ALKENE DIFUNCTIONALIZATION USING HYDROXAMIC ACIDS

Benjamin Charles Giglio

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Chemistry Department of the School of Arts and Sciences.

Chapel Hill
2014

Approved by:

Erik J. Alexanian

Simon J. Meek

David A. Nicewicz

Marcey L. Waters

Wei You

© 2014
Benjamin Charles Giglio
ALL RIGHTS RESERVED

ACKNOWLEDGEMENTS

I want to thank Erik Alexanian for the guidance needed to complete these projects, as well as the current and previous members of the group for their support.

ABSTRACT

Benjamin Charles Giglio: Alkene Difunctionalization Using Hydroxamic Acids
(Under the direction of Erik Alexanian)

Alkene difunctionalizations are a core transformation in synthetic organic chemistry. A majority of these reactions proceed through polar or transition-metal-catalyzed methods. Alkene difunctionalizations that pass through a free radical reaction manifold are less common. Even less common are radical-based alkene difunctionalizations utilizing oxygen-centered radicals, which are well known for their high reactivity.

Disclosed herein is technology which controls the reactivity of oxygen-centered radicals, allowing them to be used for useful and productive synthetic chemistry. The hydroxamic acid functional group was utilized for this purpose.

An intermolecular alkene dioxygenation using molecular oxygen as an O-atom source was developed. Derivatives of the hydroxamic acid functional group, *N*-hydroxy carbamates, were crucial to the success of the reaction.

The ability of hydroxamic acids to function as hydrogen-atom donors capable of reducing carbon-centered radicals to alkanes was also discovered. The use of this property lead to the development of an intramolecular formal alkene hydration and cascade diene carbocyclization reaction.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SPECTRA

Experimental for Chapter 2

Experimental for Chapter 3

LIST OF ABBREVIATIONS

Å	Angstrom
Ac	acetyl
acac	acetyl acetonate
AIBN	azobisisobutyronitrile
Ar	aryl
atm	atmosphere
Boc	*tert*-butoxy carbonate
Bn	benzyl
Box	bisoxazoline
br s	broad singlet
bu	butyl
C	Celsius
calcd.	Calculated
δ	chemical shift
d	doublet
d.r.	diastereomeric ratio
dd	doublet of doublets
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DLP	dilauroylperoxide
DMAP	*N*, *N*-dimethylaminopyridine
DMF	*N*, *N'*-dimethylformamide
DMS	dimethylsulfide

DMSO	dimethylsulfoxide
DPAP	α,α-dimethoxy-α-phenylacetophenone
DTAD	ditertbutylazodicarboxylate
e.e.	enantiomeric excess
eq	equivalents
e.r.	enantiomeric ratio
ESI	electrospray ionization
ESR	electron spin resonance
Et	ethyl
Et_2O	diethylether
g	gram
h	hour
Hz	Hertz
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant
kcal	kilocalorie
L	liter
L_n	ligand sphere
LDA	lithium diisopropyl amide
LDE	lithium diethyl amide
LRMS	low resolution mass spectrometry
m	multiplet or minute
M	molar
Me	methyl

mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol	mole
MTBE	methyl *tert*-butyl ether
NFSI	*N*-fluorobenzenesulfonimide
NHPI	*N*-hydroxyphthalimide
NMR	nuclear magnetic resonance
pH	negative logarithm of the concentration of hydronium ion
Ph	Phenyl
PhCN	benzonitrile
PhH	benzene
PhMe	toluene
Phthal	phthalimide
PINO	phthalimido-*N*-oxo
pKa	negative of the logarithm of the acid dissociation constant
ppm	parts per million
PTFE	Polytetrafluoroethylene (Teflon ®)
Pyr	pyridine
q	quartet
RT	room temperature
s	singlet or second
t	triplet or time
TADDOL	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
*t*Bu	*tert*-butyl

TEMPO	2,2,6,6-tetramethyl-1-piperidinyl 1-oxy
TFA	trifluoracetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	tetraphenyl porphyrin
UV	ultraviolet
μm	micrometer
hv	light

CHAPTER 1: RADICAL-MEDIATED ALKENE DIFUNCTIONALIZATIONS IN SYNTHESIS

1.1 Alkenes and Alkene Difunctionalizations

Carbon-carbon double bonds of alkenes are of key importance to synthetic organic chemistry. Due to the facility in which its reactivity can be influenced, alkenes have been utilized as substrates for hundreds of different chemical transformations. The presence of alkenes in hydrocarbon feedstocks as well as the ease by which they can be made further adds to their attractiveness as potential substrates to pursue for the development of a synthetic methodology. Among the many transformations in which alkenes can participate, alkene difunctionalization has emerged as one of the most useful. The ability to simultaneously install two different or identical atoms onto vicinal carbon atoms provides unparalleled opportunities for further chemical elaboration.

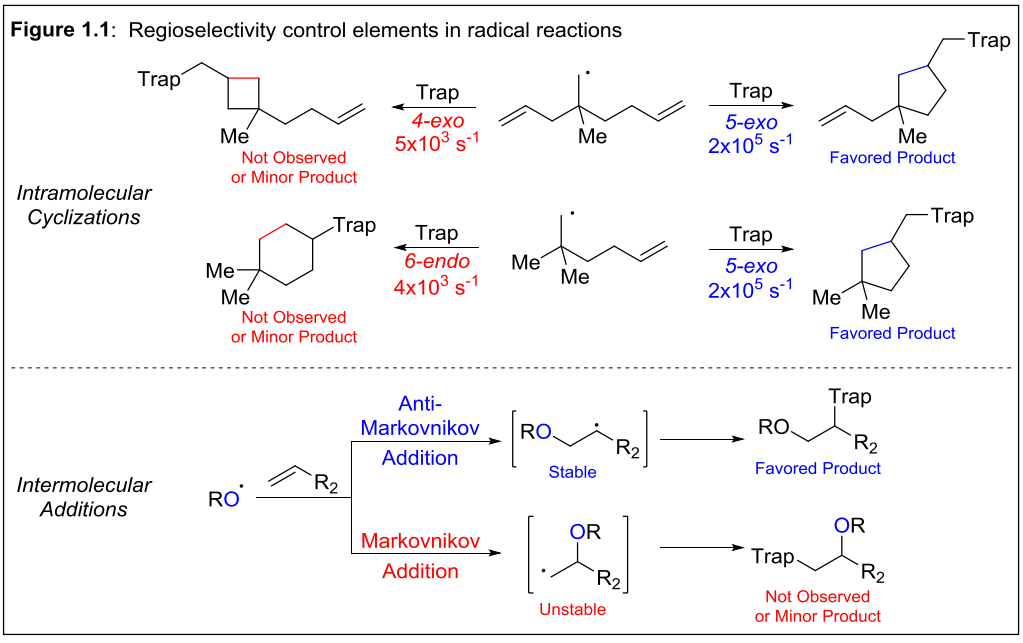
1.2 Free-Radical Reactions as an Alternative for Transition-Metal-Catalyzed Processes

Traditional alkene difunctionalization protocols involve the use of transition metals as catalysts. The Nobel Prize winning Sharpless asymmetric dihydroxylation and aminohydroxylation are important examples of transition-metal-catalyzed alkene difunctionalization.[1] Numerous other methodologies employing transition metals have appeared, and it continues to be an active and productive area of research.[2] Despite their successes, transition-metal-catalyzed protocols suffer from certain drawbacks. In particular, the metals typically employed for difunctionalization reactions are osmium and palladium. Both metals are expensive as a result of their low abundance in the Earth's crust. Furthermore, the toxicity of osmium poses a serious threat to the user as well as the environment.[3]

Free radical methods have the potential to address the shortcomings of metal-catalyzed methods, and provide reactivity that complements that of transition metals. With regard to chemical synthesis, problems associated with functional group tolerance and regioselectivity can arise when using transition-metal-catalyzed processes. For example, in order to perform difunctionalizations, osmium must exist in

the +8 oxidation state. Osmium(VIII) is a strong oxidizer, and poses a threat to chemical functionality that are vulnerable to oxidation.[1] In addition, protection is necessary for coordinating functionality within the molecule which can potentially poison the catalyst. Extra protection and deprotection steps in a synthesis will reduce the final yield. Radical reactions, on the other hand, are well known for their ability to tolerate coordinating functional groups as well as other sensitive functionality.[4]

In addition to functional group tolerance concerns, regioselectivity problems can arise when using transition-metal-catalyzed methods. For molecules containing more than one alkene, the possibility of unintentionally difunctionalizing the additional alkene or alkenes exists. For intermolecular difunctionalization reactions which deliver two different atoms to the alkene, the formation of constitutional isomers possessing the undesired atom connectivity can arise. Regioselectivity problems with radical reactions, on the other hand, rarely occur. In intramolecular radical cyclizations, the relative rates of the competing cyclizations, which are typically understood in terms of Baldwin's rules,[5] control regioselectivity (**Figure 1.1**).[6] For substrates containing multiple alkenes, the major product will be formed from the alkene that can undergo the fastest cyclization with the radical. Often, the large difference between the relative rates of the competing cyclizations (fast *5-exo* cyclization vs. slow *4-exo* cyclization, for example) ensure that only one product is observed.[7] For difunctionalizations which



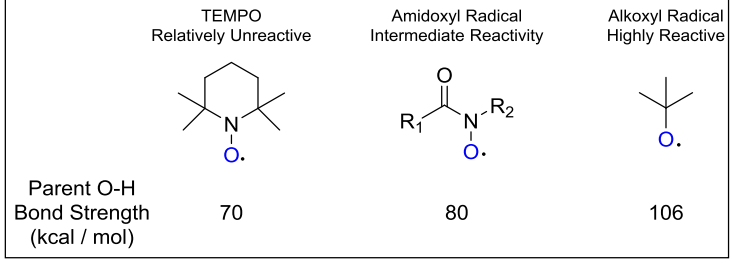
deliver two different atoms to a single alkene, the same principles are used to control the site selectivity for possible constitutional isomers (fast *5-exo* vs. slow *6-endo*). For intermolecular reactions, the relative stability of the carbon-centered radical formed following addition of the heteroatom-centered radical into the alkene dictates the regioselectivity leading to different products (Markovnikov's rule).[7]

The problems associated with transition-metal-catalyzed alkene difunctionalization reactions underscore the need for next-generation methods to address these problems. Heteroatom-centered radicals are capable of reacting with alkenes through addition into the double bond. It is this property that makes difunctionalizations possible. Radical reactions have the potential to address the toxicity, functional group tolerance, and regioselectivity issues that hinder transition-metal-catalyzed methods, thus providing a suite of reactivity that complements that of transition metals.

1.3 Developing Difunctionalization Methodology Employing Oxygen-Centered Radicals

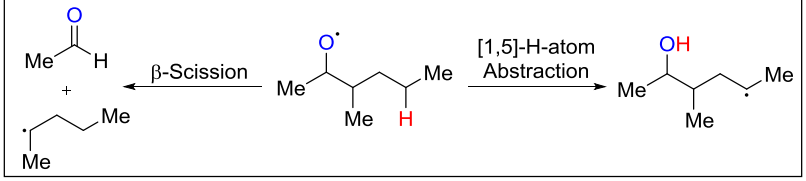
As one of the elements necessary for life, the presence of oxygen in natural products is extensive. Furthermore, the presence of oxygen in organic molecules constitutes a useful handle for subsequent transformations. Accordingly, oxygen is one of the most common atoms added to alkenes in difunctionalization reactions.

Figure 1.2: Correlation between O-H bond strength and reactivity



Oxygen-centered radicals display a broad spectrum of reactivity (**Figure 1.2**). Alkoxyl radicals are on the reactive extreme of the spectrum. These highly reactive species are difficult to control and are generally not amenable for use in synthesis. The high bond strength of the O-H bond of the parent alcohol (106 kcal/mol)[8] relative to that of the C-H bond (95 kcal/mol)[8] indicates that a strong thermodynamic driving force for hydrogen atom abstraction exists. Fragmentation via β-scission into a carbonyl group and a relatively

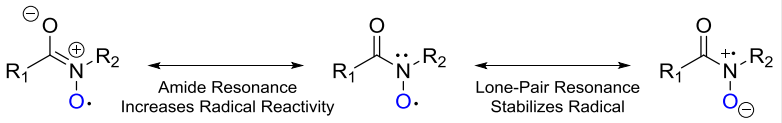
Figure 1.3: Decomposition pathways for alkoxyl radicals



more stable carbon-centered radical is also a viable decomposition pathway.[9] (**Figure 1.3**) It is the propensity for hydrogen atom abstraction from allylic hydrogen atoms, however, that presents the greatest difficulty for applying alkoxyl radicals to alkene difunctionalization methodology, as competing hydrogen atom abstraction from the substrate would lead to its decomposition.

Opposite alkoxy radicals in the reactivity spectrum are nitroxyl radicals. Nitroxyl radicals, including the commercially available TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl radical), are stable, isolable radicals. The thermodynamic stability of these radicals is a result of the delocalization of the spin density on the oxygen atom with the lone pair on the neighboring nitrogen atom.[10] Due to the weak oxygen-hydrogen bond strength (70 kcal/mol)[8] of the parent hydroxylamine, nitroxyl radicals have little thermodynamic incentive to participate in hydrogen atom abstractions. Their principle reactivity in radical chemistry involves recombination with carbon-centered radicals. Also, due to their stability, nitroxyl radicals generally do not add into alkenes in such a fashion that the process would be useful for preparative synthetic chemistry.[11]

Figure 1.4: Resonance forms of amidoxyl radicals

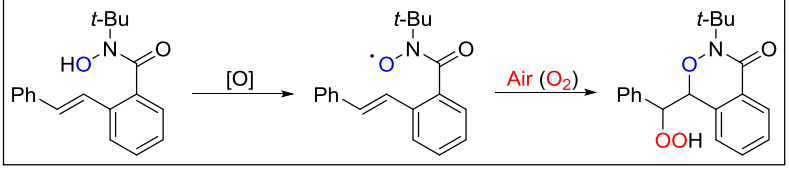


Lying between the two reactivity extremes is the amidoxyl radical (**Figure 1.4**). Like TEMPO, the amidoxyl radical derives stability from the presence of the lone pair on the nitrogen atom. However, the lone pair on nitrogen is in resonance with the carbonyl group, and resonance structures which remove the lone pair from the nitrogen atom serve to destabilize the amidoxyl radical. This mixture of stability and instability endows the amidoxyl radical with reactivity that is intermediate between the two extremes. It is reactive enough to perform useful chemical reactions, but it is stable enough to be tolerant of chemical functionality on the substrate being reacted. This intermediacy is reflected in the oxygen-hydrogen bond strength of the parent hydroxamic acid (80 kcal/mol),[12] which lies roughly in between that of the hydroxylamine and the alcohol.

The springboard for the development of a hydroxamic acid mediated alkene difunctionalization research program was provided by Perkins and coworkers in 1990.[13] In their work detailing a comparison

of intramolecular hydrogen atom abstraction and alkene addition of amidoxyl radicals, they reported a single example of an alkene dioxygenation (**Figure 1.5**), whereby the carbon-centered radical formed following addition of the amidoxyl radical into the alkene was trapped by molecular oxygen. This precedent layed the groundwork for the development of hydroxamic acid mediated intermolecular alkene difunctionalizations in our laboratory.

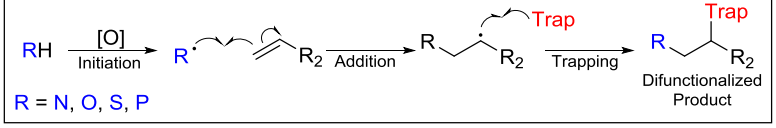
Figure 1.5: Perkins' hydroxamic acid mediated alkene difunctionalization



1.4 State-of-the-Art Heteroatom-Centered Radical Mediated Alkene Difunctionalizations

Nearly every main group element in the periodic table has radical chemistry associated with it. Radicals centered on phosphorous, sulfur, nitrogen, and oxygen atoms have been the most heavily studied. Methodologies focusing on the use of these radicals in difunctionalization typically follow a common mechanism (**Figure 1.6**). The heteroatom-centered radical is generated by oxidation or by hydrogen atom abstraction from an initiator, and adds into an alkene. This reaction creates a carbon-heteroatom bond and a carbon-centered radical on the vicinal carbon atom, which is subsequently quenched with a radical trap. Variations in the heteroatom-centered radical used and the trap employed create a diverse array of opportunities for difunctionalization of a common olefinic substrate.

Figure 1.6: General mechanism for radical mediated alkene difunctionalizations



1.4a Sulfur-Centered Radical Mediated Alkene Difunctionalization

The most well-known radical reaction associated with sulfur is hydrothiolation, which is the addition of the sulfur-hydrogen bond of a thiol across the double bond of an alkene. This reaction is also known as the thiol-ene coupling. Hydrothiolation can be initiated thermally through the addition of a free-radical initiator or photochemically through the use of a photosensitizer. The substrate scope of the reaction, in terms of both the thiol and the alkene, is extremely broad. Nearly any thiol can hydrothiolate any alkene. Furthermore, hydrothiolation reactions typically take place under mild reaction conditions and return product yields with predictable regioselectivity. For terminal alkenes, the thiyl radical adds in

an anti-Markovnikov fashion in order to generate the more stable secondary carbon-centered radical. The hydrothiolation of terminal alkenes uniformly follow this model, and the regioselectivities are excellent. For internal alkenes, however, the aforementioned controlling element is absent, and the regioselectivity is low.[14]

The versatility, efficiency, and reliability of the hydrothiolation reaction are reflected in the diversity of the applications in which it has been used, which include total synthesis and material science. In their total synthesis of cembrene, Pattenden and co-workers[15] utilized a hydrothiolation reaction which was interrupted by the ring-opening of a cyclopropane ring before the reductive termination of the carbon-centered radical with a hydrogen atom (**Figure 1.7**). Treatment of the diterpene cembrene with ethanethiol and light led to a regioselective addition of the thiyl radical into the trisubstituted alkene adjacent to the cyclopropane. The origin of the regioselectivity can be attributed to two factors. The reversibility of the thiyl radical addition reaction as well as the slow rates of radical additions into heavily substituted alkenes ensures that any undesired, normal 1,2-hydrothiolation does not occur to a significant extent.[14,16] However, the placement of the cyclopropane adjacent to the targeted alkene provides for the opportunity for a fast, irreversible cyclopropane ring opening following the desired thiyl addition event. This ring opening helps to ensure that the Casbene substrate is converted to the desired product. Following the formal 1,4-hydrothiolation, the newly installed thiol is oxidized and thermally eliminated to yield Cembrene. In addition to natural product synthesis, hydrothiolation has powerful applications in materials chemistry. One such application is surface modification of a polymer. The surface of the polymer, which can either contain free alkenes or free thiols, is reacted

Figure 1.7: Interrupted hydrothiolation strategy for Cembrene synthesis from Casbene

Pattenden et al.

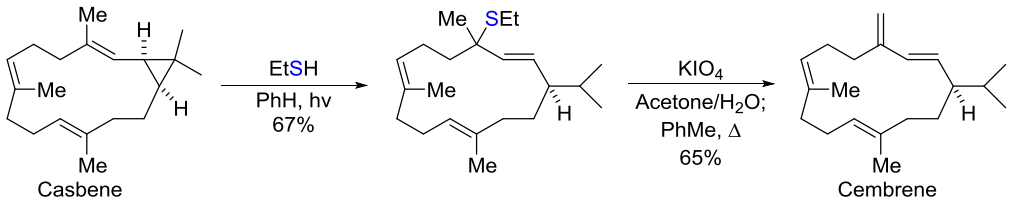
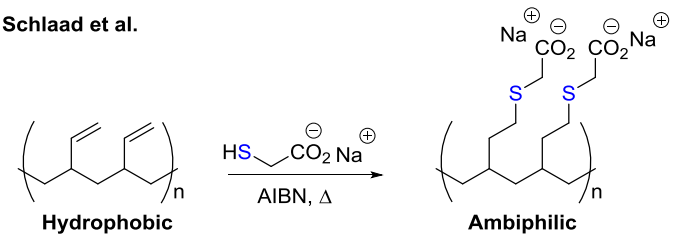


Figure 1.8: Polymer surface modification via hydrothiolation

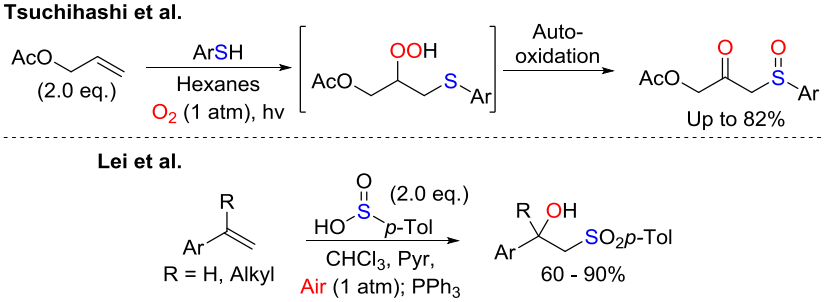
Schlaad et al.



with a thiol or alkene, respectively.[16] A dramatic application of this technique was achieved by the surface modification of the non-polar polymer 1,2-polybutadiene (**Figure 1.8**).[17] It was found that hydrothiolation of the pendant vinyl groups with hydrophilic thiols allowed for the hydrophilicity of the 1,2-polybutadiene surface to be increased to the extent that it displayed ambiphilic properties. These modified polymers are anticipated to have applications in drug delivery. A similar strategy was used in a bio-orthogonal context by Waldman and co-workers to immobilizing proteins to surfaces.[18] Waldman's approach involved attaching an allyl-containing biotin derivative to calf-liver phosphatase enzymes, and then adhering the enzymes to a thiol-containing surface through a photoinduced thiol-ene coupling. The degree of enzyme immobilization onto the surface could be tuned by varying the irradiation time. Saturation of the surface with enzyme was achieved in 10 minutes. The activity of the enzyme was retained after immobilization, which serves as an excellent example of the bio-orthogonality of the thiol-ene coupling reaction conditions.

A less common alkene difunctionalizations involving thiyl radicals is the thiol-olefin cooxidation (**Figure 1.9**). The thiol-ene co-oxidation process involves similar reaction conditions to the thiol-ene reaction, with the exception being that the reaction is carried out under aerobic conditions. In this variant, triplet oxygen intercepts the carbon-centered radical generated by thiyl radical addition into the alkene. After hydrogen atom abstraction, a hydroperoxide is formed. Due to the reducing powers of the adjacent sulfide, the hydroperoxide is immediately reduced the alcohol with simultaneous oxidation of the sulfide to the sulfoxide.[14,19,20] An oxysulfonylation, a similar variant to the thiol-olefin cooxidation reaction, was recently published.[21] In this system, however, sulfonyl radicals generated from sulfinic acids are employed and an external reductant is required to reduce the hydroperoxide to the ketone. The substrate scope is limited to activated olefins, such as styrenes and acrylates.

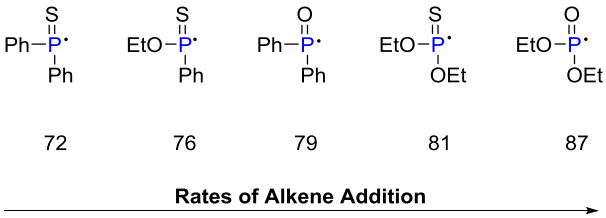
Figure 1.9: Thiol-olefin co-oxidation procedures



1.4b Phosphorus-Centered Radical Mediated Alkene Difunctionalizations

Like sulfur, phosphorus centered radicals are also capable of efficiently adding to alkenes, and a rich set of difunctionalization chemistry has stemmed from this property. Radical chemistry with phosphorus is typically carried out using pentavalent radical precursors. These can include both phosphorus(V) oxides and sulfides. Radical methods stemming from the use of trivalent phosphorus precursors are less common. The most common method for generating a phosphorus-centered radical involves hydrogen atom abstraction from a phosphorus hydride using a free-radical initiator or a photoinitiator.[22] The electronic character of the phosphorus center has a dramatic effect on the phosphorus-hydrogen bond strength, as was illustrated by Parsons and coworkers through DFT calculations (**Figure 1.10**).[23]

Figure 1.10: Rates of alkene addition for various phosphorus hydrides



In general, phosphine sulfides have weaker P-H bond strengths than their oxide counterparts. In addition, replacing phenyl substituents on the phosphorus atom with ethoxide ligands led to an increase in P-H bond strength for both phosphine oxides and sulfides. In general, the rate of addition of alkenes increases as the P-H bond strength of the precursor increases.

The two main radical difunctionalization reactions developed for phosphorus-centered radical parallel those developed for sulfur: hydrophosphorylation and oxyphosphorylation. Hydrophosphorylation has been reported several times in various forms.[24] Like hydrothiolation, the hydrophosphorylation of terminal alkenes proceeds with perfect anti-Markovnikov selectivity. However, also like hydrothiolation, this selectivity erodes significantly for internal double bonds.[25] An excellent example of hydrophosphorylation proceeding under very mild conditions was reported by Dondoni and coworkers (**Figure 1.11**).[26] This system involves the hydrophosphorylation of alkenes bearing acetylated pyranoses using dimethyl phosphite. Hydrophosphorylation was initiated using the photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DPAP) and UVA light. The yields obtained ranged from 45 to 90%, with the majority falling in the 90's. Recently, Grubbs and co-worker[27] developed an innovative

photochemical hydrophosphorylation procedure using triphenylphosphonium tetrafluoroborate as the phosphorus source. This reaction is distinct from other phosphorus-based radical reactions because it proceeds through a phosphorus radical cation intermediate, rather than a neutral radical as is shown above. Interestingly, the counterion has a significant effect on reactivity. Triphenylphosphonium bromide failed to difunctionalize 4-allyanisole and triphenylphosphonium hexafluorophosphate returned a severely diminished yield compared to that of the tetrafluoroborate analog (13 vs. 50% yield). The reaction system is capable of functionalizing unactivated olefins in high yield (72 to 95% yield). Activated alkenes, such as styrenes and acrylates, are absent from the substrate scope possibly as a result of thermoneutrality of the hydrogen atom transfer from the phosphonium salt to the stabilized carbon centered radical. To demonstrate the utility of this method, the crude hydrophosphonation product was employed as a substrate in a Wittig reaction with *p*-tolualdehyde, and was found to return the olefinated product in high yield. In addition to hydrophosphonylation reactions, phosphorus(V) hydrides can participate in oxyphosphorylation reactions (**Figure 1.12**). Ji and co-worker[28] developed such a system using diisopropyl phosphite and dioxygen as the oxygen source. The products of this reaction are β-ketophosphonates, which are substrates for the Horner-Wadsworth-Emmons olefination reaction. A mixed catalyst system consisting of copper(II) bromide and iron(III) bromide was required for reactivity. These salts are presumably responsible for the oxidation events necessary to generate the phosphorus-centered radical, as well as the oxidation/dehydration of the intermediate alkyl hydroperoxide formed following the trapping of dioxygen to the ketone. This method is applicable towards styrenes, and returns the corresponding β-ketophosphonates in good to moderate yields (52-84% yield). However,

Figure 1.11: Phosphorus radical-mediated hydrophosphorylation reactions

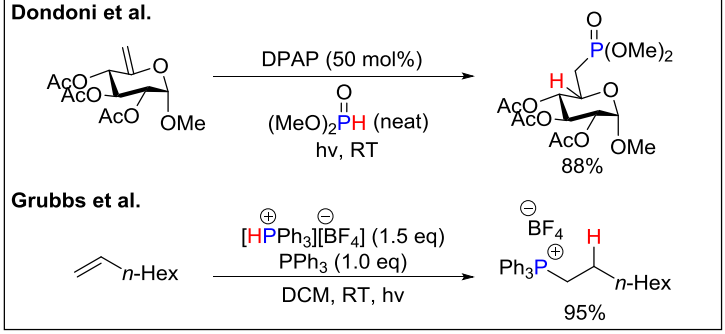
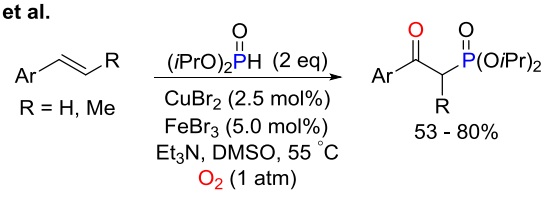


Figure 1.12: Phosphorus radical-mediated alkene oxyphosphorylation



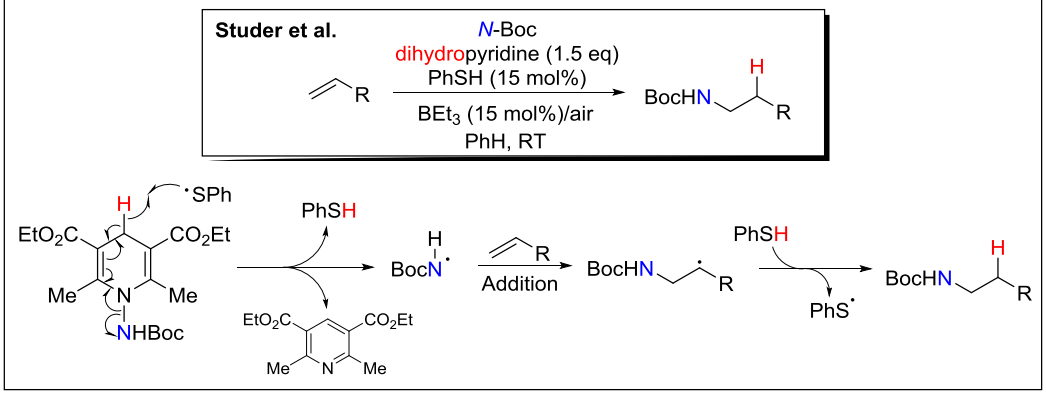
unactivated alkenes, such as octene, return low yields (26%). This is a surprising finding considering the high yields obtained with unactivated alkene substrates in the hydrophosphonylation reaction.

1.4c Nitrogen-Centered Radical Mediated Alkene Difunctionalizations

Alkene difunctionalizations utilizing nitrogen as one of the reaction components are of very high value.[29] One of the obstacles to utilizing nitrogen-centered radicals in synthesis is the generation of the radical itself. Unlike thiols (80 kcal/mol)[8] and phosphorus hydrides (85-70 kcal/mol),[23] which possess weak heteroatom-hydrogen bonds, the nitrogen-hydrogen bond in amines and amides is relatively strong (95-100 and 105-110 kcal/mol).[8] Accordingly, the methods used to generate nitrogen-centered radicals vary greatly from those used for sulfur and phosphorus, which typically involve radical formation by abstraction of hydrogen from the parent thiol or phosphorus hydride. Relative to sulfur and phosphorus, nitrogen is more prevalent in natural products, drugs, and synthetic building blocks. Accordingly, a greater effort has been exerted towards developing nitrogen-based difunctionaliztion methodologies. This is reflected in the greater variety of transformations currently available that employ nitrogen-centered radicals.

Hydroamination is an extremely important alkene monofunctionalization that has been studied extensively in the context of transition-metal-catalysis and lanthanide-metal-catalysis. Problems associated with the use of metals can include harsh reaction conditions, including high temperatures or the use of strong bases, premature β-hydride elimination to deliver enamines rather than alkyl amines, and regioselectivity issues associated with competitive formation of the Markovnikov product vs. the anti-Markovnikov product.[30] The group of Armido Studer has developed a creative hydroamination method using *N*-aminated dihydropyridines (**Figure 1.13**), which function as both the source of the nitrogen-centered radical and as a hydrogen atom donor.[31] Notably, the method takes place at low temperatures and yields, in most cases, exclusively the anti-Markovnikov product. The mechanism begins with abstraction of the hydrogen atom from the dihydropyridine by a thiyl radical (thiophenol functions as the polarity reversal catalyst).[32] Aromatization of the dihydropyridine leads to homolytic scission of the weak nitrogen-nitrogen single bond to form the carbamoyl radical, which then adds into the alkene in an anti-

Figure 1.13: Mechanism of *N*-Boc-dihydropyridine mediated alkene hydroamination

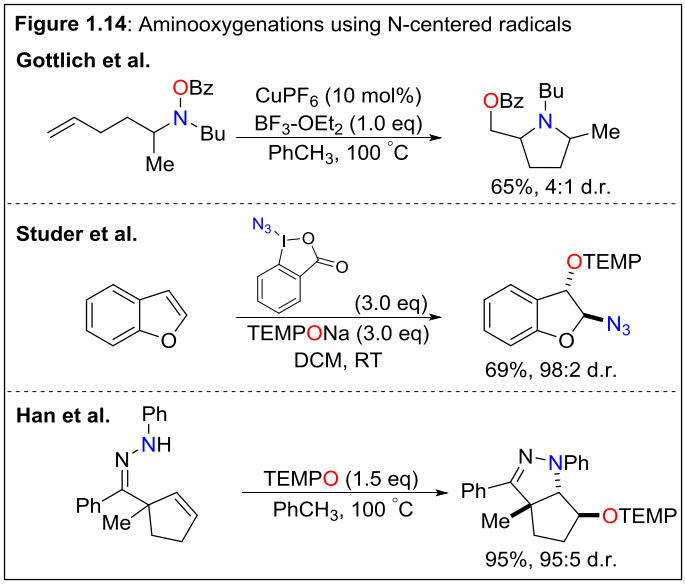


Markovnikov fashion. The resulting carbon-centered radical is reduced to the alkane by a fast hydrogen-atom abstraction from thiophenol. In the absence of the thiophenol polarity reversal catalyst, hydrogen atom-transfer would be expected to occur between the carbon-centered radical and the dihydropyridine C-H bond, which is a kinetically slow process.[33] Indeed, reactions lacking thiophenol proceeded in yields diminished by over 10%. The substrate scope of the reaction includes unactivated alkenes (such as hexene and octene), enol ethers, and silyl enol ethers. Yields range from 50 – 70%, with the highest yields being obtained using enol ethers as substrates.

The aminooxygenation reaction, particularly the Sharpless asymmetric aminohydroxylation, has found considerable use in natural product synthesis.[29] Its utility has made aminooxygenation reactions an attractive target for radical methodology involving the addition of a nitrogen-centered radical into an alkene. Oxyaminations, which involve an oxygen-centered radical adding into an alkene to produce the opposite regioisomers, will be discussed in the next section. The first example of a radical aminooxygenation appeared in 2002 from the Gottlich group (**Figure 1.14**).[34] This system depends on the cyclization of nitrogen-centered radicals derived from unsaturated *O*-benzoylhydroxylamines. The generation of the radical is achieved by reduction of the nitrogen-oxygen bond using a copper(I) catalyst. During this process, a copper(II) salt containing a benzoate ligand is formed. *Exo* cyclization of the nitrogen-centered radical generates a carbon-centered radical. This radical is oxidized by the copper(II) salt with concomitant transfer of the benzoate group to the carbon atom to effect the aminooxygenation. The substrate scope is limited to the formation of pyrrolidines through *5-exo* cyclizations. The addition of

boron trifluoride diethyletherate is necessary for high yields. Its coordination to the benzoyl group of the substrate decreases the electron density of the nitrogen-oxygen bond, making it more susceptible to reduction by the copper(I) salt. Furthermore, it is believed to coordinate to the aminyl radical, making it more electrophilic and more capable of adding into the alkene. More recently, Studer and co-worker developed an azidooxygenation procedure for alkenes (**Figure 1.14**).[35] The reaction is versatile in substrate scope, with a variety of alkenes being capable of functioning as substrates. These include styrenes, enol ethers, as well as unactivated alkenes (such as octene). The reaction is made possible by a redox event occurring between the sodium salt of TEMPO (a reductant) and an azidoiodine(III) reagent (an oxidant). Following the redox event, an azido radical and a TEMPO radical are formed. The azido radical then adds into the alkene in an anti-Markovnikov fashion, and TEMPO recombines with the carbon-centered radical formed following addition. Post-reaction modifications that can be made to the azide and alkoxyamine functionality within the molecule include a [3+2] cycloaddition with the azide group with phenylacetylene to produce a triazole, reduction of the azide to the amine (Staudinger reaction), reduction of the alkoxyamine to the alcohol, and oxidation of the alkoxyamine to the ketone. In a similar study, the Han group demonstrated that intramolecular aminohydroxylations can be performed using the radicals derived from hydrazones and the TEMPO radical (**Figure 1.14**).[36] Like the radical chemistry derived from thiols and phosphorus hydrides, the hydrazonyl radical is formed by abstraction of the N-H bond from the hydrazone, presumably by TEMPO. A variety of pyrazolines were synthesized using this method via *5-exo* cyclizations onto β,γ-unsaturated hydrazones. Substrates containing an endocyclic alkene produce aminooxygenated products with high *trans* diastereoselectivity. However, attempts to carry out a *6-exo* cyclization onto a γ,δ-

Figure 1.14: Aminooxygenations using N-centered radicals



unsaturated hydrazone led to undesired byproduct formation stemming from 1,5-hydrogen atom abstraction outcompeting the desired *6-exo* cyclization.

Like vicinal amino alcohols, vicinal diamines are important structural motifs in natural products, medicinal agents, and chiral ligands for catalysis. Efforts to extend the Sharpless strategy of employing osmium(VIII) compounds towards the asymmetric aminofunctionalization of alkenes were hindered by the bis-imido osmium(VIII) complexes inability to bind to the Cinchona alkaloids previously used for the Sharpless asymmetric dihydroxylation and aminohydroxylation. Furthermore, the osmaimidazolidines formed upon reaction of a bis-imido osmium(VIII) complex are resistant to hydrolysis, making the development of a system catalytic in osmium difficult (**Figure 1.15**). Metal hydrides, such lithium aluminum hydride or sodium borohydride, can cleave the osmaimidazolidine ring to free the 1,2-diamine, but the harshness of these reagents precludes their use in a setting where functionality vulnerable to reduction may be present.[37] Considerable effort has also been invested in developing diamination procedures using other metals, namely palladium, copper, nickel, and gold.[38] The difficulties associated with performing diamination reactions with transition metals has also spurred the development of diamination reactions proceeding through a radical mechanism. The Han group successfully applied their hydrazone radical based aminooxygenation methodology towards diamination by substituting TEMPO with the nitrogen-based radical trap diisopropyl azodicarboxylate (DIAD).[36] This diamination method faces the same limitations of the aminooxygenation method, namely that 1,5-hydrogen atom abstraction of the allylic hydrogen atom

Figure 1.15: Obstacles to developing an osmium-catalyzed alkene diamination

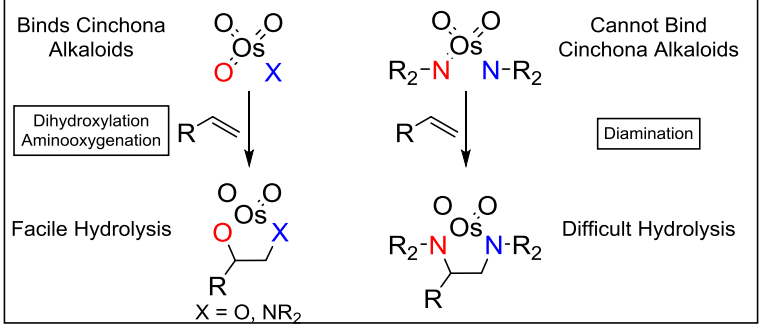
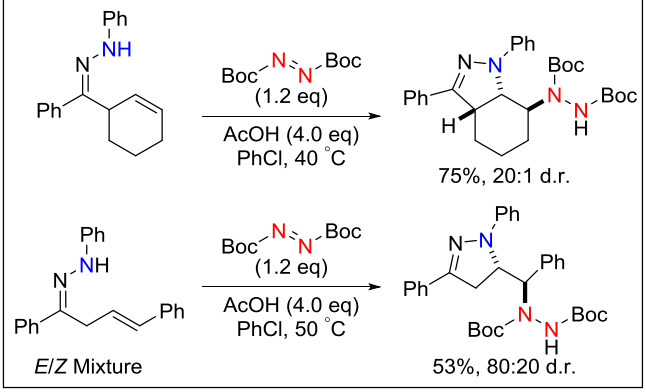


Figure 1.16: Diaminations using N-centered radicals

Loh et al.



outcompetes *6-exo* cyclization. A similar diamination methodology was simultaneously disclosed by the Loh group (**Figure 1.16**).[39] Loh group identified that acetic acid was a key additive that allowed for the reaction to be carried out at lower temperatures than those of Han (40 °C rather than 100 °C) and that di-*tert*-butyl azodicarboxylate (DTAD) could be used in place of DIAD. The use of DTAD provides for a more facile removal of the carbamate groups in the hydrazine product by treatment with trifluoracetic acid. Both the Han and Loh groups reported that 1,2-disubstituted alkenes can be diaminated with high *trans* selectivity. More recently, the Zhang group disclosed a copper catalyzed diamination of styrenes based upon the generation of the bisphenylsulfonylamidyl radical from *N*-fluorobenzenesulfonamide (NFSI) (**Figure 1.17**).[40] The nitrile solvent serves as the source of the source of the nitrogen atom attached to the benzylic carbon. The yields obtained vary from good to excellent (50% to 97% yield). Curiously, electron poor styrenes return higher yields than electron rich styrenes, despite being electronically mismatched with the electron poor bisphenylsulfonylamidyl radical. Studer and co-workers developed a similar aminoazidation protocol using a system employing NFSI and trimethylsilyl azide as the nitrogen sources (**Figure 1.17**).[41] Both the Zhang and Studer methods are postulated to proceed through the same mechanism. The bis-sulfonylamidyl radical is proposed to be generated by the reduction of the N-F bond of NFSI using the copper(I) catalyst. The radical trap is transferred to the substrate through via reductive elimination from an intermediate alkyl copper(III) species. Alternatively, the radical trap may be transferred to the substrate via a polar Ritter type reaction following oxidation of the carbon-centered radical to the carbocation. Interestingly, the aminoazidation of β-methyl styrene using Studer's method provided the *trans* diaminated product in high diastereoselectivity (98:2 d.r.), whereas the diamination of the same

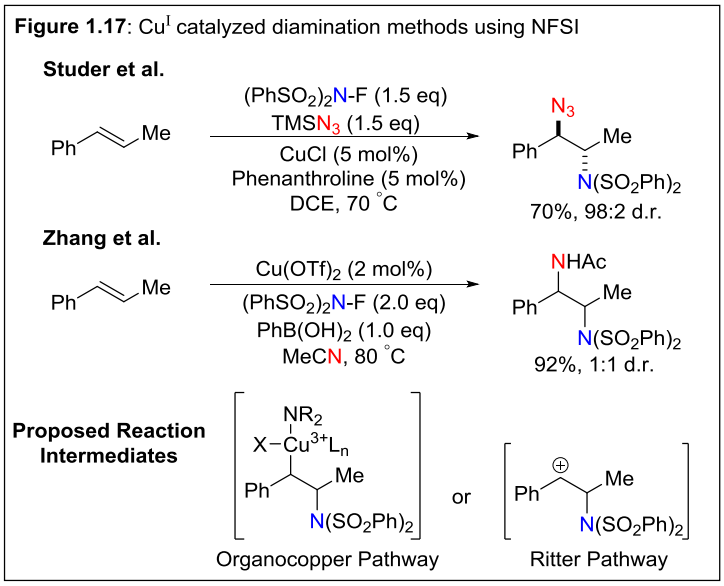


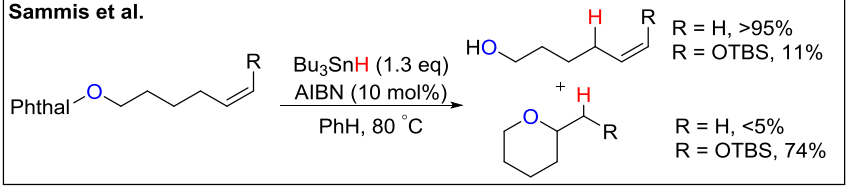
Figure 1.17: Cu^{I} catalyzed diamination methods using NFSI

substrate with the aforementioned Zhang method provided a 1:1 mixture of diastereomers of aminoamidated product. This comparison suggests that the two methods may be operating through different mechanisms.

1.4d Oxygen-Centered Radical-Mediated Alkene Difunctionalization

Being the most electronegative of the atoms so far considered, oxygen-centered radicals, such as hydroxyl and alkoxyl radicals, are the most reactive and most difficult radical species to control. The application of alkoxyl radicals to synthesis is dominated by the threat of substrate decomposition through unintended hydrogen atom abstraction from the substrate or by β-fragmentation to form a carbonyl group and a carbon-centered radical (see **Figure 1.3**). Reversion of the alkoxyl radical to the parent OH compound through hydrogen atom abstraction from the solvent is another problem that reduces reaction efficiency.[42] Another obstacle to the application of oxygen-centered radicals is the difficulty in producing them. The strong oxygen-hydrogen bond strength of the alcohol or the carboxylic acid (105 kcal/mol)[8] rules out hydrogen-atom abstraction as a means of generating the radical. Precursors with weak oxygen-heteroatom bonds, such as alkyl hypochlorites, hyponitrates, and hyponitrites, are capable of generating the oxygen-centered radical, although their inherent instability also makes them difficult to synthesize and unreliable to use. Thiohydroxamates and similar derivatives have seen success as sources of oxygen-centered radicals, and address some of the aforementioned problems. However, these substrates require a stoichiometric amount of tin in order to generate the radical.[42] The application of alkoxyl radicals towards reactions involving addition of the radical into the alkene are extremely limited by the fact that intramolecular 1,5-hydrogen atom abstraction and β-fragmentation are faster processes than radical addition.[43] Modification of the substrate, such as limiting the reaction to a *5-exo* cyclization[44] or by fully substituting the allylic carbon atom, can help to coerce the oxygen centered radical into cyclizing. The Sammis group took an alternative approach to gaining control over alkoxy radical cyclizations (**Figure**

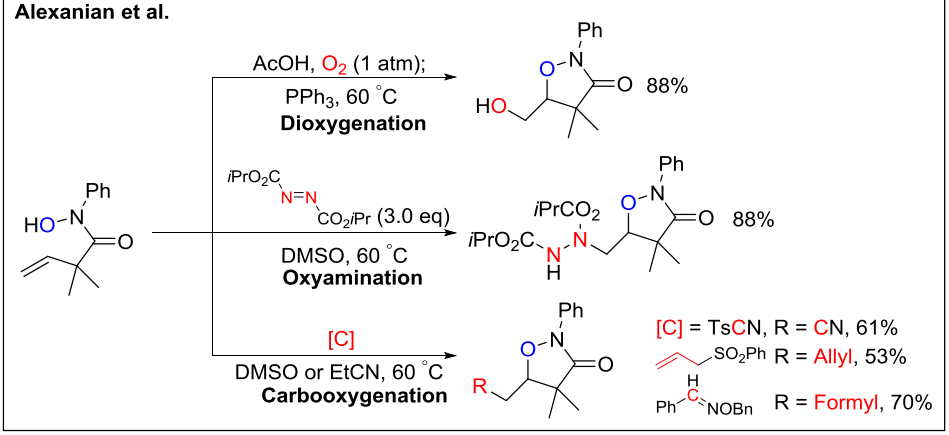
Figure 1.18: Altering relative cyclization vs. abstraction rates through alkene electronics
Sammis et al.



1.18).[45] They hypothesized that by matching the electronics of an electron rich silyl enol ether to the electron poor alkoxyl radical, they could increase the rate of cyclization relative to undesired 1,5-hydrogen atom abstraction or β-fragmentation pathways. In practice, this theory is successful. In attempting a *6-exo* cyclization with a silyl enol ether, an 8:1 preference for cyclization to the tetrahydropyran over abstraction of the allylic hydrogen atoms is observed. The olefin analog of this substrate demonstrates a 20-fold preference for abstraction over cyclization. An alternative strategy for utilizing oxygen-centered radicals is altering its chemical behavior through substitution on the oxygen atom. Nitroxyl radicals, which are oxygen-centered radicals bound to a nitrogen atom, display an attenuated reactivity profile relative to alkoxyl radicals due to the stabilization gained by resonance delocalization between the unpaired electron on the oxygen atom and the lone pair on the nitrogen atom.[46] Early evidence for the synthetic utility of nitroxyl radicals was reported by the Perkins group in the early nineties.[47] This group was studying the difference in effective molarity values between intramolecular hydrogen atom abstraction from alkanes and intramolecular addition into alkenes. *N*-tertbutyl amidoxyl radicals derived from the corresponding hydroxamic acids were the radical species employed for this study. During the preparation of a stilbene derivative, an autooxidation event occurred whereby the unsaturated amidxoyl radical cyclized and trapped molecular oxygen present in the air to yield an alkyl hydroperoxide (**see Figure 1.5**). This event is effectively a dioxygenation of the alkene. Capitalizing on this discovery, our group developed a suite of intramolecular alkene difunctionalizations based on the unique ability of hydroxamic acids to add into alkenes (**Figure 1.19**). The first of these methods was an intramolecular dioxygenation of alkenes employing unsaturated *N*-phenyl hydroxamic acids.[48] Both *5-exo* and *6-exo* cyclizations can be carried out efficiently to yield the deoxygenated products. Notably, no by-products associated with 1,5-hydrogen atom abstraction are formed. Furthermore, endocyclic alkenes react to provide the *trans* dioxygenation products in good d.r. (up to 5:1 d.r.). These results complement the *cis* dihydroxylation products that are typically obtained using osmium catalyzed methods. The initial products of the dioxygenation reaction are alkyl hydroperoxides. These products can be isolated or reduced to the alcohols upon completion of the reaction by reduction with triphenylphosphine. Cleavage

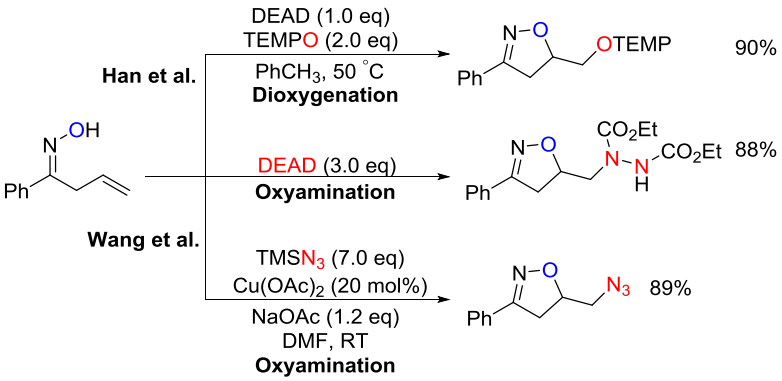
of the nitrogen-oxygen bond of the isoxazoline products can be achieved by reduction of the bond with zinc dust. An extension of this methodology was achieved by utilizing diisopropyl azodicarboxylate (DIAD) as a radical trap to effect an oxyamination.[49] Both *5-exo* and *6-exo* cyclizations could be achieved. Like the dioxygenation method, endocyclic alkenes yield difunctionalized products with high *trans* selectivity (typically >95:5 d.r.). A third method employing this difunctionalization strategy was achieved using carbon-based radical traps.[50] Three carbooxygenation variants were disclosed. Oxyallylations could be achieved using allyl sulfone radical traps, while oxycyanations were accomplished using toluenesulfonyl cyanide. Oxyacylations could be carried out over two steps using phenylsulfonyl oxime ethers.

Figure 1.19: Hydroxamic acid mediated alkene difunctionalizations



A functional group related to hydroxamic acids, the oxime, has recently been shown by other groups to be capable of carrying out similar difunctionalizations (**Figure 1.20**). The Han group recently disclosed an oxime mediated intramolecular dioxygenation and oxyamination method using TEMPO and diethylazodicarboxylate (DEAD) as oxygen and nitrogen based radical traps, respectively.[51] Cyclizations proceeding through the *5-exo* cyclization manifold proceed in good yields (77 – 90% yield) and, notably, like the hydroxamic acid methods, the difunctionalization products of endocyclic alkene substrates yield products with high *trans* selectivity. Oximes, however, lack the carbonyl group of hydroxamic

Figure 1.20: Oxime mediated alkene difunctionalizations



acids. The carbonyl group serves to remove spin density from the nitrogen atom.[12] With oximes, spin density is approximately evenly distributed between the nitrogen atom and the oxygen atom.[51] When γ,δ-unsaturated oximes are employed as substrates, the *5-exo* cyclization stemming from addition of the nitrogen-centered radical cation resonance structure of the oxime into the alkene outcompetes the *6-exo* cyclization of the oxygen-centered radical resonance structure. The products of this form of the reaction are cyclic nitrones. The use of TEMPO as the radical trap provides for the formation of formal aminooxygenation products, while the use of DEAD yields diamination products. Very recently, an extension of this oxime radical methodology was published by the Wang group in the form of an intramolecular oxyazidation procedure for unsaturated oximes.[52] Azidotrimethylsilane was utilized as the nitrogen-based radical trap, which provides for more convenient post-reaction modifications. However, only *5-exo* cyclization substrates were reported.

In considering the strengths and weaknesses of competing alkene difunctionalization methodologies in the literature, we identified several improvements that could enhance the utility of our hydroxamic acid based methods. The first area was the development of an intermolecular difunctionalization protocol. An intermolecular oxyfunctionalization of alkenes would be an unquestionably useful extension of the intramolecular versions. Due to the rapid rate of dioxygen recombining with carbon-centered radicals, as well as the well-established utility of dihydroxylated organic compounds, we selected the dioxygenation reaction as our first target for an intermolecular method. The second area of improvement would be to examine the capabilities of a hydroxamic acid to function as a reducing agent for carbon-centered radicals. With a weak OH bond strength (approximately 80 kcal/mol), we hypothesized that the hydroxamic acid itself could function as a hydrogen atom donor in a difunctionalization reaction and reduce a carbon-centered radical to the alkane. The realization of this concept would lead to a formal alkene hydration reaction, which is unprecedented in radical chemistry.

REFERENCES

[1] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

[2] For examples of recent difunctionalization methodology, see: (a) Muniz, K.; Martinez, C. *J. Org. Chem.* **2013**, *78*, 2168. (b) Yadav, J. S.; Antony, A.; Rao, T. S.; Subba Reddy, B. V. *Journal of Organometallic Chemistry*, **2011**, *696*, 16. (c) Chemler, S. *Org. Biomol. Chem.* **2009**, *7*, 3009. (d) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083.

[3] Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114.

[4] Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072.

[5] (a) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846. (b) Baldwin, J. E. *J. Chem. Soc. Chem. Comm.* **1976**, 734.

[6] (a) Zard, S. Z. in *Radical Reactions in Organic Synthesis*, Oxford University Press, New York, NY, 2003. (b) Gansauer, A.; Greb, A.; Huth, I.; Worgull, D.; Knebel, K. *Tetrahedron* **2009**, *65*, 10791.

[7] Togo, H. in *Advanced Free Radical Reactions for Organic Synthesis*, Elsevier, Amsterdam, The Netherlands, 2004.

[8] Luo, Y. R., in *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, FL, 2003.

[9] Hartung, J. *Eur. J. Org. Chem.* **2001**, 619.

[10] Szkurhan, A. R.; Lukkarila, J.; Georges, M. K., in *Stable Radicals Fundamentals and Applied Aspects of Odd-Electron Compounds*, ed. Hicks, R. G., John Wiley & Sons Ltd, West Sussex, United Kingdom, 2010.

[11] The addition of TEMPO into d_2-cyclohexene has been reported: Coseri, S.; Ingold, K. U. *Org. Lett.* **2004**, *6*, 1641.

[12] Perkins, M. J.; Berti, C.; Brooks, D. J.; Grierson, L.; Grimes, J. A. M.; Jenkins, T. C.; Smith, S. L. *Pure & Appl. Chem.* **1990**, *62*, 195.

[13] Berti, C.; Grierson, L.; Grimes, J. A. M.; Perkins, M .J.; Terem, B. *Angew. Chem. Int. Ed.* **1990**, *29*, 653.

[14] Denes, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev*. **2014**, *114*, 2587.

[15] Pattenden, G.; Smithies, A. J. *Synlett* **1992**, 577.

[16] Hoyle, C. E.; Bowman, C. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 1540.

[17] (a) Hordyjewicz-Baran, Z.; You, L.; Smarsly, B.; Sigel, R.; Schlaad, H. *Macromolecules* **2007**, *40*, 3901. (b) Justynska, J.; Hordyjewicz, Z.; Schlaad, H. *Polymer* **2005**, *46*, 12057.

[18] Jonkheijm, P.; Weinrich, D.; Kohn, M.; Engelkamp, H.; Christianen, P. C. M.; Kuhlmann, J.; Maan, J. C.; Nusse, M.; Schroeder, H.; Wacker, R.; Breinbauer, R.; Niemeyer, C. M.; Waldman, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4421.

[19] Kharasch, M. S.; Nudenberg, W.; Mantell, G.J. *J. Org. Chem.* **1951**, *16*, 524.

[20] Iriuchijima, S.; Maniwa, K.; Sakakibara, T.; Tsuchihashi, G. *J. Org. Chem.* **1974**, *39*, 1170.

[21] Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 7156.

[22] Leca, D.; Fensterbank, L.; Lacote, E.; Malacria, M. *Chem. Soc. Rev.* **2005,** *34*, 858.

[23] Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D.J. *Eur. J. Org. Chem.* **2006**, 1547.

[24] Coudray, L.; Montchamp, J. L. *Eur. J. Org. Chem.* **2008**, 3601.

[25] Reznikov, A. N.; Sokolova, M. V.; Skvortsov, N. K. *Russ. J. Gen. Chem.* **2004**, *74*, 1461.

[26] Dondoni, A.; Staderini, S.; Marra, A. *Eur. J. Org. Chem.* **2013**, 5370.

[27] Daeffler, C. S.; Grubbs, R. H. *Org. Lett.* **2011**, *13*, 6429.

[28] Wei, W.; Ji, J. X. *Angew. Chem. Int. Ed.* **2011**, *50*, 9097.

[29] Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2733.

[30] Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

[31] (a) Chou, C. M.; Guin, J.; Muck-Lichtenfeld, C.; Grimme, S.; Studer, A. *Chem. Asian. J.* **2011**, *6*, 1197. (b) Guin, J.; Frohlich, R.; Studer, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 779.

[32] For a review of the concept of polarity reversal catalysis, see: Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

[33] Warren, J. J.; Mayer, J. *PNAS*, **2010**, *107*, 5282.

[34] Noack, M.; Gottlich, R. *Chem. Commun.* **2002**, 536.

[35] Zhang, B.; Studer, A. *Org. Lett.* **2013**, *15*, 4548.

[36] Duan, X. Y.; Yang, X. L.; Fang, R.; Peng, X. X.; Yu, W.; Han, B. *J. Org. Chem.* **2013**, *78*, 10692.

[37] Muniz, K.; Iesato, A.; Nieger, M. *Chem. Eur. J.* **2003**, *9*, 5581.

[38] For a comprehensive review on diamination, see: De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067.

[39] Zhu, M. K.; Chen, Y. C.; Loh, T.P. *Chem. Eur. J.* **2013**, *19*, 5250.

[40] Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 2529.

[41] Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1790.

[42] Hartung, J. *Eur. J. Org. Chem.* **2001**, 619.

[43] Dreessen, T.; Jargstorff, C.; Lietzau, L.; Plath, C.; Stademann, A.; Wille, U. *Molecules* **2004,** *9*, 480.

[44] Hartung, J.; Gottwald, T.; Spehar, K. *Synthesis* **2002**, 1469.

[45] Zlotorzynska, M.; Zhai, H.; Sammis, G.M. *Org. Lett.* **2008**, *10*, 5083.

[46] Karoui, H.; Le Moigne, F.; Ouari, O.; Tordo, P., in *Stable Radicals Fundamentals and Applied Aspects of Odd-Electron Compounds*, ed. Hicks, R. G., John Wiley & Sons Ltd, West Sussex, United kingdom, 2010.

[47] (a) Berti, C.; Grierson, L.; Grimes, J. A. M.; Perkins, M. J.; Terem, B. *Angew. Chem. Int. Ed.* **1990**, *29*, 653. (b) Perkins, M. J.; Berti, C.; Brooks, D. J.; Grierson, L.; Grimes, J. A. M.; Jenkins, T. C.; Smith, S. L. *Pure & Appl. Chem.* **1990**, *62*, 195. (c) Hussain, S. A.; Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc. Perkin Trans. 1* **1979**, *2803*.

[48] Schmidt, V. A.; Alexanian, E. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4491.

[49] Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402.

[50] Quinn, R. K.; Schmidt, V. A.; Alexanian, E. J. *Chem. Sci.* **2013**, *4*, 4030.

[51] Han, B.; Yang, X. L.; Fang, R.; Yu, W.; Wang, C.; Duan, X. Y.; Liu, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 8816.

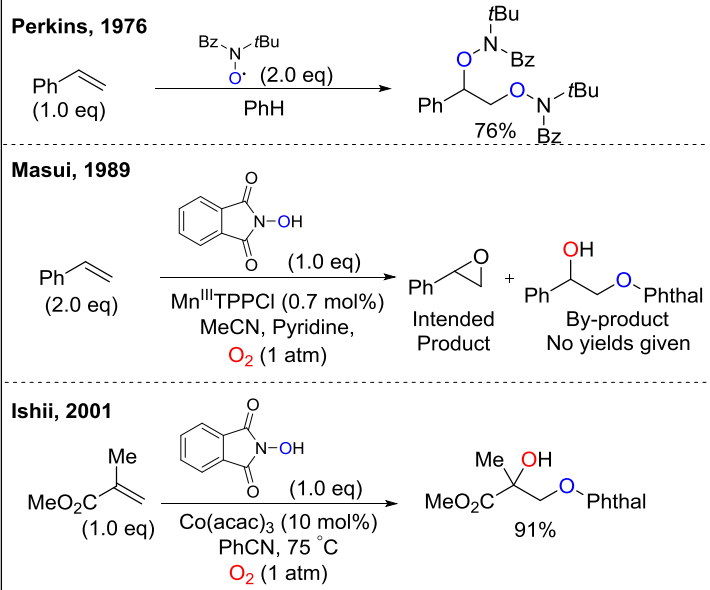
[52] Zhu, L.; Yu, H.; Xu, Z.; Jiang, X.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1562.

CHAPTER 2: DEVELOPMENT OF AN INTERMOLECULAR ALKENE DIOXYGENATION

2.1 Introduction

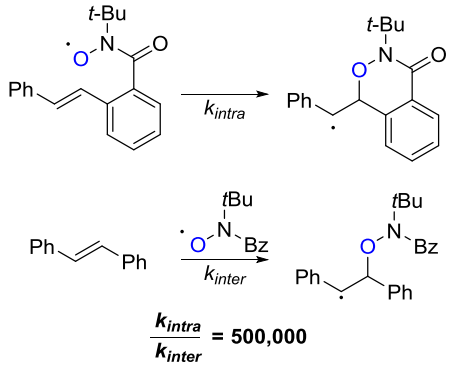
Before developing an intermolecular variant of a hydroxamic acid mediated alkene dioxygenation, we were conscious of two main challenges that we would face in pursuing this goal. The first difficulty was a lack of precedent in the synthetic literature for general difunctionalization methodologies of alkenes based on the addition of nitroxyl radicals into alkenes. Only isolated examples of this type of radical reactivity have been reported (**Figure 2.1**). One such report came from Perkins, who reported that isolated amidoxyl radicals would add into activated alkenes, including styrenes and norbornene, with subsequent recombination of the newly formed carbon-centered radical with a second molecule of amidoxyl radical.[1] Notably, however, allylic oxidation stemming from hydrogen atom abstraction was reported for β-methyl styrene. The highly reactive phthalamido-*N*-oxyl (PINO) derived from *N*-hydroxyphthalimide (NHPI) has also been reported to be capable of addition into alkenes. Masui and co-workers developed an alkene epoxidation reaction utilizing a manganese(III) porphyrin catalyst, NHPI, and a sacrificial alkene.[2] They determined that the hydroperoxide formed following PINO addition into the alkene and trapping of the carbon-centered radical with molecular oxygen oxidizes Mn^{3+} to the Mn^{5+} oxo species, which is responsible for the epoxidation of the alkene. This conclusion was based on the isolation of the corresponding dioxygenated by-products following the

Figure 2.1: Isolated examples of intermolecular alkene dioxygenations utilizing nitroxyl radicals



completion of the epoxidation reaction. Ishii and co-workers witnessed a similar dioxygenation of methyl methacrylate during the development of their cobalt and NHPI co-catalyzed oxyalkylation method.[3] These precedents for the PINO radical adding into alkenes is an important precedent because it demonstrated the feasibility of our intermolecular dioxygenation strategy. However, the PINO radical is too reactive for general use in synthesis. Its ability to abstract hydrogen atoms from hydrocarbons has been well documented and exploited.[4] The development of a general alkene dioxygenation reaction would require a less reactive radical than PINO, where radical addition into the alkene would outcompete hydrogen atom abstraction. The second difficulty to overcome would be the decrease in entropy associated with an intermolecular reaction relative to its intramolecular version, and the resulting drop in reaction rate (**Figure 2.2**). The magnitude of this challenge is best demonstrated as a ratio of the relative rates between the two processes. The kinetics work done by the Perkins group determined that the intramolecular addition of a *N-tert*-butyl amidoxyl radical onto an alkene is 500,000 times faster than the intermolecular version of the process.[5]

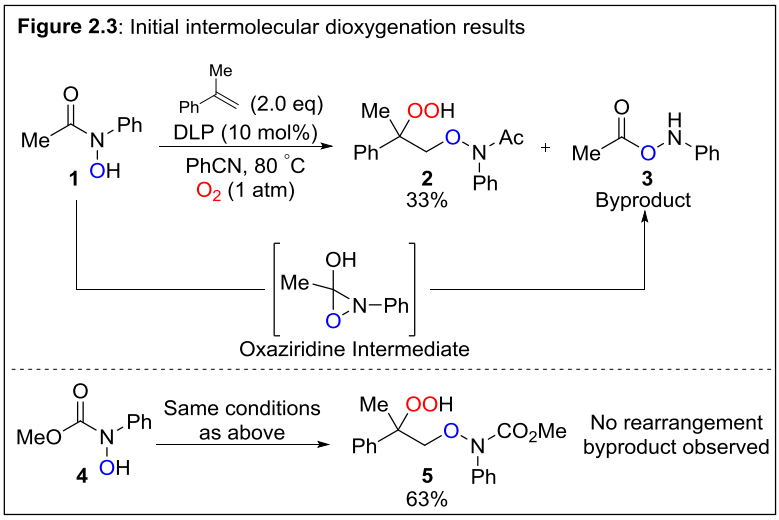
Figure 2.2: Relative rates for intramolecular and intermolecular amidoxyl radical addition



2.2 Creating a Hydroxamic Acid Reagent Capable of Intermolecular Reactivity

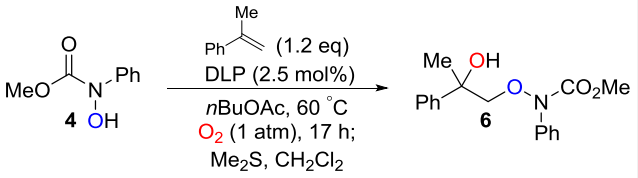
Our initial attempts to perform intermolecular alkene dioxygenations drew upon the experience that we gained during the development of the intramolecular variant. The amidoxyl radicals generated from *N*-phenyl hydroxamic acids with alkyl substitutions on the carbonyl carbon had proven to be capable of adding into alkenes. Accordingly, the first successful

Figure 2.3: Initial intermolecular dioxygenation results



derivative that was tested was *N*-phenyl acetyl hydroxamic acid **1** (**Figure 2.3**). Upon reaction with α-methyl styrene under an atmosphere of oxygen gas, the desired hydroperoxide was formed in low yield (30%). Other derivatives, such as benzoyl or trifluoroacetyl *N*-phenyl hydroxamic acids failed to yield product. During the dioxygen reaction employing derivative **1**, *O*-acetyl-*N*-phenyl hydroxylamine (**3**) was formed as a significant byproduct. The formation of this byproduct likely occurs via decomposition of an oxaziridine intermediate formed following nucleophilic attack of the hydroxamic acid OH group upon the carbonyl carbon.[6] This problem was efficiently solved by utilizing a *N*-hydroxy carbamate reagent (**4**) rather than a hydroxamic acid for the difunctionalization. Under the same conditions, reagent **4** doubled the yield of the desired dioxygenated product, and did not undergo rearrangement. The rationale for the lack of the formation of the rearrangement product is the decreased electrophilicity of the carbonyl carbon of the *N*-hydroxy carbamate relative to that of the hydroxamic acid. This reduction of electrophilicity is attributed to the cross-conjugation that is present in the carbamate derivative due to the ester portion of the molecule.

Figure 2.4: Effects of varying the optimized reaction conditions

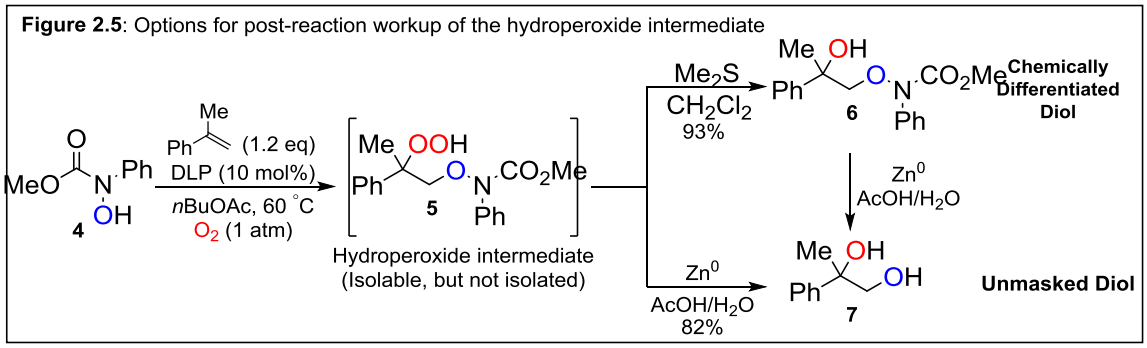


Entry	Deviation from standard conditions	Yield
1	None	93%
2	No DLP, 25 h	49%
3	1.0 eq alkene, 3 d	49%
4	1.0 eq alkene and 1.2 eq **4**, 26 h	74%

2.3 Dioxygenation Reaction Conditions and Post-Reaction Workup Options

The fully optimized conditions for the dioxygenation are depicted in **Figure 2.4**. Changes from the initial conditions shown in Figure 2.3 include a decrease in reaction temperature, initiator loading (DLP = dilauroyl peroxide), as well as a lower alkene stoichiometry. Esters proved to be the most

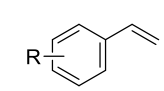
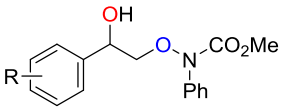
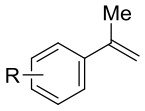
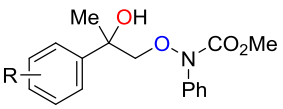
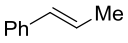
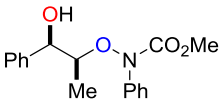
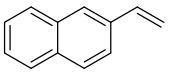
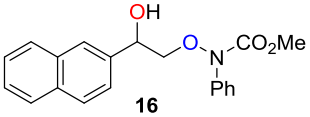
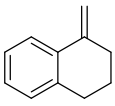
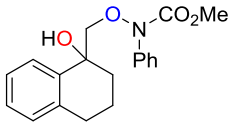
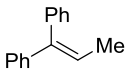
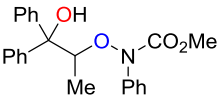
Figure 2.5: Options for post-reaction workup of the hydroperoxide intermediate



effective solvents. *n*-Butyl acetate was chosen over the more common ethyl acetate due to its decreased volatility at the reaction temperature. The removal of the initiator (DLP) (Entry 2) led to an expected increase in reaction time (8 hours) with no change in yield. The formation of amidoxyl radicals in the absence of an added initiator is attributed to auto-oxidation of the *N*-hydroxy carbamate from trace singlet oxygen present in the reaction vessel. Reacting *N*-hydroxy carbamate **4** with an equimolar amount of alkene resulted in a significantly longer reaction time and the yield being decreased by nearly 50% (Entry 3). The decreased yield could stem from the loss of the styrene substrate through polymerization. The use of one equivalent of alkene and an excess of the *N*-hydroxy carbamate reagent led to a lower, but acceptable yield of 74% (Entry 4). These conditions would be useful if the alkene substrate was valuable or in short supply.

Because molecular oxygen is incorporated into the molecule, the products of the dioxygenation reaction are alkyl hydroperoxides. The various post-dioxygenation workup options are listed in **Figure 2.5**. Hydroperoxides can be reduced to the alcohol under mild conditions through the addition of dimethyl

Figure 2.6: Dioxygenation of styrenyl substrates[a]

Entry	Substrate	Time (h)	Product	Yield[b]
				
1		17	R = H, **8**	93%
2		5	R = 4-OMe, **9**	82%
3		12	R = 4-Me, **10**	83%
4		11	R = 2-Br, **11**	89%
5		15	R = 4-CF_3, **12**	84%
				
6		8.5	R = H, **6**	92%
7		5	R = 3-NO_2, **13**	83%
8		5	R = 4-CH_2CH_2OH, **14**	78%
9		7.5	 **15**	86% 78:22 d.r. (trans:cis)
10		24	 **16**	89%
11		3	 **17**	79%
12		5	 **18**	87%

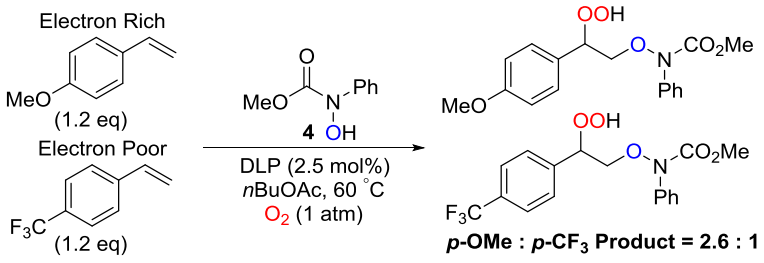
[a] Standard Conditions: **4** (1.0 eq), alkene (1.2 eq), DLP (2.5 mol%), nBuOAc (1M), 60 °C, O_2 (1 atm); Me_2S, CH_2Cl_2. [b] Isolated yields.

sulfide. The nitrogen-oxygen bond of the resulting hydroxamate can be cleaved using zinc dust or through hydrogenation. Alternatively, the diol can be immediately accessed in a one pot procedure from the crude hydroperoxide by treating it with zinc dust. The advantage of the dimethyl sulfide reduction procedure is that it allows for the chemical differentiation of the two hydroxyl groups of the diol. For example, further synthetic steps could be carried on the alcohol group while the alcohol protected as the hydroxamate ester is left untouched. When the protected alcohol is needed, it can be accessed by cleavage of the nitrogen-oxygen bond. The chemical differentiation of the diol functionality provided by this method is an important advantage over metal catalyzed methods, which typically immediately deliver the diol as the product. Selective functionalization of one of the alcohols of this diol product can pose a significant challenge.

2.4 Substrate Scope of the Intermolecular Dioxygenation

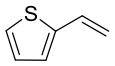
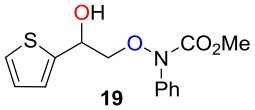
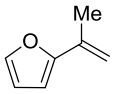
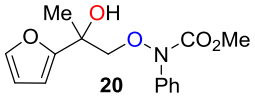
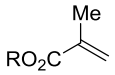
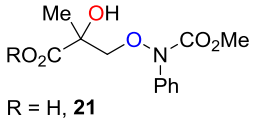
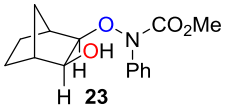
Styrenes are excellent candidates for dioxygenation (**Figure 2.6**). The yields generally remain constant regardless of the electronic character of the styrene. The reaction rates, however, vary drastically depending on the electronics of the substrate (Entries 2-5). Electron rich styrenes tend to react faster than electron poor styrenes. To explore this observation further, a competition experiment was carried out, whereby equimolar amounts of an electron rich styrene (4-methoxy styrene) and an electron poor styrene (4-trifluoromethyl styrene) were allowed to react with *N*-hydroxy carbamate **4** in the same reaction vessel (**Figure 2.7**). Based on the crude proton NMR, **4** showed close to a three-fold preference for reaction with 4-methoxy styrene, indicating that the amidoxyl radical derived from **4** is electron deficient in nature. Substitution on the alkene portion of the styrene is well tolerated also. Alkyl substitution on either the α (Entries 6-8 and 11) or β positions of the alkene leads to no erosion of the yield. Interestingly, β-methyl styrene (Entry 9) is dioxygenated with a 4 : 1 diastereoselectivity favoring the *trans* diastereomer. This contrasts with transition-metal-catalyzed

Figure 2.7: Competition experiment to probe electronic nature of amidoxyl radical



dihydroxylation methods, which deliver the *cis* dihydroxylated product. Considering that the act of a carbon-centered radical capturing oxygen is an essentially barrier-less process, the observation of a diastereoselectivity is very surprising. A possible explanation for this phenomenon is that the intermediate formed following amidoxyl addition into the alkene adopts a conformation where one face of the benzylic radical is sterically shielded by the hydroxamate portion of the molecule. In addition to disubstituted styrenes, trisubstituted alkenes are viable substrates (Entry 12). Tetrasubstituted styrenes, however, fail to react. To demonstrate the functional group tolerance of this method, a styrene with an appended, unprotected alcohol group was subjected to the reaction conditions (Entry 8). This substrate is dioxygenated without any detectable oxidation of the alcohol group. This functional group would not be compatible with transition-metal-catalyzed dihydroxylation methods, which typically employ strong oxidants that could oxidize the alcohol. Furthermore, most of the styrene substrates possess benzylic and/or allylic C-H bonds. No by-products resulting from hydrogen atom abstraction and subsequent oxidation were observed.

