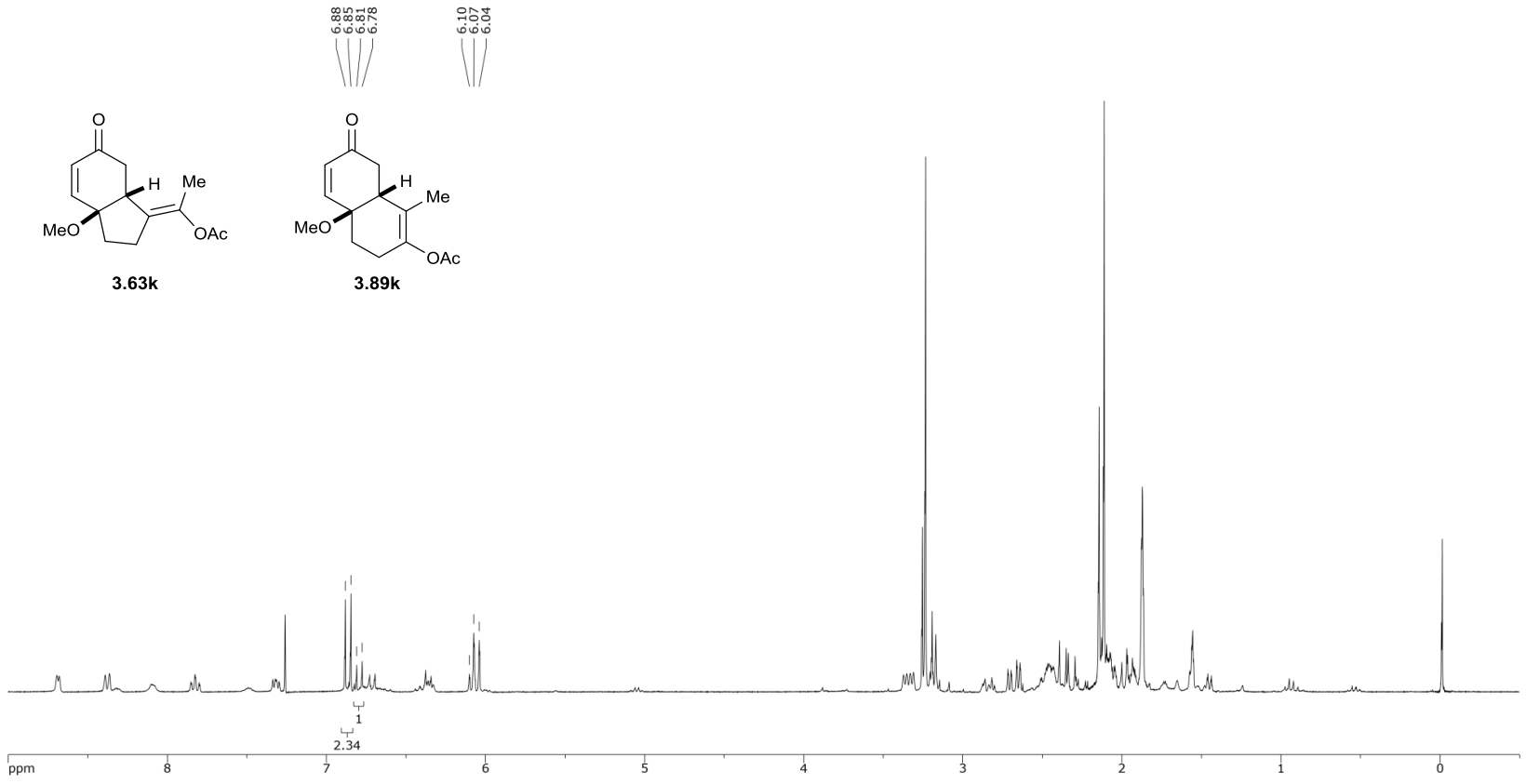
Bicyclic enone 3.63j – ^{1}H NMR



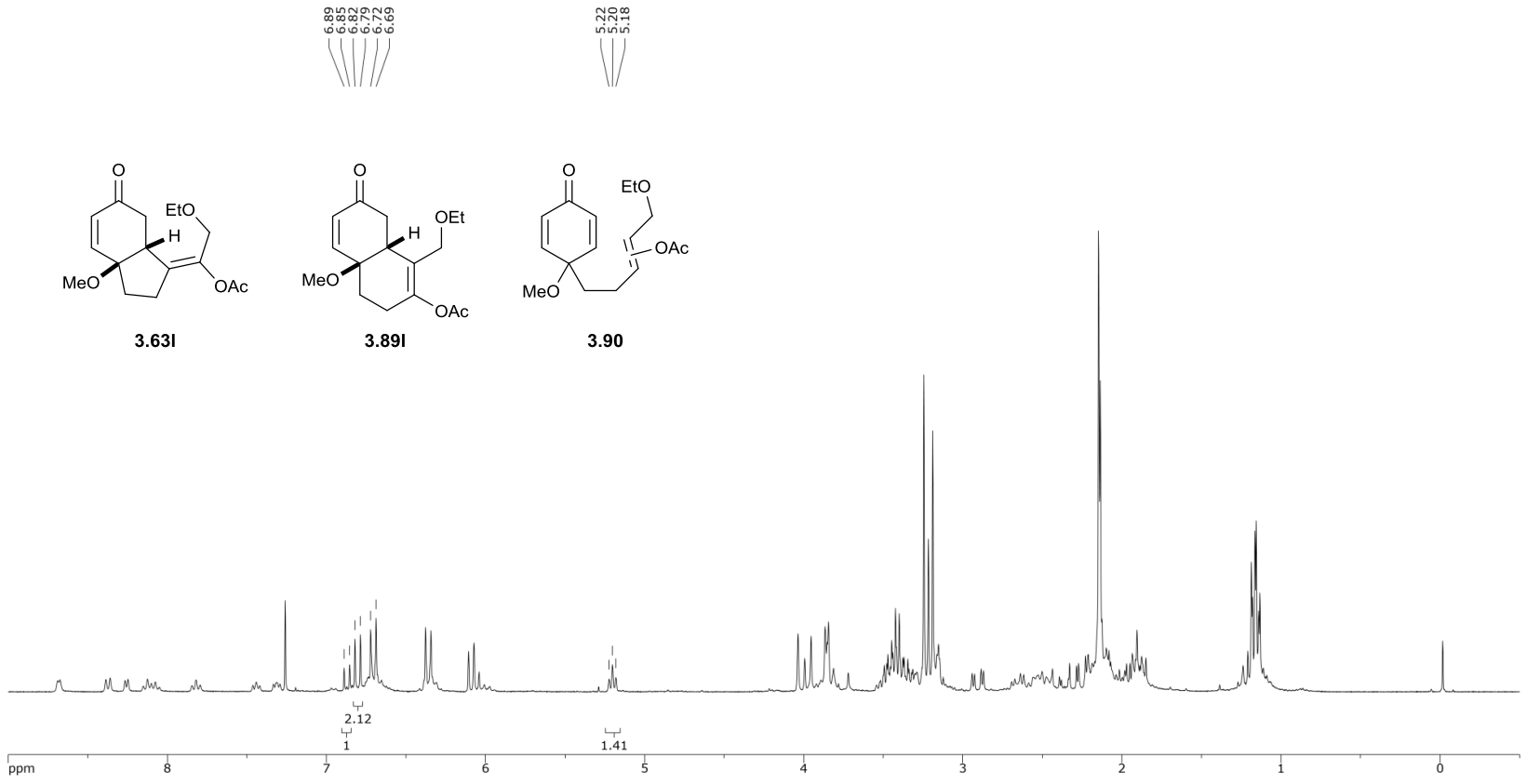
Bicyclic enone 3.63j – ^{13}C NMR



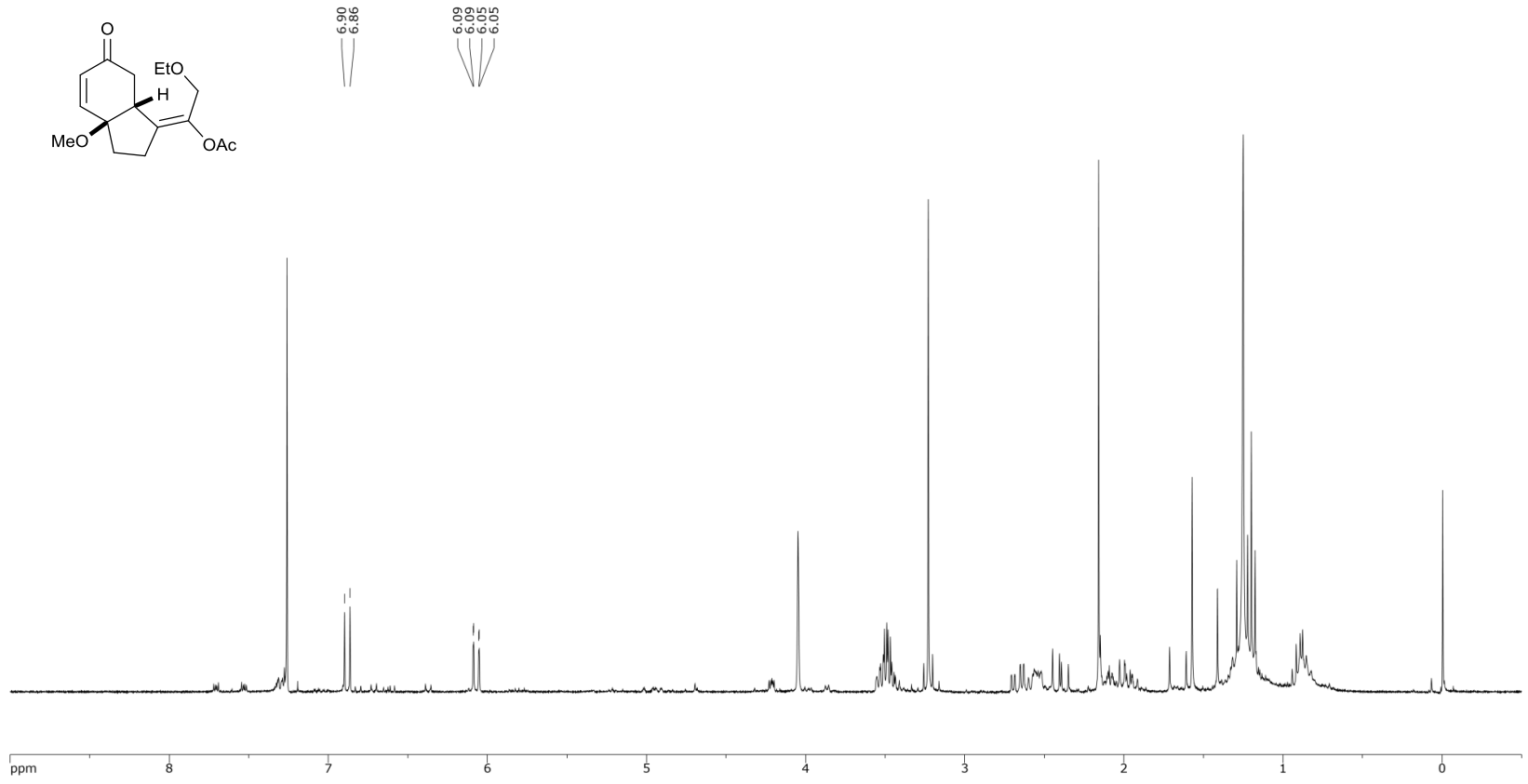
Bicyclic enones 3.63k and 3.89k – ^{1}H NMR



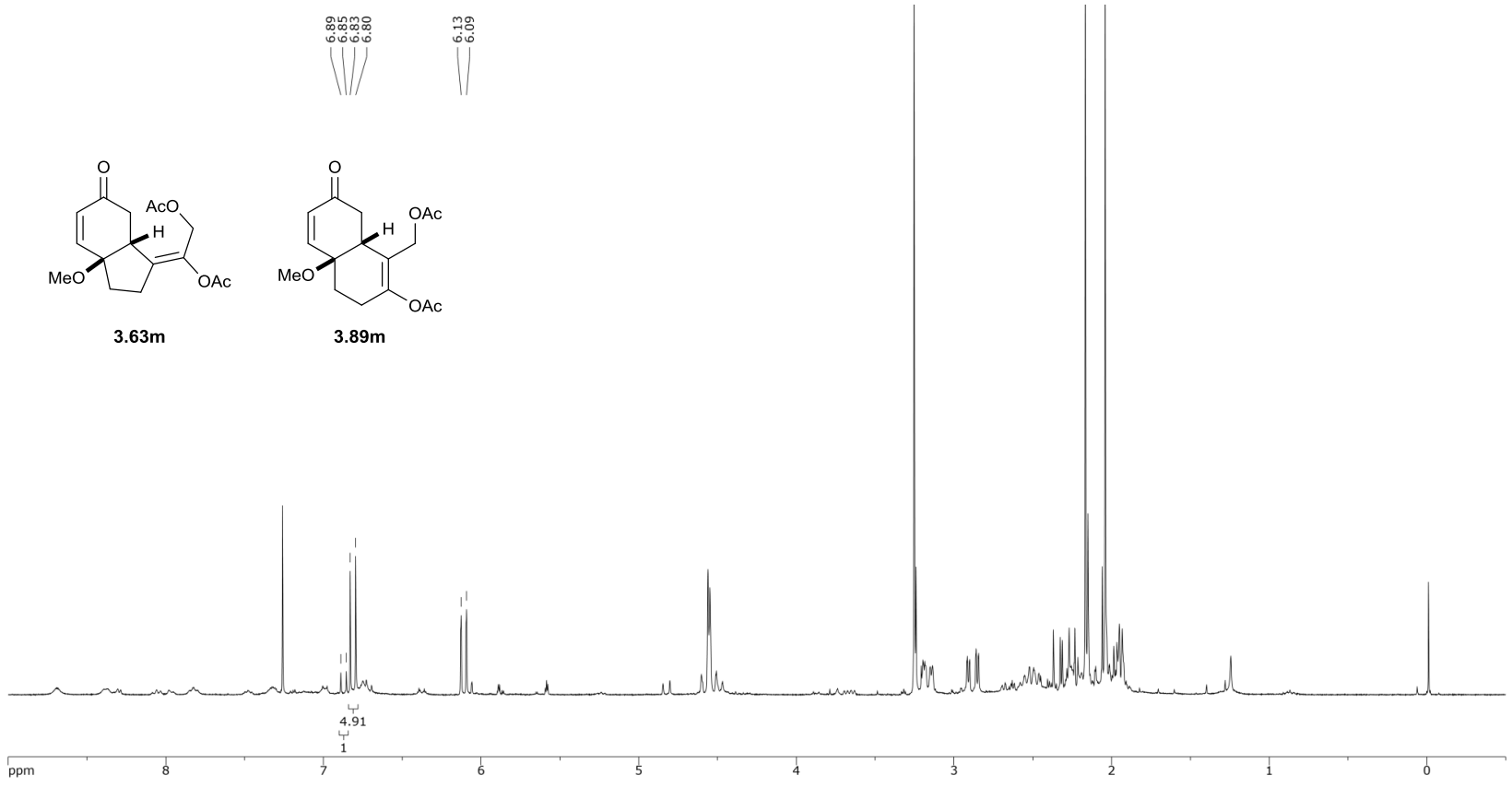
Bicyclic enones 3.63l and 3.89l, and vinyl acetate 3.90 – crude – ^{1}H NMR



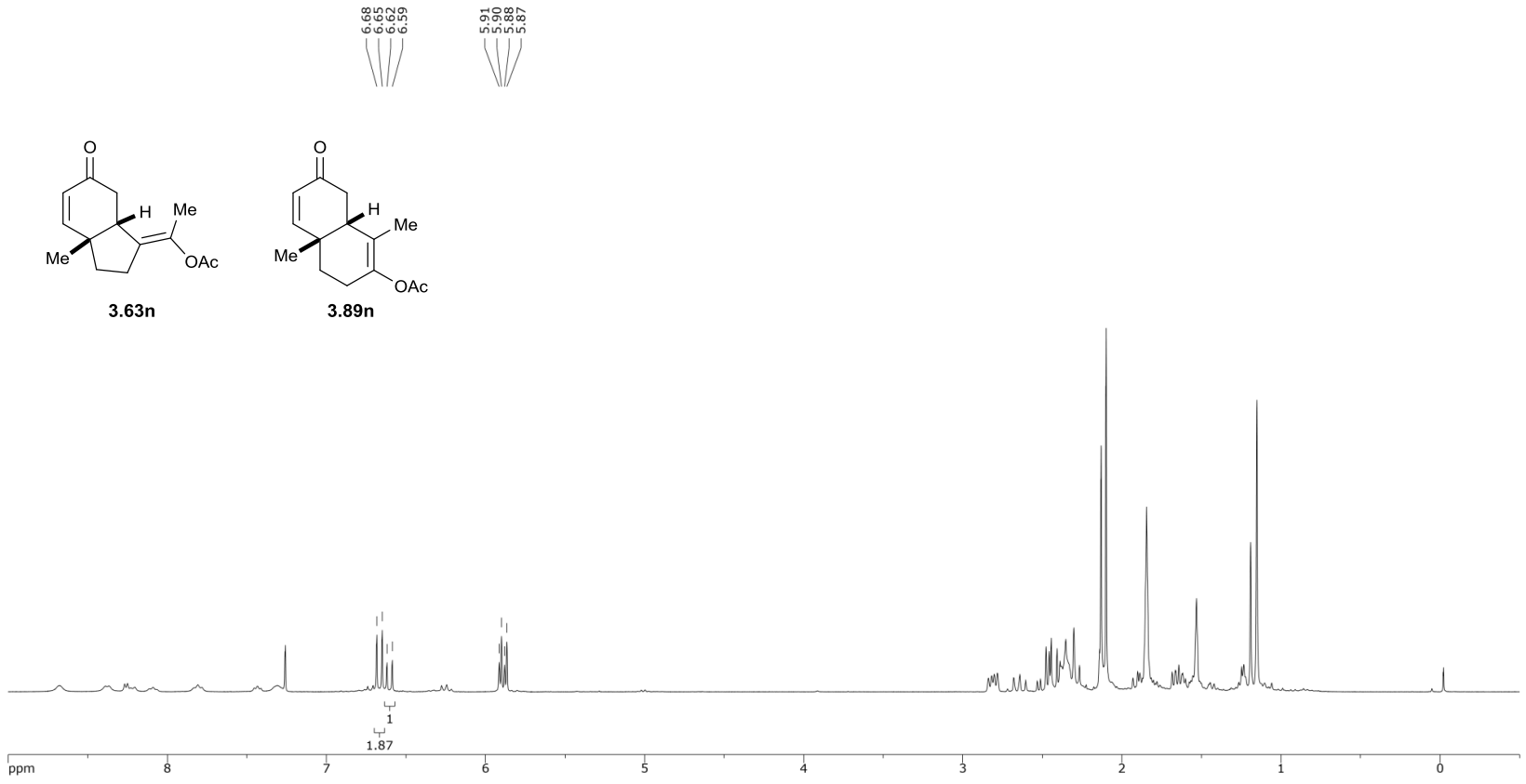
Bicyclic enone 3.63l –^{1}H NMR



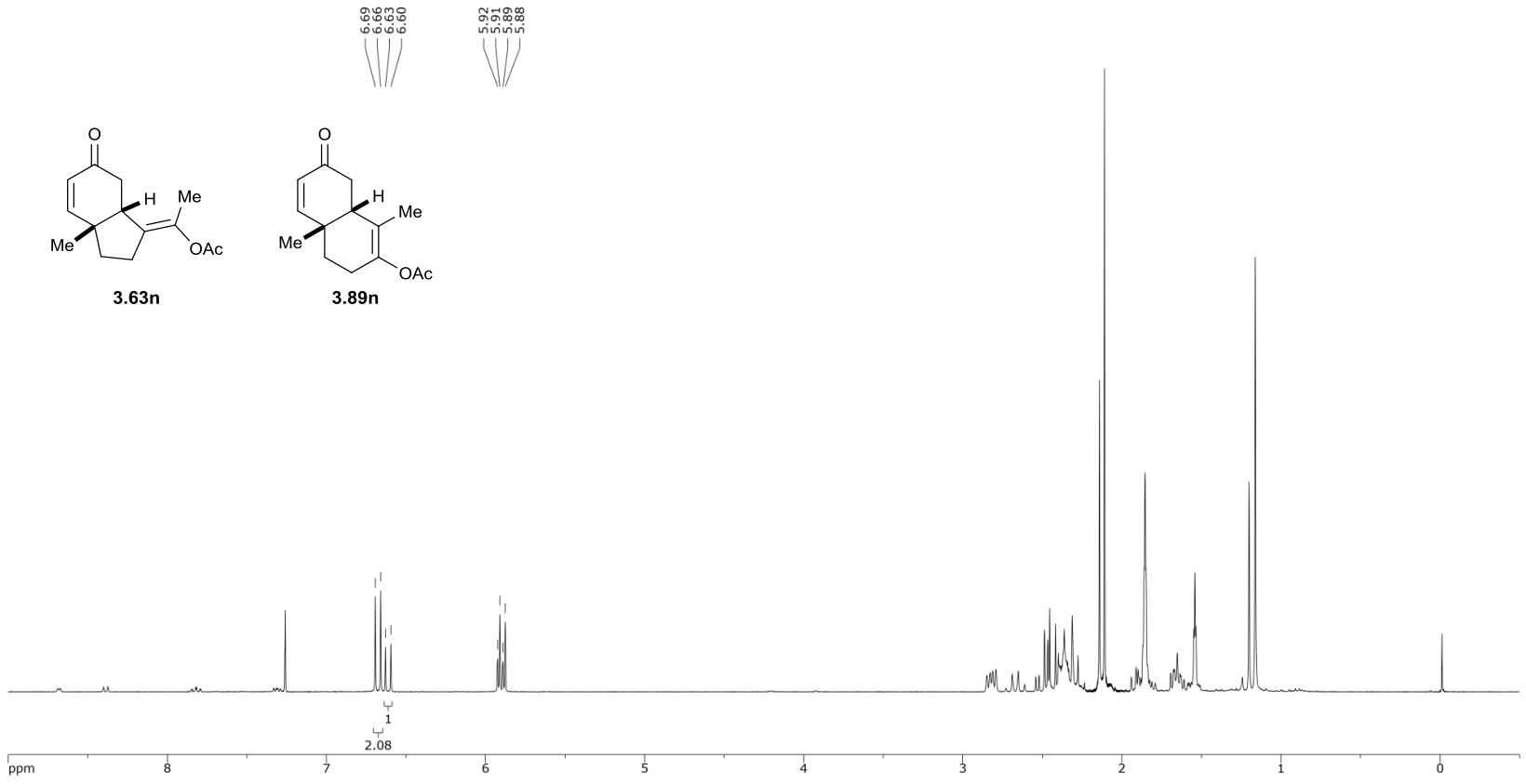
Bicyclic enones 3.63m and 3.89m – crude – ^{1}H NMR



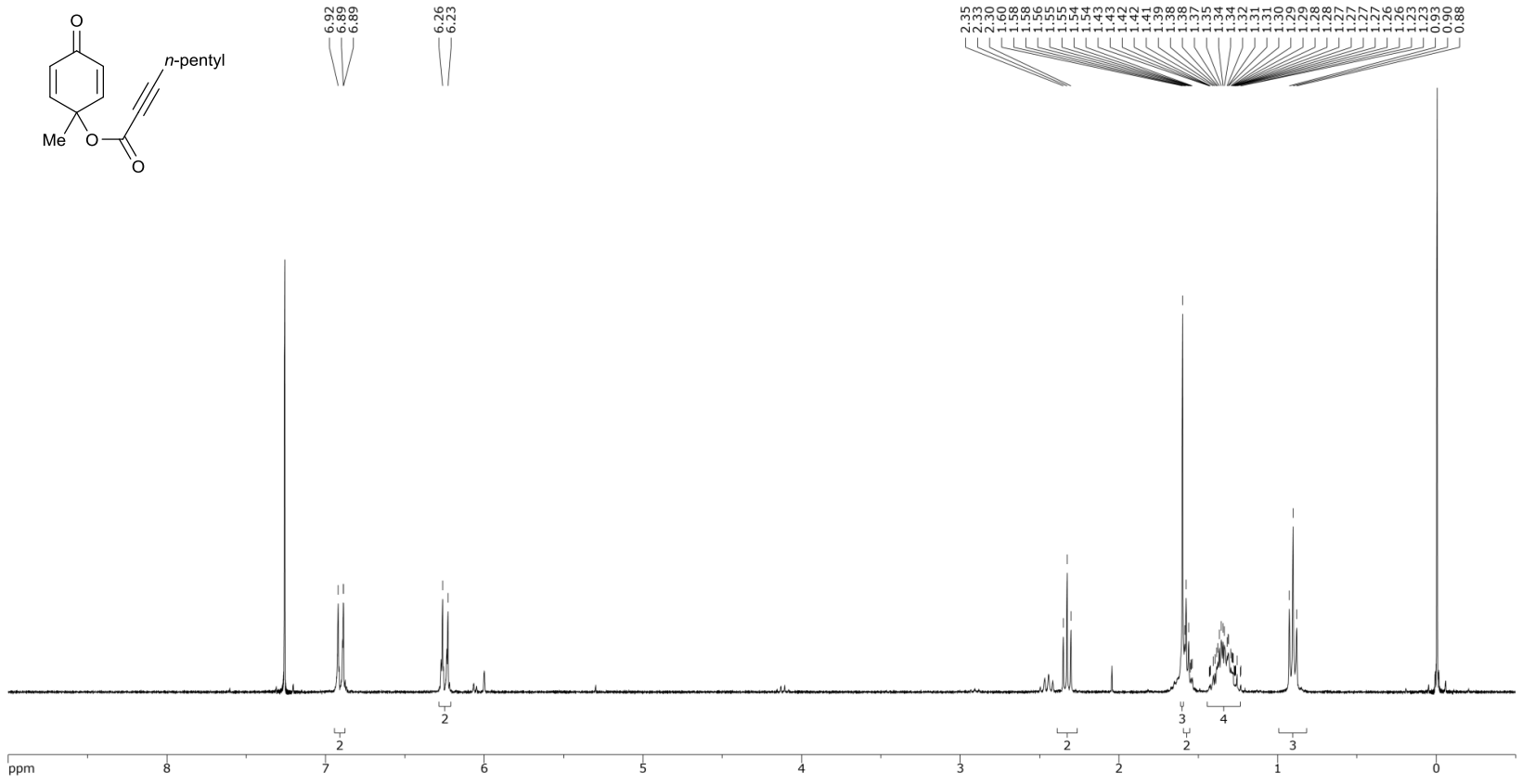
Bicyclic enones 3.63n and 3.89n – crude – ^{1}H NMR