Figure 2.8: Dioxygenation of non-styrenyl substrates[a]

Entry	Substrate	Time (h)	Product	Yield
1[c]		7	 **19**	84%
2[c]		2	 **20**	48%
3		7	 R = H, **21**	45%
4		20	R = Me, **22**	84%
5		6	 **23** Major Diastereomer	77% 1.2:1 d.r.

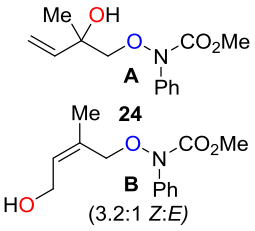
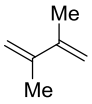
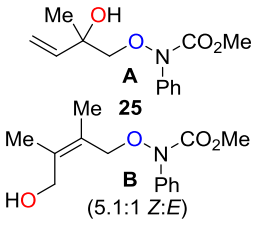
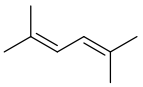
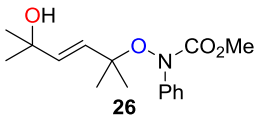
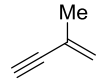
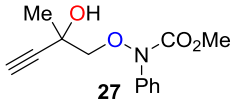
[a]: Standard Conditions: **4** (1.0 eq), alkene (5.0 eq), DLP (2.5 mol%), nBuOAc (1M), 60 °C, O_2 (1 atm); Me_2S, CH_2Cl_2. [b] Isolated yields. [c] 2.0 eq substrate used.

Non-styrenyl olefins are capable of undergoing dioxygenation as well (**Figure 2.8**). Vinyl heterocycles are viable substrates(Entries 1 and 2). Electron poor alkenes, such as acrylates (Entries 3 and 4) also participate in the dioxygenation reaction. The lower yields for the vinyl furan substrate (**2**) and methacrylic acid were likely a result of polymerization of the highly reactive monomer substrates.

Dienes, another class of activated olefins, typically give mixtures of the 1,2 and 1,4 dioxygenated products (**Figure 2.9**). The 1,2-dioxygenated products are the favored isomers for isoprene and 2,3-dimehyl-1,3-butadiene (Entries 1and 2). This selectivity is likely a result of the greater stability of the

tertiary allylic carbon-centered radical intermediate that gives rise to the 1,2 product relative to the shorter lived and less stable primary carbon-centered radical intermediate that yields the 1,4 isomer. This hypothesis is consistent with the results obtained from Entry 3. This diene substrate yields exclusively the 1,4-dioxygenated product, since this product stems from a tertiary allylic carbon centered radical. The unobserved 1,2-addition product would have been formed from a less stable secondary allylic carbon-centered radical. Enynes (Entry 4) show complete preference for addition into the alkene rather than the alkyne. Alkynes are unreactive due to the instability of the vinyl radical that would be formed following addition. The selectivity for alkenes over alkynes displayed by this method is another advantage that would likely not be observed using metal-catalyzed methods.

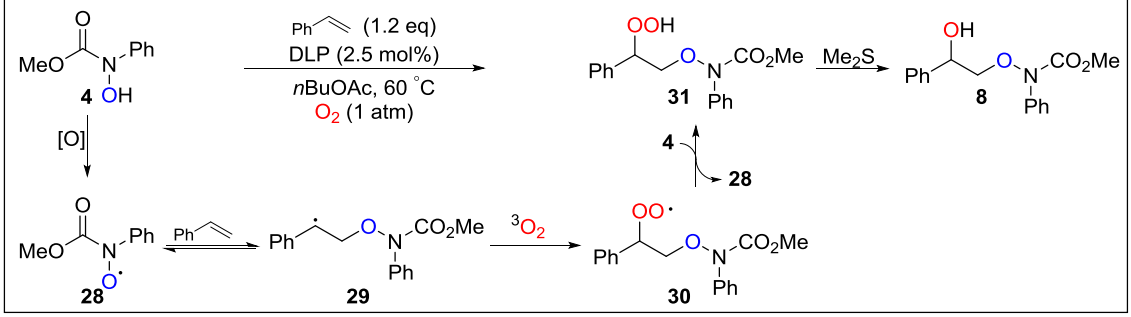
Figure 2.9: Dioxygenation of dienes[a]

Entry	Substrate	Time (h)	Product	Yield[b]
1		6	 **A** (88%, 2:1 A:B) **24** **B** (3.2:1 *Z*:*E*)	
2		3	 **A** **25** **B** (5.1:1 *Z*:*E*)	88%, 6:1 A:B
3[c]		2	 **26**	59%
4		7	 **27**	68%

[a] Standard Conditions: **4** (1.0 eq), alkene (5.0 eq), DLP (2.5 mol%), *n*BuOAc (1M), 60 °C, O_2 (1 atm); Me_2S, CH_2Cl_2. [b] Yields of isolated products [c] 2.0 eq substrate used.

Unfortunately, unactivated alkenes, such as octene, are not suitable substrates for this method due to the low rates of nitroxyl radical addition.[7] No dioxygenation products were observed following reaction of unactived alkenes under the standard conditions. The strained alkene norbornene is the closest chemical relative to unactivated alkenes that can be dioxygenated (**see Figure 2.8, Entry 2**). *Exo* addition of the amidoxyl radical is favored,[8] and oxygen trapping occurs with essentially no diastereoselectivity.

Figure 2.10: Proposed mechanism for amidoxyl radical mediated alkene dioxygenation.



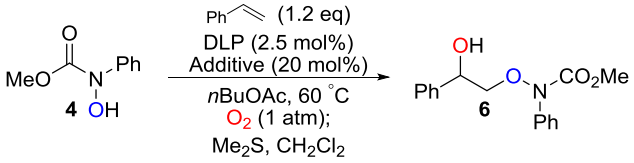
The mechanism for dioxygenation parallels that which was reported for the intramolecular method (**Figure 2.10**). The amidoxyl radical (**28**) is formed via oxidation of **4** by either oxygen or initiator. The amidoxyl radical (**28**) adds into the alkene to form a benzylic radical species (**29**), which is trapped by molecular oxygen to give a hydroperoxyl radical species (**30**). The hydroperoxyl radical abstracts a hydrogen atom from another molecule of starting material to yield the initial hydroperoxide (**31**) intermediate as well as propagate the chain reaction. The hydroperoxide can be reduced to the alcohol (**8**) using dimethyl sulfide.

2.5 Preliminary Results for an Asymmetric Alkene Dioxygenation

The next stage of development for the intermolecular dioxygenation method was to investigate the possibility of carrying out the reaction asymmetrically. Due to the extremely fast rate of recombination between molecular oxygen and carbon-centered radicals, we did not anticipate being able to control the stereochemistry of the carbon atom at which this trapping event takes place. However, the addition step presented an opportunity to control the stereochemistry of the carbon atom which receives the oxygen atom of the amidoxyl radical.

Our studies commenced with an attempt to observe an accelerated rate of the reaction (**Figure 2.11**). The observation that the use of acetic acid as a solvent drove the

Figure 2.11: Initial studies for observing accelerated reaction rates



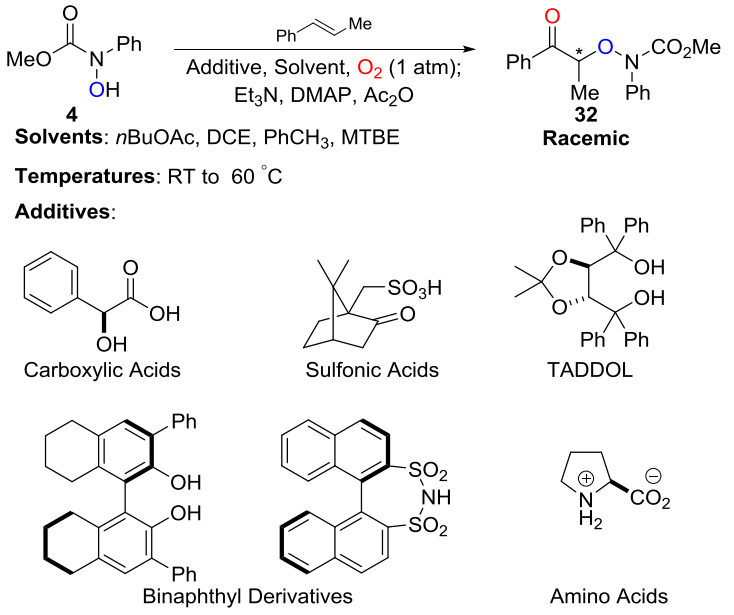
Entry	Additive	pKa(DMSO)	Reaction Time	Yield[a]
1	None	n/a	17 h	93%[b]
2	$PhSO_2NH_2$	16	8 h	92%
3	$CF_3SO_2NH_2$	10	8 h	88%
4	$(TolSO_2)_2NH$	3	4 h	70%
5	$PhSO_2NMe_2$	n/a	Incomplete after 24 h	

[a] Calculated from the crude ^1H NMR spectrum using 1,3,5-trimethoxybenzene as an internal standard. [b] Yield of isolated product.

dioxygenation reaction to completion 9 hours faster than when *n*-butyl acetate was used as solvent prompted us to investigate Brønsted acids as potential catalysts. Indeed, the addition of 20 mol% various sulfonamide-based Brønsted acids to the reaction did lead to an enhanced rate. We postulate that the origin of the enhanced rate involved increased electrophilicity of the amidoxyl radical as a result of protonation or hydrogen bonding with the carbonyl carbon of **4**. This increased electrophilicity is expected to correlate to an increase in reactivity. According to **Figure 2.11**, the reaction time generally decreases as the pKa of the sulfonamide decreases. Interestingly, no difference in reaction time was observed between benzenesulfonamide and trifluoromethanesulfonamide, despite the 6 order of magnitude difference in acidity between the two. The addition of sulfonamide derivative, *N*,*N*-dimethylbenzenesulfonamide, does not show an increase in reaction rate, which provides further evidence that hydrogen-bond catalysis was occurring.

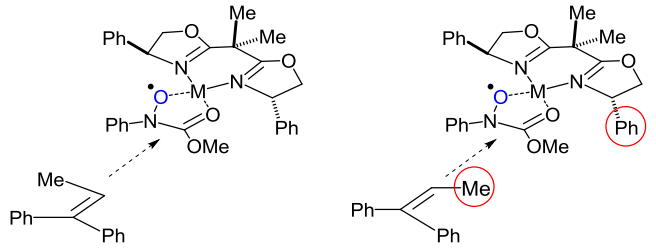
Asymmetric catalysis using hydrogen-bond donors has been explored extensively.[9] With our aforementioned results in hand, we sought to capitalize on the plethora of successful hydrogen-bond donor catalysts available. Various catalysts were screened, and a summary of the conditions and catalysts tested is listed in **Figure 2.12**. Unfortunately, all attempts led to racemic products. A likely reason for the failure of the reaction is non-specific binding of the chosen catalysts to **4**. A variety of substrate-catalyst binding structures can be envisioned, with some even placing the catalyst's chirality far away from the OH portion of the molecule where the reaction takes place. Successful applications of asymmetric hydrogen-bond donor catalysis typically involve multiple non-covalent attractions between

Figure 2.12: Survey of conditions and additives used for attempted H-bond donor catalyzed alkene dioxygenation



the catalyst and the substrate(s). This serves to create a rigid, ordered transition state that can effectively transfer the chiral information of the catalyst into the substrates.[10] The inability of **4** to participate in multiple hydrogen-bonds with the catalyst does not provide for an ordered transition state suitable for transfer of chirality, and is the likely reason for the failure of this class of catalyst.

Figure 2.13: Proposed mode of induction of chirality using chiral Lewis acids

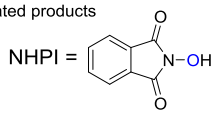


Our next attempt at performing this reaction asymmetrically involved the use of chiral Lewis acids (**Figure 2.13**). Hydroxamic acids are known to chelate metal cations.[11] We hypothesized that the amidoxyl radicals formed from hydroxamic acids could also chelate to a Lewis acid. The enhanced electrophilicity of the amidoxyl radical provided by chelation to the metal cation was expected to translate into greater reactivity and faster addition rates relative to the background, uncatalyzed addition of uncomplexed amidoxyl radicals. The chiral ligand bound to the Lewis acid could then sterically influence the approach of the alkene in such a way that facial selectivity during the addition step could be achieved. The representative results for this study are listed in **Figure 2.14**. The highest yields and enantioselectivities were obtained by using copper(II) triflate and bis-oxazoline ligands. The use of alternative counteranions on copper (Cl, Br, OAc, SbF_6) led to racemic product. Other metals, such as zinc(II), iron(II), Mn(III), or Mg(II), either did not proceed to completion or returned racemic product. Other classes of ligands tested included chiral diamines, pyridyl bisoxazolines, and

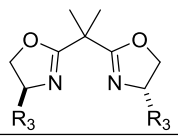
Figure 2.14: Representative results of Lewis acid catalyzed asymmetric dioxygenation studies

Entry	Hydroxamic Acid	Catalyst Loading	Ligand	Solvent	Yield[a]	ee
1	**4**	25 mol%	L_1	DCM	15%	20%
2	NHPI	10 mol%	L_2	DCM	76%	Racemic
3	NHPI	10 mol%	L_1	THF	38%	12%
4	NHPI	10 mol%	L_3	THF	28%	20%

[a] Yields of isolated products



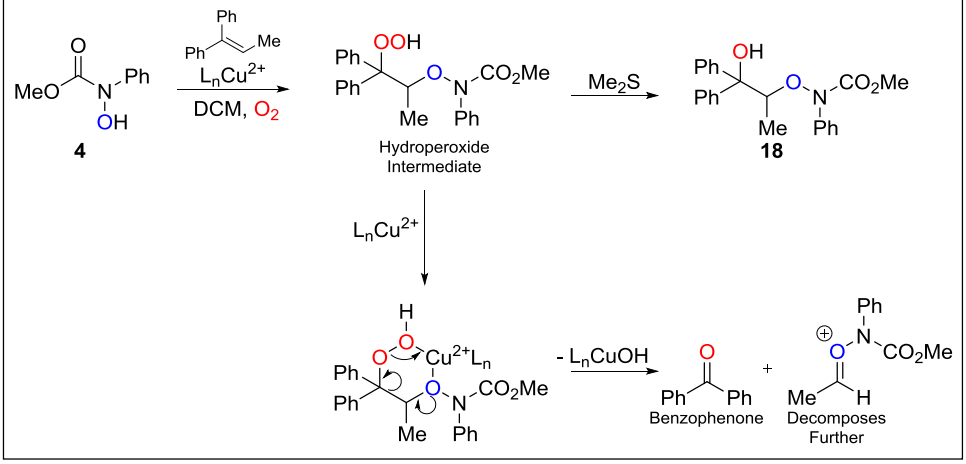
L_1: R_3 = Ph
L_2: R_3 = *i*-Pr
L_3: R_3 = *t*-Bu



salen ligands. *N*-hydroxy carbamate **4** proved to be an inferior reagent to NHPI, which typically returned higher yields and

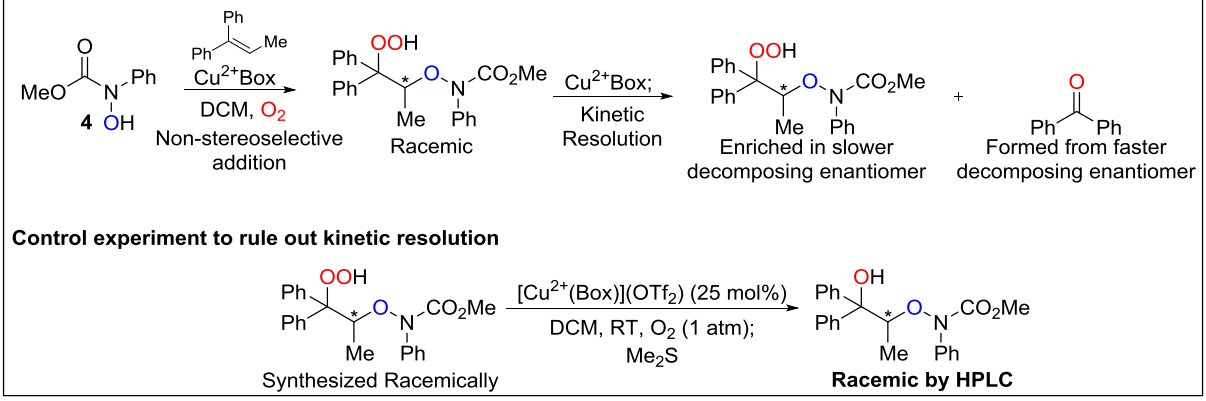
enantioselectivities. A likely explanation for the low yields is decomposition of the hydroperoxide product by the catalyst. A by-product typically observed in these reactions was benzophenone. A possible decomposition pathway is outline in **Figure 2.15**. Following chelation of the hydroperoxide

Figure 2.15: Proposed decomposition pathway of the hydroperoxide intermediate



product with copper, the complex degrades with formation of a copper oxide species, benzophenone, and an *O*-amidated acetaldehyde derivative. The formation of the copper oxide presumably removes the ability of the catalyst to bind the chiral ligands, while the formation of the highly electrophilic acetaldehyde would consume the nucleophilic hydroperoxide product as well as the hydroxamic acid starting material, resulting in low enantioselectivities and yields, respectively. The identification of this decomposition pathway raised concerns that a kinetic resolution operating through this pathway could be the origin of the enantioselectivities (**Figure 2.16**). Hypothetically, if the hydroperoxide product was actually being formed racemically, the chiral catalyst could be decomposing one enantiomer faster than the other. This would lead to an enrichment in the enantiomer which decomposes slower. To test this hypothesis, the hydroperoxide in question was synthesized racemically, isolated, and exposed to a copper(II) bis-oxazoline complex for one hour (the typical reaction time observed for the dioxygenation reactions). The remaining hydroperoxide was isolated, and found to be racemic. This control experiment suggests that the decomposition pathway is not the origin of the observed enantioselectivity.

Figure 2.16: Ruling out a kinetic resolution as the source of enantioselectivity



2.6 Conclusions

The lack of a general method for nitroxyl radical mediated, intermolecular dioxygenation was addressed upon the completion of this work. Proceeding in high yields and under mild conditions using inexpensive oxygen gas as an oxygen atom source, this method is an attractive alternative to metal-catalyzed dioxygenations. In addition, proof-of-concept was demonstrated for an asymmetric variant of the reaction.

REFERENCES

[1] Hussain, S. A.; Jenkins, T. C.; Perkins, M. J.; Siew, N. P. Y. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2803.

[2] Ozaki, S.; Hamaguchi, T.; Tsuchida, K.; Kimata, Y.; Masui, M. *J. Chem. Soc. Perkin Trans II* **1989**, 951.

[3] Hara, T.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 6425.

[4] For a comprehensive review of the uses and properties of *N*-hydroxyphthalimide, see: Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800.

[5] Perkins, M. J.; Berti, C.; Brooks, D. J.; Grierson, L.; Grimes, J. A. M.; Jenkins, T. C.; Smith, S. L. *Pure & Appl. Chem.* **1990**, *62*, 195.

[6] Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron: Asymmetry* **2001**, *12*, 3349.

[7] Mayo, F. R. *Acc. Chem. Res.* **1968**, *1*, 193.

[8] (a) Curran, D. P.; Porter, N. A.; Giese, B., in *Stereochemistry of Radical Reactions*, VCH, New York, NY, 1996. (b) Davies, D. I.; Parfitt, L. T.; Alden, C. K.; Claisse, J. A. *J. Chem. Soc. C.* **1969**, 1585.

[9] Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

[10] Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

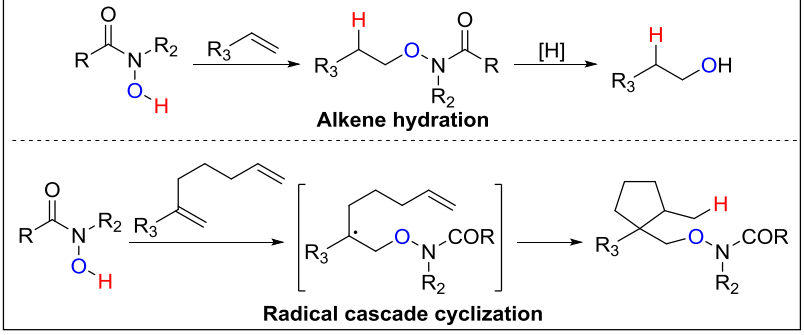
[11] Li, Z.; Yamamoto, H. *Acc. Chem. Res.* **2013**, *46*, 506.

CHAPTER 3: HYDROXAMIC ACIC-MEDIATED FORMAL ALKENE HYDRATION

3.1 Introduction

The hydrofunctionalization of an alkene delivers both a heteroatom and a hydrogen atom to the two carbon atoms of an alkene. This reaction has been applied extensively in a variety of transformations in the context of transition-metal-catalysis.[1] In addition, effective radical alkene hydrofunctionalizations have been developed using sulfur, phosphorus, and nitrogen-centered radicals (see Chapter 1). However, no analogous free-radical hydration using oxygen-centered radicals has been developed.[2] We hypothesized that, due to the weak homolytic bond strength of their OH bond, hydroxamic acids could function as a hydrogen atom donor and reduce carbon-centered radicals to the alkane (**Figure 3.1**). This capability, when coupled with the ability of amidoxyl radicals to add into alkenes, would provide for a formal free-radical alkene hydration where the hydroxamic acid acts as both as the oxygen-atom source as well as the hydrogen-atom source. In addition, by tethering two alkenes to a hydroxamic acid, a radical C-O/C-C/C-H bond-forming cascade could be carried out, allowing for the rapid construction of carbocycles.

Figure 3.1: Reactions possible by applying hydroxamic acids as H-atom sources

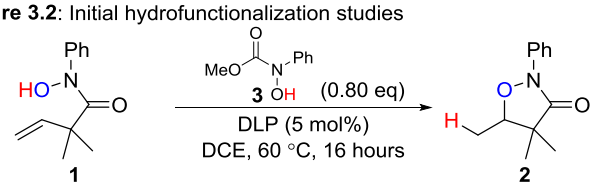


3.2 Initial Alkene Hydration Studies

Proof of concept for the claimed reaction was demonstrated using unsaturated hydroxamic acid **1**, and the initial hydrofunctionalization studies are shown in **Figure 3.2**. By heating this substrate in dichloroethane in the presence of DLP, the formal hydration product is obtained in moderate yield after

16 hours with incomplete conversion (80%, Entry 2). Interestingly, the reaction still takes place in the absence of DLP initiator (Entry 3). The formation of amidoxyl radicals in an oxygen-free environment in the absence of added initiator is attributed to trace oxidation of the hydroxamic acid during exposure to the atmosphere during synthesis and purification. In an attempt to raise the yield and conversion, various hydrogen atom donors were added to the reaction, including silanes, thiols, and catechols (Entries 3-5). *N*-hydroxy carbamate **3** was also tested as a possible hydrogen atom source, and proved to be superior to all other sources tested. Including a substoichiometric amount of **3** in the reaction boosted the yield to 90% with complete conversion (Entry 1). With the optimized conditions in hand, we sought to next investigate the scope of this reaction.

Figure 3.2: Initial hydrofunctionalization studies



Entry	Deviation from standard conditions	Conversion[a]	Yield[b]
1	none	100%	90%
2	no **3** added	80%	65%
3	no DLP added	78%	67%
4	$(Me_3Si)_3SiH$ instead of **3**	69%	69%
5	*tert*-dodecylmercaptan instead of **3**	73%	47%
6	4-*tert*-butylcatechol instead of **3**	77%	55%

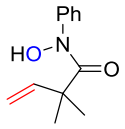
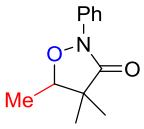
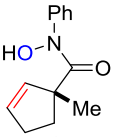
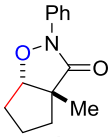
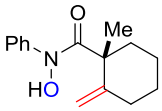
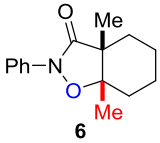
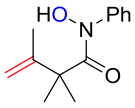
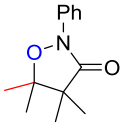
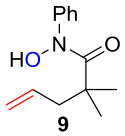
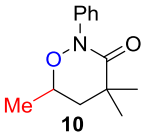
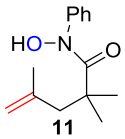
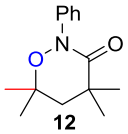
[a] Conversions calculated from the crude ^{1}H NMR spectrum using 1,3-5-trimethoxybenzene as an internal standard. [b] Yields of isolated products

3.3 Substrate Scope of Formal Alkene Hydration

A variety of unsaturated hydroxamic acids were synthesized and subjected to the optimized reaction conditions (**Figure 3.3**). Both *5-exo* and *6-exo* cyclization substrates are amenable for hydration. Substrates containing endocyclic and exocyclic alkenes are also excellent substrates, delivering the *cis* fused ring products in high yield (Entries 2 and 3). Substrates which undergo *5-exo* cyclizations and possess 1, 1-alkene disubstitution proceed rapidly, and do not require the addition of an external hydrogen atom source (Entries 3 and 4). This alkene substitution pattern was employed to enhance the rate of

the slower *6-exo* cyclization substrates. γ, δ- unsaturated hydroxamic acid **9**, which does not possess this substitution pattern, only delivered a 32% yield with 43% conversion after 42 hours, even in the presence of an excess of **3**. However, γ, δ- unsaturated 1,1-disubstituted substrate **11** reacted to completion in nearly the same amount of time with over twice the yield. For every substrate, the hydrated product is obtained as a single regioisomer, due to the relative rates of the two possible cyclization modes (i.e. fast *5-exo* vs. slow *6-endo*). This result contrasts with metal-catalyzed hydration processes, including the Brown hydroboration, which often struggle to obtain complete regioselectivity for the hydrated product.[3]

Figure 3.3: Formal alkene hydration of unsaturated hydroxamic acids[a]

Entry	Substrate	Product	Yield[b]
1	 **1**	 **2**	90%
2	 **3**	 **4**	77% >20 : 1 d.r.
3[c]	 **5**	 **6**	88% >20 : 1 d.r.
4[c]	 **7**	 **8**	85%
5[d]	 **9**	 **10**	32%
6	 **11**	 **12**	71%

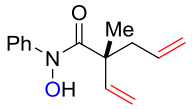
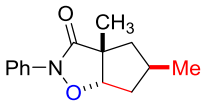
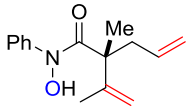
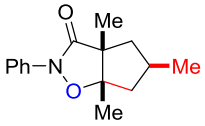
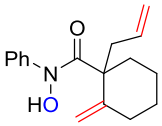
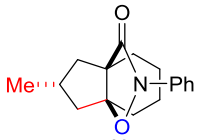
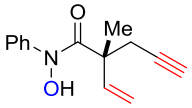
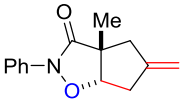
[a]: Standard Conditions: DLP (5.0 mol%), *N*-hydroxy carbamate **3** (0.80 eq), dichloroethane (0.5M), 60 °C [b] Yields of isolated products [c] Reaction carried out without added **3**. [d] 1.6 eq **3** added.

3.4 Extension to Radical Cascade Cyclizations

In adapting the hydration methodology to a carbocyclization process, several adaptions to the procedure were necessary. The primary obstacle to developing the radical cascade cyclization was premature reduction of the carbon-centered radical formed following amidoxyl radical addition. To reduce the formation of by-products resulting from premature hydrogen atom abstraction, the reaction was carried out a lower concentration and no external hydrogen atom source was added. In addition, because the hydration reaction had shown depressed rates in aromatic solvents, the solvent was switched from dichloroethane to benzene.

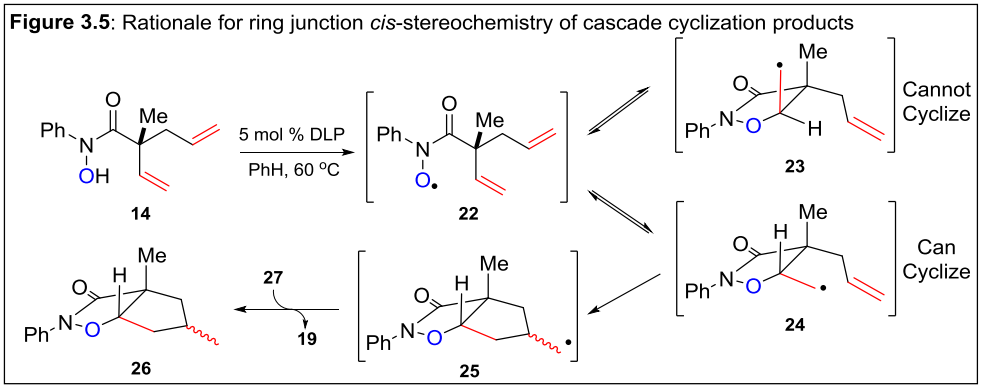
The hydroxamic acid substrates in Entries 1-3 of **Figure 3.4** undergo two sequential *5-exo-trig* cyclizations to form cyclopentane products. Hydroxamic acid **20** in Entry 4 contains an alkyne, and undergoes a *5-exo-trig*; *5-exo-dig* cascade to produce a cyclopentane ring with an exocyclic alkene. Substrates which could undergo *5-exo*; *6-exo* cyclizations (not shown) did produce cyclohexane products. However, a significant amount of a variety of inseparable, unidentified by-products were present. These by-products are presumably formed by the competing 1,5-hydrogen atom abstraction of the allylic hydrogen atoms instead of the desired carbon-carbon bond forming cyclization step.

Figure 3.4: Cascade carbocyclization of bis-unsaturated hydroxamic acids[a]

Entry	Substrate	Product	Yield[b]
1	 **14**	 **15**	54 1.2 : 1 d.r.
2	 **16**	 **17**	82 2.9 : 1 d.r.
3	 **18**	 **19**	82 2.7 : 1 d.r.
4	 **20**	 **21**	41 >20 : 1 d.r.

[a]: Standard Conditions: DLP (5.0 mol%), benzene (0.1M), 60 °C.
[b] Yields of isolated products.

The stereochemistry at the ring junction for each of the cyclopentenyl products was determined to be *cis*. The stereoselectivity of the amidoxyl radical addition step can be rationalized by considering the mechanism of the reaction (**Figure 3.5**). Following addition of the amidoxyl radical into the first alkene, the resulting carbon-centered radical can either be oriented in a *trans* (**23**) or *cis* (**24**) relationship relative to the second alkene. Only the *cis* isomer is capable of undergoing the second cyclization to form the cyclopentane ring (**25**). The overall diastereoselectivity of the reaction, however, is modest, due a lack of alkene facial selectivity during the carbocyclization step.

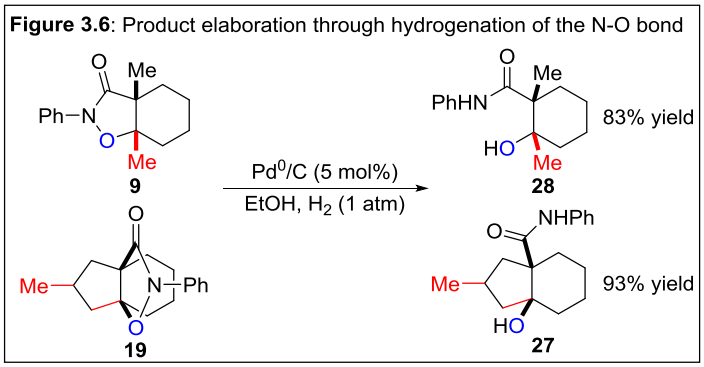


3.5 Post-Reaction Elaboration of Products

The nitrogen-oxygen bond of the isoxazolidinone product can be reduced under mild conditions through palladium catalyzed hydrogenolysis (**Figure 3.6**). The reduction procedure used for the dioxygenation methodologies, which involved using zinc as a reductant, was not used because it required extended reaction times for this class of products. Hydration product **9** and cascade cyclization product **19** were reduced to afford the cyclohexanol (**28**) and hydrindane (**27**) derivatives, respectively.

3.6 Proof-of-Concept for an Intermolecular Alkene Hydration

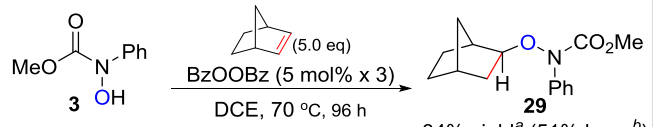
An intermolecular variant of the hydration reaction would be an extremely useful extension of this methodology. The hydration of terminal olefins using hydroxamic acids would be expected to proceed regioselectively to form the anti-Markovnikov hydration product, similar to how the thiol-ene coupling selectively forms anti-Markovnikov hydrothiolation products. The selective anti-Markovnikov hydration of olefins is an unsolved problem in chemical synthesis,[3f] and continues to be an active area of methodology research.[2,3]



The development of a hydroxamic acid mediated intermolecular hydration method faces severe challenges. Like the intermolecular dioxygenation reaction, there is an extremely high entropic barrier for

the reaction. Furthermore, the transfer of a hydrogen atom from heteroatoms to carbon-centered radicals is known to be a kinetically slow process.[4] Nonetheless, preliminary data has been obtained which demonstrates that such a reaction is possible (**Figure 3.7**). Using *N*-hydroxy carbamate **3**, the formal hydration product of norbornene (**29**) is obtained in 34% yield (with 67% conversion) after 96 hours. Other activated alkenes, such as styrenes, failed to react.

Figure 3.7: Preliminary intermolecular formal hydration result



[a] Isolated yield
[b] Calculated from the crude ^{1}H NMR spectrum using 1,3-5-trimethoxybenzene as an internal standard.

34% yield[a] (51% brsm[b])
67% conversion[b]

3.7 Conclusions

The absence of an oxygen-centered radical based hydrofunctionalizations was filled with the development of a hydroxamic acid mediated formal alkene hydration. The identification of hydroxamic acids as hydrogen atom donors capable of reducing carbon-centered radicals was key to the development of the method. The methodology was successfully extended into a carbocyclization process capable of producing oxygenated cyclopentanes. Proof of concept for an intermolecular variant of the hydration reaction was also established.

REFERENCES

[1] Yadav, J. S.; Antony, A.; Rao, T. S.; Subba Reddy, B. V. *Journal of Organometallic Chemistry* **2011**, *696*, 16.

[2] For hydroetherification and hydrocarboxylation reactions involving radical cation intermediates, see: Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577. and Perkowski, A. J.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 10334.

[3] For recent work involving Markovnikov and anti-Markovnikov hydration, see: (a) Fries, P.; Muller, M. K.; Hartung, J. *Tetrahedron* **2014**, *70*, 1336. (b) Shigesi, H.; Aoki, T.; Yamaguchi, S.; Shimizu, N.; Hiroya, K. *J. Am. Chem. Soc.* **2013**, *135*, 10306. (c) Sevov, C.; Hartwig, J. *J. Am. Chem. Soc.* **2013**, *135*, 9303. (d) Schulueter, J.; Blazejak, M.; Hinterman, L. *ChemCatChem* **2013**, *5*, 3309. (e) Atesin, A. C.; Ray, N. A.; Stair, P. C.; Marks, T. J. *J. Am. Chem. Soc.* **2012**, *134*, 14682. (f) Dong, G.; Teo, P.; Wickens, Z.; Grubbs, R. *Science* **2011**, *333*, 1609. For reviews of transition-metal-catalyzed methods, see: (g) Bruneau, C. *Top. Organomet. Chem.* **2013**, *43*, 203. (h) Huguet, N.; Echavarren, A. M. *Top. Organomet Chem.* **2013**, *43*, 291. (i) Hintermann, L. *Top. Organomet. Chem.* **2010**, *31*, 123.

[4] Warren, J. J.; Mayer, J. *PNAS*, **2010**, *107*, 5282.

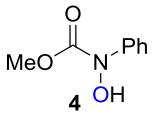
EXPERIMENTAL FOR CHAPTER 2: DEVELOPMENT OF AN INTERMOLECULAR HYDROXAMIC ACID MEDIATED ALKENE DIOXYGENATION

E2.1 General Information

Methods: Nuclear magnetic resonance spectra were obtained on either a Bruker AVANCE III 600 MHz spectrometer (^{1}H NMR at 600 MHz and ^{13}C at 151 MHz), a Bruker AVANCE III 500 MHz spectrometer (^{1}H NMR at 500 MHz and ^{13}C at 126 MHz), or a Bruker AVANCE Nanobay 400 MHz spectrometer (^{1}H NMR at 400 MHz and ^{13}C at 101 MHz). ^{1}H NMR are reported in the following format: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. All NMR spectra are calibrated relative to residual protiated solvent resonances (^{1}H NMR: $CDCl_3$ at 7.26 ppm and C_6D_6 at 7.16 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm and C_6D_6 at 128.4 ppm). Low-resolution mass spectra were obtained on a Bruker BioTOF high resolution mass spectrometer in positive ion mode using flow injection electrospray ionization or using a Micromass Quattro II (triplequad) equipped with nanoelectrospray ionization. Samples were prepared in methanol and 1% aqueous formic acid. Infrared spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer. Thin layer chromatography (TLC) was carried out on SiliaPlate 250 μm thick silica gel plates purchased from Silicycle. Visualization was achieved using short wave ultraviolet light (254 nm), alkaline aqueous potassium permanganate solution, or acidic ethanolic *p*-anisaldehyde solution followed by heating. Hydroxamic acids were visualized using a 1% aqueous solution of $FeCl_3$. Flash chromatography was carried out using SiliaFlash T60 silica gel (5-20 μm) or SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Moisture sensitive reactions were carried out under an argon atmosphere in an Innovative Technologies glovebox. Chiral HPLC analyses were carried out using an Agilent 1200 HPLC (UV detection at 210, 230, 250, and 254 nm) equipped with a Chiral pack IA column.

Materials: All chemicals were used as received from their manufacturer (Sigma-Aldrich, Fisher Scientific, and Alfa Aesar) unless otherwise noted. Dichloromethane, tetrahydrofuran, and diethyl ether were dried by passage through a column of activated alumina while under dry nitrogen gas. Norbornene was purified by sublimation and stored at -30 ºC under an argon atmosphere. Oxygen gas was purchased from Airgas National Welders.

E2.2 Substrate Preparation: Styrene, α-methylstyrene, β-methylstyrene, *para*-methylstyrene, *para*-methoxystyrene, 2-bromostyrene, isoprene, 2,3-dimethyl-1,3-butadiene, 2,5-dimethyl-2,4-hexadiene, 2-methyl-1-buten-3-yne, methyl methacrylate, and methacrylic acid were purchased from commercial sources, purified by distillation, deoxygenated via multiple freeze-pump-thaw cycles, and stored at -35 °C under an inert atmosphere prior to use. Norbornene was purified by sublimation and stored under an inert atmosphere. Hydroxamic acid 1[1] *Para*-trifluoromethylstyrene[2,3], 3-nitro-α-methylstyrene[4,3], 2-vinylnaphthalene[2,5], 1-methylene-1,2,3,4-tetrahydronaphthalene[6], 1,1-diphenylpropene[7,8], 2-vinylthiophene[9], 2-(prop-1-en-2-yl)furan[7,8,6], and 2-(4-(prop-1-en-2-yl)phenyl)ethan-1-ol[10] were prepared according to standard procedures. All physical and spectral data were in accordance with literature data. *N*-Phenylhydroxylamine was synthesized according to literature procedures.[11,12] Physical and spectral data were in accordance with literature data.[13]



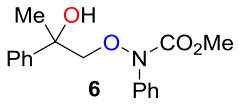
4

Synthesis of Methyl N-hydroxy(phenyl) carbamate (4): *N*-phenylhydroxylamine (1.86 g, 17.1 mmol, 1 eq) was dissolved in Et_2O (37 mL, 0.46 M). A magnetic stir bar was added, along with saturated, aqueous $NaHCO_3$ (25 mL). The reaction mixture was cooled to 0 ºC and placed under an argon atmosphere. Methyl chloroformate (1.30 mL, 17.1 mmol, 1 eq) was added dropwise via syringe pump over one hour. After addition was complete, the reaction mixture was allowed to warm to room termperature over the course of 30 minutes. The organic phase was separated, and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed three times with 1N HCl, once with brine, dried over

anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* in a room temperature water bath. The residue was purified by silica gel flash chromatography (2:1 hexanes:EtOAc) to afford **4** as a white, waxy solid (1.70 g, 10.2 mmol, 60% yield). Proton and carbon NMR spectra were in accordance with literature data.[14]

E2.3 General Dioxygenation Conditions

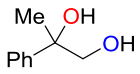
A 1-dram vial containing a magnetic stir bar was charged with **4** (50.0 mg, 0.299 mmol, 1.0 equiv.), dilauroyl peroxide (DLP, 3.0 mg, 0.007 mmol, 2.5 mol%), alkene (1.2 equiv.) and *n*BuOAc (0.30 mL, 1 M). The vial was fitted with a PTFE-lined screw cap, and the reaction mixture was oxygenated by bubbling O_2 gas through it for 3 minutes. The reaction was allowed to stir under an atmosphere of oxygen at 60 °C. Upon disappearance of **4**, as indicated by TLC analysis, the reaction solvent was removed under a positive flow of argon. The crude reaction mixture was then taken up in CH_2Cl_2 (0.30 mL, 1 M) and dimethyl sulfide (0.11 mL, 1.5 mmol, 5.0 equiv.) added. The reaction was tightly capped and heated to 40 °C until disappearance of the initially formed hydroperoxide was observed by TLC analysis. The reaction mixture was then concentrated under reduced pressure and purified by silica gel flash chromatography using the specified solvent system to yield the resultant dioxygenation product.



6

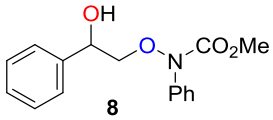
Alcohol **6** was prepared using α-methylstyrene (46.6 µL, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 8.5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (20% EtOAc/hexanes) to afford **6** (83.2 mg, 0.276 mmol, 92% yield) as a colorless residue.

Analytical data for **6**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.53 - 7.46 (m, 2 H), 7.42 - 7.18 (m, 8 H), 4.38 (br. s, 1 H), 4.24 (d, *J* = 10.1 Hz, 1 H), 4.07 (d, *J* = 10.4 Hz, 1 H), 3.80 (s, 3 H), 1.56 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.4, 144.8, 139.4, 128.8, 128.2, 127.0, 126.5, 125.0, 122.8, 83.3, 73.2 53.7, 27.0; **IR** (thin film, cm^{-1}) 3425, 3061, 3029, 2979, 2955, 2934, 2249, 1953, 1882, 1714, 1595, 1495, 1442, 1348, 1119, 912, 763, 697; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.10.



7

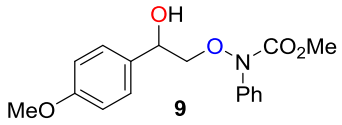
Alcohol **7** was prepared using α-methylstyrene (77.8 µL, 0.598 mmol, 2.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 8.5 h. The crude reaction mixture was concentrated, taken up in AcOH (1 mL), then water (1 mL) and Zn powder (391.0 mg, 5.98 mmol, 20 equiv.) were added. The reaction was complete, as indicated by TLC, after heating at 40 ºC for 3 h. The crude reaction mixture was taken up in CH_2Cl_2, filtered through Celite, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography (50% EtOAc/hexanes) to afford **2-phenylpropane-1,2-diol (7)** (41.5 mg, 0.273 mmol, 91% yield) as a colorless residue. Physical and spectral data were in accordance with literature values.[15]



8

Alcohol **8** was prepared using styrene (41.1 µL, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 17 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (25% EtOAc/hexanes) to afford **8** (79.8 mg, 0.278 mmol, 93% yield) as a colorless residue.

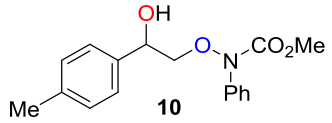
Analytical data for **8**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.44 - 7.27 (m, 10 H), 5.07 (dd, *J* = 2.5, 9.8 Hz, 1 H), 4.49 (br. s, 1 H), 4.05 (dd, *J* = 2.8, 11.3 Hz, 1 H), 3.88 (s, 3 H), 3.86 - 3.83 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 156.4, 139.5, 134.0, 129.0, 128.5, 127.9, 127.1, 126.2, 123.6, 80.6, 70.7, 54.0; **IR** (thin film, cm^{-1}) 3443, 30.63, 3031, 2955, 2928, 1715, 1595, 1494, 1440, 1348, 1117, 754, 697; **LRMS** (ESI) Calcd. for $[C_{16}H_{17}NO_4+Na]^+$ = 310.11, Found = 310.10.



9

Alcohol **9** was prepared using *para*-methoxy styrene (48.0 µL, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by flash chromatography (1:2 EtOAc/hexanes) to afford **9** (77.7 mg, 0.245 mmol, 82% yield) as a colorless residue.

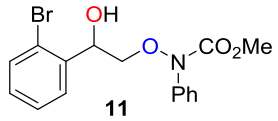
Analytical data for **9**: **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.45 (d, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 7.17 (t, *J* = 7.7 Hz, 2 H), 7.07 - 6.98 (m, 1 H), 6.87 (d, *J* = 8.2 Hz, 2 H), 5.20 (d, *J* = 9.5 Hz, 1 H), 4.91 (br. s., 1 H), 4.00 (dd, *J* = 1.9, 11.0 Hz, 1 H), 3.91 - 3.81 (m, 1 H), 3.38 (s, 6 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 159.3, 156.3, 139.5, 131.0, 128.9, 127.0, 123.5, 113.9, 80.5, 70.2, 55.3, 54.0; **IR** (thin film, cm^{-1}) 3449, 3065, 3004, 2956, 2838, 1714, 1612, 1597, 1514, 1494, 1441, 1347, 1250, 1030, 833, 753, 694; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_5+Na]^+$ = 340.12, Found = 340.11.



10

Alcohol **10** was prepared using *para*-methyl styrene (47.0 µL, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 15 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:4 to 1:3 EtOAc/hexanes) to afford **10** (74.4 mg, 0.247 mmol, 83% yield) as a colorless residue.

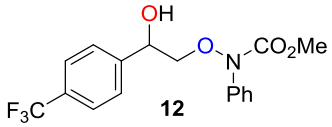
Analytical data for **10**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.46 - 7.39 (m, 4 H), 7.32 - 7.27 (m, 3 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 5.04 (dd, *J* = 2.0, 9.6 Hz, 1 H), 4.45 (br. s, 1 H), 4.03 (dd, *J* = 2.5, 11.3 Hz, 1 H), 3.88 (s, 3 H), 3.88 - 3.82 (m, 1 H), 2.36 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 156.3, 139.5, 137.6, 136.0, 129.1, 129.0, 127.0, 126.2, 123.5, 80.6, 70.5, 54.0, 21.2; **IR** (thin film, cm^{-1}) 3446, 3027, 2955, 2924, 2872, 1714, 1595, 1494, 1441, 1347, 1117, 816, 753; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.13.



11

Alcohol **11** was prepared using 2-bromostyrene (45.0 µL, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 15 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:4 to 1:3 EtOAc/hexanes) to afford **11** (96.7 mg, 0.264 mmol, 89% yield) as a colorless residue.

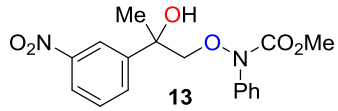
Analytical data for **11**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.73 (dd, *J* = 1.6, 7.9 Hz, 1 H), 7.52 - 7.27 (m, 6 H), 7.16 (dt, *J* = 1.9, 7.7 Hz, 1 H), 5.43 (dd, *J* = 2.2, 9.5 Hz, 1 H), 4.75 (br. s, 1 H), 4.18 (dd, *J* = 2.4, 11.5 Hz, 1 H), 3.88 (s, 3 H), 3.62 (dd, *J* = 9.5, 11.7 Hz, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 156.7, 139.4, 138.1, 132.5, 129.3, 129.0, 128.2, 127.9, 127.4, 124.2, 121.7, 78.4, 69.6, 54.1; **IR** (thin film, cm^{-1}) 3438, 2955, 1714, 1595, 1494, 1441, 1347, 1118, 1025, 911, 755, 694; **LRMS** (ESI) Calcd. for $[C_{16}H_{16}BrNO_4+Na]^+$ = 388.02, Found = 388.00.



12

Alcohol **12** was prepared using *para*-trifluoromethylstyrene (61.8 mg, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 15 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (25% EtOAc/hexanes) to afford **12** (88.9 mg, 0.250 mmol, 84% yield) as a colorless residue.

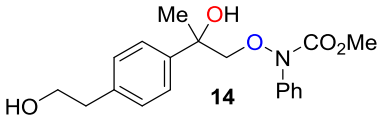
Analytical data for **12**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.3 Hz, 2 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.47 - 7.38 (m, 4 H), 7.32 (tt, *J* = 1.6, 6.9 Hz, 1 H), 5.12 (d, *J* = 9.4 Hz, 1 H), 4.77 (br. s, 1 H), 4.07 (dd, *J* = 2.6, 11.7 Hz, 1 H), 3.88 (s, 3 H), 3.82 (dd, *J* = 9.4, 11.7 Hz, 1 H); **^{13}C NMR** (151 MHz, $CDCl_3$) 156.6, 143.1, 139.4, 129.0, 127.3, 126.5, 125.42, 125.39, 125.36, 125.34, 123.8, 80.3, 70.2, 54.1; **IR** (thin film, cm^{-1}) 3435, 3068, 3044, 2958, 1714, 1620, 1326, 1123, 1017, 845, 755; **LRMS** (ESI) Calcd. for $[C_{17}H_{16}F_3NO_4+Na]^+$ = 378.09, Found = 378.11.



13

Alcohol **13** was prepared from *m*-nitro-α-methyl styrene (58.6 mg, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:3 EtOAc/hexanes) to afford **13** (85.4 mg, 0.247 mmol, 83% yield) as a colorless residue.

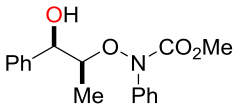
Analytical data for **13**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 8.37 (t, *J* = 2.0 Hz, 1 H), 8.16 (ddd, *J* = 0.9, 2.4, 8.0 Hz, 1 H), 7.87 (qd, *J* = 0.9, 7.8 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.40 - 7.33 (m, 2 H), 7.28 - 7.24 (m, 1 H), 7.23 - 7.19 (m, 2 H), 4.84 (br. s, 1 H), 4.32 (d, *J* = 10.7 Hz, 1 H), 4.11 (d, *J* = 10.7 Hz, 1 H), 3.79 (s, 3 H), 1.56 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.6, 148.3, 147.5, 139.2, 131.5, 129.2, 128.9, 127.0, 123.1, 122.1, 120.4, 83.0, 73.1, 53.9, 27.0; **IR** (thin film, cm^{-1}) 3417, 3090, 2981, 2875, 1695, 1595, 1531, 1349, 909; **LRMS** (ESI) Calcd. for $[C_{17}H_{18}N_2O_6+Na]^+$ = 369.11, Found = 369.10.



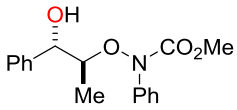
14

Alcohol **14** was prepared using 2-(4-(prop-1-en-2-yl)phenyl)ethan-1-ol (58.2 mg, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:1 EtOAc/hexanes) to afford **14** (80.5 mg, 0.233 mmol, 78% yield) as a colorless residue.

Analytical data for **14**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.46 - 7.42 (m, 2 H), 7.39 - 7.34 (m, 2 H), 7.29 - 7.22 (m, 5 H), 4.35 (br. s, 1 H), 4.23 (d, *J* = 10.1 Hz, 1 H), 4.05 (d, *J* = 10.4 Hz, 1 H), 3.88 (t, *J* = 6.6 Hz, 2 H), 3.80 (s, 3 H), 2.89 (t, *J* = 6.6 Hz, 2 H), 1.54 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.4, 143.0, 139.4, 137.2, 128.8, 128.7, 126.6, 125.3, 122.8, 83.4, 73.1, 63.7, 53.7, 38.8, 26.9; **IR** (thin film, cm^{-1}) 3418, 3061, 2954, 2876, 1713, 1595, 1494, 1349, 1048, 751; **LRMS** (ESI) Calcd. for $[C_{19}H_{23}NO_5+Na]^+$ = 368.15, Found = 368.15.



15a



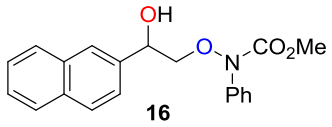
15b

Alcohol **15** was prepared using β-methylstyrene (46.6 μL, 0.359 mmol,), under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 7.5 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (15-20% EtOAc/hexanes gradient) to afford **15** as a mixture of diastereomers (56.0 mg major and 21.7 mg minor, 0.258 mmol total, 86% yield) as a colorless residue.

Analytical data for **15a (major isomer)**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 - 7.52 (m, 4 H), 7.21 - 7.37 (m, 6 H), 5.21 (d, *J*=2.51 Hz, 1 H), 4.15 - 4.44 (m, 1 H), 4.05 (dd, *J*=6.53, 2.51 Hz, 1 H), 3.88 (s, 3 H), 1.03 (d, *J*=6.53 Hz, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) 156.2, 139.9, 139.3, 129.0, 128.2, 127.2, 127.1, 125.8, 123.8, 83.8, 71.2, 54.1, 11.2; **IR** (thin film, cm^{-1}) 3455, 3063, 3030, 2989, 2955, 2925, 2854, 2250, 1954, 1884, 1714, 1595, 1494, 1441, 1337, 1117, 1067, 913, 747, 699; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.12.

Analytical data for **15b** (**minor isomer**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 - 7.26 (m, 10 H), 5.04 (br. s., 1 H), 4.65 (dd, *J* = 1.60, 5.20 Hz, 1H), 4.21 (m, 1H), 3.84 (s, 3H), 0.938 (d, *J* = 4.00 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) 157.0, 141.44, 140.3, 128.7, 128.4, 127.9, 127.0, 126.9, 123.9, 88.5, 54.0, 16.6; **IR** (thin film, cm^{-1}) 3420, 3031, 2981, 2925, 1714, 1595, 1494, 1441, 1341, 1114, 1041, 761, 698; **LRMS** (ESI) Calcd. for $[C_{17}H_{19}NO_4+Na]^+$ = 324.12, Found = 324.12.

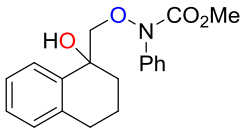
The stereochemistry of **15** was determined by reductive cleavage of the N-O bond using Zn (using an analogous procedure to that used in the 1-pot, direct dihydroxylation of α-methylstyrene reported below). Literature values for the *anti* diol report a 4.61 ppm (m, 1H), matching that obtained from reductive cleavage of **15a**, while the corresponding *syn* diol is shifted upfield at 4.28 ppm (m, 1H).[16]



16

Alcohol **16** was prepared using 2-vinylnaphthalene (55.4 mg, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 24 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (20% EtOAc/hexanes) to afford **16** (89.5 mg, 0.265 mmol, 89% yield) as a colorless residue.

Analytical data for **16**: **^{1}H NMR** (600MHz, $CDCl_3$) δ = 7.92 (s, 1 H), 7.88 - 7.81 (m, 3 H), 7.54 - 7.40 (m, 7 H), 7.34 - 7.27 (m, 1 H), 5.25 (dd, *J* = 2.4, 9.6 Hz, 1 H), 4.66 (br. s, 1 H), 4.16 (dd, *J* = 2.6, 11.3 Hz, 1 H), 3.95 (dd, *J* = 9.8, 11.3 Hz, 1 H), 3.90 (s, 3 H); **^{13}C NMR** (151 MHz, $CDCl_3$) 156.5, 139.5, 136.4, 133.3, 133.1, 129.0, 128.2, 127.9, 127.7, 127.1, 126.2, 126.0, 125.2, 124.1, 123.6, 80.5, 70.8, 54.1; **IR** (thin film, cm^{-1}) 3437, 3060, 2955, 1714, 1595, 1494, 1348, 1122, 750; **LRMS** (ESI) Calcd. for $[C_{20}H_{19}NO_4+Na]^+$ = 360.12, Found = 360.13.

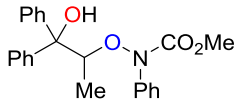


17

Alcohol **17** was prepared using 1-methylene-1,2,3,4-tetrahydronaphthalene (51.8 mg, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:4 EtOAc/hexanes) to afford **17** (76.6 mg, 0.234 mmol, 78% yield) as a colorless residue.

Analytical data for **17**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.65 - 7.56 (m, 1 H), 7.48 - 7.34 (m, 4 H), 7.30 - 7.17 (m, 3 H), 7.14 - 7.05 (m, 1 H), 4.20 (d, *J* = 9.8 Hz, 1 H), 4.03 (d, *J* = 9.8 Hz, 1 H), 3.89 (s, 3 H), 3.80 (br. s., 1 H), 2.93 - 2.82 (m, 1 H), 2.81 - 2.71 (m, 1 H), 2.42 - 2.31 (m, 1 H), 2.04 - 1.91 (m, 2 H), 1.89 - 1.74 (m, 1 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.4, 139.8, 138.0, 137.5, 128.9, 128.8, 127.7, 126.9, 126.4, 126.2, 122.6, 81.5, 71.8, 53.7, 33.5, 29.4, 19.9; **IR** (thin film, cm^{-1}) 3434, 3063, 3025, 2940, 2872,

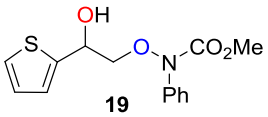
2839, 2249, 1714, 1595, 1494, 1442, 1348, 1119, 911, 735, 693; **LRMS** (ESI) Calcd. for $[C_{19}H_{21}NO_4+Na]^+$ = 350.14, Found = 350.13.



18

Alcohol **18** was prepared using 1,1-diphenylpropene (61.8 mg, 0.359 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 5 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (10% EtOAc/hexanes) to afford **18** (98.2 mg, 0.260 mmol, 87% yield) as a colorless residue.

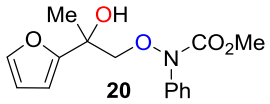
Analytical data for **18**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.70 - 7.61 (m, 2 H), 7.49 (dd, *J* = 1.1, 8.4 Hz, 2 H), 7.44 - 7.39 (m, 2 H), 7.37 - 7.32 (m, 2 H), 7.30 - 7.23 (m, 6 H), 7.19 - 7.14 (m, 1 H), 5.11 (q, *J* = 6.3 Hz, 1 H), 4.72 (br. s., 1 H), 3.64 (s, 3 H), 1.19 (d, *J* = 6.3 Hz, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.5, 145.8, 144.5, 139.8, 128.7, 128.2, 127.8, 126.6 126.4, 126.0, 125.4, 123.0, 82.9, 78.5, 53.6, 14.1; **IR** (thin film, cm^{-1}) 3515, 3396, 3060, 3031, 3000, 2954, 2852, 2250, 1953, 1882, 1714, 1595, 1494, 1441, 1344, 1190, 910, 732, 696; **LRMS** (ESI) Calcd. for $[C_{23}H_{23}NO_4+Na]^+$ = 400.15, Found = 400.13.



19

Alcohol **19** was prepared using 2-vinylthiophene (65.9 mg, 0.598 mmol, 2.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:3 EtOAc/hexanes) to afford **19** (73.6 mg, 0.251 mmol, 84% yield) as a colorless residue.

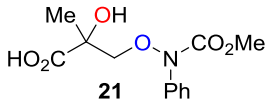
Analytical data for **19**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 4.1 Hz, 2 H), 7.33 - 7.27 (m, 2 H), 7.02 - 6.98 (m, 2 H), 5.32 (td, *J* = 2.4, 9.5 Hz, 1 H), 4.66 (br. s, 1 H), 4.12 (dd, *J* = 2.8, 11.5 Hz, 1 H), 3.98 (dd, *J* = 9.4, 11.7 Hz, 1 H), 3.88 (s, 3 H); **^{13}C NMR** (151 MHz, $CDCl_3$) 155.5, 142.2, 139.4, 129.0, 127.2, 126.7, 125.0, 124.3, 123.7, 80.1, 67.1, 54.1; **IR** (thin film, cm^{-1}) 3433, 2360, 1714, 1493, 1440, 1348, 1116, 753, 694; **LRMS** (ESI) Calcd. for $[C_{14}H_{15}NO_4S+Na]^+$ = 316.06, Found = 316.03.



20

Alcohol **20** was prepared using 2-(prop-1-en-2-yl)furan (64.7 mg, 0.598 mmol, 2.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 2.5 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (20% EtOAc/hexanes) to afford **20** (41.4 mg, 0.142 mmol, 48% yield) as a colorless residue.

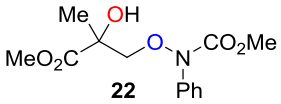
Analytical data for **20**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.40 - 7.35 (m, 3 H), 7.32 - 7.29 (m, 2 H), 7.27 - 7.23 (m, 1 H), 6.41 - 6.34 (m, 2 H), 4.53 (br. s, 1 H), 4.32 (d, *J* = 10.2 Hz, 2 H), 3.98 (d, *J* = 10.5 Hz, 1 H), 3.80 (s, 3 H), 1.55 (s, 3 H); **^{13}C NMR** (151 MHz, $CDCl_3$) 157.3, 155.6, 141.7, 139.4, 128.8, 126.7, 123.0, 110.3, 105.4, 81.0, 70.5, 53.8; **IR** (thin film, cm^{-1}) 3411, 2984, 2955, 1714, 1595, 1447, 1349, 1015, 751; **LRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_5+Na]^+$ = 314.10, Found = 314.06.



21

Alcohol **21** was prepared using methacrylic acid (130.0 µL, 1.50 mmol, 5.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (30:1 CH_2Cl_2:MeOH) to afford **21** (36.5 mg, 0.136 mmol, 45% yield) as a colorless residue.

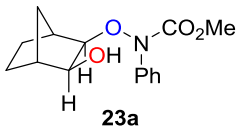
Analytical data for **21**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.43 - 7.39 (m, 2 H), 7.38 - 7.35 (m, 2 H), 7.32 - 7.29 (m, 1 H), 4.49 (d, J = 10.9 Hz, 1 H), 3.87 (d, J = 10.9 Hz, 1 H), 3.83 (s, 3 H), 1.45 (s, 3 H); **^{13}C NMR** (151 MHz, $CDCl_3$) 176.6, 156.6, 139.0, 129.0, 127.5, 123.7, 80.0, 73.8, 54.3, 22.4; **IR** (thin film, cm^{-1}) 3449, 2957, 1723, 1493, 1442, 1349, 1349, 754, 695; **LRMS** (ESI) Calcd. for $[C_{12}H_{15}NO_6+Na]^+$ = 292.08, Found = 292.05.



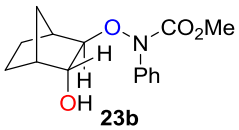
22

Alcohol **22** was prepared using methyl methacrylate (160.0 µL, 1.50 mmol, 5.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 22 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:2 to 1:1 EtOAc/hexanes) to afford **22** (70.9 mg, 0.250 mmol, 84% yield) as a colorless residue.

Analytical data for **22**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.41 - 7.35 (m, 4 H), 7.27 - 7.22 (m, *J* = 3.2, 5.7, 5.7 Hz, 1 H), 4.36 (br. s., 1 H), 4.29 (d, *J* = 10.1 Hz, 1 H), 3.89 (d, *J* = 10.1 Hz, 1 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 1.39 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 174.9, 155.6, 139.5, 128.8, 126.7, 122.8, 80.4, 73.8, 53.8, 52.8, 22.3; **IR** (thin film, cm^{-1}) 3447, 2996, 2955, 1732, 1595, 1494, 1441, 1349, 759, 695; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_6+Na]^+$ = 306.10, Found = 306.10.



23a

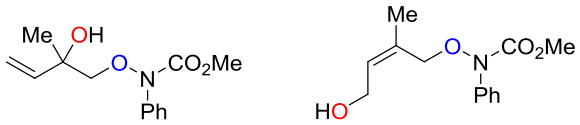


23b

Alcohol **23** was prepared using norbornene (141.0 mg, 1.50 mmol, 5.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 6 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (15-20% EtOAc/hexanes gradient) to afford **23** as a mixture of diastereomers (35.2 mg, 0.127 mmol, 42% yield **23a** and 28.8 mg, 0.104 mmol, 35% yield **23b**) as a colorless residue.

Analytical data for **23a**: **^{1}H NMR** (600 MHz, C_6D_6) δ = 7.40 - 7.33 (m, 2 H), 7.11 - 7.03 (m, 2 H), 6.95 - 6.87 (m, 1 H), 4.71 (br. s., 1 H), 3.91 (d, *J* = 5.6 Hz, 1 H), 3.71 (dd, *J* = 1.5, 5.6 Hz, 1 H), 3.26 (s, 3 H), 2.32 (d, *J* = 4.5 Hz, 1 H), 2.19 (td, *J* = 1.7, 10.1 Hz, 1 H), 2.13 (d, *J* = 4.1 Hz, 1 H), 1.15 - 1.06 (m, 1 H), 1.06 - 0.99 (m, 1 H), 0.93 - 0.89 (m, 1 H), 0.69 (ddd, *J* = 2.1, 4.1, 11.9 Hz, 1 H), 0.56 - 0.50 (m, 1 H); **^{13}C NMR** (151 MHz, C_6D_6) 155.9, 141.0, 128.6, 128.0, 126.5, 123.6, 90.2, 76.2, 53.0, 43.3, 41.2, 32.8, 25.0, 23.7; **IR** (thin film, cm^{-1}) 3432, 2961, 2874, 1708, 1646, 1493, 1341, 756; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_4+Na]^+$ = 300.12, Found = 300.12.

Analytical data for **23b**: **^{1}H NMR** (600 MHz, C_6D_6) δ = 7.55 (d, *J* = 7.5 Hz, 2 H), 7.11 (t, *J* = 8.1 Hz, 2 H), 6.94 - 6.88 (m, 1 H), 4.19 (d, *J* = 3.8 Hz, 1 H), 3.88 (s, 1 H), 3.38 (s, 3 H), 2.67 (br. s, 1 H), 2.28 (d, J = 5.3 Hz, 1 H), 2.17 - 2.11 (m, 1 H), 1.89 - 1.82 (m, 1 H), 1.75 (d, *J* = 10.2 Hz, 1 H), 1.33 - 1.25 (m, 1 H), 1.13 - 1.05 (m, 1 H), 1.04 - 0.99 (m, 1 H), 0.99 - 0.94 (m, 1 H); **^{13}C NMR** (151 MHz, C_6D_6) 156.0, 142.0, 128.5, 128.0, 125.8, 123.0, 94.5, 77.7, 52.7, 41.7, 40.8, 34.2, 24.9, 19.7; **IR** (thin film, cm^{-1}) 3428, 2958, 2876, 1712, 1440, 1341, 1107, 758; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_4+Na]^+$ = 300.12, Found = 300.11.

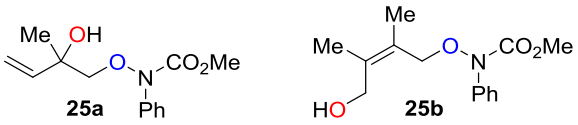


24a **24b**

Alcohol **24** was prepared using isoprene (150.0 µL, 1.50 mmol, 5.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 6 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (25% EtOAc/hexanes) to afford **24** as a mixture of isomers (44.0 mg, 0.175 mmol, 59% yield of the kinetic isomer and 21.9 mg, 0.087 mmol, 29% yield of the thermodynamic isomer) as a colorless residue.

Analytical data for **24a**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.44 - 7.38 (m, 4 H), 7.28 - 7.25 (m, 1 H), 5.93 (dd, *J* = 10.7, 17.1 Hz, 1 H), 5.43 (dd, *J* = 1.3, 17.1 Hz, 1 H), 5.18 (dd, *J* = 1.3, 10.7 Hz, 1 H), 3.95 (d, *J* = 9.8 Hz, 1 H), 3.87 - 3.85 (m, 1 H), 3.84 (s, 3 H), 1.31 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.4, 141.6, 139.5, 128.9, 128.8, 127.0, 126.6, 123.4, 122.8, 113.7, 112.6, 82.4, 78.5, 72.1, 71.8, 53.8, 24.5; **IR** (thin film, cm^{-1}) 3434, 2978, 2956, 2876, 1714, 1595, 1348, 1119, 751; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_4+Na]^+$ = 274.11, Found = 274.10.

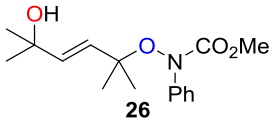
Analytical data for **24b**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.50 - 7.43 (m, 2 H), 7.42 - 7.36 (m, 2 H), 7.27 - 7.19 (m, 1 H), 5.75 - 5.66 (m, 1 H), 4.51 and 4.20 (d, *J* = 7.2 and 6.8 Hz, 2 H), 4.32 and 4.04 (s, 2 H), 3.87 and 3.85 (d, *J* = 1.1 and 0.8 Hz, 3 H), 1.75 and 1.72 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.3, 140.1, 133.0, 130.4, 128.7, 126.1, 125.9, 122.7, 122.1, 117.4, 80.5, 70.5, 67.7, 59.1, 53.4, 14.6, 13.9; **IR** (thin film, cm^{-1}) 3422, 2955, 2863, 1714, 1595, 1494, 1349, 1114, 752; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_4+Na]^+$ = 274.11, Found = 274.10.



Alcohol **25** was prepared using 2,3-dimethyl-1,3-butadiene (169.7 µL, 1.50 mmol, 5.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 3 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (25% EtOAc/hexanes) to afford **25** as a mixture of isomers (59.2 mg, 0.223 mmol, 75% yield of the kinetic isomer and 10.0 mg, 0.038 mmol, 13% yield of the thermodynamic isomer) as a colorless residue.

Analytical data for **25a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 - 7.36 (m, 4 H), 7.28 - 7.23 (m, 1 H), 5.23 - 5.16 (m, 1 H), 4.98 - 4.92 (m, 1 H), 4.17 (d, *J* = 9.8 Hz, 1 H), 3.87 - 3.81 (m, 4 H), 1.81 (s, 3 H), 1.31 (s, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.4, 127.8, 139.7, 128.9, 126.5, 122.7, 111.1, 81.5, 74.1, 53.7, 24.0, 19.4; **IR** (thin film, cm^{-1}) 3441, 3066, 2977, 2855, 1714, 1596, 1347, 1119, 905; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_4+Na]^+$ = 288.12, Found = 288.12.

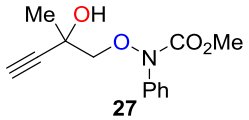
Analytical data for **25b**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.51 - 7.44 (m, 2 H), 7.44 - 7.35 (m, 2 H), 7.26 - 7.18 (m, 1 H), 4.46 (s, 2 H), 4.17 (s, 2 H), 3.87 (s, 3 H), 1.90 - 1.84 (m, 3 H), 1.84 - 1.79 (m, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) 155.2, 140.2, 136.7, 128.8, 128.6, 126.2, 126.1, 125.9, 122.5, 122.1, 75.9, 75.0, 63.6, 63.4, 53.6, 53.4, 18.7, 17.7, 17.1, 16.5; **IR** (thin film, cm^{-1}) 3425, 2954, 2924, 1715, 1596, 1494, 1349, 1107, 750; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_4+Na]^+$ = 288.12, Found = 288.12.



Alcohol **26** was prepared using 2,5-dimethyl-2,4-hexadiene (85.3 µL, 0.598 mmol, 2.0 equiv.) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 2 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (20% EtOAc/hexanes) to afford **26** (52.0 mg, 0.177 mmol, 59% yield) as a colorless residue.

Analytical data for **26**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.43 - 7.36 (m, 2 H), 7.36 - 7.27 (m, 2 H), 7.22 - 7.09 (m, 1 H), 5.66 - 5.52 (m, 2 H), 3.77 (s, 3 H), 1.44 - 1.31 (m, 6 H), 1.11 (s, 6 H); **^{13}C NMR** (101 MHz, $CDCl_3$) 157.1, 144.1, 137.8, 130.9, 128.2, 125.8, 123.7, 84.4, 70.1, 53.4, 29.2; **IR** (thin film, cm^{-1})

3456, 3030, 2977, 2933, 1723, 1595, 1364, 1133, 769; **LRMS** (ESI) Calcd. for $[C_{16}H_{23}NO_4+Na]^+$ = 316.15, Found = 316.16.

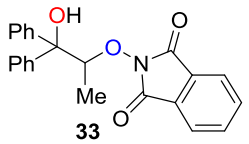


27

Alcohol **27** was prepared using 2-methyl-1-buten-3-yne (140.0 µL, 1.50 mmol) under the standard conditions. The reaction was complete, as indicated by TLC, after heating at 60 ºC for 7 h. The crude reaction mixture was reduced with DMS prior to purification by silica gel flash chromatography (1:3 EtOAc/hexanes) to afford **27** (50.6 mg, 0.203 mmol, 68% yield) as a colorless residue.

Analytical data for **27**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.48 - 7.39 (m, 4 H), 7.31 - 7.26 (m, 1 H), 4.69 (br. s, 1 H), 4.08 (d, *J* = 10.8 Hz, 1 H), 3.85 (s, 3 H), 3.82 (d, *J* = 10.5 Hz, 1 H), 2.50 (s, 1 H), 1.50 (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) 155.8, 139.2, 128.9, 126.9, 123.2, 85.5, 82.0, 71.6, 65.8, 53.9, 25.9; **IR** (thin film, cm^{-1}) 3414, 3286, 2956, 1714, 1594, 1494, 1441, 1348, 1305, 1119, 1026, 751, 694; **LRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_4+Na]^+$ = 272.09, Found = 272.09.

E2.3 Representative Procedures for Asymmetric Alkene Dioxygenation



33

In an argon filled glovebox, (*S*,*S*)-2,2′-Isopropylidene-bis(4-*tert*-butyl-2-oxazoline) (4.2 mg, 0.0144 mmol, 0.12 eq) and $Cu(OTf)_2$ (4.3mg, 0.0120 mmol, 0.10 eq) were dissolved in 0.4 mL THF and allowed to stir under overnight. *N*-hydroxyphthalimide (23.5 mg, 0.144 mmol, 1.2 eq) was added, followed by 1,1-diphenylpropene (23.6 mg, 0.120 mmol, 1.0 eq) as a solution in 0.2 mL THF. Oxygen gas was bubbled through the reaction mixture for 2 minutes. After 4 hours, the reaction was deemed complete by TLC analysis. Dimethyl sulfide (0.2mL, 2.72 mmol, 23 eq) was added and the reaction mixture was stirred until disappearance of the hydroperoxide product by TLC analysis. Volatiles were removed under a stream of nitrogen, and the residue was purified by silica gel flash chromatography (4:0.5:0.5 hexanes:EtOAc:DCM) to yield the dioxygenated product **33** (12.5 mg, 0.0335 mmol, 28% yield) as a

white solid. Enantiomeric excess was determined by elution through an IA column using an isocratic (95:5 hexanes : *i*PrOH) solvent system (60:40 e.r., 20% ee).

Analytical data for **33**: **^{1}H NMR** (500 MHz, $CDCl_3$); δ = 7.70 (m, 6 H), 7.50 (dd, *J* = 8.4, 1.1 Hz, 2 H), 7.28 (m, 2 H), 7.17 (m, 3 H), 6.97 (m, 1 H), 5.71 (q, *J* = 6.3 Hz, 1 H), 4.26 (s (br), 1 H), 1.24 (d, *J* = 6.4 Hz, 3 H) **^{13}C NMR** (101 MHz, $CDCl_3$); 164.2, 144.9, 143.9, 134.4, 128.5, 128.2, 128.0, 126.8, 126.6, 126.0, 125.3, 123.4, 85.7, 78.5, 13.5. **IR** (thin film, cm^{-1}); 3471, 3060, 3029, 3000, 2942, 2359, 2341, 2251, 1787, 1730, 1599, 1492, 1468, 1730, 1599, 1492, 1468, 1450, 1378, 1188, 1131, 1080, 1061, 1015, 979, 910, 879, 846, 768, 733, 700, 668, 653, 640, 600, 519. **LRMS** (ESI) Calcd. for $[C_{23}H_{19}NO_4 + H]^+$ = 374.14 , Found = 374.16. **HPLC**: Chiralpak IA, 95:5 hexanes:*i*PrOH, 60:40 e.r. (20% ee).

REFERENCES

[1] Boge, N.; Kruger, S.; Schroder, M.; Meier, C. *Synthesis* **2007**, 3907.

[2] Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc*. **1994**, *116*, 9869.

[3] Lebel, H.; Davi, M.; Díez-González, S.; Nolan, S. P. *J. Org. Chem.* **2007**, *72*, 144.

[4] Hui, B. W.; Chiba, S. *Org. Lett*. **2009**, *11*, 729.

[5] Denmark, S. E.; Butler, C.R. *Org. Lett*. **2006**, *8*, 63.

[6] Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354.

[7] Bunce, Richard A. and Childress, R. Shawn(1995) 'SYNTHESIS OF 5-BROMO-3,3-DIPHENYL-1-PENTENE', Organic Preparations and Procedures International, 27: 1, 122-125.

[8] Hatano, M.; Matsumura, T.; Ishihara, K. *Org. Lett.* **2005**, *7*, 573.

[9] Patent; Otsuka Chemical Co., Ltd. **2005**, EP1541550 A1.

[10] Giglio, B. C.; Schmidt, V. A.; Alexanian, E.J. *J. Am. Chem. Soc.* **2011**, *133*, 13320.

[11] Evans, D. A.; Song, H. J.; Fandrick, K. R. *Org. Lett*., **2006**, *8*, 3351.

[12] Schmidt, V. A.; Alexanian, E. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4491.

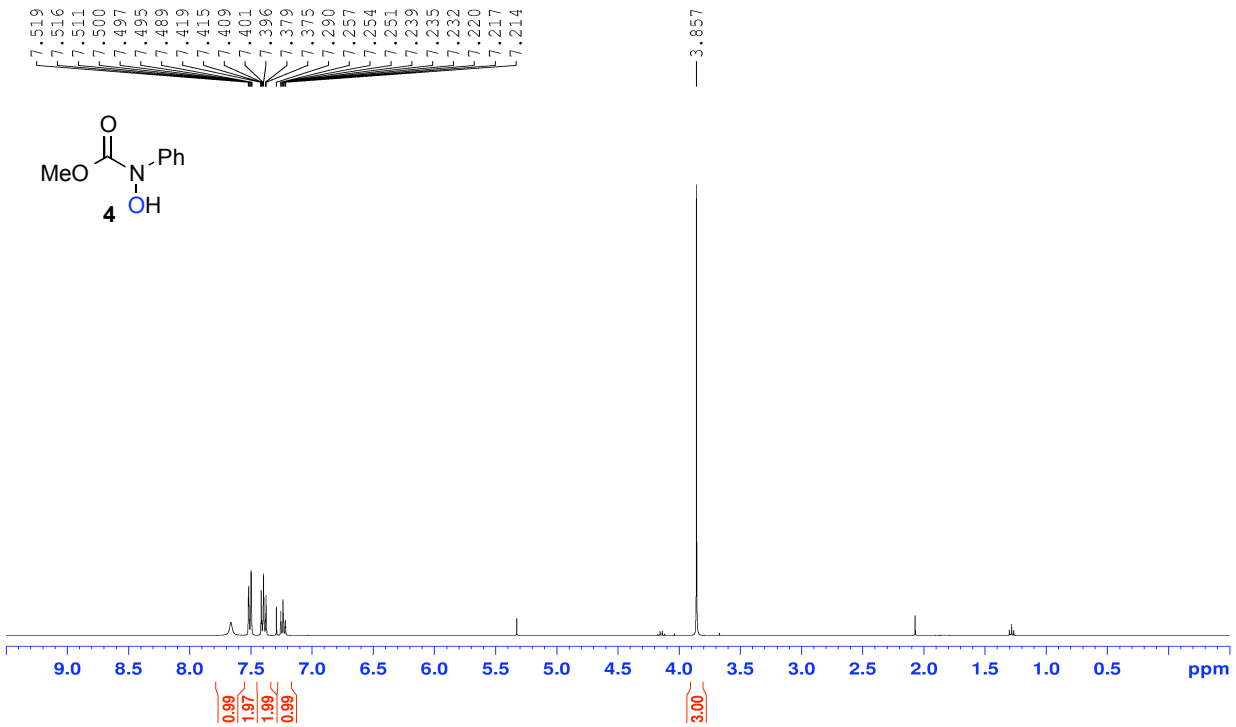
[13] Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731.

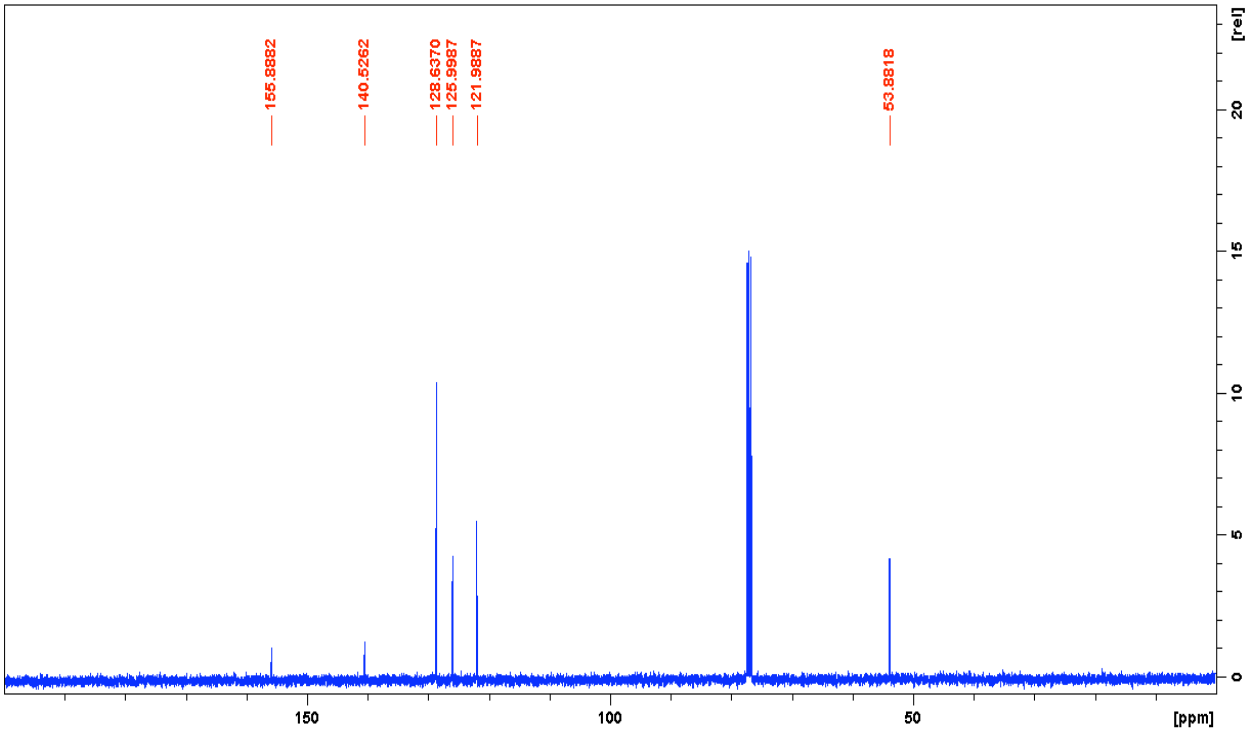
[14] Santos, P. F.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Heterocyles* **2001**, *55*, 1029.

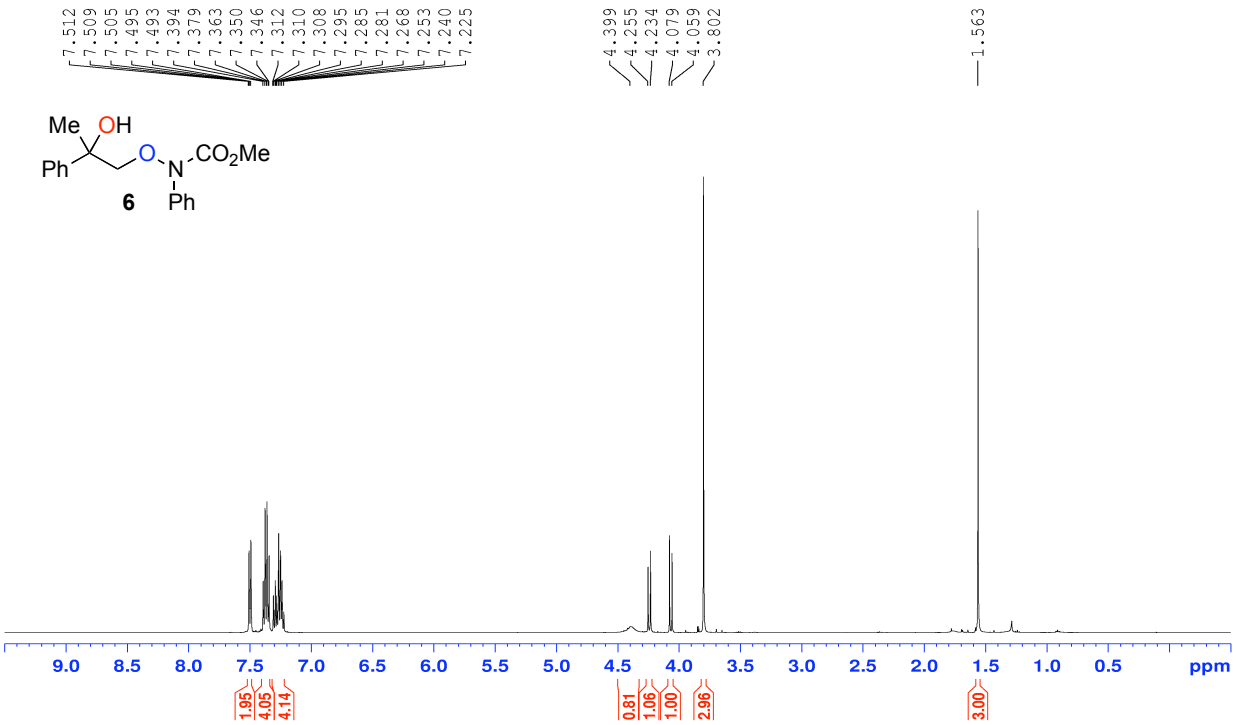
[15] Tamao, K.; Ishida, N. *Tet. Lett.* **1984**, *25*, 4245-4248.

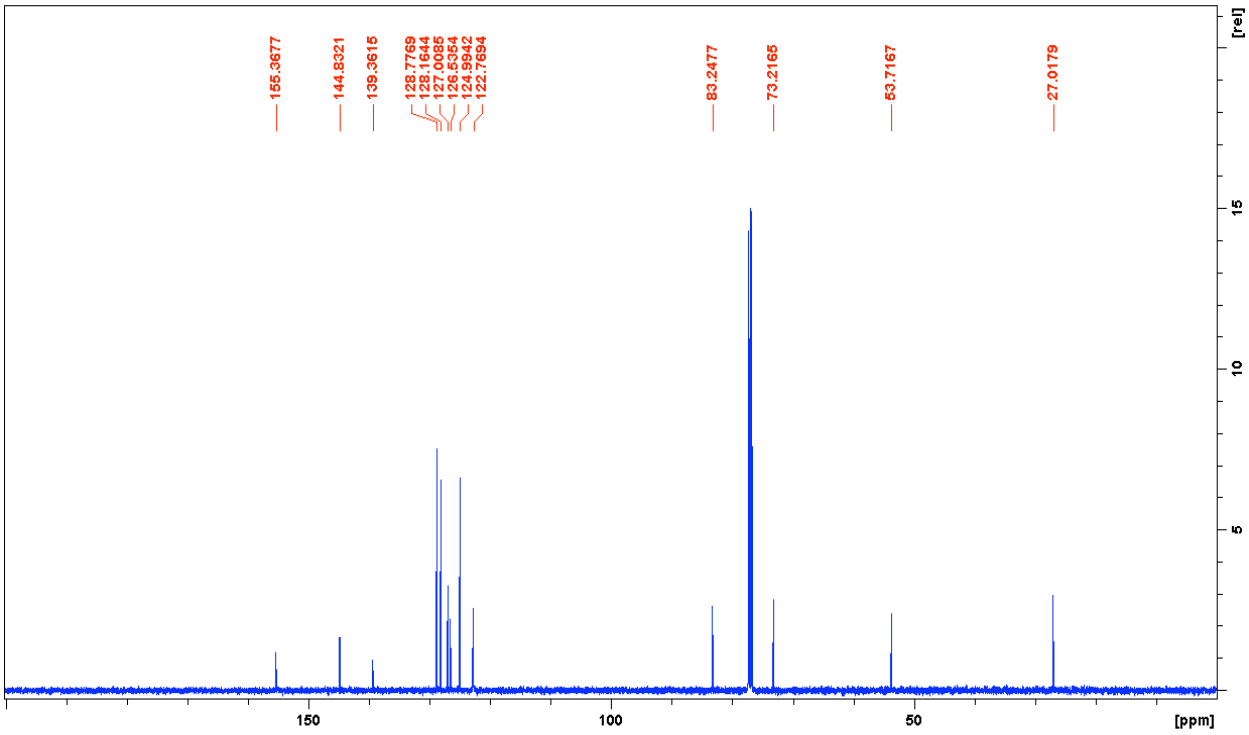
[16] Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3333-3336.

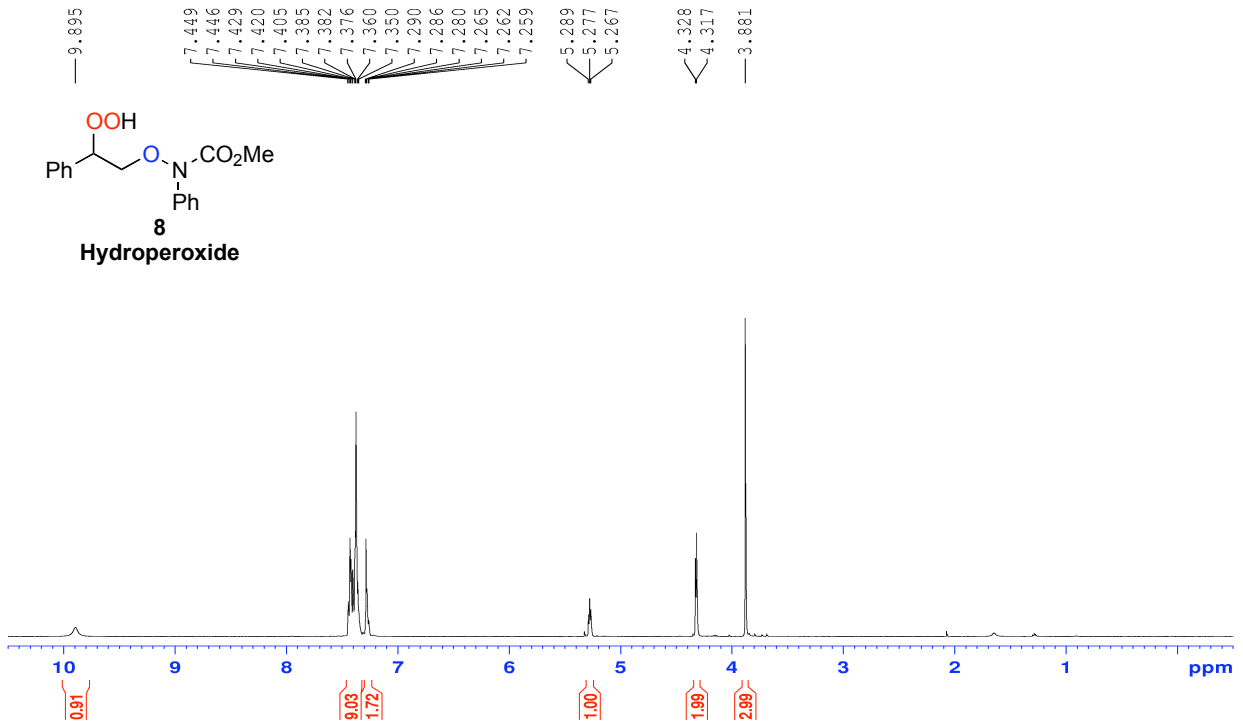
E2.5 Proton, Carbon-13, and Correlation Spectra


7.519
7.516
7.511
7.500
7.497
7.495
7.489
7.419
7.415
7.409
7.401
7.396
7.379
7.375
7.290
7.257
7.254
7.251
7.239
7.235
7.232
7.220
7.217
7.214
3.857
O
MeO
N
Ph
OH
4
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.99
1.97
1.99
0.99
3.00


155.8882
140.5262
128.6370
125.9987
121.9887
53.8818
[rel]
20
15
10
5
0
150
100
50
[ppm]

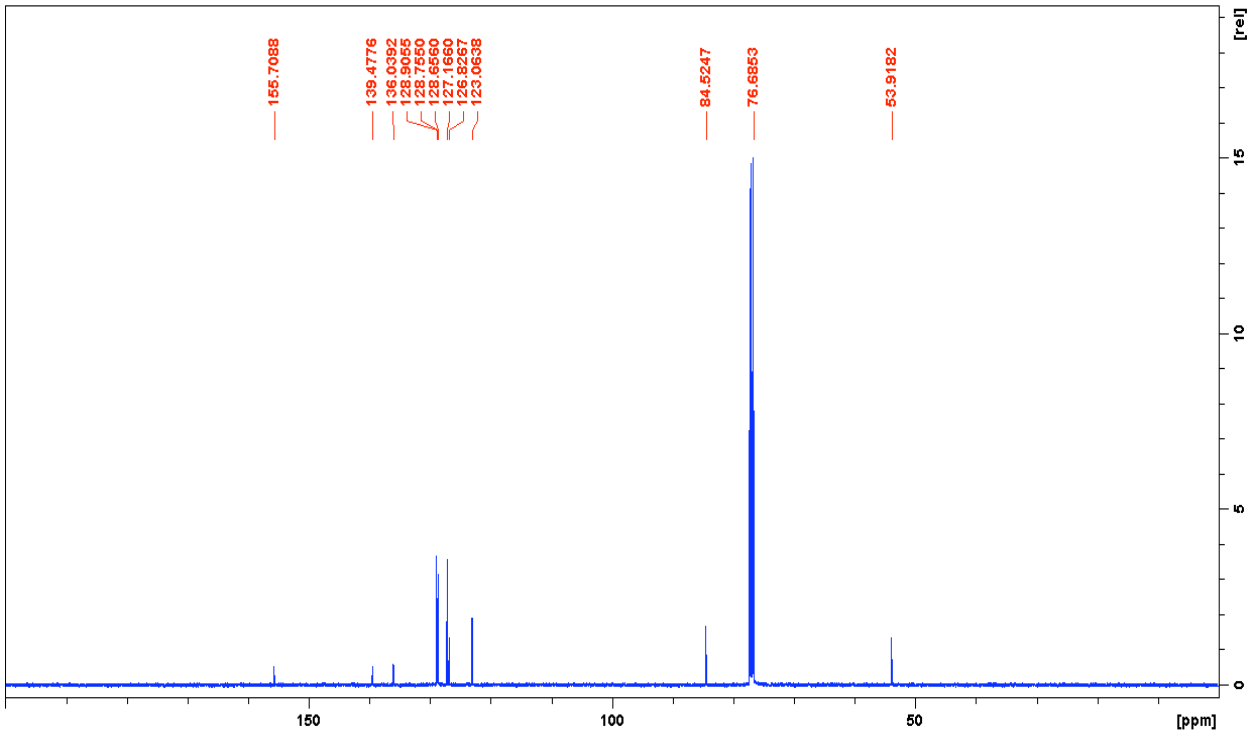

7.512
7.509
7.505
7.495
7.493
7.394
7.379
7.363
7.350
7.346
7.312
7.310
7.308
7.295
7.285
7.281
7.268
7.253
7.240
7.225
4.399
4.255
4.234
4.079
4.059
3.802
1.563
Me
OH
Ph
O
N
CO2Me
Ph
6
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.95
4.05
4.14
0.81
1.06
1.00
2.96
3.00

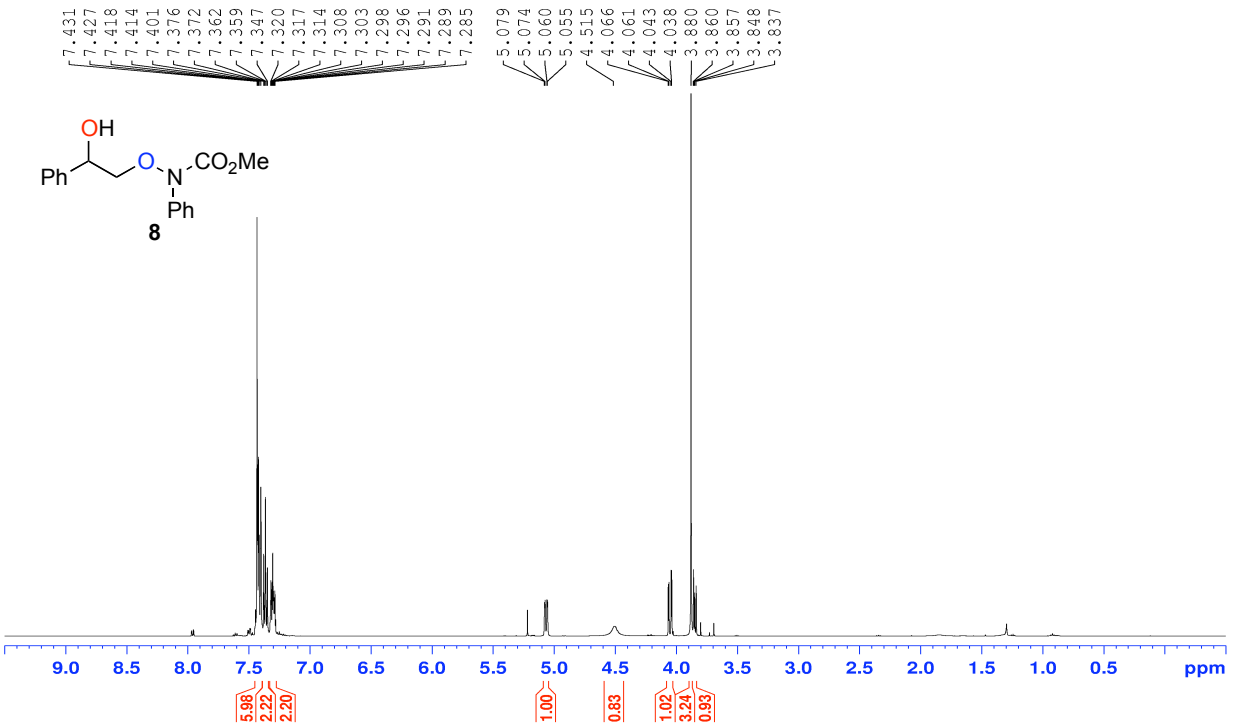

155.3677
144.8321
139.3615
128.7769
128.1644
127.0085
126.6354
124.9942
122.7694
83.2477
73.2165
53.7167
27.0179
[rel]
15
10
5
150
100
50
[ppm]

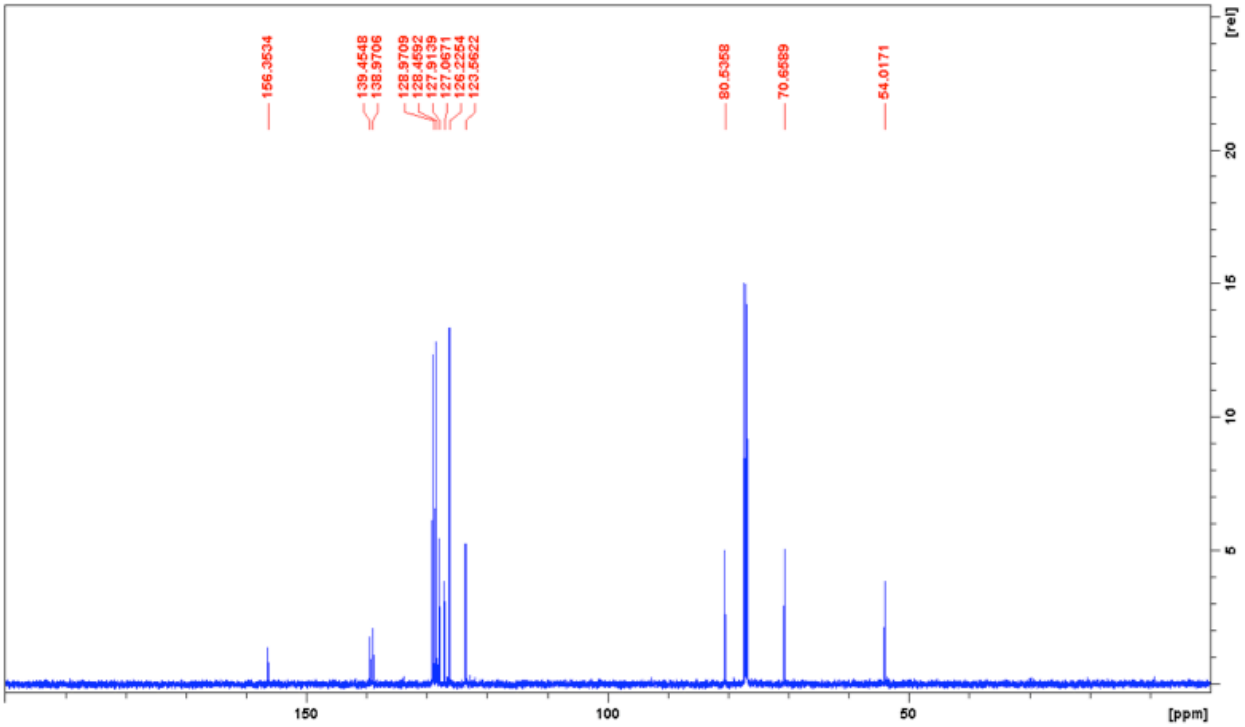


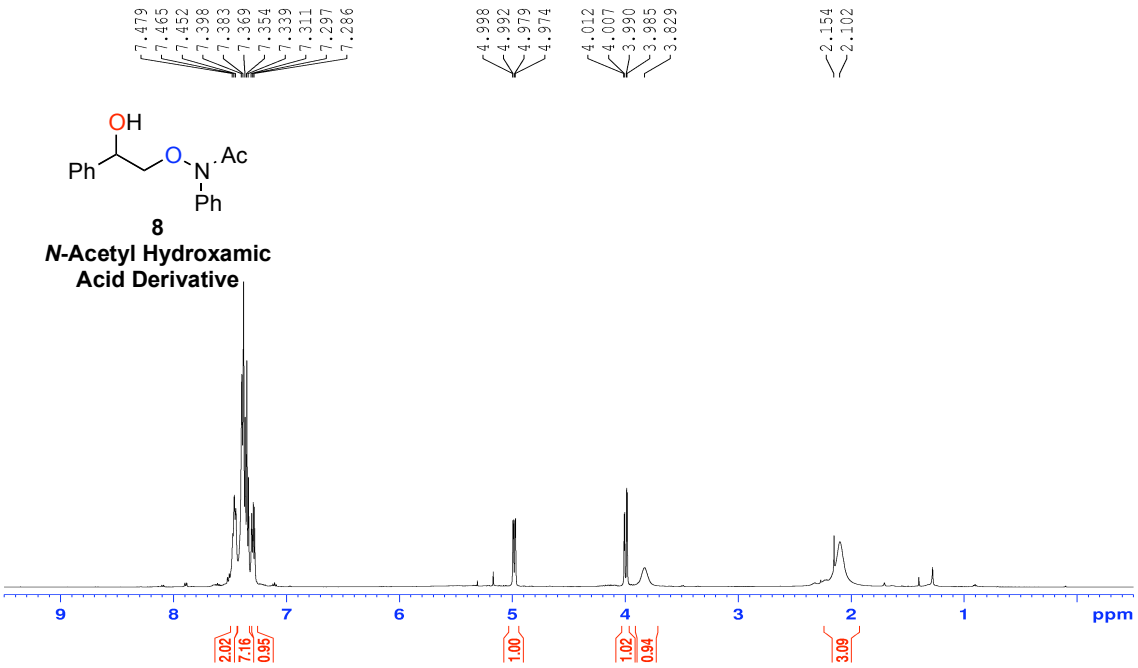
8

Hydroperoxide



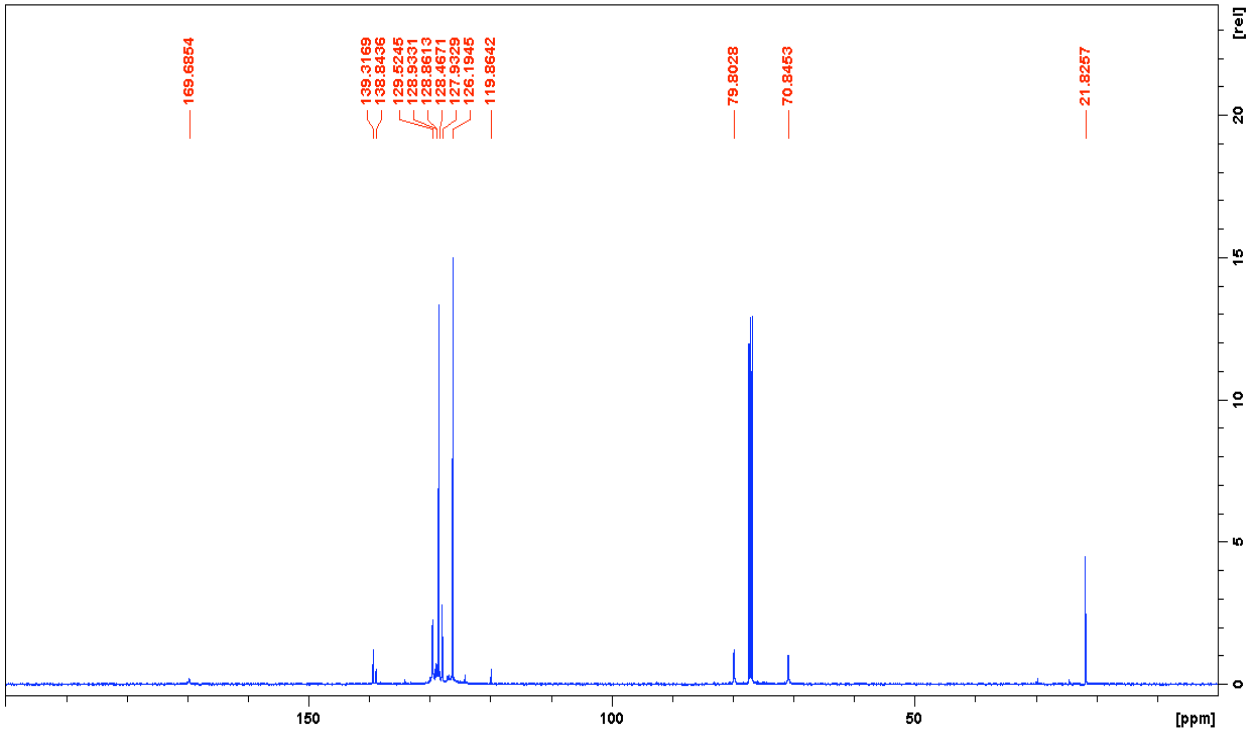

7.431
7.427
7.418
7.414
7.401
7.376
7.372
7.362
7.359
7.347
7.320
7.317
7.314
7.308
7.303
7.298
7.296
7.291
7.289
7.285
5.079
5.074
5.060
5.055
4.515
4.066
4.061
4.043
4.038
3.880
3.860
3.857
3.848
3.837
OH
Ph
O
N
CO2Me
Ph
8
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.98
2.22
2.20
1.00
0.83
1.02
3.24
0.93

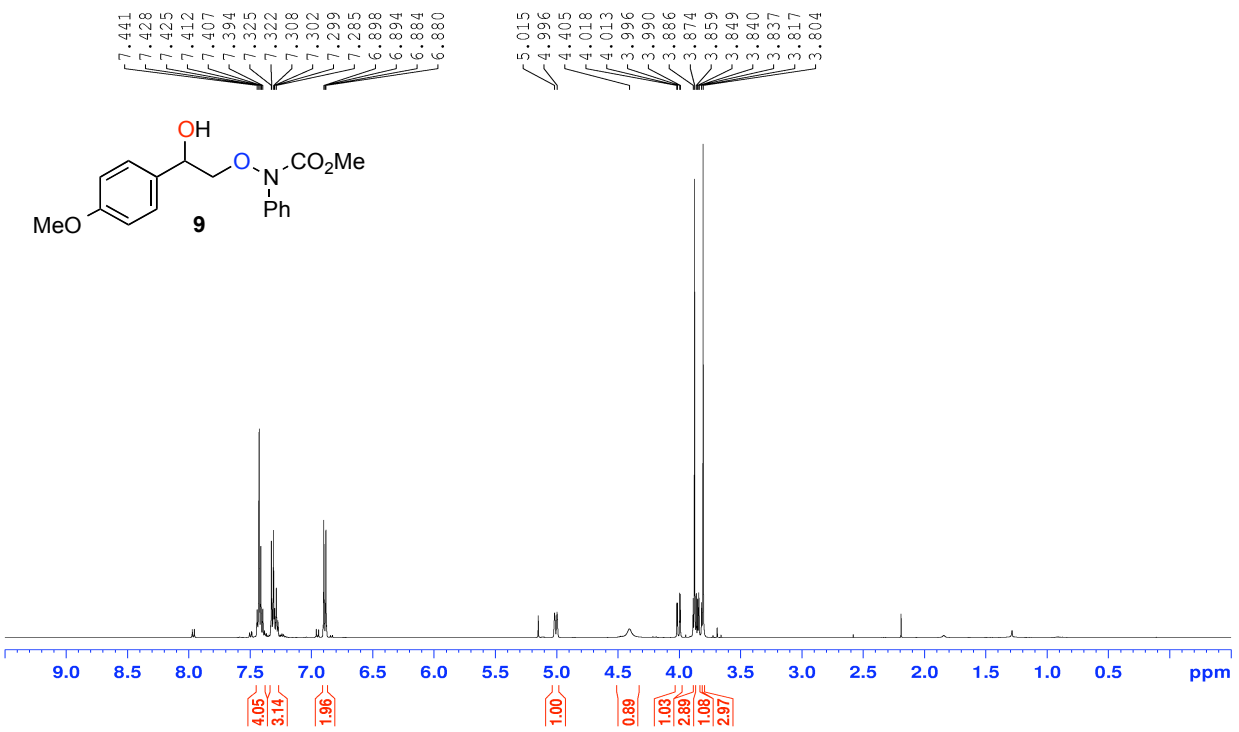

156.3534
139.4548
138.9706
128.9709
128.4592
127.9139
127.0671
126.2254
123.5622
80.5358
70.6589
54.0171
[rel]
20
15
10
5
150
100
50
[ppm]

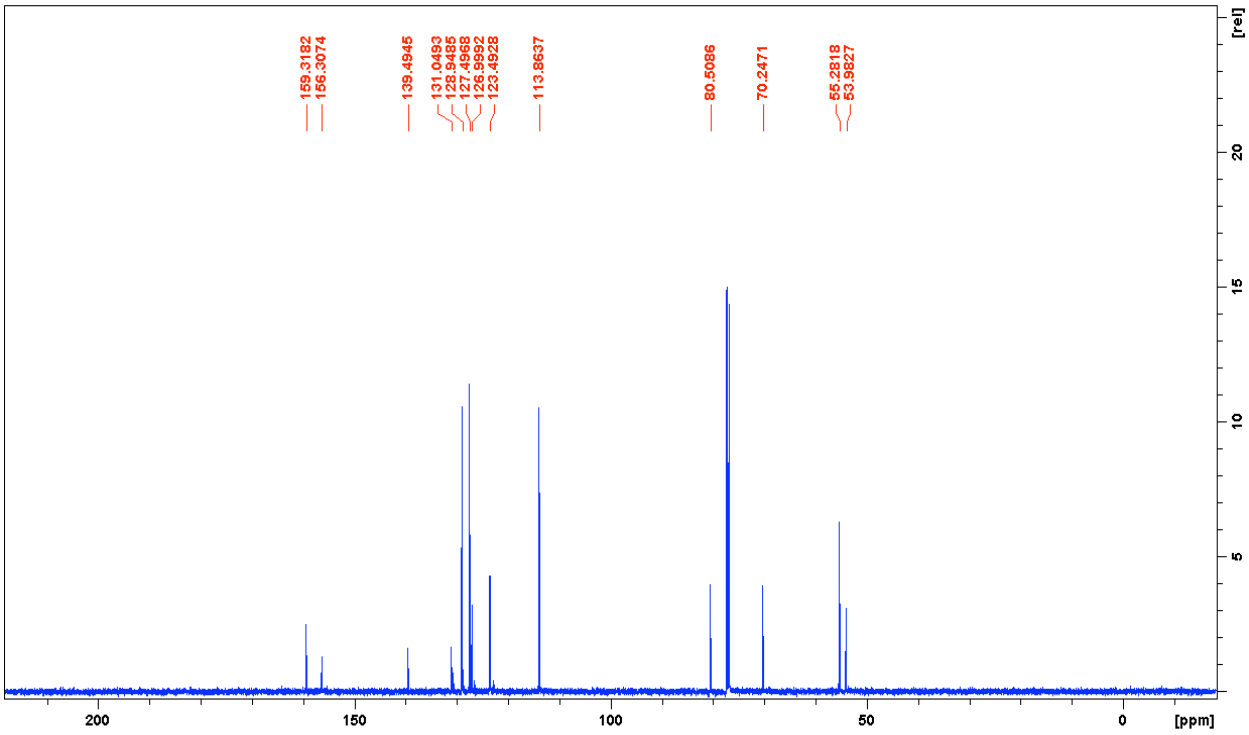


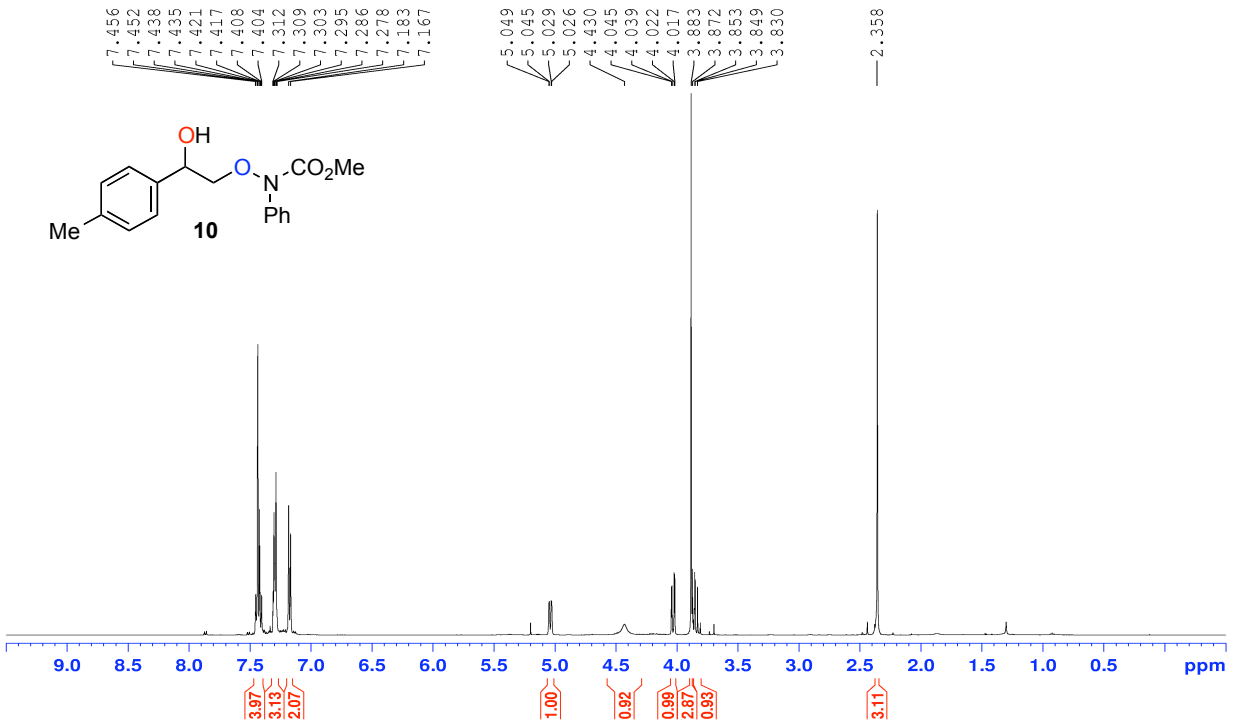
8

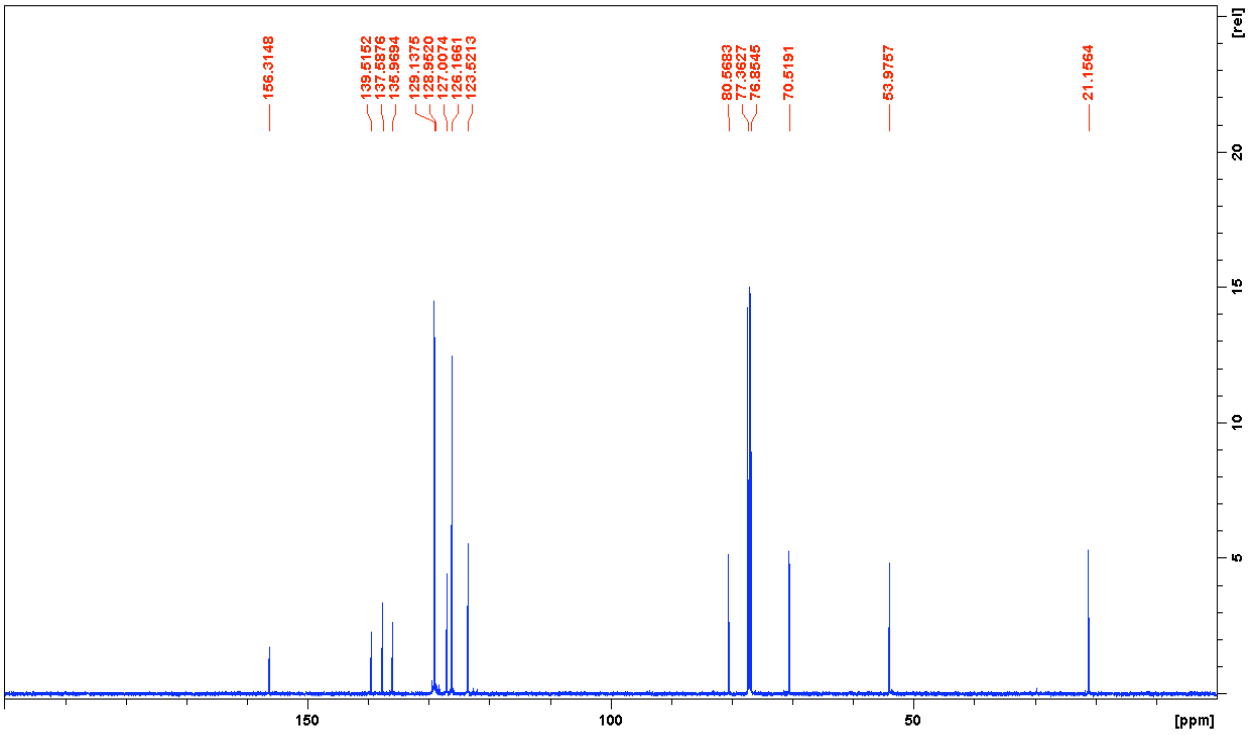
***N*-Acetyl Hydroxamic Acid Derivative**

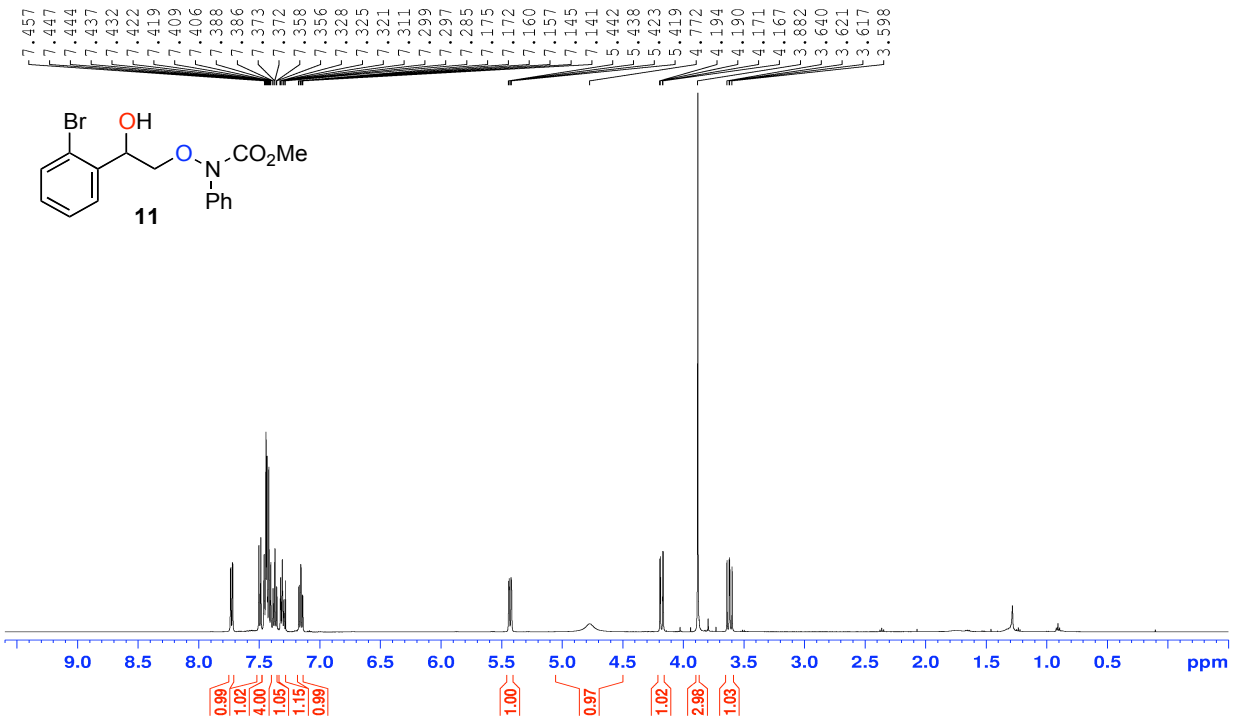


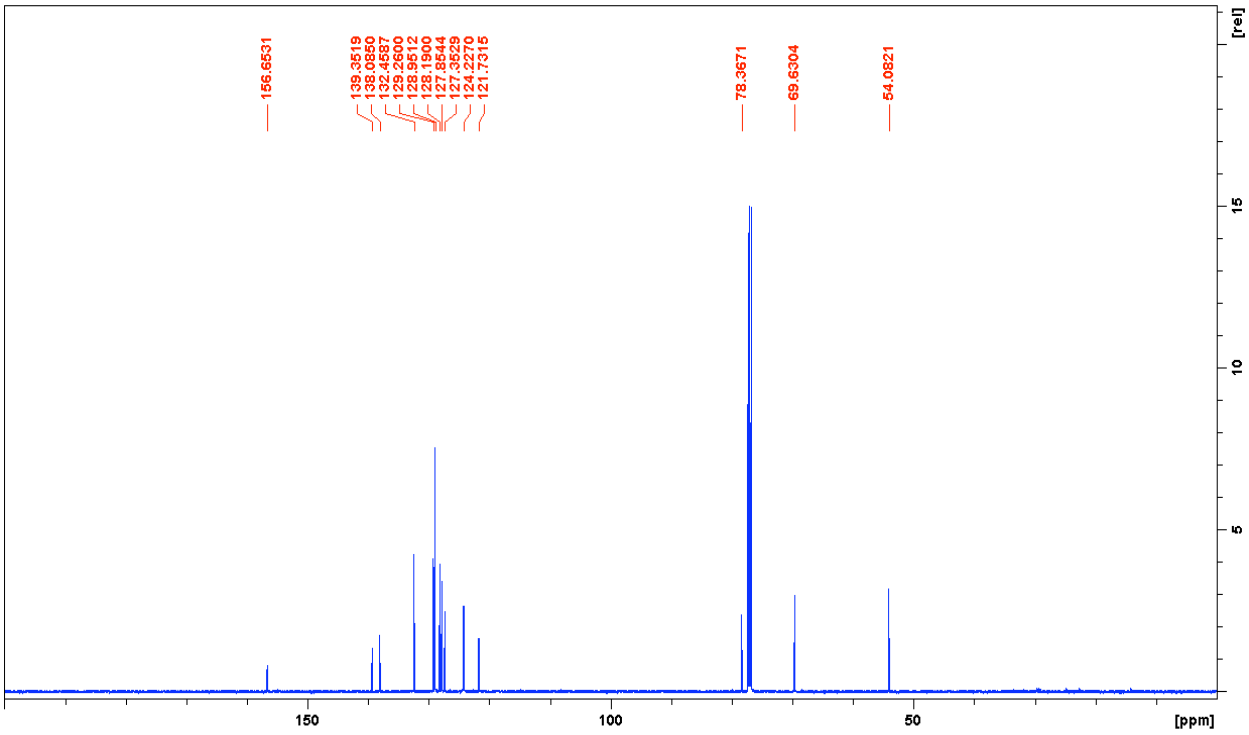

7.441
7.428
7.425
7.412
7.407
7.394
7.325
7.322
7.308
7.302
7.299
7.285
6.898
6.894
6.884
6.880
5.015
4.996
4.405
4.018
4.013
3.996
3.990
3.886
3.874
3.859
3.849
3.840
3.837
3.817
3.804
OH
O
N
CO2Me
Ph
MeO
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.05
3.14
1.96
1.00
0.89
1.03
2.89
1.08
2.97

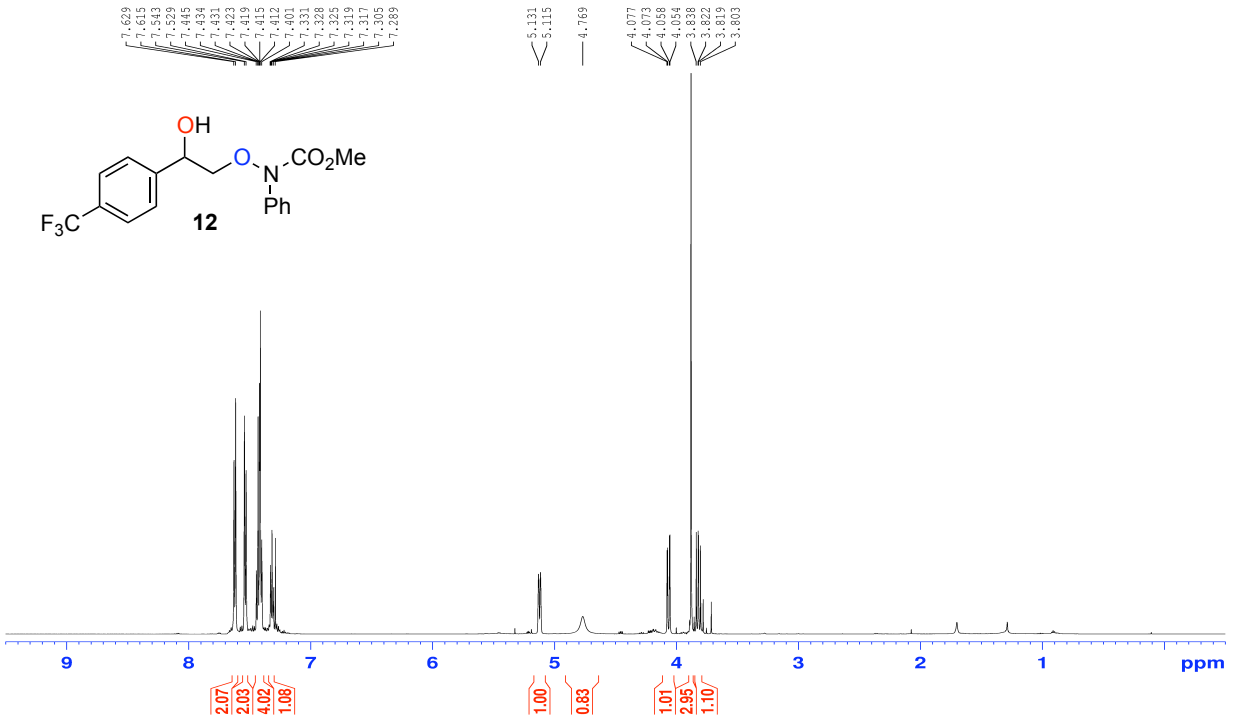

159.3182
156.3074
139.4945
131.0493
128.9485
127.4968
126.9992
123.4928
113.8637
80.5086
70.2471
55.2818
53.9827
[rel]
20
15
10
5
200
150
100
50
0
[ppm]

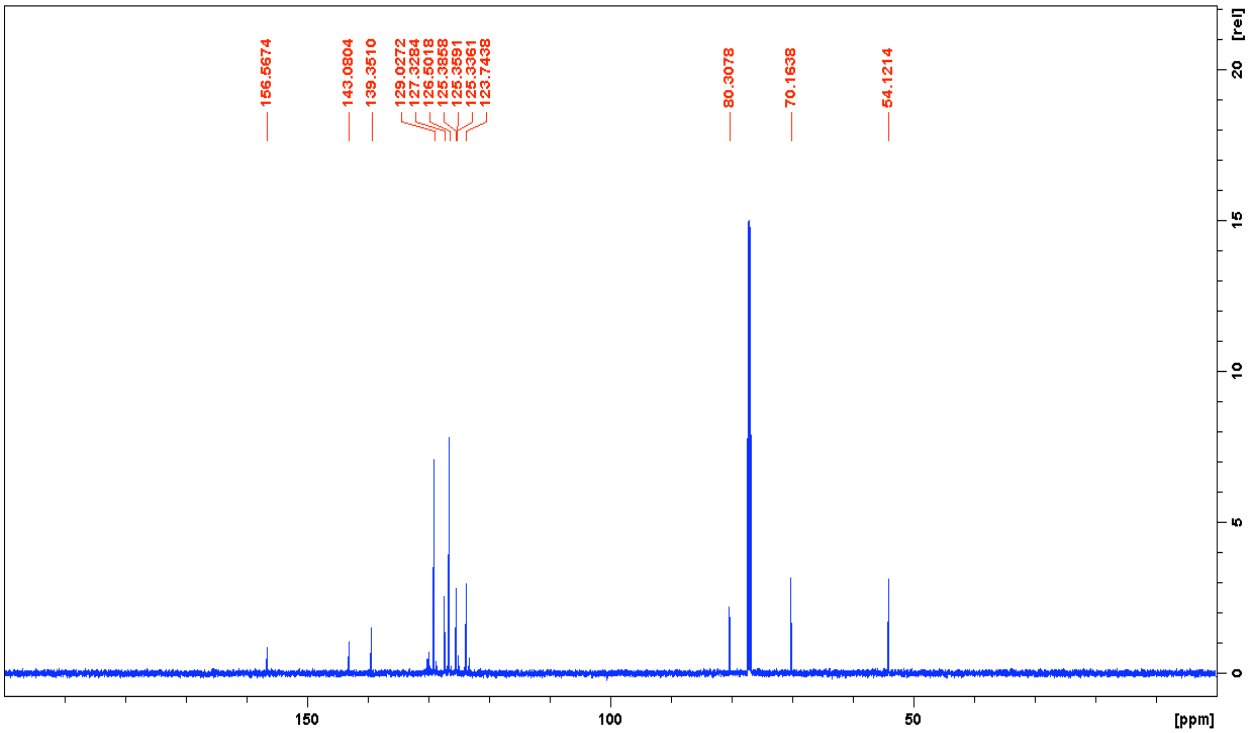

7.456
7.452
7.438
7.435
7.421
7.417
7.408
7.404
7.312
7.309
7.303
7.295
7.286
7.278
7.183
7.167
5.049
5.045
5.029
5.026
4.430
4.045
4.039
4.022
4.017
3.883
3.872
3.853
3.849
3.830
2.358
OH
O
N
CO2Me
Ph
Me
10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.97
3.13
2.07
1.00
0.92
0.99
2.87
0.93
3.11

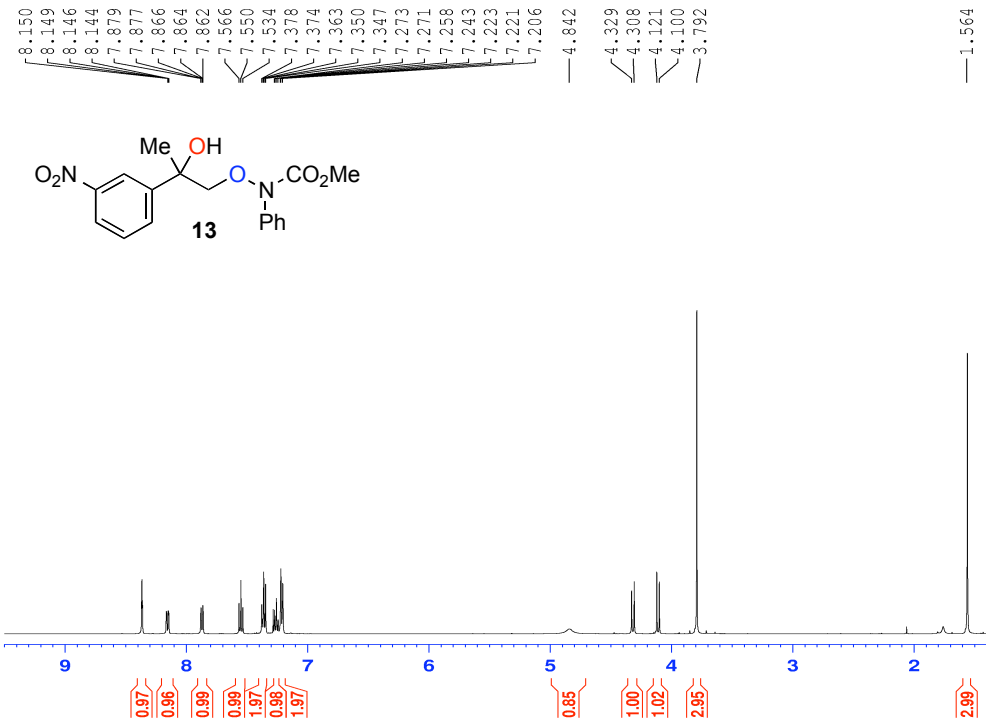

156.3148
139.5152
137.5876
135.9694
129.1375
128.9520
127.0074
126.1661
123.5213
80.5683
77.3627
76.8545
70.5191
53.9757
21.1564
[rel]
20
15
10
5
150
100
50
[ppm]

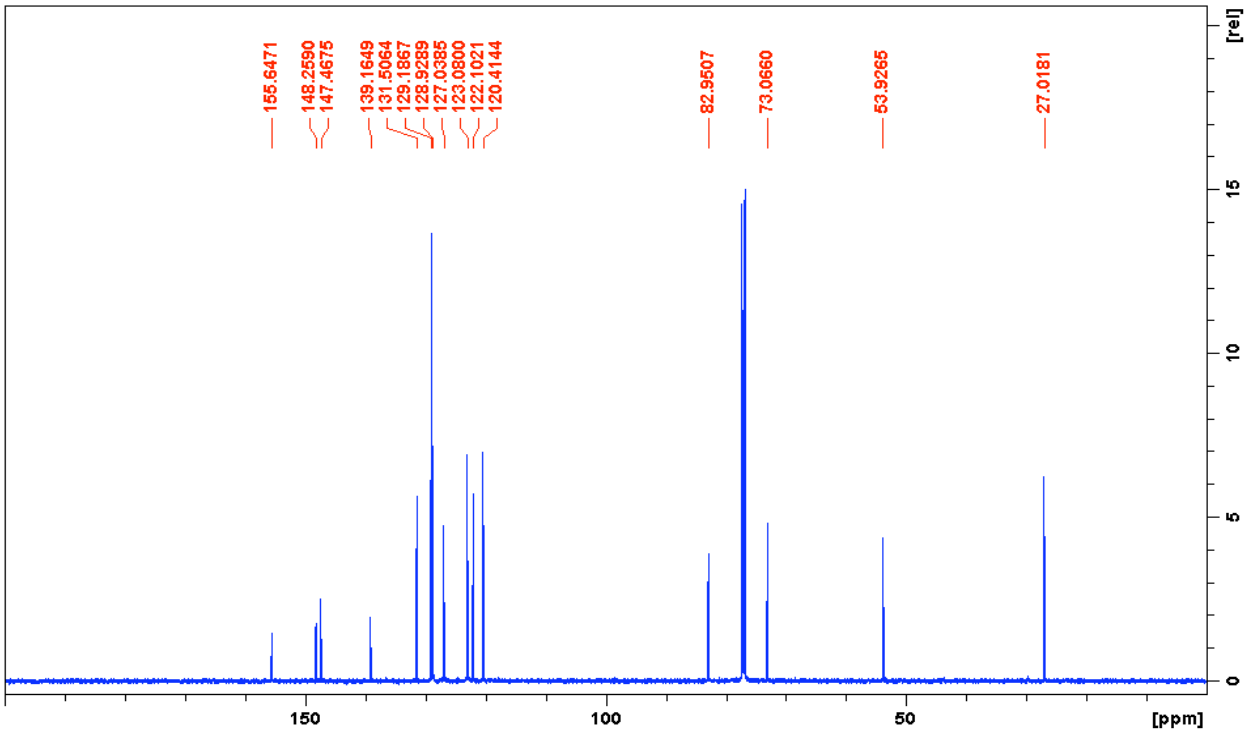

7.457
7.447
7.444
7.437
7.432
7.422
7.419
7.409
7.406
7.388
7.386
7.373
7.372
7.358
7.356
7.328
7.325
7.321
7.311
7.299
7.297
7.285
7.175
7.172
7.160
7.157
7.145
7.141
5.442
5.438
5.423
5.419
4.772
4.194
4.190
4.171
4.167
3.882
3.640
3.621
3.617
3.598
Br
OH
O
N
CO2Me
Ph
11
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.99
1.02
4.00
1.05
1.15
0.99
1.00
0.97
1.02
2.98
1.03

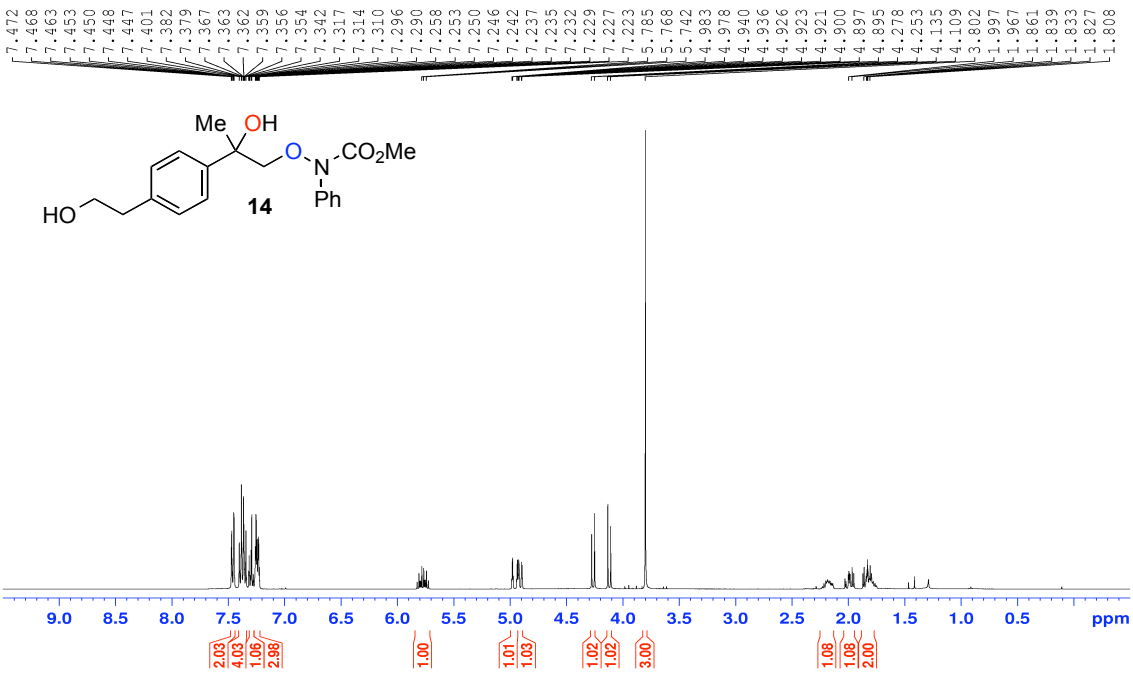

156.6531
139.3519
138.0850
132.4587
129.2600
128.9512
128.1900
127.8544
127.3529
124.2270
121.7315
78.3671
69.6304
54.0821
[rel]
15
10
5
150
100
50
[ppm]

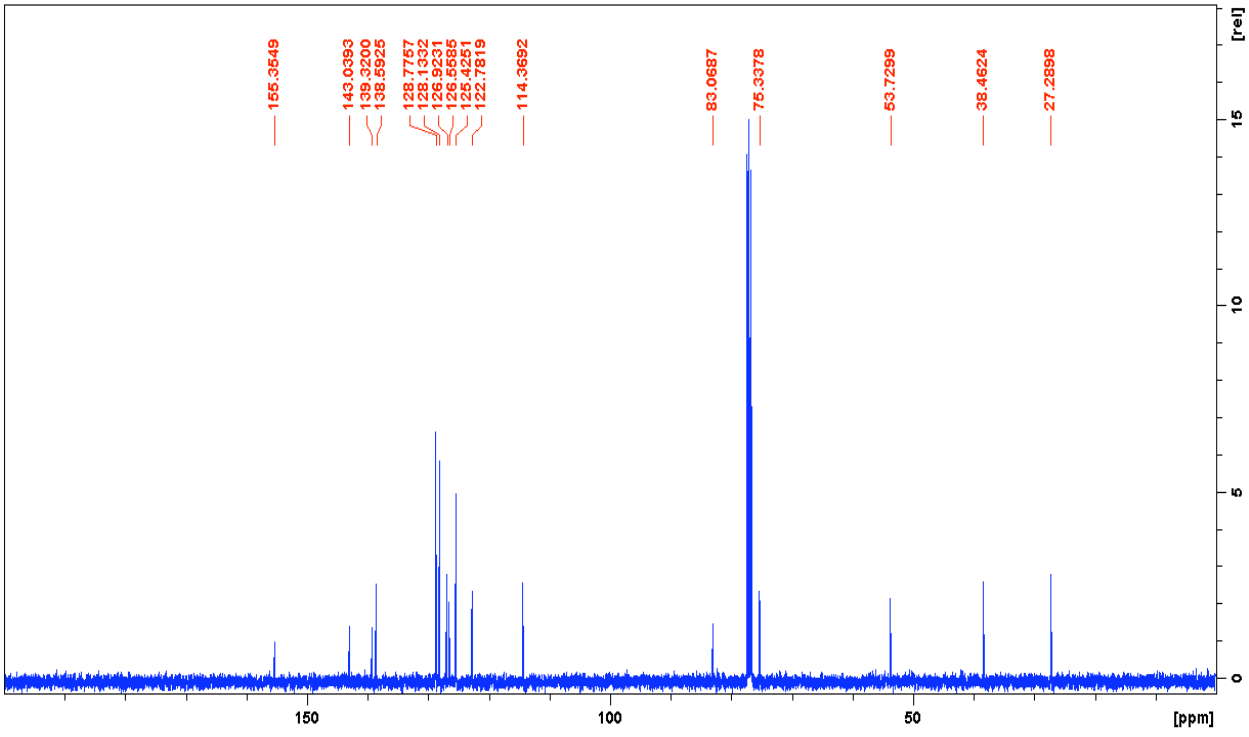

7.629
7.615
7.543
7.529
7.445
7.434
7.431
7.423
7.419
7.415
7.412
7.401
7.331
7.328
7.325
7.319
7.317
7.305
7.289
5.131
5.115
4.769
4.077
4.073
4.058
4.054
3.838
3.822
3.819
3.803
OH
O
N
CO2Me
Ph
F3C
12
9
8
7
6
5
4
3
2
1
ppm
2.07
2.03
4.02
1.08
1.00
0.83
1.01
2.95
1.10

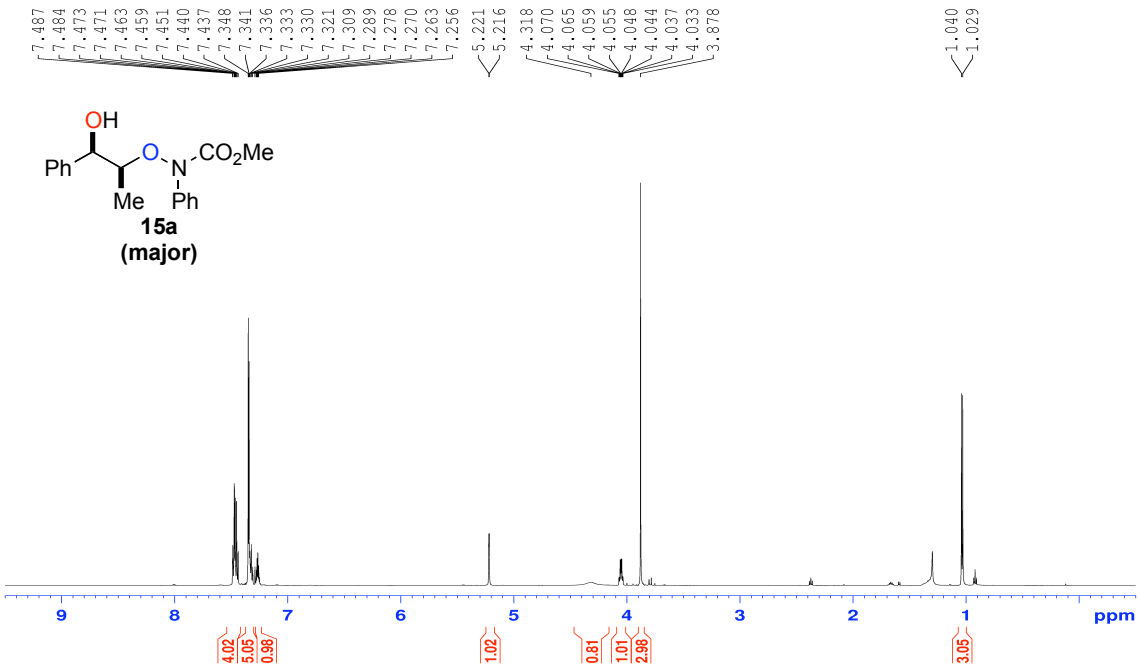

156.5674
143.0804
139.3510
129.0272
127.3284
126.5018
125.3858
125.3591
125.3361
123.7438
80.3078
70.1638
54.1214
[rel]
20
15
10
5
0
150
100
50
[ppm]

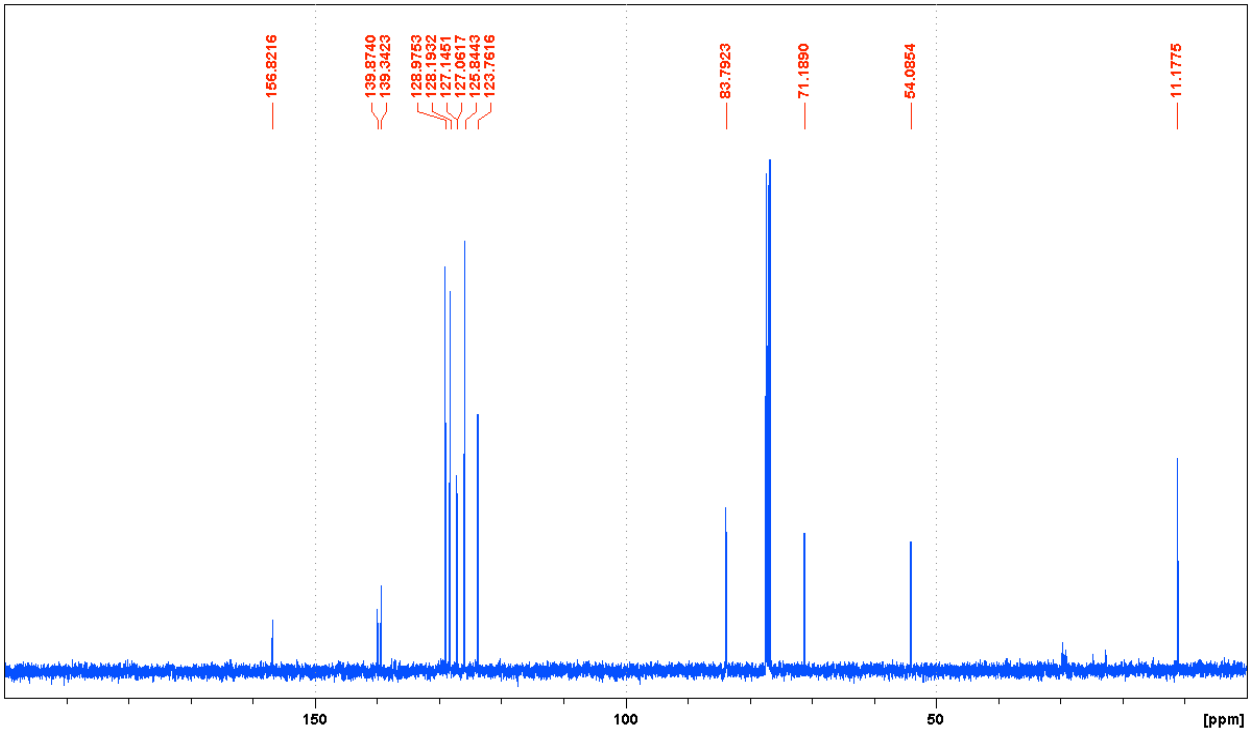

8.150
8.149
8.146
8.144
7.879
7.877
7.866
7.864
7.862
7.566
7.550
7.534
7.378
7.374
7.363
7.350
7.347
7.273
7.271
7.258
7.243
7.223
7.221
7.206
4.842
4.329
4.308
4.121
4.100
3.792
1.564
Me
OH
O2N
O
N
CO2Me
Ph
13
9
8
7
6
5
4
3
2
1
ppm
0.97
0.96
0.99
0.99
1.97
0.98
1.97
0.85
1.00
1.02
2.95
2.99

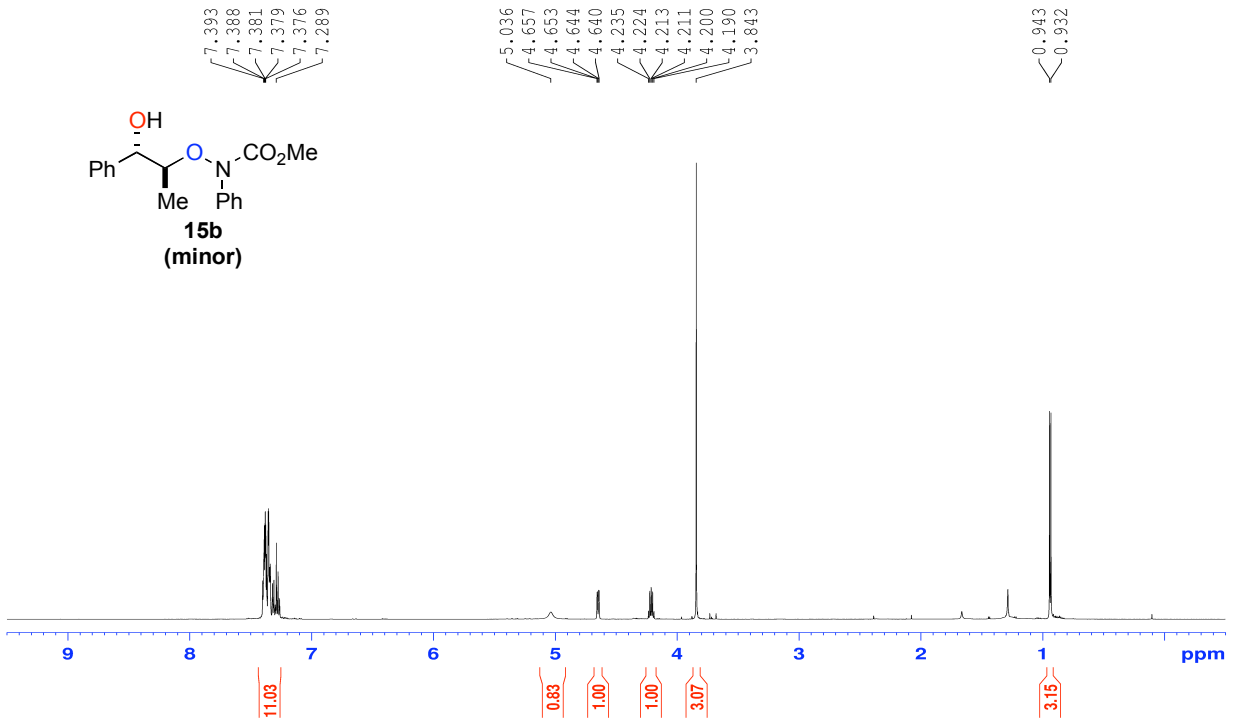

155.6471
148.2590
147.4675
139.1649
131.5064
129.1867
128.9289
127.0385
123.0800
122.1021
120.4144
82.9507
73.0660
53.9265
27.0181
[rel]
0
5
10
15
150
100
50
[ppm]