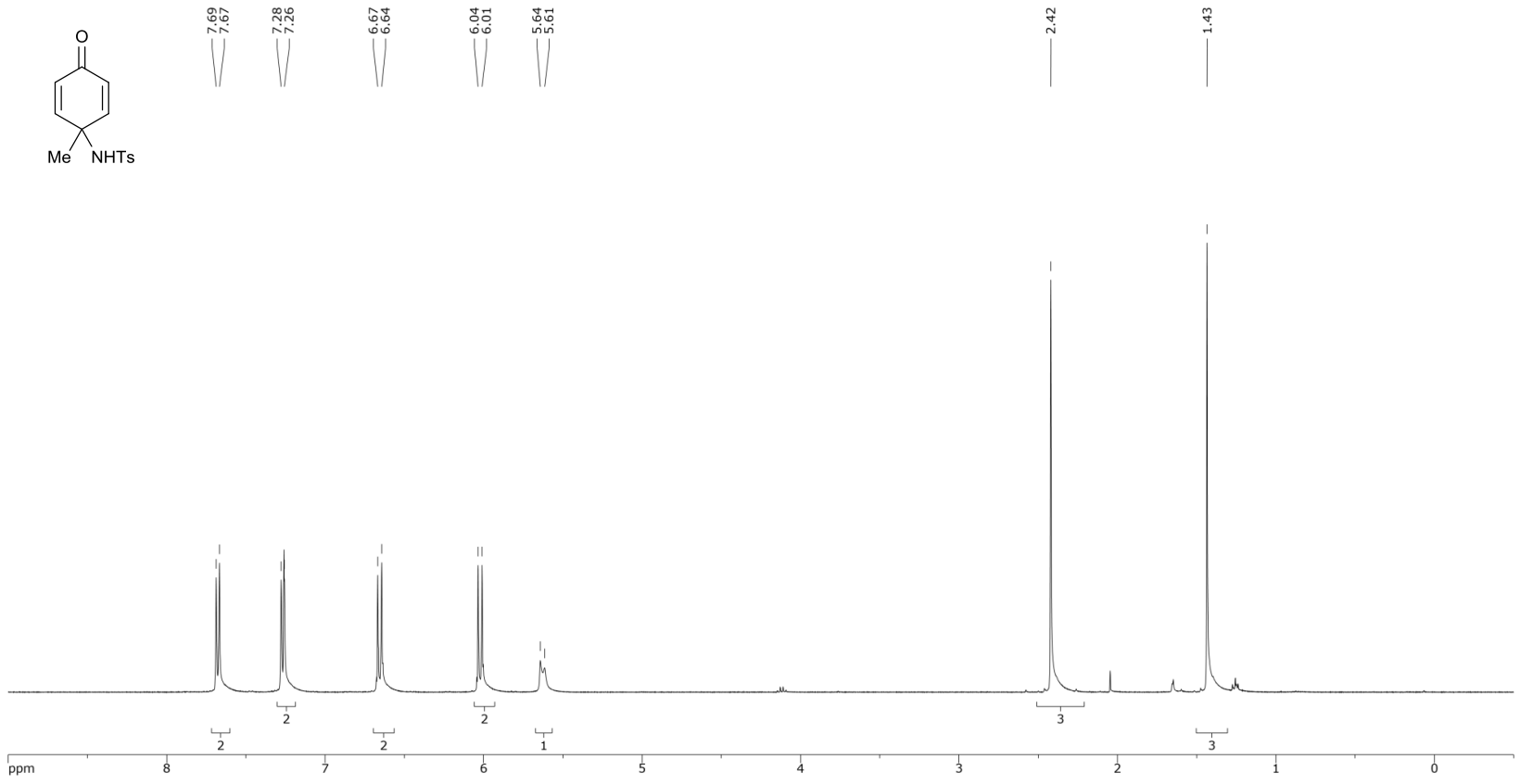
Bicyclic enones 3.63n and 3.89n – purified – ^{1}H NMR



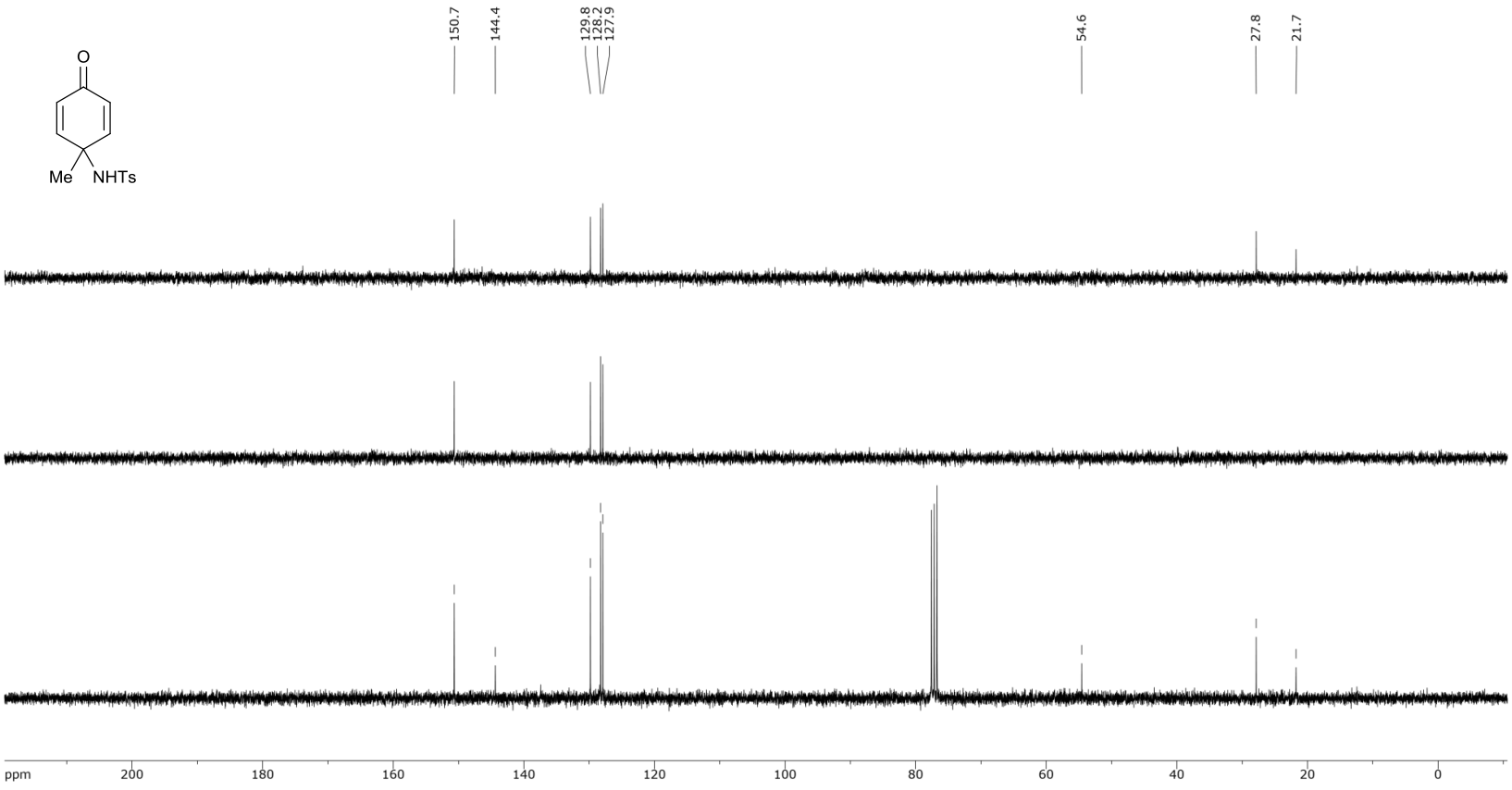
Alkynoate-tethered cyclohexadienone 3.67 – ^{1}H NMR