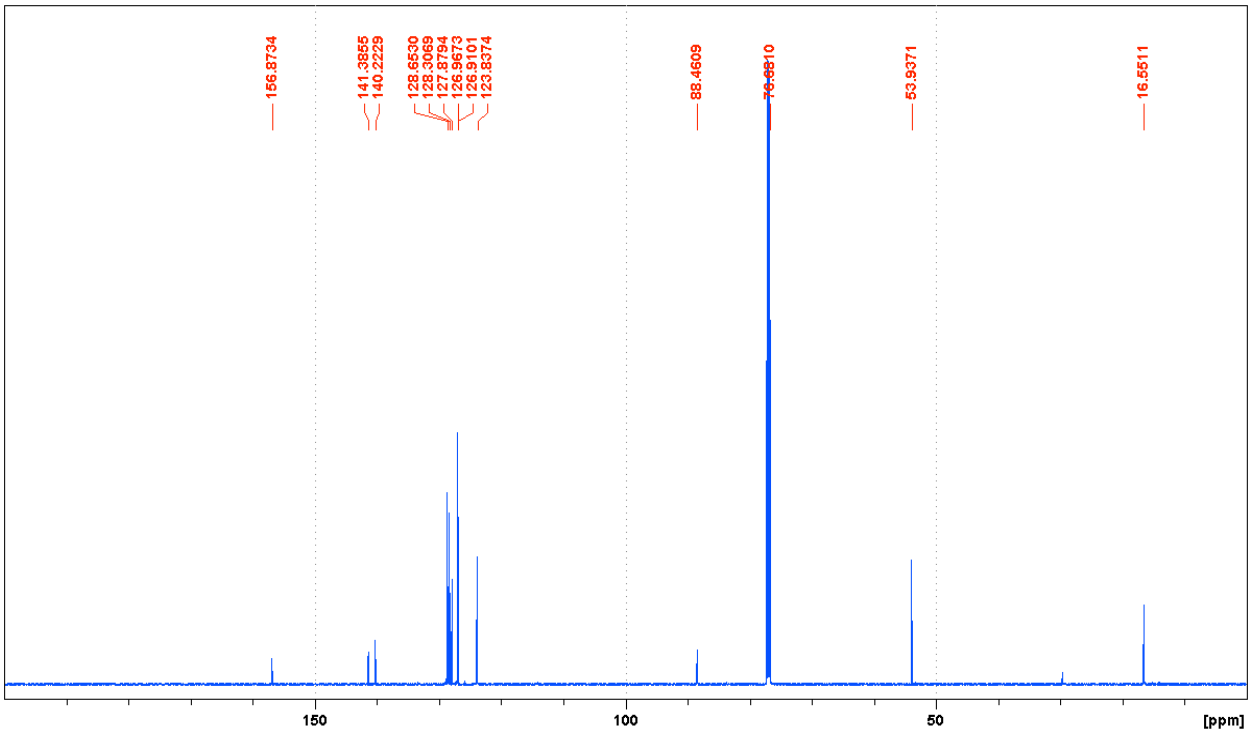

7.472
7.468
7.463
7.453
7.450
7.448
7.447
7.401
7.382
7.379
7.367
7.363
7.362
7.359
7.356
7.354
7.342
7.317
7.314
7.310
7.296
7.290
7.258
7.253
7.250
7.246
7.242
7.237
7.235
7.232
7.229
7.227
7.223
5.785
5.768
5.742
4.983
4.978
4.940
4.936
4.926
4.923
4.921
4.900
4.897
4.895
4.278
4.253
4.135
4.109
3.802
1.997
1.967
1.861
1.839
1.833
1.827
1.808
Me
OH
O
N
CO2Me
Ph
HO
14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
4.03
1.06
2.98
1.00
1.01
1.03
1.02
1.02
3.00
1.08
1.06
2.00

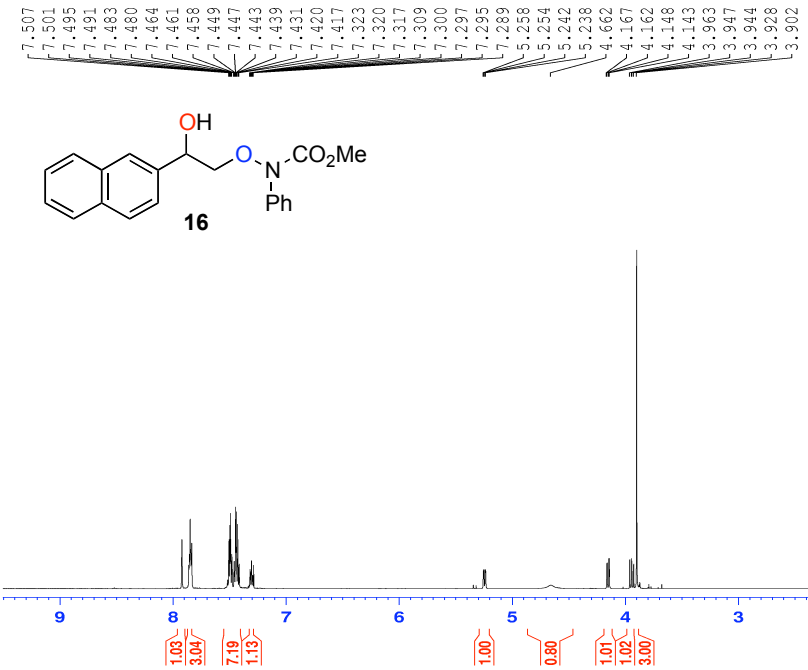

155.3549
143.0393
139.3200
138.5925
128.7757
128.1332
126.9231
126.5585
125.4251
122.7819
114.3692
83.0687
75.3378
53.7299
38.4624
27.2898
[rel]
15
10
5
0
150
100
50
[ppm]

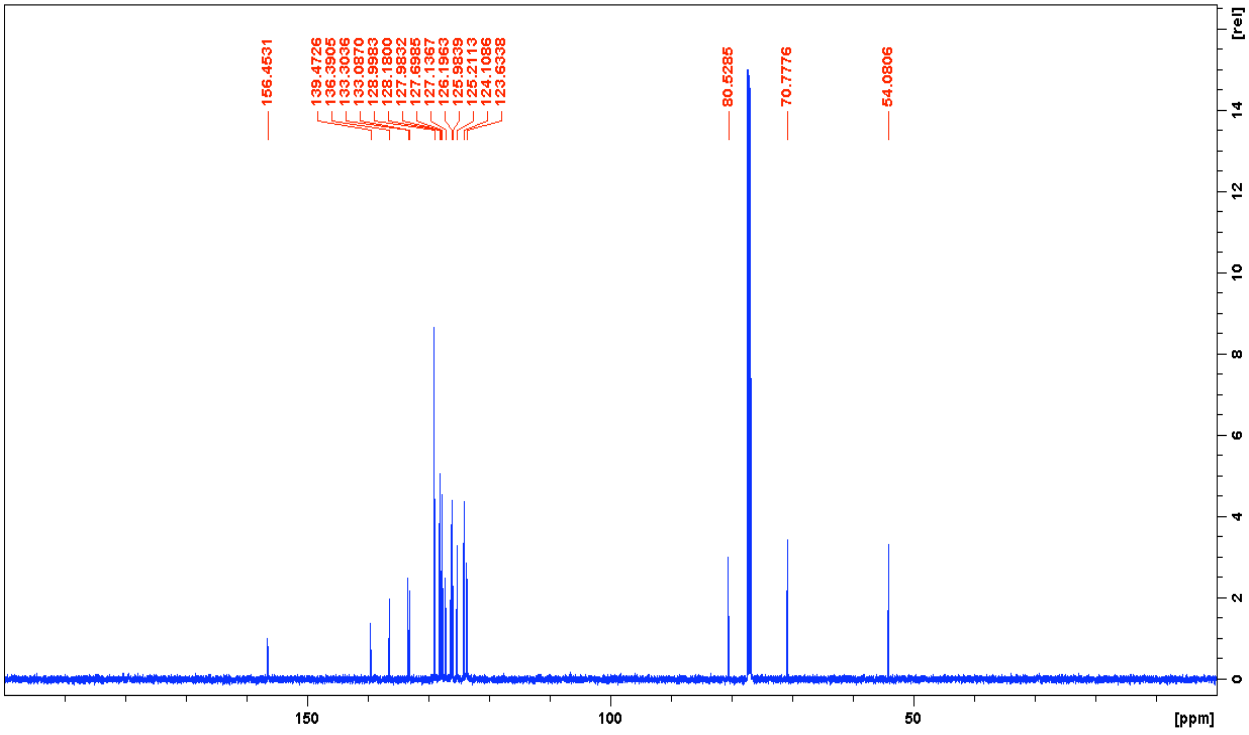

7.487
7.484
7.473
7.471
7.463
7.459
7.451
7.440
7.437
7.348
7.341
7.336
7.333
7.330
7.321
7.309
7.289
7.278
7.270
7.263
7.256
5.221
5.216
4.318
4.070
4.065
4.059
4.055
4.048
4.044
4.037
4.033
3.878
1.040
1.029
OH
Ph
O
N
CO2Me
Me
Ph
15a
(major)
9
8
7
6
5
4
3
2
1
ppm
4.02
5.05
0.98
1.02
0.81
1.01
2.98
3.05

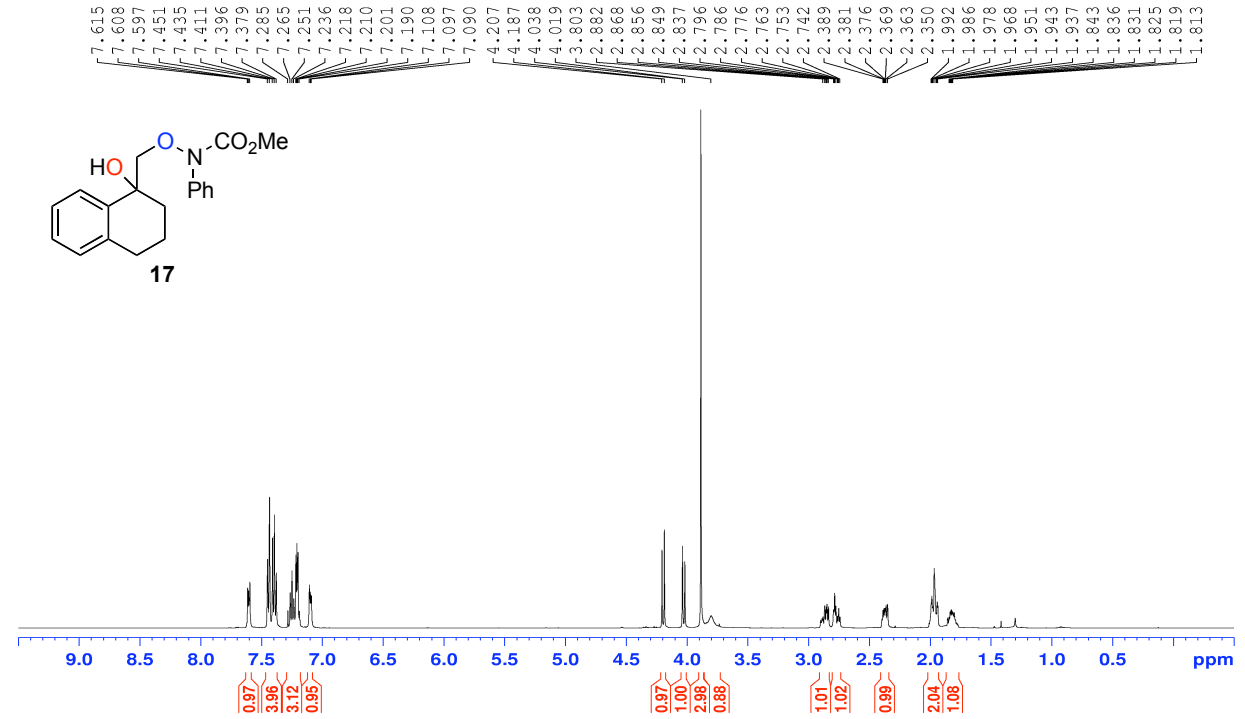

156.8216
139.8740
139.3423
128.9753
128.1932
127.1451
127.0617
125.8443
123.7616
83.7923
71.1890
54.0854
11.1775
150
100
50
[ppm]

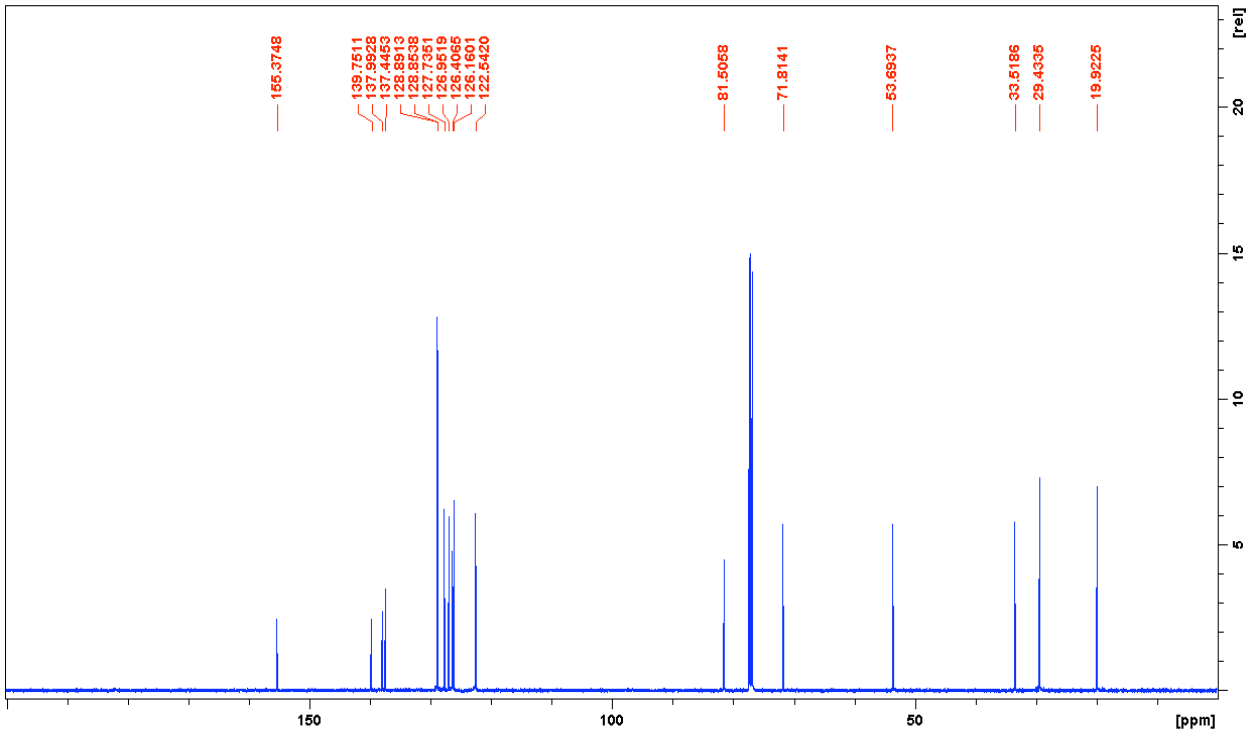

7.393
7.388
7.381
7.379
7.376
7.289
5.036
4.657
4.653
4.644
4.640
4.235
4.224
4.213
4.211
4.200
4.190
3.843
0.943
0.932
OH
Ph
O
N
CO2Me
Me
Ph
15b
(minor)
9
8
7
6
5
4
3
2
1
ppm
11.03
0.83
1.00
1.00
3.07
3.15

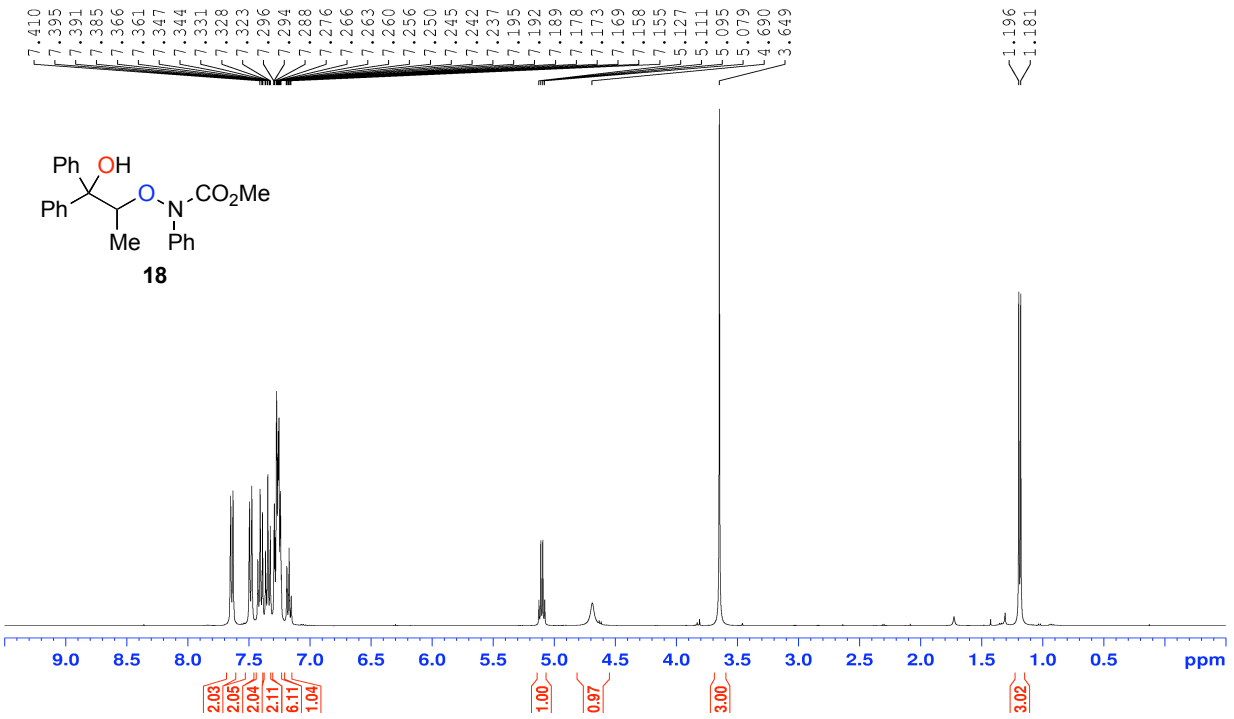

156.8734
141.3855
140.2229
128.6530
128.3069
127.8794
126.9673
126.9101
123.8374
88.4609
70.3810
53.9371
16.5511
150
100
50
[ppm]

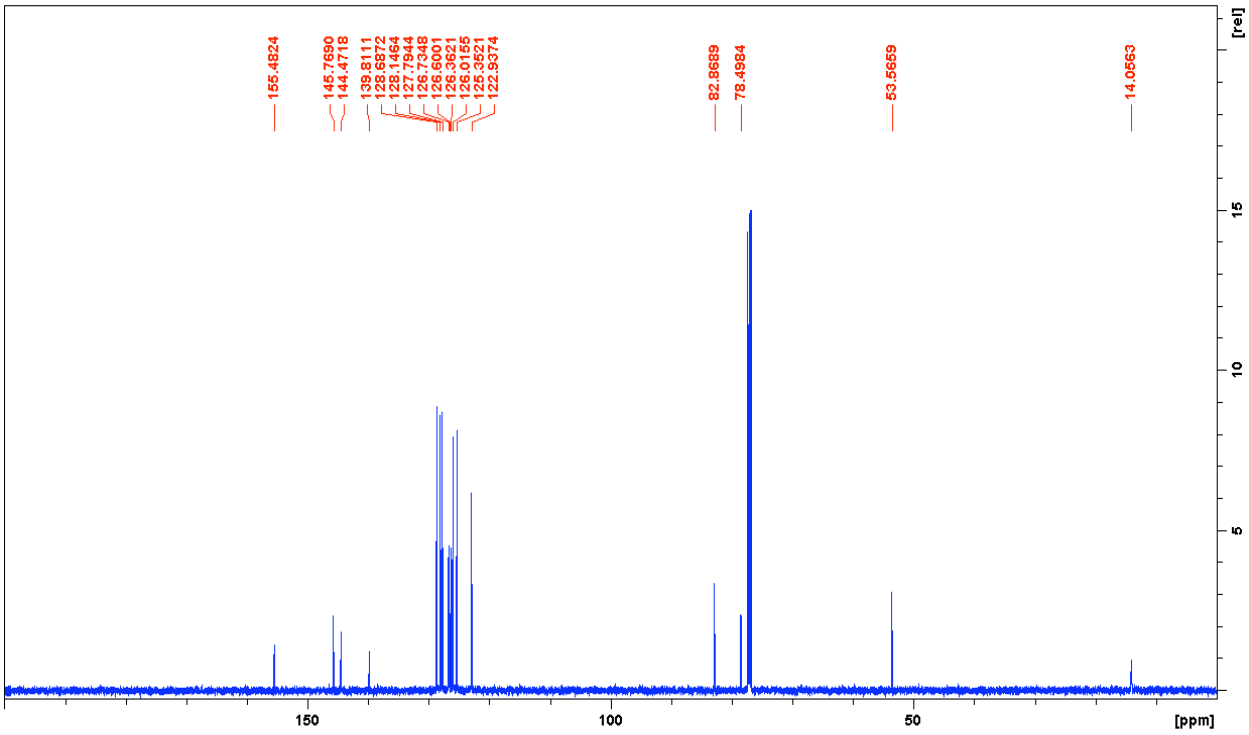

7.507
7.501
7.495
7.491
7.483
7.480
7.464
7.461
7.458
7.449
7.447
7.443
7.439
7.431
7.420
7.417
7.323
7.320
7.317
7.309
7.300
7.297
7.295
7.289
5.258
5.254
5.242
5.238
4.662
4.167
4.162
4.148
4.143
3.963
3.947
3.944
3.928
3.902
OH
O
N
CO2Me
Ph
16
9
8
7
6
5
4
3
2
1
ppm
1.03
3.04
7.19
1.13
1.00
0.80
1.01
1.02
3.00

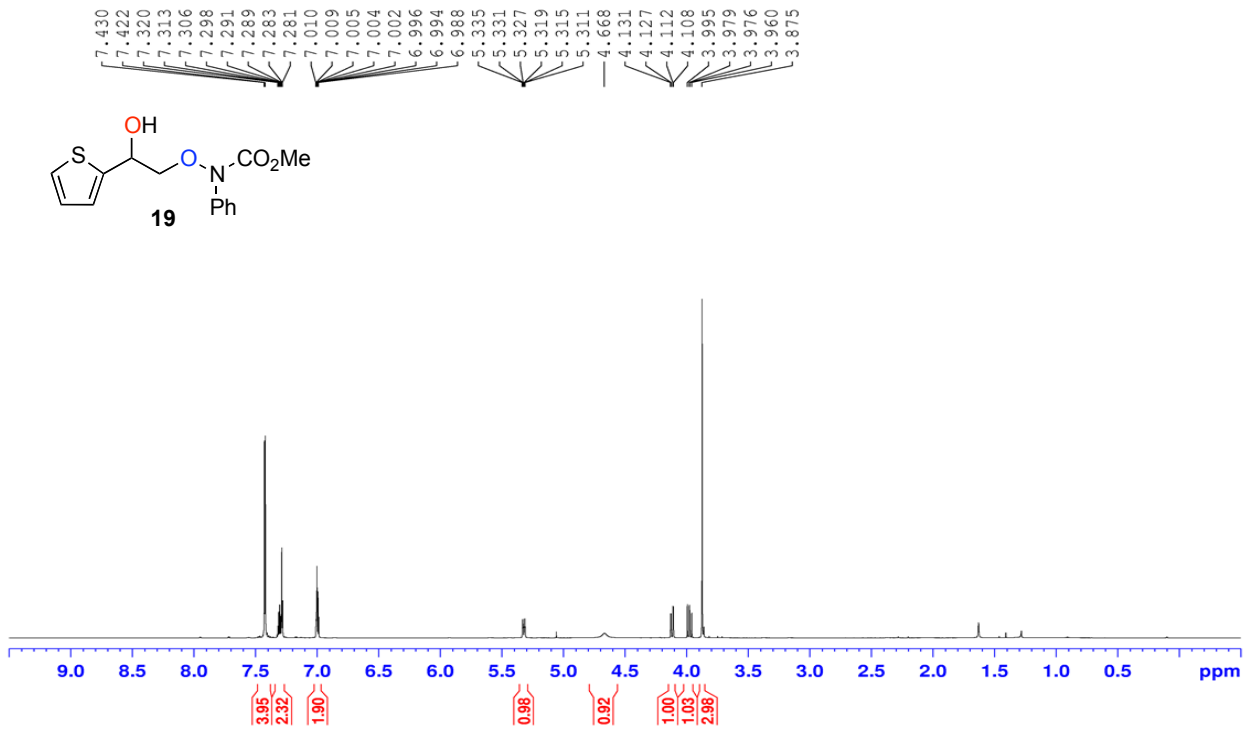

156.4531
139.4726
136.3905
133.3036
133.0870
128.9983
128.1800
127.9832
127.6985
127.1367
126.1963
125.9839
125.2113
124.1086
123.6338
80.5285
70.7776
54.0806
[rel]
14
12
10
8
6
4
2
0
150
100
50
[ppm]

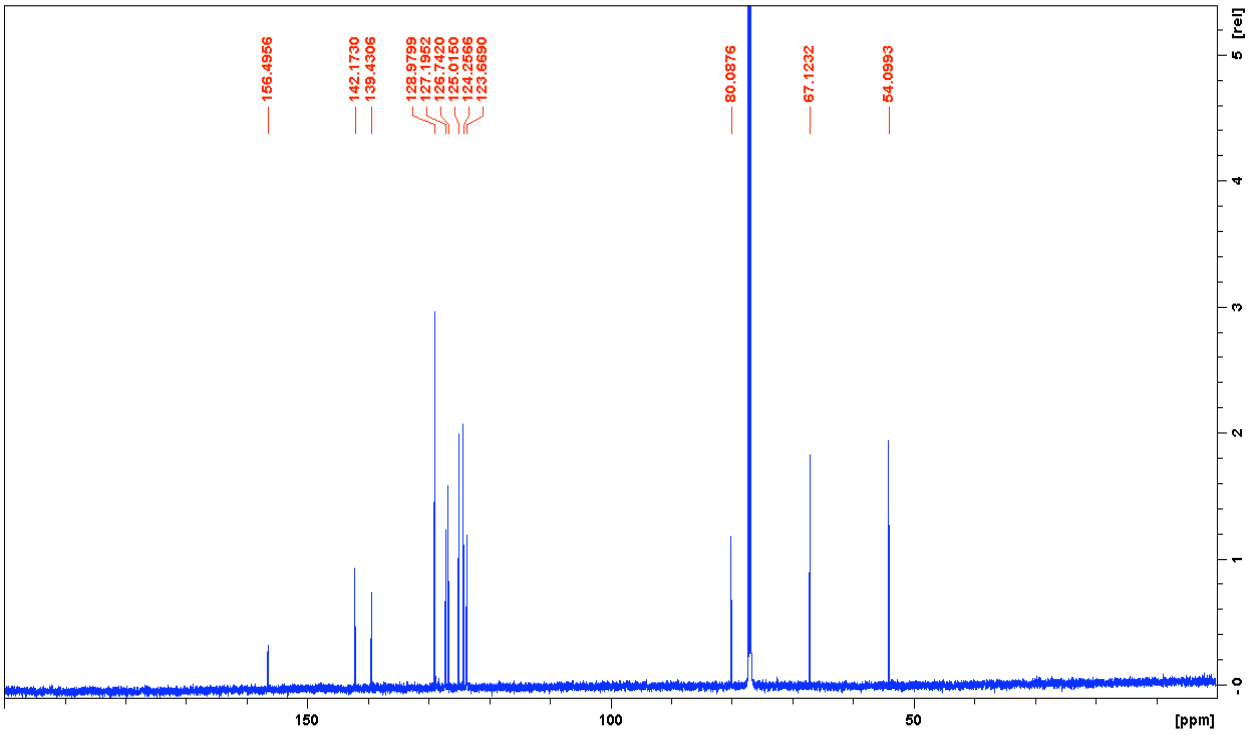

7.615
7.608
7.597
7.451
7.435
7.411
7.396
7.379
7.285
7.265
7.251
7.236
7.218
7.210
7.201
7.190
7.108
7.097
7.090
4.207
4.187
4.038
4.019
3.803
2.882
2.868
2.856
2.849
2.837
2.796
2.786
2.776
2.763
2.753
2.742
2.389
2.381
2.376
2.369
2.363
2.350
1.992
1.986
1.978
1.968
1.951
1.943
1.937
1.843
1.836
1.831
1.825
1.819
1.813
HO
O
N
CO2Me
Ph
17
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.97
3.96
3.12
0.95
0.97
1.00
2.98
0.88
1.01
1.02
0.99
2.04
1.08

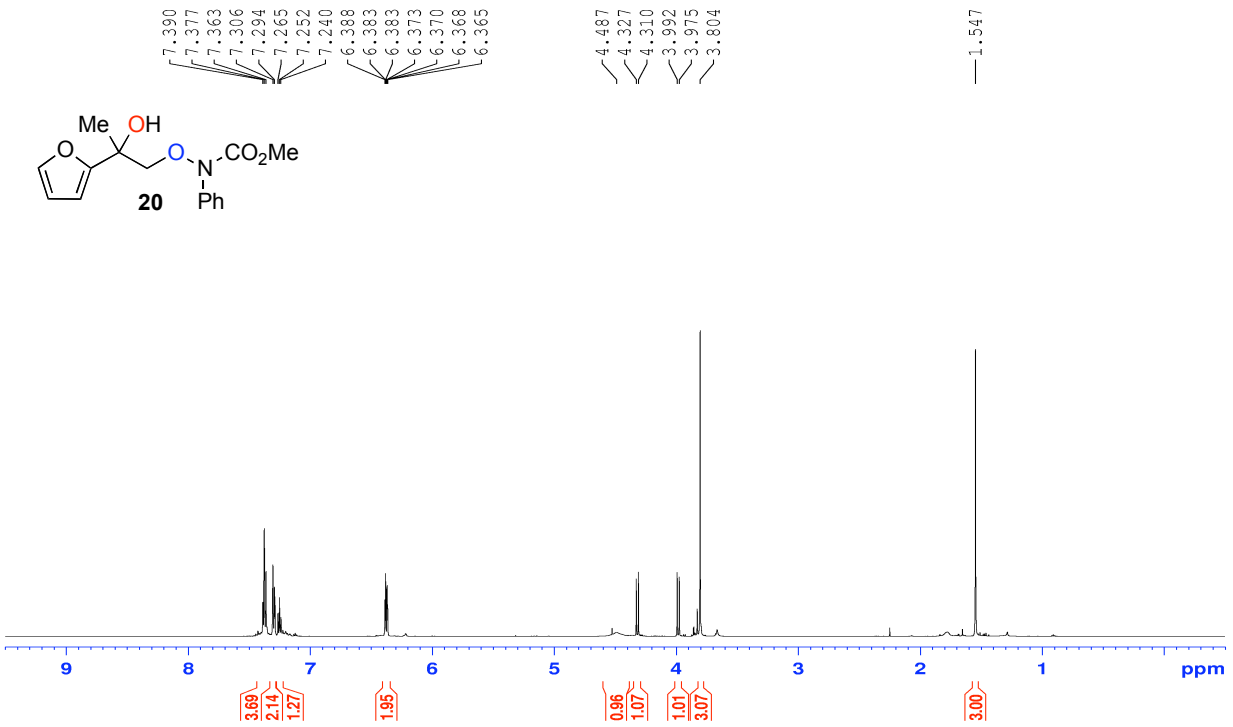

155.3748
139.7511
137.9928
137.4453
128.8913
128.8538
127.7351
126.9519
126.4065
126.1601
122.5420
81.5058
71.8141
53.6937
33.5186
29.4335
19.9225
[rel]
20
15
10
5
150
100
50
[ppm]

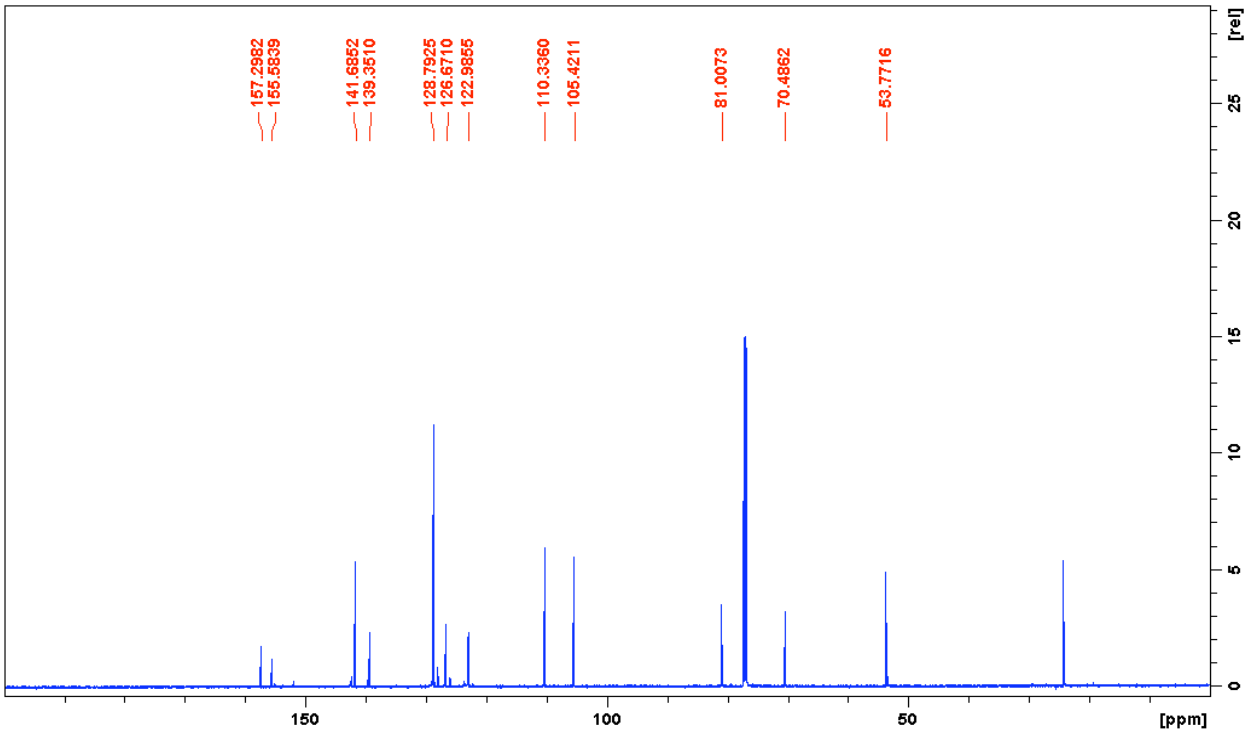

7.410
7.395
7.391
7.385
7.366
7.361
7.347
7.344
7.331
7.328
7.323
7.296
7.294
7.288
7.276
7.266
7.263
7.260
7.256
7.250
7.245
7.242
7.237
7.195
7.192
7.189
7.178
7.173
7.169
7.158
7.155
5.127
5.111
5.095
5.079
4.690
3.649
1.196
1.181
Ph
OH
Ph
O
N
CO2Me
Me
Ph
18
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
2.05
2.04
2.11
6.11
1.04
1.00
0.97
3.00
3.02

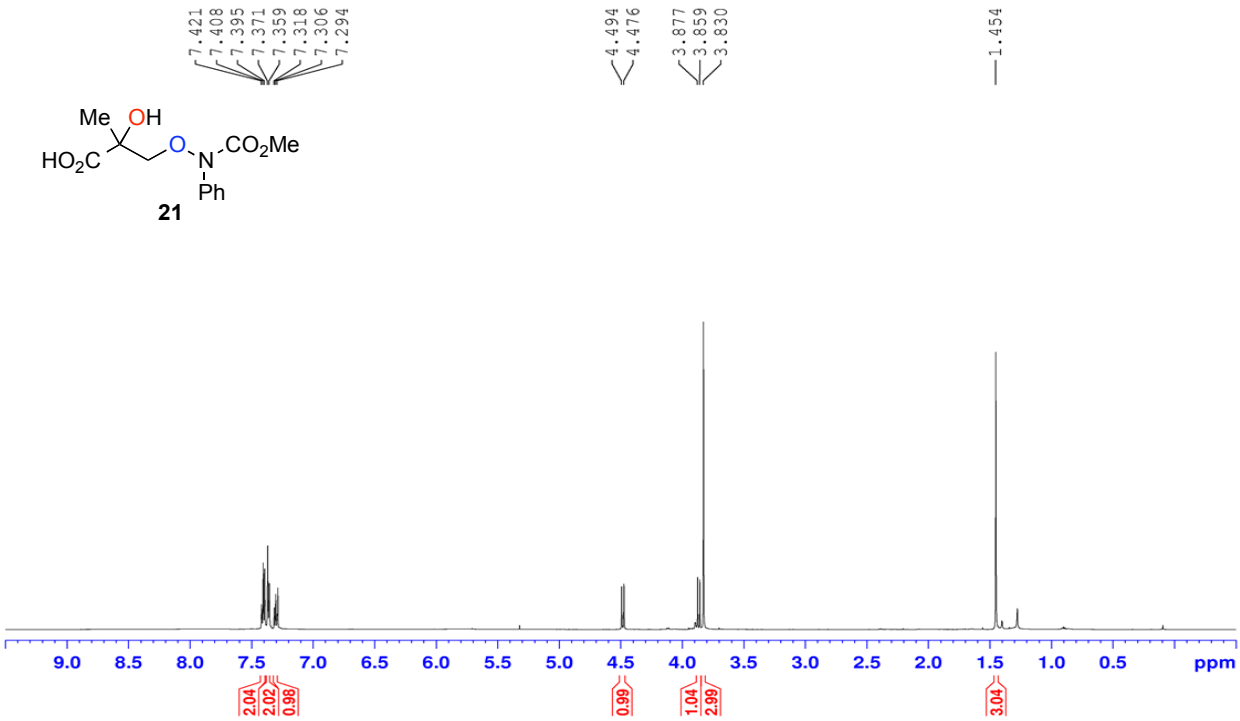

155.4824
145.7690
144.4718
139.8111
128.6872
128.1464
127.7944
126.7348
126.6001
126.3621
126.0155
125.3521
122.9374
82.8689
78.4984
53.5659
14.0563
[rel]
15
10
5
150
100
50
[ppm]

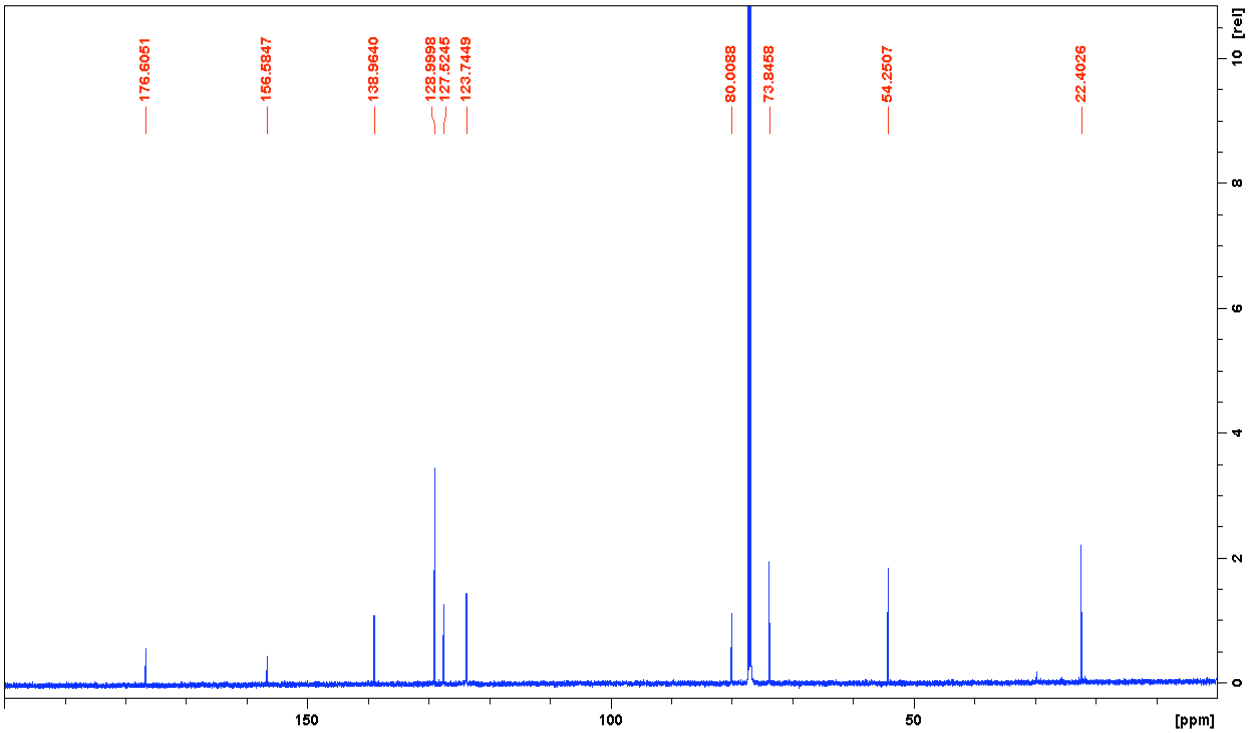

7.430
7.422
7.320
7.313
7.306
7.298
7.291
7.289
7.283
7.281
7.010
7.009
7.005
7.004
7.002
6.996
6.994
6.988
5.335
5.331
5.327
5.319
5.315
5.311
4.668
4.131
4.127
4.112
4.108
3.995
3.979
3.976
3.960
3.875
OH
S
O
N
CO2Me
Ph
19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.95
2.32
1.90
0.98
0.92
1.00
1.03
2.98

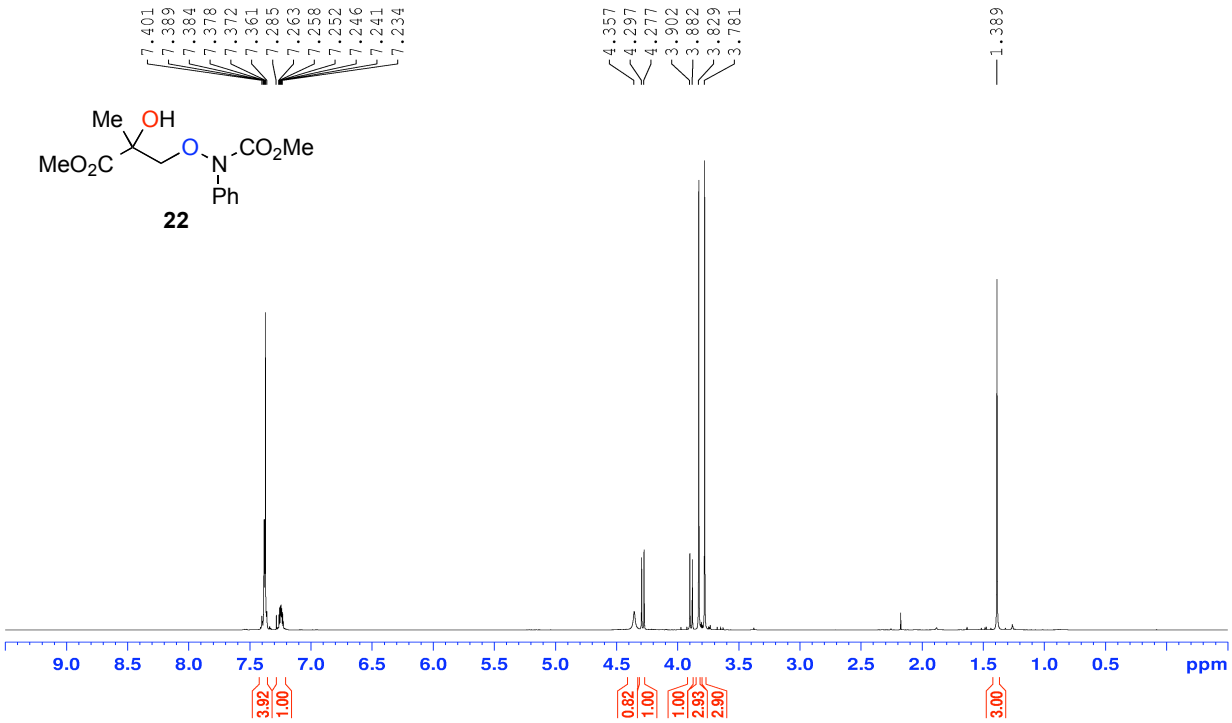

156.4956
142.1730
139.4306
128.9799
127.1952
126.7420
125.0150
124.2566
123.6690
80.0876
67.1232
54.0993
150
100
50
[ppm]
5 [rel]
4
3
2
1
0

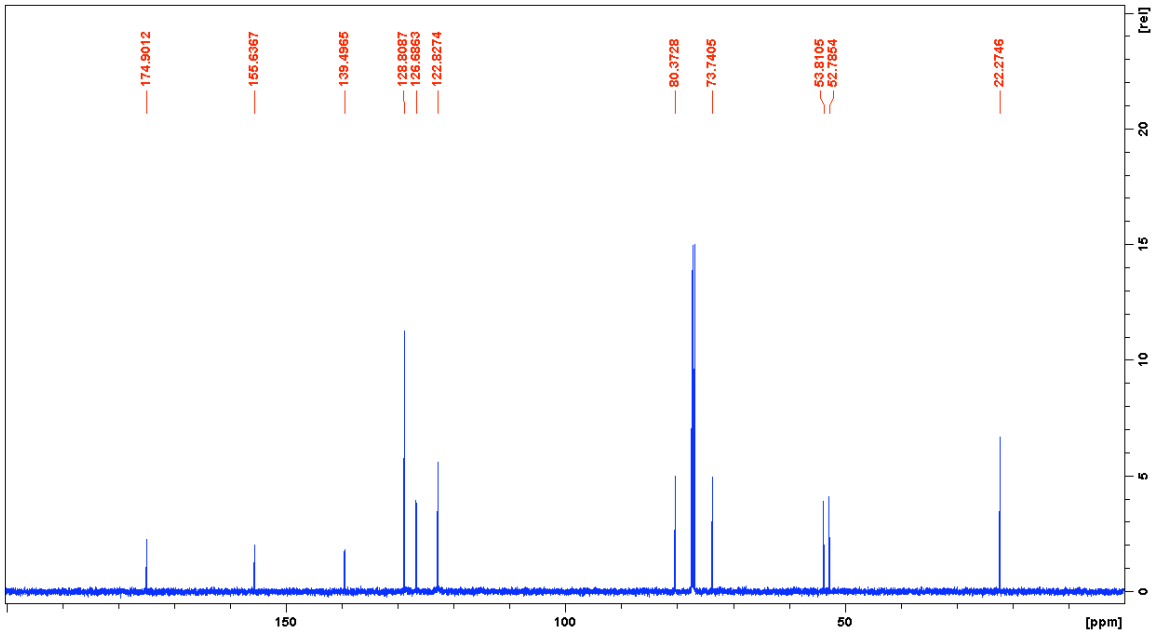

7.390
7.377
7.363
7.306
7.294
7.265
7.252
7.240
6.388
6.383
6.383
6.373
6.370
6.368
6.365
4.487
4.327
4.310
3.992
3.975
3.804
1.547
Me
OH
O
O
N
CO2Me
Ph
20
9
8
7
6
5
4
3
2
1
ppm
3.69
2.14
1.27
1.95
0.96
1.07
1.01
3.07
3.00

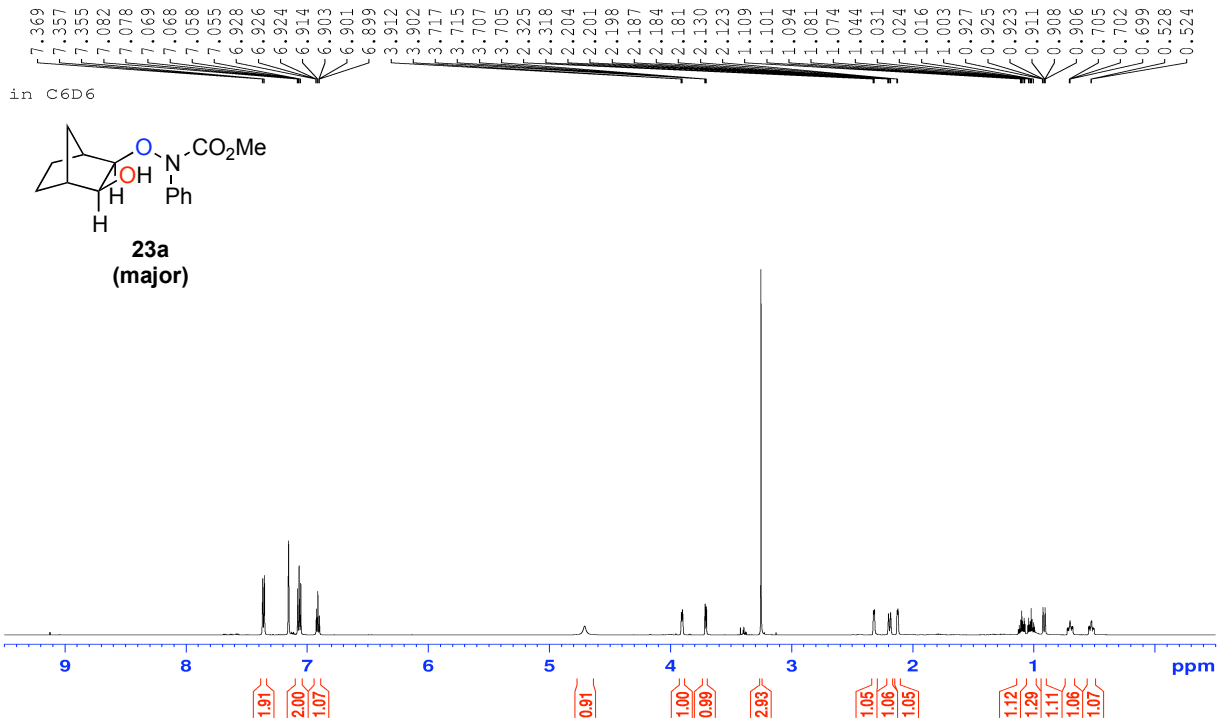

157.2982
155.5839
141.6852
139.3510
128.7925
126.6710
122.9855
110.3360
105.4211
81.0073
70.4862
53.7716
[rel]
25
20
15
10
5
0
150
100
50
[ppm]


7.421
7.408
7.395
7.371
7.359
7.318
7.306
7.294
4.494
4.476
3.877
3.859
3.830
1.454
Me
OH
HO2C
O
N
CO2Me
Ph
21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.04
2.02
0.98
0.99
1.04
2.99
3.04

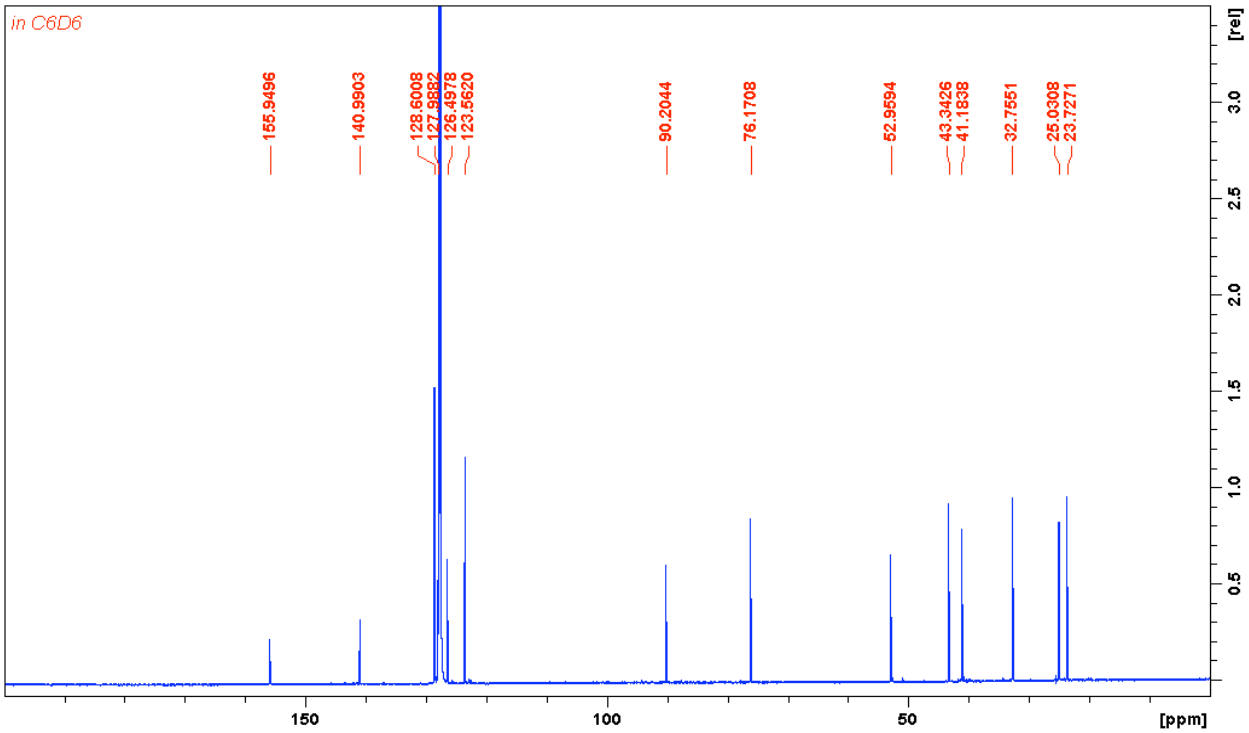

176.6051
156.5847
138.9640
128.9998
127.5245
123.7449
80.0088
73.8458
54.2507
22.4026
10 [rel]
8
6
4
2
0
150
100
50
[ppm]

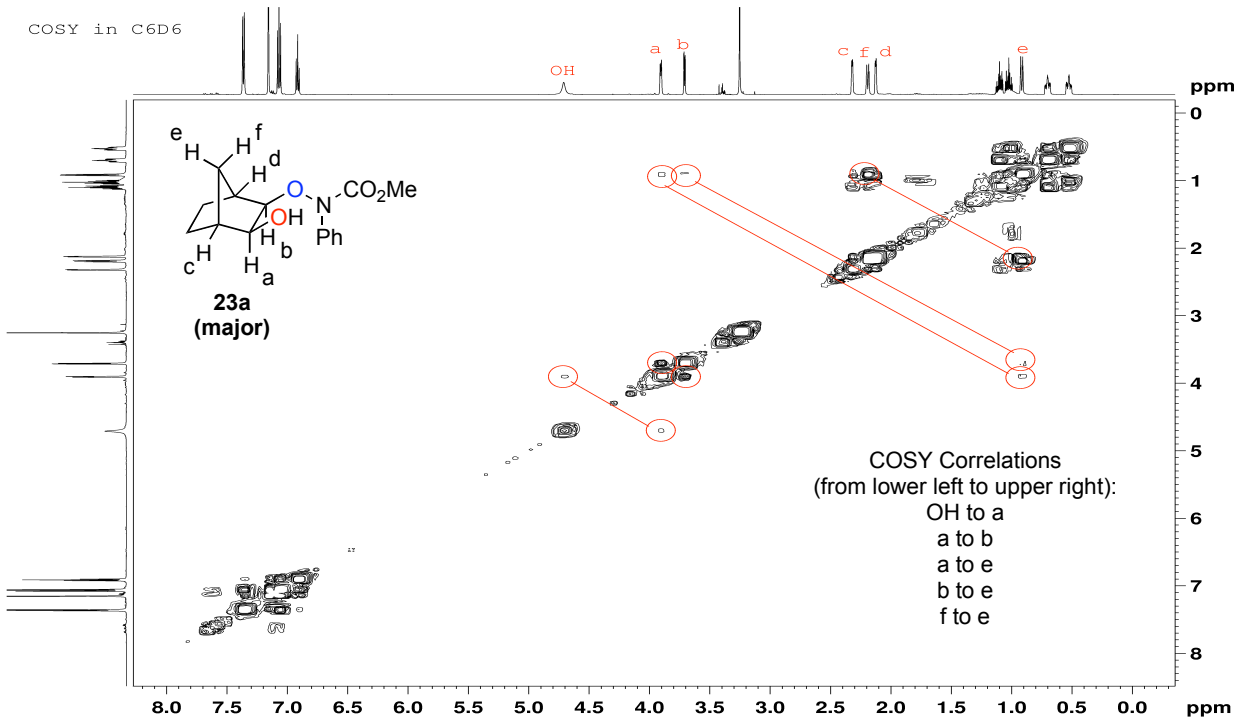

7.401
7.389
7.384
7.378
7.372
7.361
7.285
7.263
7.258
7.252
7.246
7.241
7.234
4.357
4.297
4.277
3.902
3.882
3.829
3.781
1.389
Me
OH
MeO2C
O
N
CO2Me
Ph
22
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.92
1.00
0.82
1.00
1.00
2.93
2.90
3.00

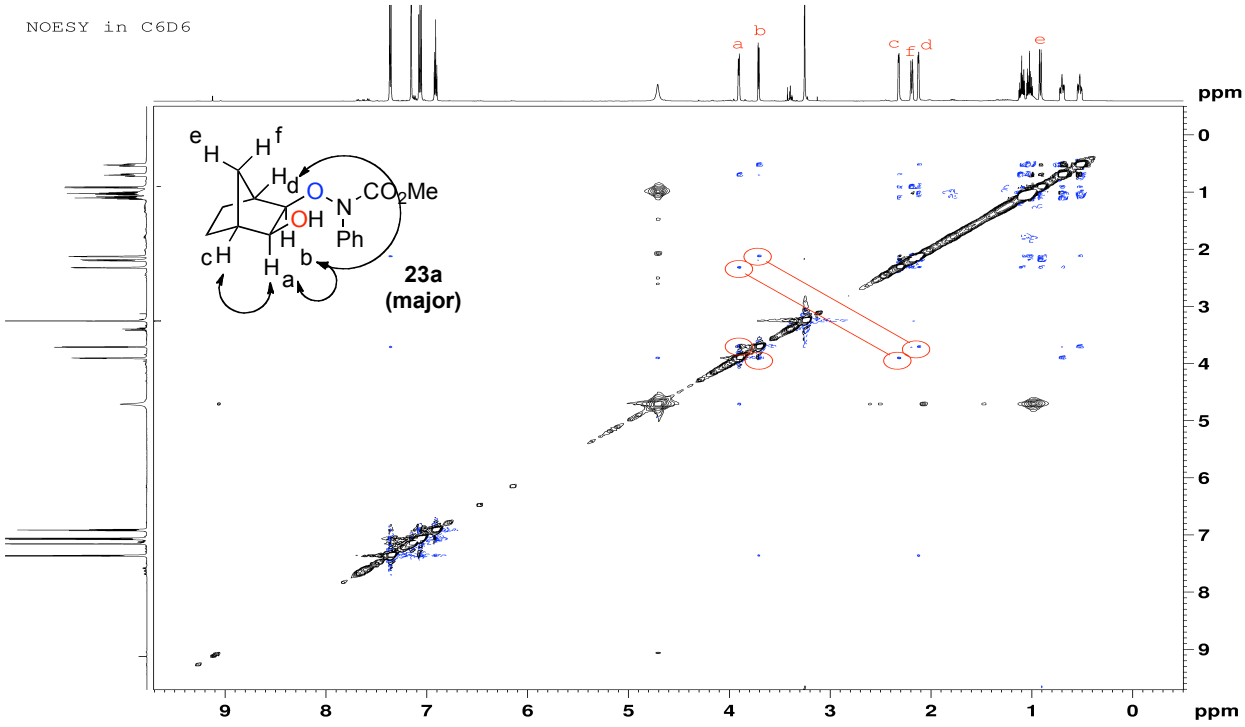

174.9012
155.6367
139.4965
128.8087
126.6853
122.8274
80.3728
73.7405
53.8105
52.7854
22.2746
[rel]
0
5
10
15
20
150
100
50
[ppm]

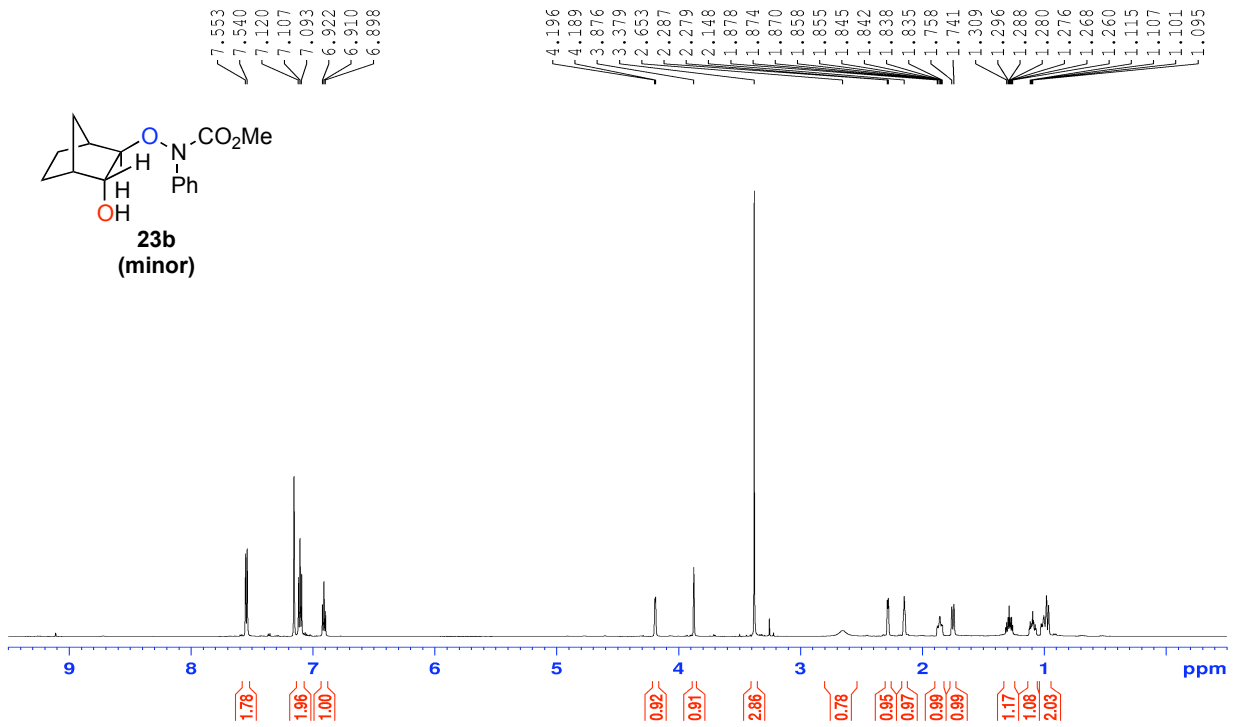

7.369
7.357
7.355
7.082
7.078
7.069
7.068
7.058
7.055
6.928
6.926
6.924
6.914
6.903
6.901
6.899
3.912
3.902
3.717
3.715
3.707
3.705
2.325
2.318
2.204
2.201
2.198
2.187
2.184
2.181
2.130
2.123
1.109
1.101
1.094
1.081
1.074
1.044
1.031
1.024
1.016
1.003
0.927
0.925
0.923
0.911
0.908
0.906
0.705
0.702
0.699
0.528
0.524
in C6D6
O
N
CO2Me
OH
H
Ph
H
9
8
7
6
5
4
3
2
1
ppm
1.91
2.00
1.07
0.91
1.00
0.99
2.93
1.05
1.06
1.05
1.12
1.29
1.11
1.06
1.07

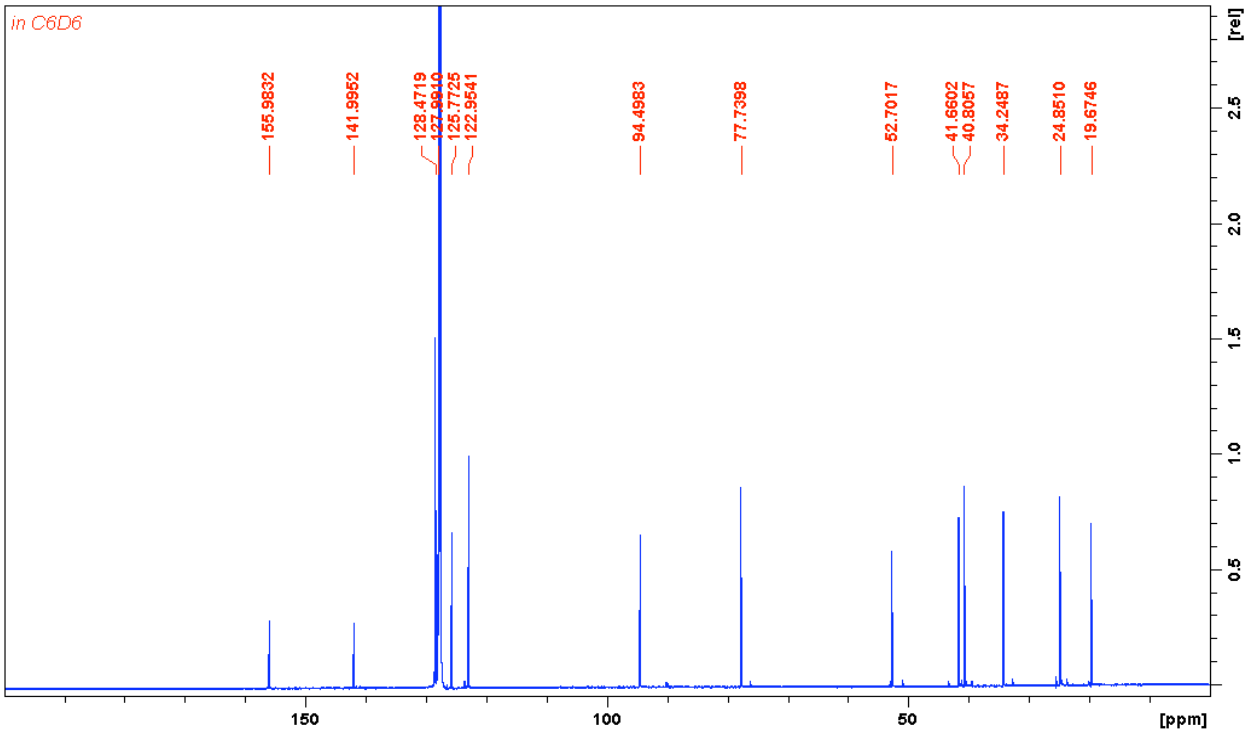
23a
(major)

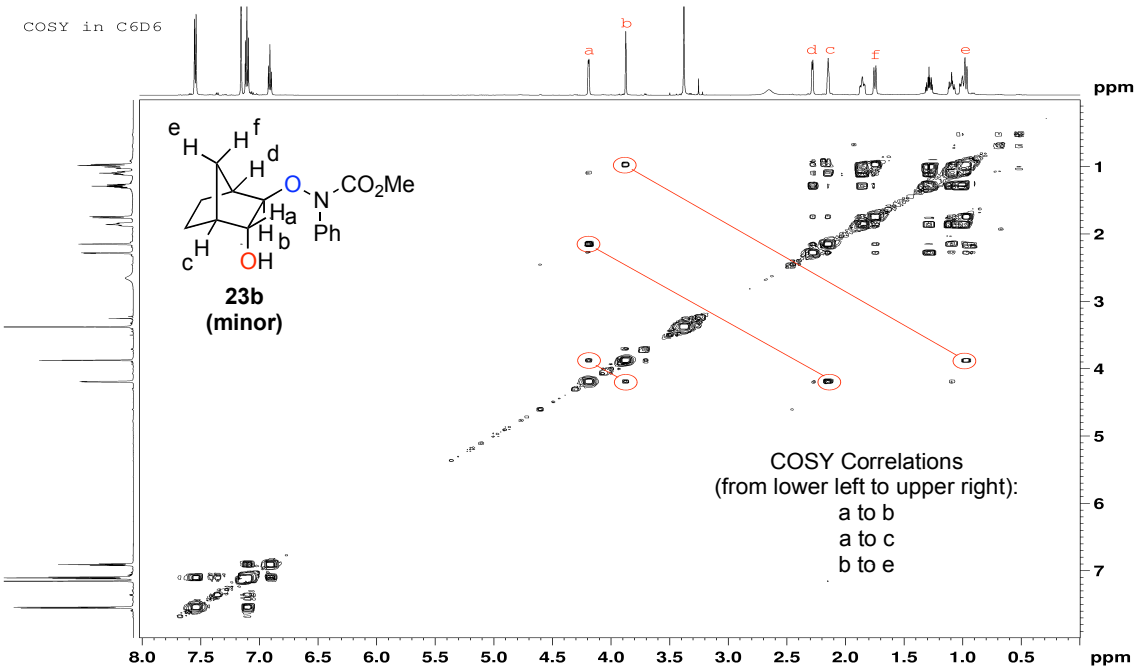

in C6D6
155.9496
140.9903
128.6008
127.9882
126.4978
123.5620
90.2044
76.1708
52.9594
43.3426
41.1838
32.7551
25.0308
23.7271
[rel]
3.0
2.5
2.0
1.5
1.0
0.5
150
100
50
[ppm]

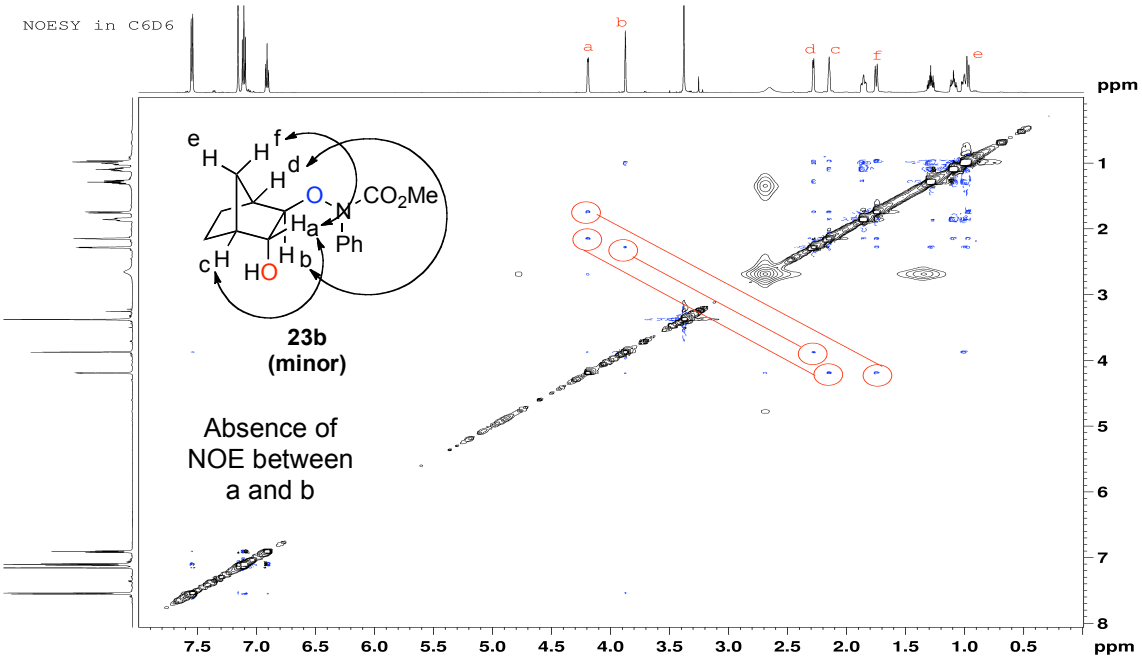

COSY in C6D6
OH
a
b
c
f
d
e
ppm
23a
(major)
COSY Correlations
(from lower left to upper right):
OH to a
a to b
a to e
b to e
f to e
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

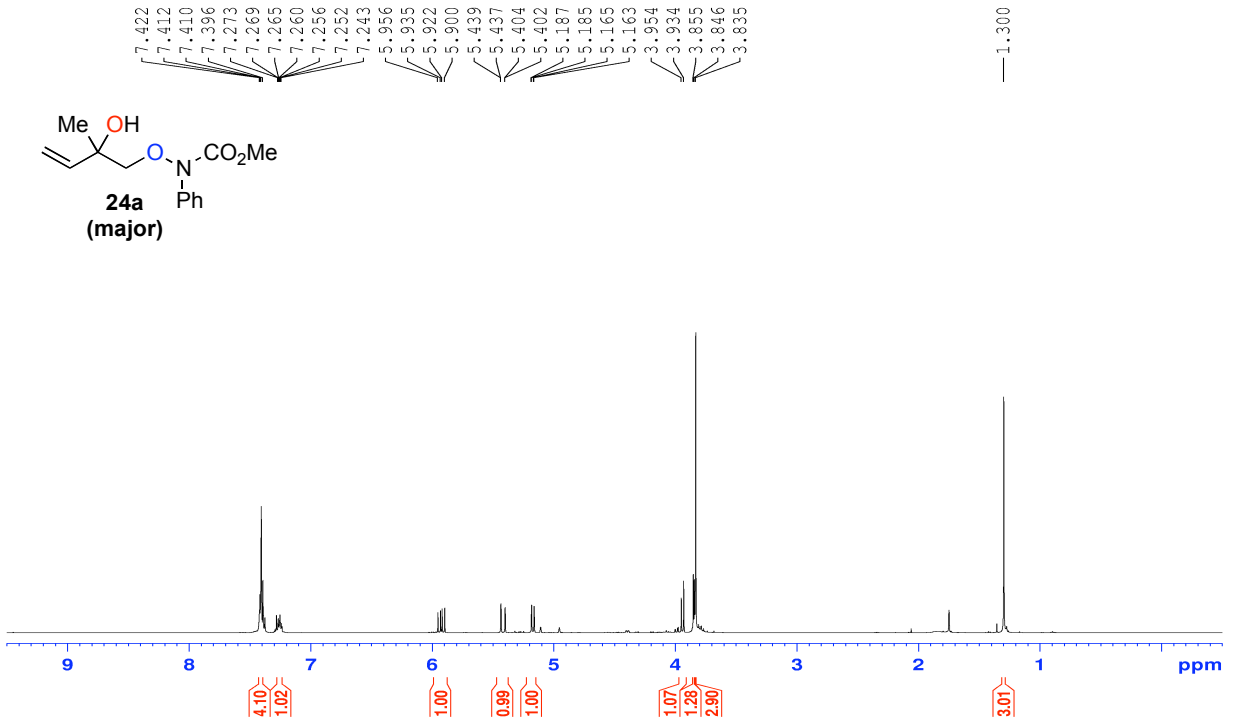

NOESY in C6D6
a
b
c
f
d
e
ppm
23a
(major)
9
8
7
6
5
4
3
2
1
0

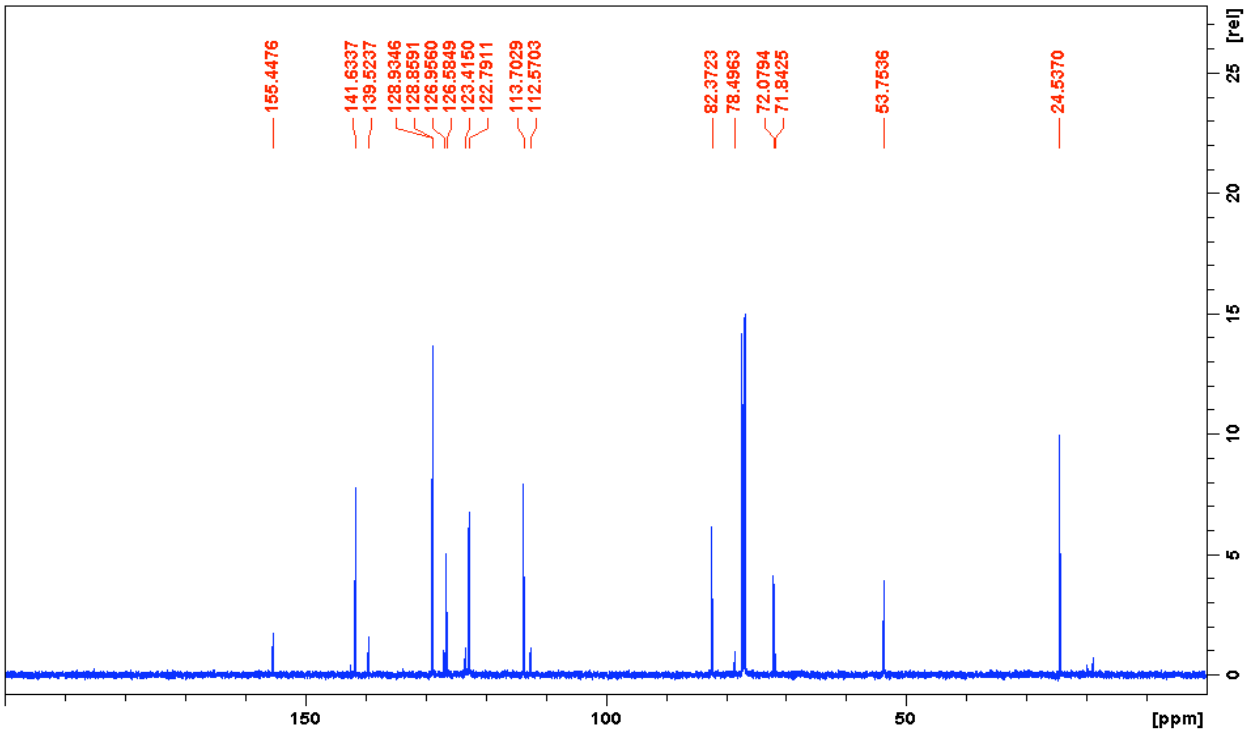

7.553
7.540
7.120
7.107
7.093
6.922
6.910
6.898
4.196
4.189
3.876
3.379
2.653
2.287
2.279
2.148
1.878
1.874
1.870
1.858
1.855
1.845
1.842
1.838
1.835
1.758
1.741
1.309
1.296
1.288
1.280
1.276
1.268
1.260
1.115
1.107
1.101
1.095
O
N
CO2Me
H
Ph
H
OH
23b
(minor)
9
8
7
6
5
4
3
2
1
ppm
1.78
1.96
1.00
0.92
0.91
2.86
0.78
0.95
0.97
0.99
0.99
1.17
1.08
2.03

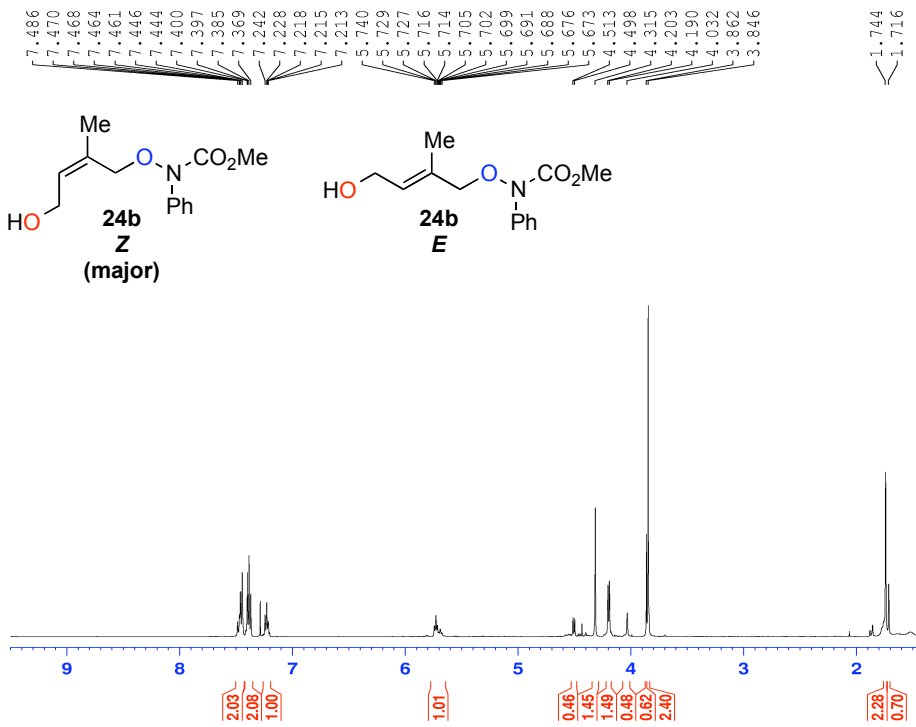

in C6D6
155.9832
141.9952
128.4719
127.9910
125.7725
122.9541
94.4983
77.7398
52.7017
41.6602
40.8057
34.2487
24.8510
19.6746
[rel]
2.5
2.0
1.5
1.0
0.5
150
100
50
[ppm]

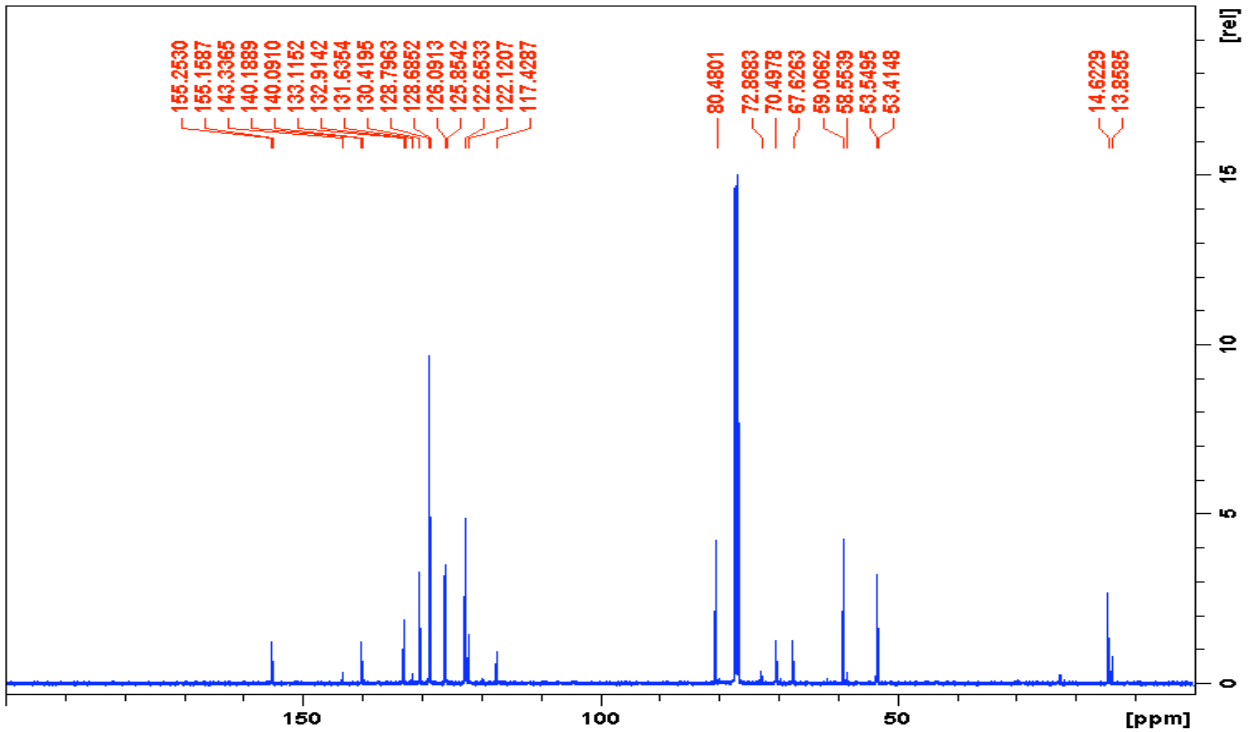

COSY in C6D6
a
b
d c
f
e
ppm
23b
(minor)
COSY Correlations
(from lower left to upper right):
a to b
a to c
b to e
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

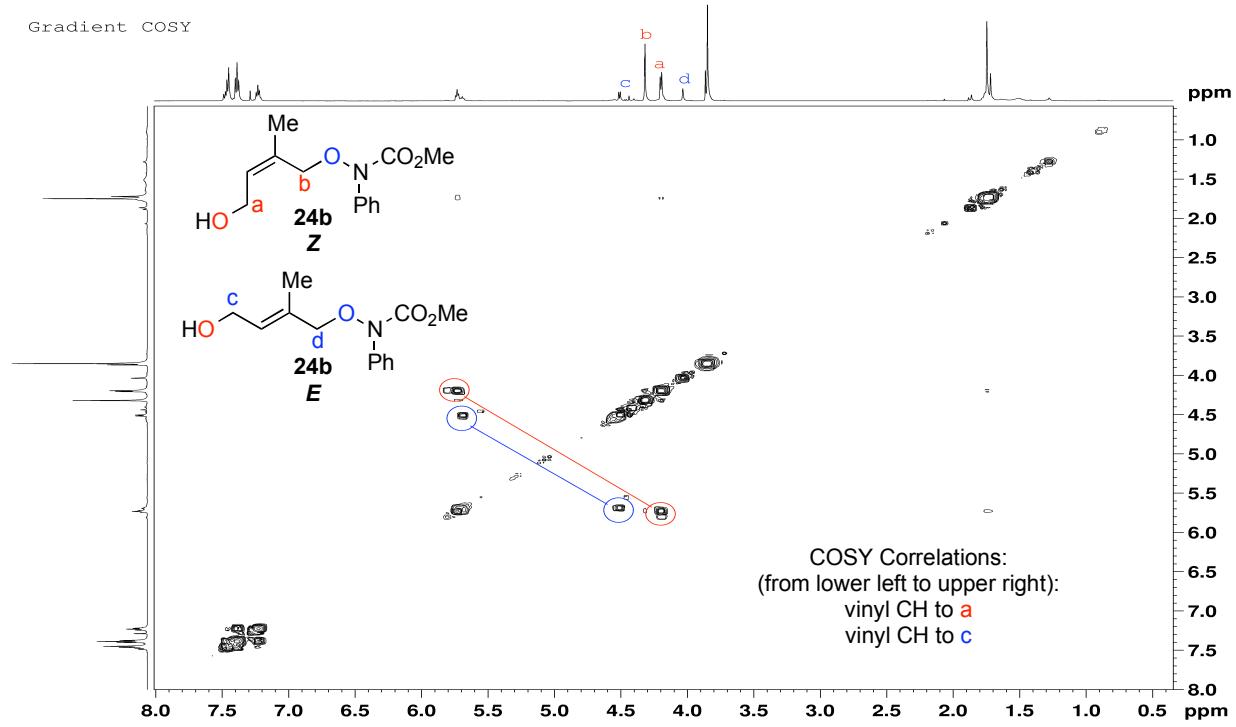

NOESY in C6D6
a
b
d c
f
e
ppm
23b
(minor)
Absence of
NOE between
a and b
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

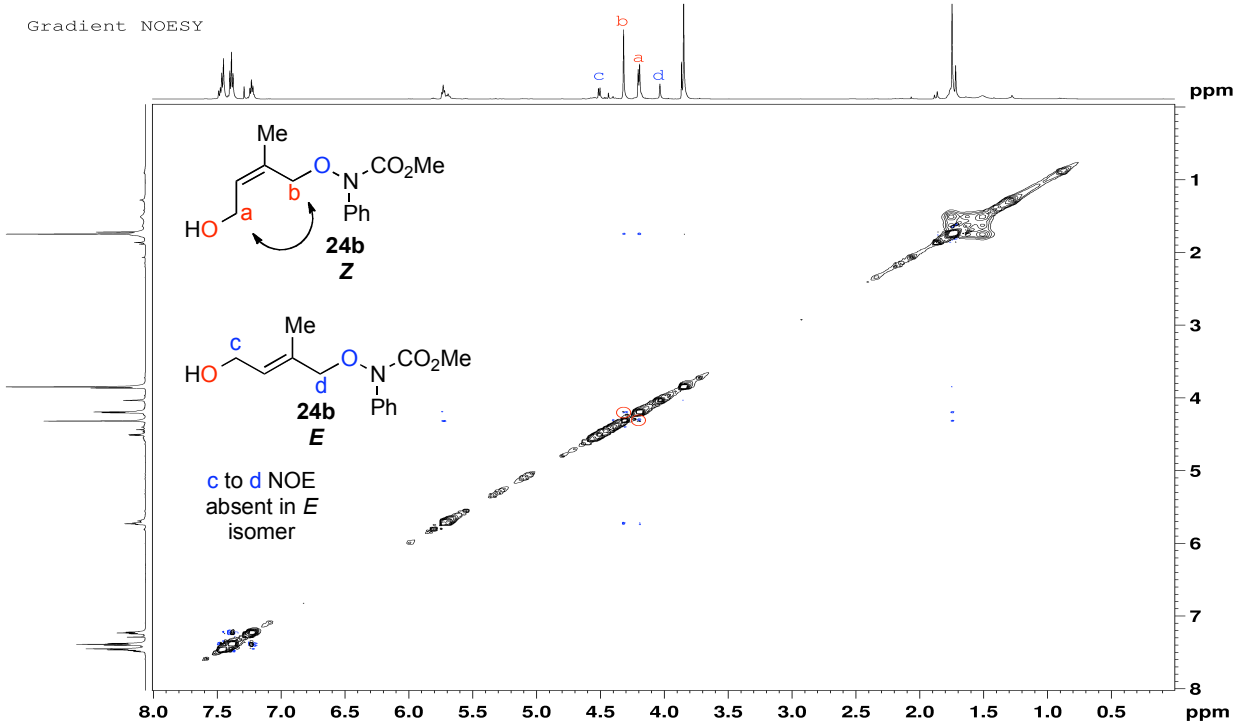

7.422
7.412
7.410
7.396
7.273
7.269
7.265
7.260
7.256
7.252
7.243
5.956
5.935
5.922
5.900
5.439
5.437
5.404
5.402
5.187
5.185
5.165
5.163
3.954
3.934
3.855
3.846
3.835
1.300
Me
OH
O
N
CO2Me
Ph
24a
(major)
9
8
7
6
5
4
3
2
1
ppm
4.10
1.02
1.00
0.99
1.00
1.07
1.28
2.90
3.01

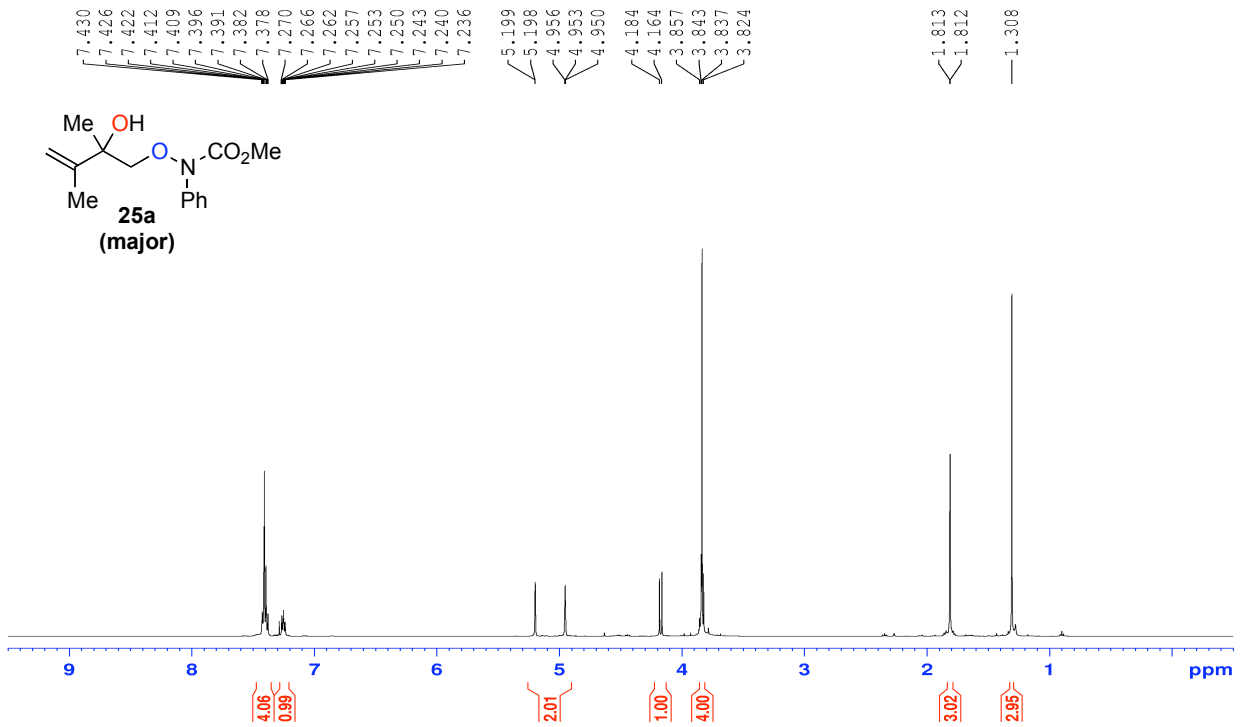

155.4476
141.6337
139.5237
128.9346
128.8591
126.9560
126.5849
123.4150
122.7911
113.7029
112.5703
82.3723
78.4963
72.0794
71.8425
53.7536
24.5370
[rel]
25
20
15
10
5
0
150
100
50
[ppm]

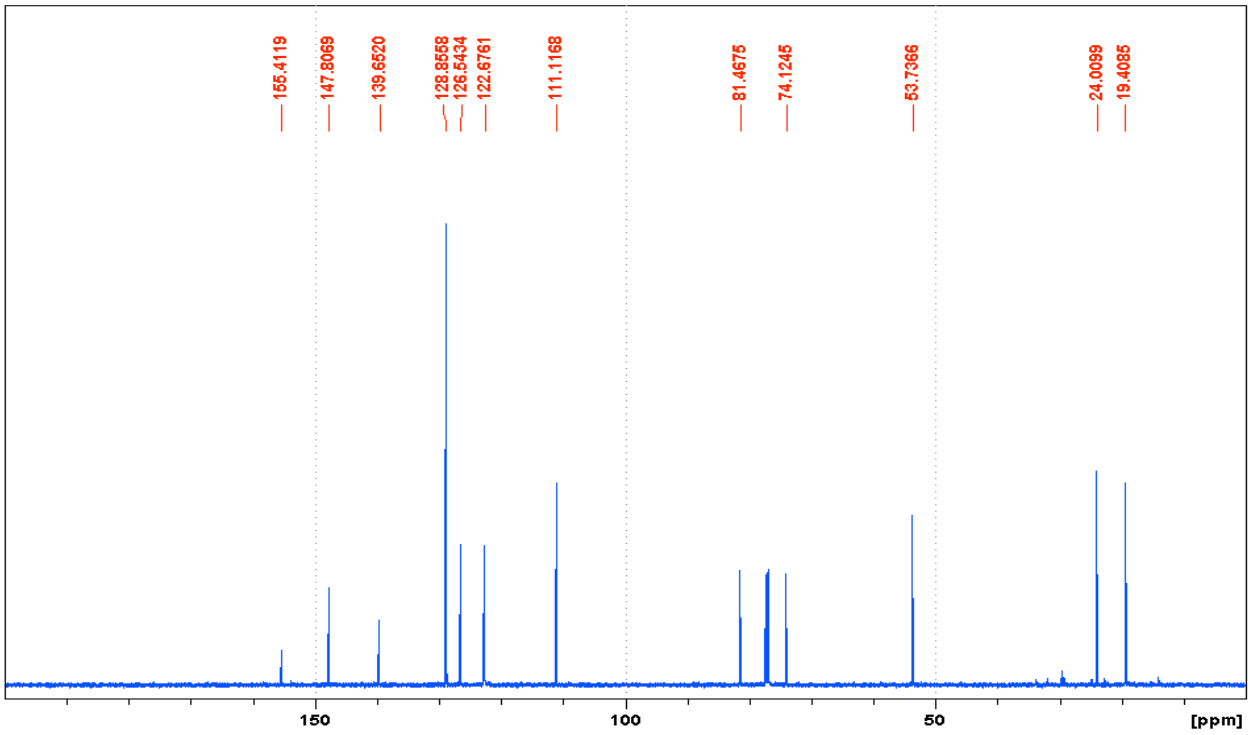

7.486
7.470
7.468
7.464
7.461
7.446
7.444
7.400
7.397
7.385
7.369
7.242
7.228
7.218
7.215
7.213
5.740
5.729
5.727
5.716
5.714
5.705
5.702
5.699
5.691
5.688
5.676
5.673
4.513
4.498
4.315
4.203
4.190
4.032
3.862
3.846
1.744
1.716
Me
O
N
CO2Me
Ph
HO
24b
Z
(major)
Me
HO
O
N
CO2Me
Ph
24b
E
9
8
7
6
5
4
3
2
1
ppm
2.03
2.08
1.00
1.01
0.46
1.45
1.49
0.48
0.62
2.40
2.28
0.70

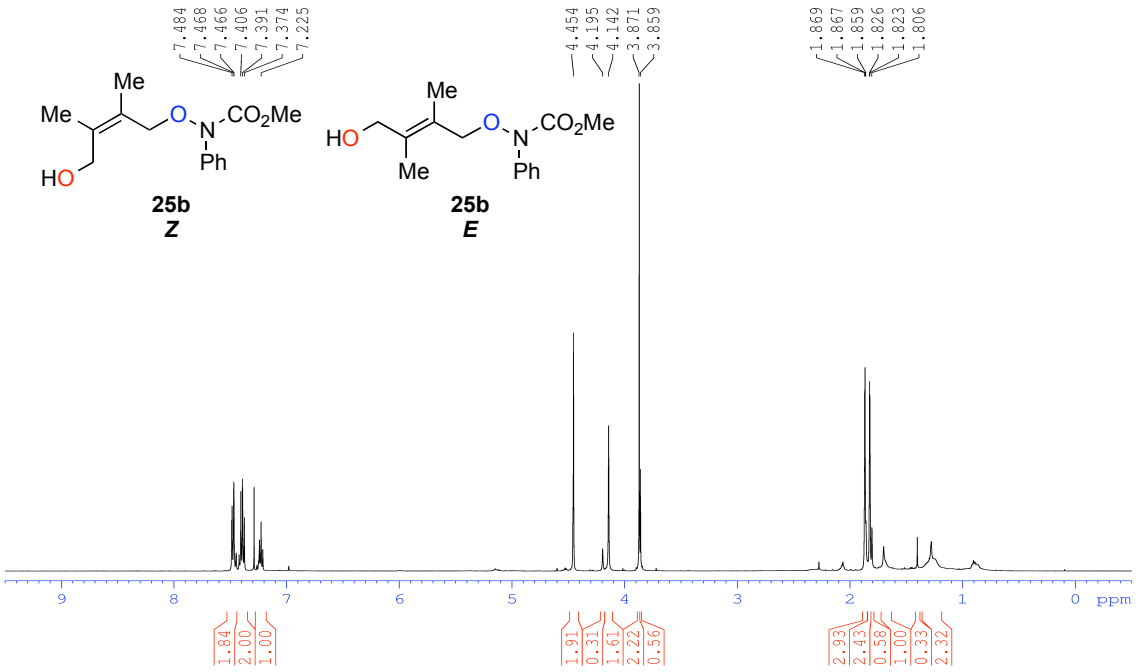

155.2530
155.1587
143.3365
140.1889
140.0910
133.1152
132.9142
131.6354
130.4195
128.7963
128.6852
126.0913
125.8542
122.6533
122.1207
117.4287
80.4801
72.8683
70.4978
67.6263
59.0662
58.5539
53.5495
53.4148
14.6229
13.8585
[rel]
0
5
10
15
150
100
50
[ppm]

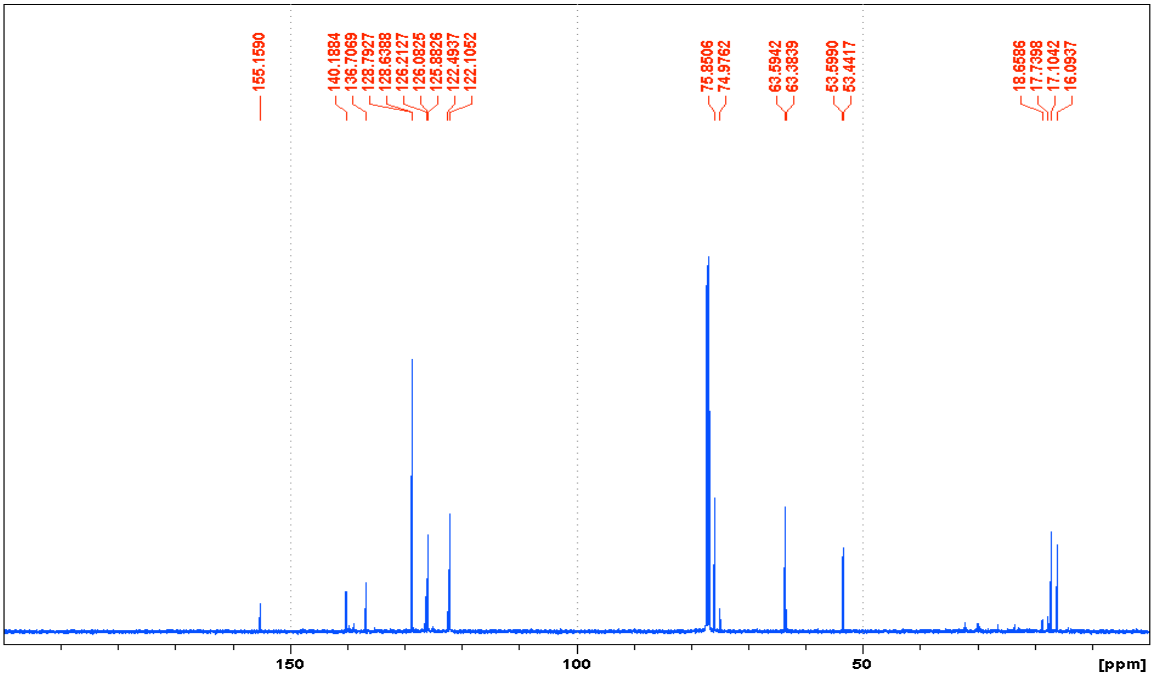

Gradient COSY
Me
HO
a
b
O
N
CO2Me
Ph
24b
Z
Me
HO
c
d
O
N
CO2Me
Ph
24b
E
COSY Correlations:
(from lower left to upper right):
vinyl CH to a
vinyl CH to c
ppm

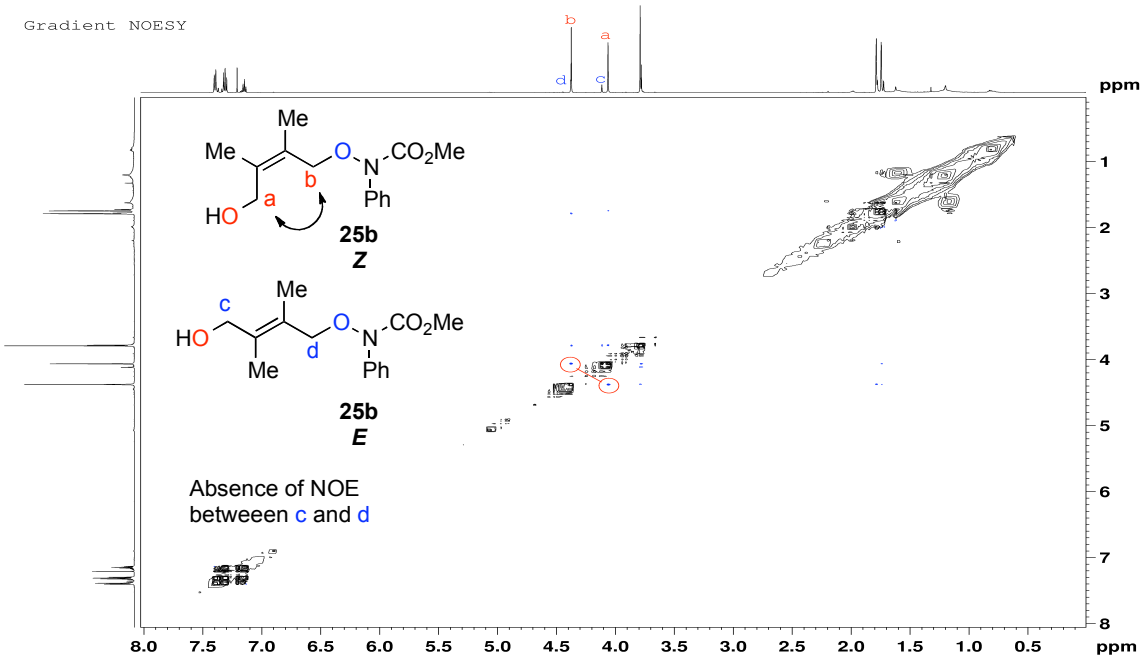

Gradient NOESY
Me
HO
a
b
O
N
CO2Me
Ph
24b
Z
Me
HO
c
d
O
N
CO2Me
Ph
24b
E
c to d NOE
absent in E
isomer
ppm

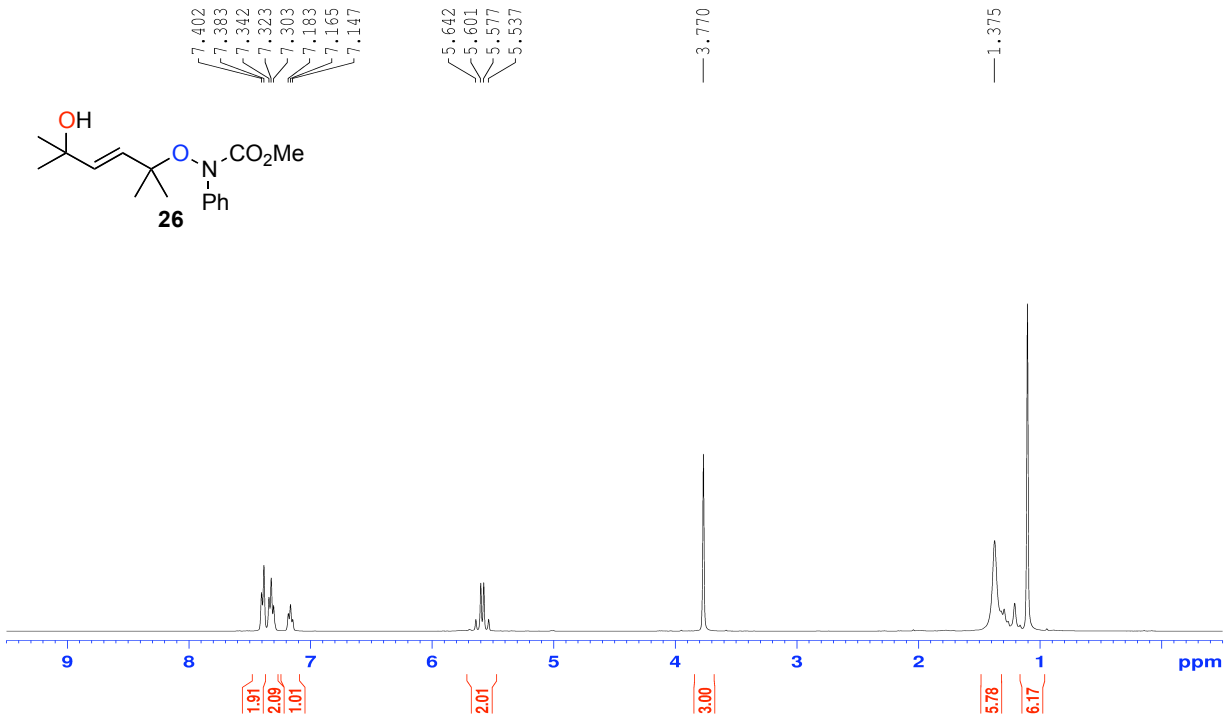

7.430
7.426
7.422
7.412
7.409
7.396
7.391
7.382
7.378
7.270
7.266
7.262
7.257
7.253
7.250
7.243
7.240
7.236
5.199
5.198
4.956
4.953
4.950
4.184
4.164
3.857
3.843
3.837
3.824
1.813
1.812
1.308
Me
OH
O
N
CO2Me
Me
Ph
25a
(major)
9
8
7
6
5
4
3
2
1
ppm
4.06
0.99
2.01
1.00
4.00
3.02
2.95

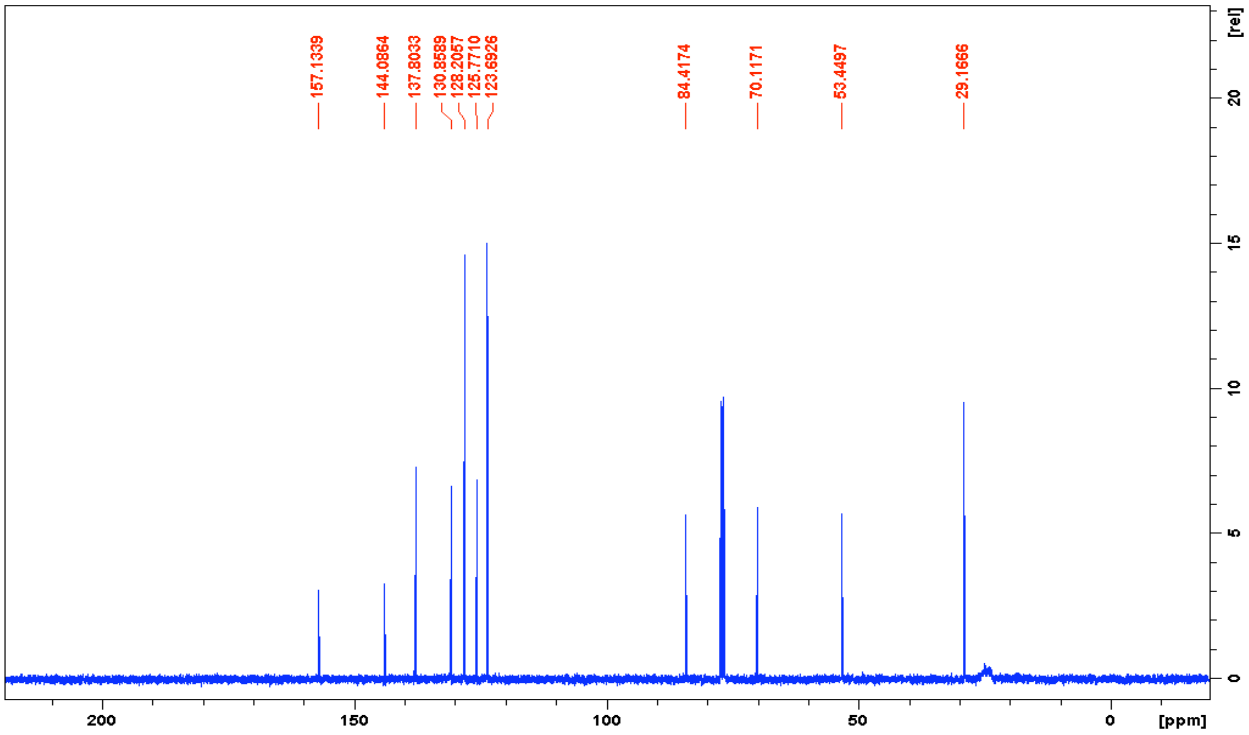

155.4119
147.8069
139.6520
128.8558
126.5434
122.6761
111.1168
81.4675
74.1245
53.7366
24.0099
19.4085
150
100
50
[ppm]


7.484
7.468
7.466
7.406
7.391
7.374
7.225
4.454
4.195
4.142
3.871
3.859
1.869
1.867
1.859
1.826
1.823
1.806
Me
Me
O
N
CO2Me
Ph
HO
25b
Z
Me
HO
Me
O
N
CO2Me
Ph
25b
E
9
8
7
6
5
4
3
2
1
0
ppm
1.84
2.00
1.00
1.91
0.31
1.61
2.22
0.56
2.93
2.43
0.58
1.00
0.33
2.32

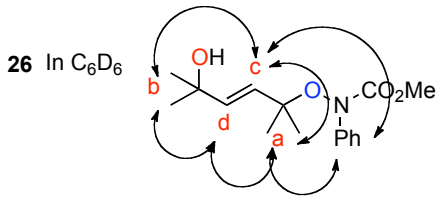

155.1590
140.1884
136.7069
128.7927
128.6388
126.2127
126.0825
125.8826
122.4937
122.1052
75.8506
74.9762
63.5942
63.3839
53.5990
53.4417
18.6586
17.7398
17.1042
16.0937
150
100
50
[ppm]

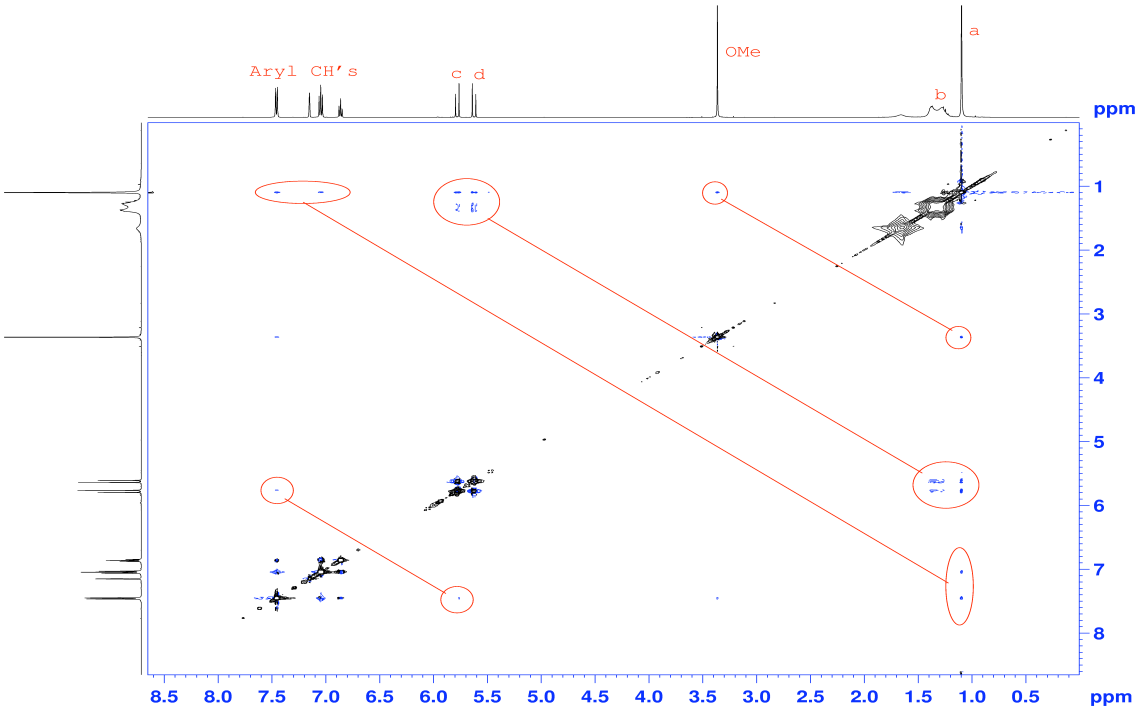

Gradient NOESY
b
a
d
c
ppm
Me
Me
O
N
CO2Me
b
HO
a
Ph
25b
Z
c
Me
HO
O
N
CO2Me
d
Me
Ph
25b
E
Absence of NOE
betweeen c and d
1
2
3
4
5
6
7
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

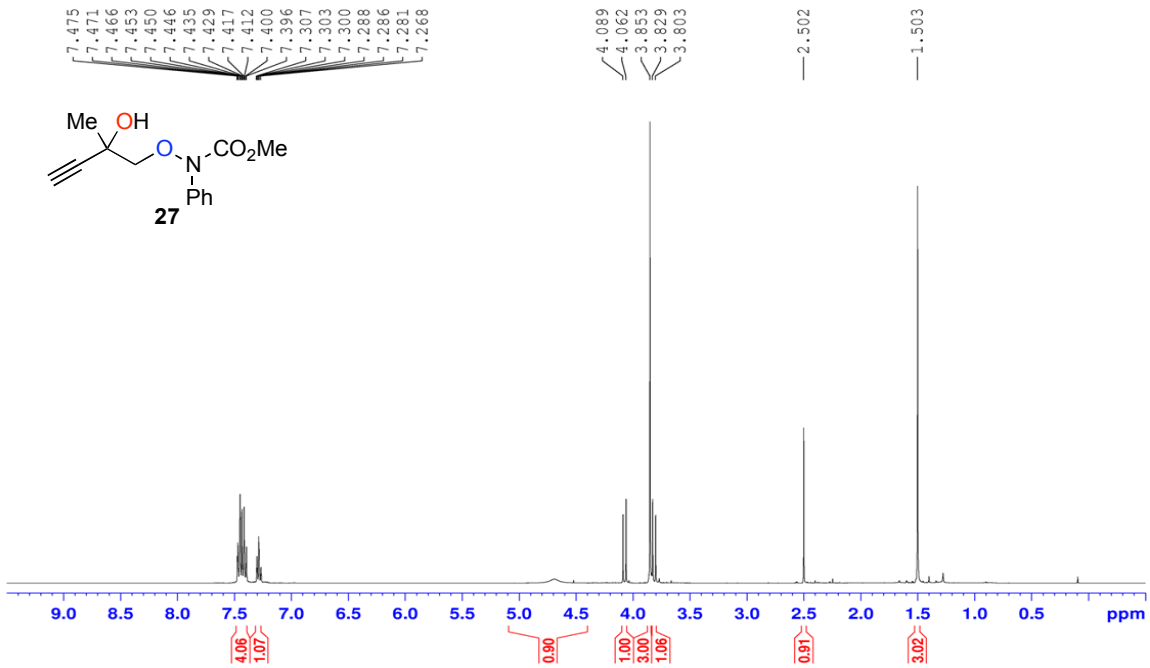

7.402
7.383
7.342
7.323
7.303
7.183
7.165
7.147
5.642
5.601
5.577
5.537
3.770
1.375
OH
O
N
CO2Me
Ph
26
9
8
7
6
5
4
3
2
1
ppm
1.91
2.09
1.01
2.01
3.00
5.78
6.17

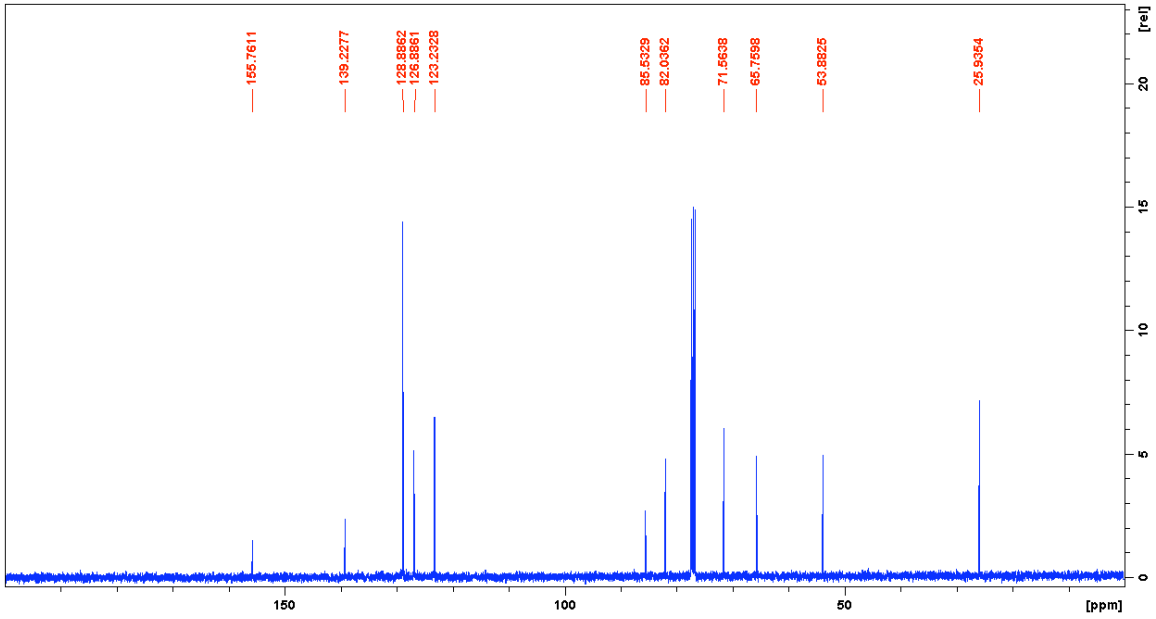

157.1339
144.0864
137.8033
130.8589
128.2057
125.7710
123.6928
84.4174
70.1171
53.4497
29.1666
[rel]
20
15
10
5
0
200
150
100
50
0
[ppm]

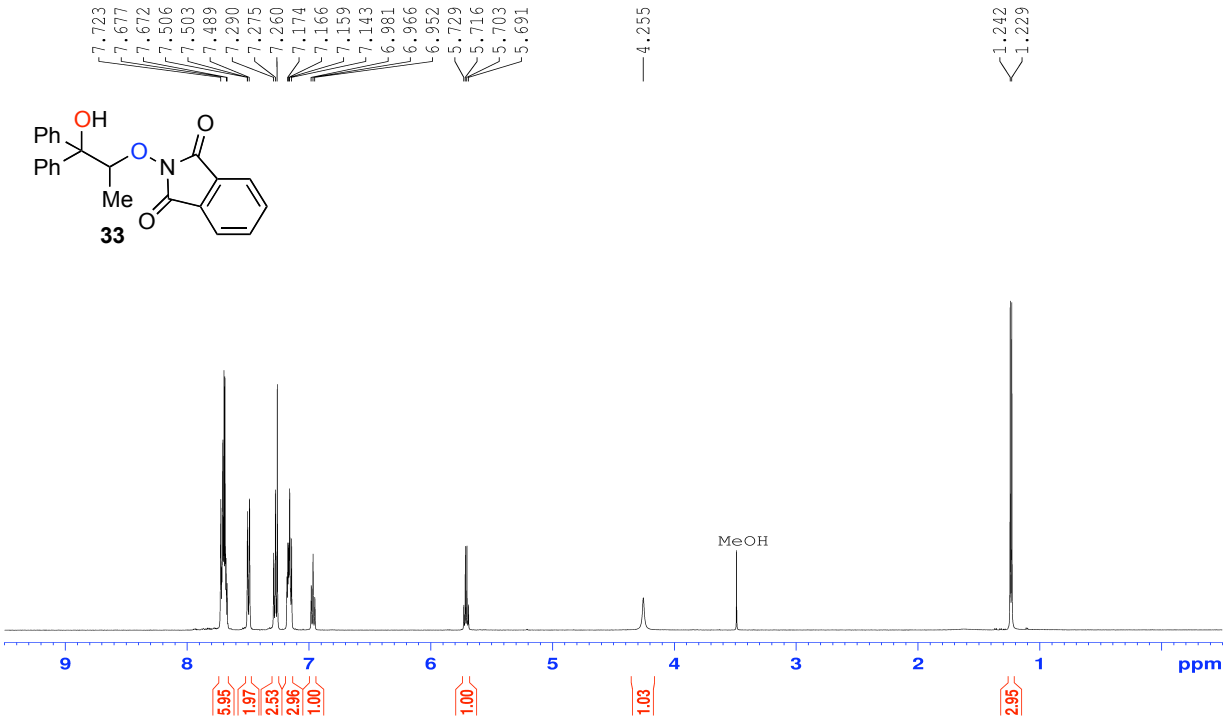
26 In C_6D_6

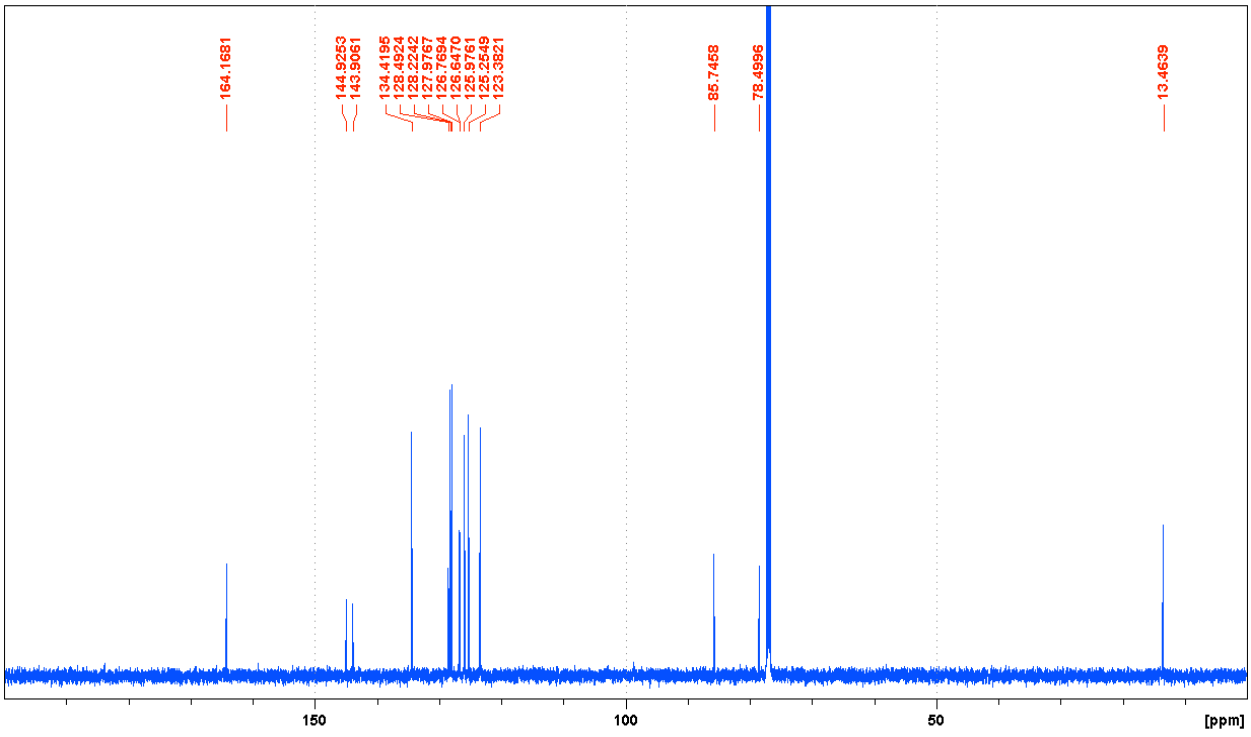

OH
c
b
d
a
O
N
Ph
CO2Me

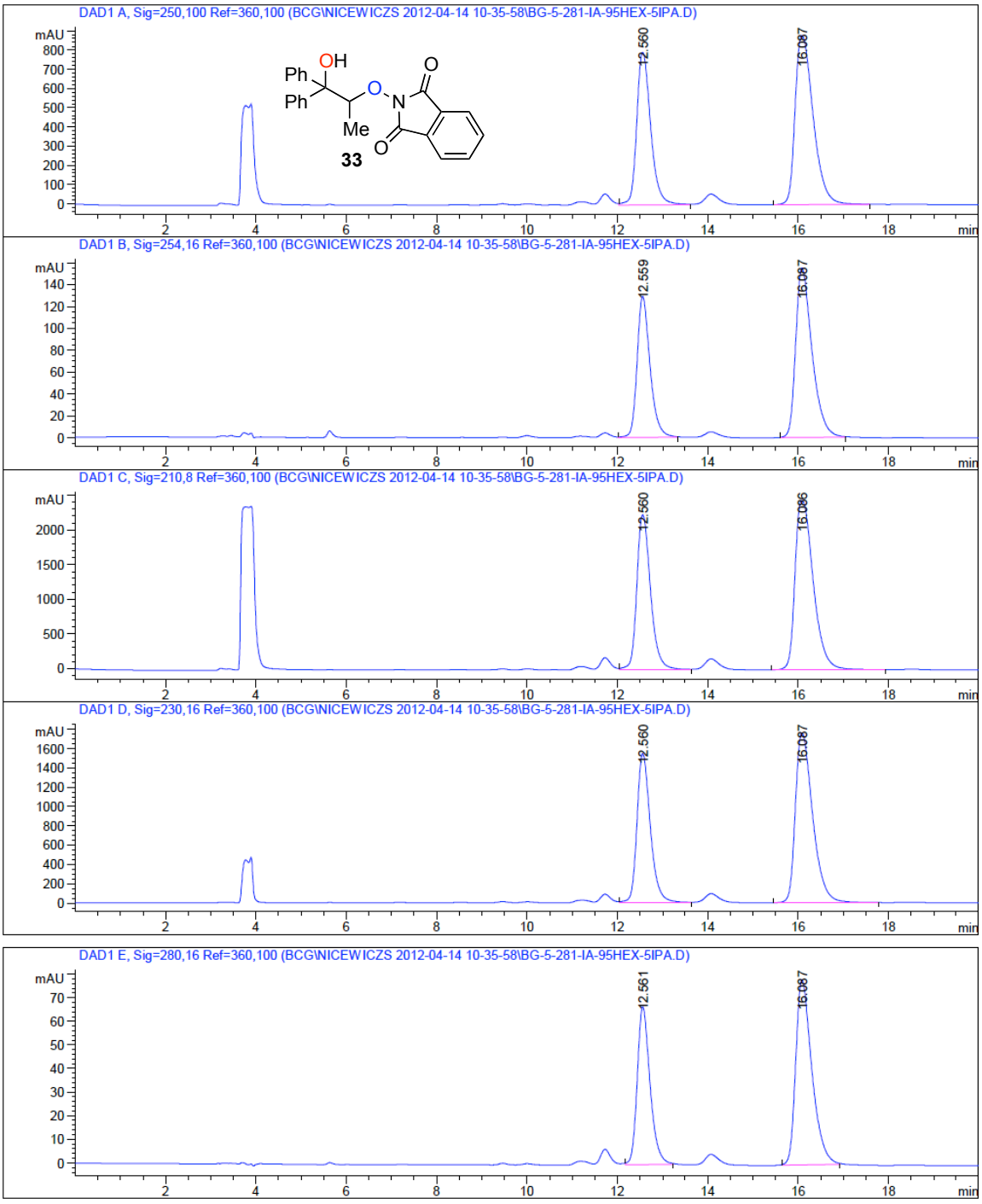

Aryl CH's
c d
OMe
b
a
ppm
1
2
3
4
5
6
7
8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


7.475
7.471
7.466
7.453
7.450
7.446
7.435
7.429
7.417
7.412
7.400
7.396
7.307
7.303
7.300
7.288
7.286
7.281
7.268
4.089
4.062
3.853
3.829
3.803
2.502
1.503
Me
OH
O
N
CO2Me
Ph
27
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.06
1.07
0.90
1.00
3.00
1.06
0.91
3.02


155.7611
139.2277
128.8862
126.8861
123.2328
85.5329
82.0362
71.5638
65.7598
53.8825
25.9354
[rel]
20
15
10
5
0
150
100
50
[ppm]


7.723
7.677
7.672
7.506
7.503
7.489
7.290
7.275
7.260
7.174
7.166
7.159
7.143
6.981
6.966
6.952
5.729
5.716
5.703
5.691
4.255
1.242
1.229
OH
Ph
Ph
O
N
O
Me
O
33
MeOH
9
8
7
6
5
4
3
2
1
ppm
5.95
1.97
2.53
2.96
1.00
1.00
1.03
2.95


164.1681
144.9253
143.9061
134.4195
128.4924
128.2242
127.9767
126.7694
126.6470
125.9761
125.2549
123.3821
85.7458
78.4996
13.4639
150
100
50
[ppm]


DAD1 A, Sig=250,100 Ref=360,100 (BCG\NICEWICZS 2012-04-14 10-35-58\BG-5-281-IA-95HEX-5IPA.D)
mAU
12.560
16.087
Ph
OH
Ph
Me
O
N
O
O
33
min
DAD1 B, Sig=254,16 Ref=360,100 (BCG\NICEWICZS 2012-04-14 10-35-58\BG-5-281-IA-95HEX-5IPA.D)
mAU
12.559
16.087
min
DAD1 C, Sig=210,8 Ref=360,100 (BCG\NICEWICZS 2012-04-14 10-35-58\BG-5-281-IA-95HEX-5IPA.D)
mAU
12.560
16.086
min
DAD1 D, Sig=230,16 Ref=360,100 (BCG\NICEWICZS 2012-04-14 10-35-58\BG-5-281-IA-95HEX-5IPA.D)
mAU
12.560
16.087
min
DAD1 E, Sig=280,16 Ref=360,100 (BCG\NICEWICZS 2012-04-14 10-35-58\BG-5-281-IA-95HEX-5IPA.D)
mAU
12.561
16.087
min

Signal 1: DAD1 A, Sig=250,100 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.560	VB	0.3308	1.70700e4	794.20074	41.1260
2	16.087	BB	0.4300	2.44366e4	879.91235	58.8740
Totals :				4.15067e4	1674.11310	

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.559	VB	0.3021	2562.64722	128.82086	39.7580
2	16.087	BB	0.3784	3882.97095	154.95180	60.2420
Totals :				6445.61816	283.77266	

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.560	VV	0.3265	4.76542e4	2237.50708	40.9869
2	16.086	BB	0.4312	6.86128e4	2446.11597	59.0131
Totals :				1.16267e5	4683.62305	

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.560	VV	0.3159	3.20174e4	1544.12280	40.6642
2	16.087	BB	0.4058	4.67187e4	1759.45129	59.3358
Totals :				7.87361e4	3303.57410	

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.561	BB	0.2994	1313.20740	66.78082	40.2992
2	16.087	BB	0.3753	1945.44031	78.45422	59.7008
Totals :				3258.64771	145.23503	

EXPERIMENTAL FOR CHAPTER 3:
HYDROXAMIC ACID MEDIATED FORMAL ALKENE HYDRATION

E3.1 General Information

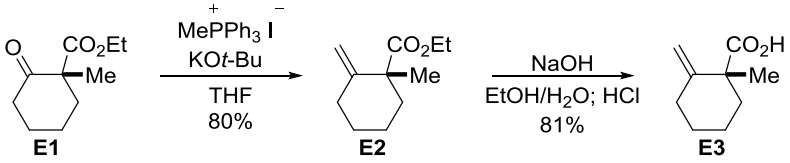
Methods: Nuclear magnetic resonance spectra were obtained on either a Varian INOVA 600 MHz spectrometer (^{1}H NMR at 600 MHz and ^{13}C at 151 MHz), a Bruker AVANCE III 600 MHz spectrometer, or a Bruker AVANCE 400 MHz spectrometer (^{1}H NMR at 400 MHz and ^{13}C at 101 MHz). ^{1}H NMR are reported in the following format: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. All NMR spectra are calibrated relative to residual protiated solvent resonances (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). High-resolution mass spectra were obtained on a Thermo Finnigan LTQ FT mass spectrometer in positive ion mode using flow injection electrospray ionization. All samples were prepared in methanol. Low resolution mass spectra were obtained using a Micromass Quattro II (triplequad) equipped with nanoelectrospray ionization. Samples were prepared in methanol and 1% aqueous formic acid. Calculated values for the monoisotopic ion masses were determined with the aid of ChemCalc.[1] Infrared spectra were recorded on a Jasco 260 Plus Fourier transform infrared spectrometer. Thin layer chromatography (TLC) was carried out on SiliaPlate 250 μm thick silica gel plates purchased from Silicycle. Visualization was achieved using short wave ultraviolet light (254 nm), alkaline aqueous potassium permanganate solution, or acidic ethanolic *p*-anisaldehyde solution followed by heating. Hydroxamic acids were visualized using a 1% aqueous solution of $FeCl_3$. Flash chromatography was carried out using SiliaFlash T60 silica gel (5-20 μm) or SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Oxygen sensitive reactions were assembled under an argon atmosphere in an Innovative Technologies glovebox. All reactions were performed under an argon atmosphere, unless otherwise noted.

Materials: All chemicals were used as received from their manufacturer (Sigma-Aldrich, Fisher Scientific, and Alfa Aesar) unless otherwise noted. Dichloromethane, tetrahydrofuran, and diethyl ether were dried by passage through a column of activated alumina while under dry nitrogen gas. Dichloroethane and benzene were degassed by multiple freeze-pump-thaw cycles and stored over activated 3 Å molecular sieves under an argon atmosphere. Norbornene was purified by sublimation and stored at -30 ºC under an argon atmosphere.

E3.2 Substrate Synthesis

N-phenylhydroxylamine[2,3] and methyl *N*-hydroxy(phenyl) carbamate **3**[4,5] were synthesized according to standard procedures. The carboxylic acids derived from hydroxamic acids **1**, **3**, **7**, and **9** were prepared using routes previously described.[3,6] Physical and spectral characteristics of the synthesized compounds matched those reported by the authors.

Synthesis of E3



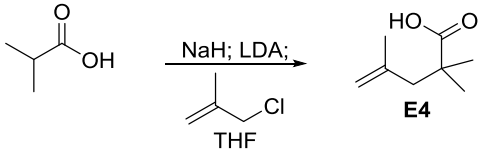
Synthesis of E2

The title compound was synthesized using an olefination procedure adapted from a protocol described by Chiba and Hui.[7] To a slurry of methyltriphenylphosphonium iodide (10.13 g, 24.9 mmol, 1.2 eq) in THF (70 mL) was added a magnetic stir bar and potassium *tert*-butoxide (2.80 g, 24.9 mmol, 1.2 eq). The slurry was stirred for 30 minutes. Ester **E1**[8,9] (3.83 g, 20.8 mmol, 1 eq) was dissolved in THF (12 mL) and added dropwise to the slurry, which was heated at 65 ºC for 2 hours. The reaction mixture was diluted with hexanes, and filtered through a short pad of silica. After rinsing the filter cake with hexanes, the filtrate was concentrated and the residue purified by silica gel flash chromatography (20:1 hexane:EtOAc). Ester **E2** was obtained in 80% yield (3.04 g, 16.7 mmol) as a colorless oil. Physical and spectral data were in agreement with literature data.[10]

Synthesis of E3

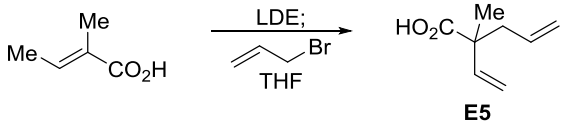
To a solution of **E2** (2.75g, 15.1 mmol, 1 eq) in absolute ethanol (15 mL) was added a magnetic stir bar and a solution of NaOH (1.33g, 33.2 mmol, 2.2 eq) in deionized water (15 mL). The reaction mixture was heated to reflux overnight. After cooling to 0 ºC, the mixture was diluted with water, acidified to a pH of 2 (Litmus paper) with 6N HCl, and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica flash chromatography (4:1 hexane:EtOAc) to yield **E3** (1.88 g, 12.2 mmol, 81% yield) as a tan semisolid. Analytical data for **E3**: ^{1}H NMR (600 MHz, $CDCl_3$): δ= 12.05 (br. s, 1 H), 4.92 (s, 1 H), 4.83 (s, 1 H), 2.34 (dt, *J* = 3.1, 13.6 Hz, 1 H), 2.26 (m, 1 H), 2.17 (td, *J* = 4.5, 13.2 Hz, 1 H), 1.76 (dt, *J* = 3.4, 12.4 Hz, 1 H), 1.66 (m, 1 H), 1.56 (m, 1 H), 1.39 (s, 3 H), 1.32 (qt, *J* = 4.1, 12.6 Hz, 1 H), 1.22 (td, *J* = 4, 13 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 183.2, 150.1, 108.8, 49.0, 38.0, 34.6, 27.9, 24.4, 23.6 ; IR (Thin film, cm^{-1}): 2938 (br), 1810, 1697, 1646, 1446, 1404, 1281, 1243, 1171, 1143, 1101, 903, 809, 732, 645, 572; HRMS (ESI) Calc. for $[C_9H_{14}O_2+Na]^+$ = 177.0891, Found = 177.0887.

Synthesis of E4



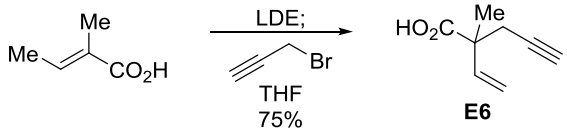
Carboxylic acid **E4** was prepared by the alkylation of the isobutyrate dianion with methallyl chloride following a procedure developed by Coates and co-workers.[11] Physical and spectral properties of the product matched those reported.

Synthesis of E5



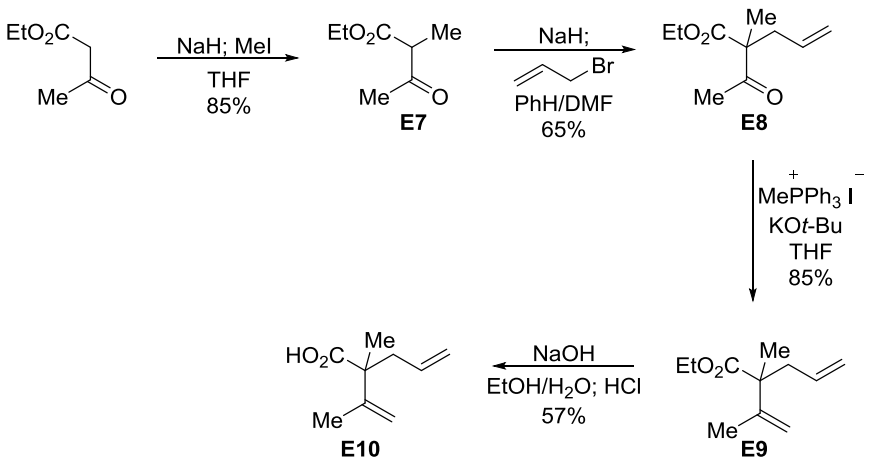
The title compound was synthesized by the α-alkylation of the lithium dienolate of tiglic acid with allyl bromide using the procedure provided by Parra and co-workers.[12] Physical and spectral properties of the product matched those reported.

Synthesis of E6



The title compound was synthesized using an adaptation of the tiglic acid alkylation procedure described by Parra and co-workers.[12] *n*-Butyllithium (58 mL of a 1.52 M solution in hexanes, 87.9 mmol, 2.2 eq) was syringed into a dry, 500 mL round-bottom flask containing a magnetic stir bar. The hexane was removed under a stream of dry nitrogen, and the residue was cooled to -78 ºC in a dry ice/acetone bath. The *n*-butyllithium was redissolved in THF (40 mL) which had been precooled to -78 ºC. Diethylamine (8.7 mL, 83.9 mmol, 2.1 eq) was then added dropwise. The reaction mixture was held at 0 ºC for 30 minutes before being cooled to -78 ºC. Propargyl bromide (4.5 mL of an 80% wt solution in toluene, 40 mmol, 1 eq) was dissolved in 67 mL of THF, and transferred via cannula into the reaction mixture. After stirring at -78 ºC for 30 minutes, the reaction mixture was warmed to room temperature over the course of an hour. The reaction was quenched by the slow addition of 150 mL H_2O and washed three times with EtOAc. The aqueous layer was cooled to 0 ºC and acidified to a pH of 2 (Litmus paper) with concentrated HCl before being extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 to 3:1 hexane:EtOAc solvent gradient) to yield **E6** (4.14 g, 30.0 mmol, 75% yield) as a yellow oil. The product formed from the alkylation of the γ-carbon of tiglic acid (2-methylhept-2-en-6-ynoic acid) was also isolated as an inseparable byproduct. This byproduct could be removed in later steps. Analytical data for **E6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.06 (br. s, 1 H), 6.00 (dd, *J* = 10.7, 17.4 Hz, 1 H), 5.24 (d, *J* = 17.6 Hz, 1 H), 5.23 (d, *J* = 10.5 Hz, 1 H), 2.65 (dd, 2.7, 16.5 Hz, 1 H), 2.51 (dd, *J* = 2.7, 16.8 Hz), 2.03 (t, *J* = 2.6 Hz, 1 H), 1.43 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.1, 139.1, 115.6, 80.1, 70.9, 48.1, 28.1, 20.6; IR (Thin film, cm^{-1}): 3925, 3303, 2988(br), 2648, 2121, 1705, 1639, 1461, 1415, 1286, 1124, 928, 762, 644, 531; HRMS (ESI) Calc. for $[C_8H_{10}O_2+Na]^+$ = 161.0578, Found = 161.0574.

Synthesis of E10



Synthesis of E7

Sodium hydride (60% wt. dispersion in mineral oil, 1.54 g, 38.4 mmol, 1 eq) was suspended in dry THF (75 mL), and cooled to 0 °C. Ethyl acetoacetate (5 g, 4.86 mL, 38.4 mmol, 1 eq) was added dropwise while stirring magnetically. After hydrogen evolution ceased and the solution became clear, iodomethane (6.54 g, 2.90 mL, 46.1 mmol, 1.2 eq) was added dropwise. The solution was allowed to warm to room temperature before being heated at 65 °C overnight. The reaction mixture was quenched with water and extracted three times with EtOAc. The combined organic extracts were washed twice with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by vacuum distillation to afford **E7** (4.69 g, 32.5 mmol, 85% yield) as a colorless oil. Physical and spectral data were in accordance with literature values.[13]

Synthesis of E8

Sodium hydride (60% wt. dispersion in mineral oil, 2.62 g, 65.6 mmol, 1.05 eq) was suspended in benzene (60 mL). **E7** (9.0 g, 62.4 mmol, 1 eq) was dissolved in benzene (60 mL), and slowly transferred via cannula into the magnetically stirring sodium hydride suspension. Dry DMF (30 mL) was added to solubilize the sodium enolate. After stirring 20 minutes, allyl bromide (7.94 g, 5.7 mL, 65.6 mmol, 1.05 eq) was added dropwise, and the reaction was heated at 80 °C overnight. The reaction was quenched with water and extracted three times with Et_2O. The combined organic extracts were washed with brine, dried

over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (8:1 hexane:EtOAc) to yield **E8** (7.47 g, 40.5 mmol, 65% yield) as a colorless oil. Physical and spectral properties of the product matched those reported.[14]

Synthesis of E9

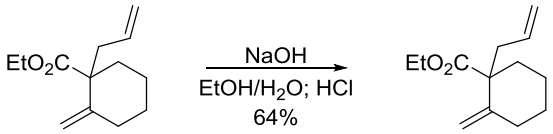
The title compound was synthesized using a procedure adapted from that described by Chiba and Hui.[7] To a slurry of methyltriphenylphosphonium iodide (2.43 g, 6.0 mmol, 1.1 eq) in Et_2O (17 mL) was added a magnetic stir bar and potassium *tert*-butoxide (0.670 g, 6.0 mmol, 1.1 eq). The slurry was stirred for 30 minutes. Ester **E8** (1.00 g, 5.43 mmol, 1 eq) was dissolved in Et_2O (3.3 mL) and added dropwise to the slurry, which was heated at 35 °C until TLC analysis indicated the completion of the reaction. The reaction mixture was cooled, diluted with hexanes, and filtered through a short pad of silica. After rinsing the filter cake with hexane, the filtrate was concentrated and the residue purified by vacuum distillation. **E9** was obtained as a colorless oil in 81% yield (0.837g, 4.59 mmol). An unidentified, inseparable by-product was present in the purified material. This by-product could be removed during later steps. A pure sample of **E9** for analysis was prepared through esterification of the acid chloride derived from **E10**. Analytical data for **E9**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.66 (m, 1 H), 5.06 (m, 2 H), 4.92 (m, 1 H), 4.86 (s, 1 H), 4.14 (m, 2 H), 2.54 (dd, J = 7.4, 13.8 Hz, 1 H), 2.43 (dd, J = 7.1, 13.8 Hz, 1 H), 1.72 (d, J = 0.7 Hz, 3 H), 1.26 (s, 3 H), 1.24 (t, J = 7.1 Hz, 3 H) ; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.5, 146.3, 134.2, 117.9, 111.6, 60.6, 51.0, 40.7, 21.2, 20.1, 14.2; IR (Thin film, cm^{-1}): 2980, 1731, 1643, 1457, 1377, 1288, 1235, 1145, 1106, 897; HRMS (ESI) Calc. for $[C_{11}H_{18}O_2+Na]^+$ = 205.1204, Found = 205.1201.

Synthesis of E10

To a solution of **E9** (0.750g, 4.12 mmol, 1 eq) in absolute ethanol (4 mL) was added a magnetic stir bar and a solution of NaOH (0.36 g, 9.05 mmol, 2.2 eq) in deionized water (4 mL). The reaction mixture was placed under an argon atmosphere and refluxed overnight. After cooling to 0 ºC, the mixture was diluted with water, acidified to a pH of 2 (Litmus paper) with 6 N HCl, and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried over anhydrous $MgSO_4$, filtered, and

concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 hexane:EtOAc) to yield **E10** (0.362 g, 2.33 mmol, 57% yield) as a colorless oil. Analytical data for **E10**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 11.88 (br. s, 1 H), 5.67 (m, 1 H), 5.08 (m, 2 H), 4.99 (s, 1 H), 4.93 (s, 1 H), 2.54 (dd, *J* = 7.5, 14 Hz, 1 H), 2.47 (dd, *J* = 7, 14 Hz, 1 H), 1.79 (d, *J* = 0.7 Hz, 3 H), 1.31 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 182.1, 145.4, 133.7, 118.3, 112.5, 50.9, 40.4, 21.0, 20.2 ; IR (Thin film, cm^{-1}): 2980(br), 2646, 1704, 1643, 1455, 1403, 1378, 1293, 1269, 1233, 1151, 1119, 1066, 994, 917, 741, 651, 586; HRMS (ESI) Calc. for $[C_9H_{14}O_2+Na]^+$ = 177.0891, Found = 177.0887.

Synthesis of E12

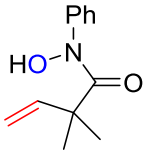


E11 **E12**

To a solution of **E11**[15] (1.27 g, 6.06 mmol, 1 eq) in absolute ethanol (6 mL) was added a magnetic stir bar and a solution of NaOH (0.533 g, 13.3 mmol, 2.2 eq) in deionized water (6 mL). The reaction mixture was placed under an argon atmosphere and heated to reflux. Additional NaOH (0.580 g, 14.5 mmol, 2.4 eq) was added after 16 hours. After 50 hours, more was added (1.00 g, 25.0 mmol, 4.1 eq) to accelerate the sluggish reaction. After a total of 62 hours of reflux, the reaction was cooled to 0 ºC, diluted with water, acidified to a pH of 2 (Litmus paper) with 6 N HCl, and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (4:1 hexane:EtOAc) to yield **E12** (0.698 g, 3.87 mmol, 64% yield) as a viscous, pale yellow oil. Analytical data for **E12**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.00 (br. s, 1 H), 5.81 (m, 1 H), 5.09 (m, 2 H), 4.95 (s, 1 H), 4.87 (s, 1 H), 2.67 (dd, *J* = 6.9, 13.8 Hz, 1 H), 2.41 (dd, *J* = 7.6, 13.9), 1 H), 2.33 (dt, *J* = 4.2, 13.6 Hz), 1 H), 2.21 (dt, *J* = 3.8, 13.4 Hz, 1 H), 2.12 (td, *J* = 4.1, 12.6 Hz, 1 H), 1.72 (m, 1 H), 1.62 (m, 2 H), 1.37 (m, 1 H), 1.27 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 181.2, 149.2, 133.5, 118.2, 109.2, 52.8, 41.1, 35.0, 34.8, 27.9, 22.9; IR (Thin film, cm^{-1}): 3079, 2937(br), 2859, 2628, 1700, 1643, 1448, 1401, 1290, 1241, 1169, 1135, 992, 915, 811, 735, 646; HRMS (ESI) Calc. for $[C_{11}H_{16}O_2+Na]^+$ = 203.1048, Found = 203.1044.

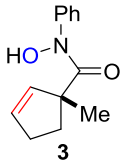
E3.3 General Procedure for the Synthesis of Hydroxamic Acids

A dry 50 mL-round-bottom flask was charged with a magnetic stir bar, carboxylic acid (3.24 mmol, 1 eq), DMF (13 µL, 0.162 mmol, 0.05 eq), and diethyl ether (6.5 mL). The vessel was then placed under an argon atmosphere and cooled to 0 ºC in an ice-water bath. Oxalyl chloride (0.30 mL, 3.57 mmol, 1.1 eq) was added dropwise, and the reaction was stirred at 0 ºC for 5 minutes and at ambient temperature for 1 hour. After chilling the flask to 0 ºC, $NaHCO_3$ (0.544 g, 6.48 mmol, 2 eq) was added, followed by 3.2 mL of deionized water. After effervescence ceased, *N*-phenylhydroxylamine (0.354 g, 3.24 mmol, 1 eq) was added portionwise. The reaction was then placed under an argon atmosphere, stirred at 0 ºC for 5 minutes, and at room temperature for 1 hour. After diluting with water, the reaction mixture was extracted three times with Et_2O. The combined organic extracts were washed three times with 1N HCl, once with brine, and dried over anhydrous $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by silica gel column chromatography and stored at 5 ºC.



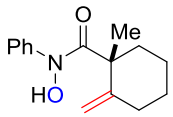
1

Hydroxamic acid **1** was synthesized according to the general procedure from the corresponding carboxylic acid (1.00 g, 8.76 mmol). The crude product was purified by silica gel flash chromatography (4:1 hexane:EtOAc), to afford a light yellow solid (1.39 g, 6.77 mmol, 70% yield). Physical and spectral properties matched those previously reported.[3]



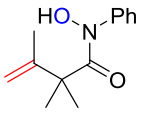
3

Hydroxamic acid **3** was synthesized according to the general procedure from the corresponding carboxylic acid (0.500 g, 3.96 mmol). The crude product was purified by silica gel flash chromatography (4:1 hexane:EtOAc) to afford a pale yellow solid (0.58 g, 2.66 mmol, 67% yield). Physical and spectra properties matched those previously reported.[3]



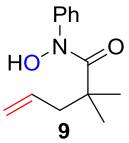
5

Hydroxamic acid **5** was prepared according to the general procedure from **E3**, with the following modifications: 1.6 equivalents of oxalyl chloride and 0.1 equivalents of DMF were employed, and 1 hour of heating at 35 °C was needed to help convert the carboxylic acid to the acid chloride. The crude product was purified by silica gel flash chromatography (5:1 hexane:EtOAc) to yield a light yellow solid (0.456 g, 1.86 mmol, 57% yield). Analytical data for **5**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41 (br. s, 2 H), 7.32 (m, 2 H), 7.28 (br. s, 1 H), 4.59 (br. s, 2 H), 2.48 (d, *J* = 12.8 Hz, 1 H), 2.20 (br. s, 1 H), 2.10 (m, 1 H), 1.75 (br. m, 2 H), 1.61 (m, 1 H), 1.37 (s, 3 H), 1.33 (br. s, 1 H), 1.11 (br. s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.6 (br.), 151.1 (br.), 140.0 (br.), 128.5, 127.8 (br.), 125.1 (br.), 109.0, 49.2 (br.), 40.0 (br.), 35.3, 28.5, 24.1 (br.), 23.4; IR (Thin film, cm^{-1}): 3238(br), 2936, 1621, 1592, 1491, 1447, 1373, 1351, 1308, 1067, 896, 758, 694; HRMS (ESI) Calc. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.1313, Found = 268.1311.