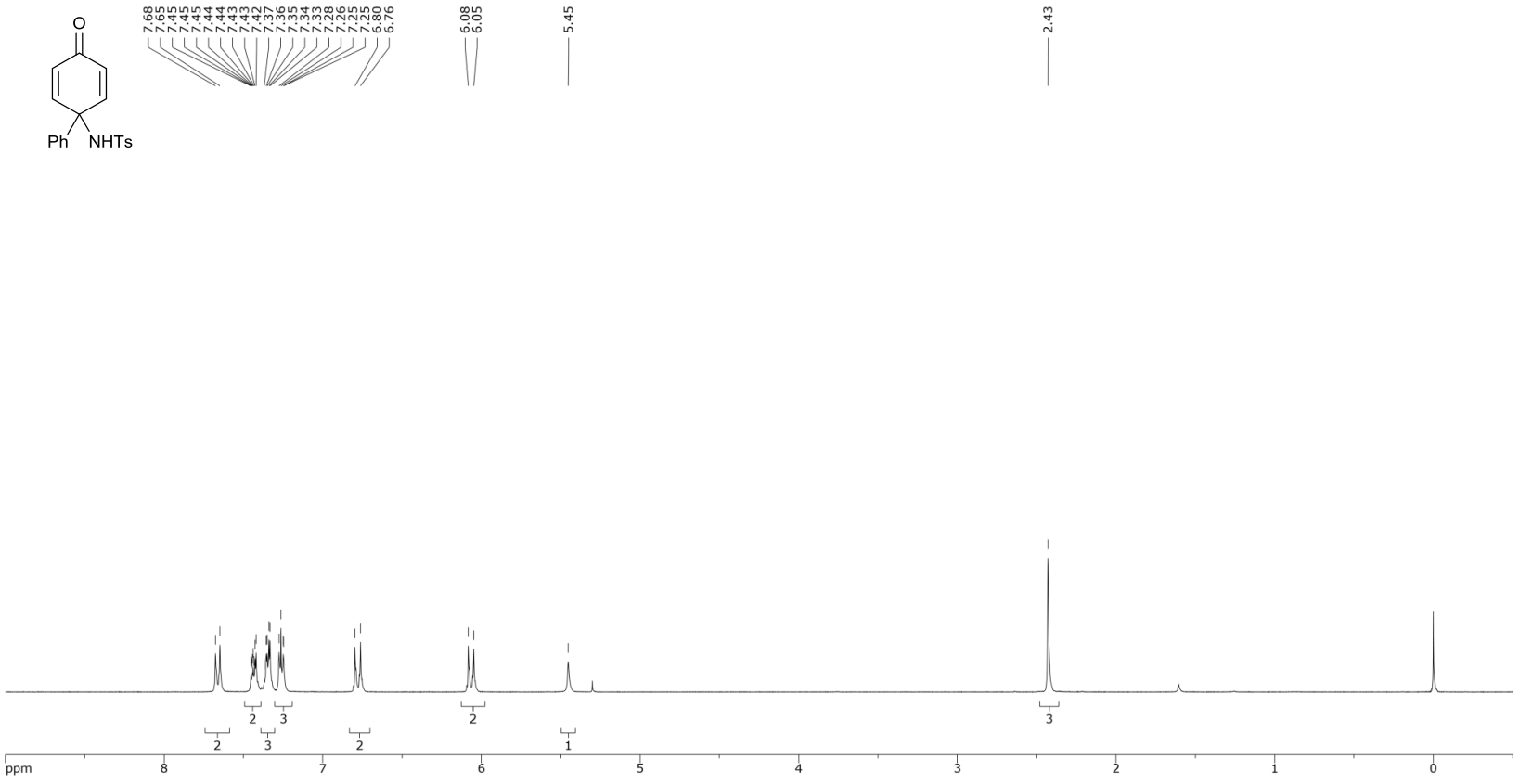
Cyclohexadienone 3.70i – ^{1}H NMR



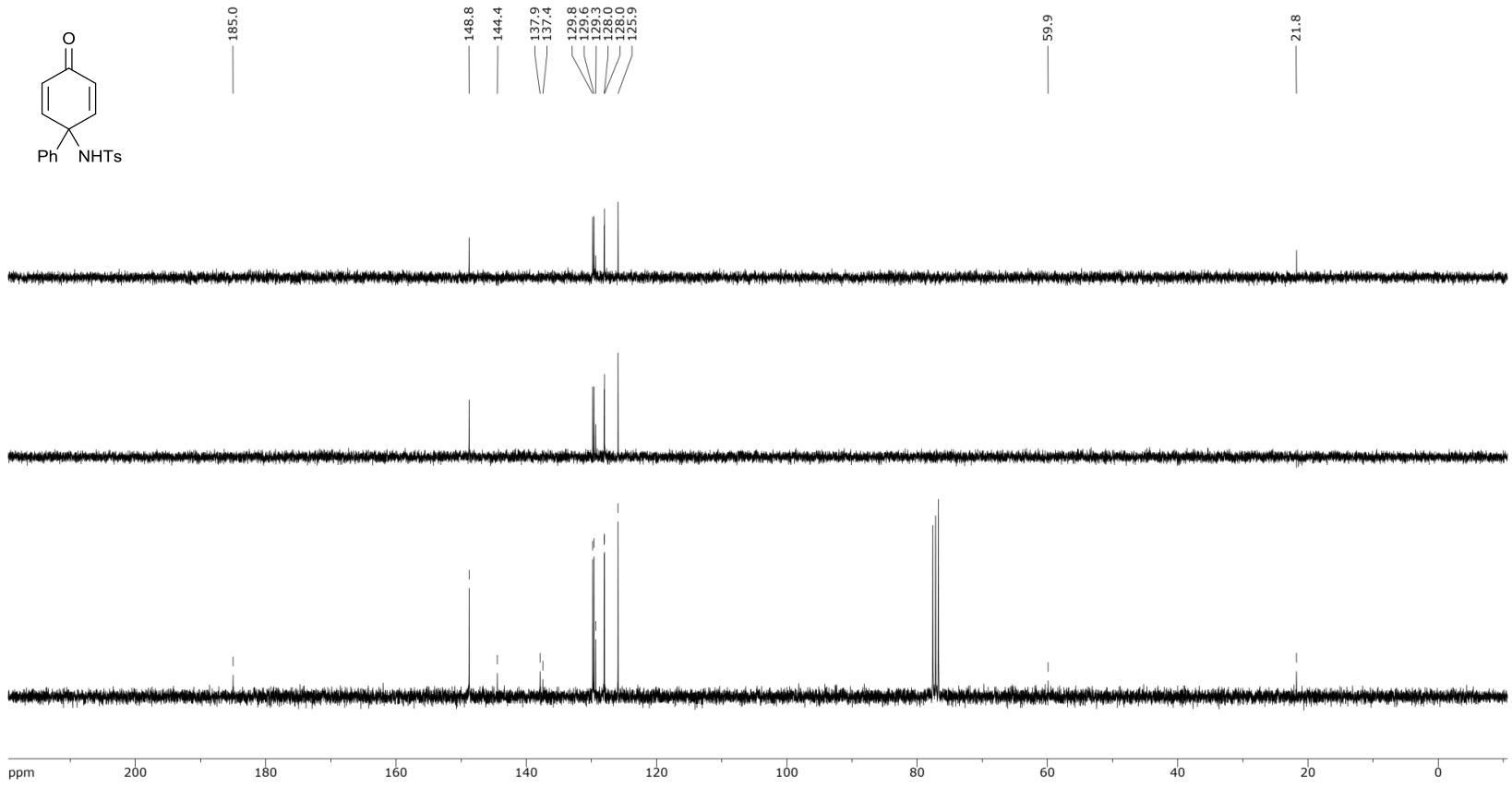
Cyclohexadienone 3.70i – ^{13}C NMR



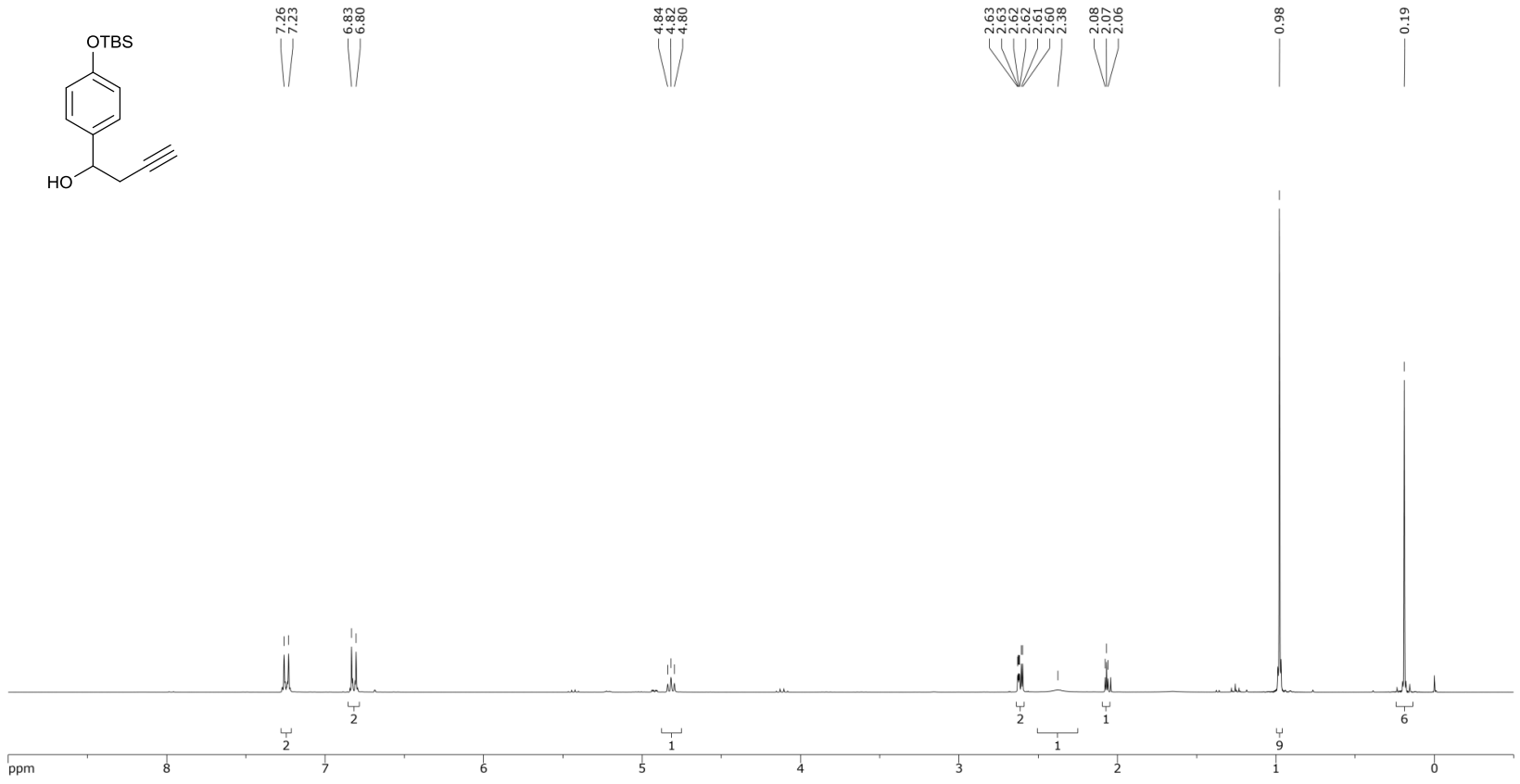
Cyclohexadienone 3.70j – ^{1}H NMR



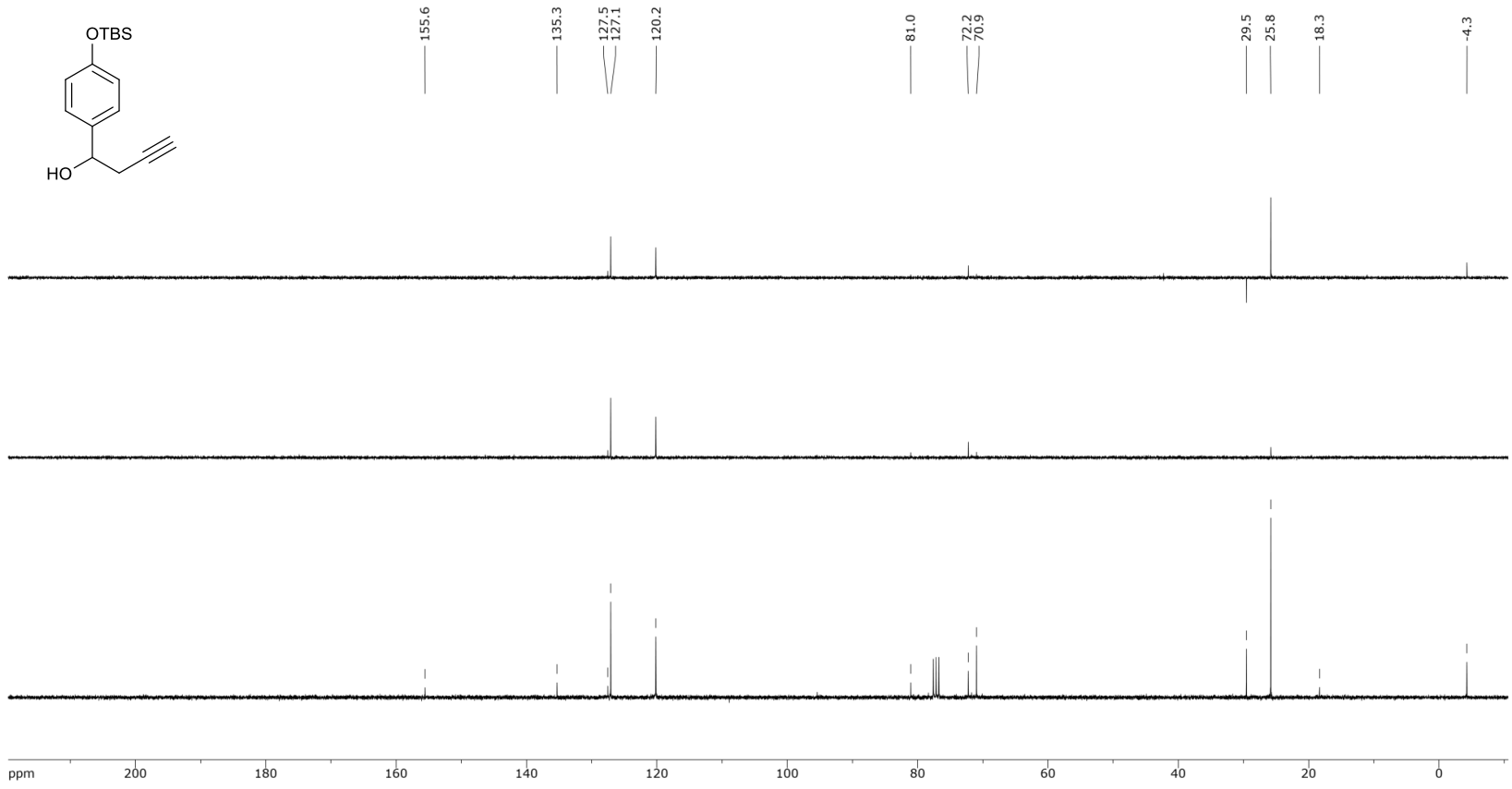
Cyclohexadienone 3.70j – ^{13}C NMR



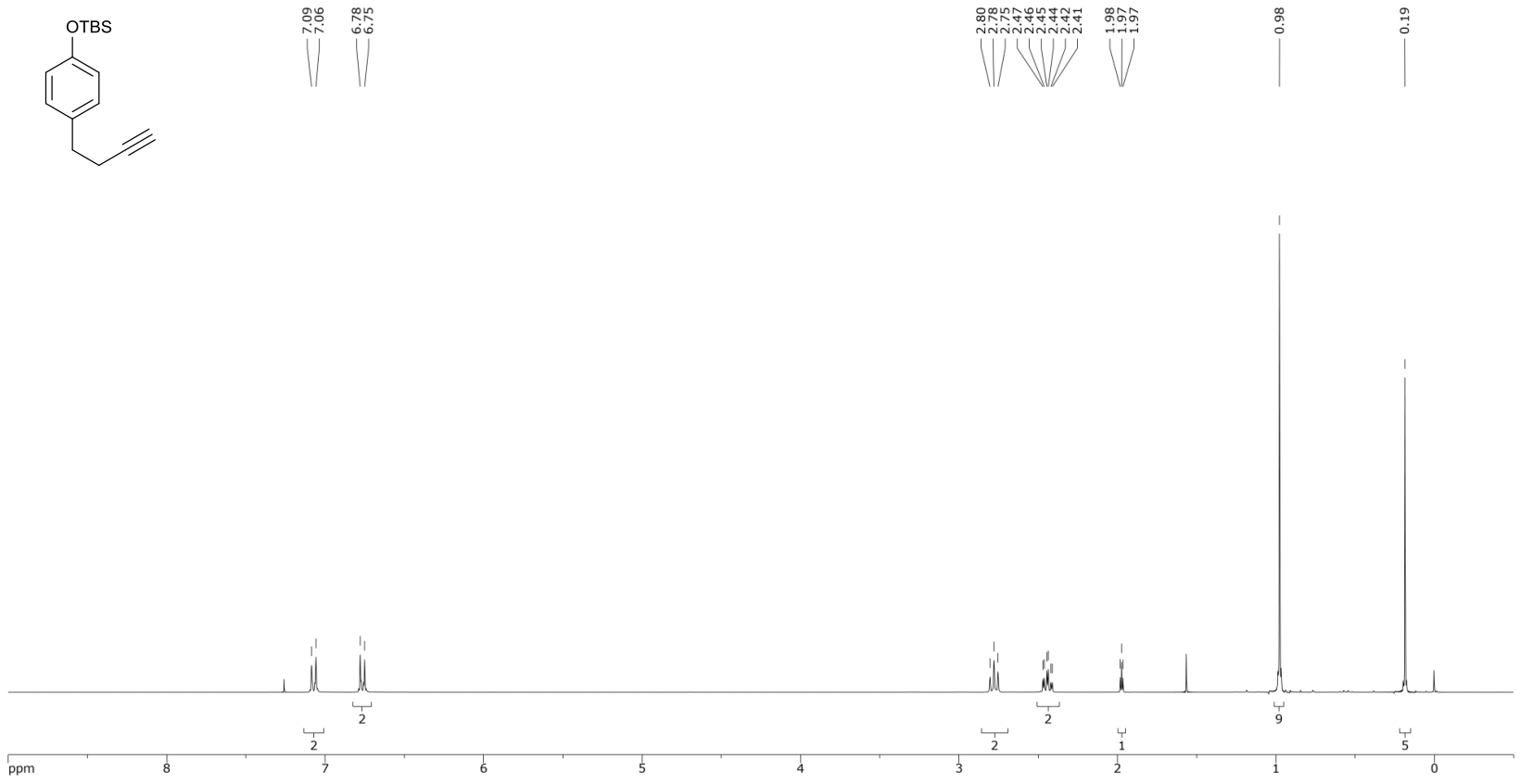
Benzyl alcohol 3.71 – ^{1}H NMR



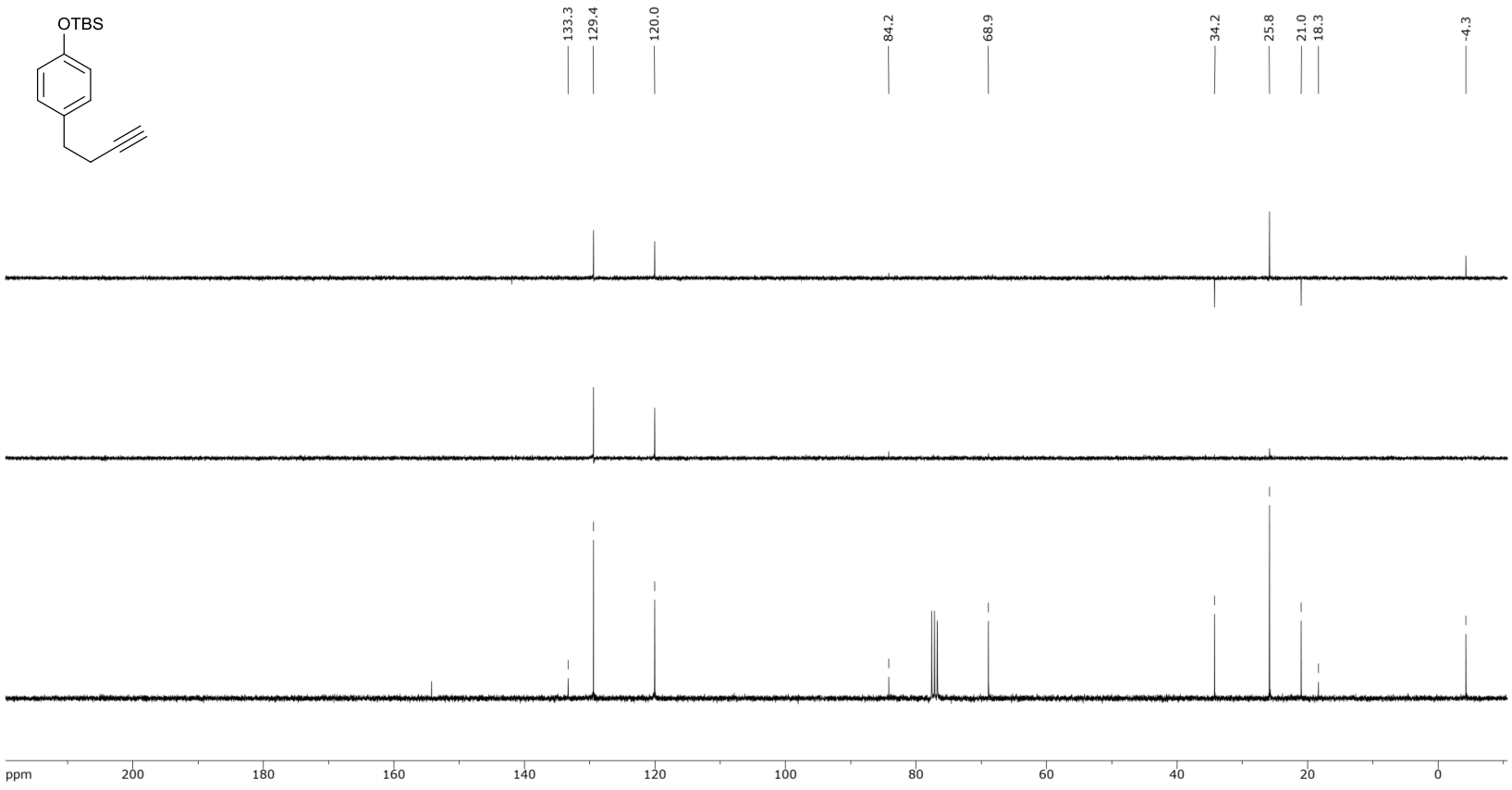
Benzyl alcohol 3.71 – ^{13}C NMR



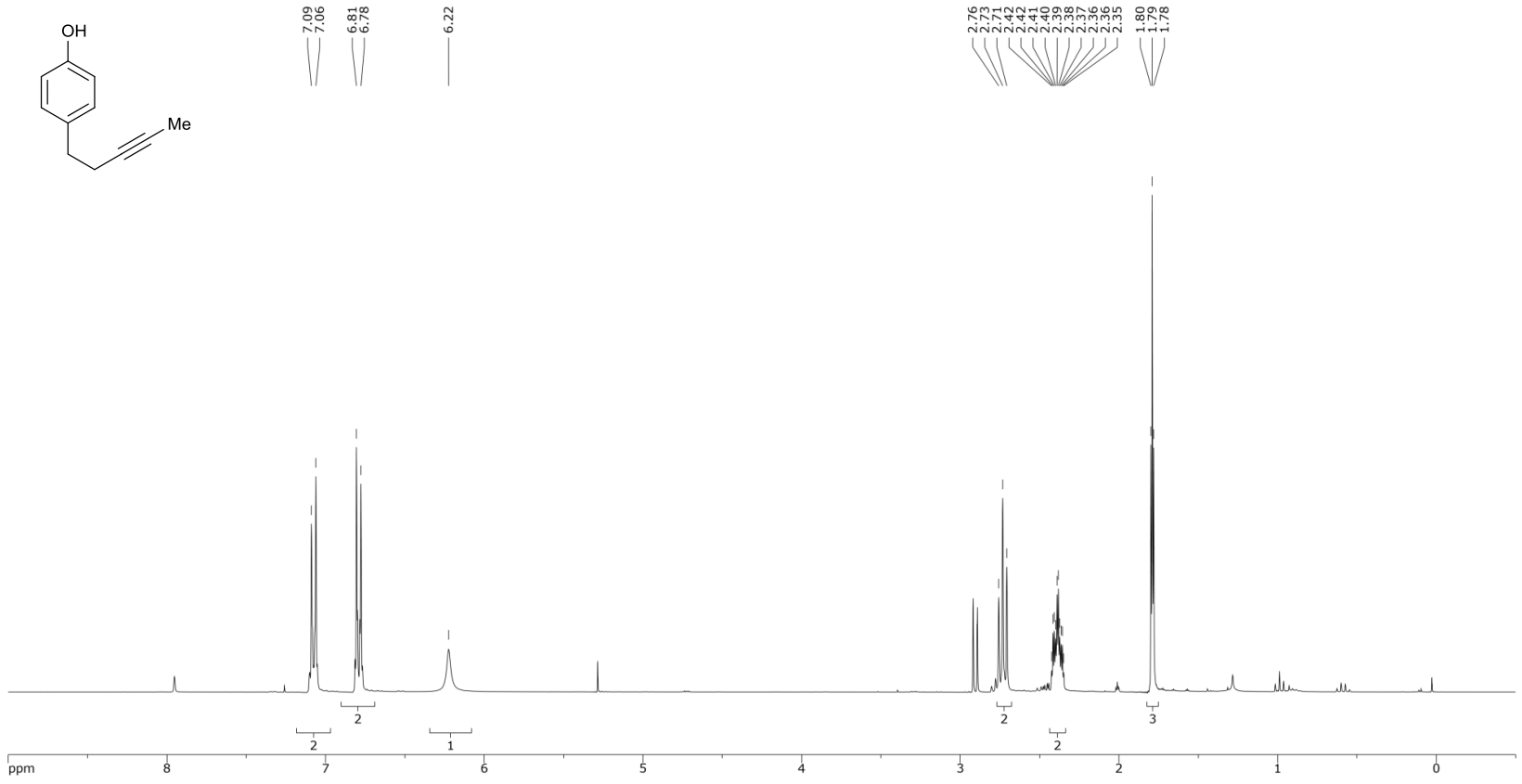
Alkyne 3.72 – ^{1}H NMR



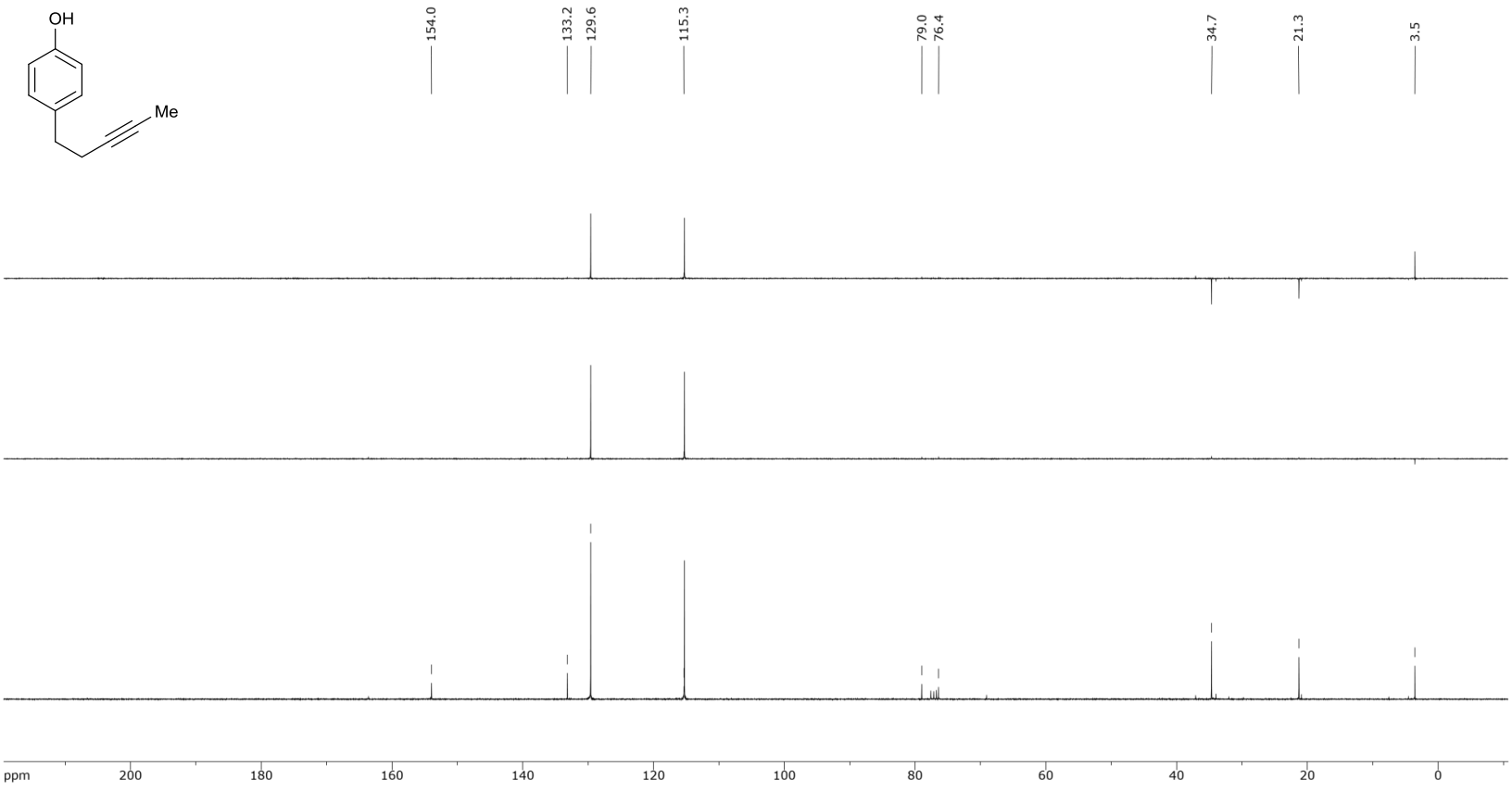