7

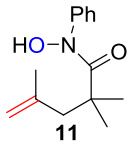
Hydroxamic acid **7** was synthesized according to the general procedure from the corresponding carboxylic acid (0.50 g, 3.90 mmol). The crude product was purified via silica gel flash chromatography (4:1 hexane:EtOAc) to give a pale green solid (0.682 g, 3.11 mmol, 77% yield). Physical and spectral properties of the product matched those previously reported.[6]



9

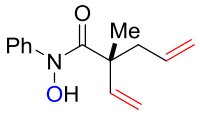
Hydroxamic acid **9** was prepared according to the general procedure from the corresponding carboxylic acid (0.100 g, 0.78 mmol). The crude product was purified by silica gel flash chromatography (4:1

hexane:EtOAc) to afford a light yellow solid (0.124 g, 0.565 mmol, 72% yield). Physical and spectral properties of the product matched those previously reported.[3]



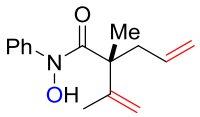
11

Hydroxamic acid **11** was prepared from **E4** (0.500 g, 3.52 mmol) according to the general procedure, with the following exceptions: 2 equivalents of oxalyl chloride, 0.1 equivalents of DMF, and 4 equivalents of $NaHCO_3$ were used, and the reaction mixture was heated at 35 °C 2 hours to assist with the conversion of the carboxylic acid to the acid chloride. The crude product was purified by silica gel flash chromatography (4:1 hexane:EtOAc) to yield an light yellow solid (0.590 g, 2.53 mmol, 72% yield). Analytical data for **13**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.76 (br. s, 1 H), 7.37 (m, 5 H), 4.81 (s, 1 H), 4.68 (s, 1 H), 2.34 (s, 2 H), 1.67 (s, 3 H), 1.11 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.6 (br), 142.7, 140.5, 128.8, 128.6 (br), 126.8 (br), 113.8, 48.3, 42.3, 26.9, 23.8; IR (Thin film, cm^{-1}): 3183(br), 2969, 1612, 1591, 1495, 1453, 1390, 1359, 1258, 1068, 891, 760, 692, 668, 622; HRMS (ESI) Calc. for $[C_{14}H_{19}NO_2+Na]^+$ = 256.1313, Found = 256.1310.



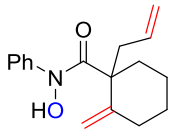
14

Hydroxamic acid **14** was prepared from **E5** (0.500 g, 3.57 mmol) according to the standard procedure. The crude product was purified by silica gel flash chromatography (5:1 hexane: EtOAc) to give **14** (0.408 g, 1.76 mmol, 49% yield) as a pale yellow oil. Analytical data for **14**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.7 Hz, 2H), 7.35 (m, 2H), 7.28(br. m, 1H), 5.92 (br. s, 1 H), 5.74 (m, 1 H), 5.08 (m, 1 H), 5.06 (s, 1 H), 4.98 (m, 2 H), 2.62 (br. s, 1 H), 2.39 (dd, *J* = 7.0, 13.8 Hz, 1 H), 1.25 (s, 3 H) ; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.7 (br), 141.8 (br.), 140.3 (br.), 133.8, 128.6, 127.8 (br.), 125.5 (br.), 118.3, 113.6, 48.4, 43.0, 22.5; IR (Thin film, cm^{-1}): 3212(br), 3078, 2979, 2936, 1945, 1837, 1615, 1592, 1495, 1454, 1374, 1307, 1262, 1223, 1065, 995, 916, 759, 699; HRMS (ESI) Calc. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.1157, Found = 254.1154.



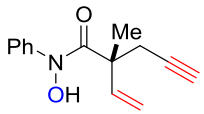
16

Hydroxamic acid **16** was prepared from **E10** (0.300 g, 1.95 mmol) according to the standard procedure, with the following exceptions: 3.3 equivalents of oxalyl chloride and 8 equivalents of $NaHCO_3$ were used. The crude product was purified by silica gel flash chromatography (4:1 hexane:EtOAc) to give **16** (0.344 g, 1.40 mmol, 72% yield) as an off-white solid. Analytical data for **16**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.0 Hz, 2 H), 7.33 (t, *J* = 7.9 Hz, 2 H), 7.24 (br. s, 1 H), 5.70 (m, 1 H), 5.06 (m, 2 H), 4.86 (br. s, 1 H), 4.74 (br. s, 1 H), 2.69 (br. s, 1 H), 2.40 (dd, *J* = 7.2, 13.9 Hz, 1 H), 1.79 (s, 3 H), 1.29 (br. s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.4 (br.), 147.5 (br.), 140.6 (br.), 134.1, 128.5, 127.1 (br.), 123.4 (br.), 118.1, 111.1, 51.4 (br.), 41.3, 21.9, 20.3; IR (Thin film, cm^{-1}): 3214(br), 2972, 1619, 1494, 1592, 1452, 1373, 1067, 757, 694; HRMS (ESI) Calc. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.1313, Found = 268.1310.



18

Hydroxamic acid **18** was prepared from **E12** (0.500 g, 2.77 mmol) according to the standard procedure. The crude product was purified by silica gel flash chromatography (6:1 hexane:EtOAc) to give **18** (0.459 g, 1.69 mmol, 61% yield) as a pale yellow solid. Analytical data for **18**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (br. s, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.27 (br. s, 1 H), 5.84 (ddt, *J* = 7.2, 10, 17.1 Hz, 1 H), 5.11 (m, 2 H), 4.82 (br. s, 2 H), 2.92 (br. s, 1 H), 2.56 (d, *J* = 12.8 Hz, 1 H), 2.26 (br. s, 2 H), 2.12 (td, *J* = 3.3, 12.3 Hz, 1 H), 1.77 (m, 2 H), 1.64 (m, 1 H), 1.37 (br. s, 1 H), 1.11 (br. s, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.8 (br.), 151.0 (br.), 140.3 (br.), 133.8, 128.5, 127.7 (br.), 122.3 (br.), 118.0, 109.1, 52.5 (br.), 40.3 (br.), 37.0, 35.6, 28.5, 23.0; IR (Thin film, cm^{-1}): 3216(br), 2935, 1620, 1591, 1492, 1447, 1363, 914, 760, 694, 668; HRMS (ESI) Calc. for $[C_{17}H_{21}NO_2+Na]^+$ = 294.1470, Found = 294.1468.



20

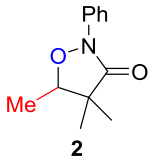
Hydroxamic acid **20** was prepared from **E6** (0.500 g, 3.61 mmol) according to the standard procedure. The crude product was purified by silica gel flash chromatography (3:1 hexane:EtOAc) to give **20** (0.540 g, 2.36 mmol, 65% yield) as a light brown solid. Analytical data for **20**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.7 Hz, 2 H), 7.35 (t, *J* = 7.7 Hz, 2 H), 7.28 (m, 1 H), 5.96 (s, 1 H), 5.05 (m, 2 H), 2.66 (m, 1 H), 2.56 (m, 1 H), 2.02 (t, *J* = 2.6Hz, 1 H), 1.40 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.8 (br.), 140.4, 128.6, 127.8 (br.), 125.1 (br.), 114.5, 80.8, 70.9, 48.3, 28.9, 22.2; IR (Thin film, cm^{-1}): 3294(br), 2979, 2937, 2118, 1621, 1592, 1494, 1454, 1375, 1308, 1258, 1066, 993, 919, 761, 700, 646; HRMS (ESI) Calc. for $[C_{14}H_{15}NO_2+Na]^+$ = 252.1000, Found = 252.0997.

E3.4 General Procedure for Intramolecular Formal Hydration of Alkenes

Condition A: A 1-dram vial was charged with a magnetic stir bar, unsaturated hydroxamic acid (0.10 mmol, 1 eq), dilauroyl peroxide (2.0 mg, 0.005 mmol, 0.05 eq), and *N*-hydroxy carbamate **3** (13.4 mg, 0.080 mmol, 0.80 eq). The vial was sealed with a screw cap lined with a PTFE septum and transferred into an argon-filled glovebox. After allowing argon to displace the air in the vial and dissolving the reagents in dichloroethane (0.20 mL), the vial was removed from the glove box and heated at 60 ºC. After TLC analysis indicated the completion of the reaction, solvent was removed in vacuo, and the residue was purified by column chromatography. Note: If the reaction was not complete after 24 hours (approximately two half-lives of dilauroyl peroxide), the reaction was re-initiated with an additional 2 mg (0.05 eq) of dilauroyl peroxide. This process was repeated until the reaction was deemed complete.

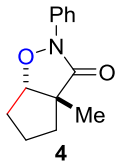
Condition B: A 1-dram vial was charged with a magnetic stir bar, unsaturated hydroxamic acid (0.50 mmol, 1 eq), and dilauroyl peroxide (5.0 mg, 0.0125 mmol, 0.025 eq). The vial was sealed with a screw cap lined with a PTFE septum and transferred into an argon-filled glovebox. After allowing argon to displace the air in the vial and dissolving the reagents in dichloroethane (1.0 mL), the vial was removed

from the glove box and heated at 60 ºC. After TLC analysis indicated the completion of the reaction, solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography.



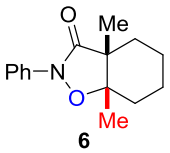
2

Isoxazolidinone **2** was prepared from hydroxamic acid **1** (20.2 mg, 0.100 mmol) according to *Condition A*. The reaction was deemed complete by TLC after 16 hours. The crude product was purified by silica gel flash chromatography (5:1 hexane:Et_2O) to afford **8** (18.1 mg, 0.0881 mmol, 90% yield) as a clear oil. Analytical data for **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (m, 2 H), 7.36 (m, 2 H), 7.12 (m, 1 H), 4.34 (q, *J* = 6.5 Hz, 1 H), 1.36 (d, *J* = 6.5 Hz, 3 H), 1.24 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1, 137.2, 128.7, 124.4, 116.4, 83.7, 46.2, 20.9, 17.3, 12.4; IR (Thin film, cm^{-1}): 2974, 2930, 2870, 1706, 1595, 1496, 1395, 1367, 1350, 1305, 1181, 1131, 1086, 1042, 889, 752, 690, 582; HRMS (ESI) Calc. for $[C_{12}H_{15}NO_2+Na]^+$ = 228.1000, Found = 228.0997.



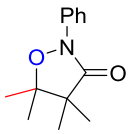
4

Isoxazolidinone **4** was prepared from hydroxamic acid **3** (20.9 mg, 0.100 mmol) according to *Condition A*. The reaction was deemed complete by TLC after 42 hours. The crude product was purified by silica gel flash chromatography (5:1 hexane:Et_2O) to afford **16** (16.8 mg, 0.0773 mmol, 77% yield) as a clear oil. Analytical data for **16**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73 (m, 2 H), 7.36 (m, 2 H), 7.13 (m, 1 H), 4.71 (dd, *J* = 1, 5 Hz, 1 H), 2.33 (m, 1 H), 2.15 (m, 1 H), 1.93 (m, 1 H), 1.83 (m, 2 H), 1.60 (m, 1 H), 1.42 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 170.9, 137.0, 128.7, 124.5, 116.7, 89.5, 55.2, 38.1, 33.8, 24.5, 21.4; IR (Thin film, cm^{-1}): 2963, 1696, 1595, 1496, 1369, 1307, 951, 752, 689; HRMS (ESI) Calc. for $[C_{13}H_{15}NO_2+Na]^+$ = 240.1000, Found =240.0997.



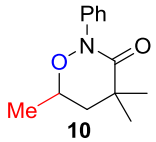
6

Isoxazolidinone **6** was prepared from hydroxamic acid **5** (122.0 mg, 0.5 mmol) according to *Condition B*. The reaction was deemed complete by TLC after 24 hours. The crude product was purified by silica gel flash chromatography (8:1 hexane:Et_2O) to afford **6** (107.8 mg, 0.439 mmol, 88% yield) as a clear, viscous oil. Analytical data for **6**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 1, 8.7 Hz, 2 H), 7.35 (m, 2 H), 7.11 (m, 1 H), 2.04 (m, 1 H), 2.04 (m, 1 H), 1.82 (m, 1 H), 1,69 (m, 1 H), 1.48 (m, 1 H), 1.37 (m, 6 H), 1.19 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.9, 137.9, 128.7, 124.1, 116.3, 86.0, 49.2, 33.5, 31.7, 22.6, 22.1, 19.6, 18.7; IR (Thin film, cm^{-1}): 2936, 1704, 1596, 1496, 1460, 1388, 1366, 1305, 1184, 867, 751, 689; HRMS (ESI) Calc. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.1313, Found = 268.1308.



8

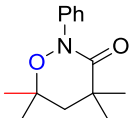
Isoxazolidinone **8** was prepared from hydroxamic acid **7** (109.4 mg, 0.5 mmol) according to *Condition B*. The reaction was deemed complete by TLC after 24 hours. The crude product was purified by silica gel flash chromatography (8:1 hexane:Et_2O) to afford **8** (92.7 mg, 0.423 mmol, 85% yield) as a clear, viscous oil. Analytical data for **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (m, 2 H), 7.36 (m, 2 H), 7.11 (m, 1 H), 1.36 (s, 6 H), 1.19 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 137.6, 128.7, 124.2, 116.4, 86.4, 49.1, 21.3, 19.3; IR (Thin film, cm^{-1}): 2978, 1704, 1596, 1496, 1394, 1361, 1137, 869, 752, 689; HRMS (ESI) Calc. for $[C_{13}H_{17}NO_2+Na]^+$ = 242.1157, Found = 242.1151.



10

Isoxazolidinone **10** was prepared from hydroxamic acid **9** (22.0 mg, 0.100 mmol) according to *Condition A,* with the exception that 1.6 equivalents of **7** (26.7 mg, 0.160 mmol) were used. After 42 hours, the reaction was stopped due to lack of progression. The crude product was purified by silica gel flash

chromatography (5:1 hexane:Et_2O) to afford **10** (7.1 mg, 0.0324 mmol, 32% yield) as a clear oil. Analytical data for **10**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 1, 8.7 Hz, 2 H), 7.35 (m, 2 H), 7.14 (m, 1 H), 4.42 (m, 1 H), 2.09 (dd, *J* = 7, 13.6 Hz, 1 H), 1.82 (dd, *J* = 8.4, 13.6 Hz, 1 H), 1.43 (s, 3 H), 1.41 (d, *J* = 6.4 Hz, 3 H), 1.34 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.7, 139.8, 128.5, 124.9, 119.4, 76.6, 44.6, 39.2, 27.3, 26.3, 20.7; IR (Thin film, cm^{-1}): 2975, 2930, 1682, 1595, 1494, 1389, 1349, 1300, 753, 690, 507; HRMS (ESI) Calc. for $[C_{13}H_{17}NO_2+Na]^+$ = 242.1157, Found = 242.1154.

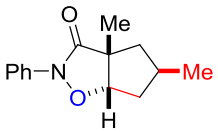


12

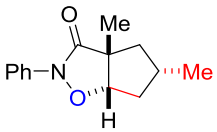
Isoxazolidinone **12** was prepared from hydroxamic acid **11** (23.5 mg, 0.100 mmol) according to *Condition A*. The reaction was deemed complete by TLC after 51 hours. The crude product was purified by silica gel flash chromatography (10:1 hexane:Et_2O) to afford **12** (16.6 mg, 0.0711 mmol, 71% yield) as a clear oil. Analytical data for **12**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (dd, *J* = 1, 8.7 Hz, 2 H), 7.34 (m, 2 H), 7.11 (m, 1 H), 1.91 (s, 2 H), 1.40 (s, 6 H), 1.36 (s, 6 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.0, 140.8, 128.4, 124.4, 118.8, 81.4, 48.9, 39.7, 28.2, 25.7; IR (Thin film, cm^{-1}): 2977, 2930, 1681, 1594, 1494, 1388, 1370, 1354, 1287, 754, 690; HRMS (ESI) Calc. for $[C_{14}H_{19}NO_2+Na]^+$ = 256.1313, Found = 256.1312.

E3.5 General Procedure for Cascade Cyclization Reactions

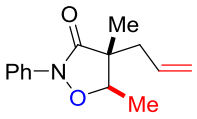
A 1-dram vial was charged with a magnetic stir bar, hydroxamic acid (0.10 mmol, 1 eq), and dilauroyl peroxide (2.0 mg, 0.005 mmol, 0.05 eq). The vial was sealed with a screw cap lined with a PTFE septum and transferred into an argon-filled glovebox. After allowing argon to displace the air in the vial and dissolving the reagents in benzene (1.0 mL), the vial was removed from the glove box and heated at 60 ºC. After TLC analysis indicated the completion of the reaction, solvent was removed in vacuo, and the residue was purified by column chromatography. Note: If the reaction was not complete after 24 hours, the reaction was re-initiated with an additional 2 mg (0.05 eq) of dilauroyl peroxide. This process was repeated until the reaction was deemed complete.



15a



15b



15c
(hydration by-product)

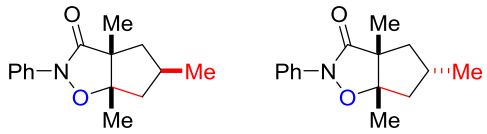
Carbocycle **15** was prepared from hydroxamic acid **14** (23.5 mg, 0.100 mmol) according to the general procedure. The reaction was deemed complete by TLC after 26 hours. The crude product was purified by silica gel flash chromatography (10 : 1 hexane : Et_2O) to afford the partially separable diastereomers **15a and 15b** (12.7 mg, 0.0549 mmol, 54% yield, 1.2 : 1 d.r.) as a clear oil. A third product, presumably the cyclohexane derived from a *5-exo*; *6-endo* cyclization, was also present and co-eluted with **15b**. The by-product stemming from hydration (**15c,** 4.1 mg, 0.0177 mmol, 17% yield) was also isolated.

Analytical data for **15a (major diastereomer)** : ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73 (m, 2 H), 7.36 (m, 2 H), 7.13 (m, 1 H), 4.70 (d, *J* = 5.1 Hz, 1 H), 2.44 (ddd, *J* = 6.5, 13.1 Hz, 1 H), 2.25 (m, 2 H), 1.56 (m, 1 H), 1.44 (s, 3 H), 1.21 (dd, *J* = 11.7, 13.2 Hz, 1 H), 1.03 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 170.7, 136.9, 128.7, 124.6, 116.7, 89.1, 55.7, 46.8, 42.8, 33.2, 22.2, 18.9; IR (Thin film, cm^{-1}): 2955, 2926, 2870, 1696, 1596, 1496, 1458, 1380, 752, 689; HRMS (ESI) Calc. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.1157, Found = 254.1154.

Analytical data for **15b** (minor diastereomer with byproduct): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 (m, 3.27 H), 7.36 (m, 3.23 H), 7.13 (m, 1.68 H), 4.65 (m, 1 H), 4.05 (dd, *J* = 3.7, 12.5 Hz, 0.67 H), 2.31 (m, 2.16 H), 2.00 (m, 0.69 H), 1.93 (m, 1.26 H), 1.90 (s, 0.95 H), 1.89 (m, 0.92 H), 1.80 (m, 0.79 H), 1.69 (m, 1.82 H), 1.56 (m, 2.09 H), 1.38 (s, 3 H), 1.22 (s, 1.78 H), 1.09 (d, *J* = 6.6 Hz), 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.0, 171.6, 137.7, 137.3, 128.7, 128.68, 124.5, 124.2, 116.7, 116.2, 90.4, 86.1, 55.1, 45.6, 44.3, 40.2, 33.4, 29.2, 23.5, 23.0, 20.7, 20.3, 19.8, 13.3; IR (Thin film, cm^{-1}): 2955, 2926, 2870, 1699, 1595, 1496, 1458, 1375, 1303, 751, 689. HRMS (ESI) Calc for $[C_{14}H_{17}NO_2+H]^+$ = 232.1338, Found = 232.1334.

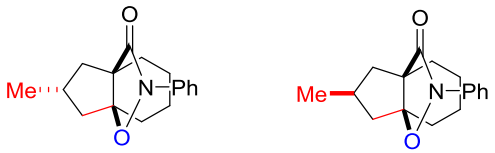
Analytical data for **15c** (hydration by-product): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73 (m, 2 H), 7.36 (m, 2 H), 7.13 (m, 1 H), 5.83 (m, 1 H), 5.15 (s, 1 H), 5.13 (m, 1 H), 4.51 (q, *J* = 6.4 Hz, 1 H), 2.49 (dd, *J* =

6.8, 14.1 Hz, 1 H), 2.33 (dd, J = 8, 14.2 Hz, 1 H), 1.34 (d, J = 6.2 Hz, 3 H), 1.18 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.0, 137.0, 132.7, 128.7, 124.5, 119.1, 116.4, 81.0, 49.2, 39.5, 15.9, 13.2; IR (Thin film, cm^{-1}): 3078, 2979, 2919, 1703, 1596, 1496, 1396, 1368, 1305, 920, 752, 689; HRMS (ESI) Calc. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.1157, Found = 254.1153.



17a (major diastereomer) **17b** (minor diastereomer)

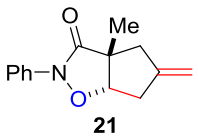
Carbocycle **17** was prepared from hydroxamic acid **16** (24.2 mg, 0.100 mmol) according to the general procedure. The reaction was deemed complete by TLC after 22 hours. The crude product was purified by silica gel flash chromatography (10:1 hexane:Et_2O) to afford **17** (19.9 mg, 0.0811 mmol, 82% yield, 2.9 : 1 d.r.) as a mixture of inseperable diastereomers. Analytical data for **17**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (m, 2.73 H), 7.36 (m, 2.72), 7.12 (m, 1.36), 2.45 (ddd, J = 1.7, 6.6, 13.4 Hz, 1 H), 2.29 (ddd, J = 1.7, 6.6, 13.8 Hz, 1 H), 2.20 (m, 1.69 H), 2.03 (m, 0.76 H), 1.86 (m, 0.72), 1.42 (m, 5.10), 1.25 (m, 6.49), 1.06 (d, J = 6.6 Hz, 1.11 H), 0.99 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.2, 171.1, 137.5, 137.0, 128.7, 128.6, 124.4, 116.7, 116.6, 94.4, 92.9, 56.5, 56.3, 48.9, 47.7, 46.1, 45.0, 31.8, 31.1, 29.7, 20.8, 20.6, 19.4, 19.2, 18.8, 17.4; IR (Thin film, cm^{-1}): 2954, 2927, 2871, 1696, 1596, 1496, 1460, 1387, 1370, 1320, 1308, 1144, 901, 851, 752, 689; HRMS (ESI) Calc. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.1313, Found = 268.1311.



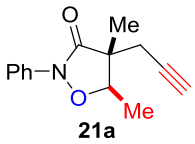
19a (major diastereomer) **19b** (minor diastereomer)

Carbocycle **19** was prepared from hydroxamic acid **18** (108.5 mg, 0.400 mmol) according to the general procedure on a 0.400 mmol scale. The reaction was deemed complete by TLC analysis after 22 hours. The crude product was purified by silica gel flash chromatography (10:1 hexane:Et_2O) to afford **19** (88.6 mg, 0.316 mmol, 82% yield, 2.7 : 1 d.r.) as an inseperable mixture of diastereomers. Analytical data for

19: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (m, 2.82 H), 7.36 (m, 2.82 H), 7.12 (m, 1.41), 2.39 (m, 2.46), 2.23 (m, 2 H), 2.11 (m, 0.76 H), 1.89 (m, 3.19 H), 1.78 (m, 0.76 H), 1.48 (m, 9.66 H), 1.11 (d, *J* = 6.6 Hz, 1.09 H), 1.05 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.7, 171.2, 137.9, 137.5, 128.7, 124.3, 124.2, 116.6, 116.5, 94.5, 93.4, 56.4, 56.2, 45.8, 45.1, 43.8, 43.1, 32.4, 31.4, 30.92, 30.90, 30.4, 28.7, 21.9, 21.8, 21.4, 21.1, 21.0, 20.8; IR (Thin film, cm^{-1}): 2934, 2861, 1699, 1596, 1496, 1458, 1372, 1320, 1306, 1186, 1142, 1047, 959, 861, 751, 689; HRMS (ESI) Calc. for $[C_{17}H_{21}NO_2+Na]^+$ = 294.1470, Found = 294.1468.



21



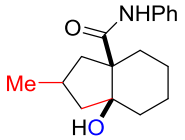
21a
(Hydration by-product)

Carbocycle **21** was prepared from hydroxamic acid **20** (22.6 mg, 0.100 mmol) according to the general procedure. The reaction was deemed complete by TLC after 72 hours. The crude product was purified by silica gel flash chromatography (10:1 hexane:Et_2O) to afford **21** (9.3 mg, 0.0406 mmol, 41% yield) as a clear oil. The hydration by-product (**21a**) and other inseparable, unidentified isomers were present as inseperable by-products. Analytical data for **21** and **21a**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.72 (m, 3.15 H, 7.37 (m, 3.43 H), 7.14 (m, 1.59), 4.97 (s, 2 H), 4.72 (dd, *J* = 2.0, 5.3 Hz, 1 H), 4.67 (q, *J* = 6.2 Hz, 0.35 H), 2.92 (dd, *J* = 1.8, 16.5 Hz, 1 H), 2.77 (m, 2 H), 2.57 (dd, *J* = 2.8, 18.9 Hz, 0.93 H), 2.41 (m, 1.36 H), 2.08 (t, *J* = 2.8 Hz, 0.34 H), 1.45 (d, *J* = 6.2 Hz, 1.05 H), 1.39 (s, 3 H), 1.27 (s, 1.12 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 170.7, 169.9, 146.6, 137.1, 136.8, 128.7, 128.68, 124.7, 124.6, 116.6, 116.5, 109.1, 89.0, 82.0, 81.7, 71.9, 54.4, 42.6, 38.3, 25.2, 24.8, 19.9, 15.2, 13.4; IR (Thin film, cm^{-1}): 3297, 3076, 2927, 1704, 1595, 1496, 1459, 1371, 1305, 1197, 1156, 1043, 1007, 897, 814, 752, 689; HRMS (ESI) Calc. for $[C_{14}H_{15}NO_2+Na]^+$ = 252.1000, Found = 252.0997.

E3.6 General Procedure for Hydrogenation of the Isoxazolidinone N-O Bond

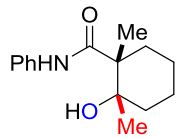
To a solution of isoxazolidinone (0.1 mmol, 1 eq) in absolute ethanol (1 mL) was added palladium on carbon (5.3 mg of 10% Pd^0/C, 0.005 mmol, 5 mol%). The reaction vessel was evacuated and refilled with hydrogen gas three times before being allowed to magnetically stir at room temperature overnight under 1

atm of hydrogen. The reaction mixture was diluted with dichloromethane and filtered through a plug of Celite. After rinsing the plug with dichloromethane, the filtrate was concentrated in vacuo, and the residue was purified by silica gel flash chromatography.[16]



27

Alcohol **27** was prepared through hydrogenation of isoxazolidinone **19** (26.8 mg, 0.100 mmol) according to the standard hydrogenation procedure. The crude product was purified by silica gel flash chromatography (3:1 hexane:EtOAc) to afford **27** (25.4 mg, 0.0929 mmol, 93% yield, 2.8 : 1 d.r.) as a viscous, clear oil. Analytical data for **27**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17 (s (br), 1.34 H), 7.49 (m, 2.76 H), 7.32 (m, 2.77), 7.10 (m, 1.39 H), 3.67 (s, 1 H), 3.46 (s, 0.36 H), 2.55 (m, 2.00 H), 2.38 (m, 0.36 H), 2.30 (m, 0.42 H), 2.10 (m, 1.00 H), 2.04 (m, 0.75 H), 1.84 (m, 6.66 H), 1.65 (s, 0.33 H), 1.56 (m, 2.44 H), 1.38 (m, 5.33 H), 1.15 (d, *J* = 6.6 Hz, 1.10 H), 1.12 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 175.7, 175.3, 137.8, 128.9, 124.3, 120.3, 120.26, 83.1, 82.8, 57.4, 56.4, 44.5, 44.4, 44.1, 43.8, 36.5, 34.83, 34.81, 33.7, 28.6, 28.1, 23.9, 23.7, 23.1, 22.9, 22.3; IR (Thin film, cm^{-1}): 3274(br), 2932, 2865, 1651, 1597, 1550, 1500, 1444, 1322, 995, 909, 754, 691; HRMS (ESI) Calc. for $[C_{17}H_{23}NO_2+Na]^+$ = 296.1626, Found = 296.1624.

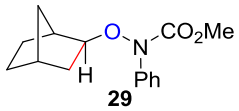


28

Alcohol **28** was prepared through hydrogenation of isoxazolidinone **6** (24.5 mg, 0.100 mmol) according to the standard hydrogenation procedure. The crude product was purified by silica gel flash chromatography (3:1 hexane:EtOAc) to afford **28** (20.6 mg, 0.0833 mmol, 83% yield) as a yellow oil. Analytical data for **28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.04 (br. s, 1 H), 7.52 (dd, *J* = 1, 8.5 Hz, 2 H), 7.32 (m, 2 H), 7.10 (m, 1 H), 3.52 (s, 1 H), 2.23 (m, 1 H), 1.7 (m, 3 H), 1.56 (m, 3 H), 1.46 (m, 1 H), 1.34 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.3, 138.1, 128.9, 124.1, 120.3, 74.1, 49.9,

37.0, 33.8, 25.7, 21.9, 21.2, 20.2; IR (Thin film, cm^{-1}): 3269(br), 2939, 2864, 1651, 1597, 1549, 1499, 1444, 1317, 1176, 1107, 1049, 755, 691; HRMS (ESI) Calc. for $[C_{15}H_{21}NO_2+Na]^+$ = 270.1470, Found = 270.1467.

E3.7 Procedure for Formal Hydration of Norborne



29

A 1-dram vial was charged with a magnetic stir bar, *N*-hydroxy carbamate **3** (40.1 mg, 0.239 mmol, 1 eq), and benzoyl peroxide (2.9 mg, 0.0120 mmol, 0.05 eq). The vial was sealed with a screw cap lines with a PTFE septum and transferred into an argon-filled glovebox. After allowing argon to displace the air in the vial, norbornene (112.6 mg, 1.20 mmol, 5 eq) and dichloroethane (0.24 mL) were added. The vial was removed from the glove box and heated at 70 ºC for four days. (After 24 and 48 hours, the reaction was dosed with an additional 0.05 equivalents of benzoyl peroxide.) The reaction was then concentrated, and the residue was purified by column chromatography (10 : 1 hexanes/EtOAc) to afford 21.4 mg (0.0819 mmol) of norbornane **29** as a clear oil (34% isolated yield). Analytical data for **29**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (m, 2 H), 7.35 (m, 2 H), 7.19 (m, 1 H), 3.98 (t, *J* = 4.7 Hz, 1 H), 3.81 (s, 3 H), 2.37 (d, *J* = 4.8 Hz, 1 H), 2.27 (s, 1 H), 1.60 (m, 1 H), 1.53 (m, 2 H), 1.43 (m, 2 H), 1.08 (d, *J* = 9.7 Hz, 1 H), 1.02 (m, 1 H), 0.93 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.0, 141.3, 128.5, 125.8, 122.7, 87.4, 53.4, 39.8, 37.1, 35.4, 34.9, 28.5, 24.0; IR (Thin film, cm^{-1}): 2956, 2871, 1717, 1595, 1494, 1439, 1338, 1302, 1254, 1191, 1155, 1104, 1073, 1047, 1026, 978, 918, 838, 757, 694, 668, 634; LRMS (ESI) Calc. for $[M+Na]^+$ = 284.13, Found = 284.08. The *exo* stereochemistry of the product was ascertained by hydrogenolysis of the N-O bond and comparing the crude spectra of the resulting product to literature chemical shifts for *exo*-norborneol.[17]

REFERENCES

[1] Patiny, L.; Borel, A. *J. Chem. Inf. Model.* **2013**, *53*, 1223.

[2] Evans, D. A.; Song, H. J.; Fandrick, K. R. *Org. Lett*. **2006**, *8*, 3351.

[3] Schmidt, V. A.; Alexanian, E.J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4491.

[4] Giglio, B.C.; Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 13320.

[5] Santos, P. F.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Heterocycles* **2001**, *55*, 1029.

[6] Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 11402.

[7] Hui, B. W.; Chiba, S. *Org. Lett.* **2009**, *11*, 729.

[8] Ramachandran, P. V.; Chen, G. M.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 88.

[9] Winfield, C. J.; Al-Mahrizy, Z.; Gravestock, M.; Bugg, T. D. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, *19*, 3277.

[10] Kato, M.; Kitahara, H.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 1647.

[11] Davis, C. E.; Duffy, B. C.; Coates, R. M. *J. Org. Chem.* **2003**, *68*, 6935.

[12] Aurell, M .J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron*, **1998**, *54*, 4357.

[13] Jomana, E.; Thaqi, A.; Prosser, A.; Jackson, W.R.; Robinson, A. J. *Tetrahedron: Asymmetry*, **2005**, *16*, 1309.

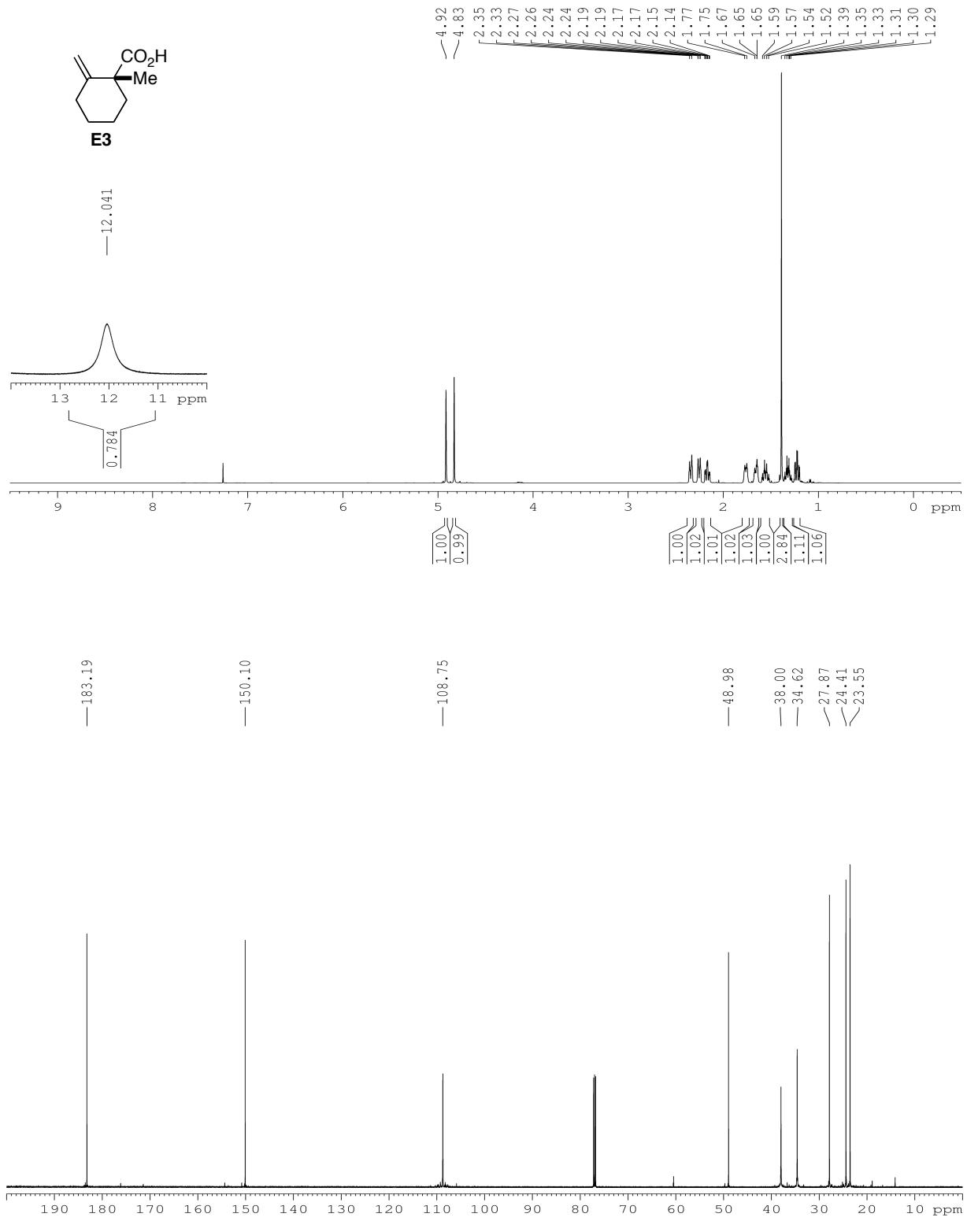
[14] Noda, H.; Motokura, K.; Miyaji, A.; Baba, T. *Adv. Synth. Catal.* **2013**, *355*, 973.

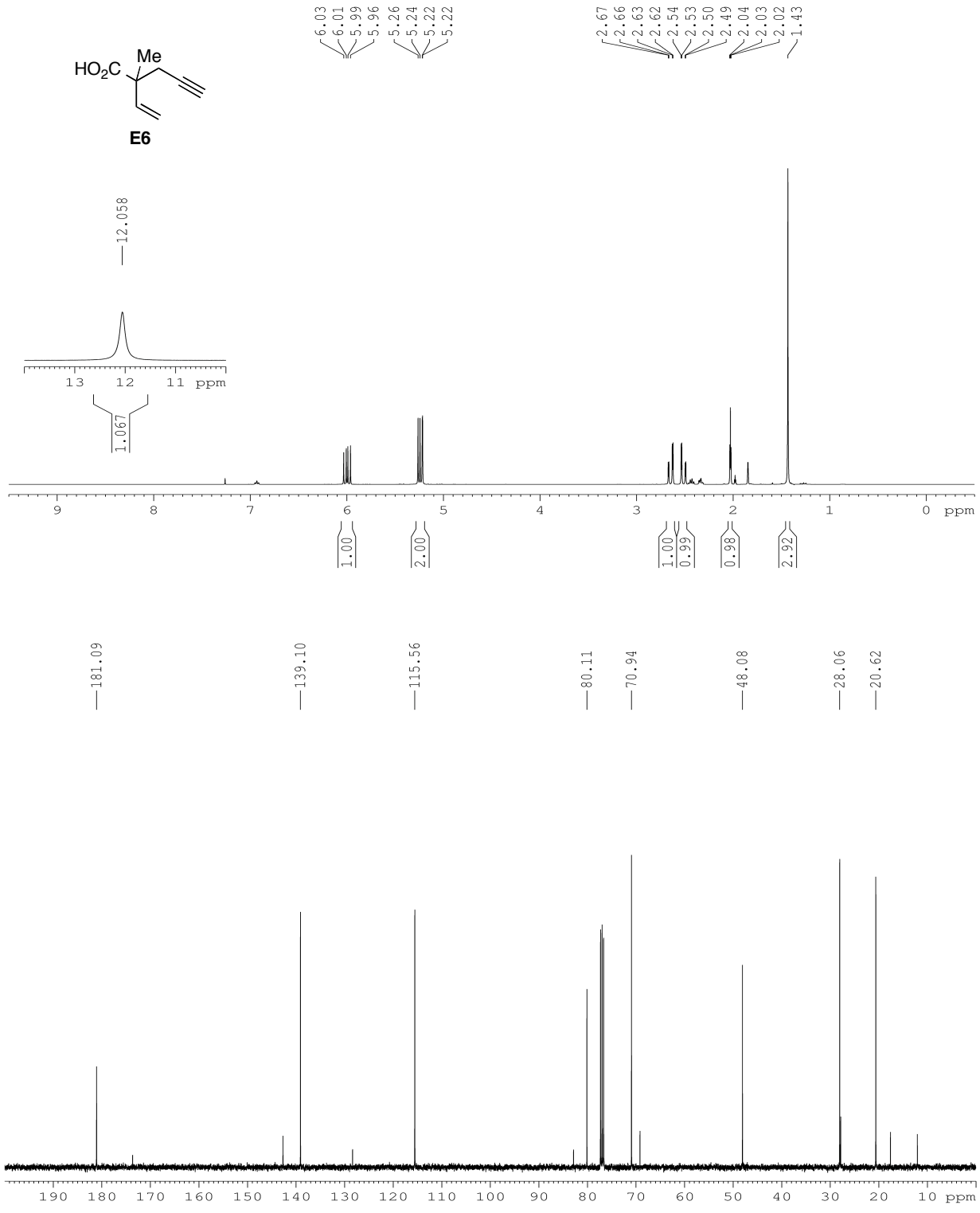
[15] Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.

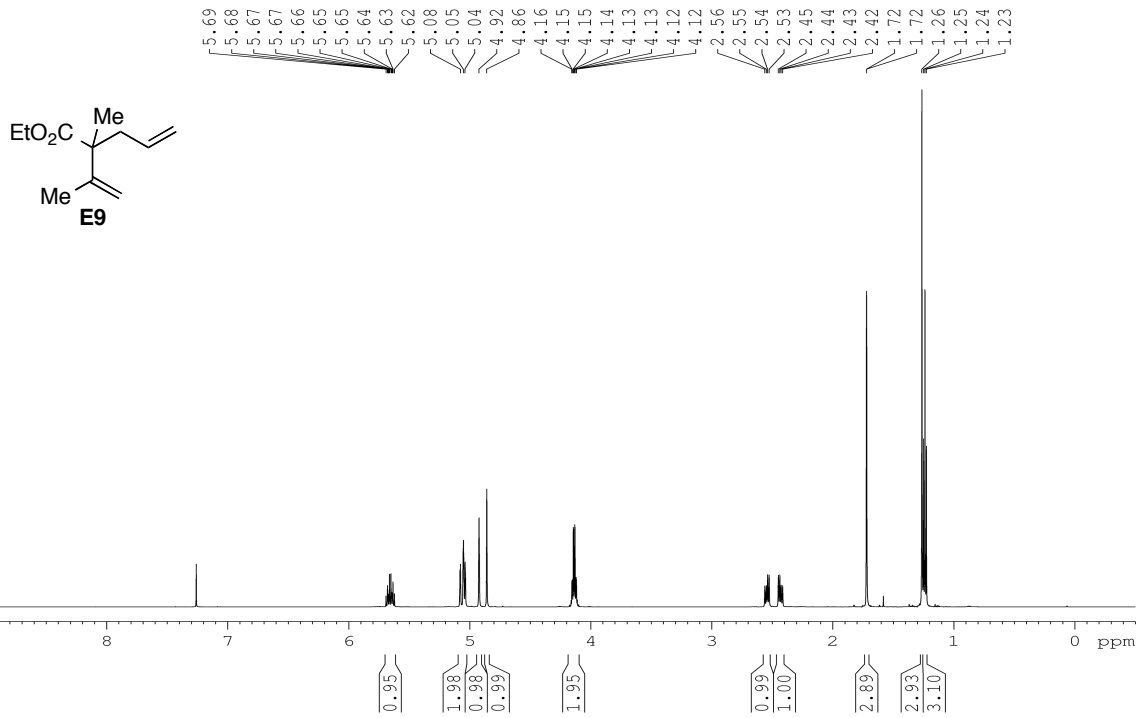
[16] Adapted from: Schmidt, V. A.; Alexanian, E. J. *Chem. Sci.* **2012**, *3*, 1672.

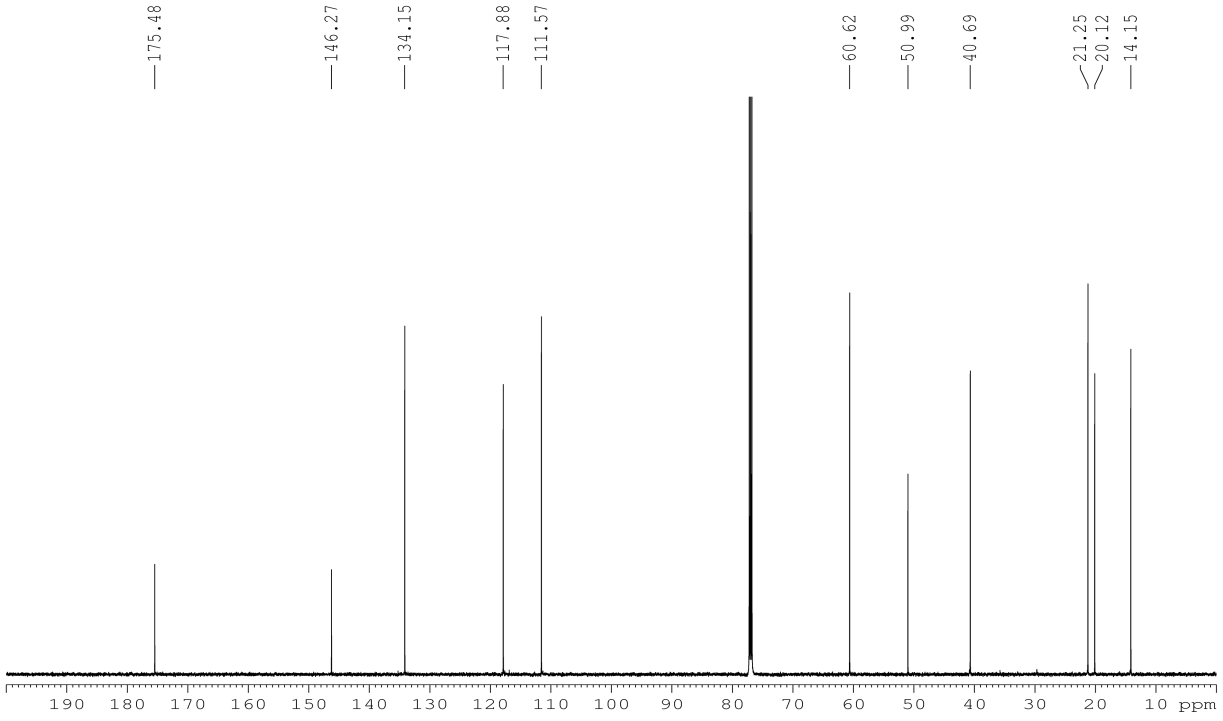
[17] Abraham, R. J.; Byrne, J. J.; Griffiths, L.; Perez, M. *Magn. Reson. Chem.* **2006**, *44*, 491.

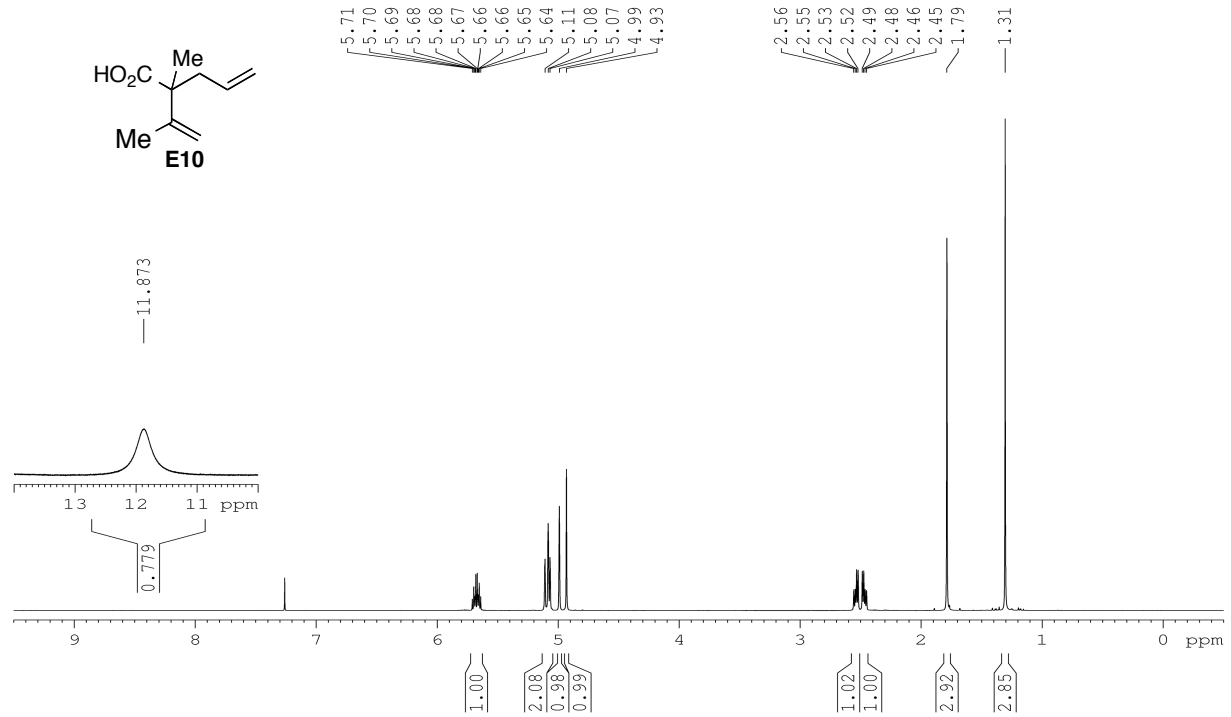
E3.9 Proton, carbon-13, and correlation spectroscopy spectra

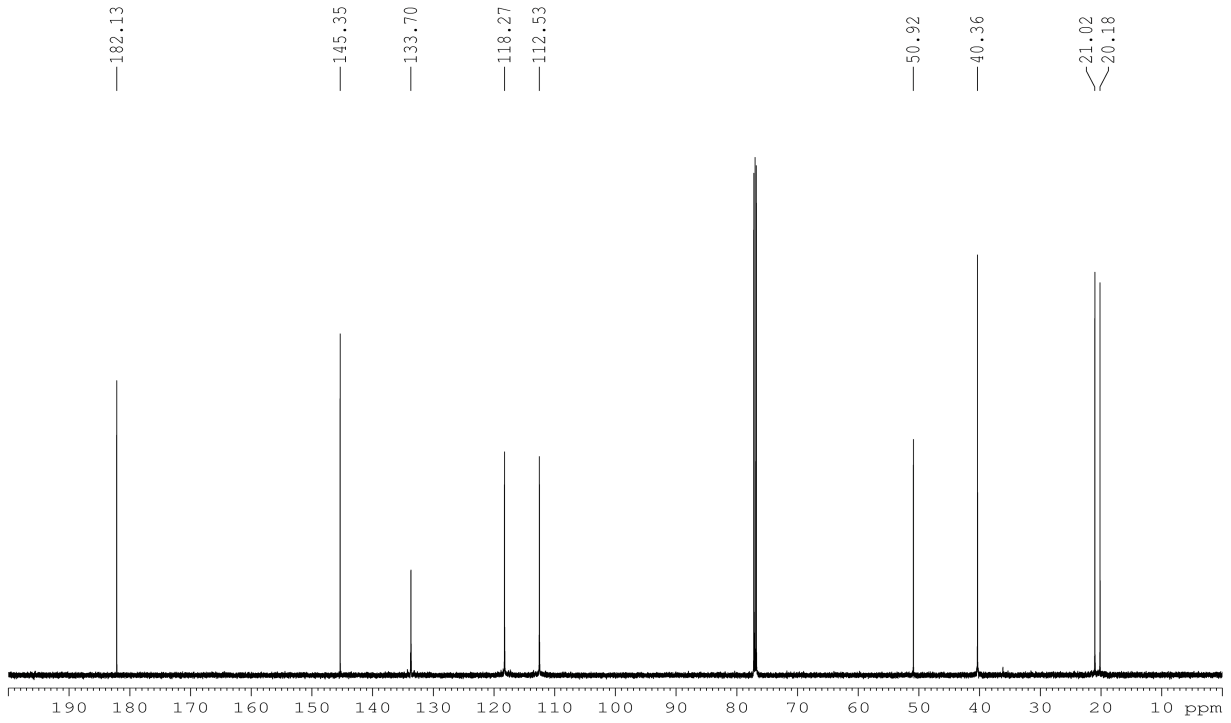

CO2H
Me
E3
4.92
4.83
2.35
2.33
2.27
2.26
2.24
2.24
2.19
2.19
2.17
2.17
2.15
2.14
1.77
1.75
1.67
1.65
1.65
1.59
1.57
1.54
1.52
1.39
1.35
1.33
1.31
1.30
1.29
12.041
13
12
11 ppm
0.784
9
8
7
6
5
4
3
2
1
0 ppm
1.00
0.99
1.00
1.02
1.01
1.02
1.03
1.00
2.84
1.11
1.06
183.19
150.10
108.75
48.98
38.00
34.62
27.87
24.41
23.55
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

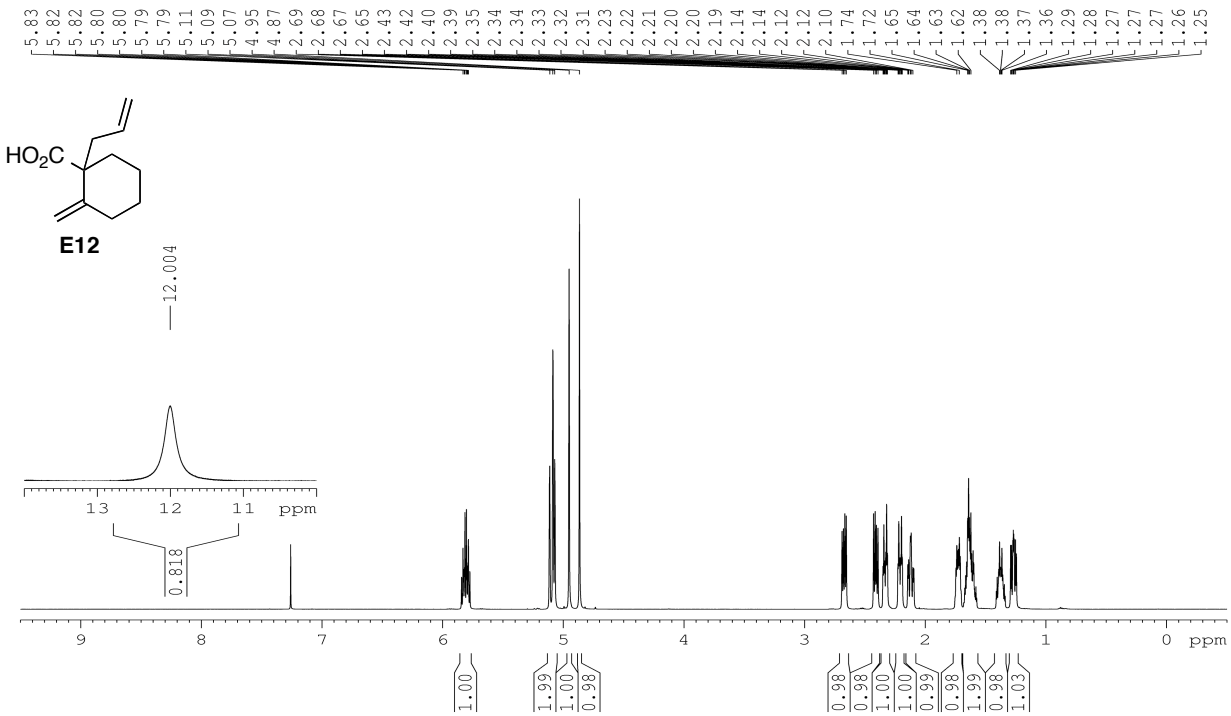

6.03
6.01
5.99
5.96
5.26
5.24
5.22
5.22
2.67
2.66
2.63
2.62
2.54
2.53
2.50
2.49
2.04
2.03
2.02
1.43
HO2C
Me
E6
12.058
13
12
11 ppm
1.067
9
8
7
6
5
4
3
2
1
0 ppm
1.00
2.00
1.00
0.99
0.98
2.92
181.09
139.10
115.56
80.11
70.94
48.08
28.06
20.62
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

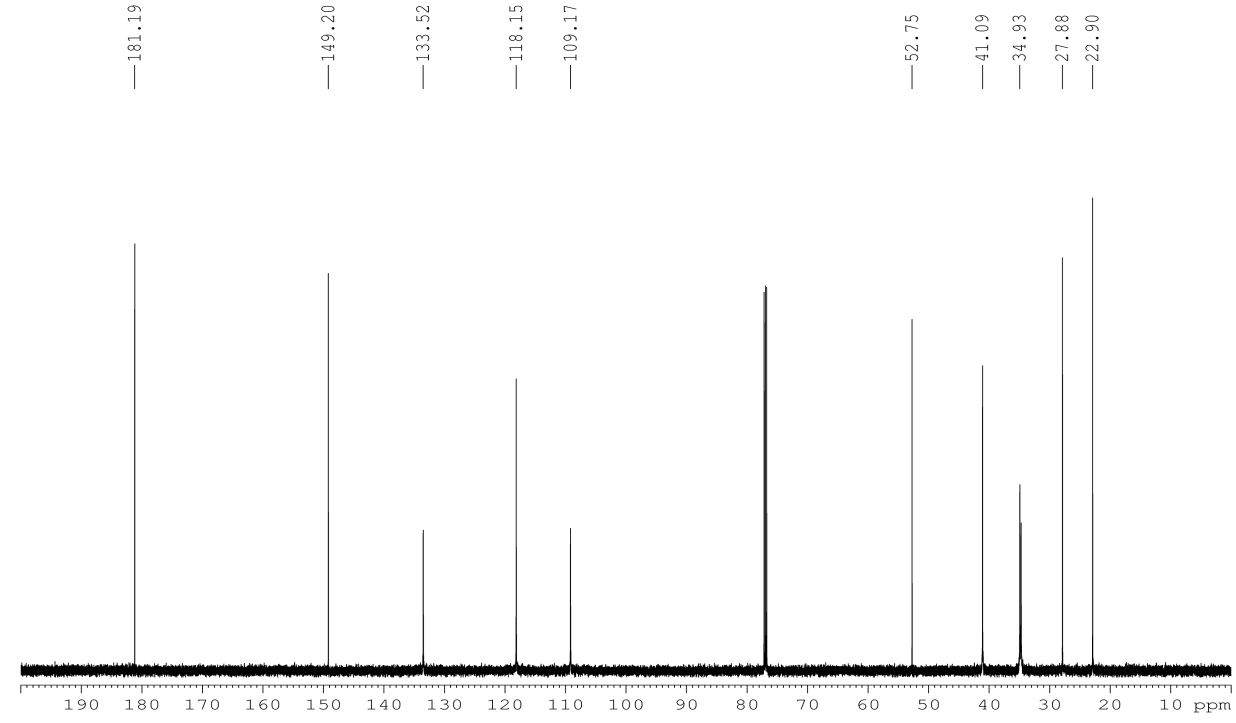

5.69
5.68
5.67
5.67
5.66
5.65
5.65
5.64
5.63
5.62
5.08
5.05
5.04
4.92
4.86
4.16
4.15
4.15
4.14
4.13
4.13
4.12
4.12
2.56
2.55
2.54
2.53
2.45
2.44
2.43
2.42
1.72
1.72
1.26
1.25
1.24
1.23
EtO2C
Me
Me
E9
9
8
7
6
5
4
3
2
1
0 ppm
0.95
1.98
0.98
0.99
1.95
0.99
1.00
2.89
2.93
3.10

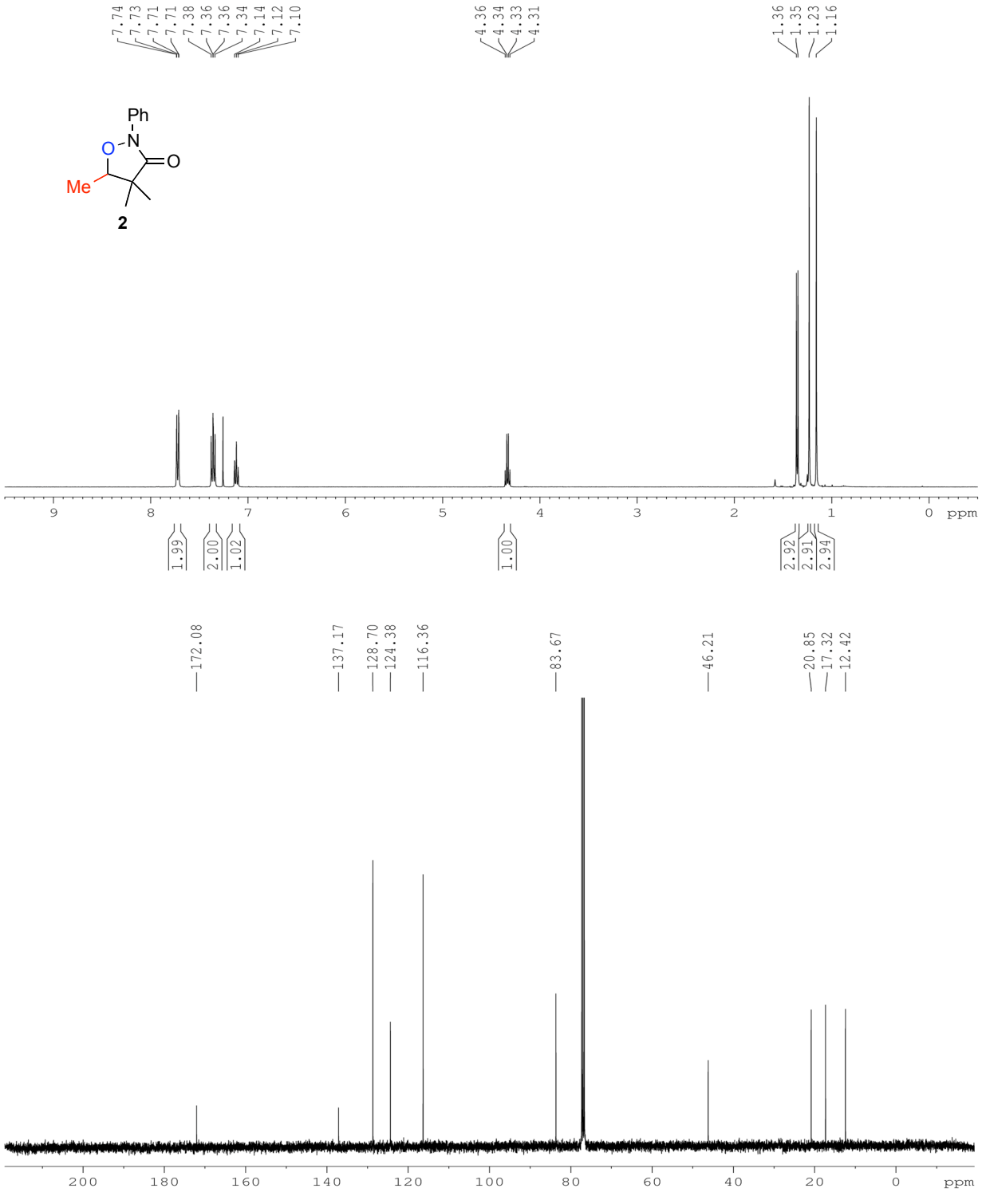

175.48
146.27
134.15
117.88
111.57
60.62
50.99
40.69
21.25
20.12
14.15
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

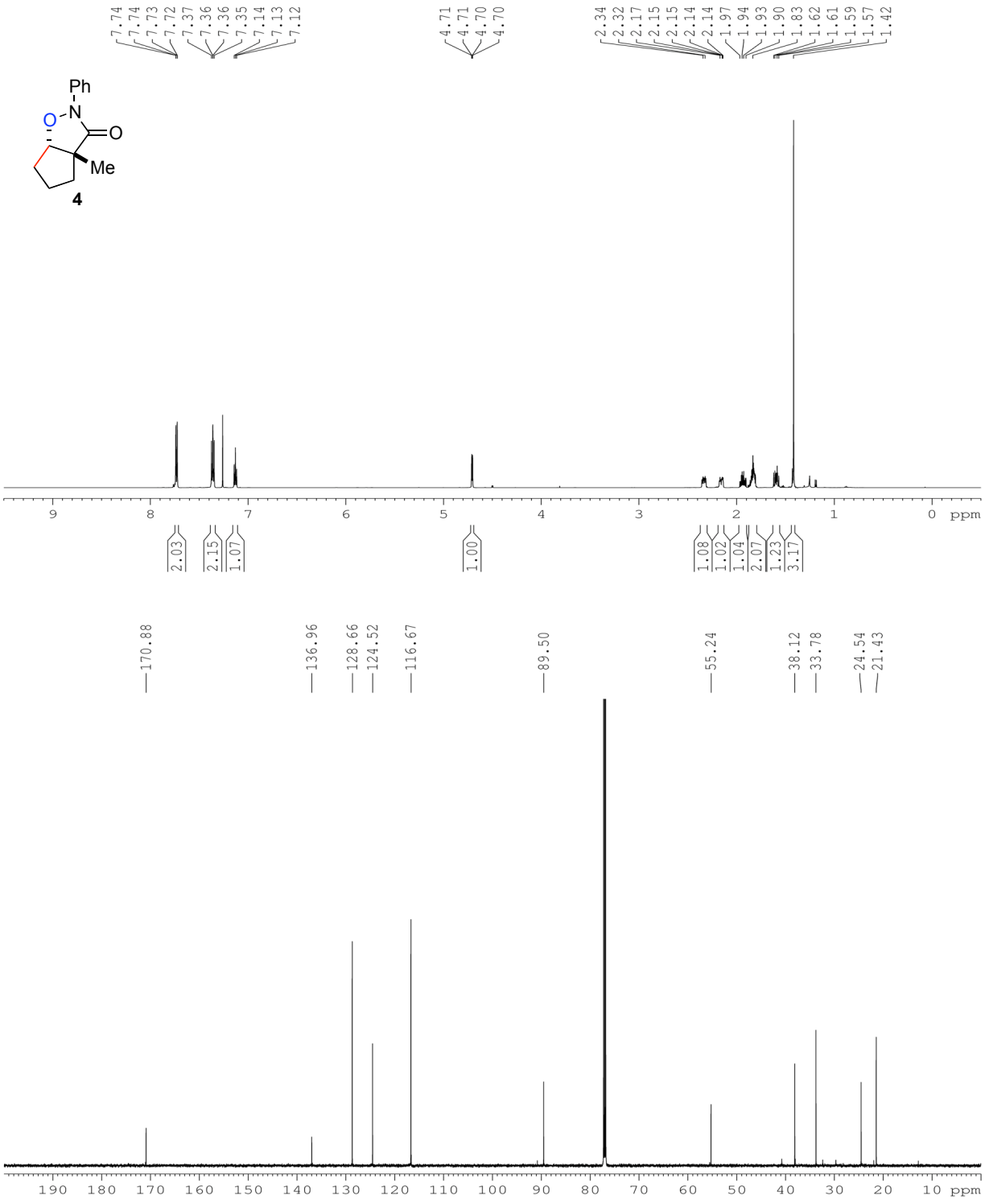

HO2C
Me
Me
E10
5.71
5.70
5.69
5.68
5.68
5.67
5.66
5.66
5.65
5.64
5.11
5.08
5.07
4.99
4.93
2.56
2.55
2.53
2.52
2.49
2.48
2.46
2.45
1.79
1.31
11.873
13
12
11 ppm
0.779
9
8
7
6
5
4
3
2
1
0 ppm
1.00
2.08
0.98
0.99
1.02
1.00
2.92
2.85

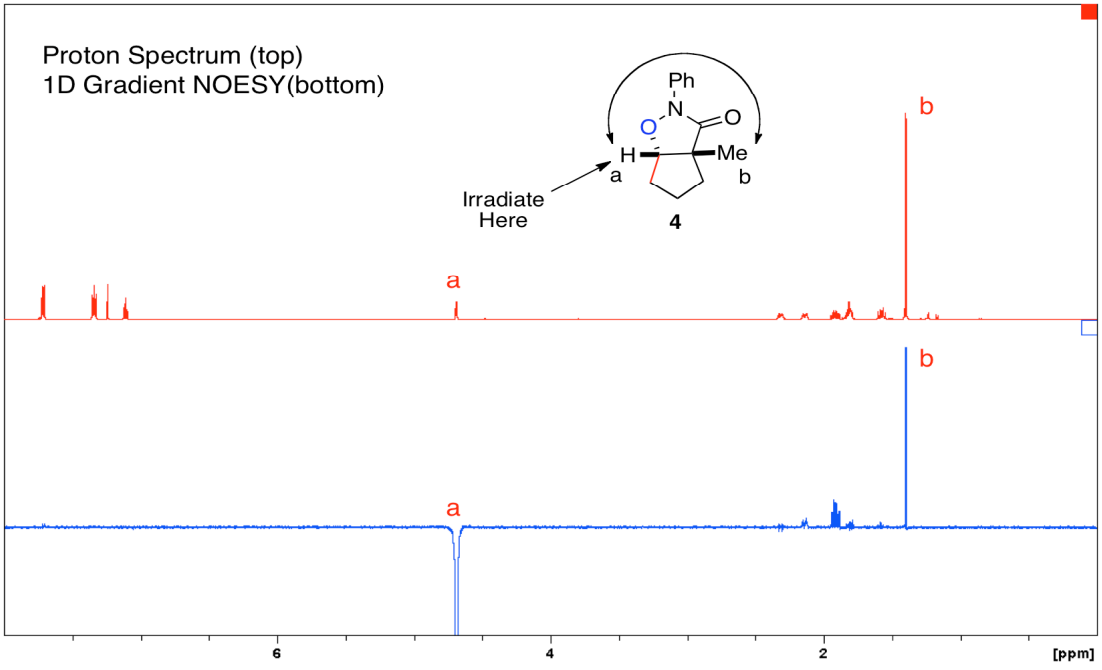

182.13
145.35
133.70
118.27
112.53
50.92
40.36
21.02
20.18
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

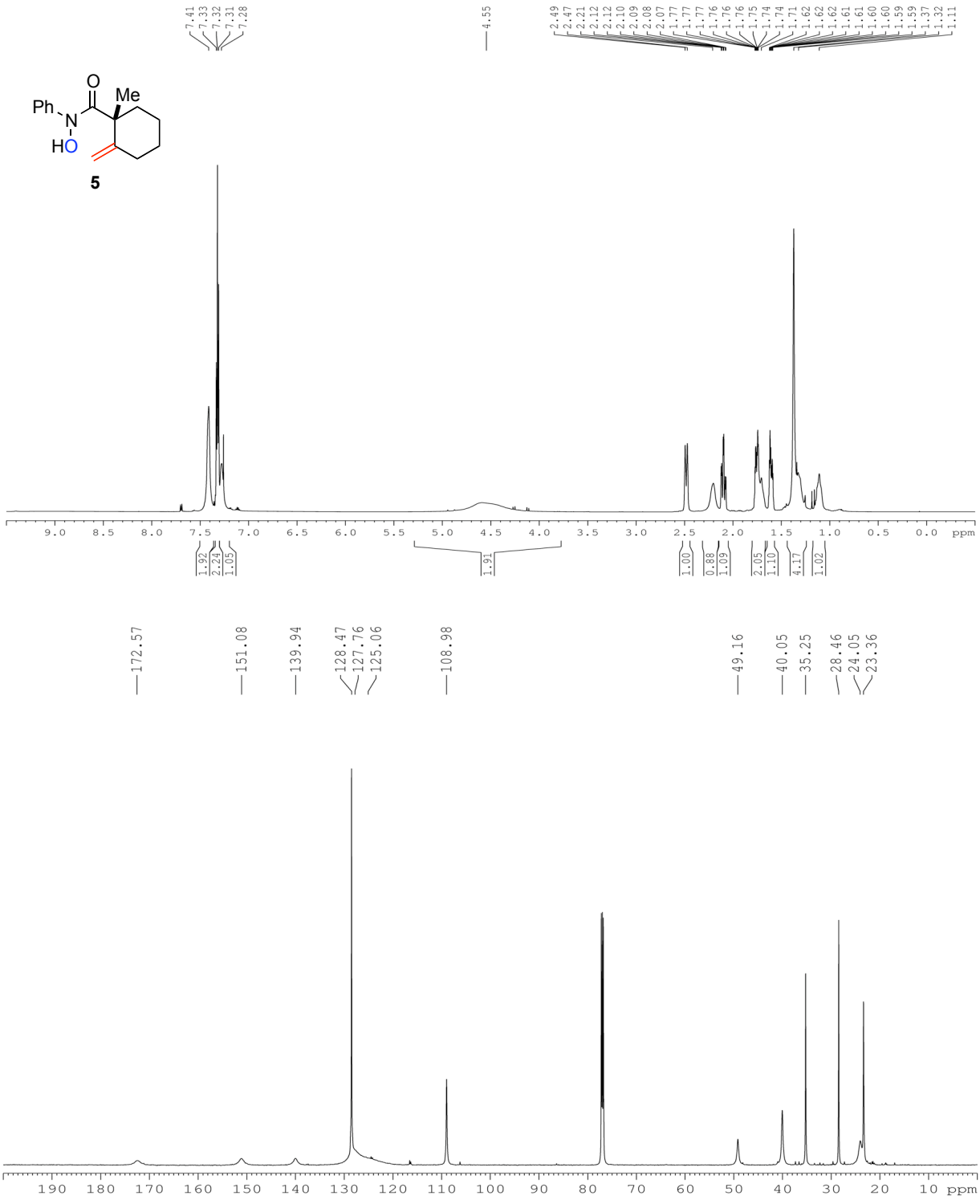

5.83 5.82 5.82 5.80 5.80 5.79 5.79 5.11 5.09 5.07 4.95 4.87 2.69 2.68 2.67 2.65 2.43 2.42 2.40 2.39 2.35 2.34 2.34 2.33 2.32 2.31 2.23 2.22 2.21 2.20 2.20 2.19 2.14 2.14 2.12 2.12 2.10 1.74 1.72 1.65 1.64 1.63 1.62 1.38 1.38 1.37 1.36 1.29 1.28 1.27 1.27 1.27 1.26 1.25
HO2C
E12
12.004
13 12 11 ppm
0.818
9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.99 1.00 0.98 0.98 0.98 1.00 1.00 0.99 0.98 1.99 0.98 1.03

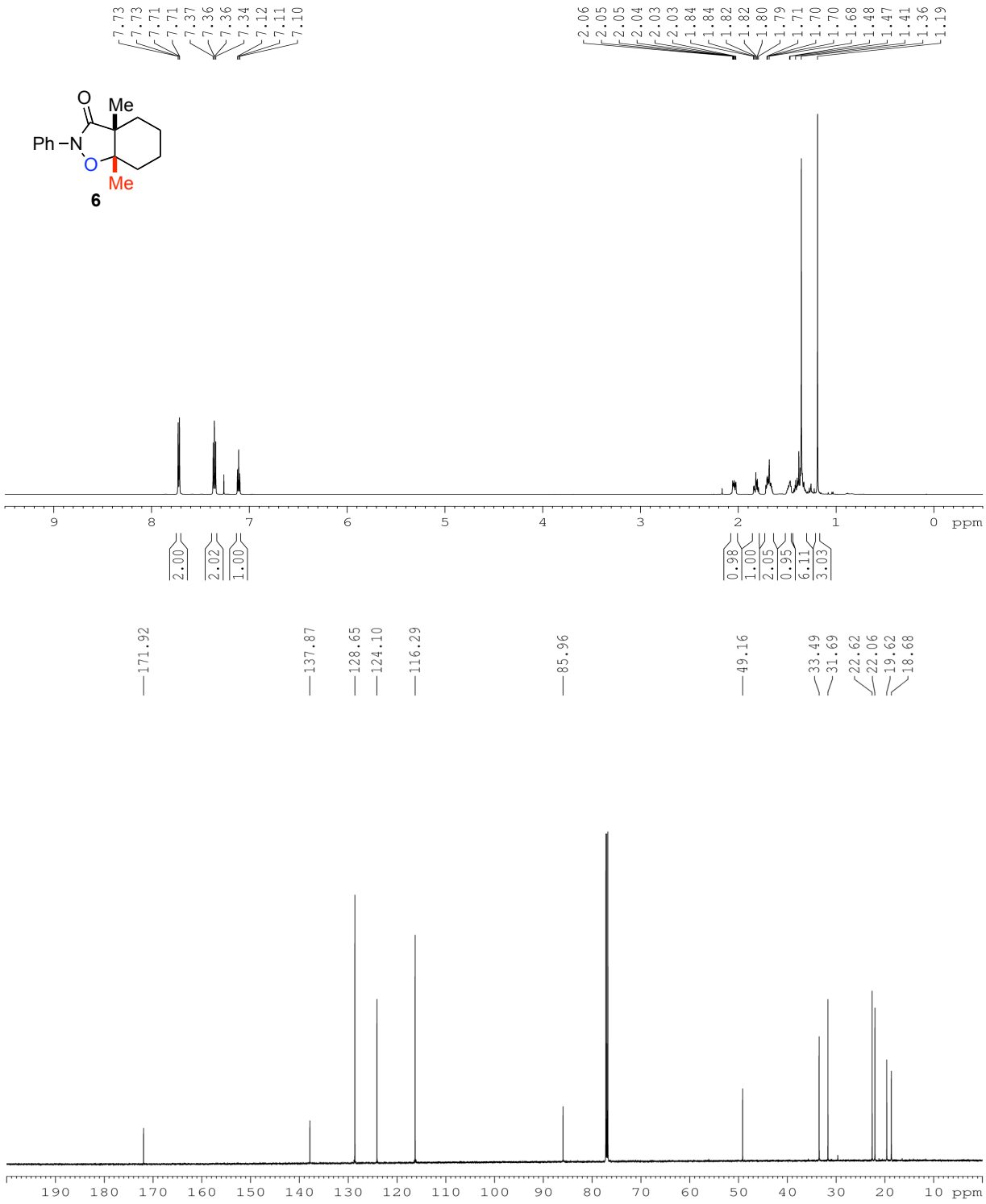

181.19 149.20 133.52 118.15 109.17 52.75 41.09 34.93 27.88 22.90
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