Alkyne 3.72 – ^{13}C NMR



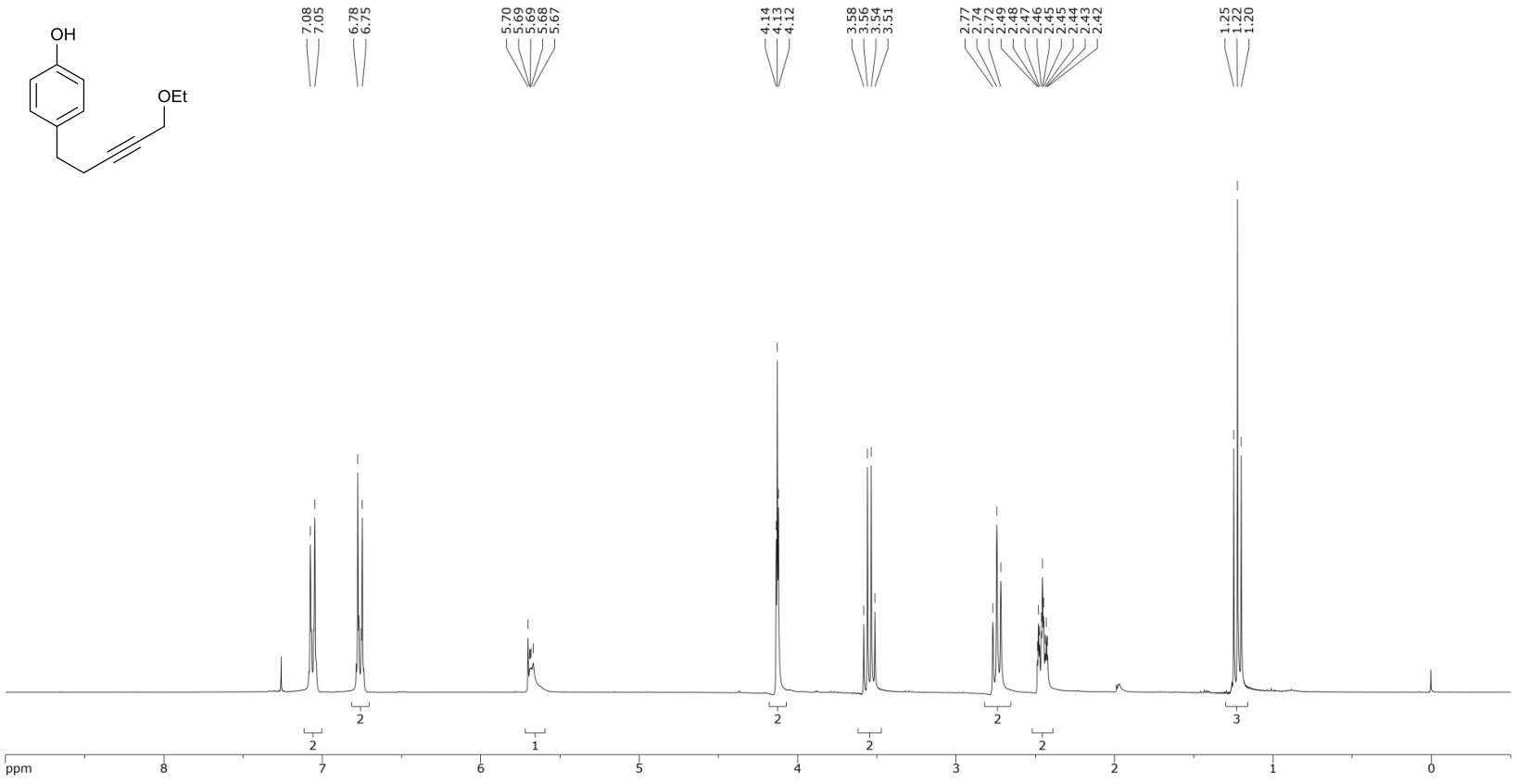
Phenol 3.73k – ^{1}H NMR



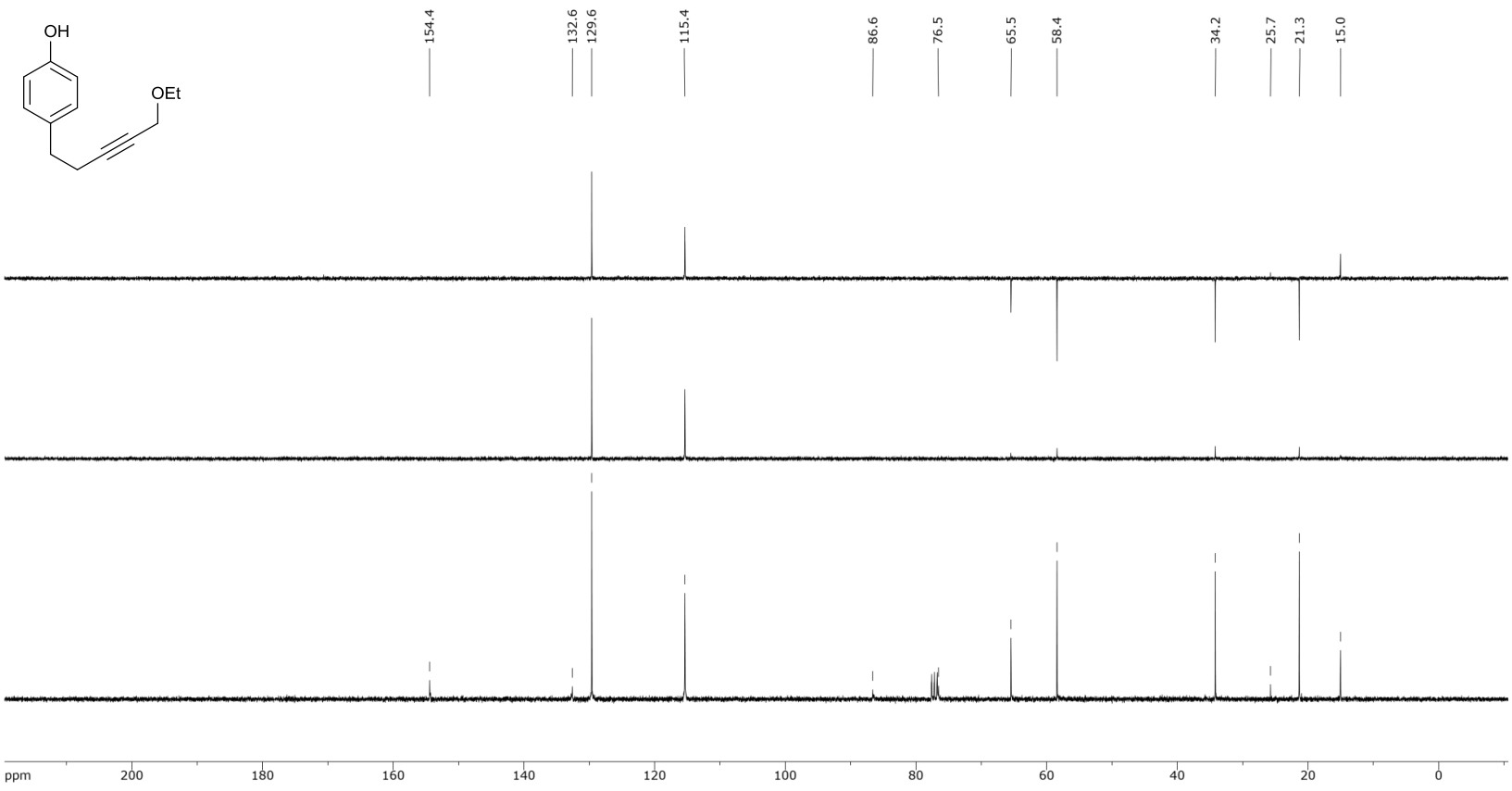
Phenol 3.73k – ^{13}C NMR



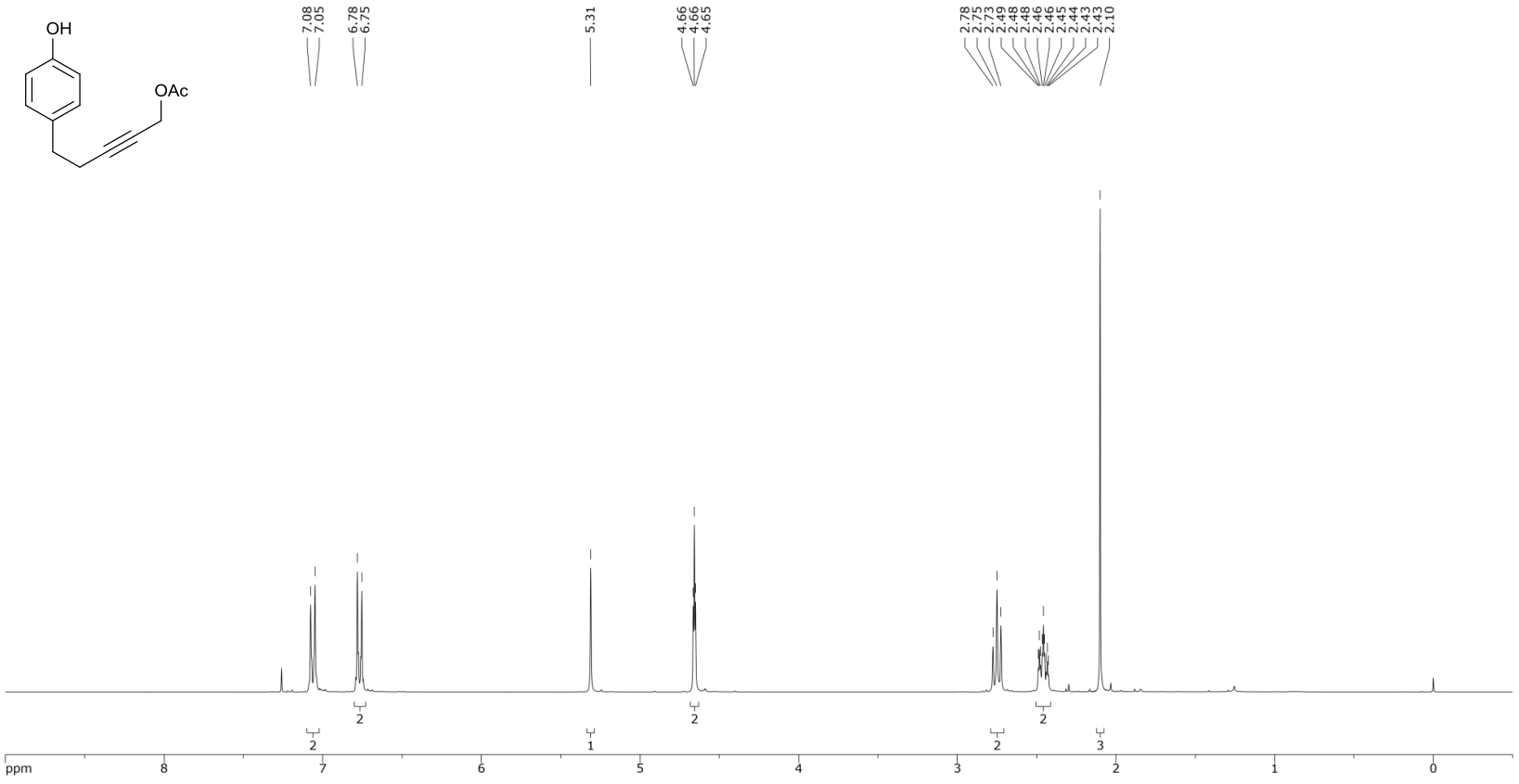
Phenol 3.73l – ^{1}H NMR



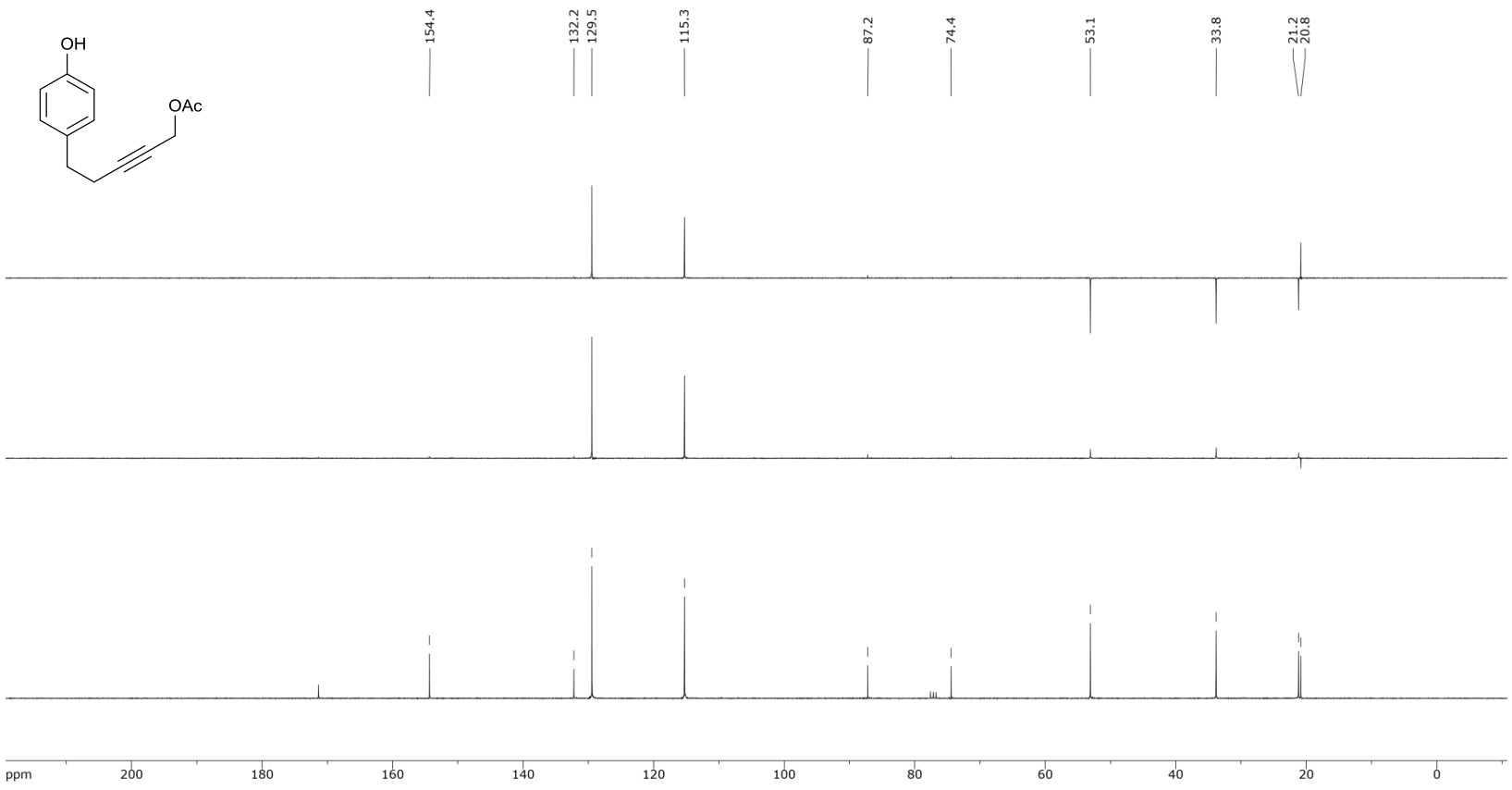
Phenol 3.73l – ^{13}C NMR



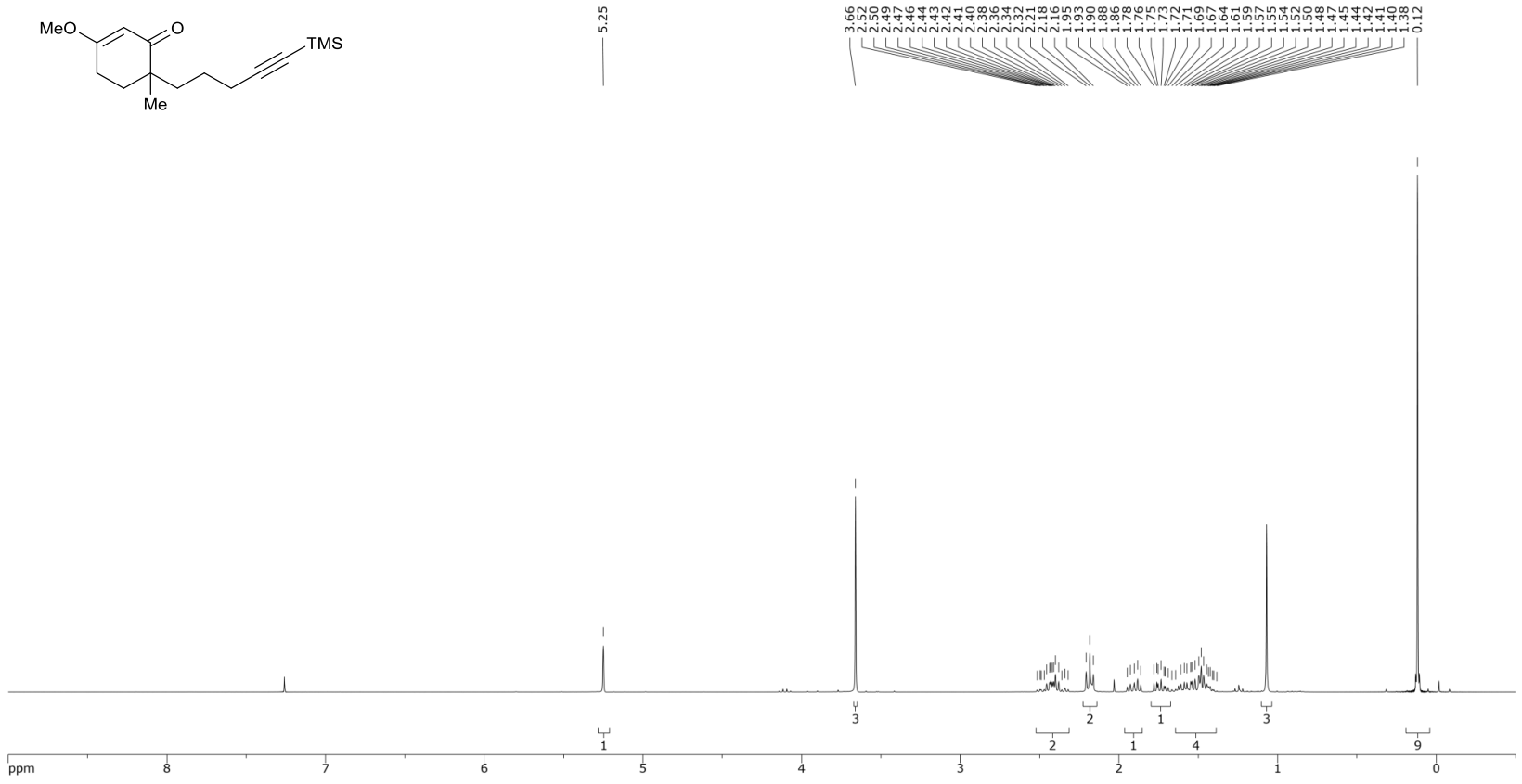
Phenol 3.73m – ^{1}H NMR



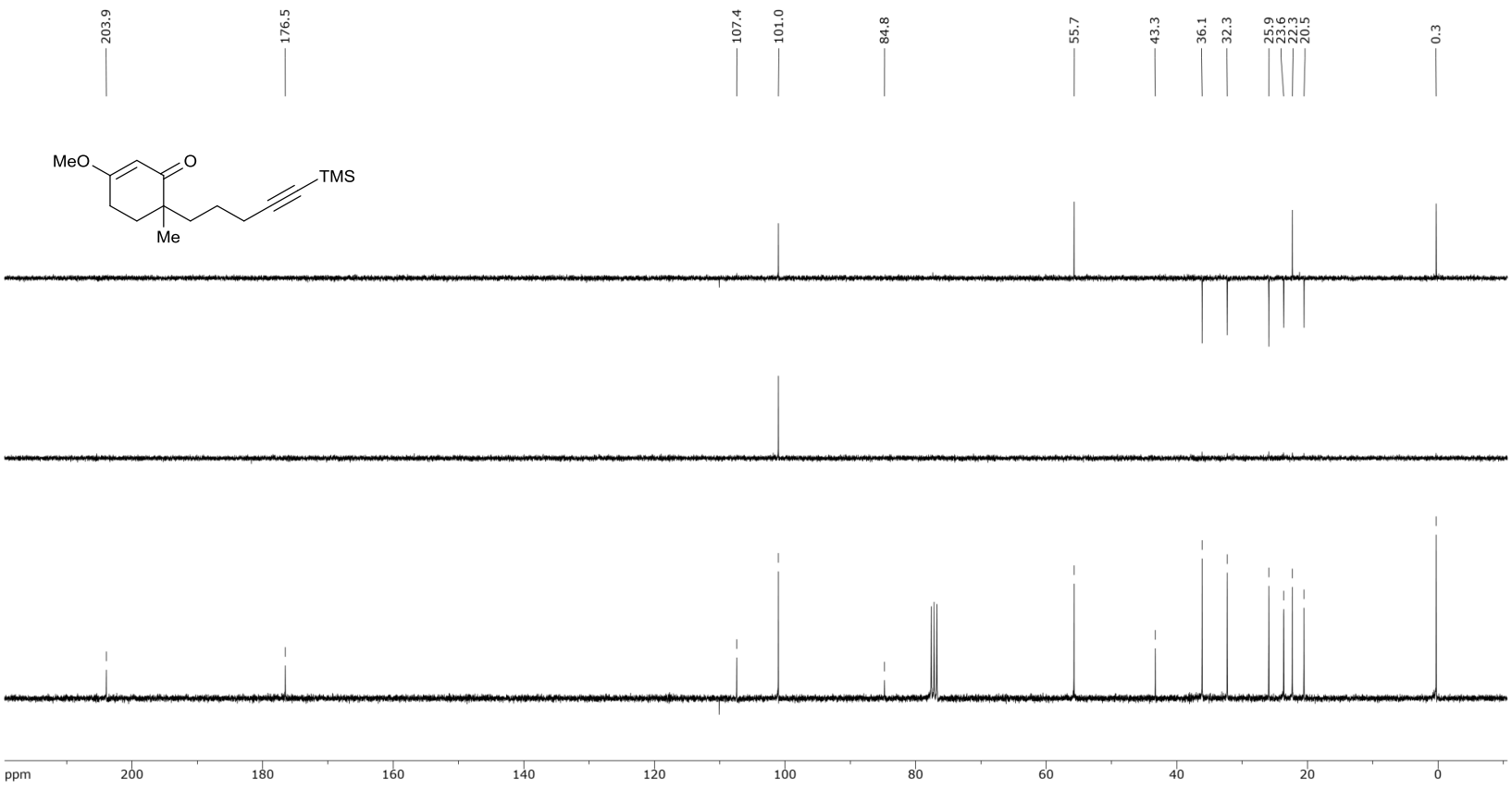
Phenol 3.73m – ^{13}C NMR



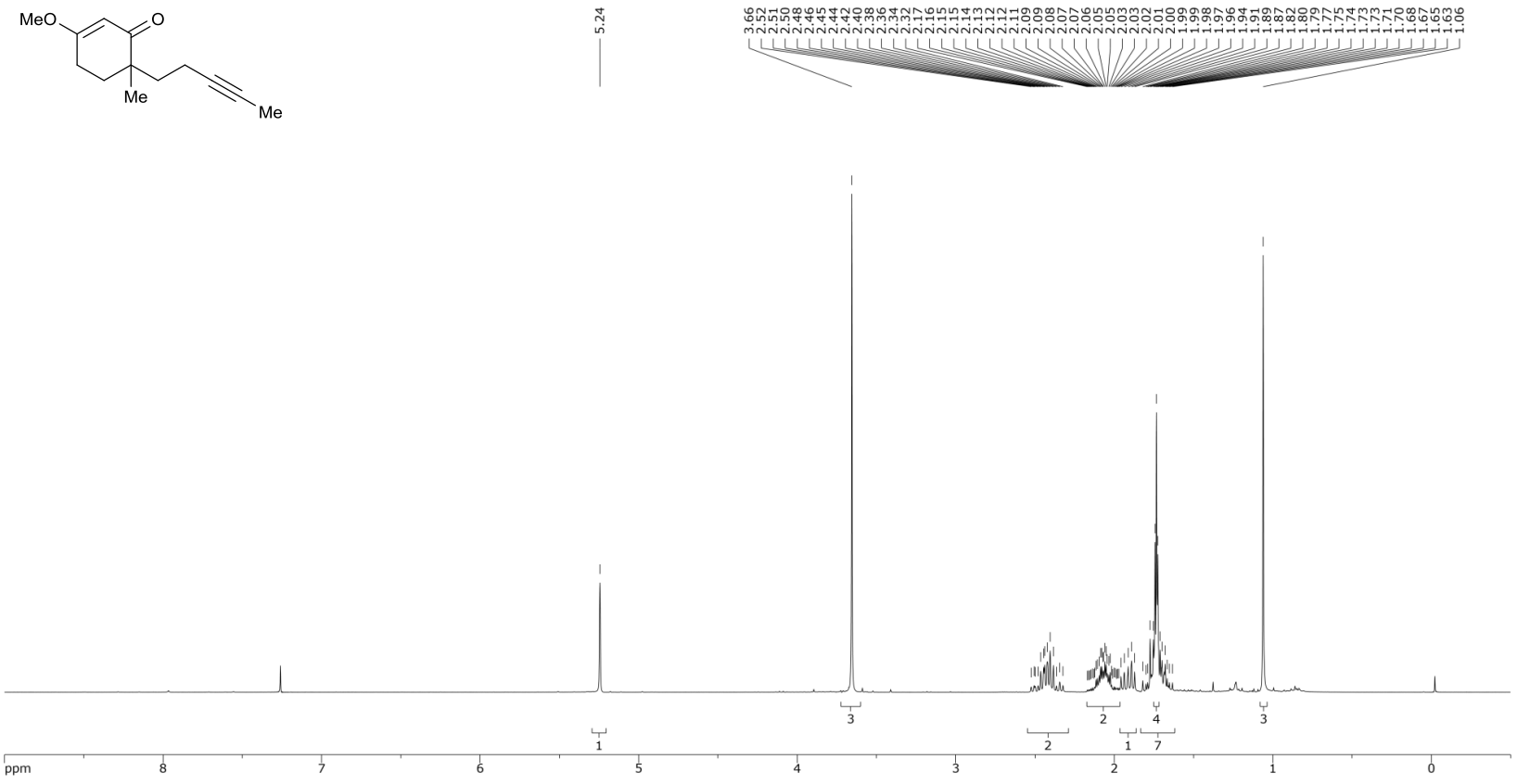
TMS alkyne 3.76 – ^{1}H NMR



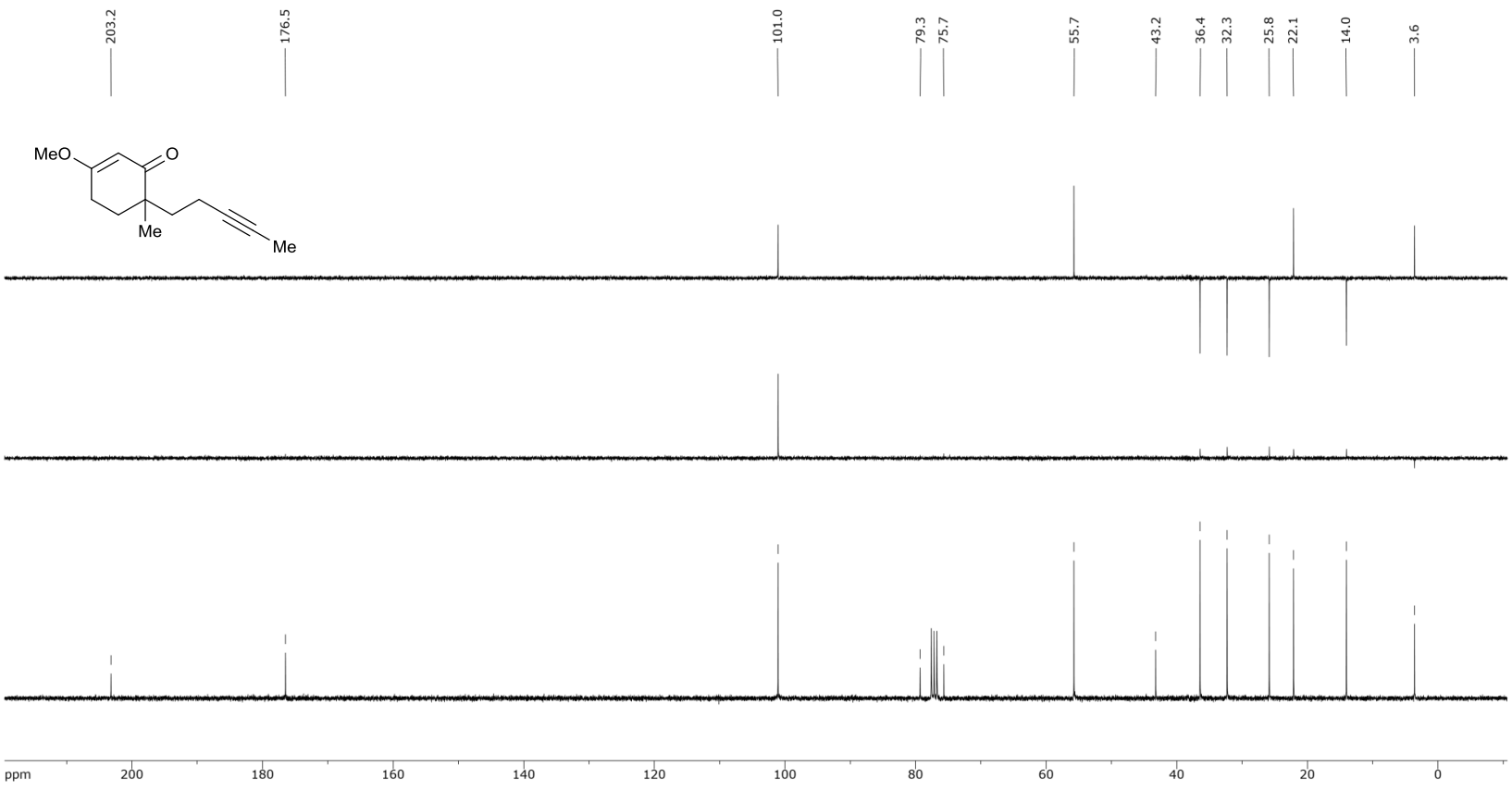
TMS alkyne 3.76 – ^{13}C NMR



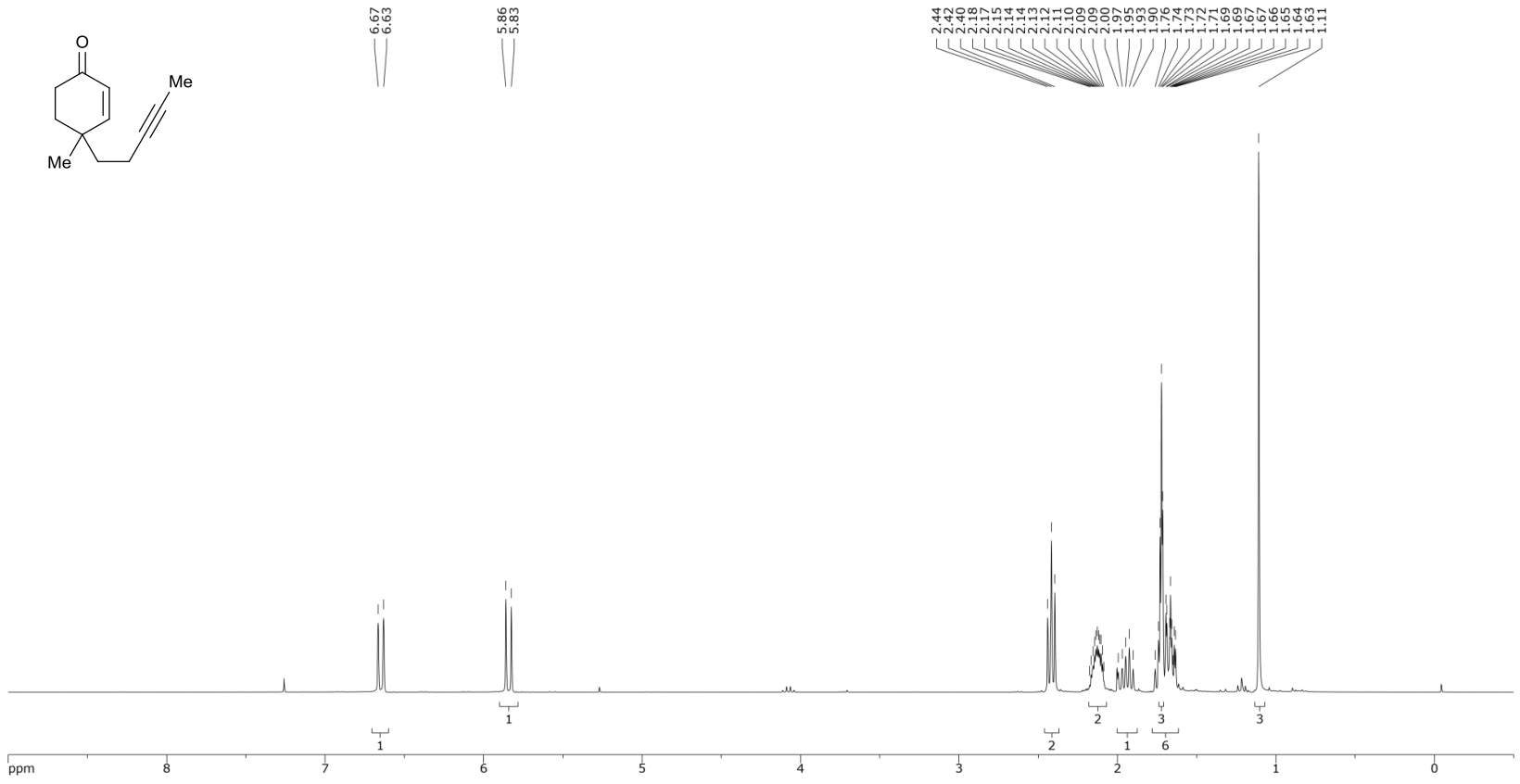
Internal alkyne 3.77 – ^{1}H NMR



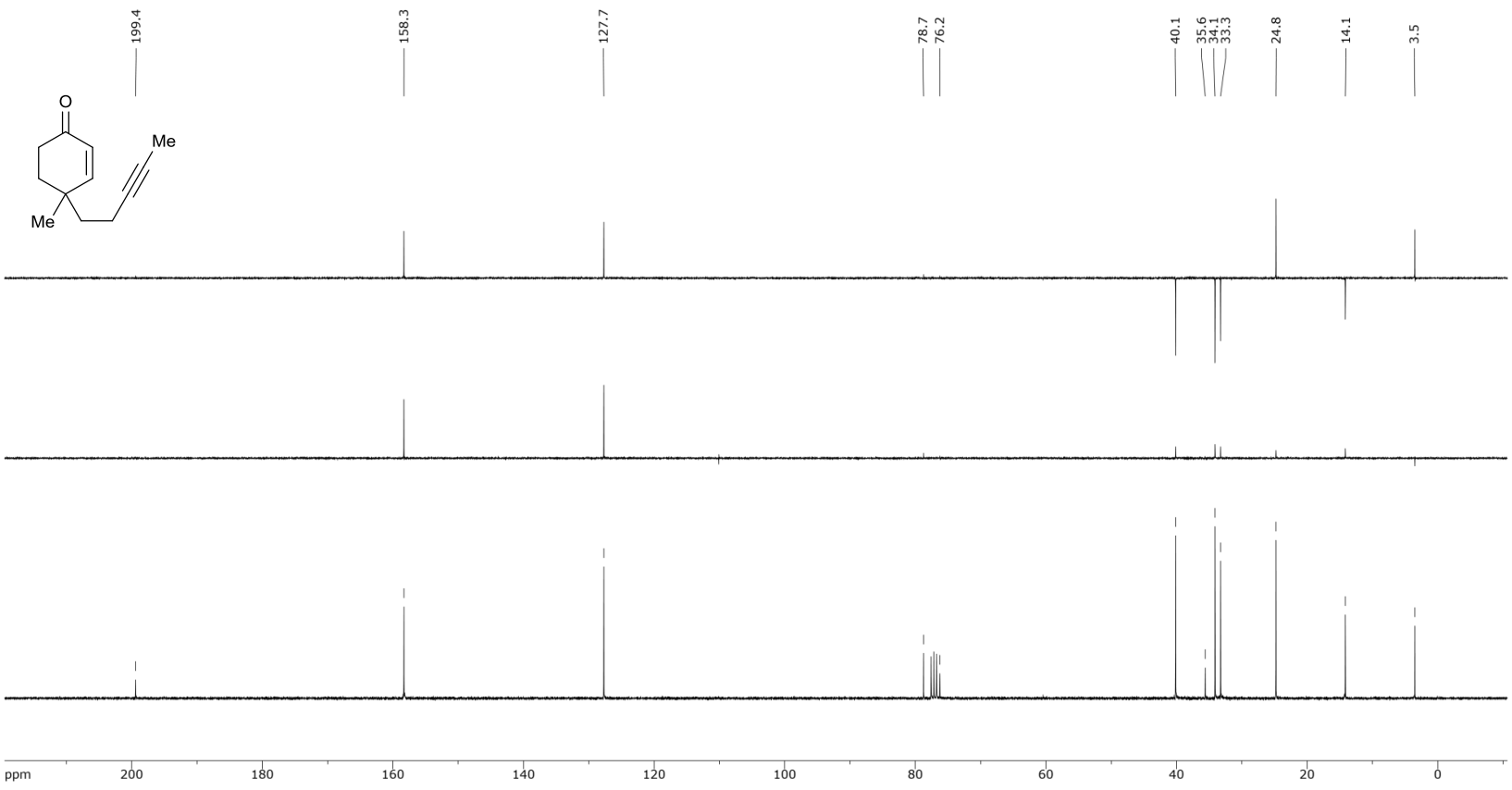
Internal alkyne 3.77 – ^{13}C NMR



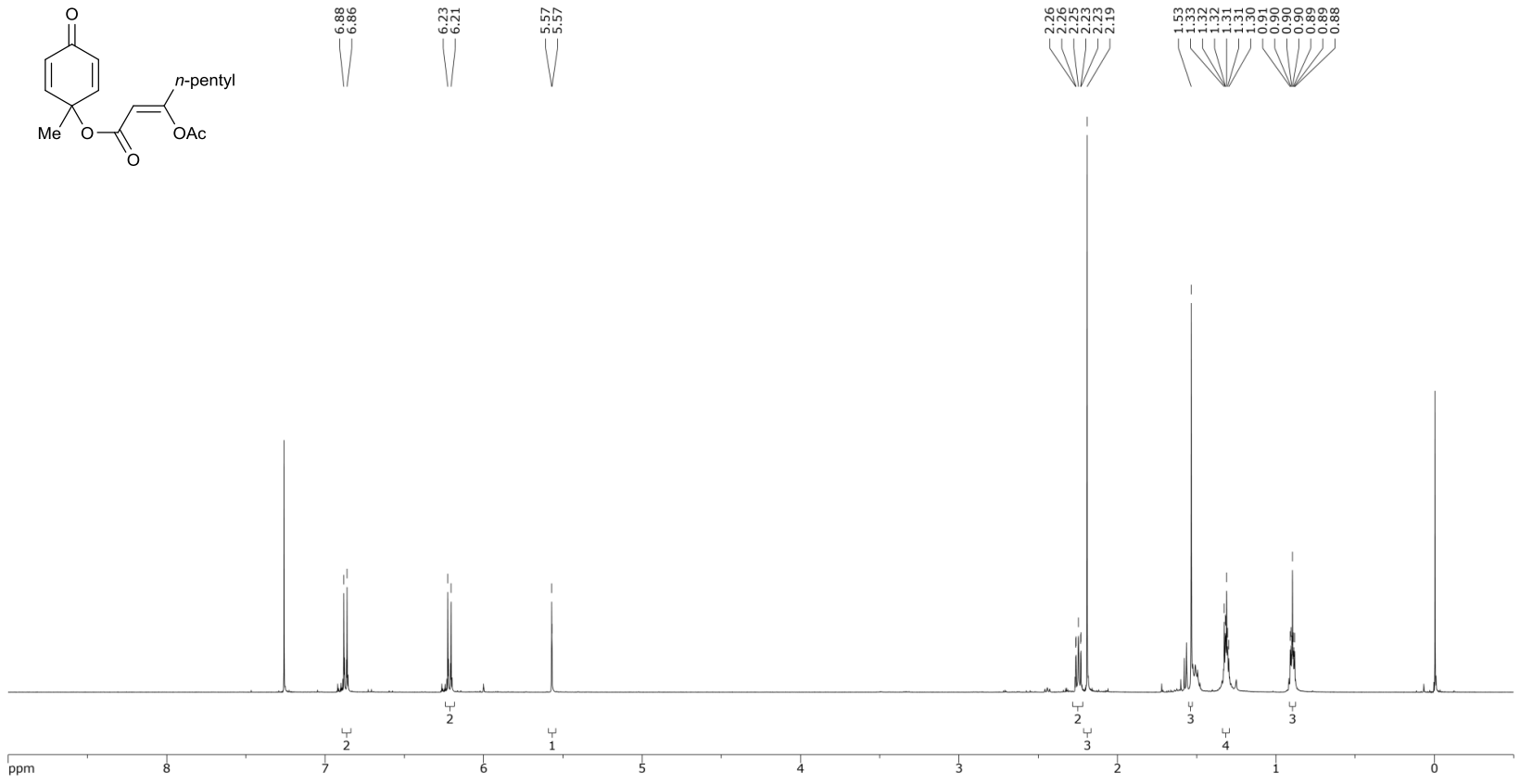
Enone 3.78 – ^{1}H NMR



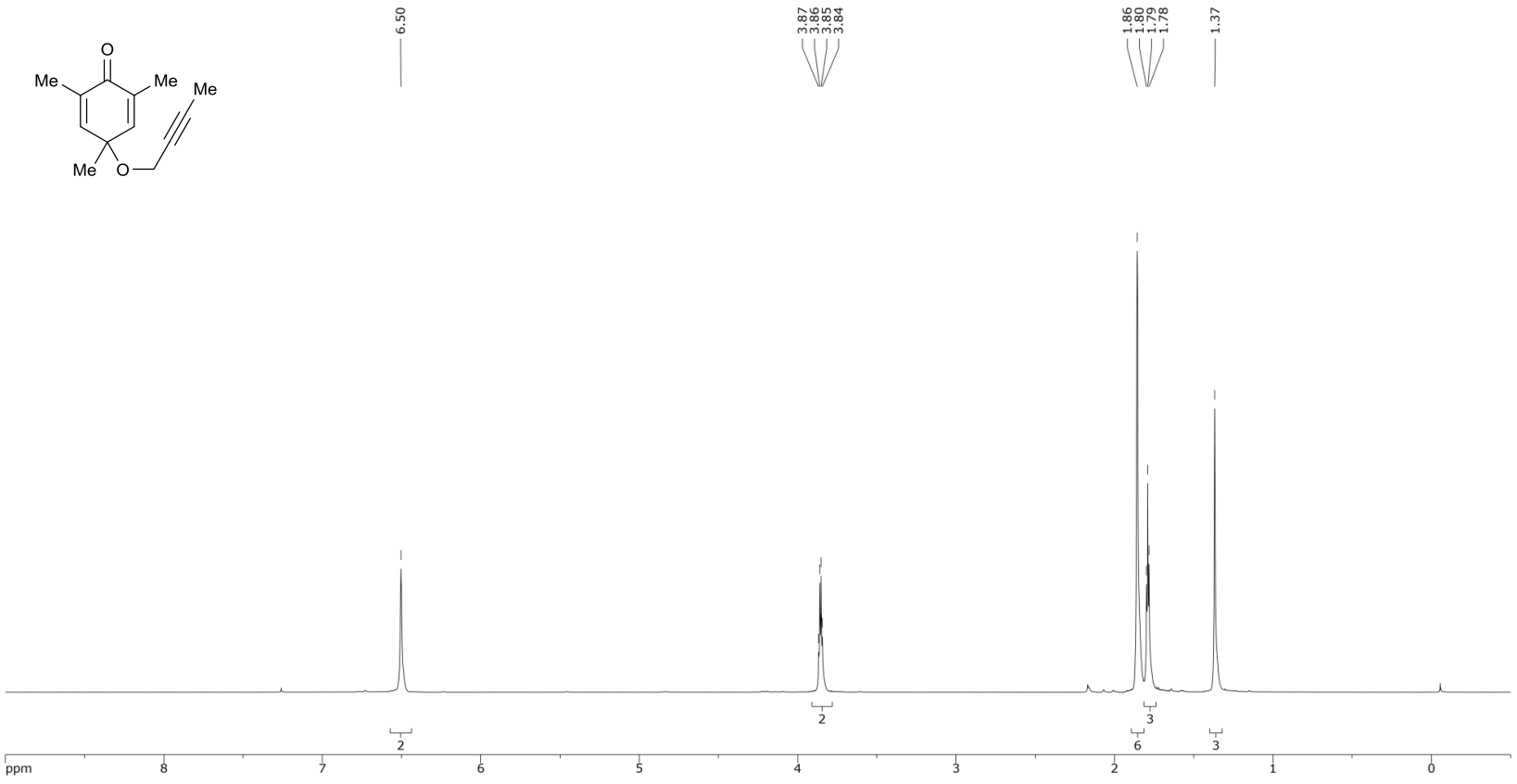
Enone 3.78 – ^{13}C NMR



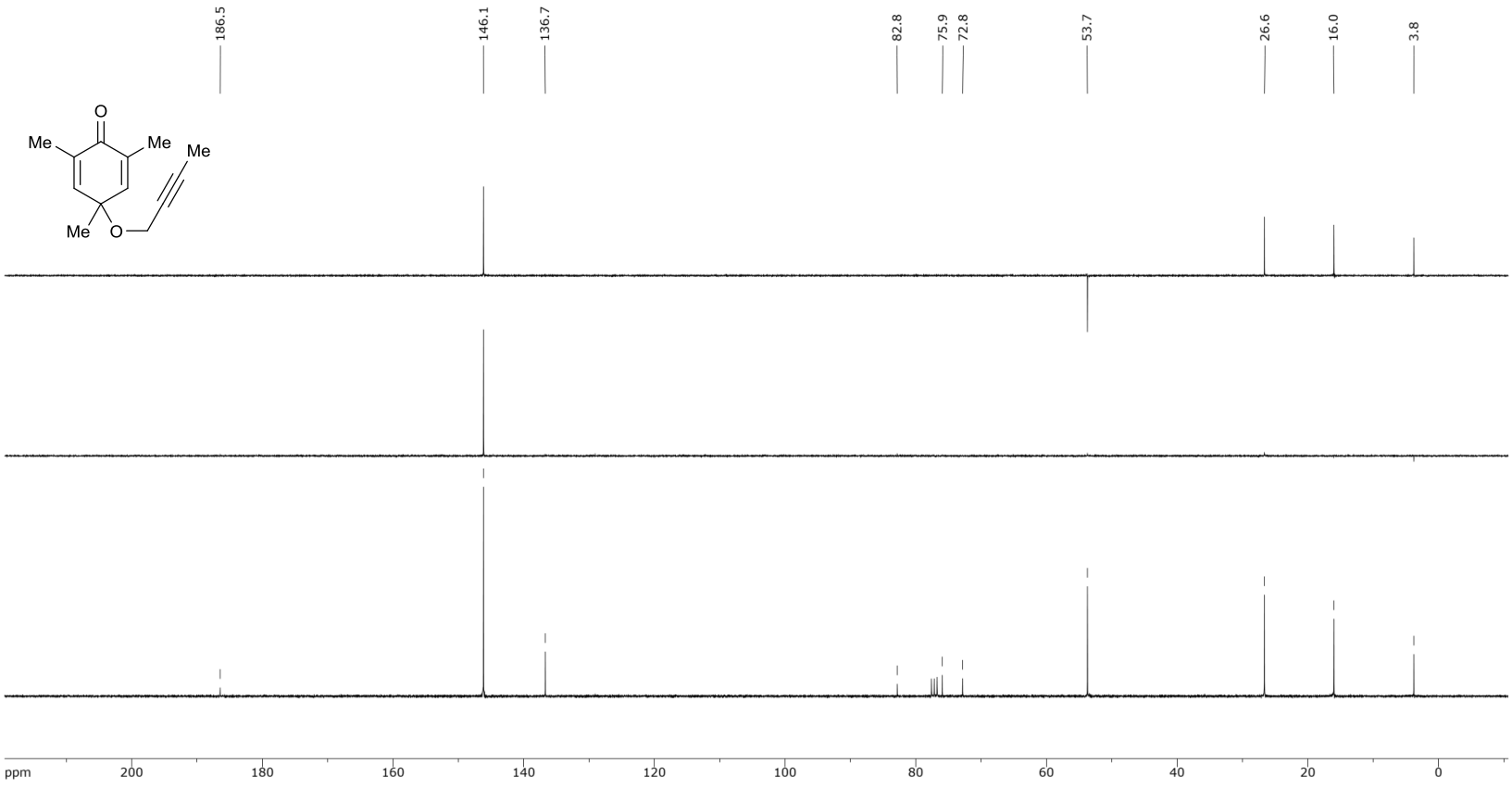
Vinyl acetate 3.86 – ^{1}H NMR



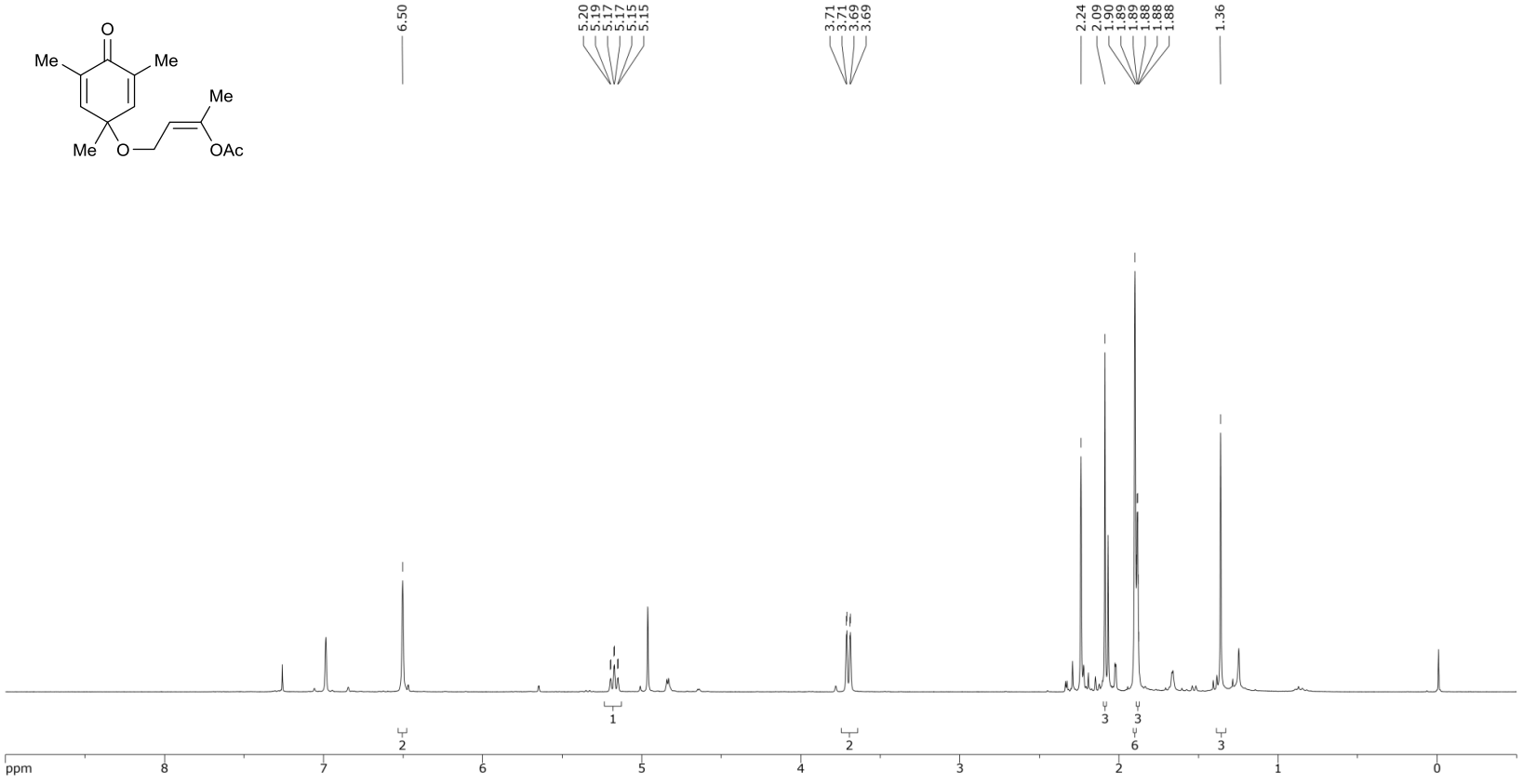
Alkyne-tethered cyclohexadienone 3.87 – ^{1}H NMR



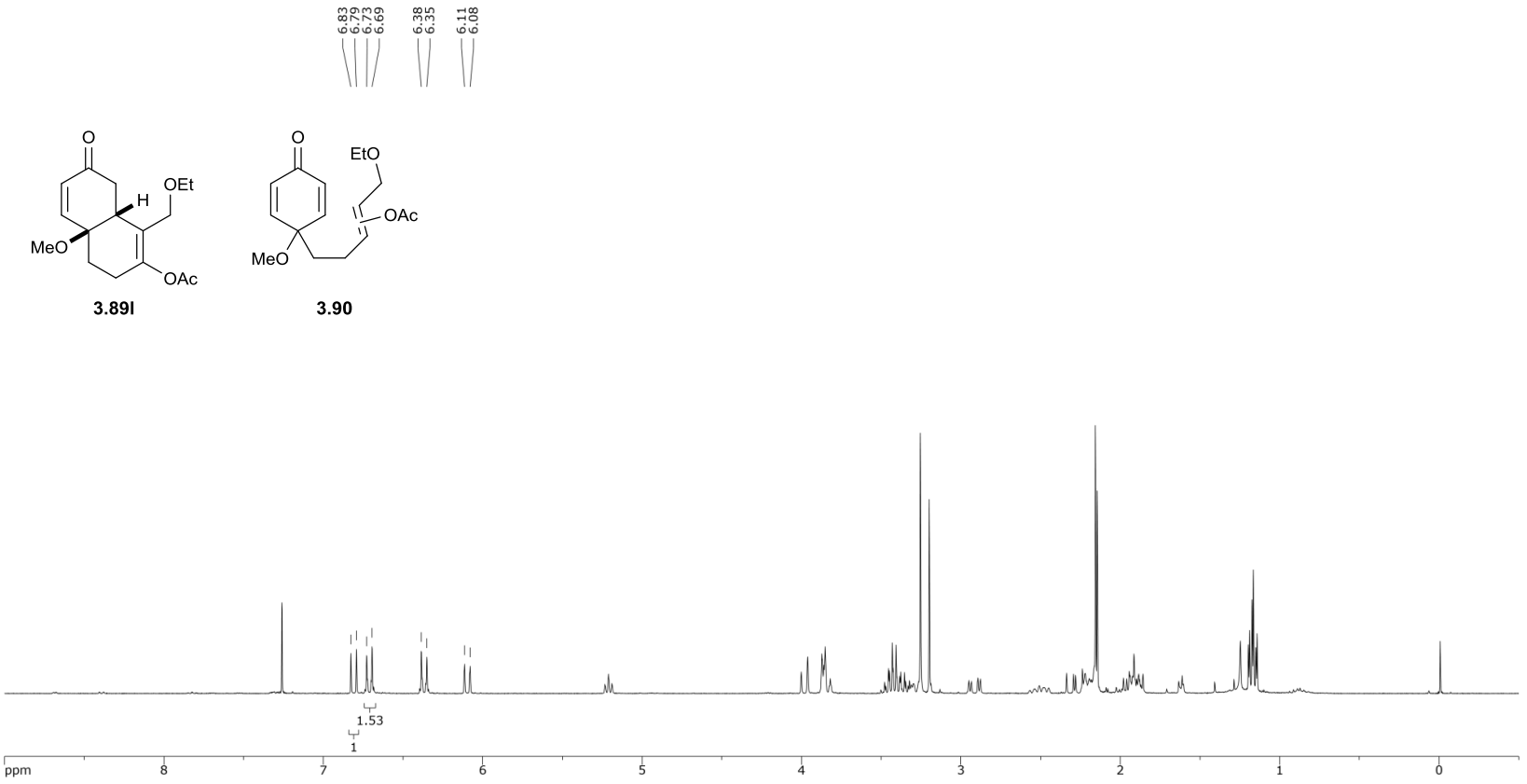
Alkyne-tethered cyclohexadienone 3.87 – ^{13}C NMR