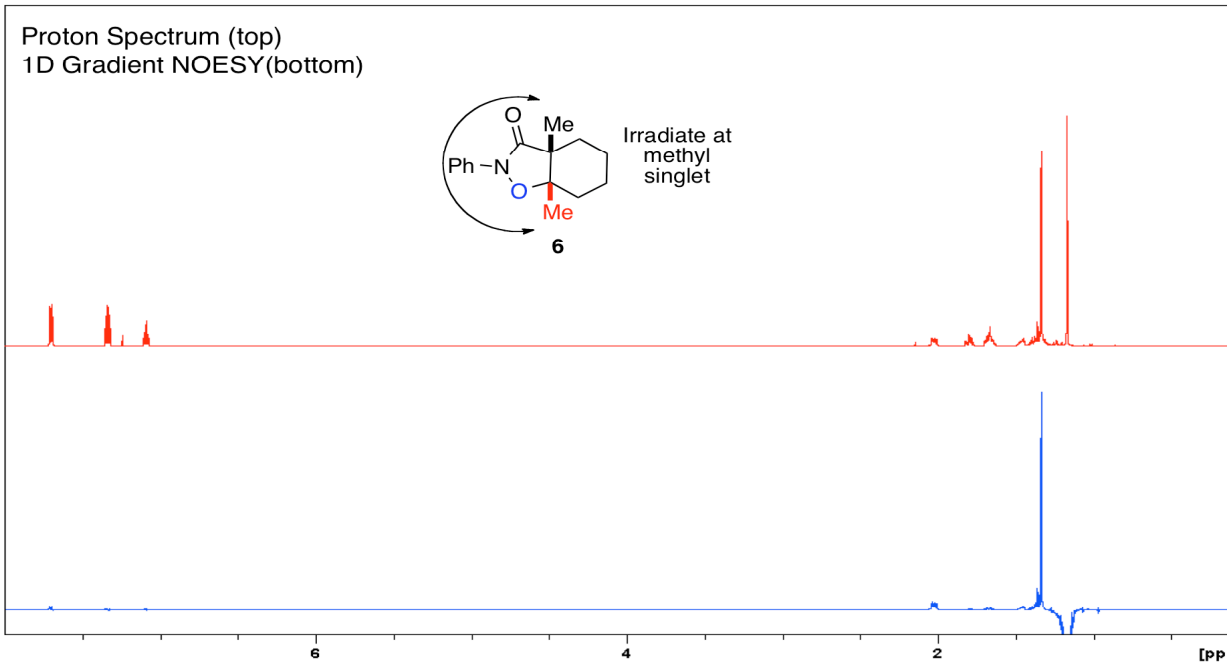

7.74
7.73
7.71
7.71
7.38
7.36
7.36
7.34
7.14
7.12
7.10
4.36
4.34
4.33
4.31
1.36
1.35
1.23
1.16
Ph
N
O
O
Me
2
9
8
7
6
5
4
3
2
1
0
ppm
1.99
2.00
1.02
1.00
2.92
2.91
2.94
172.08
137.17
128.70
124.38
116.36
83.67
46.21
20.85
17.32
12.42
200
180
160
140
120
100
80
60
40
20
0
ppm

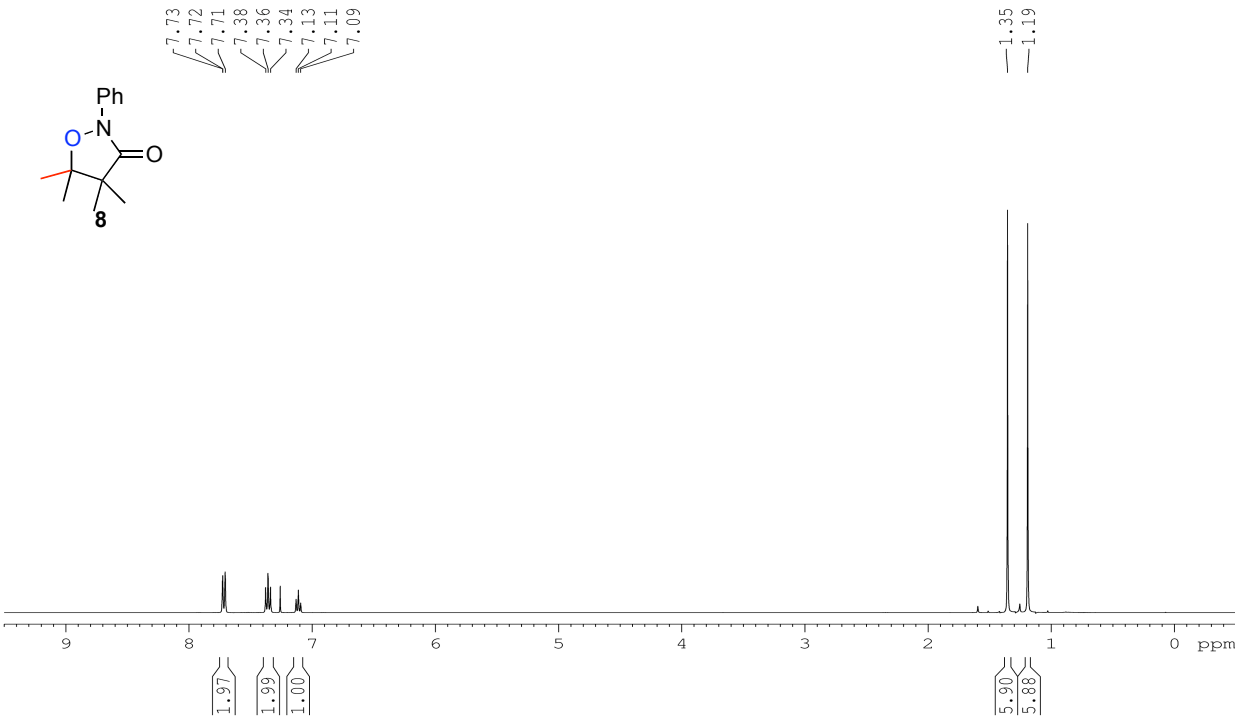

7.74
7.74
7.73
7.72
7.37
7.36
7.36
7.35
7.14
7.13
7.12
4.71
4.71
4.70
4.70
2.34
2.32
2.17
2.15
2.15
2.14
2.14
1.97
1.94
1.93
1.90
1.83
1.62
1.61
1.59
1.57
1.42
Ph
N
O
O
Me
4
9
8
7
6
5
4
3
2
1
0 ppm
2.03
2.15
1.07
1.00
1.08
1.02
1.04
2.07
1.23
3.17
170.88
136.96
128.66
124.52
116.67
89.50
55.24
38.12
33.78
24.54
21.43
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

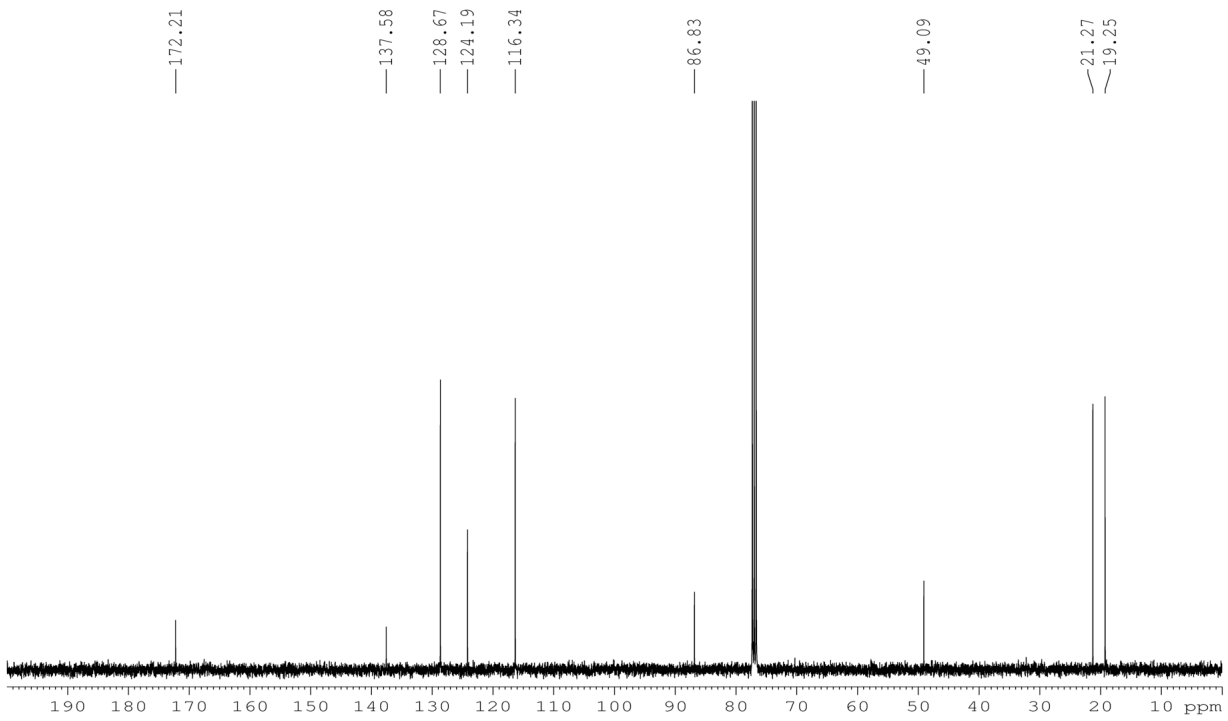

Proton Spectrum (top)
1D Gradient NOESY(bottom)
Ph
N
O
O
H
Me
a
b
Irradiate
Here
4
b
a
b
a
6
4
2
[ppm]

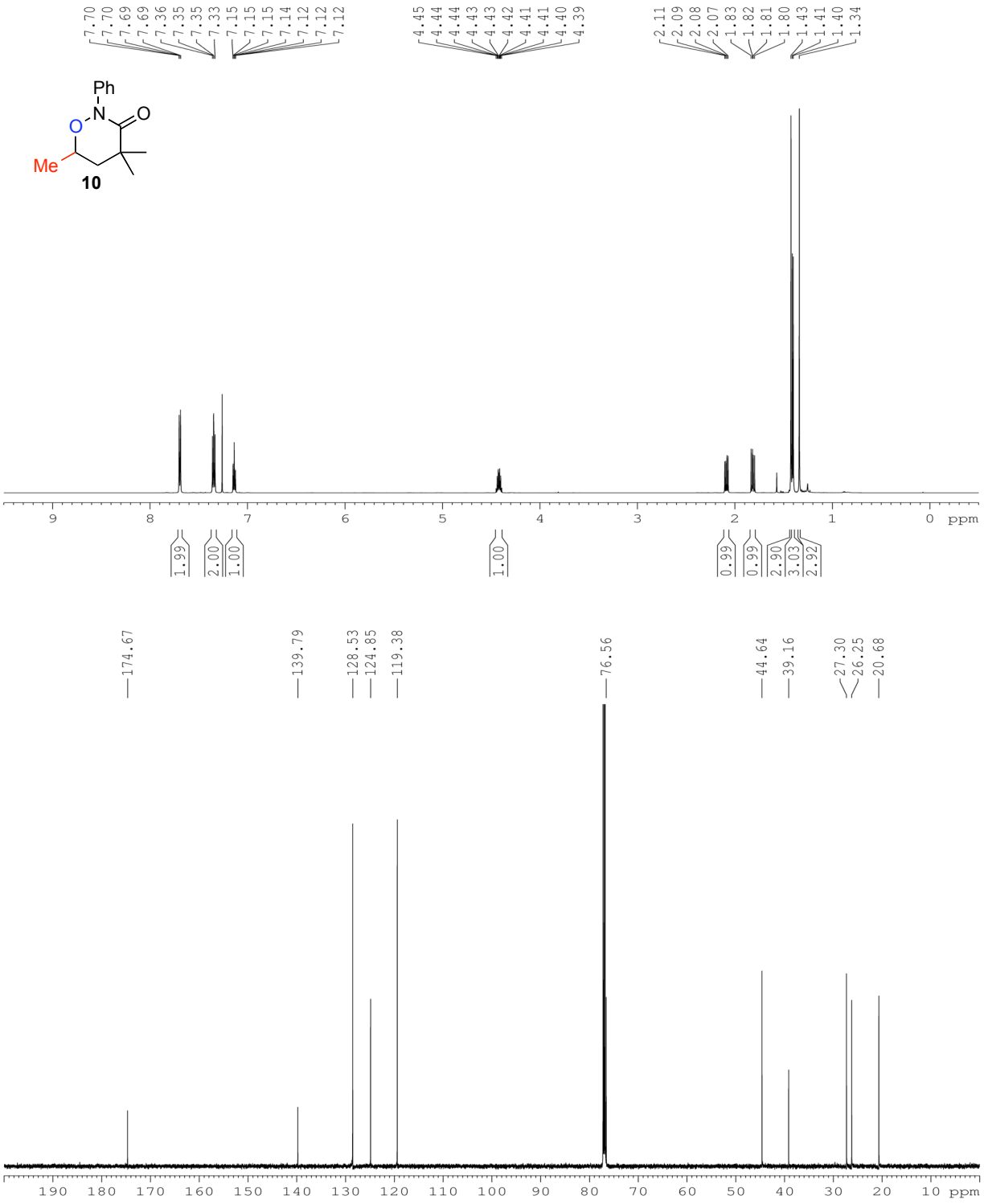

7.41
7.33
7.32
7.31
7.28
4.55
2.49
2.47
2.21
2.12
2.10
2.09
2.08
2.07
1.77
1.77
1.77
1.76
1.76
1.76
1.75
1.74
1.74
1.71
1.62
1.62
1.62
1.61
1.61
1.60
1.60
1.59
1.59
1.37
1.32
1.11
O
Me
Ph
N
HO
5
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.92
2.24
1.05
1.91
1.00
0.88
1.09
2.05
1.10
4.17
1.02
172.57
151.08
139.94
128.47
127.76
125.06
108.98
49.16
40.05
35.25
28.46
24.05
23.36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

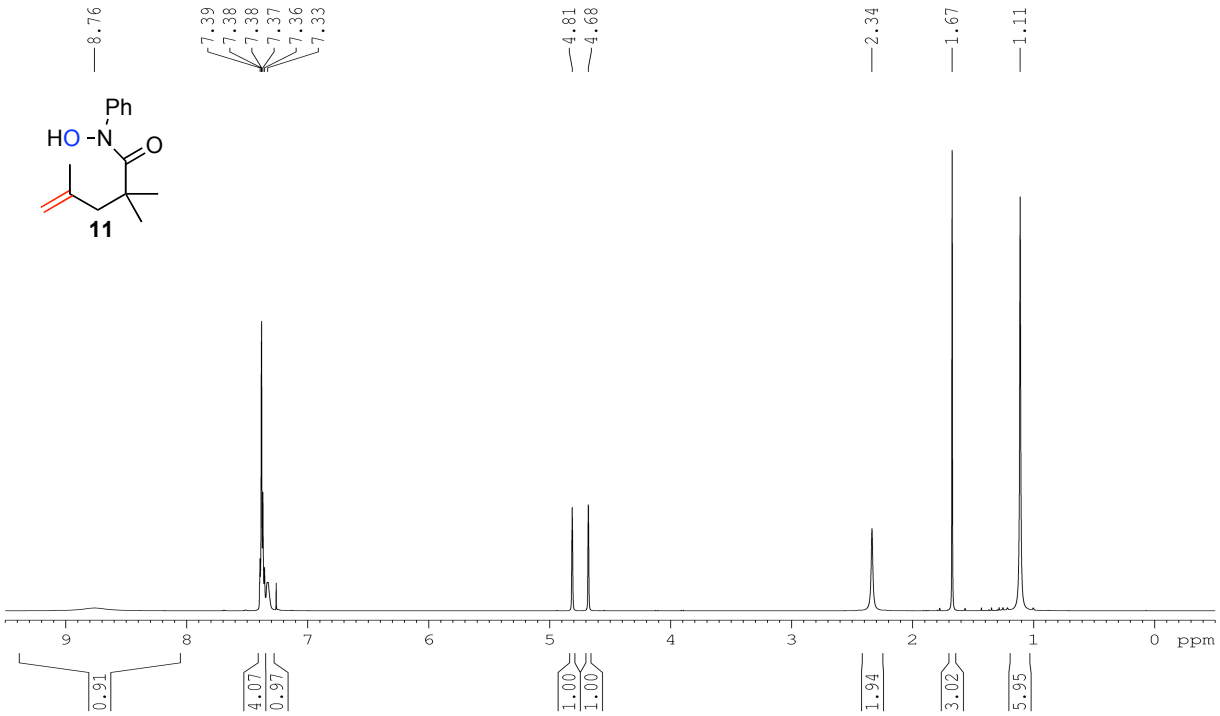

7.73
7.73
7.71
7.71
7.37
7.36
7.36
7.34
7.12
7.11
7.10
2.06
2.05
2.05
2.04
2.03
2.03
1.84
1.84
1.82
1.82
1.80
1.79
1.71
1.70
1.70
1.68
1.48
1.47
1.41
1.36
1.19
O
Me
Ph–N
O
Me
6
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.02
1.00
0.98
1.00
2.05
0.95
6.11
3.03
171.92
137.87
128.65
124.10
116.29
85.96
49.16
33.49
31.69
22.62
22.06
19.62
18.68
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

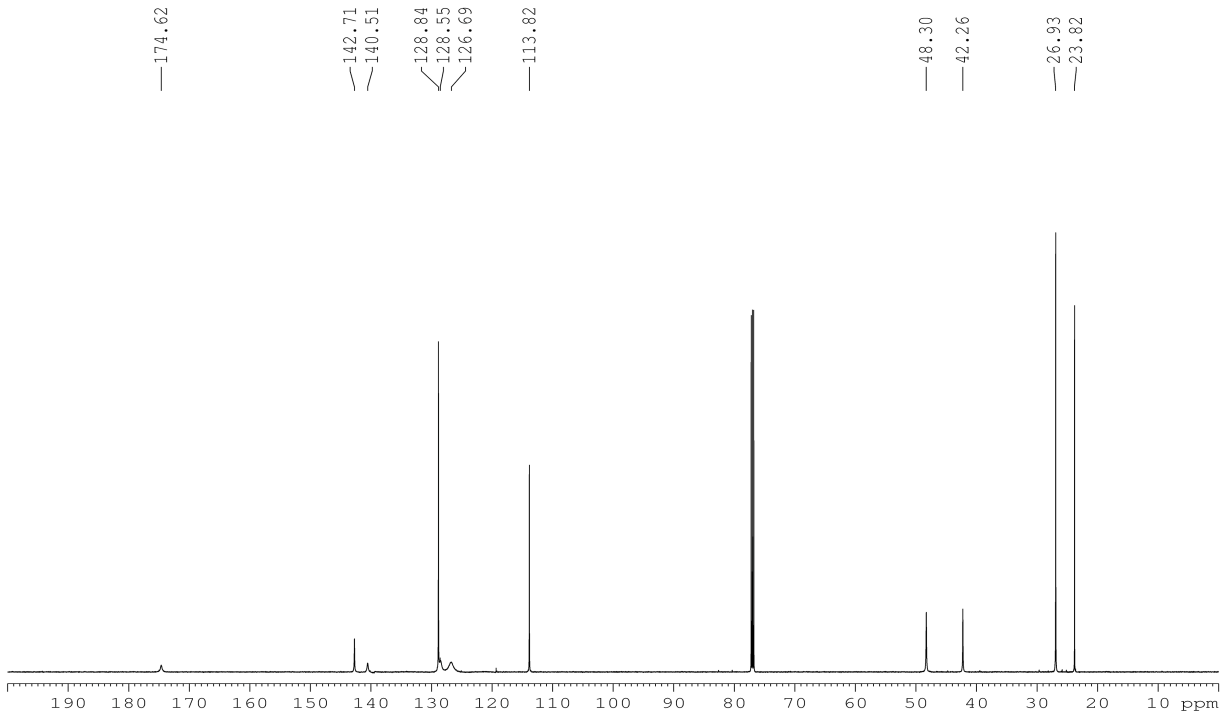

Proton Spectrum (top)
1D Gradient NOESY(bottom)
O
Me
Ph
N
O
Me
Irradiate at
methyl
singlet
6
6
4
2
[pp

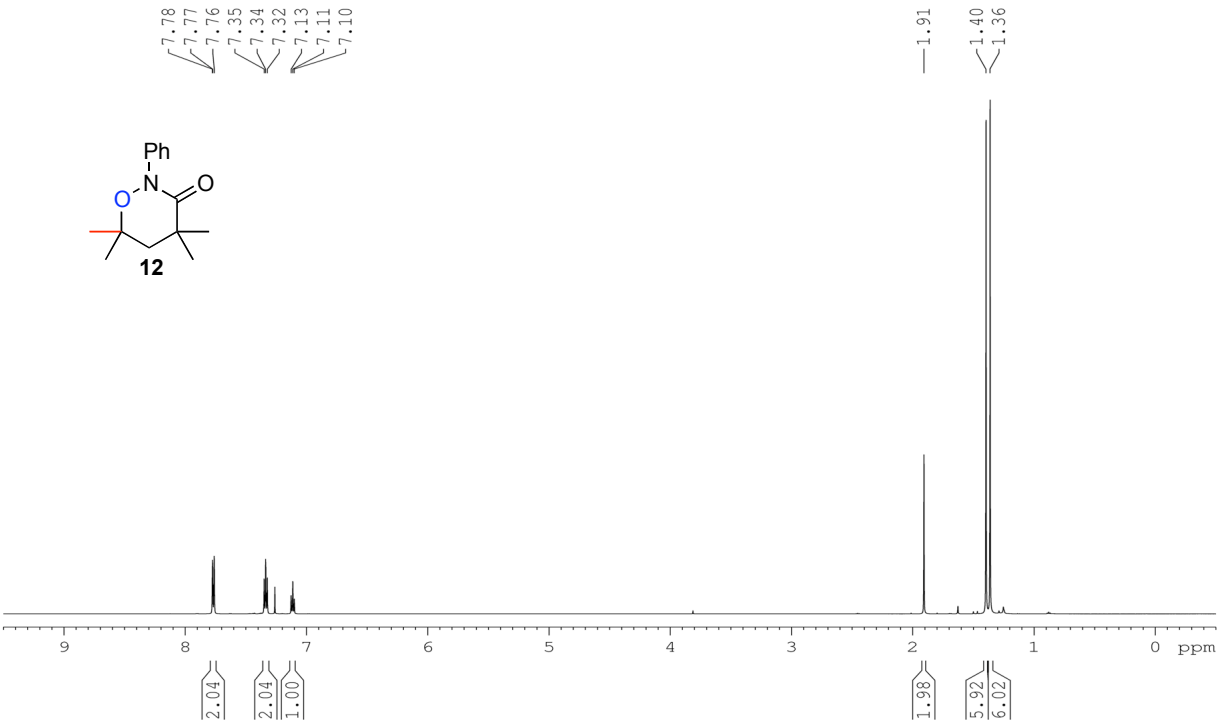

7.73
7.72
7.71
7.38
7.36
7.34
7.13
7.11
7.09
1.35
1.19
Ph
N
O
O
8
9
8
7
6
5
4
3
2
1
0 ppm
1.97
1.99
1.00
5.90
5.88

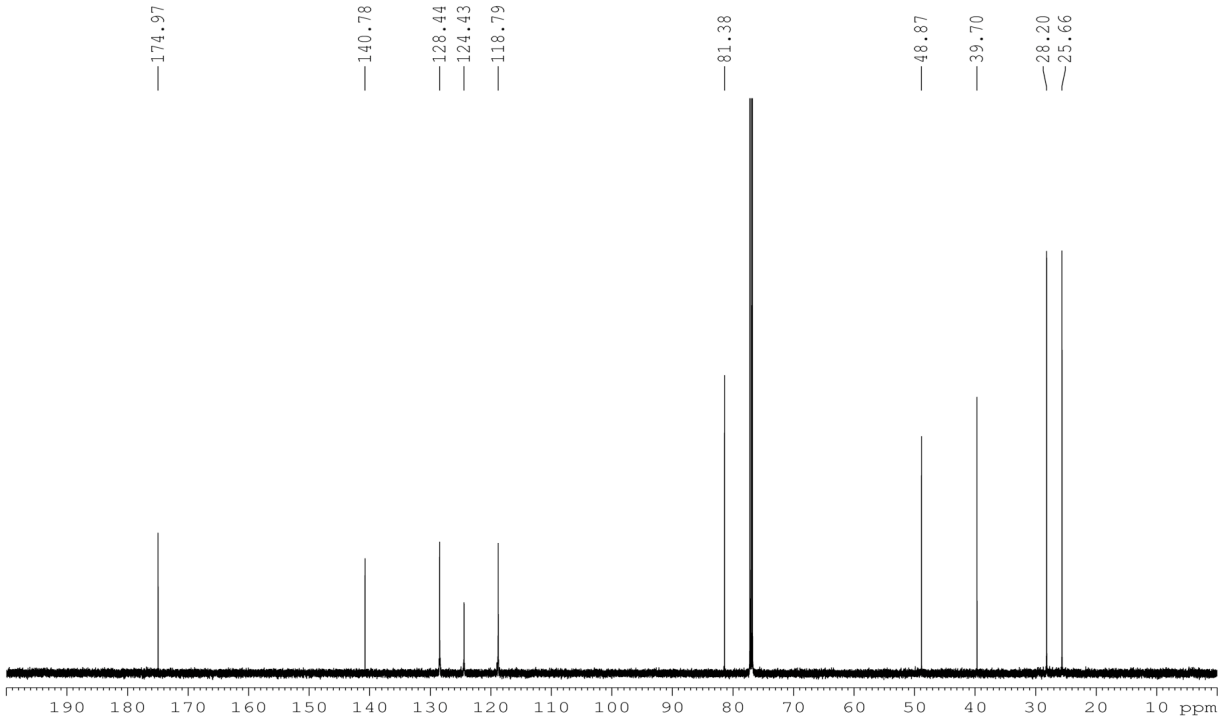

172.21
137.58
128.67
124.19
116.34
86.83
49.09
21.27
19.25
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

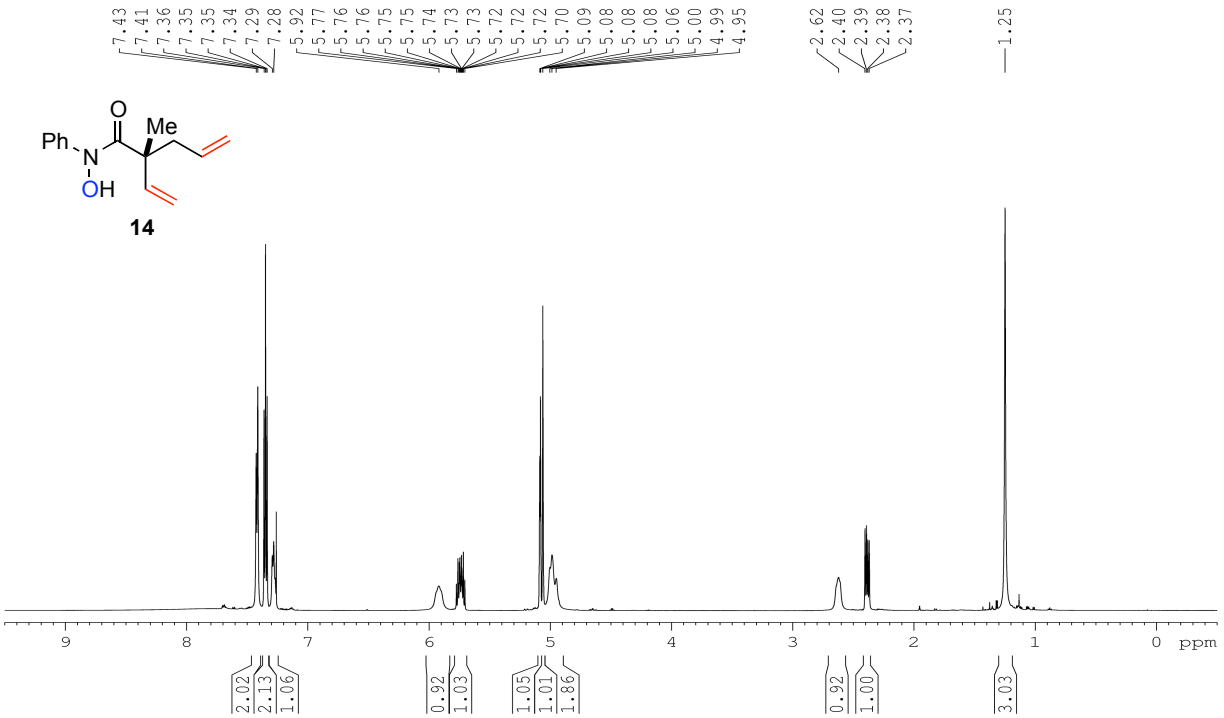

7.70
7.70
7.69
7.69
7.36
7.35
7.35
7.33
7.15
7.15
7.15
7.14
7.12
7.12
7.12
4.45
4.44
4.44
4.43
4.43
4.42
4.41
4.41
4.40
4.39
2.11
2.09
2.08
2.07
1.83
1.82
1.81
1.80
1.43
1.41
1.40
1.34
Ph
N
O
O
Me
10
9
8
7
6
5
4
3
2
1
0 ppm
1.99
2.00
1.00
1.00
0.99
0.99
2.90
3.03
2.92
174.67
139.79
128.53
124.85
119.38
76.56
44.64
39.16
27.30
26.25
20.68
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

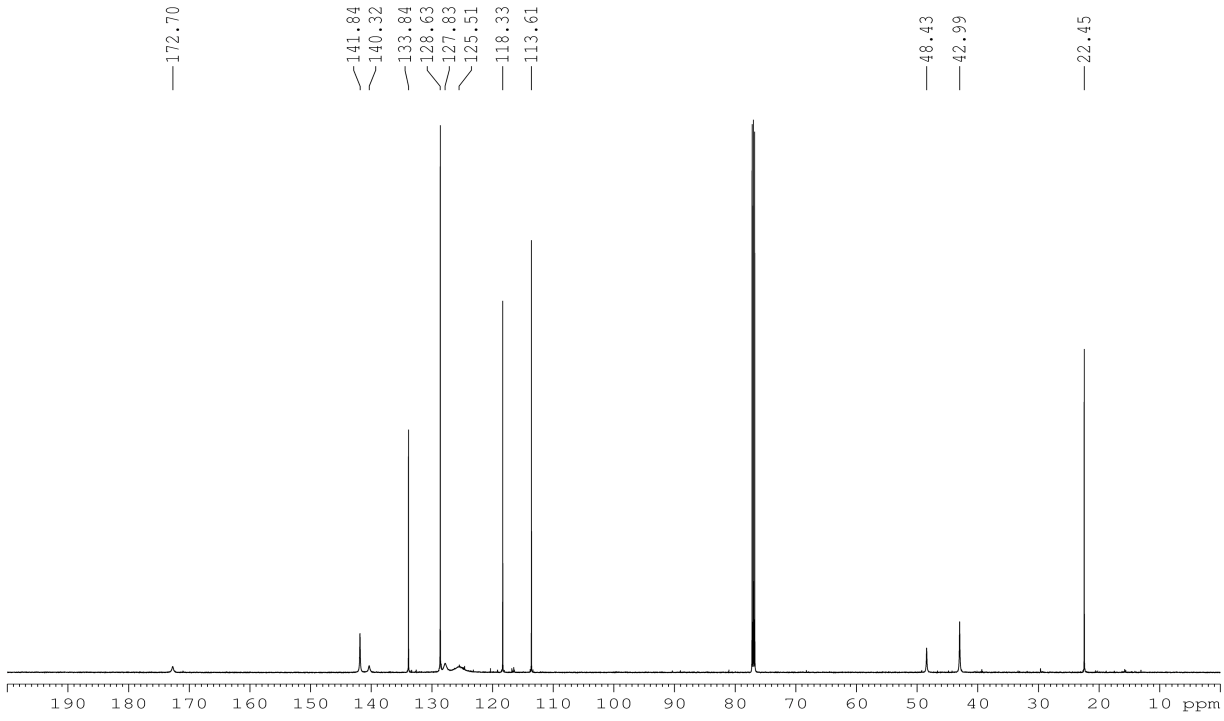

8.76
7.39
7.38
7.38
7.37
7.36
7.33
4.81
4.68
2.34
1.67
1.11
Ph
HO -N
O
11
9
8
7
6
5
4
3
2
1
0 ppm
0.91
4.07
0.97
1.00
1.00
1.94
3.02
5.95

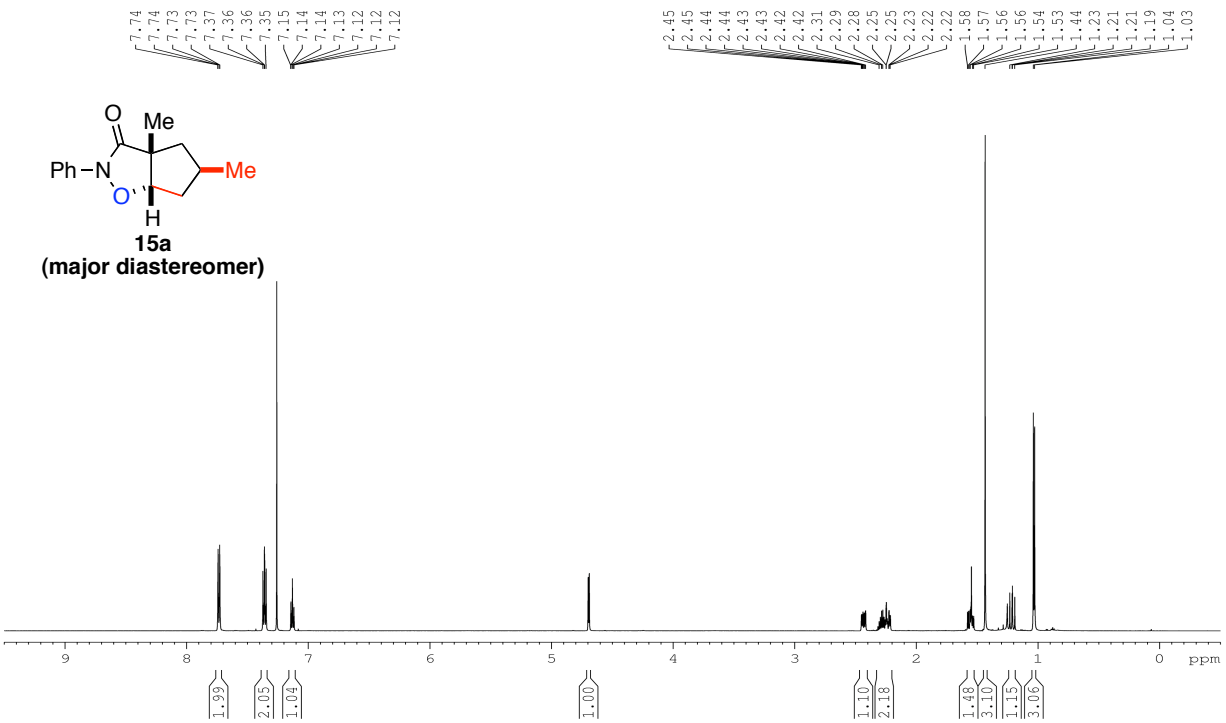

174.62
142.71
140.51
128.84
128.55
126.69
113.82
48.30
42.26
26.93
23.82
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

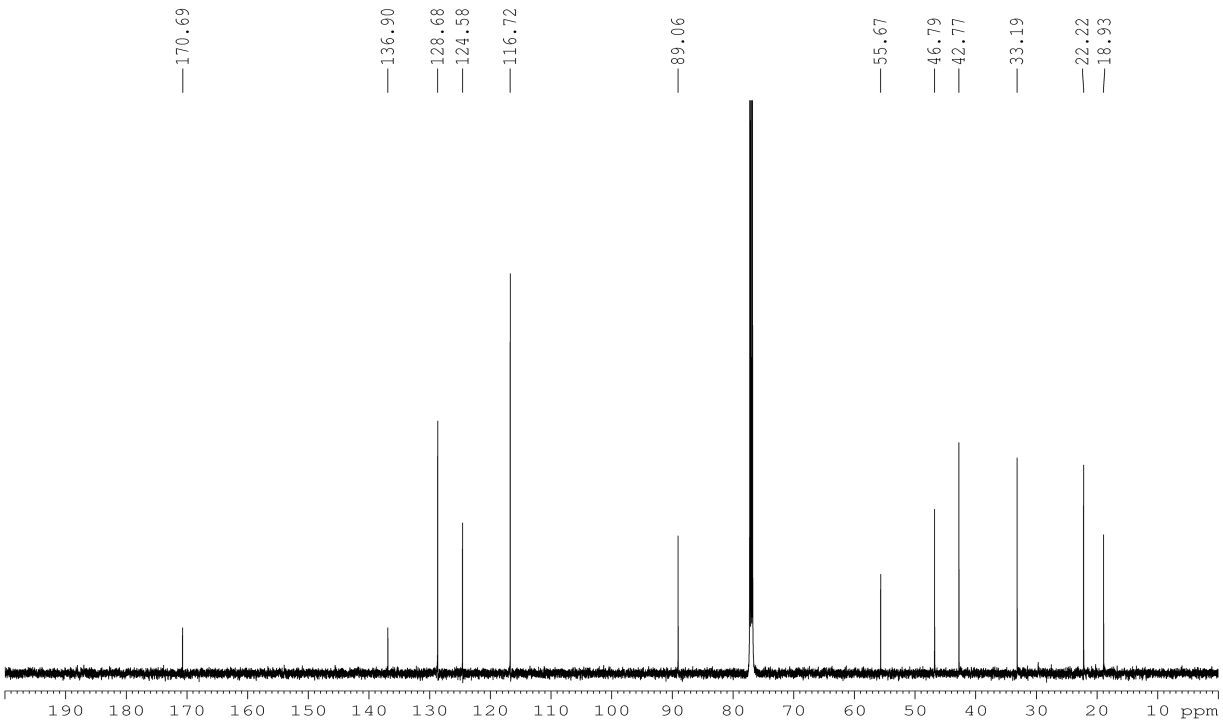

7.78
7.77
7.76
7.35
7.34
7.32
7.13
7.11
7.10
1.91
1.40
1.36
Ph
N
O
O
12
9
8
7
6
5
4
3
2
1
0
ppm
2.04
2.04
1.00
1.98
5.92
6.02

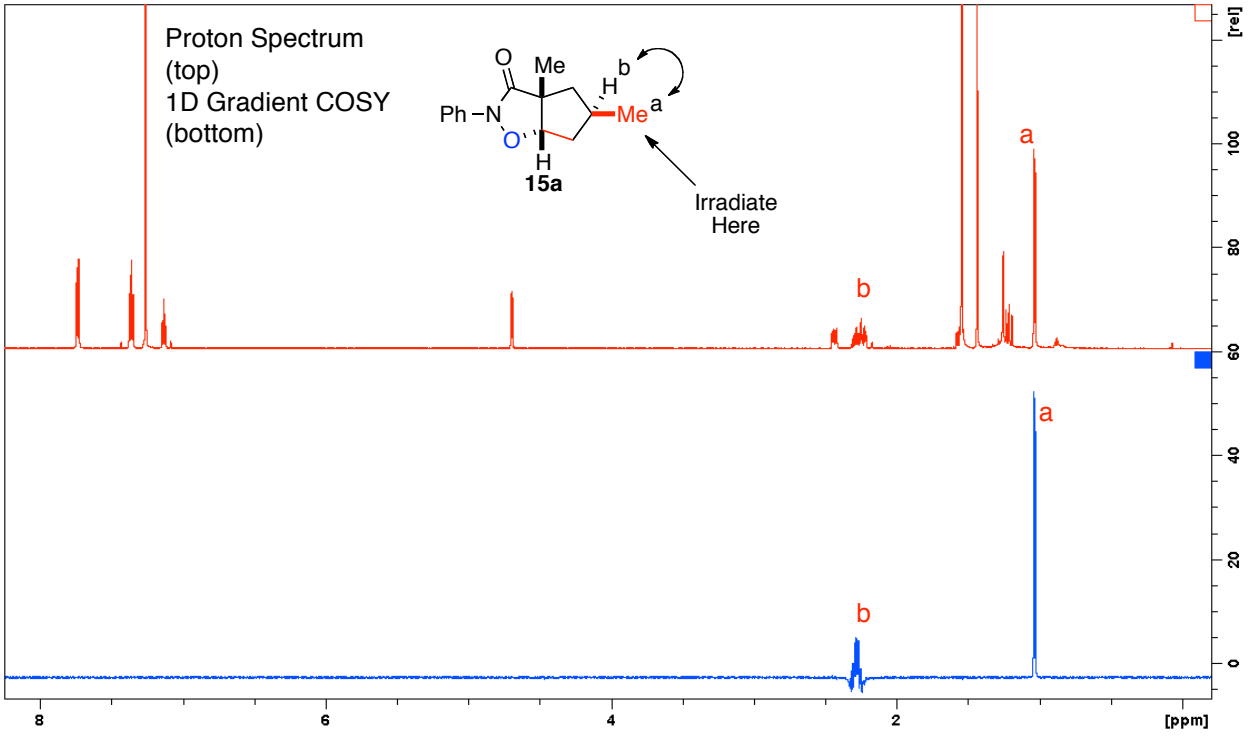

174.97
140.78
128.44
124.43
118.79
81.38
48.87
39.70
28.20
25.66
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

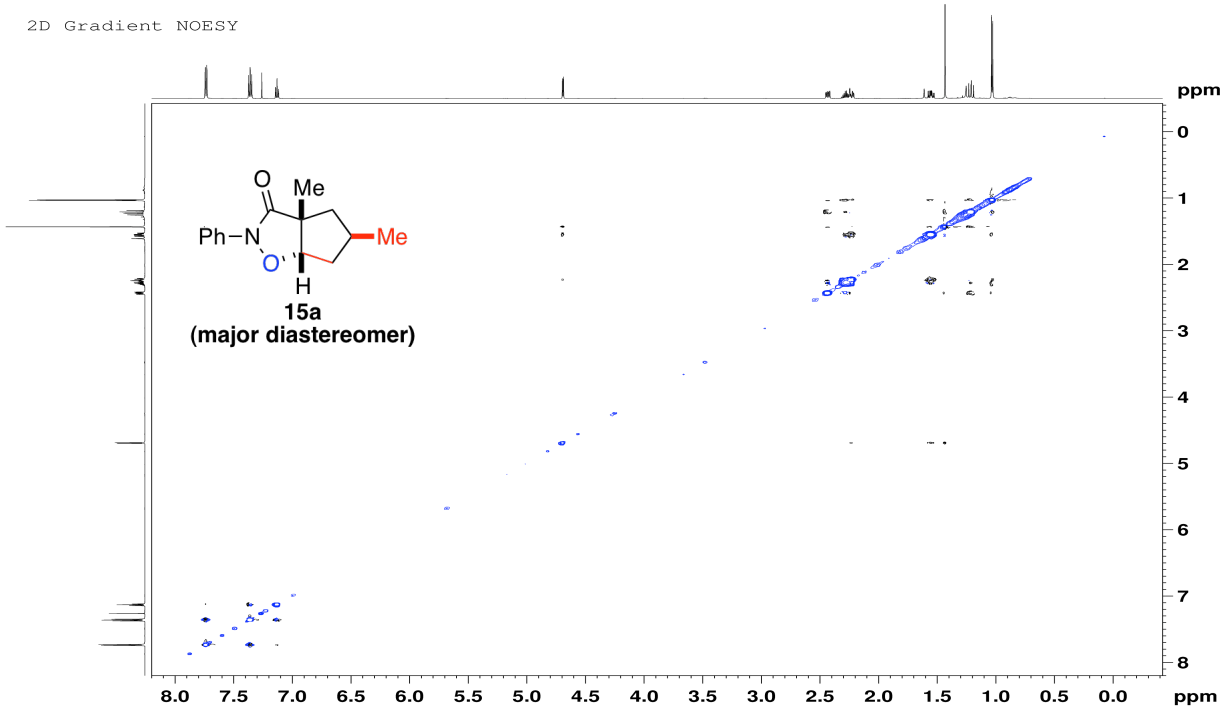

7.43
7.41
7.36
7.35
7.35
7.34
7.29
7.28
5.92
5.77
5.76
5.76
5.75
5.75
5.74
5.73
5.73
5.72
5.72
5.72
5.70
5.09
5.08
5.08
5.08
5.06
5.00
4.99
4.95
2.62
2.40
2.39
2.38
2.37
1.25
O
Me
Ph
N
OH
14
9
8
7
6
5
4
3
2
1
0
ppm
2.02
2.13
1.06
0.92
1.03
1.05
1.01
1.86
0.92
1.00
3.03

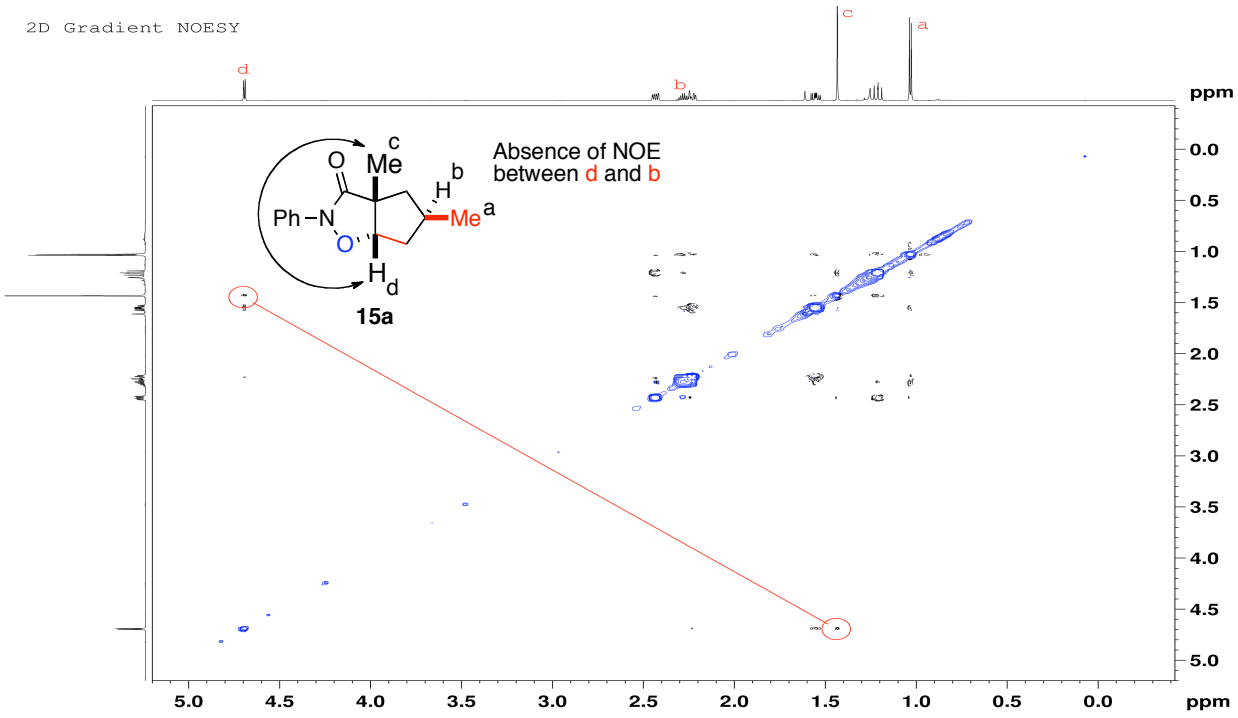

172.70
141.84
140.32
133.84
128.63
127.83
125.51
118.33
113.61
48.43
42.99
22.45
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

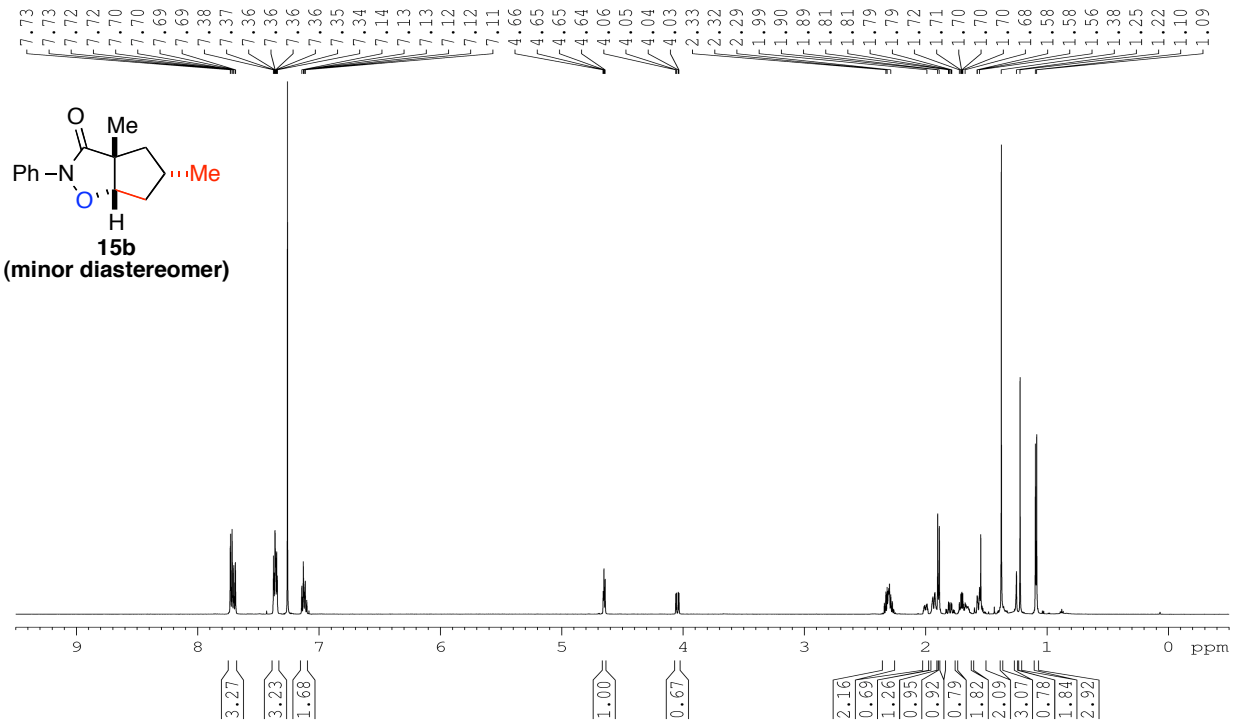

7.74
7.74
7.73
7.73
7.37
7.36
7.36
7.35
7.15
7.14
7.14
7.13
7.12
7.12
7.12
2.45
2.45
2.44
2.44
2.43
2.43
2.42
2.42
2.31
2.29
2.28
2.25
2.25
2.23
2.22
2.22
1.58
1.57
1.56
1.56
1.54
1.53
1.44
1.23
1.21
1.21
1.19
1.04
1.03
O
Me
Ph–N
O
Me
H
15a
(major diastereomer)
9
8
7
6
5
4
3
2
1
0
ppm
1.99
2.05
1.04
1.00
1.10
2.18
1.48
3.10
1.15
3.06

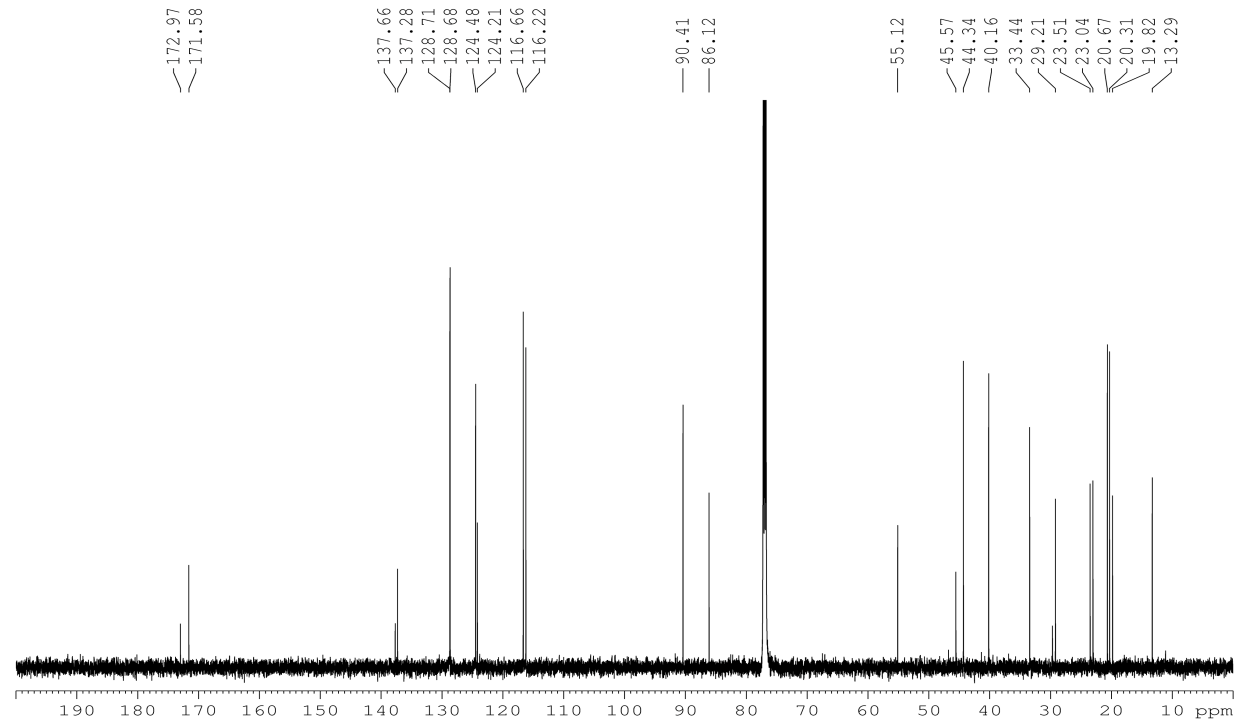

170.69
136.90
128.68
124.58
116.72
89.06
55.67
46.79
42.77
33.19
22.22
18.93
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

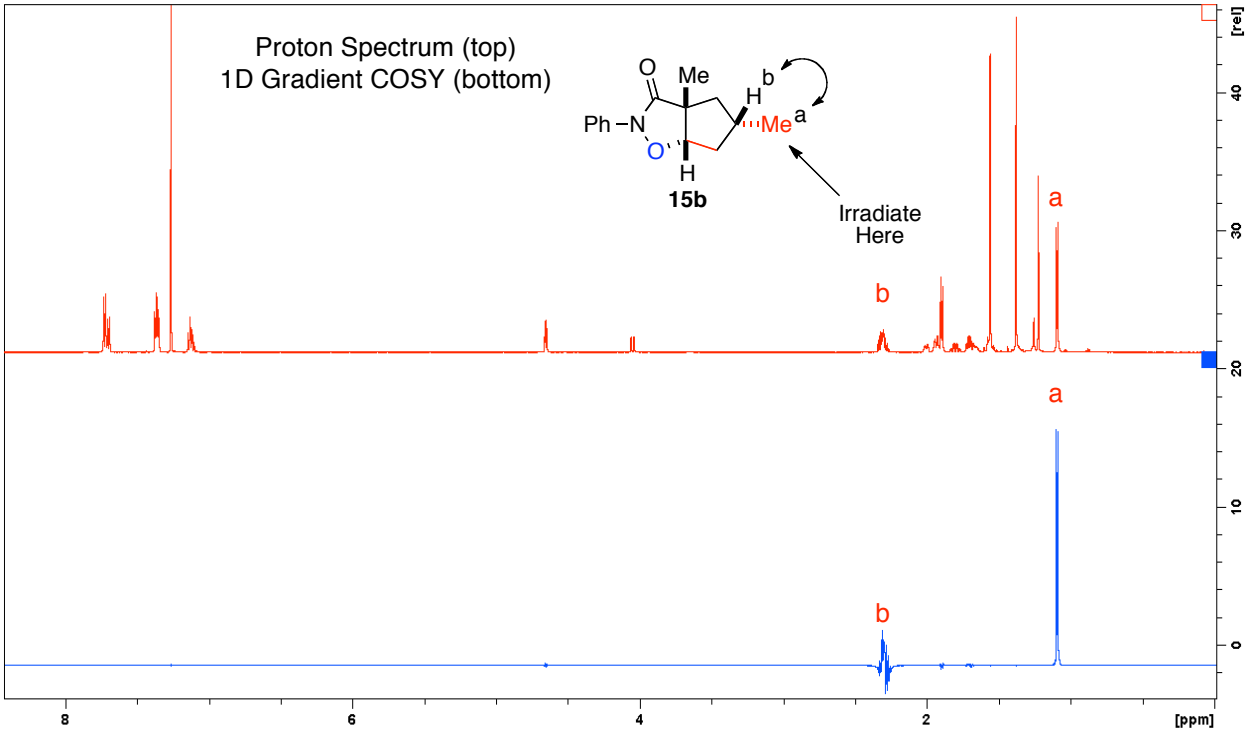

Proton Spectrum
(top)
1D Gradient COSY
(bottom)
O
Me
b
H
Ph–N
O
Me
a
H
15a
Irradiate
Here
a
b
a
b
[rel]
100
80
60
40
20
0
8
6
4
2
[ppm]

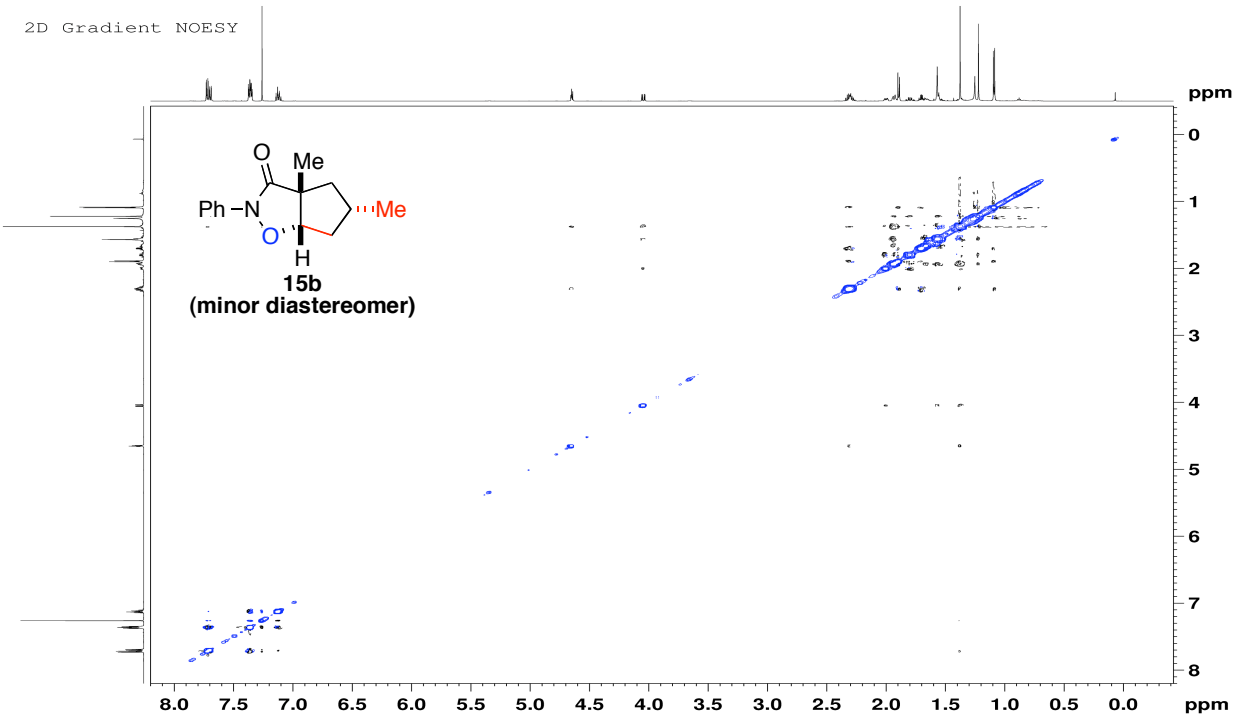

2D Gradient NOESY
O
Me
Ph–N
O
Me
H
15a
(major diastereomer)
ppm
0
1
2
3
4
5
6
7
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

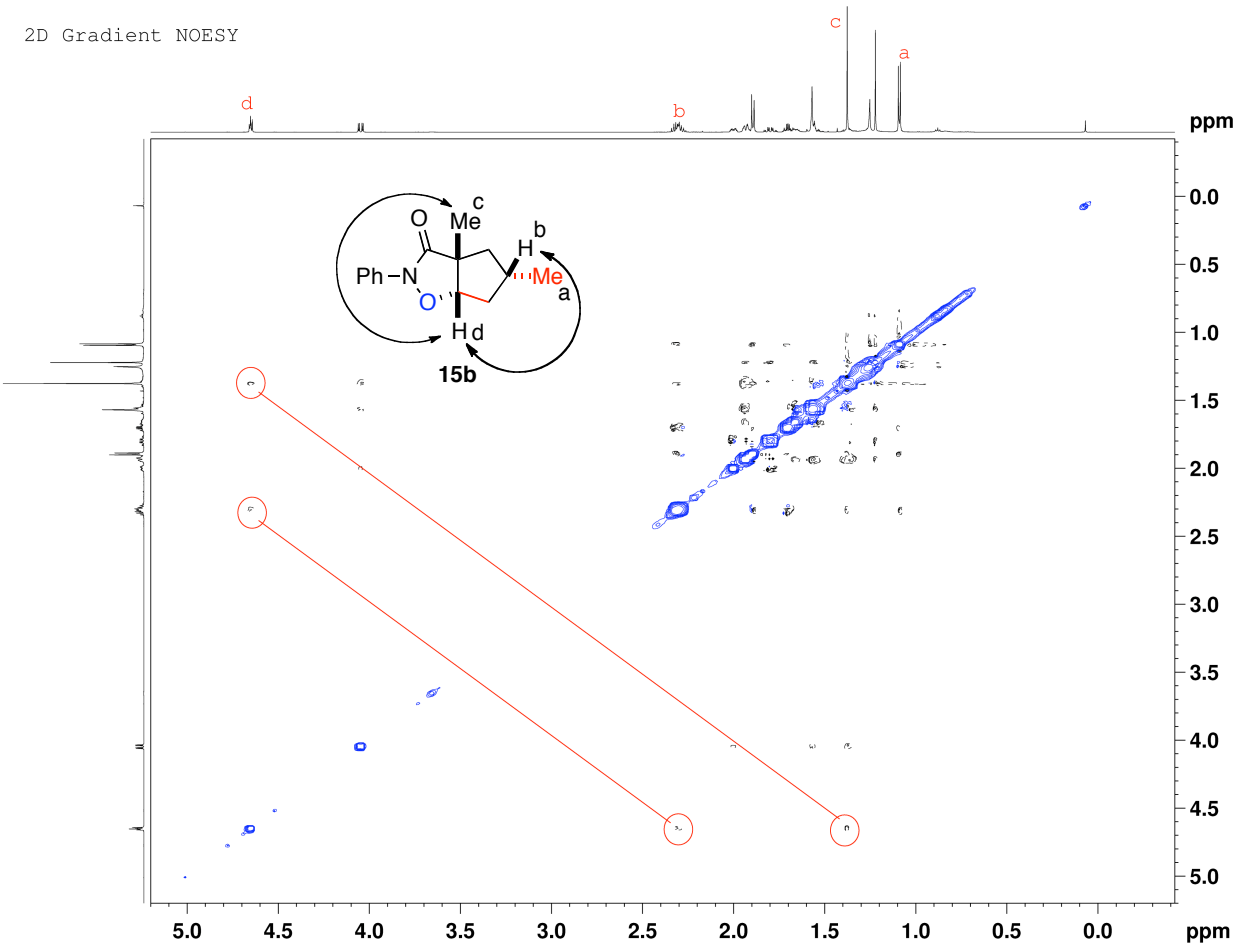

2D Gradient NOESY
d
b
c
a
ppm
Absence of NOE
between d and b
O
Me
c
b
H
Ph–N
O
Me
a
H
d
15a
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

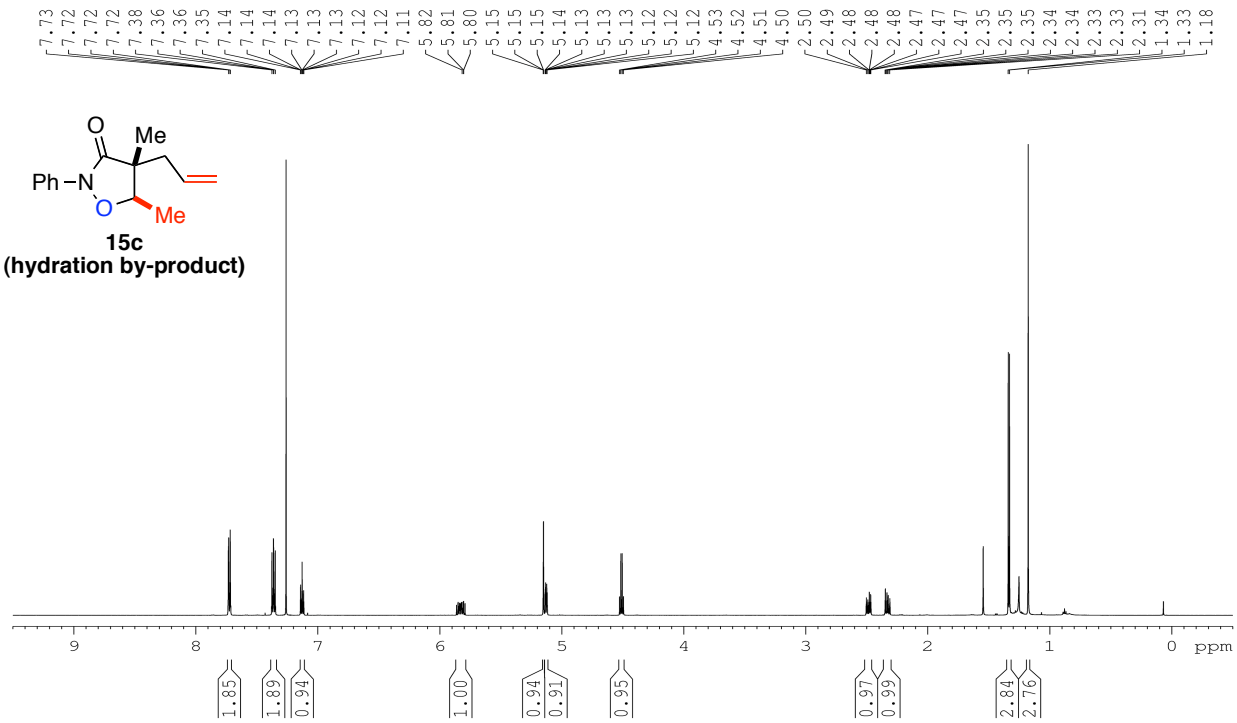

7.73 7.73 7.72 7.72 7.70 7.70 7.69 7.69 7.38 7.37 7.36 7.36 7.36 7.35 7.34 7.14 7.13 7.13 7.12 7.12 7.11 4.66 4.65 4.65 4.64 4.06 4.05 4.04 4.03 2.33 2.32 2.29 1.99 1.90 1.89 1.81 1.81 1.79 1.79 1.72 1.71 1.70 1.70 1.70 1.68 1.58 1.58 1.56 1.38 1.25 1.22 1.10 1.09
O
Me
Ph –N
O
Me
H
15b
(minor diastereomer)
9 8 7 6 5 4 3 2 1 0 ppm
3.27 3.23 1.68 1.00 0.67 2.16 0.69 1.26 0.95 0.92 0.79 1.82 2.09 3.07 0.78 1.84 2.92

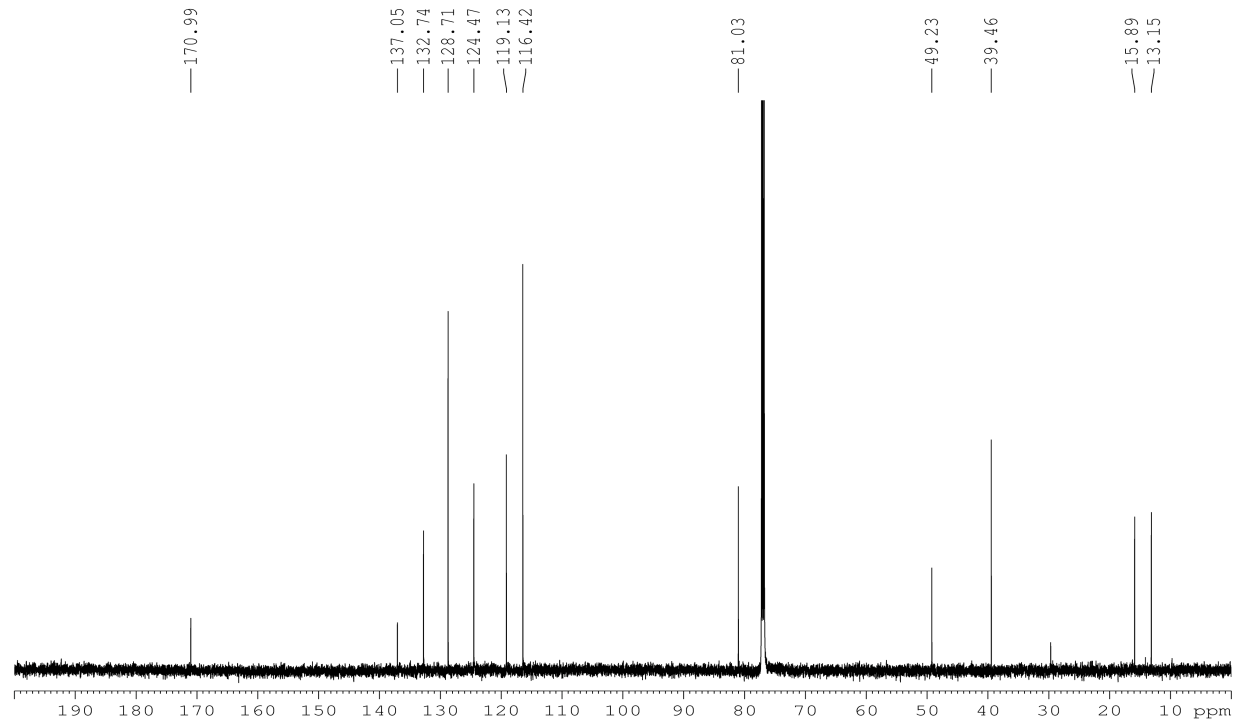

172.97 171.58 137.66 137.28 128.71 128.68 124.48 124.21 116.66 116.22 90.41 86.12 55.12 45.57 44.34 40.16 33.44 29.21 23.51 23.04 20.67 20.31 19.82 13.29
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

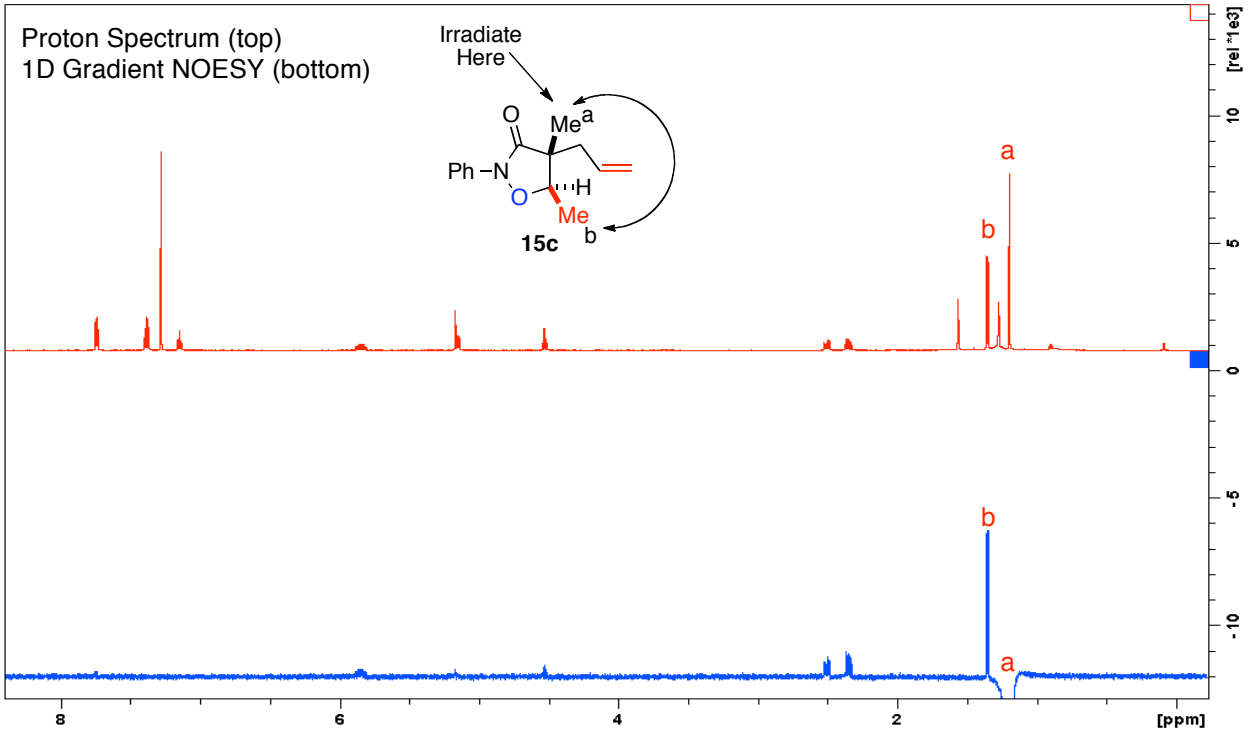

Proton Spectrum (top)
1D Gradient COSY (bottom)
O
Me
b
H
Ph –N
Me
a
O
H
15b
Irradiate
Here
a
b
a
b
[rel]
40
30
20
10
0
8
6
4
2
[ppm]