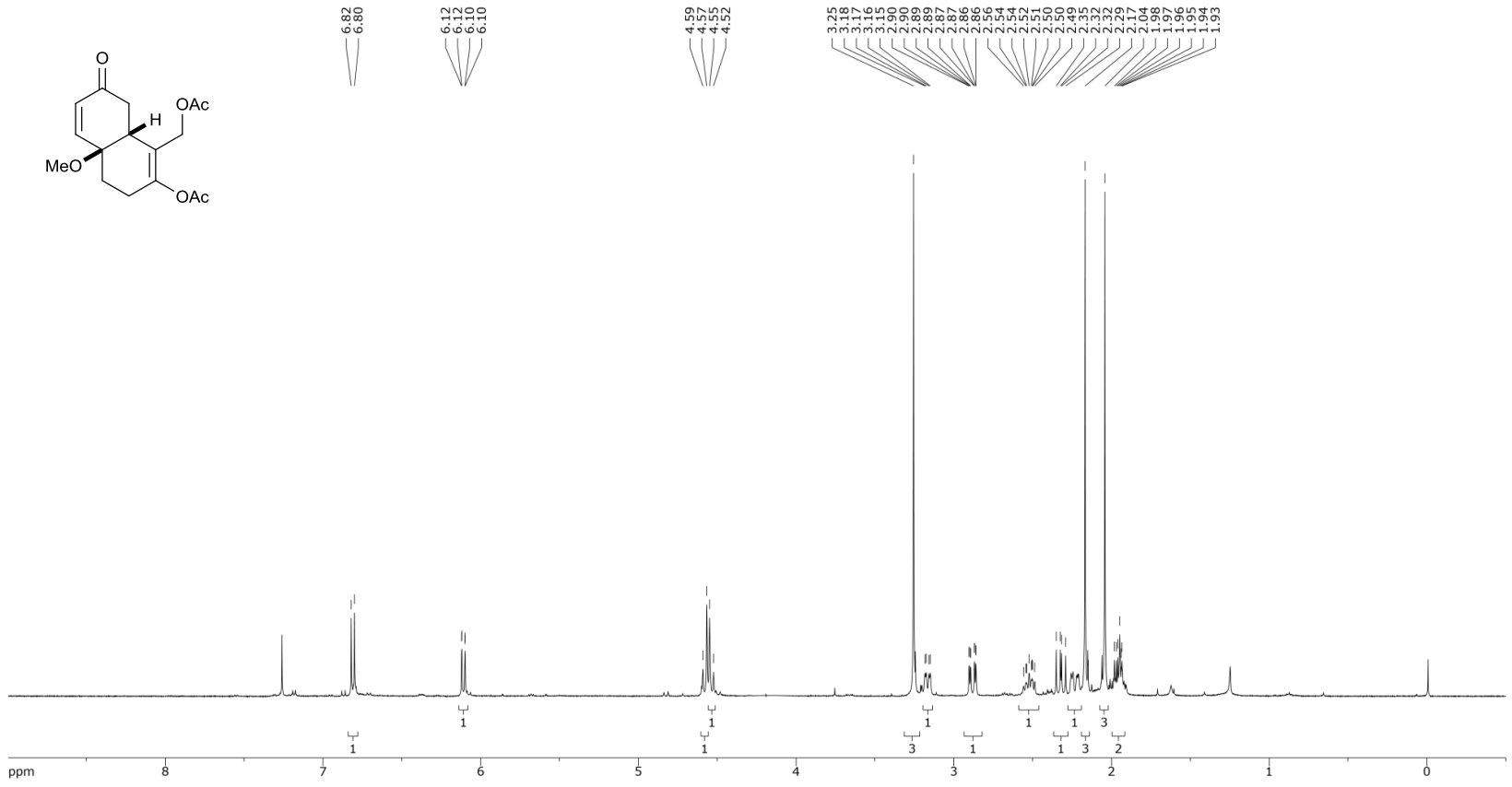
Vinyl acetate 3.88 – ^{1}H NMR



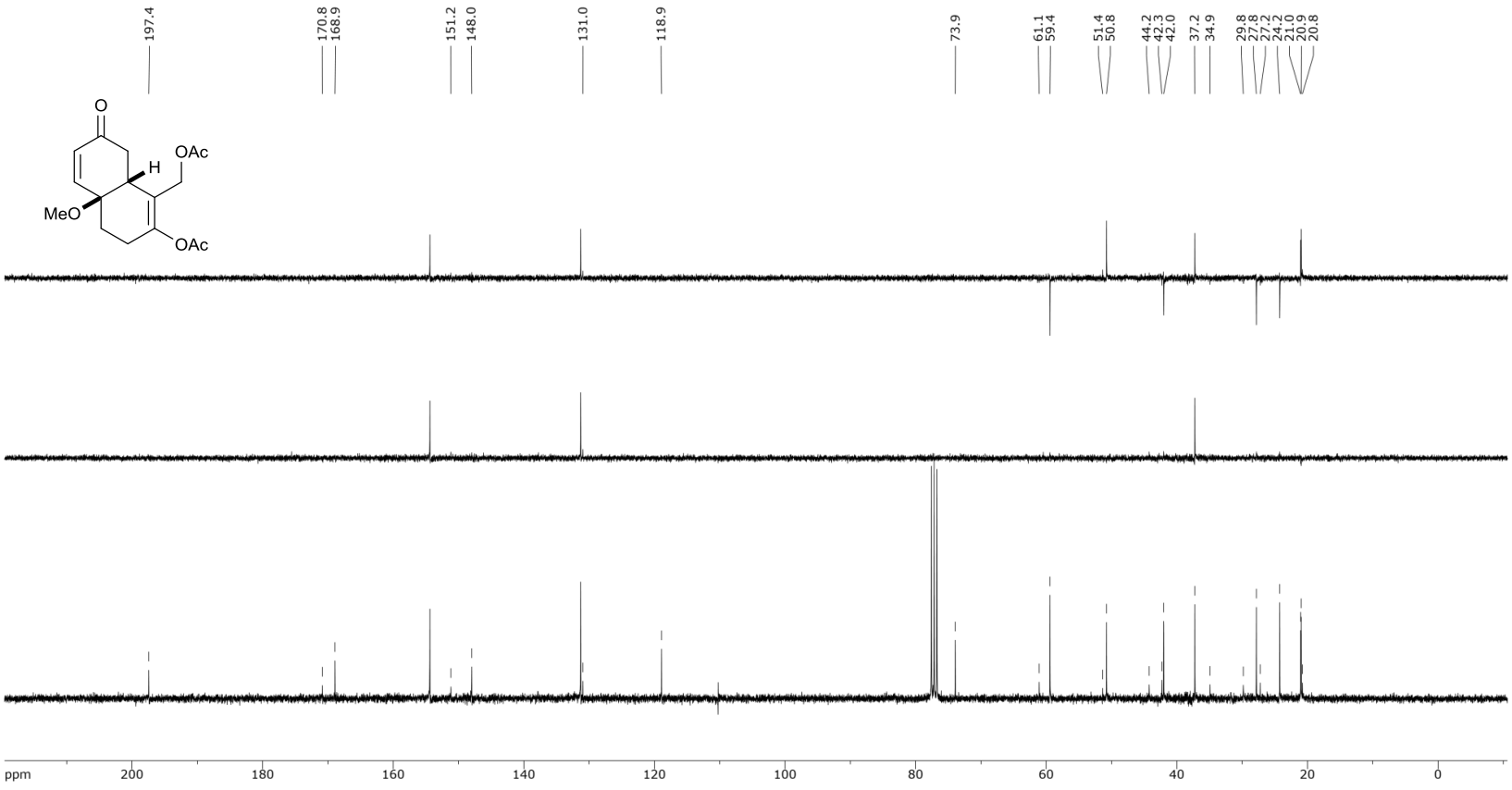
Bicyclic enone 3.89l and vinyl acetate 3.90 – ^{1}H NMR