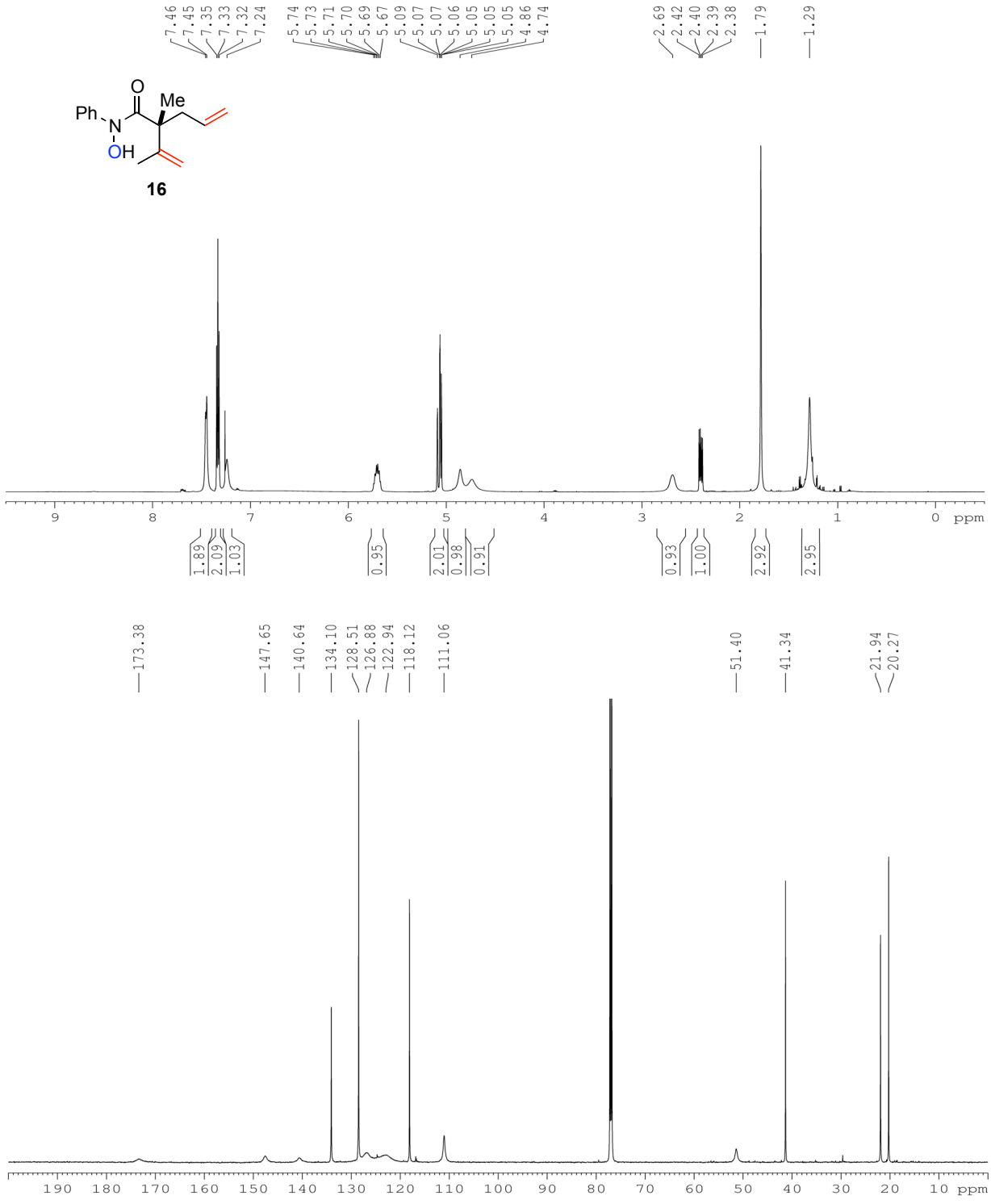

2D Gradient NOESY
O
Me
Ph –N
Me
O
H
15b
(minor diastereomer)
ppm
0
1
2
3
4
5
6
7
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

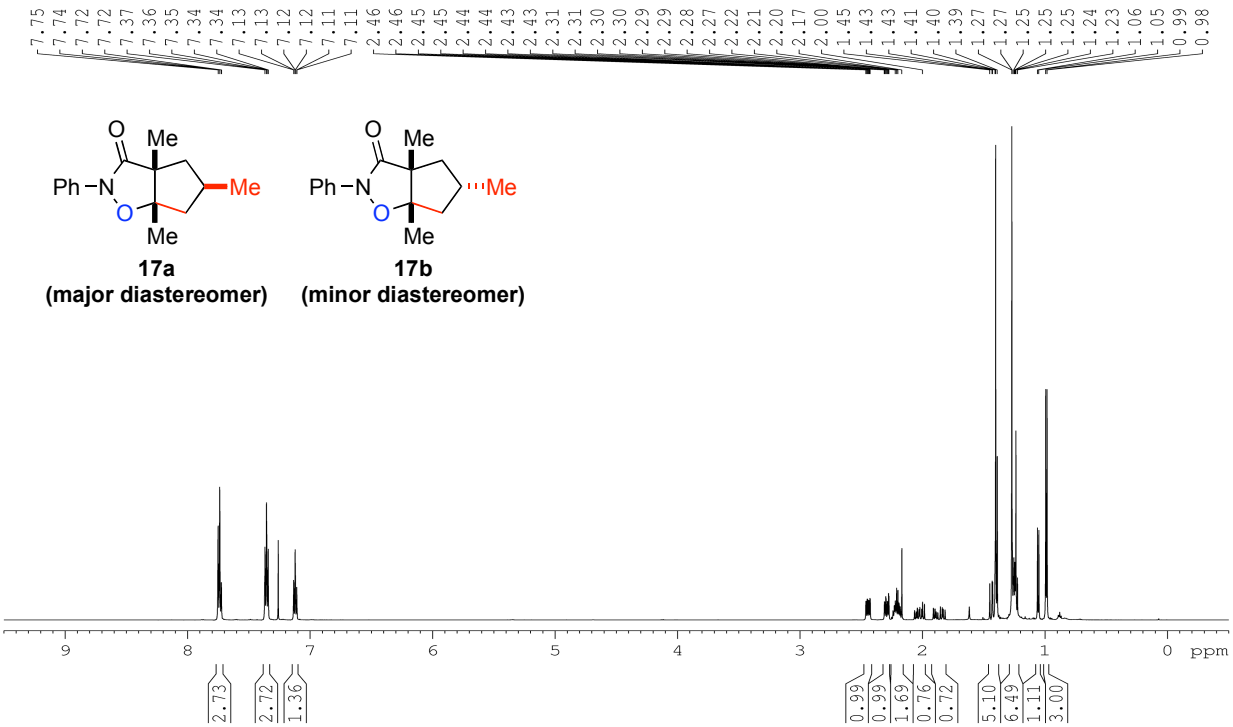

2D Gradient NOESY
d
b
c
a
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
O
Me
c
b
H
Ph–N
O
Me
a
H
d
15b
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

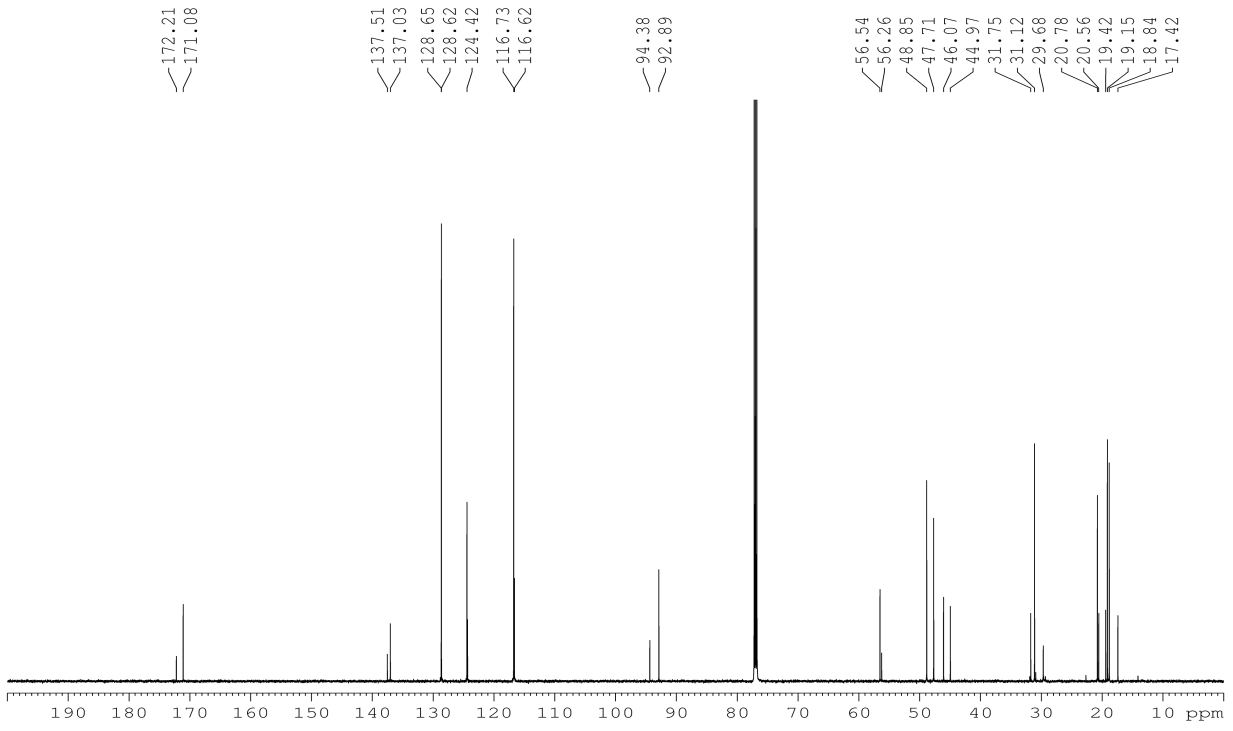

7.73 7.72 7.72 7.72 7.38 7.36 7.36 7.35 7.14 7.14 7.14 7.13 7.13 7.13 7.12 7.12 7.11
5.82 5.81 5.80
5.15 5.15 5.15 5.14 5.13 5.13 5.13 5.12 5.12 5.12 4.53 4.52 4.51 4.50
2.50 2.49 2.48 2.48 2.48 2.47 2.47 2.47 2.35 2.35 2.35 2.34 2.34 2.33 2.33 2.31 1.34 1.33 1.18
O
Me
Ph–N
O
Me
15c
(hydration by-product)
9 8 7 6 5 4 3 2 1 0 ppm
1.85 1.89 0.94 1.00 0.94 0.91 0.95 0.97 0.99 2.84 2.76

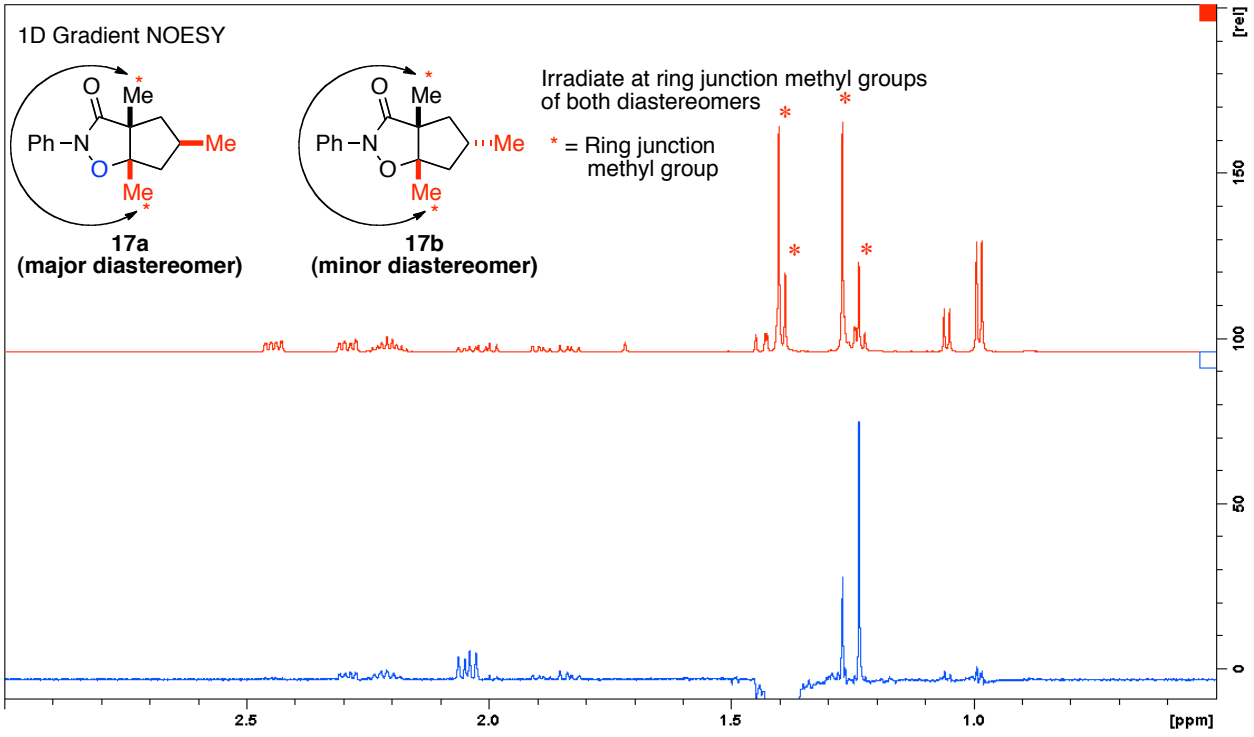

170.99
137.05 132.74 128.71 124.47 119.13 116.42
81.03
49.23
39.46
15.89 13.15
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

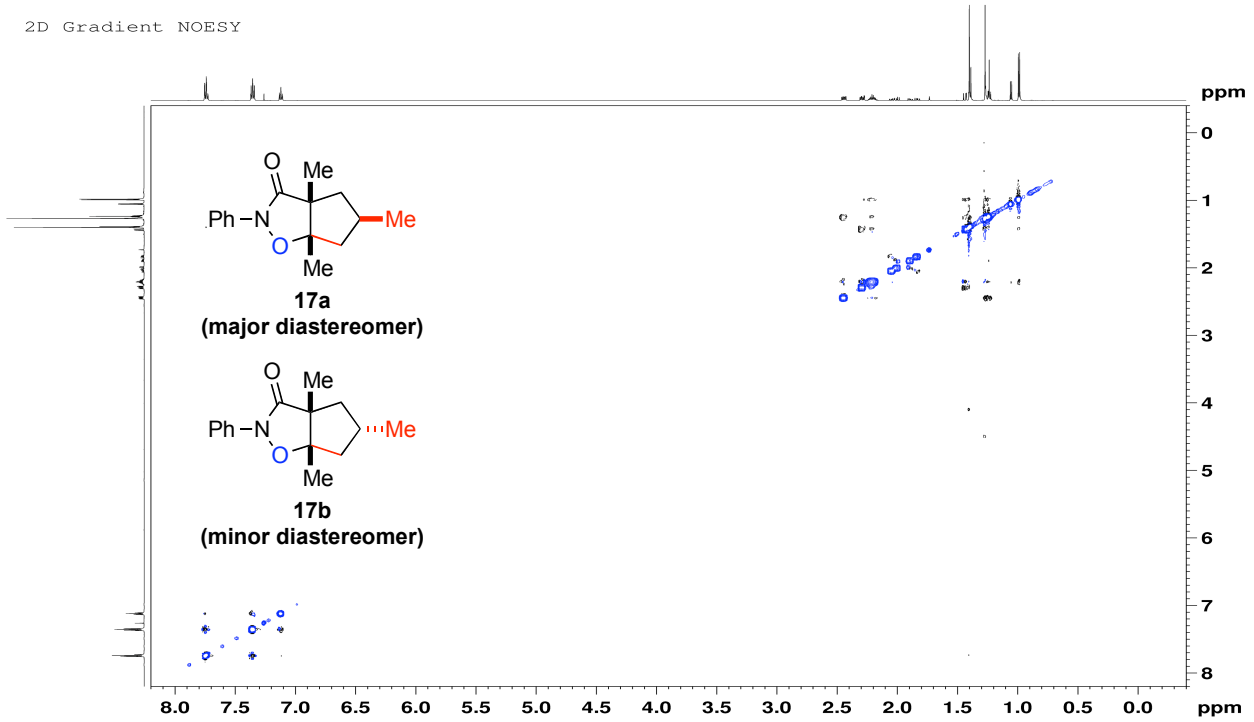

Proton Spectrum (top)
1D Gradient NOESY (bottom)
Irradiate Here
O
Me a
Ph –N
O
H
Me
b
15c
a
b
b
a
[rel. *1e3]
10
5
0
-5
-10
8
6
4
2
[ppm]

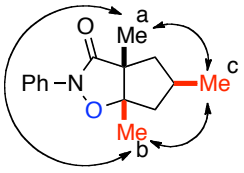

7.46
7.45
7.35
7.33
7.32
7.24
5.74
5.73
5.71
5.70
5.69
5.67
5.09
5.07
5.07
5.06
5.05
5.05
5.05
4.86
4.74
2.69
2.42
2.40
2.39
2.38
1.79
1.29
O
Me
Ph
N
OH
16
9
8
7
6
5
4
3
2
1
0 ppm
1.89
2.09
1.03
0.95
2.01
0.98
0.91
0.93
1.00
2.92
2.95
173.38
147.65
140.64
134.10
128.51
126.88
122.94
118.12
111.06
51.40
41.34
21.94
20.27
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.75 7.74 7.72 7.72 7.37 7.36 7.35 7.34 7.34 7.13 7.13 7.12 7.12 7.11 7.11
2.46 2.46 2.45 2.45 2.44 2.44 2.43 2.43 2.31 2.31 2.30 2.30 2.29 2.29 2.28 2.27 2.22 2.21 2.20 2.17 2.00 1.45 1.43 1.43 1.41 1.40 1.39 1.27 1.27 1.25 1.25 1.25 1.24 1.23 1.06 1.05 0.99 0.98
O Me Ph–N O Me Me
17a
(major diastereomer)
O Me Ph–N O Me Me
17b
(minor diastereomer)
9 8 7 6 5 4 3 2 1 0 ppm
2.73 2.72 1.36 0.99 0.99 1.69 0.76 0.72 5.10 6.49 1.11 3.00

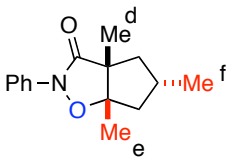

172.21 171.08 137.51 137.03 128.65 128.62 124.42 116.73 116.62 94.38 92.89 56.54 56.26 48.85 47.71 46.07 44.97 31.75 31.12 29.68 20.78 20.56 19.42 19.15 18.84 17.42
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1D Gradient NOESY
Irradiate at ring junction methyl groups of both diastereomers
* = Ring junction methyl group
17a
(major diastereomer)
17b
(minor diastereomer)
[rel]
150
100
50
0
2.5
2.0
1.5
1.0
[ppm]


2D Gradient NOESY
17a
(major diastereomer)
17b
(minor diastereomer)
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm



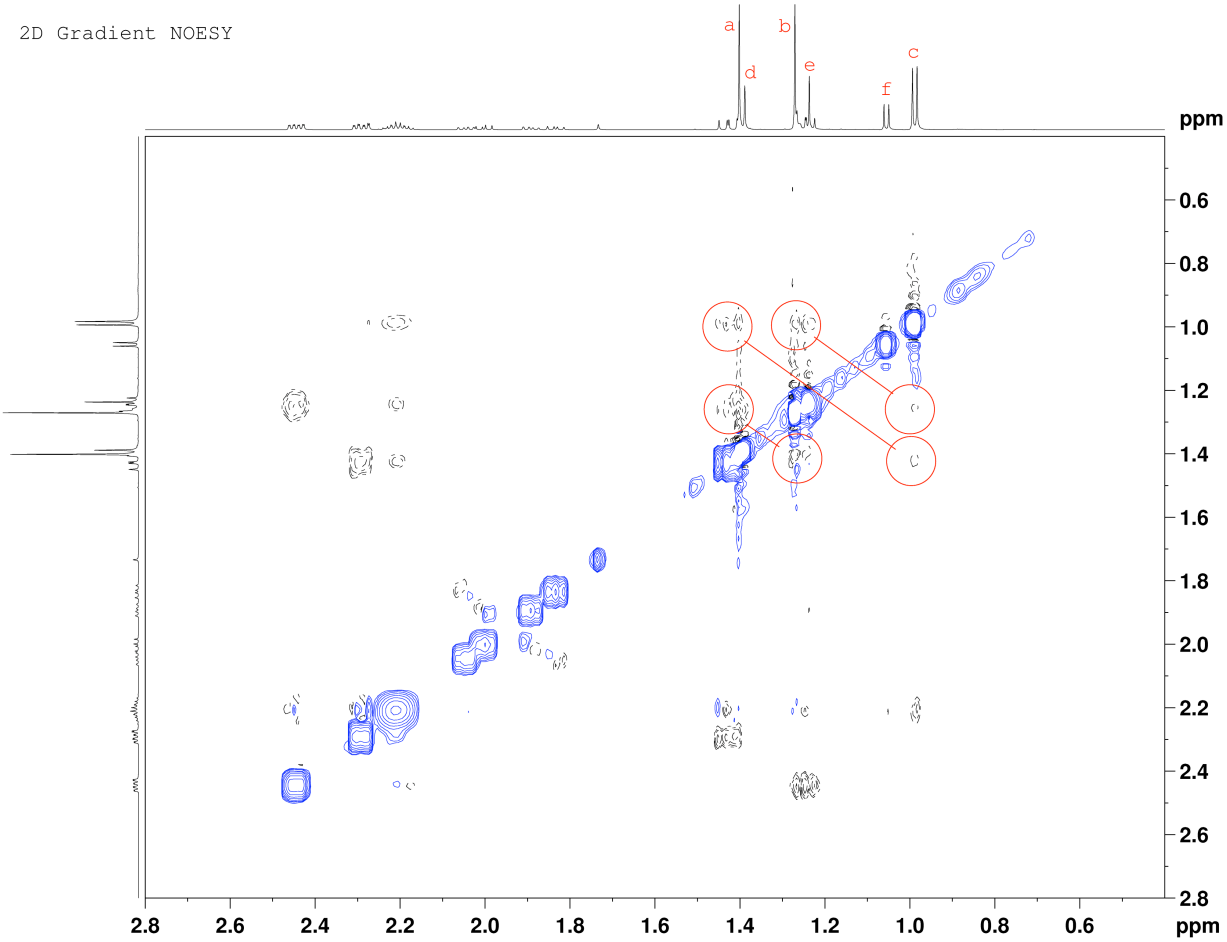
17a
(major diastereomer)

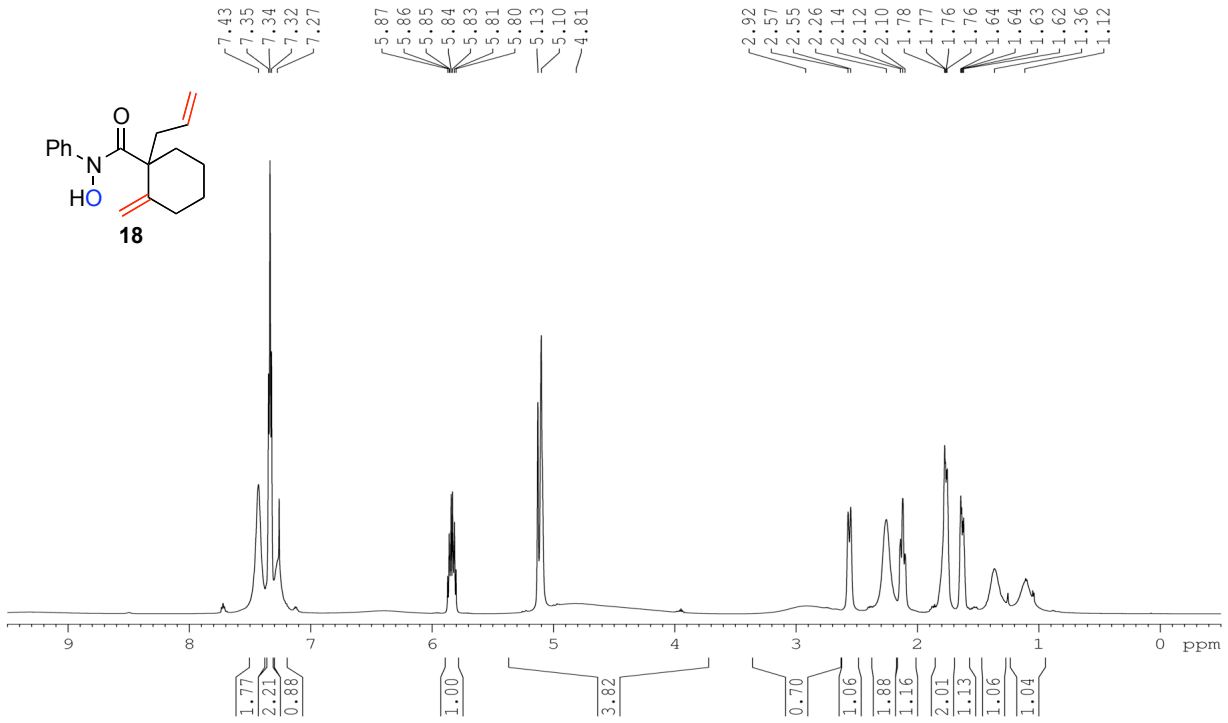


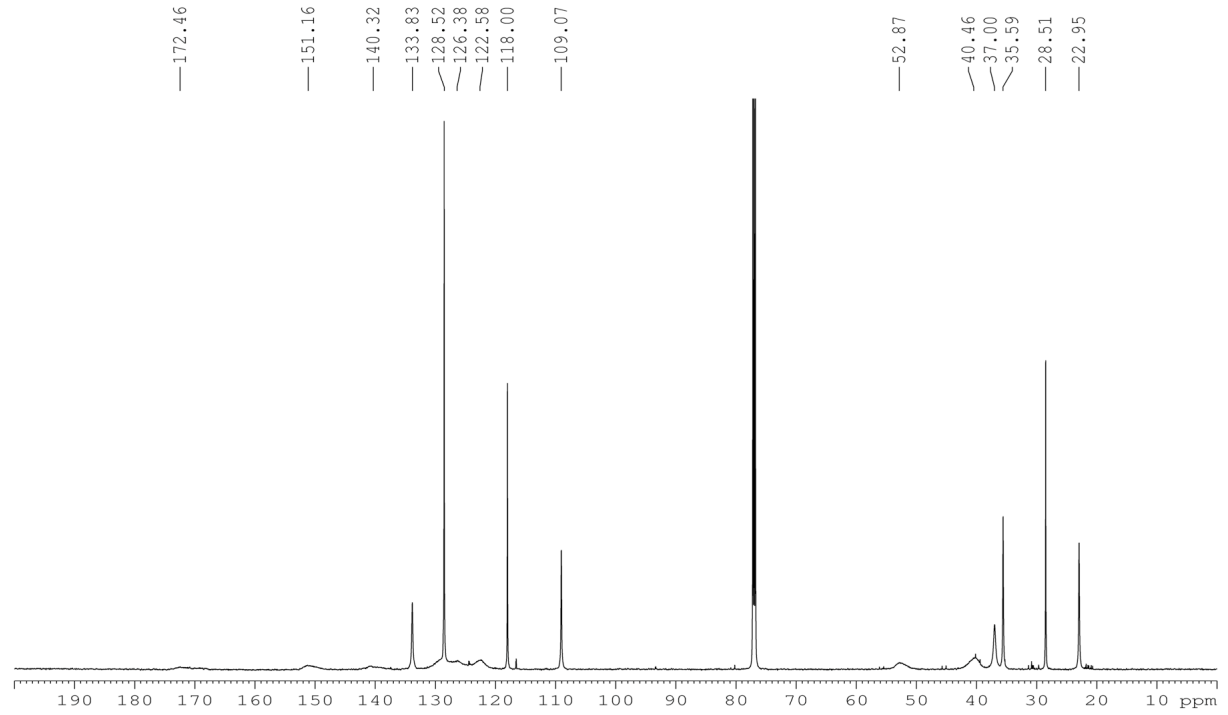
17b
(minor diastereomer)

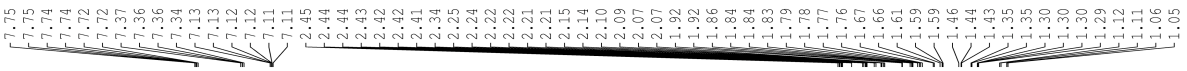
No NOE between d and f or e and f observed.

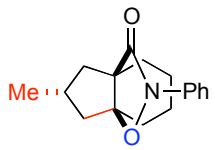
Note: Identities of peaks a, b, d, and e were arbitrarily assigned for the purpose of determining relative stereochemistry.



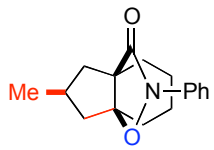

7.43
7.35
7.34
7.32
7.27
5.87
5.86
5.85
5.84
5.83
5.81
5.80
5.13
5.10
4.81
2.92
2.57
2.55
2.26
2.14
2.12
2.10
1.78
1.77
1.76
1.76
1.64
1.64
1.63
1.62
1.36
1.12
Ph
N
HO
O
18
9
8
7
6
5
4
3
2
1
0 ppm
1.77
2.21
0.88
1.00
3.82
0.70
1.06
1.88
1.16
2.01
1.13
1.06
1.04


172.46
151.16
140.32
133.83
128.52
126.38
122.58
118.00
109.07
52.87
40.46
37.00
35.59
28.51
22.95
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

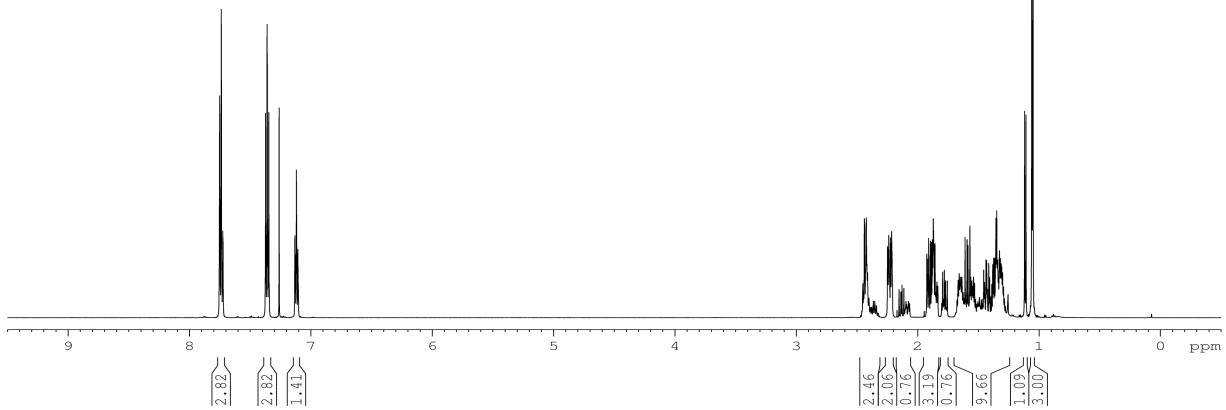


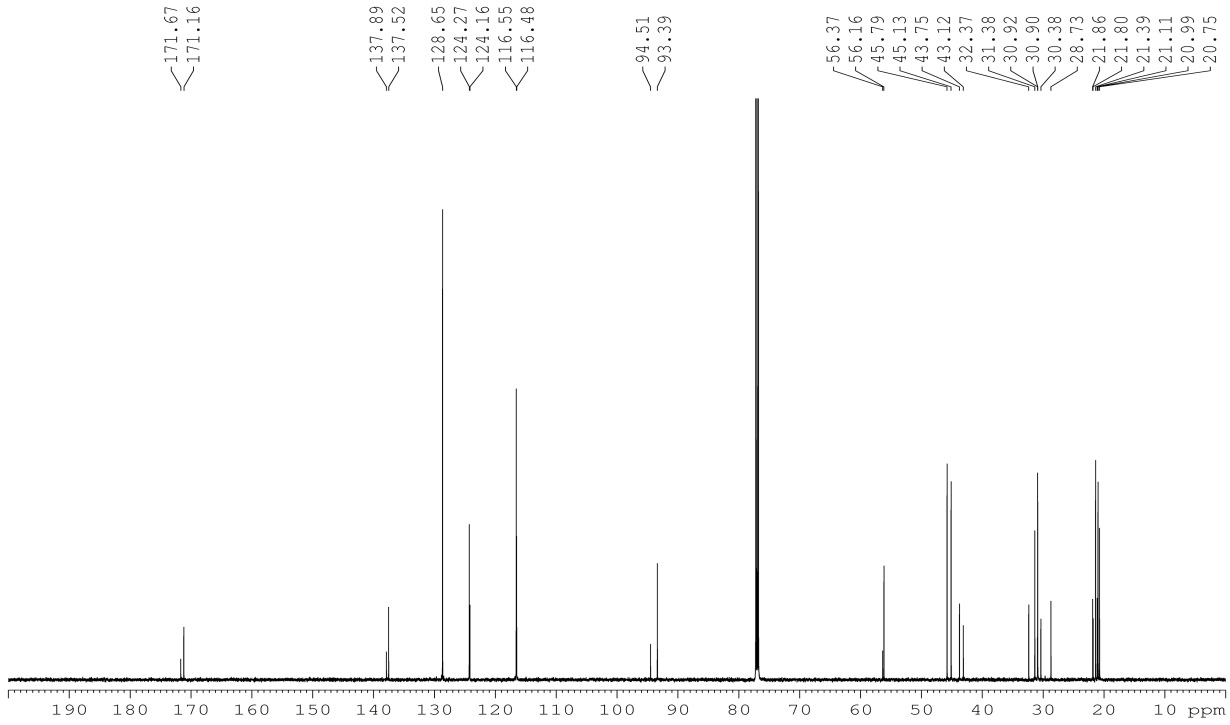


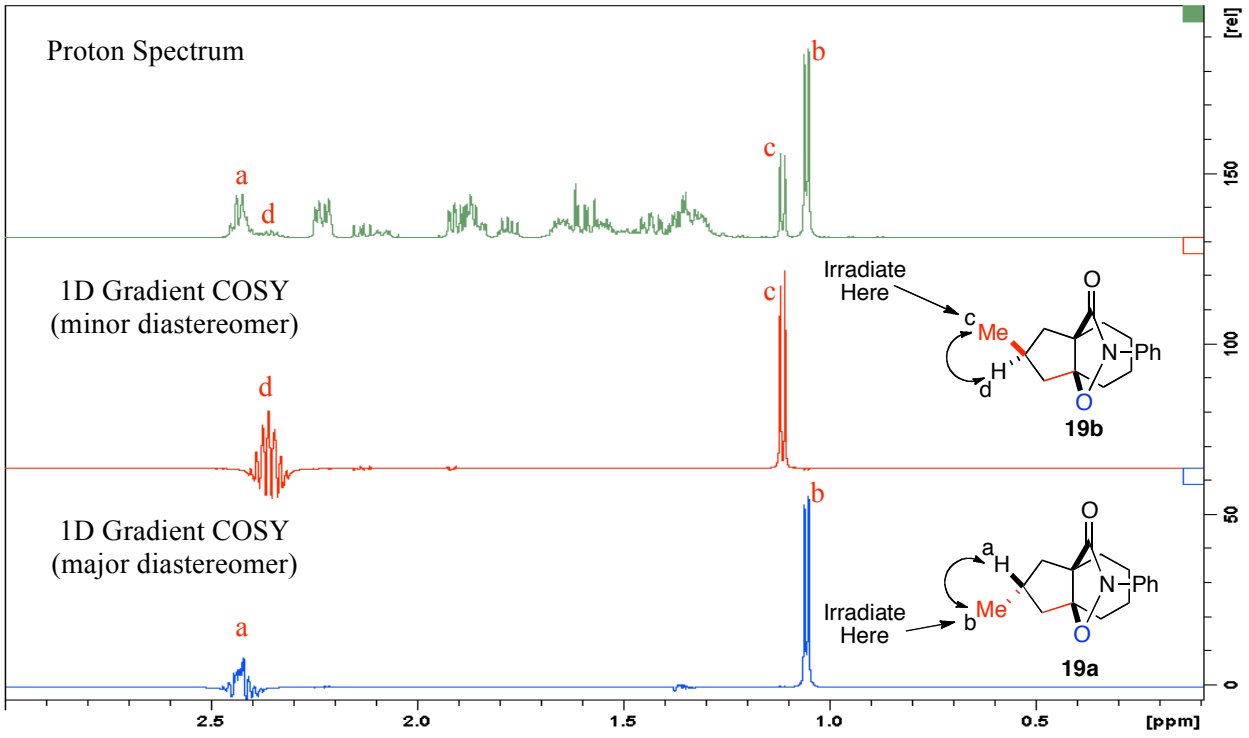
19a
(major diastereomer)

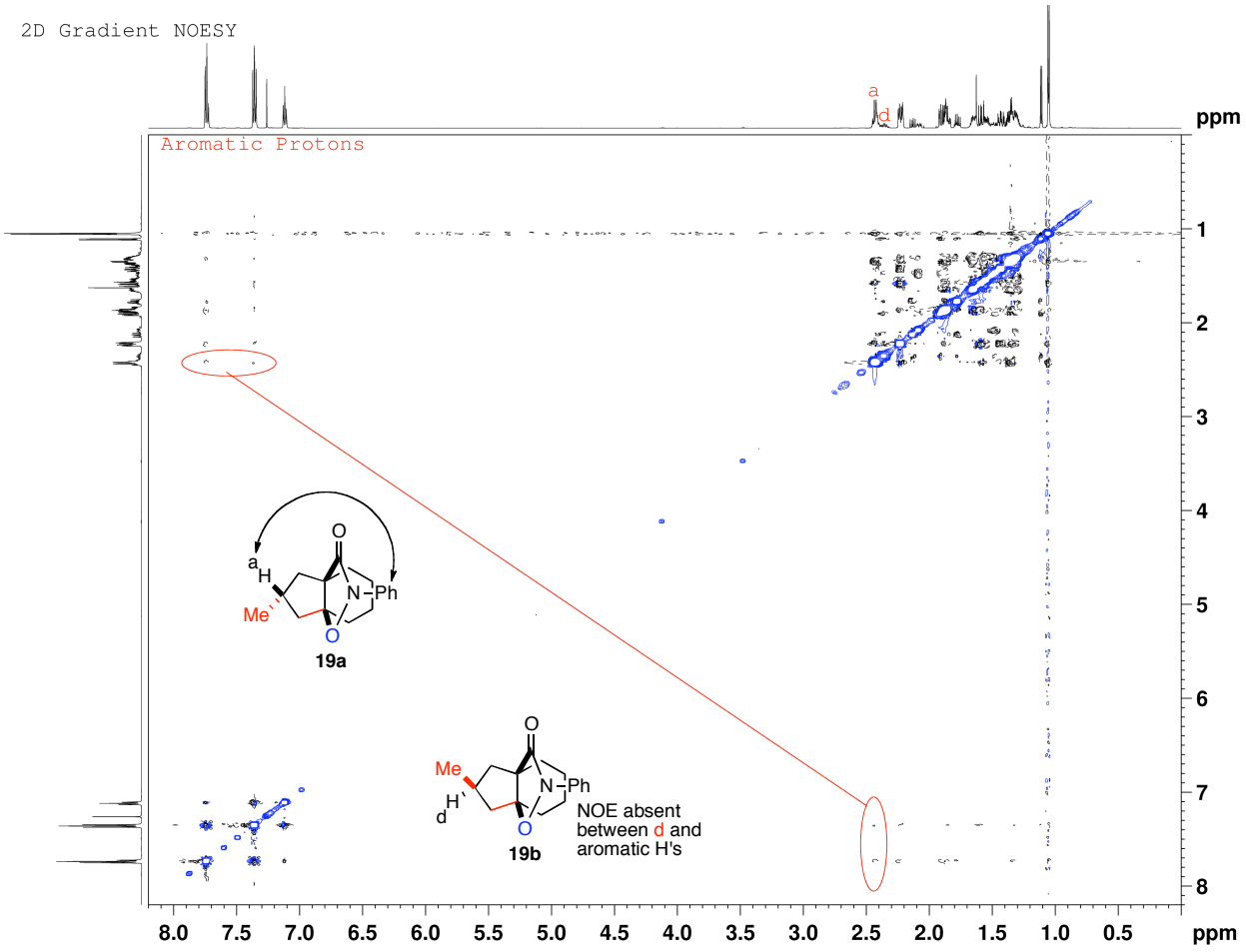


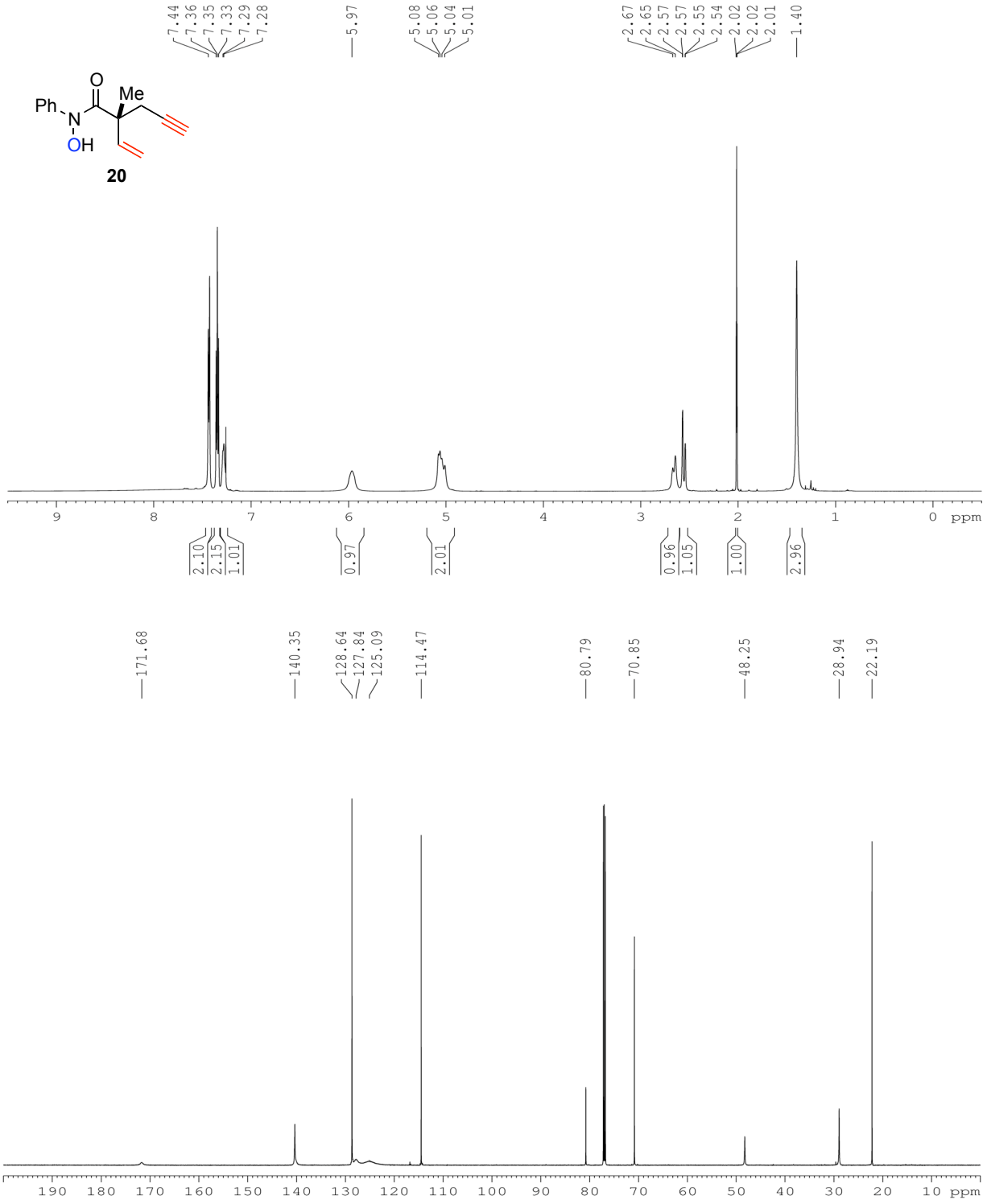
19b
(minor diastereomer)

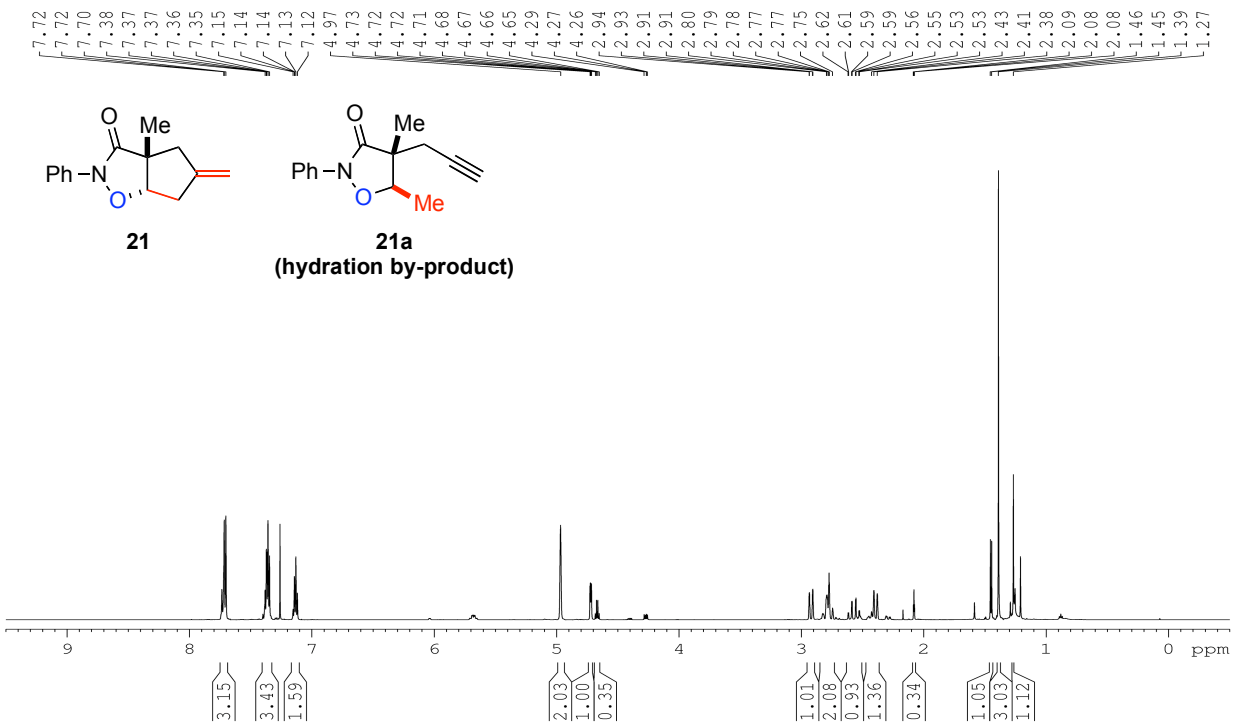


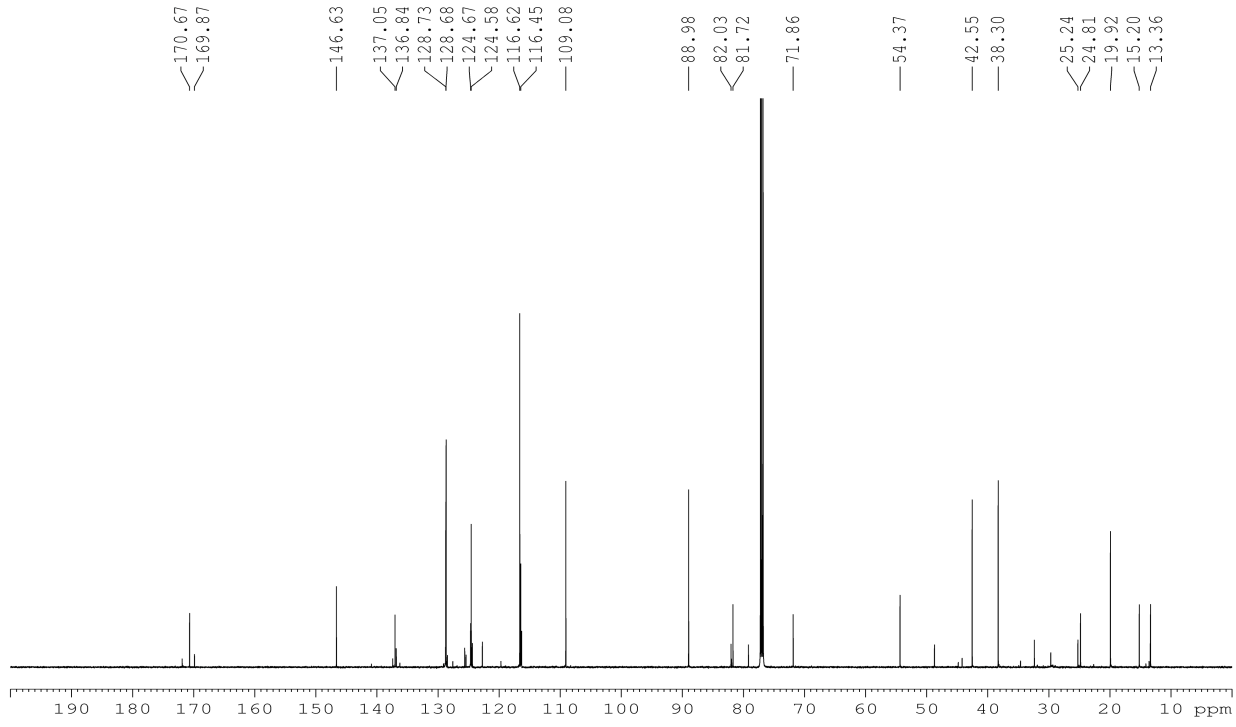


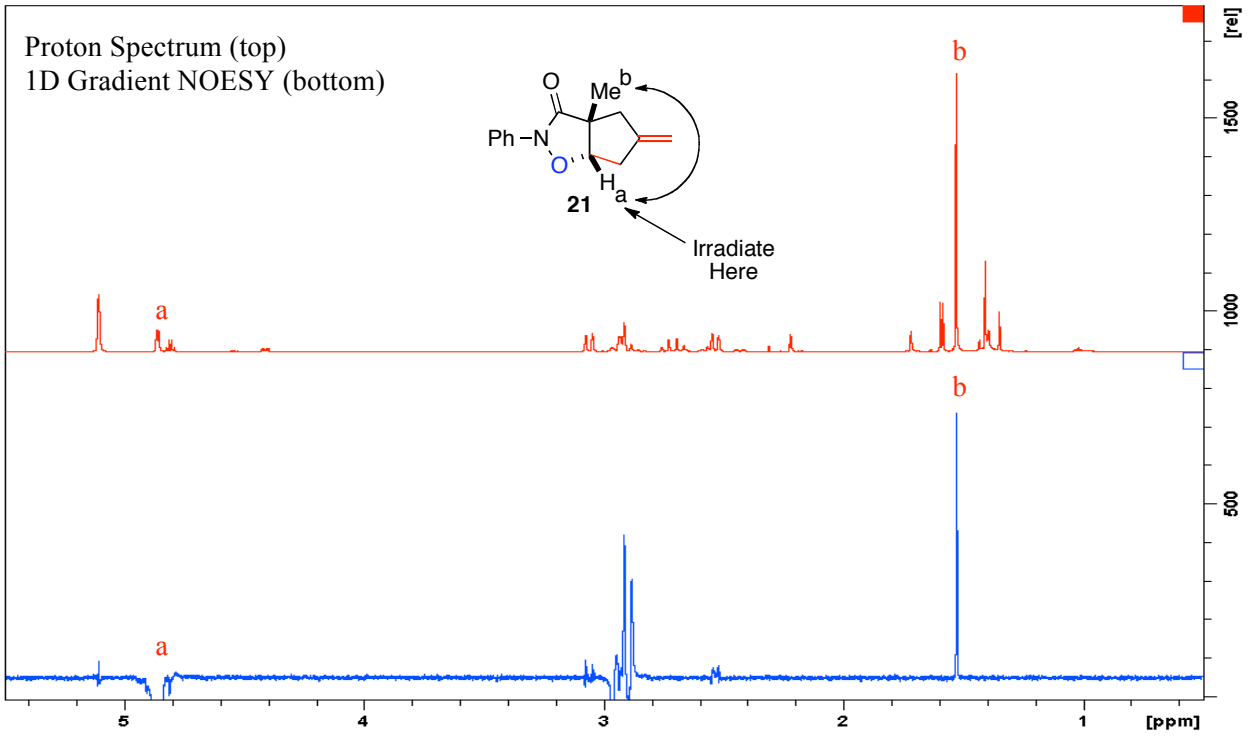

Proton Spectrum
a
d
c
b
1D Gradient COSY
(minor diastereomer)
d
c
Irradiate
Here
c
Me
H
d
O
N
Ph
O
19b
1D Gradient COSY
(major diastereomer)
a
b
Irradiate
Here
a
H
b
Me
O
N
Ph
O
19a
2.5
2.0
1.5
1.0
0.5
[ppm]
[rel]
150
100
50
0

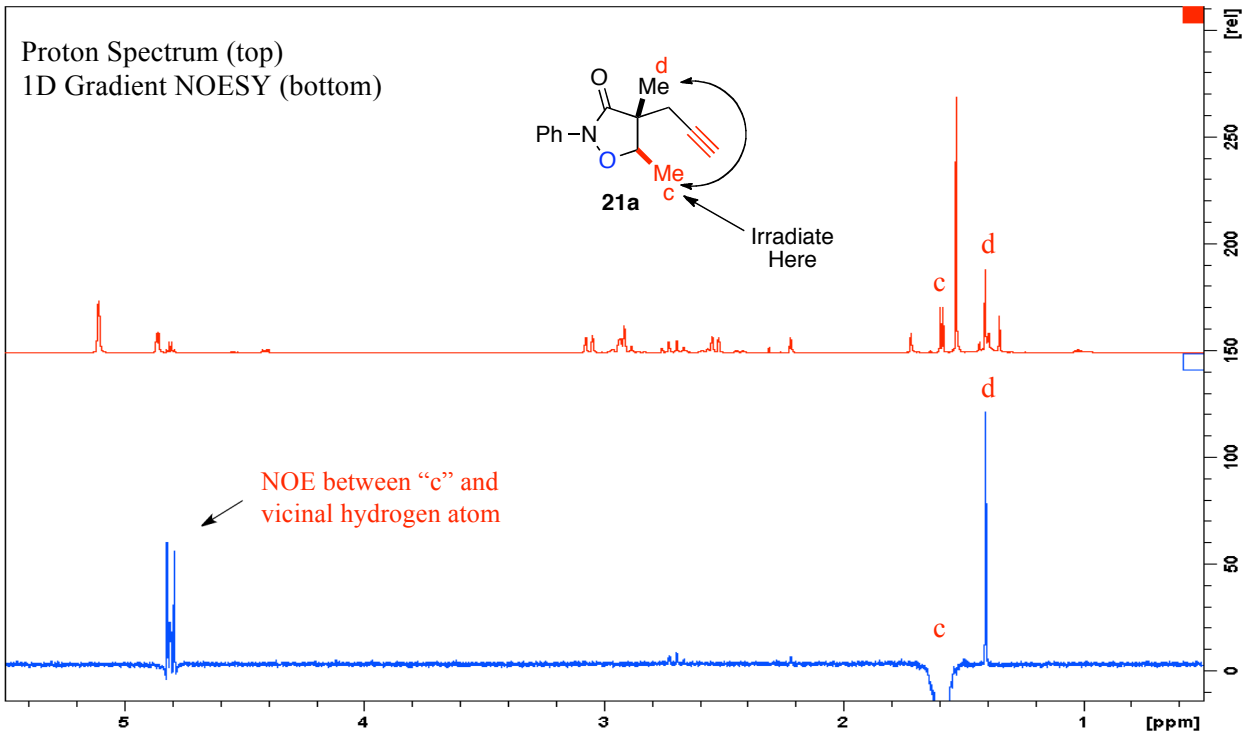

2D Gradient NOESY
a
d
ppm
Aromatic Protons
1
2
3
4
5
6
7
8
O
a
H
N–Ph
Me
O
19a
O
Me
H
d
N–Ph
O
19b
NOE absent
between d and
aromatic H's
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

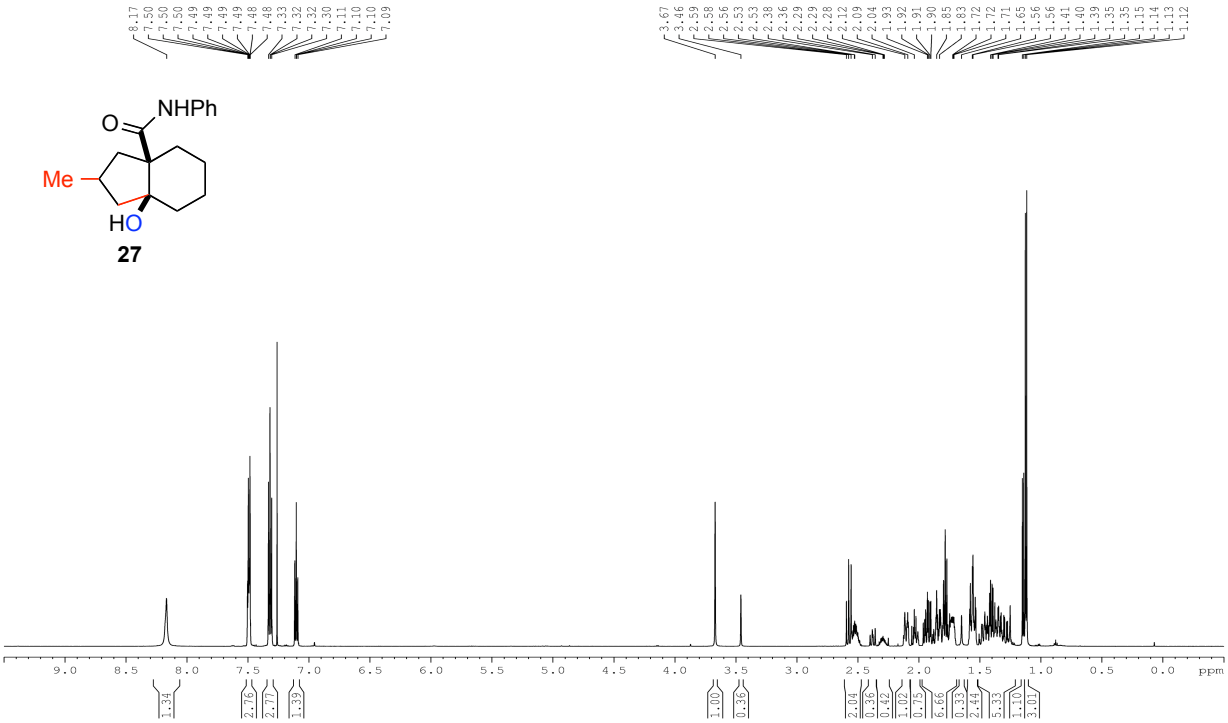

7.44
7.36
7.35
7.33
7.29
7.28
5.97
5.08
5.06
5.04
5.01
2.67
2.65
2.57
2.57
2.55
2.54
2.02
2.02
2.01
1.40
O
Me
Ph
N
OH
20
ppm
2.10
2.15
1.01
0.97
2.01
0.96
1.05
1.00
2.96
171.68
140.35
128.64
127.84
125.09
114.47
80.79
70.85
48.25
28.94
22.19
ppm

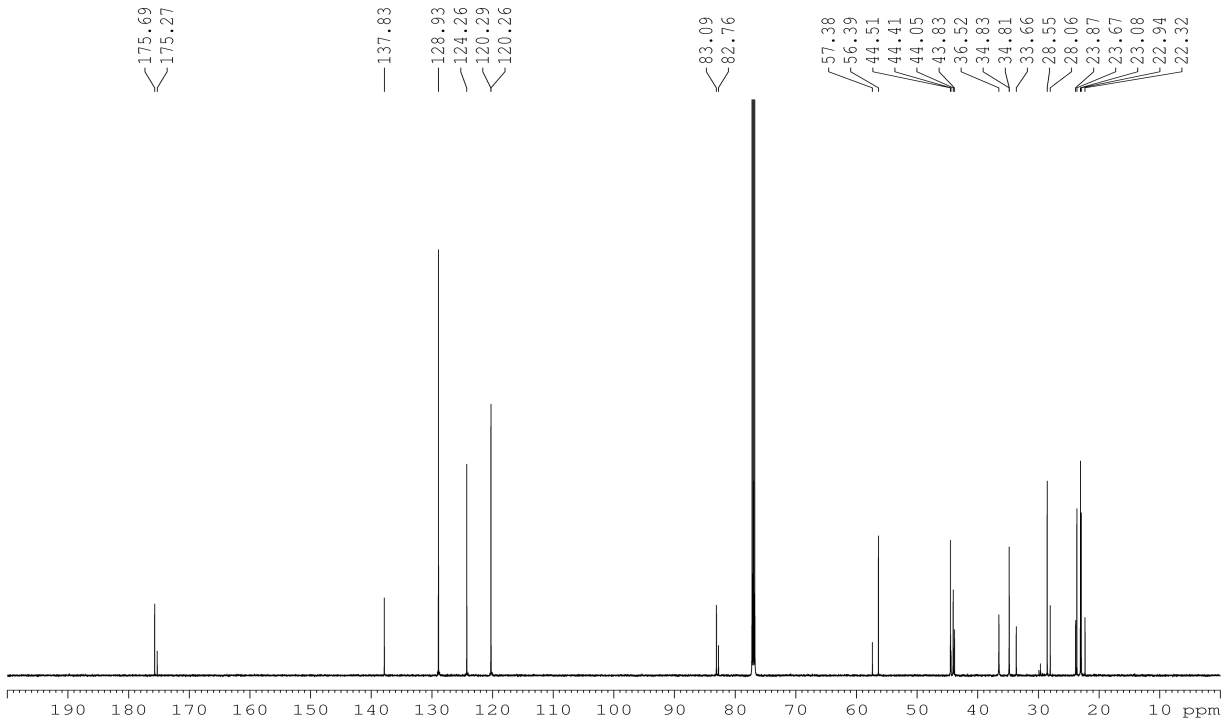

7.72 7.72 7.70 7.38 7.37 7.37 7.36 7.35 7.15 7.14 7.14 7.13 7.12 4.97 4.73 4.72 4.72 4.71 4.68 4.67 4.66 4.65 4.29 4.27 4.26 2.94 2.93 2.91 2.91 2.80 2.79 2.78 2.77 2.77 2.75 2.62 2.61 2.59 2.59 2.56 2.55 2.53 2.53 2.43 2.41 2.38 2.09 2.08 2.08 1.46 1.45 1.39 1.27
O
Me
Ph–N
O
21
O
Me
Ph–N
O
Me
21a
(hydration by-product)
9 8 7 6 5 4 3 2 1 0 ppm
3.15 3.43 1.59 2.03 1.00 0.35 1.01 2.08 0.93 1.36 0.34 1.05 3.03 1.12

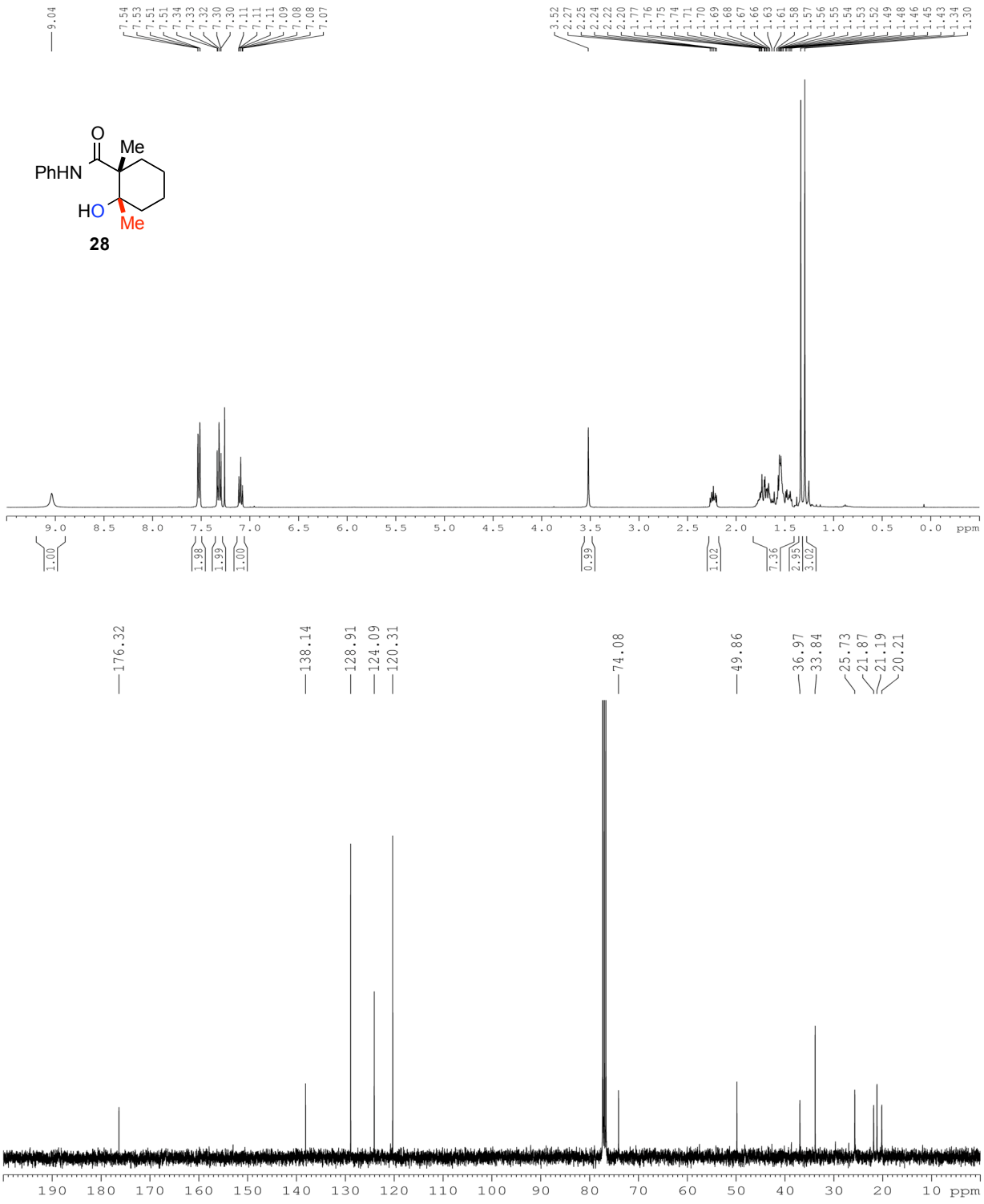

170.67 169.87 146.63 137.05 136.84 128.73 128.68 124.67 124.58 116.62 116.45 109.08 88.98 82.03 81.72 71.86 54.37 42.55 38.30 25.24 24.81 19.92 15.20 13.36
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

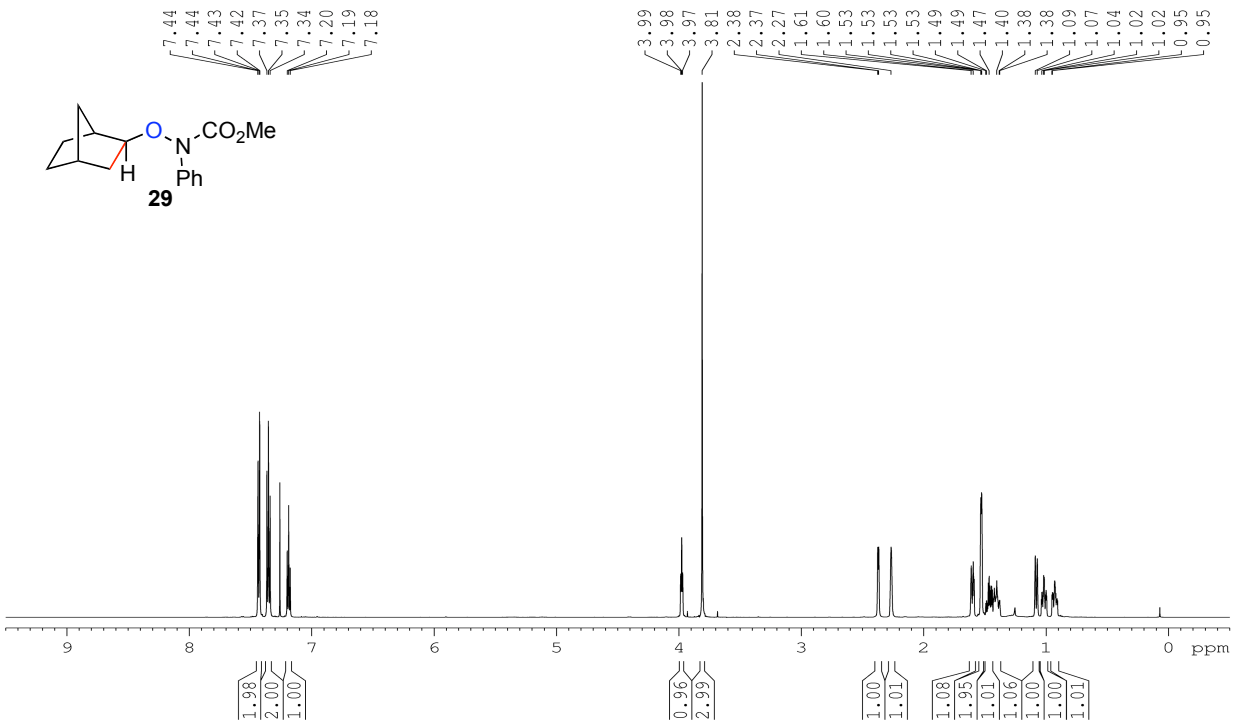

Proton Spectrum (top)
1D Gradient NOESY (bottom)
O
Me
b
Ph –N
O
H
a
21
Irradiate
Here
a
b
a
b
[rel]
1500
1000
500
5
4
3
2
1
[ppm]

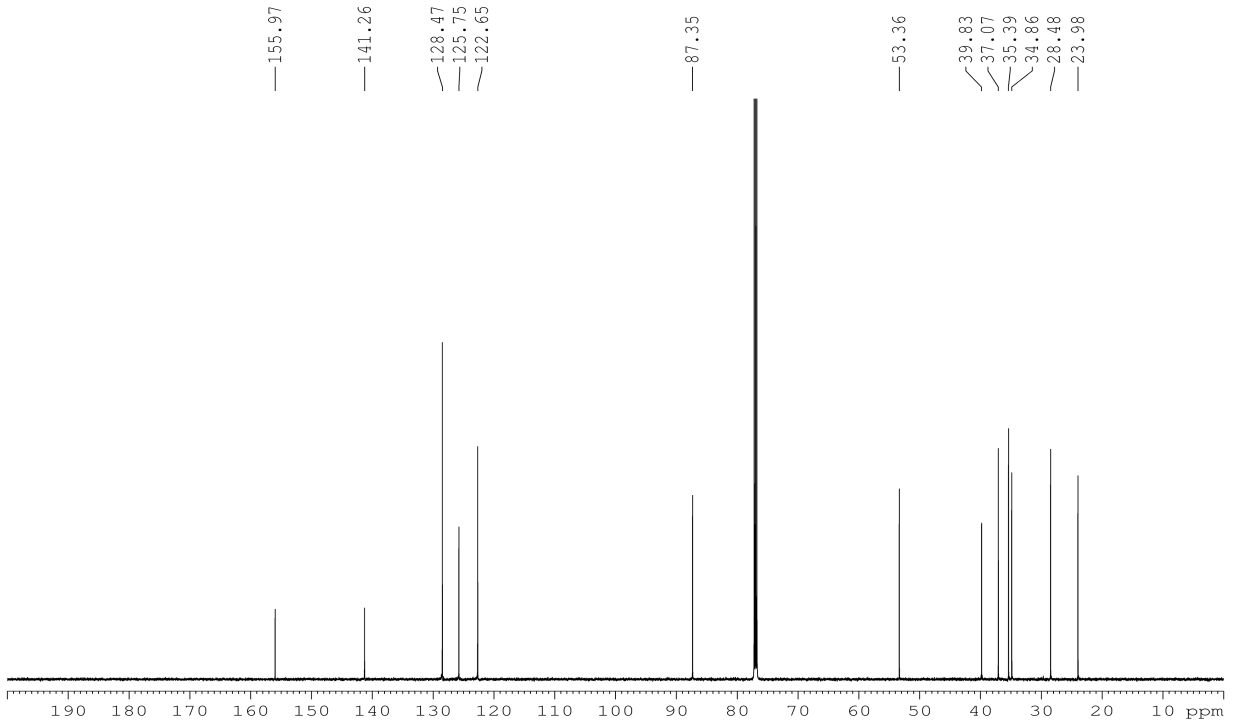

Proton Spectrum (top)
1D Gradient NOESY (bottom)
O
d
Me
Ph –N
O
Me
c
21a
Irradiate
Here
c
d
d
NOE between “c” and
vicinal hydrogen atom
c
[rel]
250
200
150
100
50
0
5
4
3
2
1
[ppm]


NHPh
O
Me
HO
27




9.04
7.54
7.53
7.51
7.51
7.34
7.33
7.32
7.30
7.30
7.11
7.11
7.09
7.08
7.08
7.07
3.52
2.27
2.25
2.24
2.22
2.20
1.77
1.76
1.75
1.74
1.71
1.70
1.69
1.68
1.67
1.66
1.63
1.61
1.58
1.57
1.56
1.55
1.54
1.53
1.52
1.49
1.48
1.46
1.45
1.43
1.34
1.30
O
Me
PhHN
HO
Me
28
ppm
1.00
1.98
1.99
1.00
0.99
1.02
7.36
2.95
3.02
176.32
138.14
128.91
124.09
120.31
74.08
49.86
36.97
33.84
25.73
21.87
21.19
20.21
ppm


7.44
7.44
7.43
7.42
7.37
7.35
7.34
7.20
7.19
7.18
3.99
3.98
3.97
3.81
2.38
2.37
2.27
1.61
1.60
1.53
1.53
1.53
1.49
1.49
1.47
1.40
1.38
1.38
1.09
1.07
1.04
1.02
1.02
0.95
0.95
O
N
CO2Me
Ph
H
29
9
8
7
6
5
4
3
2
1
0
ppm
1.98
2.00
1.00
0.96
2.99
1.00
1.01
1.08
1.95
1.01
1.06
1.00
1.00
1.01


155.97
141.26
128.47
125.75
122.65
87.35
53.36
39.83
37.07
35.39
34.86
28.48
23.98
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

APPENDIX: PUBLICATIONS

Giglio, B.C.; Schmidt, V.A.; Alexanian, E.J. "Metal-Free, Aerobic Dioxygenation of Alkenes using Simple Hydroxamic Acid Derivatives." *J. Am. Chem. Soc*. **2011**, *133*, 13320-13322.

Gupton, J.T.; Telang, N.; Banner, E.J.; Kluball, E.J.; Hall, K.E.; Finzel, K.L.; Jia, X.; Bates, S.R.; Welden, R.S.; **Giglio, B.C.**; Eaton, J.E.; Barelli, P.J.; Firich, L.T.; Stafford, J.A.; Coppock, M.B.; Worrall, E.F.; Kanters, R.P.F.; Keertikar, K.; Osterman, R. "The application of (Z)-3-aryl-3-haloenoic acids to the synthesis of (Z)-5-benzylidene-4-arylpyrrol-2(5H)-ones." *Tetrahedron*, **2010**, *66*, 9113-9122.

Gupton, J.T.; Telang, N.; Jia, X.; **Giglio, B.C.**; Eaton, J.E.; Barelli, P.J.; Hovaizi, M.; Hall, K.E.; Welden, R.S.; Keough, M.J.; Worrall, E.F.; Finzel, K.L.; Kluball, E.J.; Kanters, R.P.F.; Smith, T.M.; Smith, S.Q.; Nunes, S.R.; Wright, M.T.; Birnstihl, J.M. "Further studies on vinamidinium salt amine exchange reactions, borohydride reductions, and subsequent transformations." *Tetrahedron*, **2010**, *66*, 8485-8493.

Gupton, J.T.; **Giglio, B.C.**; Eaton, J.E.; Rieck, E.A.; Smith, K.L.; Keough, M.J.; Barelli, P.J.; Firich, L.T.; Hempel, J.E.; Smith, T.M.; Kanters, R.P.F. "The application of vinylogous iminium salt derivatives to efficient formal syntheses of the marine alkaloids lamellarin G trimethyl ether and ningalin B." *Tetrahedron*, **2009**, *65*, 4283-4292.

Gupton, J.T.; Banner, E.J.; Sartin, M.D.; Coppock, M.B.; Hempel, J.E.; Kharlamova, A.; Fisher, D.C.; **Giglio, B.C.**; Smith, K.L.; Keough, M.J.; Smith, T.M.; Kanters, R.P.F.; Dominey, R.N.; Sikorski, J.A. "The application of vinylogous iminium salt derivatives and microwave accelerated Vilsmeier-Haack reactions to efficient relay syntheses of the polycitone and storniamide natural products." *Tetrahedron*, **2008**, *64*, 5246-5253.

APPENDIX: VITA

Education

PhD Organic Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC (2009-2014)

B.S. Chemistry with honors, University of Richmond, Richmond, VA (2005-2009)

Professional Experience

The University of North Carolina at Chapel Hill
Chapel Hill, NC
Research Advisor: Prof. Erik J. Alexanian
Principle Area of Study: The development of an intermolecular alkene dioxygenation and intramolecular formal alkene hydration using radicals derived from hydroxamic acids and their derivatives. (August 2009-May 2014)

University of Richmond
Richmond, VA
Research Advisor: Prof. John Gupton
Principle Area of Study: The synthesis of pyrrole-containing marine alkaloids using vinylogous iminium salts and their derivatives.

Honors

Richard G. Hiskey Graduate Fellowship, 2011
Phi Beta Kappa, 2009
American Chemical Society Award for Outstanding Senior, 2009
Beckman Scholar, 2008
American Chemical Society Undergraduate Award in Analytical Chemistry, 2008