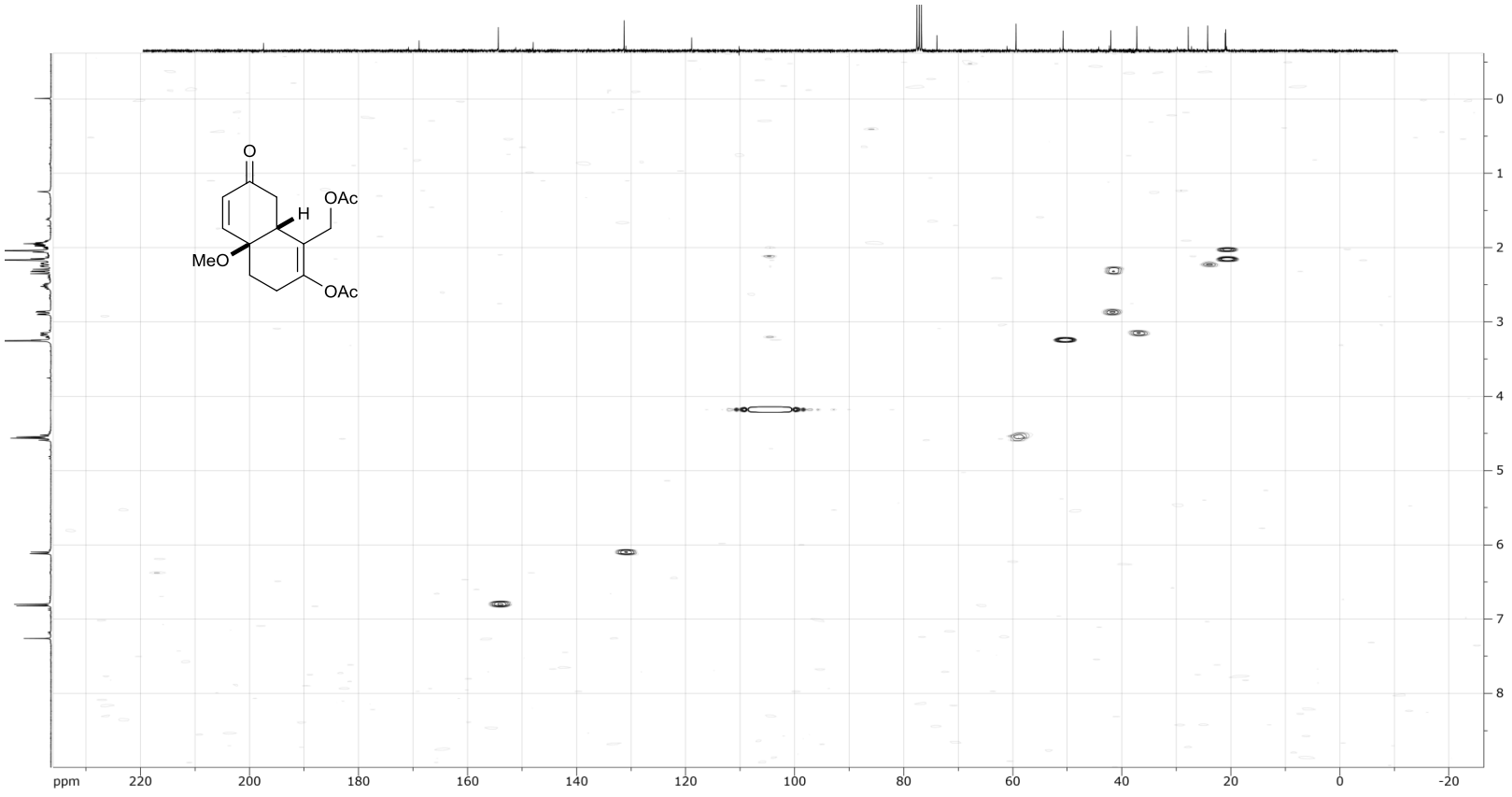
Bicyclic enone 3.89m – ^{1}H NMR



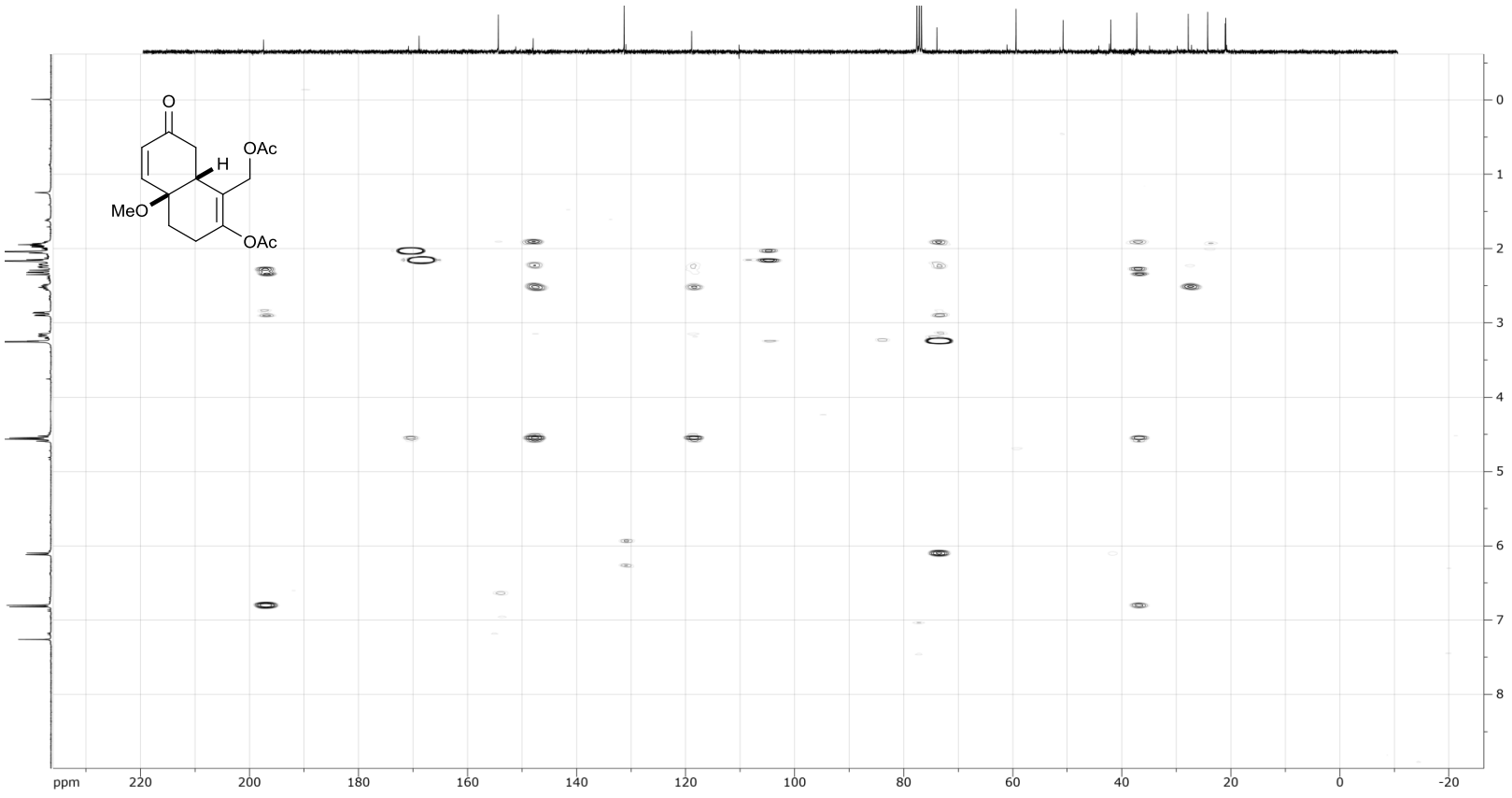
Bicyclic enone 3.89m – ^{13}C NMR



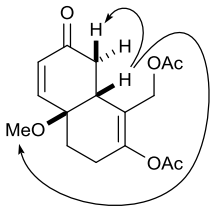
Bicyclic enone 3.89m – HMQC

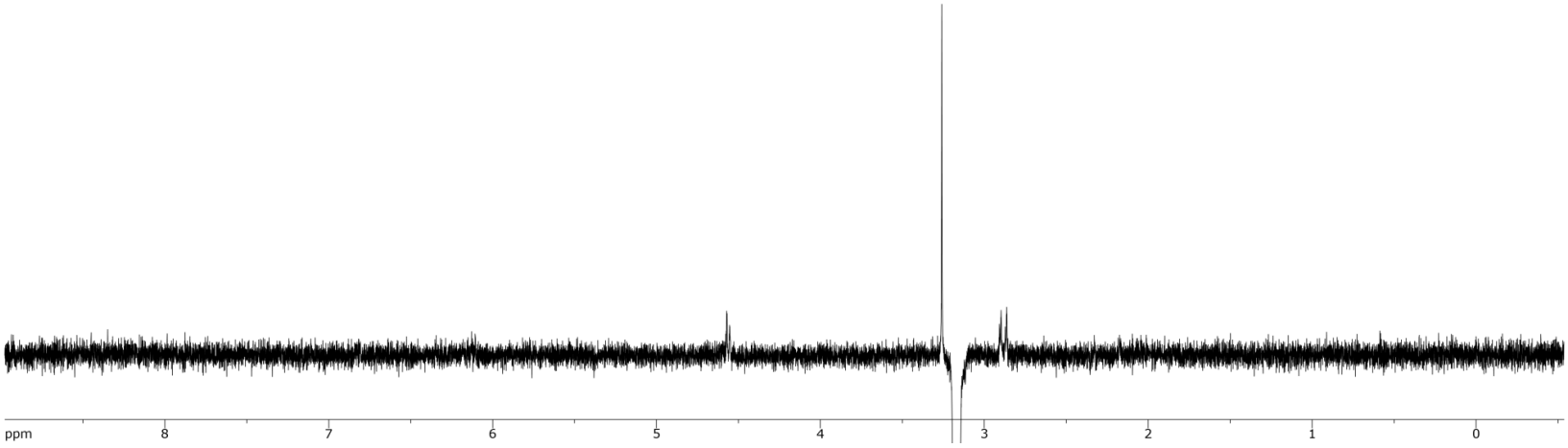


Bicyclic enone 3.89m – HMBC

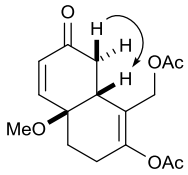


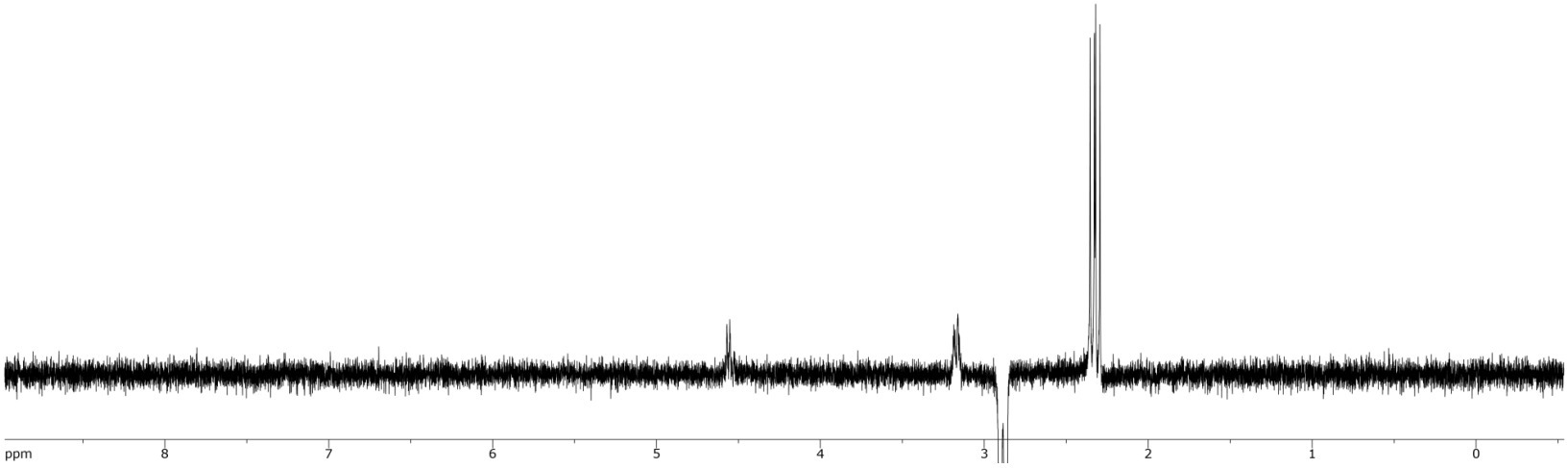
Bicyclic enone 3.89m – NOE



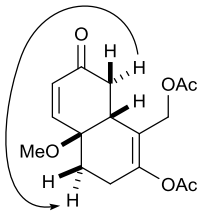


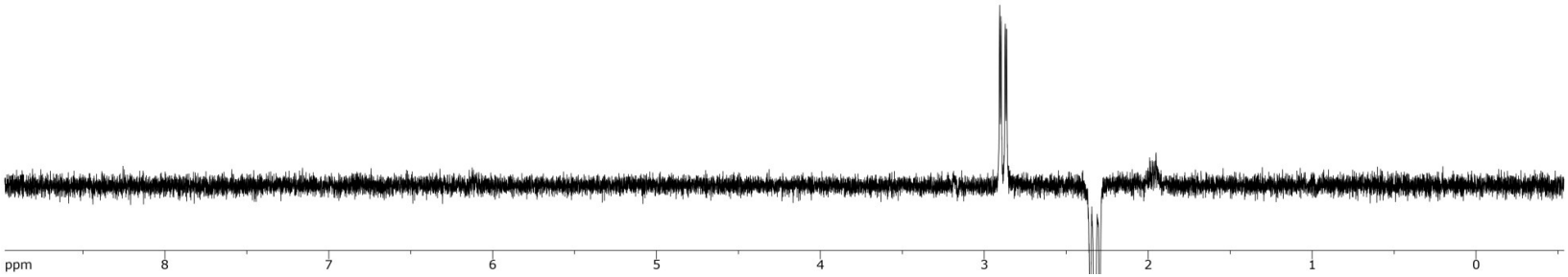
Bicyclic enone 3.89m – NOE



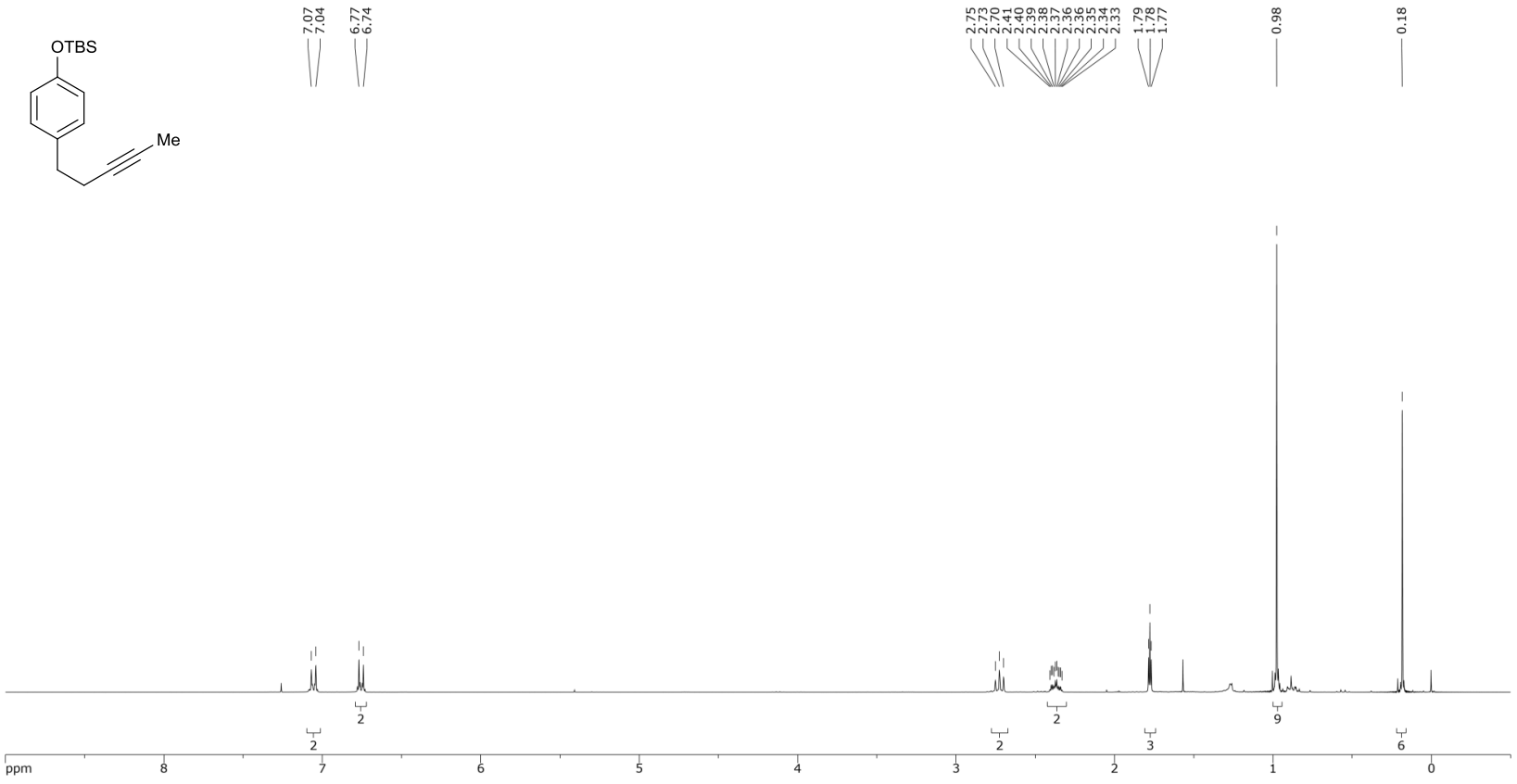


Bicyclic enone 3.89m – NOE

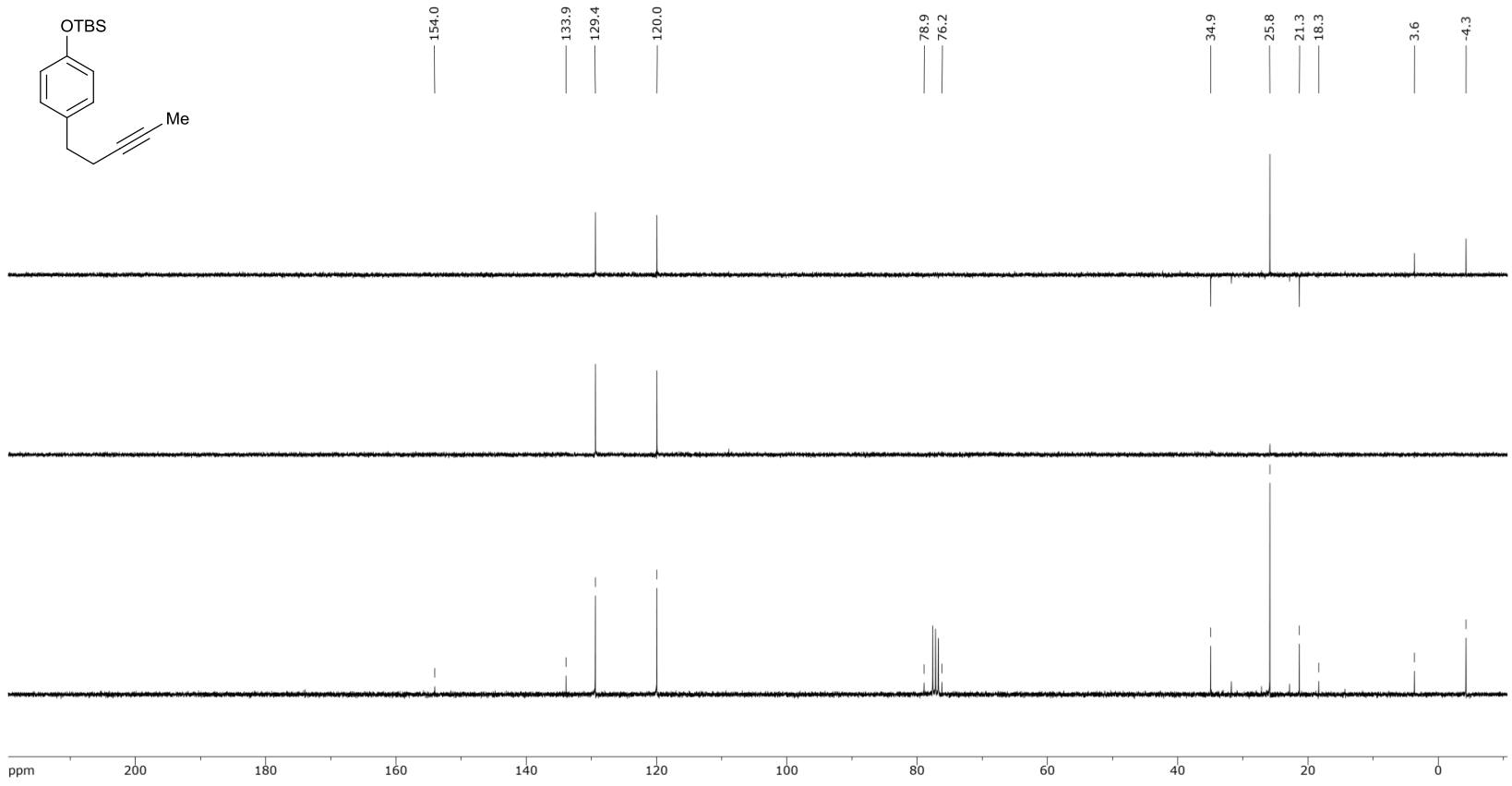




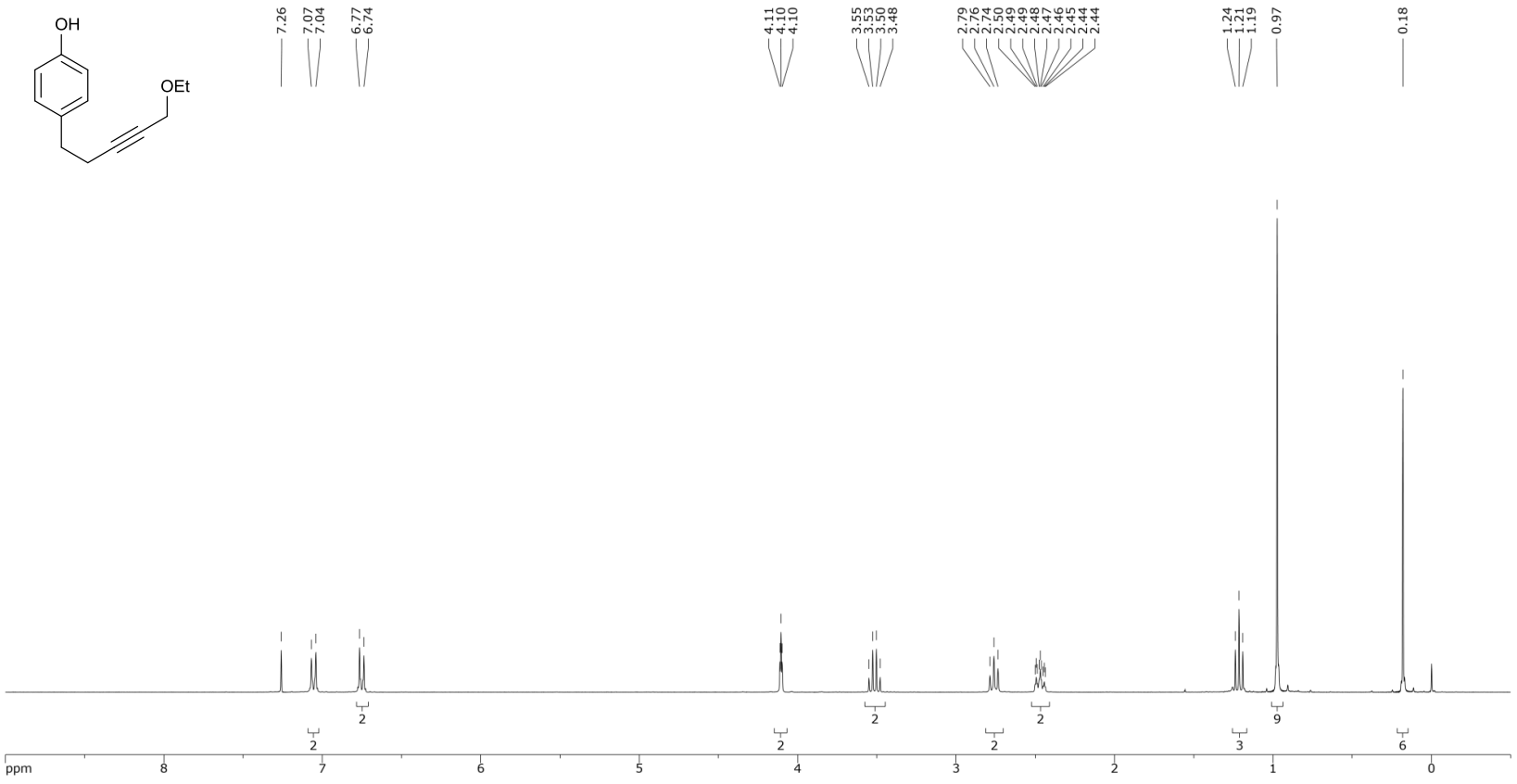
Internal alkyne S14 – ^{1}H NMR



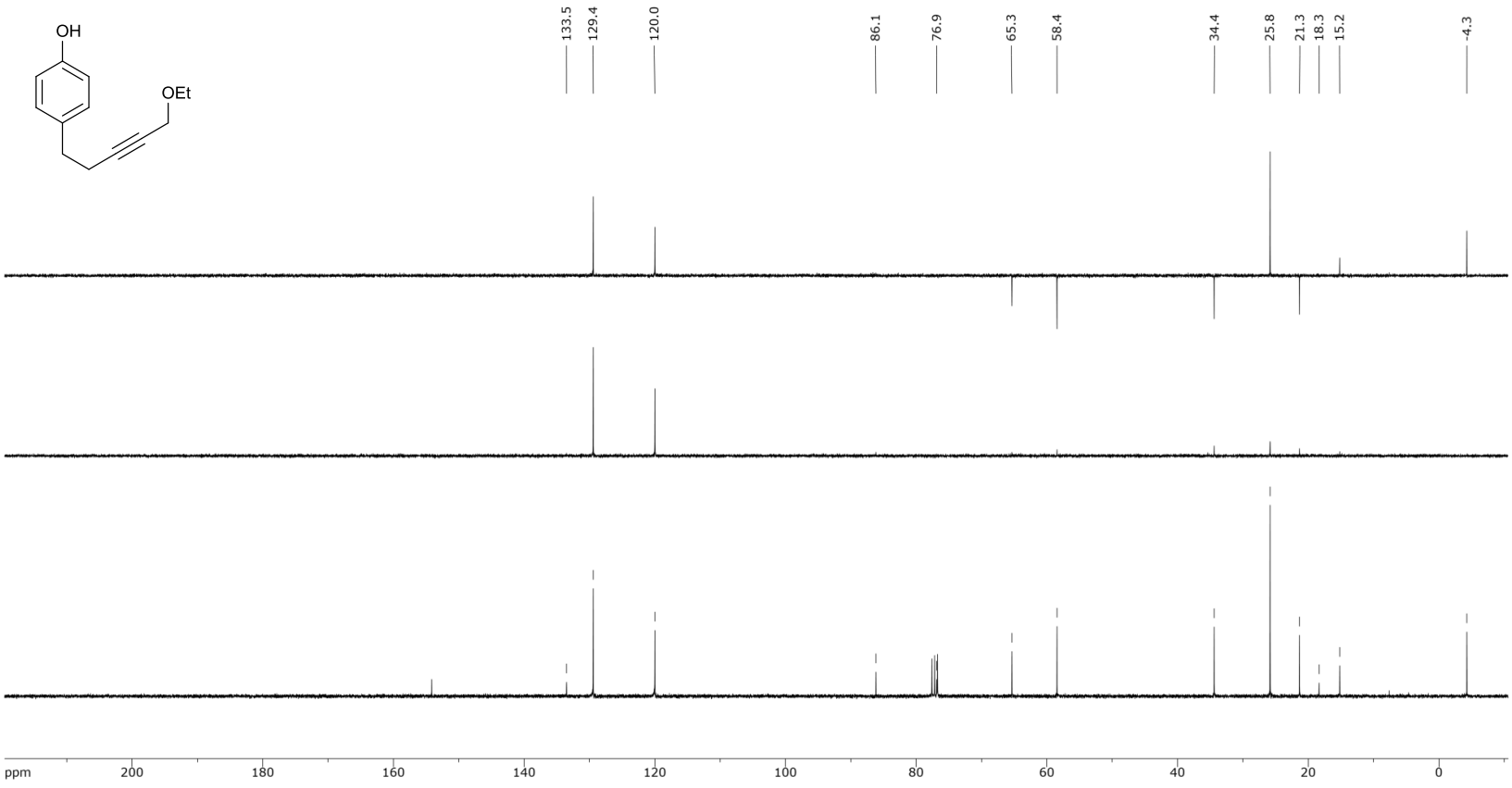
Internal alkyne S14 – ^{13}C NMR



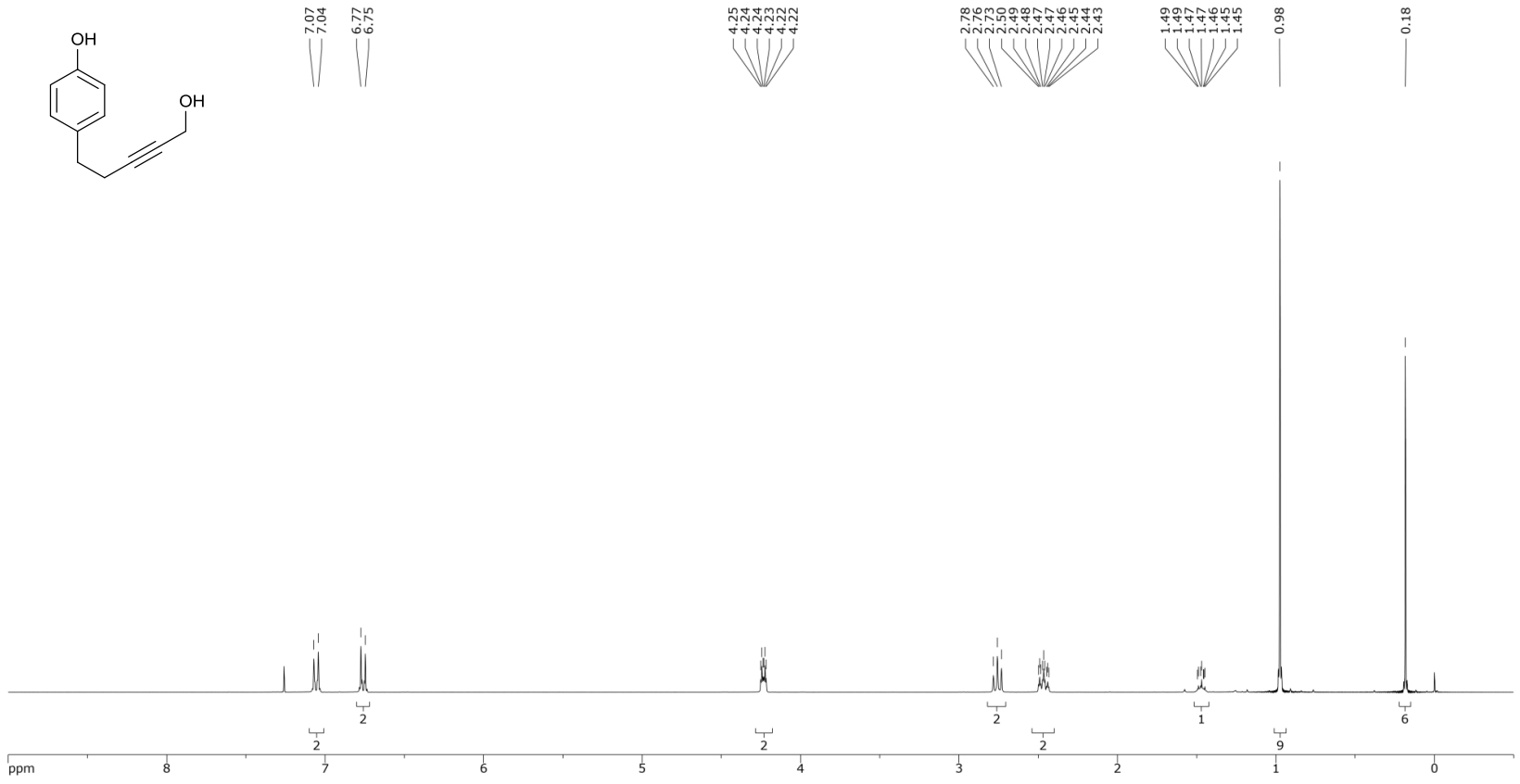
Internal alkyne S15 – ^{1}H NMR



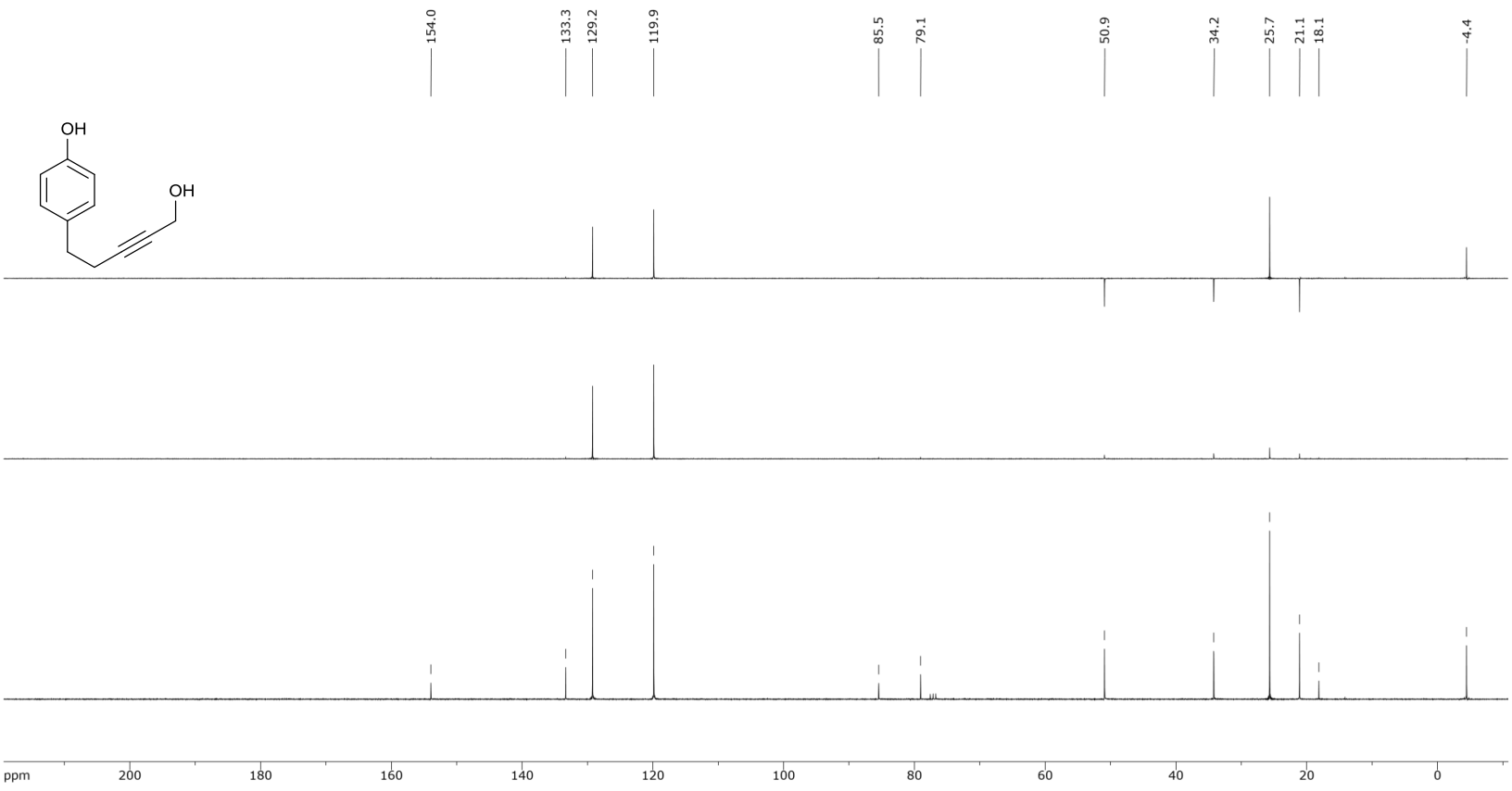
Internal alkyne S15 – ^{13}C NMR



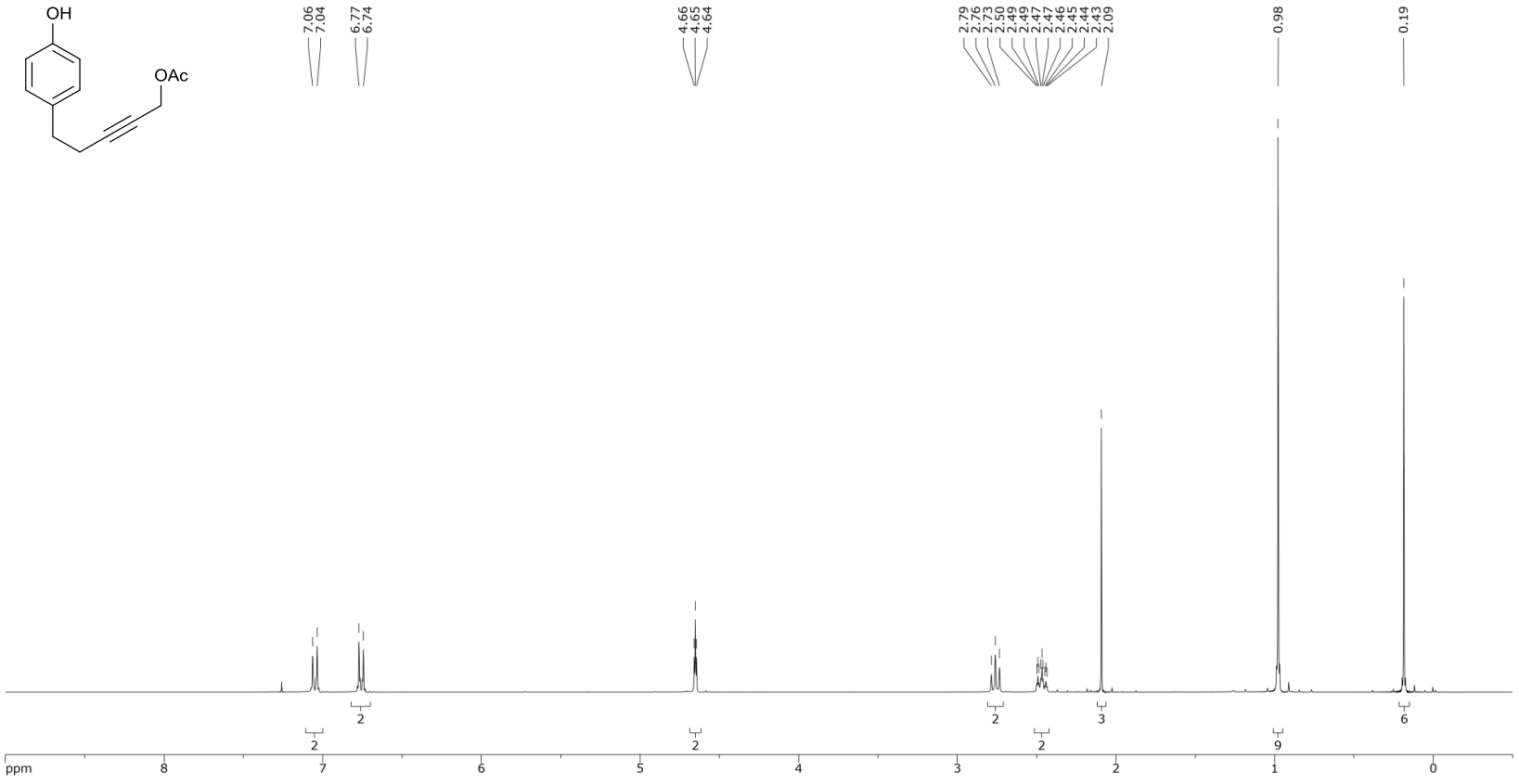
Propargyl alcohol S16 – ^{1}H NMR



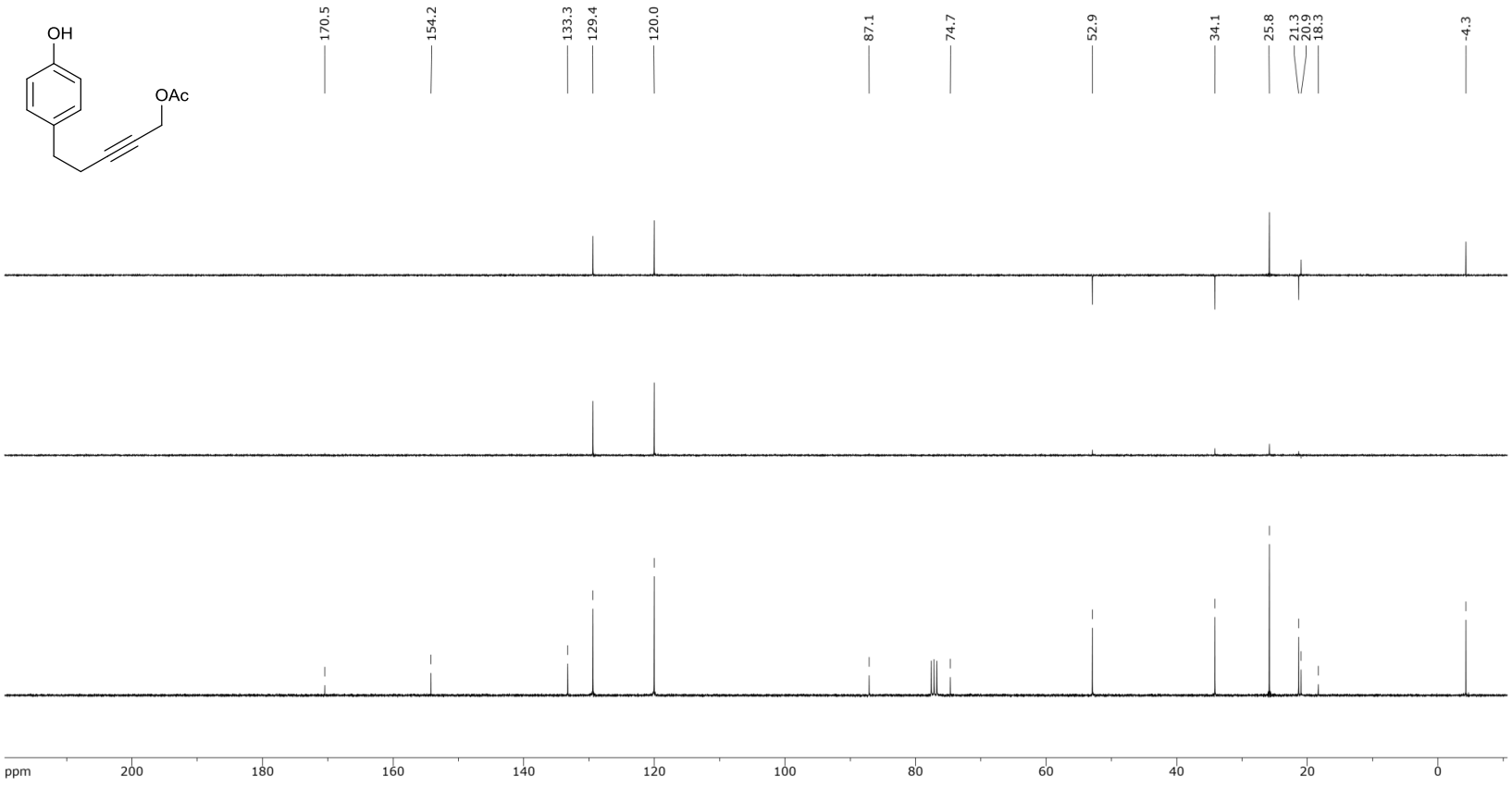
Propargyl alcohol S16 – ^{13}C NMR



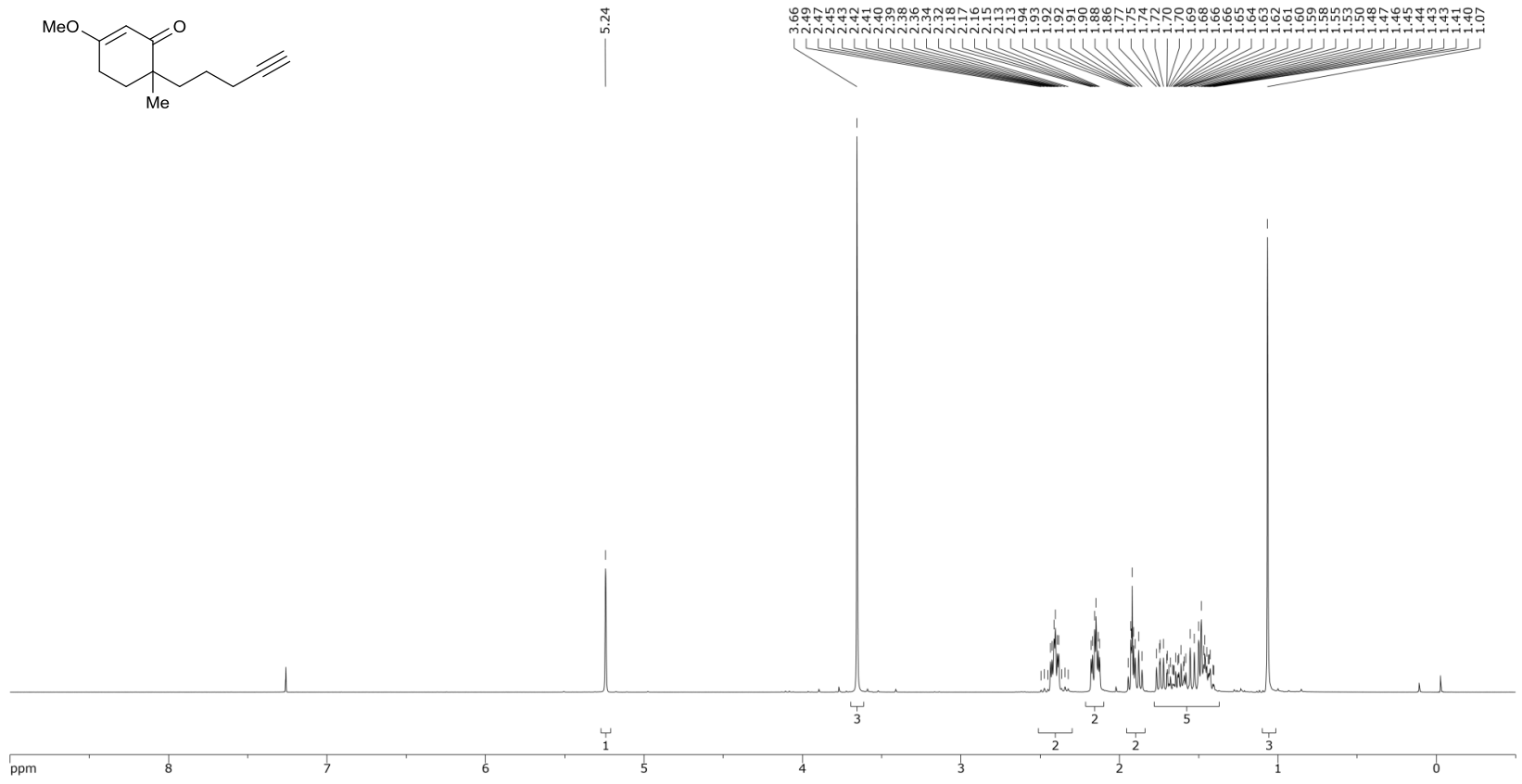
Propargyl acetate S17 – ^{1}H NMR



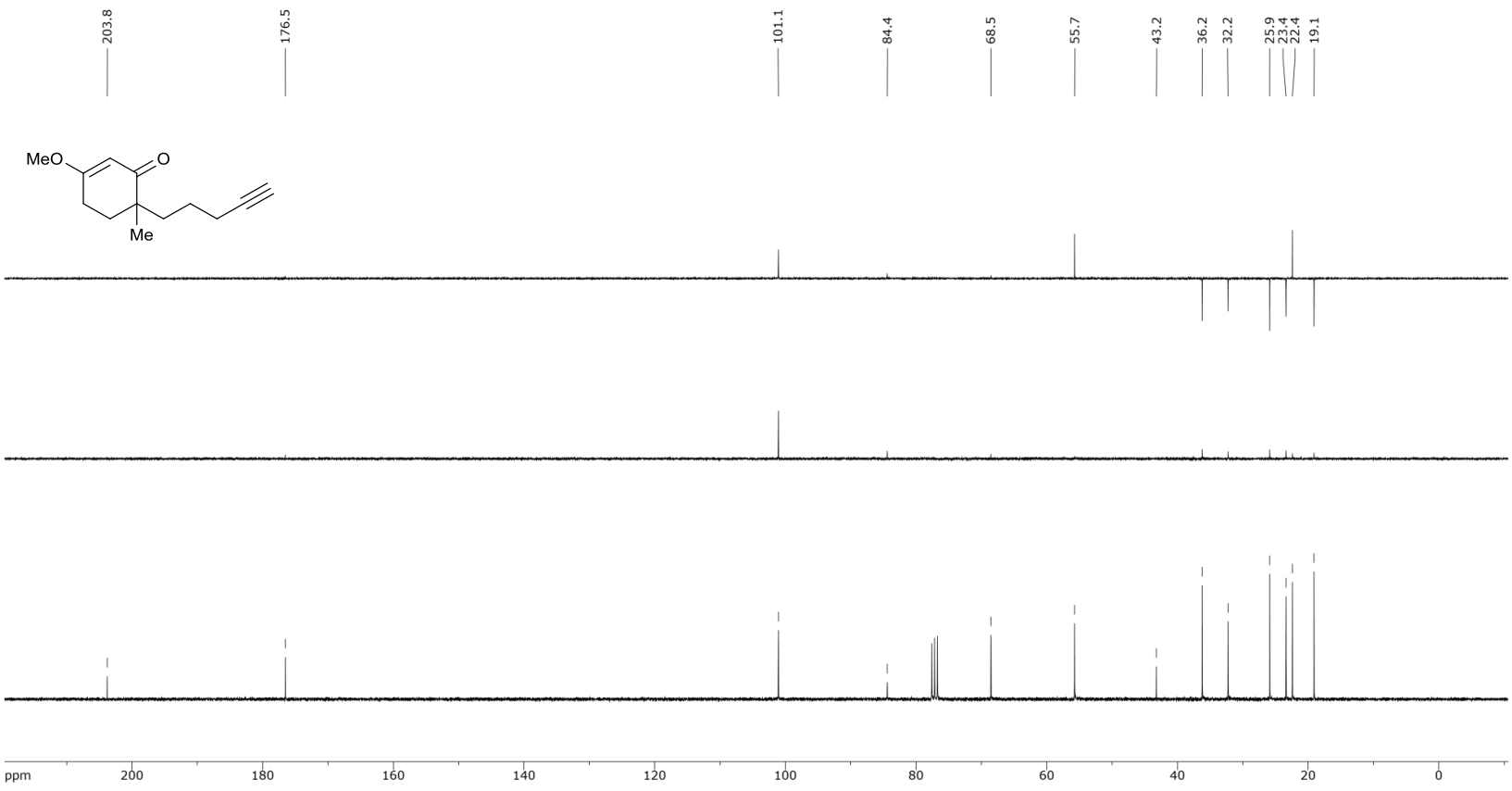
Propargyl acetate S17 – ^{13}C NMR



Terminal alkyne S18 – ^{1}H NMR

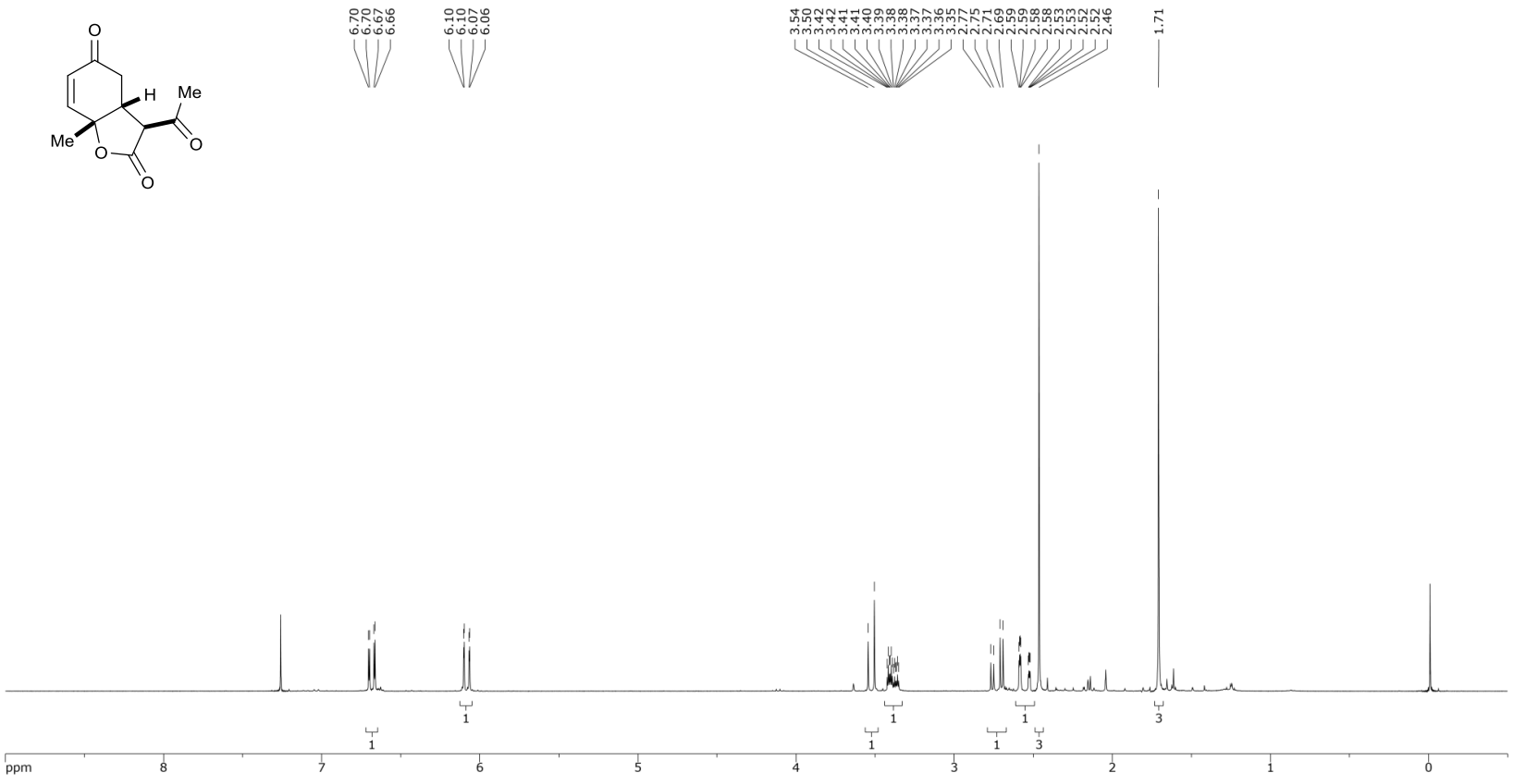


Terminal alkyne S18 – ^{13}C NMR

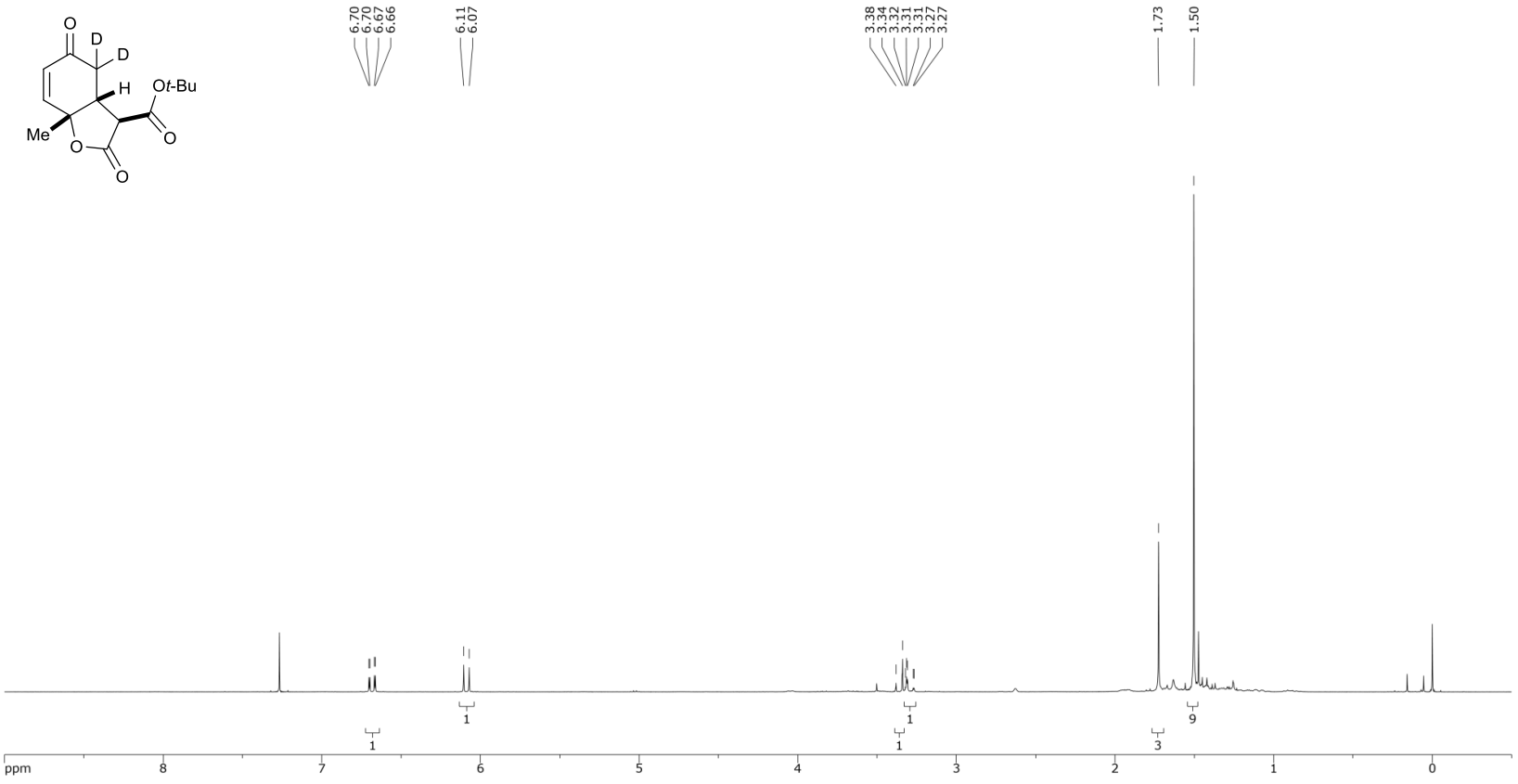


NMR Spectra – Chapter 4

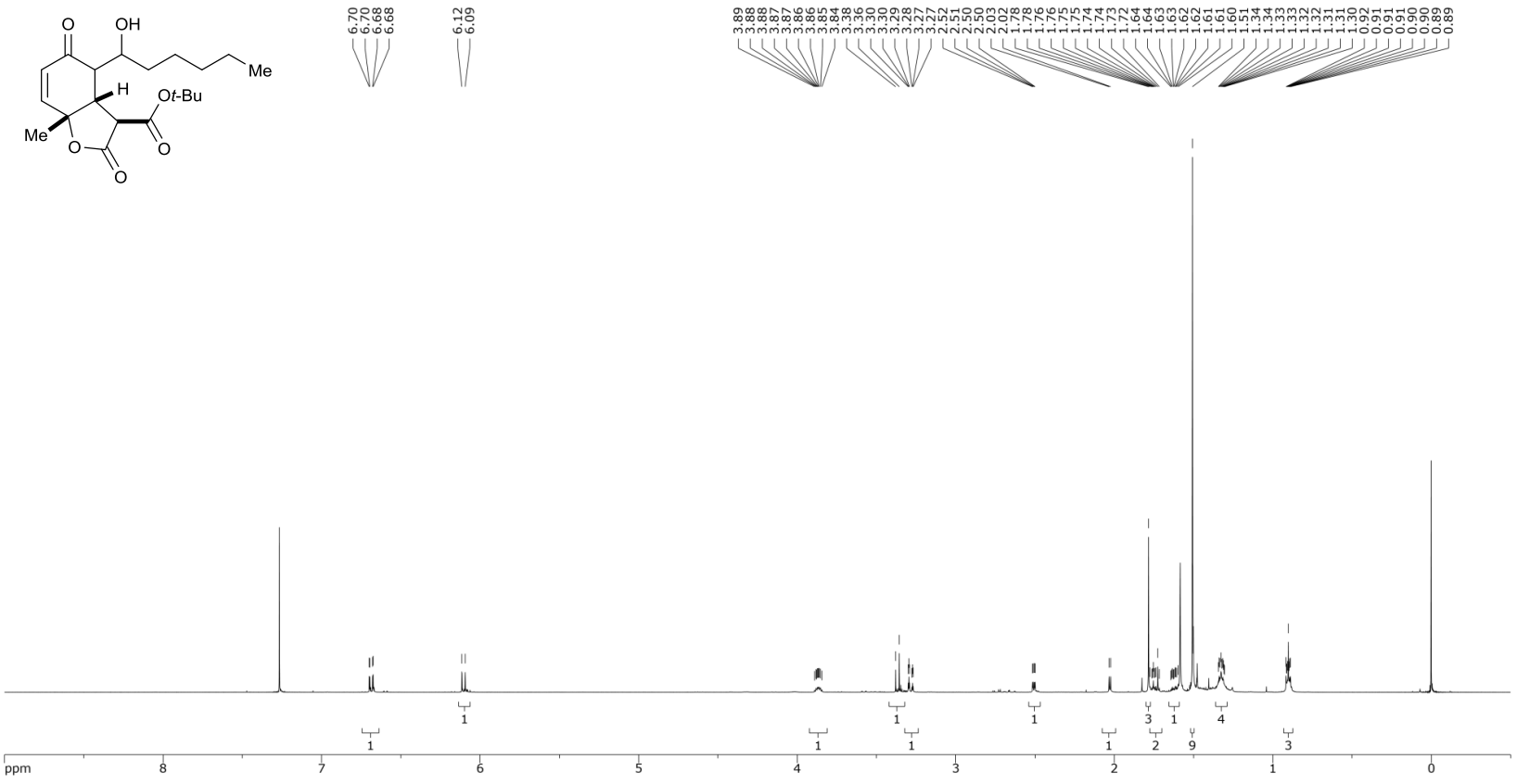
β-Ketoester 4.78 – ^{1}H NMR



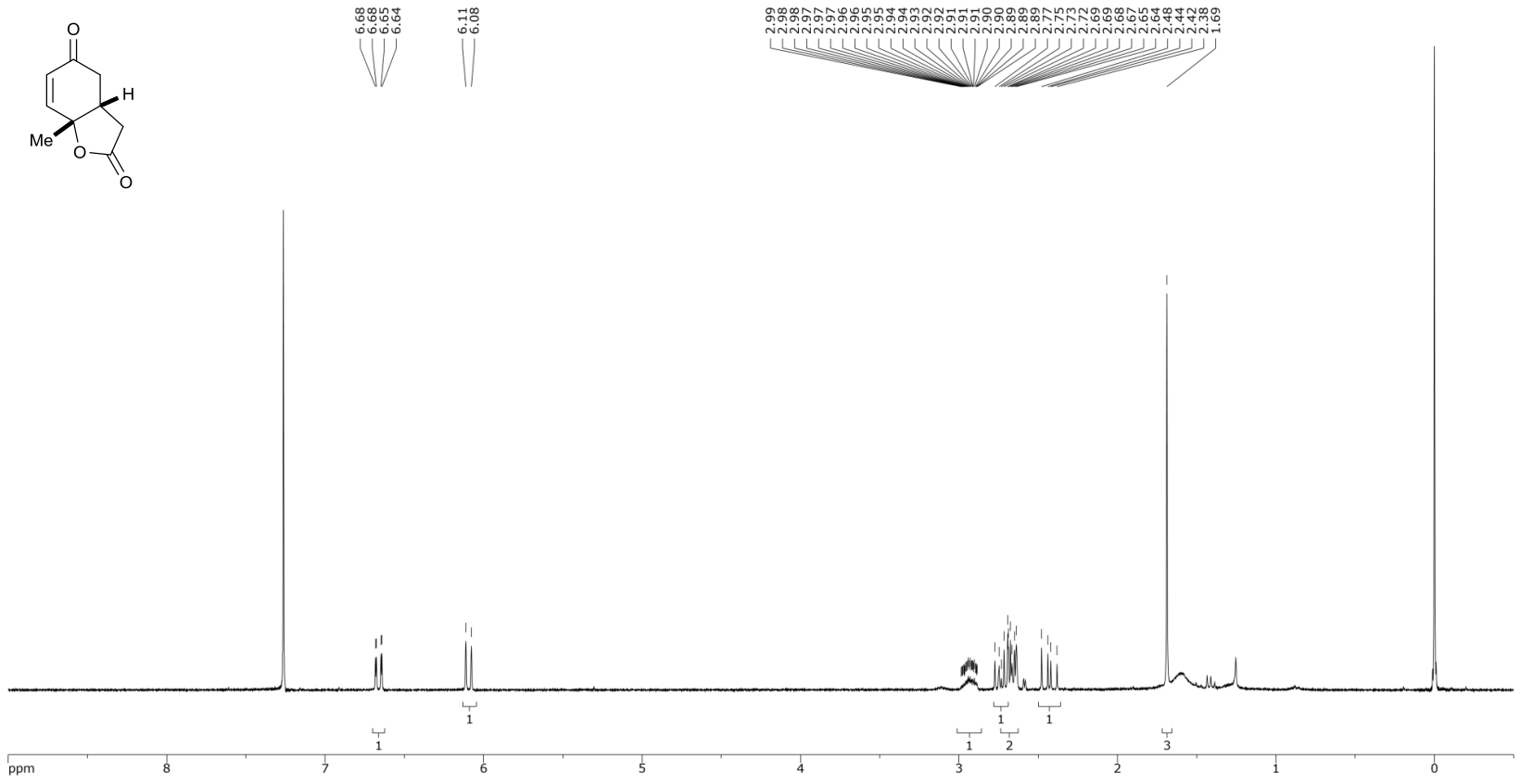
Bis-deuterated enone 4.82 – ^{1}H NMR



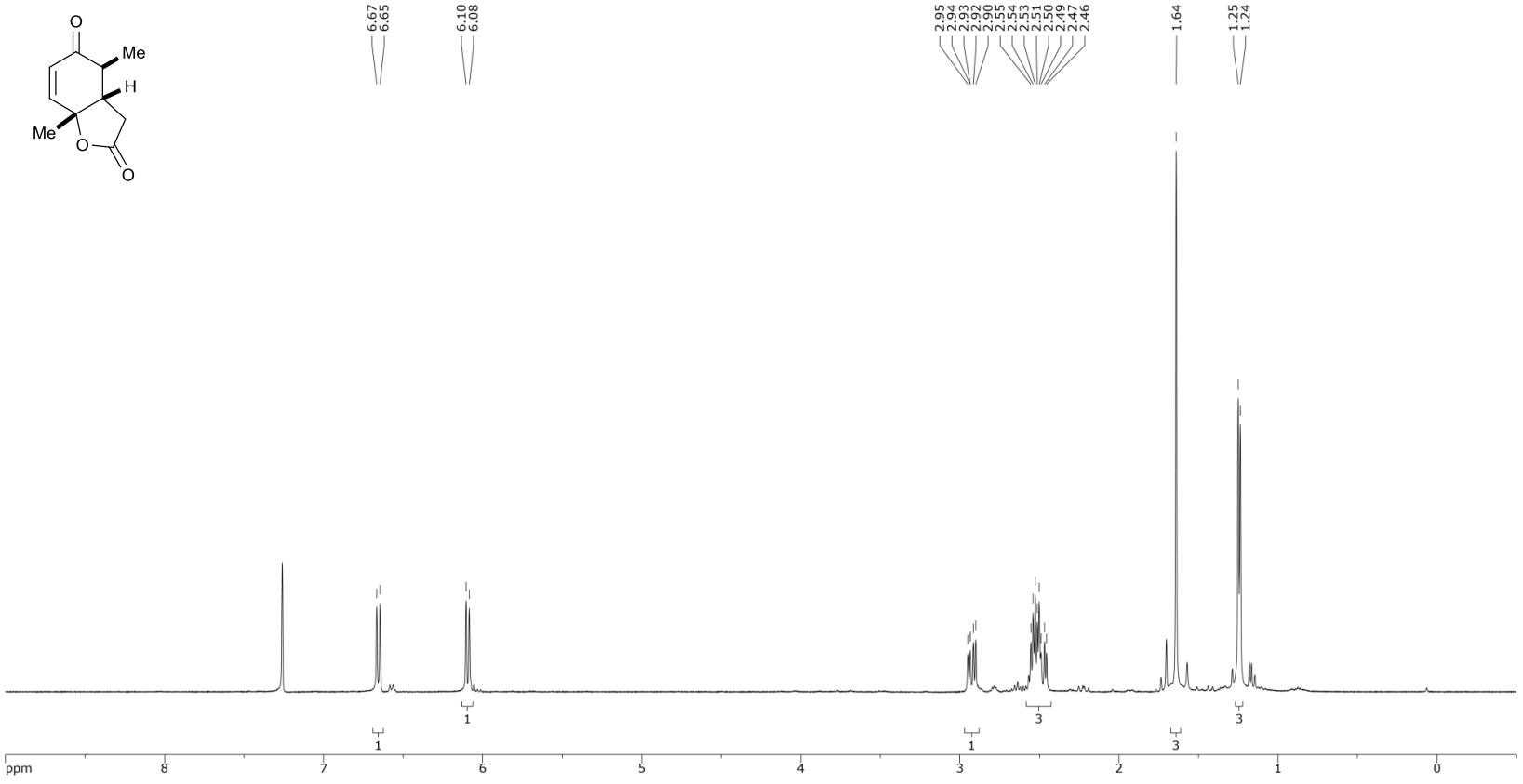
Aldol product 4.88 – ^{1}H NMR



Decarboxylated bicyclic lactone 4.90 – ^{1}H NMR



Methylated bicyclic lactone 4.91 – ^{1}H NMR



Methylated bicyclic lactone 4.91 – NOE